JEAN L. BOLOGNIA
JOSEPH L. JORIZZO
JULIE V. SCHAFFER

VOLUME ONE

Third Edition

Dermatology

SECTION EDITORS

Jeffrey P. Callen
Lorenzo Cerroni
Warren R. Heymann
George J. Hruza
Anthony J. Mancini
James W. Patterson
Martin Röcken
Thomas Schwarz

ELSEVIER
SAUNDERS

ExpertConsult.com Expert Consult Premium Edition

Third Edition

Dermatology

Content Strategist: ***Russell Gabbedy***
Content Development Specialists: ***Sven Pinczewski and Rachael Harrison***
Content Coordinator: ***Emma Cole***
Project Manager: ***Anne Collett***
Design Manager: ***Stewart Larking***
Illustration Manager: ***Gillian Richards and Jennifer Rose***
Illustrator: ***Antbits Ltd.***
Marketing Manager (UK/USA): ***Gaynor Jones and Helena Mutak***

Third Edition

Dermatology

Edited by

Jean L Bolognia MD
Professor of Dermatology
Department of Dermatology
Yale Medical School
New Haven, CT, USA

Joseph L Jorizzo MD
Professor and Former
(Founding) Chair
Department of Dermatology
Wake Forest University School of Medicine
Winston-Salem, NC;
Adjunct Professor
Department of Dermatology
Weill Cornell Medical College
New York, NY, USA

Julie V Schaffer MD
Associate Professor of Dermatology and Pediatrics
Director of Pediatric Dermatology
Department of Dermatology
New York University School of Medicine
New York, NY, USA

Section Editors

Jeffrey P Callen MD FACP
Professor of Medicine (Dermatology)
Chief, Division of Dermatology
University of Louisville
Louisville, KY, USA

Lorenzo Cerroni MD
Associate Professor of Dermatology
Director, Research Unit Dermatopathology
Department of Dermatology
Medical University of Graz
Graz, Austria

Warren R Heymann MD
Professor of Medicine and Pediatrics
Head, Division of Dermatology
Cooper Medical School of Rowan University
Camden, NJ;
Clinical Professor of Dermatology
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, PA, USA

George J Hruza MD
Clinical Professor of Dermatology and Otolaryngology-Head and Neck Surgery
St. Louis University
St. Louis, MO;
Medical Director
Laser and Dermatologic Surgery Center
Chesterfield, MO, USA

Anthony J Mancini MD
Professor of Pediatrics and Dermatology
Northwestern University Feinberg School of Medicine;
Head, Division of Pediatric Dermatology
Children's Memorial Hospital
Chicago, IL, USA

James W Patterson MD
Professor of Pathology and Dermatology
Director of Dermatopathology
University of Virginia Health System
Charlottesville, VA, USA

Martin Röcken MD
Professor and Chairman
Department of Dermatology
Eberhard Karls University of Tübingen
Tübingen, Germany

Thomas Schwarz MD
Professor and Chairman
Department of Dermatology and Allergology
University Hospital Schleswig-Holstein
Kiel, Germany

ELSEVIER
SAUNDERS

For additional online content visit
www.expertconsult.com
Expert CONSULT

ELSEVIER
SAUNDERS
An imprint of Elsevier Limited

© 2012, Elsevier Limited. All rights reserved.
© Chapters 3, 80 and 85 are US Government works in the public domain and not subject to copyright.
© Gabriele Richard retains copyright to her original figures in chapter 57.
© Daniel Hohl retains copyright to his original photographs in chapter 59.
© William Coleman III retains copyright of his original figures in chapter 156.

The right of Jean L Bolognia, Joseph L Jorizzo, Julie V Schaffer, Jeffrey P Callen, Lorenzo Cerroni, Warren R Heymann, George J Hruza, Anthony J Mancini, James W Patterson, Martin Röcken and Thomas Schwarz to be identified as authors of this work has been asserted by them in accordance with the Copyright, Designs and Patents Act 1988.

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher. Details on how to seek permission, further information about the Publisher's permissions policies and our arrangements with organizations such as the Copyright Clearance Center and the Copyright Licensing Agency, can be found at our website: www.elsevier.com/permissions.

First edition 2003
Reprinted 2003 (twice)
Reprinted 2004
Second edition 2007
Reprinted 2009

British Library Cataloguing in Publication Data
Dermatology. – 3rd ed.
1. Dermatology.
I. Bolognia, Jean.
616.5-dc22

ISBN: 9780723435716
Ebook ISBN: 9780702051821

This book and the individual contributions contained in it are protected under copyright by the Publisher (other than as may be noted herein).

Notice
Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

With respect to any drug or pharmaceutical products identified, readers are advised to check the most current information provided (i) on procedures featured or (ii) by the manufacturer of each product to be administered, to verify the recommended dose or formula, the method and duration of administration, and contraindications. It is the responsibility of practitioners, relying on their own experience and knowledge of their patients, to make diagnoses, to determine dosages and the best treatment for each individual patient, and to take all appropriate safety precautions.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

ELSEVIER your source for books, journals and multimedia in the health sciences
www.elsevierhealth.com

Working together to grow libraries in developing countries
www.elsevier.com | www.bookaid.org | www.sabre.org
ELSEVIER BOOK AID International Sabre Foundation

Printed in China
Last digit is the print number: 9 8 7 6 5 4 3 2 1

Contents

Preface x
List of Contributors xi
User Guide xxiii
Dedication xxiv
Acknowledgments xxv

VOLUME ONE

SECTION ONE: Overview of Basic Science

0 Basic Principles of Dermatology 1
Whitney A High, Carlo Francesco Tomasini, Giuseppe Argenziano and Iris Zalaudek

1 Anatomy and Physiology 43
Travis W Vandergriff and Paul R Bergstresser

2 Skin Development and Maintenance 55
Maranke I Koster, Cynthia A Loomis, Tamara Koss and David Chu

3 Molecular Biology 65
Jonathan Vogel, Carole Yee and Thomas N Darling

4 Immunology 81
Thomas Schwarz

SECTION TWO: Pruritus

5 Cutaneous Neurophysiology 99
Gil Yosipovitch and Alexandru DP Papoiu

6 Pruritus and Dysesthesia 111
Elke Weisshaar, Alan B Fleischer Jr, Jeffrey D Bernhard and Thomas G Cropley

7 Psychocutaneous Diseases 127
Chai Sue Lee and John YM Koo

SECTION THREE: Papulosquamous and Eczematous Dermatoses

8 Psoriasis 135
Peter CM van de Kerkhof and Frank O Nestlé

9 Other Papulosquamous Disorders 157
Gary S Wood and George T Reizner

10 Erythroderma 171
Wolfram Sterry and Matthias Steinhoff

11 Lichen Planus and Lichenoid Dermatoses 183
Tetsuo Shiohara and Yoko Kano

12 Atopic Dermatitis 203
Thomas Bieber and Caroline Bussmann

13 Other Eczematous Eruptions 219
Norbert Reider and Peter O Fritsch

14 Allergic Contact Dermatitis 233
Christen M Mowad and James G Marks Jr

15 Irritant Contact Dermatitis 249
David E Cohen and Aieska de Souza

16 Occupational Dermatoses 261
S Mark Wilkinson

17 Dermatoses Due to Plants 273
Thomas W McGovern

SECTION FOUR: Urticarias, Erythemas and Purpuras

18 Urticaria and Angioedema 291
Clive EH Grattan

19 Figurate Erythemas 307
Agustín España

20 Erythema Multiforme, Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis 319
Lars E French and Christa Prins

21 Drug Reactions 335
Jean Revuz and Laurence Valeyrie-Allanore

22 Purpura: Mechanisms and Differential Diagnosis 357
Warren W Piette

23 Cutaneous Manifestations of Microvascular Occlusion Syndromes 369
Warren W Piette

24 Cutaneous Vasculitis 385
Kanade Shinkai and Lindy P Fox

25 Eosinophilic Dermatoses 411
Cloyce L Stetson and Kristin M Leiferman

26 Neutrophilic Dermatoses 423
Samuel L Moschella and Mark DP Davis

27 Pregnancy Dermatoses 439
Christina M Ambros-Rudolph and Jeff K Shornick

SECTION FIVE: Vesiculobullous Diseases

28 The Biology of the Basement Membrane Zone 449
Kim B Yancey

29 Pemphigus 461
Masayuki Amagai

30 Pemphigoid Group 475
Philippe Bernard and Luca Borradori

31 Dermatitis Herpetiformis and Linear IgA Bullous Dermatosis 491
Christopher M Hull and John J Zone

32 Epidermolysis Bullosa 501
Jo-David Fine and Jemima E Mellerio

33 Other Vesiculobullous Diseases 515
José M Mascaró Jr

34 Vesiculobullous and Erosive Diseases in the Newborn 523
Deborah S Goddard, Amy E Gilliam and Ilona J Frieden

SECTION SIX: Adnexal Diseases

35 Structure and Function of Eccrine, Apocrine and Sebaceous Glands 539
Martin Schaller and Gerd Plewig

36 Acne Vulgaris 545
Andrea L Zaenglein and Diane M Thiboutot

37 Rosacea and Related Disorders 561
Frank C Powell and Síona Ní Raghallaigh

38 Folliculitis and Other Follicular Disorders 571
Amy McMichael, Ashley R Curtis, Daniela Guzman-Sanchez and A Paul Kelly

39 Diseases of the Eccrine and Apocrine Sweat Glands 587
Jami L Miller

SECTION SEVEN: Rheumatologic Dermatology

40 Autoantibodies Encountered in Patients with Autoimmune Connective Tissue Diseases 603
Heidi T Jacobe, Richard D Sontheimer and Stephanie Saxton-Daniels

41 Lupus Erythematosus 615
Lela A Lee and Victoria P Werth

42 Dermatomyositis 631
Joseph L Jorizzo and Ruth Ann Vleugels

43 Systemic Sclerosis (Scleroderma) and Related Disorders 643
M Kari Connolly

44 Morphea and Lichen Sclerosus 657
Martin Röcken and Kamran Ghoreschi

45 Other Rheumatologic Diseases 671
Jennie T Clarke

SECTION EIGHT: Metabolic and Systemic Diseases

46 Mucinoses 687
Franco Rongioletti and Alfredo Rebora

47 Amyloidosis 699
Richard W Groves and Martin M Black

48 Deposition Diseases 709
Jennifer Quist, Sven Quist and Harald Gollnick

49 Porphyria 717
Jorge Frank and Pamela A Poblete-Gutiérrez

50 Calcifying and Ossifying Disorders of the Skin 729
Janet A Fairley

51 Nutritional Diseases 737
Stephanie McLeish Schaefer and Chad M Hivnor

52 Graft-versus-Host Disease 753
Edward W Cowen

53 Dermatologic Manifestations in Patients with Systemic Disease 761
Kathryn Schwarzenberger and Jeffrey P Callen

SECTION NINE: Genodermatoses

54 Basic Principles of Genetics 783
Maija Kiuru, Amalia Martinez-Mir and Angela M Christiano

55 Genetic Basis of Cutaneous Diseases 799
Vered Molho-Pessach and Julie V Schaffer

56 Biology of Keratinocytes 825
Meral J Arin, Dennis R Roop, Peter J Koch and Maranke I Koster

57 Ichthyoses, Erythrokeratodermas and Related Disorders 837
Gabriele Richard and Franziska Ringpfeil

58 Keratodermas 871
Alfons L Krol and Dawn Siegel

59 Darier Disease and Hailey-Hailey Disease 887
Daniel Hohl

60 Primary Immunodeficiencies 899
Julie V Schaffer and Amy S Paller

61 Neurofibromatosis and Tuberous Sclerosis 925
Hensin Tsao and Su Luo

62 Mosaicism and Linear Lesions 943
Celia Moss

63 Other Genodermatoses 963
Disorders Featuring Tumorigenesis 963
Susan J Bayliss and David R Berk
Enzyme Deficiency Diseases 970
Barbara K Burton
Premature Aging Syndromes and Poikilodermas 975
Bernard A Cohen
Ectodermal Dysplasias 982
Alanna F Bree and Virginia P Sybert

64 Developmental Anomalies 993
Richard Antaya and Julie V Schaffer

SECTION TEN: Pigmentary Disorders

65 Melanocyte Biology 1011
Jean L Bolognia and Seth J Orlow

66 Vitiligo and Other Disorders of Hypopigmentation 1023
Jean-Paul Ortonne and Thierry Passeron

67 Disorders of Hyperpigmentation 1049
Mary Wu Chang

SECTION ELEVEN: Hair, Nails and Mucous Membranes

68 Biology of Hair and Nails 1075
David de Berker, Claire A Higgins, Colin Jahoda and Angela M Christiano

69 Alopecias 1093
Leonard C Sperling, Rodney D Sinclair and Laila El Shabrawi-Caelen

70 Hypertrichosis and Hirsutism 1115
Francisco M Camacho-Martinez

71 Nail Disorders 1129
Antonella Tosti and Bianca Maria Piraccini

72 Oral Disease 1149
Carl M Allen and Charles Camisa

73 Anogenital (Non-venereal) Disease 1171
Susan M Cooper and Fenella Wojnarowska

VOLUME TWO

SECTION TWELVE: Infections, Infestations and Bites

74 Bacterial Diseases 1187
Christian R Millett, Analisa V Halpern, Annette C Reboli and Warren R Heymann

75 Myobacterial Infections 1221
Marcia Ramos-e-Silva and Maria Cristina Ribeiro de Castro

76 Rickettsial Diseases 1243
David H Walker

77 Fungal Diseases 1251
Boni E Elewski, Lauren C Hughey, Jenny O Sobera and Roderick Hay

78 Cutaneous Manifestations of HIV Infection 1285
Armin Rieger, T Minsue Chen and Clay J Cockerell

79 Human Papillomaviruses 1303
Reinhard Kirnbauer and Petra Lenz

80 Human Herpesviruses 1321
Natalia Mendoza, Vandana Madkan, Karan Sra, Beau Willison, L Katie Morrison and Stephen K Tyring

81 Other Viral Diseases 1345
Anthony J Mancini and Ayelet Shani-Adir

82 Sexually Transmitted Infections 1367
Angelika Stary and Georg Stary

83 Protozoa and Worms 1391
Steven A Nelson and Karen E Warschaw

84 Infestations 1423
Craig N Burkhart, Craig G Burkhart and Dean Scott Morrell

85 Bites and Stings 1435
Dirk M Elston

SECTION THIRTEEN: Disorders Due to Physical Agents

86 Ultraviolet Light 1455
Thomas M Rünger

87 Photodermatologic Disorders 1467
Henry W Lim and John LM Hawk

88 Environmental and Sports-Related Skin Diseases 1487
Mary Beth Cole and Michael L Smith

89 Signs of Drug Abuse 1511
Josep L Genebriera de Lamo, Mark R Pittelkow and Miguel Sanchez

90 Skin Signs of Abuse 1521
Sharon S Raimer, Lauren Raimer-Goodman and Ben G Raimer

SECTION FOURTEEN: Disorders of Langerhans Cells and Macrophages

91 Histiocytoses 1529
Warren T Goodman and Terry L Barrett

92 Xanthomas 1547
W Trent Massengale, Kafele T Hodari, Erin E Boh and Lee T Nesbitt Jr

93 Non-infectious Granulomas 1557
Amy Reisenauer, Kevin P White, Veselina Korcheva and Clifton R White Jr

94 Foreign Body Reactions 1573
MA Abdallah, MMA Abdallah and Marwa A-R Abdallah

SECTION FIFTEEN: Atrophies and Disorders of Dermal Connective Tissues

95 Biology of the Extracellular Matrix 1585
Leena Bruckner-Tuderman

96 Perforating Diseases 1599
Ronald P Rapini

97 Heritable Disorders of Connective Tissue 1607
Franziska Ringpfeil and Jouni Uitto

98 Dermal Hypertrophies 1621
Marco Romanelli, Valentina Dini, Mariya Miteva and Paolo Romanelli

99 Atrophies of Connective Tissue 1631
Catherine Maari and Julie Powell

SECTION SIXTEEN: Disorders of Subcutaneous Fat

100 Panniculitis 1641
James W Patterson

101 Lipodystrophies 1663
Suat Hoon Tan, Priya Sen and Mark Tang

SECTION SEVENTEEN: Vascular Disorders

102 Vascular Biology 1679
Michael Detmar and Satoshi Hirakawa

103 Infantile Hemangiomas 1691
Anita N Haggstrom and Maria C Garzon

104 Vascular Malformations 1711
Odile Enjolras

105 Ulcers 1729
Ariela Hafner and Eli Sprecher

106 Other Vascular Disorders 1747
Robert Kelly and Christopher Baker

SECTION EIGHTEEN: Neoplasms of the Skin

107 Principles of Tumor Biology and Pathogenesis of BCCs and SCCs 1759
Edel A O'Toole, Fredrik Pontén, Joakim Lundeberg and Anna Asplund

108 Actinic Keratosis, Basal Cell Carcinoma and Squamous Cell Carcinoma 1773
H Peter Soyer, Darrell S Rigel and Elisabeth MT Wurm

109 Benign Epidermal Tumors and Proliferations 1795
Luis Requena, Celia Requena and Clay J Cockerell

110 Cysts 1817
Mary S Stone

111 Adnexal Neoplasms 1829
Timothy H McCalmont

112 Benign Melanocytic Neoplasms 1851
Harold S Rabinovitz and Raymond L Barnhill

113 Melanoma 1885
Claus Garbe and Jürgen Bauer

114 Vascular Neoplasms and Neoplastic-like Proliferations 1915
Paula E North and Jay Kincannon

115 Neural and Neuroendocrine Neoplasms (Other than Neurofibromatosis) 1943
Zsolt B Argenyi

116 Fibrous and Fibrohistiocytic Proliferations of the Skin and Tendons 1961
Hideko Kamino, Vijaya B Reddy and John Pui

117 Muscle, Adipose and Cartilage Neoplasms 1979
Steven Kaddu and Sabine Kohler

118 Mastocytosis 1993
Michael D Tharp

119 B-Cell Lymphomas of the Skin 2003
Lorenzo Cerroni

120 Cutaneous T-Cell Lymphoma 2017
Rein Willemze

121 Other Lymphoproliferative and Myeloproliferative Diseases 2037
Harry L Winfield and Bruce R Smoller

122 Cutaneous Metastases 2049
Matthew B Zook, Hong Wu and Stuart R Lessin

SECTION NINETEEN: Medical Therapy

123 Public Health and Dermatology 2057
Sarah Nakib and Abrar A Qureshi

124 Skin Barrier and Transdermal Drug Delivery 2065
Mark R Prausnitz, Peter M Elias, Thomas J Franz, Matthias Schmuth, Jui-Chen Tsai, Gopinathan K Menon, Walter M Holleran and Kenneth R Feingold

125 Glucocorticosteroids 2075
Scott M Jackson and Lee T Nesbitt Jr

126 Retinoids 2089
Anne-Marie Thielen and Jean-Hilaire Saurat

127 Antimicrobial Drugs 2105
Jack L Lesher Jr and R Carol McConnell

128 Immunomodulators 2131
J Mark Jackson and Jeffrey P Callen

129 Other Topical Medications 2153
Matthew Fox, Yolanda Helfrich and Sewon Kang

130 Systemic Drugs 2165
Julia R Nunley and Stephen E Wolverton

131 Drug Interactions 2183
Lori E Shapiro, Sandra R Knowles and Neil H Shear

132 Sunscreens 2197
Vincent A DeLeo

133 Complementary and Alternative Medicine 2205
Amy Geng and Raymond G Dufresne Jr

SECTION TWENTY: Physical Treatment Modalities

134 Ultraviolet Therapy 2219
Herbert Hönigsmann and Thomas Schwarz

135 Photodynamic Therapy 2237
Harvey Lui and Rolf-Markus Szeimies

136 Lasers and Other Energy Technologies – Principles and Skin Interactions 2251
Fernanda H Sakamoto, Mathew M Avram and R Rox Anderson

137 Laser Therapy 2261
Christopher B Zachary and Rana Rofagha

138 Cryosurgery 2283
Emanuel G Kuflik and Julianne H Kuflik

139 Radiotherapy 2291
Michael Veness and Shawn W Richards

140 Electrosurgery 2303
Sheldon V Pollack

SECTION TWENTY-ONE: Surgery

141 Biology of Wound Healing 2313
Sabine A Eming

142 Surgical Anatomy of the Head and Neck 2327
Franklin P Flowers and Thomas S Breza Jr

143 Anesthesia 2343
George J Hruza

144 Wound Closure Materials and Instruments 2353
Christie Travelute Ammirati and Glenn Goldman

145 Dressings 2365
Gregg M Menaker, Stephanie L Mehlis and Sarah Kasprowicz

146 Biopsy Techniques and Basic Excisions 2381
Suzanne Olbricht

147 Flaps 2399
David G Brodland and David B Pharis

148 Grafts 2421
Désirée Ratner

149 Nail Surgery 2435
Phoebe Rich

150 Mohs Surgery 2445
Stephen N Snow and Juliet Gunkel

151 Surgical Complications and Optimizing Outcomes 2459
Anna S Clayton and Thomas Stasko

SECTION TWENTY-TWO: Cosmetic Surgery

152 Evaluation of Beauty and the Aging Face 2473
Thomas E Rohrer, Naissan O Wesley, Richard Glogau and Jeffrey S Dover

153 Cosmetics and Cosmeceuticals 2479
Zoe Diana Draelos

154 Chemical and Mechanical Skin Resurfacing 2493
Gary D Monheit and Mark A Chastain

155 Phlebology and Treatment of Leg Veins 2509
Mitchel P Goldman and Robert A Weiss

156 Liposuction 2525
William P Coleman III, Timothy C Flynn and Kyle M Coleman

157 Hair Restoration 2535
Marc R Avram, Sharon A Keene, Dowling B Stough and Nicole E Rogers

158 Soft Tissue Augmentation 2547
Nazanin Saedi, Adam M Rotunda, Derek H Jones, Rhoda S Narins, Seth L Matarasso and Neil S Sadick

159 Botulinum Toxin 2561
Alastair Carruthers and Jean Carruthers

Index to volumes one and two I-1

Preface

The practice of dermatology is based upon a visual approach to clinical disease, with the development of an appreciation of recurrent patterns and images. The entire spectrum of our discipline, from the generation of clinicopathologic differential diagnoses to the orientation of rotational flaps, relies upon imagery. As a result, visualization also plays a critical role in how we integrate new information into pre-existing frameworks that serve as the hard drives of our medical memory.

In the textbook *Dermatology* there is a strong emphasis on visual learning. This commitment is reflected in the use of schematic diagrams to convey the principles of skin biology as well as cutaneous surgery, and the inclusion of algorithms, which provide a logical as well as practical approach to commonly encountered clinical problems. The majority of the basic science is integrated throughout the book and appears as introductory chapters to the various sections. In this edition, there are more photomicrographs demonstrating key histologic findings interspersed within the clinical chapters. These chapters also contain tables that attempt to provide weighted differential diagnoses and a "ladder" approach to therapeutic interventions. Lastly, color-coding of sections allows an easy and rapid access to required information.

The ultimate goal of *Dermatology* is for it to never make its way to the bookshelf because it is being used on a weekly, or perhaps even daily, basis. Hopefully, this book will function as a colleague, albeit a non-verbal one, who is easily approachable and possesses the necessary expertise to provide succinct, up-to-date information that is both precise and practical. It is also our hope that the organization is intuitive and information can therefore be quickly retrieved. Realizing this goal required the time and energy of our contributors who have unselfishly shared their knowledge and experience with literally thousands of patients from around the world, and we thank them.

JB, JJ and JVS
2012

List of Contributors

MA Abdallah MD
Professor of Dermatology and Sexually Transmitted Diseases
Faculty of Medicine
Ain Shams University
Cairo, Egypt

MMA Abdallah
Faculty of Medicine
Ain Shams University
Cairo, Egypt

Marwa A-R Abdallah
Professor of Dermatology and Venereology
Faculty of Medicine
Ain Shams University
Cairo, Egypt

Carl M Allen DDS MSD
Professor and Director
Oral and Maxillofacial Pathology
Division of Oral and Maxillofacial Surgery
Pathology and Anesthesiology
College of Dentistry
The Ohio State University
Columbus, OH, USA

Masayuki Amagai MD PhD
Professor and Chair
Department of Dermatology
Keio University School of Medicine
Tokyo, Japan

Christina M Ambros-Rudolph MD
Associate Professor
Department of Dermatology
Medical University of Graz
Graz, Austria

Christie Travelute Ammirati MD FAAD FACMS
Associate Professor of Dermatology
Department of Dermatology
Penn State Milton S. Hershey Medical Center
Hershey, PA, USA

R Rox Anderson MD
Professor of Dermatology,
Director of the Wellman Center for Photomedicine
Massachusetts General Hospital
Department of Dermatology
Harvard Medical School
Boston, MA, USA

Richard Antaya MD
Director, Pediatric Dermatology
Department of Dermatology
Yale University School of Medicine
New Haven, CT, USA

Zsolt B Argenyi MD
Director of Dermatopathology
Professor of Pathology and Dermatology
University of Washington Medical Center
Seattle, WA, USA

Giuseppe Argenziano MD
Dermatology Unit
1st Medical Department
Arcispedale Santa Maria Nuova
Viale Risorgimento
Reggio Emilia, Italy

Meral J Arin MD
Assistant Professor
Department of Dermatology
University of Cologne
Cologne, Germany

Anna Asplund PhD
Doctor of Pathology
Department of Genetics and Pathology
Uppsala University Hospital
Uppsala, Sweden

Mathew M Avram MD JD
Director,
Dermatology Laser and Cosmetic Center,
Massachusetts General Hospital,
Assistant Professor of Dermatology,
Faculty Director for Procedural Dermatology Training
Department of Dermatology
Harvard Medical School
Boston, MA, USA

Marc R Avram MD
Clinical Professor of Dermatology
New York Presbyterian Hospital and Weill Cornell Medical Center
New York, NY, USA

Christopher Baker MBBS FACD
Clinical Associate Professor
Department of Medicine
University of Melbourne
St Vincent's Hospital
Melbourne, VIC, Australia

Raymond L Barnhill MD
Professor of Pathology
Co-Director, Dermatopathology
Dermatopathology Division
Department of Pathology and Laboratory Medicine
University of California Los Angeles
Los Angeles, CA, USA

Terry L Barrett MD
Clinical Professor of Pathology and Dermatology
University of Texas Southwestern Medical School
Dallas, TX, USA

Jürgen Bauer MD
Professor of Dermatology
Department of Dermatology
Eberhard Karls University Tübingen
Tübingen, Germany

Susan J Bayliss MD
Professor
Division of Dermatology
Washington University School of Medicine
St. Louis, MO, USA

Paul R Bergstresser MD
Professor
Department of Dermatology
UT Southwestern Medical Center at Dallas
Dallas, TX, USA

David R Berk MD
Assistant Professor of Dermatology
Washington University School of Medicine and
St. Louis Children's Hospital
St. Louis, MO, USA

Philippe Bernard MD
Professor
Department of Dermatology
Hôpital Robert Debre
Reims, France

Jeffrey D Bernhard MD
Professor of Medicine
University of Massachusetts Medical School
Worcester, MA, USA

Thomas Bieber MD PhD
Professor of Dermatology and Allergy,
Chairman and Director
Department of Dermatology and Allergy
University of Bonn
Bonn, Germany

Martin M Black MD FRCP FRCPath
Emeritus Professor of Dermatological Immunopathology and
Honorary Consultant Dermatologist
St John's Institute of Dermatology
St Thomas' Hospital
London, UK

Erin E Boh MD PhD
Professor and Chairman, Department of Dermatology
Joseph Chastain Professor of Clinical Dermatology
Tulane University Health Sciences Center
New Orleans, LA, USA

Jean L Bolognia MD
Professor of Dermatology
Department of Dermatology
Yale Medical School
New Haven, CT, USA

Luca Borradori MD
Professor of Dermatology
Chairman
Universitätsklinik für Dermatologie
Inselspital
Bern, Switzerland

Alanna F Bree MD
Pediatric Dermatologist
Dermatology Specialists of Houston
Bellaire, TX, USA

Thomas S Breza Jr MD MS
Private Practice
Lauderdale by the Sea
Courtesy Assistant Professor
Department of Medicine (Division of Dermatology)
University of Florida
Gainesville, FL USA

David G Brodland MD
Private Practice
Assistant Clinical Professor
Departments of Dermatology and Otolaryngology
University of Pittsburgh
Pittsburgh, PA, USA

Leena Bruckner-Tuderman MD
Professor and Chair
Department of Dermatology
University of Freiburg
Freiburg, Germany

Craig G Burkhart MPH MD
Clinical Professor
Department of Medicine
The University of Toledo College of Medicine
Clinical Assistant Professor
Ohio University of Osteopathic Medicine
Sylvania, OH, USA

Craig N Burkhart MS MD
Assistant Professor
Department of Dermatology
The University of North Carolina at Chapel Hill
Chapel Hill, NC, USA

Barbara K Burton MD
Professor of Pediatrics
Northwestern University Medical School
Division of Genetics
Children's Memorial Hospital
Chicago, IL, USA

Caroline Bussmann MD
Dermatologist and Allergist
Department of Dermatology and Allergy
University of Bonn
Bonn, Germany

Jeffrey P Callen MD FACP
Professor of Medicine (Dermatology)
Chief, Division of Dermatology
University of Louisville
Louisville, KY, USA

Francisco M Camacho-Martínez MD
Professor of Dermatology
Department of Dermatology
School of Medicine
University of Seville
Seville, Spain

Charles Camisa MD
Director
Camisa Psoriasis Center
Riverchase Dermatology
Naples, FL, USA

Alastair Carruthers MD
Clinical Professor
Department of Dermatology and Skin Science
University of British Columbia
Vancouver, BC, Canada

Jean Carruthers MD FRCSC FRC(Ophth)
Clinical Professor
Department of Ophthalmology
University of British Columbia
Vancouver, BC, Canada

Lorenzo Cerroni MD
Associate Professor of Dermatology
Director, Research Unit Dermatopathology
Department of Dermatology
Medical University of Graz
Graz, Austria

Mary Wu Chang MD
Associate Clinical Professor
Dermatology and Pediatrics
University of Connecticut School of Medicine
Farmington, CT, USA

Mark A Chastain MD
Clinical Assistant Professor
Department of Dermatology
Emory University
Atlanta, GA, USA

T Minsue Chen MD
Advanced Dermatology and Skin Care
Katy, TX, USA

Angela M Christiano MD
Professor and Vice Chair for Research
Departments of Dermatology / Genetics and Development
Columbia University
College of Physicians & Surgeons
New York, NY, USA

David Chu MD PhD
Scripps Health
San Diego, CA, USA

Jennie T Clarke MD
Assistant Professor of Dermatology
Department of Dermatology
Penn State College of Medicine
Penn State Milton S. Hershey Medical Center
Hershey, PA, USA

Anna S Clayton MD
Assistant Professor
Division of Dermatology
Department of Medicine
Vanderbilt University Medical Center
Nashville, TN, USA

Clay J Cockerell MD
Clinical Professor
Department of Dermatology and Pathology
University of Texas Southwestern Medical Center
Cockerell and Associates
Dallas, TX, USA

Bernard A Cohen MD
Director
Department of Pediatric Dermatology
Johns Hopkins University School of Medicine
Baltimore, MD, USA

David E Cohen MD MPH
Vice Chairman and Associate Professor of Dermatology
Department of Dermatology
New York University School of Medicine
New York, NY, USA

Mary Beth Cole MD
Resident Physician
Department of Dermatology
Vanderbilt University
Nashville, TN, USA

Kyle M Coleman MD
Private Practice
Austin, TX, USA

William P Coleman III MD
Clinical Professor of Dermatology, and Adjunct Professor of Surgery (Plastic Surgery)
Tulane University Health Sciences Center
New Orleans, LA, USA

M Kari Connolly MD
Professor of Dermatology and Medicine
Department of Dermatopathology
University of California in San Francisco
San Francisco, CA, USA

Susan M Cooper MD MBChB MRCGP FRCP
Consultant Dermatologist
Honorary Senior Clinical Lecturer
Department of Dermatology
Churchill Hospital
Oxford, UK

Edward W Cowen MD MHSc
Staff Clinician
Dermatology Branch
Center for Cancer Research
National Cancer Institute
National Institutes of Health
Bethesda, MD, USA

Thomas G Cropley MD
Professor and Chairman
Department of Dermatology
University of Virginia Health System
Charlottesville VA, USA

Ashley R Curtis MD
Department of Dermatology
Wake Forest University School of Medicine
Medical Center Boulevard
Winston-Salem, NC, USA

Thomas N Darling MD PhD
Assistant Professor
Department of Dermatology
Uniformed Services University
Bethesda, MD, USA

Mark DP Davis MD
Professor of Dermatology
Department of Dermatology
Mayo Clinic
Rochester, MN, USA

David de Berker MD
ASWCS Skin Cancer
Lead Consultant Dermatologist and Senior Clinical Lecturer
Bristol Dermatology Centre
Bristol Royal Infirmary
Bristol, UK

Vincent A DeLeo MD
Chairman
Department of Dermatology
St Luke's Roosevelt Hospital Center and Beth Israel Medical Center
New York, NY, USA

Aieska de Souza MD
Dermatopharmacology Fellow
Langone Medical Center
New York University
New York, NY, USA

Michael Detmar MD
Professor of Pharmacogenomics
Institute of Pharmaceutical Sciences
Swiss Federal Institute of Technology, ETH Zurich
Zurich, Switzerland

Valentina Dini MD
Wound Healing Research Unit
Department of Dermatology
University of Pisa
Pisa, Italy

Jeffrey S Dover MD FRCPC
Associate Professor of Clinical Dermatology
Yale University School of Medicine
Adjunct Professor of Surgery (Dermatology)
Dartmouth Medical School
SkinCare Physicians of Chestnut Hill
Chestnut Hill, MA, USA

Zoe Diana Draelos MD
Consulting Professor
Department of Dermatology
Duke University School of Medicine
Durham NC, USA

Raymond G Dufresne Jr MD
Professor of Dermatology
University Dermatology, Inc.
Rhode Island Hospital
Brown University School of Medicine
Providence, RI, USA

Boni E Elewski MD
Professor of Dermatology
Department of Dermatology
University of Alabama at Birmingham
Birmingham, AL, USA

Peter M Elias MD
Professor of Dermatology,
UCSF and Staff Physician
Dermatology Service
VA Medical Center
San Francisco, CA, USA

Dirk M Elston MD FAAD
Director
Department of Dermatology
Geisinger Medical Center
Danville, PA, USA

Sabine A Eming MD
Professor of Dermatology
Department of Dermatology
University of Cologne
Cologne, Germany

The late Odile Enjolras MD
Consultant in Dermatology, Pediatric Dermatology, and Vascular Anomalies
Department of Dermatology
Hôpital Tarnier
Department of Plastic Surgery
Hôpital d'enfants Armand Trousseau
Paris, France

Agustín España MD
Professor of Dermatology
Department of Dermatology
School of Medicine
University Clinic of Navarra
Navarra, Spain

Janet A Fairley MD
Professor and Head of Dermatology
Department of Dermatology
University of Iowa Hospitals and Clinics
Iowa City, IA, USA

Kenneth R Feingold MD
Professor of Medicine and Dermatology,
Department of Medicine,
University of California in San Francisco,
Chief of the Endocrine-Metabolism Clinic
Department of Veterans Affairs Medical Center
San Francisco, CA, USA

Jo-David Fine MD MPH FRCP
Professor of Medicine (Dermatology) and Pediatrics and Head,
National Epidermolysis Bullosa Registry
Division of Dermatology
Vanderbilt University School of Medicine
VMG Patterson Dermatology
Nashville, TN, USA

Alan B Fleischer Jr MD
Professor and Former Chair
Department of Dermatology
Wake Forest University School of Medicine
Winston-Salem, NC, USA

Franklin P Flowers MD
Professor of Dermatology
Division of Dermatology
University of Florida
School of Medicine
Gainesville, FL, USA

Timothy C Flynn MD
Clinical Professor
Department of Dermatology
University of North Carolina at Chapel Hill
Medical Director
Cary Skin Center
Cary, NC, USA

Lindy P Fox MD
Assistant Professor of Clinical Dermatology
Director
Hospital Consultation Service
University of California at San Francisco
San Francisco, CA, USA

Matthew Fox MD
Procedural Dermatology Fellow
Department of Dermatology
University of Michigan
Ann Arbor, MI, USA

Jorge Frank MD
Professor of Dermatology
Department of Dermatology
Maastricht University Medical Center
Maastricht, The Netherlands

Thomas J Franz MD
Executive Medical Director
Clinical Dermatology
PRACS Institute, Ltd.
Portland, OR, USA

Lars E French MD
Chairman
Department of Dermatology
Zurich University Hospital
Zürich, Switzerland

Ilona J Frieden MD
Professor of Dermatology and Pediatrics,
Director of Pediatric Dermatology
University of California at San Francisco
San Francisco, CA, USA

Peter O Fritsch MD
Professor and Chairman
Department of Dermatology and Venereology
Innsbruck Medical University
Innsbruck, Austria

Claus Garbe MD
Professor of Dermatology,
Head, Dermato-oncology Section
Department of Dermatology
Eberhard Karls University Tübingen
Tübingen, Germany

Maria C Garzon MD
Professor of Clinical Dermatology and Clinical Pediatrics,
Columbia University
Director
Pediatric Dermatology
Morgan Stanley Children's Hospital of New York
Department of Dermatology
New York Presbyterian Hospital
New York, NY, USA

Josep L Genebriera de Lamo MD
Dermatologist
North Florida Dermatology
Jacksonville, FL, USA

Amy Geng MD
President
Todd Park and Amy Geng Foundation
Canton, MA, USA

Kamran Ghoreschi MD
Senior Resident
Department of Dermatology
Eberhard Karls University Tübingen
Tübingen, Germany

Amy E Gilliam MD
Assistant Clinical Professor
University of California San Francisco
Staff Physician
Department of Dermatology
Palo Alto Medical Foundation
Palo Alto, CA, USA

Richard Glogau MD
Clinical Professor of Dermatology
University of California at San Francisco
San Francisco, CA, USA

Deborah S Goddard MD
Staff Physician
Department of Dermatology
Kaiser Permanente Medical Group
San Jose, CA, USA

Glenn Goldman MD
Associate Professor of Medicine and Dermatology
Director of Dermatologic Surgery
Division of Dermatology
The University of Vermont
Fletcher Allen Health Care
Burlington, VT, USA

Mitchel P Goldman MD
Volunteer Clinical Professor of Dermatology
University of California,
San Diego, CA, USA

Harald Gollnick MD
Professor and Chairman
Department of Dermatology and Venereology
Otto-von-Guericke University
Magdeburg, Germany

Warren T Goodman MD
Staff Dermatologist / Dermatopathologist
Department of Pathology
Health Partners Medical Group
Regions Hospital
St Paul, MN, USA

Clive EH Grattan MD
Consultant Dermatologist
Dermatology Centre
Norfolk and Norwich University Hospital
Norfolk, UK

Richard W Groves MD MB BS FRCP
Head of Clinical Immunodermatology
St John's Institute of Dermatology
Guy's Hospital
London, UK

Juliet Gunkel MD
Assistant Professor and Mohs Surgeon
Department of Dermatology
University of Wisconsin
Madison, WI, USA

Daniela Guzman-Sanchez MD
Professor of Dermatology
Universidad Lamar School of Medicine
Guadalajara, Mexico

Ariela Hafner MD
Head, Chronic Wound Clinic
Department of Dermatology
The Tel Aviv Sourasky Medical Center
Tel Aviv, Israel

Anita N Haggstrom MD
Assistant Professor
Departments of Dermatology and Pediatrics
Indiana University
Bloomington, IN, USA

Analisa V Halpern MD
Assistant Professor
Department of Medicine
Division of Dermatology
Cooper University Hospital of the Rowan Medical School
Camden, NJ, USA

John LM Hawk BS cMD FRCP
Emeritus Professor of Dermatological Photobiology
St John's Institute of Dermatology
St Thomas' Hospital
London, UK

Roderick Hay DM FRCP
Professor of Cutaneous Infection
Department of Dermatology
King's College Hospital
King's College London
London, UK

Yolanda Helfrich MD
Assistant Professor
Department of Dermatology
University of Michigan Medical School
Ann Arbor, MI, USA

Warren R Heymann, MD
Professor of Medicine and Pediatrics
Head, Division of Dermatology
Cooper Medical School of Rowan University
Camden, NJ;
Clinical Professor of Dermatology
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, PA, USA

Claire A Higgins PhD
Associate Research Scientist
Departments of Dermatology / Genetics and Development
Columbia University
College of Physicians & Surgeons
New York, NY, USA

Whitney A High MD JD MEng
Associate Professor
Department of Dermatology and Division of Dermatopathology
University of Colorado
School of Medicine
Denver, CO, USA

Satoshi Hirakawa MD PhD
Associate Professor of Dermatology
Department of Dermatology
Hamamatsu University School of Medicine
Hamamatsu-shi, Shizuoka, Japan

Chad M Hivnor MD
Associate Program Director
Chief
Pediatric Dermatology
Dermatology Clinic
San Antonio Uniformed Services Health Education Consortium
Lackland Air Force Base
San Antonio, TX, USA

Kafele T Hodari MD MBA
Dermatologist
North Valley Dermatology
Chico, California, USA

Daniel Hohl MD
Professor of Medicine
Service de Dermatologie du CHUV
Hôpital de Beaumont,
Lausanne, Switzerland

Walter M Holleran MD
Department of Dermatology and Medicine
University of California San Francisco
Dermatology and Medical (Metabolism) Services
Veteran Affairs Medical Center
San Francisco, CA, USA

Herbert Hönigsmann MD
Professor of Dermatology
Emeritus Chairman
Department of Dermatology
Medical University of Vienna
Vienna, Austria

George J Hruza MD
Clinical Professor of Dermatology and Otolaryngology-Head and Neck Surgery
St. Louis University
St. Louis, MO;
Medical Director
Laser and Dermatologic Surgery Center
Chesterfield, MO, USA

Lauren C Hughey MD
Associate Professor
Department of Dermatology
University of Alabama at Birmingham
Birmingham, AL, USA

Christopher M Hull MD
Associate Professor
Department of Dermatology
University of Utah
Salt Lake City, UT, USA

J Mark Jackson MD
Clinical Professor of Medicine and Dermatology
University of Louisville
Division of Dermatology
Dermatology Specialists, PSC
Louisville, KY, USA

Scott M Jackson MD
Clinical Assistant Professor
Department of Dermatology
Louisiana State University Health Sciences Center
New Orleans, LA, USA

Heidi T Jacobe MD
Assistant Professor
Department of Dermatology
The University of Texas
Southwestern Medical Center
Dallas, TX, USA

Colin Jahoda MD PhD
Professor
School of Biological and Biomedical Sciences
Durham University
Durham, UK

Derek H Jones MD
Founder and Director
Skin Care and Laser Physicians of Beverly Hills
Clinical Associate Professor
Dermatology
University of California
Los Angeles, CA, USA

Joseph L Jorizzo MD
Professor and Former (Founding) Chair
Department of Dermatology
Wake Forest University School of Medicine
Winston-Salem, NC;
Adjunct Professor
Department of Dermatology
Weill Cornell Medical College
New York, NY, USA

Steven Kaddu MD
Professor of Dermatology
Department of Dermatology
Medical University of Graz
Graz, Austria

Hideko Kamino MD
Associate Professor
Dermatopathology Section
New York University School of Medicine
New York, NY, USA

Sewon Kang MD
Noxell Professor and Chairman
Department of Dermatology
Johns Hopkins School of Medicine
Cancer Research
Baltimore, MD, USA

Yoko Kano MD
Clinical Professor
Department of Dermatology
Kyorin University School of Medicine
Tokyo, Japan

Sarah Kasprowicz MD
Clinical Instructor of Dermatology
University of Chicago Pritzker School of Medicine
Northshore University Health System
Skokie, IL, USA

Sharon A Keene MD
President and Medical Director
Physician's Hair Institute
Tucson, AZ, USA

A Paul Kelly MD
Fulbright Regional Research Scholar 2010-2011
Sultanate of Oman and the United Arab Emirates and
Professor of Medicine, Division of Dermatology
Charles Drew University of Medicine and Science
Chief Emeritus, Division of Dermatology
Former King/Drew Medical Center
Clinical Professor of Medicine Emeritus
Division of Dermatology
The David Geffen School of Medicine at UCLA
Los Angeles, CA, USA

Robert Kelly MBBS FACD
Head of Clinical Dermatology
Department of Dermatology
St Vincent's Hospital
Melbourne, VIC, Australia

Jay Kincannon MD
Professor
Department of Dermatology
University of Arkansas for Medical Sciences
Child Study Center
Little Rock, AR, USA

Reinhard Kirnbauer MD
Associate Professor
Division of Immunology, Allergy and Infectious Diseases
Department of Dermatology
Medical University Vienna
General Hospital
Vienna, Austria

Maija Kiuru MD PhD
Dermatology Resident
Department of Dermatology
Columbia University
New York, NY, USA

Sandra R Knowles BSc Phm
Drug Safety Pharmacist
Sunnybrook Health Sciences Centre
Toronto, ON, Canada

Peter J Koch PhD
Associate Professor of Dermatology
Department of Dermatology
University of Colorado at Denver and Health Sciences Center
Aurora, CO, USA

The late Sabine Kohler MD
Professor of Pathology and Dermatology
Director of Dermatopathology
Department of Pathology
Stanford University School of Medicine
Stanford, CA, USA

John YM Koo MD
Director, Psoriasis Treatment Center
Professor and Vice Chairman
Department of Dermatology
University of California at San Francisco Medical Center
San Francisco, CA, USA

Veselina Korcheva MD
Dermatopathology Fellow
Department of Dermatology
Oregon Health Sciences University
Portland, OR, USA

Tamara Koss MD
Instructor in Clinical Dermatology
Columbia University
New York, NY, USA

Maranke I Koster PhD
Assistant Professor
Department of Dermatology
University of Colorado, Anschutz Medical Campus
Aurora, CO, USA

Alfons L Krol MD FRCPC
Professor of Dermatology and Pediatrics
Oregon Health and Sciences University
Portland, OR, USA

Emanuel G Kuflik MD
Clinical Professor of Dermatology
University of Medicine and Dentistry of New Jersey
Newark, NJ, USA

Julianne H Kuflik MD
Clinical Assistant Professor of Dermatology
University of Medicine and Dentistry of New Jersey
Newark, NJ, USA

Chai Sue Lee MD MS
Department of Dermatology
Kaiser Permanente
Milpitas, CA, USA

Lela A Lee MD
Professor of Dermatology and Medicine
University of Colorado School of Medicine
Chief of Dermatology
Denver Health Medical Center
Denver, CO, USA

Kristin M Leiferman MD
Professor of Dermatology
University of Utah Health Care School of Medicine
Salt Lake City, UT, USA

Petra Lenz MD FCAP
Physician
Clinical Monitoring Research Program
Support to Occupational and Environmental Epidemiology Branch
SAIC-Frederick-Inc.
National Cancer Institute
Rockville, MD USA

Jack L Lesher Jr MD
Professor
Section of Dermatology
Department of Medicine
Medical College of Georgia
Georgia Health Sciences University
Augusta, GA, USA

Stuart R Lessin MD
Director of Dermatology
Fox Chase Cancer Center
Philadelphia, PA, USA

Henry W Lim MD
Chairman and C.S. Livingood Chair
Department of Dermatology
Henry Ford Hospital
Henry Ford Medical Center
New Center One
Detroit, MI, USA

Cynthia A Loomis MD PhD
Assistant Professor of Dermatology and Cell Biology
New York University School of Medicine
Department of Pathology
New York, NY, USA

Harvey Lui MD FRCPC
Professor and Chairman
Department of Dermatology and Skin Science
University of British Columbia
Vancouver, BC, Canada

Joakim Lundeberg PhD
Professor of Molecular Biology
Royal Institute of Technology
Department of Gene Technology
AlbaNova University Center
Stockholm, Sweden

Su Luo MD
Dermatology Resident
Harvard Medical School
Boston, MA, USA

Catherine Maari MD
Assistant Professor in Dermatology
St-Justine Hospital and CHUM
University of Montreal
Montreal, QC, Canada

Vandana Madkan MD
Clinical Research Fellow
Center for Clinical Studies
Houston, TX, USA

Anthony J Mancini MD
Professor of Pediatrics and Dermatology
Northwestern University Feinberg School of Medicine
Head, Division of Pediatric Dermatology
Children's Memorial Hospital
Chicago, IL, USA

James G Marks Jr MD
Professor and Chair
Penn State Milton S. Hershey Medical Center
Department of Dermatology
Hershey, PA, USA

Amalia Martinez-Mir PhD
Research Scientist
Department of Medical Biochemistry and Molecular Biology
Faculty of Medicine
University of Seville
Seville, Spain

José M Mascaró Jr MD
Associate Professor
Department of Dermatology
Hospital Clinic and Barcelona University Medical School
Barcelona, Spain

W Trent Massengale MD
Assistant Clinical Professor
Department of Dermatology
Louisiana State University
Baton Rouge, LA, USA

Seth L Matarasso MD
Clinical Professor of Dermatology
University College School of Medicine
San Francisco, CA, USA

Timothy H McCalmont MD
Professor of Clinical Pathology and Dermatology
Co-Director, Dermatopathology Service
Departments of Pathology and Dermatology
University of California at San Francisco
San Francisco, CA, USA

R Carol McConnell MD
Private Practice
Greensboro, NC, USA

Thomas W McGovern MD
Private Practice
Fort Wayne Dermatology Consultants
Fort Wayne, IN, USA

Amy McMichael MD
Professor and Acting Chair
Department of Dermatology
Wake Forest University School of Medicine
Winston-Salem, NC, USA

Stephanie L Mehlis MD
Clinical Instructor
Division of Dermatology University of Chicago
Pritzker School of Medicine
Skokie, IL, USA

Jemima E Mellerio BSc MD FRCP
Consultant Dermatologist
St John's Institute of Dermatology
St Thomas' Hospital
London, UK

Gregg M Menaker MD
Clinical Assistant Professor of Dermatology,
University of Chicago Pritzker School of Medicine
Director, Dermatologic Surgery Unit
Northshore University Health System
Skokie, IL, USA

Natalia Mendoza MD MS
Senior Clinical Researcher
Center for Clinical Studies
Houston, TX, USA;
Assistant Professor
Research Department
El Bosque University
Bogota, Colombia

Gopinathan K Menon PhD
Fellow
California Academy of Sciences
San Francisco, CA, USA

Jami L Miller MD
Assistant Professor
Department of Internal Medicine
Division of Dermatology
Vanderbilt University Medical Center
Nashville, TN, USA

Christian R Millett MD
Chief Resident
Department of Dermatology
Cooper University Hospital
Camden, NJ, US

Mariya Miteva MD
Associate Scientist
Department of Dermatology and Cutaneous Surgery
University of Miami Miller School of Medicine
Miami, FL, USA

Vered Molho-Pessach MD
Instructor
Department of Dermatology
Hadassah-Hebrew University Medical Center
Jerusalem, Israel

Gary D Monheit MD
Total Skin and Beauty Dermatology Center, P.C.
Private Practice
Associate Clinical Professor
Department of Dermatology
Department of Ophthalmology
University of Alabama at Birmingham
Birmingham, AL, USA

Dean Scott Morrell MD
Associate Professor
Department of Dermatology
The University of North Carolina at Chapel Hill
Chapel Hill, NC, USA

L Katie Morrison MD
Resident in Dermatology
Department of Dermatology
University of Texas Health Sciences Center
MD Anderson Cancer Center
Houston, TX, USA

Samuel L Moschella MD FACP
Clinical Professor
Harvard Medical School
Senior Consultant
Lahey Clinic Foundation
Burlington, MA, USA

Celia Moss MB BS DM FRCP MRCPCH
Consultant Dermatologist
Department of Dermatology
Birmingham Children's Hospital
Birmingham, UK

Christen M Mowad MD
Associate Professor
Department of Dermatology
Geisinger Medical Center
Danville, PA, USA

Sarah Nakib MD
Resident
Departments of Dermatology and Internal Medicine
University of Minnesota
Minneapolis, MN, USA

Rhoda S Narins MD
Director, Dermatology Surgery and Laser Center
Clinical Professor
Department of Dermatology
New York University School of Medicine
New York University Medical Center
New York, NY, USA

Steven A Nelson MD
Instructor of Dermatology
Mayo School of Graduate Medical Education
Department of Dermatology
Mayo Clinic
Scottsdale, AZ, USA

Lee T Nesbitt Jr MD
Henry Jolly Professor and Head of Dermatology
Department of Dermatology
Louisiana State University Health Sciences Center
New Orleans, LA, USA

Frank O Nestlé MD
Mary Dunhill Chair of Cutaneous Medicine and Immunotherapy
St. John's Institute of Dermatology
King's College London and Guy's and St. Thomas' Hospitals
London, UK

Paula E North MD PhD
Professor and Chief of Pediatric Pathology
Department of Pathology
Medical College of Wisconsin
Milwaukee, WI, USA

Julia R Nunley MD FAAD FACP
Professor and Program Director
Department of Dermatology
VCU School of Medicine
Medical College of Virginia Campus
Richmond, VA, USA

Suzanne Olbricht MD
Associate Professor in Dermatology
Harvard Medical School
Chair, Department of Dermatology
Lahey Clinic
Burlington, MA, USA

Seth J Orlow MD PhD
Chairman and Professor of Pediatric Dermatology
Cell Biology and Pediatrics
The Ronald O Perelman Department of Dermatology
New York University School of Medicine
New York, NY, USA

Jean-Paul Ortonne MD
Professor
Department of Dermatology
Nice University
Nice, France

Edel A O'Toole MB PhD FRCP(UK) FRCPI
Professor of Molecular Dermatology
Centre for Cutaneous Research
Blizard Institute
Barts and the London School of Medicine and Dentistry
London, UK

Amy S Paller MD
Walter J Hamlin Professor and Chair of Dermatology
Professor of Pediatrics
School of Medicine
Northwestern University Feinberg
Attending Physician
Children's Memorial Hospital
Chicago, IL, USA

Alexandru DP Papoiu MD PhD
Instructor
Department of Dermatology
Wake Forest University School of Medicine
Medical Center Boulevard
Winston-Salem, NC, USA

Thierry Passeron MD PhD
Department of Dermatology
INSERM
University Hospital of Nice
Nice, France

James W Patterson MD
Professor of Pathology and Dermatology
Director of Dermatopathology
University of Virginia Health System
Charlottesville, VA, USA

David B Pharis MD PC
Private Practice
Atlanta, GA, USA

Warren W Piette MD
Chairman
Department of Dermatology
John H Stroger Hospital of Cook County
Chicago, IL, USA

Bianca Maria Piraccini MD PhD
Researcher in Dermatology
Department of Dermatology
University of Bologna
Bologna, Italy

Mark R Pittelkow MD
Consultant and Professor
Departments of Dermatology and Biochemistry and Molecular Biology
Mayo Clinic
Rochester, MN, USA

Gerd Plewig med. Dr. h.c.mult. FRCP
Professor of Dermatology
Department of Dermatology
Ludwig-Maximilian-University
Frauenlobstrasse
München, Germany

Pamela A Poblete-Gutiérrez MD PhD
Senior Consultant in Dermatology
Department of Dermatology
Maastricht University Medical Center
Maastricht, The Netherlands

Sheldon V Pollack MD FRCPC
Associate Professor of Medicine (Dermatology)
University of Toronto
Medical Director
Toronto Cosmetic Skin Surgery Centre, Inc.
Toronto, ON, Canada

Fredrik Pontén MD
Associate Professor of Pathology
Department of Genetics and Pathology
Uppsala University Hospital
Uppsala, Sweden

Frank C Powell FRCPI
Consultant Dermatologist
Regional Centre of Dermatology
Mater Misericordiae Hospital
Dublin, Ireland

Julie Powell MD FRCPC ABD
Director
Pediatric Dermatology
Department of Pediatrics
CHU Sainte-Justine,
Clinical Associate Professor of Dermatology/Pediatrics
University of Montreal
Montreal, QC, Canada

Mark R Prausnitz PhD
Regents' Professor of Chemical and Biomedical Engineering
Georgia Institute of Technology
Atlanta, GA, USA

Christa Prins MD
Department of Dermatology
Geneva University Hospital
Geneva, Switzerland

John Pui MD
Pinkus Dermatopathology Laboratory
Aurora Diagnostics
Garden City, MI, USA

Jennifer Quist MD
Department of Dermatology and Venereology
Otto-von-Guericke University
Magdeburg, Germany

Sven Quist MD MSc MPharm
Department of Dermatology and Venereology
Otto-von-Guericke University
Magdeburg, Germany

Abrar A Qureshi MD MPH
Vice-Chair, Department of Dermatology
Assistant Professor, Harvard Medical School
Co-Director, Center for Skin and Related Musculoskeletal Diseases
Associate Epidemiologist, Channing Laboratory
Director
Clinical Research Program
Brigham and Women's Hospital
Boston, MA, USA

Harold S Rabinovitz MD
Voluntary Clinical Professor of Dermatology
Department of Dermatology
Miller School of Medicine
University of Miami
Miami, FL, USA

Síona Ní Raghallaigh MB BAO BCh MRPI
Specialist Registrar in Dermatology
Department of Dermatology
Mater Misericordiae University Hospital
Dublin, Ireland

Ben G Raimer MD
Professor of Pediatrics
University of Texas Medical Branch
Galveston, TX, USA

Sharon S Raimer MD
Professor of Dermatology and Pediatrics
Chairman
Department of Dermatology
University of Texas Medical Branch
Galveston, TX, USA

Lauren Raimer-Goodman MD
Dermatology Resident
Department of Pediatrics
Baylor College of Medicine
Houston, TX, USA

Marcia Ramos-e-Silva MD PhD
Associate Professor and Chair
Sector of Dermatology – School of Medicine and University Hospital
Federal University of Rio de Janeiro
Rio de Janeiro, Brazil

Ronald P Rapini MD
Professor and Chair
Department of Dermatology
University of Texas Medical School and MD Anderson Cancer Center
Houston, TX, USA

Désirée Ratner MD
Professor of Clinical Dermatology
Director of Dermatologic Surgery
Department of Dermatology
Columbia University Medical Center
College of Physicians and Surgeons of Columbia University
New York, NY, USA

Maria Cristina Ribeiro de Castro MD MS
Dermatologist
Sector of Dermatology and Post Graduation Course
Federal University of Rio de Janeiro
Rio de Janeiro, Brazil

Annette C Reboli MD
Professor of Medicine
Vice Dean
Cooper Medical School of Rowan University
Camden, NJ, USA

Alfredo Rebora MD
Professor of Dermatology
Clinica Dermatologica
University of Genova
Genova, Italy

Vijaya B Reddy MD MBA
Professor
Department of Pathology
Rush Medical College
Chicago, IL, USA

Norbert Reider MD
Professor of Dermatology
Department of Dermatology
University of Innsbruck
Innsbruck, Austria

Amy Reisenauer MD
Hawaii Permanente Medical Group
Wailuku, Hawaii, USA

George T Reizner MD
Professor of Dermatology
Department of Dermatology
University of Wisconsin School of Medicine and Health Sciences
Madison, WI, USA

Luis Requena MD
Chairman and Professor of Dermatology
Department of Dermatology
Fundación Jiménez Díaz
Universidad Autónoma
Madrid, Spain

Celia Requena MD
Department of Dermatology
Instituto Valenciano de Oncología
Valencia, Spain

Jean Revuz MD
Professor of Dermatology
Chairman of the Department of Dermatology
Service de Dermatologie
Hôpital Henri Mondor
University of Paris
Paris, France

Phoebe Rich MD
Adjunct Professor of Dermatology
Oregon Health and Science University
Portland, OR, USA

Gabriele Richard MD FACMG
Chief Medical Officer
GeneDx
Gaithersburg, MD;
Adjunct Associate Professor of Dermatology
Jefferson Medical College
Philadelphia, PA, USA

Shawn W Richards MD
Consultant Dermatologist
Skin and Cancer Foundation
Westmead, NSW, Australia

Armin Rieger MD
University Clinic for Dermatology
Medical University Vienna
Vienna, Austria

Darrell S Rigel MD
Clinical Professor of Dermatology
New York University Medical Center
New York, NY, USA

Franziska Ringpfeil MD
Director
Ringpfeil Advanced Dermatology
Assistant Professor of Dermatology
Jefferson Medical College
Philadelphia, PA, USA

Martin Röcken MD
Professor and Chairman
Department of Dermatology
Eberhard Karls University Tübingen
Tübingen, Germany

Rana Rofagha MD
Assistant Clinical Professor
Department of Dermatology
University of California
Kaiser Permanente
Irvine, CA, USA

Nicole E Rogers MD
Private Practice
Old Metairie Dermatology
Metairie, LA, USA

Thomas E Rohrer MD
SkinCare Physicians
Clinical Associate Professor of Dermatology
Boston University School of Medicine
Boston, MA, USA

Marco Romanelli MD PhD
Assistant Professor
Department of Dermatology
University of Pisa
Pisa, Italy

Paolo Romanelli MD
Associate Professor
Department of Dermatology and Cutaneous Surgery
University of Miami Miller School of Medicine
Miami, FL, USA

Franco Rongioletti MD
Professor of Dermatology
Clinica Dermatologica
University of Genoa
Genoa, Italy

Dennis R Roop PhD
Professor
Department of Dermatology
University of Colorado
Anschutz Medical Campus
Aurora, CO, USA

Adam M Rotunda MD
Assistant Clinical Professor of Dermatology
David Geffen School of Medicine
University of California Los Angeles
Los Angeles, CA, USA

Thomas M Rünger MD
Professor and Vice-Chair of Dermatology
Department of Dermatology
Boston University School of Medicine
Boston, MA, USA

Neil S Sadick MD FACP FAACS
Clinical Professor of Dermatology
Cornell University Medical College
New York, NY, USA

Nazanin Saedi MD
Laser and Cosmetics Fellow
SkinCare Physicians
Chestnut Hill, MA, USA

Fernanda H Sakamoto MD PhD
Instructor in Dermatology
Wellman Center for Photomedicine
Massachusetts General Hospital,
Department of Dermatology
Harvard Medical School
Boston, MA, USA

Miguel Sanchez MD
Associate Professor of Clinical Dermatology
Department of Dermatology
New York University Medical Center
New York, NY, USA

Jean-Hilaire Saurat MD
Professor and Chairman
Dermatoxicology Swiss Centre for Human Applied Toxicology
University Medical Center
Geneva, Switzerland

Stephanie Saxton-Daniels MD
Staff Dermatologist
San Antonio Uniformed Services Health Education Consortium
San Antonio, TX, USA

Stephanie McLeish Schaefer MD
Staff Dermatologist
San Antonio Uniformed Services Health Education Consortium
San Antonio, TX, USA

Julie V Schaffer MD
Associate Professor of Dermatology and Pediatrics
Director of Pediatric Dermatology
Department of Dermatology
New York University School of Medicine
New York, NY, USA

Martin Schaller MD PhD
Professor of Dermatology
Department of Dermatology
Eberhard Karls University Tübingen
Tübingen, Germany

Matthias Schmuth MD
Professor and Chair
Department of Dermatology and Venereology
Innsbruck Medical University
Innsbruck, Austria

Thomas Schwarz MD
Professor and Chairman
Department of Dermatology and Allergology
University Hospital Schleswig-Holstein
Kiel, Germany

Kathryn Schwarzenberger MD
Associate Professor of Medicine (Dermatology)
Residency Program Director and Associate Chief
Department of Medicine
Division of Dermatology
University of Vermont
College of Medicine
Burlington, VT, USA

Priya Sen BSc(Hons) MBBS MRCP(UK) DipGU Medicine(UK) FAMS
Consultant Dermatologist
National Skin Centre
Deputy Head
Department of STI Control
Singapore

Laila El Shabrawi-Caelen MD
Department of Dermatology and Venereology
Medical University of Graz
Graz, Austria

Ayelet Shani-Adir MD
Pediatric Dermatologist
Department of Dermatology
Haemek Medical Center
Afula, Israel

Lori E Shapiro MD FRCPC
Staff Physician
Divisions of Dermatology and Clinical Pharmacology
Sunnybrook Health Sciences Centre
Assistant Professor
University of Toronto
Toronto, ON, Canada

Neil H Shear MD FRCPC
Professor and Chief
Division of Dermatology
University of Toronto Medical School
Toronto, ON, Canada

Kanade Shinkai MD PhD
Assistant Professor of Clinical Dermatology
University of California at San Francisco
San Francisco, CA, USA

Tetsuo Shiohara MD PhD
Professor and Chairman
Department of Dermatology
Kyorin University School of Medicine
Tokyo, Japan

Jeff K Shornick MD MHA
Private Practice
Salem, CT, USA

Dawn Siegel MD
Assistant Professor
Department of Dermatology and Pediatrics
Medical College of Wisconsin
Children's Hospital of Wisconsin
Milwaukee, WI, USA

Rodney D Sinclair MMBS MD FACD
Professor of Dermatology
University of Melbourne
Melbourne, VIC, Australia

Michael L Smith MD
Division of Dermatology
Vanderbilt Medical Center
Nashville, TN, USA

Bruce R Smoller MD
Professor and Chair
Department of Pathology
Aubrey J. Hough, Jr. Endowed Chair in Pathology
Professor of Dermatology
University of Arkansas for Medical Sciences
Little Rock, AR, USA

Stephen N Snow MD
Professor
Department of Dermatology
University of Wisconsin Madison
Madison, WI, USA

Jenny O Sobera MD
Village Dermatology
Birmingham, AL, USA

Richard D Sontheimer MD
Professor
Department of Dermatology
University of Utah School of Medicine
Salt Lake City, UT, USA

H Peter Soyer MD FACD
Professor of Dermatology
Dermatology Research Centre
The University of Queensland
School of Medicine
Princess Alexandra Hospital
Brisbane, QLD, Australia

Leonard C Sperling MD
Professor of Dermatology and Pathology
Chair
Department of Dermatology
Uniformed Services University
Bethesda, MD, USA

Eli Sprecher MD PhD
Chair and Professor
Department of Dermatology,
Tel Aviv Medical Center and Sackler Faculty of Medicine
Tel Aviv University
Tel Aviv, Israel

Karan Sra MD FAAD
Dermatological Association of Texas
Private Practice
Webster, TX, USA

Angelika Stary MD PhD
University Professor
Medical Director
Outpatients' Centre for Infectious Venerodermatological Diseases
Vienna, Austria

Georg Stary
Outpatients' Centre for Infectious Venerodermatological Diseases
Vienna, Austria

Thomas Stasko MD
Professor of Medicine
Division of Dermatology
Vanderbilt University
Nashville, TN, USA

Matthias Steinhoff MD
Department of Dermatology and Allergy
Skin Cancer Center Charite
Charité University Medicine
Berlin, Germany

Wolfram Sterry MD
Professor and Chairman
Department of Dermatology and Allergy
Charité University Medicine
Berlin, Germany

Cloyce L Stetson MD
Associate Professor of Dermatology
Chairman
Department of Dermatology
Texas Tech University HSC
Lubbock, TX, USA

Mary S Stone MD
Professor of Dermatology and Pathology
Department of Dermatology
University of Iowa Carver College of Medicine
Iowa City, IA, USA

Dowling B Stough MD
Clinical Assistant Professor of Dermatology
University of Arkansas Medical Sciences
Little Rock, AR, USA

Virginia P Sybert MD
Staff Dermatologist
Group Health Cooperative and Clinical Professor
Division of Medical Genetics
University of Washington
School of Medicine
Seattle, WA, USA

Rolf-Markus Szeimies MD PhD
Chairman
Department of Dermatology and Allergology
Klinikum Vest Academic Teaching Hospital
Recklinghausen, North Rhine-Westphalia, Germany

Suat Hoon Tan MD Mmed DipRCPath(DMT) FAMS
Clinical Associate Professor
Yong Loo Lin School of Medicine
National University of Singapore
Senior Consultant Dermatologist
National Skin Centre
Singapore

Mark Tang MD
Senior Consultant Dermatologist
Head of the Eczema Clinic
Director of Research
National Skin Centre
Singapore

Michael D Tharp MD
The Clark W Finnerud, MD
Professor and Chair
Department of Dermatology
Rush University Medical Center
Chicago, IL, USA

Diane M Thiboutot MD
Professor of Dermatology
Department of Dermatology
The Pennsylvania State University
College of Medicine
MS Hershey Medical Centre
Hershey, PA,USA

Anne-Marie Thielen MD
Consultant Dermatologist
Dermatology Department
University of Geneva
Geneva, Switzerland

Carlo Francesco Tomasini MD
Department of Dermatology
University of Turin
Turin, Italy

Antonella Tosti MD
Professor of Clinical Dermatology
University of Miami Miller School of Medicine
Miami, FL, USA

Jui-Chen Tsai PhD
Department of Clinical Pharmacy
College of Medicine
National Cheng Kung University
Tainan, Taiwan

Hensin Tsao MD PhD
Associate Professor of Dermatology
Harvard Medical School
Department of Dermatology
Massachusetts General Hospital
Boston, MA, USA

Stephen K Tyring MD PhD
Clinical Professor of Dermatology
University of Texas Health Science Center
Houston, TX, USA

Jouni Uitto MD PhD
Professor and Chair
Department of Dermatology and Cutaneous Biology
Jefferson Medical College
Thomas Jefferson University
Philadelphia, PA, USA

Laurence Valeyrie-Allanore MD
Assistant
Department of Dermatology
Hôpital Henri Mondor
University of Paris
Creteil, France

Peter CM van de Kerkhof MD
Head
Department of Dermatology
Radboud University Medical Centre
Nijmegen, The Netherlands

Travis W Vandergriff MD
Assistant Professor
Department of Dermatology
University of Texas Southwestern Medical Center
Dallas, TX, USA

Michael Veness MD MMed FRANZCR
Clinical Associate Professor
Senior Radiation Oncologist
Sydney University
Department of Radiation Oncology
Westmead Hospital
Westmead, NSW, Australia

Ruth Ann Vleugels MD
Attending Physician
Department of Dermatology
Brigham and Women's Hospital
Boston, MA, USA

The late Jonathan Vogel MD
Senior Investigator
Dermatology Branch
National Cancer Institute
Bethesda, MD, USA

David H Walker MD
Professor and Chairman
Department of Pathology
University of Texas Medical Branch
Director
Center for Biodefense and Emerging Infectious Diseases
Galveston, TX, USA

Karen E Warschaw MD
Associative Professor of Dermatology
Department of Dermatology
Mayo Clinic Arizona
Scottsdale, AZ, USA

Elke Weisshaar MD
Consultant Dermatologist
Department of Social Medicine
Occupational and Environmental Dermatology
University Hospital of Heidelberg
Heidelberg, Germany

Robert A Weiss MD
Associate Professor
Johns Hopkins University School of Medicine
Director
MD Laser Skin and Vein Institute
Hunt Valley, MD, USA

Victoria P Werth MD
Professor of Dermatology and Medicine
Department of Dermatology
University of Pennsylvania
Philadelphia, PA, USA

Naissan O Wesley MD
Skincare and Laser Physicians of Beverly Hills
Los Angeles, CA, USA

Clifton R White Jr MD
Professor of Dermatology and Pathology
Department of Dermatology
Oregon Health and Science University
Portland, OR, USA

Kevin P White MD
Department of Dermatology
Oregon Health and Science University
Portland, OR, USA

S Mark Wilkinson MD FRCP
Consultant Dermatologist
Department of Dermatology
The General Infirmary
Leeds, UK

Rein Willemze MD
Professor and Chairman
Department of Dermatology
Leiden University Medical Centre
Leiden, The Netherlands

Beau Willison MD
Department of Dermatology
University of Texas Health Science Center
Houston, TX, USA

Harry L Winfield MD
Clinical Assistant Professor
Department of Dermatology
Case Western Reserve School of Medicine
MetroHealth Medical Center
Cleveland, OH, USA

Fenella Wojnarowska MD FRCP
Emeritus Professor of Dermatology
Churchill Hospital
Oxford, UK

Stephen E Wolverton MD
Theodore Arlook Professor of Clinical Dermatology
Department of Dermatology
Indiana University School of Medicine
Indianapolis, IN, USA

Gary S Wood MD
Johnson Professor and Chairman
Department of Dermatology
University of Wisconsin
Madison, WI, USA

Hong Wu MD PhD
Director
Dermatopathology
Fox Chase Cancer Center
Philadelphia, PA, USA

Elisabeth MT Wurm MD
Dermatology Research Centre
The University of Queensland
School of Medicine
Princess Alexandra Hospital
Brisbane, QLD, Australia

Kim B Yancey MD
Professor and Chair
Department of Dermatology
University of Texas Southwestern Medical Center
Dallas, TX, USA

Carole Yee BS
Dermatology Branch
National Cancer Institute
National Institutes of Health
Bethesda, MD, USA

Gil Yosipovitch MD
Professor
Department of Dermatology, Neurobiology and Anatomy, and Regenerative Medicine
Wake Forest University Health Sciences
Winston-Salem, NC, USA

Christopher B Zachary FRCP MD
Professor and Chair
Department of Dermatology
University of California
Irvine, CA, USA

Andrea L Zaenglein MD
Associate Professor of Dermatology and Pediatrics
Department of Dermatology
Penn State Milton S. Hershey Medical Center
Hershey, PA, USA

Iris Zalaudek MD
Assistant Professor
Department of Dermatology
Medical University of Graz
Graz, Austria

John J Zone MD
Professor and Chairman
Department of Dermatology
University of Utah
School of Medicine
Salt Lake City, UT, USA

Matthew B Zook MD PhD
Director
Melanoma Risk Assessment Program
Fox Chase Cancer Center
Philadelphia, PA, USA

User Guide

VOLUMES, SECTIONS AND COLOR CODING

Dermatology is divided into two volumes. The book is divided into 22 sections, which are color-coded as follows for reference:

VOLUME ONE

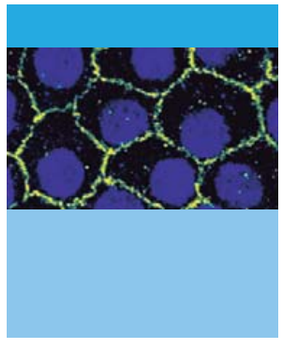
- Section 1 Overview of basic science
- Section 2 Pruritus
- Section 3 Papulosquamous and eczematous dermatoses
- Section 4 Urticarias, erythemas and purpuras
- Section 5 Vesiculobullous diseases
- Section 6 Adnexal diseases
- Section 7 Rheumatologic dermatology
- Section 8 Metabolic and systemic diseases
- Section 9 Genodermatoses
- Section 10 Pigmentary disorders
- Section 11 Hair, nails and mucous membranes

VOLUME TWO

- Section 12 Infections, infestations and bites
- Section 13 Disorders due to physical agents
- Section 14 Disorders of Langerhans cells and macrophages
- Section 15 Atrophies and disorders of dermal connective tissues
- Section 16 Disorders of subcutaneous fat
- Section 17 Vascular disorders
- Section 18 Neoplasms of the skin
- Section 19 Medical therapy
- Section 20 Physical treatment modalities
- Section 21 Surgery
- Section 22 Cosmetic surgery

Basic Science Chapters

Basic science chapters in the book are highlighted on the upper corner of each page with the following skin biology symbol:



Therapeutic Ladders

Therapeutic ladders have been standardized for measuring levels of evidence.

Key to evidence-based support:

(1) prospective controlled trial
(2) retrospective study or large case series
(3) small case series or individual case reports.

Dermatology Website

Additional 'e' references in Chapters 8 and 24 can be found in full at http://www.expertconsult.com, which includes all of the book's content plus supplementary images in a searchable format.

Expert CONSULT

Dedication

This book is dedicated to our families, in particular Dennis Cooper, MD, Andrew Schaffer and Irene Carros, who endured our work on this project and who unwittingly were part of the team, and to all the rest of the team at Elsevier who made it all happen.

Acknowledgments

We are grateful to the authors for sharing their expertise and putting forth their best efforts to bring up-to-date educational material to the readers. In addition, we wish to acknowledge the contributions of Russell Gabbedy, who was there in the early days of the first edition and who has rejoined us for the third edition; the London team, initially led by Sven Pinczewski and then Rachael Harrison with the assistance of Emma Cole; and the Oxford team, led by Anne Collett, with Susan Stuart and Elaine Leek.

We would also like to thank the following people for their help during this project: Kalman Watsky, MD, Louis A. Fragola, Jr, MD, Lisa Rao, Henry Votava, MD, PhD, Donald J. Baker, MD, Caterina Catricalà, MD, Misty Godwin, and Evan, Henry and Samuel Schaffer.

The following figures were sourced from the **Yale Residents' Slide Collection**:
0.6, 0.8, 6.11, 7.4B, 7.6, 8.5B, 8.7A, 8.8, 8.9A, 8.10, 8.11, 8.12, 8.16, 8.17A, 8.17C, 8.18A, 8.18B, 9.3A, 9.3B, 9.4D, 9.6A, 9.7, 9.13A, 10.1, 10.7, 11.7, 11.8B, 11.9, 11.10B, 11.10C, 11.11A, 11.13A, 11.13B, 11.13C, 11.15A, 11.15B, 11.15C, 11.16A, 11.17, 11.19A, 11.20A, 11.20B, 11.23A, 12.5, 12.8, 12.9, 12.12A, 12.14, 14.05A, 14.7, 14.9, 14.19, 16.3, 17.12D, 18.1A, 18.1C, 19.1B, 19.2A, 19.2B, 19.5, 20.1B, 20.1C, 20.1E, 20.8A, 20.8B, 20.2, 20.3, 20.9, 20.10A, 20.12A, 20.12B, 20.13, 21.1A, 21.1B, 21.1C, 21.2, 21.3, 21.4, 21.6B, 21.6D, 21.7, 21.10A, 21.10B, 21.11, 21.15A, 21.19A, 22.5A, 23.5C, 23.9A, 23.9B, 24.2D, 24.3B, 24.6A, 24.6B, 24.7A, 24.7B, 24.14B, 24.14C, 24.14D, 24.16A, 26.2, 26.10, 26.12B, 26.14, 27.3A, 27.3B, 27.3C, 27.3D, 27.10A, 29.7C, 30.2, 30.3A, 30.5A, 30.5B, 30.5C, 30.13, 30.16, 30.18, 31.2A, 31.2B, 31.3A, 31.10, 31.11, 32.2A, 32.4A, 32.4B, 32.4C, 32.8, 32.9A, 33.7, 34.2A, 34.3A, 34.3B, 34.6, 34.11A, 34.11B, 34.13, 34.14, 34.15B, 36.9, 37.7B, 37.8A, 37.8B, 37.12B, 38.2, 38.3, 38.4A, 38.5E, 38.6, 38.17B, 38.17C, 39.8, 39.9, 39.15B, 41.4A, 41.4B, 41.4D, 41.4E, 41.4F, 41.4G, 41.7B, 41.8B, 41.10, 41.11A, 41.12, 41.13, 41.15, 42.2A, 42.6B, 43.5, 43.7, 43.8, 44.5A, 44.5B, 44.8, 44.13B, 45.11B, 46.2A, 46.2B, 46.14C, 46.12, 47.7, 47.8B, 47.9A, 48.1, 48.4A, 49.3A, 49.5, 49.7, 50.5C, 50.8C, 50.8D, 50.9, 51.7A, 51.8A, 51.8B, 51.11A, 51.11B, 51.11C, 51.11D, 52.1E, 57.8A, 57.8B, 57.10C, 57.12B, 57.12C, 58.3A, 58.7B, 58.10, 58.12, 58.14A, 58.15, 58.16, 59.2B, 59.14, 59.15, 59.16, 60.4B, 61.3B, 61.5C, 61.7, 61.13, 61.15A, 61.16B, 61.17, , 62.6A, 62.6B, 62.7, 62.9, 62.12, 62.13, 62.15, 63.2, 63.15C, 64.4, 64.17D, 64.20, 64.23, 66.16, 66.17, 66.19A, 66.19D, 66.19E, 66.19F, 66.20, 66.21, 66.22, 66.23A, 66.24, 66.29, 66.30, 66.31A, 67.03, 67.5B, 67.9, 67.20B, 69.9D, 69.16, 69.22, 70.5, 70.6, 73.13A, 73.15A, 74.6A, 74.6B, 74.9, 74.15, 74.19, 74.23, 74.29A, 74.30, 75.14, 75.15, 75.17B, 75.18, 75.19, 75.20, 75.22B, 75.22C, 75.24A, 75.24B, 75.25, 76.5, 76.6, 77.4, 77.5B, 77.6D, 77.7, 77.8, 77.9, 77.12A, 77.12C, 77.12D, 77.12E, 77.12F, 77.15A, 77.15C, 77.20F, 77.24A, 77.33A, 77.33B, 77.33D, 77.33E, 80.6A, 80.8C, 80.15C, 80.15E, 81.10A, 82.7A, 82.7C, 82.7D, 82.7E, 82.8A, 82.8B, 82.8C, 82.9A, 82.9C, 82.13, 82.21A, 82.21C, 83.4B, 84.3A, 84.3D, 84.5, 84.12, 84.15A, 85.4, 85.16, 87.3A, 87.3C, 87.23B, 87.23E, 88.8B, 88.15, 90.6, 91.1A, 91.1C, 91.1E, 91.7, 91.15, 91.18, 92.2, 92.3, 92.11, 93.2A, 93.2E, 93.3C, 93.4, 93.8A, 93.8B, 93.9, 93.16A, 94.1, 94.3B, 96.4A, 96.4B, 96.6, 96.8, 97.5A, 97.5B, 97.6, 98.2B, 98.12, 99.5C, 100.13, 103.5B, 103.9, 103.10C, 103.11C, 104.3A, 104.12A, 104.18B, 105.4, 105.6A, 105.7, 105.8, 105.13, 105.17, 106.11, 106.13, 108.4A, 108.4B, 108.5, 108.9B, 108.14B, 109.2B, 109.7A, 109.7E, 110.2, 110.7, 110.13B, 110.16B, 110.26, 111.1, 111.3A, 111.3B, 111.5, 111.11, 111.14, 111.17A, 111.20A, 111.23A, 111.25, 111.29, 111.33, 111.35, 111.36, 111.39B, 112.1, 112.6, 112.8, 112.9, 112.25B, 112.28A, 113.9, 114.10, 114.17B, 115.18A, 116.1, 116.22, 116.24, 116.26, 117.2, 117.8, 118.6A, 118.6B, 118.8, 121.1, 122.3C, 121.4A, 121.7, 122.3B 125.8, 127.5, 128.2, 128.6, 128.12B, 130.5, 134.6, 158.1

The following figures were sourced from the **NYU Slide Collection**:
9.2B, 9.6B, 10.5, 10.6A, 10.6B, 10.8, 11.10A, 11.19B, 13.2B, 16.7, 18.13, 24.2B, 25.6, 29.7B, 29.7D, 30.6A, 30.6B, 38.9, 44.4, 44.9A, 57.9A, 57.9B, 64.19A, 67.2, 67.4A, 67.4B, 69.13B, 69.21, 70.12, 72.4, 74.13C, 74.17, 74.24A, 76.7A, 76.7B, 81.9A, 81.9B, 82.9B, 82.11, 84.3B, 84.3C, 84.15C, 87.2, 87.3B, 87.23D, 93.14A, 93.14B, 98.11, 101.16B, 105.19B, 116.2, 116.11, 116.16, 116.19, 116.34, 130.6

The following figures were sourced from the **USC Residents' Slide Collection**:
6.6B, 44.15, 46.8, 62.5C, 62.6C, 74.28, 75.7, 77.22A, 77.22B, 77.23A, 77.27A, 77.27B, 77.29A, 77.29B, 84.3B, 84.3C, 99.5A, 101.9B, 104.9, 111.28A, 114.8, 130.1

The following figure was sourced from the **SUNY Stony Brook Residents' Slide Collection:**
66.19C

This page intentionally left blank

Basic Principles of Dermatology

0

Whitney A High, Carlo Francesco Tomasini, Giuseppe Argenziano, and Iris Zalaudek

Chapter Contents

Introduction to clinical dermatology....1
The role of dermatopathology in clinicopathologic correlation....11
Introduction to the use of dermoscopy (dermatoscopy)....33

INTRODUCTION TO CLINICAL DERMATOLOGY

The skin represents the largest organ of the human body. The average adult has 1.75 m^2 (18.5 ft^2) of skin that contains a variety of complex adnexal structures, including hair, nails, glands and specialized sensory structures, all of which function in protection, homeostasis and the transmission of sensation. Dermatology is the field of medicine that deals with the macroscopic study of skin, adjacent mucosa (oral and genital) and cutaneous adnexa, while dermatopathology deals with the microscopic study of the same structures. The two fields are closely allied, as they are complementary and requisite to one another.

Multiple studies have shown that a dermatologist is the most effective diagnostician with regard to skin disease[1,2]. This enhanced acumen reflects experience in recognizing distribution patterns and configurations as well as subtle variations in morphology and colors, in addition to appreciating associated histopathologic findings. This chapter will not only serve as an introduction to the classification schemes, descriptive terminologies and diagnostic tools utilized in dermatology, it will also highlight additional means for studying the skin, including dermoscopy (dermatoscopy) and dermatopathology, with clinicopathologic correlation between macroscopic and microscopic findings.

Etiologic Premises

All students of dermatology, whether beginners or advanced scholars, require a basic conceptual framework upon which to organize thousands of skin diseases. A useful arrangement is one that is analogous to a tree, with a trunk, major branches, minor branches, twigs and, ultimately, leaves (Fig. 0.1). Instead of memorizing thousands of leaves, a logical, progressive movement along the limbs will allow for a more complete and sophisticated differential diagnosis.

Inflammatory versus neoplastic

An early and major "branch point" in classifying skin diseases is deciding simply if a skin condition is "neoplastic" (either benign or malignant) or "inflammatory" (either infectious or non-infectious) (see Fig. 0.1). However, an experienced clinician knows that one must consider possible diagnoses along multiple limbs before narrowing the differential diagnosis, because both overlap and mimicry can occur. For example, mycosis fungoides, the most common form of cutaneous T-cell lymphoma, is a clonal lymphoproliferative disorder (a "neoplasm"), yet its clinical presentation resembles an inflammatory disorder (Fig. 0.2), especially in its early stages. Conversely, sarcoidosis is an inflammatory condition, but it may present as an isolated infiltrated plaque that may mimic a neoplasm (Fig. 0.3).

Morphology

To an engineer or material scientist, the word "*morphology*" refers to the structure and appearance of a material without regard to function. In dermatology, this term is used analogously to refer to the general appearance of a skin lesion or lesions, irrespective of the etiology or underlying pathophysiology. For example, a small cutaneous blister is referred to as a "vesicle", regardless of whether it is due to an infectious process, such as herpes zoster, or an autoimmune process, such as

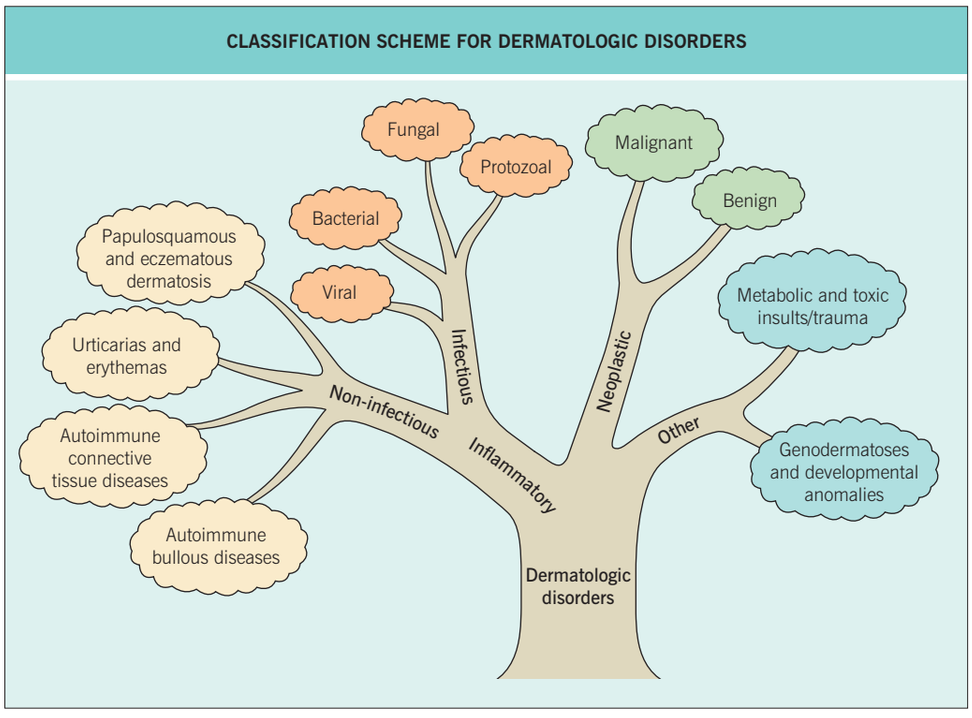


Fig. 0.1 Classification scheme for dermatologic disorders. This scheme is analogous to the structure of a tree with multiple branch points terminating in leaves.

Fig. 0.2 Mycosis fungoides, the most common form of cutaneous T-cell lymphoma. Mycosis fungoides represents a neoplastic proliferation of monoclonal lymphocytes, but it presents clinically in a manner akin to that of inflammatory conditions.

Fig. 0.3 Sarcoidosis. It is an inflammatory disorder of uncertain etiology, most prevalent in African-Americans from the southern United States, but sarcoidosis can present as a papulonodule or infiltrated plaque, mimicking a neoplastic disorder.

Fig. 0.4 Herpes zoster (A), an infectious disease, and bullous pemphigoid (B), an autoimmune disease. While disparate in etiology, both can result in a similar morphology – namely, cutaneous vesicles and bullae.

bullous pemphigoid (Fig. 0.4). Therefore, the proper use of morphological terms establishes a structural framework for grouping skin diseases based upon their macroscopic appearance.

In essence, morphologic terms become a "native language" by which dermatologists, and other health professionals, communicate with each other to *describe* skin lesions. As such, they are key elements of a lexicon. Without a basic working knowledge of morphology, it is impossible to describe cutaneous observations in a consistent manner. Therefore, one of the initial steps in studying dermatology is to learn basic morphologic definitions inherent to the specialty.

There exist both primary morphologic terms (Table 0.1), which refer to the most characteristic, representative or native appearance of skin lesions (such as a "papule"), and secondary morphologic terms (Table 0.2), which can augment or even supplant primary morphologic terms. Secondary morphologic terms often reflect the effects of exogenous factors or temporal changes (such as "scales" or "crusts") that evolve during the course of a skin disease.

Secondary changes must be considered when performing, or examining histologically, a biopsy of a skin lesion. An astute clinician will generally attempt to biopsy a well-developed but "fresh" lesion that demonstrates the expected primary pathology, free of secondary changes such as erosions, ulcers and scars. This allows the dermatopathologist to evaluate the histologic features of the lesions in their native state, without potentially confounding alterations.

Palpation and appreciation of textural changes

Any discussion of morphology must include textural change, and palpating a lesion often provides important diagnostic clues. In dermatology, palpation can prove useful in several ways. Firstly, it helps in making a distinction amongst primary morphologies (see Table 0.1). For example, the key difference between macules and patches, as opposed to papules and plaques, is that the former are flush with the surrounding skin and cannot be appreciated by palpation. On the other hand, the latter, by definition, must be palpable (Table 0.3). Secondly, palpation may augment the examination and appreciation of a disease process for which visual changes are absent, unimpressive or nonspecific. For example, in morphea, an autoimmune connective tissue disease that leads to sclerotic collagen within the dermis, the skin feels indurated (very firm) while only nonspecific hyperpigmentation may be evident with visual inspection. The same is true for other fibrotic disease processes, such as nephrogenic systemic fibrosis and scleroderma. Lastly, purpura is often classified as palpable or non-palpable, and this division implies different underlying etiologies (e.g. small vessel vasculitis aligned more with palpable purpura than macular purpura).

PRIMARY LESIONS – MORPHOLOGICAL TERMS

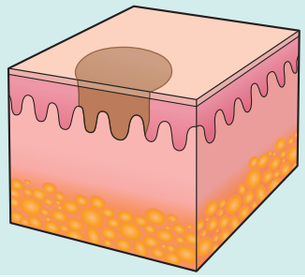
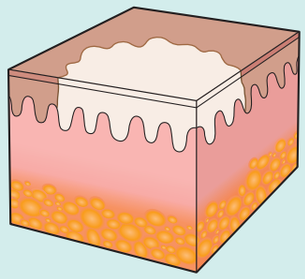
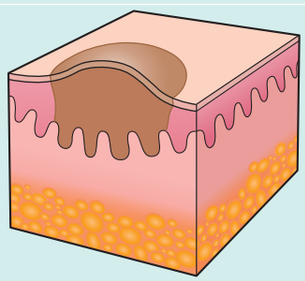
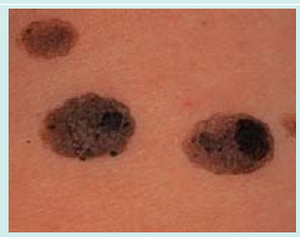
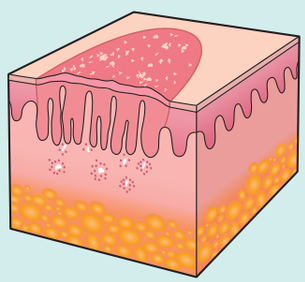
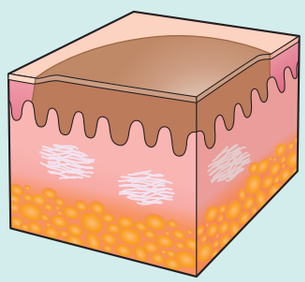
	Term	Clinical features		Clinical example	Clinical disorders
← Related by size →	**Macule**	• Flat, circumscribed • <1 cm in diameter • Often hypo- or hyperpigmented • Also other colors (e.g. pink, red, violet)		 Solar lentigines	• Ephelid (freckle) • Lentigo • Idiopathic guttate hypomelanosis • Petechiae • Flat component of viral exanthems
	Patch	• Flat, circumscribed • >1 cm in diameter • Often hypo- or hyperpigmented • Also other colors (e.g. blue, violet)		 Vitiligo	• Vitiligo • Melasma • Dermal melanocytosis (Mongolian spot) • Café–au–lait macule • Nevus depigmentosus • Solar purpura
← Related by size →	**Papule**	• Elevated, circumscribed • <1 cm in diameter • Elevation due to increased thickness of the epidermis and/or cells or deposits within the dermis • May have secondary changes (e.g. scale, crust) • Need to distinguish from vesicle or pustule		 Seborrheic keratoses	• Seborrheic keratosis • Cherry hemangioma • Compound or intradermal melanocytic nevus • Verruca or molluscum contagiosum • Lichen nitidus • Elevated component of viral exanthems • Small vessel vasculitis
	Plaque	• Elevated, circumscribed • >1 cm in diameter • Elevation due to increased thickness of the epidermis and/or cells or deposits within the dermis • May have secondary changes (e.g. scale, crust)		 Psoriasis	*Primarily epidermal* • Psoriasis • Lichen simplex chronicus • Nummular dermatitis
				 Acne scarring	*Dermal* • Granuloma annulare • Sarcoidosis • Hypertrophic scar, keloid • Morphea • Lichen sclerosus

Table 0.1 Primary lesions – morphological terms. *Photos courtesy, Jean L Bolognia, MD; Louis A Fragola, Jr, MD; Joyce Rico, MD; Julie V Schaffer, MD; Kalman Watsky, MD.*

Continued

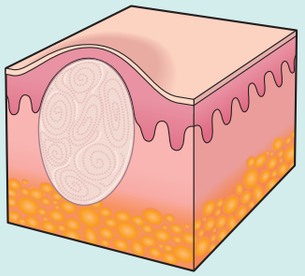
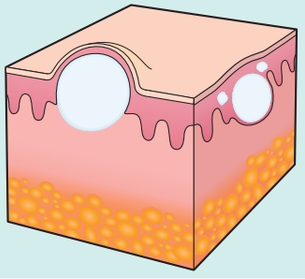
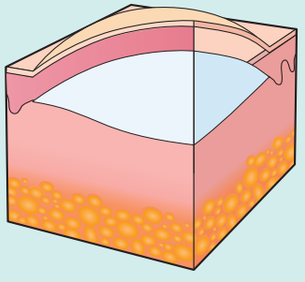
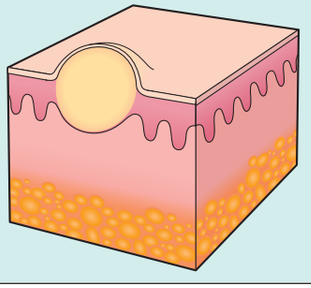
PRIMARY LESIONS – MORPHOLOGICAL TERMS				
	Term	**Clinical features**	**Clinical example**	**Clinical disorders**
	Nodule	• Elevated, circumscribed • Larger volume than papule, often >2 cm in diameter • Involves the dermis and may extend to the subcutis • Greatest mass may be beneath the skin surface	 Epidermoid inclusion cysts	• Epidermoid inclusion cyst • Lipoma • Metastases • Neurofibromas • Panniculitis, e.g. erythema nodosum • Lymphoma cutis
← Related by size →	**Vesicle**	• Elevated, circumscribed • <1 cm in diameter • Primarily filled with clear fluid • May become pustular, umbilicated or an erosion	 Herpes zoster	• Herpes simplex • Varicella or zoster • Dermatitis herpetiformis • Dyshidrotic eczema
	Bulla	• Elevated, circumscribed • >1 cm in diameter • Filled with clear fluid	 Bullous fixed drug eruption	• Friction blister • Bullous pemphigoid • Linear IgA bullous dermatosis • Bullous fixed drug eruption • Coma bullae • Edema bullae
	Pustule	• Elevated, circumscribed • Usually <1 cm in diameter • Filled primarily with purulent fluid	 Steroid folliculitis	*Follicularly centered* • Folliculitis • Acne vulgaris *Non-follicularly centered* • Pustular psoriasis • Acute generalized exanthematous pustulosis • Subcorneal pustular dermatosis

Table 0.1 Primary lesions – morphological terms (cont'd).

SECONDARY FEATURES – MORPHOLOGICAL TERMS			
Feature	**Description**		**Disorders**
Crust	• Dried serum, blood or pus on the surface • May include bacteria (usually *Staphylococcus*)	 Secondarily infected hand dermatitis	• Eczema/dermatitis (multiple types) • Impetigo • Later phase of herpes simplex, varicella or zoster • Erythema multiforme
Scale	• Hyperkeratosis • Accumulation of stratum corneum due to increased proliferation and/or delayed desquamation	 Psoriasis	• Psoriasis (micaceous scale) • Tinea (leading scale) • Erythema annulare centrifugum (trailing scale) • Actinic keratoses (gritty scale) • Pityriasis rosea (peripheral collarette of scale and central scale)

Table 0.2 Secondary features – morphological terms. *Photos courtesy, Louis A Fragola, Jr, MD and Jeffrey C Callen, MD.*

Continued

SECONDARY FEATURES – MORPHOLOGICAL TERMS			
Feature	**Description**		**Disorders**
Fissure	• Linear cleft in skin • Often painful • Results from marked drying, skin thickening, and loss of elasticity	 Hand dermatitis	• Angular cheilitis • Hand dermatitis • Sebopsoriasis (intergluteal fold) • Irritant cheilitis
Erosion	• Partial loss of the epidermis (epithelium)	 Pemphigus foliaceus	• Impetigo • Friction • Trauma • Pemphigus, vulgaris and foliaceus
Ulceration	• Full-thickness loss of the epithelium (epidermis) • May have loss of the dermis or even subcutis	 Pyoderma gangrenosum	• Ecthyma gangrenosum • Pyoderma gangrenosum • Stasis ulcer • Ecthyma • Neuropathic ulcer
Excoriation	• Exogenous injury to all or part of the epidermis (epithelium)	 Neurotic excoriations	• A secondary feature of pruritic conditions, including arthropod bites and atopic dermatitis • Neurotic excoriations • Acne excoriée
Atrophy	• Epidermal atrophy – thinning of the epidermis, leading to wrinkling and a shiny appearance • Dermal atrophy – loss of dermal collagen and/or elastin, leading to a depression (see Table 0.3)	 Striae secondary to potent corticosteroids	• Lichen sclerosus • Poikiloderma • Anetoderma • Focal dermal hyoplasia (Goltz syndrome) • Striae
Lichenification	• Thickening (acanthosis) of the epidermis, and accentuation of natural skin lines	 Lichen simplex chronicus	• Lichen simplex chronicus, isolated or superimposed on a pruritic condition, e.g. atopic dermatitis

Table 0.2 Secondary features – morphological terms (cont'd). *Photos courtesy, Louis A Fragola, Jr, MD and Jeffrey C Callen, MD.*

Color

The color of skin lesions can provide important clues as to the nature of the disease process. Sometimes our perception of color may be modified by palpation (see above). For example, while many dermatological processes appear red–purple in color, it is important to ascertain whether this is a blanchable erythema (i.e. it disappears with pressure), which suggests the color is due to vasodilation, or whether it is due to extravasation of red blood cells into the tissue (purpura), which does not blanch. Also, it is not uncommon for exogenous sources of pigment, such as topical medicaments, oral drugs and other ingestants, to be implicated in producing discoloration of the skin. Table 0.4 lists the more frequently observed colors of skin lesions and examples of associated disorders.

Variation in skin color within the human population

Many racial and ethnic descriptors are used in common parlance, including African, African-American, Asian, Middle Easterner, Northern European, Southern European, Native American, Pacific Islander, and Hispanic, to describe individuals with similar cutaneous characteristics as well as heritage. Yet even within racial and ethnic groups, gradations exist with regard to skin pigmentation. Sometimes the term "skin of color" is used to describe all skin tones darker than those of

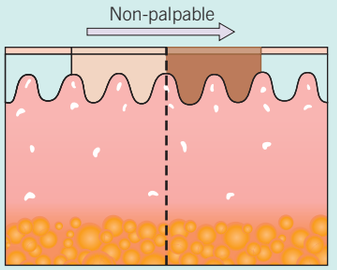
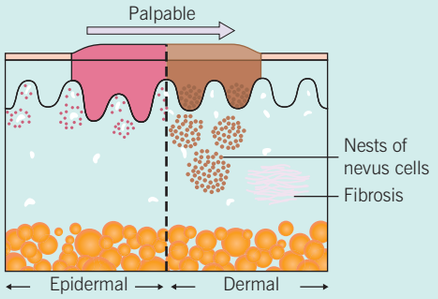
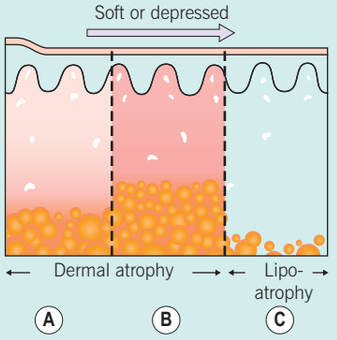
USE OF PALPATION IN DEFINING CUTANEOUS LESIONS		
Types of lesion		**Examples**
Macules & patches (non-palpable)		• Solar lentigines • Idiopathic guttate hypomelanosis • Melasma • Vitiligo • Petechiae • Dermal melanocytosis
Papules & plaques (palpable)		• Psoriasis • Lichen planus • Dermatitis • Intradermal or compound melanocytic nevus • Hypertrophic scar, keloid • Morphea
Atrophy – dermal & subcutaneous		**(A)** • Anetoderma **(B)** • Focal dermal hypoplasia (Goltz syndrome) **(C)** • Lipoatrophy due to corticosteroid injections • Lipoatrophy due to panniculitis

Table 0.3 Use of palpation in defining cutaneous lesions.

COLOR AS A CLUE TO THE CLINICAL DIAGNOSIS		
Color	**Clinical example**	**Examples of diseases with this color**
Erythema (pink to red–brown, depending upon the skin phototype)	 Morbilliform (exanthematous) drug eruption	• Dermatitis • Psoriasis • Morbilliform drug eruption • Viral exanthems • Any insult that causes vasodilation

Black	
	Necrosis secondary to vasculopathy from levamisole-contaminated cocaine
		• Necrosis of the skin:
		  • Vasculitis (Wegener's granulomatosis)
		  • Thrombosis (e.g. DIC, monoclonal cryoglobulinemia)
		  • Emboli (e.g. ecthyma gangrenosum)
		  • Vasospasm (e.g. severe Raynaud's phenomenon)
		  • Vascular compromise (e.g. atherosclerosis, calciphylaxis)
		  • Eschar (e.g. anthrax)
		• Cutaneous melanoma
		• Traumatic tattoos (e.g. asphalt)

Table 0.4 Color as a clue to the clinical diagnosis. DIC, disseminated intravascular coagulation.

Continued

COLOR AS A CLUE TO THE CLINICAL DIAGNOSIS		
Color	**Clinical example**	**Examples of diseases with this color**
Blue (ceruloderma)	Dermal melanocytosis	• Dermal melanocytosis (e.g. Mongolian spot, nevus of Ota) • Dermal melanocytomas (e.g. blue nevi) • Cyanosis • Ecchymoses • Venous congestion (e.g. venous malformations) • Drugs/deposits (e.g. minocycline, traumatic tattoos)

Brown	Phytophotodermatitis due to lime juice	• Pigmented lesions
		  • Lentigines
		  • Seborrheic keratoses
		  • Junctional, compound and congenital melanocytic nevi
		  • Café-au-lait macules
		  • Dermatofibromas
		  • Melanoma
		  • Pigmented AKs, Bowen's disease
		• Postinflammatory hyperpigmentation – epidermal (see Ch. 67)
		• Melasma
		• Phytophotodermatitis
		• Drug-induced hyperpigmentation (e.g. cyclophosphamide)
		• Metabolic (e.g. Addison's disease, hemochromatosis)

Gray	Argyria	• Postinflammatory hyperpigmentation – dermal (e.g. erythema dyschromicum perstans; see Ch. 67) • Drugs/deposits (e.g. argyria, chrysiasis) • Combined melanocytic nevus • Traumatic tattoos • See Blue (above)
Purple (violaceous)	Purpura	• Purpura, non-palpable (e.g. solar purpura) • Purpura, palpable (e.g. small vessel vasculitis) • Vascular neoplasms (e.g. angiokeratoma, angiosarcoma) • Lichen planus • Lymphoma cutis • Pyoderma gangrenosum – border • Morphea - border
White	Calcinosis cutis (systemic sclerosis)	• Absence of melanocytes or melanin production (e.g. vitiligo, piebaldism, OCA1A) • Scarring (e.g. scarring in discoid lupus erythematosus) • Vasospasm (e.g. Raynaud's phenomenon, nevus anemicus) • Deposits (e.g. calcinosis cutis, gouty tophi) • Macerated stratum corneum – mucosal surfaces (e.g. leukoplakia)
Green	Onycholysis with secondary *Pseudomonas* infection	• *Pseudomonas* infection • Tattoo • Chloroma • Green hair due to copper deposits
Orange–red (salmon)	Pityriasis rubra pilaris with islands of sparing	• Pityriasis rubra pilaris • Mycosis fungoides (sometimes)
Yellow	Xanthelasma	• Solar elastosis • Carotenemia • Xanthomas (e.g. xanthelasma, eruptive) • Xanthogranulomas • Adnexal tumors and hyperplasias with sebaceous differentiation • Necrobiosis lipoidica • Capillaritis (yellow–brown background) • Deposits/drugs (e.g. tophi, quinacrine)

Table 0.4 Color as a clue to the clinical diagnosis (cont'd). AK, actinic keratosis; OCA1A, oculocutaneous albinism, type 1A.

FITZPATRICK SCALE OF SKIN PHOTOTYPES		
Skin phototype	**Skin color**	**Response to UV irradiation**
I	White	Always burns, does not tan
II	White	Burns easily, tans with difficulty
III	Beige	Mild burns, tans gradually
IV	Brown	Rarely burns, tans easily
V	Dark brown	Very rarely burns, tans very easily
VI	Black	Never burns, tans very easily

Table 0.5 Fitzpatrick scale of skin phototypes.

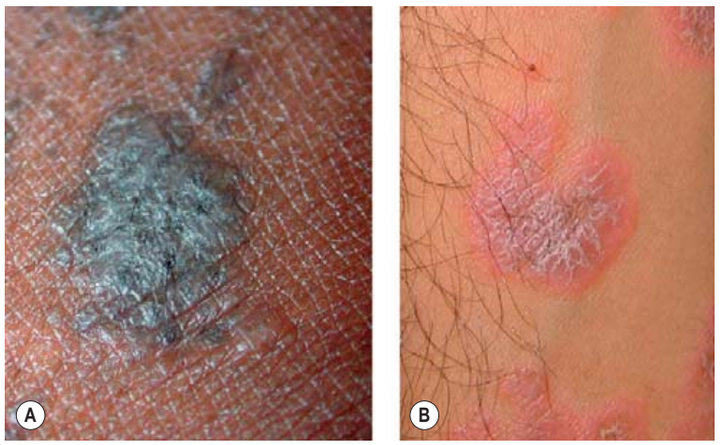


Fig. 0.5 Lichen planus presents differently in darkly pigmented (A) versus lightly pigmented (B) skin. The violaceous hue seen in **B** is more muted in **A** and these lesions appear brown–black in color. Wickham's striae (lacy white pattern) are more easily seen in **B**.

white (Caucasian) skin[3]. However, this term encompasses more than skin color and its response to ultraviolet irradiation, as is assessed by the Fitzpatrick Scale (skin phototypes I–VI; Table 0.5). It also refers to other shared characteristics, such as hair color, hair texture, and a tendency toward certain reaction patterns in the skin as a response to an insult. The practice of dermatology requires a solid understanding of the differences in clinical features (e.g. hues of red) amongst individuals with different levels of skin pigmentation.

Variations in skin color are due to differences in the amount and distribution of melanin within epidermal melanocytes and keratinocytes[4], rather than the number of melanocytes (see Ch. 65). In addition, the ratio of eumelanin (brown–black) to pheomelanin (yellow–red) influences skin color, with pheomelanin the predominant pigment in those with freckles and red hair. Exposure to ultraviolet radiation also significantly impacts melanin production (tanning).

Pigmentation of the skin clearly influences the prevalence of certain cutaneous findings and disorders. For example, individuals with darkly pigmented skin are more likely to develop multiple streaks of longitudinal melanonychia (see Ch. 71)[5,6], pigmentation of the oral mucosa[7], persistent postinflammatory hyperpigmentation (see Ch. 67), and obvious pigmentary demarcation lines[8] (Futcher's lines or Voigt's lines; see Fig. 67.10). Whether postinflammatory hypopigmentation[9] is more common or just more clinically apparent is a matter of debate. In addition, discoid lupus erythematosus and keloids are seen more often in patients with darkly pigmented skin and African ancestry, but the relationship of these disorders to melanocyte function is not clear.

There can also be differences in the physiologic properties of the skin. For example, the stratum corneum of black skin often retains more layers and is more compact and cohesive than that of white skin. In addition, darker skin produces less vitamin D_3 in response to equivalent amounts of sunlight, and this is postulated to have been a driving force in the evolution of paler skin as early humans migrated away from the equator[10].

Perhaps the most important point to remember is that erythema (redness) can be difficult to appreciate in darkly pigmented skin. Erythema is caused by vasodilation and/or increased blood flow in the dermis, and if the epidermis is deeply pigmented, the red hues of oxyhemoglobin are often less obvious. For this reason, diseases that are classically described as erythematous (e.g. dermatitis) or violaceous (e.g. lichen planus) may present more subtly in darker skin types (Fig. 0.5)[11]. Diagnostic procedures that depend upon the development of erythema, such as patch testing for the evaluation of allergic contact dermatitis, can be more challenging to interpret in dark skin. Lastly, cyanosis (blue hues indicative of poor oxygenation and a critical clinical sign) is also more difficult to appreciate when the skin is darkly pigmented.

Configuration and Distribution

After carefully considering the morphology and color of skin lesions, the dermatologist must next analyze two closely related properties – configuration and distribution – in order to hone in on the correct diagnosis. For example, pruritic and fragile vesicles on the elbows and knees would prompt consideration of dermatitis herpetiformis, whereas grouped vesicles on an erythematous base confined to a single dermatome would mandate consideration of herpes zoster (Fig. 0.6) or zosteriform herpes simplex.

Fig. 0.6 The dermatomal pattern of herpes zoster. Note the midline demarcation.

Configuration

Appreciation of the configuration or arrangement of skin lesions can provide important clues as to the diagnosis. Examples include *annular* (e.g. tinea corporis, granuloma annulare; see Ch. 19), *serpiginous* (e.g. cutaneous larva migrans), *clustered* (e.g. piloleiomyomas, herpetiform vesicles), *reticulated* (e.g. erythema ab igne), and *retiform* (e.g. purpura fulminans, purpura due to calciphylaxis [Fig. 0.7]; see Ch. 22). The latter pattern reflects occlusion of the cutaneous vasculature[12].

It also important to note if the cutaneous lesions are in a *linear* array. The lesions may follow Blaschko's lines, which reflect patterns of embryonic development (see Fig. 62.1)[13], or they may be confined to a dermatome, which represents an area of skin whose innervation is from a single spinal nerve (see Fig. 80.14). Irrespective of whether the lesions are along Blaschko's lines (e.g. epidermal nevi) or in a dermatomal pattern (e.g. herpes zoster [see Fig. 0.6]), there is often a characteristic midline demarcation. In addition to these two patterns, a linear arrangement can result from a trauma-induced Koebner phenomenon (an isomorphic response), as in vitiligo, lichen planus (Fig. 0.8) and psoriasis[14,15], or be due to trauma-induced autoinoculation, as in verrucae vulgares or verrucae planae. Lastly, linear lesions are frequently seen in acute allergic contact dermatitis due to plants (e.g. poison ivy), reflecting brushing of the branches and leaves against the skin.

Fig. 0.7 Retiform purpura and cutaneous necrosis secondary to calciphylaxis. Note the irregular shape of the purpura. *Courtesy, Amanda Tauscher, MD.*

Fig. 0.8 Koebernization (isomorphic response) of lichen planus secondary to trauma. As a result, the lesions have a linear configuration.

On occasion, lesions have an unusual, even "unnatural", shape that corresponds to an external (exogenous) insult, such as allergic or irritant contact dermatitis (Fig. 0.9), an accidental or purposeful injury (see Ch. 90)[16], or even ritualistic medicinal practices (e.g. "cupping" or "coining"; see Ch. 133).

Distribution

Stepping back and observing the anatomic distribution pattern of skin lesions can also prove very helpful. For example, plaques of psoriasis often favor *extensor* surfaces (e.g. elbows and knees) while lichenified plaques of atopic dermatitis favor *flexural* surfaces in older children and adults (e.g. the antecubital and popliteal fossae). However, to complicate matters a bit, there is an "inverse" form of psoriasis in which lesions are present in major body folds, i.e. in flexural areas (see Ch. 8). Langer's cleavage lines refer to natural skin tension lines that are often used to guide the orientation of surgical excisions (see Fig. 142.7). The long axis of oval lesions of pityriasis rosea[17] and erythema dyschromicum perstans follows these cleavage lines, and this pattern is most obvious on the posterior trunk.

A *seborrheic* distribution pattern includes the head and neck as well as the upper trunk, and it reflects areas rich in sebaceous glands; seborrheic dermatitis, acne vulgaris and pityriasis versicolor are dermatoses

Fig. 0.9 Allergic contact dermatitis to a para-phenylenediamine-based ("black henna") temporary tattoo. The shape of the lesion clearly suggests an exogenous insult/etiology. *Courtesy, Colby Evans, MD.*

that favor these sites. The term "*photodistribution*" describes lesions that are accentuated in areas exposed to ultraviolet irradiation, and photodermatoses include polymorphic light eruption, phototoxic drug reactions (e.g. to doxycycline), and subacute cutaneous lupus erythematosus. Of note, sometimes a disorder will display a combination of distribution patterns; for example, in dermatomyositis, lesions can be both photodistributed and involve extensor surfaces (e.g. elbows, knees). Table 0.6 lists common diagnoses that occur in different anatomic sites.

In addition to differences in the color of inflammatory lesions, individuals with darkly pigmented skin also have an increased frequency of several cutaneous disorders (see section on Color) and certain types of reaction and distribution patterns[18]. Examples of these reaction patterns include papular eczema and a follicular accentuation of atopic dermatitis and pityriasis versicolor, as well as an annular configuration of seborrheic dermatitis and facial secondary syphilis. An example of a favored distribution pattern is inverse pityriasis rosea in which lesions occur primarily in the axillae and groin rather than on the trunk. Although a sound explanation for these phenomena is not currently available, it is still important to be aware of their occurrence[18].

Temporal Course

Central to any medical history, including that of cutaneous disorders, is the temporal course. The patient should be queried as to duration and relative change in intensity or distribution over time. For example, there are some dermatoses that have a cephalocaudal progression over time, such as measles and pityriasis rubra pilaris. Of course, the time course is more prolonged in the latter as compared to the former.

However, the dermatologist is at an advantage because the skin is so accessible, and information provided by the patient can be readily compared to what is seen in the physical examination. With experience, the dermatologist can usually determine by observation whether the cutaneous lesions are acute, subacute or chronic. Examples of helpful signs include scale (not to be confused with crusts), which often reflects parakeratosis that requires 2 weeks to develop, and intact tense bullae, which are rarely more than a week old. Lichenification, i.e. thickening of the skin with accentuation of normal skin markings, takes weeks to months to develop. Therefore, if lichenification is present, the lesion has not appeared acutely, despite what the patient may believe.

In an otherwise generally healthy patient, there are several diseases whose cutaneous manifestations are often acute in nature (Table 0.7). This is not to indicate that these diseases necessarily require immediate or emergent management, but rather that they present to the dermatologist abruptly and are distinguished, particularly from neoplasms or chronic dermatoses, by their temporal acuity.

Finally, although emergencies are unusual in dermatology, there are a few illnesses, particularly those that present with a rash and fever, which are true emergencies and must be recognized promptly and treated appropriately. Examples include Stevens–Johnson syndrome, toxic epidermal necrolysis, Kawasaki disease, meningococcemia (including purpura fulminans), Rocky Mountain spotted fever, necrotizing

COMMON DIAGNOSES FOR PAPULES, PLAQUES AND SMALL NODULES OCCURRING ON SELECT ANATOMICAL SITES		
Anatomic location		**Common**
Scalp	Inflammatory	• Seborrheic dermatitis • Psoriasis • Folliculitis • Prurigo simplex • Tinea capitis (children)
	Neoplastic	• Cherry hemangioma • Melanocytic nevus (compound, dermal, blue) • Seborrheic keratosis • Actinic keratosis (bald scalp) • Squamous cell carcinoma > basal cell carcinoma
Face/ears	Inflammatory	• Acne vulgaris • Rosacea, including periorificial dermatitis • Seborrheic dermatitis • Irritant and allergic contact dermatitis • Vitiligo (periorificial) • Verruca • Molluscum contagiosum (primarily children) • Chondrodermatitis nodularis helicis (ear) • Keloid (ear)
	Neoplastic	• Epidermoid inclusion cyst • Seborrheic keratosis • Melanocytic nevus • Cherry hemangioma } Set 1 • Sebaceous gland hyperplasia • Milium • Lentigines • Dermatosis papulosa nigra (blacks) • Fibrous papule (nose) • Pilomatricoma • Actinic keratosis • Basal cell carcinoma • Squamous cell carcinoma } Set 2
Neck	Inflammatory	• Lichen simplex chronicus
	Neoplastic	• Acrochordons • Set 1 and set 2
Elbow	Inflammatory	• Psoriasis • Verruca • Lichen simplex chronicus • Granuloma annulare • Rheumatoid nodule
	Neoplastic	• Set 1 and set 2
Hand/wrist	Inflammatory	• Irritant and allergic contact dermatitis • Atopic dermatitis • Psoriasis • Tinea • Verruca • Vitiligo • Scabies • Dyshidrotic eczema • Granuloma annulare • Lichen planus (flexural wrist)
	Neoplastic	• Lentigines • Seborrheic keratoses • Actinic keratosis • Squamous cell > basal cell carcinoma
Chest/shoulders	Inflammatory	• Folliculitis • Seborrheic dermatitis (central chest) • Pityriasis (tinea) versicolor • Grover's disease • Miliaria rubra • Pityriasis rosea (trunk) • Subacute cutaneous lupus erythematosus
	Neoplastic	• Solitary lichenoid keratosis • Lipoma • Supernumerary nipple • Paget's disease (periareolar) • Set 1 and set 2

Table 0.6 Common diagnoses for papules, plaques and small nodules occurring on select anatomical sites.

Continued

COMMON DIAGNOSES FOR PAPULES, PLAQUES AND SMALL NODULES OCCURRING ON SELECT ANATOMICAL SITES		
Anatomic location		**Common**
Abdomen/umbilicus	Inflammatory	• Folliculitis • Psoriasis vulgaris • Grover's disease • Eczema craquelé (flanks) • Nummular dermatitis
	Neoplastic	• Set 1 • Lipoma • Metastatic carcinoma (umbilicus)
Genitalia/groin	Inflammatory	• Seborrheic dermatitis • Cutaneous candidiasis • Tinea cruris (may include buttocks) • Inverse psoriasis • Irritant and allergic contact dermatitis • Herpes simplex viral infection • Condyloma acuminatum • Molluscum contagiosum (primarily sexually active individuals) • Scabies • Lichen sclerosus • Lichen simplex chronicus • Vitiligo
	Neoplastic	• Acrochordon • Angiokeratoma • Seborrheic keratosis • Anogenital lentiginosis • Bowenoid papulosis • Squamous cell carcinoma • Extramammary Paget's disease
Lower extremity	Inflammatory	• Folliculitis • Nummular dermatitis • Psoriasis vulgaris (knee) • Verruca (especially knees)
	Neoplastic	• Dermatofibroma • Lipoma • Set 1 and set 2
Ankles/feet	Inflammatory	*Ankles:* • Eczema craquelé • Stasis dermatitis • Lichen simplex chronicus • Lichen planus • Lipodermatosclerosis • Stasis ulcer *Feet:* • Tinea pedis • Verruca • Psoriasis • Pernio • Atherosclerotic ulcer • Neuropathic ulcer (plantar surface) *Both:* • Irritant and allergic contact dermatitis • Vitiligo • Scabies • Granuloma annulare
	Neoplastic	• Stucco keratosis • Actinic keratosis • Squamous cell carcinoma

Table 0.6 Common diagnoses for papules, plaques and small nodules occurring on select anatomical sites (cont'd).

fasciitis, and endocarditis with cutaneous manifestations. An approach to critical dermatologic emergencies that present with a fever and rash is outlined in Fig. 0.10.

The next two sections of this introductory chapter focus on the basic principles of dermatopathology and dermoscopy, respectively, and it is important to remember that all the diagnostic techniques (unaided clinical examination, histological examination, dermatoscopic examination) discussed herein are complementary. In other words, synergistic strength and clinicopathologic correlation are achieved when the techniques are used in combination. As a corollary, using any one technique, to the exclusion of the others, may be misleading and potentially result in misdiagnosis.

THE ROLE OF DERMATOPATHOLOGY IN CLINICOPATHOLOGIC CORRELATION

With the introductory elements of clinical dermatology firmly in mind, we next turn to dermatopathology, the microscopic examination and assessment of both normal and diseased skin. It is noteworthy that

ACUTE CUTANEOUS ERUPTIONS IN OTHERWISE HEALTHY INDIVIDUALS	
Disorder	**Characteristic findings**
Urticaria (see Ch. 18)	• Pathogenesis involves degranulation of mast cells with release of histamine • Primary lesion: edematous wheal with erythematous flare • Widespread distribution • Very pruritic* • Individual lesions are transient (<24 h in duration) • May become chronic (>6 weeks)
Acute allergic contact dermatitis (see Ch. 14)	• Immune-mediated and requires prior sensitization • Primary lesion: dermatitis, with vesicles, bullae and weeping when severe • Primarily in sites of exposure; occasionally more widespread due to autosensitization • Pruritus, often marked • Spontaneously resolves over 2–3 weeks if no further exposure to allergen (e.g. poison ivy, nickel)
Acute irritant contact dermatitis (see Ch. 15)	• Direct toxic effect • Primary lesion: ranges from erythema to bullae (e.g. chemical burn) • At sites of exposure • Burning sensation • Spontaneously resolves over 2–3 weeks if no further exposure to irritant (e.g. strong acid, strong alkali)
Exanthematous (morbilliform) drug eruptions (see Ch. 21)	• Immune-mediated and requires prior sensitization • Pink to red–brown, blanching macules and papules; may become purpuric on distal lower extremities • Widespread distribution • May be pruritic • Spontaneously resolves over 7–10 days if no further exposure to inciting drug
Pityriasis rosea (see Ch. 9)	• May follow a viral illness • Primary lesion: oval-shaped, pink to salmon-colored papule or plaque with fine white scale centrally and peripheral collarette; occasionally vesicular • Initial lesion is often largest (herald patch) • Favors trunk and proximal extremities; may have inverse pattern (axillae & groin); long axis of lesions parallel to skin cleavage lines • Spontaneously resolves over 6–10 weeks; exclude secondary syphilis
Viral exanthems (see Ch. 81)	• Due to a broad range of viruses, including rubeola, rubella, enteroviruses, parvovirus, adenovirus (see Fig. 81. 2) • Often associated with fever, malaise, arthralgias, myalgias, nausea, upper respiratory symptoms • Primary lesions vary from blanching pink macules and papules to vesicles or petechiae • Distribution varies from acral to widespread; may have an enanthem • Spontaneously resolves over 3–10 days
*May have burning rather than pruritus with urticarial vasculitis, and lesions can last longer than 24 hours.	

Table 0.7 Acute cutaneous eruptions in otherwise healthy individuals.

very few other medical specialties place as much emphasis on *both* the clinical and the histological features of diseases within their realm[19]. This natural union between dermatology and dermatopathology exists because the domains are essential to one another, and, practically speaking, both rely heavily upon the powers of observation and classification.

With experience, clinicians can visualize the most likely associated histologic findings as they examine a cutaneous lesion or eruption – e.g. hyperkeratosis and/or parakeratosis when there is scale, or dermal hemorrhage when there are petechiae. As a result, a more sophisticated differential diagnosis accompanies the biopsy specimen. Once the histopathologic features are delineated, then the dermatologist performs a clinicopathologic correlation in order to arrive at the most likely diagnosis.

The Skin Biopsy

In no other field of medicine is tissue for histologic examination so easily accessible. As a result, the skin biopsy has become an integral component of dermatologic diagnoses. Skin biopsies are performed for a multitude of reasons, including:

- uncertainty about the clinical diagnosis
- to investigate a poor response to therapy
- to exclude or investigate the evolution of one condition into another
- to investigate symptoms in the absence of clinically recognizable disease.

Regardless of the rationale for performing a skin biopsy, it is important to realize that the process of securing appropriate tissue involves more than the mere mechanical removal of a specimen. It is a multistep process, executed with forethought, precision and care in order to obtain the maximum amount of useful information[20,21]. Pitfalls that can limit the diagnostic value of a skin biopsy are many and include inappropriate site selection, biopsy technique or tissue handling. Regardless of the specific limitation, the end result can be the same – lack of a diagnosis, an inaccurate diagnosis or a clinicopathologic disconnect.

Site selection

In general, the first step in performing a biopsy is to identify an unadulterated *primary lesion* (see above). Lesions with secondary changes, such as those resulting from rubbing or traumatic injury (e.g. lichenification, excoriations) or superimposed processes (e.g. crusting due to impetiginization), are generally avoided (unless the purpose of the biopsy is to prove their presence), as these secondary changes may alter or obscure the primary pathology.

A well-developed but "fresh" lesion is usually chosen for biopsy, based upon the assumption that it will exhibit the most characteristic, and therefore diagnostic, histopathology. The concern regarding lesions deemed too immature or too old is that they may demonstrate nonspecific histopathologic features. As to be expected, there are exceptions to this general principle, such as the need to biopsy early lesions of small vessel (leukocytoclastic) vasculitis (<24 hours old), especially when performing direct immunofluorescence.

Another commonly accepted rule is that a biopsy specimen is usually obtained from the central aspect of a primary lesion. Again, exceptions exist (Fig. 0.11), especially in the case of ulcers and when the histopathologic changes are subtle, even when compared to uninvolved skin. An example of the latter is atrophoderma, where a thin wedge biopsy that begins in involved skin and ends in normal-appearing skin (and includes the border) is recommended (see Ch. 99). In the case of ulcers, secondary changes beneath the ulcer bed, including nonspecific vasculitis, may be misinterpreted leading to misdiagnosis. For this reason, the wedge biopsy should include the ulcer, its edge and surrounding inflamed skin. Lastly, selection of a proper biopsy site may also be influenced by knowledge of the underlying pathology and pathophysiology of the most likely diagnoses.

Biopsy techniques

A wide range of biopsy techniques exists (see Ch. 146). Those most commonly performed include superficial/tangential shave, deep shave (also known as "saucerization"), punch and incisional/excisional (Fig. 0.12). For optimal results, the technique selected must obtain tissue from the level of the skin or subcutaneous tissue where the pathologic changes are expected, while simultaneously balancing concerns of cosmesis and morbidity. For example, if panniculitis (inflammation of the subcutaneous fat) is suspected, the shave technique would not provide the proper tissue required to establish or exclude this diagnosis (Table 0.8). Similarly, in the case of a benign-appearing exophytic lesion such as a verruca or skin tag, it would not be expedient, economical, or even cosmetically savvy to remove the lesion via an excision with sutured closure.

- ***Superficial shave biopsy*** **–** often employed when the pathologic process is primarily epidermal (e.g. pigmented actinic keratosis or Bowen's disease versus macular seborrheic keratosis) or when removing exophytic benign lesions such as intradermal melanocytic nevi. If the diagnostic histopathologic findings are

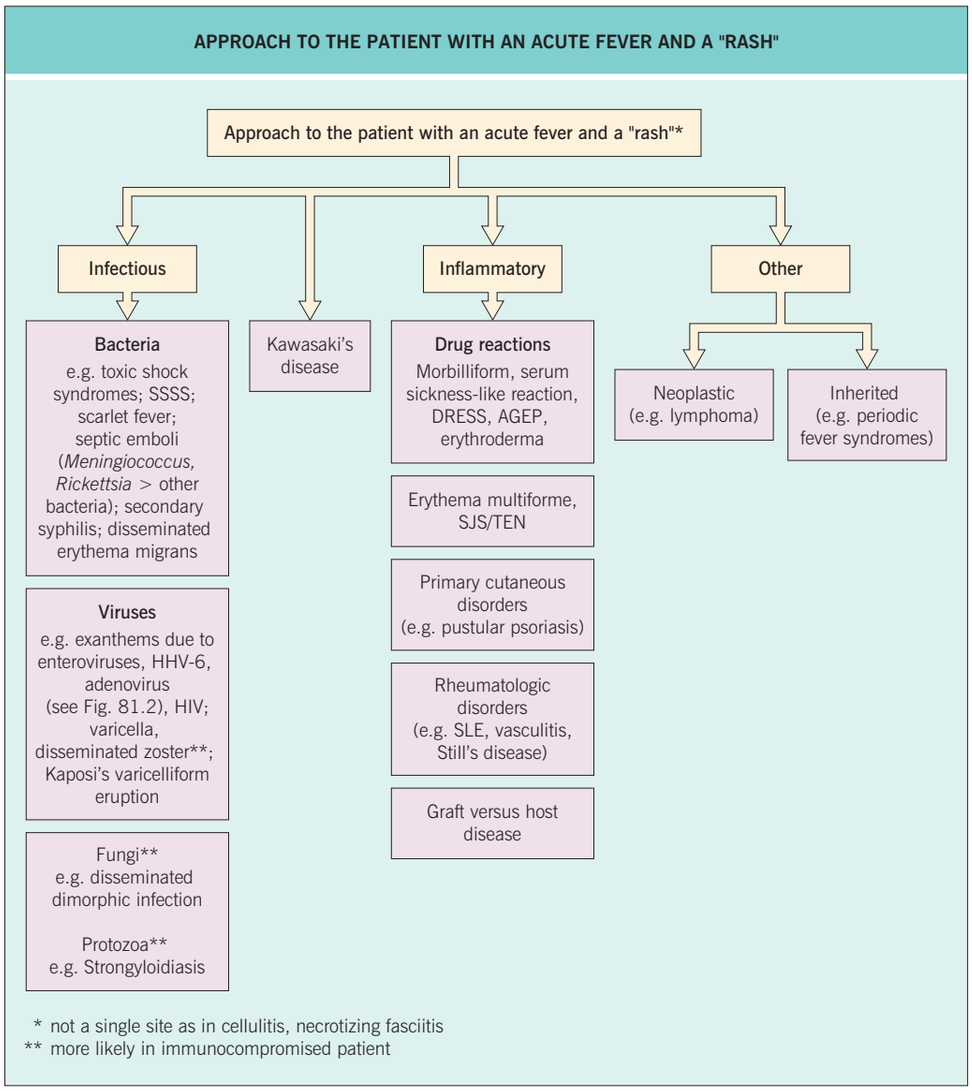


Fig. 0.10 Approach to the patient with an acute fever and a "rash". AGEP, acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms (also referred to as drug-induced hypersensitivity syndrome [DIHS]); HHV, human herpes virus; HIV, human immunodeficiency virus; SJS, Stevens-Johnson syndrome; SLE, systemic lupus erythematosus; SSSS, staphylococcal scalded skin syndrome; TEN, toxic epidermal necrolysis.

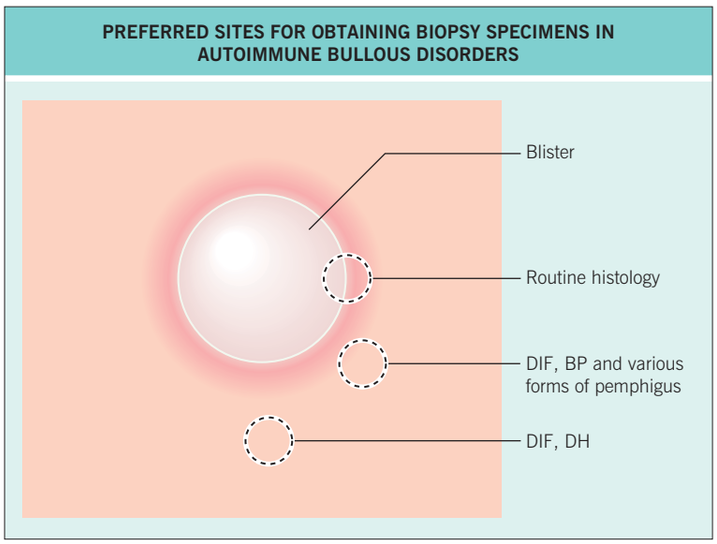


Fig. 0.11 Preferred sites for obtaining biopsy specimens in autoimmune bullous disorders. If the edematous papule or vesicle is small enough, it can be removed in its entirety for routine histology. Otherwise, a biopsy specimen that includes the inflammatory rim as well the edge of a fresh vesicle or bulla is appropriate. In bullous pemphigoid (BP) and pemphigus vulgaris a perilesional biopsy is done for direct immunofluorescence (DIF), whereas in dermatitis herpetiformis (DH), nearby normal skin is preferred for DIF.

present in the mid to deep dermis (e.g. discoid lupus erythematosus versus lichen planus, Spitz nevus versus melanoma), a superficial shave biopsy will often fail to provide all the information necessary to establish the diagnosis.

- ***Deep shave/saucerization biopsy*** – a deeper variant of the superficial shave biopsy. In the latter, the path of the blade is nearly parallel to the surface of the skin, whereas in a saucerization, the greater angle of the blade can lead to removal of the mid to deep dermis (see Fig. 0.12B). This technique is often used to biopsy neoplasms (e.g. squamous cell carcinoma versus hypertrophic actinic keratosis), and there is evidence to suggest that, when properly performed, its diagnostic value is nearly equal to that of most incisional/excisional procedures[22]. Clearly, many factors are considered when choosing between these two techniques.
- ***Punch biopsy*** – preferred for skin conditions in which the suspected pathology is within the dermis and when it is thought that a partial sampling will be representative of the entire lesion or process. The diameters of commercially available punch biopsy instruments range from 1.5 to 8.0 mm, and when the entire lesion is removed, then the issue of sampling error is rendered moot. It is controversial whether punch biopsies, even when performed in a stacked fashion, can provide adequate tissue for assessment of deeply infiltrating tumors or the full thickness of the subcutaneous fat. There are multiple studies that have shown that *partial* punch biopsies of melanocytic neoplasms can lead to erroneous diagnoses.

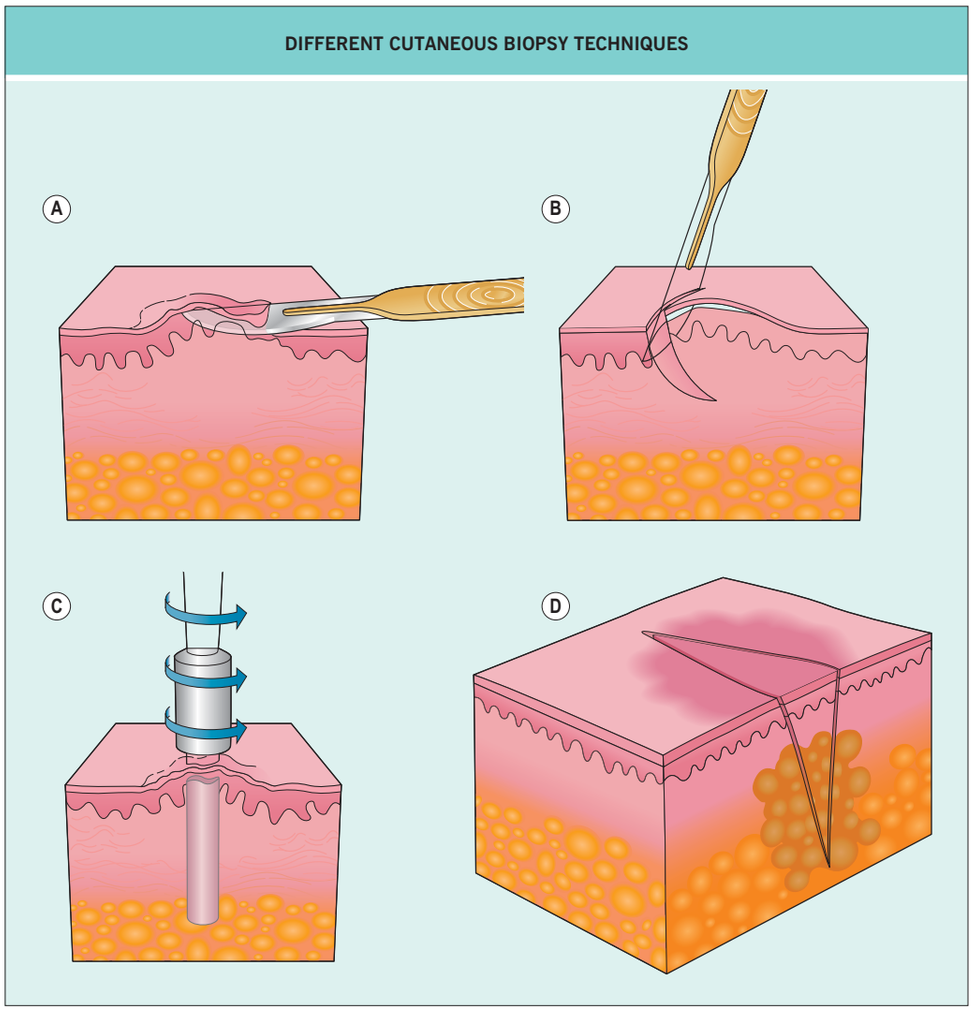


Fig. 0.12 Different cutaneous biopsy techniques. The size, topography, depth and site of the lesion, as well as the clinical differential diagnosis, influence the type of biopsy technique that is performed. **A** Superficial shave biopsy. **B** Deep shave biopsy (saucerization). **C** Punch biopsy. **D** Incisional biopsy. For more details, see text and Chapter 146. *Courtesy, Suzanne Olbricht, MD.*

OPTIMIZING INFORMATION OBTAINED FROM A SKIN BIOPSY SPECIMEN (BASED UPON PRESUMED DIAGNOSIS)

INFLAMMATORY DISEASES				
Disorders (presumed)	**Where and when to biopsy**	**Preferred technique**	**Pitfalls**	**Ancillary techniques to consider**
Vasculitides	• Center of an early lesion • Prefer sites above the knee to avoid poor wound healing or background features due to venous hypertension	Punch or incisional biopsy (depending on the size of affected vessels)	Necrotic or ulcerated lesions may be non-diagnostic	Direct immunofluorescence (early lesions, not older than 24 h)
Livedo reticularis	• Center of the pale areas defined by the surrounding venous plexus network • Corresponds to the site of the ascending arteriole (see Fig. 106.1)	Punch or incisional biopsy	Biopsy of the venous plexus or a biopsy that is too superficial can lead to false-negative results	
Autoimmune connective tissue diseases	• Fully developed lesion • In DLE, biopsy areas of inflammation, not scarred areas	Primarily punch biopsy, unless panniculitis is suspected	• In DLE, biopsies of non-inflammatory scarred areas are often non-diagnostic • Changes of acute LE may be subtle	Direct immunofluorescence of lesional skin
Panniculitides	Early evolving to fully developed lesion	Large and deep incisional biopsy (must include subcutaneous fat)	• Failure to include enough fat • Late-stage lesions often have nonspecific findings	• Fresh tissue culture and/or PCR (if infectious etiology suspected) • Direct immunofluorescence (if vasculitis suspected)

Table 0.8 Optimizing information obtained from a skin biopsy specimen (based upon presumed diagnosis). DLE, discoid lupus erythematosus; h, hour; LE, lupus erythematosus; PCR, polymerase chain reaction. *Table created with the assistance of Dr Stefano Titli.* *Continued*

OPTIMIZING INFORMATION OBTAINED FROM A SKIN BIOPSY SPECIMEN (BASED UPON PRESUMED DIAGNOSIS)

INFLAMMATORY DISEASES

Disorders (presumed)	Where and when to biopsy	Preferred technique	Pitfalls	Ancillary techniques to consider
Autoimmune blistering disorder	• An edematous papule/plaque or an early vesicle is preferred • If only large bullae are present, biopsy the edge of the bulla plus surrounding inflamed skin	Punch biopsy (e.g. 4 mm) or saucerization of: edematous papule/plaque, entire small vesicle, or edge of fresh, intact vesicle/bulla plus surrounding inflamed skin	• Biopsy of late-stage bullae undergoing re-epithelialization may lead to erroneous diagnosis • Late-stage, purulent, crusted or ulcerated lesions may be non-diagnostic	Direct immunofluorescence of perilesional skin (Fig. 0.11) or nearby skin (if dermatitis herpetiformis)
Alopecias	• Active advancing edge • Areas of perifollicular inflammation	• 4–6 mm punch biopsy oriented parallel to the direction of hair • Include subcutaneous fat	Scarred areas show only end-stage fibrosis	Vertical and horizontal sectioning of biopsy Direct immunofluorescence
Infectious diseases	• Prefer mature lesions • If ulcerated, include inflammatory border	Punch biopsy or incisional biopsy (for deep-seated infections)	• Organisms may not be appreciated in histologic sections • Fresh tissue culture and/or PCR may be necessary	Fresh tissue culture and/or PCR
Ulcerative dermatoses	Active edge of the ulcer or early lesion if the spectrum of lesions includes a pre-ulcerative stage (e.g. pyoderma gangrenosum)	Punch or incisional biopsy	Avoid center of ulcer where nonspecific changes or possible misleading secondary changes such as vasculitis	Fresh tissue culture and/or PCR (if infectious etiology suspected)
Pigmentary disorders	Include the edge of the lesion as well as normal skin for comparison	Punch biopsy, rarely incisional biopsy	Subtle findings require clinicopathologic correlation	Special stains and/or immunohistochemistry may be necessary
Urticaria	Include the edge of the lesion as well as normal skin for comparison	Punch biopsy	Small-diameter punch biopsies may lead to false-positive results as retraction of collagen bundles may simulate interstitial edema	Direct immunofluorescence (if urticarial vasculitis is suspected)

NEOPLASTIC PROCESSES

Disease	Preferred technique*	Pitfalls
Melanocytic neoplasms	Excisional biopsy (preferred when melanoma is reasonably suspected) Saucerization that includes the entire lesion When major differential diagnosis is macular seborrheic keratosis vs lentigo maligna, broad shave technique Other techniques may be appropriate depending upon the circumstances and the degree of suspicion	Partial (subtotal) punch biopsy or superficial shave biopsy may not be representative of the entire process
Keratinocytic neoplasms	Punch, saucerization, or excisional biopsies	Partial (subtotal) punch biopsy or superficial shave biopsy may not be representative of the entire process or allow assessment for possible dermal invasion
Dermal neoplasms	Punch or excisional biopsy	Partial (subtotal) punch biopsy or superficial shave biopsy may not be representative of the entire process
Deep-dermal and/or subcutaneous neoplasms	Excisional biopsy	Partial (subtotal) punch biopsy or superficial shave biopsy may not be representative of the entire process
Lymphoma and leukemia cutis	Punch or excisional biopsy When major differential diagnosis is patch-stage mycosis fungoides vs parapsoriasis, broad saucerization may be performed	Partial (subtotal) punch biopsy or superficial shave biopsy may not be representative of the entire process Crush artifact is common when lymphocytic infiltrates are sampled via a small-diameter punch biopsy

*On occasion, surgical/clinical/cosmetic constraints may, in the patient's best interest, require consideration and performance of an alternative technique, or even a subtotal biopsy, with acceptance of limitations upon the diagnostic result.

Table 0.8 Optimizing information obtained from a skin biopsy specimen (based upon presumed diagnosis) (cont'd). PCR, polymerase chain reaction. *Table created with the assistance of Dr Stefano Titli.*

- ***Incisional/excisional biopsy –*** removal of either a portion of a lesion (incisional) or the entire lesion (excisional) via a scalpel and standard surgical techniques (see Ch. 146; see Fig. 0.12D). The former is often used for disorders in which assessment of the subcutaneous fat is critical (e.g. panniculitis), while the latter is employed when the leading clinical diagnosis is invasive cutaneous melanoma and the size of the lesion allows for this procedure.

Methods for optimizing the amount of critical information one can obtain from a biopsy specimen, based on the suspected cutaneous disease, are outlined in Table 0.8.

Post-procedure handling of the skin biopsy

Even after the specimen has been obtained, it must be handled carefully. For example, if there is excessive lateral pressure, especially when exerted on small punch biopsy specimens, by forceps, a distortion of cellular infiltrates can occur ("crush" artifact). Lymphocytes are particularly susceptible to crush artifact, and when present, it may be impossible to render an accurate diagnosis.

For routine histologic study, the specimen is fixed in a buffered 10% formalin solution, with a volume 10–20 times that of the tissue itself, to prevent underfixation. For microbial tissue culture, the specimen is instead placed in a sterile container with a small amount of non-bacteriostatic saline (simply a few drops to keep it moist) and routed immediately to the laboratory. Specimens must be flash-frozen or placed in specialized transport medium (Michel's solution at room temperature) for direct immunofluorescence microscopy, while fixation in paraformaldehyde and glutaraldehyde in a cacodylate buffer is required for electron microscopy. To obtain the most information from the histologic examination, the biopsy should be accompanied by data

regarding the age and sex of the patient, anatomic site, pertinent and precise physical findings, and the differential diagnosis. Any treatments that might influence the histologic findings, as well as special instructions, such as inking eccentric pigmentation in a melanocytic neoplasm or sectioning longitudinally, should also be included. Addition of drawings or clinical photographs, especially when the case is difficult or complex, may prove useful.

Diagnosis of Inflammatory Skin Diseases by Pattern Analysis

First conceived by Dr Hermann Pinkus, but more firmly established by Dr A Bernard Ackerman[23–25], histopathologic assessment via pattern analysis has become the primary classification scheme for inflammatory skin diseases (Fig. 0.13). While the number of patterns and their

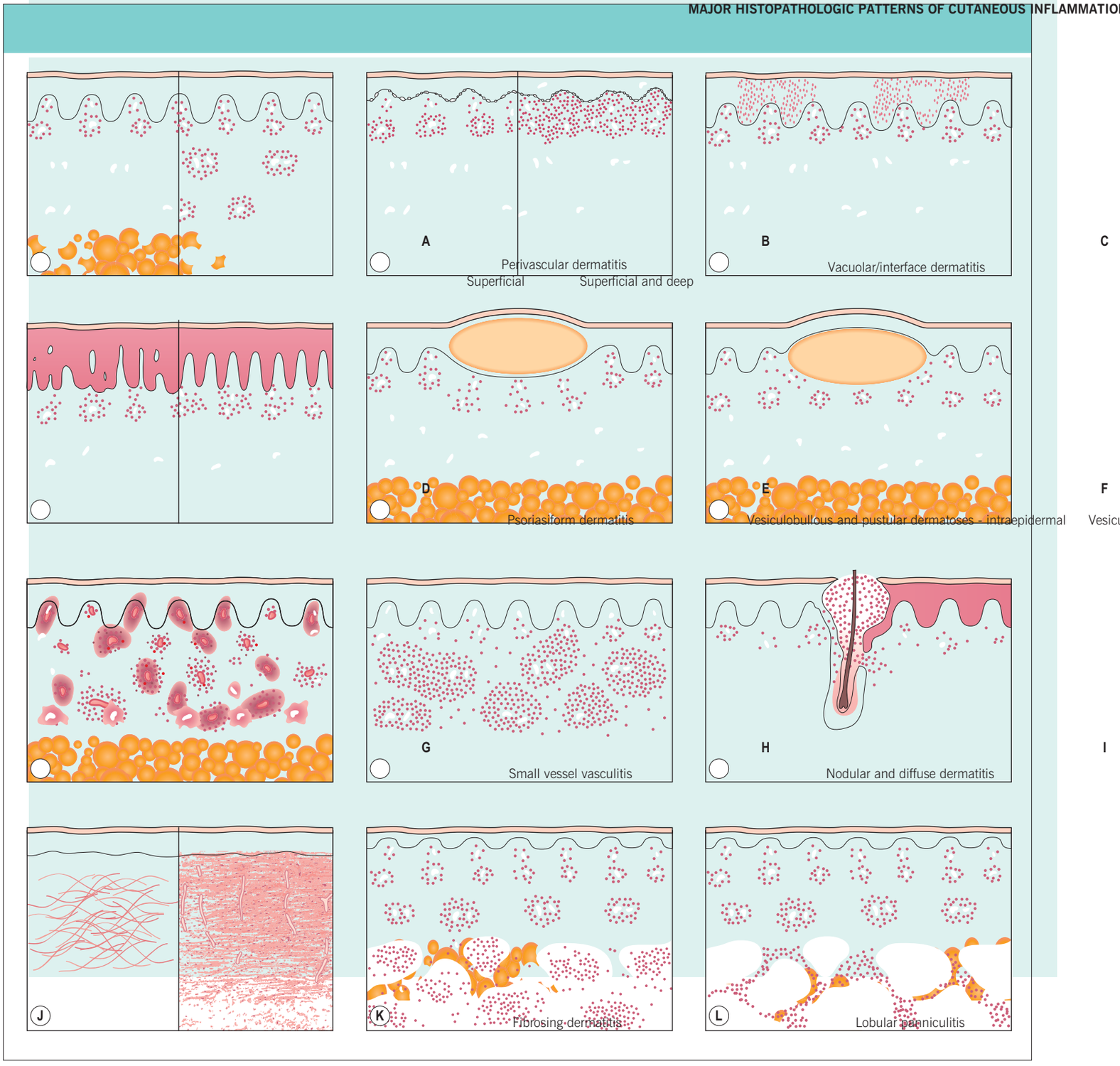


Fig. 0.13 Basic histopathologic patterns of cutaneous inflammation (based upon Ackerman's classification). Basic patterns of inflammation result primarily from the distribution of the inflammatory cell infiltrate within the dermis and/or the subcutaneous fat (e.g. nodular, perivascular). It also reflects the character of the inflammatory process itself (e.g. pustular), the presence of injury to blood vessels (e.g. vasculitis), involvement of hair follicles (e.g. folliculitis), abnormal fibrous dermal and/or subcutaneous tissue, and formation of vesicles and bullae. *Adapted from Ackerman AB. Histologic Diagnosis of Inflammatory Skin Diseases: A Method by Pattern Analysis. Philadelphia: Lea & Febiger, 1978.*

descriptors may vary, the basic principle is generally the same – once a major pattern has been identified, further histologic details are used to progressively, and more specifically, subcategorize the disease process until a final diagnosis is rendered.

The principal advantages of pattern analysis are that it is algorithmic and reproducible and serves to minimize personal subjectivity. However, the method has two important limitations; namely, it is based on artificial disease categories and does not include every single possible pattern. Furthermore, while pattern analysis clearly narrows the differential diagnosis, the final diagnosis may require clinical correlation or ancillary laboratory testing.

Ten patterns defined

Over the past several decades, a number of classification schema based upon pattern analysis have been proposed, with the number of patterns varying from as few as 9 up to 28 or even more. In this introductory chapter, 10 major patterns will be discussed.

Perivascular dermatitis

This common pattern is defined and recognized by the presence of an inflammatory infiltrate that is arranged primarily around dermal blood vessels (Fig. 0.14). Traditionally, perivascular dermatitis has been subdivided into "superficial" and "superficial and deep" variants, and while this division has some diagnostic value, histologically there is considerable overlap. In addition, inflammatory skin diseases can exhibit a spectrum of findings, depending in part on severity, duration and stage (acute vs chronic) of an individual lesion.

Once a perivascular pattern is identified (see Fig. 0.13A), the next step in the algorithm is to determine: (1) if there are accompanying epidermal changes; and (2) the types of inflammatory cell(s) present within the infiltrate, e.g. lymphocytes, neutrophils, eosinophils, plasma cells. There are disorders in which classically no detectable changes are seen within the epidermis, e.g. deep gyrate erythemas (see Ch. 19). Also, when an inflammatory process is just beginning or is resolving, epidermal changes may be subtle. A search is then required to detect a hint of *spongiosis* (intercellular edema of the epidermis), *parakeratosis* (aberrant retention of nuclei in the stratum corneum), extravasated erythrocytes, or subtle *interface* and *vacuolar changes* (see below), in an attempt to refine the diagnosis.

Interface dermatitis

This pattern is characterized by the presence of inflammation and/or degenerative change(s) at the dermal–epidermal junction (see Fig. 0.13B). Morphologically, this pattern may be subdivided into primarily *vacuolar* (degeneration of basilar keratinocytes with little or no inflammation; Fig. 0.15) versus primarily *lichenoid* (with lymphocytes directly engaged in the destruction of basilar keratinocytes; Fig. 0.16), but frequently there is overlap between these two categories.

It is important to remember that even though an entity has lichenoid features histologically (e.g. fixed drug eruption), that does not mean it must resemble lichen planus clinically. Also, some degree of lichenoid inflammation can be associated with a variety of benign and malignant neoplasms of the skin – e.g. solitary lichenoid keratosis and melanoma,

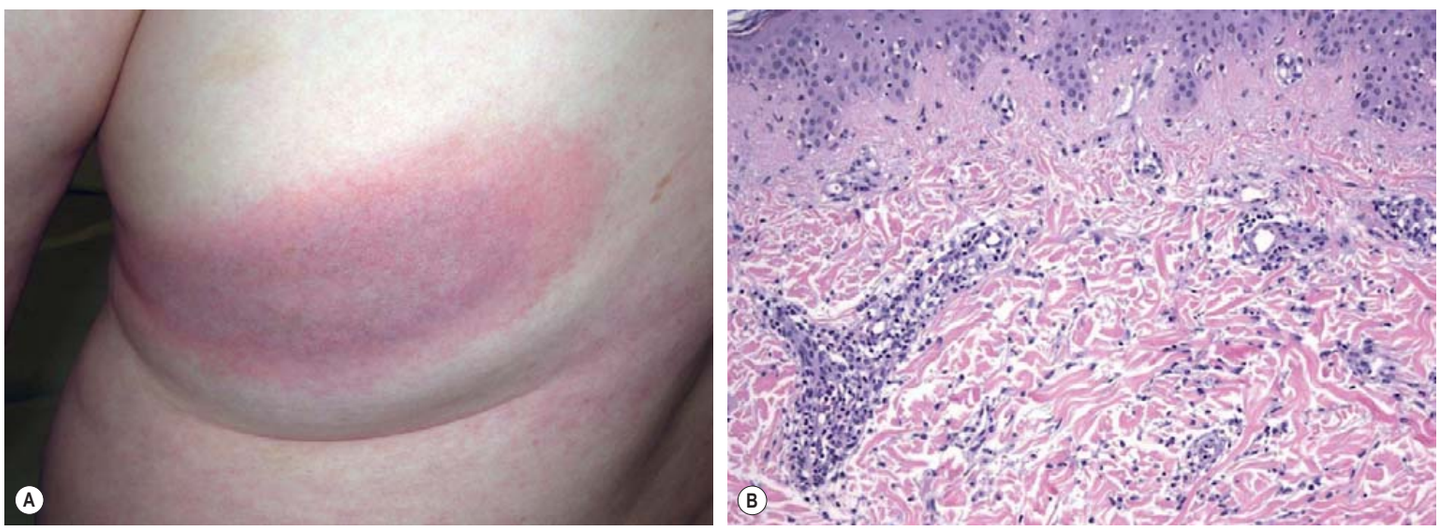


Fig. 0.14 Perivascular dermatitis. A Erythema migrans. **B** Perivascular inflammatory infiltrate composed of lymphocytes admixed with a few plasma cells. *A, Courtesy, Dennis Cooper, MD, and Frank Samarin, MD. B, Courtesy, James Patterson, MD.*

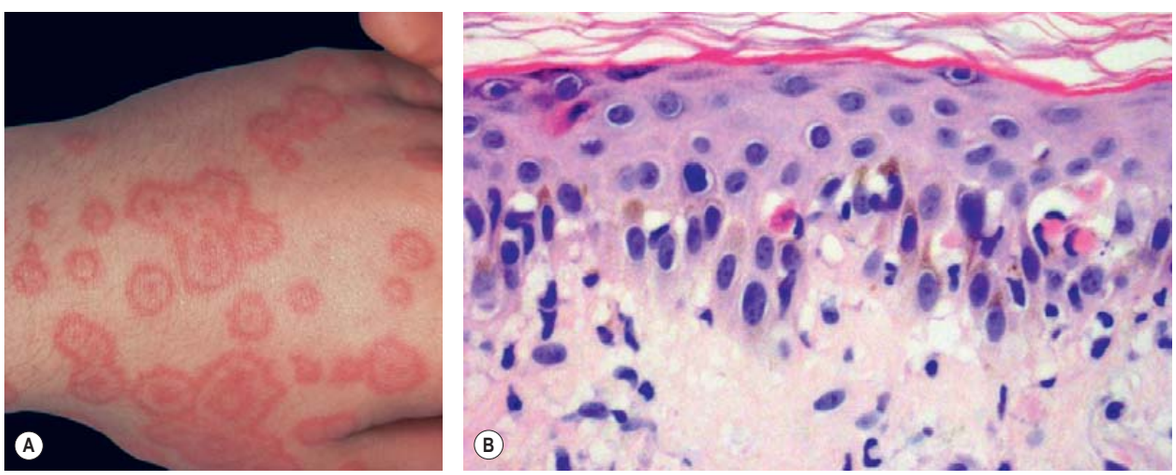


Fig. 0.15 Interface dermatitis, vacuolar type. A Erythema multiforme with target lesions. **B** Vacuolar alteration along the dermal–epidermal junction in association with exocytosis of lymphocytes and several necrotic keratinocytes.

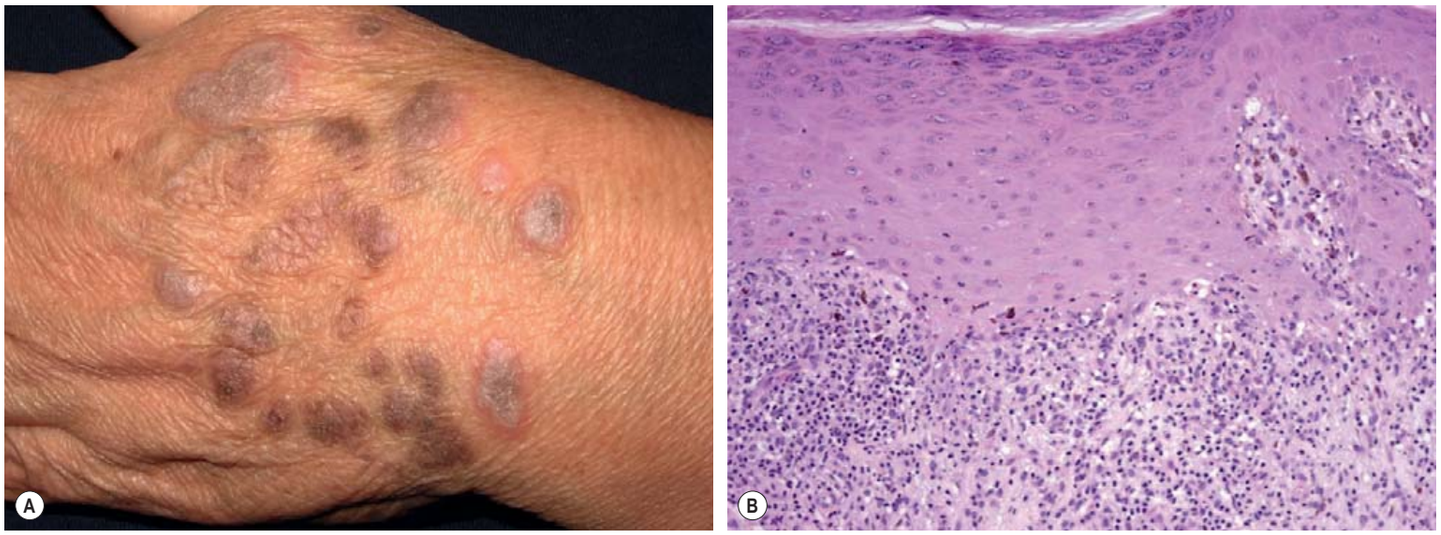


Fig. 0.16 Interface dermatitis, lichenoid type. A Lichen planus. **B** Band-like infiltrate of lymphocytes that obscures the dermal–epidermal junction in addition to jagged epidermal hyperplasia, hypergranulosis and melanophages. *A, Courtesy, Frank Samarin, MD; B, Courtesy, James Patterson, MD.*

respectively. In these instances, it appears to represent an attempted immunological response to the tumor.

Spongiotic dermatitis

A large number of inflammatory skin diseases have histologic evidence of *spongiosis* (intraepidermal edema) that manifests as widened spaces between keratinocytes with elongation of intercellular bridges (see Fig. 0.13C), usually in association with *exocytosis* of lymphocytes (exit of inflammatory cells from the vasculature with migration into the epidermis). The degree of spongiosis may vary from microscopic foci to grossly visible vesicles and even intraepidermal bullae.

Spongiotic dermatoses may be further subdivided into acute, subacute and chronic forms. In acute spongiotic dermatitis, the spongiosis is often severe, sometimes resulting in microvesicles within the stratum corneum (Fig. 0.17). Parakeratosis often overlies subacute spongiotic dermatitis, while in chronic spongiotic dermatitis, spongiosis may actually be difficult to appreciate, being overshadowed by epidermal *acanthosis* (thickening of the epidermis). Also, a predominance of other types of inflammatory cells, such as eosinophils or neutrophils, in association with a spongiotic dermatitis may serve as a clue to a hypersensitivity component or infectious aspect to the disease, respectively.

Lastly, it is important to recognize that many dermatologic disorders with eczematous features, such as allergic contact dermatitis, atopic dermatitis, nummular dermatitis and seborrheic dermatitis, may have histologic evidence of spongiosis, but this pattern is not exclusive to those diseases. In other words, spongiosis may also be seen as a reactive epidermal component of other disorders that would be better classified as having another pattern (see Fig. 0.13).

Psoriasiform dermatitis

The term "psoriasiform" refers to a regular pattern of *epidermal hyperplasia* (elongation of the rete ridges; see Fig. 0.13D) that is observed not just in psoriasis, but also in a wide spectrum of longstanding conditions. Clinically, this group of disorders is characterized by thickened, scaly papules and plaques (Fig. 0.18). Psoriasiform dermatoses may be subdivided into those diseases that are exclusively psoriasiform, as well as those that are associated with another pattern (e.g. psoriasiform *and* lichenoid; psoriasiform *and* spongiotic).

Pseudoepitheliomatous hyperplasia represents a related, but exaggerated, irregular hyperplasia of the epidermis. It may occur in response to a range of insults to the skin, such as chronic rubbing or scratching in lichen simplex chronicus and prurigo nodularis, as well as various inflammatory, neoplastic and infectious skin diseases (e.g. hypertrophic lupus erythematosus, halogenodermas, chromoblastomycosis). As with spongiotic dermatitis, psoriasiform dermatitis is a histologic concept,

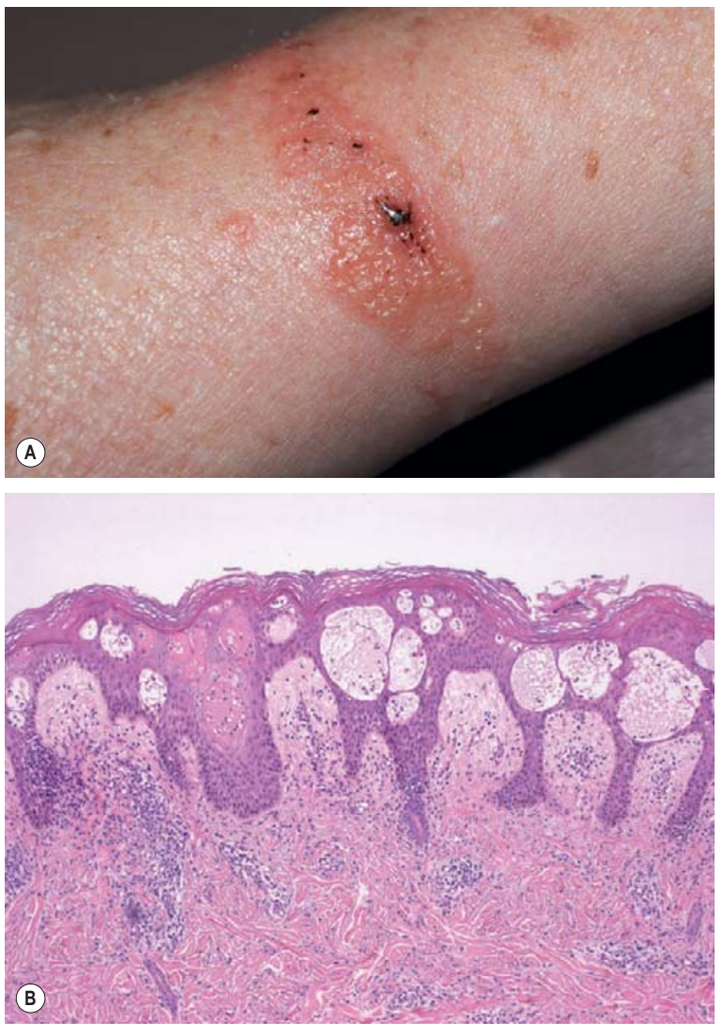


Fig. 0.17 Spongiotic dermatitis. A Acute allergic contact dermatitis to *Toxicodendron radicans* (poison ivy). The central black discoloration is due to the plant's resin. **B** Intercellular edema (spongiosis) and vesicle formation within the epidermis. Lymphocytes are also seen in both the epidermis and dermis. *A, Courtesy, Kalman Watsky, MD, B, Courtesy, James Patterson, MD.*

not a specific clinical diagnosis. Its presence mandates consideration of a variety of skin diseases that share this constellation of histopathologic findings.

Vesiculobullous and pustular dermatoses

Intraepidermal (see Fig. 0.13E)

The concept of intraepidermal vesiculation due to spongiosis has been addressed above, but there exist other disease mechanisms that may lead to intraepidermal vesicles or bullae, e.g. acantholysis, ballooning degeneration. *Acantholysis* refers to discohesion of keratinocytes as a consequence of the disruption of desmosomes (intercellular connections) and this can lead to an intraepidermal vesicle or bulla (Fig. 0.19). Although acantholysis may occur at any level of the epidermis, the location of the blister is often used as a clue to the underlying disorder; for example, superficial (subcorneal) acantholysis favors pemphigus foliaceus, while acantholysis in the deeper aspects of the epidermis is more characteristic of pemphigus vulgaris. Cytotoxic events such as herpes virus infection may also yield an intraepidermal vesicle secondary to ballooning degeneration.

An intraepidermal accumulation of neutrophils may be seen in a variety of infectious and non-infectious skin diseases, and this pustule formation is viewed as a subcategory of vesiculobullous dermatoses. In early pustule formation, neutrophils are scattered within the lower portion of the epidermis, whereas later, an accumulation is noted in the upper epidermis (Fig. 0.20). In a resolving pustule, the neutrophils may even appear within scale-crust in the cornified layer.

In both vesiculobullous and pustular dermatoses, autoimmune and non-autoimmune mechanisms may be indistinguishable histopathologically, e.g. subcorneal pustular dermatosis versus IgA pemphigus. As a result, direct and indirect immunofluorescence studies are often of great utility in determining the precise diagnosis.

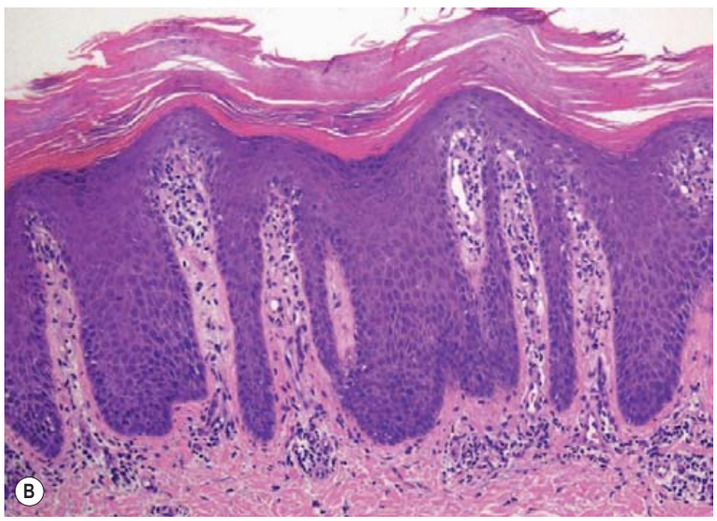


Fig. 0.18 Psoriasiform pattern. A Plaque of psoriasis vulgaris with silvery scale. **B** Regular epidermal hyperplasia and elongated dermal papillae with thin suprapapillary plates and confluent parakeratosis. The parakeratosis represents the histologic correlate of the visible scale. *A, Courtesy, Julie V Schaffer, MD.*

Subepidermal (see Fig. 0.13F)

In this subcategory, vesicle or bulla formation occurs at the junction between the epidermis and dermis (Fig. 0.21), or between the mucosa and submucosa of mucous membranes. Such clefting can be the result of autoantibodies targeting specific components of the dermal–epidermal junction (e.g. collagen XVII in bullous pemphigoid or linear IgA bullous dermatosis) or a dermal inflammatory or toxic/metabolic insult, such as in bullous cellulitis and porphyria cutanea tarda, respectively.

Within subepidermal blister cavities, the number of inflammatory cells can vary from very few, which is more characteristic of toxic insults such as porphyria cutanea tarda, to numerous, as in the majority of cases of inflammatory bullous pemphigoid. The findings often reflect the nature and mechanism of the blistering process. It is also helpful to identify the type of inflammatory cell present, e.g. eosinophil versus neutrophil, as this can serve as a clue to the diagnosis.

However, because there is considerable histologic overlap amongst the underlying disorders, the final diagnosis must depend upon cumulative information, including direct and indirect immunofluorescence microscopy, ELISA, immunoblotting, and, of course, clinicopathologic correlation.

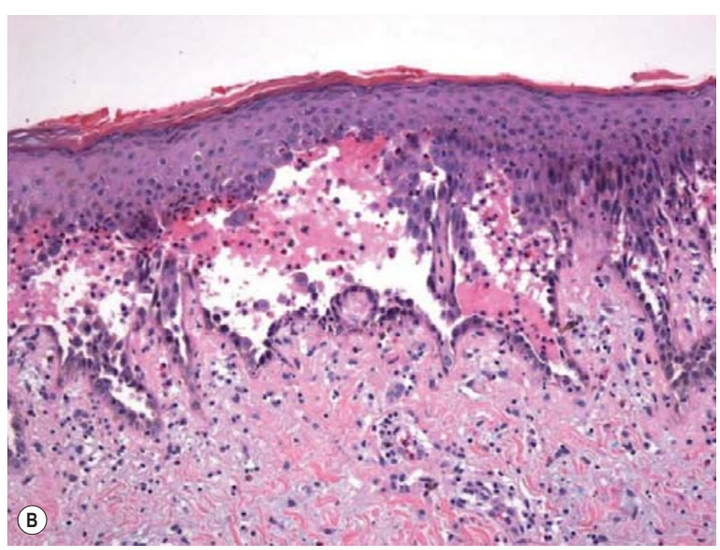


Fig. 0.19 Intraepidermal vesiculobullous dermatosis, acantholytic type. A Pemphigus vulgaris with flaccid bullae and erosions. **B** The keratinocytes within the lower epidermis have lost their intercellular attachments and have separated from one another, resulting in an intraepidermal blister. *A, Courtesy, Louis A Fragola, Jr, MD.*

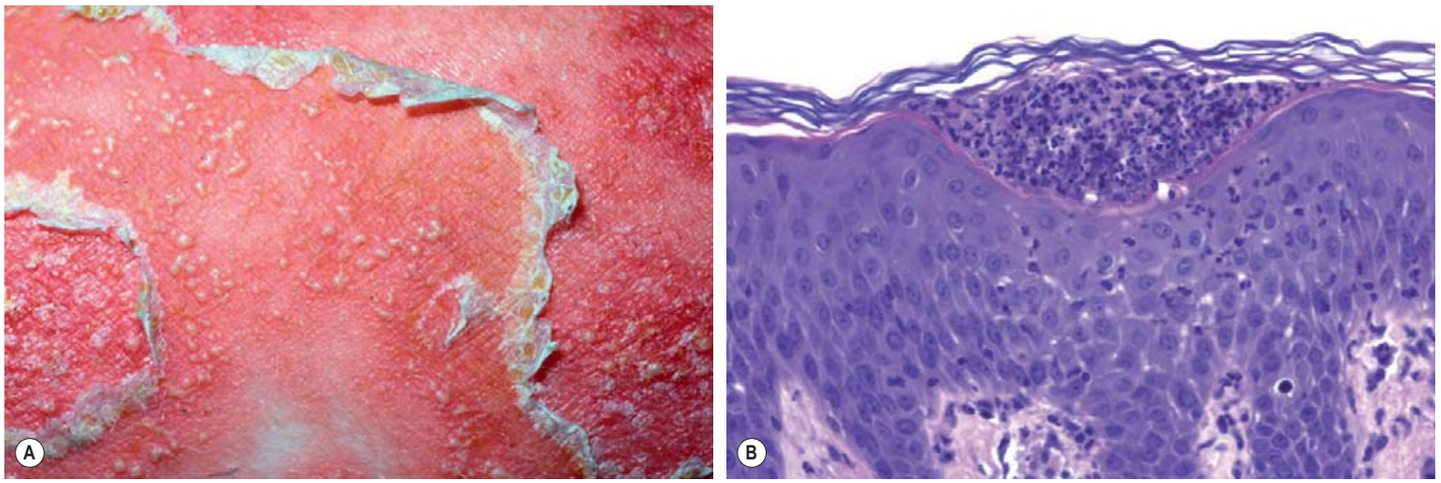


Fig. 0.20 Intraepidermal pustular dermatosis. A Pustular psoriasis. **B** Collection of neutrophils beneath the stratum corneum (subcorneal pustule). Scattered neutrophils are in the upper malpighian layer. *A, Courtesy, Kenneth Greer, MD; B, Courtesy, James Patterson, MD.*

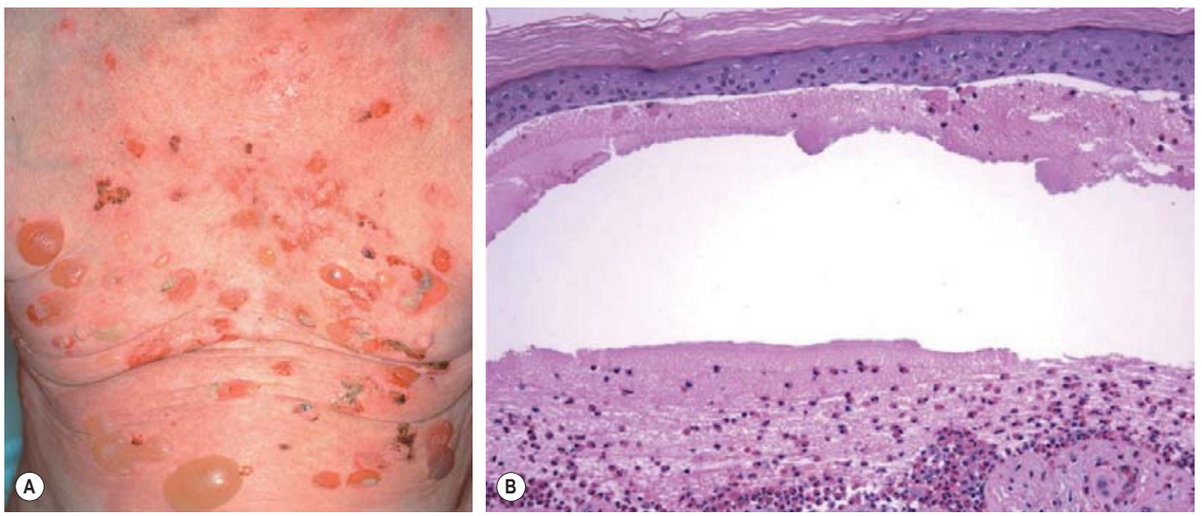


Fig. 0.21 Subepidermal vesiculobullous dermatosis. A Bullous pemphigoid with tense bullae. **B** Subepidermal blister with numerous eosinophils within the blister cavity. *B, Courtesy, James Patterson, MD.*

Vasculitis/pseudovasculitis

Vasculitis refers to inflammatory damage to and destruction of blood vessels, leading to the deposition of fibrin and/or thrombus formation (see Fig. 0.13G). The histopathologic classification of vasculitides is based on the size of the vessel involved (small, medium-sized or large vessel vasculitis; see Ch. 24) and the predominant inflammatory cell mediating the damage (neutrophils or lymphocytes more often than eosinophils or histiocytes).

In dermatopathology, the most common form of vasculitis is *leukocytoclastic vasculitis* (Fig. 0.22), a process mediated by neutrophils and primarily affecting the post-capillary venule. Leukocytoclastic vasculitis is initiated by the deposition of circulating immune complexes within and around vessel walls, with neutrophils later recruited to the site of deposition. This is followed by *leukocytoclasia* (nuclear fragmentation) and the deposition of fibrin during the ensuing vessel destruction. In some longstanding disorders that feature leukocytoclastic vasculitis, such as erythema elevatum diutinum, concentric fibrosis may evolve over time.

The concept of *lymphocytic vasculitis* is less well defined, but it is a term used to denote an inflammatory process in which there may be some fibrinoid necrosis of the vessel wall but the mediating cell is a lymphocyte. It is postulated as a mechanism chiefly in disorders such as pernio, Sneddon syndrome, and pityriasis lichenoides et varioliformis acuta, although the latter lacks fibrinoid necrosis.

Granulomatous vasculitis is defined by the presence of histiocytes (macrophages) within and around blood vessel walls in association with fibrin and/or degenerative and necrotic changes. Like lymphocytic vasculitis, it is a pattern observed in a restricted spectrum of diseases, often in association with autoimmune connective tissue diseases, and it may very well represent a later evolutionary stage of another form of vasculitis, either leukocytoclastic or lymphocytic.

In *medium-sized vessel cutaneous vasculitis*, there is involvement of the blood vessels at the dermal–subcutaneous junction and within the septa of the subcutaneous fat (Fig. 0.23). For dermatopathologists, polyarteritis nodosa is the most commonly encountered entity in this category. Temporal arteritis represents a form of large vessel vasculitis, but biopsies of this artery are rarely done by dermatologists.

Pseudovasculitis refers to a group of heterogeneous, non-inflammatory conditions that are broadly classified into disorders that primarily cause hemorrhage (*non-inflammatory purpuras*) and those that primarily occlude vessels (*occlusive vasculopathies*) (see Chs 22 & 23). Many of these disorders involve dermal hemorrhage and/or occlusion of vessels by emboli, thrombi, vasospasm, fibro-intimal-medial hyperplasia secondary to vessel trauma, or non-inflammatory

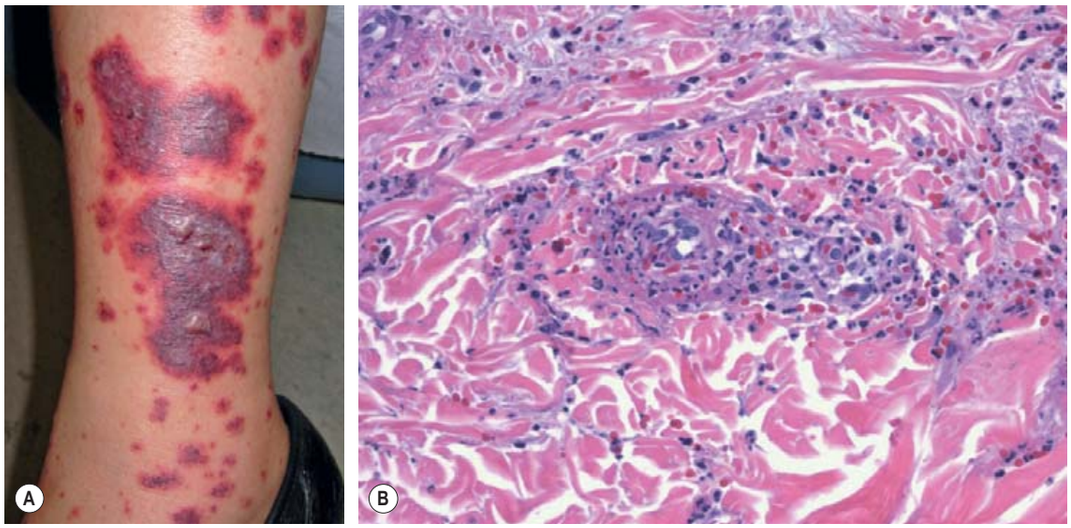


Fig. 0.22 Small vessel vasculitis. **A** Inflammatory palpable purpura of the leg. **B** Perivascular and interstitial infiltrate of neutrophils with nuclear dust (leukocytoclasia). Fibrin within the vessel wall and extravasation of erythrocytes is also seen. *B, Courtesy, James Patterson, MD.*

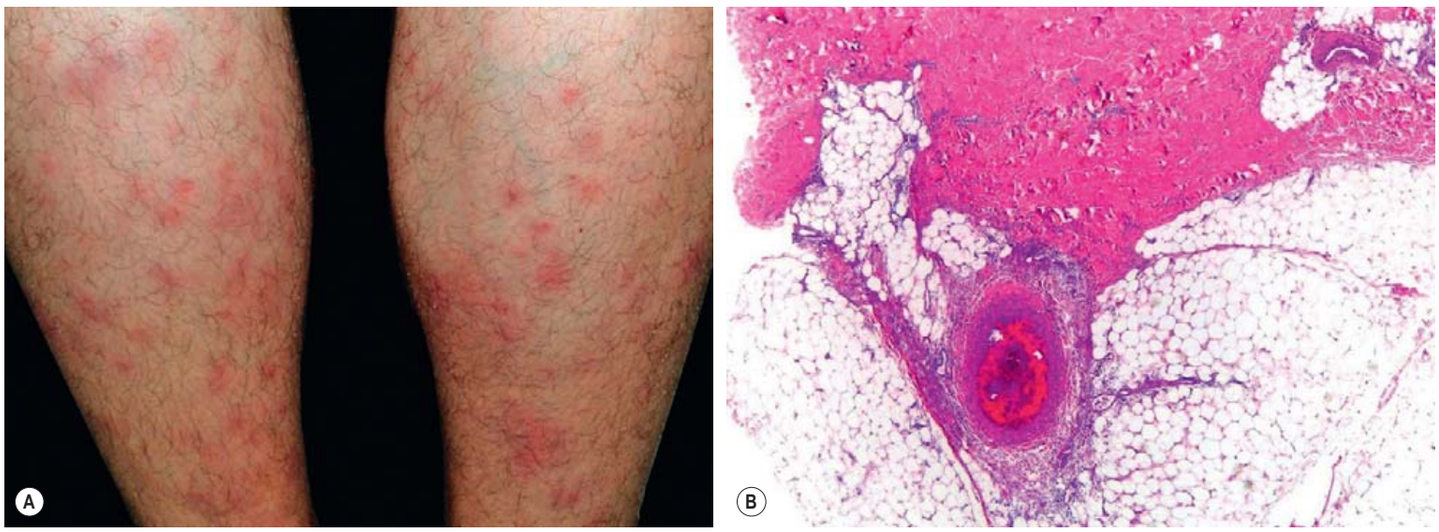


Fig. 0.23 Medium-sized vessel vasculitis. **A** Nodules of cutaneous periarteritis nodosa. **B** Inflammation and destruction of a subcutaneous arteriole.

vessel wall pathology such as calcification, cholesterol emboli, and amyloid deposition.

Nodular and diffuse dermatitis

Nodular dermatitis is somewhat similar to perivascular dermatitis, but the inflammatory infiltrate has enlarged and coalesced to form one or multiple nodules within the dermis (see Fig. 0.13H). Further expansion of the nodules can essentially fill the entire dermis, yielding the diffuse pattern (Fig. 0.24).

The nodular and diffuse pattern of dermatitis may be further subdivided, based chiefly upon the predominant inflammatory cell type. When *histiocytes* (macrophages) predominate in a nodular or diffuse infiltrate in one or more foci, the pattern is defined as *granulomatous*. Typically, in *foreign body granulomas*, the macrophages, over time, tend to fuse and multinucleate rather than divide, leading to foreign body giant cells. Two other forms of multinucleated macrophages (i.e. giant cells) are frequently observed in granulomatous dermatitides, namely the *Langhans type* and the *Touton type* of giant cells. Although none of these giant cells is pathognomonic or exclusive to just one disease, some disorders are characterized by the conspicuous presence of one or more of these three types of giant cells (e.g. Touton giant cells in juvenile xanthogranuloma).

Based on the constituent cells and other distinctive features, four major histopathologic types of granulomas can be identified (Fig. 0.25):

- *Tuberculoid* granulomas (see Fig. 0.25A) – comprised of epithelioid histiocytes, including multinucleate forms, surrounded by a dense infiltrate of lymphocytes and plasma cells; caseation may be present centrally. The *Langhans type* of multinucleated giant cell, with a horseshoe-like arrangement of nuclei, may be observed within tuberculoid granulomas. This type of granuloma is associated with cutaneous infections (e.g. *Mycobacterium tuberculosis*) and is seen in lupus miliaris disseminatus faciei.
- *Sarcoidal* granulomas (see Fig. 0.25B) – composed of discrete collections of epithelioid macrophages with only a sparse number of peripheral lymphocytes or plasma cells (i.e. a "naked" granuloma). While multinucleated cells may be identified, no particular type is associated with sarcoidal granulomas.
- *Palisaded ("necrobiotic")* granulomas (see Fig. 0.25C) – characterized by an infiltrate of epithelioid macrophages aligned in a rim around a central area of *necrobiosis* (altered connective tissue with different tinctorial qualities such as increased basophilia or eosinophilia). Of note, not all palisaded granulomas

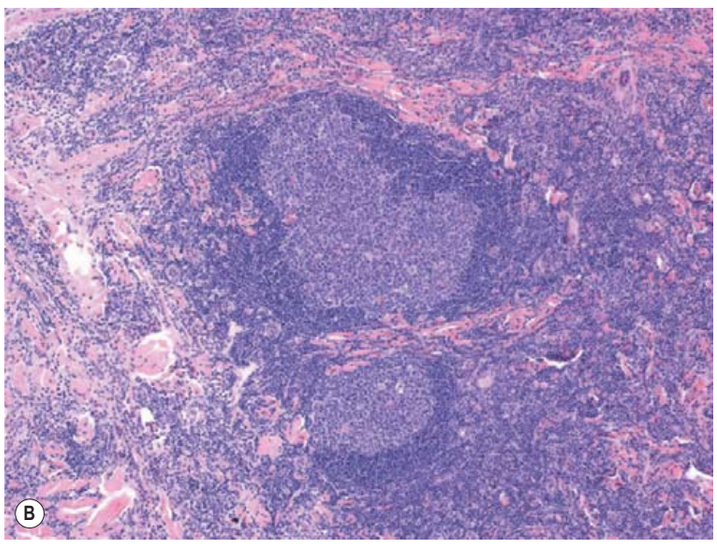


Fig. 0.24 Nodular and diffuse dermatitis, lymphocytic. A Cutaneous lymphoid hyperplasia. **B** Dense dermal infiltrate containing lymphoid follicles with formation of germinal centers. *B, Courtesy, James Patterson, MD.*

are truly *palisaded* (with a rim of aligned histiocytes), and in fact, the histiocytes may also be distributed interstitially, in strands or cords between and amongst collagen bundles (*interstitial granuloma*).

- *Suppurative* granulomas (see Fig. 0.25D) – typified by collections of neutrophils within, and sometimes among or surrounding, aggregates of epithelioid macrophages. Suppurative granulomas may be induced by infectious agents and foreign body material.

In general, all granulomatous infiltrates, but particularly tuberculoid, sarcoidal and suppurative forms, require exclusion of infectious agents and/or foreign material by special stains, immunohistochemical stains, fresh tissue culture and/or PCR, and polarization microscopy.

Nodular and diffuse infiltrates composed predominantly of histiocytes may also be further subcategorized into *Langerhans cell* and *non-Langerhans cell histiocytoses* (see Ch. 91). In Langerhans cell histiocytosis, the primary cells have the classic reniform (kidney bean-shaped) nuclei and characteristic immunohistochemical staining pattern, i.e. $S100^+$ and $CD1a^+$. Non-Langerhans histiocytes, on the other hand, have a range of both cytologic features (vacuolated, spindle-shaped, foamy, scalloped, and oncocytic) and types of admixed multinucleated giant cells (Touton type, Langhans type, foreign body type); sometimes, the histiocytes and giant cells display a homogenous "ground glass" cytoplasm. These cells are generally $S100^-$,$CD1a^-$, and $CD68^+$ (a nonspecific marker of histiocyte lineage). The varying histopathologic features of the non-Langerhans histiocytoses may possibly be related to the actual physiologic function of histiocytes within the granuloma[26].

Lastly, *xanthomas* are characterized by the accumulation of lipophages, or foamy histiocytes filled with lipid, within the dermis (see Ch. 92). It is the lipid content that imparts the yellowish hue to the lesions (Fig. 0.26). Cutaneous xanthomas may take various forms, including widespread papules (eruptive), nodules (tuberous or tendinous), and planar (xanthelasma, palmar).

Folliculitis/perifolliculitis

Folliculitis (inflammation of a hair follicle) is defined by the presence of inflammatory cells within the wall and lumen of a hair follicle (see Fig. 0.13I); perifolliculitis refers to the presence of similar cells in the adjacent dermis. Folliculitis may be due to infections (bacterial, fungal, viral, *Demodex*), drugs, occlusion, or unknown etiologies (e.g. eosinophilic folliculitis).

The classification of folliculitis (and perifolliculitis) can be made on the basis of the primary inflammatory cell (lymphocytes, neutrophils or eosinophils), the nature of the underlying pathologic process (e.g. dermatophyte infection), the temporal course (acute versus chronic), and the site of involvement along the length of the hair follicle. If the inflammatory process is severe and/or irreversibly damages epithelial stem cells located in the bulge region destruction of the hair follicle will invariably ensue with resultant scarring ("scarring alopecia"; Fig. 0.27).

Fibrosing/sclerosing conditions

Fibrosing conditions include a wide spectrum of disorders that result from altered collagen production or destruction (or both), typically related to injury or an autoimmune connective tissue disease (see Fig. 0.13J). Histopathologically, the pattern is characterized by either: (1) abnormal fibrous dermal (and sometimes subcutaneous) tissue with an increased number of fibrocytes and increased, but rather unremarkable, collagen (*fibrosis*); or (2) homogenized, abnormally enlarged and eosinophilic collagen with a paucity of admixed fibroblasts (*sclerosis*). An example of the former is nephrogenic systemic fibrosis, and the latter, morphea (Fig. 0.28) and scleroderma. Obviously, overlap between the two ends of the spectrum may occur.

Panniculitis

Panniculitis represents inflammation of the subcutis (see Fig. 0.13K,L) and it encompasses a wide range of disease processes (see Ch. 100). The diagnosis of panniculitides is difficult for both clinicians and dermatopathologists because the clinical presentation is often nonspecific and the histopathologic changes vary markedly over time and may also be rather nonspecific, especially in later stages. Adding to the challenge, biopsy specimens are often inadequate, commonly being too superficial in nature, too narrow in breadth, or too badly crushed by forceps to render a diagnosis with certainty.

An important first step in the subdivision of panniculitides is determination of the predominant location of the cellular infiltrate (Figs 0.29 & 0.30). That is, does it affect primarily the fat lobules versus the septa between the lobules versus both (mixed)? Secondly, there should be an assessment as to whether a coexisting vasculitis is present or not, and if vasculitis is detected, the size and type of the vessels involved must be determined.

With panniculitides, one must be keenly aware of the type and quality of the inflammatory infiltrate, as well as peculiarities in the pattern of fat necrosis. Early in the course of the most common form of panniculitis, erythema nodosum, the infiltrate may contain a significant number of acute inflammatory cells (neutrophils in particular), but in later stages, the infiltrate is composed chiefly of chronic inflammatory cells (lymphocytes, histiocytes and plasma cells; see Fig. 0.29). If mononuclear cells are present, the degree of cytologic atypia should be assessed, as subcutaneous panniculitis-like T-cell lymphoma may mimic an inflammatory panniculitis. Lastly, peculiarities of fat necrosis, such as the hyaline quality of the necrosis in lupus panniculitis, the basophilic saponification in pancreatic panniculitis (see Fig. 0.30), or the pseudomembranous degeneration of lipodermatosclerosis, should be appreciated.

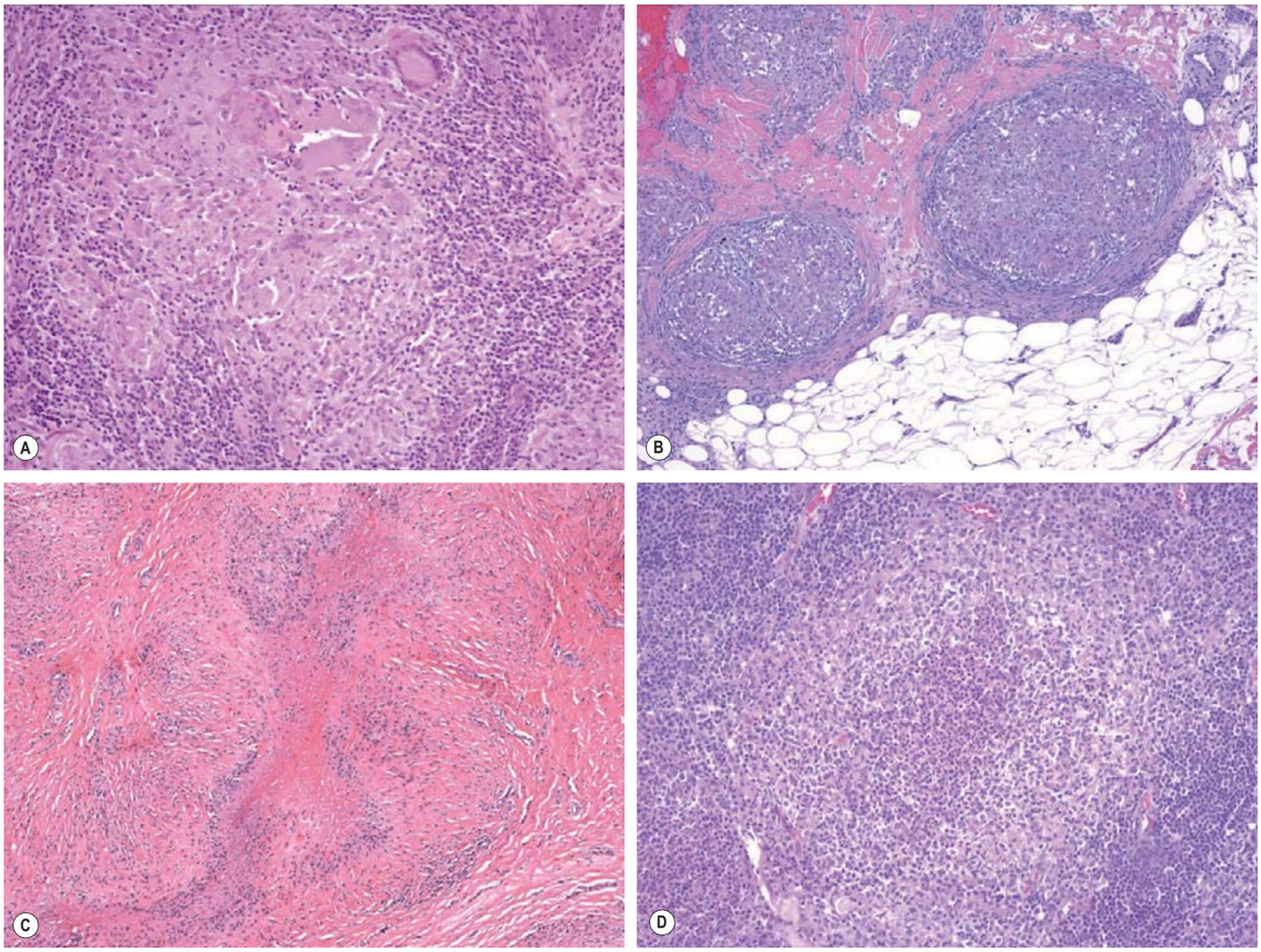


Fig. 0.25 Four major types of cutaneous granulomas. A Tuberculoid. **B** Sarcoidal. **C** Palisaded. **D** Suppurative. *A–D, Courtesy, James Patterson, MD.*

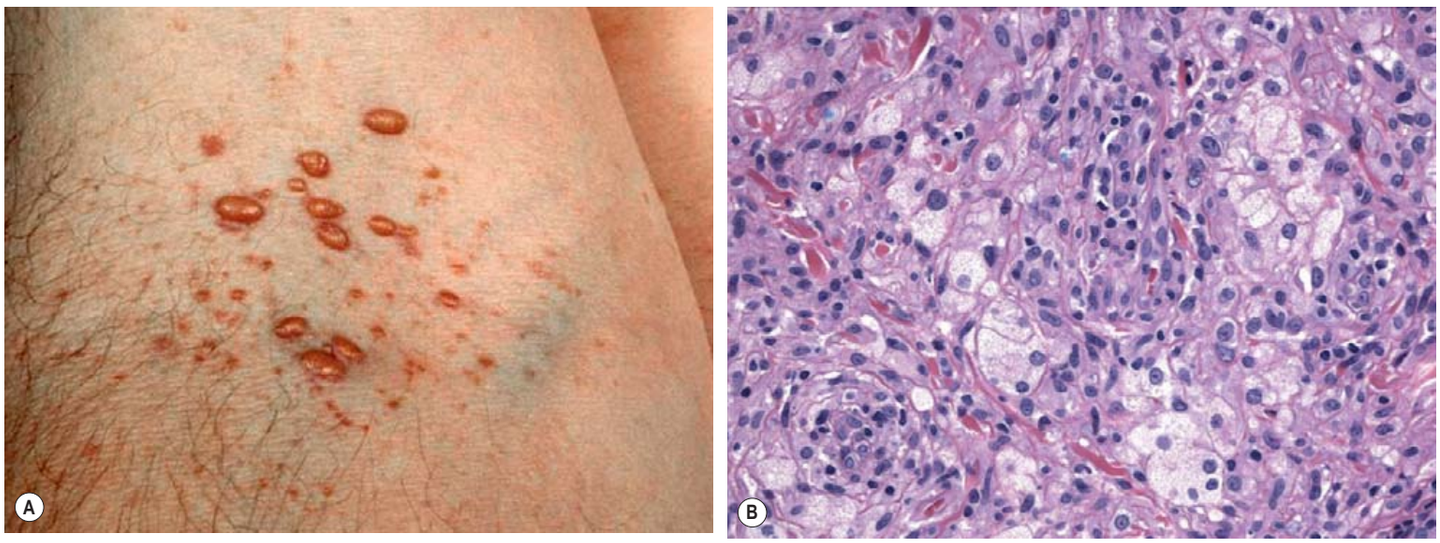


Fig. 0.26 Xanthomas. A Yellow–pink eruptive xanthomas. **B** Lipid-laden macrophages with foamy or vacuolated cytoplasm are present within the dermis. *B, Courtesy, James Patterson, MD.*

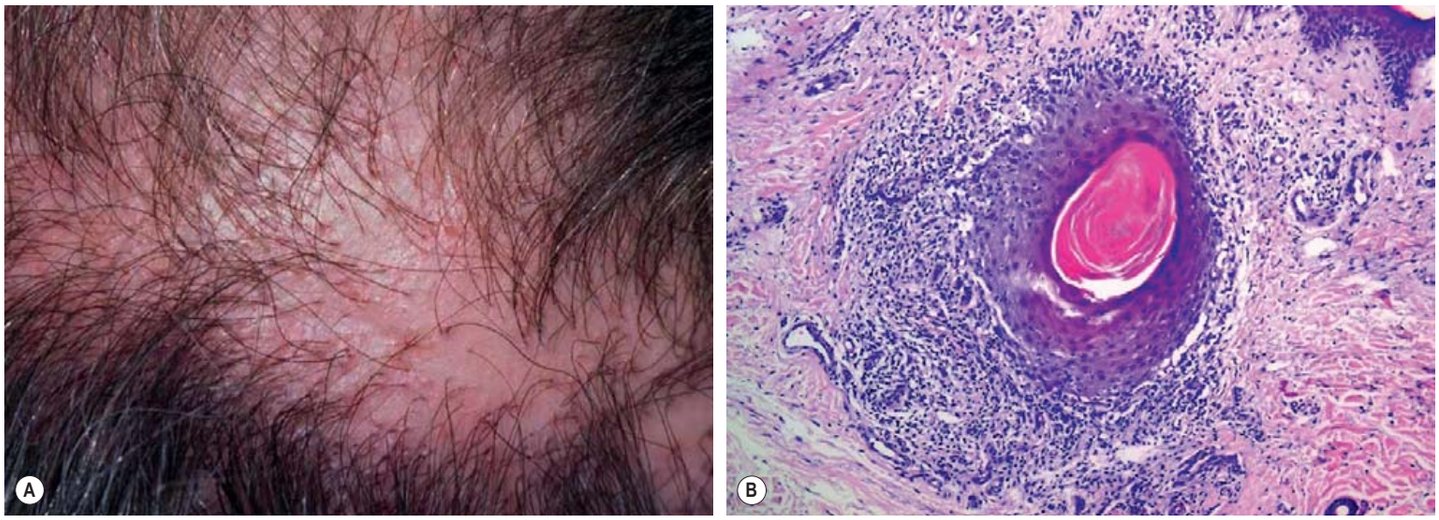


Fig. 0.27 Folliculitis. A Lichen planopilaris with areas of scarring alopecia and red–violet rims of inflammation around hair follicles. **B** Band-like lymphocytic infiltrate surrounding a hair follicle, with vacuolar alteration of basilar outer root sheath epithelium.

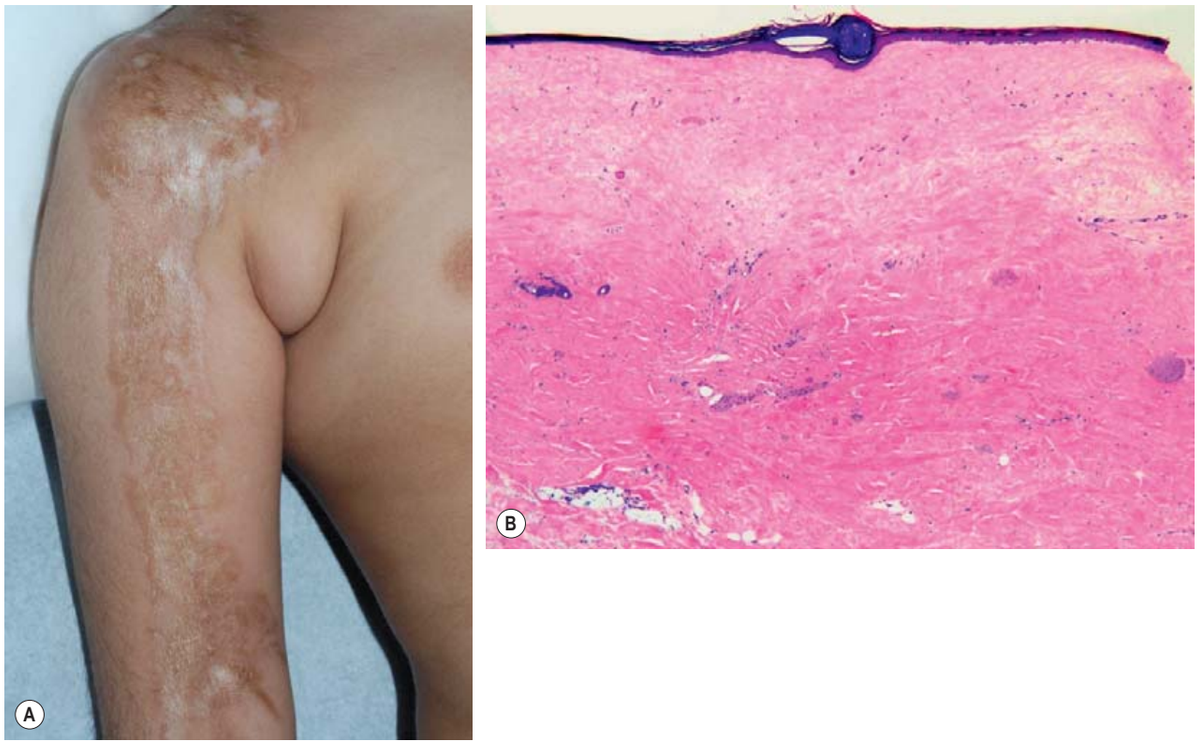


Fig. 0.28 Sclerosing disorder. A Linear morphea of the upper extremity. **B** Thickened and hyalinized collagen bundles, loss of adnexal structures and minimal inflammatory cell infiltrate. *A, Courtesy, Julie V Schaffer, MD.*

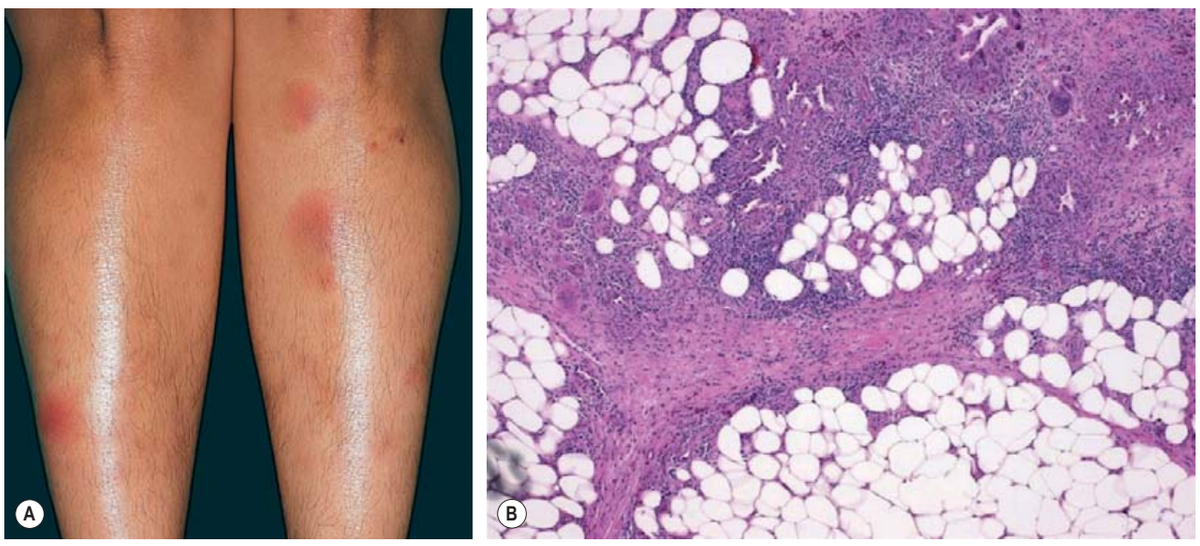


Fig. 0.29 Septal panniculitis. A Multiple red–brown nodules of erythema nodosum on the shins, admixed with healing bruise-like areas. **B** Predominantly septal granulomatous infiltrate with formation of characteristic Miescher's granulomas. *A, Courtesy, Kenneth Greer, MD; B, Courtesy, James Patterson, MD.*

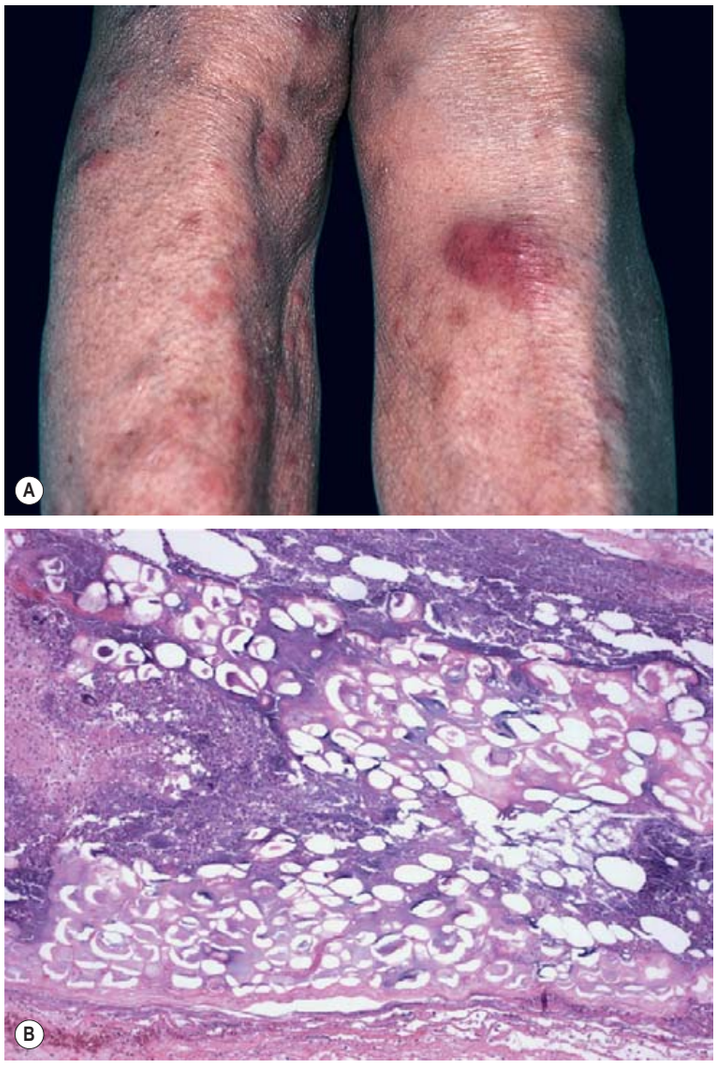


Fig. 0.30 Lobular panniculitis. A Pancreatic panniculitis. **B** Suppurative lobular panniculitis with characteristic enzyme-induced fat necrosis. *A, Courtesy, Kenneth Greer, MD. B, Courtesy, James Patterson, MD.*

INVISIBLE DERMATOSES		
Microanatomic site	**Abnormality**	**Example dermatoses**
Stratum corneum, granular cell layer	Superficial infections	Pityriasis (tinea) versicolor Dermatophytosis
	Keratinization disorders	Ichthyosis Disseminated superficial actinic porokeratosis
Basilar layer of epidermis	Pigmentation disorders	Vitiligo Café-au-lait macule
Superficial dermis	Infestations	Onchocerciasis
	Mast cell infiltration	Telangiectasia macularis eruptiva perstans
	Deposition of endogenous substances	Macular amyloidosis
Superficial and deep dermis	Deposition of exogenous substances	Argyria (basement membrane of epithelial structures)
	Deposition of endogenous substances	Dermal melanocytosis
	Collagen abnormalities	Collagenoma Atrophoderma
	Elastic tissue abnormalities	Nevus elasticus Anetoderma (non-inflammatory)
Absence of normal epithelial structure	Deficiency of eccrine sweat glands	Hypohidrotic ectodermal dysplasia

Table 0.9 Invisible dermatoses.

As is the case for granulomatous infiltrates, panniculitis requires a low threshold for performing special stains to exclude an infectious etiology and for using polarized light examination to identify foreign material.

Invisible dermatoses

Occasionally, one encounters a subcategory of dermatoses that actually lack a pattern of histopathology, and these conditions are often referred to collectively as "invisible dermatoses" (Table 0.9). From the perspective of the dermatopathologist, invisible dermatoses represent a group of skin diseases where a compelling case for disease exists clinically, but for which the histologic examination is rather unremarkable, i.e. the microscopic findings differ minimally from those of normal skin[27,28].

Among the "invisible dermatoses" are: (1) diseases with subtle pathologic changes and diseases requiring special stains to visualize diagnostic pathology (e.g. disorders of elastic and collagen tissue without significant fibrosis or sclerosis); (2) diseases with focal pathologic processes requiring serial tissue levels to identify diagnostic features (e.g. polyarteritis nodosa); and (3) diseases that require precise clinical information and/or strict clinical correlation to make the diagnosis (e.g. vitiligo, melasma, telangiectasia macularis eruptiva perstans [a form of mastocytosis]).

Because the histopathologic changes in "invisible dermatoses" are subtle and vexing, upon recognition a methodical analysis is recommended that includes: careful searching for diagnostic pathology at all levels of the skin (cornified layer, epidermis, papillary dermis, reticular dermis, hypodermis, adnexa); use of special stains where appropriate and necessary (e.g. markers for melanocytes and stains for melanin in suspected vitiligo); and comparison of the specimen with normal skin.

Deposition of Materials within the Skin

Occasionally, materials not normally present in the skin are deposited, either by exogenous or metabolic insult, and this can be appreciated histologically. In some patients, there is aberrant deposition of endogenously produced materials, such as uric acid in gouty tophi or light chain-derived amyloid due to an underlying plasma cell dyscrasia, whereas in others, exogenous material has been purposefully or accidentally inoculated into the skin (e.g. cosmetic filler material, tattoo pigment). These materials may accumulate within the dermis, the subcutaneous fat, or both. Deposits of some materials, such as the silver in patients with argyria, may be limited to cutaneous adnexa. Use of polarized light or darkfield microscopy (where light enters tissue at an angle that is not perpendicular to the slide) may be of use in identifying foreign material.

Some deposits engender a granulomatous inflammatory reaction (see Ch. 94), while others evoke no appreciable reaction at all. Deposited material is usually visualized during microscopic examination, but it may be removed during processing (e.g. siliconosis), leaving only characteristic "empty spaces" to suggest its clinical presence. Special stains may be helpful for precise identification, depending upon the suspected nature of the material.

Histologic Stains

The standard stain in dermatopathology is *hematoxylin and eosin*, ubiquitously referred to as "H&E". H&E staining yields a predictable pattern of staining, with the hematoxylin marking basophilic structures, such as cellular nuclei and the granular layer of the epidermis, a characteristic blue–purple, and eosinophilic structures, such as cytoplasm, collagen, muscle, nerve and fibrin, pink–red.

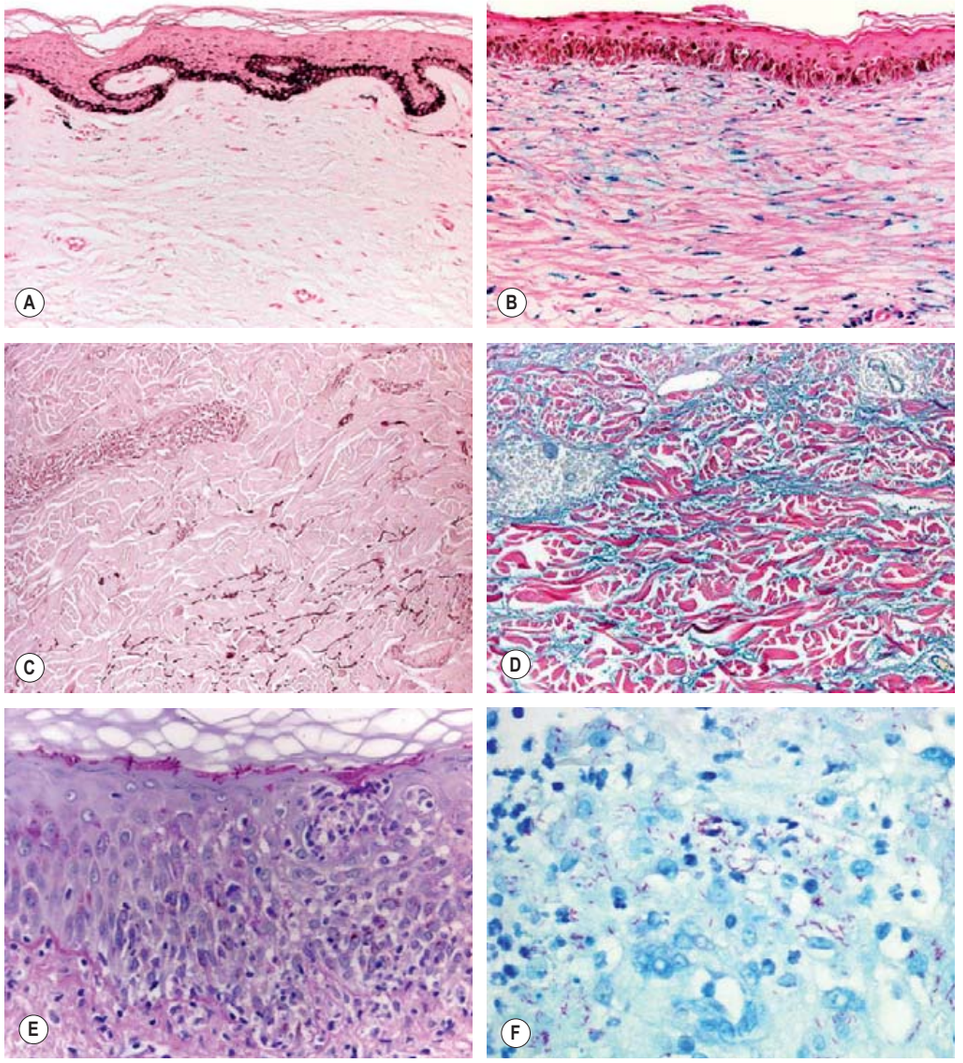


Fig. 0.31 Examples of histochemical stains. Often, histochemical stains reveal structures or substances (e.g. pigments, connective tissue elements, microorganisms) that cannot be clearly seen on H&E-stained sections. **A** Enhancement of increased *melanin* within the basal layer of the epidermis in genital melanosis (black color) – Fontana–Masson stain. **B** Demonstration of *iron* (hemosiderin) within dermal macrophages in purpura (blue color) – Prussian blue (Perls' iron) stain. **C** A near absence of dermal *elastic fibers* (upper left), compared to normal elastic fibers in the lower right, in anetoderma (black color) – orcein elastic tissue stain. **D** Increased *mucin* in the dermis in reticular erythematous mucinosis (blue color) – colloidal iron stain. **E** *Fungal hyphae* within the stratum corneum in dermatophytosis (red color) – PAS stain (also note the staining of the basement membrane zone). **F** *Mycobacteria* within a granulomatous infiltrate in cutaneous tuberculosis (red–violet color) – Fite stain (modified acid-fast stain). *A–E, Courtesy, Lorenzo Cerroni, MD. F, Courtesy, Karen Warschaw, MD.*

Although H&E staining alone enables the histopathologic diagnosis of many skin diseases, some disorders require additional "special stains" to facilitate a diagnosis[29]. For example, elastic tissue, unless significantly altered by ultraviolet radiation or calcium deposits, does not stain with H&E, and special stains such as Verhoeff–van Gieson are required to identify alterations in these fibers (e.g. in anetoderma; Fig. 0.31). Similarly, special stains exist to screen for the presence of infectious agents, such as the Brown–Brenn stain (a modified tissue Gram stain) for bacteria, the periodic acid–Schiff (PAS) or Gomori methenamine silver stain for fungus, and the Ziehl–Neelsen or Fite stain for mycobacteria (see Fig. 0.31). Additional special stains may be utilized to determine the type of infiltrating cell, such as the Giemsa or chloroacetate esterase stain for mast cells. Table 0.10 lists the more commonly employed histochemical ("special") stains used in dermatopathology.

Immunohistochemical Testing

Immunohistochemistry (IHC) is the use of immunologic techniques to identify cellular antigens (proteins) not visible on routine H&E-stained sections. It exploits the principle of antibodies binding specifically to antigens in biological tissues. Visualizing this antibody–antigen interaction may be accomplished in a number of ways. Most commonly, the antibody is conjugated to an enzyme that can catalyze a color-producing reaction when the antibody–enzyme conjugate is bound to the appropriate antigen within tissue; the enzyme is often peroxidase, hence the older terminology, immunoperoxidase technique.

While IHC is most often used to characterize the cellular lineage of neoplasms, it is also helpful in assessing the biological behavior of tumors and in identifying specific infectious agents that are not discernible or are difficult to detect in routine H&E-stained sections (Fig. 0.32)[30]. IHC is also used as a research tool to determine the distribution and localization of specific biomarkers and proteins within biological tissue.

When used rationally and appropriately, IHC is a formidable tool in diagnostic dermatopathology, but if used without insight or excessively, it can be misleading and economically wasteful. Important factors to consider when using IHC include the following: (1) practically no antibody is specific for a certain cell type, and therefore a panel of antibodies should be employed to avoid premature, incomplete or erroneous conclusions; (2) a differential diagnosis must be constructed prior to ordering an antibody panel so that the requested antibodies are appropriate; and (3) no antibody can differentiate irrefutably between a benign and malignant neoplasm (although, on occasion, evidence of an increased proliferative index or the aberrant expression of certain proteins may *support* such a conclusion).

A list of antibodies used most often in dermatopathology, the corresponding antigens, and the disease processes suggested by positive reactions is provided in Table 0.11. When reading about specific disease processes in other sections of this book, pay particular attention to the use of IHC techniques.

COMMONLY EMPLOYED SPECIAL STAINS IN DERMATOPATHOLOGY			
Stain	**Structures identified**	**Color**	**Application**
Alcian blue (pH 2.5)	Acid mucopolysaccharides (glycosaminoglycans)	Light blue	Mucinoses Lupus erythematosus Extramammary Paget's disease Mucopolysaccharidoses
Alcian blue (pH 0.5)	Sulfated mucopolysaccharides (heparin sulfate, chondroitin sulfate)	Blue	
Chloroacetate esterase (Leder)	Myeloid cells and mast cells	Red	Neutrophilic dermatoses Malignant hematopoietic infiltrates Mastocytosis
Colloidal iron	Acid mucopolysaccharides	Blue	Mucinoses Lupus erythematosus Extramammary Paget's disease
Congo red	Amyloid	Red; green in polarized light	Amyloidosis
Crystal violet	Acid mucopolysaccharides and amyloid	Metachromatically purple with blue background	Mucinoses Amyloidosis
Fite–Faraco	*Mycobacterium leprae*	Red	Leprosy (Hansen's disease)
Fontana–Masson (argentaffin)	Melanin	Black	Distinction between iron and melanin Discoloration due to drugs (e.g. minocycline) Evaluation of vitiligo
Giemsa	Nuclei of cells, microorganisms	Blue	Leishmaniasis Histoplasmosis Granuloma inguinale
	Mast cell granules	Metachromatically purple	Urticaria Mastocytosis
Gomori methenamine silver	Fungal cell walls	Black	Mycotic infections
Gram (Brown–Brenn)	Gram-positive bacteria	Blue	Bacterial infections
	Gram-negative bacteria	Red	Bacterial infections
Masson's trichrome	Smooth muscle	Pink	Useful for distinguishing leiomyomas from dermatofibromas and neural tumors
	Collagen	Blue/green	Useful in evaluating the characteristics of dermal collagen, e.g. perforating disorders
Mucicarmine	Epithelial mucin (acid or neutral mucopolysaccharides)	Red	Usually used for sialomucin (e.g. adenocarcinoma, Paget's disease) and the capsule of *Cryptococcus neoformans*
Myeloperoxidase	Immature myeloid cells	Orange	Leukemic infiltrates
Orcein (acid orcein-Giemsa)	Collagen	Pink	Elastic tissue disorders (e.g. PXE, anetoderma)
	Elastic tissue	Dark brown	
	Muscle and nerves	Yellow	
Pagoda	Amyloid	Orange	Amyloidoses
Periodic acid–Schiff (PAS)	Glycogen, fungal walls, neutral mucopolysaccharides, fibrin, basement membranes, many clear cell neoplasms	Red	Used for diagnosis of fungal infections; also to identify a thickened epidermal basement membrane in lupus erythematosus and the thickened vascular walls in porphyria cutanea tarda
Perls' iron (Prussian blue)	Hemosiderin Ferric ions	Blue	Useful for identifying iron as the source of pigment
Sudan black	Lipids (in frozen sections or formalin-fixed, unprocessed tissue)	Black	Xanthomatoses Storage diseases (e.g. Fabry disease)
Sudan orange	Lipids (in frozen sections or formalin-fixed, unprocessed tissue)	Orange	Xanthomatoses Storage diseases
Thioflavin T	Amyloid	Yellow–green by fluorescence microscopy	Amyloidoses
Truant (auramine-rhodamine)	Acid-fast organisms	Reddish-yellow by fluorescence microscopy	Mycobacterial infections
Toluidine blue	Acid mucopolysaccharides and mast cell granules	Metachromatically purple	Mastocytosis

Table 0.10 Commonly employed special stains in dermatopathology. In parentheses are alternative names or variations of the stain. PXE, pseudoxanthoma elasticum.

Continued

COMMONLY EMPLOYED SPECIAL STAINS IN DERMATOPATHOLOGY			
Stain	**Structures identified**	**Color**	**Application**
Verhoeff–Van Gieson or Weigert	Collagen	Pink to red	Elastic tissue disorders (e.g. PXE, anetoderma, mid-dermal elastolysis)
	Elastic tissue	Black	
	Muscle and nerves	Yellow	
Von Kossa	Calcium salts	Black	Pseudoxanthoma elasticum (oxalate salts may not stain with this method)
Warthin–Starry (modified Steiner)	Bacteria	Black	Granuloma inguinale Syphilis (and other diseases caused by spirochetes) Rhinoscleroma Bacillary angiomatosis
Ziehl–Neelsen	Acid-fast bacteria	Red	Mycobacterial infections

Table 0.10 Commonly employed special stains in dermatopathology (cont'd). In parentheses are alternative names or variations of the stain. PXE, pseudoxanthoma elasticum.

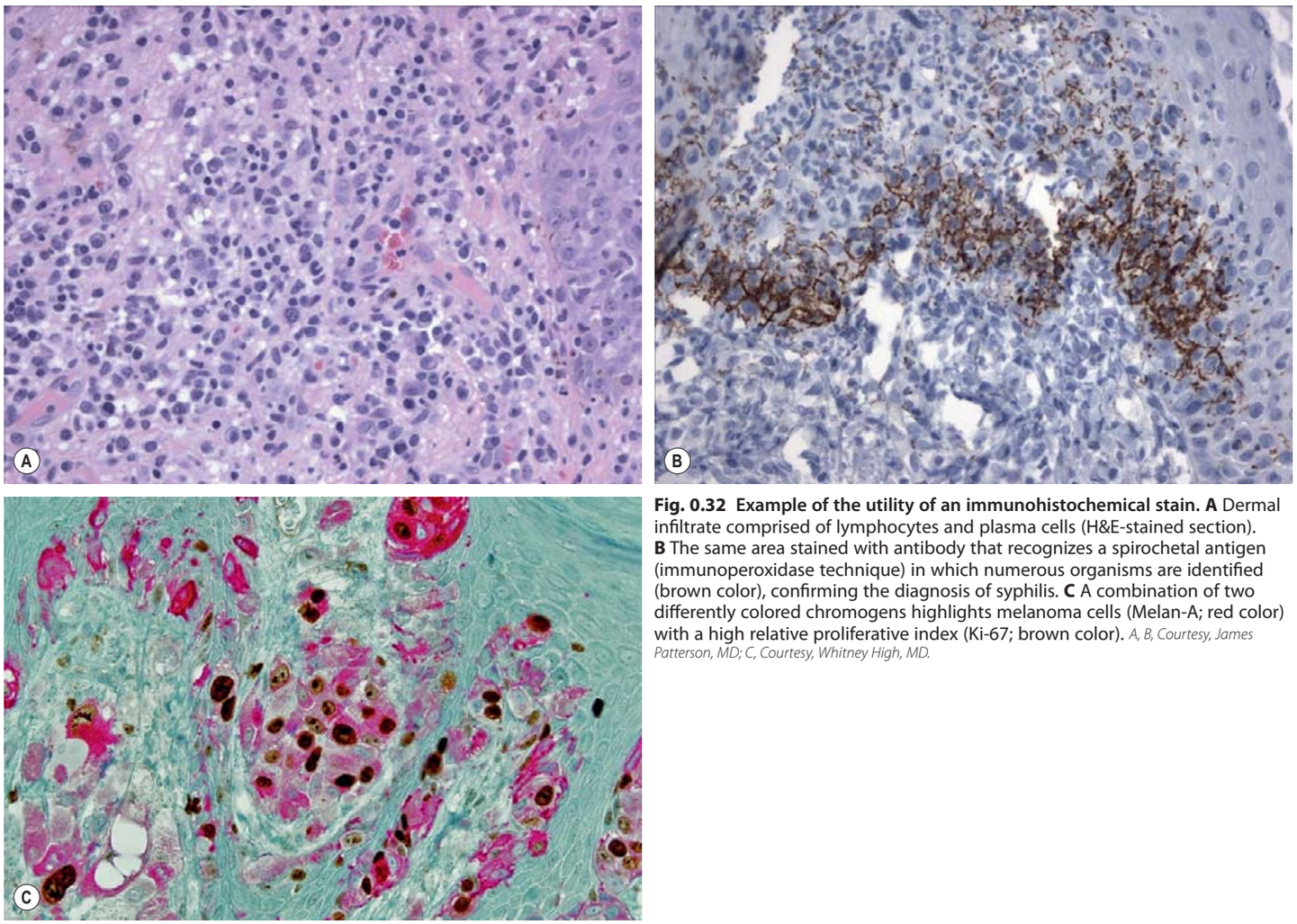


Fig. 0.32 Example of the utility of an immunohistochemical stain. A Dermal infiltrate comprised of lymphocytes and plasma cells (H&E-stained section). **B** The same area stained with antibody that recognizes a spirochetal antigen (immunoperoxidase technique) in which numerous organisms are identified (brown color), confirming the diagnosis of syphilis. **C** A combination of two differently colored chromogens highlights melanoma cells (Melan-A; red color) with a high relative proliferative index (Ki-67; brown color). *A, B, Courtesy, James Patterson, MD; C, Courtesy, Whitney High, MD.*

MOST COMMONLY EMPLOYED IMMUNOHISTOCHEMICAL STAINS IN DERMATOPATHOLOGY		
Marker	**Definition/primary cellular expression**	**Applications/comments**
	EPITHELIAL MARKERS	
Bcl-2	• Protein product of an oncogene that negatively regulates programmed cell death (apoptosis) • Expressed in the basal layer of the epidermis and in lymphoid cells (see below)	• Sometimes useful in distinguishing basal cell carcinoma from trichoepithelioma • Sometimes useful in suggesting a systemic form of B-cell lymphoma when there is cutaneous involvement
CEA (carcinoembryonic antigen)	• A protein expressed by a variety of tissues, from gastrointestinal cells to skin adnexa	• Expressed in eccrine and apocrine epithelium • Paget's disease (mammary and extramammary), although somewhat supplanted by CK 7 stain
CK 5/6	• Intermediate-sized basic keratins • Expressed in the basal layer of stratified squamous epithelia	• Spindle cell squamous cell carcinoma • May aid in distinguishing primary carcinomas of the skin from metastatic carcinoma
CK 7	• Low-molecular-weight cytokeratin	• Expressed in eccrine and apocrine epithelium • Paget's disease (mammary and extramammary) • Cutaneous metastases of breast carcinoma
CK 20	• Low-molecular-weight cytokeratin • Expressed in simple epithelia and Merkel cells	• Sometimes expressed (along with CK 7) in metastatic transitional cell carcinoma
EMA (epithelial membrane antigen)	• High-molecular-weight transmembrane glycoprotein expressed in many epithelial cells	• Often stains malignant eccrine and apocrine tumors • Stains most sebaceous glands
GCDFP-15 (gross cystic disease fluid protein-15)	• Expressed by apocrine glands, eccrine glands (variable), minor salivary glands, bronchial glands, metaplastic epithelium of the breast, benign sweat gland tumors of the skin, and the serous cells of the submandibular gland	• Breast carcinoma • Sweat gland carcinoma with apocrine differentiation
P53	• Protein product of the tumor suppressor gene *TP53* that is involved in regulation of the cell cycle	• Aberrant nuclear expression may be seen in: sun-damaged skin (confined to the basilar layer); actinic keratoses (some suprabasilar staining); squamous cell carcinoma *in situ* (full-thickness staining); and some invasive squamous cell carcinomas
P63	• P53 homolog that acts as a transcription factor, with roles in regulating differentiation and development of epithelia as well as the cell cycle • Expressed in the basal layer of the epidermis and cutaneous adnexa	• Spindle cell squamous cell carcinoma • Undifferentiated carcinomas • Adnexal carcinomas
Pancytokeratins AE1/AE3	• Mixture of low- and high-molecular-weight cytokeratins	• Screening tumors for an epithelial origin • Useful for squamous cell carcinomas
CK903 (34βE12)	• High-molecular-weight cytokeratin	• Spindle cell squamous cell carcinoma • May aid in distinguishing primary cutaneous carcinomas from metastases
	MELANOCYTIC AND NEURAL MARKERS	
HMB45	• Glycoprotein present in premelanosomes and melanosomes (Pmel17/gp100) • Matrix protein expressed in melanocytes that are synthesizing melanin	• Melanocytic nevi and melanomas (highly specific) • PEComas • Diminished staining with dermal descent favors benign tumors
MART-1/Melan-A	• Protein involved in melanosome structure and maturation • An antigen present on melanocytes and melanoma cells • Recognized by cytotoxic T lymphocytes	• Melanocytic nevi and melanomas (highly specific) • PEComas
MITF-1 (microphthalmia-associated transcription factor)	• Necessary for the development of melanocytes during embryogenesis • Regulator of multiple proteins involved in melanogenesis	• Melanocytic nevi and melanoma • Exclusive nuclear staining may be advantageous in some situations (e.g. lentigo vs lentigo maligna)[40]
P16	• One of two protein products of the tumor suppressor gene *CDKN2A* • Expressed in some melanocytic and epithelial neoplasms	• Melanocytic nevi and Spitz nevi • Strong nuclear and cytoplasmic expression may favor benignity in melanocytic processes
P75	• Common receptor for members of the neurotrophins (NT) family • Involved in programmed cell death • Marker of Schwannian differentiation	• Helpful for establishing the diagnosis of desmoplastic and neurotropic melanoma when S100 staining is weak or absent
S100	• Family of low-molecular-weight, calcium-binding proteins • Expressed in neural crest-derived cells (melanocytes, Schwann cells, glial cells), chondrocytes, fat cells, macrophages, Langerhans cells, dendritic cells, some breast epithelial cells and sweat glands	• Most sensitive marker for melanoma and spindle cell/desmoplastic melanoma • Malignant peripheral nerve sheath tumors (stains weakly in comparison to melanoma) • Clear cell sarcoma
Tyrosinase	• Enzyme involved in melanin biosynthesis	• Higher sensitivity than HMB45 • Sensitivity decreases with increased clinical stage and in metastases

Table 0.11 Most commonly employed immunohistochemical stains in dermatopathology. CDKN2A, cyclin-dependent kinase inhibitor 2A; CD, cluster of differentiation; CK, cytokeratin; CTLA-4, cytotoxic T-lymphocyte antigen-4; HTLV-1, human T-cell leukemia virus 1 (human T-cell lymphotropic virus 1); IL, interleukin; LFA-3, lymphocyte function-associated antigen-3; MAdCAM-1, mucosal addressin cell adhesion molecule-1; MART-1, melanoma antigen recognized by T cells; Melan-A, melanocyte antigen; MHC, major histocompatibility complex; NK, natural killer; PEC, perivascular epithelioid cell. *Table created with the assistance of Dr Stefano Titli.*

Continued

MOST COMMONLY EMPLOYED IMMUNOHISTOCHEMICAL STAINS IN DERMATOPATHOLOGY		
Marker	**Definition/primary cellular expression**	**Applications/comments**
	NEUROENDOCRINE MARKERS	
CD57 (Leu-7)	• Adhesion molecule • T cells, NK cells, Schwann cells	• Myelinated areas of neuromas and neurofibromas
Chromogranin	• Granules of neuroendocrine cells and sympathetic nerves	• Merkel cell carcinoma
CK 20	• Low-molecular-weight cytokeratin • Expressed in simple epithelia and Merkel cells	• The most sensitive stain for Merkel cell carcinoma (especially when used in combination with TTF-1; when the latter is negative, cutaneous metastases of small cell lung carcinoma are excluded)
Neurofilament	• Intermediate filaments within neuronal processes of central and peripheral nervous tissue	• Merkel cell carcinoma • Neural tumors
NSE (neuron-specific enolase)	• A protein originally found in neurons and neuroendocrine cells, but also demonstrated within melanocytes, striated and smooth muscle cells, megakaryocytes, T cells and some platelets	• Often humorously referred to as "non-specific enolase", the antibody is not of great utility due to the large number of tissues it stains, but it is occasionally used as a screen and supportive evidence for Merkel cell carcinoma
Synaptophysin	• Glycoprotein of presynaptic vesicles found in neurons and neuroendocrine cells	• Merkel cell carcinoma • Neural tumors
TTF-1 (thyroid transcription factor-1)	• Expressed in the epithelia of the thyroid and lung as well as some neural tissues	• Thyroid carcinoma • Small cell lung carcinoma • Visceral neuroendocrine tumors [negative in Merkel cell carcinoma]
	MESENCHYMAL CELL MARKERS	
Caldesmon	• Actin and protomyosin binding protein involved in regulation of muscle and non-muscle contraction	• Smooth muscle neoplasms
CD10	• A cell-surface enzyme with neutral metalloendopeptidase activity • Present on some fibrohistiocytic cells as well as lymphoid cells (see below)	• Dermatofibroma (strong and diffuse), atypical fibroxanthoma, renal cell carcinoma • Renal cell carcinoma, neurothekeoma
CD99 (MIC2)	• Transmembrane protein expressed on most hematopoietic cells	• Ewing sarcoma, peripheral neuroectodermal tumor
Desmin	• Intermediate filament protein expressed predominantly by striated and smooth muscle cells	• Smooth and striated muscle cell neoplasms
Factor XIIIa	• Human coagulation factor XIII • Expressed in a subset of dermal dendrocytes, monocytes and macrophages	• Non-Langerhans cell histiocytoses • Dermatofibroma; negative in dermatofibrosarcoma protuberans (DFSP)
Smooth muscle actin	• Present in smooth muscle around blood vessels, arrector pili muscle and myofibroblasts	• Benign and malignant smooth muscle tumors, myofibroblastic tumors and pseudotumors
Vimentin	• Intermediate filaments in mesenchymal cells	• All mesenchymal cells/tumors, sarcomatoid (spindle cell) carcinoma
	ENDOTHELIAL MARKERS	
CD31	• Platelet–endothelial cell adhesion molecule-1 (PECAM-1) • Highly sensitive for endothelial cells, but poor specificity	• Benign and malignant vascular neoplasms
CD34	• Surface glycoprotein involved in cell–cell adhesion • Highly sensitive for endothelial cells, but poor specificity	• Benign and malignant vascular neoplasms • DFSP; negative in dermatofibroma
Human herpesvirus-8 (HHV-8)	• HHV-8 latent nuclear antigen	• Kaposi sarcoma (earliest stage may be negative)
Podoplanin (D2-40)	• Mucin-type transmembrane glycoprotein • Expressed by lymphatic, but not vascular, endothelial cells	• Kaposi sarcoma, angiosarcomas with lymphatic differentiation • Lymphangiomas • Schwannomas
	HISTIOCYTIC MARKERS	
CD1a	• Transmembrane glycoprotein structurally related to the MHC proteins; functions in antigen presentation • Expressed in Langerhans cells and precursor T cells	• Langerhans cell histiocytoses • Some T-cell lymphoblastic lymphomas
CD68	• Glycoprotein that binds to low-density lipoprotein • Expressed in monocytes and macrophages • With some anti-CD68 monoclonal antibodies (e.g. KP1), also detected in mast cells, neutrophils and myeloid precursors	• Blastic NK cell lymphoma (some cases), myeloid leukemias • Some soft tissue tumors • Non-Langerhans cell histiocytoses • Atypical fibroxanthoma
CD163	• Protein expressed by monocytes and macrophages that functions in endocytosis and clearance of materials	• Cells of histiocytic lineage • Some cells of fibrohistiocytic lineage (dermatofibromas)
CD207 (Langerin)	• Transmembrane cell surface receptor produced by Langerhans cells and localized in the Birbeck granules (involved in internalization of antigen into Birbeck granules)	• Langerhans cell histiocytoses

Table 0.11 Most commonly employed immunohistochemical stains in dermatopathology (cont'd). CDKN2A, cyclin-dependent kinase inhibitor 2A; CD, cluster of differentiation; CK, cytokeratin; CTLA-4, cytotoxic T-lymphocyte antigen-4; HTLV-1, human T-cell leukemia virus 1 (human T-cell lymphotropic virus 1); IL, interleukin; LFA-3, lymphocyte function-associated antigen-3; MAdCAM-1, mucosal addressin cell adhesion molecule-1; MART-1, melanoma antigen recognized by T cells; Melan-A, melanocyte antigen; MHC, major histocompatibility complex; NK, natural killer; PEC, perivascular epithelioid cell. *Table created with the assistance of Dr Stefano Titli.*

Continued

MOST COMMONLY EMPLOYED IMMUNOHISTOCHEMICAL STAINS IN DERMATOPATHOLOGY		
Marker	**Definition/primary cellular expression**	**Applications/comments**
S100	• Family of low-molecular-weight, calcium-binding proteins • Expressed in Langerhans cells, activated macrophages and other cells (see melanocytic section above)	• Langerhans cell histiocytoses
	MAST CELL MARKERS	
CD117 (c-KIT)	• Stem cell factor (KIT ligand) receptor • Tyrosine kinase receptor expressed on the surface of hematopoietic stem cells, myeloid progenitor cells, mast cells and melanocytes	• Mastocytosis, mast cell neoplasms • Myeloid leukemia • Junctional component in melanocytic nevi, some melanomas • Gastrointestinal stromal tumors (GIST) • The efficacy of imatinib, a c-KIT inhibitor, is affected by the mutation status of the gene that encodes this receptor
Tryptase	• Serine protease in mast cell granules	• Mastocytosis, mast cell neoplasms
	METASTASES (See Ch. 122)	
CDX2 (caudal-type homeobox 2)	• Transcription factor expressed in all but the most distal portions of the intestinal tract during development	• Gastrointestinal and carcinoid tumors
PSA (prostate-specific antigen)	• Glycoprotein produced almost exclusively by the prostate gland	• Prostate carcinomas, benign prostatic hyperplasia
Uroplakin	• Protein of urothelial surface membrane	• Bladder carcinomas
	LYMPHOID MARKERS	
ALK (anaplastic lymphoma kinase)	• Membrane-associated tyrosine kinase receptor • Probable role in nervous system development and maintenance	• Systemic anaplastic large cell lymphoma (nodal and extranodal) • Negative in primary cutaneous T-cell lymphomas and other types of anaplastic lymphoma (especially B-cell lymphomas) with CD30 positivity
Bcl-2	• Antiapoptosis factor for T and B cells • Expressed in non-germinal center B cells and most T cells	• Diffuse large B-cell lymphoma, leg type • Most follicular lymphomas (excluding primary cutaneous follicle center lymphoma)
Bcl-6	• Nuclear protein expressed in mature B cells within normal germinal centers	• Primary cutaneous follicle center lymphoma • Reactive lymphoid follicles
Immunoglobulin light chains (kappa and lambda)	• Small polypeptide subunits of immunoglobulin • Expressed in B cells and plasma cells	• Plasma cell and plasmacytoid neoplasms • Monotypic expression (all kappa or all lambda) in clonal neoplasms
LMP1	• EBV latent membrane antigen	• AIDS-related non-Hodgkin lymphomas, post-transplant lymphoproliferative disorders, some NK/T-cell lymphomas
TdT	• Terminal deoxynucleotidyl transferase • Expressed in immature pre-B and pre-T cells	• Lymphoblastic lymphoma/leukemia • $CD4^+/CD56^+$ hematodermic neoplasm
CD3	• Complex of transmembrane proteins in the immunoglobulin superfamily involved in signal transduction to the T-cell interior following antigen recognition • Pan T-cell marker • Also expressed in NK cells (cytoplasmic staining for CD3ε)	• T-cell lymphomas • HTLV-1-associated adult T-cell leukemia/lymphoma
CD4	• Transmembrane glycoprotein involved in T-cell activation (class II MHC restricted) • Expressed in helper and regulatory T cells, monocytes, granulocytes, macrophages and Langerhans cells	• Some T-cell lymphomas, including classic mycosis fungoides
CD5	• Transmembrane glycoprotein • Expressed in mature T cells, thymocytes and a subset of mature B cells	• T-cell lymphomas, B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma, mantle cell lymphoma
CD7	• Transmembrane protein in the immunoglobulin superfamily with a role in T-cell interactions with other T cells and B cells • Expressed throughout T-cell differentiation	• T-cell lymphomas, myeloid leukemias, NK-cell neoplasms, T-cell lymphoblastic lymphoma/leukemia • Expression often lost in mycosis fungoides
CD8	• Transmembrane glycoprotein involved in T-cell activation (class I MHC restricted) • Expressed in cytotoxic T cells, NK cells, thymocytes	• Primary cutaneous aggressive epidermotropic $CD8^+$ cytotoxic cutaneous T-cell lymphoma, most subcutaneous panniculitis-like T cell lymphomas • Some peripheral T-cell lymphomas
CD10 (common acute lymphoblastic leukemia antigen; CALLA)	• Cell-surface enzyme with neutral metalloendopeptidase activity • Expressed in precursor and germinal center B cells	• Follicle center lymphoma, • B-cell lymphoblastic lymphoma/leukemia
CD15 (LeuM1; Lewis X)	• Membrane protein • Sulfated sialyl Lewis X (a component of adhesion molecules such as MAdCAM-1) binds selectins (CD62L, E and P) and mediates leukocyte rolling on activated endothelium • Expressed in monocytes and granulocytes • Absent on normal lymphocytes	• Classic Hodgkin disease (Reed Sternberg cells) • Acute myeloid leukemia

Table 0.11 Most commonly employed immunohistochemical stains in dermatopathology (cont'd). CDKN2A, cyclin-dependent kinase inhibitor 2A; CD, cluster of differentiation; CK, cytokeratin; CTLA-4, cytotoxic T-lymphocyte antigen-4; HTLV-1, human T-cell leukemia virus 1 (human T-cell lymphotropic virus 1); IL, interleukin; LFA-3, lymphocyte function-associated antigen-3; MAdCAM-1, mucosal addressin cell adhesion molecule-1; MART-1, melanoma antigen recognized by T cells; Melan-A, melanocyte antigen; MHC, major histocompatibility complex; NK, natural killer; PEC, perivascular epithelioid cell. *Table created with the assistance of Dr Stefano Titli.*

Continued

MOST COMMONLY EMPLOYED IMMUNOHISTOCHEMICAL STAINS IN DERMATOPATHOLOGY		
Marker	**Definition/primary cellular expression**	**Applications/comments**
CD20	• Unglycosylated phosphoprotein expressed only on B cells • Plays a role in B-cell activation and proliferation	• B-cell lymphomas
CD21 (complement receptor 2)	• Receptor for the C3d fragment of complement and EBV in B cells and epithelial cells • Expressed in follicular dendritic cells, mantle B cells and marginal zone B cells	• Follicular dendritic cell neoplasms • Mantle and marginal zone B-cell lymphomas
CD25 (IL-2 receptor α chain)	• Component of the high-affinity receptor for IL-2 • Expressed in activated T cells (including regulatory T cells), B cells, and macrophages	• Adult T-cell leukemia/lymphoma (associated with HTLV-1) • Targeted by denileukin diftitox (used to treat mycosis fungoides) as well as daclizumab and basiliximab (used to prevent rejection in solid organ transplant recipients)
CD30	• Member of the tumor necrosis factor (TNF) receptor family • Expressed in activated T and B cells	• Anaplastic large T-cell lymphoma, lymphomatoid papulosis, Hodgkin lymphoma • Non-neoplastic skin diseases (e.g. herpesvirus infections, poxvirus infections)
CD34	• Surface glycoprotein involved in cell–cell adhesion • Expressed in hematopoietic cell precursors	• Acute lymphoblastic lymphoma/leukemia, acute myeloblastic leukemia
CD40 and CD154 (CD40 ligand)	• Interaction between CD40 ligand on T cells and CD40 on B cells mediates immunoglobulin class switching	• Mutations in the genes encoding CD40 and CD40 ligand can lead to hyper-IgM syndrome
CD43	• Membrane glycoprotein with regulatory functions • Expressed in T cells, a subset of B cells, monocytes, mast cells and other granulocytes	• T-cell lymphomas, some B-cell lymphomas (aberrant expression), myeloid leukemias, mast cell neoplasms • B-cell chronic lymphocytic leukemia when CD20 is coexpressed
CD45 (leukocyte common antigen)	• Family of high-molecular-weight glycoproteins (all products of a single complex gene) present on the surface of leukocytes • Protein tyrosine phosphatase that functions in cellular signaling	• Most B- and T-cell lymphomas
CD45RA	• High-molecular-weight isoform of leukocyte common antigen • Found on naive T cells and B cells	• Primary cutaneous aggressive epidermotropic $CD8^+$ cytotoxic T-cell lymphoma, some subcutaneous panniculitis-like T-cell lymphomas, • Mantle cell lymphoma
CD45RO	• Low-molecular-weight isoform of leukocyte common antigen • Found on memory T cells	• T-cell lymphomas
CD52	• Glycosylphosphatidylinositol-anchored surface protein • Expressed on T cells, B cells, monocytes and dendritic cells	• Targeted by the drug alemtuzumab for the treatment of chronic lymphocytic leukemia and T-cell lymphomas
CD56	• Neural cell adhesion molecule • Expressed on NK cells, a subset of $CD3^+$ cytotoxic T cells, a subset of $CD4^+$ T cells and monocytes as well as neural cells	• Extranodal NK/T-cell lymphoma (nasal type), primary cutaneous γ/δ T-cell lymphoma (including with subcutaneous involvement), $CD4^+/CD56^+$ hematodermic neoplasm, rarely in primary cutaneous anaplastic large cell lymphoma • Some leukemias, most myelomas • Neural neoplasms
CD58 (LFA-3)	• Adhesion molecule on antigen-presenting cells that binds to CD2 on T cells and strengthens the interaction between these cells	• The drug alefacept is an LFA-3/IgG1 fusion protein
CD79a	• Surface glycoprotein associated with immunoglobulin in the B-cell membrane; involved in signal transduction after antigen binding • Appears before the pre-B-cell stage • Found on B cells (immature and mature) and plasma cells	• B-cell lymphomas (may be positive in cases where CD20 is negative) • Plasma cell neoplasms
CD80 (B7-1), CD86 (B7-2) and CD28	• Binding of CD80 or CD86 on activated B cells and antigen presentation cells to the CD28 receptor on T cells delivers a costimulatory signal for T-cell activation	
CD95 (Fas) and CD178 (Fas ligand)	• Fas ligand-expressing cytotoxic T cells induce apoptosis in Fas-expressing target cells, which can include activated B and T cells, keratinocytes and fibroblasts	
CD99	• Surface glycoprotein with roles in cellular adhesion, activation and migration • Expressed in thymocytes, T cells, other hematopoietic cells and endothelial cells	• Lymphoblastic lymphoma/leukemia • Various non-lymphoid tumors, e.g. Ewing's sarcoma, peripheral primitive neuroectodermal (PNET) tumors and Merkel cell carcinoma
CD138 (syndecan-1)	• Surface glycoprotein involved in cell–cell and cell–matrix adhesion • Expressed in plasma cells, plasmacytoid cells and activated T and B cells	• Marginal zone B-cell lymphoma, myeloma, plasmablastic lymphoma
CD152 (CTLA-4)	• Transmembrane protein on the surface of T cells that transmits an inhibitory signal • Binding to CD80 or CD86 leads to negative regulation of T-cell activation	• A CTLA-4/IgG1 fusion protein (abatacept) that inhibits T-cell costimulation is used as anti-inflammatory treatment for rheumatoid arthritis • A monoclonal antibody (ipilimumab) that *blocks* the effects of CTLA-4 activates the immune system; used to treat melanoma

Table 0.11 Most commonly employed immunohistochemical stains in dermatopathology (cont'd). CDKN2A, cyclin-dependent kinase inhibitor 2A; CD, cluster of differentiation; CK, cytokeratin; CTLA-4, cytotoxic T-lymphocyte antigen-4; HTLV-1, human T-cell leukemia virus 1 (human T-cell lymphotropic virus 1); IL, interleukin; LFA-3, lymphocyte function-associated antigen-3; MAdCAM-1, mucosal addressin cell adhesion molecule-1; MART-1, melanoma antigen recognized by T cells; Melan-A, melanocyte antigen; MHC, major histocompatibility complex; NK, natural killer; PEC, perivascular epithelioid cell. *Table created with the assistance of Dr Stefano Titli.*

Continued

MOST COMMONLY EMPLOYED IMMUNOHISTOCHEMICAL STAINS IN DERMATOPATHOLOGY		
Marker	**Definition/primary cellular expression**	**Applications/comments**
Granzyme B	• Serine protease expressed specifically by activated cytotoxic T cells	• Cytotoxic T-cell lymphomas
MUM1 (multiple myeloma oncogene 1)	• Member of the interferon regulatory factor family of transcription factors • Expressed in plasma cells, late B cells and activated T cells	• Some B-cell neoplasms • $CD30^+$ lymphoproliferative disorders, anaplastic $CD30^+$ lymphoma
Myeloperoxidase	• Lysosomal protein • Most abundant in neutrophils and monocytes	• Myeloid leukemias
Perforin	• Cytolytic protein stored in cytoplasmic granules and then released from cytotoxic T cells	• Cytotoxic T-cell lymphomas
TIA-1	• Granule-associated RNA-binding protein that defines a subset of $CD8^+$ lymphocytes with cytotoxic potential	• Cytotoxic T-cell lymphomas
	MICROORGANISMS	
Cytomegalovirus (CMV)	• Glycoproteins expressed during the immediate-early and early stages of CMV replication within infected cells	• CMV infection
Epstein-Barr virus (EBV)	• EBV membrane protein encoded by *BNLF*	• Post-transplantation lymphoproliferative disorders, Hodgkin disease
Herpes simplex virus (HSV)	• Glycoproteins present within the viral envelope and core	• HSV-1 or -2 infection
Human herpesvirus-8 (HHV-8)	• HHV-8 latency-associated nuclear antigen	• Kaposi sarcoma, primary effusion lymphoma, Castleman's disease
Varicella-zoster virus (VZV)	• Glycoprotein I of VZV	• Varicella or herpes zoster
BCG	• Anti-Bacillus Calmette-Guérin	• Mycobacterial infections • Mycotic infections • Bacterial infections
Borrelia burgdorferi	• Reacts against various antigens (e.g. flagellin) of *Borrelia burgdorferi* • Cross-reacts against *Treponema pallidum*, *B. hermsii,* and *B. parkeri*	• Lyme disease • Syphilis
Treponema pallidum	• Specific for all *Treponema pallidum* antigens	• Syphilis
	PROLIFERATION MARKERS	
Ki-67	• Prototypic antigen for cell cycle-related nuclear proteins, expressed by proliferating cells during the active phases of the cell cycle, but not during the resting phase (G0)	• Assessment of proliferative activity of tumors (with malignancy generally possessing an elevated proliferative index)
MIB-1	• Peptides from recombinant fragments of the gene for Ki-67 antigen	

CD (cluster differentiation) molecules exist as markers on the cell surface and are recognized by specific sets of antibodies used to identify the cell type, stage of differentiation and activity of a cell.

Table 0.11 Most commonly employed immunohistochemical stains in dermatopathology (cont'd). CDKN2A, cyclin-dependent kinase inhibitor 2A; CD, cluster of differentiation; CK, cytokeratin; CTLA-4, cytotoxic T-lymphocyte antigen-4; HTLV-1, human T-cell leukemia virus 1 (human T-cell lymphotropic virus 1); IL, interleukin; LFA-3, lymphocyte function-associated antigen-3; MAdCAM-1, mucosal addressin cell adhesion molecule-1; MART-1, melanoma antigen recognized by T cells; Melan-A, melanocyte antigen; MHC, major histocompatibility complex; NK, natural killer; PEC, perivascular epithelioid cell. *Table created with the assistance of Dr Stefano Titli.*

INTRODUCTION TO THE USE OF DERMOSCOPY (DERMATOSCOPY)

In the prior two sections, we reviewed the basic principles of clinical dermatology and then dermatopathology, with particular emphasis on clinicopathologic correlations. We now turn to an increasingly utilized ancillary examination technique known as dermoscopy (dermatoscopy). It is a non-invasive diagnostic technique that allows for the observation of morphologic features that are not visible to the naked eye, thus forming a link between macroscopic clinical dermatology and microscopic dermatopathology. This "sub-macroscopic" observation of colors and structures (Figs 0.33–0.37) enhances clinical assessment by providing new diagnostic criteria for the differentiation of melanoma from other melanocytic and non-melanocytic, benign and malignant neoplasms[31].

The technique of dermoscopy classically involves applying a liquid or gel to the skin surface and then inspecting the lesion using a hand-held, illuminated microscope (also called a dermatoscope), a stereomicroscope, a camera or a digital imaging system. The magnification of these instruments ranges from 6× to 40× and even up to 100×.

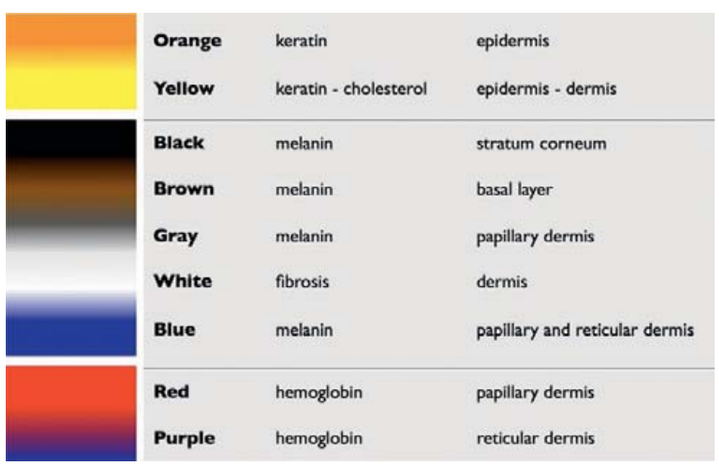


Fig. 0.33 Dermoscopy colors of keratinizing, melanocytic, and vascular tumors.

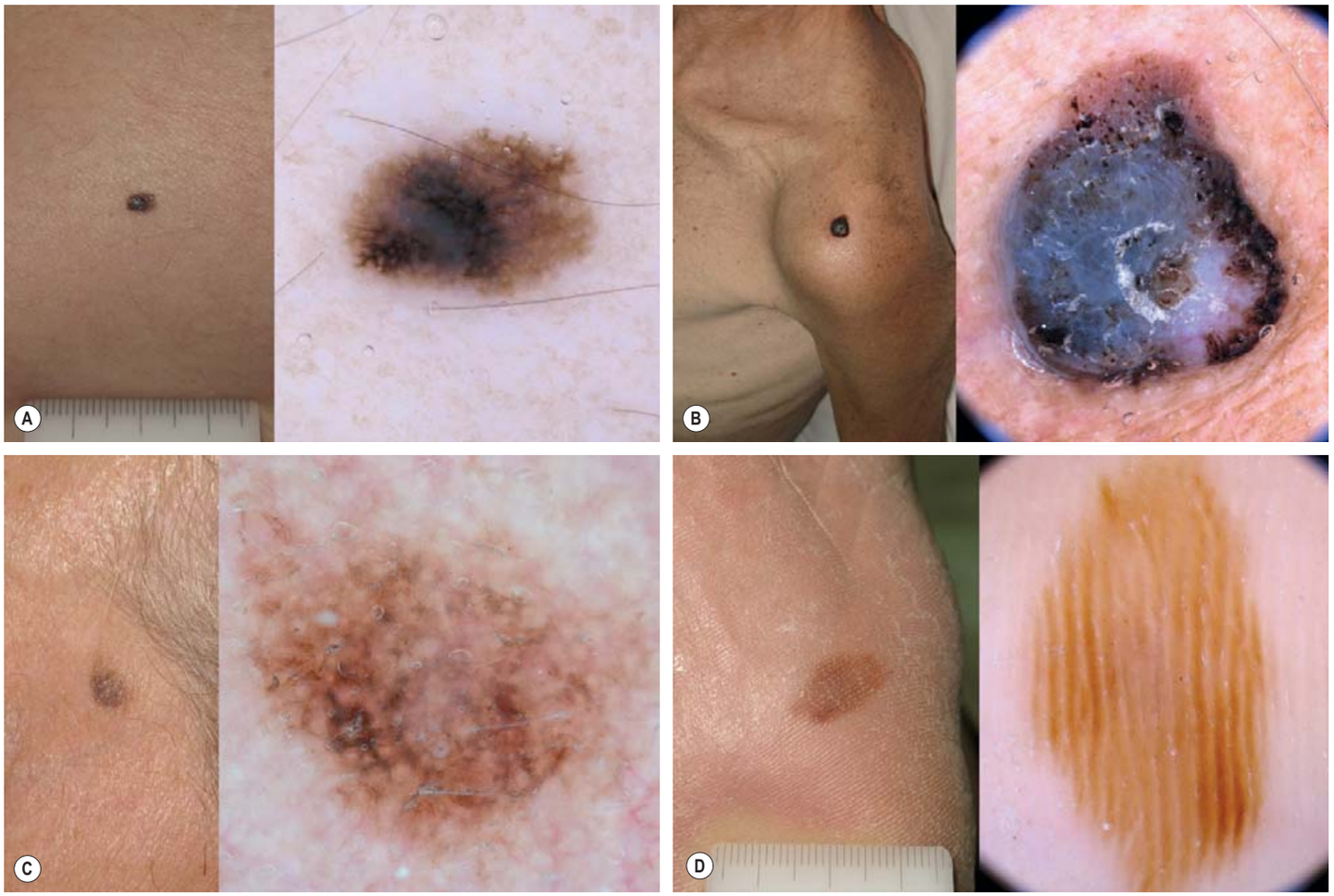


Fig. 0.34 The four most common types of melanoma. A Small superficial melanoma typified dermoscopically by asymmetry of color and structure, atypical network, blue–white structures, and irregular streaks at the periphery. **B** Large thick melanoma with predominant blue–white veil. The combination of blue color with irregular black to brown dots, globules, and blotches (as seen here) is highly specific for the diagnosis of thick melanoma. **C** Small facial melanoma *in situ* (lentigo maligna) typified by gray color and rhomboidal structures in dermoscopy. **D** Acral melanoma *in situ* typified by the characteristic parallel-ridge pattern.

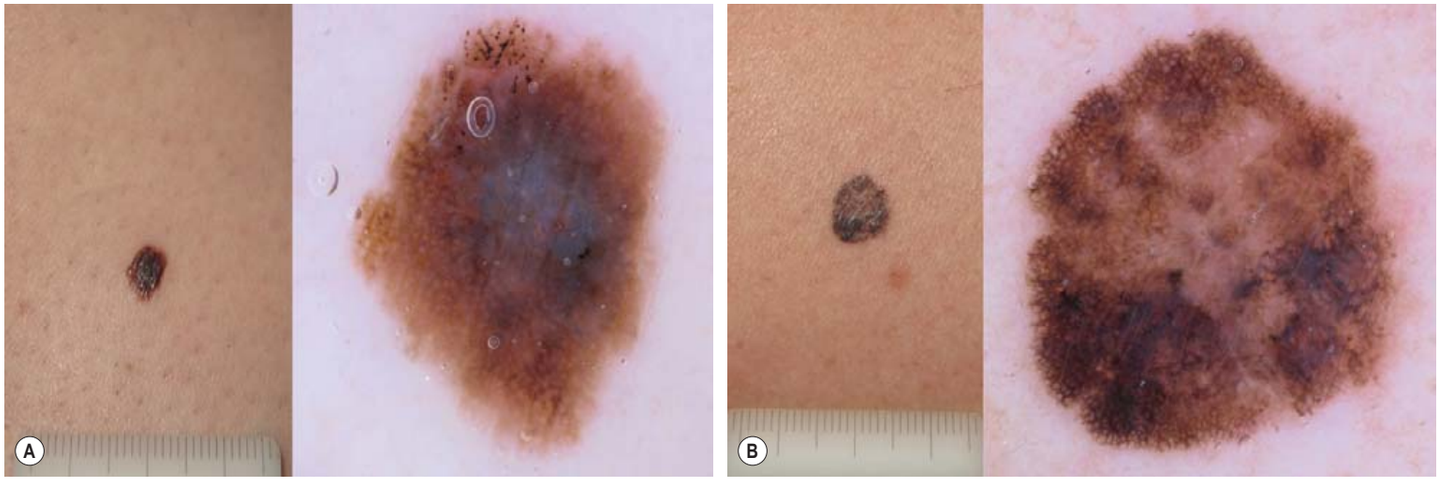


Fig. 0.35 Four examples of superficial melanomas of increasing tumor thickness. A Melanoma *in situ* typified dermoscopically by asymmetry of color and structure, atypical network, blue–white structures, and irregular black dots and globules (at the upper side of the lesion). **B** Melanoma 0.5 mm thick typified predominantly by atypical pigment network and regression structures. The latter are composed by areas of pigment loss (in the center of the lesion) and bluish pepper-like granules corresponding to melanophages.

Continued

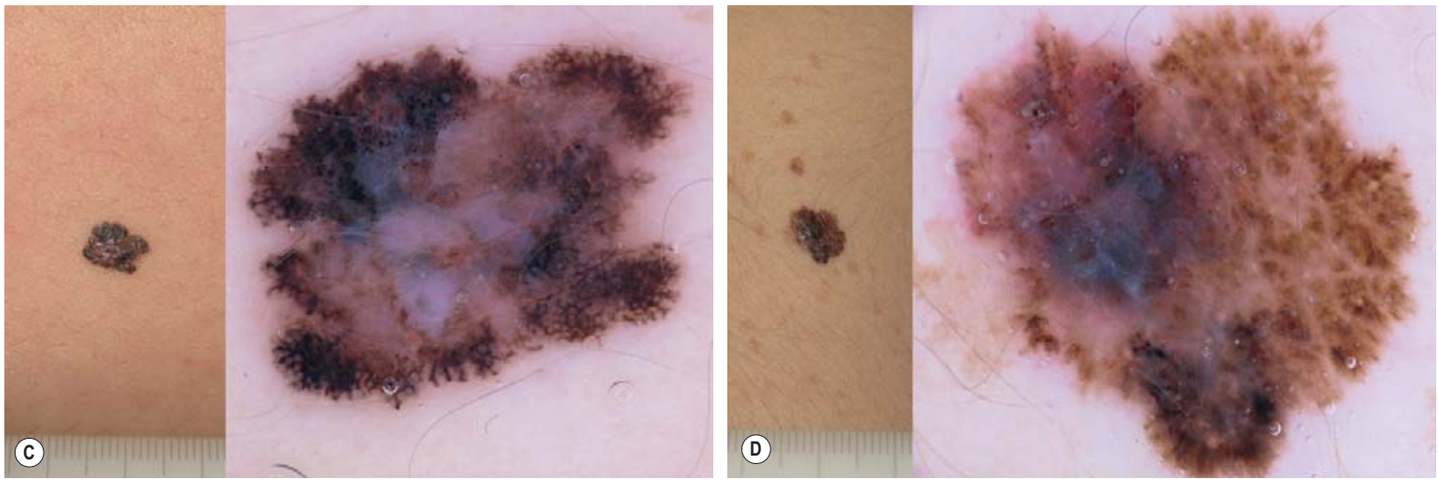


Fig. 0.35 Four examples of superficial melanomas of increasing tumor thickness (cont'd). **C** Melanoma 0.75 mm thick typified by multiple melanoma-specific criteria including asymmetry of color and structure, atypical network, irregular streaks at the periphery, irregular dots and globules (upper side of the lesion), and blue–white structures especially in the center. **D,** Melanoma 0.9 mm thick. Clinically, a palpable area is visible, corresponding dermoscopically to the presence of blue–white veil, a sign of increased tumor thickness. Irregular dots and globules (at the upper side), irregular streaks at the periphery, and uneven brown to black pigmented areas (blotches) are also observed.

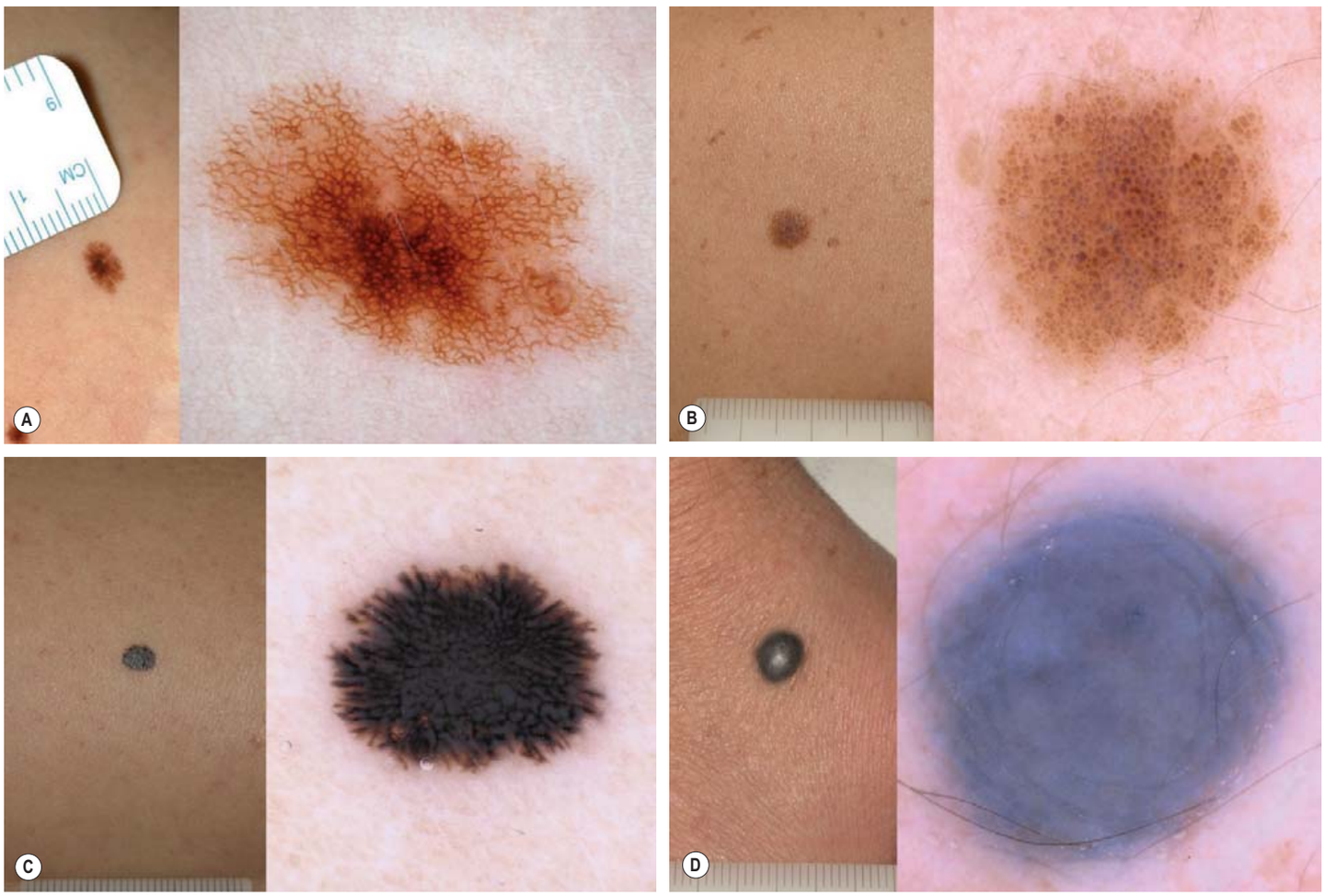


Fig. 0.36 The four most common types of melanocytic nevi – clinical and dermoscopic findings. **A** Typical acquired nevus with reticular pattern in dermoscopy. **B** Small congenital nevus with globular pattern. **C** Reed nevus typified dermoscopically by the classic starburst pattern (regular streaks at the periphery of a heavily pigmented and symmetric small macule). **D** Classic blue homogenous color typically found in blue nevi.

The widely used dermatoscope has a 10-fold magnification, sufficient for routine assessment of skin tumors. The fluid placed on the lesion eliminates surface reflection and renders the cornified layer translucent, thus allowing a better visualization of pigmented structures within the epidermis, the dermal–epidermal junction and the superficial dermis. Moreover, the size and shape of vessels of the superficial vascular plexus are better visualized with this procedure (Figs 0.38 & 0.39). More recently, hand-held devices have been introduced that utilize polarized light which renders the epidermis translucent. With these latter devices, use of a liquid medium is no longer required in order to visualize subsurface structures.

Nowadays, the dermatoscope is increasingly being used by dermatologists as a stethoscope equivalent. This is because it not only facilitates the diagnosis of pigmented and non-pigmented skin tumors, but it also

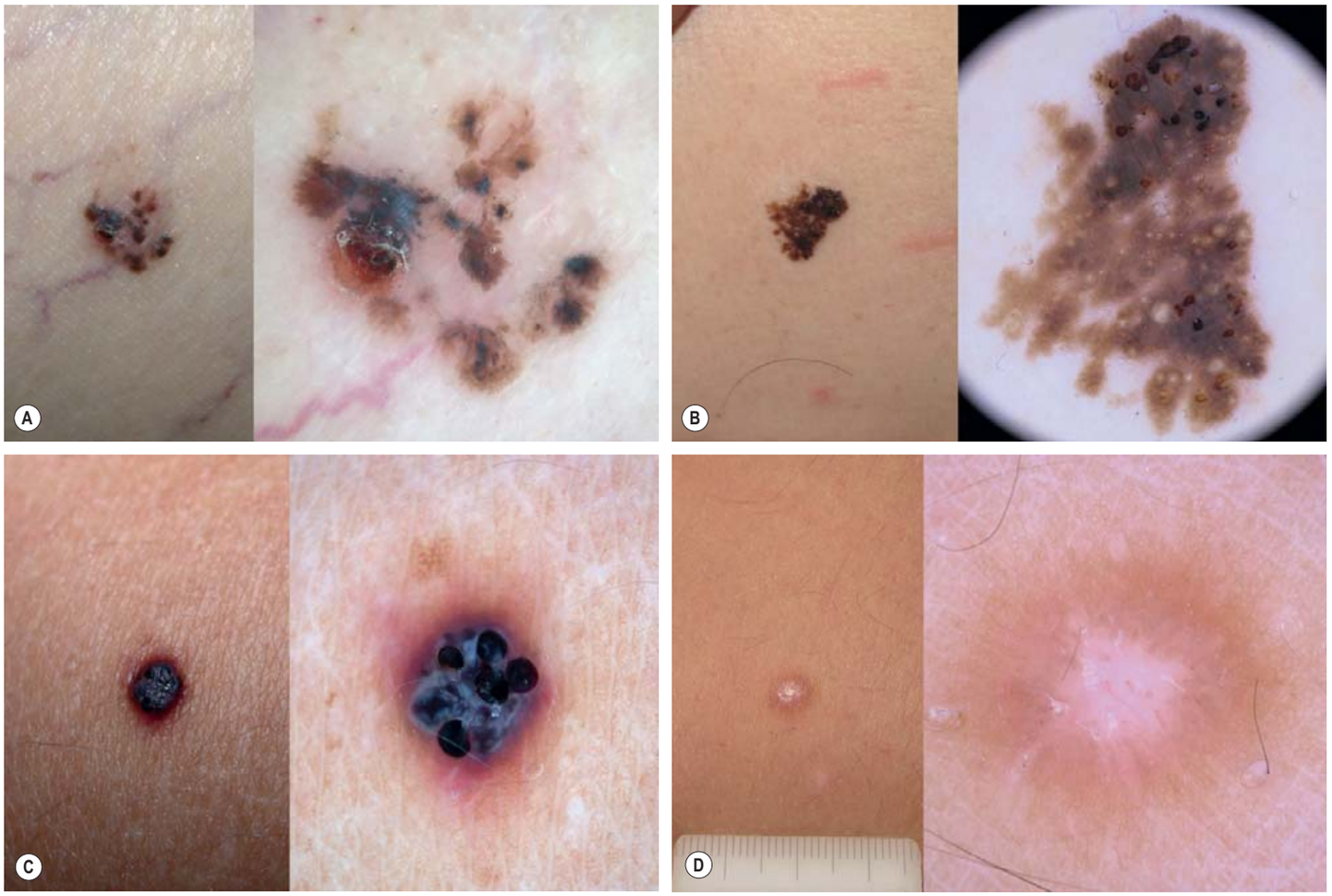


Fig. 0.37 Four non-melanocytic pigmented tumors – clinical and dermoscopic findings. A Pigmented basal cell carcinoma with leaf-like areas (islands of blue–gray color) at the periphery and a small erosion of reddish color at the left side of the lesion. **B** Seborrheic keratosis with typical milia-like cysts (white shining globules) and comedo-like openings (black targetoid globules). **C** Angiokeratoma with red–black lacunas clearly visible as well-demarcated roundish structures. **D** A dermatofibroma with characteristic central white patch and peripheral delicate pseudo-network.

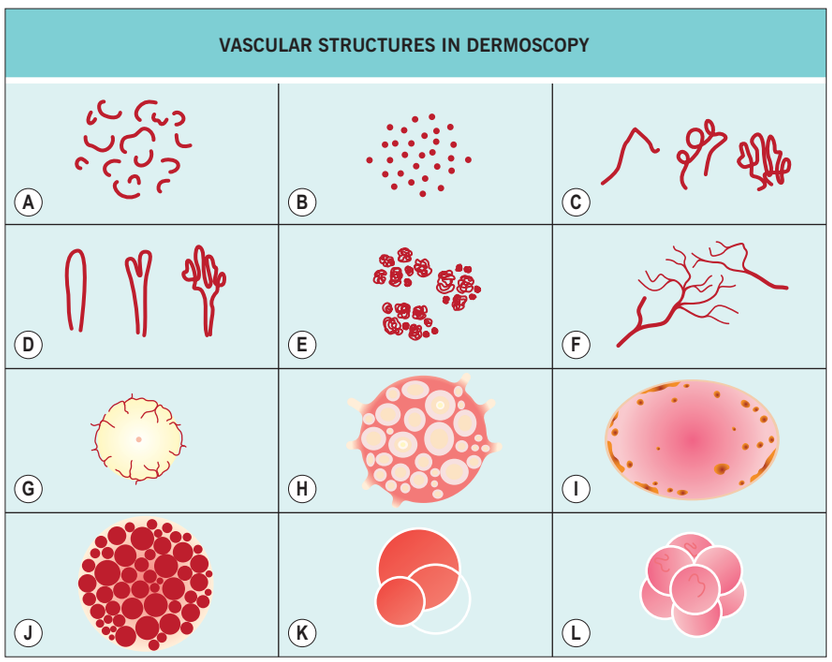


Fig. 0.38 Vascular structures in dermoscopy. (See also Table 0.13 for definitions and diagnostic significance). **A** Comma vessels (typical of dermal and congenital nevi). **B** Dotted vessels (often found in melanoma and Spitz nevi). **C** Linear-irregular vessels (typical of melanoma). **D** Hairpin vessels (most common in keratinizing tumors, such as seborrheic keratosis and squamous cell carcinoma). **E** Glomerular vessels (found in Bowen's disease). **F** Arborizing vessels (typical of basal cell carcinoma). **G** Crown vessels (common finding in sebaceous hyperplasia). **H** Strawberry pattern (typical of facial actinic keratosis). **I** Multiple blood crusts over a red background (typical finding in superficial basal cell carcinoma). **J** Red lacunas (typical finding in hemangiomas). **K** Red homogenous areas intersected by whitish lines (most common in pyogenic granuloma). **L** Milky-red areas (typical of melanoma).

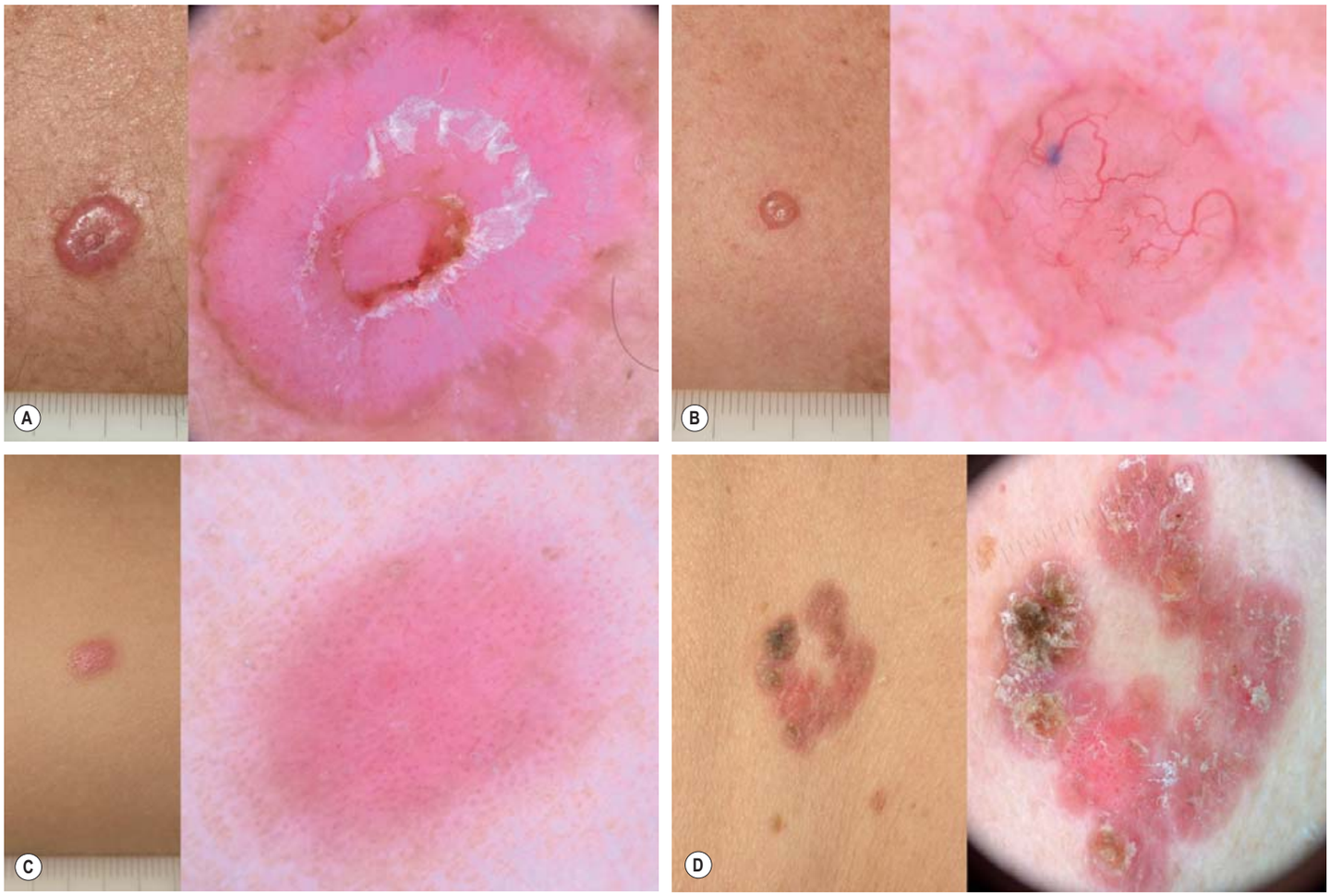


Fig. 0.39 Four non-pigmented skin tumors – clinical and dermoscopic findings. A This amelanotic melanoma is typified by a central ulceration, polymorphic vascular structures (combination of dotted and linear-irregular vessels), and milky-red color in the background. **B** Nodular basal cell carcinoma with striking arborizing vessels. **C** A Spitz nevus with dotted vessels and typical negative pigment network (reticular depigmentation) at the periphery. **D** An example of Bowen's disease with clusters of glomerular vessels that in combination with superficial scales are highly specific for the diagnosis.

improves recognition of a growing number of non-pigmented skin conditions. For example, dermoscopy can facilitate the diagnosis of scabies due to the presence of the pathognomonic "jet with contrail" sign[32] (Fig. 0.40A). Additional skin infections and infestations that may be differentiated with increased confidence include pediculosis, phthiriasis, tungiasis, tinea nigra and molluscum contagiosum. For two of the more common inflammatory skin disorders – psoriasis and lichen planus – the use of dermoscopy allows for the visualization of specific submacroscopic features, including the "red dots" pattern in psoriasis and the "whitish striae" pattern in lichen planus (Fig. 0.40B,C). Scalp psoriasis and seborrheic dermatitis may also be differentiated via dermoscopy. The most notable scalp psoriasis features are red dots and globules, twisted red loops and glomerular vessels, whereas seborrheic dermatitis is characterized by the presence of arborizing vessels and atypical red vessels, as well as featureless areas with no particular vascular pattern and no red dots or globules. In a recent review of the indications for dermoscopy, more than 35 different inflammatory and infectious skin diseases were listed[33]. One of the newest applications of this technique is trichoscopy, namely the dermoscopic observation of the scalp, which may prove helpful in the differential diagnosis of hair and scalp diseases[34] (Fig. 0.40D).

The aim of dermoscopy in melanoma screening is to maximize early detection while minimizing the unnecessary excision of benign skin tumors. Over the past few years, three meta-analyses and two randomized studies have proven definitively that dermoscopy improves the sensitivity for melanoma detection as compared to just the naked eye[35–39]. In a meta-analysis of dermoscopy studies performed in a clinical setting, the relative odds ratio for dermoscopic diagnosis of cutaneous melanoma (compared to naked eye examination) was 15.6 ($p = 0.016$). The average sensitivities for melanoma detection by naked eye versus dermoscopic examinations were 74% and 90%, respectively. Furthermore, this improved sensitivity came about without a decrease in specificity, suggesting that better melanoma detection (16% improvement) occurred without increasing the number of unnecessary excisions of benign lesions[39]. A randomized study found that combining eye and dermoscopic examinations led to a significant reduction in the percentage of patients referred for biopsy (9% vs 15.6%; $p = 0.013$)[37]. In summary, the use of dermoscopy is associated with a significant increase in the number of excised melanomas, as well as a significant reduction in the number of excised benign pigmented skin lesions.

Pattern analysis is the most well-known and reliable method for differentiating pigmented skin tumors. This is based on a two-step algorithm, where first there is recognition of basic criteria for melanocytic and non-melanocytic tumors (first step; Table 0.12) and then benign and malignant features of melanocytic nevi and melanoma, respectively (second step; Tables 0.13 & 0.14)[31]. Recent attempts to simplify the dermoscopic approach to diagnosing melanocytic nevi and melanoma include the ABCD rule, the Menzies method, and the 7-point checklist[31] (Tables 0.15–0.17).

In a virtual "Consensus Net Meeting on Dermoscopy"[31], 40 experts were able to correctly classify more than 95% of melanocytic lesions and more than 90% of non-melanocytic lesions, with pattern analysis producing the best diagnostic performance. The alternative algorithms (ABCD rule, Menzies method, and 7-point checklist) revealed similar sensitivities as compared to pattern analysis but ~10% less specificity. The favorable results of pattern analysis were not unexpected, as this method probably best reflects the workings of the human brain when categorizing morphologic images and is similar to the pattern analysis

Fig. 0.40 Four non-neoplastic skin disorders – clinical and dermoscopic findings. A A 6-month-old boy with scabies. By dermoscopy, a characteristic "jet with contrail" structure can be identified corresponding to the anterior part of the mite (arrow) and the burrow behind it. **B** By dermoscopy, classic psoriasis plaques exhibit regular dotted vessels. **C** The dermoscopic pattern of lichen planus is definitely different from the previous one. Here, dotted vessels are seen at the border of typical whitish lines and clods, which closely resemble the Wickham striae found in lichen planus of the oral mucosa. **D** Typical yellow dots seen dermoscopically in scalp patches of alopecia areata.

PATTERN ANALYSIS: FIRST-STEP ALGORITHM FOR DIFFERENTIATION BETWEEN MELANOCYTIC AND NON-MELANOCYTIC LESIONS		
Dermoscopic criterion	**Definition**	**Diagnostic significance**
Pigment network – pseudo-network[†]	Network of brownish interconnected lines over a background of tan diffuse pigmentation. In facial skin, a peculiar pigment network, also called a pseudo-network, is typified by round, equally sized network holes corresponding to the pre-existing follicular ostia	Melanocytic lesion
Aggregated globules	Numerous, variously sized, more or less clustered, round to oval structures with various shades of brown and gray–black. They should be differentiated from multiple blue–gray globules	Melanocytic lesion
Streaks	These have been previously described separately as pseudopods and radial streaming, but are now combined into the one term. They are bulbous and often kinked or finger-like projections seen at the edge of a lesion. They may arise from network structures but more commonly do not. They range in color from tan to black	Melanocytic lesion
Homogeneous blue pigmentation[‡]	Structureless blue pigmentation in the absence of pigment network or other distinctive local features	Melanocytic lesion
Parallel pattern	Seen in melanocytic lesions of palms/soles and mucosal areas. On palms/soles, the pigmentation may follow the sulci or the cristae (i.e. furrows or ridges) of the dermatoglyphics. Rarely arranged at right angles to these structures	Melanocytic lesion
Multiple milia-like cysts	Numerous, variously sized, white or yellowish, roundish structures	Seborrheic keratosis
Comedo-like openings	Brown–yellowish to brown–black, round to oval, sharply circumscribed keratotic plugs in the ostia of hair follicles. When irregularly shaped, comedo-like openings are also called irregular crypts	Seborrheic keratosis
Light-brown fingerprint-like structures	Light-brown, delicate, network-like structures with the pattern of a fingerprint	Seborrheic keratosis
Cerebriform pattern	Dark-brown furrows between ridges typifying a brain-like appearance	Seborrheic keratosis
Arborizing vessels	Tree-like branching telangiectasias	Basal cell carcinoma*

Table 0.12 Pattern analysis: first-step algorithm for differentiation between melanocytic and non-melanocytic lesions. Adapted from ref. 31.

Continued

PATTERN ANALYSIS: FIRST-STEP ALGORITHM FOR DIFFERENTIATION BETWEEN MELANOCYTIC AND NON-MELANOCYTIC LESIONS		
Dermoscopic criterion	**Definition**	**Diagnostic significance**
Leaf-like structures	Brown to gray/blue discrete bulbous structures forming leaf-like patterns. They are discrete pigmented nests (islands) never arising from a pigment network and usually not arising from adjacent confluent pigmented areas	Basal cell carcinoma*
Large blue–gray ovoid nests	Well-circumscribed, confluent or near confluent, pigmented, ovoid or elongated areas, larger than globules, and not intimately connected to a pigmented tumor body	Basal cell carcinoma*
Multiple blue–gray globules	Multiple globules (not dots) that should be differentiated from multiple blue–gray dots (melanophages)	Basal cell carcinoma*
Spoke-wheel areas	Well-circumscribed radial projections, usually tan in color but sometimes blue or gray, meeting at an often darker (dark brown, black or blue) central axis	Basal cell carcinoma*
Ulceration§	Absence of the epidermis, often associated with congealed blood, not due to a well-described recent history of trauma	Basal cell carcinoma*
Red–blue lacunas	More or less sharply demarcated, roundish or oval areas with a reddish, red–bluish, or dark-red to black coloration	Vascular lesion
Red–bluish to reddish-black homogeneous areas	Structureless homogeneous areas of red–bluish to red–black coloration	Vascular lesion
None of the listed criteria	Absence of the above-mentioned criteria	Melanocytic lesion

*To diagnose a basal cell carcinoma, the negative feature of pigment network must be absent and one or more of the positive features listed here must be present.
†Exception 1: Pigment network or pseudo-network is also present in solar lentigo and rarely in seborrheic keratosis and pigmented actinic keratosis. A delicate, annular pigment network is also commonly seen in dermatofibroma and accessory nipple (clue for diagnosis of dermatofibroma and accessory nipple: central white patch).
‡Exception 2: Homogeneous blue pigmentation (dermoscopic hallmark of blue nevus) is also seen (uncommonly) in some hemangiomas and basal cell carcinomas and (commonly) in intradermal melanoma metastases.
§Exception 3: Ulceration is also seen less commonly in invasive melanoma.

Table 0.12 Pattern analysis: first-step algorithm for differentiation between melanocytic and non-melanocytic lesions (cont'd). Adapted from ref. 31.

PATTERN ANALYSIS: SECOND-STEP ALGORITHM FOR DIFFERENTIATION BETWEEN MELANOCYTIC NEVI AND MELANOMA		
Dermoscopic criterion	**Definition**	**Diagnostic significance**
	GLOBAL FEATURES	
Reticular pattern	Pigment network covering most parts of the lesion	Melanocytic nevus
Globular pattern	Numerous, variously sized, round to oval structures with various shades of brown and gray–black	Melanocytic nevus
Cobblestone pattern	Large, closely aggregated, somehow angulated globule-like structures resembling a cobblestone	Dermal nevus
Homogeneous pattern	Diffuse, brown, gray–blue to gray–black pigmentation in the absence of other distinctive local features	Melanocytic (blue) nevus
Starburst pattern	Pigmented streaks in a radial arrangement at the edge of the lesion	Spitz/Reed nevus
Parallel pattern	Pigmentation on palms/soles that follows the sulci or the cristae (furrows or ridges), rarely arranged at right angles to these structures	Acral nevus/melanoma (see below)
Multicomponent pattern	Combination of three or more of the above patterns	Melanoma
Nonspecific pattern	Pigmented lesion lacking above patterns	Possible melanoma
	LOCAL FEATURES	
Pigment network	Typical pigment network: light- to dark-brown network with small, uniformly spaced network holes and thin network lines distributed more or less regularly throughout the lesion and usually thinning out at the periphery	Benign melanocytic lesion
	Atypical pigment network: black, brown or gray network with irregular holes and thick lines	Melanoma
Dots/globules	Black, brown, round to oval, variously sized structures regularly or irregularly distributed within the lesion	If regular, benign melanocytic lesion If irregular, melanoma
Streaks	These have been previously described separately as pseudopods and radial streaming. Streaks are bulbous and often kinked or finger-like projections seen at the edge of a lesion. They may arise from network structures but more commonly do not. They range in color from tan to black	If regular, benign melanocytic lesion (Spitz/Reed nevus) If irregular, melanoma
Blue–whitish veil	Irregular, structureless area of confluent blue pigmentation with an overlying white "ground-glass" film. The pigmentation cannot occupy the entire lesion and usually corresponds to a clinically elevated part of the lesion	Melanoma
Regression structures	White scar-like depigmentation and/or blue pepper-like granules usually corresponding to a clinically flat part of the lesion	Melanoma
Hypopigmentation	Areas with less pigmentation than the overall pigmentation of the lesion	Nonspecific
Blotches	Black, brown, and/or gray structureless areas with symmetrical or asymmetrical distribution within the lesion	If symmetrical, benign melanocytic lesion If asymmetrical, melanoma

Table 0.13 Pattern analysis: second-step algorithm for differentiation between melanocytic nevi and melanoma. Adapted from ref. 31.

Continued

PATTERN ANALYSIS: SECOND-STEP ALGORITHM FOR DIFFERENTIATION BETWEEN MELANOCYTIC NEVI AND MELANOMA		
Dermoscopic criterion	**Definition**	**Diagnostic significance**
	SITE-RELATED FEATURES	
Face	Typical pseudo-network (round, equally sized network holes corresponding to the pre-existing follicular ostia)	Benign melanocytic lesion
	Annular-granular structures (multiple blue–gray dots surrounding the follicular ostia with an annular-granular appearance)	Melanoma
	Gray pseudo-network (gray pigmentation surrounding the follicular ostia, formed by the confluence of annular-granular structures)	Melanoma
	Rhomboidal structures (gray–brown pigmentation surrounding the follicular ostia with a rhomboidal appearance)	Melanoma
	Asymmetric pigmented follicles (eccentric annular pigmentation around follicular ostia)	Melanoma
Palms/soles	Parallel-furrow pattern (pigmentation following the sulci superficiales)	Acral nevus
	Lattice-like pattern (pigmentation following and crossing the furrows)	Acral nevus
	Fibrillar pattern (numerous, finely pigmented filaments perpendicular to the furrows and ridges)	Acral nevus
	Parallel-ridge pattern (pigmentation aligned along the cristae superficiales)	Melanoma

Table 0.13 Pattern analysis: second-step algorithm for differentiation between melanocytic nevi and melanoma (cont'd). Adapted from ref. 31.

VASCULAR STRUCTURES SEEN IN VARIOUS SKIN TUMORS		
Pattern	**Definition**	**Diagnostic significance**
Comma	Coarse vessels that are slightly curved and barely branching	Congenital and dermal nevi
Dotted	Tiny red dots densely aligned next to each other	Melanocytic lesion (often Spitz nevus and melanoma)
Linear-irregular	Linear, irregularly shaped, sized and distributed red structures	Melanoma
Hairpin	Vascular loops sometimes twisted and bending. They can be surrounded by a whitish halo	With white halo: keratinizing proliferation (seborrheic keratosis, squamous cell carcinoma, keratoacanthoma, viral wart) Without white halo: melanoma
Glomerular	Variation on the theme of dotted vessels. They are tortuous capillaries often distributed in clusters mimicking the glomerular apparatus of the kidney	Bowen's disease
Arborizing	Stem vessels of large diameter branching irregularly into finest terminal capillaries. The color is bright red, being sharply focused in dermoscopic images due to their location immediately beneath the surface of the tumor	Basal cell carcinoma
Crown	Groups of orderly bending, scarcely branching vessels located along the border of the lesion	Sebaceous hyperplasia
Strawberry	Pink-to-red "pseudo-network" around hair follicles of the face, frequently intermingled with fine, linear-wavy vessels. Often hair follicles are filled with yellowish keratotic plugs	Actinic keratosis
Corkscrew	Linear vessels twisted along a central axis	Thick melanoma or melanoma metastasis
Milky-red color	Globules and/or larger areas of fuzzy or unfocused milky-red color often corresponding to an elevated part of the lesion	Melanoma
Polymorphous	Any combination of two or more different types of vascular structures. The most frequent is linear-irregular and dotted vessels	Malignant tumor (melanoma, basal cell carcinoma, squamous cell carcinoma, etc.)

Table 0.14 Vascular structures seen in various skin tumors. See also Figs 0.38 & 0.39.

ABCD RULE FOR THE DERMOSCOPIC DIFFERENTIATION BETWEEN BENIGN MELANOCYTIC LESIONS AND MELANOMA			
Dermoscopic criterion	**Definition**	**Score**	**Weight factor**
Asymmetry	In 0, 1, or 2 perpendicular axes; assess not only contour, but also colors and structures	0–2	× 1.3
Border	Abrupt ending of pigment pattern at the periphery in 0–8 segments	0–8	× 0.1
Color	Presence of up to six colors (white, red, light brown, dark brown, blue–gray, black)	1–6	× 0.5
Dermoscopic structures	Presence of network, structureless (homogeneous) areas, branched streaks, dots, and globules	1–5	× 0.5

Table 0.15 ABCD rule for the dermoscopic differentiation between benign melanocytic lesions and melanoma. Formula for calculating total score: (A score × 1.3) + (B score × 0.1) + (C score × 0.5) + (D score × 0.5). Interpretation of total score: <4.75, benign melanocytic lesion; 4.75–5.45, suspicious lesion (close follow-up or excision recommended); >5.45, lesion highly suspicious for melanoma. Adapted from ref. 31.

MENZIES SCORING METHOD FOR THE DERMOSCOPIC DIFFERENTIATION BETWEEN BENIGN MELANOCYTIC LESIONS AND MELANOMA	
Dermoscopic criterion	**Definition**
NEGATIVE FEATURES	
Symmetry of pattern	Symmetry of pattern is required across all axes through the lesion's center of gravity (center of the lesion). Symmetry of pattern does not require shape symmetry
Presence of a single color	The colors scored are black, gray, blue, dark brown, tan and red. White is not scored as a color
POSITIVE FEATURES	
Blue–white veil	An area of irregular, structureless confluent blue pigmentation with an overlying white "ground-glass" haze. It cannot occupy the entire lesion and cannot be associated with red–blue lacunas
Multiple brown dots	Focal areas of multiple brown (usually dark brown) dots (not globules)
Pseudopods	Bulbous and often kinked projections that are found at the edge of a lesion, connected either directly to the tumor body or to the pigmented network. They can never be seen distributed regularly or symmetrically around the lesion. When connected directly to the tumor body, they must have an acute angle to the tumor edge or arise from linear or curvilinear extensions. When connected to the network, the width of the bulbous ending must be greater than the width of any part of the surrounding network and at least double that of its directly connected network projection
Radial streaming	Finger-like extensions at the edge of a lesion which are never distributed regularly or symmetrically around the lesion
Scar-like depigmentation	Areas of white distinct irregular extensions (true scarring), which should not be confused with hypo- or depigmentation due to simple loss of melanin
Peripheral black dots/globules	Black dots/globules found at or near the edge of the lesion
Multiple (5–6) colors	The colors scored are black, gray, blue, dark brown, tan and red. White is not scored as a color
Multiple blue/gray dots	Foci of multiple blue or gray dots (not globules) often described as "pepper-like" granules in pattern
Broadened network	A network made up of irregular thicker "cords" of the net, often seen focally thicker

Table 0.16 Menzies scoring method for the dermoscopic differentiation between benign melanocytic lesions and melanoma. For melanoma to be diagnosed, a lesion must have neither of both negative features and one or more of the nine positive features. Adapted from ref. 31.

SEVEN-POINT CHECKLIST FOR THE DERMOSCOPIC DIFFERENTIATION BETWEEN BENIGN MELANOCYTIC LESIONS AND MELANOMA		
Dermoscopic criterion	**Definition**	**Score**
1. Atypical pigment network	More than one type of network (in terms of color and thickness of the meshes) irregularly distributed within the lesion	2
2. Blue–whitish veil	Irregular, structureless area of confluent blue pigmentation with an overlying white "ground-glass" film. The pigmentation cannot occupy the entire lesion and usually corresponds to a clinically elevated part of the lesion	2
3. Atypical vascular pattern	Linear-irregular or dotted vessels not clearly seen within regression structures	2
4. Irregular streaks	Brown to black, bulbous or finger-like projections irregularly distributed at the edge of a lesion. They may arise from network structures but more commonly do not	1
5. Irregular dots/globules	Black, brown, round to oval, variously sized structures irregularly distributed within the lesion	1
6. Irregular blotches	Black, brown, and/or gray structureless areas asymmetrically distributed within the lesion	1
7. Regression structures	White scar-like depigmentation and/or blue pepper-like granules usually corresponding to a clinically flat part of the lesion	1

Table 0.17 Seven-point checklist for the dermoscopic differentiation between benign melanocytic lesions and melanoma. By simple addition of the individual scores, a minimum total score of 3 is required for the diagnosis of melanoma, whereas a total score of less than 3 is indicative of non-melanoma. Adapted from ref. 31.

DEFINITIONS OF DERMOSCOPIC CRITERIA FOR THE 3-POINT CHECKLIST	
Criterion	**Definition**
Asymmetry	Asymmetrical distribution of colors and dermoscopic structures
Atypical network*	More than one type of network (in terms of color and thickness of the meshes) irregularly distributed within the lesion
Blue–white structures†	Presence of any type of blue and/or white color
*Usually found in early melanoma. †Usually found in both melanoma and pigmented basal cell carcinoma.	

Table 0.18 Definitions of dermoscopic criteria for the 3-point checklist. The presence of more than one criterion suggests a suspicious lesion. Adapted from ref. 38.

utilized in general clinical dermatology and dermatopathology (see above). That is, there is a subjective perception of the "gestalt" of a given lesion and its integration into an internalized knowledge base, which is the result of expertise on the subject; in contrast, "simplified" algorithms were designed to keep non-experts from failing to detect melanomas, even at the cost of decreased specificity.

Results of the virtual consensus study showed that three criteria (asymmetry, atypical network, and blue–white structures) were especially important in distinguishing malignant from benign pigmented skin tumors (Table 0.18). Using this 3-point dermoscopy rule as a screening test, general physicians previously inexperienced in the use of dermoscopy were able to perform better triage of skin lesions suggestive of skin cancer as compared to examination with the naked eye (referral sensitivity of 79% and 54%, respectively), without increasing the number of unnecessary expert consultations[38].

While the continued, skilled use of dermoscopy will undoubtedly aid in the early recognition of melanoma as well as the diagnosis of inflammatory disorders and other cutaneous neoplasms, there are additional technologies that may also have a significant impact on our specialty over the next decade.

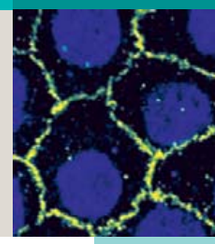
CONCLUSION

In conclusion, this chapter has sought to provide an introduction and basic structural framework to the study of dermatology by addressing terminology, morphology, pattern recognition, and a number of techniques that will all serve to enhance the practice of clinicopathologic correlation. The desired end results are more accurate diagnoses and better care of patients.

REFERENCES

1. Chen SC, Pennie ML, Kolm P, et al. Diagnosing and managing cutaneous pigmented lesions: primary care physicians versus dermatologists. J Gen Intern Med. 2006;21:678–82.
2. Tran H, Chen K, Lim AC, et al. Assessing diagnostic skill in dermatology: a comparison between general practitioners and dermatologists. Australas J Dermatol. 2005;46:230–4.
3. Taylor SC, Cook-Bolden F. Defining skin of color. Cutis. 2002;69:435–7.
4. Thong HY, Jee SH, Sun CC, Boissy RE. The patterns of melanosome distribution in keratinocytes of human skin as one determining factor of skin colour. Br J Dermatol. 2003;149:498–505.
5. Pappert AS, Scher RK, Cohen JL. Longitudinal pigmented nail bands. Dermatol Clin. 1991;9:703–16.
6. Dominguez-Cherit J, Roldan-Marin R, Pichardo-Velazquez P, et al. Melanonychia, melanocytic hyperplasia, and nail melanoma in a Hispanic population. J Am Acad Dermatol. 2008;59:785–91.
7. Meleti M, Vescovi P, Mooi WJ, et al. Pigmented lesions of the oral mucosa and perioral tissues: a flow-chart for the diagnosis and some recommendations for the management. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;105:606–16.
8. James WD, Carter JM, Rodman OG. Pigmentary demarcation lines: a population survey. J Am Acad Dermatol. 1987;16:584–90.
9. Nordlund JJ, Abdel-Malek ZA. Mechanisms for post-inflammatory hyperpigmentation and hypopigmentation. Prog Clin Biol Res. 1988;256:219–36.
10. Jablonski NG, Chaplin G. The evolution of human skin coloration. J Hum Evol. 2000;39:57–106.
11. Ben-Gashir MA, Hay RJ. Reliance on erythema scores may mask severe atopic dermatitis in black children compared with their white counterparts. Br J Dermatol. 2002;147:920–5.
12. Jones A, Walling H. Retiform purpura in plaques: a morphological approach to diagnosis. Clin Exp Dermatol. 2007;32:596–602.
13. Bolognia JL, Orlow SJ, Glick SA. Lines of Blaschko. J Am Acad Dermatol. 1994;1:157–90.
14. Boyd A, Nelder K. The isormorphic response of Koebner. Int J Dermatol. 1990;29:401–10.
15. Weiss G, Shemer A, Trau A. The Koebner phenomenon: review of the literature. J Eur Acad Dermatol Venereol. 2002;16:241–8.
16. Swerdlin A, Berkowitz C, Craft N. Cutaneous signs of child abuse. J Am Acad Dermatol. 2007;57:371–92.
17. Chuh AA. Rash orientation in pityriasis rosea: a qualitative study. Eur J Dermatol. 2002;12:253–6.
18. McLaurin CI. Unusual patterns of common dermatoses in blacks. Cutis. 1983;32:352–5, 358–60.
19. Singh S, Grummer SE, Hancox JG, et al. The extent of dermatopathology education: a comparison of pathology and dermatology. J Am Acad Dermatol. 2005;53:694–7.
20. Peters MS, Winkelmann RK. The biopsy. Dermatol Clin. 1984;2:209–17.
21. Smoller DR, Hiatt KM. How to maximize information from a skin biopsy. In: Dermatopathology: The Basics. New York: Springer Science-Business Media, 2009:37–61.
22. Pariser RJ, Divers A, Nassar A. The relationship between biopsy technique and uncertainty in the histopathologic diagnosis of melanoma. Dermatol Online J. 1999;5:4.
23. Ackerman AB. Histologic Diagnosis of Inflammatory Skin Diseases: A Method by Pattern Analysis. Philadelphia: Lea & Febiger, 1978.
24. Ackerman AB. An algorithmic method for histologic diagnosis of inflammatory and neoplastic skin diseases by analysis of their patterns. Am J Dermatopathol. 1985;7:105–7.
25. Ackerman AB, Boer A, Bennin B, et al. Histologic Diagnosis of Inflammatory Skin Diseases: An Algorithmic Method Based on Pattern Analysis, 3rd edn. New York: Ardor Scribendi, 2005.
26. Zelger BW, Sidoroff A, Orchard G, Cerio R. Non-Langerhans cell histiocytoses. A new unifying concept. Am J Dermatopathol. 1996;18:460–504.
27. Brownstein MH, Rabinowitz AD. The invisible dermatoses. J Am Acad Dermatol. 1983;8:579–88.
28. Requena L, Kutzner H. Invisible dermatoses. Pathologe. 2002;23:54–64.
29. Logan ME, Zaim MT. Histologic stains in dermatopathology. J Am Acad Dermatol. 1990;22:820–30.
30. Wasserman J, Maddox J, Racz M, et al. Update on immunohistochemical methods relevant to dermatopathology. Arch Pathol Lab Med. 2009;113:1053–61.
31. Argenziano G, Soyer HP, Chimenti S, et al. Dermoscopy of pigmented skin lesions: results of a consensus meeting via the Internet. J Am Acad Dermatol. 2003;48:679–93.
32. Dupuy A, Dehen L, Bourrat E, et al. Accuracy of standard dermoscopy for diagnosing scabies. J Am Acad Dermatol. 2007;56:53–62.
33. Zalaudek I, Argenziano G, Di Stefani A, et al. Dermoscopy in general dermatology. Dermatology. 2006;212:7–18.
34. Rudnicka L, Olszewska M, Rakowska A, et al. Trichoscopy: a new method for diagnosing hair loss. J Drugs Dermatol. 2008;7:651–4.
35. Bafounta ML, Beauchet A, Aegerter P, Saiag P. Is dermoscopy (epiluminescence microscopy) useful for the diagnosis of melanoma? Results of a meta-analysis using techniques adapted to the evaluation of diagnostic tests. Arch Dermatol. 2001;137:1343–50.
36. Kittler H, Pehamberger H, Wolff K, Binder M. Diagnostic accuracy of dermoscopy. Lancet Oncol. 2002;3:159–65.
37. Carli P, de Giorgi V, Chiarugi A, et al. Addition of dermoscopy to conventional naked-eye examination in melanoma screening: a randomized study. J Am Acad Dermatol. 2004;50:683–9.
38. Argenziano G, Puig S, Zalaudek I, et al. Dermoscopy improves accuracy of primary care physicians to triage lesions suggestive of skin cancer. J Clin Oncol. 2006;24:1877–82.
39. Vestergaard ME, Macaskill P, Holt PE, Menzies SW. Dermoscopy compared with naked eye examination for the diagnosis of primary melanoma: a meta-analysis of studies performed in a clinical setting. Br J Dermatol. 2008;159:669–76.
40. Kim J, Taube JM, McCalmont TH, Glusac EJ. Quantitative comparison of MiTF, MElan-A, HMB-45 and Mel-5 in solar lentigines and melanoma in situ. J Cutan Pathol. 2011;38:775–9.

1 Anatomy and Physiology



Travis W Vandergriff and Paul R Bergstresser

Key features

- The function and structure of skin is not demonstrated best by diagrams and figures, but rather by presenting the diseases that illustrate how skin can fail. Thus, function is revealed by disease, and disease illustrates structure
- The primary function of skin is to maintain an internal environment that allows an organism to protect its DNA and to reproduce it faithfully
- Cutaneous structures include an epidermis that serves as a barrier (e.g. to prevent fluid loss and infection) and a dermis that provides circulation and nutrition. Other functions provided by the cells that reside in the skin include immune recognition, a capacity to repair damage, thermoregulation and communication
- Evidence that skin has failed may be found in barrier disruption, infection, autoimmunity, cancer and an undesirable appearance

INTRODUCTION

Most reviews of the anatomy and physiology of skin begin with detailed descriptions of cellular composition, structural proteins, and extrafibrillar matrix ("ground substance"). Because each of these subjects, with relevant documentation, is presented in subsequent sections of this textbook, such aspects of cutaneous function will be introduced only briefly, using references to appropriate chapters. Following this, the conventional approach is reversed by examining diseases that illustrate cutaneous function in the context of the cells and structures that sustain it. This method is derived from the assertion that the structure and function of skin is revealed best through disease. The validity of this alternative methodology may be seen in five short clinical vignettes easily recognized by those who care for patients with skin disease:

- an albino Native American from Panama develops numerous squamous cell carcinomas at an early age
- a 15-year-old boy with hypohidrotic ectodermal dysplasia suffers heat stroke while competing in outdoor athletics in Texas
- toxic epidermal necrolysis leading to dehydration and sepsis develops in a 40-year-old woman treated with phenytoin
- painful leg ulcerations incapacitate a 60-year-old woman with rheumatoid arthritis
- widespread herpes simplex virus infection occurs in a young man who has atopic dermatitis unrecognized by his primary care physician.

These patients and their diseases illustrate at least five of the functions of skin: photoprotection, thermoregulation, barrier formation, cutaneous circulation, and immunologic protection. Each function is supported by the cells and structural elements that reside there.

STRUCTURE AND FUNCTION

Conventional Concepts of the Structure of Skin

Epidermis

Consistent with conventional introductory chapters on cutaneous structure and function, we begin with a histologic section through normal skin. The anatomic structures observed by light microscopy are similar in most regions of the body (Fig. 1.1). However, specialized regions of skin, including the palms (Fig. 1.2), soles, genitalia and scalp, have modified forms of these structures.

As seen in Figures 1.1 and 1.2, the outer layer of skin (epidermis) consists of a thin matrix of cells. In humans, the epidermis contains three major resident populations of cells[1]: keratinocytes (Ch. 56), melanocytes (Ch. 65) and Langerhans cells (Chs 4 & 14). In conventional H&E-stained sections, these cells are nearly indistinguishable, but substantial differences become apparent when specialized immunohistochemical techniques are employed. Keratinocytes, the major population, originate in bottom-most stem-cell pools; cells that leave this pool then undergo maturation as they move toward the stratum corneum (Ch. 56). The human epidermis averages 50 microns in thickness, with a surface density of approximately 50 000 nucleated cells/mm^2[2]. Under basal conditions, differentiated keratinocytes require about 2 weeks to exit the nucleated compartment and an additional 2 weeks to move through the stratum corneum[3]. It should be noted that keratinocytes have the capacity to increase rates of proliferation and maturation to levels far greater than this, when stimulated to do so by injury, inflammation or disease (Ch. 8).

Melanocytes, as noted in a DOPA-stained whole mount of epidermis (Fig. 1.3), have the capacity to elaborate the light-absorbing pigment melanin, which plays a major role in protecting the skin from UV radiation (Ch. 65). Melanosomes, with their complement of melanin, are produced by melanocytes and then transferred by excretion and phagocytosis into nearby keratinocytes, where they assume their preferred location above the nucleus. Members of the third major resident epidermal population, Langerhans cells, have the capacity to metabolize complex antigenic materials into peptides, some of which are immunogenic (Fig. 1.4). After activation, these cells traffic out of the epidermis toward regional lymph nodes, where they play a critical role in antigen presentation during the induction of immunity (Chs 4 & 14). Merkel cells, which contain neuroendocrine peptides within intracytoplasmic granules, are also found in the basal layer of the epidermis.

The most obvious function of epidermis lies in the stratum corneum, a semipermeable laminated surface aggregate of differentiated (keratinized) squamous epithelial cells, which serve as a physiologic barrier to chemical penetration and microbiologic invasion from the environment, as well as a barrier to fluid and solute loss from within[4] (Ch. 124).

Dermis

Beneath the epidermis, a vascularized dermis provides structural and nutritional support. It is composed of a mucopolysaccharide gel held together by a collagen- and elastin-containing fibrous matrix (Ch. 95). Vascular structures, accompanied by nerves and mast cells (Ch. 118), course through the dermis to provide nutrition, recirculating cells, and cutaneous sensation. Three additional cells, fibroblasts, macrophages and dermal dendritic cells, complete the list of dermal residents. In pathologic conditions such as acute inflammation, the functions and types of dermal cells change substantially, with a variety of infiltrating leukocytes arriving via vascular routes. In fact, the composition of cutaneous infiltrates differs depending on the disease entity, which provides students of dermatopathology useful diagnostic clues.

Dermal–epidermal interface

The boundary between epidermis and dermis consists of a specialized aggregation of attachment molecules, collectively known as the basement membrane[5] (Ch. 28). This structure is of considerable interest, because a variety of diseases originate from genetic defects in its composition; it also may serve as a target of autoimmune attack.

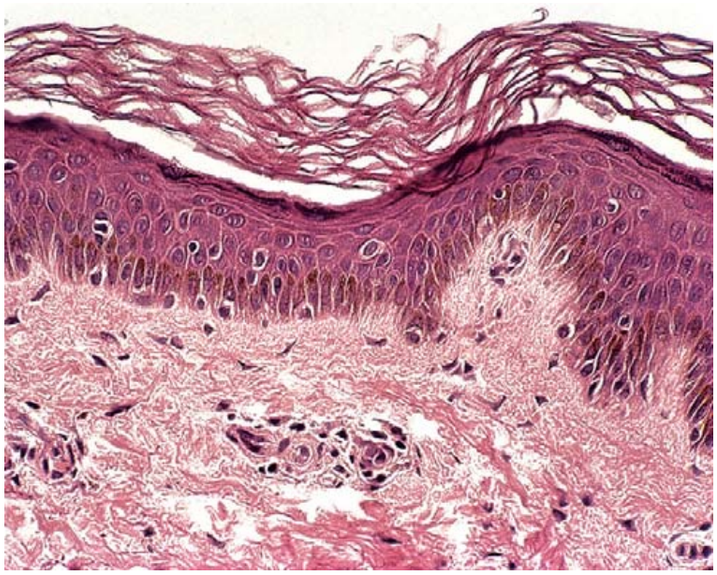


Fig. 1.1 Normal skin: trunk. Note epidermal layers from the surface: stratum corneum, stratum granulosum, stratum spinosum and stratum basale. Tightly packed dermal collagen is seen near the epidermal–dermal junction, and more loosely arranged collagen is found deeper in the dermis. A cluster of small blood vessels and nerves is seen in the dermis.

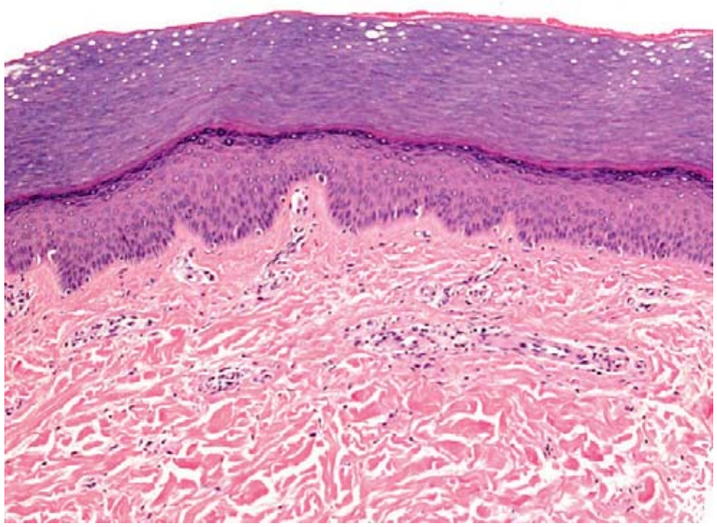


Fig. 1.2 Normal skin: palm. Note that the epidermis is thicker than that seen in Figure 1.1. The compact and thick stratum corneum is typical of skin on the palms and soles. *Courtesy, Lorenzo Cerroni, MD.*

Fig. 1.3 Normal melanocyte. A whole mount of epidermis has been stained for the presence of the enzyme tyrosinase, which typifies melanocytes. Note that the surrounding keratinocytes are virtually invisible. An adjacent hair shaft passes through the specimen. Melanocytes contain long dendritic processes that deliver protective melanosomes to nearby keratinocytes.

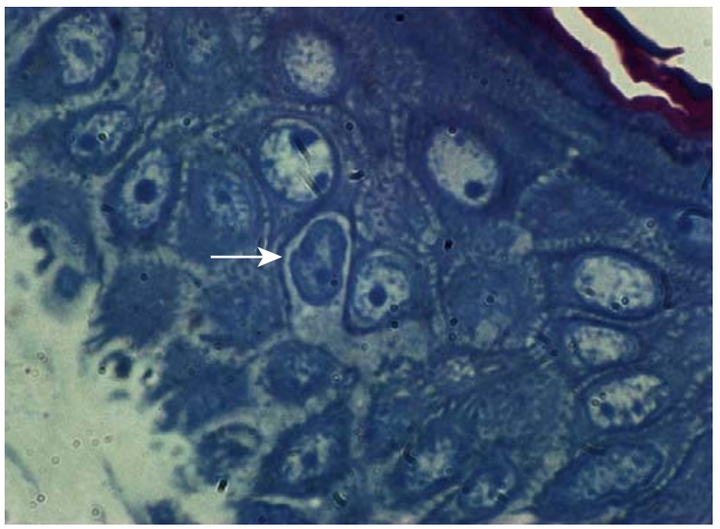


Fig. 1.4 Epon-embedded section of human epidermis. Note the pale cytoplasm and extended dendritic process of a central Langerhans cell (arrow), which resides above the basal cell layer of the epidermis.

Knowledge of the Function and Structure of Skin Begins with Skin Disease

We have chosen to present in the remainder of this chapter a conceptual framework into which the other chapters of this textbook may be placed. This framework is derived from the assertion that knowledge of cutaneous function begins with disease. One corollary of this assertion is that there may be unrecognized functions of skin, either because there is no corresponding disease or because the disease is fatal. For example, no one would have guessed that incontinentia pigmenti was lethal in males had it not been for the survival of heterozygous females with this X chromosome-linked disease[6,7]. Overwhelming apoptosis is thought to explain the death of male fetuses *in utero*.

Two other prejudices color the picture we choose to paint. First, we deviate from the concept that physicians should invariably attempt to develop a single diagnosis for an illness. Rather, we believe that it is possible and even likely that two or more disease processes and/or susceptibilities underlie an illness and that such simultaneous occurrences may alter the clinical presentation. In fact, practicing dermatologists are quite aware of the unusual morphologic features of pityriasis rosea when it occurs in a patient with underlying psoriasis or when a patient with atopic dermatitis improves substantially following treatment with an antibiotic, even in the absence of obvious infection. A growing array of genetic factors and infectious agents are known to modulate the course of otherwise conventional skin diseases. Witness the presence of numerous viral warts or tumors of molluscum contagiosum in patients with immunodeficiency from occult HIV infection or from iatrogenic immunosuppression. Thus, dermatologists have an extra assignment: to find otherwise hidden genetic, infectious and environmental factors that modify the appearance and severity of cutaneous disease.

All plants and animals possess limiting membranes that define an internal space and at the same time protect against external insults. In mammals, these membranes, which may be described functionally as "barriers", occur primarily in three organs: the lung, gastrointestinal

tract and skin (Ch. 124). Although similar in concept, the barrier properties of these organs are fundamentally different. Pulmonary and gastrointestinal barriers, by virtue of their internal location, are protected from many environmental influences, and at the same time they promote rather than retard the transfer of gases, nutrients and wastes. By contrast, and with the possible exception of UV radiation-facilitated vitamin D_3 production[8], there is no obvious benefit to skin penetration, or, at least, there are as yet no recognized diseases attributed to the failure of any material or form of energy to penetrate the skin. It should be noted, however, that biomedical scientists now try to subvert the cutaneous barrier, as skin has become a target of novel therapies based upon percutaneous penetration[9] (Chs 124–129). In addition to serving as a useful portal of entry for pharmaceutical agents, plans are underway for skin to serve as a site for immunization with gene-based materials and as a gene-driven cutaneous factory[10].

The Central Role of Protecting DNA as a Function of Skin

Although we begin with the common rhetorical question: "What are the functions of skin?", it is followed by a second and perhaps more complicated question: "What are the requirements of skin that allow it to serve those functions?". We propose that the primary function of skin is to maintain an internal environment that allows an organism to protect DNA and to reproduce it faithfully. In short, preservation and reproduction of DNA sustains the species. A second and highly related process in a changing world is the generation of useful changes in DNA that accommodate new environmental circumstances. This results in evolution of the species, which may include genetically programmed changes in the skin. Ultimately, all biologic activities serve these functions.

Although the permanent repository of DNA lies in the gonads, the protection of DNA in all sites, including the skin, is also essential for biologic success. This concept of the centrality of DNA has been developed by Reg Morrison in his monograph *The Spirit in the Gene: Humanity's Proud Illusion and the Laws of Nature*, which reviews how life-form competition may be modeled as a method of protecting DNA[11]. Morrison makes the striking observation that human DNA has in the last 300 years come to dominate all life on the earth.

The requirements of skin are identified in its failings

So, what are the requirements of skin for the protection and duplication of DNA? In fact, these requirements have not been identified through logical considerations; rather, as noted above, they have been identified through the various failures that result in skin disease. For this reason, we begin our survey with a listing of failures of skin (Table 1.1).

SELECTED REQUIREMENTS AND FAILINGS OF SKIN	
Requirement	**Selected failings**
Prevent infection via innate and adaptive immunity	Fungal, bacterial and viral infections; autoimmunity, cancer
Maintain a barrier	Infection, dehydration
Repair injury	Cancer, leg ulcers
Provide circulation	Infarction (due to embolization, vasculitis, or other forms of occlusion)
Communicate	Sensory neuropathy, pruritus
Provide nutrition	Vitamin D deficiency
Regulate temperature	Hypothermia, hyperthermia
Attract attention	Photoaging, vitiligo, alopecia

Table 1.1 Selected requirements and failings of skin.

Fig. 1.5 Verrucae vulgaris (warts). Human papillomavirus infections in humans can affect virtually any cutaneous surface. Periungual infections, as seen in this photograph, are both common and difficult to treat. *Courtesy, Louis A Fragola, Jr, MD.*

Preventing Infection: Skin as an Immunologic Organ

An intricate system of immunologic recognition, both innate and adaptive, protects skin (and underlying tissues) from infection[12] (Ch. 4). The cornerstone of adaptive immunity lies in recirculating lymphocytes and antibodies that are specifically recruited and "tuned" to recognize "foreign" materials, primarily peptides derived from infectious agents. Initial recognition occurs when sentinel dendritic cells in the epidermis (Langerhans cells) or dermis (dermal dendritic cells) are activated. Prior to activation, these cells acquire the capacity to engulf particles of many sizes and to metabolize complex proteins into small immunogenic fragments. Once activated, motility is induced, allowing these cells to travel out of their cutaneous residence, and, via draining lymphatics, move to regional lymph nodes. Thus, these residents of normal skin have the capacity to travel to a distant location where reactive lymphocytes are selected and then expanded greatly in number. Within a lymph node, activated helper T lymphocytes assist B lymphocytes to generate antibodies, while helper T lymphocytes and cytotoxic T lymphocytes begin to recirculate preferentially to and from skin. For a further discussion of innate and adaptive immunity, the reference by Janeway is highly useful[12].

Failure of immunity: infection

The diagnosis and treatment of infection constitutes a substantial portion of dermatology (Chs 74–83). Examples of chronic and recurrent infectious skin diseases illustrate the extent to which mechanisms of resistance to infection are lost or defective in some patients. In each example that follows, initial resistance depends upon the structural integrity of the stratum corneum.

Warts

Trauma to the stratum corneum interrupts a physical barrier that is ordinarily not susceptible to viral infection (Ch. 79). In addition, trauma allows implantation of infectious particles among the underlying keratinocytes, which are viable and less resistant. Following this structural failure, immunologic recognition of infected keratinocytes is ordinarily followed by a cytotoxic cellular response, destruction and cure. When this fails, chronic infection may ensue (Fig. 1.5). It is of interest that many therapies for warts, other than physical destruction, rely on modulating the immune response. On the other hand, few problems are more vexing than chronic and recurrent warts, particularly in patients who are immunosuppressed. Especially important are the viral serotypes associated with squamous cell carcinoma and the genetic disorder epidermodysplasia verruciformis[13] (Ch. 79). It is instructive that protective immunity against warts often appears to be balanced precariously, so that minor shifts in responsiveness may lead to their elimination in many sites simultaneously. This has been attempted therapeutically by the use of oral cimetidine, topical applications of imiquimod, elicitation of contact sensitivity reactions, and intralesional injection of recall antigens such as *Candida* or mumps[14,15].

Dermatophytosis

The diagnosis and treatment of infections with dermatophytes remain largely the responsibility of dermatologists (Ch. 77). Perhaps this is because dermatophyte infections are almost invariably limited to the skin, hair and nails, inasmuch as one or more serum factors (e.g. transferrin) may prevent growth where serum can reach[16] (Figs 1.6 & 1.7). As yet unidentified genetic factors protect some individuals from infection, because it is not uncommon to encounter families in which several individuals are chronically infected, whereas other family members, in the face of obvious exposure, are seemingly never infected. On the other hand, experience from tropical climates indicates that individuals who are relatively resistant in a dry environment may lose that resistance as the ambient humidity increases or when occlusive military shoes are worn[17]. Obviously, dermatophyte infection and resistance include a complicated interplay among genetic susceptibilities, immune responsiveness and environmental circumstances.

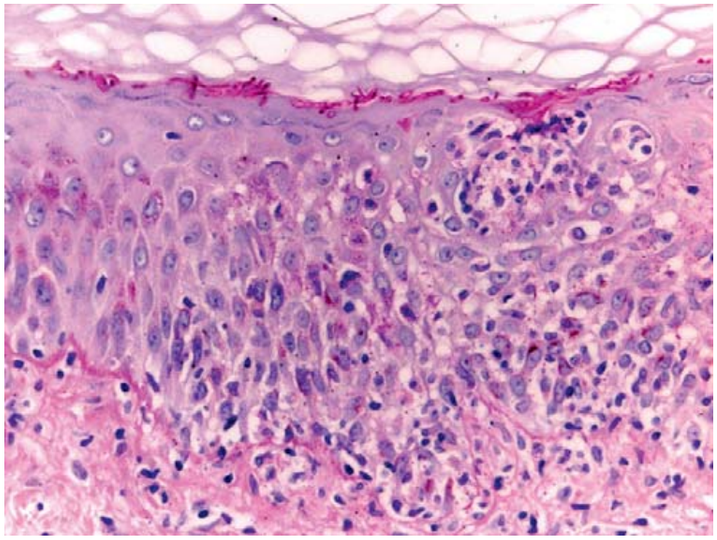


Fig. 1.6 Dermatophytosis. PAS staining for neutral mucopolysaccharides reveals branching red–purple fungal hyphae within the stratum corneum in a patient with tinea corporis. If diastase enzyme is not added, glycogen within keratinocytes also stains with PAS. *Courtesy, Lorenzo Cerroni, MD.*

Fig. 1.7 Dermatophytosis. This annular presentation of tinea corporis typifies cutaneous dermatophyte infections.

Opportunistic infections in the setting of human immunodeficiency virus infection

An enormous body of biomedical knowledge has accrued during the 30-year epidemic of HIV infection (Ch. 78). As a beginning, it appears that HIV penetrates through small tears in genital and rectal mucosae. Once infection has occurred, the virus has been impossible to delete, despite a panoply of relatively effective therapies. With the eventual loss of immunologic integrity, patients develop AIDS and thereby demonstrate the relevance of effective cellular immunity to protection against infections with a wide variety of agents, including *Mycobacterium tuberculosis, Pneumocystis jiroveci*, varicella zoster (Figs 1.8 & 1.9) and herpes simplex viruses. What more evidence would one want to demonstrate the relevance of cellular immune protection of skin than the diseases that are described in Chapter 78?

Hansen's disease (leprosy)

Hansen's disease is instructive in that the majority of humans exposed to its causative organism, *Mycobacterium leprae*, develop an effective immune response that is seemingly curative (Ch. 75). On the other hand, a small percentage of exposed individuals develop chronic infection that may take any one of several forms, based on immunologic resistance. In fact, observations made in patients with Hansen's disease have been important in formulating the Th1/Th2 paradigm (Ch. 4), with each patient's clinical response falling along a spectrum from tuberculoid to lepromatous[18]. Importantly, Hansen's disease also illustrates the relevance of cutaneous sensation to protection against traumatic injury, as will be presented later.

Warts, dermatophytosis, opportunistic infections in the setting of HIV infection, and Hansen's disease all illustrate important aspects of

Fig. 1.8 Herpes zoster. Unilateral grouped vesicles and serous crusts on an erythematous background. Note the associated edema of the eyelid and lip. *Courtesy, Louis A Fragola, Jr, MD.*

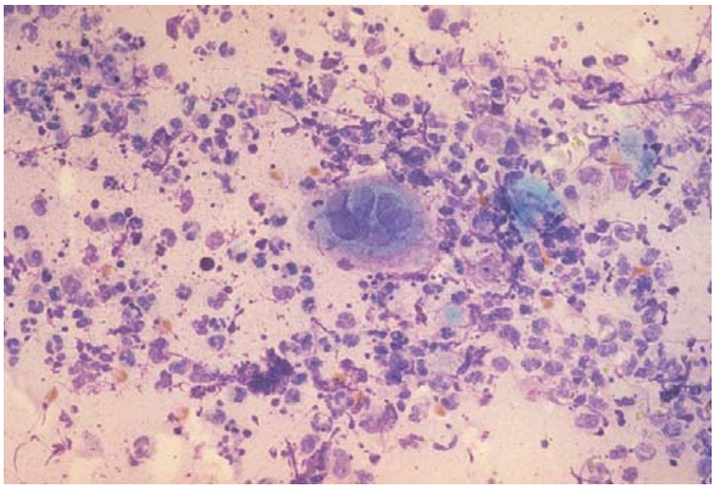


Fig. 1.9 Tzanck smear from a patient with herpes zoster. Note the multinucleated giant cell.

cutaneous function, ranging from a structural barrier provided by the stratum corneum to immunologic recognition and protective immunity.

Faulty immunity: autoimmunity

We have made a case for the concept that the primary task of immunity is to recognize and destroy infectious organisms. Having stated this, autoimmunity may then be modeled as a failure in distinguishing "self" from infection, i.e. autoimmunity is a misidentification and destruction of portions of the host, as if it were dangerous or "foreign". Autoimmune diseases are legion, with components of the epidermal basement membrane and desmosomes serving as important targets (Fig. 1.10). Moreover, cutaneous cellular elements serve as both regulators and targets of autoimmune injury. Table 1.2 lists several common autoimmune diseases that affect the skin, each with a different target. These diseases have different sets of genetic factors and environmental insults that promote their development. Subsequent chapters detail their relevant elements.

We know a substantial amount about molecular targets in these diseases, and we also know much about how immunity works in protecting against infectious diseases. However, we are only now learning about how errors in recognition lead to immune responses that target self antigens inappropriately and damage indigenous structures. It has also become apparent that autoimmunity to skin antigens may impact other organ systems. Bullous pemphigoid antigen 1, for example, has distinct isoforms in the skin and in the central nervous system, and patients with bullous pemphigoid have a higher incidence of dementia, Parkinson's disease and multiple sclerosis[19].

Failure of immunity: cancer

Data to support the concept that immune responses also protect against malignancy is strongest for those malignancies that arise in skin and lymphatic tissues[20,21], especially cutaneous melanoma and squamous cell carcinoma (SCC). Cutaneous SCC is a well-known complication of immunosuppression in solid organ transplant recipients. Additionally, we include a photomicrograph of a thick melanoma, without inflammation (Fig. 1.11). Many developments in melanoma therapy are based on attempts to enhance immune responsiveness (Ch. 113).

Maintaining a Barrier: Skin as a Protective Organ

From the outset, the most obvious function of skin is to maintain a barrier that prevents the loss of fluids, electrolytes and other molecules from within the body and, at the same time, prevents penetration by microorganisms, toxic materials and UV radiation[22,23] (Ch. 86). For all but UV radiation, the stratum corneum is the central element in that function. By contrast, protection against UV radiation occurs through several independent phenomena, including photon scattering in the stratum corneum and photon absorption by underlying melanin.

Failure of protection against toxic chemicals

The analysis of barrier failure begins with the observation that the stratum corneum is defective in disorders of keratinization[24], as it is less resistant to chemical penetration. Two diseases typify this defect: epidermolytic hyperkeratosis (Fig. 1.12) and Darier disease (keratosis follicularis)[25,26]. An instructive set of circumstances arose with the problem that patients with these diseases commonly have recurrent bacterial infections. In an attempt to treat and to prevent such infections, dermatologists and other physicians have recommended for decades the prophylactic use of topical antibacterial agents to decrease bacterial carriage and, at the same time, the associated odor.

In an article published in 1960, Medansky and Woloshin[27] described an extraordinarily high frequency of neuropsychiatric disorders in

COMMON AUTOIMMUNE SKIN DISEASES		
	Target antigen	**Chapter**
DISEASES WITH IDENTIFIED AUTOANTIGENS		
Pemphigus foliaceus	Desmoglein 1	29
Pemphigus vulgaris (Fig. 1.10)	Desmoglein 3 and 1	29
Bullous pemphigoid	Collagen XVII (BPAG2), BPAG1*	30
Epidermolysis bullosa acquisita	Collagen VII	30
Dermatitis herpetiformis	Transglutaminase-3	31
DISEASES WITH UNKNOWN OR MULTIPLE AUTOANTIGENS		
Subacute cutaneous lupus erythematosus	Unknown	41
Chronic cutaneous lupus erythematosus	Unknown	41
Psoriasis	Unknown	8

Table 1.2 Common autoimmune skin diseases. *Neural isoforms are referred to as dystonin.

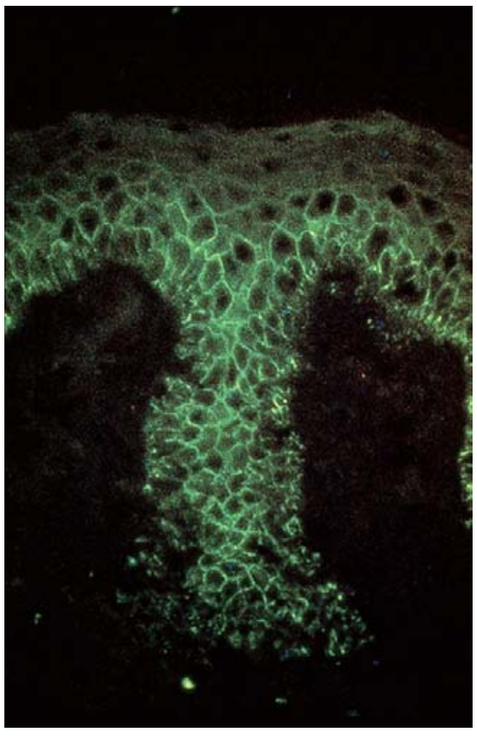


Fig. 1.10 Pemphigus vulgaris (immunofluorescence). Intercellular staining of epidermal keratinocytes reveals the *in vivo* deposition of antibodies to desmoglein 3.

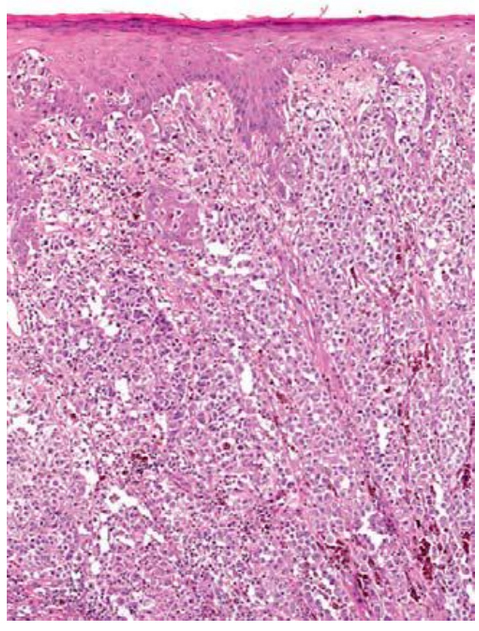


Fig. 1.11 Melanoma. This thick melanoma has virtually no associated inflammatory cells histologically. The thickness and lack of a host response indicate a poor prognosis for the patient. *Courtesy, Lorenzo Cerroni MD.*

patients with keratosis follicularis, even though no mechanism could be imagined that would link keratin function with CNS function. In retrospect, however, hexachlorophene had been recommended as a useful antibacterial agent soon after its introduction in 1944. Several decades later, it was recognized that it was potentially neurotoxic, with use eventually curtailed in the 1970s[28]. Since that time, there have been fewer reports of neuropsychiatric findings in keratosis follicularis. Our conclusion is that hexachlorophene penetrates a defective barrier in toxic amounts. However, an alternative explanation proposed by others is that dysfunction of SERCA2 within the brain may potentially lead to neuropsychiatric findings[29]. In contrast, there is no debate about the more recently reported enhanced absorption of topical tacrolimus in patients with Netherton syndrome.

In sum, the barrier for chemical penetration is invested in the stratum corneum (Ch. 124), and this barrier is defective in diseases of keratinization.

Failure to protect against dehydration and infection: toxic epidermal necrolysis

The most dramatic form of epidermal failure occurs in patients with toxic epidermal necrolysis (TEN; Ch. 20). In this drug-induced disease, rapidly progressive keratinocyte death leads to detachment of the epidermis over large areas of the body. There is a complete loss of barrier function (Figs 1.13 & 1.14). TEN is most often associated with sulfonamides, anticonvulsants and nonsteroidal anti-inflammatory drugs. It has a mortality rate that depends upon the area of skin involved, but death is not uncommon. There is as yet no specific treatment for TEN. However, there is evidence that drug-induced triggering of massive keratinocyte apoptosis may underlie the disease[30], and inhibition of the apoptosis signaling pathway (e.g. by administration of intravenous immunoglobulin) may improve survival. However, the point of this discussion is that the complications that accompany loss of the epidermis reveal all of its functions. Despite intensive treatment with similar techniques as those employed for burns, complications are common and can include enormous fluid and electrolyte losses leading to dehydration as well as infections with bacteria and yeast.

Failure to protect against UV radiation: albinism

UV radiation induces a myriad of changes in the skin, ranging from acute toxicity and immunosuppression to carcinogenesis and premature aging (Chs 86, 87, 107 & 108). However, there is an apparent contradiction in the recommendations of dermatologists: effective therapies for a number of skin diseases are based on the use of UV radiation of various wavelengths (Ch. 134), while protection from the sun's rays is in general highly recommended to prevent adverse effects from UV radiation (Ch. 132). In addition to wearing clothing and using topical preparations that include UV-absorbing or UV-blocking molecules, several characteristics of the skin itself limit UV radiation-induced damage. Due to its optical characteristics, the stratum corneum tends to reflect and scatter photons, and those that penetrate the stratum corneum are usually absorbed by molecules such as melanin. Additional mechanisms are the scavenging of reactive oxygen species by antioxidants and repair of damage with DNA repair enzymes.

The importance of cutaneous pigment in protecting the skin against UV damage is demonstrated in patients with oculocutaneous albinism (OCA)[31]. The impact of melanin in limiting UV penetration may be seen unequivocally in patients who have type 1 OCA due to an absence or reduction in tyrosinase activity and, as a result, melanin production (Fig. 1.15)[31]. Striking amongst the evidence is the experience of the Cuna Indians, residents of islands near Panama, in whom there is an extraordinarily high frequency of type 1 OCA and little relief from year-long intense exposure to sunlight. In the context of this high background genetic frequency (approximately 1%), there is a parallel high frequency of skin cancer. Likewise, acute toxicity, photosensitivity diseases and premature photoaging (Ch. 87) are known complications for these patients.

Maintaining the Integrity of Skin: Repair Mechanisms

Physical injury occurs commonly in the skin, including many small breaks from blunt and sharp objects that are repaired almost without notice. A special type of injury is caused by the penetration of UV radiation. This includes a variety of effects that range from sunburn to immune suppression, accelerated aging and carcinogenesis. Thermal injury occurs upon exposure to a hot object or radiant energy, e.g. from fire, that heats the skin excessively (see below, Thermoregulation). Injury also occurs when there is interruption of the underlying vascular supply. Each episode of injury is followed by a sequence of repair processes that eliminate foreign objects and cover defects. This "wound

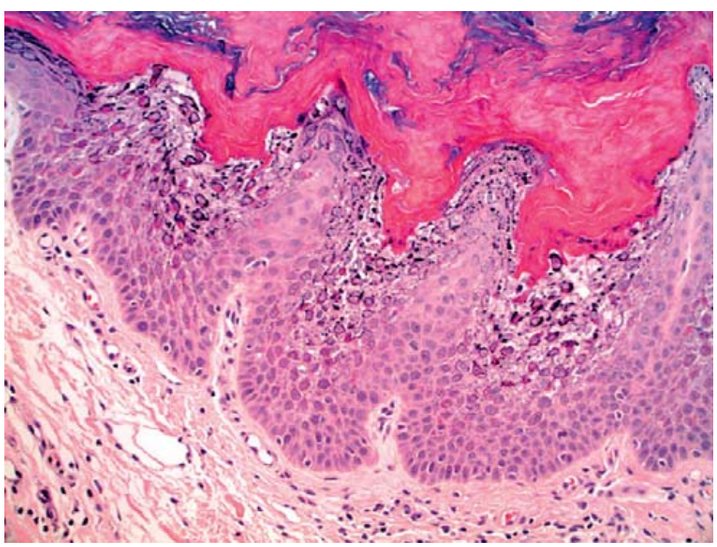


Fig. 1.12 Epidermolytic hyperkeratosis. Marked compact orthokeratosis overlies an epidermis showing granular and vacuolar change in its upper layers. *Courtesy, Lorenzo Cerroni, MD.*

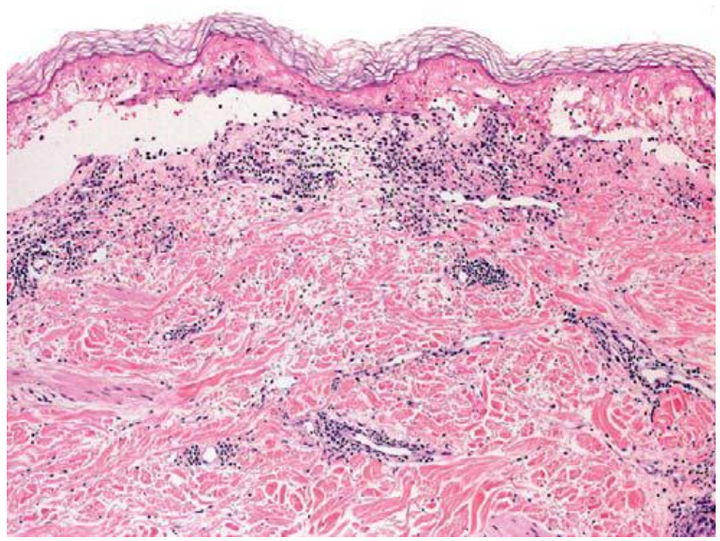


Fig. 1.13 Toxic epidermal necrolysis. Full-thickness epidermal cell death, with secondary bulla formation. *Courtesy, Jean L Bolognia, MD.*

Fig. 1.14 Toxic epidermal necrolysis. Full-thickness epidermal cell death leads to stripping off of the epidermis. In this African patient, it becomes apparent that melanin is located predominantly in the epidermis.

Fig. 1.15 Albinism in an infant. Note the normally pigmented fingers of the child's mother. Patients with albinism are at substantially higher risk for UV radiation-induced carcinogenesis.

Fig. 1.16 Ulcers secondary to Henoch-Schönlein purpura. The ulceration was preceded by coalescent purpuric papules with bulla formation and necrosis. *Courtesy, Julie V Schaffer, MD.*

healing" response has been studied in considerable detail (Ch. 141), because delays in wound healing are both incapacitating and expensive.

Failure to effectively repair injury

Delayed wound healing

Delayed and incomplete wound healing have been associated with diabetes mellitus and aging. The treatment of chronic leg ulcers, especially in the elderly, is an important part of dermatology and rehabilitation medicine (Ch. 105). The Wound Healing Society (www.woundheal.org) is a consortium of clinical and basic science investigators that includes physicians, scientists, industrial representation and governmental agencies. Only in recent years have these investigators begun to address the issues of chronic cutaneous ulceration.

Keloids

The formation of hypertrophic scars and keloids may be seen as an exuberant response to injury. It combines a unique mix of genetic and environmental factors. The most reasonable explanation of pathogenesis may be seen in studies showing that transforming growth factor β (TGF-β) activity is excessively high in fibroblasts derived from keloids[32]. Despite preliminary evidence that TGF-β may play a role in the establishment of an environment that favors overgrowth of dermal elements to form hypertrophic scars and keloids, the discipline of wound healing remains in its infancy.

Xeroderma pigmentosum

An important failure occurs when UV radiation-induced DNA damage is not repaired effectively. The prototype for this deficiency is the disease xeroderma pigmentosum[33]. The high incidence of skin cancers of many types in these patients supports the assertion that UV radiation-induced injury is an important cause of skin cancer in humans. Thus, it is necessary for the skin is to protect itself against the detrimental effects of UV radiation. This illustrates two points: first, UV radiation is dangerous; and second, when DNA repair mechanisms are defective, cancers arise much more quickly.

Providing Circulation: Skin as a Nutritive Organ

The movement of cells and soluble elements to and from skin is mediated by two circulatory systems: (1) a two-way hematologic system that conducts blood flow; and (2) a one-way lymphatic system that returns leukocytes and interstitial fluids, first to draining lymph nodes and then, via the thoracic duct, into the central venous system. Hematologic circulation, the most obvious because of the red and blue colors of blood, serves three major functions: nutritional support, the delivery of leukocytes, and thermoregulation. Although the movement of oxygen and solutes from blood into interstitial tissues occurs largely by passive diffusion, the emigration of cellular elements from the vascular space occurs by a highly ordered sequence of signaling, attachment, and migratory processes that are described in Chapter 102.

The hematologic system includes two types of vessels: (1) nutritive vessels (arteries, capillaries and veins); and (2) anastomosing arteries and veins that participate in heat regulation. This latter system includes an extensive subcutaneous venous plexus, which can hold large quantities of blood (to dissipate heat from the surface of the skin), and arteriovenous anastomoses, which are large direct connections between arterial and venous plexuses. These anastomoses are prominent in areas often exposed to maximal cooling, such as the volar surfaces of the hands and feet, lips, nose and ears.

Cutaneous lymphatic drainage begins in microscopic blind-ended dermal vessels called lymphatic capillaries. These collect both cells and interstitial substances that are then directed toward regional lymph nodes. Lymphocytes, macrophages and dendritic cells all have the capacity to exit the skin via lymphatic drainage. Stoitzner and colleagues[34] have provided an exquisite photographic description of Langerhans cells in their travels from epidermis to draining lymphatic vessels.

Failure of circulation: arteries and veins

Embolic occlusion of arteries

The most dramatic form of blood vessel occlusion occurs with embolimediated blockage, which can produce changes within hours. This is followed rapidly by necrosis of all cutaneous structures distal to that blockage. The extent of necrosis depends on the size of the vessel occluded, and occlusion due to non-infectious cholesterol emboli is usually associated with generalized arteriosclerotic cardiovascular disease. Occlusion followed by cutaneous necrosis demonstrates in vivid fashion the complete dependence of skin on arterial circulation.

Vasculitis

Cutaneous inflammation centered in the blood vessel wall is responsible for a spectrum of cutaneous findings that vary depending upon the size of vessel affected. Vasculitis is commonly associated with rheumatic skin disorders (Chs 24, 41, 42 & 45). They include inflammation associated with dermato- and polymyositis, rheumatoid arthritis, lupus erythematosus, and immune complex-mediated small vessel vasculitis (Fig. 1.16). The critical element in terms of cutaneous structure is that, once again, the survival of skin is highly dependent upon an intact circulation.

Occlusive vasculopathy

Other disorders characterized by vascular occlusion result from aberrant coagulation or cold-related "gelling" (Ch. 23). This can be precipitated by antibodies directed against regulators of coagulation, which may develop in patients with rheumatic diseases.

Venous insufficiency

Although listed last, venous insufficiency through partial occlusion and valvular incompetence contributes to the most common vascular problem, the development of venous stasis ulcers of the legs (Ch. 105).

Failure of circulation: lymphatic blockage

Blockage of lymphatic drainage may also occur in certain inflammatory skin conditions. The inflammation associated with recurrent streptococcal and staphylococcal infections may lead to scarring and loss of

lymphatic drainage, resulting in distal edema. With chronic infection, permanent edema may develop, associated with widespread verrucous change at the skin surface, a condition described as elephantiasis nostras verrucosa (Ch. 105). Likewise, blockage of lymphatic drainage in parasitic infections is known to cause deforming patterns of lymphatic blockage (Ch. 83). It is also relevant that, many years ago, Frey and Wenk[35] demonstrated that ligation of lymphatic drainage caused a back-up of leukocytes unable to return from tissue sites as well as a failure to immunize against antigens that penetrated skin affected in this way.

Interfacing with External and Internal Environments: Skin as a Communicating Organ

Communication in skin occurs by three mechanisms: conventional nerve conduction via cutaneous fibers; intercellular signaling mediated by cytokines and hormones (endocrine, paracrine and autocrine effects); and the physical movement of "message-carrying" cells from one site to another. The roles and importance of these mechanisms have been revealed through various defects in their execution.

Skin is "wired" with afferent and efferent nerve fibers that accompany vascular structures, forming an intricate network within the dermis. They envelop the pilosebaceous apparatus (Ch. 68), blood vessels and sweat glands. Although the head and distal extremities are innervated most densely, all skin contains nerves. Within the dermis, larger fibers are surrounded by a myelin sheath, but as diameters diminish, many fibers run free. In fact, most nerve fibers appear to end in the dermis, although there is clear evidence that some small endings penetrate the basement membrane and travel into the epidermis, where they have the capacity to modulate immune responsiveness[36].

Nerves control vascular tone, as demonstrated in blushing responses, and they mediate the sensations of heat, cold, itch, touch and pain (Chs 5 & 6). Defects in sensation and neurologic function occur commonly, and they may be seen in patients with chronic pain following varicella–zoster virus infection, uncontrolled itching, neurologic syndromes (e.g. trigeminal trophic syndrome), and excessive sweating. A highly useful therapeutic development has been the intradermal injection of botulinum toxin to uncouple cholinergic nerve fibers. This technique has at least two dermatologic applications: (1) to decrease muscle tone, leading to a loss of facial lines for cosmetic purposes; and (2) to inhibit the excessive sweating that characterizes disabling axillary and palmar hyperhidrosis[37] (Ch. 159).

Abnormality of neurologic communication: excessive sensitivity

Itch is a major problem for patients with skin disease (Chs 5 & 6). We presume that modest levels of itching confer some beneficial effect, but, most certainly, excessive itching can be devastating to both personal and social activities. On the other hand, there is at present little evidence for structural abnormalities that predispose to excessive itching. Postherpetic neuralgia is similarly important[38] (Ch. 80), although, once again, there is no obvious structural defect in this exquisitely painful disorder.

Abnormality of neurologic communication: excessive sweating

Hyperhidrosis is a potentially debilitating disorder of sweating, which commonly involves intertriginous areas as well as the palms and soles. Accumulated evidence favors a neurologic abnormality rather than a structural abnormality[39]. Moreover, injection of botulinum toxin now offers considerable potential for relief (Ch. 159).

Abnormality of neurologic communication: decreased sensitivity

The most obvious and devastating effects of altered touch and pain sensation may be found in patients with the peripheral neuropathies that accompany Hansen's disease[40] (Ch. 75) and diabetes mellitus[41] (Ch. 105). Similar problems may occur in patients under the influence of narcotic anesthesia. In each of these settings, the loss of sensory function leads to the failure of patients to recognize, and therefore avoid, cutaneous trauma. For patients with Hansen's disease, numerous injuries over months and years lead to a gradual loss of tissue. In a similar fashion, a loss of cutaneous sensory function in patients with longstanding diabetes mellitus leads to unappreciated pressure ulcers in weight-bearing areas of the feet. In both of these conditions, a profound loss of sensation leads to unrecognized trauma to the skin, with consequent ulcer formation and loss of tissue. What we can learn from patients with these diseases is the exquisite vulnerability of skin to traumatic injury in the absence of appropriate sensation.

Communication via hormones and cytokines

Hormones

A relevant model for indirect hormonal influences on skin is adrenocorticotropic hormone (ACTH), which was recognized in classic studies as having systemic effects through the induced secretion of adrenal corticosteroids. This, in turn, had temporarily beneficial effects on inflammatory skin disorders such as psoriasis (Ch. 8) and atopic dermatitis (Ch. 12). On the other hand, a model for pathologic changes induced by inappropriate secretion of hormones is seen in the effects of the catecholamine hormones and their precursors (norepinephrine, epinephrine or dopamine) in patients with vascular instability caused by pheochromocytomas. Likewise, several of the clinical signs of Cushing's disease (altered fat distribution, vascular dilation and striae) result from excessive secretion of corticosteroids. In contrast, diminished production of adrenocortical hormones causes excessive secretion of ACTH, which, in turn, gives rise to the hyperpigmentation seen in patients with Addison's disease (Ch. 67).

Skin also plays a unique hormonal role in calcium metabolism. Vitamin D_3 (cholecalciferol) is produced in the epidermis by the action of UV radiation on 7-dehydrocholesterol[8]. It then leaves the skin and is hydroxylated in the liver and kidneys to the active form of vitamin D (1,25-dihydroxycholecalciferol).

Cytokines

In the last 30 years, a new field of cutaneous knowledge has evolved, beginning with the recognition that keratinocytes contain large amounts of the biologically active cytokine interleukin-1 (IL-1)[42,43]. This was followed in rapid succession by the recognition that cells within skin are able to produce an array of biological response modifiers. Most prominently, keratinocytes produce IL-1, IL-8 and TGF-β[44]. The capacity of these substances to exert important physiologic functions is demonstrated by the beneficial effect TGF-β has on wound healing[45]. Looking at other cutaneous cells, Langerhans cells produce a unique spectrum of cytokines and chemotactic factors related to their immunologic properties[46]. Vascular endothelial cells produce IL-1β, IL-6 and IL-8[47]. In fact, cytokine-mediated communication within the skin is an active area of research[45,48–51], and the interplay between cytokines and cells is often reciprocal[52,53]. For example, mast cells produce tumor necrosis factor (TNF), which affects cutaneous immunity[54], but, at the same time, mast cell function is regulated by other cytokines[55]. Unraveling the complex relationships among cutaneous cells, their own hormones (autocrine), hormones from adjacent cells (paracrine), and hormones from distant cells (endocrine) will occupy the attention of skin biologists and skin pharmacologists for the next generation.

Cellular communication

We have only recently begun to appreciate that certain resident cutaneous cells, in the course of their normal function, depart from the skin while in possession of information that ultimately has direct impact on the function of the skin. Chief among these cells are dendritic cells, which, after activation, leave the skin and traffic to regional lymph nodes. In this location, they select and prime naive and resting T lymphocytes (Chs 4 & 14). The processes of activation, outward migration, and repopulation have been areas of intense investigation, with the prospect of developing methods by which immunity may be modulated.

Failure of cytokine and cellular communication

Knowledge about the roles of cytokines and cell traffic in cutaneous communication is as yet in its infancy, meaning that defects are only now being recognized. Stemming from an improved understanding of the role of cytokines in keratinocyte biology, major developments in

dermatologic therapy have been achieved during the last decade in the management of inflammatory skin diseases, most notably psoriasis. Aberrant levels of TNF-α and IL-23 have emerged as critical targets of immunobiologic agents used to treat psoriasis. As our understanding of cytokine biology increases, new developments in targeted therapy will continue to expand our therapeutic armamentarium.

Regulating Temperature: Skin as a Thermoregulatory Organ

Regulation of core temperature is a characteristic of all mammals, which, by definition, are euthermic. For humans, core temperature is maintained at approximately 37°C (98–99°F). Because environmental influences tend to change that temperature, there exists an intricate system of regulation in which skin plays a decisive role as both radiator and insulator. Temperature regulation by the skin is effected primarily through evaporative cooling after eccrine sweating (Ch. 39) and through vasodilation and vasoconstriction.

Human skin includes several million eccrine sweat glands distributed over most of its surface, with the total mass of eccrine glands approximately that of one kidney. Under neurologic control, the secretory activity of eccrine sweat glands consists of two major activities: (1) secretion of an ultrafiltrate of a plasma-like fluid; and (2) reabsorption of sodium by the duct to produce hypotonic sweat.

Failure of thermoregulation: effects of excessive heat

Excessive heating may be local or systemic, and, when this occurs, skin plays a cooling role to prevent injury. Cooling may be required under two non-exclusive circumstances: (1) in response to central heating, which occurs when heat enters skin from an external source or when energy is generated through muscular exertion in amounts sufficient to increase core temperature; and (2) in response to sustained local heating, which occurs when a portion of skin is heated to a temperature at which critical proteins begin to denature, i.e. in the neighborhood of 45–50°C (113–122°F; Ch. 88). The subsequent physiologic responses that lower temperature to prevent injury require innervation, circulation and successful sweating. Dispersion of local heat takes place by direct radiation into the environment and by heat transfer to other body locations via circulating blood. In contrast, the elimination of central heat occurs through radiation from the skin surface and from the evaporative cooling that follows sweating.

The relevance of sweating to the elimination of heat, and, ultimately, to survival may be found in the vignette of hyperthermia found at the beginning of this chapter. In this patient with the X-linked genetic disorder hypohidrotic ectodermal dysplasia, the defining defect is a nearly complete absence of sweat glands, in association with other features such as hypotrichosis and abnormal teeth (Ch. 63)[56]. This disease demonstrates the importance of sweating, as death from overheating during exercise is known to occur, especially when the environmental temperature is high. It is of interest that since evaporative cooling normally plays no role in these patients, there is virtually no effect of environmental humidity on core temperature, because all heat loss occurs through radiation. On the other hand, heat loss may be increased substantially by a relatively simple measure that allows patients with this disease to engage in vigorous outdoor activities in hot climates. Exogenous "sweat" may be created by spraying water over the body repeatedly throughout an exercise or event[56].

Heat injury as therapy

The production of local heat injury may also have a beneficial side, as electrocautery is a time-honored method of therapy in cutaneous medicine (Ch. 140). Additionally, heat therapy has been used in the management of cutaneous infection, including sporotrichosis and leishmaniasis.

Failure of thermoregulation: effects of excessive cold

In contrast to heat injury, individuals exposed to cold temperatures require heating to prevent injury. This also occurs under two related circumstances: (1) in response to heat loss to the environment in amounts that cool the body centrally (hypothermia); and (2) in response to exposure locally to sustained temperatures below freezing, which otherwise would lead to direct freezing injury ("frostbite"). With extreme exposure, of course, both may occur together.

Extreme examples of excessive core and surface cooling in association with limited central heat generation were described vividly by Jon Krakauer in his report of the Mount Everest climbing disasters of 1996[57]. Unfortunately, aside from vascular constriction to reduce radiation of heat from the skin surface and shivering (or exercise) to increase central heating, there are no intrinsic cutaneous mechanisms to protect against excessive cooling. However, humans have become quite adept at creating artificial methods to prevent cold or heat injury through clothing and shelter. These have enabled humans, and consequently human DNA, to survive successfully in geographic areas of extreme temperature. Perhaps the most obvious are the mountain climbers who scale the Himalayan mountains and the firefighters who wear insulated clothing as they enter burning buildings.

Cold injury as therapy

When properly applied, local cold injury (e.g. cryosurgery) has been used successfully as a therapeutic tool for decades (Ch. 138).

Interpersonal Communication: The Skin Conveys Beauty, Attracts Attention and Contributes to Self-Identity

An important function of skin begins with the need for humans to communicate with each other so that personal and societal goals can be met. The skin plays an important role in interpersonal communication by conveying beauty to others, attracting attention, and contributing to the development and expression of self-identity.

The presence of beauty, as seen in photographs or paintings, tends to attract attention, which is sometimes intense. It is easy to imagine that these responses are coded genetically, because high attractiveness would seem to increase the likelihood that DNA survives and also, therefore, that the species survives. In sum, without any confirming data, we assert that the desire to be attractive helps to insure the selective survival of human DNA.

Virtually all attraction that occurs at a distance beyond that of touch and smell is mediated by vision, and, thus, the skin assumes overwhelming importance as a visual target for humans. Having said this, it should not be surprising that in every society, the physical appearance and condition of the skin seems to have assumed fundamental importance. In Figure 1.17 we have included portraits of Mr Frederick H Hemming and his fiancée, Miss Mary Anne Bloxam, painted in 1824–25 by the English portrait artist Thomas Lawrence. The intrinsic "beauty" of these individuals prompts one to examine their features with interest. More recently, modern artists such as Andy Warhol have challenged us to reconsider the relationship between appearance and beauty.

There is not sufficient space to list the physical features that are considered beautiful, but let us assert that the loss of these features has much to do with the anxiety that often characterizes patients with acne, vitiligo, alopecia, aging and photoaging, as well as virtually all other skin diseases. During the past decade, increasing attention has been given by both researchers and clinicians to the effect of skin disease on quality of life. Myriad reports have been published defining the extent to which chronic skin diseases, including psoriasis, eczema, and pigmentary disorders, affect the way in which patients perceive themselves. As dermatologists become more aware of the psychosocial impact of chronic skin disease, we are better able to treat patients with these conditions.

Finally, the skin represents a "canvas" onto which individuals may make modifications in order to communicate with each other and to display aspects of self-identity. Tattoos, ritual scarification, and piercings have long been seen as expressions of self-identity. Dermatologists can participate in skin modification by interventions meant to improve the attractiveness of the patient. Many dermatologists now practice cosmetic surgery and procedures, repairing a variety of defects and moving fat from one site to another. During the last 25 years, increasing amounts of discretionary money have been diverted into procedures that improve appearance (Chs 152–159). Dermatologists and their patients have played major roles in this transition.

Failures to present an attractive appearance

Appropriately proportioned, symmetric, unblemished skin seems to be preferred in the majority of societies. Our question at this point

Fig. 1.17 Mr Frederick H Hemming and his fiancée, Miss Mary Anne Bloxam. These portraits were painted in 1824–25 by the English artist Thomas Lawrence. The intrinsic "beauty" of these individuals prompts one to examine their features with interest. *Courtesy, Kimball Art Museum, Fort Worth, Texas.*

Fig. 1.18 Vitiligo. This African-American man has vitiligo on the distal portions of his fingers. Pigmentary disorders of this sort are much more obvious in patients with substantial natural pigmentation.

concerns the types of changes that are considered to be "defective". The defects that are most disagreeable do vary from culture to culture, so that one cannot assume that what is unattractive in one culture is necessarily unattractive elsewhere.

Pigmentary turmoil

Pigmentary disorders tend to be more pronounced, and thus more important, in populations with greater amounts of natural pigmentation. For this reason, Western cultures, which until recently have been derived primarily from European immigrants, may underestimate the critical role of pigmentation throughout the world. Although dermatologists care for patients who have many different disorders of pigmentation, two diseases predominate: vitiligo (Fig. 1.18; Ch. 66)[58] and melasma (Ch. 67).

The preference for unblemished skin is exceedingly important in cultures in which altered pigmentation may be confused with Hansen's disease (Ch. 75) or viewed as hereditary. In Indian culture, for example, it is not uncommon for the discovery of vitiligo to invalidate a marriage contract[59]. The defect in vitiligo is the absence of epidermal melanocytes after physical destruction guided by autoimmune influences. Not only is vitiligo an important disease in its own right, the associated autoimmune phenomena have profound implications for melanoma therapy (Ch. 113).

Likewise, melasma has a high frequency in Hispanic individuals in the Americas, and it is often extraordinarily distressing[60] (Ch. 67). It is not uncommon to observe that money for necessities may be diverted to this seemingly inconsequential problem.

Inappropriate hair distribution

Hair performs no vital function for humans in the twenty-first century, as body hair can be removed without any physiologic disadvantage. By contrast, the psychologic contributions of hair for many humans cannot be underestimated. Scalp hair is a major social and sexual display feature for humans. The biology of hair and hair growth is detailed in Chapter 68, and additional information may be found in other useful references[61,62]. A discussion regarding excessive hair may be found in Chapter 70 and elsewhere[63]. Two phenomena predominate in concerns about hair: (1) too much hair in the wrong place; and (2) not enough hair in the right place. Too much hair in the wrong place occurs in congenital and acquired forms of hypertrichosis, in response to therapy with minoxidil and certain immunosuppressive agents, and as an effect of androgen excess (Ch. 70). However, the vast majority of patients who seek help for excessive hair do so primarily for cultural reasons.

In terms of insufficient hair (Ch. 69), three diseases predominate: (1) androgenetic alopecia in men; (2) female pattern alopecia in women[64]; and (3) alopecia areata (Fig. 1.19). Hair transplantation has become a popular procedure performed by dermatologists (Ch. 157).

Undesirable fat distribution

With the possible exception of hemifacial atrophy and lipodystrophy syndromes, indications for the absolute removal and for the movement of fat are based on psychologic needs rather than on abnormalities in the structure of the skin and subcutaneous tissues. Nevertheless, the movement of fat is becoming a fairly common procedure and, once again, dermatologists are playing increasingly important roles in this arena[65] (Ch. 156).

The next steps

We could go on at length about dermabrasion for acne scars, rejuvenation protocols, blepharoplasties, and other techniques to reverse the effects of aging. However, the point has been made. What we propose is that anxiety about appearance is genetically programmed. The discipline of cosmetic dermatology has arisen to address that anxiety, with the important goals of alleviating scars, hiding defects and preventing photoaging.

An Important Corollary, with an Eye to the Future

In this introductory chapter, we have asserted that the structure and function of skin is revealed through careful study of skin disease. An important corollary to this statement becomes apparent when we apply our knowledge of skin disease to patient care: the structure and function of skin is also revealed by observing the outcomes of our specific interventions. Whether the outcomes are anticipated or completely unexpected, much can be learned by studying the way skin responds to our attempts at manipulation through medicine and surgery. This

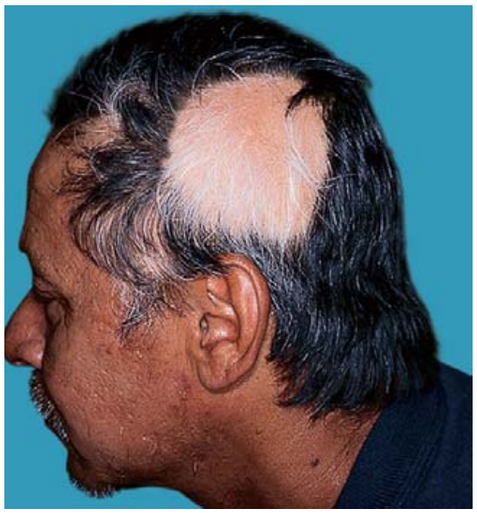
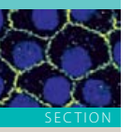


Fig. 1.19 Alopecia areata. The detrimental social impact of hair loss in patients with diseases such as alopecia areata cannot be underestimated. The disease process targets pigmented hairs, and the initial cycle of regrowth may consist of depigmented hairs.

point has been recently illustrated by the observation that keratoacanthomas may erupt in patients being treated with molecular inhibitors of mutated BRAF, which is found in approximately 40% of melanomas[66,67]. In patients with the characteristic V600E activating mutation in BRAF, molecular inhibitors of BRAF arrest melanoma growth[68]. However, when wild-type BRAF is inhibited, especially in the presence of mutated RAS, signaling pathways are enhanced and cellular proliferation ensues[66,67]. Keratoacanthomas and squamous cell carcinomas are the clinical consequence. Our understanding of the molecular pathways of keratinocyte biology has been expanded by observing the outcomes of our intervention on melanoma. Many more such observations are bound to follow as we continue to develop new ways of treating skin disease.

REFERENCES

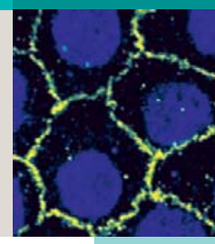
1. Fuchs E. Beauty is skin deep: the fascinating biology of the epidermis and its appendages. Harvey Lect. 2001;94:47–77.
2. Bergstresser PR, Pariser RJ, Taylor JR. Counting and sizing of epidermal cells in normal human skin. J Invest Dermatol. 1978;70:280–4.
3. Bergstresser PR, Taylor JR. Epidermal 'turnover-time' – a new examination. Br J Dermatol. 1977;96:503–9.
4. Elias PM, Choi EH. Interactions among stratum corneum defensive functions. Exp Dermatol. 2005;14:719–26.
5. Burgeson RE, Christiano AM. The dermal-epidermal junction. Curr Opin Cell Biol. 1997;9:651–8.
6. Incontinentia pigmenti. Online Mendelian Inheritance in Man 5-20-2003. Web/URLs: http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=308300
7. Inhibitor of kappa light polypeptide gene enhancer in B cells, kinase of, gamma. Online Mendelian Inheritance in Man 4-12-2007. Web/URLs: http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=300248
8. Holick MF. Calcium and vitamin D. Diagnostics and therapeutics. Clin Lab Med. 2000;20:569–90.
9. Asbill CS, El-Kattan AF, Michniak B. Enhancement of transdermal drug delivery: chemical and physical approaches. Crit Rev Ther Drug Carrier Syst. 2000;17:621–58.
10. Tuting T, Storkus WJ, Falo LD Jr. DNA immunization targeting the skin: molecular control of adaptive immunity. J Invest Dermatol. 1998;111:183–8.
11. Morrison R. The Spirit in the Gene: Humanity's Proud Illusion and the Laws of Nature. New York: Cornell University Press, 1999.
12. Janeway CA Jr. How the immune system works to protect the host from infection: a personal view. Proc Natl Acad Sci USA. 2001;98:7461–8.
13. Jackson S, Storey A. E6 proteins from diverse cutaneous HPV types inhibit apoptosis in response to UV damage. Oncogene. 2000;19:592–8.
14. Allen AL, Siegfried EC. Management of warts and molluscum in adolescents. Adolesc Med. 2001;12:229–42.
15. Buckley DA, DuVivier AW. The therapeutic use of topical contact sensitizers in benign dermatoses. Br J Dermatol. 2001;145:385–405.
16. King RD, Khan HA, Foye JC, et al. Transferrin, iron, and dermatophytes. I. Serum dermatophyte inhibitory component definitively identified as unsaturated transferrin. J Lab Clin Med. 1975;86:204–12.
17. Taplin D. Superficial mycoses. J Invest Dermatol. 1976;67:177–81.
18. Sieling PA, Ochoa MT, Jullien D, et al. Evidence for human CD4+ T cells in the CD1-restricted repertoire: derivation of mycobacteria-reactive T cells from leprosy lesions. J Immunol. 2000;164:4790–6.
19. Langan SM, Groves RW, West J. The relationship between neurological disease and bullous pemphigoid: a population-based case-control study. J Invest Dermatol. 2011;131:631–6.
20. Das PK, van den Wijngaard RM, Wankowicz-Kalinska A, Le Poole IC. A symbiotic concept of autoimmunity and tumour immunity: lessons from vitiligo. Trends Immunol. 2001;22:130–6.
21. Overwijk WW, Restifo NP. Autoimmunity and the immunotherapy of cancer: targeting the 'self' to destroy the 'other'. Crit Rev Immunol. 2000;20:433–50.
22. Ponec M, Gibbs S, Pilgram G, et al. Barrier function in reconstructed epidermis and its resemblance to native human skin. Skin Pharmacol Appl Skin Physiol. 2001;14(suppl. 1):63–71.
23. Corcuff P, Fiat F, Minondo AM. Ultrastructure of the human stratum corneum. Skin Pharmacol Appl Skin Physiol. 2001;14(suppl. 1):4–9.
24. Syder AJ, Yu Q-C, Paller AS, et al. Genetic mutations in the K1 and K10 genes of patients with epidermolytic hyperkeratosis: correlation between location and disease severity. J Clin Invest. 1994;93:1533–42.
25. Epidermolytic hyperkeratosis; keratin 10. Online Mendelian Inheritance in Man 3-6-2003. Web/URLs: http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=148080
26. Darier-White disease. Online Mendelian Inheritance in Man 4-4-2001. Web/URLs: http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=124200
27. Medansky RS, Woloshin AA. Darier's disease: an evaluation of its neuropsychiatric component. Arch Dermatol. 1960;84:482–4.
28. Shuman RM, Leech RW, Alvord EC Jr. Neurotoxicity of hexachlorophene in humans. II. A clinicopathological study of 46 premature infants. Arch Neurol. 1975;32:320–5.
29. Gordon-Smith K, Jones LA, Burge SM, et al. The neuropsychiatric phenotype in Darier disease. Br J Dermatol. 2010;163:515–22.
30. Viard I, Wehrli P, Bullani R, et al. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. Science. 1998;282:490–3.
31. Oculocutaneous albinism, type I. Online Mendelian Inheritance in Man 1-10-2005. Web/URLs: http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=203100
32. Peltonen J, Hsiao LL, Jaakkola S, et al. Activation of collagen gene expression in keloids: co-localization of type I and VI collagen and transforming growth factor-beta-1 mRNA. J Invest Dermatol. 1991;97:240–8.
33. Xeroderma pigmentosum, complementation group A. Online Mendelian Inheritance in Man 4-3-2003. Web/URLs: http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=278700
34. Stoitzner P, Pfaller K, Stüssel H, Romani N. A close-up view of migrating Langerhans cells in the skin. J Invest Dermatol. 2002;118:117–25.
35. Frey JR, Wenk P. Experimental studies on the pathogenesis of contact eczema in the guinea pig. Arch Allergy Appl Immunol. 1957;11:81–100.
36. Streilein JW, Alard P, Niizeki H. Neural influences on induction of contact hypersensitivity. Ann N Y Acad Sci. 1999;885:196–208.
37. Boni R, Kreyden OP, Burg G. Revival of the use of botulinum toxin: application in dermatology. Dermatology. 2000;200:287–91.
38. Schmader K. Herpes zoster in older adults. Clin Infect Dis. 2001;32:1481–6.
39. Bovell DL, Clunes MT, Elder HY, et al. Ultrastructure of the hyperhidrotic eccrine sweat gland. Br J Dermatol. 2001;145:298–301.
40. Croft RP, Nicholls PG, Steyerberg EW, et al. A clinical prediction rule for nerve-function impairment in leprosy patients. Lancet. 2000;355:1603–9.
41. Polydefkis M, Hauer P, Griffin JW, McArthur JC. Skin biopsy as a tool to assess distal small fiber innervation in diabetic neuropathy. Diabetes Technol Ther. 2001;3:23–8.
42. Sauder DN, Carter CS, Katz SI, Oppenheim JJ. Epidermal cell production of thymocyte activating factor (ETAF). J Invest Dermatol. 1982;79:34–9.
43. Luger TA, Stadler BM, Katz SI, Oppenheim JJ. Epidermal cell (keratinocyte)-derived thymocyte-activating factor (ETAF). J Immunol. 1981;127:1493–8.
44. Luger TA, Scholzen T, Grabbe S. The role of alpha-melanocyte-stimulating hormone in cutaneous biology. J Invest Dermatol Symp Proc. 1997;2:87–93.
45. Quaglino D Jr, Nanney LB, Ditesheim JA, Davidson JM. Transforming growth factor-beta stimulates wound healing and modulates extracellular matrix gene expression in pig skin: incisional wound model. J Invest Dermatol. 1991;97:34–42.
46. Takashima A, Bergstresser PR. Cytokine-mediated communication by keratinocytes and Langerhans cells with dendritic epidermal T cells. Semin Immunol. 1996;8:333–9.
47. Scholzen T, Hartmeyer M, Fastrich M, et al. Ultraviolet light and interleukin-10 modulate expression of cytokines by transformed human dermal microvascular endothelial cells. J Invest Dermatol. 1998;111:50–6.
48. Schrüder JM, Sticherling M, Henneicke HH, et al. IL-1 alpha or tumor necrosis factor-alpha stimulate release of three NAP-1/IL-8-related neutrophil chemotactic proteins in human dermal fibroblasts. J Immunol. 1990;144:2223–32.
49. Szabowski A, Maas-Szabowski N, Andrecht S, et al. c-Jun and JunB antagonistically control cytokine-regulated mesenchymal-epidermal interaction in skin. Cell. 2000;103:745–55.
50. Maas-Szabowski N, Stark HJ, Fusenig NE. Keratinocyte growth regulation in defined organotypic cultures through IL-1-induced keratinocyte growth factor expression in resting fibroblasts. J Invest Dermatol. 2000;114:1075–84.
51. Mauviel A, Kahari VM, Kurkinen M, et al. Leukoregulin, a T-cell derived cytokine, upregulates stromelysin-1 gene expression in human dermal fibroblasts: evidence for the role of AP-1 in transcriptional activation. J Cell Biochem. 1992;50:53–61.
52. Kothny-Wilkes G, Kulms D, Luger TA, et al. Interleukin-1 protects transformed keratinocytes from tumor necrosis



factor-related apoptosis-inducing ligand- and CD95-induced apoptosis but not from ultraviolet radiation-induced apoptosis. J Biol Chem. 1999;274:28916–21.
53. Kothny-Wilkes G, Kulms D, Poppelmann B, et al. Interleukin-1 protects transformed keratinocytes from tumor necrosis factor-related apoptosis-inducing ligand. J Biol Chem. 1998;273:29247–53.
54. Biedermann T, Kneilling M, Mailhammer R, et al. 2000. Mast cells control neutrophil recruitment during T cell-mediated delayed-type hypersensitivity reactions through tumor necrosis factor and macrophage inflammatory protein 2. J Exp Med. 2000;192: 1441–52.
55. Grutzkau A, Henz BM, Kirchhof L, et al. α-Melanocyte stimulating hormone acts as a selective inducer of secretory functions in human mast cells. Biochem Biophys Res Commun. 2000;278:14–9.
56. Ectodermal dysplasia-1. Online Mendelian Inheritance in Man 4-22-2004. Web/URLs: http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=305100
57. Krakauer J. Into Thin Air. A Personal Account of the Mount Everest Disaster. New York: Random House, 1997.
58. Shaffrali F, Gawkrodger D. Management of vitiligo. Clin Exp Dermatol. 2000;25:575–9.
59. Mosher DB, Fitzpatrick TB, Ortonne JP, Hori Y. Disorders of pigmentation. In: Fitzpatrick TB, Eisen AZ, Wolff K, et al (eds). Dermatology in General Medicine. New York: McGraw-Hill, 1987:794–876.
60. Pandya AG, Guevara IL. Disorders of hyperpigmentation. Dermatol Clin. 2000;18:91–8.
61. Paus R, Cotsarelis G. Mechanisms of disease: the biology of hair follicles. N Engl J Med. 1999;341:491–7.
62. Cotsarelis G, Millar SE. Towards a molecular understanding of hair loss and its treatment. Trends Mol Med. 2001;7:293–301.
63. Dawber RP, Sinclair RD. Hirsuties. Clin Dermatol. 2001;19:189–99.
64. Olsen EA. Female pattern hair loss. J Am Acad Dermatol. 2001;45:570–80.
65. Markey AC. Liposuction in cosmetic dermatology. Clin Exp Dermatol. 2001;26:3–5.
66. Heidorn SJ, Milagre C, Whittaker S, et al. Kinase-dead BRAF and oncogenic RAS cooperate to drive tumor progression through CRAF. Cell. 2010;140:209–21.
67. Hatzivassiliou G, Song K, Yen I, et al. RAF inhibitors prime wild-type RAF to activate the MAPK pathway and enhance growth. Nature. 2010;464:431–5.
68. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364:2507–16.

Skin Development and Maintenance

2



Maranke I Koster, Cynthia A Loomis, Tamara Koss and David Chu

Chapter Contents

Embryonic origin of the skin 55
Epidermal development 55
Development of specialized cells within the epidermis 57
Development of the dermis and subcutis 58
Development of the dermal–epidermal junction 59
Development of skin appendages 59
Skin stem cells 60
Prenatal diagnosis of genodermatoses 63
Significance of skin development in postnatal life 63

INTRODUCTION

Development of the human embryo is a complex process involving highly orchestrated cell movements, proliferation, death and differentiation. This chapter focuses on key events and regulatory mechanisms that result in skin morphogenesis, maintenance and regeneration. The spectrum of cutaneous abnormalities that can result from mutations in genes with critical roles in skin development is discussed. Ultimately, improved understanding of the pathways and signaling cascades that are disrupted in genetic skin disorders will aid in the development of therapeutic approaches for patients with acquired as well as inherited skin disorders.

EMBRYONIC ORIGIN OF THE SKIN

The skin is composed of diverse cell types of both ectodermal (e.g. keratinocytes, melanocytes, Merkel cells, neurons) and mesodermal (e.g. fibroblasts, hematopoietic cells such as Langerhans cells, endothelial cells) lineages. To understand the origins of these cells, it is important to review the early stages of embryogenesis. Immediately after fertilization, cells divide rapidly, and by the end of the first week, the embryo begins to implant into the uterine wall. During the third week, the embryo undergoes gastrulation, a complex process resulting in the formation of the three embryonic germ layers: endoderm, mesoderm and ectoderm.

During the next stage of embryogenesis, ectodermal cells commit to either a surface ectodermal or neuroectodermal fate. The surface ectodermal cells eventually differentiate into the keratinocytes of the embryonic epidermis, whereas the neuroectodermal cells invaginate to create the neural tube in a process called neurulation. As the neural tube forms, cells in its dorsal portion separate to form the neural crest. An important neural crest-derived cell in the skin is the melanocyte. Although Merkel cells were once believed to be neural crest derivatives, it was recently established that they descend from the epidermal lineage. The lineage of the dermis depends on its location. Whereas the dermis (and other mesenchymal structures) of the face and frontal scalp are derived from the neural crest, the dermis elsewhere is derived from the mesoderm. Knowing from which germ layer and lineage different cell types in the skin derive helps one to understand the pathophysiology of cutaneous disorders ranging from congenital melanocytic nevi (where "neurotization" is explained by the derivation of both melanocytes and peripheral nerve sheath cells from the neural crest) to Waardenburg syndrome (where craniofacial dysmorphism and hearing impairment as well as pigmentary abnormalities reflect disrupted migration and survival of neural crest-derived cells).

An overview of key events in the development of skin and its specialized structures is shown in Figure 2.1.

EPIDERMAL DEVELOPMENT

The ectoderm that covers the developing embryo after gastrulation is a single-layered epithelium (Fig. 2.2A). The first step in epidermal development occurs when cells of the surface ectoderm adopt an epidermal fate[1]. Although this process does not result in major morphologic changes, it is marked by dramatic alterations in gene expression that result in the formation of the embryonic epidermis, which initially consists of only a basal layer (Fig. 2.2B). Basal keratinocytes subsequently generate cells of the periderm, a single cell layer that covers the developing epidermis until the cornified cell layer is formed (Figs 2.2C–F & 2.3A,B). Although the precise function of the periderm is not known, it is believed to participate in the exchange of substances across fetal skin and protects the developing epidermis from the amniotic fluid.

The embryonic epidermis begins to stratify at approximately 8 weeks' estimated gestational age (EGA)[2]. At this time, basic organogenesis is complete and bone marrow hematopoiesis commences, marking the transition from embryo to fetus. During the first stage of epidermal stratification, an intermediate cell layer is formed between the basal layer and periderm (Figs 2.2D & 2.3B). Unlike suprabasal keratinocytes in the postnatal epidermis, the intermediate layer consists of actively proliferating cells. As a consequence, it is able to expand to accommodate the rapid growth of the embryo as well as create additional layers of intermediate cells over the next several weeks (Fig. 2.2E). However, the intermediate cell layer only exists temporarily during epidermal development, as it is eventually replaced by layers of postmitotic keratinocytes undergoing terminal differentiation.

Terminal differentiation, the process resulting in the formation of mature keratinizing epidermal cells, begins during the second trimester. Early cornification can be observed within the hair canal at approximately 15 weeks' EGA[2a], but it does not commence in the interfollicular epidermis until 22–24 weeks' EGA, occurring first in the skin on the head, palms and soles. Expression of the *p63* gene is required for the process of epidermal stratification. The process begins when cells in the intermediate layer permanently withdraw from the cell cycle and differentiate into spinous and granular cells (Fig. 2.2F). The cornified cell layer, which is composed of "dead" keratinocytes (corneocytes) held together by a matrix of proteins and lipids (see Ch. 56), subsequently starts to form and is several cells thick by 24–26 weeks' EGA. The corneocytes are a reflection of the closely regulated process of terminal differentiation that is required for normal functioning of the skin. At the same time, the periderm detaches from the underlying epidermis and is sloughed off into the amniotic fluid, with remnants contributing to the vernix caseosa that coats newborns. During the third trimester, the number of keratohyalin and lamellar granules as well as stratum corneum layers increase. By the mid third trimester, the epidermis is morphologically similar to adult skin (Figs 2.2G & 2.3C), although it does not acquire full barrier function until a few weeks after birth.

Clinical Relevance

Genetic abnormalities affecting various stages of epidermal morphogenesis have been found to underlie inherited skin disorders in humans. However, generalized abnormalities in epidermal specification, the process through which the surface ectoderm adopts an epidermal fate, have not been identified, and it is likely that such defects would be incompatible with survival past the first trimester. Mosaic

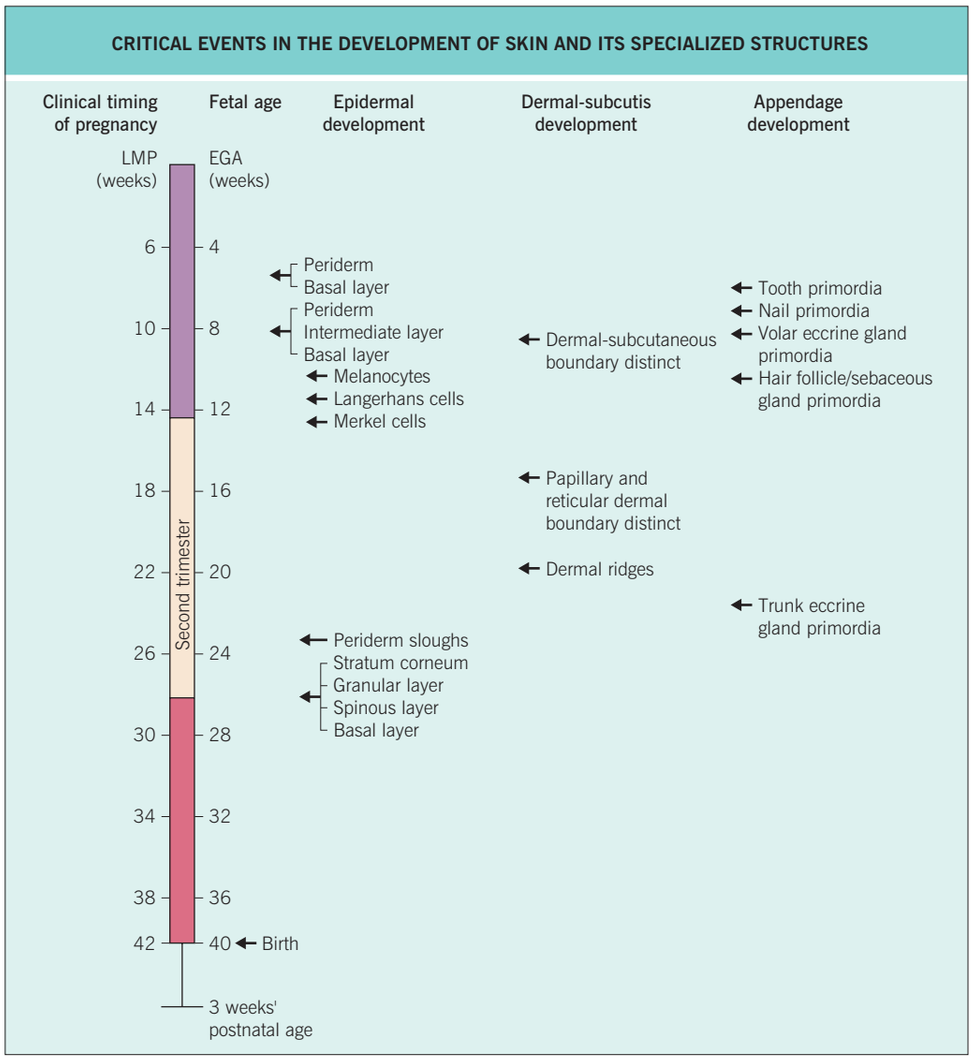


Fig. 2.1 Critical events in the development of the skin and its specialized structures. The timeline indicates the time of initiation defined by estimated gestational age (EGA) and duration of pregnancy (by last menstrual period [LMP]). Refers to skin on the back unless otherwise noted.

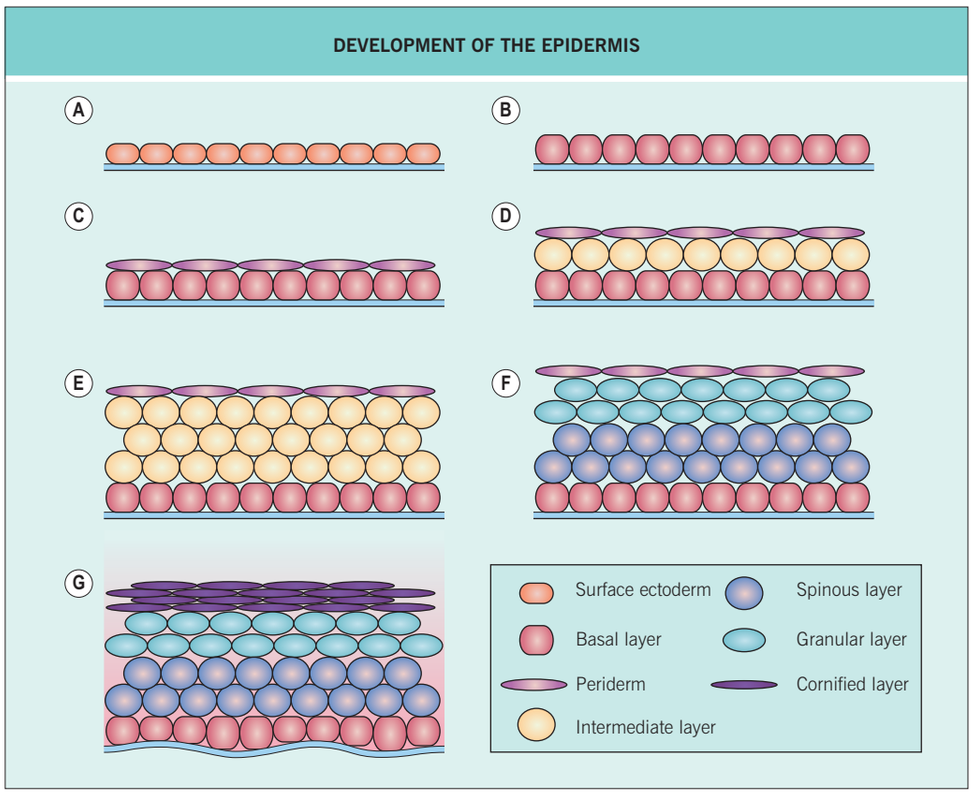


Fig. 2.2 Development of the epidermis. A The epidermis develops from the surface ectoderm, a single-layered epithelium that initially covers the developing embryo. **B** Through changes in gene expression, cells of the surface ectoderm adopt an epidermal fate, resulting in the formation of the basal layer of the epidermis. **C** Basal cells subsequently give rise to the periderm, a cell layer that covers the developing epidermis until cornification occurs. **D** Epidermal stratification begins with the formation of a highly proliferative intermediate layer between the basal layer and the periderm. **E** The intermediate layer becomes several cells thick over the next few weeks. **F** Intermediate cells ultimately withdraw from the cell cycle and differentiate into spinous and granular keratinocytes. **G** The periderm is replaced by the cornified cell layer.

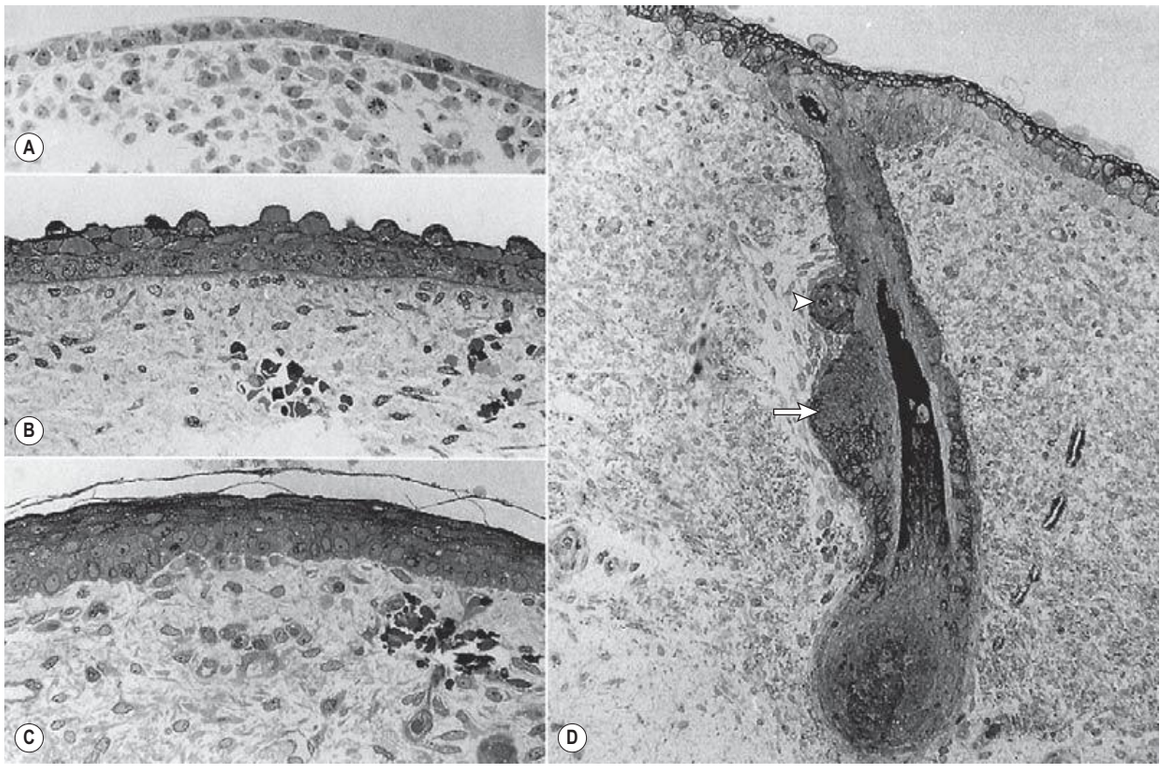


Fig. 2.3 Development of the skin. A At 36 days' estimated gestational age, the embryonic epidermis consists of two layers – a superficial periderm layer overlying a basal layer. **B** By 72 days, the basal layer has given rise to the highly proliferative intermediate cell layer. **C** A distinct granular cell layer and stratum corneum are seen in neonatal skin. **D** An early peg-stage follicle from a mid second trimester fetus. The more superficial bulge consists of the developing sebaceous gland (arrowhead), whereas the deeper bulge represents the insertion point of the future arrector pili muscle and the location of the presumptive follicular stem cells (arrow). *Photomicrographs courtesy of Dr Karen Holbrook, from Loomis CA, Koss T, Chu D. Fetal skin development. In: Eichenfield LF, Frieden IJ, Esterly NB (eds). Textbook of Neonatal Dermatology, 2nd edn. Philadelphia: WB Saunders, 2007:1–17.*

skin conditions that result in abnormalities of the epidermis (e.g. of keratinocytes or melanocytes) and/or its appendages often have a distribution pattern that follows Blaschko's lines, which are thought to represent the migration pathways of epidermal cells during embryonic development. Classic examples include epidermal nevi (with underlying defects including mosaicism for mutations in genes encoding the fibroblast growth factor receptor 3, keratin 1 or keratin 10) and sebaceous nevi (where the underlying genetic defect remains unknown but is thought to be lethal if present in all the cells of the body) (see Ch. 62).

There are a number of genetic disorders that result in abnormal epidermal differentiation and barrier formation. One clinical presentation of such conditions is a "collodion baby" born encased in a taut, shiny, transparent membrane that is formed by aberrant stratum corneum. After shedding the membrane, most of these infants manifest with lamellar ichthyosis (LI) or congenital ichthyosiform erythroderma (CIE), two forms of autosomal recessive ichthyosis that exist on a spectrum[3]. However, the phenotypes that can develop following a collodion membrane include not only the large, plate-like brown scales of LI and the erythroderma with fine white scales of CIE, but also completely normal appearing skin. Referred to as a "self-healing" collodion baby, the latter is an example of a dynamic epidermal phenotype that depends on environmental conditions. All of these outcomes can result from mutations in the same set of genes that encode proteins essential for formation of the epidermal barrier, including transglutaminase-1 (an enzyme that cross-links lipids to the cornified cell envelope; *TGM1*), lipid processing enzymes (*ALOXE3*, *ALOX12B*) and lipid transporters (*ABCA12*) (see Ch. 57).

More deleterious mutations in the *ABCA12* gene represent the cause of harlequin ichthyosis (HI), an especially severe and often fatal disorder of cornification characterized by aberrant epidermal maturation. Patients with HI are born with a tremendously thick, armor-like shell of hyperkeratosis, severe ectropion and eclabium, and underdevelopment of the nose and ears. The extreme phenotype of HI highlights the importance of lipid transport into lamellar bodies for epidermal formation and function.

Abnormalities in the stratum corneum are present not only in infants with ichthyosis, but also in premature infants, especially those born before 28 weeks' EGA. The immaturity of the stratum corneum results in impaired barrier function, which leads to an increased risk of infection, dehydration, and excessive absorption of topical medications or chemicals[4]. Even healthy full-term infants do not attain full skin barrier function until 3 weeks of age. The structural features of premature skin and adult skin are summarized in Table 2.1.

DEVELOPMENT OF SPECIALIZED CELLS WITHIN THE EPIDERMIS

Two populations of specialized cells – melanocytes and Langerhans cells – migrate to the epidermis during early embryonic development. Melanocytes are derived from the neural crest that forms along the dorsal neural tube. Melanocyte precursors migrate away from the neural tube within the mesenchyme beneath the primitive epidermis. They follow a characteristic trajectory, moving dorsolaterally and then ventrally around the trunk to the ventral midline, anteriorly over the scalp and face, and distally along the extremities. Cutaneous melanocytes can also arise from Schwann cell precursors located along nerves in the skin, which originate from the neural crest via the distinct ventral pathway[5].

Melanocytes are present in the epidermis by the middle of the first trimester, but they are not fully functional until the second trimester. Melanocytes can be first identified within the embryo's epidermis at approximately 50 days' EGA, based on their positive reactivity with the HMB45 monoclonal antibody and their dendritic morphology. Epidermal melanocyte density is high early in embryonic development (1000 cells/mm^2), and it increases further (~3000 cells/mm^2) as the epidermis stratifies (80–90 days' EGA) and the appendages begin to develop; later in gestation, the density decreases and becomes similar to that of young adults (800–1500 cells/mm^2). However, epidermal melanin production does not begin until 3–4 months' EGA, and melanosome transfer to keratinocytes is not seen until 5 months' EGA. Even though all melanocytes are functional and in place at birth, newborn skin is not fully pigmented and subsequently darkens over the first few months of life; this process is most pronounced in more darkly pigmented infants.

Active melanocytes are also present throughout the dermis during embryonic development. Eventually, most of these dermal melanocytes migrate to the epidermis or undergo apoptosis. By the time of birth, dermal melanocytes have disappeared, with the exception of certain

COMPARATIVE FEATURES OF PREMATURE, NEWBORN, AND ADULT SKIN			
	Premature	**Newborn**	**Adult**
Skin thickness	0.9 mm	1.2 mm	2.1 mm
Epidermal surface	Vernix (gelatinous)	Vernix	Dry
Epidermal thickness	~20–25 microns	~40–50 microns	~50 microns
Stratum corneum thickness	4–5 microns	9–10 microns	9–15 microns
	5–6 cell layers	>15 cell layers	>15 cell layers
Spinous cell glycogen content	Abundant	Little or none	Little or none
Melanocytes	High number of cells; few mature melanosomes	Similar number of cells to young adult; low melanin production	Numbers decrease with age; melanin production dependent on skin type, body area
Dermal–epidermal junction	All known adult antigens expressed; fewer and smaller desmosomes	Structural features and antigens similar to those of the adult	Well-developed adhesive structures; large number of antigens expressed
Papillary dermis			
• Boundary with reticular dermis	Present but not marked	Present but not marked	Marked
• Size of collagen fiber bundles	Small	Small	Small
• Cellular density	Abundant	Abundant	Moderately abundant
Reticular dermis			
• Boundary with the subcutis	Marked	Marked	Marked
• Size of collagen fiber bundles	Small	Small to intermediate	Large
• Cellular density	Abundant	Moderately abundant	Sparse
Elastic fibers	Sparse; tiny with immature structure	Small size and immature structure; distribution similar to adult	Large in reticular dermis, small and immature in papillary dermis; form network
Hypodermis	Well-developed fatty layer	Well-developed fatty layer	Well-developed fatty layer

Table 2.1 Comparative features of premature, newborn, and adult skin. *Reproduced with permission from Schachner LA, Hansen RC (eds). Pediatric Dermatology, 4th edn. London: Mosby, 2010.*

anatomic sites (head and neck, dorsal aspects of the distal extremities and presacral area), which correspond to the most common locations for dermal melanocytoses and blue nevi (see Ch. 112).

Langerhans cell precursors appear within the epidermis during the first trimester and are first detectable in this site as early as 40 days' EGA. These cells can be distinguished by their characteristic dendritic morphology; expression of CD45, HLA-DR and CD1c; and high levels of ATPase activity. Langerin expression precedes CD1a acquisition, which first occurs at 13 weeks' EGA, and the production of Birbeck granules[6]. The density of Langerhans cells in fetal skin remains low early in gestation and increases to typical adult levels during the third trimester.

Merkel cells, highly innervated neuroendocrine cells involved in mechanoreception, are initially identified within the epidermis during the first trimester. These cells are detected as early as 8–12 weeks' EGA in palmoplantar epidermis, and slightly later in interfollicular skin. Merkel cells are identified by the presence of cytoplasmic dense core granules, cytokeratin 20 and neuropeptides. They are found in the basal layer of the epidermis, are often associated with appendages and nerve fibers, and are particularly dense on volar skin. The developmental origin of Merkel cells has been the subject of longstanding controversy, but recent studies have demonstrated that mammalian Merkel cells are derived from an epidermal rather than neural crest lineage[7].

Clinical Relevance

Several inherited pigmentary disorders result from genetic defects that lead to abnormal migration and proliferation of neural crest-derived melanocyte precursors (melanoblasts). Piebaldism and Waardenburg syndrome are characterized by achromic patches of skin on the central forehead, central abdomen and extremities, a distribution pattern that reflects the failure of melanocyte precursors to survive, proliferate or travel to the distal points of their embryonic migration pathway. A number of different causative genes leading to this phenotype have been identified, including those encoding transcription factors (e.g. microphthalmia-associated transcription factor [MITF], PAX3, SOX10, SNAI2) as well as membrane receptors and their ligands (e.g. endothelin-3, endothelin B receptor, KIT receptor)[8] (see Ch. 66). The endothelin B receptor is found on melanoblast–ganglion cell precursors in the developing neural crest, explaining the Hirschsprung disease (as well as pigmentary abnormalities) that is associated with defects in this receptor or its ligand.

DEVELOPMENT OF THE DERMIS AND SUBCUTIS

The specification of dermal mesenchymal cells is a complex process that is incompletely understood. Unlike the epidermis, which is derived exclusively from the ectoderm, the origin of the dermis varies depending on the body site. As noted above, the dermal mesenchyme of the face and anterior scalp (as well as the underlying muscle and bone) is derived from neural crest ectoderm, thereby explaining the facial dysmorphia in the neurocristopathy Waardenburg syndrome. On the other hand, the dermal mesenchyme of the back originates from the dermomyotome of the embryonic somite, and the dermal mesenchyme of the extremities and ventral trunk is thought to arise from the lateral plate mesoderm.

By 6–8 weeks' EGA, presumptive dermal fibroblasts are situated under the developing epidermis[9]. However, at this developmental stage, there is no distinct demarcation between the cells that will give rise to the dermis and those that will give rise to musculoskeletal components. Although embryonic dermal cells are capable of synthesizing collagens (e.g. types I, III and IV) and some microfibrillar components, these proteins are not yet assembled into complex fibers. Of note, the ratio of collagen III to collagen I is 3:1, the reverse of what is seen in the adult dermis.

The demarcation between the dermis and underlying skeletal condensations becomes distinct at approximately 9 weeks' EGA. By 12–15 weeks' EGA, progressive changes in matrix organization and cell

morphology distinguish the fine weave of the papillary dermis located directly beneath the epidermis from the thicker, deeper reticular dermis. At this stage, the collagen proteins produced by the fibroblasts start to assemble into collagen fibers, which continue to accumulate in the reticular dermis during the second and third trimesters. Electron microscopy can first detect definitive elastic fibers at approximately 22–24 weeks' EGA. As development progresses, the watery, proteoglycan-rich, cellular dermis of the embryo is modified to the more rigid, fibrous, acellular dermis characteristic of adult skin. By the end of the second trimester, the dermis shifts from a non-scarring to a scarring form of wound repair. At birth, the dermis is still thinner and more cellular than the adult dermis.

The basic pattern of the dermal vasculature is discernible by the end of the first trimester. This pattern, however, undergoes extensive remodeling *in utero* and is not fully mature until after birth. Numerous molecular controls are involved in the regulation of angiogenesis, including the vascular endothelial growth factor (VEGF) family as well as the tyrosine kinase receptors Tie-1 and Tie-2 and their stimulatory (Ang-1) and inhibitory (Ang-2) angiopoietin ligands (see Ch. 102).

Nerve networks are formed by the mid to late first trimester, and they tend to follow the vascular pattern. Accumulation of subcutaneous fat begins during the second trimester and continues through the third trimester, when distinct lobules separated by fibrous septae are formed.

Clinical Relevance

Mutations in the genes that encode a variety of dermal structural proteins (e.g. collagens, components of elastic fibers) and the enzymes that process them underlie multiple forms of Ehlers–Danlos syndrome (characterized by skin hyperextensibility and fragility with poor wound healing) and cutis laxa (featuring lax, redundant skin). Genetic defects in regulatory proteins important for extracellular matrix development can lead to abnormalities in the skin and other organs. For example, mutations in the latent transforming growth factor-β (TGF-β) binding protein-4 gene (*LTBP4*) were recently found to underlie a form of cutis laxa associated with severe pulmonary, gastrointestinal and genitourinary malformations. The absence of LTBP4, an extracellular matrix protein that binds to fibrillin and controls the bioavailability of TGF-β, leads to aberrant TGF-β activity and defective elastic fiber assembly in many types of tissues.

Another disorder characterized by abnormal dermal development is Goltz syndrome (focal dermal hypoplasia), an X-linked dominant disorder characterized by areas of dermal hypoplasia (with fat herniation/hamartomas) in a distribution following Blaschko's lines, skeletal defects and mucosal papillomas. Goltz syndrome is caused by mutations in PORCN, an effector of the Wnt signaling pathway that is critical for normal dermal development[10]. Blaschko's lines are thought to represent pathways of epidermal development, and in a mouse model, PORCN expression and resultant Wnt signaling originating from the ectoderm have been shown to regulate development of the dermis.

DEVELOPMENT OF THE DERMAL–EPIDERMAL JUNCTION

The dermal–epidermal junction (DEJ) mediates adhesion between the basal keratinocytes and the dermis and provides resistance against shearing forces on the skin (see Ch. 28). The DEJ develops from a simple, generic basement membrane in the embryo to a highly complex, multilayered structure in the second-trimester fetus.

The embryonic DEJ consists of a lamina densa and a lamina lucida, and it is composed of molecules that are common to all basement membrane zones (e.g. type IV collagen, laminin, heparan sulfate, proteoglycans)[11]. The DEJ becomes progressively more complex, and skin-specific components of the DEJ start to appear after the embryonic–fetal transition at 8 weeks' EGA, coincident with the onset of epidermal stratification. By 12 weeks' EGA, almost all of the structures characteristic of the mature DEJ are in place (see Ch. 28). Hemidesmosomes, anchoring filaments and anchoring fibrils are synthesized by basal keratinocytes, with the type VII collagen-containing anchoring fibrils localizing to the sub-lamina densa; laminin 5 and the bullous pemphigoid antigens are also expressed. As development progresses, the flat embryonic DEJ acquires the rete ridges and dermal papillae that characterize the adult DEJ.

Clinical Relevance

Epidermolysis bullosa (EB) is a heterogeneous group of genetic disorders characterized by blister formation due to mechanical fragility of the skin. EB can result from mutations in genes that encode several different components of the DEJ[12]. The specific protein affected (and the degree to which it is altered) largely determines disease severity, depth of bulla formation, and involvement of extracutaneous tissues (see Ch. 32).

DEVELOPMENT OF SKIN APPENDAGES

Skin appendages (hair, nails, and eccrine, apocrine and sebaceous glands) have both epidermal and dermal components that are critical in embryogenesis. Normal development of skin appendages depends on tightly regulated interactions between the early dermis and epidermis (e.g. signaling molecules that are sent back and forth between these tissues), and a failure in either component (or in communication between them) leads to aberrant development. Despite the differences in the structure and function of the various types of cutaneous appendages, the developmental processes that regulate their formation are remarkably similar[13].

Hair Follicle Development

The complex dermal–epidermal interactions and genetic control mechanisms that occur in appendage development are best understood in the formation of the hair follicle. Follicle formation is initiated by signals from the dermis that direct the embryonic epidermis to form focal thickenings, called placodes (see Figs 68.2 & 68.3)[14]. Placodes are first seen on the scalp and face between 10 and 11 weeks' EGA; they subsequently develop in a caudal and then in a ventral direction. The epidermal placodes instruct the underlying dermal cells to condense and form the presumptive dermal papilla. The dermal papilla then directs the keratinocytes of the placode to proliferate and extend deeper into the dermis, thereby forming the hair germ (see Figs 68.2 & 68.3). By 12–14 weeks' EGA, the base of the developing hair follicle surrounds the presumptive dermal papilla, forming the hair peg (see Figs 68.2 & 68.3). The superficial portion of the developing hair follicle has two distinct bulges. The more superficial bulge consists of the developing sebaceous gland, whereas the deeper bulge represents the insertion point of the future arrector pili muscle and the location of the presumptive follicular stem cells.

Hair follicles undergo further maturation during the second trimester, forming seven concentric cell layers (from outer to inner): outer root sheath; inner root sheath, composed of Henley's and Huxley's layers and a cuticle; and then the hair shaft cuticle, cortex and medulla (see Fig. 68.2). The hair canal is fully formed by 18–21 weeks' EGA, and hairs are visible shortly thereafter. The hairs continue to grow until 24–28 weeks' EGA, when they leave the active growing phase (anagen) and enter the short-lasting degenerative phase (catagen) and subsequently the resting phase (telogen). The follicles then start the second hair cycle by re-entering anagen; new hairs grow and push out the first group of telogen hairs, which are shed into the amniotic fluid.

Hair cycling through anagen, catagen and telogen continues throughout life, but the hair cycles for individual hair follicles become asynchronous after birth. The third hair cycle is initiated perinatally, leading to the shedding of the second wave of fine lanugo hair follicles. Most hairs become thicker and coarser with subsequent growth cycles, leading to vellus and then adult-like terminal hairs on the scalp and in the eyebrows.

Many genes important for hair follicle development and cycling have been identified (see Ch. 68). Sonic hedgehog (SHH), a signaling molecule secreted by cells of the developing hair follicle, is required for the maturation of the dermal papilla and for the progression of the follicle placode to the peg hair stage. SHH also appears to be critical in mediating the transition from telogen to anagen during postnatal hair cycling. Members of the Wnt, bone morphogenetic protein (BMP) and fibroblast growth factor (FGF) families of signaling molecules are also important in hair follicle development and cycling. Transcription factors with roles

in follicular differentiation have also been identified, including HOXC13 and FOXN1.

Sebaceous gland development parallels follicular development. The presumptive sebaceous gland is first seen at around 13–16 weeks' EGA as the most superficial bulge on the developing hair follicle. The outer proliferative layer of the sebaceous gland generates lipogenic cells that progressively accumulate lipid/sebum until they are terminally differentiated, at which time they disintegrate and release their products into the upper portion of the hair canal. Maternal hormones contribute to sebaceous gland hypertrophy and increased synthesis and secretion of sebum during the second and third trimesters. The neonatal adrenal gland also has a disproportionately large zone of androgen production (referred to as the "fetal zone"), which involutes over the first year of life.

Nail Development

Nail development begins at 8–10 weeks' EGA and is completed by the fifth month of intrauterine development. The flat, rectangular surface of the future nail bed on the dorsal digital tips is first demarcated by folds visible at 8–10 weeks' EGA. A wedge of ectoderm invaginates obliquely into the mesenchyme along the proximal end of the early nail field, forming the proximal nail fold by 13 weeks' EGA. The presumptive nail matrix cells, which will later produce the differentiated nail plate, are found ventral to the proximal nail fold. The nail bed on the dorsal digit is the first skin structure to keratinize, at around 11 weeks; keratinization begins distally and then continues over the nail bed toward the proximal nail fold. The first, preliminary nail is shed easily and replaced by the hard, differentiated nail plate that emerges from under the proximal nail fold during the fourth month of gestation and completely covers the nail bed by the fifth month.

Eccrine and Apocrine Sweat Gland Development

Like hair and nails, palmoplantar eccrine sweat glands begin to develop during the first trimester and are fully developed by the second trimester. Sweat gland development starts with the formation of large mesenchymal bulges or pads (analogous to the paw pads of other mammals) on the palms and soles between 55 and 65 days' EGA. Parallel ectodermal ridges are induced in the epidermis overlying these pads between 12 and 14 weeks' EGA. The curves and whorls formed by these ridges result in characteristic dermatoglyphics (fingerprints), which can be seen on the digit tips by the fifth month of gestation. Unlike most other animals, the mesenchymal pads in the human fetus regress by the third trimester.

Beginning between 14 and 16 weeks' EGA, individual eccrine gland primordia bud along the ectodermal ridges at regularly spaced intervals. The buds elongate as cords of cells that enter the pad mesenchyme. By 16 weeks' EGA, glandular structures form at the terminal portion of the buds and secretory and myoepithelial cells are visible. Canalization of the dermal component of the eccrine duct is also complete by 16 weeks' EGA; this occurs via a loss of the desmosomal adhesions along the innermost ectodermal surfaces, with concomitant maintenance of the adhesion between duct cells and the gland walls. Canalization of the epidermal component of the duct is not complete until 22 weeks' EGA.

Unlike volar eccrine sweat glands, interfollicular eccrine glands and apocrine glands do not begin to form until the fifth month of gestation. Like sebaceous glands, apocrine glands typically arise from the upper portion of a hair follicle. Interfollicular eccrine glands, on the other hand, originate independently. The glandular cords of cells elongate during the ensuing weeks, and by 7 months' EGA the clear cells and mucin-secreting dark cells characteristic of apocrine glands can be visualized. Apocrine glands function transiently during the third trimester and subsequently become quiescent in the neonate. Eccrine glands, however, do not function *in utero* but mature and begin functioning postnatally.

Clinical Relevance

Ectodermal dysplasias are a large, heterogeneous group of genetic disorders that are characterized by developmental abnormalities in two or more major ectodermal appendages (hair, teeth, nails, and sweat glands); other ectodermal structures (e.g. sebaceous glands) can also be affected[15] (see Ch. 63). Hypohidrotic ectodermal dysplasia (HED) is a relatively common type of ectodermal dysplasia that affects the sweat glands (hypohidrosis), hair (hypotrichosis) and teeth (hypodontia). HED is caused by mutations in genes encoding components of the ectodysplasin A (EDA) signaling pathway, which is critical for the initiation of sweat gland, hair follicle and tooth morphogenesis. Underlying mutations can occur in the genes encoding the EDA ligand, EDA receptor (EDAR), or EDAR-associated death domain (an intracellular adaptor protein that functions in EDAR signaling). Mutations in EDA are responsible for the X-linked variety of HED (XLHED), which leads to "full-blown" disease in affected males and areas of involved skin following Blaschko's lines in heterozygous females. Because the underlying defect is in a soluble ligand that is only required for a brief period during the initiation of appendage formation, XLHED is a prime target for protein therapy. Encouragingly, studies in mice and dogs have demonstrated an almost complete correction of the XLHED phenotype upon prenatal or neonatal treatment with recombinant EDA protein[16,17]. Clinical trials with recombinant EDA protein for the treatment of infants with XLHED are planned.

In addition to mutations in genes that are required for appendage development, ectodermal dysplasias can also be caused by mutations in genes that are required for epidermal development[18]. In these instances, abnormal appendages result from disruption of cross-talk between the developing epidermis and dermis. Mutations in *p63*, a gene that is required for epidermal morphogenesis, can cause several types of ectodermal dysplasia, including the ankyloblepharon–ectodermal dysplasia–cleft lip/palate (AEC) and ectrodactyly–ectodermal dysplasia–cleft lip/palate (EEC) syndromes (see Ch. 63). The phenotypic differences between AEC and EEC are explained by underlying mutations in separate regions of the *p63* gene, which affect different functions and isotypes of the p63 protein.

Wnt signaling is critical for the development of epidermal appendages, and genetic defects in this pathway underlie conditions ranging from hereditary hypotrichosis simplex to onycho-odonto-dermal dysplasia and Schöpf–Schulz–Passarge syndrome[19]. The nevoid basal cell carcinoma syndrome (Gorlin syndrome) is caused by mutations in the *PTCH* tumor suppressor gene that result in overactivation of the sonic hedgehog (SHH) signaling pathway, which has important roles in neurologic and anterior–posterior axis development as well as hair follicle formation[20]. This explains the broad range of developmental anomalies, including craniofacial and skeletal defects, and the propensity for medulloblastomas, odontogenic keratocysts and multiple basal cell carcinomas to arise (see Ch. 108).

SKIN STEM CELLS

Stem cells are present in each self-renewing tissue and are responsible for maintaining and repairing the tissue they reside in. The epidermis, dermis, appendages, and melanocytes are each maintained by different stem cell compartments. Stem cells are self-renewing and divide infrequently during periods of homeostasis, with the latter feature believed to protect them from acquiring mutations during cell cycle progression. Under homeostatic conditions, stem cells are believed to undergo asymmetric division, generating one new stem cell and one daughter transit amplifying (TA) cell. Unlike stem cells, TA cells divide frequently and ultimately differentiate into lineage-specific cell types. Within the skin, stem cells that maintain the epidermis and hair follicles have been most extensively studied. The properties of stem cells, TA cells and terminally differentiated cells are listed in Table 2.2.

Epidermal Stem Cells

The human epidermis renews itself every 40–56 days[21]. This constant turnover is mediated by epidermal stem cells, which reside in the basal layer together with TA cells[22]; the latter constitute the majority of basal keratinocytes. Ultimately, TA cells withdraw from the cell cycle and move suprabasally, which initiates the keratinocyte terminal differentiation program. In non-acral human skin, epidermal stem cells are scattered within the basal layer, where they give rise to epidermal proliferative units (EPUs), columns of cells composed of one stem cell and its progeny (Fig. 2.4)[23]. The location of epidermal stem cells in human palmoplantar skin is less clear, but there is some evidence that they are found at the base of the rete ridges, where they are physically protected from environmental stress. However, other

PROPERTIES OF STEM CELLS, TRANSIT AMPLIFYING CELLS AND TERMINALLY DIFFERENTIATED CELLS			
	Stem cells	**Transit amplifying cells**	**Terminally differentiated cells**
Self-renewal*	Unlimited	Limited	No
Potential for differentiation*	Multipotent	Limited	None
Cycling in normal epidermis	Slow†	Rapid	None
Proliferative potential (e.g. during fetal development and wound healing)	High	Limited‡	None
Growth in culture	Sustained clonal growth	Small abortive clones‡	None
Maintenance of tissue homeostasis	Yes	Limited	No

*In order to maintain both the stem cell and differentiating cell compartments, upon division a stem cell gives rise to another stem cell and a cell that is destined to terminally differentiate (transit amplifying cell); this is referred to as asymmetry of fate.
†Retention of a DNA label (e.g. 5-bromo-2-deoxyuridine or tritiated thymidine) is utilized as an *in vivo* marker of stem cells based on their slowly cycling nature.
‡The proliferative potential of transit amplifying cells of the matrix is higher than those of the interfollicular epidermis, but still finite; the former cells can be serially passaged in culture.

Table 2.2 Properties of stem cells, transit amplifying cells and terminally differentiated cells.

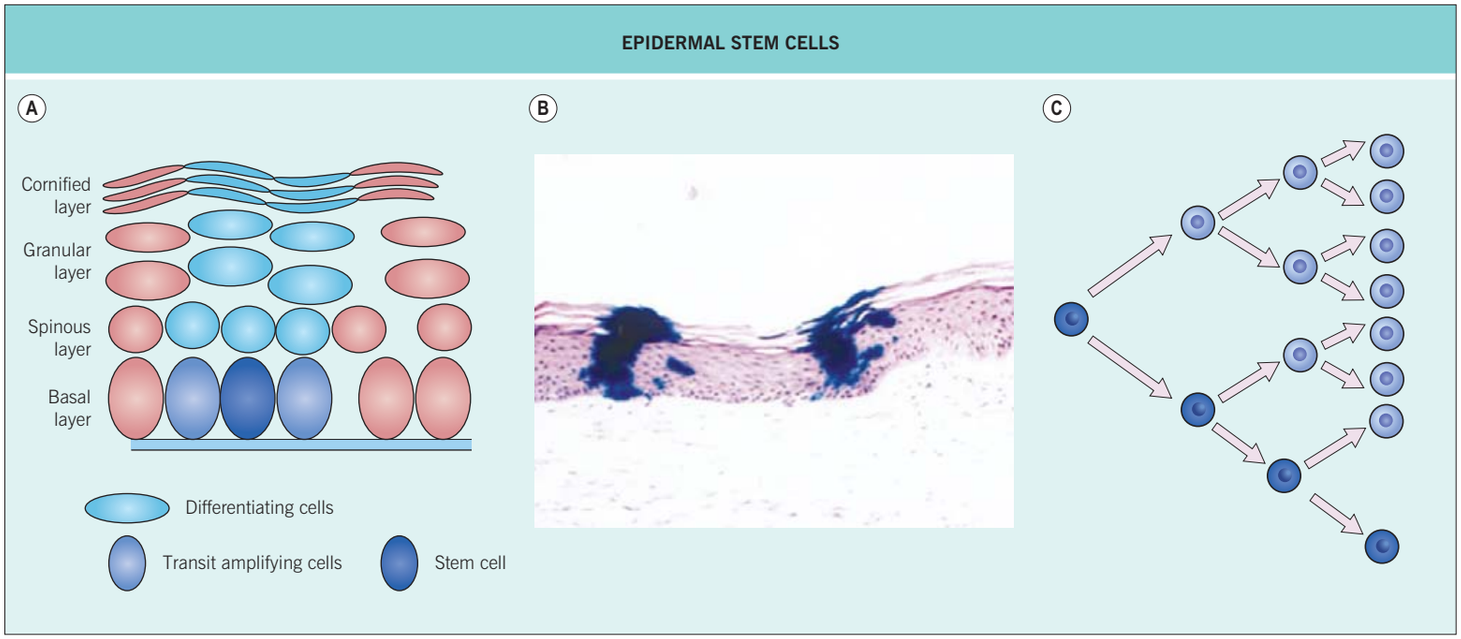


Fig. 2.4 Epidermal stem cells. A Epidermal stem cells are located in the basal layer of the epidermis. Each epidermal stem cell and its progeny forms a vertical column of progressively differentiating cells, which is known as the epidermal proliferation units (EPU) (blue). **B** EPUs in human skin grafted onto the back of a nude mouse. A subset of epidermal keratinocytes was transduced with a β-galactosidase-expressing virus. Forty weeks after grafting these cells onto nude mice, EPUs were visible. Since only epidermal stem cells and not TA cells or differentiated cells are able to persist for this length of time, the presence of EPUs indicates that they are derived from and maintained by epidermal stem cells. **C** With each cell division, another stem cell and a transit amplifying (TA) cell are generated (asymmetry of fate). The TA cells undergo a few rounds of cell division before they permanently withdraw from the cell cycle and initiate the terminal differentiation program. *Reprinted with permission from Kolodka TM, Garlick JA, Taichman LB (1998), Evidence for keratinocyte stem cells in vitro: Long term engraftment and persistence of transgene expression from retrovirus-transduced keratinocytes Proceedings of the National Academy of Sciences of the United States of America 95:4356-4361, © 1998 National Academy of Sciences, U.S.A.*

data suggest that palmoplantar epidermal stem cells are located at the top of deep rete ridges.

One distinguishing feature of stem cells is that they can be maintained in culture virtually indefinitely. A subset of epidermal basal cells forms highly proliferative colonies that can be passaged long term *in vitro*; referred to as holoclones, they presumably represent stem cells[24]. Holoclones can reconstitute epidermis *in vitro*, and they have been utilized for the treatment of burns and inherited skin disorders (see below). The properties of cutaneous stem cells, including their molecular markers, are summarized in Table 2.3.

Hair Follicle Stem Cells

The hair follicle bulge, which is located in the mid portion of the follicle (just deep to the sebaceous gland and adjacent to the arrector pili muscle attachment site), is thought to harbor hair follicle stem cells (Fig. 2.5). The bulge represents the lowest permanent portion of the hair follicle, and it contains morphologically undifferentiated cells[25]. Hair follicle bulge cells are slow-cycling and have a high proliferative potential as well as being self-renewing and multipotent. *In vivo*, they proliferate only when the hair follicle re-enters the active growing phase of anagen, in which the bottom two-thirds of the follicle must be regenerated. Such appendageal stem cells provide an important ectodermal reserve, allowing temporary reconstitution of the surface epidermis after severe wounds such as second-degree burns.

In addition to bulge cells, other cell populations in the hair follicle display stem cell characteristics. One of these populations is located in the lower outer root sheath in anagen hair follicles and is marked by the expression of Lgr5[26]. Whether these cells represent a separate stem cell population or whether they are derived from bulge stem cells (or vice versa) remains to be determined.

Stem Cell Plasticity

Under homeostatic conditions, epidermal and hair follicle stem cells only contribute to their respective tissues of origin. However, bulge-derived keratinocytes can also contribute to the repair of the interfollicular epidermis in response to injury[25]. Within the healing

CUTANEOUS STEM CELLS				
Stem cell	**Location (niche)**	**Tissue regeneration in homeostasis**	**Tissue regeneration in injury repair**	**Markers**
Keratinocyte				
Interfollicular epidermis	Basal layer	Interfollicular epidermis	Hair follicle Sebaceous gland Interfollicular epidermis	Delta 1, MCSP, α_6* and β_1 integrins, LRIG1; *low* levels of CD71
Hair follicle**	Bulge†	Hair follicle	Hair follicle Sebaceous gland Interfollicular epidermis	Keratin 15, α_6 and β_1 integrins, CD200, PHLDA1, follistatin, frizzled homolog 1, LGR5; *low* levels of CD24, CD34‡, CD71, CD146
Sebaceous gland§	At or near the bud of the sebaceous gland	Sebaceous gland	Sebaceous gland	Blimp1
Merkel cell	Touch domes of hairy skin	Interfollicular epidermis	Interfollicular epidermis	α_6 integrin*, SCA1, CD200
Melanocyte§	Lower bulge and sub-bulge region¶	Hair matrix and epidermal melanocytes	Hair matrix and epidermal melanocytes	Pax3, TYRP2; *negative* for KIT, tyrosinase, TYRP1
"Neural crest-like"	Bulge† (form spheres)	?	*In vitro*: melanocytes, neurons, smooth muscle, adipocytes, chondrocytes	Twist, SLUG, SOX10, BMI-1, Notch1
"Dermal"	Dermis (form spheres)	?	*In vitro:* melanocytes, neurons, Schwann cells, smooth muscle adipocytes, chondrocytes	NGFRp75, nestin, OCT4, SLUG
"Skin-derived precursors"	Dermal papilla (form spheres)	?	*In vitro:* neurons, Schwann cells, smooth muscle adipocytes	Nestin, OCT4, SLUG, Twist

*Also expressed by epidermal transit amplifying cells.
**Additional stem cell populations identified within the hair follicle in mice include LGR6-positive cells in the central isthmus and LRIG1-positive cells in the upper isthmus, both of which contribute to the interfollicular epidermis and sebaceous glands during homeostasis.
†Within the outer root sheath just below the sebaceous gland, at or near the site of insertion of the arrector pili muscle.
‡Upregulated in mouse bulge cells.
§Studied primarily in mice; sebaceous gland stem cells have thus far been shown to be unipotent progenitor cells.
¶Lowest permanent portion of the hair follicle.

Table 2.3 Cutaneous stem cells. CD24, glycoprotein involved in cell adhesion and signaling; CD34, marker of hematopoietic progenitor cells and endothelial cells; CD71, transferrin receptor; CD146, melanoma cell adhesion molecule/MUC18/S-Endo-1 antigen; CD200, transmembrane glycoprotein that delivers a negative immunoregulatory signal (may be involved in maintaining immune tolerance); LGR5/6, leucine-rich repeat-containing G protein-coupled receptor 5/6; LRIG1, leucine-rich repeats and immunoglobulin-like domains 1 (epidermal growth factor receptor antagonist and regulator of stem cell quiescence); MCSP, melanoma-associated chondroitin sulfate proteoglycan; NGFR, nerve growth factor receptor; PHLDA1, pleckstrin homology-like domain, family A, member1; SCA1, stem cell antigen 1; TYRP, tyrosinase-related protein.

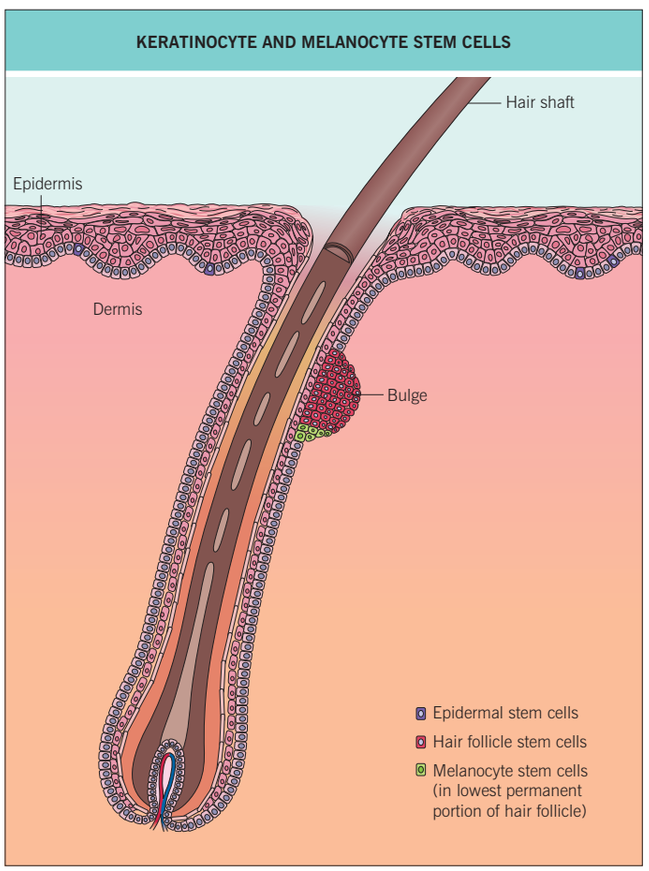


Fig. 2.5 Keratinocyte and melanocyte stem cells. Note that the bulge is continuous with the outer root sheath.

epidermis, bulge-derived cells survive only transiently, as they are rapidly replaced by progenies of epidermal stem cells. Similarly, epidermal stem cells can contribute to hair follicle formation in the center of large wounds[27].

Furthermore, emerging data indicate that cells in adult mammals are far more "flexible" in their potential to form other cell types than was previously thought. Some cell types, particularly bone marrow cells, are able to incorporate themselves into diverse tissues (such as the epidermis or heart) and to adopt the fates of resident cells, contributing progeny to the tissue. Induced pluripotent stem cells (iPS) are somatic cells (e.g. fibroblasts) that have been reprogrammed into an embryonic stem cell-like state[28]; these cells can be stimulated to differentiate into a variety of cell types, including keratinocytes. Thus, many adult cells, including different skin cell types, may be capable of dedifferentiating into pluripotent stem cells.

Stem Cell-Based Therapy for Genetic Skin Disease

Stem cells have been utilized in several strategies for gene therapy of heritable skin diseases (Fig. 2.6). Treatment via delivery of gene-corrected stem cells has the advantage of continuous protein synthesis in the skin, but it may carry a risk of oncogenesis (especially with retroviral vectors). In a pilot study, laminin-β3-deficient skin from a man with junctional EB was corrected by transplantation of stem cell-enriched epidermal grafts transduced *ex vivo* with a retroviral vector encoding normal *LAMB3* cDNA. The treatment resulted in expression of functional laminin 332 and an absence of blistering in the corrected epidermis, both sustained over several years of follow-up. Clinical trials are also ongoing to investigate the value of bone marrow-derived stem cell transplantation as a systemic treatment for the extremely severe recessive dystrophic form of EB (RDEB). In an initial report[29], bone marrow transplantation after total or partial myeloablation resulted in substantial proportions of donor cells in the skin, increased collagen VII deposition at the dermal–epidermal junction and variably decreased

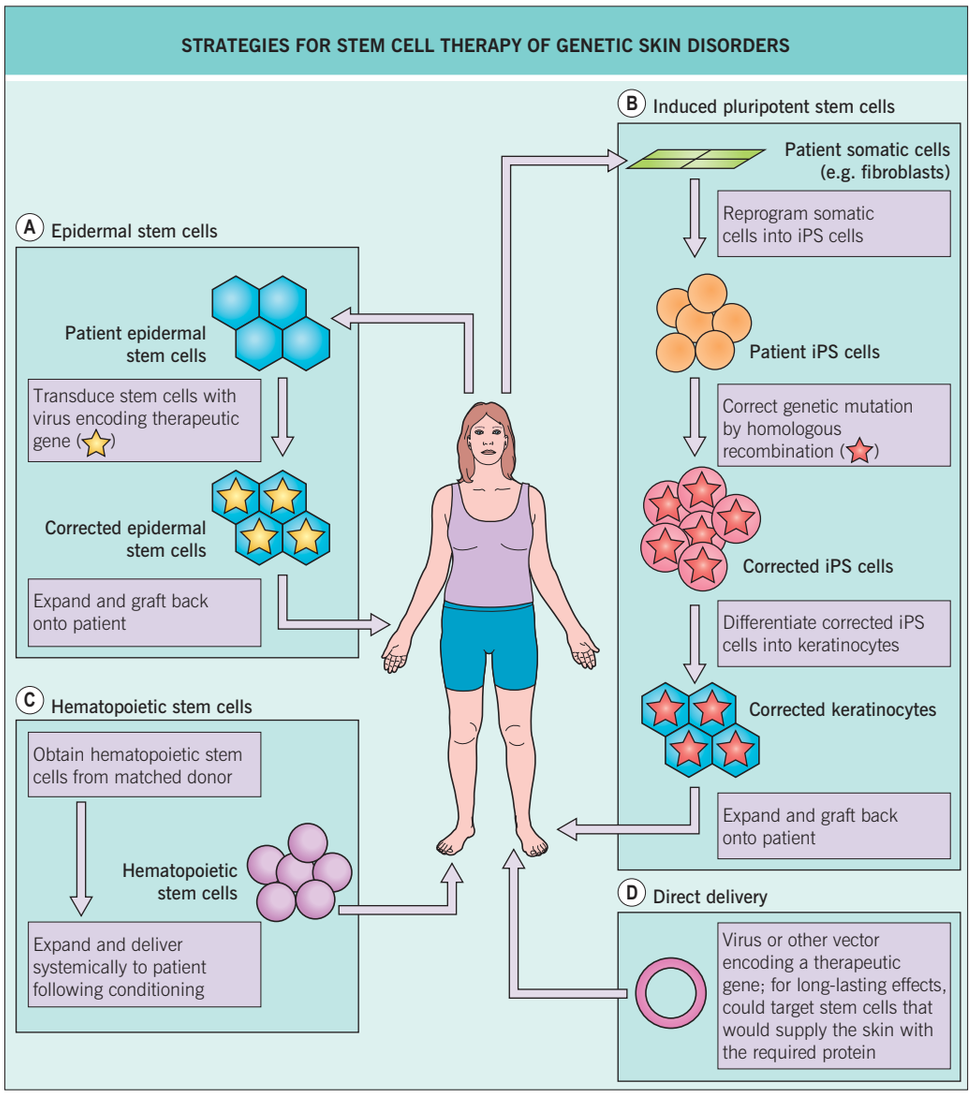


Fig. 2.6 Strategies for stem cell therapy of genetic skin disorders. A One strategy is to isolate epidermal stem cells from a patient, correct the genetic defect *in vitro* (e.g. using a viral vector), and graft epithelial sheets containing the corrected stem cells back onto the patient. **B** Gene therapy could also potentially utilize induced pluripotent stem (iPS) cells, which are generated from somatic cells (e.g. fibroblasts). The genetic defect could be corrected via homologous recombination in these cells, which would then be differentiated into keratinocytes and grafted onto the patient. **C** A third strategy involves the use of hematopoietic stem cells (HSC). Upon systemic administration (following conditioning), allogeneic HSC cells have the capacity to home to the skin (e.g. to sites of injury in patients with epidermolysis bullosa) and produce differentiated progeny cells that provide the needed skin protein (e.g. collagen VII). **D** Finally, therapeutic genes could be directly administered to patients via a virus or another vector. To achieve permanent correction, the vector must target stem cells that could supply the protein to the skin.

blistering in children with RDEB. Other investigators are studying alternative sources of stem cells for the treatment of EB.

PRENATAL DIAGNOSIS OF GENODERMATOSES

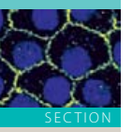
Many genodermatoses are incompatible with survival to term or are associated with significant morbidity or even mortality after birth, making prenatal diagnosis desirable. In the early 1980s, fetal skin biopsy became the first technique available for prenatal diagnosis of inherited skin diseases. Fetal biopsies are typically obtained between 19 and 22 weeks' EGA using ultrasound guidance and then analyzed via light and electron microscopy for the characteristic morphologic changes associated with the disease in question. The Herlitz form of junctional EB and epidermolytic hyperkeratosis were the first diseases diagnosed prenatally using this technique.

As the causative genes for many genodermatoses have been discovered, DNA-based testing using material obtained from chorionic villus sampling (10–12 weeks after the last menstrual period/8–10 weeks' EGA) or amniocentesis (14–16 weeks after the last menstrual period/12–14 weeks' EGA) has largely replaced fetal skin biopsy, as these techniques can be performed earlier and pose less risk to the mother and fetus. The pathogenic mutation(s) must be identified in family members prior to prenatal testing.

Preimplantation genetic diagnosis is a recently introduced technique that allows for prenatal diagnosis before the embryo is implanted and pregnancy begins. This technique requires the use of *in vitro* fertilization. One or two cells are taken from the embryo at the blastocyst (6- to 10-cell) stage. The cellular DNA is amplified using PCR and analyzed for the known family mutation(s); unaffected embryos are then selected for uterine implantation. For X-linked disorders, sex determination has been utilized both in conjunction with specific genetic analysis and to identify embryos of a particular sex for selective transfer. Preimplantation genetic diagnosis obviates the need to terminate a pregnancy with an affected fetus. However, it has several disadvantages compared to chorionic villus sampling or amniocentesis, including higher cost, technical difficulties (e.g. contamination by extraneous DNA), and a low rate of completed pregnancies.

SIGNIFICANCE OF SKIN DEVELOPMENT IN POSTNATAL LIFE

Understanding skin development is essential for the appropriate diagnosis and management of congenital skin disorders. This knowledge is useful far beyond the neonatal period, however, as many of the regulatory pathways central to development are recapitulated in postnatal life. For example, PTCH is essential for postnatal hair cycling as well as hair follicle development. In addition to the germline *PTCH* mutations that result in the nevoid basal cell carcinoma syndrome, somatic *PTCH* mutations represent a pathogenic factor in sporadic basal cell carcinomas. Elucidation of the mechanisms controlling angiogenesis during intrauterine development holds promise for improving wound healing and developing new anticancer therapies. Furthermore, delineating the factors involved in wound healing in embryos may point to interventions that may decrease scarring in children and adults. Thus, advancing the understanding of skin embryology may lead to life-saving or life-enhancing therapies.



REFERENCES

1. Koster MI, Roop DR. Mechanisms regulating epithelial stratification. Annu Rev Cell Dev Biol. 2007;23:93–113.
2. Holbrook KA. Structure and function of the developing human skin. In: Goldsmith LA (ed). Physiology, Biochemistry, and Molecular Biology of the Skin, New York: Oxford University Press, 1991:63–110.

2a. Holbrook KA, Odland GF. Structure of the human fetal hair canal and initial hair eruption. J Invest Dermatol. 1978;71:385–90.

3. Akiyama M, Shimizu H. An update on molecular aspects of the non-syndromic ichthyoses. Exp Dermatol. 2008;17:373–82.
4. Kalia YN, Nonato LB, Lund CH, et al. Development of skin barrier function in premature infants. J Invest Dermatol. 1998;111:320–6.
5. Adameyko I, Lallemend F, Aquino JB, et al. Schwann cell precursors from nerve innervation are a cellular origin of melanocytes in skin. Cell. 2009;139:366–79.
6. Schuster C, Vaculik C, Fiala C, et al. HLA-DR+ leukocytes acquire CD1 antigens in embryonic and fetal human skin and contain functional antigen-presenting cells. J Exp Med. 2009;206:169–81.
7. Van Keymeulen A, Mascre G, Youseff KK, et al. Epidermal progenitors give rise to Merkel cells during embryonic development and adult homeostasis. J Cell Biol. 2009;187:91–100.
8. Dessinioti C, Stratigos AJ, Rigopoulos D, et al. A review of genetic disorders of hypopigmentation: lessons learned from the biology of melanocytes. Exp Dermatol. 2009;18:741–9.
9. Smith LT, Holbrook KA. Development of dermal connective tissue in human embryonic and fetal skin. Scan Electron Microsc. 1982;(Pt 4):1745–51.
10. Wang X, Reid Sutton V, Omar Peraza-Llanes J, et al. Mutations in X-linked PORCN, a putative regulator of Wnt signaling, cause focal dermal hypoplasia. Nat Genet. 2007;39:836–8.
11. Fine JD, Smith LT, Holbrook KA, et al. The appearance of four basement membrane zone antigens in developing human fetal skin. J Invest Dermatol. 1984;83:66–9.
12. Uitto J, Richard G. Progress in epidermolysis bullosa: genetic classification and clinical implications. Am J Med Genet C Semin Med Genet. 2004;131C:61–74.
13. Mikkola ML. Genetic basis of skin appendage development. Semin Cell Dev Biol. 2007;18:225–36.
14. Millar SE. Molecular mechanisms regulating hair follicle development. J Invest Dermatol. 2002;118:216–25.
15. Priolo M, Lagana C. Ectodermal dysplasias: a new clinical-genetic classification. J Med Genet. 2001;38:579–85.
16. Casal ML, Lewis JR, Mauldin EA, et al. Significant correction of disease after postnatal administration of recombinant ectodysplasin A in canine X-linked ectodermal dysplasia. Am J Hum Genet. 2007;81:1050–6.
17. Gaide O, Schneider P. Permanent correction of an inherited ectodermal dysplasia with recombinant EDA. Nat Med. 2003;9:614–18.
18. Koster MI, Roop DR. p63 and epithelial appendage development. Differentiation. 2004;72:364–70.
19. Shimomura Y, Agalliu D, Vonica A, et al. APCDD1 is a novel Wnt inhibitor mutated in hereditary hypotrichosis simplex. Nature. 2010;464:1043–7.
20. High A, Zedan W. Basal cell nevus syndrome. Curr Opin Oncol. 2005;17:160–6.
21. Halprin KM. Epidermal "turnover time" – a re-examination. Br J Dermatol. 1972;86:14–9.
22. Kaur P. Interfollicular epidermal stem cells: identification, challenges, potential. J Invest Dermatol. 2006;126:1450–8.
23. Strachan LR, Ghadially R. Tiers of clonal organization in the epidermis: the epidermal proliferation unit revisited. Stem Cell Rev. 2008;4:149–57.
24. Barrandon Y, Green H. Three clonal types of keratinocyte with different capacities for multiplication. Proc Natl Acad Sci U S A. 1987;84:2302–6.
25. Cotsarelis G. Epithelial stem cells: a folliculocentric view. J Invest Dermatol. 2006;126:1459–68.
26. Haegebarth A, Clevers H. Wnt signaling, Lgr5, and stem cells in the intestine and skin. Am J Pathol. 2009;174:715–21.
27. Ito M, Yang Z, Andl T, et al. Wnt-dependent de novo hair follicle regeneration in adult mouse skin after wounding. Nature. 2007;447:316–20.
28. Zhao R, Daley GQ. From fibroblasts to iPS cells: induced pluripotency by defined factors. J Cell Biochem. 2008;105:949–55.
29. Wagner JE, Ishida-Yamamoto A, McGrath JA, et al. Bone marrow transplantation for recessive dystrophic epidermolysis bullosa. N Engl J Med. 2010;363:629–39.

Molecular Biology 3

Jonathan Vogel, Carole Yee and Thomas N Darling

INTRODUCTION

Advances in molecular biology are rapidly changing our understanding of skin biology and disease. Increased knowledge is being translated into new molecular diagnostic tests that are transforming the clinical practice of dermatology[1,2]. In order to use these tests in a prudent manner, dermatologists today have an even greater need to understand basic concepts in molecular biology. This knowledge is also leading to the development of new targeted therapies, many of which require determination of the molecular basis for disease in order to appropriately implement treatment[3]. In addition, the language and concepts of molecular biology are increasingly found in the lay media, and they are being brought into our offices by a well-educated public. The goal of this chapter is to outline basic concepts and methodologies of molecular biology and to give practicing dermatologists a fundamental appreciation of what their colleagues are doing in the laboratory and how their own clinical practice may change as molecular approaches are implemented into patient care.

In this chapter we will imagine a dermatologist confronting a representative dermatologic disease, melanoma. This dermatologist will utilize a range of techniques to elucidate the molecular basis for melanoma and then develop an effective treatment. In the first section we will begin at the bedside, as the dermatologist considers ways to examine the tissue. The next sections are divided into molecular biology techniques for analyzing DNA, RNA and protein from the melanoma cells. The dermatologist will then move on to develop animal models of melanoma, and utilize these animal models to study the pathogenesis of melanoma and develop new targeted therapies. Throughout, the use of melanoma is meant to provide a real-life construct for the discussion of scientific approaches and techniques in molecular biology; it is not intended to present data on the pathogenesis of melanoma, for which a vast literature already exists.

EXPERIMENTAL TECHNIQUES

At the Bedside

Dr A looks at a pigmented lesion on Mr B and suspects that this represents a melanoma. She plans an excisional biopsy, knowing that analyzing the histologic features of the lesion will likely determine the diagnosis. This will also lead to information important for assessment of prognosis, guidance of therapy, and future monitoring. Her inquisitive mind rapidly generates additional questions regarding melanoma. What molecular changes cause melanoma? Can the identification of these molecular changes assist in the diagnosis? What molecular differences exist between different types of melanoma? Can the molecular profiles be used to discriminate between melanomas that have a similar appearance histologically, but differ in prognosis? Can treatments be designed that target specific molecular alterations? Not content simply

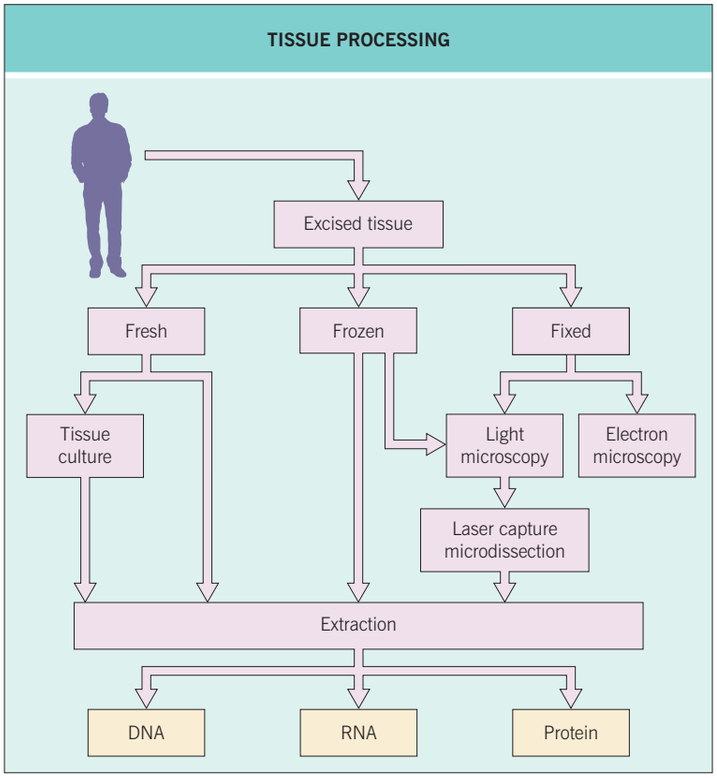


Fig. 3.1 Tissue processing. The biopsy from the melanoma tumor can be processed in four different ways, each with distinct advantages and disadvantages.

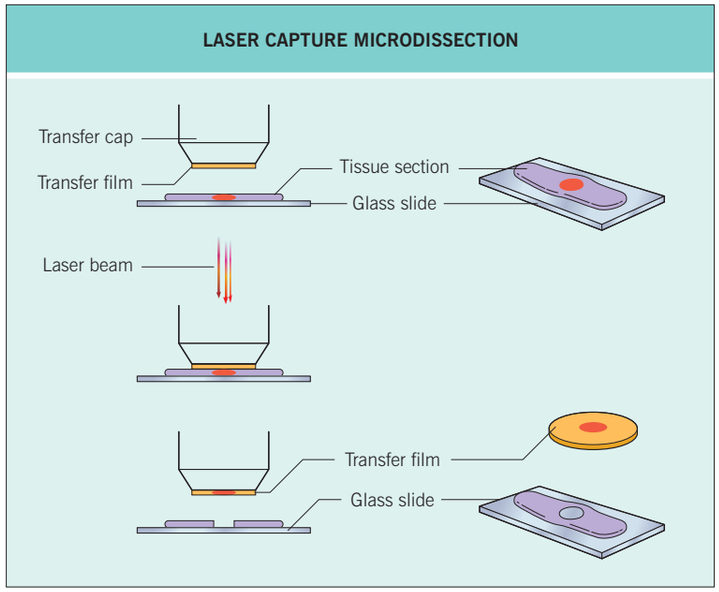


Fig. 3.2 Laser capture microdissection (LCM). LCM is used to selectively procure individual cells or clusters of cells from tissue sections. A glass slide with a section of paraffin-embedded or cryopreserved tissue is stained and placed on the microscope stage. A cap coated with a thermoplastic transfer membrane is placed directly over the tissue section. The operator identifies the cells of interest by looking through the eyepiece of the microscope or by looking at a monitor. A low-energy infrared laser is then pulsed that melts the transfer film onto the cells of interest. The cap is then lifted from the section to separate the selected cells from the remainder of the tissue section. Molecules of interest, including DNA, RNA and protein, can be extracted from the microdissected cells present on the cap[5].

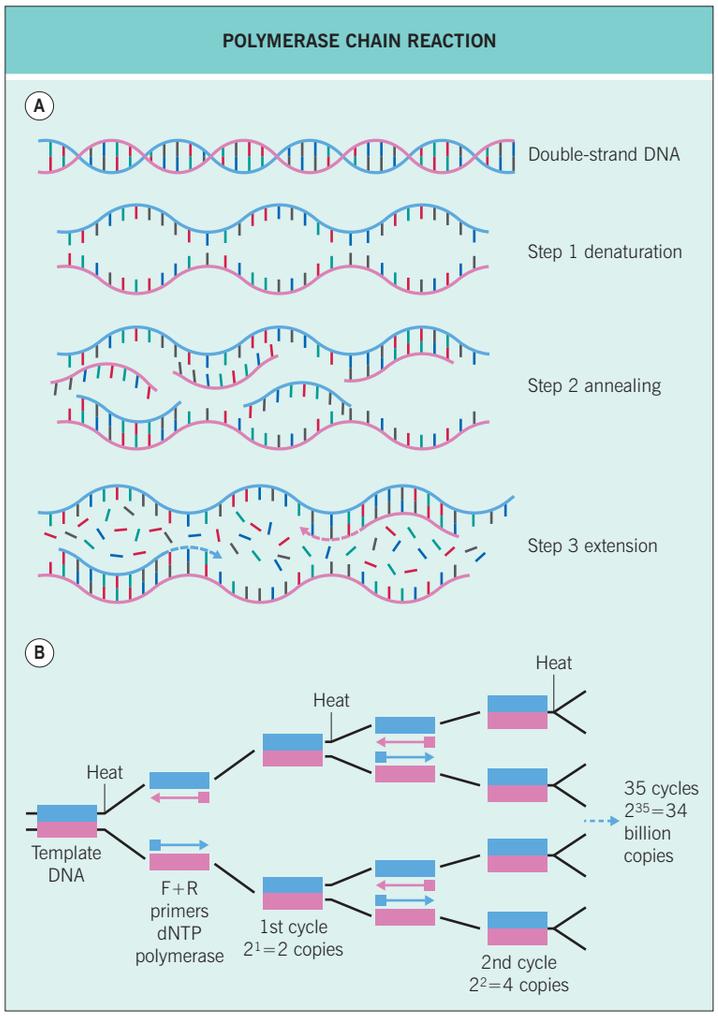


Fig. 3.3 Polymerase chain reaction. A Each cycle contains the following steps: (1) denaturation – separate the two strands of DNA by heating to >90°C; (2) primer annealing or primer hybridization – allow the oligonucleotide primers to bind to the template DNA by cooling to 50–65°C; (3) primer extension – DNA polymerase catalyzes the addition of nucleotides (A, G, C, T) that are complementary to the DNA template, beginning with the primer and extending 3′ at the optimal temperature of 72°C; and (4) repeat the complete cycle 30–40 times. **B** Each cycle increases the number of PCR products twofold. The total number of PCR products after *n* cycles will be 2^n times the original amount. F+R, forward and reverse.

to think about these things, Dr A obtains IRB approval to study melanoma and performs the excision, retaining a portion for further study in her laboratory. The immediate question is, how can this tissue be utilized?

Tissue Processing

The melanoma that Dr A has excised can be processed in four different ways, each with distinct advantages and disadvantages (Fig. 3.1). First, fresh tissue can be placed in culture medium and melanoma cells could be grown in an incubator. Culturing cells allows one to obtain more cells than in the original sample, and allows one to expose the cells to various conditions. The disadvantage of this approach is that the culturing process may change fundamental characteristics of the cells, so that they do not accurately represent the melanoma in the patient.

A second approach is to directly process the fresh tissue with buffers and reagents in order to extract DNA, RNA and protein from the whole mass of tumor cells. The advantage of this approach is that the DNA, RNA and protein will be fresh and of high quality. The disadvantage is that the extracts will not be from a pure population of cells.

In the third approach, the tumor specimen could be placed in a preservative buffer such as formalin (for light microscopy) or glutaraldehyde (for electron microscopy) for processing and sectioning, and then

POLYMERASE CHAIN REACTION
PURPOSE
• Amplify a specific piece of DNA from a complex mixture
REQUIREMENTS
• Need to know sequence of the DNA of interest (at least of its ends)
UNDERLYING CONCEPTS
• Double-stranded DNA can be melted or unwound to single strands with increased temperature (Fig. 3.3A); when cooled, the single strands come back together to form double strands (hybridize) if the nucleotide sequences are complementary* • During the hybridization process, when two complementary strands bind to each other, the A nucleotides on one strand bind to T nucleotides on the complementary strand, whereas C nucleotides of one strand bind to G nucleotides on the complementary strand, and vice versa • In PCR, short DNA strands called oligonucleotide primers are designed for hybridization to specific sequences in the template DNA
OUTLINE OF METHOD (FIG. 3.3)
• Oligonucleotide primers are designed to hybridize to specific sequences at each end of the DNA of interest. These primers are added to a reaction vessel mixture containing the template DNA along with a thermostable DNA polymerase, the nucleotides dATP (A), dTTP (T), dGTP (G) and dCTP (C), and buffer • The reaction vessel is placed in a thermal cycler, which controls the temperature of the reaction through many cycles • Each cycle contains the following steps: (1) denaturation; (2) primer annealing or primer hybridization; (3) primer extension; and (4) repeat of the complete cycle of PCR 30–40 times (see legend to Fig. 3.3 for more details)
BENEFITS
• PCR is simple and rapid • Because the PCR product is exponentially increased, it is extremely sensitive in amplifying low amounts of DNA. Each cycle increases the number of PCR products twofold. The total number of PCR products after *n* cycles will be 2^n
LIMITATIONS/ERRORS
• Because of its high degree of sensitivity, laboratory contamination of a DNA sample by trace amounts of the PCR product can cause misleading results • Primers used for PCR can anneal to sequences that are similar, but not identical, to the sequence of interest. This can be countered with "hot start" techniques (DNA polymerase prevented from acting until after first denaturation step) or nested PCR (after the PCR amplification, repeat the PCR amplification using a second set of primers that hybridize to sequences inside first set of primers). In nested PCR, the second set of primers will only hybridize to correct PCR products resulting from the first PCR amplification • DNA polymerase occasionally incorporates incorrect nucleotides. For sequencing by PCR, polymerases that possess proofreading enzymatic activity can be used. This also allows the generation of even longer PCR products, up to approximately 50 kb long
EXPERIMENTAL APPLICATIONS
• DNA can be amplified either for detection of a specific sequence or for cloning that sequence • PCR can be used to label DNA with radioactive nucleotides • PCR can be used for rapid haplotype analysis
MODIFICATIONS/ALTERNATIVES
• Quantitative PCR – the amount (number of copies) of a specific piece of DNA can be quantified by a variety of methods utilizing PCR. A relatively simple and high-throughput method, called real-time quantitative PCR, uses a specially designed thermal cycler that measures the amount of PCR product formed after each cycle (see Fig. 3.5). The higher the level of DNA, the earlier the product can be detected. This can be used to measure genetic changes in cancer such as gene amplification, to quantify the amount of residual cancer following treatment, or to quantify the amount of a pathogen in a sample. Modifications of this procedure can allow discrimination of gene polymorphisms • Southern blot, *in situ* hybridization, comparative genomic hybridization
*Hybridization actually forms the basis of several techniques in molecular biology, as the two strands can be DNA:DNA (PCR, Southern blotting), DNA:RNA (Northern blotting, **in situ** hybridization), or RNA:RNA.

Table 3.1 Polymerase chain reaction.

DNA SEQUENCING
PURPOSE
• Determine the sequence or order of nucleotides (A, G, C, T) in a stretch of DNA
REQUIREMENTS
• The piece of DNA to be sequenced can be either a PCR product or a cloned piece of DNA present in a plasmid, but it should be pure
UNDERLYING CONCEPTS
• Chain termination, or a variation thereof, is the preferred method for DNA sequencing • In chain termination, the extension of a new strand of DNA is stopped by the addition of an analogue of dATP, dCTP, dGTP or dTTP (ddATP, ddCTP, ddGTP or ddTTP, respectively) to the sequencing mixture (Fig. 3.4). When the DNA polymerase incorporates the analogue nucleotide instead of the correct normal nucleotide, DNA synthesis is terminated because the polymerase is no longer able to link to the next nucleotide • Gel electrophoresis is used to separate the different sizes of DNA fragments that result from chain termination synthesis (Fig. 3.4). The DNA fragments are forced to travel through a gel using an electric current; the smaller molecules are less impeded by the gel and travel faster than larger molecules*
OUTLINE OF METHOD (FIG. 3.4)
• An oligonucleotide primer hybridizes to the DNA to be sequenced and DNA polymerase synthesizes a second complementary strand • The synthesis of the second strand is interrupted randomly by the incorporation of the fluorescent nucleotide analogues (ddATP, ddGTP, ddCTP, ddTTP), and the DNA fragments containing this final nucleotide analogue can be identified because each of the four ddNTPs is labeled with a different color fluorochrome • The different DNA fragments are electrophoresed through a polyacrylamide gel or capillary tubes • The different-length DNA strands terminating with different fluorochrome-labeled nucleotide analogues pass a fluorescence detector and indicate the order of the DNA sequence
BENEFITS
• The fluorescent chain termination method is able to rapidly sequence large amounts of DNA with automated analysis of results
LIMITATIONS/ERRORS
• Routinely sequence only approximately 500 bases per run • Difficulty with G+C-rich regions • DNA must be high-quality
EXPERIMENTAL APPLICATIONS
• Determine previously unknown sequence • Confirm sequence following the cloning of a DNA fragment of interest and other manipulations
MODIFICATIONS/ALTERNATIVES
• Pyrosequencing • Sequencing by oligonucleotide ligation and detection • Solid-phase amplification followed by sequencing by synthesis of randomly fragmented DNA
*Gel electrophoresis is used in many molecular biologic techniques to separate DNA, RNA or protein molecules of differing sizes.

Table 3.2 DNA sequencing.

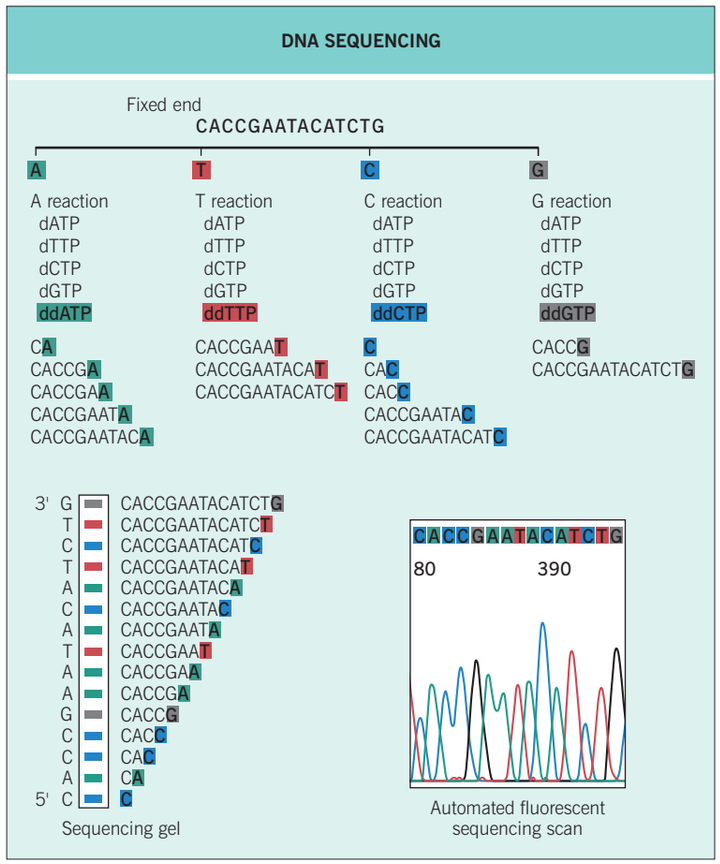


Fig. 3.4 DNA sequencing. An oligonucleotide primer hybridizes to the DNA to be sequenced and DNA polymerase synthesizes a second complementary strand. The synthesis of the second strand is interrupted randomly by the incorporation of fluorescent nucleotide analogues (ddATP, ddGTP, ddCTP, ddTTP). The DNA fragments containing this final nucleotide analogue can be identified because each of the four ddNTPs is labeled with a different color fluorochrome. Gel electrophoresis is used to separate the different sizes of DNA fragments. The different-length DNA strands terminating with different fluorochrome-labeled nucleotide analogues pass a fluorescence detector and indicate the order of the DNA sequence (see Table 3.2 for more details).

analyzed histologically in a variety of ways, including routine staining, immunohistochemistry or *in situ* hybridization. The advantage of this approach is that the cells are preserved in a very stable fashion, with well-preserved architecture, for later analysis. One disadvantage is that the cells are no longer living, and the fixation procedure places limits on the methods that can be used to analyze DNA, RNA and protein from the tumor.

Finally, the specimen could be snap-frozen, with DNA, RNA and protein being extracted at a later time[4]. The histology of the frozen melanoma tumor could also be analyzed by obtaining cryosections of the tumor for histologic analysis.

Dr A may also decide to use laser capture microdissection (LCM) to isolate individual melanoma cells for subsequent analysis (Fig. 3.2). LCM uses a laser to retrieve individual cells from a section on a slide while the specimen is viewed with a microscope[5]. The biggest advantage of this approach is that a very pure population of cells is obtained that has been precisely identified under the microscope. The disadvantage is that the total number of cells isolated is relatively low, as each cell has to be individually captured by the laser. Consequently, the procedures to extract DNA, RNA and protein from these pure (but few) cells have to be robust.

Assessing the DNA, RNA and Protein of Individual Genes that may be Responsible for Melanoma

After Dr A has extracted DNA, RNA or protein from the melanoma tumor specimen, she is ready to proceed with her analysis. Dr A knows that cancer is caused by mutations in proto-oncogenes and tumor suppressor genes (see Chs 107 & 113). She would like to identify the gene(s) mutated in her patient's melanoma, to find out what effects these mutations have on melanocytes, and to potentially use this information to design a better treatment for melanoma.

Dr A has read the literature about a new proto-oncogene, *toomuchsun*, that is normally expressed in cells and regulates cell growth but which can induce cancer when mutated. She decides to begin her studies by analyzing the tumor DNA and determining whether the gene *toomuchsun* is present in a mutated form. She knows that one can extract DNA from tumors, but her gene of interest is just a tiny fraction of the total amount of DNA. How can she obtain sequence information on just her gene of interest?

REVERSE TRANSCRIPTION PCR
PURPOSE
• To amplify mRNA by PCR, the mRNA is first converted to DNA (called complementary DNA or cDNA) (Fig. 3.5A), followed by PCR amplification of a specific region of the cDNA to detectable levels
REQUIREMENTS
• Starting material can be total cellular RNA (including ribosomal, transfer and messenger RNA [mRNA]) or purified mRNA
UNDERLYING CONCEPT
• In order to facilitate studies of RNA, many techniques that study RNA first convert the RNA to cDNA with an enzyme called reverse transcriptase, an RNA-dependent DNA polymerase
OUTLINE OF METHOD (FIG. 3.5A)
• Reverse transcriptase can convert mRNA to cDNA by three different methods, depending on the primer used for the initial RT step*. (1) Random hexamer primers contain six nucleotides (6-mer) that have all possible sequence combinations of the dA, dG, dC and dT nucleotides (4^6 possible combinations). These random hexamers will hybridize to the corresponding complementary sequences in the sample RNA. (2) Oligo dT primers contain only dT nucleotides and hybridize to the complementary string of dA nucleotides that are present at the end of mRNA molecules (poly A tail). (3) The third choice is a primer that will only hybridize to a specific mRNA sequence • After the mRNA has been converted to cDNA, primers that can hybridize to specific sequences are added and PCR amplification is performed as described in Table 3.1
BENEFITS
• As for PCR, RT-PCR is simple and rapid • RT-PCR is extremely sensitive in detecting low levels of mRNA transcripts
LIMITATIONS/ERRORS
• If the RNA sample is contaminated with DNA (that contains the gene of interest), a PCR product may be amplified from the DNA even though the corresponding mRNA for the gene is not present. To control for this, RT-PCR of RNA samples can be done with and without reverse transcriptase† • RNA is fragile and the absence of a specific mRNA transcript may result from RNA degradation during and following extraction. RNA quality can be tested by gel electrophoresis and/or by RT-PCR of housekeeping genes (genes expressed by all cells)
EXPERIMENTAL APPLICATIONS
• The mRNA gene transcripts can be amplified for subsequent cloning or sequencing • The mRNA gene transcripts (instead of the gene) could be analyzed for the presence of mutations
MODIFICATIONS/ALTERNATIVES
• Quantitative RT-PCR – by adding a reverse transcription step to quantitative PCR (see Table 3.1), the levels of mRNA transcripts from genes of interest can be quantified. This is very important because it allows us to precisely measure and compare the number of mRNA transcripts in different types of cells or cells grown under different conditions • Correspondingly, samples that contain less mRNA transcripts will require more PCR cycles before the exponential phase. Therefore, different RNA samples can be precisely compared by measuring the number of PCR cycles (x axis) needed to produce a defined amount of PCR product (y axis) (Fig. 3.5B) • By carefully designing the primers, quantitative RT-PCR can be used to measure the amounts of alternatively spliced forms of a gene • Alternative methods to measure RNA levels, not based on RT-PCR, include Northern blots and ribonuclease protection assays • Differential display – this is used to find differences in gene expression in several samples. It is an RT-PCR-based system that uses short arbitrary primers that amplify numerous genes in a sample. By comparing the complex banding pattern of PCR products observed after gel electrophoresis, bands can be observed that are present in some samples but not others. With further study, these differing bands can be identified as corresponding to known or novel genes
*In addition to the RNA, the reaction mixture contains the reverse transcriptase enzyme, an oligonucleotide primer, dNTPs and buffer. †If DNA contamination is not present, PCR products will not be amplified from RNA that has not been reverse transcribed, and PCR products will be present only in RNA samples that have been reverse transcribed into cDNA.

Table 3.3 Reverse transcription PCR (RT-PCR).

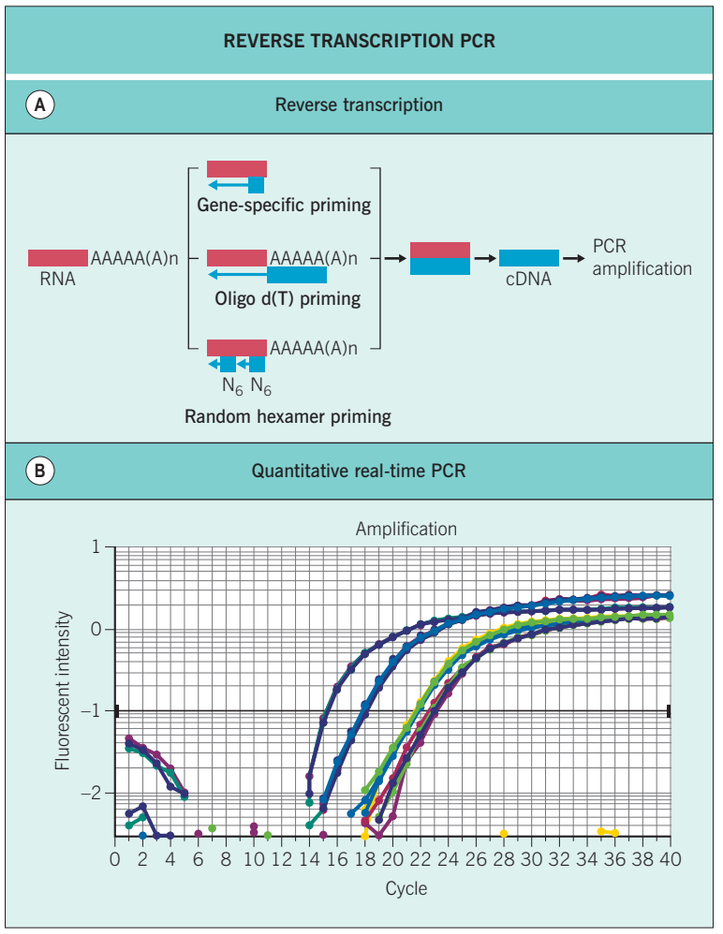


Fig. 3.5 Reverse transcription PCR (RT-PCR). A Reverse transcriptase can convert mRNA to cDNA in three different ways, depending on the primer used for the initial RT step: (1) random hexamer primers; (2) oligo dT primers; and (3) gene-specific primers (see Table 3.3 for more details). After the mRNA has been converted to cDNA, primers that can hybridize to specific sequences are added and PCR amplification is performed as described in Table 3.1. **B** Real-time PCR is able to precisely measure the amount of PCR product continuously (*y* axis) after each cycle (*x* axis). Each plotted line represents the amount of PCR product present in a different sample. In samples that initially contain more mRNA gene transcripts, real-time PCR will demonstrate an exponential increase in PCR product earlier, after fewer PCR cycles.

Although Dr A initially finds the terminology confusing, she soon discovers that the concepts behind molecular biology are simple and unifying[6]. Most of it comes down to extracting the molecules of interest, amplifying them to measurable amounts, and detecting them. Dr A chooses PCR amplification as the best technique to obtain and isolate sufficient amounts of pure DNA containing the proto-oncogene *toomuchsun* (Table 3.1; Fig. 3.3)[7]. The PCR-amplified DNA containing the gene can be sequenced using automated fluorescence sequencing techniques (Table 3.2; Fig. 3.4). Based on the sequencing results, Dr A will know whether mutations are present in the *toomuchsun* gene in these melanomas. This simple and relatively inexpensive approach is still widely used. However, it is being succeeded by rapidly evolving techniques for ultra-high-throughput sequencing[8], yielding, for example, a comprehensive catalogue of mutations in melanoma cell lines and tumors[9].

Dr A's discovery that the melanomas have mutations in the proto-oncogene *toomuchsun* has potential clinical significance. By analyzing large numbers of melanomas, nevi and normal melanocytes, she can determine whether the presence of these mutations correlates with a certain type of lesion or a melanoma with a particular prognosis. For example, it is known that activating mutations in the *BRAF* proto-oncogene can be found in the majority of superficial spreading melanomas (as well as banal and atypical melanocytic nevi), whereas *KIT* mutations characterize a subset of melanomas arising from acral sites,

WESTERN BLOT
PURPOSE
• Western analysis can measure the size and the amount of protein present in a sample (Fig. 3.6)
REQUIREMENTS
• Western analysis requires an antibody that is specific for the protein of interest (i.e. does not cross-react with other proteins)
UNDERLYING CONCEPTS
• Polyclonal antibodies that react to several epitopes on a protein antigen are obtained by injecting a protein into an animal and later isolating the antibodies from the serum immunoglobulin fraction • Monoclonal antibodies that react to only one epitope of a protein antigen are obtained by immunizing mice (or rats, rabbits, or chickens) with the antigen, then fusing the animal's reactive lymphocytes with an immortal myeloma cell line to create cells that are able to provide antibodies indefinitely • A secondary antibody is used to detect the protein or the primary antibodies bound to the protein. These detection antibodies can be visualized by attaching a fluorescent probe or by attaching an enzyme that can produce either light or a color by enzymatic action on a substrate
OUTLINE OF METHOD (FIG. 3.6)
• A solubilized protein mix is separated on a polyacrylamide gel and transferred electrophoretically to a membrane. The membrane is then soaked in a buffer containing the antibody. Bound antibody is detected by a chromogenic or chemiluminescent assay
BENEFITS
• Western analysis is a simple and sensitive method to detect and quantify proteins present in a complex mixture • Western analysis can determine the molecular weight of a specific protein relative to standard controls
LIMITATIONS/ERRORS
• Proteins are subject to degradation during extraction. The use of protease inhibitors in the extraction buffer helps to prevent degradation • To perform a Western analysis, one must possess a highly specific antibody that can recognize denatured proteins • Western blots may contain a high background of nonspecific staining. To correct this, blocking agents such as bovine serum albumin or milk protein are used • Large proteins transfer poorly from the gel to the membrane, and small proteins may transfer through the membrane without binding. Adequate transfer to the membrane can be accomplished by controlling the duration of the transfer procedure
EXPERIMENTAL APPLICATIONS
• Detection, quantification and characterization of a specific protein • Identification of antibody activity to a known antigen
MODIFICATIONS/ALTERNATIVES
• Dot blot – a drop of the protein mixture is placed on a paper membrane and the protein of interest detected with antibodies, as in the Western blot. The disadvantage of this technique is that, owing to the elimination of size separation by gel electrophoresis, specific binding to the protein of correct size cannot be distinguished from nonspecific background binding to proteins • Immunoprecipitation (IP) – in immunoprecipitations, the specific antibody is added to the protein mixture and the resulting antibody–protein complexes are then isolated. Because proteins are not first denatured in immunoprecipitation, they can be detected in a more native configuration • IP–Western – protein–protein interactions can be studied by first immunoprecipitating the protein with one antibody, bringing down a protein complex. The protein complex is then separated on a polyacrylamide gel, followed by Western blotting to detect members of the protein complex • Enzyme-linked immunosorbent assay (ELISA) – this is a sensitive and specific method for quantifying the amount of a protein. The protein of interest is captured on a plate coated with a monoclonal antibody and other proteins are washed away. The protein is then detected using a second antibody that has been modified for detection using a colorimetric or luminescent assay • Immunohistochemistry – this is used to visualize the cellular localization of a protein. An antibody to the protein of interest is applied to a tissue section. The antibody is detected using a secondary antibody coupled to an enzyme that reacts with a substrate to produce a colored precipitate

Table 3.4 Western blot.

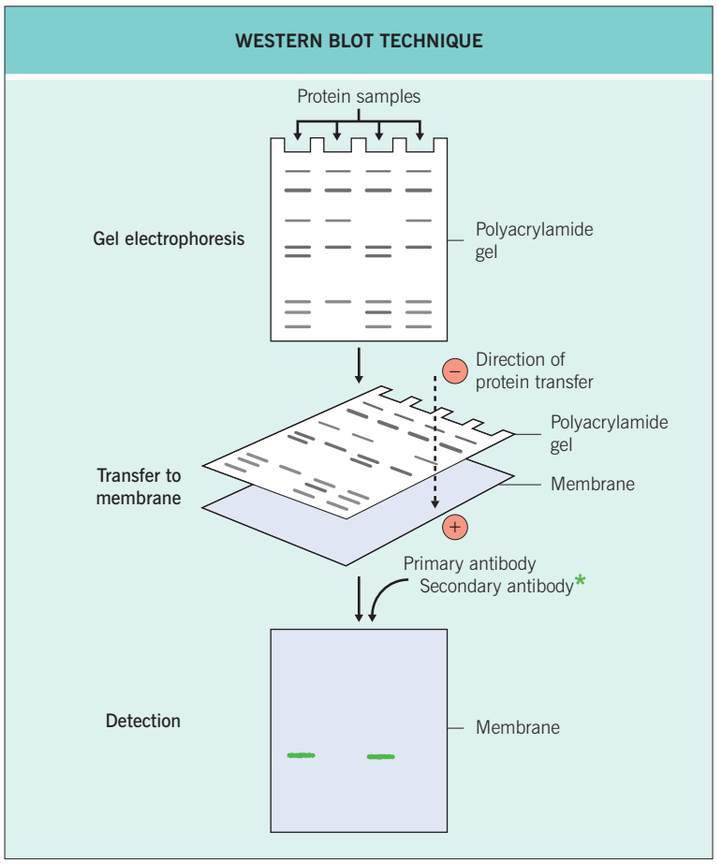


Fig. 3.6 Western blot technique. A solubilized protein mix is separated on a polyacrylamide gel and transferred electrophoretically to a membrane. The membrane is soaked in a buffer containing antibody. The bound antibody is detected by a chromogenic or chemiluminescent assay utilizing a labeled secondary antibody (green asterisk).

the mucous membranes or chronically sun-damaged skin. Knowing whether or not these mutations are present can help to direct targeted therapy, such as use of a *BRAF* inhibitor (e.g. vemurafenib) for advanced melanomas with activating BRAF mutations or a *KIT* inhibitor (e.g. imatinib) for those with KIT alterations.

Before embarking on a large study, Dr A decides to gather some information indicating whether *toomuchsun* mutations have significant consequences. She would like to determine whether these mutations influence the level of *toomuchsun* mRNA and protein inside cells.

As mutations in proto-oncogenes are frequently activating mutations that increase the amount and/or activity of the gene product, Dr A would like to determine whether these mutations increase the level of *toomuchsun* mRNA inside the melanocytes, possibly contributing to melanoma development. Although, like DNA, RNA is easy to purify, it is much more readily degraded than DNA. Therefore, a typical first step in the analysis of RNA is to convert it into DNA using reverse transcription (RT; Table 3.3; Fig. 3.5A). Following RT, the complementary DNA (cDNA) can be amplified by PCR, as described above. The technique of RT-PCR has also been modified to allow accurate quantitation of very low levels of mRNA[10]. Because the amount of PCR product is monitored throughout each cycle of amplification, this technique is referred to as "real-time" quantitative PCR (Fig. 3.5B).

Dr A observes that in cultures of melanomas, levels of *toomuchsun* mRNA are increased compared to those in normal melanocytes, and she would like to know whether these changes are also reflected in the levels of protein. The amount of protein is a complex balance of synthesis and degradation controlled at multiple steps, including efficiency of protein translation and post-translational modifications that affect protein stability. To measure the levels of *toomuchsun* protein, she decides to use a procedure called a Western blot (Table 3.4; Fig. 3.6), also known as an immunoblot, as it employs an antibody to detect the

protein of interest. In addition to measuring protein levels, Western blot analysis can determine the size of proteins and can reveal whether there are different forms of the protein[11].

Measuring and Profiling RNA and Protein Expression from Multiple Genes that may be Responsible for Melanoma

At this point, Dr A has identified mutations in the *toomuchsun* gene in melanoma, and has found that this mutation increases the levels of *toomuchsun* mRNA and protein in cells. She does not know the function of *toomuchsun* protein, but expects that the mutant protein may alter the expression patterns of many other genes inside melanoma cells and melanocytes. To better understand how melanocytes transform into melanoma cells, Dr A would like to compare the patterns of gene expression in these cells. How can Dr A investigate changes in gene expression of all the genes (i.e. the transcriptome) that occur inside melanoma cells compared with normal melanocytes? Knowing which genes are abnormally expressed in melanoma cells (either increased or decreased) will allow her to investigate the role of these genes in the development of melanoma.

Dr A decides to use gene expression profiling to quantitatively analyze the expression levels of nearly the entire genome in melanoma cells compared with normal melanocytes (Table 3.5; Fig. 3.7)[12]. Several approaches are available to accomplish this, but most are based on the hybridization of labeled sample mRNA to known oligonucleotide or cDNA sequences (representing thousands of genes) placed on chips, beads, or glass slides. The level of hybridization to the nucleotide sequence of a given gene indicates how much mRNA of that gene is present. The advantage of this approach is that it allows Dr A to quantitatively analyze the expression levels of thousands of genes at one time. In addition to using this method to profile mRNAs (the transcriptome), modified approaches allow the measurement of differences in microRNAs or changes in genomic DNA copy number. Changes in copy number can be determined by array comparative genomic hybridization (CGH) or single nucleotide polymorphism (SNP) arrays[12] (see Ch. 54). The use of these techniques for clinical purposes is expanding, such as utilization of array CGH to help classify melanocytic lesions with ambiguous histologic features (e.g. atypical spitzoid tumors).

The comparative analysis of so many different genes would be impossible for Dr A without the help of powerful software that can compare results from multiple experiments and cluster results according to changes in gene expression. The field of bioinformatics allows Dr A to analyze thousands of genes simultaneously, and it helps her to characterize the sequence, genomic location, protein structure, and related genes for any gene of interest (Fig. 3.8). This work is enhanced by the availability of large public databases of gene expression arrays as well as data-mining applications[12].

From these studies, Dr A is able to find a number of candidate genes that may contribute to the development of melanoma. All of these candidate genes are either overexpressed or underexpressed in melanoma cells compared to normal melanocytes (see Fig. 3.7). Some of the genes appear promising based on their known function. For example, a subset of the *overexpressed* genes are known to be involved in stimulating cell growth, whereas several of the *underexpressed* genes are known to inhibit cell growth. Moreover, some of the melanomas show very similar patterns of gene expression, whereas others have different patterns.

Microarray experiments similar to those portrayed in this hypothetical situation have actually been carried out. These have shown that different patterns of gene expression profiles may serve to distinguish melanomas with different biologic behaviors and prognoses.

In addition to using microarrays to analyze mRNA, Dr A would also like to analyze the proteins expressed by the melanoma cells. The term "proteome" refers to all of the proteins produced inside a cell at any point in time. A quantitative technique that is able to determine which proteins are produced by pure populations of cells in a high-throughput manner would, in theory, be more valuable than the data generated by microarray analysis. This is because the mRNA levels determined by microarray analysis do not always correspond to the protein levels inside a cell, and it is the expression level of proteins encoded by different genes that is of greatest relevance.

Technologies that allow measurement of the proteome are rapidly being developed. One technique relies on mass spectrometry, which can provide extremely accurate measurements of protein mass by ionizing the protein and measuring the "time-of-flight" through a tube to a detector on the opposite end (Table 3.6; Fig. 3.9)[13]. In most instances, the proteins are separated prior to mass spectrometry, using two-dimensional gel electrophoresis or capillary electrophoresis. This can be technically difficult and time-consuming, so mass spectrometry analysis of proteins continues to be optimized for high-throughput and quantitative analysis of proteins. One approach, called multidimensional protein identification (MudPIT), is a non-gel-based "shotgun" proteomic technique. Quantitation is accomplished

NUCLEIC ACID ARRAYS
PURPOSE
• To profile the mRNA expression of thousands of genes in one experiment
REQUIREMENTS
• Total RNA or mRNA from samples (larger amounts than required for RT-PCR)
UNDERLYING CONCEPTS
• Hybridization to DNA – the same principle of hybridization applies as in PCR (described in Table 3.1), except that many different genes are being evaluated simultaneously. DNA is attached to beads, chemically synthesized on a surface at thousands of specific locations, or spotted onto glass slides (Fig. 3.7). If cells are expressing mRNA of the corresponding gene, labeled cRNA prepared from mRNA in those cells will hybridize and generate a signal intensity related to its level of expression
OUTLINE OF METHOD (FIG. 3.7)
• RNA is reverse transcribed to generate cDNA. *In vitro* transcription of the cDNA in the presence of biotinylated nucleotides yields biotin-labeled cRNA (see Fig. 3.7). Labeled cRNA molecules are then hybridized to small DNA fragments attached to beads or on a chip. The samples are stained with streptavidin phycoerythrin, the streptavidin binding the biotin on the cRNA and the phycoerythrin generating a fluorescent signal. Usually, the patterns of gene expression of two samples are compared, such as normal versus tumor or treated versus untreated • Alternatively, oligonucleotide arrays can be used (see Fig. 3.7). Using this approach, the RNA is directly labeled with either fluorescent or radioactive nucleotides, and hybridized to oligonucleotides on a slide or membrane. When using radioactive probes, the samples are hybridized to separate microarrays. If the mRNA samples to be compared are labeled with differently colored fluorescent probes, the two samples can be hybridized to the same array simultaneously • A scanner measures the intensity of the signals at each spot and computer software determines those genes over- and underexpressed in one sample compared to the other
BENEFITS
• Thousands of genes can be rapidly and quantitatively profiled in one experiment
LIMITATIONS/ERRORS
• Genes expressed at low levels may not be detected • For some genes, the cRNA may not hybridize under the conditions used • The RNA must be of very high quality
EXPERIMENTAL APPLICATIONS
• Microarray analysis can be used to profile changes in gene expression • The patterns of gene expression can be used to group samples
MODIFICATIONS/ALTERNATIVES
• Subtractive hybridization • Serial analysis of gene expression (SAGE) • Deep sequencing • MicroRNA arrays • Comparative genomic hybridization (CGH) to detect differences in DNA copy number • Single nucleotide polymorphism (SNP) arrays to assess markers of genetic variation; useful for linkage analysis, including genome-wide association studies (GWAS; see Ch. 54)

Table 3.5 Nucleic acid arrays.

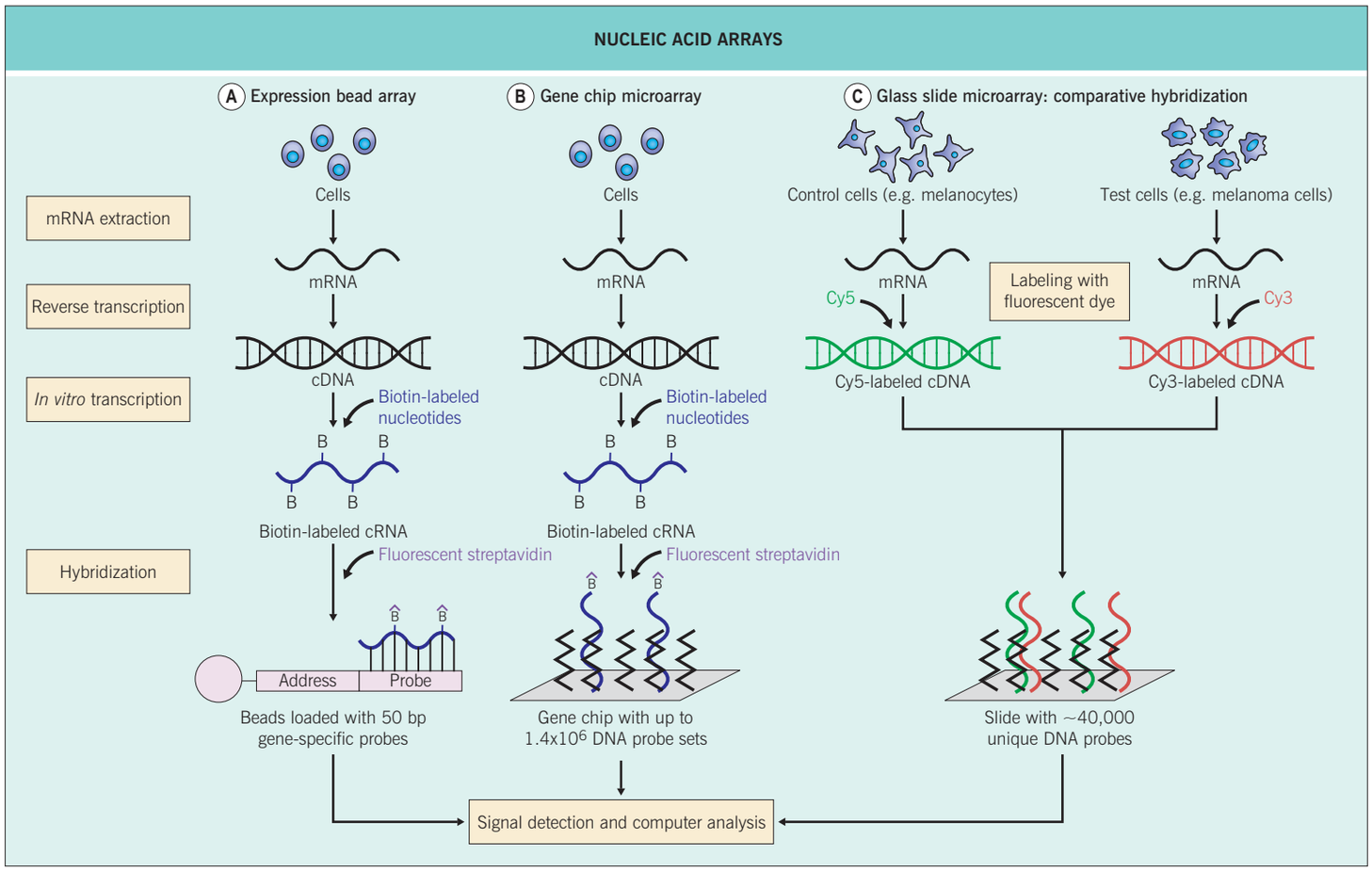


Fig. 3.7 Nucleic acid arrays. A In the expression bead array, RNA is extracted from cells and reverse transcribed to generate cDNA (see Fig. 3.5, Table 3.3). *In vitro* transcription of the cDNA in the presence of biotinylated nucleotides yields biotin-labeled cRNA. Labeled cRNAs bind to their respective 50-base probes that are linked to separate beads using additional nucleotides as an address to decode the gene. Fluorescent streptavidin is added which strongly binds to biotin. The fluorescent intensities on different beads are related to the amount of cRNA and the latter is a reflection of the level of expression of mRNA by specific genes. Usually, the patterns of gene expression of two samples are compared, such as normal versus tumor or treated versus untreated. **B** In the gene chip microarray, labeled cRNA molecules are hybridized to small DNA fragments chemically synthesized on a surface, with the surface containing thousands of specific sequences at different locations. **C** In a third approach using glass slides, two samples can be labeled with differently colored fluorescent probes (e.g. Cy5, Cy3) that are hybridized to an oligonucleotide array simultaneously (see Table 3.5 for more details). Arrays can also be used to analyze DNA rather than RNA; examples include single nucleotide polymorphism (SNP) arrays and array comparative genomic hybridization (CGH) (see Ch. 54).

by labeling proteins using stable isotopes to provide internal standards, or by label-free shotgun proteomic approaches that are being developed for greater speed and lower costs[14]. Another technique is the use of protein arrays, where, for example, antibodies to specific proteins are immobilized on a slide or membrane. These arrays can analyze complicated mixtures of proteins by capturing and detecting specific proteins[15]. If Dr A could use mass spectrometry or protein arrays, in addition to nucleotide microarray analysis, to determine and compare the precise amounts of all cellular proteins in melanoma cells versus melanocytes, she would have a much clearer picture of how melanoma cells differ from normal melanocytes, and which genes may be responsible for cancer development.

Transgenic Animal Models

After completing all these studies, Dr A has now identified a number of different genes that she believes are important in causing melanoma. In the next major phase of her research, she will begin to test these genes in animal models to see if they cause cancer. These animal model studies will allow her to investigate the mechanisms of carcinogenesis (see Ch. 107), enabling her to demonstrate that mutations in a particular gene are able to cause cancer. Although a variety of animal models have been used to study cancer, our discussion will be limited to transgenic mice, including "knockout" and conditional "knockout" mice.

As commonly used experimental models, transgenic mice are normal in all respects except that every cell contains a new gene of interest. The gene to be studied is microinjected into a fertilized mouse egg, randomly integrates into the mouse genome, and is present in every cell as the egg divides and develops into a mouse (Table 3.7; Fig. 3.10)[16,17]. Although the gene is present in every cell, the expression of the gene can be limited or targeted to specific tissues or cell types by using a promoter/enhancer that is only expressed in a given cell. Promoters/enhancers are the portion of a gene – usually on the 5′ end of the gene or upstream of its coding region – that initiates and regulates the level of mRNA expression. The promoters/enhancers that would ensure genes are only expressed in melanocytes would include the promoters of genes involved in melanin biosynthesis, such as tyrosinase.

In order to specifically express the mutated *toomuchsun* gene in melanocytes of transgenic mice, Dr A designed a gene construct that contained a promoter/enhancer from tyrosinase connected to the mutated *toomuchsun* gene, and then injected this gene construct into fertilized mouse eggs (see Fig. 3.10). Although every mouse cell will contain a randomly integrated copy of this new gene, it will be expressed only in melanocytes because of the melanocyte-specific promoter/enhancer. In the same manner, Dr A could express other candidate genes in the melanocytes of transgenic mice. Conversely, if she wanted to express a gene only in keratinocytes, she would design a gene

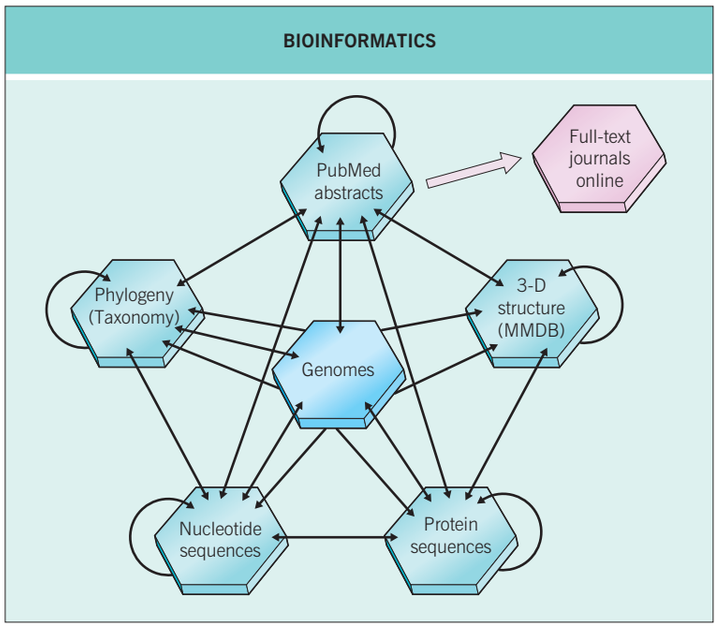


Fig. 3.8 Bioinformatics. A goal of bioinformatics is to give users access to huge amounts of biologic information in a way that is easy to use and analyze. One example is Entrez produced by the National Center for Biotechnology Information (NCBI), available at http://www.ncbi.nlm.nih.gov. This retrieval system allows the user to search the biomedical literature (PubMed), nucleotide sequence database (GenBank), protein sequence database, three-dimensional macromolecular structures, and complete genome assemblies and organisms in GenBank (taxonomy). As indicated by arrows, users may access information from a single database and also integrated information from several NCBI databases. MMDB, molecular modeling database.

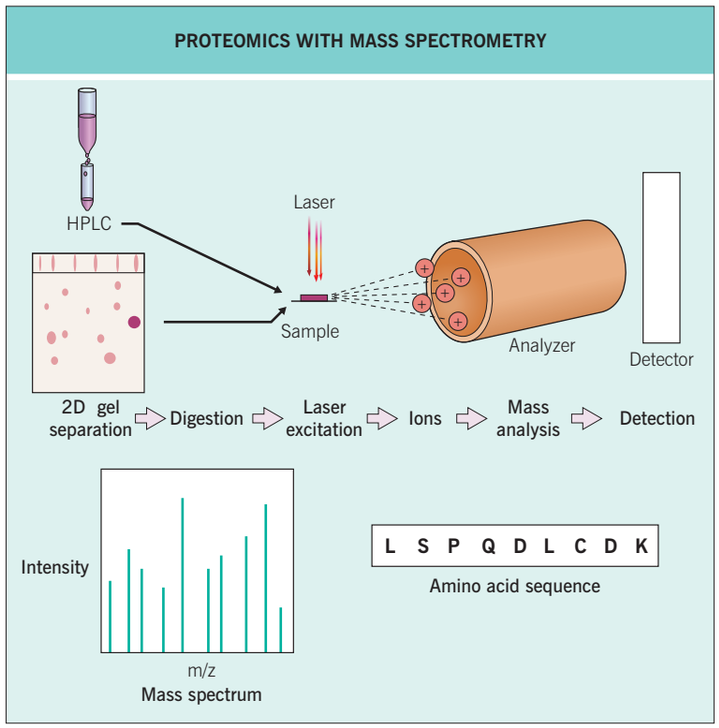


Fig. 3.9 Proteomics with mass spectrometry. The first step is to reduce the complexity of the mixture of cellular proteins or peptides to be analyzed. The two main methods to separate proteins/peptides from each other are two-dimensional gel electrophoresis and/or liquid chromatography columns. Mass spectrometry analysis is then performed by first ionizing the separated proteins/peptides into positively charged ions using lasers. Based on the time-of-flight of the charged ion, mass spectrometry can measure, record and print out the mass/charge ratio of every peptide along with signal intensity.

construct containing a promoter/enhancer from a gene that is only expressed in keratinocytes, such as a keratin promoter.

After these transgenic mice are born, Dr A will carefully examine their skin. She will first check to make sure that the transgene, such as the mutated *toomuchsun*, is expressed in melanocytes by isolating mRNA from the skin and using a RT-PCR assay to determine whether mutated *toomuchsun* mRNA transcripts are present. Alternatively, histologic sections of skin could be analyzed by immunostaining with an antibody against *toomuchsun* in order to confirm that transgenic mice were expressing the transgene in the correct location or cell type (melanocytes).

Next, Dr A will analyze the skin and take random punch biopsy specimens at different time points for histology to determine whether melanoma develops in these transgenic mice. She can determine the time course and frequency of tumor development and can investigate whether external or environmental agents, such as UV light, contribute to the development of the tumors. Finally, if melanomas develop, she can assess their metastatic potential and ability to spread to other organs, such as the lungs.

Based on her initial microarray analysis and proteomic studies, Dr A may decide that melanoma is not caused by expression or aberrant overexpression of a protein (including mutated proteins), but rather is due to the lack of a gene product or protein. In other words, the genetic basis for melanoma may be the result of a protein that normally protects a cell from cancerous growth not being expressed. Her microarray analysis and RT-PCR studies may demonstrate that certain genes which are normally expressed in melanocytes are not expressed in melanoma cancer cells. Such genes are referred to as tumor suppressor genes, and when they are missing or non-functional, the cell is more likely to become cancerous. There are a number of reasons why a tumor suppressor gene may not be expressed and contribute to cancer, including: (1) genetic alterations that delete the tumor suppressor gene from the genome; (2) significant mutations in the coding region of the gene that prevent production of a normal protein; and (3) alterations or mutations of the promoter/enhancer of the tumor suppressor gene that prevent gene expression.

Dr A is fortunate that the functional loss of tumor suppressor genes can also be studied in transgenic mouse models. In order to study the role of a suspected tumor suppressor gene in melanoma development, she can design and create mice in which the tumor suppressor gene is completely deleted and not expressed in any cells of the 'knockout' transgenic mouse (Table 3.8; Fig. 3.11)[18,19]. After these knockout mice are developed, demonstrating that gene expression is lost and assessing tumor development will be similar to the analysis described above for transgenic mice.

Technology now exists to selectively knock out or delete a gene (e.g. a tumor suppressor gene) in a specific cell type or tissue (such as melanocytes), rather than deleting the gene from all cells in the mouse (Fig. 3.12). Furthermore, this technology will also allow Dr A to delete the gene from a specific tissue at any point in time during development. One advantage of this selective approach, compared to gene deletion in all mouse cells, is that it may more faithfully mimic how gene deletion occurs in a specific tissue of a patient and contributes to tumors in those tissues. Another advantage is that gene deletion in all mouse cells may prevent normal mouse development, and selective gene deletion after development is complete will avoid this problem. Finally, selective gene deletion limited to specific target tissues provides a less complicated and cleaner animal model with fewer secondary effects resulting from gene deletion in tissues not being targeted.

Gene Therapy for Cancer

The *in vivo* transgenic mouse models are very important for demonstrating whether a candidate gene or genetic change is responsible for melanoma development. Another important function of melanoma transgenic mouse models is to develop and test novel new therapies

PROTEOMICS WITH MASS SPECTROMETRY
PURPOSE
• The proteome of a cell represents all the cellular proteins that are being expressed under a particular set of conditions. High-throughput analysis that allows investigators to rapidly and quantitatively assess the complex mixtures of proteins present in a cell at a given point in time is under development
REQUIREMENTS
• A mixture of cellular proteins, or peptides derived from these proteins, is purified from a defined population of cells. The protein mixture may represent total cellular proteins or a subcellular fraction of proteins, depending on the isolation procedure
UNDERLYING CONCEPTS
• Mass spectrometry is able to measure very precisely the size or mass of proteins, peptides, or peptide fragments by giving these peptides a positive charge (ionization) and then measuring the time required for the positively charged peptide ions to move through a tube to a detector (time-of-flight) (Fig. 3.9) • The mass of the peptide ion precisely correlates to the time-of-flight, with smaller peptides moving faster (shorter time-of-flight) than larger peptide ions (longer time-of-flight)
OUTLINE OF METHOD (FIG. 3.9)
• The first step is to reduce the complexity of the mixture of cellular proteins or peptides to be analyzed, prior to mass spectrometry analysis. The two main methods to separate proteins/peptides from each other are two-dimensional gel electrophoresis and/or liquid chromatography columns • In two-dimensional gel electrophoresis, proteins are first separated (first dimension) by isoelectric focusing in a gel containing a pH gradient. The pH gradient (acidic to basic) influences the overall charge on the protein, and in isoelectric focusing, proteins migrate through the different pH levels until they reach their isoelectric point (no charge), at which point the electrical current no longer induces their migration • Following first-dimensional separation by isoelectric focusing, these proteins are then further separated by size through a second polyacrylamide gel (second dimension), with smaller proteins moving through the gel faster than the larger ones • After the second-dimension separation, each unique protein will be present in a distinct "spot" on the gel. This protein spot can be physically cut out of the gel and analyzed by mass spectrometry • Liquid chromatography can be also used to separate proteins (or peptides derived from the proteins) as they flow through columns that contain different types of resins. These resins differentially bind the cellular proteins/peptides based on their ionic strength (ion exchange columns) or their relative hydrophobicity (reverse phase columns) • After the protein mixture is bound to the liquid chromatography columns, the proteins/peptides can be eluted from the column into different fractions or aliquots and then analyzed by mass spectrometry. Many high-throughput approaches for protein analysis utilize liquid chromatography • Mass spectrometry analysis is then performed on the separated proteins/peptides by first ionizing them into positively charged ions using lasers or the processes of electrospray ionization and nanospray ionization. Based on the time-of-flight of the charged ion, mass spectrometry can measure, record and print out the mass/charge ratio of every peptide along with signal intensity of that peptide • With the help of powerful computers and bioinformatics software, the peptide mass/charge ratio measurement may allow the identification of the peptide sequence and the protein that contained this peptide (Fig. 3.8) • Mass spectrometry machines are now available (tandem mass spectrometry [MS/MS]) that can "ion trap" a given peptide ion and then sequence the peptide by fragmenting it into its component amino acids. Bioinformatics software can use this sequence information to search protein databases for rapid protein identification
BENEFITS
• Mass spectrometry is extremely sensitive and able to detect very small amounts of proteins/peptides • The field of proteomics promises to provide a tremendous amount of information regarding cell biology and disease
LIMITATIONS/ERRORS
• Better technology to reduce the complexity of protein/peptide mixtures and differentially separate the proteins/peptides in a high-throughput manner is being developed • Although mass spectrometry can measure the mass of proteins/peptides very precisely, it is more difficult to measure the amount of protein/peptide quantitatively, and more robust techniques for quantification by mass spectrometry are being developed
EXPERIMENTAL APPLICATIONS
• Mass spectrometry can be used to determine the complete set of proteins present in a defined population of cells (e.g. melanoma cells) or cells that are being subjected to experimental conditions • Mass spectrometry can differentially compare the proteins in one population of cells (e.g. melanocytes) to those in a distinct group of cells (e.g. melanoma tumor cells) • Because of the sensitivity of mass spectrometry analysis, it holds promise as a sensitive diagnostic tool. For example, mass spectrometry could be used for early detection of small amounts of serum proteins that are characteristic of a particular cancer or systemic disease
MODIFICATIONS/ALTERNATIVES
• Liquid chromatography can be also used to separate proteins (or peptides derived from the proteins) as they flow through columns that contain different types of resins (see Outline of method described above) (Fig. 3.9). Many high-throughput approaches for protein analysis utilize liquid chromatography • Multidimensional protein identification (MudPIT) • Isotope labeling approaches for quantitative mass spectrometry, including isotope-coded affinity tag (ICAT), stable isotope labeling by amino acids in cell culture (SILAC), tandem mass tags (TT), and isobaric tags for relative and absolute quantification (iTRAQ) • Label-free quantitative proteomics, including peak intensity-based comparative liquid chromatography-mass spectrometry (LC-MS) and spectral count-based liquid chromatography-tandem mass spectrometry (LC-MS/MS) • Antibody protein arrays • Reverse-capture protein microarrays • Tissue microarrays

Table 3.6 Proteomics with mass spectrometry.

that Dr A may someday use in clinical trials against melanoma. Gene therapy is one important therapeutic approach that holds future promise as a treatment for cancers such as melanoma. In gene therapy, a gene or genes are introduced into the cells of a target tissue in order to achieve a therapeutic effect. Gene therapy may be used to treat cancer even if the genetic basis or cause of the cancer has not been established.

Two different types of transgenic animal models were described above. In the first, melanoma resulted when an oncogene or tumor-causing gene (mutated) was overexpressed in melanocytes of mice. To treat these tumors with gene therapy, gene(s) that would counteract or oppose the effects of the tumor-causing genes, and thereby inhibit or prevent tumor growth, would be introduced into the melanoma cells[20–25]. For example, tumor suppressor genes (discussed earlier) could

TRANSGENIC MICE
PURPOSE
• Transgenic mouse models allow investigators to study the effects of a transgene (the gene of interest) on a cellular, tissue and whole animal level. The transgene can be selectively expressed in a particular cell type or tissue by using a promoter/enhancer regulatory region that is specific for that cell type
REQUIREMENTS
• A transgene or gene of interest, whose biologic function is to be characterized (e.g. *toomuchsun*) in an animal model • A regulatory region (promoter/enhancer) that will selectively express the transgene in a specific tissue (e.g. melanocytes) • The facilities and technologies to create transgenic mice
UNDERLYING CONCEPTS
• After injection of a transgene into a fertilized mouse egg or single-cell embryo, the transgene randomly integrates into the genome, usually at a single site (Fig. 3.10). As the embryo undergoes many cell divisions and develops into a mouse, the integrated transgene will be present in every cell type, tissue and organ in the mouse. Transgene expression only occurs in cells and tissues where the promoter/enhancer regulatory region is active. Any phenotypes that develop in mice expressing the transgene in the desired tissue can help us understand the biologic effects of the transgene
OUTLINE OF METHOD (FIG. 3.10)
• A transgene construct, defined as the transgene and a regulatory region (promoter/enhancer), is prepared for injection • The transgene is microinjected into fertilized eggs (single-cell stage) and the transgene integrates into the genome, usually at a single site • These injected eggs are then implanted into a recipient mother, who then gives birth to a heterozygous "founder" mouse that can be either male or female. The founder mouse is referred to as a transgenic mouse because it only contains the transgene on one of the two paired chromosomes (e.g. only one copy of chromosome 7 contains the transgene, whereas the other chromosome 7 does not) • The founder mice are bred with normal non-transgenic mice of the same strain. The progeny mice will be both heterozygous transgenic and non-transgenic, according to Mendelian genetics • In order to derive homozygous transgenic mice that contain the transgene on both of the paired chromosomes (e.g. both copies of chromosome 7 contain the transgene), two heterozygous transgenic mice are mated. Homozygous transgenic mice will have a double dose of the transgene, which may lead to different phenotypes and biologic effects from those present in the heterozygous transgenic mice
BENEFITS
• Transgenic mouse models can help us understand the *in vivo* biologic effects of an unknown gene when expressed in a specific tissue
LIMITATIONS/ERRORS
• The precise regulation of the level of transgene expression as well as the timing of gene expression during development (turning the transgene on or off during development) have been relatively difficult. Advancements in transgenic design, including inducible promoters, have improved the regulation of transgene expression • When expressed in mouse tissues, a human transgene may have different biologic effects compared to its effects in human tissues • Classic transgenic mice models do not allow investigators to study the biologic effects of gene mutations or deletions that result in loss of gene expression, because the technique of creating transgenic mice does not alter endogenous genes, it only adds a new transgene to each cell
EXPERIMENTAL APPLICATIONS
• Transgenic mouse models of disease can be used to test the effectiveness of new therapeutic agents
MODIFICATIONS/ALTERNATIVES
• More precise control of transgene expression can be achieved with promoters/enhancers that are inducible and can be regulated (i.e. turned off and on at different time points)[16,17] • "Knockout" transgenic mouse models (Table 3.8) allow investigators to understand the biologic effects of gene mutations and deletions that cause a loss of specific proteins

Table 3.7 Transgenic mice.

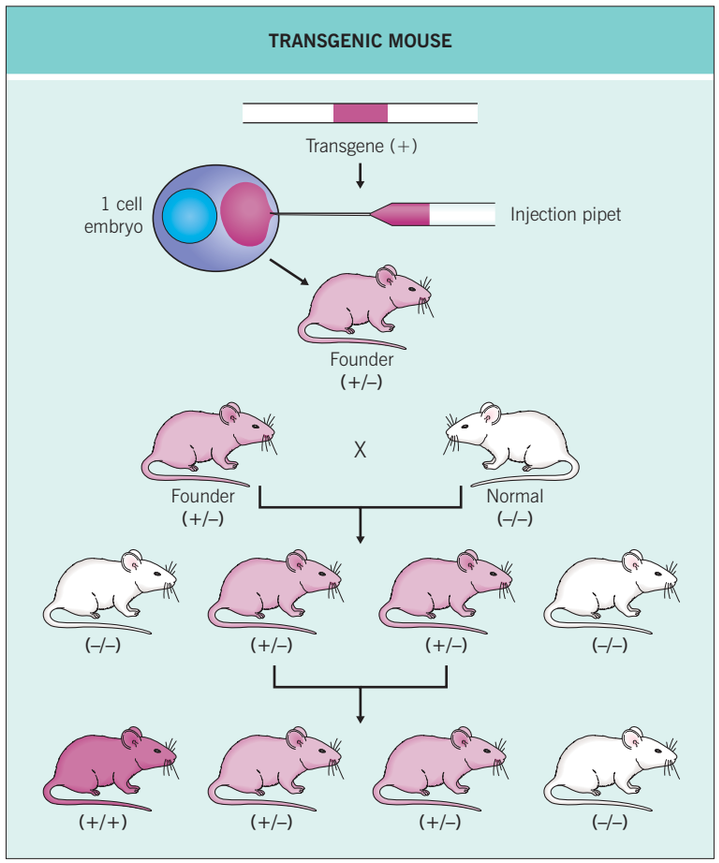


Fig. 3.10 Transgenic mouse. A transgene construct, defined as the transgene and regulatory region (promoter/enhancer), is prepared for injection. The transgene is microinjected into fertilized eggs (single cell stage) and the transgene integrates into the genome, usually at a single site. These injected eggs are then implanted into a recipient mother, who then gives birth to a heterozygous "founder" mouse. The founder mice are bred with normal non-transgenic mice of the same strain, and then two heterozygous transgenic mice are mated.

be introduced into melanomas in order to suppress tumor growth, regardless of which oncogene was stimulating growth. In knockout transgenic mice that develop melanoma, gene therapy could be used to introduce the missing tumor suppressor gene into the melanoma cells. Restoring the deleted tumor suppressor gene should inhibit the proliferation and growth of the melanoma cells.

Another effective type of cancer gene therapy is to introduce gene(s) that are capable of stimulating the immune response against the melanoma cancer cells[26]. Genes encoding cytokines or other immune-modulating proteins would be introduced into the melanoma in order to stimulate an immune response against the tumor cells. The goal here would be to develop a broad systemic immune response against the melanoma cells so that even those not expressing the introduced gene(s) will be targeted and destroyed by the immune system.

Dr A can administer these gene therapies either by introducing the gene directly into the tumor cells or by first putting the gene into a viral vector and injecting the viral vector into the melanoma (Table 3.9; Fig. 3.13). Introducing genes via viral vectors has the advantage of efficiently introducing the desired gene into a high percentage of tumor cells, often in a stable manner[27–29] (Table 3.10). The disadvantage is the additional work of constructing the viral vectors. In contrast, introducing the gene directly without first placing it in a viral vector is simpler and more straightforward. However, the percentage of tumor cells containing and expressing the introduced gene will probably be lower. As noted above, for gene therapy of cancer, it may not be necessary to introduce the gene into every tumor cell in order to elicit an immune response against the tumor cells.

An alternative and perhaps even more promising approach could be, instead of manipulating cancer cells to produce immunostimulatory

KNOCKOUT TRANSGENIC MICE
PURPOSE
• Knockout transgenic mice have both alleles of a normal endogenous gene modified, mutated, or deleted in all cells (whole animal or targeted tissue) so that protein can no longer be produced by that gene. Therefore, knockout transgenic mice allow investigators to understand what happens to a cell or tissue when a particular gene can no longer be expressed
REQUIREMENTS
• Murine embryonic stem cells (ES cells) that are totipotent and capable of forming and reconstituting all tissues and organs of a mouse • A targeting construct defined as a defective gene that can hybridize to the normal endogenous gene in ES cells and modify or delete the targeted gene so that it is no longer able to express a functional protein
UNDERLYING CONCEPTS
• In knockout transgenic mice, all cells (whole animal or targeted tissue) lack the gene that has been "knocked out" and do not express any functional protein from that gene • Technology is available to selectively target and delete an endogenous gene in its normal chromosomal location in ES cells
OUTLINE OF METHOD (FIG. 3.11)
• A targeting vector that contains some sequences of the gene to be targeted is created and introduced into ES cells. This targeting vector is able to selectively hybridize to one of the endogenous alleles of a gene, and through a process known as homologous recombination, the targeting vector modifies or deletes the endogenous gene so that no normal protein is produced. ES cells that contain this defective endogenous gene can be selected for and isolated • The ES cells containing the "knocked out" gene are introduced into early mouse embryos, known as blastocysts, which are then implanted into recipient mothers. The progeny will be chimeric mice; all tissues and organs, including testes and ovaries, will contain a mixture of normal cells and cells that lack the "knockout" gene allele • The chimeric mice are next mated to normal mice. Depending on the degree of chimerism, a certain percentage of the offspring will be heterozygous, containing one normal allele and one allele that has been modified or deleted (knocked out). As described for the mating procedure in transgenic mice (see Table 3.7), the genotypes of all progeny will follow the rules of Mendelian genetics • To obtain completely "knocked out" mice, two heterozygous mice are mated. Approximately 25% of the offspring will lack a normal endogenous gene in every cell and tissue
BENEFITS
• This approach yields mice that completely lack the gene product in all cells of the whole animal or targeted tissues
LIMITATIONS/ERRORS
• Investigators have to ascertain that no normal gene product is being produced. It is possible that the homologous recombination process used to knock out a gene may result in a gene that encodes a mutant protein that still has biologic effects. This would make it difficult to understand the biologic effects of the gene
EXPERIMENTAL APPLICATIONS
• Unlike regular transgenic mice, knockout transgenic mice allow investigators to study the biologic effects of losing gene expression. This is particularly useful in the study of genes that may normally suppress cancer development (tumor suppressors); the tumor suppressor gene can be knocked out in all mouse cells *in vivo*, and the mechanisms of cancer development in different tissues can be studied
MODIFICATIONS/ALTERNATIVES
• In order to more accurately mimic *in vivo* situations, the gene of interest can be selectively deleted in only one organ or tissue (e.g. melanocytes). These *conditional* knockout mice allow investigators to study the effects of gene loss in a particular tissue without the complications of losing gene expression in all the other tissues (Fig. 3.12) • A similar technology is also available to delete a gene of interest at a particular time during development. Initially, the endogenous gene will be expressed normally in the knockout mice and then deleted at a later time, either during intrauterine development or after birth. This is advantageous if investigators want to study the effects of a gene that, if knocked out, would prevent embryo development

Table 3.8 Knockout transgenic mice.

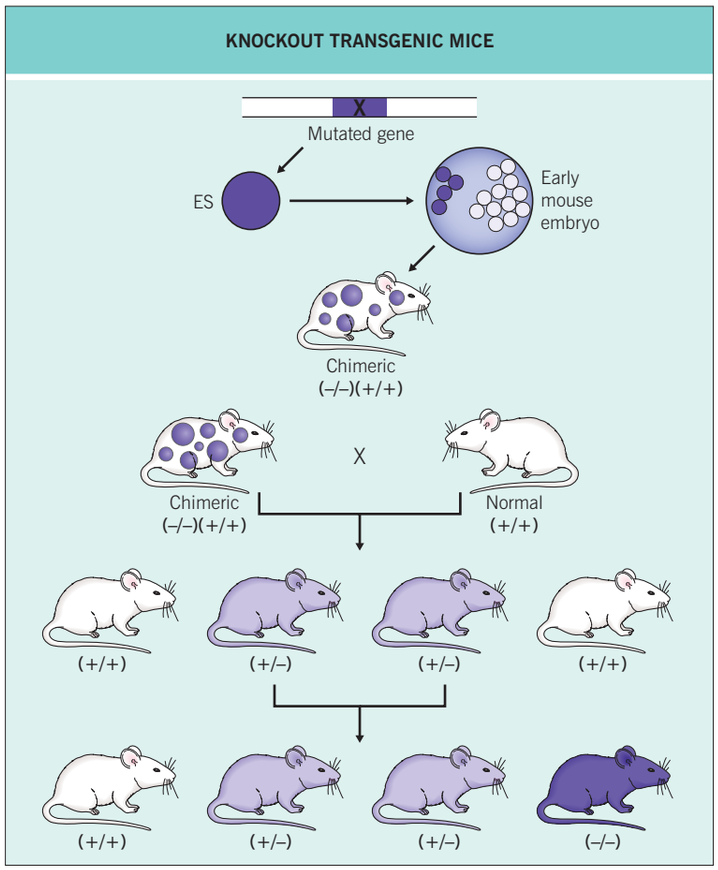


Fig. 3.11 Knockout transgenic mice. A targeting vector that contains some sequences of the gene to be targeted is created and introduced into cells. This targeting vector is able to hybridize selectively to one of the endogenous alleles of a gene, and modifies or deletes the endogenous gene so that no normal protein is produced. The embryonic stem (ES) cells containing the "knocked out" gene are introduced into early mouse embryos, which are then implanted into recipient mothers. The progeny will be chimeric mice. These chimeric mice are then mated to normal mice. To obtain completely knocked out mice, two heterozygous mice are mated.

molecules, to express tumor-associated antigens in dendritic cells for effective presentation to T cells. The feasibility of such a procedure has been demonstrated in several murine cancer models. When injected into the skin, plasmid DNA encoding a tumor-associated antigen finds its way to, among others, cutaneous dendritic cells (Langerhans cells, dermal dendritic cells), where it becomes expressed. This event also results in the activation and maturation of dendritic cells (probably because of the presence of immunostimulatory CpG sequences in plasmid DNA), allowing them to leave the skin and to migrate via the afferent lymphatics to the draining lymphoid tissue, where they induce protective anticancer immune responses.

At this point, Dr A is ready to perform gene therapy clinical trials on patients with melanoma. She has taken melanoma specimens from patients, identified several genes in melanomas that are overexpressed (oncogenes), underexpressed (tumor suppressor genes) or mutated, utilized transgenic animal models to confirm that these genes play a causative role in melanoma development, and developed a gene therapy that is effective in treating melanoma in these animal models.

Gene Therapy that Targets Keratinocyte Stem Cells

Alternatively, instead of using skin gene therapy to treat melanoma, Dr A may want to use skin gene therapy to treat a genetic skin disease by expressing a gene in keratinocytes to correct the keratinocyte genetic

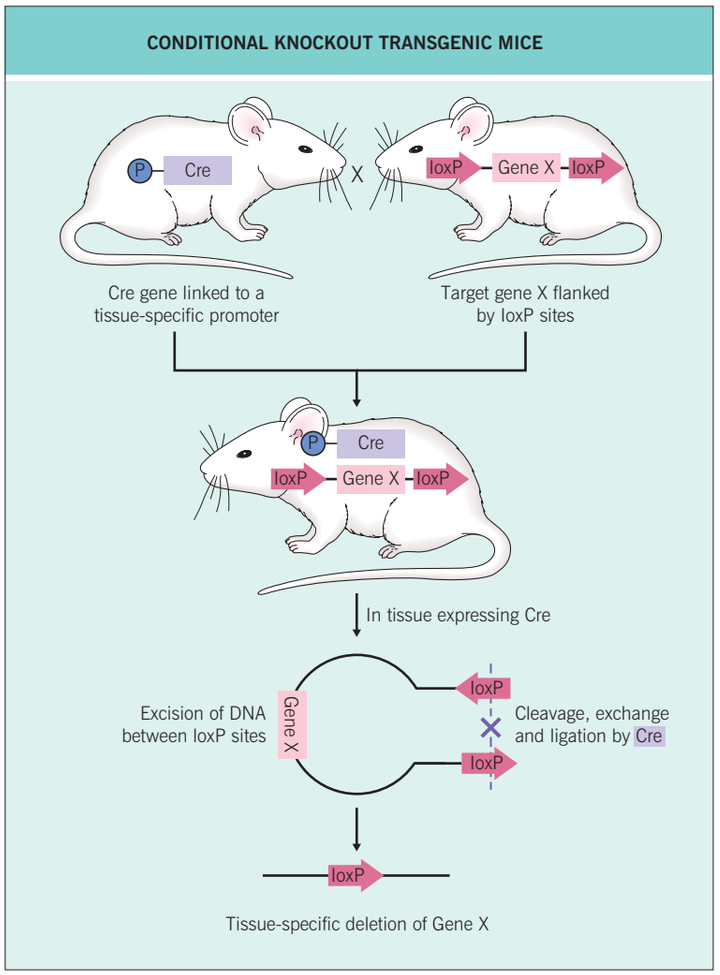


Fig. 3.12 Conditional knockout transgenic mice. In the conditional knockout model using the Cre-lox system, a target gene can be selectively deleted in a particular organ or tissue. Cre is a site-specific DNA recombinase that catalyzes recombination between two loxP sites, resulting in cleavage, exchange and ligation; this leads to excision (and subsequent degradation) of the DNA between the loxP sites. A transgenic mouse with the Cre gene linked to a tissue-specific promoter is mated to a transgenic mouse with two loxP sites flanking the target gene. Progeny inherit both of these constructs, and the target gene is knocked out only in cells that activate the tissue-specific promoter. By adding a ligand-binding domain to the Cre recombinase, such as one that binds tamoxifen, investigators can achieve temporal control of Cre expression in these cells. The target gene can be temporally deleted, inverted or translocated, depending on the orientation of the loxP sites.

SKIN GENE THERAPY
PURPOSE
• In skin gene therapy, genes are introduced and expressed in the skin for therapeutic purposes. Diseases that could be treated by this approach include both skin diseases and systemic diseases where skin is used as a vehicle for the systemic delivery of a needed factor or substance
REQUIREMENTS
• A gene that is able to achieve the desired therapeutic effect when expressed in keratinocytes or other skin cells such as fibroblasts and melanocytes • A delivery vector that can efficiently introduce the desired gene into cells. Both viral vectors and non-viral vectors can be used to deliver a desired gene to a target cell type. With viral vectors, the desired gene is incorporated into the genetic material of a modified virus that is able to efficiently infect target cells but is no longer able to cause disease and spread to other cells (Table 3.10)
UNDERLYING CONCEPTS
• Skin gene therapy is a promising field that has the potential to provide new treatments for both skin and systemic diseases • There are two general approaches for introducing genes into the skin: a direct *in vivo* approach (Fig. 3.13) and an *ex vivo* approach (Fig. 3.14), as described below • The viral vectors that have most often been used to deliver genes to skin cells are retroviral vectors and adenoviral vectors (Table 3.10). Adeno-associated viral vectors and lentiviral vectors (which are related to retroviral vectors and are derived from HIV) have also been described in association with skin gene therapy • Many issues need to be considered when choosing a vector and determining the best approach to deliver the desired gene to the skin. These include: (1) how many cells (what percentage) need to contain the gene in order to have a therapeutic effect; (2) how long the gene needs to be expressed in order to be therapeutic. In some situations, short-term or transient expression is sufficient; in other cases, long-term expression is preferable
OUTLINE OF METHOD (FIGS 3.13 & 3.14)
• In the direct *in vivo* approach, the desired gene is introduced directly into the skin as shown, either directly injected intradermally (Fig. 3.13A) or biolistically discharged into the epidermis and dermis (Fig. 3.13B). Both approaches can be made even more efficient when the skin is concomitantly exposed to an electrical charge in a process known as electroporation. Both viral vectors and non-viral vectors can be delivered to the skin using these *in vivo* approaches • In the *ex vivo* approach, keratinocytes are removed from the donor and, during *ex vivo* culture, the desired gene is efficiently introduced, usually with viral vectors (Fig. 3.14). Skin equivalents or raft cultures containing these genetically modified keratinocytes (along with a dermal portion containing fibroblasts) are constructed and then grafted back onto the donor in the correct anatomic location • The principal advantage of the *in vivo* approaches is their simple straightforward nature. A disadvantage is that expression is usually transient and not long-term because selective targeting of keratinocyte stem cells is usually not feasible with *in vivo* approaches. Another disadvantage is that the percentage of cells containing the desired transgene may be lower than desired • In contrast, the *ex vivo* approaches (Fig. 3.14) are superior at achieving long-term expression of a desired gene in a high percentage of skin cells. During the *ex vivo* culture period, the desired gene could be targeted to keratinocyte stem cells • The disadvantage of the *ex vivo* approach is that it is much more complicated and technically demanding than the *in vivo* approaches

Table 3.9 Skin gene therapy.

Continued

SKIN GENE THERAPY
BENEFITS
• Genes are the therapeutic agent in this approach to treatment of cutaneous and systemic disease. As our understanding of the molecular basis of disease increases, genetic therapies will become more important • The effectiveness of skin gene therapy can be assessed in animal models
LIMITATIONS/ERRORS
• Successful skin gene therapy with long-term expression of a desired gene in a high percentage of cells has been difficult to achieve in animal models • Skin gene therapy for recessive genetic skin diseases is problematic because of the development of an unwanted immune response against the normal protein • Risk of oncogenesis, especially with retroviral vectors
EXPERIMENTAL APPLICATIONS
• Treatment of genetic skin diseases • Treatment of non-genetic skin diseases if a sufficient understanding of the molecular basis of the disease exists • Systemic delivery of cytokines, hormones and growth factors • Genetic immunization • Suicide gene therapy
MODIFICATIONS/ALTERNATIVES
• Use of short (small) interfering RNA (siRNA) that specifically targets and silences expression of dominant negative mutant genes • Protein replacement therapies • Cellular therapies (see Fig. 2.6)

Table 3.9 Skin gene therapy (cont'd).

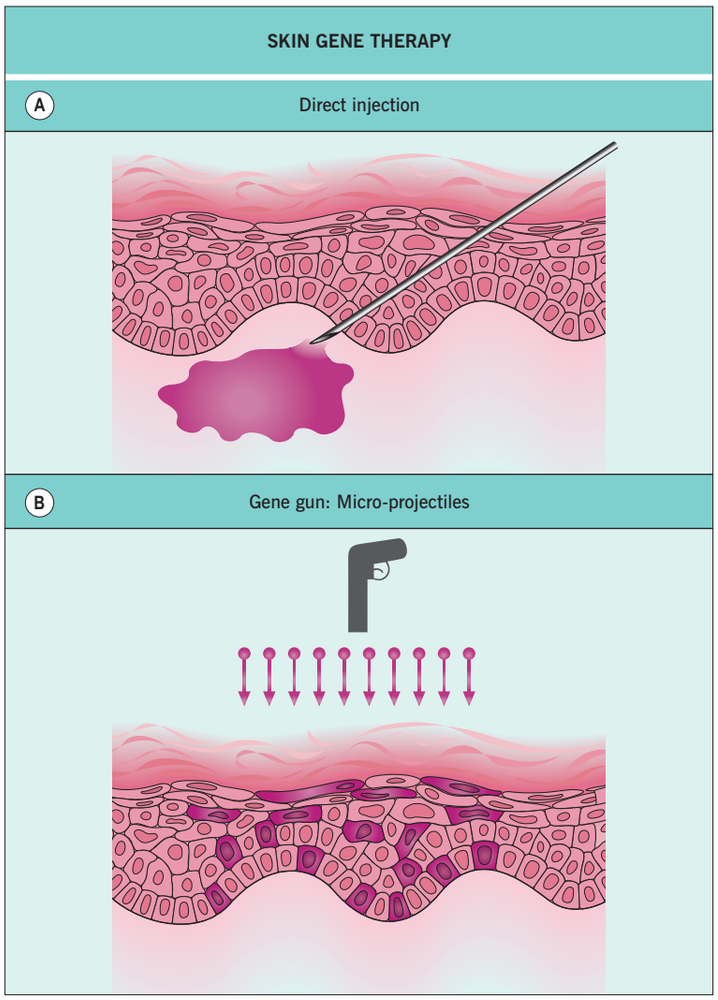


Fig. 3.13 Skin gene therapy. In the direct *in vivo* approach, the desired gene is introduced directly into the skin as shown, either directly injected intradermally (**A**) or biolistically discharged into the epidermis and dermis (**B**). Both viral and non-viral vectors can be delivered to the skin using these *in vivo* approaches

VIRAL VECTORS FOR SKIN GENE THERAPY			
	Retrovirus	**Adenovirus**	**Adeno-associated virus**
Duration of expression	Long term (integration)	Transient (no integration)	Long term possible (some integration)
Efficient gene	Replicating cells only	Replicating and non-replicating cells	Replicating and non-replicating cells
Gene cargo capacity	8–9 kb	>8–9 kb	Around 4.5 kb
Antigenicity	+ (re-administration possible)	++++	+ (not associated with human pathology)

Table 3.10 Viral vectors for skin gene therapy.

defect, or to treat a systemic disease by introducing a gene into keratinocytes and having its gene product secreted into the bloodstream for systemic effect. For these applications of skin gene therapy, Dr A will want to express the gene in the skin for a long period of time. Because skin is a renewable tissue, Dr A may need to insert the gene into keratinocyte stem cells in order to achieve long-term expression in the skin, using an *ex vivo* approach to deliver the gene (Fig. 3.14) (see Ch. 2). Keratinocyte stem cells are located in the hair follicle and scattered along the basal layer of the skin. In the hair follicle, stem cells are highly concentrated in the bulge area where the arrector pili muscle attaches (see Ch. 2). These keratinocyte stem cells are believed to divide very slowly and represent approximately 1–3% of all keratinocytes.

Molecular Therapy that Targets RNA

Another therapeutic approach is to target specific mRNAs for degradation, using short interfering RNA (siRNA) (Fig. 3.15). Double-stranded RNAs, 21–23 nucleotides in length, are designed complementary to the mRNA of interest. These are delivered to the cell, where they mediate sequence-specific mRNA degradation using an endogenous complex of proteins called the RNA-induced silencing complex (RISC).

Ribozymes also target specific sequences based on short complementary oligonucleotides, but the catalyst for target degradation is provided by the RNA enzyme without the need for protein cofactors. These approaches, and variations thereof, have been useful experimentally, but their therapeutic use has thus far been limited by difficulties with stability, efficient delivery to cells, and minimization of unwanted effects[30].

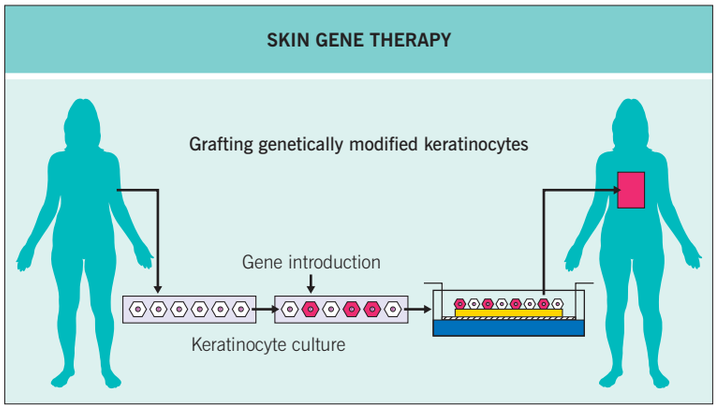


Fig. 3.14 Skin gene therapy. In the *ex vivo* approach, keratinocytes are removed from the donor and, during *ex vivo* culture, the desired gene is efficiently introduced, usually with viral vectors. Skin equivalents or raft cultures containing these genetically modified keratinocytes (along with a dermal portion containing fibroblasts) are constructed and then grafted back onto the donor.

CONCLUSIONS

In this chapter, we have presented a variety of techniques used in dermatology research and clinical practice. Some of these are new, whereas others are long established and still widely used. New technologies continue to appear and change the way research is done. These technologic advances allow experiments to be done faster and with less and less starting material. They allow the measurement of thousands of different genes or proteins in single experiments. They also automate experiments that used to require time-consuming step-by-step human involvement. To handle all the information currently produced by biologic research, advances in computers and bioinformatics are progressing along with the technologic advances. The outcome is that the pace of scientific inquiry proceeds at an increasing rate.

Advances in our scientific understanding translate into new developments in disease diagnosis and management. For dermatology, this provides hope that diseases can be diagnosed more rapidly and more reliably, and that individualized prognostic information can be provided. Therapies have been and will continue to be developed that specifically target the genetic abnormality causing the disease. In the future, therapies may be tailored to the individual, taking into consideration the genetic make-up of the individual and his or her disease process. These future possibilities are exciting.

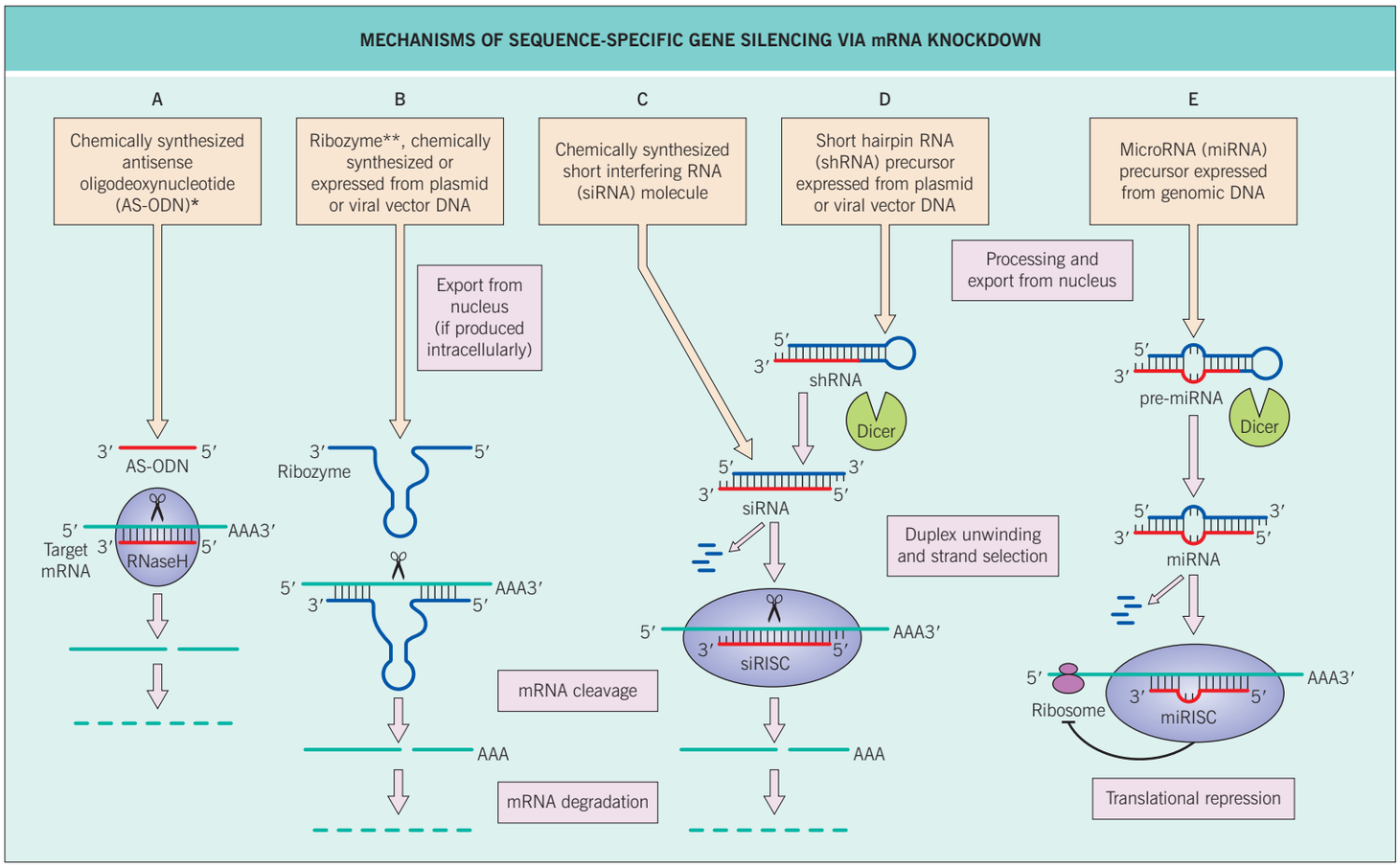


Fig. 3.15 Mechanisms of sequence-specific gene silencing via mRNA knockdown. A Antisense oligodeoxynucleotide (AS-ODN) hybridizes to target mRNA, which is subsequently cleaved by the intracellular enzyme RNase H and degraded. Some chemically modified antisense molecules prevent mRNA splicing or inhibit translation via steric hindrance. **B** Ribozymes have intrinsic catalytic activity and cleave target mRNA directly. **C** Short (small) interfering RNA (siRNA) is unwound and the "guide" antisense strand incorporated into a RNA-induced silencing complex (RISC) that degrades a specific target mRNA sequence. Processing of short hairpin RNA (shRNA; **D**) and pre-microRNA (miRNA; **E**) by the Dicer enzyme can generate siRNA and miRNA, respectively. **E** Endogenously produced miRNA regulates up to a third of human genes and tends to have less complementarity with target mRNA; it recruits RISC proteins and typically inhibits mRNA translation (rather than decreasing mRNA levels). *May also be composed of DNA and/or nucleic acid analogues. **Translocated from the nucleus via exportin-5.

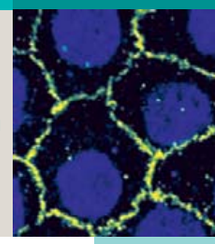
REFERENCES

1. Braun-Falco M, Schempp W, Weyers W. Molecular diagnosis in dermatopathology: what makes sense, and what doesn't. Exp Dermatol. 2009;18:12–23.
2. Carlson JA, Ross JS, Slominski AJ. New techniques in dermatopathology that help to diagnose and prognosticate melanoma. Clin Dermatol. 2009;27:75–102.
3. Uitto J. Progress in heritable skin diseases: translational implications of mutation analysis and prospects of molecular therapies. Acta Derm Venereol. 2009;89:228–35.
4. Bova GS, Eltoum IA, Kiernan JA, et al. Optimal molecular profiling of tissue and tissue components: defining the best processing and microdissection methods for biomedical applications. Mol Biotechnol. 2005;29:119–52.
5. Okuducu AF, Hahne JC, Von Deimling A, Wernert N. Laser-assisted microdissection, techniques and applications in pathology. Int J Mol Med. 2005;15: 763–9.
6. Rapley R. Basic techniques in molecular biology. In: Rapley R, Walker JM (eds). Medical Biomethods Handbook. Totowa, NJ: Humana Press, 2005: 1–12.
7. Powledge TM. The polymerase chain reaction. Adv Physiol Educ. 2004;28:44–50.
8. Fox S, Filichkin S, Mockler TC. Applications of ultra-high-throughput sequencing. Methods Mol Biol. 2009;553:79–108.
9. Pleasance ED, Cheetham RK, Stephens PJ, et al. A comprehensive catalogue of somatic mutations from a human cancer genome. Nature. 2010;463:191–6.
10. Bustin SA, Mueller R. Real-time reverse transcription PCR (qRT-PCR) and its potential use in clinical diagnosis. Clin Sci. 2005;109:365–79.
11. Cseke LJ, Wu W, Lee JS, Chang SC. Western blot hybridization. In: Cseke LJ, Kaufman PB, Podila GK, Tsai C-J (eds). Handbook of Molecular and Cellular Methods in Biology and Medicine, 2nd edn. Boca Raton, FL: CRC Press, 2004.
12. Sara H, Kallioniemi O, Nees M. A decade of cancer gene profiling: from molecular portraits to molecular function. Methods Mol Biol. 2010;576:61–87.
13. Graves PR, Haystead TAJ. Molecular biologist's guide to proteomics. Microbiol Mol Biol Rev. 2002;66:39–63.
14. Zhu W, Smith JW, Huang CM. Mass spectrometry-based label-free quantitative proteomics. J Biomed Biotechnol. 2010;2010:840518.
15. Pollard HB, Srivastava M, Eidelman O, et al. Protein microarray platforms for clinical proteomics. Proteomics Clin Appl. 2007;1:934–52.
16. Ristevski S. Transgenic studies in the mouse. Improving the technology towards a conditional temporal and spatial approach. Methods Mol Biol. 2001;158:319–34.
17. Ryding AD, Sharp MG, Mullins JJ. Conditional transgenic technologies. J Endocrinol. 2001;171:1–14.
18. DeMayo FJ, Tsai SY. Targeted gene regulation and gene ablation. Trends Endocrinol Metab. 2001;12: 348–53.
19. Sharan SK, Bradley A. Role of transgenic mice in identification and characterization of tumor suppressor genes. Cancer Surv. 1995;25:143–59.
20. Ghazizadeh S, Taichman LB. Virus-mediated gene transfer for cutaneous gene therapy. Hum Gene Ther. 2000;11:2247–51.
21. Vogel JC. Nonviral skin gene therapy. Hum Gene Ther. 2000;11:2253–9.
22. Watt FM. Epidermal stem cells as targets for gene transfer. Hum Gene Ther. 2000;11:2261–6.
23. Krueger GG. Fibroblasts and dermal gene therapy: a minireview. Hum Gene Ther. 2000;11:2289–96.
24. Cao T, Wang XJ, Roop DR. Regulated cutaneous gene delivery: the skin as a bioreactor. Hum Gene Ther. 2000;11:2297–300.
25. Igoucheva O, Yoon K. Targeted single-base correction by RNA-DNA oligonucleotides. Hum Gene Ther. 2000;11:2307–12.
26. Larregina AT, Falo LDJ. Generating and regulating immune responses through cutaneous gene delivery. Hum Gene Ther. 2000;11:2301–5.
27. Uitto J, Pulkkinen L. The genodermatoses: candidate diseases for gene therapy. Hum Gene Ther. 2000;11:2267–75.
28. Khavari PA. Genetic correction of inherited epidermal disorders. Hum Gene Ther. 2000;11:2277–82.
29. Dellambra E, Pellegrini G, Ferrari G, et al. Toward epidermal stem cell-mediated ex vivo gene therapy of junctional epidermolysis bullosa. Hum Gene Ther. 2000;11:2283–7.
30. Dallas A, Vlassov AV. RNAi: a novel antisense technology and its therapeutic potential. Med Sci Monit. 2006;12:RA67–74.

This page intentionally left blank

4 Immunology

Thomas Schwarz



Key features

- The major purpose of the immune system is protection against harmful organisms, which is achieved by a rapid "primitive" reaction, called the innate immune response, and a more highly developed specific reaction, called the adaptive immune response
- The characteristics of an adaptive immune response are specificity and the accumulation of memory, thus enabling improvement with each successive encounter with a particular antigen
- The key event in an adaptive immune response is antigen presentation, yielding either a cell-mediated or a humoral response. The cellular response involves primarily T cells, whereas the humoral response involves B cells that ultimately mature into antibody-secreting plasma cells
- Immune responses are not always protective and can even be pathogenic if the response induces severe tissue destruction or is directed against an autoantigen
- As a barrier organ to the outside environment, the skin is endowed with the capacity and the necessary cellular components to mount an immune response

INTRODUCTION

The skin is in a sense a defense organ, since it represents a major barrier against the outside environment. As such, it is constantly confronted with microbial, chemical and physical insults. Within the past three decades, there has been a greater appreciation for the fact that the skin not only functions as a mechanical barrier to the outside world, but also uses the immune system for protection. Accordingly, the skin is endowed with the capacity to generate an immune response, which gave rise to the term "skin-associated lymphoid tissues" (SALT)[1].

The classical immune response, also referred to as the adaptive immune response, is characterized by specificity that is due to immunologic memory (specific immunity)[2]. Innate immunity is a more primitive defense system that acts in a rapid but less specific manner. Both types of responses can be generated in the skin. Adaptive immune responses in the skin, however, are not always protective but can also be harmful in nature, e.g. allergic or autoimmune reactions. Numerous skin diseases are caused by T lymphocytes and are therefore immunologically mediated. Consequently, many dermatoses respond favorably to immunosuppressive therapy administered either systemically or topically.

INNATE IMMUNE RESPONSE

Innate immune responses are characterized by a lack of immunologic memory. These immune reactions are less complicated than adaptive responses and developed earlier in evolution[3]. Nevertheless, failures in these "primitive" immune responses may be associated with severe, even fatal, health problems. Essential components of the innate response are neutrophils, eosinophils, natural killer cells, mast cells, cytokines, complement and antimicrobial peptides. The innate response is more rapid and less controlled than the adaptive immune response.

Complement

The complement system plays an important role in innate immunity. It consists of at least 20 serum glycoproteins that are activated by an enzymatic amplifying cascade (see Ch. 60)[4]. Three pathways can trigger this cascade. The classical pathway is stimulated by antigen–antibody complexes, the alternative pathway by polysaccharides derived from microbial cell walls, and the more recently identified lectin pathway by the interaction of microbial carbohydrates with mannose-binding proteins. All three pathways lead to activation of the central C3 component and, finally, the generation of a number of immunologically active substances. For example, C3b, the cleavage product of C3, binds to the surface of microbes. Since phagocytic cells express receptors for C3b, phagocytosis of the microorganisms is enhanced. In addition, complement components bind to antigen–antibody immune complexes, which helps complement receptor-bearing antigen-presenting cells to target these immune complexes.

C5a is a powerful attractant for neutrophils. C3a, C4a and C5a, also called anaphylatoxins, induce the release of inflammatory mediators from mast cells. This increases vascular permeability, thereby enabling proteins (e.g. antibodies) to enter the tissue. Assembly of the complement components C5b, C6, C7, C8 and C9 forms the membrane-attack complex (MAC), which generates pores in cell membranes, causing death by osmotic lysis. Human cells are much less susceptible to killing by complement than are microbes, since human cells express the complement receptor type 1 (CR1, CD35), decay-accelerating factor (DAF, CD55) and membrane cofactor protein (MCP, CD46), which inhibit C3 convertase and thereby block progression of the complement cascade. CD59 is a protein that binds to C8 and inhibits insertion of C9 into the cell membrane.

Toll-Like Receptors

Innate immunity serves to recognize invading microorganisms and then induce a host defense response. Several families of pattern recognition receptors (PRRs) mediate responses to pathogen-associated molecular patterns (PAMPs) that are conserved among microorganisms. Toll-like receptors (TLRs; the mammalian homologues of the Toll receptors identified in *Drosophila*) are one such family of PRRs. Ten TLRs have been identified to date[5] (Fig. 4.1), with the following specificities: TLR2 (in association with either TLR1 or TLR6), recognition of lipoproteins and peptidoglycans; TLR4, lipopolysaccharide; TLR5, flagellin (a component of bacterial flagella); and TLR9, bacterial CpG DNA sequences. TLRs may also be involved in the recognition of viral components.

The signaling pathway of TLRs is highly homologous to that of the receptor for interleukin-1 (IL-1). Upon interaction with myeloid differentiation factor 88 (MyD88), IL-1 receptor-associated kinase (IRAK) is recruited, ultimately leading to activation of the transcription factor NF-κB (see Fig. 4.1). Activation of TLRs can also result in the release of interferons (IFNs) via activation of interferon regulatory factor 3 (IRF-3).

Dendritic cells express several types of TLRs. Upon activation of these receptors by microbial components, the dendritic cells mature and migrate to the lymph nodes, where they present pathogen-derived antigens to naive T cells and induce an adaptive immune response. TLRs thereby bridge the gap between the innate and adaptive immune systems[6]. These two systems constantly interact in the skin, and the innate immune system represents a potential target for modulating adaptive immune responses[7]. Cutaneous dendritic cells that are stimulated by the innate immune system not only instruct T cells to respond but also tell them how and where. Different PAMPs and danger signals polarize dendritic cells, giving them the ability to produce certain cytokines and to induce T cells to differentiate into particular subtypes. Many of these danger signals are provided by keratinocytes, which also express PRRs. In addition, TLRs expressed in the skin direct control of pathogens by the epithelium.

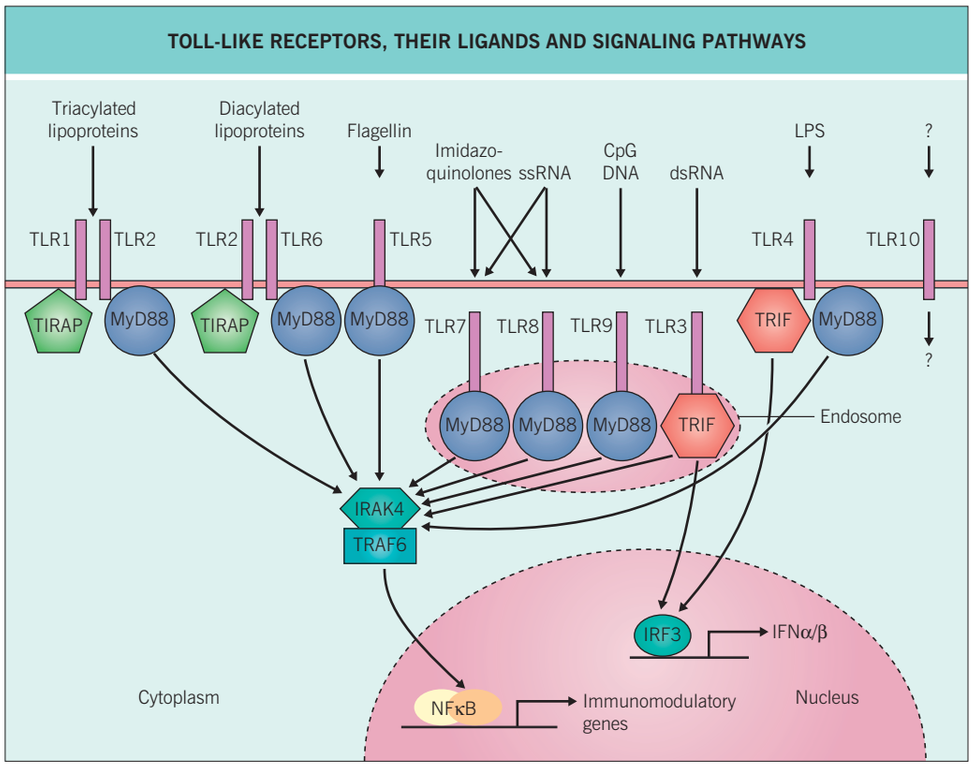


Fig. 4.1 Toll-like receptors, their ligands and signaling pathways. Toll-like receptors (TLRs) recognize pathogen-associated molecular patterns and/or synthetic compounds in a specific fashion. A TLR2/TLR1 dimer recognizes triacylated lipoproteins, and a TLR2/TRL6 dimer interacts with diacylated lipoproteins. TLR5 recognizes flagellin and TLR4 recognizes lipopolysaccharide (LPS). These TLRs are located on the cell membrane and are internalized upon ligand interaction. TLR3, TLR7, TLR8 and TLR9 are located on intracellular membranes of endosomes and lysosomes. TLR3 recognizes viral double-stranded RNA (dsRNA); TLR7 and TLR8 viral single-stranded RNA (ssRNA); and TLR9 bacterial and viral hypomethylated DNA (CpG motifs). TLR7 and TLR8 also bind to synthetic compounds (imidazoquinolones). All TLRs except TLR3 utilize myeloid differentiation factor 88 (MyD88) for signaling, while TLR2 and TLR4 also require Toll-interleukin-1 receptor domain-containing adaptor protein (TIRAP). MyD88 signaling via IL-1 receptor-associated kinase-4 (IRAK-4) and tumor necrosis factor receptor-activated factor-6 (TRAF-6) mostly results in activation of nuclear factor κB (NF-κB), ultimately inducing transcription of genes encoding immunomodulatory and proinflammatory molecules. TLR3 and TLR4 signal via TIR-domain-containing adapter-inducing interferon-β (TRIF). The TRIF pathway induces the production of interferons (IFNs) via interferon regulatory factor-3 (IRF3). Both the ligand and signaling pathway of TLR10 are still unknown. *Adapted from Miller LS. Toll-like receptors in skin. Adv Dermatol. 2008;24:71–87 and from McInturff JE, et al. The role of toll-like receptors in the pathogenesis and treatment of dermatological disease. J Invest Dermatol. 2005;125:1–8.*

Antimicrobial Peptides

To cope with an environment that is full of microorganisms, plants and invertebrates produce a variety of highly effective antimicrobial proteins. Human epithelia, including the epidermis, secrete such antimicrobial peptides as a mechanism of innate defense. The first antimicrobial peptide to be found in human skin (specifically from psoriatic scales) was human β-defensin-2 (hBD-2)[8]. A number of other antimicrobial peptides have subsequently been isolated (Table 4.1). In addition to antibacterial properties, some of these peptides possess antimycotic and likely antiviral activities. As demonstrated for psoriasin, which prevents *Escherichia coli* infection[9], these peptides may protect the skin from bacterial infections. Expression of antimicrobial peptides can be induced by bacteria, bacterial products or proinflammatory cytokines via TLRs and other mechanisms. Enhanced and decreased production of these peptides in psoriasis and atopic dermatitis, respectively, may explain why superinfections are so rare in the former disease and common in the latter[8,10]. However, others have found enhanced expression of antimicrobial peptides in atopic skin, which may reflect disruption of the epidermal barrier[11]. Ultraviolet (UV) B radiation has been shown to induce expression of antimicrobial peptides, potentially explaining the lack of UVB-related bacterial infections despite its immunosuppressive effects (see Ch. 86)[12].

Beta-defensins can also attract immature dendritic cells and memory T cells via the chemokine receptor (CCR)-6, illustrating another link between innate epithelial defense and adaptive immunity[13]. The antimicrobial peptide LL-37 (also known as cathelicidin antimicrobial peptide [CAMP]) mediates dendritic cell activation in psoriasis by binding self-DNA and forming structures that stimulate TLR9 and thereby induce IFN production[14].

Cytokines

Cytokines are a large, heterogeneous family of low-molecular-weight messenger substances that play a crucial role in intercellular communication. Cytokines can be secreted by almost any cell type, and they may act in an autocrine, paracrine or endocrine manner. Cytokines exert their biologic activities by binding to specific cell surface receptors[15]. Although the vast majority of cytokines occur in a soluble form, some can be membrane-bound, making the differentiation between cytokine and receptor difficult. Cytokines influence the proliferation, differentiation and activation of cells. Each cytokine exhibits multiple activities, a fact that complicates strict categorization.

Cytokines that are produced by leukocytes and exert effects preferentially on other white blood cells are called interleukins (IL). Colony-stimulating factors (CSFs) are mediators that induce differentiation and proliferation of hematopoietic progenitor cells, while IFNs interfere with viral replication. Cytokines that have chemoattractant activity are termed chemokines, and they play a crucial role in leukocyte migration. The main subgroups of chemokines are differentiated according to the position of two cysteine (C) residues compared with the other amino acid residues (X), CXC (α-chemokines) and CC (β-chemokines)[16]. Chemokines that recruit leukocytes are termed inflammatory chemokines, whereas those that regulate trafficking within lymphoid tissues are called lymphoid chemokines.

Early *innate* immune responses are dominated by cytokines with inflammatory (e.g. IL-1, IL-6, IL-18, tumor necrosis factor-α [TNF-α], inflammatory chemokines) and antiviral (e.g. IFN-α, IFN-β) capacities. Induction of *adaptive* immune responses is critically dependent on cytokines with immunomodulatory capacities (e.g. IL-2, IL-4, IL-12, IL-13, IL-17, IL-22, IL-23, IFN-γ). However, since most of these mediators exhibit multiple and sometimes overlapping activities, a strict separation into inflammatory and immunomodulatory cytokines is not possible. Due to structural similarities, some cytokines are grouped into families, e.g. the IL-6 family (IL-6, IL-11, oncostatin M, leukemia inhibitory factor [LIF]), the IL-10 family (IL-10, IL-19, IL-20, IL-22, IL-24, IL-26) and the IL-12 family (IL-12, IL-23, IL-27).

Macrophages and Neutrophils

Macrophages, phagocytic cells derived from blood-borne monocytes, carry receptors for carbohydrates that are usually *not* expressed on vertebrate cells (e.g. mannose). Through this mechanism, macrophages can discriminate between "foreign" and "self" molecules. Furthermore, macrophages possess receptors for antibodies and complement. Hence, microorganisms that are coated with antibodies and/or complement are more readily phagocytosed[17]. After phagocytosis, the microorganisms are exposed to a variety of toxic intracellular molecules, including

Table 4.1 Skin-derived antimicrobial peptides.

SKIN-DERIVED ANTIMICROBIAL PEPTIDES						
Name	**Size (kD)**	**Cellular source**	**Antimicrobial Activity**			**Inducibility (e.g. by bacteria, cytokines)**
			Bacteria		**Fungi**	
			Gram+	**Gram–**		
Antileukoprotease (ALP)	11.7	Keratinocytes Airway epithelia	++	++	++	–
Dermcidin (DCD)-1	4.7	Sweat glands	+++	+++	++	–
Human β-defensin (HBD)-2	4.3	Keratinocytes Airway epithelia Intestinal tract	(+)*	+++	++	+
HBD-3	5.2	Keratinocytes Airway epithelia	+++	+++	+++	+
HBD-4	6.0	Keratinocytes Airway epithelia (mRNA)	++	++	+	+
LL-37/ cathelicidin antimicrobial peptide (CAMP)/human cationic antimicrobial peptide 18 (hCAP18)	4.5	Keratinocytes Airway epithelia Urogenital tract Granulocytes	++	++	++	+
Lysozyme	14.7	Keratinocytes Airway epithelia	++	++	–	–
Psoriasin	11.4	Keratinocytes Sebocytes	(+)*	++†	(+)*	+
RNase 7	14.5	Keratinocytes Airway epithelia	+++	+++	+++	+

*In high concentrations.
†*E. coli*, others in high concentrations.

superoxide anions, hydroxyl radicals, hypochlorous acid, nitric oxide, lysozyme and antimicrobial cationic proteins. Macrophages can also present processed antigens to T and B cells. However, their T-cell stimulatory capacity is less effective than that of dendritic cells.

Activated macrophages release granulocyte colony-stimulating factor (G-CSF) and granulocyte–macrophage colony-stimulating factor (GM-CSF). These two cytokines induce the division of myeloid precursors in the bone marrow, releasing millions of neutrophils into the circulation. Under normal conditions, neutrophils circulate in the bloodstream, some rolling along the vascular endothelium[18]. To enter the site of an infection, neutrophils utilize a complex process that involves proinflammatory mediators, adhesion molecules, chemoattractants and chemokines (see Ch. 26). The recruited neutrophils phagocytose organisms and kill them within phagolysosomes by using oxygen-dependent and oxygen-independent mechanisms. The former, called the respiratory burst, involves the production of hydrogen peroxide, hydroxyl radicals and singlet oxygen. The oxygen-independent method utilizes highly toxic cationic proteins and enzymes, such as myeloperoxidase and lysozyme. Organisms that are coated with antibodies or complement components bind to Fc and complement receptors, respectively, on neutrophils (as well as macrophages) and are more effectively phagocytosed and killed.

Eosinophils

The major function of eosinophils is most likely to protect the host from infections by parasites, particularly nematodes. Infections with these organisms are associated with the production of antigen-specific IgE antibodies that coat the parasite. Via their low-affinity receptors (FcεRII, CD23), eosinophils bind to IgE antibodies and become activated. In contrast to macrophages and neutrophils, eosinophils are only weakly phagocytic. They harbor large granules that contain major basic protein, eosinophilic cationic protein, eosinophil peroxidase and eosinophil-derived neurotoxin (see Ch. 25). Upon activation, eosinophils release these toxic products, which can kill parasites, together with prostaglandins, leukotrienes and various cytokines[19]. Eosinophils also play an important role in the pathogenesis of allergic reactions.

Basophils and Mast Cells

Basophils (found in the blood) and mast cells (located within tissues) exhibit similar functional and morphologic characteristics[20]. At least two populations of mast cells exist, which can be differentiated by the enzymes they contain and by their tissue location. Mucosal mast cells contain only trypsin, while connective tissue mast cells contain both trypsin and chymotrypsin (see Ch. 118). In contrast to pulmonary, uterine and tonsillar mast cells, cutaneous mast cells express the receptor for C5a (CD88), which implies that triggering of mast cells through the anaphylatoxin C5a results in cutaneous, but not systemic, reactions[21]. Basophils and mast cells express high-affinity receptors for IgE (FcεRI) that avidly bind IgE (see Ch. 18).

When a specific antigen binds to mast cell-bound IgE, the FcεRI becomes activated, which leads to degranulation and release of preformed mediators, including histamine and serotonin. Other mediators such as prostaglandins, leukotrienes (B_4, C_4, D_4 and E_4), and platelet-activating factor are also released, and they enhance vascular permeability, bronchoconstriction and induction of an inflammatory response (see Ch. 18). Hence, basophils and mast cells play an important role in immediate-type allergic reactions such as urticaria and angioedema. There is also increasing evidence that mast cells are involved in contact hypersensitivity reactions.

Natural Killer Cells

The major task of natural killer (NK) cells is to eliminate virally infected or malignant cells[22]. NK cells can recognize their targets in two ways. Since they express Fc receptors that bind IgG (FcγRIII, CD16), NK cells can adhere to and kill target cells that are coated with IgG. This killing process is referred to as *antibody-dependent cellular cytotoxicity* (ADCC), the biological value of which remains unclear.

The second recognition system involves killer-activating and killer-inhibitory receptors. Killer-activating receptors recognize molecules that are expressed by nucleated cells. This provides a signal for the NK cell to kill the target cell by secretion of perforins, which make holes in the cell membrane through which granzymes are injected. Granzymes lyse target cells by activating the apoptotic caspase cascade. In addition, NK cells carry inhibitory receptors (KIR) on their surface

that recognize major histocompatibility complex (MHC) class I self-molecules. KIRs shut off the killer signal and thus prevent autolysis of the host. Tumor cells and viruses often down-regulate MHC class I molecules to escape recognition by cytotoxic T cells. Paradoxically, this mechanism renders "MHC class I-low" cells susceptible to recognition by NK cells and can even result in stimulation of specific cytotoxic T cells by dendritic cells.

ADAPTIVE IMMUNE RESPONSE

The characteristic features of an adaptive immune response are its specificity and enhancement with each successive antigen encounter owing to the accumulation of "memory"[2,23]. A crucial event during the generation of an adaptive immune response is antigen presentation.

Antigen-Presenting Cells

Various cells can present antigens, depending on how and where the antigen first encounters cells of the immune system. Interdigitating dendritic cells (DCs) located in the T-cell areas of the spleen and lymph nodes are the most effective antigen-presenting cells (APCs). Within the epidermis, Langerhans cells (LCs) are key APCs. Therefore, the following section will focus primarily on LCs.

Langerhans cells

In 1868, Paul Langerhans[24] first described Langerhans cells as DCs located within the epidermis[24]. Because of their dendritic shape, Langerhans thought that these cells might be of neural origin. More than 100 years later, it was shown that LCs are derived from bone marrow[25]. However, in the 1990s it was observed that LCs are intimately associated with nerve fibers and that nerves, through the release of neuropeptides such as calcitonin gene-related peptide (CGRP), can modulate LC function[26].

Morphology of Langerhans cells

LCs cannot be identified in routinely fixed and stained histologic sections; their recognition requires electron microscopy or histochemical analysis. Ultrastructurally, LCs have rod-shaped organelles termed Birbeck granules (Fig. 4.2). A Ca^{2+}-dependent lectin with mannose-binding specificity called langerin is associated with and responsible for the formation of Birbeck granules[27]. Birbeck granules are thought to result from the antigen-capture function of langerin, which routes antigen into these organelles and provides access to a non-classical antigen-processing pathway. However, langerin is not completely specific for LCs and can also be expressed by a certain type of dermal DC[28].

Histochemically, human LCs can be visualized by staining for adenosine triphosphatase (ATPase), a membrane-bound, formalin-resistant, sulfhydryl-dependent enzyme. In addition to langerin, antigenic moieties present on human LCs include the panhematopoietic marker CD45, MHC class II antigens (HLA-DR), CD1a, the S100 protein and vimentin. CD1a is a useful marker for LCs, since within the epidermis (normal or inflamed) it is exclusively expressed on LCs, whereas HLA-DR antigens are expressed on keratinocytes in inflamed skin (Table 4.2). Since CD1a does not exist in the murine system, staining for MHC class II antigens is often used for detection of murine LCs in non-perturbed skin[29] (Fig. 4.3). In addition, human LCs express the high-affinity IgE receptor (FcεRI)[30], which was initially thought to be exclusively expressed on mast cells and basophils.

The density of murine LCs is dependent on a variety of factors, including strain, age, sex and anatomic location. LCs are almost absent in the tail region, the pouch and the cornea. In humans, the numbers of LCs are reduced on the palms and soles, genitalia and buccal mucosa. In addition, the density of LCs decreases with age and is reduced in chronically UV-exposed skin[29].

PHENOTYPIC MARKERS OF RESIDENT VERSUS MIGRATING HUMAN LANGERHANS CELLS VERSUS HUMAN LANGERIN⁻ DERMAL DENDRITIC CELLS

	Resident LC	Migrating LC	Langerin⁻ dermal DC
Birbeck granules	++	++	–
Langerin (CD207)	+++	++	–
MHC class II	++	+++	++
CD45	+	+	+
CD1a	+++	+++	++
CD11c	+	+	+
CD11b	+/–	+/–	++
E-cadherin	++	+	–
Epithelial cell adhesion molecule (EpCAM)	+	+	–
CCR6	+	–	–
CCR7	–	+	+

Table 4.2 Phenotypic markers of resident versus migrating human Langerhans cells (LCs) versus human langerin⁻ dermal dendritic cells (DCs).
Adapted from ref. 28. CCR6, CC-chemokine receptor 6.

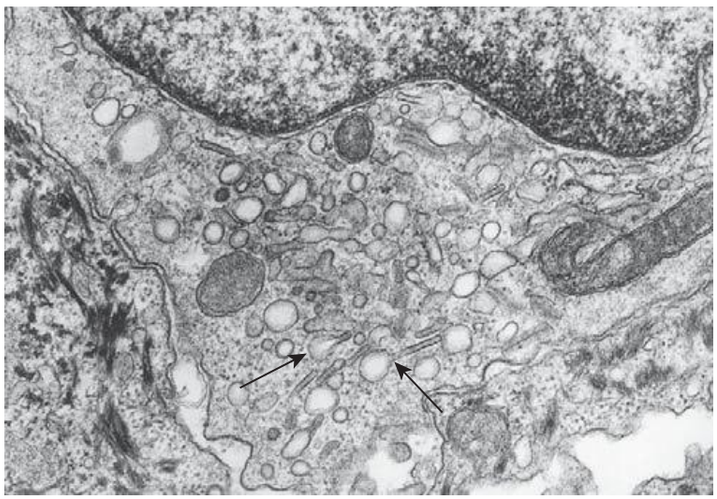


Fig. 4.2 Electron microscopic picture of a Langerhans cell. Arrows indicate the Birbeck granules, rod-shaped organelles specific for Langerhans cells. They are said to resemble tennis rackets. *Courtesy, N Romani, Department of Dermatology, University of Innsbruck.*

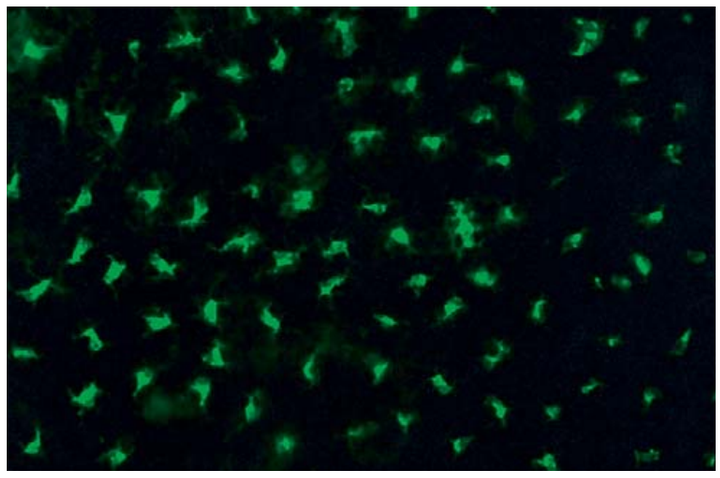


Fig. 4.3 Langerhans cells express MHC class II molecules. In a sheet preparation of murine epidermis, numerous Langerhans cells can be visualized by staining using an antibody against MHC class II molecules (Ia antigen). Note the dendritic shape of Langerhans cells, *Courtesy, N Romani, Department of Dermatology, University of Innsbruck.*

Ontogeny of Langerhans cells

Bone marrow chimera experiments showed that LCs are derived and constantly replenished from the bone marrow[25]. However, according to a recent hypothesis[28], murine LCs are derived from radioresistant hematopoietic precursor cells that reside in the skin during embryonic development (Fig. 4.4). The formation of LCs depends on transforming growth factor-β1 (TGF-β1) and macrophage colony-stimulating factor receptor (M-CSFR) ligands (M-CSF, IL-34), which are provided in an autocrine fashion. LCs that are depleted during the steady state or after minor injuries are repopulated locally, independent of circulating precursor cells. In lethally irradiated mice reconstituted with congenic bone marrow cells, half of the LCs are eliminated in the first week after transplantation, but LCs repopulate locally within 3 weeks. After UVB irradiation, which does not affect the dermis or the hair follicle, LC appear to repopulate from the hair follicle[28].

As noted above, langerin is not an exclusive marker for epidermal LCs but can also be expressed by dermal DCs (see Fig. 4.4)[28]. Langerin$^+$ dermal DCs differentiate from radiosensitive circulating precursor cells independently of TGF-β1 and M-CSFR ligands but dependent on CC-chemokine receptor 2 (CCR2), E-selectin and P-selectin. LCs that emigrate from the epidermis to the lymph nodes in a CCR7-dependent manner can also be detected in the dermis but can be distinguished from langerin$^+$ dermal DCs by the differential expression of CD11b, epithelial-cell adhesion molecule (EpCAM) and CD103 (see Fig. 4.4). Two additional types of APCs can be found in the dermis, langerin$^-$ dermal DCs and dermal macrophages with particular surface marker expression.

In humans, the situation is less clear than in mice, since only studies with tissue explants are available. Subtle differences in the surface marker expression of resident LCs, migrating LCs and langerin$^-$ dermal DCs have been described (see Table 4.2).

Other dendritic cells

Since LCs are confined to the epidermis, other DCs are responsible for antigen presentation in other sites. DCs are defined as professional APCs that display an extraordinary capacity to stimulate naive T cells and initiate a primary immune response[31]. This capacity was initially described for the interdigitating DCs in the spleen. It has become apparent that the DC system is very complex, and many questions still remain unanswered.

This complexity is based on the fact that DCs can arise from several types of progenitor cells, and a variety of functional phenotypes of DCs can also be generated from the same precursor cell[32]. In addition, differences exist between experimental systems used to study human and murine DCs. In the murine system, DCs are primarily obtained from the bone marrow or spleen, while human DCs are almost exclusively generated from peripheral blood. Furthermore, many markers/antibodies exist in the human but not the murine system, and vice versa. Whether each of the different types of DCs has a distinct immune function is still a matter of debate[32].

Concerning DC function, there is evidence in the murine system that spleen-derived CD8α$^+$ DCs induce T helper 1 (Th1) responses, while CD8α$^-$ DCs favor T helper 2 (Th2) responses[33]. In contrast, in the human system, lymphoid/plasmacytoid DCs were found to induce Th2 responses, and myeloid DCs generated Th1 reactions[34]. Consequently, myeloid DCs were referred to as DC1 and lymphoid/plasmacytoid DCs as DC2.

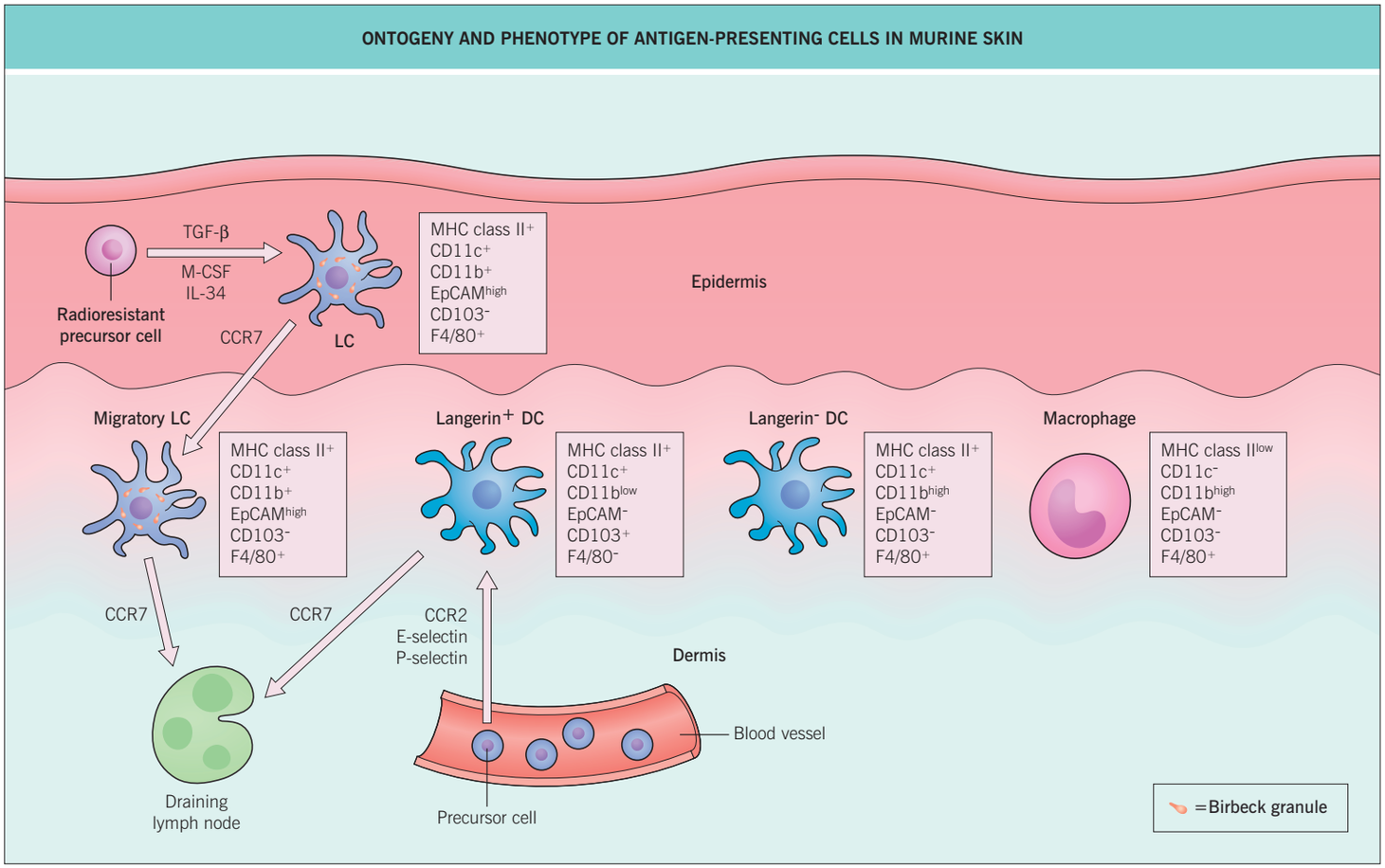


Fig. 4.4 Ontogeny and phenotype of antigen-presenting cells in murine skin. Langerhans cells (LCs) are derived from radioresistant hematopoietic precursor cells in the skin in the presence of transforming growth factor-β (TGF-β), macrophage colony-stimulating factor (M-CSF) and interleukin (IL)-34. LCs migrate to the draining lymph nodes in a CC-chemokine receptor 7 (CCR7)-dependent fashion. The dermis harbors dermal langerin$^+$ dendritic cells (DCs), which differentiate from radiosensitive circulating precursor cells in a CCR2-, E-selectin- and P-selectin-dependent manner. LCs on the way to the lymph nodes can be distinguished from dermal langerin$^+$ DCs by the differential expression of CD11b, epithelial cell adhesion molecule (EpCAM) and CD103. Two additional types of APCs are present in the dermis, dermal langerin$^-$ DCs and dermal macrophages exhibiting peculiar surface marker expression. *Adapted from Merad M, et al. Origin, homeostasis and function of Langerhans cells and other langerin expressing dendritic cells. Nat Rev Immunol. 2008;8:935–47.*

However, the type of immune response that is generated also critically depends on the state of maturation of the stimulating DC at the time of antigen presentation. For the induction of Th1 responses, the presence of IL-12 is crucial. DCs tend to produce IL-12 directly after an activating step in their maturation, driving T cells into a Th1 phenotype if they meet the DCs at this stage[35]. At later time points, the production of IL-12 decreases, thereby favoring the development of a Th2 response. This process is also heavily influenced by the innate immune system (e.g. stimulation by TLRs; see above).

Taken together, the parameters that are responsible for the type of Th cell differentiation that is induced by DCs remain to be fully defined. On the other hand, there is agreement that immature DCs induce tolerance due to incomplete T-cell activation, resulting in T cells of the regulatory type that suppress immune responses[36].

Antigen presentation

Antigen presentation cells: activation and migration

To initiate sensitization, antigens must be presented to T cells by APCs. For many years, LCs were thought to be the most important APC in the skin. It was found that contact sensitization could not be induced in areas of skin that were naturally devoid of LCs (e.g. the murine tail) or in which LCs had been depleted (e.g. by UV radiation)[37]. However, transgenic mice in which LCs are completely depleted via the diphtheria toxin receptor technique (i.e. short-term, inducible ablation) demonstrate variably diminished but not completely abrogated sensitization responses[38]; in one such model, the sensitization response was completely normal[39]. In a different knockout mouse model characterized by constitutive and durable absence of epidermal LCs[40], an enhanced sensitization response was actually observed, suggesting that LCs may have regulatory functions. This "LC paradigm" proposes that LCs may be tolerogenic when they present antigens under steady-state noninflammatory conditions, but sensitizing upon stimulation by inflammatory mediators. Which of these activities is the main function of LCs remains to be determined, and there is accumulating evidence that dermal DCs are equally if not even more important than LCs in presenting antigens.

Antigen presentation to lymphocytes takes place in the regional lymph nodes, while cutaneous APCs actively take up antigens in the skin. In the presence of inflammation, the APCs become activated and leave the skin, migrating to the draining lymph nodes. During emigration, they change their phenotypic and functional behavior and develop into mature DCs. For example, molecules involved in antigen uptake and processing (Birbeck granules, Fc receptors) are down-regulated on activated LCs[41]. In addition, expression of E-cadherin, which mediates the attachment of LCs to neighboring keratinocytes, is reduced, thereby enabling the emigration of LCs.

CD44, a hyaluronic acid receptor involved in the tissue homing of leukocytes, is upregulated on activated LCs. The splice variant CD44v6 supports binding of LCs to T-cell-rich areas of lymph nodes[42]. Furthermore, the integrins $\alpha_6\beta_1$ and $\alpha_6\beta_4$, which exhibit affinity to the basement membrane zone, are induced on the surface of emigrating LCs[43]. The release of proteolytic enzymes like matrix metalloproteinase-9 (type IV collagenase) may enable their penetration through the basement membrane. Their dendricity becomes more pronounced, and surface molecules necessary for antigen presentation and T-cell priming are upregulated (e.g. MHC class I, MHC class II, CD40, CD54, CD58, CD80, CD86). At this stage, LCs emigrating from the epidermis are almost indistinguishable from DCs obtained from lymphoid organs[41]. The same phenotypic and functional changes may occur in other APCs of the skin that have important roles in antigen presentation.

Antigen presentation to T cells

In contrast to B cells, T cells cannot recognize soluble protein antigens per se; instead, the T-cell receptor (TCR) recognizes antigen-derived peptides bound to MHC locus-encoded molecules expressed on APCs. $CD4^+$ T cells recognize antigens in association with MHC class II molecules, while $CD8^+$ T cells, the majority of which become cytotoxic, recognize antigens in association with MHC class I molecules[23] (Fig. 4.5).

Two pathways exist by which antigens can be "loaded" onto MHC molecules. If the antigen has been produced *endogenously* within the cell (e.g. viral or tumor proteins), it is complexed with *MHC class I* molecules through intracellular processing pathways (Fig. 4.6)[44]. The proteasome degrades cytosolic antigens produced by the cell. The resulting peptides (which consist of 8 to 12 amino acid residues) are imported into the endoplasmic reticulum (ER) in a TAP (transporter associated with antigen processing)-dependent manner and loaded onto MHC class I molecules[45]. After binding to the MHC class I–β_2 microglobulin complex, these peptides are transported to the cell

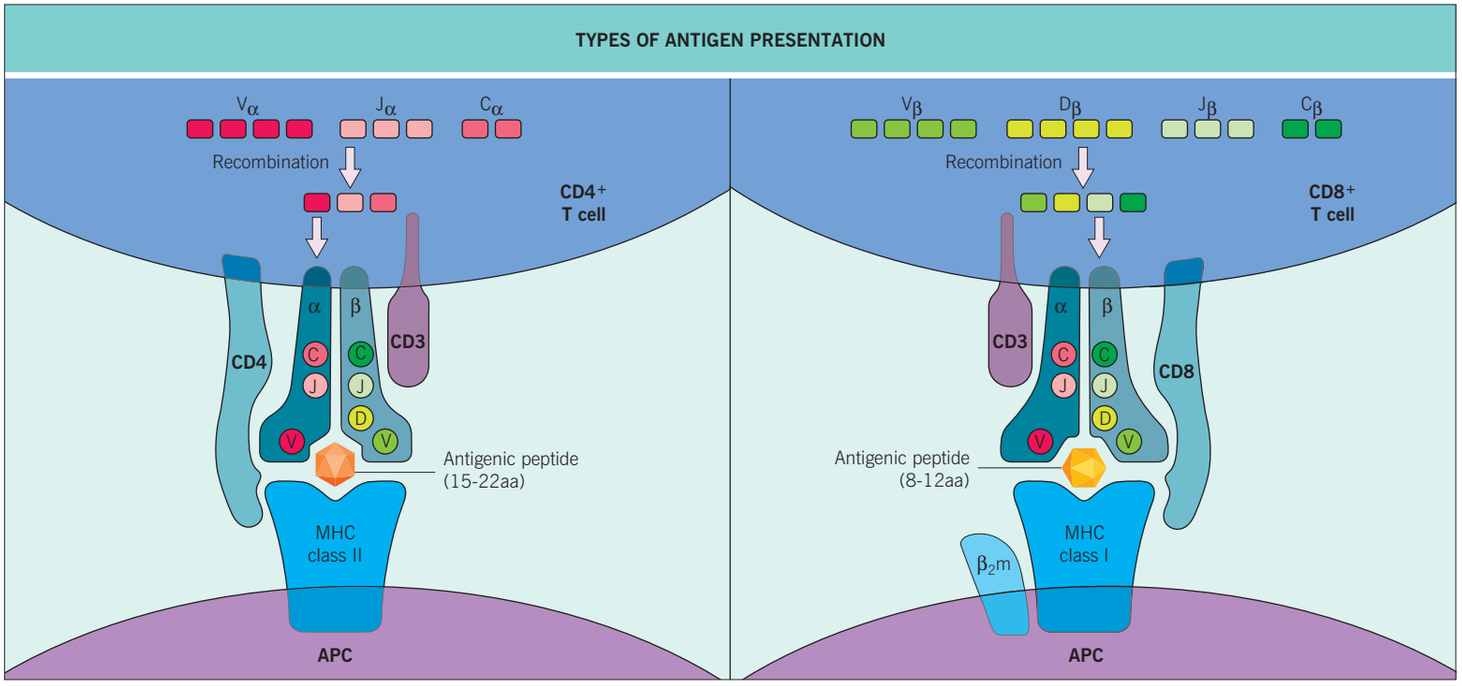


Fig. 4.5 Types of antigen presentation. Antigens are presented by antigen-presenting cells to the T-cell receptor of $CD4^+$ or $CD8^+$ T cells in association with either MHC class II or MHC class I molecules. The diversity of the T-cell receptors is generated by gene rearrangement. For reasons of clarity, the simplified gene rearrangement of the α-chain is shown only in the $CD4^+$ T cell, that of the β-chain in the $CD8^+$ T cell. aa, amino acids; β_2m, β_2-microglobulin; V, variable; D, diversity; J, joining; C, constant. *Adapted from Modlin RL. Lymphocytes. In: Freedberg IM, Eisen AZ, Wolf K, et al. (eds). Fitzpatrick's Dermatology in General Medicine, vol. 1. New York: McGraw-Hill, 1999;32:400–5.*

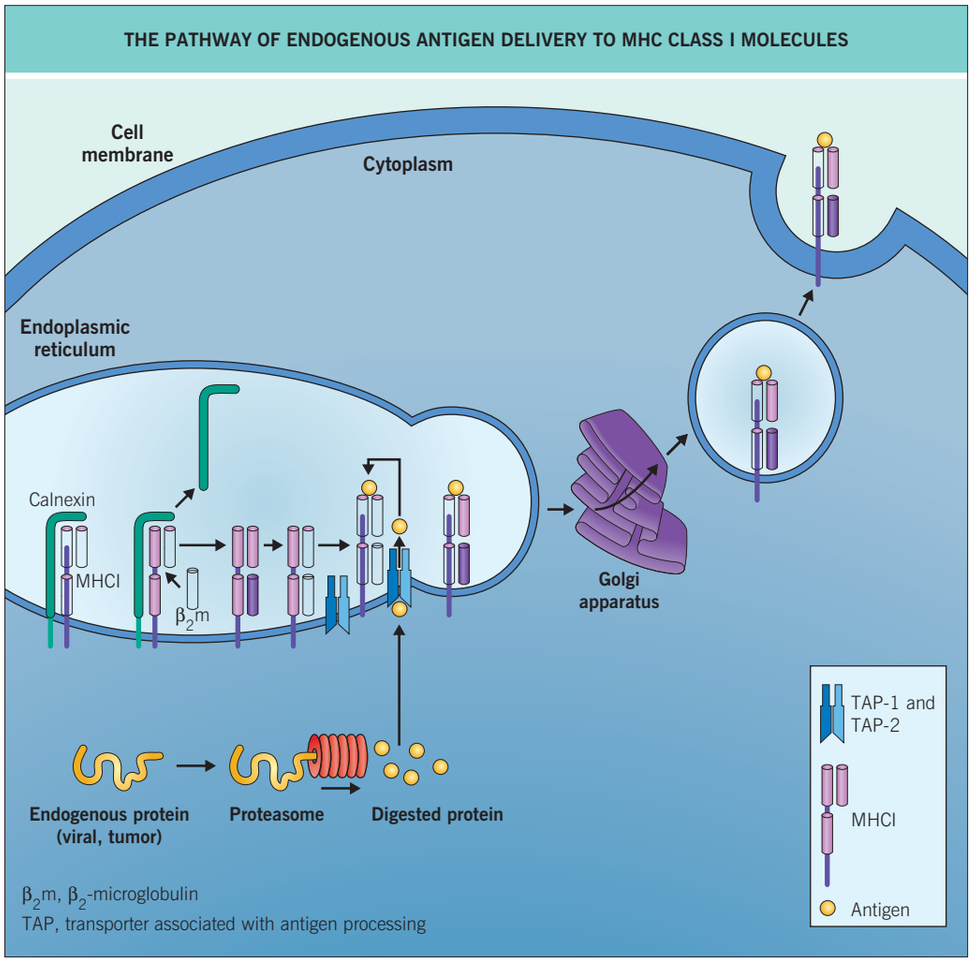


Fig. 4.6 The pathway of endogenous antigen delivery to class I MHC molecules. Newly synthesized MHC class I molecules are stabilized by calnexin. When β_2-microglobulin (β_2m) binds to the complex, calnexin dissociates. This complex associates with the TAP (transporter associated with antigen processing) protein waiting for a suitable peptide. Endogenous antigens are degraded by the proteasome and transported via TAP into the endoplasmic reticulum (ER), where they bind to the MHC class I/β_2m complex. Finally, the peptide/MHC complex is transported through the Golgi apparatus to the cell surface. Not pictured is a possible alternate pathway in which exogenous proteins are phagocytosed and the phagosome fuses to the ER. The proteins are then retransported out of the ER into the cytoplasm and degraded by proteasomes. The degraded peptides can now enter the normal pathway via the TAP protein. *Adapted from Parkin J, Cohen B. An overview of the immune system. Lancet. 2001;357:1777–89. With permission from Elsevier.*

surface via the Golgi apparatus. Alternative pathways by which exogenous proteins are phagocytosed and the phagosome fuses to the ER may also exist. The proteins are subsequently retransported out of the ER into the cytoplasm (by an as yet unclear mechanism) and then degraded by the proteasome. The degraded peptides can now enter the pathway that is normally used for endogenous proteins via the TAP protein. As the vast majority of nucleated cells express MHC class I molecules, many cell types can serve as APCs for MHC class I-restricted antigen presentation in a secondary immune response.

In contrast, MHC class II-dependent antigen presentation is critically dependent on DCs, B cells and monocytes/macrophages. *MHC class II*-associated antigen presentation targets primarily *exogenous* (Fig. 4.7) and less frequently endogenous antigens[46]. Exogenous antigens are taken up via macro- or micropinocytosis or by receptor-mediated endocytosis. One example of the latter is the DEC-205 receptor (CD205), which guides antigens into endocytic vesicles that reside deeper inside the cell and contain MHC class II molecules. As a consequence of this unique intracellular targeting, antigens endocytosed by the DEC-205 receptor stimulate respective T cells up to 500-fold greater than antigens taken up by pinocytosis or other receptors. Protein degradation eventually takes place in the endo-/lysosomes, yielding peptides with a typical length of 15 to 22 amino acid residues. These peptide fragments enter specialized endosomal compartments containing MHC class II molecules that are generated in the ER[47].

Newly synthesized MHC class II molecules are associated with an invariant chain, which inhibits dissociation of empty MHC class II molecules and transports the MHC class II complex from the ER to the specialized endosomal compartments where the molecules can interact with antigen peptide fragments (see Fig. 4.7). In this compartment, the invariant chain is cleaved by proteases, leaving a small fragment called CLIP (class II-associated invariant peptide) that binds to the class II molecule. Upon interaction with the antigenic peptides, the CLIP fragment is released from the complex. The MHC class II molecule with the bound antigen peptide is subsequently expressed on the cell surface, allowing antigen recognition by T cells carrying the appropriate TCR.

Classically, MHC class I molecules present self- or pathogen-derived antigens that are synthesized within the cell to $CD8^+$ T cells (see Fig. 4.6), whereas exogenous antigens derived via endocytic uptake are loaded onto MHC class II molecules for presentation to $CD4^+$ T cells (see Fig. 4.7). However, it has become evident that some DCs are also able to process exogenous antigens into the MHC class I pathway for presentation to $CD8^+$ T cells. This mechanism, referred to as cross-presentation[48], allows DCs to induce either tolerance (to self-antigens) or immunity (to exogenous pathogens).

T Cells

T-cell precursors continuously migrate from the bone marrow to the thymus, where T cells develop[49]. In the thymus, T cells bearing the α/β TCR are subjected to a complex selection process. In contrast to antibodies, which represent the antigen receptor on B cells and recognize antigens in their naive form, the α/β TCR recognizes only short peptide fragments that are generated during antigen processing within APCs (see above). These processed antigens are presented to the TCR by MHC molecules on the cell surface. The amino acid sequences recognized by the TCR include those from both the MHC molecule and the antigenic peptide. Consequently, the TCR recognizes a combination of "self" MHC molecules (which are highly polymorphic) and "foreign" peptides. T cells that recognize "self" MHC molecules but not "self" peptides are useful for immune defense but do not lead to undesirable autoimmunity. This requirement is achieved by a complex process that involves both positive and negative selection within the thymus.

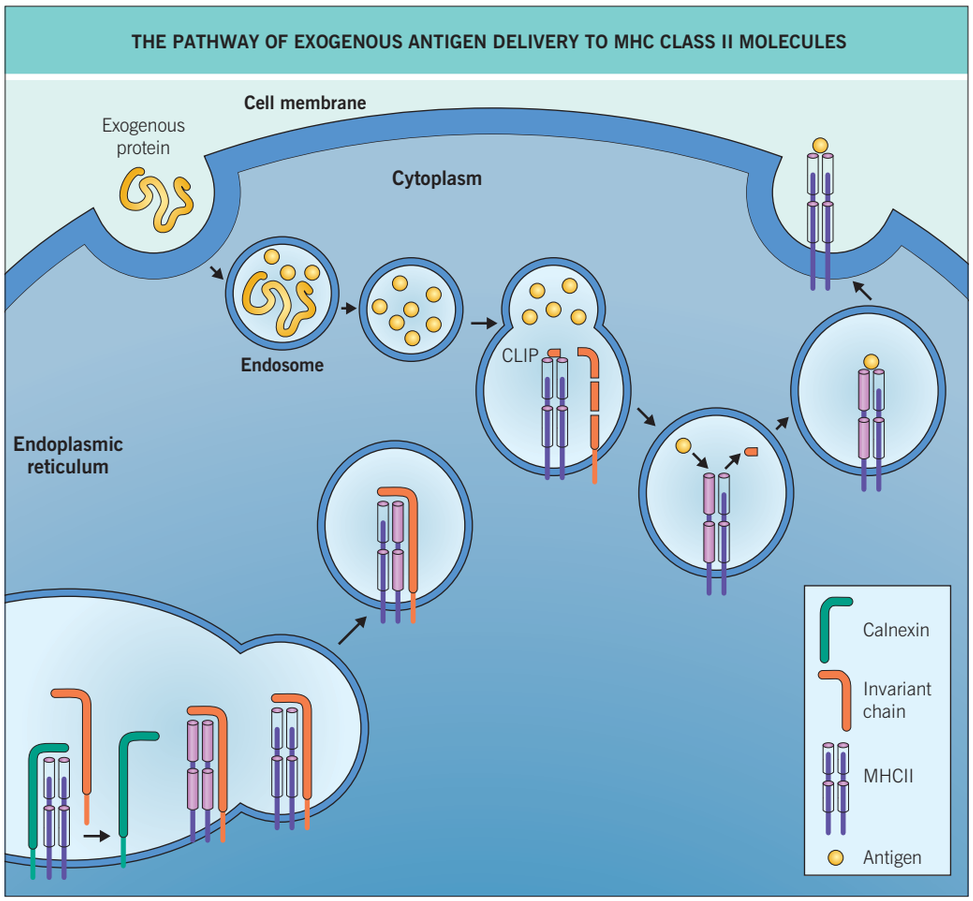


Fig. 4.7 The pathway of exogenous antigen delivery to class II MHC molecules. Exogenous antigens are taken up into the cell by endosomes. The protein is cleaved into peptides within the endosomes, which become increasingly acidic. In the endoplasmic reticulum (ER), newly synthesized MHC class II molecules bind to an invariant chain, which inhibits their disassociation while empty. During this assembly, the complex is stabilized by calnexin. The invariant chain transports the MHC class II molecule from the ER (via the Golgi apparatus) into the endosomal compartment, where the MHC class II complex meets the peptides. The invariant chain is cleaved, leaving a small fragment (CLIP) in the groove of the MHC class II molecule. Finally, CLIP is replaced by the antigenic peptide. The complex is transported to the cell membrane and expressed on the cell surface. CLIP, class II-associated invariant peptide.
Adapted from Parkin J, Cohen B. An overview of the immune system. Lancet. 2001;357:1777–89. With permission from Elsevier.

T-cell development

Developing T cells within the cortex of the thymus engage MHC complexes on thymic DCs. When the T cells are able to recognize these MHC molecules via their TCR, they receive a survival signal (*positive selection*). Otherwise, the T cells undergo apoptotic cell death[50]. At this stage, more than 95% of the developing T cells die in the thymus because they are not selected due to their uselessness (i.e. inability to recognize "self" MHC molecules)[51]. In addition, T cells that express a TCR with a very high affinity for the complex of a "self" peptide plus a "self" MHC molecule are eliminated by apoptosis, since they are potentially harmful. This process, called *negative selection*, takes place in the thymic medulla and involves DCs and macrophages that process and present a spectrum of "self" antigens. Positive and negative selection allow the survival of just those T cells that recognize foreign (but not "self") peptides in the context of "self" MHC molecules and thus are useful for immune defense without causing auto-attack[52].

During thymic education, a variety of surface molecules are switched on and off. Components of the CD3/TCR complex, together with CD4 or CD8 molecules, have roles in this process. In general, $CD4^+$ T cells function as helper T cells and recognize antigens presented by MHC class II molecules, whereas $CD8^+$ T cells are usually cytotoxic and recognize antigens in association with MHC class I molecules (see Fig. 4.5). In their early stage of development within the thymus, T cells express both CD4 and CD8[53]. Upon expression of an appropriate TCR, these immature T cells exhibit the capacity to recognize antigenic peptides associated with either MHC class I or MHC class II molecules, since they still express both CD4 and CD8 (double-positive stage). During the subsequent process of maturation, one of these surface markers is lost, resulting in single-positive T cells expressing either CD4 or CD8. These cells are specialized for peptides presented only by MHC class II or MHC class I molecules, respectively.

T-cell receptor

One major feature of an adaptive immune response is the recognition of specific antigens. This is achieved either by the TCR during a T-cell-mediated response or by antibodies during a B-cell response. TCRs are transmembrane molecules consisting of α/β (vast majority of T cells) or γ/δ (<10% of T cells) heterodimers[54]. Antigen recognition by γ/δ T cells appears to be independent of classic MHC molecules, instead utilizing other MHC molecules (e.g. CD1) that preferentially present certain lipid and glycolipid antigens[55].

T-cell receptor diversity

An amazing feature of the immune system is that it provides specific receptors for every possible antigen. B cells are capable of producing approximately 10^{15} different antibody variable regions, and T cells generate a comparable number of TCR variable regions. Remarkably, these numerous proteins are encoded by fewer than 400 genes. This tremendous diversity is created via a unique recombination process that cuts, splices and modifies genes in the variable region[56].

Four segments of genes are involved in TCR formation: the variable (V), diversity (D), joining (J) and constant (C) regions (see Fig. 4.5). In contrast to the TCRβ and TCRδ loci (both on chromosome 7), the TCRα and TCRγ loci (both on chromosome 14) do not contain D segments. The segments are cut out by nucleases and spliced together by ligases, ultimately forming the final gene sequence that encodes the receptor molecule. The tremendous diversity is explained by the multiplicity of all these regions within the genome (e.g. ~70–80 V genes and ~60 J genes for the TCRα alone), but only one of each type is used for a particular TCR.

Each lymphocyte utilizes a different combination of V, D and J gene segments to form the genetic code of its antigen receptor. Any one of the genes can join with any other one to form the final VDJ region, thereby creating tremendous diversity. In addition, the recombination process is subject to inaccuracies during splicing, which cause slight variations at the VDJ junctions, and additional nucleotides can be inserted by the enzyme deoxyribonucleotidyl-transferase at the spliced regions. These two events increase the diversity even further. Of note, only a tiny minority of these cells will become functional over a lifetime, with the vast majority dying without ever having met their antigen.

Defects in the *r*ecombination-*a*ctivating *g*enes *RAG1* and *RAG2*[57], which encode two of the enzymes that mediate the recombination of variable-region genes in both B cells and T cells, cause a form of severe combined immunodeficiency (see Ch. 60). Affected individuals are unable to produce lymphocytes bearing functional antigen receptors[58].

T-cell receptor signaling

TCRs are associated with the CD3 complex, which transmits signals upon antigen binding. CD3 consists of CD3γ, CD3δ, two molecules of CD3ε and a disulfide-linked CD3ξ homodimer[59]. Upon binding to the peptide–MHC complexes, TCRs become cross-linked. Aggregation of the TCRs causes phosphorylation of tyrosines in the cytoplasmic tails of the CD3 complex, which contain *i*mmunoreceptor *t*yrosine-based *a*ctivation *m*otifs (ITAMs). Phosphorylation involves kinases such as $p56^{lck}$ (which also binds to the cytoplasmic tails of CD4 and CD8), $p59^{fyn}$ and ZAP-70[60] (Fig. 4.8). These events ultimately lead to the transcriptional activation of genes that encode cytokines and induce cellular proliferation and differentiation.

Costimulatory signals

Signaling through the TCR complex alone does not suffice to activate T cells. The presence of costimulatory signals is needed for T cells to undergo antigen-specific clonal expansion[61]. Hence, development of a productive T-cell immune response requires exposure of these cells to at least two types of stimuli. The *first signal* is the interaction of the TCR with peptide–MHC complexes presented by APCs, which determines the specificity of the immune response. The *second signal* involves surface molecules and cytokines, which determine the clonal expansion of specific T cells and their differentiation into effector and memory cells. Without these costimuli, signaling by the antigen receptors alone will either cause anergy (non-reactivity) or apoptotic cell death (Fig. 4.9). The major receptors and ligands expressed on APCs and T cells that play a role in activation are listed in Table 4.3.

The best-investigated costimulators for T cells are two members of the B7 family, B7-1 (CD80) and B7-2 (CD86)[62]. Both molecules are induced on immature, resting APCs by various TLR ligands or by cytokines (e.g. TNF-α, IL-1). The CD28 receptor on T cells recognizes the B7 molecules and delivers activating signals, including the expression of antiapoptotic genes and the production of cytokines such as IL-2. Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4 [CD152]) also binds to the B7 molecules, with even higher avidity. Unlike CD28 binding, cross-linking of CTLA-4 to B7 down-regulates IL-2 production and cell cycle progression, whereas blockade of CTLA-4 signaling prolongs T-cell activation. Hence, CTLA-4 is regarded as a T-cell-associated co-receptor with negative regulatory effects[63].

COSTIMULATORY MOLECULES AND THEIR LIGANDS*

Receptor molecule	Expression†	Co-receptor molecule	Expression†
CD80 (B7-1)	APC	CD28, CD152 (CTLA-4)	T
CD86 (B7-2)	APC	CD28, CD152 (CTLA-4)	T
CD275 (ICOS-L, B7H2, B7h, B7RP1)	APC	CD278 (ICOS)	T
CD274 (PDL1, B7H1)	APC	CD279 (PD1)	T, B
CD273 (PDL2, B7DC)	APC	CD279 (PD1)	T, B
CD40	APC, B	CD154 (CD40L)	T
CD134 (OX40)	T	CD252 (OX40L)	APC, B
CD27	APC, T	CD70 (CD27L)	T, B
CDw137 (4-1BB)	T, B	4-1BBL	APC, B
CD265 (RANK)	APC	CD254 (RANKL, TRANCE)	APC, T
CD30	T, B	CD153 (CD30L)	T, B, APC
CD58 (LFA-3)	APC	CD2	T

*Only important costimulatory molecules and those with known ligands are included.
†Expression refers only to T cells (T), B cells (B) and antigen-presenting cells (APC) including DC and LC.

B7 family | TNF receptor family | adhesion molecules

Table 4.3 Costimulatory molecules and their ligands. APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte-associated antigen-4; ICOS, inducible costimulator; LFA-3, lymphocyte function antigen-3; PDL1, programmed death ligand 1; TNF, tumor necrosis factor.

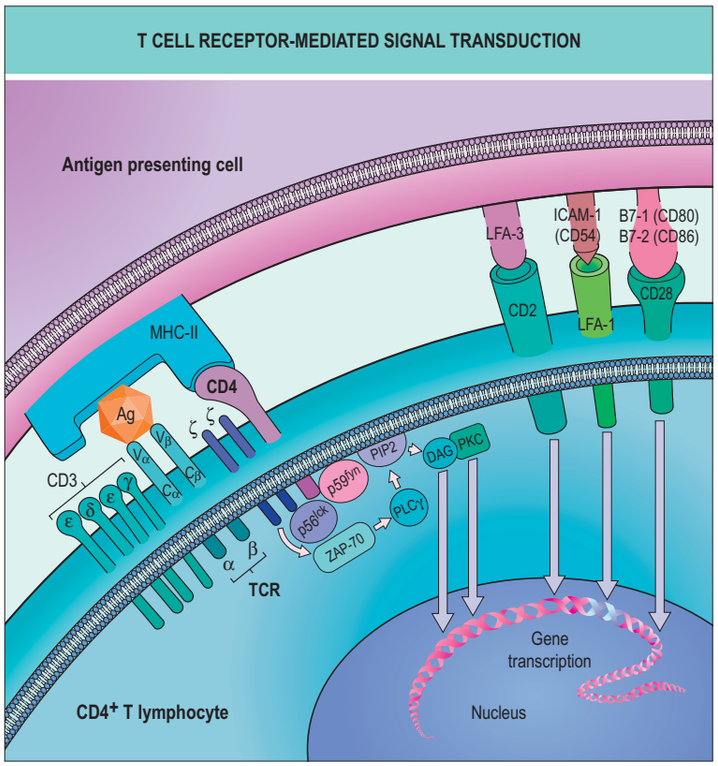


Fig. 4.8 T-cell receptor-mediated signal transduction. Activation of the T-cell receptor by presentation of the appropriate antigen by antigen-presenting cells in association with MHC molecules induces a complex signal transduction cascade. The T-cell receptor-associated signal transduction is primarily mediated by the CD3 complex and the ξ chain. Upon activation, the cytoplasmic tails of these molecules become phosphorylated by protein kinases ($p56^{lck}$, $p59^{fyn}$, ZAP70). This causes downstream signaling which ultimately leads to transcriptional activation of particular genes. Additional stimuli are provided by the signaling of costimulatory molecules (CD2, ICAM-1, CD28). DAG, diacylglycerol; PIP2, phosphatidylinositol 4,5-bisphosphate; PKC, protein kinase C; PLC, phospholipase C.

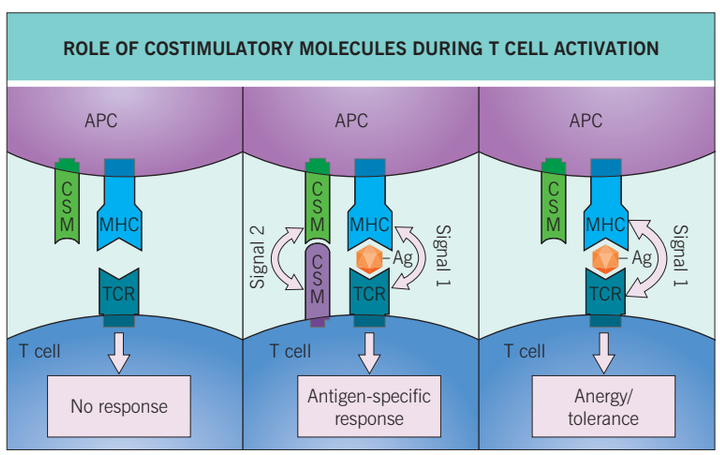


Fig. 4.9 Role of costimulatory molecules during T-cell activation. Presentation of the antigen by antigen-presenting cells to the T-cell receptor in association with MHC molecules delivers the first signal necessary for T-cell activation. The second signal is provided by the interaction of costimulatory molecules present on antigen-presenting cells and T cells. An antigen-specific response is only induced when signal 1 and signal 2 are provided. Presentation of the antigen in the absence of signal 2 does not lead to an antigen-specific response but induces anergy and tolerance, respectively. APC, antigen-presenting cell; CSM, costimulatory molecule; MHC, major histocompatibility complex; TCR, T-cell receptor.

Cytokines, especially inflammatory mediators like IL-1, IL-6 and TNF-α, also provide costimulatory signals by themselves and, in addition, upregulate costimulatory molecules. Hence, a T cell is much more likely to be activated if it meets its specific antigen via an APC that has been exposed to an inflammatory environment.

Clonal expansion

If a T cell recognizes its specific antigen peptide in association with the appropriate MHC molecules and becomes activated by costimulatory signals, division and clonal expansion take place. Memory T cells have a much longer lifespan than effector cells and are characterized by the expression of the surface molecule CD45RO, while naive T cells express CD45RA. Two functionally distinct subsets of human memory T cells have been described. *CCR7⁺ memory T cells* (*central memory T cells* [*TCM*]) express lymph node homing receptors and thus stay in the lymph nodes. These cells lack immediate effector function; however, they efficiently stimulate DCs to produce IL-12 and can differentiate into CCR7⁻ effector cells upon secondary stimulation. In contrast, *CCR7− memory T cells* (*effector memory T cells* [*TEM*]) express receptors for migration to inflamed tissues and have immediate effector functions[64].

Memory T cells react in a more rapid fashion upon re-exposure to their specific antigen. The vast majority of these progenitor cells represent effector cells with upregulated receptors that enable them to leave the lymphoid tissue. Organ-specific adhesion molecules guide these cells to various locations, including the skin[18,64]. Most of the T cells found in human skin reside in the dermis, with a minority in the epidermis (2% to 3% of all CD3⁺ cells present in normal human skin). The majority of human epidermal T cells express the α/β TCR and are either CD8- or CD4-positive. In addition, skin-homing T cells express CD2, CD5 and the skin-homing receptor cutaneous lymphocyte antigen (CLA), and they are of the memory phenotype CD45RO⁺/CD45RA⁻[65].

Effector functions of T cells

Two major types of effector T cells have been identified: T helper (Th) cells, which are CD4⁺, and cytotoxic T (Tc) cells, which are CD8⁺. CD4⁺ Th cells recognize foreign antigen peptides bound to MHC class II and activate/modulate important components of the cell-mediated immune response, mainly through cytokine production. One essential function of CD4⁺ Th cells is the activation of B cells. CD8⁺ Tc cells are crucial to antiviral and antitumor responses[66].

T helper cells

CD4⁺ Th cells recognize "their" antigenic peptides in association with MHC class II molecules. Based primarily on differences in their cytokine secretion patterns, several types of Th cells have been described[67]. Naive precursor Th cells only produce IL-2. Subsequently, preactivated precursor cells, called Th0, can release a wide variety of cytokines (e.g. IL-2, IFN-γ, TNF-β, IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-13, GM-CSF, TNF-α). As they develop into Th1, Th2 or Th17 cells, the cytokine secretion pattern becomes more restricted and specific (see below), leading to generation of different responses. The recently described Th22 cells may represent a separate type. Morphologically, the cells in the various Th subsets are almost indistinguishable, although surface differences (especially in chemokine receptors) have been described[68].

Th1 cells: Typical Th1 cytokines are IFN-γ, TNF-β, and IL-2. Production of IL-2 by Th1 cells induces proliferation of CD4⁺ cells in an autocrine manner and affects the cytokine differentiation pattern; however, it also stimulates CD8⁺ T-cell division and cytotoxicity, thereby providing "help" for CD8⁺ Tc cells.

The major Th1-derived cytokine is IFN-γ, which activates macrophages to kill intracellular pathogens (e.g. mycobacteria, fungi, protozoa) and stimulates NK-cell cytotoxicity. Therefore, Th1 cytokines preferentially induce a cell-mediated inflammatory response, such as the granulomatous lesions of tuberculosis or leprosy. Macrophages stimulated by IFN-γ release huge amounts of IL-12, the major cytokine that drives Th0 cells towards a Th1 phenotype (Fig. 4.10)[69]. The second most important cytokine in promoting Th1 differentiation is IFN-α.

A Th1 response is crucial for the host to control the replication of intracellular pathogens. In addition, Th1 cells promote the isotype switch of B cells to produce complement-binding antibodies. Augmenting the antitumor response of Th1 cells represents a potential target of cancer immunotherapy. On the other hand, Th1 cells contribute to the pathogenesis of autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, allergic contact dermatitis and, perhaps, psoriasis.

Th2 cells: Th2 cells produce primarily IL-4, IL-5, IL-6 and IL-10. These cytokines favor production of non-complement-binding antibodies. IL-4 switches B cells to produce IgE, and IL-5 promotes

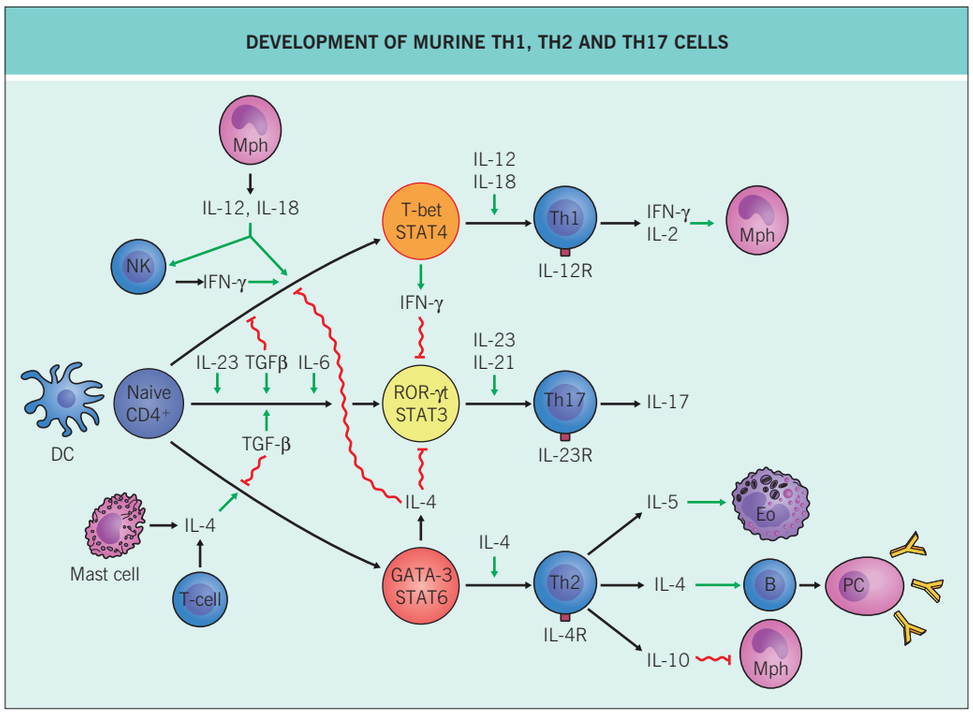


Fig. 4.10 Development of murine Th1, Th2 and Th17 cells. Th1, Th2 and Th17 cells differentiate under the influence of cytokines, which are secreted by various bystander cells and can act in a stimulatory (→) and inhibitory (⇝) fashion. The interaction of dendritic cells (DC) with naive CD4⁺ T cells in the various cytokine milieus induces certain transcription factors in the T cells (T-bet, STAT4, ROR-γt, STAT3, GATA3, STAT6), which direct differentiation. Th1 cells are crucial for T-cell-mediated immunity, Th2 cells support the development of humoral immunity, and Th17 cells are involved in chronic inflammatory and autoimmune reactions. Eo, eosinophil; IL, interleukin; IFN-γ, interferon-γ; MC, mast cell; Mph, macrophage; NK, natural killer cell; PC, plasma cell; ROR-γt, *r*etinoid acid receptor-related *o*rphan *r*eceptor-γt; STAT3/4/6, *s*ignal *t*ransducer and *a*ctivator of *t*ranscription 3/4/6; TGF-β, transforming growth factor-β.
Adapted from Miossec P, et al. Interleukin-17 and type 17 helper T cells. N Engl J Med. 2009;361:888–98.

the growth of eosinophils. Therefore, Th2 responses are often associated with allergic diseases. Comparable to the role of IL-12 in inducing Th1 responses, IL-4 is the key cytokine in driving Th2 responses. In addition, IL-4 suppresses Th1 and Th17 differentiation (see Fig. 4.10). However, IL-4 seems to exert opposing effects on $CD4^+$ T cells and DCs, since it can stimulate DCs to produce IL-12 and thus paradoxically promote Th1 development[70]. IL-10, another characteristic Th2 cytokine, also inhibits the development of a Th1 response.

Immune responses generally tend to drift into a Th1, Th2 or Th17 (see below) pattern. The Th1/Th2 decision is crucial for effective immunity and thus is regulated by a variety of factors[71]. The cytokine profile and balance induced by the antigen is critical. For example, IL-12 is a potent priming stimulus for $CD4^+$ T cells to produce IFN-γ and, thus, for Th1 cellular differentiation[72]. Many TLR signals and infections are strong inducers of IL-12 and therefore favor a Th1 response. Other TLR signals to DCs and early production of IL-4 favor the generation of Th2 cells. Additional factors that influence the Th1/Th2 decision include the dose of the antigen, the APCs involved[32], the cytokines secreted (by APCs and bystander cells), the genetic background of the host, and the presence of costimulatory molecules. Of note, many immune responses are not strongly polarized in the Th1 or Th2 direction.

Th1 and Th2 responses differ greatly in their protective roles, and the same applies with regard to their contribution to immunopathology. Acute allograft rejection, allergic contact dermatitis and multiple sclerosis are characterized by dominant Th1 responses, and Th1 clones have been isolated from patients suffering from these diseases. On the other hand, T-cell clones isolated from patients suffering from atopic dermatitis or systemic lupus erythematosus typically exhibit a Th2 profile.

Th3 cells: Th3 cells are a poorly characterized type of $CD4^+$ Th cell that primarily secretes TGF-β, provides help for IgA production, and has suppressive properties against both Th1 and Th2 cells[73].

Th17 cells: $CD4^+$ T cells that produce IL-17, but neither IFN-γ nor IL-4 (and therefore do not fit into the Th1–Th2 spectrum), are referred to as Th17 cells[74]. Besides IL-17A, these cells also secrete IL-17F, IL-21 and IL-22. Whereas the heterodimeric cytokine IL-12 (consisting of a p35 chain and a p40 chain) is crucially involved in the development of Th1 cells, the IL-12-related cytokine IL-23 (consisting of a p19 chain and the same p40 chain) is essential for the generation of Th17 cells. Naive T cells do not express the IL-23 receptor. In mice, a combination of TGF-β and IL-6 induces expression of the transcription factor *r*etinoid acid receptor-related *o*rphan *r*eceptor-γt (ROR-γt), which stimulates transcription of the IL-17 gene and expression of the IL-23 receptor (see Fig. 4.10). Of note, in the absence of IL-6, TGF-β drives naive T cells into the regulatory phenotype by inducing the transcription factor forkhead box P3 (FoxP3; see below). IL-6 and IL-23 enhance the expression of IL-17 and IL-22 and suppress production of IL-10 and IFN-γ, thereby stabilizing the Th17 phenotype. IL-21 is also produced in large amounts by mature Th17 cells and amplifies Th17-cell differentiation[74]. In human T cells, combinations of TGF-β plus IL-21, TGF-β plus IL-6 and IL-23, or IL-6 plus IL-21 appear to be involved in the differentiation of Th17 cells by inducing the expression of ROR-c, the human analogue of murine ROR-γt.

Th17 cells are rapidly induced in response to infectious agents – in particular, bacteria and fungi. Patients with a defective Th17 response due to mutations in the gene encoding *s*ignal *t*ransducer and *a*ctivator of *t*ranscription 3 (STAT3), another transcription factor involved in Th17 cell development (see Fig. 4.10), have hyperimmunoglobulin E (hyper-IgE) syndrome and suffer from recurrent *Candida albicans* and *Staphylococcus aureus* infections of the skin and lung (see Ch. 60)[75]. Th17 responses have important roles in chronic inflammation and in mediating autoimmune reactions. There is evidence that Th17 cells are involved in rheumatoid arthritis, psoriasis, multiple sclerosis and inflammatory bowel diseases[74]. Genetic studies have linked variants of the IL-23 and IL-23 receptor genes to susceptibility for psoriasis and psoriatic arthritis[76]. Since IL-23 enhances IL-17 production, inhibition of IL-23 is a target for therapeutic intervention. Indeed, a monoclonal antibody (ustekinumab) directed against the common p40 chain, thereby blocking signaling by both IL-12 and IL-23, represents an effective treatment for psoriasis[77]. Since IL-23 appears to be a more potent driving force in autoimmune reactions than IL-12, blocking IL-23 signaling by targeting the p19 chain represents another promising therapeutic strategy.

Th22 cells: Recently, a subset of human $CD4^+$ Th cells characterized by the secretion of IL-22 and TNF-α (in the absence of IFN-γ, IL-4 or IL-17) was identified, and they have been referred to as Th22 cells[78]. These cells infiltrate the epidermis in inflammatory skin disorders including psoriasis. They express proteins involved in tissue remodeling (e.g. fibroblast growth factors) and chemokines involved in angiogenesis and fibrosis.

Cytotoxic T cells

Cytotoxic T (Tc) cells are $CD8^+$, recognize "their" antigenic peptides in association with MHC class I molecules, and can directly lyse their targets (e.g. virally infected or tumor cells). For example, virally infected cells present peptides derived from intracellular viral proteins on MHC class I molecules, and Tc cells that recognize this viral peptide–MHC complex are stimulated to kill the infected cell. Tc cells have at least three different pathways of killing[79], two of which involve direct contact with the target cell. In one method, Tc cells insert perforins into the membrane of the target cell; this creates pores in the membrane, through which granzymes are released from the Tc cell into the target cell. Granzymes then activate caspases, proteolytic enzymes that induce apoptosis in the target cell. In a second mechanism, Tc cells activate the death receptor Fas (CD95) on the target cell by expressing the cognate death ligand FasL (CD95L). The activated Fas also triggers apoptosis in the target cell. The third pathway is mediated by cytokines, including TNF-α and IFN-γ, which are released as long as TCR stimulation continues. These mediators can affect distant cells as well as the target cell[79].

Naive $CD8^+$ T cells (Tc0 cells) can develop into Tc1 and Tc2 cells[80]. Comparable to Th1 and Th2 cells, Tc1 and Tc2 cells are differentiated based on their different cytokine secretion patterns. However, their functional roles still remain to be determined. Even though there is evidence that some $CD8^+$ T cells exhibit suppressor functions[81], most $CD8^+$ T cells develop a cytotoxic phenotype.

Regulatory T cells

More than three decades ago, it was postulated that a subpopulation of T cells could suppress immune responses. Consequently, these cells were designated as T suppressor cells. The most convincing evidence for their existence was provided by adoptive transfer experiments in which suppression could be transferred in an antigen-specific manner. However, the phenotype of these hypothetical cells and the molecular mechanisms underlying suppressive phenomena were poorly characterized. Consequently, the term "T suppressor cells" was almost banned and the entire concept of suppression drawn into question. Passive mechanisms such as clonal deletion, clonal anergy and immunologic ignorance were evoked to explain immunologic unresponsiveness and peripheral tolerance[82].

Nevertheless, the concept of T suppressor cells was persistently pursued in the field of photoimmunology. Application of contact allergens onto the skin of mice exposed to UV radiation not only resulted in a failure of sensitization but also actually induced antigen-specific tolerance, since at a later time these animals could not be resensitized to the same allergen[37] (see Ch. 86). Adoptive transfer of splenocytes from animals tolerized in such a manner rendered naive recipients unresponsive to the specific allergen. Depending on the model used (local or systemic immunosuppression, type of allergen, UV dose), different subtypes of T cells appeared to be responsible for the transfer of suppression[83]. Due to the lack of specific surface markers, to date these cells have not been isolated or cloned; nevertheless, the adoptive transfer experiments clearly indicated that active suppression exists.

Interest in the entire field was rekindled by the observation that chronic activation of both human and murine $CD4^+$ T cells in the presence of IL-10 induced $CD4^+$ T-cell clones with a low proliferative capacity that produced high levels of IL-10, low levels of IL-2, and no IL-4[84]. These antigen-specific T-cell clones suppressed the proliferation of $CD4^+$ T cells in response to antigen and prevented T-cell-mediated colitis in SCID mice. This $CD4^+$ T-cell subset was designated T regulatory cells 1 (Tr1).

Another subset of $CD4^+$ regulatory T cells (Tregs) is characterized by the constitutive expression of the α-chain of the IL-2 receptor (CD25). Some $CD4^+CD25^+$ Tregs are generated in the thymus and become

activated upon re-encountering their antigen in the periphery. Thymectomized mice that do not develop $CD4^+CD25^+$ T cells develop autoimmune diseases[85]. In turn, reinjection of such cells prevents the development of the autoimmune phenomena, indicating that the $CD4^+CD25^+$ cells prevent autoimmunity and thus can act in a suppressive fashion. FoxP3, a transcription factor whose inherited dysfunction leads to an autoimmune and inflammatory syndrome in humans (IPEX: *i*mmune dysregulation, *p*olyendocrinopathy, *e*nteropathy, *X*-linked) and mice (*Scurfy* strain), is specifically expressed in naturally arising $CD4^+CD25^+$ Tregs[86]. Retroviral gene transfer of *Foxp3* converts naive T cells toward a Treg phenotype. Thus, *Foxp3* is a key regulatory gene in the development of Tregs.

Natural Tregs (*nTregs*) are produced in the thymus as a functionally mature subpopulation of T cells[87]. These $CD4^+CD25^+$ T cells constitute approximately 10% of all murine peripheral $CD4^+$ T cells. However *induced Tregs* (*iTregs*) can also develop from naive T cells in the periphery through several mechanisms (Fig. 4.11). Immature DCs appear to be involved in the generation of human iTregs. Upon repeated stimulation by immature DCs, allogeneic $CD4^+$ T cells have been shown to express the negative regulatory molecule CTLA-4; lose their capacity to produce IFN-γ, IL-2 or IL-4; and differentiate into non-proliferating, IL-10-producing T cells[36]. In co-culture experiments, these T cells inhibited the antigen-driven proliferation of Th1 cells in a cell contact-dependent manner. The same may apply for damaged APCs, since the migration of UV-damaged LCs is required for the generation of Tregs by UV radiation[88].

Together, these findings show that immature and mature DCs induce different types of T-cell responses: (1) mature, IL-12-producing DCs result in inflammatory Th1 cells; (2) less well-defined "DC2s" result in Th2 cells; and (3) immature or damaged DCs result in IL-10-producing iTregs. These observations provide evidence for constant control of peripheral tolerance to self-antigens[89]. In this scenario, immature DCs constantly take up proteins from normal cells as they undergo regular cell turnover. In the absence of inflammatory signals, DCs do not mature and therefore enter the regional lymph nodes in an immature stage. Self-antigens expressed on immature DCs lead to the development of Tregs, which then migrate to the respective organ where they exhibit suppressive effects. During an infection, immature DCs take up self-antigens but mature in the presence of TLR and inflammatory signals. In the regional lymph nodes, the mature DCs prime naive $CD4^+$ or $CD8^+$ T cells, which become effector T cells. These cells re-migrate to the initial site of inflammation, where they encounter the inhibitory effects of Tregs that are already present. This process normally prevents the development of autoimmunity under both normal and inflammatory conditions.

Tregs exert their suppressive functions in several ways[87] (see Fig. 4.11). They release inhibitory cytokines (e.g. IL-10, IL-35, TGF-β) and can induce apoptosis of target effector T cells via perforin and granzymes. Tregs also interfere with metabolic functions in their target T cells by depriving them of IL-2 (which results in apoptosis), increasing their intracellular levels of cAMP (which inhibits T-cell proliferation and IL-2 production), and increasing pericellular levels of adenosine (which is cytotoxic). The latter is achieved by the conversion of ATP to adenosine via CD39 and CD73, two ectonucleotidases expressed on the Treg membrane. Furthermore, negative regulation of the maturation and function of APCs occurs through the interaction of CTLA-4 and lymphocyte-activation gene-3 (LAG-3) on Tregs with CD80/CD86 and MHC class II ligands, respectively, on APCs. Induction of the tryptophan-degrading enzyme indoleamine 2,3-dioxygenase (IDO) in DCs has been suggested as another mechanism by which Tregs exert suppression.

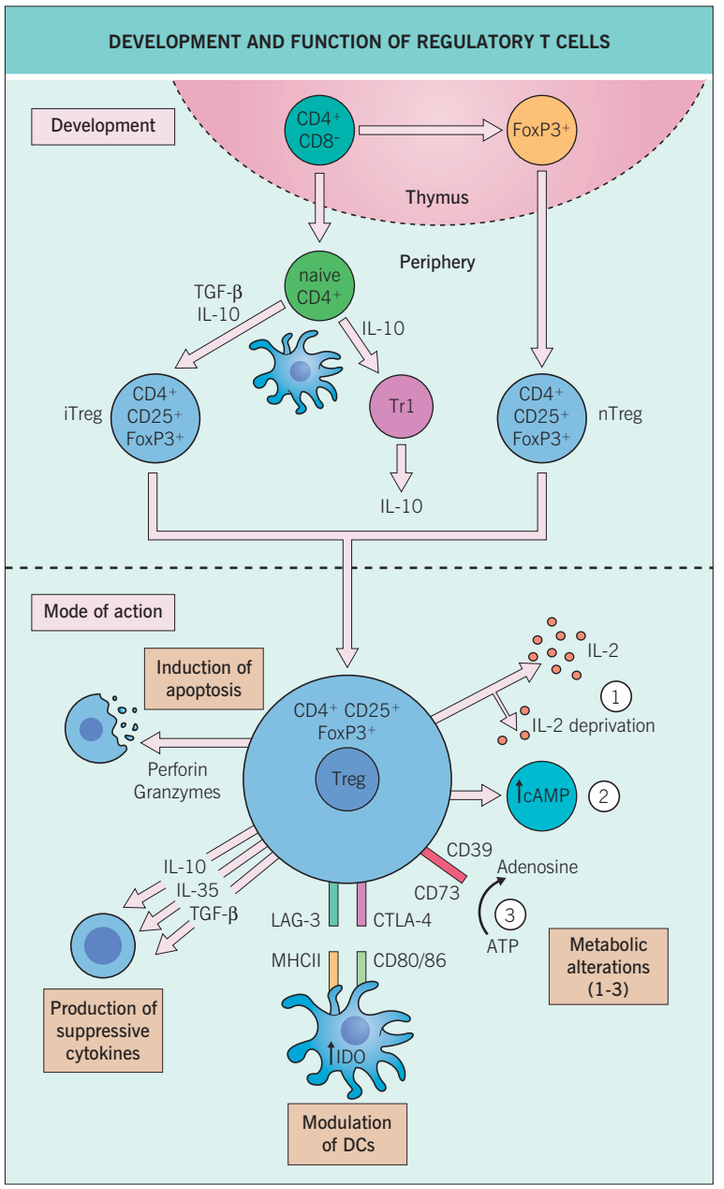


Fig. 4.11 Development and function of regulatory T cells. Natural regulatory T cells (nTregs), which express CD4, CD25 and FoxP3, develop from $CD4^+CD8^-$ T cells in the thymus. In the periphery, naive conventional $CD4^+$ T cells (in the presence of interleukin [IL]-10 and/or transforming growth factor-β [TGF-β]) can develop into $FoxP3^-$ regulatory type 1 cells (Tr1) or induced regulatory T cells (iTreg) that express CD24, CD25 and FoxP3. Tregs exert their inhibitory functions in several ways. They release inhibitory cytokines (e.g. IL-10, IL-35, TGF-β), induce apoptosis of their target effector T cells via release of granzymes and perforin, and interfere with metabolic functions of their target T cells. The latter can be accomplished by: (1) IL-2 deprivation, which triggers apoptosis; (2) transferring cAMP, which inhibits proliferation and IL-2 production, into target cells; and (3) increasing pericellular levels of cytotoxic adenosine via conversion of ATP to adenosine by CD39 and CD73, two ectonucleotidases expressed on the surface of Tregs. Tregs also modulate dendritic cell (DC) maturation and function via interaction of cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and lymphocyte-activation gene-3 (LAG-3) on Tregs with their ligands CD80/CD86 and MHC class II, respectively, on DCs and induction of the tryptophan-degrading enzyme indoleamine 2,3-dioxygenase [IDO] in DCs. *Adapted from Workman CJ, et al. The development and function of regulatory T cells. Cell Mol Life Sci. 2009;66:2603–22 and from Sakaguchi S, et al. Regulatory T cells and immune tolerance. Cell. 2008;133:775–87.*

Natural killer T cells

NK T cells are a distinct subset of thymocytes and peripheral T cells that have characteristics of both T cells and NK cells[90]. They express the NK marker NK1.1 and an invariant TCR restricted to CD1d. NK T cells produce large amounts of various cytokines, including IFN-γ, IL-4 and IL-10. Since they are present at the early stages of ontogeny in the thymus, they are thought to be involved in the differentiation of various T-cell subsets, especially Th2 cells. They may also play a role in the control of autoimmunity, since NK T cells are numerically and functionally deficient in mice with autoimmune diseases. NK T cells also seem to contribute to UV-induced immunosuppression, and they down-regulate immune responses to UV-induced tumors[91].

γ/δ T Cells

A small proportion of T cells carry a TCR composed of γ and δ (rather than α and β) protein chains. Under normal conditions, the great majority of T cells detected in the skin belong to the α/β type. However, in certain infectious diseases such as leprosy and leishmaniasis, γ/δ T cells can account for almost one-third of the T cells infiltrating the

skin. The exact functional role of γ/δ T cells remains to be determined, but they may be involved in the recognition of non-peptide moieties expressed by microbial pathogens[92].

Dendritic epidermal T cells

$CD3^+$ lymphocytes found in murine epidermis are dendritic in shape and are therefore designated as dendritic epidermal T cells (DETCs)[93]. These murine DETCs express a γ/δ type of TCR with limited diversity. The same TCR configuration is detected in early thymocytes, giving rise to speculation that fetal thymocytes are the progenitors of DETCs. Alternatively, maturation could take place in the skin. Despite extensive studies, the functional role of DETCs could not be clarified completely. It was proposed that DETCs protect stressed keratinocytes and exhibit NK function, but also down-regulate T-cell responses. To date, a human equivalent of the rodent DETC has not been identified.

Lymphocyte recruitment

A major challenge for lymphocytes is to be at the right place at the right time to meet "their" antigen. Naive lymphocytes encounter their antigens for the first time in lymphoid organs, while memory cells have their encounters in the periphery. There is continuous recirculation of naive T cells between the blood and lymphoid organs[94]. Expression of the surface molecule L-selectin (CD62L) allows naive T cells to attach to and roll on the inner surface of the high endothelial venules, specialized postcapillary venules within the lymph nodes. The venules express a chemokine, called the secondary lymphoid-tissue chemokine (SLC/CCL21)[95], which activates T cells via interaction with the chemokine receptor CCR7. Subsequently, T cells adhere tightly to the venules via interaction of endothelial intercellular adhesion molecule-1 (ICAM-1, CD54) with lymphocyte function antigen-1 (LFA-1, CD11a). Finally, T cells extravasate through the high endothelial venules into the lymph node and accumulate in the T-cell-rich areas. They can return into the bloodstream by leaving the lymph node via the efferent lymphatics. Since naive T cells lack the necessary expression of a specific combination of adhesion molecules and chemokine receptors, they cannot enter extranodal tissues from the blood, forcing them back into the lymph nodes.

Upon activation by APCs presenting specific antigenic peptides, T cells start to proliferate and begin to express activation molecules, thereby developing into memory T cells. During this process, they express new surface molecules that allow them to exit the blood vessels and enter extranodal tissues[96]. A hallmark of memory T cells is their ability to "remember" the anatomic location that the lymph node was draining. Due to the expression of specific adhesion molecules, they exhibit the capacity to migrate primarily into the sites where the antigen was first encountered by the host. Hence, lymph nodes draining different organs generate distinct, "tissue-specific" memory T cells. Approximately 10% to 20% of all memory T cells are skin-homing due to their expression of a glycoprotein called cutaneous lymphocyte antigen (CLA)[65].

CLA is generated by modification of the pre-existing P-selectin glycoprotein ligand-1 (PSGL-1, CD162) by glycosylation enzymes[97]. Memory T cells entering the skin express CLA, whereas memory T cells found in other tissues are primarily CLA-negative. The function of CLA (recognized by the antibody HECA-452) is to allow the early tethering of T cells to the endothelium of cutaneous postcapillary venules. This step leads to the subsequent slowing, arrest and extravasation of the T cells. The endothelial ligand for CLA is E-selectin (CD62E), which is constitutively expressed at low levels on cutaneous microvessels. Its expression is strongly upregulated by inflammatory stimuli. Although interaction between CLA and E-selectin is an important initial step, it does not suffice for transmigration. Interactions of LFA-1 and the β-integrin very late antigen-4 (VLA-4) on T cells with ICAM-1 (CD54) and VCAM-1 (CD106), respectively, on endothelial cells produces the firm adhesion that is required for extravasation of T cells from the blood into the skin (see Ch. 102).

B Cells

The major task of B cells is the production of immunoglobulins (antibodies) that bind to specific antigens. Antibodies also interact with components of the innate immune system by preventing foreign organisms from adhering to mucosal surfaces, activating complement and opsonizing bacteria for phagocytosis. Immunoglobulins are secreted products of mature B cells. However, during early B-cell development, immunoglobulins function as antigen-specific B-cell receptors on the cell membrane, equivalent to the TCR on T cells. CD19, CD20 and CD22 are the main markers currently used to detect B cells. Activation of B cells results in cell division and maturation into plasma cells, which secrete the specific antibodies.

Immunoglobulins

Immunoglobulins consist of two identical heavy chains and two identical light chains, linked together by disulfide bonds[98] (Fig. 4.12). The N-terminus of each chain contains a variable domain that binds the antigen through three hypervariable complementarity-determining regions (CDRs). The C-terminal domains of the heavy and light chains form the constant regions. Five classes of immunoglobulin (IgG, IgA, IgM, IgD and IgE) are defined by the amino acid sequences of the constant regions of the heavy chains, and the designation of κ or λ depends on the constant region of the light chain. The class/subclass and titer of the antibody that is formed depend on the physical and chemical properties of the antigen; the site, duration, repetition and amount of antigen exposure; and the individual's propensity to recognize the antigen as foreign.

Digestion of immunoglobulins with the enzyme papain yields an antigen-binding fragment termed Fab and a fragment that spontaneously crystallizes with time and thus is called the Fc portion. Immunoglobulins are divalent, since twice as many Fab fragments than Fc portions are obtained upon cleavage with papain. Digestion of immunoglobulins with pepsin provides Fab fragments that are disulfide bond-linked and thus called F(ab) fragments.

Through their CDRs, antibodies recognize the conformational structure of their epitopes. No antigen processing is required. As for the TCR, extensive gene rearrangement involving V, D and J regions allows the generation of a nearly infinite variety of immunoglobulins specific for any putative antigen[56] (see T-cell receptor diversity above). An even greater repertoire of B-cell receptors than TCRs is produced, since further

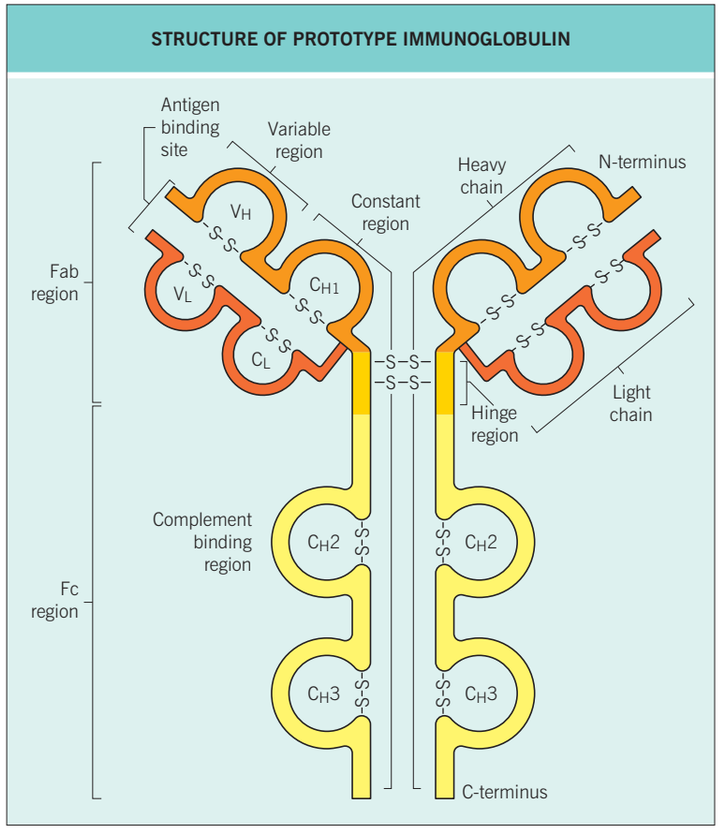


Fig. 4.12 Structure of a prototype immunoglobulin. The basic immunoglobulin structure consists of two identical light polypeptide chains and two identical heavy polypeptide chains, which are linked together by disulfide bonds. The antigen-binding site is at the N-terminal end.

gene rearrangement of immunoglobulins occurs during B-cell division after antigen stimulation, a process called somatic hypermutation.

The ability to induce effector functions resides in the Fc portion of the heavy chain. The Fc portion of IgG contains domains called C_H1, C_H2 and C_H3 for IgG. Complement activation is mediated via the C_H2 domain, while binding to macrophages or monocytes is mediated via the C_H3 domain. Binding of the Fc portion of IgG to phagocytic cells via their Fcγ receptors promotes phagocytosis of antibody–antigen complexes. Three receptors for human IgG exist. FcγRI (CD64) binds monomeric IgG with a high degree of affinity. FcγRII (CD32) is broadly distributed on cells and binds only complexed IgG with a low degree of affinity. FcγRIII (CD16) is expressed on macrophages, NK cells and some T cells, and it interacts with monomeric as well as complexed IgG. IgA binds only to the FcαR (CD89), while IgE can bind to three surface molecules: FcεRI, FcεRII (CD23) and the IgE-binding protein.

Immunoglobulin M

With a size of approximately 900 Da, IgM is the largest immunoglobulin. IgM molecules are pentamers that (in addition to light and heavy chains) contain one J chain. IgM is the major immunoglobulin produced in the primary immune response. Upon binding to its antigen, IgM induces agglutination and activates the classical complement pathway.

Immunoglobulin G

IgG is the most abundant immunoglobulin, accounting for approximately 75% of the total amount of serum immunoglobulin, and the major immunoglobulin of the secondary immune response. Four subclasses (IgG1, IgG2, IgG3, IgG4) are defined by the amino acid sequences of their constant region. They differ in their ability to activate complement. While IgG1 and IgG3 are potent activators of the classical complement pathway, IgG2 is less effective and IgG4 lacks such ability. In addition, IgG1 and IgG3 bind more avidly to mononuclear cells, i.e. they are more cytophilic. Most of the autoimmune dermatoses caused by autoantibodies are mediated by IgG, most often IgG4.

Immunoglobulin A

IgA is the predominant immunoglobulin present in mucosal surfaces, where it protects the host from invasion of microorganisms. IgA can activate the complement system via the alternative (but not the classical) pathway. Two subclasses of IgA exist, IgA1 and IgA2. IgA molecules can be joined by a J chain; this dimer form is mostly found in secretions, while in the serum, IgA circulates primarily as a monomer. IgA molecules can be involved in the pathogenesis of bullous autoimmune diseases.

Immunoglobulin E

IgE is the classic anaphylactic antibody that mediates most immediate allergic and anaphylactic reactions. Although in normal serum IgE is present in only very small amounts (10–70 microg/100 ml), just a few molecules appear to be required for sensitization. Mast cells and basophils express high-affinity receptors for the Fc portion of IgE (FcεRI). Antigens, anti-IgE antibodies or other substances that cross-link at least two IgE molecules bound on mast cells induce the release of mediators such as histamine, serotonin, leukotrienes and prostaglandins (see Ch. 18). The second IgE receptor, FcεRII (CD23), exhibits weaker binding affinity and is expressed on macrophages, eosinophils, platelets, and particular subtypes of T and B cells. Macrophages stimulated via activation of FcεRII exhibit increased phagocytic and cytotoxic activity; secrete prostaglandins, leukotrienes and lysosomal enzymes; and generate superoxides.

In the past, it was believed that mast cells and basophils were the only cells that express the high-affinity FcεRI receptor. However, it became clear that LCs[30], dermal DCs and peripheral blood DCs as well as monocytes from atopic individuals can bind monomeric IgE via the high-affinity FcεRI[99]. FcεRI, both quantitatively and qualitatively, is the crucial serum IgE-binding structure on APCs of atopic individuals and functions as an allergen-focusing molecule. Allergens are more efficiently taken up, processed and presented to T cells following targeting to APCs via the FcεRI. Thus, FcεRI-IgE-dependent allergen presentation may lower the threshold to elicit allergen-specific T-cell responses in atopic individuals[95]. This may perpetuate allergen-specific IgE production and even modulate T-cell-mediated delayed-type hypersensitivity reactions in allergen-exposed tissues.

Immunoglobulin D

The function of IgD still remains mysterious. Recent evidence suggests that IgD participates in respiratory immune defense[100]. It binds to basophils and mast cells, stimulating their production of antimicrobial factors. IgD may also exert proinflammatory functions, as illustrated by the hyperimmunoglobulinemia D with periodic fever syndrome (HIDS; see Table 45.2).

B-cell activation

B cells can respond to some antigens in a T-cell-independent manner[101]. Such antigens have numerous repeating epitopes (mainly polysaccharides), which bind and cross-link multiple B-cell receptors and activate the B cells directly to secrete IgM. However, this response is limited to IgM and is of short duration and poor specificity due to the lack of germinal center formation, affinity maturation, Ig class switching and memory.

Most B-cell responses are activated in a T-cell-dependent manner. Upon recognition by the specific IgM on the B-cell surface, the antigen is internalized, processed, and re-expressed within the MHC class II molecule on the surface. As a result, the B cell can present the antigen to a specific T cell. Primed Th cells, in turn, secrete cytokines (IL-2, IL-4, IL-5, IL-6, IFN-γ) that function as B-cell growth factors, inducing proliferation, isotype switch and maturation to plasma cells. Activation of CD40 (which is expressed on B cells) by CD40 ligand (CD154) expressed on T cells is needed for isotype switching from the initial IgM to an IgG response (Fig. 4.13). Once the switch from IgM to another isotype has occurred, some of the activated cells become long-lived memory cells that can rapidly produce antibodies upon re-challenge with the same antigen. Mutations in the genes encoding CD40 ligand and CD40 are associated with forms of primary immunodeficiency known as hyper-IgM syndromes, which are characterized by low or undetectable levels of IgG, IgA and IgE but elevated levels of IgM (see Ch. 60).

Upon subsequent antigen exposure, B cells become activated by follicular DCs, which are located in the germinal centers of the lymph nodes. Follicular DCs bear Fc and complement receptors and bind immune complexes. In contrast to "conventional" DCs, follicular DCs do not endocytose and process antigens. Instead, they trap antigen–antibody complexes and provide intact antigen for interaction with the

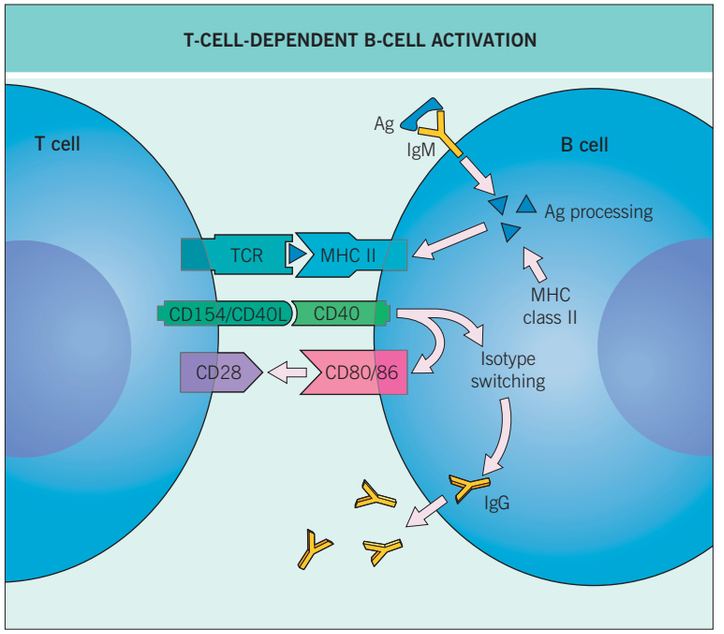


Fig. 4.13 T-cell-dependent B-cell activation. B cells present the antigen in association with MHC II molecules to $CD4^+$ T cells. This results in the upregulation of CD154/CD40 ligand which interacts with CD40 expressed on B cells. CD40–CD40 ligand interaction causes isotype switching of immunoglobulins and upregulation of CD80/86 which interacts with CD28 expressed on T cells. This results in further activation of T cells. Ag, antigen; CD40L, CD40 ligand; Ig, immunoglobulin; MHC II, major histocompatibility complex II.

B-cell receptor. This interaction stimulates B-cell activation and differentiation. In addition, follicular DCs form immune complex-coated bodies (iccosomes) that are taken up by B cells. Upon processing, B cells present this follicular DC-derived antigen to T cells and thus may obtain T-cell assistance[102].

Allergic Contact Hypersensitivity

Allergic contact hypersensitivity (CHS) is highly relevant for dermatologists, since it is the pathogenic basis for allergic contact dermatitis, a frequent inflammatory dermatosis. In addition, important basic immunologic discoveries have been made utilizing the model of CHS[103].

Induction of CHS

Most contact allergens are low-molecular-weight chemicals that, after penetrating the skin, have to couple with host proteins to be able to act as full antigens. This process is called haptenization, and the low-molecular-weight allergens are referred to as haptens. Upon epicutaneous application of a hapten in a naive host, APCs in the skin take up the hapten, migrate to the regional lymph nodes and present it to naive T cells (Fig. 4.14). Although this was previously thought to be done only by LCs, it has been established that other cutaneous APCs (e.g. dermal DCs) can present antigens, and the role of LCs as the primary APC in the skin is currently under debate (see Antigen presentation above).

During the emigration from the skin, APCs convert from a "resting" into an "activated" functional state. This process is initiated by keratinocytes, which secrete inflammatory cytokines as a result of hapten application; triggering of TLRs and direct effects of haptens on the APCs may also be involved. APC activation is associated with induction of cytokine secretion (e.g. IL-1β, IL-6, IL-12, chemokines); enhanced cell surface molecule expression (e.g. MHC class I and II molecules, adhesion molecules, costimulatory molecules); and altered antigen uptake, processing and presenting capacity[103].

Activation and induction of emigration of APCs seems to be dependent on the capacity of haptens to stimulate elaboration of IL-1β by APCs. IL-1β secretion can be immediately induced by epicutaneous hapten application and appears to be specific for haptens, since it is not observed with irritants or tolerogens. In addition, other cytokines, including chemokines, TNF-α and GM-CSF, may also contribute to APC activation and migration. Hence, the hapten itself, through its capacity to provoke a specific cytokine pattern, seems to be the initial trigger that activates APCs and induces sensitization (see Fig. 4.14).

Presentation of the hapten by APCs in the regional lymph nodes causes activation of naive T cells carrying the appropriate TCR and results in the generation of effector cells. In contrast to other types of delayed-type hypersensitivity responses, which are mediated by $CD4^+$ T cells, most haptens induce a T-cell response of predominantly $CD8^+$ effector T cells[103]. In addition, Treg populations that inhibit the CHS response are induced. The balance between effector T cells and Tregs seems to depend on the dose of the antigen applied, since application of extremely low doses of the hapten does not result in sensitization, but rather in tolerance[81].

Elicitation of CHS

T cells that have been primed in the draining cutaneous lymph nodes express the skin-homing marker CLA and thereby exhibit the capacity to enter the skin[65]. These T cells become activated when they encounter their relevant hapten presented by APCs within the skin. However, in contrast to the sensitization phase, antigen presentation can now be effectively performed by other cells (including keratinocytes, dermal mast cells and macrophages) that are capable of presenting antigen at least in a MHC class I-restricted fashion[103]. Alternatively, inflammatory cells that infiltrate the site of hapten application very early during the response may function as APCs.

The earliest histopathologic findings during a CHS response are mast cell degranulation, vasodilation and an influx of neutrophils, which is followed by infiltration of monocytes and T cells (Fig. 4.15). However, the pathophysiologic events that result in allergic contact dermatitis are clearly T-cell-dependent, since T-cell-deficient mice are unable to mount a CHS response. Furthermore, low doses of hapten that are sufficient to stimulate hapten-specific T cells are insufficient to elicit a CHS response. This indicates that the elicitation of a CHS response

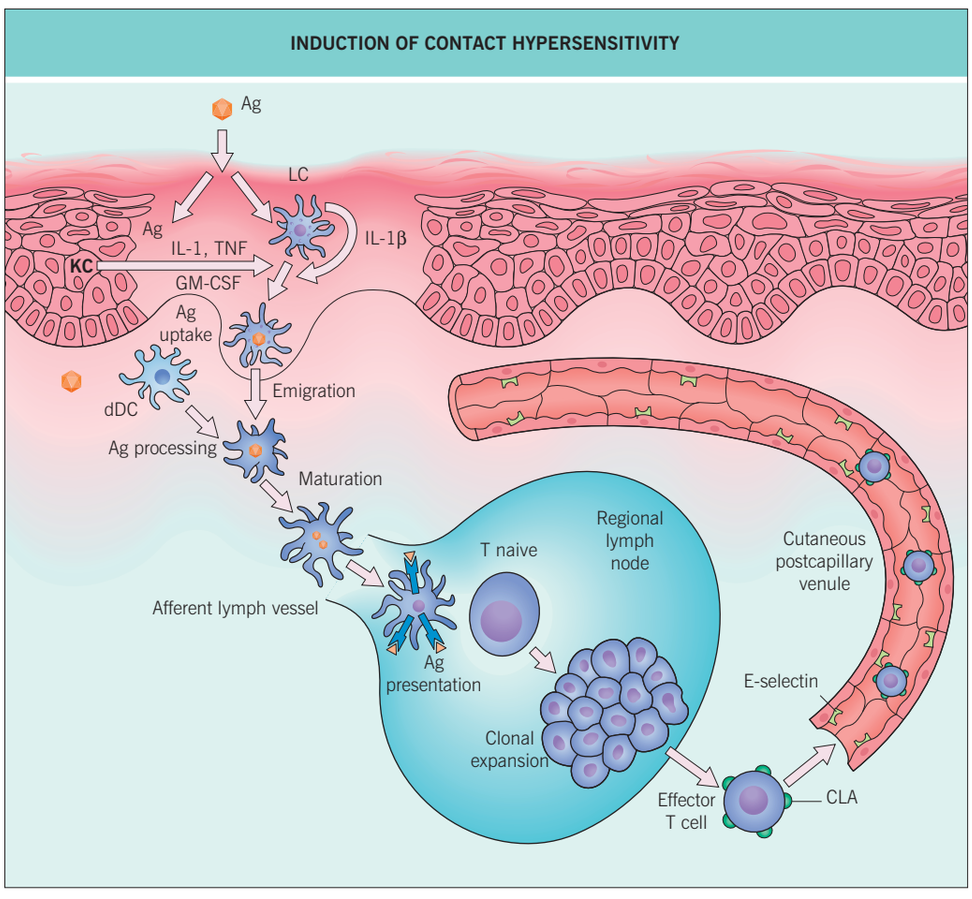


Fig. 4.14 Induction of contact hypersensitivity. Application of contact allergens (Ag) induces the release of cytokines by keratinocytes (KCs), Langerhans cells (LCs) and other cells within the skin. These cytokines in turn activate LCs and/or dermal dendritic cells (dDCs), which uptake the antigen and emigrate into the regional lymph nodes. During this process, they develop into mature antigen-presenting cells. In addition, the antigen is processed, re-expressed on the surface, and, finally, presented to naive T cells in the regional lymph node. Upon antigen presentation, T cells bearing the appropriate T-cell receptor clonally expand and become effector T cells. These alter their migratory behavior due to the expression of specific surface molecules like cutaneous lymphocyte antigen (CLA). Effector T cells recirculate into the periphery, where they may later meet the antigen again.

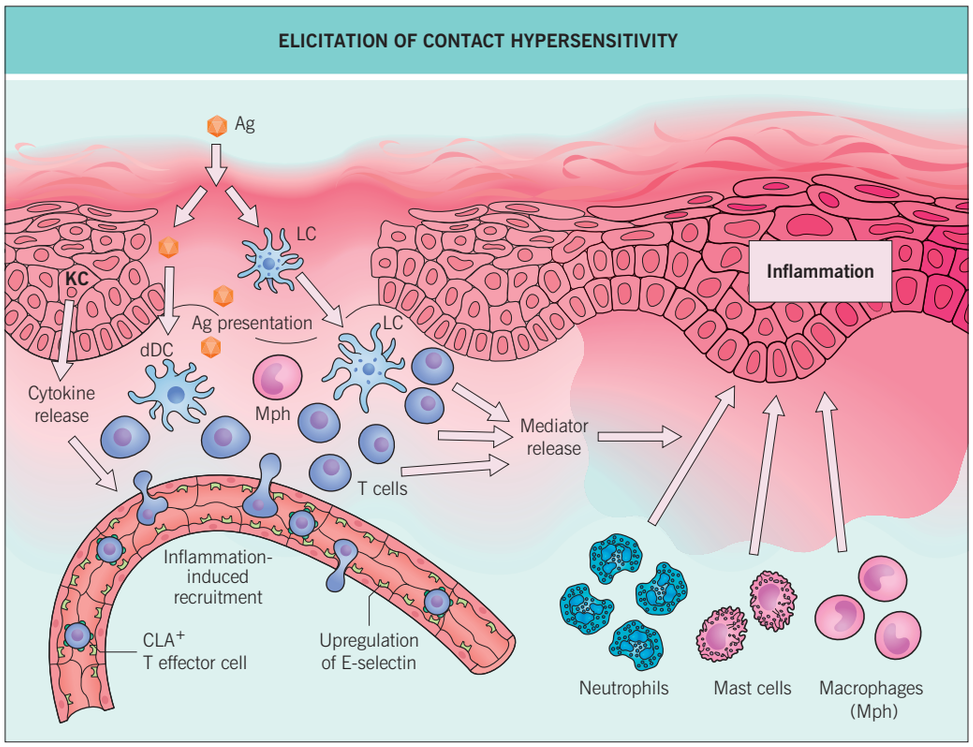


Fig. 4.15 Elicitation of contact hypersensitivity. Application of contact allergens (Ag) into a sensitized individual causes the release of cytokines by keratinocytes (KCs) and Langerhans cells (LCs). These cytokines induce the expression of adhesion molecules and activation of endothelial cells, which ultimately attracts leukocytes to the site of antigen application. Among these cells, T effector cells are present, which are now activated upon antigen presentation either by LCs, dermal dendritic cells (dDCs) or infiltrating macrophages (Mphs). Antigen-specific T-cell activation again induces the release of cytokines by T cells. This causes the attraction of other inflammatory cells, including granulocytes and macrophages, which ultimately cause the clinical manifestation of contact dermatitis. CLA, cutaneous lymphocyte antigen.

requires, in addition to hapten-specific recognition, a proinflammatory stimulus that can be provided in a dose-dependent manner by the hapten itself[104].

The Role of Keratinocytes in Skin Immune Responses

Keratinocytes are also vital contributors to the generation of a cutaneous immune response. Due to their close physical proximity, keratinocytes can affect LCs by the expression of specific surface molecules. In addition, keratinocytes are able to provide signals to LCs and other APCs in a contact-independent manner via the release of soluble mediators, particularly cytokines, eicosanoids and neurohormones.

Secretory capacity of keratinocytes

For decades, keratinocytes were regarded as primitive cells endowed only with the capacity to produce keratins and provide a mechanical barrier to the outside world. Therefore, it was quite surprising when it was discovered in the early 1980s that keratinocytes could secrete immunologic and inflammatory mediators. The first cytokine identified as being released from keratinocytes was IL-1. Subsequently, keratinocytes were shown to have the capacity to secrete a multitude of soluble mediators. These included pro- and anti-inflammatory, immunomodulatory and immunosuppressive cytokines[105]. The inflammatory mediators released by keratinocytes include IL-1, IL-6, TNF-α, IL-8 and other members of the chemokine family. Anti-inflammatory and immunosuppressive activity can be mediated by keratinocytes via the release of IL-10, the IL-1 receptor antagonist and TGF-β. Keratinocyte-derived immunomodulatory mediators also include IL-7, IL-12, IL-15, IL-18, IL-19, IL-20, IL-23, GM-CSF, G-CSF and M-CSF. Other cytokines are clearly *not* produced by keratinocytes, e.g. IL-2, IL-4 and IFN-γ.

Although some cytokines are produced in tiny quantities by keratinocytes, even low concentrations may exert an effect on the local microenvironment. Any perturbation of the skin can induce the release of mediators by the keratinocytes. For example, UV radiation is a potent inducer of cytokine production and release (see Ch. 86). Chemicals with the potential for inducing either irritant or allergic reactions also cause cytokine release from keratinocytes. In addition to cytokines, keratinocytes elaborate prostaglandins (PG) and leukotrienes. Leukotriene B_4 is a potent neutrophil chemoattractant, and PGE_2 possesses both inflammatory and immunosuppressive properties. For example, the erythema caused by UV radiation is partially mediated by PGE_2. There is additional evidence that the skin, and especially keratinocytes, can function as a source of neuropeptides, particularly substance P and pro-opiomelanocortin (POMC)-derived peptides (e.g. α-melanocyte-stimulating hormone)[105].

Keratinocytes as immune targets and initiators

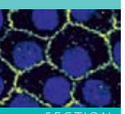
In addition to the secretion of cytokines, keratinocytes express a variety of immunologically relevant surface molecules. Thus, keratinocytes function not only as effectors, but also as targets for immune reactions. Like other nucleated cells, keratinocytes express MHC class I molecules and therefore can be attacked by $CD8^+$ Tc cells, particularly after viral infection. MHC class I-restricted T-cell-mediated cytolysis appears to be involved in CHS, lichen planus, fixed drug eruptions, cutaneous GVHD, and herpes simplex virus infections.

Although keratinocytes do not express MHC class II molecules under normal conditions, they can be induced to do so in inflammatory settings[106]. The major inducer of MHC class II expression on keratinocytes is IFN-γ. Accordingly, MHC class II expression by keratinocytes is frequently observed in association with pronounced lymphocytic infiltrates. Several studies have shown that MHC class II-bearing keratinocytes can induce proliferation of allogeneic $CD4^+$ T-cell lines, but not of resting T cells. Nevertheless, it is important to note that despite their capacity to express MHC class II molecules, keratinocytes are not able to induce a primary T-cell response, a major difference from APCs.

On the other hand, upon overexpression of immunologically relevant molecules, keratinocytes may play a pathogenic role. Transgenic mice that overexpress IFN-γ (a cytokine not derived from keratinocytes) within the basal layer of the epidermis develop an autoimmune phenotype[107]. Autoimmunity is also induced when LCs are constantly activated by keratinocytes through CD40/CD40L interactions. Transgenic mice overexpressing CD40L in the basal epidermis demonstrate a dramatic decrease in the number of LCs within the epidermis that may be due to emigration of CD40-activated LCs[108]. These mice suffer from chronic inflammation of the skin and, over time, develop systemic lupus-like features (e.g. lymphadenopathy, antinuclear antibodies, proteinuria). These models indicate that keratinocytes not only serve as targets of the immune system, but under certain conditions also directly modulate the initiation and course of immune responses.

REFERENCES

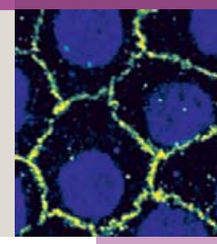
1. Streilein JW. Skin-associated lymphoid tissues (SALT): origins and functions. J Invest Dermatol. 1983;80(suppl):12s–6s.
2. Parkin J, Cohen B. An overview of the immune system. Lancet. 2001;357:1777–89.
3. Medzhitov R, Janeway C Jr. Innate immunity. N Engl J Med. 2000;343:338–44.
4. Walport MJ. Complement. First of two parts. N Engl J Med. 2001;344:1058–66.
5. Akira S, Takeda K. Toll-like receptor signalling. Nat Rev Immunol. 2004;4:499–511.
6. Akira S, Takeda K, Kaisho T. Toll-like receptors: critical proteins linking innate and acquired immunity. Nat Immunol. 2001;2:675–80.
7. McInturff JE, Modlin RL, Kim J. The role of toll-like receptors in the pathogenesis and treatment of dermatological disease. J Invest Dermatol. 2005;125:1–8.
8. Harder J, Schröder JM. Psoriatic scales: a promising source for the isolation of human skin-derived antimicrobial proteins. J Leukoc Biol. 2005;77:476–86.
9. Gläser R, Harder J, Lange H, et al. Antimicrobial psoriasin (S100A7) protects human skin from *Escherichia coli* infection. Nat Immunol. 2005;6:57–64.
10. Ong PY, Ohtake T, Brandt C, et al. Endogenous antimicrobial peptides and skin infections in atopic dermatitis. N Engl J Med. 2002;347:1151–60.
11. Harder J, Dressel S, Wittersheim M, et al. Enhanced expression and secretion of antimicrobial peptides in atopic dermatitis and after superficial skin injury. J Invest Dermatol. 2010;130:1355–64.
12. Gläser R, Navid F, Schuller W, et al. UV-B radiation induces the expression of antimicrobial peptides in human keratinocytes in vitro and in vivo. J Allergy Clin Immunol. 2009;123:1117–23.
13. Yang D, Chertov O, Bykovskaia SN, et al. Beta-defensins: linking innate and adaptive immunity through dendritic and T cell CCR6. Science. 1999;286:525–8.
14. Lande R, Gregorio J, Facchinetti V, et al. Plasmacytoid dendritic cells sense self-DNA coupled with antimicrobial peptide. Nature. 2007;449:564–9.
15. Thomson AW. The Cytokine Handbook, 2nd edn. London: Academic Press, 1996.
16. Cyster JG. Chemokines and cell migration in secondary lymphoid tissue. Science. 1999;286:2098–102.
17. Aderem A, Underhill DM. Mechanisms of phagocytosis in macrophages. Annu Rev Immunol. 1999;17:593–623.
18. von Andrian UH, Mackay CR. T-cell function and migration. Two sides of the same coin. N Engl J Med. 2000;343:1020–34.
19. Robinson DS, Kay AB, Wardlaw AJ. Eosinophils. Clin Allergy Immunol. 2002;16:43–75.
20. Abraham SN, Arock M. Mast cells and basophils in innate immunity. Semin Immunol. 1998;10:373–81.
21. Fureder W, Agis H, Willheim M, et al. Differential expression of complement receptors on human basophils and mast cells. Evidence for mast cell heterogeneity and CD88/C5aR expression on skin mast cells. J Immunol. 1995;155:3152–60.
22. Raulet DH. Development and tolerance of natural killer cells. Curr Opin Immunol. 1999;11:129–34.
23. Delves PJ, Roitt IM. The immune system. First of two parts. N Engl J Med. 2000;343:37–49.
24. Langerhans P. Über die Nerven der menschlichen Haut. Virchows Arch Pathol (Pathol Anat). 1868;44:325.
25. Katz SI, Tamaki K, Sachs DH. Epidermal Langerhans cells are derived from cells originating in bone marrow. Nature. 1979;282:324–6.
26. Hosoi J, Murphy GF, Egan CL, et al. Regulation of Langerhans cell function by nerves containing calcitonin gene-related peptide. Nature. 1993;363:159–63.
27. Valladeau J, Ravel O, Dezutter-Dambuyant C, et al. Langerin, a novel C-type lectin specific to Langerhans cells, is an endocytic receptor that induces the formation of Birbeck granules. Immunity. 2000;12:71–81.
28. Merad M, Ginhoux F, Collin M. Origin, homeostasis and function of Langerhans cells and other langerin-expressing dendritic cells. Nat Rev Immunol. 2008;8:935–47.
29. Stingl G, Maurer D, Hauser C, Wolff K. The epidermis: an immunologic microenvironment. In: Freedberg IM, Eisen AZ, Wolff K, et al. (eds). Fitzpatrick's Dermatology in General Medicine, vol. 1. New York: McGraw-Hill, 1999:343–70.
30. Wang B, Rieger A, Kilgus O, et al. Epidermal Langerhans cells from normal human skin bind monomeric IgE via Fc epsilon RI. J Exp Med. 1992;175:1353–65.
31. Banchereau J, Steinman RM. Dendritic cells and the control of immunity. Nature. 1998;392:245–52.
32. Ardavin C, Martinez del Hoyo G, Martin P, et al. Origin and differentiation of dendritic cells. Trends Immunol. 2001;22:691–700.
33. Maldonado-Lopez R, De Smedt T, Michel P, et al. CD8α+ and CD8α- subclasses of dendritic cells direct the development of distinct T helper cells in vivo. J Exp Med. 1999;189:587–92.
34. Rissoan MC, Soumelis V, Kadowaki N, et al. Reciprocal control of T helper cell and dendritic cell differentiation. Science. 1999;283:1183–6.
35. Langenkamp A, Messi M, Lanzavecchia A, Sallusto F. Kinetics of dendritic cell activation: impact on priming of TH1, TH2 and nonpolarized T cells. Nat Immunol. 2000;1:311–16.
36. Jonuleit H, Schmitt E, Schuler G, et al. Induction of interleukin 10-producing, nonproliferating CD4(+) T cells with regulatory properties by repetitive stimulation with allogeneic immature human dendritic cells. J Exp Med. 2000;192:1213–22.
37. Toews GB, Bergstresser PR, Streilein JW. Epidermal Langerhans cell density determines whether contact hypersensitivity or unresponsiveness follows skin painting with DNFB. J Immunol. 1980;124:445–53.
38. Bennett CL, van Rijn E, Jung S, et al. Inducible ablation of mouse Langerhans cells diminishes but fails to abrogate contact hypersensitivity. J Cell Biol. 2005;169:569–76.
39. Kissenpfennig A, Henri S, Dubois B, et al. Dynamics and function of Langerhans cells in vivo: dermal dendritic cells colonize lymph node areas distinct from slower migrating Langerhans cells. Immunity. 2005;22:643–54.
40. Kaplan DH, Jenison MC, Saeland S, et al. Epidermal Langerhans cell-deficient mice develop enhanced contact hypersensitivity. Immunity. 2005;23:611–20.
41. Schuler G, Steinman RM. Murine epidermal Langerhans cells mature into potent immunostimulatory dendritic cells in vitro. J Exp Med. 1985;161:526–46.
42. Weiss JM, Sleeman J, Renkl AC, et al. An essential role for CD44 variant isoforms in epidermal Langerhans cell and blood dendritic cell function. J Cell Biol. 1997;137:1137–47.
43. Price AA, Cumberbatch M, Kimber I, Ager A. Alpha 6 integrins are required for Langerhans cell migration from the epidermis. J Exp Med. 1997;186:1725–35.
44. Margulies DH. Interactions of TCRs with MHC-peptide complexes: a quantitative basis for mechanistic models. Curr Opin Immunol. 1997;9:390–5.
45. Pamer E, Cresswell P. Mechanisms of MHC class I-restricted antigen processing. Annu Rev Immunol. 1998;16:323–58.
46. Watts C. Capture and processing of exogenous antigens for presentation on MHC molecules. Annu Rev Immunol. 1997;15:821–50.
47. Watts C. Antigen processing in the endocytic compartment. Curr Opin Immunol. 2001;13:26–31.
48. Guermonprez P, Amigorena S. Pathways for antigen cross presentation. Springer Semin Immunopathol. 2005;26:257–71.
49. Kruisbeek AM. Regulation of T cell development by the thymic microenvironment. Semin Immunol. 1999;11:1–2.
50. Fink PJ, Bevan MJ. Positive selection of thymocytes. Adv Immunol. 1995;59:99–133.
51. Anderson G, Moore NC, Owen JJT, Jenkinson EJ. Cellular interactions in thymocyte development. Annu Rev Immunol. 1996;14:73–99.
52. Kruisbeek AM, Amsen D. Mechanisms underlying T-cell tolerance. Curr Opin Immunol. 1996;8:233–44.
53. Ellmeier W, Sawada S, Littman DR. The regulation of CD4 and CD8 coreceptor gene expression during T cell development. Annu Rev Immunol. 1999;17:523–54.
54. Garcia KC, Teyton L, Wilson IA. Structural basis of T cell recognition. Annu Rev Imunol. 1999;17:369–97.
55. Born W, Cady C, Jones-Carson J, et al. Immunoregulatory functions of gamma delta T cells. Adv Immunol. 1999;71:77–144.
56. Tonegawa S. Somatic generation of antibody diversity. Nature. 1983;302:575–81.
57. Agrawal A, Schatz DG. RAG1 and RAG2 form a stable postcleavage synaptic complex with DNA containing signal ends in V(D)J recombination. Cell. 1997;89:43–53.
58. Schwarz K, Gauss GH, Ludwig L, et al. RAG mutations in human B cell-negative SCID. Science. 1996;274:97–9.
59. Malissen B, Ardouin L, Lin SY, et al. Function of the CD3 subunits of the pre-TCR and TCR complexes during T cell development. Adv Immunol. 1999;72:103–48.
60. van Leeuwen JE, Samelson LE. T cell antigen-receptor signal transduction. Curr Opin Immunol. 1999;11:242–8.
61. Tamada K, Chen L. T lymphocyte costimulatory molecules in host defense and immunologic diseases. Ann Allergy Asthma Immunol. 2000;85:164–75.
62. Greenfield EA, Nguyen KA, Kuchroo VK. CD28/B7 costimulation: a review. Crit Rev Immunol. 1998;18:389–418.
63. Salomon B, Bluestone JA. Complexities of CD28/B7: CTLA-4 costimulatory pathways in autoimmunity and transplantation. Annu Rev Immunol. 2001;19:225–52.
64. Sallusto F, Lenig D, Förster R, et al. Two subsets of memory T lymphocytes with distinct homing potentials and effector functions. Nature. 1999;401:708–12.
65. Robert C, Kupper TS. Inflammatory skin diseases, T cells, and immune surveillance. N Engl J Med. 1999;341:1817–28.
66. Delves PJ, Roitt IM. The immune system. Second of two parts. N Engl J Med. 2000;343:108–17.
67. Mosmann TR, Sad S. The expanding universe of T-cell subsets: Th1, Th2 and more. Immunol Today. 1996;17:138–46.
68. Austrup F, Vestweber D, Borges E, et al. P- and E-selectin mediate recruitment of T-helper-1 but not T-helper-2 cells into inflamed tissues. Nature. 1997;385:81–3.
69. Hsieh CS, Macatonia SE, Tripp CS, et al. Development of TH1 CD4+ T cells through IL-12 produced by Listeria-induced macrophages. Science. 1993;260:547–9.
70. Biedermann T, Zimmermann S, Himmelreich H, et al. IL-4 instructs TH1 responses and resistance to Leishmania major in susceptible BALB/c mice. Nat Immunol. 2001;2:1054–60.
71. O'Garra A, Arai N. The molecular basis of T helper 1 and T helper 2 cell differentiation. Trends Cell Biol. 2000;10:542–50.
72. Trinchieri G. Interleukin-12: a cytokine at the interface of inflammation and immunity. Adv Immunol. 1998;70:83–243.
73. Weiner HL. Induction and mechanism of action of transforming growth factor-beta-secreting Th3 regulatory cells. Immunol Rev. 2001;182:207–14.
74. Miossec P, Korn T, Kuchroo VK. Interleukin-17 and type 17 helper T cells. N Engl J Med. 2009;361:888–98.
75. Milner JD, Brenchley JM, Laurence A, et al. Impaired T(H)17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. Nature. 2008;452:773–6.
76. Cargill M, Schrodi SJ, Chang M, et al. A large-scale genetic association study confirms IL12B and leads to the identification of IL23R as psoriasis-risk genes. Am J Hum Genet. 2007;80:273–90.
77. Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet. 2008;371:1665–74.
78. Eyerich S, Eyerich K, Pennino D, et al. Th22 cells represent a distinct human T cell subset involved in epidermal immunity and remodeling. J Clin Invest. 2009;119:3573–85.
79. Andersen MH, Schrama D, Thor Straten P, Becker JC. Cytotoxic T cells. J Invest Dermatol. 2006;126:32–41.
80. Mosmann TR, Li L, Sad S. Functions of CD8 T-cell subsets secreting different cytokine patterns. Semin Immunol. 1997;9:87–92.
81. Steinbrink K, Sorg C, Macher E. Low zone tolerance to contact allergens in mice: a functional role for CD8+ T helper type 2 cells. J Exp Med. 1996;183:759–68.
82. Miller JF, Basten A. Mechanisms of tolerance to self. Curr Opin Immunol. 1996;8:815–21.
83. Beissert S, Schwarz A, Schwarz T. Regulatory T cells. J Invest Dermatol. 2006;126:15–24.
84. Groux H, O'Garra A, Bigler M, et al. A CD4+ T-cell subset inhibits antigen-specific T-cell responses and prevents colitis. Nature. 1997;389:737–42.
85. Sakaguchi S. Naturally arising CD4+ regulatory T cells for immunologic self-tolerance and negative control of immune responses. Annu Rev Immunol. 2004;22:531–62.
86. Hori S, Nomura T, Sakaguchi S. Control of regulatory T cell development by the transcription factor Foxp3. Science. 2003;299:1057–61.
87. Workman CJ, Szymczak-Workman AL, Collison LW, et al. The development and function of regulatory T cells. Cell Mol Life Sci. 2009;66:2603–22.
88. Schwarz A, Maeda A, Kernebeck K, et al. Prevention of UV radiation-induced immunosuppression by IL-12 is dependent on DNA repair. J Exp Med. 2005;201:173–9.



89. Roncarolo MG, Levings MK, Traversari C. Differentiation of T regulatory cells by immature dendritic cells. J Exp Med. 2001;193:F5–9.
90. Bendelac A, Rivera MN, Park SH, Roark JH. Mouse CD1-specific NK1 T cells: development, specificity, and function. Annu Rev Immunol. 1997;15:535–62.
91. Moodycliffe AM, Nghiem D, Clydesdale G, Ullrich SE. Immune suppression and skin cancer development: regulation by NKT cells. Nat Immunol. 2000;1:521–5.
92. Stenger S, Modlin RL. T cell mediated immunity to *Mycobacterium tuberculosis*. Curr Opin Microbiol. 1999;2:89–93.
93. Payer E, Elbe A, Stingl G. Epidermal T lymphocytes – ontogeny, features and function. Springer Semin Immunopathol. 1992;13:315–31.
94. Butcher EC, Picker LJ. Lymphocyte homing and homeostasis. Science. 1996;272:60–6.
95. Campbell JJ, Bowman EP, Murphy K, et al. 6-C-kine (SLC), a lymphocyte adhesion-triggering chemokine expressed by high endothelium, is an agonist for the MIP-3β receptor CCR7. J Cell Biol. 1998;141:1053–9.
96. Picker LJ, Kishimoto TK, Smith CW, et al. ELAM-1 is an adhesion molecule for skin-homing T cells. Nature. 1991;349:796–9.
97. Fuhlbrigge RC, Kieffer JD, Armerding D, Kupper TS. Cutaneous lymphocyte antigen is a specialized form of PSGL-1 expressed on skin-homing T cells. Nature. 1997;389:978–81.
98. Davies DR, Metzger H. Structural basis of antibody function. Annu Rev Immunol. 1983;1:87–117.
99. Stingl G, Maurer D. IgE-mediated allergen presentation via Fc epsilon RI on antigen-presenting cells. Int Arch Allergy Immunol. 1997;113:24–9.
100. Chen K, Xu W, Wilson M, et al. Immunoglobulin D enhances immune surveillance by activating antimicrobial, proinflammatory and B cell-stimulating programs in basophils. Nat Immunol. 2009;10:889–98.
101. Mond JJ, Vos Q, Lees A, Snapper CM. T cell independent antigens. Curr Opin Immunol. 1995;7:349–54.
102. Tew JG, Wu J, Fakher M, et al. Follicular dendritic cells: beyond the necessity of T-cell help. Trends Immunol. 2001;22:361–7.
103. Grabbe S, Schwarz T. Immunoregulatory mechanisms involved in elicitation of allergic contact hypersensitivity. Immunol Today. 1998;19:37–44.
104. Grabbe S, Steinert M, Mahnke K, et al. Dissection of antigenic and irritative effects of epicutaneously applied haptens in mice. Evidence that not the antigenic component but nonspecific proinflammatory effects of haptens determine the concentration-dependent elicitation of allergic contact dermatitis. J Clin Invest. 1996;98:1158–64.
105. Luger TA, Schwarz T. The role of cytokines and neuroendocrine hormones in cutaneous immunity and inflammation. Allergy. 1995;50:292–302.
106. Volc-Platzer B, Majdic O, Knapp W, et al. Evidence of HLA-DR antigen biosynthesis by human keratinocytes in disease. J Exp Med. 1984;159:1784–9.
107. Seery JP, Carroll JM, Cattell V, Watt FM. Antinuclear autoantibodies and lupus nephritis in transgenic mice expressing interferon gamma in the epidermis. J Exp Med. 1997;186:1451–9.
108. Mehling A, Loser K, Varga G, et al. Overexpression of CD40 ligand in murine epidermis results in chronic skin inflammation and systemic autoimmunity. J Exp Med. 2001;194:615–28.

Cutaneous Neurophysiology

5



Gil Yosipovitch and Alexandru DP Papoiu

Chapter Contents

Pruritus pathways 99
Mediators of pruritus 101
Treatment of pruritus 105

Key features

- Two subsets of pruritoceptive C neurons (responding to histamine and cowhage, respectively) have been identified, and these parallel pathways activate distinct spinothalamic tract neurons
- Itch mediators act both peripherally (e.g. histamine, proteases, interleukin-31) and centrally (e.g. opioids, gastrin-releasing peptide receptors) via several mechanisms
- There is an overlap between chronic itch and chronic pain, including activation of multiple brain areas and associated neuromediators and receptors (e.g. nerve growth factor, neurotrophin 4, *t*ransient *r*eceptor *p*otential *v*anilloid [TRPV] receptor)
- Significant cross-talk between cutaneous nerve fibers and the stratum corneum is a possible mechanism for pruritus associated with impaired barrier function (e.g. xerosis, atopic dermatitis)
- Combination therapies with typical and systemic drugs that reduce itch sensitization by counteracting the responsible mediators represent promising treatment strategies

INTRODUCTION

The skin is a sensory organ with a dense network of highly specialized afferent sensory nerves that convey sensations such as pain, itch, touch, temperature, vibration and pressure (Table 5.1); efferent autonomic nerve branches are also present. Neuropeptides such as nerve growth factor (NGF) and substance P are secreted from nerve fibers, with multiple effects that include immune modulation. Itch (pruritus) is the dominant symptom of many cutaneous diseases. Almost all inflammatory skin disorders can result in pruritus, which is often perceived by the patient as the most unendurable symptom of his or her condition. Pruritus can also occur in association with systemic disease (e.g. renal failure or cholestasis; see Ch. 6), psychiatric conditions (see Ch. 7) and damage to nerve fibers[1,2]. Itch is a multidimensional phenomenon with sensory discriminative, cognitive, evaluative and motivational components. In most instances, itch results from interactions that involve the brain–skin axis.

Pruritus has many similarities to pain. Both are unpleasant sensory experiences that can impair quality of life in affected individuals. However, the behavioral reaction patterns differ – pain elicits a reflex withdrawal, whereas itch leads to a scratching response. Despite being an extremely common complaint[3] and a sensation so rudimentary that almost every two- or four-footed creature experiences it, medical science is still struggling to understand the mechanisms of itch and how it can be inhibited.

The connection between itch and scratching is so close that in some languages the same word refers to both itch and scratch. Itch is restricted to the skin, tracheal mucous membrane and several mucocutaneous junctions (e.g. conjunctivae). Interestingly, the nerves in the deeper layer of the reticular dermis and subcutaneous fat do not transmit itch.

PRURITUS PATHWAYS

Significant advances in our understanding of itch neurophysiology have been achieved in the past decade. Examples include identification of specific nerve fibers that transmit itch peripherally and centrally, as well as the discovery of new itch mediators[4]. While the concept of pruritus as a sensory modality entirely separate from pain was not generally appreciated until the mid-twentieth century, studies have clearly identified individual histamine-sensitive and non-histaminergic C nerve fibers that transmit itch[5,6]. C nerve fibers that transmit itch have exceptionally slow conduction velocities (2–8 cm/second), innervate unusually wide territories, and represent ≤5% of the total C fibers.

Histamine-sensitive C fibers are sensitive to thermal as well as pruritogenic stimuli but not to mechanical stimuli; in contrast, the vast majority of C fibers are sensitive to mechanical and heat stimuli but are entirely insensitive to histamine[7]. The co-responsiveness of itch-transmitting C neurons to temperature changes is clinically relevant, as raising the temperature of the skin lowers the threshold of these receptors to pruritogenic stimuli[8]; this provides an explanation for aggravation of pruritus in a warm environment. However, the fact that oral antihistamines are ineffective in the treatment of most types of pruritus suggests that other fibers have important roles in the sensation of itch[9].

Indeed, a distinct parallel pathway of non-histaminergic C nerve fibers that transmit itch was recently discovered in the peripheral nervous system of humans and the spinothalamic tract of primates[10,11]. These fibers are activated by spicules of the ubiquitous tropical legume cowhage (*Mucuna pruriens*), which is known to induce an intense sensation of itch when rubbed, inserted or injected into the skin, without producing a histaminergic axon reflex[12]. The mechanism by which cowhage induces itch involves the release of a protease (mucunain; contained within the spicules) that activates proteinase-activated receptor (PAR)-2 and PAR-4[13]. Cowhage-sensitive fibers are not itch-specific, transmitting a burning sensation together with itch and also sensitive to mechanical and other stimuli. PAR-2 receptors have a major role in mediating itch in patients with atopic dermatitis[14] (see Ch. 12), explaining the hypersensitivity to mechanical stimuli (e.g. contact with wool) in these individuals. The non-histaminergic, polymodal C nerve fibers stimulated by mucunain may also have clinical relevance in chronic itch.

Gastrin-releasing peptide receptor (GRPR)-positive neurons that transmit itch but not pain are found in the spinal cord of mice; their role in itch pathophysiology in humans remains to be determined[15,16]. Toll-like receptor 7 (TLR-7) was recently found to be expressed in C fibers and to have a role in itch (especially that elicited by non-histaminergic pruritogens) but not pain sensations in mice[17].

Another important observation is that the perceived sensation of pruritus can vary greatly in quality[18–22]. Patients may describe burning, pricking, "insects crawling" on the skin, or even a tickle, but the neurophysiologic and psychologic correlates of these qualitative differences have not yet been elucidated. Recent information obtained from itch questionnaires has enabled a better understanding of the different characteristics of itch and awaits translation into biologic explanations.

PRIMARY AFFERENT NEURONS THAT INNERVATE THE SKIN				
Fiber	**Diameter**	**Myelination**	**Conduction velocity**	**Responds to**
A-beta (Aβ)	Large	+	>30 m/s	Light touch Moving stimuli
A-delta (Aδ)	Small	+	2–30 m/s	Pain (nociceptors) Thermal Mechanical Chemical, including pruritogens
C	Small	–	<2 m/s	Pain (nociceptors) Itch*, histamine-sensitive† Itch*, cowhage-sensitive‡ Thermal† Mechanical

*~5% of total C fibers transmit itch.
†Separate C fibers carry both pruritogenic and thermal stimuli, but not mechanical stimuli.
‡Transmit pruritus accompanied by a burning sensation; also sensitive to mechanical stimuli.

Table 5.1 Primary afferent neurons that innervate the skin.

Central Pathways to Higher Nervous System Centers

In the spinal cord, nociceptor C neurons synapse with secondary transmission neurons in the gray matter of the dorsal horn (Fig. 5.1). These neurons then cross over and ascend in the lateral spinothalamic tract to the thalamus. Studies using microneurography identified a subclass of lamina I spinothalamic tract neurons that are excited by iontophoretically administered histamine[23]. Later studies have found that these nerve fibers are also able to transmit pain upon stimulation by capsaicin and bradykinin[7]. Neurophysiology experiments in primates have discovered that cowhage-induced itch stimulates a distinct population of spinothalamic tract neurons that are not involved in the transmission of histamine-mediated itch[11].

Much of our current understanding of supraspinal processing of itch and the corresponding scratch response is derived from studies in human subjects utilizing positron emission tomography (PET) and functional MRI during stimulation with histamine and (more recently) cowhage[24–28]. In healthy individuals, induction of itch in this manner can elicit co-activation of the anterior and posterior cingulate cortex, precuneus, somatosensory areas I and II, supramarginal gyrus, inferior parietal lobe and insula-claustrum complex[28]. In one study, atopic dermatitis patients exhibited significantly more activation of the posterior cingulate cortex and precuneus (a cortical area involved in integrative tasks such as visuospatial imagery, episodic memory retrieval and self-awareness) than did healthy controls[29]. This highlights the emotional and affective processing of itch experience in atopic individuals, in whom the degree of brain activation correlated with itch intensity and the severity of the atopic disease[29]. In healthy subjects, scratching has been found to inhibit the activation of the cingulate cortex and to activate the prefrontal cortex and cerebellum. The cerebellum may have a role in coordination of the itch–scratch cycle[30,31]. Scratching inhibits histamine-evoked activity of spinothalamic neurons in primates, but not spontaneous activity or that stimulated by pain[32].

Activation of multiple brain areas suggests a lack of a single "itch center", emphasizing the multidimensionality of the itch sensation. Pain demonstrates a similar pattern of brain activation involving many of the same cortical regions[33].

Seeing other people scratching can induce sensations of itch and an urge to scratch[34]. However, the central nervous mechanisms of this transmission, which appear to be beyond conscious control, are poorly understood. Psychophysical studies have shown that the perception of itch intensifies in atopic dermatitis patients when they are exposed to visual cues of itch, which also trigger a scratching response[34]. More studies are needed to verify the working hypothesis that itch "contagion" involves processing in associative cortical networks such as "mirror neurons" of the prefrontal cortex.

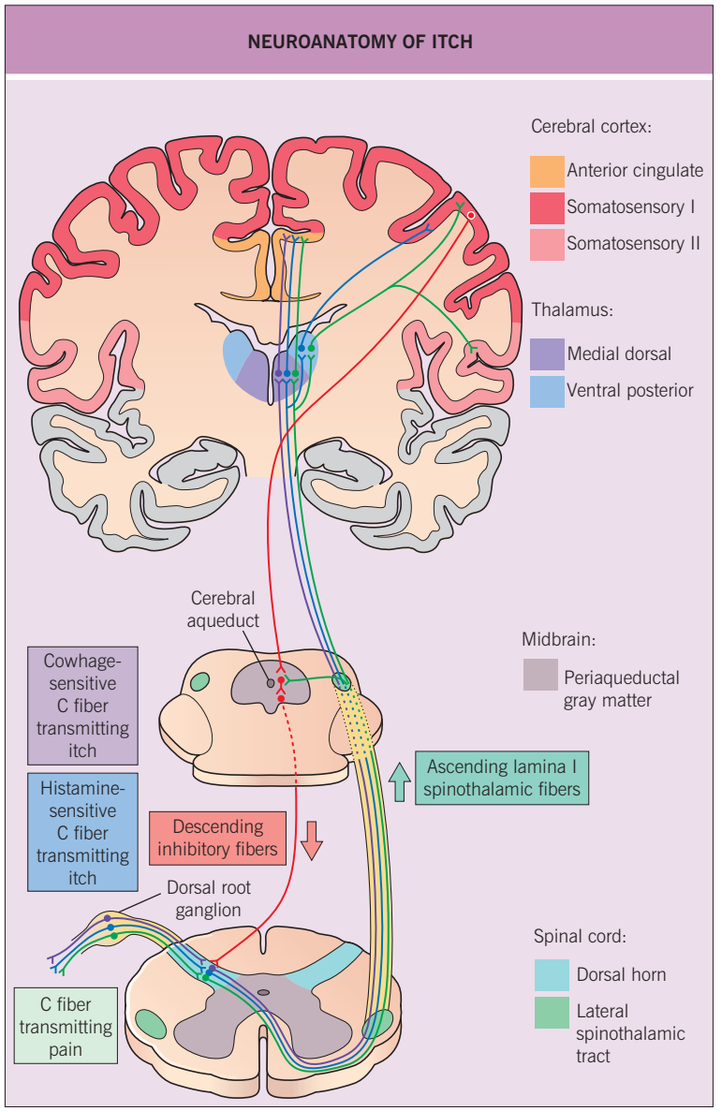


Fig. 5.1 Neuroanatomy of itch. Itch and pain transmission occur via unmyelinated C nerve fibers that excite lamina I neurons in the dorsal horn of the spinal cord. Two subsets of pruritoceptive C-fiber neurons (which respond to histamine and cowhage, respectively) are conducted through distinct lateral spinothalamic pathways, with projections to the thalamus. Processing of itch through either pathway activates several regions of the brain, which are similar to those involved in pain (see Table 5.4). Concomitant painful stimuli can reduce the sensation of itch, possibly by a descending inhibitory mechanism resulting from activation of the periaqueductal gray matter. In mice, gastrin-releasing peptide receptor-positive neurons transmit itch (but not pain) within the spinal cord; the role of such neurons in humans remains to be determined.
Adapted from Yosipovitch G. Pruritus: an update. Curr Probl Dermatol. 2003;15:137–64.

Pruritus Receptor Units

Removal of the epidermis abolishes the perception of itch, suggesting that pruritus receptor units (which have yet to be identified) are located predominantly within this layer. Light microscopic and ultrastructural studies of human skin have shown the existence of intraepidermal nerve fibers with "free" non-specialized nerve endings extending to the stratum granulosum[35]. Recent studies have identified a subclass of C nerve fibers in the epidermis that express MAS-related G protein-coupled receptors (MRGPRs) and are involved in chloroquine-induced pruritus[36]. The cell bodies of these neurons (located in the dorsal root ganglia) also express gastrin-related peptide (GRP), which binds the GRPRs that are known to relay itch-specific information in the spinal cords of mice[15] (see above).

Keratinocytes express a variety of neural mediators and receptors that appear to be involved in the sensation of itch (see Table 5.2). These

MAJOR MEDIATORS OF PRURITUS: RELATIVE POTENCIES WITH REGARD TO PRURITUS AND PAIN		
Mediator	**Pruritus**	**Pain**
PRIMARY MEDIATORS		
Histamine	+++*	+*
Tryptase	+++	+
Cathepsin S	+++	?
Interleukin-31	+++	?
SECONDARY MEDIATORS		
Prostaglandin $E_{1,2}$	+†	+
Substance P‡	+	+
μ-Opioid receptor agonists	++	–
Nerve growth factor	+	+
Interleukin-2	+++	+/–

*Superficial (intraepidermal) injection of histamine causes pruritus; deep dermal injection causes pain.
†Lowers threshold to pruritus induced by other mediators.
‡Actions partly due to histamine release from mast cells.

Table 5.2 Major mediators of pruritus: relative potencies with regard to pruritus and pain. +/–, little or no activity; +, weak activity; ++, moderately active; +++, highly active; –, no activity.

include opioids, proteases, substance P, NGF and neurotrophin 4 as well as their respective receptors, including μ- and κ-opioid receptors, PAR-2, neurotrophic tyrosine kinase receptor type 1 (NTRK1 [TRKA]), and transient receptor potential vanilloid ion channels (particularly TRPV1 and TRPV3). Keratinocytes also have ATP voltage-gated ion channels and adenosine receptor ligands similar to those observed in C nerve fibers involved in pain transmission. These structural similarities to nerve fibers suggest that keratinocytes may be involved in the transduction and generation of itch. PAR-2 receptors are thought to be involved in the itch of atopic dermatitis and mediate cowhage-induced itch (see above). Cathepsin S, an endogenous protease, also induces itch via PAR-2 and PAR-4 receptors[37].

MEDIATORS OF PRURITUS

Various mediators that act centrally and/or peripherally are involved in pruritus, including histamine, proteases, substance P, opiates, NGF and prostaglandins. In inflammatory skin diseases such as urticaria, pro-inflammatory mediators produce pruritus and also cause other signs of inflammation (e.g. erythema due to vasodilation, increased vascular permeability). The relative potencies of the major mediators with regard to these responses (including pruritus) are listed in Table 5.2. Some of these mediators cause pruritus indirectly by evoking release of histamine and other mediators (e.g. substance P and several opioid peptides) from mast cells or by potentiating the actions of other mediators (e.g. prostaglandins E_1 and E_2).

Histamine

Histamine is the archetypal mediator of signs and symptoms of inflammation, including pruritus. In the skin, histamine is contained primarily within the granules of dermal mast cells. Histamine can be released from mast cells upon activation of a range of receptors, including the high-affinity IgE receptor (FcεRI), the KIT receptor for stem cell factor, receptors for neuropeptides (e.g. substance P, NGF) and complement C5a. In IgE-mediated acute urticaria, histamine is released when a specific antigen cross-links adjacent FcεRIs via their α-chains. In autoimmune chronic urticaria, similar cross-linking occurs via functional circulating IgG or (less commonly) IgE autoantibodies that react with epitopes expressed on the α-chain of FcεRI[38] (see Fig. 18.3). Histologically, dermal mast cells and unmyelinated neurons are closely juxtaposed (Fig. 5.2), raising the possibility of a close ("synapsis-like") functional relationship between the immune and nervous systems.

Histamine's pruritic action can be potentiated by prostaglandin E_1 and E_2. Evidence for histamine as the main mediator of pruritus is limited to a few skin diseases, including acute and chronic urticaria and mastocytosis (e.g. urticaria pigmentosa). H_1 antihistamines are usually effective in these disorders.

Recognition of the histamine H_4 receptor has expanded our understanding of the physiologic actions of histamine. The H_4 receptor is expressed by neurons and bone marrow-derived cells (e.g. eosinophils, mast cells, dendritic cells, monocytes, $CD8^+$ T cells). It mediates chemotaxis in the latter group and is thought to have a role in the inflammation and pruritus of atopic dermatitis. H_4 antagonists are under development and have been shown to alleviate experimental pruritus. In animals models of itch, the effects of H_4 antagonists are synergistic with those of centrally acting H_1 antihistamines (e.g. diphenhydramine)[39,40].

Gastrin-Releasing Peptide

As noted above, itch-specific GRPR-positive neurons in the dorsal horn of the spinal cord have been identified in mice[15]. Although named for its role in regulating gastrointestinal functions, the GRP ligand of GRPRs is widely expressed in the CNS and peripheral sensory neurons, including MRGPR-expressing C-fiber neurons that terminate in the epidermis.

Proteinases

Human dermal mast cells produce two proteases: tryptase and chymase. The proximity of dermal mast cells to afferent C-neuron terminals within the skin suggests a functional relationship between these two cell types. Mast cell-derived tryptase contributes to the neurogenic inflammatory response[14]. The activated mast cell releases tryptase (along with other mediators, including histamine), which in turn activates PAR-2, a G protein-coupled receptor present on C- fiber terminals (see Fig. 5.2); specifically, "self-activation" of PAR-2 occurs after cleavage exposes a tethered ligand domain. Kallikrein and cathepsins in the skin have also been implicated in itch induction via activation of PAR-2. The activated C fibers transmit this information to the CNS, where it induces itch. In addition, activation leads to local release of neuropeptides, including substance P and calcitonin gene-related peptide, which induce neurogenic inflammation[41].

Studies using dermal microdialysis have shown that tryptase levels are elevated fourfold in non-lesional forearm skin of atopic dermatitis patients[14]. Expression of PAR-2, the receptor for tryptase, is significantly elevated in the epidermis and cutaneous nerve fibers of eczematous lesions, while non-lesional skin demonstrates a less pronounced increase in PAR-2. It is noteworthy that proteinase (e.g. cathepsin B) activity can also be found in common allergens (e.g. grass pollen, house dust mites)[42], and *Staphylococcus aureus* can induce secretion of proteases; both of these exogenous factors are known to aggravate atopic dermatitis and itch.

The role of epidermal serine proteases in eliciting itch is supported by a mouse model where overexpression of a serine protease led to severe itch and scratching (Table 5.3) as well as the serine protease inhibitor deficiency (leading to excess epidermal protease activity) that underlies Netherton syndrome, an autosomal recessive ichthyosiform disorder with prominent pruritus and atopic manifestations (see Ch. 57). These observations suggest that interactions between proteases and receptors on C fibers play important roles in itch and cutaneous inflammation.

Opioid Peptides

The concept of central pruritus (and the possible involvement of pruritic mediators located within the CNS) is becoming increasingly recognized in both cutaneous and systemic diseases, with implications for treatment. The perception of pruritus is modified by endogenous opiates via central and peripheral opioid receptors. It has been suggested that generalized pruritus is induced by an imbalance between the μ- and κ-opioid systems. Activation of μ-opioid receptors stimulates itch perception, whereas κ-opioid receptor stimulation inhibits μ-receptor effects, both centrally and peripherally[43,44].

Morphine and other endogenous and exogenous μ-opioid receptor agonists are known to cause generalized pruritus[1,2,44–46]. Morphine also causes pruritus and erythema when injected intradermally. This

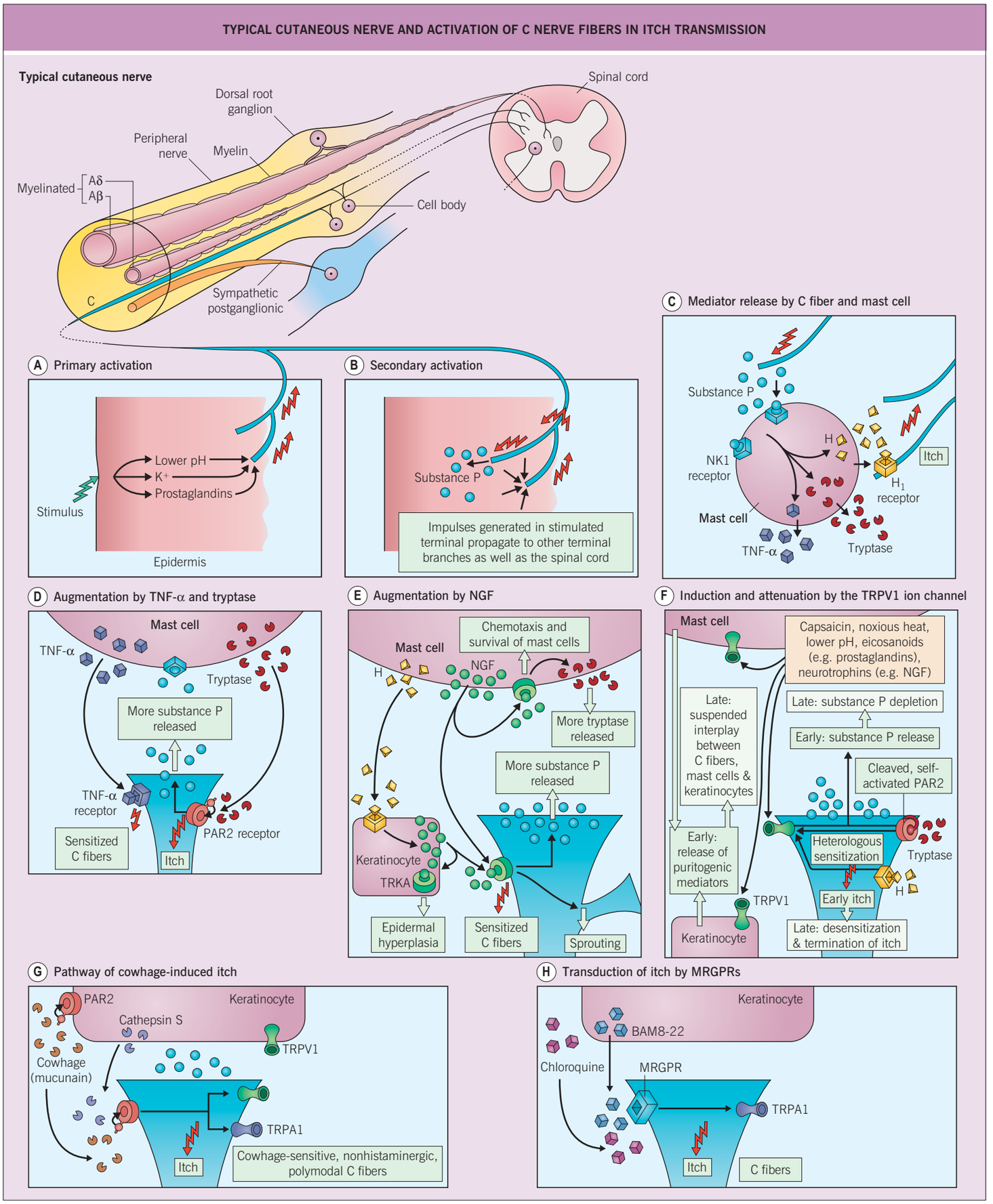


Fig. 5.2 See following page for legend.

Fig. 5.2 Typical cutaneous nerve and activation of C nerve fibers in itch transmission. There are two categories of axons in a typical cutaneous nerve: primary afferent Aβ, Aδ and C fibers (cell bodies in dorsal root ganglion) and sympathetic postganglionic fibers (cell bodies in sympathetic ganglion). Separate C fibers (~5% of total) are known to carry pruritogenic stimuli via two pathways: (1) histamine-induced itch that is transmitted by mechanically insensitive, capsaicin-sensitive (via *t*ransient *r*eceptor *p*otential *v*anilloid receptor 1 [TRPV1]) fibers; and (2) cowhage (mucunain)-induced itch accompanied by a burning sensation that is transmitted by polymodal fibers (sensitive to capsaicin, mechanical and other stimuli). **A** In primary (direct) activation of C fibers, the stimulus (e.g. impaired barrier function, environmental changes or inflammation) induces lower pH, potassium release, or synthesis of prostaglandins (the latter increasing sensitivity of C-fiber terminals to a number of substances). Environmental factors that increase (more likely to result in itch) or decrease (more likely to result in pain) stratum corneum pH can lead to C fiber activation. **B** In secondary activation, impulses generated in the stimulated terminal propagate not only to the spinal cord but also to other terminal branches (antidromic reflex arc), where they induce release of substance P. **C** Substance P primes mast cells via neurokinin-1 (NK1) receptors. Activated mast cells release histamine (H), which causes transmission of itch via H_1 receptors on histamine-sensitive C fibers. Mast cells also secrete tumor necrosis factor (TNF)-α and tryptase upon stimulation by substance P and nerve growth factor (NGF), respectively. **D** TNF-α sensitizes C fibers. Tryptase cleaves the extracellular portion of proteinase-activated receptor-2 (PAR2) on C-fiber terminals, exposing a tethered ligand domain that binds and "self-activates" PAR2. This results in transmission of itch by the C fibers as well as release of additional substance P. **E** NGF released by mast cells and keratinocytes (with increased production stimulated by histamine) activates tropomyosin-related kinase receptor A (TRKA) on C fibers, mast cells and keratinocytes. This induces C-fiber sprouting, sensitization and increased substance P release; mast cell chemotaxis, survival and increased tryptase release; and epidermal hyperplasia. Of note, TRKA is also referred to as neurotrophic tyrosine kinase receptor type 1 (NTRK1). **F** The TRPV1 ion channel on C fibers, keratinocytes and mast cells is activated by capsaicin, heat, low pH, eicosanoids and neurotrophins; although this initially stimulates transmission of itch and release of pruritogenic mediators, it may eventually lead to desensitization, neuropeptide depletion and attenuation of itch. The transmission of histamine-induced itch requires the presence of TRPV1. **G** Cowhage-induced itch occurs through the release of mucunain, a protease that activates PAR2 and PAR4 receptors (the latter not yet identified in the skin); these receptors can also be activated by endogenous proteases such as cathepsin S. Activation of PAR2/4 sensitizes TRPV1 and TRP ankyrin 1 (TRPA1) channels, resulting in cross-talk and itch transmission. **H** C nerve fibers (including those responsive to histamine) in the epidermis also express MAS-related G protein-coupled receptors (MRGPRs), which are stimulated by chloroquine or bovine adrenal medulla 8-22 peptide (BAM8-22; a proteolytically cleaved product of proenkephalin A). TRPA1 is required for transduction of itch by MRGPRs.

response is only partially inhibited by the μ-opioid receptor antagonist naloxone but is substantially inhibited by topical pretreatment of the injected skin with the potent H_1 antihistamine doxepin[47]. In contrast to morphine, the highly potent μ-opioid agonist fentanyl does not induce mast cell degranulation, even when applied in high doses. Therefore, opioids appear to induce itch via two possible mechanisms: (1) degranulation of cutaneous mast cells[48]; and (2) activation of μ-opioid receptors with a direct central and peripheral pruritogenic effect[48–51]. Morphine-induced itch was recently shown to result from activation of a heterodimeric receptor composed of the μ-opioid receptor and the gastrin-releasing peptide receptor; inhibition of the latter blocked opioid-related itch but not analgesia, an observation that may have therapeutic relevance[51a].

Nociceptin, the endogenous peptide ligand for the *o*pioid *r*eceptor-*l*ike 1 (ORL1) receptor, has also been implicated in cutaneous inflammation, pain and pruritus[52]. Investigations using a mouse model suggested that nociceptin interacts with ORL1 receptors expressed on keratinocytes, leading to the production of leukotriene B_4 that induces scratching[53]. Nociceptin-induced scratching was significantly inhibited by treatment with systemic naloxone.

Substance P

Substance P, a neuropeptide with a widespread distribution in peripheral nerves and the CNS, intensifies itch perception. Levels of substance P in the serum of patients with atopic dermatitis are elevated and correlate with disease severity[54]. Intradermal injection of substance P provokes itch as well as elements of neurogenic inflammation such as erythema and the wheal-and-flare reaction. Substance P is synthesized in the cell bodies of C neurons, transported towards the peripheral nerve terminals, and released by antidromic depolarization to cause vasodilation and increased vascular permeability (see Fig. 5.2).

Although endogenously released substance P does not degranulate mast cells in healthy human skin[55] or cause any sensation at physiologic concentrations[56], direct communication between nerve fibers and mast cells via substance P has been verified[57]. High concentrations of substance P can cause immediate mast cell degranulation, whereas low concentrations specifically activate neurokinin-1 (NK-1) receptors on mast cells, leading to sensitization of these cells and increased production of tumor necrosis factor (TNF)-α[58]. In turn, TNF-α sensitizes nociceptive nerve endings, producing a self-amplifying loop between neurons and mast cells.

Substance P co-localizes with other neurotransmitters such as serotonin, dopamine and calcitonin gene-related peptide, and it can act as

MURINE MODELS OF ITCH		
Model	**Clinical and laboratory features**	**Pathogenesis/comments**
Transgenic mice overexpressing PAR2	Epidermal hyperplasia and scaling as well as pruritus and scratching	
Transgenic mice overexpressing a serine protease	Pruritus and scratching	
TRPV1-deficient mice and Pirt-deficient mice	Lack of response to pruritogens	Pirt normally plays an important role in sensing itch (histaminergic and non-histaminergic; also pain) via TRPV1 channels (and also TRPV1-independent itch)
MRGPR-deficient mice and TRPA1-deficient mice	Lack of scratching response to chloroquine and BAM8-22, but preserved response to histamine	MGGPRs are normally activated by chloroquine and BAM8-22, so the lack of response in TRPA1-deficient mice implicates this receptor in downstream signaling
GRPR-deficient mice	Lacking of scratching response to pruritogens, but preserved response to painful stimuli	GRPR is expressed in the dorsal spinal cord
Bhlhb5-deficient mice	Enhanced scratching response to pruritogens	Selective loss of inhibitory interneurons in the dorsal horn that regulate pruritus
μ-Opioid receptor-deficient mice	Thinner epidermis, higher density of epidermal nerve endings, and less scratching	
Transgenic mice overexpressing interleukin-31	Pruritus, scratching, excoriations and alopecia	

Table 5.3 Murine models of itch. Bhlhb5, basic helix-loop-helix family member B5; GRPR, gastrin-releasing peptide receptor; MRGPR, Mas-related G protein-coupled receptors; PAR2, protease-activated receptor 2; Pirt, phosphoinositide-interacting regulator of transient receptor potential channels; TRPV1, transient receptor potential vanilloid 1.

a neuromodulator. The relationship between substance P and keratinocytes expressing vanilloid receptors remains to be elucidated.

Neurotrophins

Neurotrophins are factors that regulate the growth and function of nerve cells. The prototypic neurotrophic factor is nerve growth factor (NGF). Other members of this family include neurotrophins 3, 4 and 5 and brain-derived neurotrophic factor (BDNF)[59]. Increased levels of epidermal NGF correlate with proliferation of terminal cutaneous nerves and upregulation of neuropeptides (e.g. substance P)[60]. NGF is known to induce sprouting of nerve fibers, sensitization of nerve endings, axonal transport in dorsal root ganglia cells, and increased expression of neuropeptides (e.g. substance P)[61].

Keratinocytes express high levels of NGF, and NGF not only is required for survival and regeneration of sensory neurons but also controls the responsiveness of such neurons to external stimuli[62,63]. Patients with atopic dermatitis have increased expression of NGF in cutaneous mast cells, keratinocytes and fibroblasts[64], and their plasma levels of NGF correlate with disease activity. There is growing evidence that NGF acts as a signaling molecule between mast cells and keratinocytes in allergic skin diseases. Mast cell-derived histamine induces keratinocytes to increase NGF production, and the latter may promote infiltration of mast cells into inflamed skin[65,66]. Upregulation of other neurotrophins, such as neurotrophin 4, has also been observed in keratinocytes from atopic dermatitis patients[67].

Prostanoids

In the skin, prostaglandins enhance histamine-induced itch[68,69]. Prostaglandins are the products of the transformation of the essential fatty acid arachidonic acid by cyclooxygenase-1 (COX-1) or cyclooxygenase-2 (COX-2). They are not by themselves pruritogenic when injected into skin. However, intradermal injection of prostaglandin E_1 (PGE_1) enhances pruritus due to histamine subsequently injected into the same site[70]. It appears that only itch-mediating neurons that display lasting activation following exposure to histamine are excited by PGE_2, and mechanosensitive fibers are unresponsive to both histamine and PGE_2.

PGE_2 has also been shown to have a direct, low-level pruritogenic effect both in healthy individuals and atopic dermatitis patients (without inducing protein extravasation). This suggests that prostanoids' peripheral action is not solely via histamine and that prostanoids may potentiate pruritus via other effects on nerve fibers.

Oral administration of aspirin, a cyclooxygenase inhibitor, does not ameliorate pruritus except in polycythemia vera[71]; however, topical application of aspirin may reduce pruritus in patients with chronic localized itch[72]. The role of other eicosanoids, including leukotrienes and 12-hydroxyeicosatetraenoic acid (12-HETE), in the pathogenesis of pruritus is unclear. In a mouse model, leukotriene B_4 provoked scratching[53].

Mediators that Activate Transient Receptor Potential Receptors

Neuromediators that activate ion channels belonging to the *t*ransient *r*eceptor *p*otential (TRP) family are also involved in the sensation of itch. TRP vanilloid 1 (TRPV1) is a vanilloid receptor located on C nerve fibers, dermal mast cells, dendritic cells and keratinocytes (see Fig. 5.2)[73]. This receptor is activated by capsaicin, endogenous substances such as cannabinoids (e.g. anandamide), prostaglandins and various neurotrophins, as well as by acidosis and temperatures above 43°C (109°F; mediates heat pain). Mechano-insensitive pruritoceptive C-nerve pathways can be activated by capsaicin, indicating that TRPV1 is expressed, and the experimental induction of histamine- and serotonin-mediated itch requires cooperation of TRPV1 receptors[74]. In addition, stimulation of TRPV1-positive nerve fibers releases multiple pruritoceptive mediators (e.g. interleukins [ILs], neuropeptides). Of note, cannabinoid receptors CB1 and CB2 are also found in the epidermis, and a cannabinoid agonist has been shown to inhibit histamine-induced itch[75].

TRPV3 is a thermosensor sensitive to temperatures >33°C (91°F; detects warmth) that is expressed in keratinocytes and dorsal root ganglion neurons in humans. In mice, a gain-of-function missense mutation in TRPV3 results in chronic itch, scratching and an atopic-like dermatitis[76]. In contrast, TRP melastatin 8 (TRPM8) on C nerve fibers functions as a thermosensor for cool (<28°C, 82°F) and is activated by menthol and icilin, which provide a "cooling" sensation that has been used to relieve itch.

TRP ankyrin 1 (TRPA1), a polymodal nociceptor, was recently found to be a downstream mediator of histamine-independent itch stimulated by MRGPRs (present in a subset of epidermal C fibers; see above) in mice[77]. Like TRPM8, TRPA1 can be activated by menthol.

Other Peripheral Mediators of Itch

Neurotransmitters

Neurotransmitters that play a role in itch include acetylcholine, an important neurotransmitter in the autonomic nervous system. Intradermal injection of acetylcholine typically induces pain; however, in patients with chronic itch, it induces itch. In murine models of itch, activation of the muscarinic receptor 3 triggers pruritus[78]. Currently there are no data regarding the role of norepinephrine, epinephrine or dopamine in itch transmission.

Peptidases

Mast cells that express neuropeptides also generate neuropeptide-degrading peptidases such as angiotensin-converting enzyme (ACE) and neural endopeptidases. The role they play in itch is unclear; however, medications such as ACE inhibitors, which can induce pruritus without a rash, may induce itch by inhibiting the activity of these degrading enzymes.

Other mediators with potential roles in itch

Serotonin has been implicated as an inducer of itch in murine models; however, in humans it is a very mild pruritogen. Nitric oxide is another factor that may induce itch via neurogenic inflammation[79]**.** The bovine adrenal medulla 8-22 (BAM8-22) peptide, a proteolytically cleaved product of proenkephalin A, is a potent activator of MRGPRs and can stimulate itch, usually accompanied by a stinging or burning sensation[80]. Chloroquine can also induce itch by activating MRGPRs, which are expressed by subset of C nerve fibers in the epidermis (see above).

Immune Cells as Itch Mediators and Modulators

Interactions between the nervous and immune systems in the skin have important roles in itch induction[81]. Neuropeptides released by cutaneous sensory nerves (e.g. substance P, calcitonin gene-related peptide, vasointestinal peptide) can activate transcription factors and regulate the expression of adhesion molecules and proinflammatory cytokines, thereby modulating immune and inflammatory responses[41]. These neuropeptides also influence cellular proliferation and differentiation, tissue repair, and antigen presentation involving a number of cell types, including keratinocytes, mast cells, dermal microvascular endothelial cells, and Langerhans cells. This interaction is bidirectional, as cytokines and chemokines are also able to regulate primary nerve afferents via receptor activation.

IL-2 is produced by activated T lymphocytes and causes pruritus when injected intradermally[82]. High-dose IL-2 administered intravenously to patients with cancer (including stage IV melanoma) causes intense generalized pruritus. Moreover, treatment with topical calcineurin inhibitors, which block the production of IL-2, can result in decreased itch. IL-2-induced pruritus is not reduced by antihistamines nor nonsteroidal anti-inflammatory drugs, and whether it represents a direct receptor-mediated effect or an indirect effect (e.g. via mast cells or endothelial cells) remains to be determined.

IL-31 is produced by T helper 2 (Th2) cells and induces pruritus by modulating the function of sensory neurons. IL-31 may exert its pruritogenic effect via activation of the IL-31 receptor (IL-31R, a heterodimer composed of the oncostatin M receptor [OSMR] β protein and the IL-31 receptor A) on keratinocytes, which could subsequently stimulate C fibers in the skin; the IL-31R is also found on cutaneous C fibers and in dorsal root ganglia. Signaling via the IL-31R and OSMR (a heterodimer composed of the OSMR β protein and a gp130 subunit) can result in keratinocyte proliferation, differentiation and apoptosis, as well as cutaneous inflammation[83]. In addition, mutations in the gene encoding the OSMR β protein underlie *familial primary localized*

cutaneous amyloidosis, an autosomal dominant disorder characterized by chronic localized itching and scratching that results in deposition of keratin-derived amyloid in the dermis[84]. Higher levels of IL-31 expression are found in the skin of patients with atopic dermatitis and prurigo nodularis[85,86], suggesting an important role for this cytokine in the intense itching that characterizes these conditions.

TNF-α is known to sensitize nociceptive nerve endings via its effect on TNF receptors (see Fig. 5.2); however, its role in itch is unclear. Although targeted TNF-α inhibitors (see Ch. 128) do not directly decrease pruritus, thalidomide (which has anti-TNF-α effects) can be effective in treating the itch associated with prurigo nodularis[87].

IL-6 is expressed by immune, nerve and Schwann cells[88], and levels of this cytokine are elevated in prurigo nodularis lesions[89].

Chronic Itch

Chronic itch may occur in the setting of pruritoceptive itch (originating from skin disease) or neuropathic itch (due to pathology in the nervous system) and can also have systemic or psychiatric causes[90]. It often has a significant effect on patients' quality of life. Chronic itch and chronic pain share a number of features, with both potentially involving peripheral and central sensitization[91] (Table 5.4).

Peripheral sensitization in chronic itch

An increased density of cutaneous nerve endings is observed in some forms of chronic itch[91]. Patients with chronic itch in the setting of atopic dermatitis have increased neurotrophin levels in involved skin, including NGF and neurotrophin 4[67]. Chronic localized pain is associated with elevated levels of the same neurotrophins, which are known to sensitize nociceptive neurons[59].

Central sensitization in chronic itch

Chronic itch leads to sensitization of second-order neurons within the dorsal horn (see Fig. 5.1), thereby leading to increased sensitivity to itch. There are two forms of increased sensitivity to itch: alloknesis and punctate hyperknesis. In alloknesis, stimuli that normally do not induce itch (e.g. touch, gentle warming) do so in the skin that surrounds a pruritic area[92]. This phenomenon is analogous to allodynia, in which gentle mechanical stimuli give rise to a perception of pain. Like allodynia, alloknesis requires ongoing activity in primary afferent C fibers and is mediated by low-threshold myelinated mechanoreceptor Aβ fibers (see Fig. 5.2). Alloknesis is common and represents a prominent feature of atopic dermatitis; it explains patients' complaints of severe pruritus associated with sweating, sudden changes in temperature, dressing and undressing. Punctate hyperknesis is characterized by more intense prick-induced itch sensations in the zone surrounding an area of inflammation (including that induced by histamine iontophoresis). It is similar to the phenomenon in chronic pain termed punctate hyperalgesia.

In patients with chronic itch, painful stimuli (e.g. electrical stimuli, heat pain) may be perceived as itch[93–95]. An analogous phenomenon can occur in patients with chronic pain, in whom histamine iontophoresis is perceived as painful[96]. These findings indicate that pain-induced inhibition of pruritus may be compromised in patients with chronic itch. This may also explain why scratching aggravates itch in patients with chronic itch and thereby induces a vicious itch–scratch cycle.

COMPARISON OF CHARACTERISTICS OF CHRONIC ITCH AND CHRONIC PAIN

	Chronic itch	Chronic pain
Peripheral sensitization	Peripheral sensitization of C nerve fibers	Peripheral sensitization of C nerve fibers
Central sensitization	Alloknesis Punctate hyperknesis	Allodynia Punctate hyperalgesia
Neuromediators	Nerve growth factor Neurotrophin 4	Nerve growth factor Neurotrophin 4
Chemical mediators	Histamine Cowhage (mucunain) Most opioids induce itch	Bradykinin Most opioids reduce pain
CNS areas activated	Anterior and posterior cingulate cortex Premotor area Precuneus Supramarginal gyrus Dorsolateral prefrontal cortex Insula-claustrum complex Somatosensory cortex I, II	Anterior cingulate cortex Premotor area Somatosensory cortex I, II Dorsolateral prefrontal cortex Insula-claustrum complex

Table 5.4 Comparison of characteristics of chronic itch and chronic pain.

Itch Related to Impaired Skin Barrier Function

Itch is a common symptom of xerotic skin and is aggravated during the winter in cold climates when the relative humidity falls indoors. Damage to the stratum corneum and the impaired barrier function that results can induce itch even without inflammation. Environmental changes (e.g. in pH, temperature and humidity) may serve as triggers that activate C nerve fibers to transmit the sensation of itch. Cross-talk between the stratum corneum and nerve fibers may explain the pruritus associated with impaired barrier function. Studies have demonstrated that keratinocytes release neuromediators upon damage to the stratum corneum barrier, and nerve fibers sprout in the epidermis in response to this damage. In a murine model of dry skin, enhanced c-*fos* expression in the CNS was observed, reflecting an activation of axons[97,98].

Additional evidence comes from a murine model of atopic dermatitis in which barrier damage was associated with significantly increased scratching, and scratching activity diminished when the barrier was repaired[99]. Serine proteases that activate PAR2 (thereby stimulating itch) are secreted in response to an increasing (alkaline) stratum corneum pH, which is commonly noted during barrier damage. This suggests that environmental factors that increase stratum corneum pH may increase itch perception (see Fig. 5.2). In contrast, a low-pH extracellular environment causes C nociceptors to induce pain.

Senescent Skin and Itch

Itch is a particularly frequent dermatologic symptom in individuals over 65 years of age[100,101]. Although dry skin is probably the most common trigger, elderly patients can have idiopathic itch without xerosis. Other possible explanations include age-related changes in nerve fibers and central disinhibition of itch due to loss of input from pain fibers. Additional cutaneous changes that may contribute to pruritus (as well as xerosis) in elderly patients include decreased skin surface lipids, decreased sweat and sebum production, and diminished barrier repair[102].

TREATMENT OF PRURITUS

Pruritus can significantly impair the quality of life in affected individuals. Acute itch may lead to agitation and difficulty concentrating, while chronic pruritus can have sequelae such as depression and decreased sexual desire or function[103].

Pharmacologic Treatments

Unlike pain, for which a host of effective medications are available, there are no general-purpose, consistently beneficial antipruritic drugs. However, recent discoveries of specific neural networks that are involved in itch transmission have led to advances in this relatively unexplored area of medicine. The mechanisms, uses and side effects of currently available antipruritic drug treatments are outlined in Table 5.5. Of note, although capable of relieving pruritus due to inflammatory skin disease, corticosteroids are not intrinsically antipruritic.

Non-Pharmacologic Treatments

Cutaneous field stimulation

Cutaneous field stimulation (CFS) is a technique that electrically stimulates afferent fibers, including nociceptive C fibers. CFS is similar to transcutaneous electrical nerve stimulation (TENS), but the latter activates large myelinated nerve fibers while CFS specifically targets unmyelinated C nerve fibers. In a study of patients with localized pruritus, CFS significantly reduced patient-reported itch and caused degeneration

DRUG TREATMENT OF PRURITUS			
Medication	**Mechanism(s) of action**	**Uses and efficacy**	**Major adverse effects**
TOPICAL AGENTS			
Capsaicin (active component in hot chili peppers)	• Activates and subsequently desensitizes TRPV1, a vanilloid TRP receptor[107] • Causes release from C neurons and (eventually) depleted stores of neuropeptides (e.g. substance P, CGRP, somatostatin) • Prolonged use leads to neuronal degeneration at sites of application, which can result in a reversible decrease in epidermal nerve fiber density[108]	• Used primarily for localized, chronic pruritic disorders, especially those of neuropathic origin[109] • Controlled studies support use for: – Notalgia paresthetica – Brachioradial pruritus – Hemodialysis-associated pruritus – Postherpetic neuralgia (transdermal patch FDA-approved for this indication)[110]	• Transient burning sensation, which usually resolves after several days of consistent use; application of topical lidocaine or EMLA may be helpful
Doxepin	• Tricyclic compound with potent antihistamine effects (H_1 and H_2); also anticholinergic properties	• Shown to relieve pruritus in patients with atopic dermatitis[111]	• Drowsiness in 25% of patients due to percutaneous absorption • Allergic contact dermatitis
Menthol	• Activates TRPM8 and TRPA1, producing a cool sensation[112]	• Inconsistent results in controlled studies[113,114] • May be especially beneficial for patients whose itch is relieved by cold showers	• Skin irritation
Pramoxine	• Anesthetic (blocks transmission of nerve impulses)	• Beneficial for histamine-induced itch and uremic pruritus in end-stage renal disease[115]	• Allergic contact dermatitis (uncommon)
Tacrolimus, pimecrolimus	• Calcineurin inhibitors that block production of multiple proinflammatory cytokines (see Ch. 128) • May initially activate and subsequently desensitize TRPV1[116]	• Can decrease itch related to the inflammation of atopic dermatitis	• Transient burning sensation
"Barrier repair" creams, other emollients and humectants	• Diminish transepidermal water loss and decrease flux between a distended and desiccated state • Minimize microfissures that expose C nerve fibers • Agents that acidify the stratum corneum may reduce itch, as alkaline agents (e.g. bar soaps) can activate proteases and increase lipid rigidity	• Decrease itch in patients with atopic dermatitis	None
SYSTEMIC AGENTS			
Antihistamines (especially doxepin)	• Doxepin is a tricyclic compound with potent antihistamine effects (H_1 and H_2) and anticholinergic properties; it represents a first-generation (classic), sedating antihistamine	• Decrease wheal formation as well as pruritus in patients with urticaria	• Sedation • Anticholinergic effects • Interaction with MAO inhibitors (for doxepin)
Naloxone, naltrexone	• μ-Opioid receptor antagonists*	• Controlled trials show efficacy for cholestatic and renal pruritus[117–121] • May be of benefit for severe pruritus of other etiologies[122]	• Hepatotoxicity • Nausea/vomiting • Insomnia • Reversal of analgesia
Nalfurafine (TRK-820)†	• κ-Opioid receptor agonist*	• Controlled trials show efficacy for renal pruritus[123]	• Insomnia
Butorphanol	• κ-Opioid receptor agonist and μ-opioid receptor antagonist*	• Relieves pruritus associated with morphine (with epidural administration of both agents)[124] • May reduce severe pruritus associated with systemic disease or inflammatory skin conditions[125‡]	• Nausea/vomiting • Dependence (rare)
Mirtazapine	• Serotonin and norepinephrine inverse agonist that reduces central itch perception	• May reduce nocturnal pruritus (at low doses, e.g. 15 mg nightly)[126]	• Sedation • Weight gain
Paroxetine	• Selective serotonin reuptake inhibitor (SSRI)	• A controlled study showed benefit for pruritus related to systemic disease[127]	• Sexual dysfunction • Sedation • Insomnia • Weight gain

*Inhibit itch transmission within the central nervous system.
†Currently not commercially available in the US.
‡An intranasal spray is currently available, and transdermal formulations are being developed.

Table 5.5 Drug treatment of pruritus. Topical naltrexone[104], aspirin and cannabinoids may also have antipruritic effects, and injections of botulinum toxin type A have been used to treat neuropathic itch[105]. In the future, topical drugs for the relief of itch may include prostaglandin DP1 receptor agonists[106], and agents that inhibit serine proteases (e.g. cathepsin S), nerve growth factor or neurotrophin 4. CGRP, calcitonin gene-related polypeptide; EMLA, eutectic mixture of local anesthetics (lidocaine + prilocaine); FDA, US Food and Drug Administration; MAO, monoamine oxidase; TRP, transient receptor potential ion channel family.

Continued

DRUG TREATMENT OF PRURITUS			
Medication	**Mechanism(s) of action**	**Uses and efficacy**	**Major adverse effects**
Thalidomide	• Blocks neuropathic afferent pathways (peripherally and centrally) • Inhibits TNF-α synthesis	• May be helpful for prurigo nodularis, actinic prurigo and pruritus of advanced age	• Teratogenicity • Peripheral neuropathy
Gabapentin, pregabalin	• Structural analogues of the neurotransmitter GABA • Thought to inhibit central itch pathways	• Beneficial for neuropathic itch (e.g. brachioradial pruritus), post-burn pruritus and postherpetic neuralgia[128–130a]	• Peripheral edema • Sedation • Abdominal pain
Aprepitant	• Antagonist of the neurokinin-1 receptor, which is activated by substance P	• Primarily used as an antiemetic in oncology patients, with anecdotal reports of reduced pruritus (e.g. in Sézary syndrome or erlotinib-induced pruritus)	• Fatigue • Hiccups

Table 5.5 Drug treatment of pruritus (cont'd). Topical naltrexone[104], aspirin and cannabinoids may also have antipruritic effects, and injections of botulinum toxin type A have been used to treat neuropathic itch[105]. In the future, topical drugs for the relief of itch may include prostaglandin DP1 receptor agonists[106], and agents that inhibit serine proteases (e.g. cathepsin S), nerve growth factor or neurotrophin 4. GABA, γ-aminobutyric acid; TNF, tumor necrosis factor.

of epidermal nerve fibers[131]. However, CFS is practical only for localized disease.

Behavioral therapy targeting the CNS

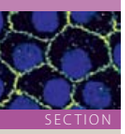
Stress and other psychogenic factors are important in itch[132]. Patients with pruritus experience higher levels of psychological stress than those without this symptom[133]. An impaired response of the autonomic nervous system to itch, scratching and emotional stress has also been identified in atopic dermatitis patients[134]. Several studies have shown that behavioral therapy reduces the intensity of itch that is perceived[135].

FUTURE DIRECTIONS

One of the most critical issues is to identify the specific mechanisms and mediators responsible for particular "itch states". Hopefully, our emerging understanding of the pathways of itch transmission will soon result in the development of effective targeted treatments.

REFERENCES

1. Yosipovitch G, Greaves MW, Schmelz M. Itch. Lancet. 2003;361:690–4.
2. Yosipovitch G, Greaves MW, Fleischer AB Jr, McGlone F (eds). Itch: Basic Mechanisms and Therapy. New York: Marcel Dekker, 2004.
3. Rea JN, Newhouse ML, Halil T. Skin disease in Lambeth. A community study of prevalence and use of medical care. Br J Prev Soc Med. 1976;30:107–14.
4. Davidson S, Giesler G Jr. The multiple pathways for itch and their interactions with pain. Trends Neurosci. 2010;33:550–8.
5. Schmelz M. Itch and pain. Neurosci Biobehav Rev. 2010;34:171–6.
6. Handwerker HO, Schmelz M. Pain: itch without pain – a labeled line for itch sensation? Nat Rev Neurol. 2009;5:640–1.
7. Schmelz M, Schmidt R, Weidner C, et al. Chemical response pattern of different classes of C-nociceptors to pruritogens and algogens. J Neurophysiol. 2003;89:2441–8.
8. Fruhstorfer H, Hermanns M, Latzke L. The effects of thermal stimulation on clinical and experimental itch. Pain. 1986;24:259–69.
9. Johanek L, Meyer R, Hartke T, et al. Psychophysical and physiological evidence for parallel afferent pathways mediating the sensation of itch. J Neurosci. 2007;27:7490–7.
10. Namer B, Carr R, Johanek LM, et al. Separate peripheral pathways for pruritus in man. J Neurophysiol. 2008;100:2062–9.
11. Davidson S, Zhang X, Yoon CH, et al. The itch-producing agents histamine and cowhage activate separate populations of primate spinothalamic tract neurons. J Neurosci. 2007;27:10007–14.
12. Shelley WB, Arthur RP. Mucunain, the active pruritogenic proteinase of cowhage. Science. 1955;122:469–70.
13. Reddy VB, Iuga AO, Shimada SG, et al. Cowhage-evoked itch is mediated by a novel cysteine protease: a ligand of protease-activated receptors. J Neurosci. 2008;28:4331–5.
14. Steinhoff M, Neisius U, Ikoma A, et al. Proteinase-activated receptor-2 mediates itch: a novel pathway for pruritus in human skin. J Neurosci. 2003;23:6176–80.
15. Sun YG, Chen ZF. A gastrin-releasing peptide receptor mediates the itch sensation in the spinal cord. Nature. 2007;448:700–3.
16. Sun YG, Zhao ZQ, Meng XL, et al. Cellular basis of itch sensation. Science. 2009;325:1531–4.
17. Liu T, Xu ZZ, Park CK, et al. Toll-like receptor 7 mediates pruritus. Nat Neurosci. 2010;13:1460–2.
18. Dawn A, Papoiu AD, Chan YH, et al. Itch characteristics in atopic dermatitis: results of a web-based questionnaire. Br J Dermatol. 2009;160:642–4.
19. Yosipovitch G, Ansari N, Goon A, et al. Clinical characteristics of pruritus in chronic idiopathic urticaria. Br J Dermatol. 2002;147:32–6.
20. Yosipovitch G, Goon AT, Wee J, et al. Itch characteristics in Chinese patients with atopic dermatitis using a new questionnaire for the assessment of pruritus. Int J Dermatol. 2002;41:212–6.
21. Darsow U, Scharein E, Simon D, et al. New aspects of itch pathophysiology: component analysis of atopic itch using the 'Eppendorf Itch Questionnaire'. Int Arch Allergy Immunol. 2001;124:326–31.
22. Yosipovitch G. Itch questionnaires as tools for itch evaluation. In: Yosipovitch G, Greaves MW, Fleischer AB Jr, McGlone F (eds). Itch: Basic Mechanisms and Therapy. New York: Marcel Dekker, 2004:169–82.
23. Andrew D, Craig AD. Spinothalamic lamina I neurons selectively sensitive to histamine: a central neural pathway for itch. Nat Neurosci. 2001;4:72–7.
24. Hsieh JC, Hagermark O, Stahle-Backdahl M, et al. Urge to scratch represented in the human cerebral cortex during itch. J Neurophysiol. 1994;72:3004–8.
25. Drzezga A, Darsow U, Treede RD, et al. Central activation by histamine-induced itch: analogies to pain processing: a correlational analysis of O-15 H_2O positron emission tomography studies. Pain. 2001;92:295–305.
26. McGlone F, Rukweid R, Howard M, Hitchcock D. Histamine-induced discriminative and affective responses revealed by functional MRI. In: Yosipovitch G, Greaves MW, Fleischer AB Jr, McGlone F (eds). Itch: Basic Mechanisms and Therapy. New York: Marcel Decker, 2004:51–61.
27. Darsow U, Drzezga A, Frisch M, et al. Processing of histamine-induced itch in the human cerebral cortex: a correlation analysis with dermal reactions. J Invest Dermatol. 2000;115:1029–33.
28. Papoiu ADP, Coghill RC, Kraft RA, et al. A Tale of two itches. Common features and notable differences in brain activation evoked by cowhage and histamine induced itch. Neuroimage. 2011 doi: 10.1016/j.neuroimage.2011.10.099.
29. Ishiuji Y, Coghill RC, Patel TS, et al. Distinct patterns of brain activity evoked by histamine-induced itch reveal an association with itch intensity and disease severity in atopic dermatitis. Br J Dermatol. 2009;161:1072–80.
30. Yosipovitch G, Ishiuji Y, Patel TS, et al. The brain processing of scratching. J Invest Dermatol. 2008;128:1806–11.
31. Vierow V, Fukuoka M, Ikoma A, et al. Cerebral representation of the relief of itch by scratching. J Neurophysiol. 2009;102:3216–24.
32. Davidson S, Zhang X, Khasabov SG, et al. Relief of itch by scratching: state-dependent inhibition of primate spinothalamic tract neurons. Nat Neurosci. 2009;12:544–6.
33. Mochizuki H, Sadato N, Saito DN, et al. Neural correlates of perceptual difference between itching and pain: a human fMRI study. Neuroimage. 2007;36:706–17. Erratum in: Neuroimage. 2008;39:911–12.
34. Papoiu AD, Wang H, Coghill RC, et al. Contagious itch in humans: a study of visual 'transmission' of itch in atopic dermatitis and healthy subjects. Br J Dermatol. 2011;164:1299–303.
35. Hilliges M, Wang L, Johansson O. Ultrastructural evidence for nerve fibers within all vital layers of the human epidermis. J Invest Dermatol. 1995;104:134–7.
36. Liu Q, Tang Z, Surdenikova L, et al. Sensory neuron-specific GPCR Mrgprs are itch receptors mediating chloroquine-induced pruritus. Cell. 2009;139:1353–65.
37. VB Reddy, SG Shimada, P Sikand, et al. Cathepsin S elicits itch and signals via protease-activated receptors. J Invest Dermatol. 2010;130:468–70.
38. Hide M, Francis DM, Grattan CE, et al. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. N Engl J Med. 1993;328:1599–604.
39. Engelhardt H, Smits RA, Leurs R, et al. A new generation of anti-histamines: histamine H4 receptor antagonists on their way to the clinic. Curr Opin Drug Discov Devel. 2009;12:628–43
40. Huang JF, Thurmond RL. The new biology of histamine receptors. Curr Allergy Asthma Rep. 2008;8:21–7.
41. Luger TA. Neuromediators – a crucial component of the skin immune system. J Dermatol Sci. 2002;30:87–93.



42. Grobe K, Poppelmann M, Becker WM, Petersen A. Properties of group I allergens from grass pollen and their relation to cathepsin B, a member of the C1 family of cysteine proteinases. Eur J Biochem. 2002;269:2083–92.
43. Pan ZZ. mu-Opposing actions of the kappa-opioid receptor. Trends Pharmacol Sci. 1998;19:94–8.
44. Umeuchi H, Togashi Y, Honda T, et al. Involvement of central mu-opioid system in the scratching behavior in mice, and the suppression of it by the activation of kappa-opioid system. Eur J Pharmacol. 2003;477: 29–35.
45. Togashi Y, Umeuchi H, Okano K, et al. Antipruritic activity of the kappa-opioid receptor agonist, TRK-820. Eur J Pharmacol. 2002;435:259–64.
46. Bigliardi PL, Tobin DJ, Gaveriaux-Ruff C, Bigliardi-Qi M. Opioids and the skin—where do we stand? Exp Dermatol. 2009;18:424–30.
47. Heyer G, Dotzer M, Diepgen TL, Handwerker HO. Opiate and H1 antagonist effects on histamine induced pruritus and alloknesis. Pain. 1997;73:239–43.
48. Fjellner B, Hagermark O. Potentiation of histamine-induced itch and flare responses in human skin by the enkephalin analogue FK-33-824, beta-endorphin and morphine. Arch Dermatol Res. 1982;274:29–37.
49. Fjellner B, Hagermark O. The influence of the opiate antagonist naloxone on experimental pruritus. Acta Derm Venereol. 1984;64:73–5.
50. Hagermark O. Peripheral and central mediators of itch. Skin Pharmacol. 1992;5:1–8.
51. Bernstein JE, Swift R. Relief of intractable pruritus with naloxone. Arch Dermatol. 1979;115:1366–7.
51a. Liu XY, Liu ZC, Sun YG, et al. Unidirectional cross-activation of GRPR by MOR1D uncouples itch and analgesia induced by opioids. Cell. 2011;147:447–58.
52. Meunier JC. Nociceptin/orphanin FQ and the opioid receptor-like ORL1 receptor. Eur J Pharmacol. 1997;340:1–15.
53. Andoh T, Yageta Y, Takeshima H, Kuraishi Y. Intradermal nociceptin elicits itch-associated responses through leukotriene B(4) in mice. J Invest Dermatol. 2004;123:196–201.
54. Toyoda M, Nakamura M, Makino T, et al. Nerve growth factor and substance P are useful plasma markers of disease activity in atopic dermatitis. Br J Dermatol. 2002;147:71–9.
55. Schmelz M, Zeck S, Raithel M, Rukwied R. Mast cell tryptase in dermal neurogenic inflammation. Clin Exp Allergy. 1999;29:695–702.
56. Weidner C, Klede M, Rukwied R, et al. Acute effects of substance P and calcitonin gene-related peptide in human skin – a microdialysis study. J Invest Dermatol. 2000;115:1015–20.
57. Suzuki R, Furuno T, McKay DM, et al. Direct neurite-mast cell communication in vitro occurs via the neuropeptide substance P. J Immunol. 1999;163:2410–15.
58. Cocchiara R, Lampiasi N, Albeggiani G, et al. Mast cell production of TNF-alpha induced by substance P evidence for a modulatory role of substance P-antagonists. J Neuroimmunol. 1999;101:128–36.
59. Mendell LM, Albers KM, Davis BM. Neurotrophins, nociceptors, and pain. Microsc Res Tech. 1999;45: 252–61.
60. Nockher WA. Neurotrophins in allergic diseases: from neuronal growth factors to intercellular signaling molecules. J Allergy Clin Immunol. 2006;117:583–9.
61. Donnerer J, Schuligoi R, Amann R. Increased content and transport of substance P and calcitonin gene-related peptide in sensory nerves innervating inflamed tissue: evidence for a regulatory function of nerve growth factor in vivo. Neuroscience. 1992;49:693–8.
62. Nakamura M, Toyoda M, Morohashi M. Pruritogenic mediators in psoriasis vulgaris: comparative evaluation of itch-associated cutaneous factors. Br J Dermatol. 2003;149:718–30.
63. Raychaudhuri SP, Raychaudhuri SK. Role of NGF and neurogenic inflammation in the pathogenesis of psoriasis. Prog Brain Res. 2004;146:433–7.
64. Groneberg DA, Serowka F, Peckenschneider N, et al. Gene expression and regulation of nerve growth factor in atopic dermatitis mast cells and the human mast cell line-1. J Neuroimmunol. 2005;161:87–92.
65. Kanda N, Watanabe S. Histamine enhances the production of granulocyte-macrophage colony-stimulating factor via protein kinase C(alpha) and extracellular signal-regulated kinase in human keratinocytes. J Invest Dermatol. 2004;122:863–72.
66. Dou YC, Hagstromer L, Emtestam L, Johansson O. Increased nerve growth factor and its receptors in atopic dermatitis: an immunohistochemical study. Arch Dermatol Res. 2006;298:31–7.
67. Grewe M, Vogelsang K, Ruzicka T, et al. Neurotrophin-4 production by human epidermal keratinocytes: increased expression in atopic dermatitis. J Invest Dermatol. 2000;114:1108–12.
68. Hagermark O, Strandberg K, Hamberg M. Potentiation of itch and flare responses in human skin by prostaglandins E2 and H2 and a prostaglandin endoperoxide analog. J Invest Dermatol. 1977;69:527–30.
69. Hagermark O, Strandberg K. Pruritogenic activity of prostaglandin E2. Acta Derm Venereol. 1977;57:37–43.
70. Greaves MW, McDonald-Gibson W. Itch: role of prostaglandins. Br Med J. 1973;3:608–9.
71. Daly BM, Shuster S. Effect of aspirin on pruritus. Br Med J (Clin Res Ed). 1986;293:907.
72. Yosipovitch G, Sugeng MW, Chan YH, et al. The effect of topically applied aspirin on localized circumscribed neurodermatitis. J Am Acad Dermatol. 2001;45:910–3.
73. Stander S, Moormann C, Schumacher M, et al. Expression of vanilloid receptor subtype 1 in cutaneous sensory nerve fibers, mast cells, and epithelial cells of appendage structures. Exp Dermatol. 2004;13:129–39.
74. Imamachi N, Park GH, Lee H, et al. TRPV1-expressing primary afferents generate behavioral responses to pruritogens via multiple mechanisms. Proc Natl Acad Sci U S A. 2009;106:11330–5.
75. Rukweid R, Dvorak M, Watkinson A, McGlone F. Putative role of cannabinoids in experimentally induced itch and inflammation in human skin. In: Yosipovitch G, Greaves MW, Fleischer AB Jr, McGlone F (eds). Itch: Basic Mechanisms and Therapy. New York: Marcel Dekker, 2004:115–30.
76. Yoshioka T, Imura K, Asakawa M, et al. Impact of the Gly573Ser substitution in TRPV3 on the development of allergic and pruritic dermatitis in mice. J Invest Dermatol. 2009;129:714–22.
77. Wilson SR, Gerhold KA, Bifolck-Fisher A, et al. TRPA1 is required for histamine-independent, Mas-related G protein-coupled receptor-mediated itch. Nat Neurosci. 2011;14:595–602.
78. Miyamoto T, Nojima H, Kuraishi Y. Intradermal cholinergic agonists induce itch-associated response via M3 muscarinic acetylcholine receptors in mice. Jpn J Pharmacol. 2002;88:351–4.
79. Andoh T, Kuraishi Y. Nitric oxide enhances substance P-induced itch-associated responses in mice. Br J Pharmacol. 2003;138:202–8.
80. Sikand P, Dong X, Lamotte RH. BAM8-22 peptide produces itch and nociceptive sensations in humans independent of histamine release. J Neurosci. 2011;31:7563–7.
81. Steinhoff M, Bienenstock J, Schmelz M, et al. Neurophysiological, neuroimmunological, and neuroendocrine basis of pruritus. J Invest Dermatol. 2006;126:1705–18.
82. Wahlgren CF, Tengvall LM, Hagermark O, Scheynius A. Itch and inflammation induced by intradermally injected interleukin-2 in atopic dermatitis patients and healthy subjects. Arch Dermatol Res. 1995;287: 572–80.
83. Zhang Q, Putheti P, Zhou Q, et al. Structures and biological functions of IL-31 and IL-31 receptors. Cytokine Growth Factor Rev. 2008;19:347–56.
84. Arita K, South AP, Hans-Filho G, et al. Oncostatin M receptor-beta mutations underlie familial primary localized cutaneous amyloidosis. Am J Hum Genet. 2008;82:73–80.
85. Sonkoly E, Muller A, Lauerma AI, et al. IL-31: a new link between T cells and pruritus in atopic skin inflammation. J Allergy Clin Immunol. 2006;117:411–7.
86. Neis MM, Peters B, Dreuw A, et al. Enhanced expression levels of IL-31 correlate with IL-4 and IL-13 in atopic and allergic contact dermatitis. J Allergy Clin Immunol. 2006;118:930–7.
87. Maurer T, Poncelet A, Berger T. Thalidomide treatment for prurigo nodularis in human immunodeficiency virus-infected subjects: efficacy and risk of neuropathy. Arch Dermatol. 2004;140:845–9.
88. Grothe C, Heese K, Meisinger C, et al. Expression of interleukin-6 and its receptor in the sciatic nerve and cultured Schwann cells: relation to 18-kD fibroblast growth factor-2. Brain Res. 2000;885:172–81.
89. Nordlind K, Chin LB, Ahmed AA, et al. Immunohistochemical localization of interleukin-6-like immunoreactivity to peripheral nerve-like structures in normal and inflamed human skin. Arch Dermatol Res. 1996;288:431–5.
90. Twycross R, Greaves MW, Handwerker H, et al. Itch: scratching more than the surface. QJM. 2003;96:7–26.
91. Yosipovitch G, Carstens E, McGlone F. Chronic itch and chronic pain: Analogous mechanisms. Pain. 2007;131:4–7.
92. Schmelz M. Itch and pain. Dermatol Ther. 2005;18:304–7.
93. Ikoma A, Handwerker H, Miyachi Y, Schmelz M. Electrically evoked itch in humans. Pain. 2005;113:148–54.
94. Ikoma A, Fartasch M, Heyer G, et al. Painful stimuli evoke itch in patients with chronic pruritus: central sensitization for itch. Neurology. 2004;62:212–7.
95. Ishiuji Y, Coghill RC, Patel TS, et al. Repetitive scratching and noxious heat do not inhibit histamine-induced itch in atopic dermatitis. Br J Dermatol. 2008;158:78–83.
96. Binder A, Koroschetz J, Baron R Disease mechanisms in neuropathic itch. Nat Clin Pract Neurol. 2008;4: 329–37.
97. Akiyama T, Merrill AW, Zanotto K, et al. Scratching behavior and Fos expression in superficial dorsal horn elicited by protease-activated receptor agonists and other itch mediators in mice. J Pharmacol Exp Ther. 2009;329:945–51.
98. Nojima H, Carstens MI,Carstens E. c-fos expression in superficial dorsal horn of cervical spinal cord associated with spontaneous scratching in rats with dry skin. Neurosci Lett. 2003;347:62–4.
99. Miyamoto T, Nojima H, Shinkado T, et al. Itch-associated response induced by experimental dry skin in mice. Jpn J Pharmacol. 2002;88:285–92.
100. Beauregard S, Gilchrest BA. A survey of skin problems and skin care regimens in the elderly. Arch Dermatol. 1987;123:1638–43.
101. Norman RA. Xerosis and pruritus in the elderly: recognition and management. Dermatol Ther. 2003;16:254–9.
102. Ward JR, Bernhard JD. Willan's itch and other causes of pruritus in the elderly. Int Dermatol. 2005;44:267–73.
103. Yosipovitch G. Pruritus: an update. Curr Probl Dermatol. 2003;15:137–64.
104. Bigliardi PL, Stammer H, Jost G, et al. Treatment of pruritus with topically applied opiate receptor antagonist. J Am Acad Dermatol. 2007;56:979–88.
105. Wallengren J, Bartosik J. Botulinum toxin type A for neuropathic itch. Br J Dermatol. 2010;163:424–6.
106. Arai I, Takaoka A, Hashimoto Y, et al. Effects of TS-022, a newly developed prostanoid DP1 receptor agonist, on experimental pruritus, cutaneous barrier disruptions and atopic dermatitis in mice. Eur J Pharmacol. 2007;556:207–14.
107. Inoue K, Koizumi S, Fuziwara S, et al. Functional vanilloid receptors in cultured normal human epidermal keratinocytes. Biochem Biophys Res Commun. 2002;291:124–9.
108. Simone DA, Nolano M, Johnson T, et al. Intradermal injection of capsaicin in humans produces degeneration and subsequent reinnervation of epidermal nerve fibers: correlation with sensory function. J Neurosci. 1998;18:8947–59.
109. Papoiu ADP, Yosipovitch G. Topical capsaicin. The fire of a "hot" medicine is reignited. Expert Opin Pharmacother. 2010;11:1359–71.
110. Backonja MM, Malan TP, Vanhove GF, Tobias JK. NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia: a randomized, double-blind, controlled study with an open label extension. Pain Med. 2011;12:99–109.
111. Drake LA, Fallon JD, Sober A. Relief of pruritus in patients with atopic dermatitis after treatment with topical doxepin cream. The Doxepin Study Group. J Am Acad Dermatol. 1994;31:613–6.
112. Peier AM, Moqrich A, Hergarden AC, et al. A TRP channel that senses cold stimuli and menthol. Cell. 2002;108:705–15.
113. Bromm B, Scharein E, Darsow U, Ring J. Effects of menthol and cold on histamine-induced itch and skin reactions in man. Neurosci Lett. 1995;187:157–60.
114. Yosipovitch G, Szolar C, Hui XY, Maibach H. Effect of topically applied menthol on thermal, pain and itch sensations and biophysical properties of the skin. Arch Dermatol Res. 1996;288:245–8.
115. Young TA, Patel TS, Camacho F, et al. A pramoxine-based anti-itch lotion is more effective than a control lotion for the treatment of uremic pruritus in adult hemodialysis patients. J Dermatol Treat. 2009;20: 76–81.
116. Pereira U, Boulais N, Lebonvallet N, et al. Mechanisms of sensory effects of tacrolimus on the skin. Br J Dermatol. 2010;163:70–7.

117. Peer G, Kivity S, Agami O, et al. Randomised cross-over trial of naltrexone in uraemic pruritus. Lancet. 1996;348:1552–4.
118. Wolfhagen FH, Sternieri E, Hop WC, et al. Oral naltrexone treatment for cholestatic pruritus: a double-blind, placebo-controlled study. Gastroenterology. 1997;113:1264–9.
119. Terg R, Coronel E, Sorda J, et al. Efficacy and safety of oral naltrexone treatment for pruritus of cholestasis, a crossover, double blind, placebo-controlled study. J Hepatol. 2002;37:717–22.
120. Bergasa NV, Talbot TL, Alling DW, et al. A controlled trial of naloxone infusions for the pruritus of chronic cholestasis. Gastroenterology. 1992;102:544–9.
121. Bergasa NV, Alling DW, Talbot TL, et al. Effects of naloxone infusions in patients with the pruritus of cholestasis. A double-blind, randomized, controlled trial. Ann Intern Med. 1995;123:161–7.
122. Metze D, Reimann S, Beissert S, Luger T. Efficacy and safety of naltrexone, an oral opiate receptor antagonist, in the treatment of pruritus in internal and dermatological diseases. J Am Acad Dermatol. 1999;41:533–9.
123. Wikstrom B, Gellert R, Ladefoged SD, et al. Kappa-opioid system in uremic pruritus: multicenter, randomized, double-blind, placebo-controlled clinical studies. J Am Soc Nephrol. 2005;16:3742–7.
124. Gunter JB, McAuliffe J, Gregg T, et al. Continuous epidural butorphanol relieves pruritus associated with epidural morphine infusions in children. Paediatr Anaesth. 2000;10:167–72.
125. Dawn AG, Yosipovitch G. Butorphanol for treatment of intractable pruritus. J Am Acad Dermatol. 2006;54:527–31.
126. Hundley JL, Yosipovitch G. Mirtazapine for reducing nocturnal itch in patients with chronic pruritus: a pilot study. J Am Acad Dermatol. 2004;50:889–91.
127. Zylicz Z, Krajnik M, Sorge AA, Costantini M. Paroxetine in the treatment of severe non-dermatological pruritus: a randomized, controlled trial. J Pain Symptom Manage. 2003;26:1105–12.
128. Ehrchen J, Ständer S. Pregabalin in the treatment of chronic pruritus. J Am Acad Dermatol. 2008;58:S36–S37.
129. Yosipovitch G, Samuel LS. Neuropathic and psychogenic itch. Dermatol Ther. 2008;21:32–41.
130. Porzio G, Aielli F, Verna L, et al. Efficacy of pregabalin in the management of cetuximab-related itch. J Pain Symptom Manage. 2006;32:397–8.
130a. Ahuja RB, Gupta R, Gupta G, Shrivastava P. A comparative analysis of cetirizine, gabapentin and their combination in the relief of post-burn pruritus. Burns. 2011;37:203–7.
131. Wallengren J, Sundler F. Cutaneous field stimulation in the treatment of severe itch. Arch Dermatol. 2001;137:1323–5.
132. Gieler U, Niemeier V, Brosig B, Kupfer J. Psychosomatic aspects of pruritus. In: Yosipovitch G, Greaves MW, Fleischer AB Jr, McGlone F (eds). Itch: Basic Mechanisms and Therapy. New York: Marcel Dekker, 2004:343–50.
133. Yamamoto Y, Yamazaki S, Hayashino Y, et al. Association between frequency of pruritic symptoms and perceived psychological stress: a Japanese population-based study. Arch Dermatol. 2009;145:1384–8.
134. Tran BW, Papoiu ADP, Russoniello C, et al. The effect of itch, scratching and mental stress on autonomic nervous system function in atopic dermatitis. Acta Derm Venereol. 2010;90:354–61.
135. Gieler U. Psychosomatic aspects of pruritus. In: Yosipovitch G, Greaves MW, Fleischer AB, McGlone F (eds): Itch: Basic Mechanisms and Therapy. New York: Marcel Dekker, 2004:343–9.

This page intentionally left blank

Pruritus and Dysesthesia 6

Elke Weisshaar, Alan B Fleischer Jr, Jeffrey D Bernhard and Thomas G Cropley

Chapter Contents

Epidemiology 111
Evaluation of the patient 111
Pruritus in dermatologic disease 113
Dermatoses that result from pruritus and associated behaviors 114
Pruritus variants 116
Pruritus in systemic disease 117
Pruritus in pregnancy 120
Pharmacologic pruritus 120
Psychogenic pruritus 120
Neurologic etiologies of pruritus and dysesthesia 120
Treatment 123

Synonyms: ■ Aquagenic pruritus: bath pruritus ■ Prurigo nodularis: chronic circumscribed nodular lichenification (Pautrier) ■ Lichen simplex chronicus: neurodermatitis ■ Brachioradial pruritus: solar pruritus, solar pruritus of the elbow, brachioradial summer pruritus ■ Notalgia paresthetica: subscapular pruritus, posterior pigmented pruritic patch, hereditary localized pruritus

Key features

- Pruritus is the most common complaint of patients with dermatologic disease
- Pruritus can occur with or (e.g. in the setting of an underlying systemic disorder) without primary skin lesions
- Pruritus is a symptom with multiple complex pathogenic mechanisms that cannot be attributed to one specific cause or disease
- Pruritus should challenge the dermatologist to search for an underlying etiology
- Management of pruritus can often be achieved by implementing specific and nonspecific treatments

INTRODUCTION

Pruritus can be defined subjectively as a sensation (usually unpleasant) that elicits a desire to scratch. The biologic purpose of pruritus is to provoke scratching in order to remove a pruritogen, a response likely to have originated when most pruritogens were parasites.

Pruritus is the most common skin-related symptom. It often arises from a primary cutaneous disorder but represents a manifestation of an underlying systemic disease in approximately 10% to 25% of affected individuals[1]. Non-dermatologic conditions that can lead to generalized pruritus include hepatic, renal or thyroid dysfunction; lymphoma, myeloproliferative disorders (e.g. polycythemia vera, hypereosinophilic syndrome) and chronic lymphocytic leukemia; HIV or parasitic infections; and neuropsychiatric disorders (see Ch. 7). In some patients, pruritus occurs in the absence of visible skin signs. Although there is no definitive system for the categorization of pruritus[2,3], in 2007 a clinical classification scheme was proposed by the International Forum for the Study of Itch[4]. This system recognizes three major groups of pruritus: (1) affecting primarily diseased/inflamed skin; (2) with chronic secondary skin lesions due to scratching; and (3) affecting non-diseased/non-inflamed skin. Underlying etiologies are categorized as dermatologic, systemic, neurologic, psychogenic and mixed. Although the limited understanding of the pathogenesis of pruritus (see Ch. 5) has hampered the development of treatments, recent discoveries provide hope for more specific therapies in the future[5].

When a patient complains of pruritus, there is a rational way to assemble the myriad of etiologies into finite groups, to evaluate the patient in a systematic manner, and then to correct the underlying cause (if possible) and treat the pruritus with currently available therapies.

EPIDEMIOLOGY

It is reasonable to assume that all humans experience the sensation of pruritus at some point in their life, e.g. from insect bites (Fig. 6.1). However, relatively few studies have investigated the overall incidence and prevalence of pruritus. A recent population-based, cross-sectional study in Germany found that the self-reported point, 12-month and lifetime prevalences of chronic pruritus (lasting at least 6 weeks) were 13.5%, 16% and 22%, respectively[5a]. In a previous Norwegian population-based, cross-sectional study on self-reported skin morbidity, pruritus was the dominant symptom among adults, more so in women than in men (experienced within the past week by 9.2% and 7.5%, respectively)[6]. Table 6.1 summarizes the reported prevalences of pruritus in a number of medical conditions.

EVALUATION OF THE PATIENT

Patients with pruritus due to either a specific dermatologic condition or an underlying systemic disease can present with nonspecific cutaneous findings such as secondary lesions (e.g. erosions, excoriations and crusts), or with no detectable cutaneous changes at all. Pruritus associated with a systemic disease may also result from a specific related dermatologic disease (e.g. eosinophilic folliculitis in a patient with AIDS). Multiple underlying factors can be identified in approximately one-third of patients with chronic pruritus[16a]. Lastly, a pruritic cutaneous condition with nonspecific clinical findings upon initial evaluation may have diagnostic features at a later date. Therefore, re-examination over time is a critical aspect of the approach to the patient with pruritus[1].

Fig. 6.1 **Insect bites – "breakfast, lunch and dinner sign" – linear pruritic papules.**

History

A precise history may provide insight into the patient's disease processes. Important characteristics of pruritus are listed in Table 6.2. The onset, duration and nature of the pruritus can help to determine its cause. If several general clues are considered, the clinician will be able to narrow the differential diagnosis:

- Localized or generalized pruritus may be a consequence of a systemic disease, and no particular clinical characteristics reliably predict the likelihood of an underlying systemic disease[17].
- An acute onset of pruritus without primary skin lesions over a few days is less suggestive of an underlying systemic disease than chronic, progressive generalized pruritus.
- Lesions on the mid upper back suggest a primary skin disease, since this difficult-to-reach region is typically spared (referred to as the "butterfly sign") in patients with skin lesions entirely due to scratching (e.g. those with pruritus of systemic or psychogenic etiology). However, although this area is generally inaccessible to the patient's hand, it can be reached with instruments (e.g. "back-scratching" devices).

PREVALENCE OF PRURITUS IN SELECTED DISEASE STATES	
Disorder	**Reported prevalence of pruritus**
Psoriasis	≤85%
Cutaneous T-cell lymphoma	70–80%
End-stage renal disease on hemodialysis	previously 60–80%, now 20–50%
Primary biliary cirrhosis	80% (presenting symptom in 25–70%)
Hepatitis C virus-infected patients	15%
Hodgkin disease	10–30%
Non-Hodgkin lymphoma	2%
Leukemias	<5%
Polycythemia vera	30–50%
Herpes zoster	≤60%
Postherpetic neuralgia	≤30%
Pregnancy	20%

Table 6.1 Prevalence of pruritus in selected disease states[1,7–16].

DESCRIPTIVE AND HISTORICAL FEATURES OF PRURITUS
DESCRIPTIVE FEATURES OF PRURITUS
• Onset: abrupt, gradual, prior history of pruritic episodes • Time course: continuous, intermittent, cyclical, nocturnal • Nature: prickling, crawling, burning, dysesthetic • Duration: days, weeks, months, years • Severity: interference with normal activities or sleep • Location: generalized or localized, unilateral or bilateral • Relationship to activities: occupational, hobbies • Provoking factors: water, skin cooling, air, exercise • Patient's personal theory as to etiology of the pruritus
OTHER HISTORICAL FEATURES
• Medications, including topical agents: prescribed, over-the-counter, illicit; duration of use and relationship to onset of pruritus • Allergies: systemic, contact • Atopic history: atopic dermatitis, allergic rhinitis, asthma • Past medical history: thyroid, liver or renal dysfunction; other systemic diseases • Family history of atopy, skin disease or similar pruritic conditions • Occupation • Hobbies • Social history: household and personal contacts, food habits, stress • Drugs: nicotine, alcohol, intravenous drugs • Bathing habits and exposure to irritants • Pets and their care • Sexual history • Travel history • Prior diagnoses made by physician or patient

Table 6.2 Descriptive and historical features of pruritus.

- Patients with pruritus that is not related to a primary dermatologic disease typically have excoriations and other secondary changes, but no primary lesions.
- Medications (prescription, over-the-counter and illicit) and supplements that the patient is taking should be reviewed and drug-induced pruritus considered.
- Some severely pruritic dermatoses such as urticaria and mastocytosis uncommonly lead to excoriations from scratching but instead result in pressing and rubbing behaviors.
- Scabies and other infestations should be considered, especially when multiple family members are affected.
- Pruritus after emergence from a bath (possibly provoked by cooling or drying of the skin) may be a sign of polycythemia vera or idiopathic aquagenic pruritus.
- Nocturnal generalized pruritus in association with chills, sweating and fever represents a classic presentation of Hodgkin disease. Pruritus may precede the onset of the lymphoma by as much as 5 years[18].
- Whereas psychogenic pruritus rarely interferes with sleep, other pruritic diseases (with or without primary skin lesions) often cause nocturnal wakening.

Examination

Careful and complete examination of the skin, nails, scalp, hair, mucous membranes and anogenital area is recommended. An assessment should be made of primary lesions and secondary changes (including their morphology and distribution), with particular attention to lichenification (Fig. 6.2), xerosis (Fig. 6.3), the presence of dermographism and

Fig. 6.2 Lichen simplex chronicus on the posterior neck. Note the increased skin markings. *Courtesy, Ronald P Rapini, MD.*

Fig. 6.3 Extreme xerosis associated with pruritus in an HIV-infected patient.

POSSIBLE LABORATORY STUDIES IN THE EVALUATION OF PATIENTS WITH GENERALIZED PRURITUS OF UNKNOWN ETIOLOGY
• Erythrocyte sedimentation rate (ESR)
• Complete blood cell count (CBC) with differential and platelet count
• Blood urea nitrogen, creatinine
• Liver transaminases, alkaline phosphatase, bilirubin
• Lactate dehydrogenase (LDH)
• Thyroid function tests (thyroid-stimulating hormone [TSH] and thyroxine levels)
• Fasting glucose, hemoglobin A1c
• Serum iron, ferritin
• Stool for ova, parasites and occult blood
• Parathyroid function (calcium, phosphate and parathyroid hormone levels)
• Chest X-ray
• Skin biopsy for routine histology
• Direct immunofluorescence studies of skin, anti-tissue transglutaminase antibodies
• Viral hepatitis screen
• HIV testing
• Anti-mitochondrial and anti-smooth muscle antibodies
• Serum IgE level; allergen-specific IgE antibody tests
• Prick tests of major atopy allergens, relevant occupational allergens; patch tests
• Serum tryptase, histamine and/or chromogranin-A levels
• Urine for sediment; 24-hour urine collection for 5-hydroxyindoleacetic acid (5-HIAA; a serotonin metabolite) and methylimidazoleacetic acid (MIAA; a histamine metabolite)
• Additional radiographic and sonographic studies, e.g. abdominal CT scan
• Serum protein electrophoresis, serum immunofixation electrophoresis

Table 6.3 Possible laboratory studies in the evaluation of patients with generalized pruritus of unknown etiology. Performance of particular tests is based upon the patient's history and physical examination. Studies with a darker background color are commonly employed as an initial screen, and the results can help to direct further evaluation.

skin signs of systemic diseases (see Ch. 53). A general physical examination (including the lymph nodes, liver and spleen) may disclose an undiagnosed extracutaneous disease (e.g. lymphoma) and should be performed in conjunction with a primary care physician in patients with pruritus of unknown etiology.

Laboratory Investigation

In the setting of generalized pruritus of unknown etiology, laboratory investigation is recommended (Table 6.3). Biopsies of skin lesions (even if nonspecific clinically) are occasionally informative, and direct immunofluorescence studies of perilesional or normal-appearing (adjacent to lesions if present) skin may point to a specific dermatologic disease such as bullous pemphigoid or dermatitis herpetiformis.

PRURITUS IN DERMATOLOGIC DISEASE

This section focuses on the sensation of pruritus in selected skin diseases where this symptom is a prominent feature. A more comprehensive discussion of the diseases mentioned and the many additional dermatoses in which pruritus is a characteristic feature (Table 6.4) may be found in other chapters.

Infestations

Scabies

In patients with scabies, pruritus can be localized or generalized and it may have a burning component. The pruritus usually begins 3 to 6 weeks after a first-time infestation (see Ch. 84), and within a few days in subsequent infestations. The itch reflects various components of the immune response against mites, eggs and scybala[1].

Pediculosis (lice)

It is rare to make the diagnosis of pediculosis without pruritus as a symptom (see Ch. 84). Pruritus of the primary sites of infestation (e.g. scalp, groin) is a clue to the diagnosis of pediculosis capitis and pediculosis pubis. Generalized pruritus is characteristic of body lice but can also occur with other types of lice[1].

DERMATOLOGIC DISEASES ASSOCIATED WITH PRURITUS	
Dermatologic disease	**Cause**
Infestation/bites & stings	• Scabies • Pediculosis • Arthropod bites
Inflammation	• Atopic dermatitis • Stasis dermatitis • Allergic or irritant contact dermatitis • Seborrheic dermatitis, especially of the scalp • Psoriasis, parapsoriasis • Pityriasis rubra pilaris • Lichen simplex chronicus • Prurigo nodularis • Prurigo pigmentosa • Bullous diseases, e.g. DH, BP • PUPPP • Eosinophilic folliculitis • Urticaria • Drug eruptions, e.g. morbilliform • Mastocytosis • Polymorphous light eruption • Papular urticaria, urticarial dermatitis
Infections	• Bacterial infections, e.g. folliculitis • Viral infections, e.g. varicella • Fungal infections, e.g. inflammatory tinea • Parasitic infections, e.g. schistosomal cercarial dermatitis
Neoplastic	• Cutaneous T-cell lymphoma, e.g. mycosis fungoides, Sézary syndrome
Genetic/Nevoid	• Darier disease • Hailey–Hailey disease • Inflammatory linear verrucous epidermal nevus (ILVEN)
Other	• Xerosis, eczema craqelé • Anogenital pruritus • Notalgia paresthetica • Primary cutaneous amyloidosis (macular, lichenoid) • Postburn and post-stroke pruritus • Scar-associated pruritus • Fiberglass dermatitis • Aquagenic pruritus

Table 6.4 Dermatologic diseases associated with pruritus. BP, bullous pemphigoid; DH, dermatitis herpetiformis; PUPPP, pruritic urticarial papules and plaques of pregnancy.

Inflammatory Dermatoses

Atopic dermatitis

Pruritus is such an important aspect of atopic dermatitis that "the diagnosis of active atopic dermatitis cannot be made if there is no history of pruritus"[19] (see Ch. 12). The itch sensation typically comes in "attacks", which may be severe and are a central component of this condition's impact on quality of life[20]. Often, pruritus is the first indication of a disease flare. A number of immunologic (e.g. exposure to aeroallergens or ingestion of foods to which the patient is sensitized) and non-immunologic (e.g. emotional stress, overheating, perspiration or contact with wool, other rough fabrics or even air [atmoknesis]) stimuli can provoke pruritus in patients with atopic dermatitis[21] (Figs 6.4 & 6.5). There is also evidence for different seasonal patterns of symptom severity (including pruritus), with most children experiencing aggravation of symptoms during the winter and others having exacerbations primarily during the summer[22].

Despite intensive research efforts, the mediators of itch in atopic dermatitis have not been clearly elucidated and the neural mechanisms of pruritus are not well understood (see Ch. 5). For example, due to inconsistent findings regarding plasma histamine levels, there is controversy with regard to the role of histamine in the pathogenesis of

Fig. 6.4 Atopic dermatitis with multiple lesions of prurigo nodularis.

Fig. 6.5 Atopic dermatitis. Multiple linear excoriations are seen on the leg.

pruritus in atopic dermatitis[23]. The minimal effectiveness of antihistamines in alleviating the itch of atopic dermatitis indicates that histamine cannot be the only pruritogen and is most likely not the predominant mediator responsible for the pruritic sensation. In general, the benefits of antihistamines in these patients are thought to result from their sedative effects[24].

Some studies indicate that antihistamines are more likely to be effective in type 2 helper T cell (Th2)-driven atopic dermatitis (i.e. early, acute flares) than in Th1-driven disease (i.e. chronic lesions)[23]. Other studies have shown that the sensations evoked by acetylcholine (ACh) and vasoactive intestinal polypeptide (VIP) are different in atopic and non-atopic individuals and depend upon the inflammatory state of atopic skin[25]. For example, ACh tends to induce burning pain in those who do not have atopic dermatitis, pruritus in patients with acute atopic dermatitis, and a mixture of pain and pruritus in atopic dermatitis patients without active eczema. These data provide evidence that pruritus can be elicited by a histamine-independent cholinergic mechanism.

Other studies suggest a possible role for neuropeptides such as substance P, calcitonin gene-related peptide (CGRP) and neurotrophins (e.g. nerve growth factor), which have been detected in the skin and peripheral blood of atopic dermatitis patients[26,27]. Down-regulation of epidermal opioid receptors may also contribute to pruritus in chronic atopic dermatitis[28]. Lesional atopic dermatitis skin contains several proinflammatory cytokines that may play a role in pruritus. Interleukin (IL)-2 has moderate pruritogenic potential[26]. IL-31 is also pruritogenic, and both this cytokine and its heterodimeric receptor are overexpressed in atopic dermatitis lesions[29,30]. In addition, mast cell tryptase (via activation of proteinase-activated receptors [PAR-2]) may be involved in the sensation of itch in atopic patients[31] (see Ch. 5). Lastly, a chronic barrage of pruritoceptive input may elicit central sensitization for itch, so that nociceptive input no longer inhibits itch but is perceived as itch. This may explain why painful stimuli can evoke itch in atopic patients with chronic pruritus[32].

Urticaria

This entity is often intensely pruritic and can also produce stinging or prickling sensations. Early lesions and small superficial wheals are particularly symptomatic[1]. Histamine plays a primary role in the pruritus of urticaria (see Ch. 18), and H_1-receptor antagonists reliably decrease or eliminate this sensation as well as the wheals themselves[33].

Psoriasis

Although it is not typically regarded as a pruritic disease, studies have shown that up to 85% of psoriasis patients suffer from pruritus[7,34]. For example, in a large American survey, 79% of patients with psoriasis reported pruritus[35]. Exacerbating factors include heat, xerosis, sweating and stress[7,34]. The back, extremities, buttocks and abdomen have been reported as the sites that are most commonly pruritic, but in one study of hospitalized patients the scalp was most often pruritic[7]. Patients frequently describe the pruritus as having tickling, crawling and burning components[7], and antihistamines rarely provide relief[1,7]. A variety of mediators of itch (e.g. substance P, nerve growth factor, IL-2) may be present in psoriatic skin, suggesting a complex, multifactorial pathophysiology for the associated pruritus[36].

Cutaneous T-Cell Lymphoma

Cutaneous T-cell lymphoma (CTCL) may be intensely pruritic, especially in patients with folliculotropic mycosis fungoides or Sézary syndrome[33] (see Ch. 120). In one study, the presence of pruritus was associated with a twofold increased risk of death[1]. Treatment strategies for severe pruritus in CTCL patients include naltrexone (50–150 mg/day), gabapentin (900–2400 mg/day in divided doses) and mirtazapine (7.5–15 mg at bedtime)[37,38].

DERMATOSES THAT RESULT FROM PRURITUS AND ASSOCIATED BEHAVIORS

Prurigo Nodularis

The lesions of prurigo nodularis are produced by chronic, repetitive scratching or picking of the skin. An underlying disorder associated with pruritus is usually present (e.g. an atopic diathesis [Fig. 6.4], psychological condition or systemic disease). The nodules themselves are also pruritic, possibly due to hypertrophy and increased density of substance P-positive nerves within affected skin, leading to perpetuation of the itch–scratch cycle. Prurigo nodularis is primarily a disease of adults, especially middle-aged women. It occasionally occurs in children and adolescents, especially those with an atopic diathesis.

Multiple lesions are characteristically distributed symmetrically on the extensor aspects of the extremities; the upper back, lumbosacral area and buttocks may also be involved, but the difficult-to-reach mid upper back is classically spared ("butterfly sign") (Fig. 6.6). Involvement of flexural areas, the face and the groin is unusual. The basic lesion is a firm, dome-shaped papulonodule with varying degrees of central scale-crust, erosion or ulceration. The color ranges from skin-toned to erythematous to brown, and hyperpigmentation is particularly common in dark-skinned individuals. Lesions can develop a verrucous or fissured surface, and lichenification of adjacent skin may be observed.

Many affected individuals have pruritus due to another dermatologic condition such as atopic dermatitis, xerosis or a systemic disease (e.g. hyperthyroidism, hepatic or renal dysfunction, lymphoma). The

Fig. 6.6 Prurigo nodularis. A Firm, hyperpigmented papulonodules on the extensor forearm. **B** Numerous lesions on the trunk, with sparing of the mid upper back ("butterfly sign"). *A, Courtesy, Ronald P Rapini, MD.*

Fig. 6.7 Lichen simplex chronicus of the scrotum. Secondary pigmentary changes are more common in patients with darkly pigmented skin. *Courtesy, Louis A Fragola, Jr, MD.*

underlying process may also be psychological, with emotional distress, obsessive–compulsive disorder, depression or other psychiatric conditions leading to repetitive scratching. The clinical differential diagnosis of prurigo nodularis may include perforating disorders (e.g. acquired perforating dermatosis), pemphigoid nodularis, hypertrophic lichen planus, hypertrophic lupus erythematosus, scabetic nodules, persistent insect bite reactions, the pruriginous type of dominant dystrophic epidermolysis bullosa, and neoplasms such as multiple keratoacanthomas or granular cell tumors.

Histologically, prurigo nodularis features massive epidermal hyperplasia and thick, compact hyperkeratosis[39]. Keratinocyte atypia is minimal or absent, and erosion may be seen. Fibrosis of the papillary dermis with vertically arranged collagen fibers, increased numbers of fibroblasts and capillaries, and a perivascular or interstitial mixed inflammatory infiltrate represent additional findings. Although hypertrophic cutaneous nerves are characteristic of this condition, they are only occasionally evident.

When a patient presents with prurigo nodularis, it is important to exclude underlying systemic causes of pruritus (see above and Table 6.3). Treatment of prurigo nodularis is usually difficult and typically requires a multifaceted approach, which should be individualized depending on etiologic factors and the extent of disease. The skin hypertrophy itself may respond to superpotent topical corticosteroids under occlusion, intralesional corticosteroids or phototherapy (e.g. broadband or narrowband UVB, psoralen plus UVA [PUVA]); benefit from excimer laser therapy has also been described. Topical (e.g. menthol, pramoxine) and systemic (e.g. antihistamines) antipruritic agents may be useful.

Treatment directed toward any underlying compulsive behavior is important. Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants have both been employed successfully, especially when a component of depression is present. Doxepin can be particularly helpful because of its antihistaminic as well as antidepressant properties. Thalidomide (50–200 mg daily) has been reported to be highly effective for patients with recalcitrant prurigo nodularis[40]. Additional treatments with reported benefit include topical capsaicin (0.025–0.3% four to six times daily), topical calcipotriene (calcipotriol), cryotherapy (which can lead to depigmentation and scarring) and (especially for patients with an atopic diathesis) oral cyclosporine.

Lichen Simplex Chronicus

Lichen simplex chronicus (LSC) represents epidermal hypertrophy that results from chronic, habitual rubbing or scratching of the skin. This leads to lesions that are broader and thinner than prurigo nodularis, which is caused by more focused picking or scratching (see above). Like prurigo nodularis, lesions of LSC itch spontaneously, leading to an "itch–rub–itch" cycle. LSC is most frequently observed in older adults and (outside the setting of lichenified lesions in atopic dermatitis) is relatively uncommon in children.

LSC is characterized by well-defined plaques exhibiting exaggerated skin lines (lichenification) with a "leathery" appearance, hyperpigmentation and varying degrees of erythema. Lesions may be solitary or multiple, with a predilection for the posterior neck (see Fig. 6.2), occipital scalp, anogenital region (e.g. scrotum, vulva) (Fig. 6.7), shins, ankles, and dorsal aspects of the hands, feet and forearms. Predisposing factors include xerosis, atopy, stasis dermatitis, anxiety, obsessive–compulsive disorder, and pruritus related to systemic disease.

The clinical differential diagnosis may include lichen amyloidosis and hypertrophic lichen planus, both of which present with chronic pruritic plaques that favor the shins. Histologic examination of LSC shows hyperkeratosis, acanthosis with irregular elongation of the rete ridges, and hypergranulosis. There may be vertically oriented collagen bundles in the papillary dermis and a sparse superficial perivascular infiltrate.

As the name implies, LSC is a chronic disorder that is often resistant to treatment. Management strategies are similar to those described above for prurigo nodularis. Underlying pruritic disorders should be identified and treated if possible. Topical corticosteroids, with or without occlusion, and intralesional corticosteroids are the mainstays of therapy. Topical calcineurin inhibitors may also be of benefit[40a]. Pruritus can be

managed with antihistamines and topical antipruritics such as menthol and pramoxine. Compulsive rubbing may improve with informal insight-oriented psychotherapy or with the use of SSRIs.

Lichen Ruber Moniliformis

First described in 1886 by Kaposi, this is a rare condition with only a handful of case reports in the literature (the most recent published almost three decades ago). Lichen ruber moniliformis manifests as erythematous, firm, cord-like linear lesions that can be composed of smaller papules. They may be both pruritic and painful. Histologic features include an atrophic epidermis, cystic dilation of eccrine sweat ducts, milia, and fibrosis of the dermis. This finding led Mehregan et al.[41] to speculate that there was an underlying abnormality in skin reactivity resulting in the formation of linear fibrotic bands, which may explain their persistence. Lesions are limited to areas of trauma, including rubbing. No effective treatments have been reported.

PRURITUS VARIANTS

Aquagenic Pruritus

Aquagenic pruritus often develops secondary to a systemic disease (e.g. polycythemia vera) or another skin disorder (Table 6.5). Criteria for the diagnosis of idiopathic aquagenic pruritus (which is uncommon) are the following: (1) severe pruritus occurring after water contact, irrespective of water temperature or salinity; (2) pruritus developing within minutes of water contact without visible skin changes, i.e. in the absence of urticaria or symptomatic dermographism; and (3) exclusion of chronic skin diseases, drug-related pruritus and systemic disorders (e.g. polycythemia vera)[42].

In aquagenic pruritus, prickling, tingling, burning or stinging sensations occur within 30 minutes of water contact and last for as long as 2 hours[1]. This is irrespective of water temperature or salinity. Typically, symptoms begin on the lower extremities and then generalize, with sparing of the head, palms, soles and mucosae[43]. Multiple etiologies for "secondary" aquagenic pruritus have been reported (see Table 6.5). The pathologic mechanism of aquagenic pruritus is unknown, although elevated dermal and epidermal levels of acetylcholine, histamine, serotonin and prostaglandin E_2 have been described[1].

Traditional therapies utilize alkalinization of bath water to a pH of 8 with baking soda. Systemic treatments including oral cyproheptadine, cimetidine and cholestyramine have shown minimal effectiveness[43]. Treatment with broadband or narrowband UVB and PUVA have been reported as efficacious, with PUVA appearing to be superior to broadband UVB[44]. Capsaicin cream (0.025%, 0.5% or 1.0%) applied three times daily for a minimum of 4 weeks can decrease symptoms, but long-term therapy may not be practical[45].

DIFFERENTIAL DIAGNOSIS OF PRURITUS OR PRICKLING SENSATIONS PROVOKED BY WATER CONTACT
DISEASE-ASSOCIATED SKIN FINDINGS TYPICALLY EVIDENT AT TIME OF VISIT
• Mastocytosis (cutaneous lesions, positive Darier's sign) • Hypereosinophilic syndrome (cutaneous lesions in >50% of patients) • Hemochromatosis (diffuse hyperpigmentation) • Polycythemia vera* (ruddy complexion)
URTICARIA BY HISTORY AND/OR CHALLENGE
• Cold urticaria • Cholinergic urticaria (secondary to hot water exposure) • Aquagenic urticaria
SKIN FINDINGS (BEYOND EVIDENCE OF SCRATCHING) TYPICALLY ABSENT
• Hodgkin disease • Myelodysplastic syndrome • Essential thrombocythemia • Itching during hot shower in sarcoidosis† • Aquagenic pruritus of the elderly (xerosis may be subtle) • Aquagenic pruritus (primary, idiopathic)
*Aspirin 300 mg once to three times daily may provide partial relief. †Single case report of a patient without cutaneous sarcoidosis.

Table 6.5 Differential diagnosis of pruritus or prickling sensations provoked by water contact.

Pruritus Ani

Pruritus ani is defined as pruritus localized to the anus and perianal skin. This condition occurs in 1–5% of the general population, with men more commonly affected than women in a ratio of 4:1[46]. The onset is insidious and symptoms may be present for weeks or years before patients seek medical attention.

Pruritus ani can be primary (idiopathic) or secondary in nature. Primary pruritus ani is defined as pruritus in the absence of any apparent cutaneous, anorectal or colonic disorder; it accounts for 25–95% of reported cases, depending upon the series[46]. Possible causes include dietary factors such as excessive coffee intake, poor personal hygiene and psychogenic disorders. Secondary pruritus ani represents perianal pruritus attributable to an identifiable etiology such as chronic diarrhea, fecal incontinence/anal seepage, hemorrhoids, anal fissures or fistulas, rectal prolapse, primary cutaneous disorders (e.g. psoriasis, lichen sclerosus, seborrheic dermatitis, allergic contact dermatitis), sexually transmitted diseases, other infections, infestations (e.g. pinworms), previous radiation therapy, and neoplasms (e.g. anal cancer)[47]. Findings on physical examination vary from normal-appearing skin to mild erythema of the perianal area to severe irritation with erythema, crusting, lichenification and erosions or ulcerations. Histologically, a nonspecific, chronic dermatitis is usually seen, but specific dermatologic diseases (e.g. lichen sclerosus) or a neoplastic disorder (e.g. extramammary Paget's disease) can be excluded.

Evaluation includes a complete history as well as a general physical and cutaneous examination, along with appropriate psychiatric screening. The latter is of importance considering that anxiety and depression have been described as aggravating factors for pruritus ani[46]. Patch testing should be considered, as one study demonstrated that 34 of 40 patients presenting with pruritus ani had an underlying dermatosis that accounted for their symptoms, including allergic contact dermatitis[48].

Rectosigmoidoscopy and/or colonoscopy may be necessary, particularly in patients with pruritus ani refractory to conventional treatment. In 109 patients with pruritus ani as their presenting complaint (mean age, 52 years), 83 (75%) had colonic or anorectal pathology ranging from hemorrhoids to cancer (26 patients had the latter diagnosis)[46]. The possibility of pinworm infection should be considered in patients with pruritus ani, especially children (see Ch. 83). If patients are receiving chronic antibiotic therapy and have liquid stools, pH testing can be performed. A pH of 8–10 has been associated with a deficiency of *Lactobacillus* spp., requiring replacement therapy.

Mild primary pruritus ani often responds to sitz baths, cool compresses, and meticulous hygiene using water-moistened, fragrance-free toilet paper or a bidet. The area is then blotted dry, with avoidance of rubbing and alkaline soaps (see Ch. 153). A mild corticosteroid cream or ointment (class 6 or 7) is often effective in controlling symptoms. However, with increasing disease severity, increasingly potent topical corticosteroids may be required, and with longstanding disease and lichenification, patients may need prolonged treatment, raising the risk of cutaneous atrophy. Topical calcineurin inhibitors (including use on a rotational basis with topical corticosteroids) may be helpful when longer courses of therapy are necessary.

Secondary pruritus ani improves with treatment of the underlying disorder, e.g. removal of a malignancy, antihelminthic therapy or hemorrhoidectomy.

Pruritus Vulvae and Scroti

These common disorders may be as incapacitating and emotionally disturbing as anal pruritus. Originally thought to be psychogenic illnesses, case series indicate that these conditions are psychogenic in only 1% to 7% of patients[1]. Like pruritus ani, patients with pruritus of the vulva or scrotum typically complain of symptoms that are worse at night, and, via repeated rubbing and scratching, lichenification often develops. The evaluation, differential diagnosis, and treatment options are similar to those for pruritus ani.

Acute pruritus of the vulva or scrotum is often related to infections, but allergic or irritant contact dermatitis should also be considered. *Chronic* pruritus in these sites may be caused by dermatoses

(e.g. psoriasis, atopic dermatitis, lichen sclerosus, lichen planus), malignancy (e.g. extramammary Paget's disease, squamous cell carcinoma) or atrophic vulvovaginitis[8,49]. Scrotal pruritus secondary to lumbosacral radiculopathy has also been described[50]. In general, irritation related to cleansing and toilet habits needs to be addressed.

Specific treatment of the underlying cause is necessary. For example, class 1 corticosteroid ointment twice daily for up to 2 months often produces a dramatic response in vulvar lichen sclerosus (see Ch. 73).

Scalp Pruritus

Skin disorders involving the scalp (e.g. seborrheic dermatitis, psoriasis, folliculitis, dermatomyositis) may present with pruritus localized to this area. However, pruritus of the scalp can also occur in the absence of any objective changes, most commonly in middle-aged individuals during periods of stress and fatigue. In such instances, various treatments such as emollients and topical corticosteroids have been employed with inconsistent efficacy[1].

Pruritus in Scars

Scar remodeling can last from 6 months to 2 years. Pruritus associated with normal wound healing is common and usually resolves over time[1]. Occasionally, pruritus and discomfort may be prolonged, sometimes in association with hypertrophic or keloidal scarring. Most likely, the pruritic sensation in immature or abnormal scars is a consequence of physical and chemical stimuli as well as nerve regeneration. Physical stimuli include direct mechanical stimulation of nerve endings during scar remodeling. Histamine, vasoactive peptides such as kinins, and prostaglandins of the E series (PGE) act as chemical mediators and may account for a "chemogenic" pruritus. The role of histamine in the early inflammatory phase of wound healing is well documented, and an increase in histamine content within keloids and hypertrophic scars appears to parallel the rate of collagen synthesis. Nerve regeneration occurs in all healing wounds, and the disproportionate number of thinly myelinated and unmyelinated C fibers present in immature or abnormal scars contributes to an increased perception of pruritus. The observation of abnormalities in small nerve fiber function within keloids has raised the possibility of a small nerve fiber neuropathy[51].

Therapy includes emollients, anti-inflammatory agents such as topical and intralesional corticosteroids, and silicone gel sheets. Oral antihistamines do not have a significant benefit. Relief of pain and pruritus associated with giant keloids was observed with oral pentoxifylline (400 mg two to three times daily)[52].

Postburn Pruritus

Approximately 85% of patients with burns experience pruritus during healing, particularly when the burns involve the limbs[53]. A gradual decrease in pruritus usually occurs, but it may be present for years. Histamine release during the inflammatory stage of the healing process correlates with collagen production. As morphine is the analgesic of choice in the treatment of burns, it may contribute to postburn pruritus as well.

Burn survivors often face psychological distress, which has been linked to an increase in pruritic sensations[54]. Reported predictors of pruritus include a deep dermal burn injury, female gender, and high psychological impact of the accident[55]. Topical emollients and antihistamines are frequently utilized but rarely provide adequate relief[54]. In a recent randomized controlled trial, oral gabapentin was found to be more effective than cetirizine for postburn pruritus[55a]. Topical anesthetics (e.g. lidocaine/prilocaine), massage therapy, and bathing in oiled water or with colloidal oatmeal may also be of benefit[56].

Miscellaneous

Fiberglass dermatitis

Fiberglass exposure is common in individuals with occupations in industry or construction, and it may provoke severe pruritus with or without visible skin lesions. Involvement of the hands and other noncovered body parts such as the upper extremities, face and upper trunk is typical. Clinically, fiberglass dermatitis may resemble scabies, eczematous dermatitis, folliculitis or urticaria (see Ch. 16)[33].

PRURITUS IN SYSTEMIC DISEASE

Renal Pruritus

Renal pruritus is a localized or generalized, paroxysmal symptom occurring in patients with chronic (not acute) renal failure. Unfortunately, the term "uremic pruritus" is often used synonymously. "Uremic pruritus" implies that the symptom is secondary to elevated serum urea levels, which is untrue.

The occurrence of renal pruritus is not associated with gender, age, race, duration of dialysis or etiology of the renal failure[1]. Patients on continuous ambulatory peritoneal dialysis (CAPD) are less affected than those on hemodialysis[1], and utilization of high-permeability rather than conventional hemodialysis may help to relieve renal pruritus[56a]. Pruritus peaks at night after 2 days without dialysis (in those on a standard hemodialysis treatment protocol), is relatively high during treatment and is lowest during the day following dialysis[9,57]. Renal pruritus has been shown to be an independent marker of mortality for patients on hemodialysis.

The etiology of renal pruritus is poorly understood, and the role of mast cells is controversial. Whereas some researchers have detected increased total numbers of mast cells (often degranulated) as well as proliferation of mast cells in the skin and various other organs (spleen, bone marrow, bowel wall), other investigators could not confirm these findings[58]. Increased plasma histamine levels in uremic patients have been detected in some but not all studies, and no relationship has been found between the plasma histamine level and severity of pruritus[58]. This is in accordance with the failure of antihistamine therapy to provide relief to affected individuals. Another possible explanation for renal pruritus is an accumulation of poorly dialyzed compounds that cross the dialysis membranes slowly[1].

Parathyroid gland activity is commonly increased in chronic renal failure, and a dramatic relief of pruritus after subtotal parathyroidectomy has been reported in some patients[1]. Serum calcium, phosphate and parathyroid hormone (PTH) levels have been shown to be significantly higher in dialysis patients with pruritus than in those without pruritus, but no correlation between the degree of symptoms and the PTH level has been observed[9,58a]. Immunohistochemical studies have failed to demonstrate PTH within the skin, nor does PTH produce pruritus when injected intradermally[9]. Additionally, pruritus is not always present in uremic patients with hyperparathyroidism[9]. In summary, the role of circulating PTH in renal pruritus is controversial.

Although xerosis is common in patients with chronic renal failure (Fig. 6.8), the presence of pruritus does not correlate with xerosis,

Fig. 6.8 Xerosis and pruritus in a patient with chronic renal failure who is receiving hemodialysis. There are a few papules of acquired perforating dermatosis admixed with the scratch marks. *Courtesy, Jean L Bolognia, MD*

THERAPEUTIC LADDER FOR RENAL PRURITUS
MEDICAL
• Topical capsaicin (0.025% three to five times daily) (2)
• Topical γ-linolenic acid (2.2% four times daily) (1)
• Topical pramoxine (1)
• Activated charcoal (6 g po daily) (1)
• Gabapentin (200–300 mg after each hemodialysis session) (1)
• Pregabalin (25 mg po daily) (2)
• UVB phototherapy (1)
• Cholestyramine (4–16 g po daily in divided doses) (2)
• Naltrexone (50 mg po daily) (2)
• Ondansetron (8 mg po or iv daily) (2)
• Nalfurafine* (TRK-820) (5 microg iv three times a week†) (1)
• Ketotifen (1–2 mg po daily) (3)
• Cromolyn sodium (135 mg po three times daily) (1)
• Montelukast (10 mg po daily) (1)
• Thalidomide (100 mg po daily) (1)
• Lidocaine (200 mg iv daily) (3)
• Erythropoietin (36 U/kg sc three times a week) (3)
SURGICAL
• Subtotal parathyroidectomy
• Renal transplant
*Kappa-opioid receptor agonist. †Post hemodialysis.

Table 6.6 Therapeutic ladder for renal pruritus. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

stratum corneum hydration or sweat secretion[59]. The role of elevated blood serotonin levels in hemodialysis patients also remains unclear[58]. Peripheral neuropathy affects up to 65% of patients who receive dialysis, raising the possibility that pruritus may be a manifestation of a neuropathy (see treatment below). The presence of specialized receptors for pruritus in chronic dialysis patients has also been proposed, but this theory does not explain the abruptness of symptom improvement after transplantation.

Opioids could potentially play a role, as they accumulate with renal failure. However, this accumulation is unrelated to the duration of disease and levels are unaltered by hemodialysis[1]. In addition, one study of hemodialysis patients found that renal pruritus was not related to serum levels of β-endorphin. Finally, it has been suggested that an immunologic alteration characterized by a proinflammatory pattern is involved in the pathogenesis of renal pruritus. In three patients, a 7-day course of topical tacrolimus ointment 0.03% led to a dramatic relief of pruritus[60]; however, these results could not be confirmed in a controlled study[61].

A brief overview of published therapeutic options for renal pruritus is provided in Table 6.6. Antihistamine use for this indication has shown only marginal efficacy[1]. Oral activated charcoal has produced good results in controlled studies, whereas cholestyramine has had variable success[1]. Ondansetron was reported as effective in patients receiving both continuous ambulatory peritoneal dialysis and hemodialysis, but these results could not be verified by more recent studies in hemodialysis patients[62]. Results of controlled trials of naltrexone have been mixed[63,64]. However, nalfurafine; a novel κ-opioid receptor agonist that is administered intravenously, was found to be effective in multicenter controlled studies[65]. In one controlled trial, thalidomide relieved pruritus in a significant number of patients[66]. There is evidence that gabapentin can also be a safe and effective therapy[67]. However, renal transplantation remains the most effective treatment, as pruritus ceases soon after this intervention.

Cholestatic Pruritus

Nearly any liver disease can present with pruritus, but the most commonly associated entities are primary biliary cirrhosis, primary sclerosing cholangitis, obstructive choledocholithiasis, carcinoma of the bile duct, cholestasis (also see drug-induced pruritus), chronic hepatitis C viral infection and other forms of viral hepatitis[1]. Pruritus in these settings tends to be generalized, migratory and not relieved by scratching. It is typically worse on the hands, feet and body regions constricted by clothing, and it tends to be most pronounced at night. In patients with chronic cholestasis, pruritus can be an early symptom that develops years before any other manifestation of the liver disease[1].

The etiology of cholestatic pruritus is unknown[10]. There are several major theories regarding mediators and mechanisms. For decades, a role for bile acids was postulated. Although intracutaneous injection of bile acids has been reported to induce pruritus, elevated serum levels of bile acids are not always associated with pruritus. Additionally, in patients with severe cholestasis, the development of hepatocellular failure tends to result in spontaneous cessation of pruritus[10]. Another hypothesis proposes that increased opioidergic neurotransmission or neuromodulation in the CNS contributes to the pruritus of cholestasis[10]. This is based upon the observation that opiate agonists induce opioid receptor-mediated scratching activity of central origin. Furthermore, cholestasis-related changes in the opioid system may lead to changes in other neurotransmitter systems such as altered serotoninergic neurotransmission. Recent studies have provided evidence that lysophosphatidic acid, a neuronal activator, may have a role in cholestatic pruritus[67a]. In summary, it is inferred that as yet unknown pruritogen(s) are produced in the liver and excreted in the bile, and they then accumulate in the plasma as a result of cholestasis[10,68].

Treatment of cholestatic pruritus depends on the underlying cause and includes gallstone removal, drug withdrawal, and interferon plus ribavirin therapy for chronic hepatitis C viral infection. Ultimately, liver transplantation for end-stage liver failure will improve symptoms. A number of systemic antipruritic therapies have been reported (Table 6.7). As there is no compelling evidence that histamine is involved in the pathogenesis of cholestatic pruritus, antihistamines have limited therapeutic benefit except for their sedating properties. Of note, gabapentin did not have a therapeutic advantage over placebo in a controlled study[68].

Hematologic Pruritus

Many hematologic diseases, especially myelodysplastic disorders, are associated with significant pruritus.

Iron deficiency

Patients with iron deficiency plus generalized or localized pruritus (especially of the perianal or vulvar region) that improved with iron supplementation have been described[1]. However, controlled trials have not been performed. Of note, iron deficiency can be a sign of polycythemia vera, other malignancies or systemic diseases that themselves cause pruritus. Excluding a gastrointestinal source of blood loss is an important consideration[11].

Polycythemia vera

Aquagenic pruritus (see above) may precede the development of polycythemia vera by several years, and approximately 30–50% of polycythemia vera patients have pruritus. Thus, this diagnosis must be suspected in all patients with aquagenic pruritus[33]. Platelet aggregation has been suggested as a possible mechanism leading to release of serotonin and other pruritogenic factors, including histamine. A mutation in the Janus kinase 2 gene (*JAK2*) that results in constitutive activation and agonist hypersensitivity in basophils has been shown to be associated with aquagenic pruritus in polycythemia vera patients. Treatment options include oral aspirin (300 mg once daily to three times a day), which is first-line therapy given the rapid relief it provides for 12–24 hours; UVB or PUVA phototherapy (reports of success); intramuscular interferon-α (good efficacy); and oral H_1- or H_2-receptor antagonists (variable results)[1,11,33].

Pruritus and Malignancy

Virtually any malignancy can induce pruritus as a paraneoplastic phenomenon, but the true relationship between cancer and this symptom is unclear. No reliable epidemiologic study has demonstrated whether malignant diseases are increased in patients suffering from unexplained pruritus. Persistent, unexplained pruritus or failure of generalized pruritus to respond to conventional therapy should warrant evaluation for an underlying malignancy[11,33]. Pruritus may be seen in advanced disease

TREATMENT OPTIONS FOR HEPATIC OR CHOLESTATIC PRURITUS	
BENEFIT CONFIRMED IN CONTROLLED CLINICAL TRIALS	
Cholestyramine*	4–16 g po daily
Ursodeoxycholic acid (ursodiol)	13–15 mg/kg po daily
Rifampin†	300–600 mg po daily (depending upon serum bilirubin level)
Naltrexone‡	25 mg po twice daily [day 1], then 50 mg po daily
Naloxone‡	0.2 microg/kg/min iv infusion preceded by 0.4 mg iv bolus
Nalmefene‡	2 mg po twice daily [day 1], 5 mg po twice daily [day 2], 10 mg po twice daily [day 3], then 20 mg po twice daily; increase as needed to maximum of 120 mg po twice daily
Propofol	10–15 mg iv (bolus), 1 mg/kg/h (infusion)
Thalidomide	100 mg po daily
EQUIVOCAL EFFECT IN CONTROLLED STUDIES	
Ondansetron§	4–8 mg iv or 8 mg po daily
BENEFIT OBSERVED IN CASE SERIES OR CASE REPORTS	
Dronabinol‖	5 mg po nightly
Sertraline¶	75 mg po daily
Paroxetine¶	10 mg po daily
Butorphanol spray**	–
Plasma perfusion (ion resin BR-350)	–
Phenobarbital	2–5 mg/kg po daily
Phototherapy: UVA, UVB	–
Stanozolol	5 mg po daily
Bright light therapy	10 000 lux reflected toward the eyes up to 60 min twice daily

*Improvement may be temporary.
†Increases hepatic metabolism of bile salts.
‡Mu-opioid receptor antagonists.
§Antagonist of 5-HT_3 receptors.
‖Cannabinoid B1 receptor agonist.
¶Selective serotonin reuptake inhibitor.
**Kappa-opioid receptor agonist and μ-opioid receptor antagonist.

Table 6.7 Treatment options for hepatic or cholestatic pruritus[33,65,68–78].

or it can be an early sign that is present for several years before the diagnosis is made[11]. However, the intensity and extent of pruritus do not correlate with the extent of tumor involvement[1].

Suggested mechanisms of tumor-associated pruritus include toxic products from necrotic tumor cells entering the systemic circulation, production of chemical mediators of pruritus by the tumor, allergic reactions to tumor-specific antigens, increased proteolytic activity and histamine release. Pruritus may also complicate malignant disease that results in obstruction of the biliary tree (e.g. carcinoma of the head of the pancreas or bile duct), and "central" pruritus (e.g. due to brain tumors) or pruritus as a consequence of treatment (e.g. surgery, radiotherapy, cytotoxic chemotherapy) can occur[11]. Pruritus associated with obstruction of the biliary tree tends to be generalized, sometimes with especially intense involvement of the palms and soles. Localized pruritus of the nose has been associated with brain tumors[1]. Symptomatic pharmacologic interventions include SSRIs, mirtazapine and thalidomide[11].

Hodgkin disease

There is a strong association between pruritus and Hodgkin disease[1]. Severe, persistent generalized pruritus is predictive of a poor prognosis, and return of this symptom may portend tumor recurrence. It has been proposed that pruritus should be added to the list of B symptoms in this disease[1].

Factors contributing to pruritus in Hodgkin disease may include eosinophilia and release of histamine (from basophils), leukopeptidases or bradykinin. Hepatic involvement by the lymphoma may occasionally play a role. Production of IL-5 by Reed–Sternberg cells can lead to eosinophilia, but whether the eosinophil count correlates with the degree of pruritus is unclear. Therapy should focus on treatment of the lymphoma, but topical corticosteroids and oral mirtazapine (7.5–30 mg/day) may be of benefit[11].

Non-Hodgkin lymphoma

Pruritus is generally less prevalent in non-Hodgkin lymphoma than in Hodgkin disease. An estimated 10% of patients with non-Hodgkin lymphoma suffer from pruritus at some time during the course of their disease. Amelioration after systemic interferon-α has been reported[11].

Leukemia

Pruritus is not a common symptom in patients with leukemia, but when it occurs, it is usually generalized. Chronic lymphocytic leukemia (CLL) and hypereosinophilic syndrome (which includes patients with eosinophilic leukemia and other hematologic malignancies; see Ch. 25) are often associated with pruritus. In addition, patients with CLL can develop exaggerated reactions to insect bites. Leukemia cutis may produce localized symptoms that include pruritus[11,33].

Endocrine Pruritus

Thyroid disease

Severe generalized pruritus may be a presenting symptom of hyperthyroidism. The cause is not known, but it is postulated to result from a direct effect of thyroid hormone on the skin[1]. Localized or generalized pruritus may also be seen in patients with hypothyroidism, but not as frequently. The skin in individuals with hypothyroidism is often dry, which can lead to asteatotic eczema accompanied by pruritus.

Diabetes mellitus

Generalized pruritus as a presenting symptom of diabetes mellitus may occur, but generalized pruritus is not significantly more common in diabetic than in non-diabetic patients[79]. Localized pruritus, especially in the genital and perianal areas (see pruritus ani), is significantly more common in diabetic women and is associated with poor glycemic control[79]. In some patients, a predisposition to candidiasis may play a role. Diabetic neuropathy is characteristically associated with pain, burning or prickling sensations, although pruritus has been described[1].

Pruritus in HIV Infection and AIDS

Occasionally, pruritus is the initial presenting symptom of AIDS. In as many as half of AIDS patients with pruritus, an additional diagnosis responsible for this symptom is not identified. However, HIV-infected individuals tend to develop a number of pruritic dermatoses such as pruritic papular eruption, eosinophilic folliculitis, severe seborrheic dermatitis, psoriasis, scabies, drug eruptions, xerosis (see Fig. 6.3) and acquired ichthyosis (see Ch. 78). Insect bites can be significantly more inflammatory and pruritic in the HIV-infected population; one hypothesis regarding the pruritic papular eruption of HIV infection is that it reflects an altered and exaggerated immune response to arthropod antigens[80]. Kaposi sarcoma lesions are occasionally pruritic, and patients with HIV infection may have causes of pruritus previously discussed (e.g. chronic renal failure, liver disease and non-Hodgkin lymphoma)[81].

Severe, treatment-resistant pruritus is relatively common in HIV-infected individuals. Immunologic analyses have shown that HIV patients with intractable pruritus have markedly elevated serum levels of IgE, peripheral hypereosinophilia and a Th2-type cytokine profile[82]. Augmented serum concentrations of IgE have been found to correlate with a faster decline in $CD4^+$ T-cell counts[1], and a possible correlation between intractable pruritus and increased HIV viral load has been observed.

Treatment should be directed at any underlying dermatoses that can be identified (see above). Topical corticosteroids, UVB phototherapy and antihistamines may be used symptomatically; antihistamines with anti-eosinophilic potential may be more effective (e.g. cetirizine). The safety of UV treatment in HIV-infected patients has been debated

COMMON PHARMACOLOGIC ETIOLOGIES OF PRURITUS	
Pathomechanism	**Medication**
Cholestasis	Chlorpromazine, erythromycin estolate, estrogens (including oral contraceptives), captopril, sulfonamides
Hepatotoxicity	Acetaminophen, anabolic steroids (including testosterone), isoniazid, minocycline, amoxicillin–clavulanic acid, halothane, phenytoin, sulfonamides
Sebostasis/xerosis	Beta-blockers, retinoids, tamoxifen, busulfan, clofibrate
Phototoxicity	8-Methoxypsoralen
Neurologic (or histamine release)	Tramadol, codeine, cocaine, morphine*, butorphanol, fentanyl, methamphetamine
Deposition	Hydroxyethyl starch
Idiopathic	Chloroquine, clonidine, gold salts, lithium
*Also non-immunologic release of histamine from mast cells.	

Table 6.8 Common pharmacologic etiologies of pruritus.

but such treatment is currently considered safe[44]. Although antiretroviral therapy (ART; formerly referred to as highly active antiretroviral therapy [HAART]) can lead to improvement in several pruritic dermatologic diseases, a variety of skin conditions (infectious, inflammatory and neoplastic) may flare when ART is started (immune reconstitution inflammatory syndrome; see Ch. 78)[81]. Another therapeutic option for pruritus and prurigo nodularis in patients with HIV infection and AIDS is thalidomide (100–300 mg/day), as it is not an immunosuppressant[33,83].

PRURITUS IN PREGNANCY

This symptom can have multiple etiologies in a pregnant patient[8] and is discussed in Chapter 27.

PHARMACOLOGIC PRURITUS

Essentially, any drug can cause a skin reaction that is associated with pruritus[1]. Pruritic drug reactions most often present as morbilliform or urticarial eruptions (see Ch. 21), but occasionally pruritus is the predominant manifestation (Table 6.8). Some medication effects (e.g. hepatotoxicity) that can lead to pruritus have a relatively long latency period. Treatment includes discontinuation of the offending agent.

PSYCHOGENIC PRURITUS

Psychogenic (somatoform) pruritus should be considered when other causes have been excluded. Psychogenic pruritus may have an intensity that parallels the emotional state and is often exaggerated[33]. No primary lesions are seen, and secondary lesions range from lichenification to excoriations. Although the patient's sleep pattern is usually uninterrupted, sedative antipruritics may be utilized as therapy, because topical agents alone are rarely effective. Generalized pruritus can be associated with anxiety disorders, depression and even psychosis (e.g. delusions of parasitosis; see Ch. 7). Consultation with a psychiatrist is recommended.

NEUROLOGIC ETIOLOGIES OF PRURITUS AND DYSESTHESIA

A dysesthesia is defined as an abnormal sensation such as tingling, burning, numbness or pruritus. It can result from abnormalities in the CNS (neurogenic) or peripheral nervous system (neuropathic). Dysesthesias, including pruritus, are usually localized (e.g. upper back, thigh; Fig. 6.9) when they are due to a neuropathy. Neurogenic causes of locoregional dysesthesia (e.g. chin, nose) include tumors of the CNS, stroke and multiple sclerosis.

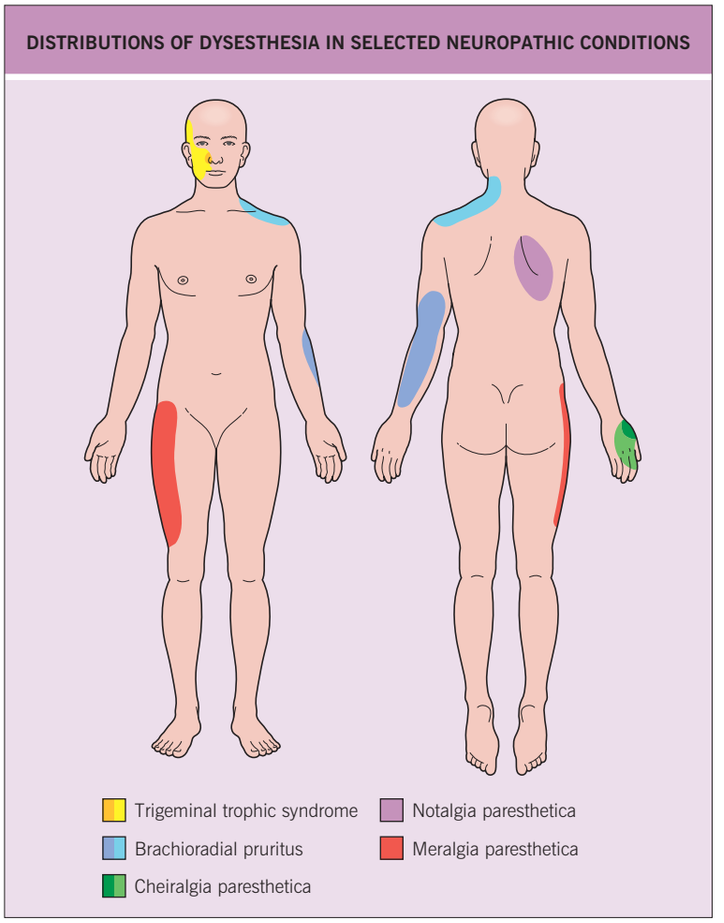


Fig. 6.9 Distributions of dysesthesia in selected neuropathic conditions. Cheiralgia paresthetica is caused by entrapment of the radial nerve. Darker shades indicate more common areas of involvement. *Courtesy, Kary Duncan, MD.*

Fig. 6.10 Brachioradial pruritus. The affected area is outlined by ink.

Brachioradial Pruritus

This chronic disorder is characterized by intermittent pruritus or burning pain on the dorsolateral aspects of the forearms and elbows (Fig. 6.10); there is sometimes more extensive involvement (e.g. of the shoulder area) (see Fig. 6.9). Cumulative solar damage and nerve root impingement due to degenerative cervical spine disease may be contributory factors[1,84]. Acute UV light exposure exacerbates the condition, and patients living in temperate climates report remissions in the fall and winter months. Sunlight is therefore an eliciting factor, and both photodamage and cervical spine disease are predisposing factors[84]. Patients may report that the application of ice provides some relief.

Examination often reveals excoriations localized to the vicinity of the brachioradialis muscle, but dermatitis of the affected area is rare. Evaluation should include a neurologic examination; if indicated, imaging of the cervical spine can be performed. In addition to sun protection, treatment options include topical capsaicin or pramoxine, gabapentin (600–1800 mg/day in divided doses), physical therapy and acupuncture[33].

Burning Mouth Syndrome

Orodynia, or burning mouth syndrome, is characterized by burning mucosal pain without clinically detectable oral lesions. The pain is typically bilateral, often involving the anterior two-thirds of the tongue, palate and lower lip[85]. The buccal mucosa and floor of the mouth are rarely involved. Histology of the affected areas in primary burning mouth syndrome is unremarkable. However, secondary causes, as listed below, may be identified.

The condition is thought to affect more than 1 million people in the US. It typically occurs in middle-aged or older adults, with a female : male ration of ~7 : 1[86]. Symptoms can last from a few months to several years. A classification system based on the pattern of disease over time has been described: *type 1* (35%) is characterized by the absence of symptoms upon awakening, with a gradual increase in severity over the course of the day; *type 2* (55%) features constant burning, both day and night; and *type 3* (10%) has days of remission that follow no identifiable pattern[86].

The evaluation of burning mouth syndrome should include a thorough physical examination to help exclude secondary causes, although the disorder is frequently idiopathic. Localized burning or itch may be the first indication of a malignant lesion (e.g. an oral squamous cell carcinoma), and a biopsy should be performed if a malignancy is suspected. Ill-fitting dentures, oral candidiasis, xerostomia (salivary flow studies in primary burning mouth syndrome have been inconclusive), and contact dermatitis to dental work have been reported as other secondary causes. All medications (prescription and over-the-counter) should be reviewed to identify any that have xerostomia as a side effect. Additional precipitating factors include iron, zinc, folate and vitamin B_{12} deficiencies, type 2 diabetes mellitus, hypothyroidism and the menopausal state[87]. Finally, depression and anxiety have been found more commonly in patients with burning mouth syndrome compared with pain-free controls[86].

When a secondary cause is identified, treatment of that disorder is indicated. Depending upon the initial evaluation, further consultations may be necessary (e.g. dentistry, psychiatry, otolaryngology, neurology). Direct questions concerning anxiety, fear of cancer and depression should be broached.

Reported successful treatments for primary burning mouth syndrome include oral tricyclic antidepressants (e.g. amitriptyline, doxepin), low-dose benzodiazepines and gabapentin, as well as topical clonazepam[88]. Initial doses of the antidepressants should be low and then increased slowly, given unwanted side effects such as xerostomia and sedation. In case reports and series, antifungal agents such as nystatin were shown to be effective (even when cultures were negative), as were topical capsaicin and anesthetics such as lidocaine or dyclonine; mouthwashes containing various combinations of anesthetics, nystatin, tetracycline, hydrocortisone, diphenhydramine and Maalox® have been utilized. There is some evidence that cognitive behavioral therapy and α-lipoic acid (600 mg daily) can improve symptoms[89].

Burning Scalp Syndrome

Burning scalp, also referred to as "scalp dysesthesia"[90], presents with diffuse burning pain, pruritus, numbness or tingling of the scalp without objective findings. Secondary causes such as seborrheic dermatitis, folliculitis, lichen planopilaris, allergic or irritant contact dermatitis and discoid lupus erythematosus should be excluded and (if present) treated. In a study examining the correlation between stressful life events and cutaneous symptoms, the most frequent body region affected was the scalp, and burning scalp syndrome is often associated with underlying depression and anxiety. Like other dysesthesias, burning scalp syndrome is often treated with gabapentin and tricyclic antidepressants[90] as well as topical capsaicin. An isolated case report noted resolution of chronic scalp pain in a patient with severe hyperlipidemia and eruptive xanthomas once the lipid abnormality was corrected[91].

Notalgia Paresthetica

Notalgia paresthetica is a common condition in adults that is characterized by focal, intense pruritus of the upper back, especially over the medial scapular borders (see Fig. 6.9); it is occasionally accompanied by pain, paresthesias or hyperesthesias[92]. A characteristic finding on physical examination is a hyperpigmented patch due to chronic rubbing of the affected area. Dermal melanophages are evident histologically, and there is considerable overlap with macular amyloidosis.

Various etiologies have been reported, including an association with Sipple syndrome (multiple endocrine neoplasia type 2A; especially if onset is during childhood or adolescence; see Ch. 63), increased dermal innervation, and viscerocutaneous reflex mechanisms. However, most evidence suggests that notalgia paresthetica represents a sensory neuropathy. In approximately 60% of affected patients, the symptoms correlate with spinal pathology, suggesting a pathogenic role for spinal nerve impingement[92].

Topical capsaicin cream applied five times daily for 1 week followed by three times daily for 3 to 6 weeks can improve symptoms[93]. Other options include topical corticosteroids, topical anesthetics (e.g. pramoxine, lidocaine), gabapentin and acupuncture. In one case report, a paravertebral block at spinal levels T3 through T6 with bupivacaine and methylprednisolone acetate produced a 12-month remission[94].

Meralgia Paresthetica

Meralgia paresthetica is a localized dysesthesia that presents with numbness, burning pain, tingling or itching of the anterolateral thigh (see Fig. 6.9). Allodynia (increased sensitivity to light touch) is another frequent manifestation, but cutaneous findings such as hyperpigmentation (Fig. 6.11) are less common than in notalgia paresthetica. Meralgia paresthetica occurs in the area of skin innervated by the lateral femoral cutaneous nerve, and it results from pressure on this nerve as it passes under the inguinal ligament. Predisposing factors include obesity, pregnancy, prolonged sitting, tight clothing and carrying heavy wallets in trouser pockets. Much less often, it results from a L1–L4 radiculopathy. Treatment is directed at relieving the pressure on the nerve. A focal nerve block at the inguinal ligament may be of benefit, and surgical decompression is sometimes required. Pharmacologic management as described for nostalgia paresthetica is occasionally helpful.

Dysesthetic Anogenital Pain Syndromes

The most common causes of anal pain are not dysesthesias, but rather hemorrhoids and fissures. Likewise, genital pain is often related to etiologies such as trauma, infection (e.g. chlamydia, herpes simplex, candidiasis) and (in men) testicular torsion. Since chronic pain may be a harbinger of malignancy, a thorough evaluation is indicated. However, patients with chronic or recurrent anogenital pain but no detectable abnormalities on physical examination may have a dysesthetic anogenital pain syndrome (Table 6.9). Vulvodynia (localized or generalized)

Fig. 6.11 Meralgia paresthetica. Hyperpigmentation and lichenification in a discrete area of dysesthesia on the anterior thigh.

DYSESTHETIC ANOGENITAL PAIN SYNDROMES	
Syndrome	**Clinical history**
Levator ani syndrome	Brief intermittent burning pain or tenesmus of the rectal or perineal area. Aggravated by sitting or elimination
Proctalgia fugax	Sudden stabbing pain in the perirectal area. Awakens patient from sleep
Coccydynia	Intermittent or persistent pain, usually burning type, localized to the coccyx
Male genital pain syndrome	Intermittent, continuous or episodic pain during penetration, ejaculation, micturition or exercise
Koro syndrome	Psychogenic disorder characterized by acute anxiety, fear of death and sensations that the genitalia are inwardly retracted and (variably) burning pain

Table 6.9 Dysesthetic anogenital pain syndromes. Vulvodynia is discussed in Chapter 73.

Fig. 6.12 Reflex sympathetic dystrophy with scaling and erosions of the fingertips. *Courtesy, Kalman Watsky, MD.*

THE STAGES OF REFLEX SYMPATHETIC DYSTROPHY
FIRST STAGE (WITHIN 1 TO 3 MONTHS)
• Hyperalgesia – pain experienced above that expected for a given stimulus • Allodynia – pain experienced from innocuous stimuli • Patients tend to categorize the pain as burning; clinical signs are rare
SECOND STAGE (WITHIN 3 TO 9 MONTHS)
• Hyperpathia – an increased pain threshold develops that, when exceeded, results in rapid maximal pain intensity that is not stimulus-dependent • Dystrophic nail changes – brittleness, thickening, and rigidity of the nail plate • Regional hypertrichosis and hyperhidrosis • Regional vasomotor dysfunction – livedo reticularis, cyanosis, edema, delayed capillary refill, and erythema may be seen • Motor dysfunction – inability to initiate movement, weakness, tremor, muscle spasms and dystonia. Upper extremity findings may include flexion-contractures of the fourth and fifth digits with adduction and flexion of the arm and wrist. When the lower extremity is involved, inversion of the foot with plantar flexion is common
THIRD STAGE (WITHIN 9 TO 18 MONTHS)
• Sudeck's atrophy – skeletal cystic and subchondral erosion with diffuse osteoporosis • Fibrous ankylosis of joints • Muscle, subcutaneous and pilar atrophy with fixed cutaneous mottling

Table 6.10 The stages of reflex sympathetic dystrophy.

TREATMENT OPTIONS FOR REFLEX SYMPATHETIC DYSTROPHY
NON-INVASIVE
Alpha-adrenergic antagonists: phenoxybenzamine, prazosin, terazosin Gabapentin Intranasal calcitonin Thalidomide
INVASIVE
Intrathecal
Baclofen, phenoxybenzamine, reserpine, corticosteroids, anesthetic agents
Surgical
Sympathectomy Acupuncture Transcutaneous nerve stimulation

Table 6.11 Treatment options for reflex sympathetic dystrophy.

is discussed in Chapter 73. Of note, anogenital pruritus (see above) can also represent a dysesthetic state.

Reflex Sympathetic Dystrophy

Reflex sympathetic dystrophy, also known as complex regional pain syndrome, is a debilitating disorder that develops in regions where damage to peripheral nerves has occurred. The most commonly affected areas are the upper limbs (especially the hands; Fig. 6.12), but the lower extremities may also be involved. Regional insult to nociceptive terminals results in a complicated signal cascade that ultimately amplifies the pain response of the CNS. The disease progresses through several stages (Table 6.10), which are thought to be due to autonomic nervous system dysfunction[95].

Many treatment modalities have been utilized and are summarized in Table 6.11. Most therapies are directed toward interruption of the autonomic nervous system and have had limited success[96].

Trigeminal Neuralgia

Trigeminal neuralgia, also known as tic douloureux, is characterized by recurrent paroxysms of sharp pain (lasting seconds to minutes) radiating into the territory of one or more of the trigeminal sensory divisions. The pain is generally unilateral (most often right-sided) and described as a stabbing, burning or shocking sensation. Attacks may occur as frequently as several times per day or as infrequently as a few times per month. Typically, the episodes increase in frequency and severity over time, occasionally culminating in a persistent pain flurry lasting for days to weeks, called acute trigeminal neuralgia crisis.

Various trigger stimuli have been reported, such as touching or washing the face, brushing the teeth, eating or talking. A thorough history is important because physical findings are nearly non-existent. Sensory and motor function should be intact, and abnormalities raise suspicion of structural neurologic abnormalities related to a tumor, stroke or multiple sclerosis. MRI is of value for detecting these entities but is low yield in primary trigeminal neuralgia[97].

The cause of trigeminal neuralgia remains unknown, although several hypotheses have been proposed. Early reports focused on trigeminal nerve demyelination. Of note, multiple sclerosis is a concurrent disease in 4–18% of patients with this condition. However, more recent theories include a component of vascular impingement on the trigeminal nerve. In one study, vascular compression of the trigeminal root was found in >90% of patients with trigeminal neuralgia, explaining high success rates (80–90%) with decompression therapy in subsequent reports[97].

Medical therapy is the first-line management of trigeminal neuralgia. Carbamazepine is the single most effective long-term oral medication (providing relief in 70–90% of patients), and phenytoin, baclofen and gabapentin can also be helpful. In an open-label study, injections of botulinum A toxin were reported as therapeutically successful[98].

Fig. 6.13 Trigeminal trophic syndrome. Erosions and ulcerations with hemorrhagic crusts favor the ala nasi (**A, B**). Obvious linear excoriations are seen in the second patient (**B**). *Courtesy, Kalman Watsky, MD.*

In cases refractory to medical therapy, surgical options such as the aforementioned microvascular decompression can be employed. Stereotactic radiosurgical techniques with gamma radiation have also been developed, providing high rates of relief with minimal invasiveness or risk for loss of neurologic function. Acute trigeminal neuralgia crisis has been controlled with intravenous phenytoin for upwards of 48 hours, thereby providing a window to modify oral therapeutic regimens.

Trigeminal Trophic Syndrome

Trigeminal trophic syndrome is a self-induced ulcerative condition of the central face that classically involves the nasal alae[99,100] (Fig. 6.13). Patients characteristically present with a small crust that develops into a crescentic ulcer that may gradually extend to involve the cheek and upper lip. The self-mutilation is triggered by paresthesias and dysesthesias that occur secondary to impingement of or damage to the sensory portion of the trigeminal nerve. The nasal tip, which is supplied by the external nasal branch of the anterior ethmoidal nerve (see Ch. 142), is typically spared. Most commonly, the underlying nerve damage is iatrogenic from ablation of the Gasserian ganglion in an attempt to treat trigeminal neuralgia. Other causes include infection (e.g. with varicella–zoster virus, herpes simplex virus or mycobacteria), stroke (with infarction of the posterior cerebellar artery), and CNS tumors or their treatment[100].

The differential diagnosis is that of a non-healing ulcer and includes cutaneous malignancies (most often basal cell or squamous cell carcinoma, but also nasal NK/T-cell lymphoma), infections (e.g. chronic herpes simplex, *Leishmania* spp., dimorphic fungi, yaws), inflammatory disorders (e.g. vasculitis including Wegener's granulomatosis, pyoderma gangrenosum) and factitial disease (see Table 45.3).

Treatment of trigeminal trophic syndrome is challenging and requires a multidisciplinary approach. Medications such as carbamazepine, diazepam, amitriptyline and pimozide have limited effectiveness. Protective barriers worn at night and patient education are important measures. Surgical repair of the defect(s) with innervated skin flaps provides the greatest chance for resolution[99,100].

TREATMENT

Thus far, no specific antipruritic drugs exist that equal aspirin's ability to relieve pain. Individualized management of each patient and disease process is necessary[33]. Patient education and elimination of provocative factors are important, including wearing soft breathable clothing (i.e. no wool or harsh synthetic fabrics, but rather cotton or silk), avoiding excessive bathing (lukewarm baths or showers with mild synthetic detergents [syndets]), using emollients on a daily basis (with application of a cream or ointment immediately after bathing) and managing dermographism if present. Elderly patients are especially prone to xerosis, and restricting bathing to once or twice weekly (with interim sponge bathing of odorous regions such as the groin and buttocks) may be helpful. Patients can be taught methods of interrupting the itch–scratch cycle, such as application of a cold washcloth or gentle pressure, and the nails should be kept short. Controlled physical exercise, relaxation therapy, and minimization of exposure to dust and heat as well as of stress and anxiety are beneficial.

Topical Treatment

A large variety of topical compounds that have antipruritic properties are available, including corticosteroids, coal tars (e.g. 5% liquor carbonis detergens) and anesthetics (e.g. pramoxine) as well as counterirritants (e.g. menthol).

Topical anesthetic agents decrease pain and pruritic sensations and may relieve tingling and dysesthesias. Lidocaine/prilocaine (EMLA®) cream has demonstrated antipruritic properties in experimentally induced pruritus and can be helpful in localized pruritic states such as notalgia paresthetica[101]. Effectiveness may be improved by combining the anesthetic with urea, also a potential antipruritic[101]. However, the therapeutic effect depends on the underlying disease; for example, in one study, no significant improvement was seen in atopic dermatitis[102].

The topical antihistamine dimethindene (not available in the US) may improve pruritus severity, depending on the underlying cause; again, no effect was seen in atopic dermatitis[101,102]. Topical doxepin has demonstrated antipruritic effects in atopic dermatitis and other eczematous dermatoses, including lichen simplex chronicus, nummular eczema and contact dermatitis[103]. Side effects such as drowsiness occur when large portions of the body are covered and young children are treated. If pruritus continues or dermatitis develops, the possibility of allergic contact dermatitis to topical doxepin should be considered; subsequent oral administration of doxepin could result in systemic contact dermatitis. Topical cromolyn sodium was recently shown to relieve allergen- and histamine-induced pruritus without blocking wheal formation, suggesting a mechanism involving inhibition of cutaneous sensory nerve fibers rather than preventing mast cell degranulation[103a].

Capsaicin is a naturally occurring alkaloid found in many botanical species of the nightshade family (Solanaceae). Capsaicin enhances the release and secondarily inhibits the reaccumulation of neuropeptides. One of these, substance P, is a powerful vasodilator that releases histamine from cutaneous mast cells by an indirect effect. In the literature, topical capsaicin therapy has reportedly been used successfully in several dermatologic disorders. However, no therapeutic benefit has been seen in atopic dermatitis[104]. Concentrations usually range from 0.025% to 0.3%, and it needs to be applied three to five times daily for maximal effect. Capsaicin has been shown to be a safe treatment even on large skin areas[105]. Side effects include stinging, burning, pain, erythema and irritation, all of which decrease with continued use.

Topical tacrolimus and pimecrolimus have both anti-inflammatory and antipruritic effects[106] (see Ch. 128). Burning and erythema at the application site are the most commonly reported adverse events.

Systemic Treatment

Most systemic drugs with antipruritic properties act centrally and have sedating effects. Placebo responses in pruritus patients are often substantial (e.g. 66% in one study)[33]. Many systemic drugs with antipruritic effects may work primarily by a placebo mechanism, demonstrating the powerful central nervous modulation of pruritus.

Physical Treatment Modalities

UV light (UVA, UVA1, broadband and narrowband UVB, UVA/UVB, PUVA) therapy has shown beneficial effects in pruritic inflammatory dermatoses, urticaria pigmentosa, renal pruritus, cholestatic pruritus due to primary biliary cirrhosis, pruritus of HIV infection, polycythemia vera-related pruritus, aquagenic pruritus and prurigo nodularis[44]. Transcutaneous electronic nerve stimulation has been reported as beneficial in different types of pruritus, such as that found in aged skin. This may be partially a placebo effect as it tends to decline with continued therapy[33]. Acupuncture has also been described as a successful treatment for pruritus vulvae, allergic contact dermatitis, and renal pruritus. Acupuncture was reported to decrease experimental histamine-induced pruritus but had no effect on maximal pruritus intensity or onset time[33].

Psychological Approaches

Pruritus may be precipitated, prolonged or enhanced by a number of stress-related mediators such as histamine and neuropeptides. There are also multiple secondary psychosomatic mechanisms through which pruritus may be generated or exacerbated, e.g. the sweat response, alterations in cutaneous blood flow and scratching[1]. Of note, psychological factors are thought to be able to diminish as well as augment pruritus.

Studies have shown that group psychotherapy, behavioral therapy, controlled physical exercise, support groups and biofeedback can help to stop scratching and improve quality of life[1,33].

REFERENCES

1. Bernhard JD. Itch: Mechanisms and Management of Pruritus. New York: McGraw-Hill, 1994.
2. Twycross R, Greaves MW, Handwerker H, et al. Itch: scratching more than the surface. QJM. 2003;96:7–26.
3. Bernhard JD. Itch and pruritus: what are they, and how should itches be classified? Dermatol Ther. 2005;18:288–91.
4. Ständer S, Weisshaar E, Mettang T, et al. Clinical classification of itch: a position paper of the International Forum for the Study of Itch. Acta Derm Venereol. 2007;87:291–4.
5. Schmelz M. A neural pathway for itch. Nat Neurosci. 2001;4:9–10.

5a. Matterne U, Apfelbacher CJ, Loerbroks A, et al. Prevalence, correlates and characteristics of chronic pruritus: a population-based cross-sectional study. Acta Derm Venereol. 2011;91:674–9.

6. Dalgard F, Svensson A, Holm JO, Sundby J. Self-reported skin morbidity among adults: associations with quality of life and general health in a Norwegian survey. J Investig Dermatol Symp Proc. 2004;9:120–5.
7. Yosipovitch G, Goon A, Wee J, et al. The prevalence and clinical characteristics of pruritus among patients with extensive psoriasis. Br J Dermatol. 2000;143:969–73.
8. Weisshaar E, Diepgen TL, Luger TA, et al. Pruritus in pregnancy and childhood – do we really consider all relevant differential diagnoses? Eur J Dermatol. 2005;15:320–31.
9. Stahle-Backdahl M. Uremic pruritus. Clinical and experimental studies. Acta Derm Venereol Suppl (Stockh). 1989;145:1–38.
10. Bergasa NV, Mehlman JK, Jones EA. Pruritus and fatigue in primary biliary cirrhosis. Baillières Best Pract Res Clin Gastroenterol. 2000;14:643–55.
11. Zylicz Z, Twycross R, Jones EA (eds). Pruritus in Advanced Disease. Oxford: Oxford University Press, 2004.
12. Mettang T, Pauli-Magnus C, Alscher DM. Uremic pruritus – new perspectives and insights from recent trials. Nephrol Dial Transplant. 2002;17:1558–63.
13. Zucker I, Yosipovitch G, David M, et al. Prevalence and characterization of uremic pruritus in patients undergoing hemodialysis: uremic pruritus is still a major problem for patients with end-stage renal disease. J Am Acad Dermatol. 2003;49:842–6.
14. Cacoub P, Poynard T, Ghillani P, et al. Extrahepatic manifestations of chronic hepatitis C. MULTIVIRC Group. Multidepartment Virus C. Arthritis Rheum. 1999;42:2204–12.
15. Cribier B, Samain F, Vetter D, et al. Systematic cutaneous examination in hepatitis C virus infected patients. Acta Derm Venereol. 1998;78:355–7.
16. Oaklander AL, Bowsker D, Galer B, et al. Herpes zoster itch: preliminary epidemiological data. J Pain. 2003;4:338–43.

16a. Sommer F, Hensen P, Böckenholt B, et al. Underlying diseases and co-factors in patients with severe chronic pruritus: a 3-year retrospective study. Acta Derm Venereol. 2007;87:510–16.

17. Weisshaar E, Apfelbacher C, Jäger G, et al. Pruritus as a leading symptom: clinical characteristics and quality of life in German and Ugandan patients. Br J Dermatol. 2006;155:957–64.
18. Lober CW. Pruritus and malignancy. Clin Dermatol. 1993;11:125–8.
19. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol Suppl (Stockh). 1980;92:44–7.
20. Thestrup-Pedersen K. Clinical aspects of atopic dermatitis. Clin Exp Dermatol. 2000;25:535–43.
21. Wahlgren CF, Ekblom A, Hagermark O. Some aspects of the experimental induction and measurement of itch. Acta Derm Venereol. 1989;69:185–9.
22. Kramer U, Weidinger S, Darsow U, et al. Seasonality in symptom severity influenced by temperature or grass pollen: results of a panel study in children with eczema. J Invest Dermatol. 2005;124:514–23.
23. Greaves MW. Antihistamines in dermatology. Skin Pharmacol Physiol. 2005;18:220–9.
24. Krause L, Shuster S. Mechanism of action of antipruritic drugs. Br Med J. 1983;287:1199–200.
25. Heyer GR, Hornstein OP. Recent studies of cutaneous nociception in atopic and non-atopic subjects. J Dermatol. 1999;26:77–86.
26. Reitamo S, Ansel JC, Luger TA. Itch in atopic dermatitis. J Am Acad Dermatol. 2001;45:S55–6.
27. Toyoda M, Nakamura M, Makino T, et al. Nerve growth factor and substance P are useful plasma markers of disease activity in atopic dermatitis. Br J Dermatol. 2002;147:41–9.
28. Bigliardi-Qi M, Lipp B, Sumanovski LT, et al. Changes of epidermal mu-opiate receptor expression and nerve endings in chronic atopic dermatitis. Dermatology. 2005;210:91–9.
29. Sonkoly E, Muller A, Lauerma AI, et al. IL-31: a new link between T cells and pruritus in atopic skin inflammation. J Allergy Clin Immunol. 2006;117:411–17.
30. Buddenkotte J, Steinhoff M. Pathophysiology and therapy of pruritus in allergic and atopic diseases. Allergy. 2010;65:805–21.
31. Ständer S, Steinhoff M. Pathophysiology of pruritus in atopic dermatitis: an overview. Exp Dermatol. 2002;11:12–24.
32. Ikoma A, Fartasch M, Heyer G, et al. Painful stimuli evoke itch in patients with chronic pruritus: central sensitization for itch. Neurology. 2004;62:212–17.
33. Fleischer AB. The Clinical Management of Itching. New York: Parthenon, 2000.
34. Gupta MA, Gupta AK, Kirkby S, et al. Pruritus in psoriasis. A prospective study of some psychiatric and dermatologic correlates. Arch Dermatol. 1988;124:1052–7.
35. Krueger G, Koo J, Lebwohl M, et al. The impact of psoriasis on quality of life. Arch Dermatol. 2001;137:280–4.
36. Nakamura M, Toyada M, Morohashi M. Pruritogenic mediators in psoriasis vulgaris: comparative evaluation of itch-associated cutaneous factors. Br J Dermatol. 2003;149:718–30.
37. Demierre M-F, Taverna J. Mirtazapine and gabapentin for reducing pruritus in cutaneous T-cell lymphoma. J Am Acad Dermatol. 2006;55:543–4.
38. Meyer N, Paul C, Misery L. Pruritus in cutaneous T-cell lymphomas: frequent, often severe and difficult to treat. Acta Derm Venereol. 2010;90:12–17.
39. Weigelt N, Metze D, Ständer S. Prurigo nodularis: systematic analysis of 58 histological criteria in 136 patients. J Cutan Pathol. 2010;37:578–86.
40. Chen M, Doherty SD, Hsu S. Innovative uses of thalidomide. Dermatol Clin. 2010;28:577–86.

40a. Kelekci HK, Uncu HG, Yilmaz B, et al. Pimecrolimus 1% cream for pruritus in postmenopausal diabetic women with vulvar lichen simplex chronicus: a prospective non-controlled case series. J Dermatolog Treat. 2008;19:274–8.

41. Mehregan AH, Heath LE, Pinkus H. Lichen ruber moniliformis and lichen ruber verrucosus et reticularis of Kaposi. J Cutan Pathol. 1984;11:2–11.
42. Steinman HK, Greaves MW. Aquagenic pruritus. J Am Acad Dermatol. 1985;13:91–6.
43. du Peloux MH, Greaves MW. Aquagenic pruritus. Semin Dermatol. 1995;14:313–16.
44. Rivard J, Lim HW. Ultraviolet phototherapy for pruritus. Dermatol Ther. 2005;18:344–54.
45. Lotti T, Teofoli P, Tsampau D. Treatment of aquagenic pruritus with topical capsaicin cream. J Am Acad Dermatol. 1994;30:232–5.
46. Daniel GL, Longo WE, Vernava AM III. Pruritus ani. Causes and concerns. Dis Colon Rectum. 1994;37:670–4.
47. Zuccati G, Lotti T, Mastrolorenzo A, et al. Pruritus ani. Dermatol Ther. 2005;18:355–62.
48. Dasan S, Neill SM, Donaldson DR, Scott HJ. Treatment of persistent pruritus ani in a combined colorectal and dermatological clinic. Br J Surg. 1999;86:1337–40.
49. Weichert GE. An approach to the treatment of anogenital pruritus. Dermatol Ther. 2004;17:129–33.
50. Cohen AD, Vander T, Medvendovsky E, et al. Neuropathic scrotal pruritus: anogenital pruritus is a symptom of lumbosacral radiculopathy. J Am Acad Dermatol. 2005;52:61–6.
51. Lee SS, Yosipovitch G, Chan YH, Goh CL. Pruritus, pain, and small nerve fiber function in keloids: a controlled study. J Am Acad Dermatol. 2004;51:1002–6.
52. Wong TW, Lee JY, Sheu HM, Chao SC. Relief of pain and itch associated with keloids on treatment with oxpentifylline. Br J Dermatol. 1999;140:771–2.
53. Vitale M, Fields-Blache C, Luterman A. Severe itching in the patient with burns. J Burn Care Rehabil. 1991;12:330–3.
54. Matheson JD, Clayton J, Muller MJ. The reduction of itch during burn wound healing. J Burn Care Rehabil. 2001;22:76–81.
55. Van Loey NEE, Faber AW, Bremer M, et al. Itch after burns: a matter of body and mind? Acta Derm Venereol. 2005;85:469.

55a. Ahuja RB, Gupta R, Gupta G, Shrivastava P. A comparative analysis of cetirizine, gabapentin and their combination in the relief of post-burn pruritus. Burns. 2011;37:203–7.

56. Kopecky EA, Jacobson S, Bch MB, et al. Safety and pharmacokinetics of EMLA in the treatment of postburn pruritus in pediatric patients: a pilot study. J Burn Care Rehabil. 2001;22:235–42.

56a. Chen ZJ, Cao G, Tang WX, et al. A randomized controlled trial of high-permeability haemodialysis against conventional haemodialysis in the treatment of uraemic pruritus. Clin Exp Dermatol. 2009;34:679–83.
57. Yosipovitch G, Zucker I, Boner G, et al. A questionnaire for the assessment of pruritus: validation in uremic patients. Acta Derm Venereol. 2001;81:108–11.
58. Weisshaar E, Dunker N, Domroese U, et al. Plasma serotonin and histamine levels in hemodialysis-related pruritus are not significantly influenced by 5-HT3 receptor blocker and antihistaminic therapy. Clin Nephrol. 2003;59:124–9.
58a. Noordzij M, Boeschoten EW, Bos WJ, et al; the NECOSAD Study Group. Disturbed mineral metabolism is associated with muscle and skin complaints in a prospective cohort of dialysis patients. Nephrol Dial Transplant 2007;22:2944–9.
59. Yosipovitch G, Reis J, Tur E, et al. Sweat secretion, stratum corneum hydration, small nerve function and pruritus in patients with advanced chronic renal failure. Br J Dermatol. 1995;133:561–4.
60. Pauli-Magnus C, Klumpp S, Alscher DM, et al. Short-term efficacy of tacrolimus ointment in severe uremic pruritus. Perit Dial Int. 2000;20:802–3.
61. Duque MI, Yosipovitch G, Fleischer AB, et al. Lack of efficacy of tacrolimus ointment 0.1% for treatment of hemodialysis-related pruritus: a randomized, double-blind, vehicle-controlled study. J Am Acad Dermatol. 2005;52:519–21.
62. Weisshaar E, Dunker N, Röhl FW, Gollnick H. Antipruritic effect of two different 5-HT3 receptor antagonists and an antihistamine in haemodialysis patients. Exp Dermatol. 2004;13:298–304.
63. Peer G, Kivity S, Agami O, et al. Randomised crossover trial of naltrexone in uremic pruritus. Lancet. 1996;348:1552–4.
64. Pauli-Magnus C, Mikus G, Alscher DM, et al. Naltrexone does not relieve uremic pruritus: results of a randomized, double blind, placebo-controlled crossover study. J Am Soc Nephrol. 2000;11:514–19.
65. Kumagai H, Ebata T, Takamori K, et al. Effect of a novel kappa-receptor agonist, nalfurafine hydrochloride, on severe itch in 337 haemodialysis patients: a phase III, randomized, double-blind, placebo-controlled study. Nephrol Dial Transplant. 2010;25:1251–7.
66. Silva SRB, Viana PCF, Lugon NV, et al. Thalidomide for the treatment of uremic pruritus: a crossover randomized double-blind trial. Nephron. 1994;67:270–3.
67. Gunal AI, Ozalp G, Yoldas TK, et al. Gabapentin therapy for pruritus in haemodialysis patients: a randomized, placebo-controlled, double-blind trial. Nephrol Dial Transplant. 2004;19:3137–9.
67a. Kremer AE, Martens JJ, Kulik W, et al. Lysophosphatidic acid is a potential mediator of cholestatic pruritus. Gastroenterology. 2010;139:1008–18.
68. Bergasa NV. The pruritus of cholestasis. J Hepatol. 2005;43:1078–88.
69. Ghent CN, Carruthers SG. Treatment of pruritus in primary biliary cirrhosis with rifampin. Results of a double-blind, crossover, randomized trial. Gastroenterology. 1988;94:488–93.
70. Wolfhagen FH, Sternieri E, Hop WC, et al. Oral naltrexone treatment for cholestatic pruritus: a double-blind, placebo-controlled study. Gastroenterology. 1997;113:1264–9.
71. Bergasa NV, Ailing DW, Talbot TL, et al. Effects of naloxone infusions in patients with the pruritus of cholestasis. A double-blind, randomized, controlled trial. Ann Intern Med. 1995;123:161–7.
72. Bergasa NV, Ailing DW, Talbot TL, et al. Oral nalmefene therapy reduces scratching activity due to the pruritus of cholestasis: a controlled study. J Am Acad Dermatol. 1999;41:431–4.
73. Borgeat A, Wilder-Smith O, Mentha G, Huber O. Subhypnotic doses of propofol relieve pruritus associated with liver disease. Gastroenterology. 1993;104:244–7.
74. McCormick PA, Scott F, Epstein O, et al. Thalidomide as therapy for primary biliary cirrhosis: a double-blind placebo controlled pilot study. J Hepatol. 1994;21:496–9.
75. Muller C, Pongratz S, Pidlich J, et al. Treatment of pruritus in chronic liver disease with the 5-hydroxytryptamine receptor type 3 antagonist ondansetron: a randomized, placebo-controlled, double-blind cross-over trial. Eur J Gastroenterol Hepatol. 1998;10:865–70.
76. Raiford DS. Pruritus of chronic cholestasis. QJM. 1995;88:603–7.
77. Walt RP, Daneshmend TK, Fellows IW, Toghill PJ. Effect of stanozolol on itching in primary biliary cirrhosis. Br Med J. 1988;296:607.
78. Bergasa NV, Link MJ, Keogh M, et al. Pilot study of bright-light therapy reflected toward the eyes for the pruritus of chronic liver disease. Am J Gastroenterol. 2001;96:1563–70.
79. Neilly JB, Martin A, Simpson N, MacCuish AC. Pruritus in diabetes mellitus: investigation of prevalence and correlation with diabetes control. Diabetes Care. 1986;9:273–5.
80. Resneck JS, Van Beek M, Furmanski L, et al. Etiology of pruritic papular eruption with HIV infection in Uganda. JAMA. 2004;292:2614–21.
81. Singh F, Rudikoff D. HIV-associated pruritus: etiology and management. Am J Clin Dermatol. 2003;4:177–88.
82. Milazzo F, Piconi S, Trabattoni D, et al. Intractable pruritus in HIV infection: immunologic characterization. Allergy. 1999;54:266–72.
83. Radomsky CL, Levine N. Thalidomide. Dermatol Clin. 2001;19:87–103.
84. Wallengren J, Sundler F. Brachioradial pruritus is associated with a reduction in cutaneous innervation that normalizes during the symptom-free remissions. J Am Acad Dermatol. 2005;52:142–5.
85. Bergdahl J, Anneroth G. Burning mouth syndrome: literature review and model for research and management. J Oral Pathol Med. 1993;22:433–8.
86. Muzyka BC, De Rossi SS. A review of burning mouth syndrome. Cutis. 1999;64:29–35.
87. Drage LA, Rogers RS. Clinical assessment and outcome in 70 patients with complaints of burning or sore mouth symptoms. Mayo Clin Proc. 1999;74:223–8.
88. Evans RW, Drage LA. Burning mouth syndrome. Headache. 2005;45:1079–81.
89. Zakrzewska JM, Forssell H, Glenny AM. Interventions for the treatment of burning mouth syndrome. Cochrane Database Syst Rev. 2005;(1):CD002779.
90. Hoss D, Segal S. Scalp dysesthesia. Arch Dermatol. 1998;134:327–30.
91. Aravindan PD, Lloyd-Mostyn RH. Scalp pain and hyperlipidaemia. Int J Clin Pract. 2000;54:478–9.
92. Savk O, Savk E. Investigation of spinal pathology in notalgia paresthetica. J Am Acad Dermatol. 2005;52:1085–7.
93. Wallengren J, Klinher M. Successful treatment of notalgia paresthetica with topical capsaicin: vehicle-controlled, double-blind, cross-over study. J Am Acad Dermatol. 1995;32:287–9.
94. Goulden V, Toomey PJ, Highet AS. Successful treatment of nostalgia paresthetica with a paravertebral anesthetic block. J Am Acad Dermatol. 1998;38: 114–16.
95. Phelps GR, Wilentz S. Reflex sympathetic dystrophy. Int J Dermatol. 2000;39:481–6.
96. Perez RS, Kwakkel G, Zuurmond WW, de Lange JJ. Treatment of reflex sympathetic dystrophy (CRPS type 1): a research synthesis of 21 randomized clinical trials. J Pain Symptom Manage. 2001;21:511–26.
97. Rovit RL, Murali R, Janetta PJ (eds.). Trigeminal Neuralgia. Baltimore: Williams & Wilkinson, 1997.
98. Piovesan EJ, Teive HG, Kowacs PA, et al. An open study of botulinum-A toxin treatment of trigeminal neuralgia. J Neurol. 2005;65:1306–8.
99. Kavanagh GM, Tidman MJ, McLaren KM, et al. The trigeminal trophic syndrome: an under-recognized complication. Clin Exp Dermatol. 1996;21:299–301.
100. Sadeghi P, Papay FA, Vidimos AT. Trigeminal trophic syndrome – report of four cases and review of the literature. Dermatol Surg. 2004;30:807–12.
101. Weisshaar E, Heyer G, Forster C, et al. Antipruritic effect of antihistaminic and local anesthetic topical agents after iontophoretic histamine stimulation. Hautarzt. 1996;47:355–60.
102. Weisshaar E, Forster C, Dotzer M, Heyer G. Experimentally induced pruritus and cutaneous reactions with topical antihistamine and local analgesics in atopic eczema. Skin Pharmacol. 1997;10:183–90.
103. Drake LA, Millikan LE. The antipruritic effect of 5% doxepin cream in patients with eczematous dermatitis. Doxepin Study Group. Arch Dermatol. 1995;131: 1403–8.
103a. Vieira Dos Santos R, Magerl M, Martus P, et al. Topical sodium cromoglicate relieves allergen- and histamine-induced dermal pruritus. Br J Dermatol. 2010;162: 674–6.
104. Weisshaar E, Heyer G, Forster C, Handwerker HO. Effect of topical capsaicin on the cutaneous reactions and itching to histamine in atopic eczema compared to healthy skin. Arch Dermatol Res. 1998;290: 306–11.
105. Breneman DL, Cardone JS, Blumsack RF, et al. Topical capsaicin for treatment of hemodialysis-related pruritus. J Am Acad Dermatol. 1992;26:91–4.
106. Ständer S, Schürmeyer-Horst F, Luger TA, Weisshaar E. Treatment of pruritic diseases with topical calcineurin inhibitors. Therap Clin Risk Manag. 2006;2:213–18.

This page intentionally left blank

Psychocutaneous Diseases

7

Chai Sue Lee and John YM Koo

INTRODUCTION

"Psychodermatology" refers to any aspect of dermatology in which psychological factors play a significant role. At least a third of patients seen in dermatology practices require consideration of associated emotional and psychosocial factors for effective management of their skin condition[1,2].

Many patients with psychodermatologic problems resist referral to a mental health professional, and some become upset or even furious if such a referral is suggested to them. While there are many reasons for their reluctance and refusal, ironically, the individuals who are the most psychologically "ill" are often the most adamant about refusing both to recognize the psychogenic nature of their condition and to be referred to a psychiatrist. For example, patients with psoriasis or eczema are usually willing to speak of how emotional stress adversely affects their condition. However, patients with delusions of parasitosis are typically resistant to any discussion of their situation in psychological terms because they have no insight into their disease.

Regardless of the reason for refusal of a referral to a psychiatrist, the dermatologist is thereby designated by the patient to handle the chief complaint, even though the main disorder is psychogenic. Given this, the dermatologist is faced with two choices. The first is to try to address the psychological/psychiatric condition. If a dermatologist decides to take this route, it is necessary to be familiar with the approach to diagnosis, therapeutic options (both pharmacologic and non-pharmacologic, including potential side effects of medications), and limitations of what can be accomplished in a dermatology practice. The other option is to "ignore" the psychological problem and allow this component of the patient's disorder to remain untreated, which is not optimal. For example, patients with delusions of parasitosis may remain delusional for decades if they do not receive an antipsychotic medication, switching from dermatologist to dermatologist in search of treatment, only to be continually disregarded by physicians. Dermatologists can learn to effectively handle psychodermatologic issues within the limits of their training and practice setting. Although less comprehensive than the treatment delivered by a psychiatrist, in the authors' opinion, management of these issues by a dermatologist is better than no treatment at all.

In this chapter, a clinically useful method of classifying psychodermatologic diseases is presented and selected psychodermatologic conditions that are commonly encountered in a dermatologic practice are discussed. These include delusions of parasitosis, body dysmorphic disorder, dermatitis artefacta, neurotic (psychogenic) excoriations, acne excoriée and trichotillomania. Strategies for the evaluation and management of patients with these disorders are presented, including pharmacologic and non-pharmacologic treatments. Prurigo nodularis and lichen simplex chronicus are covered in Chapter 6.

OVERVIEW

Psychodermatologic disorders can be classified in two ways: (1) by the type of psychodermatologic condition; or (2) by the nature of the underlying psychopathology. The second method is useful because knowledge of the psychopathology enables the clinician to choose the most appropriate first-line psychopharmacologic agent. For example, in obsessive–compulsive disorder (OCD), a selective serotonin reuptake inhibitor (SSRI; e.g. fluoxetine) is typically the first line of pharmacologic therapy. The psychodermatologic patients with the greatest need for psychopharmacologic treatment usually have "blatantly" psychiatric problems, and most of these individuals have psychiatric manifestations in one of the following categories: anxiety, depression, psychosis and OCD[3] (Fig. 7.1).

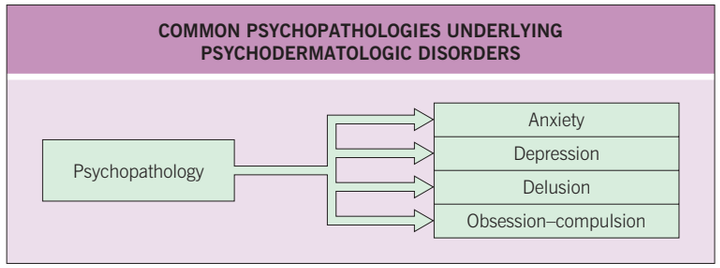


Fig. 7.1 Common psychopathologies underlying psychodermatologic disorders. *Reprinted with permission from Wolverton: Comprehensive Dermatologic Drug Therapy, W.B. Saunders, 2007.*

In the classification method based on psychodermatologic conditions, most patients can be grouped into one of five categories[3] (Fig. 7.2):

- *psychophysiologic disorders*, in which a genuine skin disorder, such as psoriasis, is exacerbated by emotional factors
- *primary psychiatric disorders*, in which the patient has no primary skin disease and all of the cutaneous findings are self-induced, such as in delusions of parasitosis
- *secondary psychiatric disorders*, in which the patient develops psychological problems as a result of a skin disease that causes physical disfigurement, as in vitiligo or alopecia areata
- *cutaneous sensory disorders*, in which the patient presents with a purely sensory complaint, such as pruritus, burning or stinging, without visible evidence of primary skin disease or a diagnosable underlying medical condition
- the use of *psychotropic medications for purely or primarily dermatologic conditions*, such as administration of doxepin to treat chronic urticaria or amitriptyline for postherpetic neuralgia.

COMMON PSYCHODERMATOLOGIC CONDITIONS

Delusions of Parasitosis

Synonyms: ■ Delusional parasitosis ■ Delusional infestation ■ Ekbom syndrome ■ Delusional disorder, somatic type ■ Monosymptomatic hypochondriacal psychosis

Key features

- False and fixed belief that an individual is infested with parasites
- May experience sensations of biting, crawling or stinging
- Need to distinguish from substance-induced formication

Introduction

Delusions of parasitosis falls under the classification of a primary psychiatric disorder. Affected individuals have the false and fixed belief that they are infested by parasites, in the absence of any objective evidence of infestation[4].

Clinical features

Patients with delusions of parasitosis are not schizophrenic but rather have the *somatic type of delusional disorder* (previously referred to as *monosymptomatic hypochondriacal psychosis*)[5] (Table 7.1). Their

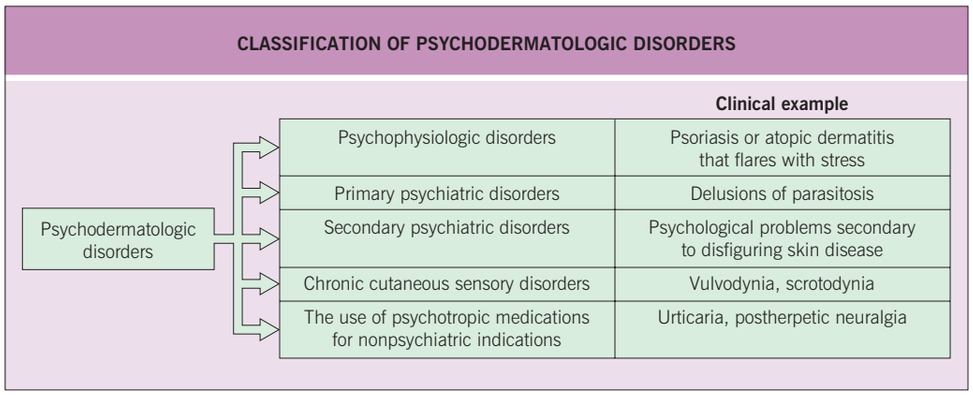


Fig. 7.2 Classification of psychodermatologic disorders. *Adapted with permission from Wolverton: Comprehensive Dermatologic Drug Therapy, W.B. Saunders, 2007*

SIGNS AND SYMPTOMS OF DELUSIONAL DISORDER, SOMATIC TYPE (MONOSYMPTOMATIC HYPOCHONDRIACAL PSYCHOSIS)
A DELUSION IS DEFINED AS:
• A false belief that the patient is absolutely convinced is true, despite a lack of objective evidence
THE DELUSION IN THIS CONDITION IS CHARACTERIZED AS:
• '*Encapsulated*' – i.e. has a narrow and specific focus, such as concerns about a particular parasite • *Somatic* (physical) and '*hypochondriac*' (health-related) in nature • Differing from the delusions of schizophrenia in that psychologic capacity outside of the specific delusion remains largely intact (e.g. proper affect, sociability, manners when discussing other aspects of life) • Not resulting directly from the effects of a drug of abuse, medication or general medical condition

Table 7.1 Signs and symptoms of delusional disorder, somatic type (monosymptomatic hypochondriacal psychosis). *Adapted with permission from Wolverton: Comprehensive Dermatologic Drug Therapy, W.B. Saunders, 2007.*

Fig. 7.3 Delusions of parasitosis. Samples of alleged "parasites" brought in by a patient ("matchbox sign").

delusional belief revolves around one particular medical concern and is "encapsulated", usually not compromising other aspects of their mental or psychosocial functioning.

Individuals with delusions of parasitosis typically present with a history of symptoms for months or even years. They have often already been evaluated by many physicians and tried to eradicate their alleged "parasites" by methods such as using pesticides, hiring exterminators or even changing their residence. The patients frequently bring in bits of skin, lint and other samples that they believe represent "parasites" (Fig. 7.3), which is referred to as the "matchbox sign". They often report cutaneous sensations of crawling, biting and/or stinging.

Skin findings in delusions of parasitosis range from none at all to excoriations, lichenification, prurigo nodularis and/or frank ulcerations. All of these are self-induced, often resulting from the patient's efforts to dig out "parasites".

One intriguing aspect of this disorder is the occurrence of a shared delusional system whereby the patient's close contacts come to believe in the delusion as well. *Folie à deux* ("craziness for two") is the term used to describe two people who share the same delusion. Interestingly, any number of people can be involved in the delusion.

Morgellons disease is a controversial condition with symptoms very similar, if not identical, to those of delusions of parasitosis[6]. A hallmark of this disorder is that patients claim to observe "fibers" exuding from their skin. Widespread coverage of Morgellons disease in the media and on the Internet has led to an increasing number of patients presenting to dermatologists. Multiple articles in the medical literature and a recent investigation by the Centers for Disease Control and Prevention have supported the categorization of Morgellons disease as a form of delusions of parasitosis[6a].

Epidemiology

The average age of onset is in the mid-50s to 60s. Among individuals over 50 years of age, women experience the disorder twice as often as men; however, prior to age 50, men and women are equally affected. Younger patients with this disorder are usually of a lower socio-economic status and may have a history of substance abuse, while older patients are usually of a higher socio-economic status.

Differential diagnosis

Additional diagnostic considerations for patients suspected to have delusions of parasitosis include:

- *formication*, in which patients experience the sensations of biting and crawling within their skin but have no firm convictions that these sensations are due to an infestation (and thus are not delusional)
- *delusionoid ideation*, in which a patient is mentally fixated on a particular perspective but, unlike a truly delusional patient, is not completely inflexible
- *formication and/or delusion as a result of substance abuse*, whereby, under the influence of substances (especially amphetamines and cocaine), patients manifest with a disorder clinically identical to idiopathic delusions of parasitosis.

One additional item in the differential diagnosis that is occasionally missed by dermatologists is a true primary skin disorder.

Management

After the diagnosis of delusions of parasitosis has been established, one of the most challenging aspects of managing these patients is getting them to agree to take an antipsychotic medication. The first step is to establish rapport with the patient and to address the chief complaint seriously, making sure to do a thorough dermatologic examination. While discussing the diagnosis with the patient, communicate it in a matter-of-fact manner and refrain from making any statements that may be misinterpreted by the patient as supporting his or her delusional ideation. Often, it is more feasible to introduce the antipsychotic medication as one that may work empirically for formication and agitation rather than to confront the individual about psychiatric issues. If the medication is presented in an objective and pragmatic manner, the patient may have less difficulty accepting it as a therapy.

The treatment of choice for delusions of parasitosis has traditionally been pimozide. As part of the discussion on therapy, the dermatologist should explain to the patient that he or she does not have Tourette syndrome or schizophrenia, the former being the condition that has

US Food and Drug Administration (FDA) approval for treatment with pimozide. Pimozide can be associated with a number of side effects, including extrapyramidal (pseudo-parkinsonian) symptoms and prolongation of the Q–T interval, as well as drug–drug interactions. There have been several reports of successful treatment of delusions of parasitosis with risperidone and olanzapine, newer antipsychotic medications (Table 7.2) that have more favorable side-effect profiles (see Treatment section below)[4].

Body Dysmorphic Disorder

Synonym: ■ Dysmorphophobia

Key features

- May affect as many as 10–14% of dermatology patients
- Often begins in early adulthood
- Preoccupation with a non-existent or slight defect in appearance
- Frequent body sites of concern are the nose, mouth, hair, breasts and genitalia
- Typically associated with compulsive or ritualistic behaviors

Introduction

Dermatologists, particularly those performing cosmetic procedures, and plastic surgeons appear to be the physicians most often seen by patients with body dysmorphic disorder, a distressing or socially impairing preoccupation with a non-existent or slight defect in appearance[7].

Clinical features

Patients with body dysmorphic disorder have a fundamental disturbance in the perception of their own body image. They are often socially isolated and preoccupy themselves with a concern about their face (especially the nose and mouth), hair, breasts or genitalia. In addition, these patients often adopt compulsive or ritualistic behaviors such as spending an excessive amount of time in front of a mirror or repeatedly checking for perceived imperfections.

A subtype of body dysmorphic disorder is *olfactory reference syndrome*, in which affected individuals are extremely preoccupied with the notion that they emit an unpleasant odor, which nobody else can perceive[8]. These patients often engage in compulsive behaviors in an attempt to eradicate the perceived odor, such as repetitive showering or excessive use of deodorants, perfumes or mouthwash.

Epidemiology

While the exact incidence of body dysmorphic disorder is unknown, it is estimated to affect up to 1% of the US population[7]. In one study, 10–14% of patients who visited a dermatologist screened positive for body dysmorphic disorder[7]; the mean age of onset was 34 years, with a male-to-female ratio of 1 : 1. This condition has been reported to last from 5 to 30 years.

Management

The spectrum of body dysmorphic disorder includes: (1) *obsessions* (preoccupation with perceived inadequacies), which fall within the *OCD spectrum* (Table 7.3); and *delusions* (fixed false beliefs about their appearance), which fall within the *psychotic spectrum* and can represent a variant of the somatic type of delusional disorder (see Table 7.1). For the purpose of treatment, it is useful to classify patients into one of these two categories, although the distinction is not always clear and individual patients sometimes fluctuate between delusional and non-delusional thinking. Those with the OCD variant of this disease will usually demonstrate behaviors such as repeatedly checking mirrors, excessive grooming and numerous visits to the physician for reassurance. In contrast, patients with the delusional variant have no insight into their disease and often go to extraordinary lengths, such as multiple surgeries, to correct their perceived deformity. It is important for cosmetic surgeons to recognize this disorder and avoid performing multiple unnecessary procedures. In addition, patients with body dysmorphic disorder are often dissatisfied with the results of any procedure that is performed[9].

SIDE EFFECTS OF PIMOZIDE AND ATYPICAL ANTIPSYCHOTIC DRUGS							
	Anticholinergic effects	**Sedation/ somnolence**	**QT prolongation**	**Increased prolactin**	**Weight gain**	**Metabolic effects***	**Extrapyramidal effects†**
Pimozide (Orap®)	++	+	++	++	++	–	++
ATYPICAL ANTIPSYCHOTIC DRUGS							
Aripiprazole (Abilify®)	–	±	±	–	–	–	+
Asenapine (Saphris®)	–	+	±	–	–	–	±
Clozapine‡ (Clozaril®)	++	++	±	–	++	++	+
Iloperidone (Fanapt®)	–	±	+	–	+	–	–
Lurasidone (Latuda®)	–	+	±	–	–	–	+
Olanzapine (Zyprexa®)	+	++	±	+	++	++	+
Quetiapine (Seroquel®)	+	++	±	–	++	+	–
Risperidone (Risperdal®)§	–	+	±	++	+	+	+
Ziprasidone (Geodon®)	–	±	+	+	–	–	+

*E.g. insulin resistance/type 2 diabetes mellitus, hyperlipidemia (especially hypertriglyceridemia).
†Parkinsonian symptoms.
‡Use is limited by a 1% incidence of potentially life-threatening agranulocytosis as well as increased risks of seizures (dose-dependent) and myocarditis.
§Another atypical antipsychotic drug, paliperidone (Invega®), represents the primary active metabolite of risperidone.

Table 7.2 Side effects of pimozide and atypical antipsychotic drugs. The use of antipsychotic drugs in elderly patients with dementia has been associated with an increased risk of mortality. A dose-dependent increased risk of sudden cardiac death has also been documented in patients receiving antipsychotic drugs.

SIGNS AND SYMPTOMS OF OBSESSIVE–COMPULSIVE DISORDER
• Presence of *obsession* – a recurrent, intrusive, ego-dystonic (i.e. feeling foreign to oneself) idea • Presence of *compulsion* – a behavioral response to an obsession. If suppressed, compulsive urges may build up • Obsession and compulsion need *not* both be present: the presence of one or the other is sufficient to make the diagnosis • Presence of varying degrees of insight (in contrast to psychosis, where, by definition, there is essentially no insight)

Table 7.3 Signs and symptoms of obsessive–compulsive disorder (OCD). *AReprinted with permission from Wolverton: Comprehensive Dermatologic Drug Therapy, W.B. Saunders, 2007.*

The first-line therapy for patients with the OCD variant of this disease is an SSRI, whereas antipsychotics are the treatment of choice for patients who are truly delusional (see Treatment section below).

Dermatitis Artefacta

Synonym: ■ Factitial dermatitis

Key features

- More common in women than men
- Motive is usually subconscious
- Self-inflicted cutaneous lesions that are often induced by foreign objects
- Typically located in areas that are easily reached by the hands

Introduction

Dermatitis artefacta is a psychocutaneous disorder in which patients inflict cutaneous lesions upon themselves to satisfy a psychological need of which they are usually not consciously aware. If asked, the patients deny having any role in creating the skin lesions. While some of these individuals create skin lesions as a maladaptive response to an acute psychosocial stress, the vast majority suffer from borderline personality disorder[10]. Given the frequent lack of honest disclosure and cooperation from the patient, this disorder is often difficult to diagnose and treat.

Clinical features

Dermatitis artefacta can mimic a wide variety of dermatoses. The lesions may be single or multiple and unilateral or bilateral. Although usually within easy reach of the hands, the lesions can be caused by methods such as carving with sharp instruments, applying chemicals and injecting foreign substances[11]. The morphology ranges from vesicles to purpura to subcutaneous emphysema. A clue to diagnosis is unusual shapes, particularly angulated edges, that suggest an external method of induction (Figs 7.4 & 7.5).

Pathology

Histologic changes seen with dermatitis artefacta vary considerably, depending upon the manner in which the lesions were produced. The findings are generally not diagnostic and can include erosion, ulceration, hyperkeratosis, irregular acanthosis, vascular proliferation, hypertrophied nerves (as observed in prurigo nodularis) and fibroplasia. Polarizing exogenous material with a variable foreign body response is occasionally evident[12].

Epidemiology

Dermatitis artefacta is uncommon and is reported to have a female-to-male ratio of 8 : 1. Although the onset is most frequently in adolescence and young adulthood, it can occur at any age. Many patients either work in or have a close family member who works in the healthcare field[13].

Differential diagnosis

In terms of the differential diagnosis (other than primary skin disorders), dermatitis artefacta must be distinguished from delusions of parasitosis, neurotic excoriations and malingering; the latter is characterized by skin lesions that are self-inflicted for a *conscious* gain. *Nonsuicidal self-injury* (e.g. "cutting"), which has received increased attention by the media and medical community in recent years, is fairly common in adolescents and young adults as a response to psychological distress; in contrast to dermatitis artefacta, the patients acknowledge that they inflicted the lesions on themselves. An additional consideration is *Münchhausen syndrome by proxy*, in which an individual

Fig. 7.4 Dermatitis artefacta. A Erosion with a "bizarre" shape and angulated borders, possibly created with a sharp instrument. **B** Erosions and ulcers with angulated borders in various stages of healing on the leg of a teenage girl. The patient denied knowing how the lesions had developed or having any role in the process.

Fig. 7.5 Scars from cigarette burns. *Courtesy, Ronald P Rapini, MD.*

produces lesions on another person in order to satisfy a psychological need that is not consciously recognized.

Management

Initially, wound care to help with healing is often indicated and the possibility of a primary dermatologic disorder needs to be excluded. There is controversy as to whether or not the patient should be confronted upon recognition of dermatitis artefacta. Given the nature of the disorder, it may be more fruitful to provide a supportive environment early in the doctor–patient relationship and then work up to the psychological aspects of the disease at subsequent visits. Antidepressant, antianxiety or antipsychotic medications (see Treatment section below) may be indicated when affected individuals have an underlying psychiatric disorder (Tables 7.4 & 7.5). Children or adults in whom the lesions represent a response to a transient stress have the most favorable prognosis. Dermatitis artefacta usually has a chronic course, with waxing and waning, depending upon circumstances in the affected individual's life[14].

Neurotic Excoriations

Synonym: ■ Psychogenic excoriation

Key features

- Most commonly seen in middle-aged women
- Repetitive, uncontrollable desire to pick, rub or scratch the skin
- Usually on the scalp, face, upper back, extensor surfaces of the forearms, shins or buttocks, but can occur on any easily reachable area of the body

Introduction

Some people have a tendency to inattentively but habitually pick incidental skin lesions, such as an arthropod bite, keratin plug, or lesion of acne or folliculitis. This action may be episodic or occur on a regular basis and, when controllable and non-destructive, can be regarded as a simple habit. In contrast, patients with neurotic excoriations have a conscious, repetitive and uncontrollable desire to pick, scratch or rub their skin, which results in characteristic lesions (Fig. 7.6). Picking activity may begin inadvertently as the hand comes across an irregularity on the skin, or it may take place in a ritualistic fashion.

Clinical features

The lesions may evolve from a pre-existing urticarial papule or acneiform lesion, or they may be created *de novo*. Repeated picking or rubbing results in excoriations with a variety of shapes (e.g. linear/angular, circular, oval). The distribution is characteristically on the extensor surfaces of the arms and forearms as well as the scalp, face, upper back and buttocks[10]. Lesions may range in size from a few millimeters to several centimeters, and several stages of evolution are often evident, from small superficial erosions to deep ulcerations with hypertrophic borders to hypo- or hyperpigmented scars. On the scalp, there may be broken hairs as well as areas of scarring alopecia.

According to more psychodynamically (i.e. Freudian) oriented investigations, individuals with neurotic excoriations often have an obsessive–compulsive personality: rigid, perfectionist, judgmental, controlling, and indecisive due to fear of making a mistake. They may have difficulty handling subconscious aggression, which may stem from unresolved feelings toward their parents. Patients may describe difficult childhoods with rejecting and punitive parents[15]. In some patients, the behaviors are thought to be a manifestation of the anxiety that results when aggressive feelings threaten to surface.

In mild cases, especially during childhood, neurotic excoriations can be a transient response to stress in someone with obsessive–compulsive personality traits. However, in severe and prolonged cases, psychiatric evaluation may reveal OCD (see Table 7.3).

Neurotic excoriations may also be an expression of generalized anxiety disorder or depression. The worries harbored by patients with generalized anxiety disorder are based in reality but are out of proportion to any actual risk. When tension mounts in these patients, there may be anxious and restless picking at any irregularity on the skin, resulting in characteristic lesions.

Epidemiology

Accurate statistics regarding the incidence of this disorder are not available, but there is a preponderance of women. Although the condition may occur at any age, the most severe and recalcitrant cases typically start in the third to fifth decades of life.

Management

Once causes of primary pruritus are excluded (see Ch. 6) and treatment of underlying cutaneous disorders (e.g. folliculitis) has been instituted,

SIGNS AND SYMPTOMS OF GENERALIZED ANXIETY DISORDER
• Excessive anxiety and worry
• Restlessness or feeling "keyed up" or "on edge"
• Difficulty concentrating or mind going blank
• Irritability
• Muscle tension
• Stress
• Sleep disturbance (difficulty falling or staying asleep; or restless, unsatisfying sleep)
• Dizziness
• Sweating
• Palpitations
• Abdominal complaints
• Frequent urination

Table 7.4 Signs and symptoms of generalized anxiety disorder. *Reprinted with permission from Wolverton: Comprehensive Dermatologic Drug Therapy, W.B. Saunders, 2007.*

SIGNS AND SYMPTOMS OF MAJOR DEPRESSION
• Depressed mood
• Anhedonia (i.e. markedly diminished interest or pleasure in activities)
• Significant weight loss when not dieting, weight gain, or change in appetite
• Insomnia or hypersomnia
• Psychomotor agitation or retardation
• Fatigue, lack of energy
• Feelings of helplessness, hopelessness or worthlessness
• Excessive guilt
• Difficulty with concentration, memory loss
• Suicidal ideation/plan
• Crying spells (i.e. finding oneself tearful for no reason or with minimal provocation)
• Somatization (i.e. preoccupation with vague, nonspecific, or exaggerated physical concerns but not of delusional intensity)

Table 7.5 Signs and symptoms of major depression. *Reprinted with permission from Wolverton: Comprehensive Dermatologic Drug Therapy, W.B. Saunders, 2007.*

Fig. 7.6 Neurotic excoriations. This patient picked vigorously at any blemish that he found on his face.

therapy can focus on associated pruritus (if present) and the psychological aspects of the condition. Treatment is based on symptom severity. When pruritus is present, topical antipruritics such as lotions containing pramoxine or menthol may be helpful. Cool compresses are soothing, hydrate the skin, and facilitate debridement of crusts. Antihistamines such as hydroxyzine can have beneficial sedative and antipruritic effects. Intralesional corticosteroids and flurandrenolide tape address the inflammatory component of existing lesions but not the formation of new lesions.

Doxepin may be particularly useful in patients with neurotic excoriations associated with depression and anxiety. If major depression is present, an antidepressant dose (usually 100 mg/day or higher) should be the goal. However, even if a patient can tolerate only 50–75 mg/day of doxepin (or 10–20 mg/day in the elderly), antidepressant efficacy may become evident.

Since obsessive–compulsive symptoms are associated with serotonin-mediated neural pathways, antidepressant drugs that selectively block serotonin reuptake (SSRIs) can be helpful in patients with neurotic excoriations. SSRIs represent the first-line treatment for OCD (see Table 7.3). Behavior modification, cognitive and psychodynamic therapy have been reported to be beneficial in case series[16,17]. The average duration of disease activity is 5–8 years without pharmacologic therapy, with the severity fluctuating in parallel with stressful situations.

Acne Excoriée

Synonym: ■ Acne excoriée des jeunes filles

Key features

- Frequently seen in young women
- Subset of neurotic excoriations
- Ritualistic picking of acne lesions

Introduction

Acne excoriée can be thought of as a subset of neurotic excoriations in which the scratching and picking is directed at acne lesions (Fig. 7.7). The underlying acne is often mild but accompanied by extensive excoriations. Lesions can become so deep that scarring may occur. Acne excoriée is most frequently seen in young women, thus the description *des jeunes filles*.

Management

Because acne excoriée is part of the broader spectrum of neurotic excoriations and is often associated with OCD, the treatment is the same as that described above. The use of doxepin and SSRIs may be beneficial, as has been described anecdotally. In addition to these agents, aggressive treatment of the underlying acne should be considered (see Ch. 36). Medications such as isotretinoin may be administered so that the substrate for the excoriations is eliminated. However, recurrence of even mild acne may be accompanied by resumption of picking unless the associated psychological disorder is addressed.

Trichotillomania

Synonym: ■ Habitual hair pulling

Key features

- More common in young girls
- Hair-pulling disorder involving scalp, eyebrows, eyelashes or pubic hair
- Varying lengths of hair distributed within areas of alopecia, with normal uninvolved areas
- Behavior modification therapy is the mainstay of treatment

Fig. 7.7 Acne excoriée. This patient compulsively picked at his acne lesions. *Courtesy, Richard Odom, MD.*

Fig. 7.8 Trichotillomania. Note the hairs of varying lengths and small areas of sparing.

Introduction

The American Psychiatric Association's *Diagnostics and Statistics Manual for Mental Health Disorders*, Fourth Edition (DSM-IV) classifies trichotillomania as an impulse disorder, but some authors have argued that it should be categorized as an obsessive–compulsive disorder[18] or stereotypic movement disorder[19]. To meet DSM-IV diagnostic criteria, a patient must feel rising tension just prior to hair pulling or during attempts to resist pulling and must experience a sense of pleasure or relief during or after the behavior. The authors favor the more simplified and straightforward definition used by dermatologists: anyone with a hair-pulling disorder.

Clinical features

Patients most commonly pull scalp hair, but eyebrows, eyelashes and pubic hair can also be targeted. The classic physical finding is hair of varying lengths distributed within the area of alopecia, with uninvolved areas of the scalp appearing completely normal (Fig. 7.8); the hairs are sometimes referred to as "irregularly irregular." This pattern likely reflects a favored hair-pulling technique of twisting multiple strands around the fingers and pulling them simultaneously. Lesions are usually single and can be large. Plucking may be confined to a specific time of the day and place, with ritualized manipulation of the pulled hairs prior to discarding. Some patients practice *trichophagy*, the chewing and swallowing of the hair that has been pulled out, possibly leading to intestinal obstruction from trichobezoars.

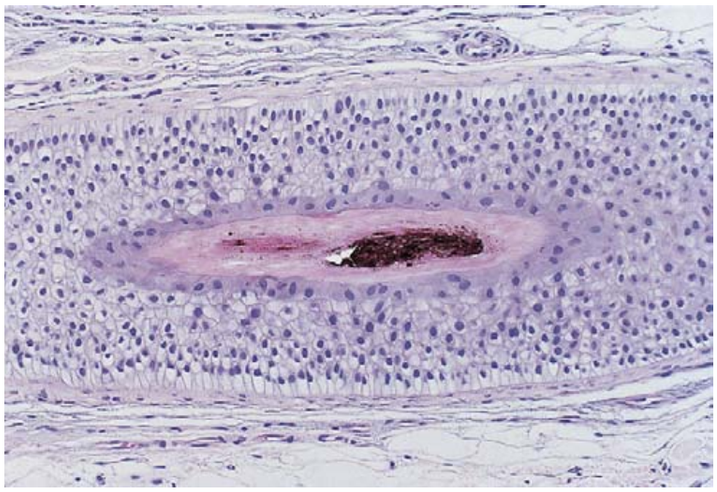


Fig. 7.9 Trichotillomania. Pigmented follicular cast. *Courtesy, Ronald P Rapini, MD.*

From a psychodynamic (i.e. Freudian) perspective, patients with trichotillomania are thought to have dysfunctional families and a lack of optimal conflict-free separation from their mother. Because adaptive mechanisms for tension release are not adequately developed, poor impulse control and unresolved subconscious anger ensue. Hair pulling is one way in which these patients manage their tension. In persistent cases, a spectrum of behavioral disorders is frequently encountered, including thumb sucking, nail biting, poor school performance, and dysfunctional peer as well as family relationships.

Epidemiology

Although encountered across the spectrum of psychiatric illnesses, in dermatologic practice trichotillomania is usually seen in relatively psychologically intact individuals. Peak onset is in childhood, with a mean age at onset of 8 years for boys and 12 years for girls[20]. There is a female preponderance, with a female-to-male ratio of 5:1[21]. The prevalence has been estimated to be approximately 0.6% of the general population using the strict DSM-IV criteria for "hair pullers". Of note, hair pulling in toddlers and preschool-aged children is more common in boys than girls and (unlike trichotillomania in older children) tends to resolve spontaneously.

Pathology

One helpful finding is the presence of pigmented hair casts (Fig. 7.9), which may also be seen with traction alopecia and other conditions that cause follicular trauma. Deformed hair shafts (trichomalacia) and empty follicles (hair shafts pulled out) are often encountered. Perifollicular lymphocytes, plasma cells and neutrophils are usually sparse or absent. Perifollicular hemorrhage is sometimes found in early lesions, and perifollicular fibrosis represents a late change. If the follicle is destroyed, a vertical fibrous tract often remains at the site.

Differential diagnosis

The differential diagnosis includes other causes of circumscribed nonscarring alopecia such as alopecia areata (see Ch. 69; occasionally coexists with trichotillomania) or tinea capitis. However, in trichotillomania there are no exclamation point hairs, scaling is absent, and fungal cultures are negative. If the hairs within a portion of the involved region are clipped close to the surface of the scalp or shaved, normal hair growth will be observed within this area over time. In difficult-to-diagnose patients, a biopsy specimen can be obtained.

Management

Management of trichotillomania is difficult and requires a flexible approach. Behavior modification therapy is the mainstay of treatment. This includes self-monitoring, teaching the patients to do something else whenever they are feeling the urge to pull their hair, relaxation techniques and positive reinforcement. In addition, a family and peer support network may be helpful. Antidepressants (especially SSRIs) have been reported to be effective in some studies[22]. However, two randomized controlled trials failed to show benefit of antidepressants compared to placebo, and several others found that behavioral therapy was more effective than antidepressants. In recent randomized controlled studies, treatment with olanzapine or *N*-acetylcysteine (a glutamatergic agent) led to more improvement in adults with trichotillomania than did placebo[23,24].

TREATMENT

As discussed earlier, the treatment of psychodermatologic disorders can be directed by classifying patients into four major psychopathologic categories: anxiety, depression, psychosis and OCD. In this section, the major psychopharmacologic agents used to treat the psychocutaneous disorders discussed previously will be presented, and non-pharmacologic therapies for these conditions will be outlined.

Pharmacologic Treatment

Anxiety disorder

In general, there are two broad categories of antianxiety medications:

- quick-acting benzodiazepines
- slow-acting non-benzodiazepines that are neither sedating nor dependency-provoking.

The prototypical fast-acting benzodiazepine is lorazepam. Usually, 0.5–2 mg every 6–8 hours on an "as needed" basis can be used to control acute anxiety. As with all benzodiazepines, addiction can develop with long-term use. Thus, the duration of treatment should be limited to no more than 4 weeks. This amount of time is usually adequate for treatment of anxiety related to acute situational stressors. Sedation is usually the only adverse effect encountered when lorazepam is used for such a short period of time, and this usually subsides after several days of treatment or can be controlled by dosage adjustment.

If a patient has chronic anxiety, the use of a non-benzodiazepine such as buspirone is preferable. This medication can be used for long-term maintenance because it is non-sedating and does not produce dependency. In this respect, it is much safer to use than benzodiazepines. Because the onset of action may be delayed for 2–4 weeks after initiating therapy, buspirone is not useful in acute anxiety. The recommended initial dose is 15 mg daily (usually divided into three doses). To achieve an optimal therapeutic response, the dosage may be increased by 5 mg a day every 2 to 3 days, up to a maximum of 60 mg a day if needed.

Antidepressants (see below) such as paroxetine (Paxil®; 20–50 mg/day), sertraline (Zoloft® 25–200 mg/day), fluoxetine (Prozac® 10–60 mg/day), escitalopram (Lexapro® 10–20 mg/day), low-dose doxepin (≤50 mg/day), and venlafaxine extended release (Effexor XR®; 75–150 mg/day) have also been shown to be useful for the treatment of chronic anxiety[25].

Depression

The numerous available antidepressants have similar efficacy rates of approximately 60–80%. The initial response to antidepressants usually begins 2–3 weeks after the therapeutic dose is reached, and at least 6 weeks of full-dose treatment is generally required before full therapeutic effectiveness is achieved. The US FDA requires that antidepressants have a black box warning noting an increased risk of suicidal thoughts and behavior (particularly during the first 1–2 months of therapy) in patients <25 years of age.

The tricyclic antidepressant that is most often used by dermatologists is doxepin. Doxepin is well suited for depressed patients with neurotic excoriations because, in addition to its antidepressant effects, it is a very powerful H_1 receptor antagonist that can help to break the itch–scratch cycle. For control of pruritus, a dosage of 10–25 mg at bedtime would be appropriate. To treat depression, this starting dose is increased by 10–25 mg every 1–2 weeks as tolerated, up to a therapeutic range of 100-300 mg daily (lower for elderly or small individuals). The most common adverse effect is sedation. Other side effects of doxepin are similar to those of other tricyclic antidepressants, including cardiac conduction abnormalities, weight gain, orthostatic hypotension, and anticholinergic effects (e.g. dry mouth, blurry vision, constipation, urinary retention).

SSRIs represent the most widely prescribed class of antidepressants and the first-line treatment for depression. They include fluoxetine (Prozac®), paroxetine (Paxil®), sertraline (Zoloft®), escitalopram (Lexapro®) and citalopram (Celexa®). These drugs are as effective as the tricyclic antidepressants but have a more favorable side-effect profile because they do not affect the cholinergic and histaminic receptors. The most common adverse effects are gastrointestinal symptoms such as nausea and diarrhea. As with all antidepressants, the clinical response is gradual. Patients showing no improvement in 6–8 weeks should be switched to another SSRI or to an agent from another class of antidepressants, such as venlafaxine or bupropion (Wellbutrin®).

Psychosis

The psychodermatologic conditions that typically require treatment with an antipsychotic medication are forms of somatic-type delusional disorder (see Table 7.1), most often delusions of parasitosis. Traditionally, the treatment of choice for delusions of parasitosis has been pimozide (Orap®). Careful titration of this medication is needed to ensure its safe use. Pimozide is usually started at a dose of 1 mg daily, which is increased by 1 mg every 1–2 weeks until the optimal clinical response is achieved, usually at 4–6 mg daily.

Although there have been reports of sudden death (presumably of cardiac cause) in patients with chronic schizophrenia who were treated with high-dose pimozide (>10 mg/day), there is less evidence for clinically significant cardiac effects at the lower doses used for psychodermatologic conditions. Since pimozide can potentially cause arrhythmias by prolonging the Q–T interval, an electrocardiogram should be performed before and after initiating treatment in patients with a history of cardiac conduction abnormalities. It has been debated whether an electrocardiogram is warranted for lower-dose pimozide therapy in young, healthy patients with no history of cardiac problems[25]. The patient's medications should be reviewed in order to identify any potential drug–drug interactions (see Ch. 131). For example, agents that inhibit the P450 CYP3A4 enzyme system (e.g. macrolide antibiotics, azole antifungals, HIV protease inhibitors; also grapefruit juice) can increase serum levels of pimozide, and some other medications (e.g. certain quinolones) also prolong the Q–T interval.

Most patients with delusions of parasitosis can be successfully tapered off pimozide after 2–6 months of therapy. Because this drug differs from haloperidol only by one methyl group, extrapyramidal side effects such as stiffness or a feeling of inner restlessness called akathisia (manifested outwardly by difficulty remaining still and fidgeting or pacing) are possible. Benztropine (Cogentin®; 1–2 mg up to four times daily) or diphenhydramine (Benadryl®; 25 mg up to four times daily) can be used to treat extrapyramidal side effects.

"Atypical" antipsychotic medications with more favorable side-effect profiles (e.g. fewer extrapyramidal symptoms, lack of Q–T prolongation; see Table 7.2) are now the most frequently prescribed medications for the treatment of psychosis. These drugs include risperidone (Risperdal®), olanzapine (Zyrexa®), quetiapine (Seroquel®), aripiprazole (Abilify®), ziprasidone (Geodon®) and lurasidone (Latuda®). This group of medications appears to be as effective as the older antipsychotics for various psychotic disorders and may prove useful and safe for somatic-type delusional disorder, although the optimal dosage range for the latter condition has not been established. Additional side effects of pimozide and (to a lesser degree) some atypical antipsychotic agents include anticholinergic symptoms (see above), increased prolactin, and weight gain.

Obsessive–compulsive disorder

Several psychodermatologic disorders have OCD-like features, including trichotillomania, onychotillomania, neurotic excoriations and acne excoriée. The SSRIs (see above) are the first-line treatment for OCD.

OCDs often require a higher dose of SSRIs and take longer to respond to therapy than depression. The initial response may appear at 4–8 weeks and a maximal response may take as long as 20 weeks. A 10–12-week trial with an SSRI at a therapeutic dosage for OCD is necessary to confirm a failure to respond. Once a therapeutic response is achieved, treatment should be continued for 6 months to a year.

Non-pharmacologic Treatments

A number of non-pharmacologic treatments exist for patients with psychodermatologic disorders. However, most dermatologists have neither the time nor the expertise to provide these treatments. Nevertheless, it is beneficial to be aware of these options, especially for patients who are willing and able to accept a referral to a mental health professional. Individual psychotherapy can be beneficial if there is a definable psychological/interpersonal issue to be discussed. Cognitive or group therapy may also provide benefit. For patients with anxiety-driven disorders, stress management courses, relaxation exercises and hypnosis may help to relieve "bottled-up" feelings. Patients with OCD-type conditions can be referred for behavior modification therapy. In an ideal situation, a comprehensive therapeutic plan involving both pharmacologic and non-pharmacologic approaches would be optimal for treating most psychiatric conditions.

SUMMARY

Psychodermatologic problems are prominent in any dermatology practice. By using a systematic approach to diagnosis and management, dermatologists can successfully treat these challenging patients.

REFERENCES

1. Savin J, Cotterill J. Psychocutaneous disorders. In: Champion RH, Burton JL, Ebling FJ (eds). Textbook of Dermatology. Oxford: Blackwell Scientific, 1992: 2479–96.
2. Gupta MA, Voorhees J. Psychosomatic dermatology: is it relevant? Arch Dermatol. 1990;126:90–3.
3. Koo J. Psychotropic agents in dermatology. Dermatol Clin. 1993;11:215–24.
4. Lee CS. Delusions of parasitosis. Dermatol Ther. 2008;21:2–7.
5. Bishop EJ. Monosymptomatic hypochondriacal syndromes in dermatology. J Am Acad Dermatol. 1983;9:152–8.
6. Accordino RE, Engler D, Ginsburg IH, et al. Morgellons disease? Dermatol Ther. 2008;21:8–12.

6a. Pearson ML, Selby JV, Katz KA, et al; for the Unexplained Dermopathy Study Team. Clinical, epidemiologic, histopathologic and molecular features of an unexplained dermopathy. PLoS One. 2012;7:e29908.

7. Phillips KA, Dufresne RG Jr, Wilkel CS, et al. Rate of body dysmorphic disorder in dermatology patients. J Am Acad Dermatol. 2000;42:436–41.
8. Lochner C, Stein DJ. Olfactory reference syndrome: diagnostic criteria and differential diagnosis. J Postgrad Med. 2003;49:328–31.
9. Cantor J. Cosmetic dermatology and physicians' ethical obligations: more than just hope in a jar. Semin Cutan Med Surg. 2005;24:155–60.
10. Koblenzer CS. Neurotic excoriations and dermatitis artefacta. Dermatol Clin. 1996;14:447–55.
11. Lyell A. Dermatitis artefacta and self-inflicted disease. Scott Med J. 1972;17:187–96.
12. Joe EK, Li VW, Magro CM, et al. Diagnostic clues to dermatitis artefacta. Cutis. 1999;63:209–14.
13. Koblenzer C. Psychocutaneous Disease. Orlando: Grune and Stratton, 1987.
14. Sneddon I, Sneddon J. Self-inflicted injury: a follow-up study of 43 patients. Br J Dermatol. 1975;3:527–30.
15. Ginsburg IH. The psychosocial impact of skin disease: an overview. Dermatol Clin. 1996;14:473–84.
16. Fruensgaard K. Psychotherapeutic strategy and neurotic excoriations. Int J Dermatol. 1991;30:198–203.
17. Fruensgaard K. Psychotherapy and neurotic excoriations. Int J Dermatol. 1991;30:262–5.
18. Stein DJ, Simeon D, Cohen LJ, et al. Trichotillomania and obsessive-compulsive disorder. J Clin Psychiatry. 1995;56(suppl. 4):28–34.
19. Stein DJ, Flessner CA, Franklin M, et al. Is trichotillomania a stereotypic movement disorder? An analysis of body-focused repetitive behaviors in people with hair-pulling. Ann Clin Psychiatry. 2008;20:194–8.
20. Messinger ML, Cheng TL. Trichotillomania. Pediatr Rev. 1999;20:249–50.
21. Greenberg H, Sarner C. Trichotillomania – symptom and syndrome. Arch Gen Psychiatry. 1965;12:482.
22. Swedo SE, Leonard HL, Rapoport JL, et al. A double-blind comparison of clomipramine and desipramine in the treatment of trichotillomania. N Engl J Med. 1989;321:497–501.
23. Van Ameringen M, Mancini C, Patterson B, et al. A randomized, double-blind, placebo-controlled trial of olanzapine in the treatment of trichotillomania. J Clin Psychiatry. 2010;71:1336–43.
24. Grant JE, Odlaug BL, Kim SW. N-acetylcysteine, a glutamate modulator, in the treatment of trichotillomania: a double-blind, placebo-controlled study. Arch Gen Psychiatry. 2009;66:756–63.
25. Lee CS, Accordino R, Howard J, et al. Psychopharmacology in dermatology. Dermatol Ther. 2008;21:69–82.

Psoriasis 8

Peter CM van de Kerkhof and Frank O Nestlé

Key features

- Psoriasis is a chronic, immune-mediated disorder that results from a polygenic predisposition combined with environmental triggers, e.g. trauma, infections or medications
- The underlying pathophysiology involves T cells and their interactions with dendritic cells and cells involved in innate immunity, including keratinocytes
- Identification of susceptibility genes has pointed to a major role for both the innate and the adaptive immune systems
- Sharply demarcated, scaly, erythematous plaques characterize the most common form of psoriasis; occasionally, sterile pustules are seen
- The most common sites of involvement are the scalp, elbows and knees, followed by the nails, hands, feet and trunk (including the intergluteal fold)
- Typical histologic findings include acanthosis with elongated rete ridges, hypogranulosis, hyper- and parakeratosis, dilated blood vessels and a perivascular infiltrate of lymphocytes with neutrophils singly or within aggregates in the epidermis
- Psoriatic arthritis is the major associated systemic manifestation and the most common presentation is asymmetric oligoarthritis of the small joints of the hands and feet; other comorbidities include cardiovascular disease in patients with moderate to severe disease
- Phototherapy, methotrexate, cyclosporine and "biologic" therapies that target key immune effector cells and cytokines lead to significant clinical improvement

INTRODUCTION

Psoriasis is an immune-mediated polygenic skin disorder. Various environmental triggering factors, e.g. trauma, infections or medications, may elicit disease in predisposed individuals[1]. The characteristic lesion is a sharply demarcated erythematous plaque with micaceous scale, and the plaques may be localized or widespread in distribution. Histologically, hyperkeratosis, parakeratosis, acanthosis of the epidermis, tortuous and dilated vessels, and an inflammatory infiltrate composed primarily of lymphocytes are observed.

Psoriasis is a systemic disease process in which up to 20–30% of the patients have or will develop psoriatic arthritis. In addition, in patients with moderate to severe psoriasis, there is an increased relative risk for metabolic syndrome and atherosclerotic cardiovascular disease. Psoriasis also has a significant impact on patients' quality of life[2], and in surveys, patients feel that the current treatments, although often effective, do not provide a satisfactory long-term solution.

HISTORY

Hippocrates and his school (460–377 BC) provided meticulous descriptions of many skin disorders. In their classification, dry scaly eruptions were grouped together under the heading "lopoi". This group probably included psoriasis and leprosy.

Between 129 and 99 BC, the word "psora" (meaning a desquamative condition) was first used by Galen to describe a skin disorder characterized by a scaliness of the eyelids, corners of the eyes, and scrotum. The condition was pruritic and excoriations were present. Although called psoriasis, this affliction was probably a type of eczema.

It was not until the nineteenth century that psoriasis was recognized as an entity distinct from leprosy. Although Robert Willan (1809) was the first to give an accurate description of psoriasis, it would be another 30 years before Hebra (in 1841) definitively separated the clinical features of psoriasis from those of leprosy. In 1879, Heinrich Koebner described the development of psoriatic plaques at sites of skin injury. He designated this phenomenon as "artificial production of the psoriatic lesion".

EPIDEMIOLOGY AND GENETICS

In most reviews, the prevalence of psoriasis is said to be 2% of the world's population. However, in the US and Canada, prevalences as high as 4.6% and 4.7% have been reported, respectively. This contrasts with frequencies in Africans, African-Americans, Norwegian Lapps, and Asians of between 0.4% and 0.7%[2]. Brandrup and Green[3] reported that two-thirds of affected individuals were suffering from mild psoriasis, while one-third had more severe involvement. In one large group of patients with psoriasis (n = 1728), 79% had nail changes[4]. Psoriatic arthritis has been found to affect 5–30% of patients with cutaneous psoriasis in different series[2].

Psoriasis can first appear at any age, from infancy to the eighth decade of life. Two peaks in age of onset have been reported: one at 20–30 years of age and a second peak at 50–60 years. In approximately 75% of patients, the onset is before the age of 40 years[5–7], and in 35–50%, it is before the age of 20 years. Although the age of onset is earlier in women than in men, the natural history is similar – chronic with intermittent remissions. In one epidemiologic study, 39% of the patients stated they had experienced remissions of 1–54 years[7].

In Europe, the overall prevalence rate for juvenile psoriasis was found to be ~0.7%[8,9], with an increase from 0.37–0.55% in those 0 to 9 years of age to 1.01–1.37% in those 10-19 years of age[8–10]. Plaque psoriasis is the most frequent form of the disease in children, followed by guttate psoriasis[11].

Genetic Factors

Depending upon the series, a positive family history has been reported by 35% to 90% of patients with psoriasis. Based on a large survey-based study in Germany, if both parents had psoriasis, the risk of their child developing psoriasis was 41%, whereas if only one parent were affected, the risk was 14%; the risk was 6% if just one sibling had psoriasis[12].

Analysis of concordance rates among monozygotic and dizygotic twins is another method for examining the influence of genetic factors on a disease. Farber and Nall[13] reviewed the published data from twin pair studies in psoriasis. Of 141 monozygotic twin pairs, 82 were concordant for psoriasis and 59 were discordant; of 155 dizygotic twin pairs, only 31 were concordant and 124 were discordant for psoriasis. Thus, there is a two- to threefold increased risk of psoriasis in monozygotic twins as compared to dizygotic twins[7], implying that genetic factors are important. The distribution of the lesions, the severity, and the age of onset were similar in the monozygotic twin pairs, whereas these features differed in the dizygotic twin pairs. This observation suggested that genetic factors also play a role in the clinical course of psoriasis.

HLA studies

Histocompatibility antigens (HLA) are surface antigens on human cells, and the corresponding chromosomal region is called the major histocompatibility complex (MHC). It is situated on the short arm (p) of chromosome 6. Psoriasis is associated with HLA-Cw6, with the

presence of HLA-Cw6 conferring a relative risk of 13 for developing psoriasis in the Caucasian population and 25 in the Japanese.

HLA-Cw6 is strongly linked to the age of onset of psoriasis. In one series, HLA-Cw6 was expressed in 90% of the patients with early-onset psoriasis, in 50% of those with late-onset psoriasis, and only in 7% of a control population. A specific MHC class II antigen (DRB1*0701/2) also appeared to be associated with early-onset psoriasis, and the psoriasis-associated HLA alleles were often in an extended haplotype: Cw6-B57-DRB1*0701-DQA1*0201-DQB1*0303[14]. Individuals carrying this haplotype were found to have a 26-fold increased risk of developing early-onset psoriasis. As a result, some clinicians have designated patients with early-onset psoriasis, a positive family history of psoriasis, and expression of HLA-Cw6 as having *type I psoriasis* and those with late-onset disease, no family history, and a lack of expression of HLA-Cw6 as having *type II psoriasis*[15]. Other HLA alleles may be associated with different psoriasis variants and related conditions. For example, the HLA-B27 allele is a marker for sacroiliitis-associated psoriasis and reactive arthritis (see below).

Genome-wide association studies

Classic genome-wide linkage analysis has identified at least nine psoriasis susceptibility regions *(PSORS1–9)* in different chromosomal locations[16]. By far the most important genetic region is *PSORS1* (on chromosome 6p), which is estimated to account for up to 50% of psoriasis risk. *PSORS1* contains genes such as *HLA-C* (with the *HLA-Cw6* risk allele; see above) and corneodesmosin (*CDSN*). Due to high linkage disequilibrium in *PSORS1* (i.e. genes within this region are inherited as a block), it has been challenging to determine which gene(s) within *PSORS1* contribute to psoriasis pathogenesis. Use of genome-wide association studies (GWAS) has recently provided new insights into the genetic basis of psoriasis. In GWAS, hundreds of thousands of *s*ingle *n*ucleotide *p*olymorphisms (SNPs) across the entire human genome are examined in thousands of patients[17] (see Ch. 54). Genes that have been associated with psoriasis through utilization of this and other methods are summarized in Table 8.1.

Several conclusions regarding the genetic factors in psoriasis can be drawn from recent GWAS[18,19]. First, most of the genes that have been implicated have immune-related functions, underscoring the importance of the innate and adaptive immune systems in the pathogenesis of psoriasis; in contrast, relatively few genes that encode skin-specific proteins have been associated with psoriasis. Second, thus far surprisingly few interactions among the genetic variants have been identified (with the exception of HLA-Cw6 and ERAP-1; see below). Third, associated genes encode proteins with roles in particular immunologic and signaling pathways, especially those involving tumor necrosis factor (TNF), NF-κB, interferons (IFN) and interleukin (IL)-23/Th17 cells (see Immunopathogenesis)[19,20]. Lastly, the *ERAP1* gene encoding an aminopeptidase involved in MHC class I antigen processing is only associated with psoriasis risk in individuals carrying the *HLA-Cw6* risk allele, providing evidence for the role of an MHC-restricted antigen and its presentation through HLA-C in the pathogenesis of psoriasis.

Functional genomic studies

Microarray technology has been utilized to obtain a comprehensive picture of the genes expressed in psoriatic skin[21]. More than 1300 genes were found to be differentially expressed when compared to normal human skin. This group of genes included known markers of psoriasis in the skin, but it also contained numerous genes not known to be expressed in the skin. These analyses confirmed the known involvement, on a genomic scale, of T cells and dendritic cells (DCs), providing evidence for sustained chronic T-cell activation and persistence in psoriatic epidermis.

Microarray-based comparison between the transcriptome of lesional skin from patients with psoriasis versus atopic dermatitis have revealed not only differences in expression of genes with immune function, but also differences in genes expressed by keratinocytes. For example, skin-derived antimicrobial proteins were expressed at high levels in psoriatic skin but at low levels in skin affected by atopic dermatitis[22].

GENETIC LOCI LINKED TO PSORIASIS

Gene/Locus	Chromosomal location	Odds ratio for psoriasis	Comments	Other disease associations
PSORS1	6p	6.4	Contains *HLA-Cw6* (putative immune function; major candidate gene) and *CDSN*	None
PSORS2	17q	–	Putative role in immune synapse formation	None
IL12B	5q	1.4	T-cell differentiation	Crohn's disease
IL23R	1p	2.0	T-cell differentiation	Crohn's disease, ankylosing spondylitis, psoriatic arthritis
ZNF313 (*RNF114*)	20q	1.25	Ubiquitin pathway	None
CDKAL1	6p	1.26	Unknown	Crohn's disease, type 2 diabetes mellitus
PTPN22	18p	1.3	T-cell signalling	Juvenile idiopathic arthritis, systemic lupus erythematosus, rheumatoid arthritis, type 1 diabetes mellitus, autoimmune thyroid disease
IL4/IL13 cytokine gene cluster	5q	1.27	T-cell differentiation	Crohn's disease (distinct variant)
LCE3B/3C/3D	1q	1.31	Epidermal differentiation	
IL23A	12q	1.68	IL-23/Th17 axis	
ERAP1	5q	1.27	MHC class I antigen processing	Ankylosing spondylitis
TNFAIP3	6q	1.28	NF-κB pathway	Rheumatoid arthritis
TNIP1	5q	1.72	NF-κB pathway	
TRAF3IP2	6q	1.36	NF-κB pathway/ IL-23/Th17 axis	Psoriatic arthritis
NFKBIA	14q	1.19	NF-κB pathway	

Table 8.1 Genetic loci linked to psoriasis[18–20]. In addition, polymorphisms in other genes, e.g. interferon induced with helicase C domain 1 (*IFIH1*), have been associated with a decreased risk of developing psoriasis. *CDKAL1,* cyclin-dependent kinase 5 regulatory protein subunit 1-like 1; CDSN, corneodesmosin; *ERAP1,* endoplasmic reticulum aminopeptidase 1; IL, interleukin; *LCE,* late cornified envelope; MHC, major histocompatibility complex; *NFKBIA,* nuclear factor of κ light chain gene enhancer in B cells inhibitor α ; *PTPN22,* protein tyrosine phosphatase non-receptor type 22; *TNFAIP3,* tumor necrosis factor-α-induced protein 3; *TNIP1,* TNFAIP-interacting protein 1; TRAF3IP2, TNF receptor-associated protein 3 interacting protein 2; *ZNF313,* zinc finger protein 313. Further references are available in the online content.

PATHOGENESIS

Because it primarily affects the interfollicular epidermis, psoriasis was long regarded as an epidermal disease in which the biochemical or cellular defect resided within the keratinocyte. Accordingly, prior to the early 1980s[23], a number of biochemical mediators, enzymes and pathways involved in epidermal function were incriminated as being abnormal in psoriasis, including cyclic AMP, eicosanoids, protein kinase C, phospholipase C, polyamines and transforming growth factor (TGF)-α. Although associated immunologic abnormalities were reported in the late 1970s[24], a major paradigm shift occurred when T-cell suppressive agents such as cyclosporine were found to result in significant improvement of psoriasis[25]. For the past two decades, psoriasis has been regarded as a T-cell-driven disease[25]. The role of lymphocyte subsets as well as cytokines involved in chemotaxis, homing and activation of inflammatory cells has been extensively investigated, culminating in the development of novel therapeutic approaches[25]. Although some regard psoriasis as an autoimmune disease, to date no true autoantigen has been definitively identified.

Immunopathogenesis

Role of T cells and dendritic cells

The association of psoriasis with particular MHC alleles, such as *HLA-Cw6*, and (in individuals carrying such alleles) variants in the *ERAP1* gene encoding an aminopeptidase involved in antigen processing strongly suggests a pathogenetic role for antigen-presenting cells and T cells (Fig. 8.1). The presence of specific T-cell subsets within the epidermis and dermis of lesional skin is well documented (see below). In addition, a number of compounds that affect T-cell function (e.g. by targeting the IL-2 receptor, CD2, CD11a and CD4) were found to result in clinical improvement of psoriasis[25]. Another argument supporting involvement of the adaptive immune system is the disappearance or development of psoriasis following hematopoietic stem cell transplantation[26,27]. In addition, analysis of lesional T cells has shown oligoclonality, indicating potential antigen-specific expansion of T-cell subpopulations, possibly triggered by exogenous microbial or viral antigens or cross-reacting autoantigens, e.g. keratins[28].

Animal models for psoriasis have also demonstrated the importance of T cells. In xenograft models in which uninvolved psoriatic skin was transplanted onto immunodeficient mice, donor immune cells (in particular resident T cells) were capable of expanding and inducing the complete lesional phenotype[29]. Induction of psoriatic lesions in these models was also shown to be dependent on TNF-α and on IFN-α derived from plasmacytoid DCs (pDCs)[29,30]. These experiments demonstrated that T cells can trigger psoriasis in a suitable patient-derived environment.

In humans, several cell types have been implicated in the initiation and maintenance of psoriatic lesions. Most of the epidermal T cells are $CD8^+$, whereas the dermal infiltrate is a mixture of $CD4^+$ and $CD8^+$ cells. The majority of the cells in both locations are memory T cells that express cutaneous lymphocyte antigen (CLA; the skin homing receptor) and chemokine receptors such as CCR4. Expression of $\alpha_1\beta_1$ integrin (VLA-1) on psoriatic T cells, which allows their interaction with basement membrane collagen IV, is key for the entrance of these cells into psoriatic epidermis and establishment of the psoriatic epithelial phenotype (see Fig. 8.1)[31]. Natural killer (NK) T cells represent another subset of T cells that are part of the innate immune system and are found in psoriatic skin lesions; they interact with CD1d on keratinocytes. The resulting production of IFN-γ could contribute to additional immune stimulation[32].

DCs are present in both uninvolved and lesional psoriatic skin, and because of their potent immunostimulatory capacity, they are likely to be involved in its pathogenesis. There is an increased number of dermal DCs in psoriatic skin, and they have an enhanced ability to activate T cells when compared to DCs from normal skin[33]. DC phenotype and function are quite plastic, with the ability to differentiate into potent proinflammatory DCs that produce inducible nitric oxide synthase (iNOS) and TNF-α (referred to as TIP [*T*NF/*i*NOS-*p*roducing] DCs)[34]. The role of DCs in psoriasis has been validated by the presence of a prominent genomic DC signature and the decrease of DCs during effective targeted therapy[35].

Based upon studies in humans and a xenograft model, another type of DC, the pDC, was shown to initiate psoriasis via the production of IFN-α[30]. Complexes of self DNA or RNA (from keratinocytes) plus antimicrobial peptide LL37 trigger IFN-α release by pDCs via a Toll-like receptor 9 (TLR9)-dependent mechanism (see Fig. 8.1). This leads to a breaking of tolerance to self nucleic acids and potentially explains the start of the inflammatory cascade in psoriasis[36,37].

The presence of neutrophils in the epidermis, either in spongiform pustules of Kogoj or in microabscesses of Munro, is a typical histopathologic feature of psoriasis, especially acute or pustular forms. Neutrophils are typically prominent in active lesions and in the marginal zone of expanding plaques, but, in contrast to T cells, they are not a consistent feature of lesional skin. Although activated neutrophils could contribute to its pathogenesis, they are not considered to be the primary cause of psoriasis.

Prominent angiogenesis is observed in plaques of psoriasis. There is increased expression of vascular endothelial growth factor (VEGF)[38], and anti-VEGF therapy leads to improvement in mouse models of psoriatic inflammation[39].

Cytokines and chemokines

Psoriasis is considered to be a disease with prominent involvement of helper T-cell subsets and their secreted cytokines[40]. Increased amounts of Th1 cytokines (IFN-γ and IL-2) are observed, whereas levels of the anti-inflammatory cytokine IL-10 are reduced. Based on animal studies and measurements in lesional skin, IL-12, IL-23 and IL-15 are likely to contribute to the disease. The striking response of psoriasis to ustekinumab, a human monoclonal antibody against the p40 subunit of IL-12 and IL-23, provides additional evidence for the role of cytokines. It is thought that IL-23 (produced by DCs) stimulates Th17 cells to release IL-17 and IL-22; the concerted action of these cytokines leads to proliferation of keratinocytes and dermal inflammation (see Fig. 8.1)[41]. Of note, circulating levels of IL-22 correlate with disease severity. It has also been proposed that there is a distinct subset of IL-22-producing helper T cells (Th22 cells) that contribute to the pathogenesis of psoriasis[42,43]. The IL-17-producing T cells in psoriatic epidermis might have a cytotoxic phenotype, qualifying them as Tc17 cells[44].

IFN-γ is released by activated T cells and NK T cells in the epidermis, and it activates members of the STAT transcription factor family, which drive the expression of a large number of immune-related genes that have roles in psoriasis pathogenesis. The IFN-γ-activated pathway is a key feature of psoriasis and explains several phenotypic alterations such as vasodilation (by the induction of iNOS) and accumulation of T cells (via the expression of various chemokines).

The innate immune cytokines IL-1, IL-6 and TNF-α are upregulated in psoriatic skin. TNF-α is a particularly relevant cytokine and its importance is underscored by the therapeutic efficacy of TNF-α inhibitors (see Treatment).

Chemokines are important mediators in the trafficking of leukocytes, and the increased presence of several chemokines and their cognate receptors in psoriatic lesions has been extensively documented. CXCL8 is thought to mediate the often-prominent infiltration by neutrophils. CCL17, CCL20, CCL27 and CXCL9-11 are implicated in attracting T cells to the psoriatic plaque. A pDC-attracting chemokine, chemerin, is increased in psoriatic skin and might contribute to the early recruitment of pDCs into psoriatic lesions[45].

Innate immunity and role of keratinocytes

In the skin, various cell types are involved in innate (non-adaptive) immune response pathways. These include DCs (myeloid DCs and pDCs), NK T cells and neutrophils (see above), as well as epidermal keratinocytes. For example, keratinocytes constitutively express antimicrobial proteins such as β-defensin-1 (hBD1) and secretory leukocyte protease inhibitor (SLPI), which have direct antimicrobial activity against a broad spectrum of pathogens. In addition, keratinocytes can be stimulated to express a wide variety of other inducible antimicrobials such as hBD2, the cathelicidin LL37, and SKALP/elafin[46]. In addition to these effector molecules, keratinocytes express TLRs and secrete signaling molecules such as IL-1, IL-6, IL-8 and TNF-α. Interestingly, the antimicrobial effector protein hBD2 was also shown to have chemotactic activity via CCR6 and to bind to TLR-4. Since most of these proteins are highly expressed in lesional psoriatic skin, it is likely that

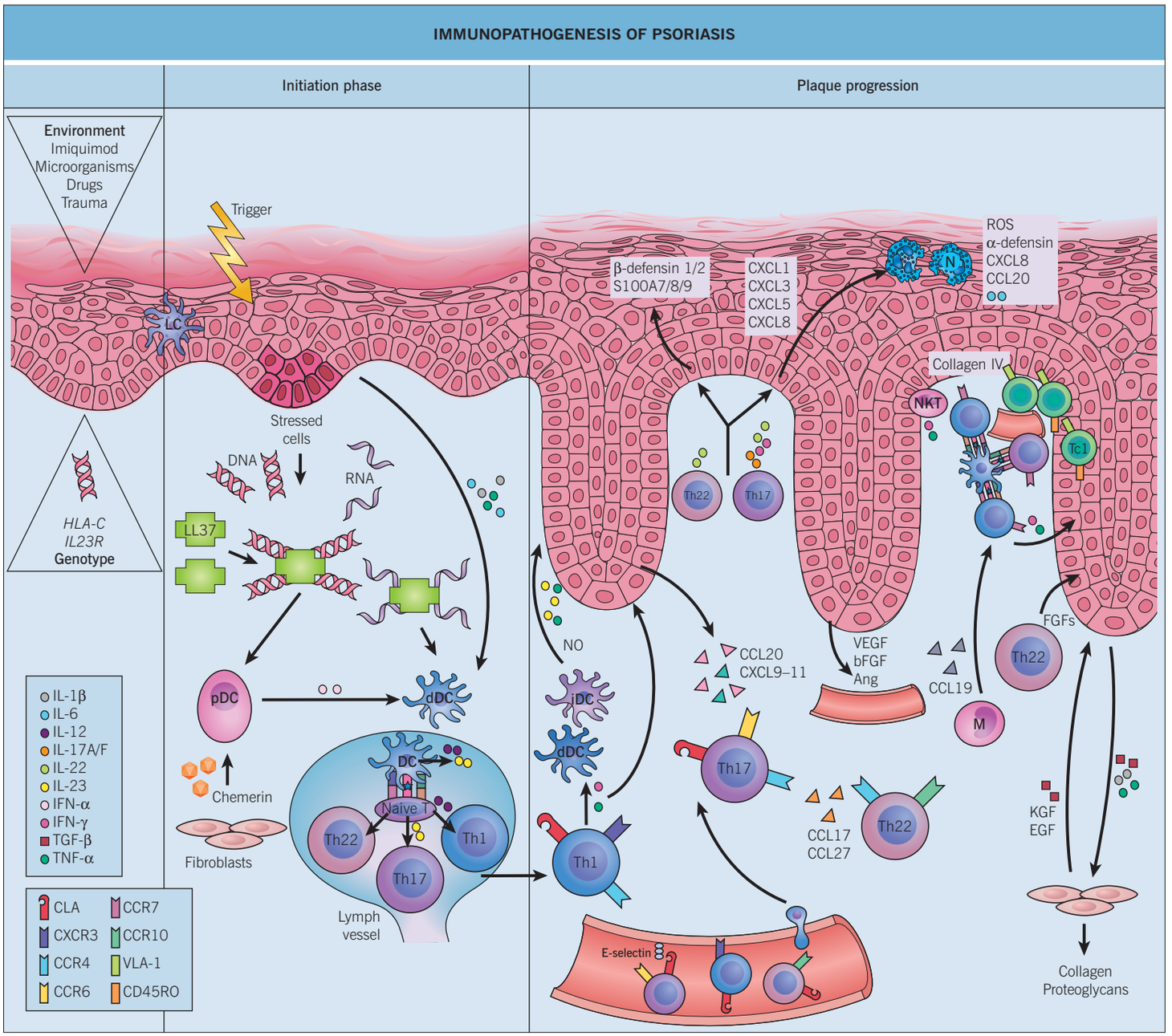


Fig. 8.1 Immunopathogenesis of psoriasis. The occurrence of triggering environmental factors in genetically predisposed individuals, carrying susceptibility alleles of psoriasis-associated genes, results in disease development. During the initiation phase, stressed keratinocytes can release self DNA and RNA, which form complexes with the cathelicidin LL37 that then induce interferon-α (IFN-α) production by plasmacytoid dendritic cells (pDCs; recruited into the skin via fibroblast-released chemerin), thereby activating dermal DCs (dDCs). Keratinocyte-derived interleukin-1β (IL-1β), IL-6 and tumor necrosis factor-α (TNF-α) also contribute to the activation of dDCs. Activated dDCs then migrate to the skin-draining lymph nodes to present an as-yet-unknown antigen (either of self or of microbial origin) to naive T cells and (via secretion of different types of cytokines by DCs) promote their differentiation into T helper 1 (Th1), Th17 and Th22 cells. Th1 cells (expressing cutaneous lymphocyte antigen [CLA], CXC-chemokine receptor 3 [CXCR3] and CC-chemokine receptor 4 [CCR4]), Th17 cells (expressing CLA, CCR4 and CCR6) and Th22 cells (expressing CCR4 and CCR10) migrate via lymphatic and blood vessels into psoriatic dermis, attracted by the keratinocyte-derived chemokines CCL20, CXCL9–11 and CCL17; this ultimately leads to the formation of a psoriatic plaque. Th1 cells release IFN-γ and TNF-α, which amplify the inflammatory cascade, acting on keratinocytes and dDCs. Th17 cells secrete IL-17A and IL-17F (and also IFN-γ and IL-22), which stimulate keratinocyte proliferation and the release of β-defensin 1/2, S100A7/8/9 and the neutrophil-recruiting chemokines CXCL1, CXCL3, CXCL5 and CXCL8. Neutrophils (N) infiltrate the stratum corneum and produce reactive oxygen species (ROS) and α-defensin with antimicrobial activity, as well as CXCL8, IL-6 and CCL20. Th22 cells secrete IL-22, which induces further release of keratinocyte-derived T cell-recruiting chemokines. Moreover, inflammatory DCs (iDCs) produce IL-23, nitric oxide (NO) radicals and TNF-α, while natural killer T (NKT) cells release TNF-α and IFN-γ. Keratinocytes also release vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and angiopoietin (Ang), thereby promoting neoangiogenesis. Macrophage (M)-derived chemokine CCL19 promotes clustering of Th cells expressing chemokine receptor CCR7 with DC in the proximity of blood vessels, with further T-cell activation. At the dermal–epidermal junction, memory $CD8^+$ cytotoxic T cells (Tc1) expressing very-late antigen-1 (VLA-1) bind to collagen IV, allowing entry into the epidermis and contributing to disease pathogenesis by releasing both Th1 and Th17 cytokines. Cross-talk between keratinocytes, producing TNF-α, IL-1β and transforming growth factor-β (TGF-β), and fibroblasts, which in turn release keratinocyte growth factor (KGF), epidermal growth factor (EGF) and TGF-β, and possibly Th22 cells releasing FGFs, contribute to tissue reorganization and deposition of extracellular matrix (e.g. collagen, proteoglycans). LC, Langerhans cell. *Courtesy, Dr Paola DiMeglio.*

they are involved in the initiation or control of the inflammatory process; however, their precise roles remain to be determined.

Any model of the pathogenesis of psoriasis also has to account for the dramatically increased proliferation rate of keratinocytes. The cytokines and chemokines found in lesional skin are generally not mitogenic for keratinocytes. For example, IFN-γ, a prominent Th1 cytokine, is itself antiproliferative, but it was found to be a crucial factor in supernatants of lesion-derived T-cell clones that could drive keratinocyte stem cell proliferation[47].

Keratinocytes within psoriatic plaques express STAT-3, suggesting that this transcription factor might be of pathogenetic importance. In a transgenic animal model, epidermal expression of STAT-3 (in cooperation with T cells) was found to induce psoriasis-like lesions in mice[48]. STAT-3 induced the upregulation of a number of genes relevant for psoriasis, such as those encoding ICAM-1 and TGF-α; the latter has been shown to stimulate proliferation of keratinocytes in psoriasis via an autocrine loop. As STAT-3 is activated by a variety of cytokines including IL-22 as well as IL-6, IL-20 and IFN-γ, this could represent a link between keratinocyte activation and immune cells in the development of the psoriatic lesion.

Triggering Factors

Triggering factors, both external (directly interacting with the skin) and systemic, can elicit psoriasis in genetically predisposed individuals.

External triggering factors

The Koebner phenomenon, i.e. the elicitation of psoriatic lesions by injury to the skin, is observed in approximately 25% of patients with psoriasis. A particular patient may be "Koebner-negative" at one point in time and later become "Koebner-positive". The Koebner phenomenon suggests that psoriasis is a systemic disease that can be triggered locally in the skin. Psoriatic lesions can also be induced by other forms of cutaneous injury, e.g. sunburn, morbilliform drug eruption, viral exanthem. The lag time between the trauma and the appearance of skin lesions is usually 2–6 weeks.

Systemic triggering factors

Infections

Infections, particularly bacterial infections, may induce or aggravate psoriasis. Provoking infections have been observed in up to 45% of psoriatic patients. Streptococcal infections, especially pharyngitis, are the most common offenders[49]. Streptococci can also be isolated from other sites, e.g. dental abscesses, perianal cellulitis, impetigo.

HIV

HIV infection has also been shown to aggravate psoriasis (see Ch. 78).

Endocrine factors

Hypocalcemia has been reported to be a triggering factor for generalized pustular psoriasis. Although active vitamin D_3 analogues improve psoriasis, abnormal vitamin D_3 levels have not been shown to induce psoriasis. Pregnancy may alter disease activity, e.g. 50% of the patients in one series reported improvement. However, pregnant women may develop pustular psoriasis, also referred to as impetigo herpetiformis (see below), sometimes in association with hypocalcemia.

Psychogenic stress

Psychogenic stress is a well-established systemic triggering factor in psoriasis[50]. It has been associated with initial presentations of the disease as well as flares of pre-existing psoriasis. In a prospective study, cognitive and behavioral patterns of worrying and scratching were both independently related to an increase in disease severity and pruritus 4 weeks later[51].

Drugs

Several drugs have been incriminated as inducers of psoriasis, in particular lithium, IFNs, β-blockers and antimalarials. Rapid taper of systemic corticosteroids can induce pustular psoriasis as well as flares of plaque psoriasis

Alcohol consumption, smoking and obesity

Obesity, increased alcohol consumption, and smoking have all been associated with psoriasis. In one analysis, smoking appeared to have a role in the onset of psoriasis, while obesity appeared to be a consequence of psoriasis[52], whereas other studies have suggested that weight gain often proceeds the development of psoriasis. Some studies have found that the prevalence of psoriasis in a population of individuals who stop smoking or who lose weight eventually reverts to background levels.

CLINICAL FEATURES

Chronic plaque psoriasis, the most common variant of psoriasis vulgaris, is characterized by sharply demarcated and erythematous papulosquamous lesions. Less often, nearly all of the body surface is involved ("*erythrodermic psoriasis*") or numerous, small, widely disseminated papules and plaques are seen ("*guttate psoriasis*"). Occasionally, there are obvious macroscopic pustules, as in generalized pustular psoriasis or pustulosis of the palms and soles.

From a clinical perspective, psoriasis can present with a spectrum of cutaneous manifestations. At any one point in time, different variants may coexist in a particular individual, but the skin lesions all share the same important hallmarks: erythema, thickening and scale. As noted in the section on Epidemiology and Genetics, there is also significant interindividual variability. For example, in patients with chronic plaque psoriasis, those with type I disease (HLA-$Cw6^+$) have an earlier onset, more widespread disease and frequent recurrences, compared to those with type II psoriasis.

Although the size of a lesion may vary from a pinpoint papule to over 20 cm in diameter, the outline of the lesion is usually circular, oval or polycyclic (the latter indicating that the lesion is derived from several smaller units). The configuration of psoriatic lesions due to the Koebner phenomenon reflects the etiology of the trauma. In addition to their highly characteristic sharp demarcation, psoriatic lesions are sometimes surrounded by a pale blanching ring, which is referred to as Woronoff's ring.

The classic findings of erythema, thickening and scale are reflections of the histologic findings of elongated dilated capillaries that are close to the skin surface, epidermal acanthosis plus cellular infiltrates, and abnormal keratinization, respectively. If the superficial silvery white scales are removed via curettage (grattage method), a characteristic coherence is observed, as if one has scratched on a wax candle ("signe de la tache de bougie"). Subsequently, a surface membrane is seen, which will also come off as a whole. If the latter is removed, then a wet surface is seen with characteristic pinpoint bleeding. This finding, called Auspitz sign, is the clinical reflection of elongated vessels in the dermal papillae together with thinning of the suprapapillary epidermis.

During exacerbations, psoriatic lesions often itch. Pinpoint papules surrounding existing psoriatic plaques indicate that the patient is in an unstable phase of the disease. In addition, expanding psoriatic lesions are characterized by an active edge with a more intense erythema. Inflamed lesions may be slightly tender. The involution of a lesion usually starts in its center, resulting in annular psoriatic lesions.

Chronic Plaque Psoriasis

In chronic plaque psoriasis, there is a relatively symmetric distribution of sharply defined, erythematous, scaly plaques (Figs 8.2 & 8.3). The degree of body surface area involvement can vary, from limited to extensive. The scalp, elbows, knees and presacrum are sites of predilection, as are the hands and feet (Figs 8.4 & 8.5). The genitalia are involved in up to 45% of patients (Fig. 8.6; see Ch. 73). Plaques may persist for months to years at the same locations. Although the course of this disease is chronic, periods of complete remission do occur and remissions of 5 years have been reported in approximately 15% of patients.

Because the percentage of body surface area involved does not reflect the severity of the individual lesions with respect to erythema, induration and scaling, the Psoriasis Area and Severity Index (PASI) was formulated (Table 8.2). This is a single score calculated from the body surface area involved (utilizing a seven-point score for involvement in each of four anatomic areas – head, upper extremities, trunk and lower extremities) and from the scores for erythema, induration and scaling (each scored using a five-point score from 0 to 4). The PASI is a cumbersome calculation and is more commonly utilized for clinical trials than for the routine management of patients with psoriasis. A score for

Fig. 8.2 Psoriatic plaques. A, B Note the sharp demarcation and silvery scale. *B, Courtesy Julie V Schaffer, MD.*

Fig. 8.3 Symmetric distribution of psoriatic plaques. A, B Both small and large plaques have a symmetric distribution pattern. Note the active border at the proximal edge of the plaques on the calves.

nail involvement has also been proposed, known as the Nail Psoriasis Severity Index (NAPSI), but it has not been widely utilized.

Guttate Psoriasis

Guttate psoriasis is more commonly seen in children and adolescents and is frequently preceded by an upper respiratory tract infection (Fig. 8.7). In over half of the patients, an elevated antistreptolysin O, anti-DNase B or streptozyme titer is found, indicating a recent streptococcal infection (see previous section).

Erythrodermic Psoriasis

This variant of psoriasis is characterized by generalized erythema and scaling, and its onset can be gradual or acute. Although there are many causes of erythroderma (see Ch. 10), clues to the diagnosis of psoriatic erythroderma include previous plaques in classic locations, characteristic nail changes, and facial sparing.

Pustular Variants

Generalized pustular psoriasis

In generalized pustular psoriasis, the infiltration of neutrophils dominates the histologic picture, while erythema and the appearance of sterile pustules dominate the clinical picture (Fig. 8.8). It is an unusual manifestation of psoriasis, and triggering factors include pregnancy, rapid tapering of corticosteroids (or other systemic therapies), hypocalcemia, infections, and, in the case of the localized pattern, topical irritants. Recently, biallelic mutations in the gene encoding the IL-36 receptor antagonist (leading to increased production of IL-8 and enhanced responses to IL-1β) have been identified in a subset of patients with generalized pustular psoriasis[53]. Generalized pustular psoriasis during pregnancy is also referred to as impetigo herpetiformis. Four distinct patterns of generalized pustular psoriasis can be seen:

- **von Zumbusch pattern**. This is a generalized eruption starting abruptly with erythema and pustulation (see Fig. 8.8). The skin is painful during this phase, and the patient has a fever and feels ill. After several days, the pustules usually resolve and extensive scaling is observed. Sometimes, chronic plaques of psoriasis, if

Fig. 8.4 Childhood psoriasis. A The scalp is a common site of involvement and psoriasis is distinguished by its sharp demarcation. **B** Annular and guttate lesions. *A, B, Courtesy, Julie V Schaffer, MD.*

present, can resolve. In the original case report by von Zumbusch (1910), nine episodes of pustulation occurred over a period of 10 years.

- **Annular pattern**. The eruption is characterized by annular lesions, consisting of erythema and scaling with pustulation at the advancing edge (Fig. 8.9). The lesions enlarge by centrifugal expansion over a period of hours to days, while healing occurs centrally.
- **Exanthematic type**. This is an acute eruption of small pustules, abruptly appearing and disappearing over a few days. It usually follows an infection or may occur as a result of administration of specific medications, e.g. lithium. Systemic symptoms usually do not occur. There is overlap between this form of pustular psoriasis and pustular drug eruptions, also referred to as acute generalized exanthematous pustulosis (AGEP; see Ch. 21).
- **"Localized" pattern**. Sometimes pustules appear within (Fig. 8.10) or at the edge of existing psoriatic plaques. This can be seen during the unstable phase of chronic plaque psoriasis and following the application of irritants, e.g. tars.

Pustulosis of the palms and soles

Pustulosis of the palms and soles is characterized by "sterile" pustules of the palmoplantar surfaces admixed with yellow–brown macules (Fig. 8.11); scaly erythematous plaques may also be seen. A minority of patients have chronic plaque psoriasis elsewhere. In contrast to the natural history of generalized pustular psoriasis, the pustules remain localized to the palmoplantar surfaces and the course of this disease is

Fig. 8.5 Palmoplantar psoriasis. Erythematous scaling plaques of the palmar (**A**) and plantar surfaces (**B**).

Fig. 8.6 Psoriasis of the genitalia. Erythematous plaques with scale on the penis and scrotum.

CALCULATION OF THE PSORIASIS AREA AND SEVERITY INDEX				
SEVERITY OF PSORIATIC LESIONS [0, none; 1, slight; 2, moderate; 3, severe; 4, very severe]				
	Head	**Trunk**	**Upper limbs**	**Lower limbs**
Erythema	0 to 4	0 to 4	0 to 4	0 to 4
Induration	0 to 4	0 to 4	0 to 4	0 to 4
Scaling	0 to 4	0 to 4	0 to 4	0 to 4
Total score = **1**	Sum of the above	Sum of the above	Sum of the above	Sum of the above
AREA OF PSORIATIC INVOLVEMENT [0, none; 1, <10%; 2, 10 to <30%; 3, 30 to <50%; 4, 50 to <70%; 5, 70 to <90%; 6, 90–100%]				
Degree of involvement = **2**	0 to 6	0 to 6	0 to 6	0 to 6
Multiply **1 × 2**	**1 × 2**	**1 × 2**	**1 × 2**	**1 × 2**
Correction factor for area of involvement = **3**	0.10	0.30	0.20	0.40
1 × 2 × 3	**A**	**B**	**C**	**D**
A + B + C + D = total PASI				

Table 8.2 Calculation of the Psoriasis Area and Severity Index (PASI). The PASI ranges from 0 to 72.

Fig. 8.7 Guttate psoriasis. A Small discrete papules and plaques of guttate psoriasis in an adolescent; note the Koebner phenomenon. **B** Numerous papules due to the Koebner phenomenon after a sunburn. *B, Courtesy, Ronald P Rapini, MD.*

Fig. 8.8 Generalized pustular psoriasis. Large areas of erythema with numerous pustules and the formation of lakes of pus.

chronic. Focal infections and stress have been reported as triggering factors and smoking may aggravate the condition. Pustulosis of the palms and soles is one of the entities most commonly associated with sterile inflammatory bone lesions, for which there are several names: chronic recurrent multifocal osteomyelitis, pustulotic arthro-osteitis, and SAPHO syndrome, which consists of *s*ynovitis, *a*cne, *p*ustulosis, *h*yperostosis and *o*steitis. Several neutrophilic dermatoses are associated with SAPHO (see Ch. 26).

Acrodermatitis continua of Hallopeau

This is a rare manifestation of psoriasis. Clinically, pustules are seen on the distal portions of the fingers (Fig. 8.12) and sometimes the toes. Pustulation is often followed by scaling and crust formation. Pustules may also form in the nail bed (beneath the nail plate), and there may be shedding of nail plates. Transition into other forms of psoriasis can occur and acrodermatitis continua may be accompanied by annulus migrans of the tongue.

Special Locations

Scalp psoriasis

The scalp is one of the most common sites for psoriasis. Unless there is complete confluence, the individual lesions are discrete, in contrast to the less well-defined areas of involvement in seborrheic dermatitis. At times, however, it is not possible to distinguish seborrheic dermatitis from psoriasis, and the two disorders may coexist. The lesions of

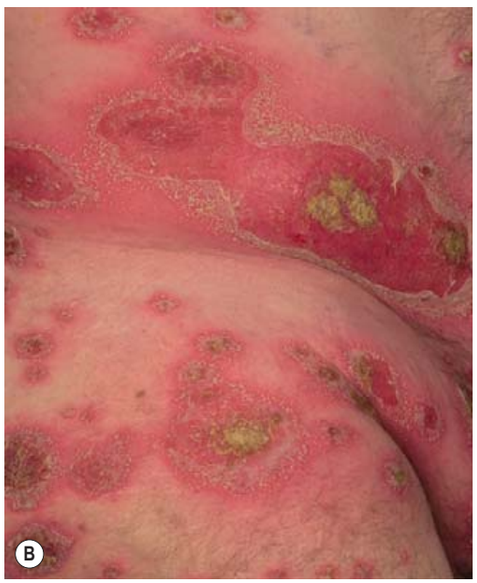


Fig. 8.9 Annular pustular psoriasis. Multiple annular inflammatory plaques studded with pustules. As the lesions enlarge, there can be central clearing, dry desquamation (**A**) and/or moist desquamation that resembles wet cigarette paper (**B**).

Fig. 8.10 "Localized" pattern of pustular psoriasis. The pustules are limited to pre-existing plaques of psoriasis.

Fig. 8.11 Pustulosis of the palms and soles. Multiple sterile papules are admixed with yellow–brown macules on the palm.

Fig. 8.12 Acrodermatitis continua of Hallopeau. Erythema and scale of the distal digit, pustules within the nail bed, and partial shedding of the nail plate.

psoriasis often advance onto the periphery of the face, the retroauricular areas and the upper neck. The scales sometimes have an asbestos-like appearance and can be attached for some distance to the scalp hairs (pityriasis amiantacea). Although pityriasis amiantacea can also be seen in patients with seborrheic dermatitis, secondarily infected atopic dermatitis and tinea capitis, psoriasis is the most common cause. Alopecia occasionally develops within involved areas (see Ch. 69). In addition, patients with dermatomyositis involving the scalp may have lesions that resemble psoriasis.

Flexural psoriasis

Flexural lesions are characterized by shiny, pink to red, sharply demarcated thin plaques (Fig. 8.13). There is much less scale than in untreated chronic plaque psoriasis. Often a central fissure is seen. The most common sites of involvement are the axillae, inguinal crease, intergluteal cleft, inframammary region and retroauricular folds. When flexural areas are the only sites of involvement, the term "inverse" psoriasis is sometimes used. Localized dermatophyte, candidal or bacterial infections can be a trigger for flexural psoriasis.

Oral mucosa

Migratory annular erythematous lesions with hydrated white scale (annulus migrans) have been observed in patients with acrodermatitis continua of Hallopeau and generalized pustular psoriasis. The most common location is the tongue, and the clinical (and histologic) appearance is similar to geographic tongue.

Fig. 8.13 Inverse psoriasis. Shiny erythematous plaques of the inframammary folds that lack scale.

Fig. 8.14 Nail psoriasis. Changes include thickening and yellow discoloration of the nail plate, distal onycholysis, pitting, red spotted lunula and subungual hyperkeratosis.

Nail psoriasis

Nail involvement (Fig. 8.14) has been reported in 10–80% of psoriatic patients, depending upon the series. The fingernails are more often affected than the toenails. In a survey from the Netherlands, 79% of patients reported involvement of their nails, with 52% experiencing associated pain and 14% major restrictions in daily life due to the nail changes. Patients with nail involvement appear to have an increased incidence of psoriatic arthritis (see below).

Psoriasis affects the nail matrix, nail bed and hyponychium. Small parakeratotic foci in the proximal portion of the nail matrix lead to pits in the nails (see Ch. 71). Leukonychia and loss of transparency (less common findings) are due to involvement of the mid portion of the matrix. If the whole nail matrix is involved, a whitish, crumbly, poorly adherent "nail" is seen. Psoriatic changes of the nail bed result in the "oil spot" or "oil drop" phenomenon, which reflects exocytosis of leukocytes beneath the nail plate. Splinter hemorrhages are the result of increased capillary fragility, and subungual hyperkeratosis and distal onycholysis are due to parakeratosis of the distal nail bed. Vigorous removal of distal subungual debris may be an exacerbating factor.

Psoriatic Arthritis

Psoriatic arthritis occurs in 5–30% of patients with cutaneous psoriasis[1], with some clinical investigators suggesting that classic studies of psoriatic arthritis may have underestimated its prevalence. In a minority of patients (10–15%), the symptoms of psoriatic arthritis appear before involvement of the skin. Currently, there are no specific serologic tests for establishing the diagnosis of psoriatic arthritis, but an important hallmark is erosive change radiographically, which may occur years after the presenting peri-articular inflammation. Psoriatic arthritis is more prevalent among patients with relatively severe psoriasis. Risk factors for a more severe course of the arthritis include: initial presentation at an early age, female gender, polyarticular involvement, genetic predisposition, and radiographic signs of the disease early on[54].The following classification has been outlined by Moll[55].

- **Mono- and asymmetric oligoarthritis**. Inflammation of the interphalangeal joints – both distal (DIP) and proximal (PIP) – of the hands and feet is the most common presentation of psoriatic arthritis (Fig. 8.15). Involvement of the PIP or both the DIP and PIP joints of a single digit can result in the classic "sausage" digit (Fig. 8.16). In contrast to rheumatoid arthritis, the metacarpophalangeal (MCP) joint is an unusual site for psoriatic arthritis. This form may be accompanied by inflammation of larger joints.
- **Arthritis of the distal interphalangeal joints**. Exclusive involvement of the DIP joints is a classic but uncommon presentation of psoriatic arthritis. This variant may occur in conjunction with contiguous nail involvement. In some patients, these joints will become fixed in a flexed position.
- **Rheumatoid arthritis-like presentation**. The clinical manifestations consist of a symmetric polyarthritis that involves small and medium-sized joints, in particular the PIP, MCP, wrist, ankle and elbow. Patients are usually seronegative, but some have a positive rheumatoid factor. Clinically, this variant is difficult to distinguish from rheumatoid arthritis. Whether seropositive patients have an overlap of the two disorders is debated.
- **Arthritis mutilans**. Fortunately, this is the least common variant of psoriatic arthritis. Patients have severe, rapidly progressive joint inflammation that results in destruction of the joints and permanent deformity. The digits become shorter, wider and softer to palpation because of osteolysis and a telescoping phenomenon. This variant can usually be distinguished from the arthritis mutilans that may accompany multicentric reticulohistiocytosis.
- **Spondylitis and sacroiliitis**. The spondylitis resembles that seen in ankylosing spondylitis, with axial arthritis as well as involvement of the knees and sacroiliac joints; many patients also have peripheral joint involvement. Individuals are often HLA-B27-positive and may have associated inflammatory bowel disease and/or uveitis.

In a recent study from Germany involving 1511 patients with chronic plaque psoriasis, 20.6% of the affected individuals had psoriatic arthritis[56]. DIP involvement was observed in ~40% of the patients with arthritis, and 5% suffered from arthritis mutilans[56]. Patients with psoriatic arthritis can have involvement of juxta-articular tendons and the sites where they insert into bone (entheses) as well as swelling of the fingers (dactylitis). Enthesitis and dactylitis have been reported in ~20% and 15–30%, respectively, of patients with "probable" or definite psoriatic arthritis[54].

Early diagnosis of psoriatic arthritis is important, as disease progression often results in loss of function.

Disorders Related to Psoriasis

A few disorders share important clinical and histologic features with psoriasis, but are distinct disease entities based upon genetic, epidemiologic or clinical features.

Inflammatory linear verrucous epidermal nevus (ILVEN)

ILVEN is characterized by linear psoriasiform lesions (i.e. scaling and erythematous plaques) that follow the lines of Blaschko (see Ch. 62). Based upon its chronicity and resistance to therapy, ILVEN is thought to be an entity separate from linear psoriasis.

Reactive arthritis (formerly Reiter's disease)

This syndrome features urethritis, arthritis, ocular findings and oral ulcers, in addition to psoriasiform skin lesions. The disorder is uncommon in children and occurs more frequently in men as compared to women. The urethritis may be mild or severe with complications such as cervicitis, salpingitis and cystitis. *Chlamydia trachomatis* is a major cause of urethritis and may trigger the entire syndrome, as may other infections such as shigellosis. Conjunctivitis is a common eye finding in affected patients, although iritis, uveitis with glaucoma, and keratitis may also occur. Polyarthritis and sacroiliitis are the most frequent joint manifestations. Cutaneous lesions occur in approximately 5% of reactive arthritis patients, with a predilection for the

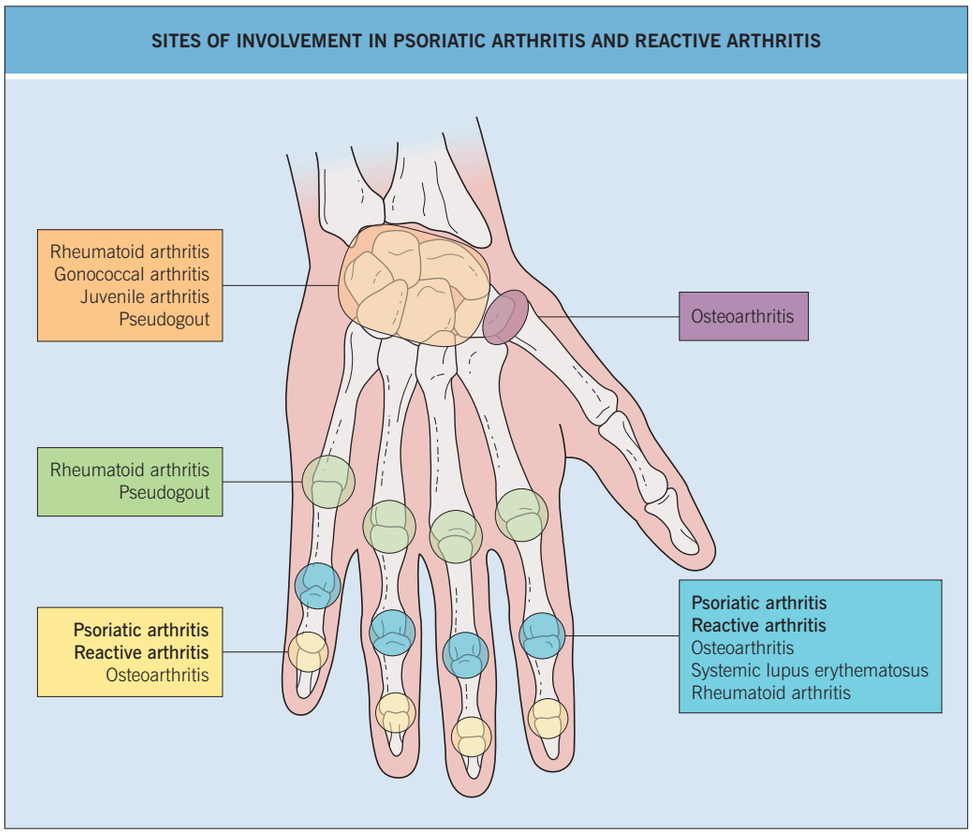


Fig. 8.15 Sites of psoriatic arthritis and reactive arthritis (formerly Reiter's disease). *Adapted from Longo DL, Fauci AS, Kasper D, et al. Harrison's Principles of Internal Medicine, 18th edn. New York: McGraw Hill, 2011.*

Fig. 8.16 Psoriatic arthritis. Asymmetric involvement of the distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints. A "sausage" digit (third digit bilaterally) results from involvement of both the DIP and PIP joints.

soles, extensor surfaces of the legs, penis, dorsal aspects of the hands, fingers, nails and scalp (Fig. 8.17). The lesions on the plantar surface usually have thick yellow scale and are often pustular (keratoderma blennorrhagicum). Psoriatic plaques on the penis are referred to as balanitis circinata.

Reactive arthritis has a strong association with HLA-B27. Although the course is often self-limited, lasting weeks to months, some patients have disease that is chronic and disabling. Of note, HIV-infected patients can also develop this disorder and it may be severe.

Sneddon–Wilkinson disease (subcorneal pustular dermatosis)

This disorder is characterized by annular or polycyclic lesions, usually commencing in the flexures (Fig. 8.18A). Very superficial (subcorneal) sterile pustules (Fig. 8.18B,C) are the hallmark of Sneddon–Wilkinson disease, hence its second name. There may be a gravity-induced demarcation in some vesicopustules, with clear fluid superiorly and pus inferiorly. This disease has a cyclic course, i.e. as the pustules resolve they are replaced by superficial scaling and then new pustules form again. Some patients with Sneddon–Wilkinson disease have an associated IgA paraproteinemia. Its response to dapsone, combined with subcorneal pustules (in the absence of spongiform pustules), provide support for this condition being a disease entity distinct from pustular psoriasis, although some authors have questioned the existence of Sneddon–Wilkinson disease as a distinct entity. Of note, immunofluorescence studies are required to distinguish the subcorneal pustular dermatosis type of IgA pemphigus from Sneddon-Wilkinson disease.

Associations between Psoriasis and Other Diseases

Associations with skin diseases

There is a pronounced under-representation of allergic skin diseases in psoriatic patients as compared to age-matched controls without psoriasis. The frequencies of atopic dermatitis, asthma, urticaria and allergic contact dermatitis have been found to be lower in psoriatic patients. For example, in one study atopic dermatitis was seen approximately 50 times less often in psoriatic compared with non-psoriatic patients[1]. An obvious explanation is the immunologic difference between these two conditions, with a predominantly Th1 response in psoriasis and a predominantly Th2 response in atopic dermatitis. However, in patients with psoriasis in atypical locations and/or treatment-resistant lesions, the possibility of allergic contact dermatitis as a triggering factor needs to be considered. In the authors' experience, longstanding psoriatic lesions of the hands and external auditory canal are indications for patch testing.

A bi-directional relationship exists between lichen simplex chronicus (LSC) and psoriasis. If a psoriatic lesion is pruritic, superimposed LSC may develop and the surface becomes shiny with increased skin markings. Because the LSC itself is pruritic, the resultant rubbing may worsen the psoriasis (Koebner phenomenon). The patient then enters a vicious cycle. The combined picture is sometimes referred to as lichenified psoriasis or psoriasis neurodermiformis. Therapeutic regimens must address both disorders.

Fig. 8.17 Reactive arthritis (formerly Reiter's disease). A, B Plantar lesions of keratoderma blennorrhagicum. **C** Papulosquamous lesions of balanitis circinata on the penis. *B, Courtesy, Gene Mirrer, MD.*

Fig. 8.18 Sneddon–Wilkinson disease. A Annular and polycyclic plaques in the axilla. **B** Subcorneal pustules with scale and crusts as well as background erythema. **C** Discrete subcorneal pustule with an erythematous rim. *C, Courtesy, Joyce Rico, MD.*

Seborrheic dermatitis is characterized by pink to red patches with yellowish, sometimes greasy, scales (see Ch. 13). The sites of predilection are the scalp, central face, ears, presternal area and intertriginous zones. As the clinical features of psoriasis and seborrheic dermatitis can be seen in the same patient, some authors use the term "sebopsoriasis", especially when diagnostic lesions of psoriasis are not present elsewhere.

Infections

In contrast to atopic dermatitis, psoriatic lesions are seldomly secondarily infected by bacteria (i.e. impetiginized). One explanation for this resistance to secondary bacterial infections is increased production of skin-derived antimicrobial peptides (e.g. defensins, SKALP/Elafin; see Pathogenesis).

The relationship between psoriasis and mycotic infections is more complex. In flexural psoriasis, concomitant *Candida* infections are frequently observed and have been incriminated as local triggering factors. *Candida* species, but not dermatophytes, are more commonly found in psoriatic nails than in normal nails.

Cancer

Patients with psoriasis may have an increased overall risk of cancer, including lymphoma, and treatment with immunosuppressive agents may increase this risk[57]. Psoriatic patients who have had specific therapies, e.g. >200 PUVA treatments, are at increased risk for the development of skin cancers, especially squamous cell carcinomas (SCCs). Of note, the use of cyclosporine in patients previously treated with PUVA significantly increases the number and rate of appearance of SCCs. Lastly, there is controversy regarding whether PUVA-treated patients have an increased risk of cutaneous melanoma.

Association with internal diseases (including comorbidities)

Cardiovascular diseases, e.g. myocardial infarctions, pulmonary emboli, peripheral arterial disease and cerebrovascular accidents, are more common in patients with severe psoriasis. Severe psoriasis is associated with a threefold increased risk for myocardial infarction and a 3.5–4.4-year reduction in life expectancy. This is largely due to an increased risk of obesity, hypertension and diabetes mellitus (components of the metabolic syndrome; see Ch. 53)[58–60]. In patients with psoriasis, serum levels of C-reactive protein (CRP) have been reported to be elevated (as compared to healthy controls), and elevated CRP levels represent a risk factor for the development of cardiovascular disease. It has also been shown that TNF-α and IL-6 can target adipocytes and induce dyslipidemia. Recently, evidence has been accumulating that treatment with methotrexate and/or TNF-α inhibitors may reduce the risk of atherosclerotic cardiovascular disease[61].

Non-alcoholic steatohepatitis, characterized by fatty infiltration, periportal inflammation and focal necrosis, is more commonly observed in patients with psoriasis. In a study of 142 adults with psoriasis, non-alcoholic fatty liver disease was detected in 59%, and it correlated with the presence of obesity, hyperlipidemia, the metabolic syndrome, an AST:ALT ratio >1 and psoriatic arthritis[62]. Chronic administration of methotrexate is associated with a significant risk for hepatic damage in patients with psoriasis, whereas similar methotrexate dosages in patients with rheumatoid arthritis do not pose such hepatotoxic potential. Although the reason for this difference is not known, several possible explanations have been put forward, including a genetic predisposition, increased alcohol consumption by psoriasis patients, and a higher incidence of non-alcoholic fatty liver disease.

Crohn's disease, ulcerative colitis and psoriasis share an association with sacroiliitis and HLA-B27 positivity[63]. Additional disorders that share susceptibility genes with psoriasis are listed in Table 8.1.

DIFFERENTIAL DIAGNOSIS

Although both seborrheic dermatitis (see above) and LSC are in the differential diagnosis of psoriasis, it is important to remember that either can coexist with psoriasis. When there is a single or limited number of erythematous plaques, especially if they are treatment-resistant, the possibility of SCC *in situ* (e.g. Bowen's disease, erythroplasia of Queyrat) needs to be excluded via histologic examination. Occasionally, a biopsy is necessary to distinguish chronic plaque psoriasis from the mycosis fungoides variant of cutaneous T-cell lymphoma (CTCL). Clinical features suggestive of the latter include wrinkling due to epidermal atrophy and progression to infiltrated plaques. Dermatomyositis can involve the scalp, elbows and knees, as well as the hands, and initially may be diagnosed as psoriasis.

When plaques of psoriasis involve the shins, they may be misdiagnosed as hypertrophic lichen planus, but characteristic violaceous lesions elsewhere and mucosal involvement usually point to the correct diagnosis. Palmoplantar plaque psoriasis can be confused with keratotic eczema of the palms and soles, as both may have scaling and fissures. Sharp margination of the lesions favors psoriasis and examination of the remainder of the skin surface can provide clues to the diagnosis, e.g. involvement of the scalp or intergluteal fold with psoriasis. Elsewhere, chronic lesions of dermatitis may develop an appearance that is similar (clinically and histologically) to partially treated psoriasis and vice versa. However, over time, characteristic lesions often become apparent. When plaques of psoriasis develop pronounced hyperkeratosis, the possibility of concomitant hypothyroidism should be considered.

There are other causes of erythroderma (see Ch. 10), in addition to psoriasis, including Sézary syndrome (see Ch. 120), pityriasis rubra pilaris (see Ch. 9) and drug reactions (see Ch. 21). In the case of guttate psoriasis, the differential diagnosis may include small plaque parapsoriasis (Ch. 9), pityriasis lichenoides chronica (Ch. 9), secondary syphilis (Ch. 82) and pityriasis rosea (Ch. 9). The lesions of guttate psoriasis rarely involve the palms or soles and are often more erythematous than those of parapsoriasis. When lesions are limited in number or have an annular configuration, the possibility of tinea corporis is raised, and when the upper trunk is the predominant site of involvement, pemphigus foliaceus may be considered.

Psoriasis of the flexures is one cause of intertrigo. Other etiologies include seborrheic dermatitis, cutaneous candidiasis, tinea incognito, necrolytic migratory erythema, extramammary Paget's disease, Bowenoid papulosis and contact dermatitis. Although KOH examination of associated scale allows a narrowing of the differential diagnosis, psoriasis and candidiasis can coexist (see above). In infants (more so than adults), the possibility of Langerhans cell histiocytosis (Ch. 91) needs to be considered. In these patients, there may also be scalp involvement with scaling and crusts. Occasionally, tinea capitis is in the differential diagnosis of scalp psoriasis.

When there are widespread pustules on a background of erythema, the possibility of a pustular drug eruption, also referred to as AGEP, needs to be considered in addition to generalized pustular psoriasis (see Ch. 21). The histologic findings of these conditions can be similar, including spongiform pustules of Kogoj and microabscesses in the stratum corneum. If eosinophils are also present, a pustular drug eruption is favored. In patients with pustulosis of the palms and soles and acrodermatitis continua, the initial evaluation includes the exclusion of a dermatophyte infection or secondarily infected dermatitis. The differential diagnosis of the annular form of pustular psoriasis includes Sneddon–Wilkinson disease and other causes of subcorneal pustules (Table 8.3). Reactive arthritis needs to be considered in any patient with the diagnosis of arthritis in the setting of psoriasiform skin lesions.

DIFFERENTIAL DIAGNOSIS OF SUBCORNEAL/INTRAEPIDERMAL NEUTROPHILIC PUSTULES

Disorder	Histologic clues
Impetigo	Gram-positive cocci in bulla cavity
Superficial candidiasis	Yeast and pseudohyphae in stratum corneum
Dermatophyte infection	Branching hyphae in stratum corneum
Superficial folliculitis	Pustule at follicular orifice and infundibulum
Pemphigus foliaceus	Acantholytic cells; DIF, IIF – intercellular IgG deposits; anti-desmoglein 1 antibody
IgA pemphigus, subcorneal pustular dermatosis type	DIF>IIF – intercellular IgA deposits; anti-desmocollin 1 antibody
Sneddon–Wilkinson disease (subcorneal pustular dermatosis)	No spongiform pustules
Pustular psoriasis	Spongiform pustules*
Acute generalized exanthematous pustulosis	Spongiform pustules, eosinophils*
Amicrobial pustulosis of the folds	Spongiform pustules*
Transient neonatal pustular melanosis	Subcorneal and intracorneal pustules
Acropustulosis of infancy	Subcorneal and intracorneal pustules

*Not all cases.

Table 8.3 Differential diagnosis of subcorneal/intraepidermal neutrophilic pustules. DIF, direct immunofluorescence; IIF, indirect immunofluorescence.

PATHOLOGY

Papulosquamous Lesions

Initial lesion

In the initial lesion, i.e. a pinhead-sized papule, the histopathologic features are not yet diagnostic. A superficial perivascular infiltrate of lymphocytes and macrophages is seen in the dermis along with papillary edema and a dilation of capillaries. In acute eruptive guttate lesions, mast cell degranulation is a constant feature.

There is mild epidermal acanthosis without parakeratosis and the keratinocytes have a swollen appearance. Macrophages (detected by CD68 staining) and lymphocytes appear in the epidermis focally and some spongiosis of the epidermis is seen at these sites. Per a large body of evidence, neutrophils are not yet detected in this early phase.

Active lesion

A fully developed guttate lesion or the marginal zone of an enlarging psoriatic plaque is designated as an "active lesion". The histopathologic findings in an active lesion are diagnostic for psoriasis.

In the dermis, the capillaries are increased in number and length and they have a tortuous appearance. Marked edema is seen, especially at the tops of the papillae. There is a mixed perivascular infiltrate of lymphocytes, macrophages and neutrophils, and lymphocytes and neutrophils have migrated into the epidermis.

The epidermis is acanthotic with focal accumulations of neutrophils and lymphocytes. At these sites, the epidermis is variably spongiotic. Above these foci, the granular layer is absent and the stratum corneum

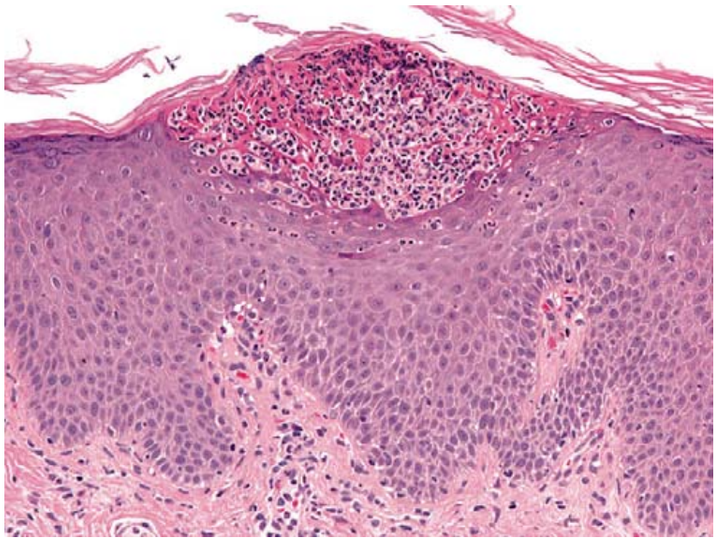


Fig. 8.19 Spongiform pustule of Kogoj. A collection of neutrophils is seen within the upper stratum spinosum. *Courtesy, Lorenzo Cerroni, MD.*

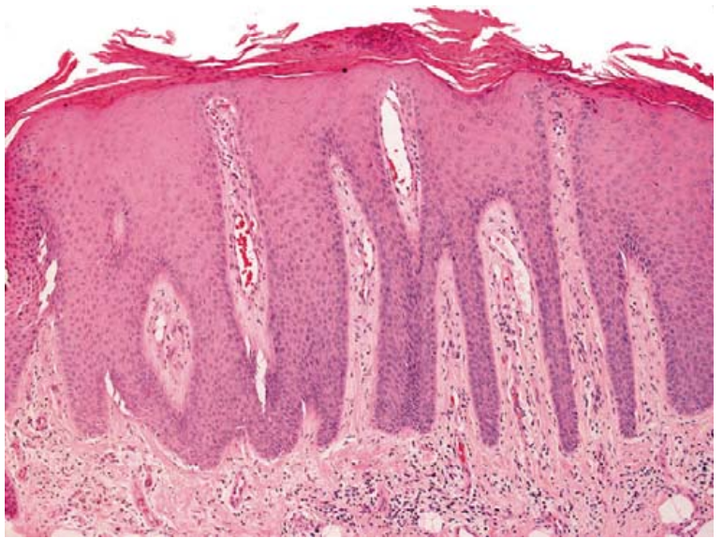


Fig. 8.20 Stable plaque psoriasis. Hyperplasia of the epidermis with "squared-off" rete ridges, elongation of the dermal papillae, dilated superficial blood vessels, hypogranulosis, and parakeratosis plus remnants of neutrophils (microabscess of Munro). *Courtesy, Lorenzo Cerroni, MD.*

still contains flattened nuclei (parakeratosis). The accumulation of neutrophils within a spongiotic pustule is referred to as a "spongiform pustule of Kogoj" (Fig. 8.19) and the accumulation of neutrophil remnants in the stratum corneum, surrounded by parakeratosis, as a "microabscess of Munro". These two findings are pathognomonic for psoriasis and AGEP.

Stable lesion

In the dermis, the capillaries are elongated and tortuous, extending upward into elongated club-shaped dermal papillae; only a small suprapapillary plate of epidermal cells covers the tip of these dermal papillae. This micromorphology explains the "Auspitz" phenomenon (see earlier). A modest perivascular infiltrate is seen that consists primarily of lymphocytes and macrophages. The psoriatic lesion is heterogeneous, consisting of active areas (hot spots) and chronic nonspecific areas (cold spots).

The hyperproliferation of the epidermis now has reached its characteristic pattern (Fig. 8.20). The rete ridges are elongated and have a squared-off appearance. Some rete ridges coalesce at the base. The horny layer has parakeratotic foci with an absence of the stratum granulosum. In some lesions, micropustules of Kogoj and microabscesses of Munro may be seen.

Pustular Psoriasis

In pustular psoriasis, accumulation of neutrophils is the predominant feature. Numerous neutrophils accumulate between eosinophilic strands of keratinocytes. In the stratum corneum, large accumulations of neutrophils are observed, surrounded by parakeratosis. As a result, exaggerated spongiform pustules of Kogoj and microabscesses of Munro, the histologic hallmarks of "active" psoriasis, are seen in pustular psoriasis (see Fig. 8.19).

Other

In reactive arthritis (formerly Reiter's disease), the cutaneous histologic findings are similar to those described for psoriasis. Spongiform pustules can be seen in palmoplantar lesions. In Sneddon–Wilkinson disease, subcorneal pustules are the characteristic finding.

TREATMENT

Care of the psoriatic patient needs to focus not only on the skin, but also on the comorbidities that exist or might develop. An appropriate treatment regimen for a particular patient is selected from available topical and systemic medications as well as phototherapies. In clinical trials, single agents are usually evaluated, but in practice most patients receive combination therapy. To date, no treatment has been shown to cure this disease, so counseling of the patient and family members regarding its natural history and management strategies is recommended.

A brief description of each available treatment for psoriasis is provided below. The management of psoriasis requires individualization of therapy, with consideration of the extent of the disease and its effects on the patient's quality of life as well as the likely benefits and potential side effects of specific treatments. The chronic nature of psoriasis necessitates adoption of a long-term approach with avoidance of dramatic short-term "fixes" that may actually produce a more reactive disease state (see below).

Topical Treatments

Guidelines of care for the treatment of psoriasis with topical therapies have been developed by the American Academy of Dermatology[64].

Vitamin D_3 analogues

In the early 1990s, vitamin D_3 analogues became commercially available as a topical treatment for psoriasis. When the epidermis is hyperproliferative, vitamin D_3 inhibits epidermal proliferation, and it induces normal differentiation by enhancing cornified envelope formation and activating transglutaminase; it also inhibits several neutrophil functions. Due to their therapeutic efficacy and limited toxicity, calcipotriene (calcipotriol) and other vitamin D_3 analogues have become a first-line therapy for psoriasis[65].

For a detailed description of topical vitamin D_3 analogues, the reader is referred to Chapter 129. Table 8.4 summarizes the major characteristics of commercially available vitamin D_3 analogues and Table 8.5 describes their indications and contraindications. Calcipotriene monotherapy has been shown to result in a ~60% reduction of PASI after 8 weeks of treatment, but practical use in psoriasis patients usually involves combination therapy with topical corticosteroids. When calcipotriene and betamethasone dipropionate are combined, an ~70% reduction in PASI has been observed (ointment formulation)[66] as has clearing/minimal disease in ~70% of patients with scalp psoriasis (gel formulation)[67].

Corticosteroids

Since their introduction in the early 1950s, topical corticosteroids have become a mainstay in the treatment of psoriasis. They are often first-line therapy in mild to moderate psoriasis and in sites such as the flexures and genitalia, where other topical treatments can induce

VITAMIN D ANALOGUES			
	Calcipotriene/Calcipotriol	**Calcitriol**	**Tacalcitol**
Concentration	50 mcg/g	3 mcg/g	2 mcg/g; 4 mcg/g
Formulations	Ointment, cream, lotion, solution	Ointment	Ointment, lotion
Frequency	BID	BID	BID; daily
Maximum weekly amount*	100 g	200 g	70 g; 70 g†
Chemical structure	26,27-cyclo-vitamin D_3 22,23 double bond Transposition of the 25-OH to the 24 position	1α,25-dihydroxy vitamin D (active natural vitamin D_3)	1α,24-dihydroxy vitamin D_3
Inactivating enzymes	22,23-reductase; 24-oxido-reductase	24-hydroxylase	25-hydroxylase

*To avoid hypercalcemia.
†Maximum weekly amount for 8 weeks of treatment.

Table 8.4 Vitamin D analogues. BID, twice daily. Calcipotriene is the US Adopted Name (USAN) and calcipotriol is the International Nonproprietary Name (INN).

INDICATIONS AND CONTRAINDICATIONS FOR VITAMIN D_3 ANALOGUES
INDICATIONS
• Mild to moderate psoriasis: first-line treatment as monotherapy or in combination • Severe psoriasis: combination treatment
CONTRAINDICATIONS
• Involvement requiring more than the maximally recommended quantity, e.g. 100 g/week of calcipotriene/calcipotriol (see Table 8.4) • Abnormality in bone or calcium metabolism* • Renal insufficiency • Allergy to the vitamin D_3 analogue or constituents of the preparation • Pregnancy or lactation
*For example, sarcoidosis, bone metastases.

Table 8.5 Indications and contraindications for vitamin D_3 analogues. If used in conjunction with phototherapy, vitamin D_3 preparations need to be applied after UV irradiation or at least several hours prior, because they may reduce UV penetration into the skin.

INDICATIONS AND CONTRAINDICATIONS FOR TOPICAL CORTICOSTEROIDS
INDICATIONS
• Mild to moderate psoriasis: first-line treatment as monotherapy or in combination • Severe psoriasis: often in combination with a vitamin D_3 analogue, a topical retinoid, anthralin or tar • Monotherapy for flexural and facial psoriasis (usually mild strength) • Recalcitrant plaques often require occlusion (plastic, hydrocolloid)
CONTRAINDICATIONS
• Bacterial, viral and mycotic infections • Atrophy of the skin • Allergic contact dermatitis due to corticosteroids or constituents of the formulation • Pregnancy or lactation*
*Can consider limited use of mild- to moderate-strength corticosteroids.

Table 8.6 Indications and contraindications for topical corticosteroids. Maximal quantities: 50 g/week of a superpotent corticosteroid; 100 g/week of a potent corticosteroid.

irritation. Chapter 125 provides detailed information on mechanisms of action, pharmacologic aspects and side effects of corticosteroid therapy.

Corticosteroids are manufactured in various vehicles, from ointments, creams and lotions to gels, foams and shampoos[68]; ointment formulations, in general, have the highest efficacy (see Ch. 125). Over the years, the anti-inflammatory properties of topical corticosteroids have been improved by increasing their lipophilicity by masking the hydrophilic 16- or 17-hydroxy groups or by introducing acetonides, valerates or propionates. Application under plastic or hydrocolloid occlusion also significantly enhances the penetration. Once-daily application has been shown to be as effective as twice-daily application, and long-term remissions may be maintained by applications on alternate days[69]. The indications and contraindications regarding the use of topical corticosteroids in the treatment of psoriasis are summarized in Table 8.6.

At least 80% of patients treated with high-potency topical corticosteroids experience clearance. In fact, the maximum improvement is usually achieved within 2 weeks. With maintenance therapy consisting of 12 weeks of intermittent applications of betamethasone dipropionate ointment (restricted to weekends), 74% of patients remained in remission, compared with 21% of the patients receiving a placebo ointment[69]. Unfortunately, no efficacy data are available on prolonged treatment for more than 3 months. As tachyphylaxis and/or rebound can occur fairly rapidly, i.e. within a few days to weeks, intermittent treatment schedules (e.g. once every 2 or 3 days or on weekends) are advised for more prolonged treatment courses. Combination topical therapy can take advantage of the rapid effect of topical corticosteroids as well as the prolonged benefits of topical vitamin D_3 analogues, anthralin or retinoids.

INDICATIONS AND CONTRAINDICATIONS FOR ANTHRALIN
INDICATIONS
• Mild to moderate or severe* psoriasis: second-line treatment as monotherapy or in combination
CONTRAINDICATIONS
• Unstable plaque psoriasis in a phase of progression • Pustular psoriasis • Erythrodermic psoriasis
*Severe psoriasis usually treated in day-care center or inpatient setting.

Table 8.7 Indications and contraindications for anthralin. To minimize irritation, concentration and application time are gradually escalated; neither should be increased more often than once every 3 days, given that peak erythema is seen 3–4 days following application.

Anthralin

Anthralin (dithranol, cignolin, 1,8-dihydroxy-9-anthrone) has been available since 1916; it is still used as a treatment for psoriasis, although it was more commonly utilized in the past (see Ch. 129). It has marked epidermal effects, including an anti-hyperproliferative effect. Anthralin also inhibits mitogen-induced T-lymphocyte proliferation and neutrophil chemotaxis. In Europe and other regions outside the US, it is used most often in day-care centers and the inpatient setting[70].

The indications and contraindications for the use of anthralin in the treatment of psoriasis are summarized in Table 8.7. In the authors'

INDICATIONS AND CONTRAINDICATIONS FOR TOPICAL TAZAROTENE
INDICATIONS
• Mild to moderate psoriasis: second-line treatment as monotherapy or in combination
CONTRAINDICATIONS
• Unstable plaque psoriasis in a phase of progression • Erythrodermic psoriasis • Allergic contact dermatitis to tazarotene or constituents of the formulation • Pregnancy or lactation

Table 8.8 Indications and contraindications for topical tazarotene.

experience, total clearing of psoriasis in at least 80% of patients occurs with 3–5 weeks of treatment in an inpatient setting or day-care center. If the anthralin treatment is performed at home, the efficacy is substantially less.

Topical retinoids

All-*trans*-retinoic acid and 13-*cis*-retinoic acid, although effective in the treatment of acne, are not effective for psoriasis. However, topical tazarotene, an acetylene retinoid that selectively binds retinoic acid receptor (RAR)-β and RAR-γ, can be used to treat psoriasis. Tazarotene has been shown to decrease epidermal proliferation and it inhibits psoriasis-associated differentiation (e.g. transglutaminase expression and keratin 16 expression). It is manufactured in cream and gel formulations and is applied once or twice daily.

Indications and contraindications of tazarotene for the treatment of psoriasis are summarized in Table 8.8. In view of its modest efficacy as monotherapy, it is usually prescribed as a second-line therapy. Irritation of the skin can limit the use of tazarotene; pruritus, burning, irritation and erythema have been observed in up to 23%, 18%, 9% and 8% of patients, respectively. For this reason, combination therapy with topical corticosteroids is useful. The maximal area that can be treated with tazarotene is 10–20% of the body surface, and safety data are available for up to 1 year of treatment.

The efficacy and safety of tazarotene as monotherapy have been investigated in several studies. After 6 weeks of treatment, at least 50% improvement (compared with baseline) was noted by 45% of the patients using twice-daily 0.05% tazarotene gel, compared to 13% of the patients using a placebo gel[71].

Additional topical treatments

If the psoriatic plaques have thick scale, this needs to be reduced to enhance penetration of topical medications and ultraviolet (UV) light. Options include salt-water baths, topical salicylic acid and oral retinoids. Salicylic acid 5–10% has a substantial keratolytic effect and, in the case of scalp psoriasis, salicylic acid can be formulated in an oil or ointment base. Application of salicylic acid to localized areas can be done daily, but, for more widespread areas, two to three times per week is preferred. This is to prevent systemic intoxication (see Ch. 129), especially in infants or those with reduced renal function.

Coal tar has a range of anti-inflammatory actions and is effective as an antipruritic. Although crude coal tar (see Ch. 129) may be the most effective tar available for the treatment of psoriasis, a distilled product, liquor carbonis detergens (LCD), is also used. In view of its mutagenic potential, tar is contraindicated in pregnant or lactating women. However, guidelines on the use of tar products may differ between countries.

Calcineurin inhibitors are used to treat facial and flexural psoriasis. Randomized, placebo-controlled studies have demonstrated efficacy and safety for this indication[71,72].

Photo(chemo)therapy and Systemic Medications

Evidence-based guidelines for the treatment of psoriasis with photo (chemo) therapy and classic systemic medications have been developed by various dermatologic organizations[73–74a], and the tables in this chapter are adapted from these recommendations.

INDICATIONS AND CONTRAINDICATIONS FOR PHOTO(CHEMO)THERAPY
INDICATIONS
• Moderate to severe psoriasis: first-line treatment as monotherapy or in combination
CONTRAINDICATIONS (ABSOLUTE OR RELATIVE)
• Genetic disorders characterized by increased photosensitivity or an increased risk of skin cancer (UVB and PUVA)* • Skin type I (UVB and PUVA)† • Photosensitive dermatoses (UVB and PUVA)† • Unavoidable phototoxic systemic or topical medications (UVB and PUVA)† • Vitiligo (UVB and PUVA)† • Previous history of arsenic exposure, ionizing irradiation or excessive photo(chemo)therapy (UVB and PUVA) • High cumulative number of PUVA treatments, i.e. >150–200 individual treatments (PUVA)* • Treatment with cyclosporine (UVB and PUVA)* • Immunosuppressive medication (UVB and PUVA) • Previous history of skin cancer (UVB and PUVA; * if current skin cancer, especially SCC or melanoma) • Atypical melanocytic nevi (UVB and PUVA) • Seizure disorder (risk of fall/injury; UVB and PUVA) • Poor compliance (UVB and PUVA) • Men and women in reproductive years without contraception (PUVA) • Pregnancy or lactation (PUVA)* • Impaired liver function or hepatotoxic medication (PUVA) • Cataracts (PUVA)
*Absolute contraindication †Need to adjust the dose and monitor closely.

Table 8.9 Indications and contraindications for photo(chemo)therapy. PUVA, psoralen + ultraviolet A; SCC, squamous cell carcinoma; UVB, ultraviolet B.

Photo(chemo)therapy

Photo(chemo)therapy represents a mainstay in the treatment of moderate to severe psoriasis. Phototherapy with broadband or narrowband ultraviolet B (UVB) and photochemotherapy with ultraviolet A (UVA) following ingestion of or topical application of a psoralen are classic treatment options. In the late 1970s, monotherapy with erythematogenic doses of broadband UVB proved to be an effective approach; later on, narrowband UVB (311–313 nm) was developed and is the optimal irradiation currently available. The 308 nm excimer laser can be used to treat a limited number of plaques in patients with localized disease.

Photo(chemo)therapy is discussed in detail in Chapter 134, and its indications and contraindications in psoriasis are summarized in Table 8.9.

Methotrexate

In 1971, amethopterin (methotrexate; MTX) was approved by the US Food and Drug Administration (FDA) as a treatment for psoriasis. The effect of MTX on lymphocytes, circulating and cutaneous, is a likely explanation for its antipsoriatic activity.

MTX is a first-line systemic therapy for psoriasis as it is highly efficacious for severe disease and all clinical variants of psoriasis. In chronic plaque psoriasis, initial improvement is observed between 1 and 7 weeks and maximum improvement can be expected after 8–12 weeks of treatment. MTX is administered weekly, usually as a single oral dose (but occasionally intramuscularly or subcutaneously) and less often every 12 hours for three doses per week; the maximum weekly dosage is usually 25 mg. Potential side effects restrict its use to moderate to severe disease resistant to topical treatments and photo(chemo)therapy and/or situations in which these are contraindicated. The use of folic acid supplementation during MTX administration is controversial due to the concern that folic acid may decrease the efficacy of MTX. Guidelines for MTX usage vary depending on the country and disease state.

Chapter 130 describes the mechanism of action, pharmacology and safety issues of MTX. Tables 8.10 and 8.11 summarize indications and contraindications as well as side effects of MTX.

INDICATIONS AND CONTRAINDICATIONS FOR METHOTREXATE
INDICATIONS
• Severe psoriasis – Chronic plaque psoriasis (>10–15% BSA or interference with employment or social functioning) – Pustular psoriasis (generalized or localized) – Erythrodermic psoriasis – Psoriatic arthritis (moderate to severe) – Severe nail psoriasis • Psoriasis not responding to topical treatments, photo(chemo)therapy and/or systemic retinoids
CONTRAINDICATIONS (ABSOLUTE OR RELATIVE)
• Impaired kidney function (creatinine clearance <60 ml/min)† • Severe anemia, leukopenia and/or thrombocytopenia* • Significant liver function abnormalities, hepatitis (active and/or recent), severe fibrosis, cirrhosis, excessive alcohol intake* • Concomitant hepatotoxic medications • Concomitant medications that increase MTX levels, e.g. trimethoprim–sulfamethoxazole* • Significantly reduced pulmonary function* • Pregnancy or lactation* • Currently planning to have children (male and female patients)‡ • Immunodeficiency syndromes • Severe infections* • Active infections • Peptic ulcer (active)* • Gastritis • Concomitant radiation therapy • Pleural effusion or ascites† • Hypersensitivity to MTX* • Unreliable patient*
*Absolute contraindication. †Requires significant reduction in dosage. ‡Because of possible mutagenic risk and teratogenicity, discontinue MTX 3 months prior to attempts to conceive; continue contraception during these 3 months.

Table 8.10 Indications and contraindications for methotrexate (MTX). BSA, body surface area.

SIDE EFFECTS OF METHOTREXATE		
Subjective symptoms	**Hematopoietic†**	**Mucocutaneous**
*Most frequent**,† Nausea Vomiting Abdominal pain Fatigue Headache *Occasional* Loss of libido Impaired memory	Leukopenia‡ Thrombocytopenia Anemia	Oral erosions† Alopecia Delayed phototoxicity Tenderness and/or necrosis of plaques due to overdose Rarely, urticaria, angioedema, vasculitis
Hepatic	**Pulmonary**	**Fetal development**
Hepatitis† Cirrhosis§	Interstitial pneumonitis (acute-onset cough, dyspnea)	Birth defects: cranial and absence of digits
Carcinogenesis‖		**Idiosyncratic reaction**
In rheumatoid arthritis patients, increased risk of lymphoma Risk factor for cutaneous SCC in PUVA-treated patients		Early in course with full dosage Severe pneumonia Gastrointestinal hemorrhage Pancytopenia
Opportunistic infections		**Additional/unusual**
Pneumocystis jiroveci pneumonia Cryptococcosis Disseminated histoplasmosis Disseminated herpes zoster		Osteopathy (pain, osteoporosis, compression fractures) Ventricular cardiac arrhythmias Lowered seizure threshold
*Same day or 2–3 days following MTX administration; may respond to folic acid, dose reduction or antiemetic drug. †May be reduced by folic acid (1–5 mg/day except on day MTX administered). ‡Up to 11% of patients on oral regimens. §Up to 25% of patients receiving long-term therapy. ‖No increased risk of malignancy was observed in large series of psoriasis patients[75,76].		

Table 8.11 Side effects of methotrexate (MTX). PUVA, psoralens + ultraviolet A; SCC, squamous cell carcinoma.

Cyclosporine

Cyclosporine is a cyclic undecapeptide that was isolated from the fungus *Tolypocladium inflatum* by Gams in 1970. Based on large controlled studies, cyclosporine is a highly effective treatment for the severe manifestations of psoriasis. As a calcineurin inhibitor, it prevents T-lymphocyte activation from being translated into the release of effector cytokines such as IL-2. Cyclosporine can be used safely, provided that the guidelines are strictly followed. In view of its nephrotoxic effects (e.g. reduced glomerular filtration rate, tubular atrophy), cyclosporine should be given for several-month courses (i.e. maximally 1 year, although duration is still a matter of debate) and alternated with other therapies. An alternative is an intermittent schedule using multiple short courses of a few weeks' duration.

The indications and contraindications of cyclosporine are summarized in Table 8.12. Cyclosporine can produce dramatic rapid improvement of psoriasis, but this must be balanced by the requirement for an appropriate replacement therapy, given the need to ultimately stop cyclosporine therapy.

Guidelines for pre-cyclosporine screening and long-term evaluation during cyclosporine administration are outlined in Chapter 130. An important aspect is assessment of renal function, and creatinine clearance should be estimated using the Cockrof-Gault formula:

$$\frac{(140 - \text{age in years}) \times (\text{weight in kg})}{\text{serum creatinine (mg/100 ml)} \times 72}$$

In elderly patients and patients with a history of hypertension, the risks of renal impairment and hypertension are increased.

Cyclosporine treatment in psoriatic patients has been reported to increase the frequency of SCCs, especially in those previously treated with PUVA. The underlying mechanism is not mutagenesis but a decrease in immunosurveillance of the skin. In particular, psoriatic patients who have been exposed to high cumulative doses of UV radiation are at risk for development of cutaneous malignancies. Although cyclosporine is an immunosuppressive agent, no increase in serious infections has been reported in patients treated with cyclosporine alone. Other side effects include: gastrointestinal discomfort, hypertrichosis, paresthesias, gingival hyperplasia, headache, vertigo, muscle cramps and tremor[77]. Metabolic side effects include hyperkalemia, hypomagnesemia, hyperuricemia (due to decreased clearance of uric acid), and elevated cholesterol and triglycerides.

The efficacy of cyclosporine for psoriasis has been clearly shown in multiple controlled and uncontrolled studies. For example, the European multicenter dose-finding studies have shown that doses of 1.25, 2.5–3 and 5 mg/kg/day of cyclosporine resulted in reductions of the PASI of 35%, 57% and 86%, respectively. An improvement in the PASI of 75% was achieved in 24%, 52% and 88% of the patients. Of note, because the criteria for these studies were different from those used for FDA approval of targeted immune modulators ("biologic" therapies), the PASI numbers are not directly comparable. Efficacy of cyclosporine has been demonstrated in all variants of psoriasis (including nail psoriasis), but less so for psoriatic arthropathy[78]. The improvement is observed within a few weeks. In general, a reduction of the PASI of 60–70% can be reached within 4 weeks of treatment[79]. During long-term treatment, there are no signs of tachyphylaxis.

Systemic retinoids

By the 1930s, vitamin A deficiency was known to cause hyperkeratosis of the skin (phrynoderma). Thirty years later, modifications of the vitamin A molecule resulted in the discovery of the so-called first generation of retinoids, including all-*trans*-retinoic acid (tretinoin) and 13-*cis*-retinoic acid (isotretinoin). Further research resulted in the

INDICATIONS AND CONTRAINDICATIONS FOR CYCLOSPORINE
INDICATIONS
• Severe psoriasis • Conventional therapies (topical treatments, photo(chemo)therapy, acitretin, methotrexate) ineffective or inappropriate
CONTRAINDICATIONS
• Impaired renal function* • Uncontrolled hypertension* • Primary or secondary immunodeficiency • Concomitant immunosuppressive therapy • Past or present* malignancy • Concomitant drugs affecting cyclosporine pharmacokinetics† • History of arsenic exposure • History of excessive photo(chemo)therapy (>200 PUVA treatments), radiotherapy* • Concurrent photo(chemo)therapy* • Severe infections* • Active infections • Pregnancy or lactation • Concurrent methotrexate administration • Significant hepatic disease • Hyperuricemia, hyperkalemia • Hypersensitivity to cyclosporine* • Vaccination with live vaccines • Seizure disorder • Poorly controlled diabetes mellitus • Severe chronic organ dysfunction • Alcohol and drug abuse • Malabsorption • Unreliable patient*
*Absolute contraindications. †Requires dose adjustment and careful monitoring; cyclosporine is inactivated by the cytochrome P450 3A isoform.

Table 8.12 Indications and contraindications for cyclosporine. The recommended starting dose is 3 mg/kg/day in two divided doses; at 2-week intervals, dosage can be increased to a maximum of 5 mg/kg/day. PUVA, psoralens + ultraviolet A.

INDICATIONS AND CONTRAINDICATIONS FOR ACITRETIN
INDICATIONS
• Severe psoriasis that cannot be managed by topical treatments or photo(chemo)therapy • Monotherapy is indicated for erythrodermic or pustular psoriasis • Combination therapy is indicated for chronic plaque psoriasis
CONTRAINDICATIONS
• Severe liver dysfunction* • Severe kidney dysfunction (elimination reduced)* • Pregnancy or lactation* • Women of childbearing potential who cannot guarantee adequate contraception during and up to 3 years following discontinuation of acitretin* • Hyperlipidemia, especially hypertriglyceridemia, that cannot be controlled* • Concomitant medications that interfere with retinoid bioavailability or whose metabolism is altered† • Concomitant hepatotoxic drugs, e.g. methotrexate‡ • Poorly controlled diabetes mellitus • History of pancreatitis • Excessive alcohol intake* • Use of contact lenses • Unreliable patient* • Atherosclerosis
*Absolute contraindications. †Requires dose adjustment and careful monitoring, e.g. phenytoin competes for plasma protein binding. ‡Reserved for treatment-resistant patients.

Table 8.13 Indications and contraindications for acitretin. Blood donation is contraindicated in patients receiving acitretin.

PRE-ACITRETIN SCREENING
• History to exclude contraindications • Complete blood count • Liver function tests (AST, ALT, γGT, alkaline phosphatase, bilirubin) • Serum triglycerides, cholesterol, HDL • Glucose • Serum creatinine • Pregnancy test • Consider spinal X-ray (often initially performed during the first 3 months of therapy if long-term treatment is anticipated)

Table 8.14 Pre-acitretin screening. ALT, alanine aminotransferase; AST, aspartate aminotransferase; γGT, gamma glutamyl transpeptidase; HDL, high-density lipoproteins

EVALUATION DURING ACITRETIN TREATMENT
• Monitor mucocutaneous side effects • Serum cholesterol/triglycerides/HDL and liver enzymes (every month for the first 2 months then every 2–3 months) • Serum creatinine (elderly patients or patients with mild to moderate renal dysfunction) • Monitor for development of hyperostosis by history (twice yearly) and by X-ray of spine (e.g. once yearly in patients receiving long-term treatment) • Pregnancy test (throughout treatment)

Table 8.15 Evaluation during acitretin treatment. HDL, high-density lipoproteins.

development of the second generation of retinoids, the mono-aromatic retinoids, etretinate and its free metabolite acitretin[79]. Acitretin is an effective treatment for psoriasis as well as disorders of keratinization and cutaneous lupus. A major problem with systemic retinoids is their teratogenicity, making contraception mandatory in women of childbearing age during treatment and (depending on the drug half-life) for a period of 2 months to 3 years after discontinuing therapy. Chapter 126 provides a description of the modes of action, pharmacologic aspects and side effects of these medications.

The indications and contraindications for the use of acitretin in the treatment of psoriasis are summarized in Table 8.13, and the recommended initial and ongoing evaluations are outlined in Tables 8.14 and 8.15, respectively.

In patients with chronic plaque psoriasis, 0.5 mg/kg/day is the initial dosage, which can be increased depending upon the clinical response and side effects. For erythrodermic psoriasis, the initial dosage is 0.25 mg/kg/day, and in pustular psoriasis, the dose should be maximized, i.e. doses up to 1 mg/kg/day. In patients with chronic plaque psoriasis, mild cheilitis (just perceived by the patient) is the goal, whereas in patients with pustular psoriasis, a dose that causes a clinically apparent but tolerable cheilitis is an endpoint.

The efficacy of acitretin monotherapy in chronic plaque psoriasis is limited, with approximately 70% of patients achieving a moderate or better response. In one study, 23% of patients treated with 50 mg of acitretin daily for 8 weeks achieved ≥75% improvement in their PASI[79]. Combination treatment with photo(chemo)-therapy and/or vitamin D_3 analogues results in a substantial improvement in clinical response. Maximal therapeutic efficacy is reached after 2–3 months. Acitretin has been shown to be an effective maintenance therapy. As monotherapy, acitretin is highly effective in erythrodermic and pustular psoriasis. Its efficacy in nail psoriasis and psoriatic arthritis is only modest.

Targeted immune modulators ("biologic" therapies)

Beginning in 2000, biologic therapies were introduced for the treatment of psoriatic arthritis and moderate to severe psoriasis. Their two major targets are T cells and cytokines, including TNF-α and IL-12/23. Table 8.16 lists the biologic agents that are currently commercially available. Although briakinumab (a human monoclonal antibody against the p40 subunit of IL-12 and IL-23) was found to have greater efficacy than methotrexate in patients with moderate to severe plaque psoriasis[79a],

COMMERCIALLY AVAILABLE BIOLOGIC AGENTS USED FOR THE TREATMENT OF PSORIASIS			
Biologic agent	**Target**	**Molecule**	**Approved***
Alefacept**	CD2	Human fusion protein	FDA
Etanercept	TNF-α†	Human fusion protein	FDA + EMA
Infliximab	TNF-α‡	Chimeric antibody	FDA + EMA
Adalimumab	TNF-α‡	Human antibody	FDA + EMA (psoriatic arthritis)
Ustekinumab	p40 subunit of IL-12/23	Human antibody	FDA + EMA

*By registration authorities for the treatment of psoriasis.
**Production of alefacept in the US was discontinued in 2011.
†Soluble form.
‡Soluble form and transmembrane TNF receptor.

Table 8.16 Commercially available biologic agents used for the treatment of psoriasis. EMA, European Medicines Agency; FDA, Food and Drug Administration; IL, interleukin; TNF, tumor necrosis factor

applications for approval by the FDA and European Medicines Agency (EMEA) were withdrawn due to safety concerns (including a possible increased risk of cardiovascular adverse events). Chapter 128 provides a description of the modes of action, dosages, side effects and monitoring recommendations for biologic agents. Of note, guidelines, including European S3-Guidelines, have been developed for the treatment of psoriasis patients with TNF-α inhibitors (adalimumab, etanercept and infliximab) and ustekinumab[74,80–82].

Biologic therapies are indicated for patients with moderate to severe psoriasis and/or psoriatic arthritis. Several guidelines restrict their use to "high-need patients" in whom all other existing treatments are contraindicated or have led to insufficient improvement, whereas some investigators have voiced the opinion that biologic therapies should be an option for patients who have failed to respond adequately to one classic systemic treatment[83]; the latter recommendation has to be balanced against the high cost of these medications. Both indications and contraindications for currently commercially available therapies are outlined in Table 8.17.

The relative efficacies of the various biologic agents are reviewed in Chapter 128. With regard to the percentage of patients achieving PASI 75 improvement, there is significant overlap between the efficacies of biologic agents (as assessed after 3 months of therapy) and those of photo(chemo)therapy and classic systemic medications such as MTX and cyclosporine, although only a few studies directly comparing biologic agents with classic systemic medications are available. In general, TNF-α inhibitors and anti-IL-12/23 antibodies have substantial efficacy and enable long-term control of psoriasis[84].

Other systemic therapies

Additional systemic therapies have been reported as beneficial in the management of psoriasis (Table 8.18). In general, they are used less often than the medications previously described in this chapter, and there are regional differences in their use.

INDICATIONS AND CONTRAINDICATIONS FOR COMMERCIALLY AVAILABLE TARGETED IMMUNE MODULATORS ("BIOLOGIC" AGENTS)
INDICATIONS
General indications
• Patients with moderate to severe psoriasis, eligible for a systemic treatment
• Patients with psoriatic arthritis, particularly those who have failed other disease-modifying antirheumatic drugs (DMARDs)
Restricted indication
• Patients with moderate to severe psoriasis who are not candidates for topical treatments, photo(chemo)therapy or classic systemic treatments because of insufficient efficacy or contraindications
CONTRAINDICATIONS
(The exact contraindications vary by agent [see Ch. 128]; some listed below are relative, while others are absolute [*])
• Guttate, pustular, or erythrodermic psoriasis
• Significant viral, bacterial or fungal infections*
• Increased risk for developing sepsis*
• Active tuberculosis*
• Immunosuppressed patient
• Past history of hepatitis B
• Pregnancy (TNF-α inhibitors, alefacept† and ustekinumab are category B)
• Breastfeeding
• Malignancy within the past 5 years (does not include adequately treated single cutaneous squamous or basal cell carcinoma)
• Excessive chronic sun exposure or photo(chemo)therapy
• Allergic reaction to the biologic agent*
• Selective for alefacept†: CD4 counts <250 cells/mcl*; HIV infection*
• Selective for TNF-α inhibitors: ANA+ (especially if high titer) or autoimmune connective tissue disease, blood dyscrasias, congestive heart failure (NYHA grade III or IV) or demyelinization disorders (the latter also in first-degree relatives)*
• Selective for ustekinumab: BCG vaccination within the past 12 months (mode of action expected to increase susceptibility to mycobacterial infections)
†Production of alefacept in the US was discontinued in 2011.

Table 8.17 Indications and contraindications for commercially available targeted immune modulators ("biologic" agents). Administration of live vaccines (see Table 128.9) is contraindicated in patients receiving biologic agents for psoriasis. BCG, Bacillus Calmette-Guérin; NYHA, New York Heart Association.

ADDITIONAL SYSTEMIC THERAPIES FOR PSORIASIS	
Medication	**Side effects**
Fumarates[85]	Renal impairment, flushing, gastrointestinal disturbances, headache, fatigue
Mycophenolate mofetil[86]	See Ch. 130
Oral calcitriol[87] (0.5–3 mcg/day)	Hypercalcemia, hypercalciuria
6-thioguanine (40–160 mg/day)	Myelosuppression, hepatotoxicity, gastrointestinal disturbances
Hydroxyurea	See Ch. 130

Table 8.18 Additional systemic therapies for psoriasis.

Therapeutic Management

General considerations

Before considering a specific treatment in an individual psoriatic patient, it is important to exclude triggering factors. Aggravating factors such as focal infections, medications and psychological stress have been described above. Furthermore, it is also crucial to assess the various aspects of disease severity, in particular[88]:

- The area of involvement and the degree of erythema, induration and desquamation of the cutaneous lesions. For research purposes, these aspects can be summarized as the PASI (see Table 8.2).
- The impairment of quality of life. The visibility of the lesions and symptoms such as pruritus are relevant factors, and psycho-emotional stress and the response of family and friends to the psoriasis should also be considered. Impact of psoriasis on quality of life can be measured by questionnaires (e.g. Dermatology Life Quality Index [DLQI], Skindex29).
- The responsiveness to previous treatments. Individual patients report a wide variation with respect to their clinical response to various treatments. For example, some patients, even those with widespread disease, may experience excellent improvement with a mild topical therapy, whereas patients with localized disease may prove recalcitrant to even high-dose systemic treatments.

Relative and absolute contraindications to the various treatment options have to be recognized, especially in the case of photo(chemo)

therapy and systemic medications. Because psoriasis is a chronic condition, patients have to cope not only with their disease, but also with their treatments, for prolonged periods of time. For example, individual circumstances may restrict the time available for intensive daily treatments. Lastly, some patients cannot accept a few coin-sized lesions in visible sites, while for others this is less of a problem. Therefore, treatment selection is a multivariable decision-making process and not a simple stepwise therapeutic ladder.

Management with topical agents

It is important before instituting topical therapy that the patient understands that due to the Koebner phenomenon, trauma (e.g. from scratching or debriding lesions) can negate therapeutic interventions. Although it may seem obvious, patients should also be told that topical agents do not prevent new lesions from appearing at additional sites. For patients with mild to moderate involvement, topical treatments are the first choice. Patients with more widespread involvement may also be treated with a topical agent; however, a high degree of compliance is required and this can be difficult to achieve.

Evidence for the efficacy of various topical treatments was reassessed in a recent meta-analysis[89]. From this analysis, it was concluded that only very potent topical corticosteroids tended to be more effective than monotherapy with the vitamin D_3 analogue calcipotriene. In ambulatory patients, calcipotriene was more effective than anthralin, coal tar, the other vitamin D_3 analogues (tacalcitol and calcitriol) and the retinoid tazarotene[89]. The efficacy of coal tar and anthralin are difficult to assess, as the success of these topicals is highly dependent on the treatment setting. A day-care or inpatient setting is optimal, as it allows the patient to more easily cope with the side effects of staining, stinging and irritation.

Combination treatment is advised for the vast majority of patients, thereby increasing efficacy and reducing side effects. For example, a fixed combination of calcipotriene and betamethasone dipropionate applied once daily proved to be superior to twice-daily calcipotriene or twice-daily betamethasone dipropionate monotherapy[90].

Based on the above discussion, the authors recommend the following: start with calcipotriene cream or ointment twice daily for a period of 8 weeks (except for sensitive skin areas and the scalp). If this regimen is not successful or if rapid clearing is required, the combination of calcipotriene and a potent topical corticosteroid is applied for 4 weeks. In the case of an insufficient response or irritation, another vitamin D_3 analogue or tazarotene may be tried as monotherapy or in combination with a topical corticosteroid. In addition, a topical corticosteroid under hydrocolloid occlusion can be used for a few recalcitrant plaques.

A trial of tar or anthralin may be tried, especially in patients with longstanding disease and incomplete responses or fast relapses. These treatments often require a day-care or inpatient facility as their use in the ambulatory setting is disappointing. With regard to maintenance therapy, some patients prefer only intermittent clearing courses with no intervening therapy, while other patients want continuous treatment. Daily use of a topical vitamin D_3 analogue (below the maximum allowed weekly dosage) provides a safe long-term form of maintenance therapy. If the therapeutic response is insufficient, intermittent application of a topical corticosteroid (once or twice weekly) is helpful.

Psoriasis in sensitive areas and on the scalp should be managed differently. Psoriasis of the face and flexures can be treated with a calcineurin inhibitor, resulting in a rapid improvement[91]. In these sensitive areas, tacalcitol and calcitriol tend to result in less irritation as compared to calcipotriene; the use of ultrapotent corticosteroids should be avoided. For scalp psoriasis, removal of scale with a formulation containing 10–20% salicylic acid is the initial step. Intermittent use of potent and ultrapotent topical corticosteroids (or corticosteroid-containing shampoos) in combination with calcipotriene lotion is our preferred regimen for scalp psoriasis.

If topical therapies do not provide adequate improvement, treatment with photo(chemo)therapy or a systemic agent is indicated.

Management with photo(chemo)therapy and classic systemic medications

For patients with moderate to severe involvement, topical therapies may be ineffective or impractical. On a chronic basis, patients with widespread disease often cannot manage their psoriasis with topical treatments and become frustrated and non-compliant. Evidence for the efficacy of photo(chemo)therapy and classic systemic treatments has been reassessed in a meta-analysis[92]. PUVA had the highest percentage of patients with clearance (70%), followed by UVB (67.9%) and cyclosporine (64%). The investigators also developed practice guidelines and recommended the following sequence of therapies: UVB, PUVA, methotrexate, acitretin and then cyclosporine[92].

However, in the selection of a systemic treatment for an individual patient, the existence of relative and absolute contraindications has to be considered. Therefore, it is not always practical to define a therapeutic ladder. For example, photo(chemo)therapy would not be chosen for patients with a history of excessive exposure to UV radiation, but these same patients could be excellent candidates for retinoid therapy (considering its anticancer effects). Methotrexate is contraindicated in patients with excessive alcohol intake or active hepatitis, while cyclosporine is contraindicated in those with renal insufficiency or hypertension.

Despite these considerations, some general recommendations can be offered. If the response to topical therapies is unsatisfactory, the first treatment to be considered is typically narrowband UVB phototherapy. If a few months of UVB therapy do not result in adequate improvement or a sufficient long-term remission is not achieved, one of the other treatment modalities previously discussed should be selected (with a consideration of individualized risk factors). An important issue is whether a maintenance treatment is needed or desired. Cyclosporine should not be used as a maintenance treatment, whereas methotrexate, acitretin and fumarates can be employed for long-term control of psoriasis; fumarates are only available in some European countries. However, long-term use of these systemic treatments is restricted by their cumulative toxicity potential. The concept of rotational therapies is valuable but complex. If neither photo(chemo)therapy nor classic systemic medications provide adequate improvement, treatment with a biologic agent is indicated.

Targeted immune modulators ("biologic" therapies)

Several biologic therapies are currently available worldwide for the treatment of psoriasis and/or psoriatic arthritis: adalimumab, etanercept, infliximab and ustekinumab. Despite the availability of effective topical and classic systemic medications as well as phototherapy, safety concerns, lack of efficacy, and inconveniences are important restrictions, in particular for long-term use[93]. For such patients, biologic agents can provide benefit for their skin disease as well as psoriatic arthritis (especially TNF-α inhibitors), with prevention of permanent destructive changes. Reduction of inflammation resulting from active psoriasis may also impact the development of metabolic syndrome and the cardiovascular diseases.

The side-effect profiles are very different from those of photo(chemo)-therapy and classic systemic medications, with no indication to date of cumulative toxicity. As a 1-year course of biologic therapy costs approximately $20 000 (~€15 000), national health authorities and managed care insurance companies have adopted a restrictive approach. Therefore, in many countries, biologic agents are available exclusively for those patients with severe psoriasis who cannot be treated adequately with the classic treatments. However, a possible impact on comorbidities (see above) may influence decisions in the future.

How to combine treatments

Enhanced clinical response and a possible reduction in side effects are the goals of combination therapy. However, for safety reasons, some combinations are contraindicated.

Beneficial combinations

The combination of calcipotriene with superpotent topical corticosteroids has been shown to be more effective than either treatment as monotherapy, whereas the combination of calcipotriene plus medium-strength corticosteroids did not have a substantial additive effect compared with each as monotherapy. However, the irritation caused by calcipotriene can be reduced by the addition of medium-strength corticosteroids. Improved efficacy has also been observed with the combination of calcipotriene–cyclosporine and calcipotriene–acitretin, compared with each as monotherapy[94,95]. For example, with low-dose cyclosporine (2 mg/kg/day) plus topical calcipotriene, marked

improvement or clearing was seen in 90% of patients. In a dose-escalating study of acitretin, the combination of acitretin and calcipotriene was more effective and permitted a lower dose of both acitretin and calcipotriene as compared to each as monotherapy. The combination of calcipotriene and PUVA is characterized by a marked reduction in the cumulative dose of UVA required and enhanced efficacy, compared with the respective monotherapies. However, evidence for a beneficial effect of the combination of UVB and calcipotriene is less convincing. Combining etanercept (25 mg subcutaneously once weekly) and acitretin has been shown to be as effective as etanercept 25 mg subcutaneously twice weekly[96].

Topical corticosteroids are frequently combined with other antipsoriatic treatments. Although increases in the duration of subsequent remission periods have been noted, controlled studies are required to substantiate these claims. The combination of phototherapy with application of anthralin or tar is a time-honored therapy. However, if phototherapy is optimized by using near-erythematogenic doses, the additive benefit of anthralin or tar above that of phototherapy alone has not been substantiated, although remission periods following the combination of anthralin and optimized phototherapy are prolonged.

Contraindicated combinations and combinations with restricted use

The combination of acitretin and cyclosporine carries the risk of accumulation of cyclosporine, because cyclosporine is inactivated by the cytochrome P450 system, which is inhibited by acitretin. An increased occurrence of SCCs has been observed in patients treated with the combination of cyclosporine and PUVA, either simultaneously or sequentially (PUVA followed by cyclosporine)[97]. As a result, the combination of cyclosporine and photo(chemo)therapy is contraindicated. Although a combination of methotrexate and PUVA has been reported to be safe[98], additional long-term studies are needed.

The combination of coal tar with PUVA is contraindicated as it may induce significant phototoxic responses. The combination of cyclosporine and methotrexate has been viewed as high risk because both are immunosuppressants. However, this combination has been used with success by rheumatologists, and, in recalcitrant psoriasis, the combination has proved to be very effective without major side effects. The combination of methotrexate and acitretin has been used in those patients in whom all treatments have failed[99]. Although this combination can be very effective, severe hepatotoxicity has been reported; therefore, careful monitoring is mandatory.

How to manage childhood psoriasis

In a recent review, the efficacy and safety of treatment modalities in children were described[100]. Only two randomized controlled trials were identified; one examined topical calcipotriene and the other etanercept. The authors recommended topical calcipotriene as first-line therapy for mild to moderate juvenile psoriasis, combined with mild- to moderate-strength topical corticosteroids (if necessary). For treatment-resistant flexural and/or facial psoriasis, tacrolimus 0.1% ointment can be added to the treatment regimen. Anthralin is then considered if this treatment regimen is not effective or the psoriasis is moderate to severe. The next step is to recommend treatment with narrowband UVB, especially in adolescents, with attention to the number of treatments. Although controversial, the use of antibiotics can be considered in patients with guttate psoriasis where there is suspicion of a streptococcal infection. Of the systemic medications, methotrexate is regarded as the treatment of choice, with retinoids considered in pustular and erythrodermic psoriasis. Cyclosporine is occasionally utilized for exceptional cases, and etanercept should be considered as a third-line drug for therapy-resistant psoriasis[100].

Future Treatments

Future treatments for psoriasis will include additional targeted biologic therapies, which focus on one key aspect of psoriasis pathogenesis. For example, antagonism of IL-17, IL-20 or IL-22 may prove to be as beneficial as targeting IL-12/IL-23. A number of small molecules are also under investigation, including oral inhibitors of kinases such as Janus kinase (JAK), protein kinase C or p38 kinase, as well as inhibitors of STAT-3 (see Pathogenesis) such as topical STA-21/ochromycinone.

REFERENCES

1. Nestlé FO, Kaplan DH, Barker J. Psoriasis. N Engl J Med. 2009;361:496–509.
2. Christophers E. Psoriasis—epidemiology and clinical spectrum. Clin Exp Dermatol. 2001;26:314–20.
3. Brandrup F, Green A. The prevalence of psoriasis in Denmark. Acta Derm Venereol. 1981;61:344–6.
4. de Jong EMGJ, Seegers BAMPA, Gulinck MK, et al Psoriasis of the nails associated with disability in a large number of patients; results of a recent interview with 1728 patients. Dermatology. 1996;193:300–3.
5. Swanbeck G, Inerot A, Martinsson T, et al. Age at onset and different types of psoriasis. Br J Dermatol. 1995;133:768–73.
6. Raychaudhuri SP, Gross J. A comparative study of pediatric onset psoriasis with adult onset psoriasis. Pediatr Dermatol. 2000;17:174–8.
7. Farber EM, Nall ML. The natural history of 5600 patients. Dermatologica. 1974;148:1–18.
8. Augustin M, Glaeske G. Radtke MA, et al. Epidemiology and comorbidity of psoriasis in children. Br J Dermatol. 2010;162:633–6..
9. de Jager ME, van de Kerkhof PCM, de Jong EMGJ, et al. Epidemiology and prescribed treatments in childhood psoriasis: a survey among medical professionals. J Dermatolog Treat. 2009;20:254–8.
10. Gelfand JM, Weinstein R, Porter SB, et al. Prevalence and treatment of psoriasis in the United Kingdom: a population-based study. Arch Dermatol. 2005;141: 1537–41.
11. Seyhan M, Coskun BK, Saglam H, et al. Psoriasis in childhood and adolescence: evaluation of demographic and clinical features. Pediatr Int. 2006;48:525–30.
12. Andressen C, Henseler T. Inheritance of psoriasis. Analysis of 2035 family histories. Hautarzt. 1982; 33:214–7.
13. Farber E, Nall L. Epidemiology: natural history and genetics. In: Roenigk HH, Maibach HI (eds). Psoriasis, 3rd edn. New York: Marcel Dekker, 1998:107–58.
14. Schmitt-Egenolf M, Eiermann TH, Boehncke WH, et al. Familial juvenile onset psoriasis is associated with the human leukocyte antigen (HLA) class I side of the extended haplotype Cw6-B57-DRB1*0701-DQA1*0201-DQB1*0303: a population- and family-based study. J Invest Dermatol. 1996;106:711–4.
15. Christophers E, Henseler T. Psoriasis type I and II as subtypes of nonpustular psoriasis. Semin Dermatol. 1992;11:261–6.
16. Bowcock AM, Krueger JG. Getting under the skin: the immunogenetics of psoriasis. Nat Rev Immunol. 2005;5:699–711.
17. Manolio TA, Collins PC, Cox NJ, et al. Finding the missing heritability of complex diseases. Nature. 2009;461: 747–53.
18. Genetic Analysis of Psoriasis Consortium & the Wellcome Trust Case Control Consortium 2. Strange A, Capon F, Spencer CC, et al. A genome-wide association study indentifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. Nat Genet. 2010;42:985–90.
19. Nair RP, Duffin KC, Helms C, et al. Genome-wide scan reveals association of psoriasis with IL-23 and NF-kappaB pathways. Nat Genet. 2009;41:199–204.
20. Capon F, Di Meglio P, Szaub J et al. Sequence variants in the genes for the interleukin-23 receptor (IL23R) and its ligand (IL12B) confer protection against psoriasis. Hum Genet. 2007;122:201–6.
21. Gudjonsson JE, Ding J, Johnston A, et al. Assessment of the psoriatic transcriptome in a large sample: additional regulated genes and comparisons with in vitro models. J Invest Dermatol. 2010;130:1829–40.
22. Ong PY, Ohtake T, Brandt C, et al. Endogenous antimicrobial peptides and skin infections in atopic dermatitis. N Engl J Med. 2002;347:1151–60.
23. Voorhees JJ. Pathophysiology of psoriasis. Annu Rev Med. 1977;28:467–73.
24. Guilhou JJ, Meynadier J, Clot J, et al. Immunological aspects of psoriasis. II. Dissociated impairment of thymus-dependent lymphocytes. Br J Dermatol. 1976;95:295–301.
25. Griffiths CE, Powles AV, Leonard JN, et al. Clearance of psoriasis with low dose cyclosporine. Br Med J (Clin Res Ed). 1986;293:731–2.
26. Eady DJ, Burrows D, Bridges JM, Jones FG. Clearance of severe psoriasis after allogenic bone marrow transplantation. BMJ 1990;300:908.
27. Gardembas-Pain M, Ifrah N, Foussard C, et al. Psoriasis after allogeneic bone marrow transplantation. Arch Dermatol. 1990;126:1523.
28. Menssen A, Trommler P, Vollmer S, et al. Evidence for an antigen-specific cellular immune response in skin lesions of patients with psoriasis vulgaris. J Immunol. 1995;155:4078–83.
29. Boyman O, Heft HP, Conrad C, et al. Spontaneous development of psoriasis in a new animal model shows an essential role for resident T cells and tumor necrosis factor-alpha. J Exp Med. 2004;199:731–6.
30. Nestlé FO, Conrad C, Tun-Kyi A, et al. Plasmacytoid predendritic cells initiate psoriasis through interferon-alpha production. J Exp Med. 2005;202:135–43.
31. Conrad C, Boyman O, Tonel G, et al. Alphabetal integrin is crucial for accumulation of epidermal T cells and the development of psoriasis. Nat Med. 2007;13:836–42.
32. Bonish B, Jullien D, Dutronc Y, et al. Overexpression of CD1d by keratinocytes in psoriasis and CD1d-dependent IFN-gamma production by NK-T cells. J Immunol. 2000;165:4076–85.
33. Nestlé FO, Turka LA, Nickoloff BJ. Characterization of dermal dendritic cells in psoriasis: autostimulation of T lymphocytes and induction of Th1 type cytokines. J Clin Invest. 1994;94:202–9.
34. Lowes MA, Chamian F, Abello MV, et al. Increase in TNF-alpha and inducible nitric oxide synthase-expressing dendritic cells in psoriasis and reduction

with efalizumab (anti-CD11a). Proc Natl Acad Sci USA. 2005;102:19057–62.
35. Chamian F, Lowes MA, Lin SL, et al. Alefacept reduces infiltrating T cells, activated dendritic cells, and inflammatory genes in psoriasis vulgaris. Proc Natl Acad Sci USA. 2005;102:2075–80.
36. Lande R, Gregorio J, Faccinetti V, et al. Plasmacytoid dendritic cells sense self-DNA coupled with antimicrobial peptide. Nature. 2007;449:564–9.
37. Ganguly D, Chamilos G, Lande R, et al. Self-RNA-antimicrobial peptide complexes activate human dendritic cells through TLR7 and TLR8. J Exp Med. 2009;206:1983–94.
38. Detmar M, Brown LF, Claffey KP, et al. Overexpression of vascular permeability factor/vascular endothelial growth factor and its receptors in psoriasis. J Exp Med. 1994;180:1141–6.
39. Schonthaler HB, Huggenberger R, Wculek SK, et al. Systemic anti-VEGF treatment strongly reduces skin inflammation in a mouse model of psoriasis. Proc Natl Acad Sci USA. 2009;106:21264–9.
40. Krueger JG, Bowcock A. Psoriasis pathophysiology: current concepts of pathogenesis. Ann Rheum Dis. 2005;64(suppl. 2):ii30–36.
41. Di Cesare A, Di Meglio P, Nestlé FO. The IL-23/Th17 axis in the immunopathogenesis of psoriasis. J Invest Dermatol. 2009;129:1339–50.
42. Eyerich S, Eerich K, Pennino D, et al. Th22 cells represent a distinct human T cell subset involved in epidermal immunity and remodeling. J Clin Invest. 2009;119:3573–85.
43. Duhen T, Geiger R, Jarrossay D, et al. Production of interleukin 22 but not interleukin 17 by a subset of human skin-homing memory T cells. Nat Immunol. 2009;10:857–63.
44. Ortega C, Fernandez AS, Carrillo JM, et al. IL-17-producing CD8+ T lymphocytes from psoriasis skin plaques are cytotoxic effector cells that secrete Th17-related cytokines. J Leukoc Biol. 2009;86: 435–43.
45. Albanesi C, Scarponi C, Pallotta S, et al. Chemerin expression marks early psoriatic skin lesions and correlates with plasmacytoid dendritic cell recruitment. J Exp Med. 2009;206:249–58.
46. Gallo RL, Huttner KM. Antimicrobial peptides: an emerging concept in cutaneous biology. J Invest Dermatol. 1998;111:739–43.
47. Bata Csorgo Z, Hammerberg C, Voorhees JJ, Cooper KD. Kinetics and regulation of human keratinocyte stem cell growth in short-term primary ex vivo culture. Cooperative growth factors from psoriatic lesional T lymphocytes stimulate proliferation among psoriatic uninvolved, but not normal, stem keratinocytes. J Clin Invest. 1995;95:317–27.
48. Sano S, Chan KS, Carbajal S, et al. Stat3 links activated keratinocytes and immunocytes required for development of psoriasis in a novel transgenic mouse model. Nat Med. 2005;11:43–9.
49. Skov L, Baadsgaard O. Bacterial superantigens and inflammatory skin diseases. Clin Exp Dermatol. 2000;25:56–61.
50. Pacan P, Szepietouski JC, Kiejuo A. Stressful life events and depression in patients suffering from psoriasis vulgaris. Dermatol Psychosom. 2003;4:142–5.
51. Verhoeven EWM, Kraaimaat FW, de Jong EMGJ, et al. Individual differences in the effect of daily stressors on psoriasis: a prospective study. Br J Dermatol. 2009;161:295–9.
52. Herron MD, Hinckley M, Hoffman MS, et al. Impact of obesity and smoking on psoriasis presentation and management. Arch Dermatol. 2005;141:1527–34.
53. Marrakchi S, Guigue P, Renshaw BR, et al. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. N Engl J Med. 2011;365:620–8.
54. Radtke MA, Reich K, Blome C, et al. Prevalence and clinical features of psoriatic arthritis and joint complaints in 2009 patients with psoriasis: results of a German national survey. J Eur Acad Dermatol Venereol. 2009;23:683–91.
55. Moll JMH. Psoriatic arthropathy. In: Mier PD, van de Kerkhof PCM (eds). Textbook of Dermatology. Edinburgh: Churchill Livingstone, 1986:55–82.
56. Reich K, Krüger K, Mössner R, Augustin M. Epidemiology and clinical pattern of psoriatic arthritis in Germany: a prospective interdisciplinary epidemiological study of 1511 patients with plaque-type psoriasis. Br J Dermatol. 2009;160:1040–7.
57. Brauchli YB, Jick SS, Miret M, Meier CR. Psoriasis and risk of incident cancer: an inception cohort study with a nested case-control analysis. J Invest Dermatol. 2009;129:2604–12.
58. Mallbris L, Akre O, Granath F, et al. Increased risk for cardiovascular mortality in psoriasis inpatients but not in outpatients. Eur J Epidemiol. 2004;19:225–30.
59. Gelfand JM, Neimann AL, Shin DB, et al. Risk of myocardial infarction in patients with psoriasis. JAMA. 2006;296:1735–41.
60. Neimann AL, Shin DB, Wang X, et al. Prevalence of cardiovascular risk factors in patients with psoriasis. J Am Acad Dermatol. 2006;55:829–35.
61. Gottlieb AB, Dann F. Comorbidities in patients with psoriasis. Am J Med. 2009;122:1150.e1–9.
62. Miele L, Vallone S, Cefalo C, et al. Prevalence, characteristics and severity of non-alcoholic fatty liver disease in patients with chronic plaque psoriasis. J Hepatol. 2009;51:778–86.
63. Lee F, Bellary S, Francis C. Increased occurrence of psoriasis in patients with Crohn's disease and their relatives. Am J Gastroenterol. 1990;85:962–3.
64. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3: guidelines of care for the management and treatment of psoriasis with topical therapies. J Am Acad Dermatol. 2009;60: 643–59.
65. Kragballe K. Vitamin D in Dermatology. New York: Marcel Dekker, 2000.
66. van de Kerkhof PCM, Wasel N, Kragballe K, et al. A two-compound product containing calcipotriol and betamethasone dipropionate provides rapid, effective treatment of psoriasis vulgaris regardless of baseline disease severity. Dermatology. 2005;210:294–9.
67. Kragballe K, Hoffmann V, Ortonne JP, et al. Efficacy and safety of calcipotriol plus betamethasone dipropionate scalp formulation compared with calcipotriol scalp solution in the treatment of scalp psoriasis: a randomized controlled trial. Br J Dermatol. 2009;161: 159–66.
68. Feldman SR, Yentzer BA. Topical clobetasol propionate in the treatment of psoriasis: a review of newer formulations. Am J Clin Dermatol. 2009;10:397–406.
69. Katz HI, Hien NT, Prower SE, et al. Betamethasone in optimized vehicle. Intermittent pulse dosing for extended maintenance treatment of psoriasis. Arch Dermatol. 1987;123:1308–11.
70. van de Kerkhof PCM. Dithranol treatment for psoriasis: after 75 years, still going strong. Eur J Dermatol. 1991;1:79–88.
71. Lew-kaya DA, Sefton J, Krueger FF, et al. Safety and efficacy of a new retinoid gel in the treatment of psoriasis. J Invest Dermatol. 1992;98:600.
72. Gribetz C, Ling M, Lebwohl M, et al. Pimecrolimus cream 1% in the treatment of intertriginous psoriasis: a double blind, randomized study. J Am Acad Dermatol. 2004;51:731–8.
73. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 5. Guidelines of care for the treatment of psoriasis with phototherapy and photochemotherapy. J Am Acad Dermatol. 2010;62:114–35.
74. Pathirana D, Ormerod AD, Saiag P, et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris. J Eur Acad Dermatol Venereol. 2009;23 (suppl 2):1–70.
74a. Hsu S, Papp KA, Lebwohl MG, et al. Consensus guidelines for the management of plaque psoriasis. Arch Dermatol. 2012;148:95–102.
75. Stern RS, Zierler S, Parrish JA. Methotrexate used for psoriasis and the risk of noncutaneous or cutaneous malignancy. Cancer. 1982;50:869–72.
76. Nyfors A, Jensen H. Frequency of malignant neoplasms in 248 long-term methotrexate-treated psoriatics. Dermatologica. 1983;167:260–1.
77. de Rie MA, Bos JD. Cyclosporine immunotherapy. Clin Dermatol. 1997;15:811–21.
78. Timonen P, Friend O, Abeywickrama K, et al. Efficacy of low dose cyclosporin A in psoriasis: results of dose finding studies. Br J Dermatol. 1990;122(suppl. 36): 33–40.
79. Gollnick H, Bauer R, Brindley C, et al. Acitretin versus etretinate in psoriasis. Clinical and pharmacokinetic results of a German multicenter study. J Am Acad Dermatol. 1988;19:458–69.
79a. Reich K, Langley RG, Papp KA, et al. A 52-week trial comparing briakinumab with methotrexate in patients with psoriasis. N Engl J Med. 2011;365:1586–96.
80. Gottlieb A, Korman NJ, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 2. Psoriatic arthritis: overview and guidelines of care for treatment with an emphasis on the biologics. J Am Acad Dermatol. 2008;58:851–64.
81. Menter A, Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol. 2008;58:826–50.
82. Smith CH, Anstey AV, Barker JN, et al. British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. Br J Dermatol. 2009;161:987–1019.
83. Sterry W, Barker J, Boehncke WH, et al. Biological therapies in the systemic management of psoriasis. International Consensus Conference. Br J Dermatol. 2004;151(suppl. 69):3–17.
84. Driessen RJ, Boezeman JB, van de Kerkhof PC, de Jong EM. Three-year registry data on biological treatment for psoriasis: the influence of patient characteristics on treatment outcome. Br J Dermatol. 2009;160:670–5.
85. Mrowietz U, Christophers E, Altmeyer P, for the German Fumaric Acid Ester Consensus Conference. Treatment of severe psoriasis with fumaric acid esters: scientific background and guidelines for therapeutic use. Br J Dermatol. 1999;141:424–9.
86. Grundmann-Kollman M, Korting HC, Behrens S, et al. Treatment of chronic plaque-stage psoriasis and psoriatic arthritis with mycophenolate mofetil. J Am Acad Dermatol. 2000;42:835–7.
87. Perez A, Raab R, Chen TC, et al. Safety and efficacy of oral calcitriol (1,25-dihydroxyvitamin D_3) for the treatment of psoriasis. Br J Dermatol. 1996;134:1070–8.
88. Kirby B, Fortune DG, Blushan M, et al. The Salford Psoriasis Index: a holistic measure of psoriasis severity. Br J Dermatol. 2000;142:728–32.
89. Mason AR, Mason J, Cork MJ, et al. Topical treatments for chronic plaque psoriasis. Cochrane Database Syst Rev 2009;(2):CD0050028.
90. Guenther L, Cambazard F, van de Kerkhof PCM, et al. Efficacy and safety of a new combination of calcipotriol and betamethasone dipropionate (once or twice daily) compared to calcipotriol (twice daily) in the treatment of psoriasis vulgaris: a randomized, double blind, vehicle controlled clinical trial. Br J Dermatol. 2002;147:316–23.
91. Lebwohl M, Freeman AK, Chapman MS, et al. Tacrolimus ointment is effective for facial and intertriginous psoriasis. J Am Acad Dermatol. 2004;51:723–30.
92. Spuls PI, Bossuyt PM, van Everdingen JJ, et al. The development of practice guidelines for the treatment of severe plaque form psoriasis. Arch Dermatol. 1998;134:1591–6.
93. Christophers E, Griffiths CEM, Gaitanis G, van de Kerkhof PCM. The unmet treatment need for moderate to severe psoriasis: results of a survey and chart review. J Eur Acad Dermatol Venereol. 2006;20:921–5.
94. van de Kerkhof PCM, Cambazard F, Hutchinson F, et al. The effect of the addition of calcipotriol ointment (50 µg/g) to acitretin therapy in psoriasis. Br J Dermatol. 1998;138:84–9.
95. Grossman RM, Thivolet J, Claudy A, et al. A novel therapeutic approach to psoriasis with combination calcipotriol ointment and very low-dose cyclosporin: result of multicenter placebo-controlled study. J Am Acad Dermatol. 1994;31:68–74.
96. Gisondi P, Del Giglio M, Cotena C, Girolomoni G. Combining etanercept and acitretin in the therapy of chronic plaque psoriasis: a 24-week, randomized, controlled, investigator-blinded pilot trial. Br J Dermatol. 2008;158:1345–9.
97. Marcil I, Stern RS. Squamous-cell cancer of the skin in patients given PUVA and cyclosporin: nested cohort crossover study. Lancet. 2001;358:1942–5.
98. Morrison WL, Momtaz K, Parrish A, et al. Combined methotrexate PUVA therapy in the treatment of psoriasis. J Am Acad Dermatol. 1982;6:46–51.
99. Vanderveen EE, Ellis CN, Campbell JP, et al. Methotrexate and etretinate as concurrent therapies in severe psoriasis. Arch Dermatol. 1982;118:660–2.
100. de Jager ME, de Jong EMGJ, van de Kerkhof PCM, et al. Efficacy and safety of treatments for childhood psoriasis: a systematic literature review. J Am Acad Dermatol. 2010;62:1013–30.

TABLE 8.1 – FURTHER REFERENCES

Trembath RC, Clough RL, Rosbotham JL, et al. Identification of a major susceptibility locus on chromosome 6p and evidence for further disease loci revealed by a two stage genome-wide search in psoriasis. Hum Mol Genet. 1997;6:813–20.

Nair RP, Henseler T, Janish S, et al. Evidence for two psoriasis susceptibility loci (HLA and 17q) and two novel candidate regions (16q and 20p) by genome-wide scan. Hum Mol Genet. 1997;6:1349–56.

Nair RP, Stuart PE, Nistor I, Hiremagalore R, et al. Sequence and haplotype analysis supports HLA-C as the psoriasis susceptibility 1 gene. Am J Hum Genet. 2006;78:827–51.

Helms C, Cao L, Krueger JG, et al. A putative RUNX1 binding site variant between SLC9A3R1 and NAT9 is associated with susceptibility to psoriasis. Nat Genet. 2003;35:349–56.

Tsunemi Y, Saeki H, Nakamura K, et al. Interleukin-12 p40 gene (IL12B) 3′-untranslated region polymorphism is associated with susceptibility to atopic dermatitis and psoriasis vulgaris. J Dermatol Sci. 2002;30:161–6.

Cargill M, Schrodi SJ, Chang M, et al. A large-scale genetic association study confirms IL12B and leads to the identification of IL23R as psoriasis-risk genes. Am J Hum Genet. 2007;80:273–90.

Cargill M, Schrodi SJ, Chang M, et al. 2007. A large-scale genetic association study confirms IL12B and leads to the identification of IL23R as psoriasis-risk genes. Am J Hum Genet. 2007;80:273–90.

Capon F, Bijlmakers MJ, Wolf N, et al. Identification of ZNF313/RNF114 as a novel psoriasis susceptibility gene. Hum Mol Genet. 2008;17:1938–45.

Wolf N, Quaranta M, Prescott NJ, et al. Psoriasis is associated with pleiotropic susceptibility loci identified in type II diabetes and Crohn disease. J Med Genet 2008;45:114–6.

Li Y, Liao W, Chang M, et al. Further genetic evidence for three psoriasis-risk genes: ADAM33, CDKAL1, and PTPN22. J Invest Dermatol. 2009;129: 629–34.

Huffmeier U, Uebe S, Ekici AB, et al. Evidence for susceptibility determinant(s) to psoriasis vulgaris in or near PTPN22 in German patients. J Med Genet 2006;43:517–22.

Li Y, Liao W, Chang M, et al. Further genetic evidence for three psoriasis-risk genes: ADAM33, CDKAL1, and PTPN22. J Invest Dermatol. 2009;129:629–34.

Chang M, Li Y, Yan C, et al. Variants in the 5q31 cytokine gene cluster are associated with psoriasis. Genes Immun 2008;9:176–81

de Cid R, Riveira-Munoz E, Zeeuwen PLJM, et al. Deletion of the late cornified envelope LCE3B and LCE3C genes as a susceptibility factor for psoriasis. Nat Genet. 2009;41:211–5.

Zhang XJ, Huang W, Yang S, et al. Psoriasis genome-wide association study identifies susceptibility variants within LCE gene cluster at 1q21. Nat Genet 2009;41:205–10.

Ellinghaus E, Ellinghaus D, Stuart PE, et al. Genome-wide association study identifies a psoriasis susceptibility locus at TRAF3IP2. Nat Genet. 2010;42:991–5.

Sun LD, Cheng H, Wang ZX, et al. Association analyses identify six new psoriasis susceptibility loci in the Chinese population. Nat Genet. 2010;42:1005–9.

Sun LD, Cheng H, Wang ZX, et al. Association analyses identify six new psoriasis susceptibility loci in the Chinese population. Nat Genet. 2010;42:1005–9.

Ellinghaus E, Ellinghaus D, Stuart PE, et al. Genome-wide association study identifies a psoriasis susceptibility locus at TRAF3IP2. Nat Genet. 2010;42:991–5.

Huffmeier U, Uebe S, Ekici AB, et al. Common variants at TRAF3IP2 are associated with susceptibility to psoriatic arthritis and psoriasis. Nat Genet. 2010;42:996–9.

Stuart PE, Nair RP, Ellinghaus E, et al. Genome-wide association analysis identifies three psoriasis susceptibility loci. Nat Genet. 2010;42:1000–4.

Other Papulosquamous Disorders

9

Gary S Wood and George T Reizner

Chapter Contents

Small plaque parapsoriasis and large plaque parapsoriasis *157*
Pityriasis lichenoides et varioliformis acuta and pityriasis lichenoides chronica *159*
Pityriasis rubra pilaris *162*
Pityriasis rosea *165*
Pityriasis rotunda *167*
Granular parakeratosis *167*

SMALL PLAQUE PARAPSORIASIS AND LARGE PLAQUE PARAPSORIASIS

Synonyms: ■ Parapsoriasis en plaques (small and large plaque parapsoriasis) ■ Digitate dermatosis (small plaque parapsoriasis) ■ Xanthoerythrodermia perstans (small plaque parapsoriasis) ■ Chronic superficial dermatitis (small plaque parapsoriasis) ■ Retiform parapsoriasis (variant of large plaque parapsoriasis) ■ Parakeratosis variegata (variant of large plaque parapsoriasis) ■ Patch stage of mycosis fungoides (some cases of large plaque parapsoriasis)

Key features

- Chronic, asymptomatic, erythematous scaly patches characterize both major forms of parapsoriasis
- In small plaque parapsoriasis, the lesions are generally less than 5 cm in diameter or digitate
- In large plaque parapsoriasis, the lesions are generally greater than 5 cm in diameter
- Histologically, superficial perivascular, interface or lichenoid lymphocytic infiltrates are seen
- There is a predominance of $CD4^+$ T cells in the infiltrate
- A dominant T-cell clonality is demonstrable in many cases

Introduction

Small plaque parapsoriasis and large plaque parapsoriasis are idiopathic, chronic dermatoses classified within the parapsoriasis group of skin diseases. Related disorders include acute and chronic variants of pityriasis lichenoides and lymphomatoid papulosis (see Ch. 120). This group is significant for the tendency of its disorders to coexist or overlap with one another and for its association with lymphomas[1].

History

Small plaque parapsoriasis and large plaque parapsoriasis were included in the parapsoriasis group as defined by Brocq in 1902[2] and refined subsequently by several authors whose work was summarized by Lambert and Everett in 1981[1]. In the mid to late twentieth century, it became widely accepted that small plaque parapsoriasis and large plaque parapsoriasis were distinct entities[3], and that large plaque parapsoriasis and its variants were closely related to the patch stage of mycosis fungoides[4].

Epidemiology

Small plaque parapsoriasis and large plaque parapsoriasis are more common in middle-aged and elderly individuals, but they may also occur in children. They peak during the fifth decade of life and occur in all racial groups and geographic regions. There is a male predominance that is greater for small plaque parapsoriasis, where it approximates 3 : 1.

Pathogenesis

The etiologies of small plaque and large plaque parapsoriasis are unknown. Both disorders are characterized by superficial cutaneous lymphoid infiltrates composed primarily of $CD4^+$ T cells[5,6]. Dominant T-cell clonality has been demonstrated in many cases of large plaque parapsoriasis and in fewer cases of small plaque parapsoriasis[6–8]. The difference may be an artifact of a lower T-cell density in small plaque parapsoriasis. Alternatively, it may be that some cases are truly polyclonal and represent a distinct biologic subset of disease. Of note, more recent studies have failed to confirm earlier reports of human herpesvirus-8 within lesions of large plaque parapsoriasis[9].

It is now well established that at least some cases of large plaque parapsoriasis and its variants are manifestations of the patch stage of mycosis fungoides (see Ch. 120). This helps to explain the progression of large plaque parapsoriasis to more overt forms of lymphoma at a rate of 10% to 35% over a period of 6–10 years[1,10,11]. The concept of "clonal dermatitis" has been put forth to describe T-cell lymphoproliferative disorders that may constitute an intermediate or transitional step between chronic dermatitis and overt cutaneous T-cell lymphomas[7] (Fig. 9.1). A mycosis fungoides pyramid can be envisioned, in which a relatively small number of cases evolve from a much larger pool of chronic dermatitis through the intermediary of clonal dermatitis. Small retrospective studies suggest that clonal dermatitis has an approximately 20% risk of progression to cutaneous T-cell lymphoma over 5 years[12].

Although both small plaque and large plaque parapsoriasis can be viewed as forms of clonal dermatitis, large plaque parapsoriasis appears to have a significantly greater risk of progression to overt lymphoma. However, in contrast to those cases of parapsoriasis in which dominant clonality precedes the evolution of histologically overt mycosis fungoides, it appears that some cases of early mycosis fungoides may still contain oligoclonal T cells from which a dominant clone has yet to evolve[13]. Other examples of clonal dermatitis can be found among cases of primary idiopathic erythroderma and chronic dermatitis.

Clinical Features

Despite inclusion of the word "plaque" in their terminology, both small plaque and large plaque parapsoriasis are diseases composed of patches rather than plaques. In both entities, skin lesions are chronic and generally asymptomatic or mildly pruritic. They may wax and wane early in their clinical course, but they typically become persistent and can slowly progress to become more extensive. Some cases regress fully, either spontaneously or after therapy, but this may require a period of several years. Lesions can be widespread on the trunk and extremities or more limited in their distribution. In the latter instance, they often favor more sun-protected sites.

Small plaque parapsoriasis typically presents as round–oval patches that are generally less than 5 cm in diameter (Fig. 9.2A). They are variably erythematous (but often less intense than psoriasis) and

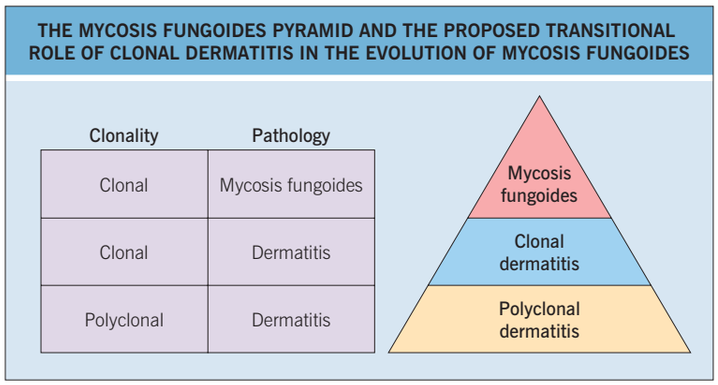


Fig. 9.1 The mycosis fungoides pyramid and the proposed transitional role of clonal dermatitis in the evolution of mycosis fungoides.

Fig. 9.2 Small plaque parapsoriasis. A Small (<5 cm), erythematous, slightly scaly patches. **B** Digitate dermatosis with elongated finger-like lesions on the flank.

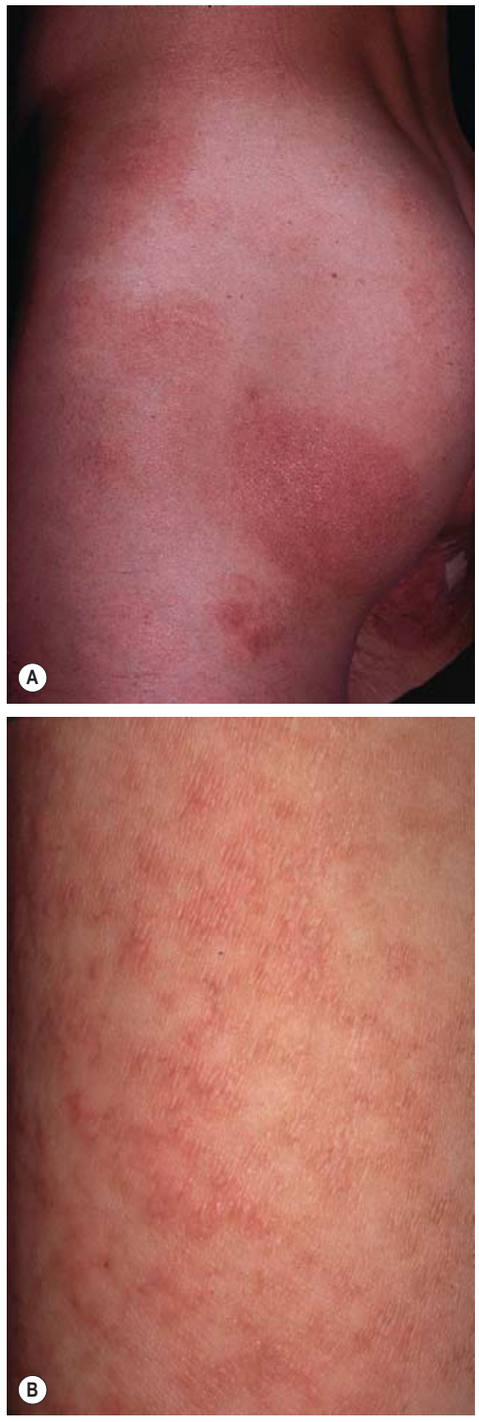


Fig. 9.3 Large plaque parapsoriasis. A Large, variably erythematous patches in the bathing trunk region is a classic presentation. **B** Retiform parapsoriasis with atrophic, red–brown papules in a net-like pattern.

covered with a fine scale. Those with a yellow hue have been termed "xanthoerythrodermia perstans"[1]. An important variant of small plaque parapsoriasis is "digitate dermatosis", which presents as elongated, finger-like patches symmetrically distributed on the flanks[3] (Fig. 9.2B). These lesions are an exception to the 5-cm rule in that they may measure 10 cm or more along their long axis. The reported risk of progression to mycosis fungoides varies from zero[14] to low[11].

Large plaque parapsoriasis presents as variably erythematous, round or irregularly shaped scaly patches that are larger than 5 cm (Fig. 9.3A). They may or may not exhibit the clinical triad of atrophy, telangiectasia and hyper/hypopigmentation that warrants the descriptive designation "poikiloderma vasculare atrophicans". Rather than being a specific entity, poikiloderma can be seen in several disorders, including certain autoimmune connective tissue diseases (e.g. dermatomyositis) and genodermatoses, in addition to large plaque parapsoriasis and mycosis fungoides. "Retiform parapsoriasis", also known as "parapsoriasis variegata", "parakeratosis variegata" or "parapsoriasis lichenoides", is a variant of large plaque parapsoriasis in which there are widespread, ill-defined patches in a net-like or zebra-stripe pattern[1] (Fig. 9.3B). Long-term follow-up has shown that virtually all of these rare retiform cases progress to overt mycosis fungoides. As noted earlier, patients with other forms of large plaque parapsoriasis develop clinically unequivocal lymphomas (mostly mycosis fungoides) at a rate of 10% to 35% per decade.

PRINCIPAL DIFFERENTIAL DIAGNOSIS OF SMALL PLAQUE PARAPSORIASIS AND LARGE PLAQUE PARAPSORIASIS	
Small plaque parapsoriasis	**Large plaque parapsoriasis**
Pityriasis rosea	Mycosis fungoides
Drug eruption, in particular pityriasis rosea-like	Drug eruption, in particular mycosis fungoides-like
Pityriasis lichenoides chronica	Psoriasis
Psoriasis, including guttate	Poikilodermatous autoimmune connective tissue disease (e.g. dermatomyositis)
Mycosis fungoides	Poikilodermatous genodermatoses (see Table 63.8)
Secondary syphilis	Chronic radiodermatitis
Nummular dermatitis	

Table 9.1 Principal differential diagnosis of small plaque parapsoriasis and large plaque parapsoriasis.

THERAPEUTIC LADDER FOR SMALL PLAQUE PARAPSORIASIS AND LARGE PLAQUE PARAPSORIASIS
Topical corticosteroids (2)
Topical calcineurin inhibitors (3)
Topical coal tar products (3)
Sunlight (2)
Ultraviolet B (UVB) phototherapy – broadband or narrowband (2)
PUVA (psoralen plus UVA) phototherapy (2)
Topical bexarotene (2)
Topical imiquimod (3)
Topical mechlorethamine (nitrogen mustard)* (2)
Topical carmustine (BCNU)* (2)
Antihistamines† (3)
*More appropriate for patch-stage mycosis fungoides.
†If there is pruritus.

Table 9.2 Therapeutic ladder for small plaque parapsoriasis and large plaque parapsoriasis. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

Pathology

Patches of small plaque parapsoriasis exhibit a mild, nonspecific spongiotic dermatitis and parakeratosis. Lesions of large plaque parapsoriasis may have similar histologic findings or an interface lymphocytic infiltrate with a variable degree of lichenoid features. Some cases of large plaque parapsoriasis are indistinguishable from the patch stage of mycosis fungoides and may contain atypical lymphoid cells (see Ch. 120). These cases should be diagnosed as mycosis fungoides; however, their proportion is difficult to establish because experts disagree on the minimum criteria required to histopathologically diagnose mycosis fungoides. The term "large plaque parapsoriasis" should be used for those remaining patients who fail to show the histopathologic features of mycosis fungoides. Poikilodermatous variants of large plaque parapsoriasis demonstrate the histopathologic triad of epidermal atrophy, telangiectasias and pigment incontinence.

Differential Diagnosis

The diagnosis of small plaque parapsoriasis and large plaque parapsoriasis is based on a correlation between clinical and histopathologic findings; other tests are of minimal value. They are distinguished from each other by their clinical features. The principal differential diagnostic considerations are listed in Table 9.1. Both small plaque and large plaque parapsoriasis are differentiated from mycosis fungoides based on failing to meet the minimum histopathologic criteria for that disorder. While some patients with lesions clinically consistent with large plaque parapsoriasis will meet microscopic criteria for mycosis fungoides, others will not. Therefore, large plaque parapsoriasis remains a useful designation for such patients. Poikilodermatous variants of large plaque parapsoriasis must be distinguished from poikilodermatous patches associated with dermatomyositis, lupus erythematosus, Rothmund–Thomson syndrome, Kindler syndrome, dyskeratosis congenita and chronic radiodermatitis.

Small plaque parapsoriasis is distinguished from pityriasis rosea by the presence of a herald patch and resolution of the latter disorder within a few months. Psoriasis and secondary syphilis are excluded on the basis of clinicopathologic and serologic features. Patients with pityriasis lichenoides, acute and chronic, generally have lesions that are smaller and more widely distributed than do patients with small plaque parapsoriasis. Drug eruptions resembling pityriasis rosea or mycosis fungoides must also be excluded by clinicopathologic correlation.

Treatment

All therapeutic approaches are based primarily on uncontrolled case series, case reports or anecdotal evidence (Table 9.2). In this author's opinion (GSW), patients with small plaque parapsoriasis should be reassured that their risk of developing mycosis fungoides is practically not an issue. Ackerman and co-workers disagree and have expressed the opinion that even small plaque parapsoriasis is mycosis fungoides. Patients with small plaque parapsoriasis may be followed without treatment if they prefer. Standard therapy includes topical corticosteroids, topical coal tar products, and various forms of phototherapy. The role of newer topical agents, such as bexarotene, calcineurin inhibitors and imiquimod, remains to be established. There is some concern that calcineurin inhibitors might be implicated if lymphoma were to develop. Until this issue is clarified, due caution should be exercised in the treatment of small plaque parapsoriasis.

Patients with large plaque parapsoriasis should be treated regardless of whether one believes that their lesions already represent or may evolve into mycosis fungoides. Initial therapy may be similar to that described for small plaque parapsoriasis. Those cases of large plaque parapsoriasis that meet the histopathologic criteria for mycosis fungoides can be treated with all the agents commonly used in the early stages of that disease. In addition to topical corticosteroids and phototherapy, these include topical mechlorethamine (nitrogen mustard), topical carmustine (BCNU), topical bexarotene, and subcutaneous interferon-α. Experimental therapies include interleukin-12[15] and the excimer laser (308 nm).

PITYRIASIS LICHENOIDES ET VARIOLIFORMIS ACUTA AND PITYRIASIS LICHENOIDES CHRONICA

Synonyms: ■ Mucha–Habermann disease (PLEVA) ■ Guttate parapsoriasis (PLC)

Key features

- Pityriasis lichenoides et varioliformis acuta (PLEVA) and pityriasis lichenoides chronica (PLC) are two ends of a disease spectrum
- Both entities are characterized by recurrent crops of spontaneously regressing erythematous papules
- Lesions of PLEVA are crusted, vesicular or pustular, whereas in PLC they are scaly
- Individual patients may show intermediate or mixed lesions
- Histologically, an interface dermatitis with necrotic keratinocytes is seen
- The infiltrate is predominantly T cells that are often monoclonal

Introduction

The acute and chronic forms of pityriasis lichenoides exist on a disease spectrum with variable presentations that can pose diagnostic and therapeutic challenges[16,17]. These are papular, clonal T-cell disorders that may rarely be associated with mycosis fungoides.

Fig. 9.4 Clinical spectrum of pityriasis lichenoides. In the acute form (PLEVA), widespread erythematous papules and papulovesicles are admixed with crusted lesions (**A**, **B**); sometimes, there can be an ulcerative component (**C**). Individuals with the chronic form (PLC) develop multiple red–brown papules, some of which have scale (**D**). A number of patients will have lesions characteristic of both PLEVA and PLC, i.e. an overlap (**E**). *A, Courtesy, Julie V Schaffer, MD. B, Courtsey, Thomas Schwarz, MD. E, Courtesy, Kalman Watsky, MD.*

History

Pityriasis lichenoides, including its two main variants PLEVA and PLC, was first described between 1894 and 1925. Mucha and Habermann are credited with recognition of PLEVA[18,19], while Juliusberg is associated with PLC[20]. Pityriasis lichenoides was included in Brocq's 1902 treatise on a group of chronic, idiopathic dermatoses that he termed "parapsoriasis".

Epidemiology

Pityriasis lichenoides is more prevalent in the pediatric population, but it affects patients in all age groups, races and geographic regions. There is a male predominance.

Pathogenesis

The etiology of pityriasis lichenoides is unknown. It has been postulated to be a response to foreign antigens such as infectious agents and drugs. A few reports describe its association with specific infections (e.g. HIV), medications (e.g. estrogen–progesterone, TNF-α inhibitors [infliximab, adalimumab]), and radiocontrast dye. Of note, increased numbers of maternally derived keratinocytes have been detected within the epidermis of young male patients with pityriasis lichenoides (as compared to normal skin) and perhaps they triggered a host-(child) versus-graft (mother) disease.

Both PLEVA and PLC contain lesional T-cell infiltrates, with a general predominance of $CD8^+$ cells in PLEVA and $CD4^+$ cells in PLC[21,22]. Both types of lesions can exhibit dominant T-cell clonality, although it is more easily demonstrated in PLEVA, where the infiltrate is denser[23–25]. This clonality indicates that pityriasis lichenoides is a T-cell lymphoproliferative disorder like lymphomatoid papulosis and some forms of T-cell cutaneous lymphoid hyperplasia. Indeed, some patients with lymphomatoid papulosis develop individual lesions indistinguishable from pityriasis lichenoides, suggesting that these two conditions may be related[21,26]. The concept of pityriasis lichenoides as a T-cell lymphoproliferative disorder may help to explain its occasional association with other lymphoproliferative disorders such as cutaneous T-cell lymphoma, Hodgkin disease and other lymphomas[27–30].

Clinical Features

Pityriasis lichenoides presents as recurrent crops of spontaneously regressing erythematous to purpuric papules. The acute form (PLEVA) and the chronic form (PLC) exist on a disease continuum. Many patients have intermediate or mixed manifestations, either serially or concurrently. In patients with PLEVA, individual lesions develop crusts, ulcers, vesicles or pustules, which may heal with varioliform scars if dermal damage is extensive (Fig. 9.4). Lesions are usually asymptomatic and typically resolve within weeks. Disease manifestations are confined to the skin, except rarely, when acute lesions are associated with malaise, fever, lymphadenopathy, arthritis and/or bacteremia. The term "febrile ulceronecrotic Mucha–Habermann disease (FUMHD)" has been used to refer to such severe variants in which mucosal, gastrointestinal and pulmonary involvement can be observed[31]. Transition from PLEVA to this febrile variant has been associated with increased serum levels of TNF-α.

In PLC, the papules are erythematous to red–brown and scaly (see Fig. 9.4). They pursue a more indolent course, regressing over weeks to months. When these lesions subside, there may be residual

hypopigmented macules; the latter are more obvious in darkly pigmented individuals and may be the presenting complaint (see Ch. 66). Pityriasis lichenoides can resolve spontaneously after weeks to months or it may pursue a chronic relapsing course, sometimes interspersed with long periods of remission. Some studies have suggested that the distribution of skin lesions is more important than their acute or chronic nature in predicting outcome[32]. Patients with a diffuse distribution of lesions had the shortest average course of disease (11 months), while those with a peripheral distribution had the longest average clinical course (33 months). The central distribution variant was intermediate.

Pathology

Pityriasis lichenoides exhibits a superficial perivascular interface dermatitis in all cases (Fig. 9.5). Those lesions at the acute end of the spectrum contain a denser infiltrate that may be top-heavy and wedge-shaped. Lymphocytes predominate in the infiltrate, although neutrophils may be admixed. The epidermis shows focal parakeratosis and evidence of damage ranging from edema to extensive epidermal necrosis in well-developed lesions. Extravasation of erythrocytes is usually present. The usual histopathologic alterations accompany the presence of crusts, vesicles, pustules and ulcers. Lymphocytic vasculitis is sometimes described, but most cases lack true fibrinoid necrosis of blood vessels (and use of this histologic term can be confusing to clinicians). All of these changes are blunted in the more chronic skin lesions, where the principal microscopic features include parakeratosis and a milder interface lymphocytic infiltrate accompanied by focal keratinocyte necrosis and mild erythrocyte extravasation. Lymphoid atypia is not a standard feature of pityriasis lichenoides. Although some pathologists allow occasional atypical lymphocytes, others regard this as a sign of lymphomatoid papulosis.

Differential Diagnosis

The diagnosis of pityriasis lichenoides is made by the correlation of clinical features with lesional histopathology. The principal differential diagnostic considerations for pityriasis lichenoides are listed in Table 9.3. For PLEVA, the main clinical and histopathologic differential diagnostic considerations include lymphomatoid papulosis, drug eruptions, arthropod reactions, cutaneous small vessel vasculitis, and varicella. For PLC, the principal differential diagnosis includes small plaque parapsoriasis, guttate psoriasis, lichen planus (exanthematous), pityriasis rosea, secondary syphilis, lymphomatoid papulosis, drug eruptions and papular dermatitis. All of these differential diagnostic possibilities can usually be excluded on the basis of key historical, clinical, pathologic and laboratory findings. More than one biopsy specimen may be required to achieve clinicopathologic correlation.

Aside from immunopathology, most other laboratory tests offer little diagnostic value. A preponderance of $CD8^+$ T cells supports the diagnosis of PLEVA because there are few skin disorders that share this feature. Conversely, the demonstration of $CD30^+$ cells generally excludes pityriasis lichenoides and helps establish the alternative diagnosis of lymphomatoid papulosis. Direct fluorescent antibody (DFA) and serologic testing as well as immunohistochemical staining are helpful in excluding varicella and syphilis.

Treatment

All treatments for pityriasis lichenoides are based primarily on uncontrolled case series, case reports or anecdotes (Table 9.4). If a drug association is suspected, trial discontinuance of the suspected agent is warranted. First-line therapy includes topical corticosteroids, topical coal tar preparations, tetracycline, erythromycin and various types of phototherapy. Oral tetracycline and erythromycin are used for their anti-inflammatory rather than antibiotic effects, with erythromycin favored in children. A several-month course is often required, followed by a gradual taper. Other antibiotics may be employed if there is secondary infection, usually with *Staphylococcus aureus*.

More fulminant cases may require low-dose weekly methotrexate. Those rare cases associated with fever and arthritis may benefit from systemic corticosteroids, IVIg or cyclosporine, once infection has been excluded. Antihistamines may be helpful in those instances where significant pruritus is present. There are recent reports of the efficacy of etanercept, oral bromelain (bromelin) and photodynamic therapy.

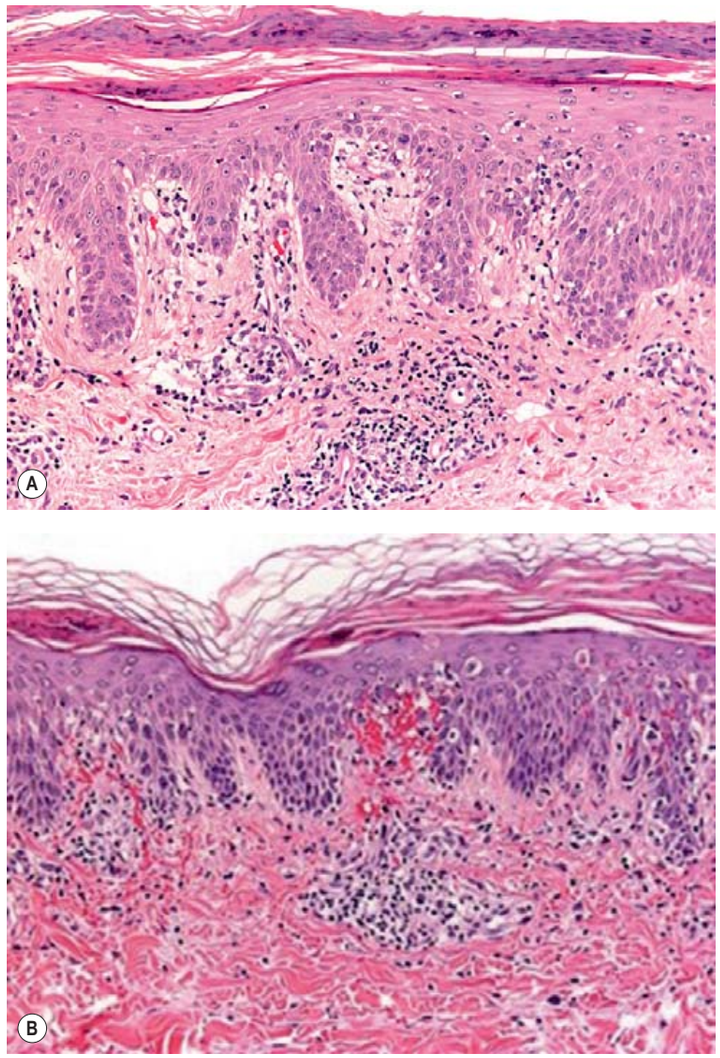


Fig. 9.5 Pityriasis lichenoides – histopathologic features. A In the chronic form (PLC), parakeratosis may be more prominent, but the epidermal destruction is less intense. **B** In the acute form (PLEVA), extravasated erythrocytes as well as apoptotic keratinocytes are seen. Uniformly present is a superficial perivascular interface dermatitis. As with the clinical presentations, there is a continuous histologic spectrum. *Courtesy, Lorenzo Cerroni, MD.*

PRINCIPAL DIFFERENTIAL DIAGNOSIS OF PITYRIASIS LICHENOIDES ET VARIOLIFORMIS ACUTA (PLEVA) AND PITYRIASIS LICHENOIDES CHRONICA (PLC)

PLEVA	PLC
Lymphomatoid papulosis	Small plaque parapsoriasis
Cutaneous small vessel vasculitis	Guttate psoriasis
Lichenoid drug eruption	Lichen planus
Arthropod reactions	Pityriasis rosea
Varicella, enteroviral exanthems	Secondary syphilis
Folliculitis	Lymphomatoid papulosis
Erythema multiforme	Papular dermatitis
Dermatitis herpetiformis	Lichenoid drug eruption

Table 9.3 Principal differential diagnosis of pityriasis lichenoides et varioliformis acuta (PLEVA) and pityriasis lichenoides chronica (PLC).

THERAPEUTIC LADDER FOR PITYRIASIS LICHENOIDES ET VARIOLIFORMIS ACUTA (PLEVA) AND PITYRIASIS LICHENOIDES CHRONICA (PLC)
Topical corticosteroids (2)
Topical coal tar products (3)
Oral erythromycin (2)
Oral tetracycline (2)
Oral azithromycin (3)
Sunlight (2)
Ultraviolet B (UVB) phototherapy – broadband or narrowband (2)
PUVA (psoralen plus UVA) phototherapy (2)
Methotrexate (2)
Cyclosporine (3)
Special treatments (3):
Antihistamines*
Systemic antibiotics†
Systemic corticosteroids‡
* If there is pruritus.
† If there is secondary infection.
‡ If there is fever, arthritis or other systemic findings.

Table 9.4 Therapeutic ladder for pityriasis lichenoides et varioliformis acuta (PLEVA) and pityriasis lichenoides chronica (PLC). Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

PITYRIASIS RUBRA PILARIS

Synonyms: ■ Lichen ruber pilaris ■ Devergie's disease ■ Lichen ruber acuminatus

Key features

- Follicular papules with an erythematous base are a characteristic finding, including on the proximal dorsal fingers
- There is a coalescence of orange–red plaques, but with obvious islands of sparing
- An orange–red waxy keratoderma of the palms and soles is often seen
- Of the five types described, the classic adult form is the most common
- The classic types (adult and juvenile) typically resolve within 3–5 years
- Histologically, there is alternating vertical and horizontal ortho- and parakeratosis

History

Pityriasis rubra pilaris (PRP) was first described in 1835 by Claudius Tarral as a variant of psoriasis. Devergie[33] later recognized it as a separate entity in 1857 and named it "pityriasis pilaris". In 1889, Besnier[34] recommended the name "pityriasis rubra pilaris", and it has persisted.

Epidemiology

Although PRP shows no gender bias, affecting both men and women equally, ethnic variations may exist. For example, in one report, the incidence in Great Britain was 1 in 5000 new patient visits whereas in India it was 1 in 50 000 visits. The incidence has either two or three peaks. The first is during the first and second decades and the second is during the sixth decade. The third peak, if real, results from splitting the first and second decades into two separate peaks.

Nearly all cases are acquired, with occasional reports of a familial form. An autosomal dominant inheritance pattern with variable penetrance is more commonly observed, although an autosomal recessive pattern has also been described. Of patients with PRP, from zero to 6.5% are reported to have a family history of PRP[35]. Except for the non-classic forms of PRP, it appears to be a self-limited disease process, resolving within 3 to 5 years in almost all cases.

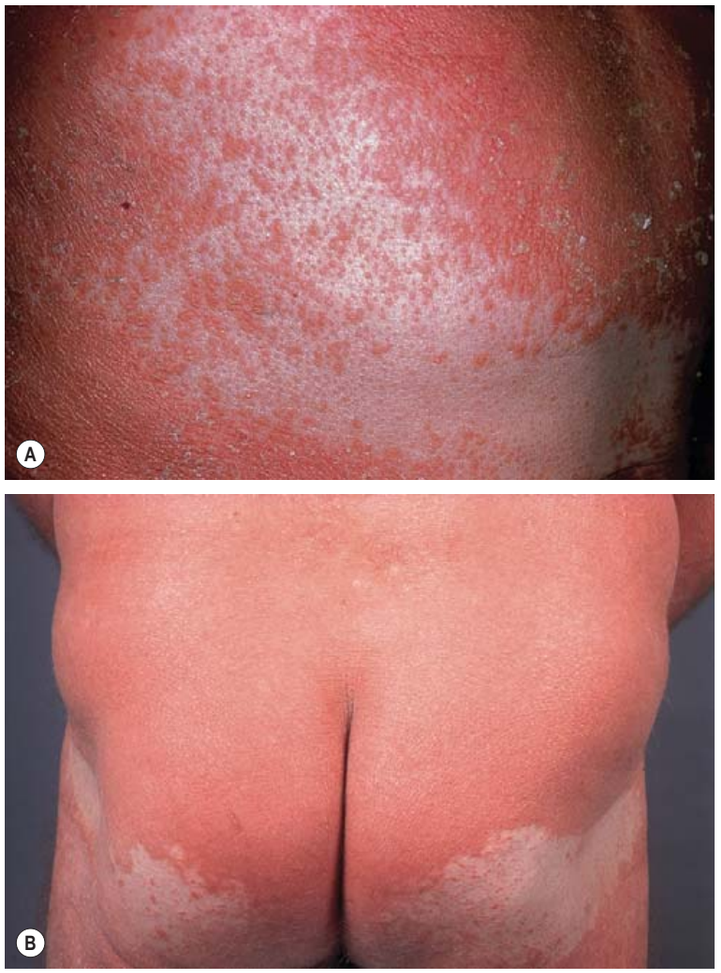


Fig. 9.6 Pityriasis rubra pilaris. A Follicular papules and confluent orange–red scaly plaques with islands of sparing. **B** The islands of sparing may be sharply demarcated; note the salmon color of the plaques.

Pathogenesis

No clear etiology has been established. Early on, a vitamin A deficiency was proposed, but this has not been substantiated. The therapeutic success of systemic retinoids suggests a possible dysfunction in keratinization or vitamin A metabolism. Infections, UV exposure and various minor traumas to the skin have been reported to precede the onset of PRP, implicating a physical trigger or superantigen in selected patients.

The possibility of an autoimmune pathogenesis has also been raised. For example, there are reports of PRP in association with myasthenia gravis, celiac disease, myositis, inflammatory arthritis, and hypothyroidism. An abnormal immunologic response to particular antigens has been suggested by the coexistence of PRP with HIV infection[36], as well as with internal malignancies (e.g. renal cell, bronchogenic and hepatocellular carcinomas)[37].

Clinical Features

The multiple, well-described clinical features of classic PRP are helpful in making the diagnosis. Follicular hyperkeratosis on an erythematous base is a key finding. This results in rough papules, especially on the dorsal aspect of the proximal fingers, which have been described as reminiscent of a nutmeg grater. These papules are also seen on the trunk and extremities, and they can coalesce to form large salmon-colored to orange–red plaques with distinctive "islands of sparing" (Fig. 9.6). The plaques can then progress to an erythrodermic appearance

Fig. 9.7 Pityriasis rubra pilaris. In areas of diffuse erythroderma, follicular hyperkeratosis (knee) may not be as apparent as within relatively spared islands (compare to Fig. 9.6A).

Fig. 9.8 Pityriasis rubra pilaris. The orange–red color of the skin, including that of the palms, aids in the clinical diagnosis; note the waxy appearance of the keratoderma. *Courtesy, Irwin Braverman, MD.*

with varying degrees of exfoliation (Fig. 9.7). The palms and soles are commonly involved with a distinctive orange–red waxy keratoderma (Fig. 9.8). Erythema with a fine diffuse scale is often seen on the scalp[35,38]. Scalp disease that mimics seborrheic dermatitis is a common initial clinical manifestation of adult PRP, and rapid progression to erythroderma can occur over several weeks.

Nail involvement is characterized by a thickened plate with a yellow–brown discoloration and subungual debris. The mucous membranes are rarely involved, but they may show features similar to oral lichen planus.

The most common form of PRP (see below) usually begins in the head and neck region and then progressively advances caudally. Pruritus and burning have been reported in 20% of patients with PRP. Although less common than in atopic dermatitis or Darier disease, Kaposi's varicelliform eruption can occur in patients with PRP. As with other forms of erythroderma (see Ch. 10), eruptive seborrheic keratoses may appear. Both photoaggravated and phototriggered forms of PRP can also occur. Resolving PRP may have a clinical appearance that resembles erythema gyratum repens (see Ch. 19).

To distinguish the different clinical presentations of PRP, Griffiths[39] proposed a classification schema based upon age, duration, and type of cutaneous involvement (Fig. 9.9). A generalized eruption is seen in all of the forms except for the circumscribed juvenile type. Type I (classic adult) PRP is the most common form, accounting for a little over half of cases. It is typically self-limited, clearing within 3 years in 80% of patients. Its features are those described above. Type II is also seen in adults and differs from type I by a palmoplantar keratoderma with a coarse and lamellated scale, a more ichthyosiform scaling on the lower extremities, and occasional alopecia. Only 20% of type II patients experience clinical resolution within 3 years.

PRP types III–V are seen in children and adolescents. Type III, the classic juvenile form, represents 10% of cases; it most closely resembles the classic adult form and also typically clears within 3 years. Type IV (circumscribed) is the most common of the juvenile forms, and its focal nature sets it apart from the other clinical presentations. Type V, the atypical juvenile form, has features similar to adult type II disease with more ichthyosiform scaling and a chronic course. In addition, scleroderma-like changes of the fingers have been described. The rare patients with familial forms of PRP present with the atypical adult (type II) and atypical juvenile (type V) forms of the disease.

A type VI has been proposed for those with HIV infection who develop PRP[36]. This type is often recalcitrant to conventional therapy for PRP, but it may respond to antiretroviral therapy. Patients can also have nodulocystic lesions of acne conglobata and hidradenitis suppurativa as well as elongated follicular spines.

Pathology

Psoriasiform dermatitis with irregular hyperkeratosis and alternating vertical and horizontal ortho- and parakeratosis ("checkerboard pattern") is distinctive (Fig. 9.10A). The hair follicles are dilated and filled with a keratinous plug, while the "shoulder" of stratum corneum surrounding the follicular opening frequently shows parakeratosis (Fig. 9.10B). The interfollicular epidermis often exhibits hypergranulosis as well as thick, shortened rete pegs. A sparse lymphohistiocytic perivascular infiltrate is seen in the underlying dermis. Acantholysis and focal acantholytic dyskeratosis within the epidermis have been described. These latter features are claimed to be helpful when distinguishing PRP from psoriasis.

Differential Diagnosis

The major entity in the differential diagnosis is psoriasis. The distinctive orange–red palmoplantar keratoderma plus the keratotic follicular papules with a nutmeg grater appearance, the classic islands of sparing of the trunk, and no family history of psoriasis help differentiate PRP from psoriasis. The presence of oil-drop changes, small pits, and marginal onycholysis of the nails favor psoriasis. Microscopically, acantholysis and focal acantholytic dyskeratosis, if present, are especially useful in diagnosing PRP. A thickened granular cell layer, short thicker rete pegs, limited vascular dilation in the dermal papillae, and the absence of both neutrophilic migration towards the epidermis and Munro microabscesses further help distinguish PRP from psoriasis.

Early PRP of the scalp can mimic seborrheic dermatitis. As additional clinical features of PRP develop, these two entities can be distinguished. Furthermore, scalp dermatitis is much more responsive to conventional therapy. The relative recalcitrant nature of scalp PRP may serve as a clue to the diagnosis. A PRP-like eruption can be seen in patients with dermatomyositis (Wong type) and cutaneous T-cell lymphoma, as can erythema and scaling of the scalp. Children with acute-onset PRP may be misdiagnosed as having Kawasaki disease, and, occasionally, PRP is confused with progressive symmetric erythrokeratoderma. The various disorders that can present as an erythroderma are discussed in Chapter 10.

Treatment

Therapy for PRP is primarily empiric because a unifying etiology remains elusive and the number of patients required for large-scale, randomized trials is generally not available. Furthermore, it is difficult to assess treatment outcomes when the natural course of the disease

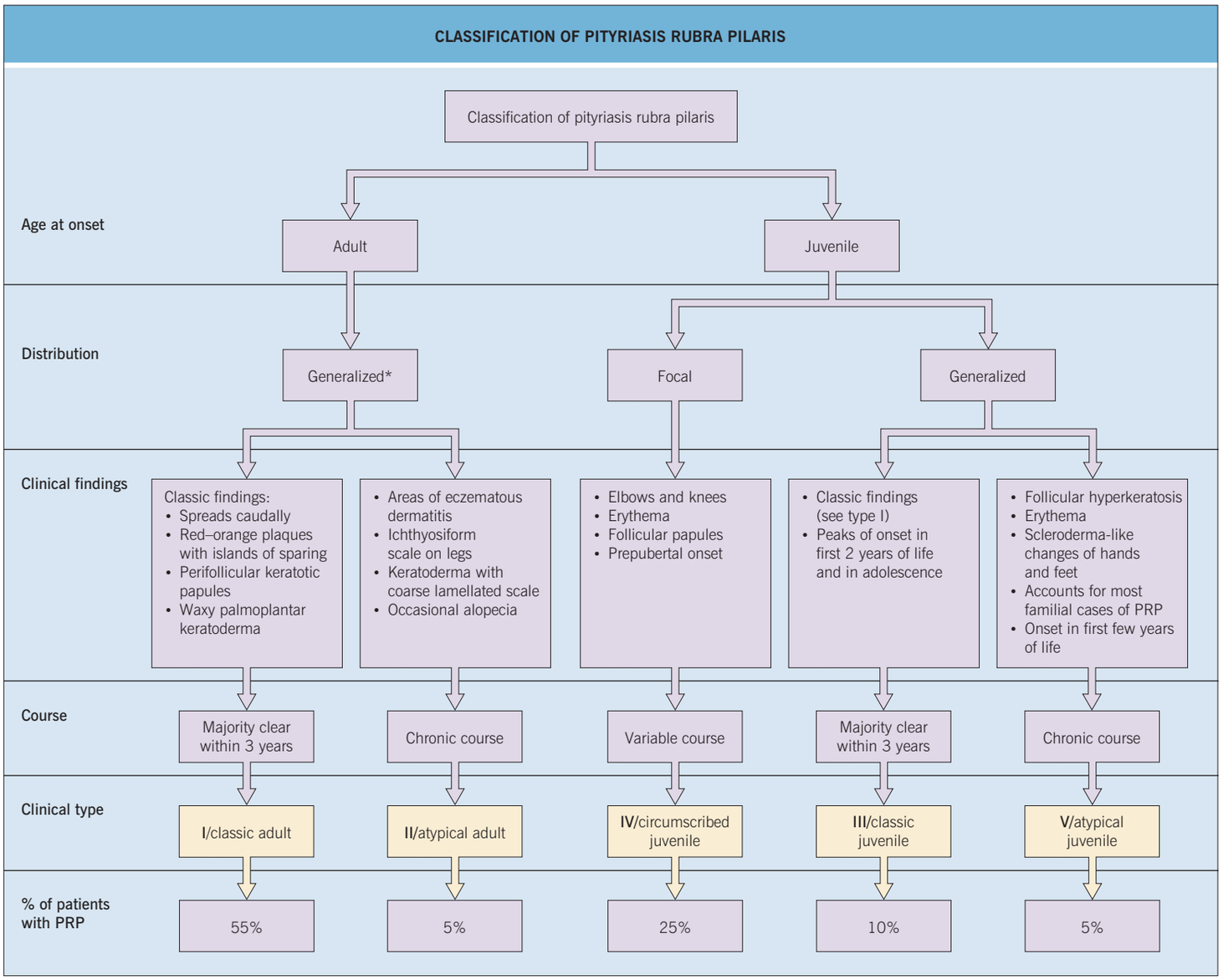


Fig. 9.9 Classification of pityriasis rubra pilaris (PRP). *A generalized distribution of PRP, often with findings similar to type I, may be seen in association with elongated follicular spines, acne conglobata and hidradenitis suppurativa in HIV-infected individuals; this is referred to as type VI PRP or the HIV-associated follicular syndrome.

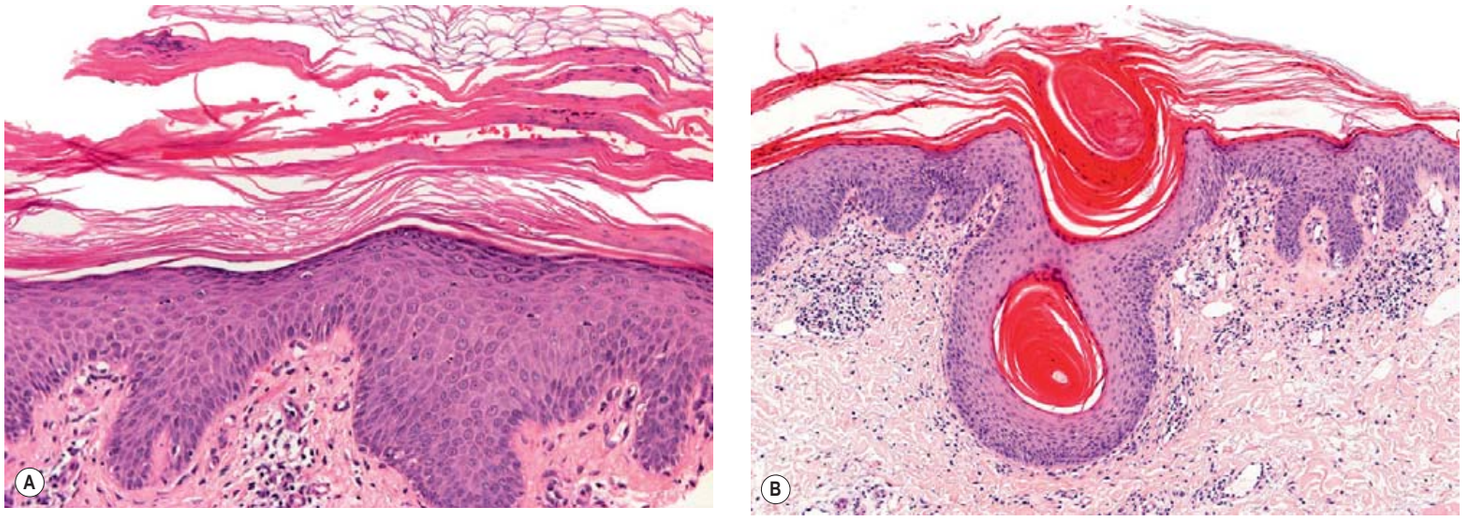


Fig. 9.10 Pityriasis rubra pilaris – histopathologic features. Psoriasiform dermatitis with alternating vertical and horizontal ortho- and parakeratosis ("checkerboard pattern") (**A**), as well as follicular hyperkeratosis with parakeratosis in the shoulders of the follicular plug (**B**). *Courtesy, Lorenzo Cerroni, MD.*

in many patients is spontaneous resolution. Regardless, PRP has been recognized as an acute cutaneous disorder for over 150 years, allowing for the collection of considerable therapeutic experience[40].

Initial reports of successful treatments for PRP involved oral vitamin A, sometimes in combination with vitamins B and D. However, toxic doses of vitamin A were often required and liver toxicity was a potential problem. Systemic retinoids have received considerable attention as a useful therapy. Isotretinoin, in doses of 1–1.5 mg/kg per day, can induce significant clearing within 3–6 months of instituting therapy. In a retrospective report of 30 PRP patients (19 years of age or younger) who were treated with oral isotretinoin, the greatest improvement was noted within 6 months, with a recurrence rate of 17% post discontinuation of the medication[41]. Higher doses (up to 2 mg/kg per day) are occasionally required. Acitretin is also beneficial in the treatment of PRP and there have been recent case reports of the successful use of alitretinoin[41a]. The effect of retinoids on familial PRP appears less certain.

Methotrexate has also been reported to lead to significant clinical improvement of PRP. Weekly oral doses of 10–25 mg are usually administered, and responses are seen within 3–6 months. Hepatotoxicity and myelosuppression are well-known potential side effects (see Ch. 130). When more toxic, but not yet proven to be more effective, regimens are used (e.g. methotrexate 5 days per week), severe myelosuppression, increased hepatotoxicity, and opportunistic infections such as *Pneumocystis jiroveci* pneumonia can be seen.

In severe cases of PRP, a combination of methotrexate (5–30 mg/week) plus a systemic retinoid (previously etretinate and now acitretin) has been utilized. Both agents can be given at the onset of therapy, or the second medication can be added if the response to the first is inadequate. In this situation, an increased risk for hepatotoxicity must be kept in mind.

There are reports and small case series in which TNF-α inhibitors and ustekinumab have led to improvement of PRP[42,42a]. Other potential therapies include topical retinoids, calcineurin inhibitors and vitamin D analogues as well as systemic immunosuppressives – azathioprine, corticosteroids, cyclosporine – and, in response to reports of decreased serum levels of retinol-binding proteins in patients with PRP, anabolic steroids. These medications have met with variable results. Although UV light therapy runs the risk of exacerbating the disease, there are some reports of success with narrowband UVB, UVA1 or PUVA in combination with an oral retinoid[43]; even one patient with UVB-provoked PRP reportedly responded to bath PUVA.

Less toxic regimens are recommended for the classic juvenile form of PRP, given the high likelihood of spontaneous remission and the potential long-term effects of aggressive systemic therapies.

PITYRIASIS ROSEA

Synonym: ■ Pityriasis rosea Gibert

Key features

- A self-limited papulosquamous eruption that is occasionally pruritic
- Seen primarily in adolescents and young adults, favoring the trunk and proximal extremities
- Individual lesions are usually oval in shape and their long axis is oriented along Langer's lines of cleavage
- Less common variants include inverse, vesicular, purpuric and pustular

Introduction

Pityriasis rosea is a common, "acute", self-limited papulosquamous eruption that favors otherwise healthy adolescents and young adults. Its striking appearance often prompts a request for medical evaluation. There is an absence of significant systemic manifestations, and its spontaneous resolution provides great consolation to the patient. Although the classic presentation is readily recognized, atypical forms may present a greater challenge. A viral etiology has been postulated, but this remains unproven.

History

Robert Willan described "roseola annulata" in 1798 as a self-limited eruption in otherwise healthy children. In 1860, the French physician Camille Melchior Gibert first named the condition pityriasis (scaly) rosea (pink)[44]. This aptly conveyed the clinical features and remains the name that is still used today.

Epidemiology

Most cases of pityriasis rosea occur in young healthy persons, the majority of whom are between the ages of 10 and 35 years[45]. Its peak incidence is during adolescence, and it is rarely diagnosed before the age of 2 years. There is no racial predilection and it is found worldwide. There is a slight female predominance, and some studies have even suggested a female : male ratio of 2 : 1. The typical eruption lasts 6 to 8 weeks, though exceptionally it can persist for 5 months or longer. Some authors report a modest seasonal variation with peaks in the spring and fall.

Pathogenesis

The precise cause of pityriasis rosea remains elusive, and a viral etiology is frequently proposed. Most recently, attention has focused on human herpesvirus-7 (HHV-7) and, less so, on HHV-6. However, some studies have shown no difference in the prevalence of DNA from HHV-6 or HHV-7 in peripheral blood mononuclear cells of patients with pityriasis rosea; attempts to identify HHV-7 DNA within cutaneous lesions have been unsuccessful[46]. Proponents of a viral etiology[47] point to the prodromal symptoms experienced by some patients, the clustering of cases, and the almost complete absence of recurrent episodes, suggesting an immunologic defense against an infectious agent.

Clinical Features

Although classic pityriasis rosea is usually easily recognized, the more unusual variants can be more challenging to diagnose. In the classic situation, a solitary lesion appears on the trunk and enlarges over several days. Less often, this initial lesion is seen on the neck or proximal extremities. It predates the remainder of the eruption by hours to days and is referred to as the "herald patch" because it heralds the onset of the disease. Its incidence varies from 12% to 94%, depending on the study, but in most series it has been seen in over 50% of cases. Multiple herald patches have also been reported.

The herald patch is a skin- to pink- to salmon-colored patch or plaque with a slightly raised advancing margin (Fig. 9.11). The size commonly varies from 2 to 4 cm, but it can be as small as 1 cm or as large as 10 cm. The center shows the characteristic small fine scales of pityriasis rosea, and the margin has a larger, more obvious trailing collarette of scale with the free edge pointing inwards. Approximately 5% of patients may experience a mild prodrome with headache, fever, arthralgias or general malaise. On occasion, the herald patch appears simultaneously with the more widespread eruption.

Fig. 9.11 Pityriasis rosea. Herald patch on the abdomen of an adolescent. *Courtesy, Kalman Watsky, MD.*

Fig. 9.12 Pityriasis rosea in darkly pigmented skin. Note the central hyperpigmentation and the follicular papules. *Courtesy, Aisha Sethi, MD.*

Fig. 9.13 Pityriasis rosea. A, B Both oval and round plaques can be seen as well as central fine scale or a collarette of scale. *B, Courtesy, Julie V Schaffer, MD.*

Fig. 9.14 Inverse pityriasis rosea. Oval annular plaques in the groin.

Typically, within the next few days, there is a blossoming of lesions on the trunk and proximal extremities. These numerous smaller thin papules and plaques are reminiscent of the larger herald patch that predated them; in darkly pigmented skin, the lesions tend to be more papular and hyperpigmented (Fig. 9.12). Again, there is a subtle advancing border, central fine scaling, and the characteristic collarette of scale (Fig. 9.13). The lesions are usually round to oval in shape, with their long axis following Langer's lines of cleavage (Fig. 9.14). On the posterior trunk, such an orientation leads to what is often referred to as a "fir tree" or "Christmas tree" pattern. Minute pustules can also be seen during this initial phase of pityriasis rosea. The face, palms and soles are usually (but not always) spared. When all these features are present, the diagnosis is easiest to establish. This is also the time when patients are most alarmed by their clinical appearance and are likely to seek medical attention.

The eruption of pityriasis rosea usually persists for 6–8 weeks and then spontaneously resolves; however, occasional patients have lesions that may last 5 months or longer. In the latter situation, the possibility of pityriasis lichenoides chronica arises. Most patients with pityriasis rosea experience few, if any, symptoms. In approximately 25% of patients, pruritus is noted that is mild to severe[48,49].

Atypical forms of pityriasis rosea require a more astute observer. Inverse pityriasis rosea involves the axillae and inguinal areas (see Fig. 9.14) and sometimes the face. It is more common in younger children and in those with darkly pigmented skin. Oral lesions are also uncommon, but they may be underreported. Urticarial, erythema multiforme-like, vesicular[50], pustular and purpuric variants have also been described.

Pathology

The microscopic features of pityriasis rosea are nonspecific. Small mounds of parakeratosis, spongiosis, and a mild lymphohistiocytic perivascular and interstitial papillary dermal infiltrate can be seen. There may be mild erythrocyte extravasation. In severe cases, these features are more pronounced, including the rare formation of epidermal pustules.

Most patients with pityriasis rosea do not have biopsies performed, because the clinical picture is quite characteristic and the histopathology relatively nonspecific.

Differential Diagnosis

Pityriasis rosea can sometimes be difficult to distinguish from secondary syphilis. The presence of cutaneous signs such as split papules and condyloma lata points to syphilis, as does the history or presence of a primary chancre. Patients with secondary syphilis usually have more systemic complaints, and they often have peripheral lymphadenopathy. Histologically, the absence of plasma cells favors pityriasis rosea and nowadays immunohistochemical staining for spirochetal antigens can be done (see Ch. 0). Serologic testing – e.g. Venereal Disease Research Laboratory (VDRL), fluorescent treponemal antibody absorbance (FTA-ABS) – allows the diagnosis of secondary syphilis to be confirmed.

There are drug eruptions that can mimic pityriasis rosea; they have been reported in patients receiving angiotensin-converting enzyme (ACE) inhibitors, metronidazole, isotretinoin, gold, arsenic, bismuth, imatinib and clonidine, as well as omeprazole, etanercept, tripelennamine, ketotifen, salvarsan and BCG vaccine. A drug-induced

pityriasis rosea-like eruption is often slower to resolve than the idiopathic form.

The herald patch or generalized eruption can resemble tinea corporis or nummular dermatitis. The presence of the collarette of scale, the orientation of the lesions, and the history can help distinguish pityriasis rosea from nummular dermatitis, but it can be difficult in the case of vesicular pityriasis rosea. Guttate psoriasis usually has a thicker scale, smaller size, and lacks the fir-tree distribution. Other papulosquamous disorders such as pityriasis lichenoides should also be considered, especially when lesions last longer than 4 months. Patients with the atypical variants of pityriasis rosea may overlap with a wider spectrum of diseases.

Treatment

Because pityriasis rosea is often asymptomatic and self-limited, patient education and reassurance represent a satisfactory treatment plan. In patients with pruritus, counterirritant antipruritic lotions or low- to medium-strength topical corticosteroids may be needed for symptomatic relief. In more severe cases, UVB phototherapy (broadband or narrowband) or natural sunlight exposure and oral antihistamines can be used. Rarely, a brief course of systemic corticosteroids may be required[51].

In a double-blind, placebo-controlled trial, 73% of patients had complete resolution after receiving 14 days of erythromycin in divided doses[52]. The placebo group showed no resolution over the same time period. In a bilateral comparison trial of UVB, a reduction in severity, but not pruritus or duration, was observed[53].

PITYRIASIS ROTUNDA

Synonyms: ■ Tinea circinata ■ Pityriasis circinata

Key features

- Asymptomatic dermatosis seen primarily in the Far East and Mediterranean basin and in individuals of African descent
- There are large circular and polycyclic scaly patches with sharp margins and no evidence of inflammation clinically
- In most patients, lesions are hyperpigmented and localized to the trunk and extremities
- Histologic features are similar to those of ichthyosis vulgaris, raising the possibility of an unusual form of ichthyosis
- In some patients it may be associated with malnutrition, mycobacterial infections and/or underlying malignancies, while in others it is familial

Introduction

Pityriasis rotunda has been associated with a number of unrelated conditions and in many patients is suspected to be due in part to malnutrition[54,55]. It is possible that malnutrition is a final common pathway for patients with underlying infectious diseases or malignancies. One proposal is that pityriasis rotunda represents a minor acquired ichthyosis that can be familial[56]. Nonetheless, it remains an unusual dermatosis, the pathogenesis of which has yet to be determined[57].

History

Pityriasis rotunda was first described by Toyama in 1906 as "tinea circinata" and was later named pityriasis rotunda by Matsura.

Epidemiology

Pityriasis rotunda is most commonly observed in adults between the ages of 25 and 45 years and has a slight female predominance[54–56,58]. It has been described in the Far East (Japan and China), the Mediterranean basin (Morocco, Italy and Israel), and in Africans, African-Americans, and Caribbean blacks in the UK.

Pathogenesis

No clear unifying cause has been identified. A pre-existing chronic disorder is often, but not invariably, found. Associations with malnutrition, mycobacterial diseases (tuberculosis and leprosy), malignancies (hepatocellular carcinoma, gastric carcinoma and multiple myeloma) and hepatic cirrhosis have been reported[54,55]. Although Caucasian patients with pityriasis rotunda are occasionally reported, they are generally in good health[55]. Some authors have suggested that pityriasis rotunda is a reflection of malnutrition in genetically susceptible patients with a possible underlying disorder. This hypothesis is supported by the observation that the lesions improve when the patient's nutritional status improves. In southern Italy, an association with glucose-6-phosphate dehydrogenase (G6PD) deficiency and favism has been reported[58].

Clinical Features

Pityriasis rotunda is typically asymptomatic, and it may be overlooked by the patient. It is characterized by large circular and polycyclic lesions that are often 10 cm (and may be up to 30 cm) in diameter. They have associated fine scale and are moderately hyperpigmented with a sharp margin and no inflammation. The trunk and extremities are favored. A hypopigmented halo has been described in some patients, and sometimes the entire lesion can be hypopigmented.

Grimalt proposed categorizing pityriasis rotunda into two groups[56]. Type I is said to occur primarily in blacks and Asians as hyperpigmented lesions, possibly in association with an internal malignancy but with no family history. Type II pityriasis rotunda is thought to occur more commonly in Caucasians and be characterized by numerous (>30) lesions; patients may have a family history of the disorder but no associated internal malignancy.

Pathology

Pityriasis rotunda has microscopic features of ichthyosis vulgaris. There is an absent or diminished granular cell layer with moderate hyperkeratosis without parakeratosis. There may be increased pigmentation of the basal cell layer, and epidermal atrophy can be seen along with areas of pigment incontinence, a minimal perivascular lymphohistiocytic infiltrate, and occasional follicular plugging[54]. Special stains for fungi are negative.

Differential Diagnosis

The differential diagnosis includes tinea corporis, tinea versicolor, leprosy and large plaque parapsoriasis. It lacks the pruritus and inflammation of dermatitis, and there is no associated anesthesia or peripheral nerve thickening. The combination of a potassium hydroxide examination, fungal culture and routine histology excludes major entities in the differential diagnosis. Of note, mycobacteria have never been isolated. Because of the large size of the lesions, the hypopigmented variant of pityriasis rotunda can resemble one form of progressive macular hypomelanosis; however, the latter has no associated scale and it lacks the histologic features of ichthyosis vulgaris.

Treatment

Pityriasis rotunda is relatively difficult to treat. Trials with topical lactic acid, urea, tars, emollients and corticosteroids have provided little benefit. Topical tretinoin cream 0.1% can result in modest improvement and systemic retinoids warrant consideration for patients with more extensive disease. However, reversal of any underlying disorder – in particular, malnutrition, infection or malignancy – should be addressed first.

GRANULAR PARAKERATOSIS

Synonyms: ■ Axillary granular parakeratosis ■ Intertriginous granular parakeratosis

Key features

- The primary lesions are brownish-red keratotic papules that can coalesce into plaques
- The adult form occurs almost exclusively in women
- In most adult cases, lesions are localized to the axillae, but other intertriginous sites can be affected
- The infantile form is associated with diaper wearing and presents as bilateral plaques in the inguinal folds or erythematous geometric plaques underlying pressure points from the diaper
- Histopathologically, there is distinct retention of basophilic keratohyaline granules within areas of parakeratosis in the stratum corneum
- A defect in processing profilaggrin to filaggrin is a proposed mechanism

Introduction

Granular parakeratosis is typically a pruritic disorder, initially reported to occur only in the axillae. It is now recognized that other intertriginous sites (i.e. the groin, inframammary and abdominal folds) can also be involved[59–61]. An underlying disorder in keratinization has been suggested that may explain its distinct histopathologic findings[62].

History

Northcutt and colleagues[59] first described granular parakeratosis in 1991. Mehregan et al. proposed renaming this condition "intertriginous granular parakeratosis" to reflect its localization to these areas.

Epidemiology

Granular parakeratosis is observed most commonly in adult women[59–61]. It affects middle-aged or older adults, and it has been reported in both darkly pigmented and lightly pigmented individuals. Although it is an unusual condition in young adults[62], there is an infantile form in which diaper-wearing plays a role[63].

Pathogenesis

Granular parakeratosis is thought to be an acquired keratotic dermatosis that was initially linked to the use of personal hygiene products. These included deodorants and antiperspirants in roll-on or stick form, as well as creams and soaps used in excess and/or in a susceptible individual[59–62]. However, patients without a known irritant have also been reported[62]. The mechanism that underlies the role of diapers is also unknown.

A disorder of keratinization characterized by a basic defect in the processing of profilaggrin to filaggrin has been proposed. Based on ultrastructural and immunohistochemical studies, Metze and Rutten[62] came to the same conclusion as Northcutt et al.[59] that the retention of keratohyalin granules within the stratum corneum could be due to a defect in filaggrin metabolism. In this model, there is a failure to degrade keratohyalin granules and to aggregate keratin filaments during cornification.

Clinical Features

The primary lesions are keratotic brownish-red papules that can have a conical shape. They can coalesce into larger well-demarcated plaques with various degrees of maceration secondary to local occlusion (Fig. 9.15). Lesions can persist for months or longer and recur. Pruritus is the most common complaint, but irritation is also a problem if there are erosions or fissures. Some patients experience a flare with an increase in ambient temperature and sweating. The axillae are the most common sites of involvement, with both unilateral and bilateral lesions having been described. Additional intertriginous areas such as the groin and inframammary fold may be affected.

In the infantile form, there may be bilateral plaques in the inguinal folds or erythematous geometric plaques underlying pressure points from the diaper.

Pathology

The characteristic feature is an unusual form of parakeratosis. The stratum corneum is thickened and compacted with increased eosinophilic staining (Fig. 9.16). Retained nuclei are present throughout this keratin layer, creating the parakeratosis. The most unusual feature is the visible retention of basophilic keratohyalin granules within these areas of parakeratosis[64].

Fig. 9.15 Granular parakeratosis. Brownish-red papules with coalescence into a keratotic plaque in the axilla. *Courtesy, David Mehregan, MD.*

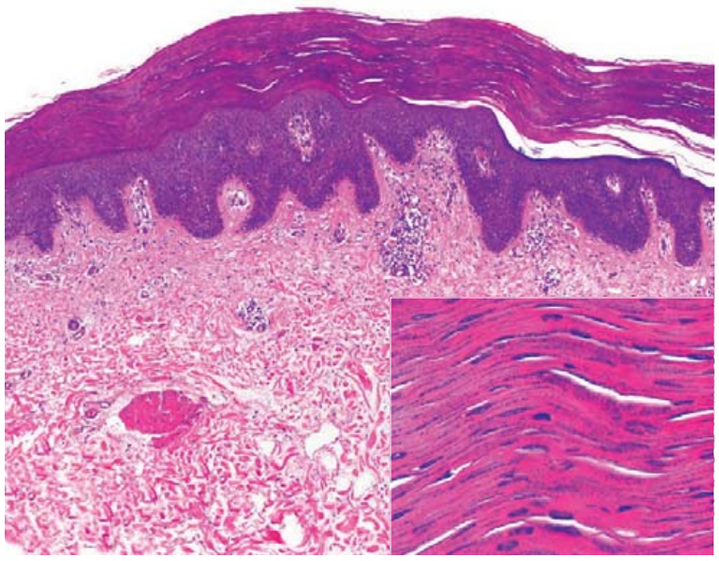


Fig. 9.16 Axillary granular parakeratosis. Marked, compact parakeratosis with small bluish granules within the stratum corneum representing keratohyaline granules (insert). *Courtesy, Luis Requena, MD.*

Differential Diagnosis

The differential diagnosis includes the most common causes of intertrigo (e.g. seborrheic dermatitis, candidiasis, inverse psoriasis, erythrasma) and Hailey–Hailey disease, Darier disease and pemphigus vegetans[59–62]. Sometimes the papules may be confused with seborrheic keratoses and the plaques with acanthosis nigricans. Irritant or allergic contact dermatitis also needs to be considered in some patients. A biopsy will confirm the diagnosis of granular parakeratosis.

Treatment

Based upon case reports and small series, therapeutic success has been reported with topical corticosteroids, vitamin D analogues, retinoids, ammonium lactate and antifungals[59–62]. In addition, cryotherapy as well as oral isotretinoin and oral antifungals have been used. Spontaneous resolution has also been observed (including in infants), as have relapses.

REFERENCES

1. Lambert WC, Everett MA. The nosology of parapsoriasis. J Am Acad Dermatol. 1981;5:373–95.
2. Brocq L. Les parapsoriasis. Ann Dermatol Syph. 1902;3: 433–68.
3. Hu C-H, Winkelmann RK. Digitate dermatosis. A new look at symmetrical, small plaque parapsoriasis. Arch Dermatol. 1973;107:65–9.
4. Sánchez JL, Ackerman AB. The patch stage of mycosis fungoides. Am J Dermatopathol. 1979;1:5–26.
5. Lindae ML, Abel EA, Hoppe RT, Wood GS. Poikilodermatous mycosis fungoides and atrophic large-plaque parapsoriasis exhibit similar abnormalities of T-cell antigen expression. Arch Dermatol. 1988;124: 366–72.
6. Haeffner AC, Smoller BR, Zepter K, Wood GS. The differentiation and clonality of lesional lymphocytes in small plaque parapsoriasis. Arch Dermatol. 1995;131: 321–4.
7. Wood GS, Tung RM, Haeffner AC, et al. Detection of clonal T-cell receptor γ gene rearrangements in early mycosis fungoides/Sézary syndrome by polymerase chain reaction and denaturing gradient gel electrophoresis (PCR/DGGE). J Invest Dermatol. 1994; 103:34–41.
8. Klemke CD, Dippel E, Dembinski A, et al. Clonal T cell receptor gamma-chain gene rearrangement by PCR-based GeneScan analysis in the skin and blood of patients with parapsoriasis and early-stage mycosis fungoides. J Pathol. 2002;197:348–54.
9. Quéreux G, André-Garnier E, Knol AC, et al. Evaluation of the role of human herpes virus 6 and 8 in parapsoriasis. Exp Dermatol. 2009;18:357–61.
10. Lazar AP, Caro WA, Roenigk HH, Pinski KS. Parapsoriasis and mycosis fungoides: the Northwestern University experience, 1970 to 1985. J Am Acad Dermatol. 1989; 21:919–23.
11. Vakeva L, Sarna S, Vaalasti A, et al. A retrospective study of the probability of the evolution of parapsoriasis en plaques into mycosis fungoides. Acta Derm Venereol. 2005;85:318–23.
12. Siddiqui J, Hardman DL, Misra M, Wood GS. Clonal dermatitis: a potential precursor of CTCL with varied clinical manifestations. J Invest Dermatol. 1997; 108:584.
13. Yamanaka K, Clark R, Rich B, et al. Skin-derived interleukin-7 contributes to the proliferation of lymphocytes in cutaneous T-cell lymphoma. Blood. 2006;107:2440–5.
14. Samman PD. The natural history of parapsoriasis en plaques (chronic superficial dermatitis) and prereticulotic poikiloderma. Br J Dermatol. 1972; 87:405–11.
15. Rook AH, Wood GS, Yoo EK, et al. Interleukin-12 therapy of cutaneous T-cell lymphoma induces lesion regression and cytotoxic T-cell responses. Blood. 1999;94:902–8.
16. Bowers S, Warshaw EM. Pityriasis lichenoides and its subtypes. J Am Acad Dermatol. 2006;55:557–72.
17. Ersoy-Evans S, Greco MF, Mancini AJ, et al. Pityriasis lichenoides in childhood: a retrospective review of 124 patients. J Am Acad Dermatol. 2007;56:205–10.
18. Mucha V. Über einen der Parakeratosis variegata (Unna) bzw: Pityriasis lichenoides chronica (Neisser-Juliusberg) nahestehenden eigentumlichen Fall. Arch Dermatol Syph. 1916;123:586–92.
19. Habermann R. Über die akut vereaufende, Nekrotisierende unterart der Pityriasis lichenoides (pityriasis lichenoides et varioliformis acuta). Dermatol Z. 1925;45:42–8.
20. Juliusberg F. Über die Pityriasis lichenoides chronica (psoriasiform lichenoides exanthem). Arch Dermatol Syph. 1899;50:359–74.
21. Wood GS, Strickler JG, Abel EA, et al. Immunohistology of pityriasis lichenoides et varioliformis acuta and pityriasis lichenoides chronica. Evidence for their interrelationship with lymphomatoid papulosis. J Am Acad Dermatol. 1987;16:559–70.
22. Muhlbauer JE, Bhan AK, Harrist TJ, et al. Immunopathology of pityriasis lichenoides acuta. J Am Acad Dermatol. 1984;10:783–95.
23. Weiss LM, Wood GS, Ellisen LW, et al. Clonal T-cell populations in pityriasis lichenoides et varioliformis acuta (Mucha-Habermann disease). Am J Pathol. 1987; 126:417–21.
24. Shieh S, Mikkola DL, Wood GS. Differentiation and clonality of lesional lymphocytes in pityriasis lichenoides chronica. Arch Dermatol. 2001;137:305–8.
25. Dereure O, Levi E, Kadin ME. T-cell clonality in pityriasis lichenoides et varioliformis acuta: a heteroduplex analysis of 20 cases. Arch Dermatol. 2000;136:1483–6.
26. Black MM. Lymphomatoid papulosis and pityriasis lichenoides: are they related? Br J Dermatol. 1982;106: 717–21.
27. Samman PD. Poikiloderma with pityriasis lichenoides. Trans St John's Hosp Dermatol Soc. 1971;57:143–7.
28. Rivers JK, Samman PD, Spittle MF, et al. Pityriasis lichenoides-like lesions associated with poikiloderma: a precursor of mycosis fungoides. Br J Dermatol. 1986; 115:17.
29. Fortson JS, Schroeter AL, Esterly NB. Cutaneous T-cell lymphoma (parapsoriasis en plaque). An association with pityriasis lichenoides et varioliformis acuta in young children. Arch Dermatol. 1990;126:1449–53.
30. Panizzon RG, Speich R, Dazzi H. Atypical manifestations of pityriasis lichenoides chronica: development into paraneoplasia and non-Hodgkin lymphomas of the skin. Dermatology. 1992;184:65–9.
31. Sotiriou E, Patsatsi A, Tsorova C. Febrile ulceronecrotic Mucha-Habermann disease: a case report and review of the literature. Acta Derm Venereol. 2008;88:350–5.
32. Glemetti C, Rigoni C, Alessi E, et al. Pityriasis lichenoides in children: a long-term follow-up of eighty-nine cases. J Am Acad Dermatol. 1990;23:473–8.
33. Devergie A. Pityriasis pilaris. Traite pratique des maladies de la peau, 2nd edn. Paris: Martinet, 1857:454–64.
34. Besnier E. Du pityriasis rubra pilaire. Ann Dermatol Syphiligr Paris. 1889;10:253–87.
35. Albert MR, Mackool BT. Pityriasis rubra pilaris. Int J Dermatol. 1999;38:1–11.
36. Miralles ES, Nunez M, De Las Heras ME, et al. Pityriasis rubra pilaris and human immunodeficiency virus infection. Br J Dermatol. 1995;133:990–3.
37. Batchelor RJ, Yung A, Merchant W, Goodfield MJ. Pityriasis rubra pilaris as the initial presentation of renal cell carcinoma? Clin Exp Dermatol. 2005;30:442–3.
38. Sehgal VN, Bajaj P, Jain S. Pityriasis rubra pilaris: report of four cases. J Dermatol. 2000;27:174–7.
39. Griffiths WAD. Pityriasis rubra pilaris. Clin Exp Dermatol. 1980;5:105–12.
40. Dicken CH. Treatment of classic pityriasis rubra pilaris. J Am Acad Dermatol. 1994;31:997–9.
41. Allison DS, El-Azhary RA, Calobrisi SD, Dicken CH. Pityriasis rubra pilaris in children. J Am Acad Dermatol. 2002;47:386–9.

41a. Molin S, Ruzicka T. Treatment of refractory pityriasis rubra pilaris with oral alitretinoin: case report. Br J Dermatol. 2010;163:221–3.

42. Muller H, Gattringer C, Zelger B, et al. Infliximab monotherapy as first-line treatment for adult-onset pityriasis rubra pilaris: case report and review of the literature on biologic therapy. J Am Acad Dermatol. 2008;59:S65–7.

42a. Wohlrab J, Kreft B. Treatment of pityriasis rubra pilaris with ustekinumab. Br J Dermatol. 2010;163:655–6.

43. Kirby B, Watson R. Pityriasis rubra pilaris treated with acitretin and narrow-band ultraviolet B (Re-TL-01). Br J Dermatol. 2000;142:376–7.
44. Gibert CM. Traite pratique des maladies de la peau et de la syphilis, 3rd edn. Paris: H Plon, 1860:402.
45. Chuang T, Ilstrup DM, Perry HO, Kurland LT. Pityriasis rosea in Rochester, Minnesota, 1969 to 1978: a 10-year epidemiologic study. J Am Acad Dermatol. 1982;7:80–9.
46. Kempf W, Adams V, Kleinhans M, et al. Pityriasis rosea is not associated with human herpesvirus 7. Arch Dermatol. 1999;135:1070–2.
47. Drago F, Broccolo F, Rebora A. Pityriasis rosea: an update with a critical appraisal of its possible herpesviral etiology. J Am Acad Dermatol. 2009;61:303–18.
48. Hartley AH. Pityriasis rosea. Pediatr Rev. 1999;20:266–9.
49. Allen RA, Janniger CK, Schwartz RA. Pityriasis rosea. Cutis. 1995;56:198–202.
50. Balci DD, Hakverdi S. Vesicular pityriasis rosea: an atypical presentation. Dermatol Online J. 2008;14:6.
51. Drago F, Rebora A. Treatment for pityriasis rosea. Skin Therapy Lett. 2009;14:6–7.
52. Sharma PK, Yadav TP, Gautam PK, et al. Erythromycin in pityriasis rosea: a double-blind, placebo-controlled clinical trial. J Am Acad Dermatol. 2000;42:241–4.
53. Leenutaphong V, Jiamton S. UVB phototherapy for pityriasis rosea: a bilateral comparison study. J Am Acad Dermatol. 1995;33:996–9.
54. Pinto GM, Tapadinhas C, Moura C, Afonso A. Pityriasis rotunda. Cutis. 1996;58:406–8.
55. Swift PJ, Saxe N. Pityriasis rotunda in South Africa: a skin disease caused by undernutrition. Clin Exp Dermatol. 1985;10:407–12.
56. Grimalt R, Gelmetti C, Brusasco A. Pityriasis rotunda: report of a familial occurrence and review of the literature. J Am Acad Dermatol. 1994;31:866–71.
57. Gupta S. Pityriasis rotunda mimicking tinea cruris/ corporis and erythrasma in an Indian patient. J Dermatol. 2001;28:50–3.
58. Lodi A, Betti R, Chiarelli G, et al. Familial pityriasis rotunda. Int J Dermatol. 1990;29:483–5.
59. Northcutt AD, Nelson DM, Tschen JA. Axillary granular parakeratosis. J Am Acad Dermatol. 1991;24:541–4.
60. Mehregan DA, Vandersteen P, Sikorski L, Mehregan DR. Axillary granular parakeratosis. J Am Acad Dermatol. 1995;33:373–5.
61. Webster CG, Resnik KS, Webster GF. Axillary granular parakeratosis: response to isotretinoin. J Am Acad Dermatol. 1997;37:789–90.
62. Metze D, Rutten A. Granular parakeratosis: a unique acquired disorder of keratinization. J Cutan Pathol. 1999;26:339–52.
63. Chang MW, Kaufmann JM, Orlow SJ, et al. Infantile granular parakeratosis: recognition of two clinical patterns. J Am Acad Dermatol. 2004;50(5 suppl.):S93–6.
64. Scheinfeld NS, Mones J. Granular parakeratosis: pathologic and clinical correlation of 18 cases of granular parakeratosis. J Am Acad Dermatol. 2005; 52:863–7.

This page intentionally left blank

Pityriasis rubra pilaris. Diffuse erythroderma with desquamation and follicular hyperkeratosis on the knee.

Pityriasis rosea in darkly pigmented skin. It tends to be more papular than that in lightly pigmented skin. Note the associated hyperpigmentation.

Erythroderma 10

Wolfram Sterry and Matthias Steinhoff

Synonyms: ■ Exfoliative dermatitis ■ Exfoliative erythroderma ■ Red man syndrome

Key features

- Erythroderma is defined clinically as generalized redness and scaling of the skin
- Systemic manifestations include peripheral edema, tachycardia, loss of fluid and proteins, and disturbances in thermoregulation
- Erythroderma has multiple etiologies; the most common causes are psoriasis, drug reactions, atopic dermatitis and cutaneous T-cell lymphoma (CTCL)
- Establishing the correct diagnosis requires consideration of initial sites of involvement, additional clinical findings, histologic and molecular features, and associated systemic abnormalities, as well as a complete medical history
- Despite an intensive evaluation, the cause remains unknown (idiopathic) in 25–30% of patients; some of these patients eventually develop CTCL
- Treatment strategies should address the dermatologic disease as well as the underlying etiology and the systemic complications of the erythroderma

INTRODUCTION

Erythroderma is defined as a generalized redness and scaling of the skin. However, it does not represent a defined entity, as it is the clinical presentation of a variety of diseases. Most commonly, erythroderma is due to generalization of pre-existing dermatoses (such as psoriasis or atopic dermatitis), drug reactions or cutaneous T-cell lymphoma (CTCL). Although up to 50% of the patients have a history of more localized skin lesions prior to the onset of the erythroderma, identification of the underlying disease process represents one of the most complex challenges in dermatology. Sustained efforts during longitudinal evaluation may lead to the precise identification of the etiology. In approximately one-quarter of the patients, no specific etiology is found, and these cases are called "idiopathic erythroderma".

Attention should also be focused on the potential systemic complications of erythroderma. Hypothermia, peripheral edema, and loss of fluid, electrolytes and albumin with subsequent tachycardia and cardiac failure are a serious threat to the erythrodermic patient. In addition, long-lasting erythrodermas may be accompanied by cachexia, diffuse alopecia, palmoplantar keratoderma, nail dystrophy and ectropion.

HISTORY

The term "erythroderma" was introduced in 1868 by Hebra to describe an exfoliative dermatitis involving more than 90% of the skin surface. Based upon the clinical course, erythroderma was classified into chronically relapsing (Wilson–Brocq), chronically persisting (Hebra), and self-limiting epidemic (Savill) variants. However, these subdivisions are no longer employed.

EPIDEMIOLOGY

No precise data exist regarding the prevalence or incidence of erythroderma as most reports are retrospective and do not address the issue of overall incidence. Large series of patients have focused on male-to-female ratios, average age, and underlying diseases[1–6]. Men are more commonly affected (male-to-female ratio from approximately 2:1 to 4:1). An even higher ratio can be found in the subset of idiopathic erythroderma, also referred to as "red man syndrome" (not to be confused with the cutaneous reaction to rapid infusion of vancomycin). The average age at onset of erythroderma was 52 years, with an average of 48 years in series including children, and 60 years in those excluding them[1,3,4,6].

Of a total of 746 patients, dermatitis (24%), psoriasis (20%), drug reactions (19%) and CTCL (8%) represented the most common underlying causes of erythroderma[1,3,4,6]. When categories within the dermatitis group were examined, atopic dermatitis (9%) was the most common type, followed by contact dermatitis (6%), seborrheic dermatitis (4%) and chronic actinic dermatitis (3%).

For adults, unusual causes include ichthyoses, bullous dermatoses (usually pemphigus foliaceus), pityriasis rubra pilaris, Ofuji's papuloerythroderma, and systemic lupus erythematosus (Table 10.1). Despite multiple skin biopsies, an in-depth clinical investigation and a detailed medical history, the underlying cause of erythroderma is not found in at least 25% of patients.

With regard to infants and neonates, ichthyoses, immunodeficiencies, dermatitides, psoriasis, and consequences of infection (e.g. staphylococcal scalded skin syndrome) represent the major causes of erythroderma (Table 10.2)[7]. In addition, the possibility of drug-induced erythroderma needs to be considered.

PATHOGENESIS

The pathogenetic mechanisms of the underlying diseases will be discussed in the respective chapters. The pathways involved in the *de novo* genesis of erythroderma or the generalization of pre-existing skin lesions are not well understood. The number of germinative cells as well as their mitotic rate is increased in erythrodermic skin, and the transit time of cells through the epidermis is shortened. Consequently, scales consist of material normally retained by the skin (nucleic acids, amino acids, soluble protein), and the daily loss of scales increases from 500–1000 mg to 20–30 g[8]. In acute erythroderma, the lost material usually has marginal metabolic significance.

CLINICAL FEATURES

Cutaneous Manifestations

Erythroderma is defined clinically by the presence of erythema and scaling involving more than 90% of the skin surface. Based upon its natural history, erythroderma can be classified into primary or secondary types. In the primary form, the erythema (often initially on the trunk) extends within a few days or weeks to involve the entire skin surface, and this is followed by scaling (Fig. 10.1). The secondary form of erythroderma is defined as a generalization of a preceding localized skin disease – for example, psoriasis or atopic dermatitis.

With the exception of very slowly progressing secondary erythroderma, erythema precedes the development of exfoliation by 2–6 days. The associated scaling varies extensively in size and color depending upon the stage of the erythroderma and nature of the underlying disease. In more acute phases, scales are usually large and crusted,

CAUSES OF ERYTHRODERMA IN ADULTS			
Underlying disease	**Clinical clues**	**Histologic clues**	**Additional hints**
		COMMON	
Psoriasis (Ch. 8)	• Pre-existing psoriatic plaques • Often spares the face • Nail changes (oil-drop, pits, onycholysis) • Subcorneal pustules • Inflammatory arthritis	• Confluent parakeratosis • Bottleneck-like rete ridges • Tortuous vessels in papillary dermis • Neutrophils within epidermis • Often reduced granular layer	• Personal or family history of psoriasis • Withdrawal of corticosteroids, methotrexate or cyclosporine (also efalizumab prior to its removal from the market)
Atopic dermatitis (Ch. 12)	• Pre-existing lesions (flexures) • Severe pruritus • Lichenification, including eyelids • Prurigo nodularis	• Mild to moderate acanthosis • Variable spongiosis • Dermal eosinophils • Parakeratosis	• Elevated serum IgE, eosinophilia • Personal or family history of atopy (e.g. asthma, allergic rhinitis) • Cataracts
Drug reactions (Ch. 21)	• Preceded by morbilliform or scarlatiniform exanthem • Facial edema • In dependent areas, may become purpuric	• Perivascular infiltrate with eosinophils • Lichenoid infiltrate • Necrotic keratinocytes at all levels of epidermis • Vacuolar degeneration of basal layer	• No history of skin diseases • Usually resolves within 2–6 weeks after withdrawal of responsible drug; possible exception is DIHS/DRESS
Idiopathic erythroderma	• Elderly men • Chronic, relapsing • Severe pruritus • Palmoplantar keratoderma • Dermatopathic lymphadenopathy	• Nonspecific	• Consider less commonly associated drugs (see Table 10.3) • Continue to re-evaluate for cutaneous T-cell lymphoma
		LESS COMMON	
Cutaneous T-cell lymphoma (Ch. 120)	• Sézary syndrome more common than erythrodermic mycosis fungoides • Intense pruritus • Deep purple–red hue • Painful, fissured keratoderma • Alopecia • Leonine facies	• Nuclear atypia in lymphocytes • Clustering of atypical cells within epidermis • Often lichenoid infiltrate	• Elevated $CD4^+$:$CD8^+$ ratio (blood), with ≥10:1 ratio seen in Sézary syndrome • Detection of clonal T-cell population in skin (and blood) • In Sézary syndrome: ≥1000 Sézary cells/mm^3; ≥40% $CD4^+/CD7^-$; or ≥30% $CD4^+/CD26^-$ (blood)
Pityriasis rubra pilaris (Ch. 9)	• Salmon-colored erythema • Islands of sparing (nappes claires) • Waxy keratoderma • Perifollicular keratotic papules	• Psoriasiform epidermal hyperplasia • Alternating parakeratosis and orthokeratosis, both vertically and horizontally • Follicular plugs with "shoulder parakeratosis"	• Flare after sun exposure • Cephalocaudal progression • Appearance of erythema gyratum-like lesions as erythroderma improves
Dermatitis (non-atopic), including contact (Chs 14 & 15) and stasis with autosensitization (Ch. 13)	• Pre-existing localized disease • Distribution of initial lesions	• Variable spongiosis	• Occupation and hobbies • Patch testing • Review oral medications (systemic contact dermatitis)
Paraneoplastic erythroderma	• Fine scaling • Melanoerythroderma • Cachexia	• Nonspecific changes	• Lymphoproliferative disorders, including other types of T-cell lymphoma • In the case of solid-organ malignancies, usually late stage
		BULLOUS DERMATOSES (CHS 29 & 30)	
Pemphigus foliaceus	• Pre-existing lesions, often on upper trunk • Impetigo-like erosions and vesicles • Moist scale-crust; cornflake scale	• Acantholysis, superficial epidermis • DIF, intercellular IgG	• IIF, intercellular
Bullous pemphigoid	• Urticarial plaques • Tense bulla • Elderly patients	• Subepidermal blister • Eosinophils • DIF, BMZ C3 and IgG	• IIF, BMZ
Paraneoplastic pemphigus	• Mucosal erosions and hemorrhagic crusts • Erythema multiforme-like lesions • Mucocutaneous lichenoid lesions	• Interface dermatitis with necrotic keratinocytes • Focal acantholysis • DIF, intercellular and BMZ IgG	• IIF, intercellular and BMZ (+ IIF rat bladder)
Congenital ichthyoses (Ch. 57)	• Present from birth or early infancy (see Table 10.2)	• See Table 10.2	• See Table 10.2
		RARE	
Papuloerythroderma of Ofuji	• Widespread, pruritic, flat-topped red–brown papules that can become confluent • Sparing of skin folds ("deck-chair" sign) • Favors elderly men	• Dense perivascular infiltrate of lymphocytes and eosinophils in the upper to mid dermis	• Multiple etiologies, including atopy, lymphomas (esp. CTCL), drugs (e.g. DDI, aspirin), infections (e.g. HIV, hepatitis C) • May have peripheral eosinophilia, lymphopenia

Table 10.1 Causes of erythroderma in adults. BMZ, basement membrane zone; DDI, dideoxyinosine; DIF, direct immunofluorescence; DIHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms; IIF, indirect immunofluorescence.

Continued

CAUSES OF ERYTHRODERMA IN ADULTS			
Underlying disease	**Clinical clues**	**Histologic clues**	**Additional hints**
Chronic actinic dermatitis (Ch. 87)	• Initial lesions in photodistribution	• Lichenoid infiltrate of lymphocytes and exocytosis • Possible lymphocyte nuclear pleomorphism	• Drug history • UVA, UVB and visible light phototesting • Photopatch testing
OTHER RARE CAUSES			
• Hypereosinophilic syndrome (Ch. 25) • Crusted (Norwegian) scabies (Ch. 84) • Lichen planus • GVHD (Ch. 52) • Autoimmune connective tissue disease (e.g. acute or subacute cutaneous lupus erythematosus, juvenile dermatomyositis [adolescents])		• Dermatophyte infection • Primary immunodeficiencies (Ch. 60) • Sarcoidosis • Mastocytosis • Hemophagocytic lymphohistiocytosis • T-cell leukemia	

Table 10.1 Causes of erythroderma in adults (cont'd).

CAUSES OF ERYTHRODERMA IN NEONATES AND INFANTS			
Underlying disease	**Clinical clues**	**Histologic clues**	**Additional findings**
INHERITED ICHTHYOSES (CH. 57)¶			
Epidermolytic ichthyosis (previously referred to as bullous congenital ichthyosiform erythroderma)	• Formation of superficial blisters and erosions during the first days of life • Later, corrugated hyperkeratosis in flexural areas	• Classic epidermolytic hyperkeratosis	• Mutations in *KRT1* and *KRT10*, which encode keratins 1 and 10
Congenital ichthyosiform erythroderma (previously referred to as non-bullous congenital ichthyosiform erythroderma)	• Collodion baby • Generalized scaling involving flexures • Cicatricial alopecia, nail dystrophy (subungual hyperkeratosis, ridging), rapid nail growth • Ectropion	• Non-diagnostic	• Mutations in *TGM1* (encodes transglutaminase 1), *ALOXE3* (lipoxygenase 3), *ALOX12B* (12[R] lipoxygenase), *NIPAL4* (ichthyin), *ABCA12**, and *CYP4F22**
Netherton syndrome	• Atopic-like dermatitis • Food allergies • Immune deficiency • Erythroderma in neonates • Erythroderma may persist or ichthyosis linearis circumflexa develops • Examine eyebrows and eyelashes as well as scalp hairs for trichorrhexis invaginata ("bamboo hair") • Failure to thrive	• Routine histology – non-diagnostic • LEKT1 antibody	• By electron microscopy: premature secretion and abnormal lamellar bodies • Elevated serum IgE levels • Mutations in *SPINK5* (encodes serine peptidase inhibitor, Kazal type 5)
Conradi–Hünermann–Happle syndrome (X-linked dominant chondrodysplasia punctata)	• Linear and swirled pattern • Skeletal (chondrodysplasia punctata) and ocular anomalies (cataracts)	• Hyperkeratosis, reduced granular layer, follicular plugging	• Mutations in *EBP* at Xp11 (encodes emopamil binding protein [sterol isomerase])
IMMUNODEFICIENCIES (CH. 60)			
Omenn syndrome	• Onset in neonatal period • Exfoliative erythroderma with diffuse alopecia • Lymphadenopathy and hepatosplenomegaly • Recurrent infections • Diarrhea	• Necrosis of keratinocytes • Dense dermal infiltrate (predominantly T cells) • Acanthosis, parakeratosis	• Leukocytosis, eosinophilia • Hypogammaglobulinemia • Elevated serum IgE levels • Lymph nodes: disruption of germinal centers and abundant $S100^+$ interdigitating reticulum cells • Mutations in *RAG1* and *RAG2* (see Ch. 60)
Other forms of SCID†, agammaglobulinemia, complement deficiencies (e.g. C3, C5)	• "Leiner phenotype" of exfoliative dermatitis, chronic diarrhea and recurrent infections	• Non-diagnostic	• See Ch. 60
Wiskott–Aldrich syndrome	• Primarily affects boys • Petechiae, ecchymoses • Atopic-like dermatitis • Recurrent sinopulmonary infections	• Non-diagnostic	• Microthrombocytopenia • Lymphopenia, eosinophilia • Elevated serum IgE levels • Mutations in *WAS*

**ABCA12* and *CYP4F22* encode ATP-binding cassette (ABC), sub-family A, member 12 and cytochrome P450, family 4, subfamily F, polypeptide 22, respectively.
†Erythroderma can also occur secondary to GVHD (see Fig. 10.10).
¶Present from birth or early infancy.

Table 10.2 Causes of erythroderma in neonates and infants. SCID, severe combined immunodeficiency.

Continued

CAUSES OF ERYTHRODERMA IN NEONATES AND INFANTS			
Underlying disease	**Clinical clues**	**Histologic clues**	**Additional findings**
PRIMARY DERMATOSES			
Atopic dermatitis	• Crusted eczematous lesions on extensor surfaces, face, scalp • Spares diaper area • Pruritus • Onset week 6–16	• See Table 10.1	• See Table 10.1
Seborrheic dermatitis	• Greasy, scaling plaques and satellite papules on scalp and in skin folds • Diaper area involvement • Non-pruritic • Early onset (week 2–12)		
Psoriasis	• Silvery white scaling and sharply demarcated plaques on face, elbows and knees • Diaper area involvement • Nail pits • Usually later onset	• See Table 10.1	• Family history of psoriasis
DRUG REACTIONS (Table 10.1)			
INFECTIONS			
Staphylococcal scalded skin syndrome	• Temperature instability/low-grade fever • Irritability • Skin-fold accentuation • Large areas of tender erythema • Superficial bulla formation followed by desquamation • Radiating perioral scale-crusts • Extracutaneous staphylococcal infections often responsible	• Blister roof consists of the cornified layer and parts of the granular layer • Subcorneal blisters contain a few neutrophils and lymphocytes	• Positive culture for *Staphylococcus aureus* (conjunctivae, nares, throat, rectum) • Identification of exfoliative toxins (ET-A & ET-B) via slide latex agglutination, double immunodiffusion, or ELISA (see Ch. 74) • ET-A produced by *S. aureus* specifically cleaves desmoglein 1
Neonatal toxic shock-like exanthematous disease	• Generalized diffuse macular erythema or morbilliform eruption with confluence • Minimal scaling • Fever • Occurs during first week of life		• Colonization of umbilical stump, nasopharynx or skin with TSST-1-producing MRSA • Thrombocytopenia
Congenital cutaneous candidiasis	• Maternal vaginal *Candida* infection with intrauterine spread • Pustules, collarettes of scale • Oral cavity spared • May have paronychia and nail dystrophy	• Yeast and pseudohyphae in the stratum corneum (PAS) • Subcorneal and spongiform pustules within the epidermis	• KOH examination, fungal culture
OTHERS			
• Pityriasis rubra pilaris (Ch. 9) • GVHD (e.g. maternal–fetal or transfusion-related in the setting of SCID) (Ch. 52) • Diffuse cutaneous mastocytosis (Ch. 118) • Rare ichthyoses – trichothiodystrophy, keratitis–ichthyosis–deafness (KID) syndrome, Sjögren–Larsson syndrome, neutral lipid storage disease with ichthyosis (Ch. 57) • Ankyloblepharon–ectodermal dysplasia–clefting (AEC) syndrome (Ch. 63) • "Nutritional dermatitis", including kwashiorkor (Ch. 51)			

Table 10.2 Causes of erythroderma in neonates and infants (cont'd). ELISA, enzyme-linked immunosorbent assay; MRSA, methicillin-resistant *Staphylococcus aureus*; SCID, severe combined immunodeficiency; TSST-1, toxic shock syndrome toxin 1.

whereas in chronic states they tend to be smaller and drier. Occasionally, the cause of the erythroderma is suggested by the character of the scale – for example, fine in atopic dermatitis or dermatophytosis, bran-like in seborrheic dermatitis, crusted in pemphigus foliaceus, and exfoliative in drug reactions.

Despite the varied causes, erythrodermas have several common clinical features. Pruritus, the most frequent complaint, is observed in up to 90% of patients. This symptom varies according to the underlying cause, and it is most severe in patients with dermatitis or Sézary syndrome[9]. Given the itch–scratch cycle, the skin may become thickened, and areas of lichenification are seen in one-third of cases. Especially in the case of chronic erythrodermas, patients develop dyspigmentation, with hyperpigmentation (40/90 patients, 45%) observed more frequently than hypo- or depigmentation (18/90 patients, 20%)[4]. Palmoplantar keratoderma appears in approximately 30% of erythrodermic patients, and it is often an early sign in pityriasis rubra pilaris[9]. A keratoderma with scale-crust can point to crusted scabies, whereas a painful and fissured keratoderma can occur in Sézary syndrome.

In cases of pre-existing dermatoses, nail changes may precede the erythroderma (e.g. pits in psoriasis or horizontal ridging in atopic dermatitis), whereas others develop subsequently. Nail changes are said to be present in approximately 40% of patients. Most often "shiny" nails are observed, but discoloration, brittleness, dullness, subungual hyperkeratosis, Beau's lines, paronychia and splinter hemorrhages can be seen. The nails may even be totally shed. Due to their slower development, nail changes are of potential value in differentiating the underlying cause. Diffuse non-scarring alopecia appears in 20% of patients with chronic erythroderma, including that due to CTCL; the latter is also associated with cicatricial alopecia.

Patients with erythroderma due to a variety of causes can begin to develop multiple seborrheic keratoses, and these papules may be pale in color compared with the background erythema (Fig. 10.2). Colonization of the skin with *Staphylococcus aureus* is common in the setting

Fig. 10.1 Erythroderma with desquamation. Obvious exfoliation of scale with underlying erythema.

Fig. 10.2 Eruptive seborrheic keratoses in a patient with idiopathic erythroderma. *Courtesy, Jean L Bolognia, MD.*

of erythroderma, and this can lead to secondary cutaneous infections. Independent of the cause of the erythroderma, bilateral ectropion and purulent conjunctivitis can develop as ocular complications. Lastly, an exacerbation of the erythroderma can follow UV irradiation or drug ingestions, and this is not restricted to patients with photosensitive eczema and drug-induced erythroderma, respectively[4].

Systemic Manifestations

An awareness of potential systemic complications of erythroderma is essential for proper patient management. Pedal or pretibial edema is observed in approximately 50% of patients (182/380)[1,3–5], and probably results from a shift of fluid into extracellular spaces. In patients with drug-induced erythroderma, facial edema may also develop. Because of the markedly increased blood flow through the skin and an increased fluid loss by transpiration, tachycardia affects 40% of patients, and there is a risk of high-output cardiac failure, particularly in elderly persons. Furthermore, increased skin perfusion leads to thermoregulatory disturbances. Although hyperthermia (37%, 146/391 patients) is more frequent than hypothermia (4%, 14/391), most patients describe chilly sensations[1,2,4,6]. The chronic and excessive loss of heat leads to a compensatory hypermetabolism with subsequent development of cachexia. Anemia, characterized by features of both iron deficiency and anemia of chronic disease, is also observed in patients with chronic erythroderma.

The most common extracutaneous manifestation of erythroderma is generalized peripheral lymphadenopathy, which is found in approximately half of the patients. Even in the absence of an underlying lymphoproliferative disorder, the lymphadenopathy may be prominent and, if so, histologic and molecular examination of a lymph node is recommended (in particular, flow cytometry and T-cell receptor gene analysis)[10]. The major differential diagnosis is between lymphomatous involvement and reactive dermatopathic lymphadenopathy. Hepatomegaly occurs in 20% of the cases (113/578), with a slight predominance in erythroderma due to drug-induced hypersensitivity. Splenomegaly is rarely seen and occurs most often in association with lymphoma[1–4,6].

Fig. 10.3 Psoriatic erythroderma. The disease flare correlated with the administration of lithium. *Courtesy, Jean L Bolognia, MD.*

Specific Findings of the Underlying Disease

In addition to the aforementioned general features, the clinical presentations can have additional, sometimes specific, features suggesting the underlying etiology (see Tables 10.1 & 10.2).

Psoriasis

Psoriasis is the most common underlying disorder in adults, whereas in children it represents the second most common cause of erythroderma, after drug eruptions. As a rule, psoriatic erythroderma is preceded by typical psoriatic plaques (see Ch. 8). Its onset is most often a result of the withdrawal of potent topical or oral corticosteroids, cyclosporine or methotrexate; occasionally, widespread flares follow irritant contact dermatitis (e.g. tar), phototoxicity or systemic infection. After generalization of the erythema, the typical features of psoriatic plaques are lost (Fig. 10.3), and disseminated sterile subcorneal pustules may develop. Due to a slower turnover rate, nail changes, such as oil-drop changes, onycholysis or nail pits (Fig. 10.4), may still be visible and provide valuable clues to the diagnosis of psoriatic erythroderma. Treatment of the erythroderma may result in the reappearance of more characteristic plaques of psoriasis.

Fig. 10.4 Psoriatic erythroderma. Nail findings (pitting and onycholysis with a proximal rim of inflammation) point to the diagnosis of psoriasis.

Atopic dermatitis

Although occurring at any age, atopic erythroderma develops most frequently in patients with a history of moderate to severe atopic dermatitis. As a result, well-established pre-existing lesions can be found, especially when the erythroderma is of recent onset. The pruritus is intense, and secondary excoriations or prurigo-like lesions are frequently observed. Lichenification is often prominent and atrophy of the skin due to topical corticosteroids may be seen. Increased serum IgE and eosinophilia may accompany other signs and symptoms of atopy.

Drug reactions

The number of drugs that can cause erythroderma is staggering (Table 10.3; see also Ch. 21). Whereas erythroderma resulting from topical medications usually begins as dermatitis, eruptions due to systemic drugs begin as a morbilliform or scarlatiniform exanthem. In areas of greatest hydrostatic pressure (ankles and feet), the lesions may become secondarily purpuric. Of the group of erythrodermas, those that are drug-induced have the shortest duration, usually resolving 2–6 weeks after withdrawal of the responsible drug. However, it is imperative to exclude a drug reaction with eosinophilia and systemic symptoms (DRESS), nowadays often referred to as drug-induced hypersensitivity syndrome (DIHS).

Idiopathic erythroderma

In approximately one-third of erythrodermic patients, no underlying disease is detectable. This group consists primarily of elderly men with a chronic course of relapsing pruritic erythroderma in association with dermatopathic lymphadenopathy and extensive palmoplantar keratoderma (Fig. 10.5); this constellation is referred to as "red man syndrome" or "l'homme rouge" (not to be confused with the red man syndrome that accompanies rapid intravenous infusions of vancomycin). When this group was compared with the entire group of erythrodermic patients, lymphadenopathy (68% vs 44%) and peripheral edema (54% vs 40%) were found to be more common than in other types of erythroderma, and hypothermia exceeded hyperthermia[12]. In one series, atopic dermatitis, drug-induced and CTCL were the most common etiologies not initially identified in patients with idiopathic erythroderma[2]. In a second series, CTCL was the most common underlying disease, using the detection of a cutaneous clonal T-cell population as a diagnostic criterion[13]. However, it is important to note that the presence of a T-cell clone in the peripheral blood of elderly individuals may reflect a diminished T-cell receptor repertoire rather than CTCL.

DRUGS ASSOCIATED WITH ERYTHRODERMA	
COMMON	
• Allopurinol	• Phenytoins
• Beta-lactam antibiotics	• Sulfasalazine
• Carbamazepine/oxcarbazepine	• Sulfonamides*
• Gold	• Zalcitabine
• Phenobarbital	
LESS COMMON	
• Captopril/lisinopril	• Lithium
• Carboplatin/cisplatin	• Mercury compounds
• Cytarabine	• Minocycline
• Cytokines (IL-2/GM-CSF)	• Omeprazole/lansoprazole
• Dapsone	• Ribavirin
• Diflunisal	• Telaprevir
• Fluindione	• Thalidomide
• Hydroxychloroquine/chloroquine	• Tocilizumab
• Isoniazid	• Vancomycin†
• Isotretinoin/acitretin	
RARE‡	
• Abacavir	• Mitomycin C
• Amiodarone	• Nifedipine/diltiazem
• Aspirin (ASA)	• Other NSAIDs
• Aztreonam	• Penicillamine
• Beta-blockers	• Pentostatin
• Chlorpromazine	• Pseudoephedrine
• Cimetidine	• Rifampin
• Ciprofloxacin	• St. John's wort
• Clofazimine	• Sulfonylureas
• Codeine	• Tear gas (CS gas)
• Erythropoietin	• Terbinafine
• Fluorouracil	• Tobramycin
• Imatinib	• Tramadol
• Indinavir	• Vinca alkaloids
• Lamotrigine	• Zidovudine
• Methotrexate	

* Includes furosemide.
† Not to be confused with red man syndrome due to rapid infusion of drug.
‡ For additional drugs, see ref. 11.

Table 10.3 Drugs associated with erythroderma.

Fig. 10.5 Idiopathic erythroderma. This is the type of patient that requires longitudinal evaluation to exclude the development of cutaneous T-cell lymphoma.

Fig. 10.6 Erythroderma secondary to pityriasis rubra pilaris. A few islands of sparing are noted on the upper back (**A**), but are more noticeable on the flank and breast (**B**). Note the salmon color.

Fig. 10.7 Erythroderma due to pityriasis rubra pilaris. Large thin scales are seen as well as the characteristic orange–red color.

Cutaneous T-cell lymphoma

Erythroderma due to CTCL is subdivided into Sézary syndrome and erythrodermic mycosis fungoides (see Ch. 120). Sézary syndrome is defined by the triad of erythroderma, circulating malignant T lymphocytes, and generalized lymphadenopathy. Additional clinical features include a painful and fissured keratoderma, diffuse alopecia, and leonine facies. The skin may be quite infiltrated or hyperpigmented (melanoerythroderma), and severe pruritus is common. To aid in distinguishing between Sézary syndrome and erythrodermic mycosis fungoides, revised criteria were recently proposed by the International Society of Cutaneous Lymphomas and the Cutaneous Lymphoma Task Force of the EORTC for the diagnosis of Sézary syndrome – erythroderma and evidence of a T-cell clone in the blood plus one of the following: (1) ≥1000 Sézary cells/mm^3; (2) a CD4:CD8 ratio of ≥10:1; or (3) an increased percentage of CD4$^+$ cells with an abnormal phenotype (≥40% CD4$^+$/CD7$^-$ or ≥30% CD4$^+$/CD26$^-$)[14].

Pityriasis rubra pilaris

Erythrodermic pityriasis rubra pilaris (PRP) can be observed in children and adults (see Ch. 9). Usually, the lesions have a salmon to orange–red color (Fig. 10.6A). The degree of scaling varies, but it can be marked with large scales (Fig. 10.7). The combination of follicular keratotic papules on the knees, elbows and dorsal aspects of the fingers plus nappes claires (islands of uninvolved skin within the erythroderma) favors the diagnosis of PRP (Fig. 10.6B). When the classic histologic features are present (see below), this is also helpful in distinguishing PRP from psoriasis. Occasionally, CTCL can have an appearance similar to PRP.

Paraneoplastic erythroderma

Paraneoplastic erythroderma is most commonly associated with lymphoproliferative malignancies, including types of T-cell lymphoma other than Sézary syndrome. In the case of solid-organ malignancies, the erythroderma usually appears late in the course of the disease. Fine scales and erythema can be accompanied by a brownish hue (i.e. melanoerythroderma). Additional signs of malignancy, such as cachexia or fatigue, may be seen.

Bullous dermatoses

Among the bullous dermatoses, pemphigus foliaceus most commonly presents as erythroderma; erythrodermic forms of paraneoplastic pemphigus and bullous pemphigoid are rare (see Table 10.1; see also Chs 29 & 30). In pemphigus foliaceus, impetigo-like blisters and erosions are followed by collarettes of scale and scale-like crusts (Fig. 10.8). Usually, the erythroderma is preceded by localized lesions on the face and upper trunk.

Ichthyoses

Erythroderma due to one of the inherited ichthyoses is usually present from birth or infancy. In neonates, one must consider congenital ichthyosiform erythroderma (CIE; previously referred to as non-bullous CIE), epidermolytic ichthyosis (previously referred to as bullous CIE), and Netherton syndrome (see Table 10.2; see also Ch. 57). As a rule, CIE presents as a collodion baby (90% of the cases)[15]. Within a few days after birth, an erythroderma with fine white scaling appears. Epidermolytic ichthyosis initially presents as generalized erythema with superimposed superficial blisters and erosions. This disorder may be mistakenly diagnosed as staphylococcal scalded skin syndrome or as a form of epidermolysis bullosa. Later, children develop spiny, corrugated hyperkeratoses, particularly in flexural areas, and blisters and erosions become less prevalent. Netherton syndrome manifests as an ichthyosiform erythroderma in neonates. It is associated with trichorrhexis invaginata ("bamboo hair"), elevated serum levels of IgE, and an immune defect that can result in life-threatening infections, particularly within the first years of life. Later, either the ichthyosiform erythroderma persists or ichthyosis linearis circumflexa develops, which is characterized by garland-like scaly eruptions.

Staphylococcal scalded skin syndrome

Staphylococcal scalded skin syndrome (SSSS; see Ch. 74) is seen primarily in children (<5 years of age), and it is due to a circulating

Fig. 10.8 Erythroderma due to pemphigus foliaceus. Generalized erythema with widespread scale-crusts and large areas of erosion.

exfoliative toxin produced by *Staphylococcus aureus*. Since desmoglein 1 is cleaved by exfoliative toxin A, pemphigus foliaceus and SSSS exhibit clinical similarities, with the latter often becoming erythrodermic. Common foci for the initial infection include the nares, nasopharynx, conjunctivae and umbilicus. After a period of 1–2 days of a low-grade fever, large areas of tender erythema develop. The skin appears tense and subcorneal blisters appear, which subsequently desquamate. A very similar syndrome, the toxic shock syndrome, can be caused by staphylococcal or streptococcal exotoxins. It favors adults, but acral exfoliation has a delayed appearance, usually 2 weeks later.

Omenn syndrome

Omenn syndrome represents an autosomal recessive form of severe combined immunodeficiency (see Ch. 60), and it is characterized by failure to thrive, leukocytosis with prominent eosinophilia, hypogammaglobulinemia, and elevated serum IgE levels. Cutaneous findings, which appear in neonates, are generally the first sign of the syndrome and include an erythroderma with diffuse alopecia. Systemic manifestations include prominent lymphadenopathy, hepatosplenomegaly and recurrent diarrhea. In the absence of hematopoietic stem cell or bone marrow transplantation, the disease is rapidly fatal with recurrent infections.

PATHOLOGY

Although sometimes subtle, histopathologic features of the underlying disease are present in about two-thirds of patients. Diagnostic findings were frequently found in psoriasis (81% of 16 patients in one series)[16], but less often in PRP or CTCL (50% of 6 and 8 patients, respectively). Erythroderma due to drug hypersensitivity and dermatitis had typical pathologic findings in 67% (4 of 6) and 64% (9 of 16) of patients, respectively[16]. Specific histopathologic clues to the underlying disease are discussed below.

Psoriasis

In 60% of erythroderma patients diagnosed as having psoriasis, changes associated with "early" psoriasis are found[17]. These findings include slight epidermal hyperplasia, a reduced or absent granular layer, focal parakeratosis, an edematous papillary dermis, and a perivascular and interstitial lymphohistiocytic infiltrate. Sometimes, extravasated erythrocytes can be observed. Epidermal hyperplasia with bottleneck-like rete ridges, confluent parakeratosis, absence of the granular layer, elongated dermal papillae, and a sparse lymphohistiocytic infiltrate define the fully developed plaque form of psoriasis, and appear in 30% of patients with psoriatic erythroderma. Ten percent of patients with psoriatic erythroderma exhibit findings of regressing psoriasis (i.e. slight epidermal hyperplasia, a normal or even thickened granular layer, and a fibrotic papillary dermis)[17].

Atopic dermatitis

A constant finding in atopic erythroderma is mild to moderate spongiosis, which is sometimes located in the follicular infundibulum. However, spongiosis is found in other forms of dermatitis, including contact dermatitis. Almost always, acanthosis and parakeratosis are additional histologic features. A perivascular, rarely epidermotropic infiltrate is observed in the upper dermis; it is accompanied by dermal edema and prominent dermal vessels. In one series, numerous eosinophils were found within the infiltrate in 77% of patients[12].

Drug reactions

Histologically, changes vary considerably (see Ch. 21). Eosinophils may or may not be present.

Idiopathic erythroderma

The findings in idiopathic erythroderma are generally nonspecific. Subacute forms may have parakeratosis, acanthosis, spongiosis, papillary edema and a superficial perivascular lymphohistiocytic infiltrate, whereas chronic forms exhibit hyperkeratosis, psoriasiform acanthosis, little (if any) spongiosis and a thickened papillary dermis[9]. In order to identify the underlying disease in patients with idiopathic erythroderma, the submission of multiple biopsies from untreated affected skin (taken either simultaneously or sequentially) is advocated. Clinicopathologic correlation is important as sometimes there is evidence of two disorders, e.g. dermatitis superimposed upon psoriasis.

Cutaneous T-cell lymphoma

The histologic features of typical erythrodermic CTCL consist of a band-like infiltrate in the papillary dermis containing small to medium-sized (and occasionally large) mononuclear cells with hyperchromatic, cerebriform nuclei as well as a variable number of admixed inflammatory cells. Neoplastic cells, or sometimes groups of neoplastic cells, colonize the basal layer of the epidermis, and the cells are either evenly distributed or form Pautrier's microabscesses; the latter are pathognomonic but occur in a minority of cases. In contrast to circumscribed forms of mycosis fungoides, there is often less epidermotropism and the morphology of the neoplastic cells is sometimes more monotonous in erythrodermic mycosis fungoides and Sézary syndrome[18].

Pityriasis rubra pilaris

The characteristic histologic finding in PRP is foci of orthokeratosis alternating with parakeratosis in both vertical and horizontal directions. These features are also found in the follicular infundibula. A slight psoriasiform hyperplasia may be present, but the granular layer is normal and the rete ridges do not become thinned. In addition, a superficial and sparse interstitial infiltrate of lymphocytes is observed, and neutrophils are absent[17].

Ichthyoses

With the exception of epidermolytic hyperkeratosis in epidermolytic ichthyosis (bullous CIE), the histopathologic findings in ichthyosiform erythrodermas are generally non-diagnostic. In the non-bullous inflammatory type, psoriasiform hyperplasia, focal spongiosis and focal parakeratosis are found to a variable extent; a sparse perivascular lymphocytic infiltrate may be present.

Bullous dermatoses

The major histologic features of the bullous dermatoses are outlined in Table 10.1, as are the immunofluorescence microscopy findings. The latter are required for precise diagnosis (see Chs 29 & 30).

Staphylococcal scalded skin syndrome

Subcorneal blisters typically contain sparse acantholytic keratinocytes and few inflammatory cells.

Omenn syndrome

The histologic features of Omenn syndrome can resemble GVHD, with vacuolar degeneration of the basal layer and keratinocyte necrosis, but the former disorder is characterized by a denser dermal infiltrate of lymphocytes (as well as macrophages and eosinophils), acanthosis and parakeratosis. Degeneration of subcutaneous fat lobules may be observed. Examination of the enlarged lymph nodes shows an absence of lymph node architecture with massive infiltration of histiocytes and eosinophils.

DIFFERENTIAL DIAGNOSIS

Erythroderma is a clinical presentation for a variety of diseases, and identification of the underlying etiology represents one of the most complex challenges in dermatology (Figs 10.9 & 10.10; see Tables 10.1 & 10.2). The evaluation starts with a complete medical history: up to 45% of the patients will have a prior history of a more localized skin disease, and approximately 20% of cases represent drug reactions[1–6].

A comprehensive clinical examination may reveal additional clues to the underlying disease. Once the number of possible underlying diseases is reduced, further laboratory investigation can aid in establishing the final diagnosis.

TREATMENT

Erythroderma can represent a serious medical threat to the patient, therefore hospitalization may be required. Regardless of the underlying disease, the initial management consists of nutritional assessment, correction of fluid and electrolyte imbalances, prevention of hypothermia, and treatment of secondary infections. Sedating oral antihistamines may ease the often severe pruritus[9]. Systemic corticosteroids may be necessary in idiopathic erythroderma and drug reactions. With an initial dose of 1–2 mg/kg/day of prednisone, and a maintenance dose of 0.5 mg/kg/day or less, rapid and often continued clearing of the erythroderma can be achieved. Caution must be exercised upon tapering, as rebound may occur. Topical therapy includes open wet dressings and bland emollients or low-potency corticosteroid ointments. High-potency topical corticosteroids should be reserved for lichenified areas, and chronic, extensive application should be avoided. Coal tar ointments may aggravate the condition.

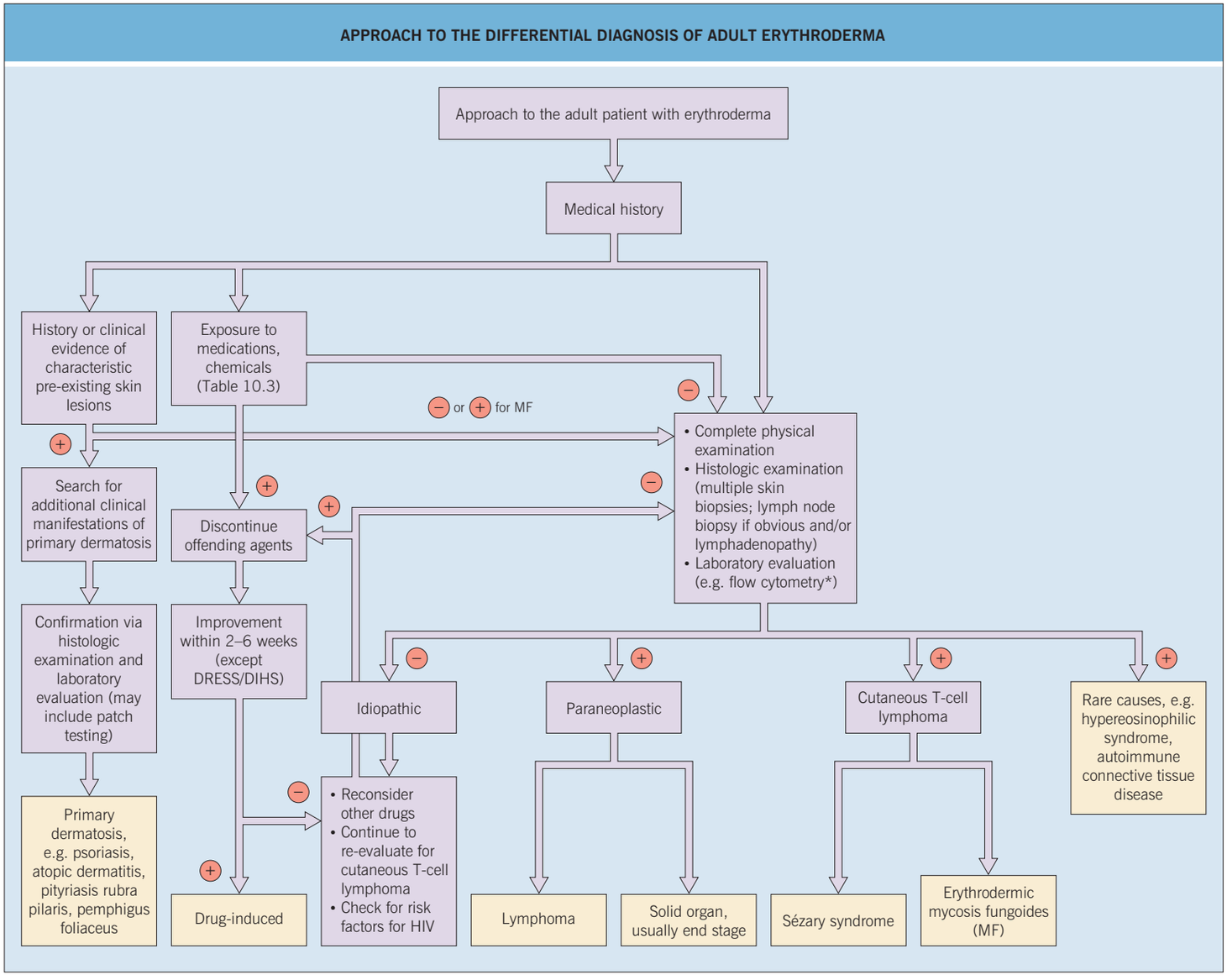
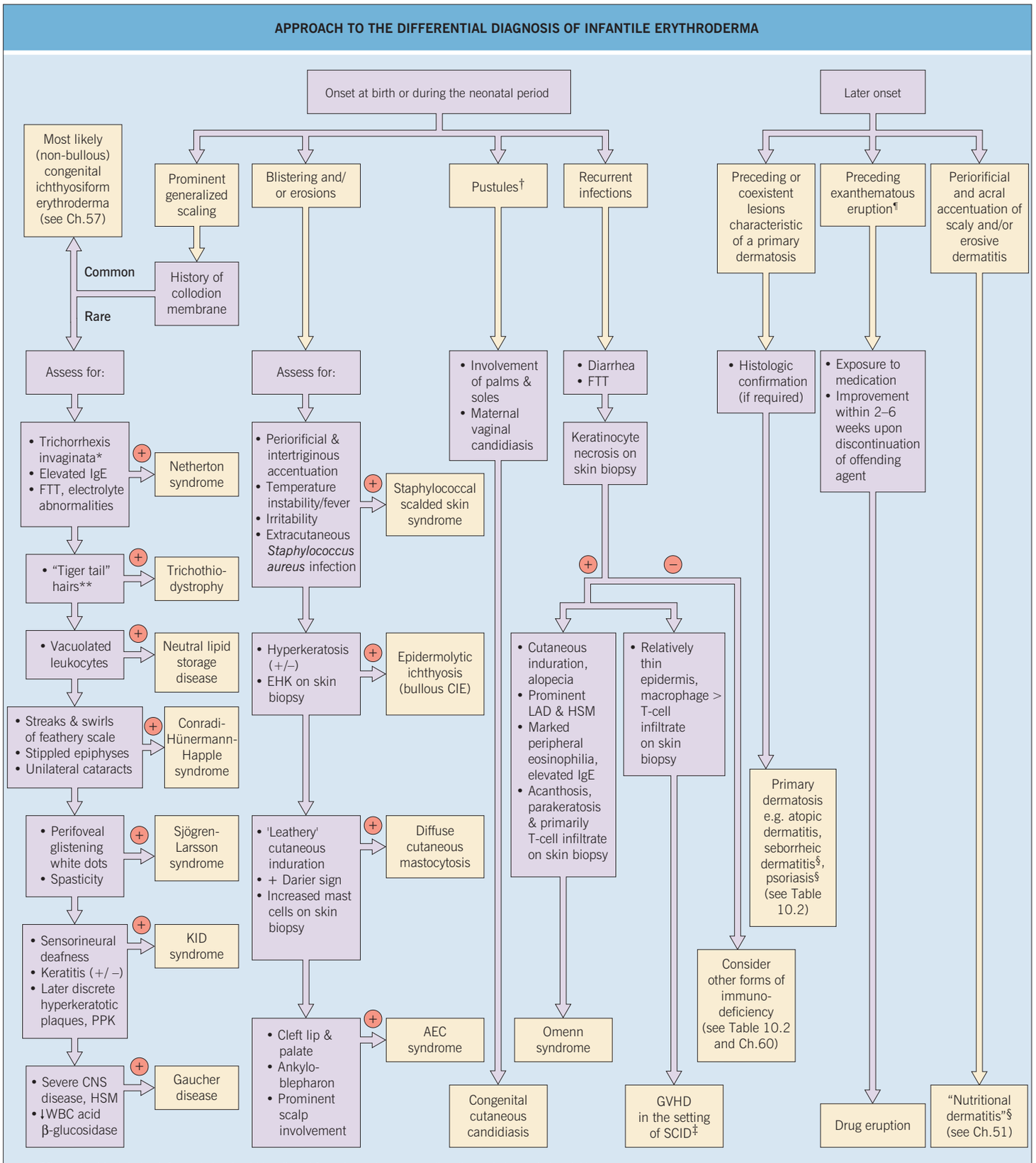


Fig. 10.9 Approach to the differential diagnosis of adult erythroderma. *Of peripheral blood and/or tissue. DRESS/DIHS, drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome.



* Often not evident during infancy; hairs should be clipped from the eyebrows as well as the scalp to maximize yield.
** Detected in virtually all hairs in patients with trichothiodystrophy.
† The differential diagnosis includes pustular psoriasis.
‡ Maternal-fetal or transfusion-related GVHD can also occur outside the setting of SCID.
¶ Progression of a morbilliform eruption to erythroderma can also characterize neonatal toxic shock-like exanthematous disease and GVHD.
§ Earlier onset is occasionally observed.

AEC, ankyloblepharon-ectodermal dysplasia-clefting; CIE, congenital ichthyosiform erythroderma; CNS, central nervous system; EHK, epidermolytic hyperkeratosis; EHK, epidermolytic hyperkeratosis; FTT, failure to thrive; GVHD, graft-versus-host disease; HSM, hepatosplenomegaly; KID, keratitis-ichthyosis-deafness; LAD, lymphadenopathy; PPK, palmoplantar keratoderma; SCID, severe combined immunodeficiency

Fig. 10.10 Approach to the differential diagnosis of infantile erythroderma.

In neonates and children with erythroderma, management of fluid and electrolyte balance is critical in order to prevent hypernatremic dehydration. Emollients, topical antibiotics and, depending upon the extent and severity of the secondary infections, systemic antibiotics are administered. Due to increased transcutaneous absorption, topical salicylic and lactic acid should be avoided[19].

Treatment of specific underlying diseases is outlined in the respective chapters (see Tables 10.1 & 10.2). In the case of psoriatic erythroderma, administration of methotrexate, acitretin, cyclosporine or targeted immunomodulators (biologic agents) is preferred over systemic corticosteroids, given the risk of a pustular flare when corticosteroids are tapered[20]. For drug reactions, following the discontinuation of all non-essential drugs and all suspected drugs, erythroderma usually improves within 2–6 weeks (with the exception of some patients with DRESS/DIHS). However, systemic prednisone (1–2 mg/kg/day) or even the administration of IVIg may be useful in severe cases. After careful exclusion of any underlying cause, idiopathic erythroderma may be treated with low-potency topical corticosteroids and oral antihistamines. In refractory cases, cyclosporine has been used successfully, with an initial dosage of 5 mg/kg/day, and subsequent reduction to 1–3 mg/kg/day. Additional steroid-sparing agents include methotrexate, azathioprine and mycophenolate mofetil, all of which have been used anecdotally, with dosages similar to those for recalcitrant atopic dermatitis. There are a few case reports of the use of etanercept.

REFERENCES

1. Sehgal VN, Srivastava G. Exfoliative dermatitis. A prospective study of 80 patients. Dermatologica. 1986;173:278–84.
2. Botella-Estrada R, Sanmartin O, Oliver V, et al. Erythroderma. A clinicopathological study of 56 cases. Arch Dermatol. 1994;130:1503–7.
3. Sigurdsson V, Toonstra J, Hezemans-Boer M, van Vloten WA. Erythroderma. A clinical and follow-up study of 102 patients, with special emphasis on survival. J Am Acad Dermatol. 1996;35:53–7.
4. Pal S, Haroon TS. Erythroderma: a clinico-etiologic study of 90 cases. Int J Dermatol. 1998;37:104–7.
5. Wong KS, Wong SN, Than SN, Giam YC. Generalised exfoliative dermatitis – a clinical study of 108 patients. Ann Acad Med Singapore. 1988;17:520–3.
6. Nicolis GD, Helwig EB. Exfoliative dermatitis. A clinicopathologic study of 135 cases. Arch Dermatol. 1973;108:788–97.
7. Pruszkowski A, Bodemer C, Fraitag S, et al. Neonatal and infantile erythrodermas: a retrospective study of 51 patients. Arch Dermatol. 2000;136:875–80.
8. Kanthraj GR, Srinivas CR, Devi PU, et al. Quantitative estimation and recommendations for supplementation of protein lost through scaling in exfoliative dermatitis. Int J Dermatol. 1999;38:91–5.
9. Rothe MJ, Bernstein ML, Grant-Kels JM. Life-threatening erythroderma: diagnosing and treating the "red man". Clin Dermatol. 2005;23:206–17.
10. Assaf C, Hummel M, Steinhoff M, et al. Early TCR-β and TCR-γ PCR detection of T-cell clonality indicates minimal tumor disease in lymph nodes of cutaneous T-cell lymphoma: diagnostic and prognostic implications. Blood. 2005;105:503–10.
11. Litt JZ. Litt's Drug Eruptions & Reactions Manual, 17th edn. London: Informa Healthcare, 2011.
12. Sigurdsson V, Toonstra J, van Vloten WA. Idiopathic erythroderma: a follow-up study of 28 patients. Dermatology. 1997;194:98–101.
13. Cherny S, Mraz S, Su L, et al. Heteroduplex analysis of T-cell receptor gamma gene rearrangement as an adjuvant diagnostic tool in skin biopsies for erythroderma. J Cutan Pathol. 2001;28:351–5.
14. Olsen E, Vonderheid E, Pimpinelli N, et al. Revisions to the staging and classification of mycosis fungoides and Sézary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). Blood. 2007;110:1713–22.
15. Judge MR, Harper JI. The ichthyoses. In: Harper JI (ed.). Inherited Skin Diseases. The Genodermatoses. Oxford: Butterworth, 1996:69–96.
16. Zip C, Murray S, Walsh NMG. The specificity of histopathology in erythroderma. J Cutan Pathol. 1993;20:393–8.
17. Tomasini C, Aloi F, Solaroli C, Pippione M. Psoriatic erythroderma: a histopathologic study of forty-five patients. Dermatology. 1997;194:102–6.
18. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. Blood. 2005;105:3768–85.
19. Hoeger PH, Harper JI. Neonatal erythroderma: differential diagnosis and management of the "red baby". Arch Dis Child. 1998;79:186–91.
20. Boyd AS, Menter A. Erythrodermic psoriasis. Precipitating factors, course and prognosis in 50 patients. J Am Acad Dermatol. 1989;21:985–91.

This page intentionally left blank

Lichen Planus and Lichenoid Dermatoses 11

Tetsuo Shiohara and Yoko Kano

Chapter Contents

Lichen planus 183
Lichen striatus 196
Lichen nitidus 197
Erythema dyschromicum perstans 199
Keratosis lichenoides chronica 201
Actinic lichen nitidus (summertime actinic lichenoid eruption) 201
Annular lichenoid dermatitis (of youth) 201

LICHEN PLANUS

Synonym: ■ Lichen ruber planus

Key features

- Idiopathic inflammatory disease of the skin, hair, nails and mucous membranes, seen most commonly in middle-aged adults
- Flat-topped violaceous papules and plaques favoring the wrists, forearms, genitalia, distal lower extremities and presacral area
- Clinical variants include annular, bullous, hypertrophic, inverse, linear, ulcerative, vulvovaginal–gingival, drug-induced and lichen planopilaris
- Some lichenoid drug eruptions have a photodistribution, while others are clinically and histologically indistinguishable from idiopathic lichen planus
- The most commonly incriminated drugs include angiotensin-converting enzyme (ACE) inhibitors, thiazide diuretics, antimalarials, quinidine and gold
- Histologically, there is a dense, band-like lymphocytic infiltrate and keratinocyte apoptosis with destruction of the epidermal basal cell layer
- In this T-cell-mediated autoimmune disorder, basal keratinocytes express altered self-antigens on their surface

Introduction

Lichen planus (LP), the prototype of lichenoid dermatoses, is an idiopathic inflammatory disease of the skin and mucous membranes. Classic LP is characterized by pruritic, violaceous papules that favor the extremities[1]. Histologically, a dense, band-like lymphocytic infiltrate is seen underlying an acanthotic epidermis with hypergranulosis, apoptosis, and destruction of the basal cell layer. The etiology and pathogenesis of LP are not fully understood, but the disorder has been associated with multiple environmental exposures, including viral infections, medications, vaccinations and dental restorative materials. LP-like lesions that resemble idiopathic LP may also develop in chronic GVHD, where alloreactive T cells that recognize foreign major histocompatibility complex (MHC) molecules are central effectors (see Ch. 52). This lends support to the hypothesis that an autoimmune reaction against epitopes on lesional keratinocytes that have been modified by viral or drug antigens may be responsible for this disorder.

Lichenoid eruptions represent a heterogeneous group of conditions that resemble idiopathic LP in terms of their clinical appearance and histologically demonstrate a lichenoid tissue reaction. The latter is a pattern characterized by vacuolar alteration of epidermal basal cells intimately associated with a band-like infiltrate of primarily lymphocytes in the papillary dermis. Many clinically distinct inflammatory dermatoses have in common varying elements of these lichenoid histologic features, and they are referred to as lichenoid dermatoses (Table 11.1).

History

The term lichen planus was initially introduced by Erasmus Wilson in 1869 to describe the condition that had been previously named leichen ruber by Hebra[1].

Epidemiology

Although its incidence varies depending upon geographic locale, cutaneous LP has been reported to affect from 0.2% to 1% of the adult population[1], whereas oral lesions have been observed in up to 1–4% of the population. There is no overt racial predisposition. The onset of LP occurs most commonly during the fifth or sixth decade, with two-thirds of patients developing the disease between the ages of 30 and 60 years. LP is rare in both infants and the elderly and, in general, only 1–4% of patients are children. However, more recent studies have suggested that LP may actually be more common in children, especially in Arab populations. Oral LP is also quite uncommon in young people and it usually affects middle-aged to elderly individuals (mean age at diagnosis being 52 years). Although LP is frequently thought to have no gender predilection, some studies have found that women were affected approximately twice as often as men.

Mucosal involvement, particularly oral lesions, may be observed in up to 75% of patients with cutaneous LP, but the former can be the only manifestation of the disease. Only 10–20% of patients whose initial presentation is oral LP will eventually develop cutaneous LP. Although reports of familial LP are rare, it may occur more frequently than previously thought; for example, LP occurs in up to 10% of first-degree relatives of affected patients. Cases of familial LP have been noted to have an earlier age of onset, a higher relapse rate, and more frequent oral mucosal involvement. Nonetheless, reports of concurrent LP in monozygotic twins who were living together suggest an environmental trigger.

Pathogenesis

There is a growing body of evidence that LP represents T-cell-mediated autoimmune damage to basal keratinocytes that express altered self-antigens on their surface.

Target antigens

Clinical observations and anecdotal evidence have long suggested a relationship between exposure to a number of exogenous agents (e.g. viruses, medications, contact allergens) and the development of LP (see Table 11.1). A critical component for the generation of effector T cells with cytotoxic potential is the presentation of these exogenous antigens in the context of antigen-presenting cells.

Hepatitis C virus

Of the many potential exogenous antigens, greater attention has been focused on the possible role of viruses, particularly hepatitis C virus

MAJOR LICHENOID DERMATOSES AND POSSIBLE ASSOCIATED TARGET ANTIGENS	
Lichenoid dermatoses	**Possible target antigens**
Lichen planus	V, D, C, T
Lichenoid drug eruption	D
Erythema dyschromicum perstans	V, D
Graft-versus-host disease (see Ch. 52)	Allo, V
Keratosis lichenoides chronica	
Pityriasis lichenoides* (see Ch. 9)	V
Lichen nitidus	V
Lichen striatus	V
Fixed drug eruption (see Ch. 21)	D
Erythema multiforme (see Ch. 20)	V, D, C
Lupus erythematosus (see Ch. 41)	V, Auto, D
Dermatomyositis (see Ch. 42)	V, Auto, T, D
Paraneoplastic pemphigus (see Ch. 29)	T
Mycosis fungoides (CTCL) (see Ch. 120)	T, V
Lichenoid pigmented purpura (see Ch. 22)	D, V
Secondary syphilis (see Ch. 82)	
*Acute and chronic.	

Table 11.1 Major lichenoid dermatoses and possible associated target antigens. The variation in clinical presentations may reflect the differences in the effector mechanisms by which epidermal cells are damaged and/or target antigens. The shaded entities are discussed in this chapter. Allo, alloantigens; Auto, autoantigens; C, contact allergens; D, drug antigens; T, tumor antigens; V, viral antigens.

(HCV). In several case–control studies, the prevalence of HCV (3.4–38%) was 2- to 13.5-fold higher in patients with LP than in controls. This association seems to be strongest in Japanese and Mediterranean populations, probably due to the high prevalence of HCV infection in these countries. In the US, one case–control study found that 12 (55%) of 22 patients with LP had anti-HCV antibodies, and this was significantly higher than the 25% of 40 psoriatic patients or the 0.17% of blood donors who tested positive[2]. While it may still be premature to conclude that HCV infection and LP are causally related, a recent systematic review and meta-analysis of existing epidemiologic studies demonstrated that an association between LP and HCV infection did exist in certain geographic regions (e.g. East and Southeast Asia, South America, the Middle East, Europe), but not in others (e.g. North America, South Asia, and Africa)[3]. It remains to be determined whether HCV infection precedes the development of LP and is directly involved in its pathogenesis.

Of the various types of LP, it is the oral form that is most commonly viewed as a manifestation of HCV infection. The PCR technique (see Fig. 3.3) detected HCV RNA in 93% of oral LP lesions[4], suggesting HCV replication within LP lesions; however, this result was not confirmed by a less sensitive immunoperoxidase staining procedure or by other PCR studies. In addition, the effects of anti-HCV therapy (e.g. a combination of interferon and ribavirin) are highly variable; some LP lesions actually appeared or flared during therapy. Possible explanations for these conflicting results include detection of HCV RNA simply reflecting the absorption of antibody-coated viral particles onto the cell surface membrane (supported by the inability to consistently detect HCV genomic sequences), HCV merely acting as a triggering factor in predisposed individuals, and technical difficulties due to the genomic diversity of HCV.

Of note, an increased frequency of the HLA-DR6 allele has been reported in Italian patients with HCV-associated oral LP[5], raising the possibility that $CD4^+$ T cells activated upon recognition of HCV-encoded peptides bound to HLA-DR6 molecules could be directly involved in the pathogenesis of LP. In support of this possibility, HCV tetramer analysis has shown that HCV-specific $CD4^+$ and/or $CD8^+$ T cells are present with higher frequency in oral LP lesions compared with the circulating compartment, suggesting that they play a role in the pathogenesis of LP[6].

Other viruses

With regard to the role of other viruses in LP, human herpesvirus *(HHV)-6* was detected in 67–100% of oral LP lesions by *in situ* hybridization and immunohistochemical techniques when it was absent from normal oral tissues. In addition, a retrospective survey of 18 lesional LP tissue samples (as well as 11 non-lesional LP and 11 lesional psoriasis samples) found that 11 of the 18 lesional LP samples contained *HHV-7* DNA as compared to 1 of 11 and 2 of 11 non-lesional LP and lesional psoriasis samples, respectively[7]. Remission of LP was associated with decreased HHV-7 protein expression, in particular within infiltrating plasmacytoid dendritic cells[8]. There are also sporadic case reports of LP lesions developing in areas recently affected by herpes simplex virus (*HSV*) or varicella zoster virus (*VZV*) infections[9], although the presence of these viruses in the lesions was not confirmed by PCR and a Koebner phenomenon represents a possible alternative explanation. Even when viral DNA is detected within LP lesions, it may simply represent a previous (unrelated) local infection, or a systemic or even distant site infection, rather than proof of causation.

While measurements (via PCR) of viral genomes within lesional skin or blood have been inconclusive, virus-specific T cells are present within lesions. This suggests that the pathology is a direct consequence of immune responses (perhaps to virally induced alterations in the antigenicity of epidermal cells; see below) rather than the viruses themselves. It is also possible that virus-specific T cells are nonspecifically trapped within sites of inflammation, having been activated systemically or locally at distant sites, and then they expand and mediate tissue damage "accidently" due to cross-reactivity with other antigens (e.g. drugs)[10].

Vaccines

A number of reports have described the appearance of LP after administration of different types of HBV vaccines[11]. The time interval between the initial dose and the development of cutaneous or mucosal lesions has varied from a few days to 5 months. Interestingly, a bullous variant was reportedly observed in five of 18 pediatric patients, in whom LP is generally rare. It is possible that HBV-reactive T cells cross-react with epitopes expressed on keratinocytes. One recommendation is that patients who develop LP before completing their vaccination series should avoid further injections because of an increased risk of developing severe LP lesions.

Bacteria

Studies investigating a possible bacterial connection in LP have been limited. Specifically, studies have not supported a definitive etiologic role for *Helicobacter pylori* in LP.

Contact allergens

The role of contact allergy to a variety of metals in the exacerbation or induction of oral LP has been well described, based on exposure to metallic dental restorations or constructions, positive patch test results, and then regression or complete clearing after removal of the sensitizing metal and replacement with other materials. Because involved allergens are dissolved and spread via saliva, mucosal reactions may extend beyond the contact areas. The metals that aggravate oral LP include amalgam (mercury), copper and gold. Although approximately 95% of patients had improvement after removal of the sensitizing metal, 75% of patients with negative patch test results also reported clearing of oral LP after removal of the metal and replacement with other materials. Such results indicate that spontaneous remissions may occur and draw into question the importance of contact allergy to metals in the pathogenesis of LP. Nevertheless, some authors have argued that even in patients who improved after the removal but had negative patch test results, mercury may have acted as an irritant factor in the pathogenesis of LP (via the Koebner phenomenon).

The development of contact allergy to metals within dental restorations in patients with LP could be explained by easy penetration of the metal via damaged mucosa. Thus, contact allergy to dental amalgam restorations should be suspected and patch tests should be performed in patients with oral LP, especially if the lesions are in close contact with amalgam fillings.

DRUGS IMPLICATED IN LICHENOID DRUG ERUPTIONS

ANTIMICROBIALS
- Ethambutol
- Griseofulvin
- Isoniazid
- Ketoconazole
- Pyrimethamine
- Streptomycin
- Sulfamethoxazole
- Tetracyclines

ANTIHYPERTENSIVES
- **Captopril**
- **Enalapril**
- **Labetalol**
- **Methyldopa**
- **Propranolol**
- Diazoxide*
- Doxazosin
- Prazosin

ANTIMALARIALS
- **Chloroquine**
- **Hydroxychloroquine**
- **Quinacrine**

ANTIDEPRESSANTS, ANTIANXIETY DRUGS, ANTIPSYCHOTICS AND ANTICONVULSANTS
- Amitriptyline
- Carbamazepine
- Chlorpromazine
- Imipramine
- Levomepromazine
- Lorazepam
- Methopromazine
- Phenytoin

TNF-α INHIBITORS
- Adalimumab
- **Etanercept**
- **Infliximab**
- Lenercept

DIURETICS
- **Chlorothiazide**
- **Hydrochlorothiazide**
- Furosemide
- Spironolactone

HYPOGLYCEMIC AGENTS
- Chlorpropamide
- Glyburide
- Tolazamide
- Tolbutamide

METALS
- **Gold salts**‡
- Arsenic
- Bismuth
- Mercury
- Palladium

NSAIDS
- Acetylsalicylic acid
- Benoxaprofen
- Diflunisal
- Fenclofenac
- Flurbiprofen
- Ibuprofen
- Indomethacin
- Naproxen
- Sulindac

MISCELLANEOUS DRUGS
- Allopurinol
- Amiphenazole
- Anakinra
- Cinnarizine
- Cyanamide
- Dapsone
- Gemfibrozil
- Hydroxyurea
- Imatinib
- Interferon-α
- Iodides
- Isotretinoin
- Levamisole
- Lithium
- Mercapto-propionylglycine
- Mesalamine
- Methycran
- Nifedipine
- Omeprazole
- Orlistat
- **Penicillamine**
- Propylthiouracil
- Procainamide
- Pyrithioxin
- Simvastatin
- Quinine
- **Quinidine**
- Rituximab
- Sildenafil
- Sulfasalazine
- Trihexyphenidyl

*Also used to treat hypoglycemia.
‡Including in alcoholic beverages.

Table 11.2 Drugs implicated in lichenoid drug eruptions. More commonly associated drugs are in **bold**. NSAIDs, nonsteroidal anti-inflammatory drugs.

Drugs

Cutaneous eruptions similar or even identical to LP (both clinically and histologically) have been linked to a variety of drugs. The terms "lichen planus-like" and "lichenoid" are often used to describe this phenomenon[12]. A wide variety of drugs have been associated with lichenoid drug eruptions and the list of such drugs steadily increases (Table 11.2). However, recurrence of the lesions subsequent to drug rechallenge has not been documented for the majority of these drugs. The mechanism by which certain drugs can induce a lichenoid tissue reaction in susceptible hosts is unknown, but appears to be similar to LP.

Autoantigens

In occasional patients, LP has been reported as a possible autoimmune reaction triggered by an underlying neoplasm. Also, a lichenoid tissue reaction is seen in patients with paraneoplastic pemphigus. The temporal relationship between LP and the underlying neoplasm in the reported patients suggests that the neoplasms may have stimulated a cell-mediated immune response against tumor antigens that led to the generation of autoreactive T cells that cross-reacted against antigens expressed on epidermal cells.

Although numerous case reports describe patients with both LP and autoimmune diseases, studies with larger numbers of patients with LP have shown no increased incidence of autoimmune diseases. Many investigators have described a significant association between specific HLA antigens and LP; for example, an increased frequency of HLA-B27, HLA-B51, HLA-Bw57 (oral LP in English patients), HLA-DR1 (cutaneous and oral LP), HLA-DR9 (oral LP in Japanese and Chinese patients) and HLA-DR6 (HCV-associated oral; see above). However, a true association with a particular HLA allele has been difficult to establish because of significant geographic heterogeneity and clinical patient selection.

A murine model of LP has been established by employing autoreactive T cells capable of producing interferon- γ (IFN-γ) and tumor necrosis factor-α (TNF-α) (Fig. 11.1)[13]. Intradermal inoculation of $CD4^+$ autoreactive T-cell clones into the footpads of syngeneic mice can induce local histologic changes similar to LP or lichenoid skin diseases. In this model, the autoreactive T cells can respond to self MHC class II antigens constitutively expressed on macrophages and Langerhans cells, and they migrate into the epidermis, resulting in epidermal injury. These T cells, therefore, can induce LP-like lesions without any alteration in the antigenicity of the epidermis. However, in the natural disease process, exogenous agents (e.g. viral infections, drugs) could induce alterations in the antigenicity of epidermal cells and trigger the activation of T cells. Of note, such autoaggressive reactions could function to eliminate abnormal keratinocytes altered by these exogenous agents. However, in the situation where T cells initially responding to self-antigens modified by exogenous agents subsequently become cross-reactive with some self-epitopes, these T cells would then chronically respond to the previously ignored self-epitopes, leading to perpetuation of an autoimmune attack by such T cells[13] rather than elimination of the abnormal keratinocytes.

Effector cells

There are conflicting data regarding the phenotype of the inflammatory infiltrate in LP lesions. Although initial immunohistochemical studies showed that the cellular infiltrate contained an increased ratio of $CD4^+$ to $CD8^+$ T cells[14], other investigators found a predominance of $CD8^+$ T cells, particularly in older lesions. Evidence to support the crucial role of $CD8^+$ T cells in autoimmune damage to basal keratinocytes has been provided by $CD8^+$ T cells isolated from lesional skin; these T cells exhibited specific cytotoxic activity against autologous lesional and normal keratinocytes[15]. One caution is that these $CD8^+$ T-cell lines and clones could represent an *in vitro* selection and/or expansion of autoreactive T cells during their culture with autologous antigen-presenting cells.

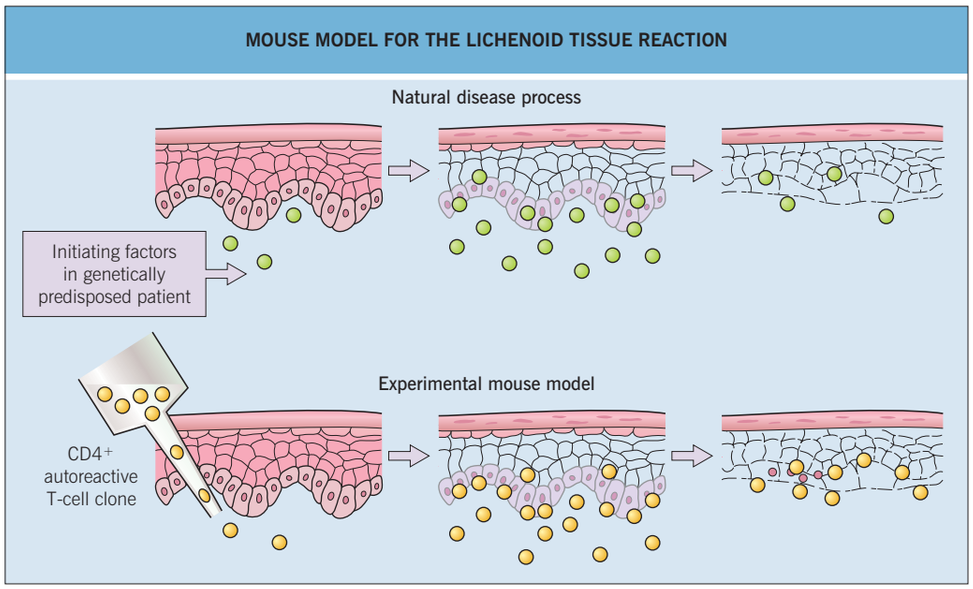


Fig. 11.1 Mouse model for the lichenoid tissue reaction. Because in humans all the analyses are performed on existing skin lesions (after the inflammatory response is underway), it is difficult to provide insight into initiating events and to establish whether the T cells present are indeed relevant to the pathogenesis. This experimentally induced animal model has the advantage that the orchestrated series of events resulting in epidermal injury can be examined from the onset and over time.

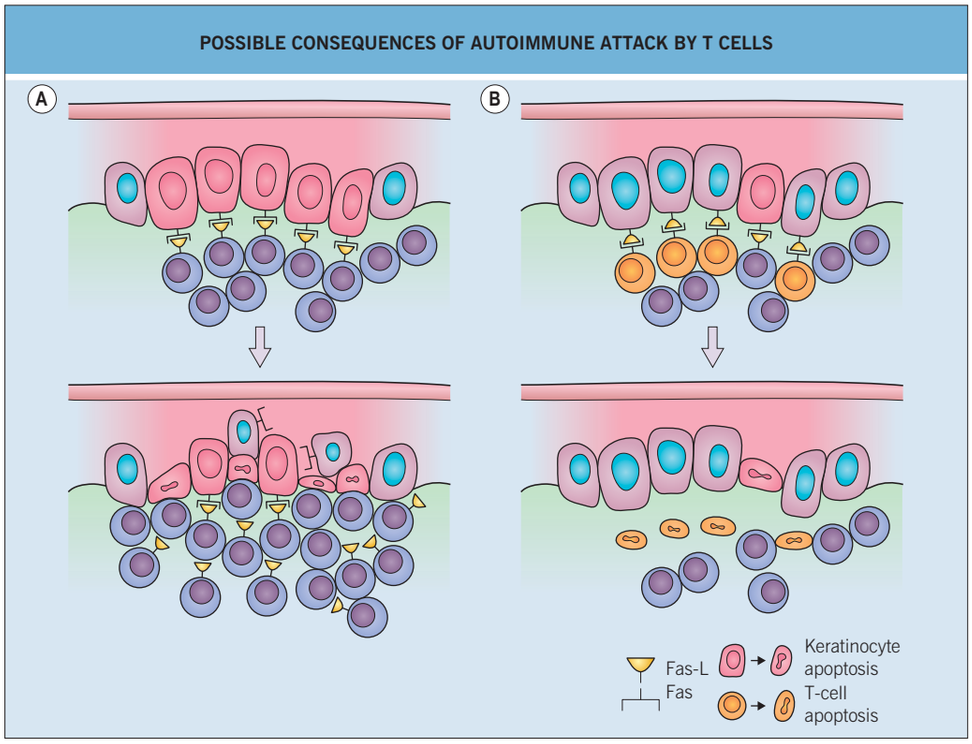


Fig. 11.2 Possible consequences of autoimmune attack by T-cells. A Activated memory T cells express Fas ligand (Fas L), which binds to Fas expressed on epidermal keratinocytes, resulting in apoptosis. Apoptosis can also be induced via the release of cytotoxic granules which contain perforin and granzyme B (see Ch. 20). Fas/Fas L and perforin/granzyme can independently trigger the cell death program, but the process leading to apoptosis is similar in both pathways. $CD8^+$ cytotoxic T cells and NK cells use both pathways.
B Because keratinocytes are not only targets but also produce granzyme B, perforin and Fas L to protect themselves from immune-mediated damage, Fas L-bearing keratinocytes can induce Fas/Fas L-mediated death in neighboring Fas-bearing T cells, contributing to the resolution of the lichenoid tissue reaction. This pathway serves to eliminate potentially harmful autoaggressive T cells. Thus, keratinocytes should not be viewed just as victims of the immune-mediated damage. Recovery from the inflammation is associated with the migration of regulatory T (Treg) cells into the site.

Basal cell damage as evidenced by apoptotic DNA fragments is greatest in the epidermis. A possible mechanism is illustrated in Figure 11.2 in which IFN-γ produced by $CD8^+$ T cells upregulates Fas expression by keratinocytes, rendering them susceptible to T-cell-mediated, Fas ligand-driven apoptosis. This interaction triggers a cascade of intracellular enzymatic reactions resulting in DNA fragmentation (see Ch. 107). In addition to Fas, death receptor-induced apoptosis involves signaling processes via TNF-R1, TRAIL-R1 and 2, and DR3 or DR6. Because type 1 helper T cells (Th1), like the autoreactive $CD4^+$ T cells in the murine model (see Fig. 11.1), can produce large amounts of IFN-γ and TNF-β upon activation and thereby induce or enhance the expression of apoptosis-associated proteins such as Fas and TRAIL, they may also play a role in extensive epidermal damage by promoting apoptotic death of keratinocytes. It is also likely that when epidermal damage is severe, perforin and granzyme are involved as well (see Ch. 20).

Additionally, IFN-γ and TNF-α, released by both $CD4^+$ T cells and $CD8^+$ T cells, can induce keratinocyte expression of ICAM-1, thereby rendering these T cells more adhesive to the keratinocytes and thus facilitating exocytosis of granules containing perforin and granzymes. Of note, these cytokines have been shown to be present at high concentrations in LP lesions. More recent studies have shown that granule exocytosis, rather than the Fas/Fas-ligand system, is the main pathway of cytotoxicity mediated by $CD4^+$ and $CD8^+$ T cells in humans[16]. However, a combination of the two mechanisms is most likely, with predominance depending upon the particular stage in the disease process.

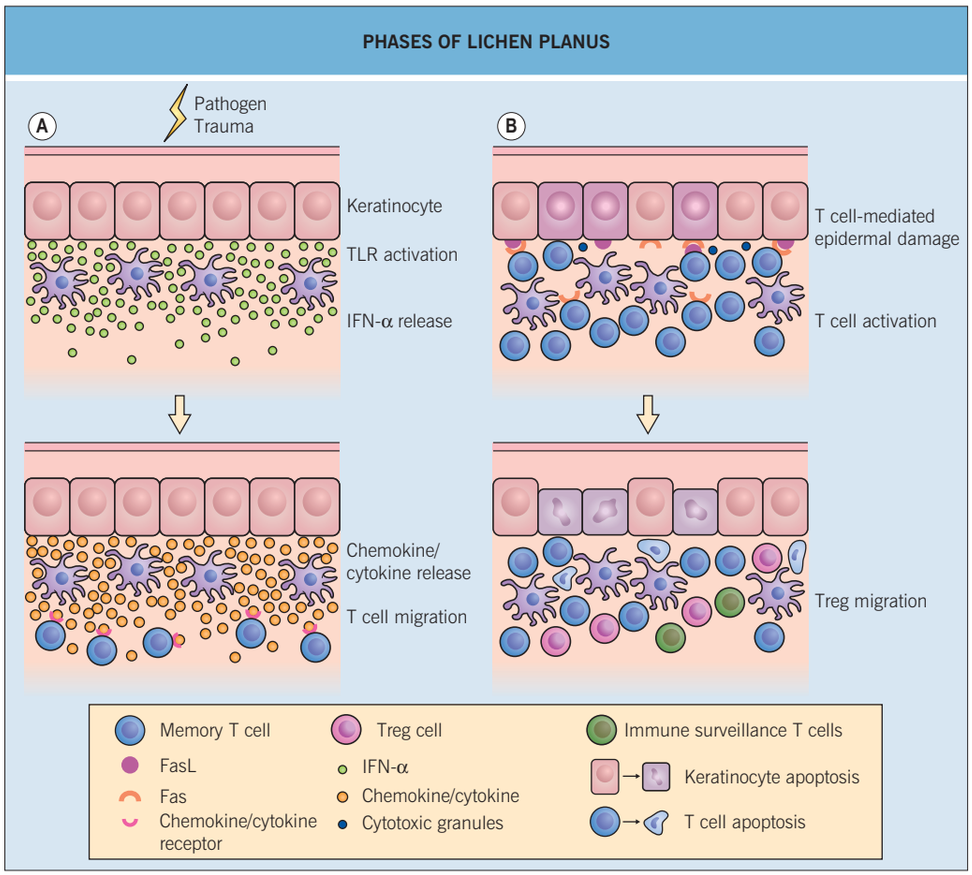


Fig. 11.3 Phases of lichen planus. A In the induction phase, keratinocytes and plasmacytoid dendritic cells (pDCs), upon stimulation of their Toll-like receptors (TLRs) by pathogens or endogenous ligands, can release type 1 IFNs (e.g. IFN-α); this represents an early event in the cascade leading to T-cell-mediated epidermal damage. Activated keratinocytes, via production of IL-1β and TNF-α, can induce activation and migration of DCs. Chemokines, such as IP10/CXCL10, released locally by pDCs, serve to attract CXCR3-expressing $CD8^+$ or $CD4^+$ effector memory T cells (which have differentiated from naive T cells within lymph nodes following presentation by DCs of self-peptides modified by exogenous antigens [viruses, medications and contact allergens]). Additional chemokine and chemokine receptor pairs have also been implicated in this process (see Table 11.3), and the precise mix of chemokines and cytokines released into the tissue plays an important role in determining the composition of the inflammatory infiltrates. **B** In the evolution phase, effector T cells (Te) that come to express skin-homing receptors (E-selectin ligands) migrate into the inflammatory site and upon recognition of antigens, are activated and release proinflammatory cytokines and cytotoxic granules, which in turn cause epidermal injury. In addition, Fas/FasL can trigger cell death (see Fig. 11.2). "Inflammatory" and "'homeostatic" chemokines produced by keratinocytes direct the traffic of not only "pathogenic" T cells (Te) but also "immune surveillance" T cells (Ts) or regulatory T cells (Treg) into the sites; the relative balance of chemokines produced may determine the outcome of the T-cell-mediated immune responses.

Effector T cells' access to the epidermis

A critical event in the initiation of immune responses in LP lesions is for memory T cells to migrate from the circulation into a particular skin site. Release of type 1 IFNs, such as IFN-α, from activated plasmacytoid dendritic cells (pDCs) and keratinocytes may be critical in inducing skin-directed migration of effector memory T cells (Fig. 11.3A). Stimulation of Toll-like receptors (TLRs) expressed on pDCs and keratinocytes by pathogens or endogenous ligands (released via skin damage) represents one of the earliest events and it is sufficient to induce type 1 IFN production. Type 1 IFN signaling and type 1 IFN-inducible chemokines (e.g. IP10/CXCL10) then serve to recruit chemokine receptor CXCR3-expressing effector memory T cells (Th1 cells) into the skin via CXCR3/IP10 interactions (Table 11.3). A number of other molecular interactions, such as CCR4/TARC, CCR10/CTACK and LFA-1/ICAM-1 expressed on T cells and keratinocytes, respectively, have also been implicated in the recruitment of memory T cells and pDCs to the dermal–epidermal junction[17–19]. Because IFN-α from pDCs induces IFN-γ production by T cells and IFN-γ also sustains IFN-α production, a positive feedback loop may be operational within LP lesions. This ordered sequence of events provides a possible explanation for why LP lesions develop within traumatized sites and virally induced lesions.

Although chemokines produced at inflammatory skin sites are thought to regulate the composition of the Th1- or Th2-driven cellular infiltrates, memory T cells with a "surveillance" function can also migrate to skin sites under non-inflamed conditions. "Homeostatic" chemokines constitutively produced under non-inflamed conditions can mediate the skin-directed migration of these "immune surveillance" T cells (Table 11.3), leading to clearance of invading pathogens such as viruses. In addition, $CD4^+$ regulatory T (Treg) cells that have the capacity to suppress activated T cells are also able to enter inflamed skin sites (Fig. 11.3B). Lastly, it should be noted that there is no definitive means of distinguishing "immune surveillance" T cells or protective regulatory T cells from "pathogenic" T cells in LP lesions.

While the epidermotropic migration of effector T cells leading to epidermal damage is clearly a complicated, multistep process, the latter can be bypassed (at least in part) in the case of fixed drug eruptions. This is because effector T cells responsible for the epidermal damage persist as a stable population in previously affected, but normal-appearing, skin. As a result, fixed drug eruption represents a simplified disease model for studying the pathogenesis of lichenoid tissue reactions, and the orchestrated series of events can be analyzed from prior to drug challenge to resolution of lesions (Fig. 11.4)[20].

Clinical Features

The characteristic primary lesion of LP is a small, polygonal-shaped, violaceous, flat-topped papule; some papules are umbilicated. The surface is slightly shiny or transparent, and a network of fine white lines called "Wickham's striae" (Fig. 11.5) or small gray–white puncta are also seen. The latter correspond histologically to focal thickening of the granular layer. The papules may be widely dispersed or they may cluster or coalesce into larger plaques (Fig. 11.6). LP is usually pruritic. Although the Koebner phenomenon (i.e. isomorphic response) is commonly seen in LP (Fig. 11.7), excoriations and impetiginization are unusual. Linear papules may be the initial presentation of the disease, presumably reflecting koebnerization into sites of previous trauma or scratching. However, such lesions need to be distinguished from the linear variant of LP which follows the lines of Blaschko (see below).

The most frequently involved sites are the flexor surfaces of the wrists and forearms; the dorsal surface of the hands, anterior aspect of the lower legs, neck and presacral area are also common sites. The mucous membranes, especially the oral mucosa (see below), are affected in more than half of patients, and this is often the only site of involvement. Lesions are also commonly seen on the glans penis, where they can have an annular or figurate configuration (Fig. 11.8A) and may become erosive. Several of the distinctive variants of LP are discussed separately.

The duration of the disease is dependent upon the LP variant. While the lesions of exanthematous LP typically resolve within a year,

CHEMOKINES AND CHEMOKINE RECEPTORS INVOLVED IN T-CELL MIGRATION INTO THE SKIN

Chemokines*	Chemokine receptors	Functional type of chemokines/T cells attracted†
RANTES (CCL5) MCP-2 (CCL8) Eotaxin-1, -2, -3 (CCL11,24,26)	CCR3	Inflammatory/Th2 cells
TARC (CCL17) MDC (CCL22)	CCR4	Inflammatory/Th2 cells
MIP-1α,β (CCL3,4) RANTES (CCL5) MCP-2 (CCL8)	CCR5	Inflammatory/Th2 cells
CCL1	CCR8	Homeostatic/memory T cells
CTACK (CCL27) MEC (CCL28)	CCR10	Homeostatic/memory T cells
MIG (CXCL9) IP-10 (CXCL10) I-TAC (CXCL11)	CXCR3	Inflammatory/Th1 cells
CXCL16	CXCR6	Inflammatory/Th1 cells

*Cytokines that have chemoattractant activity; two major groups are differentiated based on the position of two cysteine (C) residues compared with the other amino acid residues (X): CXC- or α-chemokines and CC- or β-chemokines.

†"Inflammatory" chemokines are produced at sites of cutaneous inflammation and mediate skin-directed migration of memory T cells (Th1, Th2); "homeostatic" chemokines are constitutively produced within non-inflamed skin and mediate skin-directed migration of memory T cells with an "immune surveillance" function.

Table 11.3 Chemokines and chemokine receptors involved in T-cell migration into the skin. Binding of MCP-1 (CCL2) to CCR2 on monocytes plays an important role in their recruitment to sites of cutaneous inflammation. CCR, receptor for CC chemokines; CTACK, cutaneous T-cell-attracting chemokine; CXCR, receptor for CXC chemokines; IP-10, interferon-inducible protein 10; I-TAC, interferon-inducible T cell α-chemoattractant; MCP-2, monocyte chemoattractant protein 2; MDC, macrophage-derived chemokine; MEC, mucosal-associated epithelial chemokine; MIG, monokine induced by interferon-γ; MIP-1α, macrophage inflammatory protein 1α; RANTES, regulated on activation normal T cell expressed and secreted; TARC, thymus- and activation-regulated chemokine.

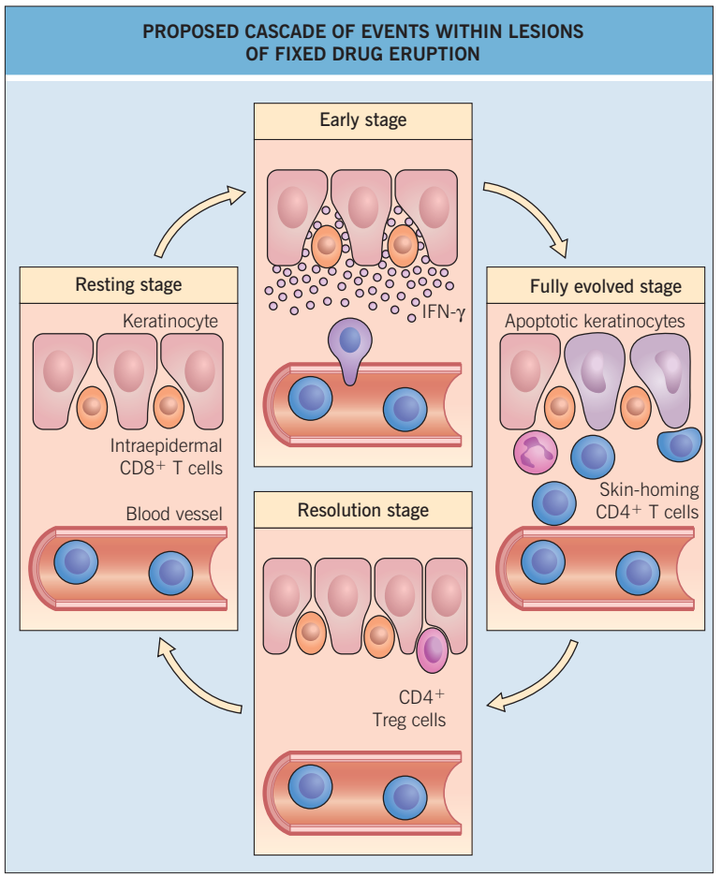


Fig. 11.4 Proposed cascade of events within lesions of fixed drug eruption (FDE). In resting lesions (previous sites of FDE but prior to drug challenge), intraepidermal CLA^+ $CD8^+$ T cells remain quiescent, but in a primed state as evidenced by CD69 expression. They also express TCR αβ, CD3, CD8, CD45RA and CD11β, but not CD27 and CD56, and therefore most closely resemble effector memory T cells. Upon administration of the causative drug, these T cells are activated to release IFN-γ and cytotoxic granules into the local environment. Nearby mast cells contribute to activation of the intraepidermal $CD8^+$ T cells by releasing TNF-α and inducing adhesion molecules on surrounding keratinocytes. In fully evolved lesions, keratinocytes are killed by the direct action of cytotoxic granules released from the $CD8^+$ T cells in concert with both $CD4^+$ effector T cells and neutrophils recruited from the circulating bloodstream. At the end of the immune response, Treg cells are recruited into the lesions and serve to ameliorate severity. Although the majority of activated cell populations are removed by apoptosis, a proportion of intraepidermal $CD8^+$ T cells is prevented from undergoing apoptosis by IL-15 (produced by surrounding keratinocytes) and persists as a stable population with a memory function. Treg, regulatory T cell.

Fig. 11.5 Lichen planus on the dorsal surface of the hand. Wickham's striae can be easily identified in the upper lesion. Note the flat-topped nature of the lesions and the post-inflammatory hyperpigmentation. *Courtesy, Frank Samarin, MD.*

Fig. 11.6 Lichen planus. Violaceous papules and plaques with white scale and Wickham's striae.

Fig. 11.7 Koebnerization of lichen planus into the site of the excision of the saphenous vein. Lesions also appeared where Steri-Strips™ had been applied.

Fig. 11.9 Exanthematous lichen planus. Papulosquamous lesions on the back.

Fig. 11.8 Annular lichen planus of the glans penis (A) and the trunk (B). On the penis, the lesions have led to a figurate outline with central hyperpigmentation.
A, Courtesy, Frank Samarin, MD.

hypertrophic, oral and nail LP tend to be more persistent. In particular, ulcerative oral LP may be a lifelong affliction.

Actinic LP

This variant is reported under a variety of names, including LP actinicus, LP subtropicus, LP tropicus and lichenoid melanodermatitis. Although the majority of reported patients have been from Middle Eastern countries, it has been observed worldwide. Most patients are young adults or children. There is no predilection for either sex. The onset of this variant is during the spring and summer, and the lesions primarily involve sun-exposed skin of the forehead and face, followed by the dorsal surfaces of the arms and hands and the neck. The lesions usually consist of red–brown plaques with an annular configuration, but melasma-like hyperpigmented patches have been observed. Summertime actinic lichenoid eruption (see below) has sometimes been regarded as a variant of or synonymous with actinic LP, but in the authors' opinion they are two separate entities with different histologic features.

Acute (exanthematous) LP

Because lesions are usually widely distributed and disseminate rapidly, this form is also known as exanthematous or eruptive LP. The commonly affected areas include the trunk (Fig. 11.9), the inner aspects of the wrists and the dorsal aspect of the feet. Reports in the literature of this form probably include lichenoid drug eruptions. The clinical course is usually self-limited and, in general, lesions resolve with hyperpigmentation within 3 to 9 months.

Annular LP

This form is thought to occur when papules spread peripherally and the central area resolves (see Fig. 11.8). The annular edge is slightly raised and typically purple to white in color, while the central portion is hyperpigmented or skin-colored; lesions can resemble granuloma annulare (except for the associated scale in annular LP). Annular lesions occur in about 10% of patients with LP and are usually scattered among more typical lesions, but the former may represent the predominant finding. The most common site of involvement is the axilla, followed by the penis (see Fig. 11.8A), extremities and groin. Most patients are asymptomatic, while some have pruritus.

Atrophic LP

Atrophic LP may represent a resolving phase of LP, given the history of the lesions: papules coalesce to form larger plaques that often, over time, become centrally depressed and atrophic with residual hyperpigmentation. The clinical appearance of atrophic LP is likely a result of thinning of the epidermis rather than degeneration of elastic fibers, and the epidermal atrophy may be accentuated by the use of potent topical corticosteroids. The most common site of involvement is the lower

extremity. This form closely resembles lichen sclerosus clinically (Fig. 11.10A); it may even mimic the early phase of morphea. Occasionally, morphea of the trunk has been reported in association with oral LP, as has the simultaneous occurrence of LP and lichen sclerosus, as well as the combination of LP, morphea and lichen sclerosus, the latter reflecting the well-known relationship between morphea and lichen sclerosus.

Recent reports have suggested the existence of another variant, referred to as "annular atrophic LP", in which there is complete loss of elastic fibers in the center (± the active borders) of the annular lesions.

Bullous LP and LP pemphigoides

Bullous or vesiculobullous lesions can develop solely within pre-existing LP lesions or more randomly, including within previously uninvolved skin. The former is called bullous LP (Fig. 11.10B), while the latter is referred to as LP pemphigoides (Fig. 11.10C).

A consensus has emerged that LP pemphigoides can be differentiated from bullous LP. In the latter, blisters occur in longstanding lesions of LP as a result of an intense lichenoid infiltration of lymphocytes and extensive epidermal damage, i.e. exaggerated Max-Joseph spaces. In contrast, in LP pemphigoides there are circulating IgG autoantibodies directed against the 180 kDa BP antigen (BPAG2, type XVII collagen), as in idiopathic BP. These findings suggest that damage to the basal layer by a lichenoid infiltrate may expose hidden antigens to the autoreactive T cells, leading to the formation of autoantibodies and subepidermal bullae. Indeed, LP pemphigoides evolving into pemphigoid nodularis has been described. To date, no reactivity against the 230 kDa BP antigen, type VII collagen or the laminin-5 subunits has been detected.

Hypertrophic LP

This variant is also referred to as LP verrucosus (Fig. 11.11). Extremely pruritic, thick hyperkeratotic plaques are seen primarily on the shins or dorsal aspect of the foot and may be covered by a fine adherent scale. The lesions are usually symmetric and tend to be chronic because of repetitive scratching. The average duration of hypertrophic LP in patients whose lesions had cleared was reported to be 6 years. Chronic venous stasis frequently contributes to the development of this condition. Squamous cell carcinoma may develop within a background of longstanding hypertrophic LP. It should be noted that there are patients who develop hypertrophic LP-like reactions with infundibulocystic follicular hyperplasia that may progress to multiple keratoacanthomas or follicularly based squamous cell carcinomas[21].

Inverse LP

In this unusual variant, an inverse distribution pattern is observed. Pink to violaceous papules and plaques appear in intertriginous zones (axillae > inguinal and inframammary folds; Fig. 11.12) and less often in the popliteal and antecubital fossae. Occasionally, LP lesions occur elsewhere on the body. Hyperpigmentation is usually present as well and it may be the sole manifestation, leading to overlap with LP pigmentosus.

LP pigmentosus

LP pigmentosus typically presents in individuals with skin types III and IV as brown to gray–brown macules in sun-exposed areas of the face and neck, usually with no preceding erythema and often evolving into diffuse or reticulated pigmentation (see Ch. 67). Involvement of intertriginous sites is occasionally observed, and a linear distribution following Blaschko's lines has also been described. Although the clinical and histologic (e.g. marked pigment incontinence and epidermal atrophy) features as well as the skin-type predilection of LP pigmentosus are similar to those of erythema dyschromicum perstans (see below), the former condition can be distinguished by its photo- and flexural distribution as well as an older mean age at onset (fourth to fifth versus first to third decades), a tendency for irregularly shaped or confluent rather than discrete oval lesions, and the coexistence of classic LP lesions in approximately 20% of patients.

Lichen planopilaris

In lichen planopilaris, involvement of the hair follicle is observed, both clinically and histologically. This variant is also called follicular LP and

Fig. 11.10 Unusual variants of lichen planus. A Atrophic lichen planus of the lower extremities. **B** Bullous lichen planus on the shin. **C** Lichen planus pemphigoides in a patient with anti-basement membrane zone autoantibodies.

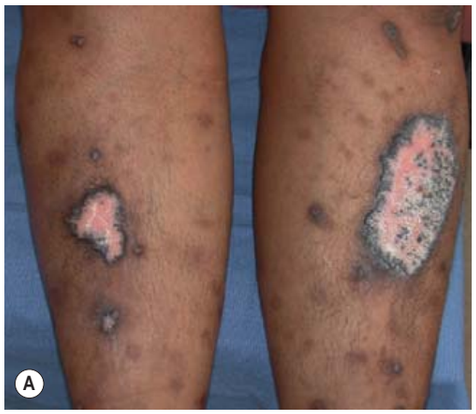


Fig. 11.11 Hypertrophic lichen planus. A On the shins, very thick discrete plaques with dyspigmentation are admixed with smaller linear plaques and areas of postinflammatory hyperpigmentation. **B** On the dorsal digits, thin violaceous plaques in addition to thick keratotic plaques that favor the knuckles. *B, Courtesy, Joyce Rico, MD.*

Fig. 11.12 Inverse lichen planus. Oval thin violaceous plaques in the axilla. Postinflammatory hyperpigmentation is also present. *Courtesy, Jeffrey P Callen, MD.*

Fig. 11.13 Lichen planopilaris. A Keratotic spines surrounded by a violaceous rim in a linear variant and **B** scattered on the trunk. **C** Cicatricial alopecia with "end-stage" changes centrally, but perifollicular inflammation at the margins.

LP acuminatus. Multiple, keratotic plugs surrounded by a narrow violaceous rim are observed primarily on the scalp, although other hair-bearing areas can also be affected (Fig. 11.13). The inflammatory process may result in scarring and loss of follicular structure, i.e. a permanent alopecia. Over time, the areas of involvement often "burn out" centrally and are indistinguishable from other causes of "end-stage" cicatricial alopecia (see Ch. 69). However, examination of the periphery may reveal the primary lesions (see Fig. 11.13C). Women are more frequently affected than men, and this form may occur alone or with typical LP lesions elsewhere.

A variant of lichen planopilaris known as Graham Little–Piccardi–Lassueur syndrome is characterized by the triad of: (1) non-cicatricial loss of pubic and axillary hairs and disseminated spinous or acuminated follicular papules (see Fig. 11.13B); (2) typical cutaneous or mucosal LP; and (3) scarring alopecia of the scalp with or without atrophy (see Fig. 11.13C). These features need not be present simultaneously. Another more recently recognized variant of LP of the scalp is frontal fibrosing alopecia which occurs primarily in elderly women.

Linear LP

Although linear lesions frequently occur in sites of scratching or trauma in patients with LP (as a result of the Koebner phenomenon), the term

linear LP (Fig. 11.14) is usually reserved for lesions that appear spontaneously within the lines of Blaschko (see Fig. 11.13A). Some authors consider linear LP an intermediate entity between LP and lichen striatus. This form has also been referred as zosteriform but the distribution pattern of LP is generally not dermatomal (with the exception of the koebnerization of LP into the site of a previous herpes zoster infection). The possibility exists that when LP has a strictly dermatomal pattern, this represents an isotopic phenomenon following "zoster sine herpete".

Although linear LP is usually seen in patients in their late 20s or early 30s, the initial presentation can be in the first to eighth decades. Presumably this pattern reflects somatic mosaicism (see Ch. 62), but how the involved and uninvolved skin differ is not known.

LP–lupus erythematosus overlap syndrome

Patients whose lesions have overlapping features of both LP and lupus erythematosus (LE) have been reported. These lesions are preferentially located in acral sites. Histologic and direct immunofluorescence (DIF) microscopic findings show features of both LP and LE. Whether systemic immunologic abnormalities such as high titers of ANA are present in these patients is controversial, but case reports suggest that some patients have disease at the chronic cutaneous LE end of the clinical spectrum while others meet the criteria for systemic LE.

Nail LP

The nails are affected in approximately 10% of patients with LP; usually, several nails are affected (see Ch. 71). The characteristic nail abnormalities include lateral thinning (Fig. 11.15A), longitudinal ridging, and fissuring (11.15B). These changes are manifestations of matrix damage, which can lead to scarring and dorsal pterygium formation (Fig. 11.15C) if left untreated. Nonspecific changes in the nail bed include yellow discoloration, onycholysis and subungual hyperkeratosis. In some patients, twenty-nail dystrophy may represent a variant of LP. Nail LP presenting as twenty-nail dystrophy is much more common in children than in adults, although other forms of nail involvement are extremely rare in children.

Fig. 11.14 Linear lichen planus. Coalescence of violaceous lesions with Wickham's striae along the lines of Blaschko on an extremity. Note the postinflammatory hyperpigmentation proximally. *Courtesy, Joyce Rico, MD.*

Oral LP

Oral LP can appear in at least seven forms, which occur separately or simultaneously: atrophic, bullous, erosive, papular, pigmented, plaque-like and reticular. The most common and characteristic form of oral LP is the reticular pattern (Fig. 11.16A). It is characterized by slightly raised whitish linear lines in a lace-like pattern or in rings with short radiating spines. This form is usually asymptomatic and the most common site of involvement is the buccal mucosa; lesions are often bilateral and symmetric. Gingival involvement is common, and oral LP affecting the gingivae exclusively is seen in approximately 10% of cases. It typically presents as chronic desquamative gingivitis. Gingivitis also occurs as a component of the "vulvovaginal–gingival syndrome" (see below).

Atrophic, erosive (Fig. 11.16B) and bullous lesions are associated with symptoms ranging from mild discomfort to severe pain. There is a higher incidence of plaque-like lesions among tobacco smokers. For unknown reasons, oral LP is very uncommon in young patients, and in some studies, women have been affected about twice as often as men.

Patients with oral LP should be questioned about symptoms related to esophageal involvement[21a] and examined for other mucosal lesions, particularly genital lesions, and vice versa, because ~70% of patients with mucosal vulvovaginal LP have clinical signs of oral LP. It has been reported that the erosive or ulcerative type of oral LP is less frequently associated with cutaneous LP than are all other types of oral LP. Such mucous membrane lesions are more therapy-resistant and less likely to spontaneously remit than cutaneous lesions. Malignant transformation of longstanding, non-healing oral LP has been reported, but it must be distinguished from pseudoepitheliomatous hyperplasia.

Several studies have reported a relationship between oral LP and chronic liver disease, particularly that due to HCV infection (see Pathogenesis)[4,5]. Some authors found that in patients with the reticular and plaque forms, there were statistically significant differences between those with and those without HCV infection, whereas other authors reported an association of HCV with the erosive type. In the HCV-positive oral LP group, oral lesions were more frequently located on the tongue, labial mucosa and gingivae[22].

Ulcerative LP

Ulcerations can occur within palmoplantar lesions of LP, particularly those on the soles. Palmoplantar LP is not as rare as was once thought

Fig. 11.15 Nail lichen planus. A Thinning of the nail plate with lateral loss. **B** Longitudinal fissuring of shortened nail plates. **C** Violaceous discoloration of the periungual area with pterygium formation.

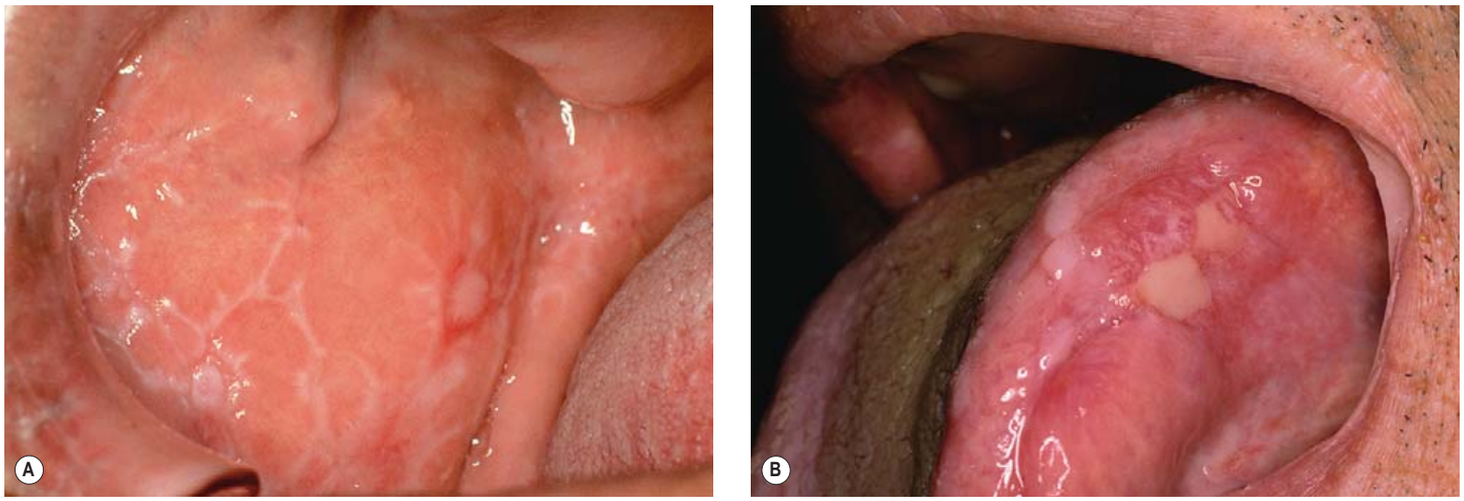


Fig. 11.16 Oral lichen planus. A White lacy pattern and an erosion on the buccal mucosa, the most common location for the reticular form. Note the ring configuration with short radiating spines. **B** Erosions on the lateral aspect of the tongue in addition to lacy white plaques and scarring. *B, Courtesy, Louis A Fragola, Jr, MD.*

and usually appears between the third and fifth decade of life. Although palmoplantar LP is more common in men than in women, ulcerative LP prevails in female patients. Typical LP lesions may be present in additional sites of the body. The ulcers are intensely painful and often recalcitrant to conventional therapy. Chronic ulcerative lesions are at risk of developing squamous cell carcinoma.

Vulvovaginal LP

LP of the vulva can present with several clinical variants, but the most common appears to be erosive disease[23]. Vaginal involvement occurs in up to 70% of women with erosive vulvar LP, and because there is often oral mucosal involvement as well, the term "vulvovaginal–gingival syndrome" has been introduced. The differential diagnosis of vulvovaginal LP includes lichen sclerosus and blistering diseases (see Ch. 73). Since scarring may be a sequela of vulvovaginal LP, patients should be carefully monitored for the development of malignancy, including after the resolution of active disease.

Lichenoid drug eruption (drug-induced LP)

Despite the significant overlap between LP and lichenoid drug eruption (Fig. 11.17), there are both clinical and histologic clues that favor one diagnosis over the other (Table 11.4)[24]. Both sexes are equally affected, but lichenoid drug eruptions tend to occur in adults approximately 10 years older than those with idiopathic LP.

There is usually a latent period of several months from drug introduction to the appearance of the cutaneous eruption. Halevy and Shai[12] reported 17 patients with lichenoid eruptions induced by a variety of drugs and found that the mean latent period was 12 months. The latent period varies depending not only on the offending drug, but also on other factors such as the frequency of drug administration, the dosage, and the intensity of the patient's individual reaction to the offending drug. For example, the latent period has been reported to be between 2 months and 3 years for penicillamine, approximately 1 year for β-blockers, and 4–6 weeks for quinacrine. In contrast to morbilliform eruptions, the time course between drug cessation and lesional resolution can be several weeks to months.

A wide range of cutaneous eruptions have been observed in patients receiving TNF-α inhibitors; they include new onset or paradoxical worsening of psoriasis (including palmoplantar pustulosis), eczematous eruptions, interstitial granulomatous dermatitis, granuloma annulare, cutaneous small vessel vasculitis, cutaneous lupus erythematosus, and lichenoid eruptions. The latter are not limited to any particular TNF-α inhibitor, and while some patients have clinical features similar to idiopathic LP, others have less specific skin lesions clinically, but on histologic examination lichenoid interface changes are seen. The time interval between initiation of TNF-α blockade and appearance of the lichenoid eruption varies from 3 weeks to 16 months. In some patients, complete resolution or significant improvement followed discontinuation of the TNF-α inhibitor, whereas in others, clearance occurred despite continued administration of the drug. In that TNF-α inhibitors are used to treat severe LP, a possible explanation for the paradoxical induction of lichenoid eruptions is a tipping of the balance between Th1 and Th2 immune responses, Treg and Th17 cellular responses, or IFN-α and IFN-γ production. Perhaps inhibition of TNF-α allows for upregulation of other cytokines such as IFN-α.

Fig. 11.17 Lichenoid drug eruption. Photodistributed lichenoid eruption due to hydrochlorothiazide (note sparing under watchband).

"Giant cell lichenoid dermatitis" is a relatively novel, usually drug-associated entity, characterized by a lichenoid dermatitis with a granulomatous infiltrate composed of histiocytes and multinucleated giant cells. Patients present with red–purple papules and plaques, and diagnosis of the disease, also called granulomatous lichenoid dermatitis, is based solely on histologic criteria. Additional histologic features include infiltration of hair follicles and eccrine structures. When this reaction pattern represents a hypersensitivity drug reaction, it may develop during the active or resolving phase of a viral infection[25]. The implicated drugs include antibiotics, ACE inhibitors, β-blockers,

FEATURES FOR DISTINGUISHING LICHENOID DRUG ERUPTION FROM LICHEN PLANUS		
	Lichenoid drug eruption	**Idiopathic lichen planus**
Mean age	66 years	50 years
Location	More generalized; often spares the "classic" sites of LP	Wrists, flexor forearms, presacral, lower legs, genitalia
Morphology	More eczematous, psoriasiform or pityriasis rosea-like	Shiny, flat-topped, polygonal, violaceous papules
Wickham's striae	Uncommon	Present
Hyperpigmentation	Very common, sometimes persistent	Common
Photodistribution	Frequent*	Unusual
Mucous membranes	Usually spared	Often involved
Histology	Varying degree of eosinophilic and/or plasma cell infiltrates	Eosinophils and plasma cells uncommon
	Deep infiltrate may be present	Dense band-like infiltrate of lymphocytes
	Parakeratosis	No parakeratosis

*Especially with medications such as hydrochlorothiazide.

Table 11.4 Features for distinguishing lichenoid drug eruption from lichen planus.

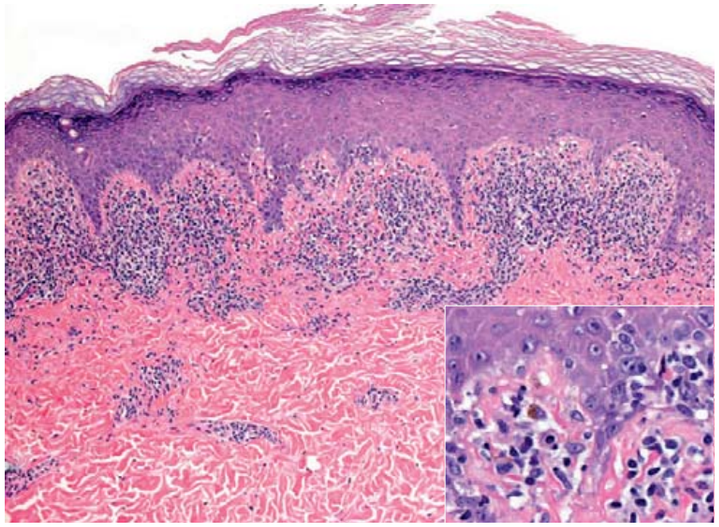


Fig. 11.18 Histopathologic features of lichen planus. Hyperkeratosis, focal increase in the granular layer, sawtoothing of the epidermis with keratinization of the basal layer, and a lichenoid infiltrate. Apoptosis of keratinocytes and melanophages are also present (insert). *Courtesy, Lorenzo Cerroni, MD.*

lipid-lowering agents, phenolphthalein, and nonsteroidal anti-inflammatory drugs (NSAIDs).

Pathology

Despite its different clinical manifestations, the histopathology of LP is fairly uniform. The primary features are hyperkeratosis without parakeratosis, focal increases in the granular cell layer, irregular acanthosis with a "sawtooth" appearance, liquefactive degeneration of the basal cell layer, and a band-like lymphocytic infiltrate at the dermal–epidermal junction (Fig. 11.18). Colloid bodies representing apoptotic or dyskeratotic keratinocytes (also referred to as Civatte, hyaline or cytoid bodies) are usually present in the lower levels of the epidermis and the superficial dermis. Vacuolar changes within the basal cell layer may become confluent and result in small separations between the epidermis and the dermis (called "Max-Joseph spaces"). There is often incontinence of pigment with multiple dermal melanophages.

The number of epidermal Langerhans cells is usually increased in active lesions. The majority of cells in the inflammatory infiltrate are lymphocytes, mainly $CD3^+$ T cells (see Pathogenesis, above). However, exocytosis of lymphocytes into the epidermis is usually not abundant in LP. Plasma cells, macrophages or eosinophils may be seen within the dermis, but not frequently and the latter more commonly in drug-induced LP. Neutrophils are not commonly seen in LP.

Oral LP lesions often show parakeratosis rather than hyperkeratosis, and the epidermis frequently becomes atrophic. Lesions of lichen planopilaris are characterized by an inflammatory cell infiltrate around the hair follicles even at an early stage. Most of the inflammation involves the upper half of the follicle, with the isthmus affected in one-third of patients. Destruction of the follicles represents a later stage. In LP pemphigoides, a primary histologic feature of the bullous lesions is a subepidermal separation with an abundance of eosinophils (occasionally neutrophil-rich infiltrates), whereas the papular lesions have the usual features of LP. DIF microscopy of peribullous skin shows linear deposition of IgG and C3 along the dermal–epidermal junction, similar to BP.

Apoptotic cells, as evidenced by Civatte bodies, tend to remain in the lower levels of the epidermis in idiopathic LP; in contrast, they are found in the spinous or granular layer in lichenoid drug eruptions. In a nonspecific "sponge-like" manner, colloid bodies often stain with IgM, IgA, IgG or C3, and this is the characteristic finding by DIF microscopy. In lichen planopilaris lesions, IgM, IgG and IgA are found in varying combinations along the follicle–dermal interface. Although the band-like inflammatory infiltrate is usually restricted to the papillary dermis in LP and involvement of the deep vascular plexus suggests a lichenoid drug eruption (though observed in <50% of cases), inflammation and destruction of the distal and proximal ends of the sweat ducts is also seen in some cases of LP; however, the secretory glands are unaffected.

The histologic changes in lichenoid drug eruption are very similar to those in idiopathic LP (see Table 11.4). Van den Haute et al.[24] conducted a retrospective study in which they compared histologic sections from 15 patients with idiopathic LP and 15 with a lichenoid drug eruption. They noted that no single feature was significantly more likely to occur in the latter than in the former. Nonetheless, they assigned some histologic signs to a list of "lichenoid drug eruption-related criteria" because they were present in more than 50% of the drug eruption cases and were not seen in idiopathic LP (in their study); these included focal parakeratosis, focal interruption of the granular layer, and cytoid bodies in the cornified and granular layers. Although eosinophils were observed exclusively in the lichenoid drug eruptions, they were found in only 2 of the 15 cases. Thus, these results indicate that the absence of eosinophils cannot be interpreted as a sign of idiopathic LP. Also, there were no significant differences in DIF findings between lichenoid drug eruptions and idiopathic LP. In sum, it would be ill advised to make the diagnosis of lichenoid drug eruption solely on the basis of histologic criteria.

Differential Diagnosis

LP can be viewed as one of the major reaction patterns in response to various exogenous agents such as drugs, viruses and contact allergens. Before labeling patients as having "idiopathic LP", an in-depth search should be undertaken to identify any such inducing factors, because there are no definite criteria (either clinical or histologic) for differentiating drug-induced LP from idiopathic LP. Patients with oral LP lesions in apposition to metallic dental restorations should undergo patch testing with relevant metals (see Ch. 14). These metals include amalgam (mercury), copper and gold. A lichenoid "id" reaction can be seen in children with contact dermatitis to nickel (e.g. in metal snaps in pants).

Other inflammatory conditions that are in the clinical differential diagnosis include lupus erythematosus (LE), lichen nitidus, lichen striatus, lichen sclerosus, pityriasis rosea, erythema dyschromicum perstans (ashy dermatosis), psoriasis, annular lichenoid eruption, lichenoid GVHD, and secondary syphilis. Patients with paraneoplastic pemphigus can have clinical features of a mucocutaneous lichenoid eruption (see Ch. 29).

The disease that is most difficult to differentiate from LP is LE, particularly in patients with oral or scalp lesions alone. In these patients, the diagnosis of LE may only be made after additional biopsies are performed or other signs of LE appear. DIF studies are helpful; granular or homogeneous bands of immunoglobulin in the basement membrane zone have been demonstrated in lesional and non-lesional mucosa in systemic LE (100% and 71%, respectively) and in lesional mucosa in chronic cutaneous (discoid) LE (73%), but only rarely in LP (4%)[26]. The situation becomes even more complicated when there is a flare of disease in a patient with cutaneous LE who is receiving an antimalarial drug, one of the more common causes of a lichenoid drug eruption (see Table 11.2).

When LP affects the mucosal surface of the vulva, the lesions may be difficult to differentiate clinically or histologically from other inflammatory diseases, especially lichen sclerosus. While LP typically involves the inner aspects of the labia minora and consists of a glazed erythema that may easily bleed on touching, lichen sclerosus is typically observed on the outer aspects of the labia minora, and the vagina and oral mucosa are usually not involved. This mucosal vulvar variant of LP affects adult women and has not been reported before puberty, while lichen sclerosus is frequently seen in children.

Treatment

It is difficult to evaluate the efficacy of different forms of therapy in LP, because the majority of reports regarding its treatment consist of small series of patients or anecdotes (Table 11.5). In addition, spontaneous remission of cutaneous and oral LP can occur after varying amounts of time. For example, spontaneous remission of cutaneous LP has been observed in up to two-thirds of patients after 1 year, whereas the reported mean duration of oral LP is about 5 years and the erosive form rarely spontaneously resolves[22].

In all instances, the possibility that LP is drug-induced should be considered before embarking on therapy. The diagnosis of lichenoid drug eruption is confirmed by withdrawal of the suspected drug followed by disappearance of the lesions and their recurrence upon re-exposure to the drug. However, rechallenge is often not performed. There are reports of patch testing and *in vitro* tests that involve incubation with the offending drug (e.g. lymphocyte stimulation and macrophage migration inhibition tests[12]) being used to identify the causative drugs, but they remain of limited value in confirming the diagnosis.

The next step is to determine which drug – or drugs, if multiple drugs are prescribed – should be withdrawn. The degree of difficulty depends upon the ability to substitute an unrelated but equally effective drug. Lastly, both the patient and the physician who prescribed the medication must be advised that withdrawal of the causative drug may not lead to quick resolution of the skin eruption and that therapies utilized for idiopathic LP may be required (see below).

Well-described therapies for LP include topical, intralesional and systemic corticosteroids, systemic retinoids, narrowband UVB, PUVA, topical calcineurin inhibitors, antimalarials and, for severe or treatment-resistant cases, oral immunosuppressive agents. In mild cases, symptomatic treatment includes topical corticosteroids and oral antihistamines for reducing pruritus. Topical corticosteroids are particularly popular for children. Hypertrophic LP lesions may benefit from intralesional corticosteroids or topical corticosteroids under occlusion. Vulvovaginal LP is best treated with topical superpotent (class I) corticosteroids and calcineurin inhibitors (see Table 11.5)[27], but if they fail, oral immunosuppressive drugs (e.g. methotrexate, mycophenolate mofetil) and/or low-dose oral prednisone may be required. Of note, despite their worldwide use as a mainstay of therapy, the efficacy of topical corticosteroids in cutaneous LP has not been systematically evaluated. Inhaled forms of corticosteroids are sometimes used for oral LP.

In several studies, tacrolimus 0.1% ointment was found to be effective in reducing the symptoms of oral LP unresponsive to more conventional therapies, including erosive disease. Most patients experienced symptomatic improvement in less than 1 month following twice-daily application. However, in one study, the median relapse time was 5 weeks (range, 2 to 20 weeks), and patients often require intermittent therapy to prevent subsequent flares[28]. Symptoms of burning did resolve with continued use of the ointment. To date, serious adverse effects from long-term use (>1 year) have not been reported. However, given the FDA warning regarding topical calcineurin inhibitors and a possible increased risk of cutaneous carcinomas plus the increased risk of developing squamous cell carcinoma in the setting of erosive oral and vulvar LP, continued safety monitoring is recommended.

In a recent small case series, topical rapamycin (sirolimus) resulted in a complete (4/6 patients) or partial (2/6 patients) remission by 3 months in individuals with refractory erosive oral LP. The proposed mechanism of action of rapamycin is an increase in the number of Treg cells, leading to decreased activation of T cells and B cells.

Systemic therapies

In severe, acute cases, systemic *corticosteroids* remain a commonly employed intervention. Although different dosage regimens have been proposed, the minimal effective daily dose of prednisone for treating LP is usually 15 to 20 mg[1]; treatment is continued for 2–6 weeks and then gradually tapered over several weeks. Rebound and relapses may occur, but long-term maintenance therapy with systemic corticosteroids should be avoided. One study demonstrated that the median time to clearing was 18 weeks in the corticosteroid-treated group and 29 weeks in the placebo group[29].

Acitretin is the only systemic retinoid that has a relatively good level of evidence regarding its efficacy in the treatment of cutaneous LP. A therapeutic regimen consisting of acitretin 30 mg/day for 8 weeks resulted in significant improvement or remission in 64% of those in the treatment group, compared with 13% in the placebo group. Retinoids tend to be used for recalcitrant cases, and, therefore, relapses may occur after discontinuation of the drug; as a result, long-term maintenance therapy may be required. The authors have successfully used etretinate (50 mg/day) to treat patients with the acute, exanthematous form of LP.

Long-term (3 to 6 months) administration of *griseofulvin* was shown to result in complete improvement in 86% of patients with LP[1]; however, the methods used in this study were not described in complete detail, so definitive conclusions cannot be made. In particular, oral erosive lesions have been reported to respond favorably to this drug. As a result, griseofulvin is often tried in such patients. A complete response or significant improvement (79%) of generalized LP (mean duration of disease, 3.5 months) was observed with *metronidazole*, 500 mg twice daily for 20 to 60 days[30]. More recently, in a

THERAPEUTIC LADDER FOR LICHEN PLANUS ℞

- Topical corticosteroids (2)
- Superpotent topical corticosteroids (oral LP (1); cutaneous LP (2))
- Topical calcineurin inhibitors (e.g. pimecrolimus and tacrolimus in oral LP (1); tacrolimus in vulvar (2) and other forms (3) of LP)
- Intralesional corticosteroids (2)
- Intramuscular triamcinolone acetonide [0.5–1 mg/kg/month × 3–6 months] (3)
- Narrowband UVB (2)
- Oral metronidazole* [500 mg po bid] (2)
- Antimalarials* (2)
- Systemic retinoids* (1 for etretinate; 3 for alitretinoin)
- Griseofulvin* (2)
- PUVA (2)
- UVA1 (2)
- 308-nm excimer laser for oral LP (2)
- Systemic corticosteroids† (1)
- Low-dose weekly methotrexate (2)
- Mycophenolate mofetil (2)
- Thalidomide (2)
- Cyclosporine (3)
- Sulfasalazine* (1 for cutaneous LP)
- Extracorporeal photochemotherapy (2)
- Targeted immunomodulators (TNF-α inhibitors, alefacept, basiliximab) (3)

*Implicated in lichenoid drug eruptions.
†Often a first-line therapy for severe, acute cutaneous LP.

Table 11.5 Therapeutic ladder for lichen planus. Systemic treatments are usually reserved for more severe disease. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

retrospective study, *hydroxychloroquine* (200 mg twice daily) was shown to improve both lichen planopilaris and frontal fibrosing alopecia[31]. Oral *sulfasalazine* administered in increasing doses from 1.5 to 3 g/day for at least 4 weeks was reported to be effective for cutaneous LP but not for mucosal LP. Recently, a randomized, double-blind, placebo-controlled trial utilizing a maximum of 2.5 gm/day of sulfasalazine found cutaneous improvement (>50%) in 82.6% vs 9.6% of patients at six weeks[31a].

Based upon a case series, weekly low-dose *methotrexate* was noted to improve oral LP[32]. Efficacy of methotrexate for generalized LP has also been described. A complete response was achieved in 10 of 11 patients within 1 month and the medication was well tolerated without adverse effects.

Based on a small case series, oral *cyclosporine* was reported as useful in inducing a remission in severe cases of LP resistant to retinoids and systemic corticosteroid therapy[33]. Complete responses have been observed with doses of cyclosporine ranging from 1 to 6 mg/kg/day. The majority of patients have not experienced a relapse during follow-up periods of several months, but a rebound in disease activity can occur upon discontinuation of cyclosporine. Similar successful results were described in lichen planopilaris; alleviation of symptoms, resolution of clinical activity, and halting the progression of hair loss was achieved within 3 to 5 months[34]. However, long-term use of cyclosporine can be associated with renal toxicity, hypertension and an increased risk of developing cutaneous squamous cell carcinomas (see Ch. 130).

Mycophenolate mofetil, an immunosuppressive agent which specifically and reversibly inhibits the proliferation of activated T cells, was reported to be effective in the management of disseminated, erosive, hypertrophic and bullous variants of LP as well as lichen planopilaris[35]. It may be preferable to other immunosuppressive drugs such as cyclosporine because of its safer side-effect profile. *Thalidomide* has also been reported to be an effective therapy.

Newer *TNF-α inhibitors* (see Ch. 128) as well as T-cell-modulating biologic therapies (e.g. *alefacept)* have been used in scattered patients with severe recalcitrant LP. For example, *basiliximab*, a chimeric antibody directed against the IL-2 receptor, reportedly improved severe erosive oral LP. Another observation was a more rapid response to alefacept in two patients with LP as compared to those with psoriasis, perhaps suggesting a more direct role for $CD4^+$ T cells. Specific recommendations await larger clinical trials.

Phototherapy

In patients with resistant longstanding LP, significant improvement has been observed after bath or systemic PUVA. However, the risk of promoting carcinogenesis, especially in patients with skin types I and II, has to be balanced against the benefits. The usefulness of PUVA has prompted evaluation of extracorporeal photopheresis (ECP) for recalcitrant LP. One case series demonstrated that erosive oral LP cleared in all seven patients after an average of 24 sessions of ECP (two consecutive days per month) and follow-up at 24 months revealed no recurrences[36].

UVA1 has been shown to be effective in the treatment of therapy-resistant LP, including disease exacerbated during PUVA therapy. The use of narrowband UVB (peak emission 311 nm) for recalcitrant LP has also been reported. In an open prospective trial in 10 patients with recalcitrant LP, complete clearance occurred after 30 exposures (mean cumulative dose, 17.7 J/cm^2) in five patients, while partial responses were observed (without any recurrences for 6 months) in the remainder. The excimer laser (308 nm) was used to treat oral LP unresponsive to conventional therapies and was reported to produce excellent results[37]. Remission times ranged from 2 to 17 months. Of note, the only poor responder in the study had chronic active HCV infection.

LICHEN STRIATUS

Synonyms: ■ Linear lichenoid dermatosis ■ *B*laschko *l*inear *a*cquired *i*nflammatory *s*kin *e*ruption (BLAISE)

Key features

- An asymptomatic, linear dermatosis that primarily affects children
- The primary lesion is a small, flat-topped papule that ranges in color from pink to skin-colored to tan (hypopigmented)
- Multiple lesions appear over the course of days to weeks along the lines of Blaschko and usually on an extremity
- Spontaneously resolves over months to a few years
- Digital involvement may result in nail dystrophy

Introduction

Lichen striatus is an asymptomatic, uncommon, self-limited, linear dermatosis of unknown etiology that generally affects children. The diagnosis is usually made clinically based upon the appearance of the primary lesions and the distinctive developmental pattern. Its distribution along Blaschko's lines plus the age of the patient usually narrows the differential diagnosis rather quickly. Occasionally, there is overlap with linear LP and "blaschkitis" (see Ch. 62).

History

In 1898, Balzer and Mercier first described a peculiar linear papular eruption that they termed "lichenoid trophoneurosis". Forty years later, Senear and Caro proposed the name "lichen striatus". Ever since the condition was first described, the pathogenesis of its linearity has been the subject of debate. Brocq proposed that it represented a locus minoris resistentiae, but we now know that it is a manifestation of mosaicism (see Ch. 62).

Epidemiology

Lichen striatus is seen primarily in children between the ages of 4 months and 15 years, although the disorder occasionally occurs in adults; the median age of onset is 2 to 3 years and the vast majority of cases occur in preschool-age children[38]. The reported female : male ratio has varied from 1.6 : 1[39] to 2 : 1[38].

Pathogenesis

Although the distribution of lichen striatus along Blaschko's lines points to somatic mosaicism (see Ch. 62), neither the gene(s) involved nor the triggering factors are known. Environmental agents, particularly viruses, have been implicated, given the predominance of the disorder in young children and its seasonal variation (it appears more commonly during spring and summer). However, to date, a viral association has not been proven via serologic testing or cultures.

In theory, during early fetal development, aberrant clone(s) of epidermal cells produced by somatic mutation migrate out along the lines of Blaschko. Exposure to an infectious agent (e.g. virus, BCG vaccine) or other precipitant could then break previous tolerance to the aberrant clone by inducing a novel membrane antigen. The presence of $CD8^+$ T cells scattered or in clusters around necrotic keratinocytes supports a cell-mediated immunologic reaction by which cytotoxic T cells would attack and eliminate the mutated or virally modified keratinocyte clones. A similar mechanism has been proposed for linear LP, and a post-transplant loss of tolerance could explain linear GVHD.

Lichen striatus may represent a manifestation of an atopic diathesis with the abnormal immune responses usually associated with atopy being a predisposing factor. The timing and relative infrequency of lichen striatus suggests that an infectious agent acts as a trigger in genetically predisposed individuals. Lastly, there are scattered reports of lichen striatus occurring at sites of injury (e.g. the periphery of a burn scar[39]) rather than along Blaschko's lines, but this could also be explained by a break in tolerance.

Clinical Features

Lichen striatus is typically asymptomatic, but intense pruritus can occasionally occur. The eruption consists of a continuous or interrupted band composed of discrete or clustered pink, skin-colored or tan

Fig. 11.19 Lichen striatus. A Linear array of pink flat-topped papules on the hand in association with dystrophy (splitting, fraying) of R2 (lateral) and R3 (medial) nails. **B** Single streak on the lower extremity composed of multiple pink flat-topped papules. The primary differential diagnosis would be blaschkitis and linear LP.

(hypopigmented) papules that are flat-topped, smooth or scaly, and range in diameter from 2 to 4 mm. Infrequently, vesicles may be present. Typically, there is a single, unilateral streak on an extremity along Blaschko's lines (Fig. 11.19); occasionally, there is a bilateral distribution pattern and/or multiple parallel bands. It is uncommon for lichen striatus to involve the trunk or head and neck region. There are reports of the eruption speading distally from the trunk down an extremity, as well as observations of proximal extension along an extremity[40]. Although lichen striatus does not usually recur, relapses may occasionally occur, either in the same site or on the same side of the body[38].

The eruption usually appears suddenly, develops fully over days to weeks, and after several months to a year or more, undergoes spontaneous resolution, leaving postinflammatory hypopigmentation, particularly in those with more darkly pigmented skin. In the latter individuals, the eruption is often first noticed as linear hypopigmentation. When lesions involve the nail apparatus, onycholysis, splitting, fraying and total nail loss may result (see Fig. 11.19A).

Pathology

The histologic features of lichen striatus are variable and depend upon the age of the lesion at the time the biopsy is performed. In addition, different areas within the same streak can have different findings. In general, there is a lichenoid tissue reaction in addition to varying degrees of involvement of the hair follicles and sweat glands and ducts. Even though the lichenoid inflammation that may be present around hair follicles is indistinguishable from that seen in lichen planopilaris, sweat gland and hair follicle involvement can still be a helpful diagnostic feature of lichen striatus[39].

The alterations within the epidermis are secondary and include intercellular and intracellular edema, exocytosis, parakeratosis, dyskeratosis, and focal or diffuse lysis of the basal layer in areas where the lichenoid infiltrate invades the epidermis. Dyskeratotic keratinocytes may be found in the granular and horny layers (similar to the corps ronds in Darier disease) and at the dermal–epidermal junction in up to half of the cases. Older lesions may have features similar to those seen in LP or lichen nitidus. By immunohistochemistry, $CD3^+$ T-cell infiltrates were noted in which $CD8^+$ T cells surrounded necrotic keratinocytes and infiltrated vesicles filled with Langerhans cells. Depending upon the age of the lesions, Langerhans cells were either decreased (earlier lesions due to the attack by $CD8^+$ T cells) or increased (later phase due to an influx of precursor cells).

Differential Diagnosis

Although the differential diagnosis includes other inflammatory diseases that can assume a linear pattern, such as linear porokeratosis, linear psoriasis, inflammatory linear verrucous epidermal nevus, and linear Darier disease, the primary differential diagnosis is linear LP, blaschkitis and linear GVHD. The latter occurs in a specific clinical setting, while blaschkitis favors the trunk, is usually seen in adults, often consists of multiple streaks, and can have features of dermatitis. Although linear LP and lichen striatus can occasionally be indistinguishable histologically, the primary lesions usually differ in size and color, and hypopigmentation is a frequent sequela of lichen striatus, while, in general, hyperpigmentation appears in the wake of LP. Lichen striatus is also characterized by minimal, if any, pruritus, as well as spontaneous resolution within a short period of time. In lichen nitidus, linear lesions reflect previous traumatic injury to the skin.

Treatment

Treatment of lichen striatus is usually not needed, except for the unusual case in which there is significant pruritus. Topical corticosteroids under occlusion have successfully been used to hasten spontaneous resolution. In scattered case reports, topical calcineurin inhibitors have also been reported to be effective, including for the nail dystrophy. Obviously, with any purported therapy, the natural history of lichen striatus must be kept in mind.

LICHEN NITIDUS

Key features

- The eruption consists of multiple, tiny, discrete, shiny papules, often in clusters
- Favored sites of involvement include the flexor aspects of the upper extremities, the genitalia and the anterior trunk
- Linear arrays of papules occur secondary to the Koebner phenomenon
- The histologic correlate of the papule is a well-circumscribed infiltrate composed of lymphocytes and epithelioid cells confined to the width of two to three dermal papillae

Introduction

Lichen nitidus is an uncommon chronic eruption consisting of multiple, tiny, discrete, skin-colored papules that are often arranged in larger clusters. The papules have a distinctive histology with a dense, well-circumscribed, lymphohistiocytic infiltrate closely apposed to the epidermis. There has been considerable debate, however, as to whether lichen nitidus represents a distinct and separate entity or should be regarded as an unusual variant of LP; their coexistence has certainly been reported and progression from lichen nitidus to LP has also been observed. It is generally accepted that lichen nitidus has no relationship to any systemic illness; only a few authors believe that it may be a cutaneous manifestation of Crohn's disease[41].

History

In 1901, Pinkus first described a peculiar papular eruption he termed "lichen nitidus" and suggested that it was a distinct entity histologically. Based upon the presence of epithelioid cells within the well-circumscribed inflammatory infiltrate, early authors believed that lichen nitidus was of tuberculous origin.

Epidemiology

Reliable epidemiologic data are difficult to accumulate because of the relative rarity of lichen nitidus. In a US study of 43 patients, primarily Caucasians and African-Americans, the disorder was not found to be restricted to any specific population group based on race, sex or age[42]. Other authors have reported that lichen nitidus is more prevalent among children or young adults, and a female predominance has been described in the generalized variant. It has also been reported in patients with Down syndrome.

Pathogenesis

Although much attention has been focused on the relationship of lichen nitidus to LP, there has been limited recent study of its pathogenesis. Lichen nitidus was initially thought to represent a tuberculous lesion or tuberculid because of its histologic features. However, no causative (infectious) agents have ever been demonstrated, even by repeated inoculations of tissue into animals.

Even though LP and lichen nitidus can coexist in the same patient and they share some similar clinical features (Table 11.6), most authors believe that lichen nitidus is a separate entity because of its distinctive clinical and histologic features. The possibility exists that the two conditions represent different responses to a similar triggering factor (e.g. hepatitis B vaccine). For example, Kano et al.[41] described a patient who had Crohn's disease in whom LP and lichen nitidus developed over different time frames. However, in view of the distinct differences in the composition of the respective cellular infiltrates, immunologic mechanisms responsible for the development of lichen nitidus are likely different from those in LP.

Clinical Features

Lichen nitidus is characterized by numerous tiny, discrete, skin-colored, uniform, pinhead-sized papules (Fig. 11.20A) that occasionally exhibit a central depression. Individual papules are usually flat with a shiny surface (Fig. 11.20B). Pruritus can occur, but it is an uncommon feature. Although most often skin-colored, the papules may exhibit a variety of hues, from pink or yellow to red–blue or brown. In darkly pigmented individuals, the papules tend to be hypopigmented, but sometimes they are hyperpigmented; marked hyperpigmentation has rarely been reported.

The lesions are usually distributed on the flexor aspects of the upper extremities as well as the genitalia, chest, abdomen and dorsal aspects of the hands. Less commonly, the face, neck, lower extremities, palms, soles and mucous membranes are involved. Oral lesions are thought to be rare but are probably underestimated; they appear as minute, flat, gray–white papules on the soft mucosa or white plaques on the tongue and hard palate. Nail involvement is observed up to 10% of patients (primarily adults) and the changes include pitting, rippling, longitudinal ridging, terminal splitting, and increased longitudinal linear striations. Occasionally, the typical papules of lichen nitidus are seen in the perungual region.

COMPARISON OF CLINICAL AND HISTOLOGIC FEATURES OF LICHEN NITIDUS VERSUS LICHEN PLANUS

	Lichen nitidus	Lichen planus
CLINICAL		
Size	Pinhead	Pinhead to larger plaques
Color	Skin-colored	Violaceous
Number	Multiple to numerous	Multiple
Distribution	Upper extremities (flexor aspects), genitalia, chest, abdomen	Wrists, flexor forearms, presacral, dorsal aspect of hands, anterior lower legs, genitalia
Oral involvement	Rare*	Common (>50%)
Nail involvement	<5–10%	~10%
Wickham's striae	Absent	Common
Hyperpigmentation	Uncommon	Common
Hypopigmentation	Common†	Unusual
Koebner phenomenon	Common	Common
Pruritus	Sometimes	Common
HISTOLOGIC		
Parakeratotic cap	Common	Rare
Granular layer	Thin to absent	Focally increased
Dermal infiltrate	Lymphocytes, epithelioid cells and occasional Langhans giant cells; usually confined to width of 2–3 dermal papillae; "ball and claw" configuration due to hyperplastic rete ridges	Band-like infiltrate of lymphocytes
Transepidermal elimination	Unusual	Rare
Deposits of immunoreactants	Absent	Globular deposits of IgG, IgA, IgM and/or C3 in lower levels of the epidermis

*May be underestimated.
†Especially in darkly pigmented individuals.

Table 11.6 Comparison of clinical and histologic features of lichen nitidus versus lichen planus.

Lichen nitidus is one of several diseases that exhibit the Koebner phenomenon. The latter is especially prevalent in patients with generalized disease. Vesicular and hemorrhagic lesions are found in some patients, and they are often admixed with the more typical papules. Several other variants have been described, including palmoplantar, linear and follicular spines. A perforating variant has also been reported, usually in association with LP. While grouped papules tend to remain distinct, they may coalesce into plaques (especially in the generalized type), and when this occurs on the elbows and knees, it can have a psoriasiform appearance. According to one study, the duration in two-thirds of the patients was 1 year or less and the longest duration was 8 years[42]. It is generally accepted that lichen nitidus is not associated with any systemic diseases or abnormal laboratory findings.

Pathology

The constellation of histologic features in lichen nitidus is very distinctive. As a result, the clinical diagnosis can be confirmed histologically. A well-circumscribed infiltrate composed of lymphocytes, epithelioid cells and occasional Langhans giant cells is typically "clutched" by the surrounding hyperplastic rete ridges in a "ball and claw" configuration (Fig. 11.21). In most lesions, the infiltrate is confined to the width of two to three dermal papillae.

The overlying epidermis is usually atrophic and frequently exhibits a parakeratotic "cap" centrally. Absence or thinning of the overlying

Fig. 11.20 Lichen nitidus. A Numerous tiny flat-topped papules on the hand. **B** A close-up view shows the shiny surface.

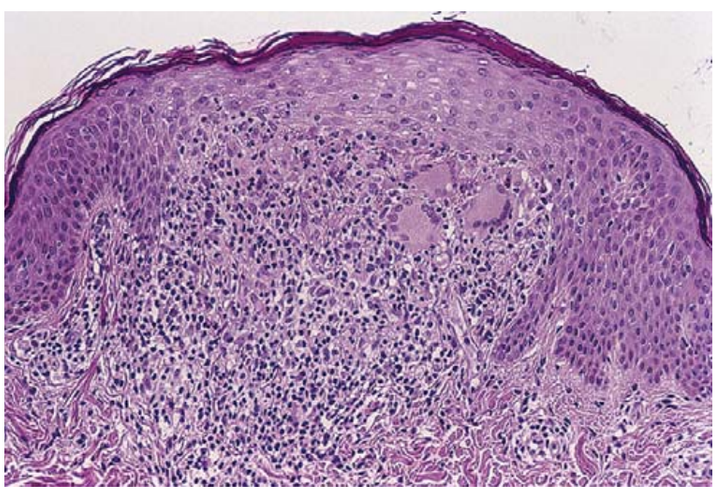


Fig. 11.21 Histopathologic features of lichen nitidus. Note the typical "ball and claw" configuration for the infiltrate and epidermis, respectively. Several Langhans giant cells are within the infiltrate.

granular layer is seen and liquefactive degeneration of the basal layer is consistently observed, often accompanied by incontinence of melanin pigment. Civatte bodies are occasionally seen. A Max-Joseph-like space, i.e. focal separation of the epidermis and dermis secondary to liquefactive degeneration, is sometimes observed. The lichenoid infiltrate closely apposes the epidermis and is thought to play a role in inducing reactive epidermal proliferation of the surrounding rete ridges and atrophy of the overlying epidermis. In perforating lichen nitidus, transepidermal elimination is observed (see Ch. 96).

The predominant cell types in the dermal infiltrate are lymphocytes and epithelioid cells, and in some cases, epithelioid cells predominate. Immunohistochemical studies have shown a marked predominance of $CD4^+$ T cells over $CD8^+$ T cells[43], as well as the presence of large numbers of $CD1^+$ Langerhans cells in the dermal infiltrates. Of note, the pattern in lichen nitidus lesions of a mixed cellular infiltrate characterized by macrophages and a helper T-cell response with few *c*utaneous *l*ymphocyte *a*ntigen-positive (CLA^+) cells is different from that seen in LP[44].

Differential Diagnosis

The differential diagnosis includes LP, lichen striatus, guttate lichen sclerosus, lichen spinulosus, lichen scrofulosorum, verruca plana, papular sarcoidosis, the lichenoid variant of secondary syphilis, frictional lichenoid dermatitis (elbows and knees), and papular eczema (especially in skin types V and VI). All of these diagnoses (except LP and perhaps lichen scrofulosorum) can usually be excluded relatively easily on the basis of clinical plus histologic findings. It is not always possible to differentiate early tiny papules of LP because they may be clinically and histologically indistinguishable from lichen nitidus (see Table 11.6). Furthermore, lesions identical to lichen nitidus can be found in 25% to 30% of patients with LP. In such cases, the lack of variation in size, the absence of a violaceous color or Wickham's striae, and no deposits of immunoglobulin in dermal papillae would suggest the diagnosis of lichen nitidus.

Periappendageal inflammation is more typical of lichen striatus, but patients with the latter have been described where both periappendageal inflammation and superficial features of lichen nitidus were present, suggesting a morphologic spectrum. Lichen spinulosus is characterized by follicular keratotic papules, 1–3 mm in size with a central horny spine, that are grouped into patches on the neck, buttocks, abdomen and upper limbs. The possibility of the spinous follicular variant of lichen nitidus should be kept in mind when a patient presents with spiny keratotic papules plus typical histologic features of lichen nitidus. Lastly, lichen nitidus-like lesions can be seen in a photodistribution in summertime actinic lichenoid eruption, also referred to as actinic lichen nitidus (see below).

Treatment

Since the majority of patients experience spontaneous clearing within one or several years, treatment is primarily symptomatic. When significant pruritus is present, topical corticosteroids and oral antihistamines may be helpful. Anecdotally, topical calcineurin inhibitors have been reported as an effective therapy in children with lichen nitidus. Generalized lichen nitidus that had failed to respond to topical corticosteroids has been successfully treated with either narrowband UVB or photochemotherapy (PUVA)[45]. In case reports, resolution of lichen nitidus has also been described with oral etretinate and oral itraconazole. Nevertheless, the anecdotal nature of these reports makes it difficult to evaluate their true effectiveness and the risk-to-benefit ratio must always be kept in mind. One patient with peripheral $CD4^+$ T-cell lymphocytopenia and lichen nitidus who was treated with topical dinitrochlorobenzene (DNCB) developed a pruritic erythematous eruption followed by resolution of the lesions of lichen nitidus[46].

ERYTHEMA DYSCHROMICUM PERSTANS

Synonyms: ■ Ashy dermatosis ■ Ashy dermatitis

Key features

- Slowly progressive appearance of gray, gray–blue or gray–brown, oval-shaped macules and patches
- Occasionally, there is a peripheral rim of erythema
- As in pityriasis rosea, the long axis of oval lesions can follow skin cleavage lines
- Seen most commonly in Latin American patients with skin types III and IV
- Histologic examination demonstrates multiple dermal melanophages

Introduction

This entity was first described in 1957 by Ramírez as an asymptomatic, slowly progressive, ashy-colored, macular hyperpigmentation and was referred to as "dermatitis cenicienta". The disorder was subsequently renamed erythema dyschromicum perstans (EDP) or ashy dermatosis. Some authors consider EDP to be a variant of LP because of the overlapping clinical and histologic features (see LP pigmentosus). However, flat-topped violaceous papules and plaques are not seen in patients with EDP, and in this textbook, they are viewed as separate entities.

History

In 1957, Ramírez referred to these patients as *los cenicientos* (the ash-colored ones) and named the condition "dermatitis cenicienta". Subsequently, five patients from Venezuela were reported who were believed to be similar to those described by Ramírez. These authors suggested calling the disorder "erythema chronicum figuratum melanodermicum" because they considered it to be a new variant of erythema perstans. Sulzberger then proposed a less cumbersome and more descriptive term, "erythema dyschromicum perstans".

Epidemiology

Although it has been observed that EDP occurs most often in more darkly pigmented Latin Americans, there have been occasional reports in Asians and Caucasians. The disorder clearly favors individuals with skin types III and IV. In general, no gender predilection exists, although a few authors reported that women were more commonly affected than men. While the age of onset is variable, EDP frequently appears during the first to third decade of life.

Pathogenesis

In 1973, Pinkus[47] speculated that an as-yet-unidentified set of pollutants in our environment, either contactants or inhaled or ingested substances, may be the cause of EDP in certain predisposed individuals. Indeed, there have been sporadic case reports of temporal associations with the ingestion of ammonium nitrate, whipworm infestation, and HIV seroconversions; in one patient, characteristic lesions occurred suddenly after a radiographic study using orally administered contrast medium (barium sulfate). However, to date, a rigorous epidemiologic study examining potential triggers has not been performed. Lastly, the possibility has been raised that some patients with multiple fixed drug eruptions or lichenoid drug eruptions are misdiagnosed as having EDP[48], emphasizing the need to carefully review all medications, including over-the-counter drugs and herbal remedies.

Clinical Features

Most patients present with a slow progression of gray, gray–brown or gray–blue macules and patches (Fig. 11.22). The presence of an erythematous, peripheral margin measuring 1–2 mm in width is actually uncommon. When present, these borders eventually disappear after several months. Most lesions measure between 0.5 and 2.5 cm but can be larger. Although the lesions may vary in shape, many are oval with their long axes following skin cleavage lines, thus assuming a pattern similar to that of pityriasis rosea.

The macules may slowly enlarge or multiply to involve large areas of the body. The most common sites of involvement are the neck, trunk and proximal arms, and the distribution is usually symmetric. Occasionally, asymmetric lesions, usually located on the face and neck, have been observed, as well as lesions along the lines of Blaschko. Characteristically, there is sparing of the palms, soles, scalp, nails and mucous membranes. Although spontaneous clearing can occur, especially in prepubertal children (~70% within 2–3 years), the lesions usually persist for years in adults.

Fig. 11.22 Erythema dyschromicum perstans. Numerous, oval to polygonal, gray–brown macules on the extremities. *Courtesy, Wake Forest University.*

Pathology

The histologic findings vary depending on the phase in the life of the lesion. In the border of active lesions, vacuolization of the basal layer, occasional colloid bodies and a lichenoid lymphocytic infiltrate of a varying degree are typically seen. These histologic findings may be seen even in the perilesional normal-appearing skin, suggesting that the pathologic processes have already begun in these areas. In inactive ashy-colored lesions, a considerable amount of pigment incontinence with variable epidermal change, including atrophy and effacement of the normal pattern of rete ridges, is seen. Again, these findings in the active and late inactive lesions are quite similar to those of the different stages of fixed drug eruptions.

DIF microscopy studies of the active border have demonstrated IgM, IgG, fibrinogen and C3 staining of colloid bodies, as in LP. However, positive staining for fibrinogen at the dermal–epidermal junction is often the only finding in immunofluorescence studies of EDP. Immunopathologic studies have shown the dermal infiltrate (when present) to be composed of $CD4^+$ and $CD8^+$ T cells, a common pattern in LP.

Differential Diagnosis

The clinical differential diagnosis includes primarily generalized fixed drug eruption and postinflammatory hyperpigmentation secondary to a lichenoid drug eruption, pityriasis rosea, small plaque parapsoriasis, LP or erythema multiforme. Although the lesions of pityriasis rosea are often oval, the resultant hyperpigmentation is predominantly epidermal, not dermal. Histologically, in fixed drug eruptions, there is incontinence of pigment, but clinically the shape of the lesions is usually more circular and the color more brown. Less common entities in the differential diagnosis are macular urticaria pigmentosa, pinta and leprosy. There is a lack of consensus as to whether idiopathic eruptive macular pigmentation is a variant of EDP seen more commonly in children or a distinct entity. Distinguishing EDP from a lichenoid drug eruption can prove quite difficult and a search for incriminating drugs is essential.

Treatment

In general, proposed treatments for EDP are unsuccessful; they include sun protection, topical corticosteroids, retinoids and vitamin C, chemical peels, oral antibiotics, vitamin A, dapsone, antimalarials, griseofulvin and corticosteroids. On the basis of a case series, clofazimine was

reported as a successful treatment. Spontaneous remission can occur, but unfortunately many patients have the disease for years.

KERATOSIS LICHENOIDES CHRONICA

This entity was first described in 1895 by Kaposi. He used the term "lichen ruber acuminatus verrucosus et reticularis" to describe a patient with a linear, warty lichenoid eruption. Since his original description, patients with similar lesions have been reported, but with a confusing nomenclature which includes lichen verrucosus et reticularis, porokeratosis striata lichenoides, keratosis lichenoides chronica, lichenoid trikeratosis and Nékam's disease[49]. Over time, keratosis lichenoides chronica has become the most consistently used name for this disorder.

Keratosis lichenoides chronica is characterized by violaceous, keratotic lichenoid papules that are arranged in a characteristic linear and reticulated pattern (Fig. 11.23A). Lesions are usually symmetrically distributed on the limbs (Fig. 11.23B) and the trunk[49]. Another prominent feature is a greasy and scaly eruption involving the upper portion of the face which has been described as a seborrheic dermatitis-like mediofacial eruption or psoriasiform scaling plaques (Fig. 11.23C). Keratotic papules are sometimes present on the palms and soles, and the nails and scalp may also be affected. Although the clinical course of keratosis lichenoides chronica is usually chronic and progressive, occasionally, regression of individual lesions during the summer or with aging has been reported.

The histologic features of keratosis lichenoides chronica are very similar to those seen in LP. Furthermore, there are no significant differences in immunofluorescence or immunopathologic findings between keratosis lichenoides chronica and idiopathic LP, suggesting that it may be an unusual variant of LP or an unusual isomorphic response. Treatment should be symptomatic and it is usually unsatisfactory; topical and systemic corticosteroids, methotrexate, cyclosporine, etretinate, oral vitamin A and PUVA have all been tried but with little success, although a beneficial effect from UVB or etretinate plus PUVA has been reported.

ACTINIC LICHEN NITIDUS (SUMMERTIME ACTINIC LICHENOID ERUPTION)

Summertime actinic lichenoid eruption was first described by Bedi[50] in 1978. Since its initial description, the disorder has been reported under a variety of names, including LP subtropicus, LP tropicus, lichenoid melanodermatitis, LP atrophicus annularis and LP actinicus. Of note, the last-mentioned is synonymous with actinic LP and the first three terms have also been used to describe actinic LP, so although many authors have regarded summertime actinic lichenoid eruption as synonymous with actinic LP, Bedi considered it to be a separate entity. The former typically occurs in young adults with skin types IV or V following prolonged exposure to the summer sun and presents with pinhead-sized lichenoid papules that are almost exclusively confined to sun-exposed areas.

Isaacson et al.[51] broadened the clinical spectrum of summertime actinic lichenoid eruption to include several types of lichenoid eruptions: annular hyperpigmented plaques, melasma-like patches, grayish-white pinhead-sized papules, and typical LP-like papules/plaques. As a result, their description of the histologic findings varied according to the morphology of the different types of clinical lesions. Hussain[52] then proposed that the designation "summertime actinic lichenoid eruption" should be limited to papular eruptions exclusively in sun-exposed areas with lichen nitidus-like histologic features, while the term actinic LP should be used to describe annular lesions with classic histopathologic features of LP. In addition, he suggested abolishing the term summertime actinic lichenoid eruption and replacing it with actinic lichen nitidus or lichen nitidus actinicus. This view has been supported by other authors.

ANNULAR LICHENOID DERMATITIS (OF YOUTH)

Annular lichenoid dermatitis of youth was first described in 2003 by Annessi and colleagues[53]. They observed, in a series of young patients, peculiar annular lesions whose clinical features appeared to overlap with those of inflammatory morphea, mycosis fungoides, inflammatory vitiligo, and figurate erythemas. In the initial reports, the annular lichenoid dermatitis occurred primarily in children and young adults (age range, 5–22 years), with no sexual predilection. However, in a more recently reported series of six patients, four were adult men, ranging in age from 33 to 45 years[54].

Patients present with erythematous macules that enlarge into annular patches with a reddish-brown, non-scaling border and central hypopigmentation. The lesions are usually 5 to 15 cm in diameter, involve

Fig. 11.23 Keratosis lichenoides chronica. **A** Linear and stellate keratotic plaques. **B** Symmetrical distribution of linear and reticulated keratotic plaques admixed with small, violaceous lichenoid papules. **C** Crusted psoriasiform scaling plaques on the face. *B, Courtesy, Kathyrn Schwarzenberger, MD; C, Courtesy, Jiro Arata, MD.*

primarily the groin and flanks, and are either solitary or multiple (range, 2–12 lesions; mean, 3).

Histologically, there is a band-like lymphocytic infiltrate within the papillary dermis, along with vacuolar changes of the epidermal basal layer and epidermotropism of lymphocytes. Although variable in number, apoptotic keratinocytes are localized to the tips of the rete ridges (a notable finding that distinguishes this entity from mycosis fungoides). Neither spongiosis nor changes in the horny and granular layers are observed. The infiltrate is composed primarily of $CD4^+$ T cells or $CD8^+$ T cells, with few B cells and macrophages. A normal number of melanocytes is present in the hypopigmented areas, a finding that is helpful in differentiating annular lichenoid dermatitis from inflammatory vitiligo. The absence of T-cell receptor rearrangements aids in excluding indolent mycosis fungoides[54].

The disease follows a chronic course, with some lesions spontaneously resolving while others are quite persistent. Although the pathogenesis remains unknown, it is thought to represent a reaction pattern to antigenic triggers (including hepatitis B vaccine), as is suspected in other lichenoid dermatoses. Topical or systemic corticosteroids and phototherapy have led to marked improvement or complete regression of the lesions.

REFERENCES

1. Boyd AS, Neldner KH. Lichen planus. J Am Acad Dermatol. 1991;25:593–619.
2. Chuang T-Y, Stitle L, Brashear R, Lewis C. Hepatitis C virus and lichen planus: a case-control study of 340 patients. J Am Acad Dermatol. 1999;41:787–9.
3. Shengyuan L, Songpo Y, Wen W, et al. Hepatitis C virus and lichen planus. A reciprocal association determined by a meta-analysis. Arch Dermatol. 2009;145: 1040–7.
4. Nagao Y, Kameyama T, Sata M. Hepatitis C virus RNA detection in oral lichen planus tissue [letter]. Am J Gastroenterol. 1998;93:850.
5. Carrozzo M, Francia Di Celle P, Gandolfo S, et al. Increased frequency of HLA-DR6 allele in Italian patients with hepatitis C virus-associated oral lichen planus. Br J Dermatol. 2001;144:803–8.
6. Pilli M, Zerbini A, Vescovi P, et al. Oral lichen planus pathogenesis: a role for the HCV-specific cellular immune response. Hepatology. 2002;36:1446–52.
7. De Vries HJ, van Marle J, Teunissen MB, et al. Lichen planus is associated with human herpesvirus type 7 replication and infiltration of plasmacytoid dendritic cells. Br J Dermatol. 2006;154:361–4.
8. De Vries HJ, Teunissen MB, Zorgdrager F, et al. Lichen planus remission is associated with a decrease of human herpes virus type 7 protein expression in plasmacytoid dendritic cells. Arch Dermatol Res. 2007;299:213–19.
9. Requena L, Kutzner H, Escalonilla P, et al. Cutaneous reactions at sites of herpes zoster scars: an expanded spectrum. Br J Dermatol. 1998;138:161–8.
10. Shiohara T, Mizukawa Y, Takahashi R, Kano Y. Pathomechanisms of lichen planus autoimmunity elicited by cross-reactive T cells. Curr Dir Autoimmun. 2008;10:206–26.
11. Al-Khenaizan S. Lichen planus occurring after hepatitis B vaccination: a new case. J Am Acad Dermatol. 2001;45: 614–15.
12. Halevy S, Shai A. Lichenoid drug eruption. J Am Acad Dermatol. 1993;29:249–55.
13. Shiohara T, Moriya N, Mochizuki T, Nagashima M. Lichenoid tissue reaction (LTR) induced by local transfer of la-reactive T-cell clones. II. LTR by epidermal invasion of cytotoxic lymphokine-producing autoreactive T cells. J Invest Dermatol. 1987;89:8–14.
14. Shiohara T, Moriya N, Nagashima M. Induction and control of lichenoid tissue reactions. Springer Semin Immunopathol. 1992;13:369–85.
15. Sugerman PB, Satterwhite K, Bigby M. Autocytotoxic T-cell clones in lichen planus. Br J Dermatol. 2000;142: 449–56.
16. Yasukawa M, Ohminami A, Arai J, et al. Granule exocytosis, and not the fas/fas ligand system, is the main pathway of cytotoxicity mediated by alloantigen-specific CD4(+) as well as CD8(+) cytotoxic T lymphocytes in humans. Blood. 2000;95:2352–5.
17. Dutz JP. T-cell-mediated injury to keratinocytes: insights from animal models of the lichenoid tissue reaction. J Invest Dermatol. 2009;129:309–14.
18. Sontheimer RD. Lichenoid tissue reaction/interface dermatitis: clinical and histological perspectives. J Invest Dermatol. 2009;129:1088–99.
19. Scheler M, Wenzel J, Tüting T, et al. Indoleamine 2,3-dioxygenase (TDO). The antagonist of type 1 interferon-driven skin inflammation? Am J Pathol. 2007;171:1936–43.
20. Shiohara T. Fixed drug eruption: pathogenesis and diagnostic tests. Curr Opin Allergy Clin Immunol. 2009;9:316–21.
21. Kossard S, Thompson C, Duncan GM. Hypertrophic lichen planus-like reactions combined with infundibulocystic hyperplasia – pathway to neoplasia. Arch Dermatol. 2004;140:1262–7.

21a. Fox LP, Lightdale CJ, Grossman ME. Lichen planus of the esophagus: what dermatologists need to know. J Am Acad Dermatol. 2011;65:175–83.

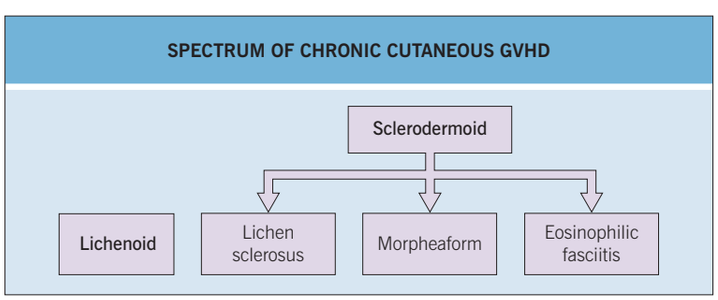
22. Mignogna MD, Muzio LL, Russo LL, et al. Oral lichen planus: different clinical features in HCV-positive and HCV-negative patients. Int J Dermatol. 2000;39: 134–9.
23. Goldstein AT, Metz A. Vulvar lichen planus. Clin Obstet Gynecol. 2005;48:818–23.
24. Van den Haute V, Antoine JL, Lachapelle JM. Histopathological discriminant criteria between lichenoid drug eruptions and idiopathic lichen planus: retrospective study on selected samples. Dermatologica. 1989;179:10–3.
25. Córdoba S, Fraga J, Bartolomé B, et al. Giant cell lichenoid dermatitis with herpes zoster scars in a bone marrow recipient. J Cutan Pathol. 2000;27:255–7.
26. Orteuu CH, Buchanan JAG, Hutchison I, et al. Systemic lupus erythematosus presenting with oral mucosal lesions: easily missed? Br J Dermatol. 2001;144: 1219–23.
27. Byrd JA, Davis MDP, Rogers RS III, et al. Recalcitrant symptomatic vulvar lichen planus. Response to topical tacrolimus. Arch Dermatol. 2004;140:715–20.
28. Byrd JA, Davis MDP, Bruce AJ, et al. Response of oral lichen planus to topical tacrolimus in 37 patients. Arch Dermatol. 2004;140:1508–12.
29. Cribier B, Frances C, Chosidow O. Treatment of lichen planus. Arch Dermatol. 1998;134:1521–30.
30. Büyük AY, Kavala M. Oral metronidazole treatment of lichen planus. J Am Acad Dermatol. 2000;43:260–2.
31. Chiang C, Sah D, Cho BK, et al. Hydroxychloroquine and lichen planopilaris: efficacy and introduction of Lichen Planopilaris Activity Index scoring system. J Am Acad Dermatol. 2010;62:387–92.

31a. Omidian M, Ayoobi A, Mapar MA, et al. Efficacy of sulfasalazine in the treatment of generalized lichen planus: randomized double-blinded clinical trial on 52 patients. J Eur Acad Dermatol Venereol. 2010;24:1051–4.

32. Torti DC, Jorizzo JL, McCarty MA. Oral lichen planus. Arch Dermatol. 2007;143:511–15.
33. Ho VC, Gupta AK, Nickoloff FJ, Voorhees JJ. Treatment of severe lichen planus with cyclosporine. J Am Acad Dermatol. 1990;22:64–8.
34. Mirmirani P, Willey A, Price VH. Short course of oral cyclosporine in lichen planopilaris. J Am Acad Dermatol. 2003;49:667–71.
35. Cho BK, Sah D, Chwalek J, et al. Efficacy and safety of mycophenolate mofetil for lichen planopilaris. J Am Acad Dermatol. 2010;62:393–7.
36. Becherel PA, Bussel A, Chosidow O, et al. Extracorporeal photochemotherapy for chronic erosive lichen planus. Lancet. 1998;351:805.
37. Trehan M, Taylor CR. Low-dose excimer 308-nm laser for the treatment of oral lichen planus. Arch Dermatol. 2004;140:415–20.
38. Patrizi A, Neri I, Fiorentini C, et al. Lichen striatus: clinical and laboratory features of 115 children. Pediatr Dermatol. 2004;21:197–204.
39. Zhang Y, McNutt NS. Lichen striatus. Histological, immunohistochemical, and ultrastructural study of 37 cases. J Cutan Pathol. 2001;28:65–71.
40. Kano Y, Inaoka M, Shiohara T. Superficial lymphangitis with interface dermatitis occurring shortly after a minor injury: possible involvement of a bacterial infection and contact allergens. Dermatology. 2002;203:217–20.
41. Kano Y, Shiohara T, Yagita A, Nagashima M. Erythema nodosum, lichen planus and lichen nitidus in Crohn's disease: report of a case and analysis of T cell receptor V gene expression in the cutaneous and intestinal lesions. Dermatology. 1995;190:59–63.
42. Lapins NA, Willoughby C, Helwig EB. Lichen nitidus. Cutis. 1978;21:634–7.
43. Shiohara T, Moriya N, Tanaka Y, et al. Immunopathological study of lichenoid skin diseases: correlation between HLA-DR-positive keratinocytes or Langerhans cells and epidermotropic T cells. J Am Acad Dermatol. 1988;18:67–74.
44. Smoller BR, Flynn TC. Immunohistochemical examination of lichen nitidus suggests that it is not a localized papular variant of lichen planus. J Am Acad Dermatol. 1992;27:232–6.
45. Park JH, Choi YL, Kim WS, et al. Treatment of generalized lichen nitidus with narrowband ultraviolet B. J Am Acad Dermatol. 2006;54:545–6.
46. Kano Y, Otake Y, Shiohara T. Improvement of lichen nitidus after topical dinitrochlorobenzene application. J Am Acad Dermatol. 1998;39:305–8.
47. Pinkus H. Lichenoid tissue reactions: a speculative review of the clinical spectrum of epidermal basal cell damage with special reference to erythema dyschromicum perstans. Arch Dermatol. 1973;107: 840–6.
48. Mizukawa Y, Shiohara T. Fixed drug eruption presenting as erythema dyschromicum perstans: a flare without taking any medications. Dermatology. 1998;197: 383–5.
49. Masouye I, Saurat J-H. Keratosis lichenoids chronica: the centenary of another Kaposi's disease. Dermatology. 1995;191:188–92.
50. Bedi TR. Summertime actinic lichenoid eruption. Dermatologica. 1978;157:115–25.
51. Isaacson D, Turner ML, Elgart ML. Summertime actinic lichenoid eruption (lichen planus actinicus). J Am Acad Dermatol. 1981;4:404–11.
52. Hussain K. Summertime actinic lichenoid eruption, a distinct entity, should be termed actinic lichen nitidus. Arch Dermatol. 1998;134:1302–3.
53. Annessi G, Paradisi M, Angelo C, et al. Annular lichenoid dermatitis of youth. J Am Acad Dermatol. 2003;49: 1029–36.
54. Cesinaro AM, Sighinolfi P, Greco A, et al. Annular lichenoid dermatitis of youth. Am J Dermatopathol. 2009;31:263–7.

Lichen planus on the dorsal surface of the hand. Wickham's striae can be easily identified in the upper right lesion. Note the flat-topped nature of the lesions.

Hypertrophic lichen planus on the dorsal aspect of the hands.



Spectrum of chronic cutaneous GVHD. *From: Schaffer JV, McNiff JM, Seropian S, et al. Lichen sclerosus and eosinophilic fasciitis as manifestations of chronic graft-versus-host disease: expanding the sclerodermoid spectrum. J Am Acad Dermatol. 2005;53:591-601.*

Linear lichen planus. Discrete lesions along the lines of Blaschko on the lower extremity of an adult.

Chronic GVHD. A Lacy white pattern on the mucosal surface of the lower lip in the lichenoid form. Note the Beau's lines of the fingernails reflecting the time of the transplant. **B** Morpheaform plaque with a healing ulceration on the shoulder in the sclerodermoid form.

Atopic Dermatitis 12

Thomas Bieber and Caroline Bussmann

Synonym: ■ Atopic eczema

Key features

- Common inflammatory skin condition that typically begins during infancy or early childhood and is often associated with other "atopic" disorders such as asthma and allergic rhinoconjunctivitis
- Complex genetic disease with environmental influences
- Characterized by intense pruritus and a chronic or chronically relapsing course
- Acute inflammation and involvement of the cheeks, scalp and extensor aspects of the extremities predominates in infants, shifting to chronic inflammation with lichenification and a predilection for flexural sites in children and adults
- A proactive approach to management is recommended, including avoidance of trigger factors, daily use of emollients, and anti-inflammatory therapy to control subclinical inflammation as well as overt flares

INTRODUCTION

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease, and its increasing prevalence presents a major public health problem worldwide[1]. Characteristic features of AD include pruritus and a chronic or chronically relapsing course, usually beginning during infancy (early onset) but occasionally first developing in adulthood (late onset)[2]. AD is a paradigmatic complex genetic disease and is often accompanied by other atopic disorders such as allergic rhinoconjunctivitis and asthma. These conditions may appear simultaneously or develop in succession. AD has a predilection for infants and young children, while asthma favors older children and pollen allergy predominates in adolescents. This characteristic age-dependent sequence is referred to as the "atopic march"[3,4] (Fig. 12.1). Considering that the atopic disease progression starts with AD, management should not be concentrated solely on the treatment of acute flares, but also be directed towards improving the underlying genetically determined epidermal barrier dysfunction and preventing active dermatitis (e.g. via maintenance therapy). Such an approach could potentially block the sensitizations and ongoing inflammation that drive the atopic march forward[5].

HISTORY AND DEFINITIONS

Since its description during the nineteenth century, the clinical phenotype of AD has been given multiple different names, including "Besnier's prurigo" and "disseminated neurodermatitis". The association of AD with allergic rhinitis and asthma was recognized by Besnier in 1892. The term "atopy" (originating from the Greek word *atopos*, meaning strange or unusual) was first applied to this triad in the 1920s, including the use of "atopic eczema". A decade later, Hill and Sulzberger proposed the name "atopic dermatitis". The list of characteristic features proposed by Hanifin and Rajka[6] in 1980 (Table 12.1) helped to establish unity in the clinical concept of AD. In 1994, Williams and co-workers[7] simplified Hanifin and Rajka's criteria to establish the UK Working Party's Diagnostic Criteria for AD, which were validated for the purpose of clinical studies; these criteria were modified slightly by Williams in 2005 (Table 12.2)[2].

According to the current consensus nomenclature by the World Allergy Organization (WAO)[8], the term "atopy" is tightly linked to the presence of allergen-specific IgE antibodies in the serum, as documented by positive fluorescence enzyme immunoassays (previously radioallergosorbent [RAST] tests) or skin prick tests. Thus, an *IgE-associated* or *allergic* form of dermatitis corresponds to AD in the strict sense (formerly known as *extrinsic AD*). The remaining 20–30% of patients with the clinical phenotype of AD who have no evidence of IgE-sensitization are categorized as having a *non-IgE-associated* or *non-allergic* form of dermatitis (formerly known as *intrinsic AD*). However, IgE-associated/allergic "true" AD and non-IgE-associated/non-allergic dermatitis have substantial overlap and cannot be considered as two separate diseases; for example, the latter often represents an early transitional form of IgE-associated AD.

EPIDEMIOLOGY

The current prevalence of AD in most high-income and some low-income countries is approximately 10–30% in children and 2–10% in adults, representing a two- to threefold increase over the past several decades[1]. In general, the prevalence of AD in rural areas and low-income countries is significantly lower than in their urban and high-income counterparts, illustrating the importance of lifestyle and environment in the pathogenesis of atopic disease. This observation supports the controversial hygiene hypothesis, which postulates that decreased exposure to infectious agents in early childhood increases susceptibility to allergic diseases.

Three subsets of AD based on age of onset have emerged from epidemiologic studies:

- *early-onset type*: defined as AD beginning in the first 2 years of life. This is the most common type of AD, which develops during the first 6 months of life in 45% of affected individuals, during the first year of life in 60%, and before 5 years of age in 85%. Approximately half of children with disease onset during the first 2 years of life develop allergen-specific IgE antibodies by 2 years of

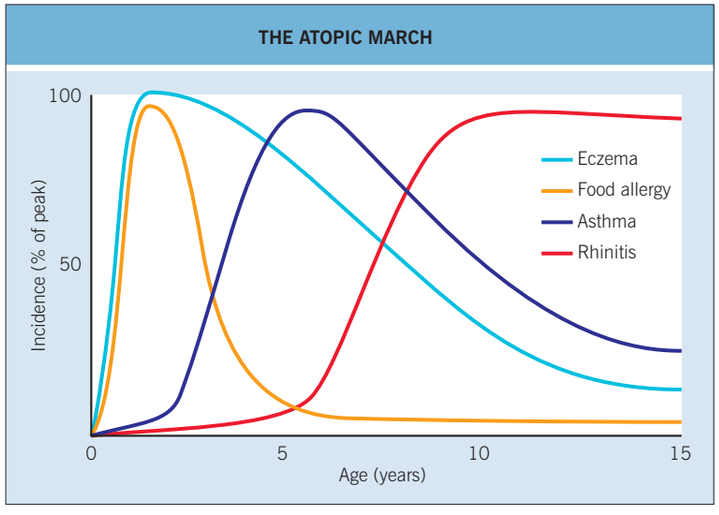


Fig. 12.1 The atopic march.

DIAGNOSTIC FEATURES OF ATOPIC DERMATITIS
MAJOR FEATURES (3 OF 4 PRESENT)
• Pruritus • Typical morphology and distribution of skin lesions • Chronic or chronically relapsing dermatitis • Personal or family history of atopy
MINOR FEATURES (3 OF 23 PRESENT)
• Xerosis • Ichthyosis/palmar hyperlinearity/keratosis pilaris • Immediate (type I) skin test reactivity • Elevated serum IgE • Early age of onset • Tendency toward cutaneous infections/impaired cell-mediated immunity • Tendency toward nonspecific hand or foot dermatitis • Nipple eczema • Cheilitis • Recurrent conjunctivitis • Dennie–Morgan infraorbital fold • Keratoconus • Anterior subcapsular cataract • Orbital darkening • Facial pallor/erythema • Pityriasis alba • Anterior neck folds • Pruritus when sweating • Intolerance to wool and lipid solvents • Perifollicular accentuation • Food intolerance • Course influenced by environmental/emotional factors • White dermographism/delayed blanch

Table 12.1 Diagnostic features of atopic dermatitis[6].

DIAGNOSTIC GUIDELINES FOR ATOPIC DERMATITIS
Must have: • An itchy skin condition (or parental report of scratching or rubbing in a child)
Plus three or more of the following: • History of involvement of the skin creases such as folds of elbows, behind the knees, fronts of ankles, the neck and around the eyes* • A personal history of asthma or hayfever (or history of atopic disease in a first-degree relative in children under 4 years of age) • A history of generally dry skin in the last year • Visible flexural eczema (or eczema involving the cheeks/forehead and extensor limbs in children under 4 years of age) • Onset under 2 years of age (not used if child is under 4 years of age)
*Original 1994 guidelines also included the cheeks in young children.

Table 12.2 Diagnostic guidelines for atopic dermatitis[2,7].

age. About 60% of infants and young children with AD go into remission by 12 years of age, but in others disease activity persists into adolescence and adulthood

- *late-onset type*: defined as AD that starts after puberty. There are few recent epidemiological studies on AD with onset in adulthood. Approximately 30% of AD patients overall are in the non-IgE-associated category, and among adults, the vast majority of such patients are women
- *senile-onset type*: an unusual subset of AD that begins after 60 years of age has been identified more recently[9].

PATHOGENESIS

Genetics

The concordance rate for AD is higher among monozygotic twins (77%) compared to dizygotic twins (15%), supporting the importance of genetic factors in its pathogenesis. Although the entities in the atopic triad cluster together in families, a parental history of AD is a stronger risk factor for the development of AD than either asthma or allergic rhinitis, suggesting the existence of genes specific to AD[10]. AD is a complex genetic disease, and both gene–gene and gene–environment interactions have pathogenic roles (Fig. 12.2). Two major sets of genes have been implicated in AD: (1) genes encoding epidermal proteins; and (2) genes encoding proteins with immunologic functions that are not specific to the skin. Selected chromosomal loci and candidate genes in these two groups that have been identified to date are listed in Table 12.3. In addition to classic genetic changes, epigenetic alterations may have a role in the development of AD.

Mutations in the filaggrin gene (*FLG*), which encodes a protein that aggregates keratin filaments during terminal differentiation of the epidermis, are responsible for ichthyosis vulgaris (see Table 12.5 and Ch. 57) and represent a major predisposing factor for AD[13]. A number of studies have shown that the same loss-of-function filaggrin variants that cause ichthyosis vulgaris have a prevalence of 20–50% in European children and adults with AD (compared to ≤10% of the general population)[14], and different loss-of-function filaggrin variants have been identified in similar proportions of Asian patients with AD (± ichthyosis vulgaris). With an overall odds ratio of ≥4, these filaggrin variants represent one of the strongest known genetic factors for a complex disease, with penetrances of ~60% for one variant allele and ~90% for two variant alleles. The presence of the filaggrin variants is correlated with early-onset, relatively severe, "extrinsic" (specific IgE-associated) AD that tends to persist into adulthood; affected individuals have an increased risk of eczema herpeticum and peanut allergies as well as a

SELECTED SUSCEPTIBILITY LOCI AND CANDIDATE GENES FOR ATOPIC DERMATITIS		
Chromosomal location	**Candidate gene(s)**	**Defective protein(s)**
GENES ENCODING EPIDERMAL PROTEINS		
1q21 (epidermal differentiation complex)	*FLG*	Filaggrin (loss-of-function variants; see text)
5q31–q32	*SPINK5*	Serine protease inhibitor LETKI
11q13.5	(rs7927894 SNP)	? (synergistic interaction with *FLG* null mutations)
19q13	*KLK7/SCCE*	Kallikrein-related peptidase 7/stratum corneum chymotryptic enzyme
GENES ENCODING IMMUNOLOGIC PROTEINS		
1q23	*FCER1A*	High-affinity IgE receptor, α chain
4q32	*TLR2*	Toll-like receptor-2
4q34	*IRF2*	Interferon regulatory factor 2
5q31	*IL4* *IL5* *IL12B* *IL13* *GM-CSF* *CD14*	Interleukin-4 Interleukin-5 Interleukin-12B Interleukin-13 Granulocyte–macrophage colony-stimulating factor Monocyte differentiation antigen CD14
8p23	*DEFB1*	β-defensin 1
11q13	*GSTP1*	Glutathione S-transferase P1
11q22	*IL18*	Interleukin-18
14q11	*CMA1*	Mast cell chymase
16p12	*IL4R*	Interleukin-4 receptor, α subunit (gain-of-function polymorphisms)
17q11	*CCL5/RANTES*	Chemokine (C-C motif) ligand 5/RANTES (gain-of-function polymorphisms in the promoter region)

Table 12.3 Selected susceptibility loci and candidate genes for atopic dermatitis[10–18]. Genome-wide association studies have identified other susceptibility loci, including 3q21, 3p26, 16q, 17q25 and 20p. FCER1A, Fc fragment of IgE high-affinity receptor I alpha polypeptide; LETKI, lymphoepithelial Kazal-type-related inhibitor; RANTES, regulated on activation, normally T-cell expressed and secreted; SNP, single nucleotide polymorphism; *SPINK5*, serine peptidase inhibitor Kazal type 5.

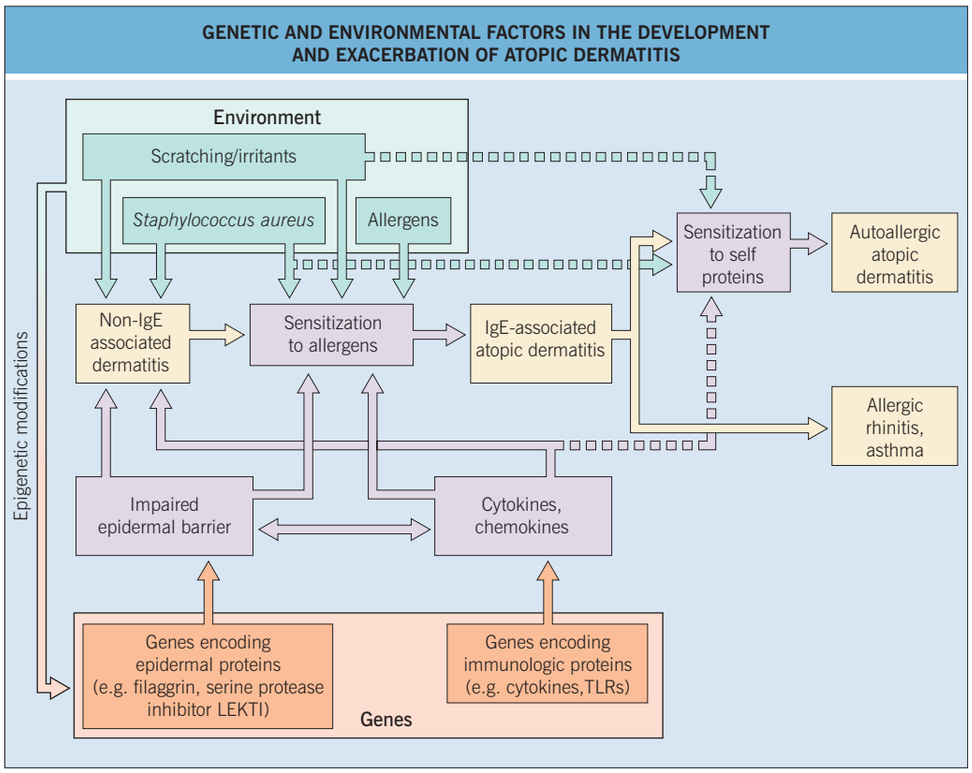


Fig. 12.2 Genetic and environmental factors in the development and exacerbation of atopic dermatitis TLR, Toll-like receptor. Adapted with permission from ref. 5.

propensity to later develop asthma[14,14a]. However, in general, there is no correlation between the filaggrin variants and asthma without prior AD, supporting a role for epicutaneous sensitization and inflammation in the skin (related to the disrupted epidermal barrier) in the subsequent development of asthma.

Epidermal Barrier Dysfunction

AD is characterized by dry, scaly skin (xerosis) in lesional and nonlesional areas, which is the consequence of epidermal barrier dysfunction and an altered stratum corneum leading to increased transepidermal water loss[19]. Factors that contribute to the impaired cutaneous barrier of AD are summarized in Table 12.4.

Immunopathology

Immunologic mechanisms involved in the pathogenesis of AD are presented in Table 12.4.

Pruritus

AD is characterized by persistent, severe pruritus, which significantly impacts the quality of life in affected individuals. The mechanisms of pruritus have just started to be understood. Since classic antihistamines are ineffective in AD, it is assumed that this mediator does not have a crucial role in AD-related pruritus. In contrast, neuropeptides, proteases, kinins, and cytokines such as interleukin (IL)-31 are known to induce itch. IL-31 is strongly pruritogenic and exerts its biologic activity through a heterodimeric receptor composed of the IL-31 receptor A and oncostatin M receptor β protein, both of which are overexpressed in lesional skin of AD[41–43]. These findings imply that IL-31 has an important role in the pruritus of AD.

CLINICAL FEATURES

Disease Course

AD is characterized by a broad clinical spectrum that varies depending upon the age of the patient, and it is divided into infantile, childhood and adolescent/adult stages. In each stage, patients may develop acute, subacute and chronic eczematous lesions, all of which are intensely pruritic and often excoriated. Acute lesions predominate in infantile AD and are characterized by edematous, erythematous papules and plaques that may exhibit vesiculation, oozing and serous crusting. Subacute eczematous lesions display erythema, scaling and variable crusting. Chronic lesions, which typify adolescent/adult AD, present as thickened plaques with lichenification as well as scale; prurigo nodule-like lesions can also develop (see below). Perifollicular accentuation and small, flat-topped papules (papular eczema) are particularly common in individuals with darkly pigmented skin. In any stage of AD, the most severely affected individuals may evolve to a generalized exfoliative erythroderma (see Ch. 10). All types of AD lesions can leave postinflammatory hyper-, hypo- or (in more severe cases) depigmentation upon resolution (Fig. 12.3).

Infantile AD (age <2 years) typically develops after the second month of life, often initially appearing as edematous papules and papulovesicles on the cheeks (often sparing the central face), which may evolve to form large plaques with oozing and crusting (Fig. 12.4). Involvement of the scalp, neck, extensor aspects of the extremities, and trunk (Fig. 12.5) can also occur, usually with sparing of the diaper area. In the first 6 months of life, the face and the neck are affected in over 90% of patients with AD[44]. Young infants may attempt to relieve itch through rubbing movements against their bedding, whereas older infants are better able to directly scratch affected areas.

In ***childhood AD (age 2 to 12 years)***, the lesions are less exudative and tend to become lichenified. The classic sites of predilection are the antecubital and popliteal fossae (flexural eczema) (Fig. 12.6). In addition, the head (especially periorificial regions), neck, wrists, hands, ankles and feet are often affected (Fig. 12.7). Xerosis typically becomes pronounced and widespread.

Adult/adolescent AD (age >12 years) also features subacute to chronic, lichenified lesions, and involvement of the flexural folds typically continues. However, the clinical picture may also change. Adults with AD frequently present with chronic hand dermatitis that has both endogenous and exogenous components (Fig. 12.8), while others have primarily facial dermatitis (Fig. 12.9), often with severe eyelid involvement (see below). Additional sites of predilection include the retroauricular region, neck and chest. Patients who have suffered from continuous AD since childhood are more likely to have extensive or even erythrodermic disease that is resistant to treatment. Such individuals may also have severe excoriations and chronic papular skin lesions (Fig. 12.10) as a result of habitual scratching and rubbing.

EPIDERMAL DEFECTS AND IMMUNOLOGIC MECHANISMS INVOLVED IN THE PATHOGENESIS OF ATOPIC DERMATITIS
IMPAIRMENT OF THE EPIDERMAL BARRIER
• Changes in the balance between proteolytic enzymes (e.g. kallikrein-related peptidase 7/stratum corneum chymotryptic enzyme) and their antiprotease counterparts (e.g. the serine protease inhibitor LETKI) lead to a net increase in protease activity that accelerates degradation of corneodesmosomes and lipid-processing enzymes; one result is a failure to generate ceramides[15,20] • Deficiency of filaggrin, which normally contributes to the assembly of the cornified envelope and (via its breakdown products) increases the water-binding capacity of the stratum corneum; of note, Th2-type inflammation can decrease the expression of filaggrin[21] • Disturbed maturation of lamellar bodies, potentially due to variations in the pH of the stratum corneum as well as alterations in epidermal lipid metabolism • Other alterations in epidermal differentiation, including changes in cornified envelope proteins (e.g. involucrin, loricrin) and lipid composition • As a result of the defective epidermal barrier, there is increased penetration of environmental irritants and allergens into the skin, triggering inflammation and sensitization[22]
MECHANISMS OF INFLAMMATION IN THE ABSENCE OF IgE-MEDIATED SENSITIZATION*
• Increased epidermal protease activity may initiate an inflammatory cascade[16] • Neuropeptides, irritants and scratching can stimulate the release of proinflammatory cytokines by keratinocytes • T-cell-mediated (but IgE-independent) reactions to epicutaneous (through the disrupted epidermal barrier) allergen exposure, as demonstrated by atopy patch testing[23]
EPICUTANEOUS SENSITIZATION
• Animal models have shown that epicutaneous sensitization can induce both a localized AD-like dermatitis and bronchial hyperreactivity to aerosolized allergens[24] • Allergens have increased cutaneous penetration due to the impaired epidermal barrier • Keratinocytes in AD patients produce high levels of thymic stromal lymphopoietin (TSLP), an IL-7-like cytokine that drives dendritic cells to induce Th2 polarization[25] • Pollen-associated prostaglandin-like bioactive lipids and water-soluble mediators also modulate dendritic cell function and promote Th2 polarization[26] • Proinflammatory mechanisms may be amplified by increased epidermal protease activity[16] • Chronic cutaneous inflammation in AD patients has systemic consequences (e.g. functional changes in circulating monocytes[27]); the skin may therefore represent the "point of entry" for atopic sensitization and deliver systemic signals promoting sensitization upon allergen exposure in the lungs or gut
ROLE OF DENDRITIC CELLS (DCS)
• Key roles that link innate and adaptive immunity[28] • *Plasmacytoid DCs* (responsible for antiviral defense) are almost absent in AD lesional skin[29] • Two distinct populations of *myeloid DCs* are present: *Langerhans cells* (*LCs*) and *inflammatory dendritic epidermal cells* (*IDECs*; only found in inflamed skin)[30] – Both express the high-affinity receptor for IgE (FcεRI) only in IgE-associated (extrinsic) AD; inflammatory signals can lead to upregulation of FcεRI expression[31] – Participate in the sensitization phase (see above) – Central roles in the uptake and presentation of allergens to Th1/Th2 cells and possibly Tregs[32] • LCs promote Th2 polarization and have a limited capacity to produce proinflammatory cytokines • IDECs promote Th1 polarization and produce proinflammatory cytokines; in acute AD, IDECs are actively recruited and large numbers invade the epidermis after 48–72 hours[33]
T-CELL RESPONSES, CYTOKINES AND CHEMOKINES
• Th2 cytokines (e.g. IL-4, IL-5, IL-13) predominate in acute AD lesions and in the systemic immunologic background of IgE-associated (extrinsic) AD • Th1 cytokines (e.g. IFN-γ, IL-12) predominate in chronic AD lesions • IDECs and eosinophils produce IL-12 and may be instrumental in the Th2 to Th1/Th0 switch • An orchestra of cytokines and chemokines produced by keratinocytes and endothelial cells contributes to inflammatory cell recruitment and evolution of the inflammatory reaction over time[34] – TSLP (see above) stimulates DCs to: (1) release CCL17 and CCL22; and (2) expand T cells that produce IFN-γ as well as those that produce IL-5 and IL-13 – CCL1, CCL27 (CTACK) and CCL18 attract $CCR4^+$ Th2 cells • IL-22-producing $CD4^+$ or $CD8^+$ T cells that do not produce IL-17 have been described in AD patients • The role of $CD25^+/Foxp3^+$ Tregs in AD is not yet fully understood – Circulating CLA^+, $CCR6^+$ Tregs are increased in AD patients – Lesional AD skin is devoid of functional Tregs[35]
ROLE OF MICROBIAL COLONIZATION
• Epidermal keratinocytes express a variety of pattern recognition receptors (e.g. Toll-like receptors [TLRs]) that bind to specific microbial structures, which induces an inflammatory response and the release of antimicrobial peptides such as defensins and cathelicidins (see Ch. 4); however, production of the latter peptides is down-regulated in the skin of patients with AD • *S. aureus* colonization of the skin occurs in >90% of AD patients due to factors such as decreased levels of antimicrobial peptides and increased bacterial adherence to eczematous/excoriated skin • *S. aureus* contributes to sensitization and inflammation in AD via several mechanisms – TLR-2 recognition of *S. aureus* cell wall components (e.g. lipoteichoic acid, peptidoglycan) stimulates an inflammatory response – Staphylococcal superantigens amplify inflammatory reactions via multiple pathways[36] and may contribute to corticosteroid resistance by inducing the competing β isoform of the glucocorticoid receptor – Staphylococcal enterotoxins A–D (SEA-D) can provoke IgE-mediated sensitization, which correlates with disease severity[37] – Staphylococcal toxins also augment inflammation by subverting the function of Tregs
ROLE OF AUTOIMMUNITY
• Some patients with AD have circulating IgE antibodies directed against self-proteins expressed by keratinocytes and endothelial cells[38] – The presence of these antibodies correlates with disease severity – Prevalence of ~25% in adult patients; have also been detected in infants[39] – Predisposing factors include early-onset AD, severe pruritus, recurrent bacterial skin infections and high serum IgE levels • Structural similarities between exogenous allergens and human proteins are thought to have a role in the development of IgE autoantibodies; this likely occurs in the context of cutaneous inflammation and scratching/cellular damage that leads to exposure of the autoantigens (see Fig. 12.2) • Some autoallergens induce Th1 responses[40] • These observations suggest that AD exists at the frontier between allergy and autoimmunity
*Commonly occurs in early-onset as well as intrinsic forms of AD.

Table 12.4 Epidermal defects and immunologic mechanisms involved in the pathogenesis of atopic dermatitis (AD). CCL or CXCL, chemokine (C-C or C-X-C motif) ligand; CCR or CXCR, chemokine (C-C or C-X-C motif) receptor; CLA, cutaneous lymphocyte antigen; CTACK, cutaneous T-cell-attracting chemokine; IL, interleukin; Tregs, regulatory T cells.

Fig. 12.3 Post-inflammatory pigmentary alteration in atopic dermatitis. **A** Ill-defined hypopigmented patches with variable residual erythema and scale on the shoulder and upper arm. **B** Postinflammatory depigmentation in a patient with widespread, severe disease and multiple lesions of prurigo nodularis. *B, Courtesy, Jean L Bolognia, MD.*

Fig. 12.4 Atopic dermatitis on the face of an infant. Acute lesions with oozing and serous crusting are common in this age group. *Courtesy, Julie V Schaffer, MD.*

Fig. 12.5 Atopic dermatitis on the extensor surface of an infant's arm. Involvement of the extensor aspects of the extremities is common in this age group. Note the follicular prominence on the trunk.

Senile AD (age >60 years) is characterized by marked xerosis. Most of these patients do not have the lichenified flexural lesions typical of AD in children and younger adults.

AD has a profound adverse impact on the quality of life of affected children and adults, with intense pruritus and stigmatization often resulting in sleep disturbances, psychological distress, social isolation, disrupted family dynamics and impaired functioning at school or work.

Regional Variants of Atopic Dermatitis

Several regional variants of AD can occur in isolation or together with the classic age-related patterns of involvement described above. The face is a frequent location for site-specific manifestations. Eczema of the lips, referred to as ***cheilitis sicca***, is common in AD patients, especially during the winter. It is characterized by dryness ("chapping") of the vermilion lips, sometimes with peeling and fissuring, and may be associated with angular cheilitis. Patients try to moisten their lips by licking, which in turn may irritate the skin around the mouth, resulting in so-called ***lip-licker's eczema.*** Another common feature of childhood AD is ***ear eczema***, presenting as erythema, scaling and fissures under the earlobe and in the retroauricular area, sometimes in association with bacterial superinfection. ***Eyelid eczema*** can represent the only manifestation of AD, especially in adults. In contrast to eyelid eczema due to other causes, it is characterized by lichenification of the periorbital skin.

"Head and neck dermatitis" represents a variant of AD that typically occurs after puberty and primarily involves the face, scalp and neck. When older children and teenagers present with this form of AD, it usually persists into adulthood. It is postulated that lipophilic *Malassezia* yeasts, members of the normal skin flora that colonize the head and neck area, represent an aggravating factor for this condition. Serum levels of *M. furfur*-specific IgE have been shown to correlate with the severity of head and neck dermatitis[45], and improvement with systemic antifungal treatment has been observed in some patients. Sweating, heat, dryness, sun exposure and emotional stress can also aggravate this form of AD.

Fig. 12.6 Atopic dermatitis extending from the antecubital fossae to the wrists and hands. Note the excoriations and lichenification.

Fig. 12.7 Lichenified atopic dermatitis on the wrists and hands of children. **A** Pink plaques with excoriation and hemorrhagic crusting as well as lichenification. **B** Thick lichenified plaques. *Courtesy, Julie V Schaffer, MD.*

Fig. 12.8 Severe chronic hand dermatitis in an adult with atopic dermatitis.

Fig. 12.9 Severe atopic dermatitis with facial involvement in an adult.

Fig. 12.10 Chronic papular lesions in an adult with atopic dermatitis. This resulted from habitual scratching and rubbing in the setting of longstanding disease.

Fig. 12.11 Nipple eczema in an adolescent with atopic dermatitis. *Courtesy, Julie V Schaffer, MD.*

Eczema variants also occur in acral sites. ***Juvenile plantar dermatosis*** presents with "glazed" erythema, scale and fissuring on the balls of the feet and plantar aspect of the toes in children with AD, especially during the winter (see Ch. 13). ***Atopic hand eczema*** (see Fig. 12.8) affects approximately 60% of adult patients with AD and may be the only manifestation of the condition. It often occurs in atopic individuals whose hands are frequently exposed to water and other irritants in household or occupational settings. Atopic hand eczema typically involves the volar wrists and dorsum of the hands. The palms and sides of the fingers may develop the deep-seated vesicles of ***dyshidrotic eczema*** (see Ch. 13).

The ***prurigo form of AD*** favors the extensor aspects of the extremities and is characterized by firm, dome-shaped papules and nodules with central scale-crust, similar to prurigo nodularis lesions in non-atopic patients. ***Nummular lesions*** also tend to develop on the extremities in children and adults with AD, appearing as coin-shaped eczematous plaques, usually 1 to 3 cm in diameter and often with prominent oozing and crusting (similar in appearance to the lesions that characterize nummular dermatitis occurring outside the setting of atopy; see Ch. 13). Colonization with *Staphylococcus aureus* is thought to represent a trigger for this type of eczema. Intense pruritus is a feature of both prurigo and nummular lesions. ***Frictional lichenoid eruption*** has a predilection for atopic children (especially boys) and presents as multiple small, flat-topped, pink to skin-colored papules on the elbows and (less often) knees and dorsal hands. It classically occurs in the spring or summer, pruritus is variable, and the histologic findings are nonspecific. Lastly, chronic ***nipple eczema*** can develop in children and adults with AD (Fig. 12.11).

Associated Features

Pruritus

Intense pruritus is a hallmark of AD. The itch is often worse in the evening and may be exacerbated by exogenous factors such as sweating or wool clothing. Rubbing and scratching in response to pruritus can initiate flares or exacerbate existing dermatitis, explaining why AD

ASSOCIATED FEATURES OF ATOPIC DERMATITIS ("ATOPIC STIGMATA")	
Xerosis	• Important feature that is present in most patients with AD • Often most prominent on the lower legs; may be generalized • Dry skin with fine scale in areas without clinically apparent inflammation • Typically worse during the winter • Impaired epidermal barrier function from decreased water content in the stratum corneum leads to easier entry of irritants, which can promote pruritus and initiate an inflammatory response
Ichthyosis vulgaris	• Autosomal semidominant disorder with incomplete penetrance caused by mutations in the filaggrin gene (*FLG*; see text and Ch. 57) • ~15% of patients with AD have moderate to severe ichthyosis vulgaris; conversely, >50% of patients with ichthyosis vulgaris have AD • Excessive fine, whitish to brown scaling that favors the lower legs (especially the shins) and spares the flexures
Keratosis pilaris	• Common condition that affects >40% of patients with AD and ~75% of those with ichthyosis vulgaris • Onset typically in childhood; may improve after puberty (especially facial involvement) • Affects the lateral aspect of the upper arms, thighs and (especially in children) lateral cheeks > trunk and extensor aspects of the distal extremities • Keratotic follicular papules, often with a rim of erythema (see Fig. 12.12A) or (especially on the cheeks) a background of patchy erythema • The *keratosis pilaris rubra (KPR)* variant features numerous tiny, "grain-like" follicular papules superimposed on prominent confluent erythema (see Fig. 12.12B&C); often widespread (face & ears > trunk & proximal extremities) and tends to persist after puberty; presence of erythema rather than hyperpigmentation differentiates KPR from erythromelanosis follicularis faciei et colli, and a lack of atrophy in KPR differentiates it from keratosis pilaris atrophicans (see Ch. 38) • Keratolytic agents and topical retinoids are sometimes used to decrease the hyperkeratotic component, but the benefit is limited and these agents can be irritating, especially in AD patients; treatment with vascular lasers (e.g. the pulsed dye laser) can improve associated erythema
Palmar and plantar hyperlinearity	• Increased prominence of the palmar and, less often, plantar creases (see Fig. 12.13) • Associated with ichthyosis vulgaris and *FLG* mutations
Dennie–Morgan lines	• Symmetric, prominent horizontal fold(s) (single or double) just beneath the margin of the lower lid, originating at or near the inner canthus and extending one-half to two-thirds the width of the lid (see Fig. 12.14)
Periorbital darkening ("allergic shiners")	• Skin around the eyes appears gray to violet–brown, while the rest of the facial skin is rather pale • Periorbital edema and lichenification may also be seen
Anterior neck folds	• Horizontal folds across the middle of the anterior neck
Hertoghe sign	• Absence or thinning of the lateral eyebrows
White dermographism	• Stroking the skin leads to a white streak that reflects excessive vasoconstriction • Most apparent on the forehead • Mid-facial pallor (see Fig. 12.14) and a delayed blanch response represent additional manifestations of aberrant vascular reactivity in patients with atopic dermatitis
Follicular prominence	• "Goose bump-like" appearance of the skin, most often on the trunk (see Fig. 12.5) • More commonly observed in children with darkly pigmented skin

Table 12.5 Associated features of atopic dermatitis ("atopic stigmata"). AD, atopic dermatitis.

Fig. 12.12 Keratosis pilaris. A Discrete perifollicular papules with central keratotic cores on the extensor surface of the upper arm. Each papule has a rim of erythema. **B, C** Keratosis pilaris rubra on the lateral face. This variant is characterized by tiny, "grain-like" follicular papules superimposed on confluent erythema. *B, C, Courtesy, Julie V Schaffer, MD.*

Fig. 12.13 Exaggerated palmar creases. This patient had both atopic dermatitis and ichthyosis vulgaris. *Courtesy, Jean L Bolognia, MD.*

Fig. 12.14 Infant with atopic dermatitis of the face with central facial sparing. Note the Dennie–Morgan lines and central facial pallor.

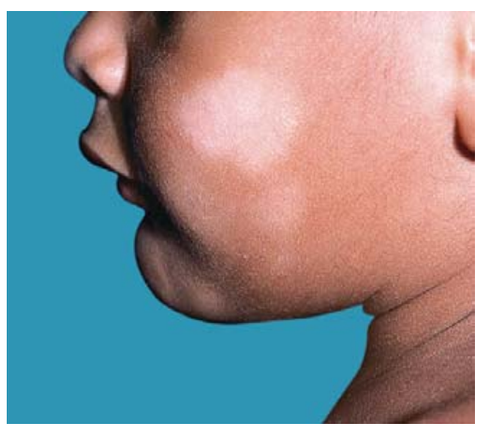


Fig. 12.15 Pityriasis alba. Note the slight scale associated with the hypopigmented macules and patches on the cheeks. *Courtesy, Anthony J Mancini, MD.*

is known as the "itch that rashes". Excoriations (linear or punctate) are frequently present, providing evidence of scratching (see Figs 12.6 & 12.7A). With repeated rubbing and scratching, the skin becomes thickened and leathery with exaggerated skin markings (see Figs 12.6 & 12.7).

Atopic stigmata

Physical findings other than dermatitis that are frequently observed in patients with AD are presented in Table 12.5 (see Figs 12.12–12.15).

Pityriasis alba

Pityriasis alba frequently affects children and adolescents with AD. It is characterized by multiple ill-defined hypopigmented macules and patches (usually 0.5 to 2 cm in diameter) with fine scaling, which are typically located on the face (especially the cheeks; Fig. 12.15) but occasionally appear on the shoulders and arms. These lesions are most obvious in individuals with darkly pigmented skin and/or following sun exposure. Pityriasis alba is thought to result from a low-grade eczematous dermatitis that disrupts the transfer of melanosomes from melanocytes to keratinocytes. Similar hypopigmented lesions can appear upon resolution of more overtly inflamed, erythematous lesions of AD (see Fig. 12.3A). The differential diagnosis of pityriasis alba also

Fig. 12.16 Infected hand dermatitis in a patient with atopic dermatitis. There is impetigo-like crusting as well as pustules. *Courtesy, Louis A Fragola, Jr, MD.*

Fig. 12.17 Eczema herpeticum. Note the monomorphic erosions and hemorrhagic crusts. *Courtesy, Julie V Schaffer, MD.*

includes postinflammatory hypopigmentation secondary to other dermatoses (e.g. psoriasis or pityriasis lichenoides chronica; usually also extrafacial involvement), pityriasis versicolor (typically more sharply demarcated, small lesions that may coalesce centrally), vitiligo (sharply demarcated and depigmented rather than hypopigmented) and (occasionally if extrafacial involvement) hypopigmented mycosis fungoides. Regular use of sunscreens and other forms of photoprotection may minimize the appearance of pityriasis alba.

Complications

Infections

Patients with AD are predisposed to the development of skin infections because of factors including an impaired skin barrier and modified immune milieu (see Table 12.4). Bacterial and viral infections represent the most common complications of AD. Considering that *S. aureus* colonizes the skin of the vast majority of patients with AD, it is not surprising that ***impetiginization*** (which can also occur due to *Streptococcus pyogenes*) occurs quite frequently (Fig. 12.16). Bacterial infections may also exacerbate AD by stimulating the inflammatory cascade, e.g. via *S. aureus* exotoxins that act as superantigens (see Table 12.4).

Eczema herpeticum represents rapid dissemination of a herpes simplex viral infection over the eczematous skin of AD patients[46]. It initially develops as an eruption of vesicles, but affected individuals more often present with numerous monomorphic, punched-out erosions with hemorrhagic crusting (Fig. 12.17). Eczema herpeticum is frequently widespread and may occur at any site, with a predilection for the head, neck and trunk. It is often associated with fever, malaise and lymphadenopathy, and complications may include superinfection with *S. aureus* or *S. pyogenes* as well as herpetic keratoconjunctivitis and meningoencephalitis[46]. Patients with mutations in t he filaggrin gene and those who have both severe AD and asthma have an increased risk for eczema herpeticum, and decreased production of antimicrobial peptides may have a pathogenic role. Patients with AD are also predisposed to the development of widespread ***molluscum contagiosum***, sometimes with several hundred lesions (see Ch. 81).

Ocular complications

Besides development of acute conjunctivitis as a component of allergic rhinoconjunctivitis, the spectrum of atopic eye disease also includes chronic manifestations such as atopic keratoconjunctivitis (typically in adults) and vernal keratoconjunctivitis (favors children living in warm climates)[47]. Symptoms include ocular itching, burning, tearing and mucus discharge, often in association with conjunctival injection and (especially in atopic keratoconjunctivitis) blepharitis that manifests as swelling and scaling of the eyelids. Vernal keratoconjunctivitis features large, cobblestone-like papillae on the upper palpebral conjunctiva, and atopic keratoconjunctivitis is more prone to scarring. Additional infrequent ocular complications of AD include subcapsular cataracts (anterior more specific to AD, posterior more common)[48], keratoconus and retinal detachment.

DIAGNOSTIC CRITERIA

Several authors and groups have suggested guidelines to assist in establishing the clinical diagnosis of AD. Major features in these sets of criteria include pruritus, eczematous skin lesions in typical age-specific distribution patterns, a chronic or chronically relapsing course, early age at onset, and a personal and/or family history of atopy. Atopic stigmata (see Table 12.5), especially xerosis, are also recognized as supporting features. The Diepgen score represents another validated set of diagnostic criteria, which is separated into objective, subjective and laboratory features[49]. Validated scores to assess the severity of AD include the EASI (Eczema Area Scoring Index), SCORAD (SCORing Atopic Dermatitis) and POEM (Patient-Oriented Eczema Measure)[50]. IgE-associated and non-IgE-associated AD are distinguished based on the evaluation of total serum IgE levels (elevated in the former; normal <150 IU/ml) and the presence or absence of specific IgE. Although recognition of the latter can support the diagnosis of an atopic state, exposures to the allergens identified are not necessarily relevant to aggravation of AD (see below).

PATHOLOGY

The histologic features of AD depend upon the stage of the lesion sampled. *Acute*, exudative eczema is characterized by marked spongiosis, with intraepidermal fluid collection leading to the formation of vesicles (micro and macro) or even bullae. Some dermal edema may also be present, together with perivascular lymphocytes that extend into the epidermis and a variable number of eosinophils (Fig.12.18A). In *subacute* lesions, vesiculation is absent whereas acanthosis, hyperkeratosis and parakeratosis become evident (Fig. 12.18B). In *chronic*, lichenified eczema, epidermal thickening is more pronounced in a pattern that may be either irregular or regular (psoriasiform). Changes in the granular layer vary from thickening secondary to rubbing (as in lichen simplex chronicus) to thinning when there is a psoriasiform pattern (seen in some nummular lesions). Spongiosis and inflammation are less conspicuous, but there may be an increased number of mast cells and dermal fibrosis.

These features are not specific, as similar findings are observed in other eczematous dermatoses such as allergic contact dermatitis. There are occasionally histologic clues to the etiology, such as individually necrotic keratinocytes that suggest an irritant contact dermatitis. However, a skin biopsy is usually more helpful in excluding other entities that can mimic AD clinically, such as mycosis fungoides.

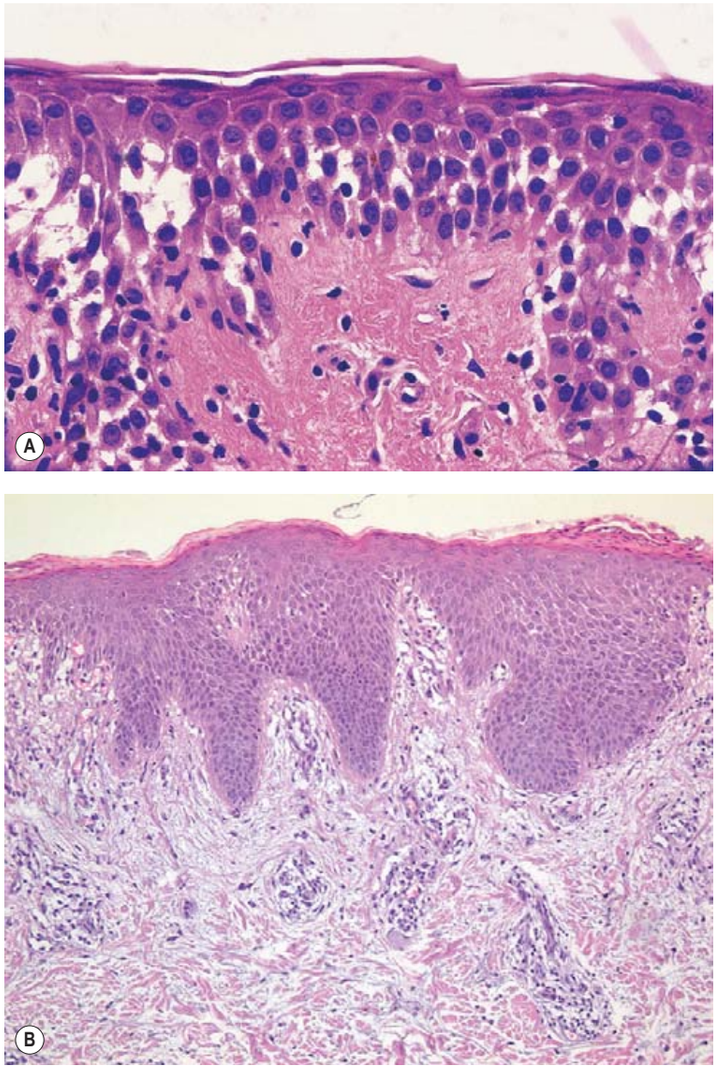


Fig. 12.18 Histologic features of acute and subacute atopic dermatitis. **A** Acute lesion showing spongiosis, intraepidermal vesicles and exocytosis of lymphocytes. **B** Subacute lesion with parakeratosis and less spongiosis.
A, Courtesy, Ronald P Rapini, MD.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of AD is broad and includes other chronic dermatoses, infections, infestations and malignancies as well as metabolic, genetic (e.g. primary immunodeficiencies) and autoimmune disorders (Table 12.6). Depending upon the age of the patient and the clinical presentation, such entities may be considered prior to diagnosing AD, especially when the history, morphology and/or distribution of the skin lesions are atypical.

In infants, AD is often preceded and/or accompanied by seborrheic dermatitis, which commonly presents during the first month of life as yellowish-white, adherent scale-crusts on the scalp. Infantile seborrheic dermatitis also has a predilection for skin folds (where lesions may be oozing and lack scale) and the forehead, in contrast to the typical distribution of infantile AD on the extensor surfaces of the extremities and cheeks as well as the scalp. Scabies in infants often has generalized involvement and can mimic AD; in addition to the presence of burrows or identification of the mite or eggs (e.g. via dermoscopy or skin scrapings), scabies can usually be distinguished by the predominance of discrete small crusted papules, involvement of the axillae and diaper area, and the presence of acral vesiculopustules. Other less common conditions that occasionally represent a diagnostic consideration in infants, such as primary immunodeficiencies, are listed in Table 12.6.

Adolescents and adults without a personal or family history of atopy who present with an eczematous eruption should have a thorough history and (when indicated) patch testing to assess for the possibility of allergic contact dermatitis. This diagnosis should also be considered

DIFFERENTIAL DIAGNOSIS OF ATOPIC DERMATITIS		
CHRONIC DERMATOSES		
C>A	Seborrheic dermatitis	Common
B	Contact dermatitis (allergic* or irritant)	Common
B	Psoriasis (especially palmoplantar)	Common
A>C	Nummular dermatitis	Uncommon (although nummular lesions can be seen in AD, nummular eczema outside this setting is uncommon)
A	Asteatotic eczema	Common
A>C	Lichen simplex chronicus (secondary to pruritus of variable etiology)	Common
INFECTIONS AND INFESTATIONS		
B	Scabies	Common
B	Dermatophytosis*	Common
B	HIV-associated dermatoses	Variable
C	HTLV-1-associated "infective dermatitis"	Variable
C	Chronic mucocutaneous candidiasis	Rare
C	Neonatal mucocutaneous candidiasis	Variable
B	Impetigo	Variable (nummular lesions of AD most commonly mimic impetigo)
C	Congenital syphilis	Variable
PRIMARY IMMUNODEFICIENCIES		
C	Wiskott–Aldrich syndrome	Rare
C	Hyperimmunoglobulin E syndrome	Rare
C	Severe combined immunodeficiency	Rare
C	DiGeorge syndrome (congenital thymic aplasia)	Rare
C	Immunoglobulin deficiencies: X-linked hypogammaglobulinemia, common variable immunodeficiency, IgA deficiency	Variable
C	Ataxia telangiectasia	Rare
MALIGNANCIES		
A>C	Mycosis fungoides and Sézary syndrome	Uncommon
C	Langerhans cell histiocytosis	Rare
METABOLIC AND GENETIC DISORDERS		
C	Netherton syndrome	Rare
C	Ectodermal dysplasias	Rare
B	Keratosis pilaris	Common
C	Hartnup disease	Rare
C	Phenylketonuria	Rare
B	Acrodermatitis enteropathica, glucagonoma syndrome, pellagra, riboflavin deficiency	Rare
C>A	Other causes of "nutritional dermatitis", e.g. biotin deficiency, essential fatty acid deficiency, organic acidurias, cystic fibrosis	Rare
AUTOIMMUNE DISORDERS		
A>C	Dermatitis herpetiformis	Uncommon
A>C	Pemphigus foliaceus	Uncommon
B	Dermatomyositis	Uncommon (but often misdiagnosed as AD in children)
A>C	Lupus erythematosus	Uncommon
OTHER		
B	Drug eruptions	Uncommon (although drug eruptions are common, those resembling atopic dermatitis are uncommon)
A>C	Photoallergic contact dermatitis	Uncommon
A	Chronic actinic dermatitis	Uncommon
B	Graft-versus-host disease	Uncommon

*More common causes of disseminated eczema ("id reaction"), which is especially frequent in the setting of stasis dermatitis + allergic contact dermatitis.

Table 12.6 Differential diagnosis of atopic dermatitis. A, adults; B, both; C, children/infants.

in children and adults with established AD who fail to respond as expected to treatment or develop lesions in an atypical distribution pattern. Components of emollients or topical corticosteroid preparations represent potential allergens in these individuals. Protein contact dermatitis can also present as a chronic eczematous dermatitis and is more common in atopic individuals. Common causes include a variety of foods and animal products (Table 12.7; see Ch. 16), and it is diagnosed by prick testing or observation of an urticarial reaction within 30 minutes of patch testing on previously affected skin.

Mycosis fungoides (MF) should be considered in adolescents and adults with chronic dermatitis poorly responsive to topical corticosteroid treatment. Because the histologic findings of early MF may be difficult to distinguish from those of AD, multiple biopsies are recommended, preferably from untreated areas of skin since corticosteroids can eliminate epidermotropic T cells that point to the diagnosis of MF. Longitudinal evaluation of such individuals is required, especially when the clinical and/or histologic features are not classic for AD, with additional biopsies as indicated.

TREATMENT

Because AD is a chronic relapsing disease, the classic approach to therapy is targeting acute flares with short-term treatment regimens, i.e. reactive management. Based on recent insights into the underlying skin barrier defect and its relationship to inflammatory processes in the skin and other organs, a proactive approach that includes long-term maintenance therapy is now recommended[51]. Currently, management of AD includes the following components:

- avoidance of trigger factors, including irritants, relevant allergens and microbial agents
- skin care that aims to compensate for the genetically determined impaired epidermal barrier function
- anti-inflammatory therapy to control subclinical inflammation as well as overt flares
- in selected cases, adjunctive or complementary modalities.

As a rule, management should be adapted to the severity of the disease. While mild cases can typically be controlled by continuous use of emollients and intermittent use of a low-potency topical corticosteroid for flares, moderate AD may also require proactive maintenance with anti-inflammatory agents. In more severe and refractory cases, the use of phototherapy and systemic drugs may be necessary to control the disease (Table 12.8). An appropriate educational program for patients and parents is another essential component of the management of AD.

Avoidance of Trigger Factors

Multiple environmental and psychological factors can trigger AD, including allergens (e.g. pollen, dust mites, animal dander), sweating, harsh soaps, wool or other rough fabrics, cigarette smoke and emotional stress. These vary depending upon the patient and may be identified (and subsequently avoided) by a careful history and (when indicated) allergy testing. Fluorescence enzyme immunoassays (which have largely replaced RAST tests) can be performed on serum samples to quantify specific IgE antibodies against suspected allergens; skin prick testing represents another option to assess for immediate hypersensitivity. The atopy patch test can provoke an eczematous reaction through the epicutaneous application of aeroallergens (for which the test has been standardized) or food allergens, with readings at 48 and 72 hours to detect delayed hypersensitivity[52]. It holds promise as a relatively specific tool to evaluate children with AD for clinically significant allergies.

Allergen-specific immunotherapy, which can abrogate allergic sensitizations, represents a strategy to block trigger factors in selected patients with AD. For example, in some randomized controlled studies, sublingual or subcutaneous immunotherapy led to improvement of skin disease in AD patients with specific sensitizations against house dust mites[53]. Modest improvement in this subset of AD patients has also been observed after reducing dust mites in the home (especially the bedroom) through methods such as utilization of mattress and pillow covers, high-filtration vacuum cleaning and miticide sprays.

Food hypersensitivity affects about 10–30% of infants and children with AD, and ~90% of reactions in this patient population are caused by five allergens: eggs (most often linked to AD exacerbations), milk, peanuts, soy and wheat. Reactivity to peanuts (as well as tree nuts, fish and shellfish) tends to persist, but children usually "outgrow" sensitivities to other foods[54]. The clinical history and (in selected instances) provocation tests should be used to determine the *relevance* of positive laboratory and skin prick tests, since results of the latter tests do not necessarily identify allergies that are exacerbating the patient's AD. For example, double-blind food challenges may be useful in young children with a history of food-induced paroxysms of pruritus. Although avoidance of food allergen triggers can help to prevent flares in a subset of patients with the IgE-associated form of AD (especially infants with severe, refractory disease), this must be balanced with the potential for

CAUSES OF PROTEIN CONTACT DERMATITIS
• Fruits (banana, fig, kiwi, lemon, pineapple) • Grains (barley, rye and wheat flours) • Latex • "Meats" (fish, seafood, beef, pork, poultry) • Mites and insects (rice flour beetle, dust mite, storage mite) • Nuts (almond, hazelnut, peanut) • Spices (caraway, curry, dill, garlic, paprika, parsley) • Vegetables (carrot, cauliflower, celery, cucumber, lettuce, mushroom, onion, parsnip, potato) • Animal dander, hair, saliva or urine (cow, deer, goat, dog, cat, rodents, hedgehog, rabbit, giraffe)

Table 12.7 Causes of protein contact dermatitis.

THERAPEUTIC LADDER FOR ATOPIC DERMATITIS	Evidence
Emollients (basic therapy)	1
Topical corticosteroids	1
Topical calcineurin inhibitors	1
UVB (narrowband>broadband), UVA-UVB, UVA1 or oral PUVA	1
Systemic corticosteroids (short term for severe acute flares; "rebound" exacerbations often occur upon discontinuation)	2
Cyclosporine (short/intermediate term)	1
Azathioprine	1
Mycophenolate mofetil/enteric-coated mycophenolate sodium	1*/2
Methotrexate	1*/2
Interferon-γ	**
IVIg	2†
Omalizumab	2†
Rituximab	2
Other (crude coal tar, hydroxychloroquine, extracorporeal photochemotherapy)	2–3
ADJUNCTIVE THERAPIES	
Wet wraps, open wet dressings or soaks (combined with topical corticosteroids for acute flares)	
Dilute sodium hypochlorite (bleach) baths	
Treatment of associated bacterial, viral or fungal infections	
Oral antihistamines for antipruritic‡ and sedative effects	
Leukotriene antagonists‡	
Sodium cromoglycate (topical or oral)‡	
Probiotics‡ (may have efficacy in primary prevention)	

*In recent randomized controlled trials in adults with severe AD, enteric-coated mycophenolate sodium was found to have similar efficacy to cyclosporine as maintenance therapy, and methotrexate was found to have similar efficacy to azathioprine (see text).
**Although found to be effective in one randomized controlled trial, results of other studies have been inconsistent (see Ch. 128).
†No significant benefit was found in a small controlled trial.
‡Inconsistent demonstration of efficacy in controlled trials.

Table 12.8 Therapeutic ladder for atopic dermatitis (AD). Key to evidence-based support: (1) prospective controlled trial; (2) retrospective trial or large case series; (3) small series or individual case reports.

adverse sequelae from unnecessarily restrictive diets (e.g. kwashiorkor due to "rice milk" diets). Modified diets should be supervised by a pediatric dietician to ensure that they are nutritionally adequate.

Because *S. aureus*, which densely colonizes the skin in most AD patients, is known to amplify the cutaneous inflammation that underlies AD (see Table 12.4), reduction of bacterial load can play a role in the management of AD. In a recent randomized controlled study, 0.005% sodium hypochlorite baths (0.5 cup of household bleach [6% sodium hypochlorite] added to a full 40-gallon bathtub) twice weekly together with intermittent use of intranasal mupirocin ointment over a 1- to 3-month period led to greater improvement of moderate to severe, superinfected AD than did placebo (with both groups initially receiving a 2-week course of oral cephalexin)[55]. Cleansers and emollients containing antiseptics such as triclosan or clioquinol represent additional options. In general, the use of topical and systemic antibiotics should be restricted to short-term treatment of superinfections in order to prevent the development of bacterial resistance. There is some evidence that the *S. aureus* strains that colonize and superinfect patients with AD are more likely to be susceptible to first-generation cephalosporins (e.g. cephalexin) than are those that cause other *S. aureus* skin infections in the same communities[55,56].

Basic Therapy (Skin Care)

Recent findings highlighting the critical role of an impaired skin barrier in the pathogenesis of AD underscore the importance of a continuous basic therapy with emollients, even in periods and sites in which the AD is not active. The formulation of the emollient should be chosen based upon the degree of dryness of the skin, the sites of application, acceptance by the patient and the season. Ointments (e.g. petrolatum) and water-in-oil creams are more occlusive and tend to cause less burning and stinging than oil-in-water creams and lotions. However, the greasiness of an ointment is not acceptable to all patients. Potentially allergy-provoking ingredients such as perfumes, lanolin and herbal extracts should be avoided. The addition of moisturizing factors that are able to bind water (e.g. glycerol, urea) leads to increased hydration of the epidermis[57]. However, emollient products with higher concentrations of urea or α- and β-hydroxy acids, which can decrease scaling as well as dryness, tend to sting when used in children and on acutely inflamed or excoriated skin. Emollients containing particular combinations of lipids that are normally present in the stratum corneum (e.g. cholesterol, fatty acids, ceramides) may optimize barrier repair[58]. Emollients should be applied twice daily to the entire cutaneous surface.

AD patients should use mild, non-alkaline cleansers (e.g. syndet bars; see Ch. 153) as needed (e.g. focusing on soiled and apocrine-containing areas). Bubble baths and scented salts or oils should be avoided. Although allowing moisture to fully evaporate from the skin following bathing can worsen xerosis, application of an emollient to the skin within 3 minutes of exiting a daily lukewarm bath or shower increases skin hydration and barrier function. If treatment with a topical corticosteroid is indicated, it should be applied immediately after bathing, prior to the emollient. For acute flares of AD, 10- to 20-minute soaks in lukewarm bathwater or tap water compresses followed directly with corticosteroid application ("soak and smear") or placement of wet wraps after topical corticosteroid application can soothe oozing or crusted lesions and result in rapid improvement. Scalp care should include a bland shampoo. Shampoos, lotions and creams containing tar (5–10% liquor carbonis detergens) are helpful in some patients but may be irritating in children and when used on acutely inflamed skin.

Topical Anti-inflammatory Therapy

Topical corticosteroids are the mainstay of pharmacologic therapy for AD, and topical calcineurin inhibitors (TCIs) also play an important role. For the treatment of acute flares of AD, *topical corticosteroids* represent the first-line therapy because of their potent anti-inflammatory effects. These agents suppress production of several transcription factors, which leads not only to reduced expression of proinflammatory cytokines, but also to inhibition of cell growth and decreased synthesis of collagen and other structural proteins (explaining side effects such as skin atrophy; see Ch. 125). Topical corticosteroids designed to have decreased systemic bioavailability and a favorable therapeutic index (e.g. prednicarbate, hydrocortisone butyrate, fluticasone propionate, mometasone furoate) may be preferable, especially for infants and young children with widespread involvement.

Considerations in selecting the potency and vehicle of the topical corticosteroid include the location, type (e.g. acute versus chronic), thickness and extent of the AD lesions as well as the age of the patient. The corticosteroid should have an appropriate potency to quickly gain control of the flare, and continuation of daily therapy until the active dermatitis is completely clear minimizes the likelihood of a rebound. Long-term daily use of an inadequately potent topical corticosteroid can result in a greater risk of side effects (as well as less control of the eczema) than relatively brief use of a more potent agent. After clinical resolution of longstanding or severe lesions, tapering to every-other-day treatment may be considered prior to decreasing to maintenance therapy. For children and adults with moderate to severe AD, randomized controlled trials have demonstrated that the risk of relapse can be significantly reduced by proactive maintenance with twice-weekly application of a mid-potency topical corticosteroid to the usual areas of involvement (in conjunction with emollient use), with no evidence of cutaneous atrophy after up to a year of treatment[59–61].

For the face and body folds, high-potency corticosteroids (particularly long-term use) should be avoided if possible due to risk of cutaneous atrophy. Potent corticosteroids (e.g. class 1–2) are often needed for thick or lichenified plaques, nummular or prurigo-like lesions, and eczema on the palms and soles. Flurandrenolide tape represents another option for prurigo-like lesions, since it physically blocks scratching and rubbing of the affected area. Corticosteroid ointments (which minimize burning/stinging) and creams are generally preferred considering the dryness of the skin in AD patients and the emollient effects of these vehicles. Application immediately after bathing improves cutaneous penetration and also decreases burning. Corticosteroid solutions, foams or (especially for children and individuals of African descent) oils represent choices for AD on the scalp.

Two *topical calcineurin inhibitors (TCIs)* have been approved by the US Food and Drug Administration (FDA) for the treatment of AD: tacrolimus 0.03% and 0.1% ointment (for "moderate to severe" disease) and pimecrolimus 1% cream (for "mild to moderate" disease) (see Ch. 128). These agents suppress T-cell activation and modulate the secretion of cytokines and other proinflammatory mediators. Their efficacy in the treatment of AD has been proven in clinical trials in adults and children at least 2 years of age (and, for pimecrolimus, infants ages 3–23 months, although it is not approved for this group)[62,63]. The major side effect of both medications is burning at the site of application; they are not associated with cutaneous atrophy.

There has been no short-term or intermediate-term (>10 years) evidence of systemic immunosuppression or an increased risk for malignancy in clinical studies or post-marketing surveillance of topical tacrolimus and pimecrolimus, and long-term data collection is ongoing[64,65]. However, in 2006 the FDA introduced black box warnings for both drugs concerning a theoretical cancer risk; this was based on the occurrence of lymphomas in mice exposed to systemic levels 30–50-fold greater than the highest recorded blood levels in human patients. Pharmacokinetic studies in children and adults with AD have demonstrated minimal systemic absorption of TCIs, with transient detectable (but low) blood levels occasionally observed in patients with severe AD involving a large portion of the body surface area.

TCIs are particularly suitable for AD affecting the face and intertriginous areas, sites where corticosteroid-induced skin atrophy is of increased concern and TCI therapy is especially effective. TCIs are also beneficial in patients with frequently flaring or persistent AD that would otherwise require almost continual use of topical corticosteroids. Recent randomized controlled studies have shown that the proactive application of tacrolimus ointment (e.g. twice weekly as maintenance) can prevent flares of AD without increasing the overall amount of medication used[66,67].

Phototherapy

AD patients can benefit from treatment with ultraviolet (UV) light. *UVA1*, *UVA combined with UVB*, and *narrowband UVB* have each been shown to improve both the eczema and associated pruritus. The immunomodulatory effects of phototherapy occur via induction of T-cell

apoptosis, reduction of dendritic cells, and modified cytokine expression (e.g. decreased IL-5, IL-13 and IL-31 after treatment of AD with UVA1)[68] (see Ch. 134). In addition, treatment with UVB has been shown to reduce *S. aureus* colonization of the skin in AD patients[69]. Narrowband UVB and high-dose UVA1 can both be helpful for chronic AD, and UVA1 may also be useful in the treatment of acute flares. Phototherapy can be combined with topical corticosteroids, particularly in the initial phase of treatment. The side-effect profile of phototherapy is favorable compared to systemic immunosuppressive agents, with potential risks of "sunburn" and, with long-term treatment, photoaging and possibly induction of cutaneous malignancies. The time and effort required to travel several times a week to a phototherapy center may be problematic for some patients (e.g. disrupting school and work), and a home UV unit may be an option for those receiving chronic treatment. In younger children, phototherapy may be difficult for practical reasons (e.g. lack of cooperation), and some centers limit its routine use to patients ≥12 years of age.

Systemic Anti-inflammatory Therapy

Systemic anti-inflammatory treatment should be restricted to severe, refractory cases of AD that do not respond adequately to intensive topical therapy. The risk–benefit profile should be carefully considered before starting an immunosuppressive agent, and patients receiving these medications require close monitoring for side effects. Of note, no systemic medications besides corticosteroids have been FDA-approved for treatment of AD. However, in general, treatment of AD with *systemic corticosteroids* should be avoided due to a propensity for significant rebound flares upon their discontinuation[69a] and the unacceptable side effects of long-term use (see Ch. 125). In the occasional exception of a severe, generalized acute flare (e.g. with a specific trigger) resistant to aggressive topical management, treatment with a systemic corticosteroid should be limited to a short course, with transition to a topical regimen, phototherapy and/or an alternative systemic agent.

Administration of *oral cyclosporine* typically leads to rapid improvement of skin disease and associated pruritus in patients with AD, and its efficacy has been established in randomized controlled trials. However, the use of oral cyclosporine to treat AD is limited by potential side effects such as nephrotoxicity (which can develop after as little as 3–6 months of therapy) and increased blood pressure, which seem to be dose-dependent. Treatment is frequently started with a dose of 5 mg/kg/day, which should be gradually reduced to the minimal effective maintenance dose (usually ~2 mg/kg/day). Of note, cyclosporine is often not sufficient as monotherapy, requiring combination with topical corticosteroids to reach an almost complete remission.

Azathioprine can be an effective treatment for moderate to severe AD in children and adults[70], with modest benefit documented in a randomized controlled trial. Because individuals with genetically determined low activity of the enzyme thiopurine methyltransferase (TPMT) have increased susceptibility to azathioprine-induced myelotoxicity, the risk of this complication can be decreased by determining TPMT activity and/or genotyping for *TPMT* polymorphisms prior to initiating therapy and adjusting the dose accordingly (2–3.5 mg/kg/day if normal, 0.5–1 mg/kg/day if low)[71]. The results of several uncontrolled studies suggest that *mycophenolate mofetil* (1–2.5 g/day; 25–50 mg/kg/day in children) is also an effective and safe treatment for moderate to severe AD[72]. A recent randomized controlled trial found that enteric-coated mycophenolate sodium and cyclosporine (3 mg/kg daily) overall had similar effectiveness for long-term maintenance treatment (following 6 weeks of cyclosporine 5 mg/kg daily) of severe AD in adults, although patients receiving mycophenolate had more flares early in maintenance and those receiving cyclosporine had shorter remissions following discontinuation of therapy[72a]. In AD patients treated with either azathioprine or mycophenolate mofetil, initial responses are often delayed a month or more, and full benefit typically occurs after 2–3 months of therapy. *Methotrexate* (7.5–25 mg/week) has shown promising results in small series of adults with AD and had similar efficacy to azathioprine in a recent randomized controlled trial[73].

Adjunctive Pharmacologic Therapy

Sedating antihistamines (e.g. hydroxyzine, diphenhydramine, doxepin) can be useful in breaking the "itch–scratch cycle" in AD when given at bedtime, especially in patients with pruritus that disrupts sleep or who scratch excessively during the night. Non-sedating antihistamines are occasionally helpful, but the most benefit is usually obtained at higher doses, that are sedating. In controlled trials, adjunctive therapy with antihistamines and other medications, including leukotriene inhibitors and antimicrobial agents aimed at reducing colonization (see above), has not consistently demonstrated efficacy (see Table 12.8).

Alternative/Complementary Therapy

Dietary lipid supplements (e.g. evening primrose and borage oils) have been studied as a treatment for AD but showed no advantage over placebo. Chinese herbal therapy for AD has been evaluated in controlled trials; although benefit was reported in some of these studies, other investigators have not been able to replicate the results. In one report, analysis of "herbal creams" noted by parents in the UK to improve their children's AD revealed that 80% contained a corticosteroid, more than half of which represented clobetasol propionate[74].

Patients with AD and parents of affected children often seek and tend to be receptive to alternative treatment methods such as biofeedback and hypnotherapy. Although beneficial effects of such modalities have been reported, efficacy has not been established in controlled studies, and placebo groups in controlled trials of AD treatments often have high response rates.

Targeted Molecular Therapy ("Biologics")

The anti-IgE monoclonal antibody *omalizumab*, which inhibits the binding of IgE to its high-affinity receptor (FcεRI), is FDA-approved for the treatment of asthma in patients ≥12 years of age with sensitization to aeroallergens and a total IgE level up to 700 IU/ml (with dosing based on the IgE level). It is administered every 2–4 weeks via subcutaneous injection, which must be performed in-office due to the risk of anaphylaxis. Improvement of AD upon treatment with omalizumab has been described in several uncontrolled series. However, in a small randomized controlled trial in adults with AD, a clinical response was not noted despite depletion of IgE and decreased responses to allergens in immediate- and delayed-type skin tests[75]. Whether a subgroup of AD patients (e.g. with acute disease) may respond better than others remains to be determined.

The anti-CD20 monoclonal antibody *rituximab* (administered via two intravenous infusions separated by 2 weeks), which inhibits mature B cells but does not affect plasma cells or IgE levels, has been shown in an open-label trial to substantially improve severe AD in adults[76]. The monoclonal antibody *mepolizumab* inhibits IL-5, a crucial factor for growth and differentiation of eosinophils. Although mepolizumab can decrease the eosinophil count in patients with AD, it failed to lead to a significant clinical improvement in a controlled trial[77].

Emerging Therapies

Additional targeted molecular therapies are currently under development for the treatment of asthma and AD, with goals of blocking factors such as cytokines involved in the regulation of IgE synthesis (e.g. IL-4) or chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2). Other potential targets are involved in the migration of inflammatory cells, such as the chemokine receptor CCR3 and phosphodiesterase 4. Since AD patients are deficient in antimicrobial peptides, the development of similar synthetic antimicrobial agents could improve control of microbial, fungal and viral infections. Designing better agents to repair the skin barrier represents another area of investigation.

Educational Programs

Education of patients and their parents about skin care and the natural history, triggers and rationale for proactive management of AD is very important. Parents often seek an eradicable cause for their child's AD and have difficulty accepting "control" rather than a "cure" of the condition[78]. The majority of patients and parents are particularly anxious about corticosteroid use, which often leads to delayed and inadequate treatment[79]. Addressing their specific concerns and acknowledging the stresses associated with this chronic disease (also noting the improvement in pruritus and sleep disturbances likely to result from

treatment) make it easier for families to deal with AD and facilitate doctor–patient/parent communication. Interdisciplinary educational programs involving psychologists and dieticians as well as dermatologists have been shown to improve both the severity of the eczema and quality of life[80]. Patients and families can also receive information and support from groups such as the National Eczema Association (www.nationaleczema.org).

Primary Prevention

Although the therapeutic armamentarium available for AD can successfully control the disease in most patients, primary prevention of AD represents a highly desirable goal. For infants with a family history of atopy, there is evidence that exclusive breastfeeding during the first 4–6 months of life or feeding with formulas based on hydrolyzed milk products rather than intact cow's milk protein can protect against the development of AD (no benefit from soy milk)[81,82]. In these high-risk infants, some studies have also shown a modest benefit with a low-allergen maternal diet during breastfeeding, but manipulated maternal diets during pregnancy have been associated with preterm labor and lower birthweights. In several randomized placebo-controlled studies, administration of probiotics (e.g. lactobacilli) or prebiotics (non-digestible oligosaccharides that promote the growth of desirable bacteria) to pregnant mothers and infants has been associated with significantly decreased frequencies of AD at 1 to 4 years of age (approximately half of the frequencies in placebo groups)[83,84]. There is no substantial evidence for effects of dietary interventions beyond 4–6 months of age (including delayed introduction of allergenic foods such as eggs) on the development of AD[81].

REFERENCES

1. Asher MI, Montefort S, Bjorksten B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet. 2006;368:733–43.
2. Williams HC. Clinical practice. Atopic dermatitis. N Engl J Med. 2005;352:2314–24.
3. Barnetson RC, Gawkrodger D. Atopic dermatitis. In: Holgate ST, Church MK (eds). Allergy. London: Gower Medical, 1993:28.
4. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. J Allergy Clin Immunol. 2003;112:S118–27.
5. Bieber T. Atopic dermatitis. N Engl J Med. 2008;358:1483–94.
6. Hanifin JM, Rajka G. Diagnostic features of atopic eczema. Acta Derm Venereol Suppl (Stockh). 1980;92:44–7.
7. Williams HC, Burney PG, Pembroke AC, Hay RJ. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. III. Derivation of a minimum set of discriminators for atopic dermatitis. Br J Dermatol. 1994;131:406–16.
8. Johansson SG, Bieber T, Dahl R, et al. Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol. 2004;113:832–6.
9. Tanei R. Atopic dermatitis in the elderly. Inflamm Allergy Drug Targets. 2009;8:398–404.
10. Barnes KC. An update on the genetics of atopic dermatitis: scratching the surface in 2009. J Allergy Clin Immunol. 2010;125:16–29.e1–11; quiz 30–1.
11. Cookson W. The immunogenetics of asthma and eczema: a new focus on the epithelium. Nat Rev Immunol. 2004;4:978–88.
12. Bowcock AM, Cookson WO. The genetics of psoriasis, psoriatic arthritis and atopic dermatitis. Hum Mol Genet. 2004;13 Spec No 1:R43–55.
13. Palmer CN, Irvine AD, Terron-Kwiatkowski A, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nat Genet. 2006;38:441–6.
14. Rodriguez E, Baurecht H, Herberich E, et al. Meta-analysis of filaggrin polymorphisms in eczema and asthma: robust risk factors in atopic disease. J Allergy Clin Immunol. 2009;123:1361–70.e7.

14a. Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases. N Engl J Med. 2011;365:1315–27.

15. Vasilopoulos Y, Cork MJ, Murphy R, et al. Genetic association between an AACC insertion in the 3′UTR of the stratum corneum chymotryptic enzyme gene and atopic dermatitis. J Invest Dermatol. 2004;123:62–6.
16. Briot A, Deraison C, Lacroix M, et al. Kallikrein 5 induces atopic dermatitis-like lesions through PAR2-mediated thymic stromal lymphopoietin expression in Netherton syndrome. J Exp Med. 2009;206:1135–47.
17. O'Regan GM, Campbell LE, Cordell HJ, et al. Chromosome 11q13.5 variant associated with childhood eczema: an effect supplementary to filaggrin mutations. J Allergy Clin Immunol. 2010;125:170–4.e1–2.
18. Weidinger S, Gieger C, Rodriguez E, et al. Genome-wide scan on total serum IgE levels identifies FCER1A as novel susceptibility locus. PLoS Genet. 2008;4:e1000166.
19. Elias PM, Schmuth M. Abnormal skin barrier in the etiopathogenesis of atopic dermatitis. Curr Opin Allergy Clin Immunol. 2009;9:265–92.
20. Hansson L, Backman A, Ny A, et al. Epidermal overexpression of stratum corneum chymotryptic enzyme in mice: a model for chronic itchy dermatitis. J Invest Dermatol. 2002;118:444–9.
21. Howell MD, Kim BE, Gao P, et al. Cytokine modulation of atopic dermatitis filaggrin skin expression. J Allergy Clin Immunol. 2009;124:R7–12.
22. Cork MJ, Robinson DA, Vasilopoulos Y, et al. New perspectives on epidermal barrier dysfunction in atopic dermatitis: gene-environment interactions. J Allergy Clin Immunol. 2006;118:3–21.
23. Ingordo V, D'Andria G, D'Andria C, et al. Results of atopy patch tests with house dust mites in adults with "intrinsic" and "extrinsic" atopic dermatitis. J Eur Acad Dermatol Venereol. 2002;16:450–4.
24. Spergel JM, Mizoguchi E, Brewer JP, et al. Epicutaneous sensitization with protein antigen induces localized allergic dermatitis and hyperresponsiveness to methacholine after single exposure to aerosolized antigen in mice. J Clin Invest. 1998;101: 1614–22.
25. Soumelis V, Reche PA, Kanzler H, et al. Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. Nat Immunol. 2002;3:673–80.
26. Traidl-Hoffmann C, Mariani V, Hochrein H, et al. Pollen-associated phytoprostanes inhibit dendritic cell interleukin-12 production and augment T helper type 2 cell polarization. J Exp Med. 2005;201:627–36.
27. von Bubnoff D, Scheler M, Hinz T, et al. Comparative immunophenotyping of monocytes from symptomatic and asymptomatic atopic individuals. Allergy. 2004;59:933–9.
28. Novak N, Koch S, Allam JP, et al. Dendritic cells: bridging innate and adaptive immunity in atopic dermatitis. J Allergy Clin Immunol. 2010;125:50–9.
29. Wollenberg A, Wagner M, Gunther S, et al. Plasmacytoid dendritic cells: a new cutaneous dendritic cell subset with distinct role in inflammatory skin diseases. J Invest Dermatol. 2002;119:1096–102.
30. Wollenberg A, Kraft S, Hanau D, et al. Immunomorphological and ultrastructural characterization of Langerhans cells and a novel, inflammatory dendritic epidermal cell (IDEC) population in lesional skin of atopic eczema. J Invest Dermatol. 1996;106:446–53.
31. Novak N, Valenta R, Bohle B, et al. FcepsilonRI engagement of Langerhans cell-like dendritic cells and inflammatory dendritic epidermal cell-like dendritic cells induces chemotactic signals and different T-cell phenotypes in vitro. J Allergy Clin Immunol. 2004;113:949–57.
32. Bieber T. The pro- and anti-inflammatory properties of human antigen-presenting cells expressing the high affinity receptor for IgE (FcepsilonRI). Immunobiology. 2007;212:499–503.
33. Gros E, Bussmann C, Bieber T, et al. Expression of chemokines and chemokine receptors in lesional and nonlesional upper skin of patients with atopic dermatitis. J Allergy Clin Immunol. 2009;124: 753–60.e1.
34. Homey B, Steinhoff M, Ruzicka T, et al. Cytokines and chemokines orchestrate atopic skin inflammation. J Allergy Clin Immunol. 2006;118:178–89.
35. Verhagen J, Akdis M, Traidl-Hoffmann C, et al. Absence of T-regulatory cell expression and function in atopic dermatitis skin. J Allergy Clin Immunol. 2006;117:176–83.
36. Cardona ID, Cho SH, Leung DY. Role of bacterial superantigens in atopic dermatitis: implications for future therapeutic strategies. Am J Clin Dermatol. 2006;7:273–9.
37. Bunikowski R, Mielke M, Skarabis H, et al. Prevalence and role of serum IgE antibodies to the *Staphylococcus aureus*-derived superantigens SEA and SEB in children with atopic dermatitis. J Allergy Clin Immunol. 1999;103:119–24.
38. Mittermann I, Aichberger KJ, Bunder R, et al. Autoimmunity and atopic dermatitis. Curr Opin Allergy Clin Immunol. 2004;4:367–71.
39. Mothes N, Niggemann B, Jenneck C, et al. The cradle of IgE autoreactivity in atopic eczema lies in early infancy. J Allergy Clin Immunol. 2005;116:706–9.
40. Aichberger KJ, Mittermann I, Reininger R, et al. Hom s 4, an IgE-reactive autoantigen belonging to a new subfamily of calcium-binding proteins, can induce Th cell type 1-mediated autoreactivity. J Immunol. 2005;175:1286–94.
41. Sonkoly E, Muller A, Lauerma AI, et al. IL-31: a new link between T cells and pruritus in atopic skin inflammation. J Allergy Clin Immunol. 2006;117:411–17.
42. Paus R, Schmelz M, Biro T, et al. Frontiers in pruritus research: scratching the brain for more effective itch therapy. J Clin Invest. 2006;116:1174–86.
43. Neis MM, Peters B, Dreuw A, et al. Enhanced expression levels of IL-31 correlate with IL-4 and IL-13 in atopic and allergic contact dermatitis. J Allergy Clin Immunol. 2006;118:930–7.
44. Eller E, Kjaer HF, Host A, et al. Development of atopic dermatitis in the DARC birth cohort. Pediatr Allergy Immunol. 2010;21:307–14.
45. Bayrou O, Pecquet C, Flahault A, et al. Head and neck atopic dermatitis and *Malassezia-furfur*-specific IgE antibodies. Dermatology. 2005;211:107–13.
46. Wollenberg A, Wetzel S, Burgdorf WH, et al. Viral infections in atopic dermatitis: pathogenic aspects and clinical management. J Allergy Clin Immunol. 2003;112:667–74.
47. Ono SJ, Abelson MB. Allergic conjunctivitis: update on pathophysiology and prospects for future treatment. J Allergy Clin Immunol. 2005;115:118–22.
48. Bair B, Dodd J, Heidelberg K, et al. Cataracts in atopic dermatitis: a case presentation and review of the literature. Arch Dermatol. 2011 E-PUB AHEAD OF PRINT.
49. Diepgen TL, Sauerbrei W, Fartasch M. Development and validation of diagnostic scores for atopic dermatitis incorporating criteria of data quality and practical usefulness. J Clin Epidemiol. 1996;49:1031–8.
50. Ricci G, Dondi A, Patrizi A. Useful tools for the management of atopic dermatitis. Am J Clin Dermatol. 2009;10:287–300.
51. Wollenberg A, Bieber T. Proactive therapy of atopic dermatitis – an emerging concept. Allergy. 2009;64:276–8.
52. Lipozencic J, Wolf R. The diagnostic value of atopy patch testing and prick testing in atopic dermatitis: facts and controversies. Clin Dermatol. 2010;28:38–44.
53. Werfel T, Breuer K, Rueff F, et al. Usefulness of specific immunotherapy in patients with atopic dermatitis and allergic sensitization to house dust mites: a multi-centre, randomized, dose-response study. Allergy. 2006;61:202–5.

54. Hon KL, Leung TF, Kam WY, et al. Dietary restriction and supplementation in children with atopic eczema. Clin Exp Dermatol. 2006;31:187–91.
55. Huang JT, Abrams M, Tlougan B, et al. Treatment of *Staphylococcus aureus* colonization in atopic dermatitis decreases disease severity. Pediatrics. 2009;123: e808–14.
56. Niebuhr M, Mai U, Kapp A, et al. Antibiotic treatment of cutaneous infections with *Staphylococcus aureus* in patients with atopic dermatitis: current antimicrobial resistances and susceptibilities. Exp Dermatol. 2008;17:953–7.
57. Loden M. The clinical benefit of moisturizers. J Eur Acad Dermatol Venereol. 2005;19:672–88.
58. Katoh N. Future perspectives in the treatment of atopic dermatitis. J Dermatol. 2009;36:367–76.
59. Peserico A, Stadtler G, Sebastian M, et al. Reduction of relapses of atopic dermatitis with methylprednisolone aceponate cream twice weekly in addition to maintenance treatment with emollient: a multicentre, randomized, double-blind, controlled study. Br J Dermatol. 2008;158:801–7.
60. Berth-Jones J, Damstra RJ, Golsch S, et al. Twice weekly fluticasone propionate added to emollient maintenance treatment to reduce risk of relapse in atopic dermatitis: randomised, double blind, parallel group study. BMJ. 2003;326:1367.
61. Schmitt J, von Kobyletzki L, Svensson A, et al. Efficacy and tolerability of proactive treatment with topical corticosteroids and calcineurin inhibitors for atopic eczema: systematic review and meta-analysis of randomized controlled trials. Br J Dermatol. 2011;164:415–28.
62. Ruzicka T, Bieber T, Schopf E, et al. A short-term trial of tacrolimus ointment for atopic dermatitis. European Tacrolimus Multicenter Atopic Dermatitis Study Group. N Engl J Med. 1997;337:816–21.
63. Reitamo S, Wollenberg A, Schopf E, et al. Safety and efficacy of 1 year of tacrolimus ointment monotherapy in adults with atopic dermatitis. The European Tacrolimus Ointment Study Group. Arch Dermatol. 2000;136:999–1006.
64. Arellano FM, Wentworth CE, Arana A, et al. Risk of lymphoma following exposure to calcineurin inhibitors and topical steroids in patients with atopic dermatitis. J Invest Dermatol. 2007;127:808–16.
65. Darsow U, Wollenberg A, Simon D, et al. ETFAD/EADV eczema task force 2009 position paper on diagnosis and treatment of atopic dermatitis. J Eur Acad Dermatol Venereol. 2010;24:317–28.
66. Wollenberg A, Reitamo S, Girolomoni G, et al. Proactive treatment of atopic dermatitis in adults with 0.1% tacrolimus ointment. Allergy. 2008;63:742–50.
67. Thaci D, Reitamo S, Gonzalez Ensenat MA, et al. Proactive disease management with 0.03% tacrolimus ointment for children with atopic dermatitis: results of a randomized, multicentre, comparative study. Br J Dermatol. 2008;159:1348–56.
68. Gambichler T, Kreuter A, Tomi NS, et al. Gene expression of cytokines in atopic eczema before and after ultraviolet A1 phototherapy. Br J Dermatol. 2008;158:1117–20.
69. Dotterud LK, Wilsgaard T, Vorland LH, et al. The effect of UVB radiation on skin microbiota in patients with atopic dermatitis and healthy controls. Int J Circumpolar Health. 2008;67:254–60.
69a. Schmitt J, Schäkel K, Fölster-Holst R, et al. Prednisolone vs. ciclosporin for severe adult eczema. An investigator-initiated double-blind placebo-controlled multicentre trial. Br J Dermatol. 2010;162:661–8.
70. Hon KL, Ching GK, Leung TF, et al. Efficacy and tolerability at 3 and 6 months following use of azathioprine for recalcitrant atopic dermatitis in children and young adults. J Dermatolog Treat. 2009;20:141–5.
71. Weinshilboum R. Inheritance and drug response. N Engl J Med. 2003;348:529–37.
72. Heller M, Shin HT, Orlow SJ, et al. Mycophenolate mofetil for severe childhood atopic dermatitis: experience in 14 patients. Br J Dermatol. 2007;157:127–32.
72a. Haeck IM, Knol MJ, Ten Berge O, et al. Enteric-coated mycophenolate sodium versus cyclosporin A as long-term treatment in adult patients with severe atopic dermatitis: a randomized controlled trial. J Am Acad Dermatol. 2011;64:1074–84.
73. Schram ME, Roekevisch E, Leeflang MM, et al. A randomized trial of methotrexate versus azathioprine for severe atopic eczema. J Allergy Clin Immunol. 2011;128: 353–9.
74. Ramsay HM, Goddard W, Gill S, Moss C. Herbal creams used for atopic eczema in Birmingham, UK illegally contain potent corticosteroids. Arch Dis Child. 2003;88:1056–7.
75. Heil PM, Maurer D, Klein B, et al. Omalizumab therapy in atopic dermatitis: depletion of IgE does not improve the clinical course – a randomized, placebo-controlled and double blind pilot study. J Dtsch Dermatol Ges. 2010;8:990–8.
76. Simon D, Hosli S, Kostylina G, et al. Anti-CD20 (rituximab) treatment improves atopic eczema. J Allergy Clin Immunol. 2008;121:122–8.
77. Oldhoff JM, Darsow U, Werfel T, et al. Anti-IL-5 recombinant humanized monoclonal antibody (mepolizumab) for the treatment of atopic dermatitis. Allergy. 2005;60:693–6.
78. Smith SD, Hong E, Fearns S, et al. Corticosteroid phobia and other confounders in the treatment of childhood atopic dermatitis explored using parent focus groups. Australas J Dermatol. 2010;51:168–74.
79. Zuberbier T, Orlow SJ, Paller AS, et al. Patient perspectives on the management of atopic dermatitis. J Allergy Clin Immunol. 2006;118:226–32.
80. Staab D, Diepgen TL, Fartasch M, et al. Age related, structured educational programmes for the management of atopic dermatitis in children and adolescents: multicentre, randomised controlled trial. BMJ. 2006;332:933–8.
81. Greer FR, Sicherer SH, Burks AW, et al. American Academy of Pediatrics Committee on Nutrition, American Academy of Pediatrics Section on Allergy and Immunology. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. Pediatrics. 2008;121;183–91.
82. von Berg A, Koletzko S, Grubl A, et al. The effect of hydrolyzed cow's milk formula for allergy prevention in the first year of life: the German Infant Nutritional Intervention Study, a randomized double-blind trial. J Allergy Clin Immunol. 2003;111:533–40.
83. Lee J, Seto D, Bielory L. Meta-analysis of clinical trials of probiotics for prevention and treatment of pediatric atopic dermatitis. J Allergy Clin Immunol. 2008;121:116–21.
84. Grüber C, van Stuijvenberg M, Mosca F, et al. Reduced occurrence of early atopic dermatitis because of immunoactive prebiotics among low-atopy-risk infants. J Allergy Clin Immunol. 2010;126:791–7.

This page intentionally left blank

Other Eczematous Eruptions 13

Norbert Reider and Peter O Fritsch

Chapter Contents

Seborrheic dermatitis 219
Asteatotic eczema 221
Stasis dermatitis 222
Disseminated eczema (autosensitization) 224
Nummular dermatitis 225
Pityriasis alba 226
Infective dermatitis 226
Dyshidrotic eczema 227
Juvenile plantar dermatosis 228
Diaper dermatitis 230

In addition to contact and atopic dermatitis, there exists a heterogeneous group of inflammatory skin diseases that obviously share the hallmarks of eczemas but display characteristic additional features. Their pathogenesis is generally less well understood than that of contact or atopic dermatitis, but most display distinctive etiologic features. There is some overlap within the entire group.

SEBORRHEIC DERMATITIS

Key features

- Infantile and adult forms
- Lesions favor the scalp, ears, face, central chest, and intertriginous areas
- Etiologic links with active sebaceous glands, abnormal sebum composition, and *Malassezia furfur* (*Pityrosporum ovale*)
- Can be a cutaneous sign of HIV infection

Introduction

Seborrheic dermatitis is a common mild chronic eczema typically confined to skin regions with high sebum production and the large body folds. Although its pathogenesis is not fully elucidated, there is a link to sebum overproduction (seborrhea) and the commensal yeast *Malassezia*.

History

Seborrheic dermatitis was first described by Unna[1], who also suspected *Malassezia furfur* (*Pityrosporum ovale*) as a causative factor. The nosologic position of seborrheic dermatitis was widely discussed for decades, the focus resting on dysfunction of the sebaceous glands and the high amounts of *M. furfur* present in scales of seborrheic dermatitis. In 1984 it was shown by Shuster[2] that seborrheic dermatitis could be suppressed by systemic ketoconazole. This finding was corroborated by later studies[3], and it became clear that seborrheic dermatitis was strongly linked to *Pityrosporum* yeasts. Today, a direct role of *M. furfur* in seborrheic dermatitis is accepted.

Epidemiology

An infantile and an adult form are distinguished, the former being self-limited and confined to the first 3 months of life, while the latter is chronic with a peak in the fourth to sixth decades. Adult seborrheic dermatitis is probably the most common type of eczema. Its prevalence is estimated at 5%, but its lifetime incidence is much higher. There are no reliable incidence data because seborrheic dermatitis of the scalp (its most common presentation) cannot be completely separated from the common problem of dandruff in population-based studies. Men are afflicted more often than women. There is neither a genetic predisposition nor horizontal transmission. Extensive and therapy-resistant seborrheic dermatitis is an important cutaneous sign of HIV infection[4], Parkinson's disease, and mood disorders[5].

Pathogenesis

Malassezia

The genus *Malassezia* is part of the normal resident skin flora (see Table 77.3)[6,7]. Studies on the predominance of certain *Malassezia* spp. have revealed conflicting results[8,9]. *M. furfur* may behave as an opportunistic pathogen (e.g. fungemia in neonates receiving intravenous lipid emulsions) or cause or aggravate a spectrum of skin (and even systemic) diseases: pityriasis versicolor, *Pityrosporum* folliculitis, seborrheic dermatitis and possibly atopic dermatitis.

Malassezia *and seborrheic dermatitis*

M. furfur can be regularly isolated from lesions of seborrheic dermatitis, including infantile seborrheic dermatitis (whereas healthy prepubertal children are not colonized to a significant degree). This coincides with the presence of enlarged sebaceous glands in the neonatal period. There is no simple stoichiometric relationship between yeast number and severity of seborrheic dermatitis, and unaffected skin may carry a load of organisms similar to seborrheic dermatitis lesions. Even in the scalp (in which *M. furfur* is the predominant organism of the resident flora), only twice as many yeasts may be recovered from areas of seborrheic dermatitis as from normal controls[6]. Similarly, severely immunodeficient HIV-infected patients with seborrheic dermatitis do not harbor more organisms than HIV-infected patients without seborrheic dermatitis[10]. However, the number of yeasts drops in parallel with the therapeutic benefit of antimycotic agents and rises again when seborrheic dermatitis relapses.

Active sebaceous glands and seborrheic dermatitis

Seborrheic dermatitis occurs predominantly in areas of the skin with active sebaceous glands and is often associated with sebum overproduction. In infants, sebum is produced for a few weeks after birth, and the adult form of seborrheic dermatitis does not develop before puberty. This argues for a role of sebaceous gland activation by androgens. However, patients with seborrheic dermatitis may have normal sebum production and those with excessive sebum production are often free of seborrheic dermatitis. Thus, the amount of sebum produced alone does not appear to be the decisive risk factor.

It has been proposed that the composition of the skin surface lipids is the relevant factor[11]. In patients with seborrheic dermatitis, triglycerides and cholesterol are elevated but squalene and free fatty acids are significantly decreased. Free fatty acids (which have a known antimicrobial effect) are formed from triglycerides by bacterial lipases, produced by the lipolytic *Propionibacterium* (*Corynebacterium*) *acnes*. A major constituent of the resident microbial skin flora, *P. acnes* has been found to be greatly reduced in seborrheic dermatitis[12]. Seborrheic dermatitis may thus be linked to an imbalance of the microbial flora.

Immune responses to M. furfur *in seborrheic dermatitis*

An etiologic role for immune mechanisms against *M. furfur* – particularly in view of the prominence of seborrheic dermatitis in HIV-infected individuals – has been suspected but never convincingly proven[13]. However, studies on cellular immunity have yielded contradictory results[6,7]. The inflammation seen in seborrheic dermatitis may be irritant, caused by toxic metabolites, lipase and reactive oxygen species[6,13,14].

Clinical Features

Seborrheic dermatitis is defined by clinical parameters, including:

- sharply demarcated patches or thin plaques that vary from pink–yellow to dull red to red–brown with bran-like to flaky "greasy" scales; vesiculation and crusting may occur but are rare and mostly due to irritation
- a predilection for areas rich in sebaceous glands – scalp, face, ears, presternal region – and, less often, the intertriginous areas
- a mild course with little or moderate discomfort.

Seborrheic dermatitis is most often limited in extent, but generalized and even erythrodermic forms can occur, albeit rarely.

Infantile seborrheic dermatitis

This form usually begins about one week after birth and may persist for several months. Initially, mild greasy scales adherent to the vertex and anterior fontanelle regions arise which may later extend over the entire scalp. Inflammation and oozing may finally result in a coherent scaly and crusty mass covering most of the scalp ("cradle cap"). Disseminated lesions, usually of lesser intensity, may appear on the face, retroauricular folds, neck, trunk and proximal extremities, often displaying a psoriasiform appearance. Lesions of the axillae and inguinal folds are acutely inflamed (Fig. 13.1), oozing, sharply demarcated and surrounded by satellite lesions. Superimposed infection with *Candida* spp. may occur.

Adult seborrheic dermatitis

In adults, seborrheic dermatitis is generally found on the scalp and, usually of milder intensity, on the face; less often, lesions occur on the central upper chest and the intertriginous areas. Erythrodermic seborrheic dermatitis has been described as a rarity.

Pityriasis simplex capillitii (dandruff) is defined as a diffuse, slight to moderate, fine white or greasy scaling of the scalp and terminal hair-bearing areas of the face (beard area), but without significant erythema or irritation. Scales accumulate visibly on dark clothing. This common condition may be the mildest form of seborrheic dermatitis of the scalp.

In seborrheic dermatitis of the scalp, there is inflammation and pruritus in addition to dandruff. The vertex and parietal regions are predominantly affected, but in a more diffuse pattern than the discrete plaques of psoriasis. Towards the forehead, the erythema and scaling are usually sharply demarcated from uninvolved skin, with the border either at the hairline or slightly transgressing beyond it. Pruritus is usually moderate but may be intense, particularly in patients with male pattern alopecia; folliculitis, furuncles and meibomitis are not uncommon complications, elicited by scratching and rubbing.

Seborrheic dermatitis of the facial skin is often strikingly symmetric, affecting the forehead, medial portions of the eyebrows, upper eyelids, nasolabial folds and lateral aspects of the nose, retroauricular areas (Fig. 13.2), and occasionally the occiput and neck. Lesions are yellowish-red, with a typical bran-like scale. Non-purulent otitis externa is often observed. If present, lesions of the trunk are preferentially found in the presternal and intertriginous areas; those in the central chest can have a petaloid appearance. Seborrheic dermatitis, like inverse psoriasis, is a cause of intertrigo.

Fig. 13.1 Infantile seborrheic dermatitis. Glistening red plaques of the neck, axillary and inguinal folds as well as the penis and umbilicus. Note disseminated lesions on the trunk and extremities. *Courtesy, Robert Hartman, MD.*

Fig. 13.2 Adult seborrheic dermatitis of the face, ear and scalp. **A** Sharply demarcated pink plaque with flaky white and greasy scale. Note the fissure in the retroauricular sulcus. **B** Sharply demarcated pink–orange thin plaques with yellow, greasy scale, especially in the melolabial fold. When this degree of severity is seen, the possibility of underlying HIV infection needs to be considered. **C** Symmetric red–brown to violet plaques of the central forehead, nasal bridge and medial cheeks with an associated hypopigmented figurate rim. *C, Courtesy, Jeffrey P Callen, MD.*

In patients with seborrheic dermatitis, the skin is sensitive to irritation, and exposure to sun or heat, febrile illnesses and overly aggressive topical therapy may precipitate flares and dissemination. Irritated seborrheic dermatitis lesions can become bright red and erosive. *Pityrosporum* folliculitis is another complication characterized by pruritic erythematous follicular papules, sometimes pustules, typically in sites rich in sebaceous glands.

Adult seborrheic dermatitis has a chronic relapsing course. Patients feel well and systemic signs are absent. Extensive and severe seborrheic dermatitis, however, should raise the suspicion of underlying HIV infection. In patients with Parkinson's disease, seborrheic dermatitis is a common finding, along with seborrhea. Its severity, however, is not correlated with that of the Parkinson's disease[15]. The facial immobility of patients with Parkinson's disease might result in a greater accumulation of sebum on the skin, resulting in a permissive effect on the growth of *Malassezia*[15,16]. Rebound flares of seborrheic dermatitis can follow tapers of systemic corticosteroids.

Pathology

Acute seborrheic dermatitis displays spongiosis with a superficial perivascular and perifollicular lymphocytic infiltrate composed mainly of lymphocytes. Older lesions show irregular acanthosis and focal parakeratosis. The latter may appear similar to psoriasis, but exocytosis of neutrophils, Munro's microabscesses and confluent parakeratotic horny layers are absent.

Differential Diagnosis

Infantile seborrheic dermatitis is distinguished from *atopic dermatitis* by its earlier onset, different distribution pattern, less intense inflammation, and, most importantly, by the absence of pruritus, irritability and sleeplessness. In contrast to atopic dermatitis, infants with seborrheic dermatitis generally feed well and are content. *Irritant diaper dermatitis* is confined to the diaper area and tends to spare the skin folds (see below). *Candidiasis* of the diaper area may result from colonization with fecal yeast. *Infantile psoriasis* may be difficult to distinguish from psoriasiform seborrheic dermatitis. It has been suggested that psoriasiform diaper dermatitis is a primary manifestation of psoriasis, but most affected infants do not subsequently develop psoriasis.

Rare conditions to be considered are Langerhans cell histiocytosis (see Ch. 91), Wiskott–Aldrich syndrome (see Ch. 60) and Leiner's disease. The last-mentioned is a questionable entity, once thought to be the maximal variant of infantile seborrheic dermatitis, but nowadays viewed as erythroderma in the setting of underlying immunosuppression (see Chs 10 & 60).

When there is scalp scaling in prepubertal, especially black, children, the possibility of *tinea capitis* due to *Trichophyton tonsurans* should be considered. In *pityriasis amiantacea*, thick asbestos-like scales adhere to tufts of scalp hairs; up to a third of the affected children and adolescents eventually develop psoriasis.

A number of entities are included in the differential diagnosis of adult seborrheic dermatitis. Distinction of seborrheic dermatitis *of the scalp* from psoriasis can be difficult, and there may be overlap (due to the Koebner phenomenon). However, the plaques of psoriasis tend to be thicker, with silvery white scale, more discrete, less pruritic and unassociated with seborrhea. In addition, features of psoriasis may be found elsewhere. Dry scaling of the scalp, along with dry brittle hair (as opposed to greasy hair), is a symptom of dispositionally dry skin (e.g. in atopic dermatitis), frequently mistaken for (and mistreated as) seborrheic dermatitis. Mild erythema and scale of the posterior scalp, often with demonstrable hair loss, can be seen in dermatomyositis (Fig. 13.3)[17].

Seborrheic dermatitis *of the face* may closely resemble both early rosacea and the butterfly lesions of systemic lupus erythematosus. Lupus erythematosus rarely affects the nasolabial folds and often has a clearly demonstrable photodistribution. Notably, seborrheic dermatitis and rosacea frequently coexist. The differential diagnosis of seborrheic dermatitis *of the trunk* includes pityriasis rosea (but, in this entity, the lesions are ellipsoid in shape, have collarette-like scaling, and there is no predilection for the central chest) as well as superficial eruptive psoriasis and subacute cutaneous lupus erythematosus.

Seborrheic dermatitis *of the intertriginous areas* must be distinguished from inverse psoriasis, erythrasma, intertriginous dermatitis, candidiasis, and, rarely, Langerhans cell histiocytosis.

Fig. 13.3 Seborrheic-like dermatitis due to dermatomyositis. This patient presented with severe pruritus of the scalp. In addition to the scalp involvement, she had Gottron's papules and a photodistributed poikiloderma. *Courtesy, Jeffrey P Callen, MD.*

Treatment

Infantile seborrheic dermatitis

Infantile seborrheic dermatitis usually responds satisfactorily to skin care measures such as bathing and application of emollients. Ketoconazole cream (2%) is indicated in more extensive or persistent cases[18]. Short courses of low-potency topical corticosteroids may be used initially to suppress inflammation. Mild shampoos are recommended for the removal of scalp scales and crusts. Avoidance of irritation (e.g. the use of strong keratolytic shampoos or mechanical measures to remove the scales from the scalp) is important.

Adult seborrheic dermatitis

The mainstay of therapy is the use of topical azoles (e.g. ketoconazole), either as shampoos (scalp) or as creams (body). The high response rate (75–90%) of this treatment has been documented in double-blind trials[3]. Ciclopirox olamine has antifungal and anti-inflammatory activities and has also been shown to be effective as a shampoo or cream in double-blind, randomized trials. Because seborrheic dermatitis is a predispositional disorder, it tends to relapse if treatments are not carried out repetitively. As *M. furfur* has a slow proliferation rate, an interval of two to several weeks will pass until relapses appear. The intervals of topical therapy should follow this rhythm.

Additional measures, particularly in the initial stages of treatment, include low-potency topical corticosteroids and emollients. Second-line treatment options include zinc pyrithione and tar shampoos as well as topical calcineurin inhibitors. Recently, a nonsteroidal cream that contains shea butter and several plant extracts has reported to be efficacious[19].

ASTEATOTIC ECZEMA

Synonyms: ■ Eczema craquelé ■ Winter eczema ■ Winter itch ■ Dessication dermatitis

Key features

- Dry, rough, scaly and inflamed skin with superficial cracking that resembles a "dried riverbed"
- Sites of predilection are the shins, lower flanks, and posterior axillary line
- Associated with aging, xerosis, low relative humidity, and frequent bathing

Introduction

Dry skin (xerosis, exsiccosis, asteatosis) may result from both exogenous and endogenous causes: a dry climate or low indoor humidity; excessive exposure to water, soaps and surfactants; marasmus and malnutrition; renal insufficiency and hemodialysis; and hereditary conditions such as ichthyosis vulgaris and atopic dermatitis. The most common cause of xerosis is aging. Rarely, but especially when widespread and refractory to therapy, eczema craquelé may be related to an underlying systemic lymphoma[20].

History

Asteatosis as the cause of "nummular eczema" was first mentioned by Gross[21] in the late 1940s.

Epidemiology

Dry skin probably occurs in everyone over the age of 60 years, but its severity is strongly linked to the exogenous factors mentioned above.

Pathogenesis

Xerosis of aging skin is not caused by deficient sebum production, but by a complex dysfunction of the stratum corneum (see Ch. 124)[22]. There is a decrease of intercellular lipids with a deficiency of all key stratum corneum lipids[23] and an altered ratio of fatty acids esterified to ceramide 1[24], persistence of corneodesmosomes[25], and premature expression of involucrin and formation of the cornified envelope[26], resulting in corneocyte retention and marked impairment of barrier recovery[23]. The water-binding capacity of the stratum corneum layer is reduced owing to decreased synthesis of "natural moisturizing factor" (NMF) which contains urea and degradation products of filaggrin[27]. Consequently, the stratum corneum desiccates, loses its pliability and forms small cracks, which render the skin surface dull, rough and scaly.

Mild xerosis is asymptomatic, but if more pronounced, the skin conveys unpleasant sensations such as itching and stinging. Inflammation is enhanced by the release of proinflammatory cytokines secondary to barrier perturbation, mechanical factors (scratching, rubbing), and the application of irritative or sensitizing substances in topical preparations and skin care products.

Clinical Features

Xerosis first arises on the shins. Later it may spread to the thighs, proximal extremities and trunk, but spares the face and neck as well as the palms and soles. It develops insidiously over many years, whereas asteatotic eczema often has a more subacute to acute onset.

Xerotic skin is dry, dull, with fine bran-like scales which may be released as powdery clouds when patients take off their stockings. If more advanced, the skin exhibits a criss-cross pattern of superficial cracks and fissures of the horny layer ("crazy-paving", eczema craquelé, "dried riverbed") and appears pink to light red in color (Fig. 13.4). The skin becomes rough, and may develop an appearance similar to ichthyosis vulgaris ("pseudo-ichthyosis"). In more advanced stages of asteatotic eczema, there is a dull erythema as well as oozing, crusting and abundant excoriations; disseminated nummular lesions are frequently seen. Vesiculation and lichenification are not regular features except when irritant or allergic contact dermatitis is superimposed.

Pathology

Histologically, xerotic skin appears rather normal except for a compact and slightly irregular stratum corneum. Asteatotic eczema in addition exhibits mild focal spongiosis, parakeratosis and a lymphocytic infiltrate with neutrophils in the superficial dermis.

Differential Diagnosis

Conditions that need to be distinguished from asteatotic eczema include stasis dermatitis, adult atopic dermatitis (which may overlap with asteatotic eczema), allergic contact dermatitis, nummular dermatitis and scabies.

Treatment

Asteatotic eczema usually clears within a few days of the application of topical corticosteroid ointment. Proper attention must be given to the care of xerosis in order to avoid relapses: regular use of emollients, including petrolatum-, urea-, ceramide- or lactic acid-containing preparations, use of bath oils, and the elimination of factors that aggravate dry skin (see above). Topical calcineurin inhibitors have also been used. Coexisting stasis dermatitis should be treated as well (see below).

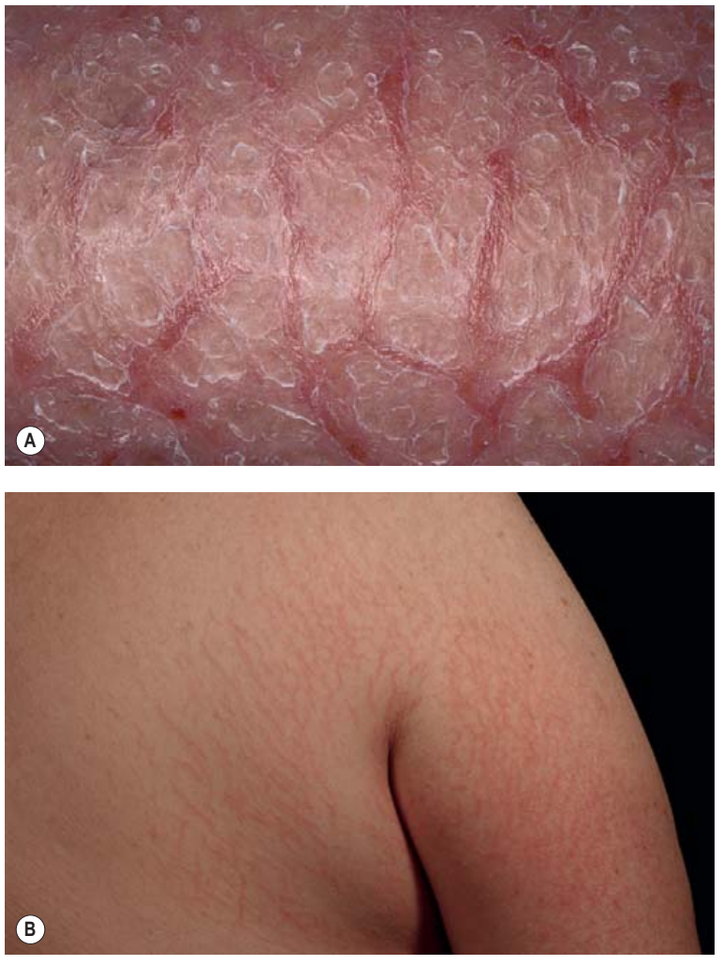


Fig. 13.4 Asteatotic eczema (eczema craquelé). A The distal lower extremity has obvious inflammation and xerosis with adherent white scales (pseudo-ichthyosis) as well as a criss-cross pattern of superficial cracks and fissures said to resemble a dried riverbed. **B** When widespread, there can be involvement of the trunk and proximal extremities. Along with the distal lower extremity, the posterior axillary line is a common site for asteatotic eczema. *A, Courtesy, Louis A Fragola, Jr, MD; B, Courtesy, Thomas Schwarz, MD.*

STASIS DERMATITIS

Synonyms: ■ Gravitational dermatitis ■ Varicose eczema ■ Congestion eczema

Key features

- Often associated with other signs of venous hypertension
- Can be complicated by allergic contact dermatitis
- One of the most common causes of disseminated eczema (autosensitization dermatitis)

Introduction

Stasis dermatitis is a common component of the clinical spectrum of chronic venous insufficiency of the lower extremities (see Ch. 105). It may arise as an early sign of chronic venous insufficiency, but can persist or recur throughout all stages and is often most prominent when ulcers are present. There is little doubt that chronic venous hypertension *per se* is the initial trigger for stasis dermatitis. Over time,

additional etiological factors may act in concert, most importantly contact sensitization to ingredients of topical therapies. Stasis dermatitis is one of the most common causes of secondary dissemination of dermatitis, and is therefore a complex and multifactorial condition.

History

The term "stasis dermatitis" was introduced by Pillsbury[28], and the term "gravitation dermatitis" by Belisario[29].

Epidemiology

The prevalence of chronic venous insufficiency is variable among different ethnic groups and societies. In Central Europe, approximately 15% of the adult population has symptoms of chronic venous insufficiency and about 1% suffers from venous ulcers. Prevalence rates clearly rise with age.

Pathogenesis

Chronic venous insufficiency and the microvasculature

Venous hypertension of the lower limbs is linked to the upright position and is caused by multiple factors, most importantly valvular incompetence of the deep leg veins. Venous hypertension slows the blood flow in the microvasculature, distends the capillaries and damages the capillary permeability barrier, allowing the passage of fluid and plasma proteins into the tissue (edema) and extravasation of erythrocytes (stasis "purpura" and hemosiderin deposition). These processes lead to microangiopathy, with serious consequences[30].

- Proteins (particularly fibrin) are deposited around the vessels as hyaline cuffs; these may, together with interstitial edema, inhibit oxygen diffusion and metabolic exchange.
- Slow blood flow induces upregulation of ICAM-1 and VCAM-1 on endothelia[31], expression of L-selectin on neutrophils[32], and activation of neutrophils and macrophages[33]. Neutrophils are attracted into and trapped within affected areas (notably the medial supramalleolar region)[34].
- Release of inflammatory mediators, free radicals and proteases by neutrophils leads to pericapillary inflammation. Free iron ions released from hemosiderin deposits create a proinflammatory vicious cycle by increasing free radical production and lipid peroxidation and activating matrix metalloproteinases[35]. Platelets accumulate in the microvasculature and may trigger focal thrombosis.
- The subsequent imbalance in the capillary network can produce fibrosis and tissue remodeling, lipodermatosclerosis (i.e. dermal sclerosis and septal sclerosis that present as sclerosing panniculitis), dysfunction of the lymphatics, and stellate sclerotic areas depleted of capillaries with the formation of peripheral giant capillaries ("atrophie blanche"). These same processes may later result in the formation of venous ulcers.

Of note, patients with stasis dermatitis (with or without ulceration) have elevated plasma levels of homocysteine, when compared to a control population[36], and hyperhomocysteinemia is associated with an increased risk of thromboses.

Pathogenesis of stasis dermatitis

Chronic inflammation and microangiopathy are likely to be responsible for stasis dermatitis. Stasis dermatitis typically occurs in the same (i.e. the medial supramalleolar) regions where microangiopathy is most intense, and the patches of dermatitis arise preferentially over dilated varicose veins. Also, dermal inflammation is known to induce epidermal dysfunction (e.g. barrier impairment).

Sometimes, patients report intense pruritus that even becomes manifest before the eczema. Pruritus may be caused both by repeated congestion and decongestion, and by the release of inflammatory mediators within the dermis. Scratching or rubbing worsens and perpetuates the dermatitis.

Complicating pathogenetic factors

- Contact sensitization. Even before stasis dermatitis is manifest, pruritus and dryness of the skin invariably prompts the patient to apply various creams and ointments (including home remedies), and even more so after ulcers have formed. Sensitizations are therefore frequently found, most notably to topical antibiotics, lanolin derivatives, emulsifiers, antiseptics (iodine), preservatives (parabens), balsam of Peru, fragrances, chemicals of plant origin, topical corticosteroids, and modern wound dressings. Patients with chronic venous insufficiency more often than not exhibit multiple contact allergies[37,38].
- Irritant dermatitis due to wound secretions. Once venous ulcers are present, draining exudates macerate the surrounding skin and increase inflammation. They also favor colonization with resident and transient skin flora bacteria which play an additional proinflammatory role ("microbial eczema").

Clinical Features

The first sign of chronic venous insufficiency is usually a cushion-like pitting edema of the medial aspects of the shin and calf around and proximal to the ankle, corresponding to the location of the major communicating veins. Edema is more pronounced in the evening and resolves overnight. Bouts of stasis purpura lead to spotty hemosiderin deposits. At this stage, stasis dermatitis is mild or absent; the skin may be dry and itchy. Later, the edema extends to the distal third of the calf and subfascial edema arises, often accompanied by inflammation which may mimic cellulitis ("pseudoerysipelas"; acute lipodermatosclerosis). Over a period of years, the skin, subcutaneous adipose tissue and deep fascia become progressively indurated and mutually adherent (chronic "lipodermatosclerosis"; see Ch. 100). A firm circular cuff is formed which appears to strangle the distal calf, creating an inverted wine bottle appearance. The skin may show intense hemosiderin pigmentation and atrophie blanche. In this setting, venous ulcers develop spontaneously or are triggered by scratching or other trauma. They arise most often in the supramalleolar region, but may later expand.

At the latest stage, stasis dermatitis appears when lipodermatosclerosis develops. Erythema and scaling are most pronounced around the inner malleoli, but may extend to involve the entire distal lower extremity. It is severely pruritic, as evidenced by multiple scratch marks, which lead to oozing and crusting. Episodes of vesiculation occur infrequently, always raising the suspicion of superimposed contact sensitization. Chronic lesions of stasis dermatitis invariably exhibit considerable lichenification. Once ulcers are formed, stasis dermatitis often becomes highly irritated, oozing and erosive.

Contact sensitization often leads to secondary dissemination. Patches of eczema arise in a strikingly symmetric distribution pattern, particularly on the anterior aspect of the contralateral leg, the anterior thighs and the extensor surface of the upper extremities (Fig. 13.5); lesions may generalize to involve the trunk and face.

Fig. 13.5 Autosensitization dermatitis in a patient with venous ulceration. Note the involvement of the extensor surfaces of the upper extremities in this patient with an allergic contact dermatitis to neomycin, as well as stasis dermatitis and venous ulceration. *Courtesy, Jean L. Bolognia, MD.*

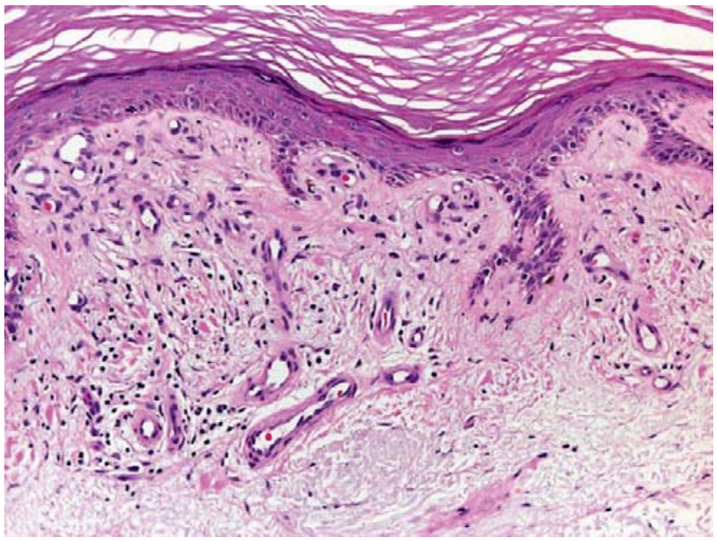


Fig. 13.6 Stasis dermatitis – histologic features. Increased number of blood vessels in a slightly fibrotic papillary dermis. Note also extravasation of erythrocytes and a mild lymphocytic infiltrate. *Courtesy, Lorenzo Cerroni, MD.*

Pathology

The histologic features of eczema, including stasis dermatitis, vary according to the stage of the lesion. In acute eczematous eruptions, intraepithelial edema predominates, with fluid accumulation as micro- or macrovesicles, accompanied by lymphocytes in a perivascular array in the superficial dermis and exocytosis of lymphocytes into the epidermis. In the subacute phase, spongiosis is still evident, but may be subtle; vesicle formation is absent. The epidermis thickens variably and parakeratosis may develop. Lymphocytes persist in the dermis and epidermis, but in fewer numbers.

In the chronic phase, thickening of the epidermis is more pronounced and it occurs in a regular, psoriasiform pattern or has a more irregular profile. Inflammation and spongiosis are mild to absent. Change in the granular layer is variable, from thickening, simulating lichen simplex chronicus, to thinning, when the pattern more closely approaches psoriasis; the latter changes are seen more often in nummular eczema (see below). Ascribing a specific cause of the dermatitis based upon this constellation of histologic findings is impossible, although individually necrotic keratinocytes suggest the diagnosis of an irritant dermatitis.

In stasis dermatitis, biopsy specimens display the histologic features just outlined, as well as signs of venous hypertension: dilated capillaries surrounded by cuffs of fibrin, hemosiderin deposits, and hyperplastic (and at times thrombotic) venules (Fig. 13.6). In later stages, there is fibrosis of the dermal connective tissue and sclerosis of the adipose tissue (see Ch. 100).

Differential Diagnosis

Stasis dermatitis is a straightforward diagnosis if the cutaneous signs of venous hypertension are present. Difficulties may arise in differentiating the individual etiologic components, such as asteatotic eczema and irritant or allergic contact dermatitis. Patch testing is required to exclude the latter. Plaques of stasis dermatitis may be mistaken for nummular eczema, psoriasis or even mycosis fungoides.

Treatment

The major aim of therapy is the management of venous hypertension – a complex goal which is reviewed in Chapter 105. Basic measures include the regular use of adequate compression bandages or stockings to improve venous return, lifestyle changes, and exercise of the calf muscles. If indicated, surgical strategies are undertaken (see Ch. 155). However, these surgical approaches do not replace the need for ongoing compression therapy. Topical treatment is the same as for other types of eczemas: judicious use of topical corticosteroids and emollients. Whether correction of hyperhomocysteinemia will have any therapeutic impact remains to be determined.

DISSEMINATED ECZEMA (AUTOSENSITIZATION)

Synonyms: ■ Autosensitization dermatitis ■ Generalized eczema ■ Id reaction

Key features

- Secondary lesions of eczema distant from the primary site of exposure or involvement
- Symmetric distribution pattern
- Most often associated with allergic contact dermatitis and stasis dermatitis

Introduction

Dermatitis caused by exogenous agents initially arises at the site of contact. Not infrequently, additional patches of eczema develop at distant sites. This phenomenon, termed secondary dissemination, has puzzled dermatologists for decades. It is most often observed in allergic contact dermatitis, particularly if associated with stasis dermatitis (see Fig. 13.5), but may occur with uncomplicated stasis dermatitis, other forms of eczema, and, occasionally, severe tinea pedis.

Disseminated eczema appears later than the primary lesions by a few days to weeks, tends to follow a strikingly symmetric distribution pattern, and shows a predilection for analogous body sites (e.g. extensor aspects of the lower and upper extremities, palms and soles). It may even arise in the absence of and without a preceding "primary" eczema, e.g. in nummular dermatitis (see below). Disseminated eczema must be distinguished from atopic dermatitis, which *a priori* arises in a disseminated fashion.

History and Pathogenesis

The phenomenon of secondary dissemination of eczemas was first described by Whitfield[39], but its pathogenesis is still not fully elucidated. The orderly and symmetric distribution pattern may reflect systemic (hematogenous) dissemination and argues against simple spread of contact irritants or allergens on the body surface. It is unclear, however, what exactly is disseminated via the bloodstream. It could be allergens; for example, the ingestion of allergens such as nickel has been shown to elicit disseminated eczema in sensitized individuals[40,41].

Hematogenous dissemination of microbial products leading to a variety of (non-infectious) manifestations distant from the site of infection, such as "tuberculids" and "bacterids", was an accepted pathogenic model in the first half of the twentieth century and was extrapolated to the phenomenon of disseminated eczema. Dyshidrotic eczema of the soles, for example, was interpreted as an "id" reaction associated with tinea pedis, and nummular eczema as an "id" reaction caused by "focal" infections of the tonsils. Because disseminated eczema could hardly be attributed to infections as a whole, attention shifted to an "autosensitization" to epidermal antigens mediated by cytotoxic autoantibodies. This hypothesis, however, was never verified.

Instead, it became clear both from animal experiments[42] and from routine patch testing ("excited skin syndrome", "angry back")[43,44] that inflammatory processes of the skin, both allergic and irritant or caused by infections, lower the irritancy threshold of distant skin and thus facilitate the development of an eczematous reaction. Obviously, circulating activated memory T cells may play an additional role in disseminated eczema associated with allergic contact dermatitis, including that seen with poison ivy dermatitis following a short, rapid taper of systemic corticosteroids. It remains to be determined which factors regulate the symmetric distribution of disseminated eczema.

Epidemiology

An estimated two-thirds or more of patients with contact dermatitis associated with stasis dermatitis develop episodes of disseminated eczema. The incidence is much lower in the other types of eczema or tinea pedis.

Clinical Features

Disseminated eczema in allergic contact dermatitis is characterized by moderately to poorly demarcated patches of eczema, most often on the extremities (Fig. 13.7A). Lesions are also found on the face, and less so on the trunk (Fig. 13.7B). The areas of involvement vary greatly in size and number and may consist of discrete papules which are often excoriated. Disseminated eczema in patients with seborrheic and asteatotic eczema differs slightly in predilection sites and morphology (see above).

Pathology

In biopsy specimens of disseminated eczema, the histologic findings are those of an acute or subacute dermatitis (see previous section).

Differential Diagnosis

Conditions to be distinguished are those eczemas that can arise in a widespread or disseminated fashion: atopic dermatitis, airborne contact dermatitis, contact dermatitis caused by constituents of textiles, and photoallergic dermatitis. Other conditions to be considered are mycosis fungoides and Sézary syndrome.

Treatment

Topical corticosteroids and systemic antihistamines are the mainstay of therapy. Short courses of systemic corticosteroids may be required, but aggressive topical treatment of the inciting dermatosis is necessary to help prevent recurrences or a rebound flare.

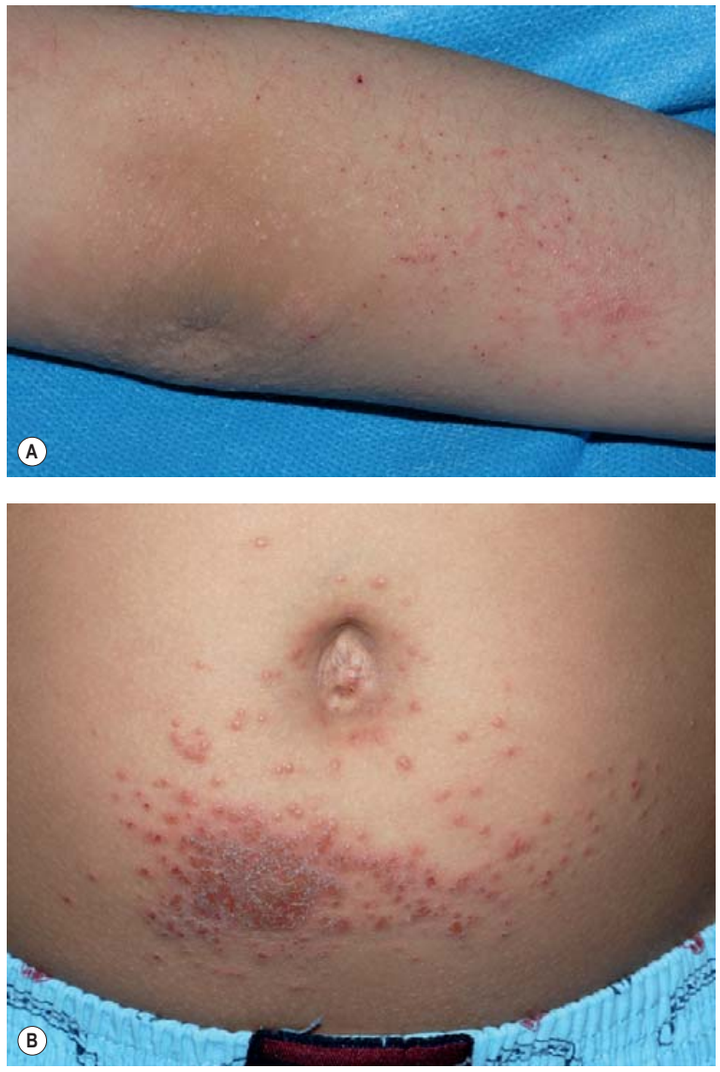


Fig. 13.7 Id reactions in children due to allergic contact dermatitis (ACD) to nickel. A Multiple flat-topped papules, several of which have been excoriated, in addition to patches of eczema. **B** Square-shaped area of ACD due to nickel in a buckle with an id reaction. The latter consists of edematous crusted papules.
Courtesy, Julie V Schaffer, MD.

NUMMULAR DERMATITIS

Synonyms: ■ Nummular eczema ■ Discoid eczema ■ Microbial eczema

Key features

- Coin-shaped, disseminated, eczematous lesions
- Usually very pruritic
- Chronic course

Introduction

Nummular dermatitis is an uncommon disseminated eczema characterized by its coin-shaped lesions. Because such lesions can occur as a feature of atopic dermatitis, asteatotic eczema and stasis dermatitis, the position of nummular dermatitis as an independent clinical entity has been questioned.

Epidemiology

Nummular lesions of eczema are not uncommon. However, in the literature there are widely discrepant data on the prevalence of nummular dermatitis, ranging from 0.1% to 9.1%[4]. Some of this variability may reflect the degree to which a distinction is made between nummular dermatitis and coin-shaped lesions observed in patients with other forms of eczema. Men are affected slightly more often and at a later age than women (>50 vs <30 years, respectively).

Pathogenesis

The pathogenesis has not been fully elucidated (see above). The traditional view of nummular dermatitis being "microbial" in origin, i.e. either secondary to bacterial colonization or due indirectly to hematogenous dissemination of bacterial toxins, has not been corroborated. However, the search for "focal" infections is still part of the routine evaluation in some institutions. Nummular lesions of dermatitis are not infrequently associated with contact sensitization as well as with xerosis and venous hypertension. Nummular dermatitis of the dorsa of the hands may be a manifestation of chronic irritant or allergic dermatitis. Clinical and laboratory signs of atopy are absent in "true" nummular dermatitis.

Clinical Features

Nummular dermatitis is defined as an eruption of round (discoid) eczematous patches almost exclusively of the extremities (Fig. 13.8), often the lower legs in men and the forearms and dorsal aspects of the hands in women. The lesions are well demarcated and measure 1–3 cm, only occasionally being larger. They may be acutely inflamed with vesicles and weeping, but are more often lichenified and hyperkeratotic. Pruritus may be intense and excoriations are often prominent. Nummular dermatitis usually takes a very chronic course. A particularly therapy-resistant variety has been termed "oid-oid disease" (Sulzberger–Garbe syndrome)[45].

Pathology

Histologically, the changes of subacute to chronic dermatitis are seen (see section "Stasis dermatitis").

Fig. 13.8 Nummular dermatitis. Coin-shaped lesions of acute and subacute dermatitis that are fairly well demarcated. There is often marked pruritus. *Courtesy, Kalman Watsky, MD.*

Fig. 13.9 Pityriasis alba. Hypopigmented macules and patches on the cheek of an African-American girl. *Courtesy, Anthony J Mancini, MD.*

Differential Diagnosis

Nummular dermatitis must be distinguished from nummular lesions of atopic dermatitis and dissemination secondary to contact dermatitis or stasis dermatitis. Other conditions to be considered are psoriasis, Bowen's disease, mycosis fungoides and tinea corporis.

Treatment

Options comprise medium- to high-potency topical corticosteroid ointments, topical tacrolimus or pimecrolimus, and emollients. Tar preparations have also been used successfully. However, a number of patients will require phototherapy to clear the lesions.

PITYRIASIS ALBA

Key features

- Minor feature of atopic dermatitis
- Ill-defined, hypopigmented patches, primarily on the face of children and adolescents
- More clinically evident in individuals with darkly pigmented skin
- Spontaneous remission

Pityriasis alba is a fairly common, low-grade, eczematous dermatosis characterized by ill-defined, patchy hypopigmentation (Fig. 13.9). It is regarded as a minor feature of atopic dermatitis (see Table 12.1). For details, see Chapter 12.

INFECTIVE DERMATITIS

Key features

- Rare dermatologic disorder of childhood and adolescence
- Association with human T-cell lymphotropic virus type I (HTLV-1)
- Eczema of the scalp, axillae and groin; watery discharge of the nose
- Prompt response to antibiotics

Introduction and Pathogenesis

Human T-cell lymphotropic virus type I (HTLV-1), also referred to as human T-cell leukemia virus type I and adult T-cell lymphoma virus type 1, was first detected in 1980[46], and it can infect T cells, B cells and monocytes. HTLV-1 is transmitted primarily via sexual intercourse, blood transfusions, needle sharing in intravenous drug users, and breastfeeding. It has been associated with adult T-cell leukemia/lymphoma (ATLL), tropical spastic paraparesis, and infective dermatitis. The activity of HTLV-1 in infected subjects appears to be low – more than 90% of carriers remain asymptomatic[47] and the majority of disease symptoms (other than infective dermatitis) emerge during adulthood. HTLV-1 induces spontaneous T-cell proliferation independent of exogenous stimuli, followed by interleukin (IL)-2 receptor expression (CD25), increased IL-2 secretion, and induction of interferon-γ, IL-5 and IL-10. In symptomatic patients, levels of tumor necrosis factor-α and IL-6 are elevated[48]. Infected individuals are more susceptible to a variety of infections and parasitoses such as scabies and strongyloidiasis[49].

Epidemiology

Major endemic areas of HTLV-1 infection include Africa, northeastern South America, the Caribbean basin, southern Japan, and Iran. Infective dermatitis was first described in 1966 by Sweet[50], preceding the detection of HTLV-1 by almost 15 years. Walshe[51], in 1967, was the first to suggest an underlying immune defect because relapses of the dermatitis frequently occurred, even after a prompt initial response to antibiotic treatment. The probability of developing infective dermatitis was estimated to be 2% amongst perinatally infected children[52].

Clinical Features

Infective dermatitis presents as an exudative and crusty eczematous dermatosis, affecting primarily the scalp, axillae and groin, ears, paranasal skin, eyelid margins and/or neck[47]. A generalized fine papular rash is occasionally observed. Complications include parasitic infestations, corneal opacities, and progression to more severe HTLV-1-associated disorders (e.g. ATLL). Infective dermatitis rarely persists until adulthood. However, according to Bittencourt[53], 44% of adult patients in Bahia with HTLV-1-associated ATLL had a history of infective dermatitis. Diagnosis is established by major and minor criteria (Table 13.1)

Differential Diagnosis

The major entity in the differential diagnosis is atopic dermatitis. Apart from serologic evidence of HTLV-1 infection, lesions of infective dermatitis are more exuberant and obviously infected, but pruritus is less intense. Crusting of the nasal vestibule and blepharoconjunctivitis are more prominent than in atopic dermatitis. Other disorders to consider include seborrheic dermatitis and impetigo.

CRITERIA FOR THE DIAGNOSIS OF INFECTIVE DERMATITIS
MAJOR
• Eczema of the scalp, axillae and groin, ears, paranasal skin, eyelid margins and/or neck
• Chronic watery nasal discharge and/or crusting of the anterior nares
• Chronic relapsing dermatitis which responds quickly to antibiotics but relapses promptly after withdrawal
• Onset during early childhood
• Seropositivity for HTLV-1
MINOR
• Positive cultures for *Staphylococcus aureus* and/or β-hemolytic streptococci from the skin or anterior nares
• Generalized fine papular rash
• Anemia, elevated erythrocyte sedimentation rate
• Hyperimmunoglobulinemia
• Elevated $CD4^+$ and $CD8^+$ T-cell counts; elevated CD4/CD8 ratio

Table 13.1 Criteria for the diagnosis of infective dermatitis. To establish the diagnosis, four major criteria are required, with mandatory inclusion of human T-cell lymphotropic/leukemia virus type I (HTLV-1) seropositivity. For the first two major criteria, the involvement of at least two body regions is required. Adapted from ref. 49.

Treatment

Oral antibiotics result in improvement of the skin lesions but do not prevent relapses. Topical treatments include antibiotics (including intranasal), corticosteroids, and bleach baths.

DYSHIDROTIC ECZEMA

Synonyms: ■ Pompholyx (larger bullae) ■ Acute and recurrent vesicular hand dermatitis

Key features

- Firm, pruritic vesicles of the palms, soles, and lateral and medial aspects of the fingers and toes
- Association with atopic dermatitis and contact dermatitis (allergic and irritant)
- No disturbance of sweat gland function

Introduction

Dyshidrotic eczema is a not-infrequent, chronic, relapsing palmoplantar eczematous dermatosis characterized by firm, pruritic vesicles and bullae. While the vesicles are due to spongiosis within the epidermis, their intact nature is explained by the thick tear-proof horny layer in these sites. Dyshidrotic eczema is not an independent disease entity because it is often a manifestation of other types of eczema, especially atopic dermatitis and irritant or allergic contact dermatitis.

Pathogenesis

Although the formation of vesicles is not linked to sweat gland dysfunction or trapping of sweat within the epidermis (as the term may suggest), hyperhidrosis can be an aggravating factor in some patients. Notably, treatment of hyperhidrosis with onabotulinumtoxinA may ameliorate dyshidrotic eczema[54].

Dyshidrotic eczema is frequently an expression of atopic dermatitis, particularly as a late-stage manifestation. In these patients, its intensity is usually low to moderate with a protracted and relapsing course, and it is accompanied by only a few other signs of atopic dermatitis. Less often, dyshidrotic eczema is a manifestation of acute or subacute allergic contact dermatitis. Flares can also result from exposure to known irritants (see Ch. 15).

Fig. 13.10 Dyshidrotic eczema. A Clinically, firm vesicles are seen along the side of the thumb and thenar eminence. Some of them are deep-seated. **B** Histopathologically, spongiosis within the epidermis is accompanied by macrovesicles; the thickened stratum corneum points to an acral location. *A, Courtesy, Louis A Fragola, Jr, MD; B, Courtesy, Lorenzo Cerroni, MD.*

Occasionally, administration of IVIg is followed by acute episodes of dyshidrotic eczema. The role of ingestants, in particular nickel and cobalt, has been debated, but improvement with a low-nickel diet (in nickel-sensitive patients with a positive oral provocation test) has been observed. Lastly, flares can also follow periods of emotional stress as well as exposure to hot climates and (rarely) sunlight.

Clinical Features

Dyshidrotic eczema is characterized by symmetric, firm, deep-seated vesicles of the palms, the lateral and medial aspects of the fingers, and less often the soles and toes (Fig. 13.10A). The size of the vesicles may vary from pinhead-sized to several centimeters ("pompholyx"). When smaller lesions are clustered, they have been likened to tapioca pudding. While the markedly pruritic vesicles initially contain clear fluid, they have a tendency for purulent superinfection. It resolves via desquamation of characteristically thick scales.

Dyshidrosis lamellosa sicca (also referred to as keratolysis exfoliativa) is a minimal variant which displays no blisters but only small annular collarettes of white scale.

Pathology

Histologically, a spongiotic dermatitis is seen with the formation of micro- and macrovesicles within the epidermis (Fig. 13.10B). There is no association with sweat glands.

Differential Diagnosis

Inflammatory tinea manuum and pedis, scabies and palmoplantar pustular psoriasis need to be considered as well as dyshidrosiform pemphigoid, dyshidrotic cutaneous T-cell lymphoma, erythema multiforme, fixed drug eruption, and, in children, infantile acropustulosis. Distinguishing between an id reaction involving the palms or soles and dyshidrotic eczema can sometimes be difficult and some clinicians view them as overlapping entities.

Treatment

Topical and systemic corticosteroids are the mainstay of treatment. Topical calcineurin inhibitors may be helpful. Bath PUVA has been shown to be more effective than oral PUVA or UVB[55]. An underlying allergic or irritant contact dermatitis needs to be considered and addressed.

JUVENILE PLANTAR DERMATOSIS

Synonyms: ■ Atopic winter feet ■ Forefoot dermatitis ■ Dermatitis plantaris sicca ■ Moon-boot foot syndrome ■ Sweaty sock dermatitis

Key features

- Dry, scaly, glazed and fissured plantar surface of the forefoot
- Prepubertal children are affected
- Association with atopy and exogenous factors

Introduction

The feet are a fairly common site for various eczematous dermatoses (Table 13.2). Juvenile plantar dermatosis is a characteristic condition that occurs primarily (but not exclusively) in children with an atopic diathesis.

History

Juvenile plantar dermatosis was first reported by Mackie and Husain[56].

Epidemiology

Juvenile plantar dermatosis occurs in prepubertal children, from the age of 3 years and upwards (when shoes are worn for longer periods of time), and is only rarely seen in adults. There is seasonal variation (worsening during the winter) and boys are affected slightly more often than girls.

Pathogenesis

An atopic disposition is clearly a risk factor, but exogenous factors play an equally important role. Juvenile plantar dermatosis has been observed more often since impermeable materials such as plastic and rubber have been used for sports shoes, which youngsters often wear all day long. The humid environment leads to hydration of the horny layer, which is then much less resistant to wear and tear. It is rubbed off by friction, leading to a characteristic glazed and thinned appearance of the skin. As involved areas become xerotic, cracks are formed. The inherently dry skin of atopic individuals may be a predisposing factor. Adults have a much thicker horny layer of their plantar skin and are thus less at risk of developing the condition.

Clinical Features

The balls of the feet and the toe pads exhibit strikingly symmetrical changes: fairly well demarcated shiny, reddish, tender, dry lesions with some scaling (Fig. 13.11), and often with painful cracks and fissures. The dorsa of the feet, the interdigital spaces and the instep are typically spared. Similar lesions may be found on the hands.

Pathology

Histologically, the features of a chronic dermatitis are seen.

DIFFERENTIAL DIAGNOSIS OF DERMATITIS OF THE FOOT
ALLERGIC CONTACT DERMATITIS (FOOTWEAR DERMATITIS)
• Dermatitis of the dorsal aspects of the feet and toes (allergen contained in the "top" of the shoes) • Dermatitis of the weightbearing areas of the soles (allergens contained in the sole of the shoes) – Most common allergens: dichromate, rubber accelerators, colophony, dyes, formaldehyde resins; also consider topical antibiotics, e.g. bacitracin – Association with atopy and hyperhidrosis – Distinguish from sock and stocking dermatitis where lesions extend more proximally (popliteal area, thighs) – most common allergen is azo dyes
TYLOSIS
• Mechanically induced hyperkeratosis, dryness and fissuring • Predilection sites: heels and weightbearing areas of the soles • In middle-aged to elderly individuals • Associated with obesity and hyperhidrosis
ACQUIRED PLANTAR KERATODERMA (KERATODERMA CLIMACTERICUM)
• Same as tylosis but more intense • Typically occurs in women over the age of 45 years, but may also be seen in men • Similar lesions may appear on palms
JUVENILE PLANTAR DERMATOSIS
See section in this chapter
TINEA PEDIS (ATHLETE'S FOOT)
• Dermatophyte infections of the plantar skin are usually accompanied by involvement of the interdigital spaces as well as lateral aspects of the foot • Often symmetric, accompanied by onychomycosis • Lesions on the lateral and dorsal aspects of the feet have well-demarcated circinate borders • Occasionally vesicular variant
PSORIASIS (SEE CH. 8)
• Diffuse erythema and thick adherent scales, dryness and fissuring • Psoriatic plaques found elsewhere on the body • Nail involvement, e.g. pitting and oil-drop changes
DYSHIDROTIC ECZEMA
See section in this chapter
RECURRENT FOCAL PALMAR AND PLANTAR PEELING
• Probably represents a mild form of dyshidrosis • Dry, circinate thin scales of palms and soles • Vesicles are absent
PUSTULOSIS OF THE PALMS AND SOLES (SEE CH. 8)
• A neutrophilic dermatosis, possibly related to pustular psoriasis • Chronic course with crops of non-pruritic, short-lived, superficial pustules, particularly of the instep • Yellow–brown macules admixed with pustules
SÉZARY SYNDROME (SEE CH. 120)
• Palms and soles are tender and exhibit scaling, which can be quite thick • Associated with hypertrophic onychodystrophy and erythroderma
OTHER
• Atopic dermatitis • Irritant contact dermatitis (e.g. due to occlusive footwear) • Pityriasis rubra pilaris • Acrokeratosis paraneoplastica • Keratoderma blennorrhagicum • Inherited palmoplantar keratodermas (see Ch. 58) • Palmoplantar keratoderma associated with hypothyroidism • Crusted scabies

Table 13.2 Differential diagnosis of dermatitis of the foot.

Differential Diagnosis

Juvenile plantar dermatosis needs to be distinguished from *allergic contact dermatitis* to chemicals contained in leather (e.g. chromates, dyes) or rubber. However, the latter is rare in children and, if present, often involves the dorsa of the feet as well. *Tinea pedis* is equally uncommon in children, and the interdigital spaces are usually

Fig. 13.11 Juvenile plantar dermatosis in a child. Erythema and scaling of the plantar surface of the great toes and fifth toes as well as the ball of the foot bilaterally. Note the glazed appearance of the skin of the left foot. *Courtesy, Kalman Watsky, MD.*

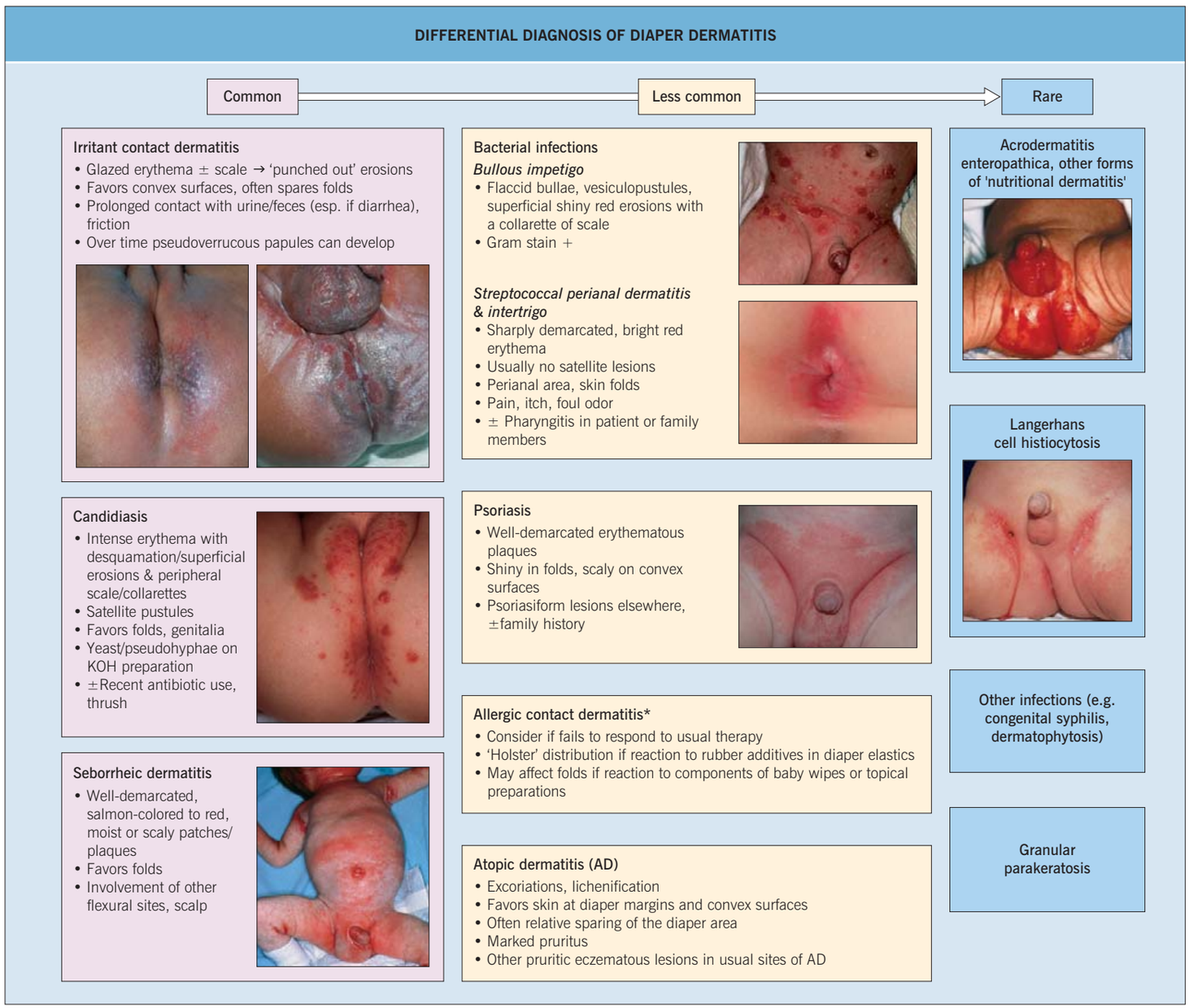


Fig. 13.12 Differential diagnosis of diaper dermatitis. While the most common etiologies are irritant contact dermatitis, cutaneous candidiasis and seborrheic dermatitis, patients often have a combination with one disorder superimposed on another. Discrete papules or nodules are seen in scabies, granuloma gluteale infantum and perianal pseudoverrucous papules, whereas congenital syphilis often presents with erosions and even ulcerations. *Potential allergens include sorbitan sesquioleate (an emulsifier in diaper balms), fragrances, disperse dyes, rubber additives (e.g. mercaptobenzothiazole), and preservatives in baby wipes (e.g. iodopropynyl butylcarbamate). *Inserts, Courtesy, Robert Hartman MD; Julie V Schaffer, MD.*

predominantly affected. Patch testing and KOH preparations may help in establishing the diagnosis.

Treatment

Juvenile plantar dermatosis is a chronic but self-limiting condition. Patients should be advised to avoid wearing impermeable socks and shoes, and the application of emollients, keratolytics and/or paraffin-type ointments is beneficial. When shoes are removed, socks, if damp, should also be removed and replaced by dry socks.

DIAPER DERMATITIS

Key features

- Frequently, an irritant dermatitis of the diaper area due to occlusion and prolonged exposure to urine and feces
- Secondary infection with *Candida albicans* often occurs
- May be associated with seborrheic dermatitis and psoriasis

Epidemiology

Diaper dermatitis develops in at least 50% of infants, and it is responsible for a considerable percentage of dermatologic consultations in infants and toddlers. Seborrheic dermatitis is a predisposing factor.

Pathogenesis

Diaper dermatitis is the cumulative result of several factors, in particular dampness and exposure to urine and feces. In the past, ammonia derived from the urea in urine was held as primarily responsible for diaper dermatitis. More recently, the blame has been placed on the (alkaline) pH of the urine and the role of fecal bacteria. Enzymes produced by fecal bacteria, as well as residual pancreatic proteases and lipase in the stool, act as irritants and these enzymes are also activated in the alkaline milieu[57,58]. In addition, ureases are produced by fecal bacteria, resulting in a further increase of the urinary pH. This explains why diaper dermatitis is more likely to appear in cow milk-fed than in breast-fed infants: cow milk formulas are colonized by a greater number of urease-producing bacteria[59].

Prolonged use of diapers, dampness, and the factors detailed above lead to the breakdown of the horny layer barrier function. An alkaline pH also facilitates the development of secondary C. *albicans* infection.

As diaper dermatitis tends to be most prominent on the inner parts of the thighs, genitalia and buttocks, friction between the skin and the diaper material likely acts as a physical factor that leads to further irritation. In addition, chemical constituents of the diaper and/or topical preparations and baby wipes may lead to contact sensitization.

Clinical Features

Diaper dermatitis is strictly confined to the diaper area, presenting with mild to pronounced erythema, erosions and scaling. In the common form due to irritant contact dermatitis, genitocrural folds are typically spared. Depending on whether there is a secondary infection or an underlying dermatosis (e.g. seborrheic dermatitis, psoriasis), the clinical picture can vary (Fig. 13.12).

Differential Diagnosis

The differential diagnosis is outlined in Figure 13.12.

Treatment

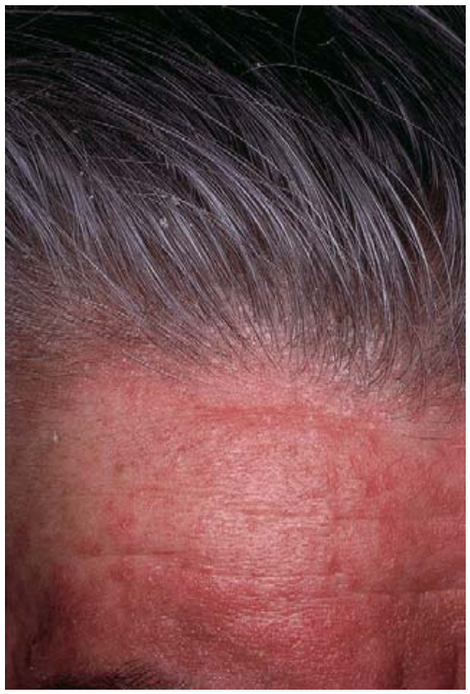
In the acute phase, mild corticosteroid preparations are helpful. Topical imidazole creams are added for secondary infection with *Candida* spp. The major goal of long-term management is avoidance of the causative factors. Frequent changing of highly absorbent disposable diapers is associated with a lower incidence and severity of diaper dermatitis, and it leads to a more physiologic pH.[60] Emollients containing white paraffin (Vaseline®) or soft zinc pastes provide both protective and soothing effects.

REFERENCES

1. Unna PG. Das seborrhoische Ekzem. Monatsschr Prakt Dermatol. 1897;6:827–46.
2. Shuster S. The aetiology of dandruff and the mode of action of therapeutic agents. Br J Dermatol. 1984;111: 235–42.
3. Faergemann J. Management of seborrheic dermatitis and pityriasis versicolor. Am J Clin Dermatol. 2000;1: 75–80.
4. Marks R (ed.). Eczema. London: Martin Dunitz, 1992.
5. Maietta G, Fornaro P, Rongioletti F, et al. Patients with mood depression have a higher prevalence of seborrhoeic dermatitis. Acta Derm Venereol. 1990;70: 432–4.
6. Nenoff P, Reinl P, Haustein UF. Der Hefepilz Malassezia. Erreger, Pathogenese und Therapie. Hautarzt. 2001;52: 73–86.
7. Faergemann J. *Pityrosporum* species as a cause of allergy and infection. Allergy. 1999;54:413–19.
8. Gupta AK, Kohli Y, Summerbell RC, et al. Quantitative culture of *Malassezia* species from different body sites of individuals with or without dermatoses. Med Mycol. 2001;39:243–51.
9. Nakabayashi A, Sei Y, Guillot J. Identification of *Malassazia* species isolated from patients with seborrhoeic dermatitis, atopic dermatitis, pityriasis versicolor and normal subjects. Med Mycol. 2000;38: 337–41.
10. Pechere M, Kirscher J, Remondat C, et al. *Malasezzia* spp carriage in patients with seborrheic dermatitis. J Dermatol. 1999;26:558–61.
11. Ostlere LS, Taylor CR, Harris DW, et al. Skin surface lipids in HIV-positive patients with and without seborrheic dermatitis. Int J Dermatol. 1996;35:276–9.
12. McGinley KJ, Leyden JJ, Marples RR, Kligman AM. Quantitative microbiology of the scalp in non-dandruff, dandruff, and seborrheic dermatitis. J Invest Dermatol. 1975;64:401–5.
13. Parry ME, Sharpe GR. Seborrhoeic dermatitis is not caused by an altered immune response to *Malassezia* yeast. Br J Dermatol. 1998;139:254–63.
14. Faergemann J, Bergbrant IM, Dohse M, et al. Seborrhoeic dermatitis and *Pityrosporum* (*Malassezia*) folliculitis: characterization of inflammatory cells and mediators in the skin by immunohistochemistry. Br J Dermatol. 2001;144:549–56.
15. Burton JL, Cartlidge M, Cartlidge NEF, Shuster S. Sebum excretion in Parkinsonism. Br J Dermatol. 1973;88:263–6.
16. Cowley NC, Farr RM, Shuster S. The permissive effect of sebum in seborrhoeic dermatitis: an explanation of the rash in neurological disorders. Br J Dermatol. 1990;122: 71–6.
17. Kasteler JS, Callen JP. Scalp involvement in dermatomyositis: often overlooked or misdiagnosed. JAMA. 1994;272:1939–41.
18. Poindexter GB, Burkhart CN, Morrell DS. Therapies for pediatric seborrheic dermatitis. Pediatr Ann. 2009;38: 333–8.
19. Elewski BE. Safe and effective treatment of seborrheic dermatitis. Cutis. 2009;83:333–8.
20. Sparsa A, Liozon E, Boulinguez S, et al. Generalized eczema craquele as a presenting feature of systemic lymphoma: report of seven cases. Acta Derm Venereol. 2005;85:333–6.
21. Gross P. Nummular eczema. Arch Dermatol Syphilol. 1941;44:1060–77.
22. Rawlings AV, Harding CR. Moisturization and skin barrier function. Dermatol Ther. 2004;17:43–8.
23. Ghadially R, Brown BE, Sequeira-Martin SM, et al. The aged epidermal permeability barrier. Structural, functional, and lipid biochemical abnormalities in humans and a senescent murine model. J Clin Invest. 1995;95:2281–90.
24. Rogers J, Harding C, Mayo A, et al. Stratum corneum lipids: the effect of ageing and the seasons. Arch Dermatol Res. 1996;288:765–70.
25. Simon M, Bernard D, Minondo AM, et al. Persistence of both peripheral and non-peripheral corneodesmosomes in the upper stratum corneum of winter xerosis skin versus only peripheral in normal skin. J Invest Dermatol. 2001;116:23–30.
26. Engelke M, Jensen JM, Ekanayake-Mudiyanselage S, Proksch E. Effects of xerosis and ageing on epidermal proliferation and differentiation. Br J Dermatol. 1997; 137:219–25.
27. Rawlings A, Scott IR, Harding CR, Bowser PA. Stratum corneum moisturization at the molecular level. J Invest Dermatol. 1994;103:731–41.
28. Pillsbury DM. The pathogenesis of eczema. Proc X Int Congress Dermatol (London, 1952). London: British Medical Association, 1953:58.
29. Belisario JC. The pathogenesis of eczema. Proc X Int Congress Dermatol (London, 1952). London: British Medical Association, 1953:3.
30. Scharfetter-Kochanek K, Schuller J, Meewes C, et al. Das chronisch venöe Ulcus cruris. Pathogenese und Bedeutung des "aggressiven Mikromilieus". J Dtsch Dermatol Ges. 2003;1:58–67.
31. Peschen M, Lahaye T, Hennig B, et al. Expression of the adhesion molecules ICAM-1, CAM-1, LFA-1 and LA-4 in the skin is modulated in progressive stages of chronic venous insufficiency. Acta Dermatol Venereol. 1999;79:27–32.
32. Jünger M, Steins A, Hahn M, Hafner HM. Microcirculatory dysfunction in chronic venous insufficiency (CVI). Microcirculation. 2000;7:S3–12.
33. Takase S, Schmid-Schönein G, Bergan JJ. Leukocyte activation in patients with venous insufficiency. J Vasc Surg. 1999;30:148–56.
34. Scurr JH, Coleridge-Smith PD. The microcirculation in venous disease. Angiology. 1994;45:537–41.
35. Cheatle T. Venous ulceration and free radicals. Br J Dermatol. 1991;124:508.
36. Durmazlar SP, Akgul A, Eskioglu F. Hyperhomocysteinemia in patients with stasis dermatitis and ulcer: a novel finding with important therapeutic implications. J Dermatolog Treat. 2009;20:336–9.
37. Tavadia S, Bianchi J, Dawe RS, et al. Allergic contact dermatitis in venous leg ulcer patients. Contact Dermatitis. 2003;48:261–5.
38. Machet L, Couhe C, Perrinaud A, et al. A high prevalence of sensitization still persists in leg ulcer patients: a

retrospective series of 106 patients tested between 2001 and 2002 and a meta-analysis of 1975–2003 data. Br J Dermatol. 2004;150:929–35.
39. Whitfield A. Lumleian lectures: on some points in the aetiology of skin disease. Lancet. 1921;2;122.
40. Hindsen M, Spiren A, Bruze M. Cross-reactivity between nickel and palladium demonstrated by systemic administration of nickel. Contact Dermatitis. 2005;53:2–8.
41. Hindsen M, Bruze M, Christensen OB. Flare-up reactions after oral challenge with nickel in relation to challenge dose and intensity and time of previous patch test reactions. J Am Acad Dermatol. 2001;44:616–23.
42. Roper SS, Jones HE. An animal model for altering the irritability threshold of normal skin. Contact Dermatitis. 1985;13:91–7.
43. Cockayne SE, Gawkrodger DJ. Angry back syndrome is often due to marginal irritants: a study of 17 cases seen over 4 years. Contact Dermatitis. 2000;43:280–2.
44. Memon AA, Friedmann PS. "Angry back syndrome": a non-reproducible phenomenon. Br J Dermatol. 1996; 135:924–30.
45. Sulzberger MB, Garbe W. Nine cases of distinctive exudative discoid and lichenoid dermatosis. Arch Dermatol Venereol. 1985;65:164–7.
46. Manns A, Hidasa M, La Grenade L. Human T-lymphotropic virus type I infection. Lancet 1999;353: 1951–8.
47. La Grenade L, Manns A, Fletcher V, et al. Clinical, pathologic, and immunologic features of human T-lymphotrophic virus type I-associated infective dermatitis in children. Arch Dermatol. 1998;134:439–44.
48. Carvalho EM, Bacellar O, Porto AF, et al. Cytokine profile and immunomodulation in asymptomatic human T-lymphotropic virus type 1-infected blood donors. J Acquir Immune Defic Syndr. 2001;27:1–6.
49. Gonçalves DU, Guedes AC, Proietti AB, et al.; Interdisciplinary HTLV-1/2 Research Group. Dermatologic lesions in asymptomatic blood donors seropositive for human T cell lymphotropic virus type-1. Am J Trop Med Hyg. 2003;68:562–5.
50. Sweet RD. A pattern of eczema in Jamaica. Br J Dermatol. 1966;78:93–100.
51. Walshe MM. Infective dermatitis in Jamaican children. Br J Dermatol. 1967;79:229–36.
52. Maloney EM, Hisada M, Palmer P, et al. Human T cell lymphotropic virus type I-associated infective dermatitis in Jamaica: a case report of clinical and biologic correlates. Pediatr Infect Dis J. 2000;19:560–5.
53. Bittencourt AL. Adult T-cell leukaemia/lymphoma (ATL) in Bahia, Brazil. Braz J Infect Dis. 2005;9:437–8.
54. Wollina U, Karamfilov T. Adjuvant botulinum toxin A in dyshidrotic hand eczema: a controlled prospective pilot study with left-right comparison. J Eur Acad Dermatol Venereol. 2002;16:40–2.
55. Tzaneva S, Kittler H, Thallinger C, et al. Oral vs. bath PUVA using 8-methoxypsoralen for chronic palmoplantar eczema. Photodermatol Photoimmunol Photomed. 2009;25:101–5.
56. Mackie RM, Husain SL. Juvenile plantar dermatosis: a new entity? Clin Exp Dermatol. 1976;1:253–60.
57. Berg RW, Buckingham KW, Stewart RL. Etiologic factors in diaper dermatitis: the role of urine. Pediatr Dermatol. 1986;3:102–6.
58. Buckingham KW, Berg RW. Etiologic factors in diaper dermatitis: the role of feces. Pediatr Dermatol. 1986;3: 107–12.
59. Yoshioka H, Iseki K, Fujita K. Development and differences of intestinal flora in the neonatal period in breast-fed and bottle-fed infants. Pediatrics. 1983;72: 317–21.
60. Campbell RL, Seymour JL, Stone LC, et al. Clinical studies with disposable diapers containing absorbent gelling materials: evaluation of effects on infant skin condition. J Am Acad Dermatol. 1987;17:978–87.

This page intentionally left blank



Adult seborrheic dermatitis of the face and scalp. Note the diffuse scaling of the scalp in addition to erythema of the forehead.

Asteatotic eczema (eczema craquelé). A The distal lower extremity has areas of dull erythema that contain a criss-cross pattern of superficial cracks and fissures said to resemble a dried river bed. **B** A close-up of the pattern. Asteatotic eczema (eczema craquelé).

Allergic Contact Dermatitis 14

Christen M Mowad and James G Marks Jr

Synonyms: ■ Contact dermatitis ■ Contact eczema

Key features

- Allergic contact dermatitis (ACD) is a pruritic, eczematous reaction
- Acute ACD and many cases of chronic ACD are well demarcated and localized to the site of contact with the allergen
- ACD can also have a diffuse, patchy distribution, depending on the allergen and/or the development of disseminated eczema (autosensitization dermatitis)
- The prototypic reactions are ACD due to poison ivy and nickel
- Patch testing remains the gold standard for accurate and consistent diagnosis

INTRODUCTION

Many adverse events can occur when the skin comes in contact with external agents. These reactions are varied, and include hyperpigmentation, hypopigmentation, acne, urticaria, phototoxic reactions and eczema. The eczema that is seen can be either allergic or irritant in nature. Irritant contact dermatitis (ICD) accounts for approximately 80% of all contact dermatitis (see Ch. 15) and allergic contact dermatitis (ACD) accounts for the remaining 20%[1]. ICD is the result of a local toxic effect when the skin comes in contact with irritant chemicals such as soaps, solvents, acids or alkalis. ACD is a delayed-type hypersensitivity reaction that is elicited when the skin comes in contact with a chemical to which an individual has previously been sensitized.

The cutaneous responses of ACD and ICD are dependent on the particular chemical, the duration and nature of the contact, and individual host susceptibility. The chemicals that cause contact dermatitis are found in jewelry, personal care products, plants, topical medications (prescription, over-the-counter or herbal) and home remedies, as well as chemicals the individual comes in contact with at work, during avocations or via contact with another individual (e.g. consort contact dermatitis). The type of cutaneous reaction discussed in this chapter is ACD.

ICD and ACD, especially the chronic forms, can take on similar clinical appearances. The classic picture of contact dermatitis is a well-demarcated erythematous vesicular and/or scaly patch or plaque with well-defined margins corresponding to the area of contact (Fig. 14.1A). The distribution can be linear, when an object such as a leaf or branch is rubbed against the skin (Fig. 14.1B), or localized to the site where there has been contact with the offending chemical or product, e.g. hand dermatitis caused by ACD to gloves or foot dermatitis due to ACD to shoes (Figs 14.2–14.4). Because ICD and ACD are not always discernible clinically, patch testing is required to help identify an allergen or exclude an allergy to a suspected allergen. Patch testing remains the gold standard for diagnosing ACD.

Patients with the most common clinical presentations of ACD often do not seek medical attention. Those who have earring dermatitis or erythema and pruritus under a ring may simply diagnose themselves as having an allergy to jewelry. An individual who is gardening over the weekend may never present to a physician, because the "poison ivy rash" is so familiar. Nickel (worldwide) and poison ivy (US; see Ch. 17) are among the most common etiologies of ACD and are often not further investigated because the cause is obvious. However, the clinical picture and history are often not sufficiently specific to identify the causative allergen, and patch testing is then necessary. For example, the patient with chronic hand dermatitis or eyelid dermatitis who comes to the office for treatment is often unaware that a personal care product could be the cause of the problem. These are the patients who can be most helped by a thorough history and cutaneous examination, as well as the diagnostic procedure of patch testing.

ACD is an exciting field of interest within dermatology. It requires an understanding of the disease process, the ability to recognize the many ways in which ACD can present, a keen level of interest and an appropriate level of suspicion for the possibility of an allergen, as well as the ability to patch test, interpret, and educate patients on this disease process. Hopefully, this chapter will raise interest and awareness and help the reader come to a better understanding of these issues.

Fig. 14.1 Allergic contact dermatitis (ACD). A This erythematous plaque with vesiculation developed in a 14-month-old boy following the application of neomycin ointment. **B** Erythematous streaks with linear vesicles due to ACD to poison ivy. *A, Courtesy, Anthony J Mancini, MD; B, Courtesy, Joyce Rico, MD.*

Fig. 14.2 Chronic allergic contact dermatitis (ACD). Chronic foot dermatitis due to ACD to rubber (mercaptobenzothiazole). *Courtesy, Louis A Fragola, Jr, MD.*

Fig. 14.3 Chronic allergic contact dermatitis leading to hand dermatitis. This golfer wore one leather glove and had positive patch tests to potassium dichromate and a piece of his glove. *Courtesy, Kalman Watsky, MD.*

Fig. 14.4 Allergic contact dermatitis to shoes – acute versus chronic. **A** Extremely pruritic erythematous papules and papulovesicles appeared within days of wearing new sneakers; note the distribution pattern. **B** Pebbled and lichenified plaques with both hypo- and hyperpigmentation. The patient had a positive patch test to potassium dichromate. *Courtesy, Louis A Fragola, Jr, MD.*

HISTORY OF PATCH TESTING

Jadassohn has been credited with describing the technique of patch testing over 100 years ago. In 1931, Sulzberger and Wise[2] formally brought the technique to the US and described its use as a diagnostic tool for identifying a causative allergen responsible for dermatitis. This technique has been further developed over the years on a worldwide basis, with standardized allergens, testing devices, and protocols.

Patch testing has remained the gold standard for diagnosing ACD. However, despite the value of this diagnostic tool, studies have shown that it is underutilized and not taught in many dermatology residency programs, including those in the US[3].

EPIDEMIOLOGY

ACD can affect individuals in all walks of life. It can affect the old, the young, individuals of all races, and of both sexes. Differences between genders may be seen but are generally based upon exposure patterns, such as nickel allergy occurring more frequently in women, presumably because of their greater exposure to jewelry[4]. Of course, occupations and avocations play an important role in the epidemiology of ACD (see

Fig. 14.5 Acute vesiculobullous allergic contact dermatitis (ACD). A ACD to poison ivy; this distribution pattern is seen in patients who wear gloves. **B** ACD to compound benzoin tincture; note the geometric shape.
B, Courtesy, Louis A Fragola, Jr, MD.

Fig. 14.6 Acute allergic contact dermatitis with a prominent component of edema. A Periorbital edema, in addition to crusted and weeping plaques, due to poison ivy. **B** Obvious edema of the shaft of the penis plus subtle crusts of the glans due to application of tiger balm (contains extracts of several plants, including mint, clove, and Chinese cinnamon).
A, Courtesy, Jean L Bolognia, MD. B, Courtesy, Louis A Fragola, Jr, MD.

Ch. 16). Allergens, and therefore patch test results, also differ from region to region, e.g. preservatives used in personal care products can vary based on government legislation. While quaternium-15 is the most common cosmetic preservative in the US to cause ACD, some have argued that it is not even needed in the European Standard Series[5] (see Table 14.3). In addition, even in a particular locale, some allergens can increase in clinical importance over time while others decrease due to usage patterns, and new allergens are continually being introduced.

PATHOGENESIS

ACD is a delayed-type hypersensitivity response. It is an allergen-specific reaction that requires prior sensitization of the individual to the chemical in question. The pathogenesis of ACD involves an initial sensitization phase when the patient first comes in contact with the chemical, which penetrates the skin and then elicits a cascade of events that results in sensitization (see Ch. 4 for details). The subsequent re-exposure of the skin leads to the presentation of the responsible allergen to an already primed T-cell milieu, causing the release of multiple cytokines and chemotactic factors and resulting in the clinical picture of eczema. Once sensitized, all that is needed to elicit a reaction is contact with a low concentration of the causative chemical.

CLINICAL FEATURES

In order to diagnose ACD and treat it adequately, the clinician needs to be familiar with its clinical presentations. The typical appearance is often a well-demarcated pruritic eczematous eruption, which may be acute (blistering, weeping and/or edema, e.g. Figs 14.1, 14.5 & 14.6) or chronic (lichenified or scaly plaques, e.g. Figs 14.3, 14.4B, 14.7 & 14.8). This reaction is typically localized to the area of skin that comes in contact with the allergen. However, the clinician must also be aware that patchy or diffuse distributions can also be seen, depending on the nature of the causative allergen (e.g. Fig. 14.9). For example, body washes or shampoos that get rinsed over the body may cause a more patchy or diffuse clinical dermatitis. Other less common presentations of allergic contact dermatitis are listed in Table 14.1.

PATHOLOGY

Although the diagnosis of ACD is in large part a clinical one aided by the diagnostic procedure of patch testing, histology can sometimes be helpful. This is especially true when excluding other diagnoses, such as mycosis fungoides. The pathology of ACD is most helpful in acute lesions, as subacute or chronic lesions often produce confusing patterns that are not diagnostic. Histologically, ACD is the prototype of

Fig. 14.7 Allergic contact dermatitis due to aloe-containing cream. The degree of involvement on the upper and lower lips is similar, as opposed to actinic cheilitis.

Fig. 14.8 Chronic allergic contact dermatitis due to glutaraldehyde. The patient was an optometrist. *Courtesy, Kalman Watsky, MD.*

LESS COMMON PRESENTATIONS OF ALLERGIC CONTACT DERMATITIS	
Based primarily upon type of primary lesion	**Based primarily upon distribution and/or pathogenesis**
• Pigmented (e.g. fragrances, bactericides; often facial) • Lichenoid (e.g. color film developers) • Erythema multiforme (e.g. tropical woods, poison ivy*) • Purpuric (e.g. rubber diving suits) • Granulomatous (e.g. zirconium) • Pseudolymphomatous (e.g. Compositae)	• Photoinduced (photoallergic contact dermatitis; see Ch. 87) • Airborne contact dermatitis • Systemic contact dermatitis (see Table 14.12) • Baboon syndrome – symmetric erythema of the gluteal and inguinal area in addition to other flexural sites†
*The lesions of erythema multiforme may favor sites previously unaffected by poison ivy. †Overlap with systemic contact dermatitis and clinical overlap with *s*ymmetrical *d*rug-*r*elated *i*ntertriginous and *f*lexural *e*xanthema (SDRIFE).	

Table 14.1 Less common presentations of allergic contact dermatitis (ACD). Contact urticaria, both immunologic and non-immunologic, can also complicate the clinical picture.

Fig. 14.9 Allergic contact dermatitis due to cashew nut shell oil. This represented an occupational exposure.

spongiotic dermatitis. In the acute stage, there is a variable degree of spongiosis, with a mixed dermal inflammatory infiltrate containing lymphocytes, histiocytes and a variable number of eosinophils. In moderate to severe reactions, marked spongiosis results in intraepidermal vesiculation. In subacute to chronic stages, epidermal hyperplasia, often psoriasiform, develops (Fig. 14.10).

However, even when spongiotic dermatitis is present, clinicopathologic correlation is always required, as ACD is not the only cause of this reaction pattern. In addition, as with any dermatitis, the application of topical corticosteroids may alter the histologic findings. Occasionally, other histopathologic patterns are seen in ACD, as outlined in Table 14.1.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of ACD includes many other forms of dermatitis, such as ICD, atopic dermatitis, stasis dermatitis and seborrheic dermatitis, as well as the erythematous form of rosacea. Hand and foot ACD also needs to be distinguished from psoriasis and tinea (see Table 13.1 & Fig. 15.6). In general, when evaluating regional dermatoses (e.g. eyelid, hand and foot), other disorders common to the area need to be considered as well as allergens specific to that area (Table 14.2). If there is widespread disease, either because of widespread contact with an allergen or autosensitization, additional causes of erythroderma (see Ch. 10), e.g. Sézary syndrome, enter the differential diagnosis.

Deciphering and differentiating these diseases can sometimes be a challenge. Distribution and history can be helpful (see Figs 14.3–14.6), as can simple tests such as a KOH preparation. In addition, dermatoses are sometimes multifactorial, and ACD may be superimposed on atopic dermatitis or stasis dermatitis. However, in order to diagnose ACD, the clinician must first consider the possibility, then ask the right questions, and, finally, use the appropriate allergens to diagnose this condition. What follows will hopefully provide the clinician with an outline to the appropriate questions to ask and procedures to use when investigating ACD.

Patch Testing

Patch testing is a deceptively simple office procedure upon which the diagnosis of ACD often rests. Although the procedure is straightforward, deciding when and what to patch test requires training and experience. Unfortunately, patch testing is still underutilized. Past surveys have shown that only 50% of all residency programs in the US have a patch test center, and 27% of the responders did no patch testing at all[3].

The TRUE Test®, which is approved by the US Food and Drug Administration (FDA), consists of panels with pre-impregnated

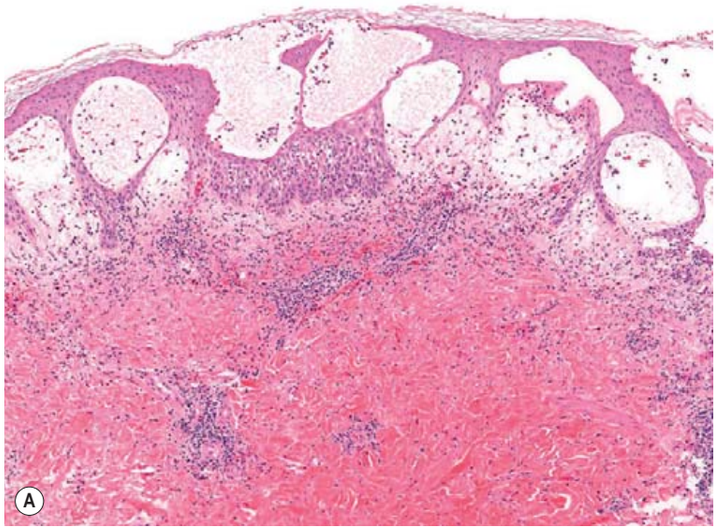


Fig. 14.10 Allergic contact dermatitis – histologic features. A Acute ACD with marked spongiosis leading to intraepidermal vesiculation. There is a perivascular infiltrate of lymphocytes and eosinophils as well as exocytosis of these cells into the epidermis. **B** Chronic ACD with irregular psoriasiform epidermal hyperplasia and significantly less spongiosis. There is also a primarily perivascular infiltrate of lymphocytes admixed with eosinophils. *Courtesy, Lorenzo Cerroni, MD.*

EYELID DERMATITIS – DIFFERENTIAL DIAGNOSIS AND MOST COMMONLY ASSOCIATED ALLERGENS	
Differential diagnosis	**Allergens most commonly associated with ACD of the eyelids***
• Atopic dermatitis • Seborrheic dermatitis • Rosacea (eyelid margin) • Allergic contact dermatitis • Irritant contact dermatitis • Dermatomyositis	• Fragrances, including *Myroxylon pereirae* (balsam of Peru) • Preservatives – quaternium-15, DMDM hydantoin, methylchloroisothiazolinone, methyldibromoglutaronitrile • Topical antibiotics – neomycin (see Fig. 14.17) • Metals – nickel, cobalt chloride, gold sodium thiosulfate • Surfactants – cocamidopropyl betaine, amidoamine
*Adapted from North American Contact Dermatitis Group (2003–2004); Dermatitis 2007;18:78–81.	

Table 14.2 Eyelid dermatitis – differential diagnosis and most commonly associated allergens. ACD, allergic contact dermatitis.

Fig. 14.11 Allergens contained within syringes being placed by nurse into Finn chambers.

allergens, allowing for increased ease of use and perhaps resulting in increased patch testing. However, it currently screens for only 28 allergens (there is one control, which accounts for the 29th spot), and, although this is helpful, extended testing beyond these allergens has been shown to be more beneficial[6–8]. For example, extended testing detected 37–76% more positive reactions, and 47% of the patients had positive reactions *only* to non-screening allergens[6–8]; these additional allergens come in multi-use syringes or tubes (Fig. 14.11). Of note, the manufacturers of TRUE Test® are continuing to work on expanding the number of allergens in their testing series in order to increase diagnostic sensitivity. If clinicians were to increase their use of patch testing and expand the number of allergens tested, they would hopefully enhance patient care through improved allergen identification and avoidance.

Prior to the application of the patch tests, the clinician should ask questions about exposures both at home and at work, and attempt to understand the mechanics of the work environment. The effect of vacations and time away from work or home should also be ascertained. In addition, all personal care products should be inventoried and hobbies explored. The information gained can help to direct allergen selection more appropriately.

Technique

Although the TRUE Test® has only 28 allergens (Table 14.3), referral centers with patch test clinics routinely patch test to an "expanded" series of 60+ allergens. Such panels include the North American Contact Dermatitis Group Screening Series and the European Standard Series, in addition to more specific allergen panels, e.g. the hairdressing tray, dental tray or florist tray, which contain allergens unique to a particular occupation. The companies from which these allergens and other supplies can be obtained are listed in the Appendix. Although these expanded series of allergens are not FDA-approved, they are often required to establish the precise etiology.

Chemicals brought by patients to the dermatologist should *not* be tested in a blinded fashion. The physician should be aware of the chemical ingredients of the product, or severe irritation such as a burn or ulceration could occur. Therefore, no unknown product or chemical should be applied as a patch test. Material safety data sheets (MSDS) can sometimes help in further evaluating the chemical. However, not all ingredients are listed on these forms: those chemicals that represent a small percentage and fall below a certain threshold do not need to be listed, even though they may be the causative allergens. Identification of the latter requires communication with the manufacturer, so that full disclosure of the chemical ingredients can be obtained.

When patients bring all their personal care products to the office for patch testing, special attention is required. The general rule regarding testing of these products is that products intended to be left on the skin

COMPONENTS OF THE NORTH AMERICAN CONTACT DERMATITIS GROUP (NACDG) SCREENING SERIES, THE EUROPEAN STANDARD (BASELINE) SERIES, AND THE TRUE TEST® SERIES	
Series/Compound	**Concentration (in NACDG series* except where compound not part of NACDG series)**
NACDG, EUROPEAN STANDARD AND TRUE TEST®	
2-Mercaptobenzothiazole	1% petrolatum
Colophony	20% petrolatum
4-Phenylenediamine base	1% petrolatum
Neomycin sulfate	20% petrolatum
Thiuram mix	1% petrolatum
Formaldehyde	1% aqueous
Epoxy resin	1% petrolatum
Quaternium-15	2% petrolatum
4-tert-Butylphenol formaldehyde resin	1% petrolatum
Mercapto mix	1% petrolatum
Potassium dichromate	0.25% petrolatum
Balsam of Peru	25% petrolatum
Nickel sulfate hexahydrate	2.5% petrolatum
Methylchloroisothiazolinone/ methylisothiazolinone	0.01% aqueous
Paraben mix	12% petrolatum
Fragrance mix I	8% petrolatum
Cobalt chloride	1% petrolatum
Tixocortol-21-pivalate	0.1% petrolatum
Budesonide	0.01% petrolatum
NACDG AND EUROPEAN STANDARD	
Benzocaine	5% petrolatum
N-Isopropyl-N-phenyl-4-phenylenediamine	0.1% petrolatum
Sesquiterpene lactone mix	0.1% petrolatum
Methyldibromoglutaronitrile	0.5% petrolatum
Fragrance mix II	14% petrolatum
NACDG AND TRUE TEST®	
Carba mix	3% petrolatum
Ethylenediamine dihydrochloride	1% petrolatum
Imidazolidinyl urea	2% petrolatum
Diazolidinyl urea	1% petrolatum
TRUE TEST® AND EUROPEAN STANDARD	
Wool alcohols	30% petrolatum
NACDG ONLY	
Cinnamic aldehyde	1% petrolatum
Amerchol L 101	50% petrolatum
DMDM hydantoin	1% petrolatum
Bacitracin	20% petrolatum
Mixed dialkyl thioureas	1% petrolatum
Glutaraldehyde	0.5% petrolatum
2-Bromo-2-nitropropane-1,3-diol	0.5% petrolatum
Propylene glycol	30% aqueous
2-Hydroxy-4-methoxybenzophenone	10% petrolatum
4-Chloro-3,5-xylenol	1% petrolatum
Ethyleneurea/melamine-formaldehyde mix	5% petrolatum
Ethyl acrylate	0.1% petrolatum
Glyceryl monothioglycolate	1% petrolatum
Tosylamide/formaldehyde resin	10% petrolatum
Methyl methacrylate	2% petrolatum
Disperse 106/124 mix	1.0% petrolatum
Iodopropynyl butyl carbamate	0.2% petrolatum
Compositae mix II	5% petrolatum
Hydrocortisone-17-butyrate	1% petrolatum
Dimethylol dihydroxyethyleneurea	4.5% aqueous
Cocamidopropyl betaine	1% aqueous
Triamcinolone acetonide	1% petrolatum
EUROPEAN STANDARD ONLY	
Clioquinol	5% petrolatum
Lyral® (fragrance)	5% petrolatum
Primin	0.01% petrolatum
TRUE TEST® ONLY	
Caine mix (benzocaine, tetracaine, dibucaine)	0.63 mg/cm^2 in polyvidone
Black rubber mix (N-isopropyl-N′-phenyl PPD, N-cyclohexyl-N′-phenyl PPD, and N,N′-diphenyl PPD)	0.075 mg/cm^2 in polyvidone
Thimerosal	0.008 mg/cm^2 in hydroxypropyl cellulose
Quinoline mix	0.19 mg/cm^2 in polyvidone
*Concentrations in European Series can differ, e.g. higher for mercapto mix, nickel, paraben mix and lower for quaternium-15.	

Table 14.3 Components of the North American Contact Dermatitis Group (NACDG) Screening Series, the European Standard (Baseline) Series, and the TRUE Test® Series. NACDG allergens represent those that are commercially available as the "North American Screening (Baseline) Series (50)". PPD, paraphenylenediamine.

Table 14.3 Continued

(so-called "leave-on" products), such as moisturizers and make-up, may be tested "as is". Products that are intended to be diluted by water or rinsed off (so-called "rinse-off" products), such as soaps and shampoos, need to be diluted prior to patch testing. There are helpful guides for determining appropriate patch test concentrations for numerous chemicals[9]. When these non-standard allergens are tested, controls (including vehicles) must be tested to evaluate for the possibility of ICD.

After allergen selection has been finalized, appropriate technique is necessary to ensure adequate testing. The most common site is the upper back. The patient should not have a sunburn in this area and should not have applied topical corticosteroids to the sites of patch testing for 1 week[10,11]. Systemic and longer-lasting injectable corticosteroids should also be avoided for at least 1–2 weeks[12]. (If necessary for disease control, the daily oral AM dose of corticosteroids should not exceed the equivalent of 20 mg of prednisone during testing.) Any one of these factors may decrease the individual's ability to elicit a reaction when challenged by an allergen, resulting in a false-negative test[10–12].

A nurse or technician in the office can be trained to apply the patches, and this leads to improved efficiency. Either the pre-packaged allergens are placed on the back, as in the case of the TRUE Test®, or the allergens are poured into Finn chambers (see Fig. 14.11) (Epitest Ltd, Tuusula, Finland; available in the US from Allerderm Laboratories, Inc.) that are adhered to Scanpor® tape (Norgeplaster, Vennesia, Norway; available in the US from Allerderm Laboratories, Inc.) or IQ Chambers™ (Chemotechnique® Diagnostics; distributed by Dormer Laboratories, Inc.) and then applied to the back (Fig. 14.12). These patches are then reinforced with more Scanpor® tape and the patient is sent home with instructions to keep the back dry and the patches secured

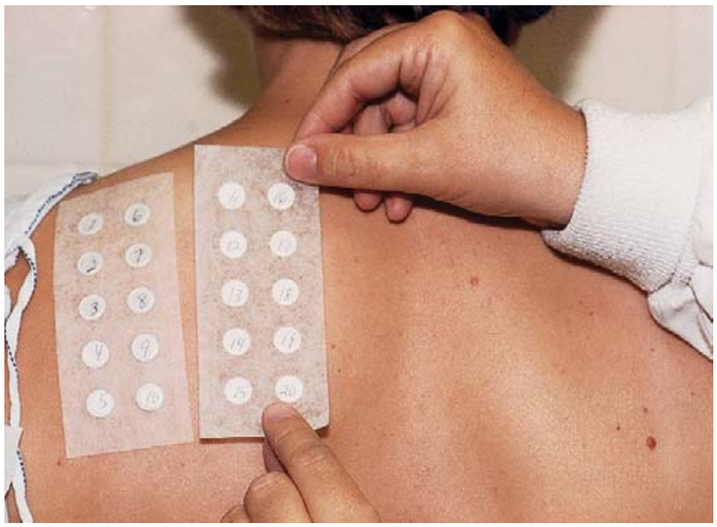


Fig. 14.12 Fixing allergens to patient's back using Scanpor® tape.

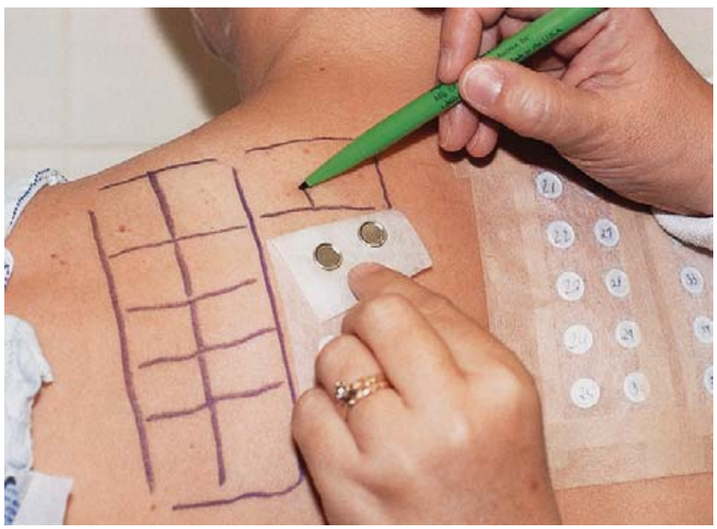


Fig. 14.13 Allergens being marked upon removal of Scanpor® tape.

until the second visit at 48 hours. Patients should also be told to avoid excessive sweating and to avoid heavy lifting, as the patches may come loose. Antihistamines can be prescribed, as they will not affect the outcome of the testing. A map of where the allergens were placed should be constructed for future reference.

When the patient returns at 48 hours, the patches need to be examined to ensure that the testing technique was adequate. Initial inspection can determine that the patches are still in place. Confirmation comes from observing whether the chambers have adhered adequately so as to leave an impression in the skin (see Fig. 14.14F). As the patches are removed, their sites of application should be marked in order to identify the location of the particular allergens (Fig. 14.13). Two types of marking pen are recommended for this procedure: either a permanent surgical marker or a fluorescent highlighter. Highlighters are less messy and do not rub off as easily as the permanent marker. Because of the latter property, permanent markers can soil clothing and make interpretations at the second reading more difficult. Any positive reactions are scored according to the International Grading System (Table 14.4; Fig. 14.14). The patient is again asked to keep the back dry until the second reading, which can be performed from 72 hours to 1 week after the initial application of patches.

When the patient returns for the second reading, the map is used to identify any positive reactions. If a fluorescent marker has been utilized, a Wood's lamp may be needed to identify the markings. Positive reactions are again graded according to the standard system (see Table 14.4).

INTERNATIONAL GRADING SYSTEM FOR PATCH TESTS	
+/–	Doubtful reaction, faint macular erythema
+	Weak, non-vesicular reaction with erythema, infiltration and papules
++	Strong, vesicular reaction with erythema, infiltration and papules
+++	Spreading bullous reaction
–	Negative reaction
IR	Irritant reaction

Table 14.4 International Grading System for patch tests. See Figure 14.14.

A delayed reading is necessary as patch test responses to some allergens such as gold and disperse blue dyes may be delayed. The actual products the patient uses in his or her work and/or home environment are examined and the ingredients compared with the positive reactions. In so doing, products can be divided into groups: those that are free of the suspected allergen(s) and are safe to use, and those that contain these chemical(s) and should be avoided. There will usually be some products with no ingredients listed, and these will have to be further investigated by the patient or physician by contacting companies and inquiring about ingredients.

Interpreting the test

Through the process of reviewing exposures and products, the clinical *relevance* of positive test results can be determined. Allergens may have past relevance. For example, the patient who presents with a known allergy to nickel and reactions to costume jewelry is found on patch testing to have a positive reaction to nickel. The nickel may have past relevance to the patient's problem with costume jewelry but no current relevance to the chronic hand dermatitis. Relevance may also be determined to be current. For example, a positive reaction to tuliposidase A (see Ch. 17) in a florist who has hand dermatitis and contact with *Alstroemeria* when arranging flowers would have present relevance. In some individuals, relevance may be unknown, as in a patient with an eyelid dermatitis and a positive reaction to thimerosal but no past history of an allergy to contact lens solutions and no identifiable contact with thimerosal.

TREATMENT AND PATIENT EDUCATION

Once allergens are positively identified, the patient should be given written information on all of these chemicals. The information sheets should contain data regarding the name of the chemical, possible synonyms, typical uses for the chemical, how to avoid exposure, and, when appropriate, substitutions. The sheets can be individually composed or obtained from books and copied for patient use[13] (Table 14.5). In addition, the American Contact Dermatitis Society website (www.contactderm.org) is an excellent resource for allergen and product information, including patient information sheets. The Contact Allergen Management Program (CAMP) is another feature of the website (available to members of the society): this allows the user to input the known allergens and the database assembles a list of products free of the allergens entered. With this CAMP-generated list, the patients can then purchase products that lack the ingredients to which they are allergic. In addition, this website contains a Contact Dermatitis Alternatives Database which assists both patients and physicians with regard to appropriate substitutions for known allergens.

The patient should also be instructed on how to read the labels of any new or old products not reviewed, in order to avoid future exposure. Each time the patient considers buying a product, he or she should utilize updated information sheets, because ingredients in a given product can change over time. In addition, ingredients in a particular product can change from location to location (e.g. between countries, or between the East and West Coast of the US) without a change in the packaging.

After identifying the substances to which the patient is allergic, the most important step a physician takes is to educate the patient regarding the names of the allergens and how to avoid them. This empowers

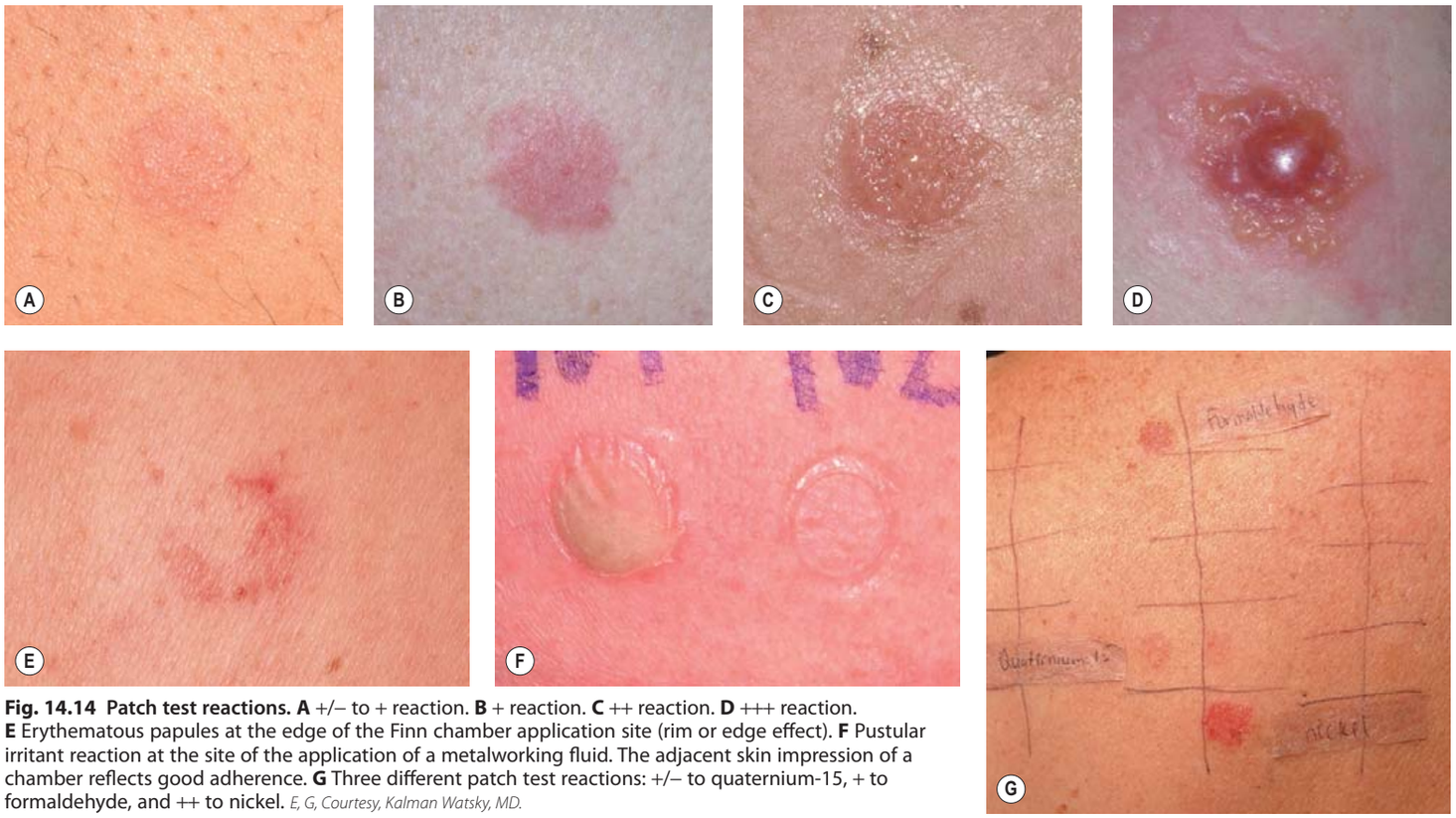


Fig. 14.14 Patch test reactions. A +/– to + reaction. **B** + reaction. **C** ++ reaction. **D** +++ reaction. **E** Erythematous papules at the edge of the Finn chamber application site (rim or edge effect). **F** Pustular irritant reaction at the site of the application of a metalworking fluid. The adjacent skin impression of a chamber reflects good adherence. **G** Three different patch test reactions: +/– to quaternium-15, + to formaldehyde, and ++ to nickel. *E, G, Courtesy, Kalman Watsky, MD.*

EXPOSURE INFORMATION SHEET: BALSAM OF PERU (*MYROXYLON PEREIRAE*)	
SYNONYMS AND OTHER NAMES	
Balsamum peruvianim	Indian balsam
Black balsam	Peruvian balsam
China oil	Surinam balsam
Honduras balsam	
USES	
Balsam of Peru is a natural mixture of resins and essential oils. A positive patch test response is an indication of allergy to fragrances and flavors used in the cosmetic, pharmaceutical, tobacco, and food industries and may indicate sensitivity to the following products: 1. Fragrances in cosmetics and household products 2. Baby products (diaper powders and ointments) 3. Flavors (pastries, cakes, soft drinks, tea, wines, liqueurs, and tobacco) 4. Spices (cinnamon, cloves, vanilla, and curry) 5. Medicated creams, ointments, suppositories, cough syrups and lozenges, and traditional Chinese medicaments 6. Sensitivity (cross-reactions) may also occur to colophony, balsam of Tolu, wood tars, turpentine, propolis, storax, and benzoin	
PREVENTION	
A positive patch test response to balsam of Peru strongly suggests a fragrance allergy. Thus the patient needs to use fragrance-free cosmetics and household products and avoid fragranced medicines. Diaper rash, stasis dermatitis, and hemorrhoids must be treated with topical medications not containing fragrances or balsam of Peru.	
Generalized rash or hand dermatitis has uncommonly occurred after the ingestion of spices by patients who are allergic to balsam of Peru. The wholesale avoidance of this flavor additive or spices in foods such as peel of citrus fruit, chocolate, baked goods, ice cream, soft drinks, candy, chewing gum, tea, and aperitifs should be a last resort in patients with generalized or hand eczema.	

Table 14.5 Exposure information sheet: Balsam of Peru (*Myroxylon pereirae*). With permission from Marks et al.[13]

the individual and allows the physician to transfer to the patient the responsibility for avoiding said chemicals. When trying to identify allergens in the patient's environment, one must also consider allergens transferred from other sources – so-called consort dermatitis (e.g. from spouse to spouse, such as the cologne on the husband causing a reaction on the face of his wife).

Treatment of ACD primarily involves identification of the causative allergens. Once the allergens have been identified, the physician should try to clear the dermatitis with appropriate treatments, such as topical or, if necessary, systemic corticosteroids. The educated patient then needs to be diligent in avoiding the identified allergens. It may take 6 weeks or more to see complete and prolonged clearing, even when allergens are being avoided (Fig. 14.15). If the ACD is superimposed upon another dermatosis (e.g. stasis dermatitis, atopic dermatitis), then the latter will also need to be addressed and will hopefully prove easier to manage.

If a patient is unable to undergo patch testing for some reason, or confirmation of patch test results is desired, a repeat open application test may be performed. This open use test, sometimes referred to as the "poor man's patch test", can prove useful. In an open use test, the patient applies the product in question to the same predetermined location (where there is no dermatitis) twice daily for 1–2 weeks; a common site is the antecubital fossa or flexor forearm. If dermatitis develops, it can be concluded that the patient is reacting to that product. Unfortunately, this type of testing does not allow the identification of individual ingredients. Avoidance of the product in question may result in clearing of the dermatitis. However, many products in the same class use similar ingredients, and therefore the information may not be as useful as first anticipated, i.e. switching to another product may not result in continued clearance of the dermatitis.

ALLERGENS

With an understanding of how to patch test, the next step is a review of some common allergens. The top 10 allergens, as identified by the North American Contact Dermatitis Group (NACDG) in 2006, are nickel sulfate, *Myroxylon pereirae* (balsam of Peru), fragrance mix I, quaternium-15, neomycin sulfate, bacitracin, formaldehyde, cobalt

Fig. 14.15 Allergic contact dermatitis to fragrance found in cologne. A Patient at the time of diagnosis. **B** Patient after avoidance of fragrances and his cologne.

TOP TEN ALLERGENS AS IDENTIFIED BY THE NORTH AMERICAN CONTACT DERMATITIS GROUP		
Test substance	**Allergic reactions (%)**	**Relevant reactions (%) (definite, probable, possible [combined])**
Nickel sulfate	19	57
Myroxylon pereirae (balsam of Peru)	12	87
Fragrance mix I	11.5	86
Quaternium-15	10	89
Neomycin sulfate	10	28
Bacitracin	9	39
Formaldehyde	9	91
Cobalt chloride	8.5	48
Methyldibromoglutaronitrile/ phenoxyethanol	6	75
p-Phenylenediamine	5	56

Table 14.6 Top 10 allergens as identified by the North American Contact Dermatitis Group. The two new members are methyldibromoglutaronitrile/ phenoxyethanol and p-phenylenediamine, which replaced thimerosal and sodium gold thiosulfate.
Adapted from Patch-test results of the North American Contact Dermatitis Group 2005–2006. Dermatitis. 2009;20:149–60.

chloride, methyldibromoglutaronitrile, and p-phenylenediamine[14] (Table 14.6). It should be noted that the list contains three preservatives, two metals, two topical antibiotics, two fragrance components and one dye. Table 14.7 provides a list of additional important allergens (and the frequently identified routes of exposure). Of note, ACD in children is becoming increasingly recognized, and the most common allergens, as identified by the NACDG, in this age group are outlined in Table 14.8. Lastly, the modern era has brought us new products (e.g. cellular phones), changes in manufacturing sites and a craving for "natural" products (Table 14.9).

The following section will briefly discuss pertinent information regarding several key allergens.

Nickel

Nickel ranks as the most common allergen tested by the NACDG, with 19% of patch test clinic patients reacting to it. In patch test clinics worldwide, nickel is the most common allergen. The relevance of these reactions has been estimated to be 50%, suggesting that although this is a common allergen it is not always relevant to the dermatitis in question[15]. However, upon questioning, past relevance may be discovered (e.g. previous mid-abdomen dermatitis). Nickel is a strong silver-colored metal that is commonly used in jewelry, buckles and snaps, as well as other metal-containing objects.

It has been proposed that the high rate of nickel sensitivity, which in some patch test clinics approaches 30–40%, can be attributed in large part to ear piercing. Studies have shown that the metal posts used in ear piercing release varying amounts of nickel, allowing for direct exposure to an injured cutaneous surface[16]. Traditionally, the prevalence of nickel sensitivity has been higher in women; however, with newer trends toward piercing multiple body sites by both men and women, a gender difference may become less apparent[4].

Clinically, nickel dermatitis can have many presentations. One of the most common is an earring dermatitis, or dermatitis under a necklace or a watch back that consists of a nickel-containing metal. Dermatitis of the mid-abdomen caused by a belt buckle or snap is common (Fig. 14.16A), and eyelid dermatitis from metal eyelash curlers can also be seen. In children, the former can be accompanied by a widespread lichenoid papular eruption (see Ch. 13). More recently, facial dermatitis due to ACD to nickel within cellular phones has been described (Fig. 14.16B).

ADDITIONAL IMPORTANT ALLERGENS	
Allergens	**Uses/found in**
PRESERVATIVES	
Methylchloroisothiazolinone/ methylisothiazolinone (Kathon CG®)	Preservative/cosmetics, personal care products
Iodopropynyl butylcarbamate	Preservative/cosmetics, personal care products
Thimerosal	Preservative/otic and ophthalmic drops (otherwise often lacks clinical relevance)
PRESERVATIVES – FORMALDEHYDE RELEASERS	
2-Bromo-2-nitropropane-1,3-diol (Bronopol®)	Preservative/cosmetics, personal care products
Diazolidinyl urea	Preservative/same as above
Imidazolidinyl urea	Preservative/same as above
DMDM hydantoin	Preservative/same as above
COMPONENTS OF RUBBER PRODUCTS	
Carba mix	Rubber accelerator/rubber, latex products
Mercaptobenzothiazole (MBT), mercapto mix	Rubber accelerator/rubber, latex products
Thiuram mix	Rubber accelerator/rubber, latex products
Mixed dialkyl thioureas	Rubber accelerator/rubber, latex products, photocopying, photography
HAIR AND NAIL ALLERGENS	
Glyceryl thioglycolate	Alters disulfide bonds/permanent wave solutions ("acid", "heat"); can persist for months
Tosylamide formaldehyde resin	Film former/nail polish
Acrylates	Artificial nails/nail glues
TEXTILE ALLERGENS	
Ethyleneurea/melamine formaldehyde resin	Thermosetting resin/permanent press clothing
Disperse blue 106 and 124	Textile dyes/darkly colored > lightly colored clothing
ADHESIVE ALLERGENS	
Colophony	Resin/adhesives, cosmetics, topical medications
Epoxy resin	Resin/adhesives
p-tert-Butylphenol formaldehyde resin	Resin/adhesives
OTHER	
Potassium dichromate	Metals, leather, cement
Sodium gold thiosulfate	Metal/jewelry, dental implants (clinical relevance can be difficult to determine)
Propylene glycol	Emulsifier/cosmetics, topical medicaments
Cinnamic aldehyde	Fragrance/flavoring
Budesonide	Corticosteroid/topical creams, ointments
Tixocortol-21-pivalate	Corticosteroid/topical creams, ointments
Ethylenediamine dihydrochloride	Antihistamine/topical creams
Lanolin (wool alcohol)	Emollient/topical creams, lotions
Benzocaine	Anesthetic/topical preparations
Cocamidopropyl betaine	Surfactant/shampoos, cosmetics
Amidoamine	Contaminant of cocamidopropyl betaine

Table 14.7 Additional important allergens. See Table 14.6 for 'Top 10' allergens identified by the North American Contact Dermatitis Group.

TOP 20 ALLERGENS IN CHILDREN AND ADOLESCENTS (<18 YEARS OF AGE) AS IDENTIFIED BY THE NORTH AMERICAN CONTACT DERMATITIS GROUP
Metals – nickel sulfate, cobalt chloride*, gold sodium thiosulfate, potassium dichromate†
Preservatives – thimerosal, quaternium-15, formaldehyde, diazolidinyl urea
Topical antibiotics – neomycin sulfate, bacitracin
Fragrances, including *Myroxylon pereirae* (balsam of Peru)
Components of rubber products – mercaptobenzothiazole, carba mix
Other – lanolin alcohol, colophony, propylene glycol, benzalkonium chloride, p-phenylenediamine, disperse blue dye
*Also contained in ceramics (see text). †Also contained in leather.

Table 14.8 Top 20 allergens in children and adolescents (<18 years of age) as identified by the North American Contact Dermatitis Group. *Adapted from Contact allergy in children referred for patch testing, North American Contact Dermatitis Group Data, 2001–2004. Arch Dermatol. 2008;144:1329–36.*

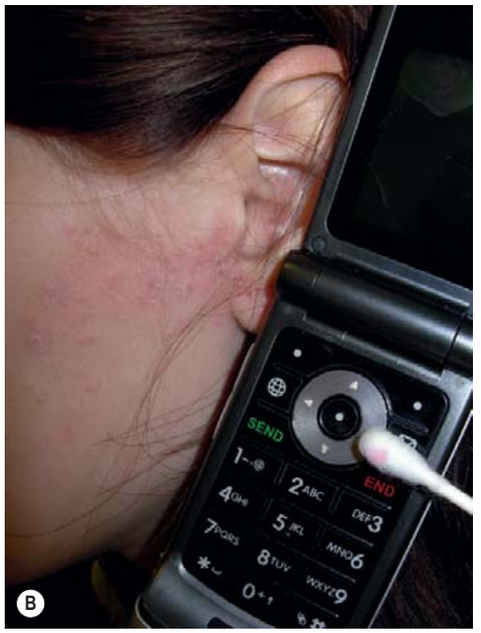


Fig. 14.16 Allergic contact dermatitis to nickel. A Excoriated pink plaques due to nickel within the belt buckle. **B** Facial dermatitis due nickel within a cellular phone. The latter is demonstrated by a positive dimethylglyoxime test (pink indicator). *A, Courtesy, Julie V Schaffer, MD.*

Concomitant reactions to nickel and cobalt have been reported and may be due to the frequency with which the two metals are used in combination[17]. Sweating can increase the amount of metal leached from a product. A useful test to determine whether a particular item contains nickel is the dimethylglyoxime test (see Appendix), which identifies objects that release nickel using a pink color indicator (see Fig. 14.16B). A color indicator test to detect the presence of cobalt is now available based on disodium-1-nitroso-2-naphthol-3, 6-disulfonate.

Individuals with nickel allergy should avoid costume jewelry. They can usually wear jewelry made of stainless steel, platinum or gold, but

ALLERGIC CONTACT DERMATITIS IN THE MODERN ERA		
Product	**Allergen**	**Clinical presentation**
Mobile (cellular) phones	Nickel	Facial dermatitis (see Fig. 14.16B)
Sanitary (baby or wet) wipes	Methylchloroisothiazolinone*	Direct contact – anogenital dermatitis (all ages) Indirect contact – posterior thighs (commode seat)
Anti-mold sachets inside leather products to prevent mold formation during shipping (e.g. couches, chairs, shoes)	Dimethylfumarate	When heated, fumes are created which penetrate through leather and clothing, leading to dermatitis of the back, buttocks and posterolateral thighs if in furniture
"Natural" botanical products resurgence plus grooming practices, e.g. beeswax-containing lip balm	Propolis	Cheilitis of both the upper and lower lip
Increase in temporary tattoos	Paraphenylenediamine	Allergic reaction at site of temporary tattoo
*Also cause of allergic contact dermatitis to moistened toilet paper.		

Table 14.9 Allergic contact dermatitis in the modern era.

not white gold. Some clinicians advocate coating nickel-containing surfaces such as snaps on jeans with clear nail polish to prevent leaching by sweat onto the skin. However, the nail polish can rub off and should be reapplied if it is effective. A new cream containing calcium carbonate nanoparticles has been shown in animals to protect against nickel-induced reactions in the setting of nickel allergy[17a].

Myroxylon Pereirae

Myroxylon pereirae (balsam of Peru) is a naturally occurring fragrance material that is the second most common allergen identified by the NACDG. The International Fragrance Association has recommended that balsam of Peru not be used as a fragrance ingredient[13,18]. Allergy to balsam of Peru is most commonly found in those with fragrance allergy (see below), but it is also seen in those with allergies to spices, particularly cloves, Jamaican pepper and cinnamon[18].

A positive reaction to balsam of Peru requires counseling of the patient to avoid fragrances. Occasionally, spices and other sources such as colas, tobacco, wines and vermouth can also be the cause of allergy to balsam of Peru[13,18].

Fragrance Mix

Fragrances are ubiquitous in our environment. They are used to provide a pleasant odor and have been used extensively for centuries. Fragrances were identified as the third most common allergen according to the NACDG, with a rate of 11.5%, and the most common cosmetic allergen to cause ACD[19].

The detection of a fragrance allergy was made easier with the introduction of a fragrance mix in the 1970s. Prior to that, fragrance allergy was identified primarily through testing with balsam of Peru, which detected only about 50% of those affected[20]. The current fragrance mix I contains eight different fragrance components (at 1% each; Table 14.10).

Of note, the first fragrance mix I had each of the components in Table 14.10 at a 2% concentration, but this was changed to try to reduce the number of false-positive reactions[21,22]. Fragrance mix I is the most useful tool for detecting fragrance allergy[20,23]. However, the composition of fragrance-containing products continually changes. Therefore, by including additional allergens such as those in fragrance mix II (see Table 14.10), the detection rate of fragrance allergy can be increased. It is estimated that 26% of patients allergic to fragrance would be missed if fragrance mix II were not used[23a].

In product formulations, fragrances can be used to provide a pleasant odor. However, they can also be used to mask an unpleasant odor – a so-called masking fragrance. This often occurs in products labeled "unscented". Patients who are identified as being allergic to fragrance must be instructed to read all labels and to avoid any product that lists a fragrance, is labeled "unscented", or has an obvious scent (see Fig. 14.15). They should be instructed to look instead for "fragrance-free" products. Unfortunately, there are several fragrance ingredients that have other purposes, i.e. they act as a preservative or emollient. These covert fragrances, e.g. balsam of Peru, benzylaldehyde, benzyl alcohol, bisbalol and others[24], can be used in a product and the product may still be labeled fragrance-free as long as the potentially allergenic ingredient has been identified as being used for a purpose other than fragrance. Obviously, this causes significant problems for the individual with fragrance allergy who is trying to avoid fragrances. Label reading may not always be enough unless the patient is educated about some of these practices. Complete disclosure on labels of all ingredients regardless of intended function would be helpful, but this is not yet part of industry practice. For the individual allergic to fragrances, repeat open application testing is very helpful in screening for an allergy to new or old products.

COMPONENTS IN FRAGRANCE MIX I AND FRAGRANCE MIX II	
FRAGRANCE MIX I	**FRAGRANCE MIX II**
• Cinnamic aldehyde • Cinnamyl alcohol • Hydroxycitronellal • Isoeugenol • Eugenol • Oak moss absolute • α-Amyl cinnamic aldehyde • Geraniol	• Lyral® • Citral • Farnesol • Citronellol • Hexyl cinnamic aldehyde • Coumarin

Table 14.10 Components in fragrance mix I and fragrance mix II.

Formaldehyde

Formaldehyde is ubiquitous. It is a colorless gas that can be found in the workplace as well as in cosmetics, medications, textiles, paints, cigarette smoke, paper and formaldehyde resins (e.g. plastic bottles)[25]. Formaldehyde can cause several different forms of reactions, ICD being the most common[26]. ACD, contact urticaria and mucous membrane irritation, especially of the conjunctiva and respiratory tract, can also be seen. Formaldehyde is in the air, as it is released in cigarette smoke and automobile exhaust.

Today, formaldehyde is rarely used in personal care products or cosmetics. However, allergy to formaldehyde is commonly seen in association with other formaldehyde-releasing preservatives, such as quaternium-15, imidazolidinyl urea, diazolidinyl urea, DMDM hydantoin, 2-bromo-2-nitropropane-1,3-diol and tris(hydroxymethyl) nitromethane, and therefore formaldehyde-sensitive individuals should generally avoid these substances[25].

Textile dermatitis can be caused by formaldehyde resins, because the latter are used as a finish on "wash-and-wear" or wrinkle-resistant clothes. Of the various textiles, 100% polyester is believed to have the least amount of formaldehyde[13,26]. A study of many fabrics showed that some free formaldehyde was present in all of those tested[13]. Washing clothes, especially those that are "permanent press" or "drip dry", several times prior to wearing will decrease the amount of formaldehyde present but will not eliminate it.

Another occult source of formaldehyde is "formaldehyde-free" products that are packaged in containers coated with a formaldehyde outer resin. Studies have demonstrated that formaldehyde can be released from these containers into the product[27].

As formaldehyde is so widespread, avoidance is often difficult. As a result, the positive patch test can be difficult to manage and clinical relevance should be determined.

Quaternium-15

Quaternium-15 is a quaternium compound that is used as a preservative. It is an effective biocide against *Pseudomonas aeruginosa* and *P. cepacia*, as well as other bacteria and fungi. Although quaternium-15 is used in several industries, the incidence of associated occupational contact dermatitis is very low[25,28]. Quaternium-15 more typically plays a role as an allergen in personal care products such as shampoos, moisturizers, conditioners and soaps. Quaternium-15 is the most common cosmetic preservative to cause ACD[13]. Its allergenicity could be due to its release of formaldehyde[28,29]. Studies have shown that up to 80% of those reacting to quaternium-15 are also formaldehyde-sensitive[30–32]. Allergy to quaternium-15 is often relevant to the patient's dermatitis[30,31].

In addition to coexisting with formaldehyde sensitivity, allergy to quaternium-15 can be seen in association with other formaldehyde-releasing preservatives, such as imidazolidinyl urea, diazolidinyl urea, 2-bromo-2-nitropropane-1,3-diol, DMDM hydantoin and tris(hydroxymethyl)nitromethane[13,25,28]. Avoidance of quaternium-15 is possible through careful label reading. If the individual allergic to quaternium-15 is not allergic to the other formaldehyde-releasing preservatives mentioned above, they need only avoid quaternium-15. Obviously, avoidance of the other formaldehyde-releasing preservatives may be necessary depending on the patch test results. Quaternium-15, formaldehyde, diazolidinyl urea and imidazolidinyl urea are in the TRUE Test® series. However, other formaldehyde-releasing preservatives may be missed if expanded patch testing beyond the TRUE Test® is not performed (see Table 14.3). As a group, the quaternium amino compounds are infrequent sensitizers and the other quaternium compounds can be safely used in those allergic to quaternium-15[25].

Neomycin Sulfate

Neomycin is an antibiotic that is used topically rather than orally because it has poor gastrointestinal absorption. It is the most commonly used topical antibiotic and is the most common sensitizer among the topical antibiotics[13].

Neomycin is found in many over-the-counter preparations, including antibacterial ointments, hemorrhoid creams, and otic and ophthalmic preparations (Fig. 14.17). It is frequently used in conjunction with other antibacterial agents, such as bacitracin and polymyxin, as well as with topical corticosteroids. Co-reactivity is commonly seen with neomycin and bacitracin. These antibiotics are not chemically related and therefore this reaction is believed to be co-sensitization, as the chemicals are so frequently used together (e.g. Neosporin®)[13].

Bacitracin

Bacitracin is a topical antibiotic with activity against Gram-positive bacteria and spirochetes. It is used in topical antibacterial creams as well as in otic and ophthalmic preparations. Bacitracin is commonly used in combination with other topical antibiotics and corticosteroids.

Fig. 14.17 Allergic contact dermatitis to neomycin. Note the erythema and edema of the upper eyelids.

It is frequently used in combination with neomycin, and although the two antibacterial agents are chemically unrelated, they often show co-reactivity. This is believed to be due to sensitization to both, as they are so frequently used in combination[33,34]. In addition to ACD, bacitracin rarely causes anaphylaxis and/or contact urticaria[35,36].

Cobalt

Cobalt is a metal that is often used in association with other metals to add hardness and strength. It is frequently combined with nickel, chromium, molybdenum and tungsten. This may be the cause of the frequent finding of sensitization to cobalt in combination with sensitization to either nickel or chromium. Approximately 80% of individuals with a cobalt sensitivity have a co-sensitivity to chromate (more common in men) or nickel (more common in women)[13].

Exposure to cobalt is typically through a metal, e.g. in jewelry, snaps, buttons and tools. However, it is also found in cosmetics, hair dyes, joint replacements, ceramics and enamel, as well as in cement, paints and resins[13]. Exposure can come from hobbies such as pottery making and occupations such as bricklaying.

When patch testing to cobalt, one may see a particular reaction, described as "poral", that appears as erythematous to violaceous dots. This is not an allergic reaction but is believed to result from the allergen residing in the acrosyringia[37].

Methyldibromoglutaronitrile/Phenoxyethanol

Methyldibromoglutaronitrile is a preservative that can be found alone or in combination with phenoxyethanol. It is used in both leave-on and rinse-off products. In Europe, this chemical has been banned due to reports of a significant risk of ACD. As the same level of allergic reactions has not been identified in the US and the number of positive reactions has remained relatively stable over the past several years, it is still present in personal care products in the US.

p-Phenylenediamine

Paraphenylenediamine (PPD) is the most commonly used permanent hair colorant and it is recognized as a common cause of ACD. Once fully oxidized, the disperse dye is no longer allergenic, but in reality the chemical is not always fully oxidized. More recently, PPD has been found in temporary tattoos in concentrations higher than those present in hair color products. As a result, PPD has resurfaced as an allergen in a new population.

Thimerosal

Thiosalicylic acid and ethylmercuric chloride are the two components that are combined to form thimerosal – sodium ethylmercurithiosalicylate – a preservative that is used in a few products. It is believed that the most likely cause of sensitization to thimerosal comes from its use as a preservative in vaccines[38,39]. Reports of sensitivity to ethylmercuric chloride and thiosalicylic acid have been published and both compounds have been found to be capable of inducing a delayed hypersensitivity reaction[38,40,41].

Many positive reactions to thimerosal are found on patch testing. Clinical relevance may be found in patients who use otic or ophthalmic drops. However, positive reactions often lack identifiable clinical relevance, and some argue that although positive reactions are common, clinical relevance is low and therefore routine testing to this allergen should be reconsidered[42]. Currently, thimerosal is in neither the NACDG Screening Series nor the European Standard Series (see Table 14.3), but is still an allergen in the TRUE Test®.

Gold

Worldwide rates of positive gold reactions vary, and with routine testing they range from 0.78% to 10%[43–45]. In one NACDG series, 90% of gold-allergic patients were women, and there appeared to be a higher rate of nickel (33.5%) and cobalt allergies (18%) in patients with gold allergy than in the general population (14% and 9%, respectively)[15]. Similar findings have been reported in other studies[45].

When relevant, the most common clinical presentation is that of a hand, facial or eyelid dermatitis[15,43]. One of the difficulties with gold patch testing is that the relevance of positive reactions is usually difficult to determine[15,43–45]. Gold sodium thiosulfate is not included

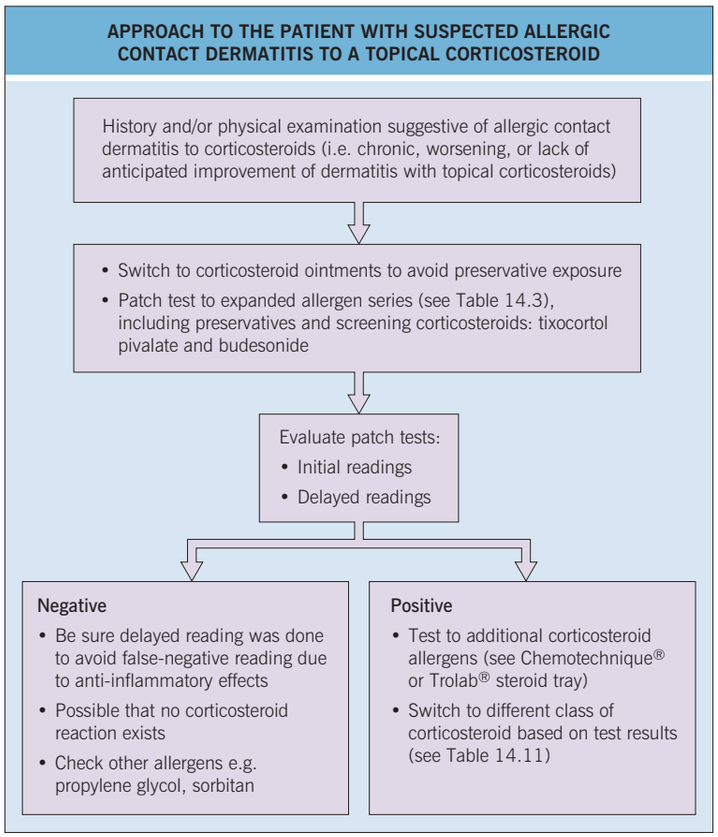


Fig. 14.18 Approach to the patient with suspected allergic contact dermatitis to a topical corticosteroid.

in the NACDG Screening Series, the European Standard Series or the TRUE Test®, with patch testing to gold done only in selected situations[14].

Corticosteroids

Corticosteroids are administered in many different forms: topical, oral, intravenous, intralesional, inhalational and intra-articular. They are anti-inflammatory agents and have been shown to cause ACD in 0.2–6% of patients[46,47]. Four classes of corticosteroids have been identified based primarily on chemical structure (Table 14.11). It is suspected that ACD to these agents may be underdiagnosed, either because of insufficient testing to the allergens or perhaps owing to incomplete testing, as a second reading is necessary given the anti-inflammatory nature of these compounds[46,48,49]. Clinical scenarios that should raise the question of a possible allergy to topical corticosteroids include chronic dermatitis, failure to clear with topical corticosteroids, and exacerbation of dermatitis after use of topical corticosteroids. This should lead to a consideration of patch testing.

Tixocortol-21-pivalate and budesonide are believed to be adequate screening agents for this problem (see Table 14.11), with 91.3% of corticosteroid allergic reactions detected with these allergens in one study[47]. Adding other corticosteroid allergens, such as hydrocortisone-17-butyrate, will increase the yield. It may be prudent to screen with tixocortol-21-pivalate and budesonide and then test to a broader corticosteroid tray if either of these two allergens is positive. Positive patch test reactions to corticosteroids are often unexpected results in routine testing, but are usually relevant. They are often seen with other positive reactions. Figure 14.18 may help direct the clinician in approaching the patient suspected of having an ACD to topical corticosteroids.

In addition to the anti-inflammatory nature of corticosteroids complicating patch test interpretation, an edge effect has also been observed. During the first reading, there may be erythema only at the rim of the test chamber, with a clear center that may later become involved. This is believed to be due to the anti-inflammatory effect of corticosteroids. In the center, the corticosteroid may be concentrated, inhibiting a reaction, but be less concentrated at the rim, where a reaction may occur more readily[50].

CORTICOSTEROID CLASSES AND PATCH TEST CONCENTRATIONS

Drug	Concentration (%)**
CLASS A: HYDROCORTISONE AND TIXOCORTOL TYPE	
Cortisone	
Cortisone acetate	25
Hydrocortisone[*†]	2.5 ethanol (1, 2, 5, 10, 25, ethanol or petrolatum)
Hydrocortisone acetate*	25
Methylprednisolone	
Methylprednisolone acetate	10
Prednisolone	5 (10)
Prednisolone acetate	5
Tixocortol pivalate[†]	0.1
CLASS B: TRIAMCINOLONE ACETONIDE TYPE	
Triamcinolone acetonide[†]	1
Triamcinolone alcohol	
Halcinonide	1
Flucinonide	1
Flucinolone acetonide[†]	0.5 (0.05, 1, 5, 10)
Desonide	0.05
Budesonide[†]	0.01
Amcinonide	0.5
CLASS C: BETAMETHASONE TYPE	
Betamethasone	
Betamethasone–disodium phosphate	1
Desoximetasone	1
Dexamethasone	
Dexamethasone–disodium phosphate	1
Fluocortolone	
CLASS D: HYDROCORTISONE-17-BUTYRATE AND CLOBETASONE-17-BUTYRATE TYPE	
D1	
Alclometasone dipropionate	1
Betamethasone dipropionate	5
Betamethasone-17-valerate	1
Clobetasone butyrate	0.5
Clobetasol propionate	1
Fluocortolone hexanoate	1
Fluocortolone pivalate	1
Mometasone furoate	1 alcohol
D2	
Hydrocortisone butyrate[†]	1 alcohol
Hydrocortisone valerate	1
Prednicarbate	

*Available without prescription in the US.
†Suggested screening agents (in italics); all but hydrocortisone are in the NACDG screening series.
**In petrolatum unless stated otherwise. Parentheses contain additional suggested concentrations or vehicles.

Table 14.11 Corticosteroid classes and patch test concentrations.

TEXTILE DERMATITIS

Textile dye dermatitis often goes undetected because of low suspicion and a lack of routine testing with screening allergens. The allergens most likely to cause textile dermatitis are not the synthetic or natural fibers from which the textiles are made, but rather the dyes used to color them and the resins (e.g. ethyleneurea/melamine formaldehyde

Fig. 14.19 Systemic contact dermatitis. This patient, who was previously sensitized to ethylenediamine, received intravenous aminophylline.

EXAMPLES OF TOPICAL ALLERGENS THAT MAY RESULT IN SYSTEMIC CONTACT DERMATITIS AFTER SYSTEMIC EXPOSURE	
Cutaneous allergen	**Systemic exposure**
Ethylenediamine hydrochloride	Aminophylline, hydroxyzine/cetirizine
Poison ivy	Cashews, mangoes
Fragrance (balsam of Peru)	Foods (tomatoes, citrus), sodas, mouthwashes, spices
Sorbic acid	Preservative in food
Nickel and other metal salts	Nickel (and other metal salts) in food, nickel from catheter hub
Quinolones	Oral antibiotics
Ampicillin	Surgical solution
Neomycin	Streptomycin, kanamycin
Thiuram	Disulfiram (Antabuse®)

Table 14.12 Examples of topical allergens that may result in systemic contact dermatitis after systemic exposure.

resin, dimethylol dihydroxyethyleneurea) used to make clothes less likely to wrinkle or shrink[51,52]. Textile dermatitis typically occurs in areas where clothing fits more tightly, and it is more common in women[51]. Dyes, particularly disperse blue dyes 106 and 124, have been found to be a common cause of textile dermatitis and can be used as screening agents[51]. They frequently cross-react and positive patch test reactions can be delayed up to 7–10 days[51]. Although p-phenylenediamine is a disperse dye, it is not a good screening allergen for textile dye dermatitis[51]. Screening with an individual's garment can also produce a relevant positive patch test reaction.

SYSTEMIC CONTACT DERMATITIS

Systemic exposure to a chemical may result in a diffuse dermatitis. This reaction generally involves a chemical to which the patient has had a prior contact allergy; the patient is then exposed to the same chemical (or one that cross-reacts) via a systemic route, such as an injection or oral, intravenous or intranasal administration. This reaction is believed to be due to a delayed T-cell-mediated immune response. Historically, one of the most common examples of systemic contact dermatitis was the patient with a history of ACD to ethylenediamine who then developed a diffuse dermatitis secondary to intravenous aminophylline, which contains ethylenediamine (Fig. 14.19).

Other causes of systemic contact dermatitis due to ingestion of allergens that have previously caused an ACD include antibiotics, plants/plant products, propylene glycol, sorbic acid and metals[53–59]. Marks et al.[53] reported the ingestion of cashews tainted with oil from the cashew nut shell resulting in a systemic contact dermatitis in patients with a prior history of poison ivy dermatitis. In addition, ingestion of a pesto sauce made with cashew nuts resulted in systemic contact dermatitis in the form of the "baboon syndrome" (symmetric, sharply demarcated erythema of the gluteal or inguinal area plus other intertriginous or flexural sites)[54]. Ingestion of both cashews and mangoes has been shown to cause reactions in patients sensitive to poison ivy and poison oak, as they are all members of the Anacardiaceae family (see Ch. 17).

In the proper clinical setting, patch tests demonstrating a sensitivity to balsam of Peru or fragrance mixture can support the diagnosis of a systemic contact dermatitis due to balsam-related foods or spices. A diet avoiding such foods or spices may result in an improvement of the dermatitis[60]. The ingestion of metals can also cause systemic contact dermatitis, and nickel is the metal most commonly implicated[61]. However, the use of low-nickel diets to treat dermatitis in patients with positive patch tests to nickel is controversial. Of note, Fowler[61] reported a patient with systemic contact dermatitis following ingestion of chromium picolinate, a nutritional supplement. Patch testing was positive to potassium dichromate, and upon discontinuation of the chromium picolinate, the dermatitis subsided.

Examples of other cutaneous allergens and their common sources of systemic exposure are listed in Table 14.12. An extensive chapter on this subject is in *Fisher's Contact Dermatitis* textbook[55] and the reader is referred there for additional information.

Fig. 14.20 Airborne contact dermatitis. Note the significant involvement of the eyelids. *Courtesy, Joyce Rico, MD.*

AIRBORNE CONTACT DERMATITIS

Allergens that are airborne can come in contact with the skin and result in several different reactions, including ACD and ICD. Photoallergic contact dermatitis, phototoxic contact dermatitis, and phototoxicity or photoallergy secondary to systemic medications are reactions that can clinically resemble airborne contact dermatitis (see Fig. 87.16). Ragweed dermatitis, a good example of an airborne contact dermatitis, is most noticeable on the face[62]. Prolonged and repetitive exposure to airborne allergens generally produces an ACD that is lichenified and dry and is predominantly located in the exposed portions of the skin: face, eyelids, V of the neck, arms and legs (Fig. 14.20)[63]. The most common causative agents are plants, especially Compositae allergen, natural resins, woods, plastics, rubbers, glues, metals, pharmaceutical chemicals, insecticides and pesticides[64].

Airborne ACD has been associated with a wide range of allergens, from common allergens such as plants (see above) to more obscure causes such as essential oils volatilized during aromatherapy, preservatives in paints, and thyme dust in farmers, to name but a few[64–67]. Occupationally induced reactions appear to be the most common cause of airborne contact dermatitis. Dermatoses in exposed areas should raise the possibility of a possible airborne contact allergy, leading to a series of questions regarding possible exposure sources and to appropriate patch testing when indicated.

APPENDIX			
Company	**Supplies**	**Company**	**Supplies**
Allerderm Laboratories 3400 E. McDowell Road Phoenix, AZ 85008–7899, USA Tel: 1–800–365–6868; 1–800–878–3837 Fax: 1–800–926–4568 Email: info@allerderm.com Website: *www.allerderm.com; www.truetest.com*	T.R.U.E. Test® Finn chambers Scanpor® tape Nickel spot test (dimethylglyoxime) Cobalt spot test	Smart Practice Canada 2175 29th Street NE, Unit 90 Calgary, Alberta TIY 7H8 Canada Tel: 866-903-2671 Fax: 866-903-2672 Email: info@allergeaze.com Website: *www.allergeaze.com*	AllergEAZE allergens and chambers NACDG Screening Series European Standard Series Specific allergen panels
Chemotechnique Diagnostics Modemgatan 9 S-235 39 Vellinge Sweden Tel: 46–40–46 60 77 Fax: 46–40–46 67 00 E-mail: info@chemotechnique.se Website: *www.chemotechnique.se*	NACDG Screening Series (listed under National Series) European Standard Series Specific allergen panels, e.g. hairdressing, bakery, dental, plant, shoe, cosmetic, corticosteroid, leg ulcer, photopatch series IQ chambers	Almirall Hermal GmbH Scholtzstrasse 3 21465 Reinbek Germany Tel: 49-40-727-04-0 Fax: 49-40-722-92-96 E-mail: info@hermal.de Website: *www.almirall.de/al/en/*	European Standard Series Other Trolab® allergen panels
Dormer Laboratories Inc. 91 Kelfield Street, Suite 5 Rexdale, Ontario M9W 5A3 Canada Tel: 416–242–6167 Fax: 877–436–7637 E-mail: info@dormer.com Website: *www.dormer.com*	Chemotechnique® products		

REFERENCES

1. Marks JG Jr, Elsner P, DeLeo VA. Allergy and ICD. In: Contact and Occupational Dermatology, 3rd edn. Philadelphia: Mosby, 2002:3–15.
2. Sulzberger MB, Wise F. The contact or patch test in dermatology. Arch Dermatol Syphilol. 1931;23:519–31.
3. James WD, Rosenthal LE, Brancaccio RR, Marks JG Jr. American Academy of Dermatology Patch Testing Survey: use and effectiveness of this procedure. J Am Acad Dermatol. 1992;26:991–4.
4. Nethercott JR, Holness DL, Adams RM, et al. Patch testing with a routine screening tray in North America, 1985 through 1989: II. Gender and response. Am J Contact Dermatitis. 1991;2:130–4.
5. De Groot AC, Coenraads P. Twenty-five years quaternium-15 in the European baseline series: does it deserve its place there? Contact Dermatitis. 2010:62:210–20.
6. Cohen DE, Brancaccio R, Andersen D, Belsito DV. Utility of a standard allergen series alone in the evaluation of ACD: a retrospective study of 732 patients. J Am Acad Dermatol. 1997;36:914–18.
7. Zug KA, Warshaw EM, Fowler JF, et al. Patch test results of the North American Contact Dermatitis Group 2005–2006. Dermatitis. 2009;20:266–318.
8. Sherertz EF, Swartz SM. Is the screening patch test tray still worth using? J Am Acad Dermatol. 1993;29: 1057–8.
9. deGroot AC. Patch Testing: Test Concentrations and Vehicles for 4350 Chemicals, 3rd edn. The Netherlands: Acdegroot Publishing, 2008.
10. Adams RM, Fisher T. Diagnostic patch testing. In: Adams RM (ed). Occupational Skin Disease. Philadelphia: Saunders, 1999:221–35.
11. Bruze M. Seasonal influence on routine patch test results. Contact Dermatitis. 1986;14:184.
12. Condie MW, Adams RM. Influence of oral prednisone on patch-test reactions to Rhus antigen. Arch Dermatol. 1973;107:540–3.
13. Marks JG Jr, Elsner P, DeLeo VA. Standard allergens. In: Contact and Occupational Dermatology, 3rd edn. Philadelphia: Mosby, 2002:139.
14. Zug KA, Warshaw EM, Fowler JF, et al. Patch-test results of the North American Contact Dermatitis Group 2005–2006. Dermatitis. 2009;20:149–60.
15. Fowler J Jr, Taylor J, Storrs F, et al. Gold allergy in North America. Am J Contact Dermatitis. 2001;12:3–5.
16. Larsson-Stymne B, Widstrom L. Ear piercing: a cause of nickel allergy in schoolgirls? Contact Dermatitis. 1985;13:289–93.
17. van Joost T, van Everdingen JJ. Sensitization to cobalt associated with nickel allergy: clinical and statistical studies. Acta Derm Venereol. 1982;62:525–9.

17a. Vemula PD, Anderson RR, Karp JM. Nanoparticles reduce nickel allergy by capturing metal ions. Nature Nanotechnol. 2011;6:291–5.

18. Guin JD. Balsam of Peru. In: Practical Contact Dermatitis. New York: McGraw-Hill, 1995:265–70.
19. Marks JG Jr, Elsner P, DeLeo VA. Cosmetics and fragrances. In: Contact and Occupational Dermatology, 3rd edn. Philadelphia: Mosby, 2002:172–200.
20. Adams RM, Maibach HI. A five-year study of cosmetic reactions. J Am Acad Dermatol. 1985;13:1062–9.
21. Larsen WG. How to test for fragrance allergy. Cutis. 2000;65:39–41.
22. deGroot AC, van der Kley AM, Bruynzeel DP, et al. Frequency of false-negative reactions to the fragrance mix. Contact Dermatitis. 1993;28:139–40.
23. Larsen WG. Perfume dermatitis. J Am Acad Dermatol. 1985;12:1–9.

23a. Heisterberg MV, Andersen KE, Avnstorp C, et al. Fragrance mix II in the baseline series contributes significantly to detection of fragrance allergy. Contact Dermatitis. 2010;63:270–6.

24. Scheinman PL. The foul side of fragrance-free products: what every clinician should know about managing patients with fragrance allergy. J Am Acad Dermatol. 1999;41:1020–4.
25. Rietschel RL, Fowler JF. Preservatives and vehicles in cosmetics and toiletries. In: Fisher's Contact Dermatitis. 6th edn. Ontario: BC Decker, 2007:266–318.
26. Feinman SE. Formaldehyde. In: Guin JD (ed). Practical Contact Dermatitis. Philadelphia: McGraw-Hill, 1995;195–210.
27. Tegner E, Fregert S. Contamination of cosmetics with formaldehyde from tubes. Contact Dermatitis Newslett. 1973;13:353.
28. Fransway AF. Quaternium-15. In: Guin JD (ed). Practical Contact Dermatitis. New York: McGraw-Hill, 1995:223–32.
29. Beyer KH, Bergfeld WF, Bernot WO. Final report on the safety assessment of quaternium-15. J Am Coll Toxicol. 1986;5:61–101.
30. Ford GP, Beck MH. Reactions to quaternium-15, Bronopol, and Germall 115 in a standard series. Contact Dermatitis. 1986;14:271–4.
31. Parker LU, Taylor JS. A 5-year study of contact allergy to quaternium-15. Am J Contact Dermatitis. 1991; 2:231–4.
32. Fisher AA. Cosmetic dermatitis. Part II: Reactions to some commonly used preservatives. Cutis. 1980;26:136–7, 141–2, 147–8.
33. Bjorkner B, Moller H. Bacitracin: a cutaneous allergen and histamine liberator. Acta Derm Venereol. 1973;53:487–92.
34. Katz BE, Fisher AA. Bacitracin: a unique topical antibiotic sensitizer. J Am Acad Dermatol. 1987;17:1016–24.
35. Comaish JS, Cunliffe WJ. Absorption of drugs from varicose ulcers: a cause of anaphylaxis. Br J Clin Pract. 1967;21:97–8.
36. Roupe G, Strannegard O. Anaphylactic shock elicited by topical administration of bacitracin. Arch Dermatol. 1969;100:450–2.
37. Storrs FJ, White CR Jr. False-positive 'poral' cobalt patch test reactions reside in the eccrine acrosyringium. Cutis. 2000;65:49–53.
38. Osawa J, Kitamura K, Ikezawa Z, Nakajima H. A probable role for vaccines containing thimerosal in thimerosal hypersensitivity. Contact Dermatitis. 1991;24:178–82.
39. Cox NH, Forsyth A. Thimerosal allergy and vaccination reactions. Contact Dermatitis. 1988;18:229–33.
40. Gruvberger B, Bruze M. Contact allergens – what's new? Preservatives. Clin Dermatol. 1997;15:493–7.
41. Wantke F, Demmer CM, Gotz M, Jarisch R. Contact dermatitis from thimerosal. Contact Dermatitis. 1994;30:115–17.
42. Moller H. All these positive tests to thimerosal. Contact Dermatitis. 1994;31:209–13.
43. Bruze M, Edman B, Bjorkner B, Moller H. Clinical relevance of contact allergy to gold sodium thiosulfate. J Am Acad Dermatol. 1994;31:579–83.
44. Leow YH, Ng SK, Goh CL. A preliminary study of gold sensitization in Singapore. Contact Dermatitis. 1998;38:169–70.
45. Silva R, Pereira F, Bordalo O, et al. Contact allergy to gold sodium thiosulfate. Contact Dermatitis. 1997;37: 78–81.
46. Cohen DE, Brancaccio R. What is new in clinical research in contact dermatitis. Dermatol Clin. 1997;15:137–48.
47. Boffa MJ, Wilkinson SM, Beck HM. Screening for corticosteroid contact hypersensitivity. Contact Dermatitis. 1995;33:149–51.
48. Lauerma AI, Reitamo D, Forstrom L. Allergy to corticosteroids. In Guin JD (ed). Practical Contact Dermatitis. New York: McGraw-Hill, 1995:573–83.
49. Marks J, Elsner P, DeLeo VA. Medicaments. In: Marks JG, Elsner P, DeLeo VA (eds). Contact and Occupational Dermatology. Philadelphia: Mosby, 2002:201–16.

50. Bjarnason B, Flosadottir E, Fischer T. Reactivity at edges of corticosteroid patch tests may be an indicator of a strong positive test response. Dermatology. 1999;199:130–4.
51. Pratt M, Taraska V. Disperse blue dyes 106 and 124 are common causes of textile dermatitis and should serve as screening allergens for this condition. Am J Contact Dermatitis. 2000;11:30–41.
52. Lazarov A, Trattner A, David M, Inger A. Textile dermatitis in Israel: a retrospective study. Am J Contact Dermatitis. 2000;11:26–9.
53. Marks J, DeMelfi T, McCarthy MA. Dermatitis from cashew nuts. J Am Acad Dermatol. 1984;10:627–31.
54. Hamilton TK, Zug KA. Systemic contact dermatitis to raw cashew nuts in a pesto sauce. Am J Contact Dermatitis. 1998;9:51–4.
55. Rietschel RL, Fowler JF. Systemic contact-type dermatitis. In: Fisher's Contact Dermatitis. 6th edn. Ontario: BC Decker Inc, 2007:110–24.
56. Fisher A. Systemic contact dermatitis due to intravenous Valium in a person sensitive to propylene glycol. Cutis. 1995;55:327–8.
57. Silvestre JF, Alfonso R, Moragon M, et al. Systemic contact dermatitis due to norfloxacin with a positive patch test to quinoline mix. Contact Dermatitis. 1998;39:83.
58. Kiec-Swierczynska M, Kreicisz B, Fabicka B. Systemic contact dermatitis from implanted disulfiram. Contact Dermatitis. 2000;43:246–7.
59. Raison-Peyron N, Meynadier JM, Meynadier J. Sorbic acid: an unusual cause of systemic contact dermatitis in an infant. Contact Dermatitis. 2000;43:247–8.
60. Salam TN, Fowler JF. Balsam-related systemic contact dermatitis. J Am Acad Dermatol. 2001;45: 377–81.
61. Fowler JF. Systemic contact dermatitis caused by oral chromium picolinate. Cutis. 2000;65:116.
62. Rietschel RL, Fowler JF. Regional contact dermatitis. In: Fisher's Contact Dermatitis. 6th edn. Ontario: BC Decker Inc, 2007:66–87.
63. Rietschel RL, Fowler JF. Noneczematous contact dermatitis. In: Fisher's Contact Dermatitis. 6th edn. Ontario: BC Decker Inc, 2007:88–109.
64. Huygens S, Goossens A. An update on airborne contact dermatitis. Contact Dermatitis. 2001;44:1–6.
65. Schaller M, Korting HC. Allergic airborne contact dermatitis from essential oils used in aromatherapy. Clin Exp Dermatol. 1995;20:143–5.
66. Bohn S, Niederer M, Brehm K, Bircher AJ. Airborne contact dermatitis from methylchloroisothiazolinone in wall paint. Abolition of symptoms by chemical allergen inactivation. Contact Dermatitis. 2000; 42:196–201.
67. Spiewak R, Skorska C, Dutkiewicz J. Occupational airborne contact dermatitis caused by thyme dust. Contact Dermatitis. 2001:44:235–9.

Irritant Contact Dermatitis 15

David E Cohen and Aieska de Souza

Synonyms: ■ Irritant reaction ■ Irritant dermatitis ■ Irritant dermatitis syndrome ■ Irritant contact dermatitis syndrome ■ Toxic contact dermatitis ■ "Housewife's eczema" ■ "Chemical burn"

Key features

- Irritant contact dermatitis (ICD) is a localized, non-immunologically initiated, cutaneous inflammatory reaction. Its clinical characteristics are polymorphous, and they include erythema, scaling, edema, vesiculation and erosions in acute cases, and erythema, lichenification, hyperkeratosis and fissures in chronic cases
- ICD results from a direct cytotoxic effect due to single or repeated application of a chemical substance or physical insult to a cutaneous site
- ICD is a frequent disorder and represents an important spectrum of diseases in both general and occupational dermatology, occurring when the normal epidermal barrier is disrupted and secondary inflammation develops
- Despite different pathogeneses, allergic contact dermatitis and ICD have similar clinical appearances, especially their chronic variants
- ICD is a multifactorial syndrome determined by the properties of the irritating substance as well as host and environmental factors; a dose–response relationship is related to exposure parameters such as concentration, pH, temperature, occlusion, repetition and duration of contact
- Strong or absolute irritants such as strong acids and alkalis, as well as oxidants, produce erythema, edema, vesicles that may coalesce into bullae, oozing, and, in severe cases, necrosis and ulceration. The latter is vernacularly termed a "chemical burn"
- The clinical features of chronic ICD from repeated exposure to low-grade or marginal irritants (such as soaps, solvents, cleansers) include erythema, lichenification, excoriations, scaling and fissures

INTRODUCTION

There are two major forms of contact dermatitis: irritant and allergic. Irritant contact dermatitis (ICD) is a cutaneous inflammatory disorder resulting from activation of the innate immune system by direct cytotoxic effect of a chemical or physical agent, whereas allergic contact dermatitis is a delayed-type hypersensitivity immune reaction mediated by hapten-specific T cells[1].

Occupational contact dermatitis is a matter of public health importance[1], contributing to combined direct and indirect annual costs in the US of up to $1 billion when accounting for medical costs, workers' compensation, and lost time from work[2–4]. Overall, the impact of occupational skin diseases for both society and the individual is formidable in light of both prevalence and economic factors.

HISTORY

One of the earliest documented irritant skin reactions is in the writings of Celsus around 100 AD, when he described skin ulceration resulting from corrosive metals[5]. Little attention was then paid to the skin problems incurred by tradesmen for several centuries. The first accounts of occupational skin diseases focused on ill health among miners, and in 1556, Georg Agricola detailed the deep ulcers observed among metal workers. Eleven years later in 1567, Paracelsus discussed the etiology, pathogenesis and therapy of skin changes caused by salt compounds. In 1700, Bernardino Ramazzini of Modena published a clear and detailed historic treatise on the diseases of tradespeople, where he described skin disorders incurred by bath attendants, bakers, gilders, midwives, millers and miners[5]. Physicians began to more widely recognize occupational irritant dermatitis during the Industrial Revolution with the development of new materials and chemicals, both natural and synthetic, for both industrial and household use[6]. Germany and France were the first to enact laws compensating workers for industrial skin diseases. Early prospective studies of ICD in 1919 involved experimentation with the irritant mustard gas dichloroethylsulfide[7].

EPIDEMIOLOGY

ICD is the most common form of occupational skin disease, estimated to constitute between 70% and 80% of all occupational skin disorders. Data from the North American Contact Dermatitis Group indicate that in groups of patients with contact dermatitis, ICD (as a primary diagnosis) accounts for 9–10% of those screened for allergic contact dermatitis via patch testing, and when hands are affected, ICD predominates over all other causes of contact dermatitis[8,9].

The US Bureau of Labor Statistics data show that occupational skin diseases accounted for a consistent 30% to 45% of all patients with occupational illnesses from the 1970s through the mid-1980s. However, occupational skin disease rates have fallen dramatically (e.g. from an average rate of 16.2 events/10 000 full-time workers in 1972 to 3.7 events in 2007), and in 2007, skin disease accounted for only 17% of all recorded non-fatal occupational illnesses. In addition to a decline in the rates of disease, the raw reported cases of occupational skin disease decreased from 89 400 in 1974 to 35 300 in 2007, with work in the areas of natural resources (e.g. agriculture, forestry, fishing, mining), manufacturing, education/health services, leisure/hospitality and construction accounting for the highest rates of non-fatal occupational skin diseases[10]. Nonetheless, because of limitations in the Bureau of Labor Statistics annual survey of approximately 250 000 US employers, it has been estimated that the number of actual occupational skin disease cases may be of the order of 10–50 times higher than that reported by the Bureau. The incidence of occupational contact dermatitis in several other countries is similar to that in the US, with a range of 50 to 70 cases per 100 000 workers per year[11]. In 1996, the United Kingdom created a voluntary reporting system that combined information from the EPIDERM study with the occupational physicians' reporting activity (OPRA). The annual incidence of occupational contact dermatitis reported by dermatologists was 0.9 per 10 000 workers, and for occupational physicians, it was 3.1 per 10 000 workers[1,12]. Rubber chemicals, soaps and cleansers, wet work, resins, acrylics and nickel were the most common sources for contact dermatitis (Table 15.1), and high-risk occupations included workers in the petrochemical, rubber, plastic, metal and automotive industries[1,12].

Clinical manifestations of ICD are determined by the properties of the irritating substance as well as host and environmental factors. These include concentration, pH, mechanical pressure, temperature, humidity, and duration of contact. Low ambient humidity and cold are important factors in decreasing the water content of the stratum corneum and, consequently, increasing the permeability to irritants such as soaps, detergents and solvents. Cold alone may also reduce the

CAUSES OF OCCUPATIONAL CONTACT DERMATOSES IN THE UNITED KINGDOM (1996–2001)		
Exposure	**Contact dermatitis Number of cases (%)**	**Contact urticaria Number of cases (%)**
Rubber chemicals and materials	377 (12)	78 (51)
Wet work	297 (10)	9 (6)
Soaps and cleansers	235 (8)	5 (3)
Nickel	188 (6)	6 (4)
Resins and acrylics	160 (5)	5 (3)
Chromium and chromates	114 (4)	1 (1)
Foods and flour	112 (4)	16 (10)
Petroleum products	104 (3)	1 (1)
Preservatives	100 (3)	1 (1)
Aromatics amines (*p*-phenylenediamine)	98 (3)	0
Cutting oils and coolants	86 (3)	0
Hairdressing chemicals	82 (3)	1 (1)
Fragrances and cosmetics	79 (3)	3 (2)
Colophony and flux	79 (3)	2 (1)
Solvents and alcohols	77 (3)	1 (1)
Aldehydes	66 (2)	10 (6)
Cobalt and compounds	55 (2)	1 (1)
Bleaches and sterilizers	43 (1)	0
Cement, plaster and masonry work	41 (1)	4 (3)
Glues and paints	34 (1)	0
Acids and caustics	9 (<1)	0
Other agents	633 (21)	12 (8)
Total	3068 (100)	154 (100)

Table 15.1 Causes of occupational contact dermatoses in the United Kingdom (1996–2001), as reported by dermatologists. There was a total of 3068 cases of contact dermatitis and 154 cases of contact urticaria; patients could have more than one cause. Adapted from ref. 12.

Fig. 15.1 Bilateral irritant contact dermatitis of the feet and ankles due to chronic occlusive footwear.

IRRITANTS AND MECHANISMS OF TOXICITY	
Irritant	**Mechanisms of toxicity**
Detergents	Barrier disruption Protein denaturation Membrane toxicity
Acids	Protein denaturation Cytotoxicity
Alkalis	Barrier lipid denaturation Cytotoxicity through cellular swelling
Oils	Disorganization of barrier lipids
Organic solvents	Solubilization of membrane lipids Membrane toxicity
Oxidants	Cytotoxicity
Reducing agents	Keratolysis
Water	If barrier is disrupted, cytotoxicity through swelling of viable epidermal cells

Table 15.2 Irritants and mechanisms of toxicity.

plasticity of the horny layer, with consequent cracking of the stratum corneum. However, in one study, the application of cold had a protective effect on the development of ICD if applied during the provocative exposure, in this case to sodium lauryl sulfate[13]. Occlusion, excessive humidity and maceration increase the water content of the stratum corneum, with consequent enhanced percutaneous absorption of water-soluble substances (Fig. 15.1). In addition, irritated skin may become more susceptible to superimposed allergic sensitization.

Important predisposing characteristics of the individual include age, sex, pre-existing skin disease, anatomic region exposed, and sebaceous activity. There are age-associated changes in the skin that can alter the skin's response to irritants. Both infants and the elderly are more often affected by ICD because of their less robust epidermal barrier, and they also develop more severe symptoms. While skin irritation may be seen more often on the upper extremities of women than men, this higher prevalence of ICD may be due to increased frequency of exposure rather than inherent gender differences. Genetic factors also play a role in the development of ICD, as shown in studies with monozygotic twins[14]. Patients with a history of atopic dermatitis have a 13.5 times greater risk of developing occupational dermatitis[15], and a reduction in epidermal filaggrin can reduce the inflammatory threshold for irritants[16]. Lastly, the most commonly affected sites are exposed areas such as the hands and the face, with hand involvement seen in approximately 80% of patients and facial involvement in 10%[11]. Excessive exposure to water, soaps and detergents, common causes of ICD, obviously play a role.

PATHOGENESIS

Although the cellular mechanisms of ICD remain unknown, increasing evidence suggests that activated keratinocytes act as signal transducers in controlling the host homeostatic responses to exogenous stimuli and serve as the key immunoregulators. While other mediators such as prostaglandins, leukotrienes and neuropeptides may possibly play a role, cytokines carry the most interest in ICD as they are the central mediators in T-cell inflammation.

Several mechanisms have been commonly associated with ICD, including denaturation of epidermal keratins, disruption of the permeability barrier (see Ch. 124), damage to cell membranes, and direct cytotoxic effects, with different mechanisms at work with different irritants (Table 15.2). The mechanisms involved in the acute and chronic phases of ICD are fundamentally different. Acute reactions involve direct cytotoxic damage to keratinocytes, while repeated exposures to solvents and surfactants cause slower damage to cell membranes by removal of surface lipids and water-retaining substances.

The pathogenic pathway in the acute phase of ICD, common to many chemically unrelated irritants, begins by penetration through the permeability barrier, mild damage to keratinocytes, and the release of mediators of inflammation with resultant T-cell activation. In this manner, once activation is initiated via epidermal cells, continuous T-cell activation independent of the exogenous antigen may be maintained. Tumor necrosis factor-α (TNF-α) and interleukin (IL)-1α are the major mediators, and they are capable of inducing production of other

cytokines, chemokines and adhesion molecules, leading to leukocyte recruitment to the site. Specifically, TNF-α, IL-6 and IL-1β upregulate expression of intercellular adhesion molecule-1 (ICAM-1)[17]. This is a predominant feature of ICD. In addition, IL-1 receptor antagonist (IL-1RA) and IL-8 increase substantially after exposure to the common irritant sodium lauryl sulfate.

In the chronic phase of ICD, the role of the stratum corneum as a barrier is disrupted. Damage to the stratum corneum lipids (which mediate barrier function) is associated with loss of cohesion of corneocytes, desquamation, and an increase in transepidermal water loss. Transepidermal water loss is one of the triggering stimuli that promote lipid synthesis, keratinocyte proliferation and transient hyperkeratosis during the restoration of the cutaneous barrier. However, damage with a solvent can disrupt this protective mechanism by occlusion and blockage of water evaporation, thus halting lipid synthesis and barrier recovery. After chronic exposure, the result is increased epidermal turnover manifested clinically by the chronic eczematoid irritant reaction[18].

CLINICAL FEATURES

Several different types of ICD have been described[19] (see below). Consequences of the myriad forms of ICD range from postinflammatory pigmentary changes to poorly healing ulcers (Table 15.3).

Acute Irritant Contact Dermatitis

Acute ICD, commonly seen with occupational accidents, develops when the skin is exposed to a potent irritant. The irritant reaction reaches its peak quickly, usually within minutes to hours after exposure, and then starts to heal. This is termed the decrescendo phenomenon. Symptoms of acute ICD include burning, stinging and soreness of the directly affected sites. Physical signs include erythema, edema, bullae and possibly necrosis. These lesions are restricted to the area where the irritant or toxicant damaged the tissue, with sharply demarcated borders and asymmetry pointing to an exogenous cause. If there is no dermal injury, there should be no permanent scarring[20]. The potent irritants that most frequently lead to ICD are acids and alkaline solutions, resulting in chemical burns.

Acute Delayed Irritant Contact Dermatitis

Acute delayed ICD is a retarded inflammatory response characteristic of certain irritants, such as anthralin (dithranol), benzalkonium chloride (preservative/disinfectant) and ethylene oxide. Adverse reactions to these chemicals are considered idiosyncratic, except when they are applied to previously injured skin (sites of xerosis or atopic dermatitis)[20]. Clinically, visible inflammation is not seen until 8 to 24 hours (or more) after exposure, and thus may mimic allergic contact dermatitis; however, the associated symptom is more frequently burning rather than pruritus. Sensitivity to touch and water is elicited. This form of ICD is commonly seen during diagnostic patch testing.

Irritant Reaction Irritant Contact Dermatitis

Irritant reaction ICD is a type of subclinical irritant dermatitis in individuals exposed to wet chemical environments, such as hairdressers, caterers or metal workers. It is characterized by one or more of the following signs: scaling, redness, vesicles, pustules and erosions, often beginning under occlusive jewelry (e.g. rings) and then spreading onto the fingers and then the hands and the forearms. It may simulate dyshidrotic dermatitis and ultimately result in cumulative ICD if exposure is prolonged; however, ICD tends to resolve if exposure is discontinued.

Cumulative Irritant Contact Dermatitis

Cumulative ICD is a consequence of multiple sub-threshold skin insults, without sufficient time between them for complete restoration of skin barrier function. It may be due to a variety of stimuli or frequent repetition of one factor (i.e. exposure to water both at the work place and at home). Clinical symptoms develop only after the cumulative damage exceeds an individually determined manifestation or elicitation threshold, which may decrease with progression of the disease. Weak irritants do not lead to clinical ICD if they are encountered far enough apart to allow for restoration of skin barrier function. However, if the same irritant exposures follow each other closely in time, or when the manifestation threshold is reduced (e.g. in a patient with active atopic dermatitis), cumulative ICD can develop. The properties of the irritating substance (e.g. pH, solubility, detergent action, physical state) are also important. In contrast to acute ICD, the lesions of chronic ICD are less sharply demarcated. Pruritus and pain due to fissures of hyperkeratotic skin are symptoms of chronic ICD. Signs may include xerosis, erythema and vesicles, but lichenification and hyperkeratosis predominate.

CLINICAL FEATURES SUGGESTING AN IRRITANT OR TOXIC ETIOLOGY

Clinical feature	Possible irritant or toxin
Ulcerations	Inorganic acids (chromic, hydrofluoric, nitric, hydrochloric, sulfuric) Strong alkalis (calcium oxide, sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, sodium metasilicate, sodium silicate, potassium cyanide, trisodium phosphate, sodium carbonate, potassium carbonate) Salts (arsenic trioxide, dichromates) Solvents (acrylonitrile, carbon bisulfide) Gases (ethylene oxide, acrylonitrile)
Folliculitis	Arsenic trioxide Glass fibers Oils and greases Tar Asphalt Chlorinated naphthalenes Polyhalogenated biphenyls
Miliaria	Occlusive clothing and overheating Adhesive tape Ultraviolet radiation Infrared radiation Aluminum chloride
Pigmentary changes	
• Hyperpigmentation	Any irritant or allergen, especially phototoxic agents such as psoralens, tar, asphalt, psoralen-containing plants Metals, such as inorganic arsenic (systemically), silver, gold, bismuth, mercury Radiation: ultraviolet, infrared, microwave, ionizing
• Hypopigmentation	*p*-Tert-amylphenol *p*-Tert-butylphenol Hydroquinone Monobenzyl ether of hydroquinone Monomethyl ether of hydroquinone *p*-Tert-catechol *p*-Cresol 3-Hydroxyanisole Butylated hydroxyanisole 1-Tert-butyl-3, 4-catechol 1-Isopropyl-3, 4-catechol 4-Hydroxypropriophenone
Alopecia	Borax Chloroprene dimers
Urticaria	Animals (arthropods, caterpillars, corals, jellyfish, moths, sea anemones) Balsam of Peru Cosmetics (e.g. sorbic acid) Drugs (alcohol [ethanol], benzocaine, camphor, capsaicin, chloroform, iodine, methyl salicylate, resorcinol, tar extracts) Foods (cayenne pepper, fish, mustard, thyme) Fragrances and flavoring agents (cinnamon oil, cinnamic acid and aldehyde, benzaldehyde) Metals (cobalt) Plants (seaweed, stinging nettles), woods Preservatives (benzoic acid) Textiles (e.g. blue dyes)

Table 15.3 Clinical features suggesting an irritant or toxic etiology.

Asteatotic Dermatitis

Asteatotic dermatitis, also referred to as asteatotic eczema or exsiccation eczematid ICD, is a special variant seen primarily during the dry winter months. Elderly individuals who frequently bathe without remoisturizing are at particular risk of developing asteatotic dermatitis. Intense pruritus is common, with the skin appearing dry with ichthyosiform scale and characteristic patches of superficially cracked skin termed "eczema craquelé" (see Ch. 13).

Traumatic Irritant Contact Dermatitis

Traumatic ICD may develop after acute skin trauma, such as from burns, lacerations or acute ICD. Patients should be asked whether they have cleansed the skin with strong soaps or detergents. It is characterized by eczematous lesions, most commonly on the hands, that last for weeks to months with persistent redness, infiltration, scale and fissuring in the affected areas.

Pustular and Acneiform Irritant Contact Dermatitis

Pustular and acneiform ICD results from exposure to certain irritants, such as metals, croton oil, mineral oils, tars, greases, cutting and metal working fluids, and naphthalenes (see Table 15.3 and Ch. 16). This syndrome should be considered in conditions in which folliculitis or acneiform lesions develop in settings outside of typical acne, particularly in patients with atopic dermatitis, seborrheic dermatitis or prior acne vulgaris. The pustules are sterile and transient. Miliarial reactions, which may become pustular, can develop in response to occlusive clothing, adhesive tape, or ultraviolet and infrared radiation.

Non-erythematous Irritant Contact Dermatitis

Non-erythematous ICD may be defined as a subclinical form of ICD with early stages of skin irritation seen as changes in the stratum corneum barrier function without a clinical correlate.

Subjective or Sensory Irritant Contact Dermatitis

Subjective or sensory ICD is characterized by reports of a stinging or burning in the absence of visible cutaneous signs of irritation. Irritants capable of eliciting this reaction include propylene glycol, hydroxy acids, ethanol, and topical medications such as lactic acid, azelaic acid, benzoic acid, benzoyl peroxide, mequinol and tretinoin. Sorbic acid, a preservative in concentrations of up to 0.2% in foods, cosmetics and drugs, may also produce sensory irritation in predisposed individuals. This reaction to irritants such as lactic or sorbic acid may be reliably reproduced with dose responsiveness in double-blinded exposure tests.

Airborne Irritant Contact Dermatitis

Airborne ICD develops in irritant-exposed sensitive skin of the face and periorbital regions. While this often simulates photoallergic reactions, involvement of the upper eyelids, philtrum and submental regions in patients with airborne ICD may aid in distinguishing between these two entities.

Frictional Irritant Contact Dermatitis

Frictional ICD is a distinct ICD subtype resulting from repeated low-grade frictional trauma. It is often acknowledged to also play an adjuvant role in allergic contact dermatitis and ICD. The frictional response involves hyperkeratosis, acanthosis and lichenification, often progressing to hardening, thickening and increased toughness.

Contact Urticaria

Contact urticaria is divided into non-immunologic and immunologic subtypes (see Ch. 16), with the former occurring more frequently and in the absence of previous exposure. Irritants that can produce *immunologic* contact urticaria include parabens (preservatives), henna, ammonium persulfate (oxidizing agent), and latex. *Non-immunologic* contact urticaria can be caused by a number of exposures, from caterpillars and jellyfish to stinging nettles and foods (see Table 15.3)[21]. Risk factors include atopy, hand dermatitis, previous mucosal exposure to latex (e.g. urinary catheterization), and allergies to fruits (e.g. kiwi, avocado, banana, melon; see Table 16.6).

PATHOLOGY

The histologic features of ICD vary, but often include mild spongiosis, necrosis of epidermal keratinocytes, and an inflammatory infiltrate. The combination of an upper dermal perivascular infiltrate of lymphocytes with minimal extension of inflammatory cells into the overlying epidermis and widely scattered necrotic keratinocytes is most typical. True features of interface dermatitis are absent, and spongiosis should be focal or absent. Over time, additional histologic findings include acanthosis with mild hypergranulosis and hyperkeratosis. In aggregate, these elements are not specific, and they cannot be confidently differentiated from either chronic allergic contact dermatitis or other types of chronic eczematous dermatoses.

Classification of Irritant Chemicals

Acids

A variety of both inorganic and organic acids can be corrosive to the skin. Acids cause epidermal damage via protein denaturation and cytotoxicity. Principally, all strong acids give the same symptoms and major features, including erythema, vesication and necrosis.

Inorganic acids are commonly used in industry, especially hydrofluoric, sulfuric, hydrochloric, chromic, nitric and phosphoric acids (Table 15.4). Hydrofluoric acid and sulfuric acid cause the most severe burns, even at low concentrations[24,25].

In general, the organic acids tend to be less irritating. Among the organic acids, acetic, acrylic, formic, glycolic, benzoic and salicylic acids are the most common irritants, particularly after prolonged exposure. The uses and properties of *acrylic acid* and *formic acid* are outlined in Table 15.4. *Acetic acid* is a constituent of vinegar, flavoring agents and astringent mouthwashes, whereas *glycolic*, *benzoic* and *salicylic acids* are mild irritants whose properties can be harnessed for therapeutic and cosmetic purposes, when used in low concentrations.

Alkalis

Alkalis or bases often cause more painful and severe damage than most acids, with the exception of hydrofluoric acid. There are generally no vesicles, but rather necrotic skin that first appears dark brown, then black, and ultimately becomes hard, dry and cracked. Alkalis disrupt barrier lipids and denature proteins with subsequent fatty acid saponification, thus subjecting the cell to edema and resultant cytotoxicity. The emulsifying effect of soaps formed in the process facilitates the further penetration of the alkali into the deeper layers of the skin. Strong alkalis include sodium, ammonium, calcium and potassium hydroxide; sodium and potassium carbonate; and calcium oxide, used primarily in the manufacture of bleaches, dyes, vitamins, pulp, paper, plastics, and soaps and detergents[26,27]. Calcium hydroxide is liberated from wet cement, which has an initial pH of 10–12 that rises to 12–14 as the cement sets (see Table 15.4).

Metal salts

A wide variety of metal salts can cause irritation, ranging from folliculitis and pigmentary changes to ulceration (see Table 15.4).

Solvents

A wide variety of solvents are used daily in processes such as chemical reactions, hydraulic systems, metal refining, dry cleaning and metal degreasing. Nearly all of them are primary irritants to varying degrees (see Table 15.4), with only a few, such as turpentine, also being able to elicit allergic sensitization. Solvents act mainly by dissolving the intercellular lipid barrier of the epidermis, thereby increasing percutaneous penetration. Prolonged skin contact can result in severe burns as well as systemic symptoms and even death, making early recognition of skin manifestations important in the prevention of systemic toxicity. After repeated exposure, the hands, and occasionally the hands and face, develop erythema, scaling and dryness, eventually evolving into eczema (Fig. 15.2). The irritating capacity of organic solvents, attributed mainly

IRRITANT CHEMICALS: USES, PROPERTIES AND SIDE EFFECTS		
Compound	**Uses/Exposures**	**Properties and side effects**
	INORGANIC ACIDS	
Chromic acid	• Metal treatments (chrome plating, copper stripping and aluminum anodizing)	• Ulcerations known as "chrome holes" • Nasal septal perforation
Hydrochloric acid	• Production of fertilizers, dyes, paints and soaps • Electroplating, oil refining and food processing	• Erythema, vesication and necrosis
Hydrofluoric acid	• Semiconductor industry (etching glass, metal and stone; can dissolve silicon) • Household and commercial rust, stain and lime-scale removers	• Extremely cytotoxic agent that can lead to severe tissue damage • Penetrates intact skin due to its limited dissociation constant • Painful penetration may continue for days after exposure • With low concentrations, the onset of symptoms may be delayed for up to a day • Intense pain is due to the capacity of fluoride ions to bind tissue calcium, thereby affecting nerve conduction • Hypomagnesemia and a fluoride-mediated increase in pulmonary vascular resistance may also play a role in toxicity
Nitric acid	• Production of fertilizers and explosives; metal etching and cleaning • Fuming nitric acid – a chemical intermediate used in rocket fuels and as a laboratory reagent	• Chemical burns • Irritant contact dermatitis • Distinctive yellow discoloration • Fuming nitric acid – highly corrosive
Phosphoric acid	• Phosphate fertilizer, pharmaceuticals, water treatment, animal feeds, soaps and detergents, and cotton dyeing	• Erythema, vesication and necrosis
Sulfuric acid	• Manufacture of fertilizers, inorganic pigments, textile fibers, explosives, pulp and paper • Occupational risk: jewelers, electroplaters, metal cleaners and storage battery makers	• Erythema, vesication and necrosis
	ORGANIC ACIDS	
Acrylic acid	• Monomer for acrylic plastics, synthetic resins, dentures, artificial nails, adhesives and paints	• Highly irritating and corrosive • Capable of penetrating rubber gloves • Also allergic contact dermatitis
Formic acid	• Neutralizer in leather manufacture, an antiseptic in brewing, and a coagulant in the production of natural latex	• Greatest corrosive potential of the organic acids
	ALKALIS	
Cement (mixed with water)	• Construction	• Acute ulcerative damage as a result of the high alkalinity of wet cement (due to liberation of calcium hydroxide) • Necrotic skin changes appear 8–12 hours after exposure • Chronic irritant cement dermatitis – develops over months to years from continued exposure; can accompany allergic contact dermatitis to chromium • Most common locations – lower limbs (kneeling, contaminated footwear), hands (glove contamination)
	METAL SALTS	
Arsenic compounds (including arsenic trioxide)	• Aerosolized during the smelting of copper, gold, lead and other metals • Manufacture of pesticides and herbicides • Semiconductor industry and smelting operations	• Persistent folliculitis • Potential for systemic toxicity (see Ch. 88)
Beryllium	• Production of hard, corrosion-resistant alloys	• Ulcerated granulomatous skin lesions (local reaction; see Ch. 94) • Sarcoidosis-like granulomas of the skin and lung (systemic reaction)
Calcium oxide (quicklime)	• Manufacture of pulp, steel and paper	• Releases heat on contact with water, causing painful cutaneous ulcerations
Cobalt salts	• Alloys, ceramics, electroplating, electronics, magnets, paints, varnishes and hair dyes	• Irritant and allergic contact dermatitis
Copper salts (e.g. sulfates, oxides and cyanides)	• Used as a biostatic surface and in wood preservatives and fungicides	• Impart a greenish-black color to hair, skin and teeth if persistent exposure to dust forms • Inhalation of copper oxides (as well as magnesium and zinc oxides) can cause metal fume fever, a brief influenza-like illness usually associated with welding operations

Table 15.4 Irritant chemicals: uses, properties and side effects. Glycols/alcohols and detergents/cleansers are discussed in the text.

Continued

IRRITANT CHEMICALS: USES, PROPERTIES AND SIDE EFFECTS		
Compound	**Uses/Exposures**	**Properties and side effects**
Mercury, inorganic	• Products containing inorganic mercury have been banned since 1990; limited exposure possible from old cans of latex paint	• Bluish linear pigmentation of the tongue and gums, which may serve as a marker for systemic mercury poisoning
Mercury, organic	• Phenyl mercury salts are used as preservatives in cosmetics and vaccines, as fungicides, herbicides and pesticides in agriculture, and in dental restorative materials	• Although once used as skin disinfectants, both irritant and allergic contact dermatitis have restricted use • Positive patch tests to mercury (as well as other metals such as gold) observed in patients with oral lichenoid reactions to dental materials (see Ch. 11) • Mercury within the amalgam may act as an irritant via a Koebner phenomenon
Selenium compounds (including sulfide)	• Therapeutic shampoo (selenium sulfide)	• Skin irritation, conjunctivitis
Thimerosal	• Topical medicaments, vaccines, cosmetics	• Common cause of both allergic and irritant patch-test reactions[22,23]
	SOLVENTS	
Benzene	• Manufacture of polymers, plastics, resins, adhesives, rubber, lubricants, dyes, detergents, drugs, explosives and pesticides	• Petechial eruption of the trunk, extremities and mucous membranes • Petechiae considered to be a marker for aplastic anemia
Chlorinated hydrocarbons (e.g. carbon tetrachloride, trichloroethylene, tetrachloroethane, methylene chloride, ethylene chloride)	• Production of vinyl chloride, which is then converted to polyvinyl chloride • Pesticides • Dry cleaning	• Cutaneous irritation • Systemic effects: liver and kidney damage, CNS depression, and carcinogenesis • Methylene chloride can hydrolyze to form hydrochloric acid, thus leading to significant cutaneous irritation (see above) • "Degreaser's flush" – sudden erythema in extensive areas of the face, neck and shoulders; caused by alcohol ingestion shortly before or during inhalation of trichloroethylene
Coal tar derivatives (e.g. toluene, xylene, ethyl benzene, cumene)	• Medications • Solvents	• Skin drying and defatting • Exposure solely to vapors can cause xerosis
Petrochemicals (e.g. gasoline, hexane, kerosene, Stoddard solvent)	• Fuels • Insecticides • Dry cleaning • Hexanes – gasoline, glues and for extraction of cooking oils from seeds	• Irritant contact dermatitis • Absorption of hexane via inhalation or percutaneously can also cause paresthesias, hypoesthesia and motor weakness
	DISINFECTANTS	
Aldehydes (e.g. formaldehyde, glutaraldehyde, hexa-methylenetetramine)	• Adhesives, resins • Disinfectants, biocides • Tissue fixative, embalming agent	• More irritating than alcohols • Formaldehyde – high chemical reactivity with proteins; both allergen and irritant, even at low concentrations
Ethylene oxide	• Sterilization of medical equipment	• Oxidizing agent • Severe chemical burns
Halogens – Chlorines	• Disinfectants, including wounds* • Bleach (sodium hypochlorite)	• Denature proteins via deaminating or chlorinating amino acids • Oxidizing agent (sodium hypochlorite) • Acute skin and mucosal irritant reactions, particularly at high temperatures
Halogens – Iodines	• Broad-spectrum antimicrobial and sporicidal agents • Surgical scrub, shampoo and skin cleanser (povidone-iodine in a surfactant base)	• Inhibit DNA, RNA and protein synthesis • Irritant contact dermatitis • Contact urticaria
Phenolic compounds (e.g. Lysol® [cresol and soap solution], pentachlorophenol, chloroxylenol)	• Disinfectants • Preservative in over-the-counter products (baby powders, shampoos), especially chloroxylenol	• Irritant contact dermatitis • Chemical leukoderma (amyl- and butyl-phenol compounds; see Table 15.3)
Quaternary ammonium salts (e.g. benzalkonium chloride)	• Cosmetics, medications (e.g. ophthalmic solutions) • Antiseptics (e.g. cleaning surgical instruments) • Detergent	• Cationic surfactants that can precipitate or denature proteins and destroy microorganisms • Local skin irritation depends on the solution concentration • Benzalkonium chloride – irritant reactions frequent during patch testing (concentration, 0.1%); can also be an allergen (e.g. healthcare workers, leg ulcer patients) so clinical correlation required
*Dakin's solution contains sodium hypochlorite and EUSOL (Edinburgh solution of lime) contains chlorinated lime and boric acid.		

Table 15.4 Irritant chemicals: uses, properties and side effects (cont'd). Glycols/alcohols and detergents/cleansers are discussed in the text.

Fig. 15.2 Bilateral irritant contact dermatitis of the palms secondary to repeated contact with paint solvents. Extensive patch testing excluded allergic contact dermatitis in this professional paint and crayon illustrator. *Courtesy, Kalman Watsky, MD.*

Fig. 15.3 Moderately severe irritant contact dermatitis of the hands due to chronic exposure to disinfecting solutions and antiseptics. The results of patch testing, latex challenge testing, and RAST testing were negative in this practicing dentist.

to their lipophilicity, follows the order: aromatic > aliphatic > chlorinated > turpentine > alcohols > esters > ketones[28].

Alcohols/Glycols

Alcohols are used widely as solvents, disinfectants, preservatives in cosmetics, and penetration enhancers in drug delivery systems. Most have only mild irritating effects, with irritancy decreasing (and bactericidal activity increasing) as the molecular weight and length of the carbon side chain increases[29]. Alcohols are the safest known topical antiseptic compounds, providing bactericidal activity against most Gram-positive and Gram-negative bacteria as well as many fungi and viruses. Most appropriate for this use are diluted solutions of ethyl alcohol, propyl alcohol and isopropyl alcohol, which act by means of protein denaturation. In cosmetics, alcohol is used as a preservative to prevent microbial contamination and to decrease viscosity. The principal mechanism by which alcohols enhance percutaneous absorption is hypothesized to be the extraction of intercellular lipids from the stratum corneum[30,31].

Glycols, or diols, such as ethylene glycol and propylene glycol, are aliphatic alcohols commonly used in cosmetic products as solvents, emulsifiers, humectants or keratolytics. Propylene glycol can produce both allergic and irritant contact dermatitis and sources of exposure include personal care products, topical corticosteroids and other topical medications[32]. Of note, propylene glycol is typically used in cosmetics in concentrations less than 50%[33].

Detergents and cleansers

A detergent includes almost any surface-active agent (surfactant) that concentrates at oil–water interfaces and holds both cleansing and emulsifying properties. Detergents most commonly cause chronic forms of ICD and are present in skin cleansers, cosmetics and household cleaning products. With normal use, ICD is rare from skin cleansers, the exception being in individuals with susceptible skin. Detergents' cleansing actions are derived from their ability to lower the surface tension between two non-mixable phases due to their hydrophilic (polar head) and lipophilic (apolar tail) components. Skin toxicity arises from their damaging influence on the stratum corneum, which impairs barrier function. Surfactants concomitantly bind to keratin and cause protein denaturation. When the stratum corneum is disrupted, detergents can damage viable epidermis and papillary dermal structures.

Irritancy from detergents is best evaluated by measuring transepidermal water loss since the latter represents the surrogate measurable change indicative of irritancy damage with this group of chemicals. As a group, anionic detergents such as alkyl sulfates and alkyl carboxylate salts (soap) are more irritating than are non-ionic and amphoteric groups. Greater length of the carbon chain also correlates with increased irritant potential. Sodium lauryl sulfate is often used as a reference irritant in studies because of its consistent, non-allergic, rapid toxic response. Amphoteric surfactants such as *cocamidopropyl betaine* – which are used in therapeutic formulations, personal care products and cosmetics – have the lowest irritation potential[34,35].

Cocamide DEA (diethanolamine) is a non-ionic, biodegradable surfactant that is used as a viscosity booster, stabilizer and foam booster. It is found in hand soaps, liquid shampoos, detergents and dishwashing liquids. Cocamide DEA is one of the more irritating surfactants[36], and it is commonly involved in occupation-related contact dermatitis in North American healthcare workers[37]. *Cocamide MEA* (monoethanolamine) is also a surfactant that is used as a foaming or emulsifying agent and is derived from fatty acids present in coconut oils that have been reacted with ethanolamine. Cocamide MEA at a concentration of 50% was found to be non-irritating to mildly irritating in animal tests, in contrast to cocamide DEA 30% which produced moderate irritation. Cocamide MEA can be used in a concentration of up to 10% in leave-on products[38]. Skin cleansers may be solid or liquid, based on soap and/or synthetic detergents, and may contain solvents or abrasives, depending on use requirements (see Ch. 153). Although the primary factor that determines skin irritancy is the detergent component, skin tolerance cannot be adequately predicted from the composition of products alone. Such an assessment is largely left to trial and error.

Disinfectants

Most disinfectants used to destroy pathogens in the environment act as weak toxic agents and cause chronic ICD as a result of cumulative doses of subclinical irritancy (Fig. 15.3). Various compounds may be used, such as alcohols (see above), aldehydes, phenolic compounds, halogenated compounds and quaternary ammonium salts (see Table 15.4), in addition to dyes, oxidizing agents and mercury compounds[39–42].

Dyes of the triphenylmethane family are also extensively used as topical antiseptics; they are capable of producing phototoxic dermatitis but uncommonly cause irritant reactions. Benzoyl peroxide is a common *oxidizing agent* used as an anti-acne antimicrobial topical medication that is capable of causing mild irritation. Most *mercury* compounds are skin irritants by way of precipitation of proteins, but have fallen into disuse as a result of hazards of systemic toxicity.

Plastics

Plastics are synthetic macromolecular end products consisting of large polymers formed by the linkage of small monomers into large chain-like units. A large number of plastic resins are commercially important and they can be divided into three categories:

- thermoplastics – polyacrylates, polyethylene, polystyrene, polyvinyl chloride and saturated polyesters

- thermosettings – epoxy resins, phenol–formaldehyde resins, and polyurethanes
- elastomers – synthetic rubbers.

Skin damage is almost exclusively attributable to the monomer ingredients, hardeners, and other additives such as stabilizers. The final hardened plastic product is generally considered inert and non-hazardous to the skin, but residual non-polymerized monomers may be the offending agents. Both irritant and allergic contact dermatitis are common, and they may only be differentiated by patch testing[43].

Food

Food and food additives often contain compounds that elicit contact sensitivity and irritation, particularly in those working in agriculture, fishing, catering, and food processing industries. Most of the work in these sectors is done without gloves under damp working conditions with frequent hand washing – factors further aggravating skin irritation. Mechanical, thermal and climatic factors also contribute. A large majority of exposed persons in food handling and fishing professions may be affected by chronic irritant hand dermatitis[44]. Slight irritant skin changes are often accepted as "normal" for the patient's occupation and medical advice is often not sought.

Examples of foods that can lead to ICD include pineapples, which contain the proteolytic enzyme bromelain (bromelin; see Ch. 17), and garlic, which contains allicin and diallyl disulfide. Mustard, horseradish, cabbage, broccoli, cauliflower, brussels sprouts and radish contain allyl isothiocyanate, and the latter can cause ICD after exposure to water.

Foods can also lead to contact urticaria (see Table 15.3) and protein contact dermatitis; both of these entities are discussed in detail in Chapter 16.

Water

Water, the universal solvent, is a particularly ubiquitous skin irritant. Wet workers such as hairdressers, hospital cleaners, cannery workers, and bartenders have an increased incidence of hand eczema. Several mechanisms such as osmolarity, pH, hardness and temperature might account for the irritancy of water. Stratum corneum hydration may facilitate penetration of polar and non-polar substances via connections in the lacunar network (see Ch. 124) as well as support the overgrowth of pathogenic organisms. The irritancy of water is often exacerbated by occlusion, as it changes the barrier properties of the stratum corneum and may activate Langerhans cells and trigger cytokine production[45].

Bodily fluids

Urine, feces (especially in the setting of diarrhea) and saliva can lead to ICD. In babies, irritant diaper dermatitis is a common problem and is often characterized by glazed erythema of convex surfaces and at the diaper margins, with sparing of the skin folds; edema, scaling and superficial erosions may be observed (see Fig. 13.12). Incontinence can lead to similar problems in the elderly[46].

Children, more so than adults, develop the habit of lip licking. In these patients, irritant dermatitis may involve the perioral skin as well as the lips (Fig. 15.4). In a series of 75 patients with cheilitis who were referred for patch testing, ICD was the most common cause of cheilitis (Table 15.5)[47,48]. Figure 15.5 outlines the clinical approach to a patient with cheilitis. Periurethral ICD may be seen in patients with bladder-drained pancreatic allografts and in those receiving foscarnet.

DIFFERENTIAL DIAGNOSIS

Despite their different pathogeneses, allergic and irritant contact dermatitis, especially of the chronic type, show a remarkable similarity with respect to clinical appearance, histology and immunohistology. Clinically, the reactions often look identical, with erythema, plaques, xerosis, scaling and lichenification locally distributed and sharp borders delineating the areas of contact. In the clinical setting, the substance in question is often unknown, as is the concentration and duration of exposure. As a result, the diagnosis of ICD has remained a diagnosis of exclusion – when the dermatitis cannot be explained by a positive patch test to a known allergen. Another helpful, but not conclusive, clinical feature is the more frequent complaint of burning and stinging with ICD, in contrast to pruritus in areas of allergic contact dermatitis (Fig. 15.6).

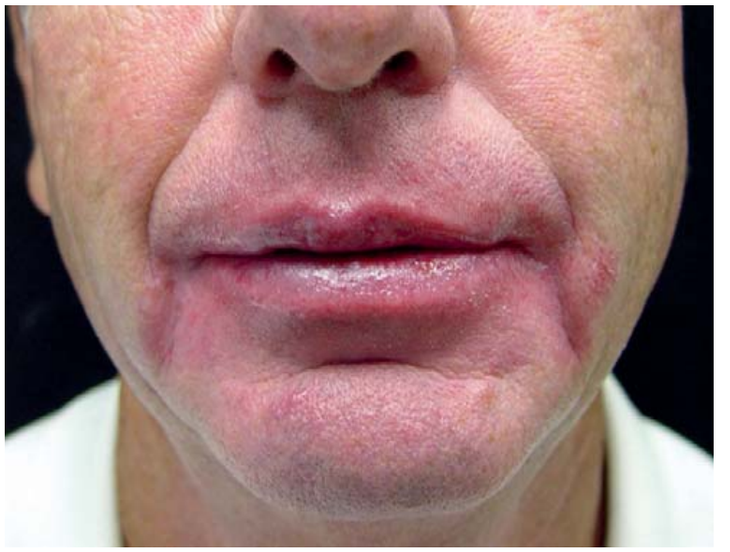


Fig. 15.4 Cheilitis due to irritant contact dermatitis. This patient had the habit of licking his lips and there is involvement of the vermilion and cutaneous lips as well as the perioral region. *Courtesy, Jeffrey P Callen, MD.*

CAUSES OF CHEILITIS IN PATIENTS REFERRED FOR PATCH TESTING	
Irritant contact dermatitis Most frequent cause: lip licking	36%
Allergic contact dermatitis Most common allergens [% of patients in a second series]*: fragrance mix, 30%; *Myroxilon pereirae* (balsam of Peru), 23%; nickel, 22%; gold, 13%; neomycin, 12%; cobalt, 10%; propylene glycol, 8%; lanolin, 7%; cinnamic aldehyde, 7%; bacitracin, 5%; benzophenone, 5%; methyldibromoglutaronitrile/ phenoxyethanol, 5%; tea tree oil, 5%; budesonide, 5%	25%
Atopic dermatitis	19%
Eczema (cause unknown)	9%
Non-eczematous causes (angioedema, photosensitivity, psoriasis, erosive candidal cheilitis, functional)	9%
Seborrheic dermatitis	1%
*See ref. 48.	

Table 15.5 Causes of cheilitis in patients who were referred for patch testing (n = 75). Adapted from ref. 47.

PROGNOSIS

In many individuals, ICD resolves spontaneously even with continuous exposure, a process referred to as "accommodation" or "hardening"[49]. The exact mechanisms are still unclear, but the following changes have been observed after repetitive cutaneous exposure to irritants:

- improvement of the physical barrier via formation of a thicker stratum corneum and a thicker stratum granulosum and increased production of ceramide 1
- increased skin permeability to irritants and changes in vascular reactivity that allow faster removal of irritants
- immunologic alterations that favor an anti-inflammatory response to irritants, e.g. increased ratio of IL-1RA (an anti-inflammatory cytokine) to IL-1α (a proinflammatory cytokine)
- a systemic hyporeactive state following repetitive exposure to low-dose irritants[49].

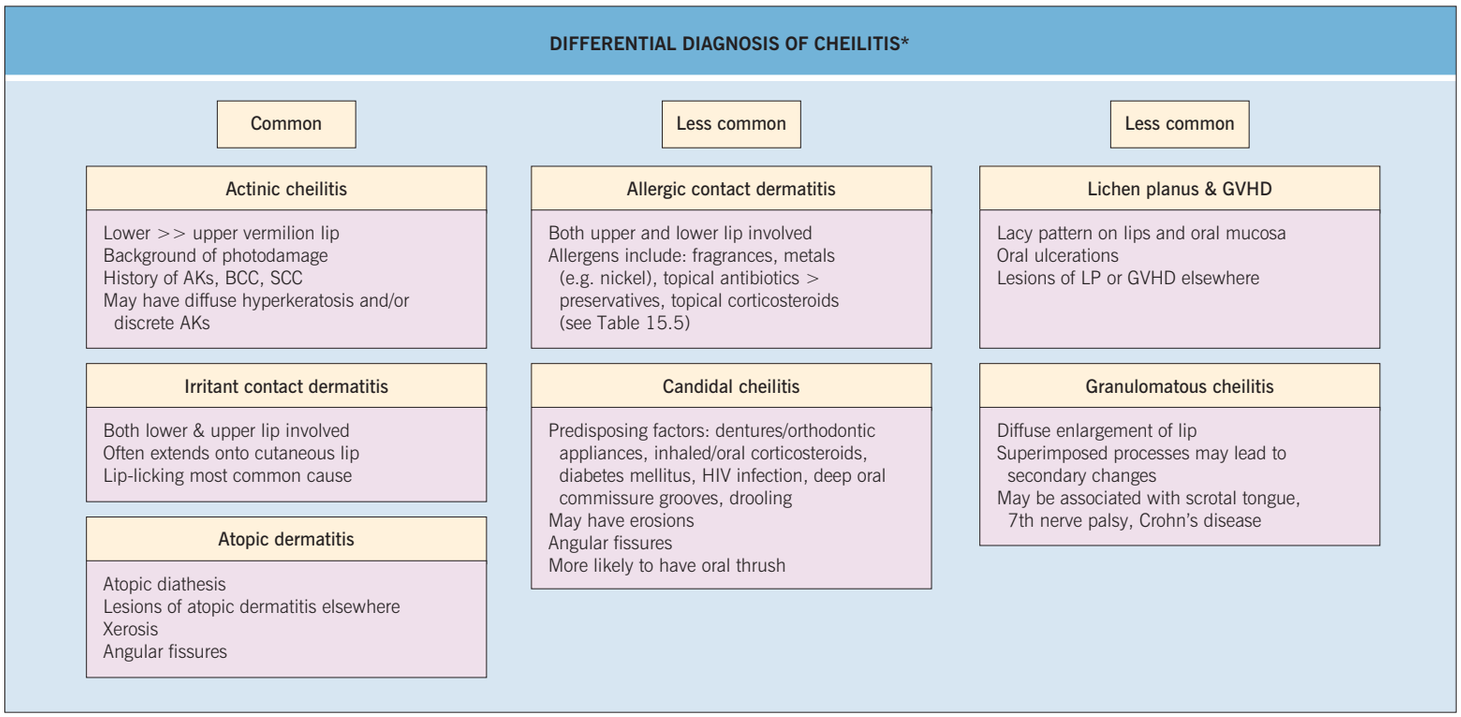


Fig. 15.5 Differential diagnosis of cheilitis. Uncommon causes include cheilitis glandularis, actinic prurigo, lichen sclerosus, and nutritional deficiencies. *Often a combination, e.g. atopic dermatitis plus irritant contact dermatitis. AKs, actinic keratoses; BCC, basal cell carcinoma; GVHD, graft-versus-host disease; LP, lichen planus; SCC, squamous cell carcinoma. *Courtesy, Jean L Bolognia, MD.*

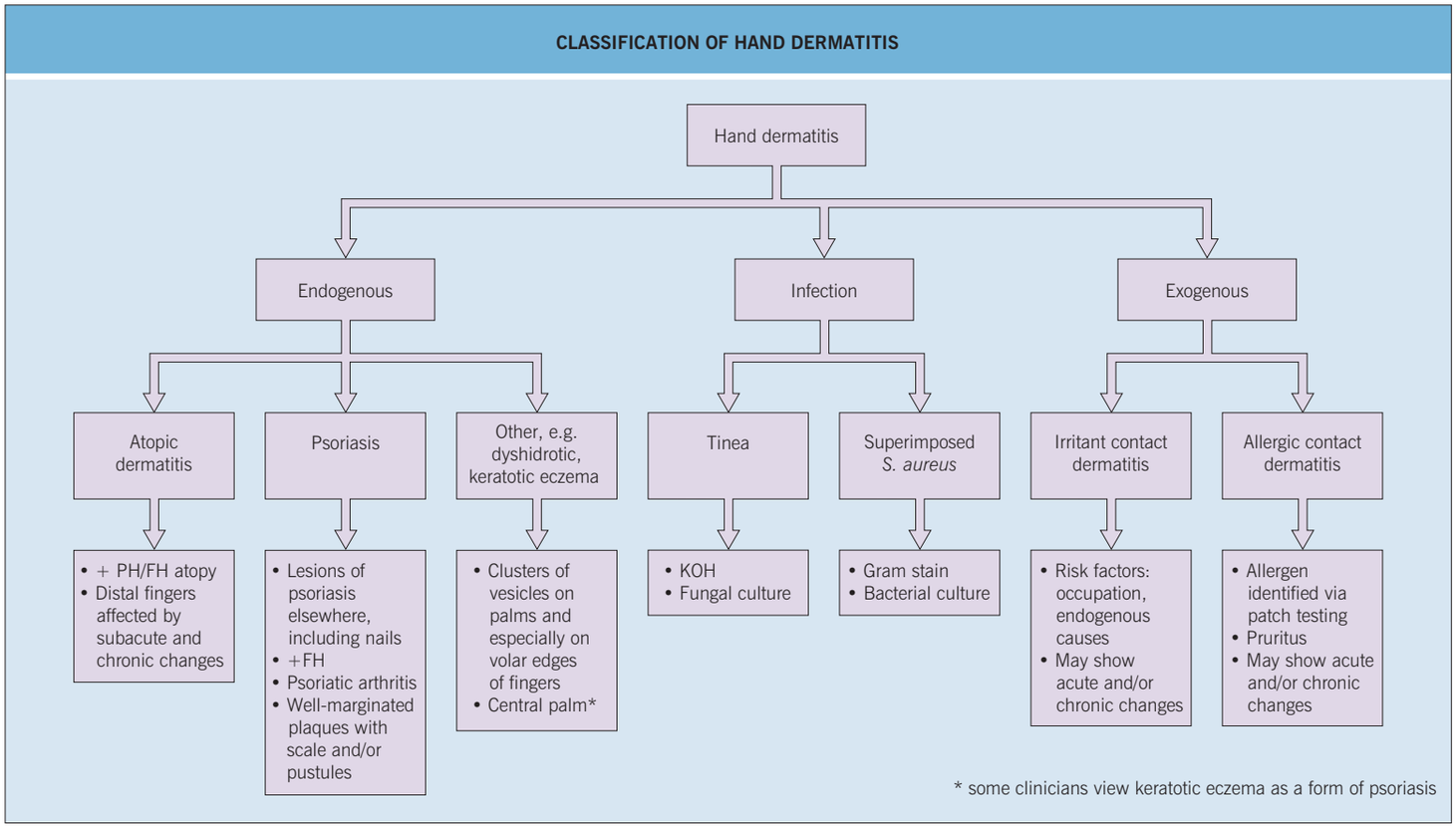


Fig. 15.6 Classification of hand dermatitis. More than one etiology may be present, e.g. atopic dermatitis plus irritant contact dermatitis. For further details, see reference 48a. FH, family history; PH, personal history.

The time required for "accommodating" to the aggravating stimulus varies amongst individuals, and for some individuals, ICD can be a chronic and devastating problem. Poor prognosis is related to a previous history of atopy, female gender, and the presence of allergic contact dermatitis (as well as ICD). Factors that can potentially improve prognosis are early diagnosis, treatment, and patient knowledge about the disease[50].

TREATMENT

Avoidance of causative irritants in the home or the workplace is the primary treatment for ICD. Strategies in the prevention of ICD include the identification of irritants with appropriate substitution, the establishment of engineering controls to reduce exposure, the utilization of personal protective equipment such as gloves and special clothing, and barriers such as ointments, emollients or creams. Other preventive strategies include emphasizing personal and occupational hygiene, establishing educational programs to increase awareness in the workplace, and providing health monitoring.

In the workplace, by far the most effective measure to reduce the incidence of contact dermatitis is technical avoidance. This can be accomplished via shielding and personal protection of the workers and limiting the use of potent irritants to closed or automated systems. Preventive skin care at the workplace incorporates pre-exposure protection by application of protective creams to intact skin, removal of irritants by mild cleaning agents, and enhancement of barrier function generation by emollients or moisturizers[51]. Non-irritating fatty substances such as petrolatum preclude hydrophilic chemical penetration and restore barrier function. The efficacy of barrier creams for skin protection (as compared to bland emollients) remains a topic of debate[52]. In a randomized controlled trial, both barrier creams and moisturizing vehicles were found to positively influence skin status and hydration without significant differences in efficacy[53]. Newer moisturizers containing ceramides can also improve barrier function, but further trials are necessary to ascertain their efficacy[54,55]. Lastly, while new bioengineering techniques have been proposed for the assessment of individual irritant sensitivity, their value in predicting occupational ICD, especially of the cumulative type, remains unclear.

The establishment of appropriate educational prevention programs is essential. A project in Finland showed a significantly better outcome for employees with occupational hand dermatitis attending an "eczema school"-like clinic run by a specialized nurse compared with an unschooled control group[56]. Another study found that most occupational skin diseases responded to effective secondary preventive measures, combining employee medical treatment and exposure analysis-based individual and group training in preventive measures[57]. Education was important in making the employees aware of initial skin changes, such as slight erythema and scaling in the interdigital folds, indicating the need to optimize skin protection and care measures in order to prevent exacerbation and chronicity.

The goal of treatment is to restore normal epidermal barrier function. Topical corticosteroids are frequently used, but their efficacy has been controversial, as experimental studies have provided conflicting results[58]. In one double-blind, vehicle-controlled study, statistically lower values of erythema and transepidermal water loss were observed in sites irritated by sodium lauryl sulfate after 7 days of treatment with betamethasone valerate[59]. Systemic corticosteroids, although potentially helpful in reducing acute inflammation, are not useful in the treatment of chronic ICD unless corrective measures are taken to avoid the offending contactants. Photochemotherapy (PUVA) or narrowband ultraviolet B irradiation may be considered for chronic dermatitis that does not respond to any other form of therapy. Hyperkeratotic palmoplantar dermatitis from frictional or chronic ICD or a combination of dermatitis and psoriasis may benefit from the adjunctive use of systemic retinoids such as acitretin and alitretinoin or systemic immunomodulators such as methotrexate, cyclosporine and possibly targeted (biologic) therapy[60].

REFERENCES

1. Keegel T, Moyle M, Dharmage S, et al. The epidemiology of occupational contact dermatitis (1990–2007): a systematic review. Int J Dermatol. 2009;48:571–8.
2. Mathias CG, Morrison JH. Occupational skin diseases, United States. Results from the Bureau of Labor Statistics Annual Survey of Occupational Injuries and Illnesses, 1973 through 1984. Arch Dermatol. 1988;124:1519–24.
3. American Academy of Dermatology. National Conference on Environmental Hazards to the Skin, Comprehensive Position Statement. 1992.
4. Cohen DE. Occupational dermatoses. In: Harris RL (ed.). Patty's Industrial Hygiene, 5th edn. New York: John Wiley, 2000:165–210.
5. White RP. The Dermatergoses or Occupational Affections of the Skin, 4th edn. London: HK Lewis, 1934.
6. Clayton GD, Clayton FE (eds). Patty's Industrial Hygiene and Toxicology, 4th edn. New York: John Wiley, 1991.
7. Marshall EK, Lynch V, Smith HW. Variations in susceptibility of the skin with dichloroethylsulfide. J Pharmacol Exp Ther. 1919;12:291.
8. Rietschel RL, Mathias CG, Fowler JF Jr, et al; North American Contact Dermatitis Group. Relationship of occupation to contact dermatitis: evaluation in patients tested from 1998 to 2000. Am J Contact Dermat. 2002;13:170–6.
9. Zug KA, Warshaw EM, Fowler JF Jr, et al. Patch-test results of the North American Contact Dermatitis Group 2005–2006. Dermatitis. 2009;20:149–60.
10. Bureau of Labor Statistics. Industry and illness data, 2009. www.bls.gov.
11. Lushniak BD. Occupational skin diseases. Primary Care. 2000;27:895–916.
12. McDonald JC, Beck MH, Chen Y, Cherry NM. Incidence by occupation and industry of work-related skin diseases in the United Kingdom, 1996–2001. Occup Med (Lond). 2006;56:398–405.
13. Fluhr JW, Bornkessel A, Akengin A, et al. Sequential application of cold and sodium lauryl sulphate decreases irritation and barrier disruption in vivo in humans. Br J Dermatol. 2005;152:702–8.
14. Holst R, Moller H. One hundred twin pairs patch tested with primary irritants. Br J Dermatol. 1975;93:145–9.
15. Perry AD, Trafeli JP. Hand dermatitis: review of etiology, diagnosis, and treatment. J Am Board Fam Med. 2009;22:325–30.
16. Scharschmidt TC, Man MQ, Hatano Y, et al. Filaggrin deficiency confers a paracellular barrier abnormality that reduces inflammatory thresholds to irritants and haptens. J Allergy Clin Immunol. 2009;124:496–506.
17. Nosbaum A, Vocanson M, Rozieres A, et al. Allergic and irritant contact dermatitis. Eur J Dermatol. 2009;19: 325–32.
18. Berardesca E, Distante F. Mechanisms of skin irritations. Curr Probl Dermatol. 1995;23:1–8.
19. Iliev D, Elsner P. Clinical irritant contact dermatitis syndromes. Immunol Allergy Clin North Am. 1997;17:365–75.
20. Beltrani VS. Occupational dermatoses. Curr Opin Allergy Clin Immunol. 2003;3:115–23.
21. Lahti A. Non-immunologic contact urticaria. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI (eds). Handbook of Occupational Dermatology. Heidelberg: Springer-Verlag, 2000:221–4.
22. Seidenari S, Giusti F, Pepe P, Mantovani L. Contact sensitization in 1094 children undergoing patch testing over a 7-year period. Pediatr Dermatol. 2005;22:1–5.
23. Pratt MD, Belsito DV, DeLeo VA, et al. North American Contact Dermatitis Group patch-test results, 2001–2002 study period. Dermatitis. 2004;15:176–83.
24. Vance MV. Hydrofluoric acid burns. In: Adams RM (ed.). Occupational Skin Disease, 3rd edn. Philadelphia: WB Saunders, 1999.
25. Dunser MW, Ohlbauer M, Rieder J, et al. Critical care management of major hydrofluoric acid burns: a case report, review of the literature, and recommendations for therapy. Burns. 2004;30:391–8.
26. van der Valk PG, Maibach HI (eds). The Irritant Contact Dermatitis Syndrome. Boca Raton: CRC Press, 1995.
27. Mehta RK, Handfield-Jones S, Bracegirdle J, Hall PN. Cement dermatitis and chemical burns. Clin Exp Dermatol. 2002;27:347–8.
28. Boman AS, Wahlberg JE. Irritants – organic solvents. In: Chew AL, Maibach HI (eds). Irritant Dermatitis. Berlin: Springer-Verlag, 2006:269–77.
29. Sato A, Obata K, Ikeda Y, et al. Evaluation of human skin irritation by carboxylic acids, alcohols, esters and aldehydes, with nitrocellulose-replica method and closed patch testing. Contact Dermatitis. 1996;34:12–6.
30. de Haan P, Meester HM, Bruynzeel DP. Irritancy of alcohols. In: van der Valk PG, Maibach HI (eds). The Irritant Contact Dermatitis Syndrome. Boca Raton: CRC Press, 1995:65–70.
31. Brinkmann I, Muller-Goymann CC. Role of isopropyl myristate, isopropyl alcohol and a combination of both in hydrocortisone permeation across the human stratum corneum. Skin Pharmacol Appl Skin Physiol. 2003;16:393–404.
32. Warshaw EM, Botto NC, Maibach HI, et al. Positive patch-test reactions to propylene glycol: a retrospective cross-sectional analysis from the North American Contact Dermatitis Group, 1996 to 2006. Dermatitis. 2009;20:14–20.
33. Johnson W Jr; Cosmetic Ingredient Review Expert Panel. Final report on the safety assessment of propylene glycol and polypropylene glycols. J Am Coll Toxicol. 1994;13:437–91.
34. Effendy I, Maibach HI. Detergent and skin irritation. Clin Dermatol. 1996;14:15–21.
35. Moreau L, Sasseville D. Allergic contact dermatitis from cocamidopropyl betaine, cocamidoamine, 3-(dimethylamino)propylamine, and oleamidopropyl dimethylamine: co-reactions or cross-reactions? Dermatitis. 2004;15:146–9.
36. Turkoglu M, Sakr A. Evaluation of irritation potential of surfactant mixtures. Int J Cosmet Sci. 1999;21: 371–82.
37. Warshaw EM, Schram SE, Maibach HI, et al. Occupation-related contact dermatitis in North American health care workers referred for patch testing: cross-sectional data, 1998 to 2004. Dermatitis. 2008;19:261–74.
38. Andersen FA. Final report on the safety assessment of cocamide MEA. Int J Toxicol. 1999;18:9–16.
39. Timmer C. Disinfectants. In: van der Valk PG, Maibach HI (eds). The Irritant Contact Dermatitis Syndrome. Boca Raton: CRC Press, 1995:77–94.

40. Basketter DA, Marriott M, Gilmour NJ, White IR. Strong irritants masquerading as skin allergens: the case of benzalkonium chloride. Contact Dermatitis. 2004;50: 213–17.
41. Davis MD, Scalf LA, Yiannias JA, et al. Changing trends and allergens in the patch test standard series: a Mayo Clinic 5-year retrospective review, January 1, 2001, through December 31, 2005. Arch Dermatol. 2008;144: 67–72.
42. Saap L, Fahim S, Arsenault E, et al. Contact sensitivity in patients with leg ulcerations: a North American study. Arch Dermatol. 2004;140:1241–6.
43. Kanerva L, Jolanki R, Alanko K, Estlander T. Patch-test reactions to plastic and glue allergens. Acta Derm Venereol. 1999;79:296–300.
44. Brancaccio RR, Alvarez MS. Contact allergy to food. Dermatol Ther. 2004;17:302–13.
45. Tsai TF, Maibach HI. How irritant is water? An overview. Contact Dermatitis. 1999;41:311–14.
46. Smith WJ, Jacob SE. The role of allergic contact dermatitis in diaper dermatitis. Pediatr Dermatol. 2009;26:369–70.
47. Freeman S, Stephens R. Cheilitis: analysis of 75 cases referred to a contact dermatitis clinic. Am J Contact Dermat. 1999;10:198–200.
48. Zug KA, Kornik R, Belsito DV, et al; North American Contact Dermatitis Group. Patch-testing North American lip dermatitis patients: data from the North American Contact Dermatitis Group, 2001 to 2004. Dermatitis. 2008;19:202–8.
48a. Johansen JD, Hald M, Andersen BL, et al. Classification of hand eczema: clinical and aetiological types. Based on the guideline of the Danish Contact Dermatitis Group. Contact Dermatitis. 2011;65:13-21.
49. Watkins SA, Maibach HI. The hardening phenomenon in irritant contact dermatitis: an interpretative update. Contact Dermatitis. 2009;60:123–30.
50. Cahill J, Keegel T, Nixon R. The prognosis of occupational contact dermatitis in 2004. Contact Dermatitis. 2004;51: 219–26.
51. Wigger-Allberti W, Elsner P. Prevention of irritant contact dermatitis – new aspects. Immunol Allergy Clin North Am. 1997;17:443–50.
52. Korinth G, Geh S, Schaller KH, Drexler H. In vitro evaluation of the efficacy of skin barrier creams and protective gloves on percutaneous absorption of industrial solvents. Int Arch Occup Environ Health. 2003;76:382–6.
53. Berndt U, Wigger-Alberti W, Gabard B, Elsner P. Efficacy of a barrier cream and its vehicle as protective measures against occupational irritant contact dermatitis. Contact Dermatitis. 2000;42:77–80.
54. Anderson PC, Dinulos JG. Are the new moisturizers more effective? Curr Opin Pediatr. 2009;21:486–90.
55. Draelos ZD. An evaluation of prescription device moisturizers. J Cosmet Dermatol. 2009;8:40–3.
56. Kalimo K, Kautiainen H, Niskanen T, Niemi L. "Eczema school" to improve compliance in an occupational dermatology clinic. Contact Dermatitis. 1999;41: 315–19.
57. Bauer A, Kelterer D, Stadeler M, et al. The prevention of occupational hand dermatitis in bakers, confectioners and employees in the catering trades. Preliminary results of a skin prevention program. Contact Dermatitis. 2001;44:85–8.
58. van der Valk PG, Maibach HI. Do topical corticosteroids modulate skin irritation in human beings? Assessment by transepidermal water loss and visual scoring. J Am Acad Dermatol. 1989;21:519–22.
59. Ramsing DW, Agner T. Efficacy of topical corticosteroids on irritant skin reactions. Contact Dermatitis. 1995;32: 293–7.
60. Cohen DE, Heidary N. Treatment of irritant and allergic contact dermatitis. Dermatol Ther. 2004;17:334–40.

This page intentionally left blank

Occupational Dermatoses 16

S Mark Wilkinson

INTRODUCTION

Occupational dermatoses[1] comprise any skin disease in which occupational exposure is a major causal or contributory factor. In all the diverse occupations that people pursue, there are thousands of chemicals and other potentially noxious insults which can impinge on the skin. These may harm the skin in many different ways and induce pathologic processes. When this occurs via occupational exposure, they are referred to as "occupational dermatoses". Traditionally, the types of hazardous exposure are categorized as:

- mechanical – friction, pressure, vibration, mechanical disruption
- chemical – elements and chemical compounds (organic, inorganic and proteins)
- physical – heat, cold, radiation (UV and ionizing)
- biological – organisms including viruses, bacteria, fungi and parasites.

The types of dermatoses induced by exposure to these noxious occupational hazards can be grouped as outlined in Table 16.1.

This chapter differs from many of the others in that it deals with diverse conditions, many of which are also covered in detail in specific chapters.

CLINICAL CLASSIFICATION OF OCCUPATIONAL DERMATOSES
CONTACT DERMATITIS
• Irritant chemically induced photoinduced mechanical • Allergic
CHEMICAL BURN
CONTACT URTICARIA
CANCER
• Sunlight/UV-induced • Ionizing radiation-induced • Chemically induced
FOLLICULAR DISEASE
• Acne • Folliculitis • Chloracne
AUTOIMMUNE CONNECTIVE TISSUE DISEASE
• Systemic sclerosis (silica; see Ch. 43) • Scleroderma-like (vinyl chloride, organic solvents; see Ch. 43) • Vibration-induced
PIGMENTARY DISORDERS
• Hypopigmentation (see Ch. 66) • Hyperpigmentation (see Ch. 67)
FOREIGN BODY REACTIONS (see Ch. 94)
INFECTION
• Viral • Bacterial • Fungal • Parasitic

Table 16.1 Clinical classification of occupational dermatoses.

In a UK household survey, a rate of occupational dermatosis of 15/10 000 population for those who had ever been employed demonstrates the high frequency of affected individuals and compares with 5.1/10 000 reported by physicians in Denmark and Finland, where occupational disease is notifiable. After musculoskeletal disorders (45%), skin diseases (23%) are the most common cause of medical illness. In the US in 1985 it was estimated that the annual cost of occupational skin disease due to lost productivity, medical care and disability payments was between $222 million and $1 billion[2]. In the 1990s, the average cost per claim for occupational dermatitis was US$3550 and the period of disability 24 days[3].

HISTORY

Occupational disease has existed for a long time. For example, on their long-distance voyages in the sixteenth century, Drake and Magellan experienced significant problems from scurvy due to the lack of vitamin C from fresh fruit and vegetables. However, one of the first written descriptions of occupational dermatoses was by the Italian Bernardino Ramazzii (1633–1714). He described diseases associated with a variety of occupations, including the different characteristics of ulceration in fresh- and salt-water fishermen. In 1747, James Lind performed the first controlled trial to show the protective effects of citrus fruits against scurvy. In 1795, the British Navy included lemon juice in ships' stores as one of the earliest forms of prevention for an occupational skin disease.

EPIDEMIOLOGY

The reported distribution of occupational skin disease varies with the specialty of the physician[4] (Fig. 16.1). The difference in the incidence of neoplasia as reported by dermatologists and occupational physicians reflects the delay between exposure and development of disease as well as the fact that the majority of workers have left employment when the cancer develops. Differences between occupations in terms of reporting disease also reflect the distribution of occupational health departments in industry: vehicle assembly, glass and ceramic workers, and scientific technicians were often seen by occupational physicians, whereas hairdressers, for example, were seen primarily by dermatologists.

THE OCCUPATIONAL DERMATOSES

Contact Dermatitis

Synonym: ■ Contact eczema

Key features

- Pruritus, vesicles, erythema and scale
- Develops within hours to days of exposure and persists for weeks, sometimes longer
- The most common causes of occupational *allergic* contact dermatitis are (in order of decreasing frequency): rubber, nickel, epoxy and other resins, and aromatic amines
- The most common causes of occupational *irritant* contact dermatitis are (in order of decreasing frequency): soaps, wet work, petroleum products, and cutting oils and coolants

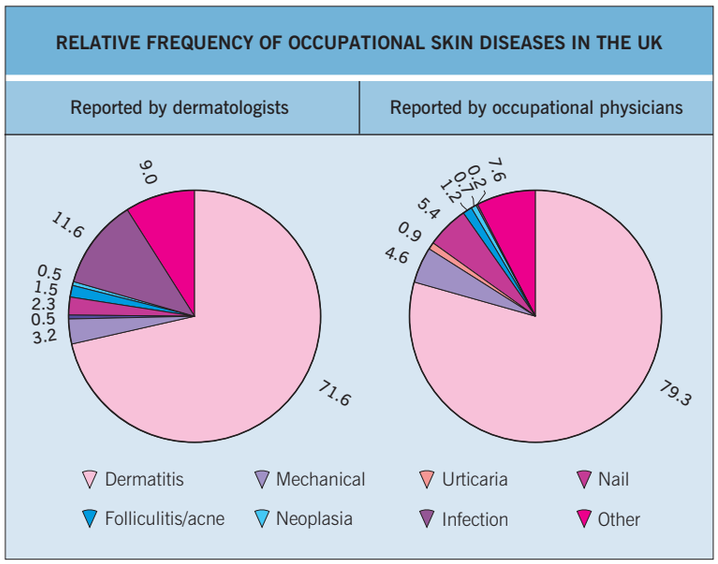


Fig. 16.1 Relative frequency of occupational skin diseases in the UK[1].

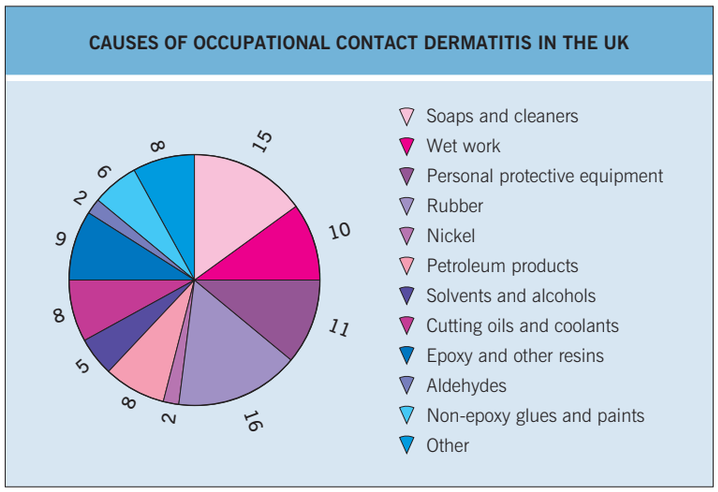


Fig. 16.2 Causes of occupational contact dermatitis in the UK. Materials identified by occupational physicians.

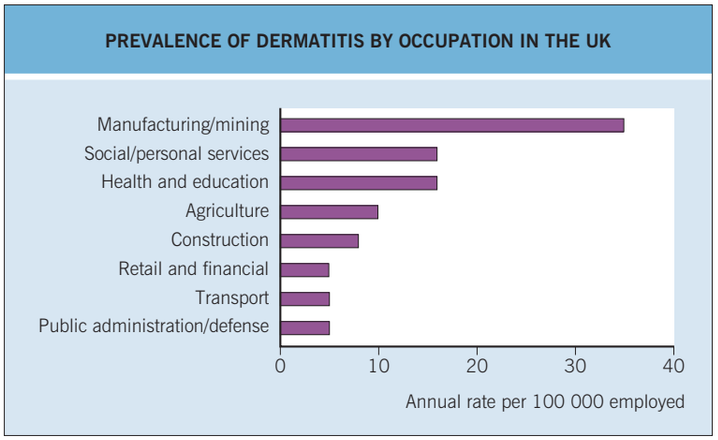


Fig. 16.3 Prevalence of dermatitis by occupation in the UK (annual rate per 100 000 employed)[2].

Introduction

Contact dermatitis accounts for the majority of occupational skin disease that predominantly affects the hands. The prevalence of hand dermatitis in the population has been estimated at approximately 0.5%, rising in some studies to 10% when an industrial workforce has been examined. While most individuals will remain at work, over half will change jobs and a large proportion will be absent from work for a month or more.

History

In the first century AD, Pliny the Younger recorded dermatitis in some individuals after they cut down pine trees.

Epidemiology

An age-related increase in rates of occupational dermatitis is seen in men, but in women the peak age of incidence is 16–29 years with a reduction in older age groups. However, a comparison of rates by age within specific occupational groups suggests that the sexes follow a similar pattern. Among chefs and cleaners of either sex, higher rates are seen in young workers, whereas rates among machine tool operators steeply increase with age, reflecting the type of occupational exposure. Materials reported in the UK as giving rise to contact dermatitis are shown in Figure 16.2, and UK occupations at greatest risk in Figure 16.3[5]. In contrast to the UK, in Finland and the US, the highest rate of skin disease is among agricultural workers. Over the past decade, there has been a consistent decline in the reported incidence of contact dermatitis in the UK[6].

Pathogenesis

The initial events of both irritant and allergic contact dermatitis (see Chs 14 & 15) are basically identical. The skin responds to chemical perturbation with a complex response designed to recruit immunologic surveillance mechanisms to assess the nature and "danger" level of the perturbing agent. This reaction exhibits dose-responsiveness: strong irritants and sensitizers both evoke a stronger response than weak irritants and sensitizers, and even supposedly bland agents such as white soft paraffin can evoke some degree of response in some individuals.

Whether this acute response becomes clinically apparent will be determined by the strength of the perturbing insult, but even if it does not, a tissue response still occurs. If the irritant insult is repeated before the tissue response has subsided, it will boost the response to a higher level. Following repeated exposures to the irritant insult, the tissue response is ultimately boosted to the point at which it becomes clinically apparent as cutaneous inflammation (Fig. 16.4). If the level of tissue perturbation is maintained via repeated insults, the changes of chronic irritant dermatitis ensue, while an early withdrawal of insults may result in healing.

Clinical features

Contact dermatitis, both allergic and irritant, is morphologically indistinguishable from an endogenous eczema (Fig. 16.5). Not all patients will have a clinical configuration and/or distribution of lesions that suggests an exogenous insult. To induce contact dermatitis, a chemical must first penetrate the stratum corneum and then interact either directly with keratinocytes to cause irritant contact dermatitis or with the cutaneous immune system to cause an allergic contact dermatitis.

Although most cases of dermatitis will result from direct exposure that leads to localized dermatitis, it should be remembered that other routes of absorption can lead to dermatitis. In the case of solvents, inhalation may result in widespread dermatitis, often with systemic involvement.

Diagnosis is dependent on a thorough dermatologic and occupational history (Table 16.2) combined with examination of the entire skin. The material safety data sheets (MSDS) provide a guide to the nature of materials handled at work. They usually list the main ingredients and the hazards associated with the product, i.e. irritant, corrosive or known to contain a sensitizer. Total reliance should not be placed on the MSDS, as they may not list all ingredients of relevance, and communication with the manufacturer may prove helpful. When occupational dermatitis is suspected but a cause cannot be established from the history, a workplace visit may prove invaluable and may also elucidate the source of an allergen previously detected via patch testing.

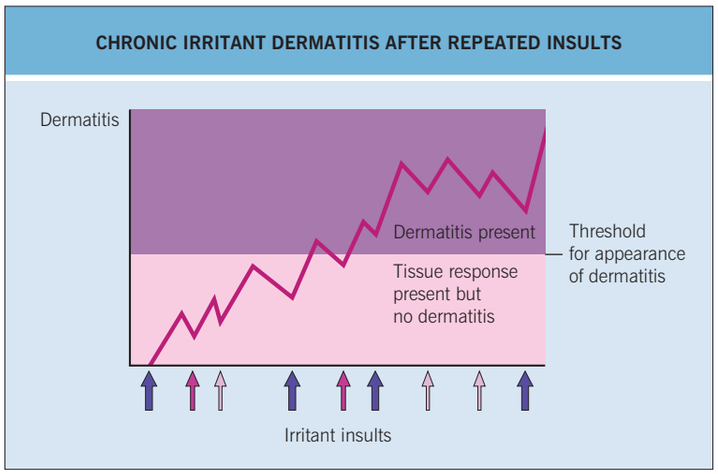


Fig. 16.4 Chronic irritant dermatitis after repeated insults. Initial subclinical response to tissue perturbation by an irritant becomes manifest as chronic irritant dermatitis after repeated insults. Each arrow represents an irritant insult of different intensity.

Fig. 16.5 Hand of a builder who presented with a dyshidrotic (pompholyx) pattern of eczema. Investigation demonstrated allergic contact dermatitis to chromate found in cement and contact urticaria to latex in the gloves he was using for hand protection.

POINTS TO CONSIDER WHEN TAKING AN OCCUPATIONAL HISTORY	
Primary (initial) site of disease	In 90%, it is the hands
• Time course	Is this consistent with work exposure as a cause?
	Does time off result in improvement?
Materials handled	
• Labels and material safety data sheets (MSDS)	Irritant, corrosive or sensitizing
• Other persons affected	Suggests an irritant contact dermatitis
• Protection provided	Is it appropriate?
	Is there an allergy to personal protective equipment?
Previous skin disease or history of atopy	Is this a recurrence of a previous problem?
Known allergies	Is there unrecognized exposure?
Treatment	May cause allergic contact dermatitis
Hobbies	May be a more likely cause than occupation

Table 16.2 Points to consider when taking an occupational history.

Although the primary site is usually the hands, spread to *adjacent* areas of skin (even without primary contact) is relatively common. Spread to *distant* sites, such as the face and feet, is more frequently seen in allergic contact dermatitis than in irritant contact dermatitis. Notably, airborne allergens, e.g. from paint sprayers, can lead to a pattern of dermatitis that suggests the exposure. Covered areas such as the trunk and feet are unusual sites of onset of disease. Improvement of the dermatitis during periods away from work is important in determining a primarily occupational cause, but it should be remembered that an endogenous eczema may also be exacerbated by workplace exposures. As the dermatitis becomes chronic, the relationship between work and exacerbations becomes less clearcut.

Allergic contact dermatitis

Allergic contact dermatitis (see Ch. 14) is not as common as irritant contact dermatitis. Once sensitization has occurred, very small amounts of allergen are required to perpetuate the dermatitis. As a consequence, avoidance may prove difficult, especially if the allergen is widely distributed within the home environment as well as at work. Patch testing is essential for establishing the diagnosis and should be performed in any individual with a dermatitis that may be work-related or for whom a change of job is being contemplated. Testing with work materials is essential (Table 16.3) if contact allergy is not to be missed, as not all allergens are commercially available and the MSDS may not disclose all relevant ingredients. A guide to testing 4350 chemicals has been published[7]. When a reaction occurs to an unknown substance, the use of a dilutional series and the testing of approximately 20 controls is essential to confirm that the reaction is allergic rather than irritant.

In an extensive surveillance report, the most common causes of an occupational allergic contact dermatitis were rubber (23.4% of cases), nickel (18.2%), epoxy and other resins (15.6%), aromatic amines (8.6%), chromate (8.1%), fragrances and cosmetics (8.0%), and preservatives (7.3%)[5]. Rarely, substances can cause an allergic contact dermatosis that mimics other conditions such as erythema multiforme (Table 16.4). Patch testing with the suspect material will confirm the correct diagnosis. Typically there is an eczematous patch test reaction, but features of these other dermatoses may appear.

Irritant contact dermatitis (see Ch. 15)

An irritant is a chemical capable of causing direct cell damage. Strong irritants are usually recognized and protection provided. Most occupational dermatitis results from repeated exposures to weak irritants which cause cumulative damage to the skin (see Fig. 16.4). Individual susceptibility varies widely and differs from one chemical to another. Employees with previous atopic dermatitis, especially with hand involvement, are particularly at risk. In a recent study, loss-of-function mutations in the filaggrin gene conferred susceptibility to hand dermatitis due to combined allergic and irritant contact dermatis[8].

Soaps (22.0% of cases), wet work (19.8%), petroleum products (8.7%), solvents (8.0%), and cutting oils and coolants (7.8%) are the most frequently cited causes of occupational irritant dermatitis[5].

Chemical burns

A chemical burn is an acute irritant reaction in which the injury to the skin is irreversible and cell death occurs. Depending on the nature of the chemical, it can occur following a single exposure. Initial symptoms consist of burning and smarting with progressive development of erythema, blisters, erosions and then ulceration. Symptoms usually develop in close association with the exposure, but some chemicals, such as phenols and weak hydrofluoric acid, can have a delayed onset. Common occupational causes[9] include:

- **strong acids:** e.g. sulfuric, nitric, hydrochloric, chromic. Most coagulate skin proteins and as a result form a barrier which impedes further penetration. Hydrofluoric acid differs in that it causes a liquefactive necrosis: penetration, even down to bone, can continue for several days after exposure. Pain, which can last several days, is typical of hydrofluoric acid and other fluorides. If more than 1% of the body surface area is affected, systemic toxicity can develop

SUGGESTED CONCENTRATIONS FOR PATCH TESTING SELECTED WORK MATERIALS		
Sample	**Dilution**	**Occupation(s)**
Personal care products		
• Leave on	As is	Hairdresser/beautician
• Wash off	1–5% aqueous or open[†]	Hairdresser/beautician
Plants[‡]		
Bulb, leaf, flower	As is	Gardener/florist Agriculture/vegetable processing
Woods – sawdust	As is/10% petrolatum	Joiner/woodworker
Dyes (clothing)	1% petrolatum	Textiles
• Cloth	As is – moistened	
Foods[§]	As is	Catering/chef
Glue	10% aqueous/ petrolatum	Various
• Methacrylate monomer	1% petrolatum	Dentist/orthopedic surgeon
• Acrylate monomer	0.1% petrolatum	
• Epoxy resin	1% petrolatum	Painter – 2 part paints
• Epoxy hardener	0.1% petrolatum	
Ink	As is	Printing
• UV cured	1% petrolatum	
Oil		
• Cutting (coolant) – water miscible	10% aqueous or open	Metal machining
• Lubricant – immiscible with water	As is	Various-use machinery
Paint	10% aqueous/ petrolatum	Painter/decorator
Photographic chemicals	10% aqueous	Photographer
Solvents/thinners	10% acetone	Various

[†]Open test: apply the substance to a 3 cm diameter area of skin and allow to dry. Read as normal but do not occlude.
[‡]Do not test unless the plant has been identified and is recognized not to be irritant. There may be a risk of sensitization.
[§]Prick testing is essential to exclude contact urticaria.

Table 16.3 Suggested concentrations for patch testing selected work materials. This is a guide only: the final decision must always be made in light of the information available in relation to the suspected material. Tests are usually performed on the upper back.

NON-ECZEMATOUS ALLERGIC CONTACT DERMATOSES		
Dermatosis	**Occupation**	**Exposure**
Erythema multiforme-like	Woodworker	Tropical woods – *Dalbergia nigra; Machaerium scleroxylon; Eucalyptus saligna*
	Laboratory worker	9-bromofluorene
	Textile worker	Para-phenylenediamine (PPD) Nickel
Pigmented purpura-like	Various	Black rubberized clothing: N-phenyl-N-isopropyl PPD
Lichen planus-like	Photography: color developer	CD2, CD3, CD4
	Motor vehicle manufacture	Methacrylic acid ester

Table 16.4 Non-eczematous allergic contact dermatoses. CD, color developer; CD2, 4-N,N-diethyl-2-methyl-1,4-phenylenediamine; CD3, 4-(ethyl-N-2-methan-sulfonamidoethyl)-2-methyl-1,4-phenylenediamine; CD4, 4-(ethyl-N-hydroxyethyl)-2-methyl-1,4-phenylenediamine.

Fig 16.6 Cement burns. Ulcerations on the fingertips of a construction worker exposed to wet cement. *Courtesy, PJ Coenraads, MD.*

- **strong alkalis:** e.g. sodium, calcium, potassium hydroxides; wet concrete (Fig. 16.6); sodium and potassium cyanides. Degradation of lipids and saponification of the resulting fatty acids form soaps which aid the penetration of alkalis deeper into the skin. As a consequence, damage is more severe than with most acids (apart from hydrofluoric acid) and pain is also a feature
- **organic and inorganic chemicals:** e.g. dichromates; arsenates; phenolic compounds. Phenols and unhardened phenolic resins easily penetrate the skin. Nerve damage may cause anesthesia, but rarely in the absence of visible skin damage. Vasoconstriction may contribute to the necrosis that develops and, following systemic absorption, shock and renal damage may ensue
- **solvents and gases:** e.g. acrylonitrile; ethylene oxide; carbon disulfide; mustine. Ethylene oxide gas is used to sterilize medical instruments, textiles and plastic materials, and it can remain on these items for several days if not allowed to evaporate off prior to use. The possibility of exposure may therefore not be obvious.

Fiberglass dermatitis

Glass fibers are subdivided into various types, depending on fiber diameter, and are used for their insulating (thermal, acoustic and electrical), strengthening and filtering abilities. They are chemically inert and the mechanism of skin injury is via direct penetration, which is directly proportional to the diameter (>3.5 microns) of the fiber and inversely proportional to its length. Histologically, eczematous changes including spongiosis are seen.

Pruritus and tingling are the usual initial symptoms. Subsequently, erythematous papules develop (often with follicular accentuation), either on exposed areas when there is airborne exposure or on the forearms when there is contamination of a work surface (Fig. 16.7)[10]. Contamination of clothing causes problems, especially in the flexural areas and where there is contact with the skin. Paronychia is common and airborne exposure may also cause burning eyes, sore throat and cough.

The diagnosis is often based on clinical findings, but it can be confirmed by detecting the fibers in tape strippings of affected skin or by examining skin scrapings in 20% potassium hydroxide. The dermatitis resolves rapidly after cessation of exposure. In most individuals, hardening occurs and symptoms resolve over a few weeks despite continued exposure; of note, the use of resins to bind glass fibers can result in an allergic contact dermatitis.

Phototoxic eruptions

Chemical photosensitivity occurs when a chemical becomes activated through interaction with light. The photoactivated chemical has altered properties which can be directly tissue damaging (phototoxic reaction) or may be immunogenic (photoallergic reaction). Most occupational photosensitivity is phototoxic in nature and commonly heals with hyperpigmentation. The most common scenario is exposure to

naturally derived psoralens from plants in outdoor workers. This may be from a food such as celery or parsnip, members of the Apiaceae (formerly Umbelliferae) family, or weeds as in "strimmer" dermatitis when plant sap splatters the body of a worker inadequately protected when cutting down plants such as cow parsley and wild chervil (see Ch. 17).

Coal tar and its products, including creosote, cause a reaction known as tar/pitch smarts. A burning or stinging sensation develops after as little as 15 minutes of sun exposure.

Mechanical

Occupational marks are usually areas of lichenification or calluses and corns that develop at sites of friction and are specific to a particular job (Fig. 16.8). Mechanical injury to the skin is also thought to cause dermatitis analogous to irritant chemical damage. It may result in a keratotic hand dermatitis or post-traumatic eczema (Koebner phenomenon).

Pathology

The histologic features of allergic contact dermatitis and irritant contact dermatitis are discussed in Chapters 14 and 15, respectively.

Differential diagnosis

The etiology of occupational dermatitis is frequently multifactorial and endogenous eczema (e.g. atopic, dyshidrotic, nummular) may contribute to the clinical appearance. Tinea manuum may resemble hand dermatitis, especially following treatment with topical corticosteroids, and scabies infestation of the interdigital spaces can simulate irritant dermatitis.

Psoriasis frequently affects the palms, resulting in keratotic plaques, sometimes with fissures. This can be difficult to distinguish from dermatitis when there are no lesions elsewhere. Furthermore, it may be work-related with repeated trauma leading to Koebner phenomena. Nail involvement and plaques over the interphalangeal joints are helpful clues.

Fig. 16.7 Fiberglass dermatitis. Multiple pruritic pink papules at the site of exposure.

Treatment

Prevention reduces the possibility of needing to treat dermatitis[11]. During pre-employment screening, a history of severe childhood atopic dermatitis, particularly with hand involvement, indicates an individual at risk of developing dermatitis from exposure to irritants. Employment in a "dry" job should be recommended. In the workplace, the use of protective equipment and skin care preparations should be encouraged (Table 16.5). As an interim measure, dermatitis requires palliation of symptoms with emollients and topical corticosteroids. In severe cases, short-term therapy with systemic drugs such as prednisone, azathioprine, methotrexate, mycophenolate mofetil or cyclosporine may be required.

The most important aspect of treatment, however, is avoidance of the cause. Ideally, a change in the production process may avoid the need for exposure, but this may be costly. A practical compromise is frequently the use of personal protective equipment and/or substitution of a particular chemical. It is often forgotten that natural rubber latex gloves are effective protection against water-miscible materials but may be inappropriate for other exposures, e.g. organic solvents. Advice on appropriate glove type may be found on the material safety data sheets or from manufacturers (e.g. www.ansellpro.com). A further issue is the passage of some allergens through latex gloves, e.g. acrylate glues (orthopedic surgeons and dentists), the hair dye para-phenylenediamine and acid perm solutions containing glycerol monothioglycolate (hairdressers).

Initial treatment of chemical burns requires irrigation with large volumes of water. When the chemical is insoluble in water, a soap solution may be used instead. High pressures should not be used, in order to avoid splashing other areas of the body or bystanders with the corrosive material. For some chemicals, specific antidotes can then be used, e.g. 2.5% calcium gluconate gel for hydrofluoric acid; disappearance of pain is a sign of successful treatment. When there is a risk of toxicity from systemic absorption, as with chromic acid, early debridement of necrotic areas reduces blood levels.

Ulcerated areas should be managed with antibacterial creams or ointments to prevent secondary infection while re-epithelialization occurs. If there is a surrounding inflammatory reaction, a moderately potent topical corticosteroid can be applied. Frequent evaluation is required

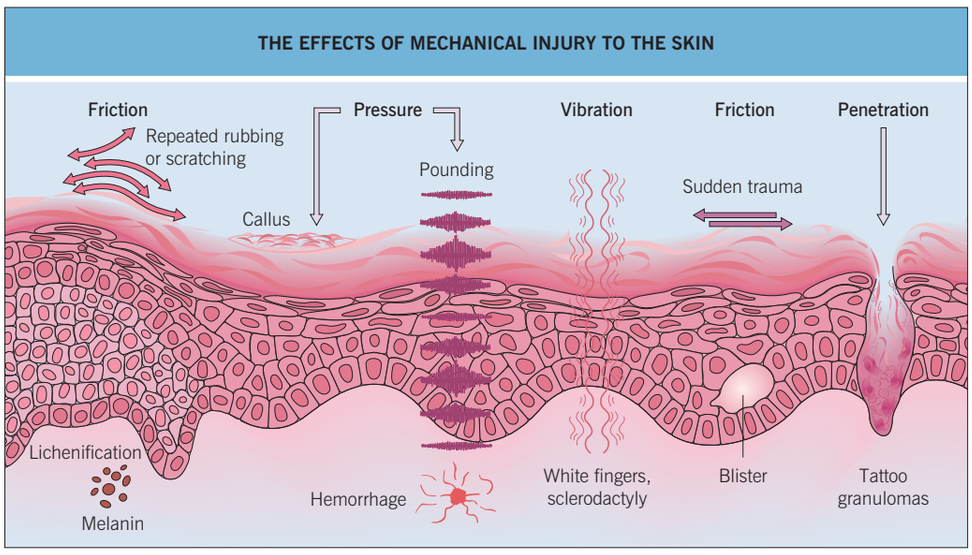


Fig. 16.8 The effects of mechanical injury to the skin. Both friction and pressure lead to callus formation. *Adapted from Adams RM. Occupational Skin Disease, 3rd edn. Philadelphia: WB Saunders, 1999:36.*

GUIDELINES AIMED AT PREVENTING CONTACT DERMATITIS		
Advice		**Explanation**
Do not wear rings		Chemicals/water accumulate underneath
Hand washing	• Use lukewarm water and dry thoroughly	• Skin damage from detergent is reduced at a low temperature • Dermatitis often begins at sites that are missed, e.g. fingerwebs
Wear gloves	• For wet work • For as short a time period as possible • With a cotton inner liner if prolonged exposure • That are dry, clean and intact	• Wet work is the major risk factor for contact dermatitis • Glove occlusion also damages the skin • Liners absorb moisture and reduce irritation • Occlusion of chemicals inside gloves increases irritancy
Use moisturizer	• Frequently throughout the day • To the whole hand • That is fragrance-free and preservative-free	• Encourages barrier repair • Need to include web spaces • Prevents sensitization and development of ACD to common allergens
For antisepsis	• Use alcohol gel	• Less irritating than soaps or antiseptic detergents
Follow the same advice at home		Domestic exposures are additive

Table 16.5 Guidelines aimed at preventing contact dermatitis. ACD, allergic contact dermatitis.

because the ulcers can progress over several days. Subsequent management with excision, debridement, semi-permeable membrane dressings and/or grafting may speed the healing process. When the ulcer extends into the dermis, healing frequently results in a scar and pigmentary change is common.

Several chemicals (e.g. hydrofluoric acid, phenolic compounds, chromic acid, gasoline) carry a significant risk of systemic toxicity even when the area of skin involved is small (approximately 1% of body surface area). In these instances, regular monitoring of blood, liver and kidney function plus appropriate supportive treatment (e.g. dialysis) is required. When the chemical is a sensitizer, allergic contact dermatitis may subsequently appear on re-exposure to non-irritant concentrations, as burns and irritant dermatitis appear to promote sensitization.

Once it has developed, the outlook for occupational contact dermatitis is poor[12]. In a follow-up study of 954 patients with occupational dermatitis seen over 8 years, in which at least 60% were assessed more than 2 years after diagnosis, 55% still had disease. Of those who were still in the same job or occupation, 68% were still symptomatic, compared with 37% of those who had moved to a different work environment. Notably, when changing jobs, 25% of individuals had inappropriately moved to a workplace with the same or similar chemical exposures. Of the total, 11.5% had persistent disease in the absence of any obvious cause, for which the term "persistent post-occupational dermatitis" was coined.

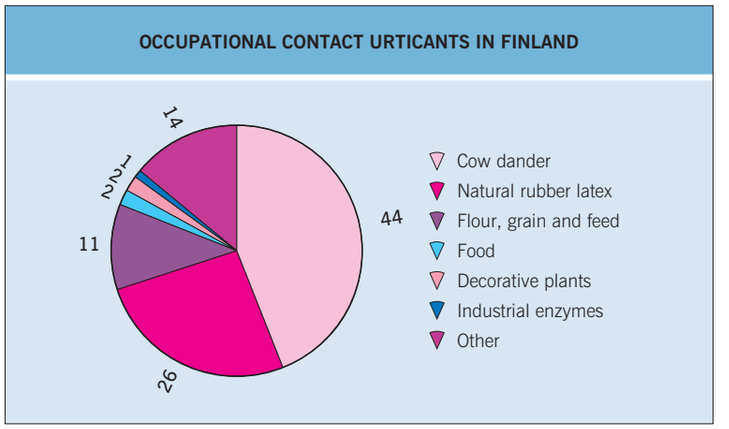


Fig. 16.9 Occupational contact urticants in Finland. Relative frequencies are represented[1].

Contact Urticaria

Synonyms: ■ Contact urticaria syndrome ■ Immediate contact reaction ■ Protein contact dermatitis

Key features

- Pruritus and wheal-and-flare reaction
- Develops within 60 minutes of exposure and resolves within 24 hours
- It is the protein content of latex rubber that is responsible for the associated contact urticaria
- In suspected cases of latex-induced contact urticaria, the specific IgE test may be negative, requiring prick testing with a commercial latex extract and a usage test

Introduction

Contact urticaria has been reported following exposure to a wide range of substances[13]. With regard to occupational skin disease, plant- and animal-derived proteins are recognized causes, especially among food handlers and agricultural, animal laboratory and veterinary workers. In extreme circumstances, systemic symptoms (i.e. rhinoconjunctivitis, bronchospasm and anaphylaxis) may be seen. With the introduction of universal precautions in the 1980s and increased use of natural rubber gloves, latex protein emerged as an important cause of contact urticaria, particularly in the healthcare setting.

History

Contact urticaria was first defined as a clinical entity during the 1970s but it had long been recognized.

Epidemiology

Based on official statistics, occupational causes of contact urticaria have been well classified in Finland[1]. The relative frequency of various urticants is shown in Figure 16.9 and reflects the high prevalence of reactions in the farming community. The reactions to cow dander are probably the result of high exposure, as cattle are kept indoors from September to May/June. The prevalence varied from 140/100 000 for bakers to 2.1/100 000 for shop assistants and was higher in women, irrespective of occupation. For the occupations most at risk, the relative risk by occupation is shown in Figure 16.10. The incidence of contact urticaria falls with age, and approximately 30% of individuals have coexistent contact dermatitis.

Pathogenesis

Contact urticaria is classified as either irritant/nonimmune-mediated or allergic/immune-mediated. An additional category includes those cases in which the mechanism is uncertain, the most common cause of which is ammonium persulfate in hairdressing.

The mechanism of nonimmune contact urticaria is not well defined but involves the release of vasoactive mediators. It is inhibited by non-steroidal anti-inflammatory drugs but not antihistamines, suggesting a

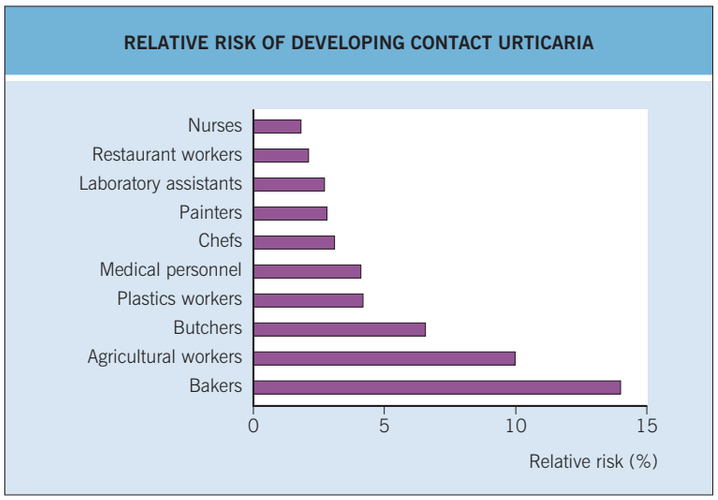


Fig. 16.10 Relative risk of developing contact urticaria by occupation.

POTENTIAL CROSS-REACTIONS BETWEEN CAUSES OF CONTACT URTICARIA

Food/natural product	Risk (%)	Cross-reactions
Fruit (kiwi, avocado, banana)	11	Latex
Latex	35	Fruits (e.g. kiwi, avocado, banana)
A shellfish (e.g. crab)	75	Other shellfish (e.g. prawn, lobster)
A fish (e.g. salmon)	50	Other fish (e.g. swordfish, sole)
A grain (e.g. barley)	20	Other grains (e.g. wheat, rye)
A legume (e.g. peanut)	5	Other legumes (e.g. peas, beans, lentils)
Peach	55	Other Rosaceae fruit (e.g. apple, pear, cherry, plum)
Melon	92	Other fruits (e.g. watermelon, banana, avocado)

Table 16.6 Potential cross-reactions between causes of contact urticaria. If allergic to item in column 1, risk of cross-reacting with item in column 3.

role for prostaglandins. Symptoms develop in the majority of those exposed and are most often due to simple chemicals, e.g. sorbic acid.

Immunologic contact urticaria is mediated by allergen-specific IgE (see Ch. 18). Binding of antigen, usually protein, to mast cells in a previously sensitized individual results in degranulation and release of mast cell mediators, including histamine. Atopic individuals are at greater risk of this type of reaction.

Clinical features

Signs and symptoms range from nonspecific, i.e. pruritus, tingling and burning, to more typical urticaria with a wheal and flare, usually developing within 30 minutes of exposure at the site of contact. Resolution occurs within hours. Individuals with immunologically mediated urticaria[14] may also experience systemic symptoms with generalized urticaria, rhinoconjunctivitis, orolaryngeal and gastrointestinal symptoms, asthma, and, at worst, anaphylaxis.

Foods

One of the more common causes of contact urticaria is foodstuffs, which can provoke either orolaryngeal symptoms when ingested or hand symptoms when handled (e.g. in fish processors, slaughterhouse workers or those in the catering industry). There is a diverse range of responsible foods, including meats, fish, eggs, fruits, vegetables and flour, as well as associated enzymes such as α-amylase (found as an additive in flour). In Scandinavia, a strong association is seen between the incidence of birch pollen allergy and contact urticaria to fruits and vegetables, due to the presence of similar peptides. Birch pollen is a common aeroallergen in Scandinavia, whereas in the UK the most common aeroallergens are the house dust mite and grass pollen; this may explain why there are fewer reports of contact urticaria in food handlers in the UK. If contact urticaria is confirmed, there are recognized cross-reactions between the various foodstuffs (Table 16.6)[15].

Latex

Contact urticaria to latex was first described in 1979. The term "latex" defines an aqueous dispersion of a rubber. The rubber obtained from latex by drying or coagulation is termed "latex rubber". Natural latex is derived from the sap of the tree *Hevea brasiliensis*. Natural latex contains polyisoprene (30–40%) together with a variety of other plant chemicals, including proteins (2.3%).

After 1985, the demand for latex gloves for medical and dental use to prevent the transmission of infectious agents[16] more than doubled. Paralleling this rise in usage were reports of type I allergy to latex gloves. Occupational latex contact urticaria occurs more frequently in women, atopic patients (particularly those with hand eczema), and workers frequently exposed to latex gloves (e.g. hairdressers). Rates ranging from 3% to 16% have been reported in groups of healthcare workers.

Most problems arise from items made by coating a mold with concentrated liquid latex, e.g. gloves, balloons, condoms. Nowadays, however, many gloves are manufactured by methods designed to leave lower levels of protein allergen in the final product. Latex which is allowed to dry before processing by compression molding or extrusion (e.g. syringe plungers, vial stoppers) causes fewer problems, as a result of degradation of the protein allergen during the manufacturing process. When latex protein is absorbed onto starch particles in gloves, it can become airborne and cause conjunctivitis, rhinitis and asthma. Ideally, powder-free gloves should be used to avoid this risk.

In latex there is more than one protein against which an immunologic reaction may develop, and in a subgroup of patients, hypersensitivity reactions to bananas, avocados, chestnuts, kiwis and other fruits also occur (see Table 16.6). Radioallergosorbent inhibition studies have shown that they contain a similar antigen. In some individuals, the primary sensitization is to the fruit, with latex sensitivity being a secondary phenomenon.

Common household sources of exposure to latex are gloves, balloons, latex contraceptives, latex mattresses and pillows, rubber bands, swimming caps and baby pacifiers. The term "hypoallergenic glove" refers to latex gloves with reduced levels of accelerators and antioxidants (causes of allergic contact dermatitis); these gloves are not suitable for individuals allergic to latex (with immediate-type hypersensitivity).

Non-latex alternatives should be sought. Vinyl (PVC) gloves are suitable for home use. For those in the medical and dental professions, alternative gloves, typically nitrile (both sterile and non-sterile), are available from the major glove suppliers. Affected individuals should warn any doctor or dentist that they visit of their sensitivity so that measures can be taken to prevent a reaction. The most severe reactions have followed mucosal and parenteral exposures. Death has occurred following the use of a natural rubber latex cuff on a barium enema device and anaphylaxis after intraoperative, oral or vaginal exposure to latex gloves. Wearing a bracelet or necklace to alert the medical profession in the event of an emergency has been advocated.

Low-molecular-weight chemicals

Although rare, these chemicals can be important causes of occupational contact urticaria in the industrial setting. Some are also potential causes of occupational asthma. The diagnosis may prove difficult to establish because skin testing may require conjugation of the low-molecular-weight chemical with protein to form the allergen. Chemicals (and industries) associated with contact urticaria include: antibiotics (pharmaceutical industry); ammonium persulfate and paraphenylenediamine (hairdressing); phthalic anhydrides, epoxy resin systems and poly-functional aziridines (plastics and glue industry); and reactive dyes (textile workers).

Protein contact dermatitis

The term "protein contact dermatitis" was originally used to describe an eczematous reaction to protein-containing material in food handlers. The reactions were both allergic and non-allergic, although many had a positive prick test or the presence of specific IgE antibodies, implying an IgE-mediated mechanism. In some, positive patch tests pointed to the coexistence of delayed-type hypersensitivity. The clinical picture is

usually that of a chronic eczema with episodic exacerbations following contact with the allergen[17].

Pathology

The histologic findings of contact urticaria are described in Chapter 18.

Differential diagnosis

After a detailed history and clinical examination, skin testing may be undertaken to confirm the diagnosis of contact urticaria. When the patient has experienced anaphylactic symptoms and a specific IgE test is available, the blood test may confirm the diagnosis, avoiding the risk of anaphylaxis as a result of skin tests. Skin testing should be performed with appropriate positive and negative controls. With an unknown allergen, exposure should be graded; an initial application test (open and subsequently occluded) is followed by a prick test and, if necessary, an intradermal test. If the patient has a positive test, control individuals should be tested; a positive response in the latter group points to the presence of a nonimmune contact urticant. While commercial allergen extracts are available, it should be remembered that, unless adequately standardized, they may not contain the relevant protein allergens, resulting in a false-negative test result. The gold standard for testing is a sample of fresh material. Skin tests should only be performed where resuscitation facilities are available.

In the case of latex, the specific IgE blood test is not sensitive and a negative test does not exclude the diagnosis (Fig. 16.11). While skin tests with glove extracts have been recommended, many gloves now contain low levels of latex protein and prick testing with these home-made extracts frequently leads to false-negative results. Prick test solutions of latex are commercially available, some of which claim >98% sensitivity and 100% specificity (Fig. 16.12). If a particular glove type appears to elicit symptoms, a so-called "prick to prick" test can be used: the suspected item itself is pricked with the lancet, after which the patient's skin is pricked with the antigen-"contaminated" lancet. The final arbiter is a usage test in which a patient wears the suspect glove on a moistened hand and is observed for any reaction.

Although reactions to gloves are common, a proportion of individuals have symptoms caused by irritation. In the absence of a latex allergy, localized symptomatic dermographism is a common cause of urticaria to gloves (see Fig. 16.11).

Treatment

Management consists of avoidance, as desensitization for the majority of involved allergens is not available. Avoidance may be achieved by improved occupational hygiene and the use of personal protective equipment, but in extreme circumstances may necessitate a change of occupation. Treatment of the acute episode includes the use of systemic antihistamines and epinephrine (adrenaline), depending on the severity of the attack. In the case of latex, the use of powder-free gloves containing low levels of protein has been shown to prevent the development of latex hypersensitivity by reducing the level of exposure in the at-risk population[18]. There has also been a movement in healthcare facilities to use only non-latex gloves. The development of a commercial method for latex desensitization without significant risk of systemic adverse reactions also offers the potential for better symptom control in those who are unable to completely avoid exposure[19].

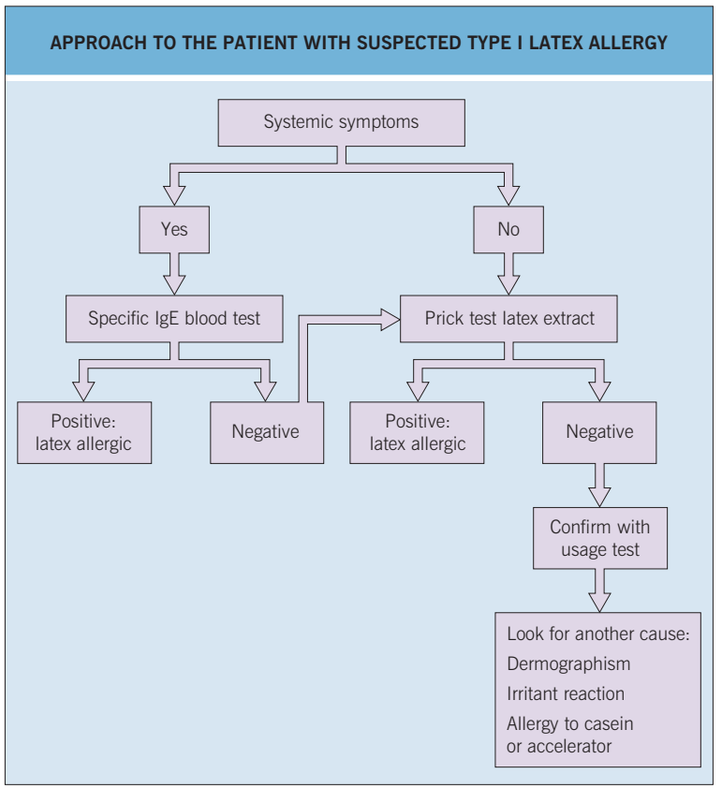


Fig. 16.11 Approach to the patient with suspected type I latex allergy. IgE-mediated immediate hypersensitivity is detected by prick tests, whereas delayed-type hypersensitivity which manifests as contact dermatitis is detected by patch testing. In the open usage test, the patient wears the suspect glove on a moistened hand.

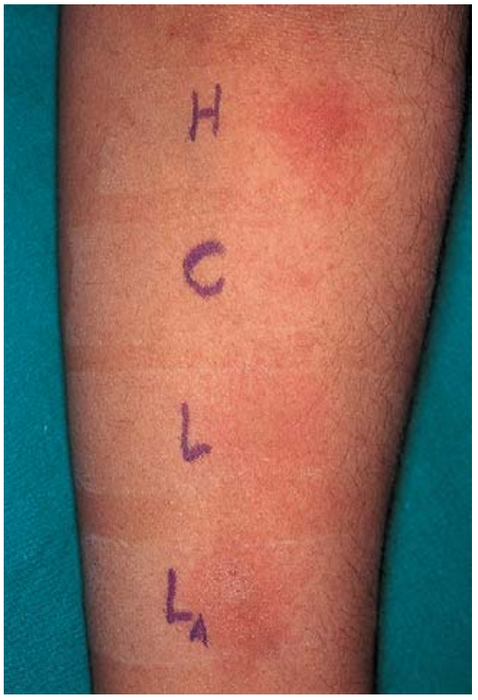


Fig. 16.12 Positive prick test with a commercial latex extract (L) and high ammoniated natural rubber latex (L_A). Histamine (H; 10 mg/ml) and saline (C) controls are appropriately positive and negative. The histamine-positive control confirms that the effects of previous medications (including antihistamines) are no longer an issue and the saline-negative control assesses for dermographism. When a standardized allergen is available for a prick test, a small drop is placed on the skin and the skin is pierced with a special lancet with a 1 mm tip. Surplus allergen is blotted off and a fresh lancet is used for each test substance to prevent cross-contamination. Reactions develop over 15 minutes and a wheal 3 mm larger than the negative control is considered positive.

Occupational Skin Cancer

Key features

- A skin cancer in which occupation has played a major role in the etiology
- In the workplace, the most important exposures are to UV radiation, ionizing radiation and carcinogenic chemicals (e.g. polycyclic hydrocarbons)

Introduction

Occupational skin cancers[20] have been estimated to account for less than 1% of all skin cancers. In a study of workers exposed to coal and diesel combustion products, the relative risk for developing

non-melanoma skin cancer was 1.5%[21]. The tumor most frequently associated with occupational chemical exposure is squamous cell carcinoma (SCC).

History

The first association between occupation and cancer was made in 1775. Sir Percival Pott, a surgeon at St Bartholomew's Hospital in London, described the occurrence of scrotal cancer in chimney sweeps. The latter was often preceded by keratotic lesions known as soot warts. In 1873, von Volkman described skin cancers from exposure to the distillation products of tar and pitch.

In the early 1800s, inorganic arsenic was associated with skin cancers, especially of the scrotum in smelter workers, but also from exposure in the mining industry and in users of end products (e.g. sheep dip). In the early twentieth century, ionizing radiation was recognized as a cause of radiodermatitis followed by skin cancer, particularly of the hands of medical workers administering radiotherapy.

Epidemiology

As carcinogens have become recognized and limits on occupational exposure introduced, solar UV exposure has risen to account for ~95% of cases of occupational skin cancer reported in the UK. In Australia, the most common cause of compensated occupational cancer (of all types) was UV exposure (22%), followed by asbestos (21%)[22]. It was estimated that 34 000 cases of non-melanoma skin cancer per year and 4% of cases of cutaneous melanoma in men were attributable to occupation.

Occupations at high risk of occupational skin cancer include:

- outdoor workers[23], especially in agriculture and building industries, and welders (UV exposure)
- workers exposed to polycyclic hydrocarbons (e.g. tars, pitches, oil fractionation products); in addition to direct skin contact, fumes may be inhaled
- workers exposed to arsenic in glass production, copper, zinc or lead smelting, and the production of pesticides, herbicides and semiconductors
- radiologists, dentists, X-ray technicians, and those who work with radioactive materials (ionizing radiation).

Pathogenesis

The major carcinogenic hazards include UV radiation, ionizing radiation and carcinogenic chemicals. Occupationally induced cancers are not pathologically different from those which arise spontaneously. However, the former tend to occur at an earlier age than spontaneous tumors at the same site. They arise following repeated or continuous exposure to the carcinogen, and there is a long latency period between the exposure to the carcinogen and appearance of the tumor.

While ionizing radiation results in DNA base changes and strand breaks, which lead to mutation through errors in repair, UV radiation acts as a "complete carcinogen" by initiating carcinogenesis and promoting tumor progression. Initiation begins with formation of thymine dimers, followed by erroneous base substitutions during DNA repair (see Ch. 86). In addition, UV radiation acts as a tumor promoter by driving a diverse array of cell-activating signal transduction pathways. This results in the production of growth factors and cells being driven through the cell cycle when they should have been arrested in the cycle in order to undergo DNA repair. This enforced cycling augments DNA replication errors involving critical genes normally involved in regulating growth, cell cycling and apoptosis (see Ch. 107).

There are two major classes of chemical carcinogens: (1) polycyclic aromatic hydrocarbons including benzo(a)pyrene; and (2) aromatic amines such as dichlorobenzidine, an intermediate in the dyestuffs industry. For many compounds, carcinogenic mechanisms are not well understood, but there are general analogies to UV-induced carcinogenesis. Alkylating agents damage DNA, resulting in base substitutions and errors during replication.

Clinical features and diagnosis

In evaluating a patient with suspected UV-related occupational skin cancer, a careful history is required to establish the relative contributions of work versus leisure exposure. The final judgment is essentially clinical.

With polycyclic aromatic hydrocarbons, a variety of skin changes may precede the development of cancer and aid in the clinical diagnosis. Associated changes include (in order of development) erythema and burning, folliculitis, poikiloderma, and keratotic papillomas (tar warts) within the poikilodermatous skin. The verrucous tumors may then develop into SCC, although basal cell carcinomas and keratoacanthomas also occur.

The clinical features and diagnosis of these cutaneous malignancies are discussed in detail in Chapters 108 and 113.

Pathology and treatment

The pathology and treatment of skin cancers are discussed in detail in Chapters 108 and 113.

Occupational Acne

Key features

- Open and closed comedones
- Non-inflamed nodules and cysts
- Inciting factors include exposures to oils, halogenated polycyclic hydrocarbons, and repeated frictional trauma

Introduction

Occupational acne is a form of acne resulting from various chemical exposures as well as particular environmental and physical factors. Chloracne is a rare acne-like skin condition caused by certain toxic chemicals (see later) and may be a cutaneous manifestation of systemic exposure.

History

Chloracne was first reported in 1897. In 1949, the first descriptions of human exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD)-contaminated chemicals were reported after a trichlorophenol reactor explosion in Nitro, West Virginia, USA. The majority of health effects have been reported among groups with high exposure, including occupational populations such as chemical production workers, pesticide applicators, and individuals who handled or were exposed to materials treated with 2,3,7,8-TCDD-contaminated pesticides. In addition, residents of communities contaminated with tainted waste oil (Missouri, USA) and industrial effluent (Seveso, Italy) have been affected[24]. During the Vietnam War, chloracne in US troops was ascribed to exposure to the defoliant Agent Orange.

Epidemiology

Oil acne is the most common form of occupational acne.

Pathogenesis

Continued exposure to oils results in reactive hyperkeratosis and subsequently follicular occlusion with typical manifestations of acne vulgaris.

Chloracne is caused by exposure to certain halogenated polycyclic hydrocarbons such as polychlorinated dibenzodioxins (PCDDs) and dibenzofurans (PCDFs)[25] which are most often found in fungicides, insecticides, herbicides and wood preservatives. It occurs within 2 months of exposure to chloracnegens and can persist for years despite cessation of exposure. The condition is always a sign of systemic exposure to the causal agent(s), but entry may occur via percutaneous absorption as well as from inhalation or ingestion of the chemicals. After exposure of workers in a large chemical factory to hexachlorobenzene[26], blood levels in those with chloracne were compared to the levels in workers without chloracne. Levels were calculated as toxicity equivalents of tetrachlorodibenzo-*p*-dioxin (TCDD). In the chloracne group, blood levels ranged from 1168 to 22 308 pg/g blood lipid. In the exposed but chloracne-free group, the range was from 424 to 662 pg/g. It was thus concluded that chloracne developed at blood levels between 650 and 1200 pg/g.

Fig. 16.13 Chloracne. Note involvement of retroauricular skin with numerous comedones (primarily closed) and cysts. The clinical differential diagnosis includes folliculotropic mycosis fungoides.

Clinical features

Oil acne and tar acne

Contact with acnegenic substances, such as creosote, oils and greases, can worsen existing acne. Oils used in industry, such as cutting oils (paraffin/oil mixtures), tars (pitch and creosote), and crude petroleum oils such as diesel oil, can all cause acne. Lesions may develop both in the usual sites for acne and in unusual sites such as the arms or abdomen. The latter are often the sites in contact with the oil, being beneath clothing that is saturated with the oils. Oils mists can also induce acneiform eruptions.

Acne mechanica

Acne mechanica is a form of acne, usually inflammatory, that is exacerbated by repeated frictional trauma that occludes the follicle. It is localized to sites of pressure, e.g. the back in long-distance drivers, the neck in violinists, and the chin in football players who wear helmets with chin straps.

Acne cosmetica

Certain cosmetic ingredients used by models and thespians can induce comedone formation, e.g. lanolin, petrolatum and some vegetable oils.

Chloracne

Chloracne is distinguished from ordinary acne vulgaris by the predominance of open (over closed) comedones and a concentration of lesions over the malar crescent and behind the ears (Fig. 16.13). The first sign of chloracne may be excessive oiliness of the skin. This is accompanied or followed by the appearance of numerous open comedones (i.e. blackheads). In mild cases, open comedones may be limited to the area around the eyes, extending across the temples to the ears. In more severe cases, they may appear more extensively on the body, especially in the malar region, other facial areas, behind the ears, and on the arms. The open comedones are usually accompanied by fluid-filled cysts and by an increased or darker growth of body hair.

As the disease progresses, milia form together with distinctive yellowish epidermoid inclusion cysts (some of which may become inflamed) on the face, behind the ears, and on the neck, buttocks, scrotum and thighs. Some authors have proposed using the term "metabolizing acquired dioxin-induced skin hamartomas" for these dioxin-induced cysts[27]. The skin may become thicker and even desquamate or peel. In severe cases, the acne can result in ulcerations and permanent scars. The condition fades slowly after exposure. Minor cases may disappear altogether, but more severe cases may persist for years. Chloracne is difficult to treat and can last for long periods without known additional exposure to chloracnegens. Sites of systemic involvement are the eyes, liver and nervous systems; some chloracnegens can be oncogenic.

Acne due to halogens

Chemicals that contain iodides, bromides and other halogens can induce an acneiform eruption similar to that of corticosteroid acne; however, the iodide-induced eruptions (i.e. iododerma) may be more severe. Patients with bromoderma may also have lesions that resemble pyoderma gangrenosum.

Pathology

Histologic features of comedones are reviewed in Chapter 36. Small infundibular cysts and dilated infundibula filled with orthokeratotic plugs are seen in chloracne. A disappearance of sebaceous glands has been described[27].

Treatment

Treatment consists primarily of avoidance of the cause, although some forms can be persistent and require treatments designed for acne vulgaris, e.g. topical or oral retinoids (see Ch. 36). However, chloracne is particularly recalcitrant.

Vibration White Finger

Synonyms: ■ Hand-arm vibration syndrome ■ Dead finger

Key features

- Development of a white finger or fingers in response to cold
- Associated transient loss of sensation
- Possible permanent finger neuropathy and pain in the affected limb
- Associated with exposures to vibrations between 30 and 300 Hz
- Workers at risk include operators of chainsaws and pneumatic tools

Introduction

Vibration white finger is a relatively frequent disorder among operators of chainsaws, pneumatic tools and hand grinders in cold climates[28]. Up to half of the exposed workforce can be affected.

History

Loriga first described the disorder in Italian marble-quarry workers in 1911. Six years later, this was followed by a description in sandstone cutters in Indiana, USA.

Epidemiology

Prevalence studies have suggested a relationship between symptoms and degree of exposure. This varies, however, with the type of tool and the work process involved. From 1972 to 1990, the prevalence amongst Finnish lumberjacks fell from 40% to 5%. This was attributed to a reduction in the weight and acceleration-induced vibration of their chainsaws[29].

It has been suggested that vibration white finger does not occur in countries with a warm climate. However, this may reflect the absence of the cold that serves as a trigger for symptoms rather than the absence of vibration-induced vascular changes.

Pathogenesis

Vibrations between 30 and 300 Hz are most strongly associated with development of this disorder. While increased activity of the sympathetic nervous system is viewed as the major cause of vibration white finger, it seems probable that local factors are also important. Vibration-induced damage to endothelial vasoregulatory mechanisms with alteration in α-adrenoceptors and impaired release of nitric oxide have been described.

OCCUPATIONAL INFECTIONS ACQUIRED FROM ANIMALS OR HUMANS WITH CUTANEOUS MANIFESTATIONS			
Occupation	**Infection**	**Organism**	**Animals/other humans**
Healthcare Sex industry Laboratory worker	Herpetic whitlow	HSV	Humans
	Scabies	*Sarcoptes scabiei*	
	Syphilis	*Treponema pallidum*	
	AIDS	HIV	
Farmer Abattoir* worker Veterinarian	Orf	Parapoxvirus	Sheep, goats, reindeer
	Milker's nodule	Parapoxvirus	Cows
	Brucellosis	*Brucella suis, B. abortus, B. melitensis*	Pigs, cattle, sheep
Farmer Wool sorter Dock worker Butcher	Anthrax	*Bacillus anthracis*	Cattle, sheep, goats, buffaloes, camels
Fisherman Tropical fish keeper Fish market worker	Fish tank granuloma	*Mycobacterium marinum*	Fish
Butcher Abattoir worker Meat and fish packers	Butcher's warts	Human papillomavirus, primarily types 2 and 7	Humans
	Impetigo	*Staphylococcus aureus*	
	Erysipelas	Group A streptococci	
Fisherman Abattoir worker Farmer Butcher, cook Veterinarian	Erysipeloid	*Erysipelothrix rhusiopathiae (insidiosa)*	Shellfish, fish, birds and mammals (esp. pigs)
Fisherman	Cellulitis	*Vibrio vulnificus*	Salt water
Farmer Veterinarian	Tinea corporis, capitis, barbae due to zoophilic species	*Microsporum canis*	Cats, dogs
		M. nanum	Pigs
		Trichophyton mentagrophytes var *mentagrophytes*	Small mammals
		T. verrucosum	Cattle
		T. gallinae	Chickens

*Slaughterhouse.

Table 16.7 Occupational infections acquired from animals or humans with cutaneous manifestations. Laboratory personnel can also acquire primary cutaneous forms of dimorphic fungal infections. HSV, herpes simplex virus.

Smoking is known to contribute to the development of the disorder, presumably because of the vasoconstrictive effect of nicotine.

Clinical features

Onset may occur within 3 months of beginning work but more frequently it takes 2–3 years to develop. Typically, a white patch of skin develops in response to cold-induced vasospasm. It is well demarcated from surrounding areas. Reduction in sensation occurs because the touch receptors are unable to function without adequate blood supply and this results in reduced dexterity. Episodes cease upon rewarming, often with the development of reactive hyperemia. Although caused by vibrating tools, attacks are not usually triggered by work with the vibrating tool.

The condition is graded according to the severity and frequency of symptoms, starting on the tips of the fingers (stage 1) and spreading to affect the whole digit (stage 3). In the most severe form, there are trophic changes and ulceration (stage 4). To aid in the diagnosis, finger skin temperature and finger systolic blood pressure can be measured in response to cold exposure, but the results are not discriminatory.

Pathology

The histologic features of vibration white finger include a significant reduction in the number of unmyelinated nerve fibers containing the neuropeptide calcitonin gene-related peptide (CGRP). There also may be hypertrophy of arterial smooth muscle. However, histology is not routinely utilized in the diagnosis of vibration white finger.

Differential diagnosis

In contrast to the symmetric distribution seen in Raynaud's disease, in vibration white finger the blanching is asymmetric and occurs on those digits most exposed to vibration; the thumbs are usually spared. However, Raynaud's phenomenon can also result from repeated occupational trauma, particularly in those who use tools that require a squeezing action, e.g. farmers and mechanics.

The hypothenar hammer syndrome results from occlusion of the ulnar artery as a consequence of repeated trauma to the palms and may be misdiagnosed as Raynaud's phenomenon.

Treatment

The prognosis for affected individuals is good: the disease regresses upon cessation of exposure. This is particularly true in the early stages, provided there are no other environmental or constitutional factors contributing to the disorder. As a consequence, no specific treatment may be required other than avoidance[30]. Therapeutically, topical nitroglycerin ointment or sustained-release glyceryl trinitrate patches are effective, but the condition relapses upon withdrawal. Various systemic agents used for Raynaud's disease, e.g. calcium channel blockers, have also been used for symptom control.

Infections

Many occupations, particularly those involving contact with animals, are associated with exposure to infectious agents. For example, individuals with occupations that involve wet work combined with rough physical conditions, such as butchers, slaughterhouse workers, and meat and fish packers, commonly develop infections with pyogenic bacteria and human papillomavirus (butcher's warts) through cuts and abrasions. Epidemics of methicillin-resistant *Staphylococcus aureus* infection have also occurred in professional football players in the US and these outbreaks are often difficult to control[31].

In the metal working industry, staphylococcal folliculitis can develop as a result of exposure to contaminated work materials such as coolant fluid. In addition, outdoor workers are exposed to environmental pathogens both by direct contact or implantation with soil or plants (e.g. mycetoma, chromomycosis) as well as following inoculation, most commonly via insect bites (e.g. Lyme disease, tularemia, typhus, spotted fevers).

Common infections may also occur more frequently as a result of environmental factors in the workplace. Increased humidity may lead to bacterial and fungal infections (due to dermatophytes or *Candida* spp.) in flexural body sites along with maceration of the skin. Pitted keratolysis caused by *Corynebacterium* spp. or *Micrococcus sedentaris* occurs on the soles in association with the use of occlusive footwear.

The main infectious organisms related to specific occupations are summarized in Table 16.7. Further information on these infections[32] can be obtained by reference to the relevant chapter in this book (Section Twelve).

ACKNOWLEDGMENT

I am grateful for the significant contribution of Peter Friedmann, MD, who collaborated in writing this chapter in previous editions.

REFERENCES

1. Kanerva L, Elsner P, Wahlberg JE, et al. Handbook of Occupational Dermatology. Berlin: Springer Verlag, 2000.
2. Lushniak BD. The importance of occupational skin disease in the United States. Int Arch Occup Environ Health. 2003;76:325–30.
3. McCall BP, Horwitz IB, Feldman SR, et al. Incidence rates, costs, severity, and work-related factors of occupational dermatitis. Arch Dermatol. 2005;141:713–18.
4. Turner S, Carder M, van Tongeren M, et al. The incidence of occupational skin disease as reported to The Health and Occupational Reporting (THOR) network between 2002 and 2005. Br J Dermatol. 2007;157: 713–22.
5. Meyer JD, Chen Y, Holt DL, et al. Occupational contact dermatitis in the UK: a surveillance report from EPIDERM and OPRA. Occup Med. 2000;50:265–73.
6. McNamee R, Carder M, Chen Y, Agius R. Measurement of trends in incidence of work-related skin and respiratory diseases, UK 1995–2005. Occup Environ Med. 2008;65: 808–14.
7. DeGroot AC. Patch Testing – Test Concentrations and Vehicles for 4350 Chemicals, 3rd edn. Wapserveen: AC deGroot, 2008.
8. Molin S, Vollmer S, Weiss EH, et al. Filaggrin mutations may confer susceptibility to chronic hand eczema characterized by combined allergic and irritant contact dermatitis. Br J Dermatol. 2009;161:801–7.
9. Pruitt VM. Work-related burns. Clin Occup Environ Med. 2006;5:423–33.
10. Sertoli A, Giorgini S, Farli M. Fiberglass dermatitis. Clin Dermatol. 1992;10:167–74.
11. Royal College of Physicians. Dermatitis: Occupational Aspects of Management. A National Guideline. London: Royal College of Physicians, 2009.
12. Wall LM, Gebauer KA. A follow-up study of occupational skin disease in Western Australia. Contact Dermatitis. 1991;24:241–3.
13. Wakelin SH. Contact urticaria. Clin Exp Dermatol. 2001;26:132–6.
14. Amaro C, Goossens A. Immunological occupational contact urticaria and contact dermatitis from proteins: a review. Contact Dermatitis. 2008;58:67–75.
15. Sicherer SH. Clinical implications of cross-reactive food allergens. J Allergy Clin Immunol. 2001;108:881–90.
16. Taylor JS, Erkek E Latex allergy: diagnosis and management. Dermatol Ther. 2004;17:289–301.
17. Janssens J, Morren M, Dooms-Goossens A, et al. Protein contact dermatitis: myth or reality? Br J Dermatol. 1995;132:1–6.
18. Allmers H, Schmengler J, John SM. Decreasing incidence of occupational contact urticaria caused by natural rubber latex allergy in German health care workers. J Allergy Clin Immunol. 2004;114:347–51.
19. Nettis E, Colanardi MC, Soccio AL, et al. Double-blind, placebo-controlled study of sublingual immunotherapy in patients with latex-induced urticaria: a 12-month study. Br J Dermatol. 2007;156:674–81.
20. Gawkrodger DJ. Occupational skin cancers. Occup Med (Lond). 2004;54:458–63.
21. Nokso-Koivisto P, Pukkala E. Past exposure to asbestos and combustion products and incidence of cancer among Finnish locomotive drivers. Occup Environ Med. 1994;51:330–4.
22. Fritschi L, Driscoll T. Cancer due to occupation in Australia. Aust N Z J Public Health. 2006;30:213–19.
23. Young C. Solar ultraviolet radiation and skin cancer. Occup Med (Lond). 2009;59:82–8.
24. Sweeney MH, Mocarelli P. Human health effects after exposure to 2,3,7,8-TCDD. Food Addit Contam. 2000;17:303–16.
25. Tindall JP. Chloracne and chloracnegens. J Am Acad Dermatol. 1985;13:539–58.
26. Coenraads PJ, Olie K, Tang NJ. Blood lipid concentrations of dioxins and dibenzofurans causing chloracne. Br J Dermatol. 1999;141:694–7.
27. Saurat JH, Sorg O. Chloracne, a misnomer and its implications. Dermatology. 2010;221:23–6.
28. Pelmear PL Vibration (hand-arm and whole body). In: Baxter PJ, Adams PH, Aw T-C, et al. (eds). Hunter's Diseases of Occupations, 9th edn. London: Arnold, 2004:307–14.
29. Sutinen P, Toppila E, Starck J, et al. Hand-arm vibration syndrome with the use of anti-vibration chain saws: 19-year follow-up study of forestry workers. Int Arch Occup Environ Health. 2006;79:665–71.
30. Faculty of Occupational Medicine. Clinical Testing and Management of Individuals Exposed to Hand Transmitted Vibration. An Evidence Review. London: Faculty of Occupational Medicine, 2004.
31. Kazakova SV, Hageman JC, Matava M, et al. A clone of methicillin-resistant *Staphylococcus aureus* among professional football players. N Engl J Med. 2005; 352:468–75.
32. Harries MJ, Lear JT. Occupational skin infections. Occup Med (Lond). 2004;54:441–9.

Dermatoses Due to Plants 17

Thomas W McGovern

Chapter Contents

Introduction 273
Immunologic contact urticaria 274
Toxin-mediated (non-immunologic) contact urticaria 276
Mechanical irritant dermatitis 277
Chemical irritant dermatitis 278
Phytophotodermatitis 279
Allergic contact dermatitis 281
Occupational plant dermatoses 288

Important botanical synonyms

New family name	Old family name
Apiaceae	Umbelliferae (Parsnip family)
Arecaceae	Palmae (Palm family)
Asteraceae	Compositae (Daisy family)
Brassicaceae	Cruciferae (Mustard family)
Fabaceae	Leguminosae (Pea family)
Lamiaceae	Labiatae (Mint family)
Poaceae	Gramineae (Grass family)

Rhus ≠ Poison ivy or *Toxicodendron* (see text)
Non-immunologic urticaria = Toxin-mediated urticaria

INTRODUCTION

Plants and their products cause a variety of adverse cutaneous reactions, including the vast majority of cases of allergic contact dermatitis. This chapter describes the small minority of plants that cause such problems. (Reactions to members of the kingdoms Fungi and Protista are less common and will not be discussed here.) Plant dermatoses will be presented based on both their clinical features and the plant families that cause them. The major plants that cause allergic contact dermatitis (poison ivy, poison oak, chrysanthemums, and their relatives) are reviewed.

Plant reactions can be classified into urticaria (immunologic and toxin-mediated; see Chs 16 & 18), irritant dermatitis (mechanical and chemical), phototoxic dermatitis (phytophotodermatitis) and allergic contact dermatitis. Table 17.1 lists the most common plant reactions.

Botanical Aspects

To better understand the literature that addresses plant-related dermatoses, one should become familiar with basic botanical nomenclature[1].

Poison ivy as an example of nomenclature

It is occasionally necessary to alter the names of plants. As an example, the genus *Rhus* was once thought to be a cohesive, widespread genus with many species (including poison ivy, known previously as *Rhus radicans* or *Rhus toxicodendron*). Research in the 1950s and 1960s showed that poison ivy and its immediate relatives represented a distinct developmental lineage that should not be classified as *Rhus* but as a distinct genus[2]. The ICBN (International Code of Botanical Nomenclature) showed that the correct genus for the poison ivies and their relatives was *Toxicodendron*, and thus the correct scientific name for common poison ivy is *Toxicodendron radicans*.

Binomial nomenclature

The nomenclatural scheme of botany and zoology gives every entity two names: a generic name followed by a specific epithet, e.g. *Toxicodendron radicans* for poison ivy. It is customary to place after the binomial name a reference to the person (authority) who first published the specific epithet. The full binomial name of common poison ivy reads "*Toxicodendron radicans* (L.) O. Ktze". "(L.)" refers to Carl Linnaeus, who first named the plant with the specific epithet *radicans*. "O. Ktze" refers to Otto Kuntze, who transferred the epithet *radicans* from the genus *Rhus* into the genus *Toxicodendron*.

The genus, species and any infraspecific epithets are called the "minor categories of nomenclature" and these names are used when citing the name of a plant (Table 17.2). Genera are grouped into families, and if you know the family to which a plant belongs, you will probably be able to determine what kind of dermatologic manifestations (if any) it can cause.

Plant identification

Plant identification is difficult for the neophyte botanist (i.e. the vast majority of dermatologists). Therefore, the following recommendations should be followed to identify an unknown plant that you or your patient thinks is causing an eruption.

- *Collect specimens*. Herbs (low-growing plants with fleshy stems) should be collected in their entirety with their flowering and/or fruiting materials intact. For shrubs (low-growing plants with woody stems), the end of a branch (up to 60 cm) should be collected, with the leaves attached, and with any flowering or fruiting materials present. You may press plants before submitting them for identification, or you can put them into a plastic bag with *no water added* and submit them with data on (a) where that plant was collected and (b) a habitat description (cultivated in a garden, wild along a creek bank, in an open field, in high-elevation woodlands, etc.).
- *Involve a plant taxonomist*. Every US state and most Canadian provinces have an established mechanism for routine and rapid plant identification, and in most places the service is free. In suburban and rural areas, the county or regional agricultural extension service or farm advisors are knowledgeable about the procedures for immediate plant identification, and they have access to the regional herbaria. Urban areas have similar services, usually accessed through the urban horticulturist of the state extension service, or through the local garden center or botanical garden. In other countries, one should look for a nearby herbarium housing a collection of flora of the region. A botanist who works there would likely be willing to help identify an unknown plant.

Patch Testing

Details of patch testing are beyond the scope of this chapter (see Ch. 14). The reader is also referred to the excellent paper by Mitchell[3]. He rightly points out that identifying a plant causing a reaction in an individual patient is "a minor or even a major research exercise". He recommends collecting samples of all plants that a patient thinks could be causing his or her dermatitis. Then, all these plants must be identified by a plant expert. After that, one should start patch testing the patient to those plants known to cause allergic reactions. The most common allergenic plants and a proposed botanical screening tray are found in Table 17.3.

MOST COMMON PLANT DERMATOSES			
Binomial name	**Common name**	**Reaction type**	**Inciting agent**
Allium sativum	Garlic	ACD ICD Urticaria	Diallyldisulfide, allicin Probably the same Unknown
Alstroemeria spp.	Peruvian lily	ACD	Tulipalin A > B
Apium graveolens	Celery	Phytophotodermatitis	Furocoumarins, particularly in plants infected by "pink-rot" fungus
Capsicum annuum	Hot peppers	Erythema/edema/burning	Capsaicin
Citrus latifolia	Persian lime	Phytophotodermatitis	Furocoumarins
Dieffenbachia picta	Dumb cane	ICD	Calcium oxalate
Narcissus pseudonarcissus	Daffodils	ICD	Calcium oxalate
Opuntia spp.	Prickly pear and others	Mechanical irritant dermatitis	Glochids
Toxicodendron radicans	Poison ivy	ACD ICD (black-spot reaction)	Alkyl-catechols and resorcinols in urushiol
Toxicodendron diversilobum	Poison oak	ACD ICD (black-spot reaction)	Alkyl-catechols and resorcinols in urushiol
Tulipa spp.	Tulips	ACD ICD	Tulipalin A > B Coarse hair on bulbs
Urtica dioica	Stinging nettle	Urticaria	Histamine
X *Dendranthema* cultivars	Chrysanthemums	ACD	Sesquiterpene lactones

Table 17.1 Most common plant dermatoses. These are admittedly biased by the anecdotal and unscientific observations of the author. ACD, allergic contact dermatitis; ICD, irritant contact dermatitis.

THE BASIC NOMENCLATURAL SCHEME FOR PLANTS, USING COMMON POISON IVY AS THE EXAMPLE	
Kingdom	**Plantae (Metaphyta)**
Division	Magnoli<u>ophyta</u> (flowering plants)
Class	Magnoli<u>opsida</u> (dicots)
Subclass	Rosi<u>dae</u>
Order	Sapind<u>ales</u>
Family	Anacardi<u>aceae</u> (sumac or cashew family)
Genus	*Toxicodendron*
Species	*radicans*
(Author's name)	(L.) O. Ktze

Table 17.2 The basic nomenclatural scheme for plants, using common poison ivy as the example. The distinctive ending for each category is underlined. Note that the minor categories of nomenclature have no special endings.

MOST COMMON RELEVANT BOTANICAL ALLERGENS AND PROPOSED BOTANICAL SCREENING TRAY		
Plant name	**Plant family**	**Test solution**
Achillea millefolium (yarrow) *Arnica* spp. *Chrysanthemum* cultivars *Matricaria chamomilla* (chamomile) *Tanacetum parthenium* (feverfew)	Asteraceae	Compositae mix 6% in petrolatum
Cananga odorata	Anonaceae	Cananga (ylang-ylang) oil 2% in petrolatum
Citrus aurantium var. *amara*	Rutaceae	Neroli oil 4% in petrolatum
Lavandula spp.	Lamiaceae	Lavender (absolute) 2% in petrolatum
Lichens (fungus–alga dual organisms)		Lichen acid mix 0.3% in petrolatum
Melaleuca alternifolia	Myrtaceae	Tea tree oil 5% in petrolatum
Mentha spp.	Lamiaceae	Spearmint oil 5% in petrolatum
Pelargonium cultivars	Geraniaceae	Geranium oil (Bourbon) 2% in petrolatum
Rosa damascena	Rosaceae	Rose oil (Bulgarian) 2% in petrolatum
Santalum album	Santalaceae	Sandalwood oil 2% in petrolatum
Taraxacum officinale	Asteraceae	Dandelion 2.5% in petrolatum

Table 17.3 Most common relevant botanical allergens and proposed botanical screening tray. This list may be helpful to narrow down a potential botanical allergy in a patient who brings his or her specimens into your office to examine[4].

IMMUNOLOGIC CONTACT URTICARIA

Key features

- Atopic patients
- Frequent contact with fresh fruits and vegetables
- May present as urticaria, pruritus, burning or chronic dermatitis
- Oral allergy syndrome is mucosal contact urticaria to antigens similar to allergenic pollen
- Protein contact dermatitis represents an eczematous eruption arising from repeated urticarial reactions

Urticarial reactions due to plants are divided into immune and non-immune (toxin-mediated causes). Several cutaneous reaction patterns besides wheals are possible, e.g. erythema, dermatitis.

Epidemiology

Immunologic contact urticaria is fairly uncommon and classically affects individuals who are long-time food handlers and/or atopic. However, fully half of patients with "protein contact dermatitis" (an eczematous eruption arising from repeated urticarial reactions) are not atopic.

Examples of reported urticants include common vegetables, fruits, herbs, nuts, shrubs, algae, lichens, trees and grasses. Perhaps all plants are capable of causing immunologic urticaria, but only the ones handled most frequently cause problems clinically (Table 17.4). Celery (*Apium graveolens*) is the plant most likely to cause a generalized urticarial or anaphylactoid reaction.

SOME OF THE MANY PLANTS IMPLICATED AS CAUSES OF IMMUNOLOGICALLY MEDIATED URTICARIA		
Binomial name	**Common name**	**Notes**
Actinida chinensis	Kiwi	
Agave americana	Century plant	
Allium cepa	Onion	
Allium sativum	Garlic	
Allium schoenoprasum	Chives	
Ananas comosus	Pineapple	
Apium graveolens	Celery	Most common cause of systemic contact urticaria syndrome
Brassica oleraceae capaitata	Cabbage	
Brassica oleraceae botrytis	Cauliflower	
Carum carvi	Caraway	
Cichorium endiva	Endive	
Cichorium intybus	Chicory	
Cinnamomum spp.	Cinnamon	
Cirsium spp.	Thistle	
Citrus limon	Lemon	
Citrus paradisi	Grapefruit	
Citrus sinensis	Sweet orange	
Coffea arabica	Coffee	
Cucumis melo	Melon	
Cucumis sativus	Cucumber	
Daucus carota	Carrot	
***Dendranthema* spp.**	Chrysanthemum	
Ficus carica	Fig	
Foeniculum vulgare	Dill	
Hevea brasiliensis	Rubber tree	Numerous cross-reactors (see text)
Lactuca sativa	Lettuce	
Lycopersicon lycopersicum	Tomato	
Malus spp.	Apple	
Mangifera indica	Mango	
Medicago sativa	Alfalfa	
***Musa* spp.**	Banana	
Pastinaca sativa	Parsnip	
Petroselinum crispum	Parsley	
Prunus armeniaca	Apricot	
Prunus domestica	Plum	
Prunus persica	Peach	
Pyrus commuis	Pear	
Ricinus communis	Castor oil plant	
Solanum tuberosum	Potato	Most common cause in one review
Tulipa spp.	Tulip	
Zea mays	Corn	

Table 17.4 Some of the many plants implicated as causes of immunologically mediated urticaria. Those in bold have also been demonstrated to cause protein contact dermatitis. Any plant can probably cause urticaria, and this list probably reflects frequency of contact.

Pathogenesis (see Ch. 18)

The IgE-mediated release of vasoactive mediators from mast cells leads to local urticaria and, rarely, a "contact urticaria syndrome" that includes local wheals with systemic symptoms involving the nose, throat, lungs, gastrointestinal tract or cardiovascular system. The main factor seems to be histamine, but prostaglandins, kinins and leukotrienes probably augment the inflammatory response.

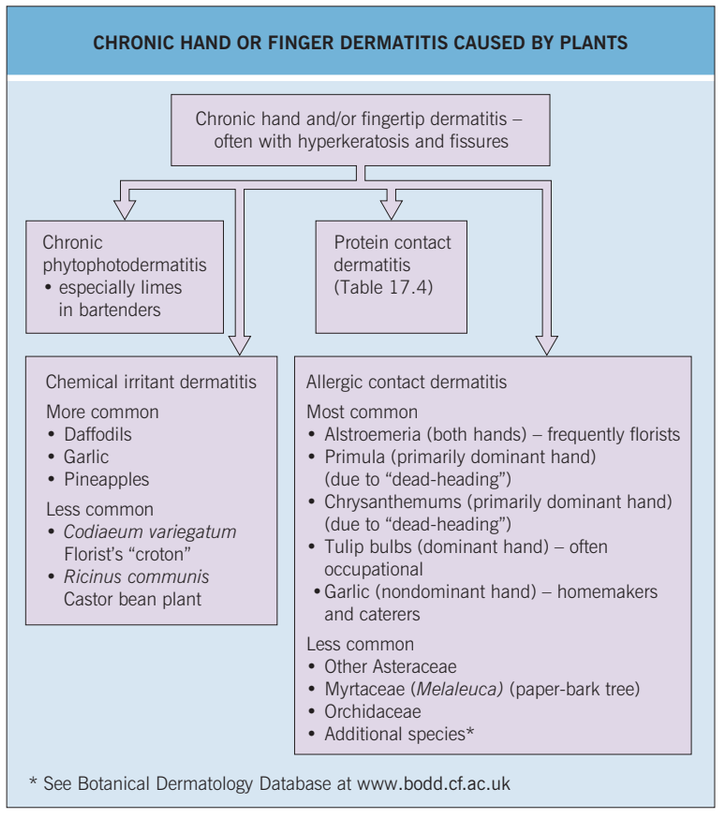


Fig. 17.1 Causes and types of chronic hand or finger dermatitis caused by plants.

Clinical Features

Within 30 minutes of contact with certain fresh foods, affected individuals experience pruritus, erythema, urticarial swelling, and even dyshidrotic-like vesicles. Sometimes, individuals experience only symptoms of pruritus, burning or tingling without objective findings[5]. Theoretically, any plant could cause contact urticaria, but continued exposure on the wet, macerated skin of food handlers has caused certain foodstuffs to be the most notorious offenders (see Table 17.4). Cooking, processing, deep-freezing or crushing fruits and vegetables generally reduces their allergenicity.

Some individuals become cross-sensitized to pollen and similar allergens in fruits or vegetables[6]. Upon eating a cross-reacting food, they experience sudden, IgE-mediated, oral cavity itching, stinging and pain. Edema of the lips, tongue, palate and pharynx typically ensue as the "oral allergy syndrome" (OAS) progresses. Gastrointestinal symptoms and anaphylaxis are possible if enough allergens are ingested. As an example, 70% of European patients with immediate hypersensitivity to birch pollen develop OAS while eating apples, pears, cherries, peaches, plums, apricots, almonds, celery, carrots, potatoes, kiwis, hazelnuts or mangoes. Pollen-associated foods are often, but not always, edible when heated.

The term "protein contact dermatitis" is used to describe a chronic dermatitis in which patch tests are typically negative but prick tests to large protein allergens are positive[7]. Patients develop a chronic dermatitis that acutely urticates within minutes of contact with the offending allergen. There are multiple mechanisms by which plants can cause chronic hand and fingertip eczema (Fig. 17.1).

Differential Diagnosis and Pathology

See Toxin-mediated (Non-immunologic) Contact Urticaria and Chs 16 & 18.

Treatment

Prevention is the preferred form of "treatment", but oral antihistamines are sometimes helpful. Parenterally administered epinephrine (adrenaline) is required for anaphylactic reactions.

TOXIN-MEDIATED (NON-IMMUNOLOGIC) CONTACT URTICARIA

Key features

- Anyone can be affected
- Stinging nettles (*Urtica* spp.) are most common cause
- Reaction can be subjective only
- Plants contain histamine, serotonin and acetylcholine within sharp hairs

History

Plants causing toxin-mediated urticaria have been used since antiquity as counterirritants in folk medicine. *Urtica dioica* parts have been used to produce homemade diuretics. Stem fibers were even used to make cloth until the early parts of the twentieth century. Native Americans used *U. dioica* subsp. *gracilis* to treat rheumatism, stomach upset, childbirth, paralysis, fevers, colds and tuberculosis.

Epidemiology

Members of the family Urticaceae cause the majority of plant-induced contact urticaria. Because all persons exposed to the toxins develop urticaria, toxin-mediated urticaria is far more common than immunologic urticaria. Because very few affected people seek medical attention, the true incidence of toxin-mediated urticaria is unknown. The most common culprit in the US is the stinging nettle (*Urtica dioica*) (Fig. 17.2A). It is now widely scattered throughout the northern hemisphere (except in lowland tropical areas), especially in moist woods, roadsides and on waste land. Other common urticating plants are listed in Table 17.5.

Pathogenesis (see Ch. 18)

Inciting plants possess sharp hairs (trichomes) on leaves (Fig. 17.2B) and stems (Fig. 17.2C). The proximal silicaceous hair is attached to a distal calcified portion that possesses a terminal bulb. When rubbed against, the bulb dislodges to reveal a beveled, hypodermic needle-like silicaceous hollow (Fig. 17.2D). These hollows release irritant chemical cocktails (histamine, acetylcholine, serotonin) that supposedly act as a defense mechanism against herbivores.

Clinical Features

Wheals achieve maximal size between 3 and 5 minutes after contact, and erythema, burning and itching last for 1–2 hours. A persistent tingling sensation may last 12 hours or more.

Reactions to stinging nettle pale in comparison to those elicited by members of the *Dendrocnide* genus of the Urticaceae family. Found mostly in eastern Australian rain forests, these trees grow up to 40 m in height. Young shoots are covered with stiff stinging hairs. Severe urticaria from these may last for weeks, and contact with water or cold objects reactivates the urticaria. Severe, intermittent, stabbing pains may follow the course of lymphatics. Many equine deaths and one human death due to contact with *Dendrocnide* have been documented.

Pathology (see Ch. 18)

Five minutes after contact with *Urtica dioica*, dermal edema and telangiectasias with or without mild spongiosis are seen. At 12 hours, the edema resolves but vasodilation persists. Some patients develop spongiosis plus neutrophilic and/or lymphocytic infiltrates. Mast cells are observed within the papillary dermis at 12 hours, but not at 5

THE MOST COMMON PLANTS CAUSING TOXIN-MEDIATED URTICARIA

Family	Genus	Species	Notes
Urticaceae (nettle family)	*Urtica*	*dioica, urens, pilulifera*	Stinging nettles – worldwide
	Laportea	*canadensis*	"Wood nettle", 5-foot-tall perennial herb – NE USA
	Dendrocnide	*gigas, moroides, photinophylla*	Potentially deadly stinging trees – eastern Australian rainforests
Euphorbiaceae (spurge family)	*Acidoton*	*urens*	Tropical Americas
	Cnidosculus	*stimulosus*	Spurge nettle – SE USA
		other species	Spurge nettles of tropical Americas
Hydrophyllaceae (water-leaf family)	*Wigandia*	*caracasana, urens*	Large-leafed shrubs – tropical Americas

Table 17.5 The most common plants causing toxin-mediated urticaria[8].

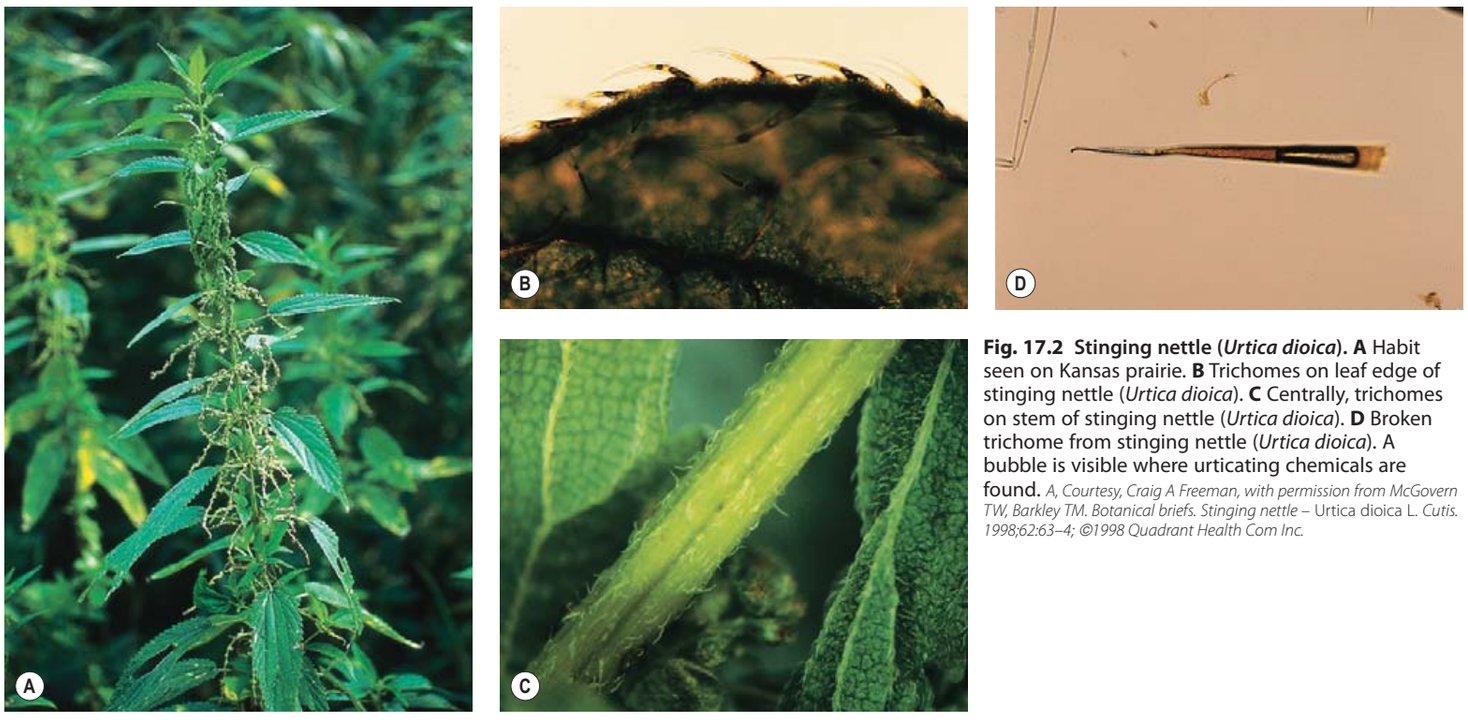


Fig. 17.2 Stinging nettle (*Urtica dioica*). A Habit seen on Kansas prairie. **B** Trichomes on leaf edge of stinging nettle (*Urtica dioica*). **C** Centrally, trichomes on stem of stinging nettle (*Urtica dioica*). **D** Broken trichome from stinging nettle (*Urtica dioica*). A bubble is visible where urticating chemicals are found. *A, Courtesy, Craig A Freeman, with permission from McGovern TW, Barkley TM. Botanical briefs. Stinging nettle –* Urtica dioica L. *Cutis. 1998;62:63–4; ©1998 Quadrant Health Com Inc.*

minutes[9]. Although histamine, acetylcholine and serotonin explain the early reaction (triple response of Lewis), they do not account for the persistent paresthesias.

Differential Diagnosis (see Ch. 18)

Although the evaluation of such patients is difficult, office testing of suspected allergens or toxin-containing plants may assume one of seven methods[5]. The most sensitive tests for immunologic contact dermatitis are the prick and scratch-chamber tests. For the scratch-chamber test, a 5-mm scratch is made on the back or forearm. Test material is applied and occluded with a Finn chamber for 15 minutes. The site is examined following Finn chamber removal and every 15 minutes for an hour. After reading, the chamber can be replaced for 48 hours to test for delayed hypersensitivity.

The method of choice for diagnosing toxin-mediated urticaria is the open application test: 0.1 ml of the suspected urticant is spread on a 3 × 3 cm area of skin. Dilution series are often used. The sites are observed every 10–15 minutes for an hour. Maximal erythema and edema typically occur 30–40 minutes after application. Test sites should be examined at 24 hours for irritant reactions.

For unusual plant products, 10–20 controls should be tested so that toxin-mediated urticaria and irritant dermatitis can be excluded as causes. Serologic tests such as the radioallergosorbent test (RAST) usually do not convey as much information as prick or scratch-chamber tests.

Treatment

Most stings are benign, self-limited, and require no treatment. Spines may be removed via glue or "sticking plaster" plus gauze as described in the next section. Topical agents, e.g. pramoxine, or oral analgesics may provide some relief of symptoms.

MECHANICAL IRRITANT DERMATITIS

Key features

- Large spines and thorns cause penetrating injuries and secondary infection
- Smaller emergences (glochids) act like small fishhooks and embed in skin
- Prickly pears are a cause of glochid dermatitis

Epidemiology

Mechanical irritant dermatitis can affect anyone. Most cacti and several other plants can inflict mechanical injury by large (spines) or small (glochids) emergences. Generally, the amount of damage to the skin is inversely proportional to the size of the emergence. Many of the plant families and genera that cause mechanical irritant dermatitis are found in Table 17.6.

Pathogenesis

Whereas cacti possess large spines, the smaller glochids cause more notorious dermatologic problems. The glochids – tufts of hundreds of short, barbed or hooked hairs – arise from pincushion-like structures named "areoles", from which larger spines, if present, also arise. The minute, barbed glochids (Fig. 17.3A) often point outward and backward like a fishhook and produce considerable irritation and pruritus after penetrating the skin. As an example, *Opuntia microdasys* ("polkadot cactus", "bunny ears cactus"), a house and garden favorite, bears disarming-appearing "fluffy" clusters of 100–200 glochids on its pads (see Fig. 17.13).

Clinical Features

Glochid dermatitis from prickly pears (*Opuntia* spp.) is a well-recognized entity[10]. One such species, *Opuntia ficus-indica* (the Indian or Barbary fig), causes "Sabra dermatitis". This pruritic, papular eruption occurs among prickly-pear pickers and those who unwarily stumble into burglar-proof hedges of this native Mexican plant (Fig. 17.3B). The fruit contains the highest concentration of glochids (Fig. 17.3C), and the latter can cause an eruption that is easily confused with fiberglass dermatitis or even scabies. There are some 200 species of *Opuntia*, all native to the New World, ranging from New England and British Columbia southward to the Straits of Magellan. Numerous species have become established in the Mediterranean basin, South Africa, South Asia and Australia.

Glochids may be transferred from clothing to other individuals. The prickly pear should be picked only when wetted, and picking should cease when it is windy, as the glochids can become airborne. As with the urticating plants, irritant hairs and thorns defend against plant-eaters.

Penetrating injuries can also lead to inoculation of microorganisms. *Clostridium tetani* and *Staphylococcus aureus* can be introduced by spines and thorns, and grasses, sphagnum moss and rose thorns can transmit *Sporothrix schenckii*. Atypical mycobacteria such as *Mycobacterium kansasii* (blackberries), *M. marinum* (cactus spines) and *M. ulcerans* (spiky tropical vegetation) have also added infectious insult to mechanical injury.

Treatment

Many intriguing methods of removing glochids have been recommended. Warm wax, glue, sticking plaster, facial gels and masks, or cellophane tape are applied to the affected area and the glochids are then quickly ripped off[11]. In perhaps the only controlled study (in rabbits), glochids (of *Opuntia ficus-indica*) were most effectively removed by first detaching the larger clumps with tweezers and then applying glue and gauze to the affected area. After the glue dried, the gauze was grasped and peeled off, resulting in the removal of 95% of implanted glochids.

COMMON PLANTS KNOWN TO CAUSE MECHANICAL IRRITANT REACTIONS

Family	Genus species	Notes
Araliaceae	*Hedera helix*	Common ivy – leaf-borne stellate hairs detach as leaves age
Asteraceae	*Carduus* and *Cirsium* spp.	Thistles
Asteraceae	*Lactuca serriola*	Prickly lettuce
Boraginaceae	*Borago officianalis*	Borage – sharp, stiff leaf and stem hairs
Cactaceae	*Opuntia* spp.	Prickly pears; "Sabra dermatitis"
Liliaceae	*Tulipa* spp.	Coarse fibers on tulip bulb tunics cause irritant component of "tulip fingers"
Moraceae	*Ficus* spp.	Figs – abrasive bristles on leaves and fruit
	Morus spp.	Mulberries – abrasive bristles on leaves and fruit
Poaceae	Many spp.	Grasses – fine hairs, prickly spikes, and cutting leaf edges
Proteaceae	*Grevillea* spp.	Terminal, sharp points on leaves – Australia
Rosaceae	*Rosa* spp.	Thorns can cause penetrating injuries, tenosynovitis and foreign body granulomata
Rubiaceae	*Galium aparine*	"Goose-grass" – hooked prickles on fruit, stems, leaves
Scrophulariaceae	*Verbascum thapsus*	"Mullein" or "flannel-plant" – woolly hairs on leaves used as facial rubefacient
Sterculiaceae	*Fremontodendron* spp.	"California glory" possesses stiff, stellate hairs

Table 17.6 Common plants known to cause mechanical irritant reactions. Although numerous plants possess irritant appendages, some of the well-known ones are listed here.

Fig. 17.3 Prickly pears (*Opuntia* spp.) and their glochids. A Microscopic appearance of glochids from *Opuntia microdasys*. **B** Prickly pear (*Opuntia ficus-indica*) habit. **C** Prickly pear (*Opuntia ficus-indica*) fruit. Fine spines and glochids are visible. *Courtesy, Dirk Elston, MD.*

CHEMICAL IRRITANT DERMATITIS

Key features

- Calcium oxalate in daffodils is a major cause of plant-related irritant dermatitis in florists and horticulturalists
- Spurges (including poinsettias) contain irritant phorbol esters in latex
- Capsaicin in hot peppers affects cutaneous nerves, but not the skin

History

Chemical irritants derived from plants have been well known for centuries. Native Mexican Indians once used smoke from burning peppers (*Capsicum*) as a weapon against enemies. Latex from the Manchineel tree (*Hippomane mancinella*, Euphorbiaceae) was used by Caribbean people as poison for arrow tips. Approximately 2000 years ago, Dioscorides gave careful instructions for making pills from spurges (Euphorbiaceae) because of the severe skin and eye irritation that could ensue after contact with the latex.

Epidemiology

Several major plant families contain chemical irritants (Table 17.7). These include crystalline calcium oxalate and a wide range of chemicals (e.g. phorbol esters, saponins) dissolved or suspended in plant latex or specific organelles.

Pathogenesis, Clinical Features and Treatment

(see Ch. 15)

Members of many plant families contain chemical irritants (see Table 17.7), and one of the most common irritants is calcium oxalate. A typical calcium oxalate-containing plant, *Dieffenbachia picta* (Araceae), decorates millions of homes and public places. Upon contact with a moist surface, the leaves release the water-insoluble calcium oxalate. If

PLANTS MOST COMMONLY IMPLICATED IN CAUSING CHEMICAL IRRITANT DERMATITIS

Family	Binomial name	Common name	Irritant chemical (location)
Agavaceae	*Agave americana*	Century plant	Calcium oxalate, saponins (latex throughout plant)
Alliaceae	*Allium sativum*	Garlic	Thiocyanates (bulbs)
Amaryllidaceae	*Narcissus* spp.	Daffodil, narcissus	Calcium oxalate (stems, leaves, bulbs)
Anacardiaceae	*Anacardium occidentale*	Cashew tree	Cashew nut shell oil (mesocarp [middle layer] of nut shell [irritant and allergenic])
Araceae	*Dieffenbachia picta*	Dumb cane	Calcium oxalate (leaves and fruits)
	Philodendron spp.	Philodendron	Calcium oxalate (leaves)
Brassicaceae	*Brassica nigra*	Black mustard	Thiocyanates (all parts)
	Raphanus sativus	Radish	
Bromeliaceae	*Ananas comosus*	Pineapple	Bromelain (stem > fruit) Calcium oxalate (all parts)
Euphorbiaceae	*Codiaeum variegatum*	Florist's "croton"	Phorbol esters (latex in stems, leaves, fruits)
	Euphorbia esula	Leafy spurge	
	Hippomane mancinella	Manchineel tree	
	Euphorbia pulcherrima	Poinsettia	
Liliaceae	*Hyacinthus orientalis*	Hyacinth	Calcium oxalate (bulbs)
Polygonaceae	*Rheum rhaponticum*	Rhubarb	Calcium oxalate (leaves)
Ranunculaceae	*Ranunculus* spp.	Buttercups	Protoanemonin (freshly damaged plant parts)
	Aquilegia spp.	Columbine	
	Caltha spp.	Marsh-marigold	
Solanaceae	*Capsicum annuum*	Hot pepper	Capsaicin (placenta of fruit [no dermatitis, only erythema, edema, burning])

Table 17.7 Plants most commonly implicated in causing chemical irritant dermatitis.

plant parts are chewed, salivation, burning, mucosal edema, and blistering ensue. This causes hoarseness or aphonia (hence "dumb cane"). Treatment includes parenteral corticosteroids, antacid mouthwashes, and analgesics. Antihistamines are of no benefit. The pain and edema wane over 4–12 days.

Calcium oxalate enhances the irritancy of other chemicals, such as the proteolytic enzyme bromelain (bromelin), found in pineapples. Pineapple workers often develop cracks, fissures, fingerprint loss, and microhemorrhages on their hands. Calcium oxalate-induced microabrasions allow bromelain to exert its proteolytic effect on dermal blood vessels. Gloves (e.g. nitrile) can be worn for protection.

Bulb dermatitis, though less dramatic, is more common[12]. Daffodil sap contains calcium oxalate and causes "daffodil itch", probably the most common dermatitis in florists. Dryness, scaling, fissures and erythema affect the fingertips, hands and forearms. Bulbs of several other plants (e.g. tulips, hyacinths) are also common causes of dermatitis; these include garlic, the allergens from which are also irritants at high concentrations (Fig. 17.4).

Spurges (Euphorbiaceae) are notorious for their irritant latex but derive their common name from the purgative properties of the seeds. The milky latex contains irritant phorbol esters, diterpenes and/or daphnane esters that may cause a painful, blistering dermatitis and even temporary blindness if the latex contacts the eye. The best-known family member, the poinsettia (*Euphorbia pulcherrina*), possesses a mildly irritating latex.

Buttercups (Ranunculaceae) contain the glycoside ranunculin that is converted to protoanemonin after plant injury. Protoanemonin causes severe, linear vesiculation that may resemble phytophotodermatitis, but without causing subsequent hyperpigmentation. Because protoanemonin rapidly polymerizes to the non-irritant anemonin, only freshly damaged plants cause reactions.

"Chili burns" or "Hunan hand syndrome" occurs commonly among those who remove the skins from large batches of roasted chili peppers (*Capsicum annuum*). The active principle is capsaicin, and when applied to the skin, it depolarizes nerves, causing vasodilation, smooth muscle stimulation, glandular secretion, and sensory nerve activation. Because only nerves are affected, dose-related cutaneous burning, irritation and erythema ensue without blistering. Symptoms may be delayed and last hours to days. The best home remedy for chili burns is handwashing with soap and water followed immediately by 1 hour of immersion in vegetable oil to help remove the fat-soluble capsaicin.

The "century plant" (*Agave americana*) grows in temperate, subtropical and tropical climates and forms rosettes of tough, sword-shaped leaves that often possess spiny margins. There was one report of ten Israeli soldiers who deliberately rubbed broken leaves on their skin and elicited a severe irritant dermatitis with erythema, confluent papulovesicles, and pustules[13]. The marked pruritus and stinging that follows within 5 minutes of contact with agave leaf is thought to be caused by latex-derived calcium oxalate crystals and saponins. Patients often develop a sore throat, headache, diarrhea and/or myalgias. Lesions can be purpuric.

PHYTOPHOTODERMATITIS

Key features

- Non-immunologic – it can happen to anyone
- Need UVA light plus topical or oral contact with photosensitizer
- Furocoumarins (psoralens and angelicins) are most common agents
- Limes, celery and rue are most common causes
- Potential photosensitizing plants of the family Apiaceae can be identified by umbel flower structure

Phytophotodermatitis connotes phototoxic reactions consisting of erythema (with or without blistering) and delayed hyperpigmentation. Phototoxicity implies an inflammatory reaction caused by the combination of a topical or oral photosensitizing agent followed by exposure to the appropriate wavelength of UV radiation. Because this is not an immunologic reaction, no prior sensitization is necessary and anybody can be affected.

Fig. 17.4 Erythematous, burning, edematous scrotum from irritant reaction after applying garlic (*Allium sativum*) to treat a "rash". *Courtesy, Martin Giandoni, MD.*

IMPORTANT MEMBERS OF THE APIACEAE FAMILY (FORMERLY UMBELLIFERAE) IMPLICATED IN PHOTOTOXIC REACTIONS

Scientific name	Common name(s)	Comments
Ammi majus	False Bishop's weed	Historical and economic importance
Angelica archangelica	Angelica	Candied portions used in cakes; characteristic Benedictine flavor
Angelica sylvestris	Wild angelica	
Anthriscus sylvestris	Cow parsley, wild chervil	"Strimmer dermatitis"*
Apium graveolens	Celery	Infected plants have more psoralens
Foeniculum vulgare	Fennel	
Heracleum laciniatum	Tromsø palm	Scandinavia
Heracleum lanatum	Cow parsnip	North America
Heracleum mantegazzianum	Giant Russian hogweed, wild rhubarb, hogweed tree	Giant weed naturalized across UK, Canada, US
Heracleum sphondylium	Common hogweed	Main cause of "strimmer dermatitis"*
Pastinaca sativa	Parsnip	Furocoumarins in leaves, roots, stem, fruits
Petroselinum crispum	Parsley	

*Strimmer = string-trimmer garden tool for cutting weeds.

Table 17.8 Important members of the Apiaceae family (formerly Umbelliferae) implicated in phototoxic reactions.

History[14]

As early as 2000 BC, vitiligo patients were encouraged to lie in the sun after picking *Ammi majus* from the Nile River valley and rubbing the juice on their skin. By 1400 BC, Indian doctors were using boiled extracts of *Psoralea corylifolia* (babchi or scurf-pea), from which we derive the term "psoralen". In 1897, Apiaceae-induced dermatitis was first reported, but the need for concomitant UV radiation went unnoticed. In 1942, Klaber introduced the term "phytophotodermatitis" to emphasize that a combination of plants and light is required for the reaction.

Epidemiology

Members of two plant families are the most common causes of phytophotodermatitis (Tables 17.8 & 17.9): Apiaceae (formerly Umbelliferae) and Rutaceae (includes the citrus fruits). Members of the mulberry family (Moraceae) and pea family (Fabaceae) also contain furocoumarins.

Apiaceae

Plants of the family Apiaceae cause more phytophotodermatitis than do plants of any other family (see Table 17.8). A distinctive floral umbel makes them easy to recognize: numerous small flowers are held in a simple umbel (a cluster of flowers on stalks of roughly equal length arising from a single point). Many small umbels can form "compound

PHOTOTOXIC MEMBERS OF THE FAMILY RUTACEAE	
Citrus aurantiifolia	Key lime
Citrus latifolia	Persian lime or seedless lime
Citrus aurantium	Bitter orange
Citrus bergamia	Bergamot orange
Citrus limetta	Sweet lemon
Citrus limon	Lemon
Citrus sinensis	Sweet orange
Citrus paradisii	Grapefruit
Cneoridium dumosum	Coast spice bush, berry rue
Dictamnus albus	Burning bush, gas plant
Phebalium argenteum	Blister plant
Pelea anisata	Mokihana
Ruta graveolens	Rue (UK)

Table 17.9 Phototoxic members of the family Rutaceae.

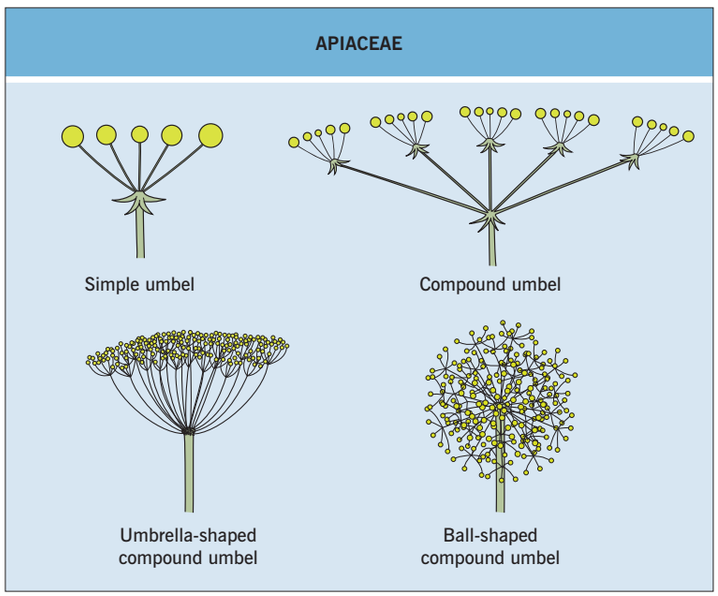


Fig. 17.5 Apiaceae. Compound umbels can be umbrella-shaped or ball-shaped.

umbels" (Fig. 17.5). Compound umbels may be umbrella-shaped or ball-shaped. The flower heads are sheathed at the base by one or more leaf-like bracts.

Heracleum sphondylium, common hogweed, is a major cause of phytophotodermatitis in Europe and North America. Once introduced into a new area, *Heracleum* species tend to grow out of control. The black seeds and leaves contain the highest concentrations of psoralens. The greatest threat from *Heracleum* occurs in the autumn, when the weather favors the development of many seeds. The hollow stems of *H. mantegazzianum and H. laciniatum* (Tromsø palm, Norway) used as peashooters and trumpets have caused perioral blisters in children.

Rutaceae

The Rutaceae family includes plants from tropical (*Citrus* spp.), subtropical, and temperate (*Ruta* spp.) climates and is the second most common family of plants reported to cause phytophotodermatitis (see Table 17.9). Many Rutaceae grow as shrubs or small trees, with flowers having four or five sepals (modified leaves that comprise a calyx) and petals as well as fleshy fruit. A major cause of phototoxic reactions in the US, especially in Florida and the desert southwest, is the rind of the Persian lime, *Citrus latifola*. Bartenders commonly develop vesicles on their index and middle fingers from squeezing limes to make cocktails. Although limes are notorious for this, even the sweet orange, *Citrus sinensis*, can cause a phototoxic cheilitis after contact with the rind.

Ruta graveolens, garden rue, is a native sub-shrub of the Mediterranean area with a long history as a folk medicine remedy for urticaria, warts and erysipelas. Its taste and smell are incredibly bitter. Extracts of the plant have been used to repel biting insects. It is probably the most common cause of phototoxicity acquired in English gardens. This plant contains 5-MOP (5-methoxypsoralen; bergapten), 8-MOP (xanthotoxin) and angelicins.

Dictamnus albus, the gas plant or burning bush, exudes an aromatic oil that can be ignited briefly without harming the plant. It has become a common yard plant in the US and Canada, and it grows wild in central and southern Europe, eastern Siberia and northern China. The seed pods have high concentrations of both 5-MOP and 8-MOP.

Moraceae

The mulberry family includes *Ficus carica* (the fig tree). This Middle Eastern native has been widely cultivated throughout warm, temperate regions of the world. Psoralens and 5-MOP are found chiefly in the sap of leaves and shoots[15]. Furocoumarins are generally not found in ripe or unripe fruit[15].

Fabaceae (Leguminosae)

The main source of psoralens for treatment of vitiligo in India is *Psoralea corylifolia*. It has been used to treat vitiligo since 1400 BC, and its seeds are still used for this purpose.

Other families

Other plant families have been reported to contain furocoumarins and other photosensitizing chemicals, but none have been shown to cause clinical phytophotodermatitis except St John's wort (*Hypericum perforatum*). In 11 of 23 (48%) HIV-infected patients receiving systemic hypericin as a potential antiretroviral agent, severe cutaneous phototoxicity developed.

Pathogenesis

Furocoumarins include linear (psoralens) and angular (angelicins) tricyclic structures. The most severe reactions occur with 5-MOP (bergapten), originally isolated from *Citrus bergamia* (Rutaceae), the bergamot orange, and 8-MOP (xanthotoxin), first isolated from *Fagara xanthoxyloides* (Rutaceae).

The first phase of phytophotodermatitis is an acute, oxygen-dependent skin injury. By electronic microscopy, cytoplasmic vacuolization and membrane rupture of keratinocytes are observed immediately following UVA irradiation of psoralen-exposed skin. Within 2 hours, desmosomal plaques have detached and degenerated[16]. It is known that UVA has the ability to excite psoralens to form covalent monoadducts with pyrimidines and interstrand DNA cross-links (see Ch. 134). Psoralen-induced hyperpigmentation occurs via increased melanocyte mitosis and dendricity, melanocyte hypertrophy, increased tyrosinase activity, and change in the size and distribution of melanosomes.

Furocoumarins appear necessary to defend plants from fungal attack. *Apium graveolens*, fresh celery, contains 10–100 mcg/g wet weight of psoralens in healthy plants, but may have 320 mcg/g when infected with *Sclerotinia sclerotium* (pink-rot disease). Disease-resistant celery unfortunately possesses high levels of furocoumarins concentrated in the leaf sap and stem sap.

Clinical Features

Cutaneous sensitivity to UV light peaks 30–120 minutes after contact with furocoumarins. Bizarre configurations of erythema, edema and bullae appear after 24 hours and peak at 72 hours (Fig. 17.6). These painful, non-pruritic reactions are more often seen in mid to late summer, when psoralen concentrations are highest in the offending plants and more skin is exposed to direct sunlight. To avoid misdiagnosis as poison ivy dermatitis, physicians must note that the initial erythematous and bullous reaction only occurs in sun-exposed areas. Hyperpigmentation appears 1–2 weeks later and lasts months to years. Occasionally, low-dose UVA and/or psoralens cause hyperpigmentation without a preceding vesicular or erythematous eruption (Fig. 17.7; see

Fig. 17.6 Bullous phase of phytophotodermatitis. There was associated burning but no pruritus, and the linear bullae were replaced by hyperpigmentation. *Courtesy, Jean L Bolognia, MD.*

Fig. 17.7 Phytophotodermatitis. Streaky hyperpigmentation due to contact with lime followed by exposure to sunlight. *Courtesy, Anthony J Mancini, MD.*

Ch. 67). Involved areas may remain hypersensitive to UV radiation for years. Wet skin, sweating and heat enhance the phototoxic response.

Furocoumarin exposure occurs in many settings (Table 17.10). Modern power tools such as a weed-whacker or strimmer (string trimmer) deliver a buckshot spray of weeds that may include Apiaceae members. "Strimmer dermatitis" appears 12–24 hours later as red, irregular macules and papules, not bizarre linear and angular streaks, on the anterior chest and arms. Implicated species, especially in Europe, include hogweed (*Heracleum sphondylium*), giant hogweed (*Heracleum mantegazzianum*) and cow parsley (*Anthriscus sylvestris*).

Berlock (or berloque) dermatitis comes from the German word "berlock" or the French word "berloque", meaning a trinket or charm. It described pendant-like streaks of pigmentation on the neck, face, arms or trunk after the application of colognes containing 5-MOP.

Phytophotodermatitis has been mistaken for child abuse. If parents touch plants or fruit containing furocoumarins, they can transfer them to their children. A week or more later, these children may develop digitate hyperpigmentation in sun-exposed sites of parental hand contact. Multiple hues are not seen in the skin lesions, as would be expected in healing bruises.

Xanthotoxin (8-MOP) is the most effective photosensitizer in limes, and it is over ten times more plentiful in the rind than in the pulp. Non-dermatologists frequently misdiagnose lime-induced phytophotodermatitis. In addition to child abuse, misdiagnoses include allergic contact dermatitis (e.g. poison ivy), impetigo, cellulitis, and infectious lymphangitis.

RISK ACTIVITIES FOR PHYTOPHOTODERMATITIS	
Cosmetics	Tan promoters or perfumes containing bergamot oil (berlock dermatitis) or a fig leaf decoction
Fruit and vegetable processing	Canning celery or stocking celery in grocery stores Making lemonade or limeade, especially if selling it outside Squeezing lime juice for margaritas and other drinks or guacamole
Gardening	Brushing against *Dictamnus* spp. ("gas plant/burning bush") (US, Europe, N China) or *Ruta* (UK) Cultivating celery, parsnip or parsley Clearing weeds with a "weed-whacker" (US) or "string trimmer" (UK) Pruning or harvesting figs Growing *Angelica* for herbal medicine (Korea), cake decorating (when candied), tonic and flavoring in wines (esp. Benedictine, US)
Hiking	Through fields and riverbanks (*Heracleum* spp.) (Pacific NW, Europe) Rolling in meadows Hiking in southern California and Baja California (*Cneoridium dumosum*, coast spice bush [Rutaceae])
Ingestion	Ingestion of massive quantities of psoralens (esp. celery) before UVA tanning Ingestion of *Chlorella* (an alga) (Japan)
Medications	Excessive exposure to UV radiation after taking or applying psoralens for PUVA Application of rue (*Ruta* spp.) as an insect repellant
Play	Making peashooters with *Heracleum* spp. Playing among rue bushes or Apiaceae Fighting with parsnips/celery Wearing leis of *Pelea anisata* (Hawaii)

Table 17.10 Risk activities for phytophotodermatitis.

Phototoxicity following the ingestion of naturally occurring psoralens is rare. Two fair-skinned "volunteers" ate 20 stalks of celery, 25 dried figs and 250 g of parsley, yet they developed no reaction after 30 minutes' exposure to midday sun. Oral ingestion of large quantities of celery broth 1–2 hours before UVA tanning or PUVA treatment has caused severe burns.

Celery harvesters and canners are at high risk for developing phytophotodermatitis. Only 1 mcg of 8-MOP/cm^2 of skin is necessary to produce blisters after 2.4 J/cm^2 (less than 10 minutes of summer sunlight in Colorado)! In one study of 320 randomly selected Michigan celery workers, 163 (51%!) displayed various stages of vesicular and bullous dermatitis on the fingers, hands and forearms[17]. In this study, the authors could not induce phytophotodermatitis except by using celery infected with pink-rot disease (*Sclerotina sclerotiorum*). The furocoumarins are concentrated in the leaf sap and stem sap.

Phytophotoallergic Contact Dermatitis

At least one photoallergic reaction to a plant (*Parthenium hysterophorus*) has been proven. Photoallergy due to plants is exceedingly rare.

Treatment

Prevention is the best treatment for phytophotodermatitis. Known furocoumarin-containing plants should not be planted near play areas. When using weed-whackers or strimmers, operators must cover their extremities. If one has been in contact with a suspected phototoxic plant, prompt washing with soap and water may prevent a reaction.

ALLERGIC CONTACT DERMATITIS (see also Ch. 14)

Key features

- Poison ivy/poison oak plant identification
  - Compound leaves with three leaflets
  - Flowers or fruit arise from axillary position
  - Black dots of urushiol often present on leaves and fruit
  - Common poison ivy climbs by aerials roots with "hairs"

Epidemiology

Anacardiaceae

Members of the family Anacardiaceae cause more allergic contact dermatitis than do all other plant families combined. Most allergenic family members belong to the genus *Toxicodendron*, including poison ivy, poison oak and poison sumac.

Toxicodendron identification[18]

Toxicodendron leaves are compound, possessing three or more leaflets. The old saying about poison ivy, "Leaves of three; leave them be", refers to each leaf having three leaflets. Flowers and fruit arise in an axillary position in the angle between the leaf and the twig from which it arises (Fig. 17.8). In contrast, the flowers and fruit of *Rhus* arise at the end of a branch. The leaf stalk is enlarged at its origin from the supporting twig and leaves a "U"- or "V"-shaped scar after it falls off. Green fruit turn off-white when mature. Plants cling to trees via "hairy" aerial rootlets.

Toxicodendron oleoresin contains urushiol and the enzyme laccase. Laccase oxidizes urushiol at temperatures of 68–86°F and humidity of 75–85%. The black, oxidized, plastic-like polymer has great tensile strength and is insoluble. Therefore, black spots are commonly found on the leaves of plants. The "black-spot test" helps identify toxic Anacardiaceae, but performing it also increases one's likelihood of contracting a nasty dermatitis! Use a stone to thoroughly crush plant contents, especially the leaf stalks, between folds of white paper. Urushiol turns dark brown within 10 minutes and black by 24 hours.

Allergenic Anacardiaceae

As noted in Table 17.11, there are two species each of poison ivy and poison oak and one species of poison sumac listed that are common to the US (Fig. 17.9). Some of these have multiple subspecies. Poison oak and poison ivy are weeds that grow along roads, trails or streams; they possess three leaflets (sometimes five) per leaf (compound leaves). Poison sumac contains 7–13 leaflets per leaf (see Fig. 17.8). Young leaves are frequently red in color, and the mature fruit (drupes) are tan or cream colored and have no hairs (the young drupes will have hairs). Classically, poison ivy leaves have pointed tips and are ovate (widest point below the center). Poison oak leaves usually have rounded ends. Western poison oak has oval leaves, whereas Eastern poison oak has variable leaf appearances that can mimic white oak leaves.

Remember that the non-leaf portions of the plant can induce dermatitis, even in the winter. The "winter" shape of poison ivy on fence posts resembles "Medusa heads" that are identifiable while driving down the highway. Strongly suspect any vine climbing by aerial rootlets

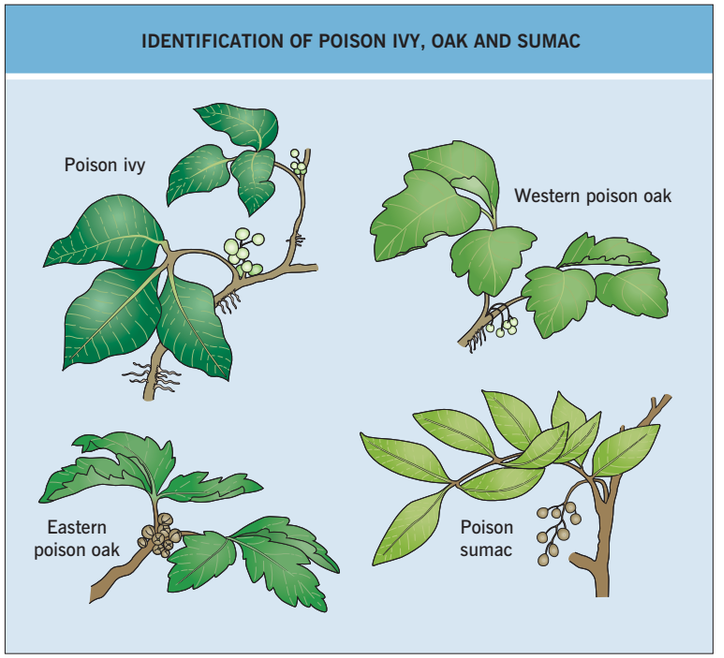


Fig. 17.8 Characteristic features useful for identifying poison ivy, poison oak and poison sumac. *With permission from the American Journal of Contact Dermatitis.*

MOST COMMON ALLERGENIC MEMBERS OF THE ANACARDIACEAE FAMILY AND MEMBERS OF TWO OTHER PLANT FAMILIES THAT ALSO CONTAIN URUSHIOL CROSS-REACTING CHEMICALS		
Binomial name	**Common name**	**Notes**
Toxicodendron radicans	Common or Eastern poison ivy	Eastern half of USA Climbs trees with aerial rootlets Some subspecies in Mexico, Japan, China
Toxicodendron rydbergii	Northern or Western poison ivy	Western half of USA (except CA) and northern border states Non-climbing shrubs
Smodingium argutum	South African poison ivy	South Africa
Toxicodendron toxicarium	Eastern poison oak	Southeast USA
Toxicodendron diversilobum	Western poison oak	Pacific Coast of USA Usually a shrub but can climb
Toxicodendron vernix	Poison sumac	Eastern third of USA Not a weed Grows in standing water
Anacardium occidentale	Cashew nut tree	Tropical Americas
Mangifera indica	Mango tree	Tropics
Metopium toxiferum	Poisonwood tree	Caribbean basin
Semecarpus anacardium	Indian marking nut tree	Southeast Asia, Pacific Islands, Australia
Toxicodendron verniciflua	Japanese lacquer tree	Japan and China
Gluta renghas	Rengas tree	Malaysia lumber source
Schinus terebinthifolius	Brazilian pepper tree or Florida holly	Native to South America, but now a problem in southern Florida, Hawaii, Central America, the Pacific Rim and Pacific Islands
	CROSS REACTORS	
Ginkgo biloba (Ginkgoaceae)	Ginkgo tree	Cultivated worldwide in temperate climates – only the seed coat is allergenic
Grevillea spp. (Proteaceae)	Spider flower, silk oak, Hawaiian tree, kahili tree	Widely cultivated Australian natives

Table 17.11 Most common allergenic members of the Anacardiaceae family and members of two other plant families that also contain urushiol cross-reacting chemicals.

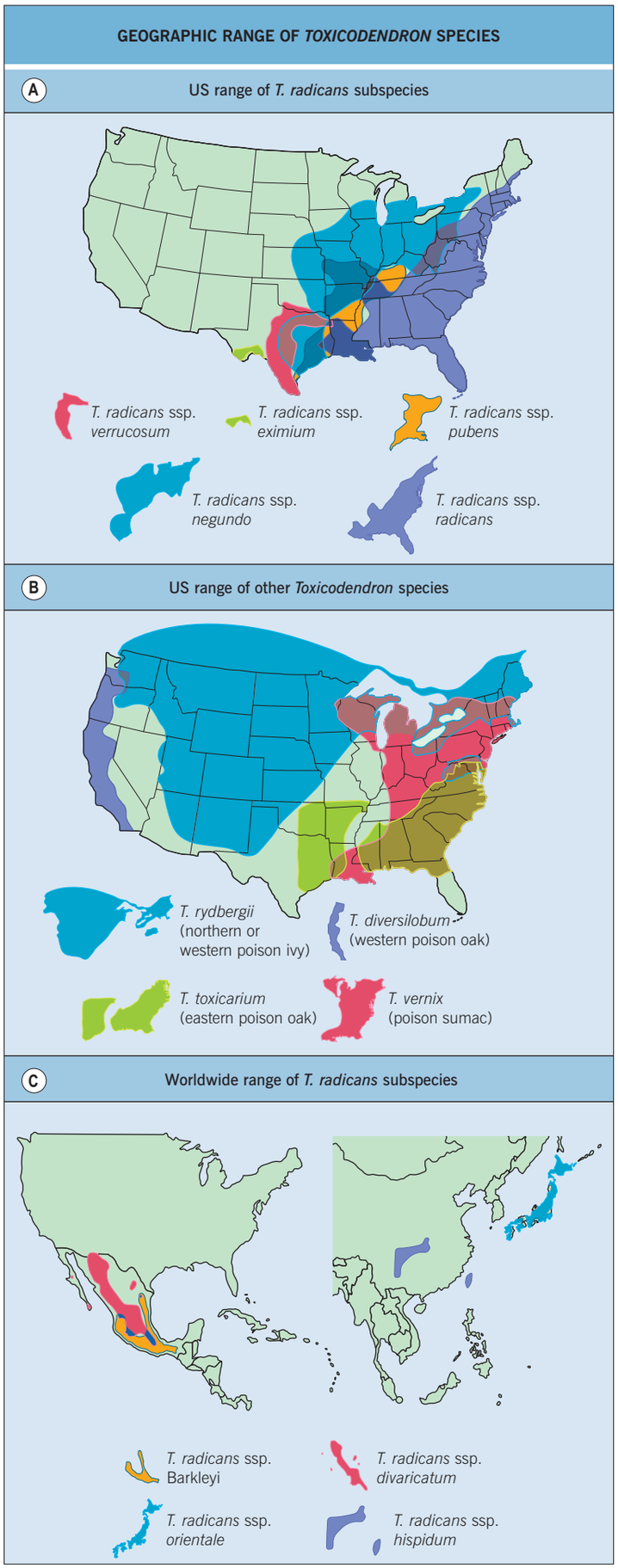


Fig. 17.9 Geographic range of *Toxicodendron* spp.

connected at the bottom to a tree or log. In snow, *T. rydbergii* grows so low to the ground that the upward, tine-like branches may be the only clue to its identification.

The cashew nut tree (*Anacardium occidentale*) grows in the tropics worldwide. The nuts contain an oily, brown juice between the two layers of its shell. The concentration of phenols in the nutshell and bark is so high that contact causes an immediate vesicant reaction. Africans have used cashew nut shell oil in ritual scarification. Any part of the tree, except the nut, can cause dermatitis.

Mango (*Mangifera indica*) is the most popular fruit tree in tropical and subtropical America, and some 35 species grow throughout Southeast Asia. The leaves, bark, stems and fruit skin contain sensitizing resorcinols. Peeling the fruit before eating it typically prevents allergic contact dermatitis, although allergy to mango pulp has been demonstrated; the pulp allergens appear to be distinct from the resorcinols. Hawaiian natives rarely react to mango, perhaps because early oral exposure induces immunologic tolerance.

The Florida holly (*Schinus terebinthifolius*, Brazilian pepper tree) is probably the most common cause of allergic contact dermatitis in southern Florida. The sap and crushed berries possess a variety of sensitizing phenols.

Although the mango, cashew and Brazilian pepper trees are incredibly common throughout Latin America, dermatitis to them there is rare, in contrast to the frequent reactions developed by US residents. The main allergens in toxicodendrons are catechols, whereas those in the listed trees are resorcinols. Of note, catechols possess greater allergenicity than resorcinols. Early cutaneous exposure to catechols may allow cross-reactions to other Anacardiaceae, whereas early oral exposure to resorcinols may induce a state of tolerance. However, some mango-allergic patients may also react to catechols in toxicodendrons.

The Japanese lacquer tree (*Toxicodendron vernicifluа*), 15–20 m in height, provides a thick, self-melanizing, viscous bark sap used for varnishing wood. Because polymerized urushiol remains in the lacquer, it has been known to maintain its allergenicity for many years. Patients allergic to poison ivy usually react to Japanese lacquer tree catechols. In a survey of 232 lacquer craftsmen, 189 (81%) developed dermatitis from the lacquer, but 83% of these reactions resolved with continued lacquer exposure (natural hyposensitization)[19]!

The black juice of the Indian marking tree nut (*Semecarpus anacardium*) is mixed with alum to mark laundry in India and Malaysia. Indian laundry workers (dhobies) often develop "dhobie mark dermatitis". During World War II, 15–20% of English soldiers stationed in India were affected after wearing marked garments.

Cross-reactors from other families

The seed of the Ginkgo tree (*Ginkgo biloba*), the only living member of the family Ginkgoaceae, possesses an allergenic ginkgolic acid. Because of the tree's large size, beauty and resistance to air pollution, it is widely grown in suburban North America and Europe. Only the male trees of this dioecious species are cultivated. The yellowish seeds of female trees disintegrate, forming butyric acid, which smells like rancid butter. Contact with the soft outer layer (pulp) of the seed is responsible for the vast majority of allergic reactions. Dermatitis following contact with the seed kernel, seed shell and leaves has been reported, but these parts likely cause only irritant reactions. Handling the intact seed (without the seed coat) (Fig. 17.10) supposedly does not cause dermatitis in sensitized individuals. The unique, fan-shaped leaf makes the ginkgo easy to recognize.

Fig. 17.10 Leaves and seeds of *Ginkgo biloba*. Only the fresh seed covering contains the allergen, ginkgolic acid, which typically cross-reacts with urushiol.

Grevillea (Proteaceae) includes 250 plant species common to Australia that contain pentadecylresorcinol. Having no side-chain double bonds, it is less allergenic than poison ivy and poison oak allergens. The flower of the Hawaiian kahili tree (*Grevillea banksii*) is a significant cause of allergic contact dermatitis in Hawaii.

Asteraceae and related families

Key features

- Asteraceae (Compositae) identification
  - Flower head with all strap-like florets (e.g. dandelion)
  - Flower head with small, central tubular florets and peripheral strap-like florets (e.g. daisy, sunflower)
  - Leaf-like bracts surround undersurfaces of flowers

Prevalence of sesquiterpene lactone allergy[20–22]

Up to 4.3% of European patch-test patients are allergic to members of the Asteraceae (Compositae) family. A sesquiterpene lactone (SQL) mix detected 16–65% of relevant allergies in various studies, and the Compositae mix detected 33–87%. Typically, the Compositae mix is two to three times as sensitive as the SQL mix. Feverfew (*Tanacetum parthenium*) extract usually detects Asteraceae-sensitive individuals who do not respond to the SQL mix. Ideally, patients who are thought to be sensitive to a particular member of the Asteraceae family should be tested to portions of the suspect plant. The next best option is to use both the SQL mix and Compositae mix. Finally, if this is not possible, patients should be tested to the SQL mix and feverfew extract.

Identification of Asteraceae[23]

The classic Asteraceae member has many tiny flowers (florets) clustered to form a flower head (capitulum) subtended by an involucre (whorl of bracts) (Fig. 17.11). In some plants (e.g. dandelions), all the florets are similar. In others (e.g. sunflowers), an inner "disc" of short, tubular florets is surrounded by long, strap-like "ray" florets.

Allergenic Asteraceae[23]

The daisy family includes many troublesome weeds, ornamentals, herbaceous perennials, and vegetables (Table 17.12). Over 200 species of Asteraceae are important causes of contact dermatitis worldwide. The florist's chrysanthemum belongs to a hybrid genus known as X *Dendranthema*, a segregate of the genus *Chrysanthemum*. Dermatitis occurs in amateur florists who "dead-head" plants to encourage larger blooms.

In 1956, *Parthenium hysterophorus* (the "Scourge of India") accidentally traveled with a consignment of US wheat to Poona, India, where it found an inviting ecologic niche without natural enemies. Within 7 years it became abundant in Poona, and it has now become a major urban and rural weed throughout India. Unlike South American *P. hysterophorus*, the Indian plant contains large amounts of SQLs.

Pathogenesis

Anacardiaceae allergens[25–27]

The allergenic substance urushiol derives its name from the Japanese word for the sap (kiurushi) of the Japanese lacquer tree (*T. verniciflua*). It contains a mixture of catechols (1,2-dihydroxybenzenes) and resorcinols (1,3-dihydroxybenzenes) that avidly binds to skin but is readily degraded by water.

Catechols and their alkyl side chains are immunologically inert. However, combining them produces potent sensitizers. The immunologic activity of alkyl side chains results from van der Waals forces, not ionic interaction, hydrogen bonding or covalent linkage. Longer side chains increase irritancy and allergenicity; location at position 3 of the catechol ring increases antigenicity, but placement at position 6 induces tolerance. Although virtually all individuals who are allergic to poison ivy react to the C15 catechol with two double bonds (a diolefin), only 37% respond to the C15 catechol with an unsaturated side chain (pentadecylcatechol). Therefore, pentadecylcatechol, which is easily synthesized, is an inappropriate patch-test allergen for Anacardiaceae sensitivity, because the diolefin is the major component in poison ivy and poison oak urushiols.

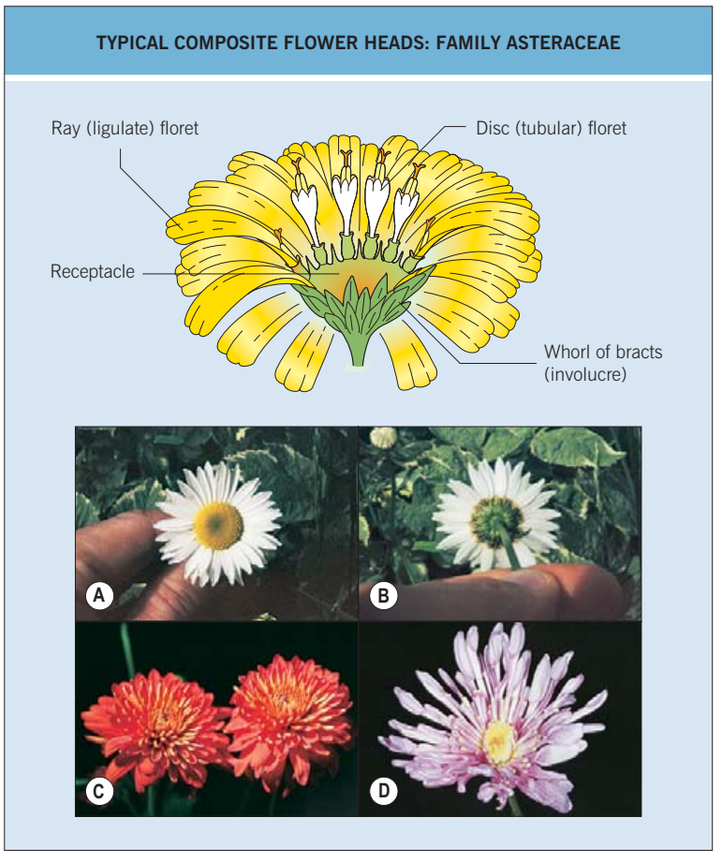


Fig. 17.11 Typical composite flower heads of members of the family Asteraceae (Compositae). Note the leaf-like bracts underneath the flower head. Daisy (*Leucanthemum* spp.), demonstrating composite flower head (**A**) and leaf-like bracts beneath the flower head (**B**) that are characteristic of flower heads of the family Asteraceae. **C** A cushion chrysanthemum (X *Dendranthema* cvs), demonstrating all ray, or strap-like, florets. **D** A composite chrysanthemum (X *Dendranthema* cvs), demonstrating central tubular florets and peripheral ray florets. This composite type of flower head gave rise to the former family name, Compositae.

Asteraceae allergens[23,28]

The major sensitizers, SQLs, are found in the leaves, stems and flowers, and are composed of a sesquiterpene ($C_{15}H_{24}$) and a lactone ring (cyclic ester). Over 1350 SQLs have been described, and the composition of SQLs produced by any species varies according to location and weather. An α-methylene group attached to the lactone ring increases allergenicity. Because SQL cross-reactivity follows no apparent rules, even the SQL patch-test mix (alantolactone, dehydrocostus lactone and costunolide) does not reliably screen for SQL allergy.

Clinical Features

Anacardiaceae dermatitis[25,29,30]

Key features

- Urushiol is a partially water-soluble allergen and must be washed off quickly
- Treat for at least 2 weeks, otherwise rebound phenomenon common
- Eruption "progresses" to "new areas" because of variability in antigen concentration and stratum corneum/epidermal thickness

Damage is usually required for plants to release urushiol, so lightly brushing against uninjured leaves is innocuous. However, in the late fall, plants release urushiol spontaneously. Urushiol may be spread by contaminated clothing, dogs, cats, lacquered furniture, sawdust and smoke. Allergen-containing smoke can cause severe respiratory tract inflammation, dermatitis, and even temporary blindness.

SOME OF THE MORE THAN 200 ALLERGENIC MEMBERS OF ASTERACEAE (COMPOSITAE) FOUND THROUGHOUT TEMPERATE WORLD CLIMATES			
Category	**Binomial name**	**Common name**	**Notes**
Wild flowers and weeds	*Achillea millefolium*	Yarrow, milfoil	A cause of allergic contact "strimmer" or "weed-whacker" dermatitis
	Ambrosia spp.	American ragweeds	Allergic contact dermatitis throughout growing season; allergic rhinitis only during pollen season
	Arnica montana	Arnica, mountain tobacco	
	Artemisia vulgaris	Mugwort	Grow in temperate climates worldwide
	Helenium autumnale	Sneezeweed	
	Iva spp.	Marsh elder, swamp weed	
	Parthenium hysterophorus	Wild feverfew	Scourge of India; Australian and Danish "bush dermatitis"
	Tanacetum cinerarilifolium	Pyrethrum	
	Tanacetum vulgare	Tansy	
	Tanacetum parthenium	Feverfew	Perhaps the best single plant to screen for SQL allergy
	Taraxacum officinale	Dandelion	Airborne contact dermatitis after mowing
Ornamental flowers	*Dahlia* spp.	Dahlia	
	X *Dendranthema* cultivars	Chrysanthemum	Most common cause of SQL dermatitis
	Helianthus annuus	Sunflower	Windblown trichomes can cause airborne contact dermatitis
	Rudbeckia hirta	Black-eyed Susan	
	Tagetes spp.	Marigold	Contain no SQLs
In herbal medicine	*Achillea millefolium*	Yarrow, milfoil	
	Arnica montana	Arnica, mountain tobacco	
	Calendula officinalis	Pot marigold	
	Chamaemelum nobile	Sweet/Roman chamomile	
	Helianthus annuus	Sunflower	
	Inula helenium	Elecampane	
	Tanacetum parthenium	Feverfew	
	Tanacetum vulgare	Tansy	
	Taraxacum officinale	Dandelion	
Vegetables	*Cichorium endiva*	Endive	
	Cichorium intybus	Chicory	
	Cynara scolymus	Globe artichoke	
	Lactuca sativa	Lettuce	

Table 17.12 Some of the more than 200 allergenic members of Asteraceae (Compositae) found throughout temperate world climates[24]. SQL, sesquiterpene lactone.

After contact with urushiol, a sensitized person typically develops an erythematous, pruritic eruption within 2 days (4–96 hours) that peaks within 1–14 days. However, dermatitis may occur up to 3 weeks after primary contact or within hours of secondary contact. Streaks of erythema and edematous papules typically precede vesicles and bullae (Fig. 17.12A,B). If the antigen load is lower, only erythematous, edematous reactions may be seen (Fig. 17.12C). Although allergic contact dermatitis is the most common cause of such a streaky, vesicular dermatitis, plants may cause this picture by other means (e.g. chemical irritant dermatitis or the initial phase of phytophotodermatitis). Patch tests of bulla fluid are routinely negative. The illusion that this fluid propagates the eruption results from variations in the time it takes for a clinical reaction to occur at different sites that receive differing antigen loads and have variable stratum corneum and epidermal thicknesses.

Erythema multiforme appears to be an underreported sequela of severe poison ivy reactions that may appear 2 weeks following onset of the dermatitis[31] (Table 17.13). Uncommonly, nephritis or eruptions resembling measles, scarlatina or urticaria develop and are ascribed to immune complex deposition. Without treatment, the allergic contact dermatitis lasts about 2–3 weeks. More severe peak reactions take longer to resolve. Prolonged postinflammatory hyperpigmentation may occur in darkly pigmented individuals.

Over 70% of the US population react to poison ivy allergens after patch testing, but only 50% react to plants in the field. Interestingly, only 15% of atopic persons are sensitive, and studies suggest that sensitivity is hereditary. Urushiol-sensitive AIDS patients with $CD4^+$ counts <200/mcl maintain sensitivity to poison ivy allergens[32]. The predominant effector T cells against poison ivy catechols are $CD8^+$.

In "black-spot" poison ivy dermatitis, urushiol acts as both irritant and allergen. An acute irritant contact dermatitis is superimposed on an acute allergic contact dermatitis[33]. Oxidized resin can be found on the skin, resulting in a black discoloration (Fig. 17.12D). If the lacquer stains clothes black, it cannot be washed off and will retain its allergenicity indefinitely. A more widespread spotted pattern in non-covered sites is seen if a patient has been weed-whacking areas of poison ivy (Fig. 17.12E).

PLANTS AND PLANT PRODUCTS THAT CAN LEAD TO ERYTHEMA MULTIFORME IN THE SETTING OF SEVERE ALLERGIC CONTACT DERMATITIS		
Common name (binomial name)	**Family**	**Notes**
Poison ivy, oak, sumac (*Toxicodendron* spp.)	Anacardiaceae	US and Canada
Tea tree oil (*Melaleuca alternifolia*)	Myrtaceae	Australia, exported products
Wild feverfew (*Parthenium hysterophorus*)	Asteraceae	India

Table 17.13 Plants and plant products that can lead to erythema multiforme in the setting of severe allergic contact dermatitis.

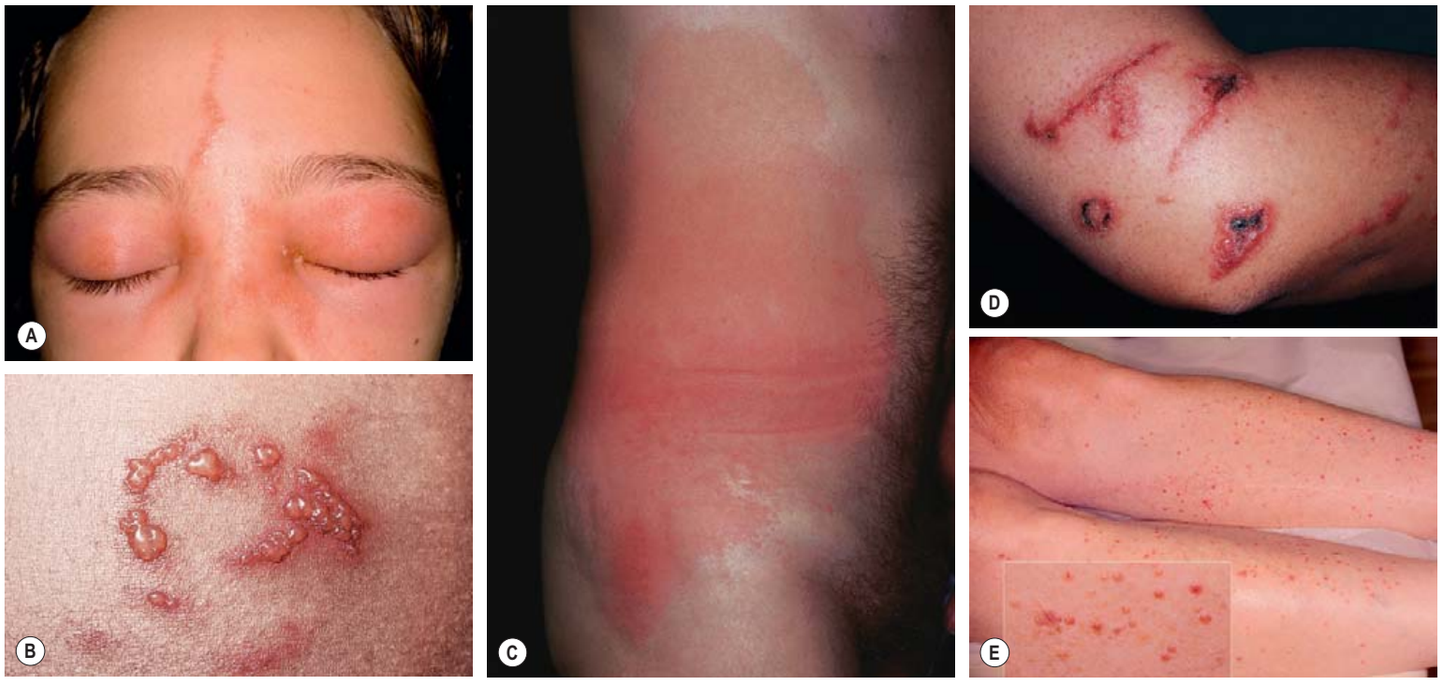


Fig. 17.12 Clinical manifestations of Anacardiaceae dermatitis. A Poison ivy (*Toxicodendron radicans*) dermatitis: erythema and edema of the eyelids as well as streaks of erythema plus tiny vesicles. **B** Poison ivy dermatitis: acute streaks of erythema with superimposed vesicles and bullae. **C** Widespread erythema and edema associated with intense pruritus after carrying logs of the poisonwood tree (*Metopium toxiferum*) of the family Anacardiaceae. **D** "Black-spot" poison ivy dermatitis: note the black discoloration in the central portion of the edematous plaques due to plant resin. **E** Weed-whacker dermatitis with widespread spotted pattern. *A, E, Courtesy, Louis A Fragola, Jr, MD; B, Courtesy, Fitzsimons Army Medical Center Dermatology slide teaching library.*

Asteraceae dermatitis[23]

Key features

- Caused by sesquiterpene lactones
- Most common cause is chrysanthemums
- Often presents with airborne contact pattern
- Patients frequently become photosensitive

Chrysanthemums are probably the most common house plant to cause allergic contact dermatitis (Fig. 17.13). The flowers and leaves are more potent sensitizers than are the stems.

The form of Asteraceae dermatitis that classically afflicts middle-aged men with a history of outdoor exposure typically resembles airborne contact dermatitis (ABCD) (Fig. 17.14). It has finally been demonstrated that SQLs (e.g. from feverfew [*Tanacetum parthenium*]), though not volatile, are bound to airborne trichomes in nature in sufficient concentrations to cause ABCD[34]. Typically, a single region of the body is involved for several years. The dermatitis flares in the summer during the plant's growing season and disappears in the winter. Later, all exposed areas develop a chronic pruritic and lichenified dermatitis (chronic actinic dermatitis [CAD]), presumably mediated by UV-induced antigens in the skin (see below). However, the eyelids, melolabial folds, retroauricular sulci and antecubital fossae are generally involved, unlike the situation in photosensitive dermatitis (see Fig. 87.16).

While ragweed (*Ambrosia artemisiifolia*) commonly causes immediate hypersensitivity ocular and airway reactions, it is a rare cause of allergic contact dermatitis. Type I allergic reactions are caused by high-molecular-weight, water-soluble antigens found in pollen. Although pollen can rapidly penetrate the skin[35], it contains no SQLs and has not been demonstrated to cause contact dermatitis. Cutaneous reactions to ragweed SQLs include ABCD (see above) and dyshidrotic eczema[36].

Parthenium hysterophorus (Congress weed, "Scourge of India") dermatitis in India affects adult men more than adult women or children, even though in India exposure is similar for all groups. Early studies estimated a male-to-female ratio of 20:1. The large male preponderance was not found in an American study demonstrating a 1.4:1 male-to-female ratio in those sensitive to Asteraceae. There is surprisingly little cross-reactivity between various Asteraceae family members.

Photosensitivity and Asteraceae allergy

SQLs possess neither phototoxic nor photoallergic properties, yet 85% of patients with chronic photosensitivity dermatoses may react to Asteraceae[37]. The development of abnormally low minimal erythema and minimal phototoxic doses following the onset of Asteraceae/SQL allergy has been demonstrated. The CAD that develops in some patients who are allergic to SQLs is thought to be an autoimmune photodermatosis mediated by sunlight-induced antigens in the skin. For example, the SQL isoalantolactone has been shown to be highly reactive with DNA in solution during UVA irradiation, and the UV action spectrum for CAD corresponds with the UV absorption peak for DNA. An interaction between SQLs and DNA in the presence of UV light may alter DNA to make it antigenic and trigger a CAD response[38].

Asteraceae-allergic individuals frequently react to plant allergens in perfumes, woods, balsam of Peru, colophony and lichens[39]. These allergies often precede the development of CAD. Although α-terthienyl and various polyacetylenes with phototoxic properties have been found in some Asteraceae, no link has been established between their presence and dermatitis[38].

Treatment

As soon as exposure to poison ivy or related plants is recognized, the entire body should be thoroughly washed with copious amounts of water. Soap may be used afterwards, but early use of soap or alcohol may expand the area of resin on the body since these are better solvents for urushiol than is water[40]. Fisher[41] has shown that urushiol (which is water-degradable) can be removed in significant amounts only if washed off very early. After 10 minutes, only 50% can be removed; after 15 minutes, only 25%; after 30 minutes, only 10%; and after 60 minutes, none of it can be removed.

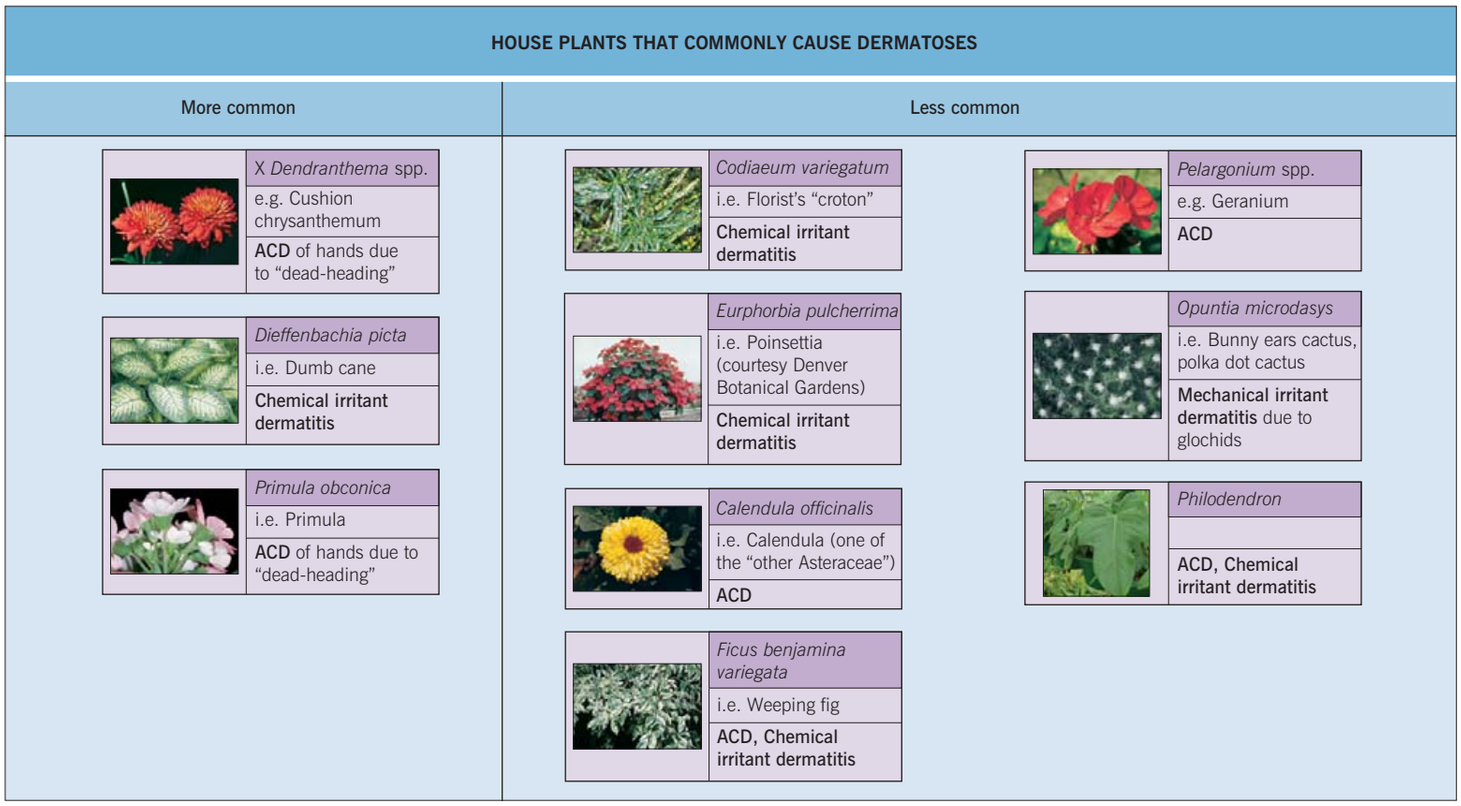


Fig. 17.13 House plants that commonly cause dermatoses. ACD, allergic contact dermatitis.

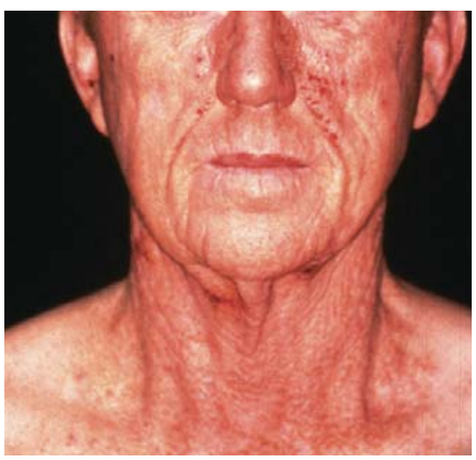


Fig. 17.14 Airborne contact dermatitis. Example of the airborne contact dermatitis pattern seen in a patient allergic to sesquiterpene lactones. Note involvement of the submental region and upper anterior neck, which would not be expected if this were a photodermatitis. *Courtesy, Dirk Elston, MD.*

For all causes of acute allergic contact dermatitis, the following general measures can be followed. Weepy lesions are best treated with tepid baths, wet-to-dry soaks, or bland shake lotions (calamine) that can dry the lesions. An astringent such as Burow's solution (aluminum subacetate) works well to cool and dry lesions when applied as a wet-to-dry dressing. Topical antihistamines, anesthetics containing benzocaine, and antibiotics should be avoided to prevent sensitization[40].

The most potent topical corticosteroids only help if applied during the earliest stages of the outbreak, when vesicles and blisters are not yet present. Abrupt discontinuation of these can lead to rebound inflammation. Both pimecrolimus and tacrolimus have been ineffective at treating urushiol-induced dermatitis. One surfactant product (Zanfel™) has been demonstrated to significantly relieve itch and erythema even after the eruption has been present for several days[42].

Systemic corticosteroids are extremely effective when indicated. These are best given in a dose of 1–2 mg/kg/day based upon ideal weight, gradually tapered over 2–3 weeks[43]. Many patients are referred for a "recurrence" of their poison ivy dermatitis after completing a short, 6-day course of oral corticosteroids, most commonly methylprednisolone given as a tapered "dose pack" (24 mg on day 1, decreasing by 4 mg each day over 6 days). As a result, the initial dose for an adult is often too low and the duration is too short. Soporific oral antihistamines can help patients sleep.

Hyposensitization programs for Anacardiaceae- and Asteraceae-allergic individuals have failed. Patients develop pruritus ani and/or generalized pruritus and urticaria and comment that the "treatment is worse than the disease". Natural desensitization probably occurs through early, oral ingestion of allergens. It appears that hyposensitization after becoming cutaneously sensitized to the potent allergens in poison ivy and poison oak is difficult, but not impossible, as demonstrated by Japanese lacquer craftsmen[20].

Marks and co-workers[44] demonstrated that 5% quaternium-18 bentonite lotion (Ivy-Block®) helps prevent poison ivy dermatitis in patch-test-positive individuals. Patients should realize that poison ivy allergens pass through rubber gloves, but not through heavy-duty vinyl gloves.

In CAD or other widespread Asteraceae-induced dermatitis, potent topical corticosteroids and oral prednisone are relatively ineffective unless employed early (before year-round dermatitis occurs). Azathioprine (2 mg/kg/day) or mycophenolate mofetil may be necessary for refractory disease (see Ch. 87). Low-dose PUVA therapy (with or without prednisone) may also prove helpful[23,45]. Whole-body application of mechlorethamine (nitrogen mustard) works, but only temporarily, and oral cyclosporine works, but the disease rapidly rebounds upon discontinuation[45].

Other Plant Families Causing Allergic Contact Dermatitis

Alliaceae

The genus *Allium* includes onions, garlic and chives. Garlic is the most frequent cause of fingertip dermatitis in homemakers and those who cook. It typically presents on the thumb, index and middle fingertips of the non-dominant hand with hyperkeratosis, desquamation and fissuring in an asymmetric pattern. Fresh garlic is a potent irritant that

Fig. 17.15 Allergic contact dermatitis in a florist. A Flowers of the Peruvian lily (*Alstroemeria* spp.). **B** Florist with fingertip *Alstromeria* allergic contact dermatitis showing how he holds Peruvian lily while cutting off the leaves. **C** Index finger of the same florist, showing the chronic, lichenified, hyperkeratotic dermatitis caused by allergy to Peruvian lily and tulipalin A (*Alstroemeria*). *B, C, With permission from the American Journal of Contact Dermatitis. 1999;10(3):172–6.*

has caused second- and third-degree burns when applied to injured skin (see Fig. 17.4). Therefore, patch testing to whole garlic should never be done. The irritants and allergens are thought to be diallyl disulfide (the most important one), allylpropyl disulfide and allicin. Onion (*Allium cepa*) dermatitis is rare. Common disposable gloves, such as vinyl, latex, polyethylene and nitrile, do not protect sensitized individuals who handle garlic or onions. Reusable domestic rubber gloves are protective.

Alstroemeriaceae and Liliaceae

"Tulip fingers" is a combined allergic and irritant contact dermatitis caused by tulip bulbs (*Tulipa* spp.). Erythematous, scaling plaques mark the fingertips and periungual skin, particularly on the first and second fingers of the dominant hand. Although this classic appearance can occur, most commonly a diffuse, dry hand dermatitis is seen. Pulpitis, paronychia, and spread of dermatitis to the face, neck, arms and anogenital area may ensue. Tuliposide A, a glycoside, is found in the white epidermis of bulbs. Acidic hydrolysis converts it to tulipalin A, the allergen. Tuliposide B (and therefore its hydrolytic product, tulipalin B), the α-hydroxy derivative of tuliposide A, is commonly found in tulips, and is a much weaker sensitizer.

Since their popularization in Holland in 1963, Peruvian lilies (*Alstroemeria auriantiaca* and *A. ligtu*) have become incredibly popular in floral arrangements (Fig. 17.15A). Handlers remove individual flowers, thread wire through the stems and/or cut off leaves (Fig. 17.15B). These workers often develop erythema, fissuring, vesicles, hyperkeratosis and exfoliation of the fingertips, greater on the dominant hand (Fig. 17.15C)[46]. Most frequently, it presents as non-inflamed distal finger fissuring and hyperkeratosis. Unfortunately, the allergen passes through vinyl (polyvinyl chloride) gloves[46]. Although nitrile (synthetic rubber) gloves are protective, few florists will wear them. Tuliposide A and B are found in virtually all portions of the plant. The flowers have more allergen than the stems, and the leaves have the least amount. Attempts are being made to grow hypoallergenic cultivars that contain only tuliposide B[46].

Myrtaceae

Tea tree oil distilled from the leaves of *Melaleuca alternifolia* Cheel has been increasingly reported as a cause of allergic contact dermatitis since 1991. At least two-thirds of Australians have been exposed to it, and approximately 7% of them are allergic to it. While tea tree oil possesses broad-spectrum antimicrobial and anti-inflammatory effects, at least 16 different constituents are strong sensitizers. Most sensitizers are degradation products formed after exposure of tea tree oil to light, warmth and moisture[47]. Fresh tea tree oil is a weak sensitizer. The most common sensitizers are terpinolene, ascaridol, α-terpinene and 1,2,4-trihydroxy menthane.

Botanical products

Hundreds of botanical extracts are added to numerous skin care products for fragrance and purported healing properties. When testing patients with a presumed contact allergy who were using products with botanical extracts, two studies demonstrated that 50–60% of patients had at least one relevant positive reaction. The most common culprit was tea tree oil, followed by feverfew and lichen acid mix (found in deodorants). Balsam of Peru (*Myroxylon pereirae*), fragrance mix, Compositae mix and SQL mix were poor screens for botanical allergy in that they uncovered only 33%, 30%, 20% and 7% of relevant allergic reactions, respectively. The authors of this study suggested creating a new botanical screen tray that included all items found relevant in at least two patients[4].

OCCUPATIONAL PLANT DERMATOSES

Florists[48,49]

Irritant dermatitis outweighs allergic contact dermatitis in frequency and importance. Estimates of hand dermatitis in florists range from an 8% point prevalence to a 25–30% annual incidence to a nearly 50% lifetime incidence, especially amongst floral designers. Most importantly, most cases of hand dermatitis are mild, periodic and self-limited. Because florists' hands are often wet, primary irritant reactions may lead to sensitization over long periods of time.

For florists, the most common sensitizers are sesquiterpene lactones, tulipalin A and primin (*Primula obconica*). Daffodil itch (caused by calcium oxalate), from handling daffodil stems and bulbs, is probably the most common cause of irritant contact dermatitis in florists.

Horticulturalists

Fully 10% of 250 horticultural workers were allergic to Asteraceae and one-third had urticaria[50]. An atopic family history increases one's likelihood of developing urticaria.

Grocery Store Workers

Among grocery store workers, two factors have been identified that raise the risk for phytophotodermatitis: the amount of exposure to fresh produce (especially celery) and the use of tanning salons (UVA exposure). The prevalence ratio of phytophotodermatitis is >40 for those with both risk factors compared to those with neither.

Outdoor Workers

Among outdoor workers, poison ivy and poison oak (*Toxicodendron* spp.) are the main causes of occupational contact dermatitis. *Toxicodendron* contact accounts for 10% of all lost-time injuries for the US Department of Agriculture Forest Service. Foresters, especially when fighting forest fires, have virtually no control over avoiding these plants. Up to 25% of firefighters need to leave the fire line because of severe *Toxicodendron* dermatitis. Forestry workers often suffer from "woodcutter's eczema", an allergic reaction caused by airborne SQLs in *Frullania* (liverworts) growing on tree trunks in the American and Canadian Pacific Northwest. The dermatitis is worse in wet winter months and presents in a pseudo-photodistribution, involving the upper eyelids but sparing the submental area. This suggests dispersal of oleoresin by rainwater.

REFERENCES

1. McGovern TW. The language of plants. Am J Contact Dermatol. 1999;10:45–7.
2. Gillis WT. The systematics and ecology of poison-ivy and the poison-oaks (*Toxicodendron*, Anacardiaceae). Rhodora. 1971;73:72–159.
3. Mitchell JC. Patch testing to plants. Clin Dermatol. 1986; 4:77–82.
4. Simpson EL, Law SV, Storrs FJ. Prevalence of botanical extract allergy in patients with contact dermatitis. Dermatitis. 2004;15:67–72.
5. Lahti A. Contact urticaria to plants. Clin Dermatol. 1986; 4:127–36.
6. Kondo Y, Urisu A. Oral allergy syndrome. Allergol Int. 2009;58:1–7.
7. Janssens V, Morren M, Dooms-Goossens A, Degreef H. Protein contact dermatitis: myth or reality? Br J Dermatol. 1995;132:1–6.
8. Lovell CR. Plants and the Skin. Oxford: Blackwell Scientific, 1993.
9. Oliver F, Amon EU, Breathnach A, et al. Contact urticaria due to the common stinging nettle (*Urtica dioica*) – histological, ultrastructural, and pharmacological studies. Clin Exp Dermatol. 1991;16:1–7.
10. McGovern TW, Barkley TM. Botanical briefs: prickly pear cactus – *Opuntia* Miller. Cutis. 2001;68: 188–90.
11. Lindsey D, Lindsey WE. Cactus spine injuries. Am J Emerg Med. 1988;6:362–9.
12. Bruynzeel DP. Bulb dermatitis: dermatological problems in the flower bulb industries. Contact Dermatitis. 1997;37:70–7.
13. Brenner S, Landau M, Goldberg I. Contact dermatitis with systemic symptoms from *Agave americana*. Dermatology. 1998;196:408–11.
14. Pathak MA. Phytophotodermatitis. Clin Dermatol. 1986; 4:102–21.
15. Zaynoun ST, Aftimos BG, Abi Ali L, et al. *Ficus carica*: isolation and quantification of the photoactive components. Contact Dermatol. 1984;11:21–5.
16. De Almeida HL Jr, Sotto MN, de Castro LAS, Rocha NM. Transmission electron microscopy of the preclinical phase of experimental phytophotodermatitis. Clinics (Sao Paulo). 2008;63:371–4.
17. Birmingham DJ, Key MM, Tublich GE. Phototoxic bullae among celery harvesters. Arch Dermatol. 1961;83:73.
18. Guin JD, Beaman JH. Toxicodendrons of the United States. Clin Dermatol. 1986;4:137–48.
19. Kawai K, Nakagawa M, Kawaki K, et al. Hyposensitization to urushiol among Japanese lacquer craftsmen: results of patch tests on students learning the art of lacquerware. Contact Dermatol. 1991;25:290–5.
20. Paulsen E, Andersen KE, Hausen BM. An 8-year experience with routine SL mix patch testing supplemented with Compositae mix in Denmark. Contact Dermatitis. 2001;45:29–35.
21. Green C, Ferguson J. Sesquiterpene lactone mix is not an adequate screen for Compositae allergy. Contact Dermatol. 1994;31:151–3.
22. Goulden V, Wilkinson SM. Patch testing for Compositae allergy. Br J Dermatol. 1998;138:1018–21.
23. Warshaw EM, Zug KA. Sesquiterpene lactone allergy. Am J Contact Dermatol. 1996;7:1–23.
24. Wrangsjo K, Ros AM. Compositae allergy. Semin Dermatol. 1996;15:87–94.
25. Baer H. Chemistry and immunochemistry of poisonous Anacardiaceae. Clin Dermatol. 1986;4: 152–9.
26. Mitchell J. The poisonous Anacardiaceae of the world. Adv Econ Botany. 1990;8:103–29.
27. Kalish RS. Poison ivy dermatitis: pathogenesis of allergic contact dermatitis to urushiol. In: Progress in Dermatology. Evanston, IL: Dermatology Foundation, 1995;29:1–12.
28. Guin JD. Sesquiterpene-lactone dermatitis. Immunol Allergy Clin North Am. 1989;9:447–61.
29. Fisher AA. Poison ivy/oak/sumac. Part II: specific features. Cutis. 1996;58:22–4.
30. Williams JV, Light J, Marks JG Jr. Individual variations in allergic contact dermatitis from urushiol. Arch Dermatol. 1999;135:1002–3.
31. Werchniak AE, Schwarzenberger K. Poison ivy: an underreported cause of erythema multiforme. J Am Acad Dermatol. 2004;51(5 suppl.):S159–60.
32. Smith KJ, Skelton HG, Nelson A, et al. Preservation of allergic contact dermatitis to poison ivy (urushiol) in late HIV disease. The implications and relevance to immunotherapy with contact allergens. Dermatology. 1997;195:145–9.
33. Kurlan JG, Lucky AW. Black spot poison ivy: a report of 5 cases and a review of the literature. J Am Acad Dermatol. 2001;45:246–9.
34. Paulsen E, Christensen LP, Andersen KE. Compositae dermatitis from airborne parthenolide. Contact Dermatitis. 2007;156:510–15.
35. Jacobi U, Engel K, Patzelt A, et al. Penetration of pollen proteins into the skin. Skin Pharmacol Physiol. 2007; 20:297–304.
36. Moller H, Spiren A, Svensson A, et al. Contact allergy to the Asteraceae plant *Ambrosia artemisiifolia* L. (ragweed) in sesquiterpene lactone-sensitive patients in southern Sweden. Contact Dermatitis. 2002;47;157–60.
37. Frain-Bell W. Photosensitivity and Compositae dermatitis. Clin Dermatol. 1986;4:122–6.
38. Menage HD, Hawk JLM, White IR. Sesquiterpene lactone mix contact sensitivity and its relationship to chronic actinic dermatitis: a follow-up study. Contact Dermatol. 1998;39:119–22.
39. Frain-Bell W, Johnson BE. Contact allergic sensitivity to plants and the photosensitivity dermatitis and actinic reticuloid syndrome. Br J Dermatol. 1979;101:503–12.
40. Williford PM, Sheretz EF. Poison ivy dermatitis: nuances in treatment. Arch Fam Med. 1994;3:184–8.
41. Fisher AA. Poison ivy/oak dermatitis. Part I: prevention – soap and water, topical barriers, hyposensitization. Cutis. 1996;57:384–6.
42. Davila A, Lucas J, Laurora M, et al. A new topical agent, Zanfel, ameliorates urushiol-induced *Toxicodendron* allergic contact dermatitis. Ann Emerg Med. 2003;42 (4 suppl. 1):601.
43. Resnick SD. Poison-ivy and poison-oak dermatitis. Clin Dermatol. 1986;4:208–12.
44. Marks JG Jr, Fowler JF Jr, Sheretz EF, Rietschel RL. Prevention of poison ivy and poison oak allergic contact dermatitis by quaternium-18 bentonite. J Am Acad Dermatol. 1995;33:212–16.
45. Burke DA, Corey G, Storrs FJ. Psoralen plus UVA protocol for Compositae photosensitivity. Am J Contact Dermatol. 1997;7:171–6.
46. McGovern TW. *Alstroemeria* L (Peruvian lily). Am J Contact Dermatol. 1999;10:172–6.
47. Hausen BM. Evaluation of the main contact allergens in oxidized tea tree oil. Dermatitis. 2004;15:213–14.
48. Santucci B, Picardo M. Occupational contact dermatitis to plants. Clin Dermatol. 1992;10:157–65.
49. Paulsen E. Occupational dermatitis in Danish gardeners and greenhouse workers (II). Etiological factors. Contact Dermatitis. 1998;38:14–9.
50. Paulsen E, Sogaard J, Andersen KE. Occupational dermatitis in Danish gardeners and greenhouse workers (III). Compositae-related symptoms. Contact Dermatitis. 1998;38:140–6.

This page intentionally left blank

Urticaria and Angioedema 18

Clive EH Grattan

Synonyms: ■ Wheals – hives, nettle rash ■ Angioedema – Quincke edema

Key features

- Urticaria is characterized by transient skin or mucosal swellings due to plasma leakage. Superficial dermal swellings are wheals, and deep swellings of the skin or mucosa are termed angioedema. Wheals are characteristically pruritic and pink or pale in the center, whereas angioedema is often painful, less well defined and shows no color change.
- There are several recognizable clinical patterns of urticaria and different causes. The latter include allergy, autoimmunity, drugs, dietary pseudoallergens, and infections. Many cases remain unexplained ("idiopathic") even after an extensive evaluation. C1 esterase inhibitor deficiency needs to be considered as a cause of recurrent angioedema without wheals.
- Diagnosis is based primarily on the history and clinical examination. Determination of the etiology or triggers, as well as exclusion of other diagnoses, may require further investigations, including blood tests, physical and dietary challenges, skin tests and skin biopsy.
- Urticaria is a common disorder that may cause considerable distress and last for years, but the associated symptoms can often be alleviated by appropriate management.

INTRODUCTION

Urticaria is a common reason for patients to present to primary care practitioners, emergency rooms, dermatologists and allergists. It is characterized by the rapidity of its fluctuation. As a rule, individual wheals last no more than 24 hours, but the whole attack usually lasts much longer. With nearly all clinical patterns of urticaria, wheals may be accompanied by angioedema, but the occurrence of isolated angioedema (without wheals) is of special significance because some of these patients will have a deficiency of C1 esterase inhibitor (C1 inh). The latter is a rare disorder that is often inherited and can prove fatal without treatment. Urticarial vasculitis is a systemic disease defined by damage to small blood vessels (see Ch. 24), but it may sometimes present with wheals or angioedema that, without confirming a duration of more than 24 hours (by serial examination of marked lesions) and a biopsy, are indistinguishable from other patterns of urticaria. While urticaria rarely progresses to anaphylaxis, it is often a feature of that condition. Good management of urticaria depends on a thorough understanding of etiologies, triggers and aggravating factors, in addition to the most appropriate drug therapies.

Definition of Urticaria

Urticaria is often used as a descriptive term for recurrent whealing of the skin, with angioedema being viewed as a separate entity. However, there is increasing acceptance that the term "urticaria" is more appropriately used to define a disease in which the clinical presentation is determined by the depth of swelling. Thus, urticaria may present with wheals, angioedema, or both. Similarly, the term "angioedema" may be used to describe a physical sign or a distinct clinical subgroup of urticaria characterized by deep swellings without wheals.

Wheals are pruritic, pink or pale swellings of the superficial dermis that may have an initial flare around them (Fig. 18.1). Lesions may be a few millimeters in diameter or as large as a hand, and the number can vary from a few to numerous. The hallmark of wheals is that *individual* lesions come and go rapidly, by definition, in general within 24 hours.

Angioedema swellings occur deeper in the dermis and in the subcutaneous or submucosal tissue. They may also affect the mouth and, rarely, the bowel. The areas of involvement tend to be normal or faint pink in color, painful rather than red and itchy, larger and less well defined than wheals, and often last for 2 to 3 days (Fig. 18.2).

EPIDEMIOLOGY

Estimates of the lifetime occurrence of urticaria range from less than 1% to as high as 30% in the general population, depending on the age range and method of sampling. The true figure is likely to be in the range of 1–5%[1]. The prevalence of specific types of urticaria, e.g. chronic idiopathic urticaria or cold urticaria, will be lower. There is no reliable literature on racial variation, but an estimate of prevalence in China was appreciably higher than that in European studies, at 23%[1]. Urticaria is a worldwide disease and may present at any age. The peak incidence depends on etiology. The proportion of cases due to different etiological agents is likely to relate to the frequency of environmental exposures, such as infections and allergens, in different countries, but estimates of this are not available. It is also often difficult to prove a cause and effect, and so an underlying condition may be inappropriately "blamed" for causing urticaria. Overall, urticaria is more common in women, with a female : male ratio of approximately 2 : 1 for chronic urticaria, but the ratio varies with the different physical urticarias. For example, women outnumber men in dermographism and cold urticaria, but more men develop delayed pressure urticaria[2]. Hereditary angioedema has an autosomal dominant inheritance pattern and occurs in approximately 1 : 50 000 individuals.

PATHOGENESIS

The Mast Cell

Distribution and diversity

The mast cell is the primary effector cell of urticaria. Mast cells are widely distributed throughout the body but vary in their phenotype and response to stimulation. This may explain why systemic features, such as those seen in anaphylaxis, do not accompany the activation of cutaneous mast cells in urticaria. The majority of mast cells in the skin and intestinal submucosa contain the neutral proteases tryptase and chymase (MC_{TC}), whereas those in the bowel mucosa, alveolar wall and nasal mucosa contain only tryptase (MC_T). Both types, however, express high-affinity IgE receptors (FcεRI) and are therefore capable of participating in IgE-dependent allergic reactions[3]. There is conflicting evidence on the number of cutaneous mast cells in chronic urticaria, but there is agreement that they may be more likely to degranulate in response to certain stimuli, such as intradermal codeine injection, and in this sense may be in general more "releasable". Little is known about the beneficial effects of mast cells, but there is some evidence that they may be involved in the innate immune response to infection, wound healing, and the neuroendocrine system. Recently, they have been

Fig. 18.1 Wheals. Wheals can be small or large in size (**A**) as well as annular (**B**), but they still retain the classic central pallor and erythematous flare. **C** Occasionally, more uniform edematous plaques are seen. *B, Courtesy, Julie V Schaffer, MD.*

Fig. 18.2 Angioedema. The swelling is deeper than wheals and may affect mucosal surfaces. Note the swelling of the lips and periorbital region and the lack of erythema.

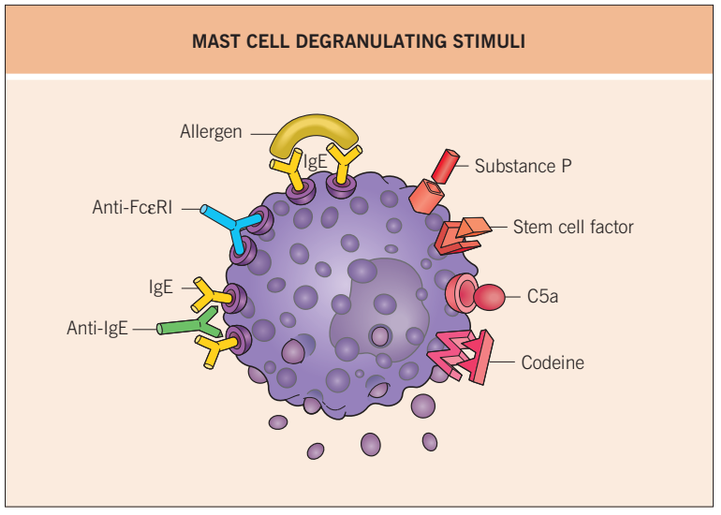


Fig. 18.3 Mast cell degranulating stimuli. Both immunologic and non-immunologic stimuli can lead to release of mediators. Stem cell factor is also known as KIT ligand.

shown to help initiate the extracellular matrix formation and angiogenesis required for neurofibroma development.

Degranulating stimuli

Cross-linking of two or more adjacent FcεRI on the mast cell membrane will initiate a chain of calcium- and energy-dependent steps leading to fusion of storage granules with the cell membrane and externalization of their contents. This is known as degranulation. Classic immediate hypersensitivity reactions involve binding of receptor-bound specific IgE by allergen. There are also several recognized immunologic degranulating stimuli that act through the IgE receptor, such as anti-IgE and anti-FcεRI antibodies (Fig. 18.3). Non-immunologic stimuli, including opiates, C5a anaphylatoxin, stem cell factor and some neuropeptides (e.g. substance P), can cause mast cell degranulation by binding specific receptors, independent of the FcεRI (see Fig. 18.3).

Proinflammatory mediators

Mast cell granules contain preformed mediators of inflammation, the most important of which is histamine (Fig. 18.4). A wide range of cytokines has been demonstrated in human mast cells from different tissues, including tumor necrosis factor-α (TNF-α), interleukins (IL)-3, -4, -5, -6, -8 and -13, and granulocyte–macrophage colony-stimulating factor (GM-CSF). Synthesis and secretion are upregulated following FcεRI stimulation. TNF-α is expressed constitutively in resting human cutaneous mast cells. Prostaglandins and leukotrienes are synthesized

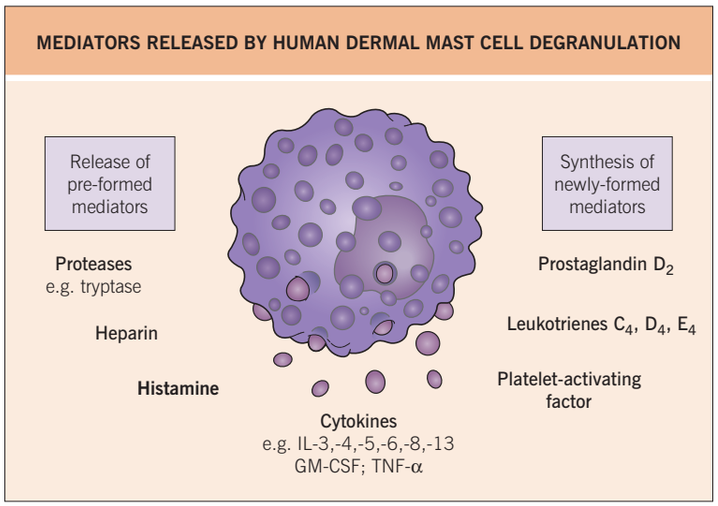


Fig. 18.4 Mediators released by human dermal mast cell degranulation. Both preformed and newly synthesized proinflammatory mediators are released from mast cells.

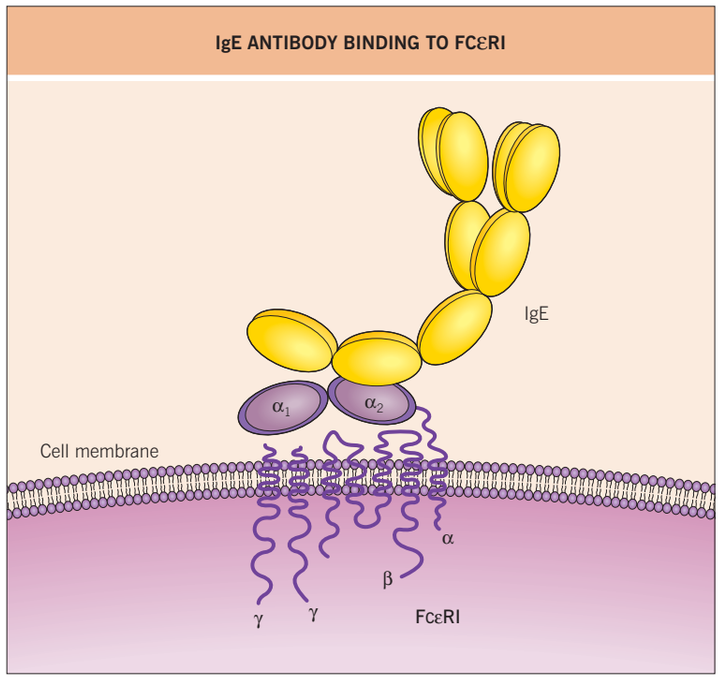


Fig. 18.5 Histamine-releasing autoantibodies bind the extracellular α subunit of the high-affinity IgE receptor (FcεRI). Autoantibodies directed against the terminal α_1 domain are able to bind the receptor in the presence of IgE and are therefore non-competitive, whereas those recognizing the α_2 domain compete with IgE for the binding site.

from arachidonic acid derived from cell membrane phospholipids (see Fig. 130.7). The most important proinflammatory eicosanoids are prostaglandin (PG) D_2 and the leukotrienes (LT) C_4, D_4 and E_4 (slow releasing substance of anaphylaxis). PGE_2 has inhibitory effects on immunologic mast cell degranulation and may therefore have a protective role in urticaria.

Blood Vessels

Histamine and other proinflammatory mediators released on degranulation bind receptors on postcapillary venules in the skin, leading to vasodilation and increased permeability to large plasma proteins, including albumin and immunoglobulins. Furthermore, histamine, TNF-α and IL-8 upregulate the expression of adhesion molecules on endothelial cells, thereby promoting the migration of circulating inflammatory cells from the blood into the urticarial lesion.

Blood

Autoantibodies

Functional IgG autoantibodies that release histamine (and other mediators) from mast cells and basophils have been detected in the serum of 30–50% of patients with chronic "ordinary" urticaria using *in vitro* assays[4]. The majority of these autoantibodies bind the extracellular α subunit of FcεRI. Those recognizing the α_2 domain compete with IgE for the binding site, whereas non-competitive autoantibodies directed against the terminal α_1 domain are able to bind the receptor in the presence of IgE (Fig. 18.5). Approximately 10% of chronic urticaria sera contain functional autoantibodies directed against the Fc portion of IgE itself (see Fig. 18.3). Binding of the autoantibodies to mast cells may initiate complement activation with the generation of C5a anaphylatoxin, which in turn facilitates or augments degranulation[5]. Other mast cell activating factors may also exist in urticaria sera: a non-IgG "mast cell-specific factor" has been described, although its identity remains unknown[6]. There is currently no evidence that characterized cytokines cause mast cell degranulation in urticaria.

The pathogenesis of urticarial vasculitis (see Ch. 24) is thought to involve circulating immune complexes, although the antigen has not been identified except in hepatitis B and C viral infections.

Leukocytes

The importance of peripheral blood leukocytes in the pathogenesis of urticaria is becoming clearer. Blood basophils in chronic ordinary urticaria patients are less responsive *in vitro* to the immunologic stimulus anti-IgE, possibly through desensitization, and these cells are reduced in number[7]. These patients can be classified into responders and non-responders based upon the release of histamine by their basophils in response to anti-IgE. The functional phenotype appears to remain stable during the course of the active illness, but then, during disease remission, the basophils become more responsive to anti-IgE[8]. Expression of the negative regulator SHIP (src homology 2-containing inositol phosphatase) is increased in the basophils from anti-IgE non-responders[9], although the significance of this to the pathogenesis of chronic urticaria is unknown. Evidence is emerging that basophils are recruited into urticarial wheals and may sustain the inflammatory response by releasing histamine and other mediators, analogous to the delayed phase of immediate hypersensitivity reactions.

Eosinophil, neutrophil and lymphocyte numbers are normal in the peripheral blood, but these cells are often present in biopsy specimens from spontaneous wheals. Eosinophils may contribute to the persistence of wheals by generating LTC_4, LTD_4 and LTE_4 and by releasing toxic granule proteins, including major basic protein (MBP), which can release histamine from basophils. The function of neutrophils and lymphocytes in urticaria has not been elucidated.

Nerves

Substance P and other neuropeptides release histamine from mast cells *in vitro* and can induce a wheal and flare reaction in human skin when injected intradermally. Vasoactive intestinal polypeptide (VIP) caused a greater wheal reaction in those with chronic urticaria than did other skin-tested neuropeptides[10], but the relevance of this to urticaria is still uncertain.

Mechanisms of Urticaria Formation

Mast cell-dependent urticaria

Potential mechanisms for mast cell-dependent urticaria are included in Table 18.1. Cross-linking of the Fab portion of specific IgE on mast cells by percutaneous or circulating allergen (see Fig. 18.3) undoubtedly accounts for some cases of acute or episodic urticaria but is probably never the cause of adult chronic continuous urticaria. Examples of the former would be contact urticaria from natural rubber latex and acute urticaria from foods, including nuts, fish and fruit. However, the majority of acute urticaria cases do not relate to allergen exposure.

IgE has been implicated in the pathogenesis of symptomatic dermographism, cold urticaria and solar urticaria, but the mechanism by

ETIOLOGIES AND PATHOMECHANISMS OF URTICARIAL LESIONS
IDIOPATHIC
IMMUNOLOGIC
• Autoimmune (autoantibodies against FcεRI or IgE) • IgE-dependent (allergic) • Immune complex (vasculitic) • Kinin- and complement-dependent (C1 esterase inhibitor deficiency)
NON-IMMUNOLOGIC
• Direct mast cell-releasing agents (e.g. opiates) • Vasoactive stimuli (e.g. nettle stings) • Aspirin, other nonsteroidal anti-inflammatory drugs, dietary pseudoallergens • Angiotensin-converting enzyme inhibitors

Table 18.1 Etiologies and pathomechanisms of urticarial lesions. It is often difficult to know the exact pathogenesis of individual cases of urticaria, and many cases remain idiopathic after evaluation. See figs 18.3 and 18.6.

which it renders skin mast cells more sensitive to physical stimulation is not certain[11]. It is proposed that the physical stimulus in these patients induces a neoantigen that reacts with specific IgE antibody bound to mast cells. An additional mechanism, such as neuropeptide release, could initiate or potentiate mast cell activation. Using electron microscopy, localized platelet clumping has been demonstrated in cold urticaria, and the release of platelet mediators, including platelet-activating factor (PAF) and factor IV, could contribute to the urticaria.

Cholinergic urticaria develops in response to stimulation of cholinergic sympathetic innervation of the sweat glands. How release of acetylcholine from the nerve endings leads to mast cell activation and histamine release is unknown. An allergy to sweat has been demonstrated by one group of investigators. It has been proposed that pressure-induced wheals may be due to a late-phase reaction, but an antigen has never been identified.

The initiating event for spontaneous urticaria wheals is unclear but may involve plasma leakage due to local factors such as heat or pressure, which allow the extravasation of autoantibodies, leading to mast cell degranulation and a subsequent urticarial response. As functional autoantibodies cannot be detected in approximately 40% of chronic urticaria sera by currently available tests, other mechanisms may operate in "non-autoantibody" urticaria, which, nevertheless, has a similar clinical presentation[12]. Increased plasma levels of prothrombin fragment 1 + 2 (F 1 + 2) and D-dimer (a measure of fibrinolysis) have been demonstrated in chronic urticaria[13] and relate to disease severity, but the contribution of coagulation abnormalities to the pathogenesis remains unclear.

A popular hypothesis is that dietary and drug pseudoallergens may cause urticaria through the diversion of arachidonic acid metabolism from prostaglandin to leukotriene formation. How this leads to urticaria is not clear, but it is known that intradermal injections of LTC_4, LTD_4 and LTE_4 cause whealing by a direct action on small blood vessels. There is some evidence from studies of rat peritoneal mast cells that PGD_2 and PGE_2 have inhibitory effects on immunologic mast cell degranulation[14], so a reduction in their formation may facilitate the latter. Aspirin can *aggravate* urticaria in up to 30% of patients with chronic disease[15], and while some clinical studies of dietary pseudoallergen avoidance have given encouraging results, the proportion of complete responders confirmed by rechallenge is small[16]. Aspirin allergy as a *cause* of urticaria is much less common, and the proportion of patients with urticaria due solely to pseudoallergens is probably low.

Understanding "idiopathic" urticaria remains an important challenge. From a clinical perspective, it should be regarded as a multifactorial problem, and searching for aggravating factors is just as important as looking for causes.

Mast cell-independent urticaria

There are several recognized circumstances where angioedema or wheals are due to mechanisms that do not involve mast cells. These need special consideration because their management and prognosis are different. For example, prostaglandins are involved in the pathogenesis of some patterns of non-immunologic contact urticaria (e.g. to sorbic acid), and the latter can be suppressed by nonsteroidal anti-inflammatory drugs (NSAIDs)[17]. In the cryopyrin-associated periodic syndromes (CAPS; see below), patients often develop urticarial lesions. The significant improvement that results from the administration of *anakinra*, an IL-1 receptor antagonist[18], *rilonacept* (IL-1 TRAP), a fusion protein that contains the extracellular domain of the IL-1 receptor (which binds IL-1)[19], or *canakinumab*, a human anti-IL-1β monoclonal antibody[20], points to the role of the cryopyrin inflammasome (see Fig. 45.1) and its production of IL-1β.

C1 esterase inhibitor (C1 inh) deficiency

C1 inh deficiency is usually hereditary, but may be acquired. Three types of hereditary angioedema (HAE) are now recognized (see Fig. 18.18). Types I and II are caused by mutations in one allele of the structural gene for C1 inh, resulting in reduced levels of C1 inh (85% of cases; type I) or reduced C1 inh function (15% of cases; type II). Because the mutations lead to levels of 5–30% of normal (rather than the expected 50%) in patients with type I HAE, it is thought that there is *trans* inhibition of the normal allele or increased catabolism of C1 inh.

Deficiency of C1 inh leads to loss of inhibition of Hageman factor (FXII), resulting in the generation of bradykinin by the action of kallikrein on high-molecular-weight kininogen (Fig. 18.6). Activation of the C1 component of complement by proteolytic enzymes, including plasmin and FXIIa, leads to low levels of C4 in the serum, which is an almost constant feature between and during attacks in untreated patients. Of note, type III HAE may be due to an *activating* mutation in one allele of the gene that encodes FXII, leading to increased formation of bradykinin. One possible explanation for the preponderance of women is the enhancement of transcription of this gene by estrogens. In addition, there is a positive feedback loop between kallikrein and FXII.

Acquired deficiency of C1 inh may result from persistent low-level activation of C1q by anti-idiotypic antibodies (directed against a paraprotein) in patients with B-cell lymphoproliferative disorders and plasma cell dyscrasias, or in autoimmune connective tissue diseases. This leads to *consumption* of C1 inh plus low serum levels of C1q as well as C4 (acquired, type I) or the formation of *inhibitory autoantibodies* directed against the C1 inh (acquired, type II).

Angiotensin-converting enzyme (ACE) inhibitor-induced urticaria is believed to result from the inhibition of endogenous kininase II (also known as ACE), which leads to increased production of bradykinin via inhibition of its metabolism (see Fig. 18.6). It usually presents with angioedema, which is often orofacial and may be life-threatening.

CLINICAL FEATURES

Clinical Diversity

It is important to distinguish *urticaria* from *urticarial dermatoses*, such as urticarial drug eruptions, eosinophilic cellulitis and bullous pemphigoid. The individual wheals of urticaria are "here today and gone tomorrow" (i.e. they generally last less than 24 hours), whereas with urticarial dermatoses, the individual lesions last for days or longer. Although urticarial vasculitis is often included in classifications of urticaria because the wheals resemble urticaria, it is actually an urticarial dermatosis. Clinically, the lesions last longer than 24 hours (as determined by circling and observing individual wheals), and histologically there is evidence of leukocytoclastic vasculitis (see Ch. 24).

Wheals may be small or large, single or multiple. In the physical urticarias, the distribution pattern and morphology can be helpful in separating the different clinical types (see Physical Urticarias). Angioedema can merge with wheals and these two can be difficult to separate, especially around the eyelids. Angioedema may also be a feature of anaphylaxis, if the throat is involved. In this sense, wheals, angioedema and anaphylaxis form parts of a clinical spectrum.

Classification

Because the etiology is often unknown at the time of the first consultation, the most practical classification of urticaria relies on clinical

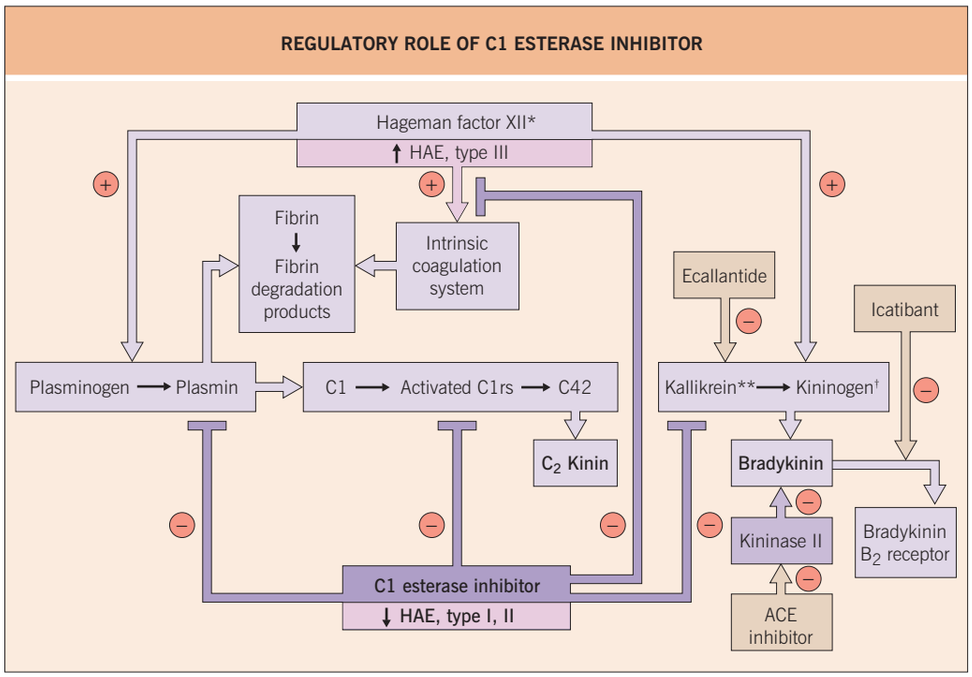


Fig. 18.6 Regulatory role of C1 esterase inhibitor on the fibrinolytic, coagulation, complement and kinin systems. Angiotensin-converting enzyme (ACE) inhibitor-induced urticaria is believed to result from the inhibition of endogenous kininase and a subsequent increase in bradykinin. Icatibant and ecallantide have recently been approved for the emergency treatment of hereditary angioedema (HAE). Icatibant, a decapeptide, is a specific bradykinin B_2 receptor antagonist. Ecallantide, a 60-amino acid recombinant protein, selectively inhibits kallikrein. *The active form of Hageman factor (XII) is XIIa. **Kallikrein is formed from prekallikrein. †High-molecular-weight.

CLINICAL CLASSIFICATION OF URTICARIA AND ANGIOEDEMA
• "Ordinary" (spontaneous) urticaria (all urticarias not classified below)
• Physical (inducible) urticarias (see Table 18.3)
• Urticarial vasculitis (defined by vasculitis on skin biopsy)
• Contact urticaria (induced by percutaneous or mucosal penetration)
• Angioedema without wheals
• Distinctive urticarial syndromes

Table 18.2 Clinical classification of urticaria and angioedema. All clinical patterns of urticaria can be acute, episodic or chronic.

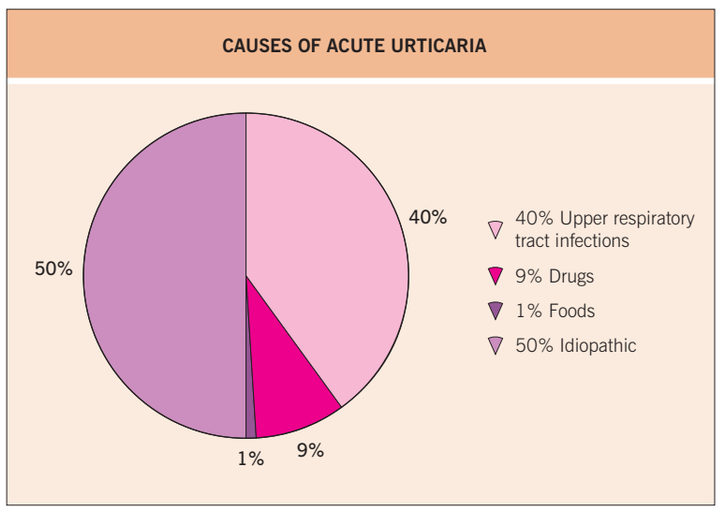


Fig. 18.7 Causes of acute urticaria. *Data from Zuberbier, 1996*[21].

characteristics rather than etiology to define groups of patients (Table 18.2). Most spontaneous urticaria can be considered to behave in an ordinary manner (i.e. fluctuating wheals which may be accompanied by angioedema) whatever its etiology or duration, unless it has a predominantly physical trigger, has evidence of vasculitis, or is caused by exogenous contact. If no cause for ordinary (spontaneous) urticaria can be defined, it is called idiopathic, but the use of this label as an automatic prefix to chronic urticaria is no longer tenable as a significant number of these patients will have autoimmune disease. It is worth separating angioedema without wheals from the other patterns of urticaria, because some of these cases will be due to HAE, acquired C1 inh deficiency, or drug reactions (e.g. ACE inhibitors, NSAIDs), and these are managed differently.

Acute versus Chronic Urticaria

All urticarias are acute initially. Some will become chronic after a period of time that is usually defined as 6 weeks or more. The term "chronic urticaria" should only be applied to continuous urticaria occurring at least twice a week off treatment. Urticaria occurring less frequently than this over a long period is better called episodic (or recurrent), because this presentation is more likely to have an identifiable environmental trigger. The causes of acute urticaria presenting to emergency dermatology clinics in one survey[21] are shown in Figure 18.7. Most of these patients probably fall into the ordinary category, because physical urticarias and urticarial vasculitis tend to persist beyond 6 weeks and contact urticarias would not normally present to the hospital. The high frequency of associated viral infections is notable, as is the lack of food allergy as a cause. The different clinical patterns of chronic urticaria and their causes (where known) are shown in Figure 18.8. These data reflect the experience of specialist urticaria clinics in dermatology departments and may not represent the experience of other medical practitioners, such as those in general practice, internal medicine, pediatrics and allergy.

"Ordinary" (Spontaneous) Urticaria

The condition can present at any age. Acute urticaria is common in young children with atopic dermatitis, but chronic urticaria peaks in the fourth decade. Multiple pruritic wheals of different sizes erupt anywhere on the body and then fade within 2–24 hours without bruising; angioedema lasts longer. Urticaria may occur at any time, but often appears in the evening or is present on waking. Irritation tends to be most intense at night and may disturb or prevent sleep. This, in turn, compounds the distress of the condition. Substantial impairment in quality-of-life measures, including self-image, sexual relationships and social interaction, has been demonstrated[22]. Women may describe premenstrual exacerbations. Systemic symptoms of fatigue, lassitude, sweats and chills, indigestion or arthralgias are common with severe attacks, but the occurrence of pyrexia or arthritis should alert the clinician to another explanation, such as urticarial vasculitis, Schnitzler's

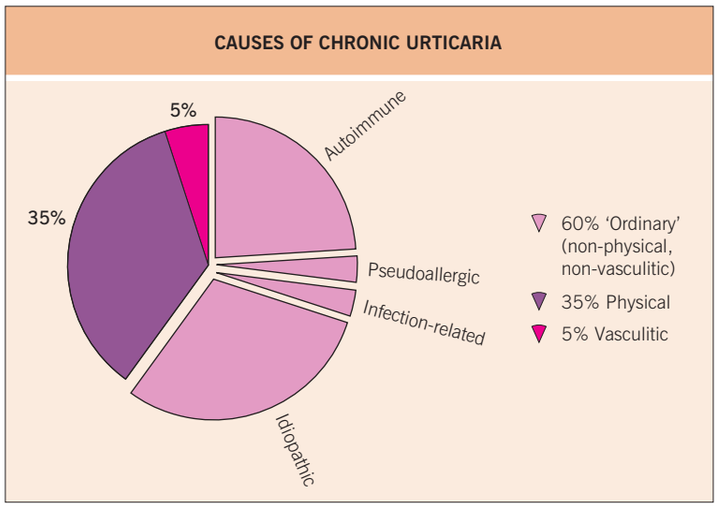


Fig. 18.8 Causes of chronic urticaria. Autoimmune represents those patients with functional autoantibodies against FcεRI or the Fc portion of IgE.

syndrome or cryopyrin-associated periodic syndrome (e.g. Muckle–Wells syndrome).

Associations

Chronic urticaria has been associated with autoimmune thyroid disease[23] and other autoimmune conditions, including vitiligo, insulin-dependent diabetes, rheumatoid arthritis and pernicious anemia[12]. Patients with demonstrable histamine-releasing autoantibodies have a very strong association with HLA-DR4 and its associated allele HLA-DQ8[24]. A possible association between *Helicobacter pylori* gastritis and chronic urticaria was suggested by a systematic review of therapeutic studies, which showed a higher frequency of urticaria remission when the infection was eradicated than when it was not[25]. Parasitic infections, such as intestinal strongyloidiasis, are an uncommon cause of urticaria in developed countries, but may be a significant problem where they are endemic. Acute urticaria due to gastric *Anisakiasis simplex* has been reported from Spain[26]. Possible associations between dental infections or gastrointestinal candidiasis and chronic urticaria have not been substantiated by large epidemiologic studies. Although there have been anecdotal reports linking urticaria to malignancy, no statistically significant association was found in a large Swedish survey[27].

Physical (Inducible) Urticarias

The physical urticarias represent a distinct subgroup of the urticarias that are induced by an exogenous physical stimulus rather than occurring spontaneously. Because cholinergic urticaria is triggered by factors that lead to sweating (e.g. a rise in core body temperature, stress or spicy foods), rather than an external physical stimulus, it is often classified separately from other inducible urticarias; for the sake of convenience, it will be included here. The physical urticarias are classified by the predominant stimulus that triggers wheeling, angioedema or anaphylaxis[28] (Table 18.3). Of all the urticarias, they may affect the quality of life most severely, particularly delayed pressure urticaria and cholinergic urticaria[29]. While the lesions of most physical urticarias occur within minutes of provocation and generally resolve within 2 hours, a few physical urticarias (e.g. delayed pressure urticaria, delayed dermographism) develop after a delay of several hours and persist for 24 hours or longer.

The wheals are usually localized to the stimulated area of skin. However, sometimes the physical stimuli need to produce a systemic effect, e.g. a rise or drop in core body temperature, to induce urticaria of a reflex type. Thus, generalized heating of the body can induce cholinergic urticaria (which is common), and generalized cooling, cold reflex urticaria (which is rare). Here, multiple small wheals occur on widespread areas of the body.

CLASSIFICATION OF PHYSICAL URTICARIAS
URTICARIA DUE TO MECHANICAL STIMULI

Dermographism
• Immediate
  • Simple
  • Symptomatic
• Delayed
Delayed pressure urticaria
Vibratory angioedema
• Inherited
• Acquired

URTICARIA DUE TO TEMPERATURE CHANGES

Heat
• Heat contact urticaria
Cold
• Cold contact urticaria
  • Primary
  • Secondary (cryoglobulins, cryofibrinogen)

URTICARIA DUE TO SWEATING OR STRESS
Cholinergic urticaria Adrenergic urticaria Exercise-induced urticaria • Exercise-induced anaphylaxis • Food- and exercise-induced anaphylaxis
SOLAR URTICARIA
AQUAGENIC URTICARIA
Rare variants are not shown here for simplicity (see text).

Table 18.3 Classification of physical urticarias by the eliciting stimulus.

Angioedema may be seen with all the physical urticarias except with symptomatic dermographism. Vibratory angioedema manifests with subcutaneous swellings but not wheals. Also, several forms of physical urticaria can coexist in the same patient. Common combinations include symptomatic dermographism and cholinergic urticaria; cold and cholinergic urticaria; and delayed pressure urticaria and delayed dermographism. Delayed pressure urticaria may coexist with chronic urticaria. Some rare forms of physical urticaria, such as familial delayed cold urticaria, are beyond the scope of this chapter.

Urticaria due to mechanical stimuli

Dermographism (literally "skin writing") (syn. factitious urticaria)

Immediate dermographism

This is divided into simple or symptomatic. Simple immediate dermographism occurs in ~5% of normal people in response to moderate stroking of the skin and may be regarded as an exaggerated physiologic response.

Symptomatic dermographism[30] is the most common of the physical urticarias (Fig. 18.9). It manifests as linear wheals at sites of scratching or sites of friction, such as collars and cuffs of clothes. Wheeling occurs after gentle stroking of the skin in response to a shearing force. Patients, most frequently young adults, often complain of pruritus before the wheals appear and may not associate them with scratching. It is worst in the evening and often occurs in bouts. The lesions usually resolve within an hour. Mucosal involvement does not occur, but vulvar swelling during sexual intercourse has been reported. The general course is unpredictable, but usually there is a gradual tendency towards improvement over several years. Symptomatic dermographism occasionally follows scabies infestation and penicillin allergy. There is no association with systemic disease, atopy, food allergy or autoimmunity.

Rarer forms of dermographism

These include delayed dermographism, which appears at least 30 minutes after a stroking stimulus, red dermographism (in response to rubbing, not stroking, the skin), localized dermographism, cholinergic dermographism, and dermographism associated with mastocytosis. The blanching response seen in patients with atopic and other forms of dermatitis, known as white dermographism, is not a form of urticaria.

Fig. 18.9 Symptomatic dermographism within minutes of scratching. *Courtesy, Jean L Bolognia, MD.*

Fig. 18.10 Delayed pressure urticaria.

Delayed pressure urticaria

Delayed pressure urticaria (DPU) is important because it can interfere severely with quality of life; it may be underdiagnosed and its treatment is difficult[31]. DPU is characterized by the development of deep erythematous swellings at sites of sustained pressure to the skin, after a delay of 30 minutes to 12 hours (Fig. 18.10); sometimes it resembles angioedema. The swellings are usually pruritic, painful, or both, and may persist for several days, unlike the spontaneous wheals of ordinary urticaria. Sites frequently involved are the waistline after wearing tight clothing, below the elastic of socks, the feet in tight shoes, the palms after manual work, the soles after walking or climbing ladders, and the genitalia after intercourse.

Systemic features such as malaise, "flu-like" symptoms and arthralgias may occur. If the swellings occur over joints, the resulting restriction of motion may be mistaken for arthritis. The prognosis is variable, but the mean duration in different series was 6–9 years. Up to 37% of patients with chronic ordinary urticaria attending a hospital specialist clinic had associated DPU[32]. Conversely, nearly all patients with DPU have associated spontaneous wheals. Because of this association and the delayed onset, patients may not be aware of any relationship to pressure unless specifically questioned.

Vibratory angioedema

This is a very rare form of urticaria, where a vibratory stimulus induces localized swelling and erythema within minutes, lasting 30 minutes. Stimuli include jogging, vigorous rubbing with a towel, and the use of vibrating machinery such as lawnmowers and motorcycles. Avoidance of vibratory stimuli enables patients to live a normal life. Vibratory angioedema may be acquired or familial. The acquired form is often milder, and it may be associated with other physical urticarias such as DPU and immediate symptomatic dermographism. The familial form is dominantly inherited, and intense vibratory stimuli may induce generalized erythema and headache.

Urticaria due to temperature changes

Heat exposure

Heat contact urticaria

This is one of the rarest forms of urticaria, where, within minutes of contact with heat from any source, itching and whealing occur at the site of contact, lasting up to 1 hour. This must be distinguished from cholinergic urticaria. Patients can present after contact with hot water (e.g. washing dishes), but also after contact with radiant heat or warm sunlight. Systemic symptoms of faintness, headache, nausea and abdominal pain have occurred when the urticaria is extensive. There is an even rarer delayed form.

Cold exposure

Cold urticaria represents a heterogeneous group of conditions in which whealing occurs within minutes of rewarming after cold exposure[33].

Fig. 18.11 Cold urticaria. Wheals developed on the forearm after placement of an ice cube for 10 minutes, followed by rewarming. *Courtesy, Thomas Schwarz, MD.*

Primary cold contact urticaria

The most commonly encountered form is primary cold contact urticaria; it accounts for at least 95% of cases (Fig. 18.11). Although cold urticaria may follow respiratory infections, arthropod bites or stings, and perhaps HIV infection, the cause of most cases remains unknown (idiopathic). It may occur at any age, but is most frequently seen in young adults. Itching, burning and whealing occur in cold-exposed areas minutes after rewarming the skin. Commonly, primary cold contact urticaria occurs in rainy, windy weather and after contact with cold objects, including ice cubes. Patients often relate symptoms to changes in temperature as much as to the absolute external temperature. Systemic symptoms of flushing, headache, syncope and abdominal pain can develop if large areas are affected. Cold baths and swimming should usually be avoided as there is a potential risk of anaphylaxis. The mean duration was 6–9 years in one series, though primary cold contact urticaria may be more transient if it follows a viral infection.

Secondary cold contact urticaria

Cases due to serum abnormalities such as cryoglobulinemia or cryofibrinogenemia are rare, and are associated with other manifestations such as Raynaud's phenomenon or purpura. The wheals are usually similar to those of primary cold contact urticaria, but may last longer. The presence of circulating cryoglobulins or cryofibrinogen should be determined, and serum protein and immunofixation electrophoreses performed. Underlying causes, such as hepatitis B or C viral infections, lymphoproliferative disease or infectious mononucleosis, should be excluded.

Fig. 18.12 Cholinergic urticaria on the trunk after exercising and sweating.

Fig. 18.13 Urticarial vasculitis. Lesions look like ordinary urticaria but last longer and may bruise. An incidental finding is a skin graft donor site.

Reflex cold urticaria

In this form, generalized cooling of the body induces widespread wheal-ing. Patients with this disorder can experience life-threatening reactions from exposures such as diving into a cold lake. The ice cube test is negative, but placing the patient in a cold room at 4°C can reproduce lesions. This is no longer performed, as fatal anaphylaxis can occur.

Familial cold urticaria

Familial cold urticaria, also referred to as familial cold autoinflammatory syndrome, belongs to the group of disorders known as cryopyrin-associated periodic syndromes (see Table 45.2). The patients have mutations in *NLRP3,* which encodes the protein cryopyrin, and they develop cold-induced urticarial papules.

Urticaria due to sweating or stress

Cholinergic urticaria

Cholinergic urticaria is characterized by multiple, transient, papular wheals that are 2–3 mm in diameter and surrounded by an obvious flare. They occur within 15 minutes of sweat-inducing stimuli, such as any form of physical exertion, hot baths or sudden emotional stress (Fig. 18.12). Other eliciting stimuli include moving from a cold to a hot room, drinking alcohol and eating spicy food. It occurs more frequently in young adults with an atopic diathesis and is unusual in the elderly.

After the appropriate stimulus, pruritus is followed by the development of small, monomorphic wheals that are symmetrically distributed. They are most prominent on the upper half of the body, but can also affect the lower legs and forearms and even become generalized. Angioedema and systemic manifestations consisting of faintness, headache, palpitations, abdominal pain and wheezing may occur. Reduced forced expiratory volumes (in the absence of respiratory symptoms) have been recorded by spirometry. In more severely affected individuals, cholinergic urticaria can cause severe personal and occupational disability.

Cold urticaria, symptomatic dermographism or aquagenic urticaria may be associated with cholinergic urticaria. There is usually a gradual tendency towards improvement, but the condition may last for years. Rarer forms include cholinergic pruritus, cholinergic erythema (in which pruritic, symmetric, small erythematous macules appear to be persistent, but individual lesions actually last for up to 1 hour), and cholinergic dermographism. Severe exercise-induced cholinergic urticaria may sometimes progress to anaphylaxis.

Exercise-induced anaphylaxis (EIA)

This can occur without the typical wheals of cholinergic urticaria and appears to be a syndrome in its own right[34]. Food- and exercise-induced anaphylaxis (FEIA) is an increasingly recognized syndrome[35]. In FEIA, angioedema and/or anaphylaxis occur within minutes of exercise if it follows either prior ingestion of a specific food (e.g. α-gliadin in wheat), or sometimes within 4 hours of a heavy meal. FEIA may be due to priming of the mast cell by prior exposure to an allergen, or to an unknown mechanism. EIA is produced by exercise, but not by an increase in core temperature induced by other means capable of provoking cholinergic urticaria (e.g. a hot bath), and this distinction can be used to differentiate between the two conditions.

Adrenergic urticaria

Adrenergic urticaria can be distinguished from cholinergic urticaria by the presence of blanched vasoconstricted skin surrounding small pink wheals induced by sudden stress, as opposed to pale wheals surrounded by a pink halo. The lesions can be reproduced by intradermal injections of norepinephrine (noradrenaline).

Urticaria due to other exposures

Solar urticaria

Itching and whealing occur within minutes of exposure to UV or visible wavelengths of solar radiation specific to the patient (see Ch. 87).

Aquagenic urticaria

In aquagenic urticaria, contact with water of any temperature induces an urticarial eruption resembling a sparse form of cholinergic urticaria. Lesions occur most frequently on the upper part of the body and last for less than an hour. Other physical urticarias must be excluded and the condition must be differentiated from aquagenic pruritus (see Ch. 6).

Urticarial Vasculitis

Urticarial vasculitis is a clinicopathologic entity in which cutaneous lesions resemble urticaria clinically (but last longer than 24 hours) (Fig. 18.13) and histologically show evidence of leukocytoclastic vasculitis (Table 18.4; see Ch. 24)[37].

Contact Urticaria (see Ch. 16)

Contact urticaria is defined by the development of urticaria at the site(s) of contact with skin or mucosa, but contact erythema and even burning and stinging without erythema are sometimes embraced in the definition[17]. Percutaneous or mucosal penetration of the urticant may have distant effects, including acute urticaria or even anaphylaxis. Contact urticaria may be more common than reported, as patients often do not present to the hospital or tertiary care clinics, because the diagnosis can be self-evident.

Immunologic and non-immunologic forms are recognized, depending on whether the contact urticaria is due to allergen interaction with specific IgE or is IgE-independent. Allergic contact urticaria can be seen in children with atopic dermatitis who become sensitized to environmental allergens, such as grass, animals and foods, or in glove-wearers who are allergic to latex. In those individuals repeatedly exposed to latex via mucosal surfaces (e.g. urinary catheterization in spina bifida patients), allergic contact urticaria can be complicated by anaphylaxis. Non-immunologic (i.e. non-allergic) contact urticaria is due to direct effects of urticants on blood vessels, such as from exposure to sorbic

URTICARIAL VASCULITIS	
Epidemiology	Favors middle-aged women
Characteristics of urticarial lesions	>24 hours in duration; painful & burning sensation as well as pruritus; residual purpura as they resolve
Sites of involvement	Often occur at pressure points
Concurrent angioedema	Up to 40% of pts
Extracutaneous manifestations (% of pts affected)*	Arthralgias (50%) – transient, migratory GI involvement (20%) – abdominal pain, nausea, vomiting, diarrhea Pulmonary obstructive disease (20%) Renal (5–10%) – proteinuria, hematuria Ocular (unusual) – conjunctivitis, episcleritis, uveitis Other (unusual) – Raynaud's phenomenon, livedo reticularis, splenomegaly, lymphadenopathy, idiopathic intracranial HTN, pericardial or muscle involvement
Associated disorders	Systemic lupus erythematosus Sjögren's syndrome Serum sickness Cryoglobulinemia Infections – hepatitis B or C virus, Epstein-Barr virus Rarely, solar or cold urticaria, drugs, hypergammaglobulinemia
Laboratory evaluation	CBC with differential, platelet count; ESR, CRP; LFTs, BUN, crt Complement assays – C3, C4, CH50; if C4 low, C1q Urinalysis If indicated, PFTs, CXR, SPEP, IFE Tests for associated disorders, e.g. ANA, anti-Ro Ab
Disease course	Average of 3 years
Treatment (primarily based upon small case series and case reports; see Table 24.9)	Antihistamines for associated pruritus NSAIDs – improvement in 50% of pts Colchicine, dapsone, hydroxychloroquine, methotrexate, plasmapheresis Corticosteroids ± immunosuppressants†

*Higher incidence and greater severity in patients with hypocomplementemia.
†Especially for hypocomplementemic urticarial vasculitis.

Table 18.4 Urticarial vasculitis. In a series of 132 patients, an elevated ESR (28%), hypocomplementemia (18%) and an ANA titer >1 : 160 (11%) were the more common abnormalities[36]. Ab, antibodies; ANA, antinuclear antibodies; BUN, blood urea nitrogen; CRP, C-reactive protein; crt, creatinine; CXR, chest X-ray; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; HTN, hypertension; IFE, immunofixation electrophoresis; LFTs, liver function tests; NSAIDs, nonsteroidal anti-inflammatory drugs; PFTs, pulmonary function tests; pts, patients; SPEP, serum protein electrophoresis.

acid and benzoic acid in eye solutions and foods or cinnamic aldehyde in cosmetics; it may be mediated by PGD_2 and can be inhibited by NSAIDs. Percutaneous microinjection of vasomediators (e.g. histamine, acetylcholine, serotonin) via nettle stings or contact with histamine liberators that degranulate mast cells (e.g. dimethylsulfoxide, cobalt chloride) can lead to contact urticaria within minutes.

Food contact hypersensitivity syndrome

The oral allergy syndrome presents with itching and mild swelling of the mouth, tongue and soft palate within minutes of eating fresh fruits such as apples, pears, peaches and cherries, but not cooked fruit. It usually occurs in hayfever sufferers and represents a cross-reaction between panallergens in grass or birch pollens with fruit proteins. Angioedema and anaphylaxis are fortunately very rare. Recently, the term "food contact hypersensitivity syndrome" was proposed to include all forms of mucosal food contact reactions, including oral allergy syndrome[38].

Angioedema Without Wheals

Recurrent angioedema without wheals is in many instances idiopathic, but it is important to exclude a drug reaction and to consider the possibility of C1 inh deficiency. The latter can be inherited or acquired (e.g. B-cell lymphoproliferative disorders, plasma cell dyscrasias).

Drug reactions

A number of drugs can cause angioedema without wheals. The most common are NSAIDs[39] and ACE inhibitors[40]. Aspirin intolerance may present with angioedema alone, or with urticaria or anaphylaxis; cross-reactions with other NSAIDs can occur. A causative link to ACE inhibitors may be overlooked because angioedema can present over a year after starting the medication. For practical purposes, ACE inhibitors should be discontinued in favor of other antihypertensive medications if angioedema occurs without wheals. ACE inhibitors are contraindicated in patients with HAE and acquired C1 inh deficiency.

Hereditary angioedema, types I and II (inherited C1 inh deficiency)

The likelihood of inherited C1 inh deficiency as a cause of recurrent angioedema is increased if there is a family history or previous laryngeal edema or colicky abdominal pain (sometimes presenting as a surgical emergency). Trauma (emotional or physical) and estrogens can trigger attacks. The usual duration is 48–72 hours, and episodes are often followed by a refractory period. Some families with HAE describe a transient, prodromal erythematous eruption, but urticarial wheals does not occur and so a history of recurrent wheals effectively excludes the disorder.

Hereditary angioedema, type III

Type III HAE refers to individuals with a heterozygous gain-of-function mutation in the gene that encodes FXII (see above). Compared to patients with an inherited deficiency of C1 inh, the age of onset is later (usually in the second decade) and there is a higher frequency of facial angioedema.

Distinctive Urticarial Syndromes

Hereditary periodic fever syndromes (autoinflammatory syndromes)

Cryopyrin-associated periodic syndromes (CAPS)

The allelic disorders Muckle–Wells syndrome, familial cold autoinflammatory syndrome (familial cold urticaria), and neonatal-onset multisystem inflammatory disease (NOMID/CINCA) are now known to be

all due to mutations in *NLRP3*, which encodes the protein cryopyrin (see Table 45.2)[41,42]. These patients can develop wheals from an early age that may prove quite resistant to antihistamines.

Other syndromes

In hyperimmunoglobulinemia D with periodic fever syndrome (HIDS) and TNF receptor-associated periodic syndrome (TRAPS), erythematous and edematous urticarial plaques can occur in addition to periorbital edema (TRAPS). The cutaneous lesions in familial Mediterranean fever are more erysipeloid in appearance (see Table 45.2).

Schnitzler's syndrome

Schnitzler et al.[43] in 1974 described an unusual variant of chronic urticaria characterized by recurrent, non-pruritic wheals plus intermittent fevers, bone pain, arthralgia or arthritis, an increased ESR and a monoclonal IgM gammopathy. The clinical presentation has many similarities to CAPS. Skin biopsy specimens usually show a neutrophil-predominant dermal infiltrate, but fully developed vasculitis is uncommon. Some clinicians believe that these patients are best considered as having a variant of urticarial vasculitis that simply requires additional biopsies to demonstrate fully developed leukocytoclastic vasculitis. Schnitzler's syndrome has been reported to respond very well to anakinra, and the use of rilonacept is currently under investigation.

Episodic angioedema with eosinophilia

A syndrome of episodic angioedema with hypereosinophilia, weight gain and fever has been described (Gleich syndrome). The cause is uncertain, but increased serum levels of IL-5 have been found[44].

Systemic capillary leak syndrome

Also known as Clarkson's syndrome, this rare acquired disorder is characterized by episodic massive plasma exudation from blood vessels, leading to potentially life-threatening hypotension, analogous to anaphylaxis. Angioedema may be a feature. It is associated with an IgG paraproteinemia. Medications, in particular IL-2, can also produce a systemic capillary leak syndrome.

PATHOLOGY

The histopathology of urticaria is characterized by upper dermal edema with a mild mixed perivascular infiltrate of lymphocytes, eosinophils and some neutrophils (Fig. 18.14). A predominantly neutrophilic pattern has been described in a minority of patients, but this does not appear to carry any diagnostic significance[45]. Previous reviews of biopsy specimens from large series of patients with chronic urticaria have emphasized a spectrum of changes, ranging from mild lymphocytic infiltrates with rare neutrophils to occasionally showing fully developed leukocytoclastic vasculitis[46], emphasizing the potential for confusion between chronic urticaria and urticarial vasculitis. Features of the latter include endothelial cell damage, a perivenular cellular infiltrate rich in neutrophils, and leukocytoclasis. Some extravasation of erythrocytes and fibrinoid deposits in and around blood vessels may also be seen.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The differential diagnosis of urticaria includes all dermatologic conditions with an urticarial component, including insect bite reactions (papular urticaria), acute febrile neutrophilic dermatosis (Sweet's syndrome), pre-bullous pemphigoid (i.e. urticarial bullous pemphigoid), acute facial contact dermatitis (versus angioedema), urticarial drug reactions (e.g. antibiotics) and the urtication that may occur when lesions of urticaria pigmentosa are rubbed. In all these conditions, the urticarial component is part of a more prolonged inflammatory process (or mast cell proliferation in the case of mastocytosis) than is true urticaria and should be readily distinguishable by the prolonged duration of individual lesions.

Diagnosis

A comprehensive history is essential in every patient with urticaria. It should cover the duration of disease, frequency of attacks, duration of individual lesions, associated illness, previous treatment, known adverse reactions, past and family history, occupation and leisure activities, and an assessment of the impact of the disease on the patient's quality of life. The use of a detailed questionnaire in conjunction with a complete blood count and ESR was found to be almost as good as a complete diagnostic evaluation[47]. A full physical examination looking for the morphology and duration (by circling individual lesions) of wheals, bruising, livedo reticularis and signs of systemic disease should always be undertaken, but it is often normal. The patient's own photographs can often be useful because it is common for urticaria to have cleared by the time of consultation. Investigation should be targeted at specific features identified in the clinical assessment, as outlined below, and may include blood tests, skin biopsy (obtained in all patients with lesions lasting more than 24 hours), challenges for physical urticarias, food additives and drugs, and, infrequently, skin tests for allergy and the measurement of histamine-releasing autoantibodies. Most patients with antihistamine-responsive urticaria do not need an extensive investigation. A diagnostic algorithm is given in Figure 18.15.

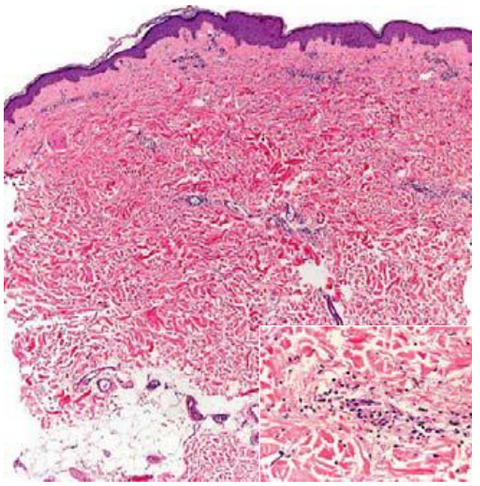


Fig. 18.14 Ordinary urticaria – histologic findings. A sparse, mainly perivascular inflammatory infiltrate and scant edema within the superficial and mid dermis. Note several neutrophils and a few eosinophils (insert). *Courtesy, Lorenzo Cerroni, MD.*

Acute urticaria

IgE-mediated reactions to environmental allergens as a cause of acute urticaria and contact urticaria can be confirmed by skin prick testing and serum radioallergosorbent tests (RAST). Results of both have to be interpreted in the clinical context.

Chronic urticaria

No investigations are routinely required for the majority of patients with mild disease that responds to antihistamines. A useful screening profile for non-responders with more severe disease could include a complete blood count and white cell differential (for instance, to detect the eosinophilia of intestinal parasitosis) and ESR (usually normal in chronic urticaria). The ESR may be elevated in urticarial vasculitis, and it is consistently high in the cryopyrin-associated periodic syndromes in which patients also have an elevated C-reactive protein level and an elevated serum amyloid A (SAA) protein level. Thyroid autoantibodies should be considered and thyroid function tests performed if indicated clinically. The prevalence of thyroid autoantibodies is higher in patients with chronic urticaria than in controls and may be an indicator of autoimmune urticaria. Tests for bowel parasites may be considered in the appropriate clinical setting.

Although the term "autoimmune" urticaria is increasingly being used for patients with evidence of functional serum autoantibodies (see Fig. 18.3), there is still a lack of agreement with regard to establishing such a diagnosis because of the lack of reliable, readily available or practical confirmatory tests. Demonstration of a localized wheal and flare response to intradermal injection of autologous serum (the autologous serum skin test; ASST) provides useful evidence of functional factors in the blood, but is not specifically a test for autoantibodies[48] (Fig. 18.16). A negative test, however, has very good negative predictive value for the absence of functional antibodies[49]. In the future, stricter regulatory guidelines regarding the handling of blood products will increasingly limit performance of this assay.

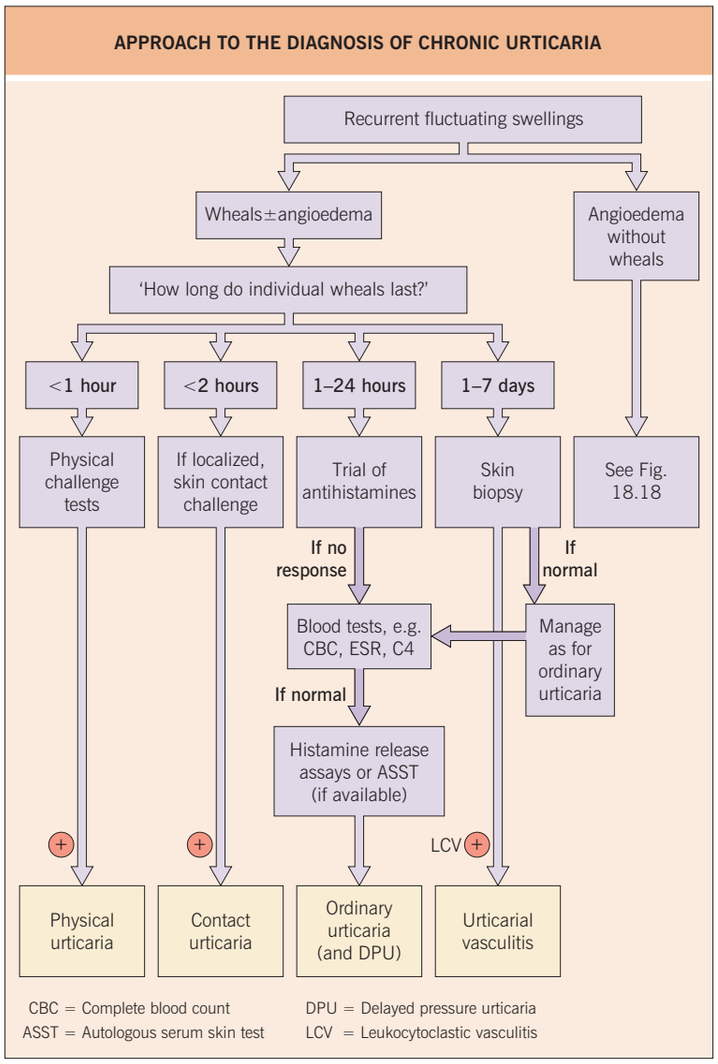


Fig. 18.15 Approach to the diagnosis of chronic urticaria.

Fig. 18.16 Autologous serum skin test (ASST). At 30 minutes, a red wheal response is present at the site of an intradermal injection of autologous serum, but not at that of a normal saline control. For the test to be positive, the wheal response at the serum injection site must be at least 1.5 mm greater in diameter than the control site. The ASST is a reasonably sensitive and specific screening test for functional autoantibodies as detected by the basophil release assay. Spontaneous wheals are also present at the venipuncture site and above the serum skin test.

Immunoassays for anti-FcεRI and anti-IgE antibodies (commercially available) do not necessarily correlate with basophil and mast cell histamine-releasing assays (sometimes commercially available) because non-functional as well as functional autoantibodies have been detected by Western blot and ELISA. The overlap between the ASST ("autoreactivity"), functional autoantibodies (detected via basophil or mast cell assays) and immunoassays ("immunoreactivity") is illustrated in Figure 18.17. The strongest evidence for an autoimmune etiology of urticaria is provided by demonstrating all three features, but many clinicians would accept a positive ASST and/or a positive functional assay as providing sufficient proof of autoimmunity to guide therapies and prognosis.

Physical urticarias

International standards for the diagnosis of physical urticarias and definitions of challenge testing have been proposed[28]. Symptomatic dermographism can be tested for simply by stroking the skin of the back lightly with the rounded edge of a wooden spatula. A calibrated instrument called a dermographometer, which is a spring-loaded stylus, the pressure of which can be adjusted to a predetermined setting (36 g/mm^2), can be used to quantify the sensitivity of the skin. Delayed pressure urticaria is confirmed if applying either a 2.5-kg weight to the thigh or back for 20 minutes (using a rod with a diameter of 1.5 cm) or a dermographometer set at 100 g/mm^2 for 70 seconds, results in a palpable wheal at 30 minutes to 8 hours (usually at 6 hours). Provocation tests for cholinergic urticaria include exercise to the point of sweating in an overheated environment, or partial immersion in a hot bath at 42°C for 10 minutes. A positive hot bath test excludes exercise-induced anaphylaxis. Cold contact urticaria is confirmed by the development of whealing at the site of application of an ice cube in a thin polyethylene bag or glove for 5 minutes (the most sensitive individuals may react after 30 seconds, with the least sensitive requiring up to 20 minutes of ice application; see Fig. 18.11).

Phototesting confirms the diagnosis of solar urticaria, with the development of wheals within minutes of exposure to natural or artificial radiation. The action spectra of the inducing wavelengths can be determined by narrowband monochromators (see Ch. 87). The diagnosis of aquagenic urticaria is made by inducing wheals after a bath or shower at body temperature, or under wet gauze applied at body temperature for 20 minutes. Localized heat urticaria is confirmed by applying a heated cylinder (temperature increments up to 45°C) to the skin for 30 seconds to 5 minutes.

Urticarial vasculitis

Lesional skin biopsy is essential and should be undertaken if circled lesions last more than 24 hours, in order to confirm the presence or absence of leukocytoclastic vasculitis histologically. The sampled lesion should have been present for 12–24 hours. Direct immunofluorescence microscopy is generally uninformative and should not be routinely performed. Patients with urticarial vasculitis need a full vasculitis screen (see Table 18.4 & Ch. 24).

Angioedema without wheals

Detection of a low serum level of C4 is a very sensitive, but nonspecific, screening test for types I and II HAE and acquired C1 inh deficiency (the level is normal in type III HAE). Measurement of the *amount* of C1 inh by immunochemical assay for type I HAE and C1 inh *function* to detect type II HAE should be performed if indicated by the history and supported by a low serum C4 level. Serum C1q levels are also reduced in acquired C1 inh deficiency (Fig. 18.18).

TREATMENT

Patients should be given advice and information on common precipitants, treatments and prognosis. Antipruritic lotions and the avoidance of aggravating factors, including NSAIDs, may be sufficient for some, but many will need additional interventions, including systemic medications. These can be stratified into first-, second- and third-line therapies (Fig. 18.19). The management of urticarial vasculitis (see Table 18.4) and that of C1 inh deficiency are considered separately because their pathogenesis and response to treatment are different. Patients must understand that although systemic corticosteroids may be the

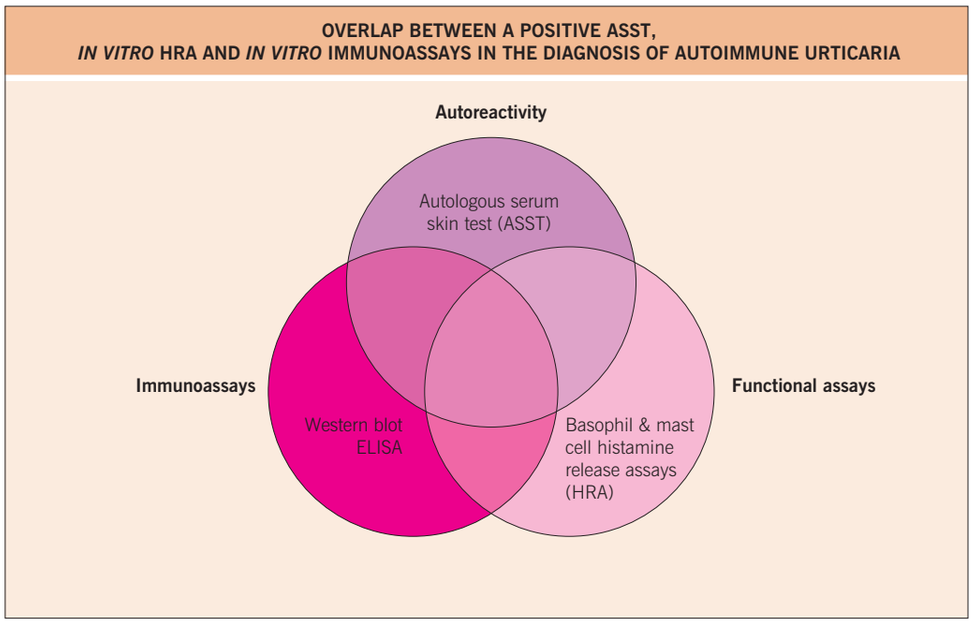


Fig. 18.17 Overlap between a positive autologous serum skin test (ASST), *in vitro* histamine release assays (HRA) and *in vitro* immunoassays in the diagnosis of autoimmune urticaria. The ASST will become increasingly difficult to perform in the future as regulations regarding blood products become more restrictive.

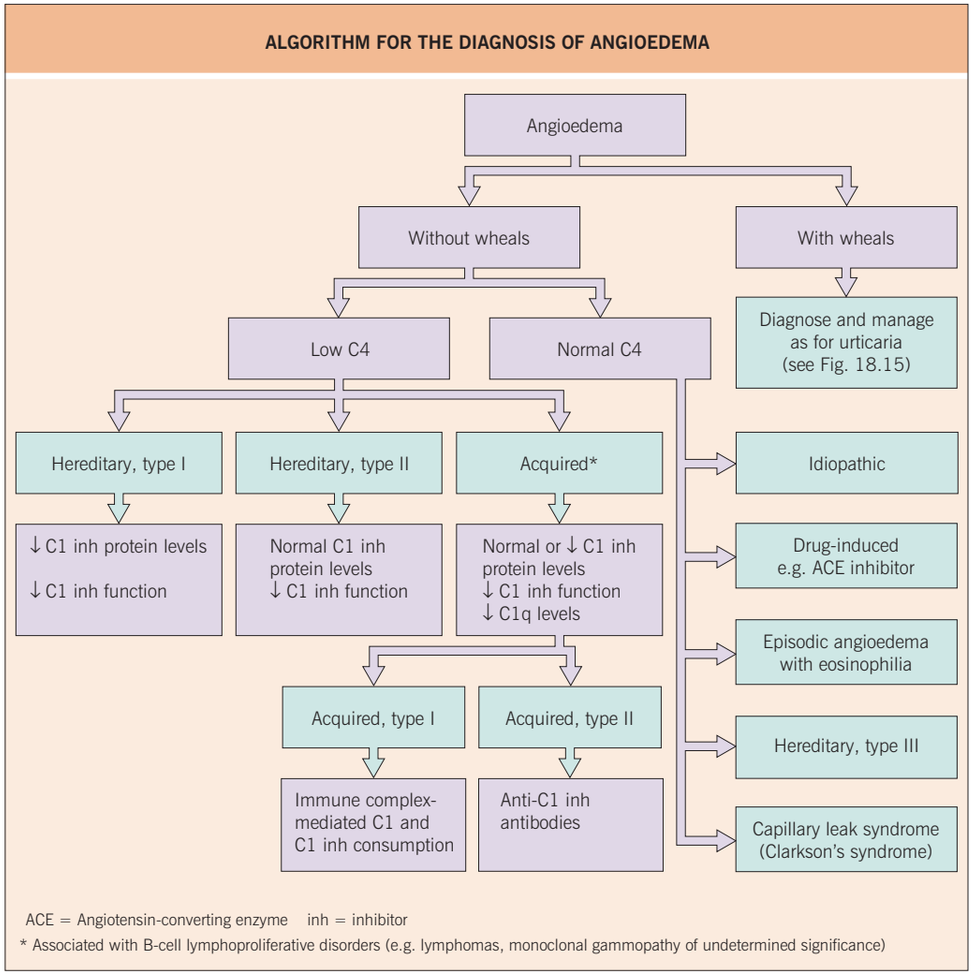


Fig. 18.18 Algorithm for the diagnosis of angioedema. Episodic angioedema with hypereosinophilia, along with weight gain and fever, is known as Gleich syndrome.

only treatment that completely eliminates their lesions, long-term use is unacceptable and combinations of other therapies can nearly always control symptoms and significantly improve quality of life.

Acute, Chronic and Physical Urticarias

First-line therapies

Antihistamines are the mainstay of management for most patients with urticaria, although not all patients will respond and only about 40% of those attending tertiary care clinics will clear or almost clear at licensed doses. Antihistamines reduce pruritus, flatten wheals, shorten wheal duration and reduce wheal numbers, even though they may not clear urticaria completely. It is worth discussing the relative benefit with patients who feel that "they haven't worked".

Antihistamines should be taken on a daily basis, the frequency depending on their half-life. In other words, they should not be taken only when the patient is symptomatic. As a general rule, antihistamines are safe and have few significant adverse effects. They can be

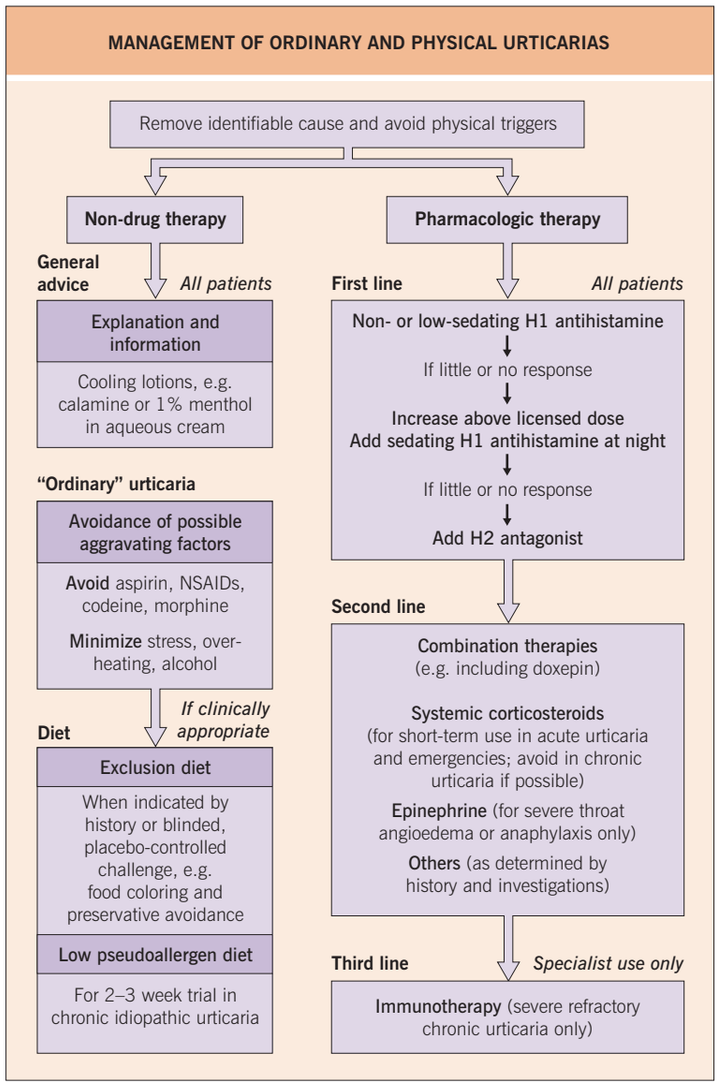


Fig. 18.19 Management of ordinary and physical urticarias.

grouped into first-generation (classic) antihistamines, second-generation (non- or minimally sedating) antihistamines and their derivatives, and the H_2 antagonists (Table 18.5). Combining drugs from the different groups can lead to better control of urticaria symptoms.

Classic antihistamines

Classic antihistamines are problematic because sedation and anticholinergic side effects are often dose-limiting. However, in combination with a daytime non-sedating antihistamine, they can be taken at night if sleep is disturbed by urticaria, but the following day they may interfere with skilled tasks (e.g. operating machinery and driving) or reduce the ability to concentrate at work or school. Chlorpheniramine is often chosen for pregnant women when antihistamines are essential, because it has a long safety record; however, it is not licensed for this indication and should be avoided in the first trimester if possible.

Second-generation antihistamines

Second-generation antihistamines are usually well tolerated, with the majority of patients requiring only once-daily oral dosing (see Table 18.5). For chronic urticaria, there is probably little distinction between the second-generation antihistamines when they are taken at the licensed dosages. A European consensus paper has recommended increasing the daily dose of second-generation H_1 antihistamines up to fourfold for difficult urticaria[50]. It is possible that their additional anti-allergic and anti-inflammatory properties may be clinically beneficial at these higher doses, but direct evidence for this is lacking and they do represent unlicensed dosages.

Fexofenadine is licensed for urticaria at 180 mg daily. It is the active metabolite of terfenadine, but does not appear to have the potential for ventricular arrhythmias of its parent drug at licensed doses. Desloratadine (an active metabolite of loratadine) and levocetirizine (the active enantiomer of cetirizine) probably offer no clinical advantage over their parent drugs at equivalent doses.

Clinically important drug interactions are infrequent, but coadministration of mizolastine with systemic erythromycin and ketoconazole is contraindicated because of concern about possible cardiac arrhythmias. Caution is also recommended with regard to other hepatic cytochrome P450 3A4 inhibitors or substrates (see Ch. 131), including cimetidine and cyclosporine, which may be used for urticaria in special circumstances.

Addition of H_2 antagonists to conventional H_1 antihistamines

The addition of H_2 antagonists to conventional H_1 antihistamines may be helpful in some patients with chronic urticaria, although the evidence for combining H_1 and H_2 antihistamines is poor and not all authorities recommend this therapeutic approach. H_2 antihistamines have no effect on histamine-induced pruritus and should not be used as monotherapy. Ranitidine is preferable to cimetidine because, unlike cimetidine, it does not interfere with hepatic metabolism of other drugs and does not bind androgen receptors. Nizatidine and famotidine have similar properties to ranitidine, but have not been evaluated in clinical trials for chronic urticaria and cannot be specifically recommended.

Second-line therapies (targeted interventions)

Second-line therapies may be considered when urticaria does not respond well to antihistamines, but high-quality evidence to support their use is lacking. They should usually be prescribed as additive therapies (to antihistamines) rather than as alternatives. The choice of second-line drugs should be guided by specific indications, summarized in Table 18.6. Here, the management of urticaria can be influenced considerably by a full clinical assessment and the experience of the clinician. It is unusual for children to need second-line therapies, except the occasional use of prednisolone for very severe acute exacerbations of chronic urticaria. Second-line drugs should be used with considerable care in pregnancy, and only after the risks have been carefully considered against the likely benefits. Non-drug interventions include diets, phototherapy and cold desensitization.

Drug therapies

Prednisone or *prednisolone* is effective for nearly all presentations of chronic urticaria, but often needs to be used at reasonably high doses (30–50 mg daily) to achieve good initial control of severe disease. It should be considered primarily for the short-term management of "crisis" urticaria and serious angioedema of the throat, when, often, a single dose or several daily doses will be sufficient to re-establish control with regular full-dose antihistamines. Regular treatment with oral corticosteroids should be avoided because of the usually prolonged duration of chronic urticaria and because of their predictable side effects (e.g. hypertension, weight gain, glucose intolerance, osteoporosis). Rebound is also a common problem and the long-term course of the urticaria is often not altered.

Epinephrine (adrenaline) by subcutaneous or intramuscular injection is the treatment of choice for anaphylactic shock or severe anaphylactoid reactions, whether due to an allergy, pseudoallergy or physical urticaria. Epinephrine may also be necessary for angioedema of the oropharynx in severe acute allergic urticaria and idiopathic angioedema, but it is rarely required for chronic urticaria and is not effective for HAE. Directing epinephrine mist from an aerosol inhaler onto mucosal angioedema may be helpful for minor episodes, but it is usually better to administer the drug intramuscularly or subcutaneously, if it is required. Side effects of epinephrine include tachycardia, anxiety and headache. It should be used with caution in patients with hypertension, ischemic heart disease, cerebrovascular disease and diabetes mellitus. Coadministration of tricyclic antidepressants (including doxepin) and β-blockers should be avoided. For reassurance, patients who are prone to severe acute allergic urticaria and idiopathic angioedema may carry a self-administered epinephrine pen and they need to be aware of side effects, drug interactions and potential rebound phenomenon.

Doxepin is a tricyclic antidepressant with very potent H_1 and H_2 antihistaminic properties. Although it has significant sedative and

ANTIHISTAMINES FOR URTICARIA			
Class	**Examples**	**Plasma half-life (hours)**	**Daily adult dose***
Classic (sedating) H_1 antihistamines	Chlorpheniramine (1)	12–15	4 mg three times daily (up to 12 mg at night)
	Hydroxyzine (1)	20	10–25 mg three times daily (up to 75 mg at night)
	Diphenhydramine (2)	4	10–25 mg at night
	Doxepin† (1)	17	10–50 mg at night
Second-generation H_1 antihistamines	Acrivastine‡ (1)	2–4	8 mg three times daily
	Cetirizine§(1)	7–11	10 mg once daily
	Loratadine (1)	8–11	10 mg once daily
	Mizolastine‖ (1)	13	10 mg once daily
Newer second-generation H_1 antihistamines	Desloratadine (1)	19–35	5 mg once daily
	Fexofenadine (1)	17	180 mg once daily
	Levocetirizine (1)	7–10	5 mg once daily
	Rupatadine (1)	6	10 mg once daily
H_2 antagonists¶	Cimetidine (1)	2	400 mg twice daily
	Ranitidine (2)	2–3	150 mg twice daily

*Current prescribing manuals should be consulted for details on doses in children.
†Possesses potent H_1 and H_2 antihistamine properties.
‡Only available in the US as a combination product with pseudoephedrine for seasonal allergic rhinitis.
§The active metabolite of hydroxyzine.
‖Not available in the US.
¶Used in combination with H_1 antagonists.

Table 18.5 Antihistamines for urticaria. A short-acting classic antihistamine may be added at night to a daily second-generation antihistamine, with or without the addition of an H_2 antagonist for maximal antihistamine blockade. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

SECOND-LINE MEDICATIONS FOR CHRONIC OR PHYSICAL URTICARIA				
Generic name	**Drug class**	**Route**	**Dose**	**Special indication/associated diseases**
Prednisone (2)	Corticosteroid	Oral	0.5 mg/kg daily	Severe exacerbations (days only)
Epinephrine (2)	Sympathomimetic	Subcutaneous, IM (self-administered)	300–500 mcg	Idiopathic or allergic angioedema of throat/ anaphylaxis
Montelukast (3)	Leukotriene receptor antagonist	Oral	10 mg daily	Aspirin-sensitive urticaria, ? delayed pressure urticaria
Thyroxine (2)	Thyroid hormone	Oral	50–150 mcg daily	Autoimmune thyroid disease
Colchicine (3)	Neutrophil inhibitor	Oral	0.5/0.6–1.5/1.8 mg* daily	Neutrophilic infiltrates in lesional biopsy specimens or urticarial vasculitis
Sulfasalazine (3)	Aminosalicylates	Oral	2–4 g daily	Delayed pressure urticaria

Table 18.6 Some second-line medications for chronic or physical urticaria. Current prescribing manuals should be consulted for details on dose, drug interactions and contraindications for individual patients. The stated doses represent guidelines only. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports. *Available in doses of 0.5 mg or 0.6 mg, depending upon the country. IM, intramuscular.

anticholinergic properties, it may be valuable, especially when dosed at night in adult patients with chronic urticaria.

Montelukast, a leukotriene receptor antagonist (see Ch. 130), may be beneficial for aspirin-sensitive chronic urticaria[51], due to the likely involvement of leukotrienes in its pathogenesis. *Zafirlukast* has also been used. There have been anecdotal reports of responses in refractory chronic urticaria associated with delayed pressure urticaria, but clinical experience to date has been less encouraging. Side effects are uncommon, but urticaria, angioedema and anaphylaxis have been reported when it has been given for other indications.

Thyroxine supplementation has been reported to suppress chronic ordinary urticaria in biochemically euthyroid patients with elevated levels of antithyroid autoantibodies. Although there may be occasional successes from this approach, the results are inconsistent.

Sulfasalazine can be helpful for chronic urticaria when delayed pressure urticaria (DPU) symptoms predominate, providing it is tolerated. Otherwise, these patients often require systemic corticosteroids. The drug should be avoided in patients with aspirin sensitivity and glucose-6-phosphate dehydrogenase (G6PD) deficiency. Complete blood count and hepatic enzymes must be monitored monthly for the first 3 months, and then regularly during therapy. Stevens–Johnson syndrome, nephrotic syndrome and oligospermia have been reported. Dapsone can be considered in DPU patients who are sensitive to NSAIDs.

Colchicine may be beneficial for chronic urticaria when predominantly neutrophilic infiltrates are seen histologically ("neutrophilic urticaria") and it is also used for urticarial vasculitis. Possible side effects include nausea, vomiting and abdominal pain. Peripheral neuritis,

myopathy, alopecia and myelosuppression have been reported rarely with prolonged treatment. Patients with liver or renal disease who are receiving colchicine should avoid P-glycoprotein or strong CYP3A4 inhibitors.

Nonsteroidal anti-inflammatory drugs have been used to treat DPU, with conflicting results, but may exacerbate chronic urticaria.

Anabolic steroids, such as danazol, may be useful for severe cholinergic urticaria, but virilizing side effects and long-term concern regarding liver toxicity are disadvantages.

Miscellaneous drug therapies described for chronic urticaria include tranexamic acid, heparin and warfarin, but convincing evidence for their use is lacking and there are no specific situations where they appear to be better than other treatments.

Non-drug therapies

Exclusion of food additives and natural salicylates from the diet has been advocated in a number of reports. The high success rates in some series may have been due in part to the natural history of remission in chronic urticaria, as less than 20% of patients responding to low-pseudoallergen diets flare after double-blind placebo-controlled challenge with individual additives[52]. Diets nevertheless remain popular with chronic urticaria patients and are always worth considering when antihistamines have failed and second-line drugs are inappropriate. There is general agreement that food allergy as a cause of adult chronic urticaria is exceptional, and that investigation for relevant immediate hypersensitivity reactions should not be undertaken without a strong lead from the history.

Induction of tolerance by repeated frequent graduated exposures to the precipitating physical factor can be helpful for cold urticaria, solar urticaria and localized heat contact urticaria. The schedule is time consuming, not all patients can be rendered tolerant, and repeated daily exposures are necessary to maintain tolerance.

Ultraviolet therapy and photochemotherapy (PUVA) have been used for chronic urticaria, but the reported results have been inconclusive. A retrospective survey suggested that narrowband UVB (NB-UVB) phototherapy might be effective. There is limited evidence that PUVA and NB-UVB are helpful for highly symptomatic dermographism at doses usually administered for psoriasis.

Third-line therapies

The recognition that some patients with severe urticaria unresponsive to antihistamines have an autoimmune etiology has opened up the option of immunotherapy for selected cases of chronic autoimmune urticaria.

Plasmapheresis was used successfully in some patients with chronic autoimmune urticaria in a small, open, proof-of-concept study, but it is not recommended as monotherapy because of its expense, its potential morbidity, and the early relapse of the urticaria[53].

IVIg infusions (total of 2 g/kg over 5 days) were beneficial in the majority of chronic autoimmune urticaria patients in another small open study, with remissions in some lasting at least 3 years[54]. Expense and potential morbidity remain a concern for this approach, which has not been subject to controlled studies.

Cyclosporine (3–4 mg/kg/day) appears to clear or substantially benefit approximately two-thirds of patients with chronic autoimmune urticaria refractory to antihistamines. This benefit has been confirmed in a double-blind study of cyclosporine at 4 mg/kg/day for 4–8 weeks; there were no serious adverse effects (e.g. renal impairment)[55]. However, only 25% of responders remained clear or almost clear 4–5 months after discontinuing therapy, and symptomatic side effects (e.g. gastrointestinal) were common. In addition, the risk of maintaining the "impossible to wean" patient on long-term cyclosporine is potentially considerable, as is the risk of rebound after discontinuation. Optimal treatment protocols have yet to be confirmed.

Other *immunosuppressive therapies*, including methotrexate, mycophenolate mofetil, azathioprine and cyclophosphamide, may work for some patients with severe chronic urticaria, if cyclosporine fails. Responses to *methotrexate* may be seen in steroid-dependent chronic urticaria patients with and without evidence of functional autoantibodies[56].

Omalizumab (humanized anti-IgE monoclonal antibody) has been reported anecdotally to be effective for spontaneous and inducible urticarias at doses equivalent to those used in asthma. Its effectiveness in chronic spontaneous urticaria has been demonstrated in a double-blind study[56a].

Urticarial Vasculitis

Treatment options are outlined in Tables 18.4 and 24.9.

C1 Esterase Inhibitor (C1 inh) Deficiency

The treatment of C1 inh deficiency differs from that of other types of angioedema. C1 inh concentrate should be given in an emergency, as it may prove to be life-saving. Fresh frozen plasma may be given as an alternative to C1 inh concentrate if the latter is unavailable. Antihistamines, corticosteroids and epinephrine are not effective in patients with C1 inh deficiency[57]. To treat an acute life-threatening attack, patients with the acquired form of C1 inh deficiency often require much higher doses of C1 inh concentrate than the 20 units/kg recommended for HAE.

C1 inh concentrate may also be given as prophylaxis 1 hour before elective surgery, especially when intubation or tooth extraction is necessary. For minor surgical procedures, oral tranexamic acid (1 g four times daily in adults or 500 mg four times daily in children) for 48 hours before and after the procedure, or an increase in established maintenance doses of tranexamic acid or anabolic steroids, can be effective prophylaxis. Maintenance therapy is only necessary for patients with symptomatic recurrent angioedema or related abdominal pain.

Oral danazol is the treatment of choice for most patients, since stanozolol is now difficult to obtain. Virilizing side effects may occur even at the low doses needed for long-term maintenance therapy. Regular monitoring for hepatic inflammation and adenomas is essential. Oral tranexamic acid (an inhibitor of the activation of plasminogen to plasmin) may be used for maintenance, but it is contraindicated if there is a history of thrombosis. The manufacturer recommends regular eye examinations and liver function tests in the setting of long-term administration. ε-Aminocaproic acid has also been prescribed for some patients. Icatibant, a specific bradykinin B_2 receptor antagonist, and ecallantide, a kallikrein inhibitor, have recently been approved for the emergency management of HAE (see Fig. 18.6); both are administered as subcutaneous injections. Because HAE may be induced or exacerbated by estrogens in oral contraceptive pills or hormone replacement therapy, they should be avoided if possible.

PROGNOSIS

Most patients with chronic urticaria can expect to benefit from treatment, but the prognosis for complete recovery has probably changed little from that in a survey done over 40 years ago, which identified that 50% of patients attending a tertiary referral center with urticaria alone were clear within a year, but that 20% with urticaria and angioedema continued to have symptoms 20 years from the time of onset[58].

REFERENCES

1. Schäfer T, Ring J. Epidemiology of urticaria. Monogr Allergy. 1993;31:49–60.
2. Henz BM. Physical urticaria. In: Henz BM, Zuberbier T, Grabbe J, Monroe E (eds). Urticaria. Clinical, Diagnostic and Therapeutic Aspects. Berlin: Springer, 1998: 55–89.
3. Hawrylowicz CM, MacGlashan DW, Saiko H, et al. Effector cells of allergy. In: Holgate ST, Church MK, Lichtenstein LM (eds). Allergy, 3rd edn. London: Mosby, 2006: 351–73.
4. Grattan CEH. Autoimmune urticaria. Immunol Allergy Clin North Am. 2004;24:163–81.
5. Ferrer M, Nakazawa K, Kaplan AP. Complement dependence of histamine release in chronic urticaria. J Allergy Clin Immunol. 1999;104: 169–72.
6. Niimi N, Francis DM, Kermani F, et al. Dermal mast cell activation by autoantibodies against the high affinity IgE receptor in chronic urticaria. J Invest Dermatol. 1996;106:1001–6.
7. Sabroe RA, Francis DM, Barr RM, et al. Anti-FcεRI autoantibodies and basophil histamine releasability in chronic idiopathic urticaria. J Allergy Clin Immunol. 1998;102:651–8.

8. Eckman JA, Hamilton RG, Gober LM, et al. Basophil phenotypes in chronic idiopathic urticaria in relation to disease activity and autoantibodies. J Invest Dermatol. 2008;128:1956–63.
9. Vonakis BM, Vasagar K, Gibbons SP Jr, et al. Basophil FcepsilonRI histamine release parallels expression of Src-homology 2-containing inositol phosphatases in chronic idiopathic urticaria. J Allergy Clin Immunol. 2007;119:441–8.
10. Smith CH, Atkinson B, Morris RW, et al. Cutaneous responses to vasoactive intestinal polypeptide in chronic idiopathic urticaria. Lancet. 1992;339:91–3.
11. Kaplan AP. Urticaria and angioedema. In: Kaplan AP (ed.). Allergy, 2nd edn. Philadelphia: WB Saunders, 1997:573–92.
12. Sabroe RA, Seed PT, Francis DM, et al. Chronic idiopathic urticaria: comparison of the clinical features of patients with and without anti-FcεRI or anti-IgE autoantibodies. J Am Acad Dermatol. 1999;40:443–50.
13. Asero R, Tedeschi A, Coppola R, et al. Activation of the tissue factor pathway of blood coagulation in patients with chronic urticaria. J Allergy Clin Immunol. 2007;119:705–10.
14. Chan CL, Jones RL, Lau HYA. Characterisation of prostanoid receptors mediating inhibition of histamine release from anti-IgE-activated rat peritoneal mast cells. Br J Pharmacol. 2000;129:589–97.
15. Doeglas HMG. Reactions to aspirin and food additives in patients with chronic urticaria, including the physical urticarias. Br J Dermatol. 1975;93:135–43.
16. Bunselmeyer B, Laubach HJ, Schiller M, et al. Incremental build-up food challenge – a new diagnostic approach to evaluate pseudoallergic reactions in chronic urticaria: a pilot study: stepwise food challenge in chronic urticaria. Clin Exp Allergy. 2009;39:116–26.
17. Wakelin S. Contact urticaria. Clin Exp Dermatol. 2001;26:132–6.
18. Leslie KS, Lachmann HJ, Bruning E, et al. Phenotype, genotype, and sustained response to anakinra in 22 patients with autoinflammatory disease associated with CIAS-1/NALP3 mutations. Arch Dermatol. 2006;142:1591–7.
19. Church LD, McDermott MF. Rilonacept in cryopyrin-associated periodic syndromes: the beginning of longer-acting interleukin-1 antagonism. Nat Rev Rheumatol. 2009;5:14–5.
20. Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB, et al. Use of canakinumab in the cryopyrin-associated periodic syndrome. N Engl J Med. 2009;360: 2416–25.
21. Zuberbier T, Iffländer J, Semmler C, Henz BM. Acute urticaria: clinical aspects and therapeutic responsiveness. Acta Dermatol Venereol (Stockh). 1996;76:295–7.
22. O'Donnell BF, Lawlor F, Simpson J, et al. The impact of chronic urticaria on the quality of life. Br J Dermatol. 1997;136:197–201.
23. Leznoff A, Sussman GL. Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity: a study of 90 patients. J Allergy Clin Immunol. 1989;84:66–71.
24. O'Donnell BF, Neill CM, Francis DM, et al. Human leucocyte antigen class II associations in chronic idiopathic urticaria. Br J Dermatol. 1999;140: 853–8.
25. Federman DG, Kirsner RS, Moriarty JP, Concato J. The effect of antibiotic therapy for patients infected with *Helicobacter pylori* who have chronic urticaria. J Am Acad Dermatol. 2003;49:861–4.
26. Daschner A, Alonzso-Gómez A, Caballero T, et al. Gastric anisakiasis: an underestimated cause of acute urticaria and angio-oedema? Br J Dermatol. 1998;139:822–8.
27. Lindelöf B, Sigurgeirsson B, Wahlgren CF, Eklund G. Chronic urticaria and cancer: an epidemiological study of 1155 patients. Br J Dermatol. 1990;123:453–6.
28. Magerl M, Borzova E, Giménez-Arnau A, et al. The definition and diagnostic testing of physical and cholinergic urticarias – EAACI/GA2LEN/EDF/UNEV consensus panel recommendations. Allergy. 2009;64:1715–21.
29. Poon E, Seed PT, Greaves MW, Kobza-Black A. The extent and nature of disability in different urticarial conditions. Br J Dermatol. 1999;140:667–71.
30. Breathnach SM, Allen R, Milford-Ward A, Greaves MW. Symptomatic dermographism: natural history, clinical features, laboratory investigations and response to therapy. Clin Exp Dermatol. 1983;9:463–7.
31. Kobza-Black A. Delayed pressure urticaria. J Invest Dermatol. 2001;6:148–9.
32. Barlow RJ, Warburton F, Watson K, et al. Diagnosis and incidence of delayed pressure urticaria in patients with chronic urticaria. J Am Acad Dermatol. 1993;29:954–8.
33. Wanderer AA. Cold urticaria syndromes: historical background, diagnostic classification, clinical and laboratory characteristics, pathogenesis and management. J Allergy Clin Immunol. 1990;85: 965–81.
34. Horan RF, Sheffer AL. Exercise-induced anaphylaxis. Immunol Allergy Clin North Am. 1992;12:559–69.
35. Volcheck GW, Li JTC. Exercise-induced urticaria and anaphylaxis. Mayo Clin Proc. 1997;72:140–7.
36. Davis MDP, Daoud MS, Kirby B, et al. Clinicopathologic correlation of hypocomplementemic and normocomplementemic urticarial vasculitis. J Am Acad Dermatol. 1998;38:899–905.
37. Kobza-Black A. Urticarial vasculitis. Clin Dermatol. 1999;17:565–9.
38. Konstantinou GN, Grattan CE. Food contact hypersensitivity syndrome: the mucosal contact urticaria paradigm. Clin Exp Dermatol. 2008;33:383–9.
39. Stevenson DD, Simon RA. Sensitivity to aspirin and nonsteroidal antiinflammatory drugs. In: Middleton E, Reed CE, Ellis EF, et al. (eds). Allergy. Principles and Practice, 4th edn. Chicago: Mosby, 1993:1747–65.
40. Sabroe RA, Kobza-Black A. Angiotensin-converting enzyme (ACE) inhibitors and angio-oedema. Br J Dermatol. 1997;136:153–8.
41. Shinkai K, McCalmont TH, Leslie KS. Cryopyrin-associated periodic syndromes and autoinflammation. Clin Exp Dermatol. 2008;33:1–9.
42. Hoffman HN, Mueller JL, Broide DH, et al. Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle-Wells syndrome. Nat Genet. 2001;29:241–2.
43. Schnitzler L, Schubert B, Boasson M, et al. Urticaire chronique, lésions osseuses, macroglobulinémie IgM: maladie de Waldenström? Bull Soc Franc Dermatol Syphilogr. 1974;81:363.
44. Butterfield JH, Leiferman KM, Abrams J, et al. Elevated serum levels of interleukin-5 in patients with the syndrome of episodic angioedema and eosinophilia. Blood. 1992;79:688–92.
45. Toppe E, Haas N, Henz BM. Neutrophilic urticaria: clinical features, histological changes and possible mechanisms. Br J Dermatol. 1998;138:248–53.
46. Russell Jones R, Bhogal B, Dash A, Schifferli J. Urticaria and vasculitis: a continuum of histological and immunopathological changes. Br J Dermatol. 1983;108:695–703.
47. Kozel MMA, Mekkes JR, Bossuyt PMM, Bos JD. The effectiveness of a history-based diagnostic approach in chronic urticaria and angioedema. Arch Dermatol. 1998;134:1575–80.
48. Sabroe RA, Grattan CEH, Francis DM, et al. The autologous serum skin test: a screening test for autoantibodies in chronic idiopathic urticaria. Br J Dermatol. 1999;140:446–52.
49. Konstantinou GN, Asero R, Maurer M, et al. EAACI/GA(2) LEN task force consensus report: the autologous serum skin test in urticaria. Allergy. 2009;64:1256–68.
50. Zuberbier T, Asero R, Bindslev-Jensen C, et al. EAACI/GA(2)LEN/EDF/WAO guideline: management of urticaria. Allergy. 2009;64:1427–43.
51. Pacor ML, Di Lorenzo G, Corrocher R. Efficacy of leukotriene receptor antagonist in chronic urticaria. A double-blind, placebo-controlled comparison of treatment with montelukast and cetirizine in patients with chronic urticaria with intolerance to food additive and/or acetylsalicylic acid. Clin Exp Allergy. 2001;31:1607–14.
52. Zuberbier T, Chantraine-Hess S, Hartmann K, Czarnetzki BM. Pseudoallergen-free diet in the treatment of chronic urticaria. A prospective study. Acta Dermatol Venereol (Stockh). 1995;75:484–7.
53. Grattan CEH, Francis DM, Slater NGP, et al. Plasmapheresis for severe, unremitting, chronic urticaria. Lancet. 1992;339:1078–80.
54. O'Donnell BF, Barr RM, Kobza Black A, et al. Intravenous immunoglobulin in autoimmune chronic urticaria. Br J Dermatol. 1998;138:101–6.
55. Grattan CEH, O'Donnell BF, Francis DM, et al. Randomised double-blind study of cyclosporin in chronic "idiopathic" urticaria. Br J Dermatol. 2000;143:365–72.
56. Perez A, Woods A, Grattan CE. Methotrexate: a useful steroid-sparing agent in recalcitrant chronic urticaria. Br J Dermatol 2010;162:191–4.
56a. Maurer M, Altricher S, Beiber T, et al. Efficacy and safety of omalizumab in patients with chronic urticaria who exhibited IgE against thyroperoxidase. J Allergy Clin Immunol. 2011;128:202–9.
57. Gompels MM, Lock RJ, Abinum M, et al. C1 inhibitor deficiency: consensus document. Clin Exp Immunol. 2005;139:379–94.
58. Champion RH, Roberts SOB, Carpenter RG, Roger JH. Urticaria and angio-oedema: a review of 554 patients. Br J Dermatol. 1969;81:588–97.

Figurate Erythemas 19

Agustín España

Chapter Contents

Erythema annulare centrifugum 307
Erythema marginatum 312
Erythema migrans 313
Erythema gyratum repens 316

INTRODUCTION

Erythemas represent a change in the color of the skin that is due to the dilation of blood vessels, especially those in the papillary and reticular dermis. The color, which is blanchable, can vary from pink to dark red to violaceous. Most erythemas last for days to months, but some may last only minutes (e.g. flushing). Although erythemas represent a broad and heterogenous group of cutaneous disorders, i.e. they can range from palmar erythema of pregnancy to a diffuse scarlatiniform eruption, the erythemas discussed in this chapter all share a common feature – a figurate configuration.

In figurate erythemas, the lesions have an annular, arciform or polycyclic appearance. While a wide range of cutaneous diseases can have an annular configuration (Table 19.1), there are four "classic" figurate erythemas: erythema annulare centrifugum, erythema marginatum (rheumaticum), erythema (chronicum) migrans, and erythema gyratum repens.

ERYTHEMA ANNULARE CENTRIFUGUM

Synonyms: ■ Superficial or deep gyrate erythema ■ Erythema perstans ■ Palpable migrating erythema

Key features

- Erythematous annular lesions that migrate centrifugally
- Superficial lesions have the classic "trailing" white scale, while the deep gyrate erythemas have a more infiltrated border
- The disorder occurs more commonly in adults, and superficial lesions favor the thighs and hips
- Individual lesions usually last for several days to a few months
- Although often idiopathic in nature, it can be associated with infections (e.g. tinea pedis) and anecdotally with other disorders or exposures

Introduction

The term "erythema annulare centrifugum" (EAC) has been applied to a broad spectrum of clinical findings. As a result, it has come to encompass more than just annular erythematous plaques with trailing scale. One explanation for this is that once the other three major figurate erythemas (with specific etiologies; see below) and the disorders listed in Table 19.1 are excluded, EAC often becomes a "default" diagnosis. Unfortunately, this has led to some confusion, but until a specific "trigger" can be identified for each individual patient, this situation will persist. As a consequence, some authors have come to the conclusion that EAC, especially the deeper form, represents a clinical reaction pattern rather than a specific clinicopathologic entity[1]. Adding to the confusion is the school of thought in which the term EAC is reserved for only the superficial form.

History

In 1881, Colcott-Fox described persistent, ring-shaped lesions with pruritus, to which he gave the name "erythema gyratum perstans". Twenty-five years later, Wende described "erythema figuratum perstans", which was characterized by recurrent lesions with scale-crust. The term "EAC" was actually introduced by Darier in 1916. Lastly, the name "erythema perstans" has been used by some authors to describe these various presentations[2]. It is now thought that all of these terms refer to clinical or pathologic variants of the entity now referred to as EAC[3]. However, Ackerman[4] preferred to call the two histologically different forms (superficial and deep) of EAC "superficial gyrate erythema" and "deep gyrate erythema", whereas Weyers et al.[5] believe that the superficial and deep forms of EAC are unrelated to one another and should not be referred to by the same name. These latter authors recommend that the term EAC be reserved for the superficial type, which in their opinion represents a specific clinicopathologic entity.

Epidemiology

Although EAC can appear in any age group, its peak incidence is during the fifth decade of life. There is no known gender difference. A rare dominantly inherited form of EAC has been described that has also been referred to as "familial annular erythema"[6]. The overall duration of the disorder can range from several days to decades[3], and an unusual form that recurs annually has been described.

Pathogenesis

It has been suggested that EAC, especially the superficial form with epidermal spongiosis histologically, represents a reaction pattern or "hypersensitivity" to one of many antigens. EAC has been associated with infectious agents, particularly dermatophytes, but also with other fungi (e.g. *Candida, Penicillium* in blue cheese[7]), viruses (e.g. poxvirus, EBV, varicella-zoster virus, HIV), parasites and ectoparasites (e.g. *Phthirus pubis*). Less commonly, EAC has been linked to drugs (e.g. diuretics, nonsteroidal anti-inflammatory drugs, antimalarials, gold, finasteride, amitriptyline, etizolam), pregnancy, particular foods, autoimmune endocrinopathies, hypereosinophilic syndrome and, occasionally, neoplasms (e.g. lymphomas, leukemias)[8]. However, these associations are anecdotal, and, in the last group, Curth's postulates have not been consistently fulfilled (see Ch. 53). There are patients with EAC who noted resolution of their lesions after the diseases that presumably triggered the EAC were successfully treated.

Another unresolved aspect of EAC is the mechanism by which the lesions migrate at their periphery. Localized areas of cutaneous inflammation are thought to reflect localized production of proinflammatory cytokines and vasoactive peptides. However, how and why this process spreads centrifugally remains an enigma[9]. The disappearance of EAC lesions after the administration of interferon suggests that TNF-α and IL-2 may have a role in its pathogenesis[10].

Clinical Features

The initial lesions of EAC begin as firm pink papules that expand centrifugally and then develop central clearing. An individual lesion can enlarge to greater than 6 cm in diameter over a period of 1 to 2 weeks. If expansion of the annular plaque is not uniform, incomplete arcs appear, as do polycyclic lesions, or simply festooned bands. In the superficial form, the lesions are minimally elevated, and there is desquamation at the inner margin, i.e. trailing scale (Fig. 19.1A).

DIFFERENTIAL DIAGNOSIS OF FIGURATE ERYTHEMA			
Disorders	**Clinical features**	**Histologic findings**	**Cross references**
TRANSIENT LESIONS (TYPICALLY LASTING <24 HOURS)			
Urticaria	Transient and recurrent wheals; pruritus	Superficial perivascular infiltrate of eosinophils and lymphocytes; occasionally neutrophils (then sometimes referred to as neutrophilic figurate erythema of infancy)	Ch. 18
Erythema marginatum	Polycyclic erythematous eruption; antecedent group A streptococcal infection; additional manifestations of acute rheumatic fever, e.g. arthritis and carditis	Scant perivascular infiltrate of neutrophils in the papillary dermis without vasculitis	See text
Erythema marginatum-like lesions of hereditary angioedema	Transient polycyclic erythematous eruption; favors trunk; precedes or accompanies episodes of angioedema	Minimal to no inflammatory infiltrate; dense perivascular and interstitial dermal deposits of bradykinin	Ch. 18
African trypanosomiasis	Annular erythematous patches on the trunk associated with fever spikes	Perivascular lymphocytic infiltrate; parasites are occasionally seen within the dermis	Ch. 83
Erythrokeratodermia variabilis	Transient gyrate or circinate erythematous patches (usually fade/migrate within a few hours); also fixed figurate hyperkeratotic plaques; *GJB4* mutations	Scant perivascular lymphocytic infiltrate; dilated capillaries	Ch. 57
URTICARIAL LESIONS LASTING >24 HOURS			
Allergic urticarial eruption	Annular edematous plaques; favors trunk	Superficial and deep lymphocytic infiltrate with eosinophils	
Annular erythema of infancy	Recurrent annular erythematous plaques, usually lasting a few days; typically affects infants 3–11 months of age (see Fig. 19.4)	Perivascular lymphocytes and eosinophils	
Wells' syndrome	Edematous erythematous plaques, often annular or arcuate with a greenish color centrally; pruritus; peripheral blood eosinophilia	Diffuse infiltrate of eosinophils; flame figures	Ch. 25
Urticarial vasculitis	Urticarial plaques, often annular, that may have a purpuric component; pain, burning and/or pruritus; systemic manifestations in hypocomplementemic form	Leukocytoclastic vasculitis	Ch. 24
Erythema migrans	Erythema slowly migrates from site of tick bite; influenza-like syndrome; secondary distant lesions	Superficial and deep perivascular lymphohistiocytic infiltrate; eosinophils and plasma cells in erythema migrans; mucin in LE tumidus and annular erythema of Sjögren's syndrome	See text and Ch. 74
Erythema annulare centrifugum (deep)	Annular erythema with raised borders		See text
Lymphocytic infiltrate of Jessner	Annular erythematous plaques; favors face and upper trunk		Ch. 121
LE tumidus	Annular erythematous plaques; favors face, upper trunk > extensor forearms		Ch. 41
Annular erythema of Sjögren's syndrome*	Annular erythematous plaques; favors face, arms, upper trunk; most common in Asian patients; anti-Ro antibodies		Ch. 45

*Considered by many authors to be a form of SCLE.

Table 19.1 Differential diagnosis of figurate erythema. Key clinical features and histologic findings are provided. Additional conditions that can present with figurate erythema include **Kawasaki disease (may be erythema marginatum-like), hereditary periodic fever syndromes (especially *T*NF *r*eceptor-*a*ssociated *p*eriodic *s*yndrome [TRAPS]; see Table 45.2), relapsing polychondritis, polymorphous light eruption, inflammatory vitiligo (including a papulosquamous variant), eosinophilic vasculitis, Sweet's syndrome, neutrophilic eccrine hidradenitis, pyoderma vegetans (expanding pustular lesions) and leukemia cutis**. AFB, acid-fast bacilli; BMZ, basement membrane zone; FTA-ABS, fluorescent treponemal absorption; GI, gastrointestinal; LE, lupus erythematosus; RPR, rapid plasma reagin; SCLE, subacute cutaneous LE.

Continued

DIFFERENTIAL DIAGNOSIS OF FIGURATE ERYTHEMA			
Disorders	**Clinical features**	**Histologic findings**	**Cross references**
GRANULOMATOUS LESIONS			
Granuloma annulare	Skin-colored to pink annular and arcuate plaques with borders composed of multiple papules; favors acral and extensor sites	Palisading granulomas with altered collagen and mucin	Ch. 93
Annular elastolytic giant cell granuloma	Pink annular plaques with atrophy and hypopigmentation centrally; favors sites of chronic sun exposure	Granulomatous infiltrate with elastophagocytosis by giant cells (border of lesion); absence of elastic fibers (center of lesion)	Ch. 93
Interstitial granulomatous dermatitis (IGD); interstitial granulomatous drug reaction (IGDR)	Annular erythematous plaques (or, in IGD, linear cords); favors axillae, groin, lateral trunk and legs; associated arthralgias/arthritis; IGDR is most often due to antihypertensive and lipid-lowering agents	Palisading granulomas surrounding tiny foci of degenerated collagen; neutrophils and eosinophils; little to no mucin	Ch. 45
Sarcoidosis	Red-brown annular plaques and papules; favors face; systemic manifestations	Sarcoidal granulomas ("naked tubercles")	Ch. 93
Borderline or tuberculoid leprosy	Annular plaques with raised erythematous borders and (in tuberculoid lesions) central hypopigmentation; asymmetric distribution; hypoesthesia, alopecia	Linear or oval perineural granulomas in the dermis; foamy macrophages and AFB in borderline lesions	Ch. 75
PAPULOSQUAMOUS LESIONS			
Erythema annulare centrifugum (superficial)	Annular lesions with trailing scale; favors thighs, hips and trunk	Superficial perivascular lymphocytes with focal parakeratosis and spongiosis; focal hemorrhage in pityriasis rosea	See text
Erythema gyratum repens	Concentric erythematous rings with wood-grain appearance; erythema moves ~1 cm per day; associated with cancer		See text and Ch. 53
Pityriasis rosea	Herald patch on trunk; oval annular papules and plaques with central fine scaling plus a collarette of trailing scale; Christmas-tree distribution on posterior trunk		Ch. 9
Pityriasis rubra pilaris	Appears as the primary "classic" lesions resolve; resembles erythema gyratum repens	Alternating vertical and horizontal ortho-and parakeratosis; follicular plugging with shoulders of parakeratosis	See text and Ch. 9
Tinea corporis	Annular plaques with scale (exception: tinea incognito); pustules in border; concentric lesions in tinea imbricata; KOH-positive	Dermatophytes in the stratum corneum	Ch. 77
Lichen planus (LP)	Violaceous annular plaques; gray-brown to brown hyperpigmentation centrally; mucosal involvement; photodistribution in actinic LP	Hypergranulosis, band-like lymphocytic infiltrate at dermal–epidermal junction, necrotic keratinocytes	Ch. 11
Annular LE (subacute > discoid), neonatal LE, mothers of boys with chronic granulomatous disease	Photosensitivity; favors face (discoid), extensor upper extremities/upper trunk (SCLE), periorbital area (neonatal LE); anti-Ro antibodies (SCLE, neonatal LE)	Vacuolar interface dermatitis; often periadnexal lymphohistiocytic inflammation	Ch. 41
Seborrheic dermatitis	Erythematous annular plaques with scaling; favors face and central chest	Psoriasiform epidermal hyperplasia, spongiosis, perivascular lymphocytes	Ch. 13
Psoriasis	Annular scaly plaques with slow expansion	Parakeratosis, diminished granular layer, elongated rete ridges, neutrophils migrating into epidermis	Ch. 8
Ichthyosis linearis circumflexa of Netherton syndrome	Serpiginous or circinate erythematous plaques bordered by double-edged scale; trichorrhexis invaginata; atopic diathesis, elevated serum IgE	Psoriasiform features	Ch. 57

Table 19.1 Differential diagnosis of figurate erythema (cont'd). Key clinical features and histologic findings are provided. Additional conditions that can present with figurate erythema include **Kawasaki disease (may be erythema marginatum-like), hereditary periodic fever syndromes (especially *T*NF *r*eceptor-*a*ssociated *p*eriodic *s*yndrome [TRAPS]; see Table 45.2), relapsing polychondritis, polymorphous light eruption, inflammatory vitiligo (including a papulosquamous variant), eosinophilic vasculitis, Sweet's syndrome, neutrophilic eccrine hidradenitis, pyoderma vegetans (expanding pustular lesions) and leukemia cutis.** AFB, acid-fast bacilli; BMZ, basement membrane zone; FTA-ABS, fluorescent treponemal absorption; GI, gastrointestinal; LE, lupus erythematosus; RPR, rapid plasma reagin; SCLE, subacute cutaneous LE.

Continued

DIFFERENTIAL DIAGNOSIS OF FIGURATE ERYTHEMA			
Disorders	**Clinical features**	**Histologic findings**	**Cross references**
LESIONS WITH ABSENCE OR VARIABLE PRESENCE OF SCALE			
Annular lichenoid dermatitis of youth	Red-brown annular patches or thin plaques with central hypopigmentation; favors groin and flanks; affects children and young adults	Lichenoid infiltrate; marked keratinocyte necrosis limited to the tips of rete ridges	
Secondary syphilis	Annular plaques with central hyperpigmentation; favors face; flu-like symptoms; additional cutaneous manifestations; positive for RPR and FTA-ABS	Perivascular and interstitial infiltrate with plasma cells; also lichenoid or granulomatous infiltrate, exocytosis	Ch. 82
Mycosis fungoides	Annular erythematous or hypopigmented plaques, some with scale; admixed with classic lesions; often with pruritus	Infiltrate of atypical lymphocytes in the dermis and clustering in the epidermis; also plasma cells and eosinophils	Ch. 120
PUSTULAR LESIONS			
Pustular psoriasis (annular pattern)	Rapid expansion with erythematous borders studded with pustules	Subcorneal and spongiform pustules; neutrophils in the epidermis	Ch. 8
Sneddon–Wilkinson disease, IgA pemphigus	Pustules in a circinate pattern; peripheral expansion with central clearing; axillae, groin, inframammary areas	Subcorneal pustules; neutrophils in the epidermis; intercellular epidermal IgA deposition in IgA pemphigus	Chs 8 & 29
Eosinophilic pustular folliculitis (Ofuji's disease)	Grouped follicular pustules and papulopustules in an annular or serpiginous configuration; favors the face, trunk and arms	Infundibular eosinophilic pustules	Ch. 38
EROSIVE/VESICULOBULLOUS LESIONS			
Erythema multiforme (EM), Stevens–Johnson syndrome	Association with HSV vs. drugs and *Mycoplasma*, respectively; target lesions more common in EM; mucosal involvement	Necrotic keratinocytes, vacuolar degeneration of the basal layer and variable inflammation	Ch. 20
Necrolytic migratory erythema	Erosion and crusting of advancing edge; periorificial involvement; glossitis; association with glucagonoma or liver/GI disorders (pseudoglucagonoma); constitutional symptoms	Pallor and edema of the upper epidermis; variable erosion	Ch. 53
Bullous pemphigoid, pemphigoid gestationis	Annular urticarial plaques; tense bullae; pruritus	Subepidermal bullae with eosinophils > neutrophils; linear deposits of IgG and/or C3 in BMZ	Ch. 30
Linear IgA bullous dermatosis	Annular urticarial plaques; vesicles and bullae within border ("string of pearls"); pruritus	Subepidermal bullae with neutrophils > eosinophils; linear deposits of IgA in BMZ	Ch. 31
Epidermolysis bullosa simplex (especially Dowling–Meara subtype)	"Herpetiform" blisters in figurate array; episodic flares of migratory circinate erythema and blistering (K5 mutations)	Split through basal layer of epidermis	Ch. 32
Annular epidermolytic ichthyosis	Migratory, annular or polycyclic, erythematous plaques with superficial blistering/peeling and scaling at the border; episodic flares; K1 or K10 mutations	Epidermolytic hyperkeratosis	Ch. 57
PURPURIC LESIONS[†]			
Purpura annularis telangiectoides	"Cayenne pepper" petechiae and telangiectasias in annular configuration; favors legs	Capillary dilation and tight perivascular infiltrate of lymphocytes; extravasated erythrocytes	Ch. 22
Acute hemorrhagic edema of infancy	Annular or targetoid, edematous, erythematous plaques that become purpuric; favors face, ears and extremities; febrile but non-toxic-appearing child <2 years of age	Leukocytoclastic vasculitis; perivascular IgA deposition in fewer than one-third of cases	Ch. 24
PERFORATING LESIONS			
Elastosis perforans serpiginosa	Peripheral edge composed of keratotic papules; favors neck and other flexural areas	Excess of elastic fibers in clumps in the superficial dermis with transepidermal elimination	Ch. 96

[†]Purpura can also occur in urticarial vasculitis.

Table 19.1 Differential diagnosis of figurate erythema (cont'd). Key clinical features and histologic findings are provided. Additional conditions that can present with figurate erythema include **Kawasaki disease (may be erythema marginatum-like), hereditary periodic fever syndromes (especially *T*NF *r*eceptor-*a*ssociated *p*eriodic *s*yndrome [TRAPS]; see Table 45.2), relapsing polychondritis, polymorphous light eruption, inflammatory vitiligo (including a papulosquamous variant), eosinophilic vasculitis, Sweet's syndrome, neutrophilic eccrine hidradenitis, pyoderma vegetans (expanding pustular lesions) and leukemia cutis** AFB, acid-fast bacilli; BMZ, basement membrane zone; FTA-ABS, fluorescent treponemal absorption; GI, gastrointestinal; LE, lupus erythematosus; RPR, rapid plasma reagin; SCLE, subacute cutaneous LE.

Fig. 19.1 Erythema annulare centrifugum. A Superficial form, with polycyclic plaque and delicate scale on the inner margin of the advancing edge (trailing scale). The scale is detached centrally. **B** Deep form, with obvious elevation of advancing edges and without trailing scale.

Fig. 19.2 A comparison of erythema annulare centrifugum and urticaria. The lesions in **A** have no scaling and may be confused with annular urticaria (**B**). However, individual lesions of urticaria are evanescent.

The scale may not be present in all the lesions in a particular patient (Fig. 19.2A). There may be associated pruritus, especially in lesions that histologically show spongiosis. Occasionally, vesicles develop within the peripheral margin, raising the clinical possibility of linear IgA bullous dermatosis. In deep gyrate erythema, the advancing edges are obviously elevated (Fig. 19.1B) and there is usually no associated scale. The majority of these lesions are non-pruritic.

As lesions resolve, there is no residual scarring, but postinflammatory hyperpigmentation can be seen and, on occasion, purpura. Although the lesions of EAC may be localized or generalized, they rarely, if ever, involve the palms, soles, scalp or mucous membranes. Individual lesions can persist for weeks to months, but there are usually no associated systemic manifestations. While new lesions can appear just as older ones resolve, there may be prolonged intervals of time between flares. When EAC is due to an underlying disorder, flares of the former may correlate with recurrences of the latter. Most patients with EAC do not have an underlying disorder that can be identified, nor can the onset, fluctuations or duration be related to a specific antigen.

Pathology

In superficial lesions of EAC, the findings are nonspecific, with mild spongiosis and microvesiculation with associated focal parakeratosis, as well as a mild superficial perivascular lymphohistiocytic infiltrate. These histologic features correspond to the scale on the inner margin of the advancing edge of the lesion. Characteristically, the inflammatory cells form a fairly tight aggregate around vessels, the so-called "coat sleeve" anomaly. Rarely, eosinophils are found in the perivascular infiltrate. The advancing edge, which is slightly raised, is the result of edema in the papillary dermis. The central area of clearing may contain dermal melanophages.

In deep lesions of EAC, the epidermis is usually unremarkable, and a mononuclear cell infiltrate with a sharply demarcated perivascular arrangement is present primarily within the mid and lower dermis. For this reason, the lesions are generally elevated and are more indurated than in the superficial form of EAC, and do not have trailing scale.

Differential Diagnosis

EAC must be differentiated from other annular erythematous lesions (see Table 19.1), particularly tinea corporis and annular psoriasis, when there is associated scale. Additional entities to consider include annular urticaria (Fig. 19.2B), allergic urticarial eruption, cutaneous lymphoid hyperplasia (pseudolymphoma), and lymphoma cutis. Patients with autoimmune disorders, including linear IgA bullous dermatosis, Sjögren's syndrome and lupus erythematosus (LE tumidus, subacute cutaneous LE), can also have erythematous annular, arciform and polycyclic lesions.

Treatment

If EAC is due to an underlying disorder, the skin lesions will usually resolve once the latter has been successfully treated. Topical corticosteroids applied to the advancing border of the lesions may be of benefit. Topical antipruritics and sedating antihistamines can be prescribed if there is associated pruritus. Even in the absence of an identifiable cause, some authors have advocated the empiric use of antibiotics or antifungal agents. Although systemic corticosteroids can induce a clinical remission, recurrences are common when the medication is discontinued. Based solely on case reports, the following have been reported as beneficial: topical tacrolimus, topical calcipotriene (calcipotriol), oral metronidazole, subcutaneous etanercept and subcutaneous interferon-α (2×10^6 IU three times per week)[10]. However, systemic approaches to therapy are seldom necessary.

ERYTHEMA MARGINATUM

Synonyms: ■ Erythema marginatum rheumaticum ■ Erythema annulare rheumaticum

Key features

- Migratory annular and polycyclic erythematous eruption
- Cutaneous manifestation of acute rheumatic fever
- Associated findings include carditis, migratory polyarthritis, Sydenham's chorea and subcutaneous nodules
- Seen more commonly in children than in adults

Introduction

Rheumatic fever is characterized by an abnormal immunologic response to a preceding infection with group A β-hemolytic streptococci and by the triad of fever, arthritis and carditis. Cutaneous manifestations include erythema marginatum and subcutaneous nodules, but they are seen in a minority of patients. Jones originally established the criteria for the diagnosis of rheumatic fever, and, in 1992, they were revised by the American Heart Association: major criteria are carditis, migratory polyarthritis, Sydenham's chorea, erythema marginatum and subcutaneous nodules. Minor criteria include fever, arthralgias and abnormal laboratory findings (elevated ESR, elevated C-reactive protein, or prolonged PR interval on an ECG). To establish the diagnosis of acute rheumatic fever, two major or one major and two minor criteria must be accompanied by evidence of an antecedent group A streptococcal infection, e.g. a positive culture or raised or rising antistreptolysin O or anti-DNase B titer[11]. More recently, a group of international experts on rheumatic fever reaffirmed the validity of the major and minor Jones criteria and recommended no further revisions[12].

History

In 1831, Bright noted the presence of annular erythematous lesions in patients with rheumatic fever. In 1889, Cheadle gave these lesions the name "erythema marginatum rheumaticum"[13]. Carol and van Krieken first described the histopathologic findings in 1935. Two years later, Perry reported that rapid migration of these lesions is a characteristic finding[14]. In 1944, Jones established the criteria for diagnosing rheumatic fever[15].

Epidemiology

Attacks of acute rheumatic fever are associated with antecedent group A β-hemolytic streptococcal infections of the pharynx. Approximately 3% of patients with untreated infections can develop acute rheumatic fever. It is estimated that in high-income countries, the incidence is 5 per 100 000, whereas in low-income countries, it ranges from 100 to 1000 per 100 000. Erythema marginatum is seen in less than 10% of patients with acute rheumatic fever. The higher incidence of erythema marginatum in children (as compared to adults[16]) reflects the predominance of rheumatic fever in children; the peak age-related incidence is between 5 and 15 years.

Pathogenesis

The mechanisms that underlie the appearance of cutaneous lesions of erythema marginatum are unknown. Presumably, there is an abnormal humoral and cellular immune response to one or more antigens associated with group A β-hemolytic streptococci (e.g. M protein). Antigenic mimicry may play a role in that epitopes cross-reacting with group A streptococcal antigens have been identified in human myosin, actin, tropomyosin, keratin, laminin, N-acetylglucosamine and vimentin[17]. Specific characteristics of certain strains of group A β-hemolytic streptococci, such as higher M protein content and mucoid colony formation, may facilitate the development of acute rheumatic fever[18]. Of note, there have been scattered reports of erythema marginatum-like lesions in association with cat scratch disease and psittacosis[19,20]. The latter may reflect an overlap between erythema marginatum and EAC.

Clinical Features

Following the initial streptococcal pharyngitis, there is usually a latency period of 2–5 weeks before the development of the acute attack of rheumatic fever. The lesions of erythema marginatum begin as erythematous macules that spread peripherally and become patches or plaques, but in the absence of associated scale. Erythema marginatum can also have a polycyclic arrangement (Fig. 19.3). The lesions are usually asymptomatic, and, over a period of 12 hours, they can migrate by 2–12 mm; in areas of previous involvement, the skin may appear pale or lightly pigmented.

The most common locations for erythema marginatum are the trunk, axillae and proximal extremities, with sparing of the face. New lesions usually last from a few hours to a few days and are often most noticeable during the afternoon. Recurrent crops can occur over a number of weeks. Erythema marginatum is associated primarily with the active phase of rheumatic fever, and, in general, it is seen in conjunction with the carditis. Of note, children less than 5 years of age appear to have a higher incidence of erythema marginatum as well as carditis and arthritis[21].

Subcutaneous nodules are another cutaneous manifestation of rheumatic fever. These lesions appear primarily over bony prominences, especially the wrists, elbows, knees and ankles, in patients with long-standing disease. The nodules are usually painless and they are rare during the initial attack of rheumatic fever. Similar nodules can be seen in patients with polyarticular juvenile idiopathic arthritis (see Ch. 45). In addition to the major and minor criteria (see Introduction), patients may also have malaise, chest or abdominal pain, epistaxis, tachycardia and anemia, as well as a nonspecific urticarial eruption[18].

Pathology

An interstitial and perivascular infiltrate composed predominantly of neutrophils without vasculitis is observed. There can be extravasation of erythrocytes in the later stages. Direct immunofluorescence microscopy for immunoglobulins and complement is negative. Although

Fig. 19.3 Erythema marginatum (rheumaticum). Polycyclic and evanescent annular lesions are seen on the trunk of this young patient.

Fig. 19.4 Annular erythema of infancy. Expanding annular urticarial plaques in a 6-month-old boy. *Courtesy, Julie V Schaffer MD.*

these histologic findings are not unique to erythema marginatum, they are helpful in excluding other entities in the differential diagnosis, such as annular erythema of infancy.

Differential Diagnosis

The differential diagnosis includes primarily annular urticaria, annular erythema of infancy (Fig. 19.4) and neutrophilic figurate erythema of infancy[22]. Less often, Still's disease, hereditary periodic fever syndromes (particularly *T*NF *r*eceptor-*a*ssociated *p*eriodic *s*yndrome [TRAPS]; see Table 45.2), EAC, Kawasaki disease and the other entities listed in Table 19.1 need to be considered. There is also an annular erythema with an appearance similar to erythema marginatum that precedes or accompanies episodes of hereditary angioedema[23].

Treatment

There is no specific therapy for this dermatosis. In general, its clinical course is unaltered by treatment of the underlying acute rheumatic fever; however, symptoms are usually mild and lesions resolve spontaneously.

ERYTHEMA MIGRANS

Synonyms: ■ Erythema chronicum migrans ■ Lyme borreliosis ■ Lyme disease ■ Afzelius' disease

Key features

- Annular erythema develops at the site of the bite of a *Borrelia*-infected tick
- Several species of *Ixodes* ticks are infected with different genospecies of *Borrelia burgdorferi*
- Erythema migrans represents the initial cutaneous manifestation of Lyme disease and is seen in 60–90% of patients diagnosed with the disease
- Multiple secondary lesions that are smaller in size can occur as a result of spirochetemia or lymphatic spread

Introduction

Lyme disease is an infection due to *Borrelia burgdorferi* spirochetes that are transmitted by bites from several species of *Ixodes* ticks (e.g. *I. scapularis, I. pacificus, I. ricinus*; see Ch. 85). Erythema migrans represents the initial cutaneous manifestation.

History

The first report of an annular erythema developing after a tick bite was by Afzelius in 1909 and he coined the term "erythema migrans". Lipschütz then referred to these cutaneous lesions as "erythema chronicum migrans". In the US, Steere described an epidemic form of childhood arthritis preceded by erythema migrans in several communities in the vicinity of Lyme, Connecticut. In the 1980s, Burgdorfer isolated a new spirochete in lesions of erythema migrans and the organism was subsequently named *B. burgdorferi*[24].

Epidemiology

Although Lyme disease has a worldwide distribution, it is seen most commonly in the US (northeast, midwest and west coast) and in Europe (Scandinavia and central Europe). The natural hosts for *Borrelia* are white-footed mice and white-tailed deer. In the Netherlands, the risk of developing both tick bites and erythema migrans was shown to be related to the proportion of the land covered by woods, sandy soil or dry uncultivated land, as well as the density of the sheep and cattle populations[25]. More than 28 000 cases of Lyme disease were reported in the US during 2008, and the actual number may be as high as 60 000 to 100 000. In Europe, the highest reported incidences are from middle Europe, in particular Germany, Austria, Slovenia and Sweden[26]. For example, in Poland, there was a notable increase from a few cases in 1969–1976 to 11.5 per 100 000 in 2005. However, not all patients who have had tick bites or positive serologic tests for *B. burgdorferi* develop Lyme disease. For example, in Switzerland, where the prevalence of a positive serology for this spirochete is 28%, only 4% developed Lyme disease, and in France, the figures were 15% and a very few cases, respectively.

Pathogenesis

In mice, *B. burgdorferi* has been shown to usurp a tick salivary protein, Salp15, as a means of enhancing transmission[27]. By binding to the outer surface protein C (OspC) of *B. burgdorferi*, Salp15 provides protection against antibody-mediated killing. In addition, Salp15 inhibits adaptive immune responses against both *Borrelia* and tick antigens[28]. Of note, one of the strategies for preventing Lyme disease in the future is the development of anti-tick vaccines that utilize tick salivary proteins.

Once the *Borrelia* organisms have entered the body, some of the spirochetal lipoproteins may trigger the innate immune system, with cytokines being produced by macrophages[29]. In addition, a Th1 response is triggered as part of the adaptive immune system. Both adaptive T-cell and B-cell responses facilitate the synthesis of antibodies against different antigens of *B. burgdorferi*. Spirochetemia is present in approximately 45% of patients at the time of their presentation with erythema migrans[30], and these organisms can disseminate widely due to their ability to resist elimination by macrophages, adhere to brain and epithelial cells, penetrate into the cytoplasm via intracellular junctions, and induce TNF-α production[31].

Even though the lesion expands centrifugally, *B. burgdorferi* organisms have been found both in the center and at the periphery of lesions of erythema migrans. The persistence of the spirochete in the skin for a long time after the tick bite may be due to an absence of the production of interferon-γ and an ineffective immune response[29]. Also, different immune responses to the various genospecies of the *B. burgdorferi* sensu lato complex (*B. burgdorferi* sensu stricto, *B. afzelii, B. garinii*) may lead to different clinical presentations[32] (e.g. borrelial lymphocytoma in Europe but not the US; see Ch. 74).

Clinical Features

Lyme borreliosis is divided into three clinical stages: (1) early localized disease; (2) early disseminated disease; and (3) chronic disease (Table 19.2). Erythema migrans is an important clinical feature of early disease. Typically, 7–15 days (range, 2–28 days) after tick detachment, an erythematous, expanding annular plaque appears that may have a

STAGES AND MAJOR ORGAN MANIFESTATIONS OF LYME BORRELIOSIS			
Organ	**Early localized disease**	**Early disseminated disease**	**Chronic disease**
Skin	Erythema migrans		Acrodermatitis chronica atrophicans (Europe)
	Disseminated erythema migrans Borrelial lymphocytoma (Europe)		
Nervous system		Meningo-polyradiculoneuritis Cranial neuritis Bell's palsy	Encephalopathy Encephalomyelitis Neuropathy
Musculoskeletal system		Arthralgias, arthritis Myositis	Chronic arthritis
Heart		Atrioventricular block Myopericarditis, pancarditis Tachycardia	
Lymphatic	Regional lymphadenopathy	Regional or generalized lymphadenopathy	
Other		Conjunctivitis, iritis Hepatitis Non-productive cough Microscopic hematuria or proteinuria	

Table 19.2 Stages and major organ manifestations of Lyme borreliosis. *Adapted from Müllegger RR. Dermatological manifestations of Lyme borreliosis. Eur J Dermatol. 2004;14:296–309.*

Fig. 19.5 Erythema migrans. Annular erythema that spreads centrifugally. The peripheral erythematous border may or may not be sharply demarcated and is usually 1–2 cm in width.

Fig. 19.6 Disseminated erythema migrans. Multiple circular and a few annular plaques are scattered on the lower extremities as well as the trunk (not shown). *Courtesy, Thomas Schwarz, MD.*

lighter-colored central area or a bull's-eye appearance (Fig. 19.5). The eventual diameter is usually at least 5 cm. Lesions of primary erythema migrans favor the trunk, axilla, groin and popliteal fossa. Occasionally, the advancing edge may be crusted or even vesicular. Untreated, the lesions usually last less than 6 weeks (median, 4 weeks). In 20–25% of patients, multiple lesions can appear due to multiple tick bites or as a result of disseminated disease secondary to spirochetemia or lymphatic spread[29]. Disseminated lesions tend to be smaller in size and less pronounced and usually appear days to weeks after the appearance of the primary erythema migrans (Fig. 19.6)[33].

Erythema migrans is seen in 60–90% of patients diagnosed with Lyme disease. In the US, the systemic manifestations of this initial phase tend to be more acute, with influenza-like symptoms, including fatigue, headache, arthralgias, myalgias and fever, as well as lymphadenopathy, conjunctivitis or hepatitis (see Table 19.2)[34,35]. In Europe, this initial clinical phase is usually less severe, and the lesions of erythema migrans tend to last longer. Of the patients with erythema migrans who are not treated, approximately 60% will go on to have monoarticular or oligoarticular arthritis (usually the knee) within weeks to months after the initial infection; approximately 10%, a neurologic manifestation (most commonly facial nerve palsy); and approximately 5%, a cardiac complication (usually varying degrees of atrioventricular block)[30]. For a discussion of borrelial lymphocytoma and acrodermatitis chronica atrophicans, see Chapter 74. Of note, *Ixodes* ticks may transmit more than one disease, in particular babesiosis (a malaria-like illness) and human anaplasmosis (see Ch. 85) as well as Lyme disease.

Pathology

The histologic features of erythema migrans are similar to those of a deep gyrate erythema (Fig. 19.7). While routine histology is often not specific, many specimens will contain eosinophils and plasma cells in the infiltrate. Immunohistochemical studies have shown a reduction in the number of Langerhans cells; in the dermis, the inflammatory infiltrate contains macrophages, $CD4^+$ helper T cells and $CD45RO^+$ memory T cells[36]. In addition, multiple apoptotic cells may be observed in the epidermis[37]. A silver stain such as the Warthin–Starry stain that has been used to detect *Treponema pallidum* can also demonstrate *Borrelia* spirochetes in the skin.

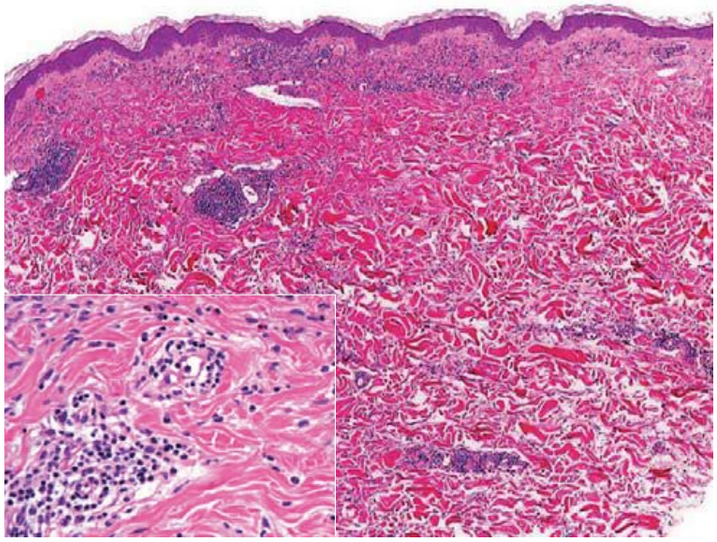


Fig. 19.7 Erythema migrans. A superficial and deep perivascular infiltrate is present within the dermis as well as a scattered interstitial pattern. The infiltrate is composed of lymphocytes and plasma cells (insert). *Courtesy, Lorenzo Cerroni, MD.*

2008 CDC LYME DISEASE SURVEILLANCE CASE DEFINITION
Definition of erythema migrans (EM)
A skin lesion that typically begins as a red macule or papule and expands over a period of days to weeks to form a large round lesion, often with partial central clearing. A single primary lesion must reach ≥5 cm in diameter. Secondary lesions also may occur. Annular erythematous lesions occurring within several hours of a tick bite represent hypersensitivity reactions and do not qualify as EM.
Confirmed
• A case of EM (as defined above) with a known exposure* • A case of EM with laboratory evidence of infection and without a known exposure • A case with at least one late manifestation† that has laboratory evidence of infection
Probable
• Any other case of physician-diagnosed Lyme disease that has laboratory evidence of infection
Suspected
• A case of EM where there is no known exposure and no laboratory evidence of infection
*Exposure is defined as having been (≤30 days before onset of EM) in wooded, brushy or grassy areas (i.e. potential tick habitats) in a county in which Lyme disease is endemic (in which at least two confirmed cases have been acquired or in which established populations of a known tick vector are infected with *B. burgdoferi*). ***A history of tick bite is not required.*** †Recurrent, brief attacks of joint swelling; lymphocytic meningitis, cranial neuritis (particularly facial palsy [may be bilateral]), radiculoneuropathy or, rarely, encephalomyelitis (requires CSF antibody production); acute onset of high-grade (2nd-degree or 3rd-degree) atrioventricular conduction defects that resolve in days to weeks and are sometimes associated with myocarditis.

Table 19.3 2008 CDC Lyme disease surveillance case definition. From www.cdc.gov/ncphi/disss/nndss/casedef/lyme_disease_2008.htm. CDC, Centers for Disease Control and Prevention.

TREATMENT OPTIONS FOR BORRELIOSIS			
	Antibiotic		
Clinical features	**First choice for adults and children ≥8 years*,†**	**First choice for children <8 years and pregnant women; second choice otherwise***	**Alternative choice***
Early localized disease	Doxycycline 100 mg (2 mg/kg) po q12h, 14–21 days‡	Amoxicillin 500 mg po q8h (50 mg/kg po per day divided q8h), 14–21 days§	Cefuroxime axetil 500 mg (15 mg/kg) po q12h, 14–21 days
Early disseminated disease or chronic disease, **mild** Cranial nerve palsy, 1st or 2nd degree heart block	Doxycycline 100 mg (2 mg/kg) po q12h, 14–28 days‡	Amoxicillin 500 mg po q8h (50 mg/kg po per day divided q8h), 14–28 days	Cefuroxime axetil 500 mg (15 mg/kg) po q12h, 14–28 days
	First choice	**Second choice**	**Third choice**
Early disseminated disease or chronic disease, **severe** Meningitis, radiculopathy, 3rd degree heart block	Ceftriaxone 2 g (75–100 mg/kg) iv once daily, 14–28 days	Cefotaxime 2 g (50–70 mg/kg) iv q8h, 14–28 days	Penicillin G 18–24 million units (200 000–400 000 units/kg) iv per day divided q4h, 14–28 days
*No comparative trials for early localized disease, so no established superior treatment; doxycycline also treats human anaplasmosis. †Avoid doxycycline in children <8 years and pregnant women. ‡In a randomized, double-blind, controlled trial, similar outcomes were observed for a 10-day versus 20-day course of doxycycline[42]. §Recommended for 21 days for pregnant women.			

Table 19.4 Treatment options for borreliosis[31]. Doses for children are in parentheses, with adult dose as maximum. A Jarisch-Herxheimer-like reaction with an increase in systemic symptoms and in the size or intensity of the inflammation of the erythema migrans lesion occurs in ~15% of patients within 24 hours after the initiation of antimicrobial therapy[30].

Differential Diagnosis

The recently revised CDC case definition for Lyme disease now includes three categories: "confirmed", "probable" and "suspected" (Table 19.3)[38]. Of relevance to dermatologists, a confirmed diagnosis of Lyme disease requires the presence of characteristic lesions of erythema migrans *plus* either a known exposure or laboratory evidence of infection. The latter includes the isolation of *Borrelia* from tissues (including lesions of erythema migrans) or fluids, or more commonly, the detection of anti-*Borrelia* antibodies by the two-test approach of an ELISA followed by a Western blot[34]. Of note, the peak specific IgM response (usually directed against the 41 kDa flagellar antigen) occurs 3–6 weeks into the infection[31]. As a result, a patient who presents with an early lesion of erythema migrans may not have elevated anti-*Borrelia* antibodies, and the false-negative rate may be as high as 60%[30].

Because antibodies often persist for months or years following infection, serologic tests can not accurately distinguish between active and past infections. In general, if the Western blot analysis yields negative results (even if there are positive findings by ELISA or indirect fluorescent antibody testing), the diagnosis of Lyme disease cannot be supported. This is especially true if the Western blot is performed more than 2 to 4 weeks after exposure. Lastly, positive serologic tests and a history of Lyme disease do not ensure protective immunity[39].

B. burgdorferi DNA can be detected via PCR in skin biopsy specimens and urine of patients with erythema migrans[31], but this is usually reserved for clinical trials[40]. Culture of tissue from the perimeter of erythema migrans lesions is essentially 100% specific and can distinguish live from dead organisms, but this diagnostic test is also not routinely performed. Both a special bacteriologic agar (modified Barbour–Stoenner–Kelly medium) and prolonged observation of cultures are required[41], making it impractical in the routine clinical setting.

Erythema migrans must be distinguished from exaggerated local arthropod reactions, erysipelas, cellulitis, allergic contact dermatitis and non-pigmented fixed drug eruption, and, less often, other entities outlined in Table 19.1. In addition, the southern tick-associated rash illness (STARI or Masters disease) that follows the bite of the *Amblyomma americanum* tick may have a similar-appearing lesion[30].

Treatment

Recommended antibiotic regimens are outlined in Table 19.4. It is estimated that in areas epidemic for this disease, only 1% of the

individuals who are bitten by ticks develop Lyme disease. This may be due to the observation that the tick must be attached for at least 24 hours for transmission to occur[43]. Therefore, routine treatment of tick bites with 2–3-week courses of antibiotics is not recommended. In patients from endemic areas (>20% of ticks infected) in whom the tick, identified as a nymphal or adult *I. scapularis*, has been attached for >36 hours and prophylaxis can be started within 72 hours of tick removal, a single 200 mg dose of doxycycline may decrease the risk of developing Lyme borreliosis (from 3.2% in the placebo group to 0.4% in the treatment group in one study)[44].

ERYTHEMA GYRATUM REPENS

Synonym: ■ Gammel's disease

Key features

- A figurate erythema that is migratory and composed of concentric rings with a wood-grain appearance
- It represents a paraneoplastic phenomenon and the most common underlying neoplasm is carcinoma of the lung
- The lesions may have associated pruritus and scale, and they characteristically exhibit rapid migration (up to 1 cm per day)
- The cutaneous lesions resolve when the neoplasm is successfully treated

Introduction

In the vast majority of patients, erythema gyratum repens represents a paraneoplastic figurate erythema. In theory, the cutaneous lesions arise as a result of an immune reaction against tumor-associated antigens with the subsequent recognition of similar antigens in the skin. There are, however, a number of other entities that can have an erythema gyratum repens-like appearance.

History

Erythema gyratum repens was first reported by Gammel in 1952, and his original description clearly identified its key clinical features.

Epidemiology

Erythema gyratum repens is a very rare disorder seen primarily in adults. Risk factors parallel those for the underlying neoplasms.

Pathogenesis

A leading hypothesis is that erythema gyratum repens represents an immune reaction in which there is a cross-reaction between tumor and cutaneous antigens[45]. In a few patients, direct immunofluorescence (DIF) has demonstrated deposits of IgG and C3 in the basement membrane zone (BMZ) of the skin, and, in isolated cases, similar deposits were seen in the associated neoplasm[46]. However, this could simply represent a nonspecific finding. Caux et al.[46] suggested that the tumor produces a modification in its basement membrane and this subsequently induces an immune response. Recognition of similar antigens in the BMZ of the skin then leads to the cutaneous eruption. The responsible antigen(s) is not known, but a curious finding is an accumulation of active Langerhans cells in the upper layers of the epidermis[47].

Clinical Features

Patients usually have multiple, annular, erythematous lesions that develop scale at their edges and advance at a rapid rate (up to 1 cm per day). This rate of peripheral spread is significantly faster than that of EAC. Lesions have a wood-grain or zebra-like pattern, due to the development of "rings within rings" (Fig. 19.8). In some patients, the eruption is also pruritic. Additional findings in patients with erythema gyratum repens include acquired ichthyosis, palmoplantar keratoderma and hypereosinophilia.

Fig. 19.8 Erythema gyratum repens. Multiple gyrate erythematous plaques, showing a wood-grain pattern. *Courtesy, Agustin Alomar, MD.*

Fig. 19.9 Resolving pityriasis rubra pilaris. The lesions can resemble erythema gyratum repens. *Courtesy, Irwin Braverman, MD.*

In at least 80% of patients, erythema gyratum repens is associated with an underlying neoplasm, most commonly of the lung, breast, esophagus or stomach[48,49]. The cutaneous lesions usually develop from 1 year prior to 1 year after the diagnosis of the neoplasm. Erythema gyratum repens may coincide with underlying pulmonary tuberculosis, and patients with other disorders (see below) can also have erythema gyratum repens-like lesions. However, occasionally, individuals are otherwise healthy.

Pathology

The histopathologic findings are nonspecific and include hyperkeratosis, focal parakeratosis, moderate patchy spongiosis and a mild, perivascular lymphohistiocytic infiltrate. In some cases, eosinophils and melanophages are seen in the dermis. By immunoelectron microscopy, DIF-detected immune deposits of IgG at the BMZ (see Pathogenesis) were shown in one patient to be beneath the lamina densa[46]. In addition, anti-EGF receptor, anti-vimentin and anti-α-actin staining was more intense in lesional skin and tumor tissue than in controls. Nevertheless, the meaning of these findings is unknown, given their anecdotal nature, and DIF is not required for confirmation of the diagnosis.

Differential Diagnosis

In addition to excluding the other types of figurate erythema, erythema gyratum repens-like lesions may be seen in patients with erythrokeratodermia variabilis and resolving pityriasis rubra pilaris (Fig. 19.9) as well

as bullous pemphigoid (both paraneoplastic and classic) and epidermolysis bullosa acquisita[50]. The differential diagnosis also includes erythema gyratum-like lesions due to mycosis fungoides, psoriasis, linear IgA bullous dermatosis, Sjögren's syndrome, cutaneous small vessel vasculitis (including urticarial forms), or hypersensitivity reactions to azathioprine. In certain regions of the world, tinea imbricata would also be included in the differential diagnosis.

Treatment

Erythema gyratum repens resolves when the associated neoplasm is successfully treated. There may be a return of cutaneous lesions in association with the development of metastases or local recurrences of the malignancy.

REFERENCES

1. Ziemer M, Eisendle K, Zelger B. New concepts on erythema annulare centrifugum: a clinical reaction pattern that does not represent a specific clinicopathological entity. Br J Dermatol. 2009;160:119–26.
2. White JW, Perry HO. Erythema perstans. Br J Dermatol. 1969;81:641–51.
3. Bressler GS, Jones RE Jr. Erythema annulare centrifugum. J Am Acad Dermatol. 1981;4:597–602.
4. Ackerman AB. Histologic Diagnosis of Inflammatory Skin Disease. Philadelphia: Lea-Febiger, 1978:174–5, 231–3, 283–4.
5. Weyers W, Diaz-Cascajo C, Weyers I. Erythema annulare centrifugum: results of a clinicopathologic study of 73 patients. Am J Dermatopathol. 2003;25:451–62.
6. Watsky KL, Hansen T. Annular erythema in identical twins. Cutis. 1989;44:139–40.
7. Shelley WB. Erythema annulare centrifugum. A case due to hypersensitivity to blue cheese *Penicillium*. Arch Dermatol. 1964;90:54–8.
8. Braverman IM. Skin Signs of Systemic Disease, 3rd edn. Philadelphia: WB Saunders, 1988:335–72.
9. Stone OJ. A mechanism of peripheral spread or localization of inflammatory reactions – role of the localized ground substance adaptive phenomenon. Med Hypoth. 1989;29:167–9.
10. Guillet MH, Dorval JC, Larregue M, Guillet G. Darier's erythema annulare centrifugum of neonatal onset with a 15 years' follow-up. Efficacy of interferon and role of cytokines. Ann Dermatol Venereol. 1995;122:422–6.
11. Anonymous. Guidelines for the diagnosis of rheumatic fever. Jones criteria, 1992 update. Special Writing Group of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young of the American Heart Association. JAMA. 1992;268:2069–73.
12. Ferrieri P, for the Jones Criteria Working Group. Proceedings of the Jones Criteria Workshop. Circulation. 2002;106:2521–3.
13. Troyer C, Grossman ME, Silvers DN. Erythema marginatum in rheumatic fever: early diagnosis by skin biopsy. J Am Acad Dermatol. 1983;8:724–8.
14. Secord E, Emre U, Shah BR, Tunnessen WW. Erythema marginatum in acute rheumatic fever. Am J Dis Child. 1992;146:637–8.
15. Jones TD. The diagnosis of rheumatic fever. JAMA. 1944:126:481–4.
16. Leirisalo M, Laitinen O. Rheumatic fever in adult patients. Ann Clin Res. 1975;7:244–50.
17. Carapetis JR. Rheumatic fever. In: Cohen J, Powderly WG (eds). Infectious Diseases, 2nd edn. Philadelphia: Mosby, 2004:669–76.
18. Lee JL, Naguwa SM, Cheema GS, Gershwin ME. Acute rheumatic fever and its consequences: A persistent threat to developing nations in the 21st century. Autoimmun Rev. 2009;9:117–23.
19. Day S, McHenry JA, Roscelli JD. Pruritic rash associated with cat scratch disease. Pediatrics. 1988;81:559–61.
20. Green ST, Hamlet NW, Willocks L, et al. Psittacosis presenting with erythema-marginatum-like lesions – a case report and a historical review. Clin Exp Dermatol. 1990;15:225–7.
21. Tani LY, Veasy LG, Minich LL, Shaddy RE. Rheumatic fever in children younger than 5 years: is the presentation different? Pediatrics. 2003;112:1065–8.
22. Patrizi A, Savoia F, Varotti E, et al. Neutrophilic figurate erythema of infancy. Pediatr Dermatol. 2008;25:255–82.
23. Farkas H, Harmat G, Fay A, et al. Erythema marginatum preceding an acute oedematous attack of hereditary angioneurotic oedema. Acta Derm Venereol. 2001;81:376–7.
24. Burgdorfer W, Barbour AG, Hayes SF, et al. Lyme disease – a tick-borne spirochetosis? Science. 1982;216:1317–19.
25. de Mik EL, van Pelt W, Docters-van Leeuwen BD, et al. The geographical distribution of tick bites and erythema migrans in general practice in the Netherlands. Int J Epidemiol. 1997;26:451–7.
26. Steere AC. Lyme borreliosis in 2005, 30 years after initial observations in Lyme Connecticut. Wien Klin Wochenschr. 2006;118:625–33.
27. Ramamoorthi N, Narasimhan S, Pal U, et al. The Lyme disease agent exploits a tick protein to infect the mammalian host. Nature. 2005;436:573–7.
28. Hovius JWR, Levi M, Fikrig E. Salivating for knowledge: potential pharmacological agents in tick saliva. PLoS Med. 2008;5:e43.
29. Muellegger RR, McHugh G, Ruthazer R, et al. Differential expression of cytokine mRNA in skin specimens from patients with erythema migrans or acrodermatitis chronica atrophicans. J Invest Dermatol. 2000;115:1115–23.
30. Wormser GP. Early Lyme disease. N Engl J Med. 2006;354:2794–801.
31. Megraud F, Thijsen SFT. Curved and spiral bacilli. In: Cohen J, Powderly WG (eds). Infectious Diseases, 2nd edn. Philadelphia: Mosby, 2004:2236–9.
32. Wormser GP, Liveris D, Nowakowski J, et al. Association of specific subtypes of *Borrelia burgdorferi* with hematogenous dissemination in early Lyme disease. J Infect Dis. 1999;180:720–5.
33. Asbrink E, Hovmark A. Comments on the course and classification of Lyme borreliosis. Scand J Infect Dis Suppl. 1991;77:41–3.
34. Steere AC. Lyme disease. N Engl J Med. 2001;345:115–25.
35. Müllegger RR. Dermatological manifestations of Lyme borreliosis. Eur J Dermatol. 2004;14:296–309.
36. Silberer M, Koszik F, Stingl G, Aberer E. Downregulation of class II molecules on epidermal Langerhans cells in Lyme borreliosis. Br J Dermatol. 2000;143:786–94.
37. Bartak P, Hulinska D. Apoptosis in the morphology of Lyme borreliosis. Cas Lek Cesk. 1997;136:146–7.
38. Centers for Disease Control and Prevention. Lyme Disease (*Borrelia burgdoferi*) 2008 Case Definition. Online. Available: www.cdc.gov/ncphi/disss/nndss/casedef/lyme_disease_2008.htm.
39. Bratton RL, Whiteside JW, Hovan MJ, et al. Diagnosis and treatment of Lyme disease. Mayo Clin Proc. 2008;83:566–71.
40. Dumler JS. Molecular diagnosis of Lyme disease: review and meta-analysis. Mol Diagn. 2001;6:1–11.
41. Bunikis J, Barbour AG. Laboratory testing for suspected Lyme disease. Med Clin North Am. 2002;86:311–40.
42. Wormser GP, Ramanathan R, Nowakowski J, et al. Duration of antibiotic therapy for early Lyme disease: a randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2003;138:697–704.
43. Wormser GP, Nadelman RB, Dattwyler RJ, et al. Practice guidelines for the treatment of Lyme disease. Clin Infect Dis. 2000;31(suppl. 1):S1–14.
44. Nadelman RB, Nowakowski J, Fish D, et al. Prophylaxis with single-dose doxycycline for the prevention of Lyme disease after an *Ixodes scapularis* tick bite. N Engl J Med. 2001;345:79–84.
45. Holt PA, Davies MG. Erythema gyratum repens: an immunologically mediated dermatosis? Br J Dermatol. 1977;96:343–7.
46. Caux F, Lebbe C, Thomine E, et al. Erythema gyratum repens. A case studied with immunofluorescence, immunoelectron microscopy and immunohistochemistry. Br J Dermatol. 1994;131:102–7.
47. Wakeel RA, Ormerod AD, Sewell HF, White MI. Subcorneal accumulation of Langerhans cells in erythema gyratum repens. Br J Dermatol. 1992;126:189–92.
48. Boyd AS, Neldner KH, Menter A. Erythema gyratum repens: a paraneoplastic eruption. J Am Acad Dermatol. 1992;26:757–62.
49. Skolnick M, Mainman ER. Erythema gyratum repens with metastatic adenocarcinoma. Arch Dermatol. 1975;11:227–9.
50. España A, Sitaru C, Pretel M, et al. Erythema gyratum repens-like eruption in a patient with epidermolysis bullosa acquisita associated with ulcerative colitis. Br J Dermatol. 2007;156:773–5.

This page intentionally left blank

Erythema Multiforme, Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

20

Lars E French and *Christa Prins*

Chapter Contents

Erythema multiforme 319
Stevens–Johnson syndrome and toxic epidermal necrolysis 323

Until recently, the nosology of severe acute bullous disorders due to infectious agents or drugs has been confusing. It has now become clear that Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are variants within a continuous spectrum of adverse drug reactions, whereas erythema multiforme (EM) is a distinct disorder with different clinical signs and precipitating factors, e.g. herpes simplex virus (HSV) infections. Therefore, EM will be discussed separately from SJS and TEN.

ERYTHEMA MULTIFORME

Synonym: ■ Erythema multiforme minor – erythema multiforme von Hebra

Key features

- A self-limited but potentially recurrent disease
- Abrupt onset of papular "target" lesions, with the vast majority of lesions appearing within 24 hours
- Two types of target lesions are recognized: (1) typical, with at least three different zones; and (2) atypical papular, with only two different zones and/or a poorly defined border
- Target lesions favor acrofacial sites
- Erythema multiforme minor: typical and/or occasionally atypical papular target lesions with little or no mucosal involvement and no systemic symptoms
- Erythema multiforme major: typical and/or occasionally atypical papular target lesions with severe mucosal involvement and systemic features
- A preceding HSV infection is the most common precipitating factor; occasionally, there are other preceding infections or, rarely, drug exposure
- Diagnosis of erythema multiforme requires clinicopathologic correlation and is not based solely on histologic findings
- Erythema multiforme does not carry the risk of progressing to toxic epidermal necrolysis

Introduction

Erythema multiforme (EM) is an acute, self-limited skin disease characterized by the abrupt onset of symmetric fixed red papules, some of which evolve into typical and/or occasionally "atypical" papular target lesions[1–4]. The eruption is often precipitated by an infection, particularly HSV. Two forms of EM are recognized – EM minor and EM major. Both are characterized by the same type of elementary lesions (targets), but are distinguished by the presence or absence of mucosal involvement and systemic symptoms (Table 20.1). In the vast majority of patients, EM can be distinguished clinically from SJS and TEN based upon the type of elementary skin lesions and their distribution[2,3,5].

History

EM was first described by the Austrian dermatologist Ferdinand von Hebra in 1860[6,7]. The disease he described was mild with a sudden onset of hundreds of red papules. By daily observation, von Hebra recognized that some of the original papules evolved into lesions with concentric zones of color change, which he termed "target" lesions. He mentioned that some of the target lesions resembled a "herpes iris". However, von Hebra described neither a prodrome nor the presence of mucosal lesions. He recognized that the condition could be recurrent and mentioned a "typus annuus" which recurred every spring.

EM was later divided into EM minor and EM major by Bernard Thomas in 1950[8]. Thomas considered von Hebra's disease to be EM minor, and severe mucosal necrosis with "EM-like" cutaneous lesions to be EM major. Since 1950, much confusion has developed regarding the definition of EM, in part because some authors, especially in the US, have stated that EM major includes SJS. However, recent investigations have clarified the situation by providing strong evidence that the term "EM minor" should be reserved for von Hebra's disease and the term "EM major" should be used for EM associated with mucosal lesions and systemic symptoms, but not for describing SJS, because SJS and EM major are distinct clinical disorders[2,3,5]. That said, because these are biologic processes, there can be patients where the distinction proves challenging.

Epidemiology

EM is predominantly observed in young adults and is very uncommon during childhood[5,9]. There is a slight male preponderance, but no racial bias. The exact incidence rate of EM is not known.

Pathogenesis

Current understanding suggests that EM is most likely, and in most patients, a mucocutaneous manifestation of a distinct skin-directed immune reaction that occurs in the setting of an infection in certain "predisposed" individuals. HSV is clearly the most common associated infectious agent, with *Mycoplasma pneumoniae*[10] (which also may be associated with SJS), *Histoplasma capsulatum* and parapoxvirus (orf) observed less frequently (Table 20.2). Histoplasmosis-associated EM has been said to occur more often in those patients with concomitant erythema nodosum. To date, evidence for EBV as a precipitating factor is incomplete[9]. Rarely, EM has been diagnosed as being due to drugs or systemic disease (see Table 20.2). Consequently, the possibility of SJS, generalized fixed drug eruption, polymorphous exanthematous drug eruption or urticaria[9,11] should be strongly considered if the presumed diagnosis is drug-induced EM. Of note, several physical agents such as trauma, cold, and UV and orthovoltage irradiation have been described as triggers for outbreaks of EM related to infectious agents, drugs or systemic disease.

To date, there is no clearly defined genetic predisposition for the development of EM. Several small studies of HLA antigen association have found different associations: HLA-DQw3 (specifically the DQB1*301 split), DRw53 and Aw33[12,13]. These HLA associations differ from those reported for SJS and TEN (see below).

COMPARISON OF ERYTHEMA MULTIFORME (EM) MINOR, EM MAJOR AND STEVENS–JOHNSON SYNDROME (SJS)						
	Type of skin lesions	**Distribution**	**Mucosal involvement**	**Systemic symptoms**	**Progression to TEN**	**Precipitating factors**
EM minor	• Typical targets • ± *Papular* atypical targets	Extremities (especially elbows, knees, wrists, hands), face	Absent or mild	Absent	No	• Herpes simplex virus • Other infectious agents
EM major	• Typical targets • ± *Papular* atypical targets • Occasionally bullous lesions	Extremities, face	Severe	Present	No	• Herpes simplex virus • *Mycoplasma pneumoniae* • Other infectious agents • Rarely, drugs
SJS	• Dusky macules with or without epidermal detachment • *Macular* atypical targets • Bullous lesions (<10% BSA detachment)	Trunk, face	Severe	Present	Possible	• Drugs • Occasionally, *Mycoplasma pneumoniae* • Rarely, immunizations

Table 20.1 Comparison of erythema multiforme (EM) minor, EM major and Stevens–Johnson syndrome (SJS). BSA, body surface area; TEN, toxic epidermal necrolysis.

Herpes simplex virus

In the majority of children and adults with EM, the disease is precipitated by HSV types 1 and 2[14–17]. Preceding herpes labialis is noted in approximately 50% of subjects with EM[14–17]. The herpes labialis may precede the onset of the cutaneous lesions, occur simultaneously, or be evident after the target lesions of EM have appeared. Most commonly, herpes labialis precedes target lesions of EM by 3–14 days. It is presumed that most cases in children and young adults are due to HSV type 1, but documented cases of HSV type 2 in adolescents and young adults have been reported[15,17].

Most of our current knowledge regarding EM is related to the study of HSV-associated EM. Not only are HSV-encoded proteins found within affected epidermis[14–17], but HSV DNA can be detected within the early red papules or the outer zone of target lesions in 80% of individuals with EM[7]. The presence of fragments of HSV DNA (most often comprised of sequences that encode its DNA polymerase) within the cutaneous lesions, as well as the expression of virally encoded antigens on keratinocytes, may be interpreted as evidence for replicating HSV within affected skin sites[14,15,18–20]. However, replication must be at a low level, because usually HSV cannot be cultured from EM lesions.

The inflammation within cutaneous lesions is believed to be a part of the HSV-specific host response[15]. Individuals with HSV-associated EM have normal immunity to HSV, but may have difficulty clearing the virus from infected cells; within sites of cutaneous lesions, HSV DNA may persist for 3 months after a lesion has healed[19]. Development of cutaneous lesions is initiated by the expression of HSV DNA sequences within the skin, and the recruitment of virus-specific T-helper type 1 (Th1) cells that produce interferon-γ in response to viral antigens within the skin[21]. This is thought to be followed by an "autoimmune" response resulting from the recruitment of T cells that respond to autoantigens released by lysed/apoptotic viral antigen-containing cells. Most recently it was shown that the HSV DNA fragments described above are transported (by peripheral blood $CD34^+$ Langerhans cell precursors) to the sites where EM skin lesions will develop prior to each eruption[22].

PRECIPITATING FACTORS IN ERYTHEMA MULTIFORME		
Infections (approx. 90% of cases)	Viral	• **Herpes simplex virus (HSV-1, HSV-2)** • Parapoxvirus (orf) • Vaccinia (smallpox vaccine) • Varicella zoster virus (chickenpox) • Adenovirus • Epstein-Barr virus • Cytomegalovirus • Hepatitis virus • Coxsackievirus • Parvovirus B19 • Human immunodeficiency virus
	Bacterial	• ***Mycoplasma pneumoniae**** • *Chlamydophila* (formerly *Chlamydia*) *psittaci* (ornithosis) • *Salmonella* • *Mycobacterium tuberculosis*
	Fungal	• *Histoplasma capsulatum* • Dermatophytes
Drugs (unusual)		Primarily: • Nonsteroidal anti-inflammatory drugs • Sulfonamides • Anticonvulsants • Other antibiotics, e.g. aminopenicillins • Allopurinol
Exposures (unusual)		• Poison ivy
Systemic disease (rare)		• Inflammatory bowel disease • Lupus erythematosus† (Rowell's syndrome) • Behçet's disease†

*Also precipitating factor for Stevens–Johnson syndrome and isolated oral mucositis.
†May be a pattern of cutaneous lesions in the disease rather than a precipitating factor.

Table 20.2 Precipitating factors in erythema multiforme. This is a *non-exhaustive* list based primarily on case reports and small series of cases. The most common causes are in bold.

Clinical Features

Due to a certain degree of clinical similarity, EM minor, EM major, SJS and TEN have, until quite recently, all been considered to be part of a single disease spectrum. However, as discussed previously, there is now strong evidence to support the concept that EM is a disease distinct from SJS and TEN at several levels – clinical, prognostic and etiologic. Clinical criteria allow the distinction of both forms of EM from SJS/TEN in the vast majority of patients[2,3,5]. These clinical criteria are as follows: (1) the type of elementary skin lesion; (2) the distribution of skin lesions (topography); (3) the presence or absence of overt mucosal lesions; and (4) the presence or absence of systemic symptoms (see Table 20.1).

Elementary skin lesions (Fig. 20.1)

The characteristic elementary skin lesion of EM is the *typical target lesion*. The latter measures <3 cm in diameter, has a regular round shape and a well-defined border, and it consists of at least three distinct zones, e.g. two concentric rings of color change surrounding a central circular zone that has evidence of damage to the epidermis in the form of bulla

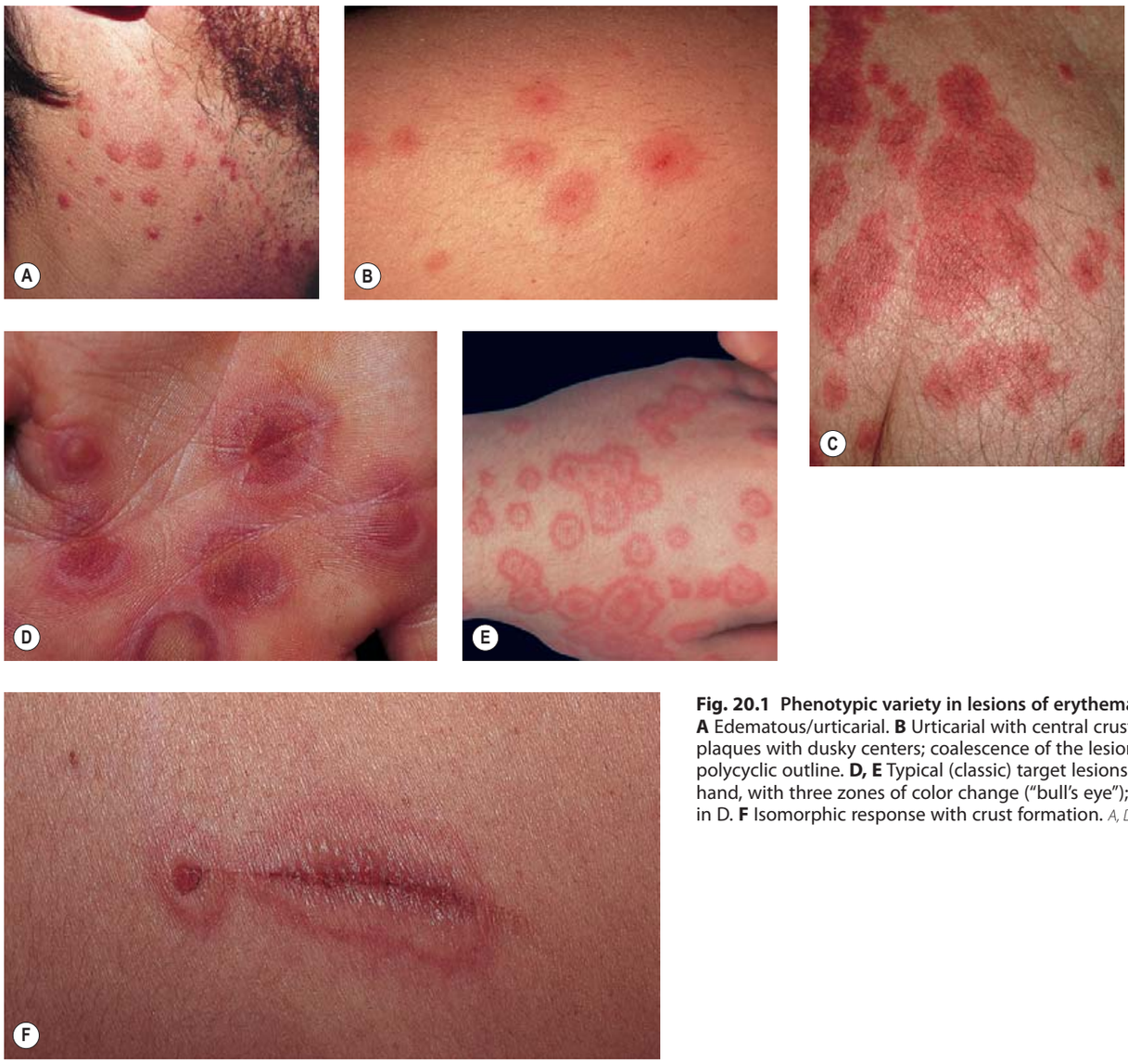


Fig. 20.1 Phenotypic variety in lesions of erythema multiforme. **A** Edematous/urticarial. **B** Urticarial with central crusting. **C** Erythematous plaques with dusky centers; coalescence of the lesions leads to a well-defined polycyclic outline. **D, E** Typical (classic) target lesions on the palms and dorsal hand, with three zones of color change ("bull's eye"); note the central vesicles in D. **F** Isomorphic response with crust formation. *A, D, F, Courtesy, William Weston, MD.*

formation or crust[2,3]. Frequently, this central circular zone also has a dusky appearance and over time, the lesion may resemble a "bull's eye".

While early target lesions often have a central dusky zone and a red outer zone ("iris" lesion), they can evolve to three zones of color change. Each concentric ring within the target lesion most likely represents one of a sequence of events of the same ongoing pathologic process. This may explain why some patients have only a limited number of fully developed, typical targets amidst a number of target lesions that are not yet typical or fully evolved, while in others all the lesions are at the same stage of development, thus creating a monomorphic clinical appearance. Given the possibility that only a few typical target lesions may present, a complete skin examination is essential.

In EM, elevated *atypical papular target lesions* can either accompany typical target lesions or constitute the primary cutaneous lesion. These particular lesions are defined as round, edematous, palpable and reminiscent of EM, but with only two zones and/or a poorly defined border. They must be distinguished from the flat (macular) atypical targets that are seen in SJS or TEN, but not EM. The latter are defined as round lesions that are also reminiscent of EM, but with only two zones and/or a poorly defined border, as well as being non-palpable (with the exception of a potential central vesicle or bulla).

Distribution of skin lesions (topography)

Although there is considerable variation from individual to individual, numerous lesions are usually present[9]. In general, lesions of EM develop preferentially on the extremities and the face; target lesions favor the upper extremities, as does the entire eruption of EM[9,17,23]. The dorsal aspects of the hands and the forearms are the most frequently involved sites, but the palms, neck, face and trunk (Fig. 20.2) are common locations as well[23]. Involvement of the legs is seen less frequently. EM lesions may also appear within areas of sunburn[9]. In addition, lesions tend to be grouped, especially on the elbows or knees[9,24].

The Koebner phenomenon may be observed, with target lesions appearing within areas of cutaneous injury such as scratches[9,24] (see Fig. 20.1F) or as erythema and swelling of the proximal nail folds at sites of chronic self-trauma. The injury must precede the onset of the EM eruption because the Koebner phenomenon does not occur once the EM lesions have appeared.

Mucosal lesions

Severe mucosal involvement is characteristic of EM major. Mucosal involvement is usually absent in EM minor, and, when present, lesions are few in number and mildly symptomatic[5,9,14,15,23–25]. The primary mucosal lesions of EM are vesiculobullous and rapidly develop into painful erosions that involve the buccal mucosa and lips (Fig. 20.3) and less commonly the ocular and genital mucosae. On the lips, the erosions rapidly become covered by painful crusts. Erosions of the anogenital mucosa are often large and polycyclic with a moist base.

Systemic symptoms

Systemic symptoms are almost always present in EM major and absent or limited in EM minor. In EM major, the systemic symptoms that

Fig. 20.2 Multiple lesions of erythema multiforme on the trunk. The dusky or crusted centers within the papules help to differentiate it from a morbilliform drug eruption.

Fig. 20.3 Mucosal involvement in erythema multiforme major. Typical target lesions are seen as well as serous crusting of the vermilion lips and eyelid margin. At the margin of the serous crusting of the lip, there are two zones of color with a polycyclic outline.

usually precede and accompany the skin lesions are fever and asthenia of varying degrees. Arthralgias with joint swelling have occasionally been described, as has pulmonary involvement resembling atypical pneumonia. Whether the latter is a pulmonary manifestation of EM versus one of the associated infections such as *M. pneumoniae* is unclear. Renal, hepatic and hematologic abnormalities in the context of EM major are rare[17].

By integrating these four clinical criteria, a distinction can be made between EM minor, EM major and SJS (see Table 20.1).

Natural history

In EM, a history of an abrupt onset of skin lesions is obtained, with almost all of the lesions appearing within 24 hours and full development by 72 hours[9,17]. Pruritic or burning sensations within the lesions may be described. The individual lesions remain fixed at the same site for 7 days or longer[6,7,26].

For most individuals with EM, the episode lasts 2 weeks and heals without sequelae[9,17]; one possible rare exception is ocular sequelae in the setting of EM major, which may occur if adequate eye care is not promptly instituted. Occasionally, postinflammatory hyper- or hypopigmentation is seen. Patients with EM usually have an uncomplicated clinical course, although recurrences, in the case of HSV-associated EM, are quite common[9,17,24]. One recurrence each spring, as described by von Hebra, may occur[6]. Most individuals with recurrent HSV-associated EM have one or two episodes a year, an exception being those receiving immunosuppressive drugs[17,24,27,28]. The use of immunosuppressive agents such as oral corticosteroids may be associated with more frequent and longer episodes of EM[9,17,25]. These individuals may have five or six episodes per year or even almost continuous disease in which one attack has not completely resolved before another occurs. The incidence of secondary bacterial infections also increases in the setting of prolonged corticosteroid use[9,17].

Pathology

EM is a clinicopathologic, not a purely histologic, diagnosis. Histologic findings are characteristic but not specific, and are most useful for excluding entities in the differential diagnosis such as lupus erythematosus (LE) and vasculitis[9,17,27]. In EM, the keratinocyte is the target of the inflammatory insult, with apoptosis of individual keratinocytes being the earliest pathologic finding (Fig. 20.4)[27]. As the process evolves, mild spongiosis and focal vacuolar degeneration of basal keratinocytes are observed. Superficial dermal edema and a perivascular infiltrate of mononuclear leukocytes and T lymphocytes with exocytosis into the epidermis are also seen.

Immunofluorescence findings are nonspecific[9]. Granular deposits of IgM and C3 around superficial blood vessels and focally at the dermal–epidermal junction have been described. Specific HSV antigens have been detected within keratinocytes by immunofluorescence, and HSV genomic DNA has been detected by PCR amplification of skin biopsy specimens[14,18,19].

Compared to SJS, the dermal inflammation component is more prominent in EM and the epidermal "necrolysis" component is more discrete[29]. Large sheets of epidermal necrosis are not seen in EM.

Differential Diagnosis

Many non-dermatologists overdiagnose EM by labeling individuals with giant urticaria as having EM (Fig. 20.5)[11]. The clinical criteria of Brice et al.[9] for distinguishing EM from urticaria should be strictly observed (Table 20.3). These include the presence of symmetrical fixed red papules or atypical papular target lesions, at least some of which evolve into typical target lesions. Particular attention should be given to the duration of individual lesions at a specific site and to epidermal damage in the center of the target lesions. EM papules are "fixed" at the same skin site for at least 7 days, whereas urticarial lesions last less than 24 hours at a particular site. The center of EM lesions demonstrates epithelial damage in the form of crusting or blisters, whereas the center of giant urticaria is characterized by normal skin or erythema without epidermal damage. Administration of subcutaneous epinephrine (adrenaline) will clear urticaria within 20 minutes, but will not change EM lesions. Edema of the face, hands and feet can be associated with urticaria, but is usually not observed in EM[9,11,17].

A number of conditions can sometimes have "target-like" lesions and mimic EM, including the aforementioned giant urticaria, fixed drug eruptions, subacute cutaneous LE, Kawasaki disease, erythema annulare centrifugum, and several forms of vasculitis[30]. A skin biopsy to exclude these entities is helpful. However, there is significant clinical and histologic overlap between EM and generalized fixed drug eruption. The total number of lesions is helpful, especially when there are hundreds, but it is also important to try to determine the number of lesions present in the first outbreak (i.e. fewer lesions in fixed drug eruption).

Recurrent EM during childhood may mimic polymorphous light eruption or juvenile spring eruption in that it may be sun-induced and develop with the first significant sun exposure in the spring[31]. In

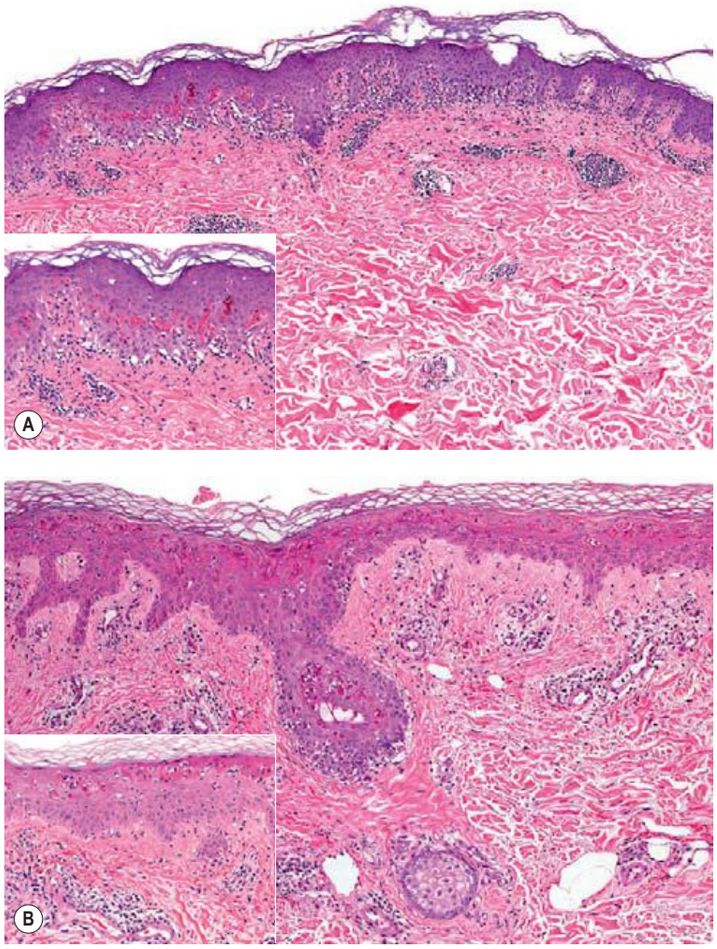


Fig. 20.4 Histopathologic features of erythema multiforme. A Early lesion – focal sites of apoptosis of keratinocytes with an interface dermatitis and vacuolar degeneration of the basal layer (insert). A perivascular lymphocytic infiltrate is also present. **B** Late lesion – more confluent necrosis of keratinocytes within the upper layers of the stratum spinosum (insert). The hair follicle still has evidence of an interface dermatitis. *Courtesy, Lorenzo Cerroni, MD.*

Fig. 20.5 Urticaria in an infant misdiagnosed as erythema multiforme. These migratory, annular plaques are markedly edematous. Some of the lesions have central erythema but there are no crusts or blisters. *Courtesy, Julie V Schaffer, MD.*

DIFFERENCES BETWEEN URTICARIA AND ERYTHEMA MULTIFORME	
Urticaria	**Erythema multiforme**
Central zone is normal skin	Central zone is damaged skin (dusky, bullous or crusted)
Lesions are transient, lasting less than 24 hours	Lesions "fixed" for at least 7 days
New lesions appear daily	All lesions appear within first 72 hours
Associated with swelling of face, hands or feet (angioedema)	No edema

Table 20.3 Differences between urticaria and erythema multiforme.

patients with systemic LE, occasional individual lesions will mimic true target lesions of EM, but other lesions characteristic of systemic LE are usually present[9]. Early lesions of vasculitis, particularly urticarial vasculitis, may mimic target lesions of EM. Histologic examination assists in distinction; additional clues include an elevated ESR, autoantibodies and low serum complement levels[9].

Treatment

Therapeutic options include topical and systemic treatment of the acute eruption as well as prophylactic treatment of recurrent disease. Topical therapy includes topical antiseptics for eroded skin lesions and antiseptic/antihistamine rinses and local anesthetic solutions for oral lesions. Administration of topical ophthalmic preparations should be done in conjunction with an ophthalmologist.

There are no double-blind or open trials of systemic therapies for the acute episode of EM[9,17]. When a precipitating factor can be identified (e.g. HSV or *M. pneumoniae*), specific therapy should be instituted; in the case of HSV, this represents chronic suppressive antiviral therapy (see below). As a rule, antiviral therapy has minimal impact if given after the appearance of the acute episode of EM. In most cases of EM, especially EM minor, symptomatic treatment will suffice. Oral antihistamines for 3 or 4 days may reduce the stinging and burning of the skin. In severe forms of EM with functional impairment, early therapy with systemic corticosteroids (e.g. prednisone [0.5–1 mg/kg/day]) or pulse methylprednisolone [20 mg/kg/day for 3 days]) should be considered, despite the absence of controlled studies and the long-existing controversy regarding increasing the risk of infectious complications[32].

In individuals with HSV-associated EM with frequent recurrences, prophylaxis for at least 6 months with oral acyclovir (10 mg/kg/day in divided doses), valacyclovir (500–1000 mg/day, with dose depending upon frequency of recurrences) or famciclovir (250 mg twice daily) should be considered. A double-blind, placebo-controlled study in young adults did demonstrate efficacy of acyclovir prophylaxis[28]. In addition to reducing the frequency of recurrences, occasionally the beneficial effect can continue even after the antiviral drug is discontinued. In non-responsive patients, the dose of the medication may be doubled, or a substitution made of the antiviral drug. Acyclovir or valacyclovir begun after symptoms appear is ineffective[17]. Obviously, in those patients in whom EM is precipitated by factors other than reactivation of HSV, antivirals will be of no benefit.

In patients with recurrent EM that is resistant to prophylactic antiviral therapy, especially severe cases of recurrent EM, several therapeutic approaches have been described; however, none have been validated by controlled trials and none are consistently effective or free of side effects. Among these are: azathioprine (100 mg/day for several months), prednisone (0.5 mg/kg/day for several months), thalidomide, dapsone, cyclosporine, mycophenolate mofetil and PUVA[17,33–36].

STEVENS–JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS

Synonym: ▪ Toxic epidermal necrolysis – Lyell's syndrome

Key features

- Prodrome of upper respiratory tract symptoms, fever and painful skin
- Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are two rare, potentially fatal, adverse cutaneous drug reactions of differing severity, characterized by mucocutaneous tenderness and erythema as well as extensive exfoliation
- SJS is characterized by <10% body surface area of epidermal detachment, SJS–TEN overlap by 10–30%, and TEN by >30%
- The medications most frequently incriminated are allopurinol, nonsteroidal anti-inflammatory drugs, antibiotics and anticonvulsants. TEN and SJS usually occur 7–21 days after initiation of the responsible drug
- The average mortality rate is 1–5% for SJS and 25–35% for TEN; it can be even higher in elderly patients and in those TEN patients with a very large surface area of epidermal detachment
- Exfoliation is due to extensive death of keratinocytes via apoptosis; the latter is mediated via the cytotoxic secretory protein granulysin and interaction of the death receptor–ligand pair Fas–FasL
- Optimal medical management of SJS and TEN requires early diagnosis, immediate discontinuation of the causative drug(s), and rapid initiation of supportive care and specific therapy
- Specific therapies that have the potential to selectively block keratinocyte apoptosis, such as high-dose IVIg, may provide added benefit over supportive care alone

CLINICAL FEATURES THAT DISTINGUISH STEVENS–JOHNSON SYNDROME (SJS), TOXIC EPIDERMAL NECROLYSIS (TEN), AND SJS–TEN OVERLAP

Clinical entity	SJS	SJS–TEN	TEN
Primary lesions	Dusky and/or dusky red lesions Flat atypical targets	Dusky and/or dusky red lesions Flat atypical targets	Poorly delineated erythematous plaques
			Epidermal detachment – spontaneous or by friction
			Dusky red lesions
			Flat atypical targets
Distribution	Isolated lesions	Isolated lesions	Isolated lesions (rare)
	Confluence (+) on face and trunk	Confluence (++) on face and trunk	Confluence (+++) on face, trunk and elsewhere
Mucosal involvement	Yes	Yes	Yes
Systemic symptoms	Usually	Always	Always
Detachment (% BSA)	**<10**	**10–30**	**>30**

Table 20.4 Clinical features that distinguish Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and SJS–TEN overlap. BSA, body surface area.

Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, acute and life-threatening mucocutaneous diseases that are nearly always drug-related. They are a consequence of extensive keratinocyte cell death that results in the separation of significant areas of skin at the dermal–epidermal junction, producing the appearance of scalded skin. This extensive cell death also results in mucous membrane detachment, and it contributes to the characteristic symptoms of SJS and TEN, which include: high fever, moderate to severe skin pain, anxiety and asthenia. The disease runs an unpredictable course. An initially benign-appearing dermatosis can progress rapidly, and once overt skin detachment has occurred, it is difficult to determine when it will end. Several studies have addressed the clinical signs of SJS and TEN, and there is now a framework of diagnostic criteria. Risk of death can also be accurately predicted by applying a severity-of-illness score specifically developed for predicting the clinical outcome of TEN (SCORTEN; see below).

As prognosis is correlated with the speed at which the culprit drug is identified and withdrawn, it is crucial to establish the correct clinical diagnosis rapidly, so the causal drug(s) can be discontinued and appropriate medical treatment begun as soon as possible. Although TEN, and especially SJS, were historically considered to be part of a spectrum of diseases that included EM major (all of which have clinically similar mucosal lesions), these disorders should now be distinguished, as their cause, management and prognosis are usually distinct (Table 20.4; see Table 20.1). SJS and TEN should also be distinguished from dermatoses such as staphylococcal scalded skin syndrome, generalized fixed drug eruption, drug-induced linear IgA bullous dermatosis, toxic erythema of chemotherapy, and acute generalized exanthematous pustulosis, as their management and prognosis are also quite different.

High-quality supportive treatment, ideally in intensive care units with modern equipment and trained nursing staff, is the current standard of care and can improve outcome. No specific therapy for SJS and TEN has yet shown efficacy in prospective, controlled clinical trials (i.e. attained evidence-based medicine standards of acceptance). Their low prevalence and life-threatening potential make randomized clinical trials difficult to perform. Despite this, conceptually interesting approaches based upon known elements of the pathogenesis of SJS and TEN and small case series have been described (see below).

History

In 1922, two US physicians, Stevens and Johnson, described an acute mucocutaneous syndrome in two young boys. The condition was characterized by severe purulent conjunctivitis, severe stomatitis with extensive mucosal necrosis, and "EM-like" cutaneous lesions. It became known as Stevens–Johnson syndrome (SJS) and was recognized as a severe mucocutaneous disease with a prolonged course and occasional fatalities[2,5,37]. SJS was later designated as EM major by Bernard Thomas in 1950[8]. However, recent clinical investigations have made it clear that the term "EM major" should not be used to describe SJS as they are distinct disorders (see Table 20.1)[2,3,5,37].

In 1956, Alan Lyell described four patients with an eruption "resembling scalding of the skin objectively and subjectively", which he called "toxic epidermal necrolysis". "Toxic" referred to toxemia – circulation of a toxin – which was thought to be responsible for the constitutional symptoms and epidermal necrosis. Lyell coined the term "necrolysis" by combining the key clinical feature "epidermolysis" with the characteristic histopathologic feature "necrosis". He also described an attack on the mucous membranes as part of the syndrome, and noted that there was very little inflammation in the dermis, a feature that was later referred to as "dermal silence"[38]. This feature contrasted with the obvious inflammatory infiltrate of other blistering disorders such as EM, dermatitis herpetiformis and bullous pemphigoid. TEN was considered at the time to be a cutaneous reaction pattern to multiple stimuli, including drugs (e.g. sulfonamides) and microbes (e.g. *Staphylococcus*)[39].

The description of a subgranular epidermal split in neonatal mice following exposure to phage group II *S. aureus*, the subsequent discovery of a new staphylococcal exotoxin called epidermolytic toxin, and the absence of overt keratinocyte necrosis led to the distinction of TEN from what would come to be known as the "staphylococcal scalded skin syndrome" (SSSS; see Ch. 74)[40]. It should be noted here that one of Lyell's original patients actually represented SSSS, and, although by that time he had already noted the histologic differences between TEN and SSSS, they were attributed to different degrees of injury.

As more patients with TEN were reported in the years following Lyell's treatise, it became clear that certain drugs such as sulfonamides, pyrazolones, barbiturates and anticonvulsants were principally associated with TEN. At the same time, drugs were increasingly being incriminated as a cause of EM associated with severe stomatitis. Hence, EM epidermal type (as defined by Orfanos et al.[41]), SJS and TEN were, at the time, considered to be part of a continuous spectrum of cutaneous reactions. It was clear, however, that HSV was the major cause of EM,

and that this virus was not associated with cases of TEN. Recently, the group of Jean-Claude Roujeau has clarified this issue by providing clinical evidence that EM and SJS are clinically distinct disorders with different causes and prognoses[3,5]. Increasingly, SJS and TEN are considered to be two ends of a spectrum of severe epidermolytic adverse cutaneous drug reactions, differing only by the extent of skin detachment (see Table 20.4).

Epidemiology

SJS and TEN are rare diseases that affect women more often than men (Table 20.5). Certain patient groups have an increased risk of developing SJS/TEN, including those who have slow acetylator genotypes, are immunocompromised (e.g. HIV infection), are undergoing radiotherapy while concomitantly receiving anticonvulsants (see Fig. 139.10), or have specific human leukocyte antigen (HLA) alleles. Examples of the latter are HLA-B*1502 in Asians and East Indians (but not Europeans) who are exposed to carbamazepine and HLA-B*5801 in Han Chinese exposed to allopurinol. Consequently, the FDA recently recommended genotyping of all Asians for the allele HLA-B*1502 prior to the administration of carbamazepine. In individuals with AIDS, the risk of developing TEN is 1000-fold higher than in the general population[45].

Death rates reported in large case series in which supportive therapy was used alone are quite variable, and it is known that these rates are heavily dependent on factors such as patient age and extent of epidermal detachment. Nevertheless, mortality rates range from 25% to 50% (average, 25–35%) for patients with TEN, and they are reported to be approximately 5% for patients with SJS[43,48].

Use of medications is reported in over 95% of patients with TEN. A strong association between drug ingestion and development of the cutaneous eruption is observed in 80% of cases. Other rare causes include infections and immunizations. The literature reflects a less clear relationship between drugs and SJS, as only 50% of reported SJS cases are claimed to be drug-related. This is certainly an underestimation, however, and most likely is due, in part, to the confusion that previously existed regarding the diagnostic distinction between SJS and EM.

More than 100 drugs have been identified to date as being associated with SJS/TEN. The most frequently implicated drugs are listed in Table 20.6 and consist primarily of allopurinol, antibiotics, nonsteroidal anti-inflammatory drugs, and anticonvulsants. Among the antibiotics, sulfonamides are the most strongly associated with SJS/TEN; other antimicrobials include aminopenicillins, quinolones, cephalosporins, tetracyclines and antifungals. In general, the risk of developing SJS/TEN is reported to be highest during the initial week(s) of therapy. For the aromatic anticonvulsants, the risk is highest during the first 2 months of treatment[49]. Furthermore, drugs with long half-lives are more likely to cause drug reactions and a fatal outcome than those with short half-lives, even if they are chemically related[50].

STEVENS–JOHNSON SYNDROME (SJS) AND TOXIC EPIDERMAL NECROLYSIS (TEN): EPIDEMIOLOGY AND RISK FACTORS	
Annual incidence	1.2–6 per million (SJS) 0.4–1.2 per million (TEN)
Ratio women : men	1.5 : 1
Risk factors	Slow acetylator genotypes
	Immunosuppression (e.g. HIV infection, lymphoma)
	Concomitant administration of radiotherapy and anticonvulsants (most commonly, those with brain tumors)
	HLA-B*1502: Asians and East Indians exposed to carbamazepine
	HLA-B*5801: Han Chinese exposed to allopurinol
	HLA-A*3101: Europeans exposed to carbamazepine

Table 20.5 Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN): epidemiology and risk factors. Adapted from refs 55, 56, 56a.

Pathogenesis

To date, the precise sequence of molecular and cellular events that lead to the development of SJS/TEN is only partially understood. The proposed pathogenesis must take into account the rarity of the reaction and the involvement of specific types of drugs.

Compelling evidence suggests that SJS/TEN is associated with an impaired capacity to detoxify reactive intermediate drug metabolites. It is thought to be initiated by an immune response to an antigenic complex formed by the reaction of such metabolites with certain host tissues[48,51–54]. Genetic susceptibility may also play a role, as evidenced by the identification of specific drug-related HLA alleles as major susceptibility genes for the development of SJS and TEN[42,55,56]. In addition to the alleles listed in Table 20.5, the HLA-DQB1*0601 allele has been reported in a significantly disproportionate number of white patients with SJS *and* ocular complications, suggesting that this allele may confer an increased risk for this specific clinical phenotype[57].

Cytotoxic T cells expressing the skin-homing receptor, cutaneous lymphocyte-associated antigen (CLA), are seen early in the development of cutaneous lesions[58–62]. These are likely to be drug-specific cytotoxic T cells[63]. Important cytokines such as interleukin (IL)-6, TNF-α, interferon-γ, IL-18 and Fas ligand (FasL) are also present in the lesional epidermis and/or blister fluid of patients with TEN, and their actions could explain some of the constitutional symptoms of TEN as well as the frequently observed discrepancy between the extent of epidermal damage and the paucity of the inflammatory infiltrate[58,64,65]. Lastly, the typical interval between the onset of drug therapy and SJS/TEN is between 1 and 3 weeks, suggesting a period of sensitization and providing further support for the role of the immune system in their pathogenesis. This period ("memory") is considerably shortened in patients who are unfortunately re-exposed to a drug that previously resulted in SJS or TEN.

Recently, it has been clearly shown that the tissue damage described by pathologists as epidermal necrolysis is a reflection of massive keratinocyte cell death via apoptosis[66]. The apoptosis of individual keratinocytes is a hallmark of the early stages of SJS and TEN, and it is the first clear morphologic sign of specific tissue damage. The more classic histologic image of extensive epidermal "necrolysis" is, in fact, an image of the aftermath of keratinocyte apoptosis. Indeed, the apoptotic state of cells is transient in nature, and it is followed by necrosis if the apoptotic cells are not rapidly phagocytosed. In SJS and TEN, within hours, keratinocyte apoptosis becomes very abundant in lesional skin, thus

MEDICATIONS MOST FREQUENTLY ASSOCIATED WITH STEVENS–JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS
Allopurinol
Aminopenicillins
Amithiozone (thioacetazone)*,†
Antiretroviral drugs, especially NNRTIs
Barbiturates
Carbamazepine
Chlormezanone*,‡
Phenytoin anticonvulsants
Lamotrigine
Phenylbutazone*,§
Piroxicam
Sulfadiazine*,†
Sulfadoxine†
Sulfasalazine
Trimethoprim–sulfamethoxazole
*Not available in the US. †Antibacterial. ‡Sedative/hypnotic. §Nonsteroidal anti-inflammatory drug.

Table 20.6 Medications most frequently associated with Stevens–Johnson syndrome and toxic epidermal necrolysis. Amifostine may join this list. NNRTIs, non-nucleoside reverse transcriptase inhibitors (in particular, nevirapine, efavirenz, etravirine). For a complete updated list of drugs associated with SJS and TEN, refer to: Litt J, Litt JZ. Litt's Drug Eruption Reference Manual Including Drug Interactions. London: Informa Healthcare.

rapidly overwhelming the phagocytic capacity of the affected skin. Over a period of hours to days, these apoptotic keratinocytes become necrotic and lose their cohesion to adjacent keratinocytes as well as the basement membrane. The whole epidermis then loses viability, creating the familiar histologic image of full-thickness epidermal necrolysis.

Fas ligand (FasL, CD95L), a member of the TNF family of cytokines, has the ability to induce apoptosis by binding to its specific cell surface receptor, the Fas (CD95, Apo-1) death receptor[67]. Such death receptors function as cell surface sensors that detect the presence of specific extracellular death signals and rapidly trigger cellular destruction by apoptosis (Fig. 20.6). Notably, keratinocyte apoptosis within lesional skin of patients with TEN is associated with highly increased expression of keratinocyte FasL, together with conserved levels of keratinocyte Fas expression[64,65,68,69]. Overlaying cryostat sections of lesional skin with Fas-sensitive cells as targets has demonstrated that keratinocyte FasL is cytolytically active in TEN; cytolysis can be prevented by monoclonal antibodies that block the interaction of Fas and FasL.

In 2008, Chung et al.[70] provided evidence that another cytotoxic molecule plays a role in the keratinocyte apoptosis observed in SJS/TEN. High concentrations of granulysin, a secreted, cationic, cytolytic protein produced by cytotoxic T lymphocytes (CTLs), natural killer (NK) cells and natural killer T (NKT) cells, were found in blister fluid from patients with SJS/TEN. Moreover, injection of recombinant granulysin into mouse skin induced epidermal necrolysis and an inflammatory cell infiltrate.

The current model for the pathogenesis of SJS/TEN (Fig. 20.7) is as follows: upon exposure to certain types of drugs (see Table 20.6), an individual with particular predisposing factors (see Table 20.5) mounts a specific immune reaction to the drug or one of its metabolites. As a result of an interplay of cell types and cytokines that remains to be totally defined, there is a strong expression of the cytolytic molecule FasL on keratinocytes as well as granulysin secretion from CTLs, NK cells and NKT cells. This leads to FasL- and granulysin-mediated apoptosis of keratinocytes and subsequent epidermal necrosis and detachment.

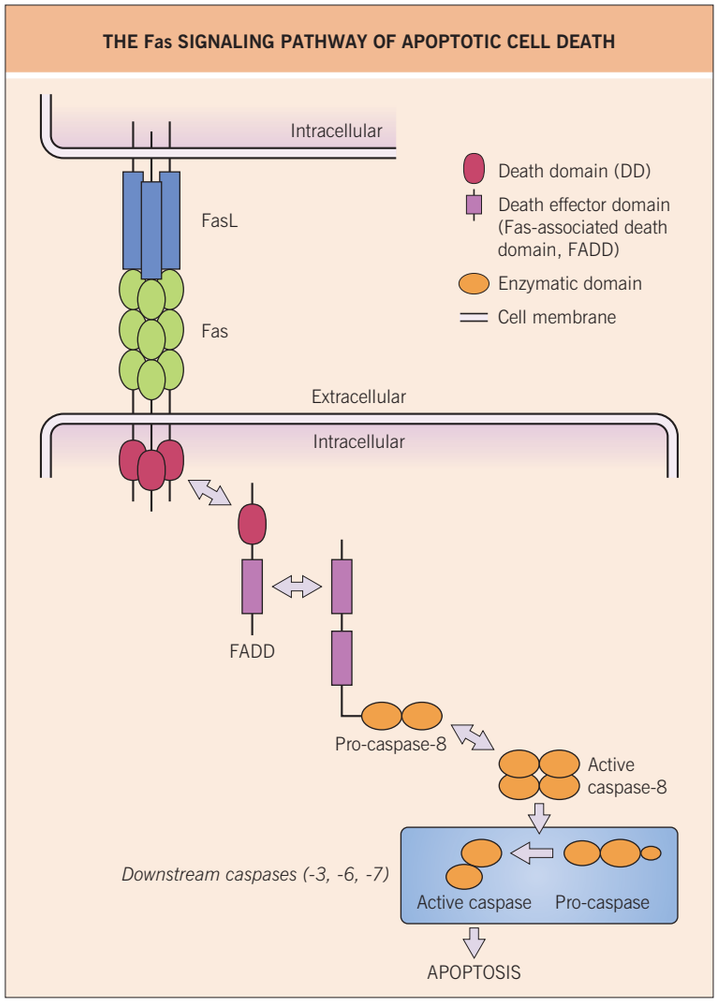


Fig. 20.6 The Fas signaling pathway of apoptotic cell death. The death receptor Fas and its ligand FasL are transmembrane proteins. Fas signaling is triggered in the target cells by receptor tri(multi)-merization, induced upon contact with membrane-bound FasL from an adjacent cell. Subsequently, recruitment of intracellular signaling proteins FADD and pro-caspase-8 leads to autoactivation of the protease caspase-8 as well as apoptosis due to subsequent activation of downstream effector caspases (caspases-3, -6, -7), which cause cellular disintegration and death. Stimuli that induce apoptosis include cellular stress, growth factor withdrawal, DNA damage and cytokines.

Clinical Features

Initial symptoms of both TEN and SJS can be fever, stinging eyes, and pain upon swallowing, any of which can precede cutaneous manifestations by 1 to 3 days. Skin lesions tend to appear first on the trunk, spreading to the neck, face and proximal upper extremities. The distal portions of the arms as well as the legs are relatively spared, but the palms and soles can be an early site of involvement. Erythema and erosions of the buccal, ocular and genital mucosae are present in more than 90% of patients (Fig. 20.8). The epithelium of the respiratory tract is involved in 25% of patients with TEN, and gastrointestinal lesions (e.g. esophagitis, diarrhea) can also occur[71]. The skin lesions are usually tender, and mucosal erosions are very painful. Additional systemic manifestations include fever, lymphadenopathy, hepatitis and cytopenias.

The morphology of the skin lesions has been studied in detail. First, lesions appear as erythematous, dusky red or purpuric macules of irregular size and shape, and they have a tendency to coalesce (Fig. 20.9). At this stage, and in the presence of mucosal involvement and tenderness, the risk of rapid progression to SJS or TEN should be strongly suspected. In the absence of spontaneous epidermal detachment, a Nikolsky sign should be sought by exerting tangential mechanical pressure with a finger on several erythematous zones. This sign is considered positive if dermal–epidermal cleavage is induced. In some patients, the macular lesions observed at the onset can have a dusky center, giving them a target-like appearance. However, such lesions lack the three concentric rings characteristic of typical target lesions (as originally described by Hebra) and are not papular as in atypical target lesions of EM.

As the epidermal involvement progresses toward full-thickness necrosis, the dusky red macular lesions take on a characteristic gray hue. This process can be very rapid (hours), or take several days. The necrotic epidermis then detaches from the underlying dermis, and fluid fills the space between the dermis and the epidermis, giving rise to blisters. The blisters have special features: they break easily (flaccid) and can be extended sideways by slight pressure of the thumb as more necrotic epidermis is displaced laterally (Asboe–Hansen sign). The skin resembles wet cigarette paper (see Fig. 20.12B) as it is pulled away by trauma, often revealing large areas of raw and bleeding dermis, which is referred to as "scalding" (Fig. 20.10). These patients must therefore be handled with extreme care. Tense blisters are usually seen only on the palmoplantar surfaces, where the epidermis is thicker and, therefore, more resistant to mild trauma.

When admitting such patients, the extent of necrolysis must be carefully and correctly evaluated, since it constitutes a major prognostic factor. The rules characteristically used to evaluate the surface area of thermal burns are appropriate for this purpose (see Ch. 88). Experience has shown that the extent of skin detachment is easily overestimated. Measurements should include detached and detachable epidermis (positive Nikolsky sign) but not purely erythematous areas (negative Nikolsky sign)[2]. The extent of skin detachment allows classification of the patient into one of three groups (Fig. 20.11; see Table 20.4):

- SJS: <10% of body surface area (BSA)
- SJS–TEN overlap (an intermediate category): 10–30% of BSA (Fig. 20.12)
- TEN: >30% of BSA.

Mucosal erosions are present in >90% of patients (Fig. 20.13). Patients complain of photophobia and painful micturition.

It is also important to distinguish between SJS and EM, which are now considered to be different illnesses with different prognoses (see above)[5]. Their histologic features are similar and, therefore, not helpful

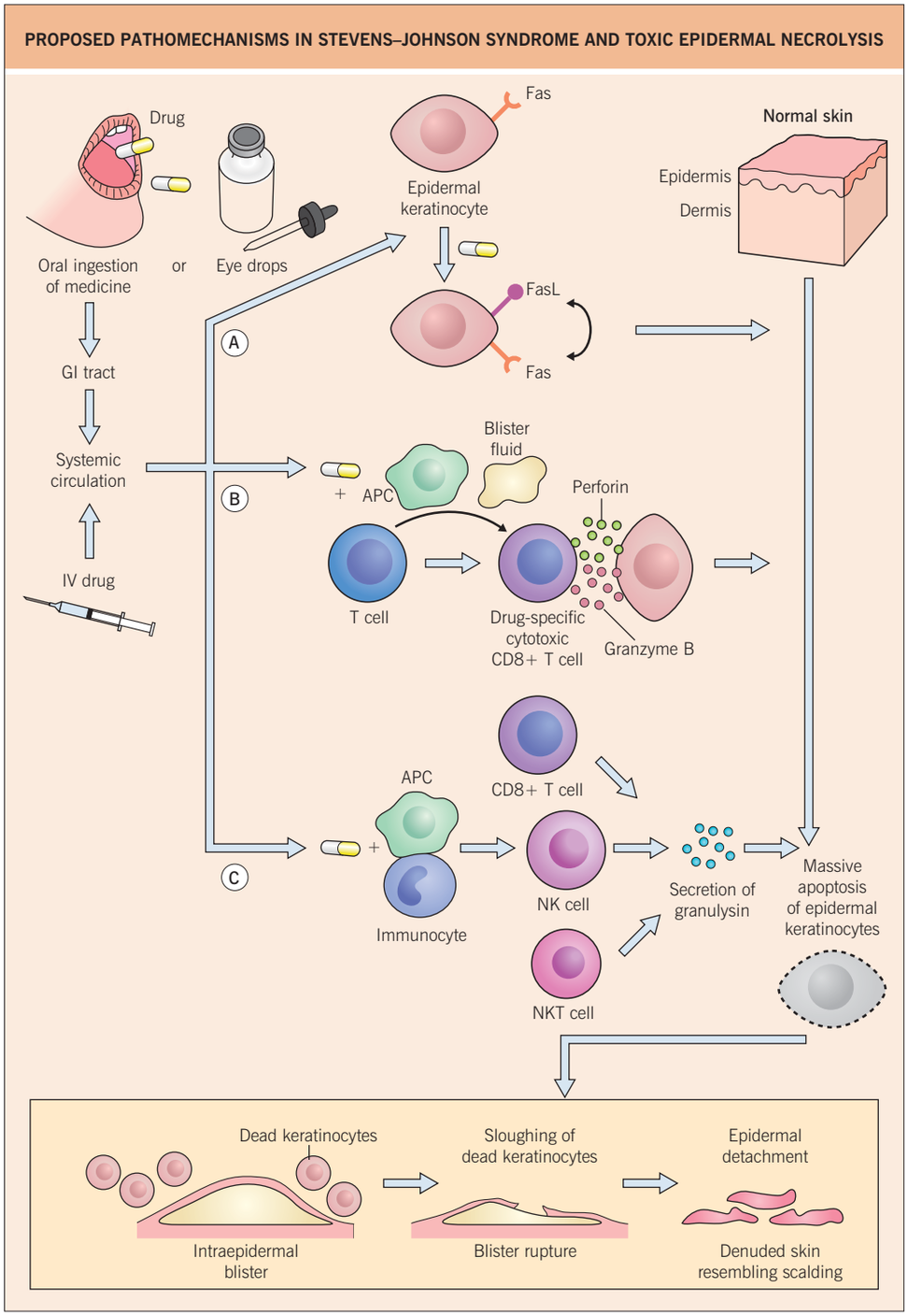


Fig. 20.7 Proposed pathomechanisms to explain apoptosis of epidermal keratinocytes in Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). A number of medications can trigger widespread apoptosis of epidermal keratinocytes in individuals with SJS or TEN, leading to skin blistering and denudation. Several theories have been proposed for this condition: (**A**) the medication might induce upregulation of FasL by keratinocytes constitutively expressing Fas, leading to a death receptor-mediated apoptotic pathway; (**B**) the drug might interact with MHC class I-expressing cells and then drug-specific $CD8^+$ cytotoxic T cells accumulate within epidermal blisters, releasing perforin and granzyme B that kill keratinocytes; and (**C**) the drug may also trigger the activation of $CD8^+$ T cells, NK cells and NKT cells to secrete granulysin, with keratinocyte death not requiring cell contact. IVIg contains antibodies against Fas that can block the binding of FasL to Fas. *From Nickoloff BJ. Saving the skin from drug-induced detachment. Nat Med. 2008;14:1311–13, with permission of Nature Publishing Group.*

Fig. 20.8 Mucosal involvement in Stevens–Johnson syndrome. **A** Erythema and conjunctival erosions. **B** Erosions of the genital mucosa.

Fig. 20.9 Cutaneous features of toxic epidermal necrolysis (TEN). Characteristic dusky red color of the early macular eruption in TEN. Lesions with this color often progress to full-blown necrolytic lesions with dermal–epidermal detachment.

Fig. 20.10 Clinical features of toxic epidermal necrolysis (TEN). A Detachment of large sheets of necrolytic epidermis (>30% body surface area), leading to extensive areas of denuded skin. A few intact bullae are still present. **B** Hemorrhagic crusts with mucosal involvement. **C** Epidermal detachment of palmar skin.

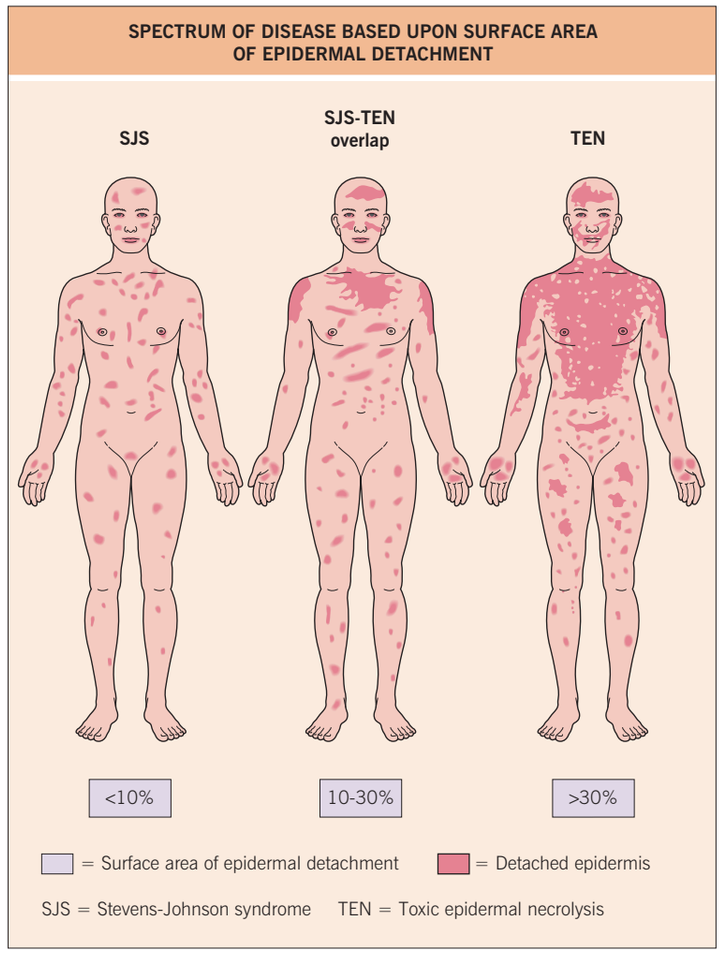


Fig. 20.11 Spectrum of disease based upon surface area of epidermal detachment.

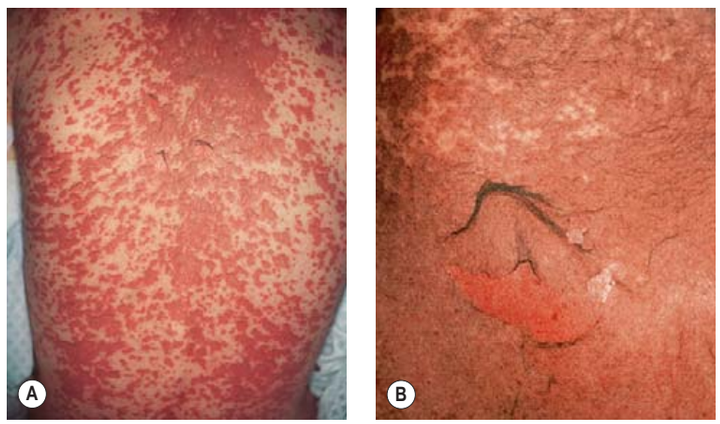


Fig. 20.12 Stevens–Johnson syndrome (SJS) versus SJS–TEN overlap. A In addition to mucosal involvement and numerous dusky lesions with flaccid bullae, there are areas of coalescence and multiple sites of epidermal detachment. Because the latter involved >10% body surface area, the patient was classified as having SJS–TEN overlap. **B** Close-up of epidermal detachment, whose appearance has been likened to wet cigarette paper.

in distinguishing between the two diseases. Differentiation is based primarily on clinical characteristics, especially the appearance of the target lesions and their distribution. To retain the diagnosis of EM, typical target lesions must exist, whereas SJS should be considered if target lesions are atypical (see Table 20.1). Unfortunately, criteria for predicting which patients with SJS are likely to progress towards full-blown TEN are currently unavailable.

In TEN, there are several factors that have been correlated with poor outcome, including increasing age and extent of epidermal detachment. In addition, the number of medications, elevation of serum urea, creatinine and glucose levels, neutropenia, lymphopenia and thrombocytopenia have been statistically linked to poor outcome. Late withdrawal of the causative drug is also associated with a less favorable outcome.

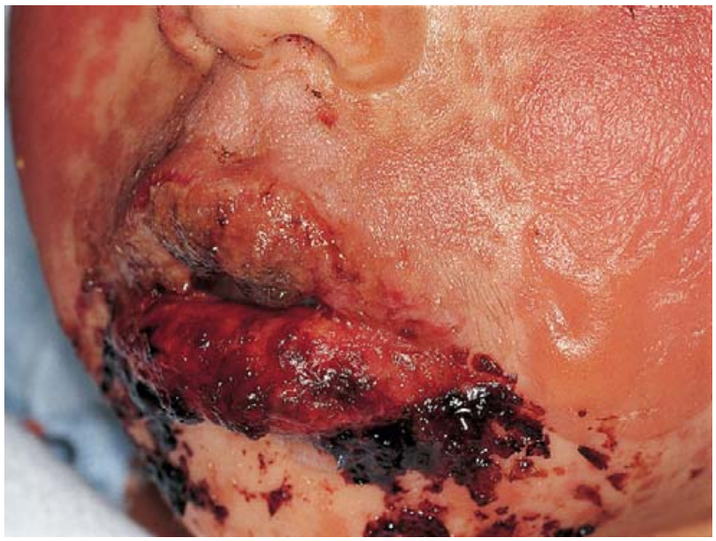


Fig. 20.13 Childhood Stevens–Johnson syndrome secondary to trimethoprim–sulfamethoxazole therapy. Note the hemorrhagic crusts and denudation of the lips as well as bullous cutaneous lesions. *Courtesy, William Weston, MD.*

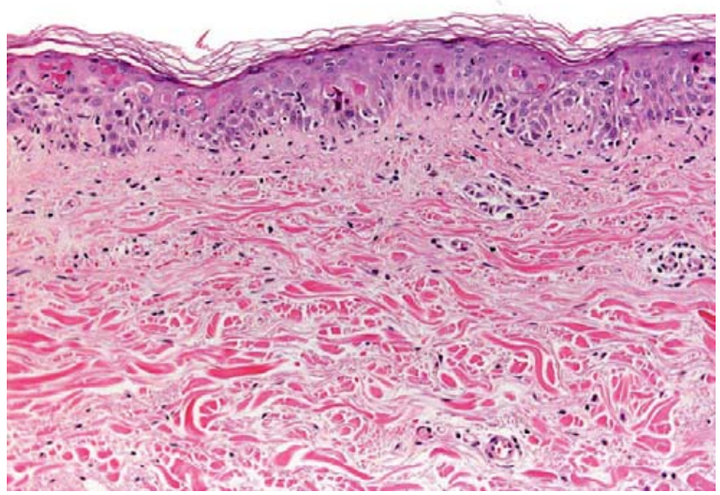


Fig. 20.14 Toxic epidermal necrolysis – histopathologic features. Apoptotic keratinocytes are present individually and in clusters within the epidermis. Subtle vacuolar changes along the basal layer are accompanied by minimal inflammation, with scattered lymphocytes within the epidermis. *Courtesy, Lorenzo Cerroni, MD.*

SCORTEN	
Prognostic factors	**Points**
Age >40 years	1
Heart rate >120 bpm	1
Cancer or hematologic malignancy	1
BSA involved on day 1 above 10%	1
Serum urea level (>10 mmol/l)	1
Serum bicarbonate level (<20 mmol/l)	1
Serum glucose level (>14 mmol/l)	1
SCORTEN	**Mortality rate (%)**
0–1	3.2
2	12.1
3	35.8
4	58.3
≥5	90

Table 20.7 SCORTEN. It represents a prognostic scoring system for patients with toxic epidermal necrolysis[72]. The score is based upon the number of prognostic factors in a particular patient. BSA, body surface area.

It has been estimated that prompt withdrawal of the offending drug reduces the risk of death by 30% per day[50]. A severity-of-illness score for TEN has recently been proposed (SCORTEN), in which seven parameters with equal weight have been integrated so as to make it possible to predict outcome (Table 20.7)[72,73].

On average, death occurs in every third patient with TEN, and it is mainly due to infections (*S. aureus* and *Pseudomonas aeruginosa*). Massive transepidermal fluid loss associated with electrolyte imbalance, inhibition of insulin secretion, insulin resistance, and onset of a hypercatabolic state can also be contributive factors. All these complications of TEN (that can also be observed in SJS) are best managed in intensive care units. They can unfortunately culminate in adult respiratory distress syndrome and multiple organ failure despite adequate supportive therapy.

Healing of areas of detached epidermis through re-epithelialization usually starts within days, and it is complete in most cases within 3 weeks. This process results from proliferation and migration of keratinocytes from "reservoir" sites, such as healthy epidermis surrounding denuded areas and hair follicles within the areas of detachment. Due to this conserved capacity for re-epithelialization, skin grafting is not required in SJS or TEN. Unfortunately, however, healing can be imperfect, and survivors may have sequelae such as symblepharon, conjunctival synechiae, entropion, ingrowth of eyelashes, cutaneous scarring, irregular pigmentation, eruptive melanocytic nevi, persistent erosions of the mucous membranes, phimosis, vaginal synechiae, nail dystrophy and diffuse hair loss. These can often be minimized by optimal skin care (see below), but, in TEN, up to 35% of survivors can have ocular symptoms ranging from sicca syndrome to blindness[48].

Identification of the offending drug is an important and difficult task, but it should be among the first priorities. As noted previously, delayed withdrawal of the causative drug(s) is associated with increased mortality. Currently, there is no reliable *in vitro* test for the rapid identification of causative drugs. Patch testing shows weak sensitivity in SJS/TEN, and it is not appropriate for identification purposes; re-exposing the patient to the proposed causative drug is obviously not an acceptable option in such severe drug reactions. The clinician, therefore, has to rely on previously reported associations and determine the probability (unlikely, possible, plausible, probable, very probable) for each medication based on the intrinsic ability of a particular drug to cause SJS/TEN (see Table 20.6 and reference therein) and extrinsic factors such as the onset of a given medication with respect to the onset of SJS/TEN. SJS and TEN usually occur 7–21 days after initiation of the causative drug in the setting of a first exposure to the drug, but can occur within 2 days in the case of re-exposure to a drug that previously caused SJS or TEN. In general, the medication list of patients with SJS and TEN should be reduced to a strict minimum, appropriate substitutions made, and drugs with short half-lives favored.

Pathology

Histopathologic examination of lesional skin is a very useful tool for confirming the diagnosis of SJS and TEN (Fig. 20.14), as the morphologic findings are distinct from those observed in SSSS (subcorneal blister with cleavage located in the granular layer of the epidermis) and acute generalized exanthematous pustulosis (AGEP; a rich neutrophilic infiltrate, superficial epidermal pustules and spongiosis, but no full-thickness epidermal necrolysis). Frequently, immediate analysis of frozen cryostat sections is sufficient for this purpose.

In early lesions of SJS and TEN, apoptotic keratinocytes are observed scattered in the basal and immediate suprabasal layers of the epidermis. This is most likely the histologic correlate of the dusky to gray color that clinicians familiar with SJS/TEN consider as a warning sign of pending full-blown epidermal necrolysis and detachment. At later stages, lesional biopsy specimens show a subepidermal blister with overlying confluent necrosis of the entire epidermis and a sparse

perivascular infiltrate composed primarily of lymphocytes. At an immunopathologic level, variable numbers of lymphocytes (usually $CD8^+$) and macrophages are observed within the epidermis, whereas lymphocytes in the papillary dermis are primarily $CD4^+$ cells[59,60].

Differential Diagnosis

The differential diagnosis of SJS and TEN consists primarily of EM (see above), SSSS, AGEP and generalized fixed drug eruption. Paraneoplastic pemphigus, drug-induced linear IgA bullous dermatosis (LABD), Kawasaki disease, LE, toxic erythema of chemotherapy, and severe acute GVHD can also be considered in some patients, depending upon the clinical setting. Patients with drug reactions with eosinophilia and systemic symptoms (DRESS) can sometimes develop vesicles and bullae due to dermal edema (see Ch. 21).

In most instances, SSSS and AGEP can be easily distinguished from TEN on clinical grounds. SSSS usually occurs in newborns and young children, but can also occur in adults who have renal failure or are immunosuppressed. SSSS is induced by a staphylococcal exotoxin (epidermolysin) that targets desmoglein 1 (see Ch. 74)[74]. The areas of erythema are tender and widespread, but spare the mucous membranes, palms and soles. The Nikolsky sign may be positive as in TEN, but it results in a superficial subcorneal cleavage, not a dermal-epidermal separation. Fragile bullous lesions then develop, and they are rapidly followed by exfoliation of sheets of epidermis. For the trained clinician, the exfoliation is clearly more superficial, leaving a bed of intact epidermal layers instead of the wet and bright red dermal tissue observed in TEN. Furthermore, in SSSS a purulent nasal discharge is frequently present. The distinction between TEN and SSSS is also very evident histologically, as the former results in full-thickness epidermal necrolysis, whereas the latter shows a subcorneal split with a normal underlying epidermis.

AGEP, also considered an important adverse cutaneous drug reaction, presents as large areas of erythema studded with multiple, small (<3 mm), non-follicular pustules. Neutrophilia and eosinophilia are frequently observed, and, together with the pustules, go against the diagnosis of TEN. The Nikolsky sign may be positive and is, therefore, not a good diagnostic marker in this situation. In addition, the pustules may coalesce into rather large lesions and then slough. Mucous membrane involvement occurs in approximately 20% of cases. Histology is a useful complement to clinical examination as it reveals a dense neutrophilic infiltrate and intraepidermal and subcorneal pustules, but no full-thickness epidermal necrolysis. Multiple mucocutaneous lesions of fixed drug eruption can overlap clinically and histologically with SJS; determination of the number of lesions present during the first outbreak may prove useful (see Ch. 21).

An acute onset of paraneoplastic pemphigus, drug-induced LABD, and acute severe GVHD can, in some circumstances, be reminiscent of TEN. However, the clinical context, as well as the histologic and immunohistochemical findings (by direct and indirect immunofluorescence microscopy), can rapidly aid in establishing the correct diagnosis. Vancomycin is the most common cause of drug-induced LABD and is an uncommon cause of SJS/TEN.

Kawasaki disease is sometimes confused with SJS in children[9]. In the former, the lips are red and dry ("chapped") and the hemorrhagic crusts and mucosal denudation observed with SJS are absent (see Ch. 81). The bulbar conjunctivae are injected in Kawasaki disease but there is no exudate as is seen in SJS. In Kawasaki disease, target-like lesions are seen occasionally but bullous lesions are generally not observed. However, there is an epidermal split which results in perineal peeling and peeling of the fingertips.

TEN-like vesiculobullous skin disease has been observed in patients with both acute and subacute LE as well as in individuals with systemic LE who are on no medications. Sontheimer and colleagues have proposed the term "acute syndrome of apoptotic pan-epidermolysis" (ASAP) to describe this clinical syndrome[75].

Thermal burns, phototoxicity, and coma bullae (see Ch. 33) can be associated with full-thickness epidermal necrosis, but the overall clinical setting is very different. Notably, the distribution of lesions and the patient's history are not compatible with TEN. In any patient receiving chemotherapy assigned the diagnosis of TEN, the possibility of extensive toxic erythema of chemotherapy needs to be considered (see Ch. 21). The bullae tend to be more tense and do not rupture as easily.

Treatment

Optimal medical management of SJS and TEN requires early diagnosis, immediate discontinuation of the causative drug(s), supportive care, and specific therapy (Fig. 20.15).

Supportive care is similar to that performed for severe thermal burns, and it is aimed at limiting associated complications, which are the main cause of mortality. These include hypovolemia, electrolyte imbalance, renal insufficiency and sepsis. Careful daily wound care, hydration and nutritional support are essential and, preferably, done in an intensive care unit if there is epidermal detachment involving 10–20% (or more) of BSA[76]. Use of a controlled pressure, thermoregulated bed and an aluminum survival sheet, instead of a regular bed and sheets, is recommended. All patient manipulations should be performed sterilely, and venous catheters should be placed, if possible, in a region of non-involved skin.

Wound care is best performed once daily with the help of, or in the presence of, a dermatologist. The patient should be manipulated as

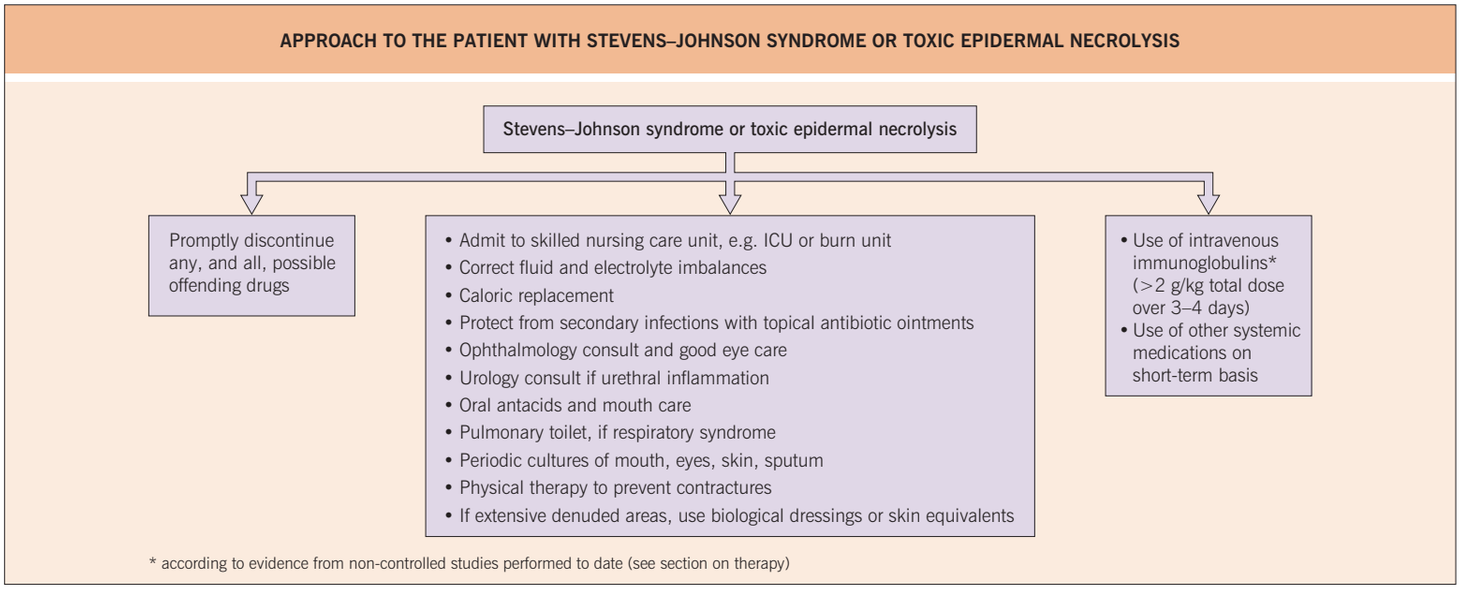


Fig. 20.15 Approach to the patient with Stevens–Johnson syndrome or toxic epidermal necrolysis. ICU, intensive care unit.

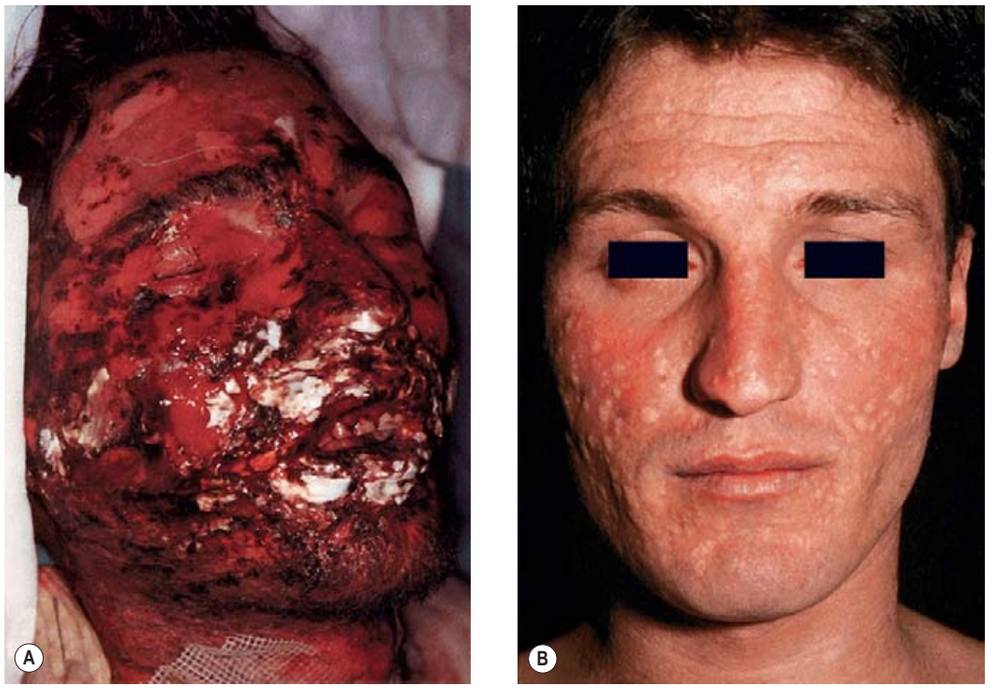


Fig. 20.16 Treatment of toxic epidermal necrolysis (TEN). Facial involvement of a patient with TEN (50% body surface area involvement) before (**A**) and 3 weeks after (**B**) treatment with IVIg (0.75 g/kg/day for 4 days).

PUBLISHED STUDIES (WITH ≥10 PATIENTS) ON THE USE OF IVIG FOR THE TREATMENT OF TOXIC EPIDERMAL NECROLYSIS											
	Viard 1998	**Trent 2003**	**Prins 2003**	**Campione 2003**	**Al-Mutairi 2004**	**Shortt 2004**	**Tan 2005**	**Stella 2007**	**Bachot 2003**	**Brown 2004**	**Schneck 2008**
Study	Prospect	Retro	Retro	Prospect	Prospect	Retro	Retro	Retro	Prospect	Retro	Retro
	NC	NC	NC	NC	NC	NC	NC	C	NC	NC	C
No. of patients	10	24	48	10	12	16	12	23	34	24	75
Detachment of epidermis (% BSA)	39	44	45	49	58	"65"	—	—	19	49	—
Dose of IVIg (g/kg)*	3	4	3	2	2–5	2.8	2	—	2	1.6	1.9 (0.7–2.3)
Predicted mortality (scoring system)	—	33% (SCORTEN)	—	35% (SCORTEN)	—	38% (APACHE)	—	36% (SCORTEN)	24% (SCORTEN)	29% (SCORTEN)	25% (SCORTEN)
Actual mortality	6%	4%	12%	10%	0%	25%	8%	26%	32%	42%	34%

*Usually administered over 3-4 days

Table 20.8 Published studies (with ≥10 patients) on the use of IVIg for the treatment of toxic epidermal necrolysis. The green boxes denote those studies where the actual mortality rate was less than the predicted mortality rate and the pink boxes represent those studies where the mortality rate was greater than the predicted mortality rate. For SCORTEN scoring system, see Table 20.7 and for APACHE scoring system, see ref 86a. BSA, body surface area; C, controlled; NC, non-controlled; Prospect, prospective; Retro, retrospective; — information not available.

little as possible, as every movement is a potential cause of epidermal detachment. Cutaneous care should concentrate on the face, eyes, nose, mouth, ears, anogenital region, axillary folds and interdigital spaces. Non-detached areas are kept dry and not manipulated. Detached areas, particularly on the back and pressure sites in contact with the bed, should be covered with Vaseline® gauze until re-epithelialization has occurred (see Ch. 145). For the face, serous and/or bloody crusts can be cleaned daily with isotonic sterile sodium chloride solution. An antibiotic ointment (e.g. mupirocin) should be applied around orifices (ears, nose, mouth), and silicone dressings can be used to cover erosive denuded areas of skin. The silicone dressing does not need to be changed and can be left in place until re-epithelialization occurs, but its surface must be cleansed daily with isotonic sterile sodium chloride solution. Another option is to place a large non-adherent layered dressing (e.g. Exu-Dry™) over the patient and on the bed.

For the eyes, regular examination by an ophthalmologist is recommended. Eyelids should be gently cleansed daily with isotonic sterile sodium chloride solution, and an ophthalmic antibiotic ointment applied to the eyelids. In addition, antibiotic eyedrops should be administered three times a day to the cornea to reduce bacterial colonization, which can lead to scarring. Nostrils should be cleaned daily with a sterile cotton swab, moistened with isotonic sterile sodium chloride solution, and then the same procedure used to apply a little antibiotic ointment (e.g. mupirocin). The mouth should be rinsed several times a day using a syringe with isotonic sterile sodium chloride solution, and then aspirated if the patient is unconscious. In the anogenital region and interdigital spaces, cutaneous care is performed daily by short applications of silver nitrate solution (0.5%) in the case of maceration, or simply sterile sodium chloride solution if there is no maceration.

To date, no specific therapies for SJS and TEN have shown efficacy in prospective, controlled clinical trials, i.e. attained evidence-based medicine standards of acceptance. In general, therapy for severely affected patients with SJS has mirrored therapy for TEN, while those patients with milder non-progressive forms of SJS may receive only supportive care. The low prevalence of SJS and TEN makes randomized clinical trials hard to perform. As a consequence, the literature for the most part consists of case reports and small uncontrolled series. In such studies, several treatments, including cyclosporine (3–4 mg/kg/day), cyclophosphamide (100–300 mg/day), plasmapheresis, N-acetylcysteine

(2 g/6 h), and TNF-α antagonists (e.g. etanercept, infliximab) have shown promising results[58,77–83]. Systemic corticosteroids have been a mainstay of therapy for decades, but their use remains controversial[84], despite a recent study suggesting efficacy when administered acutely and over a short period of time as pulse therapy (intravenous dexamethasone 1.5 mg/kg for three consecutive days)[85]. Recently, a controlled study using thalidomide was interrupted because of higher mortality in the thalidomide group compared with the placebo group[86].

In theory, therapies that have the potential to selectively block keratinocyte apoptosis have significant potential for treating SJS and TEN. The demonstration that Fas-mediated cell death (induced *in vitro* by lesional skin from patients with TEN) can be abrogated by monoclonal antibodies against FasL or by Fas : Fc (soluble form of Fas receptor) suggested that blocking antibodies might be useful in the treatment of TEN. Approximately 10 years ago, we observed that commercial preparations of IVIg contained antibodies against Fas that are able to block the binding of FasL to Fas[64]. Furthermore, IVIg, by blocking Fas, inhibited cell death mediated by recombinant FasL *in vitro*. When used in high doses (0.75 g/kg/day for four consecutive days) to treat patients with TEN, IVIg consistently and rapidly blocked the progression of epidermal detachment and disease in 10 of the 10 patients treated in a preliminary pilot study[64] (Fig. 20.16). To date, numerous case reports and 10 additional case series (that included at least 10 patients) have analyzed the therapeutic effect of IVIg in TEN (Table 20.8). Taken together, although each study has its potential biases, 8 of the 11 studies suggest that IVIg (at a total dose of >2 g/kg administered over 3–4 days) may reduce TEN-associated mortality[87–90].

Detailed analyses of studies published to date strongly suggest that total doses of ≤2 g/kg may be insufficient for obtaining an optimal therapeutic effect. In a recently published systematic review of the literature, higher doses of IVIg correlated with an increased survival rate and lower mortality rate[91]. Furthermore, for every additional 1 g/kg increase in the total dose of IVIg, there was a 4.2-fold increase in the survival rate. Therefore, our currently recommended treatment regimen is 1 g/kg/day of IVIg for three consecutive days, thus giving a total dose of 3 g/kg (this total dose is equivalent to that used in our first pilot study[64]). Some authors who reported successful results used an even higher total dose of 4 g/kg over 4 days[88]. In conclusion, high-dose IVIg appears to be a reasonable and relatively safe choice among the selective therapies currently available and previously tested. Further trials are required, however, to firmly establish its efficacy.

REFERENCES

1. von Hebra F. Erythema exsudativum multiforme. Vienna, Austria: Kaiserliche Akademie der Wissenschaften, 1866.
2. Bastuji-Garin S, Rzany B, Stern RS, et al. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch. Dermatol. 1993;129:92–6.
3. Auquier-Dunant A, Mockenhaupt M, Naldi L, et al. Correlations between clinical patterns and causes of erythema multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis: results of an international prospective study. Arch Dermatol. 2002;138:1019–24.
4. Bachot N, Roujeau JC. Differential diagnosis of severe cutaneous drug eruptions. Am J Clin Dermatol. 2003;4:561–72.
5. Assier H, Bastuji-Garin S, Revuz J, Roujeau JC. Erythema multiforme with mucous membrane involvement and Stevens-Johnson syndrome are clinically different disorders with distinct causes. Arch Dermatol. 1995;131:539–43.
6. von Hebra F. Acute exantheme und hautkrankheiten. Handbuch der Speciellen Pathologie und Therapie. Erlangen: Verlag von Ferdinand von Enke, 1860:198–200.
7. von Hebra F. On Diseases of the Skin, Including the Exanthemata. Translated and edited by CH Fagge. London: The New Sydenham Society, 1866:285.
8. Thomas BA. The so-called Stevens-Johnson syndrome. BMJ. 1950;1:1393–7.
9. Brice SL, Huff JC, Weston WL. Erythema multiforme. Curr Probl Dermatol. 1990;II:3–26.
10. Schalock PC, Brennick JB, Dinulos JG. *Mycoplasma pneumoniae* infection associated with bullous erythema multiforme. J Am Acad Dermatol. 2005;52:705–6.
11. Weston JA, Weston WL. The overdiagnosis of erythema multiforme. Pediatrics. 1992;89:802.
12. Lepage V, Douay C, Mallet C, et al. Erythema multiforme is associated to HLA-Aw33 and DRw53. Tissue Antigens. 1988;32:170–5.
13. Khalil I, Lepage V, Douay C, et al. HLA DQB1*0301 allele is involved in the susceptibility to erythema multiforme. J Invest Dermatol. 1991;97:697–700.
14. Weston WL, Brice SL, Jester JD, et al. Herpes simplex virus in childhood erythema multiforme. Pediatrics. 1992;89:32–4.
15. Weston WL, Morelli JG. Herpes simplex virus-associated erythema multiforme in prepubertal children. Arch Pediatr Adolesc Med. 1997;151:1014–18.
16. Brice SL, Stockert SS, Bunker JD, et al. The herpes-specific immune response of individuals with herpes-associated erythema multiforme compared with that of individuals with recurrent herpes labialis. Arch Dermatol Res. 1993;285:193–6.
17. Schofield JK, Tatnall FM, Leigh IM. Recurrent erythema multiforme: clinical features and treatment in a large series of patients. Br J Dermatol. 1993;128:542–5.
18. Darragh TM, Egbert BM, Berger TG, et al. Identification of herpes simplex virus DNA in lesions of erythema multiforme by the polymerase chain reaction. J Am Acad Dermatol. 1991;24:23–6.
19. Brice SL, Leahy MA, Ong L, et al. Examination of non-involved skin, previously involved skin and peripheral blood for herpes simplex virus DNA in patients with recurrent herpes-associated erythema multiforme. J Cutan Pathol. 1994;21:408–12.
20. Aslanzadeh J, Helm KF, Espy MJ, et al. Detection of HSV-specific DNA in biopsy tissue of patients with erythema multiforme by polymerase chain reaction. Br J Dermatol. 1992;126:19–23.
21. Kokuba H, Aurelian L, Burnett J. Herpes simplex virus associated erythema multiforme (HAEM) is mechanistically distinct from drug-induced erythema multiforme: interferon-gamma is expressed in HAEM lesions and tumor necrosis factor-alpha in drug-induced erythema multiforme lesions. J Invest Dermatol. 1999;113:808–15.
22. Ono F, Sharma BK, Smith CC, et al. CD34+ cells in the peripheral blood transport herpes simplex virus DNA fragments to the skin of patients with erythema multiforme (HAEM). J Invest Dermatol. 2005;124:1215–24.
23. Dikland WJ, Oranje AP, Stolz E, et al. Erythema multiforme in childhood and early infancy. Pediatr Dermatol. 1986;3:135–9.
24. Huff JC, Weston WL. Recurrent erythema multiforme. Medicine (Baltimore). 1989;68:133–40.
25. Farthing PM, Maragou P, Coates M, et al. Characteristics of the oral lesions in patients with cutaneous recurrent erythema multiforme. J Oral Pathol Med. 1995;24:9–13.
26. Weston WL. What is erythema multiforme? Pediatr Ann. 1996;25:106–9.
27. Howland WW, Golitz LE, Weston WL, et al. Erythema multiforme: clinical, histopathologic and immunologic study. J Am Acad Dermatol. 1984;10:438–46.
28. Tatnall FM, Schofield JK, Leigh IM. A double-blind, placebo-controlled trial of continuous acyclovir therapy in recurrent erythema multiforme. Br J Dermatol. 1995;132:267–70.
29. Cote B, Wechsler J, Bastuji-Garin S, et al. Clinicopathologic correlation in erythema multiforme and Stevens-Johnson syndrome. Arch Dermatol. 1995;131:1268–72.
30. Weston WL, Brice SL. Atypical forms of herpes-simplex associated erythema multiforme. J Am Acad Dermatol. 1998;39:124–6.
31. Wolf P, Soyer HP, Fink-Puches R, et al. Recurrent post-herpetic erythema multiforme mimicking polymorphic light and juvenile spring eruption: report of two cases in young boys. Br J Dermatol. 1994;131:364–7.
32. Martinez AE, Atherton DJ. High-dose systemic corticosteroids can arrest recurrences of severe mucocutaneous erythema multiforme. Pediatr Dermatol. 2000;17:87–90.
33. Cherouati K, Claudy A, Souteyrand P, et al. Treatment by thalidomide of chronic multiforme erythema: its recurrent and continuous variants. A retrospective study of 26 patients. Ann Dermatol Venereol. 1996;123:375–7.
34. Bakis S, Zagarella S. Intermittent oral cyclosporin for recurrent herpes simplex-associated erythema multiforme. Australas J Dermatol. 2005;46:18–20.
35. Davis MD, Rogers RS 3rd, Pittelkow MR. Recurrent erythema multiforme/Stevens-Johnson syndrome: response to mycophenolate mofetil. Arch Dermatol. 2002;138:1547–50.
36. Morison WL, Anhalt GJ. Therapy with oral psoralen plus UV-A for erythema multiforme. Arch Dermatol. 1997;133:1465–6.
37. Leaute-Labreze C, Lamireau T, Chawki D, et al. Diagnosis, classification and management of erythema multiforme and Stevens-Johnson syndrome. Arch Dis Child. 2000;83:347–52.
38. Achten G, Ledoux-Corbusier M. Lyell's toxic epidermal necrolysis: histologic aspects. Arch Belg Dermatol Syphiligr. 1970;26:97–114.
39. Lyell A. A review of toxic epidermal necrolysis in Britain. Br J Dermatol. 1967;79:662–71.
40. Melish ME, Glasgow LA. The staphylococcal scalded-skin syndrome. N Engl J Med. 1970;282:1114–19.
41. Orfanos CE, Schaumburg-Lever G, Lever WF. Dermal and epidermal types of erythema multiforme. A histopathologic study of 24 cases. Arch Dermatol. 1974;109:682–8.
42. Chung WH, Hung SI, Chen YT. Human leukocyte antigens and drug hypersensitivity. Curr Opin Allergy Clin Immunol. 2007;7:317–23.
43. Roujeau J-C, Guillaume J-C, Fabre JP, et al. Toxic epidermal necrolysis (Lyell syndrome). Incidence and drug etiology in France, 1981–1985. Arch Dermatol. 1990;126:37–42.
44. Naldi L, Locati F, Marchesi L, Cainelli T. Incidence of toxic epidermal necrolysis in Italy. Arch Dermatol. 1990;126:1103–4.
45. Rzany B, Mockenhaupt M, Stocker U, et al. Incidence of Stevens-Johnson syndrome and toxic epidermal necrolysis in patients with the acquired immunodeficiency syndrome in Germany. Arch Dermatol. 1993;129:1059.
46. Dupuis M, Schaerer E, Krause KH, Tschopp J. The calcium-binding protein calreticulin is a major constituent of lytic granules of cytolytic T lymphocytes. J Exp Med. 1993;177:1–7.
47. Duncan KO, Tigelaar RE, Bolognia JL. Stevens-Johnson syndrome limited to multiple sites of radiation therapy in a patient receiving phenobarbital. J Am Acad Dermatol. 1999;40:493–6.

48. Revuz J, Penso D, Roujeau JC, et al. Toxic epidermal necrolysis. Clinical findings and prognosis factors in 87 patients. Arch Dermatol. 1987;123:1160–5.
49. Roujeau JC, Kelly JP, Naldi L, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med. 1995;333:1600–7.
50. Garcia-Doval I, LeCleach L, Bocquet H, et al. Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death? Arch Dermatol. 2000;136:323–7.
51. Spielberg SP, Gordon GB, Blake DA, et al. Predisposition to phenytoin hepatotoxicity assessed in vitro. N Engl J Med. 1981;305:722–7.
52. Shear NH, Spielberg SP, Grant DM, et al. Differences in metabolism of sulfonamides predisposing to idiosyncratic toxicity. Ann Intern Med. 1986;105:179–84.
53. Wolkenstein P, Carriere V, Charue D, et al. A slow acetylator genotype is a risk factor for sulphonamide-induced toxic epidermal necrolysis and Stevens-Johnson syndrome. Pharmacogenetics. 1995;5:255–8.
54. Dietrich A, Kawakubo Y, Rzany B, et al. Low N-acetylating capacity in patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. Exp Dermatol. 1995;4: 313–16.
55. Hung SI, Chung WH, Liou LB, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. Proc Natl Acad Sci USA. 2005;102: 4134–9.
56. Chung WH, Hung SI, Hong HS, et al. Medical genetics: a marker for Stevens-Johnson syndrome. Nature. 2004;428:486.
56a. McCormack M, Alfirevic A, Bourgeois S, et al. HLA-A*3101 and carbamazepine hypersensitivity reactions in Europeans. N Engl J Med. 2011;364:1134–43.
57. Power WJ, Saidman SL, Zhang DS, et al. HLA typing in patients with ocular manifestations of Stevens-Johnson syndrome. Ophthalmology. 1996;103:1406–9.
58. Heng MC, Allen SG. Efficacy of cyclophosphamide in toxic epidermal necrolysis: clinical and pathophysiologic aspects. J Am Acad Dermatol. 1991;25:778–86.
59. Villada G, Roujeau JC, Clerici T, et al. Immunopathology of toxic epidermal necrolysis. Keratinocytes, HLA-DR expression, Langerhans cells, and mononuclear cells: an immunopathologic study of five cases. Arch Dermatol. 1992;128:50–3.
60. Correia O, Delgado L, Ramos JP, et al. Cutaneous T-cell recruitment in toxic epidermal necrolysis. Further evidence of CD8+ lymphocyte involvement. Arch Dermatol. 1993;129:466–8.
61. Friedmann PS, Strickland I, Pirmohamed M, et al. Investigation of mechanisms in toxic epidermal necrolysis induced by carbamazepine. Arch Dermatol. 1994;130:598–604.
62. Le Cleach L, Delaire S, Boumsell L, et al. Blister fluid T lymphocytes during toxic epidermal necrolysis are functional cytotoxic cells which express human natural killer (NK) inhibitory receptors. Clin Exp Immunol. 2000;119:225–30.
63. Nassif A, Bensussan A, Boumsell L, et al. Toxic epidermal necrolysis: effector cells are drug-specific cytotoxic T cells. J Allergy Clin Immunol. 2004;114:1209–15.
64. Viard I, Wehrli P, Bullani R, et al. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. Science. 1998;282:490–3.
65. Nassif A, Moslehi H, Le Gouvello S, et al. Evaluation of the potential role of cytokines in toxic epidermal necrolysis. J Invest Dermatol. 2004;123:850–5.
66. Paul C, Wolkenstein P, Adle H, et al. Apoptosis as a mechanism of keratinocyte death in toxic epidermal necrolysis. Br J Dermatol. 1996;134:710–14.
67. Wehrli P, Viard I, Bullani R, et al. Death receptors in cutaneous biology and disease. J Invest Dermatol. 2000;115:141–8.
68. Ito K, Hara H, Okada T, et al. Toxic epidermal necrolysis treated with low-dose intravenous immunoglobulin: immunohistochemical study of Fas and Fas-ligand expression. Clin Exp Dermatol. 2004;29:679–80.
69. Viard-Leveugle I, Bullani RR, Meda P, et al. Intracellular localization of keratinocyte Fas ligand explains lack of cytolytic activity under physiological conditions. J Biol Chem. 2003;278:16183–8.
70. Chung WH, Hung SI, Yang JY, et al. Granulysin is a key mediator for disseminated keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis. Nat Med. 2008;14:1343–50.
71. Lebargy F, Wolkenstein P, Gisselbrecht M, et al. Pulmonary complications in toxic epidermal necrolysis: a prospective clinical study. Intensive Care Med. 1997;23: 1237–44.
72. Bastuji-Garin S, Fouchard N, Bertocchi M, et al. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. J Invest Dermatol. 2000;115:149–53.
73. Trent JT, Kirsner RS, Romanelli P, Kerdel FA. Use of SCORTEN to accurately predict mortality in patients with toxic epidermal necrolysis in the United States. Arch Dermatol. 2004;140:890–2.
74. Amagai M, Matsuyoshi N, Wang ZH, et al. Toxin in bullous impetigo and staphylococcal scalded-skin syndrome targets desmoglein 1. Nat Med. 2000;6:1275–7.
75. Ting W, Stone MS, Racila D, et al. Toxic epidermal necrolysis-like acute cutaneous lupus erythematosus and the spectrum of the acute syndrome of apoptotic pan-epidermolysis (ASAP): a case report, concept review and proposal for new classification of lupus erythematosus vesiculobullous skin lesions. Lupus. 2004;13:941–50.
76. Fine JD. Management of acquired bullous skin diseases. N Engl J Med. 1995;333:1475–84.
77. Hewitt J, Ormerod AD. Toxic epidermal necrolysis treated with cyclosporin. Clin Exp Dermatol. 1992;17:264–5.
78. Arevalo JM, Lorente JA, Gonzalez-Herrada C, et al. Treatment of toxic epidermal necrolysis with cyclosporin A. J Trauma. 2000;48:473–8.
79. Trautmann A, Klein CE, Kampgen E, Brocker EB. Severe bullous drug reactions treated successfully with cyclophosphamide [letter]. Br J Dermatol. 1998; 139:1127–8.
80. Kamanbroo D, Schmitz-Landgraf W, Czarnetski BM. Plasmapheresis in severe drug-induced toxic epidermal necrolysis. Arch Dermatol. 1985;121:1548–9.
81. Redondo P, de Felipe I, de la Pena A, et al. Drug-induced hypersensitivity syndrome and toxic epidermal necrolysis. Treatment with N-acetylcysteine. Br J Dermatol. 1997;136:645–6.
82. Hunger RE, Hunziker T, Buettiker U, et al. Rapid resolution of toxic epidermal necrolysis with anti-TNF-alpha treatment. J Allergy Clin Immunol. 2005;116:923–4.
83. Gubinelli E, Canzona F, Tonanzi T, et al. Toxic epidermal necrolysis successfully treated with etanercept. J Dermatol. 2009;36:150–3.
84. Kelemen JJ 3rd, Cioffi WG, McManus WF, et al. Burn center care for patients with toxic epidermal necrolysis. J Am Coll Surg. 1995;180:273–8.
85. Kardaun SH, Jonkman MF. Dexamethasone pulse therapy for Stevens-Johnson syndrome/toxic epidermal necrolysis. Acta Derm Venereol. 2007;87:144–8.
86. Wolkenstein P, Latarjet J, Roujeau J-C, et al. Randomised comparison of thalidomide versus placebo in toxic epidermal necrolysis. Lancet. 1998;352:1586–9.
86a. Knaus WA, Zimmerman JE, Wagner DP, et al. APACHE – acute physiology and chronic health evaluation: a physiologically based classification system. Crit Care Med. 1981;9:591–7.
87. Prins C, Kerdel FA, Padilla RS, et al. Treatment of toxic epidermal necrolysis with high-dose intravenous immunoglobulins: multicenter retrospective analysis of 48 consecutive cases. Arch Dermatol. 2003;139:26–32.
88. Trent JT, Kirsner RS, Romanelli P, Kerdel FA. Analysis of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis using SCORTEN: The University of Miami Experience. Arch Dermatol. 2003;139:39–43.
89. Bachot N, Revuz J, Roujeau JC. Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis: a prospective noncomparative study showing no benefit on mortality or progression. Arch Dermatol. 2003;139:33–6.
90. Brown KM, Silver GM, Halerz M, et al. Toxic epidermal necrolysis: does immunoglobulin make a difference? J Burn Care Rehabil. 2004;25:81–8.
91. Trent JT, Ma F, Kerdel F, et al. Dose of intravenous immunoglobulin and patient survival in SJS and toxic epidermal necrolysis. Exp Rev Dermatol. 2007;2:299–303.

This page intentionally left blank

21 Drug Reactions

Jean Revuz and Laurence Valeyrie-Allanore

Key features

- The skin is one of the most common targets for adverse drug reactions
- To determine the cause of the eruption, a logical approach based on clinical characteristics, chronologic factors and a literature search is required
- Exanthematous eruptions and urticaria are the two most common forms of cutaneous drug reactions
- When an exanthematous eruption is associated with fever, lymphadenopathy, and/or edema of the face, the possibility of drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS) must be considered and an evaluation for systemic involvement conducted
- Less common drug reactions include fixed, lichenoid, pustular, photo-, bullous and vasculitic reactions, as well as Stevens–Johnson syndrome and toxic epidermal necrolysis
- Early withdrawal of all potentially responsible drugs is essential, particularly in the case of severe drug reactions

INTRODUCTION

The skin is one of the most common targets for adverse drug reactions[1]. Eruptions are observed in 0.1% to 1% of patients enrolled in premarketing trials of most systemic drugs. In the case of medications such as antibiotics (e.g. aminopenicillins, sulfonamides) and anticonvulsants, at least 1%, and sometimes more than 5%, of patients receiving these drugs may develop a skin eruption. Approximately 2% of all drug-induced skin reactions are considered "serious" according to the following World Health Organization (WHO) definition: "if it results in death, requires hospitalization or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, or is life-threatening". Toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS; also referred to as drug-induced hypersensitivity syndrome [DIHS]) are examples of such "serious reactions". Roujeau and Stern[2] estimated that 1 of every 1000 hospitalized patients has a serious cutaneous drug reaction. Prompt identification of severe cutaneous adverse reactions (SCARs) is an important goal, as it is a necessary step prior to discontinuing the offending agent and thus decreasing morbidity (Table 21.1).

It may be tempting to consider most eruptive cutaneous drug reactions, especially the severe ones, as various presentations of a "hypersensitivity syndrome". However, in order to begin to understand these entities, it is more useful to examine the specificity of the clinical, pathologic and biologic patterns, thus eventually allowing classification of each type of adverse cutaneous reaction as a single entity with a well-defined and specific mechanism[3].

This chapter focuses on adverse cutaneous reactions due to systemically administered medications. In addition, several specific types of drug reactions are discussed in other chapters (Table 21.2).

SEVERE CUTANEOUS ADVERSE REACTIONS (SCARs)
Anaphylaxis
Anticoagulant-induced skin necrosis
Acute generalized exanthematous pustulosis (AGEP)
Drug rash with eosinophilia and systemic symptoms (DRESS)/Drug-induced hypersensitivity syndrome (DIHS)
Generalized fixed drug eruption
Stevens–Johnson syndrome and toxic epidermal necrolysis

Table 21.1 Severe cutaneous adverse reactions (SCARs).

EPIDEMIOLOGY

Cutaneous reactions to drugs are responsible for approximately 3% of all disabling "injuries" that occur during hospitalization. In departments of dermatology, they represent 2% of consultations and approximately 5% of the admissions to an inpatient dermatology department. The incidence of fatalities due to drug reactions (systemic and cutaneous) among inpatients is between 0.1% and 0.3%[4].

Risk factors for developing an adverse drug reaction include an older age and female gender, and, as expected, the risk increases with the number of drugs taken by the patient. Paradoxically, the incidence of most immunologically mediated drug eruptions is increased in the setting of immunosuppression; e.g. in patients with AIDS ($CD4^+$ <200/mm^3), the risk of developing an exanthematous eruption to sulfamethoxazole is 10- to 50-fold greater than in the general population[5]. Whether an atopic diathesis acts as a risk factor remains debatable[6]. More recently, morbilliform drug reactions to hydroxychloroquine were observed more commonly in patients with dermatomyositis as compared to those with lupus erythematosus (LE).

ADDITIONAL REVIEWS OF SPECIFIC TYPES OF DRUG REACTIONS	
Psoriasiform	Chapters 8 and 128
Erythroderma	Table 10.3
Lichenoid	Table 11.2
Urticaria	Chapter 18
Stevens–Johnson syndrome and toxic epidermal necrolysis	Table 20.6
Warfarin- and heparin-induced necrosis	Chapter 23
Vasculitis	Table 24.3
Pemphigus and bullous pemphigoid	Chapters 29 & 30
Linear IgA bullous dermatosis	Table 31.5
Acneiform/folliculitis	Table 36.1
Hyper- and hypohidrosis	Tables 39.4 & 39.9
Lupus erythematosus (systemic and subacute cutaneous)	Chapter 41
Granulomatous (interstitial)	Table 45.5
Pseudoporphyria	Table 49.5
Hypopigmentation (skin and hair)	Tables 66.9 & 66.11
Hyperpigmentation and dyschromatosis	Tables 67.3 & 67.8
Nail abnormalities	Table 71.8
Gingival enlargement	Table 72.1
Phototoxic and photoallergic	Table 87.6
Cutaneous lymphoid hyperplasia (pseudolymphoma)	Table 121.1

Table 21.2 Additional reviews of specific types of drug reactions.

SKIN REACTIONS TO "DRUGS" RECEIVED BY AT LEAST 1000 PATIENTS	
Drugs	**Reaction rate (per 1000 recipients)**
Ampicillin	52
Penicillin G	16
Cephalosporins	13
Packed red blood cells	8.1
Heparin	7.7
Nitrazepam	6.3
Barbiturates	4.7
Chlordiazepoxide	4.2
Diazepam	3.8
Propoxyphene	3.4
Guaifenesin	2.9
Furosemide	2.6
Phytonadione	0.9
Flurazepam	0.5
Chloral hydrate	0.2

Table 21.3 Skin reactions to "drugs" received by at least 1000 patients[1].

DRUGS RECEIVED BY MORE THAN 1000 PATIENTS WITH NO SKIN REACTIONS (RATES ESTIMATED TO BE ≤3 PER 1000)
• Potassium chloride • Milk of magnesia • Digoxin • Meperidine hydrochloride • Dioctyl sodium sulfosuccinate • Magnesium hydroxide • Aluminum hydroxide • Acetaminophen • Multivitamins • Bisacodyl • Diphenhydramine hydrochloride • Aspirin • Aminophylline • Prochlorperazine • Ferrous sulfate • Thiamine • Prednisone • Atropine • Codeine • Vitamin B complex and ascorbic acid • Pentazocine • Hydrochlorothiazide* • Phosphate enema • Castor oil • Tetracycline* • Morphine • Regular insulin • Warfarin • Spironolactone
*Notably phototoxic reactions were not included.

Table 21.4 Drugs received by more than 1000 patients with no skin reactions (rates estimated to be ≤3 per 1000)[1].

The epidemiology of common adverse cutaneous drug reactions is still in its infancy. As a result, the incidence of drug reactions is difficult to establish precisely. Pre-marketing clinical trials, conducted before a new drug is licensed, include a limited number of patients, thus preventing a clear estimate of the true incidence. It is usually after several months or years of greater utilization that a more precise profile of the side effects of a newly released drug is established. Moreover, available information must be interpreted with caution, depending upon the method of data collection[1].

One preferred method of determining rates of cutaneous reactions to drugs is a prospective systematic survey such as the Boston Collaborative Drug Surveillance Program, which included 22 000 monitored patients[7]. This program allowed the potential risk of skin reactions to specific drugs to be determined (Tables 21.3 & 21.4). Reaction rates to commonly administered drugs have been confirmed by several prospective studies; however, the latter have been limited to inpatients[8]. In one series, adverse skin reactions occurred in 2.7% of 48 000 patients hospitalized over a 20-year period on a general internal medicine service; maculopapular exanthemas (91.2%), urticaria (5.9%) and vasculitis (1.4%) were the reactions most commonly observed. The primary responsible drugs were penicillins, sulfonamides and nonsteroidal anti-inflammatory drugs (NSAIDs).

Except for studies in hospitalized populations and those focusing on the most severe reactions, data regarding the incidence of cutaneous drug reactions in the general population are minimal, in part due to the absence of comprehensive post-marketing surveillance programs. In a retrospective cohort study from the Netherlands of 13 679 patients from general practices, the most frequently reported skin reactions to antimicrobials were due to trimethoprim–sulfamethoxazole (2.1% of users), fluoroquinolones (1.6%) and penicillins (1.1%).

PATHOGENESIS

Common eruptive cutaneous drug eruptions are hypersensitivity reactions with an underlying immunologic mechanism. Drugs or their metabolites may act as haptens, inducing a specific cell-mediated or humoral response. Cutaneous reactions also may arise as a result of non-immunologic mechanisms (Table 21.5). Some of these reactions are predictable given their relationship to the dose and/or the pharmacologic properties of the drug. However, the responsible pathophysiology may be difficult to identify simply on the basis of clinical appearance as the skin responds to a wide variety of stimuli through a limited number of morphologic reaction patterns. This may explain, at least in part, why the underlying mechanism of many cutaneous drug eruptions is still unknown.

Immunologically Mediated Drug Reactions

- *IgE-dependent drug reactions* (formerly type I, Gell–Coombs classification): urticaria, angioedema and anaphylaxis.
- *Cytotoxic drug-induced reactions* (antibody against a fixed antigen; formerly type II): petechiae secondary to drug-induced thrombocytopenia.
- *Immune complex-dependent drug reactions* (formerly type III): vasculitis, serum sickness and certain types of urticaria.
- *Possible delayed-type, cell-mediated drug reactions* (formerly type IV; sometimes not well defined): exanthematous, fixed and lichenoid drug eruptions, as well as Stevens–Johnson syndrome (SJS) and TEN.

The precise mechanisms have not yet been clearly defined for all of these reactions, and attempting to identify a unique mechanism for every drug eruption can certainly prove difficult. It has also become clear that the Gell–Coombs classification of immune reactions is an oversimplification when applied to drug reactions in which there is a mixture of humoral and cellular effectors. Also, additional types of reactions, e.g. granulomatous, acneiform, pseudolymphomatous, have been described.

Non-immunologic Mechanisms

Overdose

The clinical manifestations are predictable and represent an exaggeration of the drug's pharmacologic actions. It may occur as a consequence of a prescribing error or deliberate excess by the patient. In addition, drug overdoses can be observed in patients given the usual dose of a medication, but in whom there are differing rates of absorption, metabolism or excretion. An example would be methotrexate toxicity in elderly patients with reduced renal function.

MECHANISMS OF CUTANEOUS DRUG-INDUCED REACTIONS	
Immunologic mechanism (unpredictable)	• IgE-dependent drug reactions • Cytotoxic drug-induced reactions • Immune complex-dependent drug reactions • Cell-mediated reactions
Non-immunologic mechanisms (sometimes predictable)	• Overdose • Pharmacologic side effects • Cumulative toxicity • Delayed toxicity • Drug–drug interactions • Alterations in metabolism • Exacerbation of disease
Idiosyncratic with a possible immunologic mechanism (unpredictable)	• DRESS (DIHS) • TEN/SJS • Drug reactions in the setting of HIV infection • Drug-induced lupus erythematosus

Table 21.5 Mechanisms of cutaneous drug-induced reactions. DIHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

LOGICAL APPROACH TO DETERMINE THE CAUSE OF A DRUG ERUPTION	
DRUG RESPONSIBILITY ASSESSMENT	
Clinical characteristics	• Type of primary lesion (e.g. urticaria, erythematous papule, pustule, purpuric papule, vesicle or bulla) • Distribution and number of lesions • Mucous membrane involvement, facial edema • Associated signs and symptoms: fever, pruritus, lymph node enlargement, visceral involvement
Chronological factors	• Document all drugs to which the patient has been exposed (including OTC and complementary) and the dates of administration • Date of eruption • Time interval between drug introduction (or reintroduction) and skin eruption • Response to removal of the suspected agent • Consider excipients (e.g. soybean oil) • Response to rechallenge*
Literature search	• Bibliographic research (e.g. Medline) • Drug Alert Registry or Medwatch • Data collected by pharmaceutical companies • In the case of more recently released medications, extrapolation based on the class of drug and in particular the first drug released in the class
*Often inadvertent.	

Table 21.6 Logical approach to determine the cause of a drug eruption. OTC, over-the-counter.

Pharmacologic side effects

These reactions include undesirable or toxic effects that cannot be separated from the desired pharmacologic actions of the drug. For example, chemotherapeutic agents target rapidly dividing cells and their side effects include alopecia, mucositis and pancytopenia.

Cumulative toxicity

Prolonged exposure to a medication may lead to cumulative toxicity. For example, the accumulation of drugs such as silver, minocycline and amiodarone or their metabolites within the skin can lead to distinctive discoloration of the skin. Methotrexate can also lead to hepatic fibrosis.

Delayed toxicity

This corresponds to a toxic, dose-dependent effect that occurs months to years after the discontinuation of a medication. Examples would be arsenic and the development of squamous cell carcinomas and palmoplantar keratoses, or alkylating agents and acute leukemia.

Drug–drug interactions

Interactions between two or more drugs administered simultaneously may occur at several different steps: (1) intestinal drug interactions; (2) displacement from binding proteins or receptor sites; (3) enzyme stimulation or inhibition; and (4) altered drug excretion (see Ch. 131). Examples of each include the interactions between tetracycline and calcium, methotrexate and sulfonamides, cyclosporine and azoles, and methotrexate and probenecid, respectively.

Alterations in metabolism

Drugs may induce cutaneous changes by their effects on the nutritional or metabolic status of the patient. Bexarotene may induce severe hypertriglyceridemia and eruptive xanthomas, while isoniazid may be associated with pellagra-like changes.

Exacerbation of disease

A variety of drugs can exacerbate pre-existing dermatologic disease, such as androgens in patients with acne vulgaris or lithium and interferon in patients with psoriasis.

Idiosyncratic with Possible Immunologic Mediation

Idiosyncratic drug eruptions represent reactions that are unpredictable and cannot be explained on the basis of the pharmacologic properties of the drug. For several of these reactions, an immunologic mechanism is suspected and supporting evidence is available (see below). Reactive metabolites of drugs can bind covalently to proteins, and the altered protein, considered as foreign, then induces an immune response. However, the way in which a drug is metabolized into a reactive species (or fails to be metabolized) differs in nature and amount depending upon the patient's specific metabolic pathways. These variations are genetically influenced (see Ch. 131). Examples would be the increased incidences of the procainamide-induced systemic lupus syndrome and sulfonamide-induced TEN in slow acetylators as opposed to rapid acetylators. In addition, certain HLA alleles increase the risk of adverse drug reactions, e.g. the association of HLA-B*5701 with hypersensitivity reactions to abacavir and HLA–B*1502 with SJS/TEN in Han Chinese.

The pathophysiology of drug-induced skin reactions such as exanthematous drug eruptions, DRESS (DIHS), acute generalized exanthematous pustulosis (AGEP) and TEN, as well as the increased susceptibility of HIV-infected patients, may be partially explained by an interplay between immune mechanisms and genetic predisposition.

DIAGNOSTIC FEATURES

Drug eruptions, both suspected and unsuspected, are a frequent reason for consultation, and it is often (although not always) possible to categorize a drug as having a high, medium or low probability of being responsible. A logical approach begins with an accurate description of the skin lesions and their distribution as well as associated signs and symptoms (Table 21.6). Data regarding all the drugs taken by the patient, including prescription, non-prescription/over-the-counter and complementary or alternative treatments, as well as the dates of administration and doses need to be collected. The chronology of drug administration is of paramount importance (Table 21.7). The time between initiation of the drug and the onset of the skin eruption is a key element in identifying the offending drug, as most immunologically mediated reactions occur within 8 to 21 days after initiation of a new medication.

Evolution after drug withdrawal may be helpful, as the cutaneous eruption usually clears when the suspected drug is discontinued. However, this assessment may prove difficult in the case of drugs with a long half-life or "persistent" drug reactions such as lichenoid and photoallergic eruptions or drug-induced pemphigus foliaceus and subacute cutaneous LE.

The suspect drug should be withdrawn as soon as possible. The usual practice is to discontinue all drugs that are non-essential. However, in some instances, it is necessary to weigh the risks versus the benefits

CHARACTERISTICS OF MAJOR DRUG-INDUCED ERUPTIONS				
Clinical presentation	**Percentage that are drug-induced (%)**	**Time interval**	**Mortality (%)**	**Selected responsible drugs**
Exanthematous eruption	Child: 10–20 Adult: 50–70	4–14 days	0	Aminopenicillins Sulfonamides Cephalosporins Anticonvulsants Allopurinol
Urticaria	<10	Minutes to hours	0	Penicillins Cephalosporins NSAIDs Monoclonal antibodies Contrast media†
Anaphylaxis	30	Minutes to hours	5	
Fixed drug eruption	100	First exposure: 1–2 weeks Re-exposure: <48 hours, usually within 24 hours	0	TMP-SMX NSAIDs Tetracyclines Pseudoephedrine*
Acute generalized exanthematous pustulosis (AGEP)	70–90	< 4 days	1–2	β-Lactam antibiotics Macrolides Calcium channel blockers
Drug reaction with eosinophilia and systemic symptoms (DRESS)/ Drug-induced hypersensitivity syndrome (DIHS)	70–90	15–40 days	5–10	Anticonvulsants (aromatic) Sulfonamides Allopurinol Lamotrigine (especially in combination with valproate) Minocycline
Stevens-Johnson syndrome (SJS)	70–90	7–21 days	5	Sulfonamides Anticonvulsants (aromatic) Allopurinol NSAIDs Lamotrigine
Toxic epidermal necrolysis			30	

*Non-pigmenting.
†Often anaphylactoid reaction.

Table 21.7 Characteristics of major drug-induced eruptions. NSAIDs, nonsteroidal anti-inflammatory drugs; TMP-SMX, trimethoprim–sulfamethoxazole.

for each drug and to determine if a similar-acting, but non-cross-reactive, drug is available as a substitute.

In the process of identifying the responsible drug, access to drug databases is very helpful[9–11]. However, if application of these databases is too rigid, then a new or unusual drug reaction may not be identified. Moreover, the drug most frequently associated with adverse reactions may be innocent in a particular patient, and the physician dealing with a suspected drug reaction must remain open-minded.

With the exception of assays for IgE antibodies, diagnostic or confirmatory tests to establish the responsible drug are not available. A number of *in vitro* tests have been designed, including the migration inhibition factor test, the lymphocyte toxicity assay, the lymphocyte transformation test and the basophil degranulation test[12]. However, their sensitivity and specificity have not been assessed in a reliable way with relevant controls. As a result, they are of little help in the clinical setting.

Patch testing has been used in the diagnosis of the anticonvulsant-associated drug hypersensitivity syndrome, but with inconsistent results[13]. Barbaud et al.[14] emphasized the importance of delayed readings of prick, intradermal and patch tests in amoxicillin-induced morbilliform eruptions. Unfortunately, investigations involving series of patients with several different types of drug reactions have shown heterogeneous results. Of note, cutaneous patch tests with the offending agent are frequently positive (80% of patients) after recovery from AGEP, but are positive in only a minority of cases of SJS or TEN[15]. In general, these tests, when positive, may be helpful in preventing readministration of the offending drug, but except for patch tests in AGEP, their specificity and sensitivity are low.

Rechallenge carries the risk of inducing a more severe reaction, thus limiting its use for both ethical and medico-legal reasons. Furthermore, the recurrence rate is not 100% with rechallenge (e.g. there are refractory periods) and a negative result may give an erroneous sense of security. Even with these limitations, in patients with fixed drug eruptions, topical provocation or rechallenge may prove helpful.

CLINICAL FEATURES

Exanthematous Drug Eruptions

Synonyms: ■ Morbilliform drug eruption ■ Maculopapular drug eruption ■ Urticarial drug eruption

Exanthematous or morbilliform eruptions are the most common adverse drug reactions affecting the skin. They are often referred to as maculopapular drug eruptions or, in the case of non-dermatologists, "drug rashes".

The major underlying mechanism is probably immunologic, and they are often considered to be cell-mediated hypersensitivity reactions. However, the pathophysiology is likely to be more complex. The drug hapten presented by dendritic cells to T lymphocytes can bind covalently or non-covalently to MHC II–peptide complexes[16]. $CD4^+$ and $CD8^+$ T cells, strongly expressing perforin and granzyme, are recruited. Both cell types have cytotoxic activity leading to death of keratinocytes. Certain drugs such as sulfamethoxazole may actually bind directly to the MHC–peptide complex and T-cell receptor in a non-covalent way[17,18]. Furthermore, viral infections may increase the incidence of drug reactions, e.g. aminopenicillin-induced exanthematous eruptions in patients with infectious mononucleosis is close to 100% (see Ch. 80). One theory is that reactive drug metabolites disturb the balance between cytotoxic and regulatory phenomena, allowing cytotoxicity against virally infected cutaneous cells[19].

The cutaneous eruption classically begins 7 to 14 days after the start of a new medication and can even occur a few days after the drug has been discontinued. However, the eruption may develop sooner, especially in cases of inadvertent rechallenge. The lesions begin as erythematous macules in a symmetric distribution that sometimes become slightly palpable. The eruption begins on the trunk and upper

extremities and progressively becomes confluent (Fig. 21.1A). It is typically polymorphous with morbilliform or sometimes urticarial lesions on the limbs, confluent areas on the thorax (Fig. 21.1B), and purpuric lesions on the ankles and feet. Mucous membranes are usually spared. Pruritus and low-grade fever are often present. On the trunk, the eruption may appear scarlatiniform. Annular plaques (Fig. 21.1C) or atypical, irregularly-shaped "target" lesions may be present, leading to the misdiagnosis, and therefore overdiagnosis, of erythema multiforme. The eruption disappears spontaneously after 1, sometimes 2, weeks, without complications and/or sequelae.

Clinical features that can alert the clinician to the possibility of a more severe drug-induced eruption include edema of the face or a marked peripheral blood hypereosinophilia (suggestive of DRESS [DIHS]) and mucous membrane lesions or painful or dusky skin, which may announce TEN or SJS. Histologic examination of morbilliform eruptions is not particularly helpful, as it shows nonspecific changes consisting of a mild superficial perivascular and interstitial lymphocytic infiltrate; eosinophils may be present (~30% of cases) as well as interface changes (~50% of cases)[20].

The major entity in the differential diagnosis of morbilliform drug reactions is a viral exanthem (e.g. Epstein-Barr virus, enteroviruses, adenovirus, early HIV, human herpesvirus type 6 [HHV-6], parvovirus B19), which is often indistinguishable (see Fig. 81.2). The polymorphic nature of the cutaneous eruption as well as the presence of peripheral blood eosinophilia favor a drug reaction. In the absence of definite evidence, a drug etiology is favored in adults, whereas a viral cause is favored in the pediatric population. Moreover, viral infections may enhance the risk of a drug eruption (see above)[19]. Toxic shock syndromes, scarlet fever, acute GVHD, Kawasaki disease and Still's disease should be excluded on the basis of associated clinical features.

Treatment is largely supportive. Topical antipruritics and corticosteroids may help to alleviate pruritus. Discontinuing the offending agent is the first therapeutic measure. "Treating through", i.e. continuing the drug despite the cutaneous eruption, can be considered when the suspected drug is of paramount importance for the patient and there is no satisfactory substitute drug. Usually, the eruption will disappear, but a few patients may experience a progressive worsening, leading to erythroderma. Whether continuation of the drug can lead to SJS is debatable. Early morbilliform lesions and early target lesions often have a similar appearance and the possibility exists that although the eruptions appear to be "leaving the same station", they may be on different tracks from the beginning. Another approach which has been used successfully in HIV-infected patients requiring sulfonamides is desensitization.

Many drugs induce an exanthematous eruption in approximately 1% of patients. However, the following classes of drugs have a significantly higher incidence: aminopenicillins, sulfonamides, cephalosporins and anticonvulsants.

Fig. 21.1 Exanthematous drug eruptions. Numerous pink papules on the trunk due to a cephalosporin (**A**). Confluence of lesions on the trunk (**B**) and annular plaques on the forehead (**C**) secondary to phenobarbital.

Urticaria, Angioedema and Anaphylaxis (see Ch. 18)

Several different mechanisms may be responsible, with dramatic outbreaks of acute urticaria usually representing an immediate hypersensitivity reaction mediated by IgE antibodies, especially when the urticaria is associated with angioedema and/or anaphylaxis. This type of anaphylactic reaction is frequently due to penicillin and occurs within minutes of the drug exposure. "Anaphylactoid" reactions may mimic IgE-induced histamine release, but are secondary to a non-immunologic liberation of histamine and/or other mediators of inflammation. Clinically, it can be difficult to distinguish between anaphylaxis and an anaphylactoid reaction.

Urticaria

Urticaria is characterized by transient erythematous and edematous papules and plaques that are usually associated with pruritus. Central pallor can be seen as in the wheal-and-flare reaction to histamine. The lesions vary in size and number and may assume a figurate or polycyclic configuration (Fig. 21.2). They can appear anywhere on the body, including the palms, soles or scalp.

The duration of an individual lesion is usually a few hours to 24 hours; when the urticaria resolves, the skin is normal in appearance. Urticarias are considered "acute" when they last for less than 6 weeks and "chronic" when they persist for longer periods of time. Although drugs are thought to be responsible for <10% of all cases of urticaria,

Fig. 21.2 Urticaria secondary to penicillin. Several of the lesions have a figurate appearance.

CUTANEOUS SIDE EFFECTS OF INSULIN INJECTIONS
Immediate hypersensitivity
Local reaction (erythema, pruritus)
Urticaria, angioedema
Anaphylaxis (rare)
Delayed hypersensitivity
Reaction at injection sites (erythema, induration)
Morbilliform eruption (rare)
Acute generalized exanthematous pustulosis (AGEP) (rare)
Exfoliative dermatitis (rare)
Lipodystrophy
Lipoatrophy (occurs less frequently with rapidly absorbed analogue insulins, e.g. insulin lispro)
Lipohypertrophy

Table 21.8 Cutaneous side effects of insulin injections. Use of an insulin pump also carries the risk of scarring and abscess formation.

they are more often associated with acute rather than chronic urticaria. Nonetheless, any evaluation of a patient with chronic urticaria should include a review of all medications. Patients with chronic urticaria should avoid acetylsalicylic acid (ASA; aspirin), as well as other NSAIDs, as they can lead to an exacerbation.

Immunologic assays, e.g. radioallergosorbent tests (RAST), for the detection of specific IgE antibodies and skin tests (prick tests) can be useful in confirming the diagnosis. However, the number of drugs for which there are commercially available assays is limited, consisting primarily of penicillin, aminopenicillin, cephalosporin and insulin (Table 21.8). Because prick tests can occasionally induce an anaphylactic reaction, they must be performed with caution in an appropriate clinical setting. Clinicians will often withhold medications based on patients' self-reports, but in sone series, only 10% to 20% of patients reporting a history of penicillin allergy were truly allergic when assessed by skin testing[21]. Thus, patients with a compelling need for penicillin who have a history of an immediate type (IgE-mediated) reaction to penicillin should undergo skin testing.

A number of drugs can induce acute urticaria, with lesions appearing within minutes to days of drug administration, depending upon whether there has been prior sensitization (immediate versus accelerated) and whether the mechanism is immunologic or non-immunologic. The major drugs responsible for immunologically based urticaria are antibiotics, especially penicillins and cephalosporins, and, less often, sulfonamides and tetracyclines (in particular minocycline). As the use of monoclonal antibodies for neoplastic and inflammatory diseases increases, so will cases of urticaria (and vasculitis; see below) due to these exogenous proteins (see Ch. 128). Acetylsalicylic acid is the classic example of a drug that induces an anaphylactoid reaction; the majority of urticarial reactions to radiocontrast media are non-immunologic (Table 21.9), as are many, but not all, reactions to NSAIDs (e.g. ibuprofen, naproxen). Allergic reactions to latex in gloves or medical devices can induce local or generalized urticaria, especially in the case of direct contact with mucosal surfaces (see Chs 16 & 18).

ADVERSE REACTIONS TO RADIOCONTRAST MEDIA
IODINATED
Immediate (<1 hour)
Urticaria (usually non-immunologic), angioedema
Anaphylactoid reaction
Delayed (1 hour to 1 week)
Morbilliform eruption
Acute generalized exanthematous pustulosis (AGEP)
Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE)
Iododerma (also >1 week)
GADOLINIUM
Urticaria, erythema (rare)
Anaphylactoid reactions, anaphylaxis (rare)
Nephrogenic systemic fibrosis (in the setting of renal insufficiency; see Ch. 43)

Table 21.9 Adverse reactions to radiocontrast media.

The most important step in the treatment of drug-induced urticaria is withdrawal of the causative agent. Treatment consists primarily of H_1 antihistamines. Additional therapeutic options are discussed in Chapter 18.

Of note, the clinical differential diagnosis of urticaria includes urticarial lesions due to vasculitis and/or serum sickness. In the latter disorders, there is antigen–antibody formation with deposition of immune complexes within postcapillary venules. This leads to activation of the complement cascade with liberation of vasoactive amines and proinflammatory cytokines that increase vascular permeability and attract polymorphonuclear cells (see Ch. 24), resulting in the histologic features of leukocytoclastic vasculitis. These immune complexes may also induce the formation of anaphylatoxins which trigger the direct release of mediators from mast cells and basophils, leading to urticaria as well as the clinical and pathologic features of serum sickness.

Angioedema

Angioedema is a reflection of transient edema of the deep dermal, subcutaneous and submucosal tissues. It is associated with urticaria in 50% of cases and may be complicated by life-threatening anaphylaxis. Angioedema occurs in 1 to 2 per 1000 new users of angiotensin-converting enzyme (ACE) inhibitors, a rate that is probably higher than the risk associated with penicillin[22]. The most severe cases of angioedema may start within a few minutes after drug administration. However, in the case of ACE inhibitor-induced angioedema, lesions may appear from 1 day to several years after starting the drug; most appear within the first year. African-Americans and those with a history of idiopathic angioedema are at increased risk for developing ACE inhibitor-induced angioedema.

The clinical picture of angioedema is that of an acute pale or pink subcutaneous swelling, usually of the face (eyelids, lips, ears, nose), and less often of the extremities or genitalia. The areas of involvement are frequently unilateral or asymmetric. Involvement of the larynx, epiglottis and surrounding tissues may impair swallowing and lead to upper airway obstruction (stridor). Edema of the oropharynx (including the buccal mucosa and tongue) can also occur. Occasionally, in drug-induced angioedema, there is edema of the intestinal wall with abdominal pain, nausea, vomiting and diarrhea.

The major drugs implicated in angioedema, besides penicillins and ACE inhibitors, are NSAIDs, radiographic contrast media and, more recently, monoclonal antibodies (see Ch. 128). It is important to note that drug-induced angioedema may actually represent an unmasking of another cause for angioedema, e.g. acquired C1 inhibitor deficiency due to autoimmune or lymphoproliferative disorders. In patients with ACE inhibitor-induced angioedema, substituting angiotensin II receptor

antagonists may not be the answer, even though the antagonists represent a different class of drugs which do not increase levels of bradykinin (see Fig. 18.6). The receptor antagonists are also associated with angioedema, albeit less frequently.

Anaphylaxis

Anaphylaxis consists of an acute life-threatening reaction that can result from exposure to a number of drugs. It occurs in about 1 per 5000 exposures to penicillin and combines skin (urticaria and/or angioedema) with systemic manifestations such as hypotension and tachycardia. Occasionally, there is hypotension in the absence of cutaneous lesions. In severe cases, the patient becomes unconscious as a result of cardiovascular shock and may die. Serious cases of anaphylactic shock tend to appear shortly (within minutes) after drug administration and are more commonly seen with parenteral administration as compared to oral ingestion.

Prompt discontinuation of the offending drug is mandatory, as is strict avoidance of the drug in the future. Patients who have serious angioedema or an anaphylactic reaction should be hospitalized and monitored. Systemic corticosteroids are often prescribed, and, in cases of life-threatening angioedema or anaphylaxis, subcutaneous epinephrine (adrenaline). Patients who have been receiving β-blockers may have a stunted response to the epinephrine.

Antibiotics, in particular penicillin, are the major causes of drug-induced anaphylaxis. Anaphylaxis can also be seen following exposure to latex (see Ch. 16) and anaphylactoid reactions are seen with radiographic contrast media. Rarely, anaphylaxis occurs following cutaneous injections (e.g. local anesthetics) or topical applications of medications (e.g. bacitracin, chlorhexidine).

Photosensitivity (see Ch. 87)

Cutaneous photosensitivity disorders may be idiopathic, due to endogenous photosensitizers (e.g. porphyrins), or result from exogenous photosensitizers (e.g. medications). The combination of light plus drug can lead to several forms of cutaneous inflammation. The photosensitivity drug reactions are classically divided into two major types: phototoxic and photoallergic[23]. The former is more common than the latter.

Phototoxicity

Phototoxic reactions are fairly common and usually predictable. They can occur in any person who receives a sufficient amount of a phototoxic drug together with sufficient exposure to ultraviolet radiation (UVR). There is a direct interaction of the UVR with the drug (or its metabolite) in the skin such that an unstable singlet or triplet state is created, leading to the generation of reactive oxygen species. The latter are responsible for cellular damage.

Clinically, a phototoxic drug reaction usually has the appearance of an exaggerated sunburn (Fig. 21.3), but after a shorter-than-expected exposure time. It is limited to sun-exposed areas and is followed by hyperpigmentation. Histologically, phototoxicity is characterized by necrotic keratinocytes, edema, a sparse dermal lymphocytic infiltrate and vasodilation.

Photo-onycholysis and pseudoporphyria are less common clinical presentations. In the former, the nail plate separates from the nail bed of several digits, with minimal nail bed changes. Fragility, erosions and vesicles of the dorsal hands and face are observed in pseudoporphyria, but plasma porphyrins are normal (see Ch. 49).

The drugs most commonly responsible contain ringed structures and include the tetracyclines (particularly doxycycline and demeclocycline), the NSAIDs (especially propionic acid derivatives) and the fluoroquinolones. Additional drugs that can produce phototoxic reactions include amiodarone, psoralens and phenothiazines (see Table 87.6). In the case of pseudoporphyria, the most likely culprit is naproxen (see Table 49.5).

For drugs with a short half-life, administration of the drug in the evening may be enough to decrease the risk below the clinical threshold for phototoxicity.

Photoallergy

Photoallergic reactions occur as a result of cell-mediated hypersensitivity to an allergen activated or produced by the effect of light on a drug (or its metabolite). UVR is required to convert the drug into an immunologically active compound (photoallergen) that induces the immune response. These reactions are idiosyncratic and can be maintained in the absence of excessive sun exposure.

Fig. 21.3 Phototoxic reaction in a patient receiving methotrexate. The erythema and bullae are obviously limited to sun-exposed sites and resemble an exaggerated sunburn. Patients on methotrexate can also experience a "sunburn-recall" phenomenon.

Fig. 21.4 Photolichenoid drug eruption due to hydrochlorothiazide. The lesions favored the extensor surfaces of the forearms.

Photoallergic eruptions are more chronic in nature than phototoxic reactions. Clinically, the lesions are pruritic and resemble dermatitis or lichen planus (Fig. 21.4; see Ch. 11), but are primarily in sun-exposed sites. Over time, lesions may spread to non-sun-exposed areas. The associated pruritus can lead to superimposed lichenification. Chronic exposure to photoallergic drugs can, in an occasional patient, lead to extreme photosensitivity that persists for months to even years after the responsible drug is eliminated. These patients then fall within the spectrum of chronic actinic dermatitis (see Ch. 87). Phototesting can be useful in the clinical evaluation.

Several classes of drugs are commonly associated with photoallergic reactions; they include thiazide diuretics, sulfonamide antibiotics, sulfonylureas and phenothiazines, all of which contain a sulfur moiety (Fig. 21.5). Additional medications that have been reported as photoallergens include quinine, quinidine, tricyclic antidepressants, antimalarials and NSAIDs.

In photoallergic reactions, drug withdrawal is recommended, given the risk of exacerbation even with relatively low-dose exposures to UVR plus the risk of chronicity. Topical corticosteroids, physical barriers, reduced sun exposure, and broad-spectrum sunscreens may prove useful.

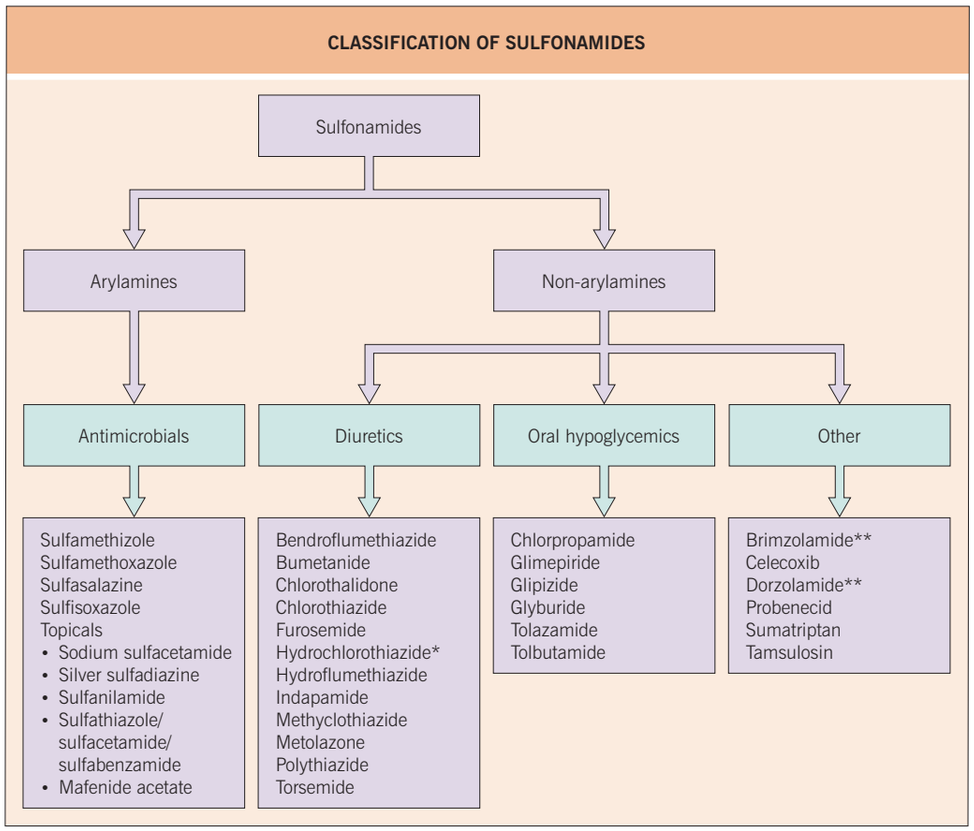


Fig. 21.5 Classification of sulfonamides. *Often combined with other antihypertensives, e.g. triamterene, angiotensin-converting enzyme inhibitors, β-blockers. Approximately 10% of the patients with a history of a drug reaction to antimicrobial sulfonamides will also react to the non-arylamine sulfonamides. However, this is thought to be a reflection of a predisposition to allergic reactions rather than cross-reactivity. **Eyedrops.

Vasculitis (see Ch. 24)

Although many cases of cutaneous small vessel vasculitis (CSVV) are idiopathic, secondary causes such as infections, autoimmune connective tissue diseases, and drugs (~10% of cases) need to be considered. Drug-induced vasculitis typically involves small vessels (but can involve medium-sized vessels) and is thought to be triggered by deposition of immune complexes.

Clinically, drug-induced CSVV usually presents as purpuric papules, primarily on the lower extremities. Urticaria-like lesions, hemorrhagic blisters, pustules, digital necrosis and ulcers may also be seen. Systemic involvement is very unusual, but suggestive symptoms are fever, myalgias, arthralgias and/or headache. Internal manifestations include arthritis, nephritis, peripheral neuropathy and gastrointestinal bleeding. Histopathologic examination of early lesions should be performed.

Vasculitis usually occurs 7 to 21 days after drug administration and less than 3 days following rechallenge. Systemic corticosteroids may benefit patients with systemic involvement; otherwise, they are not indicated. Additional management options are discussed in Chapter 24.

The primary medications associated with drug-induced CSVV include penicillins, NSAIDs (both oral and topical), sulfonamides and cephalosporins; additional drugs are propylthiouracil, thiazide diuretics, furosemide, allopurinol, phenytoin, fluoroquinolones and biologic agents (e.g. granulocyte and granulocyte–macrophage colony-stimulating factors [G-CSF, GM-CSF], interferons). ANCA-positive vasculitis with anti-myeloperoxidase antibodies has been associated with several drugs, including propylthiouracil, hydralazine and minocycline, and polyarteritis nodosa has been observed following hepatitis B vaccination[24].

Neutrophilic Drug Eruptions

Acute generalized exanthematous pustulosis

Synonyms: ■ Pustular drug eruption ■ Toxic pustuloderma

Acute generalized exanthematous pustulosis (AGEP) is an acute febrile drug eruption characterized by numerous small, primarily non-follicular, sterile pustules, arising within large areas of edematous erythema[25]. The incidence of AGEP has been underestimated and many cases have been confused with pustular psoriasis. More than 90% of cases of AGEP are drug-induced[26]. Occasionally, it may be due to other causes, e.g. an enteroviral infection or exposure to mercury.

HLA-B5, -DR11 and -DQ3 have been found more frequently in patients with AGEP[27]. A prior sensitization (including a contact sensitization) would explain the short interval (<4 days) between drug administration and the onset of the eruption, as this suggests an immunologic recall phenomenon. The percentage of positive patch tests to the incriminated drugs is high (up to 80%) (Fig. 21.6A)[15,28]. Blood neutrophilia and the accumulation of neutrophils within the lesions suggest the release of neutrophil-activating cytokines by drug-specific T lymphocytes (e.g. IL-3, IL-8, G-CSF), but the precise underlying mechanisms of AGEP are still unknown.

Clinically, AGEP is characterized by a high fever, with lesions beginning on the face or in the major intertriginous zones (i.e. axillae and groin) and then disseminating over a few hours. Numerous small (<5 mm), non-follicular, sterile pustules arise within large areas of edematous erythema (Fig. 21.6B,C). There may be associated burning or pruritus or both. Edema of the face and hands, purpura, vesicles, bullae, erythema multiforme-like lesions and mucous membrane involvement are additional findings observed in approximately 50% of patients[26]. The lesions last 1 to 2 weeks and are followed by a superficial desquamation.

Histologically, spongiform pustules are seen within the most superficial layers of the epidermis, beneath the stratum corneum (Fig. 21.6D). Edema of the papillary dermis and a perivascular mixed infiltrate with neutrophils and some eosinophils are usually present. CSVV and necrotic keratinocytes are unusual findings. A marked leukocytosis with an elevated neutrophil count is frequently seen. Additional laboratory abnormalities include mild to moderate eosinophilia, transient renal dysfunction, and hypocalcemia.

AGEP must be differentiated from acute pustular psoriasis of the von Zumbusch type. The pustules are clinically indistinguishable, but additional skin lesions such as petechiae, purpura, atypical target-like lesions and vesicles are more frequently observed in AGEP. Histologically, massive edema in the superficial dermis, exocytosis of

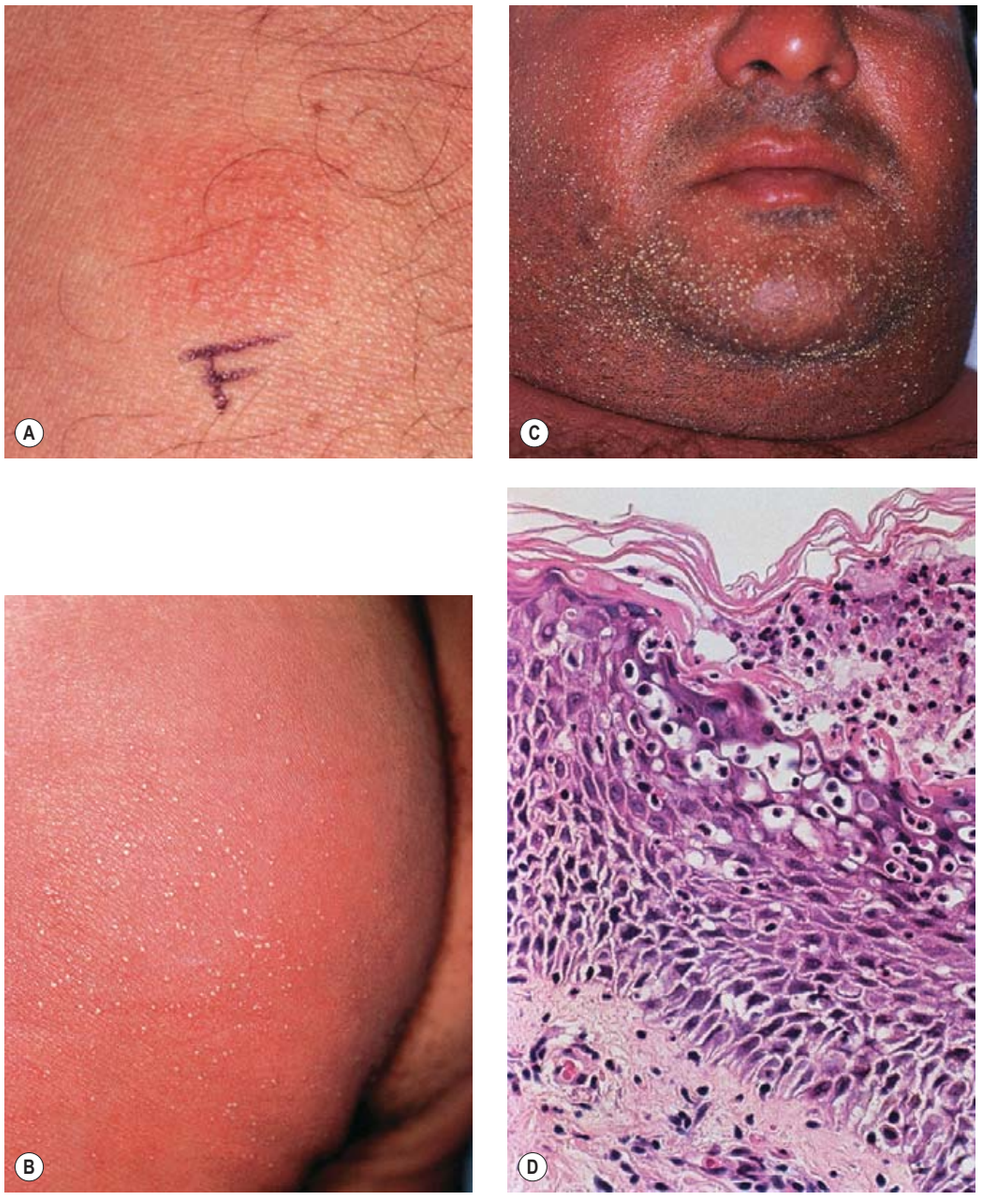


Fig. 21.6 Acute generalized exanthematous pustulosis (AGEP). A A positive patch test result 4 days following the application of 0.75% metronidazole in a patient with a previous pustular drug eruption to that medication. Diffuse erythema of the buttock (due to cephalosporin, **B**) and face (due to metronidazole, **C**) studded with sterile pustules. Spongiform pustules are seen within the epidermis of lesional skin (**D**). *A & C, Courtesy, Kalman Watsky, MD.*

eosinophils, vasculitis, and necrosis of keratinocytes are all suggestive of AGEP, whereas acanthosis is more characteristic of pustular psoriasis. The two major differences are the acuteness of the disease and the history of drug exposure in AGEP. However, AGEP may occur more frequently in patients with a history of psoriasis, thus making the distinction even more difficult.

Common exanthematous drug eruptions may have a few pustules, but they are usually follicular. In severe forms of AGEP, the confluence of the pustules may lead to confusion with TEN. However, the presence of subcorneal pustules in biopsy specimens allows one to distinguish between the two entities. In addition to facial edema, pustules may also be observed in DRESS (DIHS), but the prolonged evolution, atypical lymphocytosis, marked hypereosinophilia, and visceral involvement usually permit differentiation.

Antibiotics are the primary drugs implicated in AGEP. Beta-lactam antibiotics (e.g. penicillins, aminopenicillins, cephalosporins) and macrolides are the most frequently responsible medications[29], followed by calcium channel blockers (in particular diltiazem) and antimalarials. Additional cases have been associated with carbamazepine, acetaminophen (paracetamol) and a wide range of antimicrobials (e.g. terbinafine, metronidazole, isoniazid, vancomycin, doxycycline). As recognition of this clinical entity has increased, so has the number of implicated drugs. Both a literature search and an open mind are required in the evaluation of a patient with AGEP, as this eruption has been associated with ingestion of lacquer chicken and chromic picolinate as well as exposure to icodextrin during peritoneal dialysis. The withdrawal of the responsible drug is the main treatment, in conjunction with topical corticosteroids and antipyretics.

Sweet's syndrome (acute febrile neutrophilic dermatosis)

(see Ch. 26)

Since a limited number of cases of Sweet's syndrome have been reported as drug reactions, they probably represent <5% of all cases. This syndrome is characterized by fever, peripheral blood neutrophilia, and painful erythematous plaques that favor the face and upper extremities and contain dense neutrophilic dermal infiltrates. There are also reports of the lesions being limited to a lymphedematous extremity. In drug-induced Sweet's syndrome, neutrophilia is often absent, probably due to the fact that a number of these cases are related to the use of hematopoietic growth factors to reverse chemotherapy-induced neutropenia. The lesions of drug-induced Sweet's syndrome usually develop about a week after the onset of drug administration[30]. Although the differential diagnosis includes malignancy-associated Sweet's syndrome, it would be very unlikely for malignancies to recur 2–3 weeks post appropriate chemotherapy.

After withdrawal of the responsible drug, the fever abates in 1 to 3 days and the lesions disappear within 3 to 30 days[31]. Systemic corticosteroids may be required in severe cases. The major drugs associated

with drug-induced Sweet's syndrome are: (1) all-*trans*-retinoic acid; and (2) G-CSF or GM-CSF, which facilitate the differentiation and the proliferation of neutrophils, respectively[32]. Neutrophilic infiltrates can be seen elsewhere, including the muscles and lung. Additional cases attributed to trimethoprim–sulfamethoxazole[30], norfloxacin, furosemide, celecoxib and tetracyclines have been reported.

Halogenoderma

Bromoderma, fluoroderma and iododerma are rare dermatoses that develop following exposure to bromides, fluorides, iodides and iodine-containing compounds. The latter two groups are used as radiation protectants, in combination therapy for hyperthyroidism, and as expectorants (saturated solution of potassium iodide; SSKI). Dermatologists are familiar with SSKI as a treatment for erythema nodosum (see Ch. 100) and sporotrichosis. Systemic exposure to iodine-containing contrast media, irrigation of wounds with povidone-iodine, ingestion of iodide-containing supplements and the use of amiodarone are additional causes of iododerma. Bromides act as sedatives, and, outside the US, potassium bromide is sometimes prescribed for the treatment of seizures.

Some authors have suggested that halogenodermas represent hypersensitivity reactions. However, accumulation of the halogenide does seem to be an important factor. For example, one risk factor for the development of these reactions is acute or chronic renal failure.

Halogens may induce acneiform eruptions and pustules, and, less commonly, granulomatous or vegetative plaques, ulcers and even bullae (Fig. 21.7). Although cutaneous lesions often appear after long-term exposure, they can appear in as quickly as a few days. Histologically, an accumulation of neutrophils within the dermis is seen and exocytosis of neutrophils into the epidermis can lead to intraepidermal abscesses. In longer-standing lesions, papillomatosis develops.

Bromodermas and iododermas must be differentiated from folliculitis, dimorphic fungal infections (e.g. blastomycosis), pyoderma gangrenosum, Sweet's syndrome, blastomycosis-like pyoderma, and pemphigus vegetans. Histologic evaluation and measurement of blood levels of iodine (40–92 mcg/l = normal range) and bromide (5–10 mg/dl = normal range) aid in establishing the diagnosis. Halogenodermas may persist for weeks after drug withdrawal because of the slow elimination rate of iodides and bromides. Topical and systemic corticosteroids, in addition to diuretics, may hasten resolution, and, in severe cases, cyclosporine may be administered.

Other neutrophilic eruptions

Neutrophilic eccrine hidradenitis is characterized by erythematous papules and plaques due to neutrophilic infiltrates around and within eccrine glands (Fig. 21.8). It is most commonly seen in patients with acute myelogenous leukemia receiving cytarabine and less often in those receiving other chemotherapeutic agents (e.g. bleomycin, anthracyclines, methotrexate, cyclophosphamide). G-CSF can also induce lesions of neutrophilic eccrine hidradenitis, as can acetaminophen. Neutrophilic eccrine hidradenitis can also precede acute and chronic myelogenous leukemia, and, occasionally, it has been observed in conjunction with infections due to Gram-negative bacilli, streptococci, staphylococci and HIV.

In patients with chemotherapy-induced neutropenia, neutrophils may be absent from the biopsy specimens, so an alternative name, "chemotherapy-induced eccrine hidradenitis", has been suggested. Neutrophilic eccrine hidradenitis may reflect a toxic insult to eccrine glands and ducts and it can be a histologic finding, along with eccrine squamous syringometaplasia, in patients with toxic erythema of chemotherapy. Of note, neutrophilic eccrine hidradenitis can be seen in sites of bleomycin injections.

Drug-induced pyoderma gangrenosum is quite rare. There are scattered case reports linking pyoderma gangrenosum with G-CSF, GM-CSF and isotretinoin; questionable associations exist for methotrexate, azathioprine and hydralazine.

Drug Reaction with Eosinophilia and Systemic Symptoms (Drug-Induced Hypersensitivity Syndrome)

The acronym DRESS, for *d*rug *r*eaction with *e*osinophilia and *s*ystemic *s*ymptoms, has been advocated as a more specific term for what was previously referred to as systemic hypersensitivity syndrome[2,33]. More recently, another acronym has been proposed, DIHS, which stands for *d*rug-*i*nduced *h*ypersensitivity *s*yndrome. To aid in the diagnosis of this disorder, a scoring system has been put forth (Table 21.10)[34].

The underlying mechanisms probably include a specific alteration in the metabolism of particular drugs; for example, a defect in the detoxification of anticonvulsants and sulfonamides has been demonstrated in patients recovering from DRESS (DIHS). For anticonvulsants, the inability to detoxify toxic arene oxide metabolites is probably a key factor; cross-reactivity between phenytoin, carbamazepine and phenobarbital is well documented, both *in vivo* and *in vitro*[35]. Risk factors for developing DRESS (DIHS) secondary to sulfonamides include acetylator phenotype and the susceptibility of the patient's lymphocytes to the toxic metabolite hydroxylamine.

Immune mechanisms are also implicated: IL-5, released by activated T lymphocytes, contributes to the generation of eosinophilia, a key feature of this syndrome[36]. A possible role for viruses such as HHV-6 and HHV-7 in the pathogenesis of DRESS (DIHS) has been proposed[37–39]. Increased titers of antiviral antibodies and active viral replication have been observed, pointing to a potential role for the viral infection. However, this could just represent nonspecific activation of a ubiquitous virus.

Fig. 21.7 Iododerma. Edematous erythematous vesicopustules on the buttocks with central crusts.

Fig. 21.8 Neutrophilic eccrine hidradenitis. Erythematous plaques on the leg, which may be confused with Sweet's syndrome.

DIAGNOSTIC SCORING SYSTEM FOR DRESS/DIHS			
Criteria	**No**	**Yes**	**Unknown/ unclassifiable**
Fever (≥ 38.5°C)	–1	0	–1
Lymphadenopathy (≥ 2 sites; > 1 cm)	0	1	0
Circulating atypical lymphocytes	0	1	0
Peripheral hypereosinophilia	0		0
0.7–1.499 × 10^9/L - *or* - 10–19.9%*		1	
≥ 1.5 × 10^9/L - *or* - ≥ 20%*		2	
Skin involvement			
– Extent of cutaneous eruption > 50% BSA	0	1	0
– Cutaneous eruption suggestive of DRESS**	–1	1	0
– Biopsy suggests DRESS	–1	0	0
Internal organs involved†	0		0
One		1	
Two or more		2	
Resolution in ≥ 15 days	–1	0	–1
Laboratory results negative for at least three of the following (and none positive): (1) ANA; (2) blood cultures; (3) HAV/HBV/ HCV serology; and (4) *Chlamydia* and *Mycoplasma* serology	0	1	0
Final score: < 2, no case; 2–3, possible case; 4–5, probable case; >5, definite case			

*If leukocytes < 4.0 x 10^9/L

**At least two of the following: edema, infiltration, purpura and scaling.

†Liver, kidney, lung, muscle/heart, pancreas, or other organ and after exclusion of other explanations.

Table 21.10 Diagnostic scoring system for DRESS (drug reaction with eosinophilia and systemic symptoms)/DIHS (drug-induced hypersensitivity syndrome. Proposed by the RegiSCAR-group[34]. ANA, antinuclear antibody; BSA, body surface area; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

Fig. 21.9 Drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS). Multiple edematous papules are present. *Courtesy, Kenneth Greer, MD.*

The incidence of DRESS (DIHS) has been estimated to be between 1 in 1000 and 1 in 10 000 exposures to drugs such as anticonvulsants (e.g. phenytoin, carbamazepine, phenobarbital) and sulfonamides. The incidence may be higher in African-Americans and patients from the Caribbean basin. In Northern European populations, the presence of the HLA-A*3101 allele significantly increases the risk of developing carbamazepine-induced hypersensitivity syndrome[39a].

Clinically, this hypersensitivity syndrome develops 2 to 6 weeks after drug initiation, later than most other immunologically mediated skin reactions. Fever and a cutaneous eruption are the most common symptoms, seen in 85% and 75% of patients, respectively. Cutaneous involvement usually begins as a morbilliform eruption, which later becomes edematous, often with a follicular accentuation. Additional manifestations include vesicles, tense bullae induced by dermal edema, follicular as well as non-follicular pustules, erythroderma and purpuric lesions. The face, upper trunk and extremities are usually the initial sites of involvement (Fig. 21.9). Edema of the face is a frequent finding and is a hallmark of DRESS (DIHS).

Lymph nodes are often enlarged, and sometimes arthralgias or even arthritis may be seen. The most common (and usually the most severe) site of visceral involvement is the liver. The hepatitis is sometimes fulminant and is responsible for the majority of deaths associated with this syndrome (~10% of cases). Myocarditis, interstitial pneumonitis, interstitial nephritis, thyroiditis and even infiltration of the brain by eosinophils may be observed. In the case of DRESS (DIHS) due to allopurinol, gastrointestinal bleeding can occur. The cutaneous and visceral involvement may persist for several weeks or months after drug withdrawal, and additional sites of involvement (e.g. cardiac) may develop weeks or months later, including following a taper of corticosteroids.

Prominent eosinophilia is common and is a very characteristic feature. It is often accompanied by mononucleosis-like atypical lymphocytosis. Elevation of hepatic enzymes can be a worrisome finding and requires serial evaluation. Evidence of thyroid or cardiac dysfunction (as detected by an echocardiogram) are additional abnormalities in some patients. Histologic examination of the skin demonstrates a mild to dense lymphocytic infiltrate in the superficial dermis associated with eosinophils and dermal edema. If the rash persists, the dermal infiltrate may become quite dense, as in pseudolymphoma.

The differential diagnosis includes other cutaneous drug eruptions, acute viral infections, hypereosinophilic syndrome, lymphoma and pseudolymphoma[37,38]. Involvement of multiple viscera differentiates DRESS (DIHS) from the more common morbilliform eruptions. Serum sickness-like reactions and drug-induced vasculitis are usually easily differentiated from DRESS (DIHS).

In addition to the most common etiologies – the aromatic anticonvulsants (phenobarbital, carbamazepine and phenytoin), lamotrigine (especially when co-administered with valproate) and the sulfonamides – minocycline, allopurinol (in particular, full doses in the setting of renal dysfunction), gold salts and dapsone may also induce this syndrome, as well as drugs used to treat HIV infection, e.g. abacavir. Early withdrawal of the offending drug is, of course, mandatory, but may not be sufficient for obtaining a rapid full recovery. Corticosteroids represent the first line of therapy. In milder cases, topical high-potency corticosteroids may be helpful. Systemic corticosteroids are recommended for life-threatening involvement of the lung and heart because the inflammation is responsive to corticosteroids. The latter are not particularly useful for reversing kidney and/or liver disease. Relapse can occur when the dosage is tapered, and, as a result, steroid therapy sometimes has to be maintained for several weeks and even months.

Bullous Eruptions

Fixed drug eruption

In fixed drug eruptions (FDE), the lesions develop 1 to 2 weeks after a first exposure. With subsequent exposures, they appear within 24 hours. Clinically, one or a few, round, sharply demarcated erythematous and edematous plaques are seen (Fig. 21.10A), sometimes with a dusky, violaceous hue, central blister or detached epidermis (Fig. 21.10B,C). The lesions can be found anywhere on the body, but favor the lips, face, hands, feet and genitalia. An erosion may develop centrally (Fig. 21.10D,E) and the lesions progressively fade over several days, often leaving a residual postinflammatory brown pigmentation (Fig. 21.10F). Upon readministration of the causative drug, the lesions recur at exactly the same sites. With each recurrence, additional sites of involvement may appear or the number of lesions may remain constant. The

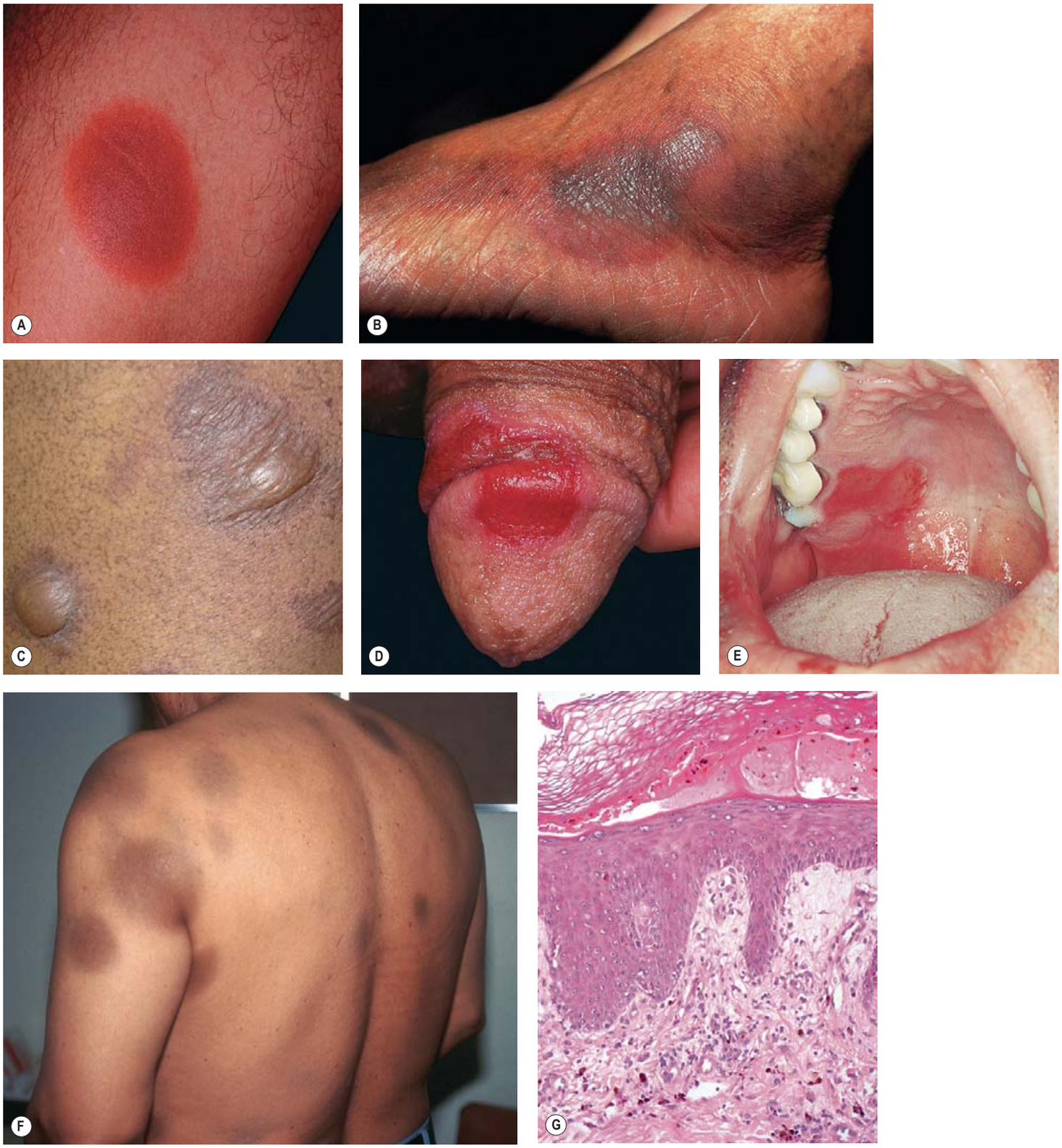


Fig. 21.10 Fixed drug eruptions. Well-demarcated erythematous (**A**) to violet–brown plaques that can develop a detached epidermis (**B**), bulla (**C**) or erosion (**D,E**) centrally. As lesions heal, circular or oval areas of hyperpigmentation are commonly seen (**F**). Histologically, serous crust, a few necrotic keratinocytes, mild vacuolar changes at the dermal–epidermal junction, papillary dermal edema and melanophages can be seen as well as a mononuclear infiltrate (**G**). Responsible drugs were phenolphthalein (**A**), naproxen (**B**), ciprofloxacin (**D**), allopurinol (**E**) and trimethoprim–sulfamethoxazole (**F**). *D & E, Courtesy, Kalman Watsky, MD. F, Courtesy, Mary Stone, MD.*

presence of numerous lesions is referred to as generalized FDE, and it may be difficult to distinguish from erythema multiforme or SJS (when the oral mucosa is also involved).

A non-pigmenting variant of FDE, with large erythematous edematous plaques has also been described, occurring primarily after administration of pseudoephedrine. It has been also observed with other drugs, e.g. NSAIDs, acetaminophen, tetrahydrozoline (eyedrops). Linear FDE is a rare variant and could be confused with linear lichen planus.

Histopathology reveals a superficial and deep interstitial and perivascular infiltrate within the dermis, composed of lymphocytes, eosinophils and sometimes neutrophils. There may be necrotic keratinocytes in the epidermis (Fig. 21.10G). Dermal melanophages are often the only histologic finding in non-inflammatory lesions.

The drugs most frequently associated with FDE are sulfonamides (in some series, up to 75% of cases), NSAIDs (in particular, phenazone derivatives), barbiturates, tetracyclines and carbamazepine[40,41]. Phenolphthalein-induced FDE is seen less commonly because it has been removed from a number of laxative preparations. Sometimes, the inducing drug can be readministered without exacerbation, and there may be a refractory period after the occurrence of a fixed eruption. Provocation via patch testing in a previously *involved* site may be useful in determining the responsible drug (as long as not performed during the refractory period).

When there is a single lesion, the differential diagnosis includes a spider or arthropod bite reaction, and when there are many lesions, erythema multiforme or SJS. On the genitalia, herpes simplex viral infections are often considered and a periungual lesion can be mistaken for paronychia.

Linear IgA bullous dermatosis

Linear IgA bullous dermatosis is an autoantibody-mediated subepidermal blistering disease that may be associated with drug exposure. Tense vesicles and bullae appear 24 hours to 15 days after the offending medication is begun. The blisters often have an annular configuration, as in the idiopathic version of the disease (see Ch. 31), but there are reports of a TEN-like presentation. Histologic examination shows subepidermal bullae with neutrophils in the dermis. Direct immunofluorescence reveals linear deposition of IgA in the basement membrane zone, within the lamina lucida or rarely below the lamina densa. Most patients lack circulating IgA autoantibodies[42]. Resolution follows within 2 to 5 weeks of discontinuation of the responsible medication. The major implicated drugs are vancomycin[43], followed by β-lactam antibiotics, captopril, NSAIDs, phenytoin, rifampin, sulfonamides, amiodarone, furosemide, lithium and G-CSF (see Table 31.5).

Drug-induced bullous pemphigoid

Drug-induced bullous pemphigoid can resemble the "classic" form of this autoimmune disorder, (see Ch. 30) or the cutaneous lesions may have an erythema multiforme-like appearance. Responsible drugs include furosemide, penicillin and its derivatives, and sulfasalazine. Because the histologic and direct immunofluorescence findings are similar to those observed in bullous pemphigoid, it is the clinician who has to consider the diagnosis of drug-induced disease, especially in younger patients (<60 years of age). The differential diagnosis also includes the inflammatory form of epidermolysis bullosa acquisita and erythema multiforme.

Drug-induced pemphigus

Drug-induced pemphigus is an autoimmune blistering disease whose exact pathogenesis is unknown, but appears to be multifactorial. The binding of an active thiol (sulfhydryl) group of a drug to the desmosomal antigen complex could act as a hapten and induce a humoral immune response directed against the desmosomes. The latter then results in acantholysis and intraepidermal blisters.

The clinical, histologic and immunofluorescent microscopy findings in drug-induced pemphigus are similar to those in the spontaneous form of the disease, except that direct immunofluorescence of perilesional skin is positive in only 90% of cases[44]. Circulating antidesmoglein autoantibodies are found in 70% of patients.

In developed countries, up to 10% of cases of pemphigus could be drug-induced. Lesions characteristic of pemphigus foliaceus or pemphigus vulgaris appear several weeks or months after the responsible drug is begun. Approximately 80% of cases are due to drugs that contain a thiol group, such as penicillamine, ACE inhibitors (e.g. captopril), gold sodium thiomalate and pyritinol. Non-thiol drugs include antibiotics (especially β-lactams), pyrazolone derivatives, nifedipine, propranolol, piroxicam and phenobarbital. A spontaneous remission after drug withdrawal is not always observed, especially in patients whose pemphigus is due to drugs that do not contain a thiol moiety.

Stevens–Johnson syndrome and toxic epidermal necrolysis (see Ch. 20)

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are considered rare, life-threatening, drug-induced skin reactions within a clinical spectrum (Fig. 21.11)[45] and early detection is essential.

Fig. 21.11 Stevens–Johnson syndrome. Flaccid bullae leading to epidermal detachment (<10% body surface area). Note the resemblance to wet cigarette paper.

SYMMETRICAL DRUG-RELATED INTERTRIGINOUS AND FLEXURAL EXANTHEMA (SDRIFE) – CLINICAL CRITERIA
• Exposure to a *systemically* administered drug*, occurring with either the initial or a repeated dose (excluding contact allergens)
• Sharply demarcated erythema of the gluteal/perianal area and/or V-shaped erythema of the inguinal/perigenital area
• Involvement of at least one other intertriginous site/flexural fold
• Symmetry of affected areas
• Absence of systemic symptoms and signs
*Not a chemotherapeutic agent so as to not confuse with toxic erythema of chemotherapy.

Table 21.11 Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) – clinical criteria. This entity is also referred to as drug-induced intertrigo, flexural drug eruption and baboon syndrome. The latter term is also used to describe a form of systemic contact dermatitis.
Adapted from Häusermann P, Harr Th, Bircher AJ. Baboon syndrome resulting from systemic drugs: is there strife between SDRIFE and allergic contact dermatitis syndrome? Contact Derm 2004;51:297–310.

An interesting phenomenon is the markedly increased incidence of TEN in individuals with AIDS[46]. Three explanations have been proposed: (1) an increased number of drugs are given to AIDS patients; (2) the HIV infection itself is responsible; and (3) the paradoxical increase (in the setting of immunodeficiency) is due to an alteration in the balance between $CD4^+$ and $CD8^+$ T lymphocytes.

These diseases are discussed in detail in Chapter 20.

Other Drug-Induced Cutaneous Reactions

Symmetrical drug-related intertriginous and flexural exanthema

In symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), sharply demarcated, symmetrical areas of erythema develop in the anogenital region following exposure to a systemically administered drug, usually an aminopenicillin or cephalosporin and less often other antibiotics or contrast media (Table 21.11). Typically, there is involvement of at least one other flexural site. Confusion arises because some patients with systemic contact dermatitis may have erythema of the buttocks and upper inner thighs, with both the latter clinical presentation – as well as SDRIFE – sometimes referred to as baboon syndrome. The differential diagnosis also includes toxic erythema of chemotherapy due to drugs such as intravenous busulfan, but the history of chemotherapy administration 2–4 weeks earlier is usually easily obtained.

Pseudolymphoma (see Ch. 121)

Synonym: ▪ Cutaneous lymphoid hyperplasia

Fig. 21.12 Heparin-induced thrombocytopenia with thrombosis syndrome. **A** Ischemia and necrosis of the foot. **B** Petechiae due to thrombocytopenia and an irregular area of cutaneous necrosis due to thrombosis. *A, Courtesy, Kalman Watsky, MD. B, Courtesy, Jean L Bolognia, MD.*

DRUG-INDUCED ALOPECIA	
Telogen phase	– **Anticoagulants:** heparin > warfarin – Anticonvulsants: carbamazepine, valproic acid, phenytoin, lamotrigine – Antidepressants: imipramine, desipramine, maprotiline, fluoxetine – Antihypertensive agents: • **β-blockers:** timolol, acebutolol, propanolol • ACE inhibitors: captopril, enalapril, ramipril • Diuretics: spironolactone – Antimicrobials: terbinafine, gentamicin, thiamphenicol, fluconazole – Antithyroid drugs: carbimazole, thiouracils – Colchicine – **Interferons** – Lipid-lowering agents: clofibrate, cholestyramine – **Lithium** – NSAIDs: piroxicam, naproxen, indomethacin, ibuprofen – Oral contraceptives (discontinuation) – **Retinoids** – Others: allopurinol, cimetidine, L-dopa, amphetamines, pyridostigmine, bromocriptine, buspirone
Anagen phase	– Antineoplastic agents (see Table 21.13) – Others: arsenic, bismuth, gold, thallium

Table 21.12 Drug-induced alopecia. The more commonly incriminated medications are in bold. ACE, angiotensin-converting enzyme.

Fig. 21.13 Serum sickness due to antithymocyte globulin. The purpuric lesions are due to small vessel vasculitis in this patient with aplastic anemia. *Courtesy, Jean L Bolognia, MD.*

Drug-induced pseudolymphoma represents an insidious disease which simulates lymphoma clinically and histologically[47]. It has a benign biological behavior and does not satisfy the criteria for non-Hodgkin lymphoma. Although this disorder was originally thought to represent a hypersensitivity reaction, current evidence indicates that the responsible drugs may depress immunologic functions and impair immunosurveillance, leading to an abnormal proliferation of lymphocytes, increased T-cell activity and hypogammaglobulinemia.

Pseudolymphoma develops months or even years after the incriminated drug is begun. The cutaneous lesions may be solitary or multiple, localized or widespread, and consist of erythematous to violet papules, plaques or nodules. Numerous generalized tumors are rare. An erythroderma simulating Sézary syndrome has also been described[48]. There is often associated lymphadenopathy, but it may be an isolated finding[33].

Histologically, a dense lymphocytic infiltrate is seen within the dermis that can mimic a T- or B-cell lymphoma. In some patients, the lymphocytic infiltrate is band-like, resembling mycosis fungoides. Atypical nuclei with a cerebriform outline and epidermotropism may also be observed. The lymphocytes are predominantly T cells and are polyclonal in most cases. In the lymph nodes, focal necrosis and eosinophilic and histiocytic infiltrates may destroy the normal architecture. Atypical lymphoid hyperplasia may also be observed.

Complete recovery occurs within a few weeks after withdrawal of the responsible drug. The majority of drug-induced pseudolymphomas have been reported with anticonvulsants (phenytoin, phenobarbital, carbamazepine), antipsychotics (chlorpromazine, promethazine), imatinib mesylate, and angiotensin II receptor antagonists (see Table 121.1).

Granulomatous reactions

There are granulomatous drug reactions that can mimic interstitial granulomatous dermatitis and granuloma annulare and they are discussed in Chapter 45. In addition, sarcoidal reactions can be seen in patients with hepatitis C viral infections receiving interferon-α and ribavirin.

Anticoagulant-induced skin necrosis

Anticoagulant-induced skin necrosis is a rare, sometimes life-threatening reaction induced by warfarin (Coumadin®) or heparin. Lesions of warfarin necrosis typically begin 2 to 5 days after therapy is initiated and coincide with the expected early drop in protein C function (see Ch. 23).

Clinically, erythematous painful plaques evolve into hemorrhagic blisters and necrotic ulcers as a consequence of ischemic infarcts. The latter are due to occlusive thrombi within blood vessels of the skin and subcutaneous tissue[2]. The most common sites of involvement are the breasts, thighs and buttocks. One in every 10 000 individuals who receives warfarin will develop this phenomenon and those with hereditary deficiency of protein C are at highest risk. Therapy includes discontinuing warfarin and administering vitamin K, heparin (as the anticoagulant), and intravenous infusions of protein C concentrate. Warfarin necrosis should not be confused with anticoagulant-induced cholesterol emboli, which, despite the name "warfarin blue toe syndrome", is not restricted to this medication.

MUCOCUTANEOUS SIDE EFFECTS OF CHEMOTHERAPEUTIC AGENTS	
Reactions	**Responsible drugs**
Alopecia, reversible	Alkylating agents: cyclophosphamide, ifosfamide, mechlorethamine Anthracyclines: daunorubicin, doxorubicin, idarubicin Taxanes: paclitaxel, docetaxel Topoisomerase 1 inhibitors: topotecan, irinotecan Etoposide, vincristine, vinblastine, busulfan, actinomycin D, gemcitabine
Alopecia, irreversible	Busulfan
Mucositis	Daunorubicin, doxorubicin, high-dose methotrexate, high-dose melphalan, topotecan, cyclophosphamide, taxanes, continuous infusions of 5-fluorouracil (5-FU) and prodrugs of 5-FU
Extravasation reactions (e.g. chemical cellulitis, ulceration)	Anthracyclines, carmustines, 5-fluorouracil, vinblastine, vincristine, mitomycin C
Chemotherapy recall (tender sterile inflammatory nodules at sites of previous chemotherapy extravasation or administration)	5-fluorouracil, mitomycin C, paclitaxel, doxorubicin, epirubicin
Hyperpigmentation (see Ch. 67)	Alkylating agents: busulfan, cyclophosphamide, cisplatin, mechlorethamine Antimetabolites: 5-fluorouracil (5-FU), capecitabine (5-FU prodrug), methotrexate, hydroxyurea Antibiotics: bleomycin, doxorubicin
Serpentine supravenous hyperpigmentation	5-Fluorouracil, doxorubicin, docetaxel, vinorelbine
Mucosal hyperpigmentation	Busulfan, 5-fluorouracil, hydroxyurea, cyclophosphamide
Nail hyperpigmentation	5-Fluorouracil, cyclophosphamide, daunorubicin, doxorubicin, hydroxyurea, methotrexate, bleomycin
Onycholysis	Paclitaxel, docetaxel
Radiation recall	Methotrexate, doxorubicin, daunorubicin, taxanes (e.g. paclitaxel, docetaxel), dacarbazine, melphalan, capecitabine, gemcitabine, cytarabine, pemetrexed
Radiation enhancement	Doxorubicin, hydroxyurea, taxanes, 5-fluorouracil, etoposide, gemcitabine, methotrexate
Photosensitivity	5-Fluorouracil (5-FU) and 5-FU prodrugs (e.g. capecitabine, tegafur), methotrexate, hydroxyurea, dacarbazine, mitomycin C, docetaxel
Inflammation of "keratoses"	*Actinic keratoses*: 5-fluorouracil (5-FU) and 5-FU prodrugs (e.g. capecitabine), pentostatin *Seborrheic keratoses*: cytarabine, taxanes *Disseminated superficial actinic porokeratosis*: 5-fluorouracil (5-FU) and 5-FU prodrugs, taxanes
Toxic erythema of chemotherapy: – Acral erythema (erythrodysesthesia) – Eccrine squamous syringometaplasia – Pseudocellulitis Neutrophilic eccrine hidradenitis	 Cytarabine, anthracyclines, 5-fluorouracil (5-FU) and 5-FU prodrugs, taxanes, methotrexate, busulfan, cisplatin Cytarabine, busulfan, cyclophosphamide, carmustine, taxanes Gemcitabine, clofarabine Cytarabine, bleomycin, anthracyclines, cyclophosphamide, cisplatin, topotecan
Ulcerations	Hydroxyurea (lower extremities)
Nodulosis	Methotrexate (but usually in patients with rheumatoid arthritis)
Flushing	Asparaginase, high-dose BCNU, mithramycin
Others:	*Urticaria*: asparaginase, bleomycin, chlorambucil, cyclophosphamide, daunorubicin *Exanthematous eruption*: bleomycin, carboplatin, cytarabine, methotrexate, liposomal doxorubicin, paclitaxel, cladribine, gemcitabine, pemetrexed, bortezomib *SJS/TEN*: bleomycin, busulfan, cyclophosphamide, doxorubicin, etoposide, methotrexate, docetaxel *Cutaneous vasculitis*: gemcitabine, busulfan, cyclophosphamide, hydroxyurea, levamisole, pemetrexed *Dermatomyositis-like eruption*: hydroxyurea *Pseudoscleroderma tous reaction (especially extremities)*: paclitaxel, gemcitabine *Palmoplantar hyperkeratosis*: capecitabine, tegafur *Acquired cutaneous adherence*: doxorubicin (plus ketoconazole)

Table 21.13 Mucocutaneous side effects of chemotherapeutic agents. The mucocutaneous side effects of kinase inhibitors and blocking antibodies are reviewed in Table 21.14. Cutaneous squamous cell carcinomas are most commonly associated with fludarabine, hydroxyurea, and topical BCNU. SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

Heparin-induced cutaneous necrosis is due to antibodies that bind to complexes of heparin and platelet factor 4 and induce platelet aggregation and consumption (see Ch. 23). Platelet counts are usually depressed, but, unless the baseline platelet count is known, this may not be appreciated. In addition to relative thrombocytopenia, heparin can induce thrombosis and cutaneous necrosis, both at the site of injection and at distant sites (Fig. 21.12) as well as in internal organs (e.g. CNS). This is sometimes referred to as heparin-induced thrombocytopenia with thrombosis syndrome. Discontinuation of the heparin and administration of anticoagulants, such as argatroban, danaparoid or lepirudin, is recommended.

Serum sickness-like eruption

This syndrome is more commonly observed in children and typically includes fever, arthralgias, arthritis, a rash (urticarial, morbilliform) and lymphadenopathy[2,3]. It occurs 1 to 3 weeks after drug exposure. Unlike in "true" serum sickness due to non-human proteins (e.g. antithymocyte globulin, tositumomab, infliximab; Fig. 21.13), hypocomplementemia, circulating immune complexes, vasculitis and renal disease are absent. This reaction occurs in approximately 1 in 2000 children given cefaclor. Other drugs associated with serum sickness-like reactions are penicillins, NSAIDs, bupropion, phenytoin, sulfonamides, minocycline and propranolol.

Drug-induced lupus

There are several theories regarding the pathogenesis of drug-induced lupus. Reactive drug metabolites interacting with nuclear histones could act as haptens and activate the complement cascade. As an example, procainamide-induced systemic LE occurs more frequently in patients who are slow acetylators as compared to rapid acetylators.

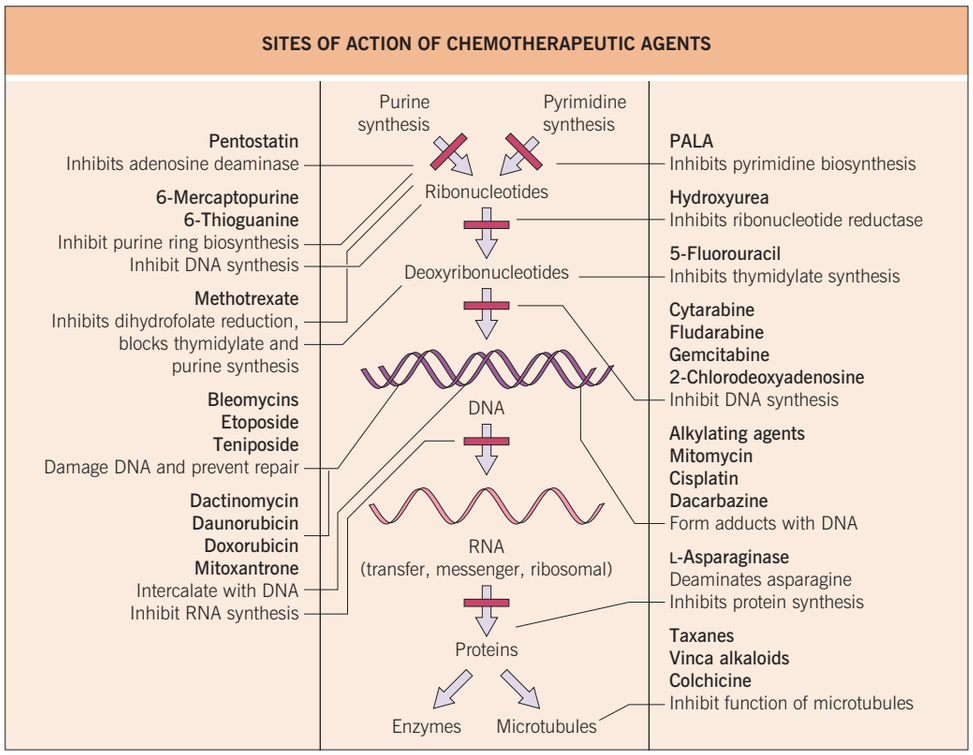


Fig. 21.14 Sites of action of chemotherapeutic agents. PALA, N-phosphonoacetyl-<H>L-aspartate; TMP, thymidine monophosphate. *Modified with permission from Brunton L, Lazo J, Parker K (eds.). Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th edn. New York: McGraw-Hill Medical, 2005.*

Drug-induced *systemic* LE is associated with fever, weight loss, pericarditis and pleuro-pulmonary inflammation; it has no gender predilection. Cutaneous involvement is rare, but includes a malar erythema, photoeruptions, and discoid or erythema multiforme-like lesions. Vasculitis and renal or neurologic involvement are also rare. The symptoms usually develop more than a year after the medication was initiated.

Drug-induced systemic LE is characterized by the presence of antihistone antibodies in up to 95% of cases, but these antibodies are not specific and may be seen in patients with idiopathic systemic LE. Antibodies against double-stranded DNA are typically absent. The seroconversion from negativity to positivity for antinuclear antibodies alone is not sufficient to discontinue a particular medication. However, if symptoms develop, the offending drug should be withdrawn. The clinical symptoms usually resolve within 4 to 6 weeks, but positivity for antinuclear antibodies may persist for 6 to 12 months. Responsible drugs include procainamide and hydralazine, followed by chlorpromazine, isoniazid, methyldopa, propylthiouracil, quinidine, practolol, D-penicillamine, and PUVA. Minocycline's association with this disorder is well described, but patients may not have antihistone antibodies[49]. Several patients with drug-induced lupus attributed to minocycline have had antineutrophil cytoplasmic antibodies, which may be directed against myeloperoxidase or elastase.

Drug-induced *subacute cutaneous* LE presents with psoriasiform and annular lesions, usually of the upper trunk and extensor surfaces of the arms, that are clinically and histologically indistinguishable from those seen in the idiopathic form of the disease (see Ch. 41). Anti-Ro/SSA and anti-La/SSB antibodies can be present. Responsible drugs include hydrochlorothiazide, calcium channel blockers, terbinafine, NSAIDs, griseofulvin, docetaxel, PUVA and interferon. Resolution of the eruption may or may not occur after discontinuation of the responsible drug.

In the case of TNF-α inhibitors, antinuclear and anti-DNA antibodies can develop (see Ch. 128) and patients may develop cutaneous lesions of chronic (discoid), subacute and acute cutaneous LE.

Mucosal ulceration

Stomatitis with erosions and ulcerations may occur either as part of a drug-induced mucocutaneous syndrome (e.g. fixed drug eruption, pemphigus, TEN) or as a direct side effect. Agents used for immunosuppression or as chemotherapy are the major drugs associated with the development of stomatitis, including methotrexate, doxorubicin and 5-fluorouracil (see below)[50]. Severe ulcerative stomatitis has also been observed with metamizole, phenylbutazone, oxyphenbutazone, D-penicillamine and gold therapy, sometimes in the setting of drug-induced neutropenia and agranulocytosis. Allergic reactions to dental materials and exposure to metals such as mercuric chloride or copper sulfate may cause stomatitis.

In a prospective study of 100 patients treated with nicorandil, a potassium channel activator, five individuals developed chronic buccal ulcerations with severe dysphagia, whereas none were observed in the 100 control patients. This side effect may be seen in up to 14% of patients treated with this drug[51]. A more recent review of the literature on drug-induced mucosal ulcerations identified eight different compounds as "plausible" causes: niflumic acid (topical use), captopril, nicorandil, phenindione, piroxicam, gold salts, phenobarbital and sodium hypochlorite (topical antiseptic). Penile ulceration can also be observed secondarily to contact toxicity by secreted drugs such as foscarnet.

Drug-induced hair loss and hair growth

A considerable number of medications have been reported to induce hair loss[52]. They affect the hair follicles via two major mechanisms: anagen effluvium and telogen effluvium. In the former, hair loss occurs within 2 to 3 weeks of drug administration, whereas in telogen effluvium, the delay is usually 2 to 4 months. Clinically, both are classified as diffuse non-scarring alopecias (see Ch. 69). The prevalence and severity of drug-induced alopecia depend upon the drug as well as an individual's predisposition, and the hair loss is usually reversible after discontinuation of the responsible agent. Diagnosis of drug-induced telogen effluvium can be difficult, as confirmation requires an appreciation of an improvement after the suspected drug has been withdrawn. Table 21.12 lists a number of the drugs associated with alopecia, including β-blockers, lithium, retinoids and heparin.

With regard to drug-induced hair growth, it is important to distinguish between hypertrichosis and hirsutism. The associated medications for both entities are discussed in Chapter 70.

Reactions to chemotherapy

Chemotherapeutic agents may induce local or systemic skin toxicity. There is a wide range of cutaneous manifestations of chemotherapy,

Fig. 21.15 Cutaneous side effects of chemotherapeutic agents. A Ulceration due to extravasation of doxorubicin. **B** Horizontal melanonychia due to 5-fluorouracil. **C** Erythema of the ears due to cytarabine (cytosine arabinoside), sometimes referred to as "Ara-C ears"; the petechiae are due to thrombocytopenia. **D** Toxic erythema of chemotherapy due to cytarabine, with obvious acral erythema involving the plantar surface. **E** Inflammation surrounding a seborrheic keratosis in a patient receiving paclitaxel. **F** Necrosis of psoriatic plaques due to an "overdose" of methotrexate. **G** Raynaud's phenomenon and digital necrosis due to systemic bleomycin. *B–F, Courtesy, Jean L Bolognia, MD.*

from benign to life-threatening[50] (Table 21.13), as well as a wide diversity of drugs used to treat neoplastic disease (Fig. 21.14).

Alopecia

One of the most common adverse reactions to chemotherapy is alopecia due to anagen effluvium in which there is an abrupt cessation of mitotic activity. The alopecia involves primarily the scalp hairs, but other sites may be affected, such as the eyebrows and axillary and pubic regions. The hair loss is almost always reversible, and the severity of alopecia depends primarily upon the specific drugs administered. Occasionally, patients with straight hair will develop curly hair when it regrows.

Stomatitis

Mucositis of the oral and gastrointestinal mucosae is a major, often dose-limiting, cause of morbidity in patients receiving chemotherapy. Stomatitis occurs in approximately 40% of patients, and there are two possible underlying mechanisms:

- Direct drug-induced cytotoxic effects on the oral epithelial cells, which have a high mitotic index. Mucosal involvement appears 4 to 7 days after the drugs are administered, and the erythematous, edematous and ulcerated oral mucosa produces symptoms of pain, burning and xerostomia. Spontaneous healing is observed within 2 to 3 weeks.
- Indirect effects on the oral mucosa due to superimposed infections (e.g. *Candida*, herpes simplex virus) and/or hemorrhage, reflections of bone marrow suppression. These effects are typically observed at the therapeutic nadir of the white blood cell count. However, the prophylactic use of antivirals (e.g. acyclovir) and antifungals (e.g. fluconazole) as well as colony-stimulating factors (which reduce the duration of neutropenia) have decreased the impact of this second mechanism.

Preventive measures include maintaining oral hygiene via the use of soft toothbrushes and rinsing with water and sodium bicarbonate.

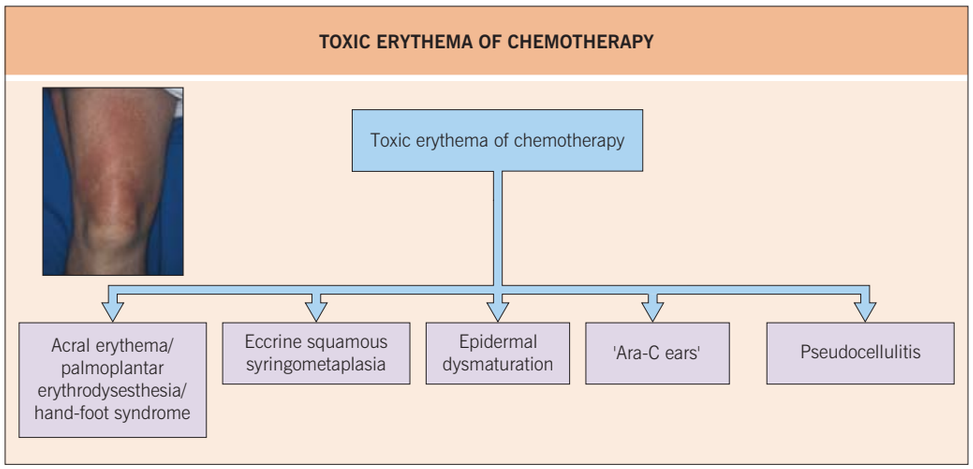


Fig. 21.16 Toxic erythema of chemotherapy. Use of a number of terms (especially those based on histologic findings), including palmoplantar erythrodysesthesia, eccrine squamous syringometaplasia and epidermal dysmaturation, has created some confusion for clinicians. There is considerable overlap in the appearance of the symmetric erythematous patches which can develop edema, erosions, desquamation or purpura (depending on the patient's platelet count), whether they favor acral sites, intertriginous zones, or the elbows and knees. "Toxic erythema of chemotherapy" has been suggested as an encompassing term that allows simplification. In addition, there is no need to implicate additional diagnoses when lesions are not limited to the hands and feet. *Courtesy, Jean L Bolognia, MD.*

In addition to specific antimicrobial agents, topical anesthetics may be helpful; in some patients, systemic analgesics are required. More recently, palifermin (keratinocyte growth factor) has been introduced to treat mucositis due to high-dose chemotherapy ± total body irradiation. However, administration of palifermin is associated with the appearance of a white coating of the tongue and transient keratoses within areas of cutaneous inflammation.

Other reactions

Chemotherapeutic agents are also responsible for other mucocutaneous reactions such as ulcerations at sites of extravasation of intravenous medications (Fig. 21.15A), skin, oral and nail hyperpigmentation (Fig. 21.15B), and acral erythema (Fig. 21.15C,D), also known as erythrodysesthesia. The frequency of extravasations has been markedly reduced by the use of "permanent" central venous catheters, whereas the incidence of acral erythema has increased in the setting of prolonged infusions of drugs and the chronic use of oral kinase inhibitors.

A variety of terms have been used to describe the cutaneous toxic effects of chemotherapy, e.g. "palmoplantar erythrodysesthesia", "hand–foot syndrome", "eccrine squamous syringometaplasia" "intertrigo eruption of chemotherapy" and "epidermal dysmaturation", creating some confusion. There is considerable overlap in the appearance of the symmetric erythematous patches which can develop edema, desquamation or purpura (depending on the patient's platelet count), whether they favor acral sites, intertriginous zones, the scrotum, or the elbows and knees. "Toxic erythema of chemotherapy" has been suggested as an encompassing term that allows simplification (Fig. 21.16).

Additional reactions to chemotherapy include radiation recall or enhancement, photosensitivity, inflammation of actinic or seborrheic keratoses (Fig. 21.15E), necrosis of plaques of psoriasis (Fig. 21.15F) or mycosis fungoides, Raynaud's phenomenon with digital necrosis (Fig. 21.15G), and neutrophilic eccrine hidradenitis (see above; Fig. 21.8). Long-term administration of hydroxyurea is associated with the development of painful ulcerations of the malleolar region of the lower extremities. The ulcers may be difficult to heal unless the hydroxyurea is discontinued.

The cutaneous side effects of the more recently introduced kinase inhibitors overlap with those of "standard" chemotherapy, including alopecia and toxic erythema of chemotherapy. However, there are also more unique side effects such as hypopigmentation of the skin and hair and periorbital edema from those that block c-KIT and platelet-derived growth factor receptor (PDGFR) as well as folliculitis due to inhibitors of epidermal growth factor receptor (EGFR; Table 21.14).

Fig. 21.17 Psoriasiform eruptions due to TNF-α inhibitors. A Widespread papulosquamous lesions in a patient being treated with infliximab for gastrointestinal GVHD. Histologically, there was no evidence of cutaneous GVHD. **B** Sterile pustulosis of the plantar surface developed in this patient with rheumatoid arthritis who had received infliximab for the previous 5 years. Neither patient had had a reduction in immunosuppression prior to the onset of the psoriasiform eruption. *A, Courtesy, Dennis Cooper, MD. B, Courtesy, Chris Bunick, MD.*

Drug reactions in HIV infection

Patients with HIV infection are at increased risk for drug eruptions (see Ch. 78). For example, the incidence of SJS-TEN in HIV-infected patients is 1/1000 per year (versus 1/1 000 000 per year in the general population) and this increase has been reported since the beginning of the AIDS epidemic[46]. An acquired glutathione deficiency in HIV-infected patients could contribute to an altered metabolism of trimethoprim–sulfamethoxazole (TMP-SMX) and therefore increase the risk of cutaneous reactions to that drug combination. However, this would not explain the multitude of drug eruptions to a variety of medications.

This increased susceptibility to drug reactions is most commonly observed in patients whose $CD4^+$ count is between 100 and 400/mm^3. It has been proposed that drugs or their metabolites disturb the balance between cytotoxic and regulatory phenomena, allowing a resurgence of cytotoxicity against virally infected cutaneous cells[19]. The target of the cytotoxic reaction would be viral antigens rather than drug haptens.

The major offending drugs include TMP-SMX, aminopenicillins, dapsone, abacavir, nevirapine and anticonvulsants. For example, up to

40% of HIV-infected patients may develop a "rash" during treatment with TMP-SMX[53]. These adverse cutaneous reactions, especially when severe, necessitate discontinuation of the drug. In the case of mild reactions, "treating through", i.e. continuing the drug despite the cutaneous eruption, is possible and has been followed by the disappearance of the rash. Corticosteroids may lower the rate of reactions to sulfonamides in AIDS patients[54]. Desensitization has been performed in these patients with varying results.

Drug-induced psoriasis

Drugs may be associated with the precipitation or exacerbation of psoriasis. A drug can affect the patient with psoriasis or a psoriatic diathesis in several ways: (1) exacerbation of pre-existing psoriasis; (2) induction of lesions of psoriasis in clinically normal skin in a person with psoriasis; (3) precipitation of psoriasis *de novo*; and (4) development of treatment resistance[55]. In addition, in sites of involvement by other cutaneous drug reactions (e.g. exanthematous), psoriatic lesions may appear secondary to the Koebner phenomenon, and plaques may develop at sites of injections of interferon.

The clinical manifestations of drug-induced psoriasis span the spectrum of psoriasis, from limited or generalized plaques to erythroderma and pustulosis of the palms and soles. Nail changes and scalp involvement may also be seen. The latency period depends on the offending drug. It can be categorized as short (<4 weeks), intermediate (4 to 12 weeks), and long (>12 weeks); examples of drugs that have been categorized in this manner are terbinafine and NSAIDs (short), antimalarials and ACE inhibitors (intermediate), and lithium and β-blockers (long)[56]. Lesions of drug-induced psoriasis usually regress within weeks to a few months of discontinuing the inciting drug. However, psoriasiform eruptions, including palmoplantar pustulosis, may be more persistent in patients receiving TNF-α inhibitors (see Ch. 128). The latter occur not just in individuals with psoriasis or rheumatoid arthritis, but also in patients being treated for other conditions, e.g. GVHD or inflammatory bowel disease, who have no personal or family history of psoriasis (Fig. 21.17). These eruptions may or may not follow a reduction in immunosuppression.

Histologic findings are not always characteristic. They may suggest psoriasis or be more compatible with a lichenoid drug eruption.

CUTANEOUS SIDE EFFECTS OF KINASE INHIBITORS AND BLOCKING ANTIBODIES

	Sorafenib	Sunitinib	Vemurafenib	Erlotinib, gefitinib, cetuximab (MoAb)	Imatinib	Dasatinib	Nilotinib
Targeted receptors	VEGFR1, 2 and 3, PDGFRβ, c-KIT, RET, CRAF, BRAF, BRAF (V600E), FLT3	VEGFR1, 2 and 3, PDGFRα/β, c-KIT, FLT3, RET	BRAF (V600E)	EGFR	BCR-ABL, PDGFR, c-KIT	BCR-ABL, PDGFRβ, c-KIT, ephrin A receptor kinase	BCR-ABL, TEL-PDGFRβ, FIP1L1-PDGFRα, c-KIT
Hair depigmentation	–	+	–	–	+	+	–
Hair repigmentation	–	–	–	–	+	–	–
Alopecia	+	+	+	+ (non-scarring and scarring)	+	+	+
Curly, brittle hair	–	–	–	+	–	–	–
Facial hair growth and/or trichomegaly of eyelashes	–	–	–	+	–	–	–
Paronychia	–	–	–	+	–	–	–
Periorbital edema	+	+	–	–	+	+	+
Facial erythema	+	+/–	+	+/–	–	+/–	–
Subungual splinter hemorrhages	+	+	–	–	–	–	–
Acral erythema*	+	+	+	–	+/–	+	+/–
Folliculitis§	–	–	–	++ (see Ch. 36)	–	+	+
Bullous dermatosis	–	+	–	–	–	–	–
Flushing	+	–	–	–	–	–	–
Cutaneous hypopigmentation	–	–	–	–	+	–	–
Morbilliform exanthem	+	+	+	–	+	+	+
Photosensitization	–	–	+	–	+	+	+
Stomatitis	+	+	–	–	–	+	+/–
Other	Palmoplantar hyperkeratosis, keratoacanthomas, SCCs, squamous papillomas, scalp pruritus, SJS, angioedema	Palmoplantar hyperkeratosis, yellow skin discoloration, pyoderma gangrenosum	Keratoacanthomas, SCCs, squamous papillomas, pruritus, anaphylaxis, SJS, panniculitis	Seborrheic dermatitis, blepharitis, xerosis, skin fragility, periungual pyogenic granulomas	SJS, AGEP, Sweet's syndrome, lichenoid eruption, peripheral edema, pruritus, cutaneous hyperpigmentation, pseudolymphoma	Sweet's syndrome, panniculitis, hyperhidrosis, pruritus, urticaria	Pruritus, hyperhidrosis

*May be bullous.
§Also referred to as papulopustular eruption.

Table 21.14 Cutaneous side effects of kinase inhibitors and blocking antibodies. –, not seen; +, typically seen; +/– occasionally seen; AGEP, acute generalized exanthematous pustulosis; EGFR, epidermal growth factor receptor; FLT3, FMS-related tyrosine kinase 3; MoAb, monoclonal antibody; PDGFR, platelet-derived growth factor receptor; RAF, name derived from ability of 3611–MSV virus to induce "*ra*pidly growing *f*ibrosarcomas" in mice; SCCs, squamous cell carcinomas; SJS, Stevens–Johnson syndrome; VEGFR, vascular endothelial growth factor receptor. *Adapted from Robert C, et al. Lancet Oncol. 2005;6:491–500 and Heidary N, et al. J Am Acad Dermatol. 2008;58:545–70.*

Fig. 21.18 Gray–violet discoloration of the face due to amiodarone. Biopsy specimens demonstrate yellow–brown granules within dermal macrophages. Note sparing of the lower eyelid. *Courtesy, Jean L Bolognia, MD.*

Fig. 21.19 Local reactions to vitamin K injections. A This patient was originally diagnosed as having erythema multiforme. **B** Large pink–violet plaque with areas of hemorrhage in an infant. *B, Courtesy, Julie V Schaffer, MD.*

REACTIONS LOCALIZED TO SITES OF INJECTIONS OF MEDICATIONS	
Etanercept*	Erythematous plaques, vasculitis, eosinophilic cellulitis
Adalimumab	Erythematous or urticarial plaques
GM-CSF*, G-CSF*	Pustular reaction, urticarial plaque
Interferon*	Vasculopathy with necrosis, development of plaque of psoriasis
Interleukin-2	Lobular panniculitis, granulomas
Vitamin K	Erythematous plaque, often annular (Fig. 21.19); morpheaform plaque (Texier's disease)
Heparin	Necrosis, ecchymosis (see Ch. 23)
Low-molecular-weight, calcium-containing heparin	Calcinosis cutis
Glatiramer acetate	Fibrosis, panniculitis, lipoatrophy, vasospasm, Nicolau syndrome
Iron	Brown discoloration, hyperpigmentation
Hyaluronic acid, silicone	Swelling, granulomatous reaction (see Ch. 94)
Corticosteroids	Dermal atrophy, lipoatrophy, telangiectasias, deposits, hypopigmentation
Vitamin B_{12}	Pruritus, morpheaform plaque
Enfuvirtide	Erythematous or morpheaform plaque
VACCINES	
Aluminium-containing vaccine	Nodules, foreign body reaction

*Discussed in Chapter 128.

Table 21.15 Reactions localized to sites of injections of medications (in addition to extravasation of those administered intravenously). See Table 21.8 and Table 89.3 for reactions to insulin and illicit drugs, respectively. CSF, colony stimulating factor; G, granulocyte; GM, granulocyte–macrophage

Acneiform eruptions (including folliculitis)

Acneiform eruptions represent approximately 1% of drug-induced skin eruptions. Clinically, papules and/or pustules are seen primarily on the face and upper trunk, the same sites favored by acne; comedones are usually absent. The interval between drug exposure and the acneiform eruption depends on the offending agent. The major drugs implicated in acneiform eruptions include corticosteroids, androgens, hydantoins, lithium, halogenides, and oral contraceptives (more often those that contain progestins with androgen-like effects). Less commonly, azathioprine, quinidine and adrenocorticotropic hormone are the culprits. With the introduction of blocking antibodies and inhibitors of EGFR (see Table 21.14), follicular eruptions are increasingly seen by dermatologists (see Fig. 36.15).

Pigmentary changes

Drug-induced cutaneous hyperpigmentation may result from a variety of mechanisms, including enhanced melanin production, deposition of drugs or their metabolites (sometimes complexed with melanin or iron, and, in some instances, better described as discoloration), and simply postinflammatory changes. The hyperpigmentation may be more pronounced in sun-exposed areas. The drugs most commonly implicated in cutaneous hyperpigmentation (or discoloration) include minocycline, antimalarials, amiodarone (Fig. 21.18), oral contraceptives, imipramine, chemotherapeutic agents and clofazimine (see Ch. 67). Exposure to heavy metals such as silver and gold as well as arsenic may also induce darkening of the skin, and bleomycin can lead to linear "flagellate" hyperpigmentation.

Hypopigmentation can occur with the chronic use of several topical medications, including retinoic acid and corticosteroids; depigmentation is associated primarily with the application of monobenzyl ether of hydroquinone or exposure to catechols, phenols or quinones (i.e. contact or occupational leukoderma; see Ch. 66). Cutaneous hypopigmentation can result from tyrosine kinase inhibitors, in particular imatinib.

A few drugs are capable of changing the color of hair. For example, chloroquine, imatinib, dasatinib and sunitinib (see Table 21.14) can lead to lightening or even depigmentation. Imatinib can also lead to darkening of the hair.

Eruptions induced by vaccines

With the discontinuation of vaccinations for smallpox in the general population, the incidence of significant cutaneous side effects due to

vaccines is now low[57] (see Ch. 81). Local inflammatory reactions consisting of erythema, swelling and tenderness can be seen, as well as urticaria, angioedema and anaphylaxis; the latter occurs primarily with live measles vaccines. Lichenoid eruptions[58], erythema multiforme and occasionally autoimmune reactions, e.g. polyarteritis nodosa, have been observed[24]. Vaccination with BCG can lead to a benign, self-limited local reaction consisting of a plaque, pustule or even ulcer (see Ch. 75). Occasionally, local abscess formation may follow vaccination of strongly reactive individuals, administration of a large amount of vaccine, or a deep injection.

Localized reactions to injected medications

In addition to the cutaneous reactions to vaccines discussed previously, Table 21.15 outlines cutaneous reactions that are localized to the sites of injections of medications. Table 21.8 reviews the side effects of insulin injections.

TREATMENT

Only a small fraction of drug eruptions are life-threatening or lead to disabling sequelae. Management begins with the withdrawal of the suspect drug as soon as possible[59]. Frequently, however, several drugs may be incriminated. As there is no clinical or laboratory test which permits identification of the offending agent with certainty, the decision is usually made to discontinue all drugs that are non-essential as well as the "high-probability" drugs. Appropriate substitutions may also be required; for example if phenytoin is discontinued, then levetiracetam or valproate would be prescribed rather than phenobarbital or carbamazepine.

For mild drug eruptions, topical corticosteroids and antihistamines may be helpful. In the case of "acute skin failure" as in TEN, management must be undertaken in specialized intensive care units. Supportive interventions include warming of the environment, correction of electrolyte disturbances, high caloric supplementation, and prevention of sepsis.

The hypothesis of an immunologic etiology for drug eruptions has led to the use of systemic corticosteroids, immunosuppressives and anticytokine therapies. Although corticosteroids have been advocated by some clinicians, there is minimal evidence for their usefulness either as a preventive or as a therapeutic agent in the most common forms of drug reactions, e.g. exanthematous. In patients with mild reactions that occur during the treatment of a severe disease, it is sometimes possible to "treat through" the rash and continue the incriminated drug. In this situation, systemic corticosteroids may be helpful, as has been recently observed with TMP-SMX in previously intolerant patients who had AIDS-associated *Pneumocystis jiroveci* pneumonia[54]. However, there is no agreement regarding this clinical approach and, in the case of severe reactions, administration of systemic corticosteroids as a preventive measure may prove detrimental. Of note, corticosteroids can improve the cutaneous and visceral (lung, heart) manifestations of DRESS (DIHS) and may be life-saving; however, relapses are often observed when the corticosteroids are tapered.

Finally, after recovery, patients should be advised to avoid the drug thought to be responsible for the reaction and all chemically related compounds.

REFERENCES

1. Arndt KA, Jick H. Rates of cutaneous reactions to drugs. J Am Med Assoc. 1976;235:918–23.
2. Roujeau J-C, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med. 1994;331:1272–85.
3. Knowles SR, Uetrecht J, Shear NH. Idiosyncratic drug reactions: the reactive metabolite syndromes. Lancet. 2000;356:1587–91.
4. Caranasos GJ, May FE, Stewart RB, Cluff LE. Drug associated deaths of medical inpatients. Arch Med Int. 1976;136:872–5.
5. Coopman SA, Johnson RA, Platt R, Stern RS. Cutaneous disease and drug reactions in HIV infection. N Engl J Med. 1993;328:1670–4.
6. Sanchez-Borges A, Capriles-Hulett M. Atopy is a risk factor for non-steroidal anti-inflammatory drug sensitivity. Ann Allergy Asthma Immunol. 2000;84:101–6.
7. Hunziker T, Künzi U, Braunschweig S, et al. Comprehensive hospital drug monitoring (CHDM): adverse skin reactions, a 20-year survey. Allergy. 1997;52:388–93.
8. Bigby M. Rates of cutaneous reactions to drugs. Arch Dermatol. 2001;137:765–70.
9. Zürcher K, Krebs A. Cutaneous Drug Reactions. Berlin: Karger Editorial, 1992.
10. Bruinsma W. A Guide to Drug Eruptions. Side Effects in Dermatology, 7th edn. Amsterdam: IMP, 2000.
11. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis and management. Lancet. 2000;356:1255–9.
12. Shear NH. Diagnosing cutaneous adverse reactions to drugs. Arch Dermatol. 1990;126:94–7.
13. Puig L, Nadal C, Fernandez-Figueras M, et al. Carbamazepine-induced drug rashes: diagnostic value of patch tests depends on clinico-pathologic presentation. Contact Dermatitis. 1996;34:435–7.
14. Barbaud AM, Bene MC, Schmutz JL, et al. Role of delayed cellular hypersensitivity and adhesion molecules in amoxicillin-induced morbilliform rashes. Arch Dermatol. 1997;133:481–6.
15. Wolkenstein P, Chosidow O, Flechet ML, et al. Patch testing in severe cutaneous adverse drug reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis. Contact Dermatitis. 1996;35:234–6.
16. Pichler WJ, Yawalkar N. Allergic reactions to drug: involvement of T cells. Thorax. 2000;55(suppl. 2):S61–5.
17. Schnyder B, Mauri-Hellweg D, Zanni MP, et al. Direct MHC dependent presentation of the drug sulfamethoxazole to human αβ T cell clones. J Clin Invest. 1997;100:136–41.
18. Zanni MP, Mauri-Hellweg D, Brander C, et al. Characterization of lidocaine T cells. J Immunol. 1997;158:1139–48.
19. Chosidow O, Bourgault I, Roujeau JC. Drug rashes. What are targets of cell mediated cytotoxicity? Arch Dermatol. 1994;130:627–9.
20. Gerson D, Sriganshan V, Alexis JB. Cutaneous drug eruptions: a 5 years experience. J Am Acad Dermatol. 2008;59:995–9.
21. Salkind AR, Cuddy PG, Foxworth JW. The rational clinical examination. Is this patient allergic to penicillin? An evidence-based analysis of the likelihood of penicillin allergy. JAMA. 2001;285:2498–505.
22. Hedner T, Samuelsson O, Lunde H, et al. Angio-oedema in relation to treatment with angiotensin converting enzyme inhibitors. BMJ. 1992;304:941–6.
23. Gould JW, Mercurio MG, Elmets CA. Cutaneous photosensitivity diseases induced by exogenous agents. J Am Acad Dermatol. 1995;33:551–73.
24. De Keyser F, Naeyaert JM, Hindryckx P, et al. Immune-mediated pathology following hepatitis B vaccination. Two cases of polyarteritis nodosa and one case of pityriasis rosea-like drug eruption. Clin Exp Rheumatol. 2000;18:81–5.
25. Staughton RC, Payne CM, Harper JI, et al. Toxic pustuloderma: a new entity. J R Soc Med. 1984;77(suppl. 4):6–8.
26. Roujeau J-C, Bioulac-Sage P, Bourseau C, et al. Acute generalized exanthematous pustulosis. Analysis of 63 cases. Arch Dermatol. 1991;127:1333–8.
27. Bernard P, Lizeaux Parneix V, Miossec P, et al. HLA et prédisposition génétique dans les PEAG et les exanthémes maculo-papuleux. Ann Dermatol. 1995;122:538–9.
28. Kempinaire A, De Raeve L, Merckx M, et al. Terbinafine induced acute generalized exanthematous pustulosis confirmed by a positive patch test result. J Am Acad Dermatol. 1997;37:653–5.
29. Sidoroff A, Dunant A, Viboud C, et al. Risk factors for acute generalized exanthematous pustulosis (AGEP). Results of a multinational case-control study (Euro SCAR). Br J Dermatol. 2007;157:989–96.
30. Walker DC, Cohen PR. Trimethoprim-sulfamethoxazole-associated acute febrile neutrophilic dermatosis: case report and review of drug-induced Sweet's syndrome. J Am Acad Dermatol. 1996;34:918–23.
31. Roujeau JC. Neutrophilic drug eruption. Clin Dermatol. 2000;18:331–7.
32. Hasegawa M, Sato S, Nakada M, et al. Sweet's syndrome associated with granulocyte colony-stimulating factor. Eur J Dermatol. 1998;8:503–5.
33. Callot V, Roujeau J-C, Bagot M, et al. Drug-induced pseudolymphoma and hypersensitivity syndrome. Two different clinical entities. Arch Dermatol. 1996;132:1315–21.
34. Kardaun S, Sidoroff A, Valeyrie-Allanore L, et al. Variability in the clinical pattern of cutaneous side effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol. 2007;156:609–10.
35. Pirmohamed M, Graham A, Roberts P, et al. Carbamazepine hypersensitivity: assessment of clinical and *in vitro* chemical cross reactivity with phenytoin and oxcarbazepine. Br J Clin Pharmacol. 1991;32:741–9.
36. Choquet-Kastylevsky G, Intrator L, Chenal C, et al. Increased levels of interleukin 5 are associated with the generation of eosinophilia in drug-induced hypersensitivity syndrome. Br J Dermatol. 1998;139:1026–32.
37. Descamps V, Bouscarat F, Laglenne S, et al. Human herpes virus 6 infection associated with anticonvulsant hypersensitivity syndrome and reactive haemophagocytic syndrome. Br J Dermatol. 1997;137:605–8.
38. Suzuki Y, Inagi R, Aono T, et al. Human herpesvirus 6 infection as a risk factor for development of severe drug-induced hypersensitivity syndrome. Arch Dermatol. 1998;134:1108–22.
39. Shiohara T, Lijima M, Ikezawa Z, Hashimoto K. The diagnosis of a DRESS syndrome has been sufficiently established on the basis of typical clinical features and viral reactivations. Br J Dermatol. 2007;156:1083–4.
39a. McCormack M, Alfirevic A, Bourgeois S, et al. HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. N Engl J Med. 2011;364:1134–43.
40. Kauppinen K, Stubb S. Fixed eruptions: causative drugs and challenge tests. Br J Dermatol. 1985;112:575–8.
41. Stubb S, Alanko K, Reitamo S. Fixed drug eruptions: 77 cases from 1981 to 1985. Br J Dermatol. 1989;120:583.
42. Kuechle MK, Stegemeir E, Maynard B, et al. Drug-induced linear IgA bullous dermatosis: report of six cases and review of the literature. J Am Acad Dermatol. 1994;30:187–92.
43. Klein PA, Callen JP. Drug-induced linear IgA bullous dermatosis after vancomycin discontinuance in a patient with renal insufficiency. J Am Acad Dermatol. 2000;42:316–23.

44. Brenner S, Bialy-Golan A, Ruocco V. Drug-induced pemphigus. Clin Dermatol. 1998;16:393–7.
45. Mockenhaupt M, Viboud C, Dunant A, et al. Stevens–Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. J Invest Dermatol. 2008;128:35–44.
46. Saïag P, Caumes E, Chosidow O, et al. Drug-induced toxic epidermal necrolysis (Lyell syndrome) in patients infected with the human immunodeficiency virus. J Am Acad Dermatol. 1992;26:567–74.
47. Ploysangam T, Breneman DL, Mutasim DF. Cutaneous pseudolymphomas. J Am Acad Dermatol. 1998;38:877–95.
48. D'Incan M, Souteyrand P, Bignon YJ, et al. Hydantoin-induced cutaneous pseudolymphoma with clinical, pathological, and immunological aspect of Sézary syndrome. Arch Dermatol. 1992;128:1371–4.
49. Gough A, Chapman S, Wagstaff K, et al. Minocycline induced autoimmune hepatitis and systemic lupus erythematosus-like syndrome. BMJ. 1996;312:169–72.
50. Susser WS, Whitaker-Worth DL, Grant-Kels JM. Mucocutaneous reactions to chemotherapy. J Am Acad Dermatol. 1999;40:367–98.
51. Marquart-Elbaz C, Lipsker D, Grosshans E, Cribier B. Oral ulcers induced by nicorandil: prevalence and clinicopathological aspects. Ann Dermatol Venereol. 1999;126:587–90.
52. Pillans PI, Woods DJ. Drug-associated alopecia. Int J Dermatol. 1995;34:149–58.
53. Coopman SA, Johnson RA, Platt R, Stern RS. Cutaneous disease and drug reactions in HIV infection. N Engl J Med. 1993;328:1670–4.
54. Iborra C, Jouan M, Baril L, et al. High-dose trimethoprim-sulfamethoxazole therapy with corticosteroids in previously intolerant patients with AIDS-associated *Pneumocystis carinii* pneumonia. Arch Dermatol. 1999;135:350–1.
55. Abel EA, DiCicco LM, Orenberg EK, et al. Drugs in exacerbation of psoriasis. J Am Acad Dermatol. 1986;15:1007–22.
56. Gupta AK, Sibbald RG, Knowles SR, et al. Terbinafine therapy may be associated with the development of psoriasis de novo or its exacerbation: four case reports and a review of drug-induced psoriasis. J Am Acad Dermatol. 1997;36:858–62.
57. McMahon BJ, Helminiak C, Wainwright RB, et al. Frequency of adverse reactions to hepatitis B vaccine in 43,618 persons. Am J Med. 1992;92:254–6.
58. Saywell CA, Wittal RA, Kossard S. Lichenoid reaction to hepatitis B vaccination. Australas J Dermatol. 1997;38:152–4.
59. Garcia-Doval I, Le Cleach L, Bocquet H, et al. Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death? Arch Dermatol. 2000;136:323–7.

Purpura: Mechanisms and Differential Diagnosis

22

Warren W Piette

PURPURA

Introduction

The differential diagnosis of purpura is extensive, but the evaluation of a patient with purpura can be greatly facilitated by categorizing purpuric lesions into morphologic subsets[1]. This chapter serves as an introduction to a method to evaluate and classify patients presenting with this important dermatologic sign. Purpura is defined as visible hemorrhage into the skin or mucous membranes. The differential diagnosis presented in this chapter is directed toward syndromes of primary purpura, where the hemorrhage is an integral part of lesion formation, rather than secondary hemorrhage into established lesions (e.g. stasis dermatitis, dependent cellulitis). Purpuric lesions are divided into six subsets: (1) petechiae (Fig. 22.1A, Table 22.1); (2) macular purpura (Table 22.2); (3) macular ecchymoses (Fig. 22.1B, Table 22.3); (4) palpable purpura (Fig. 22.1C, Table 22.4); (5) non-inflammatory retiform purpura (Fig. 22.1D; Table 22.5); and (6) inflammatory retiform purpura (Table 22.6). Lesions in the first three groups are categorized on the basis of size, while those in the last three groups can range in size from a few millimeters to several centimeters in diameter. The relevance of these morphologic subsets in sorting through the differential diagnosis is outlined in Figure 22.2.

Two major causes of purpura, microvascular occlusion syndromes and vasculitis, will be discussed in Chapters 23 and 24, respectively. The former are important to recognize because they may mimic vasculitis but require a very different approach to diagnosis and therapy. The most typical presentation of microvascular occlusion syndromes is non-inflammatory retiform purpura (see Table 22.5). Early lesions seldom show much erythema, and in the uncommon instance in which early erythema is present, purpura or necrosis typically comprises at least two-thirds of the lesion.

In the skin, livedo reticularis is a reflection of the physiologic anatomy of slow flow states (see Ch. 106). It is the three-dimensional structure and flow regulation of the dermal and subcutaneous vasculature that gives rise to the violaceous or bluish net-like pattern of livedo reticularis, and this flow pattern is reproducible in any given individual. The diameter of the almost-circular individual units within the net-like grid varies from 2 cm or larger on the back to 5 mm or less on the palms or soles.

Retiform purpura morphology results from occlusion of the vessels that produce the livedo reticularis pattern (see Fig. 23.5), but the two entities can be distinguished based upon the presence or absence of purpura, respectively, hence the term "retiform purpura". Given the size of dermal vessels, the clot within the vessel is often too small to be seen grossly. What is actually observed is hemorrhage around the vessel within the dermis, presumably due to ischemia with hemorrhage prior to complete occlusion of the vessel. The shape of such a hemorrhagic lesion is determined by the anatomy of the slow flow network, though a complete reticulate pattern is very rarely seen. Instead, the morphology of retiform purpura is composed of "puzzle pieces" of the livedo reticularis pattern. Some lesions might be called river-like or serpentine purpura because of their likeness to a winding river or snake, and others could be referred to as branching purpura because of their likeness to the angled course of a tree branch. However, very few of these lesions are truly stellate, i.e. characterized by a central area of necrosis or hemorrhage with radiating extensions.

Retiform lesions should be carefully examined to confirm the presence of purpura, and it is important to inquire about the duration of the lesions. Inflammatory retiform purpura (see Table 22.6) may have a reticulate or branching morphology, but (unlike non-inflammatory retiform purpura) early lesions typically exhibit prominent erythema. However, just as the wound healing response can eventually lead to erythema and leukocytoclasis in lesions initiated by non-inflammatory occlusion, vasculitis sometimes produces lesions that show minimal early inflammation. Among the inflammatory disorders that can result in retiform purpura, the ANCA-positive vasculitides (especially Wegener's granulomatosis and microscopic polyangiitis) are the ones most likely to present with lesions that are difficult to distinguish from retiform purpura due to occlusion. Despite this overlap of clinical presentations, careful examination of early lesions to determine whether there is a substantial inflammatory component can greatly aid in focusing the differential diagnosis and directing the evaluation.

This morphologic approach to the differential diagnosis of purpura represents a departure from traditional categorization by pathophysiology. Because the pathophysiology of purpuric syndromes is what the clinician is attempting to ascertain, sorting by pathophysiology is of limited clinical utility. The morphology-based method is designed to streamline the process of generating clinical hypotheses (i.e. most likely diagnoses) to facilitate a rapid, efficient and accurate evaluation to prove or disprove the suspected diagnosis.

The Time Course of Purpura

The three subsets of macular (non-palpable) purpura (see Tables 22.1–22.3) cause purpura primarily through mechanisms of simple hemorrhage, with extravasated red blood cells and minimal inflammation observed in biopsy specimens. As such, these lesions have a very simple evolution, from initial hemorrhage to steady clearing of red blood cells and hemoglobin. Clinically, this correlates with fading of lesions and, in larger lesions, transition of color from red–blue or purple to green, yellow or brown before complete fading.

In syndromes of inflammatory hemorrhage, such as cutaneous small vessel vasculitis, and in microvascular occlusion, the evolution and clearing of lesions is more complicated. This is outlined in Figure 22.3. Because of the different evolution patterns of these two processes, it is possible for a biopsy specimen of a late lesion of vasculitis to resemble an early lesion of occlusion histologically. Conversely, a late lesion of occlusion with some resulting dermal necrosis may on histologic examination show features characteristic of leukocytoclastic vasculitis. This means that the biopsy specimen of a purpuric lesion must be interpreted within the context of the lesion's age and clinical setting. The clinical and histologic assessment of purpuric lesions are equally important in properly evaluating and diagnosing a purpuric syndrome.

COAGULATION

Primary hemostasis consists of the formation of a platelet plug, and this is sufficient for the many daily minor injuries to the microvascular system. When a platelet plug is inadequate due to the size of the vessel or the size of the injury, secondary hemostasis with clot formation is needed. The control of clot formation is critically important: too little clotting can lead to death by hemorrhage; inappropriate clotting produces thrombosis, embolus or necrosis; and uncontrolled clotting with fibrinolysis can produce both thrombosis and hemorrhage, as in disseminated intravascular coagulation. Therefore, a thrombus must form rapidly at sites of injury, it must not extend beyond where it is needed,

Fig. 22.1 Clinical examples of petechiae and purpura. A Round to oval petechiae, <3 mm in diameter. **B** Actinic (solar) purpura and pseudoscars, both in sites of actinic damage plus trauma. **C** Palpable purpura due to cutaneous small vessel vasculitis (inflammation plus hemorrhage). **D** Non-inflammatory (bland) retiform purpura as well as hemorrhagic bullae in a patient with disseminated intravascular coagulation (DIC). *D, Courtesy, Judit Stenn, MD.*

and clotting factors that escape the local injury site must be prevented from triggering clotting at distant sites. As might be expected for a system that requires exquisite regulation to perform properly, the control of coagulation is multifaceted and still not completely understood[2,3]. Basal coagulation encompasses the constant low-level activation of some components of the procoagulant, natural anticoagulant and fibrinolytic pathways, so that these systems are ready for a rapid response when needed. An overview of the controls and interconnections of these pathways is shown in Figure 22.4.

The initiation stage of clot formation generates small amounts of thrombin (factor IIa) via formation of a tissue factor–factor VIIa complex that activates factor IX to IXa and factor X to Xa (a process formerly referred to as the extrinsic pathway of coagulation)[2,3]. This phase may take place on any cell that expresses tissue factor and is exposed to plasma; inflammatory cells and injured endothelial cells are common sites. Only small amounts of these factors are released in this phase, usually insufficient to produce a clot. However, these small amounts are critical for triggering the propagation/amplification phase of coagulation. The thrombin released during initiation activates platelets. Platelet membrane surfaces are then inverted to expose phospholipids (especially phosphatidyl serine) critical for localizing membrane procoagulant complexes, starting with the binding of factors VIIIa and Va (cofactors for factors IXa and Xa, respectively). Thrombin molecules also stimulate the release of factor V from platelet granules and activate factor V as well as factor VIII, freeing the latter from von Willebrand factor. Finally, thrombin activates factor XI to XIa (which leads to further activation of IX to IXa). As shown in Figure 22.4, the activated platelet surface is now the site of complexes capable of rapid amplification of thrombin generation, which then catalyzes the cleavage of fibrinogen to fibrin with subsequent polymerization of fibrin monomers into a clot.

Classically, factor XII and the contact activation complex have been considered as part of the coagulation cascade (formerly referred to as the intrinsic pathway). However, while patients deficient in factor XII, high-molecular-weight kininogen or prekallikrein may have prolonged activated partial thromboplastin times (APTT), they do not bleed excessively and may actually be prone to thrombosis. These findings, plus other recent investigations, have challenged traditional concepts of the role of the contact activation system[4,5]. Factor XII may play a role in clot propagation, particularly in pathologic states, but the contact activation system seems more targeted toward other physiologic functions.

The contact activation complex is formed by the assembly of high-molecular-weight kininogen (HMWK) and prekallikrein (PK) on a multiprotein receptor complex on endothelial cell membranes; this complex consists of cytokeratin 1, the globular head of the C1q receptor and the urokinase plasminogen activator receptor. Binding of HMWK, PK and sometimes factor XII to this receptor complex results in the production of the powerful vasodilator bradykinin and other vasoactive mediators. In addition, fibrinolytic activity is generated through both activation of single- and two-chain urokinase-like plasminogen activator and release of tissue plasminogen activator, which subsequently convert plasminogen to plasmin. C1 esterase inhibitor, well known in controlling complement reactions, also has a major role in regulating this pathway. Of note, the episodic edema of hereditary angioedema is probably due more to deficient C1 esterase inhibitor-mediated down-regulation of bradykinin production than to deficient inhibition of complement (see Ch. 18). The contact activation system is likely

DIFFERENTIAL DIAGNOSIS OF MACULAR PETECHIAE (≤4 MM IN DIAMETER)
PATHOPHYSIOLOGY: HEMOSTATICALLY RELEVANT THROMBOCYTOPENIA (<50 000/mm³)*
Major etiologies†
1. Idiopathic thrombocytopenic purpura 2. Thrombotic thrombocytopenic purpura 3. Disseminated intravascular coagulation 4. Other acquired thrombocytopenias, including drug-related a. Peripheral destruction (e.g. quinine, quinidine) b. Drug-induced decreased production, idiosyncratic or dose-related (e.g. chemotherapy) c. Bone marrow infiltration, fibrosis or failure
PATHOPHYSIOLOGY: ABNORMAL PLATELET FUNCTION
Major etiologies†
1. Congenital or hereditary platelet function defects 2. Acquired platelet function defects a. Aspirin, NSAIDs b. Renal insufficiency c. Monoclonal gammopathy 3. Thrombocytosis secondary to myeloproliferative disorders (often >1 000 000/mm³)
PATHOPHYSIOLOGY: NON-PLATELET ETIOLOGIES
Major etiologies†
1. Spiking elevations of intravascular venous pressure (Valsalva maneuver-like, e.g. repetitive vomiting, childbirth, paroxysmal coughing, seizure) 2. Fixed increased pressure (e.g. stasis, ligatures) or intermittent pressure (e.g. blood pressure cuff – Rumpel–Leede sign) 3. Trauma (often linear) 4. Perifollicular (vitamin C deficiency) 5. Mildly inflammatory conditions a. Pigmented purpuric eruptions b. Hypergammaglobulinemic purpura of Waldenström
*Most patients do not have petechiae until platelets ≤20 000/mm³. †Partial list.

Table 22.1 Differential diagnosis of macular petechiae (≤4 mm in diameter). NSAIDs, nonsteroidal anti-inflammatory drugs.

DIFFERENTIAL DIAGNOSIS OF INTERMEDIATE MACULAR PURPURA (5–9 mm)
MAJOR ETIOLOGIES*
1. Hypergammaglobulinemic purpura of Waldenström 2. Infection/inflammation in patients with thrombocytopenia 3. Rarely, minimally inflamed cutaneous small vessel vasculitis (usually dependent distribution)
*Partial list.

Table 22.2 Differential diagnosis of intermediate macular purpura (5–9 mm).

responsible for some of the fibrinolysis and refractory hypotension seen in sepsis, following cardiopulmonary bypass ("post-pump" systemic inflammatory response syndromes), and in other settings where contact activation is likely to be extensive.

Natural anticoagulant control of clot extension is likewise complex[2,3]. The initiation phase of clotting is down-regulated by *tissue factor pathway inhibitor* (TFPI) and *antithrombin III* (ATIII). TFPI and ATIII are bound to heparan sulfate molecules on the surface of endothelial cells, and their presence in close proximity to sites of desired clot formation allows them to capture activated clotting factors and prevent them from leaving the area. TFPI can inactivate factor Xa, and the TFPI–factor Xa complex can efficiently bind to and inhibit factor VIIa (which is found in a complex with tissue factor); in the absence of factor Xa, TFPI reacts with factor VIIa at a much slower rate. ATIII can

DIFFERENTIAL DIAGNOSIS OF MACULAR ECCHYMOSES (≥1 cm)
PATHOPHYSIOLOGY: PROCOAGULANT DEFECT PLUS MINOR TRAUMA
Major etiologies*
1. Anticoagulant use 2. Hepatic insufficiency with poor procoagulant synthesis 3. Vitamin K deficiency 4. Disseminated intravascular coagulation (some)
PATHOPHYSIOLOGY: POOR DERMAL SUPPORT OF VESSELS PLUS MINOR TRAUMA
Major etiologies*
1. Actinic (solar, senile) purpura 2. Corticosteroid therapy, topical or systemic 3. Vitamin C deficiency (scurvy) 4. Systemic amyloidosis (light chain-related, some familial types) 5. Ehlers–Danlos syndrome
PATHOPHYSIOLOGY: PLATELET PROBLEMS PLUS MINOR TRAUMA
Major etiologies*
1. Platelet function defects, including von Willebrand disease and those induced by medications and metabolic diseases 2. Acquired or congenital thrombocytopenia
*Partial list.

Table 22.3 Differential diagnosis of macular ecchymoses (≥1 cm).

PALPABLE PURPURA: INFLAMMATORY PURPURA WITH PROMINENT EARLY ERYTHEMA
I. PATHOPHYSIOLOGY: LEUKOCYTOCLASTIC VASCULITIS DUE TO IMMUNE COMPLEX DISEASE
A. Small vessels only
1. Idiopathic, infection- or drug-associated IgG or IgM complexes 2. Idiopathic IgA complexes (HSP), or IgA complexes associated with drugs or infection 3. Hypergammaglobulinemic purpura of Waldenström 4. Urticarial vasculitis: often minimally purpuric 5. Pustular vasculitis (e.g. bowel bypass syndrome)
B. Small- and medium-sized (macroscopic) vessels may be involved
1. Mixed cryoglobulinemia 2. Rheumatic vasculitides (LE, RA), Sjögren's syndrome
II. PATHOPHYSIOLOGY: PAUCI-IMMUNE LEUKOCYTOCLASTIC VASCULITIS
A. ANCA-associated
1. Wegener's granulomatosis 2. Microscopic polyangiitis 3. Churg–Strauss syndrome
B. Other
1. Erythema elevatum diutinum 2. Sweet's syndrome (vasculitis unusual)
III. PATHOPHYSIOLOGY: NOT LEUKOCYTOCLASTIC VASCULITIS
A. Small vessels only
1. Erythema multiforme 2. Pityriasis lichenoides et varioliformis acuta (PLEVA) 3. Pigmented purpuric eruptions (especially pigmented purpuric lichenoid dermatitis of Gougerot and Blum) 4. Hypergammaglobulinemic purpura of Waldenström (although some lesions have histologic evidence of leukocytoclastic vasculitis)
Classic target lesion (usually erythema multiforme, but can be small vessel vasculitis, especially IgA-associated)

Table 22.4 Palpable purpura: inflammatory purpura with prominent early erythema. HSP, Henoch–Schönlein purpura; LE, lupus erythematosus; RA, rheumatoid arthritis.

DIFFERENTIAL DIAGNOSIS OF NON-INFLAMMATORY RETIFORM PURPURA
PATHOPHYSIOLOGY: OCCLUSION PRIMARILY DUE TO MICROVASCULAR PLATELET PLUGS
Major etiologies*
1. Heparin necrosis 2. Thrombocytosis secondary to myeloproliferative disorders 3. Paroxysmal nocturnal hemoglobinuria 4. Thrombotic thrombocytopenic purpura (though platelet plugs form primarily in visceral vessels, and skin hemorrhage is due more often to thrombocytopenia)
PATHOPHYSIOLOGY: COLD-RELATED GELLING OR AGGLUTINATION
Major etiologies*
1. Cryoglobulinemia, monoclonal (early lesions of mixed cryoglobulinemia are often inflammatory and leukocytoclastic due to immune complex deposition) 2. Cryofibrinogenemia (though most cryofibrinogens are incidental findings in hospitalized patients) 3. Cold agglutinins (rarely cause occlusion; usually cause hemolysis or are asymptomatic)
PATHOPHYSIOLOGY: OCCLUSION DUE TO ORGANISMS GROWING IN VESSELS
Major etiologies*
1. Vessel-invasive fungi (e.g. *Mucor* spp., *Aspergillus* spp.; usually in immunocompromised patients) 2. Ecthyma gangrenosum (often *Pseudomonas* spp. or other Gram-negative bacilli proliferating in adventitia of subcutaneous arterioles) 3. Disseminated strongyloidiasis
PATHOPHYSIOLOGY: SYSTEMIC ALTERATION IN CONTROL OF COAGULATION
Major etiologies*
1. Protein C- and S-related a. Homozygous protein C or protein S deficiency b. Acquired protein C deficiency (some patients with sepsis-associated DIC) c. Coumadin®/warfarin necrosis (protein C dysfunction) d. Post-infectious purpura fulminans (protein S dysfunction) 2. Antiphospholipid antibody, lupus anticoagulant
PATHOPHYSIOLOGY: VASCULAR COAGULOPATHY
1. Livedoid vasculopathy/atrophie blanche (may also have a systemic prothrombotic component) 2. Malignant atrophic papulosis/Degos' disease (antiphospholipid antibody syndrome can mimic this disease) 3. Sneddon syndrome (in most patients it is related to antiphospholipid antibody syndrome)
PATHOPHYSIOLOGY: EMBOLIZATION OR CRYSTAL DEPOSITION
Major etiologies*
1. Cholesterol emboli 2. Oxalate crystal deposition (rare) 3. Marantic endocarditis, atrial myxoma, crystal globulins, hypereosinophilic syndrome (all rare)
PATHOPHYSIOLOGY: RETICULOCYTE, RED BLOOD CELL OCCLUSION
High reticulocyte states
1. Sickle cell disease; occlusion worsened by red cell sickling 2. Other severe hemolytic anemias 3. Severe malaria (vWF strands, platelets, RBCs)
PATHOPHYSIOLOGY: MISCELLANEOUS
1. Cutaneous calciphylaxis 2. Brown recluse (*Loxosceles*) spider bite reaction 3. Intravascular B-cell lymphoma (see Ch. 23)
*Partial list.

Table 22.5 Differential diagnosis of non-inflammatory retiform purpura. DIC, disseminated intravascular coagulation; RBC, red blood cell; vWF, von Willebrand factor.

DIFFERENTIAL DIAGNOSIS OF INFLAMMATORY RETIFORM PURPURA
VASCULITIS
A. Primarily dermal vessels 1. IgA vasculitis B. Dermal and subcutaneous vessels usually involved 1. Mixed cryoglobulinemia 2. Rheumatic vasculitides (LE, RA) 3. Polyarteritis nodosa 4. Microscopic polyangiitis 5. Wegener's granulomatosis 6. Churg–Strauss syndrome
DERMAL VESSEL INFLAMMATION/OCCLUSION/CONSTRICTION
A. Livedoid vasculopathy B. Septic vasculitis C. Chilblains (pernio) D. Pyoderma gangrenosum

Table 22.6 Differential diagnosis of inflammatory retiform purpura. LE, lupus erythematosus; RA, rheumatoid arthritis.

neutralize thrombin as well as factors IXa, Xa and XIIa; this process is greatly enhanced by heparin sulfate or heparin binding to ATIII. However, the factor IXa produced during initiation is not inhibited by TFPI and is only slowly bound by ATIII.

The *thrombomodulin/protein C/protein S* system is the other major natural anticoagulant pathway. While both ATIII and protein C pathways are important in large vessels, the protein C system seems to be more critical for normal function of the microvasculature. Thrombin that escapes the clot site can bind to thrombomodulin on the endothelial cell surface. Once bound to thrombomodulin, thrombin loses its ability to activate procoagulant factors, and instead avidly binds and activates protein C, a vitamin K-dependent anticoagulant protein. The anticoagulant function of activated protein C is enhanced by its binding to a phospholipid surface as well as a high-density lipoprotein (HDL) and protein S (another vitamin K-dependent anticoagulant). This complex then inactivates factors Va and VIIIa. The factor V Leiden mutation results in a single amino acid change at the site of cleavage by activated protein C, and this change renders it much more resistant to inactivation.

The prothrombin 20210A mutation is a polymorphism located at the polyadenylation site in the 3′ untranslated region of the prothrombin gene that does not affect the final structure of prothrombin. However, it increases the levels of prothrombin, leading to a prothrombotic tendency in some patients.

Overlap of Coagulation and Inflammatory Vessel Disease

Hemostasis is one aspect of the host response to injury. It is clear that inflammatory injury can lead to fibrin deposition in vessels, as exemplified by fibrinoid necrosis in vasculitis (see Fig. 22.3). Conversely, coagulation factors may play an important role in inflammatory responses and wound healing[2,6]. It can be argued that the vertebrate coagulation system is an extension of the innate immune response system observed in the living fossil the horseshoe crab[7]. In this arthropod, 99% of the circulating cells are hematocytes that express pathogen-recognition receptors; upon activation, these cells release multiple proteins with both clotting and complement-like functions which localize and immobilize invading pathogens. The serine proteases involved in blood clotting in vertebrates appear to have diverged from primitive complement precursors, providing a link between the inflammatory and coagulant pathways.

Thrombin not only is a procoagulant factor, but it also can act to promote monocyte, fibroblast and endothelial cell migration into an area of recent injury in order to begin removal of damaged tissue and wound repair. Thrombin bound to thrombomodulin activates protein C, which (in addition to its potent anticoagulant action) also appears to have important anti-inflammatory properties. Of note, administration of activated protein C has been shown in some, but not all, studies to decrease mortality and improve organ function in patients with severe sepsis. In addition, the anti-inflammatory and antithrombotic effects of the protein C pathway may play a role in multiple disorders, from inflammatory bowel disease and rheumatoid arthritis to asthma and atherosclerosis[6].

Platelets release many growth factors and cytokines that affect wound healing (e.g. platelet-derived growth factor, transforming growth

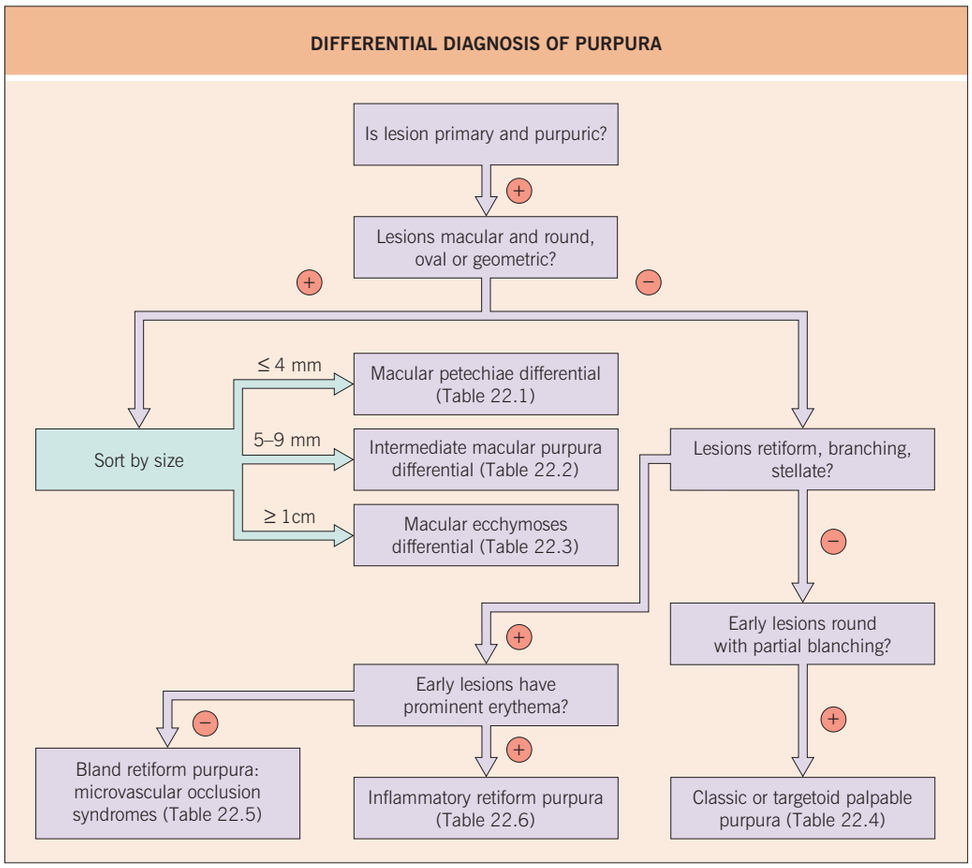


Fig. 22.2 Differential diagnosis of purpura.

factor-β)[7]. Also, a powerful angiogenesis inhibitor, angiostatin, is a cleavage product of plasminogen. These and many other findings suggest that coagulation, inflammation and wound healing pathways are richly and importantly integrated.

Tests for Coagulation

A thorough history (including family history) and physical examination are crucial in the proper selection and interpretation of tests measuring coagulation and anticoagulation parameters. A basic laboratory assessment of clotting includes a platelet count, prothrombin time (PT) and APTT. A prolonged PT with a normal APTT suggests a factor VII deficiency or the use of an oral anticoagulant (at a relatively low dose)[8]. A prolonged APTT with a normal PT can result from the use of heparin, a lupus anticoagulant, an acquired factor VIII inhibitor, von Willebrand disease (which results in a functional deficiency of factor VIII as well as defective platelet adhesion) or a significant deficiency of one of the following: factor VIII, IX, XI, or XII, high-molecular-weight kininogen (HMWK) or prekallikrein (PK). If both the PT and the APTT are prolonged, there may be a deficiency (or inhibitor) of fibrinogen, prothrombin, factor V or factor X or a combined deficiency of multiple procoagulant factors (e.g. due to severe vitamin K deficiency or high doses of an oral anticoagulant). Platelet function tests (e.g. bleeding time, ristocetin-induced platelet aggregation studies) are performed in settings suggesting platelet function defects unexplained by medications (e.g. aspirin, nonsteroidal anti-inflammatory drugs [NSAIDs]) or metabolic disorders such as renal failure. An example would be the platelet dysfunction observed in patients with Hermansky–Pudlak syndrome.

If the PT or APTT is prolonged, repeating the test using a 1:1 mixture of the patient's plasma and normal plasma can be helpful in distinguishing between a deficiency state and the effects of an inhibitor. A 1:1 dilution will usually normalize the time if there is a factor deficiency, but the time will remain prolonged if an inhibitor is present. Other tests, such as the dilute Russell viper venom time, may be helpful in confirming the presence of lupus anticoagulant activity.

Laboratory tests that are useful in the evaluation of a patient suspected to have a hypercoagulable state are presented in Table 105.10.

New Anticoagulant Agents

Over the past decade, a number of agents have joined heparin, low-molecular-weight heparins, and warfarin (Coumadin®) as useful anticoagulant medications, and more are undergoing clinical evaluation (Table 22.7)[9–11]. While offering advantages over warfarin such as reduced drug–drug interactions, the newer agents listed in Table 22.7 all require parenteral administration. However, several oral anticoagulants have recently been approved by the FDA that do not require monitoring of the international normalized ratio (INR), i.e. prothrombin ratio (Table 22.8)[12].

SELECTED PURPURA SYNDROMES

Some syndromes that are not traditionally discussed in chapters on microvascular occlusion (see Ch. 23) or vasculitis (see Ch. 24) will be addressed here.

Pigmented Purpuric Eruptions

Synonyms: ■ Capillaritis ■ Purpura pigmentosa chronica ■ Purpura simplex ■ Majocchi–Schamberg disease

Variants:
- Schamberg's disease: Schamberg's purpura, progressive pigmentary dermatosis of Schamberg, purpura pigmentosa progressiva
- Purpura annularis telangiectodes of Majocchi: Majocchi's disease
- Pigmented purpuric lichenoid dermatitis of Gougerot and Blum
- Eczematid-like purpura of Doucas and Kapetanakis: itching purpura
- Lichen aureus: lichen purpuricus

Key features

- Clustered petechial hemorrhage
- Often a background of yellow–brown discoloration due to hemosiderin deposition
- The location and pattern depends on the particular variant

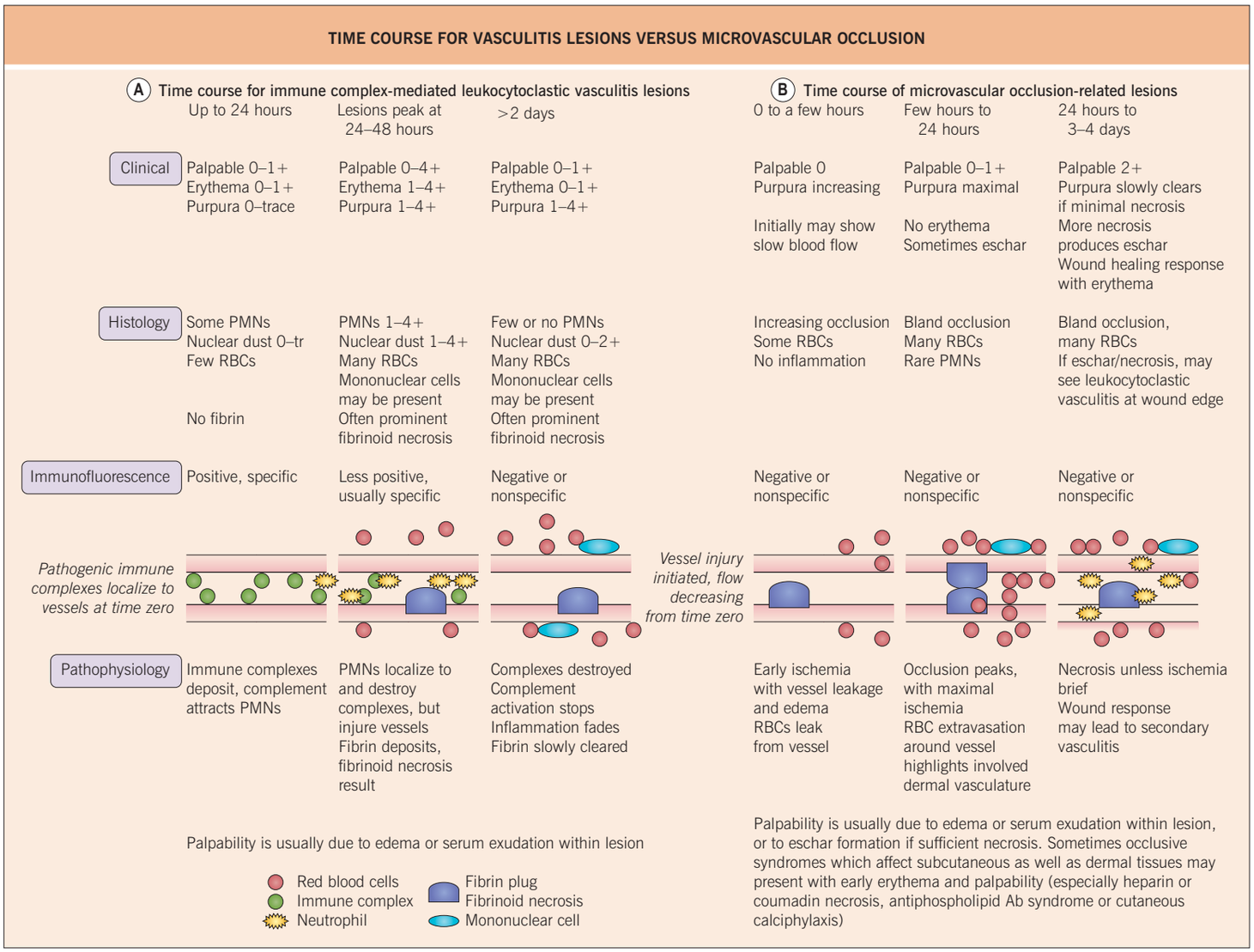


Fig. 22.3 Time course for vasculitis lesions versus microvascular occlusion. A Time course for immune complex-mediated leukocytoclastic vasculitis lesions. **B** Time course of microvascular occlusion-related lesions. Ab, antibody; tr, trace.

Introduction

Pigmented purpuric eruptions represent a group of diseases characterized by petechial hemorrhage thought to be secondary to capillaritis[13]. These diseases have no systemic findings, but they occasionally lead to a patient evaluation to exclude thrombocytopenia or vasculitis because of the purpuric (usually petechial) nature of the lesions and clinical misdiagnosis, especially of the rarer forms.

Pathogenesis

These diseases all result from minimal inflammation and hemorrhage of superficial papillary dermal vessels, usually capillaries. The reason for the inflammation is unknown. This group of chronic inflammatory disorders is not associated with any abnormality of coagulation.

Clinical features

The characteristics of the various forms of pigmented purpuric eruptions are outlined in Table 22.9.

Pathology

Histopathologic features include red cell extravasation, endothelial cell swelling, a perivascular lymphocytic infiltrate and hemosiderin-containing macrophages (Fig. 22.8). The lichen aureus and Gougerot–Blum variants are characterized by a lichenoid infiltrate, and epidermal spongiosis with patchy parakeratosis is often observed in the latter as well as in eczematid-like purpura of Doucas and Kapetanakis.

Differential diagnosis

The clinical picture is often sufficient for diagnosis, but a biopsy specimen may be required to distinguish the lichenoid variant from cutaneous small vessel vasculitis. Although usually on one extremity, angioma serpiginosum may occasionally be misdiagnosed as pigmented purpura. Lesions resembling capillaritis have been reported in patients with mycosis fungoides, allergic contact dermatitis (e.g. due to rubber or azo dyes such as Disperse Blue), non-allergic reactions to topical medications (e.g. fluorouracil or eutectic mixture of local anesthetics [EMLA]), drug eruptions (e.g. carbromal, meprobamate, acetaminophen, infliximab, pseudoephedrine), suction-induced purpura (e.g. cupping or pressing the back against a bathtub) and hypergammaglobulinemic purpura of Waldenström. Pigmented purpuric eruptions on the legs must be differentiated from dermal hemorrhage secondary to venous hypertension, which presents with petechiae superimposed on diffuse hemosiderosis (Fig. 22.5B) rather than the discrete yellow–brown patches that characterize Schamberg's disease.

Treatment

Topical corticosteroid therapy is occasionally helpful, especially in patients who report pruritus or have more evident erythema. Effective treatment of more extensive pigmented purpuric eruptions with PUVA and narrowband UVB has been described[14–16]. Successful therapy with ascorbic acid (500 mg twice daily) plus rutoside (50 mg twice daily) has also been reported.

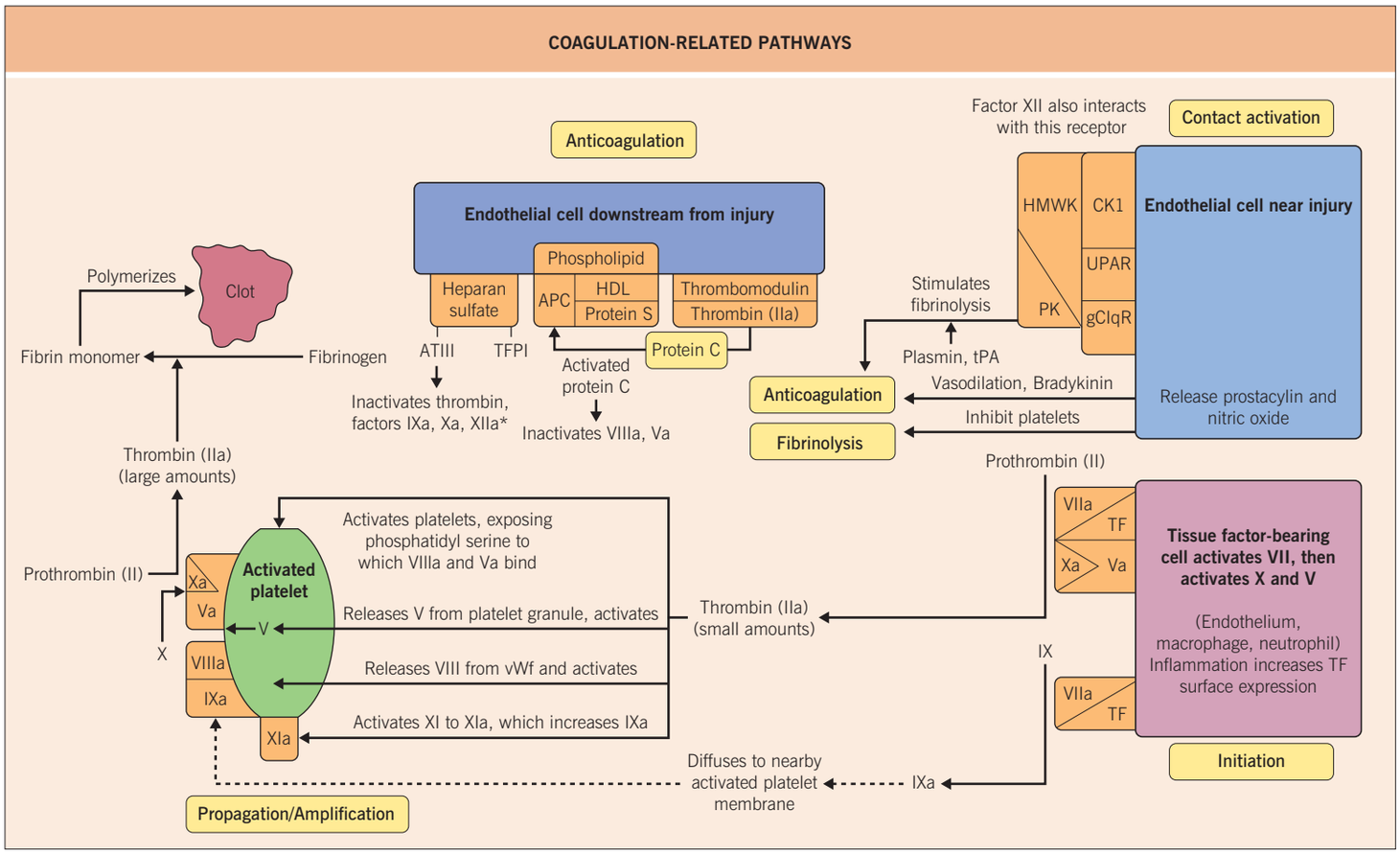


Fig. 22.4 Coagulation-related pathways. TFPI can inactivate factor Xa, and the TFPI–factor Xa complex can inhibit VIIa. *Enhanced by binding of heparin to ATIII. APC, activated protein C; ATIII, antithrombin III; CK1, cytokeratin 1; gC1qR, globular head of the C1q receptor; HDL, high-density lipoprotein; HMWK, high-molecular-weight kininogen; PK, prekallikrein; TF, tissue factor; TFPI, tissue factor pathway inhibitor; tPA, tissue plasminogen activator; UPAR, urokinase plasminogen activator receptor; vWF, von Willebrand factor.

Hypergammaglobulinemic Purpura of Waldenström

Synonym: ▪ Benign hypergammaglobulinemic purpura

Key features

- Usually affects women
- Recurrent crops of petechiae and larger purpuric macules on the lower extremities, which often burn or sting
- Patients typically have a polyclonal hypergammaglobulinemia and high titers of IgG or IgA rheumatoid factor
- An autoimmune connective tissue disease, most often Sjögren's syndrome, develops in a subset of patients

Introduction

This syndrome was first described in 1943 by Waldenström, who reported three women with chronic relapsing purpura, hypergammaglobulinemia, an elevated ESR, and mild anemia. Hypergammaglobulinemic purpura of Waldenström is often associated with an autoimmune connective tissue disease, especially Sjögren's syndrome.

Pathogenesis

Although associated with hypergammaglobulinemia, a strong argument can be made that a more specific feature of this condition is the presence of small circulating immune complexes containing IgG or IgA rheumatoid factor (RF). Such complexes of this size have been identified in individuals with a clinical presentation that fits this syndrome but who lacked polyclonal hypergammaglobulinemia[17,18]. IgG and IgA RFs are highly soluble, which might explain the rapidity with which lesions appear and resolve. The presence of monoclonal RF early in the disease in some patients as well as the tendency of affected individuals to develop autoimmune and (less often) lymphoproliferative disorders supports the presence of a mild immune dysregulation syndrome.

Clinical features

The purpura is often preceded by a slight itch, mild tingling or burning, and it may be aggravated by tight-fitting garments, prolonged standing and heat. Macular hemorrhage (e.g. petechiae or larger purpuric macules) on the lower extremities represents the most common presentation, but the lesions may be fleeting. Some patients have palpable purpura with histologic evidence of vasculitis (see below), which has led many authors to classify hypergammaglobulinemic purpura of Waldenström as a subset of cutaneous small vessel vasculitis.

Hypergammaglobulinemic purpura of Waldenström can be primary or secondary[19]. In younger patients it is usually primary, but over time some patients develop evidence of an autoimmune connective tissue disease, most frequently Sjögren's syndrome and occasionally rheumatoid arthritis or lupus erythematosus. Much less often, a monoclonal gammopathy or, very rarely, a lymphoma or multiple myeloma develops.

Laboratory evaluation typically reveals polyclonal hypergammaglobulinemia and an elevated ESR. Standard RF assays identify only IgM RF, so they will not detect the IgG and IgA RFs that are frequently found in this syndrome (although specific tests for IgG and IgA RF can be performed). Anti-Ro (SS-A) and -La (SS-B) antibodies are commonly present and may predict a higher likelihood of developing an associated autoimmune connective tissue disease.

ANTICOAGULANTS			
Agent	**Action**	**Origin/current form**	**Half-life (T1/2), Comments**
		CLASSIC ANTICOAGULANTS	
Heparin	Binds to AT (ATIII) to enhance 1000-fold the AT inhibition of thrombin and Xa Heparin/AT complex also inhibits IXa, Xa and XIIa of the intrinsic and VIIa–TF (tissue factor) of the extrinsic pathways, respectively	Biologic extract from bovine and swine lung and intestine that consists of multiply-sized glycosaminoglycan polymers	• T1/2 = 30 min–2.5 h iv; 2 h delay but 10 h effect sc
Warfarin (coumarin; Coumadin®)	Impairs γ-carboxylation of vitamin K-dependent clotting factors (VII, X, IX, II [prothrombin]) and anticoagulants (proteins C and S), with reduced levels of functional factors	Synthetic	• T1/2 = 35–45 h orally, but effect depends on impaired synthesis of proteins • Usually 5–6 days of stable dose required to reach maximum effect • Effect inhibited by vitamin K • Multiple drug–drug interactions*
		EXTRINSIC PATHWAY INHIBITORS	
Tissue factor pathway inhibitor (TFPI)	Binds, inactivates Xa, then inhibits VIIa	Plasma, platelet α-granules, endothelial cell surface/recombinant	• Clinical trials (iv)
Nematode anticoagulant peptide (NAPc2)	Binds X or Xa, then inhibits VIIa	Canine hookworm/recombinant	• T1/2 = 50 h sc • Clinical trials
Active-site blocked factor VIIa (factor VIIai)	Inhibits by competing with VIIa for tissue factor binding		• T1/2 = 45 min in plasma, but acts up to 6 h after single sc injection • Animal studies
		FACTOR Xa INHIBITORS: INDIRECT (VIa ATIII)	
Low-molecular-weight heparins (LMWH), including ardeparin, dalteparin, enoxaparin, nadroparin, tinzaparin	Like heparin, bind to AT (ATIII) to inhibit thrombin, Xa and other serine protease clotting factors (unlike heparin, inhibit Xa > thrombin)	Chemical or enzymatic treatment of native heparin to produce molecules that are 4000–5000 daltons (native heparin 5000–30 000 daltons)	• T1/2s allow once- or twice-daily sc administration • Adjust dose if renal insufficiency • Multiple prophylactic and therapeutic anticoagulant regimens
Danaparoid	ATIII-dependent anti-Xa inhibition	Mixture of 84% heparan sulfate, 12% dermatan sulfate, 4% chondroitin sulfate	• T1/2 = 24 h; daily or twice-daily sc administration • Renal clearance • Used to treat HIT
Fondaparinux	ATIII-dependent Xa inhibition; dissociates to bind additional ATIII molecules	Synthetic analogue of pentasaccharide sequence of heparin that interacts with ATIII	• T1/2 = 17 h sc; once-daily administration • Contraindicated in patients with crt cl <30 ml/min • Unlike heparin, no antidote • Does not bind to Plt factor 4, so should not cause HIT
Idraparinux	As above (fondaparinux)	As above (fondaparinux)	• T1/2 = 80–130 h sc; once-weekly administration
		FACTOR Xa INHIBITORS: DIRECT	
DX-9065a	Binds to active site of Xa	Non-peptide arginine derivative	• Continuous iv infusion
Razaxaban	Binds to active site of Xa	Imidazole derivative	• Oral; twice-daily administration
		INHIBITORS OF FACTORS Va & VIIIa	
Activated protein C	Inactivates Va, VIIIa	Recombinant	• Infusion over 96 h • Non-coagulant properties may play a role in sepsis therapy
Soluble thrombomodulin	Binds thrombin, activates protein C	Recombinant	• sc administration, every 2–3 days
		THROMBIN INHIBITORS (UNLIKE HEPARIN, INACTIVATE FIBRIN-BOUND AS WELL AS FLUID-PHASE THROMBIN)	
Hirudin	Irreversible bivalent binding to two sites on thrombin	Leech salivary gland	• T1/2 = 60 min iv, 120 min sc • Adjust dose if renal function decreased • No antidote
Lepirudin	65-amino acid analogue of hirudin	Biosynthetic peptide closely related to hirudin	• T1/2 = 1–3 h sc, longer if renal function decreased • No antidote • Approved for use in HIT
Bivalirudin	20-amino acid analogue of hirudin	Recombinant	• T1/2 = 25 min iv • Minimal renal excretion • No antidote
Argatroban	Reversible complex with active site of thrombin	Synthetic small molecule that is arginine derivative	• T1/2 = 45 min iv • Metabolized in liver • Approved for treatment of HIT

*Includes antibiotics, lipid-lowering agents, antiplatelet agents (see Ch. 131).

Table 22.7 Anticoagulants[9–11]. This list does not include the antiplatelet agents that block platelet ADP receptors (e.g. clopidogrel, prasugrel). AT (ATIII), antithrombin (antithrombin III); crt cl, creatinine clearance; HIT, heparin-induced thrombocytopenia; iv, intravenous; Plt, platelet; sc, subcutaneous.

NEWER ORAL ANTICOAGULANTS				
Agent	**Action**	**Oral bioavailability**	**Half-life (T1/2) and metabolism**	**Comments**
Apixaban	Directly inhibits factor Xa (both within and outside the prothrombinase complex)	50%, with peak plasma level 3–4 h post-ingestion	• T1/2 = 10–14 h • Partially metabolized by CYP3A4 and by CYP-independent hepatic mechanisms • Partially eliminated via kidneys (25%)	Neither induces nor inhibits CYP enzymes
Dabigatran	Directly inhibits thrombin (both free and clot-bound)	• 7%, with peak plasma level 1.5 h post-ingestion • Pro-drug dabigatran etexilate converted in the liver to dabigatran	• T1/2 = 14–17 h • Primarily fecal excretion, but up to 80% of active drug may be eliminated via kidneys	• Significant renal dysfunction a contraindication • Drug–drug interactions with quinine, quinidine and verapamil
Rivaroxaban	Directly inhibits factor Xa (both free and complex-bound)	>80%, with peak plasma level 3 h post-ingestion	• T1/2 = 4–9 h* • 66% excreted via kidneys	Contraindicated in patients with crt cl <30 ml/min

*Up to 12 h in patients >75 years of age.

Table 22.8 Newer oral anticoagulants. From ref. 12. crt cl, creatinine clearance; CYP, cytochrome P450.

TYPES OF PIGMENTED PURPURIC DERMATOSES			
Type	**Age/Sex**	**Morphology**	**Location**
Schamberg's disease	• Most common form • Can occur in children • Peak frequency in middle-aged to older men	• Yellow–brown patches with an oval to irregular outline (Fig. 22.5A) • Pinpoint petechiae within patches – likened to "cayenne pepper" • Successive crops	• Favors lower legs • Can also involve thighs, buttocks, trunk and arms
Purpura annularis telangiectodes of Majocchi	• Uncommon • Adolescents and young adults, especially women	• 1–3 cm annular plaques that may slowly expand • Punctate telangiectasias and petechiae within the border (Fig. 22.6)	Trunk, proximal lower extremities
Pigmented purpuric lichenoid dermatitis of Gougerot and Blum	• Rare • Middle-aged to older men	• Admixture of two types of lesions: 1) Schamberg-like 2) Purpuric red–brown lichenoid papules • Chronic • Occasionally pruritic	On lower extremity, may be confused with small vessel vasculitis
Eczematid-like purpura of Doucas and Kapetanakis	• Rare • Middle-aged to older men	• Scaly petechial or purpuric macules, papules and patches • Pruritic	Primarily lower extremities
Lichen aureus	• Rare	• Solitary patch • Color varies from golden to rust to purple–brown	Usually lower extremity, often over a perforator vein
Linear pigmented purpura	• Rare • Can occur in children and adolescents	• Linear array, usually unilateral (Fig. 22.7) • Individual lesions similar in appearance to lichen aureus or Schamberg's disease	Often a single extremity
Granulomatous pigmented purpura	• Very rare	• Brown patches with superimposed hemorrhagic papules*	Lower legs

*Histologically, hemorrhagic granulomatous inflammation in upper dermis.

Table 22.9 Types of pigmented purpuric dermatoses. Rarely, the first two types are familial.

Pathology

Simple hemorrhage, a mild perivascular lymphocytic infiltrate or leukocytoclastic vasculitis can characterize these lesions.

Differential diagnosis

The clinical picture is often characteristic. Some patients develop palpable purpura mimicking classic cutaneous small vessel vasculitis syndromes, but most patients present with recurring crops of burning or stinging macular hemorrhage.

Treatment

Some agents used to treat this syndrome, such as aspirin or support stockings, have also been reported to exacerbate the condition. Avoidance of precipitating factors such as alcohol and prolonged standing may be helpful. In secondary cases, treatment is aimed at the underlying disease.

Gardner–Diamond Syndrome

Synonyms: ■ Psychogenic purpura ■ Autoerythrocyte sensitization

Key features

- Factitial disorder that typically affects women with an underlying psychiatric illness
- Painful, swollen ecchymoses are observed at sites of trauma

Introduction

In 1955, Gardner and Diamond described four women with an abnormal response to bruising characterized by the development of painful ecchymoses at sites of trauma followed by progressive erythema and edema[20]. The largest series (71 patients) to date of Gardner–Diamond syndrome was reported by Ratnoff[21] in 1989.

Fig. 22.5 Schamberg's disease versus petechiae and hemosiderin secondary to venous hypertension. A Discrete yellow–pink patches with superimposed petechiae in Schamberg's disease. **B** Petechiae superimposed on more diffuse hemosiderin deposits in venous hypertension, referred to as "stasis purpura". *B, Courtesy, Jean L Bolognia, MD.*

Fig. 22.6 Purpura annularis telangiectodes of Majocchi. Annular plaques with cayenne pepper petechiae in the border.

Fig. 22.7 Linear pigmented purpuric dermatosis. Linear array of yellow–brown macules and patches with superimposed petechiae and small, red–brown purpuric papules on the arm of a child. The eruption had been present for several months and was limited to this segment of skin.

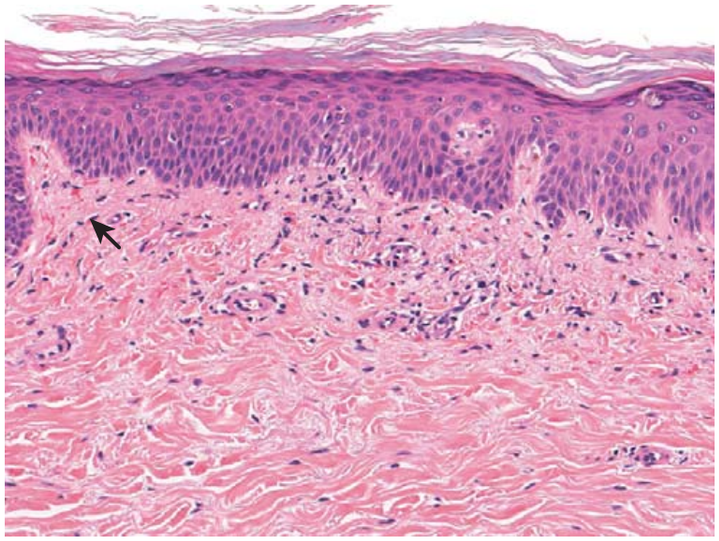


Fig. 22.8 Pigmented purpuric eruption – histologic features. Minimal perivascular lymphocytic infiltrate with extravasation of red blood cells (arrow) and hemosiderin deposits. *Courtesy, Lorenzo Cerroni, MD.*

Clinical features

This condition is seen predominantly in women, and has been associated with psychiatric illness in the majority of patients: depression, anxiety, difficulties in handling aggression and hostility, hypochondriasis, sexual maladjustments, masochism, hysterical and borderline personality disorders, and obsessive–compulsive behavior.

Lesions are characterized by the sudden onset of painful, swollen bruises of variable size in any area of the body. They usually resolve within a 2-week period and then typically recur. Original reports described appearance of these atypical purpuric lesions at sites of injection of a patient's own blood or other agents. However, later studies showed that in some patients, lesions were reproduced at injection sites that the investigator suggested were "test" sites but not at those suggested to be "control" sites (but injected with the same agent). Patients were observed to induce the lesions traumatically (i.e. factitial disease).

Pathology

The histologic features of early lesions consist of edema, a minimal perivascular mononuclear infiltrate and extravasated red blood cells in the upper dermis.

Differential diagnosis and treatment

The lesions in this syndrome are usually suggestive of a factitial origin, with atypical locations, geometric or peculiar morphologies, and a lack of clearcut precipitating factors. However, proving a factitial origin is generally difficult, and it is usually not helpful to confront the patient. Gentle probing for an underlying and potentially treatable psychiatric

condition may be beneficial. Effective management of this syndrome can prove to be very difficult.

Mondor's Syndrome of Superficial Thrombophlebitis

Synonym: ■ Mondor's disease

Key features

- Superficial thrombophlebitis affecting the anterolateral thoracoabdominal wall
- Pathogenic factors include trauma, surgical procedures, infections and cancer of the breast
- Presents with the sudden onset of chest pain and subsequent appearance of a cord-like thrombosed vein

Introduction

Mondor's syndrome is characterized by superficial thrombophlebitis of subcutaneous veins within the anterolateral thoracoabdominal wall (e.g. lateral thoracic, thoracoepigastric and superior epigastric veins). Though previously reported by others, Henry Mondor provided a very detailed description of this condition in 1939[22]. A similar cord-like superficial thrombophlebitis can occur in other sites (e.g. the upper and lower extremities, abdomen, groin and penis).

Pathogenesis

Common pathogenic factors in chest wall thrombophlebitis include trauma, excessive physical activity, a surgical procedure on the breast, mastitis, a breast abscess and pendulous breasts[22–24]. Up to 10% of patients with Mondor's syndrome have an underlying breast carcinoma. The condition is also occasionally associated with rheumatoid arthritis, filariasis, pregnancy, oral contraceptive use, intravenous drug use, intravenous catheters, a non-breast malignancy or a hypercoagulable state (e.g. hereditary protein C deficiency, anticardiolipin antibodies).

Clinical features

Sudden onset of chest pain followed by the appearance of one or more visible or palpable cords (representing thrombophlebitic veins) typify this syndrome. Associated findings include tenderness, a sensation of tension, erythema, ecchymosis, pruritus, arthralgia and, rarely, fever. Symptoms worsen on pulling the skin or elevating the breast and the ipsilateral upper extremity. The condition is usually unilateral and is three times more common in women than in men.

Pathology

A biopsy is rarely required. The process may involve arteries and lymphatic vessels as well as veins. Sclerosing endophlebitis with complete or partial obliteration of the lumen by thrombus and inflammatory cells is typical. The time period between the onset of the condition and ultimate recanalization of the affected vessels varies from 2 weeks to more than 6 months.

Differential diagnosis

The clinical presentation is unique, and etiologic factors should be identified. Recurrent superficial thrombophlebitis (migratory thrombophlebitis) is frequently associated with an underlying malignancy (Trousseau's syndrome; most often pancreatic or lung carcinoma), a hypercoagulable state (inherited or acquired) or an inflammatory condition (e.g. Behçet's disease).

Treatment

The disease is usually benign and self-limited, except when associated with breast cancer. Aching pain typically ends within 10 days, but the cord often persists for weeks to months and may be tender. Local heat, rest of the arm, and breast support can improve symptoms. The rate of recurrence is approximately 5%.

Superficial venous thrombophlebitis may occur in other locations (e.g. lower extremities), but is not considered Mondor's syndrome. In a Cochrane review of treatment options for superficial thrombophlebitis of the lower extremity, NSAIDs and low-molecular-weight heparin reduced extension or recurrences by ~70% (compared to placebo)[25]. Superficial venous thrombosis involving the main trunk of the saphenous vein has the strongest association with venous thromboembolism, and when the thrombosis is at or near the sapheno-femoral or saphenopopliteal junction, it should probably be removed, followed by venous ligation/stripping and possibly three months of low-molecular-weight heparin.

REFERENCES

1. Piette WW. The differential diagnosis of purpura from a morphologic perspective. Adv Dermatol. 1994; 9:3–24.
2. Roberts H, Monroe D, Hoffman M. Molecular biology and biochemistry of the coagulation factors and pathways of hemostasis. In: Lichtman M, Beutler E, Kaushansky K, et al (eds). Williams Hematology, 7th edn. New York: McGraw-Hill, 2006:1665–93.
3. Griffin J. Control of coagulation reactions. In: Lichtman M, Beutler E, Kaushansky K, et al (eds). Williams Hematology, 7th edn. New York: McGraw-Hill, 2006:1695–714.
4. Motta G, Rajkjaer R, Hasan AA, et al. High molecular weight kininogen regulates prekallikrein assembly and activation on endothelial cells: a novel mechanism for contact activation. Blood. 1998;91:516–28.
5. Mahdi F, Madar ZS, Figueroa CD, Schmaier AH. Factor XII interacts with the multiprotein assembly of urokinase plasminogen activator receptor, gC1qR, and cytokeratin 1 on endothelial cell membranes. Blood. 2002;99:3585–96.
6. Danese S, Vetrano S, Zhang L, et al. The protein C pathway in tissue inflammation and injury: pathogenic role and therapeutic implications. Blood. 2010;115:1121–30.
7 Delvaeye M, Conway EM. Coagulation and innate immune responses: can we view them separately? Blood. 2009;114:2367–74.
8. Seligsohn U, Kaushansky K. Classification, clinical manifestations, and evaluation of disorders of hemostasis. In: Lichtman M, Beutler E, Kaushansky K, et al (eds). Williams Hematology, 7th edn. New York: McGraw-Hill, 2006:1741–7.
9. Weitz J. New anticoagulant drugs. J Thromb Thrombolysis. 2001;12:7–17.
10. Hirsh J, O'Donnell M, Weitz JI. New anticoagulants. Blood. 2005:105:453–63.
11. Francis, CW, Kaplan, K. Principles of antithrombotic therapy. In: Lichtman M, Beutler E, Kaushansky K, et al (eds). Williams Hematology, 7th edn. New York: McGraw-Hill, 2006:283–300.
12. Garcia D, Libby E, Crowther MA. The new oral anticoagulants. Blood. 2009;115:15–20.
13. Kim HJ, Skidmore RA, Woosley JT. Pigmented purpura over the lower extremities: purpura annularis telangiectodes of Majocchi. Arch Dermatol. 1998;134:1477, 1480.
14. Ling TC, Goulden V, Goodfield MJ. PUVA therapy in lichen aureus. J Am Acad Dermatol. 2001;45:145–6.
15. Krizsa J, Hunyadi J, Dobozy A. PUVA treatment of pigmented purpuric lichenoid dermatitis (Gougerot-Blum). J Am Acad Dermatol. 1992;27:778–80.
16. Gudi VS, White MI. Progressive pigmented purpura (Schamberg's disease) responding to TL01 ultraviolet B therapy. Clin Exp Dermatol. 2004;29:683–4.
17. Capra JD, Winchester RJ, Kunkel HG. Hypergammaglobulinemic purpura: studies on the unusual anti-gamma-globulins characteristic of the sera of these patients. Medicine (Baltimore). 1971;50:125–38.
18. Preud'homme JL, Duarte F, Aucouturier P. Isolation of monoclonal rheumatoid factors in hypergammaglobulinemic purpura. Diagn Immunol. 1984;2:219–23.
19. Finder KA, McCullough ML, Dixon SL, et al. Hypergammaglobulinemic purpura of Waldenstrom. J Am Acad Dermatol. 1990;23:669–76.
20. Uthman IW, Moukarbel GV, Salman SM, et al. Autoerythrocyte sensitization (Gardner-Diamond) syndrome. Eur J Haematol. 2000;65:144–7.
21. Ratnoff OD. Psychogenic purpura (autoerythrocyte sensitization): an unsolved dilemma. Am J Med. 1989;87:16N–21N.
22. Mayor M, Buron I, de Mora JC, et al. Mondor's disease. Int J Dermatol. 2000;39:922–5.
23. Hacker SM. Axillary string phlebitis in pregnancy: a variant of Mondor's disease. J Am Acad Dermatol. 1994;30:636–8.
24. Samlaska CP, James WD. Superficial thrombophlebitis II. Secondary hypercoagulable states. J Am Acad Dermatol. 1990;23:1–18.
25. Di Nisio M, Wichers IM, Middeldorp S. Treatment for superficial thrombophlebitis of the leg. Cochrane Database Syst Rev. 2007;(2):CD004982.

This page intentionally left blank

Cutaneous Manifestations of Microvascular Occlusion Syndromes

23

Warren W Piette

Chapter Contents

Disorders of platelet plugging 369
Disorders of cryogelling or cryoagglutination 373
Disorders of occlusion by opportunistic organisms proliferating within vessels 375
Disorders of occlusion by emboli 375
Systemic coagulopathies with cutaneous manifestations 377
Disorders of vascular coagulopathies with cutaneous manifestations 380
Disorders of cellular vascular occlusion 382

INTRODUCTION

The differential diagnosis of microvascular syndromes involving the skin is extensive, and the evaluation can be confusing, but it is critical to distinguish between inflammatory injury and non-inflammatory occlusive injury to vessels. The diagnosis of occlusive syndromes in the skin is greatly facilitated by finding the telltale lesions of retiform purpura (see Ch. 22). Recognition of retiform purpura allows one to focus on the clues from the history and the remaining physical examination which may favor or exclude major subsets of cutaneous occlusive disease.

Diseases that produce skin lesions secondary to microvascular occlusion have often been lumped with cutaneous vasculitic syndromes, or discussed primarily as systemic diseases with little attention paid to cutaneous findings. While there is some overlap in the pathogenesis of deep venous thrombosis and pulmonary emboli and the pathogenesis of cutaneous microvascular occlusion syndromes, the two differ substantially with respect to disease etiology and treatment (see Ch. 22).

The differential diagnosis for occlusive syndromes is best approached through major pathophysiologic categories (Table 23.1). These major pathophysiologic categories frequently have sufficiently distinctive clinical settings that even a minimal history and physical examination plus laboratory findings can usually allow an efficient sorting of diagnostic possibilities (Fig. 23.1). This is especially important in life-threatening situations where making timely decisions is crucial. A reasonable panel of initial laboratory tests plus comments on their relevance are listed in Table 23.2.

It must be emphasized that some inflammatory syndromes capable of producing retiform purpura may occasionally present with lesions that have minimal inflammation (see Ch. 22). In particular, this may occur with the ANCA-positive syndromes of Wegener's granulomatosis and microscopic polyangiitis, as well as ANCA-negative cutaneous polyarteritis nodosa. Therefore, it is reasonable to order an ANCA test, even in a setting where occlusion is believed to be the most likely diagnosis.

Because treatment depends directly on pathogenesis, accurate diagnosis is critical to appropriate therapy. Therapies for inflammatory disease differ greatly from therapies for occlusive disease. The use of anti-inflammatory therapy for occlusive disease may not only be useless but also harmful, and the same may be true for anticoagulant therapy in most vasculitides.

DISORDERS OF PLATELET PLUGGING

Heparin Necrosis

Synonyms: ■ Heparin-induced thrombocytopenia (HIT) syndrome – platelet activation stage ■ Heparin-associated thrombocytopenia with thrombosis (HATT) syndrome – includes patients who develop thrombosis

Key features

- Exposure to heparin
- Retiform, branching purpura or non-inflammatory necrosis
- Lesions may be distant or at sites of heparin infusion or injection

Introduction

Heparin necrosis is an unusual but important iatrogenic syndrome first recognized in the early 1970s. Necrosis may occur with heparin exposure after subcutaneous or intravenous administration, including the trace amounts of heparin used to keep infusion lines open.

Heparin-induced thrombocytopenia occurs in 1–5% of adults exposed to heparin, with 30–90% of these patients developing thrombosis. However, the latter figures are primarily from retrospective series where the diagnosis of heparin-induced thrombocytopenia was made following a thrombotic episode; as a result, it is likely that the true incidence of thrombosis is ≤30%. In one study of 612 pediatric Intensive Care Unit patients who received heparin, the associated incidence of thrombosis was reported at 2.3%[1].

Pathogenesis

Heparin necrosis is caused by an antibody which binds not to heparin alone, but to complexes of heparin plus platelet factor 4, a protein expressed on the platelet surface. Antibodies which bind simultaneously to antigens on both these molecules appear to activate the platelet by Fc binding to platelet Fc receptors. Platelet aggregation and consumption follows. Vascular occlusion, involving veins, arteries or the cutaneous microvasculature, may result, leading to such complications as stroke, digital or limb necrosis, or cutaneous necrosis.

Clinical features

Heparin necrosis usually occurs between days 5 and 10 of heparin therapy, although it may develop much earlier in patients previously sensitized to heparin. In a study examining the timing of its onset in 243 patients who developed this syndrome, 70% developed thrombocytopenia 4 or more days (usually 5 to 10) after starting therapy, with or without a previous history of heparin therapy. In the remaining 30% of patients, a rapid onset was seen (median time 10.5 hours after start of heparin), which was dependent on exposure to heparin within the previous 100 days[2]. There is also a delayed-onset form of heparin necrosis, in which lesions can occur up to 3 weeks after exposure to heparin[3]. Heparin-dependent antibodies do not invariably reappear with subsequent heparin use *after* 100 days. Most patients with heparin-related thrombocytopenia do not develop clinically evident thrombosis, but heparin necrosis may occur without thrombocytopenia.

Lesions are usually tender, sharply demarcated, non-inflammatory (erythema unusual), and typically purpuric or necrotic with a retiform

DIAGNOSIS OF CUTANEOUS MICROVASCULAR OCCLUSION BASED ON PATHOPHYSIOLOGY	
PLATELET PLUGGING	
• Heparin necrosis*	
• Thrombocytosis secondary to myeloproliferative disorders	
• Paroxysmal nocturnal hemoglobinuria	
• Thrombotic thrombocytopenic purpura (rare)	
COLD-RELATED GELLING OR AGGLUTINATION	
• Cryoglobulinemia	
• Cryofibrinogenemia	
• Cold agglutinins	
VESSEL-INVASIVE ORGANISMS	
• Ecthyma gangrenosum (primarily Gram-negative bacteria)	
• Opportunistic fungi (e.g. *Aspergillus* spp., *Rhizopus* spp.)	
• Disseminated strongyloidiasis	
• Lucio's phenomenon of leprosy	
EMBOLIZATION	
• Cholesterol embolus	
• Oxalate embolus	
• Atrial myxoma	
• Marantic endocarditis	
• Libman–Sacks endocarditis (lupus, often in association with antiphospholipid antibodies)	
• Infective endocarditis (acute, fungal) (rare)†	
• Crystalglobulin vasculopathy	
• Hypereosinophilic syndrome	
SYSTEMIC COAGULOPATHIES	
• Neonatal purpura fulminans	
• Warfarin (Coumadin®) necrosis	
• Purpura fulminans of sepsis/DIC	
• Postinfectious purpura fulminans	
• Antiphospholipid antibody/lupus anticoagulant syndrome	
VASCULAR COAGULOPATHIES	
• Sneddon syndrome	
• Livedoid vasculopathy	
• "Malignant" atrophic papulosis	
CELL OCCLUSION SYNDROMES	
• Stress reticulocyte adhesion with major hemolytic anemias and/or sickling	
• Intravascular lymphoma	
MISCELLANEOUS/UNKNOWN MECHANISM	
• Cutaneous calciphylaxis	• Local interferon injection reaction
• Hydroxyurea-induced ulcers	• Large hematoma occlusion syndrome
• Brown recluse *(Loxosceles)* spider bite	
*Encompasses heparin-induced thrombocytopenia (HIT)/heparin-associated thrombocytopenia and thrombosis (HATT).	
†Usually inflammatory.	

Table 23.1 Differential diagnosis of cutaneous microvascular occlusion based on pathophysiology. DIC, disseminated intravascular coagulation.

morphology; large necrotic areas with irregular branching margins can also be seen. Lesions may occur at the site of subcutaneous injections (Fig. 23.2) or may develop at sites distant to the heparin infusion. Although consumption of platelets is part of this syndrome, and thrombocytopenia is often cited as a feature of the syndrome, absolute thrombocytopenia is often not present in patients with significant vascular occlusion. Without knowing the platelet count immediately prior to starting heparin, it is impossible to know when a platelet count of 200 000/μl, for example, may in fact represent a decrease by half from a pretreatment reactive thrombocytosis of 400 000/μl. Any organ or limb is potentially at risk for vascular occlusion, including the CNS.

Pathology

Heparin necrosis usually leads to non-inflammatory occlusion of vessels, including microvascular, venous or arterial occlusion. Although platelet plugs are traditionally referred to as white clots, even a skilled pathologist may have difficulty reliably distinguishing "white clot" platelet plugs from the usual "red clot" of fibrin thrombi.

Differential diagnosis

A recent history of heparin administration should prompt consideration of this diagnosis in any patient who develops retiform purpura or bland necrosis, whether or not the patient is thrombocytopenic. Of note, a drop in the platelet count is common in patients on heparin as an incidental finding, unrelated to the development of this syndrome. Conversely, a normal platelet count does not exclude the diagnosis, especially if the pretreatment platelet count is unknown. Other cutaneous occlusion syndromes likely to be associated with thrombocytopenia include antiphospholipid antibody syndrome, purpura fulminans secondary to sepsis, and thrombotic thrombocytopenic purpura (although lesions of cutaneous necrosis secondary to platelet plugging are rare in this last syndrome). Specialized antibody testing can confirm the presence of heparin–platelet factor 4 antibodies in patients, but clinical decisions usually have to be made before the results of these tests are known.

Treatment

Treatment requires cessation of heparin therapy. Although most heparin necrosis has occurred with unfractionated heparin, low-molecular-weight heparin appears to have a much lower, but still real, risk of inducing or supporting this reaction[4,5]. For a patient with heparin-induced thrombocytopenia or heparin-associated thrombocytopenia with thrombosis syndrome in need of acute anticoagulation, selection of an alternate anticoagulant strategy can be challenging, requiring expertise in anticoagulant options and assessment of risk of discontinuing therapy. Argatroban, danaparoid or lepirudin may be useful in this setting (see Table 22.7)[6]. Of note, if warfarin (Coumadin®) monotherapy is instituted during acute heparin-induced thrombocytopenia, the resulting decline in protein C activity may lead to progression of thrombosis and necrosis (see below, Warfarin necrosis).

Thrombocytosis Secondary to Myeloproliferative Disorders

Key features

- Retiform purpura
- Thrombocytosis due to myeloproliferative disorders
- Platelet plugs within dermal vessels or subcutaneous arterioles
- Some patients may develop secondary erythromelalgia

Introduction

Reactive or postsplenectomy thrombocytosis is not believed to be a risk factor for platelet occlusion syndromes, but thrombocytosis due to myeloproliferative (and, rarely, myelodysplastic [e.g. due to 5q deletion]) disorders clearly is. Essential thrombocythemia (thrombocytosis) is the most likely myeloproliferative disorder to result in cutaneous lesions of platelet plug occlusion, and polycythemia vera the second. Both of these syndromes, though rare, are more common in young people and in women.

Pathogenesis

Platelets in myeloproliferative and some myelodysplastic disorders can function abnormally, leading to hemorrhage or occlusion. Whether the platelet dysfunction in myeloproliferative disorders can lead to occlusive phenomena when the platelet count is within the normal range has not been proven.

Clinical features

The exact molecular or physiologic defects of platelets in myeloproliferative disorders have been poorly characterized, so it is not yet possible to predict the risk of bleeding or thrombosis in patients with these hematologic diseases. Cutaneous lesions have been reported in approximately 20% of patients with essential thrombocythemia, including purpura, hematomas, livedo reticularis, erythromelalgia, Raynaud's phenomenon, urticaria, cutaneous small vessel vasculitis, leg ulcers, gangrene and recurrent superficial thrombophlebitis[7]. Lesions of

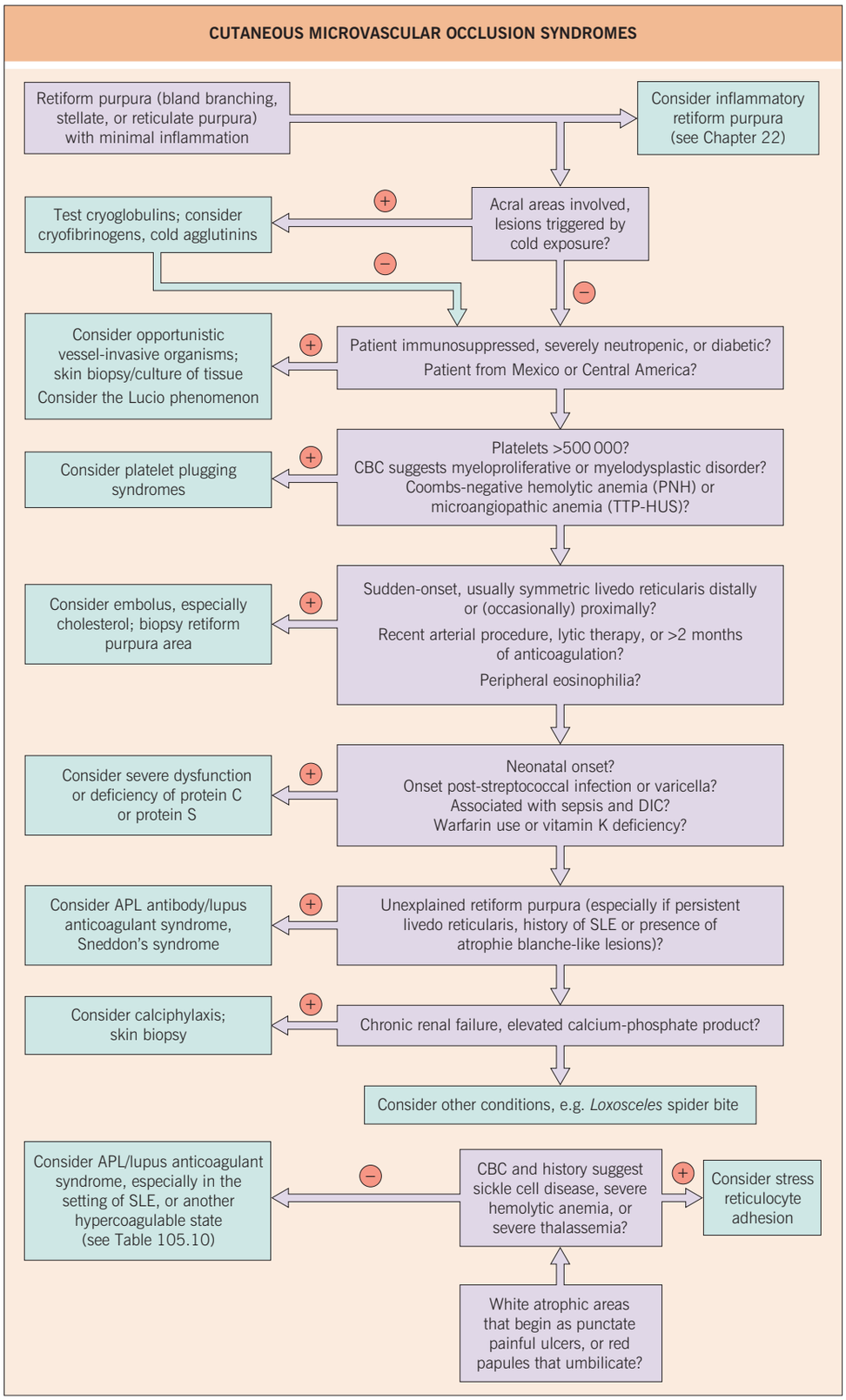


Fig. 23.1 Cutaneous microvascular occlusion syndromes. APL, antiphospholipid; DIC, disseminated intravascular coagulation; PNH, paroxysmal nocturnal hemoglobinuria; TTP-HUS, thrombotic thrombocytopenic purpura–hemolytic uremic syndrome.

microvascular occlusion are an important subset of these cutaneous lesions. Sometimes, the cutaneous lesion of platelet plugging can be the clue to an underlying myeloproliferative disorder[8].

Erythromelalgia is a syndrome that can occur as a primary (idiopathic) or a secondary phenomenon (see Ch. 106). It is characterized by intensely burning and uncomfortable paroxysmal bright erythema of the distal extremities. Most closely associated with essential thrombocythemia, and less often with polycythemia vera, this syndrome can occur in association with any myeloproliferative or myelodysplastic disorder if the platelet counts are sufficiently elevated[9]. This particular form of secondary erythromelalgia is caused by platelet-mediated acral vasodilation, inflammation, and microvascular occlusion. With abnormal platelets, but not in other erythromelalgia syndromes, one may also see discrete areas of purpura or necrosis, often retiform, that represent microvascular occlusion by platelet plugs. This version of erythromelalgia is typically dramatically responsive to aspirin administration, while idiopathic or other secondary forms typically show minimal to no benefit with aspirin.

BASIC SCREENING TESTS FOR OCCLUSIVE SYNDROMES
COMPLETE BLOOD COUNT WITH DIFFERENTIAL, PLATELET COUNT AND BLOOD SMEAR
• Polycythemia or anemia, granulocytosis, thrombocytosis, poikilocytosis – May be sign of myeloproliferative or myelodysplastic diseases • Evidence of red cell fragmentation (schistocytes) and microangiopathy, consider: – TTP-hemolytic uremic syndrome – Purpura fulminans with DIC, occasionally – Antiphospholipid antibody syndrome, occasionally • Thrombocytopenia, consider: – Heparin necrosis, some patients – Purpura fulminans with DIC – TTP-hemolytic uremic syndrome – Antiphospholipid antibody syndrome, some patients • Severe neutropenia – Immunocompromised; opportunistic infections very likely • Eosinophilia – Cholesterol emboli
PARTIAL THROMBOPLASTIN TIME (PTT)
• Minimally prolonged in TTP-hemolytic uremic syndrome • Prolonged in purpura fulminans and DIC • Prolonged if lupus anticoagulant activity present and assay sensitive
CRYOGLOBULINS (OCCASIONALLY CRYOFIBRINOGEN AND COLD AGGLUTININS) WHEN LOCATION AND HISTORY SUGGEST COLD OCCLUSION SYNDROME
BIOPSY
• Confirms occlusion versus other mechanisms of vessel injury • May suggest platelet plugs instead of fibrin thrombi • May suggest cryoglobulin gelling • May diagnose calciphylaxis • May suggest cholesterol, oxalate or crystal globulin occlusion • Special stains for organisms in immunocompromised hosts, when appropriate
BASIC HEPATIC AND RENAL FUNCTION SCREENS
• Hepatic function can affect vitamin K-dependent factors and warfarin (Coumadin®) metabolism • Renal disease moves cutaneous calciphylaxis higher in the differential diagnosis
ANCA
• To reduce the likelihood of the uncommon non-inflammatory retiform purpura presentation of Wegener's granulomatosis or microscopic polyangiitis. • ANCA may be available before permanent histologic sections

Table 23.2 Basic screening tests for occlusive syndromes. Elevated levels of fibrin degradation products, including D-dimers, are seen in purpura fulminans with DIC. DIC, disseminated intravascular coagulation; TTP, thrombotic thrombocytopenic purpura.

Fig. 23.2 Heparin necrosis at site of subcutaneous heparin injection. Note branching or retiform pattern of intense hemorrhage and necrosis in the center of lesion. *From Robson K, Piette W. Adv Dermatol. 1999;15:153–82, used with permission.*

Other clinical features of patients with myeloproliferative disorders depend on the diagnosis. All patients may develop splenomegaly. Polycythemia patients may have a ruddy cyanosis. Chronic myelogenous leukemia patients have elevated neutrophil counts and, frequently, elevated eosinophil or basophil counts. Patients with essential thrombocythemia may present initially with an isolated elevation in their platelet count or with thrombotic complications. Anemia and altered red cell morphology may occur in several of these disorders over time, sometimes culminating in leukemia or myelofibrosis with severe anemia and dyspoiesis.

Pathology

Microvascular platelet-plug occlusion of dermal vessels or subcutaneous arterioles is expected in biopsy specimens from retiform purpura/necrotic lesions in patients with these disorders, and may sometimes present as "white clot" on histologic examination.

Differential diagnosis

Useful findings which suggest platelet occlusive disease in the setting of a myeloproliferative disorder include anemia or an elevated hematocrit, abnormal white count or differential, and abnormal platelet count or platelet morphology. The differential diagnosis of reactive thrombocytosis, especially due to iron deficiency, infection or malignancy, must be considered when assessing the significance of an elevated platelet count. The presence of mutation in *JAK-2* (which encodes a protein kinase) can be confirmatory, as 90–95% of patients with polycythemia vera and 50–70% of those with essential thrombocythemia have such a mutation.

Treatment

Patients with essential thrombocythemia and polycythemia vera are more likely than patients with other myeloproliferative disorders to present with platelet counts of one million or greater, to have a good prognosis, and also to be young and female[10]. However, compared to the general population, these patients have an increased risk of morbidity from thrombotic complications, as well as from transformation into myelofibrosis with myeloid metaplasia or acute myelogenous leukemia. The cytostatic drug anagrelide has become an important therapeutic agent for thrombocytosis, as it is capable of substantially decreasing the platelet count at doses lower than those required to inhibit platelet activity[11].

Low-dose aspirin is often used for prophylaxis of thrombosis in patients with myeloproliferative thrombocytosis, but, despite widespread acceptance, its efficacy still awaits conclusive proof. Hydroxyurea may also be effective, alone or in combination with aspirin or anagrelide. The prompt and lasting relief of burning pain by low-dose aspirin is a characteristic finding in thrombocythemic erythromelalgia.

Paroxysmal Nocturnal Hemoglobinuria

Key features

- Retiform purpura
- Coombs-negative intravascular hemolytic anemia due to mutations in *PIG-A*

Introduction

Although considered to be a hemolytic anemia, paroxysmal nocturnal hemoglobinuria (PNH) is actually a rare hematopoietic stem cell disorder, probably first reported as overnight hemoglobinuria in 1882[12].

Pathogenesis

This disease is due to a somatic mutation in hematopoietic stem cells that affects the X-linked phosphatidyl inositol glycan class A (*PIG-A*) gene. This gene encodes a glycosyl phosphatidyl inositol (GPI) anchor required for the cell membrane attachment of several important membrane proteins. Some of these proteins are responsible for protecting blood cells and platelets from complement-mediated injury (e.g. CD55,

CD59). This relative lack of protection leads to red cell lysis and activation of platelets[13].

Clinical features

This acquired clonal hematologic disorder presents with intravascular hemolysis, deficient hematopoiesis, and a thrombotic tendency, with venous thrombosis affecting up to 40% of patients[14]. Venous thrombosis, including an increased incidence of Budd–Chiari syndrome with hepatic vein thrombosis, is likely multifactorial, but is due in part to microparticle formation from platelets and other blood component membranes. A variety of cutaneous findings have been reported in PNH, including hemorrhagic bullae, petechiae, leg ulcers, and lesions consistent with non-inflammatory retiform purpura[15,16]. Cytopenia of any or all blood elements is expected. Prior to 1990, red cell sucrose hemolysis was used as a screening test[12]. However, currently, a proaerolysin-based flow cytometry assay is utilized that is more specific, more sensitive, and quantitative (proaerolysin is a toxin that binds to GPI-anchored proteins).

Pathology

Biopsy specimens reveal findings consistent with microvascular occlusion secondary to platelet plugs.

Differential diagnosis

The differential diagnosis of the various skin lesions possible in this syndrome is quite diverse. However, the presence of hemolytic anemia, often with pancytopenia, should suggest the diagnosis.

Treatment

Both corticosteroid therapy and anticoagulants may be useful in the treatment of thrombotic episodes[12]; the role of antiplatelet therapy is unclear and there have been case reports of the successful use of thrombolytic therapy. Eculizumab (Soliris™), which inhibits the terminal phase of the complement cascade at the C5 stage, can reduce intravascular hemolysis and venous thrombosis[17]. Because eculizumab can increase the risk of meningococcemia via C5 inhibition, patients should receive the meningococcal vaccine at least 2 weeks before instituting therapy.

Thrombotic Thrombocytopenic Purpura–Hemolytic Uremic Syndrome

Key features

- Skin lesions of thrombotic thrombocytopenic purpura are usually macular, round petechiae due to simple hemorrhage
- Skin lesions are not part of the hemolytic uremic syndrome
- Fever, renal dysfunction (more severe in hemolytic uremic syndrome) and CNS involvement
- Microangiopathy, with red blood cell fragmentation and thrombocytopenia
- Prothrombin and partial thromboplastin times are usually normal

Introduction

Classic primary thrombotic thrombocytopenic purpura (TTP) was first described in 1925, but less classic syndromes are now included under the term TTP–hemolytic uremic syndrome (HUS). However, only TTP includes purpura in its clinical presentation. There is a consistent female predominance of 60–70% for TTP-HUS[18].

Pathogenesis

It is useful to distinguish between primary (idiopathic) TTP and secondary forms of TTP-HUS. Precipitants of secondary disease include hemorrhagic colitis and other infections (in the elderly, this can have a very high mortality rate), pregnancy, systemic drugs (particularly cyclosporine, mitomycin C, gemcitabine, tacrolimus, ticlopidine, quinine), metastatic carcinoma, autoimmune connective tissue disease (e.g. systemic lupus erythematosus), and the antiphospholipid antibody syndrome[19].

In primary acquired TTP, autoantibodies against ADAMTS13 are present, which lead to decreased activity of this metalloprotease, whose function is to cleave von Willebrand factor (vWF). As a result, large multimers of vWF are allowed to persist within the plasma and this leads to platelet aggregation and the formation of microthrombi. In the rare inherited form of TTP, there is reduced activity of ADAMSTS13 due to genetic mutations (as opposed to autoantibodies). In secondary TTP-HUS, the pathophysiology is less well understood, but is not thought to be related to dysfunction of ADAMTS13 (with the possible exception of drug-induced disease).

HUS in childhood epidemic form is usually secondary to hemorrhagic colitis with Shiga toxin-producing organisms (*Escherichia coli* 0157:H7 infection, less commonly other *E. coli* or *Shigella dysenteriae* serotypes).

Clinical features

Purpuric skin or mucous membrane lesions of TTP are most likely due to thrombocytopenia with simple petechiae formation, but rarely may be due to platelet plugging. The complete syndrome is characterized by fever, petechiae, thrombocytopenia, microangiopathic hemolytic anemia (schistocytes or fragmented red cells prominent on peripheral smear), renal disease and neurologic symptoms (most commonly headache and confusion).

Pathology

Microvascular occlusion of visceral terminal arterioles and capillaries is expected, but is rare in the cutaneous microvasculature; petechial (cutaneous) hemorrhage in TTP is most likely secondary to thrombocytopenia.

Differential diagnosis

Fever, CNS findings, renal disease, microangiopathic findings in the blood smear (red cell fragmentation), and thrombocytopenia can be seen in sepsis syndromes with disseminated intravascular coagulation (DIC), and rarely in the antiphospholipid antibody syndrome. A normal or minimally elevated prothrombin time plus profound thrombocytopenia strongly favors TTP-HUS over DIC in adults[20]. Sepsis with purpura fulminans and DIC is characterized by elevation of the prothrombin time and partial thromboplastin time.

Treatment

Treatment of primary acquired TTP includes plasmapheresis (to remove the autoantibodies) plus either plasma exchange or administration of fresh frozen plasma. It is also important to review medications for possible drug-induced variants of TTP-HUS. If plasma exchange is ineffective, rituximab has led to improvement in some TTP-HUS syndromes, including idiopathic and gemcitabine-associated[21].

DISORDERS OF CRYOGELLING OR CRYOAGGLUTINATION

Key features

- Retiform purpura in an acral location
- Due to type I cryoglobulins, cryofibrinogen or, rarely, cold agglutinins
- In acute lesions, hyaline plugs within vessels

Introduction

Cryoglobulins are immunoglobulins that reversibly precipitate or gel on cold exposure, and they are present in both serum and plasma. Cryofibrinogens are fibrinogens which gel in the cold, are consumed in clotting, and are therefore detectable only in plasma samples. Cold agglutinins are antibodies which promote agglutination of red cells on exposure to cold. All three groups can cause occlusive syndromes in the skin triggered by cold exposure. While cryofibrinogens and cold

agglutinins can be detected in many patients in association with a variety of illnesses, they are only rarely the cause of cold-related occlusion syndromes[22]. Clinical syndromes due directly to cryogelling or cryoagglutination are uncommon to rare.

Pathogenesis

Cryoglobulins, by definition, gel in the cold, but many of these proteins gel only at refrigerator temperatures, not at skin temperatures typically seen with cold exposure of acral areas. Cryoglobulins can cause disease through two mechanisms: occlusion or immune complex-mediated vasculitis. Simple occlusion with minimal early inflammation and often retiform purpura/necrosis develops when cryoproteins gel on cold exposure, and this is primarily a reflection of monoclonal immunoglobulins (IgG, IgM >> IgA, light chains), i.e. type I cryoglobulinemia, that is due to an underlying plasma cell dyscrasia or lymphoproliferative disorder. Immune complex disease leads to inflammatory purpura that is palpable, and this is a reflection of mixed cryoglobulinemia (types II or III) that is often due to hepatitis C viral infection (see Table 24.6).

Cryofibrinogen precipitate is composed of fibrinogen, fibrin, fibronectin, and, occasionally, small amounts of immunoglobulins or other plasma proteins. Cold agglutinins bind to red cells in the cold, often triggering complement activation and red cell lysis. Only IgM antibodies have enough binding sites to hold multiple red cells together.

Clinical features

Purpuric or necrotic lesions, often retiform, at acral sites of cold exposure, are cardinal signs (Fig. 23.3). Other cutaneous findings include acral cyanosis, Raynaud's phenomenon and livedo reticularis. Though some reports describe cutaneous small vessel vasculitis in patients with type I cryoglobulins, it is likely that this finding is a secondary form of leukocytoclastic vasculitis that occurs following occlusive necrosis or ulceration (see Fig. 22.3). Mixed (types II and III) cryoglobulins may cause occlusion by cryogelling if they are unstable at close to body temperature, but more frequently they induce lesions by immune complex mechanisms, with clustering in dependent areas of lesions of classic palpable purpura.

Fig. 23.3 Type I cryoglobulinemia in a patient with multiple myeloma (IgG type). Note the retiform purpura (**A**) and the areas of necrosis within the purpuric areas (**B**). Patients also have purpuric lesions on the helices of the ear and the nose. *Courtesy, Jean L Bolognia, MD.*

Since cryofibrinogenemia may be present in up to 3% of hospitalized patients, clinicopathologic correlation is critical in judging the significance of the finding of cryofibrinogenemia[23,24]. Cutaneous findings are the same as those induced by cryogelling of cryoglobulin. In a single hospital study, 22% (515/2312) of patients had cryofibrinogenemia[25], and of these, 88% also had cryoglobulinemia. Of the remaining 12% who only had cryofibrinogenemia (60 patients), 47% developed purpura, 37% skin necrosis, and 40% a thrombotic event, suggesting that cryofibrinogenemia may have greater morbidity than currently acknowledged.

Cold agglutinins are frequently asymptomatic, incidental findings, as with mycoplasmal infections. When symptomatic, cold agglutinins are usually responsible for post cold exposure hemolysis, which can be severe. Very rarely, cold exposure in patients with cold agglutinins can induce red cell agglutination, sludging and vascular occlusion in cold-exposed sites. Cold exposure includes infusion of cold blood products, with lesions at infusion sites[26]. Skin lesions are rare and include acrocyanosis, livedo reticularis, Raynaud's phenomenon or necrosis.

Pathology

Characterization of cryoglobulins by types has been discussed (see above). Histologic examination of new lesions of cold occlusion syndromes should reveal bland hyaline or red cell occlusion of vessels (Fig. 23.4). Biopsy specimens of lesions due to cryofibrinogen can demonstrate eosinophilic thrombi within small dermal vessels and necrosis.

Differential diagnosis

A sudden onset of acral disease with cold exposure should suggest this group of disorders. Occasionally, syndromes of distal occlusion, e.g. cholesterol emboli or acral antiphospholipid antibody syndrome, may have a similar appearance, but without the history of cold exposure and with sparing of the nose and ears. Chilblains (pernio) must also be considered, but lesions are usually slow in onset and seldom have significant acute purpura or necrosis.

Treatment

Therapy for cryogelling is primarily directed at minimizing cold exposure and controlling the underlying plasma cell dyscrasia or lymphoproliferative disorder (when possible) to reduce the titer of monoclonal cryoglobulin. Treatment of cryofibrinogen cryogelling is again aimed primarily at keeping acral areas warm. Stanozolol and other androgenic steroids with fibrinolysis-enhancing effects are sometimes useful adjuncts.

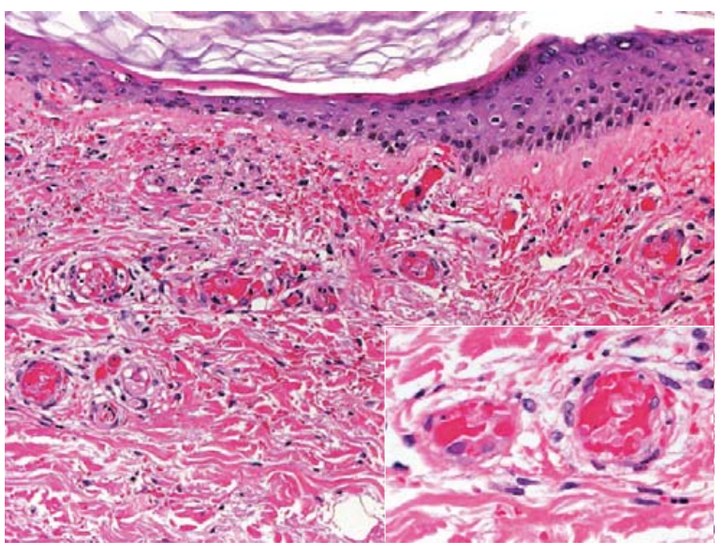


Fig. 23.4 Thrombotic vasculopathy due to type I cryoglobulinemia. In the dermis, there are fibrin thrombi within several blood vessels (insert) with hemorrhage and only a minimal inflammatory infiltrate. *Courtesy, Lorenzo Cerroni, MD.*

DISORDERS OF OCCLUSION BY OPPORTUNISTIC ORGANISMS PROLIFERATING WITHIN VESSELS

Key features

- Retiform purpura or non-inflammatory necrosis
- Often associated with administration of immunosuppressive agents or severe neutropenia
- Poorly controlled diabetes mellitus is a risk factor for mucormycosis

Introduction/pathogenesis

These syndromes share the feature of vessel invasion by organisms (see Chs 74 & 77), and they usually occur in severely immunocompromised patients. All but disseminated strongyloidiasis share the features of organism growth within the endothelium or vascular wall, usually in severely immunocompromised patients. Immunocompromise is usually due to severe neutropenia and/or to the administration of multiple potent immunosuppressive agents, but may be due to chronic disease or malnutrition.

Clinical features/pathology

Ecthyma gangrenosum is the syndrome of occlusion by organisms (usually bacterial) proliferating in the adventitia of subcutaneous blood vessels. The classic organism is *Pseudomonas aeruginosa*, but ecthyma gangrenosum-like skin lesions have also been described with other organisms, including other *Pseudomonas* spp. (*P. cepacia, P. maltophilia), Serratia marcescens, Aeromonas hydrophila, Klebsiella pneumoniae, Vibrio vulnificus, Moraxella* spp., *Morganella morganii, Escherichia coli* and *Staphylococcus aureus*; these lesions may also be due to fungal organisms, e.g. *Candida albicans, Mucor* spp., *Aspergillus fumigatus, Fusarium* spp. and *Scytalidium dimidiatum*[22].

Ecthyma gangrenosum begins as erythematous, painless macules, but typically progresses to purpuric or escharotic lesions which may be bullous or pustular, and frequently show retiform or branching features. There is extensive bacillary infiltration of the adventitia, media and perivascular regions of blood vessels, typically with sparing of the lumen and intima. As the bacteria proliferate, gradual compression of the vessel wall narrows and then ultimately occludes the lumen of a subcutaneous arteriole that supplies an overlying cone of skin. This is followed by clot formation within many blood vessels in that skin zone. Immediate antibiotic therapy is crucial, although the prognosis is poor if the neutropenia persists, if the antimicrobial agents are ineffective, or if the disease process is advanced. Of note, many authors include cutaneous lesions and histopathologic findings in this category which might more properly be classified as septic vasculitis due to bacteremia from Gram-negative rods, when sufficient neutrophils exist to provide a local response.

In severely immunocompromised patients, *vessel-invasive fungi* can result in necrotic lesions secondary to vessel invasion and thrombosis[22]. The most common opportunistic fungi in this group are *Aspergillus, Mucor, Absidia* and *Rhizopus* spp. The latter three are causes of mucormycosis. In diabetic patients, mucormycosis may present in the central face with cutaneous necrosis, presumably originating from a sinus cavity infection. Opportunistic fungi that produce retiform purpura tend to proliferate and invade from within the lumen into the vessel wall and into vascular branches. Thrombus develops around the hyphal elements within the vessels and presumably also on the altered endothelium.

Disseminated strongyloidiasis can occur in patients infected with the human nematode *Strongyloides stercoralis*. Reticulated purpuric lesions, especially in the periumbilical region, have been described with dissemination, though such lesions are rare[27]; their appearance has been likened to thumbprints (see Ch. 83). Histologically, the purpuric lesions demonstrate extravasated erythrocytes and larvae within capillaries and between collagen bundles. The mortality rate in disseminated disease is high.

Lucio's phenomenon is common in Mexico and Central America, but rare in other areas. The associated thrombotic lesions are distinguished from erythema nodosum leprosum (an immune complex-mediated neutrophilic vasculitis with variable involvement of the panniculus) by an absence of fever, leukocytosis and tenderness; being less responsive to thalidomide; and restriction to patients with diffuse non-nodular lepromatous leprosy. Acute lesions, described as having arcuate borders, seem to correspond to retiform purpura[28]. These lesions frequently progress to chronic ulcers. The histology of acute lesions shows extensive endothelial proliferation and thrombus formation in dermal and some subcutaneous vessels, with a sparse lymphocytic inflammatory infiltrate. There are a few reports of the presence histologically of leukocytoclastic vasculitis in early lesions. Acid-fast stains show aggregates of bacilli within the proliferating endothelial cells[28,29].

Differential diagnosis

Vessel-invasive organisms should be suspected in patients who are immunosuppressed or have severe neutropenia. Central facial necrotic lesions are typical of mucormycosis. Lucio's phenomenon is seen primarily in patients with diffuse lepromatous leprosy from Mexico and Central America.

Treatment

Treatment is directed at mitigating the immunocompromised state where possible, and by selecting appropriate antimicrobial therapy based on identification of the invading organism. Oral thiabendazole is the treatment of choice for disseminated strongyloidiasis, but the treatment period may be quite protracted due to the difficulty in eradicating disease in immunocompromised individuals.

DISORDERS OF OCCLUSION BY EMBOLI

Cholesterol Embolus

Synonym: ■ Warfarin blue toe syndrome

Key features

- Usually abrupt onset
- Livedo reticularis is usually much more prominent than retiform purpura
- Distal extremities, especially the legs, are the most likely site of cutaneous involvement

Introduction

Cholesterol embolus is primarily a disease of men 50 years of age or older[30]. In autopsy studies, cholesterol embolism was observed in 15–20% of patients older than 60 who had histories of atherosclerotic disease[31]. Given the relatively low frequency rate of the clinical diagnosis of cholesterol embolus, this figure suggests that cholesterol emboli are frequently undiagnosed.

Pathogenesis

Since fragmentation of ulcerated atheromatous plaques is the cause of cholesterol embolus, affected patients usually have severe (but sometimes unknown) atherosclerotic disease. Although spontaneous fragmentation of plaques with distal embolization may occur, there are three clinical settings in particular that are known to prompt embolization. The first is *arterial or coronary catheterization*, which may disrupt a plaque, leading to emboli within hours to days of catheterization. The second is *prolonged anticoagulation*, which slowly lyses the clot which reinforces a friable plaque, leaving exposed areas of the plaque subject to the shear stress of arterial flow. The anticoagulant-induced syndrome of cholesterol embolus typically occurs after 1 to 2 months of therapy. This "warfarin blue toe syndrome" is not restricted to warfarin anticoagulation and should not be confused with warfarin necrosis (see below). The third setting for cholesterol embolus is *acute thrombolytic therapy* given for myocardial infarction or stroke. Embolization may occur within hours to days of lytic therapy.

Clinical features

Clinical findings include fever, weight loss, myalgias, altered mental status and a sudden onset of arterial hypertension. Transient ischemic attacks, strokes, renal failure, gastrointestinal ulcerations and hemorrhagic pancreatitis can also occur. Patients with multisystem involvement can have significant morbidity, and occasionally they may die from complications of their emboli.

Cutaneous findings are frequent, reported in 35% of patients with cholesterol embolization[30]. Findings in these patients included: livedo reticularis (49%), multiple sites of peripheral gangrene (35%), cyanosis (28%), ulceration (17%), nodules (10%) and purpura (9%) (Fig. 23.5). Because these figures come from a review that included patients in whom the diagnosis was not made premortem (41%), it may have underestimated the incidence of cutaneous findings in cholesterol embolus patients. This point is emphasized by a study of eight patients with acute renal insufficiency of unknown cause, whose history suggested cholesterol embolus. On careful examination, all eight were found to have previously unrecognized livedo reticularis, which on biopsy confirmed the diagnosis of cholesterol embolus[32]. In two patients, the livedo reticularis was visible only in the upright, not the supine, position. Personal experience suggests that retiform purpura occurs frequently in cholesterol embolus patients with livedo reticularis, rather than in only 9% of patients. Retiform purpura is usually a purpuric accentuation of the livedo reticularis pattern, and therefore may be included as livedo reticularis in some reports. Upper extremity lesions may occur if the plaque is in the aortic arch.

Peripheral blood eosinophilia is common, occurring in up to 80% of recognized cases, and may be related to generation of the complement component C5[31]. Other reported laboratory findings include decreased complement levels, leukocytosis, pyuria, eosinophiluria, elevations in the ESR, serum creatinine, BUN and amylase, and heme-positive urine or stool[30,31].

Pathology

Biopsy specimens of the livedo reticularis generally need to be obtained by elliptical incisions centered on the blanched portion of the livedo reticularis and deep enough to include fat (see Ch. 106). Areas of retiform purpura usually provide diagnostic findings in punch biopsy specimens and should be the first choice for biopsy when present.

Histologically, cholesterol emboli produce elongated clefts within lumina of small vessels (Fig. 23.5E), often in association with thrombi[33]. The clefts are created by dissolution of cholesterol crystals during the fixation process. The affected arteriole is usually at the dermal–subcutaneous junction. Neutrophils, eosinophils and mononuclear cells may be seen in arterial walls within 24–48 hours in an experimentally produced cholesterol embolus, followed by multinucleated histiocytes within 3 to 6 days, and sometimes intimal fibrosis. Lesions of different ages may be found in the same patient, consistent with recurrent showers of emboli.

Differential diagnosis

The abrupt onset of distal livedo reticularis should prompt consideration of cholesterol or oxalate embolism. Retiform purpura, especially when it occurs distally in concert with more extensive distal livedo reticularis, is especially suggestive of this diagnosis. Acral cold occlusion syndromes (see above) need to be considered when only distal lesions are present, as well as antiphospholipid antibody syndrome.

Fig. 23.5 Cholesterol emboli. A Livedo reticularis is seen proximally on the thigh; **B** both livedo reticularis and retiform purpura are seen distally. **C** Purpura of the digits in warfarin blue toe syndrome. **D** Several irregularly shaped ulcers with eschars surrounded by retiform purpura. **E** Histologically, intravascular clefts are seen which are due to dissolution of cholesterol crystals during fixation. *A,B,E, Courtesy, Norbert Sepp, MD. D, Courtesy, Kalman Watsky, MD.*

Treatment

Treatment is mainly supportive, unless surgical bypass or endarterectomy can eliminate the source of embolism. Aspirin or other antiplatelet agents, HMG-CoA reductase inhibitors ("statins"), discontinuation of anticoagulation, initiation of anticoagulation in patients with severe renal damage, systemic corticosteroids, and infusion of the prostacyclin analogue iloprost have all been advocated as effective in occasional patients, but no therapeutic standard exists[31,33,34].

Oxalate Embolus

Introduction

Oxalate embolism is a rare event, usually occurring in association with primary hyperoxaluria. Primary hyperoxaluria results from rare metabolic disorders of increased oxalic acid production or increased intestinal absorption, leading to hyperoxalemia and calcium oxalate deposition in tissues[35,36].

Clinical features

Primary hyperoxaluria usually presents during childhood with recurrent urolithiasis. The kidney is the major site of oxalate deposition until progressive renal insufficiency develops, then clinical signs of deposition in other organs become evident. Therefore, oxalate embolus typically occurs after the development of renal failure. Death by the age of 20 years is not unusual in patients with a childhood onset. Secondary or acquired oxalosis may result from excessive intake of oxalate precursors, increased dietary absorption of oxalate, pyridoxine deficiency, impaired renal excretion, or bowel diseases such as Crohn's disease.

Cutaneous findings in systemic oxalosis include acrocyanosis, Raynaud's phenomenon, peripheral gangrene, acral cutaneous necrosis, livedo reticularis, erythematous ulcerated nodules, miliary calcified deposits, and a cutaneous calciphylaxis-like presentation[35]. The calciphylaxis-like presentation can be misleading, not only because of lesional similarity, but also because both oxalate embolus and calciphylaxis typically occur in a patient with renal failure.

Pathology

Skin biopsy specimens demonstrate findings that are characteristic, with yellow–brown, birefringent crystal deposition in rectangular or radial patterns within and around vessels in the deep dermis and subcutaneous tissue. Crystals are yellow to golden-brown in routinely stained sections and birefringent under polarized light[36]; they also stain with alizarin red S at pH 7.0 but not at pH 4.2. Although clinical lesions may mimic those of cutaneous calciphylaxis, calcium deposition in vessels is not a characteristic finding in cutaneous oxalate emboli.

Differential diagnosis

This disorder is most likely to be confused with cholesterol embolus or cutaneous calciphylaxis in a patient with renal failure, but the differential diagnosis includes all the causes of retiform purpura or livedo reticularis. The history of renal stones in a patient with sudden-onset livedo reticularis or retiform purpura suggests hyperoxaluria as a prime diagnostic possibility.

Treatment

Renal transplantation is contraindicated without correction of the underlying abnormality, since the transplanted kidney will be destroyed by the same oxalate deposition. Hepatic transplantation may reverse the metabolic effect in some patients, and in those patients renal transplantation would then be possible[36]. Simple measures include hydration and alkalinization of the urine.

Other Embolus-Associated Syndromes

In addition to emboli from acute bacterial or fungal endocarditis (which are usually inflammatory in nature), cutaneous emboli or thrombi have been rarely described in patients with atrial myxomas, marantic endocarditis, crystalglobulins and hypereosinophilic syndrome. Emboli from these disorders may produce retiform purpura, but cutaneous findings are diverse.

Atrial myxomas are rare, typically present between the third and sixth decades of life, and may be associated with constitutional symptoms of fever, malaise, arthralgias, weight loss, obstruction of blood flow mimicking valvular disease, or embolic phenomena[22]. Cutaneous findings of myxomatous emboli include acral papules (with claudication), purpuric, serpiginous or annular violaceous fingertip lesions, splinter hemorrhages, livedo reticularis, Raynaud's phenomenon, toe necrosis, a red-violet malar flush, and distal petechiae. The hereditary syndromes (Carney complex/NAME/LAMB) associated with cardiac myxomas may have other cutaneous findings such as lentigines and blue nevi, unrelated to the emboli. Treatment of atrial myxoma consists of surgical removal.

Marantic endocarditis results in focal deposits of fibrin and other blood elements on heart valves, similar to those with Libman–Sacks (antiphospholipid antibody-related) or acute rheumatic endocarditis. Portions of these loose sterile deposits may occasionally embolize. Vegetations of *infective endocarditis* may also embolize. Emboli are more likely to occur with acute bacterial endocarditis, whereas cutaneous lesions in subacute bacterial endocarditis are more likely to be the result of immune complex disease, not embolization, despite frequent localization to hands.

Crystalglobulin vasculopathy is a rare syndrome of usually IgG or light chain paraproteins which spontaneously crystallize intravascularly. The crystalglobulinemia syndrome presents with rapidly progressive renal failure, polyarthropathy, peripheral neuropathy and skin lesions. Cutaneous findings include ulcerations, petechiae and ecchymoses. Skin biopsies show intravascular crystalline deposits and thrombosis.

In the *hypereosinophilic syndrome*, intracardiac mural thrombus formation often occurs, and thrombi in smaller vessels are not uncommon at autopsy in patients with this syndrome[37,38]. However, there are very few reports of documented thrombotic or embolic skin lesions[38–40]. Clinical presentations described to date include splinter hemorrhages, "non-blanching livedoid discoloration", and necrotic, blistering or purpuric lesions. The more frequently observed cutaneous lesions in hypereosinophilic syndrome (e.g. pink plaques) are a reflection of infiltrates of eosinophils (and lymphocytes) (see Ch. 25).

SYSTEMIC COAGULOPATHIES WITH CUTANEOUS MANIFESTATIONS

While understanding of the exact mechanisms remains incomplete, it is clear that disorders of the thrombomodulin, protein C and protein S pathways are important causes of sometimes fulminant microvascular occlusion syndromes. Antiphospholipid antibodies and lupus anticoagulants are also a major known cause of microvascular occlusion, including the catastrophic antiphospholipid antibody syndrome. Many different pathways of antiphospholipid antibody-enhanced coagulation are known or suspected; some include interference with protein C or S function.

Protein C and S Disorders, Congenital and Acquired

Relevant associations: ■ Neonatal purpura fulminans – congenital severe protein C or S deficiency ■ Warfarin necrosis – acquired protein C dysfunction ■ Purpura fulminans of sepsis – probable acquired severe protein C deficiency or dysfunction ■ Purpura fulminans in children during recovery from streptococcal or varicella infections – severe acquired protein S dysfunction, probably antibody-mediated

Key feature

■ Retiform, branching or stellate purpura in one of the above clinical settings

Introduction

Warfarin necrosis has been recognized since the mid-1950s[41]. The term "purpura fulminans" was first used in the late 1800s to describe a syndrome of extensive purpura in severely ill patients, usually children, in the setting of an acute or convalescent infection. Nowadays, this term includes at least three different syndromes (see below), and is typically applied to septic patients with widespread purpura of any type (petechiae, ecchymoses, palpable purpura or retiform purpura). It would be more helpful in choosing or assessing therapy to restrict the term purpura fulminans to the subset of septic patients with clinical features of occlusion, including retiform, branching or necrotic purpura, and/or bland thrombi as the primary histologic finding.

Pathogenesis/clinical features

Despite some overlap in pathophysiologies, the differential diagnosis for cutaneous microvascular occlusion is quite different from that of deep venous thrombosis (DVT) or pulmonary embolus (PE), as discussed in Chapter 22. With respect to skin, the protein C–protein S–thrombomodulin pathway is critically important (see Fig. 22.4).

Neonatal purpura fulminans

While severe congenital deficiency of antithrombin III may result in repeated DVT or PE, the only cutaneous finding is venous stasis ulcers from DVT-induced valve destruction. In contrast, however, homozygous (or compound heterozygous) deficiency or severe dysfunction of either protein C or protein S leads invariably to neonatal purpura fulminans within a few hours to 5 days after birth; the latter is fatal unless treated. Lesions of neonatal purpura fulminans are those of non-inflammatory retiform purpura (until confluence results in large-scale cutaneous and limb necrosis) and, ultimately, visceral organ involvement. In addition, such infants are often born with cerebral thrombosis or retinal vessel occlusion with congenital blindness.

For protein C-deficient individuals, intravenous protein C concentrate is used as initial therapy and then warfarin is begun, followed by tapering of the concentrate. The warfarin is continued for life, and, occasionally, patients require chronic subcutaneous administration of protein C concentrate. Otherwise, initial anticoagulation with heparin is followed by lifelong warfarin therapy.

Warfarin (Coumadin®) necrosis

Warfarin therapy results in abnormal γ-carboxylation by the liver of the vitamin K-sensitive factors; presumably, severe vitamin K deficiency results in a similar dysfunction. The vitamin K-sensitive factors are II, VII, IX, X, protein C and protein S. Of these factors, the two with the shortest half-life are factor VII and protein C. As discussed in Chapter 22, factor VII is needed primarily to switch the idling coagulation system into progressive amplification of clotting, and there is considerable redundancy of the procoagulant cascade. Protein C, however, is critical in preventing the distal spread of clot from the initial point of coagulant activation. In warfarin necrosis, the *pro*coagulant system takes significantly longer to reach its low-point equilibrium than does the protein C-dependent *anti*coagulant activity (i.e. protein C function can drop dramatically within days).

Warfarin necrosis usually develops within 2–5 days of starting warfarin in the absence of heparin, and it is much more likely to occur if loading doses of warfarin are used[22,41]. This would coincide with the expected early drop of protein C function. In addition, reversal of warfarin necrosis via replacement with protein C concentrates and confirmation of very low functional levels of protein C support this proposed pathophysiology. The incidence of warfarin necrosis is four times higher in women, with a peak incidence in the sixth and seventh decades of life. Although up to one-third of cases of warfarin necrosis may involve inherited partial deficiency of protein C, the disorder occurs more commonly in individuals without inherited defects in protein C.

Affected sites usually overlie abundant subcutaneous fat, such as the breast, hip, buttock or thigh. Pain is often the first sign, followed by well-demarcated erythema, which rapidly becomes hemorrhagic and then necrotic (Fig. 23.6). Partial retiform or branching purpura typically can be seen within or at the margin of the cutaneous lesions. Biopsy specimens reveal bland (non-inflammatory) thrombosis of most of the dermal vessels. Treatment begins with discontinuing the warfarin; administration of vitamin K and heparin at therapeutic doses is recommended. Use of protein C concentrate should also be strongly considered.

Fig. 23.6 Warfarin (Coumadin®) necrosis. Striking areas of purpura and ischemia on the scrotum (**A**) and pannus (**B**). Note the branching outline of the purpura and central necrosis in the lesions on the abdomen. *A, Courtesy, Kenneth Greer, MD. B, Courtesy, Jean L Bolognia, MD.*

Purpura fulminans with sepsis

Recognition of the importance of the protein C–thrombomodulin pathway in maintaining cutaneous microvascular integrity suggested that careful examination of patients with DIC in the setting of sepsis might detect morphologic differences (amongst associated purpuric lesions) that were reflective of differences in pathophysiology. In a small study, the presence of retiform palpable purpura (non-inflammatory and irregular in a branching or retiform pattern) in patients with sepsis and DIC correlated with a severe protein C deficiency or dysfunction (approximately ≤20%) and it correlated histologically with extensive dermal vessel occlusion with bland thrombi[42]. This study suggests that careful assessment of physical findings could provide evidence crucial to guiding the acute care of such patients. While acquired purpura fulminans is most famously associated with meningococcal infection (see Ch. 74), it can occur in association with sepsis syndromes from a variety of bacteria, including *S. aureus*, groups A and B β-hemolytic streptococci, *S. pneumoniae, Haemophilus influenzae* and *H. aegyptius*[22].

Purpura fulminans postinfection

While protein C abnormalities seem to correlate with acquired purpura fulminans in the setting of sepsis in both children and adults, a second clinical presentation has been recognized in children which occurs during the recovery period from either group A streptococcal or varicella–zoster viral infections. These patients do not have deficient protein C activity; instead, they have an acquired antibody which interferes with protein S function[43,44]. The development of postinfectious purpura fulminans roughly 2 weeks after the onset of the initial infection would correlate well with the production of infection-triggered antibodies which interfere with protein S function. It is known that protein S requires phospholipid binding for full activity. One study has shown that transient antibodies to phospholipids or coagulation proteins are common in children with varicella–zoster viral infections, but are not predictive of thrombotic complications[45].

Treatment of this syndrome is even more challenging than treating protein C deficiency, because currently there is no commercially available protein S concentrate. In addition, it is significantly more difficult to overcome antibody-mediated inhibition of protein S than to restore

a deficiency of protein S. A combination of plasma exchange and prednisone is recommended as well as heparin anticoagulation.

Antiphospholipid Antibody/Lupus Anticoagulant Syndrome

Key features

- Livedo reticularis, retiform purpura or atrophie blanche-like lesions are typical
- The definite diagnosis of antiphospholipid antibody syndrome requires at least one clinical and one laboratory criterion (Table 23.3)

Introduction

Antiphospholipid antibody was first detected in patients with syphilis in 1906. A false-positive serologic test for syphilis in patients with lupus was recognized in 1952. This lupus anticoagulant activity was first thought to cause bleeding, but was soon associated with thrombosis. In the early 1990s, investigators recognized that clinically significant antiphospholipid/anticardiolipin antibodies often require the presence of an additional phospholipid-binding protein (e.g. β_2-glycoprotein I) in order to bind to cardiolipin[46,46a].

Epidemiology

In a 1000-patient cohort of individuals with antiphospholipid antibody syndrome (APLS), there was a strong female predominance (82% women, 18% men) and the mean age was 42 ± 14 years at study entry. Fifty-three percent of the patients had primary APLS; secondary APLS was associated with lupus in 36%, with lupus-like syndromes in 5%, and with other diseases in the remaining 6%[47]. Catastrophic APLS occurred in 0.8% of the cohort. In contrast to primary cases, patients with lupus and APLS had more episodes of arthritis, livedo reticularis, thrombocytopenia and leukopenia. Female patients had a higher frequency of arthritis, livedo reticularis and migraine, while male patients had a higher incidence of myocardial infarction, epilepsy and arterial thrombosis in the lower legs and feet. The onset of symptoms occurred most often in young to middle-aged individuals (2.8% before age 15 years, 12.7% after age 50 years).

INTERNATIONAL CONSENSUS STATEMENT – PRELIMINARY CRITERIA FOR ANTIPHOSPHOLIPID ANTIBODY SYNDROME
CLINICAL CRITERIA
1. Vascular thrombosis • One or more clinical episodes of arterial, venous or small vessel thrombosis
2. Complications of pregnancy • One or more unexplained deaths of morphologically normal fetuses at or after the 10th week of pregnancy; or • One or more premature births of morphologically normal neonates at or before the 34th week of gestation; or • Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation
LABORATORY CRITERIA
1. Anticardiolipin antibodies*, IgG or IgM, present at moderate or high levels† on two or more occasions at least 12 weeks apart
2. Lupus anticoagulant antibodies on two or more occasions at least 12 weeks apart
3. Anti-β_2-glycoprotein I antibodies, IgG or IgM (in titer >99th percentile) on two or more occasions at least 12 weeks apart
*β_2-glycoprotein I-dependent. †Several thresholds exist for low versus moderate-to-high: (1) >40 international "phospholipid" units; (2) 2–2.5× the median level of anticardiolipin antibodies (ACA); and (3) 99th percentile for ACA in the normal population.

Table 23.3 International Consensus Statement – preliminary criteria for antiphospholipid antibody syndrome[46]. Definite diagnosis requires at least one clinical and one laboratory criterion.

Pathogenesis

Antiphospholipid antibodies/lupus anticoagulants are a very important cause of purpuric cutaneous lesions and microvascular occlusion. Platelet activation leads to exposure of negatively charged platelet membrane phospholipids, followed by the sequential membrane-bound assembly of procoagulant enzyme–cofactor–substrate complexes, thrombin generation, and enzymatic conversion of fibrinogen to fibrin clot[46,48]. Thrombin, which escapes downstream from clot formation, may bind to an endothelial surface protein, thrombomodulin (see Fig. 22.4). Thrombin–thrombomodulin binding converts thrombin activity from procoagulant to anticoagulant with high-affinity activation of protein C. Disturbance of the platelet or endothelial membrane may lead to exposure of neoantigens coexpressed with negatively charged phospholipids which localize to these enzyme assembly sites. It is likely that some physiologically relevant antiphospholipid or lupus anticoagulant antibodies are directed at these altered sites, and may subsequently interfere either with normal surface protection against procoagulant enzyme assembly, or with the normal anticoagulant function of the thrombomodulin–protein C pathway.

Evidence suggests multiple mechanisms for antiphospholipid antibody-mediated thrombosis, including interference with production and release of prostacyclin by endothelial cells, interference with protein C and S pathways, activation of platelets by interaction with platelet membrane phospholipids, interference with antithrombin III activity, interference with prekallikrein activation to kallikrein, interference with endothelial plasminogen activator release, or interference with possible protective functions of proteins such as β_2-glycoprotein I or annexin V[46,48].

Clinical features

Cutaneous findings in patients with the APLS are listed in Table 23.4. In one large study, the incidences of cutaneous findings were: livedo reticularis, 24%; leg ulcers, 5.5%; pseudovasculitic lesions, 3.9%; digital gangrene, 3.3%; cutaneous necrosis, 2.1%; and splinter hemorrhages, 0.7%[47] (Fig. 23.7). Cutaneous lesions may also develop indirectly, i.e. by embolization from heart valve vegetations (see embolus section).

In addition to the skin, many other organ systems may be involved, although deep vein thrombosis/pulmonary embolus and CNS disease are the most common extracutaneous manifestations. Catastrophic APLS is an uncommon variant. Precipitating factors include surgical procedures, drugs (e.g. sulfur-containing diuretics, captopril, oral contraceptives), discontinuation of anticoagulant therapy, and especially infections. These patients often present with multi-organ failure; the majority present with renal involvement as well as evidence of acute respiratory distress syndrome.

Pathology

Antiphospholipid antibodies and lupus anticoagulants are detected by different assays. Patients positive for one type of antibody may also be

CUTANEOUS FINDINGS IN PATIENTS WITH THE ANTIPHOSPHOLIPID ANTIBODY SYNDROME
• Livedo reticularis, with or without retiform purpura
• Cholesterol embolus-like proximal livedo reticularis with distal retiform purpura
• Acral livedo reticularis
• Sneddon syndrome
• Livedoid vasculopathy or Degos-like lesions
• Anetoderma-like lesions with microthrombosis
• Raynaud's phenomenon
• Vasculitis-like lesions
• Behçet's-like lesions
• Pyoderma gangrenosum-like ulcers
• Nailfold ulcers
• Splinter hemorrhages
• Widespread cutaneous necrosis, typically as part of catastrophic APL antibody syndrome
• Pseudo-Kaposi sarcoma
• Superficial thrombophlebitis migrans

Table 23.4 Cutaneous findings in patients with the antiphospholipid (APL) antibody syndrome.

Fig. 23.7 Antiphospholipid antibody syndrome. Purpura and ischemia of the distal portion of the foot. The purpuric lesions have irregular borders (marked with ink). *Courtesy, Jean L Bolognia, MD.*

Fig. 23.8 Antiphospholipid antibody syndrome (APLS). Atrophie blanche-like scarring in a lupus patient with APLS. The lesions can also resemble those seen in malignant atrophic papulosis (Degos' disease).

positive for another, but usually because both subsets of antibodies are present rather than because of cross-reactivity between the antibodies responsible for anticardiolipin and lupus anticoagulant positivity. Screening for *antiphospholipid antibodies* is most often performed by anticardiolipin antibody testing, which detects antibodies that have an affinity for negatively charged membrane phospholipids. However, screening for anti-β_2-glycoprotein I (β_2-GPI) antibody may be more specific than that for anticardiolipin antibody, and this test is increasingly available. The *lupus anticoagulant* is an antibody which interferes with procoagulant assembly in the test tube measurement of the partial thromboplastin time, the dilute Russell viper venom test, and, uncommonly, the prothrombin time. Despite prolonging coagulation assays *in vitro* (due to the interference of the antiphospholipid antibodies with the assembly of the procoagulant complex), *in vivo* (i.e. in patients) the lupus anticoagulant antibody usually interferes with anticoagulant activity, leading to thrombosis.

Anticardiolipin antibodies are positive much more often than lupus anticoagulant antibodies, but their specificity for clinically significant disease is lower. Despite the lower specificity, clinical disease secondary to anticardiolipin antibody-positive APLS is roughly five times more common than lupus anticoagulant-positive APLS[49]. Clinically relevant antiphospholipid antibodies usually do not bind to phospholipid directly, but require a cofactor (usually a protein) before binding. The first recognized cofactor, β_2-GPI, may function *in vivo* to protect binding sites for procoagulant molecular assembly. An antibody which binds to this site might disrupt this protection, leading to thrombosis. Of note, the antibodies in patients with syphilis react directly with cardiolipin.

Other known cofactors include bound prothrombin, annexin V or components of the thrombomodulin–protein C system. Some antiphospholipid antibodies may interfere with prostacyclin production by the endothelium, leading to decreased endothelial cell anticoagulant properties. Still other antibodies may bind to platelets in a way that stimulates aggregation. Unfortunately, cofactor-dependent anticardiolipin antibodies (to β_2-GPI, annexin V or other suspected targets) or lupus anticoagulants are present often enough in patients who do not develop thromboses that they are poor predictors of thrombosis risk in asymptomatic patients without previous thromboses.

Histologic features of early lesions typically reveal non-inflammatory thrombosis of small dermal vessels; later lesions may show inflammation following necrosis or with wound healing.

Differential diagnosis

The differential diagnosis of APLS, beyond those syndromes discussed in this chapter, includes the diseases or syndromes associated with the findings in Table 23.4. In lupus patients, APLS is particularly likely to present as persistent moderate to extensive livedo reticularis or as livedoid vasculopathy (atrophie blanche; Fig. 23.8). Catastrophic APLS may mimic TTP or DIC.

Treatment

Treatment of the APLS is unfortunately empiric. Better understanding of the mechanism of thrombosis in an individual patient should lead to a better determination of prognosis and risk for future thrombosis, as well as a more specific therapy. Anticoagulation and antiplatelet agents are currently the mainstay of therapy, and are associated with variable success. In lupus patients with this syndrome, antimalarial therapy may be helpful in treating the atrophie blanche-type lesions and may be protective against arterial or venous thromboses[46]. Based upon case reports, rituximab has been used to treat severe disease[49a].

DISORDERS OF VASCULAR COAGULOPATHIES WITH CUTANEOUS MANIFESTATIONS

Sneddon Syndrome

Synonym: ■ Idiopathic livedo reticularis with cerebrovascular accidents

Key features

- Usually affects young women
- Persistent livedo reticularis or livedo racemosa
- Labile hypertension
- Recurrent neurologic symptoms due to cerebrovascular disease

Introduction

This uncommon syndrome was first described in 1965[50]. An estimated four new cases of Sneddon syndrome occur per million inhabitants per year[51,52].

Pathogenesis

Sneddon syndrome is, in a number of patients, a manifestation of the APLS (see the previous section), while in other patients it apparently represents a distinctive vasculopathy or vascular coagulopathy affecting smaller arteries and larger arterioles, especially in the skin and the brain.

Clinical features

Sneddon syndrome is characterized by persistent and usually widespread livedo reticularis, labile hypertension and CNS disease (usually transient ischemic attacks, strokes or dementia). There is a female

predominance, with onset in the third or fourth decade of life. A history of fetal loss and Raynaud's phenomenon are other features. The livedo reticularis may precede neurologic symptoms by several years.

In one comparative study, the antiphospholipid antibody-negative group was *less likely* than the antiphospholipid antibody-positive group to have seizures, mitral regurgitation by echocardiography, clinically audible mitral regurgitation, and thrombocytopenia (<150 000/μl), and *more likely* to have larger-pattern livedo reticularis with rings >1 cm in diameter[50].

Pathology

A 1–2 cm biopsy specimen from normal-appearing skin in the center of a livedo ring has been reported to have a sensitivity of 27% with one biopsy, 53% with two biopsies, and 80% with three biopsies. The characteristic, but not diagnostic, changes reported include endothelial inflammation, followed by subendothelial myointimal hyperplasia, with partial and complete occlusion of the involved arterioles[53].

Differential diagnosis

With livedo reticularis or livedo racemosa ("broken" livedo) as the characteristic cutaneous finding of this syndrome, other syndromes with persistent livedo reticularis should be considered (see Ch 106). In a group of 32 patients with generalized broken ("racemose") livedo and cerebrovascular accidents, 16 had an autoimmune disorder, thrombophilia, atherosclerosis or an atrial myxoma[54].

Screening for the presence of antiphospholipid antibodies should be part of the initial evaluation in patients with signs and symptoms of Sneddon syndrome. If, in addition to the traditional screens for antiphospholipid antibody and lupus anticoagulant activity, screening for antiprothrombin antibody is included, as many as 78% of the patients can have associated antiphospholipid antibodies[55].

Treatment

The primary treatment for Sneddon syndrome is warfarin, although this is not routinely effective[47]. Certainly, in patients with antiphospholipid antibodies or lupus anticoagulants, maintenance of anticoagulation at an international normalized ratio (INR) of 2–3 seems warranted. Corticosteroid therapy or immunosuppressive agents do not appear to prevent cerebrovascular disease.

Livedoid Vasculopathy

Synonyms: ■ Atrophie blanche ■ Livedo reticularis with summer ulceration ■ Segmental hyalinizing vasculitis ■ Livedoid vasculitis

Key features

- Favors the distal lower extremities, especially the ankles
- Female predominance
- Painful, punched-out ulcers
- White, round or stellate scars with peripheral telangiectasias
- Reticulated violaceous erythema may extend from ulcer

Introduction

This is a chronic cutaneous disease seen predominantly in young to middle-aged women. It can be divided into a primary (or idiopathic) form and a secondary form; the latter has been associated with a number of diseases, including chronic venous hypertension and varicosities as well as hypercoagulable states[56]. It would seem important in trying to understand this syndrome to exclude or separate cases of atrophie blanche-like scarring without a history of the characteristic ulcerations or surrounding livedo reticularis seen in the primary form.

Pathogenesis

The pathogenesis of livedoid vasculopathy is unknown, but it is believed to involve an alteration in local or systemic control of coagulation with formation of fibrin thrombi focally within superficial dermal blood vessels.

Clinical features

Painful, persistent and often punched-out ulcerations on the legs, especially over the malleoli and in women, should suggest this diagnosis (Fig. 23.9A)[22]. Some patients, particularly those with prominent livedo reticularis surrounding these ulcers, may develop retiform or stellate purpura or ulcer extension. Lesions tend to heal as white atrophic scars with peripheral papular telangiectasias. Some patients appear to have identifiable reasons for an occlusive proclivity, such as factor V Leiden, hyperhomocysteinemia, antiphospholipid antibodies, altered fibrinolysis or platelet activation (see Ch. 105)[56–58]. Lesions which mimic livedoid vasculopathy can be seen in patients with idiopathic and lupus-associated APLS (see above).

Pathology

The characteristic histologic findings in livedoid vasculopathy are mild perivascular lymphocytic infiltrates and extravasated red cells surrounding superficial dermal vessels with hyalinized walls and luminal fibrin deposition[22,56] (Fig. 23.9B). Although immunofluorescence findings are nonspecific, a recent study reported homogenous deposits of IgM, C3 and fibrinogen in the superficial and deep vascular plexus as supportive findings[59].

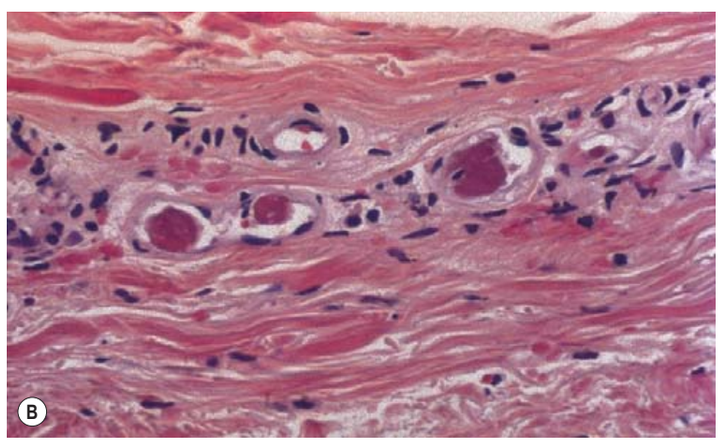


Fig. 23.9 Livedoid vasculopathy.
A Punched-out ulcers are seen on the ankle as well as multiple stellate purpuric macules.
B Thrombi are seen in the dermal blood vessels as well as a mild perivascular lymphocytic infiltrate.

Differential diagnosis

The clinical presentation of this syndrome must be distinguished from other disorders that can cause inflammatory retiform purpura (see Ch. 22). Atrophie blanche-like lesions are not specific for this syndrome, so a history of the characteristic ulcers should be used to distinguish this form of skin injury from other disorders that can lead to atrophic scarring, such as the APLS, cutaneous small vessel vasculitis, sickle cell anemia- and hydroxyurea-related leg ulcers, and, especially, venous stasis with varicosities.

Treatment

Anecdotally, successful treatment of this syndrome has been observed with antiplatelet, anticoagulant and fibrinolytic therapies[57]. Anabolic agents such as danazol and stanozolol have been helpful in some instances, as has PUVA therapy[60]. In patients with atrophie blanche-like lesions and lupus, antimalarial drugs may be helpful. Patients on hydroxyurea with atrophie blanche-like lesions may need a trial off the drug, since hydroxyurea may mimic this syndrome through unknown mechanisms.

Malignant Atrophic Papulosis

Synonym: ■ Degos' disease

Introduction

Malignant atrophic papulosis typically occurs between the second and fourth decades of life. The incidences in men and women appear to be roughly equal.

Pathogenesis

The pathogenesis of malignant atrophic papulosis is unknown, though a vasculopathy would seem to be a leading possibility.

Clinical features

Malignant atrophic papulosis is a rare vaso-occlusive disorder that predominantly affects the skin, gastrointestinal tract and CNS[22]. Cutaneous lesions begin as crops of small (2 to 5 mm) erythematous papules on the trunk or extremities. These evolve over 2 to 4 weeks, with the development of central depression and ultimately a porcelain white scar, often with a rim of telangiectasias and an appearance similar to atrophie blanche. Cutaneous findings typically precede systemic manifestations. Gastrointestinal lesions can lead to bowel perforation, and, along with CNS manifestations (e.g. cerebrovascular accidents), are the leading causes of death.

Pathology

Skin lesions are characterized histologically by a wedge-shaped area of altered dermis with a sparse perivascular lymphocytic infiltrate and an atrophic but slightly hyperkeratotic overlying epidermis. The dermis is usually altered by edema, mucin deposition and slight sclerosis, but occasionally it may be necrotic. The base of the lesion shows vascular damage with thrombosis[61].

Differential diagnosis

There are reports of a benign form with skin-limited disease, which may have a different underlying pathogenesis[62]. In addition, lesions mimicking those of malignant atrophic papulosis, i.e. Degos-like lesions, have been seen in patients with autoimmune connective tissue diseases (e.g. systemic lupus)[63]. Recognition that the APLS can produce similar lesions suggests that this entity should be excluded, particularly in patients with lupus and other autoimmune connective tissue disorders.

Treatment

There is still no proven treatment for idiopathic malignant atrophic papulosis, though occasional patients appear to respond to aspirin with or without pentoxifylline[64]. It is unclear how often those who are responsive have antiphospholipid antibodies.

DISORDERS OF CELLULAR VASCULAR OCCLUSION

Stress Reticulocyte Adhesion/Occlusion and Sickling Disorders

Just as endothelial cells are recognized to play an active role in the pathogenesis of adhesion and occlusion disorders, so too are red blood cells – specifically, stress reticulocytes – now recognized as active participants in some microvascular occlusion syndromes. The first evidence for this concept accrued from studies of cerebral malaria, where brain dysfunction and injury was shown to be related in part to adhesion by the large and sticky early reticulocytes that are released in settings of severe anemic stress. More recently, in sickle cell disease, the progressive vascular occlusion syndromes caused by ischemia-related cell sickling may be triggered by microvascular adhesion of these same stress reticulocytes. Once the vessel is occluded by these large red cells, perfusion of tissue drops, hypoxia ensues, and sickling of red cells follows, which may lead to expression of more adhesion molecules. The red cell adhesion has been attributed to thrombospondin-mediated adhesion to receptors on endothelium and on red blood cells, or by phosphatidylserine exposure on red cell membranes[65]. This binding can be blocked by coating the cells with annexin V. Interestingly, antibody interference with annexin V function on endothelial and platelet membranes has also been implicated as a mechanism for thrombosis in some patients with the APLS.

Intravascular Lymphoma

While chronic lymphocytic leukemia is the most common cause of a marked elevation of circulating atypical leukocytes, these cells are fragile and do not lead to vascular occlusion syndromes. Reduced perfusion of various organ systems may accompany high blast counts, nearly always of myelogenous origin. Cutaneous bland leukemic occlusion syndromes have not been reported, although repeated arterial occlusion from myeloblasts has been described (e.g. the retinal artery)[66]. Leukemic vasculitis in the skin has also been reported[67].

Intravascular lymphoma (B cell > T cell) is a very rare syndrome which is typically diagnosed post mortem, usually because of vague clinical findings. CNS involvement is often the most severe clinical manifestation. Skin lesions are commonly observed (40% of patients) but nonspecific and include erythematous, sometimes painful plaques or nodules and macular or telangiectatic lesions[68]. The lower extremities are the most common location (often in association with edema), followed by the trunk. Occasionally, it may present as retiform purpura (Fig. 23.10). The histopathologic finding of intraluminal occlusion by atypical lymphocytes can be missed on initial interpretation.

Fig. 23.10 Intravascular B-cell lymphoma. The clinical presentation in this patient was retiform purpura and necrosis with livedo. *Courtesy, Lucinda Buescher, MD.*

DISORDERS OF OCCLUSION, MISCELLANEOUS

Cutaneous Calciphylaxis

Synonyms: ■ Calcific arteriolopathy ■ Calcific uremic arteriolopathy

This syndrome of progressive cutaneous purpura and necrosis is most typically seen in patients with chronic renal failure (see Ch. 50). Vascular occlusion likely accounts for these cutaneous findings in most, if not all, cases, but the mechanism is controversial.

Brown Recluse Spider (*Loxosceles*) Bite

A *Loxosceles* envenomation may induce lesions of retiform purpura along with a systemic coagulopathy. While the cutaneous necrosis is undoubtedly multifactorial, the absence of bleeding during surgical debridement, a retiform morphology and extensive necrosis argue for a local microvascular occlusion syndrome in at least some of these patients.

Hydroxyurea-Associated Vascular Occlusion

By unknown mechanisms, patients with myeloproliferative diseases treated with hydroxyurea may develop painful ulcers, usually in the perimalleolar region. Some ulcers resemble those of livedoid vasculopathy, while others are larger and more shallow. Histologically, vessel findings range from inflammatory to thrombotic occlusion[69,70].

Interferon-Associated Cutaneous Necrosis

A number of cutaneous findings have been reported at β-interferon injection sites, with cutaneous microvascular occlusion and evidence of necrosis or necrotic panniculitis clinically[71,72]. While some blood vessels may have prominent perivascular inflammation, the thromboses are typically noted in the deep dermis or fat, often without inflammation.

Hematoma-Associated Retiform Purpura

Retiform purpura with necrosis, best explained by compression of subcutaneous arterioles by large trauma-induced hematomas, has been observed in multiple patients, including those with hemophilia[73].

REFERENCES

1. Schmugge M, Risch L, Huber AR, et al. Heparin-induced thrombocytopenia-associated thrombosis in pediatric intensive care patients. Pediatrics. 2002;109:E10.
2. Warkentin TE, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. N Engl J Med. 2001;344:1286–92.
3. Warkentin TE, Kelton JG. Delayed-onset heparin-induced thrombocytopenia and thrombosis. Ann Intern Med. 2001;135:502–6.
4. Santamaria A, Romani J, Souto J, et al. Skin necrosis at the injection site induced by low-molecular-weight heparin: case report and review. Dermatology. 1998;196:264–5.
5. Tietge UJ, Schmidt HH, Jackel E, et al. Low molecular weight heparin-induced skin necrosis occurring distant from injection sites and without thrombocytopenia. J Intern Med. 1998;243:313–15.
6. Lewis BE, Wallis DE, Berkowitz SO, et al. Argatroban anticoagulant therapy in patients with heparin-induced thrombocytopenia. Circulation. 2001;103:1838–43.
7. Itin PH, Winkelmann RK. Cutaneous manifestations in patients with essential thrombocythemia. J Am Acad Dermatol. 1991;24:59–63.
8. Stone MS, Robson KJ, Piette WW. Erythematous plaques due to platelet plugging: a clue to underlying myeloproliferative disorder. J Am Acad Dermatol. 2000;43:355–7.
9. Michiels JJ, ten Kate FJ. Erythromelalgia in thrombocythemia of various myeloproliferative disorders. Am J Hematol. 1992;39:131–6.
10. Tefferi A, Solberg LA, Silverstein MN. A clinical update in polycythemia vera and essential thrombocythemia. Am J Med. 2000;109:141–9.
11. Tefferi A, Silverstein MN, Petitt RM, et al. Anagrelide as a new platelet-lowering agent in essential thrombocythemia: mechanism of actin, efficacy, toxicity, current indications. Semin Thromb Hemost. 1997;23:379–83.
12. Beutler E. Paroxysmal nocturnal hemoglobinuria. In: Beutler E, Coller B, Lichtman M, et al. (eds). Williams Hematology, 6th edn. New York: McGraw-Hill, 2001:419–24.
13. Maciejewski JP, Young NS, Yu M, et al. Analysis of the expression of glycosylphosphatidylinositol anchored proteins on platelets from patients with paroxysmal nocturnal hemoglobinuria. Thromb Res. 1996;83:433–47.
14. Rosse W, Bunn H. Hemolytic anemias and acute blood loss. In: Fauci A, Braunwald E, Isselbacher K, et al. (eds). Harrison's Principles of Internal Medicine. New York: McGraw-Hill, 1998:659–71.
15. Draelos ZK, Hansen RC. Hemorrhagic bullae in an anemic woman. Arch Dermatol. 1986;122:1326–7, 1329–30.
16. Rietschel RL, Lewis CW, Simmons RA, et al. Skin lesions in paroxysmal nocturnal hemoglobinuria. Arch Dermatol. 1978;114:560–3.
17. Brodsky RA. How I treat paroxysmal nocturnal hemoglobinuria. Blood. 2009;113:6522–7.
18. Melnyk AM, Solez K, Kjellstrand CM. Adult hemolytic uremic syndrome - a review of 37 cases. Arch Intern Med. 1995;155:2077–84.
19. George J, Rizvi M. Thrombocytopenia. In: Beutler E, Lichtman M, Coller B, et al. (eds). Williams Hematology, 6th edn. New York: McGraw-Hill, 2001:1495–539.
20. Park YA, Waldrum MR, Marques MB. Platelet count and prothrombin time help distinguish thrombotic thrombocytopenic purpura-hemolytic uremic syndrome from disseminated intravascular coagulation in adults. Am J Clin Pathol. 2010;133:460–5.
21. Gourley BL, Mesa H, Gupta P. Rapid and complete resolution of chemotherapy-induced thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) with rituximab. Cancer Chemother Pharmacol. 2010;65:1001–4.
22. Robson K, Piette W. The presentation and differential diagnosis of cutaneous vascular occlusion syndromes. Adv Dermatol. 1999;15:153–82.
23. Stathakis NE, Karamanolis D, Koukoulis G, et al. Characterization of cryofibrinogen isolated from patients plasma. Haemostasis. 1981;10:195–202.
24. Beightler E, Diven DG, Sanchez RL, et al. Thrombotic vasculopathy associated with cryofibrinogenemia. J Am Acad Dermatol. 1991;24:342–5.
25. Saadoun D, Elalamy I, Ghillani-Dalbin P, et al. Cryofibrinogenemia: new insights into clinical and pathogenic features. Am J Med. 2009;122:1128–35.
26. Stone MS, Piette WW, Davey WP. Cutaneous necrosis at sites of transfusion: cold agglutinin disease. J Am Acad Dermatol. 1988;19:356–7.
27. Purvis RS, Beightler EL, Diven DG, et al. *Strongyloides* hyperinfection presenting with petechiae and purpura. Int J Dermatol. 1992;31:169–71.
28. Rea TH, Levan NE. Lucio's phenomenon and diffuse nonnodular lepromatous leprosy. Arch Dermatol. 1978;114:1023–8.
29. Pursley TV, Jacobson RR. Lucio's phenomenon. Arch Dermatol. 1980;116:201–4.
30. Falanga V, Fine MJ, Kapoor WN. The cutaneous manifestations of cholesterol crystal embolization. Arch Dermatol. 1986;122:1194–8.
31. Lawson JM. Cholesterol crystal embolization: more common than we thought? Am J Gastroenterol. 2001;96:3230–2.
32. Chaudhary K, Wall BM, Rasberry RD. Livedo reticularis: an underutilized diagnostic clue in cholesterol embolization syndrome. Am J Med Sci. 2001;321:348–51.
33. Kang K, Botella R, White C Jr. Subtle clues to the diagnosis of cholesterol embolism. Am J Dermatopathol. 1996;18:380–4.
34. Elinav E, Chajek-Shaul T, Stern M. Improvement in cholesterol emboli syndrome after iloprost therapy. BMJ. 2002;324:268–9.
35. Spiers EM, Sanders DY, Omura EF. Clinical and histologic features of primary oxalosis. J Am Acad Dermatol. 1990;22:952–6.
36. Marconi V, Mofid MZ, McCall C, et al. Primary hyperoxaluria: report of a patient with livedo reticularis and digital infarcts. J Am Acad Dermatol. 2002;46:S16–S18.
37. Ommen SR, Seward JB, Tajik AJ. Clinical and echocardiographic features of hypereosinophilic syndromes. Am J Cardiol. 2000;86:110–13.
38. Fitzpatrick JE, Johnson C, Simon P, Owenby J. Cutaneous microthrombi: a histologic clue to the diagnosis of hypereosinophilic syndrome. Am J Dermatopathol. 1987;9:419–22.
39. Sanchez JL, Padilla MA. Hypereosinophilic syndrome. Cutis. 1982;29:490–2, 494.
40. Weller PF, Bubley GJ. The idiopathic hypereosinophilic syndrome. Blood. 1994;83:2759–79.
41. Comp PC, Elrod JP, Karzenski S. Warfarin-induced skin necrosis. Semin Thromb Hemost. 1990;16:293–8.
42. Piette W, Shasby DM, Kealey P, Olson J. Retiform purpura is a sign of severe acquired protein C deficiency and risk of progression to purpura fulminans in sepsis and disseminated intravascular coagulation. Clin Res. 1993;41:253A.
43. Madden RM, Gill JC, Marlar RA. Protein C and protein S levels in two patients with acquired purpura fulminans. Br J Haematol. 1990;75:112–17.
44. Levin M, Eley BS, Louis J, et al. Postinfectious purpura fulminans caused by an autoantibody directed against protein S. J Pediatr. 1995;127:355–63.
45. Josephson C, Nuss R, Jacobson L, et al. The varicella-autoantibody syndrome. Pediatr Res. 2001;50:345–52.
46. Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. N Engl J Med. 2002;346:752–63.

46a. Ruiz-Irastorza G, Crowther M, Branch W, Khamashta MA. Antiphospholipid syndrome. Lancet. 2010;376:1498–1509.

47. Cervera R, Piette JC, Font J, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1000 patients. Arthritis Rheum. 2002;46:1019–27.
48. Angles-Cano E, Guillin MC. Antiphospholipid antibodies and the coagulation cascade. Rheum Dis Clin North Am. 2001;27:573–86.
49. Gibson GE, Su WP, Pittelkow MR. Antiphospholipid syndrome and the skin. J Am Acad Dermatol. 1997;36:970–82.

49a. Sciascia S, Naretto C, Rossi D, et al. Treatment-induced downregulation of antiphospholipid antibodies: effect of rituximab alone on clinical and laboratory features of antiphospholipid syndrome. Lupus. 2011;20:1106–8.
50. Frances C, Piette JC. The mystery of Sneddon syndrome: relationship with antiphospholipid syndrome and systemic lupus erythematosus. J Autoimmun. 2000;15:139–43.
51. Lahti J, Yu T, Burnett JW, et al. Sneddon's syndrome: a case report. Cutis. 2001;67:211–14.
52. Zelger B, Sepp N, Stockhammer G, et al. Sneddon's syndrome: a long-term follow-up of 21 patients. Arch Dermatol. 1993;129:437–47.
53. Wohlrab J, Fischer M, Wolter M, Marsch WC. Diagnostic impact and sensitivity of skin biopsies in Sneddon's syndrome. A report of 15 cases. Br J Dermatol. 2001;145:285–8.
54. Schellong SM, Weissenborn K, Niedermeyer J, et al. Classification of Sneddon's syndrome. Vasa. 1997;26:215–21.
55. Kalashnikova LA, Korczyn AD, Shavit S, et al. Antibodies to prothrombin in patients with Sneddon's syndrome. Neurology. 1999;53:223–5.
56. Maessen-Visch MB, Koedam MI, Hamulyak K, Neumann HA. Atrophie blanche. Int J Dermatol. 1999;38:161–72.
57. Acland KM, Darvay A, Wakelin SH, Russell-Jones R. Livedoid vasculitis: a manifestation of the antiphospholipid syndrome? Br J Dermatol. 1999;140:131–5.
58. Calamia KT, Balabanova M, Perniciaro C, Walsh J. Livedo (livedoid) vasculitis and the factor V Leiden mutation: additional evidence for abnormal coagulation. J Am Acad Dermatol. 2002;46:133–7.
59. Hsiao PF, Wu YH. Distinct pattern of direct immunofluorescence in livedoid vasculopathy. Am J Dermatopathol. 2010;32:240–3.
60. Lee JH, Choi HJ, Kim SM, et al. Livedoid vasculitis responding to PUVA therapy. Int J Dermatol. 2001;40:153–7.
61. Harvell JD, Williford PL, White WL. Benign cutaneous Degos' disease: a case report with emphasis on histopathology as papules chronologically evolve. Am J Dermatopathol. 2001;23:116–23.
62. Katz SK, Mudd LJ, Roenigk HH Jr. Malignant atrophic papulosis (Degos' disease) involving three generations of a family. J Am Acad Dermatol. 1997;37:480–4.
63. Tsao H, Busam K. Barnhill RL, Haynes HA. Lesions resembling malignant atrophic papulosis in a patient with dermatomyositis. J Am Acad Dermatol. 1997;36: 317–19.
64. Vicktor C, Schultz-Ehrenburg U. Malignant atrophic papulosis (Kohlmeier-Degos): diagnosis, therapy and course [German]. Hautarzt. 2001;52:734–7.
65. Setty BNY, Kulkarni S, Stuart M. Role of erythrocyte phosphatidylserine in sickle red cell-endothelial adhesion. Blood. 2002;99:1564–71.
66. Reisch N, Roehnisch T, Sadeghi M, et al. AML M1 presenting with recurrent acute large arterial vessel thromboembolism. Leuk Res. 2007;31:869–71.
67. Seckin D, Senol A, Gurbuz O, Demirkesen C. Leukemic vasculitis: an unusual manifestation of leukemia cutis. J Am Acad Dermatol. 2009;61:519–21.
68. Roglin J, Boer A. Skin manifestations of intravascular lymphoma mimic inflammatory diseases of the skin. Br J Dermatol. 2007;157:16–25.
69. Romanelli M, Dini V, Romanelli P. Hydroxyurea-induced leg ulcers treated with a protease-modulating matrix. Arch Dermatol. 2007;143:1310–13.
70. Weinlich G, Schuler G, Greil R, et al. Leg ulcers associated with long-term hydroxyurea therapy. J Am Acad Dermatol. 1998;39:372–5.
71. Ohata U, Hara H, Yoshitake M, Terui T. Cutaneous reactions following subcutaneous β-interferon-1b injection. J Dermatol. 2010;37;179–81.
72. Ball NJ, Cowan BJ, Hashimoto SA. Lobular panniculitis at the site of subcutaneous interferon beta injections for the treatment of multiple sclerosis can histologically mimic pancreatic panniculitis. A study of 12 cases. J Cutan Pathol. 2009;36:331–7.
73. Kaya G, Jacobs F, Prins C, et al. Deep dissecting hematoma: an emerging severe complication of dermatoporosis. Arch Dermatol. 2008;144:1303–8.

Cutaneous Vasculitis 24

Kanade Shinkai and *Lindy P Fox*

Chapter Contents

Classification ... 385
Epidemiology ... 387
Pathogenesis ... 387
General clinical features ... 387
Pathology ... 388
Differential diagnosis ... 388
Cutaneous small vessel vasculitis ... 389
Predominantly small and medium-sized vessel vasculitides ... 397
Predominantly medium-sized vessel vasculitis ... 405
Temporal arteritis ... 407
Diagnostic approach to patients with vasculitis ... 407

Key features

- Cutaneous signs of vasculitis are a reflection of the size of the vessels involved
- Vasculitis can be limited to the small vessels of the skin or it can be a sign of life-threatening internal organ involvement
- The clinical diagnosis of cutaneous vasculitis requires histopathologic confirmation and multiple biopsies may be required

INTRODUCTION

Vasculitis represents a specific pattern of inflammation of the blood vessel wall and it can occur in any organ system of the body. Cutaneous vasculitis may be: (1) a skin-limited disease; (2) a primary cutaneous vasculitis with secondary systemic involvement; or (3) a cutaneous manifestation of a systemic vasculitis.

Vasculitis can affect small, medium-sized or large vessels of the arterial and/or venous systems (Table 24.1). Small vessels include arterioles, capillaries and postcapillary venules, which are found in the superficial and mid dermis of the skin. Medium-sized vessels refer to the small arteries and veins that reside within the deep dermis or subcutis. Large vessels include the aorta and named arteries. Cutaneous involvement occurs almost exclusively with vasculitis of small and medium-sized vessels; therefore, the large vessel vasculitides are discussed briefly or mentioned in Table 24.1.

In this chapter, cutaneous vasculitis refers to vasculitis with any underlying etiology and affecting any sized vessel where the clinical manifestations affect the skin. Cutaneous small vessel vasculitis (CSVV) is synonymous with cutaneous leukocytoclastic vasculitis (LCV) and refers to involvement of the postcapillary venules of the dermis by intense neutrophilic vascular inflammation.

CLASSIFICATION

The current classification scheme for cutaneous vasculitis is based upon the *predominant* size of the vessel involved (see Table 24.1).

CUTANEOUS VASCULITIS CLASSIFICATION SCHEME

Caliber of the predominantly affected vessel	Classification	Subclassification or etiologies	Morphology of cutaneous lesions
Small	Cutaneous small vessel vasculitis (CSVV)	Henoch–Schönlein purpura Acute hemorrhagic edema of infancy Urticarial vasculitis Erythema elevatum diutinum Secondary causes of CSVV (see Table 24.3): – Drug exposure – Infections – Malignancies, most often hematologic	Palpable purpura (most common) Petechiae Macular purpura Urticarial papules Vesicles Pustules Targetoid papules and plaques
Small and medium-sized ("mixed")	Cryoglobulinemia	Types II and III	Petechiae Palpable purpura Livedo racemosa Retiform purpura Ulcers Subcutaneous nodules Digital necrosis
	ANCA-associated	Microscopic polyangiitis Wegener's granulomatosis Churg–Strauss syndrome	
	Secondary causes	Infections Inflammatory disorders (e.g. AI-CTD)	
Medium-sized	Polyarteritis nodosa (PAN)	Classic (systemic) PAN	Livedo racemosa Retiform purpura Ulcers Subcutaneous nodules Digital necrosis
		Cutaneous PAN	
Large*	Temporal arteritis		Early – erythematous or cyanotic skin, alopecia, purpura, tender nodules on frontotemporal scalp Late – Ulceration and/or gangrene of frontotemporal scalp or tongue
	Takayasu's arteritis		Erythematous subcutaneous nodules +/– ulceration, pyoderma gangrenosum-like lesions on the extremities (lower > upper) May have evidence of small and/or medium-sized vessel vasculitis

*Cutaneous manifestations are rare.

Table 24.1 Cutaneous vasculitis classification scheme. AI-CTD, autoimmune connective tissue diseases.

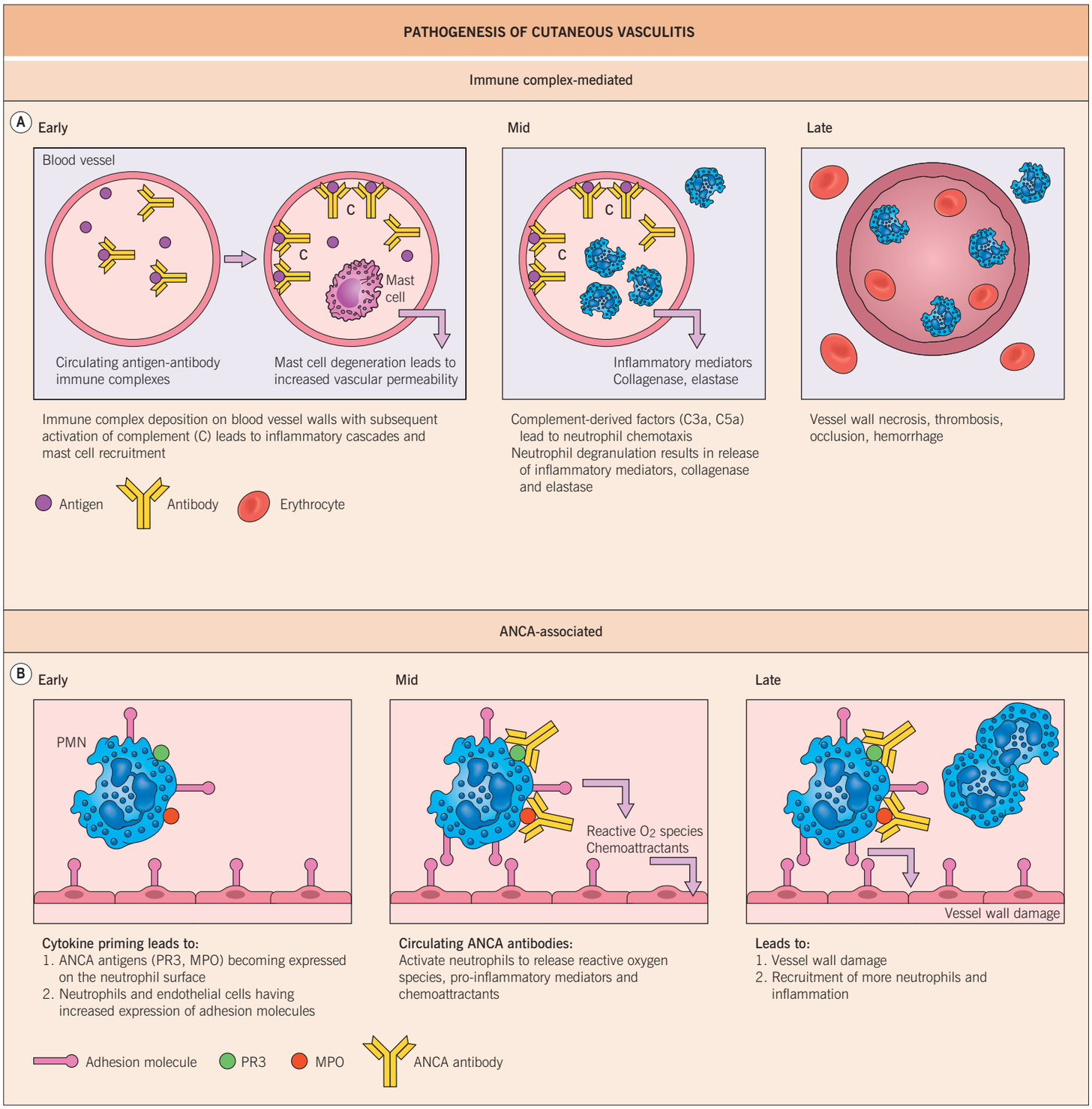


Fig. 24.1 Pathogenesis of cutaneous vasculitis – immune complex- versus ANCA-mediated. A In immune complex-mediated vasculitis, circulating antigens (e.g. infectious agents, medications, neoplasms) induce antibody formation. Binding of antibodies to circulating antigens creates immune complexes. Immune complex deposition within postcapillary venules activates complement and subsequently leads to an increase in adhesion molecule expression on the endothelium. Complement split products (C3a and C5a) induce mast cell degranulation and neutrophil chemotaxis. Mast cell degranulation leads to increased vascular dilation and permeability, enhancing immune complex deposition and leukocyte tethering to endothelium. Increased adhesion between inflammatory cells (especially neutrophils) and the endothelium is mediated by elevated expression of selectins (E-selectin, P-selectin) and members of the immunoglobulin superfamily (ICAM-1, VCAM-1, PECAM-1) on endothelial cells in concert with the upregulation of their corresponding ligands and receptors/adhesion molecules on leukocytes (e.g. P-selectin glycoprotein ligand-1, LFA-1, Mac-1) (see Ch. 102 for details). Neutrophils release proteolytic enzymes (such as collagenases and elastases) and free oxygen radicals that damage the vessel wall. In addition, formation of the membrane attack complex (C5–C9) on the endothelium leads to the activation of the clotting cascade and the release of cytokines and growth factors with ensuing thrombosis, inflammation and angiogenesis. **B** In ANCA-mediated vasculitis, intracellular proteins from neutrophils (e.g. proteinase 3 [PR3], myeloperoxidase [MPO]) become expressed on the cell surface. After formation of ANCA that recognize these antigens, binding of the autoantibodies to neutrophils leads to increased neutrophil adhesion to vessel walls and subsequent cellular activation. Neutrophils then release reactive oxygen species and other toxic mediators that result in vessel wall damage (see **A**). Because the vessel damage in ANCA-positive vasculitides is directly mediated by neutrophils rather than by immune complexes, they are referred to as "pauci-immune" vasculitides.

This then determines the clinical presentation and the corresponding histologic findings. Additional features that aid in classifying cutaneous vasculitis are systemic manifestations, direct immunofluorescence findings, and the presence or absence of antineutrophil cytoplasmic antibodies (ANCA). Despite descriptions of distinct vasculitic syndromes, there are no unique diagnostic criteria and clinicopathologic correlation is always required.

EPIDEMIOLOGY

The incidence of biopsy-proven cutaneous vasculitis of all types is 15–60 patients per million per year[1]. Cutaneous vasculitis occurs in all age groups (mean age in adults, 47 years; mean age in children, 7 years), has a slight female predominance[1,2], and is much more common in adults than in children. The majority of children have Henoch–Schönlein purpura.

PATHOGENESIS

All forms of CSVV and some forms of mixed and medium-sized vessel vasculitides (e.g. cryoglobulinemic vasculitis, polyarteritis nodosa) are mediated by immune complexes that form in the presence of antigen excess. Immune complex deposition in postcapillary venules activates complement, which, in turn, induces mast cell degranulation and neutrophil chemotaxis. Neutrophils release proteolytic enzymes and free oxygen radicals, leading to damage of the vessel wall (Fig. 24.1A). Increased adhesiveness between inflammatory cells and the endothelium, due to enhanced expression of adhesion molecules (e.g. selectins, LFA-1), also plays a role in the pathogenesis of cutaneous vasculitis (see Ch. 102).

ANCA are primarily directed against intracellular neutrophilic proteins (e.g. proteinase-3, myeloperoxidase), which can translocate to the neutrophil's cell surface following primary activation by cytokines such as tumor necrosis factor (TNF)-α. Binding to the surface of neutrophils results in neutrophil-mediated vessel damage (Fig. 24.1B). Because the vessel damage in ANCA-positive vasculitides is directly mediated by neutrophils rather than by immune complex deposition, they are referred to as "pauci-immune" vasculitides. Formation of ANCA may be related to an impairment in neutrophil apoptosis which results in a prolonged opportunity for autoantibody development.

GENERAL CLINICAL FEATURES

The skin lesions of CSVV usually appear 7–10 days after the triggering event. In systemic vasculitic syndromes, signs of systemic involvement often precede the appearance of associated cutaneous lesions (average, 6 months), but the interval can be as short as days or as long as years[1]. As noted previously, the cutaneous findings of vasculitis depend upon the predominant size of the vessels that are involved. CSVV typically presents with palpable or macular purpura, but urticarial papules, pustules, vesicles, petechiae or targetoid lesions can be seen (Figs 24.2 & 24.3). The lesions favor dependent sites, as well as areas under tight-fitting clothing, reflecting the influence of hydrostatic pressure and stasis on the pathophysiology. In general, the lesions are asymptomatic, but they may itch, burn or sting.

In medium-sized vessel vasculitis, the affected blood vessels reside within the reticular dermis or subcutis. As a result, the latter typically presents with livedo racemosa, retiform purpura, ulcers, subcutaneous nodules and/or digital necrosis. In general, the presence of ulcers or necrosis suggests deeper arterial involvement. The combination of palpable purpura (or other signs of CSVV) plus signs of medium-sized vessel disease points to a "mixed" pattern of vasculitis (see Table 24.1), as is seen in ANCA-associated vasculitides, mixed cryoglobulinemia, or autoimmune connective tissue disease-associated vasculitis. Since polyarteritis nodosa affects only medium-sized vessels, it rarely presents with cutaneous signs of small vessel involvement.

Arthralgias and arthritis as well as constitutional symptoms such as fever, weight loss and malaise can be manifestations of vasculitis of any size vessel[2]. For patients with systemic involvement, presenting symptoms and signs (e.g. abdominal pain, paresthesias, hematuria) will vary according to the affected organs.

Fig. 24.2 Cutaneous small vessel vasculitis. A Classic presentation of purpuric papules on the distal lower extremities; a few lesions have become vesicular. **B** Early lesions may be pink papules. **C** Central necrosis with formation of hemorrhagic crusts. **D** Digital infarcts.
A, Courtesy, Kalman Watsky, MD.
C, Courtesy, Frank Samarin, MD.

Fig 24.3 Clinical variants of cutaneous small vessel vasculitis. **A** Targetoid appearance that can resemble erythema multiforme. **B** Hemorrhagic crusts in annular configuration. **C** Lesions limited to the upper extremities – an unusual distribution pattern.

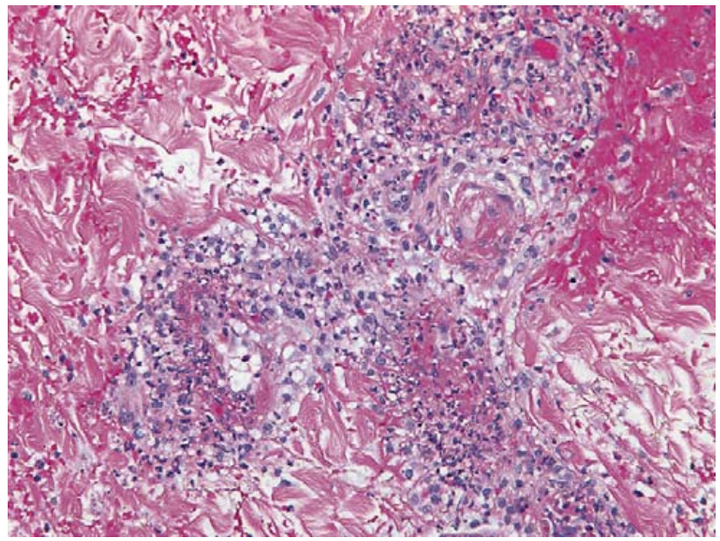


Fig. 24.4 Cutaneous small vessel vasculitis – histologic features. Angiocentric segmental inflammation with endothelial swelling, a neutrophilic infiltrate with leukocytoclasia, red blood cell extravasation, and fibrinoid necrosis of blood vessel walls. The neutrophils are present around and within the walls of small dermal blood vessels. *Courtesy, David F Fiorentino, MD.*

PATHOLOGY

Timing and appropriate sampling of the most likely involved vessel increase the diagnostic yield of a skin biopsy. Ideally, lesions should be biopsied within the first 24 to 48 hours of appearance. When CSVV is suspected, a biopsy specimen for direct immunofluorescence should be obtained, as the presence of certain immunoglobulins (e.g. IgA) may suggest a particular diagnosis and influence prognosis. In general, punch biopsies are adequate for the diagnosis of CSVV while an incisional or excisional biopsy may be required to diagnose vasculitis of larger vessels.

In cutaneous vasculitis, the histologic findings vary depending upon the type and age of the sampled lesion in addition to the size of the affected vessel. The classic histopathologic features of CSVV are referred to as leukocytoclastic vasculitis and consist of transmural infiltration of the walls of small vessels (primarily postcapillary venules) by neutrophils undergoing karyorrhexis of their nuclei, as well as fibrinoid necrosis of the damaged vessel walls (Fig. 24.4). Other findings include leukocytoclasia (degranulation and fragmentation of neutrophils, leading to the production of nuclear dust), extravasated erythrocytes, and signs of endothelial cell damage. However, lesions present for greater than 48 to 72 hours may have a predominantly mononuclear rather than neutrophilic infiltrate. Palpable purpura, the most common clinical lesion of CSVV, can be explained by the infiltrate of leukocytes (palpability) and the resulting extravasation of RBCs from the damaged blood vessel (purpura).

Vasculitis of medium-sized blood vessels is characterized by similar changes involving the vessels (e.g. small arteries) of the deep reticular dermis and subcutaneous fat. Neovascularization of the adventitia, in the form of small capillaries, is commonly seen in older lesions of medium-sized vessel vasculitis.

In ~80% of cases of CSVV, direct immunofluorescence (DIF) demonstrates deposition of C3, IgM, IgA and/or IgG (generally in that order of frequency) in a granular pattern within the vessel walls[1]. Immunoglobulin deposition is highest (up to 100%) in skin lesions present for ≤48 hours[1]. On the other hand, in 30% of samples obtained 48–72 hours after lesion onset, DIF will be negative for immunoglobulins, and only C3 will be detected in lesions present for >72 hours[1]. In patients with an ANCA-positive vasculitis, the DIF of lesional skin is usually negative.

DIFFERENTIAL DIAGNOSIS

Several disorders can present with skin lesions that resemble the various cutaneous manifestations of vasculitis and they are listed in Table 24.2.

CLINICAL DIFFERENTIAL DIAGNOSIS OF CUTANEOUS VASCULITIS

Clinical presentation	Differential diagnosis
Palpable purpuric papules/plaques	Arthropod bites Morbilliform drug eruptions with hemorrhage in dependent sites Erythema multiforme Pityriasis lichenoides et varioliformis acuta Infectious emboli (septic vasculitis) due to bacteria (e.g. *Neisseria meningococcus* [acute meningococcemia]), rickettsiae, fungi (e.g. *Rhizopus)* Lichenoid capillaritis (pigmented purpura) Cellulitis
Purpuric macules/patches	**Hemorrhage** – Trauma – Solar (actinic) purpura* – Medication-related (i.e. aspirin, topical or systemic corticosteroids)* – Thrombocytopenia and platelet dysfunction – Coagulopathies* – Viral exanthems (e.g. enterovirus, parvovirus B19) – Scurvy – Primary systemic amyloidosis **Thromboses** – Hypercoagulable state (e.g. antiphospholipid antibody; see Table 105.9) – Livedoid vasculopathy – Purpura fulminans (e.g. due to sepsis/DIC) – Heparin necrosis – Coumadin necrosis – Thrombotic thrombocytopenic purpura – Hemolytic uremic syndrome – Paroxysmal nocturnal hemoglobinuria **Emboli** – Cholesterol – Cardiac (infective endocarditis >> myxomatous or marantic) – Fat – Air **Cold-related gelling** – Cryoglobulins (primarily type I) **Inflammation** – Pigmented purpura (capillaritis) – Hypergammaglobulinemic purpura of Waldenström **Infection** – Lucio's phenomenon (leprosy) – Strongyloidiasis
Urticarial lesions	Urticaria (including neutrophilic urticaria) Arthropod bites and papular urticaria Urticaria multiforme Serum sickness-like reaction Autoinflammatory diseases (e.g. periodic fevers; see Table 45.2) Still's disease Schnitzler's syndrome Viral exanthems Kawasaki disease Sweet's syndrome Urticarial phase of bullous pemphigoid
Ulcers ± atrophie blanche	Venous or arterial disease Pyoderma gangrenosum Livedoid vasculopathy Hypercoagulable state (e.g. antiphospholipid antibodies; see Table 105.9) Hemoglobinopathies Calciphylaxis Infections (e.g. bacterial, mycobacterial, dimorphic or opportunistic fungal, protozoal) Factitial Halogenodermas Degos' disease See Fig. 105.1 for additional entities
Nodules	Panniculitis Superficial migratory thrombophlebitis Dermal neoplasms Infections (e.g. bacterial, mycobacterial, dimorphic or opportunistic fungal)
Livedo reticularis	See Chapter 106
Digital gangrene	Arterial occlusive disease (atherosclerosis, etc.) Diabetes mellitus Thromboangiitis obliterans (Buerger's disease) Systemic sclerosis Emboli (e.g. cholesterol, septic) Cryoglobulinemia (type I) > cryofibrinogenemia or cold agglutinin disease Thrombosis (e.g. antiphospholipid syndrome, purpura fulminans, myeloproliferative thrombocytosis) Calciphylaxis Hypereosinophilic syndrome Paraneoplastic acral vascular syndrome (e.g. with lung or ovarian carcinoma)

*Element of trauma.

Table 24.2 Clinical differential diagnosis of cutaneous vasculitis. DIC, disseminated intravascular coagulation.

CUTANEOUS SMALL VESSEL VASCULITIS

Synonyms: ■ Cutaneous leukocytoclastic vasculitis ■ Cutaneous leukocytoclastic angiitis ■ Hypersensitivity angiitis ■ Cutaneous necrotizing venulitis

Key features

- Palpable purpura, urticarial lesions, hemorrhagic macules or vesicles
- Lesions favor the lower extremities (especially the ankles), dependent areas or pressure points
- Only involves small vessels (primarily postcapillary venules)
- Histopathologically, leukocytoclastic vasculitis is seen
- Extracutaneous involvement occurs, but it is uncommon and usually mild

Introduction

CSVV is a vasculitic process that involves primarily the dermal postcapillary venules and is characterized histologically by leukocytoclastic vasculitis (LCV). Although CSVV with LCV can be seen in the setting of mixed (small and medium-sized vessel) vasculitides (see Table 24.1), the term *CSVV* is generally reserved for small vessel vasculitis of the skin without medium-sized vessel involvement, irrespective of the clinical severity of the skin disease or the underlying etiology. CSVV is often idiopathic in nature, but may be secondary to an underlying cause such as an infection or medication (Table 24.3). Within the spectrum of CSVV are several subtypes whose rather unique epidemiologic and clinical features warrant subclassification (see Table 24.1) and separate discussion.

Epidemiology

CSVV occurs in both sexes and at all ages[3], but is more common in the adult population. It is estimated that ~10% of those affected are children. The incidence of CSVV is ~15 cases per million[1].

Pathogenesis

As depicted in Figure 24.1A, CSVV is mediated by immune complex deposition (see General Pathogenesis for details).

UNDERLYING CAUSES OF SECONDARY CUTANEOUS VASCULITIS				
Association	**Incidence**	**Agent/Disease**		
		Common	**Uncommon**	**Rare**
Idiopathic	50%			
Infection	15–20%	**Bacterial**		
		Beta-hemolytic streptococci, especially group A *Mycobacterium leprae*	*Neisseria meningococcus* (in chronic meningococcemia) *Mycobacterium tuberculosis* Atypical mycobacteria	*Mycoplasma pneumoniae* *Chlamydophila pneumoniae, Chlamydia trachomatis* *Brucella* *Bartonella henselae* *Salmonella* *Campylobacter* *Yersinia enterocolitica* *Treponema pallidum*
		Septic vasculitis*		
		Infective endocarditis	*Neisseria meningitidis* (acute) *Neisseria gonorrhea* *Staphylococcus aureus* Rickettsiae Gram-negative rods *Escherichia coli* *Klebsiella* *Pseudomonas* Disseminated fungal infections (immunocompromised hosts) *Candida* *Aspergillus* *Fusarium* *Mucor*	*Francisella tularensis*
		Viral		
		Upper respiratory tract infection Hepatitis C > B >> A, including vaccines	HIV Parvovirus B19	Cytomegalovirus Varicella zoster virus Influenza virus, including vaccine
Inflammatory disorders	15–20%	Autoimmune connective tissue diseases – Rheumatoid arthritis – SLE – Sjögren's syndrome	Inflammatory bowel disease Behçet's disease Hypergammaglobulinemic purpura of Waldenström Seronegative spondyloarthropathies	Sarcoidosis Cystic fibrosis‡ Primary biliary cirrhosis Bowel-associated dermatosis–arthritis syndrome Gluten enteropathy (adult HSP)
Drug-exposure†	10–15%	Allopurinol Bortezomib Cephalosporins, esp. cefaclor D-penicillamine G-CSF Hydralazine‡ Methotrexate Minocycline‡ NSAIDs Oral contraceptives Penicillins Phenytoin Propylthiouracil/other antithyroid agents‡ Quinidine Quinolones Serum (e.g. ATG) Streptokinase Sulfonamides Thiazides	ACE inhibitors TNF-α inhibitors Beta-blockers Cocaine adulterated with levamisole‡ COX-2 inhibitors Furosemide Interferons Leukotriene inhibitors‡,§ Macrolide antibiotics Quinine Retinoids Sirolimus Sulfonylureas Vancomycin Warfarin	Amiodarone Aspirin Atypical antipsychotics Gabapentin Insulin Leflunomide Mefloquine Metformin Methamphetamine 3,4-methylenedioxymethamphetamine Phenothiazines Radiographic contrast media Rituximab SSRIs Tocolytics (e.g. ritodrine, terbutaline) Vitamins Food/drug additives SSKI
Neoplasms	2–5%	Plasma cell dyscrasias – Monoclonal gammopathies – Multiple myeloma Myelodysplasia Myeloproliferative disorders Lymphoproliferative disorders Hairy cell leukemia	Solid organ carcinomas (adults with IgA-positive vasculitis)	
Genetic disorders	Rare			Immunodeficiency syndromes (see Table 60.1) Familial Mediterranean fever and other periodic fever syndromes (see Table 45.2)

*Histopathology varies and includes leukocytoclastic vasculitis, organisms within the vessel wall and non-inflammatory thrombotic purpura.
†Peripheral blood eosinophilia may be present in up to 80% and 20% of patients with systemic and skin-limited diseases, respectively[7a,7b].
‡May be associated with antineutrophil cytoplasmic antibodies (ANCA).
§Associated with Churg–Strauss syndrome.

Table 24.3 Underlying causes of secondary cutaneous vasculitis. ACE, angiotensin-converting enzyme; ATG, antithymocyte globulin; COX, cyclooxygenase, G-CSF, granulocyte colony-stimulating factor; HSP, Henoch–Schönlein purpura; NSAIDs, nonsteroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus; SSKI, saturated solution of potassium iodide; SSRI, selective serotonin reuptake inhibitor; TNF, tumor necrosis factor. Adapted from refs 3 & 4.

Clinical features

CSVV typically presents 7 to 10 days after exposure to an inciting agent with a single crop of lesions consisting of palpable purpura, erythematous papules, urticarial lesions or vesicles that range in size from 1 mm to several centimeters (see Fig. 24.2). Lesions often begin as a purpuric macule or partially blanching urticarial papule. Occasionally, pustules and targetoid lesions are seen (see Fig. 24.3). CSVV favors dependent areas, as well as areas affected by trauma (Koebner phenomenon) or under tight-fitting clothing. Although they are usually asymptomatic, the lesions can be associated with burning, pain or pruritus. Residual postinflammatory hyperpigmentation may persist for months after the primary process resolves.

Constitutional symptoms, such as fevers, weight loss and myalgias, may accompany flares of CSVV. Systemic symptoms develop in 5–25% of patients with CSVV, with arthralgias and arthritis occurring most commonly (15–65%), followed by genitourinary (3–7%) signs or symptoms and gastrointestinal involvement (3–5%)[5]. In general, signs or symptoms of gastrointestinal, renal or neurologic involvement should increase the clinical suspicion for a systemic vasculitis. In one study, the presence of paresthesias or fever and the absence of painful lesions were identified as risk factors for an associated systemic disease[6].

While the prognosis of patients with CSVV depends upon the severity of systemic involvement, approximately 90% of patients will have spontaneous resolution of cutaneous lesions within several weeks or a few months, while another 10% will have chronic or recurrent disease at intervals of months to years[7]. In the latter, the average duration of disease activity is 28 months[1]. The presence of arthralgias or cryoglobulinemia and an absence of fever may portend chronicity[6]. An underlying cause for the CSVV, such as an autoimmune connective tissue disease or neoplasm, will also affect prognosis.

Differential diagnosis

In addition to determining if the patient has a particular subtype of CSVV (see Table 24.1) or has CSVV as a manifestation of cryoglobulinemic vasculitis or a systemic vasculitic syndrome, causes of secondary cutaneous vasculitis also need to be considered (Table 24.3; Figs 24.5 & 24.6). Entities listed in Table 24.2, especially the first three categories, need to be included in the clinical differential diagnosis as well.

Treatment

The initial intervention in CSVV consists of supportive care and identifying possible triggers. The need for and choice of additional treatments depends on the severity of the cutaneous involvement, chronicity and whether or not systemic involvement is present. Specific therapeutic options are outlined in Table 24.10.

CSVV often resolves without any treatment other than avoidance of the inciting trigger. For mild skin-limited disease, supportive measures (e.g. leg elevation, avoiding tight clothing, rest) or symptomatic therapy (e.g. antihistamines, NSAIDs) may be all that is necessary.

Chronic (>4 weeks' duration) or more severe cutaneous disease may require more aggressive systemic therapy. Colchicine and dapsone may be used either alone or in combination. Oral colchicine (0.6 mg two to three times daily) is helpful for both skin and joint manifestations. However, gastrointestinal side effects are fairly common, even at low doses. Oral dapsone (50–200 mg/day) can lead to improvement of mild to moderate chronic lesions.

Patients with severe, ulcerating or progressive cutaneous disease who require rapid control of symptoms can be treated with a short course of high-dose oral corticosteroids (e.g. up to 1 mg/kg/day of prednisone). Because of the multiple adverse effects of long-term oral corticosteroids, a taper over 4 to 6 weeks should be attempted. If the patient develops recurrent CSVV as the dosage is decreased, addition of a steroid-sparing agent is warranted. Immunosuppressive agents such as azathioprine

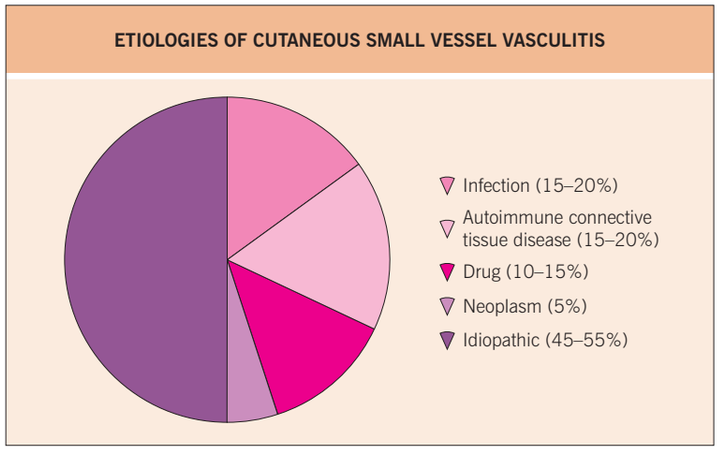


Fig. 24.5 Etiologies of cutaneous small vessel vasculitis.

Fig. 24.6 Cutaneous small vessel vasculitis associated with systemic disorders. The underlying diseases were Sjögren's syndrome (**A**), rheumatoid arthritis (**B**), and relapsing polychondritis with myelodysplasia (**C**). Note the Koebner phenomenon in **A** and rheumatoid nodules in **B**. *C, Courtesy, Jean L Bolognia, MD.*

(2 mg/kg/day) and methotrexate (<25 mg weekly) have been reported to be useful in recalcitrant CSVV.

Henoch–Schönlein Purpura

Synonyms: ■ Schönlein–Henoch purpura ■ Anaphylactoid purpura ■ Purpura rheumatica ■ Cutaneous small vessel vasculitis secondary to circulating IgA immune complexes

Key features

- Most commonly occurs in children <10 years of age and in association with a preceding respiratory infection, but may also be seen in adults
- Intermittent palpable purpura on extensor extremities and buttocks
- IgA-dominant immune deposits in walls of small blood vessels
- Arthralgias and arthritis
- Abdominal pain and/or melena
- Renal vasculitis often mild but can be chronic
- May be associated with an underlying malignancy in adults

Introduction

Henoch–Schönlein purpura (HSP) is a specific form of CSVV with vascular IgA deposition that typically affects children following a respiratory tract infection, but may also occur in adults. The classic tetrad consists of palpable purpura, arthritis, abdominal pain and hematuria. Although the relationship between HSP and other forms of vasculitis in which vascular IgA deposition is present remains controversial, the presence of IgA deposition within the walls of small blood vessels has clinical and prognostic implications in both children and adults.

Epidemiology

HSP is the most common form of vasculitis in children, with an incidence of 10 to 20 cases per 100 000 children per year. The average age of onset is 6 years and 90% of cases occur in children <10 years of age[8,9]. In adults, the incidence of HSP is 3 to 14 cases per million[10]. The disorder follows a seasonal pattern, with a peak occurrence during the winter. HSP has a slight male predominance in both children and adults.

Pathogenesis

HSP frequently presents 1 to 2 weeks following an upper respiratory tract infection, especially in children. Although several studies have reported that 20–50% of HSP patients have positive antistreptolysin O titers[8], no causal role for group A β-hemolytic streptococci has been demonstrated.

IgA (specifically IgA1) is thought to play a significant role in the pathogenesis of HSP, as IgA deposits in the postcapillary venules of the skin and mesangium, and, less commonly, circulating IgA-containing immune complexes and increased serum levels of IgA, have been demonstrated in patients with HSP[9]. Lack of glycosylation of the hinge region of IgA1 may promote the formation of macromolecular complexes that lodge within the mesangium and activate the alternate complement pathway[8].

Certain genetic polymorphisms may predispose to more severe disease in HSP, including polymorphisms in genes whose protein products are involved in the regulation of inflammation (Table 24.4). HLA-B35 positivity may predispose to renal disease, while patients who do not have the ICAM-1 469 K/E variant have less severe gastrointestinal involvement[9].

Clinical features

HSP classically presents with purpura (100% of patients) in association with arthritis, abdominal pain and/or nephritis[8]. Fever occurs in approximately 20% of adults and 40% of children[11]. Cutaneous lesions begin as erythematous macules or urticarial papules (Fig. 24.7) that evolve into palpable purpura ranging in size from pinpoint to several millimeters. Urticaria, vesicles, bullae, and foci of necrosis can also be seen.

GENETIC POLYMORPHISMS OR MUTATIONS THAT PREDISPOSE TO HENOCH–SCHÖNLEIN PURPURA OR WEGENER'S GRANULOMATOSIS	
HENOCH–SCHÖNLEIN PURPURA	
Protein product	
Mannose-binding lectin (MBL)	
MBL-associated serine protease	
Interleukin-1 receptor antagonist	
Interleukin-1β	
Interleukin-8	
Vascular endothelial growth factor	
α_1-antitrypsin (deficiency)	
Gene	
Paired box gene 2	
Inducible nitric oxide synthetase 2A promoter	
MEFV (familial Mediterranean fever gene)	
Other	
HLA-B35 positivity – predisposes to renal disease	
ICAM-1 469 K/E negative genotype – less severe gastrointestinal involvement	
WEGENER'S GRANULOMATOSIS	
PTPN22 (PR3 antibodies)	
MHC (HLA-DPB1*0401)	
CTLA4	
Protease inhibitors	
Fc gamma	
PR3 promoter	

Table 24.4 Genetic polymorphisms or mutations that predispose to Henoch–Schönlein purpura or Wegener's granulomatosis. Either the gene or the protein product is listed. PR, proteinase.

Typically, lesions are symmetrically distributed on the buttocks and lower extremities, but may also involve the trunk, upper extremities and face. Individual lesions usually regress within 10 to 14 days, with resolution of skin involvement over a period of several weeks to months. Recurrences of skin disease are observed in 5–10% of patients[7].

Extracutaneous manifestations of HSP are common. Arthritis occurs in up to 75% of patients with HSP and most commonly affects the joints of the lower extremities (knees and ankles). Gastrointestinal involvement (50–75% of patients) may precede the purpura and presents with colicky abdominal pain (65%), gastrointestinal bleeding (30%) and/or vomiting. Intussusception and bowel perforation are rare complications. Renal involvement occurs in 40–50% of patients and typically presents with microscopic hematuria (40%), often accompanied by proteinuria (25%). Although the appearance of cutaneous lesions often precedes the development of nephritis, the latter is clinically evident within 3 months. Persistent renal disease (requiring longitudinal monitoring until all abnormalities resolve), is present in 30–50% of patients, but only 1–3% of children will develop long-term renal impairment[8]. Orchitis is a rare form of involvement in young boys. Poor prognostic factors include renal failure at the time of onset, nephrotic syndrome, hypertension and decreased factor XIII activity[1].

IgA small vessel vasculitis in adults, termed adult HSP by some authors, should be considered separately, as the clinical presentation and prognosis differ from that in children. For example, necrotic skin lesions are present in 60% of adults while cutaneous necrosis is observed in <5% of children[12,13]. Adults with IgA vasculitis are also more likely than children to develop chronic renal insufficiency (up to 30%)[13], especially if they have purpura above the waist, fever and an elevated ESR[12]. In addition, when CSVV is due to an underlying neoplasm, the latter is usually a hematologic malignancy (see Table 121.6). However, 60–90% of adult patients with neoplasm-associated IgA vasculitis will have cancer of a solid organ, in particular lung[14,15]. Adults are also more likely than children to have diarrhea and leukocytosis, to require more aggressive therapy, and to have a longer hospital stay[16].

Pathology

Leukocytoclastic vasculitis of the small dermal blood vessels is seen. DIF demonstrates perivascular IgA, C3 and fibrin deposits. Other immunoglobulins may be seen, but are generally not as prominent as IgA. By indirect immunofluorescence, IgA ANCA may be present in some patients.

Fig. 24.7 Henoch–Schönlein purpura. A Multiple pink papules on the lower extremities that are becoming purpuric. **B** More developed lesions with central necrosis.

Differential diagnosis

The clinical differential diagnosis includes any of the vasculitides involving small vessels (see Table 24.1) as well as several of the entities in Table 24.2. Of the several proposals for diagnostic criteria, the one developed by the European League against Rheumatism/Pediatric Rheumatology European Society (EULAR/PReS), may be the most clinically relevant to the dermatologist[17]. In addition to palpable purpura (a required criterion), at least one of the following must be present:

- arthritis (acute, any joint) or arthralgia
- diffuse abdominal pain
- any biopsy demonstrating predominant IgA deposition
- renal involvement (hematuria and/or proteinuria).

Because up to 80% of all adults with CSVV may demonstrate some vascular IgA deposition[18] and IgA deposition can be seen in other diseases (e.g. drug hypersensitivity), a diagnosis of HSP is supported by IgA *predominance* in the correct clinical setting. Evidence of medium-sized vessel disease or widespread lesions (including the face) may indicate an underlying IgA paraproteinemia.

Treatment

Because HSP is generally self-limited and resolves over the course of weeks to months, treatment is mainly supportive. Dapsone and colchicine may decrease the duration of cutaneous lesions (see Table 24.10)[19]. Systemic corticosteroids are effective in treating the arthritis and abdominal pain associated with HSP, as well as reducing the duration of skin lesions, but do not prevent recurrences of purpura[20]. Referral to a nephrologist is appropriate for patients with evidence of renal involvement. Because IgA vasculitis in adults is a more recently recognized disorder, most studies, including those discussed here, typically reflect treatment outcomes in children.

Considerable controversy surrounds the use of corticosteroids and/or immunosuppressive medications for the treatment of severe renal disease and for preventing renal sequelae in individuals who have severe renal involvement. In one study, the use of prednisone was associated with a more rapid resolution of renal disease during the 4-week treatment period (in addition to improvement of abdominal pain, arthritis and purpuric skin lesions)[20]. However, a Cochrane review of interventions for preventing and treating the renal disease of HSP found no difference in the risk of persistent kidney disease (at 6–12 months) in those children treated with prednisone (2–4 weeks) at the time of presentation as compared to placebo or supportive therapy[21]. This review also found no difference in the risk of persistent renal disease in patients with severe kidney disease who were treated with cyclophosphamide versus supportive care. A meta-analysis that examined the use of systemic corticosteroids at the time of diagnosis versus supportive care found a decrease in the mean (but not the median) time to resolution of abdominal pain, while the odds of developing persistent renal disease were decreased[22]. In sum, the current consensus appears to be that corticosteroids do not prevent renal disease but could be used to treat severe nephritis[9].

Acute Hemorrhagic Edema of Infancy

Synonyms: ■ Acute hemorrhagic edema of childhood ■ Infantile acute hemorrhagic edema ■ Finkelstein's disease ■ Seidlmayer syndrome ■ Finkelstein–Seidlmayer disease ■ Purpura en cocarde avec edema ■ Postinfectious cockade purpura

Key features

- The child is well-appearing
- Seen primarily in children between 4 and 24 months of age
- Annular, circular or targetoid purpuric plaques on the face and extremities
- Tender, non-pitting edema of acral sites
- Extracutaneous involvement rare
- Benign clinical course with spontaneous resolution within 1 to 3 weeks

Introduction

Acute hemorrhagic edema of infancy (AHEI) is a rare form of CSVV that usually affects children 4 to 24 months of age. Cutaneous lesions typically begin as plaques with variable degrees of hemorrhage which favor the head and extremities. They subsequently become edematous and targetoid in appearance. Previously considered a benign form of HSP, acute hemorrhagic edema of infancy is now recognized as its own clinical entity.

Epidemiology

AHEI is a relatively rare disorder, with approximately 300 cases reported to date in the world literature. It affects children <2 years of age, with

TRIGGERS AND ASSOCIATIONS IN ACUTE HEMORRHAGIC EDEMA OF INFANCY AND URTICARIAL VASCULITIS	
ACUTE HEMORRHAGIC EDEMA OF INFANCY – TRIGGERS	
Infections	
– Adenovirus	– Rotavirus
– Coxsackievirus	– Varicella zoster virus
– Cytomegalovirus	– *Campylobacter* spp.
– Epstein-Barr virus	– *Escherichia coli*
– Herpes simplex virus	– *Mycobacterium tuberculosis*
– Hepatitis A virus	– *Streptococcus* spp.
– Measles	
Medications	
– Acetaminophen	
– Penicillins	
– Cephalosporins	
– Trimethoprim–sulfamethoxazole	
– NSAIDs	
URTICARIAL VASCULITIS – ASSOCIATIONS	
Autoimmune connective tissue diseases (Sjögren's syndrome, SLE)	
Serum sickness	
Cryoglobulinemia	
Infections	
– Hepatitis B virus	
– Hepatitis C virus	
– Epstein-Barr virus	
– Lyme disease	
Medications	
– Cimetidine	– Methotrexate
– Cocaine	– NSAIDs
– Diltiazem	– Potassium iodide
– Etanercept	– Procainamide
– Fluoxetine	– Procarbazine
– Infliximab	
Hematologic malignancies	
– Plasma cell dyscrasias (IgM, IgG, IgA)	
– Leukemias	
– Lymphomas	
– Castleman's disease	
Solid organ malignancies – rare	
– Colon carcinoma	
– Renal cell carcinoma	

Table 24.5 Triggers and associations in acute hemorrhagic edema of infancy and urticarial vasculitis. NSAIDs, nonsteroidal anti-inflammatory drugs.

Fig. 24.8 Acute hemorrhagic edema of infancy. A, B Multiple edematous erythematous plaques on the face and extremities of a toddler. Some of the lesions have begun to become dusky. *Courtesy, Ilona J Frieden, MD.*

~70% of cases occurring in boys[23]. A seasonal variation is observed, with a peak incidence during the winter months.

Pathogenesis

Although the etiology of AHEI is unknown, 75% of patients have an associated infection, drug exposure or immunization[24]. An infectious prodrome is observed in two-thirds of patients, most commonly a respiratory tract infection (80%), diarrheal illness (12%), or urinary tract infection (6%)[23]. There are multiple reported triggers and they are listed in Table 24.5. As with other forms of CSVV, the pathogenesis of AHEI is thought to involve immune complex deposition in response to an antigenic trigger[25].

Clinical features

Children typically do not appear ill, although fever is present in ~45% of patients. The typical interval between the inciting event (see above) and the onset of disease is 1–2 weeks[26]. Cutaneous involvement presents abruptly with large erythematous patches or urticarial plaques that then evolve into medallion, annular, iris or targetoid purpuric plaques. The latter favor the cheeks, ears and extremities (Fig. 24.8), but truncal involvement may also occur. Lesions may be asymptomatic, painful, or, less commonly, pruritic. Arcuate, polycyclic, scalloped or rosette-shaped lesions and vesicobullae occur less commonly, as does healing with atrophic scars[26]. Tender, non-pitting edema of the face, ears, extremities (including the hands and feet) and scrotum is characteristic. Although mucosal and visceral involvement is rare, oral petechiae, conjunctival injection, abdominal pain, arthralgias, glomerulonephritis and intussusception (<1%) may occur[23]. The course is benign, with spontaneous and complete resolution without sequelae within 1 to 3 weeks. Although exacerbations may occur, once a remission has lasted 2 weeks, relapses as a rule are not observed[23].

Pathology

Leukocytoclastic vasculitis involving the capillaries and postcapillary venules of the upper and mid dermis is observed. By DIF, IgA deposits in a vascular pattern are seen in one-quarter to one-third of cases[23,25].

Differential diagnosis

Patients with features of both AHEI and HSP have been reported[25]. An age of onset <2 years, disease confined to the skin, and a briefer duration are characteristic of AHEI. In young children with urticarial lesions and acrofacial edema, urticaria multiforme should be considered[27]. The differential diagnosis also includes erythema multiforme, urticaria, urticarial drug eruptions, serum sickness-like reactions, Kawasaki disease, urticarial vasculitis and Sweet's syndrome. Given the significant cutaneous hemorrhage, trauma, acute meningococcemia and purpura fulminans are sometimes considered. Routine laboratory tests are nonspecific, and the diagnosis is based on appropriate clinicopathologic correlation.

Treatment

Treatment is supportive (see Table 24.10). Antibiotics should be given to treat concurrent bacterial infections. Antihistamines may be useful

for symptomatic relief. Systemic corticosteroids have not been shown to alter the course of the disease[24].

Urticarial Vasculitis

Synonyms: ■ Chronic urticaria as a manifestation of venulitis ■ Urticaria and arthralgia with necrotizing angiitis
If hypocomplementemia:
■ Hypocomplementemic vasculitis ■ Hypocomplementemia with cutaneous vasculitis and arthritis

Key features

- Recurrent episodes of painful, persistent urticarial lesions that last >24 hours and often resolve with residual hyperpigmentation
- May occur with or without angioedema
- May be associated with constitutional symptoms and arthritis
- Patients with hypocomplementemia are more likely to have systemic involvement
- Associated disorders include autoimmune connective tissue diseases (especially systemic lupus erythematosus, Sjögren's syndrome) and viral infections

Introduction

Urticarial vasculitis is a clinicopathologic entity consisting of persistent urticarial lesions that demonstrate the histopathologic features of leukocytoclastic vasculitis. Its association with autoimmune connective tissue diseases and potential overlap with systemic lupus erythematosus (SLE) distinguishes this disorder from typical CSVV. Although the relationship between urticarial vasculitis and neutrophilic urticaria is an area of debate, in this chapter, the definition of urticarial vasculitis is as follows: urticarial lesions that histopathologically demonstrate vasculitis as defined by a minimum of leukocytoclasia with vessel wall necrosis, but with or without fibrinoid deposits, perivascular inflammation or red blood cell extravasation[28].

Epidemiology

In patients with chronic urticaria in whom a strict definition of urticarial vasculitis (see above) is applied, the prevalence of urticarial vasculitis is approximately 5%[28], although this may be an overestimation. The peak incidence is during the fifth decade, and 60–80% of patients with urticarial vasculitis are female. The hypocomplementemic form occurs almost exclusively in women[29]. From 70% to 80% of cases of urticarial vasculitis are normocomplementemic and they follow a benign course with an average duration of 3 years.

Pathogenesis

The pathogenesis of urticarial vasculitis is similar to that of typical CSVV. In urticarial vasculitis, it is thought that complement activation triggers mast cell release of inflammatory mediators such as TNF-α that in turn increase the expression of ICAM on mast cells (important for eosinophil transmigration) and E-selectin on endothelial cells[28].

Although urticarial vasculitis is most often idiopathic, it can be associated with autoimmune connective tissue diseases (especially Sjögren's syndrome and SLE), serum sickness, cryoglobulinemia, infections, medications, and hematologic malignancies (Table 24.5)

Clinical features

Lesions of urticarial vasculitis consist of erythematous, indurated wheals (Fig. 24.9), with or without angioedema, that favor the trunk and proximal extremities. Urticarial vasculitis is distinguished from chronic urticaria by individual lesions that persist beyond 24 hours, are associated with burning and pain rather than pruritus, and resolve with postinflammatory hyperpigmentation. With diascopy or as residua, hemorrhage can be observed. However, these features are not always present. Rarely, bullae, erythema multiforme-like lesions, livedo reticularis, Raynaud's phenomenon and laryngeal edema are clinical manifestations of urticarial vasculitis[28].

When faced with urticarial lesions that histopathologically demonstrate features of LCV, the most important prognostic feature is the presence or absence of hypocomplementemia. Patients with normal complement levels tend to have skin-limited disease, whereas those with hypocomplementemia are much more likely to have systemic manifestations. The hypocomplementemic urticarial vasculitis syndrome (HUVS) is a more severe syndrome defined by specific diagnostic criteria[28]. They are as follows:

two major criteria: (1) urticaria for 6 months and (2) hypocomplementemia – plus –

two or more minor criteria: (1) vasculitis on skin biopsy; (2) arthralgia or arthritis; (3) uveitis or episcleritis; (4) glomerulonephritis; (5) recurrent abdominal pain; or (6) positive C1q precipitin test with a low C1q level.

Patients with hypocomplementemia who do not meet the criteria for HUVS are considered to have hypocomplementemic urticarial vasculitis (but not HUVS). While these disorders exist on a spectrum, they are not thought to transition from one to another.

Musculoskeletal involvement is the most common extracutaneous manifestation of urticarial vasculitis. Arthralgias of the hands, elbows, knees, ankles and feet occur in half of all patients with urticarial vasculitis, but up to 50% of patients with HUVS have frank arthritis[28]. Up to 20% of patients have pulmonary symptoms (cough, laryngeal edema, hemoptysis, dyspnea, asthma, chronic obstructive pulmonary disease [COPD])[7]. COPD is especially severe in smokers with urticarial vasculitis, and it is worse than would be expected due to smoking alone. Renal involvement, manifesting as proteinuria or microscopic hematuria, occurs in 5–10% of patients with HUVS[28]. Gastrointestinal manifestations (abdominal pain, nausea, vomiting, diarrhea) occur in up to 30% of patients; cardiac and central nervous system involvement are rare, but reported. HUVS shares features with SLE, but distinctive clinical findings in HUVS include ocular inflammation (30%; conjunctivitis, episcleritis, iritis, uveitis), angioedema (>50%), and COPD-like symptoms (50%)[28].

In patients with urticarial vasculitis, the most common abnormal laboratory studies are an elevated ESR, low serum C3 and C4 levels, and a positive ANA. HUVS is marked by low serum complement levels (which may vary, however, from non-detectable to normal, even during attacks) plus the presence of anti-C1q precipitin and depressed C1q levels. Although up to a third of patients with SLE have circulating anti-C1q antibodies and up to half of patients with HUVS have a positive ANA, patients with HUVS, rarely have anti-dsDNA or anti-Sm antibodies[28].

Pathology

Histopathologically, urticarial vasculitis is defined as a minimum of leukocytoclasia with vessel wall necrosis, with or without fibrinoid deposits, perivascular inflammation or red blood cell extravasation[28]. Although findings may be subtle and consist only of interstitial neutrophils or perivascular lymphocytes with extravasated erythrocytes (especially in older lesions), these findings alone do not fulfill the histologic criteria for the diagnosis of urticarial vasculitis.

Fig. 24.9 Urticarial vasculitis. Several erythematous urticarial plaques on the foot and ankle. *Courtesy, Cora Whitney Hannon, MD, and Robert Swerlick, MD.*

Eosinophils may also be noted. By DIF, 70% of lesions demonstrate deposits of immunoglobulin, C3 or fibrin around blood vessels[28]. A granular pattern of immunoreactants along the basement membrane zone occurs in ~80% of lesions and, when accompanied by hypocomplementemia, suggests the diagnosis of SLE[28]. Basement membrane immunoreactants have also been associated with renal disease[28].

Differential diagnosis

The main entity in the differential diagnosis is urticaria (including delayed pressure urticaria, in which lesions can last longer than 24 hours). Urticarial vasculitis should also be distinguished from neutrophilic urticaria, which, although considered by some to be within the spectrum of urticarial vasculitis, is not associated with hypocomplementemia or autoimmune disease and is better thought of as a subset of urticaria that histologically demonstrates a neutrophilic infiltrate without vasculitis. The differential diagnosis also includes disorders that clinicopathologically present with urticarial lesions and an interstitial neutrophilic infiltrate, including Schnitzler's syndrome, erythema marginatum (of rheumatic fever), adult-onset Still's disease, and cryopyrin-associated periodic syndromes (see Ch. 45). Additional entities to consider are the urticarial phase of bullous pemphigoid, atypical erythema multiforme, urticaria multiforme[30], Sweet's syndrome, tumid lupus erythematosus, SLE (see above), and rheumatoid neutrophilic dermatitis. For lesions of angioedema, the differential diagnosis includes acquired and inherited forms of angioedema (see Ch. 18).

Treatment

No randomized clinical trials have been performed to date to evaluate possible therapeutic options. Antihistamines may reduce the swelling and pain associated with cutaneous lesions, but do not alter the course of the disease. Oral corticosteroids are effective, but the duration of use should be kept to a minimum (see Ch. 125). Indomethacin, dapsone (with or without pentoxifylline), colchicine, hydroxychloroquine and mycophenolate mofetil have all been reported to be beneficial (see Table 24.10). Rituximab[31] or intravenous immunoglobulin[32,33] may also be a useful therapy for recalcitrant hypocomplementemic urticarial vasculitis.

Erythema Elevatum Diutinum

Key features

- Symmetric red–violet to red–brown papules and plaques
- Persistent lesions that develop on extensor surfaces
- Fibrosing leukocytoclastic vasculitis

Introduction

Erythema elevatum diutinum (EED) is a rare, chronic dermatosis, characterized by red–violet to red–brown papules, plaques and nodules that favor extensor surfaces. Histopathologic features consist of LCV in early lesions, followed by fibrotic replacement of the dermis in older lesions.

Epidemiology

Erythema elevatum diutinum is rare, with descriptions of several hundred cases in the literature. The disease can develop at any age, but is more common in middle-aged and older adults (ages 30–60 years). An earlier onset occurs more often in the setting of HIV infection[34]. The male-to-female ratio is approximately equal, and no racial predilection has been observed[35].

Pathogenesis

Although the etiology of EED is unknown, circulating immune complexes, with repeated deposition, associated inflammation and partial healing, are thought to represent the underlying pathogenesis[34]. Immune complex deposition results in complement activation, neutrophilic infiltration, and the release of destructive enzymes. The latter results in fibrin deposition in and around small dermal vessels during the later stages of the disease.

EED has been described in association with a number of systemic diseases, including infections, autoimmune diseases, and both benign and malignant hematologic disorders, especially an IgA paraproteinemia. Associated infections include β-hemolytic streptococci, HBV, HIV, tuberculosis, and syphilis[34]. Lesions identical to EED, both clinically and histologically, have been reproduced by the intradermal injection of streptococcal antigen into non-lesional skin of patients with EED[35]. In patients with HIV infection, EED may be due to either HIV-related antigen–antibody complexes directly damaging small blood vessels or HIV-induced immunosuppression allowing other infectious agents to serve as an antigenic stimulus. The observation that in patients with HIV infection EED responds to antiretroviral therapy supports an etiologic role for HIV[34].

Autoimmune or inflammatory conditions associated with EED include Wegener's granulomatosis, inflammatory bowel disease, celiac disease, relapsing polychondritis, SLE and rheumatoid arthritis. In addition to plasma cell dyscrasias (especially IgA monoclonal gammopathies), associated hematologic disorders include myelodysplasia, myeloproliferative disorders and hairy cell leukemia.

Clinical features

The typical cutaneous lesions of EED are violaceous, red–brown or yellowish papules, plaques or nodules that are symmetrically distributed. They favor acral and periarticular sites, in particular the extensor surfaces of the elbows, knees, ankles, hands and fingers (Fig. 24.10). Additional sites of involvement include the face, retroauricular area,

Fig. 24.10 Erythema elevatum diutinum. **A** Erythematous papulonodules on the knee (acute lesions) admixed with resolving lesions. **B** Firm nodule on the dorsum of the hand in a patient with HIV infection (late-stage lesion). *A, Courtesy, Kenneth Greer, MD. B, Courtesy, Rachel Moore, MD.*

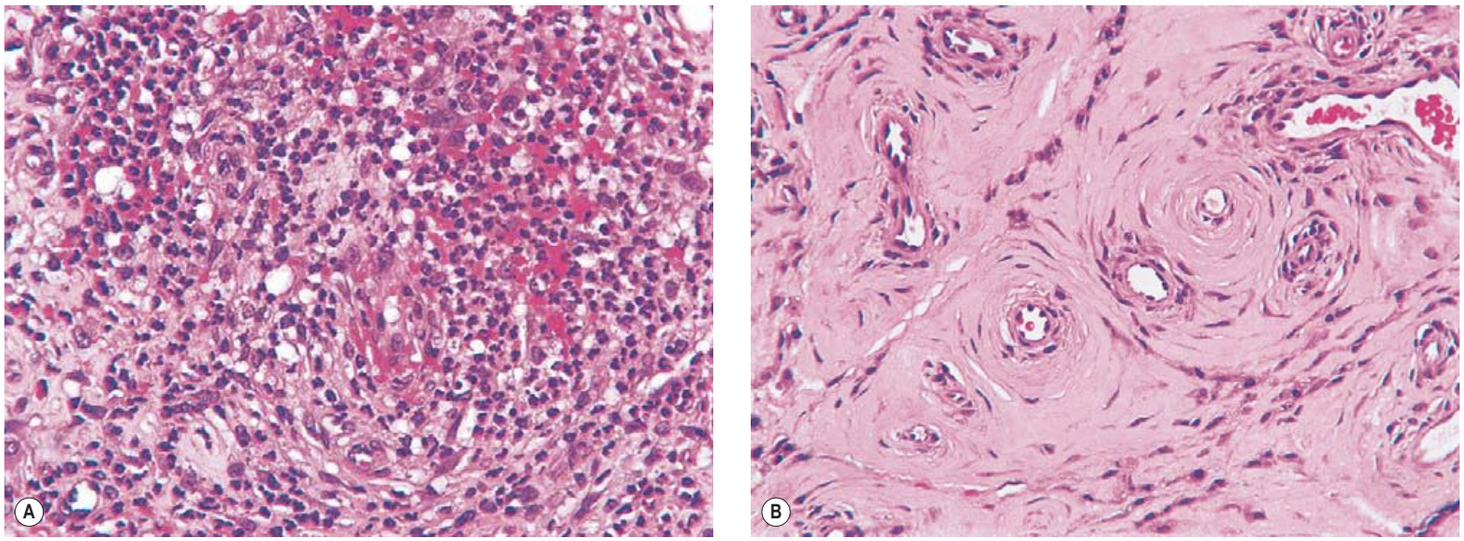


Fig. 24.11 Erythema elevatum diutinum – histologic features. A An early-stage lesion, demonstrating a dense perivascular infiltrate of neutrophils admixed with lymphocytes and histiocytes. In addition, there is evidence of scattered nuclear dust and red blood cell extravasation. **B** A late-stage lesion, demonstrating a minimal inflammatory infiltrate and marked perivascular fibrous thickening. *Courtesy, Cora Whitney Hannon, MD, and Robert Swerlick, MD.*

trunk, axillae, buttocks and genitalia[36]. Initially, the lesions are erythematous and soft, but with time become red–brown or violaceous in color and doughy or firm to palpation due to fibrosis.

In general, the lesions are asymptomatic, but they can be associated with a burning sensation or pruritus, especially early on[34]. Annular plaques with a raised border[36] and verrucous plaques on the soles[37] have also been described. Nodular lesions, primarily palmoplantar, that progress to form bulky masses are characteristic of EED in the setting of HIV infection[34]. Arthralgias may develop in underlying joints[35], but extracutaneous involvement, with the exception of ocular disease, is extremely rare. There has been an increasing number of reports of associated peripheral keratitis, nodular scleritis, panuveitis and blindness[38,39]. The disease is chronic and has a relapsing and remitting course; the majority of cases resolve spontaneously over a period of 5 to 10 years, but the disease can last up to 40 years[35].

In patients presenting with EED, evaluation for an associated infection (e.g. streptococcal, viral hepatitis, HIV, syphilis), monoclonal gammopathy (serum immunofixation electrophoresis) or autoimmune disorder (see above) should be considered, based upon the clinical context.

Pathology

Early lesions of EED demonstrate the changes of LCV, with a neutrophilic infiltrate within the upper and mid dermis (Fig. 24.11A), admixed with some eosinophils. Involvement of the papillary and perifollicular adventitial dermis (without a grenz zone) is observed in more mature lesions[40]. The latter are also characterized by granulation tissue and perivascular, concentric or storiform fibrosis with mixed inflammation that is composed predominantly of neutrophils. In the late stage, capillary walls may have fibrinoid necrosis or fibrosis (Fig. 24.11B); vertically oriented capillaries can also be seen and it may be difficult to discern the features of vasculitis. Intracellular lipidosis, previously termed "extracellular cholesterolosis", is a classic finding in late-stage lesions[41].

Differential diagnosis

The clinical differential diagnosis depends upon the stage of the lesion. For earlier lesions, one needs to consider neutrophilic dermatoses (e.g. pustular vasculitis of the dorsal hands, Sweet's syndrome, rheumatoid neutrophilic dermatitis) and palisaded neutrophilic and granulomatous dermatitis. Late-stage lesions may be confused primarily with tuberous xanthomas, granuloma annulare, rheumatoid nodules, fibroid nodules of *Borrelia* and multicentric reticulohistiocytosis. Other granulomatous disorders (e.g. sarcoidosis, leprosy, necrobiotic xanthogranuloma) are sometimes in the differential diagnosis, and for an isolated lesion, dermatofibroma or dermatofibrosarcoma protuberans (DFSP). Occasionally, lesions with a prominent vascular component, especially in an HIV-infected patient, might be mistaken for Kaposi sarcoma or bacillary angiomatosis.

Histopathologically, the earliest lesions may share features with the neutrophilic dermatoses, but foci of LCV help to distinguish EED. Granuloma faciale may also be considered, but a predominance of eosinophils and plasma cells and the presence of a grenz zone are distinguishing features, as is the localization of lesions to the face. The differential diagnosis of later lesions includes tuberous xanthomas, fibrotic disorders or tumors (e.g. DFSP; see Chs 98 &, 116), and, occasionally, fibroid nodules of *Borrelia*, Kaposi sarcoma and bacillary angiomatosis[34].

Treatment

Dapsone induces dramatic improvement[42], but relapses frequently occur upon discontinuation. Other therapies include NSAIDs, niacinamide, tetracyclines, chloroquine, colchicine and plasmapheresis (see Table 24.10). Intralesional corticosteroids may be helpful for mild cases, but systemic corticosteroids are rarely indicated.

PREDOMINANTLY SMALL AND MEDIUM-SIZED VESSEL VASCULITIDES

Cryoglobulinemic Vasculitis

Synonyms: ■ Type II or III cryoglobulinemia ■ Idiopathic mixed cryoglobulinemia ■ Cryoglobulinemic purpura ■ Essential cryoglobulinemic vasculitis

Key features

- Palpable purpura, typically on the lower extremities
- Myalgias and arthralgias
- Associated with mixed serum cryoglobulins (IgM and IgG), most commonly in the setting of HCV infection
- Peripheral neuropathy and glomerulonephritis can develop

Introduction

Cryoglobulins are cold-precipitable immunoglobulins that can be divided into three subtypes, all of which have cutaneous manifestations (Table 24.6). Type I cryoglobulinemia, composed primarily of monoclonal IgM (and less frequently IgG > IgA), results in microvascular occlusion without vasculitis (see Ch. 23). In contrast, vasculitis is only seen with types II and III ("mixed cryoglobulins", composed of monoclonal and polyclonal components). This form of vasculitis may involve both small and medium-sized vessels (see Table 24.1), but preferentially

CLASSIFICATION OF CRYOGLOBULINS				
Subtype	**Molecular composition**	**Associations**	**Pathophysiology**	**Clinical manifestations**
I	Monoclonal IgM > IgG[¶]	Plasma cell dyscrasias, lymphoproliferative disorders	Vascular occlusion	Raynaud's phenomenon, retiform purpura, gangrene, acrocyanosis
II*	Monoclonal IgM[†] (>IgG[†]) against polyclonal IgG	HCV, HIV, autoimmune connective tissue diseases, lymphoproliferative disorders	Vasculitis	Palpable purpura, arthralgias, peripheral neuropathy, glomerulonephritis
III*	Polyclonal IgM[†] against polyclonal IgG			

*Referred to as "mixed" cryoglobulins because either monoclonal or polyclonal immunoglobulins bind to polyclonal immunoglobulins.
[†]Typically have rheumatoid factor activity (i.e. are directed against the Fc portion of IgG).
[¶]Rarely IgA.

Table 24.6 Classification of cryoglobulins. HCV, hepatitis C virus; HIV, human immunodeficiency virus.

involves small vessels. Approximately 15% of patients with circulating mixed cryoglobulins present with symptoms due to cryoglobulinemic vasculitis[7]. Cryoglobulinemic vasculitis typically affects the skin, peripheral nervous system and kidneys.

Epidemiology

The frequency of mixed cryoglobulinemia varies according to geographic location, e.g. there is a higher prevalence in Southern Europe than in Northern Europe or North America[43]. In northwest Spain, the annual incidence was determined to be 4.8 cases per million. Geographic variations in the frequency of mixed cryoglobulinemia likely reflect differences in the prevalence of HCV infection. While greater than 50% of patients with HCV infection have cryoglobulinemia, overt cryoglobulinemic vasculitis develops in approximately 5% of these individuals.

Pathogenesis

Mixed cryoglobulinemia occurs in the setting of specific infections, autoimmune connective tissue diseases, and hematologic malignancies[44] (see Table 24.6). When the association between HCV infection and mixed cryoglobulinemia was discovered in 1989, a cause for 70–90% of "essential" cryoglobulinemia became apparent. Only 5% of cases are associated with HBV infection, and, occasionally, EBV, cytomegalovirus, *Leishmania* and *Treponema* spp. have been implicated. In a minority of patients, mixed cryoglobulinemia has been associated with autoimmune connective tissue diseases, in particular rheumatoid arthritis, followed by Sjögren's syndrome and systemic sclerosis. Approximately 5% of the patients with mixed cryoglobulinemia have a lymphoproliferative disorder (e.g. B-cell non-Hodgkin lymphoma, chronic lymphocytic leukemia, macroglobulinemia).

It is poorly understood why mixed cryoglobulins are produced in these clinical settings. In the case of HCV and HBV infections, their production is thought to be related, at least in some patients, to the associated liver disease, e.g. patients with end-stage liver disease are at higher risk of developing mixed cryoglobulins. A significant percentage of lymphocytes in HCV-infected individuals possess a t(14;18) translocation that results in a rearrangement of *bcl-2*, whose protein product has an antiapoptotic function; this can lead to B-lymphocyte proliferation and may contribute to production of cryoglobulins. In HCV-infected patients who do not possess this *bcl-2* rearrangement, B-cell activation and subsequent cryoglobulin and autoantibody production is believed to result from chronic immune stimulation (e.g. by the virus)[43].

Cryoglobulinemic vasculitis occurs when immune complexes form from circulating cryoglobulins and then deposit within the walls of small and medium-sized vessels, but preferentially small vessels. As with other forms of cutaneous vasculitis, this immune complex deposition is believed to initiate complement activation and vascular inflammation. The presence of hepatitis C virion (in association with IgM and IgG antibodies) within vessel walls raises the possibility that viral particles are a component of the cryoprecipitate[44].

Clinical features

Cutaneous involvement occurs in up to 90% of patients with cryoglobulinemic vasculitis, most commonly manifesting as palpable purpura of the lower extremities (Fig. 24.12). Other cutaneous findings include erythematous papules, ecchymoses and dermal nodules; rarely, urticaria, livedo reticularis, necrosis, ulcerations and bullae are observed. The disease usually has a chronic course[7], and the types of lesions can reflect the size of the involved vessel (see Table 24.1). They are not typically cold-induced (as opposed to vascular occlusive lesions seen in type I cryoglobulinemia).

Common extracutaneous findings include arthritis or arthralgias (70%), peripheral (typically sensory) neuropathy (40%), gastrointestinal disease or hepatitis (30%), and membranoproliferative glomerulonephritis (25%)[7]. The hepatitis may reflect the underlying viral infection or an associated autoimmune hepatitis, or it may be a direct result of the cryoglobulinemia. Occasionally, patients have

Fig. 24.12 Cutaneous small vessel vasculitis due to mixed cryoglobulinemia. **A** The most common cause is hepatitis C viral infection. **B** Macular purpura mimicking Cullen's sign in a patient with hepatitis C infection.

xerostomia or xerophthalmia and endocrinologic disorders, e.g. thyroid, gonadal.

The most commonly associated infections, autoimmune connective tissue diseases and hematologic disorders are listed in the Pathogenesis section. Non-Hodgkin B-cell lymphoma is the most common associated malignancy. Rarely, solid tumors such as hepatocellular carcinoma and papillary thyroid carcinoma have been reported to have a relationship to cryoglobulinemic vasculitis.

With regard to the laboratory evaluation, tests for cryoglobulins can be falsely negative and need to be assayed during clinical flares on more than one occasion. In addition, the blood sample should be kept at 37°C while being transported to the laboratory. Approximately 70% of patients have circulating rheumatoid factor activity, while 20% have antinuclear antibodies. Up to 15% of patients with mixed cryoglobulinemia have a monoclonal gammopathy as detected by serum protein electrophoresis and/or immunofixation electrophoresis[7]. HBV, HCV and HIV serologies should be evaluated, followed by a determination of viral load if there is evidence of infection. Patients typically have low serum complement levels, often with low or undetectable C4 levels; however, complement levels do not necessarily correlate with the severity of the disease[43].

Pathology

Histopathologically, papular lesions show LCV, while necrotic or ulcerated lesions may demonstrate medium-sized vessel vasculitis. By DIF, granular deposits consisting predominantly of IgM and C3 in a vascular pattern are observed in the papillary dermis[1].

Differential diagnosis

The differential diagnosis of cryoglobulinemic vasculitis includes all forms of small and medium-sized vessel vasculitis (see Table 24.1). Cryoglobulinemic vasculitis can be differentiated from these disorders by the detection of circulating mixed cryoglobulins. Patients with Sjögren's syndrome can also have arthralgias, arthritis, xerostomia/xerophthalmia, and the presence of rheumatoid factor and/or mixed cryoglobulins; however, they are typically SSA (Ro)/SSB(La)-positive, have distinct histopathologic findings in salivary gland biopsies, and less frequently are found to have hepatitis, glomerulonephritis or hypocomplementemia[43].

Treatment

The treatment of mixed cryoglobulinemia should first be directed toward any underlying disease. All patients with HCV-associated mixed cryoglobulinemia should be treated with interferon-α plus ribavirin (see Table 24.10), which can lead to resolution of the cutaneous (100% of patients), renal (50%), and neurologic (25–75%) manifestations[44]. Interferon-α alone may improve the cutaneous vasculitis (50–100% of patients), but is less effective in reversing the neurologic or renal involvement. In rare cases, interferon may trigger or worsen the peripheral neuropathy. The role of newer antiviral medications such as telaprevir remains to be determined.

Plasma exchange or cytotoxic agents, such as cyclophosphamide, are often used for severe neurologic or renal involvement[43]. Corticosteroids in conjunction with cytotoxic agents may be necessary to control organ-threatening disease. Interestingly, cytotoxic drugs do not seem to affect the progression of the HCV infection and/or liver damage. More recently, use of rituximab has been shown to benefit patients with refractory HCV-associated cryoglobulinemic vasculitis as well as those with recalcitrant HCV-negative mixed cryoglobulinemia, and it has not been reported to worsen the underlying HCV infection. Sequential therapy, i.e. rituximab followed by interferon-α and ribavirin, has also been proposed for the treatment of cryoglobulinemic vasculitis[43].

ANCA-Associated Vasculitides

Introduction

The ANCA-associated vasculitides are characterized by involvement of small to medium-sized vessels, the presence of antineutrophil cytoplasmic antibodies (ANCA), and an overlapping spectrum of organ involvement, but with each having distinguishing clinical and laboratory features. The three ANCA-associated vasculitides discussed here are microscopic polyangiitis (MPA), Wegener's granulomatosis and Churg–Strauss syndrome.

ANCA are predominantly IgG autoantibodies directed against components of both primary granules of neutrophils and monocyte lysosomes and likely have an important role in the pathogenesis of ANCA-associated vasculitides[45]. By immunofluorescent staining, there are two vasculitis-relevant patterns: (1) cytoplasmic (c)-ANCA – directed against the antigen proteinase 3 (PR3); and (2) perinuclear (p)-ANCA – directed against the antigen myeloperoxidase (MPO), with other antigens (e.g. lactoferrin, cathepsin G, elastase) serving as targets in the setting of nonspecific inflammation. ANCA are detected in 85–95% of patients with Wegener's granulomatosis and MPA, and they are useful diagnostically and for monitoring disease activity[46]. These autoantibodies are also found in patients receiving certain medications and who have underlying chronic infections, rheumatologic or inflammatory disorders, and malignancies (see Table 40.6)[47].

In order to improve specificity with regard to ANCA-associated vasculitides, the indirect immunofluorescence (IIF) test should be used as a screening evaluation (detects perinuclear versus cytoplasmic staining), followed by an ELISA that specifically detects anti-PR3 and anti-MPO antibodies. However, up to 5% of serum samples are positive by ELISA only, so when there is a high index of suspicion for an ANCA-associated vasculitis, an ELISA should be performed even if the IIF screening test is negative. Anti-PR3 ANCA occur in up to 90% of patients with Wegener's granulomatosis and 30% of patients with MPA, while anti-MPO ANCA are seen in up to 60% of patients with MPA and Churg–Strauss syndrome[47]. Semi-quantitative analysis may allow for disease monitoring and response to treatment. Of note, the presence of ANCA within the first year following remission has been associated with disease relapse.

Pathogenesis

ANCA are primarily directed against intracellular neutrophilic proteins (e.g. PR3, MPO) which can translocate to the neutrophil's cell surface following primary activation by cytokines such as TNF-α. Binding to surface antigens on neutrophils results in enhanced adhesion of neutrophils to vessel endothelium and release of inflammatory mediators, with subsequent vessel damage and recruitment of additional inflammatory cells (see Fig. 24.1B). As ANCA are pathogenic, the ANCA-associated vasculitides are classically characterized by a lack of immune complex deposition in and around vessel walls ("pauci-immune").

Natural history

The morbidity and mortality of ANCA-associated vasculitides are relatively high, stemming from both systemic manifestations and complications of immunosuppressive therapy[48]. Delay in diagnosis, renal impairment, propensity for relapse, the presence of ANCA, and an older age group are risk factors for a reduction in the survival rate.

Microscopic polyangiitis

Synonyms: ■ Microscopic polyarteritis ■ Microscopic polyarteritis nodosa

Key features

- Vasculitis of capillaries, venules and medium-sized arteries
- Palpable purpura, erythematous macules and patches, splinter hemorrhages and ulcers
- Constitutional symptoms, crescentic necrotizing glomerulonephritis and alveolar hemorrhage
- Presence of p-ANCA
- Absence of granuloma formation

Introduction

Microscopic polyangiitis (MPA) is a systemic vasculitis that involves small and medium-sized arteries, with cutaneous, pulmonary and renal involvement most commonly observed. Although MPA is often recognized as a distinct clinical entity, it can have varying presentations such that some, but not all, of the characteristic clinical and laboratory findings are present in an individual patient. For example, patients may be diagnosed as having polyarteritis nodosa (PAN) if there is no evidence of

small vessel vasculitis (e.g. glomerulonephritis) or ANCA. In an attempt to allow distinction from PAN and Wegener's granulomatosis, clinical criteria for MPA have been proposed and are undergoing validation[49].

Epidemiology

Determining a precise incidence of MPA is complicated due to the lack of consensus regarding diagnostic criteria, but the estimated incidence is 3 to 24 cases per million. Men are more commonly affected than women and the reported mean age of onset is 57 years, with a peak incidence between the ages of 65 and 75 years. More severe renal vasculitis favors older patients[50].

Pathogenesis

The etiology of MPA is unknown. Unlike PAN, MPA is not associated with HBV infection; however, it may be associated with infectious endocarditis[50]. Medications or malignancy may play a role in triggering the disease[52]. ANCA are thought to play a role in the pathogenesis of MPA (see General Pathogenesis).

Clinical features

Most patients with MPA initially experience constitutional symptoms, such as fever, weight loss, arthralgias and myalgias, for months to years before other symptoms occur. Depending upon the series, from 20% to 70% of patients will have cutaneous involvement, most commonly palpable purpura (Fig. 24.13). In one study, additional skin findings, in decreasing order of frequency, were erythematous patches (50% of patients), livedo racemosa (17%), and splinter hemorrhages, urticarial plaques and ulcers (each 6%)[51]. These skin lesions developed after the renal and/or pulmonary involvement in three-quarters of patients. In another series, acral erythematous macules were described as the most common cutaneous manifestation[52]. Skin manifestations are associated with an increased incidence of arthralgias, ocular disease and mononeuritis multiplex[53].

Renal involvement occurs in nearly all patients with MPA (>90%), and a pauci-immune, crescentic, necrotizing glomerulonephritis is the primary pathology in MPA (almost identical to that observed in Wegener's granulomatosis). Pulmonary capillaritis (with dyspnea and pulmonary infiltrates) occurs in 30–50% of patients, which can result in diffuse alveolar hemorrhage (10%). Neurologic involvement is also common, usually presenting as a peripheral neuropathy or mononeuritis multiplex in up to a third of patients. However, upper respiratory tract involvement that resembles Wegener's granulomatosis develops at a much lower frequency than in the other ANCA-associated vasculitides. The progressive clinical course of MPA typically leads to renal failure and/or pulmonary hemorrhage.

Anti-MPO antibodies occur in 60% of patients, while anti-PR3 antibodies can be seen in 30% of patients with MPA in European and American series. Of note, in Chinese and Japanese patients, anti-PR3 antibodies are rarely observed[47,50]. Rare patients without renal involvement are typically ANCA-negative[48]. Additional diagnostic testing for systemic involvement is outlined in Tables 24.7 and 24.8.

Pathology

The characteristic histologic findings in microscopic polyangiitis include a segmental necrotizing vasculitis of the smallest blood vessels (capillaries, venules and arterioles) and, less often, a vasculitis of small and/or medium-sized arteries. There is no evidence of granulomatous inflammation.

Differential diagnosis

MPA frequently presents with palpable purpura and constitutional symptoms. If no additional internal organ involvement is evident at initial presentation, it may be difficult to distinguish MPA from CSSV. The differential diagnosis includes PAN, other ANCA-associated vas-

Fig. 24.13 Microscopic polyangiitis. A Petechiae and multiple purpuric papules with central necrosis on the plantar surface. **B** Confluent hemorrhagic plaque on the medial and plantar aspect of the foot. *Courtesy, Cora Whitney Hannon, MD, and Robert Swerlick, MD.*

BASIC LABORATORY EVALUATION FOR PATIENTS WITH CONFIRMED CUTANEOUS VASCULITIS	
Organ system/ Suspected association	**Laboratory tests**
Hematologic	**Complete blood count with differential, platelets***; **ESR**; C-reactive protein; serum and urine protein electrophoresis, serum immunofixation electrophoresis; cryoglobulins
Gastrointestinal	**Liver function tests*; stool guaiac***
Renal	**Blood urea nitrogen***, **creatinine***; **urinalysis***; electrolytes
Infectious	Anti-hepatitis C antibody, hepatitis B surface antigen; antistreptolysin O/anti-DNase B titer; HIV antibody; urine, blood or throat culture
Immunologic	Rheumatoid factor; C3, C4, CH50; ANA; anti-dsDNA and -ENA antibodies, ANCA†
Neoplasms	CT chest/abdomen/pelvis, bone marrow biopsy, age-appropriate screening for solid tumors

*Repeated with flares of disease activity.
†Indirect immunofluorescence (IIF) should be done for screening, followed by ELISA as a confirmatory test because 5% of negative IIF test results are false-negative.

Table 24.7 Basic laboratory evaluation for patients with confirmed cutaneous vasculitis. Initial recommended tests (performed even when drug-induced vasculitis is suspected in a healthy-appearing patient) are in bold. Additional tests are done based upon suspicion of an underlying disorder or signs and symptoms of internal organ involvement. ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibodies; CT, computerized tomography; ds, double-stranded; ENA, extractable nuclear antigen (includes Sm, SSA/Ro, SSB/La).

POSSIBLE ADDITIONAL DIAGNOSTIC TESTING FOR PATIENTS WITH SUSPECTED ANCA-ASSOCIATED VASCULITIDES								
	Chest X-ray and/or chest CT scan	Electromyogram/ nerve conduction studies	Lung, nerve or kidney biopsy	Upper respiratory tract or muscle biopsy	ECG, echocardiogram	CT scan of sinuses	Serum IgE level	Consider GI and ophthalmologic examination
Microscopic polyangiitis	√	√	√					
Wegener's granulomatosis	√	√	√*	√*	√	√		√
Churg–Strauss syndrome	√	√	√		√	√	√	√
*Depends upon signs and symptoms.								

Table 24.8 Possible additional diagnostic testing for patients with suspected ANCA-associated vasculitides. This is in addition to the evaluation outlined in Table 24.7. CT, computerized tomography; ECG, electrocardiogram; GI, gastrointestinal.

KEY DISORDERS IN THE DIFFERENTIAL DIAGNOSIS OF ANCA-ASSOCIATED VASCULITIDES AND THEIR DISTINGUISHING FEATURES		
ANCA-positive vasculitic syndrome	**Disorder in differential diagnosis**	**Distinguishing features of the disorder in the differential diagnosis**
Microscopic polyangiitis	Churg–Strauss syndrome	• Eosinophilia • Asthma and sinus disease • Increased incidence of cardiac involvement
	Wegener's granulomatosis	• Granulomatous inflammation • Increased incidence of ocular and severe upper respiratory tract involvement
	Polyarteritis nodosa	• Absence of glomerulonephritis • Lower incidence of pulmonary involvement • Vasculitis of renal arteries rather than small vessel vasculitis • Renovascular hypertension • ANCA-negative
	Goodpasture syndrome	• Kidney-bound or circulating anti-glomerular basement membrane antibodies
	SLE or rheumatoid vasculitis	• Distinct rheumatologic serologies • In SLE, develops in individuals with longstanding disease
Wegener's granulomatosis	Churg–Strauss syndrome	• Eosinophilia • Asthma • Lower incidence of severe renal disease
	Microscopic polyangiitis	• Absence of granulomatous inflammation
	NK/T-cell lymphoma	• Destructive nasal midline lesion (see Table 45.3) • Characteristic histology
	Tuberculosis (lupus vulgaris), leprosy	• Destructive nasal midline lesion • Characteristic histologic features and laboratory findings
	Cocaine-induced destructive nasal midline lesion	• By ELISA, ANCA is positive for both human neutrophil elastase and proteinase 3
	Goodpasture syndrome, SLE, rheumatoid arthritis	• See above
Churg–Strauss syndrome	Microscopic polyangiitis	• No granulomatous inflammation • No history of asthma • No hypereosinophilia
	Wegener's granulomatosis	• Increased incidence of glomerulonephritis • Lower incidence of cardiac or peripheral nerve involvement
	Hypereosinophilia, secondary	• Due to medications, parasitic infections, allergic disease, malignancy
	Hypereosinophilic syndrome	• Pruritus, eczematous or urticarial eruptions, oral ulcerations and angioedema

Table 24.9 Key disorders in the differential diagnosis of ANCA-associated vasculitides and their distinguishing features. ANCA, antineutrophil cytoplasmic antibodies; ELISA, enzyme-linked immunosorbent assay.

culitides (see below), Goodpasture syndrome, SLE and rheumatoid vasculitis (Table 24.9).

Treatment

Treatment of MPA is divided into two phases: induction of remission and maintenance therapy. To induce remission, corticosteroids (e.g. 1 mg/kg/day of prednisone) are initially used, with addition of cyclophosphamide for patients with significant organ involvement (e.g. renal, pulmonary or neurologic) (see Table 24.10)[54]. Cyclophosphamide may be given for 6 months, either orally (2 mg/kg/day) or as intravenous pulses (0.5–1.0 g/m^2/month); pulse therapy reduces the total drug dose and incidence of side effects such as bladder carcinoma. Recent data suggest that corticosteroids plus rituximab may be equally effective as corticosteroids plus cyclophosphamide[55,56]. Methotrexate, azathioprine, mycophenolate mofetil and IVIg may be useful as corticosteroid-sparing agents, particularly in maintenance of remission[57]. Plasma exchange has proved beneficial in ANCA-positive patients. Targeted systemic immunomodulators ("biologics") such as infliximab show promise, but further evidence is required[50]. Patients with MPA have a higher rate of relapse compared to patients with classic PAN (regardless of disease severity)[54], but a lower rate than those with Wegener's granulomatosis. Persistence of ANCA despite induction of a remission is associated with an increased risk of relapse.

THERAPEUTIC LADDER FOR PATIENTS WITH VASCULITIS

Disorder	First-line treatment	Evidence levels	Second-line treatment	Evidence levels	Third-line treatment	Evidence levels
Cutaneous small vessel vasculitis	Discontinue incriminated drugs Supportive care Treat underlying infections, neoplasms NSAIDs Antihistamines	 3 3	Colchicine (0.6 mg bid–tid) Dapsone (50–200 mg/day) CS Hydroxychloroquine	2[1e] 3[2e] 2[3e] 3[4e]	AZA (2 mg/kg/day) MTX IVIg CSA CYC PEX	3[5e] 3[6e] 3[4e] 3[4e] 3[4e] 3[4e]
Henoch–Schönlein purpura	Supportive care		Dapsone Colchicine CS AZA ± CS CYC ± CS CSA ± CS Antihistamines	2[7e] 3 1[8e], 2[9e] 2[10e–12e] 2[10e,13e,14e] 3[13e,15e,16e]	IVIg Rituximab MYC CS + tacrolimus ACA PEX Factor XIII	3[17e] 3[18e] 3[13e,19e,20e] 3[13e] 2[21e] 2[22e], 3[23e] 2[24e]
Acute hemorrhagic edema of infancy	Supportive care			3[25e]	CS	3[25e]
Urticarial vasculitis	Antihistamines Indomethacin Dapsone (100–200 mg/day) ± pentoxifylline CS	3[26e] 3[26e] 3[27e,28e] 3[26e]	Colchicine (0.6 mg bid–tid) Hydroxychloroquine (200–400 mg/day) AZA MTX	3[29e] 3[30e] 3[26e,28e] 3[37e]	MYC IVIg Rituximab CSA PEX	3[31e] 3[32e,33e] 3[34e,35e] 3[28e] 3[28e,36e]
Erythema elevatum diutinum	NSAIDs Intralesional CS Dapsone	3 3 3	Colchicine Chloroquine Tetracyclines	3 3 3	Niacinamide PEX	3 3
Cryoglobulinemic vasculitis (+ HCV)	IFN + ribavirin CS	1[38e,39e] 3[38e,39e]	CS + CYC	3[38e,39e]	IVIg Rituximab (± ribavirin, IFN) PEX	3[40e] 2[41e,42e] 3[38e,39e]
Cutaneous polyarteritis nodosa	Treat underlying infections Discontinue incriminated drugs NSAIDs CS (topical, intralesional or oral)	 3 2	MTX (7.5–15 mg/wk) Dapsone/sulfapyridine IVIg	3 3 3	Pentoxifylline Colchicine AZA or MYC TNF-α inhibitors	3 3 3 3
Classic polyarteritis nodosa (+ HBV)	CS CS + PEX + IFN/lamivudine	2[43e] 2[44e,45e]	CS + CYC	2[43e]	IVIg	3
Microscopic polyangiitis	CS CS + Rituximab ± CYC	3[43e] 1[46e,47e]	CS + CYC MTX	3[43e,48e] 3[48e]	AZA MYC IVIg Rituximab Infliximab	2[49e,50e] 3[49e] 3[49e,51e] 3[52e] 3[53e]
Wegener's granulomatosis (to induce remission in *limited* disease)	CS + MTX	1[48e,54e–57e]	TMP-SMX (± CS)	2[58e]		
Wegener's granulomatosis (to induce remission in *generalized* disease)	CS + CYC (pulse) CS + Rituximab ± CYC	1[48e,55e–57e,59e] 1[46e,47e], 2[60e,61e]	CS + CYC + PEX (if severe renal disease, may be first line)	1[75e]	MYC IVIg PEX Infliximab T cell depletion Alemtuzumab	3[62e,67e] 3[63e] 3 2[53e,77e] 3 3
Wegener's granulomatosis (to maintain remission)	CS + AZA CS + MTX	1[50e,64e] 1[50e,65e,66e]	CS + CYC TMP-SMX	2[59e] 1[58e]	MYC AZA or MTX Leflunomide	2[62e,67e,76e] 3[50e,64e] 3[66e]
Churg–Strauss syndrome	CS	2[43e]	CS + CYC (first line in severe disease)	3[43e]	IVIg ± PEX Rituximab AZA MYC MTX IFN-α	2[68e] 2[43e,69e,71e] 2[72e] 3[70e] 3[72e] 3[73e,74e]

Table 24.10 Therapeutic ladder for patients with vasculitis. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports. ACA, aminocaproic acid; AZA, azathioprine; CS, corticosteroids; CYC, cyclophosphamide; CSA, cyclosporine; HBV, hepatitis B virus; HCV, hepatitis C virus; IFN, interferon; IVIg, intravenous immunoglobulin; MTX, methotrexate; MYC, mycophenolate mofetil; NSAIDs, nonsteroidal anti-inflammatory drugs; PEX, plasmapheresis; TMP-SMX, trimethoprim–sulfamethoxazole. Key references for treatment are summarized in refs 43, 45, 48, 64, 70 & 73. References cited in this table (e) are available in the online content.

Wegener's granulomatosis

Synonyms: ■ Granulomatosis with polyangiitis (Wegener's)

Key features

- Necrotizing granulomatous inflammation of the upper and lower respiratory tracts
- Pauci-immune glomerulonephritis
- Systemic vasculitis that can involve the skin and oral mucosa

Introduction

Wegener's granulomatosis is classically described as the triad of granulomatous inflammation of the upper and lower respiratory tracts, systemic necrotizing small vessel vasculitis, and pauci-immune glomerulonephritis. Patients with Wegener's granulomatosis exist along a spectrum of severity, from localized to systemic involvement. Patients with systemic disease typically have multi-organ involvement with (generalized disease) or without (limited or early systemic disease) functional impairment, and they have a high mortality rate if left untreated. On the other hand, patients with localized forms of Wegener's granulomatosis have primarily airway disease without constitutional symptoms or systemic vasculitis. The initial evaluation of patients with Wegener's granulomatosis should establish the extent of organ involvement, as recent evidence supports distinct treatment approaches for localized versus generalized forms of the disease[45,48].

Epidemiology

The incidence of Wegener's granulomatosis is estimated to be 5 to 12 cases per million, with a slight female predominance. The disease occurs most often in Caucasians, with a peak age of onset of 45–65 years. Wegener's granulomatosis is one of the more common systemic vasculitides of children, with an incidence of 0.03 to 3.2 per 100 000 children per year[58].

Pathogenesis

The pathophysiology of Wegener's granulomatosis is reflected in two clinicopathologic hallmarks of the disease – granuloma formation and small to medium-sized vessel vasculitis. ANCA, environmental factors and genetic polymorphisms (see Table 24.4) all contribute to immune dysregulation. Although the specific pathogenic roles of PR3 or anti-PR3 antibodies remain unclear, surface expression of PR3 on apoptotic and/or activated neutrophils may stimulate dendritic cell maturation and proinflammatory cytokine release by antigen-presenting cells, thereby favoring development of Th1-mediated granuloma formation (termed "neutrophil priming"). Expression of PR3 on the cell surface of neutrophils may impede phagocytosis by macrophages, thus prolonging the opportunity for autoantibody development. In turn, ANCA binding to PR3 on neutrophils results in vessel damage (e.g. pauci-immune or nonimmune complex-mediated vasculitis; see Fig. 24.1B)[46,59]. Neutrophil priming may occur as a result of certain infections, such as *Staphylococcus aureus*. Of note, nasal carriage of *S. aureus* is associated with relapse of Wegener's granulomatosis and treatment of nasal carriage with antibiotics improves outcome.

Clinical features

Several groups have defined clinical criteria for Wegener's granulomatosis, having reached some consensus[58]. Existing criteria consist of: nasal and sinus or oral inflammation; typical radiologic features on chest radiograph or chest CT scan; abnormal urinalysis; biopsy-proven granulomatous inflammation; airway stenosis; and serologic findings (e.g. anti-PR3 ANCA). Mucocutaneous involvement occurs in ~40% of patients, and it can be the presenting sign in 10%[7]. The most common lesions are palpable purpura, followed by oral ulcers (Fig. 24.14). The gingival tissue is often red, friable and hyperplastic ("strawberry gums"). Painful subcutaneous nodules and ulcers that resemble

Fig. 24.14 Wegener's granulomatosis. A Sharply demarcated ulcer on the distal lower extremity, sometimes misdiagnosed as pyoderma gangrenosum. **B** Ulceration of the tongue. **C** Subungual digital infarcts resembling splinter hemorrhages. **D** Palpable purpura of the distal lower extremity due to small vessel vasculitis (leukocytoclastic vasculitis). *A, Courtesy, Irwin Braverman, MD.*

pyoderma gangrenosum can also be seen. Papulonecrotic lesions are common and usually occur on the extremities (particularly the elbows), but can also affect the face and scalp.

The upper or lower respiratory tracts are involved in up to 90% of patients with Wegener's granulomatosis. Nasal, sinus, tracheal and ear involvement represent the presenting complaints in >70% of patients. Suggestive symptoms and signs include recurrent epistaxis, mucosal ulcerations, nasal septal perforation and saddle nose deformity. Patients with pulmonary involvement typically present with dyspnea, cough, hemoptysis or pleuritis, and chest X-rays demonstrate irregular infiltrates or nodules. Renal disease is present in only 20% of patients at presentation, but approximately 75% of patients eventually develop glomerulonephritis[60]. Other organ systems commonly affected by necrotizing vasculitis in Wegener's granulomatosis include musculoskeletal (70%), ocular (30–60%), neurologic (20–50%), gastrointestinal (5–10%) and cardiac (5–40%).

Laboratory findings are consistent with an inflammatory process, including elevated acute phase reactants (ESR, C-reactive protein), anemia and leukocytosis. Up to 50% of patients have a positive rheumatoid factor. C-ANCA with anti-PR3 specificity occurs in approximately 80–90% of patients with generalized Wegener's granulomatosis, but only 60% of patients with localized disease. Anti-MPO antibodies occur in approximately 10% of patients. Patients with renal involvement have active urine sediments with proteinuria, hematuria and red blood cell casts as well as progressive renal failure. Additional diagnostic testing for systemic involvement is outlined in Table 24.8.

Pathology

Although the majority of skin biopsy specimens show nonspecific histopathologic changes (e.g. perivascular lymphocytic infiltrates), up to 50% demonstrate leukocytoclastic vasculitis and/or granulomatous inflammation. Biopsies of papulonecrotic lesions show a palisading neutrophilic dermatitis with areas of granulomatous inflammation that surround foci of basophilic necrobiosis (see Ch. 45).

Differential diagnosis

The primary differential diagnosis for Wegener's granulomatosis includes the other ANCA-associated vasculitides, in particular Churg–Strauss syndrome, as both diseases are characterized by necrotizing, granulomatous vasculitis. Additional disorders and their distinguishing features are outlined in Table 24.9.

Treatment

The standard treatment for patients with generalized Wegener's granulomatosis is systemic corticosteroids (e.g. 1 mg/kg/day of prednisone) in conjunction with oral daily cyclophosphamide (see Table 24.10), resulting in a remission in up to 75% of patients and an 87% survival rate (in one study that followed patients for 6 months to 2 years after treatment)[45,60]. Pulsed intravenous cyclophosphamide also induces remissions and is associated with less toxicity, but a prolonged regimen of less frequent, reduced-dose pulses may be required to prevent relapses (occur in up to half of patients within 5 years)[46]. Cyclophosphamide-related side effects are observed in ~40% of patients, including cystitis, infertility, infection and malignancy; they occur in up to half of patients within five years.

Recent data suggest that corticosteroids plus rituximab may be equally effective as corticosteroids plus cyclophosphamide[55,56]. Remission was induced while the B lymphocytes (and the associated ANCA) were depleted, but the effect of rituximab on the granulomatous manifestations of Wegener's granulomatosis is less clear. Targeted systemic immunomodulators ("biologics") are also being studied for the treatment of Wegener's granulomatosis[45,61]. A large randomized controlled trial found that etanercept was not effective for the maintenance of remission and was associated with treatment-related complications including malignancy[45]. In contrast, limited studies of infliximab plus conventional therapy suggested an accelerated remission and a steroid-sparing effect[62]. However, the addition of infliximab may result in more infectious complications. Azathioprine can maintain a remission following induction with cyclophosphamide[63], but it is associated with a higher relapse rate in patients who are PR3-positive at the time of the switch to azathioprine.

Patients with localized forms of Wegener's granulomatosis may be treated with trimethoprim–sulfamethoxazole (TMP-SMZ), alone or in combination with corticosteroids[45]. Of note, TMP-SMZ is a component of the treatment regimen for all patients with Wegener's granulomatosis, as relapses can be associated with *S. aureus* infections and nasal carriage (see above). Methotrexate is typically used in combination with corticosteroids to treat limited systemic disease[45].

Additional alternative treatment regimens are summarized in Table 24.10.

Churg–Strauss syndrome

Synonyms: ■ Granulomatous vasculitis of Churg–Straus ■ Churg–Strauss vasculitis ■ Allergic angiitis and granulomatosis

Key features

- Asthma and allergic rhinitis typically precede vasculitic phase
- Peak peripheral blood eosinophil count >10^9/l
- Cutaneous vasculitis in approximately half of patients
- Histologic features consist of eosinophils, extravascular granulomas and vasculitis

Introduction

Churg–Strauss syndrome is characterized by an ANCA-associated vasculitis with vascular and extravascular granulomas, eosinophil-rich pulmonary infiltrates, and necrotizing vasculitis that involves small to medium-sized vessels within multiple organ systems. It is distinguished by an association with asthma and eosinophilia.

Epidemiology

Churg–Strauss syndrome is the rarest of the necrotizing vasculitides, with an incidence ranging from 0.5 to 2.7 cases per million[64]. The mean age at diagnosis is 48 years and it has no gender predominance. The incidence of Churg–Strauss syndrome in patients with asthma ranges from 35 to 65 per million.

Pathogenesis

The onset of symptoms has been associated with various triggering factors, including vaccination, desensitization therapy, leukotriene inhibitors and rapid discontinuation of corticosteroids. T lymphocytes, eosinophils and ANCA all play a role in the pathogenesis of this syndrome. Tissue infiltration and then degranulation of eosinophils can lead to tissue injury while T cells, especially Th2 cells, are postulated to contribute to granuloma formation. ANCA-dependent activation of neutrophils results in vasculitis (see above). The pathogenesis of vasculitis in patients who are ANCA-negative may be distinct and is an area of active research.

Clinical features

The clinical presentation can be divided into three successive phases: (1) first phase – symptoms of allergic rhinitis, nasal polyps and asthma, which may persist for years; (2) second phase – peripheral eosinophilia, respiratory tract infections and gastrointestinal symptoms; and (3) third phase – systemic necrotizing vasculitis with granulomatous inflammation, which can occur several years to decades after the initial symptoms. Asthma, frequently severe, affects almost all patients and often precedes the onset of additional systemic manifestations by a decade or more[65]. Cutaneous findings occur in 40–75% of patients, typically during the third phase of the disease. Palpable purpura is seen most commonly, typically on the lower extremities and often with necrosis. Subcutaneous nodules may be seen on the scalp or extremities[66], and, less often, urticaria, livedo racemosa, retiform purpura and papulonecrotic lesions are present (Fig. 24.15).

In addition to the respiratory tract, patients with Churg–Strauss syndrome often have neurologic and cardiac involvement, presenting as mononeuritis multiplex and cardiomyopathy or pericarditis. The cardiac manifestations are due to granulomatous inflammation, occur in up to half of patients, and are the leading cause of death[67]. Necrotizing glomerulonephritis and pulmonary capillaritis resulting in diffuse

Fig. 24.15 Churg–Strauss syndrome. **A** Palpable purpura of the buttocks due to small vessel vasculitis (leukocytoclastic vasculitis). **B** Purpuric dermal plaques of the palm that histologically demonstrated vasculitis of a small muscular artery. **C** Crusted, firm papules of the elbow. *C, Courtesy, Kalman Watsky, MD.*

alveolar hemorrhage occur less commonly than in the other ANCA-associated vasculitides, affecting ~35% of patients. Musculoskeletal, gastrointestinal and ocular involvement can also occur.

Laboratory findings are similar to those in patients with Wegener's granulomatosis, with the additional findings of peripheral eosinophilia (>10^9/l) and elevated serum IgE levels. The majority of ANCA in Churg–Strauss syndrome are directed against MPO (55–60% of patients); fewer patients have anti-PR3 ANCA[47]. The presence or absence of ANCA may be clinically relevant, with creation of two subsets of patients[67]. ANCA positivity has been associated with a higher risk of cardiac involvement, pleural effusions, fever and livedo reticularis, while their absence was associated with cutaneous purpura as well as renal, sinus and neurologic complications. Histologic evidence of vasculitis was observed in 80% of ANCA-positive patients versus 40% of ANCA-negative patients, with no difference in granulomatous inflammation[67].

Pathology

The histopathologic hallmarks are infiltrates of eosinophils, formation of extravascular granulomas, and necrotizing vasculitis of small to medium-sized vessels; both arteries and veins are affected. Biopsy specimens obtained from papulonecrotic lesions demonstrate a palisading dermatitis with eosinophil infiltration, granuloma formation and eosinophilic necrobiosis.

Differential diagnosis

Other ANCA-associated vasculitides can mimic Churg–Strauss syndrome (see Table 24.9). Secondary hypereosinophilia and hypereosinophilic syndrome (HES; see Ch. 25) must also be differentiated from Churg–Strauss syndrome[65]. Superficial thrombophlebitis and rarely purpura, splinter hemorrhages and/or digital necrosis develop in patients with HES, mimicking Churg–Strauss syndrome.

Treatment

Over 80% of patients respond to treatment with corticosteroids alone, although relapses may occur in up to a quarter of patients achieving remission[68]. Of note, asthma persists in the majority of patients. Individuals with severe internal organ involvement (CNS or myocardial disease, glomerulonephritis, gastrointestinal ischemia) or who are refractory to corticosteroids are treated with concurrent cytotoxic agents, similar to patients with Wegener's granulomatosis or MPA. Pulsed intravenous cyclophosphamide is considered to be first-line therapy for inducing a remission, with azathioprine, IVIg or interferon-α as alternatives (see Table 24.10)[65].

Because interleukin-5 (IL-5) is a critical eosinophil differentiation factor, chemokine and growth factor, there has been recent interest in IL-5 blockade as a therapeutic strategy. Rituximab can reduce both levels of IL-5 and eosinophil counts, and it has demonstrated efficacy in refractory cases[64]. The anti-IL-5 antibody mepolizumab, which has been used to treat hypereosinophilic syndrome, is being investigated[67,69], and it shows early promise in reducing eosinophil counts and enabling corticosteroids to be tapered, but relapses frequently follow its discontinuation[69a,69b,69c]. Omalizumab, an anti-IgE antibody, is also being investigated. Of note, there is one report of a patient who developed Churg–Strauss syndrome following the administration of omalizumab[64].

PREDOMINANTLY MEDIUM-SIZED VESSEL VASCULITIS

Polyarteritis Nodosa

Synonyms: ■ Periarteritis nodosa ■ Panarteritis nodosa

Key features

- Segmental vasculitis of predominantly medium-sized arteries
- Systemic and cutaneous variants both can present with palpable purpura, livedo racemosa, retiform purpura, ulcers, subcutaneous nodules or peripheral gangrene
- Extracutaneous manifestations of the systemic variant include fever, arthralgias, myalgias, paresthesias, abdominal pain, orchitis and renovascular hypertension
- The cutaneous variant has a chronic, more benign course; it may be accompanied by mild systemic symptoms (fever, myalgias, arthralgias and peripheral neuropathy)

Introduction

Polyarteritis nodosa (PAN) is a multisystem vasculitis characterized by segmental necrotizing vasculitis that involves predominantly medium-sized blood vessels. Cutaneous PAN is a "skin-limited" variant which typically follows a benign yet chronic course.

Epidemiology

The incidence of classic PAN ranges from 4 to 16 cases per million, with a male:female ratio of 4:1. PAN can occur at any age, but typically affects middle-aged adults (40–60 years). Cutaneous PAN represents approximately 10% of all cases of PAN, and it is the most common form of PAN in children.

Pathogenesis

PAN has been associated with infections, inflammatory diseases, malignancies (especially hairy cell leukemia), and medications. Concurrent HBV infection is present in approximately 7% of patients with classic PAN, and this may represent a distinct clinical subtype with a higher risk of gastrointestinal, neurologic and renal involvement, as well as a lower 1-year survival rate (82% for HBV-associated PAN compared to 91% for non-HBV PAN)[70]. HCV infection is also associated with classic PAN. Cutaneous PAN has been associated with other infections, including streptococcal (especially in children), parvovirus B19, and HIV, as well as administration of minocycline. Inflammatory conditions associated with both classic and cutaneous PAN include inflammatory bowel disease, SLE and familial Mediterranean fever. Hairy cell leukemia has also been observed in association with classic PAN.

Clinical features

Approximately 25% of patients with classic (systemic) PAN have cutaneous involvement[71]. The most common findings are palpable purpura, livedo racemosa, retiform purpura and "punched-out" ulcers (Fig. 24.16). The palpable purpura may be pustular and/or ulcerative. Painful subcutaneous nodules and digital infarcts occur less commonly in classic PAN. In a study that compared the cutaneous manifestations of systemic PAN and MPA, palpable purpura was the most common skin finding in both diseases – 19% and 26% of patients, respectively; urticarial lesions were more frequent in PAN (6%) than in MPA (1–2%). Overall, however, the cutaneous findings alone did not allow distinction of the two entities[53]. As with Wegener's granulomatosis, cutaneous involvement in PAN and MPA is associated with arthralgias and ocular disease.

Extracutaneous disease is the rule in classic PAN, and patients present with constitutional symptoms, such as weight loss and fever, as well as multiple organ involvement. The lungs are often spared. Common symptoms include arthralgias, paresthesias (mononeuritis multiplex), myalgias (due to myopathy), abdominal pain, and shortness of breath (due to congestive heart failure). Involvement of the kidneys occurs at the level of the interlobar renal arteries, resulting in renovascular hypertension and renal failure, but not glomerulonephritis. In male patients, orchitis frequently occurs, especially in association with HBV infection. Cerebral infarcts are a rare complication of classic PAN and may result from thrombotic microangiopathy or vasculitic arterial occlusion. Gastrointestinal involvement, specifically mesenteric ischemia, heralds a poor prognosis, with a 1-year survival rate of <50%[70].

In classic PAN, laboratory evaluation demonstrates nonspecific inflammation with leukocytosis, an elevated ESR, and thrombocytosis. ANCA are rare in systemic PAN. Microscopic hematuria can be seen, but evidence of glomerulonephritis is absent. Microaneurysms of the renal, mesenteric and/or celiac arteries that are detected by traditional or magnetic resonance angiography are highly suggestive of classic PAN.

Cutaneous PAN, a "skin-limited" form of the disease, represents about 10% of PAN cases. Painful or tender subcutaneous nodules on the lower extremities, livedo racemosa, cutaneous necrosis and ulcers are commonly seen (Fig. 24.16B,C). Occasionally, the subcutaneous nodules develop elsewhere on the body. Lesions may resolve with persistent hyperpigmentation, sometimes in a retiform pattern. Patients may have mild systemic symptoms, consisting of fever, myalgias, arthralgias and peripheral neuropathy. Cutaneous PAN is the most common form in children, and it is often associated with streptococcal infections. A chronic, relapsing clinical course is typical, but progression to systemic PAN is rare. P-ANCA may be present in 10–20%

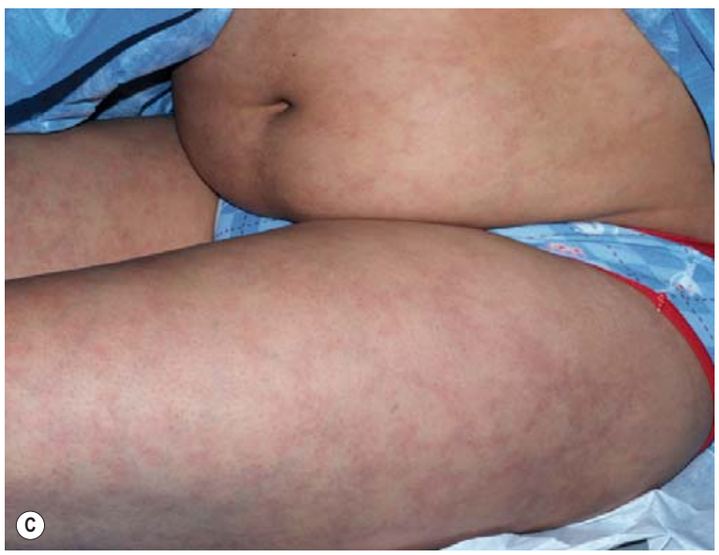


Fig. 24.16 Polyarteritis nodosa (PAN). A Retiform purpura of the dorsal foot in a patient with systemic PAN. **B, C** Livedo reticularis of the abdomen and lower extremities with multiple small "punched-out" ulcers in an adolescent with cutaneous PAN. This entity can overlap with the PAN-like syndrome with anti-phosphatidylserine-prothrombin complex antibodies that responds to anticoagulation. *B, C, Courtesy, Julie V Schaffer, MD.*

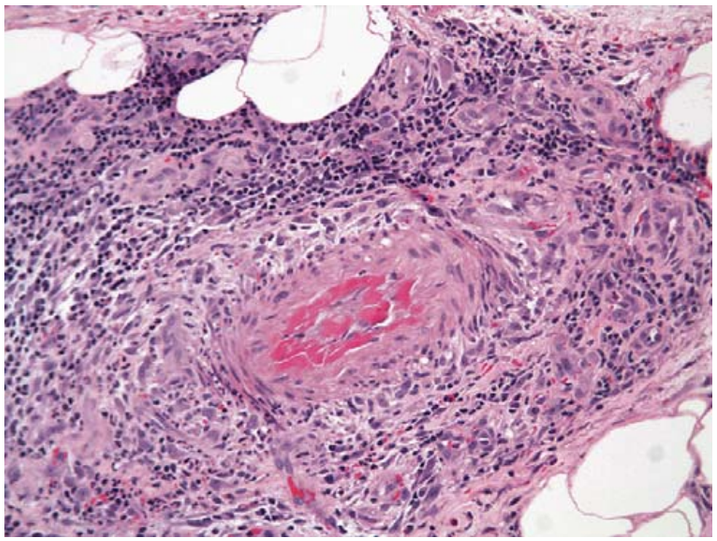


Fig. 24.17 Cutaneous polyarteritis nodosa – histologic features. Medium-sized vessel vasculitis with neutrophilic debris, fibrin and red blood cells within the arteriolar wall situated at the junction of the reticular dermis and fat. *Courtesy, Thomas Horn, MD.*

Fig. 24.18 Temporal arteritis. Two ulcerations of the scalp in association with alopecia and scarring in an elderly patient. *Courtesy, Steve Feldman, MD.*

patients with cutaneous PAN, in contrast to systemic PAN, in which ANCA are almost never present.

Pathology

The histology of PAN is characterized by a segmental necrotizing vasculitis of medium-sized arteries (Fig. 24.17). Vessels located within the upper dermis may only demonstrate nonspecific perivascular inflammation. Cutaneous PAN often involves the arteries of the deeper dermis and subcutaneous fat[71]. Focal areas of involvement result in vessel wall weakening and necrosis, leading to aneurysmal dilation and/or stenosis. DIF may show deposits of C3, IgM and fibrin within or around vessel walls.

Differential diagnosis

The diagnosis of classic PAN requires either a tissue biopsy of an involved organ (e.g. skin, muscle, nerve, kidney, testicle) with demonstration of characteristic findings or the detection of microaneurysms via angiography (usually renal, celiac and/or mesenteric).

The differential diagnosis of classic PAN is broad and includes cryoglobulinemic vasculitis, autoimmune connective tissue disease, MPA, Wegener's granulomatosis and Churg–Strauss syndrome (see Table 24.9). In general, the latter three disorders can be distinguished from PAN by the presence of glomerulonephritis and pulmonary involvement in association with circulating ANCA. There are several non-vasculitic diseases where aneurysmal dilations can be seen by angiography, including fibromuscular dysplasia, atherosclerosis, SLE, cholesterol emboli, neurofibromatosis, Ehlers–Danlos syndrome, and emboli from infective endocarditis and left atrial myxoma.

Cutaneous ulcers superimposed on a background of livedo reticularis could be due to cutaneous PAN, but the differential diagnosis includes cholesterol emboli, antiphospholipid syndrome and vasculopathies (see Ch. 105). Nodular tuberculid may mimic the cutaneous lesions of PAN, both clinically and histologically, so its exclusion prior to instituting immunosuppressive therapy is recommended.

Treatment

Patients with *classic* PAN should be treated with systemic corticosteroids (e.g. 1 mg/kg/day of prednisone) with the dose tapered over 6 months. Approximately one-half of patients will achieve remission or cure with corticosteroids alone[54]. For patients who are refractory to corticosteroids or who have significant internal organ involvement, cyclophosphamide should be added to their regimen for up to 12 months (see dosages in MPA section)[54]. Treatment of HBV-associated PAN is aimed at eradication of the virus; currently, interferon-2α and lamivudine are employed and may improve overall mortality[70]. Therapeutic alternatives are listed in Table 24.10[72].

Although it is often chronic with relapses, cutaneous PAN follows a benign clinical course. Topical or intralesional corticosteroids may resolve localized areas of cutaneous involvement, but progressive or extensive disease may warrant systemic corticosteroids. Based upon case reports and series, there are therapeutic alternatives and these are listed in Table 24.10. Symptomatic relief may be achieved with NSAIDs alone. Digital necrosis has been reported to improve with intravenous prostaglandins or calcium channel blockers (see Ch. 43).

TEMPORAL ARTERITIS

Occasionally, in this form of large vessel vasculitis, cutaneous ulcers, primarily of the frontolateral scalp and tongue, can develop (Fig. 24.18). However, earlier in the course of the disease, purpuric lesions and tender nodules may also be seen (see Table 24.1). Patients may have a history of tenderness along the course of the temporal artery, visual disturbances and the muscle weakness of polymyalgia rheumatica.

DIAGNOSTIC APPROACH TO PATIENTS WITH VASCULITIS

In Figures 24.19 and 24.20, a morphologic approach and a diagnostic algorithm are presented, respectively, for the patient with signs and symptoms suggestive of cutaneous vasculitis. Proper management includes diagnosis, determination of associated conditions, investigation for systemic involvement, and treatment.

History and Physical Examination

The clinician should assess the duration and acuity of symptoms and inquire about antecedent illnesses or exposures (e.g. medications). A history of autoimmune connective tissue disease or malignancy may be evident, but patients can present with cutaneous vasculitis as the initial symptom of these diseases. The presence of systemic involvement (suggested by fever, weight loss or focal symptoms) should be assessed via a thorough review of systems.

The cutaneous examination may be helpful in identifying the predominant vessel size affected (see Table 24.1 and Fig. 24.19). A complete head and neck, cardiopulmonary, abdominal, musculoskeletal and neurologic examination should be performed in any patient in whom systemic vasculitis is suspected.

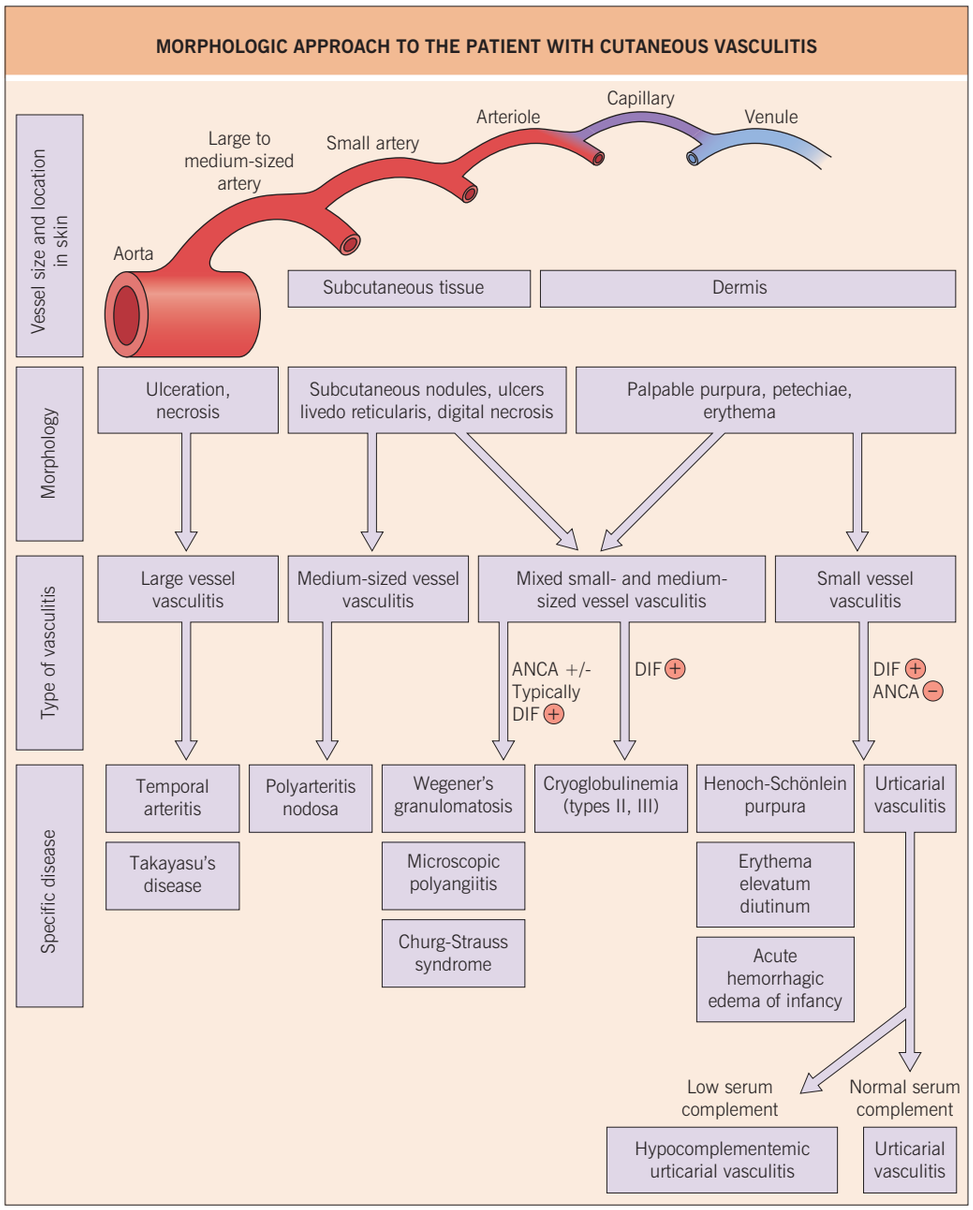


Fig. 24.19 Morphologic approach to the patient with suspected cutaneous vasculitis. ANCA, antineutrophil cytoplasmic antibodies; DIF, direct immunofluorescence.

Laboratory Evaluation

The laboratory diagnostic process begins with a skin biopsy in order both to exclude entities that can mimic cutaneous vasculitis (see Table 24.2) and to identify the size of vessel involved. If medium-sized vessel involvement is suspected, a deep incisional or excisional biopsy that includes subcutaneous tissue should be performed. Biopsies obtained from nodules tend to have a higher diagnostic yield for medium-sized vessel vasculitis than those taken from an ulcer edge or livedo racemosa. Ulcers should be biopsied at their edge and include the peripheral rim of inflammation (if present), as incidental vasculitis can often be found underlying ulcers and is not a diagnostic finding. DIF is best performed on the earliest lesion.

The initial evaluation of a patient with cutaneous vasculitis is outlined in Table 24.7. Additional tests can be performed based upon the suspected associated disease or the suspected vasculitic syndrome (Table 24.8). Laboratory tests to determine extent of disease should be repeated with each subsequent episode of vasculitis. Tests for associated disease are performed at baseline and only repeated if dictated by new information (e.g. screening for HCV infection).

Treatment

The first step in the treatment of patients with cutaneous vasculitis is to determine whether the disease is either primary or secondary to an underlying condition (e.g. infection, drug exposure) that can be treated (or, in the case of medications, discontinued). Treatment is then based on the extent and severity of systemic involvement. Specific and detailed therapeutic approaches are discussed in conjunction with each disease and are outlined in Table 24.10.

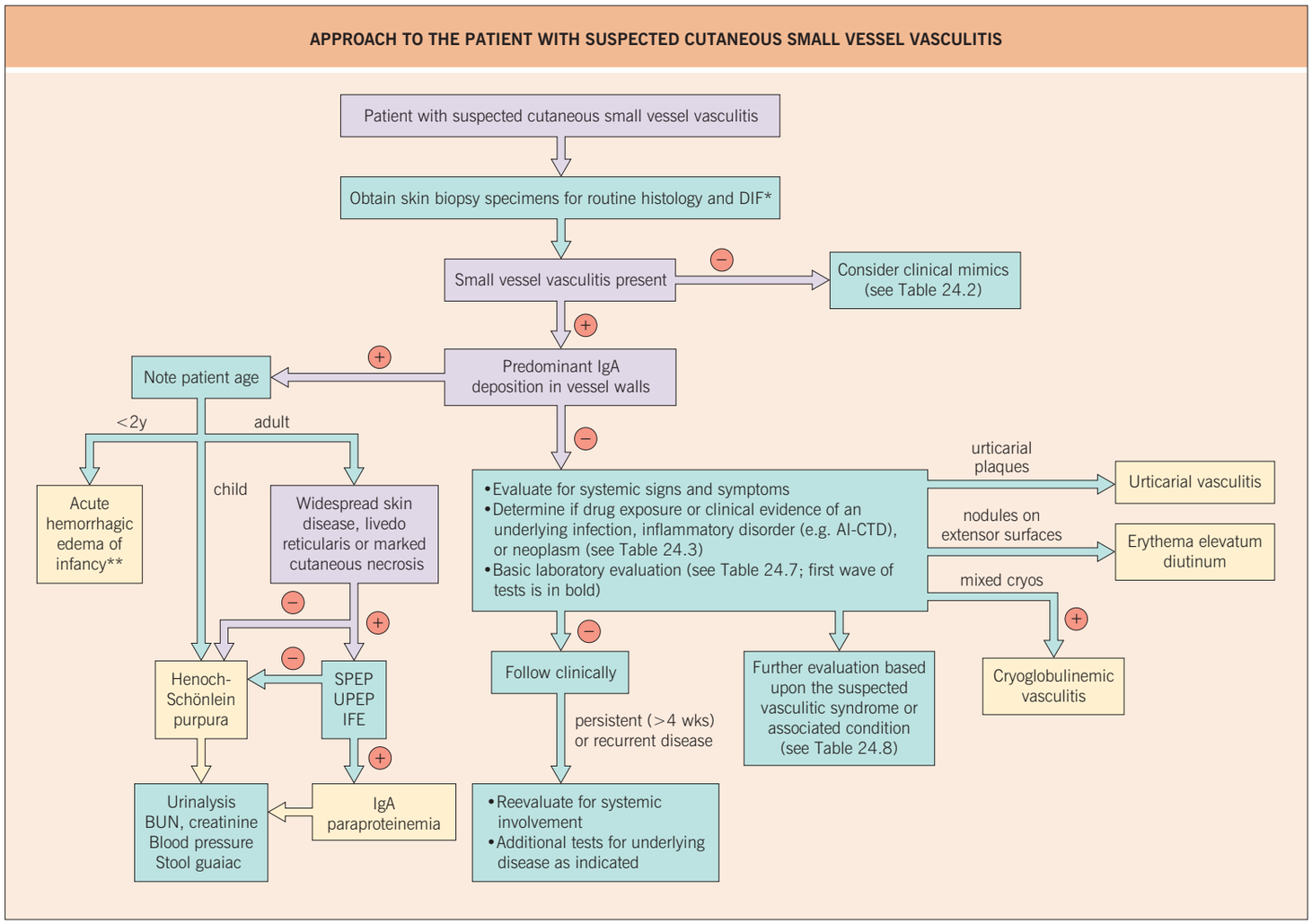


Fig. 24.20 Approach to the patient with suspected cutaneous small vessel vasculitis. *Best performed on an early lesion. **Vascular IgA deposits are found in less than one-third of cases. AI-CTD, autoimmune connective tissue disease; BUN, blood urea nitrogen; cryos, cryoglobulins; DIF, direct immunofluorescence; IFE, immunofixation electrophoresis; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis.

REFERENCES

1. Carlson JA, Ng BT, Chen KR. Cutaneous vasculitis update: diagnostic criteria, classification, epidemiology, etiology, pathogenesis, evaluation and prognosis. Am J Dermatopathol. 2005;27:504–28.
2. Chen KR, Carlson JA. Clinical approach to cutaneous vasculitis. Am J Clin Dermatol. 2008;9:71–92.
3. Lotti T, Ghersetich I, Comacchi C, Jorizzo JL. Cutaneous small-vessel vasculitis. J Am Acad Dermatol. 1998;39:667–87.
4. ten Holder SM, Joy MS, Falk RJ. Cutaneous and systemic manifestations of drug-induced vasculitis. Ann Pharmacother. 2002;36:130–47.
5. Carlson JA, Chen KR. Cutaneous vasculitis update: small vessel neutrophilic vasculitis syndromes. Am J Dermatopathol. 2006;28:486–506.
6. Sais G, Vidaller A, Jucgla A, et al. Prognostic factors in leukocytoclastic vasculitis: a clinicopathologic study of 160 patients. Arch Dermatol. 1998;134:309–15.
7. Fiorentino DF. Cutaneous vasculitis. J Am Acad Dermatol. 2003;48:311–40.

7a. Bahrami S, Malone JC, Webb KG, Callen JP. Tissue eosinophilia as an indicator of drug-induced cutaneous small-vessel vasculitis. Arch Dermatol. 2006;142:155–61.

7b. Merkel PA. Drug-induced vasculitis. Rheum Dis Clin North Am. 2001;27:849–62.

8. Saulsbury F. Clinical update: Henoch-Schönlein purpura. Lancet. 2007;369:976–8.
9. Eleftheriou D, Brogan PA. Vasculitis in children. Best Pract Res Clin Rheumatol. 2009;23: 309–23.
10. Watts RA, Lane S, Scott DG. What is known about the epidemiology of the vasculitides? Best Pract Res Clin Rheumatol. 2005;19:191–207.
11. Blanco R, Martinez-Taboada VM, Rodriguez-Valverde V, et al. Henoch-Schönlein purpura in adulthood and childhood: two different expressions of the same syndrome. Arthritis Rheum. 1997;40:859–64.
12. Tancrede-Bohin E, Ochonisky S, Vignon-Pennamen MD, et al. Schonlein-Henoch purpura in adult patients. Predictive factors for IgA glomerulonephritis in a retrospective study of 57 cases. Arch Dermatol. 1997;133:438–42.
13. Pillebout E, Thervet E, Hill G, et al. Henoch-Schönlein purpura in adults: outcome and prognostic factors. J Am Soc Nephrol. 2002;13:1271–8.
14. Zurada JM, Ward KM, Grossman ME. Henoch-Schönlein purpura associated with malignancy in adults. J Am Acad Dermatol. 2006;55:s65–70.
15. Mutsui H, Shibagaki N, Kawamura T, et al. A clinical study of Henoch-Schönlein purpura associated with malignancy. J Eur Acad Dermatol Venereol. 2009;23:394–401.
16. Uppal SS, Hussain MA, Al-Raqum HA, et al. Henoch-Schönlein's purpura in adults versus children/adolescents: a comparative study. Clin Exp Rheumatol. 2006;24(2 Suppl 41):S26–30.
17. Ozen S, Ruperto N, Dillon MJ, et al. EULAR/PReS endorsed consensus criteria for the classification of childhood vasculitides. Ann Rheum Dis. 2006;65:936–41.
18. Barnadas MA, Perez E, Gich I, et al. Diagnostic, prognostic and pathogenic value of the direct immunofluorescence test in cutaneous leukocytoclastic vasculitis. Int J Dermatol. 2004;43:19–26.
19. Iqbal H, Evans A. Dapsone therapy for Henoch-Schönlein purpura: a case series. Arch Dis Child. 2005;90:985–6.
20. Ronkainen J, Koskimies O, Ala-Houhala M, et al. Early prednisone therapy in Henoch-Schönlein purpura: a randomized, double-blind, placebo-controlled trial. J Pediatr. 2006;149:241–7.
21. Chartapisak W, Opastirakul S, Hodson EM, et al. Interventions for preventing and treating kidney disease in Henoch-Schönlein purpura (HSP). Cochrane Database Syst Rev. 2009;(3):CD005128.
22. Weiss PF, Feinstein JA, Luan X, et al. Effects of corticosteroid on Henoch-Schönlein purpura: a systematic review. Pediatrics. 2007;120:1079–87.
23. Fiore E, Rizzi M, Ragazzi M, et al. Acute hemorrhagic edema of young children (cockade purpura and edema): a case series and systematic review. J Am Acad Dermatol. 2008;59:684–95.
24. Poyrazoglu HM, Per H, Gunduz Z, et al. Acute hemorrhagic edema of infancy. Pediatr Int. 2003;45:697–700.
25. Di Lernia V, Lombardi M, Lo Scocco G. Infantile acute hemorrhagic edema and rotavirus infection. Pediatr Dermatol. 2004;21:548–50.
26. AlSufyani MA. Acute hemorrhagic edema of infancy: unusual scarring and review of the English language literature. Int J Dermatol. 2009;48:617–22.
27. Shah KN, Honig PJ, Yan AC. "Urticaria multiforme": a case series and review of acute annular urticarial hypersensitivity syndromes in children. Pediatrics. 2007;119:e1177–83.
28. Davis MD, Brewer JD. Urticarial vasculitis and hypocomplementemic urticarial vasculitis syndrome. Immunol Allergy Clin North Am. 2004;24:183–213, vi.

29. Davis MD, Daoud MS, Kirby B, et al. Clinicopathologic correlation of hypocomplementemic and normocomplementemic urticarial vasculitis. J Am Acad Dermatol. 1998;38:899–905.
30. Shah KN, Honig PJ, Yan AC. "Urticaria multiforme": a case series and review of acute annular urticarial hypersensitivity syndromes in children. Pediatrics. 2007;119:e1177–83.
31. Mukhtyar C, Misbah S, Wilkinson J, Wordsworth P. Refractory urticarial vasculitis responsive to anti-B-cell therapy. Br J Dermatol. 2009;160:470–2.
32. Yamazaki-Nakashimada MA, Duran-McKinster C, Ramírez-Vargas N, Hernandez-Bautista V. Intravenous immunoglobulin therapy for hypocomplementemic urticarial vasculitis associated with systemic lupus erythematosus in a child. Pediatr Dermatol. 2009;26:445–7.
33. Shah D, Rowbottom AW, Thomas CL, et al. Hypocomplementaemic urticarial vasculitis associated with non-Hodgkin lymphoma and treatment with intravenous immunoglobulin. Br J Dermatol. 2007;157:392–3.
34. Gibson LE, el-Azhary RA. Erythema elevatum diutinum. Clin Dermatol. 2000;18:295–9
35. High WA, Hoang MP, Stevens K, Cockerell CJ. Late-stage nodular erythema elevatum diutinum. J Am Acad Dermatol. 2003;49:764–7.
36. Di Giacomo TB, Marinho RT, Nico MM. Erythema elevatum diutinum presenting with a giant annular pattern. Int J Dermatol. 2009;48:290–2.
37. Barzegar M, Davatchi CC, Akhyani M, et al. An atypical presentation of erythema elevatum diutinum involving palms and soles. Int J Dermatol. 2009;48:73–5.
38. Aldave AJ, Shih JL, Jovkar S, McLeod SD. Peripheral keratitis associated with erythema elevatum diutinum. Am J Ophthalmol. 2003;135:389–90.
39. Mitamura Y, Fujiwara O, Miyanishi K, et al. Nodular scleritis and panuveitis with erythema elevatum diutinum. Am J Ophthalmol. 2004;137:368–70.
40. Carlson JA, LeBoit PE. Localized chronic fibrosing vasculitis of the skin: an inflammatory reaction that occurs in settings other than erythema elevatum diutinum and granuloma faciale. Am J Surg Pathol. 1997;21:698–705.
41. Kanitakis J, Cozzani E, Lyonnet S, Thivolet J. Ultrastructural study of chronic lesions of erythema elevatum diutinum: "extracellular cholesterosis" is a misnomer. J Am Acad Dermatol. 1993;29(2 Pt 2):363–7.
42. Grabbe J, Haas N, Moller A, Henz BM. Erythema elevatum diutinum - evidence for disease-dependent leucocyte alterations and response to dapsone. Br J Dermatol. 2000;143:415–20.
43. Ferri C, Mascia MT. Cryoglobulinemic vasculitis. Curr Opin Rheumatol. 2006;18:54–63.
44. Cacoub P, Costedoat-Chalumeau N, Lidove O, Alric L. Cryoglobulinemia vasculitis. Curr Opin Rheumatol. 2002;14:29–35.
45. Bosch X, Guilabert A, Espinosa G, Mirapeix E. Treatment of antineutrophil cytoplasmic antibody-associated vasculitis: a systematic review. JAMA. 2007;298:655–69.
46. Bosch X, Guilabert A, Font J. Antineutrophil cytoplasmic antibodies. Lancet. 2006;358:404–18.
47. Wiik AS. Clinical use of serological tests for antineutrophil cytoplasmic antibodies. What do the studies say? Rheum Dis Clin North Am. 2001;27:799–813, vi–vii.
48. Jayne D. Review article: progress of treatment in ANCA-associated vasculitis. Nephrology (Carlton). 2009;14:42–8.
49. Watts R, Lane S, Hanslik T, et al. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. Ann Rheum Dis. 2006;66:222–7.
50. Jayne D. Challenges in the management of microscopic polyangiitis: past, present, and future. Curr Opin Rheumatol. 2008;20:3–9.
51. Niiyama S, Amoh Y, Tomita M, Katsuoka K. Dermatological manifestations associated with microscopic polyangiitis. Rheumatol Int. 2008;28:593–5.
52. Kawakami T, Kawanabe T, Saito C, et al. Clinical and histopathologic features of 8 patients with microscopic polyangiitis including two with a slowly progressive clinical course. J Am Acad Dermatol. 2007;57:840–8.
53. Kluger N, Pagnoux C, Guillevin L, et al. Comparison of cutaneous manifestations in systemic polyarteritis nodosa and microscopic polyangiitis. Br J Dermatol. 2008;159:615–20.
54. Gayraud M, Guillevin L, le Toumelin P, et al. Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: analysis of four prospective trials including 278 patients. Arthritis Rheum. 2001;44:666–75.
55. Jones R, Cohen Tervaert J, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med. 2010;363:211–20.
56. Stone J, Merkel P, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010;363:221–32.
57. Pagnoux C, Mahr A, Hamidou MA, et al. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. N Engl J Med. 2008;359:2790–803.
58. Cabral D, Uribe AG, Benseler S, et al. Classification, presentation, and initial treatment of Wegener's granulomatosis in childhood. Arthritis Rheum. 2009;60:3413–24.
59. Jennette JC, Falk RJ. New insight into the pathogenesis of vasculitis associated with antineutrophil cytoplasmic autoantibodies. Curr Opin Rheumatol. 2008;20:55–60.
60. Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med. 1992;116:488–98.
61. Hellmich B, Lamprecht P, Gross WL. Advances in the therapy of Wegener's granulomatosis. Curr Opin Rheumatol. 2006;18:25–32.
62. Booth A, Harper L, Hammad T, et al. Prospective study of TNF alpha blockade with infliximab in antineutrophilic cytoplasmic antibody-associated systemic vasculitis. J Am Soc Nephrol. 2004;15:717–21.
63. Jayne D, Rasmussen N, Andrassy K, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med. 2003;349:36–44.
64. Grau RG. Churg-Strauss syndrome: 2005-2008 update. Curr Rheumatol Rep. 2008;10:453–8.
65. Kahn JE, Bletry O, Guillevin L. Hypereosinophilic syndromes. Best Pract Res Clin Rheumatol. 2008;22:863–82.
66. Davis MD, Daoud MS, McEvoy MT, Su WP. Cutaneous manifestations of Churg-Strauss syndrome: a clinicopathologic correlation. J Am Acad Dermatol. 1997;37:199–203.
67. Pagnoux, C, Guilpain P, Guillevin L. Churg-Strauss syndrome. Curr Opin Rheumatol. 2007;19:25–32.
68. Ribi C, Cohen P, Pagnoux C, et al. Treatment of Churg-Strauss syndrome without poor-prognosis factors. Arthritis Rheum. 2008;58:586–94.
69. Pepper RJ, Fabre MA, Pavesio C, et al. Rituximab is effective in the treatment of refractory Churg-Strauss syndrome and is associated with diminished T-cell interleukin-5 production. Rheumatology. 2008;47:1104–5.
69a. Vaglio A, Moosig F, Zerina J. Churg-Strauss syndrome: update on pathophysiology and treatment. Curr Opin Rheum. 2012;24:24–30.
69b. Moosig F, Gross WL, Herrmann K, et al. Targeting interleukin-5 in refractory and relapsing Churg-Strauss syndrome. Ann Intern Med. 2011;155:341–3.
69c. Kim S, Marigowda G, Oren E, et al. Mepolizumab as a steroid-sparing treatment option in patients with Churg-Strauss syndrome. J Allergy Clin Immunol. 2010;125:1336–43.
70. Segelmark M, Selga D. The challenge of managing patients with polyarteritis nodosa. Curr Opin Rheumatol. 2007;19:33–8.
71. Kaushik VV, Reddy HV, Bucknall RC. Successful use of rituximab in a patient with recalcitrant Churg-Strauss syndrome. Ann Rheum Dis. 2006;65:1116–7.
72. Kahn JE, Bletry O, Guillevin L. Hypereosinophilic syndromes. Best Pract Res Clin Rheumatol. 2008;22:863–82.
73. Mukhtyar C, Flossmann O, Hellmich B, et al. Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism systemic vasculitis task force. Ann Rheum Dis. 2008;67:1004–10.

TABLE 24.10 FURTHER REFERENCES

1e. Sais G, Vidaller A, Jucgla A, et al. Colchicine in the treatment of cutaneous leukocytoclastic vasculitis. Results of a prospective, randomized controlled trial. Arch Dermatol. 1995;131:1399–402.
2e. Fredenberg MF, Malkinson FD. Sulfone therapy in the treatment of leukocytoclastic vasculitis. Report of three cases. J Am Acad Dermatol. 1987;16:772–8.
3e. Swerlick RA, Lawley TJ. Cutaneous vasculitis: its relationship to systemic disease. Med Clin North Am. 1989;73:1221–35.
4e. Fiorentino DF. Cutaneous vasculitis. J Am Acad Dermatol. 2003;48:311–40.
5e. Callen JP, Spencer LV, Burruss JB, Holtman J. Azathioprine. An effective, corticosteroid-sparing therapy for patients with recalcitrant cutaneous lupus erythematosus or with recalcitrant cutaneous leukocytoclastic vasculitis. Arch Dermatol. 1991;127:515–22.
6e. Jorizzo JL, White WL, Wise CM, et al. Low-dose weekly methotrexate for unusual neutrophilic vascular reactions: cutaneous polyarteritis nodosa and Behcet's disease. J Am Acad Dermatol. 1991;24:973–8.
7e. Saulsbury FT. Henoch-Schönlein purpura in children. Report of 100 patients and review of the literature. Medicine (Baltimore). 1999;78:395–409.
8e. Ronkainen J, Koskimies O, Ala-Houhala M, et al. Early prednisone therapy in Henoch-Schönlein purpura: a randomized, double-blind, placebo-controlled trial. J Pediatr. 2006;149:241–7.
9e. Weiss PF, Feinstein JA, Luan X, et al. Effects of corticosteroid on Henoch-Schönlein purpura: a systematic review. Pediatrics. 2007;120:1079–87.
10e. Wyatt RJ, Hogg RJ. Evidence-based assessment of treatment options for children with IgA nephropathies. Pediatr Nephrol. 2001;16:156–67.
11e. Foster BJ, Bernard C, Drummond KN, Sharma AK. Effective therapy for severe Henoch-Schonlein purpura nephritis with prednisone and azathioprine: a clinical and histopathologic study. J Pediatr. 2000;136:370–5.
12e. Bergstein J, Leiser J, Andreoli SP. Response of crescentic Henoch-Schoenlein purpura nephritis to corticosteroid and azathioprine therapy. Clin Nephrol. 1998;49:9–14.
13e. Andersen RF, Rubak S, Jespersen B, Rittig S. Early high-dose immunosuppression in Henoch-Schönlein nephrotic syndrome may improve outcome. Scand J Urol Nephrol. 2009;43:409–15.
14e. Flynn JT, Smoyer WE, Bunchman TE, et al. Treatment of Henoch-Schönlein purpura glomerulonephritis in children with high-dose corticosteroids plus oral cyclophosphamide. Am J Nephrol. 2001;21:128–33.
15e. Ohtsuka T. Successful oral cyclosporin therapy for Henoch-Schönlein purpura nephropathy. J Dermatol. 2009;36:314–16.
16e. Ronkainen J, Autio-Harmainen H, Nuutinen M. Cyclosporin A for the treatment of severe Henoch-Schönlein glomerulonephritis. Pediatr Nephrol. 2003;18:1138–42.
17e. Rostoker G, Desvaux-Belghiti D, Pilatte Y, et al. High-dose immunoglobulin therapy for severe IgA nephropathy and Henoch-Schönlein purpura. Ann Intern Med. 1994;120:476–84.
18e. Donnithorne KJ, Atkinson TP, Hinze CH, et al. Rituximab therapy for severe refractory chronic Henoch-Schönlein purpura. J Pediatr. 2009;155:136–9.
19e. Martin S, Cramer CH, Heikenen J, Gitomer JJ. Gastrointestinal symptoms of Henoch-Schönlein purpura treated with mycophenolate mofetil. J Pediatr Gastroenterol Nutr. 2006;43:245–7
20e. Dede F, Onec B, Ayli D, et al. Mycophenolate mofetil treatment of crescentic Henoch-Schönlein nephritis with IgA depositions. Scand J Urol Nephrol. 2008;42:178–80.
21e. Prandota J, Pankow-Prandota L, Kotecki L. Impaired activation of the fibrinolytic system in children with Henoch-Schönlein purpura: beneficial effect of hydrocortisone plus Sigma-aminocaproic acid therapy on disappearance rate of cutaneous vasculitis and fibrinolysis. Am J Ther. 2001;8:11–9.
22e. Hattori M, Ito K, Konomoto T, et al. Plasmapheresis as the sole therapy for rapidly progressive Henoch-Schönlein purpura nephritis in children. Am J Kidney Dis. 1999;33:427–33.
23e. Donghi D, Schanz U, Sahrbacher U, et al. Life-threatening or organ-impairing Henoch-Schönlein purpura: plasmapheresis may save lives and limit organ damage. Dermatology. 2009;219:167–70.
24e. Fukui H, Kamitsuji H, Nagao T, et al. Clinical evaluation of a pasteurized factor XIII concentrate administration in Henoch-Schönlein purpura. Japanese Pediatric Group. Thromb Res. 1989;56:667–75.
25e. Legrain V, Lejean S, Taieb A, et al. Infantile acute hemorrhagic edema of the skin: study of ten cases. J Am Acad Dermatol. 1991;24:17–22.
26e. Mehregan DR, Hall MJ, Gibson LE. Urticarial vasculitis: a histopathologic and clinical review of 72 cases. J Am Acad Dermatol. 1992;26:441–8.
27e. Fortson JS, Zone JJ, Hammond ME, Groggel GC. Hypocomplementemic urticarial vasculitis syndrome responsive to dapsone. J Am Acad Dermatol. 1986;15:1137–42.
28e. Davis MD, Brewer JD. Urticarial vasculitis and hypocomplementemic urticarial vasculitis syndrome. Immunol Allergy Clin North Am. 2004;24:183–213, vi.
29e. Wiles JC, Hansen RC, Lynch PJ. Urticarial vasculitis treated with colchicine. Arch Dermatol. 1985;121: 802–5.
30e. Lopez LR, Davis KC, Kohler PF, Schocket AL. The hypocomplementemic urticarial-vasculitis syndrome: therapeutic response to hydroxychloroquine. J Allergy Clin Immunol. 1984;73:600–3.
31e. Worm M, Sterry W, Kolde G. Mycophenolate mofetil is effective for maintenance therapy of hypocomplementaemic urticarial vasculitis. Br J Dermatol. 2000;143:1324.
32e. Shah D, Rowbottom AW, Thomas CL, et al. Hypocomplementaemic urticarial vasculitis associated with non-Hodgkin lymphoma and treatment with intravenous immunoglobulin. Br J Dermatol. 2007;157:392–3.
33e. Yamazaki-Nakashimada MA, Duran-McKinster C, Ramírez-Vargas N, Hernandez-Bautista V. Intravenous immunoglobulin therapy for hypocomplementemic urticarial vasculitis associated with systemic lupus erythematosus in a child. Pediatr Dermatol. 2009;26:445–7.
34e. Saigal K, Valencia IC, Cohen J, Kerdel FA. Hypocomplementemic urticarial vasculitis with angioedema, a rare presentation of systemic lupus erythematosus: rapid response to rituximab. J Am Acad Dermatol. 2003;49(Suppl5):S283–5.
35e. Mukhtyar C, Misbah S, Wilkinson J, Wordsworth P. Refractory urticarial vasculitis responsive to anti-B-cell therapy. Br J Dermatol. 2009;160:470–2.
36e. Alexander JL, Kalaaji AN, Shehan JM, et al. Plasmapheresis for refractory urticarial vasculitis in a patient with B-cell chronic lymphocytic leukemia. J Drugs Dermatol. 2006;5:534–7.
37e. Brown NA, Carter JD. Urticarial vasculitis. Curr Rheumatol Rep. 2007;9:312–19.
38e. Ferri C, Giuggioli D, Cazzato M, et al. HCV-related cryoglobulinemic vasculitis: an update on its etiopathogenesis and therapeutic strategies. Clin Exp Rheumatol. 2003;21(6 suppl. 32):S78–84.
39e. Ferri C, Mascia MT. Cryoglobulinemic vasculitis. Curr Opin Rheumatol. 2006;18:54–63.
40e. Kuhl V, Vogt T, Anghelescu I. [Intravenous immunoglobulin and prednisolone treatment of cryoglobulinemic polyneuropathy]. Nervenarzt. 2001;72:445–8.
41e. Lamprecht P, Lerin-Lozano C, Merz H, et al. Rituximab induces remission in refractory HCV associated cryoglobulinaemic vasculitis. Ann Rheum Dis. 2003;62:1230–3.
42e. Saadoun D, Resche-Rigon M, Sene D, et al. Rituximab combined with PEG-interferon-ribavirin in refractory hepatitis C virus-associated cryoglobulinaemia vasculitis. Ann Rheum Dis. 2008;67:1431–6.
43e. Gayraud M, Guillevin L, Ie Toumelin P, et al. Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: analysis of four prospective trials including 278 patients. Arthritis Rheum. 2001;44:666–75.
44e. Guillevin L, Mahr A, Cohen P, et al. Short-term corticosteroids then lamivudine and plasma exchanges to treat hepatitis B virus-related polyarteritis nodosa. Arthritis Rheum. 2004;51:482–7.
45e. Segelmark M, Selga D. The challenge of managing patients with polyarteritis nodosa. Curr Opin Rheumatol. 2007;19:33–8.
46e. Stone J, Merkel P, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010;363:221–32.
47e. Jones R, Cohen Tervaert J, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med. 2010;363:211–20.
48e. De Groot K, Rasmussen N, Bacon PA, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic anti-neutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2005;52:2461–9.
49e. Lhote F, Guillevin L. Polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome. Clinical aspects and treatment. Rheum Dis Clin North Am. 1995;21:911–47.
50e. Pagnoux C, Mahr A, Hamidou MA, et al. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. N Engl J Med. 2008;359:2790–803.
51e. Ito-Ihara T, Ono T, Nogaki F, et al. Clinical efficacy of IVIG for patients with MPO-ANCA-associated rapidly progressive glomerulonephritis. Nephron Clin Pract. 2006;102:c35–42.
52e. Brunner J, Freund M, Prelog M, et al. Successful treatment of severe juvenile microscopic polyangiitis with rituximab. Clin Rheumatol. 2009;28:997–9.
53e. Booth A, Harper L, Hammad T, et al. Prospective study of TNF alpha blockade with infliximab in antineutrophilic cytoplasmic antibody-associated systemic vasculitis. J Am Soc Nephrol. 2004;15:717–21.
54e. Stone JH. Limited versus severe Wegener's granulomatosis: baseline data on patients in the Wegener's granulomatosis etanercept trial. Arthritis Rheum. 2003;48:2299–309.
55e. De Groot K, Muhler M, Reinhold-Keller E, et al. Induction of remission in Wegener's granulomatosis with low dose methotrexate. J Rheumatol. 1998;25:492–5.
56e. De Groot K, Harper L, Jayne DRW, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis. Ann Intern Med. 2009;150:670–80.
57e. Bosch X, Guilabert A, Espinosa G, Mirapeix E. Treatment of antineutrophil cytoplasmic antibody-associated vasculitis: a systematic review. JAMA. 2007;298:655–69.
58e. Stegeman CA, Tervaert JW, de Jong PE, Kallenberg CG. Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. Dutch Co-Trimoxazole Wegener Study Group. N Engl J Med. 1996;335:16–20.
59e. Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med. 1992;116:488–98.
60e. Keogh KA, Ytterberg SR, Fervenza FC, et al. Rituximab for refractory Wegener's granulomatosis. Am J Respir Crit Care Med. 2006;173:180–7.
61e. Keogh KA, Wylam ME, Stone JH, Specks U. Induction of remission by B lymphocyte depletion in eleven patients with refractory antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2005;52:262–8.
62e. Stegeman C, Cohen Tervaert J. Mycophenolate mofetil for remission induction in patients with active Wegener's granulomatosis intolerant to cyclophosphamide. J Am Soc Nephrol. 2000;11:98A.
63e. Jayne DR, Chapel H, Adu D, et al. Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. QJM. 2000;93:433–9.
64e. Jayne, D, Rasmussen N, Andrassy K, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med. 2003;349:36–44.
65e. Langford CA, Talar-Williams C, Barron KS, Sneller MC. A staged approach to the treatment of Wegener's granulomatosis: induction of remission with glucocorticoids and daily cyclophosphamide switching to methotrexate for remission maintenance. Arthritis Rheum. 1999;42:2666–73.
66e. Metzler C, Wagner-Bastmeyer R, Gross W, Reinhold Keller E. Leflunomide versus methotrexate for maintenance of remission in Wegener's granulomatosis: unexpected high relapse rate under oral methotrexate. Ann Rheum Dis. 2005;64(S3):85.
67e. Langford CA, Talar-Williams C, Sneller MC. Mycophenolate mofetil for remission maintenance in

the treatment of Wegener's granulomatosis. Arthitis Rheum. 2004;51:278–83.
68e. Martinez V, Cohen P, Pagnoux C, et al. IVIG for relapses of systemic vasculitis associated with antineutrophil cytoplasmic autoantibodies: results of a multicenter, prospective, open-label study of twenty-two patients. Arthritis Rheum. 2008;58:308–17.
69e. Pepper RJ, Fabre MA, Pavesio C, et al. Rituximab is effective in the treatment of refractory Churg-Strauss syndrome and is associated with diminished T-cell interleukin-5 production. Rheumatology. 2008;47:1104–5.
70e. Koukolaki M, Jayne DR. Mycophenolate mofetil in antineutrophil cytoplasm antibodies-associated systemic vasculitis. Nephron Clin Pract. 2006;102: c100–7.
71e. Kaushik VV, Reddy HV, Bucknall RC. Successful use of rituximab in a patient with recalcitrant Churg-Strauss syndrome. Ann Rheum Dis. 2006;65:1116–17.
72e. Kahn JE, Bletry O, Guillevin L. Hypereosinophilic syndromes. Best Pract Res Clin Rheumatol. 2008;22:863–82.
73e. Tatsis E, Schnabel A, Gross WL. Interferon-alpha treatment of four patients with the Churg-Strauss syndrome. Ann Intern Med. 1998;129:370–4.
74e. Termeer CC, Simon JC, Schopf E. Low-dose interferon alfa-2b for the treatment of Churg-Strauss syndrome with prominent skin involvement. Arch Dermatol. 2001;137:136–38.
75e. Szpirt WM, Heaf JG, Petersen J. Plasma exchange for induction and cyclosporine A for maintenance of remission in Wegener's granulomatosis—a clinical randomized controlled trial. Nephrol Dial Transplant. 2011;26:206–13.
76e. Nowack R, Gobel U, Klooker P, et al. Mycophenolate mofetil for maintenance therapy of Wegener's granulomatosis and microscopic polyangiitis: a pilot study in 11 patients with renal involvement. J Am Soc Nephrol. 1999;10:1965–71.
77e. Gause A, Arbach O, Reinhold-Keller E, et al. Induction of remission with infliximab in active generalized Wegener's granulomatosis is effective but complicated by severe infections. Arthritis Rheum. 2003;48(suppl.): S208.

Eosinophilic Dermatoses 25

Cloyce L Stetson and Kristin M Leiferman

Chapter Contents

Eosinophil biology 411
Eosinophilic dermatoses 412
Granuloma faciale 412
Papuloerythroderma of Ofuji 416
Wells' syndrome 416
Hypereosinophilic syndrome 418

Key features

- Many cutaneous diseases have prominent eosinophilic infiltrates, and clinicopathologic correlation is often needed to arrive at a specific diagnosis
- Eosinophilic infiltrates are frequently associated with arthropod bites or drug eruptions ("bugs and drugs") as well as autoimmune blistering diseases (especially bullous pemphigoid), in addition to other eosinophilic dermatoses (e.g. Wells' syndrome)
- Because eosinophils commonly disrupt and lose their morphologic integrity as they deposit toxic granule proteins and other mediators into tissue, the involvement of eosinophils in various inflammatory disorders may not be appreciated, given the absence of intact identifiable cells

EOSINOPHIL BIOLOGY

The eosinophilic leukocyte possesses distinctive cytoplasmic granules and circulates in the peripheral blood. With the exception of the gastrointestinal tract, lymphoid tissue (including the spleen, thymus and lymph nodes) and the bone marrow, eosinophils are found in tissues only during inflammation, and the latter is often associated with allergic reactivity or extra-gastrointestinal parasitic disease. In 1879, Paul Ehrlich named this cell the "eosinophil" because of the intense staining of its cytoplasmic granules with the acidic dye eosin. Ultrastructurally, the distinctive, membrane-bound, specific eosinophil granules show an electron-dense core and a less dense matrix (Fig. 25.1). The eosinophil produces multiple factors (e.g. toxic cationic proteins within specific granules and oxidative products) that reflect its role in inflammation[1,2,2a] and are released into tissues following activation. Surface molecule expression is important in activation and/or priming and further directs eosinophil involvement in inflammation. Many of the surface molecules expressed on eosinophils are included in Figure 25.1; they are also extensively reviewed in References 1 and 2.

Eosinophils are attracted into tissues and activated by at least three interrelated signals: (1) chemokines; (2) other cytokines; and (3) adhesion molecules. Several members of the C-C chemokine gene superfamily are chemotactic for eosinophils, and these chemoattractants include the eotaxin family and *r*egulated on *a*ctivation, *n*ormal *T* cell *e*xpressed and *s*ecreted (RANTES). Eosinophil-active chemokines signal primarily through C-C chemokine receptor (CCR)-3, which is expressed by eosinophils. Eotaxins 1–3 are specifically chemotactic for eosinophils, while RANTES is chemotactic not only for eosinophils but also for monocytes, T lymphocytes, natural killer cells and basophils (but not neutrophils). In addition to their chemotactic properties, the eotaxins and RANTES induce production of reactive oxygen species by eosinophils, indicating that they have both chemotactic and functional activation effects. As eosinophil chemoattractants, the eotaxins are stronger than RANTES, and eotaxins 1 and 2 are also stronger in inducing reactive oxygen species by eosinophils than are eotaxin 3 and RANTES. Eotaxins 1, 2 and 3 and RANTES are produced by dermal fibroblasts; RANTES is also produced by keratinocytes, positioning them well for participation in cutaneous inflammation[3].

For eosinophils to migrate from the peripheral blood into tissues, the cells must transmigrate blood vessels. Similar to other leukocytes, selectin, integrin and immunoglobulin gene superfamily members (see Ch. 102) contribute to the signaling needed for eosinophil transmigration[1,2]. In particular, eosinophils constitutively express the integrin very late antigen (VLA)-4, which interacts with its ligand, vascular cell adhesion molecule (VCAM)-1, which is induced on endothelial cells by chemokines and cytokines. After movement through vessels, eosinophils are present in the extracellular matrix. Here, integrins, expressed on the cell surface, recognize as receptors substances that exert effects on eosinophil activity, such as fibrous proteins (in particular, fibronectin, laminin and collagen) and glycosaminoglycans (especially hyaluronic acid and chondroitin sulfate). Integrin expression, specifically CD11b/CD18 (MAC-1), is critical for eosinophil effector functions, including degranulation.

Activating cytokines such as granulocyte–macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-3 and IL-5 are also important for the effector functions of eosinophils[1,2]. Several lines of investigation indicate that eosinophils are recruited to and activated in tissues by cytokine activity from the Th2 subset of T cells, which produces IL-4, IL-5, IL-10 and IL-13, in addition to cytokines common to Th1 cells. Mast cell-derived cytokines also contribute indirectly to eosinophil activation via the induction of IL-5 and GM-CSF. Of note, human natural killer cells, which respond to some of the same C-C chemokines as eosinophils, also produce IL-5. Eosinophils themselves elaborate important inflammatory and regulatory cytokines; these include IL-1α, TGF-α and TGF-β_1, GM-CSF, IL-3, IL-5, IL-6, IL-8, TNF-α, and macrophage inflammatory protein 1α (see Fig. 25.1). As a result, eosinophil activation also occurs in an autocrine manner. In cytotoxicity assays, eosinophils are maximally activated by GM-CSF, followed by IL-3, IL-5, TNF-α and IL-4, in order of potency.

Granular contents

With activation, eosinophils release granule contents into their extracellular spaces via three mechanisms[1]: cytolytic degranulation, piecemeal degranulation, and regulated secretion. Cytolytic degranulation occurs in many inflammatory disorders, including skin diseases (e.g. atopic dermatitis), as well as all affected organs in patients with the hypereosinophilic syndromes. It is characterized by organelle rupture, chromatolysis of nuclei with loss of morphologic integrity and identity of eosinophils, and extensive deposition of eosinophil granules and granule products within tissue[1,4]. *Major basic protein-1* (MBP-1), the constituent of the crystalline cores of specific eosinophils (see Fig. 25.1), directly damages helminths and also damages mammalian cells and tissues, an example of which is its ability to cause exfoliation of bronchial epithelial cells. MBP-1, but none of the other eosinophil granule proteins, stimulates histamine release from human basophils. Furthermore, MBP-1 stimulates neutrophils, inducing release of superoxide and lysozyme. *Eosinophil cationic protein* (ECP or RNase3) and *eosinophil-derived neurotoxin* (EDN or RNase2) are members of the RNase family. ECP is a potent toxin for parasites through a different mechanism than MBP-1, and it is more effective at killing certain helminths than MBP-1. EDN, as its name implies, is a neurotoxin and also has antiviral activity against RNA viruses.

Eosinophil peroxidase (EPO) kills numerous microorganisms in the presence of hydrogen peroxide, generated by eosinophils and other phagocytes, and halide. This combination of products also initiates mast cell secretion. Binding of EPO to microbes, including *Staphylococcus aureus*, greatly potentiates their killing by phagocytes. EPO-coated

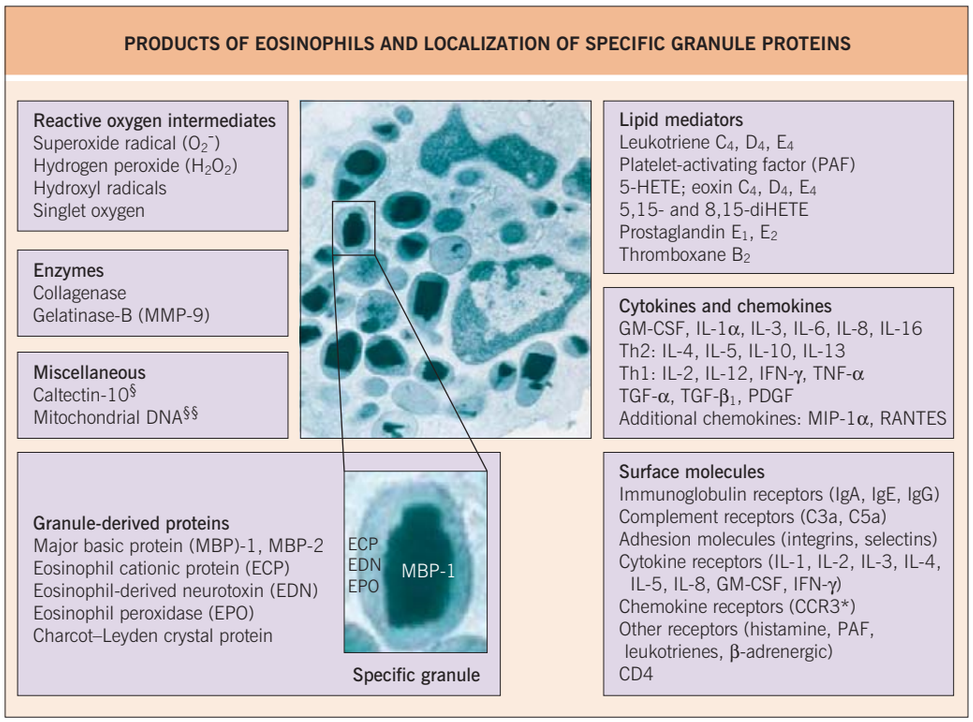


Fig. 25.1 Products of eosinophils and localization of specific granule proteins. The eosinophil produces myriad products that reflect its role in inflammation. Specific granules contain major basic protein (in the electron-dense core) and other toxic proteins (in the matrix). In addition eosinophils produce Calectin-10 (Charcot-Leyden crystal protein) Mitochondrial DNA (forms DNA traps with ECP and MBP-1). *Receptor for eotaxins and RANTES. §Charcot-Leyden crystal protein. §§Forms DNA traps with ECP and MBP-1. CCR, CC chemokine receptor; GM-CSF, granulocyte–macrophage colony-stimulating factor; HETE, *h*ydroxy*e*icosa*t*etra*e*noic acid; IFN, interferon; IL, interleukin; MIP, macrophage inflammatory protein; MMP, matrix metalloproteinase; PDGF, platelet-derived growth factor; RANTES, *r*egulated on *a*ctivation *n*ormal *T* cell *e*xpressed and *s*ecreted; TGF, transforming growth factor; TNF, tumor necrosis factor.

tumor cells are spontaneously lysed by activated macrophages, and MBP-1 is also toxic to tumor cells. EPO and MBP-1 are potent platelet agonists that lead to release of 5-hydroxytryptamine (serotonin) and promote clotting. Eosinophils also are associated with fibrotic processes, with resulting fibrosis in areas of infiltration. The presence of eosinophils in certain normal organs suggests a role in homeostasis. Eosinophils may act as antigen-presenting cells for microbial (including staphylococcal superantigens), viral and parasitic antigens to promote T cell proliferation. They can also regulate mast cell function. In addition, eosinophils are able to generate mitochondrial DNA traps that contain ECP and MBP-1 and display antimicrobial activity, demonstrating that eosinophils can participate in innate and acquired immunity[2a]. In summary, the functional diversity of eosinophils[1,2] has numerous ramifications in tissues and in disease.

EOSINOPHILIC DERMATOSES

Eosinophilic dermatoses encompass a wide variety of diseases that are characterized histologically by the presence of eosinophils in the inflammatory infiltrate and/or evidence of eosinophil degranulation[4] (Fig. 25.2). The most common causes of eosinophilic infiltrates include arthropod bites, drug eruptions, allergic contact dermatitis and atopic dermatitis (Fig. 25.3). In addition, several of the autoimmune blistering diseases frequently have prominent eosinophilic infiltrates. Bullous pemphigoid, in particular, should be considered whenever a biopsy specimen from an elderly patient has numerous eosinophils throughout the dermis. Parasitic infections, particularly with ectoparasites and helminths, often have a marked eosinophilic host response (see Chs 83 & 84). Urticaria, urticarial vasculitis, Churg–Strauss syndrome, and urticarial allergic eruption may have significant numbers of eosinophils. Table 25.1 lists the diseases associated with cutaneous eosinophilic infiltrates.

GRANULOMA FACIALE

Key features

- Granuloma faciale is an idiopathic cutaneous disorder characterized by red–brown plaques on the face and is unusual elsewhere
- Biopsy specimens demonstrate a diffuse, mixed, dermal infiltrate of lymphocytes, neutrophils and numerous eosinophils
- Leukocytoclastic vasculitis is classically present histopathologically, but it may be subtle or undetected in a single lesion
- A prominent Grenz zone is present with a narrow band of papillary dermal sparing that separates the epidermis from the dermal infiltrate

History

Wigley described the first patient, and labeled the disease "eosinophilic granuloma"[15] (a name now used instead for a variant of Langerhans cell histiocytosis). Subsequently, it was renamed "facial granuloma with eosinophilia". Pinkus recommended the current name, granuloma faciale[16].

Epidemiology

Granuloma faciale occurs predominantly in middle-aged white men, but it has been observed in black and Asian men as well as women.

Pathogenesis

Immunofluorescence microscopy has demonstrated IgG, IgA, IgM and C3 within blood vessel walls, a nonspecific finding that supports a role for immune complexes. While the precise pathogenesis remains unknown, a role for interferon-γ as an important proinflammatory mediator in this disorder has been suggested[17], as has elevated local IL-5 production.

Clinical Features

Granuloma faciale usually presents as a solitary, asymptomatic, smooth red–brown to violaceous plaque on the face[18] (Fig. 25.4). Upon closer inspection, prominent follicular openings are often observed. Less often, multiple papules or plaques may be present[19]; in one retrospective analysis of 66 patients, one-third were noted to have multiple sites of involvement[20]. As the name suggests, lesions of granuloma faciale appear predominantly on the face. Occasionally (7% of patients in above series[20]), there is involvement of extrafacial sites, e.g. the trunk, extremities and/or scalp, but facial lesions are present as well in the vast majority[21]. A sinonasal mucosal variant termed "eosinophilic angiocentric fibrosis" has been described and rarely there is involvement of other sites in the upper respiratory tract. Individual lesions of granuloma faciale are chronic and only occasionally spontaneously resolve. Granuloma faciale has not been associated with systemic disease.

Pathology

The epidermis is usually not affected. Within the dermis, a dense, nodular and diffuse polymorphous infiltrate of lymphocytes, neutrophils and plasma cells with numerous eosinophils is characteristic. This infiltrate spares the upper papillary dermis, creating a prominent Grenz zone (Fig. 25.5). Biopsy specimens taken from early lesions typically show many neutrophils, with neutrophilic dust and hemorrhage.

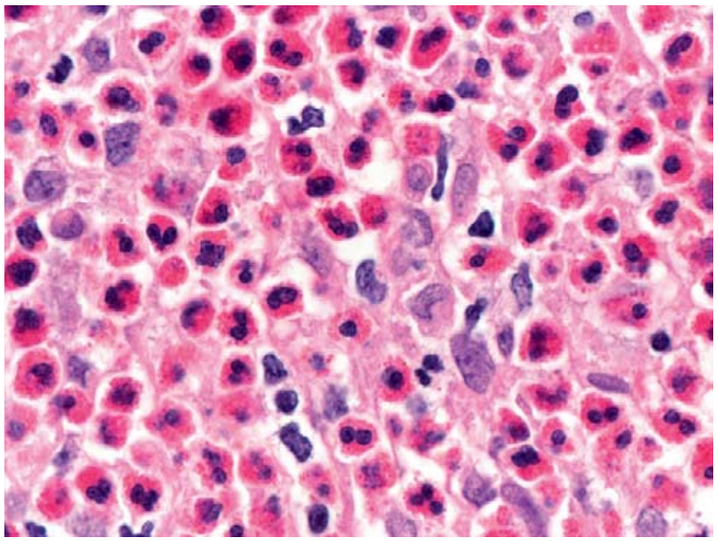


Fig. 25.2 Eosinophils within the dermis. Note the red-staining granules within their cytoplasm. *Courtesy, Lorenzo Cerroni, MD.*

Older lesions have fewer neutrophils and more eosinophils and macrophages. In addition, fibrosis may be pronounced in older lesions. Leukocytoclastic vasculitis is classically described as being present, but it may be subtle or multiple sections may be required to demonstrate diagnostic changes.

Differential Diagnosis

The clinical appearance of granuloma faciale is usually quite distinctive, but the clinical differential diagnosis includes lymphoma and pseudolymphoma, sarcoidosis, tumid lesions of lupus erythematosus, fixed drug eruption, rhinophyma, and other granulomatous diseases such as leprosy, foreign body granuloma and the granulomatous variant of rosacea. The histology of granuloma faciale may superficially resemble lymphoma, pseudolymphoma and granulomatous rosacea, but the prominent Grenz zone, normal epidermis, and polymorphous infiltrate with significant numbers of eosinophils aid in differentiating granuloma faciale.

Extrafacial granuloma faciale can be difficult to distinguish from erythema elevatum diutinum (EED), both clinically and histologically. EED usually presents as red–brown to violaceous papules, plaques or nodules on the extensor aspects of the extremities and the buttocks, with a predilection for the skin overlying joints. In addition to histologic evidence of leukocytoclastic vasculitis, epidermal changes are usually present and range from epidermal necrosis to epidermal hyperplasia; EED typically lacks a Grenz zone. The vasculitis is usually more pronounced and neutrophils predominate over eosinophils in EED. Prominent lipid-laden macrophages may be seen in EED, but not in granuloma faciale.

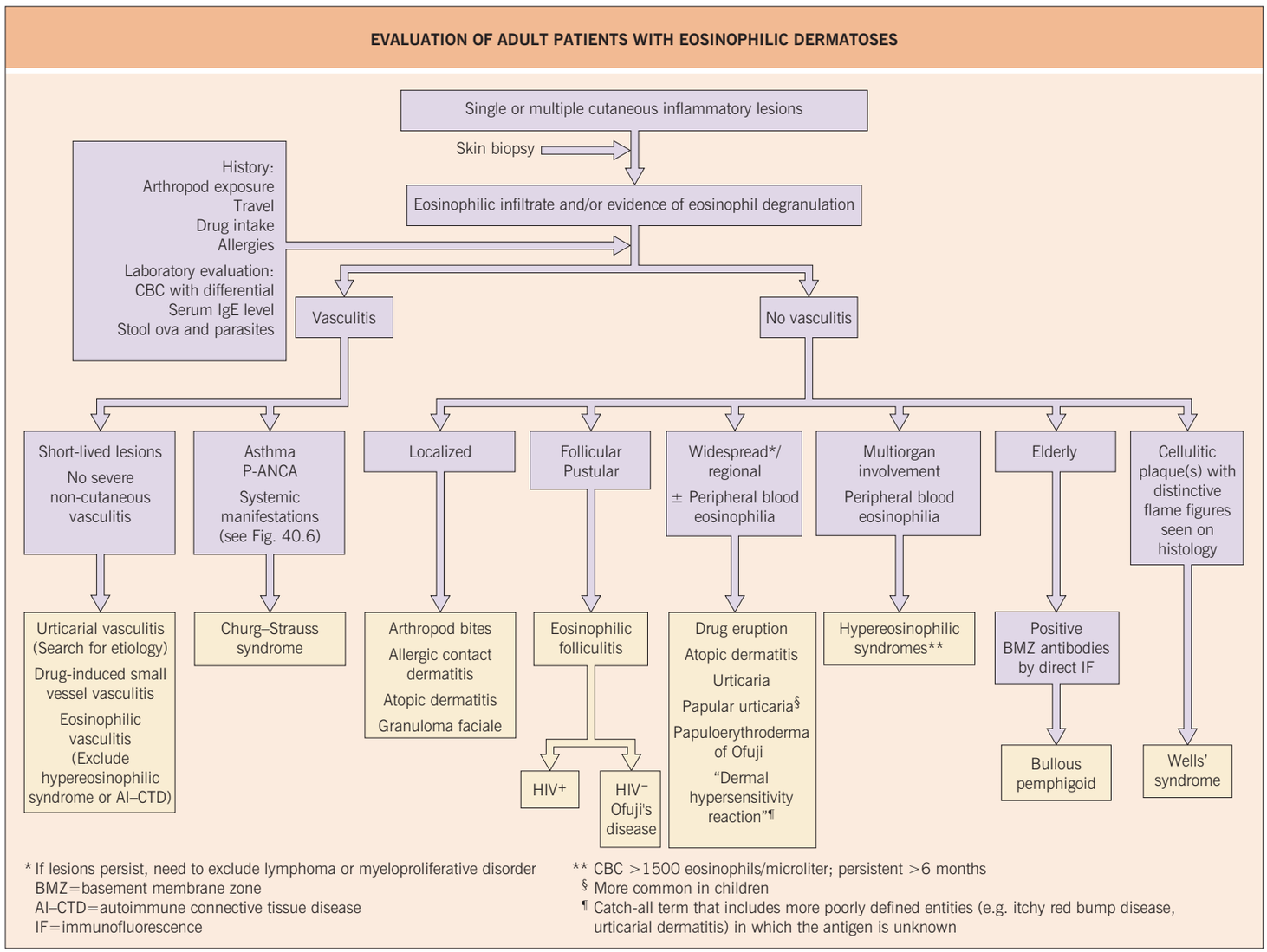


Fig. 25.3 Evaluation of adult patients with eosinophilic dermatoses. Histologically, these dermatoses are characterized by a prominent eosinophilic infiltrate and/or eosinophil granule protein deposition. Of note, systemic corticosteroids can significantly reduce the peripheral blood eosinophil count.

DIFFERENTIAL DIAGNOSIS OF EOSINOPHILIC DERMATOSES	
Diagnosis	**Clinical clues**
Allergic contact dermatitis	History of exposure; suggestive distribution; positive patch test
Angiolymphoid hyperplasia with eosinophilia (and Kimura's disease)	Single or multiple nodules on face, scalp and ears; histologically, prominent vascular channels and endothelial cells with vacuolization and "hobnail" appearance in addition to eosinophils
Annular erythema of infancy[5]	Annular or serpiginous non-pruritic plaques in infants
Arthropod assault	Primarily involves exposed skin; spiders, ticks, fleas, mites and mosquitoes; exaggerated reactions in patients with chronic lymphocytic leukemia
Atopic dermatitis	History of atopy; pruritus; flexural and extremity accentuation
Bullous pemphigoid	Initial phase may be urticarial; flexural sites and legs favored; elderly patients
Churg–Strauss syndrome (allergic granulomatosis)	Palpable purpura and tender papulonodules on the extremities or scalp; asthma and peripheral blood eosinophilia; peripheral neuropathy, cardiac involvement and glomerulonephritis may be present
Coccidioidomycosis	Verrucous plaques and nodules; history of travel to southwestern US; 30–80 μm spherules with endospores in biopsy specimens
Drug eruption	Drug history, especially new drugs within previous 2 weeks*
Eosinophilic fasciitis (Shulman syndrome)	Sudden onset of symmetric induration of the skin and subcutaneous tissues of the limbs
Eosinophilic (pustular) folliculitis	*HIV variant:* HIV+ patient with severe pruritus and papules on the face and upper trunk
	Ofuji's disease: typically a Japanese patient with chronic, recurrent follicular pustules in a seborrheic distribution with tendency to form circinate plaques
	Pediatric: follicular pustules on the scalp of an infant
Eosinophilic, polymorphic and pruritic eruption associated with radiotherapy (EPPER)[5a]	Local and generalized pruritus, erythematous papules and wheals, and vesicobullae
Eosinophilic vasculitis[6]	Pruritic urticarial and purpuric papules; angioedema
Eosinophilic ulcer of the oral mucosa	Rapidly enlarging nodule that develops a central ulceration; usually on the tongue
Erythema toxicum neonatorum	Newborn with erythematous macules, papules and pustules on the trunk; often have a prominent erythematous flare
Hypereosinophilic dermatitis of Nir-Westfried[7,†]	Pruritic, papular eruption with peripheral eosinophilia; often dapsone-responsive
Incontinentia pigmenti	Vesicles and bullae along Blaschko's lines in neonate (stage I); peripheral blood eosinophilia; biopsy specimen showing eosinophilic spongiosis with dyskeratosis
Itchy red bump disease (papular dermatitis)[†]	Markedly pruritic pink to red papules; may be associated with eczematous patches and/or dermographism
Juvenile xanthogranuloma	Yellow to red–brown papules or nodules on the head and neck, upper trunk or proximal extremities; early lesions may have numerous eosinophils
Langerhans cell histiocytosis (especially eosinophilic granuloma)	Disseminated pink and yellow–brown papules (often with crusts) to nodulo-ulcerative periorificial lesions; eosinophilic component may be intense
Lymphoma, especially Hodgkin disease and mycosis fungoides	Patches, plaques or nodules; lymphadenopathy
Mastocytosis	Pink–tan to red–brown macules, papules and plaques that urticate with stroking (Darier's sign)
Nummular dermatitis	Discrete round eczematous plaques on the extremities; pruritic
Oid-oid disease (exudative discoid and lichenoid chronic dermatosis of Sulzberger and Garbe)[8,†]	Middle-aged, predominantly Jewish, men; pruritic lesions commonly involving genitals; progressive stages: discoid → exudative → lichenified; peripheral blood eosinophilia
Pachydermatous eosinophilic dermatitis[9]	South African black teenage girls with generalized pruritic papules, hypertrophic genital lesions and peripheral blood eosinophilia; dapsone-responsive; possibly a variant of hypereosinophilic dermatitis of Nir-Westfried
Papular eruption of blacks[10]	Young, black men with intensely pruritic papules on the trunk and upper arms
Parasitic infestations	Cysticercosis, dirofilariasis, larva migrans, myiasis, onchocerciasis, tungiasis, schistosomiasis and others
Pemphigoid gestationis	Pregnant patient; periumbilical lesions; urticarial plaques and bullae
Pemphigus variants	Flaccid vesicles and crusted erosions; distribution depends on subtype
Polymorphic eruption of pregnancy (PEP; also referred to as pruritic urticarial papules and plaques of pregnancy [PUPPP])	Usually primigravida in third trimester; urticarial papules and plaques, especially in striae
Pruritic papular eruption of HIV disease[11]	Pruritic non-follicular papules in symmetric distribution; HIV infection; may be an exaggerated reaction to arthropod antigens
Pseudolymphoma	Association with arthropod bite or drug intake (especially phenytoin)
Scabies	Marked nocturnal pruritus; webspace, umbilical and groin involvement
Seabather's eruption (larvae of *Linuche unguiculata* and *Edwardsiella lineata*)	Pruritic papules in distribution of swimsuit; occurs after ocean swimming
Urticaria	Pruritic, migratory, transient (lasting <24 hours) wheals

*Eosinophils may also be present in drug-induced small vessel vasculitis[14].
†Not clearly defined entities.

Table 25.1 Differential diagnosis of eosinophilic dermatoses. Granuloma faciale, Wells' syndrome, papuloerythroderma of Ofuji, and the subtypes of hypereosinophilic syndrome are discussed in the text. Eosinophilic infiltrates are occasionally seen in epidermolysis bullosa.

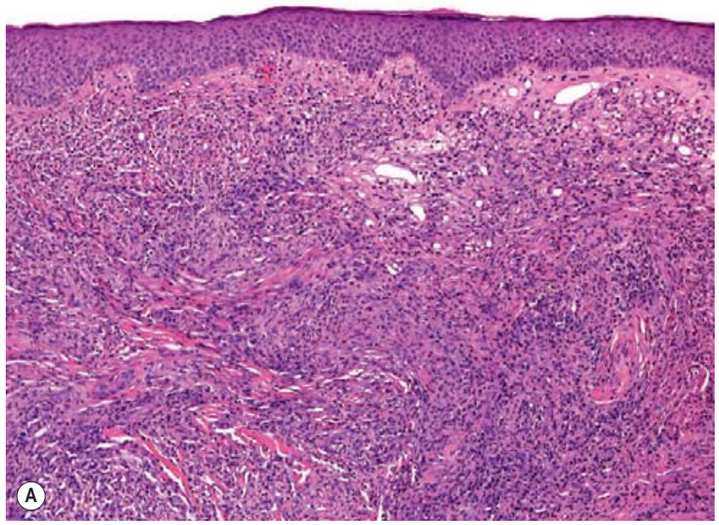
Continued

DIFFERENTIAL DIAGNOSIS OF EOSINOPHILIC DERMATOSES	
Diagnosis	**Clinical clues**
Urticarial allergic eruption[12]	Annular or gyrate urticarial plaques that persist >24 hours; histologically more cellular than urticaria
Urticarial dermatitis[13,†]	Very pruritic lesions (sometimes eczematous, other times urticarial) on the trunk, sacrum and proximal extremities of elderly individuals (1.8 female : 1 male); persist for days to weeks; often accompanied by excoriated papules; minimally responsive to topical corticosteroids and oral antihistamines
Urticarial vasculitis	Lesions can burn rather than itch and persist >24 hours; associated with autoimmune disease and decrease in complement

[†]Not clearly defined entities.

Table 25.1 Differential diagnosis of eosinophilic dermatoses (cont'd). Granuloma faciale, Wells' syndrome, papuloerythroderma of Ofuji, and the subtypes of hypereosinophilic syndrome are discussed in the text. Eosinophilic infiltrates are occasionally seen in epidermolysis bullosa.

Fig. 25.4 Granuloma faciale. Red–brown plaques on the lateral cheek (**A**) and nose (**B**). Note the prominent follicular openings.



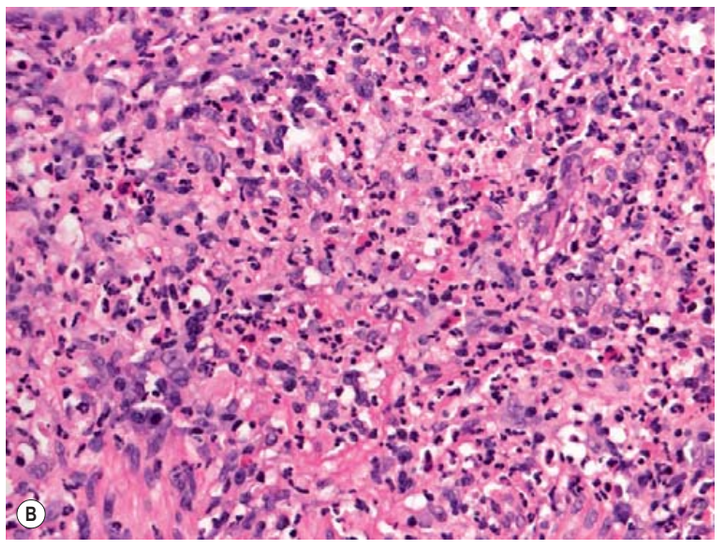


Fig. 25.5 Granuloma faciale. A Dense diffuse dermal infiltrate with a Grenz zone. **B** Higher-power view of polymorphous infiltrate of lymphocytes, eosinophils, neutrophils and plasma cells. *Courtesy, Lorenzo Cerroni, MD.*

Treatment

Because of the prominent location on the face, treatment is often desired. Unfortunately, granuloma faciale is frequently resistant to therapy. Intralesional triamcinolone (2.5–5 mg/ml) is often recommended as a first-line, non-scarring therapeutic intervention. As with other recalcitrant dermatoses, there are many anecdotal alternatives reported. Oral dapsone (50–150 mg daily) and oral clofazimine (300 mg daily) have been reported to be effective, as have topical PUVA and topical calcineurin inhibitors (pimecrolimus, tacrolimus).

With regard to physical modalities, surgical excision, cryosurgery, dermabrasion, electrosurgery, and CO_2 or pulsed dye laser therapy have all been advocated, but each carries a significant risk of scarring given

the depth of inflammation. Recurrences after excision have also been reported. Laser treatments that target the prominent vascular component, e.g. the 595 nm pulsed dye laser and 532 nm potassium-titanyl-phosphate laser, have also been reported to be effective.

PAPULOERYTHRODERMA OF OFUJI

Key features

- Occurs most commonly in elderly men
- Widespread red–brown papules can evolve into a confluent erythroderma with characteristic sparing of the skin folds ("deck-chair" sign)
- Chronic course, with periodic acute exacerbations
- Peripheral blood eosinophilia, lymphopenia and elevated serum IgE level in more than two-thirds of patients
- While most patients have no associated disorders, there can be an underlying disorder such as a T-cell lymphoma or gastric carcinoma
- Often responds to oral corticosteroids or PUVA, alone or in combination with a systemic retinoid

History

Papuloerythroderma of Ofuji was first described by Ofuji in 1984[22].

Epidemiology

Approximately 100 cases of papuloerythroderma of Ofuji have been reported to date. Over two-thirds of these individuals have been elderly Japanese men, with an average age of 72 years at presentation. The disorder is much less common in Caucasians. Overall, men outnumber women by a ratio of 7 : 1.

Pathogenesis

The pathogenesis remains unknown.

Clinical Features

Papuloerythroderma of Ofuji presents as a widespread, symmetrically distributed, pruritic eruption composed of flat-topped, red–brown papules. The trunk and extremities are typically involved. There are periodic acute exacerbations, often leading to an erythroderma that strikingly spares the skin folds; the latter finding is referred to as the "deck-chair" sign. A majority of the patients have peripheral blood eosinophilia and lymphopenia, and many will have peripheral lymphadenopathy. Reported neoplastic and infectious associations are listed in Table 25.2. The most commonly associated malignancies are T-cell lymphoma and gastric carcinoma.

Pathology

Histologic features are usually nonspecific. The epidermis is often normal in appearance, but there may be mild spongiosis, mild acanthosis and parakeratosis. Within the dermis, a superficial and mid-dermal mixed infiltrate composed of lymphocytes and eosinophils, along with a few plasma cells and histiocytes, is often seen. In patients with an associated T-cell lymphoma, epidermotropism of atypical lymphocytes may be present. Laboratory evaluation usually demonstrates peripheral blood eosinophilia, lymphopenia, and an elevated serum IgE level.

Differential Diagnosis

During an erythrodermic flare, the clinical presentation of papuloerythroderma is quite striking. In these patients, the differential diagnosis includes other causes of erythroderma such as psoriasis, cutaneous T-cell lymphoma, atopic dermatitis, pityriasis rubra pilaris, and drug eruptions (see Ch. 10). Sparing of skin folds (the "deck-chair" sign) aids in the clinical diagnosis. For those patients with predominantly flat-topped pruritic papules, the differential diagnosis includes pityriasis lichenoides chronica, lichen planus, papular eczema, arthropod bite reactions, a drug eruption and other entities listed in Table 25.1.

PAPULOERYTHRODERMA OF OFUJI – REPORTED ASSOCIATIONS	
NEOPLASMS	**INFECTIONS**
• Lymphomas: T-cell lymphoma (most common), Hodgkin disease, B-cell lymphoma	• Viruses: hepatitis C, human immunodeficiency virus
• Leukemias: chronic lymphocytic leukemia, acute myelogenous leukemia	• Fungi: dermatophytes
• Solid organ malignancies: gastric (most common), lung, colon, hepatocellular, prostate, renal, laryngeal	• Parasites: strongyloidiasis
DRUGS	**OTHER**
• Furosemide, ranitidine, dideoxyinosine (DDI), aspirin, isoniazid	• Atopic dermatitis

Table 25.2 Papuloerythroderma of Ofuji – reported associations.

Treatment

Systemic corticosteroids are usually effective. In a recent review, PUVA, alone or in combination with acitretin or etretinate, led to complete clearance in two-thirds of patients, with an additional one-quarter improved[23]. Additional reportedly effective treatments include UVB radiation, cyclosporine, etretinate and azathioprine. Topical corticosteroids, however, are usually ineffective as monotherapy.

Although often idiopathic, the possibility of an underlying neoplasm or infection or an inciting drug needs to be considered. Laboratory evaluation and diagnostic imaging should be directed by the history, physical examination and entities listed in Table 25.2.

WELLS' SYNDROME

Synonym: ■ Eosinophilic cellulitis

Key features

- Cutaneous lesions of Wells' syndrome present as recurrent painful or pruritic plaques that can resemble infectious cellulitis, infiltrative disorders, or other causes of pseudocellulitis (e.g. exaggerated arthropod bite reactions, Sweet's syndrome)
- Histologically, a diffuse eosinophilic infiltrate throughout the dermis is seen, as well as characteristic "flame figures"
- Flame figures can be seen in other disorders with numerous activated eosinophils, and, therefore, they are not diagnostic of Wells' syndrome
- Wells' syndrome usually improves dramatically after administration of systemic corticosteroids

Introduction

Wells' syndrome is a cutaneous disorder of unknown etiology characterized clinically by indurated plaques resembling cellulitis. The classic histologic appearance is that of a diffuse dermal infiltrate of eosinophils and characteristic "flame figures".

History

Wells described the first patient in 1971, and named the disease "recurrent granulomatous dermatitis with eosinophilia". He later renamed it "eosinophilic cellulitis"[24]. Spigel and Winkelmann[25] proposed the eponym Wells' syndrome in 1979.

Epidemiology

Over 100 cases of Wells' syndrome have been reported to date, ranging from newborns to patients over 70 years of age. Associated systemic diseases are extremely rare.

Pathogenesis

The pathogenesis of Wells' syndrome is unknown, but the possibility of local hypersensitivity has been proposed. So-called "triggers" have been described in some patients, including myeloproliferative disorders, infections/infestations (including dermatophytes, viruses and *Toxocara canis*), insect bites or stings, and drugs. Activated eosinophils are present and play a major role in Wells' syndrome. Simon and colleagues[26] have suggested that IL-2 primes eosinophil degranulation in patients with eosinophilia (including those with Wells' syndrome). This hypothesis was based on the following findings: (1) eosinophils from patients with eosinophilia expressed the α chain of the IL-2 receptor (CD25); and (2) IL-2 enhanced platelet-activating factor (PAF)-stimulated release of eosinophil cationic protein from CD25-expressing eosinophils. More recently, peripheral lymphocytes isolated from patients with Wells' syndrome were reported to have exaggerated responses to mosquito salivary gland extracts[27].

Clinical Features

Classically, Wells' syndrome presents as recurrent episodes of prodromal itching or burning, followed by markedly edematous nodules and plaques (Fig. 25.6), which may have an annular or arcuate configuration and sometimes have violaceous borders[28]. Blistering may occur. Initially, the lesions are bright red, and then they fade to a pink–brown, green, brown or slate-gray color. The plaques can become indurated and thereby resemble infiltrative skin disorders such as sarcoidosis, but lesions usually resolve over 4 to 8 weeks. Less common clinical presentations include papules, vesicles and hemorrhagic bullae. The most common systemic complaint in patients is malaise, with fever occurring in less than a quarter of patients. The extremities are most frequently affected, but truncal involvement also occurs. Peripheral blood eosinophilia is common. Patients have often been previously misdiagnosed as having erysipelas or acute cellulitis. Precipitating events, including arthropod bites and stings, have been described in a minority of Wells' syndrome patients.

Pathology

Wells' syndrome is characterized histologically by an interstitial infiltrate of eosinophils, with an admixture of lymphocytes and histiocytes (Fig. 25.7). The infiltrate is usually most impressive in the deep dermis, with occasional involvement of the subcutaneous fat, fascia and skeletal muscle. The superficial dermis may be affected with massive papillary dermal edema to the point of subepidermal bulla formation. Epidermal spongiosis and intraepidermal vesiculation may also be seen.

With the tremendous number of activated eosinophils, extracellular eosinophil granules are present in the dermis. Characteristic eosinophilic-staining flame figures consist of collagen fibers coated with eosinophil granule proteins[29] (Fig. 25.7, insert). Extracellular major basic protein from eosinophil granules has been localized to flame figures using indirect immunofluorescent assays[30]. These flame figures are a hallmark of Wells' syndrome, but they are not specific. Other diseases featuring flame figures include arthropod bites and stings (namely, ticks, bees, fleas and spiders), mastocytomas, scabies and other parasitic infestations, prurigo nodularis, eczema and dermatophyte infections. Vasculitis of dermal vessels is not seen.

Differential Diagnosis

Wells' syndrome often has a striking clinicopathologic presentation[31]. Bacterial cellulitis and erysipelas are said to be the most common clinical mimics of Wells' syndrome. The histopathologic findings of both erysipelas and bacterial cellulitis can include significant edema similar to that seen in Wells' syndrome, but usually neutrophils are the predominant inflammatory cell in those two entities, in contrast to the eosinophils of Wells' syndrome. Other causes of pseudocellulitis, including exaggerated reactions to arthropod bites, are listed in Table 74.10. Reports of Wells' syndrome occurring in patients with chronic lymphocytic leukemia and non-Hodgkin lymphoma may represent the latter.

Fig. 25.6 Wells' syndrome. Edematous nodules and plaques.

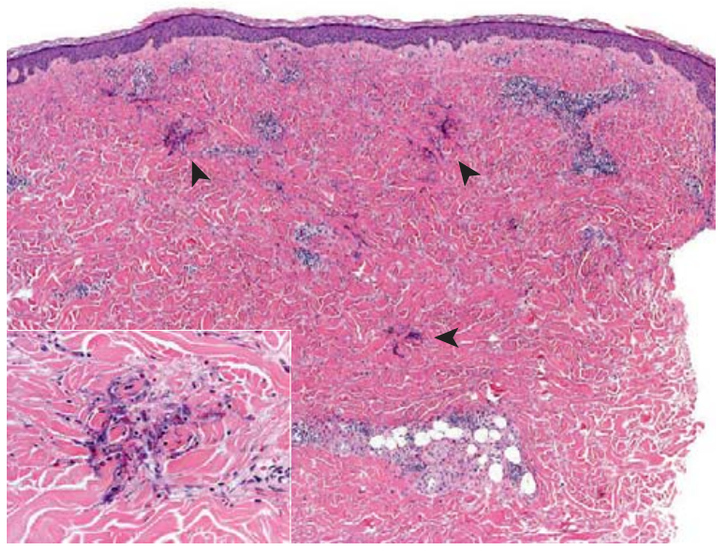


Fig. 25.7 Wells' syndrome. Perivascular and interstitial inflammatory infiltrate with a significant number of eosinophils within the dermis. There are also several flame figures at sites of degranulation of eosinophils (arrowheads; insert).

Toxocara canis and other parasitic disorders can present with clinical and pathologic findings similar to Wells' syndrome. When a parasitic infection is suspected, laboratory evaluation includes stool examinations, serum IgE levels and specific antibody assays. Allergic contact dermatitis (especially the dermal form) can also closely mimic Wells' syndrome. A careful history along with patch testing may be useful in establishing the former diagnosis. Several of the other disorders listed in Table 25.1 may present with urticarial plaques clinically and diffuse dermal infiltrates of eosinophils histologically. Nonetheless, there is rarely confusion between Wells' syndrome and the clinicopathologic presentations of these entities.

Treatment

Initial therapy usually consists of oral corticosteroids, typically prednisone at a dose of 10–80 mg daily, and this typically results in dramatic improvement within a few days. Tapering of the corticosteroid dose over 1 month is well tolerated in most patients. Flares may be treated with repeat courses. For patients who fail to respond completely, or who flare often enough to raise concerns about the long-term side effects of systemic corticosteroid therapy (see Ch. 125), other treatments may prove beneficial. Minocycline, colchicine, antimalarials, dapsone, griseofulvin, interferon-α and antihistamines have been reported to clear some patients. Cyclosporine (1.25–2.5 mg/kg/day) for 3–4 weeks resulted in clinical resolution in two patients, with no

relapse during the following 10 months. For mild cases, potent topical corticosteroids may be used.

HYPEREOSINOPHILIC SYNDROME

Key features

- With the discovery of the *FIP1L1-PDGFRA* fusion gene, whose protein product is a constitutively activated tyrosine kinase, the classification and treatment of hypereosinophilic syndrome (HES) have become more precise
- The *FIP1L1-PDGFRA* fusion gene is present in patients with the myeloproliferative form of HES, which includes eosinophilic leukemia
- In the lymphocytic variant of HES, there is a clonal proliferation of T cells with increased production of Th2 cytokines, particularly IL-5
- Mucocutaneous lesions are seen in over half of patients with HES and vary from pruritic erythematous papules or nodules to urticaria and angioedema; mucosal ulcers are associated with an aggressive course
- The 5-year survival rate is 80%, with a major cause of death being congestive heart failure from restrictive cardiomyopathy

Introduction

The term "hypereosinophilic syndrome (HES)" was originally coined in the late 1960s to refer to a spectrum of eosinophil-associated diseases with common clinical features, including skin disease in more than 50% of patients. In the 1990s, a subset of patients with HES was found to have clonal proliferations of T cells with increased production of Th2 cytokines (in particular, IL-5); that is, the *lymphocytic* form of HES was identified. Building upon the clinical observations that a subgroup of patients with HES responded to hydroxyurea, interferon and, more recently, imatinib mesylate (Gleevec®), i.e. treatments for chronic myelogenous leukemia (CML), a molecular explanation was subsequently discovered. The patients with this particular form of *myeloproliferative* HES possessed a *FIP1L1-PDGFRA* fusion gene[32], whose protein product is a constitutively activated tyrosine kinase that is over 100 times more sensitive to the inhibitory effects of imatinib than is the BCR-ABL kinase from CML patients (see Pathogenesis). There are some patients with HES who have neither the lymphocytic nor the myeloproliferative form of the disease, and additional subtypes of HES have been partially classified[33,34,34a] (Table 25.3), along with a corresponding treatment algorithm (Fig. 25.8). However, as pathogenetic mechanisms continue to evolve so will the classification and recommended evaluation of hypereosinophilia and HES.

History

Prior to 1968, patients with marked blood eosinophilia, in the absence of helminthiasis or allergic disease, were diagnosed using various terms. In 1968, Hardy and Anderson coined the term "hypereosinophilic syndromes (HES)" to refer to these patients. Chusid and colleagues[35] proposed diagnostic criteria in 1975, and the clinical spectrum of HES was defined. More recently, the two major forms of HES, lymphocytic and myeloproliferative, were described.

Epidemiology

HES occurs worldwide. Up to 25% of patients may have the lymphocytic form of HES, which has an equal gender distribution, while *FIP1L1-PDGFRA*-positive myeloproliferative HES has a striking male predominance (>90%, with few reported female cases). Other HES subtypes likely have an equal gender distribution. HES affects all age groups, including children, but principally affects adults. The average age of onset for the various HES subtypes is unknown, in part, because of delay in diagnosis. However, defining when HES begins is becoming more precise as disease markers are discovered.

Myeloproliferative HES includes patients with eosinophilic leukemia (who may have multiple cytogenetic abnormalities[37]). While individuals with the *FIP1L1-PDGFRA* fusion gene may be regarded as having chronic eosinophilic leukemia, there are clearly some patients who develop more aggressive disease with transformation to frank leukemia. Patients with lymphocytic HES are at risk of developing lymphoma.

DIAGNOSTIC CRITERIA AND CLASSIFICATION OF HYPEREOSINOPHILIC SYNDROMES

DIAGNOSTIC CRITERIA

- Peripheral blood eosinophil counts >1500/microliter for at least 6 months, or less than 6 months with evidence of organ damage
- Lack of evidence for parasitic, allergic, or other recognized causes of eosinophilia
- Symptoms and signs of organ system involvement

SUBTYPES

Myeloproliferative*	Lymphoproliferative	Other‡
• *FIP1L1-PDGFRA* fusion gene; other mutations are possible • Includes "classic HES" with endomyocardial disease and a male predominance • Mucosal ulcers are associated with severe disease • High serum tryptase and vitamin B_{12} levels, tissue fibrosis, splenomegaly, and bone marrow biopsies with increased numbers of $CD25^+$ atypical spindle-shaped mast cells†	• T-cell clone producing Th2 cytokines • T-cell clones have occurred in rare cases of EAE and NERDS	• Eosinophilic vasculitis • Episodic angioedema with eosinophilia (EAE; Gleich syndrome) • *N*odules, *e*osinophilia, *r*heumatism, *d*ermatitis and *s*welling (NERDS) syndrome • A variety of other diseases, including eosinophilic gastroenteritis

*Includes patients with eosinophilic leukemia, who may have other cytogenetic abnormalities; can also screen for other rare fusion genes or rearrangements involving *PDGFRB* or *FGR1*, which encode platelet-derived growth factor receptor (beta polypeptide) and fibroblast growth factor receptor-1, respectively

†In the WHO classification of mastocytosis, such patients (who have the *FIP1L1-PDGFRA* fusion gene) are designated as having systemic mastocytosis with associated clonal hematological non-mast cell-lineage disease (AHNMD).

‡Other HES subtypes have recently been reviewed and partially classified[33,34].

Table 25.3 Diagnostic criteria and classification of hypereosinophilic syndromes (HES)[35,36].

Pathogenesis

Eosinophils have been implicated as the cause of much of the end-organ damage in all forms of HES via the elaboration of eosinophil products (see Fig. 25.1), and clinical improvement usually parallels a decrease in the eosinophil count[35a]. While the pathogenesis of the lymphocytic and myeloproliferative forms is now better understood (see below), the etiologies of the other forms are likely varied[33,34,36]. Occasional patients with episodic angioedema and eosinophilia (Gleich syndrome) as well as those with *n*odules, *e*osinophilia, *r*heumatism, *d*ermatitis and *s*welling (NERDS) syndrome have developed T-cell clones (see Table 25.3). Therefore, as outlined in Figure 25.8, patients who do not have the lymphocytic or myeloproliferative forms of HES should continue to be monitored for the development of T-cell clonality or cytogenetic abnormalities.

Lymphocytic HES

Patients with the lymphocytic variant of HES have abnormal clonal lymphocyte populations, frequently with unique surface phenotypes such as $CD3^+CD4^-CD8^-$ or $CD3^-CD4^+$. Upon activation, these T cells secrete Th2 cytokines (IL-5, IL-4, IL-13). IL-5 induces eosinophilopoiesis and activates eosinophils, which then release their toxic granule contents. IL-2 may also play a role by enhancing platelet-activating factor (PAF)-stimulated eosinophil granule protein release from eosinophils (see above)[24]. In lymphocytic HES, high serum IgE levels are often found along with eosinophilia, likely attributable to IL-4 and IL-13 production. These patients develop severe pruritus, eczema, erythroderma and/or urticaria and angioedema.

Although, in general, the lymphocytic variant of HES appears to be a relatively benign disease and the T-cell clones can remain stable for

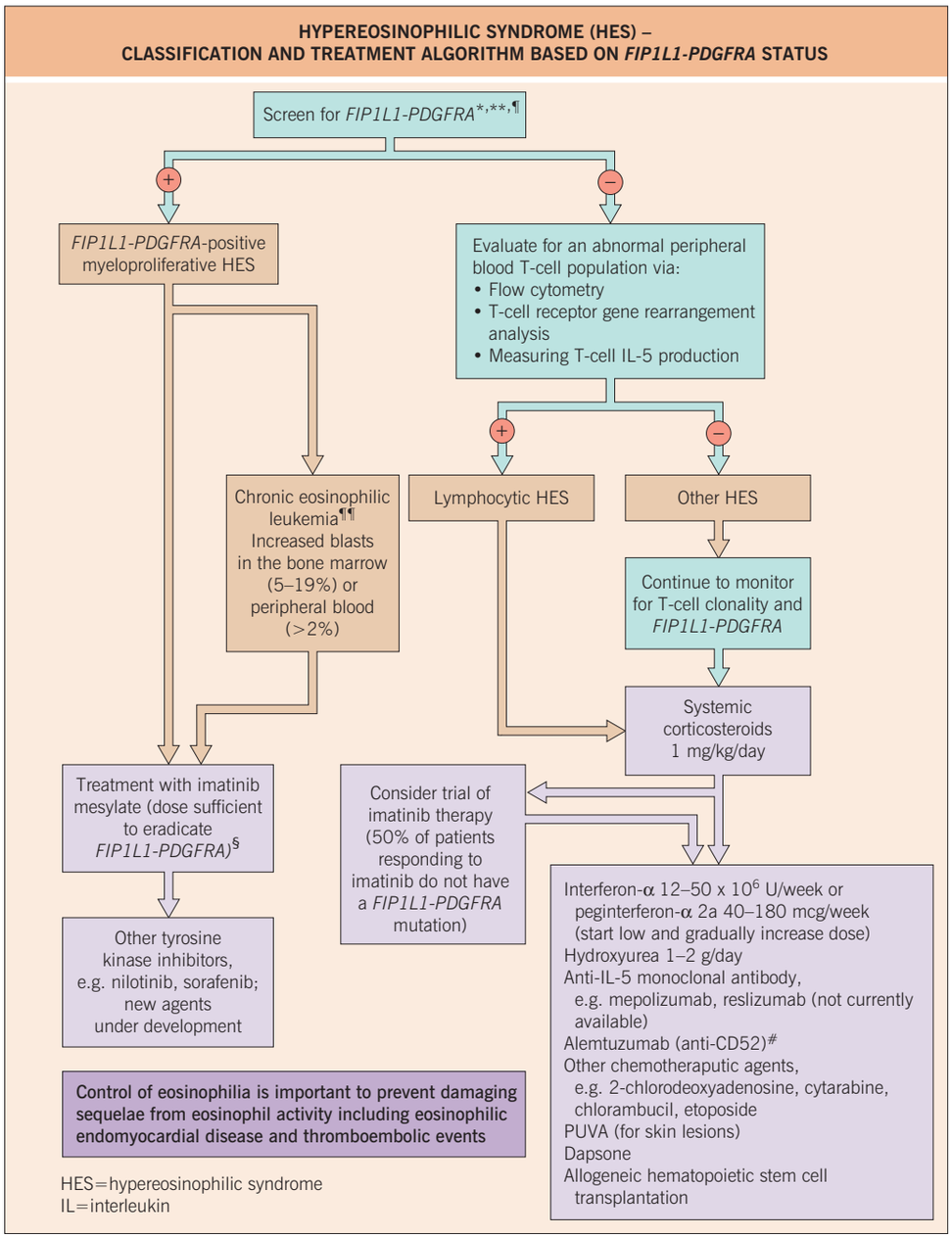


Fig. 25.8 Hypereosinophilic syndrome (HES) – classification and treatment algorithm based on *FIP1L1-PDGFRA* status. *An 800 kb deletion on chromosome 4 produces a fusion gene composed of a portion of the *PDGFRA* (platelet-derived growth factor receptor α) gene that encodes its kinase domain linked to a previously uncharacterized gene that resembles *Fip1*, which encodes an essential component of the *Saccharomyces cerevisiae* polyadenylation machinery. The resultant product is a constitutively activated tyrosine kinase. Screening can be performed on a peripheral blood sample via reverse transcriptase-PCR or fluorescence *in situ* hybridization (FISH). **Bone marrow biopsy with cytogenetic studies should be done to exclude hematologic disorders that can be accompanied by eosinophilia. Increased bone marrow mast cells and elevated serum tryptase may be observed. ¶Can also screen for other rare fusion genes or rearrangements involving *PDGFRB* or *FGR1*, which encode platelet-derived growth factor receptor (beta polypeptide) and fibroblast growth factor receptor-1, respectively. ¶¶May have other clonal cytogenetic and molecular genetic abnormalities; in the presence of eosinophilia, this is usually sufficient for diagnosis even in the absence of excess blasts. §Plus systemic corticosteroids if cardiac involvement. #CD52 is expressed on the surface of normal and malignant B and T lymphocytes, NK cells, monocytes, macrophages and eosinophils.

years, $CD3^{-}CD4^{+}$ T cells and other clonal T cells may undergo progressive transformation and evolve into lymphoma. Therefore, patients with such clones should be regarded as having premalignant or malignant T-cell lymphoma and be closely observed[38].

Myeloproliferative HES

Myeloproliferative HES includes patients with eosinophilic leukemia as well as individuals with the *FIP1L1-PDGFRA* fusion gene that results from an 800-kilobase deletion on chromosome 4q12, which, when present, may be regarded as evidence of chronic eosinophilic leukemia (see Fig. 25.8). Sensitive reverse transcriptase (RT)-PCR-based assays and fluorescence *in situ* hybridization (FISH) probes have been developed to detect the deletion which produces this fusion gene; the latter is composed of the portion of the platelet-derived growth factor receptor-α gene (*PDGFRA*) that encodes its tyrosine kinase domain linked to a previously uncharacterized gene resembling *Fip1*, which encodes an essential component of the *Saccharomyces cerevisiae* polyadenylation machinery. The resultant protein product is a constitutively activated tyrosine kinase that transforms hematopoietic cells *in vitro* and *in vivo*, analogous to the BCR-ABL kinase that results from the translocation [t(9;22)] that leads to the Philadelphia chromosome in CML. This molecular discovery provided an explanation for the clinical observation that a subgroup of patients with HES responded to imatinib (Gleevec®), a tyrosine kinase inhibitor first introduced for the treatment of CML (see Treatment)[36,39]. Unfortunately, as in CML where patients can develop new mutations in *BCR-ABL* (e.g. T315I) that lead to resistance, a few HES patients who initially responded to imatinib later became resistant, having developed T674I mutations (during blast crisis) or tandem S601P/L629P mutations (during the chronic phase)[40].

Some patients with HES have elevated serum tryptase levels and increased atypical, spindle-shaped mast cells in bone marrow biopsies (see Table 25.3)[36,41]. These patients develop splenomegaly, endomyocardial fibrosis, cardiomyopathy and elevated serum vitamin B_{12} levels; some also have mucosal ulcers. However, they lack the clinical manifestations of systemic mastocytosis as well as tissue mast cell aggregates and c-*KIT* mutations. These patients have the *FIP1L1-PDGFRA* fusion gene and are responsive to imatinib. In the World Health Organization (WHO) classification of mastocytosis, such patients are designated as systemic mastocytosis with *a*ssociated clonal *h*ematological *n*on-*m*ast cell-lineage *d*isease (AHNMD; see Ch. 118), although others would argue they are more appropriately considered a subset of HES. In some patients, the *FIP1L1-PDGFRA* fusion gene was detected in

mast cells, neutrophils and mononuclear cells; this is interesting because many HES patients also show marked neutrophilia. Presently, it is not clear whether the cell lineages mutated independently or if a common, yet unknown, precursor cell mutated.

Clinical Features

Diagnostic criteria for HES are as follows: (1) peripheral blood eosinophilia (≥1500 eosinophils/mcl) for at least 6 months *or* if less than 6 months, with evidence of organ damage; (2) signs and symptoms of multiorgan involvement; and (3) no evidence of parasitic or allergic disease, or other known causes of peripheral blood eosinophilia. Thus, HES is a diagnosis of exclusion. Patients with HES present with signs and symptoms related to the organ systems affected by eosinophilic infiltrates, and cutaneous lesions occur in more than half of all patients. The skin findings range from pruritic erythematous macules, papules, plaques or nodules on the trunk and extremities to urticaria and angioedema[42]. Occasionally, the nodules ulcerate. Mucosal ulcers may also occur, either in the oropharynx or in the anogenital region, and they are associated with myeloproliferative HES, with a majority of patients dying within 2 years of presentation unless treated[43]; recent reports indicate that these patients are very responsive to imatinib. Other cutaneous manifestations include erythema annulare centrifugum-like lesions, purpuric papules, retiform purpura, livedo reticularis and superficial thrombophlebitis.

Lymphocytic HES is commonly associated with severe pruritus, dermatitis, erythroderma and/or urticaria and angioedema, in addition to lymphadenopathy. These patients rarely develop endomyocardial fibrosis. In myeloproliferative HES, the usual presenting complex includes fever, weight loss, fatigue, malaise and skin lesions, in addition to increased serum vitamin B_{12} levels and increased serum tryptase levels[44]. The heart is often involved, with thrombus formation and progression to subendocardial fibrosis and restrictive cardiomyopathy. Mitral or tricuspid valvular insufficiency results from tethering of chorda tendineae. Hepatosplenomegaly is often present as well, indicating liver and spleen involvement. The central and peripheral nervous systems may also be affected, in addition to the lungs and, rarely, the kidneys[44a].

Eosinophilic endomyocardial disease can develop in any patient with prolonged peripheral blood eosinophilia, and HES patients must be monitored for its development by periodic performance of echocardiography. Embolic events may occur, particularly during the thrombotic stage, and constitute a medical emergency because of their likely serious sequelae; cutaneous involvement with splinter hemorrhages and/or nailfold infarcts may be present and can provide the initial clues to thromboembolic disease. More recently, intramural cardiac damage has been observed in patients with HES in the absence of appreciable blood eosinophilia.

Pathology

The histopathology of cutaneous lesions in HES is nonspecific and varies depending upon the type of skin lesion biopsied. Urticarial lesions have histologic findings that resemble urticaria, i.e. perivascular or interstitial infiltrates of lymphocytes, eosinophils, and occasional neutrophils. Biopsies from papules or plaques occasionally exhibit spongiosis in addition to the dermal infiltrate that nearly always contains at least a few eosinophils. Flame figures may also be present. When studied with stains for specific eosinophil granule proteins, episodic angioedema with eosinophilia and HES with mucosal ulcers show extensive deposition of granule proteins in the absence of morphologically identifiable intact eosinophils. Similar findings are observed in synovial tissues in the NERDS syndrome. Thrombosis of dermal blood vessels has been observed in biopsy specimens from retiform purpura and necrotic skin lesions in HES patients.

Differential Diagnosis

The differential diagnosis of HES includes those dermatoses that are characterized by prominent eosinophilic infiltrates (see Table 25.1), along with other dermatoses in which eosinophil degranulation occurs but infiltrates of intact eosinophils are not observed. The principal means of eosinophil degranulation is via cytolysis and the eosinophil disrupts within tissue soon after infiltrating or as it infiltrates. The footprints are its granule proteins which remain in the tissue while the cell itself is not morphologically identifiable, although parts of the eosinophil are often recognizable by electron microscopy.

In contrast to Wells' syndrome, patients with myeloproliferative HES may be more systemically ill, with fever and signs and symptoms of multiorgan involvement. Histologic features can be similar, but the classic flame figures of Wells' syndrome are less commonly seen in HES.

Churg–Strauss syndrome can resemble HES and is considered by some authors to be an HES-associated disease[33]. Characteristically, patients with Churg–Strauss syndrome have asthma along with other organ involvement. Cutaneous lesions classically consist of papulonodules located on the scalp or extremities and hemorrhagic lesions ranging from petechiae to hemorrhagic eschars. Cardiac involvement may occur and the histologic features are distinctive. Churg–Strauss syndrome exhibits vasculitis of the medium-sized arteries and veins, with extravascular granulomas in addition to the eosinophilic infiltrate. No vasculitis is seen in HES, although thromboembolic phenomena may produce lesions that mimic vasculitis (see Ch. 22).

Parasitic infections and infestations may closely resemble HES. A history of travel to endemic areas or a suggestive dietary history implicates helminthiasis. In such patients, serologic testing for anti-*Strongyloides* antibodies and three stool samples for ova and parasites should be obtained. A total serum IgE greater than 500 IU/ml is often seen in helminth infections. Inappropriate treatment of *Stronglyloides stercoralis* with systemic corticosteroids or other immunosuppressives may result in severe sequelae, including death.

In patients with HES whose cutaneous eruption consists of isolated urticarial plaques with or without angioedema, the differential diagnosis includes urticaria. Histopathology of such a cutaneous lesion may be indistinguishable from that of ordinary urticaria, and clinical correlation is required to distinguish between the two. Specifically, demonstration of multiorgan involvement favors HES. In addition, HES with episodic angioedema may resemble hereditary or acquired angioedema clinically, but complement studies help to make a distinction (see Fig. 18.18). Furthermore, the patients with hereditary angioedema often have a family history of the disease and rarely are their peripheral blood eosinophil counts as elevated as in HES.

Patients with lymphocytic HES commonly have pruritic skin lesions that become eczematous. The differential diagnosis in these patients includes atopic dermatitis, contact dermatitis, drug reaction, id reaction to a bacterial or fungal infection, and other types of T-cell lymphoma.

Treatment

In light of the *FIP1L1-PDGFRA* fusion gene discovery, an algorithmic approach for the evaluation and treatment of HES is provided in Figure 25.8. If *FIP1L1-PDGFRA* is present, imatinib therapy is warranted. Imatinib, a 2-phenylaminopyrimidine tyrosine kinase inhibitor, exerts its effect by binding to the amino acids of the fusion tyrosine kinase's ATP-binding site and stabilizes the inactive, non-ATP-binding form of the FIP1L1-PDFGRA fusion protein. This prevents autophosphorylation of the fusion protein and phosphorylation of other substrates. As a result, the signaling cascade that induces genes related to eosinophil proliferation and activation is terminated. Patients respond to varying doses of imatinib, depending upon the sensitivity of the particular patient and the ability of the given dosage to suppress the mutant clone. Imatinib doses ranging from 400 mg daily to 100 mg weekly or less have proven effective. A majority of patients with the fusion protein have achieved hematologic and molecular remission when treated with imatinib; however, maintenance therapy is required to avoid relapse. Of note, endomyocardial disease may worsen during the first several days of imatinib therapy so serum levels of troponin and NT-proBNP should be monitored. Preemptive and concurrent treatment with corticosteroids is also recommended to maintain cardiac function. For patients who lack the *FIP1L1-PDGFRA* fusion gene, further evaluation to detect clonal cytogenetic abnormalities or abnormal clonal T-cell populations is warranted.

First-line therapy for HES patients who lack the *FIP1L1-PDGFRA* fusion gene consists of prednisone at a dose of 1 mg/kg/day. Approximately 70% of patients will respond, with the peripheral eosinophilia returning to normal levels. As the peripheral eosinophilia normalizes, cardiac function improves. For those patients who fail corticosteroid monotherapy or develop significant long-term side effects, multiple

other agents have been reported to be beneficial (see Fig. 25.8). For example, imatinib treatment of patients with no detectable *FIP1L1-PDGFRA* fusion gene has resulted in partial hematologic responses, although the mechanism of response in these patients is unclear. Perhaps some patients had diagnostically occult *PDGFRA* or *PDGFRB* rearrangements, especially those individuals with the rare complete responses[40]. As a result, imatinib represents a reasonable therapeutic option, given its relative safety.

Interferon (IFN)-α (12–50 × 10^6 U/week) has been beneficial in the treatment of patients with both myeloproliferative and lymphocytic HES. Its mode of action is likely via myelosuppression but may include effects on Th2 helper cells by changing the cytokine milieu (including a decrease in IL-5 levels). Some patients tolerate pegylated interferon better (peginterferon -2α), responding to various doses, and it can be administered weekly. After prolonged therapy with IFN-α, a clinical and molecular remission may occur in patients with the *FIP1L1-PDGFRA* fusion gene, suggesting that prolonged IFN-α treatment may modify the disease in unanticipated ways. One concern regarding the use of IFN-α, based upon the findings of an *in vitro* study in which IFN-α acted as a growth factor for $CD3^-CD4^+$ cells, is probably minimized in patients receiving corticosteroids concomitantly. For some patients, pegylated IFN is better tolerated, and it can be administered weekly.

Two monoclonal antibodies against human IL-5 have been used for HES in clinical trials, mepolizumab and reslizumab. Analyses of cytokine production by lymphocytes before and after treatment with mepolizumab showed a striking reduction in Th2 cytokine production (e.g. IL-13, IL-10) in addition to the expected IL-5 reduction[45]. In a randomized, double-blind, placebo-controlled trial involving 85 *FIP1L1-PDGFRA*-negative patients who were already receiving prednisone (20–60 mg/day), administration of mepolizumab (750 mg IV every 4 weeks for 9 cycles) led to twice as many individuals (84% vs 43%) being successfully tapered to a stable prednisone dose of ≤10 mg/day[46]. Lastly, other kinase inhibitors (e.g. nilotinib, sorafenib) may be useful in treating patients who do not respond to imatinib or become resistant as a consequence of mutations such as T674I in *FIP1L1-PDGFRA*[40].

The overall goal in treating the HES is relief of the patient's symptoms while keeping the peripheral blood eosinophil count in the range of 1000–2000/mcl (by using single- or multiple-agent therapy) as well as minimizing side effects from the therapy. Patients also need to be monitored for organ involvement, particularly cardiac involvement, and treated appropriately. Those who fail corticosteroid monotherapy have a worse prognosis. Overall, HES is associated with a 5-year survival rate of 80%, with the leading cause of death usually being congestive heart failure followed by sepsis.

REFERENCES

1. Leiferman KM, Beck LA, Gleich GJ. Regulation of the production and activation of eosinophils. In: Goldsmith LA, Katz SI, Gilchrest B, et al. (eds). Fitzpatrick's Dermatology in General Medicine, 8th edn. New York: McGraw-Hill, 2012.
2. Rothenberg ME, Hogan SP. The eosinophil. Annu Rev Immunol. 2006:24:147–74.
2a. Blanchard C, Rothenberg ME. Biology of the eosinophil. Adv Immunol. 2009;101:81–121.
3. Dulkys Y, Schramm G, Kimmig D, et al. Detection of mRNA for eotaxin-2 and eotaxin-3 in human dermal fibroblasts and their distinct activation profile on human eosinophils. J Invest Dermatol. 2001;116: 498–505.
4. Kita H. Eosinophils: multifaceted biological properties and roles in health and disease. Immunol Rev. 2011;242:161–77.
5. Hebert AA, Esterly NB. Annular erythema of infancy. J Am Acad Dermatol. 1986;14:339–43.
5a. Rueda RA, Valencia IC, Covelli C, et al. Eosinophilic, polymorphic, and pruritic eruption associated with radiotherapy. Arch Dermatol. 1999;135:804–10.
6. Chen KR, Pittelkow MR, Su D, et al. Recurrent cutaneous necrotizing eosinophilic vasculitis. A novel eosinophil-mediated syndrome. Arch Dermatol. 1994;130:1159–66.
7. Nir MA, Westfried M. Hypereosinophilic dermatitis. A distinct manifestation of the hypereosinophilic syndrome with response to dapsone. Dermatologica 1981;162:444–50.
8. Sulzberger MB, Garbe W. Nine cases of a distinctive exudative discoid and lichenoid chronic dermatosis. Arch Dermatol Syphilol. 1937;36:247–72.
9. Jacyk WK, Simson IW, Slater DN, Leiferman KM. Pachydermatous eosinophilic dermatitis. Br J Dermatol. 1996;134:469–74.
10. Rosen T, Algra RJ. Papular eruption in black men. Arch Dermatol. 1980;116:416–18.
11. Resneck JS Jr, Van Beek M, Furmanski L, et al. Etiology of pruritic papular eruption with HIV infection in Uganda. JAMA. 2004;292:2614–21.
12. Ackerman AB. Urticarial allergic eruption. In: Ackerman AB (ed). Histologic Diagnosis of Inflammatory Skin Diseases, 1st edn. Philadelphia: Lea & Febiger, 1978:181–3.
13. Kossard S, Hamann I, Wilkinson B. Defining urticarial dermatitis: a subset of dermal hypersensitivity reaction pattern. Arch Dermatol. 2006;142:29–34.
14. Bahrami S, Malone JC, Webb KG, Callen JP. Tissue eosinophilia as an indicator of drug-induced cutaneous small-vessel vasculitis. Arch Dermatol. 2006;142:155–61.
15. Wigley JEM. Sarcoid of Boeck? Eosinophilic granuloma. Br J Dermatol. 1945;57:68–9.
16. Pinkus H. Granuloma faciale. Dermatologica. 1952;105:85–99.
17. Smoller BR, Bortz J. Immunophenotypic analysis suggests that granuloma faciale is a gamma-interferon-mediated process. J Cutan Pathol. 1993;20: 442–6.
18. Pedace FJ, Perry HO. Granuloma faciale. Arch Dermatol. 1966;94:387–95.
19. Rusin LJ, Dubin HV, Taylor WB. Disseminated granuloma faciale. Arch Dermatol. 1976;112:1575–7.
20. Ortonne N, Wechsler J, Bagot M, et al. Granuloma faciale: a clinicopathologic study of 66 patients. J Am Acad Dermatol. 2005;53:1002–9.
21. De D, Kanwar AJ, Radotra BD, Gupta S. Extrafacial granuloma faciale: report of a case. J Eur Acad Dermatol Venereol. 2007;21:1284–6.
22. Ofuji S, Furukawa F, Miyachi Y, Ohno S. Papuloerythroderma. Dermatologica. 1984;169:125–30.
23. Mutluer S, Yerebakan O, Alpsoy E, et al. Treatment of papuloerythroderma of Ofuji with Re-PUVA: a case report and review of the therapy. J Eur Acad Dermatol Venereol. 2004;18;480–3.
24. Wells GC, Smith NP. Eosinophilic cellulitis. Br J Dermatol. 1979;100:101–9.
25. Spigel GT, Winkelmann RK. Wells' syndrome. Recurrent granulomatous dermatitis with eosinophilia. Arch Dermatol. 1979;115:611–13.
26. Simon HU, Plotz S, Simon D, et al. Interleukin-2 primes eosinophil degranulation in hypereosinophilia and Wells' syndrome. Eur J Immunol. 2003;33:834–9.
27. Koga C, Sugita K, Kabashima K, et al. High responses of peripheral lymphocytes to mosquito salivary gland extracts in patients with Wells syndrome. J Am Acad Dermatol. 2010;63:160–1.
28. Fisher GB, Greer KE, Cooper PH. Eosinophilic cellulitis (Wells' syndrome). Int J Dermatol. 1985;24:101–7.
29. Brehmer-Andersson E, Kaaman T, Skog E, Frithz A. The histopathogenesis of the flame figure in Wells' syndrome based on five cases. Acta Derm Venereol. 1986;66:213–19.
30. Peters MS, Schroeter AL, Gleich GJ. Immunofluorescence identification of eosinophil granule major basic protein in the flame figures of Wells' syndrome. Br J Dermatol. 1983;109:141–8.
31. Aberer W, Konrad K, Wolff K. Wells' syndrome is a distinctive disease entity and not a histologic diagnosis. J Am Acad Dermatol. 1988;18:105–14.
32. Gotlib J, Cools J, Malone JM III, et al. The FIP1L1–PDGFRalpha fusion tyrosine kinase in hypereosinophilic syndrome and chronic eosinophilic leukemia: implications for diagnosis, classification, and management. Blood. 2004;103:2879–91.
33. Klion AD, Bochner BS, Gleich GJ, et al. Approaches to the treatment of hypereosinophilic syndromes: a workshop summary report. J Allergy Clin Immunol. 2006;117:1292–302.
34. Simon D, Simon HU. Eosinophilic disorders. J Allergy Clin Immunol. 2007;119:1291–300.
34a. Klion AD, Alam R, eds. Hypereosinophilic syndromes. Immunol Allergy Clin NA. 2007;27:334–570.
35. Chusid MJ, Dale DC, West BC, Wolff SM. The hypereosinophilic syndrome: analysis of fourteen cases with review of the literature. Medicine (Baltimore). 1975;54:1–27.
35a. Gleich GJ. Mechanisms of eosinophil-associated inflammation. J Allergy Clin Immunol. 2000;105: 651–63.
36. Gleich GJ, Leiferman KM. The hypereosinophilic syndromes: still more heterogeneity. Curr Opin Immunol. 2005;17:1–6.
37. Oliver JW, Deol I, Morgan DL, Tonk VS. Chronic eosinophilic leukemia and hypereosinophilic syndromes. Cancer Genet Cytogenet. 1998;107:111–17.
38. Roufosse F, Weller PF. Practical approach to the patient with hypereosinophilia. J Allergy Clin Immunol. 2010;126:39–44.
39. Leiferman KM, Gleich GJ. Hypereosinophilic syndrome: case presentation and update. J Allergy Clin Immunol. 2004:113:50–8.
40. Gotlib J. Eosinophilic myeloid disorders: new classification and novel therapeutic strategies. Current Opin Hematol. 2010;17:117–24.
41. Pardanani A, Brockman SR, Paternoster SF, et al. FIP1L1–PDGFRA fusion: prevalence and clinicopathologic correlates in 89 consecutive patients with moderate to severe eosinophilia. Blood. 2004;104:3038–45.
42. Kazmierowski JA, Chusid MJ, Parrillo JE, et al. Dermatologic manifestations of the hypereosinophilic syndrome. Arch Dermatol. 1978;114:531–5.
43. Leiferman KM, O'Duffy JD, Perry HO, et al. Recurrent incapacitating mucosal ulcerations. A prodrome of the hypereosinophilic syndrome. JAMA. 1982;247: 1018–20.
44. Gleich GJ, Leiferman KM. The hypereosinophilic syndromes: current concepts and treatments. Br J Haematol. 2009;145:271–85.
44a. Ogbogu PU, Bochner BS, Butterfield JH, et al. Hypereosinophilic syndrome: a multicenter, retrospective analysis of clinical characteristics and response to therapy. J Allergy Clin Immunol. 2009;124:1319–25.
45. Plotz SG, Simon HU, Darsow U, et al. Use of an anti-interleukin-5 antibody in the hypereosinophilic syndrome with eosinophilic dermatitis. N Engl J Med. 2003;349:2334–9.
46. Rothenberg ME, Klion AD, Roufosse FE, et al., for the Mepolizumab HES Study Group. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. N Engl J Med. 2008;358:1215–28.

This page intentionally left blank

Neutrophilic Dermatoses 26

Samuel L Moschella and Mark DP Davis

The neutrophilic dermatoses constitute a heterogeneous but linked spectrum of diseases[1], with significant overlapping histopathologic findings and similar pathogenic mechanisms and therapeutic approaches. They are often associated with underlying internal diseases, which may have significant morbidity and mortality. Histologically, these disorders are characterized by perivascular and diffuse neutrophilic infiltrates without any identifiable infectious agents (Fig. 26.1). The cutaneous manifestations vary from vesiculopustules and plaques to nodules and ulcers. It is noteworthy that there may be several different types of lesions in the same patient. The dermatosis may be localized or more widespread, and, in an occasional patient, similar sterile neutrophilic infiltrates may occur in the eyes, joints, bones, lung, liver and lymph nodes. The neutrophilic infiltrate may be most prominent in the epidermis, dermis or even the panniculus. Distinct entities have been defined by the nature of their clinical and histologic presentations as well as their associated diseases.

NEUTROPHIL BIOLOGY

Granulocytes (neutrophils, eosinophils and basophils) are cells essential to our defense against microbes as well as other inflammatory responses. The neutrophil is a terminally differentiated, non-dividing cell which is packed with granules whose contents kill and degrade target microorganisms. Recent advances in our understanding of neutrophil biology include the molecular and cellular mechanisms responsible for their production and release from the bone marrow (e.g. chemokine CXC receptor 4; see Ch. 60); their recruitment, priming and activation within inflamed tissues (Table 26.1); and the events resulting in their removal.

Granulocytes, including neutrophils, originate in the bone marrow from pluripotent cells. In order to supply baseline requirements for sufficient numbers of circulating cells, neutrophils are produced within the bone marrow at a prodigious rate (>5–10 × 10^{10} neutrophils daily). The bone marrow also has the capacity to upregulate granulocyte production sharply in response to a number of stresses such as infection. Mature neutrophils circulate in the peripheral bloodstream for only 3–12 hours before migrating into tissues, where they survive for 2–3 days. Despite their short half-life within the bloodstream, neutrophils, unlike platelets and erythrocytes, appear to be removed from the circulation in a random rather than an age-related manner.

Transcriptional profiling studies suggest that granulocytes arise via the selective expression of a subset of transcription factors (e.g. Egr1, HoxB7, STAT3), granulocyte proteins (e.g. S100A8, S100A9, neutrophil elastase), and receptors (e.g. N-formyl-methionyl-leucyl-phenylalanine [FMLP], granulocyte–macrophage colony-stimulating factor). Differentiation from pluripotent stem cells requires 7–10 days, and during this period, under the influence of cytokines, neutrophils acquire their characteristic appearance and granules (primary, secondary and tertiary). The following stages of myeloid maturation are recognized: myeloblast, promyelocyte, myelocyte, metamyelocyte, band, and, finally, the segmented neutrophil. The progressive gain of differentiated characteristics is accompanied by a loss in the potential to proliferate, i.e. beyond the myelocyte stage, the cells are non-dividing. The intracellular granules acquired during maturation contain many of the enzymes that mediate the oxidative and non-oxidative killing functions of the neutrophil:

- primary (azurophilic) granules – acquired at the promyelocyte stage and their contents include myeloperoxidase, lysozyme, neutrophil elastase, defensins and myeloblastin
- secondary granules – acquired at the transition to the myelocyte stage and their contents include lactoferrin, neutrophil collagenase, neutrophil gelatinase, neutrophil gelatinase-associated lipocalin and transcobalamin 1
- tertiary granules – acquired during later stages of neutrophil maturation and contain neutrophil gelatinase.

Inflammation

A critical role of inflammation is to deliver neutrophils and other leukocytes to a site of injury and to activate these cells to perform their function of protecting the host against infection. Neutrophils are among the first cells to arrive at sites of inflammation; reasons for this include their abundance in the bloodstream and their rapid response to chemokines. When activated, neutrophils move at speeds up to 30 microns/min – the fastest cell in the body.

The motile responses of neutrophils to microbial infection include emigration out of the vasculature and movement toward the source of the inflammatory chemoattractant. This culminates in the phagocytic ingestion of opsonized microbes. In order to arrive at the site of infection, leukocytes must migrate out of the vasculature via margination, rolling, activation and tight adhesion (see Ch. 102). They then move toward the site of injury or infection (see Table 26.1) and eventually undergo degranulation then apoptosis.

The price to be paid for the defensive potency of neutrophils for destroying microbes and necrotic tissues is that they can injure normal tissue. During activation and phagocytosis, neutrophils release products (e.g. lysosomal enzymes, reactive oxygen intermediates, products of arachidonic acid metabolism [prostaglandins and leukotrienes]) not just within the phagolysosome, but also into the extracellular space. Endothelial injury and tissue damage ensue, thus contributing to a number of acute and chronic diseases that affect the skin as well as other organs.

SWEET'S SYNDROME

Synonym: ■ Acute febrile neutrophilic dermatosis

Key features

- Constitutional signs and symptoms such as fever and malaise
- Clinically, erythematous plaques that are occasionally bullous
- Histologically, dense perivascular neutrophilic infiltrate, edema and, infrequently, bullae; leukocytoclasia with minimal to no evidence of vasculitis
- Associated conditions include infections, malignancies (especially acute myelogenous leukemia), inflammatory bowel disease, autoimmune disorders, drugs and pregnancy

History

The prototype of the neutrophilic dermatoses is Sweet's syndrome. In 1964, Sweet[2] described eight middle-aged women who had an acute

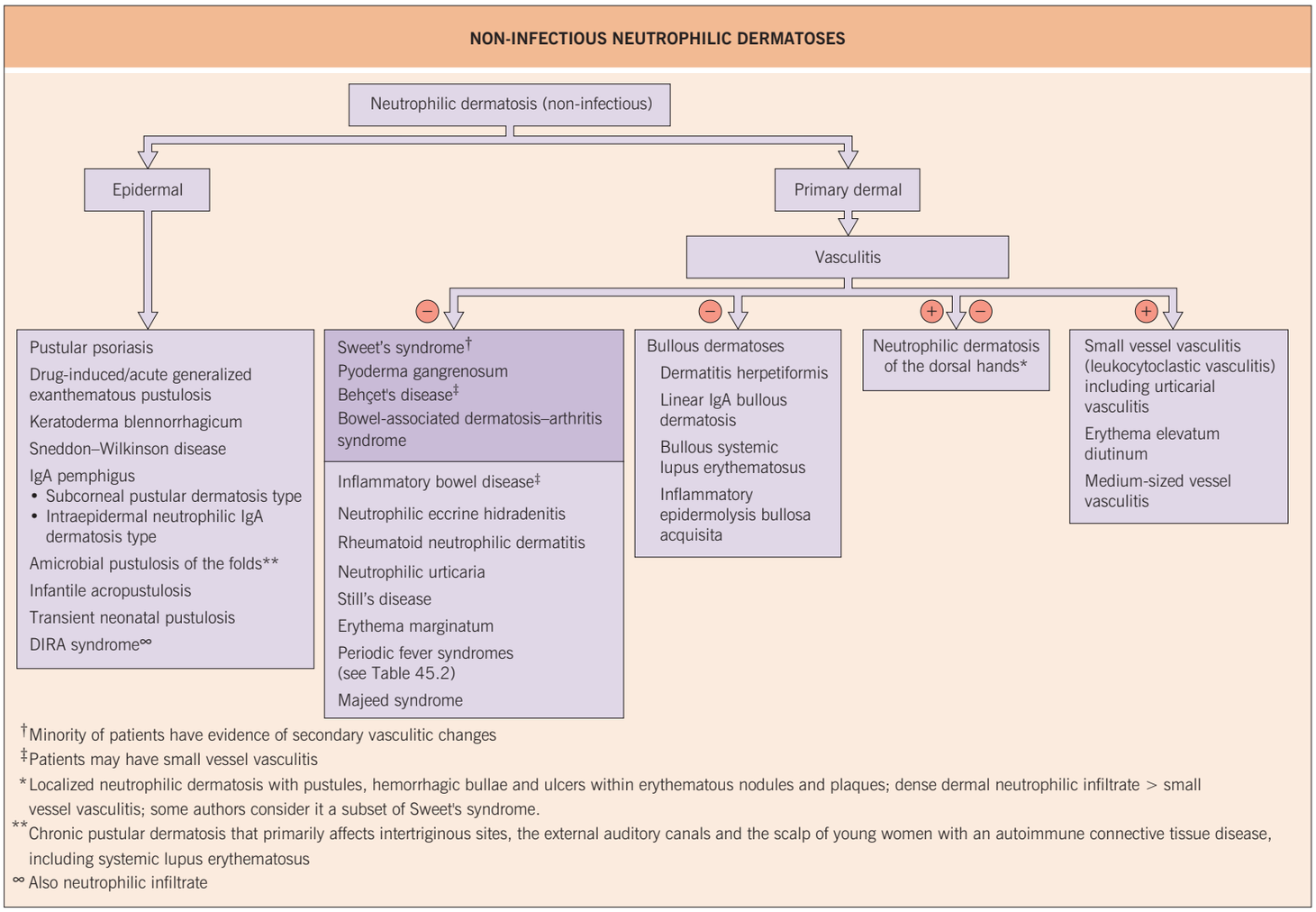


Fig. 26.1 Non-infectious neutrophilic dermatoses. Entities in the darker box are discussed in this chapter. DIRA, deficiency of the interleukin-1 receptor antagonist.

onset of fever and erythematous plaques associated with a nonspecific infection of the respiratory tract or gastrointestinal tract. Histologically, the skin lesions were characterized by a neutrophilic infiltrate. He named this constellation of findings "acute febrile neutrophilic dermatosis". In 1968, Whittle et al.[3] reported a similar case and named it "Sweet's syndrome".

Epidemiology

Sweet's syndrome is an uncommon disease, with a worldwide distribution and no obvious racial predilection, although the disorder appears to be more frequent in Japan. The average age of onset is 30–60 years, but infants, children and the elderly may be affected; there is a female predominance of 4 to 1. Up to 20% of patients have internal malignancies, and, in this subgroup, there is no female predominance. Drug-induced Sweet's syndrome occurs more frequently in women.

Pathogenesis

The pathogenesis of Sweet's syndrome is unknown. The association with underlying diseases suggests a hypersensitivity reaction. One hypothesis is a local or systemic dysregulation of cytokine secretion, involving interleukin (IL)-1, granulocyte colony-stimulating factor (G-CSF), granulocyte–macrophage colony-stimulating factor (GM-CSF) and interferon-γ[4,5].

Sweet's syndrome may be associated with inflammatory and autoimmune disorders (e.g. inflammatory bowel disease) or an underlying malignancy (paraneoplastic) as well as be drug-induced, postinfectious, or pregnancy-related. Up to 50% of patients may have idiopathic disease.

Clinical Features

The initial cutaneous lesions are tender, non-pruritic, erythematous plaques or papules (Fig. 26.2), which may enlarge or coalesce to form plaques with an uneven mammillated surface. Because of the pronounced associated edema (Fig. 26.3A), the lesions may have a pseudovesicular or pseudopustular appearance; however, some patients actually do develop vesiculation, bullae or pustules within their plaques. Occasionally, the plaques have a central yellowish discoloration creating a targetoid appearance (Fig. 26.3B). A facial erysipelas-like eruption has also been described. The vesiculobullous variant, which is most frequently associated with myelogenous leukemia, can progress to ulceration resembling superficial pyoderma gangrenosum (PG). In this form, there may be a single lesion or multiple, asymmetrically distributed lesions.

The cutaneous eruption of Sweet's syndrome favors the head (Fig. 26.4), neck and upper extremities (including the dorsal aspect of the hands), but can occur anywhere. In true malignancy-associated cases, the lesions tend to have a more widespread distribution. Papulonodules involving the lower legs may resemble erythema nodosum and, in fact, a small number of patients have concurrent erythema nodosum. As with PG, specific lesions may be initiated by wounding injuries such as needle sticks (pathergy). Oral lesions are uncommon, except in patients with hematologic disorders; initially they appear pseudopustular, and later ulcerate and appear as aphthae. The cutaneous eruption of Sweet's syndrome usually resolves spontaneously within 5–12 weeks but recurs in up to 30% of patients.

An upper respiratory tract infection or flu-like illness frequently precedes the development of the syndrome. Fever occurs in 40–80% of patients and can be intermittent. Extracutaneous involvement is also frequently seen (Fig. 26.5; Table 26.2).

NEUTROPHILS – THEIR RELATIONSHIP TO SITES OF INFLAMMATION
INTRAVASCULAR ADHESION, ACTIVATION AND MIGRATION
• Neutrophils are activated by chemoattractants, ligands of selectins, immune complexes and activated complement components to express β_2 integrins (e.g. LFA-1) that then adhere to ICAM-1 on endothelial cells (see Fig. 102.10) • Endothelial cells can be activated by thrombin, histamine, cytokines (e.g. IL-1, TNF-α), endotoxin and immune complex–C1q aggregates to express adhesive molecules (e.g. P-selectin, E-selectin, ICAM-1, VCAM-1) • Diapedesis represents migration of cells through inter-endothelial spaces towards a chemical concentration gradient (i.e. towards a site of infection or injury)
MIGRATION WITHIN TISSUE
• Leukocytes adhere to matrix proteins and move via chemotaxis (along a chemical gradient) • In response to the binding of chemoattractants (e.g. FMLP, C5a, PAF, LTB_4), neutrophils change their shape and crawl by alternating the extrusion and retraction of frontal lamellipodia
ACTIVATION WITHIN TISSUE
• Upon arrival at the site of injury or infection, neutrophils become activated via several signaling pathways (e.g. PKC, phospholipase A2, cytosolic [Ca^{2+}]) and surface receptors are expressed (e.g. Toll-like receptors, receptors for cytokines and opsonins) • Activation results in degranulation and secretion of lysosomal enzymes, activation of the oxidative burst, production of arachidonic acid metabolites and secretion of cytokines
PHAGOCYTOSIS
• Recognition and attachment of the particle to be ingested by the neutrophil is greatly enhanced by opsonization (coating by opsonins such as antibodies, complement or lectins), which targets it for phagocytosis • Binding of the particle to phagocytic neutrophil receptors initiates engulfment of the particle, which then fuses with a lysosomal granule, forming a phagolysosome
DESTRUCTION OF INGESTED MATERIAL
• Microbes are killed preferentially by oxygen-dependent, rather than oxygen-independent, mechanisms with formation of reactive oxygen intermediates • With discharge of the granule's contents into the phagolysosome, the neutrophil becomes degranulated • Neutrophils then rapidly undergo apoptosis and are ingested by macrophages

Table 26.1 Neutrophils – their relationship to sites of inflammation. FMLP, N-formyl-methionyl-leucyl-phenylalanine (formylated tripeptide isolated from bacteria); ICAM, intercellular adhesion molecule; IL, interleukin; LFA, lymphocyte function-associated antigen; LT, leukotriene; PAF, platelet-activating factor; PKC, phosphokinase C; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule.

Fig. 26.3 Sweet's syndrome. A Markedly edematous lesions on the upper back. **B** Sometimes, edematous lesions have a targetoid appearance. *A, Courtesy, Kalman Watsky, MD.*

Fig. 26.2 Sweet's syndrome. Pink papules coalescing into plaques on the neck of a patient with acute myelogenous leukemia.

Fig. 26.4 Sweet's syndrome. Multiple edematous and crusted papules and plaques. *Courtesy, Kalman Watsky, MD.*

Fig. 26.5 Sweet's syndrome. Obvious erythema and hemorrhage involving the sclera and conjunctiva in a patient with ocular involvement. *Courtesy, Kalman Watsky, MD.*

SYSTEMIC MANIFESTATIONS OF SWEET'S SYNDROME
COMMON (≥50%)
Fever
Leukocytosis
LESS COMMON (20–50%)
Arthralgias
Arthritis: asymmetric, non-erosive, favors knees and wrists
Myalgias
Ocular involvement: conjunctivitis, episcleritis, limbal nodules, iridocyclitis
UNCOMMON
Neutrophilic alveolitis: cough, dyspnea and pleurisy; radiographic findings include interstitial infiltrates, nodules, pleural effusions
Multifocal sterile osteomyelitis (SAPHO syndrome)
Renal involvement (e.g. mesangial glomerulonephritis): hematuria, proteinuria, renal insufficiency, acute renal failure
UNUSUAL/RARE
Hepatitis
Acute myositis
Aseptic meningitis, encephalitis
Pancreatitis
Gastrointestinal involvement

Table 26.2 Systemic manifestations of Sweet's syndrome[6–8]. SAPHO, *s*ynovitis, *ac*ne, *p*ustulosis, *h*yperostosis and *o*steitis.

Associated Diseases

Among the more frequently reported diseases or conditions associated with Sweet's syndrome are: infections such as upper respiratory tract infections due to *Streptococcus* spp. and gastrointestinal yersiniosis; hematologic malignancies (10–20% of cases), in particular acute myelogenous leukemia; solid tumors, e.g. carcinoma of the genitourinary tract, breast and colon; inflammatory bowel disease; and drugs such as G-CSF[7,9]. Less common associations are other infections (e.g. atypical mycobacteria, cytomegalovirus, chronic active hepatitis, HIV, BCG vaccination), Behçet's disease, autoimmune connective tissue diseases (e.g. systemic lupus erythematosus [SLE], rheumatoid arthritis, dermatomyositis, relapsing polychondritis, Sjögren's syndrome), autoimmune thyroid disease and sarcoidosis. Recently, there has been greater recognition of the association with SLE. Additional drugs reported to induce this neutrophilic dermatosis include furosemide, hydralazine, minocycline, trimethoprim–sulfamethoxazole, and all-*trans*-retinoic acid given in the setting of acute promyelocytic leukemia (see Ch. 21).

Pathology

The histopathologic features are contingent upon the type of cutaneous lesion sampled. The characteristic histologic presentation is a diffuse nodular and perivascular neutrophilic infiltrate without evidence of vasculitis (Fig. 26.6), although occasionally leukocytoclastic vasculitis (LCV) can be observed. Leukocytoclasia with endothelial swelling, but without the fibrinoid necrosis that fulfills the criteria for LCV, is the usual finding. Occasionally, the dermal infiltrate may extend into the subcutis, creating a septal or, less frequently, a lobular panniculitis.

In general, epidermal changes are not significant. However, neutrophils occasionally invade the epidermis, producing subcorneal pustules, and they may also infiltrate the adnexa. In the setting of significant edema, there can be epidermal spongiosis and sometimes reticular degeneration as well as intraepidermal and subepidermal vesiculation.

The histiocytoid variant is characterized by a dermal, and sometimes subcutaneous, infiltrate composed of histiocyte-like immature myeloid cells[10,11]. These cells have myeloperoxidase activity (Fig. 26.7) and must be distinguished from those of leukemia cutis.

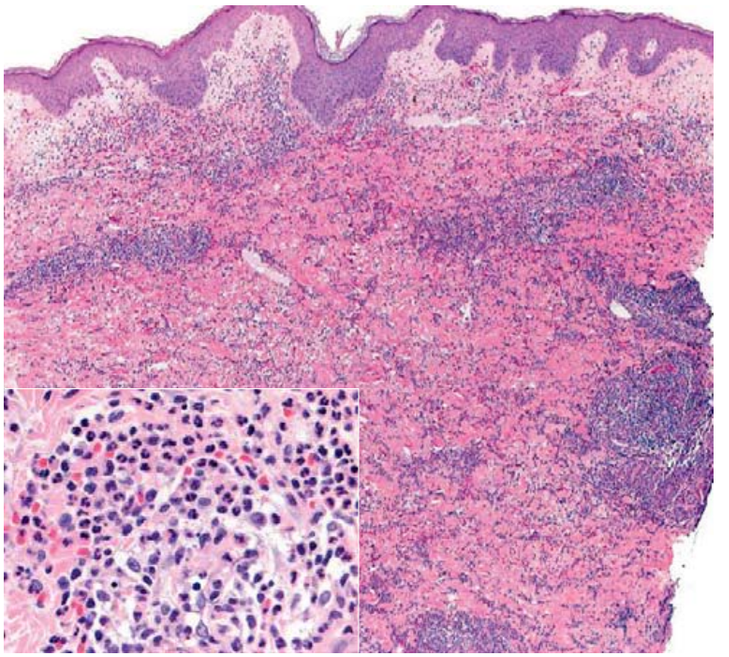


Fig. 26.6 Histologic features of Sweet's syndrome. Mild edema in the papillary dermis and a rather dense dermal infiltrate composed predominantly of neutrophils (insert). *Courtesy, Lorenzo Cerroni, MD.*

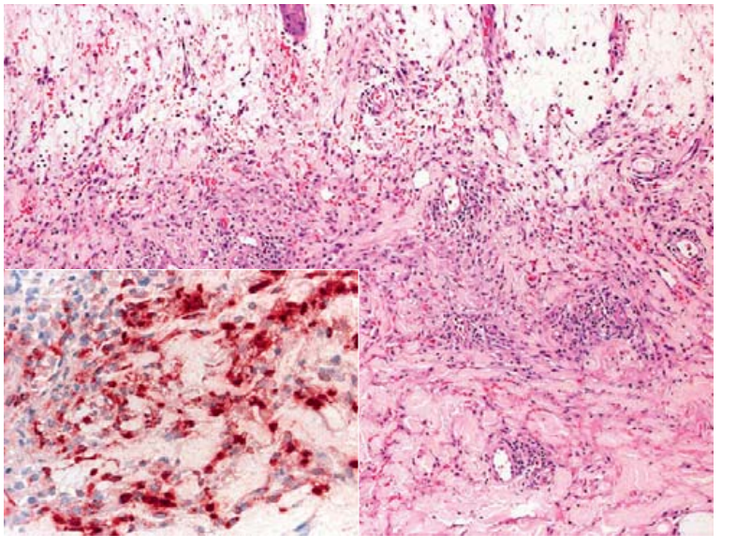


Fig. 26.7 Histologic features of histiocytoid Sweet's syndrome. There is edema in the papillary dermis as well as a dermal infiltrate composed of histiocytoid cells admixed with neutrophils, a few eosinophils, and hemorrhage. The histiocytoid cells represent immature myeloid cells and therefore have stained positively for myeloperoxidase (insert). *Courtesy, Lorenzo Cerroni, MD.*

CRITERIA FOR DIAGNOSIS OF SWEET'S SYNDROME
MAJOR CRITERIA
1. Abrupt onset of typical cutaneous lesions 2. Histopathology consistent with Sweet's syndrome
MINOR CRITERIA
1. Preceded by one of the associated infections or vaccinations; accompanied by one of the associated malignancies or inflammatory disorders; associated with drug exposure or pregnancy 2. Presence of fever and constitutional signs and symptoms 3. Leukocytosis 4. Excellent response to systemic corticosteroids

Table 26.3 Criteria for diagnosis of Sweet's syndrome[13]. Both of the major and two minor criteria are needed for the diagnosis.

Erythema nodosum-like lesions as well as PG can occur concomitantly in patients with Sweet's syndrome.

Differential Diagnosis

Although there are no specific diagnostic findings in this disease, a peripheral leukocytosis with neutrophilia, an elevated ESR and C-reactive protein, and an increased α_2-globulin fraction are frequently seen. In patients with an associated malignancy, there may be a high or low white cell count, lymphocytosis or lymphopenia, and thrombocytosis or thrombocytopenia. Although elevated serum levels of antineutrophil cytoplasmic antibody (ANCA) have been reported[12], there is no strong evidence that it is a serologic marker for this disease.

In 1986, Su and Liu[13] proposed two major and four minor criteria for the diagnosis of Sweet's syndrome, which have been widely accepted and are shown with minor revisions in Table 26.3. The differential diagnosis of the syndrome depends on the nature and age of the lesions and on the associated disease or condition (Table 26.4). Patients with neutrophilic dermatosis of the dorsal hands develop tender erythematous to violaceous plaques that may become bullous or ulcerative (Fig. 26.8)[14–16]. There is a spectrum of associated histologic features, from pustular vasculitis to those of PG or Sweet's syndrome. Hence, some authors consider this to be a variant of Sweet's syndrome.

In patients with hematologic malignancies, especially myelogenous leukemia, several neutrophilic dermatoses, e.g. Sweet's syndrome, atypical (bullous) pyoderma gangrenosum, and neutrophilic eccrine hidradenitis, can occur alone or in combination. The approach to such a patient is presented in Table 26.5.

Treatment

Sweet's syndrome is a benign condition which, if left untreated, may persist for weeks or months. Cutaneous lesions then involute spontaneously, leaving no scars. However, recurrences occur in approximately 30% of patients (with or without treatment) and occur even more often in those with hematologic disorders (approximately 50%). Although the early clinical presentation often suggests sepsis, antibiotics, in general, are ineffective. However, when the disease is associated with a recognized infection, such as that caused by *Streptococcus, Yersinia* or *Staphylococcus* spp., treatment of the underlying infection may result in improvement.

The most effective therapy for Sweet's syndrome is oral prednisone (0.5–1.0 mg/kg/day) for 4–6 weeks. There is prompt relief of not only the cutaneous but also the extracutaneous manifestations. In some patients, prolonged low-dose prednisone for an additional 2–3 months may be necessary to suppress recurrences. When the lesions are few and localized, topical superpotent or intralesional corticosteroids and/or topical calcineurin inhibitors may be helpful.

The major alternative drugs are potassium iodide (900 mg/day; see Table 100.6), dapsone (100–200 mg/day) and colchicine (1.5 mg/day). They can also be used as corticosteroid-sparing agents. Nonsteroidal anti-inflammatory drugs (e.g. indomethacin, naproxen, sulindac), clofazimine, cyclosporine, thalidomide and interferon-α have also been reported to lead to improvement of Sweet's syndrome. Evidence for any of these therapeutic regimens is based on small case series rather than double-blind placebo-controlled trials.

THE DIFFERENTIAL DIAGNOSIS OF SWEET'S SYNDROME
INFLAMMATORY DERMATOSES
• Pyoderma gangrenosum (bullous) • Neutrophilic eccrine hidradenitis • Rheumatoid neutrophilic dermatitis • Neutrophilic dermatosis of the dorsal hands* • Erythema multiforme • Urticaria with a prominent neutrophilic infiltrate (e.g. Schnitzler syndrome) • Urticarial vasculitis • Cutaneous small vessel vasculitis • Behçet's disease • Bowel-associated dermatosis–arthritis syndrome • Erythema elevatum diutinum • Panniculitis, including erythema nodosum • Halogenoderma (iododerma or bromoderma) • Wells' syndrome • Exaggerated arthropod bite reactions • Autoimmune connective tissue diseases – acute, subacute, tumid and neonatal lupus erythematosus • Granulomatous diseases – actinic granuloma, sarcoidosis, inflammatory granuloma annulare, interstitial granulomatous dermatitis • Periodic fever syndromes • Other neutrophilic dermatoses (see Fig. 26.1)
INFECTIONS
• Cellulitis, pyoderma, furunculosis • Septic vasculitis • Erythema migrans • "Deep" fungal infections (blastomycosis, cryptococcosis, coccidioidomycosis, histoplasmosis) • Mycobacterial infections (atypical and leprosy) • Leishmaniasis
NEOPLASMS
• Lymphoma cutis (T- and B-cell lymphomas including mycosis fungoides, cutaneous angiocentric lymphomas), leukemia cutis • Metastatic visceral carcinoma
*Some authors consider this a variant of Sweet's syndrome.

Table 26.4 The differential diagnosis of Sweet's syndrome[6,7].

Fig. 26.8 Neutrophilic dermatosis of the dorsal hands. This entity has overlapping clinical and histologic features with both Sweet's syndrome and pyoderma gangrenosum. Some patients have an associated pustular vasculitis. *Courtesy, Jean L Bolognia, MD.*

PYODERMA GANGRENOSUM

Key features

- Four major clinical forms: ulcerative, bullous, pustular and superficial granulomatous
- Initial lesion is often a pustule on an erythematous or violaceous base, an erythematous nodule, or a bulla
- Characteristic lesion is an ulcer with a necrotic undermined border; the base may be purulent or vegetative
- Histologically, a sterile dermal or adnexal abscess (without a vasculopathy) is seen in active, untreated, expanding lesions
- Associated illnesses include inflammatory bowel disease, arthritis, monoclonal gammopathies and other hematologic disorders

NEUTROPHILIC DERMATOSES ASSOCIATED WITH HEMATOLOGIC MALIGNANCIES			
	Sweet's syndrome	**Atypical (bullous) pyoderma gangrenosum**	**Neutrophilic eccrine hidradenitis**
1. Clinical manifestations			
a. Cutaneous	Painful plaques and nodules with occasional blisters and pustules within lesions Favors face, upper extremities and trunk Can recur (30–50% of patients)	Hemorrhagic bullae and superficial ulcerations Favors face and upper extremities (especially dorsal hands) Can recur	Erythematous edematous plaques and papules which may be painful, infrequent pustules Favors face, extremities, trunk Resolves spontaneously over ~2 weeks without scarring Can recur
b. Systemic	Fever, arthralgia or arthritis Multiorgan involvement (Table 26.2) Neutrophilia Elevated ESR	Systemic features usually absent	Fever, neutropenia*
2. Histopathology	Papillary edema with dermal neutrophilic infiltrate Histiocytoid variant – histiocyte-like immature myeloid cells	Subepidermal hemorrhagic bullae Pustules with neutrophilic dermal infiltrate	Neutrophilic† infiltrate about and within eccrine apparatus, necrosis of eccrine epithelium, and eccrine squamous syringometaplasia
3. Associations	Infections, hematologic malignancies, solid tumors, IBD, autoimmune diseases, pregnancy, G-CSF, all-*trans*-retinoic acid	Hematologic disorders, especially acute myelogenous leukemia and myelodysplasia, IBD, G-CSF	Leukemia with or without chemotherapy; post-chemotherapy for lymphoma and solid tumors; G-CSF; and rarely infections
4. Primary treatment (in addition to treatment of underlying disease)	Systemic corticosteroids (0.5–1 mg/kg/day for 4–6 weeks), potassium iodide (900 mg/day), dapsone (100–200 mg/day), colchicine (1.5 mg/day)	Systemic corticosteroids (Table 26.10)	None (spontaneous resolution)

*Usually In setting of chemotherapy.
†May be lymphocytic in setting of chemotherapy-induced neutropenia.

Table 26.5 Neutrophilic dermatoses associated with hematologic malignancies[7,17]. G-CSF, granulocyte colony-stimulating factor; IBD, inflammatory bowel disease.

Introduction

Pyoderma gangrenosum (PG) is an uncommon, chronic, recurrent, cutaneous ulcerative disease with a distinctive morphologic presentation. The laboratory and histopathologic findings can vary and therefore the diagnosis requires clinicopathologic correlation. This neutrophilic dermatosis is frequently associated with systemic disease[17–20].

History

In 1930, Brunsting, Goeckerman and O'Leary coined the term "pyoderma gangrenosum" and advanced the theory that it had an infectious etiology (streptococci and staphylococci)[18].

Epidemiology

PG is a global disease. It can occur at any age but most commonly afflicts women between 20 and 50 years of age. Fifty percent of patients have an underlying systemic disease, most commonly inflammatory bowel disease, arthritis or a hematologic disorder (e.g. IgA monoclonal gammopathy, acute myelogenous leukemia, myelodysplasia). Approximately 4% of cases of PG occur in infants and children.

Pathogenesis

Although the disease is idiopathic in 25–50% of patients, an underlying immunologic abnormality is currently favored, given its frequent association with systemic diseases that have a suspected autoimmune pathogenesis. Defects in cell-mediated immunity, neutrophil and monocyte function, and humoral immunity have been reported, but none of these findings have been demonstrated consistently and it is not clear whether they may represent an epiphenomenon[17]. Pathergy, which is a reflection of trivial trauma (Fig. 26.9), not only initiates the cutaneous lesions but also aggravates them, and is seen in 20–30% of patients with PG.

Clinical Features

Although the classic morphologic clinical presentation of PG is an ulcer, there are several variants (bullous, pustular and superficial granulomatous/vegetative) which differ by their clinical presentation, location and associated diseases (Table 26.6)[17]. Cutaneous lesions are painful and most frequently occur on the lower extremities, especially the pretibial area (Fig. 26.12A), but they can occur anywhere, including on mucous membranes and peristomal sites (Fig. 26.13A).

The lesions of PG usually begin as a tender papulopustule (Fig. 26.14) with surrounding erythematous or violaceous induration, an erythematous nodule, or a bulla on a violaceous base; the papulopustule may be

CLINICAL VARIANTS OF PYODERMA GANGRENOSUM
VESICULOBULLOUS (ALSO REFERRED TO AS ATYPICAL OR BULLOUS PG)
• Lesions favor the face and upper extremities, especially the dorsal hands • Clinical appearance overlaps with the superficial bullous variant of Sweet's syndrome (Fig. 26.10) • Occurs most commonly in the setting of acute myelogenous leukemia, myelodysplasia and myeloproliferative disorders such as chronic myelogenous leukemia
PUSTULAR
• Multiple, small, sterile pustules • Lesions usually regress without scarring, but can evolve into classic PG • Most commonly observed in patients with inflammatory bowel disease • Similar eruption may be seen in patients with Behçet's disease or bowel-associated dermatosis–arthritis syndrome
SUPERFICIAL GRANULOMATOUS PYODERMA
• Localized, superficial vegetative or ulcerative lesion[21], which favors the trunk and usually follows trauma (e.g. surgery) • Histologically, a superficial granulomatous response with a less intense neutrophilic infiltrate • Responds to less aggressive anti-inflammatory therapy • Controversy as to whether it is a variant of PG, a separate disorder, or related to Wegener's granulomatosis
PYOSTOMATITIS VEGETANS
• Chronic, vegetative, sterile pyoderma of the labial and buccal mucosa (Fig. 26.11A) • May be associated with vegetative or ulcerative cutaneous PG (Fig. 26.11B) • Seen in patients with inflammatory bowel disease

Table 26.6 Clinical variants of pyoderma gangrenosum (PG).

Fig. 26.9 Pathergy in a patient with pyoderma gangrenosum. The lesion appeared at the site of an intravenous catheter.

Fig. 26.10 Bullous pyoderma gangrenosum. This patient had ulcerative colitis.

Fig. 26.11 Variants of pyoderma gangrenosum. **A** Pyostomatitis vegetans in a patient with ulcerative colitis. **B** Vegetative form following trauma to the skin.

Fig. 26.12 Classic ulcerative pyoderma gangrenosum. A The edge of this ulceration on the shin is undermined with a violet–gray color as well as an inflammatory rim. Note the central scarring. **B** In addition to an overhanging border, this deep ulceration on the elbow has a purulent base.

follicular. All these lesions then undergo necrosis leading to a central shallow or deep ulcer; loss of tissue can expose underlying tendons or muscles. When fully developed, the ulcer has a purulent base with an irregular, undermined and overhanging, gunmetal-colored border which extends centrifugally (see Fig. 26.12). Re-epithelialization occurs from the margins and the ulcers heal with atrophic cribriform pigmented scars.

In PG, the number of ulcers can vary from one to over a dozen, and sometimes they coalesce (Fig. 26.13B). Although the ulcers are classically described as rapidly expanding, some are less inflammatory and expand rather slowly. The latter require less aggressive therapeutic interventions (see below).

In patients with hematologic disorders or in drug-induced cases, the clinical course is characterized by an acute onset of hemorrhagic or purulent bullous lesions, with a more widespread distribution that can include the dorsal hands. These lesions rapidly necrose and are often associated with fever and signs of toxicity. In those patients with associated inflammatory diseases, such as inflammatory bowel disease or arthritis, the more characteristic presentation is a chronic, slowly enlarging ulcer with excessive granulation tissue in its base and sometimes with evidence of spontaneous regression.

Clinical variants have been described based on the clinical presentation (see Table 26.6) or the location of the lesion (e.g. genital, peristomal[22]) or the age of the afflicted[19]. While the clinical appearance of PG in children is similar to that in adults, the lesions more frequently involve the head and anogenital region[23]. As with Sweet's syndrome,

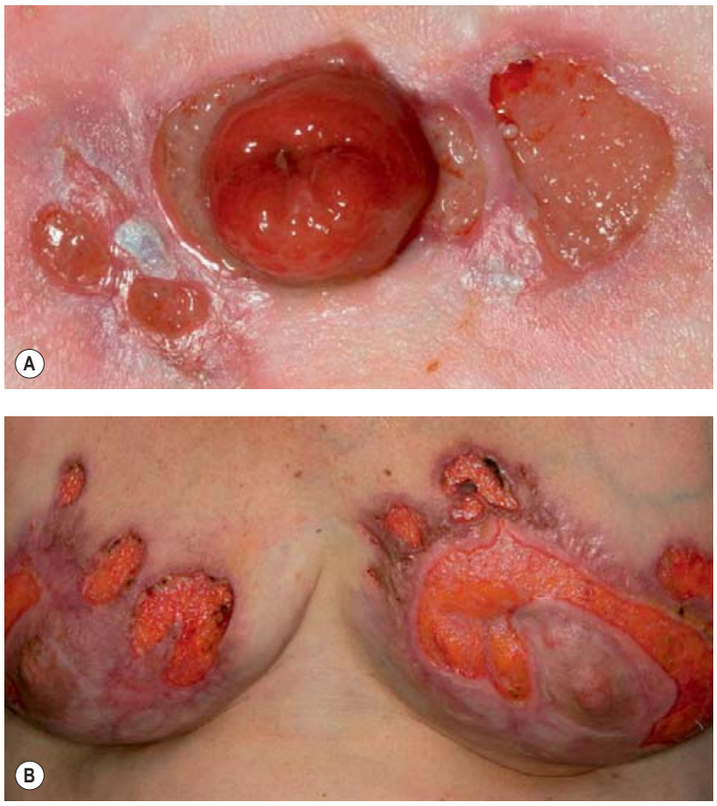


Fig. 26.13 Peristomal and postsurgical pyoderma gangrenosum (PG). **A** Multiple ulcers surround an ileostomy (following a total proctocolectomy) in a patient with refractory chronic ulcerative colitis. While periostomal PG occurs most commonly following intestinal resection of inflammatory bowel disease, it can also follow resection of gastrointestinal or bladder carcinoma. **B** Multiple ulcerations of the breasts following breast reduction. Because the original diagnosis postoperatively was soft tissue infection, multiple debridements had been performed and systemic antibiotics administered.

Fig. 26.14 The earliest clinical lesion in pyoderma gangrenosum is a pustule with an inflammatory base. This patient had Crohn's disease.

Fig. 26.15 Pyoderma gangrenosum in a patient with PAPA syndrome. Individuals with this autosomal dominant disorder have pyogenic sterile arthritis, pyoderma gangrenosum and acne. *Courtesy, Maria Chanco Turner, MD.*

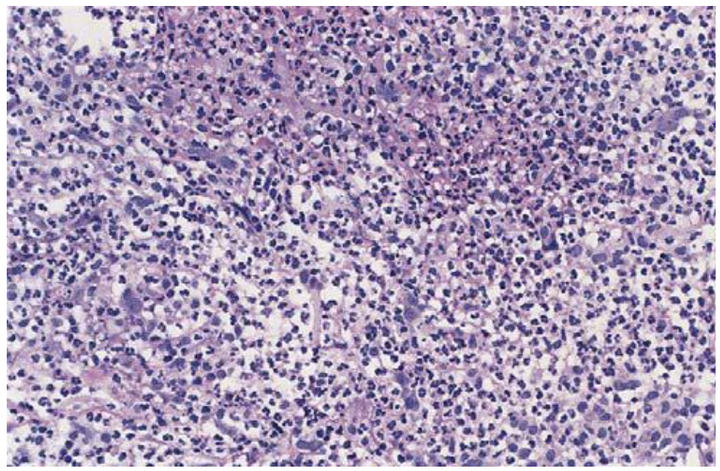


Fig. 26.16 Pyoderma gangrenosum. In expanding untreated lesions, a diffuse infiltrate of neutrophils is present at the base of an ulceration. *Courtesy, Ronald P Rapini, MD.*

extramucocutaneous sterile neutrophilic infiltrates have been reported in the bones, lung, liver, pancreas, spleen, kidneys and CNS of patients with PG[24].

Associated Diseases

Between 50% and 70% of patients with PG have an antecedent, coincident or subsequent associated disease or condition. The most common associations are inflammatory bowel disease (ulcerative colitis or Crohn's disease, 20–30%), arthritis (seronegative arthritis, spondylitis of inflammatory bowel disease or rheumatoid arthritis, 20%), and hematologic disease (in particular, acute and chronic myelogenous leukemia, hairy cell leukemia, myelodysplasia and monoclonal gammopathy, 15–25%). A monoclonal gammopathy is seen in up to 15% of patients and is often composed of IgA. Individuals with the *p*yogenic sterile *a*rthritis, *P*G and *a*cne (PAPA) syndrome (Fig. 26.15) have been shown to have mutations in the gene that encodes CD2-binding protein 1, presumably leading to abnormal inflammatory responses. Other so-called neutrophilic dermatoses that have been reported in association with PG are subcorneal pustular dermatosis, Behçet's disease and Sweet's syndrome.

Pathology

The histopathology of PG can be nonspecific, especially when the disease is partially treated or minimally inflamed, and therefore be non-diagnostic. In early lesions, there is a neutrophilic vascular reaction, which can be folliculocentric. Neutrophilic infiltrates, often with leukocytoclasia, are seen in active, untreated, expanding lesions (Fig. 26.16). In fully developed ulcers, there is marked tissue necrosis with surrounding mononuclear cell infiltrates. In most patients with typical PG, chronic ulcers have fibrosing inflammation at the edge of the ulcer bed. In one study, up to 10% of the patients who fulfilled the authors' diagnostic criteria for PG, rather than other entities in the differential diagnosis of PG, had histologic features inconsistent with PG[20]. This most likely results from a delay in suspecting the diagnosis of PG, with resultant sampling of chronic lesions that have been partially treated.

Differential Diagnosis

Since there are no specific or diagnostic laboratory tests or histopathologic features and some of the associated conditions may not have declared themselves, the physician must exclude other causes of ulceration of the skin and search for a treatable associated disease. PG can be misdiagnosed: of 157 consecutive patients seen at one tertiary care

PROPOSED DIAGNOSTIC CRITERIA FOR CLASSIC ULCERATIVE PYODERMA GANGRENOSUM
MAJOR CRITERIA
1. Rapid[a] progression of a painful[b], necrolytic cutaneous ulcer[c] with an irregular, violaceous and undermined border
2. Other causes of cutaneous ulceration have been excluded[d]
MINOR CRITERIA
1. History suggestive of pathergy[e] or clinical finding of cribriform scarring
2. Systemic diseases associated with pyodermal gangrenosum[f]
3. Histopathologic findings (sterile dermal neutrophilia, ± mixed inflammation, ± lymphocytic vasculitis)
4. Treatment response (rapid response to systemic corticosteroids)[g]
[a]Characteristic margin expansion of 1 to 2 cm per day, or a 50% increase in ulcer size within 1 month.
[b]Pain is usually out of proportion to the size of the ulceration.
[c]Typically preceded by a papule, pustule or bulla.
[d]Usually necessitates skin biopsy and additional evaluation (see Table 26.8) to exclude other causes (see Table 26.9).
[e]Ulcer development at sites of minor cutaneous trauma.
[f]Inflammatory bowel disease, arthritis, IgA gammopathy, or underlying malignancy.
[g]Generally responds to prednisone (1–2 mg/kg/day) or another corticosteroid at an equivalent dosage, with a 50% decrease in size within 1 month.

Table 26.7 Proposed diagnostic criteria for classic ulcerative pyoderma gangrenosum. Diagnosis requires both of the major criteria and at least two minor criteria[26].

EVALUATION OF A PATIENT WITH PRESUMED PYODERMA GANGRENOSUM
1. Thorough history and physical examination; review medications
2. Sterile skin biopsy of *active* skin lesion with sufficient depth (panniculus) and sufficient tissue for special stains and culture (bacterial, mycobacterial, fungal and viral). Possibility of future additional biopsies for immunofluorescence or PCR studies
3. Gastrointestinal tract studies – stool for occult blood and parasites, colonoscopy, biopsy, radiography, liver function tests and, if indicated, hepatitis evaluation
4. Hematologic studies – complete blood and platelet count, peripheral blood smear, and if indicated, bone marrow examination
5. Serologic studies – serum protein electrophoresis, immunofixation electrophoresis, antinuclear antibodies, antiphospholipid antibodies, ANCA antibodies, VDRL
6. Chest X-ray and urinalysis

Table 26.8 Evaluation of a patient with presumed pyoderma gangrenosum[17,20]. ANCA, antineutrophil cytoplasmic antibodies; PCR, polymerase chain reaction.

medical center with a referral diagnosis of resistant ulcers due to PG, 15 (approximately 10%) were found not to have PG[25]. Criteria for the diagnosis of classic PG have been proposed (Table 26.7)[27], but to date have not been validated. They basically serve as a guide and no one criterion can be used in isolation because each is seen in multiple disorders. The evaluation of a patient with presumed PG is summarized in Table 26.8.

The differential diagnosis clearly depends on the evolutionary stage of the process – the initial inflammatory process characterized by erythematous papules, pustules, plaques and nodules versus the later characteristic vegetative or ulcerative lesions (Table 26.9).

Treatment

There is neither specific nor uniformly effective therapy for PG. The nature and intensity of the therapeutic approach depend on the number, size and depth of the lesions, the rate of expansion and appearance of new lesions, the associated disorder, the medical status of the patient, and the risk and patient tolerance of prolonged therapy. The therapeutic goal is to reduce the inflammatory process of the wound in order to promote healing and reduce pain and to control the contributing underlying disease (especially leukemias and inflammatory bowel disease) with the least adverse side effects. The standard treatment of PG is local or combined local and systemic corticosteroid therapy with or without adjunctive systemic therapy[28].

THE DIFFERENTIAL DIAGNOSIS OF PYODERMA GANGRENOSUM
EARLY INFLAMMATORY NON-ULCERATIVE STAGE (PAPULES, PUSTULES, PLAQUES OR NODULES)
• Follicular infections (folliculitis, furuncle, carbuncle of bacterial, fungal or viral origin)
• Cellulitis or cellulitis-like lesion (bacterial, mycobacterial or fungal origin)
• Insect bite reaction
• Cutaneous T- and B-cell lymphomas
• Halogenoderma (iododerma or bromoderma)
• Panniculitides (inflammatory, infectious, metabolic, neoplastic)
• Cutaneous polyarteritis nodosa
• Sweet's syndrome (see Table 26.4 for additional entities)
• Behçet's disease
• Bowel-associated dermatosis–arthritis syndrome
LATER ULCERATIVE OR VEGETATIVE STAGE
• Infections – streptococcal synergistic gangrene, botryomycosis, ecthyma gangrenosum, gummatous treponemal ulcers, cutaneous lesions of the deep mycoses (e.g. blastomycosis, coccidioidomycosis, paracoccidioidomycosis, chromomycosis) and atypical and typical mycobacterial infections
• Parasitic infections – leishmaniasis, amebiasis, schistosomiasis
• Vascular diseases – ulcerations due to venous hypertension, arterial insufficiency, non-septic emboli, hemoglobinopathies, and thrombosis (secondary to hypercoagulability; see Ch. 105)
• Vasculitis – cutaneous polyarteritis nodosa, microscopic polyangiitis, granulomatous vasculitides (Wegener's granulomatosis, Churg–Strauss syndrome, temporal arteritis), autoimmune connective tissue disease (systemic lupus erythematosus, rheumatoid arthritis) and Behçet's disease
• Malignancy – squamous cell carcinoma, basal cell carcinoma, cutaneous T- and B-cell lymphoma
• Miscellaneous – brown recluse spider bite, ulcerative necrobiosis lipoidica, pemphigus vegetans of the Hallopeau or Neumann type, blastomycosis-like pyoderma, non-healing surgical wound, factitious ulcers, ulcers in patients with Chédiak–Higashi syndrome and leukocyte adhesion deficiency

Table 26.9 The differential diagnosis of pyoderma gangrenosum (PG)[17,20]. In a series of 95 patients *misdiagnosed* with PG, the most common etiologies were vascular (venous or arterial; 28), vasculitis (21), malignancy (16), infection (14) and drug-induced or exogenous tissue injury (13)[25].

Systemic corticosteroids have generally been the most predictable and effective medication when delivered in adequate dosage. Unfortunately, the more resistant lesions require more protracted therapy (>3 months) at a higher than desirable dosage, thus inviting adverse side effects. Such patients should be closely monitored and should receive supplemental calcium (1500 mg/day), vitamin D (800 IU/day) and, in most instances, bisphosphonates (see Ch. 125). Additional therapies, e.g. systemic calcineurin inhibitors, TNF-α inhibitors, are outlined in Table 26.10.

BEHÇET'S DISEASE

Key features

- A multisystem, polysymptomatic disease
- Diagnosis is based on International Study Group criteria of recurrent oral ulceration, recurrent genital ulceration, ocular abnormalities (e.g. uveitis, retinal vasculitis) and cutaneous lesions
- Cutaneous findings range from sterile papulopustules and palpable purpura to erythema nodosum-like lesions
- Histologically, a neutrophilic angiocentric infiltrate with leukocytoclastic (early) or lymphocytic (late) vasculitis is the characteristic finding

Introduction

Behçet's disease is a multisystem, polysymptomatic disease with unpredictable exacerbations and remissions[30–33]. All organs of the body can be affected concomitantly or consecutively. As a result, all subspecialties can be involved in the care of these patients.

THERAPEUTIC LADDER FOR THE TREATMENT OF PYODERMA GANGRENOSUM		
Treatment	**Dose**	**Level of evidence**
INFLAMMATORY DISEASE		
Mild disease and/or adjunctive therapy		
Superpotent topical corticosteroids		3
Intralesional corticosteroids		2
Topical tacrolimus		2
Oral antibiotics (e.g. sulfonamides, minocycline)		2
Colchicine	0.6 mg po thrice daily	3
Dapsone	50–150 mg po daily	3
Combination colchicine/dapsone		3
Clofazimine	100–400 mg po daily	2
Other (e.g. oral potassium iodide, intralesional cyclosporine, topical cromolyn sodium, nicotine patch or cream)		3
More severe disease		
Prednisone	60–120 mg po daily usual starting dose (including split-dose), with taper to alternate days	2
Methylprednisolone	1 g daily for 3–5 days (IV pulse)*	3
Thalidomide†	50–150 mg po nightly	2
Cyclosporine	2.5–5 mg/kg po daily	2
Tacrolimus	0.1–0.2 mg/kg po daily	3
TNF-α inhibitors‡	Infliximab 5 mg/kg IV at weeks 0, 2 and 6; adalimumab 80 mg sc as initial dose then 40 mg sc weekly or every other week; etanercept 50–100 mg sc weekly (in 1 or 2 doses)	1 (infliximab§); 3 (adalimumab); 3 (etanercept)
Methotrexate¶	2.5–25 mg po or IM weekly	3
Azathioprine¶	50–100 mg po twice daily	3
Mycophenolate mofetil¶	1–1.5 g po twice daily	3
Cyclophosphamide	Variable oral (50–200 g daily) or IV pulse (500–1000 mg monthly) dosing	3
Chlorambucil	4–6 mg po daily	3
IVIg	2–3 g/kg IV monthly (given over 2–5 consecutive days)	3
Granulocyte apheresis, plasmapheresis		3
Total colectomy (severe chronic ulcerative colitis)		3
NON-INFLAMMATORY DISEASE		
• Bio-occlusive dressings • Compression, limb elevation		

*Followed by daily oral prednisone.
†Especially in patients with Behçet's disease.
‡Especially in patients with inflammatory bowel disease.
§50–70% response rate.
¶Often used in combination with other agents or as maintenance therapy.

Table 26.10 Therapeutic ladder for the treatment of pyoderma gangrenosum[28,29]. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

History

In the fifth century BC, Hippocrates first described the symptomatology of this disease, and in 1936, Behçet reported a patient with eye disease and orogenital ulcers.

Epidemiology

Most patients are from Japan, the Middle East or the Mediterranean basin. Turkey has the highest prevalence, at 80 per 100 000. In Japan, it is 10 per 100 000; in the UK, 0.64 per 100 000; and in the US, 0.12 per 100 000[31]. In Japan and Korea, the incidence of Behçet's disease is greater in women, but in Middle Eastern countries it is seen more frequently in men. The peak incidence is between 20 and 35 years of age. The familial form usually comprises 2–5% of cases, except in the Middle East, where it represents 10–15%.

Pathogenesis

Epidemiologic evidence suggests that genetic and environmental factors contribute to the development of this disease. More than 80% of Asian patients have the HLA-B51 allele, but it is present in only about 15% of Caucasians from Western countries; thus, the allele appears to be an important risk factor for those who live along the Silk Road.

Earlier theories of pathogenesis entertained the possibility of an infectious etiology (viral or bacterial), but subsequent evidence failed to substantiate this hypothesis. Among the infectious agents investigated

were HSV, hepatitis C virus and parvovirus B19; more recently, in Japan, streptococcal strains were thought to be responsible[31]. These infections may potentially trigger an immunoregulatory defect in the genetically predisposed.

The pathomechanisms of Behçet's disease involve vascular injuries and autoimmune responses. Circulating immune complexes and neutrophils appear to be responsible for the mucocutaneous lesions that are characterized histologically by a neutrophilic vascular reaction or even leukocytoclastic vasculitis. The neutrophils of Behçet's disease produce an increased amount of superoxides and an excess of lysosomal enzymes, and they have enhanced chemotaxis, all of which bring about tissue injury. The elevated circulating levels of TNF-α, IL-1β and IL-8 may result in activation of neutrophils and augmentation of cellular interactions between neutrophils and endothelial cells. Clonal expansion of autoreactive T cells that recognize a peptide derived from heat shock protein 60 has also been described.

Clinical Features and Differential Diagnosis

Mucocutaneous involvement

Aphthous stomatitis, the major criterion, is frequently the first symptom of Behçet's disease (65–70% of patients), and it is almost always present during the course of the disease. The aphthosis may precede the other manifestations by many years, but a dramatic increase in severity often occurs in concert with the onset of other features. Oral ulcers begin as an erythematous papule, which develops a yellowish pseudomembrane and then forms a painful non-scarring ulcer (Fig. 26.17A), which heals over a period of weeks. The ulcers are indistinguishable from those that occur with complex aphthosis or inflammatory bowel disease[34] and must be differentiated from other causes of oral ulcers (e.g. pemphigus vulgaris). The genital aphthae involve primarily the scrotum and penis in men and the vulva in women. Compared to oral lesions, the anogenital aphthae tend to be larger with irregular margins (Fig. 26.17B), and they are more painful. Distinction of genital lesions from lesions of HSV requires viral culture, direct fluorescent antibody stain or PCR.

Among the primary cutaneous lesions are acral and facial sterile vesicopustules as well as pustular and/or purpuric papules[35]. Although the papulopustular lesions are usually not folliculocentric, they have nonetheless been described as acneiform, leading to some confusion (see Pathology below). The erythema nodosum-like lesions favor women and appear on their legs and buttocks, and less often on the face and neck; they have to be differentiated from both superficial thrombophlebitis (which occurs in 30% of patients with Behçet's disease) and erythema nodosum (which is seen in patients with Behçet's disease as well). Pathergy also occurs, as in pyoderma gangrenosum. Patients with features of both Behçet's disease and relapsing polychondritis have been described and reported as MAGIC (*m*outh *a*nd *g*enital *u*lcers with *i*nflamed *c*artilage) syndrome (see Ch. 45)[36].

Systemic involvement

Systemic manifestations are summarized in Table 26.11 and distinctions between Behçet's disease with bowel involvement and inflammatory bowel disease are outlined in Table 26.12.

Fig. 26.17 Behçet's disease: mucocutaneous lesions. A Oral aphthosis. **B** Perianal aphthosis.

SYSTEMIC MANIFESTATIONS OF BEHÇET'S DISEASE	
OCULAR (LEADING CAUSE OF MORBIDITY)[30,32,33]	**NEUROLOGIC**
• Occurs in 90% of patients; favors men, in whom it is more severe • Can be painful and may lead to blindness • Retinal vasculitis (more frequently associated with blindness) • Posterior uveitis (most characteristic ocular finding) • Anterior uveitis (Fig. 26.18), hypopyon • Secondary glaucoma, cataracts • Conjunctivitis, scleritis, keratitis, vitreous hemorrhage, optic neuritis	• Usually appears later during the evolution of the disease • Associated with a poor prognosis • Acute meningo-encephalitis which may resolve spontaneously • Cranial nerve palsies • Brainstem lesions that can induce swallowing difficulties, laughter and crying • Pyramidal or extrapyramidal signs
JOINTS	**VASCULAR**
• Approximately 50% of patients develop arthritis • In majority (~80% of patients), duration of attacks is <2 months • Mono- or poly-arthritic and non-erosive • Most commonly knees, wrists and ankles	• Aneurysmal or occlusive arterial disease • Superficial or deep venous thrombosis
	CARDIOPULMONARY
	• Coronary arteritis, valvular disease, myocarditis • Recurrent ventricular arrhythmias • Pulmonary artery aneurysms
GASTROINTESTINAL	**RENAL**
• Abdominal pain and/or hemorrhage may be difficult to distinguish from IBD (see Table 26.12) • Ulcerations* develop within the small bowel (in particular the ileocecal region) as well as the transverse and ascending colon and esophagus; perforation can occur	• Glomerulonephritis
*Resemble anogenital aphthae.	

Table 26.11 Systemic manifestations of Behçet's disease. IBD, inflammatory bowel disease.

Fig. 26.18 Behçet's disease: systemic involvement. Iritis and cutaneous pustular vasculitis.

NEUTROPHILIC DERMATOSES ASSOCIATED WITH BOWEL DISORDERS				
		Behçet's disease	**Bowel-associated dermatosis–arthritis syndrome**	**Inflammatory bowel disease**
Cutaneous lesions	Aphthosis	+ (oral and anogenital)	+ (oral)	+ (oral)
	Vesicopustular dermatosis	+	+	+
	Sweet's syndrome-like dermatosis	+	–	+
	Pyoderma gangrenosum	+	–	+
	Pyostomatitis vegetans	–	–	+
	Pyoderma vegetans	–	–	+
	Vasculitis	+	±	+ (including cutaneous polyarteritis)
	Superficial thrombophlebitis	+	–	+
	Erythema nodosum	+	+	+
	Neutrophilic lobular panniculitis	+	+	+
	Pathergy	+	–	+
Systemic signs and symptoms	Fever/flu-like syndrome	+	+	+ (fever)
	Ocular involvement	+	–	+ (iritis)
	Arthritis	+	+ (plus tenosynovitis)	+
	Neurologic involvement	+	–	–
Bowel pathology		Typical aphthae can occur in the esophagus and throughout the stomach and intestine and can produce severe, cramping pain; ulcerations similar in appearance to chronic ulcerative colitis	Blind loop of bowel	Ulcerations in Crohn's disease are superficial, linear, and segmental or diffuse and on biopsy reveal granulomatous disease

Table 26.12 Neutrophilic dermatoses associated with bowel disorders.

Pathology

The histopathology of the cutaneous lesions (especially the acneiform lesions) is an area of controversy, perhaps due in part to the age of the lesion sampled. The cutaneous vasculopathy can involve all sizes of blood vessels within the dermis and subcutis. It can present as a neutrophilic vascular reaction characterized by angiocentric, neutrophilic infiltrates with leukocytoclasia and erythrocyte extravasation, or as a leukocytoclastic vasculitis with or without mural thrombosis and necrosis; some authors suggest that the vasculitis may be secondary to the intense inflammation observed[37]. There may be a predominance of histiocytes associated with the vasculitis, which leads to the diagnosis of granulomatous vasculitis. An angiocentric lymphocytic infiltrate characterizes older lesions. With regard to the acneiform lesions, a sterile neutrophilic vasculopathy is now favored over a suppurative or mixed suppurative and granulomatous folliculitis.

Vascular thrombosis is not infrequent and should prompt investigation for an underlying coagulopathy. The histologic features of the erythema nodosum-like lesions can vary from a neutrophilic lobular panniculitis to a septal and lobular panniculitis with a mixed inflammatory infiltrate, fat necrosis and evidence of lymphocytic vasculitis; the above vascular changes may also be seen.

Diagnosis

Since Behçet's disease has no diagnostic test and is characterized by a complex constellation of signs and symptoms, various sets of clinical criteria have been created to assist in the diagnosis. Among the reported diagnostic criteria are those of the Japanese (1974), O'Duffy (1974), Zhang (1980), James (1986), and the International Study Group (ISG; 1990)[38]. The latter are presented in Table 26.13.

The development of the ISG criteria was based on the discriminating performance of various criteria-grouped combination sets, and the ISG criteria exhibited the highest sensitivity, specificity and relative value. Controversy exists, however, about the failure of these criteria to require exclusion of inflammatory bowel disease.

Treatment

The management of the disease is difficult because of its variable course and lack of sufficient double-blind studies. The therapeutic approach is a symptomatic one and is dictated by the nature of the mucocutaneous and visceral involvement. Because of the frequent vital organ involvement (e.g. the eye), and the tendency for the disease to recur, early and aggressive treatment is vital. CNS and large artery and vein involvement respond less favorably to therapy. There are multiple drugs available, both topical and systemic, that can be used as monotherapy or as combination therapy (Table 26.14). Evidence for many of the therapies is based on case-series data rather than double-blind, placebo-controlled trials.

INTERNATIONAL STUDY GROUP CRITERIA FOR THE DIAGNOSIS OF BEHÇET'S DISEASE	
Major criterion	**Required features**
Recurrent oral ulceration	Aphthous (idiopathic) oral ulceration observed by physician or patient, recurring at least three times in a 12-month period
PLUS ANY TWO OF THE FOLLOWING MINOR CRITERIA:	
Recurrent genital ulceration	Aphthous genital ulceration or scarring, observed by physician or patient
Eye lesions	Anterior or posterior uveitis; cells in the vitreous by slit lamp examination; or retinal vasculitis observed by ophthalmologist
Cutaneous lesions	Erythema nodosum-like lesions observed by physician or patient; papulopustular lesions or pseudofolliculitis; or characteristic acneiform nodules observed by physician in postadolescent patient not on corticosteroids
Pathergy test*	Interpreted at 24–48 h by physician

*Pathergy test is performed on the flexor forearm by obliquely inserting a 20–22-gauge sterile hypodermic needle to a depth of 5 mm ± an intradermal injection of 0.1 ml of normal saline. A positive reaction is defined as the development of a papule or pustule.

Table 26.13 International Study Group criteria for the diagnosis of Behçet's disease[38].

TREATMENT OF BEHÇET'S DISEASE		
Treatment	**Dose**	**Level of evidence**
MUCOCUTANEOUS DISEASE		
Viscous lidocaine, topical sucralfate and other symptomatic treatments		3
Topical and inhalant corticosteroids		2
Intralesional corticosteroids		3
Colchicine	0.6 mg po thrice daily	1
Dapsone	50–150 mg po daily (or sulfapyridine equivalent)	1
Combination oral colchicine and dapsone		3
SEVERE MUCOCUTANEOUS DISEASE		
Thalidomide	50–150 mg po nightly	1
Methotrexate	2.5–25 mg po or IM weekly	3
Prednisone, intermittent with taper	40–80 mg po daily usual starting dose	2
Interferon-α-2a	Variable dose (3–9 × 10^6 IU sc 3× weekly)	1
TNF-α inhibitors (e.g. etanercept, infliximab)	See Table 26.10	1 (etanercept)
SYSTEMIC DISEASE		
Prednisone	60–120 mg po daily usual starting dose (including split-dose), with taper to alternate days	2
Methylprednisolone acetate	40 mg IM 3× weekly	2
Azathioprine	50–100 mg po twice daily	1
Cyclophosphamide	Variable oral dose (50–200 mg daily) or iv pulse (500–1000 mg monthly then 500–1000 mg every 3 months)	3
Chlorambucil	4–6 mg po daily	1
Mycophenolate mofetil	1–1.5 g po twice daily	3
Cyclosporine	Variable doses (2–10 mg/kg po daily)	1
Tacrolimus	0.1–0.2 mg/kg po daily	2
IVIg	2–3 g/kg IV monthly (given over 2–5 consecutive days)	3
TNF-α inhibitors (e.g. etanercept, infliximab)	See Table 26.10	2

Table 26.14 Treatment of Behçet's disease[39–41]. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

BOWEL-ASSOCIATED DERMATOSIS–ARTHRITIS SYNDROME

Synonyms: ■ Bowel bypass syndrome ■ Bowel bypass syndrome without bowel bypass ■ Intestinal bypass arthritis–dermatitis syndrome

Key features

- Constitutional signs and symptoms are serum sickness-like
- Cutaneous lesions include erythematous and purpuric papules and vesicopustules as well as nodular panniculitis
- Associated polyarthritis and tenosynovitis
- Histopathology includes dermal nodular perivascular neutrophilic infiltrates with edema as well as a lobular neutrophilic or septal panniculitis

Introduction

Bowel-associated dermatosis–arthritis syndrome is characterized by diarrhea with resultant malabsorption, arthritis and skin lesions. It is seen in patients who have undergone intestinal bypass surgery, have blind loops of bowel following surgery, had biliopancreatic diversion or have gastrointestinal disorders (Table 26.15)[42,43].

CONDITIONS ASSOCIATED WITH BOWEL-ASSOCIATED DERMATOSIS–ARTHRITIS SYNDROME	
Surgical	**Medical**
• Gastric resection • Jejunoileal bypass • Blind loops of bowel following surgery • Biliopancreatic diversion	• Inflammatory bowel disease • Diverticulitis • Peptic ulcer disease

Table 26.15 Conditions associated with bowel-associated dermatosis–arthritis syndrome.

History

During the 1960s and 1970s, morbid obesity was being treated surgically by jejunoileal bypass surgery and 20% of these patients developed a syndrome initially referred to as bowel bypass syndrome. In the 1980s, a similar syndrome was described in patients with inflammatory bowel disease or with blind loops of bowel after intestinal surgery[43].

Pathogenesis

In bowel-associated dermatosis–arthritis syndrome, there is usually bacterial overgrowth in a blind loop of bowel. It is postulated that resultant immune complexes containing bacterial antigens are then deposited within the skin and synovium[44]. The pathogenic role of

Fig. 26.19 Bowel-associated dermatosis–arthritis syndrome. Multiple papulopustules on the upper extremity. *Courtesy, Joseph L Jorizzo, MD.*

THERAPEUTIC APPROACHES FOR BOWEL-ASSOCIATED DERMATOSIS–ARTHRITIS SYNDROME
MILD CLINICAL EXPRESSION
• Oral antibiotics to reduce bacterial overgrowth (4–8 weeks): tetracycline (500 mg 2–4 times daily), doxycycline (100 mg once to twice daily), minocycline (100 mg once to twice daily), clindamycin (600 mg daily), metronidazole (250–500 mg twice daily) • Aseptic neutrophilic inhibiting drugs (4–8 weeks): colchicine (0.6 mg thrice daily), dapsone (50–100 mg daily), thalidomide (50–200 mg daily)
SEVERE CLINICAL EXPRESSION
• Potent anti-inflammatory and immunomodulatory drugs (2–3 months): prednisone (40–60 mg daily then tapered), cyclosporine (200–300 mg daily), azathioprine (50–150 mg daily), mycophenolate mofetil (500 mg twice daily) • Surgical restoration of normal bowel anatomy • Possible role for TNF-α inhibitors (e.g. infliximab, adalimumab, etanercept)

Table 26.16 Therapeutic approaches for bowel-associated dermatosis–arthritis syndrome. Treatments based upon small case series and case reports.

bacteria in this syndrome is supported by the disappearance of the disease with antibiotic therapy or surgery.

Clinical Features

Bowel-associated dermatosis–arthritis syndrome is characterized clinically by constitutional symptoms, skin lesions[45], and a variety of serious complications. It can occur from 1 to 6 years after the responsible bowel surgery. Constitutional symptoms, which are usually present and may precede the cutaneous eruption, are similar to those of serum sickness, e.g. fever, chills, malaise, arthralgias and myalgias.

The characteristic skin lesions are erythematous macules, which progress to papules and purpuric vesicopustules within 48 hours and last for 2–4 weeks (Fig. 26.19); they may recur at 4–6-week intervals. The lesions may be few or many, and they favor the proximal extremities and trunk.

Recurrent tender erythematous subcutaneous nodules are also seen in these patients and may be associated with fever. They are due to either a nodular, non-suppurative, lobular neutrophilic panniculitis (involving both the trunk and extremities and healing with depressed scars) or erythema nodosum (generally involving only the lower extremities), two entities which differ clinically and histologically[46]. Among the more common non-cutaneous findings are tenosynovitis and non-destructive polyarthritis. Associated systemic complications include electrolyte imbalance from persistent diarrhea, hepatic dysfunction and failure, renal calculi composed of calcium oxalate, gallstones, zinc deficiency, vitamin A deficiency, beriberi, hyperuricemia and emotional disturbances.

Pathology

The characteristic lesions exhibit a perivascular, nodular neutrophilic infiltrate with nuclear dust and papillary and reticular dermal edema[45]. The infiltrate may be admixed with lymphocytes and histiocytes and may extend into the mid dermis and panniculus. A similar neutrophilic vascular pattern is seen in lesions of Sweet's syndrome, Behçet's disease and the early phase of PG.

Differential Diagnosis

The papular eruption must be differentiated from that seen in urticarial vasculitis and erythema multiforme, whereas the pustular vasculitic lesions must be distinguished from other causes of small vessel vasculitis, disseminated gonococcemia (septic vasculitis), systemic candidiasis, subacute bacterial endocarditis and Behçet's disease. Pustular lesions may be misdiagnosed as arthropod bites (e.g. fire ants) or folliculitis.

Treatment

Surgically, either revision of the bowel bypass or surgical resection of the blind loop of bowel is curative. Medically, systemic prednisone can produce significant symptomatic improvement of the cutaneous and rheumatologic manifestations, but it is not curative[43]. It is inadvisable to administer systemic corticosteroids as a long-term therapy. Antibiotics that have proven to be beneficial are listed in Table 26.16.

SYNOVITIS, ACNE, PUSTULOSIS, HYPEROSTOSIS AND OSTEITIS (SAPHO) SYNDROME

Key features

- Presence of aseptic pustular dermatosis and osteoarticular lesions
- Usually a gradual onset of painful, multifocal osteoarticular lesions, especially of the anterior chest and axial skeleton
- The course of the osteoarticular lesions oscillates and is protracted, with gradual improvement that can be hastened by anti-inflammatory drugs

Introduction

SAPHO syndrome consists of a wide spectrum of aseptic neutrophilic dermatoses in association with aseptic osteoarticular lesions that have distinctive histologic and radiographic features[47,48]. Recognition of SAPHO syndrome is important so as to avoid misdirected therapies and unnecessary invasive procedures.

History

In 1972, chronic recurrent multifocal osteomyelitis was described as a rare chronic inflammatory musculoskeletal process in children and adults. Although cutaneous pustulosis and acne were reported in association with osteomyelitis and arthritis in the 1960s, it was not until 1987 that the acronym SAPHO (*s*ynovitis, *a*cne, *p*ustulosis, *h*yperostosis and *o*steitis) syndrome was coined to describe this clinicoradiologic entity that involves skin, bone and joints.

Epidemiology

The syndrome affects primarily children and young and middle-aged adults, and rarely presents after 60 years of age. There is no sexual predilection, with the exception of a male predominance in those with acne. It has been observed most frequently in Japan, less often in Scandinavia, Germany and France, and infrequently in the US and Canada.

Pathogenesis

The pathogenesis of SAPHO is not understood. Some hypothesize that it is the result of an autoimmune response triggered by microorganisms and enhanced chemotaxis of neutrophils.

CUTANEOUS DISORDERS ASSOCIATED WITH SAPHO SYNDROME
• Palmar and plantar pustulosis
• Follicular occlusion tetrad, in particular acne conglobata
• Acne fulminans
• Pustular psoriasis
• Sneddon–Wilkinson disease
• Psoriasis
• Linear IgA bullous dermatosis
• Behçet's disease
• Sweet's syndrome
• Pyoderma gangrenosum
• Lyme disease

Table 26.17 Cutaneous disorders associated with SAPHO syndrome. SAPHO – synovitis, acne, pustulosis, hyperostosis and osteitis. A SAPHO phenotype can occur in the setting of PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum and acne), which is inherited in an autosomal dominant manner (*PSTPIP1* mutations). Majeed syndrome (congenital dyserythropoietic anemia; *LPIN2* mutations) and deficiency of the interleukin-1 receptor antagonist (DIRA) syndrome (*IR1RN* mutations; Fig. 26.20) are autosomal recessive conditions that feature the aseptic osteoarticular lesions of SAPHO together with Sweet's syndrome-like and pustular skin lesions, respectively.

Fig. 26.20 Deficiency of the interleukin-1 receptor antagonist (DIRA) syndrome. This infant has figurate lesions with multiple pustules and might be misdiagnosed as having pustular psoriasis. *Courtesy, Gillian Clarke, MD.*

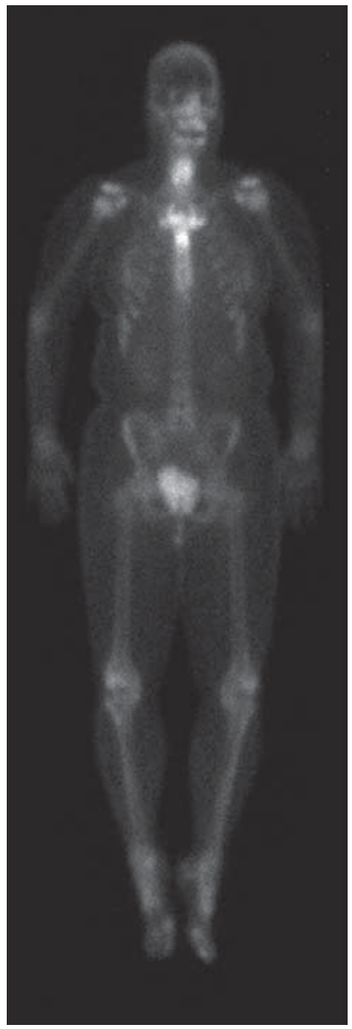


Fig. 26.21 Abnormal bone scan in a patient with SAPHO syndrome. There is abnormal tracer uptake within the mid and lower cervical spine and multiple thoracic vertebral bodies (T3 to T9) in addition to the manubrium and sternoclavicular joints bilaterally. The pattern and anatomic distribution are indicative of increased osteoblastic activity as is seen in the SAPHO syndrome.

Clinical Features

The cutaneous disorders that have been described to date as components of the SAPHO syndrome are listed in Table 26.17; the neutrophil is the "tie that binds" these disorders. The osteoarticular lesions of SAPHO are synovitis, arthrosteitis (inflammation of the osseous structures of a joint), and chronic recurrent multifocal aseptic osteomyelitis. The sites of involvement are usually the anterior chest wall (sternum, clavicles and ribs) and other axial skeleton sites (spine and pelvis). The affected bones are tender and the swollen joints are painful. Patients may be febrile with a leukocytosis and elevated ESR.

Bone scintigraphy demonstrates an increased uptake at involved sites (Fig. 26.21). MRI is very sensitive and can provide information about adjacent joint and tissue involvement and it helps in monitoring the disease. The osteoarticular involvement is intermittent with periodic exacerbations and remissions and there is no correlation with the activity of the associated sterile neutrophilic cutaneous disorders.

SAPHO is also regarded as one of the seronegative spondyloarthropathies because of its frequent association with inflammatory bowel disease, with the latter being an HLA-B27 phenotype with axial skeleton involvement (sacroiliitis).

Pathology

Early in the process, medullary bone contains an inflammatory cellular infiltrate, consisting primarily of neutrophils, osteoclasts and osteoblasts. Later on, cicatricial fibrosis surrounded by hypertrophic inactive bone is seen.

Differential Diagnosis

The differential diagnosis of the bone lesions includes classic bacterial osteomyelitis, primary bone tumors, metastases, and Langerhans cell histiocytosis. In children, the possibility of SAPHO developing in the setting of either Majeed syndrome (congenital dyserythropoietic anemia; *LPIN2* mutations) or deficiency of the interleukin-1 receptor antagonist (DIRA) syndrome (*IR1RN* mutations) should be considered[49].

THERAPIES FOR OSTEOARTICULAR LESIONS OF ADULT SAPHO SYNDROME	
Variable effectiveness	NSAIDs
	Colchicine
	Sulfasalazine
	Oral antibiotics (doxycycline, azithromycin, clindamycin)
More effective	Methotrexate (20 mg po/week)
	Corticosteroids (intralesional/oral*)
	Bisphosphonates†
	TNF-α inhibitors

*Usually prednisone 30 mg po daily.
†Pamidronate (30–60 mg IV), zoledronic acid (4 mg IV).

Table 26.18 Therapies for osteoarticular lesions of adult SAPHO syndrome. NSAIDs, nonsteroidal anti-inflammatory drugs; TNF, tumor necrosis factor.

Treatment

Since precise knowledge of the pathogenesis of SAPHO syndrome is lacking, a variety of anti-inflammatory therapies have been tried (Table 26.18). Although isotretinoin is used to treat associated severe acne, there are scattered case reports of isotretinoin-associated flares of SAPHO.

REFERENCES

1. Jorizzo JL, Solomon AR, Zanolli MD, Leshin B. Neutrophilic vascular reactions. J Am Acad Dermatol. 1988;19:983–1005.
2. Sweet RD. An acute febrile neutrophilic dermatosis. Br J Dermatol. 1964;76:349–56.
3. Whittle CH, Beck GA, Champion RH. Recurrent neutrophilic dermatosis of the face – a variant of Sweet's syndrome. Br J Dermatol. 1968;80:806–10.
4. Giasuddin AS, El-Orfi AH, Ziu MM, El-Barnawi NY. Sweet's syndrome: is the pathogenesis mediated by helper T cell type 1 cytokines? J Am Acad Dermatol. 1998;39:940–3.
5. Kawakami T, Ohashi S, Kawa Y, et al. Elevated serum granulocyte colony-stimulating factor levels in patients with active phase of Sweet syndrome and patients with active Behcet disease: implication in neutrophil apoptosis dysfunction. Arch Dermatol. 2004;140: 570–4.
6. Fett DL, Gibson LE, Su WPD. Sweet's syndrome: signs and symptoms and associated disorders. Mayo Clin Proc. 1995;70:234–40.
7. Von den Driesch P. Sweet's syndrome (acute febrile neutrophilic dermatosis). J Am Acad Dermatol. 1994; 31:535–56.
8. Fett DL, Gibson LE, Su WPD. Sweet's syndrome: systemic signs and symptoms and associated disorders. Mayo Clin Proc. 1995;70:234–40.
9. Cohen PR, Holder WR, Tucker SB, et al. Sweet syndrome in patients with solid tumors. Cancer. 1993;72:2723–31.
10. Chow S, Pasternak S, Green P, et al. Histiocytoid neutrophilic dermatoses and panniculitides: variations on a theme. Am J Dermatopathol. 2007;29:334–41.
11. Gerami P, Guitart J. Panniculitis with histiocytoid/ immature neutrophils is not limited to histiocytoid panniculitic Sweet syndrome. Am J Dermatopathol 2007; 29:596.
12. Kemmet D, Harrison DJ, Hunter JAA. Antibodies to neutrophil cytoplasmic antigens: serologic marker for Sweet's syndrome. J Am Acad Dermatol. 1991;24:967–9.
13. Su WPD, Liu HNH. Diagnostic criteria for Sweet's syndrome. Cutis. 1986;37:167–74.
14. Galaria NA, Junkins-Hopkins JM, Kligman D, James WD. Neutrophilic dermatosis of the dorsal hands: pustular vasculitis revisited. J Am Acad Dermatol. 2000;43:870–4.
15. Weenig RH, Bruce AJ, McEvoy MT, et al. Neutrophilic dermatosis of the hands: four new cases and review of the literature. Int J Dermatol. 2004;43:95–102.
16. DiCaudo DJ, Connolly SM. Neutrophilic dermatosis (pustular vasculitis) of the dorsal hands: a report of 7 cases and review of the literature. Arch Dermatol. 2002;138:361–5.
17. Powell FC, Su WPD, Perry HO. Pyoderma gangrenosum: classification and management. J Am Acad Dermatol. 1996;34:395–409.
18. Brunsting AL, Goeckerman WH, O'Leary PA. Pyoderma gangrenosum: clinical and experimental observations in five cases occurring in adults. Arch Dermatol Syphilol. 1930;22:655–80.
19. Callen JP. Pyoderma gangrenosum. Lancet. 1998;351:581–5.
20. Bennett ML, Jackson JM, Jorizzo JL, et al. Pyoderma gangrenosum. A comparison of typical and atypical forms with an emphasis on time to remission. Case review of 86 patients from 2 institutions. Medicine (Baltimore). 2000;79:37–46.
21. Quimby SR, Gibson LE, Winkelmann RK. Superficial granulomatous pyoderma: clinicopathologic spectrum. Mayo Clin Proc. 1989;64:37–43.
22. Cairns BA, Herbst CA, Sartor BR, et al. Peristomal pyoderma gangrenosum and inflammatory bowel disease. Arch Surg. 1994;129:769–72.
23. Graham JA, Hansen KK, Rabinowitz LG, Esterly NB. Pyoderma gangrenosum in infants and children. Pediatr Dermatol. 1994;11:10–17.
24. Vignon-Pennamen MD, Wallach D. Neutrophilic disease: a review of extracutaneous neutrophilic manifestations. Eur J Dermatol. 1996;5:449–55.
25. Weenig RH, Davis MD, Dahl PR, Su WP. Skin ulcers misdiagnosed as pyoderma gangrenosum. N Engl J Med. 2002;347:1412–18.
26. Su WP, Davis MD, Weenig RH, et al. Pyoderma gangrenosum: clinicopathologic correlation and proposed diagnostic criteria. Int J Dermatol. 2004;43:790–800.
27. Su WP, Davis MD, Weenig RH, et al. Pyoderma gangrenosum: clinicopathologic correlation and proposed diagnostic criteria. Int J Dermatol. 2004;43:790–800.
28. Chow RKP, Ho VC. Treatment of pyoderma gangrenosum. J Am Acad Dermatol. 1996;34:1047–60.
29. Miller J, Yentzer BA, Clark A, et al. Pyoderma gangrenosum: a review and update on new therapies. J Am Acad Dermatol. 2010;62:646–54.
30. Schirmer M, Calamia KT, Direskeneli H. Ninth International Conference on Behçet's Disease, Seoul, Korea, May 27–29, 2000. J Rheumatol. 2001;28:636–9.
31. Arbesfeld SJ, Kurban AK. Behçet's disease. New perspectives on an enigmatic syndrome. J Am Acad Dermatol. 1988;19:767–79.
32. Sakane T, Takeno M, Suzuki N, Inaba G. Behçet's disease. N Engl J Med. 1999;341:1284–91.
33. Kaklamani VG, Vaviopoulos G, Kaklamanis PG. Behçet's disease. Semin Arthritis Rheum. 1988;27:197–217.
34. Letsinger JA, McCarty MA, Jorizzo JL. Complex aphthosis: a large case series with evaluation algorithm and therapeutic ladder from topicals to thalidomide. J Am Acad Dermatol. 2005;52:500–8.
35. Magro CM, Crowson AN. Cutaneous manifestations of Behçet's disease. Int J Dermatol. 1995;34:159–65.
36. Firestein GS, Gruber HE, Weisman MH, et al. Mouth and genital ulcers with inflamed cartilage: MAGIC syndrome. Am J Med. 1985;79:65–72.
37. Chun SI, Su WP, Lee S. Histopathologic study of cutaneous lesions in Behçet's syndrome. J Dermatol. 1990;17:333–41.
38. International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. Lancet. 1990;335: 1078–80.
39. Kaklamani VG, Kaklsamanis PG. Treatment of Behçet's disease – an update. Semin Arthritis Rheum. 2001;30: 299–312.
40. Alpsoy E, Akman A. Behçet's disease: an algorithmic approach to its treatment. Arch Dermatol Res. 2009;301: 693–702.
41. Fresko I, Yazici H. Treatment strategies for Behçet's disease. Expert Opin Pharmacother. 2008;9: 3211–19.
42. Dicken CH, Seehafer JR. Bowel bypass syndrome. Arch Dermatol. 1979;115:837–9.
43. Jorizzo JL, Apisarnthanarax P, Subrt P, et al. Bowel bypass syndrome without bowel bypass. Bowel-associated dermatosis-arthritis syndrome. Arch Intern Med. 1983; 143:457–61.
44. Ely PH. The bowel bypass syndrome: a response to bacterial peptidoglycans. J Am Acad Dermatol. 1980; 2:473–87.
45. Kennedy C. The spectrum of inflammatory skin disease following jejuno-ileal bypass for morbid obesity. Br J Dermatol. 1981;105:425–35.
46. Williams HJ, Samuelson CO, Zone JJ. Nodular nonsuppurative panniculitis associated with jejunoileal bypass surgery. Arch Dermatol. 1979;115:1091–3.
47. Kahn MF, Khan MA. The SAPHO syndrome. Baillières Clin Rheumatol. 1994;8:333–62.
48. Beretta-Picolli BC, Sauvain MJ, Gal I, et al. Synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome: a report of ten cases and review of the literature. Eur J Pediatr. 2000;159:594–601.
49. El-Shanti HI, Ferguson PJ. Chronic recurrent multifocal osteomyelitis: a concise review and genetic update. Clin Orthop Relat Res. 2007;462:11–19.

Classic ulcerative pyoderma gangrenosum. In this patient with chronic ulcerative colitis, the ulcers on the skin have an undermined gunmetal gray border.

Behçet's disease: systemic involvement. Superficial migratory thrombophlebitis.

Behçet's disease: mucocutaneous lesions.
A Oral aphthosis.
B Perianal aphthosis.

27 Pregnancy Dermatoses

Christina M Ambros-Rudolph and Jeff K Shornick

Chapter Contents

Pemphigoid gestationis 439
Polymorphic eruption of pregnancy 441
Intrahepatic cholestasis of pregnancy 443
Atopic eruption of pregnancy 445
Approach to the pregnant woman with pruritus 447
Physiologic changes during pregnancy 447
Autoimmune progesterone dermatitis 447

The specific dermatoses of pregnancy are a heterogeneous group of pruritic skin disorders that, for decades, represented a confusing group of overlapping entities, understood largely through anecdotes and case reports. However, more recent reviews have simplified and condensed the list of pregnancy-specific dermatoses (Table 27.1)[1–3]. For example, impetigo herpetiformis is now generally recognized as pustular psoriasis, perhaps induced by the relative hypocalcemia of pregnancy (see Ch. 8). Also, prurigo annularis, first reported in 1941 (without histology or laboratory information), and linear IgM disease of pregnancy (described in 1988) have not been subsequently reported, yet are frequently perpetuated in reviews.

Much of the confusion can be dispelled by reviewing the original articles: Besnier (1904) first used the term "prurigo gestationis" to include all patients with pregnancy-related dermatoses, other than those with pemphigoid gestationis. Costello (1941) subsequently referred to these patients as "prurigo gestationis of Besnier" and estimated an incidence of 2% of all pregnancies. Bourne (1962) characterized a subset of patients with intensely pruritic papules or urticarial plaques that tended to appear during the later part of the third trimester, coining the term "toxaemic rash of pregnancy". Initial lesions typically developed within the abdominal striae of short women who experienced excessive weight gain during pregnancy. Unfortunately, he offered neither histopathologic nor laboratory insight.

Spangler et al. (also 1962) reported on a series of women with intensely pruritic, widely scattered, excoriated papules. Initial onset was during the second or third trimester and all patients suffered recurrences during subsequent gestations. The hallmarks of Spangler's cases were biochemical: elevated urinary human chorionic gonadotropin (HCG), decreased plasma hydrocortisone, and decreased serum half-life of hydrocortisone. Liver function tests and histopathology were not reported and immunofluorescence (IF) was not yet available. Most notably, Spangler's papular dermatitis was associated with high fetal wastage, a finding now thoroughly discredited.

Nurse (1968) cited all of the above literature but ignored it, dividing patients with (non-pemphigoid gestationis) pregnancy eruptions into "early" and "late" forms. The late papular/urticarial form clearly overlapped with Bourne's "toxaemic rash of pregnancy", and has since been described as "pruritic urticarial papules and plaques of pregnancy" (PUPPP), "toxic erythema of pregnancy", and, most recently, "polymorphic eruption of pregnancy" (PEP). Nurse's "early onset" patients and Spangler's "papular dermatitis" patients were undoubtedly drawn from the same clinical spectrum, and subsequently these entities were reclassified as forms of "prurigo of pregnancy" (see Table 27.1).

Pruritic folliculitis of pregnancy was added to the list of pregnancy-specific diseases in 1981, yet all six of the original patients were thought to have papular dermatitis clinically. They were classified as different based solely upon shared histologic features (i.e. sterile folliculitis). In spite of their clinical similarity to the patients reported by Spangler, none had appropriate biochemical investigations. In 1998, an adaptation of the Holmes and Black classification scheme (1983)[2] was published[3] and listed pruritic folliculitis as a variant of prurigo of pregnancy (see Table 27.1).

Introduction of the term "atopic eruption of pregnancy (AEP)" represents the most recent revision to the classification of dermatoses of pregnancy[1]. Based upon an analysis of over 500 pregnant women with pruritus[1], significant overlap, both clinical and histologic, was noted amongst those patients (~50% in this series) with the diagnoses of prurigo of pregnancy, pruritic folliculitis of pregnancy, and eczema in pregnancy[4]. AEP was thought to be a useful diagnostic term that encompassed these three disorders and reminded the clinician that the eczema was more likely to be of new onset as opposed to a flare of previously diagnosed atopic dermatitis.

Because of the lack of primary lesions, intrahepatic cholestasis of pregnancy (ICP) had long been omitted from the list of pregnancy dermatoses. However, failure to appreciate ICP in a pregnant woman with widespread excoriations or even prurigo nodularis surely, in retrospect, accounts for some of the confusion in terminology. Furthermore, ICP is the most important diagnosis to exclude in a pregnant patient with pruritus, as it is associated with significant fetal risk (see below).

PEMPHIGOID GESTATIONIS

Synonyms: ■ Gestational pemphigoid ■ Herpes gestationis

Key features

- Rare pruritic vesiculobullous eruption that develops during late pregnancy or the immediate postpartum period
- Linear C3 deposition along the basement membrane zone (BMZ) by direct IF
- IgG1 autoantibodies directed against a transmembrane hemidesmosomal protein (BP180; collagen XVII)
- Increased risk of prematurity and small-for-gestational age neonates; the risk correlates with disease severity
- Commonly recurs in subsequent pregnancies

Introduction

Pemphigoid gestationis is a rare, self-limited, autoimmune bullous disease. It is the most clearly characterized dermatosis of pregnancy and the only one that may also affect the skin of the newborn.

History

Milton first coined the term "herpes gestationis" in 1872 and Bulkley (1874) canonized the term "as embodying the clinical characters of the eruption and signifying at the same time the sex and state of the body in which it appears". Little additional insight was gained until IF techniques revealed complement deposition along the BMZ in 1973, a feature now accepted as essential for the diagnosis of pemphigoid gestationis.

Epidemiology

The incidence of pemphigoid gestationis has been estimated at 1 : 1700–1 : 50 000 pregnancies[5,6], correlating with the prevalence of HLA-DR3

CLASSIFICATION OF THE DERMATOSES OF PREGNANCY	
Classification	**Synonym(s)**
Pemphigoid gestationis*	Herpes gestationis† **Gestational pemphigoid**
Polymorphic eruption of pregnancy (PEP)	Pruritic urticarial papules and plaques of pregnancy (PUPPP)† Toxic erythema of pregnancy Late-onset prurigo of pregnancy Toxemic rash of pregnancy
Intrahepatic cholestasis of pregnancy (ICP)	Cholestasis of pregnancy† Obstetric cholestasis Jaundice of pregnancy Pruritus/prurigo gravidarum
Atopic eruption of pregnancy (AEP)	Prurigo of pregnancy*,† Prurigo gestationis (Besnier) Early-onset prurigo of pregnancy (Nurse) Papular dermatitis of pregnancy (Spangler) Pruritic folliculitis of pregnancy* Linear IgM disease of pregnancy Eczema in pregnancy

*Former classification by Holmes & Black (1983)[2].
†Former classification by Shornick (1998)[3].

Table 27.1 Classification of the dermatoses of pregnancy[1]. The preferred terms are in bold.

Fig. 27.1 Pemphigoid gestationis. Intact tense bullae arising within areas of edematous erythema as well as erosions due to ruptured bullae. Lesions typically involve the umbilical region.

and -DR4 in different populations. While occurring primarily during pregnancy and the immediate postpartum period, pemphigoid gestationis has rarely developed in association with trophoblastic tumors (hydatidiform mole, choriocarcinoma). Interestingly, no case of a pemphigoid-like disease has been reported in men with choriocarcinoma, who have a biochemically similar yet entirely syngenic tumor; of note, the nuclear genome in placental tissue (and hence choriocarcinoma in women) is primarily paternal in origin. Patients with a history of pemphigoid gestationis appear to be at increased risk for the development of Graves' disease[7].

Pathogenesis

Historically, pemphigoid gestationis was thought to be caused by an anti-BMZ "serum factor" (the "herpes gestationis [HG] factor") that induces C3 deposition along the dermal–epidermal junction. This factor is now known to be complement-fixing autoantibodies of the IgG1 subclass directed against a 180 kDa transmembrane hemidesmosomal protein (BPAG2; collagen XVII). As in patients with bullous pemphigoid (BP), it is the non-collagenous (NC) segment closest to the plasma membrane of the basal keratinocyte (NC16A) that constitutes the immunodominant region of BP180. Circulating antibodies are almost exclusively directed against this domain, as demonstrated by ELISA and immunoblot studies of maternal or neonatal sera.

What initiates the production of autoantibody remains enigmatic. Because the antibodies also bind to amniotic basement membrane[8] (a structure derived from fetal ectoderm and antigenically similar to skin), attention has focused on immunogenetics and potential cross-reactivity between placental tissue and skin. Immunogenetic studies have revealed a marked increase in HLA antigens DR3 or DR4, and, curiously, nearly 50% of patients have the simultaneous presence of both. There is essentially a 100% incidence of anti-HLA antibodies in patients with a history of pemphigoid gestationis[9]. Since the only source of disparate HLA antigens is typically the placenta (which is primarily of paternal origin), the universal finding of anti-HLA antibodies implies a high frequency of immunologic insult during gestation. Women with pemphigoid gestationis also have increased expression of MHC class II antigens (DR, DP, DQ) within the villous stroma of their chorionic villi. It has therefore been proposed that pemphigoid gestationis is a disease, initiated by the aberrant expression of MHC class II antigens (of paternal haplotype), that serves to initiate an allogeneic response to placental BMZ, which then cross-reacts with skin[10].

Clinical Features

Pemphigoid gestationis may develop during any trimester as well as immediately postpartum, but classically it presents during late pregnancy. There is an abrupt onset of cutaneous lesions on the trunk, in particular the abdomen and often within or immediately adjacent to the umbilicus. Rapid progression to a generalized pemphigoid-like eruption then occurs (Fig. 27.1), with pruritic urticarial papules and plaques, followed by clustered (herpetiform) vesicles or tense bullae on an erythematous base. The eruption may involve the entire body, sparing only the mucous membranes. While the clinical presentation and course may vary considerably, spontaneous improvement during late gestation is common. This is followed, however, by a flare at the time of delivery in 75% of patients. Such flares may be dramatic, with an explosive onset of blistering within hours.

Most disease activity spontaneously remits during the weeks to months following delivery, but there are isolated reports of a protracted course postpartum. Flares and/or recurrences in association with menstruation are common, and in 25–50% of patients, they may also be induced by oral contraceptives (Table 27.2). Pemphigoid gestationis may not develop during the patient's first pregnancy, but, once established, it is quite likely to recur in subsequent pregnancies, usually with an earlier onset and more severe course. "Skipped" pregnancies have been observed in 5–8% of women.

Approximately 10% of newborns develop mild skin involvement due to passive transfer of maternal antibodies and this resolves spontaneously within days to weeks (see Ch. 34). There seems to be an increased risk of prematurity and small-for-gestational age neonates, presumably due to chronic placental insufficiency. Recently, it was shown that this risk correlates with disease severity (i.e. occurrence of blistering and early onset) and not with the use of systemic corticosteroids[11].

Pathology

The classic histologic finding of a subepidermal vesicle is seen in the minority of patients. Instead, a nonspecific mixed cellular infiltrate containing a variable number of eosinophils is more common. The presence of eosinophils is the most constant histologic feature of pemphigoid gestationis.

The essential component for the diagnosis of pemphigoid gestationis is a linear deposition of C3 along the BMZ of perilesional skin by direct IF microscopy (Fig. 27.2). This is observed in 100% of patients, and linear IgG deposition is seen in 30% of patients. When salt-split skin specimens are employed for *conventional* indirect IF, deposition of IgG along the bottom of the epidermal fragment is observed in 30% of

DERMATOSES OF PREGNANCY – FETAL RISK, INVOLVEMENT OF NEWBORN SKIN, AND RISK OF RECURRENCE			
Dermatosis	**Fetal risk**	**Newborn skin involvement**	**Risk of recurrence**
Pemphigoid gestationis	Increased risk of prematurity and small-for-gestational age neonates; risk correlates with disease severity	Mild and transient lesions of pemphigoid gestationis in up to 10% (see Ch. 34)	Commonly recurs ("skipped" pregnancies in only 5–8% of women); recurrences induced by oral contraceptives in 25–50%
Polymorphic eruption of pregnancy	None	None	Usually does not recur
Intrahepatic cholestasis of pregnancy	Increased risk of premature labor (20–60%), intrapartal fetal distress (20–30%) and stillbirths (1–2%)	None	Recurrence in 45–70% of subsequent pregnancies; may be triggered by oral contraceptives
Atopic eruption of pregnancy	None	None	Commonly recurs due to atopic diathesis

Table 27.2 Dermatoses of pregnancy – fetal risk, involvement of newborn skin, and risk of recurrence.

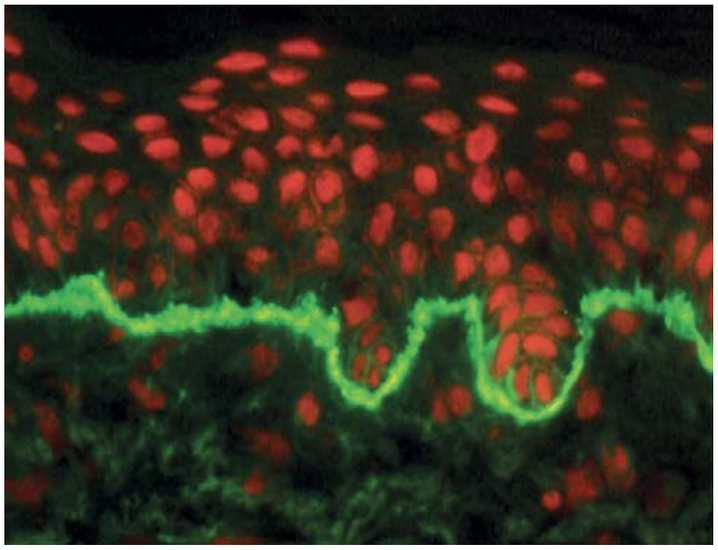


Fig. 27.2 Pemphigoid gestationis – direct immunofluorescence (IF) microscopy. Linear deposits of C3 are seen along the dermal–epidermal junction. *Courtesy, Immunofluorescence Department, St. John's Institute of Dermatology, St. Thomas' Hospital, London, UK.*

patients. However, *complement-added* indirect IF reveals the circulating anti-BMZ IgG1 autoantibodies in essentially all patients. Determination of antibody titers via BP180-NC16A ELISA may be helpful in following disease activity and monitoring therapy.

An increased incidence of antithyroid antibodies has been documented, but clinically apparent thyroid dysfunction is uncommon[7]. Routine laboratory investigations are normal.

Differential Diagnosis

The most frequent considerations in the differential diagnosis are PEP and drug eruptions. PEP is a particularly challenging exclusion, given the difficulty of distinguishing PEP and urticarial lesions of pemphigoid gestationis. IF and, more recently, the BP180-NC16A ELISA are key to the differentiation and are especially relevant in helping the patient plan for future pregnancies.

Treatment

The primary goal in treating this self-limited disease is to relieve pruritus and suppress blister formation. In mild cases, the use of potent topical corticosteroids combined with emollients and systemic antihistamines may be adequate. However, systemic corticosteroids remain the cornerstone of therapy (Table 27.3). Most patients respond to 0.5 mg/kg of prednisolone daily; the dose is tapered as soon as blister formation is suppressed. The common flare associated with delivery usually requires a temporary increase in dosage. Those rare patients with refractory disease may benefit from plasmapheresis during pregnancy. Persistent disease after delivery is uncommon and is treated like BP.

Anecdotal alternatives to corticosteroids (dapsone, doxycycline or minocycline ± nicotinamide, pyridoxine, cyclosporine) or adjuvants (methotrexate, cyclophosphamide, gold, IVIg) have been tried. None of these medications, with the possible exception of cyclosporine, are safe prior to term and thus should be avoided.

POLYMORPHIC ERUPTION OF PREGNANCY

Synonyms: ■ Pruritic urticarial papules and plaques of pregnancy (PUPPP) ■ Bourne's "toxaemic rash of pregnancy" ■ Nurse's "late onset prurigo" of pregnancy ■ Toxic erythema of pregnancy

Key features

- Urticarial papules and plaques that usually first appear within striae distensae during the latter portion of the third trimester or immediately postpartum
- Development of polymorphous features (vesicles; erythema; target and eczematous lesions) with disease progression
- Most frequent in primiparous women
- Nonspecific histologic features, negative IF, and normal routine laboratory evaluation
- No maternal or fetal risks; usually does not recur

Introduction

Polymorphic eruption of pregnancy (PEP), formerly known as PUPPP, is a common gestational dermatosis. It is characterized by a typical clinical presentation, normal laboratory tests, and negative IF or ELISA.

History

The term PUPPP, introduced by Lawley et al.[12] in 1979, focuses on the initial clinical findings in this disorder but overlooks its later polymorphous features. In order to encompass the entire clinical spectrum, the term "polymorphic eruption of pregnancy" has been introduced[3] and is now generally accepted.

Epidemiology

The incidence is ~1 in 160 deliveries[13]. It is seen predominantly in primiparous women and tends not to recur in subsequent pregnancies. There is neither an autoimmune diathesis nor an association with a specific HLA type.

Pathogenesis

The cause of PEP is unknown. Reference has been made to increased maternal weight gain and an increased frequency of multiple-gestation pregnancies[14,15]. It has therefore been suggested that rapid, late stretching of abdominal skin may lead to damage of connective tissue and elicitation of an allergic-type reaction, resulting in the initial appearance of the eruption within striae[16]. The lesions then become generalized as the inflammatory response develops cross-reactivity to collagen in otherwise normal-appearing skin. Immune tolerance during subsequent pregnancies might prevent recurrence. Additional theories

SPECIAL CONSIDERATIONS FOR CORTICOSTEROID AND ANTIHISTAMINE USE DURING PREGNANCY	
CORTICOSTEROIDS	
Topical	• Overuse of high-potency products can lead to systemic absorption and halogenated corticosteroids do cross the placenta; they may also add to the already considerable risk of striae • Class 6 and 7 corticosteroids are safest • Corticosteroids that have enhanced cutaneous metabolism, e.g. mometasone furoate, prednicarbate, methylprednisolone aceponate, can also be considered
Systemic	• Prednisolone is the systemic corticosteroid of choice for dermatologic indications as it is largely inactivated in the placenta (mother : fetus = 10 : 1) • During the first trimester, particularly between weeks 8 and 11, there is a possible (debated) slightly increased risk of cleft lip/cleft palate, especially if high doses prescribed and for >10 days; during this same period, a longer duration of therapy appears safe if dosages are <10–15 mg daily • If use is long-term and extends late into gestation, fetal growth should be monitored and the risk of adrenal insufficiency in the newborn should be addressed
ANTIHISTAMINES	
Systemic	• During the first trimester, the classic sedating agents (e.g. chlorpheniramine, clemastine, dimethindene) are preferred • During the second and third trimesters, if a non-sedating agent is requested, loratadine and cetirizine are considered safe

Table 27.3 Special considerations for corticosteroid and antihistamine use during pregnancy[25].

include increased levels of progesterone in association with multiple gestations and peripheral chimerism (deposition of fetal DNA) that favors skin with increased vascularity and damaged collagen.

Clinical Features

Pruritic erythematous and edematous papules and plaques usually first appear within the abdominal striae, typically with periumbilical sparing (Fig. 27.3). Onset is most often during the latter part of the third trimester (85%) or in the immediate postpartum period (15%)[15]. The eruption typically spreads over a matter of days, but in general spares the face, palms and soles. While pruritic urticarial papules are the initial lesions in almost all patients, approximately half will develop more polymorphic features as the disease evolves, including widespread erythema, target lesions, tiny vesicles, and eczematous plaques (Fig. 27.4). Irrespective of whether the eruption starts during pregnancy or postpartum, lesions resolve over an average of 4 weeks.

There are no maternal or fetal morbidities, and recurrences are unusual except for subsequent multiple-gestation pregnancies. To date, only a single possible case of newborn skin involvement has been described; however, the possibility of pemphigoid gestationis was not excluded by IF studies[17]. Thus, it is generally agreed that neonatal skin is not affected by PEP.

Pathology

Skin biopsy specimens reveal nonspecific findings. Epidermal changes vary from modest spongiosis to acanthosis with hyperkeratosis and parakeratosis, depending upon the stage of the disease. The dermis shows a nonspecific perivascular lymphocytic infiltrate with a variable degree of dermal edema and a variable number of neutrophils or eosinophils. Early lesions may resemble arthropod bite reactions, with a deeper dermal infiltrate and an absence of epidermal changes (Fig. 27.5). The histologic correlate of microvesiculation is severe epidermal spongiosis and/or dermal edema. Direct IF reveals no relevant abnormalities and indirect IF is negative. Routine laboratory evaluation is normal.

Differential Diagnosis

Since lesions of PEP may show microvesiculation, contact dermatitis must be considered. Drug eruptions, urticaria or viral exanthems may also be in the clinical differential diagnosis. The most important entity to exclude is urticarial pemphigoid gestationis, whose lesions tend to

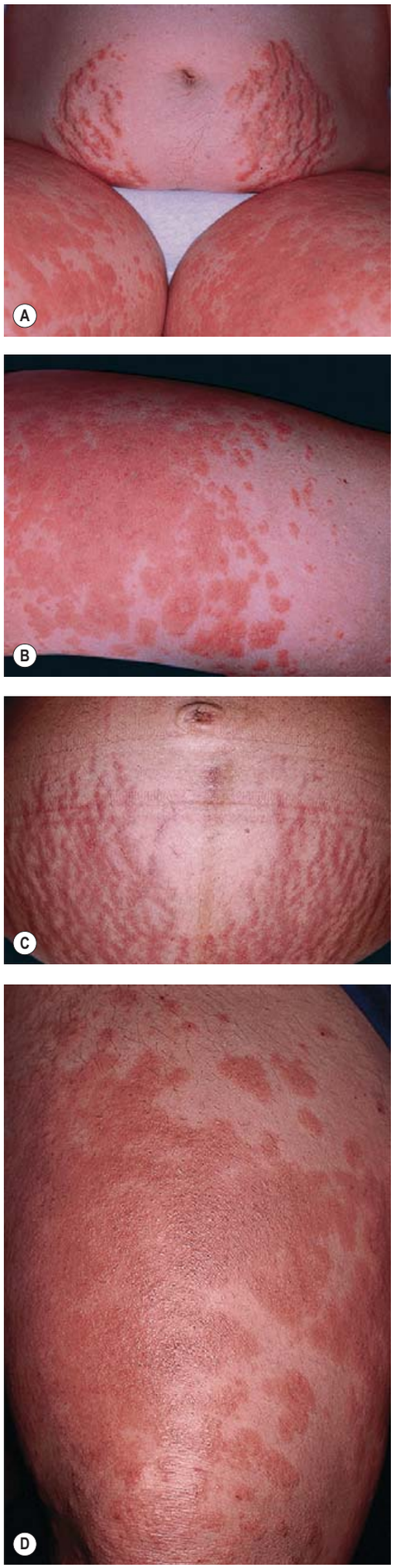


Fig. 27.3 Polymorphic eruption of pregnancy. The edematous urticarial lesions favor the striae (**A,C**) and the upper thighs (**B,D**) and spare the umbilicus. Note the pink color in a woman with skin phototype II versus the red–brown color in a more darkly pigmented patient.

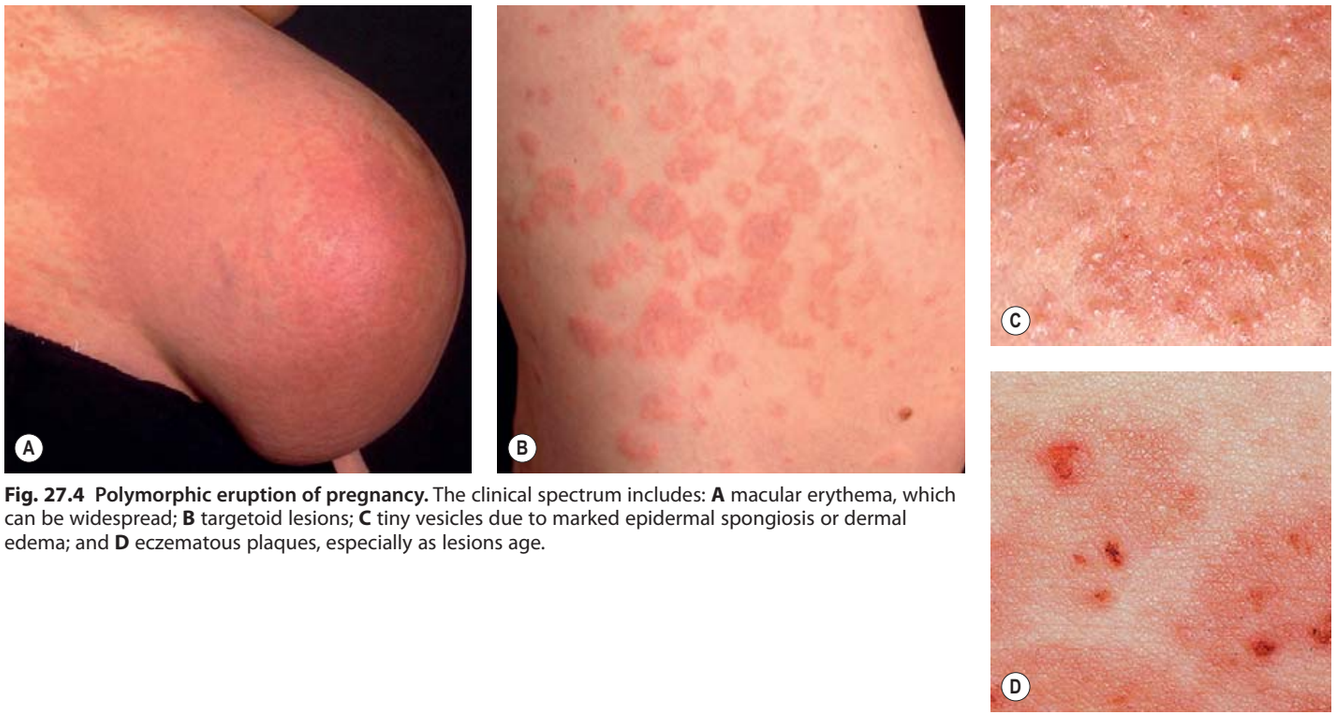


Fig. 27.4 Polymorphic eruption of pregnancy. The clinical spectrum includes: **A** macular erythema, which can be widespread; **B** targetoid lesions; **C** tiny vesicles due to marked epidermal spongiosis or dermal edema; and **D** eczematous plaques, especially as lesions age.

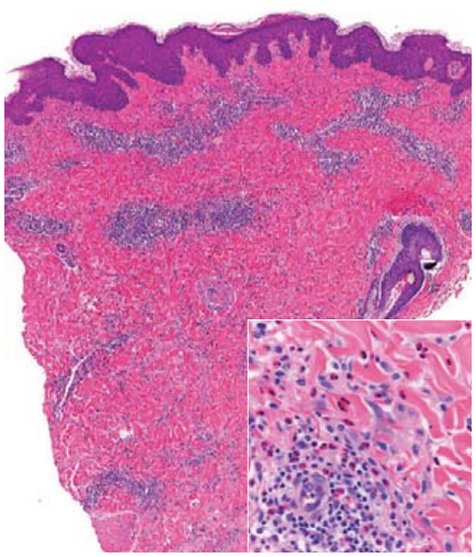


Fig. 27.5 Polymorphic eruption of pregnancy – histologic features. In this early lesion, a superficial and deep perivascular and interstitial lymphohistiocytic infiltrate is seen within the dermis. Numerous eosinophils are also present (insert).

appear earlier during gestation, have no association with abdominal striae and often involve the umbilicus, along with positive IF of perilesional skin.

Treatment

The majority of patients benefit from topical corticosteroids and oral antihistamines. More severe disease with a distressing degree of pruritus can be safely treated with a short course of systemic corticosteroids (see Table 27.3). Since the disease is self-limited and without serious sequelae, a conservative approach is justified.

INTRAHEPATIC CHOLESTASIS OF PREGNANCY

Synonyms: ■ Cholestasis of pregnancy ■ Obstetric cholestasis ■ Cholestatic jaundice of pregnancy ■ Pruritus/prurigo gravidarum

Key features

- Pruritus without primary skin lesions with an onset during the third trimester
- Secondary changes correlate with disease duration and vary from subtle excoriations to severe prurigo nodularis
- Elevated total serum bile acid levels are diagnostic; histology is nonspecific and IF is negative
- Increased risk of prematurity, intrapartum fetal distress, and stillbirths
- Recurs in 45–70% of subsequent pregnancies

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a rare form of genetically linked, hormone-dependent, reversible cholestasis. It typically presents late during pregnancy with dramatic pruritus. Although maternal prognosis is usually good (a small minority may develop steatorrhea and vitamin K deficiency), fetal risk is significant. As a result, ICP is the most important pruritic gestational condition to consider and promptly diagnose and treat in order to prevent fetal impairment.

History

ICP was first described in 1907 by Kehrer. In the past, much of the confusion arose from applying descriptive names such as "pruritus gravidarum" for ICP without skin changes or "prurigo gravidarum" if skin lesions associated with scratching were present. While the first term was often combined with the mild unexplained pruritus that occurs in many women during pregnancy (most likely related to an atopic diathesis), the latter was confused with "prurigo of pregnancy" (see below). Because laboratory evaluation, including measurement of serum bile acid levels, was performed in only a minority of women, ICP was often missed.

Epidemiology

There are striking geographic and ethnic differences in the incidence of ICP. For example, it is most commonly observed in South America, with the highest incidence rates in Bolivia and Chile (9–16%), particularly among Araucanian Indian women (28%). In contrast, rates of 0.1% to 1.5% have been described in Europe and North America, with relative "hot spots" in Scandinavia and the Baltic states (1–2%)[18]. Some of

the variance is probably explained by different reporting criteria; however, endemic clustering and a positive family history in up to 50% of those affected point towards a genetic predisposition. A higher incidence of ICP is also seen in multiple-gestation pregnancies, which may be related to higher hormonal levels (e.g. estrogen) in these patients.

Pathogenesis

The key element is reduced excretion of bile acids, which leads to increased serum levels. This not only provokes severe pruritus in the mother, but also may have deleterious effects on the fetus. Toxic bile acids crossing the placenta can lead to acute fetal anoxia due to abnormal uterine contractility and vasoconstriction of chorionic veins as well as impaired fetal cardiomyocyte function[18]. One predisposing factor is mutations in genes (e.g. *ABCB4*) that encode bile transporter proteins[19]. While mild dysfunction of these canalicular transporters may not lead to clinical symptoms in non-pregnant individuals, when the transporters' capacity to secrete substrates is exceeded (as occurs in the setting of high levels of sex hormones during pregnancy), signs and symptoms of cholestasis can develop. Other contributing factors are the cholestatic effect of estrogen and progesterone metabolites, which peak late during pregnancy, and hepatitis C viral infection (see below). Furthermore, dietary factors such as selenium deficiency and increased intestinal permeability ("leaky gut") have been suggested as possible triggers.

Clinical Features

Patients typically present during their last trimester with a sudden onset of intense, generalized pruritus that often starts on the palms and soles. No primary skin lesions are seen, and secondary changes due to scratching vary from subtle excoriations early on to pronounced prurigo nodularis in those with pruritus of longer duration (Fig. 27.6). The extensor surfaces of the extremities, buttocks and abdomen are usually most severely affected.

Although jaundice is often mentioned as a common finding in ICP, it actually occurs in only 10% of patients. Jaundice is usually a complication in those with the most severe and prolonged episodes of ICP. In such patients, concomitant extrahepatic cholestasis may be associated with steatorrhea and subsequent vitamin K deficiency, leading to an increased risk of intra- and postpartum hemorrhage.

Pruritus typically persists until delivery and then it resolves spontaneously within days. A protracted course is very unusual and should prompt one to exclude other liver diseases, especially primary biliary cirrhosis. Recurrence during subsequent pregnancies occurs in 45–70% of patients, and recurrence with oral contraceptives is routine. No detectable abnormalities are generally present between gestations.

ICP is associated with significant fetal risk, in particular an increase in premature births (20–60%), intrapartum fetal distress (20–30%; e.g. meconium staining of amniotic fluid, abnormal fetal heart rate), and fetal loss (1–2%)[18]. Fetal risk correlates with the elevation in serum bile acid levels, especially when levels exceed 40 µmol/l[20]. Thus, prompt diagnosis and treatment is essential, as is close obstetric surveillance.

Pathology

Histologic findings in the skin and the liver are nonspecific and direct IF of perilesional skin is negative. The diagnosis is confirmed by an increase in total serum bile acid levels (>11 µmol/l in a pregnant woman; normal range in non-pregnant women, 0–6 µmol/l). Levels may range from 3 to 100 times normal. During pregnancy, alkaline phosphatase levels typically increase (placental origin) even in the absence of ICP, and γ-glutamyl transferase levels are usually lower than in the non-pregnant state. Serum levels of transaminases are usually elevated in those with ICP, but may be normal in 30% of patients[21]. In women with jaundice, conjugated (direct) bilirubin levels are increased and the prothrombin time may be prolonged. Hepatic ultrasonography generally is normal but may reveal gallstones in jaundiced patients (who are at increased risk for their development).

Differential Diagnosis

In the absence of primary lesions, the clinical differential diagnosis includes other causes of primary pruritus (see Ch. 6), including those that lead to cholestatic pruritus. Viral hepatitis is a common disorder and should be excluded by appropriate serologies. Of note, a history of hepatitis C viral infection is considered a risk factor for the development of ICP, and in one study, 20% of the women who were HCV RNA-positive developed ICP[22].

Fig. 27.6 Intrahepatic cholestasis of pregnancy. Marked pruritus leads to secondary skin lesions that vary based on disease duration, from subtle linear excoriations and prurigo simplex early on (**A**) to pronounced prurigo nodularis when the pruritus is longstanding (**B**). *From Ambros-Rudolph CM, Glatz M, Trauner M, Kerl H, Müllegger RR. The importance of serum bile acid level analysis and treatment with ursodeoxycholic acid in intrahepatic cholestasis of pregnancy: a case series from central Europe. Arch Dermatol. 2007;143:757–62. © (2006) American Medical Association. All rights reserved.*

Treatment

Since fetal prognosis correlates with disease severity, the therapeutic goal is reduction of serum bile acid levels. This allows prolongation of the pregnancy and lessens both fetal risk and maternal symptoms. To date, the only successful agent has been oral ursodeoxycholic acid (UDCA)[18,21,23,24]. It is a naturally occurring, hydrophilic, non-toxic bile acid that has been used for a variety of cholestatic liver diseases. Although the exact mechanism of action in ICP is still not fully understood, there is evidence that UDCA corrects the maternal serum bile acid profile, decreases the passage of maternal bile acids to the fetoplacental unit, and improves the function of the bile acid transport system

across the trophoblast. UDCA is safe for mother and fetus, with its only side effect being mild diarrhea. Use of UDCA for ICP is off-label as it is only approved for primary biliary cirrhosis. The recommended oral dose is 15 mg/kg daily or, independent of body weight, 1 g daily. It should be started as early as possible and administered until delivery.

The use of S-adenosylmethionine, dexamethasone, epomediol, silymarin, phenobarbital or activated charcoal is not recommended as none have been shown to decrease fetal risk. Cholestyramine is contraindicated as it can further reduce vitamin K absorption and increase the risk of bleeding[24]. In jaundiced patients, the prothrombin time should be monitored, and intramuscular vitamin K administered as necessary. Close interdisciplinary collaboration with the obstetrician is essential and close monitoring of the fetus is recommended.

ATOPIC ERUPTION OF PREGNANCY

Synonyms: ■ Prurigo of pregnancy ■ Besnier's "prurigo gestationis" ■ Nurse's "early onset prurigo" of pregnancy ■ Spangler's "papular dermatitis of pregnancy" ■ Pruritic folliculitis of pregnancy ■ Eczema in pregnancy

Key features

- Eczematous and/or papular skin lesions in a patient with an atopic diathesis in whom other specific dermatoses have been excluded
- Most common pruritic disorder during pregnancy
- Generally appears earlier than other pregnancy-related dermatoses (75% before the third trimester)
- Nonspecific histology; negative direct IF; elevated serum IgE levels in up to 70% of patients
- No maternal or fetal risks; commonly recurs in subsequent pregnancies

Introduction

Atopic eruption of pregnancy (AEP) is defined as either an *exacerbation* or the *first occurrence* of eczematous and/or papular skin changes during pregnancy in atopic individuals. As the majority of patients belong to the second group, the atopic link is often overlooked, leading to a number of different diagnoses, as evidenced by the many synonyms.

History

In retrospect, an association with atopy dates back to the first reports. When Besnier described the disorder "prurigo gestationis" in 1904, "prurigo" was the term dermatologists used for atopic dermatitis (Besnier was the first to note the association between atopic dermatitis, allergic rhinitis and asthma). Nurse, in 1968, described accompanying eczematous features in most of the 31 patients in his "early onset" prurigo group. In 1983, Holmes and Black were the first to suggest that "prurigo of pregnancy" could simply result from pregnancy-related pruritus in women with an atopic diathesis rather than being a distinct entity[3].

Epidemiology

AEP is by far the most common pruritic disorder in pregnant women and it tends to appear earlier than the other pregnancy-related dermatoses[1]. Its incidence is not known but may be as high as 1 in 5 to 1 in 20.

Pathogenesis

To prevent fetal rejection, a normal pregnancy is characterized by a lack of strong maternal cell-mediated immune function and reduced Th1 cytokine production (e.g. IL-12, interferon-γ) as well as a dominant humoral immune response with increased Th2 cytokine production (e.g. IL-4, IL-10). This natural switch towards a dominant Th2 response, which worsens the imbalance already present in most atopic patients, is thought to favor the development of AEP[1].

Clinical Features

In contrast to the other specific dermatoses of pregnancy, AEP appears earlier, often during the first trimester, with 75% of patients presenting before the third trimester. Approximately 20% of women experience an exacerbation of pre-existing atopic dermatitis, while the remaining 80% develop atopic skin changes for the first time during pregnancy. Two-thirds of patients present with eczematous lesions (Fig. 27.7), often involving "atopic sites" such as the face, neck, and flexural aspects of the extremities. One-third develop a papular eruption on the trunk and extremities, composed of either classic prurigo lesions or small erythematous papules (Fig. 27.8). Findings typically include xerosis (often marked) and other signs of the underlying atopic diathesis (see Ch. 12). Fetal and maternal prognoses are excellent and recurrences in subsequent pregnancies are common.

Pathology

Depending on the stage of the lesion, histologic features can vary. Epidermal changes include spongiosis, acanthosis and erosions; the dermal infiltrate is composed of lymphocytes and usually admixed eosinophils. If the histologic section includes a hair follicle, there may be sterile follicular inflammation. Direct IF is negative. Serum IgE levels may be elevated in up to 70% of patients, usually to a mild degree.

Differential Diagnosis

Of the specific pregnancy dermatoses, PEP and ICP are the ones that in particular need to be excluded. In AEP, the eruption starts significantly earlier during gestation and has no association with striae; serum bile acid levels are also normal. Furthermore, other pruritic dermatoses not specifically associated with pregnancy (e.g. scabies, viral exanthems, drug eruptions) must be considered.

Fig. 27.7 Atopic eruption of pregnancy. Eczematous lesions often involving flexural areas and friction sites (**A,B**), as well as the breasts and abdomen (**B**). These changes are seen in approximately two-thirds of patients.

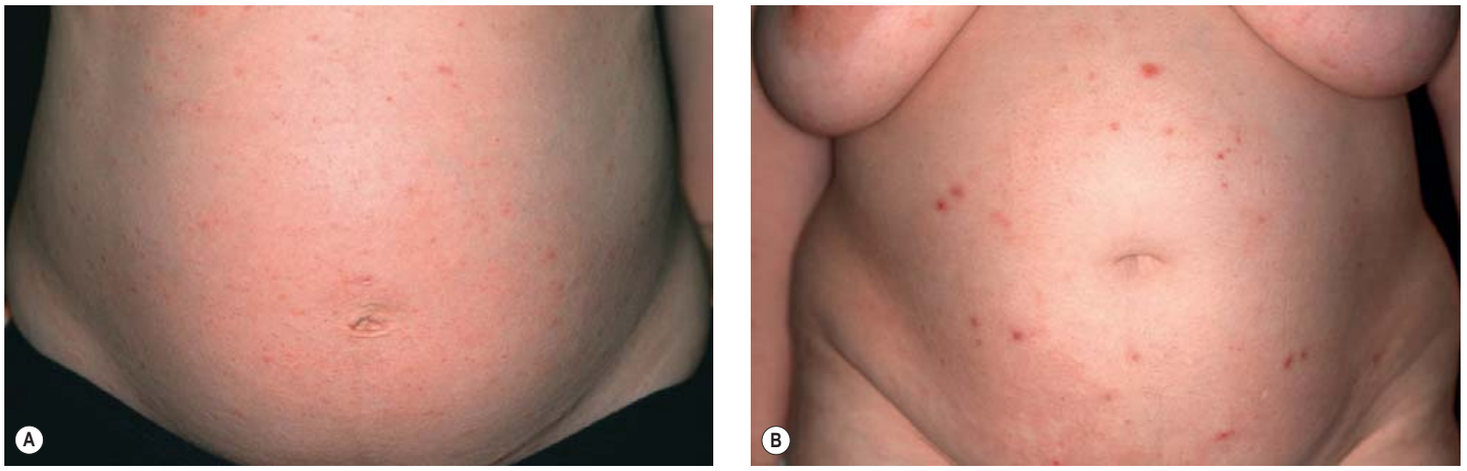


Fig. 27.8 Atopic eruption of pregnancy. Scattered small erythematous papules (**A**) or excoriated prurigo lesions (**B**) favor the abdomen and extremities. These changes are seen in approximately one-third of patients. Note the absence of striae distensae.

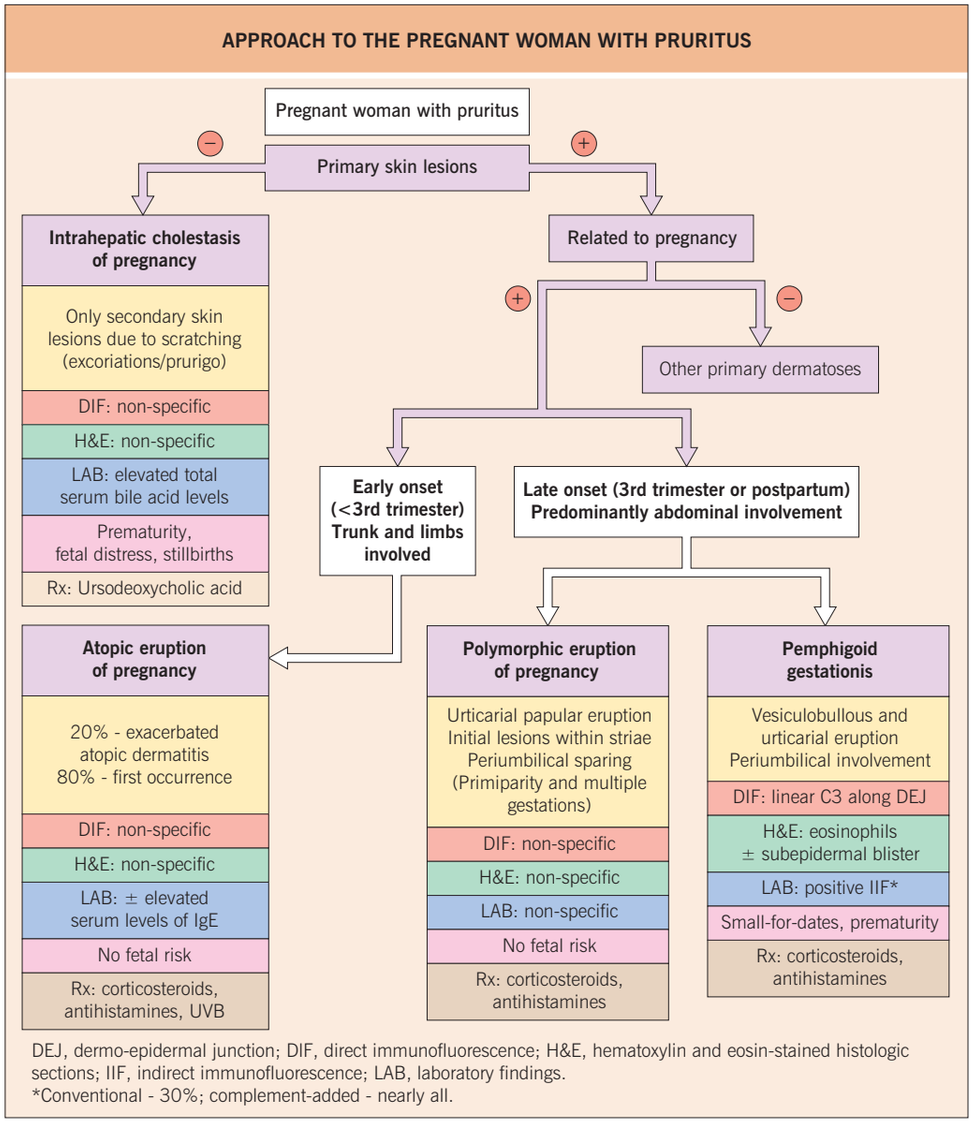


Fig. 27.9 Approach to the pregnant woman with pruritus[1]**.** Patients with refractory pemphigoid gestationis may benefit from plasmapheresis during pregnancy. See Table 27.3 for special considerations regarding the use of corticosteroids (topical and oral) and antihistamines during pregnancy.

Treatment

Cutaneous lesions respond rapidly to topical corticosteroids with or without systemic antihistamines. Emollients, humectants and topical antipruritic agents also play a role, as they do in non-pregnant patients with atopic dermatitis. Topical urea (10%), polidocanol and menthol are considered safe during pregnancy. UVB irradiation is very helpful for severe disease. Secondary bacterial infection may require systemic antibiotics (e.g. penicillins, cephalosporins).

APPROACH TO THE PREGNANT WOMAN WITH PRURITUS

Pruritus is the major symptom in all four of the pregnancy-related dermatoses, but it may also be associated with coincidental dermatoses (e.g. scabies, urticaria, pityriasis rosea). A pregnant woman with severe pruritus and skin lesions requires urgent clinicopathologic assessment, given the possibility of associated fetal risks. Figure 27.9 is an algorithm that has proven helpful in distinguishing amongst the various pruritic dermatoses of pregnancy[1]. Primiparity and multiple gestations are significantly linked to PEP, while a history of identical skin findings in past pregnancies (recurrence) suggests ICP. An early presentation (75% before the third trimester) is typical for AEP, while the other disorders present late during pregnancy or postpartum. Abdominal location of skin lesions is characteristic of pemphigoid gestationis and PEP, involvement of the trunk and extremities of AEP, and predominant involvement of the extremities of ICP. Pruritus as the sole presenting symptom followed by exclusively secondary cutaneous lesions due to scratching is only seen in ICP.

PHYSIOLOGIC CHANGES DURING PREGNANCY

Table 27.4 outlines many of the physiologic changes that have been associated with pregnancy. While some are very common, such as hyperpigmentation, others are more loosely associated, for example, nail changes. The majority of changes spontaneously regress following delivery[26].

AUTOIMMUNE PROGESTERONE DERMATITIS

Although autoimmune progesterone dermatitis is not a specific dermatosis of pregnancy, it can first appear during pregnancy or postpartum[27]. Classically, there are recurrent cyclic flares of dermatitis that correspond to the luteal phase of the menstrual cycle (when progesterone levels increase). In addition to eczematous changes, lesions can vary from urticaria to papulovesicles to erythema multiforme-like. Some patients have primarily pruritus or oral erosions. At sites of intradermal

PHYSIOLOGIC CHANGES DURING PREGNANCY	
PIGMENTARY	
Hyperpigmentation (e.g. areolae, linea nigra; Figure 27.10) Melasma	Hyperpigmentation (up to 90% of patients) and melasma (up to 70% of patients) are presumably of hormonal etiology. Melasma tends to persist postpartum in those with darkly pigmented skin types
HAIR	
Hirsutism Postpartum telogen effluvium Postpartum androgenetic alopecia	Some hirsutism is normal and typically regresses postpartum. Telogen effluvium may last up to 15 months. Postpartum patterned alopecia may or may not revert to normal
NAIL	
Subungual hyperkeratosis Distal onycholysis Transverse grooving Brittleness	There are no pathognomonic nail changes
GLANDULAR	
Increased eccrine function (except palms) Increased sebaceous function Decreased apocrine function	The effect of pregnancy on glandular function is contradictory. Eccrine function seems to increase (except on the palms). However, the effect on apocrine function and sebaceous gland activity is incompletely understood
CONNECTIVE TISSUE	
Striae	Striae gravidarum develop in up to 90% of patients and often resolve. Both hormonal factors and physical stretching of the skin appear to be relevant in their development
VASCULAR	
Spider angiomas Palmar erythema (Figure 27.10) Non-pitting edema Varicosities Vasomotor instability Purpura Gingival hyperemia or hyperplasia Pyogenic granuloma Hemorrhoids	Vascular changes result from distention, instability and new vessel formation. Clinically obvious changes are most pronounced during the third trimester and most changes regress spontaneously following delivery

Table 27.4 Physiologic changes during pregnancy. *Adapted from Kroumpouzos G, Cohen LM. Dermatoses of pregnancy. J Am Acad Dermatol. 2001;45:1–19.*

Fig. 27.10 Physiologic changes during pregnancy. Palmar erythema of pregnancy (**A**) and linea nigra (**B**).

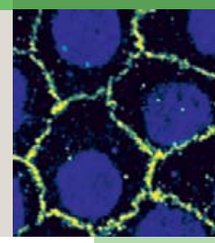
injection of progesterone (e.g. 50 mg/ml), the vast majority of affected patients develop a cutaneous reaction characterized by urticaria (immediate [30 min]) and/or erythema and induration (delayed [24–48 h])[27]. Injections of saline and estrogen (e.g. estrone [1 mg/ml]) are often done concurrently, to serve as a control and to examine for evidence of estrogen dermatitis[28], respectively. Both oral and intramuscular progesterone have been used as a challenge test in patients with delayed reactions. Treatment consists primarily of inhibiting ovulation via estrogen-containing preparations. Anecdotally, additional reported therapies include tamoxifen and danazol, each possibly suppressing ovulation via interaction with the hypothalamic–pituitary axis. Of note, some patients have had remissions during pregnancy.

REFERENCES

1. Ambros-Rudolph CM, Müllegger RR, Vaughan-Jones SA, et al. The specific dermatoses of pregnancy revisited and reclassified. Results of a retrospective two-center study on 505 pregnant patients. J Am Acad Dermatol. 2006;54:395–404.
2. Holmes RC, Black MM. The specific dermatoses of pregnancy. J Am Acad Dermatol. 1983;8:405–12.
3. Shornick JK. Dermatoses of pregnancy. Semin Cutan Med Surg. 1998;17:172–81.
4. Vaughan Jones SA, Hern S, Nelson-Piercy C, et al. A prospective study of 200 women with dermatoses of pregnancy correlating clinical findings with hormonal and immunopathological profiles. Br J Dermatol. 1999;141:71–81.
5. Roger D, Vaillant L, Fignon A, et al. Specific pruritic diseases of pregnancy. A prospective study of 3192 pregnant women. Arch Dermatol. 1994;130:734–9.
6. Kolodny RC. Herpes gestationis: a new assessment of incidence, diagnosis and fetal prognosis. Am J Obstet Gynecol. 1969;104:39–45.
7. Shornick JK, Black MM. Secondary autoimmune diseases in herpes gestationis (pemphigoid gestationis). J Am Acad Dermatol. 1992;26:563–6.
8. Ortonne JP, Hsi BL, Verrando P, et al. Herpes gestationis factor reacts with the amniotic epithelial basement membrane. Br J Dermatol. 1987;117:147–54.
9. Shornick JK, Jenkins RE, Briggs DC, et al. Anti-HLA antibodies in pemphigoid gestationis (herpes gestationis). Br J Dermatol. 1993;129:257–9.
10. Kelly SE, Black MM, Fleming S. Pemphigoid gestationis: a unique mechanism of initiation of an autoimmune response by MHC class II molecules? J Pathol. 1989;158:81–2.
11. Chi CC, Wang SH, Holmes RC, et al. Pemphigoid gestationis: early onset and blister formation are associated with adverse pregnancy outcomes. Br J Dermatol. 2009;160:1222–8.
12. Lawley TJ, Hertz KC, Wade TR, et al. Pruritic urticarial papules and plaques of pregnancy. JAMA. 1979;241:1696–9.
13. Holmes RC. Polymorphic eruption of pregnancy. Semin Dermatol. 1989;8:18–22.
14. Kroumpouzos G, Cohen LM. Specific dermatoses of pregnancy: an evidence-based systematic review. Am J Obstet Gynecol. 2003;188:1083–92.
15. Rudolph CM, Al-Fares S, Vaughan-Jones SA, et al. Polymorphic eruption of pregnancy: clinicopathology and potential trigger factors in 181 patients. Br J Dermatol. 2006;154:54–60.
16. Ahmadi D, Powell FC. Pruritic urticarial papules and plaques of pregnancy: current status. Australas J Dermatol. 2005;46:53–8.
17. Uhlin SR. Pruritic urticarial papules and plaques of pregnancy. Involvement of mother and infant. Arch Dermatol. 1981;117:238–9.
18. Lammert F, Marschall HU, Glantz A et al. Intrahepatic cholestasis of pregnancy: molecular pathogenesis, diagnosis and management. J Hepatol. 2000;33:1012–21.
19. Ropponen A, Sund R, Riikionen S, et al. Intrahepatic cholestasis of pregnancy as an indicator of liver and biliary diseases: a population-based study. Hepatology. 2006;43:723–8.
20. Glantz A, Marschall HU, Mattsson LA. Intrahepatic cholestasis of pregnancy: relationships between bile acid levels and fetal complication rates. Hepatology. 2004;40:467–74.
21. Ambros-Randolph CM, Glatz M, Trauner M, et al. The importance of serum bile acid level analysis and treatment with ursodeoxycholic acid in intrahepatic cholestasis of pregnancy. Arch Dermatol. 2007;143:757–62.
22. Paternoster DM, Fabris F, Palù G, et al. Intra-hepatic cholestasis of pregnancy in hepatitis C virus infection. Acta Obstet Gynecol Scand. 2002;81:99–103.
23. Zapata R, Sandoval L, Palma J, et al. Ursodeoxycholic acid in the treatment of intrahepatic cholestasis of pregnancy. A 12-year experience. Liver Int. 2005;25:548–54.
24. Kondrackiene J, Beuers U, Kupcinskas L. Efficacy and safety of ursodeoxycholic acid versus cholestyramine in intrahepatic cholestasis of pregnancy. Gastroenterology. 2005;129:895–901.
25. Briggs GG, Freeman RK, Yaffe, SJ. Drugs in Pregnancy and Lactation. A Reference Guide to Fetal and Neonatal Risk, 8th edn. Philadelphia: Lippincott Williams & Wilkins, 2008.
26. Kroumpouzos G, Cohen LM. Dermatoses of pregnancy. J Am Acad Dermatol. 2001;45:1–19.
27. Herzberg AJ, Strohmeyer CR, Cirillo-Hyland VA. Autoimmune progesterone dermatitis. J Am Acad Dermatol. 1995;32:333–8.
28. Shelley WB, Shelley ED, Talanin NY, Santoso-Pham J. Estrogen dermatitis. J Am Acad Dermatol. 1995;32:25–31.

The Biology of the Basement Membrane Zone

28



Kim B Yancey

Chapter Contents

Origin of the epidermal basement membrane *450*
Hemidesmosome-anchoring filament complexes and integrins in the plasma membranes of basal keratinocytes..... *450*
The lamina densa *452*
Anchoring fibrils and the sublamina densa region *455*
The epidermal basement membrane in bullous diseases..... *456*

Synonyms: ■ Bullous pemphigoid antigen 1: BP230 ■ Bullous pemphigoid antigen 2: BP180; type XVII collagen ■ Laminin 332: laminin 5; epiligrin; kalinin; nicein; GB3 antigen; BM600 ■ Type VII collagen: the epidermolysis bullosa acquisita antigen ■ Nidogen: entactin

Key features

- Basement membranes serve as: (1) a substrate for attachment of cells; (2) a template for tissue repair; (3) a matrix for cell migration; (4) a substratum to influence differentiation, morphogenesis and apoptosis of epithelial cell layers; and (5) a permeability barrier for cells and macromolecules
- By transmission electron microscopy, the major ultrastructural subregions (from superior to inferior) of the epidermal basement membrane are: (1) the cytoskeleton, hemidesmosomal plaques and plasma membranes of basal keratinocytes; (2) an electron-lucent region termed the lamina lucida; (3) the lamina densa (or basement membrane proper); and (4) the sublamina densa region of the papillary dermis
- In the "laminated" model of the epidermal basement membrane, keratin intermediate filaments in basal keratinocytes attach to small (i.e. <0.5 microns), electron-dense units (hemidesmosomes) on the basal plasma membranes of these cells. In turn, anchoring filaments (small thread-like strands) connect hemidesmosomes to the lamina densa. The lamina densa is tethered to the dermis by anchoring fibrils, units that by originating and ending in the underside of the lamina densa create ultrastructural loops that serve as attachment sites for fibrillar proteins in the papillary dermis
- Acquired or inherited abnormalities in structural proteins within the epidermal basement membrane often result in a disease phenotype characterized by blister formation

INTRODUCTION

Basement membranes are specialized structures located between cells and their underlying stroma or between different cell types[1]. Basement membranes of various tissues differ ultrastructurally, biochemically and functionally. All basement membranes contain an electron-dense, somewhat granular matrix of variable thickness that is referred to as the lamina densa. Major components of the lamina densa include type IV collagen, laminin and heparan sulfate proteoglycan. Other components of the lamina densa vary depending upon the tissue type. Basement membranes serve a variety of functions that are manifest in a tissue-specific manner. Roles common to virtually all basement membranes include acting as: (1) substrates for attachment of cells; (2) templates for tissue repair; (3) matrices for cell migration; (4) substrata to influence differentiation, morphogenesis and apoptosis of epithelial cell layers; and (5) permeability barriers for cells and macromolecules. The two major basement membrane complexes in skin are found at the epidermal–dermal interface and around the dermal microvasculature. This chapter will deal largely with the epidermal basement membrane.

The epidermal basement membrane is a highly specialized structure that contains numerous tissue-specific elements (Table 28.1). The first characterization of this ultrastructural region in the skin was made by electron microscopists, who identified four distinct subregions of the epidermal basement membrane (Fig. 28.1). These subregions, from superior to inferior distribution, are:

- the cytoskeleton, hemidesmosomal plaques and plasma membranes of basal keratinocytes

REPRESENTATIVE ADHESION PROTEINS IN THE EPIDERMAL BASEMENT MEMBRANE
CYTOSKELETON OF BASAL KERATINOCYTES
• Keratin 5 • Keratin 14
HEMIDESMOSOME-ANCHORING FILAMENT COMPLEXES
• Plectin • Bullous pemphigoid antigen 1 • Bullous pemphigoid antigen 2 (type XVII collagen) • Integrin subunit α_6 • Integrin subunit β_4 • Tetraspan CD151 • Laminin 332 (formerly laminin 5)
LAMINA DENSA
• Heparan sulfate proteoglycans (e.g. perlecan) • Laminin 332 • Laminin 311 (formerly laminin 6) • Laminin 511 (formerly laminin 10) • Nidogen • Type IV collagen
SUBLAMINA DENSA REGION
• Type VII collagen • Type IV collagen • Elastin • Fibulins (glycoproteins found in microfibrillar bundles in the papillary dermis) • Fibrillins (large proteins that form an integral part of the microfibril structure) • Latent TGF-β-binding proteins • Linkin (main component of microthread-like fibers that comprise a delicate mesh-like network in the upper papillary dermis) • Type III collagen • Type I collagen

Table 28.1 Representative adhesion proteins in the epidermal basement membrane. TGF-β, transforming growth factor β.

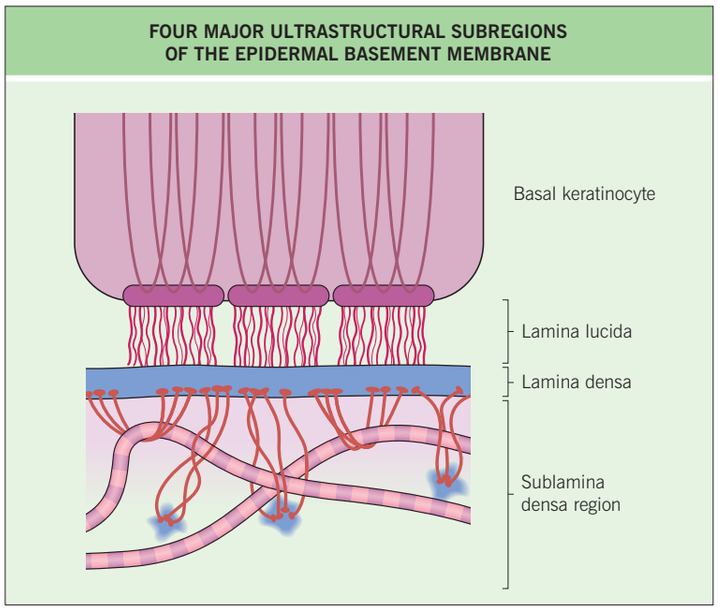


Fig. 28.1 Four major ultrastructural subregions of the epidermal basement membrane. The four major ultrastructural subregions of the epidermal basement membrane consist of the following: (1) cytoskeleton, hemidesmosomal plaques and plasma membranes of basal keratinocytes; (2) electron-lucent lamina lucida; (3) lamina densa; and (4) sublamina densa region of the papillary dermis.

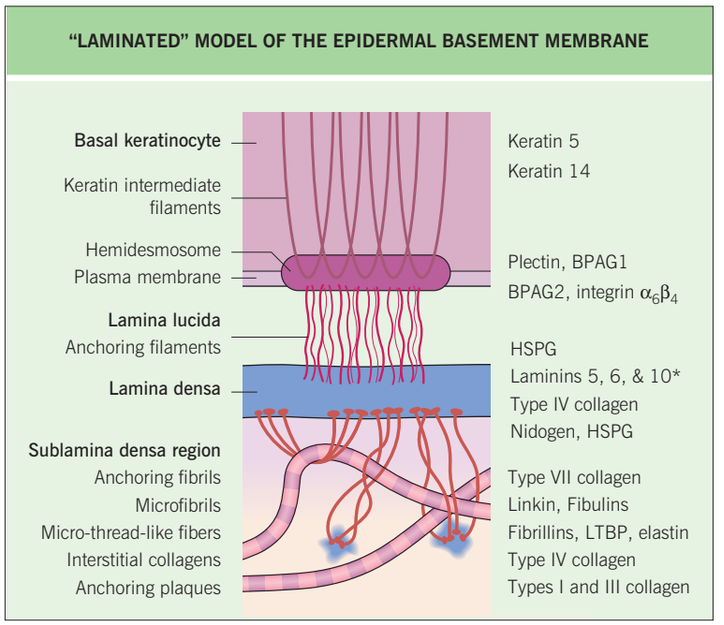


Fig. 28.2 "Laminated" model of the epidermal basement membrane. In the laminated model, keratin intermediate filaments attach to electron-dense hemidesmosomes on the basal plasma membranes of keratinocytes. Hemidesmosomes connect to the underlying lamina densa (basement membrane proper) by small thread-like strands termed anchoring filaments. The lamina densa and the overlying epidermis are tethered to the papillary dermis by anchoring fibrils, a series of looping elements along the underside of the lamina densa that serve as attachment sites for fibrillar proteins in the papillary dermis. *Laminins 5, 6 and 10 are now termed laminins 332, 311 and 511 (see Table 28.3). HSPG, heparan sulfate proteoglycans; LTBP, latent TGF-β-binding proteins.

- an electron-lucent region called the lamina lucida that contains delicate filaments connecting hemidesmosomes (HDs) in basal keratinocytes to the underlying lamina densa
- the lamina densa or basement membrane proper
- the sublamina densa region containing anchoring fibrils, anchoring plaques and filamentous proteins of the papillary dermis.

These subregions of the epidermal basement membrane, readily identified in fixed skin samples by transmission electron microscopy, have served as a useful conceptual model of a highly complex adhesion unit that preserves the integrity of the skin (Fig. 28.2). Interestingly, specialized transmission electron microscopy studies of cryopreserved skin have suggested that the lamina lucida may actually represent an artifact of tissue dehydration[2]. Nonetheless, the classic laminated model of the epidermal basement membrane serves as a useful framework to guide understanding of its structure, function and impairment in disease.

ORIGIN OF THE EPIDERMAL BASEMENT MEMBRANE

The epidermal basement membrane is comprised of proteins derived from keratinocytes of ectodermal origin as well as dermal fibroblasts of mesodermal origin. Proteins in HDs (i.e. plectin, bullous pemphigoid antigen 1 [BPAG1], bullous pemphigoid antigen 2 [BPAG2] and integrin subunits α_6 and β_4), CD151 tetraspan, types IV and VII collagen, laminins 332 ($\alpha3\beta3\gamma2$; formerly known as laminin 5) and 311 ($\alpha3\beta1\gamma1$; formerly known as laminin 6), and heparan sulfate proteoglycans are produced by basal keratinocytes and incorporated within the epidermal basement membrane. Dermal fibroblasts produce nidogen (entactin), types IV and VII collagen, and other proteins that are translocated to plasma membranes of basal keratinocytes where they condense and are incorporated within the epidermal basement membrane. Integrins and other proteins within the plasma membrane of basal keratinocytes are thought to provide key localization and organizational cues that facilitate the incorporation of fibroblast-derived proteins within the epidermal basement membrane. The major proteins that comprise the various subregions of the epidermal basement membrane are described below (Fig. 28.3).

HEMIDESMOSOME-ANCHORING FILAMENT COMPLEXES AND INTEGRINS IN THE PLASMA MEMBRANES OF BASAL KERATINOCYTES

Plectin

Plectin is a 500 kDa protein associated with the cytoplasmic plaque of HDs[3]. It is a member of the plakin family and consists of large, multidomain cytolinker proteins that connect cytoskeletal networks to each other and to adhesive junctions such as desmosomes and HDs; additional members of the plakin family include BPAG1 (see below), desmoplakin, periplakin and envoplakin (see Ch. 29).

The carboxy terminus of plectin binds intermediate filaments (specifically, keratins or vimentin) and the amino terminus contains domains that bind the cytoplasmic tail of integrin subunit β_4, BPAG2 and actin[4]. Hence, plectin attaches intermediate filaments to HDs and plasma membranes of basal keratinocytes and also cross-links other proteins associated with the cytoplasmic plaques of HDs[5]. Mutations in the gene encoding plectin are responsible for epidermolysis bullosa (EB) simplex associated with muscular dystrophy as well as for the Ogna type of EB simplex and a rare subset of EB simplex with pyloric atresia (see Ch. 32). Targeted inactivation of the gene encoding plectin impairs the cytoarchitecture of skin, muscle and heart in mice[6].

Bullous Pemphigoid Antigen 1

Circulating autoantibodies from patients with bullous pemphigoid (BP) were used to define two autoantigens that reside in HDs of basal keratinocytes. The first of these autoantigens characterized (BPAG1) is a plakin and, like other proteins of this family, plays an important role in promoting adhesion of the intermediate filament cytoskeleton with adhesion units (in this case, HDs) in plasma membranes[7].

BPAG1 is a 230 kDa non-collagenous protein localized to the cytoplasmic plaque of HDs[8]. It has a central coiled-coil α-helical rod domain that contains a regular periodicity of acidic and basic amino acid

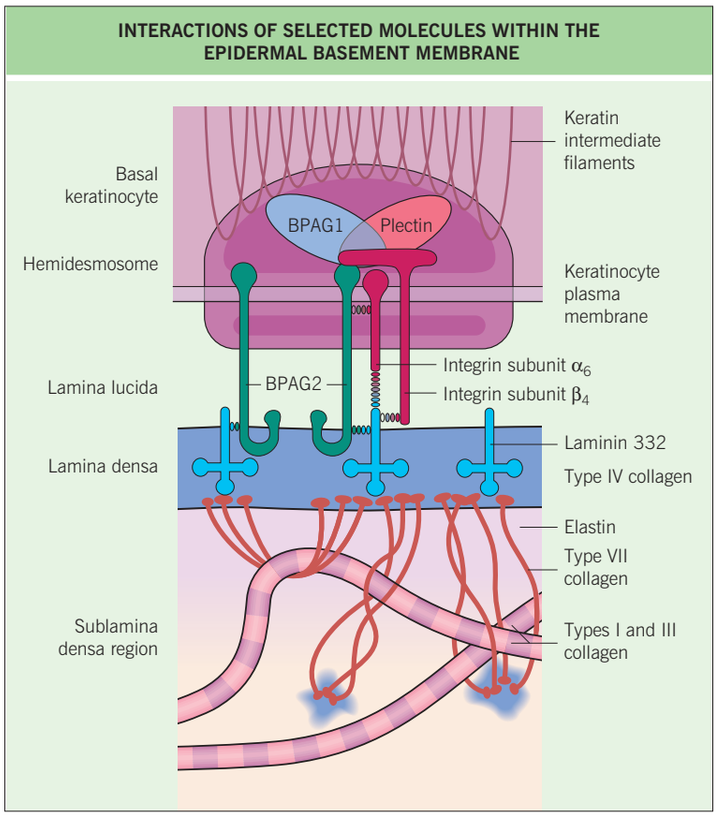


Fig. 28.3 Interactions of selected molecules within the epidermal basement membrane. These interactions promote epidermal adhesion and also play a key role in a number of dermatologic diseases. Important molecular interactions include those between: (1) plakin family members, BPAG1 and plectin, with keratin intermediate filaments; (2) the former with BPAG2 and integrin $\alpha_6\beta_4$ (specifically, the large cytoplasmic domain of integrin subunit β_4); (3) the cytoplasmic domains of BPAG2 and integrin subunit β_4; (4) the extracellular domains of BPAG2 and integrin subunit α_6 as well as laminin 332 (formerly laminin 5); (5) integrin $\alpha_6\beta_4$ in hemidesmosomes and laminin 332 in the lamina densa; (6) laminin 332 and type VII collagen; (7) type VII collagen with type IV collagen, fibronectin, and type I collagen in the sublamina densa region.

TARGETS COMMON TO AUTOIMMUNE AND INHERITED BLISTERING DISEASES

Protein target	Structural target	Autoimmune disease	Genetic disease
BPAG1	HD	BP	Recessive EB simplex
Type XVII collagen (BPAG2)	HD-anchoring filament complexes	BP, PG, MMP, linear IgA bullous dermatosis	Junctional EB-non-Herlitz
Integrin subunit β_4	HD-anchoring filament complexes	Ocular MMP	Junctional EB with pyloric atresia
Laminin 332 (formerly 5)	Lamina lucida–lamina densa interface	Anti-epiligrin MMP	Junctional EB-Herlitz
Type VII collagen	Anchoring fibrils	EB acquisita Bullous eruption of SLE	Dystrophic EB (dominant and recessive)

Table 28.2 Targets common to autoimmune and inherited blistering diseases. BP, bullous pemphigoid; EB, epidermolysis bullosa; HD, hemidesmosome; MMP, mucous membrane (cicatricial) pemphigoid; PG, pemphigoid gestationis; SLE, systemic lupus erythematosus.

residues. Studies showing that the periodicities of these residues are 180 degrees out of phase suggested that these proteins may self-aggregate by ionic interactions. The globular carboxy terminus of BPAG1 contains acidic and basic amino acids with a periodicity that promotes association with keratin intermediate filaments. The amino terminus of BPAG1 associates with the cytoplasmic domain of BPAG2, the integrin subunit β_4 and ERBIN (a protein that interacts with the transmembrane tyrosine kinase receptor Erb-B2, thus serving as a potential link between HD biology and Erb-B2 signaling)[5,9].

Consistent with the role that BPAG1 plays in cytoskeletal organization, BPAG1 knockout mice show signs of epithelial fragility in basal keratinocytes[10]. Unexpectedly, these mice also demonstrate neurologic impairment characterized by dystonia and ataxia. Neurologic manifestations in BPAG1 knockout mice develop as a consequence of concomitant inactivation of neuronal isoforms of BPAG1 referred to as nBPAG1 (or dystonin). The amino termini of neuronal isoforms of BPAG1 differ from their epithelial counterparts in that nBPAG1 contains either actin- or microtubule-binding domains essential for maintaining the cytoarchitecture of neurons. Recently, a homozygous mutation in each copy of the gene that encodes BPAG1 (affecting the epithelial isoform and a putative minor neuronal isoform with an unknown expression pattern) was found to underlie a novel form of EB simplex in a man who also had neurologic abnormalities[11].

Bullous Pemphigoid Antigen 2

BPAG2 is a type II transmembrane collagen (specifically, type XVII collagen) associated with HD-anchoring filament complexes in basal keratinocytes[12]. The cytoplasmic amino terminus of BPAG2 consists of approximately 500 amino acid residues, containing several potential phosphorylation sites within its central portion. The extracellular domain of BPAG2 contains 15 interrupted repeats that have multiple glycine-X-Y amino acid sequences; the latter are characteristic of proteins in the collagen family (see Ch. 95) and therefore are referred to as collagenous domains (coll 1–15; see Fig. 31.9). The deduced length of the largest collagenous domain of BPAG2 (coll 15) suggests that this portion of the protein spans the lamina lucida. By rotary shadowing of purified BPAG2, the intracytoplasmic region appears as a globular head and the extracellular region as a central rod (corresponding to coll 15) with a flexible tail (corresponding to coll 1–14)[13]. Immunoelectron microscopy studies suggest that the rod domain of BPAG2 inserts into the lamina densa and that its carboxy-terminal tail then loops back through the lamina densa into the lamina lucida (see Fig. 28.3)[14,15].

BPAG2 occurs in two forms[16]: (1) the 180 kDa full-length protein; and (2) the 120 kDa extracellular domain that is shed from plasma membranes of basal keratinocytes by proteolysis. Proteolytic processing of BPAG2 is mediated by "sheddases" of the disintegrin and metalloproteinase (ADAM) family (in particular the tumor necrosis factor-α-converting enzyme, TACE). Phosphorylation of BPAG2 by ecto-casein kinase 2 inhibits its proteolysis by TACE, a mechanism whereby the adhesion and motility of adjacent basal keratinocytes may be modulated[17].

After processing, the extracellular domain of BPAG2 is retained within the epidermal basement membrane as a homotrimer in which the collagenous domains form a cross-linked triple helix. The helix forms independently of amino acid sequences in the amino terminal portion of BPAG2 and is apparently organized in a 5′ to 3′ orientation using the 16th *n*on-collagenous portion of the protein (NC16) as a nucleation site[18]. The cytoplasmic domain of BPAG2 associates with BPAG1, integrin subunit β_4 and plectin[5]. The first extracellular segment of BPAG2 (NC16) contains 73 amino acid residues that are thought to bind integrin subunit α_6[19]. Immunogold electron microscopy studies have suggested that the carboxy-terminal portion of BPAG2 interacts with laminin 332 at the interface of these two proteins near the junction of the lamina lucida and the lamina densa (see Fig. 28.3)[14].

BPAG2 is targeted by autoantibodies from patients with BP, pemphigoid gestationis (PG), mucous membrane (cicatricial) pemphigoid (MMP) and linear IgA bullous dermatosis (LABD)[20]. Autoantibodies from patients with BP, PG and LABD typically target the NC16A domain of BPAG2 (see Fig. 31.9), whereas those from patients with MMP tend to target the distal carboxy terminus of BPAG2 (which extends deeper into the basement membrane) as well as NC16A. Patients with non-Herlitz subtypes of junctional EB often possess null mutations in the gene encoding BPAG2 (*COL17A1*) (Table 28.2). These individuals characteristically demonstrate a complete lack of BPAG2 in their epidermal basement membrane, along with a tendency for skin

fragility, subepidermal blister formation, alopecia, dystrophic nails and dental enamel hypoplasia[21]. Interestingly, *COL17A1* mutations resulting in deletion of the intracellular domain of BPAG2 that associates with BPAG1, plectin and integrin subunit β_4 result in a phenotype characterized by intraepidermal as well as junctional blister formation[22].

Integrins

Integrins are heterodimeric transmembrane receptors that promote cell–cell and cell–matrix interactions. Ligand binding to integrin receptors modulates cell adhesion, signal transduction, gene expression, growth and other fundamental biologic processes. All integrins are αβ-heterodimers. Numerous α- and β-subunits have been identified; several of these have alternatively spliced cytoplasmic domains (e.g. α_{IIb}, α_3, α_6, α_1 and α_4). Although some of the α-subunits can associate with more than one β-subunit, there is restriction in the number of heterodimers that actually form. Both α- and β-integrin subunits are transmembrane glycoproteins with a single hydrophobic transmembrane domain and a short cytoplasmic domain (i.e. ≤50 amino acid residues). An exception to this design is integrin subunit β_4, which contains a large cytoplasmic domain of >1000 amino acid residues.

The extracellular domains of integrin subunits associate to form dimers; subunits do not rely upon associations in their cytoplasmic or transmembrane regions for dimerization. Both subunits of the heterodimer are required for ligand binding. In fact, α- and β-subunits are thought to form a pocket that serves as a specific ligand-binding site. Switching either the α- or β-subunit can change ligand specificity.

Individual integrins can often bind to more than one ligand, and, similarly, individual ligands are often recognized by more than one integrin. Integrins often bind specific sequences of peptides in a given group of adhesion molecules (e.g. the Arg-Gly-Asp [RGD] sequence present in fibronectin, vitronectin and other adhesion proteins). Integrin ligand binding is divalent cation-dependent, and the cation itself (e.g. Ca^{2+}, Mg^{2+}, Mn^{2+}) can affect the affinity and the ligand specificity of the integrin. Cytoplasmic domains of integrins typically interact with cytoskeletal elements (e.g. talin, vinculin, actin filaments) as well as other intracellular proteins. The cytoplasmic domains and associations of integrin $\alpha_6\beta_4$ represent an exception to this model in that they are concentrated within HDs of epithelial cells[23].

Hemidesmosome-associated integrin $\alpha_6\beta_4$

The large cytoplasmic tail of integrin subunit β_4 contains sequences that appear to be required for HD assembly. The membrane-proximal region of integrin subunit β_4 directly associates with plectin, while its distal carboxyl-terminal region binds BPAG2 (see Fig. 28.3)[24]. Integrin subunit α_6 exists in two forms, A and B; the former predominates in keratinocytes. The proximal extracellular domain of integrin subunit α_6 binds the NC16A region of BPAG2[19]. Using K562 cells stably expressing $\alpha_{6A}\beta_4$ and $\alpha_{6B}\beta_4$, investigators demonstrated that laminins 111 and 332 serve as the preferred ligands for this HD-integrin[25].

Patients harboring biallelic mutations in genes encoding either α_6 or β_4 integrin subunits develop junctional EB associated with pyloric atresia. Such individuals typically have subepithelial blistering of the oral and respiratory epithelia as well as the skin. Targeted deletions of genes encoding murine integrin subunits α_6 or β_4 also result in extensive subepithelial blisters of the same tissues. Evidence of nuclear and cytoplasmic degeneration in basal keratinocytes of β_4-null mice suggests that this integrin subunit plays a role in cell survival[26]. Transgenic mice carrying a targeted deletion of the cytoplasmic domain of integrin subunit β_4 have a proliferative defect of stratified and simple epithelia[27]. However, targeted deletion of integrin subunit α_6 does not result in obvious developmental problems in murine epithelia.

Plasma membrane-associated integrins

Non-hemidesmosomal integrins expressed in basal keratinocytes include integrins $\alpha_2\beta_1$ and $\alpha_3\beta_1$[28]. The former is located predominantly along lateral and apical aspects of basal keratinocytes, and the latter is found in the same distribution as well as along the basal aspect of these cells' plasma membranes. Integrins bind the actin cytoskeleton and are thought to play a key role in cell–cell adhesion. Keratinocytes in culture utilize integrin $\alpha_3\beta_1$ to mediate initial adhesion to extracellular matrix via interaction with laminin 332.

Though integrin $\alpha_3\beta_1$ does not play a role in HD assembly, it is thought to provide key signals regulating cytoskeletal assembly, function of integrin $\alpha_6\beta_1$, and the establishment and/or maintenance of basement membrane integrity[29]. Mice with targeted deletion of integrin subunit α_3 have disorganized basement membranes in the kidney and skin[30]. More specifically, while the lamina densa in these mice is missing (or sparse) at sites between HDs, that beneath their HDs appears to be normal. Mild blistering in mice lacking integrin subunit α_3 further substantiates the idea that this polypeptide plays an important role in maintaining the integrity of the epidermal basement membrane and assembly of extracellular matrix.

Tetraspan CD151

CD151 is a cell surface protein that belongs to the tetraspan superfamily. Tetraspan proteins, named for their four membrane-spanning domains, form "web-like" networks with other membrane proteins and have roles in regulating a variety of cellular processes. To date, CD151 is the only tetraspan known to be associated with HDs. In human skin, CD151 associates with integrins $\alpha_6\beta_4$ (via its α-subunit) and $\alpha_3\beta_1$ in the basolateral plasma membrane of basal keratinocytes. Immunoelectron microscopy studies show that CD151 is concentrated in HDs.

In integrin subunit β_4-deficient keratinocytes, CD151 clusters with $\alpha_3\beta_1$ at the basal cell surface. Introduction of integrin subunit β_4 into the latter cells yields $\alpha_6\beta_4$ integrins that become incorporated into $\alpha_3\beta_1$–CD151 clusters, where they are thought to induce the formation of HDs. Soon thereafter, the amount of $\alpha_3\beta_1$ integrins in such clusters diminishes, and CD151 becomes predominantly associated with $\alpha_6\beta_4$ integrins within HDs. CD151 is therefore considered to be a component of pre-HDs whose recruitment is regulated by integrin $\alpha_6\beta_4$. CD151 is thought to provide a framework for the spatial organization of different HD components[31].

THE LAMINA DENSA

Laminins

Laminins are a family of heterotrimeric glycoproteins composed of at least 15 members[32]. Laminins consist of three subunits (α, β and γ) that are joined and stabilized by interchain disulfide bonds and other associations (Fig. 28.4). Each laminin subunit is encoded by a different

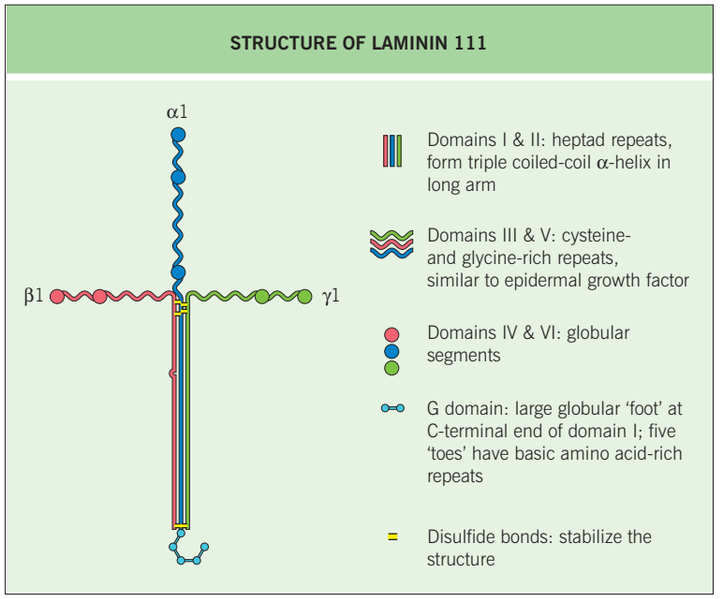


Fig. 28.4 Structure of laminin 111. Laminin 111 (laminin 1) serves as a prototype for the other laminin isoforms, which have similar structure and organization. Laminins consist of three subunits (α, β,γ), each encoded by a different gene and composed of six primary domains (domains I to VI).

gene. To date, five α-subunits, three β-subunits and three γ-subunits have been characterized[32]. Of note, the laminin subunit α3 gene (*LAMA3*) encodes two transcripts, α3A and α3B, corresponding to short and long variants, respectively.

Different laminin isoforms are created by the pairing of various α-, β- and γ-subunits. In the current laminin nomenclature (introduced in 2005 to replace the previous convention of naming isoforms based on the order of their discovery), each isoform's name reflects the numbers of its α-, β- and γ-subunits (e.g. α3, β3 and γ2 in laminin 332, formerly termed laminin 5). Laminin isoforms are distributed in a tissue-specific manner, with each displaying a wide variety of biologic functions. Laminins within basement membranes serve as ligands for overlying cell surface receptors (e.g. integrins), thereby providing key signals regarding the epithelial microenvironment.

The predominant laminins in epidermal basement membranes are 332 (α3β3γ2; formerly laminin 5), 311 (α3β1γ1; formerly laminin 6) and 511 (α5β1γ1; formerly laminin 10). The overall structure of laminins is presented in Figure 28.4 using laminin 111 (α1β1γ1; formerly laminin 1), a primary component of dermal microvascular (but not epidermal) basement membranes, as a prototype. The salient features of the aforementioned laminin isoforms are summarized in Table 28.3.

The essential role that laminin 332 plays in the epidermal basement membrane is exemplified by inherited disruptions in the genes that encode its subunits (*LAMA3, LAMB3, LAMC2*), which yield a phenotype characterized by extensive subepidermal blister formation and often early death in junctional EB-Herlitz. Moreover, patients with one form of MMP have IgG anti-basement membrane autoantibodies against laminin 332[39,40]. Passive transfer of rabbit anti-laminin 332 IgG to mice or of patient IgG to grafts of human skin on immunodeficient mice elicit non-inflammatory subepithelial blisters with clinical, histologic and immunopathologic features like those seen in patients with this form of MMP[41,42].

Type IV Collagen

Type IV collagen is a unique macromolecule that is specifically localized within basement membranes[1,43]. The structure of type IV collagen most closely resembles a procollagen (i.e. an intracellular form that retains globular domains at its amino and carboxy termini). Like all collagens,

FEATURES OF SELECTED LAMININS

Laminin isoform (αβγ)*	Previous numerical name†	Other names	Molecular weight, KDa	Processing, structure and assembly	Distribution	Interactions and functions
111	1	EHS laminin, "classic" laminin	~800 (α: ~400; β: ~220; γ: ~210)	• Asymmetric cross: 3 short arms, 1 long arm (see Fig. 28.4) • Self-assembles into a network *in vitro*	• Dermal microvascular BMs • Little or none in epidermal BM	• Diverse biologic functions, largely mediated by interactions with integrin receptors • Nidogen binds with high affinity to domain III of the γ1-subunit, connecting this laminin to the type IV collagen network, heparan sulfate proteoglycans (e.g. perlecan) and fibulins (see Fig. 28.6)
332	5	Epiligrin, kalinin, nicein, GB3 antigen, BM600	~410 (α: 200 for precursor/165 post processing; β: 140; γ: 155 for precursor/105 post processing)	• Cell-associated precursors of the α3- & γ2-subunits are processed following secretion • α3-subunit is truncated, lacks key N-terminal domains, and has a small G domain • β3-subunit is homolog of β1-subunit but does not undergo processing after secretion and has a truncated short arm • γ2-subunit's aa sequence has ~50% identity to that of the γ1-subunit, but the former's domains are truncated (I, II, III, IV, V) or absent (VI) • *Not* able to self-assemble into networks	• Found at interface of lamina lucida and lamina densa in epidermal BM • Produced and secreted by growing/migrating keratinocytes • Also in BMs of the trachea, gastrointestinal tract and amnion	• Attaches keratinocytes to the epidermal BM • γ2-subunit *lacks* domain that binds nidogen; instead, N-terminus of laminin 332 covalently associates with the branch points of the short arms of laminins 311 and 321, forming a complex that contains binding sites for nidogen (on γ1-subunit) and polymerization (on β1-, β2- & γ1-subunits) (see Fig. 28.6) • α3-subunit's G domain (positioned superiorly) binds integrins $\alpha_6\beta_4$ (in HDs; see Fig. 28.3) and $\alpha_3\beta_1$ (in plasma membrane) • β3- or γ2-subunits of monomeric laminin 332 can bind the N-terminal NC1 domain of type VII collagen of anchoring fibrils (see Fig. 29.3) • Thereby links HD-anchoring filament complexes with underlying anchoring fibrils
311	6		~600 (α: 200 for precursor/165 post processing; β: ~220; γ: ~210)	• See above for processing and structure of α3-subunit	• As for laminin 332	• Joined with laminin 332 in a disulfide-bonded complex (see above) • Connected to type IV collagen and other molecules in the lamina densa via nidogen bound to the γ1-subunit (see laminin 111 above and Fig. 28.6)
511	10		~640–880 (α: 450 for precursor/210–380 post processing; β: ~220; γ: ~210)	• α5-subunit is thought to be processed	• BMs of many tissues	

*Each isoform's name reflects the numbers of its α-, β- and γ-subunits.
†Numbers reflect the order of the isoforms' discovery.

Table 28.3 Features of selected laminins[32–38]. aa, amino acid; BM, basement membrane; C-terminal, carboxy-terminal; EHS, Engelbreth–Holm–Swarm (a mouse tumor from which laminin 111 was initially isolated); G domain, globular segment at C-terminal end of domain I; HD, hemidesmosome; NC1, non-collagenous 1; N-terminal, amino-terminal.

type IV collagen consists of three α-chain subunits; these subunits can be identical or genetically distinct but structurally related. To date, six type IV collagen α-chain subunits have been identified (polypeptides: α_1(IV)–α_6(IV); corresponding genes: *COL4A1–COL4A6*).

Type IV collagen is a heteropolymer that contains either two genetically identical α-chain subunits and one dissimilar α-chain subunit or three different α-chain subunits. Subunits α_1(IV) and α_2(IV) are ubiquitous components of basement membranes, where their highly cross-linked organization provides considerable structural support. Subunits α_5(IV) and α_6(IV) are present in the epidermal basement membrane, whereas α_3(IV), α_4(IV) and α_5(IV) subunits are found within renal glomerular basement membranes.

Like all collagens, the α-chain subunits of type IV collagen associate to form a triple-helical structure[1]. The stability of this triple helix is dependent upon characteristic repeating glycine-X-Y amino acid sequences, accompanying residues rich in proline, and post-translational hydroxylation of the latter to hydroxyproline (see Ch. 95). The resulting triple helix has an extended, somewhat rigid conformation that is resistant to "ordinary" proteases (e.g. trypsin) and sensitive to specialized proteases (i.e. collagenases). Unlike classic fibrillar collagens, type IV collagen is not helical through its entire length. Short discontinuities in glycine-X-Y repeats within its α-subunits create non-helical domains that confer increased flexibility to this macromolecule as well as sites susceptible to damage by "ordinary" proteases.

The retained globular domains at the ends of type IV collagen make it resemble a procollagen[1]. The globular amino terminus of this protein is referred to as its 7S domain; a smaller globular domain at its carboxy terminus is referred to as its non-collagenous 1 (NC1) domain. The macromolecular structure of type IV collagen has been described as resembling a "hockey stick", where the blade of the stick corresponds to the amino-terminal 7S domain, the handle corresponds to the largely continuous triple-helical portion of the molecule, and the handle grip corresponds to the short globular NC1 domain at its carboxy terminus[1]. This model is particularly useful when one relates the lattice structure of type IV collagen matrices to an arrangement of hockey sticks created by: (1) the overlapping of four 7S blades to create a type IV collagen "spider" in which the handles are oriented at roughly right angles to each other; and (2) the subsequent polymerization of "spiders" at sites of their abutting carboxy termini (the handle grips/ends of the spiders' "legs") (Fig. 28.5). Such end-to-end, antiparallel interactions result in a two-dimensional type IV collagen lattice that serves as a key matrix within the lamina densa.

Defective type IV collagen underlies several diseases of basement membranes. For example, the majority of patients with Alport syndrome (characterized by hematuria, progressive renal failure, sensorineural hearing loss, and, occasionally, ocular abnormalities) have mutations in the *COL4A5* gene encoding α_5(IV). In addition to this X-linked form of Alport syndrome, an autosomal recessive form of the disorder is caused by mutations in *COL4A3* or *COL4A4,* and a rare autosomal dominant variant results from mutations in *COL4A3*.

Goodpasture disease, a potentially lethal autoimmune disorder characterized by pulmonary hemorrhage and glomerulonephritis, is caused by anti-basement membrane antibodies directed against the NC1 domain of α_3(IV) and α_5(IV)[44]. Exposure of potentially pathogenic epitope(s) within α_3(IV) and/or α_5(IV) by infections or other events may represent an essential element in the development of this disease. Interestingly, antibodies against α_5(IV) ± α_6(IV) can cause a rare disorder characterized by subepidermal blisters and glomerulonephritis[45].

Fragments of type IV collagen α-chain subunits have important biologic activities. One such fragment is canstatin, a human basement membrane-derived inhibitor of angiogenesis and tumor growth that corresponds to a fragment of α_2(IV)[46]. Another example is tumstatin, a fragment of the NC1 domain of α_3(IV) that possesses antiangiogenic activity[47].

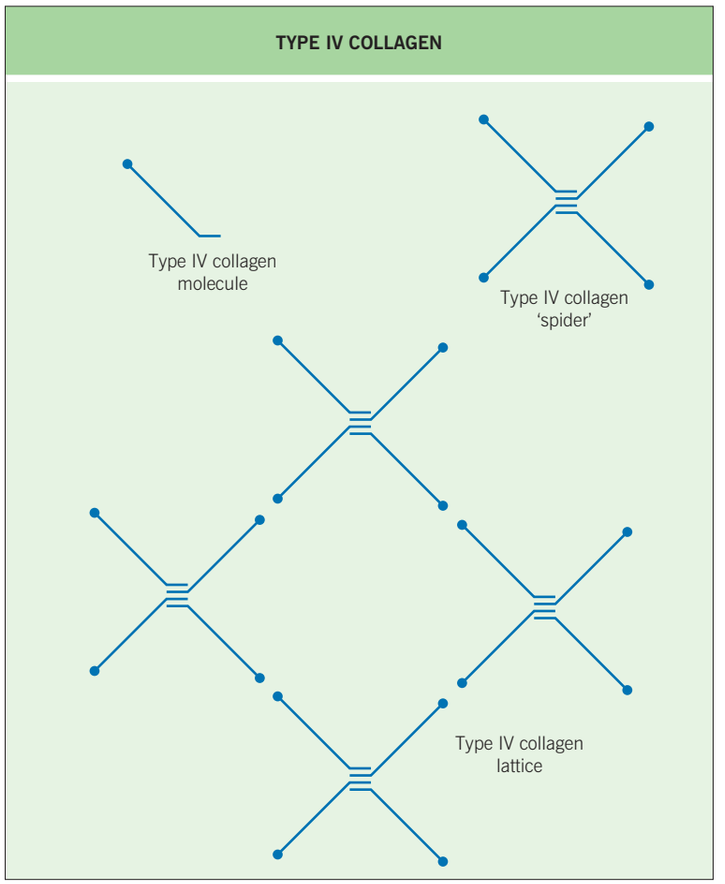


Fig. 28.5 Type IV collagen. A monomer, a tetramer "spider" and a lattice are depicted. The latter results from the aggregation of type IV collagen molecules.

Nidogen

Nidogen (entactin) is a 150 kDa glycoprotein localized to the lamina densa of basement membranes, where it links networks of type IV collagen and various laminin isoforms (Fig. 28.6)[1]. By rotary shadowing, nidogen has the shape of a dumbbell[1]. Nidogen binds laminin isoforms containing the γ1-subunit (e.g. laminins 111, 311 and 511; see Table 28.3) with high affinity. More specifically, the G3 domain at the carboxy terminus of nidogen binds the cysteine-rich, epidermal growth factor-like repeat in domain III of the γ1-subunit[34]. In turn, the G2 domain at the amino terminus of nidogen binds with high affinity to type IV collagen. In addition to binding type IV collagen, complexes of nidogen and laminin can also bind the core protein of heparan sulfate proteoglycan and fibulins 1 and 2. Nidogen is thought to stabilize various macromolecules in the lamina densa. A second form of nidogen (nidogen 2) that has ~45% identity with classic nidogen has been identified[48]. Nidogen 2 is thought to link fibulins to heparan sulfate proteoglycans as well as to types I and IV collagen. No autoimmune or inherited blistering diseases have been linked to nidogen. Interestingly, mice engineered to lack nidogen 1 show no overt abnormalities; they have basement membranes that appear to be normal and they are fertile.

Heparan Sulfate Proteoglycans

Heparan sulfate proteoglycans (HSPGs) are a diverse group of macromolecules that are ubiquitous components of basement membranes. They consist of a central core protein that is lined with laterally emanating glycosaminoglycans in a so-called "bottle-brush" configuration[1] (see Ch. 95). Different basement membranes contain HSPGs of various types and configurations, with perlecan representing the best-characterized basement membrane HSPG. HPSGs can interact with various components of the lamina densa (e.g. type IV collagen, nidogen; see Fig. 28.6) and also self-polymerize to contribute to the overall matrix of the basement membrane proper. The high sulfate content of HSPGs confers an overall negative charge to basement membranes and thereby restricts the permeability of these matrices. By immunoelectron microscopy, HSPGs are found within, just above, and just below the lamina densa of the epidermal basement membrane[49].

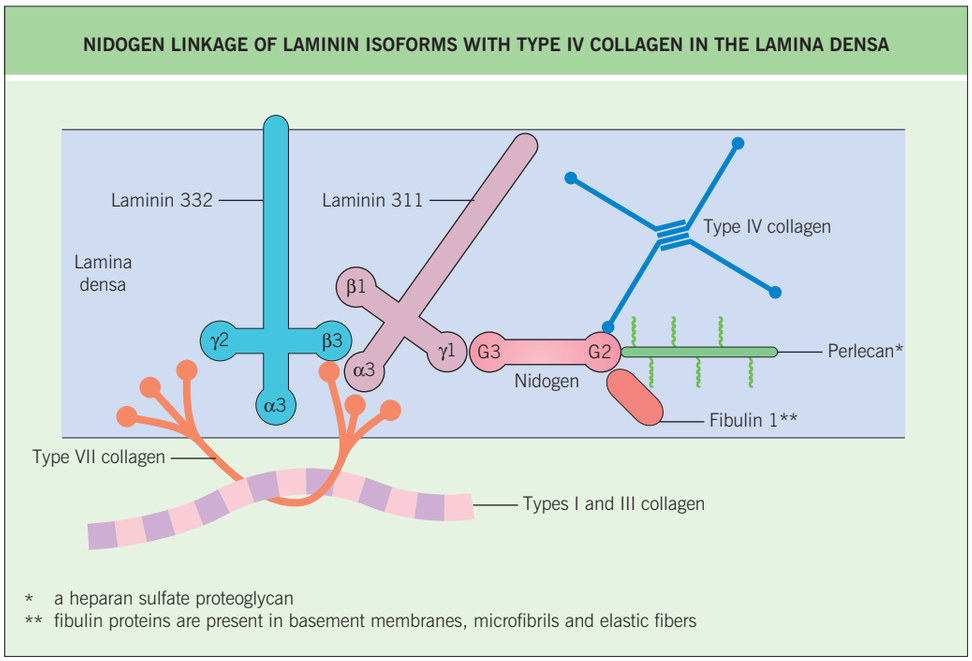


Fig. 28.6 Nidogen linkage of laminin isoforms with type IV collagen in the lamina densa. Nidogen binds the γ-subunit of laminin 311 (formerly laminin 6), linking it to networks of type IV collagen, heparan sulfate proteoglycans, and fibulins. Laminin 332 (formerly laminin 5), which lacks the γ-domain required for nidogen binding, is stably bound to the basement membrane via a covalent association with the branch points of the short arms of laminin 311. Note that this figure is not drawn to scale.

ANCHORING FIBRILS AND THE SUBLAMINA DENSA REGION

Type VII Collagen

Type VII collagen is restricted to the basement membrane of stratified squamous epithelia, where it localizes to the sublamina densa in the upper papillary dermis[1]. It is the major component of anchoring fibrils and consists of three identical α-chains, each with a molecular weight of approximately 290 kDa[50]. At its amino terminus, it contains a large globular non-collagenous domain termed NC1. A smaller non-collagenous domain termed NC2 lies at its carboxy terminus (see Ch. 95).

The assembly of anchoring fibrils initiates when NC2 "tails" of individual type VII collagen molecules align in an antiparallel fashion and unite via disulfide bonds[1]. Once these tail-to-tail dimers form, the NC2 domain is proteolytically cleaved, leaving a long thread-like macromolecule characterized by a central rod with large globular NC1 domains at each end. Newly formed type VII collagen dimers then aggregate laterally with other dimers to form bundles resembling "wheat-stacks", which are termed anchoring fibrils (see Fig. 28.2). The aggregated globular NC1 domains in anchoring fibrils are free to bind matrix elements in basement membranes of stratified squamous epithelia.

Ultrastructural studies have suggested that the globular NC1 domains of type VII collagen molecules bind the lamina densa at one end and either loop back into the lamina densa or connect to electron-dense elements in the sublamina densa region termed anchoring plaques (see Fig. 28.2). More recently, it has been suggested that anchoring plaques are actually portions of lamina densa that have "dropped out" and fallen into the sublamina densa region as a consequence of basement membrane remodeling[51]. On a molecular level, specific subdomains within the NC1 domains of type VII collagen demonstrate affinity for type I fibrillar collagen in the dermis as well as type IV collagen in the lamina densa (and anchoring plaques)[52,53]. Type VII collagen also interacts with laminin 332 as outlined in Table 28.3[38], and the network of looping bands and tethers formed by anchoring fibrils connects the lamina densa with a series of fibrillar elements in the sublamina densa region.

The gene encoding type VII collagen, *COL7A1*, contains 118 exons but is compact due to its extremely small introns. Mutations in *COL7A1* cause both dominant and recessive forms of dystrophic EB[54] (see Ch. 32). Patients with recessive dystrophic EB typically have mutations that result in premature termination codons, nonsense-mediated mRNA decay, and no detectable type VII collagen mRNA or protein. Accordingly, these patients have no anchoring fibrils in their epidermal basement membrane and manifest extreme skin fragility, mutilating scars and an increased risk for cutaneous squamous cell carcinomas. Because carriers of recessive dystrophic EB harbor only one mutant allele (that is, for the reasons outlined above, "silent"), sufficient amounts of type VII collagen are derived from the normal allele to maintain basement membrane integrity and a normal skin phenotype. In contrast, patients with dominant dystrophic EB usually have a missense mutation in one *COL7A1* allele that creates a dominant-negative effect on protein derived from the patient's other, normal *COL7A1* allele. Most dominant-negative *COL7A1* mutations result in glycine substitutions at critical points in the collagenous portion of type VII collagen. These abnormal proteins are incorporated (together with normal α-chains) into type VII collagen trimers and disrupt their function. Consequently, patients with dominant dystrophic EB produce abnormal-appearing and/or reduced numbers of anchoring fibrils and demonstrate a blistering phenotype that is usually less severe than that seen in patients with recessive dystrophic EB.

EB acquisita (EBA) is an acquired autoimmune subepidermal bullous disease in which blister formation occurs in the sublamina densa region, usually as the result of mechanical trauma[55]. A 290 kDa protein in extracts of lamina densa/dermis was identified as the autoantigen in EBA. Subsequent studies showed that this "EBA antigen" was type VII collagen and that IgG from most EBA patients binds four immunodominant epitopes within the NC1 domain of this protein[56,57].

It has been postulated that such autoantibodies disrupt the assembly of type VII collagen into anchoring fibrils and/or interfere with the interaction of type VII collagen with other extracellular matrix molecules, resulting in skin fragility and the development of non-inflammatory, trauma-induced subepidermal blisters. Passive transfer of anti-type VII collagen IgG into mice can elicit lesions with clinical, histologic and immunopathologic features like those seen in patients with EBA[58,59]. Of note, the bullous eruption of systemic lupus erythematosus (SLE), which tends to be more inflammatory, is also caused by antibodies directed against type VII collagen. IgG targeting the same four immunodominant epitopes that are recognized in EBA has been identified in patients with the bullous eruption of SLE[57].

Microfibrils

By transmission electron microscopy, elastic fibers have two distinct components: (1) an amorphous, non-banded component that consists of the protein elastin; and (2) a microfibrillar component that has a regular diameter of 10–12 nm and consists primarily of fibrillins, which are associated with other proteins such as microfibril-associated glycoproteins, fibulins, and latent transforming growth factor (TGF)-β-binding proteins (see Ch. 95). In the papillary dermis, microfibrillar elements insert vertically into the lamina densa and

comprise what has classically been referred to as oxytalan fibers. At their inferior aspect, oxytalan fibers merge with microfibrillar elements oriented parallel to the skin's surface. These parallel microfibrillar elements contain some amorphous component, and they have been designated elaunin fibers. The network of oxytalan and elaunin fibers is contiguous with elastic fibers within the reticular dermis. The latter consist of microfibrillar elements associated with substantial amounts of amorphous material. The gradient of increasing amorphous component deeper in the dermis has been suggested to reflect maturation of elastic fibers in a top-down manner within the skin.

Microthread-like Fibers

Linkin is an 80 kDa protein localized to the upper papillary dermis just beneath the epidermal basement membrane[33]. Linkin is the major component of a microthread-like filamentous network within the sublamina densa that appears to interconnect microfibrillar bundles, anchoring fibrils and interstitial collagen fibers.

Basement Membrane Remodeling

Though the epidermal basement membrane is thought of as a physical barrier between cells of the epidermis and the underlying dermis, this matrix (like other basement membranes) is a dynamic structure that is constantly remodeled. For example, the epidermal basement membrane is routinely penetrated by Langerhans cells trafficking into and out of the epidermis under normal physiologic conditions. Lymphocytes also cross the epidermal basement membrane in both inflammatory and neoplastic diseases. However, other non-immune and non-malignant cells rarely cross this ultrastructural barrier. Indeed, an absence of basement membranes in tumors correlates with malignancy, and propensity for metastasis. Metalloproteinases expressed by immune or malignant cells enable penetration of basement membranes. Such proteases also have important functions in remodeling epidermal (and other) basement membranes during morphogenesis, development and various physiologic processes (e.g. modification of mammary epithelia during pregnancy and lactation). In addition, metalloproteinases play a key role in alterations (e.g. thinning) of the epidermal basement membrane in aged and photoaged skin.

THE EPIDERMAL BASEMENT MEMBRANE IN BULLOUS DISEASES

Patients with acquired immunobullous diseases have autoantibodies directed against autoantigens in the epidermis (e.g. pemphigus) or epidermal basement membrane (e.g. various forms of pemphigoid). Autoantibodies from such patients were used to establish the identity of many autoantigens and demonstrate that individuals with a given disease have (in most instances) autoantibodies directed against the same protein. Patient autoantibodies were also used to isolate cDNAs corresponding to genes encoding autoantigens. These autoantigens were often recognized as important structural proteins in the skin, and some of the genes encoding them were found to harbor mutations in patients with various forms of EB. Hence, acquired or inherited alterations in key adhesion proteins in the skin result in disease phenotypes characterized by blister formation (see Table 28.2). The biology of the epidermal basement membrane in patients with various autoimmune or inherited blistering diseases is briefly summarized below. Further details are provided in Chapters 30, 31 and 32.

Autoimmune Subepidermal Blistering Diseases

The autoantigens recognized in patients with well-characterized subepidermal immunobullous diseases are outlined in Table 28.4. These disorders were once only partially classified based on their clinical and histologic features, but they are now defined by the autoantigen that is targeted (Fig. 28.7). In addition to improving diagnostic capabilities,

WELL-CHARACTERIZED SUBEPIDERMAL IMMUNOBULLOUS DISEASES

Disease	Antigen	Size (kDa)	Localization
Bullous pemphigoid	BPAG1 BPAG2	230 180	Intracytoplasmic plaque of hemidesmosomes Hemidesmosome-anchoring filament complexes
Pemphigoid gestationis	BPAG2	180	Hemidesmosome-anchoring filament complexes
Linear IgA bullous dermatosis	BPAG2	120→97	Hemidesmosome-anchoring filament complexes
Mucous membrane (cicatricial) pemphigoid	BPAG2	180	Hemidesmosome-anchoring filament complexes
Anti-epiligrin mucous membrane (cicatricial) pemphigoid	Laminin 332	400–440	Lamina lucida–lamina densa interface
EB acquisita	Type VII collagen	290	Anchoring fibrils
Bullous eruption of systemic lupus erythematosus	Type VII collagen	290	Anchoring fibrils

Table 28.4 Well-characterized subepidermal immunobullous diseases. EB, epidermolysis bullosa.

LOCALIZATION OF AUTOANTIGENS IN SUBEPIDERMAL IMMUNOBULLOUS DISEASES AND MUTATED PROTEINS IN EPIDERMOLYSIS BULLOSA

Epidermal basement membrane	Autoantigens in immunobullous diseases	Mutated proteins in epidermolysis bullosa (EB)
Basal keratinocytes — Keratins 5 & 14		EB simplex (classic)
Lamina lucida — BPAG1, plectin; BPAG2, integrin $\alpha_6\beta_4$	Bullous pemphigoid, pemphigoid gestationis LABD, mucous membrane pemphigoid	EB simplex with MD, with PA, Ogna & recessive Junctional EB–non-Herlitz & with PA
Lamina densa — Laminin 332	Anti-epiligrin mucous membrane pemphigoid	Junctional EB–Herlitz
Sublamina densa — Type VII collagen	Epidermolysis bullosa acquisita Bullous eruption of systemic lupus erythematosus	Dystrophic EB

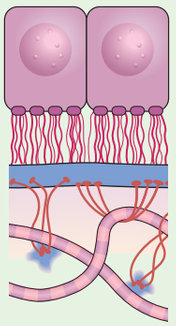


Fig. 28.7 Localization of autoantigens in immunobullous diseases and mutated proteins in epidermolysis bullosa. BPAG, bullous pemphigoid antigen; LABD, linear IgA bullous dermatosis; MD, muscular dystrophy; PA, pyloric atresia.

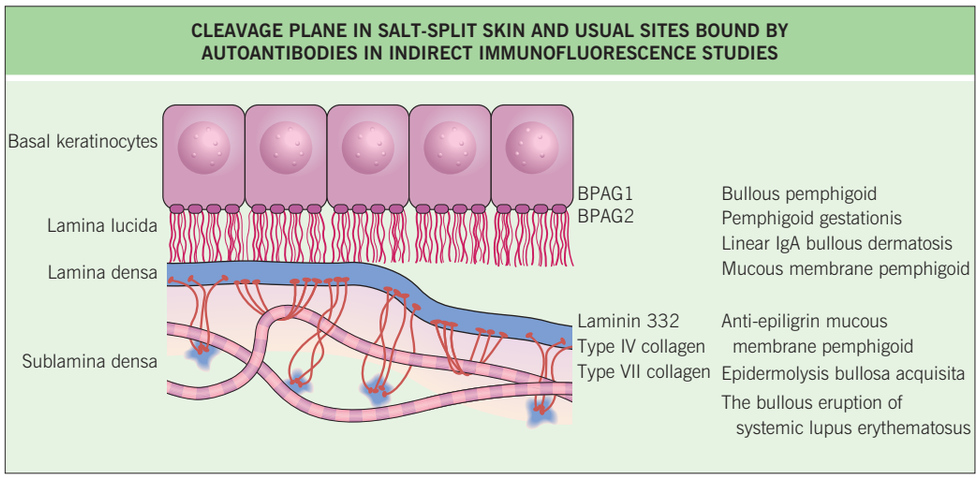


Fig. 28.8 Cleavage plane in salt-split skin and usual sites bound by autoantibodies in indirect immunofluorescence studies. The cleavage plane in 1 M NaCl salt-split skin is in the lower portion of the lamina lucida. Circulating autoantibodies from patients with various subepidermal immunobullous diseases bind to different sites, e.g. the epidermal versus dermal side of the split.

profiling patients' autoantibodies for classification of their bullous diseases has led to an ever-growing appreciation of the polymorphic nature of these conditions. For example, while EBA was once largely considered to be a diagnosis of exclusion for a rare, acquired skin fragility disorder, it is now recognized as a disease that may clinically resemble "classic" BP or MMP as well as dystrophic EB.

Advances in our understanding of the epidermal basement membrane, the proteins that comprise this matrix, and how this ultrastructural unit is targeted in various immunobullous diseases have also led to the development of a number of immunopathologic techniques that have great utility in clinical dermatology. One example of these techniques is the utilization of 1 M NaCl salt-split skin (cleaved within the lamina lucida) in immunofluorescence (IF) microscopy studies of patient sera and skin[60–62] (Fig. 28.8; Table 28.5). Indirect IF studies of salt-split skin first gained widespread attention when it was shown that patients with "inflammatory" EBA could be distinguished from those with "classic" BP in that IgG anti-basement membrane autoantibodies from these patients bound dermal and epidermal sides, respectively, of salt-split skin[60]. When it was found that IgG anti-basement membrane autoantibodies from patients with one form of MMP bound the dermal side of salt-split skin yet showed no reactivity to type VII collagen, the search began for a previously unrecognized autoantigen in the epidermal basement membrane[39]. This autoantigen, specific to patients with this form of MMP (anti-epiligrin cicatricial pemphigoid), is now known to be laminin 332[39,40].

For individuals who lack detectable circulating anti-basement membrane autoantibodies, the direct salt-split skin technique has been applied to studies of patient skin[61,62] (see Table 28.5). This approach has, in many instances, replaced the need for direct immunoelectron microscopy. In this technique, skin from a patient is split in the laboratory with 1 M NaCl then studied by direct IF microscopy to determine where immunoreactants localize *in situ*. Patients with EBA and anti-epiligrin MMP have deposits of immunoreactants (i.e. IgG and C3) that localize to the dermal side of salt-split skin. In contrast, patients with BP have deposits of IgG that localize to the epidermal (or both) side(s) of the split within the lamina lucida created by this treatment. Interestingly, patients with BP may have *in situ* deposits of C3 that exclusively localize to the dermal side of their salt-split skin. Accordingly, direct IF mapping studies of patient salt-split skin are most accurate when based on the localization of IgG rather than C3.

LOCALIZATION OF IMMUNOREACTANTS IN IMMUNOFLUORESCENCE MICROSCOPY STUDIES OF 1 M NaCl SALT-SPLIT SKIN

INDIRECT IMMUNOFLUORESCENCE MICROSCOPY STUDIES

Disease	Localization
Bullous pemphigoid	IgG characteristically epidermal; occasionally both sides with higher titer against the epidermal side
Pemphigoid gestationis	IgG characteristically epidermal; occasionally both sides with higher titer against the epidermal side
Linear IgA bullous dermatosis	IgA characteristically epidermal; rare patients with "IgA EBA" bind the dermal side
MMP	IgG characteristically epidermal; occasionally both sides with higher titer against the epidermal side
Anti-epiligrin MMP	IgG against dermal side of substrate
EB acquisita	IgG against dermal side of substrate
p200 pemphigoid (anti-laminin γ1 pemphigoid)*	IgG against dermal side of substrate
p105 pemphigoid*	IgG against dermal side of substrate

DIRECT IMMUNOFLUORESCENCE MICROSCOPY STUDIES†

Disease	Localization of IgG	Localization of C3
Bullous pemphigoid	Epidermal	Epidermal, dermal, or both
Pemphigoid gestationis	Epidermal	Epidermal, dermal, or both
Anti-epiligrin MMP	Dermal	Dermal
EB acquisita	Dermal	Dermal

*See Schmidt & Zillikens[20] for specific information about these incompletely characterized immunobullous diseases.
†These studies utilize patient skin after it is split with 1 M NaCl.

Table 28.5 Localization of immunoreactants in immunofluorescence microscopy studies of 1 M NaCl salt-split skin. EB, epidermolysis bullosa; MMP, mucous membrane (cicatricial) pemphigoid.

Inherited Subepidermal Blistering Diseases

Advances in the understanding of the epidermal basement membrane structure and composition paralleled (and in many instances were derived from) studies of patients with various forms of EB[63] (Table 28.6; see Fig. 28.7). Moreover, advances in cutaneous immunopathology facilitated the study of patients with EB. For example, rather than relying upon transmission electron microscopy to map the plane of blister formation in the skin of patients with EB, investigators garnered this information from IF microscopy studies using antibodies directed against known structural components of the epidermal basement membrane. For example, because patients with EB simplex display cleavage within the cytoplasm of their basal keratinocytes, BPAG1 and type IV collagen localize to the dermal side of their blistered skin. In patients with various forms of junctional EB, BPAG1 localizes to the epidermal side of blistered skin while type IV collagen remains attached to the dermis. Lastly, in patients with dystrophic EB, both BPAG1 and type IV collagen localize to the epidermal side of the cleavage plane, which sits within the sublamina densa region.

REPRESENTATIVE FORMS OF EPIDERMOLYSIS BULLOSA (EB)			
Disease	**Gene**	**Protein**	**Localization**
EB simplex	*KRT5*	Keratin 5	Intermediate filament cytoskeleton of basal keratinocytes
	KRT14	Keratin 14	Intermediate filament cytoskeleton of basal keratinocytes
EB simplex with muscular dystrophy EB simplex, Ogna EB simplex with pyloric atresia	*PLEC1*	Plectin	Intracytoplasmic plaque of hemidesmosomes
Recessive EB simplex	*DST*	BP230	Intracytoplasmic plaque of hemidesmosomes
Junctional EB, non-Herlitz	*COL17A1*	BPAG2 (type XVII collagen)	Hemidesmosome-anchoring filament complexes
	ITGB4	β_4 integrin	Hemidesmosome-anchoring filament complexes
	LAMA3	Laminin 332, α3 subunit	Lamina lucida–lamina densa interface
	LAMB3	Laminin 332, β3 subunit	Lamina lucida–lamina densa interface
	LAMC2	Laminin 332, γ2 subunit	Lamina lucida–lamina densa interface
Junctional EB with pyloric atresia	*ITGA6*	α_6 integrin subunit	Hemidesmosome-anchoring filament complexes
	ITGB4	β_4 integrin subunit	Hemidesmosome-anchoring filament complexes
Junctional EB, Herlitz	*LAMA3*	Laminin 332, α3 subunit	Lamina lucida–lamina densa interface
	LAMB3	Laminin 332, β3 subunit	Lamina lucida–lamina densa interface
	LAMC2	Laminin 332, γ2 subunit	Lamina lucida–lamina densa interface
Dominant dystrophic EB	*COL7A1*	Type VII collagen	Anchoring fibrils
Recessive dystrophic EB	*COL7A1*	Type VII collagen	Anchoring fibrils

Table 28.6 Representative forms of epidermolysis bullosa (EB). BPAG, bullous pemphigoid antigen.

In addition to mapping the plane of blister formation in patients with various forms of EB for purposes of classification, studies of the immunoreactivity and ultrastructure of skin from EB patients have provided key insights regarding disease pathophysiology. For example, monoclonal antibodies against various subunits of laminin 332 generally fail to bind the skin of patients with junctional EB-Herlitz. Similarly, monoclonal antibodies against BPAG2 (type XVII collagen) almost always fail to bind the skin of patients with junctional EB-non-Herlitz. Beyond the diagnostic utility of these observations was the implication that these (and other) inherited bullous diseases developed as a consequence of mutations in genes encoding structural proteins in the epidermal basement membrane (rather than unrestrained activity of proteases resulting in degradation of the epidermal basement membrane). Consequently, skin samples from patients with EB have been studied extensively with panels of antibodies against constituents of the epidermal basement membrane in the hope of finding "candidate genes" that might harbor pathogenic mutations. Such IF microscopy "screens" can guide molecular genetic studies. Hence, a patient with junctional EB who lacks integrin subunit β_4 in the epidermal basement membrane would be screened for mutations in *ITGB4* before genes responsible for other forms of junctional EB (e.g. *COL17A1*, *LAMA3*, *LAMB3*, *LAMC2*, *ITGA6*) were analyzed[64].

SUMMARY

The basement membranes of various tissues differ in their ultrastructure, biochemical composition and biological function. The epidermal basement membrane contains many highly specialized structures that are largely tissue-specific. Cell–matrix interactions between keratinocytes and the epidermal basement membrane provide key positional and environmental clues that directly modulate tissue morphogenesis, homeostasis, differentiation, wound healing, and acquisition of specialized functions.

REFERENCES

1. Woodley DT, Chen M. The basement membrane zone. In: Freinkel RK, Woodley DT (eds). The Biology of the Skin. New York: Parthenon Publishing, 2001: 137–52.
2. Goldberg M, Escaig-Haye F. Is the lamina lucida of the basement membrane a fixation artifact? Eur J Cell Biol. 1986;42:365–8.
3. Wiche G, Becker B, Luber K, et al. Cloning and sequencing of rat plectin indicates a 466-kD polypeptide chain with a three-domain structure based on a central alpha-helical coiled coil. J Cell Biol. 1991; 114:83–99.
4. Wiche G. Role of plectin in cytoskeleton organization and dynamics. J Cell Sci. 1998;111:2477–86.
5. Borradori L, Sonnenberg A. Structure and function of hemidesmosomes: more than simple adhesion complexes. J Invest Dermatol. 1999;112:411–18.
6. Andra K, Lassmann H, Bittner R, et al. Targeted inactivation of plectin reveals essential function in maintaining the integrity of skin, muscle, and heart cytoarchitecture. Genes Dev. 1997;11:3143–56.
7. Stanley JR, Hawley-Nelson P, Yuspa SH, et al. Characterization of bullous pemphigoid antigen: a unique basement membrane protein of stratified squamous epithelia. Cell. 1981;24:897–903.
8. Stanley JR. Cell adhesion molecules as targets of autoantibodies in pemphigus and pemphigoid, bullous diseases due to defective epidermal cell adhesion. Adv Immunol. 1993;53:291–325.
9. Favre, B, Fontao L, Koster J, et al. The hemidesmosomal protein bullous pemphigoid antigen 1 and the integrin β_4 subunit bind to ERBIN. Molecular cloning of multiple alternative splice variants of ERBIN and analysis of their tissue expression. J Biol Chem. 2001;276:32427–36.
10. Guo L, Degenstein L, Dowling J, et al. Gene targeting of BPAG1: abnormalities in mechanical strength and cell migration in stratified epithelia and neurologic degeneration. Cell. 1995;81:233–43.
11. Groves RW, Liu L, Dopping-Hepenstal PJ, et al. A homozygous nonsense mutation within the dystonin gene coding for the coiled-coil domain of the epithelial isoform of BPAG1 underlies a new subtype of autosomal recessive epidermolysis bullosa simplex. J Invest Dermatol. 2010;130:1551–7.
12. Diaz LA, Ratrie H III, Saunders WS, et al. Isolation of a human epidermal cDNA corresponding to the 180-kD autoantigen recognized by bullous pemphigoid and herpes gestationis sera. Immunolocalization of this protein to the hemidesmosome. J Clin Invest. 1990;86: 1088–94.
13. Hirako Y, Usukura J, Nishizawa Y, Owaribe K. Demonstration of the molecular shape of BP180, a 180-kDa bullous pemphigoid antigen and its potential for trimer formation. J Biol Chem. 1996;271:13739–45.
14. Masunaga T, Shimizu H, Yee C, et al. The extracellular domain of BPAG2 localizes to anchoring filaments and its carboxyl terminus extends to the lamina densa of normal human epidermal basement membrane. J Invest Dermatol. 1997;109:200–6.
15. Nonaka S, Ishiko A, Masunaga T, et al. The extracellular domain of BPAG2 has a loop structure in the carboxyl terminal flexible tail *in vivo*. J Invest Dermatol. 2000; 115:889–92.
16. Schacke H, Schumann H, Hammami-Hauasli N, et al. Two forms of collagen XVII in keratinocytes. A full-length transmembrane protein and a soluble ectodomain. J Biol Chem. 1998;273:25937–43.
17. Zimina EP, Fritsch A, Schermer B, et al. Extracellular phosphorylation of collagen XVII by ecto-casein kinase 2 inhibits ectodomain shedding. J Biol Chem. 2007; 282:22737–46.
18. Areida SK, Reinhardt DP, Muller PK, et al. Properties of the collagen type XVII ectodomain. Evidence for n- to c-terminal triple helix folding. J Biol Chem. 2001;276: 1594–601.

19. Hopkinson SB, Baker SE, Jones JC. Molecular genetic studies of a human epidermal autoantigen (the 180-kD bullous pemphigoid antigen/BP180): identification of functionally important sequences within the BP180 molecule and evidence for an interaction between BP180 and alpha 6 integrin. J Cell Biol. 1995;130:117–25.
20. Schmidt E, Zillikens D. Autoimmune and inherited subepidermal blistering diseases: advances in the clinic and the laboratory. Adv Dermatol. 2000;16:113–57.
21. Darling TN, Bauer JW, Hintner H, Yancey KB. Generalized atrophic benign epidermolysis bullosa. Adv Dermatol. 1997;13:87–119.
22. Fontao L, Tasanen K, Huber M, et al. Molecular consequences of deletion of the cytoplasmic domain of bullous pemphigoid 180 in a patient with predominant features of epidermolysis bullosa simplex. J Invest Dermatol. 2004;122:65–72.
23. Sonnenberg A, Calafat J, Janssen H, et al. Integrin $\alpha_6\beta_4$ complex is located in hemidesmosomes, suggesting a major role in epidermal cell-basement membrane adhesion. J Cell Biol. 1991;113:907–17.
24. Rezniczek GA, de Pereda JM, Reipert S, Wiche G. Linking integrin $\alpha_6\beta_4$-based cell adhesion to the intermediate filament cytoskeleton: direct interaction between the beta4 subunit and plectin at multiple molecular sites. J Cell Biol. 1998;141:209–25.
25. Niessen CM, Hogervorst F, Jaspars LH, et al. The $\alpha_6\beta_4$ integrin is a receptor for both laminin and kalinin. Exp Cell Res. 1994;211:360–7.
26. Dowling J, Yu QC, Fuchs E. β_4 integrin is required for hemidesmosome formation, cell adhesion and cell survival. J Cell Biol. 1996;134:559–72.
27. Murgia C, Blaikie P, Kim N, et al. Cell cycle and adhesion defects in mice carrying a targeted deletion of the integrin β_4 cytoplasmic domain. EMBO J. 1998;17: 3940–51.
28. Marchisio PC, Bondanza S, Cremona O, et al. Polarized expression of integrin receptors ($\alpha_6\beta_4$, $\alpha_2\beta_1$, $\alpha_3\beta_1$, and $\alpha_v\beta_5$) and their relationship with the cytoskeleton and basement membrane matrix in cultured human keratinocytes. J Cell Biol. 1991;112:761–73.
29. Dogic D, Rousselle P, Aumailley M. Cell adhesion to laminin 1 or 5 induces isoform-specific clustering of integrins and other focal adhesion components. J Cell Sci. 1998;111:793–802.
30. DiPersio CM, Hodivala-Dilke KM, Jaenisch R, et al. $\alpha_3\beta_1$ integrin is required for normal development of the epidermal basement membrane. J Cell Biol. 1997;137: 729–42.
31. Sterk LM, Geuijen CA, Oomen LC, et al. The tetraspan molecule CD151, a novel constituent of hemidesmosomes, associates with the integrin alpha6beta4 and may regulate the spatial organization of hemidesmosomes. J Cell Biol. 2000;149:969–82.
32. Aumailley M, Rousselle P. Laminins of the dermoepidermal junction. Matrix Biol. 1999;18:19–28.
33. Carter WG, Ryan MC, Gahr PJ. Epiligrin, a new cell adhesion ligand for integrin alpha 3 beta 1 in epithelial basement membranes. Cell. 1991;65:599–610.
34. Mayer U, Nischt R, Poschl E, et al. A single EGF-like motif of laminin is responsible for high affinity nidogen binding. EMBO J. 1993;12:1879–85.
35. Rousselle P, Lunstrum GP, Keene DR, Burgeson RE. Kalinin: an epithelium-specific basement membrane adhesion molecule that is a component of anchoring filaments. J Cell Biol. 1991;114:567–76.
36. Marinkovich MP, Lunstrum GP, Burgeson RE. The anchoring filament protein kalinin is synthesized and secreted as a high molecular weight precursor. J Biol Chem. 1992;267:17900–6.
37. Rousselle P, Aumailley M. Kalinin is more efficient than laminin in promoting adhesion of primary keratinocytes and some other epithelial cells and has a different requirement for integrin receptors. J Cell Biol. 1994;125: 205–14.
38. Rousselle P, Keene DR. Ruggiero F, et al. Laminin 5 binds the NC-1 domain of type VII collagen. J Cell Biol. 1997; 138:719–28.
39. Domloge-Hultsch N, Gammon WR, Briggaman RA, et al. Epiligrin, the major human keratinocyte integrin ligand, is a target in both an acquired autoimmune and an inherited subepidermal blistering skin disease. J Clin Invest. 1992;90:1628–33.
40. Kirtschig G, Marinkovich MP, Burgeson RE, Yancey KB. Anti-basement membrane autoantibodies in patients with anti-epiligrin cicatricial pemphigoid bind the alpha subunit of laminin 5. J Invest Dermatol. 1995;105:543–8.
41. Lazarova Z, Yee C, Darling T, et al. Passive transfer of anti-laminin 5 antibodies induces subepidermal blisters in neonatal mice. J Clin Invest. 1996;98:1509–18.
42. Lazarova Z, Hsu R, Yee C, Yancey KB. Human anti-laminin 5 autoantibodies induce subepidermal blisters in an experimental human skin graft model. J Invest Dermatol. 2000;114:178–84.
43. Hudson BG, Reeders ST, Tryggvason K. Type IV collagen: structure, gene organization, and role in human diseases. Molecular basis of Goodpasture and Alport syndromes and diffuse leiomyomatosis. J Biol Chem. 1993;268:26033–6.
44. Pedchenko V, Bondar O, Fogo AB, et al. Molecular architecture of the Goodpasture autoantigen in anti-GBM nephritis. N Engl J Med. 2010;363:343–54.
45. Ghohestani RF, Hudson BG, Claudy A, Uitto J. The alpha 5 chain of type IV collagen is the target of IgG autoantibodies in a novel autoimmune disease with subepidermal blisters and renal insufficiency. J Biol Chem. 2000;275:16002–6.
46. Kamphaus GD, Colorado PC, Panka DJ, et al. Canstatin, a novel matrix-derived inhibitor of angiogenesis and tumor growth. J Biol Chem. 2000;275:1209–15.
47. Maeshima Y, Sudhakar A, Lively JC, et al. Tumstatin, an endothelial cell-specific inhibitor of protein synthesis. Science. 2002;295:140–3.
48. Kohfeldt E, Sasaki T, Gohring W, Timpl R. Nidogen-2: a new basement membrane protein with diverse binding properties. J Mol Biol. 1998;282:99–109.
49. Caughman SW, Krieg T, Timpl R, et al. Nidogen and heparan sulfate proteoglycan: detection of newly isolated basement membrane components in normal and epidermolysis bullosa skin. J Invest Dermatol. 1987;89:547–50.
50. Sakai LY, Keene DR, Morris NP, Burgeson RE. Type VII collagen is a major structural component of anchoring fibrils. J Cell Biol. 1986;103:1577–86.
51. Shimizu H, Ishiko A, Masunaga T, et al. Most anchoring fibrils in human skin originate and terminate in the lamina densa. Lab Invest. 1997;76:753–63.
52. Chen M, Marinkovich MP, Veis A, et al. Interactions of the amino-terminal noncollagenous (NC1) domain of type VII collagen with extracellular matrix components. A potential role in epidermal-dermal adherence in human skin. J Biol Chem. 1997;272:14516–22.
53. Chen M, Marinkovich MP, Jones JC, et al. NC1 domain of type VII collagen binds to the beta3 chain of laminin 5 via a unique subdomain within the fibronectin-like repeats. J Invest Dermatol. 1999;112:177–83.
54. Christiano AM, Uitto J. Molecular diagnosis of inherited skin diseases: the paradigm of dystrophic epidermolysis bullosa. Adv Dermatol. 1996;11:199–213.
55. Woodley DT, Briggaman RA, O'Keefe EJ, et al. Identification of the skin basement-membrane autoantigen in epidermolysis bullosa acquisita. N Engl J Med. 1984;310:1007–13.
56. Woodley DT, Burgeson RE, Lunstrum G, et al. Epidermolysis bullosa acquisita antigen is the globular carboxyl terminus of type VII procollagen. J Clin Invest. 1988;81:683–7.
57. Lapiere JC, Woodley DT, Parente MG, et al. Epitope mapping of type VII collagen. Identification of discrete peptide sequences recognized by sera from patients with acquired epidermolysis bullosa. J Clin Invest. 1993;92:1831–9.
58. Sitaru C, Mihai S, Otto C, et al. Induction of dermal-epidermal separation in mice by passive transfer of antibodies specific to type VII collagen. J Clin Invest. 2005;115:870–8.
59. Woodley, DT, Chang C, Saadat P, et al. Evidence that anti-type VII collagen antibodies are pathogenic and responsible for the clinical, histological, and immunological features of epidermolysis bullosa acquisita. J Invest Dermatol. 2005;124:958–64.
60. Gammon WR, Briggaman RA, Inman AO III, et al. Differentiating anti-lamina lucida and anti-sublamina densa anti-BMZ antibodies by indirect immunofluorescence on 1.0 M sodium chlorideseparated skin. J Invest Dermatol. 1984;82: 139–44.
61. Gammon WR, Kowalewski C, Chorzelski TP, et al. Direct immunofluorescence studies of sodium chloride separated skin in the differential diagnosis of bullous pemphigoid and epidermolysis bullosa acquisita. J Am Acad Dermatol. 1990;22:664–70.
62. Domloge-Hultsch N, Bisalbutra P, Gammon WR, Yancey KB. Direct immunofluorescence microscopy of 1 mol/L sodium chloride-treated patient skin. J Am Acad Dermatol. 1991;24:946–51.
63. Fine JD, Eady RAJ, Bauer EA, et al. The classification of inherited epidermolysis bullosa (EB): Report of the Third International Consensus Meeting on Diagnosis and Classification of EB. J Am Acad Dermatol. 2008;58: 931–50.
64. McGrath JA, Handyside AH. Preimplantation genetic diagnosis of severe inherited skin diseases. Exp Dermatol. 1998;7:65–72.

This page intentionally left blank

Pemphigus 29

Masayuki Amagai

Synonyms: ■ Fogo selvagem: endemic pemphigus foliaceus; Brazilian pemphigus ■ Pemphigus erythematosus: Senear–Usher syndrome ■ IgA pemphigus: intercellular IgA dermatosis; intraepidermal neutrophilic IgA dermatosis; intercellular IgA vesiculopustular dermatosis ■ Paraneoplastic pemphigus: paraneoplastic autoimmune multiorgan syndrome

Key features

- Pemphigus is a group of autoimmune blistering diseases of the skin and mucous membranes that is characterized by:
  - histologically, intraepidermal blisters due to the loss of cell–cell adhesion of keratinocytes
  - immunopathologically, the finding of *in vivo* bound and circulating IgG autoantibodies directed against the cell surface of keratinocytes
- Pemphigus is divided into three major forms: pemphigus vulgaris, pemphigus foliaceus and paraneoplastic pemphigus
- The functional inhibition of desmogleins, which play an important role in cell–cell adhesion of keratinocytes, by IgG autoantibodies results in blister formation
- Patients with pemphigus vulgaris and pemphigus foliaceus have IgG autoantibodies against desmoglein 3 and desmoglein 1, respectively, while patients with paraneoplastic pemphigus have IgG autoantibodies against plakin molecules in addition to autoantibodies against desmogleins
- IgA autoantibodies directed against the keratinocyte cell surface define IgA pemphigus, the pathophysiology of which is yet to be clarified

INTRODUCTION

The term pemphigus stems from the Greek *pemphix*, meaning blister or bubble, and it describes a group of chronic blistering skin diseases in which autoantibodies are directed against the cell surface of keratinocytes, resulting in the loss of cell–cell adhesion of keratinocytes through a process called acantholysis[1]. Pemphigus can be divided into three major forms: pemphigus vulgaris, pemphigus foliaceus and paraneoplastic pemphigus (Table 29.1).

Pemphigus vulgaris and pemphigus foliaceus are the originally characterized, classic forms of pemphigus. All patients with pemphigus vulgaris have mucosal membrane erosions, and more than half will also have cutaneous blisters and erosions. The blisters of pemphigus vulgaris develop in the deeper portion of the epidermis, just above the basal cell layer. Patients with pemphigus foliaceus have only cutaneous involvement without mucosal lesions, and the splits occur in the superficial part of the epidermis, mostly at the granular layer. Pemphigus vegetans is a variant of pemphigus vulgaris, and pemphigus erythematosus and fogo selvagem represent localized and endemic variants of pemphigus foliaceus, respectively.

More recently, paraneoplastic pemphigus was recognized as a disease distinct from the classic forms of pemphigus[2]. Patients with paraneoplastic pemphigus have a known or occult associated neoplasm, usually of lymphoid tissue. Painful, severe oral and conjunctival erosions are a prominent feature of paraneoplastic pemphigus.

IgA pemphigus is characterized by IgA, but not IgG, autoantibodies directed against keratinocyte cell surfaces and is divided into two major subtypes:

- intraepidermal neutrophilic (IEN) type, with pustule formation throughout the entire epidermis
- subcorneal pustular dermatosis (SPD) type, with pustules primarily in the upper epidermis.

History

The modern history of pemphigus began with the discovery by Beutner and Jordon in 1964 of circulating antibodies directed against the cell surface of keratinocytes in the sera of pemphigus vulgaris patients[3] (Fig. 29.1). This was followed by the finding of *in vivo* IgG deposition on the cell surface of keratinocytes in patients' skin. These findings formed the basis of our understanding of pemphigus as a tissue-specific autoimmune disease of the skin and mucous membranes. In the late 1970s and early 1980s, pemphigus autoantibodies were shown to be pathogenic, i.e. they could induce blister formation in skin organ-culture systems as well as by passive transfer of patients' IgG to neonatal mice[4]. In the mid and late 1980s, the target antigens of pemphigus were characterized by immunochemical methods, such as immunoprecipitation and immunoblotting[5]. In the early 1990s, the isolation of cDNA for pemphigus antigens demonstrated that pemphigus is an anti-cadherin autoimmune disease[6].

EPIDEMIOLOGY

The prevalence of pemphigus vulgaris and pemphigus foliaceus in men and women is approximately equal. The mean age of onset of disease is 50 to 60 years, although the range is broad and disease arising in the elderly and in children has been described. Pemphigus can be found all over the world. Although limited data are available regarding the incidence of pemphigus, in general it ranges from 0.76 to 5 new cases per million per year. However, the incidence is much higher (16 to 32 cases per million per year) in those of Jewish ancestry. Occasionally, this ancestry may not be readily apparent, as in the Hispanic descendants of the *conversos*, who currently reside in the southwestern USA. In most countries, pemphigus vulgaris is more common than pemphigus foliaceus; exceptions include Finland, Tunisia and Brazil. For example, in Japan (incidence of pemphigus: 3.5 cases per million per year), the ratio of pemphigus vulgaris to pemphigus foliaceus is 2:1. In France (incidence: 1.7 cases per million per year), pemphigus vulgaris accounts for the majority of all cases (73%), as it does in Bulgaria. In contrast, in Finland (incidence: much lower at 0.76 cases per million per year) and in Tunisia (incidence: 6.7 cases per million per year), pemphigus foliaceus is twice as common as pemphigus vulgaris. More interestingly, the female-to-male ratio in Tunisia is 4:1, and the incidence is higher in young women ages 25 to 34 years (15.5 cases per million per year). In addition to Brazil, Tunisia may have endemic foci of pemphigus foliaceus (see below).

CLASSIFICATION OF PEMPHIGUS
• Pemphigus vulgaris
• Pemphigus vegetans
• Pemphigus foliaceus
• Pemphigus erythematosus: localized
• Fogo selvagem: endemic
• Herpetiform pemphigus
• Drug-induced pemphigus
• Paraneoplastic pemphigus
• IgA pemphigus

Table 29.1 Classification of pemphigus.

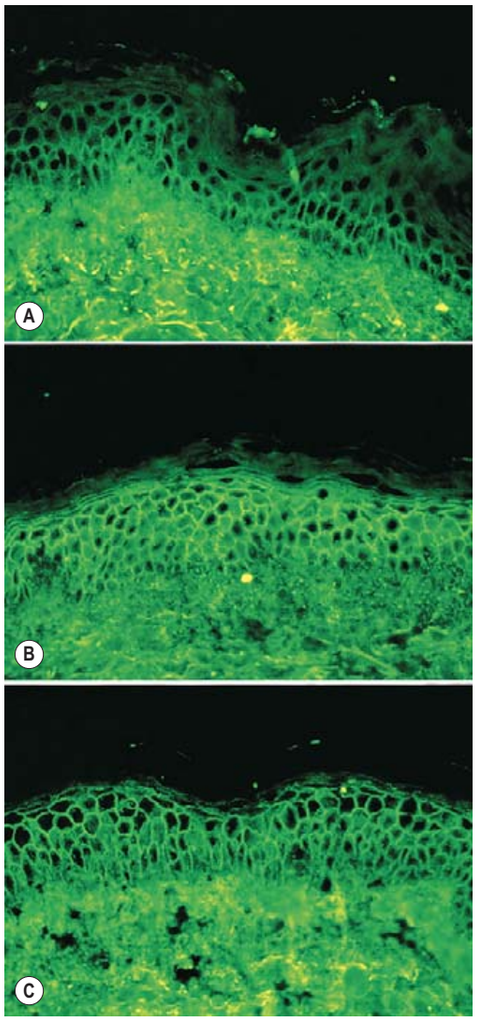


Fig. 29.1 Indirect immunofluorescence of pemphigus sera with normal human epidermis as a substrate. The hallmark of pemphigus is the finding of IgG autoantibodies directed against the cell surface of keratinocytes. **A** Pemphigus vulgaris sera containing anti-desmoglein 3 (anti-Dsg3) IgG alone stain the cell surfaces in the lower epidermis. **B** Pemphigus vulgaris sera containing both anti-Dsg3 IgG and anti-Dsg1 IgG stain the cell surfaces throughout the epidermis. **C** Pemphigus foliaceus sera, which contain only anti-Dsg1 IgG, stain the cell surfaces throughout the epidermis, but more intensely in the superficial layers.

Fogo Selvagem

Patients with fogo selvagem are clinically, histologically and immunopathologically similar to patients with sporadic pemphigus foliaceus. However, fogo selvagem occurs in an endemic fashion in certain regions of Brazil and is thought to be caused by an environmental factor(s)[7]. Unlike sporadic pemphigus foliaceus, which is a disease of mostly middle-aged and older patients, fogo selvagem affects young adults and children of either sex or any race who are exposed to the local ecology in rural areas, and the incidence gradually decreases as the area is developed. The majority of patients live close to rivers and within the 10–15 km flying range of black flies (*Simulium* spp.), which may be the vector that precipitates the disease. There is also a high frequency of hematophagous insects (bedbugs and kissing bugs) in the homes of patients with fogo selvagem.

Fogo selvagem frequently occurs in genetically related family members, although it is not contagious, and, to date, spread by blood products or body fluids has not been documented. In rural Brazil, the ratio of pemphigus foliaceus to pemphigus vulgaris is a remarkable 17:1. The prevalence in some rural areas of Brazil is as high as 3.4% of the population[8]. Furthermore, in these areas, more than 50% of normal individuals have anti-desmoglein 1 (anti-Dsg1) IgG autoantibodies, and it has been shown that the onset of the disease is preceded by a sustained antibody response consisting of non-pathogenic IgG1 and IgG4 antibodies. In certain genetically predisposed individuals, predominant IgG4 antibodies directed against the N-terminal extracellular EC1 and EC2 domains are responsible for inducing disease[9]. Certainly, fogo selvagem provides a fascinating model for understanding the pathophysiologic and immunologic mechanisms involved in triggering an autoimmune response against skin components.

PATHOGENESIS

Pathogenic Autoantibodies in Pemphigus

The hallmark of pemphigus is the finding of IgG autoantibodies against the cell surface of keratinocytes (see Fig. 29.1)[3]. The pemphigus autoantibodies found in patients' sera play a primary pathogenic role in inducing the loss of cell adhesions between keratinocytes, and subsequent blister formation. Neonates of mothers with pemphigus vulgaris may have a transient disease caused by maternal IgG that crosses the placenta. As maternal antibody is catabolized, the disease subsides. IgG fractions from patients can induce blister formation in the absence of complement or inflammatory cells in a skin organ-culture system[4]. Furthermore, passive transfer of patients' IgG to neonatal mice results in blisters in the mice with typical histologic findings[4]. Even monovalent Fab' fragments of IgG from patients with endemic pemphigus foliaceus are sufficient to cause blisters in neonatal mice, indicating complement activation and surface cross-linking may not be relevant in keratinocyte detachment[10]. Although it was shown that pemphigus IgG causes release of plasminogen activator resulting in acantholysis in a skin organ-culture system[11], pemphigus IgG caused blisters to the same degree in plasminogen activator knockout mice and control mice, demonstrating that plasminogen activator is not absolutely required for antibody-induced blisters[12].

The direct and indirect immunofluorescent (IF) staining pattern of paraneoplastic pemphigus differs from that of classic forms of pemphigus. In perilesional skin, direct IF shows deposition of IgG and the third component of complement (C3) on epidermal cell surfaces as well as variably along the basement membrane zone. Unlike classic forms of pemphigus, in which autoantibodies only bind to stratified squamous epithelia, as detected by indirect IF, autoantibodies in paraneoplastic pemphigus also react with simple or transitional epithelia such as urinary bladder epithelium. The latter can be used to differentiate paraneoplastic pemphigus from classic pemphigus.

Desmogleins as Pemphigus Antigens

Immunoelectron microscopy localized both pemphigus vulgaris and pemphigus foliaceus antigens to the desmosomes, the most prominent cell–cell adhesion junctions in stratified squamous epithelia[13]. Immunochemical characterization of pemphigus antigens by immunoprecipitation or immunoblotting with extracts from cultured keratinocytes or epidermis demonstrated that the pemphigus vulgaris and foliaceus antigens were 130 kDa and 160 kDa transmembrane glycoproteins, respectively (Table 29.2)[6,14]. By comparative immunochemical studies using anti-Dsg1 monoclonal and polyclonal antibodies, the 160 kDa protein recognized by pemphigus foliaceus sera was subsequently shown to be identical to Dsg1. An 85 kDa plaque protein, plakoglobin, was co-immunoprecipitated with the 130 kDa and 160 kDa pemphigus antigens, demonstrating that plakoglobin forms a molecular complex with pemphigus vulgaris and foliaceus antigens[15].

Molecular cloning of cDNA encoding Dsg1 and pemphigus vulgaris antigens indicated that both molecules were members of the cadherin supergene family[6,16]. Thus, pemphigus was discovered to be an anti-cadherin autoimmune disease. The pemphigus vulgaris antigens were

termed desmoglein 3 (Dsg3). The basic pathophysiology of pemphigus is as follows: autoantibodies inhibit the adhesive function of desmogleins and lead to the loss of the cell–cell adhesion of keratinocytes, resulting in blister formation.

Cadherins are a family of calcium-dependent cell–cell adhesion molecules that play an important role in the formation and maintenance of complex tissue integrity[17]. Based on sequence similarity, cadherins have two major subgroups, classic cadherins (e.g. E-, P-, N-cadherins) and desmosomal cadherins (desmogleins and desmocollins). All members of the cadherin family contain conserved repeated amino acid sequences (cadherin repeats) with calcium-binding motifs in their extracellular domains (Fig. 29.2). When classic cadherins were introduced by gene transfection into non-adhesive mouse fibroblast L cells, the cells acquired strong cell adhesion activity mediated by a homophilic type of interaction. Cadherins require their well-conserved cytoplasmic domains in order to associate with the plaque proteins, α-catenin, β-catenin and plakoglobin, which mediate and regulate binding to the cytoskeleton network. As a consequence of these interactions, cadherins produce strong cellular adhesion and morphologic changes in the cells. Cadherin molecules form dimers as their functional unit, with the distal extracellular domain (EC1) of the cadherin from one cell binding to the same region of a second cadherin from an opposing cell[18] (Fig. 29.3).

Based on morphologic and biochemical criteria, two major types of adhering junctions of epithelial cells are commonly distinguished: adherens junctions and desmosomes (see Fig. 29.3)[19]. The adherens junction anchors bundles of actin microfilaments and contains classic cadherins as its transmembrane components and α-catenin, β-catenin and plakoglobin as its cytoplasmic components. In contrast, the desmosome anchors intermediate filaments like keratins and contains desmosomal cadherins as its transmembrane components and plakoglobin, plakophilin and desmoplakin as its cytoplasmic components. In general, adherens junctions mediate quick but weak cellular adhesion, whereas desmosomes mediate slow but strong cellular adhesion.

Desmogleins have four cadherin repeats in their extracellular domain, as do classic cadherins, and they have unique repeats of 29 ± 1 amino acid residues in their intracytoplasmic domain (see Fig. 29.2). Desmogleins have four isoforms (Dsg1–4). Expression of Dsg1 and Dsg3 is basically restricted to stratified squamous epithelia, where blisters are formed in pemphigus, while Dsg2 is expressed in all desmosome-possessing tissues, including simple epithelia and myocardium. Dsg4 plays an important adhesive role primarily in hair follicles, and mutations in the *DSG4* gene can lead to abnormal hair development (e.g. localized autosomal recessive hypotrichosis)[20].

Desmocollins are another group of transmembrane glycoproteins within desmosomes and they have three isoforms (Dsc1–3). Each isoform has two products derived from alternatively spliced mRNA of a single gene. Desmosomes always have desmoglein and desmocollin as a pair, but the exact molecular fashion of their interaction as well as the reason why desmocollin does not compensate for the loss of desmoglein in pemphigus remain to be elucidated.

Plakoglobin and plakophilin, together with β-catenin, are members of the armadillo family of nuclear and junctional proteins, which are not only simple anchoring molecules but also dynamic regulators of cellular adhesion and proliferation. Desmoplakin is a dumbbell-shaped molecule composed of three domains: a central α-helical coiled-coil rod, flanked by globular carboxyl- and amino-terminal domains that interact with intermediate filaments and armadillo family members, respectively (see Fig. 29.3). Desmoplakin has two products derived from alternatively spliced mRNA of a single gene: desmoplakin I (250 kDa) and II (210 kDa) (see Table 29.2). Desmoplakin, a member of the

TARGET ANTIGENS IN PEMPHIGUS

Disease	Autoantibodies	Antigens	MW (kDa)
Pemphigus vulgaris			
Mucosal-dominant type	IgG	Desmoglein 3	130
Mucocutaneous type	IgG	Desmoglein 3	130
		Desmoglein 1	160
Pemphigus foliaceus	IgG	Desmoglein 1	160
Paraneoplastic pemphigus	IgG	Desmoglein 3	130
		Desmoglein 1	160
		Plectin*	500
		Desmoplakin I*	250
		Desmoplakin II*	210
		BPAG1*	230
		Envoplakin*	210
		Periplakin*	190
		A2ML1	170
Drug-induced pemphigus	IgG	Desmoglein 3	130
		Desmoglein 1	160
IgA pemphigus†			
Subcorneal pustular dermatosis type	IgA	Desmocollin 1	110/100
Intraepidermal neutrophilic type	IgA	?	?

*Members of plakin family.
†A subset of patients have IgA autoantibodies against Dsg1 or Dsg3.

Table 29.2 Target antigens in pemphigus. A2ML1, alpha-2-macroglobulin-like-1 protease inhibitor; BPAG1, bullous pemphigoid antigen 1.

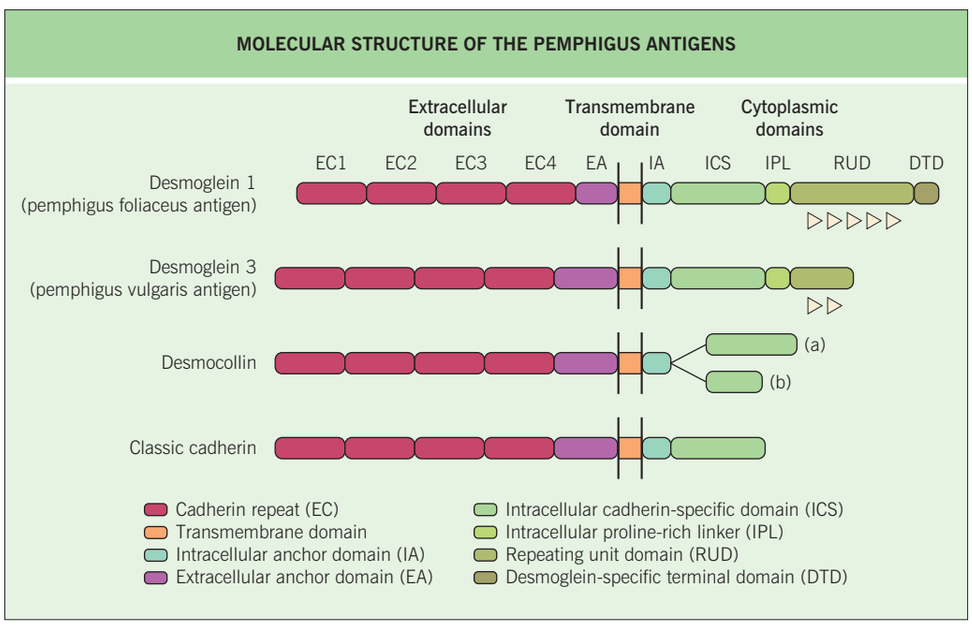


Fig. 29.2 Molecular structure of the pemphigus antigens. The extracellular (EC) region has four cadherin repeats, which have calcium-binding motifs. The intracellular cadherin-specific (ICS) domain is well conserved among cadherins and it is responsible for interactions with β-catenin or plakoglobin (see Fig. 29.3). Desmogleins have their own unique sequences (repeating unit domain or RUD) of repeats of 29 ± 1 residues (arrowheads). Each desmocollin isotype has two products (a and b) derived from alternatively spliced transcripts of a single gene.

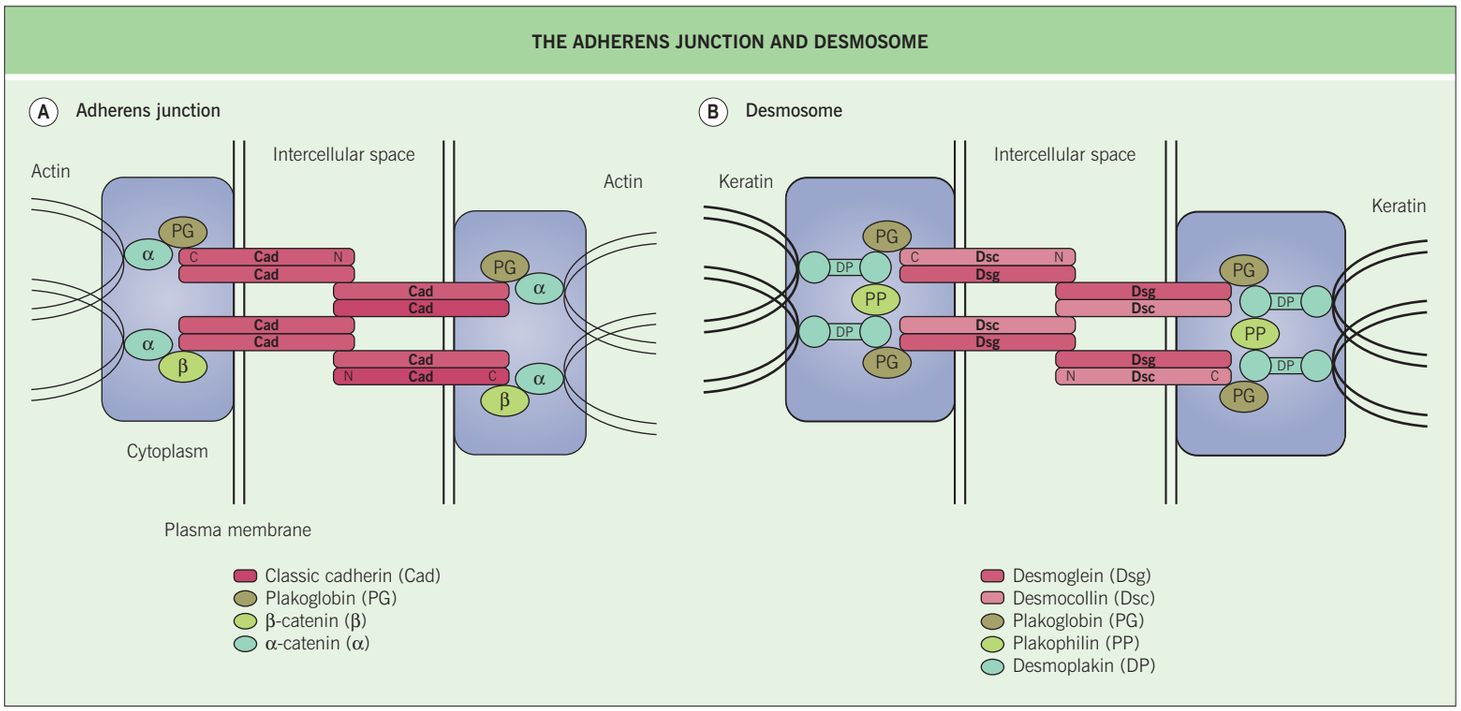


Fig. 29.3 The adherens junction and desmosome. A The adherens junction complex contains classic cadherins as transmembrane constituents and α-catenins, β-catenins and plakoglobin as cytoplasmic constituents. A classic cadherin is directly coupled through its cytoplasmic tail to β-catenin or plakoglobin, which in turn is linked to α-catenin, which binds to actin. **B** The desmosome complex includes desmogleins and desmocollins as transmembrane constituents, and plakoglobin, plakophilin and desmoplakin as cytoplasmic constituents. Desmogleins and desmocollins associate with plakoglobin, which in turn binds to desmoplakin, which links keratin to the membrane. N = amino-terminus; C = carboxy-terminus.

plakin family, plays an important role in the anchorage of the cytoskeleton to filament attachment sites on desmosomes. This intermediate filament-associated plakin family includes bullous pemphigoid antigen 1 (230 kDa), plectin (500 kDa), envoplakin (210 kDa) and periplakin (190 kDa), which are recognized by IgG autoantibodies in paraneoplastic pemphigus.

Compelling evidence has accumulated that IgG autoantibodies against Dsg1 and Dsg3 are pathogenic and play a primary role in inducing the blister formation in pemphigus. Essentially, all patients with pemphigus have IgG autoantibodies against Dsg1 and/or Dsg3, depending on the subtype of pemphigus[21,22]. When anti-desmoglein IgG autoantibodies are removed from the sera of patients with pemphigus vulgaris, pemphigus foliaceus or paraneoplastic pemphigus (by immunoadsorption with recombinant desmoglein proteins), the sera are no longer pathogenic in inducing blister formation[23,24]. Furthermore, anti-desmoglein IgG autoantibodies that have been affinity-purified from pemphigus sera via desmoglein recombinant proteins can cause blisters when injected into neonatal mice[24,25]. Some pemphigus sera react with Dsg4 due to cross-reactivity of a subset of anti-Dsg1 IgG, although Dsg4/Dsg1-cross-reacting IgG has no demonstrable pathogenic effect[26]. IgG autoantibodies against acetylcholine receptors or annexin-like molecules have also been detected, but their pathogenic relevance in pemphigus remains to be determined.

Desmoglein Compensation Theory as Explanation for Localization of Blisters

The sites of blisters in pemphigus vulgaris and foliaceus are explained logically by the desmoglein compensation theory: Dsg1 and Dsg3 compensate for each other when they are coexpressed in the same cell (Fig. 29.4)[27,28]. While patients with pemphigus foliaceus have only anti-Dsg1 IgG autoantibodies, individuals with the mucosal-dominant type of pemphigus vulgaris have only anti-Dsg3 IgG autoantibodies. Those with the mucocutaneous type of pemphigus vulgaris have both anti-Dsg3 and anti-Dsg1 IgG autoantibodies[29]. Of note, the intraepithelial expression pattern of Dsg1 and Dsg3 differs between the skin and mucous membranes. In the skin, Dsg1 is expressed throughout the epidermis, but more intensely in the superficial layers (see Fig. 29.1C), whereas Dsg3 is expressed in the lower portion of the epidermis, primarily in the basal and parabasal layers (see Fig. 29.1A). In contrast to the skin, Dsg1 and Dsg3 are expressed throughout the squamous layer of mucosa, but Dsg1 is expressed at a much lower level than Dsg3 (see Fig. 29.4B)[30].

When sera contain only anti-Dsg1 IgG (which interferes with the function of Dsg1), blisters appear only in the superficial epidermis of the skin because that is the only area in which Dsg1 is present without coexpression of Dsg3. In the unaffected deep epidermis, the presence of Dsg3 compensates for the loss of function of Dsg1. Although the anti-Dsg1 IgG binds to mucosa, no blisters are formed, because of the coexpression of Dsg3. Thus, sera containing only anti-Dsg1 IgG cause superficial blisters in the skin without mucosal involvement, as is seen in patients with pemphigus foliaceus.

When sera contain only anti-Dsg3 IgG, they are inefficient in producing cutaneous blisters because coexpressed Dsg1 compensates for the impaired function of Dsg3, resulting in no, or only limited, skin lesions. However, in the mucous membranes, Dsg1 cannot compensate for the impaired Dsg3 function because of its low expression. Therefore, sera containing only anti-Dsg3 IgG cause oral erosions without apparent skin involvement, as is seen in patients with the mucosal-dominant type of pemphigus vulgaris.

When sera contain both anti-Dsg1 and anti-Dsg3 IgG, they interfere with the function of both Dsg1 and Dsg3, resulting in extensive blisters and erosions of the skin as well as the mucous membranes, as is seen in patients with the mucocutaneous type of pemphigus vulgaris. It is not clear why splits appear just above the basal layer instead of the whole epithelium falling apart. However, it is speculated that cell–cell adhesion in the basal and parabasal layers might be weaker than in other parts of the epithelium because there are fewer desmosomes. In addition, autoantibodies, which penetrate from the dermis, might have better access to the lower part of the epithelia.

In pregnant women with pemphigus, autoantibodies cross the placenta and bind to the fetal epidermis. However, neonates develop blisters if the mother has pemphigus vulgaris, but very rarely if she has pemphigus foliaceus. This confusing observation is also explained by the desmoglein compensation theory[31]. The distribution of Dsg3 within neonatal epidermis is unlike that in adult epidermis; it is

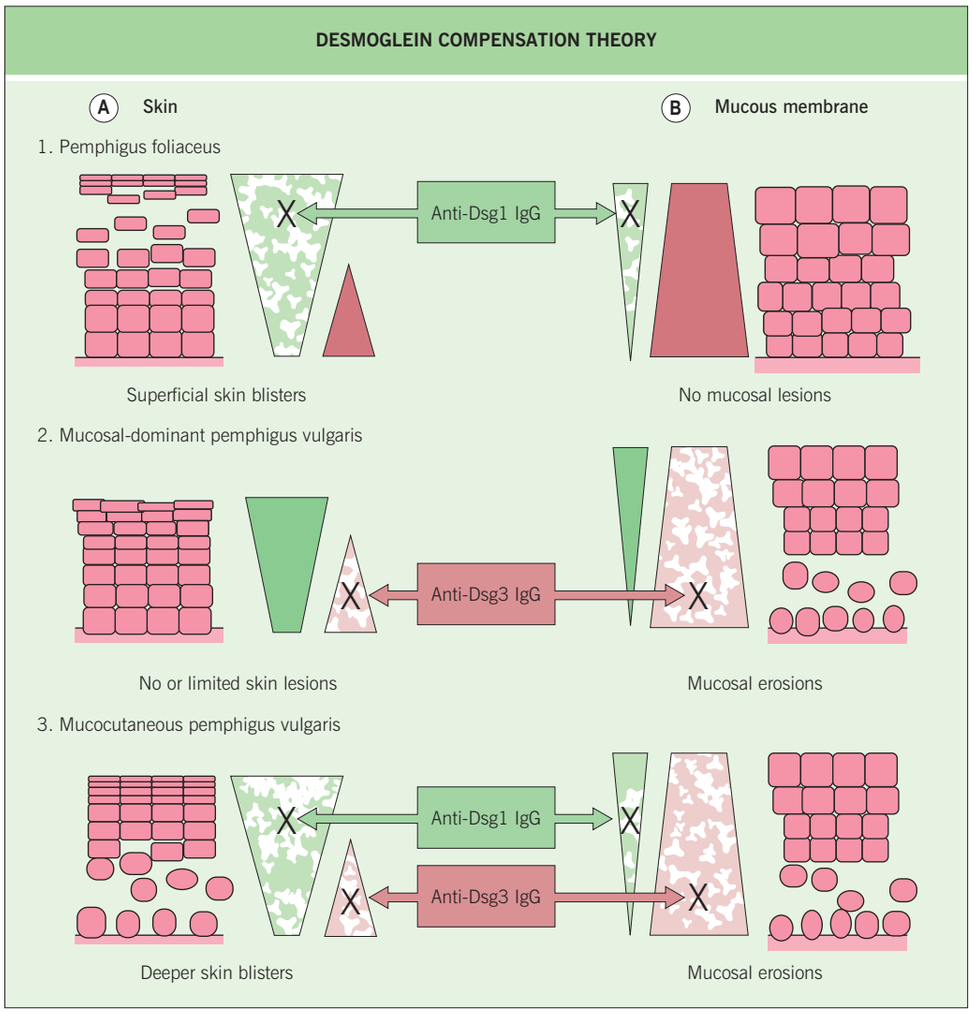


Fig. 29.4 Logical explanation for the localization of blister formation in classic pemphigus by desmoglein compensation theory. The colored triangles represent the distribution of desmoglein 1 (Dsg1) and desmoglein 3 (Dsg3) in the skin (**A**) and mucous membranes (**B**). Pemphigus foliaceus sera contain only anti-Dsg1 IgG, which causes superficial blisters in the skin because Dsg3 functionally compensates for the impaired Dsg1 in the lower part of the epidermis (**A1**), whereas those antibodies do not cause blisters in the mucous membranes because cell–cell adhesion is mainly mediated by Dsg3 (**B1**). Sera containing only anti-Dsg3 IgG cause no or only limited blisters in the skin because Dsg1 compensates for the loss of Dsg3-mediated adhesion (**A2**); however, these sera induce separation in the mucous membranes, where the low expression of Dsg1 will not compensate for the loss of Dsg3-mediated adhesion (**B2**). When sera contain both anti-Dsg1 and anti-Dsg3 IgG, the function of both Dsgs is compromised and blisters occur in both the skin and mucous membranes (**A3, B3**). In neonatal skin, the situation is similar to that shown here for mucous membranes.

found on the surface of keratinocytes throughout the epidermis, which is similar to its distribution in mucous membranes (remember, neonatal skin is bathed in amniotic fluid). Therefore, pemphigus foliaceus sera containing only anti-Dsg1 IgG cannot induce blisters in neonatal skin.

As an extension of this compensation theory, exfoliative toxins, which are produced by *Staphylococcus aureus* and lead to bullous impetigo as well as staphylococcal scalded skin syndrome, specifically cleave Dsg1[32]. Inactivation of Dsg1 by this toxin induces superficial blisters in the epidermis that are clinically and histologically similar to those seen in pemphigus foliaceus.

The exact mechanisms responsible for acantholysis remain to be elucidated; however, it is currently thought that the disruption of cell–cell adhesion is mediated via the combined effects of direct inhibition by antibodies and subsequent signal transduction induced by antibody binding. The direct inhibition is mediated by steric hindrance, i.e. the binding of autoantibodies to desmogleins spatially interferes with the adhesive interaction of desmogleins between cells. This possibility, supported by the observation that dominant epitopes are localized to the functionally important N-terminal region of desmogleins in pemphigus vulgaris and foliaceus[25,33,34], and pathogenic anti-Dsg3 mouse or human monoclonal antibody, but not non-pathogenic monoclonal antibodies, recognizes the N-terminal adhesive surface of Dsg3[34,35]. The phenotype of the *Dsg3* null mouse (whose *Dsg3* gene is genetically deleted) closely resembles that of human pemphigus vulgaris patients and it also supports this direct interference explanation[36]. The role of signal transduction induced by antibody binding is supported by the *in vitro* observation that IgG from pemphigus vulgaris sera (when added to the media of cultured keratinocytes) causes a transient increase in intracellular calcium and/or inositol 1,4,5-triphosphate, activation of protein kinase C, or phosphorylation of Dsg3[37,38]. Furthermore, with desmosomal disassembly, Dsg3 is internalized or endocytosed from the cell surface in association with keratin retraction[39,40]. Further studies are needed to clarify this issue.

Autoimmunity Against Desmogleins and Plakins in Paraneoplastic Pemphigus

Patients with paraneoplastic pemphigus develop characteristic IgG autoantibodies against multiple antigens, including those originally described with molecular weights of 250, 230, 210, 190 and 170 kDa (see Table 29.2)[2]. By immunochemical studies and cDNA cloning, these antigens have been identified. The 250 kDa and 210 kDa antigens are desmoplakins I and II, respectively. The 230 kDa antigen is bullous pemphigoid antigen 1, the major plaque protein of the epidermal hemidesmosome and also a target antigen in bullous pemphigoid. The 210 kDa band also contains envoplakin, and the 190 kDa antigen is periplakin. Later, plectin (500 kDa) was also found to be recognized, as were Dsg3 and Dsg1[24]. Most recently, the 170 kDa antigen was identified as alpha-2-macroglobulin-like-1, a broad-range protease inhibitor expressed in stratified epithelia and other tissues[40a]. In summary, all the members of the plakin family, as well as desmogleins, are targeted by IgG autoantibodies in paraneoplastic pemphigus.

Anti-desmoglein antibodies play a role in inducing the loss of cellular adhesion of keratinocytes and initiate blister formation, while the pathophysiologic relevance of the anti-plakin autoantibodies is unclear. The intracellular location of plakin proteins makes it unlikely that anti-plakin autoantibodies initiate pathology in paraneoplastic pemphigus, because IgG cannot penetrate cell membranes. It is also important to bear in mind that not only humoral immunity but also cell-mediated cytotoxicity is involved in the pathogenesis of paraneoplastic pemphigus, in which more severe and refractory oral erosions and stomatitis as well as more polymorphic skin eruptions are seen, in comparison with classic forms of pemphigus.

Immunologic Mechanism of Pathogenic Autoantibody Production in Pemphigus

In contrast to the significant progress since the late 1980s in understanding the pathophysiologic mechanisms of blister formation in pemphigus, it is still unclear why patients with pemphigus begin to produce the pathogenic autoantibodies.

Pemphigus autoantibodies are composed of IgG isotypes, which may be produced after isotype switching, and they have a high affinity towards the antigen, which may be a result of affinity maturation of the antibodies. In addition, pemphigus sera recognize several distinct epitopes on desmogleins[33], and the presence of autoantibodies is associated with specific HLA class II alleles, including DRB1*0402, DRB1*1401 and DQB1*0302 in Caucasians[41] and DRB1*14 and DQB1*0503 in Japanese[42]. All of these features suggest that autoantibody production in pemphigus is T cell-dependent. More recently, T cells reactive against Dsg3 were shown to be present in peripheral blood from patients with pemphigus vulgaris as well as healthy individuals[43–45]. Certain peptides from Dsg3, predicted to fit into the DRB1*0402 pocket, were able to stimulate T cells from the pemphigus patients. An essential step in the clarification of the immunologic mechanism of autoantibody production will be the characterization of those T cells involved in autoantibody production.

Another advance that will allow the study of T cells and B cells is the development of an active disease mouse model for pemphigus vulgaris using autoantigen knockout mice, in which self-tolerance to the absent gene product is not acquired[46]. When lymphocytes from Dsg3 knockout mice are adoptively transferred into mice expressing Dsg3, anti-Dsg3 IgG is stably produced in the recipient mice and they develop the phenotype of pemphigus vulgaris. This model is valuable not only for dissecting the cellular and molecular mechanisms involved in antibody production but also for developing novel therapeutic strategies[47,48].

CLINICAL FEATURES

Pemphigus Vulgaris

Essentially all patients with pemphigus vulgaris develop painful erosions of the oral mucosa. More than half of the patients also develop flaccid blisters and widespread cutaneous erosions. Pemphigus vulgaris is therefore divided into two subgroups: (1) the *mucosal-dominant* type with mucosal erosions but minimal skin involvement; and (2) the *mucocutaneous* type with extensive skin blisters and erosions in addition to mucosal involvement (see Fig. 29.4).

Mucous membrane lesions usually present as painful erosions (Fig. 29.5A,B). Intact blisters are rare, probably because they are fragile and break easily. Although scattered or extensive erosions may be seen anywhere in the oral cavity, the most common sites are the buccal and palatine mucosa. The erosions are of different sizes with an irregular ill-defined border, which, when extensive or painful, may result in decreased oral intake of food or liquids. The diagnosis of pemphigus vulgaris tends to be delayed in patients presenting with only oral involvement, as compared to patients with skin lesions.

The lesions may extend out onto the vermilion lip and lead to thick, fissured hemorrhagic crusts. Involvement of the throat produces hoarseness and difficulty in swallowing. The esophagus also may be involved and sloughing of its entire lining in the form of a cast has been reported. The conjunctivae, nasal mucosa, vagina, penis, anus and labia can develop lesions as well. Cytology of vaginal cells may be misread as a malignancy when vaginal lesions are present.

The primary skin lesions of pemphigus vulgaris are flaccid, thin-walled, easily ruptured blisters (Fig. 29.5C). They can appear anywhere on the skin surface and arise on either normal-appearing skin or erythematous bases. The fluid within the bullae is initially clear but may become hemorrhagic, turbid, or even seropurulent. The blisters are fragile and soon rupture to form painful erosions that ooze and bleed easily. These erosions often attain a large size and can become generalized. The erosions soon become partially covered with crusts that have little or no tendency to heal. Those lesions that do heal often leave hyperpigmented patches with no scarring. Associated pruritus is uncommon. Table 29.3 outlines more unusual clinical presentations of pemphigus vulgaris (Fig. 29.5D).

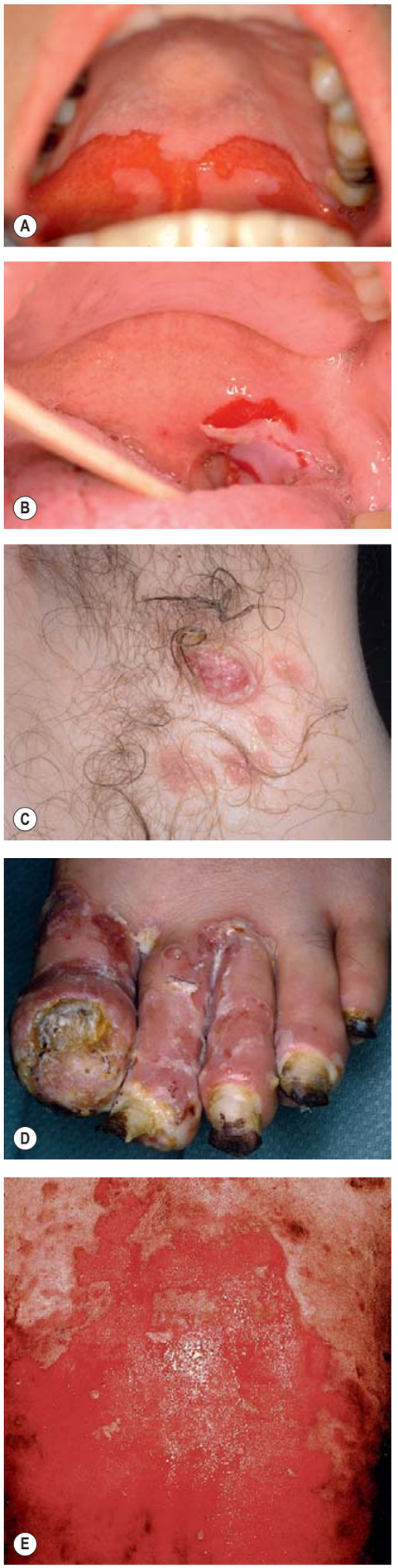


Fig. 29.5 Pemphigus vulgaris. A,B Essentially all patients develop painful oral mucosal erosions, with the most common sites being the buccal and palatine mucosae. **C** Flaccid blisters and an erosion due to rupture of a bulla. **D** The dyshidrosiform variant is uncommon. **E** In a severe case, a large area of the back is affected, leading to a loss of body fluids and secondary bacterial infections. *B–D, Courtesy, Louis A Fragola, Jr, MD. E, Courtesy, Department of Dermatology, Hamamatsu University School of Medicine.*

UNUSUAL CLINICAL PRESENTATIONS OF PEMPHIGUS VULGARIS
Isolated crusted plaque on face or scalp
Paronychia
Foot ulcers
Dyshidrotic eczema or pompholyx
Macroglossia

Table 29.3 Unusual clinical presentations of pemphigus vulgaris.

Fig. 29.6 Pemphigus vegetans. Extensive vegetating papillomatous lesions are noted.

Because of an absence of cohesion within the epidermis, its upper layers easily move laterally with slight pressure or rubbing in patients with active disease (Nikolsky sign). The lack of cohesion of the skin may also be demonstrated with the "bulla-spread phenomenon" – gentle pressure on an intact bulla forces the fluid to spread under the skin away from the site of pressure (Asboe–Hansen sign, also referred to as the "indirect Nikolsky" or "Nikolsky II" sign). Without appropriate treatment, pemphigus vulgaris can be fatal because a large area of the skin loses its epidermal barrier function, leading to the loss of body fluids or to secondary bacterial infections (Fig. 29.5E).

Pemphigus Vegetans

Pemphigus vegetans is a rare vegetative variant of pemphigus vulgaris, and it is thought to represent a reactive pattern of the skin to the autoimmune insult of pemphigus vulgaris.

Pemphigus vegetans is characterized by flaccid blisters that become erosions and then form fungoid vegetations or papillomatous proliferations, especially in intertriginous areas and on the scalp or face (Fig. 29.6). Pustules rather than vesicles characterize early lesions, but these soon progress to vegetative plaques. The tongue may show cerebriform-like changes. Two subtypes are recognized: the severe Neumann type and the mild Hallopeau type. A vegetative response may occasionally also be seen in lesions of pemphigus vulgaris that tend to be resistant to therapy and remain for long periods of time in one location.

Pemphigus Foliaceus

Patients with pemphigus foliaceus develop scaly, crusted cutaneous erosions, often on an erythematous base, but they do not have clinically apparent mucosal involvement even with widespread disease.

The onset of disease is often subtle, with a few scattered crusted lesions that are transient and are frequently mistaken for impetigo. They are usually well demarcated and have a seborrheic distribution, i.e. they favor the face, scalp and upper trunk (Fig. 29.7A,B). Because the vesicle is so superficial and fragile, often only the resultant crust and scale are seen (Fig. 29.7C,D). The disease may stay localized for years or it may rapidly progress, in some cases to generalized involvement and an exfoliative erythroderma (see Ch. 10). The Nikolsky sign is present. In contrast to the extensive oral lesions in pemphigus vulgaris, it is extremely rare, if ever, for patients with pemphigus foliaceus to develop mucosal involvement. Generally, patients with pemphigus foliaceus are not severely ill. They do complain of burning and pain in association with the skin lesions.

Pemphigus Erythematosus (Senear–Usher Syndrome)

Pemphigus erythematosus is simply a localized variant of pemphigus foliaceus. Typical scaly and crusted lesions of pemphigus foliaceus appear in the malar region of the face (Fig. 29.8) and in other "seborrheic" areas. Originally, the term "pemphigus erythematosus" was introduced to describe patients with immunologic features of both lupus erythematosus and pemphigus, i.e. *in vivo* IgG and C3 deposition on cell surfaces of keratinocytes as well as the basement membrane zone, in addition to circulating antinuclear antibodies[49]. However, only a few patients have been reported to actually have the two diseases concurrently.

Herpetiform Pemphigus

Most patients with herpetiform pemphigus have a clinical variant of pemphigus foliaceus and the remainder may have a variant of pemphigus vulgaris. This disorder is characterized by: (1) erythematous urticarial plaques and tense vesicles that present in a herpetiform arrangement; (2) eosinophilic spongiosis and subcorneal pustules with minimal or no apparent acantholysis histologically; and (3) IgG autoantibodies directed against the cell surfaces of keratinocytes[50]. The target antigen is Dsg1 in most cases and Dsg3 in the remainder[51]. Some patients with herpetiform pemphigus will have features of pemphigus foliaceus or vulgaris during the course of their disease, and some patients will evolve into having pemphigus foliaceus or vulgaris. It is assumed that the pathogenic blister-inducing activity of the IgG autoantibodies in herpetiform pemphigus might be weaker than that seen in classic forms of pemphigus. Although often clinically less severe than pemphigus vulgaris, the course may be more chronic[52].

Drug-Induced Pemphigus

There are sporadic cases of pemphigus associated with the use of drugs, in particular penicillamine and captopril[53]. In patients receiving penicillamine, pemphigus foliaceus is seen more commonly than pemphigus vulgaris, with a ratio of approximately 4 : 1. Although most patients with drug-induced pemphigus are shown to have autoantibodies against the same molecules involved in sporadic pemphigus, evidence suggests that some drugs may induce acantholysis without the production of antibodies. Both penicillamine and captopril contain sulfhydryl groups that are speculated to interact with the sulfhydryl groups in Dsg1 and Dsg3. This interaction may modify the antigenicity of the desmogleins, which may lead to autoantibody production, or their interaction may directly interfere with the adhesive function of the desmogleins. Most, but not all, patients with drug-induced pemphigus go into remission after the offending drug is discontinued.

Paraneoplastic Pemphigus

Paraneoplastic pemphigus is associated with underlying neoplasms, both malignant and benign. The most commonly associated neoplasms are non-Hodgkin lymphoma (40%), chronic lymphocytic leukemia (30%), Castleman's disease (10%), malignant and benign thymomas (6%), sarcomas (6%) and Waldenström's macroglobulinemia (6%)[2]. Non-Hodgkin lymphoma and chronic lymphocytic leukemia together account for two-thirds of patients. Castleman's disease, a very rare lymphoproliferative disorder, is the third most commonly associated neoplasm in adults and the most commonly associated tumor in children and adolescents; its association with paraneoplastic pemphigus is strikingly disproportionate to its general occurrence. The absence of

Fig. 29.7 Pemphigus foliaceus. A Scaly, crusted erosions widely distributed on the back. **B** As the disease progresses, the lesions become confluent. **C** Because the vesicles are fragile and rupture easily, the typical lesions of pemphigus foliaceus are erosions with scale-crust. **D** The scales have been likened to cornflakes.

Fig. 29.8 Pemphigus erythematosus. Erythematous plaques with scale-crust and erosions on the nose and malar area of the face. *Courtesy, Ronald P Rapini, MD.*

Fig. 29.9 Paraneoplastic pemphigus. The characteristic clinical feature is severe intractable stomatitis that extends onto the vermilion lip. Erosions and hemorrhagic crusts are also present.

common tumors, such as adenocarcinomas of the breast or colon and squamous cell carcinomas, is notable.

The most constant clinical feature of paraneoplastic pemphigus is the presence of intractable stomatitis. Severe stomatitis is usually the earliest presenting sign and, after treatment, it is the one that persists and is extremely resistant to therapy. This stomatitis consists of erosions and ulcerations that affect all surfaces of the oropharynx and characteristically extend onto the vermilion lip (Fig. 29.9). Most patients also have a severe pseudomembranous conjunctivitis, which may progress to scarring and obliteration of the conjunctival fornices. Esophageal, nasopharyngeal, vaginal, labial and penile mucosal lesions may also be seen.

Cutaneous findings are quite polymorphic and may present as erythematous macules, flaccid blisters and erosions resembling pemphigus vulgaris, tense blisters resembling bullous pemphigoid, erythema multiforme-like lesions, and lichenoid eruptions. The occurrence of

Fig. 29.10 IgA pemphigus. **A** Subcorneal pustular dermatosis (SPD) type. Pustules tend to coalesce to form an annular or circinate pattern with crusts present centrally. Note the accumulation of the pustular component in the dependent portion of the vesiculopustule. **B** Intraepidermal neutrophilic (IEN) type. The characteristic sunflower-like configuration of pustules is seen.

blisters and erythema multiforme-like lesions on the palms and soles is often used to differentiate paraneoplastic pemphigus from pemphigus vulgaris, in which lesions on the palms and soles are unusual. In the chronic form of the disease, a lichenoid eruption may predominate over blistering lesions. Some patients with paraneoplastic pemphigus develop bronchiolitis obliterans, which can be fatal as a result of respiratory failure, although its pathophysiologic mechanism is still unclear[54]. Of note, a chest X-ray or CT scan obtained at the onset of bronchiolitis obliterans may be normal but pulmonary function tests will show small airway obstruction that does not reverse with bronchodilators.

IgA Pemphigus

IgA pemphigus represents a more recently characterized group of autoimmune intraepidermal blistering diseases presenting with a vesiculopustular eruption, neutrophilic infiltration of the skin, and *in vivo* bound and circulating IgA autoantibodies against the cell surface of keratinocytes, but with no IgG autoantibodies. IgA pemphigus usually occurs in middle-aged or elderly persons. Two distinct types of IgA pemphigus have been described: the subcorneal pustular dermatosis type and the intraepidermal neutrophilic type. Patients with both types of IgA pemphigus present with flaccid vesicles or pustules on either erythematous or normal skin. In both types, the pustules tend to coalesce to form an annular or circinate pattern with crusts in the center of the lesion (Fig. 29.10A), although a sunflower-like configuration of pustules is a characteristic sign of the intraepidermal neutrophilic type (Fig. 29.10B)[55]. The most common sites of involvement are the axilla and groin, but the trunk and proximal extremities can also be involved. Mucous membrane involvement is rare, and pruritus is often a significant symptom. Because the subcorneal pustular dermatosis type of IgA pemphigus is clinically and histologically indistinguishable from classic subcorneal pustular dermatosis (Sneddon–Wilkinson disease; see Ch. 8), immunologic evaluation is essential to differentiate the two diseases.

IgA deposition on cell surfaces of epidermal keratinocytes is present in all cases, as shown by direct IF, and many patients have detectable circulating IgA autoantibodies, as shown by indirect IF. In the subcorneal pustular dermatosis type, IgA autoantibodies react against upper epidermal surfaces, while in the intraepidermal neutrophilic type, IgA autoantibodies are found throughout the entire epidermis. The subclass of IgA autoantibodies is exclusively IgA1. IgA autoantibodies in the subcorneal pustular dermatosis type were shown to recognize desmocollin 1 when it was expressed on COS7 cells[56], while the autoimmune targets of the intraepidermal neutrophilic type remain to be identified. A subset of IgA pemphigus patients have IgA autoantibodies directed against Dsg1 or Dsg3, making the autoimmune targets of IgA pemphigus more heterogeneous. The exact pathogenic role of IgA autoantibodies in inducing pustular formation in IgA pemphigus remains to be elucidated.

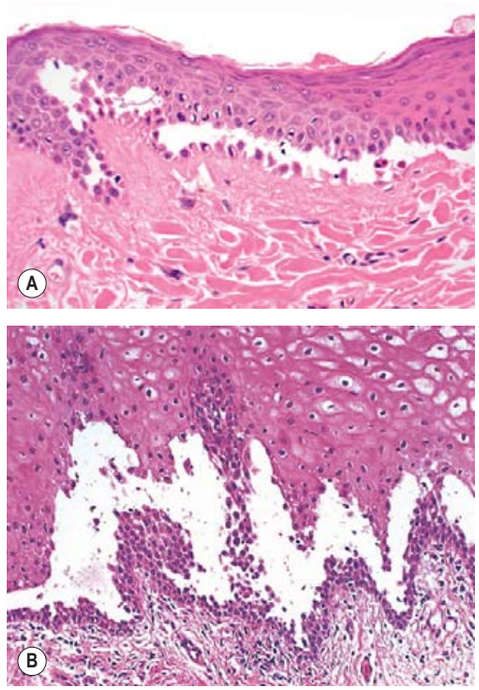


Fig. 29.11 Histology of pemphigus vulgaris. **A** Blisters in the skin show suprabasilar acantholysis with a few acantholytic cells in the blister cavity. Attachment of the basal cells to the basement membrane via hemidesmosomes leads to the "tombstones" appearance. **B** The border of a blister on the buccal mucosa shows intraepithelial separation in the lower part of the mucosal epithelia. *A, Courtesy, Lorenzo Cerroni, MD.*

PATHOLOGY

Pemphigus Vulgaris

The characteristic histologic finding in this form of pemphigus is intraepidermal blister formation due to a loss of cell–cell adhesion of keratinocytes (acantholysis) without keratinocyte necrosis (Fig. 29.11A). Whereas acantholysis usually occurs just above the basal cell layer (suprabasilar acantholysis), intraepithelial separation may occasionally be higher in the stratum spinosum (Fig. 29.11B). A few rounded-up (acantholytic) keratinocytes as well as clusters of epidermal cells are often seen in the blister cavity. Although the basal cells lose lateral desmosomal contact with their neighbors, they maintain their attachment to the basement membrane via hemidesmosomes, thus giving the appearance of a "row of tombstones". The acantholytic process may involve hair follicles.

The dermal papillary outline is usually maintained and, frequently, the papillae protrude into the blister cavity. The blister cavity may contain a few inflammatory cells, notably eosinophils, and in the dermis there is a moderate perivascular mononuclear cell infiltrate with

CAUSES OF EOSINOPHILIC SPONGIOSIS
Pemphigus vulgaris
Pemphigus foliaceus
Bullous pemphigoid
Pemphigoid gestationis (herpes gestationis)
Polymorphic eruption of pregnancy (pruritic urticarial papules and plaques of pregnancy)
Linear IgA bullous dermatosis
Insect-bite reaction
Drug eruptions
Erythema toxicum neonatorum
Incontinentia pigmenti
Atopic dermatitis
Contact dermatitis
Transient acantholytic dermatosis (Grover's disease)

Table 29.4 Causes of eosinophilic spongiosis.

conspicuous eosinophils. In rare instances, the earliest histologic finding consists of eosinophilic spongiosis (Table 29.4), in which eosinophils invade a spongiotic epidermis with little or no evidence of acantholysis.

It is essential to take a biopsy from an early lesion in order to establish the correct diagnosis because pemphigus blisters rupture easily. In patients with only oral lesions, a biopsy specimen should be obtained from the active border of a denuded area because intact blisters are rarely encountered (see Fig. 29.11B). Cytologic examination (Tzanck smear) is useful for the rapid demonstration of acantholytic epidermal cells in the blister cavity. However, this bedside test merely represents a preliminary diagnostic tool, and it should not supplant histologic examination because acantholytic keratinocytes are occasionally seen in various non-acantholytic vesiculobullous or pustular diseases as a result of secondary acantholysis.

In pemphigus vegetans, suprabasilar acantholysis is seen, in addition to considerable papillomatosis and acanthosis. Characteristically, there is an intense inflammatory cell infiltrate containing numerous eosinophils, and intraepidermal microabscesses are often seen.

Pemphigus Foliaceus

The histologic changes of pemphigus foliaceus, pemphigus erythematosus and fogo selvagem are identical. Early blisters in pemphigus foliaceus have acantholysis in the upper epidermis, within or adjacent to the granular layer (Fig. 29.12). As the blisters are superficial and fragile, it is often difficult to obtain an intact lesion for histologic examination. As a result, acantholysis is sometimes difficult to detect, but usually a few acantholytic keratinocytes can be found attached to the roof or floor of the blister. Although the deeper epidermis usually remains intact, secondary clefts may develop, leading to detachment of the epidermis in its midlevel, but rarely giving rise to limited areas of separation above the basal layer. These superficial blisters are histologically indistinguishable from those seen in staphylococcal scalded skin syndrome or bullous impetigo, because Dsg1 is targeted in both diseases[32]. Sometimes the blister cavity contains numerous acute inflammatory cells, particularly neutrophils. Eosinophilic spongiosis can be also seen in very early lesions of pemphigus foliaceus (see Table 29.4). The dermis shows a moderate number of inflammatory cells, among which eosinophils are often present.

Paraneoplastic Pemphigus

The histologic findings of cutaneous lesions in paraneoplastic pemphigus show considerable variability, reflecting the polymorphism seen clinically. The lesions show a unique combination of pemphigus vulgaris-like, erythema multiforme-like, and lichen planus-like histologic features, sometimes in the same specimen (Fig. 29.13). Intact cutaneous blisters demonstrate suprabasilar acantholysis and individual keratinocyte necrosis with lymphocytes within the epidermis. In addition, basal cell liquefactive degeneration or a band-like dense lymphocytic infiltrate in the upper dermis can be seen. Eosinophils are rare. Biopsy specimens of the severe ulcerative stomatitis usually yield only nonspecific changes of inflammation, but the perilesional oral epithelium should show suprabasilar acantholysis.

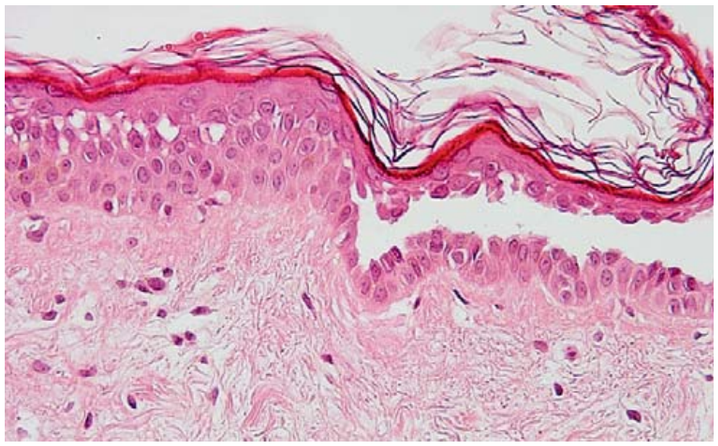


Fig. 29.12 Histology of pemphigus foliaceus. Clefting is seen in the upper spinous layer of the epidermis with several acantholytic cells detaching from the roof of the blister.

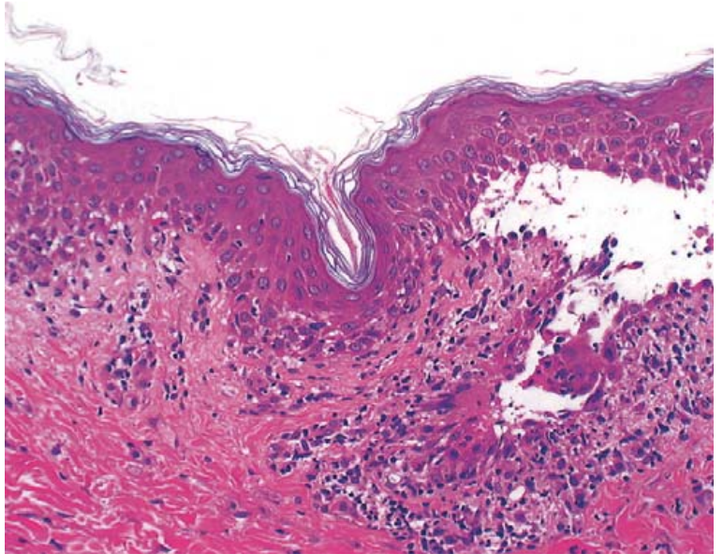


Fig. 29.13 Histology of paraneoplastic pemphigus. Suprabasilar acantholysis is seen along with a combination of basal cell vacuolar change, necrotic keratinocytes, and lymphocytes within the epidermis.

IgA Pemphigus

The characteristic histologic feature in IgA pemphigus is formation of an intraepidermal pustule or vesicle (Fig. 29.14). The contents of the pustules consist predominantly of neutrophils. Acantholysis is usually not seen. IgA pemphigus is divided into two subtypes depending on the level of intraepidermal pustule; in the subcorneal pustular dermatosis type, pustules are located subcorneally in the upper epidermis, while in the intraepidermal neutrophilic type, suprabasilar pustules involving the lower or entire epidermis are present.

DIFFERENTIAL DIAGNOSIS

Demonstration of IgG (or IgA for IgA pemphigus) autoantibodies directed against the cell surface of keratinocytes is the gold standard for the diagnosis of pemphigus. By detection of these autoantibodies, pemphigus can be differentiated from other vesiculobullous or pustular diseases. Methods for demonstrating pemphigus autoantibodies include direct IF, indirect IF, immunoprecipitation, immunoblotting and enzyme-linked immunosorbent assay (ELISA).

Direct IF examines patients' skin or mucous membranes in order to demonstrate *in vivo* bound IgG deposition on the keratinocyte cell surfaces. The biopsy specimen should be taken from perilesional normal skin or mucous membrane. Direct IF is the most reliable and

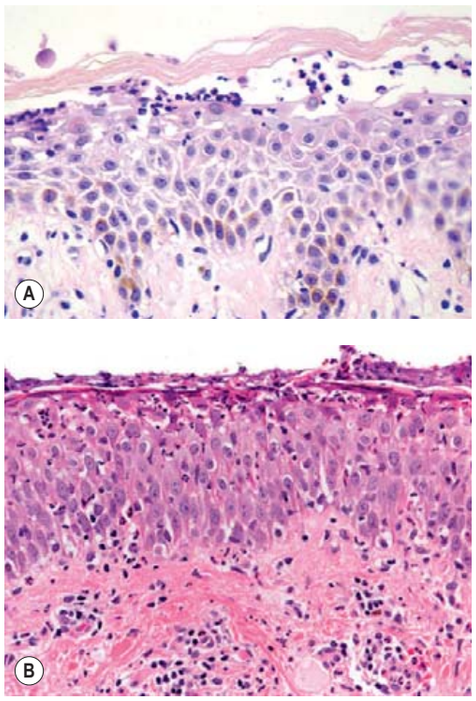


Fig. 29.14 Histology of IgA pemphigus. Intraepidermal pustule with neutrophils present subcorneally in the subcorneal pustular dermatosis type (**A**), and within the entire epidermis in the intraepidermal neutrophilic type (**B**). *B, Courtesy, Lorenzo Cerroni, MD.*

sensitive diagnostic test for all forms of pemphigus. However, on occasion, nonspecific cell surface staining may occur in other skin diseases, such as spongiotic dermatitis, burns, toxic epidermal necrolysis, systemic lupus erythematosus and lichen planus, or in patients with antibodies directed against blood groups A and B. If the direct IF is negative, the diagnosis of pemphigus should be seriously questioned. IgG deposition is seen in up to 100% of patients with active pemphigus vulgaris, pemphigus foliaceus and paraneoplastic pemphigus. IgM deposition is not found, but occasionally IgA deposition may also be seen. Complement (C3) deposition is not necessarily observed, probably because the dominant subclass of IgG is IgG4, which does not fix complement. In IgA pemphigus, IgA deposition (but not IgG deposition) is detected on keratinocyte cell surfaces.

Indirect IF examines patients' sera in order to demonstrate circulating IgG autoantibodies directed against epithelial cell surfaces (see Fig. 29.1). As a substrate for indirect IF staining, monkey esophagus is more sensitive for pemphigus vulgaris (anti-Dsg3 autoantibodies) and normal human skin or guinea pig esophagus is better for pemphigus foliaceus (anti-Dsg1 autoantibodies)[57]. Rat bladder is used to detect paraneoplastic pemphigus (antiplakin autoantibodies). Except for a few patients with early localized disease or those in remission, most patients with pemphigus have circulating anti-epithelial cell surface IgG as determined by indirect IF. Despite the different antigens involved in pemphigus vulgaris and foliaceus, the staining pattern using direct or indirect IF is similar, which makes it difficult to serologically distinguish the two diseases (compare Fig. 29.1B & C). Immunoprecipitation, immunoblotting and ELISA can be used to demonstrate the target molecules of these autoantibodies.

Immunoprecipitation and immunoblotting detect the target antigens as protein bands of a particular molecular weight that have been separated by electrophoresis (see Ch. 3). Immunoblotting requires denaturation of the protein substrates, but immunoprecipitation does not. Therefore, immunoprecipitation is superior to immunoblotting in detecting antibodies that react with epitopes dependent on three-dimensional structure (conformational epitopes), while immunoblots detect antibodies that react with epitopes that are preserved even after denaturation (linear epitopes). However, an immunoblot is easier to perform because immunoprecipitation requires radioisotopes to label protein substrates.

A recent innovation has been the introduction of an antigen-specific ELISA for the diagnosis of pemphigus[21,22]. The patient's serum is tested on ELISA plates pre-coated with recombinant Dsg1 or Dsg3 protein. Thus, specific antibodies directed against Dsg1 or Dsg3 can be detected. This assay has enabled investigators to serologically distinguish subtypes of pemphigus vulgaris and foliaceus. If a serum is positive against Dsg1 but negative against Dsg3, this suggests a diagnosis of pemphigus foliaceus. If negative against Dsg1 but positive against Dsg3, this suggests a diagnosis of the mucosal-dominant type of pemphigus vulgaris. If positive against both Dsg1 and Dsg3, this suggests a diagnosis of mucocutaneous type of pemphigus vulgaris (see Fig. 29.4). Furthermore, ELISA scores demonstrate parallel fluctuations with disease activity and are useful in monitoring disease activity, planning schedules for tapering corticosteroids, and predicting flares or relapses before there is clinical evidence.

Differential Diagnosis of Pemphigus Vulgaris

Establishing the diagnosis in patients with only oral lesions is more difficult than in those with cutaneous blisters and erosions. The differential diagnosis of mucosal lesions of pemphigus vulgaris includes acute herpetic stomatitis, aphthous stomatitis, erythema multiforme or Stevens–Johnson syndrome, lichen planus, systemic lupus erythematosus and mucous membrane (cicatricial) pemphigoid. For cutaneous lesions of pemphigus vulgaris, the differential diagnosis includes other forms of pemphigus, bullous pemphigoid, linear IgA bullous dermatosis, erythema multiforme, Hailey–Hailey disease and transient acantholytic dermatosis (Grover's disease). The differential diagnosis of pemphigus vegetans includes Hailey–Hailey disease, blastomycosis-like pyoderma, pemphigoid vegetans and pyodermatitis–pyostomatitis vegetans.

The demonstration of IgG autoantibodies against keratinocyte cell surfaces and anti-Dsg3 IgG, as mentioned above, will exclude these diseases (with the exception of drug-induced pemphigus vulgaris and paraneoplastic pemphigus). Fresh blisters of bullous pemphigoid are tense due to a subepidermal split. Hailey–Hailey disease has full-thickness acantholysis ("dilapidated brick wall") with epidermal hyperplasia and an impetiginized scale, and the acantholysis does not extend down follicles as it does in pemphigus. Transient acantholytic dermatosis exhibits only small foci of intraepidermal acantholysis.

Differential Diagnosis of Pemphigus Foliaceus

This differential includes other forms of pemphigus, bullous impetigo, subcorneal pustular dermatosis, subacute cutaneous lupus erythematosus, and seborrheic dermatitis. As discussed earlier for pemphigus vulgaris, the demonstration of IgG autoantibodies against epidermal cell surfaces is essential for separating these disorders from the pemphigus family. A complete review of medications should be done to exclude the possibility of drug-induced pemphigus foliaceus. Because the lesions of pemphigus foliaceus may become secondarily infected, the finding of bacteria does not confirm a diagnosis of bullous impetigo. Likewise, a clinical flare or recalcitrant disease may represent a superimposed disorder, e.g. tinea corporis, especially in patients on systemic corticosteroids.

Differential Diagnosis of Paraneoplastic Pemphigus

This differential includes pemphigus vulgaris, mucous membrane (cicatricial) pemphigoid, erythema multiforme or Stevens–Johnson syndrome, lichen planus, GVHD, persistent HSV infection, and other viral infections; stomatitis due to chemotherapy will be limited in duration (7–14 days). In two-thirds of patients with paraneoplastic pemphigus, it arises in the context of a known underlying neoplasm, usually a lymphoproliferative disorder, which may have been treated for years before the mucocutaneous lesions appear. In approximately one-third of patients, the underlying neoplasm is undiagnosed at the time the mucocutaneous disease develops. In these latter patients, examination for an occult neoplasm is required, and, given the most commonly associated ones (see earlier), a CT scan of the chest, abdomen and pelvis should accompany a complete blood count, flow cytometry, LDH, and serum protein and immunofixation electrophoreses. Severe intractable stomatitis that extends onto the vermilion lip is a key clinical feature in differentiating paraneoplastic pemphigus from most cases of pemphigus vulgaris or cicatricial pemphigoid. The gold standard for the diagnosis of paraneoplastic pemphigus is the demonstration of the characteristic combination of IgG autoantibodies (anti-plakin autoantibodies by immunoprecipitation or immunoblotting and anti-desmoglein autoantibodies by ELISA).

Differential Diagnosis of IgA Pemphigus

The differential diagnosis includes subcorneal pustular dermatosis, pemphigus foliaceus, bullous impetigo, dermatitis herpetiformis, linear IgA bullous dermatosis, and pustular psoriasis. The clinical and histologic features of the SPD type of IgA pemphigus and classic subcorneal pustular dermatosis are indistinguishable. The demonstration of IgA autoantibodies is essential for separating these other disorders from IgA pemphigus.

TREATMENT

Pemphigus Vulgaris

Before the advent of systemic corticosteroids, pemphigus vulgaris was usually a fatal disease; most patients died within 2–5 years of the onset of the disease because large areas of the skin lost their epidermal barrier function, leading to the loss of body fluids or to secondary bacterial infections. Pemphigus foliaceus had a better prognosis, except for the occasional acute cases with generalized involvement. Because pemphigus is caused by pathogenic autoantibodies, therapy must be designed to reduce autoantibody production, not just to suppress local inflammation. The introduction of systemic corticosteroids and immunosuppressive agents has greatly improved the prognosis of pemphigus; however, the morbidity, and occasional mortality, is still significant due to complications of therapy. Systemic corticosteroids are the mainstay of therapy for pemphigus. Immunosuppressive agents are often used for their corticosteroid-sparing effect in order to reduce the side effects of the corticosteroids (Table 29.5), with the goal of therapy being to control the disease with the lowest possible dose of corticosteroids. High-dose IVIg and rituximab represent promising new treatment options. More recently, PDAI (pemphigus disease area index) and ABSIS (autoimmune bullous skin disorder intensity score) have been introduced as a means of standardizing the assessment of disease extent in patients with pemphigus[58].

Systemic corticosteroid therapy, usually in the form of oral prednisone, is standard treatment (see Ch. 125). Prednisone at 1.0 mg/kg/day (usually 60 mg/day) is a typical initial dosage. The therapeutic effects are clinically estimated by the number of new blisters per day and the rate of healing of new lesions, and the prednisone is then gradually tapered. Once clinical remission is obtained, changes in the titer of circulating autoantibodies, as determined by indirect IF or ELISA, are helpful in gauging the dose of prednisone[22]. If there is no response in 3–7 days, other options may be employed, as discussed below. Intravenous pulse therapy with 1 g/day methylprednisolone (over a period of 2–3 hours, with continuous cardiac monitoring) for 3–5 consecutive days is an alternative choice for severe cases.

In general, immunosuppressive agents, such as *azathioprine*, *mycophenolate mofetil* and *cyclophosphamide*, when combined with corticosteroids, may result in gaining early control of the disease and an increased percentage of clinical remissions[59–63a]. For example, in patients with mild to moderate disease who received corticosteroids plus either placebo or mycophenolate mofetil in a prospective, randomized trial, the latter group showed faster and more durable responses[63b]. Azathioprine is used at a dose of 2–4 mg/kg/day (usually 100–300 mg/day) and its major side effects are nausea and dose-dependent myelosuppression (see Ch. 130). Mycophenolate mofetil is used at a dose of 2–3 g/day and it has a similar action to azathioprine, with less myelosuppression but more gastrointestinal toxicity[62]. Cyclophosphamide is given at a dose of 1–3 mg/kg/day (usually 50–200 mg/day) and its major side effects are hemorrhagic cystitis, sterility and leukopenia. If complete remission is achieved with the combined therapy, the dosage of the immunosuppressive drug is maintained while the prednisone is slowly tapered; when a dose of 5–10 mg/day is reached, careful tapering of the immunosuppressive drug is attempted. In young patients, the potential increase in malignancies that might be associated with the use of these drugs must be taken into account. In some patients, especially those who are elderly with limited disease or those in whom corticosteroids are contraindicated, immunosuppressive agents alone may be used.

While in some patients with pemphigus vulgaris, *cyclosporine* (5 mg/kg/day) has been used as an immunosuppressive agent, gold therapy is rarely utilized nowadays. One factor has been its replacement by newer agents, especially bioengineered immunomodulators, for the treatment of rheumatoid arthritis (historically, gold's major indication). *Plasmapheresis* is useful for quickly reducing the titers of circulating autoantibodies and should be considered for severe pemphigus if the disease is unresponsive to a combination of prednisone and immunosuppressives[63]. Concomitant immunosuppression with corticosteroids and cyclophosphamide prevents a post-plasmapheresis rebound increase in the production of autoantibody.

High-dose IVIg is another option for resistant disease. IVIg is a blood product prepared from pooled plasma that has immunomodulatory effects when used in a high dose. It is thought to exert its effect via multiple modes of action, including modulation of expression and function of Fc receptors and the cytokine network; provision of anti-idiotypic antibodies; and modulation of dendritic cell, T-cell and B-cell activation, differentiation and effector functions[64]. A multicenter, randomized, placebo-controlled, double-blind trial demonstrated that high-dose IVIg is an effective and safe treatment for steroid-resistant pemphigus[65].

Rituximab is a potent B-cell-depleting chimeric anti-CD20 monoclonal antibody that was first used to treat B-cell malignancies, but increasingly is used for a variety of autoimmune diseases, including pemphigus. CD20 is a transmembrane glycoprotein specifically expressed on B cells (from the pre-B stage in the bone marrow to the activated and memory B stage in blood or secondary lymphoid organs), but its expression is lost upon plasma cell differentiation[66]. Rituximab seems not only to induce a depletion of $CD20^+$ B cells and a decline in IgG (including anti-desmoglein autoantibodies), but also decreases desmoglein-specific T cells[67]. When used as adjuvant therapy in nonrandomized prospective studies, rituximab led to a complete remission in most of the patients with refractory pemphigus vulgaris and foliaceus[68,69]. The side effects of rituximab, including progressive multifocal leukoencephalopathy, are discussed in Chapter 130.

In the future, desmoglein-specific immune suppression, via targeting T cells or B cells, needs to be developed. It would represent an ideal therapeutic strategy given that the target antigens and pathophysiological mechanisms of pemphigus have been well characterized.

THERAPEUTIC LADDER FOR PEMPHIGUS VULGARIS	
STANDARD TREATMENT	
Oral prednisone	1.0 mg/kg/day as an initial dose (usually 60 mg/day) (1)
AGGRESSIVE TREATMENT	
Immunosuppressive agents in combination with oral prednisone:	
Azathioprine	2–4 mg/kg/day (usually 100 to 300 mg/day) (1)
Mycophenolate mofetil	2–3 g/day (2)
Cyclophosphamide	1–3 mg/kg/day (usually 50 to 200 mg/day) (2)
Cyclosporine	5 mg/kg/day (2)
Pulse methylprednisolone	1 g/day over a period of 2–3 hours for 3–5 consecutive days (2)
Methotrexate	7.5–20 mg/week (3)
Pulse cyclophosphamide	50 mg/kg/day × 4 days (3)
Plasmapheresis	1–2 times per week, at the onset (2)
High-dose IVIg	400 mg/kg/day for 5 consecutive days (1); may need to be repeated
Rituximab	375 mg/m^2 once weekly for 4 weeks (2)
Extracorporeal photopheresis	2 days per month (3)
TOPICAL TREATMENT	
Topical corticosteroids (1), especially Class I to localized persistent sites Topical antibiotics (2) Topical immunomodulators (e.g. cyclosporine, tacrolimus) (3)	

Table 29.5 Therapeutic ladder for pemphigus vulgaris. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

Pemphigus Foliaceus

When pemphigus foliaceus is active and widespread, the treatment is, in general, similar to that for pemphigus vulgaris. In some patients, pemphigus foliaceus may be localized for many years; they do not necessarily have to be treated with systemic therapy, and superpotent

topical corticosteroids may be sufficient to control the disease. Dapsone can also be used when neutrophils are dominant histologically.

Paraneoplastic Pemphigus

Patients with benign tumors, such as thymomas or localized Castleman's disease, should have the tumor surgically excised. The majority of these patients will either improve substantially or clear completely. However, it may take 6–18 months to see complete resolution of lesions after excision of a benign neoplasm. In patients with malignant neoplasms, there is no consensus on a standard effective therapeutic regimen. Administration of tumor-specific chemotherapy may result in complete resolution of the malignancy and a slow resolution of the skin lesions. Cutaneous lesions respond more rapidly to therapy, in contrast to the stomatitis, which is generally refractory to most forms of treatment. Overall, the prognosis of paraneoplastic pemphigus is poor due to its resistant nature to treatment.

IgA Pemphigus

Dapsone is the drug of choice for most patients with IgA pemphigus. A clinical response usually occurs within 24–48 hours. If dapsone is not well tolerated, sulfapyridine and acitretin are useful alternatives. Occasionally, those drugs are not effective, and low- to medium-dose prednisone may be considered, as well as photochemotherapy (PUVA) or colchicine.

REFERENCES

1. Stanley JR. Pemphigus. In: Freedberg IM, Eisen AZ, Wolff K, et al. (eds). Dermatology in General Medicine. New York: McGraw-Hill, 1998:654–66.
2. Anhalt GJ, Kim S, Stanley JR, et al. Paraneoplastic pemphigus. An autoimmune mucocutaneous disease associated with neoplasia. N Engl J Med. 1990;323:1729–35.
3. Beutner EH, Jordon RE. Demonstration of skin antibodies in sera of pemphigus vulgaris patients by indirect immunofluorescent staining. Proc Soc Exp Biol Med. 1964;117:505–10.
4. Anhalt GJ, Labib RS, Voorhees JJ, et al. Induction of pemphigus in neonatal mice by passive transfer of IgG from patients with the disease. N Engl J Med. 1982;306:1189–96.
5. Stanley JR, Yaar M, Hawley NP, et al. Pemphigus antibodies identify a cell surface glycoprotein synthesized by human and mouse keratinocytes. J Clin Invest. 1982;70:281–8.
6. Amagai M, Klaus-Kovtun V, Stanley JR. Autoantibodies against a novel epithelial cadherin in pemphigus vulgaris, a disease of cell adhesion. Cell. 1991;67:869–77.
7. Diaz LA, Sampaio S, Rivitti EA, et al. Endemic pemphigus foliaceus (fogo selvagem): II. Current and historical epidemiological aspects. J Invest Dermatol. 1989;92:4–12.
8. Warren SJ, Lin MS, Giudice GJ, et al. The prevalence of antibodies against desmoglein 1 in endemic pemphigus foliaceus in Brazil. N Engl J Med. 2000;343:23–30.
9. Li N, Aoki V, Hans-Filho G, et al. The role of intramolecular epitope spreading in the pathogenesis of endemic pemphigus foliaceus (fogo selvagem). J Exp Med. 2003;197:1501–10.
10. Rock B, Labib RS, Diaz LA. Monovalent Fab' immunoglobulin fragments from endemic pemphigus foliaceus autoantibodies reproduce the human disease in neonatal Balb/c mice. J Clin Invest. 1990;85:296–9.
11. Hashimoto K, Shafran KM, Webber PS, et al. Anti-cell surface pemphigus autoantibody stimulates plasminogen activator activity of human epidermal cells. J Exp Med. 1983;157:259–72.
12. Mahoney MG, Wang ZH, Stanley JR. Pemphigus vulgaris and pemphigus foliaceus antibodies are pathogenic in plasminogen activator knockout mice. J Invest Dermatol. 1999;113:22–5.
13. Karpati S, Amagai M, Prussick R, et al. Pemphigus vulgaris antigen, a desmoglein type of cadherin, is located within keratinocyte desmosomes. J Cell Biol. 1993;122:409–15.
14. Hashimoto T, Ogawa MM, Konohana A, et al. Detection of pemphigus vulgaris and pemphigus foliaceus antigens by immunoblot analysis using different antigen sources. J Invest Dermatol. 1990;94:327–31.
15. Korman NJ, Eyre RW, Klaus-Kovtun V, et al. Demonstration of an adhering-junction molecule (plakoglobin) in the autoantigens of pemphigus foliaceus and pemphigus vulgaris. N Engl J Med. 1989;321:631–5.
16. Koch PJ, Walsh MJ, Schmelz M, et al. Identification of desmoglein, a constitutive desmosomal glycoprotein, as a member of the cadherin family of cell adhesion molecules. Eur J Cell Biol. 1990;53:1–12.
17. Takeichi M. Cadherin cell adhesion receptors as a morphogenetic regulator. Science. 1991;251: 1451–5.
18. Shapiro L, Fannon AM, Kwong PD, et al. Structural basis of cell-cell adhesion by cadherins. Nature. 1995;374:327–37.
19. Green KJ, Gaudry CA. Are desmosomes more than tethers for intermediate filaments? Nat Rev Mol Cell Biol. 2000;1:208–16.
20. Kljuic A, Bazzi H, Sundberg JP, et al. Desmoglein 4 in hair follicle differentiation and epidermal adhesion: evidence from inherited hypotrichosis and acquired pemphigus vulgaris. Cell. 2003;113:249–60.
21. Ishii K, Amagai M, Hall RP, et al. Characterization of autoantibodies in pemphigus using antigen-specific enzyme-linked immunosorbent assays with baculovirus-expressed recombinant desmogleins. J Immunol. 1997;159:2010–17.
22. Amagai M, Komai A, Hashimoto T, et al. Usefulness of enzyme-linked immunosorbent assay (ELISA) using recombinant desmogleins 1 and 3 for serodiagnosis of pemphigus. Br J Dermatol. 1999;140:351–7.
23. Amagai M, Hashimoto T, Shimizu N, et al. Absorption of pathogenic autoantibodies by the extracellular domain of pemphigus vulgaris antigen (Dsg3) produced by baculovirus. J Clin Invest. 1994;94:59–67.
24. Amagai M, Nishikawa T, Nousari HC, et al. Antibodies against desmoglein 3 (pemphigus vulgaris antigen) are present in sera from patients with paraneoplastic pemphigus and cause acantholysis in vivo in neonatal mice. J Clin Invest. 1998;102:775–82.
25. Amagai M, Karpati S, Prussick R, et al. Autoantibodies against the amino-terminal cadherin-like binding domain of pemphigus vulgaris antigen are pathogenic. J Clin Invest. 1992;90:919–26.
26. Nagasaka T, Nishifuji K, Ota T, et al. Defining the pathogenic involvement of desmoglein 4 in pemphigus and staphylococcal scalded skin syndrome. J Clin Invest. 2004;114:1484–92.
27. Mahoney MG, Wang Z, Rothenberger KL, et al. Explanation for the clinical and microscopic localization of lesions in pemphigus foliaceus and vulgaris. J Clin Invest. 1999;103:461–8.
28. Stanley JR, Amagai M. Pemphigus, bullous impetigo, and the staphylococcal scalded-skin syndrome. N Engl J Med. 2006;355:1800–10.
29. Amagai M, Tsunoda K, Zillikens D, et al. The clinical phenotype of pemphigus is defined by the anti-desmoglein autoantibody profile. J Am Acad Dermatol. 1999;40:167–70.
30. Shirakata Y, Amagai M, Hanakawa Y, et al. Lack of mucosal involvement in pemphigus foliaceus may be due to low expression of desmoglein 1. J Invest Dermatol. 1998;110:76–8.
31. Wu H, Wang ZH, Yan A, et al. Protection against pemphigus foliaceus by desmoglein 3 in neonates. N Engl J Med. 2000;343:31–5.
32. Amagai M, Matsuyoshi N, Wang ZH, et al. Toxin in bullous impetigo and staphylococcal scalded skin syndrome targets desmoglein 1. Nat Med. 2000;6:1275–7.
33. Sekiguchi M, Futei Y, Fujii Y, et al. Dominant autoimmune epitopes recognized by pemphigus antibodies map to the N-terminal adhesive region of desmogleins. J Immunol. 2001;167:5439–48.
34. Payne AS, Ishii K, Kacir S, et al. Genetic and functional characterization of human pemphigus vulgaris monoclonal autoantibodies isolated by phage display. J Clin Invest. 2005;115:888–99.
35. Tsunoda K, Ota T, Aoki M, et al. Induction of pemphigus phenotype by a mouse monoclonal antibody against the amino-terminal adhesive interface of desmoglein 3. J Immunol. 2003;170:2170–8.
36. Koch PJ, Mahoney MG, Ishikawa H, et al. Targeted disruption of the pemphigus vulgaris antigen (desmoglein 3) gene in mice causes loss of keratinocyte cell adhesion with a phenotype similar to pemphigus vulgaris. J Cell Biol. 1997;137:1091–102.
37. Kitajima Y. Adhesion molecules in the pathophysiology of bullous diseases. Eur J Dermatol. 1996;6:399–405.
38. Aoyama Y, Owada MK, Kitajima Y. A pathogenic autoantibody, pemphigus vulgaris-IgG, induces phosphorylation of desmoglein 3, and its dissociation from plakoglobin in cultured keratinocytes. Eur J Immunol. 1999;29:2233–40.
39. Calkins CC, Setzer SV, Jennings JM, et al. Desmoglein endocytosis and desmosome disassembly are coordinated responses to pemphigus autoantibodies. J Biol Chem. 2006;281:7623–34.
40. Delva E, Jennings JM, Calkins CC, et al. Pemphigus vulgaris IgG-induced desmoglein-3 endocytosis and desmosomal disassembly are mediated by a clathrin- and dynamin-independent mechanism. J Biol Chem. 2008;283:18303–13.

40a. Schepens I, Jaunin F, Begre N, et al. The protease inhibitor alpha-2-macroglobulin-like-1 is the p170 antigen recognized by paraneoplastic pemphigus autoantibodies in humans. PLoS One. 2010;18;5(8): e12250.

41. Ahmed AR, Yunis EJ, Khatri K, et al. Major histocompatibility complex haplotype studies in Ashkenazi Jewish patients with pemphigus vulgaris. Proc Natl Acad Sci USA. 1990;87:7658–62.
42. Niizeki H, Inoko H, Mizuki N, et al. HLA-DQA1, -DQB1 and -DRB1 genotyping in Japanese pemphigus vulgaris patients by the PCR-RFLP method. Tissue Antigens. 1994;44:248–51.
43. Wucherpfennig KW, Yu B, Bhol K, et al. Structural basis for major histocompatibility complex (MHC)-linked susceptibility to autoimmunity: charged residues of a single MHC binding pocket confer selective presentation of self-peptides in pemphigus vulgaris. Proc Natl Acad Sci USA. 1995;92:11935–9.
44. Lin MS, Swartz SJ, Lopez A, et al. Development and characterization of desmoglein-3 specific T cells from patients with pemphigus vulgaris. J Clin Invest. 1997;99:31–40.
45. Veldman CM, Gebhard KL, Uter W, et al. T cell recognition of desmoglein 3 peptides in patients with pemphigus vulgaris and healthy individuals. J Immunol. 2004;172:3883–92.
46. Amagai M, Tsunoda K, Suzuki H, et al. Use of autoantigen-knockout mice in developing an active autoimmune disease model of pemphigus. J Clin Invest. 2000;105:625–31.
47. Takahashi H, Amagai M, Nishikawa T, et al. Novel system evaluating in vivo pathogenicity of desmoglein 3-reactive T cell clones using murine pemphigus vulgaris. J Immunol. 2008;181:1526–35.
48. Takahashi H, Kuwana M, Amagai M. A single helper T cell clone is sufficient to commit polyclonal naive B cells to produce pathogenic IgG in experimental pemphigus vulgaris. J Immunol. 2009;182:1740–5.
49. Senear FE, Usher B. An unusual type of pemphigus combining features of lupus erythematosus. Arch Dermatol Syphilol. 1926;13:761–81.
50. Jablonska S, Chorzelski TP, Beutner EH, et al. Herpetiform pemphigus, a variable pattern of pemphigus. Int J Dermatol. 1975;14:353–9.
51. Ishii K, Amagai M, Komai A, et al. Desmoglein 1 and desmoglein 3 are the target autoantigens in herpetiform pemphigus. Arch Dermatol. 1999;135:943–7.

52. Lebeau S, Muller R, Masouye I, et al. Pemphigus herpetiformis: analysis of the autoantibody profile during the disease course with changes in the clinical profile. Clin Exp Dermatol. 2010;35:366–72.
53. Brenner S, Bialy-Golan A, Ruocco V. Drug-induced pemphigus. Clin Dermatol. 1998;16:393–7.
54. Nousari HC, Deterding R, Wojtczack H, et al. The mechanism of respiratory failure in paraneoplastic pemphigus. N Engl J Med. 1999;340:1406–10.
55. Nishikawa T, Hashimoto T. Dermatoses with intraepidermal IgA deposits. Clin Dermatol. 2000;18: 315–18.
56. Hashimoto T, Kiyokawa C, Mori O, et al. Human desmocollin 1 (Dsc 1) is an autoantigen for the subcorneal pustular dermatosis type of IgA pemphigus. J Invest Dermatol. 1997;109:127–31.
57. Sabolinski ML, Beutner EH, Krasny S, et al. Substrate specificity of anti-epithelial antibodies of pemphigus vulgaris and pemphigus foliaceus sera in immunofluorescence tests on monkey and guinea pig esophagus sections. J Invest Dermatol. 1987;88:545–9.
58. Rosenbach M, Murrell DF, Bystryn JC, et al. Reliability and convergent validity of two outcome instruments for pemphigus. J Invest Dermatol. 2009;129:2404–10.
59. Aberer W, Wolff SE, Stingl G, Wolff K. Azathioprine in the treatment of pemphigus vulgaris. A long-term follow-up. J Am Acad Dermatol. 1987;16:527–33.
60. Fellner MJ, Katz JM, McCabe JB. Successful use of cyclophosphamide and prednisone for initial treatment of pemphigus vulgaris. Arch Dermatol. 1978;114: 889–94.
61. Fine JD. Management of acquired bullous skin diseases. N Engl J Med. 1995;333:1475–84.
62. Beissert S, Werfel T, Frieling U, et al. A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of pemphigus. Arch Dermatol. 2006;142:1447–54.
63. Bystryn JC, Steinman NM. The adjuvant therapy of pemphigus. An update. Arch Dermatol. 1996;132:203–12.
63a. Strowd LC, Taylor SL, Jorizzo JL, Namazi MR. Therapeutic ladder for pemphigus vulgaris: emphasis on achieving complete remission. J Am Acad Dermatol 2011;64:490–4.
63b. Beissert S, Mimouni D, Kanwar AJ, et al. Treating pemphigus vulgaris with prednisone and mycophenolate mofetil: A multicenter, randomized, placebo-controlled trial. J Invest Dermatol. 2010;130: 2041–8.
64. Kazatchkine MD, Kaveri SV. Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. N Engl J Med. 2001;345:747–55.
65. Amagai M, Ikeda S, Shimizu H, et al. A randomized double-blind trial of intravenous immunoglobulin for pemphigus. J Am Acad Dermatol. 2009;60:595–603.
66. Edwards JC, Cambridge G. B-cell targeting in rheumatoid arthritis and other autoimmune diseases. Nat Rev Immunol. 2006;6:394–403.
67. Eming R, Nagel A, Wolff-Franke S, et al. Rituximab exerts a dual effect in pemphigus vulgaris. J Invest Dermatol. 2008;128:2850–8.
68. Ahmed AR, Spigelman Z, Cavacini LA, et al. Treatment of pemphigus vulgaris with rituximab and intravenous immune globulin. N Engl J Med. 2006;355:1772–9.
69. Joly P, Mouquet H, Roujeau JC, et al. A single cycle of rituximab for the treatment of severe pemphigus. N Engl J Med. 2007;357:545–52.

Pemphigoid Group 30

Philippe Bernard and Luca Borradori

Chapter Contents

Bullous pemphigoid 475
Mucous membrane (cicatricial) pemphigoid 482
Epidermolysis bullosa acquisita 487

BULLOUS PEMPHIGOID

Synonym: ■ Pemphigoid

Key features

- Bullous pemphigoid (BP) is the most common autoimmune subepidermal blistering disease; it predominantly affects the elderly
- It is usually a chronic disease, with spontaneous exacerbations and remissions, which may be accompanied by significant morbidity
- BP is associated with tissue-bound and circulating autoantibodies directed against BP antigen 180 (BP180, BPAG2 or type XVII collagen) and BP antigen 230 (BP230 or BPAG1e), components of junctional adhesion complexes called hemidesmosomes that promote dermal–epidermal cohesion
- The spectrum of clinical presentations is extremely broad. Characteristically, BP is an intensely pruritic eruption with widespread blister formation. In early stages, or in atypical variants of the disease, only excoriated, eczematous or urticarial lesions (either localized or generalized) are present
- Diagnosis relies on immunopathologic examinations, particularly direct and indirect immunofluorescence microscopy as well as anti-BP180/BP230 ELISAs

Introduction

Bullous pemphigoid (BP) is the most common autoimmune subepidermal blistering disease of the skin. The disease typically presents in the elderly with a generalized pruritic bullous eruption, and it is potentially associated with significant morbidity. The clinical presentation can be quite polymorphic, particularly during the early stages of the disease or in atypical variants, in which full-blown bullous lesions may be absent. In these cases, establishing the diagnosis of BP requires a high degree of suspicion. BP has emerged as a paradigm of organ-specific autoimmune disease. The antigens targeted by patients' autoantibodies represent two components of hemidesmosomes – the junctional adhesion complexes found in skin and mucosae.

History

During the eighteenth century, the term "pemphigus" was often used to describe any type of bullous eruption. It was not until 1953 that Lever, on the basis of specific clinical and histologic features, recognized BP as a disorder distinct from the various types of "true" pemphigus[1].

A decade later, Jordon, Beutner and colleagues[2] demonstrated that BP patients had tissue-bound and circulating autoantibodies directed against the cutaneous basement membrane zone (BMZ), an observation that suggested that subepidermal dysadhesion was due to autoantibodies directed against structural components of the skin that promoted dermal–epidermal adhesion[2]. Further milestones in our understanding of BP included the immunochemical characterization of targeted proteins, the cloning of their genes, and the development of animal models of the disease[3–5].

Epidemiology

BP is typically a disease of the elderly, with an onset after 60 years of age. The annual incidence has been estimated to be at least 6–13 new cases per million population (with a rapid increase after the age of 60 years); however, these figures require further refinement (e.g. utilizing age-matched individuals as the denominator).[6] The relative risk for patients over 90 years of age appears to be about 300-fold higher than for those 60 years of age or younger, with an apparent higher predominance in men than in women[6]. The disease also occurs in children, but rarely. Certain HLA class II alleles are more prevalent in patients with BP than in the general population[7]. In Caucasians, a significant association with the allele DQB1*0301 has been found, while an increased frequency of the alleles DRB1*04, DRB1*1101 and DQB1*0302 has been observed in Japanese patients.

Pathogenesis

BP is an example of an immune-mediated disease that is associated with a humoral and cellular response directed against two well-characterized self-antigens: BP antigen 180 (BP180, BPAG2 or type XVII collagen) and BP antigen 230 (BP230 or BPAG1e) (Table 30.1)[3,4]. While the former is a transmembrane protein with a large collagenous extracellular domain, the latter is a cytoplasmic protein belonging to the plakin family (see Ch. 28). These two antigens are components of the hemidesmosomes, which are adhesion complexes promoting epithelial–stromal adhesion in stratified and other complex epithelia.

In vitro studies and *in vivo* animal models have provided strong evidence for the pathogenic role of autoantibodies in BP[5]. Furthermore, in gestational pemphigoid, a disease closely related to BP, the transplacental transfer of autoantibodies to BP180 from the mother into the neonate can result in a transient bullous eruption (see Ch. 34). Finally, the autoimmune etiology of BP is indirectly supported by its association with distinct class II major histocompatibility complex (MHC) haplotypes and its response to immunosuppressive therapy.

Humoral and cellular responses

Almost all patients with BP have circulating IgG autoantibodies that bind to BP180. More specifically, it is the non-collagenous NC16A domain, a region of BP180 located extracellularly but close to the transmembrane domain, that constitutes the immunodominant region (see Fig. 31.9). However, additional antigenic sites exist within both the extracellular and intracellular domains of BP180, and they are recognized by up to 70% of BP sera[3,8–12]. Patients with BP also exhibit significant autoreactivity to intracellular BP230[4,11,12]. BP230-reactive autoantibodies bind predominantly, but not exclusively, to the C-terminal region of this autoantigen. The presence of several antigenic sites throughout BP180 and BP230 most likely results from the phenomenon known as "epitope spreading" (see below). This phenomenon may also account for the finding that patients' sera rarely contain autoantibodies targeting additional components of the BMZ.

Patients with BP develop an autoreactive T-cell response to BP180 and BP230, and this is probably crucial for stimulating B cells to produce autoantibodies[13]. The responsiveness of anti-BP180

MAJOR AUTOANTIGENS OF SUBEPIDERMAL AUTOIMMUNE-MEDIATED BLISTERING DISEASES			
Disease	**Target antigen(s)**	**Mol. wt. (kDa)**	**Morphologic structures**
Bullous pemphigoid (BP)	BP180/BPAG2/collagen XVII	180	Hemidesmosomal plaque/anchoring filaments
	BP230/BPAG1e	230	Hemidesmosomal plaque
Gestational pemphigoid	BP180/BPAG2/collagen XVII	180	Hemidesmosomal plaque/anchoring filaments
	BP230/BPAG1e	230	Hemidesmosomal plaque
Mucous membrane (cicatricial) pemphigoid	BP180/BPAG2/collagen XVII	180	Hemidesmosomal plaque/anchoring filaments
	BP230/BPAG1e†	230	Hemidesmosomal plaque
	Laminin 5 (332; $\alpha_3\beta_3\gamma_2$; epiligrin)	165, 140, 105	Anchoring filaments
	Laminin 6 (311; $\alpha_3\beta_1\gamma_1$)‡	165, 220, 200	Anchoring filaments/extracellular matrix
	Integrin β_4 subunit§	200	Hemidesmosomal plaque/anchoring filaments
Linear IgA bullous dermatosis (LABD)	LAD antigen¶	97/120	Anchoring filaments
	BP180/BPAG2/collagen XVII	180	Hemidesmosomal plaque/anchoring filaments
	BP230/BPAG1e†	230	Hemidesmosomal plaque
	Type VII collagen†	290/145	Anchoring fibrils
Epidermolysis bullosa acquisita	Type VII collagen†	290/145	Anchoring fibrils
Anti-p200 pemphigoid	Laminin gamma-1 chain	200 kDa	Extracellular matrix
Bullous systemic lupus erythematosus	Type VII collagen†	290/145	Anchoring fibrils

†Detectable in a subset of patients
‡Binding to laminin 6 (331) depends on the presence of cross-reactive autoantibodies directed against the α-chain of laminin 5 (332).
§Reactivity with the cytoplasmic domain of the β4 subunit of the $\alpha6\beta4$ integrin described in a subset of patients with ocular cicatricial pemphigoid.
¶It constitutes the most characteristic serologic marker for LABD. The 120 kDa LAD antigen corresponds to the cleaved, shed extracellular domain of BP180/BPAG2. The 97 kDa protein results from its further proteolytic degradation.

Table 30.1 Major autoantigens of subepidermal autoimmune-mediated blistering diseases. Not an exhaustive list. In the course of these diseases, it is possible to detect autoantibodies directed against additional antigens, the significance of which remains to be established. In certain cases, a so-called "intermolecular epitope spreading" phenomenon is thought to occur.

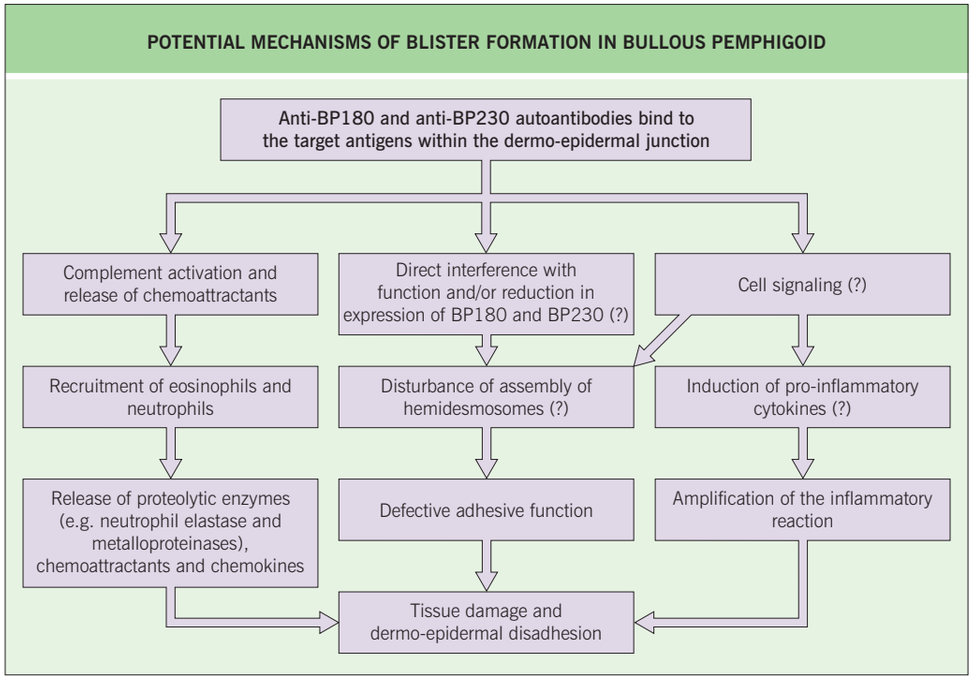


Fig. 30.1 Potential mechanisms of blister formation in bullous pemphigoid. IgG autoantibodies are classically involved in the pathogenesis, but more recently IgE autoantibodies have also been described. (?), possible explanation.

autoreactive T cells is restricted by certain HLA class II alleles (e.g. HLA-DQB1*0301), which are prevalent in BP patients. These T lymphocytes, whose major relevant epitopes seem to be harbored within the NC16 domain, have a $CD4^+$ phenotype and produce both Th1 (e.g. interferon-γ) and Th2 cytokines (e.g. interleukin [IL]-4, IL-5 and IL-13; see Ch. 4)[13]. Th2 cytokines may be particularly relevant to the pathophysiology of BP; they predominate within lesional tissue and in patients' sera. Also, the IgG4 subclass, the secretion of which is regulated by Th2 cytokines, is one of the major isotypes of the anti-BP180 autoantibodies.

Upon binding of autoantibodies to their target antigens, subepidermal blister formation results from a cascade of events that involves complement activation, recruitment of inflammatory cells (mainly neutrophils and eosinophils), and liberation of various chemokines and proteases, such as matrix metalloproteinase-9 and neutrophil elastase[14,15]. These proteinases proteolytically degrade various extracellular matrix proteins as well as BP180. Infiltrating mast cells and eosinophils (that can be activated by specific IgE anti-BP180 autoantibodies) are also significantly implicated in producing tissue damage via the release of proteases and proinflammatory mediators, such as IL-5

Fig. 30.2 Bullous pemphigoid – bullous presentation. Classic presentation with multiple tense bullae arising on normal and erythematous skin. Several of the bullae have ruptured, leaving circular erosions.

Fig. 30.3 Bullous pemphigoid – urticarial (and bullous) presentation. A Pink urticarial papules and plaques as well as tense bullae containing serous fluid. **B** Firm annular urticarial plaques.

Fig. 30.4 Bullous pemphigoid – eczematous presentation. A,B Large pink eczematous plaques on the trunk and upper extremities.

and eotaxin.[15] Autoantibodies to BP180 can probably also amplify the inflammatory response by directly stimulating keratinocytes to express various cytokines (e.g. IL-6 and IL-8) (Fig. 30.1)[16]. Finally, IgG autoantibodies reduce hemidesmosomal BP180 content and by this means may contribute to weakening of dermal–epidermal cohesion[17].

Various animal models have provided strong evidence that autoantibodies against BP180 are pathogenic. When passively transferred to neonatal mice (in which BP180 had been fully or partially humanized by genetic engineering), human autoantibodies against the NC16A domain (the immunodominant determinant of human BP180) were able to induce a blistering disorder that reproduced all the key features of BP[5,18]. In contrast, autoantibodies against BP230 caused an inflammatory reaction in rabbits only after additional injury to their epidermis; however, recent findings suggest that anti-BP230 antibodies are able to induce an inflammatory reaction and subepidermal blistering in a murine model[19]. Together, these studies have led to the speculation that antibodies against the ectodomain of BP180 are pathophysiologically critical, whereas the development of antibodies against BP230 represents a secondary event that contributes to tissue damage.

Clinical Features

Non-bullous phase

The cutaneous manifestations of BP can be extremely polymorphic (Figs 30.2–30.6)[1,20]. In the prodromal, non-bullous phase of the disease, signs and symptoms are frequently nonspecific, with mild to severe intractable pruritus alone or in association with excoriated, eczematous, papular and/or urticarial lesions that may persist for several weeks or months. These nonspecific skin findings may remain as the only signs of the disease.

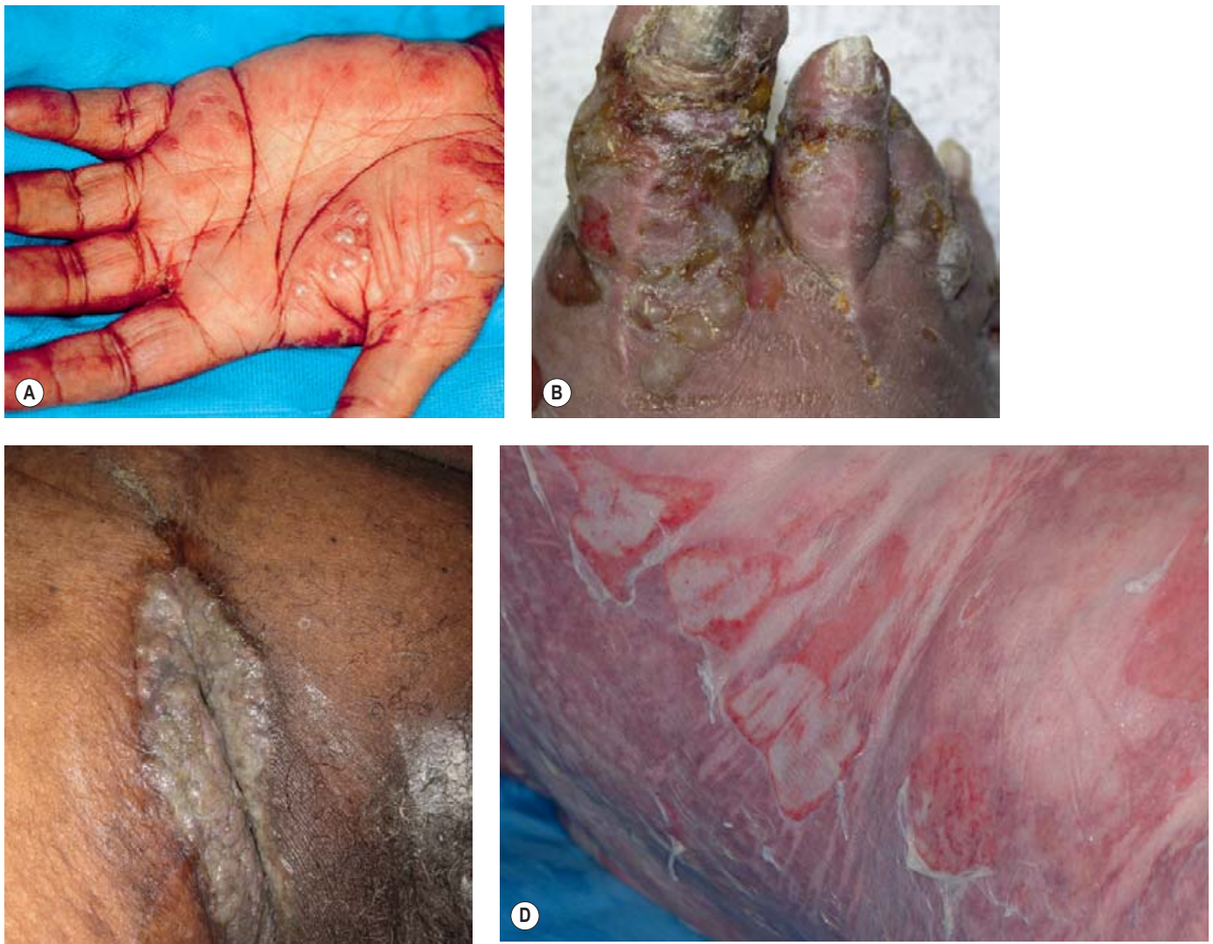


Fig. 30.5 Bullous pemphigoid – unusual clinical variants. Grouped vesicles and bullae on the palms **(A)** and toes **(B)** that can resemble pompholyx (dyshidrosiform pemphigoid). **C** Vegetating plaque in the inguinal crease (pemphigoid vegetans). **D** Toxic epidermal necrolysis-like lesions with large erosions.

Bullous phase

The bullous stage of BP is characterized by the development of vesicles and bullae on apparently normal or erythematous skin together with urticarial and infiltrated papules and plaques that occasionally assume an annular or figurate pattern (see Figs 30.2 & 30.3). The blisters are tense, up to 1–4 cm in diameter, contain a clear fluid, and may persist for several days, leaving eroded and crusted areas. Occasionally, the blister fluid becomes blood-tinged. The lesions frequently have a symmetrical distribution pattern, and they predominate on the flexural aspects of the limbs and the lower trunk, including the abdomen. Within intertriginous zones, vegetating plaques can be observed (see Fig. 30.5C). Residual postinflammatory changes include hyper- and hypopigmentation and, only occasionally, milia. Involvement of the oral cavity is observed in 10–30% of patients. The mucosae of the eyes, nose, pharynx, esophagus and anogenital region are more rarely affected. In approximately 50% of patients, a peripheral blood eosinophilia is noted.

Clinical variants

Several clinical variants of BP have been described and are outlined in Table 30.2[20]. *Pemphigoid gestationis* (or *gestational pemphigoid*) is also a variant of BP, which typically occurs during pregnancy (see Ch. 27).

While the individual lesions of BP in infants and in older children (*infantile* and *childhood BP*) are similar to those observed in the elderly, the sites of involvement can differ. In infants, bullae often first appear acrally and then can generalize to other sites, including the face. Involvement of the genital region (e.g. *vulvar childhood pemphigoid*) as well as other mucosal sites/mucosae has been observed in children[20].

Associated Diseases

The association of internal malignancies with BP is probably related primarily to the older age of the patient. Although some reports have suggested an increased frequency of certain cancers (e.g. digestive tract, urinary bladder, lung) as well as lymphoproliferative disorders, in three case–control studies, the trend towards an increased risk of malignancy in patients with BP appeared to be marginal[6,20]. Nonetheless, patients with BP should be up-to-date with age-related cancer screening tests recommended for the general population.

Rarely, BP has been described in patients with inflammatory bowel disease or other autoimmune disorders such as rheumatoid arthritis, Hashimoto's thyroiditis, dermatomyositis, lupus erythematosus and autoimmune thrombocytopenia. It is thought that these associations are not fortuitous but reflect a genetically determined susceptibility to develop autoimmune diseases. Nevertheless, a case–control study did not find any increased risk for autoimmune disorders in those with BP[21].

In some patients, BP appears to be triggered by trauma, burns, radiotherapy or UV irradiation (including PUVA). BP has also been found in association with certain dermatoses, such as psoriasis and lichen planus, and the bullae may be localized to the psoriatic plaques (Fig. 30.7). It has been speculated that a chronic inflammatory process at the dermal–epidermal junction results in the exposure of antigens to

Fig. 30.6 Childhood bullous pemphigoid. **A** Generalized tense bullae and crusted erosions. **B** Localized vulvar involvement (vulvar childhood pemphigoid).

Fig. 30.7 Bullous pemphigoid localized to a psoriatic plaque. No obvious trigger was detected, as the patient was not receiving phototherapy. *Courtesy, Jean L Bolognia, MD.*

UNUSUAL CLINICAL VARIANTS OF BULLOUS PEMPHIGOID

Dyshidrosiform pemphigoid – palmoplantar vesicles and bullae (Fig. 30.5A,B)
Pemphigoid vegetans – intertriginous vegetating plaques (Fig. 30.5C)
Pemphigoid nodularis – prurigo nodularis-like lesions
Vesicular pemphigoid – dermatitis herpetiformis-like presentation with small grouped vesicles
Large erosive TEN-like lesions (Fig. 30.5D)
Papular pemphigoid
Eczematous pemphigoid (Fig. 30.4)
Erythrodermic pemphigoid
Lichen planus pemphigoides (see Ch. 11)
Localized lesions:
- pretibial
- vulvar
- peristomal
- umbilical
- distal end of amputated limb*
- paralyzed limb
- sites of radiotherapy†
- Brunsting–Perry form‡

*Also referred to as "stump" pemphigoid.
†Radiotherapy can also provoke generalized form of pemphigoid.
‡Also variant of mucous membrane (cicatricial) pemphigoid.

Table 30.2 Unusual clinical variants of bullous pemphigoid.

autoreactive T lymphocytes, leading to a secondary immune response (epitope spreading phenomenon)[22].

Finally, BP is significantly associated with neurological disorders, such as Parkinson's disease, dementia, psychiatric disorders (unipolar and bipolar disorders), and stroke. A strong association with multiple sclerosis was also observed in a population-based study[23]. It should be noted that neuronal variants of BP230 are expressed in the central and peripheral nervous systems.

Drug-induced bullous pemphigoid

In certain patients, systemic medications can lead to the development of BP[24]. The implicated drugs are numerous, including diuretics (e.g. furosemide, bumetanide), analgesics (e.g. phenacetin), D-penicillamine, antibiotics (e.g. amoxicillin, ciprofloxacin), potassium iodide, gold and captopril. Reproduction of BP lesions following drug rechallenge has been observed with some medications (e.g. furosemide), but for others, the association is based on less evidence. In a case–control study assessing the drugs used on a long-term basis prior to onset of the disease, it was found that two classes of drugs, diuretics and neuroleptics, were used more frequently by BP patients than by control subjects. Among diuretics, the risk was linked to aldosterone antagonists[24]. Hence, in all patients, a careful drug history is mandatory to exclude the triggering effect of a drug, since its prompt discontinuation may result in rapid improvement.

The mechanisms by which drugs favor the development of BP remain to be elucidated. It is likely that the drugs act as triggers in patients with an underlying genetic susceptibility by either modifying the immune response or altering the antigenic properties of the epidermal basement membrane.

Diagnosis and Differential Diagnosis

The diagnosis of BP is based upon the typical clinical presentation, the histologic features, and, most importantly, the positive findings of direct and indirect immunofluorescence (IF) microscopy studies[20], or BP180 ELISA. In the majority of cases, IF microscopy provides clues that are essential and sufficient for a correct classification of patients. Nevertheless, particularly in patients in whom indirect IF microscopy is negative, additional immunochemical studies (e.g. ELISA; see below) are helpful and are required to demonstrate an autoantibody response to the targets of the disease, BP180 and/or BP230. In the absence of full-blown bullous lesions, such as in early stages or in atypical variants of the disease, the diagnosis of BP uniquely relies on the positive results of direct IF microscopy and the characterization of the targeted autoantigens (see Table 30.1).

Light microscopy and electron microscopy

In the non-bullous phase or in atypical variants of BP, light microscopy studies may provide less specific information, since only subepidermal clefts, eosinophilic spongiosis and/or dermal infiltrates of eosinophils may be found (Fig. 30.8). In biopsy specimens of an early bulla, a subepidermal blister accompanied by a dermal inflammatory infiltrate composed of eosinophils and mononuclear cells is typically observed.

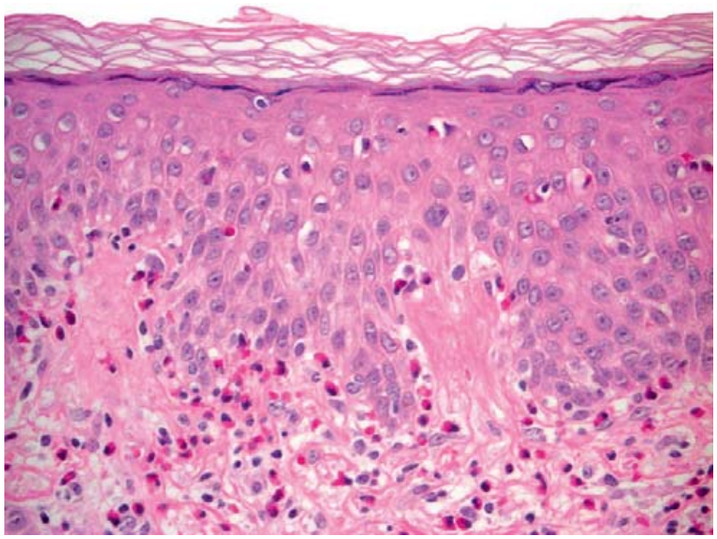


Fig. 30.8 Urticarial phase of bullous pemphigoid – histologic features. Eosinophils are present within the dermis as well as the epidermis (eosinophilic spongiosis). Some of the eosinophils have lined up at the dermal–epidermal junction, a typical finding in the urticarial stage of BP. *Courtesy, Lorenzo Cerroni, MD.*

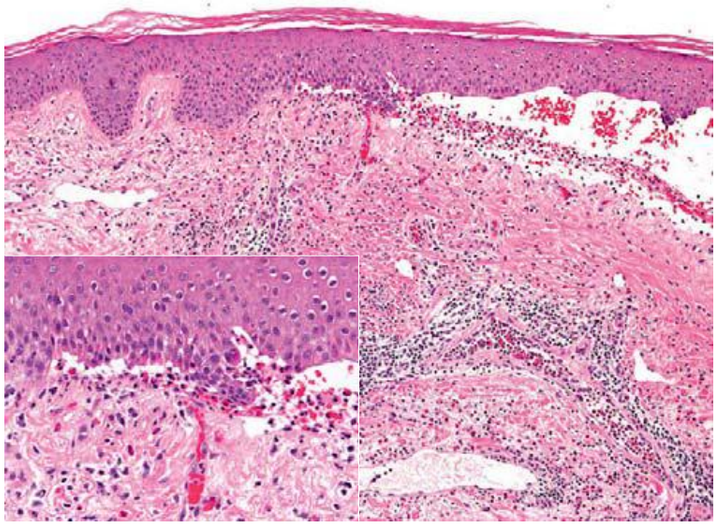


Fig. 30.9 Bullous pemphigoid – histologic features. Subepidermal blister which contains fibrin, eosinophils and mononuclear cells (see insert). *Courtesy, Lorenzo Cerroni, MD.*

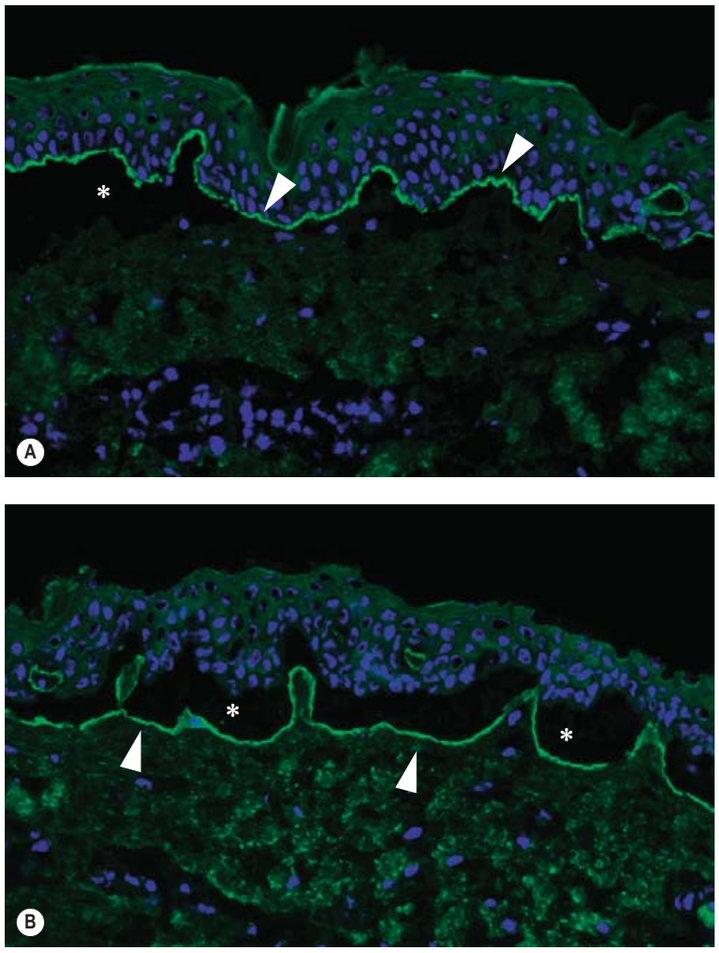


Fig. 30.10 Immunofluorescence microscopy (indirect) utilizing salt-split human skin. A Circulating IgG autoantibodies from BP patients bind to the epidermal side (roof) of the salt-induced split (arrows); the artificial separation is indicated by an asterisk. **B** IgG autoantibodies from patients with EBA, anti-p200 pemphigoid and certain forms of mucous membrane pemphigoid (e.g. with antibodies against laminin 5/332) react with the dermal side (floor) of the blister (arrows). *Courtesy, H Pas, MD.*

The infiltrate favors the uppermost dermis, and the cavity of the bulla contains a net of fibrin with a variable inflammatory infiltrate (Fig. 30.9). Electron microscopy studies have shown that subepidermal blister formation occurs at the level of the lamina lucida.

Immunofluorescence microscopy

In almost all patients, direct IF microscopy studies of *perilesional, uninvolved* skin will characteristically demonstrate the presence of fine, linear, continuous deposits of IgG and/or C3 (and, more rarely, other Ig classes) along the epidermal basement membrane (see Ch. 27). IgG4 and IgG1 are the predominant IgG subclasses. Close analysis of the linear fluorescence pattern at the BMZ (n-serrated in BP and linear IgA bullous dermatosis *versus* u-serrated in epidermolysis bullosa acquisita)[25] as well as examination of perilesional skin after treatment with 1 M NaCl (referred to as salt-split skin; see Fig. 28.8) can be helpful in distinguishing BP from other autoimmune blistering disorders. In BP, immune deposits are found in the epidermal side (roof) or in both the epidermal and dermal sides of the split. Although not routinely available, the computer-aided fluorescence overlay antigen mapping (FOAM) technique allows one to determine more precisely the localization of deposited immunoreactants[26].

In 60–80% of patients, circulating anti-basement membrane autoantibodies of the IgG class, and, less frequently, of the IgA and IgE classes, are detectable. These autoantibodies typically bind to the epidermal side or, less frequently, to both the epidermal and dermal sides of saline-separated normal human skin (Fig. 30.10)[26]. For indirect IF studies, salt-split normal human skin is the substrate of choice, rather than intact normal human skin or monkey esophagus. Finally, when available, testing of circulating autoantibodies against skin substrates or keratinocyte cell lines that are deficient in specific basement membrane proteins, such as BP180 or type VII collagen, represents an easy method for determining their exact reactivity pattern.

Immunoelectron microscopy

Although less often utilized nowadays, immunoelectron microscopy studies using gold labeling demonstrate that *in vivo*-deposited IgG antibodies are predominantly localized to the outside of the basal cell membrane beneath hemidesmosomes, in a distribution corresponding to the location of the extracellular domain of BP180. By indirect immunoelectron microscopy, circulating autoantibodies to BP230 and BP180 can be seen to bind to the hemidesmosomal plaque (Fig. 30.11) and at the level of the lamina lucida beneath the hemidesmosomes, respectively[27].

Immunochemical studies

In immunoblot and immunoprecipitation studies of keratinocyte extracts, 60–100% of patients' sera contain IgG autoantibodies that bind to BP180 and BP230, respectively (see Table 30.1; Fig. 30.12A,B)[3,4]. Patients' sera also frequently contain specific IgA and IgE autoantibodies. Recombinant forms of BP180 and BP230 expressed in prokaryotic or eukaryotic systems have been used increasingly for the detection of autoantibodies (Fig. 30.12C)[8,20].

ELISAs utilizing recombinant proteins that encompass specific regions of the BP antigens (e.g. the NC16A domain of BP180 and the C-terminus of BP180 or BP230) have been found to be fairly *specific* (>90%)[8,20]. Occasionally, low-titer, false-positive results are observed in healthy subjects and elderly patients with pruritic cutaneous eruptions. Overall *sensitivity* of the BP180-NC16A ELISA is probably comparable to that of indirect IF (with salt-split skin as a substrate) when the test is performed in unselected BP patients[12,20]. To increase overall sensitivity, various ELISAs for BP180 and BP230 proteins should be combined[11,12,20]. In contrast to immunoblotting, ELISA antigens are tested under native conditions, and, as a result, binding activity against conformational antigens is not lost. These tests are now commercially available and enable rapid characterization of the reactivity of patients' sera[20].

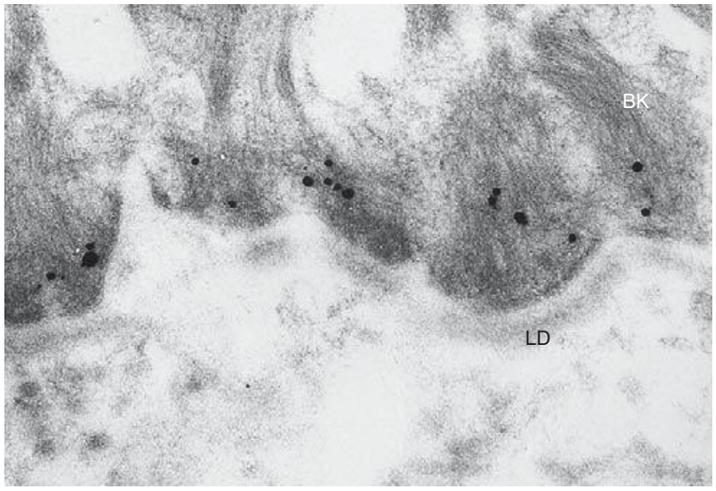


Fig. 30.11 Bullous pemphigoid – indirect immunoelectron microscopy utilizing immunogold labeling. Autoantibodies directed against BP230 specifically label the hemidesmosomal plaque of the hemidesmosomal adhesion complex (gold labeling = black dots). BK, basal keratinocyte; LD, lamina densa. *Courtesy, Professor H Shimizu.*

Differential diagnosis

Because the clinical findings in the non-bullous phase of BP may be nonspecific, they can resemble a variety of dermatoses, including drug reactions, contact dermatitis, prurigo (simplex and nodularis), urticarial dermatoses, arthropod reactions, and scabies[20]. These disorders are usually distinguished on the basis of the clinical history and setting, pathologic features, and the negative findings with IF microscopy. The presence of bullae raises the possibility of bullous arthropod bites, allergic contact dermatitis, Stevens–Johnson syndrome, bullous drug eruptions (see Ch. 33), dyshidrotic eczema, pseudoporphyria or porphyria cutanea tarda. In children, bullous impetigo, inherited epidermolysis bullosa, and bullous mastocytosis must also be considered.

The pemphigus group, paraneoplastic pemphigus, and dermatitis herpetiformis can be differentiated on the basis of distinctive immunopathologic findings and clinical context. A recent study found that, in patients with a subepidermal blistering disorder associated with linear deposits of IgG or C3 along the epidermal basement membrane, the presence of the following four clinical criteria strongly indicated a diagnosis of BP: (1) absence of skin atrophy, (2) absence of mucosal involvement, (3) absence of head and neck involvement, (4) age greater than 70 years[28]. Nevertheless, the distinction of BP from the following autoimmune subepidermal blistering disorders can sometimes prove challenging (see Table 30.1).

- **Epidermolysis bullosa acquisita (EBA)** has a wide spectrum of clinical presentations (see below). While the classic "non-inflammatory" form of EBA is sufficiently distinctive, the "inflammatory" form closely mimics BP. As with BP, mucosal involvement may be present.
- **Linear IgA bullous dermatosis (LABD)** represents a group of subepidermal blistering diseases rather than a single entity (see Ch. 31). While features of LABD are polymorphic in adults, during childhood the condition is frequently associated with annular and polycyclic lesions as well as involvement of the genital and perioral region. However, identical features are also observed in childhood BP.
- **Mucous membrane (cicatricial) pemphigoid** is a heterogeneous group of diseases which have in common the predominant involvement of the mucosae, a chronic course, and a scarring tendency (see below). Skin lesions are only found in up to 25–30% of patients, and they generally involve the head and upper trunk.

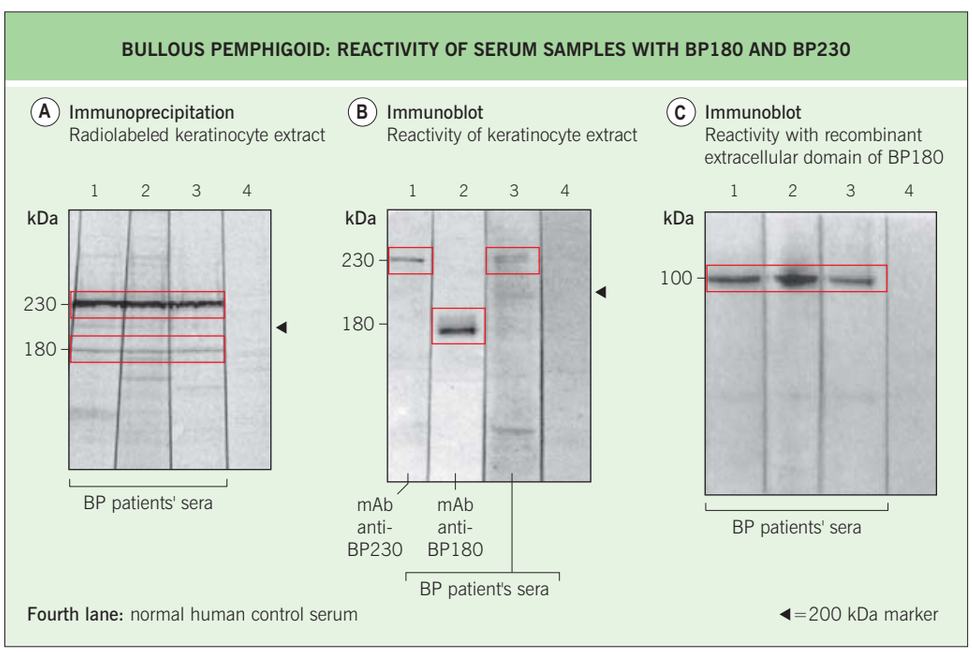


Fig. 30.12 Bullous pemphigoid (BP): reactivity of serum samples with BP180 and BP230. A Immunoprecipitation studies utilizing radiolabeled human keratinocyte extracts: lanes 1–3, serum samples from BP patients immunoprecipitate proteins of 230 kDa (BP230) and 180 kDa (BP180); lane 4, reactivity of normal human serum. **B** Immunoblot studies of keratinocyte extracts: lane 1, reactivity of monoclonal antibodies directed against BP230; lane 2, reactivity of monoclonal antibodies directed against BP180; lane 3, reactivity of a BP serum sample with a protein of approximately 230 kDa; lane 4, reactivity of normal human serum. **C** Reactivity with the extracellular domain of BP180, which was expressed by transfection of COS-7 cells: lanes 1–3, serum samples from BP patients; lane 4, normal human serum.

In patients with both oral and cutaneous lesions, the differentiation of mucous membrane pemphigoid from BP is difficult, and classification relies on the presence of an obvious scarring tendency of involved mucosal sites and limited skin involvement, and, occasionally, on the results of immunologic assays (see Table 30.1).

- **Pemphigoid incipiens**. A difficult issue is how to categorize the group of elderly patients with generalized pruritus (with or without skin lesions), in whom circulating autoantibodies to the epidermal BMZ and reactivity with BP180 and/or BP230 are found, but routine IF microscopy remains negative. Some of these patients, with initially negative direct IF microscopy findings, eventually do develop BP and could be thought of as having pemphigoid incipiens[20].
- **Anti-p200 pemphigoid**. A small group of patients have been described with features identical to those observed in BP, i.e. vesicles and tense blisters as well as eczematous and urticarial papules and plaques. Occasionally, grouped papulovesicles with a dermatitis herpetiformis-like presentation are also present. There may also be mucosal involvement. These patients have circulating autoantibodies that specifically bind the dermal side of salt-split human skin. The targeted 200 kDa BMZ protein is the gamma 1 chain of laminin (see Table 30.1)[29,30].

Prognosis

BP is a chronic disease characterized by spontaneous exacerbations and remissions. Because of the intractable pruritus, and the presence of bullous, eroded or impetiginized lesions, the disease is often accompanied by significant morbidity with a profound impact on quality of life. Although the majority of patients finally go into clinical remission with treatment, the mortality is considerable among elderly patients. The estimated death rate during the first year varies between 10% and 40%, depending on the series[31,32]. Age and a Karnofsky score that is <40 (range, 0–100) have been shown to significantly affect prognosis. It is likely that comorbidities and practice patterns (use of systemic corticosteroids and/or immunosuppressive drugs) also influence overall morbidity and mortality.

ELISA-based studies have recently shown that the serum level of IgG and IgE autoantibodies to BP180 correlated with disease severity[20,33]. Furthermore, IgG reactivity with both the NC16A domain *and* the C-terminus of BP180 has been associated with a distinct clinical phenotype of BP, presenting with a preferential mucosal involvement[9,11]. While the practical use of ELISA results as a means of guiding treatment remains to be established, a recent study found that a high BP180-NC16A ELISA score and (to a lesser degree) positive direct IF findings at cessation of therapy are both good indicators of future relapse of BP[33].

Treatment

The treatment of BP is grounded more on clinical experience than on controlled studies (Tables 30.3 & 30.4)[19,32,34–42].

Systemic corticosteroids represent the most endorsed treatment. For patients with generalized disease, a regimen of oral prednisone at a dose of 0.5–1 mg/kg/day usually controls the disease within 1 or 2 weeks. This dose is then progressively tapered over a period of 6–9 months, or occasionally longer. The use of corticosteroids in the elderly, however, is associated with significant side effects (see Ch. 125). Recent large controlled studies have emphasized the role of potent topical corticosteroids, which appeared to control even generalized BP with the same efficacy as oral corticosteroids, and, most importantly, with fewer systemic side effects[40,42]. However, these studies did not address the patients' ability to achieve complete disease-free remissions as compared with systemic corticosteroids. Occasionally, pulse therapy with methylprednisolone may be required for rapid control of the disease.

The use of immunosuppressive drugs is a matter of debate. Some clinicians prefer to use them solely as second-line therapy when corticosteroids alone fail to control the disease, or if the latter are contraindicated. The most frequently employed agents are azathioprine, mycophenolate mofetil (1.5–3 g/day), methotrexate, chlorambucil (0.1 mg/kg/day, frequently 4–6 mg/day), and cyclophosphamide (1–3 mg/kg/day) (see Table 30.4). The dosage of azathioprine (0.5–2.5 mg/kg/day) should be adjusted according to the level of thiopurine methyltransferase, in order to increase efficacy and reduce toxicity. The choice of a particular immunosuppressive drug depends on its side-effect profile (see Ch. 130), the patient's overall condition, and the experience of the physician.

The combination of nicotinamide (500–2000 mg/day) and minocycline or tetracycline has been tried with some success in small series and can serve as a therapeutic alternative in mild disease when obvious contraindications to corticosteroids exist. Unless there is glucose-6-phosphate dehydrogenase deficiency, the use of dapsone may also be warranted, particularly in the presence of mucosal involvement. The benefit of topical immunomodulators, such as tacrolimus, remains to be confirmed. In treatment-resistant cases, IVIg, plasma exchange or anti-CD20 immunotherapy (rituximab) may be tried.

While the optimal duration of therapy has not been established, BP patients usually need to be treated for approximately 12–18 months. This includes a maintenance phase in which low-dose oral prednisone (<10 mg/day) or topical clobetasol propionate (10 g/week) is continued for 3 to 6 months after any evidence/cessation of clinically active disease[33]. Finally, in all patients with BP, it is important to minimize the complications of both the cutaneous lesions and the systemic treatment, including using osteoporosis prophylaxis, gastric protection, and assessment of cardiovascular function and infection risk (see Ch 125).

MUCOUS MEMBRANE (CICATRICIAL) PEMPHIGOID

Synonyms: ■ Desquamative gingivitis, benign mucous membrane pemphigoid, ocular pemphigus, scarring pemphigoid ■ Anti-epiligrin cicatricial pemphigoid ■ Anti-laminin 5 cicatricial pemphigoid

Key features

- Mucous membrane pemphigoid is a chronic, autoimmune, subepithelial blistering disorder characterized by predominant involvement of the external mucosal surfaces and a tendency for scarring
- It is associated with tissue-bound and, less often, circulating autoantibodies directed against distinct structural components of basement membranes in stratified and some complex epithelia, e.g. bullous pemphigoid antigen 180 (BP180, BPAG2 or type XVII collagen), laminin 332 (laminin 5)
- The condition should not be regarded as a clinical entity, but as a "disease phenotype" shared by a heterogeneous group of diseases with lesions that favor the mucosal surfaces and, less frequently, the skin
- When scarring and fibrosis affect the conjunctivae, the disorder can be devastating and ultimately lead to blindness
- Diagnosis relies on immunopathologic examinations, especially immunofluorescence microscopy, and immunochemical studies

Introduction

Mucous membrane pemphigoid is a rare autoimmune subepithelial blistering disorder characterized by predominant involvement of the mucosae, a chronic course, and a tendency towards scarring of the affected areas. The disorder should not be regarded as a clinical entity, but rather as a "disease phenotype" shared by a heterogeneous group of blistering diseases, with predilection for the mucosal surfaces[43]. The majority of patients have linear deposits of immunoglobulins and/or complement components along the epithelial BMZ of the skin and mucosae. Circulating anti-basement membrane autoantibodies are detected in the serum of some patients (20–30% by standard indirect IF), usually at a low titer. It is a chronic and progressive disease, which may result in serious local complications. When atrophic scarring and fibrosis affect the conjunctivae, the disorder can be devastating and ultimately lead to blindness.

SURVEY OF CONTROLLED TRIALS FOR THE TREATMENT OF PATIENTS WITH BULLOUS PEMPHIGOID						
Authors (year)	**Design**	**Intervention**		**Number of patients**	**Response**	**Remarks**
Roujeau et al.[34] (1984)	Randomized multicenter	Group 1: Group 2:	Prednisolone (0.3 mg/kg/day) Prednisolone + 8 plasma exchanges	41	Total and daily corticosteroid doses needed for disease control lower in group 2	Low prednisolone dose
Morel & Guillaume[35] (1984)	Randomized multicenter	Group 1: Group 2:	Prednisone (0.75 mg/kg/day) Prednisone (1.25 mg/kg/day)	42	At day 51, remission in group 1 (33%) and group 2 (55%) not significantly different	Trend for a better response in group 2
Guillot et al.[36] (1986)	Non-randomized retrospective	Group 1: Group 2:	Prednisolone alone Prednisolone plus long-term plasma exchange	21	At month 6, relapse rate and total corticosteroid doses lower in group 2	Risk of severe side effects in group 2
Dreno et al.[37] (1993)	Randomized multicenter	Group 1: Group 2:	Methylprednisolone (1–1.5 mg/kg/day) Prednisolone (1–1.5 mg/kg/day)	57	At day 10, no difference in response except for better decline of pruritus in group 1	Analysis of early response only
Guillaume et al.[38] (1993)	Randomized multicenter	Group 1: Group 2: Group 3:	Prednisolone (1 mg/kg/day) alone Prednisolone and azathioprine (100–150 mg/day) Prednisolone and 4 plasma exchanges	98	At month 6, no significant difference in remission rate between group 1 (42%), group 2 (39%) and group 3 (29%)	More complications in group 2. No adjustment of doses of azathioprine based on TPMT levels
Fivenson et al.[39] (1994)	Randomized single center	Group 1: Group 2:	Nicotinamide (1.5 g/day) plus tetracycline (2 g/day) Prednisone (40–80 mg/day)	18	At month 1, no difference in response, but fewer side effects in group 1	Low number of studied patients. High drop-out rate
Joly et al.[40] (2002)	Randomized multicenter	Group 1: Group 2:	Topical clobetasol propionate Prednisone 0.5–1 mg/kg/day	341	At week 3, control rates better in group 1	At year 1, topical therapy is associated with a significantly reduced mortality and complication rate
Beissert et al.[41] (2007)	Randomized multicenter prospective	Group 1 Group 2	Methylprednisolone (0.5 mg/kg) with azathioprine (2 mg/kg) Methylprednisolone (0.5 mg/kg) with mycophenolate mofetil (2 g daily)	38 35	Disease control similar in the two groups	In group 1, higher incidence and severity of liver toxicity. Trend for faster disease control and less total cumulative doses of steroids in group 1. No adjustment of doses of azathioprine based on TPMT
Joly et al.[42] (2009)	Randomized multicenter prospective	Group 1 Group 2	Topical clobetasol propionate *standard* regimen for 12 months (40 g daily as starting dose) Topical clobetasol propionate, *mild* regimen for 6 months (10–30 g daily as starting dose)	153 159	Time to achieve disease control of BP similar in both groups. At 1 year, trend for higher relapse rate in patients with moderate BP treated with mild regimen	In moderate BP treated with mild regimen, decrease in the risk of death/side effects. Lower cumulative dose of clobetasol in mild regimen

Table 30.3 Survey of controlled trials for the treatment of patients with bullous pemphigoid. TPMT, thiopurine methyltransferase.

THERAPEUTIC LADDER FOR BULLOUS PEMPHIGOID
MILD AND/OR LOCALIZED DISEASE
Superpotent topical corticosteroids (1*)
Nicotinamide in association with minocycline, doxycycline or tetracycline (3)
Erythromycin, penicillins (3)
Dapsone, sulfonamides (3)
Topical immunomodulators (e.g. tacrolimus) (3)
EXTENSIVE/PERSISTENT CUTANEOUS DISEASE
Superpotent topical corticosteroids (1*)
Oral corticosteroids† (1‡)
Azathioprine (2)
Mycophenolate mofetil (2)
Methotrexate§ (2)
Chlorambucil (3)
Cyclophosphamide (3)
IVIg (3)
Plasma exchange (2)
Rituximab (3)
Note: Superpotent topical corticosteroids should be considered in any patient and may be combined with a systemic therapy.
*Validated.
†Prednisone doses of at least 0.5–0.75 mg/kg/day seem to be necessary to control extensive disease, but increase serious side effects, including mortality.
‡Validated for prednisone.
§In elderly patients, low-dose regimen (2.5–10 mg/wk) can be effective.

Table 30.4 Therapeutic ladder for bullous pemphigoid. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

Fig. 30.13 Mucous membrane (cicatricial) pemphigoid. Erythema and erosions of the gingival margins (desquamative or erosive gingivitis).

History

In 1794, Wichmann first described a chronic blistering disease associated with involvement of the eyes. In 1949, Civatte separated this disorder from pemphigus on the basis of peculiar histopathologic findings, and Lever later suggested the name "benign mucous membrane pemphigoid", a misnomer in view of the potentially devastating complications of the disorder. Over the past few decades, the term "cicatricial pemphigoid" has been used with increasing frequency. Demonstration of immunoreactants deposited along the epithelial BMZ by IF microscopy pointed to an autoimmune origin.

Epidemiology

Mucous membrane pemphigoid is rare, with an annual incidence in Western Europe of approximately 1–5 cases per million[44]. The disorder typically occurs in the elderly, with a mean age at the time of diagnosis of between 60 and 80 years. Nonetheless, isolated cases have been reported in children. Women are affected more often than men (estimated ratio 1.5–2 : 1). Although no geographic or racial predilection has been described, several studies have shown an association with specific immunogenetic haplotypes, primarily HLA-DQw7 (subtyped HLA-DQB1*0301), in both oral and ocular forms of the disease[45]. There is no overall association with malignancy, but in a distinct subtype associated with autoantibodies directed against laminin 332 (laminin 5), also known as anti-epiligrin cicatricial pemphigoid, an increased relative risk for cancer has been reported[46].

Pathogenesis

Mucocutaneous lesions are thought to result from the binding of autoantibodies to the BMZ of stratified epithelia of mucosae and skin. These autoantibodies recognize distinct structural components of the hemidesmosomal adhesion complex. Specifically, they appear to bind predominantly to antigenic sites located extracellularly within the anchoring filament zone rather than within the hemidesmosomal plaque[47]. However, the pathogenicity of various autoantibodies associated with this disease phenotype (see Table 30.1) has not yet been established unequivocally and other mechanisms may also be involved. In a minority of patients with mucous membrane pemphigoid, NC16A domain-specific T cells were detectable[48]. For patients with ocular disease, increased expression of collagen-binding *h*eat *s*hock *p*rotein 47 (HSP47) and TGF-β1 by conjunctival fibroblasts may contribute to conjunctival scarring[49]. Nonetheless, mucous membrane pemphigoid can be separated into four distinct subgroups on the basis of the reactivity profile of patients' autoantibodies.

The *first* subgroup includes patients with autoantibodies directed against laminin 332 (previously termed laminin 5), and is known as anti-laminin 5 cicatricial pemphigoid or anti-epiligrin cicatricial pemphigoid[50]. These patients with anti-laminin 5 (332) autoantibodies cannot be distinguished clinically from those with other variants of mucous membrane pemphigoid. They have circulating IgG autoantibodies that bind to the dermal side of salt-split skin and react with the α_3 chain (G domain) and, less frequently, the β_3 and/or γ_2 chain of laminin 5 (332) ($\alpha_3\beta_3\gamma_2$). Occasionally, binding to the α_3 chain of laminin 311 (previously termed laminin 6; a heterotrimer of $\alpha_3\beta_1\gamma_1$ chains) is also observed, because of the presence of cross-reacting antibodies. *In vitro* and *in vivo* studies have provided convincing evidence that autoantibodies to laminin 5 (332) are pathogenic[51].

The *second* group of patients has pure or predominant ocular disease. In this subset with so-called ocular mucous membrane pemphigoid, the presence of autoantibodies that bind to the β_4 subunit of $\alpha_6\beta_4$ integrin, a transmembrane hemidesmosomal component that interacts with laminin 5 (332), has been described[52]. A *third* group of patients, who present with lesions affecting both mucosae and the skin, have tissue-bound and circulating IgG antibodies that react with the same target antigens as for BP, especially BP180 (see above)[53]. Hence, these patients should be classified as having anti-BP antigen mucous membrane pemphigoid. The antigenic regions targeted on BP180 are probably preferentially located on its distal C-terminal portion, which ultrastructurally appears to extend into the lamina densa region[20,47]. The *fourth* group is rather heterogeneous. It includes patients who have variable involvement of mucosae without involvement of the skin. In these patients, it is as yet unclear whether injury occurs as a result of an autoantibody-mediated response to proteins of the epithelial basement membrane.

Clinical Features

Mucous membranes

The two most frequently involved sites in patients with the "mucous membrane pemphigoid phenotype" are the oral and conjunctival mucosae. However, the disease may also start in, and affect, any mucosal site, including the external genitalia, the anus, the upper aerodigestive tract, and/or the esophagus[54,55]. Approximately 85% of patients have oral involvement (often in the absence of skin lesions), and the oral cavity may be the only site of disease activity. Lesions often involve the gingiva, buccal mucosa, and palate; the alveolar ridges, tongue and lips are less frequently affected.

A common oral presentation is desquamative gingivitis (Fig. 30.13), accompanied by bleeding erosions and paresthesias; small intact

blisters are rarely observed. Chronic inflammation may lead to periodontal ligament damage and loss of teeth. In other areas of the mouth, transient vesicles give rise to chronic erosions, especially on the palate (Fig. 30.14), with variable associated pain. Lesions on the tongue are usually localized to its lateral and ventral surfaces. Adhesions may develop in the area of the uvula and tonsillar fossae as well as between the tongue and the floor of the mouth. After healing, lesions may lead to white, reticulated striations, resembling lichen planus.

Conjunctival involvement is common and may result in blindness[56]. The conjunctiva is frequently the only site affected. Although the disease can begin unilaterally, in the majority of cases, lesions appear in both eyes. Ocular involvement starts as a nonspecific, chronic conjunctivitis, with burning, soreness, foreign-body sensation, or mucus production. Both exacerbations and remissions are typical, with eventual progression to subepithelial conjunctival fibrosis (Fig. 30.15).

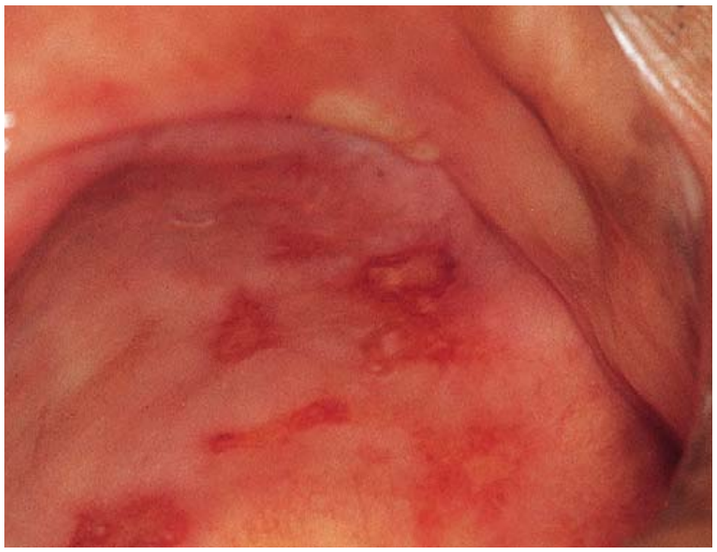


Fig. 30.14 Mucous membrane (cicatricial) pemphigoid. Chronic erosions on the hard palate. *Courtesy, C Prost, MD.*

Conjunctival vesicles or blisters are rare on the tarsal conjunctiva. Chronic inflammation may result in progressive scar tissue formation, including shortened inferior fornices and symblepharon formation (adhesion between bulbar and palpebral conjunctival surfaces; Fig. 30.16). Conjunctival fibrosis can also lead to trichiasis (inwardly angled eyelashes) and entropion[56]. In uncontrolled disease, trichiasis, entropion and xerosis (due to scarring of the lacrimal ducts) result in superficial corneal trauma, corneal neovascularization with subsequent corneal ulceration, and blindness.

Nasopharyngeal involvement is typically chronic and can be associated with extensive lesions of the upper aerodigestive tract. It results in crusted ulcerations, epistaxis, fibrous adhesions between adjacent mucosal surfaces, and airway obstruction. Pharyngeal involvement presents as ulcerations of the posterior or lateral pharynx and dysphagia. Laryngeal involvement is a potentially serious manifestation, presenting as hoarseness, loss of speech, and even life-threatening stenosis, which requires tracheostomy.

Although esophageal disease may be accompanied by dysphagia resulting from erosions of the esophageal mucosa, involvement can be entirely asymptomatic. Chronic inflammation can lead to strictures and stenosis, with associated dysphagia.

Involvement of genital and anal mucosae is relatively rare. Early lesions consist of blisters and chronic erosions. In female patients, progressive disease leads to atrophic scarring and narrowing of the introitus. In male patients, adhesions can form between the prepuce and the glans penis. Anal involvement can also lead to scarring and, in severe cases, to stricture formation.

Cutaneous lesions

The skin is involved in 25–30% of patients. The most frequently involved sites are the scalp, face, neck and upper trunk. Lesions typically present as erythematous plaques, which become sites for recurrent blister formation and erosions, with subsequent atrophic scarring (Fig. 30.17). Their extent and number are generally limited, but an occasional patient can have a BP-like clinical presentation.

In the Brunsting–Perry variant, skin lesions are limited to the head and neck region and mucosal involvement is usually absent or minimal. On the scalp, scarring alopecia can result.

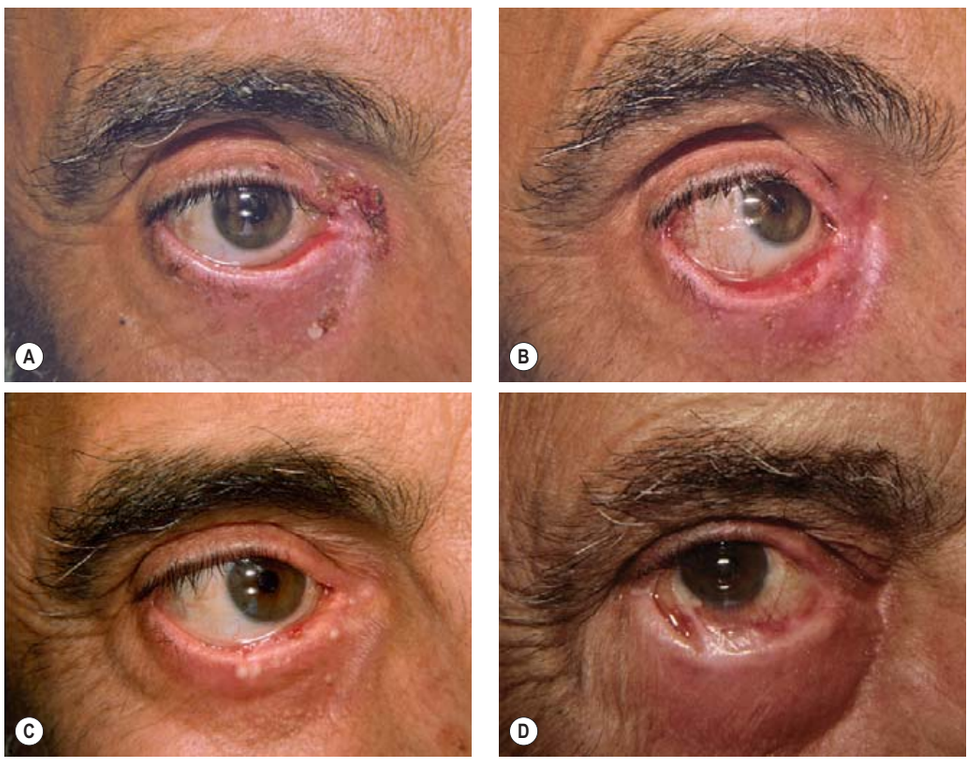


Fig. 30.15 Mucous membrane (cicatricial) pemphigoid progression. A Erosion of the lower eyelid margin and erythema plus scale-crust of the inner canthus and lower eyelid. **B** Three months later, ectropion and thickening of the lower eyelid in addition to erosions. **C** Six months later, smaller erosions but scarring and milia formation. **D** Seven years later, further scarring with significant shortening of the inferior fornix due to symblepharon. *Courtesy, Louis A Fragola, Jr, MD.*

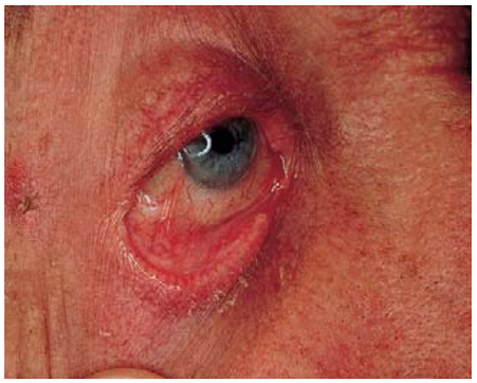


Fig. 30.16 Mucous membrane (cicatricial) pemphigoid. Typical ocular involvement as manifested by fibrous tracts, representing partial or incomplete symblepharon.

Fig. 30.17 Mucous membrane (cicatricial) pemphigoid. Cutaneous involvement of the scalp with scarring and atrophy resulting in alopecia.

Diagnosis and Differential Diagnosis

Light microscopy and electron microscopy

The histopathologic features of mucous membrane pemphigoid and BP are often similar. Examination of an intact vesicle demonstrates subepidermal or subepithelial blister formation (without acantholysis) and a mixed infiltrate of variable intensity, composed primarily of mononuclear cells. Older lesions tend to demonstrate fibrosis in the upper dermis. In oral lesions, the inflammatory infiltrate typically contains some plasma cells. The epithelium of affected conjunctivae is often invaded by inflammatory cells, including mononuclear cells and mast cells, while granulation tissue is found in the submucosa.

As in BP, electron microscopy studies of a recent blister demonstrate that the dermal–epidermal cleavage occurs within the lamina lucida. In advanced conjunctival lesions with scarring, the lamina densa appears to be discontinuous, focally thickened or duplicated.

Immunofluorescence microscopy

By *direct* IF microscopy, 80–95% of patients with mucous membrane pemphigoid have *in vivo* bound autoantibodies directed against the BMZ of mucosae and/or skin. The majority of patients exhibit continuous, fine, linear deposits of IgG and/or C3 along the epithelial BMZ in perilesional biopsy specimens. It should be noted that direct IF microscopy studies of mucosae are more frequently positive (50–90%) than those of skin (20–50%). IgG deposits belong primarily to the IgG4 and IgG1 subclasses; linear deposits of IgA and IgM are less common. Direct IF microscopy of salt-split skin is of less diagnostic value. Although a combined pattern with staining of both the epidermal and dermal sides is frequently observed, reactivity with either the epidermal roof or the dermal floor of the separated skin is occasionally noted.

By standard *indirect* IF, anti-BMZ antibodies can be detected in serum samples from 20–30% of patients with mucous membrane pemphigoid. Antibodies are mainly of the IgG class, but circulating IgA and, less frequently, IgM autoantibodies are also observed. Antibody titers are usually very low. Some authors have suggested that patients with higher titers and both IgG and IgA circulating anti-BMZ autoantibodies have more severe disease[57]. The sensitivity of indirect IF can be increased either by the use of normal oral or genital mucosa and conjunctiva as substrates, or by utilizing salt-split skin. Using this latter technique, most patients with mucous membrane pemphigoid have antibodies that bind to the epidermal roof, whereas patients with anti-laminin 5 (332) cicatricial pemphigoid have IgG antibodies that bind to the dermal side (see Fig. 30.10B). The use of salt-split oral mucosa does not improve the overall sensitivity. Distinguishing anti-epiligrin cicatricial pemphigoid (anti-laminin 5[332]) from EBA may be possible by indirect IF microscopy using either "knockout" skin substrates (i.e. substrates deficient in specific basement membrane proteins) or the FOAM technique (see above)[58].

Immunoelectron microscopy

Direct immunoelectron microscopy studies in mucous membrane pemphigoid have demonstrated immune deposits distributed either in the lower lamina lucida and over the lamina densa or, alternatively, on and around hemidesmosomes, with most of the labeling on the outside of basal keratinocytes below the plasma membrane[47]. By indirect electron microscopy, autoantibodies typically bind to the lower lamina lucida at the interface with the lamina densa, beneath and beside hemidesmosomes[47]. Although electron microscopy studies are not routinely available and are time consuming, they may be extremely useful for establishing the diagnosis of mucous membrane pemphigoid in patients in whom the presence of tissue-deposited immunoreactants cannot be demonstrated by conventional IF studies.

Immunochemical studies

Immunochemical techniques, especially immunoblotting and immunoprecipitation studies, have demonstrated that the autoantigens targeted in patients with a mucous membrane pemphigoid phenotype are heterogeneous[46,50–53,57,59–61]. Circulating autoantibodies react with various proteins located within the epithelial BMZ, e.g. laminin 5 (332), BP180 (see Table 30.1). These targeted antigens appear to constitute serologic markers for different clinical subsets (see above).

Patients frequently have IgA autoantibodies directed against the ectodomain of BP180[59]. In certain cases, these autoantibodies appear to preferentially bind to antigenic reactive sites present on the proteolytically cleaved and shed portion of the extracellular domain of BP180, the linear IgA bullous dermatosis antigen (see Ch. 31). Other target antigens have been reported, including a 168 kDa antigen (which appears to be strongly expressed in buccal mucosa) and a 45 kDa antigen in certain patients with pure ocular disease.

ELISAs utilizing recombinant proteins or affinity-purified native proteins (e.g. BP180, laminin 5 [332]) appear to be very useful in the search for circulating autoantibodies, with excellent sensitivity and specificity, and hold significant promise as diagnostic and prognostic tests[61].

Differential diagnosis

The diagnosis of mucous membrane pemphigoid has to be considered in all patients who have blistering or erosive lesions that predominantly involve mucous membranes and whose affected tissues exhibit linear, continuous deposits of immunoreactants along the epithelial basement membrane. Distinction from other subepidermal autoimmune bullous diseases (including BP, EBA and linear IgA bullous dermatosis) may be very difficult and often requires sophisticated immunopathologic studies (see above). On the contrary, pemphigus vulgaris and non-autoimmune bullous diseases are more easily eliminated by histology and IF microscopy.

When they are the only manifestation of the disease, oral lesions are clinically difficult to differentiate from those of pemphigus vulgaris or erosive lichen planus. End-stage, scarring conjunctival lesions may mimic severe chronic infectious conjunctivitis, ocular pseudopemphigoid due to ophthalmologic preparations (including pilocarpine, idoxuridine, guanethidine, β-blockers), or late stages of Stevens–Johnson syndrome and toxic epidermal necrolysis. The rare, generalized skin eruption of mucous membrane pemphigoid is impossible to distinguish from that of BP. Nevertheless, a prominence of mucosal lesions along with scarring favors the former.

Prognosis

Mucous membrane pemphigoid is a particularly chronic, potentially devastating, but rarely fatal disease. The most important complication is impairment of vision due to ocular involvement. It can also lead to

weight loss as well as respiratory, sexual or urinary complications. Even with localized involvement, this disease can have a major negative impact on quality of life. Life-threatening complications, due to severe laryngeal, tracheal or esophageal disease, are rare. Patients with anti-laminin 5 (332) autoantibodies have an increased relative risk for solid organ carcinomas, especially adenocarcinomas[50].

Treatment

Treatment can be difficult and is often disappointing. Therapeutic regimens are based primarily on clinical experience[62].

Local therapy is crucial and, in some cases, may be sufficient to control the disease. Mild to moderate disease activity may be successfully treated with potent topical corticosteroids. Oral lesions can respond to topical corticosteroids (as mouthwashes or topical preparations in a gel or occlusive base) in conjunction with tetracycline mouthwashes and good hygiene. Corticosteroid sprays and inhalers may prove useful in nasal, pharyngeal or esophageal disease. Recalcitrant lesions of both skin and mucous membranes may improve with intralesional injections of corticosteroids. Esophageal strictures may require dilatations to prevent dysphagia, while severe tracheal involvement may require a tracheostomy to prevent asphyxiation.

Systemic medications include dapsone (50–150 mg/day) as a first-line therapy for controlling oral and cutaneous lesions, and it may also be used for mild ocular disease without rapid worsening. Cyclophosphamide (1–2 mg/kg/day) is the treatment of choice for rapidly progressive or severe ocular disease[56] – alone, in combination with oral corticosteroids, or as pulse therapy. Such regimens are effective in resolving severe conjunctival inflammation and preventing recurrences and scarring. Azathioprine (2 mg/kg/day) and mycophenolate mofetil (2 g/day) have also been reported to be helpful in partially controlling ocular disease and cutaneous lesions.

Systemic corticosteroids alone are generally insufficient therapy for patients with significant disease, and they are less effective for mucosal than for cutaneous disease. Patients with significant esophageal or laryngotracheal involvement should be treated aggressively with the combination of prednisone and cyclophosphamide or mycophenolate mofetil to prevent potentially life-threatening complications. Other therapies reported to be of potential value in the treatment of mucous membrane pemphigoid include sulfapyridine, minocycline, a combination of tetracycline and niacinamide, topical tacrolimus, topical or systemic cyclosporine, thalidomide and subconjunctival mitomycin. Recent studies and case series have suggested that IVIg[63], methotrexate, TNF-α inhibitors such as etanercept, and rituximab could be helpful in controlling progressive ocular involvement[62,64,65].

Surgical therapy may occasionally be necessary for severe scarring involving the eye, larynx, esophagus or genitalia. It should be performed when the disease is fully controlled by medical therapy. For ocular disease, surgical intervention includes corneal grafts, allograft limbal transplantation, amniotic membrane transplantation, and tarsorrhaphy.

EPIDERMOLYSIS BULLOSA ACQUISITA

Synonym: ■ Acquired epidermolysis bullosa; dermolytic pemphigoid

Key features

- Epidermolysis bullosa acquisita is a rare, acquired, subepidermal bullous disease associated with autoimmunity to type VII collagen, the major component of the anchoring fibrils of the dermal–epidermal junction
- Patients may present either with a mechanobullous disorder, mimicking dystrophic epidermolysis bullosa, or with clinical features indistinguishable from those found in bullous pemphigoid or, more rarely, mucous membrane pemphigoid
- The disease is usually chronic and more refractory to treatment than is BP
- Diagnosis relies on immunopathologic examinations, especially immunofluorescence microscopy, immunochemical studies and immunoelectron microscopy

Introduction

Epidermolysis bullosa acquisita (EBA) is a rare, acquired, subepidermal bullous disease associated with autoimmunity to type VII collagen, the major component of the anchoring fibrils of the dermal–epidermal junction. Patients may present either with a mechanobullous disorder, the features of which strikingly resemble those observed in patients with dystrophic epidermolysis bullosa, or with clinical features indistinguishable from those typically found in BP or mucous membrane pemphigoid.

History

The first cases of an acquired bullous disease with clinical features mimicking hereditary dystrophic epidermolysis bullosa were described by Elliot in 1895. In the early 1970s, before the era of cutaneous immunopathology, Roenigk and colleagues proposed the initial clinical criteria for EBA. A few years later, IF microscopy studies demonstrated that EBA patients have anti-BMZ antibodies, similar to BP patients. In the early 1980s, immunoelectron microscopy studies separated EBA from BP by demonstrating that IgG deposits in EBA were located in the sublamina densa region. In the 1990s, using sophisticated immunopathologic techniques, it was shown that EBA autoantibodies bind to type VII collagen, the major component of anchoring fibrils.

Epidemiology

EBA has been reported in both children and adults and may occur at any age. It is one of the rarest subepidermal bullous diseases in Western Europe, with an estimated annual incidence of approximately 0.25 per million[44]. It may be more common among Korean/Asian populations as well as in African-Americans.

Pathogenesis

The idea that EBA is an immune-mediated disease is supported by several observations:

- Patients have tissue-bound and circulating autoantibodies to a well-characterized structural component of the dermal–epidermal junction.
- Tissue injury occurs where antibody–antigen complexes are found.
- *In vitro* models and *in vivo* animal models of the disease have provided evidence for the pathogenic role of autoantibodies.
- The disease appears to occur in association with distinct class II MHC haplotypes.
- The disease responds, although inconstantly, to immunosuppressive therapy.

Patients with EBA possess IgG autoantibodies directed against the basement membrane of stratified squamous and other complex epithelia. Specifically, these autoantibodies characteristically react with type VII collagen, the major component of anchoring fibrils located in the lamina densa and sublamina densa region (see Table 30.1). Type VII collagen is composed of three identical α-chains, each of which consists of a central 145 kDa collagenous triple helical segment, flanked by a large 145 kDa non-collagenous N-terminal domain (NC1) and a short 30 kDa C-terminal region (NC2). Patients' autoantibodies target immunodominant epitopes within the NC1 domain of the protein. However, reactivity with either the central collagenous domain or the NC2 domain is also observed, albeit rarely. It is, as yet, unclear if binding activity to certain antigenic regions of the molecule correlates with a distinct clinical phenotype (see below).

In vitro, EBA autoantibodies, together with the complement system and neutrophil elastase and gelatinase B, are able to mediate leukocyte infiltration and dermal–epidermal separation[14]. Furthermore, passive and active transfer studies in mice have shown that antibodies to type VII collagen can induce a subepidermal bullous disease resembling EBA[66–68].

EBA autoantibodies may be pathogenic by interfering with the association and assembly of type VII collagen molecules into anchoring fibrils and/or by critically affecting the interactions between type VII collagen and other matrix proteins, such as laminin 5 (332)[68].

As in the case of other autoimmune diseases, certain HLA class II alleles appear to be more prevalent in EBA, e.g. an association with

Fig. 30.18 Epidermolysis bullosa acquisita – mechanobullous presentation. Milia and scarring that favors sites of trauma overlying joints, in association with skin fragility.

Fig. 30.19 Epidermolysis bullosa acquisita – inflammatory bullous pemphigoid-like presentation. Bullous and erosive lesions in a patient with multiple myeloma.

DRB1*1501 and DR5 in Caucasians and African-Americans or DRB1*13 in Koreans. It is likely that the expression of distinct HLA alleles has a critical impact on the susceptibility for developing EBA. The observation that deficient expression of type VII collagen in patients with various forms of dystrophic epidermolysis bullosa causes skin fragility and dermal–epidermal separation demonstrates unequivocally the importance of this protein in maintaining the integrity of the epidermal BMZ.

Clinical Features

EBA usually occurs in adult patients, although pediatric cases have been reported. The classic presentation is that of a non-inflammatory mechanobullous disease characterized by the development of acral blisters that heal with atrophic scarring, milia and hyper- or hypopigmentation[68]. Cutaneous blisters and subsequent erosions, which appear within non-inflamed skin or on areas of scarring, may be serous, or, less frequently, hemorrhagic. They are localized to trauma-prone surfaces (Fig. 30.18), especially the elbows, knees, and dorsal aspects of the hands, feet and toes. Acral involvement may be mutilating, leading to a "mitten" deformity of the digits, syndactyly, nail dystrophy and complete nail loss. Scalp involvement occurs in up to 20% of patients, and, in isolated cases, extensive non-healing erosions with scarring alopecia have been described.

Other clinical variants include an "inflammatory" BP-like presentation[69,70] with widespread vesicles and bullae involving intertriginous and flexural areas that heal without milia or atrophic scars (Fig. 30.19), and a mucous membrane pemphigoid-like presentation, including the Brunsting–Perry pemphigoid phenotype with scarring alopecia[71]. Most of these patients are clinically indistinguishable from those with BP or mucous membrane pemphigoid. Of note, during the course of the disease, the clinical features can convert from one variant to another or, alternatively, a mixture of inflammatory and non-inflammatory features may coexist.

Mucous membrane involvement is variable. Erosions and intact vesicles may be seen in the mouth (Fig. 30.20), larynx and esophagus, and they may lead to dysphagia and laryngeal stenosis. Ocular involvement and blindness have been reported in the mucous membrane pemphigoid-like phenotype. Finally, features of childhood EBA have substantial overlap with those observed in childhood BP and linear IgA bullous dermatosis.

In anecdotal reports, a number of systemic diseases have been described in association with EBA, including inflammatory bowel disease, myeloma, systemic lupus erythematosus, rheumatoid arthritis, thyroiditis and diabetes mellitus. Among these, inflammatory bowel disease, particularly Crohn's disease, is the most frequently associated condition.

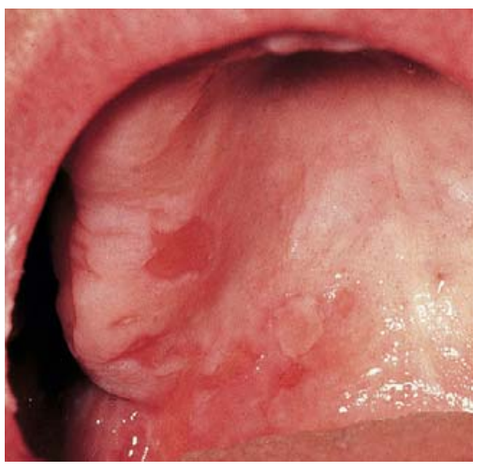


Fig. 30.20 Epidermolysis bullosa acquisita. Multiple erosions of the palate reminiscent of mucous membrane (cicatricial) pemphigoid. *Courtesy, C Prost, MD.*

Diagnosis and Differential Diagnosis

Light microscopy and electron microscopy

By light microscopy, biopsy specimens of bullae show a subepidermal cleavage without acantholysis. In the BP-like or mucous membrane pemphigoid-like variants of EBA, there is a variable inflammatory infiltrate within the dermis, composed of neutrophils, eosinophils or lymphocytes. In the mechanobullous, non-inflammatory lesions, there is a minimal-to-absent cellular infiltrate.

Electron microscopy studies of fresh vesicles demonstrate that dermal–epidermal cleavage occurs within the sublamina densa zone. In addition, a reduction in the number of anchoring fibrils may be observed. However, in some cases, separation within the lamina lucida has been noted, most likely reflecting the formation of a subepidermal blister at the *locus minoris resistentiae*. The cleavage plane is, therefore, not always a reliable criterion for discriminating EBA from other subepidermal bullous disorders.

Immunofluorescence microscopy

Direct IF microscopy studies of perilesional skin demonstrate IgG deposits distributed in a continuous, rather broad, linear pattern along the epidermal BMZ. Less commonly, linear deposits of C3, IgA or IgM

are found. In salt-split skin preparations of perilesional skin, the immune deposits are typically located on the dermal side of the cleavage. Finally, in EBA, the FOAM technique (see above), employing a confocal laser scanning microscope, localizes the immunoreactants to below the lamina densa in a relatively simple and inexpensive way, compared with electron microscopy.

By standard indirect IF, circulating anti-BMZ antibodies can be detected in approximately half of the patients with EBA. They are primarily of the IgG class, but circulating IgA autoantibodies have also been reported. By indirect IF on salt-split skin, circulating antibodies bind to the dermal side of the artificial blister[70]. Although rarely available, testing of patients' sera against a panel of skin substrate specimens lacking distinct basement membrane molecules (e.g. BP180, type VII collagen or laminin 5[332]) can prove helpful in characterizing the antigens targeted by circulating autoantibodies.

Immunoelectron microscopy

By immunogold techniques, which allow a more precise localization than direct immunoelectron microscopy utilizing peroxidase labeling, EBA autoantibodies specifically bind to the anchoring fibrils and the lamina densa where anchoring fibrils originate and terminate[72]. When circulating autoantibodies are absent and therefore cannot be characterized by indirect IF microscopy, immunoblotting studies or ELISA (see below), then immunoelectron microscopy constitutes the "gold standard" for the diagnosis of EBA.

Immunochemical studies

In Western immunoblotting studies of dermal extracts, circulating autoantibodies from patients with EBA bind to proteins of approximately 290 kDa and, less frequently, 145 kDa. These proteins have been clearly shown to correspond to type VII collagen and its NC1 N-terminal half, respectively[73,74]. Epitope mapping studies using recombinant forms of type VII collagen have demonstrated that immunodominant epitopes are located within the NC1 domain[75]. An ELISA utilizing a eukaryotic-expressed recombinant protein consisting of the entire NC1 domain has been found to be more sensitive than immunoblotting studies[76]. The advantage of this ELISA is that, in addition to its rapid performance and high specificity, antigens are tested under non-denaturing conditions; thus, reactivity against conformational epitopes is also assessed.

Differential diagnosis

EBA may be confused with inherited dystrophic epidermolysis bullosa, BP, mucous membrane pemphigoid, porphyria cutanea tarda, pseudoporphyria or rare variants of porphyria (e.g. porphyria variegata). Clinically, the mechanobullous type of EBA most closely resembles mild dominant dystrophic epidermolysis bullosa, but the lack of a family history, late onset, and the positive direct IF findings allow the distinction. The involvement of the hands may mimic porphyria cutanea tarda, but the latter can easily be excluded by porphyrin studies. Occasionally, patients with EBA on incriminating medications are misdiagnosed as having pseudoporphyria. The inflammatory type of EBA is clinically indistinguishable from BP or mucous membrane pemphigoid, including Brunsting–Perry pemphigoid. These conditions may be distinguished by using indirect IF (with salt-split skin as a substrate), BP180-NC16A ELISA, Western immunoblotting of both epidermal and dermal extracts, and direct immunoelectron microscopy studies.

Bullous systemic lupus erythematosus (SLE) usually presents as a transient, widespread, inflammatory subepidermal blistering condition (see Ch. 41), and, less frequently, as a mechanobullous eruption with milia and scarring[59]. In a number of these cases, circulating autoantibodies show binding activity with type VII collagen and the possibility of SLE–associated EBA might be considered. In addition to differences in histology, EBA in adults has a poor response to treatment, whereas a dramatic improvement following initiation of dapsone or azathioprine therapy is generally seen in patients with bullous SLE[77].

Treatment

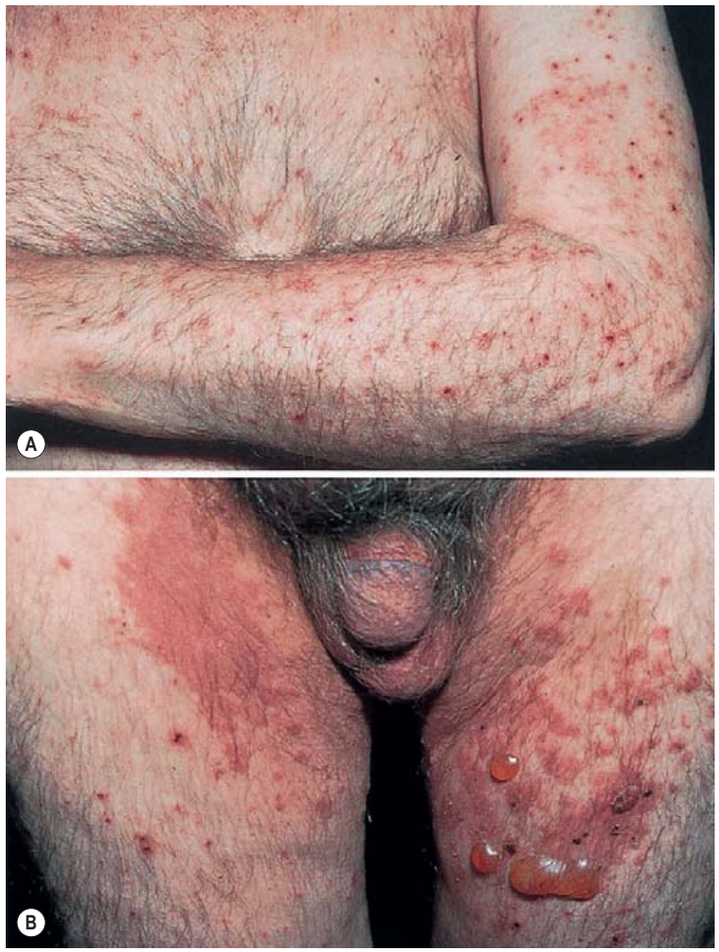
The treatment of EBA is difficult and often unsatisfactory. Because of the rarity of the condition, most data on treatment are based on anecdotal reports[62,69]. Systemic corticosteroids and standard immunosuppressive agents, such as azathioprine, methotrexate, mycophenolate mofetil and cyclophosphamide, are sometimes helpful in controlling the BP-like variant of EBA, which may go into remission. Colchicine, dapsone, gold, IVIg and cyclosporine have also been reported to have some benefit. A combination of dapsone and prednisolone has been recommended by some authors for the treatment of childhood EBA.

REFERENCES

1. Lever WF. Pemphigus. Medicine. 1953;32:1–123.
2. Jordon RE, Beutner EH, Witebsky E, et al. Basement zone antibodies in bullous pemphigoid. JAMA. 1967;200:751–6.
3. Giudice GJ, Emery DJ, Diaz LA. Cloning and primary structural analysis of the bullous pemphigoid autoantigen BP180. J Invest Dermatol. 1992;99:243–50.
4. Stanley JR, Tanaka T, Mueller S, et al. Isolation of complementary DNA for bullous pemphigoid antigen by use of patients' autoantibodies. J Clin Invest. 1988;82:1864–70.
5. Liu Z, Li N, Diaz LA, et al. Synergy between a plasminogen cascade and MMP-9 in autoimmune disease. J Clin Invest. 2005;115:879–87.
6. Marazza G, Pham HC, Schärer L, et al. Incidence of bullous pemphigoid and pemphigus in Switzerland: a 2-year prospective study. Br J Dermatol. 2009;161:861–8.
7. Delgado JC, Turbay D, Yunis EJ, et al. A common major histocompatibility complex class II allele HLA-DQB1*0301 is present in clinical variants of pemphigoid. Proc Natl Acad Sci U S A. 1996;93:8569–71.
8. Zillikens D, Rose PA, Balding SD, et al. Tight clustering of extracellular BP180 epitopes recognized by bullous pemphigoid autoantibodies. J Invest Dermatol. 1997;109:573–9.
9. Di Zenzo G, Grosso F, Terracina M, et al. Characterization of the anti-BP180 autoantibody reactivity profile and epitope mapping in bullous pemphigoid patients. J Invest Dermatol. 2004;122:103–10.
10. Hofmann S, Thoma-Uszynski S, Hunziker T, et al. Severity and phenotype of bullous pemphigoid relate to autoantibody profile against the NH2- and COOH-terminal regions of the BP180 ectodomain. J Invest Dermatol. 2002;119:1065–73.
11. Thoma-Uszynski S, Uter W, Schwietzke S, et al. BP230- and BP180-specific auto-antibodies in bullous pemphigoid. J Invest Dermatol. 2004;122:1413–22.
12. Di Zenzo G, Thoma-Uszynski S, Fontao L, et al. Multicenter prospective study of the humoral autoimmune response in bullous pemphigoid. Clin Immunol. 2008;128:415–26.
13. Thoma-Uszynski S, Uter W, Schwietzke S, et al. Autoreactive T and B cells from bullous pemphigoid (BP) patients recognize epitopes clustered in distinct regions of BP180 and BP230. J Immunol. 2006;176:2015–23.
14. Shimanovich I, Mihai S, Oostingh GJ, et al. Granulocyte-derived elastase and gelatinase B are required for dermal-epidermal separation induced by autoantibodies from patients with epidermolysis bullosa acquisita and bullous pemphigoid. J Pathol. 2004;204:519–27.
15. Zone JJ, Taylor T, Hull C, et al. IgE basement membrane zone antibodies induce eosinophil infiltration and histological blisters in engrafted human skin on SCID mice. J Invest Dermatol. 2007;127:1167–74.
16. Schmidt E, Reimer S, Kruse N, et al. Autoantibodies to BP180 associated with bullous pemphigoid release interleukin-6 and interleukin-8 from cultured human keratinocytes. J Invest Dermatol. 2000;115:842–8.
17. Iwata H, Kamio N, Aoyama Y, et al. IgG from patients with bullous pemphigoid depletes cultured keratinocytes of the 180-kDa bullous pemphigoid antigen (type XVII collagen) and weakens cell attachment. J Invest Dermatol. 2009;129:919–26.
18. Nishie W, Sawamura D, Goto M, et al. Humanization of autoantigen. Nat Med. 2007;13:378–83.
19. Kiss M, Husz S, Janossy T, et al. Experimental bullous pemphigoid generated in mice with an antigenic epitope of the human hemidesmosomal protein BP230. J Autoimmun. 2005;24:1–10.
20. Di Zenzo G, Marazza G, Borradori L. Bullous pemphigoid: physiopathology, clinical features and management. Adv Dermatol. 2007;23:257–88.
21. Taylor G, Venning V, Wojnarowska F, et al. Bullous pemphigoid and autoimmunity. J Am Acad Dermatol. 1993;29:181–4.
22. Chan LS, Vanderlugt CJ, Hashimoto T, et al. Epitope spreading: lessons from autoimmune skin diseases. J Invest Dermatol. 1998;110:103–9.
23. Langan SM, Groves RW, West J. The relationship between neurological disease and bullous pemphigoid: a population-based case-control study. J Invest Dermatol. 2011;131:631–6.
24. Bastuji-Garin S, Joly P, Lemordant P, et al. Risk Factors for bullous pemphigoid in the elderly. A prospective case-control study. J Invest Dermatol. 2011;131:637–43.
25. Vodegel RM, Jonkman MF, Pas HH, de Jong MC. U-serrated immunodeposition pattern differentiates type VII collagen targeting bullous diseases from other subepidermal bullous autoimmune diseases. Br J Dermatol. 2004;151:112–18.
26. De Jong MC, Bruins S, Heeres K, et al. Bullous pemphigoid and epidermolysis bullosa acquisita. Differentiation by fluorescence overlay antigen mapping. Arch Dermatol. 1996;132:151–7.
27. Ishiko A, Shimizu H, Kikuchi A, et al. Human autoantibodies against the 230-kD bullous pemphigoid antigen (BPAG1) bind only to the intracellular domain of the hemidesmosome, whereas those against the 180-kD bullous pemphigoid antigen (BPAG2) bind along the plasma membrane of the hemidesmosome in normal human and swine skin. J Clin Invest. 1993;91:1608–15.
28. Joly P, Courville P, Lok C, et al. Clinical criteria for the diagnosis of bullous pemphigoid: a reevaluation according to immunoblot analysis of patient sera. Dermatology. 2004;208:16–20.

29. Dilling A, Rose C, Hashimoto T, et al. Anti-p200 pemphigoid: a novel autoimmune subepidermal blistering disease. J Dermatol. 2007;34:1–8.
30. Dainichi T, Kurono S, Ohyama B, et al. Anti-laminin gamma-1 pemphigoid. Proc Natl Acad Sci U S A. 2009;106:2800–5.
31. Bystryn JC, Rudolph JL. Why is the mortality of bullous pemphigoid greater in Europe than in the US? J Invest Dermatol. 2005;124:xx–xxi.
32. Joly P, Benichou J, Lok C, et al. Prediction of survival for patients with bullous pemphigoid: a prospective study. Arch Dermatol. 2005;141:691–8.
33. Bernard P, Reguiai Z, Tancrède-Bohin E, et al. Risk factors for relapse in patients with bullous pemphigoid in clinical remission: a multicenter, prospective, cohort study. Arch Dermatol. 2009;145:537–42.
34. Roujeau JC, Guillaume JC, Morel P, et al. Plasma exchange in bullous pemphigoid. Lancet. 1984;2: 486–8.
35. Morel P, Guillaume JC. Treatment of bullous pemphigoid with prednisolone only: 0.75mg/kg/day versus 1.25mg/kg/day. A multicenter randomized study. Ann Dermatol Venereol. 1984;111:925–8.
36. Guillot B, Donadio D, Guilhou JJ, et al. Long term plasma exchange therapy in bullous pemphigoid. Acta Derm Venereol. 1986;66:73–5.
37. Dreno B, Sassolas B, Lacour P, et al. Methylprednisolone versus prednisolone methylsulfobenzoate in pemphigoid: a comparative multicenter study. Ann Dermatol Venereol. 1993;120:518–21.
38. Guillaume JC, Vaillant L, Bernard P, et al. Controlled trial of azathioprine and plasma exchange in addition to prednisolone in the treatment of bullous pemphigoid. Arch Dermatol. 1993;129:49–53.
39. Fivenson DP, Breneman DL, Rosen GB, et al. Nicotinamide and tetracycline therapy of bullous pemphigoid. Arch Dermatol. 1994;130:753–8.
40. Joly P, Roujeau JC, Benichou J, et al. A comparison of oral and topical corticosteroids in patients with bullous pemphigoid. N Engl J Med. 2002;346:321–7.
41. Beissert S, Werfel T, Frieling U, et al. A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of bullous pemphigoid. Arch Dermatol. 2007;143:1536–42.
42. Joly P, Roujeau JC, Benichou J, et al. A comparison of two regimens of topical corticosteroids in the treatment of patients with bullous pemphigoid: a multicenter randomized study. J Invest Dermatol. 2009;129:1681–7.
43. Chan LS, Yancey KB, Hammerberger C, et al. Immune-mediated subepithelial blistering diseases of mucous membranes. Pure ocular cicatricial pemphigoid is a unique clinical and immunopathological entity distinct from bullous pemphigoid and other subsets identified by antigenic specificity of autoantibodies. Arch Dermatol. 1993;129:448–55.
44. Bernard P, Vaillant L, Labeille B, et al. Incidence and distribution of subepidermal autoimmune bullous skin diseases in three French regions. Bullous Diseases French Study Group. Arch Dermatol. 1995;131: 48–52.
45. Yunis JJ, Mobini N, Yunis EJ, et al. Common major histocompatibility complex class II markers in clinical variants of cicatricial pemphigoid. Proc Natl Acad Sci U S A. 1994;91:7747–51.
46. Egan CA, Lazarova Z, Darling TN, et al. Anti-epiligrin cicatricial pemphigoid and relative risk for cancer. Lancet. 2001;357:1850–1.
47. Bedane C, McMillan J, Balding S, et al. Bullous pemphigoid and cicatricial pemphigoid autoantibodies react with ultrastructurally separable epitopes on the BP180 ectodomain: evidence that BP180 spans the lamina lucida. J Invest Dermatol. 1997;108:901–7.
48. Black AP, Seneviratne SL, Jones L, et al. Rapid effector function of circulating NC16A-specific T cells in individuals with mucous membrane pemphigoid. Br J Dermatol. 2004;151:1160–4.
49. Razzaque MS, Foster CS, Ahmed AR. Role of collagen-binding heat shock protein 47 and transforming growth factor-beta1 in conjunctival scarring in ocular cicatricial pemphigoid. Invest Ophthalmol Vis Sci. 2003;44:1616–21.
50. Egan CA, Lazarova Z, Darling TN, et al. Anti-epiligrin cicatricial pemphigoid: clinical findings, immunopathogenesis, and significant associations. Medicine (Baltimore). 2003;82:177–86.
51. Lazarova Z, Hsu R, Yee C, Yancey KB. Human anti-laminin 5 autoantibodies induce subepidermal blisters in an experimental human skin graft model. J Invest Dermatol. 2000;114:178–84.
52. Bhol KC, Dans MJ, Simmons RK, et al. The autoantibodies to $\alpha_6\beta_4$ integrin of patients affected by ocular cicatricial pemphigoid recognize predominantly epitopes within the large cytoplasmic domain of human β_4. J Immunol. 2000;165:2824–9.
53. Bernard P, Prost C, Durepaire N, et al. The major cicatricial pemphigoid antigen is a 180-kD protein that shows immunologic cross-reactivities with the bullous pemphigoid antigen. J Invest Dermatol. 1992;99:174–9.
54. Fleming TE, Korman NJ. Cicatricial pemphigoid. J Am Acad Dermatol. 2000;43:571–91.
55. Person JR, Rogers RS III. Bullous and cicatricial pemphigoid. Clinical, histopathologic, and immunopathologic correlations. Mayo Clin Proc. 1977;52:54–66.
56. Foster CS. Cicatricial pemphigoid. Trans Am Ophthalmol Soc. 1986;84:527–63.
57. Setterfield J, Shirlaw PJ, Kerr-Muir M, et al. Mucous membrane pemphigoid: a dual circulating antibody response with IgG and IgA signifies a more severe and persistent disease. Br J Dermatol. 1998;138:602–10.
58. Vodegel RM, de Jong MC, Pas HH, et al. Anti-epiligrin cicatricial pemphigoid and epidermolysis bullosa acquisita: differentiation by use of indirect immunofluorescence microscopy. J Am Acad Dermatol. 2003;48:542–7.
59. Murakami H, Nishioka S, Setterfield J, et al. Analysis of antigens targeted by circulating IgG and IgA autoantibodies in 50 patients with cicatricial pemphigoid. J Dermatol Sci. 1998;17:39–44.
60. Yeh SW, Usman AQ, Ahmed AR. Profile of autoantibody to basement membrane zone proteins in patients with mucous membrane pemphigoid: long-term follow-up and influence of therapy. Clin Immunol. 2004;112: 268–72.
61. Lazarova Z, Salato VK, Lanschuetzer CM, et al. IgG anti-laminin-332 autoantibodies are present in a subset of patients with mucous membrane, but not bullous, pemphigoid. J Am Acad Dermatol. 2008;58:951–8.
62. Kirtschig G, Murrell DF, Wojnarowska F, et al. Interventions for mucous membrane pemphigoid and epidermolysis bullosa acquisita. Cochrane Database of Systematic Reviews, 2009, Issue 2.
63. Letko E, Miserocchi E, Daoud YJ, et al. A nonrandomized comparison of the clinical outcome of ocular involvement in patients with mucous membrane (cicatricial) pemphigoid between conventional immunosuppressive and intravenous immunoglobulin therapies. Clin Immunol. 2004;111:303–10.
64. Canizares MJ, Smith DI, Conners MS, et al. Successful treatment of mucous membrane pemphigoid with etanercept in 3 patients. Arch Dermatol 2006;142:1457–61.
65. Le Roux-Villet C, Prost-Squarcioni C, Alexandre M, et al. Rituximab for patients with refractory mucous membrane pemphigoid. Arch Dermatol. 2011;147:843–9.
66. Woodley DT, Chang C, Saadat P, et al. Evidence that anti-type VII collagen antibodies are pathogenic and responsible for the clinical, histological and immunological features of epidermolysis bullosa acquisita. J Invest Dermatol. 2005;124:958–64.
67. Sitaru C, Chiriac MT, Mihai S, et al. Induction of complement-fixing autoantibodies against type VII collagen results in subepidermal blistering in mice. J Immunol. 2006;177:3461–8.
68. Sitaru C. Experimental models of epidermolysis bullosa acquisita. Exp Dermatol. 2007;16:520–31.
69. Briggaman RA, Gammon WR, Woodley DT. Epidermolysis bullosa acquisita of the immunopathological type (dermolytic pemphigoid). J Invest Dermatol. 1985;85(suppl. 1):79s–84s.
70. Gammon WR, Briggaman RA, Inman AO III, et al. Differentiating anti-lamina lucida and anti-sublamina densa anti-basement zone antibodies by indirect immunofluorescence on 1.0M sodium chloride-separated skin. J Invest Dermatol. 1984;82:139–44.
71. Kurzhals G, Stolz W, Meurer M, et al. Acquired epidermolysis bullosa with the clinical feature of Brunsting-Perry cicatricial bullous pemphigoid. Arch Dermatol. 1991;127:391–5.
72. Ishiko A, Hashimoto T, Shimizu H, et al. Epidermolysis bullosa acquisita: report of a case with comparison of immunogold electron microscopy using pre- and postembedding labelling. Br J Dermatol. 1996;134:147–51.
73. Parente M, Chung L, Ryynanen J, et al. Human type VII collagen: cDNA cloning and chromosomal mapping of the gene. Proc Natl Acad Sci U S A. 1991;88:6931–5.
74. Woodley D, Briggaman RA, O'Keefe E, et al. Identification of the skin basement-membrane autoantigen in epidermolysis bullosa acquisita. N Engl J Med. 1984;310:1007–13.
75. Lapiere JC, Woodley DT, Parente M, et al. Epitope mapping of type VII collagen. J Clin Invest. 1993;92:1831–9.
76. Chen M, Chan LS, Cai X, et al. Development of an ELISA for rapid detection of anti-type VII collagen autoantibodies in epidermolysis bullosa acquisita. J Invest Dermatol. 1997;108:68–72.
77. Gammon WR, Briggaman RA. Epidermolysis bullosa acquisita and bullous systemic lupus erythematosus. Dermatol Clin. 1993;11:535–47.

Bullous pemphigoid – progression of disease. A Urticarial, infiltrated and annular erythematous plaques on the trunk and upper extremity. **B** Generalized eruption with blisters as well as numerous erosions and hemorrhagic crusts in the same patient later in the course of the disease.



Bullous pemphigoid. A Excoriated eczematous lesions on the upper extremity. **B** Confluent plaques with tense blisters in the inguinal area and inner aspect of the thighs in the same patient.

Dermatitis Herpetiformis and Linear IgA Bullous Dermatosis

31

Christopher M Hull and John J Zone

Chapter Contents

Dermatitis herpetiformis 491
Linear IgA bullous dermatosis 496

Key features

- Dermatitis herpetiformis (DH) is differentiated from linear IgA bullous dermatosis (LABD) on the basis of granular IgA versus linear IgA deposition at the basement membrane zone, as observed by direct immunofluorescence
- DH is a cutaneous manifestation of celiac disease (CD) and is associated with gluten sensitivity in virtually all cases
- DH and CD are genetic disorders strongly associated with the HLA-DQ2 genotype, in which IgA anti-endomysial antibodies are directed against *tissue* transglutaminase; the presumed autoantigen within the skin is *epidermal* transglutaminase
- The intestinal and cutaneous disease in DH can be controlled by gluten restriction; both DH and LABD respond to sulfone therapy
- In adults, LABD is frequently drug-induced

DERMATITIS HERPETIFORMIS

Synonym: ■ Duhring's disease

Introduction

Dermatitis herpetiformis (DH) is a cutaneous manifestation of gluten sensitivity. Although over 90% of DH patients have evidence of a gluten-sensitive enteropathy, only about 20% have intestinal symptoms of celiac disease (CD). Both the skin disease and the intestinal disease respond to gluten restriction and recur with institution of a gluten-containing diet.

Four findings support the diagnosis of DH:

- pruritic papulovesicles or excoriated papules on extensor surfaces
- neutrophilic infiltration of the dermal papillae with vesicle formation at the dermal–epidermal junction
- granular deposition of IgA within the dermal papillae of clinically normal-appearing skin adjacent to a lesion
- a response of the skin disease, but not the intestinal disease, to dapsone therapy.

Although DH is usually a lifelong condition, the course may wax and wane. A spontaneous remission may occur in up to 10% of patients, but most clinical remissions are related to dietary gluten restriction[1].

History

Dr Louis Duhring described DH at the University of Pennsylvania in 1884. It was the first skin disease described by an American dermatologist. The subsequent critical discoveries in our understanding of DH are listed in Table 31.1.

Epidemiology

DH occurs most commonly in people of northern European origin. It is uncommon in African-Americans and Asians. According to a study in Finland in 1978, the prevalence of DH is 10.4 per 100 000 individuals and the annual incidence is 1.3 per 100 000. The mean age of onset is during the fourth decade, but it may first appear from age 2 to 90 years. Adolescent and prepubescent children are infrequently affected. Men outnumber women two to one, but in children with DH, there is a female preponderance. From 1979 to 1996, the familial incidence of DH in Finland was studied prospectively. DH was diagnosed in 1018 patients and 10.5% of these patients had one or more affected first-degree relatives[2].

With regard to the US, a study in Utah (1987) found a prevalence of 11.2 per 100 000. The incidence during the years 1978 to 1987 was 0.98 per 100 000 per year. Mean age of onset for men was 40.1 years and for women was 36.2 years. The male-to-female ratio was 1.44 : 1[3].

Pathogenesis

Our knowledge of the pathogenesis of DH is based on a number of clinical and laboratory observations. The key observations that have been integrated into theories of pathogenesis are:

- a strong genetic association with the HLA genotype DQ A1 *0501, B1 *02 (which encodes HLA-DQ2 heterodimers), in addition to other unidentified non-HLA genes
- some degree of gluten-sensitive enteropathy on small bowel biopsy in virtually all patients, accompanied by stimulation of the mucosal immune system
- granular IgA deposition within the papillary dermis of the skin (this is essential for the diagnosis and occurs at the site of eventual inflammation)
- neutrophilic infiltration into the dermal papillae
- improvement of symptoms with dapsone therapy and worsening of symptoms with inorganic iodide ingestion.

Genetic predisposition

Specific HLA genes, which encode molecules that interact with T-cell receptors, are believed to provide the antigenic specificity that processes the gliadin antigen in genetically susceptible individuals. This HLA association is the same for patients with CD and DH. Genes encoding the DQ2 (A1 *0501, B1 *02) heterodimer are carried by 90% of CD and DH patients. Genes encoding the DQ8 (A1 *03, B1 *03) heterodimer are carried by the remaining DH patients[4]. Previous descriptions of associations with HLA-B8, as well as HLA-DR3 and HLA-DR5/DR7, represent class I and class II molecules that are in linkage dysequilibrium with DQ2. However, it has been established that less than 50% of the genetic predisposition in CD and DH is due to specific HLA genes. Genomic searches for non-HLA genes are currently underway and a susceptibility locus for CD (chromosome 4q27) has been proposed which includes the genes for IL-2 and IL-21[5]. Monozygotic twins, one with DH and the other with CD, have been reported, indicating that environmental as well as genetic factors play a role in the development of CD and/or its extraintestinal manifestation, DH[6].

Gluten-sensitive enteropathy

On small bowel biopsy, more than 90% of DH patients have some degree of gluten-sensitive enteropathy. The bowel abnormality is caused by gluten, a family of grain proteins present in wheat, rye, barley and hybrids of these grains (e.g. kamut, spelt and triticale), but not oats. Gliadin is the alcohol-soluble fraction of gluten and is believed to be the antigenic component. The spectrum of intestinal involvement ranges from minimal infiltration of the lamina propria by lymphocytes (with normal villi), to minimal atrophy of the jejunum accompanied by intraepithelial lymphocytic infiltrates, to total villous atrophy of the

DERMATITIS HERPETIFORMIS – HISTORIC LANDMARKS	
1884	Louis Adolphus Duhring of Philadelphia described in detail "dermatitis herpetiformis" (DH)
1888	Jean Louis Brocq of Paris renamed the condition "dermatite polymorphe prurigineuse"
1890	T Caspar Gilchrist outlined the histologic changes of DH, which were included in the 1897 edition of Duhring's textbook *Cutaneous Medicine: A Systemic Treatise on Diseases of the Skin*
1940	Sulfapyridine was reported to be an effective treatment for DH. The clinical response to sulfapyridine became a diagnostic test
1950	Dicke, a Dutch pediatrician, observed that patients with celiac disease (CD) improved during World War II when bread was in short supply, and their disease worsened when grain supplies were restored
1953	Diamino-diphenyl sulfone (dapsone), the parent compound of sulfapyridine, also proved to be effective in DH
1969	JB van der Meer demonstrated IgA deposits in the papillae of uninvolved skin in DH
1967	Independent accounts connect DH with CD
1972	Stephen Katz links DH to the HLA-B8 antigen. This strengthens the association between CD and DH
1986	IgA class anti-endomysial antibodies were found to be highly specific for DH and CD
1997	DH and CD were found to have a common immunogenetic background with strict association with HLA alleles DQ A1 *0501 and B1 *02, which encode HLA-DQ2 heterodimers
2003	Epidermal transglutaminase was identified as an autoantigen in DH

Table 31.1 Dermatitis herpetiformis – historic landmarks.

small intestine. The enteropathy is often patchy and may require multiple small bowel samples for diagnosis. Symptomatic malabsorption occurs in 20% of patients with DH.

The proposed pathogenesis of DH and CD is presented in Figure 31.1. Following ingestion of gluten-containing grains (see above), one of the products of digestion is gliadin (Fig. 31.1A). Once gliadin is absorbed via the lamina propria, glutamine residues within gliadin are deamidated by tissue transglutaminase (TG2) and covalent cross-links (isopeptidyl bonds) are formed between lysine residues in TG2 and glutamines in gliadin. Deamidation by TG2 is thought to be a critical step as it serves to optimize antigen presentation.

Deamidated gliadin peptides bind to the groove of the HLA-DQ2 molecule on dendritic antigen-presenting cells (Fig. 31.1B), and the gliadin antigen is then presented to sensitized helper T cells in the context of HLA-DQ2 specificity. These helper T cells can stimulate B cells, with differentiated plasma cells producing IgA antibodies to multiple antigens, including gliadin, gliadin cross-linked to TG2, TG2, and epidermal transglutaminase (TG3). In addition, stimulated natural killer lymphocytes cause crypt hyperplasia and villous atrophy. Of note, IgA anti-TG2 antibodies have become the serologic hallmark for CD.

In the setting of continued exposure to gliadin, epitope spreading is thought to lead to development of IgA anti-TG3 antibodies in patients who already have IgA anti-TG2 antibodies; a subgroup of those who develop IgA anti-TG3 antibodies then develop DH (see Fig. 31.1). Epitope spreading is a possible explanation for why DH tends to present at a later age than symptomatic CD (the latter often manifests in childhood) and why patients with CD (but not DH) tend to have more severe intestinal disease than patients with DH. Formation of IgA anti-TG3 antibodies is thought to require time and continued exposure to gluten and this would be more likely to occur in patients with less severe, relatively asymptomatic intestinal involvement. Findings in support of

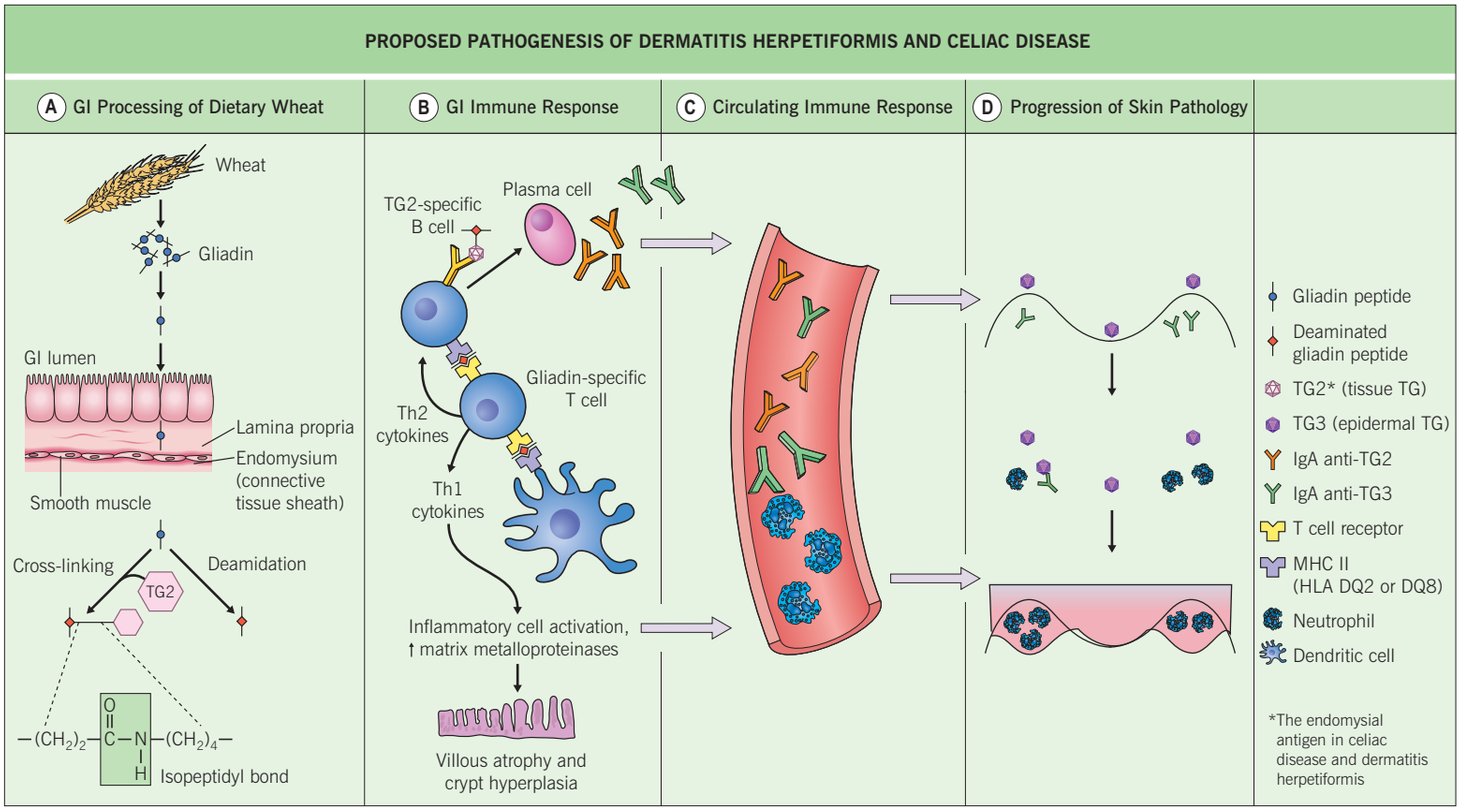


Fig. 31.1 Proposed pathogenesis of dermatitis herpetiformis and celiac disease. A Dietary wheat, barley or rye is processed by digestive enzymes into antigenic gliadin peptides, which are transported intact across the mucosal epithelium. Within the lamina propria, tissue transglutaminase (TG2): (1) deamidates glutamine residues within gliadin peptides to glutamic acid; and (2) becomes covalently cross-linked to gliadin peptides via isopeptidyl bonds (formed between gliadin glutamine and TG2 lysine residues). **B** $CD4^+$ T cells in the lamina propria recognize deamidated gliadin peptides presented by HLA-DQ2 or -DQ8 molecules on antigen-presenting cells, resulting in the production of Th1 cytokines and matrix metalloproteinases that cause mucosal epithelial cell damage and tissue remodeling. In addition, TG2-specific B cells take up TG2–gliadin complexes and present gliadin peptides to gliadin-specific helper T cells, which stimulate the B cells to produce IgA anti-TG2. **C** Over time, IgA directed against TG3 (IgA anti-TG3) forms as a result of epitope spreading and both IgA anti-TG2 and IgA anti-TG3 circulate in the bloodstream. **D** When IgA anti-TG3 antibodies reach the dermis, they complex with TG3 antigens which have been produced by keratinocytes (epidermal TG) and then have diffused into the dermis. That is, IgA/TG3 immune complexes are formed *locally* within the papillary dermis. This leads to neutrophil chemotaxis (with formation of neutrophilic abscesses), proteolytic cleavage of the lamina lucida, and subepidermal blister formation.

AUTOIMMUNE DISORDERS ASSOCIATED WITH DERMATITIS HERPETIFORMIS
COMMON
• Autoimmune thyroid disease (Hashimoto's thyroiditis) • Insulin-dependent diabetes mellitus
UNCOMMON
• Pernicious anemia
RARE
• Addison's disease • Autoimmune chronic active hepatitis • Alopecia areata • Myasthenia gravis • Sarcoidosis • Systemic sclerosis (scleroderma) • Sjögren's syndrome • Systemic lupus erythematosus • Vitiligo

Table 31.2 Autoimmune disorders associated with dermatitis herpetiformis.

this theory include the presence of IgA anti-TG2 antibodies in most DH patients and a higher prevalence of IgA anti-TG3 antibodies in adults than in children with CD (i.e. developing later in the evolution of the disease).

The formation of IgA anti-TG3 antibodies also activates circulating neutrophils (Fig. 31.1C). Deposition of these antibodies within the dermal papillae results in the infiltration of activated neutrophils from the circulation into the dermal papillae (Fig. 31.1D). Degranulation of neutrophils releases proteases which disrupt the lamina lucida and produce a subepidermal blister.

Since both the skin disease and the intestinal disease resolve with dietary gluten restriction and recur with return to a regular diet, it is clear that the dietary protein gluten is central to the pathogenesis of the cutaneous eruption. In addition, it is the HLA class II antigen that acts as a gate through which gluten can reach the inflammatory cells and initiate the autoimmune process[7,8].

Circulating antibodies

The first serologic difference between DH and CD was initially described in 2002, with TG3 identified as the autoantigen in DH[9]. Additional studies have demonstrated that IgA anti-TG3 antibodies not only are elevated in patients with DH, but also represent a sensitive serologic assay[10,11]. TG3 was also found to co-localize with IgA in dermal papillae of DH patients (see Fig. 31.5)[9,12]. TG3 is expressed in many tissues of the body, including the epidermis. When IgA anti-TG3 antibodies reach the dermis, they complex with TG3 antigens which have been produced by keratinocytes (epidermal TG) and then have diffused into the dermis. In other words, IgA/TG3 immune complexes are formed *locally* within the papillary dermis (see Fig. 31.1D). Circulating immune complexes are not known to be involved in the deposition of these immune complexes in the papillary dermis.

Granular IgA deposition

Granular IgA deposition within dermal papillae is the hallmark of DH (see Fig. 31.5). The deposits are composed of IgA1 antibodies directed against TG3 antigen that has diffused from the epidermis. Circulating IgA antibodies to TG2 (an endomysial antigen) have been identified by indirect immunofluorescence microscopy using a monkey esophagus substrate, and the presence of these antibodies correlates with the degree of gluten-sensitive enteropathy. IgA anti-TG2 antibodies are not responsible for the IgA deposition in skin.

Iodide and dapsone

Ingestion of iodide can lead to worsening of DH and topical application of iodide onto the normal skin of DH patients produces lesions that are histologically identical to spontaneous lesions[13]. Even in normal subjects, topical iodides may produce follicular neutrophilic pustules. The mechanism by which iodide stimulates neutrophil infiltration into the skin is unclear. Dapsone is known to have an effect on neutrophil

Fig. 31.2 Dermatitis herpetiformis. A A few pink papulovesicles, erosions and hemorrhagic crusts on the elbow. **B** Multiple urticarial pink papules on the knee, in addition to a few erosions and small subtle intact vesicles (arrows); a collarette of scale is seen at the site of a previous vesicle. **C** Pink plaques on the knee composed of grouped papules and papulovesicles, admixed with tiny hemorrhagic crusts. *C, Courtesy, Thomas Horn, MD.*

Fig. 31.3 Dermatitis herpetiformis. **A** Grouped pink papulovesicles on the upper back, neck and scalp in a child. **B** Pruritic pink papules on the buttocks, some of which have central hemorrhagic crusts. *B, Courtesy, Louis A Fragola, Jr, MD.*

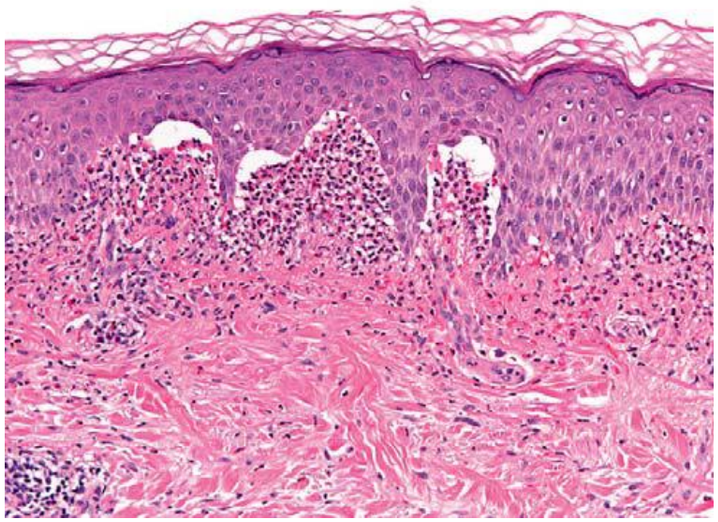


Fig. 31.4 Dermatitis herpetiformis – histopathologic features. Subepidermal clefts beneath which are collections of neutrophils within dermal papillae. Scattered eosinophils are also present. *Courtesy, Lorenzo Cerroni, MD.*

chemotaxis and neutrophil attachment to IgA *in vitro*[14]. Although the exact mechanism of its beneficial effect in DH is unknown, it seems likely that dapsone blocks the neutrophil-mediated inflammatory process.

Associated Disorders and Malignancies

A strong association exists between DH and thyroid disease, particularly Hashimoto's thyroiditis. In one study, the presence of some type of thyroid abnormality was found in 26 of 50 patients with DH[15]. Although the pathogenetic relationship between DH and thyroid disease is unknown, it may represent a coexistence of autoimmune disease[15]. The incidence of enteropathy-associated T-cell lymphoma is also increased in patients with DH and warrants increased surveillance. Of note, adhering to a gluten-free diet protects against lymphoma in this population. This further supports advising patients with DH to adhere to a strict gluten-free diet for life. Other autoimmune disorders reported to be associated with DH and CD are listed in Table 31.2.

Clinical Features

DH has a symmetric distribution and favors the elbows, extensor forearms, back, buttocks and knees (Figs 31.2 & 31.3). Isolated scalp involvement is an occasional clinical presentation. The primary lesions are pleomorphic, with urticarial plaques, papules and vesicles. Grouped or "herpetiform" papulovesicles with an erythematous base are characteristic of this autoimmune disorder. Intense pruritus leads to secondary excoriation and crusting. Even if only hemorrhagic crusts or secondary changes from scratching are present, the diagnosis should be suspected on the basis of the distribution of lesions. Less common presentations are isolated facial involvement, exclusively macular lesions, and hemorrhagic acral macules (usually palmoplantar).

Pathology

For routine histology, it is optimal to capture a small, intact vesicle. If this is not available, an area of erythema should be biopsied. Areas of erythema will show dermal papillary edema and neutrophil infiltration associated with a superficial perivascular lymphocytic infiltrate. When an intact vesicle is biopsied, a subepidermal blister containing predominantly neutrophils will be seen (Fig. 31.4).

In patients with DH, IgA is not uniformly distributed throughout the skin. IgA deposits are present in greater amounts near active lesions. The optimal biopsy site for direct immunofluorescence (DIF) testing is normal-appearing skin immediately adjacent to a lesion. A false-negative DIF can occur if lesional skin is biopsied, since the inflammatory infiltrate can destroy the IgA[16]. A definitive diagnosis of DH cannot be made without this diagnostic DIF finding. Granular IgA deposits localized to the dermal papillae are found in 85% of cases of DH (Fig. 31.5), while continuous granular deposition of IgA along the basement membrane occurs in 5% to 10% of cases. A fibrillar pattern of IgA deposition occurs rarely.

The lack of histologic and immunopathologic confirmation is a source of misdiagnosis and confusion in DH. Since DH is a lifelong diagnosis with significant systemic and therapeutic implications, definitive immunopathologic confirmation of the diagnosis is essential in all cases.

Laboratory evaluation

Anti-endomysial antibodies are very specific for CD and DH. Their levels indicate the severity of the gluten-sensitive enteropathy and reflect the degree of compliance to dietary gluten restriction. Anti-endomysial antibodies are found in approximately 80% of patients with DH and >95% of patients with active CD. The endomysium is the connective tissue covering the smooth muscle layers of the esophagus, stomach and small intestine (see Fig. 31.1A). Studies have confirmed a high sensitivity and specificity for IgA class antireticulin and anti-endomysial antibodies in DH patients with villous atrophy.

The endomysial antigen has been identified as TG2, and antibodies directed against transglutaminase are important in the pathogenesis of DH and CD (see Pathogenesis section). The normal physiologic function of transglutaminase is to repair injured tissue by cross-linking extracellular matrix proteins in the tissue, protecting the surrounding tissue from further damage. Transglutaminase facilitates the linkage of the carboxamide group of the amino acid glutamine, found in gluten,

to an ε-amino group of a lysine residue in transglutaminase located in the intestinal tract (see Fig. 31.1A). The glutamine in gliadin is especially vulnerable to a cross-linkage with transglutaminase, and this linkage is perceived as a foreign antigen by the host immune system. As antibodies to transglutaminase are produced, the normal function of transglutaminase in repairing the damaged intestinal mucosa is impaired.

An approach to the patient with suspected DH is outlined in Figure 31.6.

Differential Diagnosis

The differential diagnosis includes erythema multiforme, bullous lupus erythematosus, linear IgA bullous dermatosis (LABD) and bullous pemphigoid. Table 31.3 outlines the clinical and histologic features that help differentiate DH from LABD and bullous pemphigoid. Erythema multiforme is characterized by target lesions that are often acral in distribution and show vacuolar degeneration and epidermal necrosis histologically; also there are no IgA deposits at the basement membrane zone (BMZ; see Ch. 20). Bullous lupus erythematosus presents with urticarial papules and vesicles on an erythematous base and a histologic picture similar to LABD and DH. However, the patients have clinical and serologic findings of systemic lupus erythematosus. DIF reveals multiple immunoglobulins (including IgA) in a granular and band-like pattern along the BMZ, whereas in LABD there is a fine linear IgA deposition.

Crusted papules are also seen on the elbows and knees in patients with Wegener's granulomatosis and Churg–Strauss syndrome, but histologic features of vasculitis are observed. Additional entities in the differential diagnosis include urticarial vasculitis, scabies and arthropod bites.

Treatment

The treatment of DH includes dapsone and a gluten-free diet, as well as a combination of the two therapies. The pruritus of DH is relieved within 48–72 hours of instituting dapsone (4′,4′ diamino-diphenyl sulfone). The lesions abruptly recur within 24–48 hours of discontinuation of therapy. Unfortunately, dapsone has no effect on the intestinal pathology.

Dapsone is begun after screening for glucose-6-phosphate dehydrogenase (G6PD) deficiency, with initial dosages of 25–50 mg in adults and 0.5 mg/kg in children. Initiation of therapy with higher doses may precipitate severe hemolysis and cardiac decompensation in susceptible individuals. The average maintenance dose in adults on a normal diet is 100 mg daily. The half-life ranges from 12 to 24 hours, so divided doses are seldom of benefit. The daily dose can be regulated on a weekly

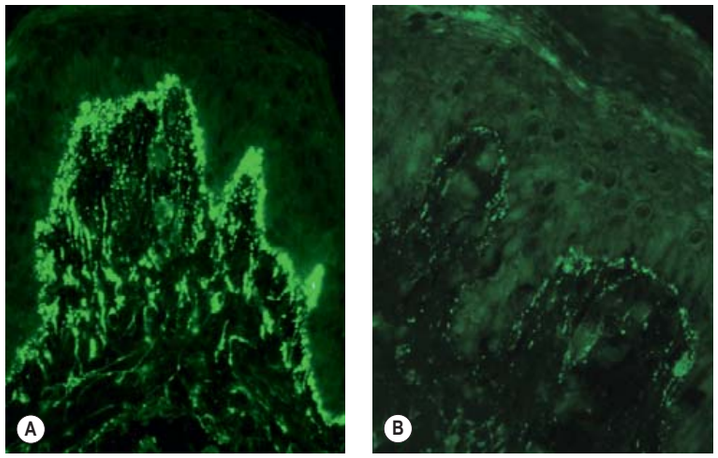


Fig. 31.5 Dermatitis herpetiformis – direct immunofluorescence. **A** Granular IgA deposition along the dermal–epidermal junction of normal-appearing skin adjacent to a lesion. **B** Granular deposition of epidermal transglutaminase (TG3) within the dermal papillae, which co-localizes with the IgA. *A, Courtesy, Kristin Leiferman, MD.*

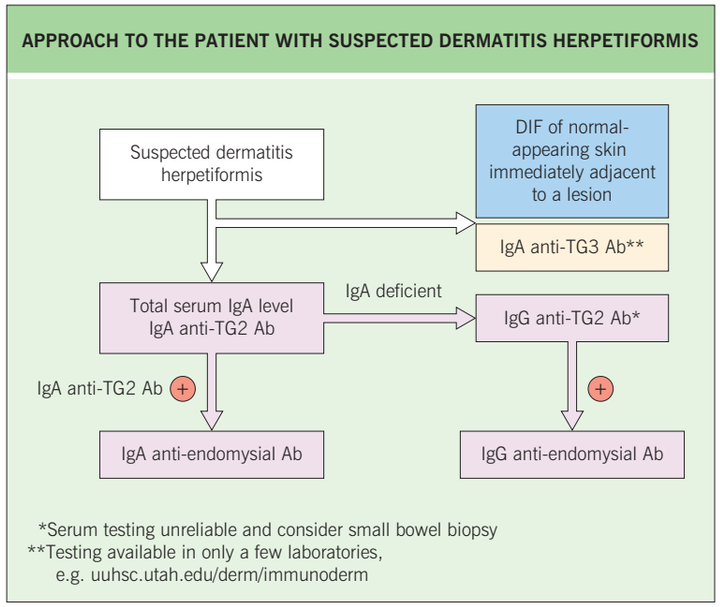


Fig. 31.6 Approach to the patient with suspected dermatitis herpetiformis. IgA anti-TG2 and anti-endomysial antibodies can be monitored over time to assess compliance with a gluten-free diet. The authors do not recommend anti-gliadin antibody testing because of high false-positive rates. Ab, antibody; DIF, direct immunofluorescence; TG, transglutaminase.

CHARACTERISTICS THAT DIFFERENTIATE DH, LABD AND BP

	DH	LABD	BP
Cutaneous lesion	Grouped papules and small vesicles, often excoriated	Small vesicles and/or large bullae	Large tense bullae
Distribution	Extensor surfaces, symmetrical	Similar to DH or BP	Trunk, extremities, occasionally mucosal surfaces
Histology	Subepidermal bullae with neutrophilic infiltrate	Subepidermal bullae with neutrophilic infiltrate	Subepidermal bullae with eosinophilic infiltrate
Direct IF	Granular IgA in dermal papillae	Linear IgA at BMZ, possibly also IgG	Linear IgG and C3 at BMZ
Site to biopsy for direct IF	Adjacent normal-appearing skin	Perilesional	Perilesional
Indirect IF	Negative	Linear IgA at BMZ (70%)	Linear IgG at BMZ (70%)
Enteropathy	>90%	Rare	None
HLA-DQ2	>90%	30%	Normal (20%)
Dapsone responsiveness	Excellent	Good, may also require systemic corticosteroids	Minimal to moderate

Table 31.3 Characteristics that differentiate dermatitis herpetiformis (DH), linear IgA bullous dermatosis (LABD) and bullous pemphigoid (BP). BMZ, basement membrane zone; IF, immunofluorescence.

SIDE EFFECTS OF DAPSONE	
Red blood cell toxicity	• Hemolytic anemia • Methemoglobinemia
White blood cell toxicity	• Leukopenia • Agranulocytosis
Dapsone hypersensitivity syndrome	• Hepatitis, lymphadenopathy, fatigue, anorexia
Cutaneous reactions	• Morbilliform eruption • Urticaria • Fixed drug eruption • Erythema nodosum • Exfoliative dermatitis • Stevens–Johnson syndrome • Toxic epidermal necrolysis • Phototoxicity • Drug-induced cutaneous lupus erythematosus
Gastrointestinal manifestations*	• Anorexia, nausea • Hepatitis • Cholestatic jaundice • Severe hypoalbuminemia
Neurologic associations*	• Headache, dizziness • Peripheral neuropathy • Blurred vision, tinnitus • Insomnia • Psychosis
Miscellaneous	• Fever • Nephrotic syndrome

*In decreasing order of frequency.

Table 31.4 Side effects of dapsone.

basis to optimize control. One to two new lesions per week should be expected on the optimal dose. Higher doses simply increase toxicity with little benefit.

Outbreaks of facial and scalp lesions while on otherwise adequate treatment can occur, but are not common. Facial disease may prove refractory to dapsone therapy. Breaking the vesicles followed by application of a potent corticosteroid gel may be helpful.

Although there are many side effects of dapsone (Table 31.4), the drug is well tolerated for years in more than 90% of patients (see Ch. 130). Hemolysis occurs in virtually every patient on dapsone therapy, since sulfones produce an oxidant stress on aging red blood cells. In patients with G6PD deficiency, dapsone may produce severe hemolysis. Although most patients have evidence of drug-induced hemolysis, a compensated hemolytic anemia does develop. Drug-induced hemolysis can be confirmed and followed by a reticulocyte count, which should show increased erythropoiesis. Of note, dapsone is secreted in breast milk and may cause hemolytic anemia in breastfed infants. In the setting of a persistent severe anemia, a search for contributing causes, such as iron, vitamin B_{12} or folate deficiencies or hereditary spherocytosis, should be performed.

Methemoglobin is present in the blood of most patients taking 100 mg of dapsone daily. Although the amount of methemoglobin usually does not exceed 5%, there are patients who have maintained levels between 10% and 15%. Methemoglobinemia in the absence of cardiopulmonary symptoms does not require alteration of dapsone dose.

Fatal agranulocytosis has developed in patients with DH treated with dapsone. This drug-induced agranulocytosis usually occurs after 2–12 weeks of continuous dapsone treatment. A hypersensitivity reaction involving the formation of leukocyte agglutinins seems to be the underlying mechanism. Re-administration of dapsone then causes leukopenia within hours. A simple measure is to warn the patient to discontinue the drug and report immediately if fever, a sore throat, or other signs of infection develop.

Dapsone hypersensitivity syndrome (see Ch. 21) is a rare, but potentially severe, reaction, characterized by fever, a cutaneous eruption and internal organ involvement, which is usually seen 2–7 weeks after initiation of therapy. The cutaneous manifestations vary from a morbilliform eruption to exfoliative dermatitis, while the systemic manifestations include fever, pruritus, lymphadenopathy, hepatitis, an elevated ESR, leukocytosis, and, rarely, eosinophilia[17]. Patients should be educated about this syndrome and instructed to discontinue therapy and notify their medical provider if any signs or symptoms of the dapsone hypersensitivity syndrome develop.

Peripheral neuropathy induced by dapsone may occur as early as during the first 4 months of therapy. Indeed, neuropathic signs can develop within the first few weeks of therapy. The neuropathy was initially reported as a pure motor neuropathy (involving primarily distal extremity muscles); however, pure motor, pure sensory, and combined motor and sensory neuropathies have subsequently been reported. Relatively high daily doses of dapsone (200–500 mg) and high cumulative doses in the range of 25 to 500 g have been implicated[17a].

If patients are intolerant to dapsone, therapy with sulfapyridine should be considered. The initial dose of sulfapyridine is usually 500 mg three times a day and it can be safely increased to 2 g three times a day; however, some patients may not respond to sulfapyridine at any dose. Adequate fluid intake and alkalinization of the urine minimizes the risk of nephrolithiasis.

Dapsone therapy monitoring includes a baseline complete blood count (CBC) and liver function tests, then weekly CBCs for the first month, monthly CBCs for the next 5 months, and semiannual CBCs thereafter while the patient remains on therapy. Liver function tests should be repeated at 6 months and annually thereafter. Some clinicians measure baseline G6PD activity in all patients, while others focus on those of African, Asian or southern Mediterranean ancestry. Sulfapyridine produces less hemolytic anemia, but the potential for agranulocytosis does exist. Consequently, similar monitoring is recommended for chronic sulfapyridine therapy.

Patients can also be treated with a gluten-free diet (which includes corn, rice and oats). Because several months of gluten-free diet therapy are needed for a response, concurrent suppression of symptoms with dapsone is usually necessary. Most patients with granular IgA deposits respond to a strict gluten-free diet such that they can either decrease or eliminate their need for dapsone. With a prolonged gluten-free diet, IgA in the skin decreases and eventually disappears, but with the reintroduction of gluten, IgA deposits and skin disease return. In addition, minor fluctuations in disease severity are most likely related to oral gluten intake. The gluten-free diet is inconvenient and unacceptable to some patients.

Patient Support

The Gluten Intolerance Group and the Celiac Disease Foundation (www.celiac.org) offer information on acceptable foods as well as foods and additives that should be avoided. The former patient support group has a *Quick Start Diet Guide for Celiac Disease* that may be useful for patients. Their website is www.gluten.net.

LINEAR IgA BULLOUS DERMATOSIS

Synonyms:
Adults: ■ Linear IgA dermatosis (LAD) ■ Linear IgA disease of adults ■ Linear IgA disease ■ Linear IgA dermatitis herpetiformis ■ Linear dermatitis herpetiformis ■ Adult linear IgA disease ■ IgA bullous pemphigoid ■ Pemphigoid linear IgA

Children: ■ Chronic bullous disease of childhood ■ Benign chronic bullous dermatosis of childhood ■ Childhood linear IgA dermatitis herpetiformis ■ Linear IgA disease of childhood

Introduction

LABD is an immune-mediated, subepidermal vesiculobullous eruption that occurs in both adults and children. It has been defined on the basis of a unique immunopathology consisting of linear deposition of IgA along the cutaneous BMZ. In adults, the clinical findings associated with this immunopathologic pattern may resemble those of DH or bullous pemphigoid (BP) (see Table 31.3), but in children, the cutaneous features may be clinically unique.

Fig. 31.7 Linear IgA bullous dermatosis. The circumferential and linear vesicles and bullae are typical of this disorder.

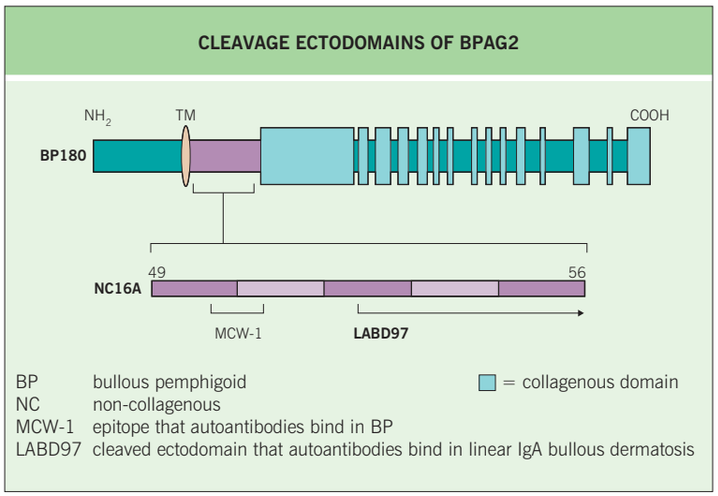


Fig. 31.9 Cleavage ectodomains of BPAG2. COOH, carboxy terminus; NH_2, amino terminus; TM, transmembrane region.

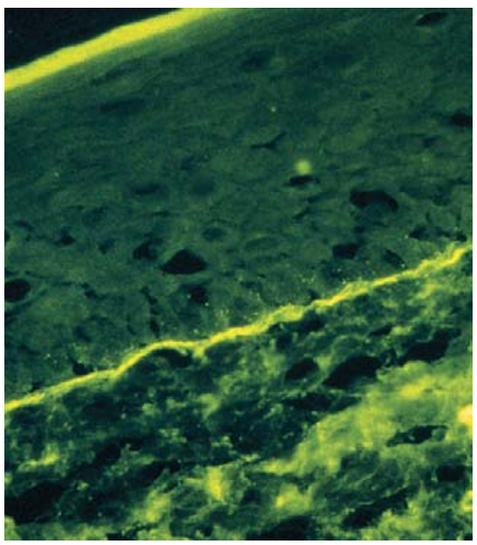


Fig. 31.8 Linear IgA bullous dermatosis – direct immunofluorescence. A linear pattern of IgA deposition is present within perilesional skin.

The childhood form is most frequently termed "chronic bullous disease of childhood" (CBDC). It is a subepidermal vesiculobullous disease that was initially described on the basis of its clinical findings of annular erythema and blisters (often referred to as a "crown of jewels"; Fig. 31.7), which developed predominantly in flexural areas, particularly the lower trunk, thigh and groin in preschool children. However, it is invariably characterized by the linear deposition of IgA along the BMZ (Fig. 31.8) as well as circulating antibodies against the same BMZ antigens described in the adult form[18].

Based upon the site of IgA deposition as determined by immunoelectron microscopy, there are at least two distinct types of LABD: a lamina lucida type (majority) and a sublamina densa type. In adults, LABD is frequently drug-induced.

History

In 1969, it was noted that patients with vesiculobullous lesions and the histologic findings of DH could have linear rather than granular deposits of IgA along the epidermal BMZ[19]. In 1975, Chorzelski and Jablonska[20] first suggested that LABD was a separate entity based on its immunopathologic findings. Subsequently, there has been general agreement that LABD is a distinct disease entity[21,22].

In 1970, Jordon et al.[23] first proposed the name "benign chronic bullous dermatosis of childhood". Subsequent investigators, using antisera specific for IgA, identified the characteristic linear IgA deposition along the epidermal BMZ in children with CBDC[24]. On a molecular basis, CBDC is the same disease as LABD in that the circulating IgA antibody found in the serum of patients with CBDC binds to the same 97 kDa antigen described in LABD of adults[18].

Epidemiology

The true incidence of LABD is unknown. The incidence in southern England has been estimated to be 1 in 250 000 per year. The incidence in the US has not been reported, but we have estimated the prevalence of LABD in Utah to be 0.6 per 100 000 adults. In adults, the average age of onset of LABD is after 60 years of age[21]. There appears to be a slight female preponderance, although this has not been observed in all series[21,25]. Childhood LABD occurs at a mean age of 4.5 years[25–27].

Pathogenesis

Both BP and the lamina lucida type of LABD have lamina lucida deposition of immunoglobulin and are associated with BMZ vesiculation. However, the antigenic specificity differs. In BP, the pathogenic IgG antibodies bind the MCW-1 region of the NC16 domain of BP antigen 2 (BPAG2; BP180), whereas the epitopes that have stimulated an IgA response in LABD are more toward the carboxy terminus of the same molecule (Fig. 31.9). In adult and childhood LABD patients, this IgA antibody was found, on immunoblot, to react against a 97 kDa antigen in an epidermal extract[28]. Subsequently, the 97 kDa antigen was found to represent a cleaved ectodomain of BPAG2, referred to as LABD97 (see Fig. 31.9). Why BP antibodies should react predominantly with antigens near the transmembrane portion of BPAG2 and LABD antibodies react with cleaved epitopes near or within the collagenous domain is unclear[29].

IgA class antibodies from patients with the sublamina densa type of LABD have been reported to bind to type VII collagen in anchoring fibrils[30,31]. However, in a series of 10 sera from such patients, this was not substantiated (authors' observations). Currently, the antigenic specificity of these sublamina densa-binding antibodies is not known.

There have been reports in the literature of the association of LABD with various disorders such as gastrointestinal diseases, autoimmune diseases, malignancies and infections (see below). The significance of these associations has yet to be determined, but they may play a role in the initial stimulation of the IgA mucosal immune system.

The incidence of gluten-sensitive enteropathy in LABD has been reported in the literature to range from 0 to 24%[20,22,32]. Leonard et al.[32] noted that two of six patients with LABD had gluten-sensitive enteropathy, and two of six patients' skin lesions improved on a gluten-free diet; however, none of the patients completely cleared. In contrast, Lawley et al.[22] found no histologic evidence of gluten-sensitive enteropathy in the six patients they studied. LABD clearly has a much lower prevalence of small bowel histologic abnormalities than does DH. Ulcerative colitis, Crohn's disease and gastric hypochlorhydria have also been described in association with LABD[21,33]. LABD associated with ulcerative colitis was reported to remit after colectomy[34].

DRUG-INDUCED LINEAR IgA BULLOUS DERMATOSIS
COMMON
• Vancomycin*
LESS COMMON
• Penicillins • Cephalosporins • Captopril > other ACE inhibitors • NSAIDs: diclofenac, naproxen, oxaprozin, piroxicam
UNCOMMON
• Phenytoin • Sulfonamide antibiotics: sulfamethoxazole, sulfisoxazole
RARE
• Amiodarone • Angiotensin receptor blockers: candesartan, eprosartan • Atorvastatin • Carbamazepine • Cyclosporine • Furosemide • Gemcitabine • Glyburide • Granulocyte colony-stimulating factor • Influenza vaccination • Interferon-α and interferon-γ • Interleukin-2 • Lithium carbonate • PUVA • Rifampin • Somatostatin • Verapamil • Vigabatrin
*Unusual variants include toxic epidermal necrolysis-like and morbilliform.

Table 31.5 Drug-induced linear IgA bullous dermatosis. ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs.

Data on the association of autoimmune diseases with LABD are not sufficient to allow statistical analysis of prevalence. However, there are reports in the literature of the association of systemic lupus erythematosus and dermatomyositis with LABD, as well as thyrotoxicosis, autoimmune hemolytic anemia, rheumatoid arthritis, and one case of glomerulonephritis[20,35,36].

An association between LABD and malignancy has also been described. Tumors that have been reported in patients with LABD include: B-cell lymphoma, chronic lymphocytic leukemia, and carcinoma of the bladder, thyroid, colon and esophagus; single case reports of plasmacytoma, hydatiform mole, renal cell carcinoma and ocular melanoma have also been described[21,37–41]. In addition, LABD has been reported to be associated with several infections, including varicella zoster virus, antibiotic-treated tetanus, and upper respiratory infections. It has been postulated that the infectious agent may have triggered an immune response[41–43].

There are multiple reports of drug-induced LABD; the drugs associated with LABD are listed in Table 31.5, with vancomycin being one of the more common inducers (Fig. 31.10)[44,45]. In the case of these medications, they may stimulate the immune system to produce an IgA class antibody in a predisposed individual. Drug-induced LABD usually remits within 2–6 weeks of cessation of the drug. However, some cases have persisted for months[45].

Clinical Features

Clinical manifestations in LABD are variable and patients can present with findings suggestive of DH as well as subepidermal tense bullae that are often indistinguishable from BP. However, the vesiculobullous lesions often appear in a herpetiform arrangement on erythematous and/or normal-appearing skin (Figs 31.11 & 31.12). Some patients present with expanding annular plaques (Fig. 31.13), while others have lesions that are scattered and asymmetric[21]. An isomorphic response, including lesions appearing at previous sites of adhesive tape, has been reported.

Fig. 31.10 Drug-induced linear IgA bullous dermatosis. Annular vesicopustules are seen in this patient receiving vancomycin.

Fig. 31.11 Linear IgA bullous dermatosis. Annular and herpetiform vesiculobullae on the face of a child.

Fig. 31.12 Linear IgA bullous dermatosis. Bullae, erosions and erythematous patches of linear IgA bullous dermatosis. Note the peripheral locations of blisters in some areas.

Fig. 31.13 Linear IgA bullous dermatosis. Annular and polycyclic plaques of the trunk in two women with the disorder.

LABD may present as a variant of mucous membrane (cicatricial) pemphigoid, with oral, nasal, pharyngeal and esophageal lesions. Involvement of the tracheobronchial mucosa was reported in a severe case[46]. The ocular form of LABD is clinically indistinguishable from ocular mucous membrane pemphigoid[47].

Pathology

LABD is a subepidermal vesicular dermatosis in which neutrophils predominate. In early urticarial papules or plaques, neutrophils are aligned along the BMZ, accompanied by vacuolar change and sometimes by neutrophilic microabscesses in dermal papillae. These papillary dermal collections, if numerous enough, can resemble the picture seen in DH[21]. In fully developed lesions, there are subepidermal bullae in which neutrophils are present in the underlying dermis, either alone or with eosinophils. Eosinophils can become more numerous over time. While distinguishing between DH and LABD can, on occasion, be impossible by light microscopy, a linear distribution of neutrophils along the BMZ and neutrophils at the very tips of dermal papillae favor LABD[48].

LABD can be subdivided on the basis of immunoelectron microscopy findings: most patients have IgA deposits within the lamina lucida[22,49]. Less commonly, there is deposition of IgA in the sublamina densa, associated with anchoring fibrils[22]. In a few cases, deposits of IgA have been observed in both sites[50]. In one report, the deposition of IgA was initially in the lamina lucida, but later had a combined pattern[50].

Differential Diagnosis

LABD can be difficult to diagnose clinically, especially in adults, and is often confused with DH and BP. By definition, LABD is separated from DH and BP on the basis of findings by DIF (see Table 31.3). Linear IgA deposition along the BMZ in perilesional skin biopsy specimens is characteristic of LABD, in contrast to DH, which shows granular deposition of IgA in dermal papillary tips or in a continuous pattern along the basement membrane[20–22], or BP, which shows linear deposition of IgG along the epidermal BMZ. The classification of cases demonstrating both IgG and IgA along the BMZ is problematic. Some authorities include only those patients with IgA as the sole BMZ immunoglobulin under the term LABD and categorize all others as BP. Others categorize patients with both IgG and IgA along the BMZ on the basis of the predominant immunoglobulin on DIF. Distinguishing the sublamina densa form of LABD from epidermolysis bullosa acquisita is also made on the basis of the class of immunoreactant and classification can be problematic.

Circulating anti-BMZ antibodies of the IgA class can be demonstrated in 60–70% of LABD sera. In contrast, patients with DH have not been shown to have circulating antibodies that bind to skin, and 60–70% of patients with BP demonstrate circulating IgG class antibodies (see Table 31.3)[20]. Circulating IgA class anti-BMZ antibodies from the lamina lucida type of LABD have been shown to adhere to the epidermal side (roof) of salt-split skin, while patients with sublamina densa binding of IgA on direct immunoelectron microscopy have serum antibodies which bind to the dermal side of salt-split skin. Patients with both IgA and IgG at the BMZ demonstrate binding to the epidermal side of salt-split skin[51]. Whether or not such antibody titers correlate with disease activity has not yet been established.

LABD secondary to drugs, in particular vancomycin, may have a toxic epidermal necrolysis-like or morbilliform presentation. Routine microscopy plus DIF can allow a distinction.

Treatment

The majority of patients with LABD respond to either oral dapsone or sulfapyridine therapy. These medications have been reviewed in detail in the section on the treatment of DH. Most patients with LABD have a clinical response within 48–72 hours. In occasional patients, it may be necessary to add oral prednisone in doses up to 40 mg daily to achieve complete control of the disease[21,22,49,50]. The majority of our patients have been controlled by dapsone alone. It is our observation that cases in which both IgG and IgA deposits are present in the BMZ are those that are likely to require additional therapy with systemic corticosteroids. The average dose of dapsone required to control LABD in adults is 100 mg daily, but doses as high as 300 mg daily may be needed. If doses greater than 200 mg per day are necessary, close monitoring should be undertaken. Children usually respond to a dose of 1–2 mg/kg daily.

Successful treatment of both adult and childhood LABD with antibiotics, including dicloxacillin, erythromycin, tetracycline (in those >9 years of age), and trimethoprim–sulfamethoxazole, has been reported. No specific microorganism was incriminated in these cases and therapeutic trials were empirical. A clinical trial of these relatively benign therapies may be undertaken, but no method of predicting a response has been identified. Mycophenolate mofetil, azathioprine and IVIg can be used as steroid-sparing agents in patients who do not respond to a combination of prednisone and dapsone or in patients with severe disease.

The natural course of the disease is characterized by persistence for several years with eventual spontaneous remission in many patients. Although a remission rate of 10–15% was originally described[21,39], additional studies have reported remission rates of 30–60%. There should be repeated attempts to taper medications given, on the chance that a spontaneous remission has occurred. Childhood LABD remits within 2–4 years.

REFERENCES

1. Zone J. Dermatitis herpetiformis. Curr Probl Dermatol. 1991;3:6–41.
2. Reunala T. Incidence of familial dermatitis herpetiformis. Br J Dermatol. 1996;134:394–8.
3. Smith JB, Tulloch JE, Meyer LJ, Zone JJ. The incidence and prevalence of dermatitis herpetiformis in Utah. Arch Dermatol. 1992;128:1608–10.
4. Spurkland A, Ingvarsson G, Falk ES, et al. Dermatitis herpetiformis and celiac disease are both primarily associated with the HLA-DQ (alpha 1 *0501, beta 1 *02) or the HLA-DQ (alpha 1 *03, beta 1 *0302) heterodimers. Tissue Antigens. 1997;49:29–34.
5. van Heel DA, Franke L, Hunt KA, et al. A genome-wide association study for celiac disease identifies risk variants in the region harboring IL2 and IL21. Nat Genet. 2007;39:827–9.
6. Reunala T. Dermatitis herpetiformis: coeliac disease of the skin. Ann Med. 1998;30:416–18.
7. Farrell RJ, Kelly CP. Celiac sprue. N Engl J Med. 2002;346:180–8.
8. Godkin A, Jewell D. The pathogenesis of celiac disease. Gastroenterology. 1998;115:206–10.
9. Sardy M, Karpati S, Merkl B, et al. Epidermal transglutaminase (TGase 3) is the autoantigen of dermatitis herpetiformis. J Exp Med. 2002;195:747–57.
10. Hull CM, Liddle M, Hansen N, et al. Elevation of IgA anti-epidermal transglutaminase antibodies in

dermatitis herpetiformis. Br J Dermatol. 2008;159: 120–4.
11. Rose C, Brocker EB, Zillikens D. Clinical, histological and immunopathological findings in 32 patients with dermatitis herpetiformis Durhring. J Dtsch Dermatol Ges. 2009;7:1–6.
12. Donaldson MR, Zone JJ, Schmidt LA, et al. Epidermal transglutaminase deposits in perilesional and uninvolved skin in patients with dermatitis herpetiformis. J Invest Dermatol. 2007;127:1268–71.
13. Blenkinsopp WK, Haffenden GP, Fry L, et al. Histology of linear IgA disease, dermatitis herpetiformis, and bullous pemphigoid. Am J Dermatopathol. 1983;5:547–54.
14. Thuong-Nguyen V, Kadunce DP, Hendrix JD, et al. Inhibition of neutrophil adherence to antibody by dapsone: a possible therapeutic mechanism of dapsone in the treatment of IgA dermatoses. J Invest Dermatol. 1993;100:349–55.
15. Cunningham MJ, Zone JJ. Thyroid abnormalities in dermatitis herpetiformis. Ann Intern Med. 1985;102: 194–6.
16. Zone JJ, Meyer LJ, Petersen MJ. Deposition of granular IgA relative to clinical lesions in dermatitis herpetiformis. Arch Dermatol. 1996;132:912–18.
17. Agrawal S, Agarwalla A. Dapsone hypersensitivity syndrome: a clinico-epidemiological review. J Dermatol. 2005;32:883–9.
17a. Gutmann L, Martin J, Welton W. Dapsone motor neuropathy – An axonal disease. Neurology. 1976; 26:514–6.
18. Zone JJ, Taylor TB, Kadunce DP, et al. IgA antibodies in chronic bullous disease of childhood react with 97 kDa basement membrane zone protein. J Invest Dermatol. 1996;106:1277–80.
19. van der Meer JB. Granular deposits of immunoglobulins in the skin of patients with dermatitis herpetiformis: an immunofluorescent study. Br J Dermatol. 1969;81: 493–503.
20. Chorzelski TP, Jablonska S. Diagnostic significance of immunofluorescent pattern in dermatitis herpetiformis. Int J Dermatol. 1975;14:429–36.
21. Mobacken H, Kastrup W, Ljundhall K, et al. Linear IgA dermatosis: a study of ten adult patients. Acta Derm Venereol. 1983;63:123–8.
22. Lawley TJ, Strober W, Yaoita H, Katz SI. Small intestinal biopsies and HLA types in dermatitis herpetiformis patients with granular and linear IgA skin deposits. J Invest Dermatol. 1980;74:9–12.
23. Jordon RE, Bean SF, Triftshauser CT, Winkelmann RK. Childhood bullous dermatitis herpetiformis. Arch Dermatol. 1970;101:629–34.
24. Chorzelski TP, Jablonska S. IgA linear dermatosis of childhood (chronic bullous disease of childhood). Br J Dermatol. 1979;101:535–42.
25. Esterly NB, Furey NL, Kirschner BS, et al. Chronic bullous dermatosis of childhood. Arch Dermatol. 1977;113:42–6.
26. Provost TT, Maize JC, Ahmed AR, et al. Unusual subepidermal bullous diseases with immunologic features of bullous pemphigoid. Arch Dermatol. 1979; 115:156–60.
27. Wojnarowska F, Marsden RA, Bhogal B, et al. Childhood cicatricial pemphigoid with linear IgA deposits. Clin Exp Dermatol. 1984;9:407–15.
28. Zone JJ, Taylor TB, Kadunce DP, Meyer LJ. Identification of the cutaneous basement membrane zone antigen and isolation of antibody in linear immunoglobulin A bullous dermatosis. J Clin Invest. 1990;85:812–20.
29. Zone JJ, Taylor TB, Meyer LJ, Peterson MJ. The 97 kDa linear IgA bullous disease antigen is identical to a portion of the extracellular domain of the 180 kDa bullous pemphigoid antigen, BPAg2. J Invest Dermatol. 1998;110:207–10.
30. Gammon WR, Fine JD, Forbes M, et al. Immunofluorescence on split skin for the detection and differentiation of basement membrane zone autoantibodies. J Am Acad Dermatol. 1992;27:79–87.
31. Hashimoto T, Ishiko A, Shimizu H, et al. A case of linear IgA bullous dermatosis with IgA and anti-type VII collagen autoantibodies. Br J Dermatol. 1996;134: 336–9.
32. Leonard JN, Griffith CEM, Powles AV, et al. Experience with a gluten free diet in the treatment of linear IgA disease. Acta Derm Venereol. 1987;67:145–8.
33. Barberis C, Doutre MS, Bioulac-Sage P, et al. Dermatose bulleuse á IgA lineare associée á une maladie de Crohn. Gastroenterol Clin Biol. 1988;12:76–7.
34. Egan CA, Meadows KP, Zone J. Ulcerative colitis and immunobullous disease cured by colectomy. Arch Dermatol. 1999;135:214–15.
35. Barrow-Wade L, Jordan RE, Arnett FC Jr. Linear IgA bullous dermatosis associated with dermatomyositis (letter). Arch Dermatol. 1992;128:413–14.
36. Davies MG, Marks R, Nuki G. Dermatitis herpetiformis: a skin manifestation of a generalized disturbance in immunity. Q J Med. 1978;186:221–48.
37. Lacour JP, Vitetta A, Ortonne J-P. Linear IgA dermatosis and thyroid carcinoma. J Am Acad Dermatol. 1992;26:257–9.
38. McEnvoy MT, Connolly SM. Linear IgA dermatosis: association with malignancy. J Am Acad Dermatol. 1990;22:59–63.
39. Sekula SA, Tschen JA, Bean SF, Wolf JE Jr. Linear IgA bullous disease in a patient with transitional cell carcinoma of the bladder. Cutis. 1986;38:354–6, 362.
40. Leonard JN, Tucker WFG, Fry JS, et al. Increased incidence of malignancy in dermatitis herpetiformis. Br Med J. 1983;285:16–18.
41. Godfrey K, Wojnarowska F, Leonard J. Linear IgA disease of adults: association with lymphoproliferative malignancy and possible role of other triggering factors. Br J Dermatol. 1990;123:447–52.
42. Thune P, Eeg-Larsen T, Nilsen R. Acute linear IgA dermatosis in a child following varicella. Arch Dermatol. 1984;120:1237–8.
43. Blickenstaff RD, Perry HO, Peters MS. Linear IgA deposition associated with cutaneous varicella-zoster infection: a case report. J Cutan Pathol. 1988;15:49–52.
44. Carpenter S, Berg D, Sidhu-Malik N, et al. Vancomycin-associated linear IgA dermatosis. J Am Acad Dermatol. 1992;26:45–8.
45. Kuechle MK, Stegemeir E, Maynard B, et al. Drug-induced linear IgA bullous dermatosis: report of six cases and review of the literature. J Am Acad Dermatol. 1994;30:187–92.
46. Verhelst F, Demedts M, Verschakelen J, et al. Adult linear IgA bullous dermatosis with bronchial involvement. Br J Dermatol. 1987;116:587–90.
47. Kelly SE, Frith PA, Millard PR, et al. A clinicopathological study of mucosal involvement in linear IgA disease. Br J Dermatol. 1988;119:161–70.
48. Smith SB, Harrist TJ, Murphy GF, et al. Linear IgA bullous dermatosis versus dermatitis herpetiformis: quantitative measurements of dermoepidermal alterations. Arch Dermatol. 1984;120:324–8.
49. Yaoita H, Hertz KC, Katz SI. Dermatitis herpetiformis: immunoelectronmicroscopic and ultrastructural studies of a patient with linear deposition of IgA. J Invest Dermatol. 1976;67:691–5.
50. Dabrowski J, Chorzelski TP, Jablonska S, et al. Immunoelectron microscopic studies in IgA linear dermatosis. Arch Dermatol Res. 1979;265: 289–98.
51. Zone JJ, Smith EP, Powell D, et al. Antigenic specificity of antibodies from patients with linear basement membrane deposition of IgA. Dermatology. 1994;189:64–6.

Epidermolysis Bullosa 32

Jo-David Fine and Jemima E Mellerio

Synonyms: ■ All forms of EB: EB hereditaria ■ EB simplex: epidermolytic EB ■ Junctional EB: EB atrophicans, EB letalis ■ Dystrophic EB: EB dystrophica

Key features

- Epidermolysis bullosa (EB) encompasses multiple clinically distinctive disorders that share three major features: genetic transmission, mechanical fragility of the skin, and blister formation
- There are four major forms of inherited EB – EB simplex, junctional EB, dystrophic EB, and Kindler syndrome – which differ in the ultrastructural site within which cutaneous blisters form
- EB may be diagnosed by immunofluorescence antigenic mapping, transmission electron microscopy or genetic analysis
- Any epithelial-lined or epithelial-covered organ is at potential risk for involvement in the more severe forms of inherited EB
- In the absence of specific therapy, management is primarily focused on prevention of blisters and the correction of extracutaneous complications

INTRODUCTION

Inherited epidermolysis bullosa (EB), the prototypic mechanobullous disease, is characterized by the development of blisters following seemingly minor or insignificant trauma or traction to the skin[1]. It traditionally encompasses three major forms (simplex, junctional and dystrophic) and at least 30 distinctive clinical phenotypes[2] (Table 32.1). Kindler syndrome, an inherited disease characterized by poikiloderma, photosensitivity and mechanically fragile skin (see Ch. 63), is now classified as a fourth major form of EB. Inherited EB can result from mutations within the genes for any of at least 15 structural proteins: keratins 5 and 14; the subunits of laminin 332 (formerly laminin 5); type VII and XVII collagens; plectin; $\alpha_6\beta_4$ integrin; dystonin (bullous pemphigoid antigen 1); kindlin; and the desmosomal components plakophilin-1, plakoglobin and desmoplakin. Although most of these diseases are rare, research into their underlying pathophysiologic bases has led to major advances in our understanding of the cell and molecular biology of keratins, other keratinocyte-associated structural proteins, collagens and the cutaneous extracellular matrix (ECM). Study of EB has also helped to elucidate mechanisms of epithelial cell adhesion, migration and differentiation and to highlight the role of the basement membrane zone in health and disease. The creation of *in vitro* and animal models of EB has enabled principles of gene therapy to be tested and refined, with development of novel approaches for the treatment of EB patients.

HISTORY

Epidermolysis bullosa was first described in 1870 by von Hebra under the name "erblichen pemphigus"[3]. Its current name, "epidermolysis bullosa hereditaria", was coined by Koebner in 1886. Hallopeau recognized the distinct clinical features of simplex and dystrophic forms of EB in 1898. Junctional EB was first identified in 1935 by Herlitz and termed "EB letalis". Precise characterization of these three major EB types via the use of transmission electron microscopy was first achieved by Pearson in 1962[4]. In the ensuing years, additional EB phenotypes were described. Monoclonal antibody studies provided the first suggestion that specific protein defects underlie individual types and subtypes of this disease[5–8]. In 1986, the National EB Registry was established in the US by the National Institutes of Health, facilitating epidemiologic, clinical and laboratory characterization of each major EB type and subtype[9,10]. In 1991, Bonifas et al.[11] (through utilization of linkage analysis) were the first to demonstrate the molecular basis for a specific form of EB (simplex). Subsequent work by others has established the precise molecular basis for each of the EB subtypes.

EPIDEMIOLOGY

Based on National EB Registry data[12], the estimated prevalence and incidence of EB in the US are 8.2 per 1 million population and 19.6 per 1 million live births, respectively. Carrier frequencies have also been reported[13]. The approximate prevalences and incidences (respectively) of the major types of EB are as follows: EB simplex, 4.6 and 10.8; junctional EB, 0.4 and 2.0; dominant dystrophic EB, 1.0 and 2.9 and recessive dystrophic EB, 0.9 and 2.0.

PATHOGENESIS

EB is caused by mutations within genes that encode structural proteins that reside within the epidermis (EB simplex), dermo-epidermal junction (junctional EB), or uppermost papillary dermis (dystrophic EB). The site within which each of these proteins resides determines the ultrastructural location where the blisters arise (Table 32.1 & Fig. 32.1).

EB Simplex

Most forms of EB simplex (EBS) are transmitted in an autosomal dominant manner. There are two main subgroups of EBS, suprabasal and basal, which differ in the ultrastructural level of the intraepidermal blistering (see Table 32.1). The vast majority of EBS cases are in the basal group, most often resulting from a dominant-negative mutation (see Ch. 54) within the keratin 5 (*K5*) or 14 (*K14*) genes, expression of which is primarily within the basal layer of the epidermis[14,15]. The clinical severity and other phenotypic features of EBS are closely associated with the genotype. For example, mutations in the helix initiation and termination motifs of K5 and K14 (see Fig. 56.5) lead to the Dowling–Meara subtype of EBS (EBS-DM), which is more severe than EBS due to mutations in other regions of these keratins. An autosomal recessive form of EBS due to mutations in the gene encoding plectin is associated with muscular dystrophy (EBS-MD), which is not surprising considering that this protein is expressed in skeletal muscle as well as in the hemidesmosomes of basilar keratinocytes; other patients with plectin deficiency present with pyloric atresia (EBS-PA). Suprabasal forms of EBS caused by mutations in the genes encoding the desmosomal proteins plakophilin-1, plakoglobin and desmoplakin and a basal variant due to a homozygous mutation in the dystonin gene have also been reported (see Table 32.1).

Junctional EB

Junctional EB (JEB) was transmitted in an autosomal recessive manner in all but one family reported to date (see Table 32.1). The most severe subtype, JEB-Herlitz (JEB-H), typically results from homozygous or compound heterozygous truncating mutations within a gene encoding one of the three subunits of laminin 332, a key component of the lamina lucida of the dermo-epidermal junction (see Ch. 28)[16]. The milder generalized form of junctional EB, JEB-non-Herlitz

EPIDERMOLYSIS BULLOSA: SIMPLEX, JUNCTIONAL AND DYSTROPHIC SUBTYPES		
Subtype	**Inheritance**	**Defective protein(s)**
SUPRABASAL INTRAEPIDERMAL CLEAVAGE		
Lethal acantholytic EBS*	AR	Desmoplakin
Plakophilin deficiency	AR	Plakophilin-1
Lethal congenital EBS Acantholytic ectodermal dysplasia	AR	Plakoglobin
EBS superficialis (EBSS)	Unknown	Unknown
BASAL INTRAEPIDERMAL CLEAVAGE		
EBS, localized (EBS-loc; formerly EBS, Weber–Cockayne)	AD	Keratins 5 and 14
EBS, Dowling–Meara (EBS-DM)		
EBS, other generalized (EBS-nDM/gen; formerly EBS, Koebner)		
EBS with muscular dystrophy (EBS-MD)	AR	Plectin
EBS with pyloric atresia (EBS-PA)†		
EBS, Ogna (EBS-Og)	AD	
EBS with mottled pigmentation (EBS-MP)	AD	Keratin 5
EBS, migratory circinate (EBS-migr)		
EBS, autosomal recessive (EBS-AR)	AR	Keratin 14
		Dystonin (BPAG1)
INTRA-LAMINA LUCIDA CLEAVAGE		
JEB, Herlitz (JEB-H)	AR	Laminin 332
JEB, non-Herlitz generalized (JEB-nH/gen)‡	AR >> AD§	Laminin 332 Type XVII collagen (BPAG2)
JEB non-Herlitz, localized (JEB-nH/loc)	AR	Type XVII collagen
JEB with pyloric atresia (JEB-PA)	AR	α6β4 integrin
JEB, inversa (JEB-I) JEB, late onset	AR	Laminin 332
Laryngo-onycho-cutaneous (LOC) syndrome	AR	Laminin 332, α_3 subunit
SUB-LAMINA DENSA CLEAVAGE		
DDEB, generalized (DDEB-gen)	AD	Type VII collagen
DDEB, acral		
DDEB, pretibial		
DDEB, pruriginosa		
DDEB, nails only		
DDEB, bullous dermolysis of the newborn (DDEB-BDN)		
RDEB, severe generalized (RDEB-sev/gen; formerly RDEB, Hallopeau–Siemens)	AR	
RDEB, generalized other (RDEB-o)		
RDEB, inversa (RDEB-I)		
RDEB, pretibial		
RDEB, centripetalis		
RDEB, bullous dermolysis of the newborn (RDEB-BDN)		
MIXED CLEAVAGE PLANES		
Kindler syndrome	AR	Kindlin-1

*Desmoplakin defects also cause the skin fragility/woolly hair syndrome (see Table 32.4).
†May also be caused by defects in $\alpha_6\beta_4$ integrin, which more often lead to JEB-PA.
‡Formerly referred to as generalized atrophic benign EB.
§One kindred with a dominant-negative mutation in the gene encoding type XVII collagen has been reported to date.

Table 32.1 Epidermolysis bullosa (EB): simplex, junctional and dystrophic subtypes. Entities with a lighter background represent rare variants. AD, autosomal dominant; AR, autosomal recessive; BPAG, bullous pemphigoid antigen; DDEB, dominant dystrophic EB; EBS, EB simplex; JEB, junctional EB; RDEB, recessive dystrophic EB.

(JEB-nH; previously named generalized atrophic benign EB, GABEB), results from mutations within the genes for either a subunit of laminin 332 or type XVII collagen. JEB with pyloric atresia (JEB-PA) is caused by mutations within either of the two genes that encode the subunits of $\alpha_6\beta_4$ integrin. In the laryngo-onycho-cutaneous (LOC) syndrome, the underlying mutations are in the α_3 chain of laminin 332.

Dystrophic EB

Dystrophic EB (DEB) is transmitted in either an autosomal dominant or autosomal recessive manner. Dominant DEB (DDEB) results from a dominant-negative mutation within the type VII collagen gene[17,18]. Typically, a missense mutation results in substitution of another amino acid for a glycine within the triple-helical domain of this collagen.

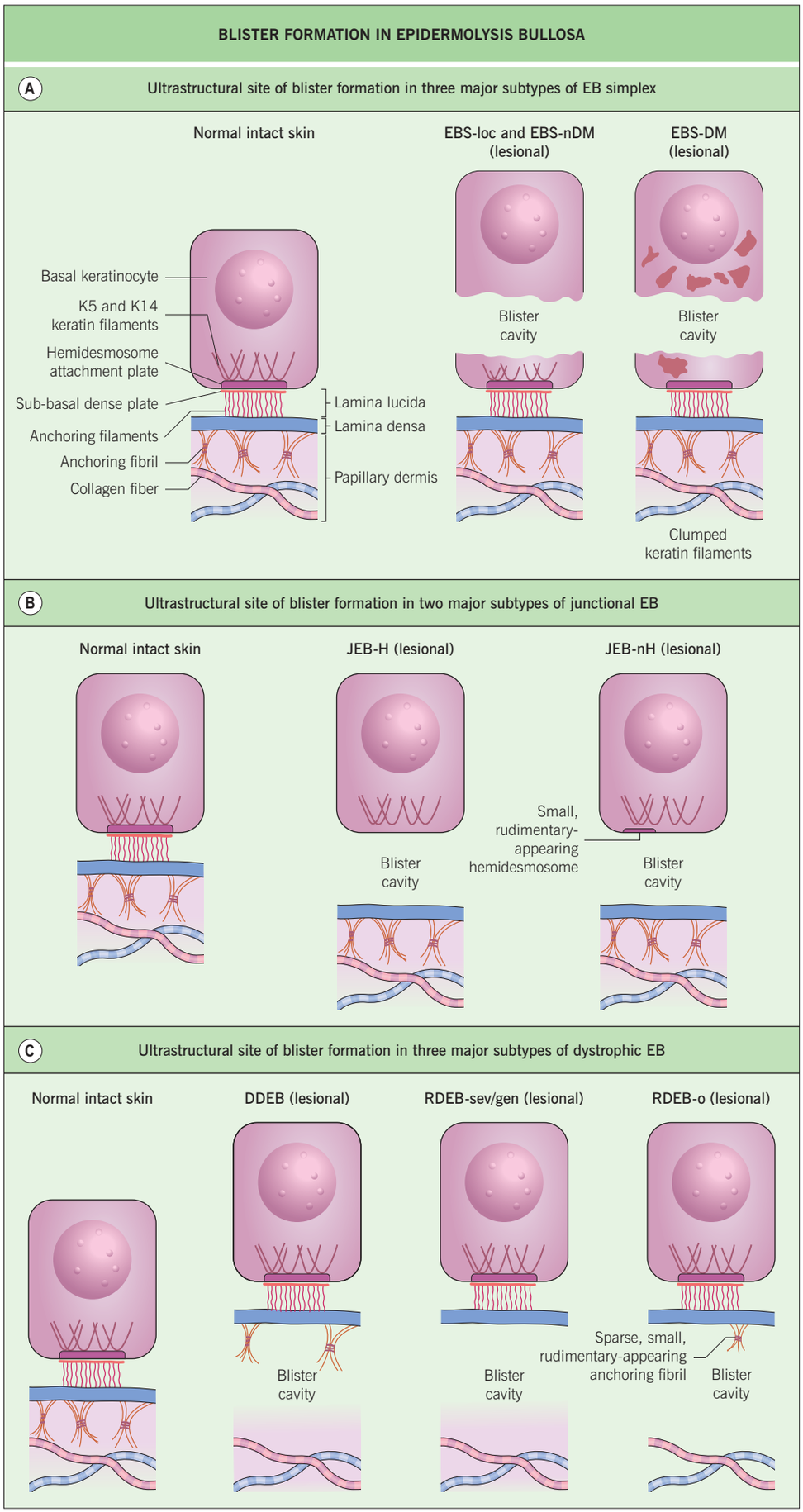


Fig. 32.1 Ultrastructural sites of blister formation in major forms of epidermolysis bullosa (EB). **A** Ultrastructural sites of blister formation in three subtypes of EB simplex. The ultrastructure of normal intact skin is presented for comparison. In all three major subtypes of EB simplex – localized (EBS-loc), generalized non-Dowling–Meara (EBS-nDM) and Dowling–Meara (EBS-DM) – blisters arise within the lowermost intracytoplasmic portion of the basilar keratinocyte. In one subtype, EBS-DM, keratin filaments tend to coalesce into larger electron-dense clumps. **B** Ultrastructural sites of blister formation in two major subtypes of junctional EB (JEB). All forms of JEB are characterized by blister formation within the lamina lucida of the dermal–epidermal junction. As such, the lamina densa remains firmly attached to the dermis which forms the base of the blister cavity. Sub-basal dense plates and anchoring filaments are absent in both subtypes of JEB. Hemidesmosomes are absent in JEB-Herlitz (JEB-H), whereas they are reduced in number and appear rudimentary in structure within skin from patients with the JEB-non-Herlitz (JEB-nH) subtype. **C** Ultrastructural sites of blister formation in three major subtypes of dystrophic EB. Blister formation occurs beneath the lamina densa in all forms of dystrophic EB. Whereas anchoring fibrils appear normal in size and structure in dominant dystrophic EB (DDEB) skin, they may be somewhat reduced in number. Consistent with the presence of sub-lamina densa cleavage, these anchoring fibrils remain attached to the blister roof, which is composed of intact epidermis and an attached basement membrane (which includes the lamina densa). In contrast, anchoring fibrils are completely absent in lesional skin from patients with severe generalized recessive dystrophic EB (RDEB-sev/gen). If detectable in skin from patients with other generalized forms of recessive dystrophic EB (RDEB-o), they are both markedly reduced in number and rudimentary in appearance.

Continued

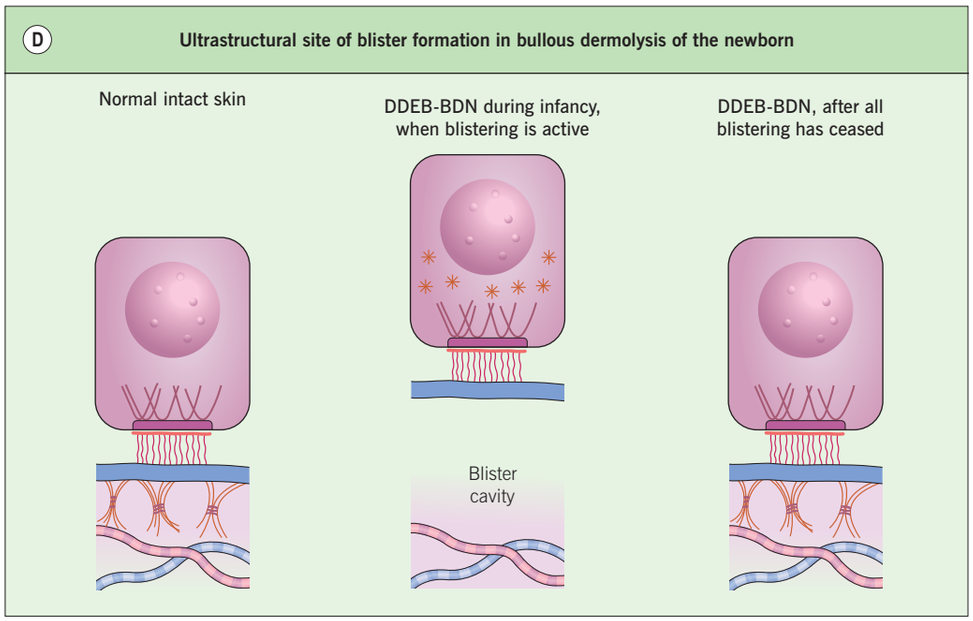


Fig. 32.1 Ultrastructural sites of blister formation in major forms of epidermolysis bullosa (EB) (cont'd). D Ultrastructural findings in the form of dominant dystrophic EB (DDEB) referred to as bullous dermolysis of the newborn (DDEB-BDN). With age, there is improvement in the transport and deposition of type VII collagen from the keratinocyte cytoplasm to the anchoring fibrils of the basement membrane.

Although the resultant protein is structurally abnormal, immunohistochemical staining of the dermal–epidermal junction is usually indistinguishable from that of normal skin.

Recessive DEB (RDEB) usually results from compound heterozygous mutations within the type VII collagen gene[17–19]. Premature stop codons (which result in truncated proteins) are characteristic of the severe generalized RDEB subtype (RDEB-sev/gen; traditionally known as RDEB-Hallopeau–Siemens). Consistent with the severity of these mutations, anchoring fibrils are undetectable or extremely sparse and poorly formed in skin biopsy specimens, and immunohistochemical staining with antibodies against the major epitopes of the type VII collagen molecule is absent or barely detectable. Milder forms of generalized RDEB are associated with less severe biallelic mutations in the type VII collagen gene.

Some patients with RDEB retain a specific fragment of type VII collagen (the amino terminal non-collagenous domain [NC1]), and this may contribute to an increased susceptibility to develop squamous cell carcinomas (SCCs)[20]. In a Ras-driven model of tumorigenesis, keratinocytes from RDEB patients that contained no collagen VII did not form tumors in mice, whereas RDEB keratinocytes that produced the NC1 domain of collagen VII (and null keratinocytes forced to express NC1) were tumorigenic. Additional studies pointed to the fibronectin-like sequences within NC1 as key to promoting tumor cell invasion. However, SCCs can develop in RDEB patients who do not express the NC1 domain[21].

In a rare form of DEB referred to as bullous dermolysis of the newborn, inheritance is usually dominant and blistering is typically confined to the first 1–2 years of life[22–24]. Clinical expression coincides with a time during which type VII collagen is present primarily within basilar keratinocytes in these patients' skin, rather than along the dermal–epidermal junction (see Fig. 32.1D). This suggests that there is a temporary disruption in the transport of this protein from the keratinocyte cytoplasm to the underlying ECM.

Fig. 32.2 Localized epidermolysis bullosa simplex. A, B Bullae arising on the toes and plantar surfaces at sites of lateral or rotary traction. The majority of blisters occur in acral sites. *B, Courtesy, Julie V Schaffer, MD.*

CLINICAL FEATURES

Cutaneous Findings

Patients with EB are classified on the basis of the ultrastructural level of blister formation, antigenic alterations in the skin, the mode of inheritance, and the clinical phenotype[2,25]. Although cutaneous findings play an important role in the overall determination of the EB phenotype, there is overlap in the frequency of cutaneous manifestations in different subtypes of EB. In addition, the severity, distribution and type of skin findings in an individual patient may change over time

Fig. 32.3 Epidermolysis bullosa simplex, other generalized. Extensive blistering on the buttocks (**A**) and blistering in association with focal keratoderma on the soles (**B**) of a 2-year-old girl. *Courtesy, Julie V Schaffer, MD.*

Fig. 32.4 Dominant dystrophic epidermolysis bullosa. A, B Erosions, scarring and milia on the digits, as well as partial shedding of a toenail (**A**). **C** A discrete area of scarring on the elbow with blisters, crusting and milia.

(e.g. evolution from generalized to localized blistering or delayed development of sequelae such as scarring and nail dystrophy)[2]. Mutational analysis is not currently considered to be a first-line diagnostic test for EB, with the exceptions of prenatal and preimplantation diagnosis[2].

All forms of inherited EB are characterized by mechanically fragile skin, erosions and (with rare exceptions) macroscopic blisters (Figs 32.2 & 32.3). In most forms of EB, minimal lateral or rotary traction on the skin leads to shearing within ultrastructurally uniform cleavage planes, resulting in blister formation. Blisters can usually be readily induced in EB patients (e.g. by rotating a pencil eraser on intact skin), facilitating diagnosis by immunohistochemical or ultrastructural techniques (see below). However, in localized EBS and DDEB, it may be difficult to induce blisters in clinically uninvolved areas.

Scarring (almost always atrophic) can occur in any type or subtype of EB (Fig. 32.4), including localized EBS. However, its frequency is greatest in the subtypes that are characterized ultrastructurally by disruption of the basement membrane zone (particularly the lamina densa) and clinically by generalized cutaneous and extracutaneous disease activity (Fig. 32.5). Whereas scarring is estimated to occur in only 15% of patients with localized EBS, it is present in essentially every patient with RDEB[26]. Other cutaneous findings that have similar variations in frequency across the major types and subtypes of EB include dystrophic or absent nails (see Fig. 32.4), milia, and scarring alopecia of the scalp.

Some cutaneous findings have diagnostic implications (Fig. 32.6)[2]. Reticulated hyperpigmented macules distinguish a rare subset of EB simplex termed *EBS with mottled pigmentation (EBS-MP)*. Superficial peeling of the skin, often in the absence of overt blistering, is seen in *EBS superficialis (EBSS)*. Grouped ("herpetiform") blisters, often in an arcuate (Fig. 32.7) or polycyclic array, are highly characteristic of *EBS-DM*, which is also associated with the gradual development of a diffuse palmoplantar keratoderma (Fig. 32.8). Migratory circinate erythema with vesiculation of the advancing edge has been described in patients with EBS caused by a frameshift mutation that leads to an elongated K5 protein. Excessive or exuberant granulation tissue, usually in a symmetric distribution involving the periorificial skin, axillary vaults, upper back, nape of the neck and periungual areas, is typical of *JEB-H* (Fig. 32.9).

Distribution of skin disease activity is also useful in the subclassification of EB[25], although the pattern of involvement tends to be less distinctive in infants than in adults. Patients with the *"inversa" subtypes of JEB and RDEB* experience disease activity primarily in intertriginous areas (e.g. axillae, inguinal creases). Lesions primarily affect acral sites in patients with *localized JEB-nH* and are almost exclusively on the shins in those with *pretibial DEB*. Another extremely rare subtype is *RDEB centripetalis*, which initially features acral blistering,

followed by slow progression of disease activity toward the trunk over the years.

Extracutaneous Findings

The same molecular defects that affect the skin in patients with EB are also present in other tissues with an epithelial lining or surface[27,28], including the eye, oral cavity, and gastrointestinal and genitourinary tracts. The extracutaneous manifestations that result are summarized in Table 32.2[29]. Although exceptions exist, extracutaneous involvement occurs most frequently in RDEB and (to a lesser extent) JEB, and it can result in blisters, erosions, ulcers and/or scarring. Pyloric atresia is evident at birth in patients with the rare JEB-PA and EBS-PA subtypes. In other forms of EB, complications related to extracutaneous disease may arise as early as the first year of life. Repeated blistering of the external eye can result in neovascularization and blindness[30]. Chronic involvement of the esophagus leads to scarring, stricture formation and, rarely, even complete obstruction[31]. Involvement of the small intestine presents with chronic malabsorption, whereas disease activity within the large intestine is associated with severe constipation and anal fissures or strictures. Recurrent genitourinary tract blistering may result in urethral or ureterovesical strictures; if persistent, the latter may lead to ureteric reflux and hydronephrosis. Lastly, tracheolaryngeal blistering and associated soft tissue edema, seen most often in infants and young children with *JEB-H*, may lead to potentially fatal acute airway obstruction[32].

Dental enamel hypoplasia, which occurs in all forms of *JEB*[33,34], is associated with pitting of the surfaces of primary and permanent teeth. If untreated, these patients lose teeth during childhood due to excessive caries[35]. Severe caries and resultant tooth loss also occur in *RDEB-sev/gen*, likely resulting from impaired clearance of food from the mouth and poor dental hygiene in the setting of intraoral injury and scarring, ankyloglossia and microstomia.

Pseudosyndactyly ("mitten" deformities of the hands and feet) primarily affects patients with RDEB, especially *RDEB-sev/gen*, although it occasionally occurs to a lesser degree in *DDEB* and *JEB*[36] (Fig. 32.10). Initially presenting as proximal "web" formation between adjacent digits, the digits may eventually become totally fused and encased by scar tissue. Lack of mobility leads to bony resorption and muscular atrophy, eventuating in marked impairment of hand function.

Osteoporosis, detectable by dual-emission X-ray absorptiometry (DEXA) scanning, is common in severe generalized forms of EB, most notably *RDEB-sev/gen* and *JEB-H*. Radiographs may demonstrate vertebral crush fractures in severe cases. EBS due to plectin deficiency is associated with mild to severe muscular dystrophy. The muscle disease presents during infancy in some patients, but weakness often develops insidiously during later childhood or early adulthood in those who are less severely affected.

Chronic renal failure develops in a minority of patients with severe generalized forms of EB, most notably RDEB-sev/gen, which is associated with a 12% risk of death from renal failure by age 35 years[37]. Renal disease may result from untreated outflow obstruction, glomerulonephritis or secondary systemic amyloidosis. Nephrotic syndrome associated with altered expression of laminin isoforms in renal basement membranes has been reported in an infant with JEB-H. A small subset of patients with severe generalized forms of EB, especially RDEB-sev/gen, develop potentially fatal dilated cardiomyopathy[38]. Although as yet unproven, selenium or carnitine deficiency may be a contributing factor.

Although it was a common occurrence several decades ago, potentially lethal bacterial sepsis is now relatively rare in inherited EB[39], presumably due to improved wound care and the availability and judicious use of broad-spectrum antibiotics. When sepsis does occur in EB, it tends to affect infants with generalized disease, especially EBS-DM, JEB-H and RDEB-sev/gen[40]. However, failure to thrive is still common among infants with JEB-H and may lead to death.

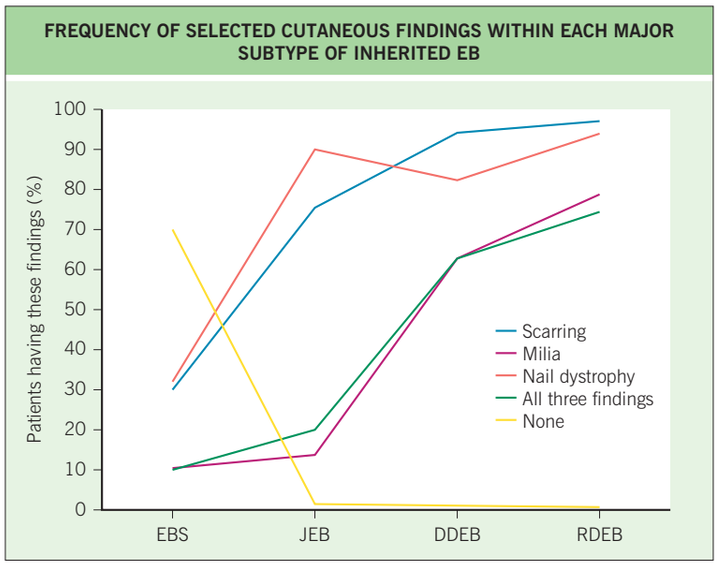


Fig. 32.5 Frequency of selected cutaneous findings within each major subtype of inherited epidermolysis bullosa (EB). Note the increasing frequency from localized EB simplex (EBS) to recessive dystrophic EB (RDEB). JEB, junctional EB; DDEB, dominant dystrophic EB.

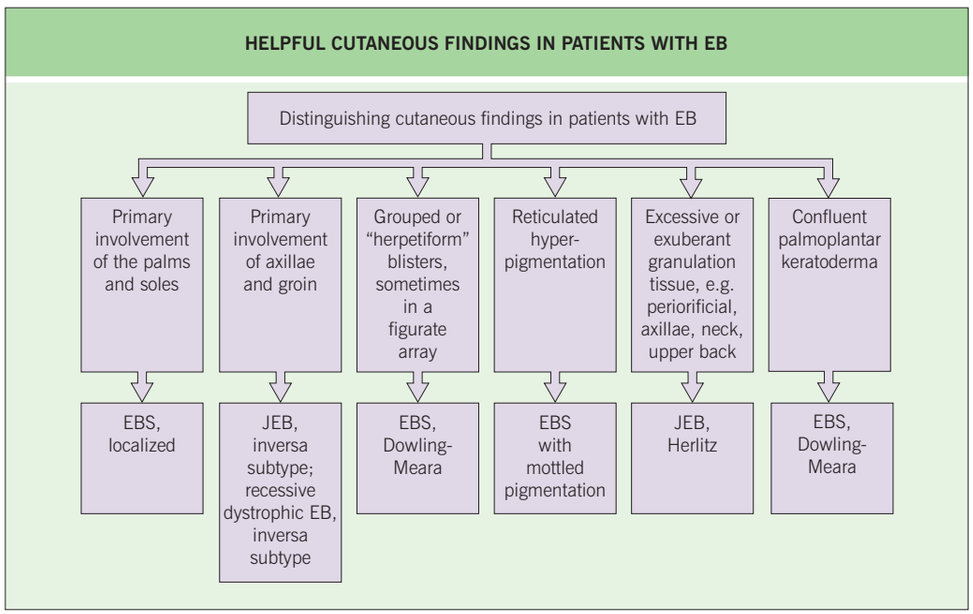


Fig. 32.6 Helpful cutaneous findings in patients with epidermolysis bullosa (EB). EBS, EB simplex; JEB, junctional EB.

Fig. 32.7 Epidermolysis bullosa simplex, Dowling–Meara. Clustered vesicles in an arcuate array on the arm (**A**) and thigh (**B**) of this child. *Courtesy, Julie V Schaffer, MD.*

Fig. 32.8 Epidermolysis bullosa simplex, Dowling–Meara. Diffuse keratoderma of the palm in an adult.

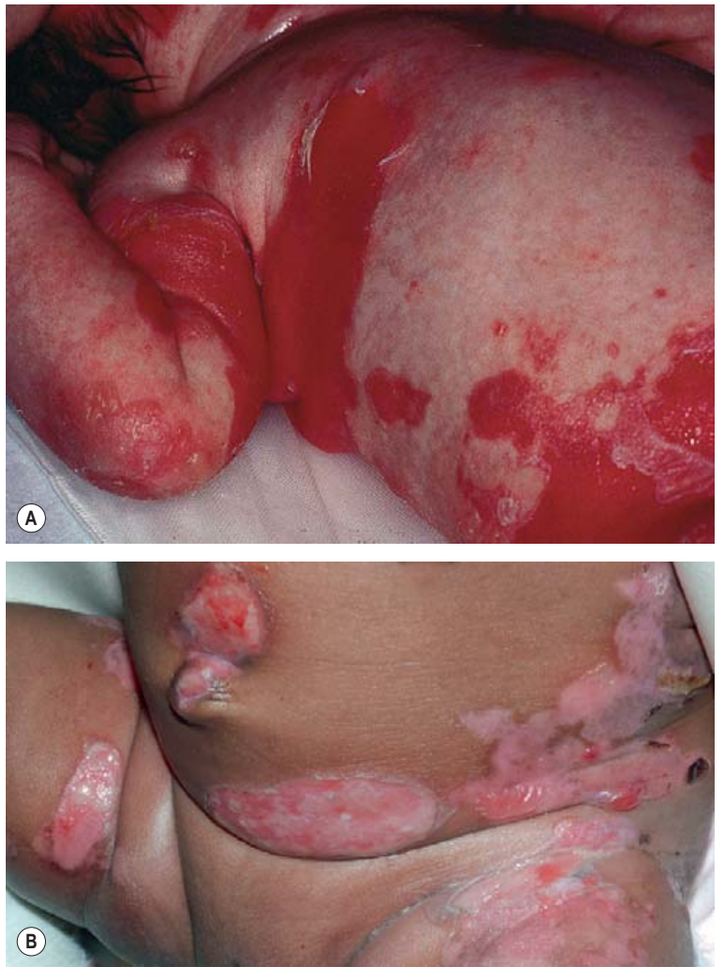


Fig. 32.9 Junctional epidermolysis bullosa, Herlitz. A Blisters on the elbow and large areas of denuded skin; note the bright red color in the axilla and groin. **B** Blisters and large erosions on the abdomen of an infant. *B, Courtesy, Julie V Schaffer, MD.*

Cutaneous Malignancies

A major complication, usually of RDEB, is the development of multiple cutaneous SCCs[41]. These tumors most often arise in chronic non-healing wounds or hyperkeratotic lesions (Fig. 32.11). Histologically, they are usually well differentiated. However, the borders of the lesions are often indistinct and they are difficult to completely excise, with a tendency to recur locally. In addition, SCCs in EB patients frequently metastasize and are strikingly unresponsive to chemotherapy or radiotherapy. Indeed, they represent the leading cause of death in EB at or after mid-adolescence, with death from an SCC of cutaneous origin occurring in most patients within 5 years of the diagnosis of their first SCC[39]. These tumors occur almost exclusively in RDEB (especially RDEB-sev/gen), although rare patients with JEB have also developed SCCs. The cumulative risk of at least one SCC in patients with RDEB-sev/gen is only 7.5% by age 20 years but rises to 68%, 80% and 90% by ages 35, 45 and 55 years, respectively[29]. In contrast, the risk of SCC in other forms of RDEB is <25% by age 45 years[41].

MAJOR EXTRACUTANEOUS COMPLICATIONS OF EPIDERMOLYSIS BULLOSA		
Complication	**EB subtype(s) most commonly affected**	
	≥50% of patients	**<50% of patients**
EYES		
Corneal blisters, ulcers and scarring	RDEB-sev/gen	JEB-H > RDEB-o, RDEB-I, JEB-nH
Ectropion formation		JEB-H; Kindler
ORAL CAVITY AND UPPER AIRWAY (EXCLUDING BLISTERS)		
Microstomia	RDEB-sev/gen	JEB-H, RDEB-I
Enamel hypoplasia	JEB (all subtypes)	
Excessive caries and premature loss of teeth	RDEB sev/gen; JEB-H	
Tracheolaryngeal stenosis	JEB-H	JEB-nH
GASTROINTESTINAL TRACT		
Esophageal strictures	RDEB-sev/gen, RDEB-I	RDEB-o, Kindler > JEB-H
Pyloric atresia	JEB-PA, EBS-PA	
Malnutrition/failure to thrive	RDEB-sev/gen, JEB-H	JEB-nH
Severe constipation	RDEB-sev/gen	JEB-H
GERD	RDEB	JEB, EBS-DM
GENITOURINARY TRACT		
Urethral meatal stenosis		RDEB-sev/gen, JEB-H, Kindler
Chronic renal failure*		RDEB-sev/gen
Hydroureter and hydronephrosis		JEB-PA, JEB-H
HEART		
Dilated cardiomyopathy		RDEB-sev/gen > JEB, RDEB-o
MUSCULOSKELETAL SYSTEM		
Pseudosyndactyly	RDEB-sev/gen	RDEB-o
Osteoporosis or osteopenia	RDEB-sev/gen	RDEB-o, JEB-H
Muscular dystrophy	EBS-MD	
BONE MARROW		
Severe multifactorial anemia	RDEB/sev-gen, JEB-H	

*Causes include renal amyloidosis and glomerulonephritis.

Table 32.2 Major extracutaneous complications of epidermolysis bullosa (EB). EBS, EB simplex; EBS-DM, EBS, Dowling–Meara; EBS-MD, EBS with muscular dystrophy; EBS-PA, EBS with pyloric atresia; GERD, gastroesophageal reflux disease; JEB, junctional EB; JEB-H, JEB, Herlitz; JEB-PA, JEB with pyloric atresia; RDEB, recessive dystrophic EB; RDEB-I, RDEB inversa; RDEB-o, RDEB, other generalized; RDEB-sev/gen, RDEB, severe generalized.

Fig. 32.10 Severe generalized recessive dystrophic epidermolysis bullosa. Note the partial "mitten" deformities of the hands in this child.

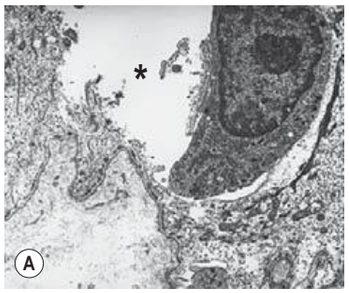
Fig. 32.11 Squamous cell carcinoma. Large squamous cell carcinoma on the ankle of a 21-year-old man with severe generalized recessive dystrophic epidermolysis bullosa. *Courtesy, Julie V Schaffer, MD.*

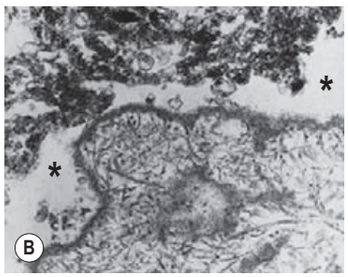
Melanoma occurs in a small number of children with RDEB-sev/gen, with a cumulative risk of 2.5% by the age of 12 years[41]. Although this is a relatively infrequent complication, careful surveillance during childhood is indicated. Children with EB, in particular those with JEB-nH, can develop large, irregularly shaped, darkly pigmented melanocytic nevi ("EB nevi") (Fig. 32.12) that clinically resemble melanoma, although they are histologically and biologically benign. A large size from the onset rather than a relatively slow horizontal expansion is a clue to the diagnosis of these EB-associated nevi.

Fig. 32.12 Large acquired melanocytic nevus at a site of blistering in a patient with junctional epidermolysis bullosa. *Courtesy, Julie V Schaffer, MD.*

PATHOLOGY

Light microscopy has no role in the diagnosis of classic forms of inherited EB, since it may be difficult to distinguish between even lower intraepidermal and subepidermal blister formation, let alone between intra-lamina lucida (i.e. JEB) and sub-lamina densa (i.e. DEB) types, without more sophisticated staining techniques[42]. However, suprabasal





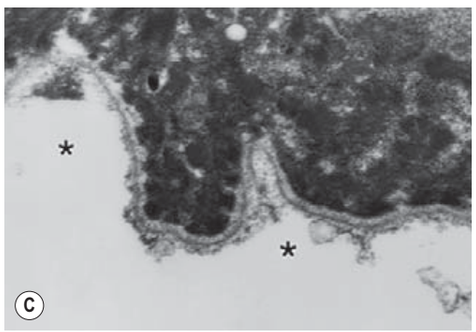


Fig. 32.13 Ultrastructure of epidermolysis bullosa simplex (EBS), junctional epidermolysis bullosa (JEB) and recessive dystrophic epidermolysis bullosa (RDEB). A Electron microscopy (EM) of an induced blister in localized EBS demonstrates skin cleavage (asterisk) within the inferior-most portion of the basilar keratinocyte. **B** EM of a spontaneous blister from a patient with the Herlitz subtype of JEB reveals skin cleavage (asterisks) within the lamina lucida. Hemidesmosomes, sub-basal dense plates and anchoring filaments are all absent, diagnostic of Herlitz disease. In contrast, anchoring fibrils are still present in normal amounts within the underlying dermis. **C** EM of the roof of a spontaneous blister from a patient with severe generalized RDEB reveals cleavage (asterisks) beneath the level of the lamina densa. Anchoring fibrils are absent along the epidermal roof of the blister, diagnostic of severe generalized RDEB.

forms of EBS due to desmoplakin, plakophilin or plakoglobin deficiency share the histologic finding of acantholysis (see Table 32.4). The two diagnostic tests that are routinely employed are transmission electron microscopy (TEM) and immunofluorescence antigenic mapping. Discrepancies between these two techniques arise in only about 3% of all specimens, suggesting that either approach may serve as the gold standard for the non-molecular diagnosis of inherited EB.

TEM distinguishes among the four major EB types by defining the ultrastructural level of blister formation (Figs 32.1 & 32.13). TEM can also be used to quantitatively and qualitatively assess specific structures, such as basilar tonofilaments, hemidesmosomes, sub-basal dense plates, anchoring filaments and anchoring fibrils[2]. Ultrastructural features of the major EB types and subtypes are summarized in Table 32.3. Immunofluorescence antigenic mapping, when coupled with the use of selected anti-basement membrane monoclonal antibodies, can distinguish among EB subtypes by the qualitative or semiquantitative assessment of the expression of specific skin-associated proteins (in particular, laminin 332 and types VII and XVII collagen)[2]. Abnormal skin staining may be seen with antibodies to plectin, $\alpha_6\beta_4$ integrin, kindlin-1 and several other structural proteins in selected EB subtypes.

DIFFERENTIAL DIAGNOSIS

Although it is difficult to determine the subtype of inherited EB on the basis of clinical findings alone, the diagnosis of EB itself is usually straightforward in anyone beyond early childhood. There is a limited differential diagnosis for a chronic mechanobullous disease with early onset and/or a positive family history[2]. The clinicopathologic features of the rare suprabasal EBS subtypes (which have adnexal and histologic manifestations that differ from classic forms of EB) and other genodermatoses that can be associated, at least transiently, with blisters and therefore potentially misdiagnosed as EB are outlined in Table 32.4. Less often, EB may be confused with acrodermatitis enteropathica, incontinentia pigmenti or pachyonychia congenita. The differential diagnosis of blisters and erosions in neonates or young infants may also include infectious diseases (e.g. herpes simplex, staphylococcal scalded

ULTRASTRUCTURAL (ELECTRON MICROSCOPIC) FINDINGS IN EPIDERMOLYSIS BULLOSA		
EB type or subtype	**Level of skin cleavage**	**Associated findings**
EB SIMPLEX (EBS)		
EBS, localized	Intracytoplasmic within basilar keratinocytes	–
EBS, Dowling–Meara	Subnuclear cytoplasm within basilar keratinocytes	Electron-dense clumps of keratin filaments (more often in lesional than perilesional skin sites)
EBS with muscular dystrophy	Intracytoplasmic within basilar keratinocytes (above the level of the HD attachment plaque)	Lack of integration of keratin filaments into the underlying HDs
EBS, autosomal recessive	Intracytoplasmic within basilar keratinocytes	Absent or reduced keratin filaments within basilar keratinocytes
EBS superficialis	Between granular and cornified cell layers	–
EBS, lethal acantholytic	Suprabasal, with acantholysis	Perinuclear retraction of keratin filaments
EBS, plakophilin-1 deficiency	Mid-epidermal	Diminutive suprabasal desmosomes; perinuclear retraction of keratin filaments
JUNCTIONAL EB (JEB)		
JEB, Herlitz	Intra-lamina lucida	Absent HDs or markedly reduced number of rudimentary HDs; absent SBDPs
JEB, non-Herlitz	Intra-lamina lucida	Normal or reduced number of HDs, which may be rudimentary
JEB with pyloric atresia	Intra-lamina lucida	Small HD plaques; attenuated SBDPs
DOMINANT DYSTROPHIC EB (DDEB)		
DDEB, generalized	Sub-lamina densa	Normal or diminished AFs
DDEB, bullous dermolysis of newborn	Sub-lamina densa	Electron-dense perinuclear stellate bodies within basilar keratinocytes; diminished AFs
RECESSIVE DYSTROPHIC EB (RDEB)		
RDEB, severe generalized	Sub-lamina densa	Absent AFs or markedly reduced number of rudimentary AFs
RDEB, generalized other	Sub-lamina densa	Reduced number of rudimentary AFs
RDEB, bullous dermolysis of newborn	Sub-lamina densa	Electron-dense perinuclear stellate bodies within basilar keratinocytes (only during time of clinically active disease); diminished AFs

Table 32.3 Ultrastructural (electron microscopic) findings in epidermolysis bullosa (EB). AFs, anchoring fibrils; HD, hemidesmosome; SBDPs, sub-basal dense plates.

SUPRABASAL FORMS OF EPIDERMOLYSIS BULLOSA SIMPLEX AND ADDITIONAL GENODERMATOSES ASSOCIATED (AT LEAST TRANSIENTLY) WITH BLISTERS		
Disorder	**Defective protein (inheritance)**	**Clinicopathologic features**
SUPRABASAL FORMS OF EPIDERMOLYSIS BULLOSA SIMPLEX (EBS)		
EBS, plakophilin deficiency (ectodermal dysplasia/skin fragility syndrome)	Plakophilin 1 (AR)	Trauma-induced blisters and erosions, especially of perioral area and extremities; PPK; hypotrichosis; nail dystrophy; occasionally defective sweating; acantholysis in skin biopsy specimens
Lethal acantholytic EBS	Desmoplakin (AR)	Generalized erosions at birth; universal alopecia; natal teeth, anonychia; variable cardiomyopathy; acantholysis in skin biopsy specimens
Skin fragility/woolly hair syndrome*	Desmoplakin (AR)	Acral blisters and erosions; focal or diffuse PPK; sparse, woolly hair; nail dystrophy; acantholysis in skin biopsy specimens
Lethal congenital EBS	Plakoglobin (AR)	Generalized erosions at birth; universal alopecia; onycholysis; acantholysis in skin biopsy specimens
Acantholytic ectodermal dysplasia	Plakoglobin (AR)	Trauma-induced blisters and erosions; hyperkeratotic, fissured perioral plaques; woolly hair; nail dystrophy; acantholysis in skin biopsy specimens
ADDITIONAL GENODERMATOSES ASSOCIATED WITH BLISTERING		
Ichthyosis bullosa of Siemens	Keratin 2 (AD)	Mauserung phenomenon (desquamation); superficial intraepidermal blistering in skin biopsy specimens
Epidermolytic ichthyosis (bullous congenital ichthyosiform erythroderma)	Keratin 1 and 10 (AD)	Blistering primarily in first few years of life; later corrugated hyperkeratosis; epidermolytic hyperkeratosis in skin biopsy specimens
Günther disease (congenital erythropoietic porphyria)	Uroporphyrinogen III synthase (AR)	Severe photosensitivity leading to blistering and deep ulcerations; elevated uroporphyrin I and coproporphyrin I; red urine; hemolytic anemia
AEC (ankyloblepharon–ectodermal dysplasia–clefting) syndrome	p63 (AD)	Ankyloblepharon; ectodermal dysplasia; cleft lip/palate; erythroderma and widespread erosions in neonates; chronic erosive scalp dermatitis; patchy alopecia
Mendes da Costa syndrome	? (X-linked)	Spontaneous formation of bullae (not provoked by trauma); absence of hair; acrocyanosis; dyspigmentation; microcephaly; mental retardation

*Patients with the additional findings of cardiomyopathy (as in Carvajal syndrome) ± dental enamel defects have also been described.

Table 32.4 Suprabasal forms of epidermolysis bullosa simplex and additional genodermatoses associated (at least transiently) with blisters.
AD, autosomal dominant; AR, autosomal recessive; PPK, palmoplantar keratoderma.

skin syndrome, bullous impetigo), sucking blisters, bullous mastocytosis, autoimmune blistering diseases, and congenital erosive and vesicular dermatosis (see Ch. 34).

The differential diagnosis of EBSS includes peeling skin syndrome[43]. Bart syndrome, which is defined as the coexistence of any type of EB and congenital localized absence of skin (CLAS; aplasia cutis congenita; see Ch. 64), is distinguished from other causes of CLAS by the presence of blisters and mechanical fragility of the skin, as well as the anatomic location of EB-associated CLAS (i.e. typically acral rather than favoring the scalp).

TREATMENT

There are currently no specific therapies for any form of inherited EB. In the future, effective gene therapy may become a reality for at least some forms of EB[44]. For example, there are reports of the successful transfer of genes, such as those that encode one of the chains of laminin 332[45], into keratinocytes from affected individuals; when these genetically corrected keratinocytes are transplanted onto immunodeficient mice, the resultant epithelium has no evidence of blistering. In a proof-of-principle experiment, a small portion of *ex vivo*-produced skin equivalent containing a corrected laminin 332 gene was transplanted onto a recipient with JEB-nH, and after several years has yet to develop blistering within its borders[46].

It has been shown that injection of either human type VII collagen or normal allogeneic fibroblasts into a mouse engrafted with type VII collagen-deficient RDEB skin can result in increased deposition of this protein along the dermo-epidermal junction and the cessation of blistering[47,48]. There are now several clinical trials in progress that are exploring the therapeutic benefit of intradermally injecting allogeneic fibroblasts into non-healing wounds in RDEB patients. Clinical trials are also ongoing to investigate the value of bone marrow-derived stem cell transplantation as a systemic treatment for RDEB[49]. In an initial report[50], bone marrow transplantation after total or partial myeloablation resulted in substantial proportions of donor cells in the skin, increased collagen VII deposition at the dermal–epidermal junction and variably decreased blistering in children with RDEB. Other investigators are studying alternative sources of stem cells for the cellular correction of this disease.

Revertant mosaicism in the skin of EB patients represents "natural gene therapy" that can restore wild-type function to a clone of cells, providing a model for potential gene manipulation strategies and possibly explaining the tendency for improvement with age in some subtypes of EB. Mitotic gene conversion, true back mutations and second-site mutations that prevent a premature termination codon or restore the reading frame have been shown to reverse disease-causing type XVII collagen mutations in individuals with JEB-nH, leading to decreased blistering in discrete areas of skin[51]. Second-site nonsense mutations have also been shown to abrogate blistering by silencing a dominant-negative keratin 14 allele in those with EBS-DM.

For now, day-to-day management of EB revolves around the prevention of mechanical trauma (including padding over bony prominences and soft/loose-fitting clothing) and infection. Bathing or soaking with 0.005% sodium hypochlorite (0.5 cup household bleach [6% sodium hypochlorite] in a full standard bathtub) or 0.25% acetic acid (1 part white vinegar [5% acetic acid] to 20 parts water) may help to reduce bacterial colonization. Antibiotics should be used judiciously, with avoidance of chronic treatment with topical mupirocin or oral antibiotics. Problematic plantar hyperhidrosis in EBS patients may improve following the topical application of aluminum chloride hexahydrate, although its effect on blistering is less certain, and injection of botulinum toxin A can reduce plantar blistering and associated pain in individuals with EBS[52].

A number of dressings are available for cutaneous wounds in EB patients (Table 32.5; see Ch. 145). As a general rule, only those that are non-adhesive or "low-tack" should be applied to EB skin. Soft silicone dressings, some of which incorporate an absorbent foam backing, are

DRESSINGS FREQUENTLY USED IN PATIENTS WITH EPIDERMOLYSIS BULLOSA		
Dressing type	**Use**	**Examples®™**
Soft silicone dressings ("low-tack")	• Suitable as primary or secondary dressings in many types of EB • May have a foam backing for mechanical protection or to wick exudate away from the wound	Mepitel, Mepilex, Mepilex Transfer, Mepilex Border
Non-adherent lipido-colloid dressings	• Suitable for primary contact	Urgotul
Hydrogel dressings	• Provide moisture to drier wounds to facilitate healing • May provide relief from pain or itch	Flexigel, Curagel, ActiForm Cool
Foam dressings	• Useful to absorb moderate amounts of wound exudate	Mepilex, Allevyn
Absorptive dressings	• Useful to absorb heavy amounts of wound exudate	Eclypse, Sorbion Sana
Silver-containing dressings	• Clinically infected or highly colonized wounds • Avoid prolonged use due to risk of silver absorption	Urgotul SSD, Mepilex AG
Other antimicrobial dressings	• Clinically infected or highly colonized wounds	Polymem, Cutimed Sorbact, Activon Tulle, Suprasorb X + PHMB

Table 32.5 Dressings frequently used in patients with epidermolysis bullosa (EB).

widely used. Silver-impregnated dressings may be helpful for heavily colonized or infected wounds, although long-term application should be avoided to minimize systemic silver absorption. Less expensive Vaseline®-impregnated gauze is another suitable dressing for non-infected wounds. Tissue culture-derived artificial skin bioequivalents are also available for use in the management of chronic, recalcitrant ulcers[53].

Systemic phenytoin inhibits collagenase and has been used in the past in JEB and RDEB patients[54], but it was not found to be effective in a randomized controlled trial[55]. Other systemic drugs that may be of benefit include tetracycline for EBS[56] and thalidomide and cyclosporine for symptomatic relief in DEB pruriginosa[57,58].

There are few reports on the use of systemic retinoids in any form of EB, although these drugs appear to be tolerated, at least in low dosage, in patients with RDEB[59]. Whether long-term treatment with low-dose systemic retinoids would help to prevent the development of SCCs in RDEB-sev/gen patients remains to be determined.

Strategies for the medical and surgical management of long-term complications of EB are outlined in Table 32.6. Multidisciplinary clinics can provide care and support for the wide range of needs that patients with EB and their families have. Families can also obtain helpful information from several educational websites, in particular www.debra.org and www.debra-international.org.

MANAGEMENT OF LONG-TERM COMPLICATIONS OF EPIDERMOLYSIS BULLOSA		
Complication	**Prevention and monitoring/detection**	**Management**
	ORAL AND GASTROINTESTINAL	
Excessive caries	• Diligent oral hygiene • Antiseptic and fluoride mouthwashes • Periodic evaluation and cleaning by a dentist	• Restorative dentistry
Microstomia		• Physical therapy • "Mouth expanding" devices
Oral ulceration		• Topical antiseptics, topical NSAIDs, barrier preparations (e.g. sucralfate suspension)
Esophageal strictures	• Evaluate dysphagia with contrast studies	• Dietary modification (soft foods/purées, caloric supplementation) • Fluoroscopically guided balloon dilatation; repeated procedures are often required • In severe and recalcitrant cases, surgical options include colonic interposition
Gastroesophageal reflux disease		• Proton pump inhibitors, H_2 blockers, prokinetic agents (e.g. domperidone [not available in the US])
Constipation	• Ensure adequate fluid intake and dietary fiber	• Osmotic laxatives (e.g. containing polyethylene glycol), mineral oil • Avoid suppositories and enemas
	NUTRITIONAL	
Growth retardation/inadequate intake to meet nutritional needs	• Monitor height, weight and body mass index • Periodically assess serum zinc, selenium, iron, vitamin D and carnitine levels (e.g. yearly) • Oral supplements to optimize intake of calories, protein, vitamins and minerals	• Consider gastrostomy feedings
	HEMATOLOGIC	
Anemia due to iron deficiency and chronic inflammation	• Monitor CBC and measures of iron stores	• Iron supplementation (oral or IV) • Consider erythropoietin or darbepoetin alpha • Consider blood transfusion if hemoglobin ≤7–8 g/dl and/or symptomatic

Table 32.6 Management of long-term complications of epidermolysis bullosa (EB)[29,60,61]. CBC, complete blood count; NSAID, nonsteroidal anti-inflammatory drug.

Continued

MANAGEMENT OF LONG-TERM COMPLICATIONS OF EPIDERMOLYSIS BULLOSA		
Complication	**Prevention and monitoring/detection**	**Management**
	GENITOURINARY AND RENAL	
Urinary outflow obstruction (e.g. urethral or ureteral strictures)	• Consider annual ultrasound of the urinary tract and urodynamic studies (especially for JEB)	• Dilatation procedures as needed to treat obstruction • Avoid unnecessary instrumentation
Renal disease (e.g. hydronephrosis, post-infectious glomerulonephritis, renal amyloidosis, IgA nephropathy)	• Blood urea nitrogen & serum electrolyte levels, urinalysis and blood pressure evaluation every 6 months in RDEB patients • Adequately treat streptococcal infections	• Hemodialysis or peritoneal dialysis if renal failure develops
	MUSCULOSKELETAL	
Osteopenia and osteoporosis	• Annual DEXA scan and spinal radiographs beginning at age 5 years in RDEB and JEB patients • Calcium and vitamin D supplementation	• Consider IV bisphosphonate therapy
Pseudosyndactyly of hands/feet	• Cushioned splints on hands/forearms and individual wrapping of fingers in RDEB patients	• Surgery to release contractures and webbing
	ONCOLOGIC	
Cutaneous squamous cell carcinoma	• Periodic total-body skin examinations; for RDEB patients, approximately every 3–6 months beginning at age 10 years and every 3 months after age 16 years • Biopsy or monitor non-healing ulcers (see Fig. 32.11) • Consider taking serial photographs	• Excision ± skin grafting (sometimes amputation); consider MRI to assess extent of local disease • Consider staging with CT, PET-CT, sentinel lymph node biopsy
	OCULAR	
Chronic complications include corneal scarring, symblepharon, ectropion	• Periodic ophthalmologic evaluation for patients with eye involvement • Lubricating eye drops	• Surgical procedures, e.g. division of symblepharon, amniotic membrane transplantation
	CARDIAC	
Dilated cardiomyopathy	• Consider annual echocardiography beginning in late childhood for RDEB patients	• Medical management • Supplement selenium and carnitine if deficient
	PSYCHOLOGICAL AND PSYCHIATRIC	
Disrupted family unit (e.g. via divorce)	• Consider family counseling, support groups	• Psychological/family counseling
Depression and suicidal ideation/attempts	• Consider psychological counseling, support groups	• Psychiatric evaluation, antidepressant therapy

Table 32.6 Management of long-term complications of epidermolysis bullosa (EB) (cont'd)[29,60,61]. CT, computed tomography; JEB, junctional EB; MRI, magentic resonance imaging; PET, positron emission tomography; RDEB, recessive dystrophic EB.

REFERENCES

1. Gedde-Dahl T Jr. Epidermolysis Bullosa. A Clinical, Genetic and Epidemiologic Study. Baltimore: Johns Hopkins University Press, 1971:1–180.
2. Fine J-D, Eady RAJ, Bauer EA, et al. The classification of inherited epidermolysis bullosa (EB): report of the Third International Consensus Meeting on diagnosis and classification of EB. J Am Acad Dermatol. 2008;48:931–50.
3. Fine JD, Bauer EA, Gedde-Dahl T. Inherited epidermolysis bullosa: definition and historical overview. In: Fine JD, Bauer EA, McGuire J, Moshell A (eds). Epidermolysis Bullosa: Clinical, Epidemiologic, and Laboratory Advances, and the Findings of the National Epidermolysis Bullosa Registry. Baltimore: Johns Hopkins University Press, 1999:1–19.
4. Pearson RW. Studies on the pathogenesis of epidermolysis bullosa. J Invest Dermatol. 1962;39:551–75.
5. Goldsmith LA, Briggaman RA. Monoclonal antibodies to anchoring fibrils for the diagnosis of epidermolysis bullosa. J Invest Dermatol. 1983;81:464–6.
6. Fine JD, Breathnach SM, Hintner H, Katz SI. KF-1 monoclonal antibody defines a specific basement membrane antigenic defect in dystrophic forms of epidermolysis bullosa. J Invest Dermatol. 1984;82:35–8.
7. Heagerty AHM, Kennedy AR, Leigh IM, et al. Identification of an epidermal basement membrane defect in recessive forms of dystrophic epidermolysis bullosa by LH 7:2 monoclonal antibody: use in diagnosis. Br J Dermatol. 1986;115:125–31.
8. Heagerty AHM, Kennedy AR, Eady RAJ, et al. GB3 monoclonal antibody for diagnosis of junctional epidermolysis bullosa. Lancet. 1986;1:860.
9. Fine JD, Johnson LB, Suchindran CM. The National Epidermolysis Bullosa Registry. J Invest Dermatol. 1994;102:54S–6S.
10. Fine JD, Bauer EA, McGuire J, Moshell A. Epidermolysis Bullosa: Clinical, Epidemiologic, and Laboratory Advances, and the Findings of the National Epidermolysis Bullosa Registry. Baltimore: Johns Hopkins University Press, 1999:520.
11. Bonifas JM, Rothman AL, Epstein E. Linkage of epidermolysis bullosa simplex to probes in the region of keratin gene clusters on chromosomes 12q and 17q. J Invest Dermatol. 1991;39:503A.
12. Fine JD, Johnson LB, Suchindran C, et al. The epidemiology of inherited EB: findings within American, Canadian, and European study populations. In: Fine JD, Bauer EA, McGuire J, Moshell A (eds). Epidermolysis Bullosa: Clinical, Epidemiologic, and Laboratory Advances, and the Findings of the National Epidermolysis Bullosa Registry. Baltimore: Johns Hopkins University Press, 1999:101–13.
13. Pfendner E, Uitto J, Fine J-D. Epidermolysis bullosa carrier frequencies in the US population. J Invest Dermatol. 2001;116:483–4.
14. Fuchs E, Coulombe P, Cheng J, et al. Genetic bases of epidermolysis bullosa simplex and epidermolytic hyperkeratosis. J Invest Dermatol. 1994;103(suppl.):25S–30S.
15. Fuchs EV. The molecular biology of epidermolysis bullosa simplex. In: Fine JD, Bauer EA, McGuire J, Moshell A (eds). Epidermolysis Bullosa: Clinical, Epidemiologic, and Laboratory Advances, and the Findings of the National Epidermolysis Bullosa Registry. Baltimore: Johns Hopkins University Press, 1999:280–99.
16. Pulkkinen L, Uitto J, Christiano AM. The molecular basis of the junctional forms of epidermolysis bullosa. In: Fine JD, Bauer EA, McGuire J, Moshell A (eds). Epidermolysis Bullosa: Clinical, Epidemiologic, and Laboratory Advances, and the Findings of the National Epidermolysis Bullosa Registry. Baltimore: Johns Hopkins University Press, 1999:300–25.
17. Christiano AM, Uitto J. Molecular diagnosis of inherited skin diseases: the paradigm of dystrophic epidermolysis bullosa. Adv Dermatol. 1996;11:199–214.
18. Uitto J, Pulkkinen L, Christiano AM. The molecular basis of the dystrophic forms of epidermolysis bullosa. In: Fine JD, Bauer EA, McGuire J, Moshell A (eds). Epidermolysis Bullosa: Clinical, Epidemiologic, and Laboratory Advances, and the Findings of the National Epidermolysis Bullosa Registry. Baltimore: Johns Hopkins University Press, 1999:326–50.
19. Uitto J, Christiano AM. Molecular basis for the dystrophic forms of epidermolysis bullosa: mutations in the type VII collagen gene. Arch Dermatol Res. 1994;287:16–22.
20. Ortiz-Urda S, Garcia J, Green CL, et al. Type VII collagen is required for Ras-driven epidermal tumorigenesis. Science. 2005;307:1773–6.
21. Pourreyron C, Cox G, Mao X, et al. Patients with recessive dystrophic epidermolysis bullosa develop squamous-cell carcinoma regardless of type VII collagen expression. J Invest Dermatol. 2007;127:2438–44.
22. Fine JD, Horiguchi Y, Stein DH, et al. Intraepidermal type VII collagen. Evidence for abnormal intracytoplasmic processing of a major basement protein in rare patients with dominant and possibly localized recessive forms of dystrophic epidermolysis bullosa. J Am Acad Dermatol. 1990;22:188–95.
23. Christiano AM, Fine JD, Uitto J. Genetic basis of dominantly inherited transient bullous dermolysis of the newborn: a splice site mutation in the type VII collagen gene. J Invest Dermatol. 1997;109:811–14.
24. Fine JD, Johnson LB, Cronce D, et al. Intracytoplasmic retention of type VII collagen and dominant dystrophic epidermolysis bullosa: reversal of defect following

cessation of or marked improvement in disease activity. J Invest Dermatol. 1993;101:232–6.
25. Fine JD. The classification of inherited epidermolysis bullosa: current approach, pitfalls, unanswered questions, and future directions. In: Fine JD, Bauer EA, McGuire J, Moshell A (eds). Epidermolysis Bullosa: Clinical, Epidemiologic, and Laboratory Advances, and the Findings of the National Epidermolysis Bullosa Registry. Baltimore: Johns Hopkins University Press, 1999:20–47.
26. Fine JD, Johnson LB, Suchindran C, et al. Cutaneous and skin-associated musculoskeletal manifestations of inherited EB: the National Epidermolysis Bullosa Registry experience. In: Fine JD, Bauer EA, McGuire J, Moshell A (eds). Epidermolysis Bullosa: Clinical, Epidemiologic, and Laboratory Advances, and the Findings of the National Epidermolysis Bullosa Registry. Baltimore: Johns Hopkins University Press, 1999:114–46.
27. Fine JD, Johnson LB, Suchindran C, et al. Extracutaneous features of inherited EB: the National Epidermolysis Bullosa Registry experience. In: Fine JD, Bauer EA, McGuire J, Moshell A (eds). Epidermolysis Bullosa: Clinical, Epidemiologic, and Laboratory Advances, and the Findings of the National Epidermolysis Bullosa Registry. Baltimore: Johns Hopkins University Press, 1999:147–74.
28. Fine JD, Johnson LB, Moshell A, Suchindran C. The risk of selected major extracutaneous outcomes in inherited epidermolysis bullosa: lifetable analyses of the National Epidermolysis Bullosa Registry study population. In: Fine JD, Bauer EA, McGuire J, Moshell A (eds). Epidermolysis Bullosa: Clinical, Epidemiologic, and Laboratory Advances, and the Findings of the National Epidermolysis Bullosa Registry. Baltimore: Johns Hopkins University Press, 1999:193–205.
29. Fine JD, Mellerio J. Extracutaneous manifestations and complications of inherited epidermolysis bullosa. Parts I & II. J Am Acad Dermatol. 2009;61:367–402.
30. Fine JD, Johnson LB, Weiner M, et al. Eye involvement in inherited epidermolysis bullosa (EB): experience of the National EB registry. Am J Ophthalmol. 2004;138:254–62.
31. Fine JD, Johnson LB, Weiner M, Suchindran C. Gastrointestinal complications of inherited epidermolysis bullosa (EB): experience of the National EB registry. J Pediatr Gastroenterol Nutr. 2008;46:147–58.
32. Fine JD, Johnson LB, Weiner M, et al. Tracheolaryngeal complications of inherited epidermolysis bullosa: cumulative experience of the National EB Registry. Laryngoscope. 2007;117:1652–60.
33. Wright JT, Fine JD, Johnson LB. Hereditary epidermolysis bullosa: oral manifestations and dental management. Pediatr Dent. 1993;15:242–8.
34. Wright JT. Oral manifestations of epidermolysis bullosa. In: Fine JD, Bauer EA, McGuire J, Moshell A (eds). Epidermolysis Bullosa: Clinical, Epidemiologic, and Laboratory Advances, and the Findings of the National Epidermolysis Bullosa Registry. Baltimore: Johns Hopkins University Press, 1999:236–57.
35. Wright JT, Fine JD, Johnson L. Dental caries risk in hereditary epidermolysis bullosa. Pediatr Dent. 1994;16:427–32.
36. Fine JD, Johnson LB, Weiner M, et al. Pseudosyndactyly and musculoskeletal deformities in inherited epidermolysis bullosa (EB): experience of the National Epidermolysis Bullosa Registry, 1986–2002. J Hand Surg [Br]. 2005;30:14–22.
37. Fine JD, Johnson LB, Weiner M, et al. Inherited epidermolysis bullosa (EB) and the risk of death from renal disease: experience of the National Epidermolysis Bullosa Registry. Am J Kidney Dis. 2004;44:651–60.
38. Fine JD, Hall M, Weiner M, et al. The risk of cardiomyopathy in inherited epidermolysis bullosa. Br J Dermatol. 2008;159:677–82.
39. Fine JD, Johnson LB, Suchindran C, et al. Premature death and inherited epidermolysis bullosa: contingency table and lifetable analyses of the National Epidermolysis Bullosa Registry study population. In: Fine JD, Bauer EA, McGuire J, Moshell A (eds). Epidermolysis Bullosa: Clinical, Epidemiologic, and Laboratory Advances, and the Findings of the National Epidermolysis Bullosa Registry. Baltimore: Johns Hopkins University Press, 1999:206–24.
40. Fine, JD, Johnson LB, Weiner M, et al. Cause-specific risks of childhood death in inherited epidermolysis bullosa. J Pediatr. 2008;152:276–80.
41. Fine JD, Johnson LB, Suchindran C, et al. Cancer and inherited epidermolysis bullosa: lifetable analyses of the National Epidermolysis Bullosa Registry study population. In: Fine JD, Bauer EA, McGuire J, Moshell A (eds). Epidermolysis Bullosa: Clinical, Epidemiologic, and Laboratory Advances, and the Findings of the National Epidermolysis Bullosa Registry. Baltimore: Johns Hopkins University Press, 1999:175–92.
42. Fine JD, Smith LT. Non-molecular diagnostic testing of inherited epidermolysis bullosa: current techniques, major findings, and relative sensitivity and specificity. In: Fine JD, Bauer EA, McGuire J, Moshell A (eds). Epidermolysis Bullosa: Clinical, Epidemiologic, and Laboratory Advances, and the Findings of the National Epidermolysis Bullosa Registry. Baltimore: Johns Hopkins University Press, 1999:48–78.
43. Fine JD, Johnson L, Wright T. Epidermolysis bullosa simplex superficialis: a new variant of epidermolysis bullosa characterized by subcorneal skin cleavage mimicking peeling skin syndrome. Arch Dermatol. 1989;125:633–8.
44. Fenjves ES. Gene therapy: principles and potential application in inherited epidermolysis bullosa. In: Fine JD, Bauer EA, McGuire J, Moshell A (eds). Epidermolysis Bullosa: Clinical, Epidemiologic, and Laboratory Advances, and the Findings of the National Epidermolysis Bullosa Registry. Baltimore: Johns Hopkins University Press, 1999:407–19.
45. Ortiz-Urda S, Thyagarajan B, Keene DR, et al. PhiC31 integrase-mediated nonviral genetic correction of junctional epidermolysis bullosa. Human Gene Ther. 2003;14:923–8.
46. Mavilio F, Pellegrini G, Ferrari S, et al. Correction of junctional epidermolysis bullosa by transplantation of genetically modified epidermal stem cells. Nat Med. 2006;12:1397–402.
47. Woodley DT, Remington J, Huang Y, et al. Intravenously injected human fibroblasts home to skin wounds, deliver type VII collagen, and promote wound healing. Mol Ther. 2007;15:628–35.
48. Remington J, Wang X, Hou Y, et al. Injection of recombinant human type VII collagen corrects the disease phenotype in a murine model of dystrophic epidermolysis bullosa. Mol Ther. 2009;17:26–33.
49. Tolar J, Ishida-Yamamoto A, Riddle M, et al. Amelioration of epidermolysis bullosa by transfer of wild-type bone marrow cells. Blood. 2009;29:1167–74.
50. Wagner JE, Ishida-Yamamoto A, McGrath JA, et al. Bone marrow transplantation for recessive dystrophic epidermolysis bullosa. N Engl J Med. 2010;363 :629–39.
51. Jonkman MF, Pasmooij AM. Revertant mosaicism: patchwork in the skin. N Engl J Med. 2009;360: 1680–2.
52. Swartling C, Karlqvist M, Hymnelius K, et al. Botulinum toxin in the treatment of sweat-worsened foot problems in patients with epidermolysis bullosa simplex and pachyonychia congenita. Br J Dermatol. 2010;163:1072–6.
53. Fine JD. Skin bioequivalents and their role in the treatment of inherited epidermolysis bullosa [Editorial]. Arch Dermatol. 2000;136:1259–60.
54. Fine JD, Johnson L. Efficacy of systemic phenytoin in the treatment of junctional epidermolysis bullosa. Arch Dermatol. 1988;124:1402–6.
55. Caldwell-Brown D, Stern RS, Lin AN, Carter DM. Lack of efficacy of phenytoin in recessive dystrophic epidermolysis bullosa. N Engl J Med. 1992;327:163–7.
56. Fine JD, Eady RAJ. Tetracycline and epidermolysis bullosa simplex – a new indication for one of the oldest and most widely used drugs in dermatology? Arch Dermatol. 1999;135:981–2.
57. Ozanic BS, Fassihi H, Mellerio J, et al. Thalidomide in the management of epidermolysis bullosa pruriginosa. Br J Dermatol. 2005;152:1332–4.
58. Yamasaki H, Tada J, Yoshioka T, Arata J. Epidermolysis bullosa pruriginosa (McGrath) successfully controlled by oral cyclosporin. Br J Dermatol. 1994;130:717–25.
59. Fine JD, Weiner M, Stein A, et al. Systemic isotretinoin and recessive dystrophic epidermolysis bullosa (RDEB): results of a Phase 1 clinical trial. J Invest Dermatol. 2001;117:543.
60. Fine JD, Bauer EA, McGuire J. The treatment of inherited epidermolysis bullosa: nonmolecular approaches. In: Fine JD, Bauer EA, McGuire J, Moshell A (eds). Epidermolysis Bullosa: Clinical, Epidemiologic, and Laboratory Advances, and the Findings of the National Epidermolysis Bullosa Registry. Baltimore: Johns Hopkins University Press, 1999:374–406.
61. Fine JD, McGuire J. Altered nutrition and inherited epidermolysis bullosa. In: Fine JD, Bauer EA, McGuire J, Moshell A (eds). Epidermolysis Bullosa: Clinical, Epidemiologic, and Laboratory Advances, and the Findings of the National Epidermolysis Bullosa Registry. Baltimore: Johns Hopkins University Press, 1999: 225–35.

This page intentionally left blank

Other Vesiculobullous Diseases 33

José M Mascaró Jr

Chapter Contents

Bullosis diabeticorum 515
Coma blisters 515
Friction blisters 517
Bullous small vessel vasculitis 518
Bullous drug eruptions 518
Bullous insect bite reactions 518
Delayed postburn/postgraft blisters 520
Edema blisters 520
PUVA-induced acrobullous dermatosis 521

Vesiculobullous diseases of the skin encompass a wide range of entities, including autoimmune bullous diseases and hereditary blistering dermatoses. However, there are other diseases or situations in which blisters may develop. This chapter will focus on the latter group of vesiculobullous diseases.

BULLOSIS DIABETICORUM

Synonyms: ■ Diabetic bullae ■ Bullous eruption of diabetes mellitus

Key features

- A rare condition associated with diabetes mellitus
- Tense blisters develop on normal-appearing skin in acral sites (feet, lower legs, hands); there is frequently an association with peripheral neuropathy
- Histologically, intraepidermal and/or subepidermal blisters are observed
- Spontaneous healing usually occurs within 2 to 6 weeks

History

Bullosis diabeticorum was first described by Kramer in 1930. In 1967, Cantwell and Martz[1] introduced the term "bullosis diabeticorum".

Epidemiology

The exact prevalence of bullosis diabeticorum is unknown. Although it has often been described as one of the rarest cutaneous complications of diabetes[2], the authors of a more recent case series argued that it is probably more common than previously thought[3]. The age of onset ranges from 15 to 85 years, with a mean age of 55 years. A 2:1 male-to-female ratio has been reported.

Pathogenesis

Although bullosis diabeticorum has been related to trauma and the microangiopathy of diabetes, little is known about its cause. Diabetics can develop blisters after minimal trauma, and some authors have found a reduced threshold for inducing suction blisters in these patients[2,4]. There is no evidence of an infectious etiology.

Clinical Features

Bullosis diabeticorum is characterized by a sudden and spontaneous appearance of bland vesicles and bullae on the distal extremities of diabetics. The most frequent locations (in decreasing order) are the feet, lower legs, hands, and forearms. Lesions are rarely seen on the trunk. There are usually no symptoms, except for a mild burning sensation. The lesions often develop "overnight", and in the absence of known trauma. Blisters arise within normal-appearing skin, are tense, and vary in diameter from 0.5 to several centimeters (Fig. 33.1). They contain a clear, sterile fluid that can be more viscous than that found in friction blisters.

Most patients are longstanding diabetics, but in some cases bullosis diabeticorum has been the presenting sign of diabetes mellitus. It can be associated with insulin-dependent diabetes mellitus, as well as non-insulin-dependent (type 2) diabetes mellitus. Many of these patients have associated polyneuropathy, retinopathy or nephropathy.

Pathology

The histologic findings are heterogeneous. Initial reports described intraepidermal blisters, whereas recent publications have usually described subepidermal bullae. It has been suggested that the level of cleavage is subepidermal, and that intraepidermal blisters represent older lesions undergoing re-epithelialization. Direct immunofluorescence (DIF) examination is usually negative, although one report described nonspecific IgM and C3 deposits within dermal blood vessel walls. By electron microscopy, subepidermal blisters with a separation at the level of the lamina lucida or below the lamina densa have been observed[3].

Differential Diagnosis

In porphyria cutanea tarda and pseudoporphyria associated with dialysis and medications, the blisters are usually <1 cm in diameter and favor the hands rather than the feet and ankles. Because chronic renal failure, atherosclerotic cardiovascular disease and bacterial infections are well-established complications of diabetes, patients may be receiving dialysis, diuretics and/or antibiotics. Localized bullous pemphigoid, epidermolysis bullosa acquisita (EBA) and linear IgA bullous dermatosis (including drug-induced) are differentiated by histologic examination, DIF, and, if needed, indirect immunofluorescence (IIF) or ELISA. In addition, there is an accentuation of lesions at sites of friction in the majority of patients with EBA. If there is surrounding erythema, warmth and tenderness, the possibility of bullous cellulitis must be considered, and if serous crusts, bullous impetigo.

Treatment

Most patients have spontaneous healing of their lesions in 2 to 6 weeks. Treatment focuses on aspiration of blisters or placement of a small window in the blister roof and application of topical antiseptics to reduce discomfort and prevent secondary infection.

COMA BLISTERS

Synonyms: ■ Coma bullae ■ Drug-induced coma blisters ■ Barbiturate blisters ■ Neurologic blisters

Fig. 33.1 Bullosis diabeticorum. A tense blister on the palm as well as desquamation at sites of previous bullae.

Fig. 33.2 Coma bullae. Blisters developed in an area of pressure in a previously comatose patient.

Fig. 33.3 Neurologic blisters. Tense blisters on the dorsal aspect of the fingers on the hemiplegic side of a patient with a previous cerebrovascular accident.

Key features

- Associated with loss of consciousness, neurologic diseases or prolonged immobilization
- Tense blisters develop on normal-appearing skin
- Biopsy specimens show intraepidermal or subepidermal blisters, with a characteristic necrosis of sweat glands
- Spontaneous healing occurs in 1 to 2 weeks

Introduction

In some comatose patients, blisters will develop within 48–72 hours of loss of consciousness, primarily at pressure sites. Although classically associated with barbiturate overdose, they can be seen in the setting of coma due to other medications (e.g. opioids), infections (e.g. viral encephalitis), metabolic disturbances (e.g. hypoglycemia) and neurologic dysfunction (e.g. cerebrovascular accidents).

History

Coma blisters were first described in 1806 by Larrey, Napoleon's surgeon, who noticed these lesions in soldiers who had been comatose from carbon monoxide intoxication.

Epidemiology

In 1952, Holten reported the appearance of coma blisters in 4% of a series of 501 patients with barbiturate poisoning[5]. In another study, blisters were found in 6.5% of barbiturate overdoses[6]. Although most reported cases have been associated with barbiturate overdose, blisters have also been observed in those whose comas were induced by overdosage of other medications, such as benzodiazepines, tricyclic antidepressants, opioids, hypnotics or antipsychotics, as well as alcohol intoxication[7]. Similar lesions have also been described in patients with non-drug-induced coma, e.g. coma resulting from carbon monoxide poisoning, head trauma, cerebrovascular accidents, viral encephalitis, hypoglycemia, diabetic ketoacidosis or hepatic encephalopathy[8,9]. In addition, bullous lesions have been observed in non-comatose patients, in particular those with severe neurologic disease or prolonged immobilization (e.g. secondary to accidents or postoperative)[9].

Pathogenesis

The pathogenesis is unclear. Originally, a direct toxic drug effect was implicated, particularly because of the association with drug intoxication and the frequent finding of eccrine gland necrosis (many drugs are thought to be excreted by sweat glands). However, this did not explain the non-drug-induced cases. Therefore, pressure, friction and local hypoxia have been implicated as etiologic factors. The pressure/ischemic hypothesis is supported by the fact that most, if not all, lesions appear at sites of pressure.

Clinical Features

Lesions appear at body sites exposed to maximum pressure during unconsciousness or prolonged immobilization. They first appear 24 hours after the onset of coma as blanchable erythematous patches or plaques that progress to violaceous plaques. Blisters or erosions then develop within 48–72 hours after the onset of coma within these locations (Fig. 33.2). If the patient survives, the erosions usually heal spontaneously over 1 or 2 weeks. In some patients, residual scarring can result. Compression neuropathies and non-traumatic rhabdomyolysis are additional complications seen in patients with coma bullae[7–10]. As previously mentioned, the same type of blisters can occur in patients with neurologic diseases (Fig. 33.3).

Pathology

The blisters are predominantly subepidermal. However, intraepidermal blisters are also observed as the result of re-epithelialization of older lesions or epidermal spongiosis. There is a variable degree of epidermal necrosis. Sweat gland necrosis is a characteristic finding (Fig. 33.4), and focal necrosis of the epithelium of the pilosebaceous follicles can also be seen. There is only a sparse inflammatory cell infiltrate. DIF is usually negative, but nonspecific granular deposits of IgM and C3 have been found within the walls of dermal blood vessels[7].

Differential Diagnosis

In most patients, the clinical setting alone is sufficient to make the diagnosis (Table 33.1). A cutaneous biopsy will allow differentiation from friction blisters. An intraepidermal blister cavity just below the granular layer is seen in friction blisters, whereas a subepidermal split with sweat gland/follicular necrosis is characteristic of coma bullae. Based upon distribution, clinical appearance and histologic findings, multiple fixed drug eruptions can be excluded (see Fig. 33.8).

Treatment

Coma blisters heal spontaneously over 1 or 2 weeks. In non-comatose patients, frequent postural changes help to resolve and prevent the disorder.

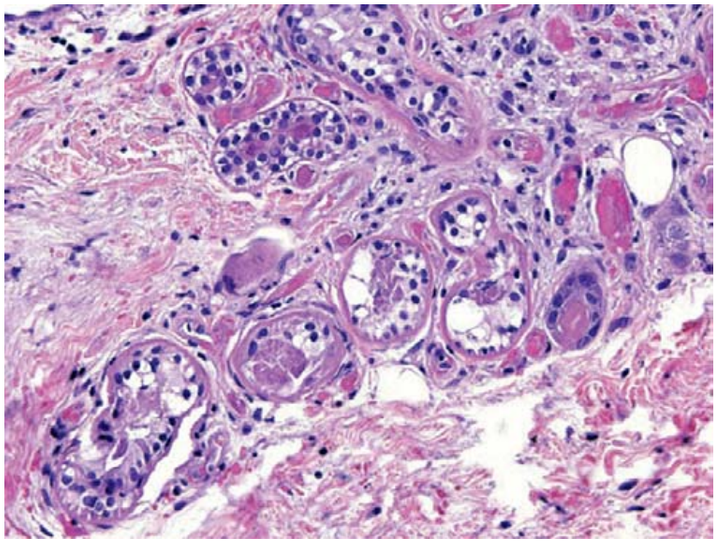


Fig. 33.4 Bulla due to prolonged immobilization – histologic features. The patient had sustained a hip fracture and was immobilized for 2 days on the floor. Detection of the characteristic sweat gland necrosis aided in the diagnosis.

FRICTION BLISTERS

Key features

- Friction blisters occur most commonly on the soles and heels
- They are the result of repeated friction, e.g. walking or running in ill-fitting shoes; they may also develop on the palms and fingers if a repetitive action is performed
- Histologically, blistering occurs just below the stratum granulosum

Epidemiology

Friction blisters are very common in the general population. Almost every person remembers developing such lesions when wearing a new pair of shoes. They are particularly common in young and active persons, especially those engaged in the military and sports.

Pathogenesis

Frictional shearing forces occur within the epidermis when the surface of an object rubs against the skin surface. Repetition of this rubbing action over a period of time can induce the appearance of blisters. Rubbing of moist skin produces higher frictional forces than with very dry or very wet skin[11]. Poorly fitting shoes, heat and sweating are predisposing factors.

DIFFERENTIAL DIAGNOSIS OF VESICULOBULLOUS DISEASES*

Disease	Clinical setting	Clinical features	Histopathology
Bullosis diabeticorum	Longstanding diabetes mellitus	Tense blisters in acral sites	Subepidermal or intraepidermal blisters with minimal inflammation
Coma blisters	Coma (drug- and non-drug-induced), neurologic disease, prolonged immobilization	Tense blisters at sites of maximal pressure	Subepidermal blister Necrosis of eccrine glands
Friction blisters	Primarily on soles (secondary to shoes) or hands	Burning, erythematous macules and blisters at friction sites	Initially intraepidermal blisters (below stratum granulosum)
Bullous small vessel vasculitis	Patients with small vessel vasculitis (cutaneous or systemic)	Palpable purpura, hemorrhagic vesicles and bullae, ulceration Usually on the distal extremities	Leukocytoclastic vasculitis Subepidermal blister with epidermal necrosis
Bullous drug eruptions	Patients receiving medications	Depends on eruption type (see Table 33.2)	Depends on eruption type (see Table 33.2)
Bullous insect bites	Any (more common in children) Underlying hematologic malignancy (e.g. CLL, mantle cell lymphoma, NK/T-cell lymphoma)†	Grouped pruritic papules with central blistering and/or bland vesicobullae May also have persistent papulonodules	Intraepidermal blisters with spongiosis; coalescence leads to subepidermal blisters Abundant eosinophils Flame figures, especially in exaggerated reactions
Delayed postburn/ postgraft blisters	Patients with burns (burn site, graft recipient site, graft donor site) or injured skin	Blisters and vesicles appear within injured skin several weeks after healing	Subepidermal or intradermal blisters with minimal inflammation
Edema blisters	Acute exacerbation of chronic edema Anasarca	Tense blisters in areas of edema, often in dependent sites, e.g. feet or ankles	Marked spongiosis and dermal edema

*Excluding autoimmune bullous diseases, hereditary blistering dermatoses, infections, lichenoid dermatoses (e.g. lichen planus, lichen sclerosus) and entities covered in Tables 34.1 and 34.2.
†Also develop insect bite-like reactions with similar clinical appearance and histologic findings.

Table 33.1 Differential diagnosis of vesiculobullous diseases. CLL, chronic lymphocytic leukemia; NK, natural killer.

Clinical Features

Friction blisters most frequently develop in areas with thick stratum corneum (soles, heels, palms, fingers). They are particularly common in regions where friction is intense and repeated (e.g. feet). The lesions initially present as erythematous macules at sites of friction and later develop into blisters. The patients complain of an associated burning sensation or pain, and the blister fluid may be clear or blood-tinged.

Pathology

Friction blisters are intraepidermal blisters resulting from necrosis of keratinocytes. The level of the split is variable but usually in the stratum spinosum just below the stratum granulosum. The roof of the blister is formed by the stratum corneum, the stratum granulosum, and some cellular debris. The upper portion of the floor of the blister cavity contains pale and degenerated keratinocytes that stain faintly. The deeper layers of the epidermis are normal[12]. There is only a sparse perivascular inflammatory infiltrate in the superficial dermis.

Differential Diagnosis

Most cases of friction blisters can be easily diagnosed clinically (see Table 33.1). The localized variant of epidermolysis bullosa simplex (Weber–Cockayne) is suspected when there is an exaggerated response to friction; histologic examination of a fresh or induced blister should show separation subepidermally or within the basal layer of the epidermis. Immunofluorescence antigenic mapping provides confirmation of the diagnosis. EBA can mimic friction blisters, but it is differentiated by histologic examination and DIF (see Fig. 33.8).

Treatment

Friction blisters can heal spontaneously without treatment. Drainage of blister contents via a small "window" in the blister roof relieves pressure and discomfort and prevents the accumulation of fluid; it also allows the blister roof to remain largely intact. Hydrocolloid or simple dressings can also be utilized.

BULLOUS SMALL VESSEL VASCULITIS

Occasionally, patients with small vessel vasculitis will develop superimposed vesicles and bullae, especially on the distal extremities (Fig. 33.5). These are often hemorrhagic and can progress to ulceration. Histopathologically, a leukocytoclastic vasculitis is seen, which differentiates this entity from other blistering diseases. This may be a sign of more severe disease (see Ch. 24).

Fig. 33.5 Bullous variant of small vessel vasculitis. Histologic examination demonstrated leukocytoclastic vasculitis. *Courtesy, Jean L. Bolognia, MD.*

BULLOUS DRUG ERUPTIONS

Key features

- Some drug eruptions can present as blistering eruptions
- Eruptions can be both localized and widespread
- Clinical, histologic and immunofluorescence findings vary, depending on the type of drug eruption

Vesicles and bullae can develop in a variety of drug eruptions. The latter include fixed drug eruption, Stevens–Johnson syndrome, toxic epidermal necrolysis, drug-induced variants of linear IgA bullous dermatosis, bullous pemphigoid and pemphigus, pseudoporphyria, toxic erythema of chemotherapy, halogenodermas, acute generalized exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS), and phototoxic drug eruptions (e.g. doxycycline; see Ch. 87). These eruptions are discussed elsewhere in detail and are briefly summarized in Table 33.2.

BULLOUS INSECT BITE REACTIONS

Key features

- Bullous insect bite reactions are frequent, particularly in children, although patients rarely recall being bitten
- Severe insect bite reactions as well as insect bite-like reactions can be seen in patients with hematologic malignancies

Introduction

Although most insect bite reactions present as pruritic erythematous papules (see Ch. 85), vesiculobullous reactions are not uncommon.

Epidemiology

There seems to be no difference in the incidence of insect bites based on sex, race or age. Certain individuals may be bitten more frequently because of their body temperature, odor, use of perfumes, or carbon dioxide excretion. Children tend to have more severe reactions than adults because the latter tend to become desensitized by repeated exposures over time. Over the past 15 years, it has been increasingly recognized that patients with chronic lymphocytic leukemia (CLL), as well as other hematologic malignancies (e.g. mantle cell lymphoma, natural killer [NK]/T-cell lymphoma), can develop both exaggerated reactions to insect bites and insect bite-like reactions[13]. The latter term is used to describe lesions that resemble insect bites clinically and histologically, but for which a clear link to insect bites cannot be established[14]. Of note, these exaggerated reactions can precede the diagnosis of the lymphoma or be associated with a relapse.

Pathogenesis

Most lesions are the result of an individual's immune response to insect antigens introduced by the bite. Both humoral (IgE-mediated) and cell-mediated immunity (delayed hypersensitivity) are involved. Initial bites typically do not produce significant lesions, but sensitization occurs over a few weeks. Subsequent bites then induce a stronger reaction and even bullae formation. With time, repeated bites can result in desensitization.

In patients with NK/T-cell lymphomas, severe hypersensitivity to mosquito bites has been well documented and a possible role for an EBV-induced clonal proliferation of NK cells has been raised[15]. For patients with ALK-positive anaplastic large cell lymphoma, the possibility has been raised that insect bite-associated antigens lead to an influx of T lymphocytes, some of which bear t(2;5). The release of cytokines then results in activation of these cells, expression of NPM-ALK protein and subsequent uncontrolled proliferation[15a]. Malignant B cells, on the other hand, may stimulate Th2 cells to produce interleukin-5, explaining the associated tissue eosinophilia.

BULLOUS DRUG ERUPTIONS		
Disease	**Characteristic features**	**Commonly implicated drugs**
Fixed drug eruption (see Ch. 21)	• Sharply circumscribed erythematous to dusky violaceous patches • Central blisters or erosions may appear • Often resolves with postinflammatory hyperpigmentation • Recurrence at same location(s) following drug re-exposure	Sulfonamides, NSAIDs, tetracyclines, barbiturates, aspirin, acetaminophen (paracetamol), metronidazole, phenolphthalein
Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (see Ch. 20)	• Prodrome of fever and painful skin • Areas of dusky erythema associated with epidermal detachment (varying from <10% [SJS] to >30% [TEN]) • Mucosal involvement	NSAIDs, antibiotics (sulfonamides and β-lactams), anticonvulsants, allopurinol
Drug-induced autoimmune blistering diseases (see Chs 29–31)	• Primarily, linear IgA bullous dermatosis, pemphigus, bullous pemphigoid • Diagnosis based on histologic findings, immunofluorescence studies and drug history	• Linear IgA bullous dermatosis: vancomycin > β-lactams, captopril, NSAIDs • Pemphigus: penicillamine, captopril, β-lactams, gold • Bullous pemphigoid: diuretics (especially furosemide), antibiotics
Drug-induced pseudoporphyria (see Ch. 49)	• Eruption resembles porphyria cutanea tarda • Porphyrin determinations are within normal limits	NSAIDs (especially naproxen), nalidixic acid, thiazides, furosemide, tetracyclines
Acute generalized exanthematous pustulosis (see Ch. 21)	• Acute onset, usually occurring within 2 days of drug exposure • Areas of erythema studded with pustules; occasionally vesicles • Fever, malaise, leukocytosis	β-lactams, macrolides, pristinamycin, terbinafine, calcium channel blockers (diltiazem), hydroxychloroquine, carbamazepine, acetaminophen, metronidazole
Phototoxic drug eruptions (see Ch. 87)	• Limited to sun-exposed areas • Resembles exaggerated sunburn	Tetracyclines (especially doxycycline), quinolones, psoralens, NSAIDs, diuretics
Bromoderma and iododerma (see Ch. 21)	• Acneiform lesions, papulopustules, nodules, or even vegetating lesions simulating pemphigus vegetans • Clear or hemorrhagic blisters can develop (more common in iododerma)	Bromides, iodine-containing drugs (e.g. amiodarone), radiographic contrast media
Palmoplantar erythrodysesthesia (acral variant of toxic erythema of chemotherapy; see Ch. 21)	• Painful erythema develops primarily on the palms, soles and digits following chemotherapy administration • The skin becomes edematous, its color changes to dark red or violet, and blisters and erosions may develop	Cytarabine, doxorubicin, capecitabine, 5-fluorouracil (especially prolonged infusions), multikinase inhibitors (e.g. sorafenib, sunitinib), busulfan, taxanes, clofarabine, pralatrexate

Table 33.2 Bullous drug eruptions. Occasionally, eczematous drug reactions (e.g. secondary to warfarin, calcium channel blockers) and systemic contact dermatitis can be papulovesicular; patients with drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS) can also develop vesicles. See Table 33.1 for coma blisters and bullous small vessel vasculitis. NSAIDs, nonsteroidal anti-inflammatory drugs.

Clinical Features

Insect bites usually appear as intensely pruritic erythematous papules or nodules. They are usually grouped, and a linear arrangement is commonly seen. Vesicular and bullous bite reactions are not uncommon. Flea bites are the most likely to cause blisters, especially on the legs, and bedbug bites can also be bullous. Some insects (e.g. fire ants) can produce pustular lesions. In patients with hematologic malignancies, the exaggerated reactions consist of persistent papulonodules, vesicles, bullae and even necrotic lesions (Fig. 33.6).

Fig. 33.6 Exaggerated insect bite-like reactions in a patient with chronic lymphocytic leukemia. There are multiple bullae as well as hemorrhagic crusts.

Pathology

The typical pattern is that of a superficial and deep perivascular and periadnexal lymphocytic infiltrate with abundant eosinophils. A wedge-shaped pattern is characteristic. During the initial phase, intraepidermal spongiotic vesicles are present and they can be associated with eosinophilic spongiosis. With time, confluence of these vesicles leads to subepidermal blisters. Sometimes, epidermal necrosis develops. Flame figures (extruded eosinophilic granules aggregated onto collagen fibers that are classically associated with eosinophilic cellulitis) can be observed, particularly in the exaggerated reactions seen in patients with hematologic malignancies.

Differential Diagnosis

The presence of intense pruritus and lesion distribution usually suggests a bullous bite reaction. However, these reactions can mimic bullous pemphigoid, linear IgA bullous dermatosis, bullous erythema multiforme, bullous impetigo or allergic contact dermatitis (see Fig. 33.8). "Eosinophilic dermatosis associated with hematological disorders" is another name for the phenomenon described above and is a more appropriate and less restrictive term than "eosinophilic dermatosis of myeloproliferative disease"[16] (strictly speaking, CLL is not categorized as one of the myeloproliferative disorders).

Treatment

Most patients with bullous insect bites can be managed with drainage of blisters, topical corticosteroids, and systemic antihistamines to relieve pruritus. In the most severe reactions, a short course of systemic corticosteroids may be necessary. Treatment of the exaggerated reactions seen in patients with hematologic malignancies may prove more

difficult. While systemic corticosteroids can lead to improvement, lesions tend to recur when the dose is reduced. Dapsone has been suggested as a therapeutic option for these patients[17]. Protective clothing and insect repellants are an important intervention (see Ch. 85).

DELAYED POSTBURN/POSTGRAFT BLISTERS

Key features

- Delayed postburn and postgraft blisters represent an underreported condition
- Tense blisters develop weeks to months after the initial injury has healed
- Blistering can persist for several weeks or months

Introduction

Delayed blisters have been observed weeks to months after the initial healing of second-degree thermal burns, donor sites of split-thickness skin grafts, and recipient sites of split-thickness skin grafts[18,19].

History

The first report of this phenomenon is attributed to Barker and Cotterill in 1980.

Epidemiology

Delayed blisters have received little attention in the literature. However, it appears to occur to some degree in almost every patient with a thermal burn involving more than 30% of the body surface area[19]. Most descriptions refer to patients with thermal burns, where delayed blisters have been observed on the spontaneously healed skin, graft donor sites, and graft recipient sites[18]. They have also been seen after skin grafting for toxic epidermal necrolysis and within laser-resurfaced skin[20].

Pathogenesis

The exact pathogenesis is not known. The antigenic components of the normal dermal–epidermal junction appear sequentially during fetal life or wound healing. Therefore, it has been hypothesized that this phenomenon is due to the enhanced fragility of a newly synthesized, "immature" dermal–epidermal junction[18,19].

Clinical Features

Tense vesicles or blisters develop weeks after the injured skin (burned, donor site, recipient site) has completely healed. In one study, blisters appeared between 19 and 55 days after the patients had sustained their burns, with an average of 37 days[19]. Blisters do not develop within uninvolved skin. Although they heal spontaneously, there is a tendency for recurrences over a period of weeks to months.

Pathology

Histologically, subepidermal blisters with a minimal inflammatory infiltrate are seen. Electron microscopy has shown that the blisters occur either in the dermis (below the dermal–epidermal junction) or intraepidermally through the basal keratinocytes. DIF studies have been negative. Immunofluorescence mapping has shown a diminished or variable expression of dermal–epidermal junction antigens, including type IV and type VII collagens, laminin, and bullous pemphigoid antigen[18].

Differential Diagnosis

Blistering associated with a healed injured site can also be due to herpetic infection, ischemia (in the case of graft recipient sites) or autoimmune bullous diseases. Herpetic infection can be excluded by a negative Tzanck smear, direct fluorescent antibody test, viral culture, and/or biopsy findings; ischemia is diagnosed on the basis of clinical findings; and autoimmune blistering diseases can be excluded by histologic features and DIF/IIF examinations (see Fig. 33.8).

Treatment

These blisters heal spontaneously with simple care, topical antibiotics, wound dressings, and local compression.

EDEMA BLISTERS

Synonyms: ■ Stasis blisters ■ Hydrostatic bullae ■ Edema bullae

Key features

- Edema blisters develop in patients with an acute exacerbation of chronic edema, particularly of the lower extremities, and in the setting of anasarca
- The tense lesions are usually non-inflammatory and surrounded by edematous skin
- Blisters resolve when the edema resolves

Epidemiology

This phenomenon has received little attention in the literature. These blisters are not infrequent and usually develop in elderly and immobile hospitalized patients as well as in the setting of anasarca. In a recent study of 13 patients, the mean age was 74 years[21].

Pathogenesis

The bullae usually develop on the legs in association with an acute exacerbation of chronic edema. Edema develops when the capillary filtration rate exceeds lymphatic drainage. This can be due to heart failure, renal disease, hepatic cirrhosis, hypoalbuminemia, venous occlusion (thrombosis) or drugs, particularly calcium channel blockers. Cutaneous vesicles and bullae also occur with acute exacerbations of lymphedema.

Clinical Features

Most patients develop blisters on the distal lower extremities (particularly the dorsum of the foot and ankle). With acute exacerbations of chronic edema, blisters appear and enlarge slowly to reach a diameter of up to several centimeters. The bullae are tense and asymptomatic,

Fig. 33.7 Edema bullae on the thigh of an infant. The bullae are tense and are surrounded by edema. Desquamation from a ruptured bulla is also seen.

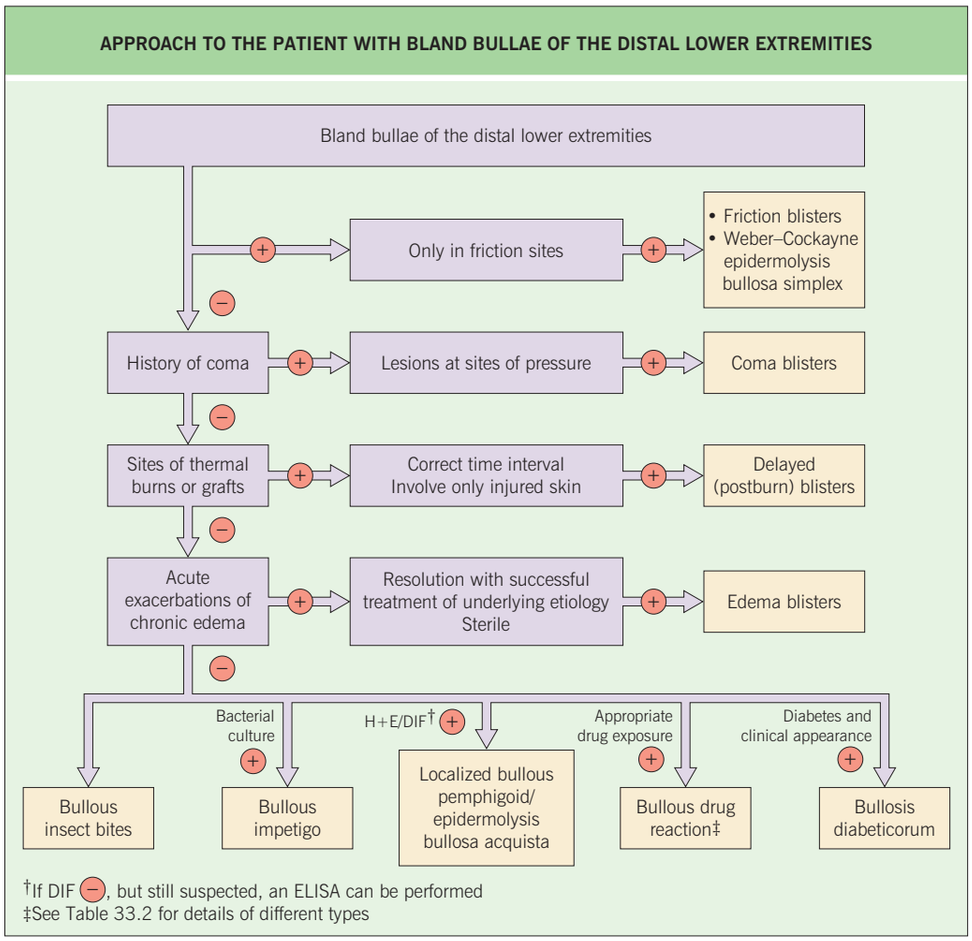


Fig. 33.8 Approach to the patient with bland bullae of the distal lower extremities.

and the surrounding skin is edematous. The sterile blister fluid is usually clear, but it can be serous or bloody. In patients with anasarca, there is a more widespread distribution (Fig. 33.7).

Pathology

Marked epidermal spongiosis is observed, with dilated dermal blood vessels and a mild inflammatory infiltrate. The dermis is markedly edematous with wide separation of collagen bundles. In some cases, subepidermal blisters can be found. DIF is negative.

Differential Diagnosis

Blistering in the setting of acute edema is usually not difficult to diagnose. However, the possibility of bullous pemphigoid, bullosis diabeticorum or a drug eruption must also be considered. The correct diagnosis can usually be established via the clinical history and physical examination (Fig. 33.8). If needed, bullous pemphigoid can be excluded by negative DIF and IIF examinations.

Treatment

These blisters resolve rapidly when the etiology of the edema is successfully treated. Diuretics, discontinuation of calcium channel blockers, leg elevation, and compressive bandages (followed by maintenance compression hose) may prove helpful.

PUVA-INDUCED ACROBULLOUS DERMATOSIS

This disease is characterized by the sudden occurrence of tense blisters, usually on the distal extremities, during long-term PUVA therapy. The tense bullae apparently arise as a result of chronic PUVA-induced weakening of epidermal–dermal cohesion coupled with friction or trauma. This disorder needs to be distinguished from phototoxic reactions due to PUVA overdosage, which usually affect the entire skin surface, not just acral sites, and from PUVA-induced bullous pemphigoid. There is no need to interrupt PUVA therapy, but mechanical stress should be avoided.

REFERENCES

1. Cantwell AR Jr, Martz W. Idiopathic bullosis in diabetics. Bullous diabeticorum. Arch Dermatol. 1967;96:42–4.
2. Toonstra J. Bullosis diabeticorum. Report of a case with a review of the literature. J Am Acad Dermatol. 1985; 13:799–805.
3. Lipsky BA, Baker PD, Ahroni JH. Diabetic bullae: 12 cases of a purportedly rare cutaneous disorder. Int J Dermatol. 2000;39:196–200.
4. Bernstein JE, Levine LE, Medenica MM, et al. Reduced threshold to suction-induced blister formation in insulin-dependent diabetics. J Am Acad Dermatol. 1983;8:790–1.
5. Holten C. Cutaneous phenomena in acute barbiturate poisoning. Acta Derm Venereol (Stockh). 1952; 32(suppl. 29):162–8.
6. Beveridge GW, Lawson AAH. Occurrence of bullous lesions in acute barbiturate intoxication. Br Med J. 1965;5438:835–7.
7. Taniguchi Y, Wada Y, Takahashi M, et al. Multiple bullae and paresis after drug-induced coma. Acta Derm Venereol (Stockh). 1991;71:536–8.
8. Mehregan DR, Daoud M, Rogers RS III. Coma blisters in a patient with diabetic ketoacidosis. J Am Acad Dermatol. 1992;27:269–70.
9. Arndt KA, Mihm MC Jr, Parrish JA. Bullae: a cutaneous sign of a variety of neurologic diseases. J Invest Dermatol. 1973;60:312–20.
10. Miyamoto T, Ikehara A, Kobayashi T, et al. Cutaneous eruptions in coma patients with nontraumatic rhabdomyolysis. Dermatology. 2001;203:233–7.
11. Knapik JJ, Reynolds KL, Duplantis KL, et al. Friction blisters. Pathophysiology, prevention, and treatment. Sports Med. 1995;20:136–47.
12. Sulzberger MB, Cortese TA Jr, Fishman L, et al. Studies on blisters produced by friction. I. Results of linear rubbing and twisting technics. J Invest Dermatol. 1966;47: 456–65.
13. Davis MD, Perniciaro C, Dahl PR, et al. Exaggerated arthropod-bite lesions in patients with chronic lymphocytic leukemia: a clinical, histopathologic, and immunopathologic study of eight patients. J Am Acad Dermatol. 1998;39:27–35.
14. Barzilai A, Shapiro D, Goldberg I, et al. Insect bite-like reaction in patients with hematologic malignant neoplasms. Arch Dermatol. 1999;135:1503–7.

15. Tsuge I. Morishima T, Morita M, et al. Characterization of Epstein-Barr virus (EBV)-infected natural killer (NK) cell proliferation in patients with severe mosquito allergy; establishment of an IL-2-dependent NK-like cell line. Clin Exp Immunol. 1999;115:385–92.
15a. Lamant L, Pileri S, Sabattini E, et al. Cutaneous presentation of ALK-positive anaplastic large cell lymphoma following insect bites: evidence for an association in five cases. Haematologica. 2010;95: 449–55.
16. Byrd JA, Scherschun L, Chaffins ML, Fivenson DP. Eosinophilic dermatosis of myeloproliferative disease: characterization of a unique eruption in patients with hematologic disorders. Arch Dermatol. 2001;137:1378–80.
17. Ulmer A, Metzler G, Schanz S, Fierlbeck G. Dapsone in the management of "insect bite-like reaction" in a patient with chronic lymphocytic leukaemia. Br J Dermatol. 2007;156: 172–4.
18. Chetty BV, Boissy RE, Warden GD, et al. Basement membrane and fibroblast aberration in blisters at the donor, graft, and spontaneously healed sites in patients with burns. Arch Dermatol. 1992;128:181–6.
19. Compton CC. The delayed postburn blister. A commonplace but overlooked phenomenon. Arch Dermatol. 1992;128:249–52.
20. Alora MB, Dover JS. Spontaneous bullae over laser resurfaced skin. J Am Acad Dermatol. 2000;42: 288–90.
21. Bhushan M, Chalmers RJG, Cox NH. Acute oedema blisters: a report of 13 cases. Br J Dermatol. 2001;144:580–2.

34 Vesiculobullous and Erosive Diseases in the Newborn

Deborah S Goddard, Amy E Gilliam and Ilona J Frieden

A number of conditions can cause vesicles, pustules, bullae, erosions and ulcerations during the newborn period. Accurate and prompt diagnosis is important because several of the disorders presenting with these skin findings can be life-threatening; conversely, others are benign and self-limited. Therefore, it is essential to develop a systematic approach to the evaluation and treatment of newborns with these types of cutaneous lesions. This chapter highlights many of the causes, and more exhaustive lists are provided in Tables 34.1 and 34.2. The majority of infectious causes are covered in these tables as well as in Chapters 74–82.

COMMON CAUSES

Erythema Toxicum Neonatorum

Synonyms: ■ Erythema toxicum ■ Toxic erythema of the newborn

Key features

- Common benign vesiculopustular neonatal eruption
- Affects ~50% of full-term neonates
- Most often involves the face, trunk, proximal limbs and buttocks
- Almost always spares the palms and soles
- Small, highly inflammatory papules, pustules and/or vesicles surrounded by blotchy erythema
- Resolves spontaneously over a few days without therapy

Erythema toxicum neonatorum (ETN) is a common benign condition. Originally described by Netlinger in 1472, it was called "toxic erythema of the newborn" and was renamed erythema toxicum neonatorum by Leiner in 1912[1]. The condition has no gender or racial predilection, although discrepancies in incidence rates may be related to the difficulty in discerning erythema in darker-skinned infants. ETN occurs in approximately half of full-term neonates and only rarely in premature infants or those weighing less than 2500 g[2].

Occasionally presenting at birth, most cases of ETN begin 24 to 48 hours after delivery and wax and wane for a few days. There are rare reports of an onset as late as 2 weeks of age. Four distinct skin lesions may present in varying combinations: erythematous macules, wheals, pustules (or vesicles) and papules. The papules, pustules and vesicles are small, generally measuring 1 to 3 mm. The central papule with a surrounding erythematous flare is reminiscent of a flea bite (Fig. 34.1). Mechanical irritation may precipitate new lesions.

ETN usually begins on the face, and then progresses to involve the proximal extremities, trunk and buttocks; it almost always spares the palms and soles[3]. Individual lesions rarely persist for more than a day, are asymptomatic, heal without sequelae, and require no therapy.

The diagnosis of ETN is usually made on clinical grounds. When necessary, the demonstration of numerous eosinophils via Wright's stain of the pustular contents can help to confirm the diagnosis. Peripheral eosinophilia is occasionally present. Histologically, the outer root sheaths of hair follicles are infiltrated by eosinophils, and coalescing subcorneal pustules composed of eosinophils are found in a perifollicular distribution. An eosinophilic infiltrate is also evident in the upper dermis and around blood vessels. The pathogenesis of ETN is unknown. Mechanisms related to hypersensitivity and fragility of newborn skin have been suggested[1,4].

Because the differential diagnosis includes other pustular disorders of the newborn, some of which may have important medical sequelae, rapid diagnosis is important (see Table 34.1). Transient neonatal pustular melanosis (TNPM) is primarily neutrophilic, usually affects infants with darkly pigmented skin, and resolves as pigmented macules that last weeks to months. However, an overlap between ETN and TNPM has been suggested[5]. Infantile acropustulosis is an acral, rather than truncal, eruption that usually appears after the neonatal period (3–6 months of age). Eosinophilic pustular folliculitis in infancy favors the scalp and features lesions that often become crusted and recur in crops over a period of months to years. Herpes simplex viral (HSV) infection is typically more vesicular, with hemorrhagic crusting. *Staphylococcus aureus* infections manifest as more well-developed pustules or bullae that rapidly rupture, resulting in an erythematous base with a surrounding collarette (remnant) of the blister roof (Fig. 34.2A). Congenital candidiasis presents with multiple tiny pustules, scrapings of which are positive on potassium hydroxide (KOH) examination, and often there is associated desquamation (Fig. 34.2B). Both staphylococcal and candidal infections result in more persistent lesions that do not undergo the rapid spontaneous resolution characteristic of ETN. Miliaria rubra (prickly heat) is usually concentrated on the head, neck and upper torso, with somewhat longer-lived lesions that lack a prominent erythematous flare or eosinophilic infiltrate[3].

Transient Neonatal Pustular Melanosis

Synonyms: ■ Transient neonatal pustulosis ■ Lentigines neonatorum

Key features

- Develops in up to 5% of newborns with darkly pigmented skin
- Prominent pustules without erythema that rupture, leaving a collarette of scale and hyperpigmentation that may last several months
- Sterile subcorneal neutrophilic pustules
- Favors the forehead, chin, neck, back and shins but may be widespread
- The infants are otherwise well and no treatment is necessary

Originally described in 1961 as "lentigines neonatorum"[6], the full spectrum of TNPM was not recognized until 15 years later[7]. It occurs in 4–5% of African-American and 0.5% of Caucasian newborns who are full-term, and lesions are virtually always present at birth.

Clinically, TNPM manifests as a continuum of three phases. At delivery, superficial, 2–10 mm vesiculopustules (Fig. 34.3A) are present at sites such as the chin, forehead, nape of the neck, lower back, buttocks and shins, and, less often, the remainder of the face, trunk, palms and soles. This phase may go undetected, as the fragile intra- and subcorneal pustules can be absent, overlooked or wiped away during the first bath. The second phase features slightly hyperpigmented macules with fine collarettes of scale at sites of ruptured and resolving pustules (Fig. 34.3B). The final phase features residual hyperpigmented

DIFFERENTIAL DIAGNOSIS OF VESICULOPUSTULAR DISEASES					
Disease	**Usual age of onset**	**Skin: morphology**	**Skin: distribution**	**Diagnostic studies (skin)**	**Comments**
INFECTIOUS DISEASES					
Staphylococcal diseases: pyoderma and bullous impetigo (see Ch. 74) (Fig. 34.2A)	Few days to weeks	Pustules, bullae, occasional vesicles	Favors diaper and periumbilical areas	Gram stain: Gram-positive cocci in clusters; bacterial culture	Boys more than girls; may occur in epidemics
Group A streptococcal infection (see Ch. 74)	Few days to weeks	Isolated pustules, honey-colored crusts	Any body region; may affect moist umbilical stump	Gram stain: Gram-positive cocci in chains; bacterial culture	Occasional cellulitis, meningitis, pneumonia
Group B streptococcal infection	Birth to first few days	Vesicles, bullae, erosions, pustules, honey-colored crusts	Any body region	Gram stain: Gram-positive cocci in chains; bacterial culture	Pneumonia, bacteremia, meningitis
Listeria monocytogenes infection (see Ch. 74)	Birth to first few hours	Hemorrhagic pustules and petechiae	Generalized, especially trunk and extremities	Gram stain: Gram-positive rods; bacterial culture	Sepsis; respiratory distress; history of maternal fever and premature labor
Haemophilus influenzae infection (see Ch. 74)	Birth to first few days	Vesicles, crusted papules	Any body region	Gram stain: Gram-negative bacilli; bacterial culture	Bacteremia, meningitis
Pseudomonas aeruginosa infection (see Ch. 74)	Days to weeks	Erythema, pustules, hemorrhagic bullae, necrotic ulcerations	Any region, especially anogenital area	Gram stain: Gram-negative rods; bacterial culture	Prematurity, low birthweight, immunodeficiency
Congenital candidiasis (Fig. 34.2B)	Birth to first few days	Erythema, small papules and pustules, fine scaling	Any region; palms/soles often involved; nails may be affected	KOH: budding yeast; fungal culture; placental/umbilical cord lesions may be present	Prematurity, foreign body in cervix/uterus are risk factors; ascending *in utero* infection
Neonatal candidiasis	1–2 weeks of age	Scaly red patches with satellite pustules and papules	Diaper area, other intertriginous zones, face	KOH: budding yeast, pseudohyphae; fungal culture	Usually otherwise healthy; acquisition during delivery or postnatally; oral thrush
Aspergillus infection (see Ch. 77)	Few days to weeks	Pustules (often clustered) rapidly evolve to necrotic ulcers	Any region, especially macerated skin in the diaper area and under adhesive tape/occlusive dressings	Skin biopsy: septate hyphae; tissue fungal culture	Extreme prematurity
Neonatal HSV infection (see Ch. 80) (Fig. 34.11)	Birth to 2 weeks, usually after 5 days	Vesicles, pustules, crusts, erosions	Any region, especially scalp, torso; may involve mucosa	Tzanck preparation, DFA or immunoperoxidase slide test, PCR, viral culture	Signs of sepsis; irritability, lethargy; must exclude herpes meningitis and encephalitis
Intrauterine HSV infection	Birth	Vesicles, pustules, widespread erosions, scars, areas of absent skin	Any body region	Tzanck preparation, DFA or immunoperoxidase slide test, PCR, viral culture	Low birthweight, microcephaly, chorioretinitis
Neonatal varicella (see Ch. 80)	Birth to 2 weeks	Vesicles on an erythematous base	Generalized distribution	Tzanck preparation, DFA, viral culture, serology	Maternal primary varicella infection 7 days before to 2 days after delivery
Herpes zoster (see Ch. 80)	Typically 2 weeks or older	Vesicles on an erythematous base	Dermatomal pattern	Tzanck preparation, DFA, viral culture	Maternal primary varicella infection during pregnancy or up to a few days after delivery
Scabies (see Ch. 84)	Typically 3–4 weeks or older	Papules, nodules, crusted areas, vesicles, pustules, burrows	Any region; accentuated in axillae and groin and on palms/soles, wrists	Mineral oil preparation; dermoscopy	Family members may have pruritus, similar lesions

Table 34.1 Differential diagnosis of vesiculopustular diseases. Additional etiologies include irritant contact dermatitis (see Table 34.2), dermatophyte infection and intrauterine coxsackievirus infection. CNS, central nervous system; DFA, direct fluorescent antibody; HSV, herpes simplex virus; KOH, potassium hydroxide examination; PCR, polymerase chain reaction. *Adapted from Frieden IJ, Howard R. In: Eichenfield LF, Frieden IJ, Esterly NB (eds). Textbook of Neonatal Dermatology. Philadelphia: WB Saunders, 2008:134–5.*

Continued

brown macules, which may persist for several months. The name "lentigines" is a misnomer since the lesions actually represent postinflammatory hyperpigmentation. Sometimes only the brown macules are noted at birth, suggesting that the first two phases occurred *in utero*. Less commonly, infants with TNPM may present at a few weeks of life with extensive pigmented macules without a history of preceding pustules.

Histologic examination is rarely necessary to make the diagnosis, but, when performed on early lesions, it demonstrates intra- or subcorneal pustules containing neutrophils, fibrin and (rarely) eosinophils. Neutrophils also predominate within a spongiotic epidermis. In the pigmented macules, an increase in melanin within basilar keratinocytes is noted[7,8].

The pathogenesis is unknown. Some authors have postulated that TNPM is a clinical variant of ETN, based on reports of the two conditions coexisting in the same patient, and have proposed the term *sterile transient neonatal pustulosis* because of this potential clinical overlap[5]. The differential diagnosis is similar to that discussed above for ETN, and no treatment is necessary. Parents should be reassured of the benign and self-limited nature of the condition.

DIFFERENTIAL DIAGNOSIS OF VESICULOPUSTULAR DISEASES					
Disease	**Usual age of onset**	**Skin: morphology**	**Skin: distribution**	**Diagnostic studies (skin)**	**Comments**
COMMON TRANSIENT CONDITIONS					
Erythema toxicum neonatorum (Fig. 34.1)	Typically 24–48 hours but can be birth to 2 weeks	Erythematous macules, papules, pustules > vesicles, wheals	Any region, except almost always spares palms/soles	Clinical; Wright's stain: eosinophils	Term infants >2500 g
Transient neonatal pustular melanosis (Fig. 34.3)	Birth	Pustules without erythema; collarettes of scale; hyperpigmented macules	Any region; most often forehead, neck, lower back, shins; may affect palms/soles	Clinical; Wright's stain: neutrophils, occasional eosinophils, cellular debris	Term infants; more common in infants of African descent
Miliaria crystallina (see Ch. 39) (Fig. 34.4)	Birth or early infancy	Fragile vesicles without erythema	Forehead, upper trunk, arms most common	Clinical; Wright's, Gram stains and Tzanck preparation negative	Sometimes history of overheating, fever
Miliaria rubra (see Ch. 39)	Typically ≥1 week	Erythematous papules with superimposed pustules	Forehead, neck, upper trunk and occluded areas most common	Clinical; Wright's stain: variable inflammatory cells but not prominent eosinophils; Gram stain and Tzanck preparation negative	Sometimes history of overheating, fever
Neonatal cephalic pustulosis (neonatal "acne") (Fig. 34.5)	Days to weeks	Papules and pustules on erythematous base	Cheeks, forehead, chin, eyelids; less commonly neck, upper chest, scalp	Clinical; Giemsa stain: yeast forms, neutrophils	Otherwise well
UNCOMMON AND RARE NON-INFECTIOUS DISEASES					
Acropustulosis of infancy (Fig. 34.7)	Typically 3–6 months, occasionally birth to weeks	Vesicles and pustules	Hands and feet; occasionally scalp, trunk	Clinical; assess for scabies infestation; skin biopsy: intraepidermal vesicle/pustule; neutrophils, occasionally eosinophils	Severe pruritus; lesions recur in crops
Eosinophilic pustular folliculitis in infancy (Fig. 34.8)	Birth to months	Follicular papules and pustules	Mainly scalp and face; occasionally trunk, extremities	Skin biopsy: dense perifollicular mixed infiltrate with eosinophils	Pruritus; waxing and waning course with recurrent crops of lesions
Congenital Langerhans cell histiocytosis (see Ch. 91) (Fig. 34.9)	Birth to days	Vesicles, crusts, papules, nodules, petechiae	Any body region, especially flexural sites, palms/soles, scalp	Skin biopsy: histiocytes with reniform nuclei, focal invasion of epidermis; S100- and CD1a-positive cells	Occasional mucosal or extracutaneous involvement; pure cutaneous form often resolves spontaneously; cutaneous and systemic relapses possible
Incontinentia pigmenti (see Ch. 62) (Fig. 34.10)	Birth to weeks	Vesicles, hyperkeratotic papules in linear or whorled array along the lines of Blaschko	Vesicular lesions most common on the extremities	Skin biopsy: eosinophilic spongiosis with dyskeratosis	Extracutaneous involvement possible (dental, ocular, CNS) but often not evident at birth
Hyper-IgE syndrome (autosomal dominant form; see Ch. 60)	Birth to weeks	Single and grouped vesicles or papulopustules	Face, scalp, upper trunk, axillae, diaper area	Skin biopsy: intraepidermal vesicle with eosinophils, eosinophilic folliculitis; genetic analysis (*STAT3*)	Eosinophilia; elevated IgE levels, *S. aureus* infections, abscesses, eczematous dermatitis, pneumonias and pneumatoceles often develop after neonatal period
Vesiculopustular eruption of transient myeloproliferative disorder in Down syndrome	Few days	Vesicles and pustules	Face > trunk, extremities; sites of adhesive dressings, minor trauma	Intraepidermal spongiotic vesiculopustules, infiltrate containing immature myeloid cells	Trisomy 21 or mosaicism for trisomy 21; severe leukocytosis with immature myeloid cells; increased risk of leukemia
Neonatal Behçet's disease (see Ch. 26)	First week of life	Vesiculopustular, purpuric and necrotic skin lesions as well as oral and genital ulcers	Lesions favor hands and feet as as well as oral and genital mucosae	Clinical	Maternal history of Behçet's disease; diarrhea, vasculitis
Pustular psoriasis (see Ch. 8)	First weeks of life	Pustules and pustular lakes within areas of erythema	Generalized (erythroderma); pustules in any body region, especially the palms/soles	Skin biopsy: spongiform pustules and microabscesses within the epidermis, parakeratosis, dilated dermal capillaries	Often resistant to therapy

Table 34.1 Differential diagnosis of vesiculopustular diseases (cont'd). Additional etiologies include irritant contact dermatitis (see Table 34.2), dermatophyte infection and intrauterine coxsackievirus infection. CNS, central nervous system; DFA, direct fluorescent antibody; HSV, herpes simplex virus; KOH, potassium hydroxide examination; PCR, polymerase chain reaction. *Adapted from Frieden IJ, Howard R. In: Eichenfield LF, Frieden IJ, Esterly NB (eds). Textbook of Neonatal Dermatology. Philadelphia: WB Saunders, 2008:134–5.*

DIFFERENTIAL DIAGNOSIS OF BULLAE, EROSIONS AND ULCERATIONS					
Disease	**Usual age**	**Skin: morphology**	**Skin: distribution**	**Diagnostic studies (skin)**	**Comments**
INFECTIOUS DISEASES					
Staphylococcal scalded skin syndrome (see Ch. 74) (Fig. 34.14)	Few days to weeks; rarely congenital	Erythematous patches, fragile bullae, superficial erosions, peeling in sheets	Generalized with periorificial and intertriginous accentuation	Biopsy: epidermal separation at granular cell layer; culture positive only at primary site(s) of infection (toxin-mediated)	Irritability; temperature instability; high risk of secondary sepsis, fluid/electrolyte abnormalities
Group B streptococcal infection	(see Table 34.1)				
Pseudomonas aeruginosa infection	(see Table 34.1)				
Congenital syphilis (see Ch. 82)	Birth to first few days	Bullae or erosions; erythema and desquamation	Any region, especially perioral, palms/soles	Darkfield examination of serous exudates, DFA, serologic studies (treponemal and non-treponemal)	Snuffles, hepatosplenomegaly, periostitis with pseudoparalysis
Aspergillus infection	(see Table 34.1)				
Zygomycosis/trichosporonosis (see Ch. 77)	Days to weeks	Generalized peeling and skin breakdown or cellulitis evolving into necrotic ulcer	Any body region	Skin biopsy and tissue fungal culture	Extreme prematurity
Intrauterine HSV infection	(see Table 34.1)				
Congenital varicella (see Ch. 80)	Birth	Erosions, scarring	Any region, especially extremities	Tzanck preparation, DFA, viral culture, serology	Maternal varicella in the first or early second trimester; limb atrophy, CNS/eye abnormalities
CONDITIONS WITH EXOGENOUS CAUSES					
Sucking blisters	Birth	Flaccid bulla or linear erosion; most often solitary	Radial forearm, wrist, hand, fingers, occasionally foot	Clinical	Due to sucking on affected areas *in utero*
Irritant contact dermatitis	First few days to weeks	"Glazed" erythema, vesiculation, "punched-out" erosions	Diaper area, especially on convex surfaces	Usually clinical	Severe form referred to as "Jacquet's erosive diaper dermatitis"
Perinatal trauma/iatrogenic injury	Birth or neonatal period	Erosions, ulcerations, scars, atrophic lesions	Depends on cause of trauma	Usually clinical	Perinatal history of fetal scalp electrode monitor, prolonged labor and/or vacuum or forceps delivery, history of amniocentesis, etc.
UNCOMMON AND RARE NON-INFECTIOUS DISEASES					
Mastocytosis (see Ch. 118) (Fig. 34.15)	Birth to weeks or months	**Localized/discrete lesions**: papules, plaques or nodules with intermittent superimposed wheals or bullae; often hyperpigmented **Diffuse form**: blistering superimposed on infiltrated skin with *"peau d'orange"* appearance	Any body region	Skin biopsy: increased mast cells in dermis	Variably present: flushing, irritability, diarrhea, abdominal pain
Epidermolysis bullosa (see Ch. 32)	Birth to first few days	Mechanically induced blisters and erosions; depending on type: mucosal erosions, aplasia cutis of anterior legs, scarring, milia, nail dystrophy	Widespread or limited, depending on type; most often extremities, especially hands/feet	Biopsy of induced blister for immunofluorescent mapping ± electron microscopy; genetic analysis	Difficulty feeding, failure to thrive; occasionally corneal, respiratory tract or gastrointestinal (e.g. pyloric atresia) involvement; anemia
Bullous congenital ichthyosiform erythroderma (see Ch. 57) (Fig. 34.13)	Birth	Erythroderma with blisters and erosions	Generalized	Skin biopsy: epidermolytic hyperkeratosis	Risk of sepsis, fluid and electrolyte imbalances
Kindler syndrome (see Ch. 63)	Birth to weeks	Trauma-induced blisters and erosions; progressive poikiloderma	Bullae most common in acral sites; poikiloderma is widespread with skip areas	Skin biopsy: immunostaining with anti-kindlin-1 antibody; genetic analysis (*KIND1/FERMT1*)	Photosensitivity; gingivitis, colitis, mucosal stenoses (e.g. esophageal, urethral); acquired syndactyly (toes, proximal fingers)
Maternal autoimmune bullous disease (Fig. 34.16)	Birth	Depends on type of maternal disease: tense or flaccid bullae, erosions	Variable; often widespread	Maternal history; skin biopsy with DIF usually diagnostic	Maternal history of blistering disease (but occasionally inactive during pregnancy)
Bullous pemphigoid (see Ch. 30)	Usually 2 months of age or older	Tense bullae	Favor hands and feet but may be generalized	Skin biopsy: subepidermal bullae with eosinophils; DIF: linear pattern IgG at DEJ	

Table 34.2 Differential diagnosis of bullae, erosions and ulcerations. CNS, central nervous system; CSF, cerebrospinal fluid; DEJ, dermal–epidermal junction; DFA, direct fluorescent antibody; DIF, direct immunofluorescence; FDP, fibrin degradation product; GVHD, graft-versus-host-disease; PT, prothrombin time; PTT, partial thromboplastin time. *Adapted from Frieden IJ, Howard R. In: Eichenfield LF, Frieden IJ, Esterly NB (eds). Textbook of Neonatal Dermatology. Philadelphia: WB Saunders, 2008:136–8.*

Continued

DIFFERENTIAL DIAGNOSIS OF BULLAE, EROSIONS AND ULCERATIONS					
Disease	**Usual age**	**Skin: morphology**	**Skin: distribution**	**Diagnostic studies (skin)**	**Comments**
Linear IgA bullous dermatosis (see Ch. 31)	Rarely at birth, usually develops in late infancy or childhood	Tense blisters often form rosette or sausage shapes	Widespread but often concentrated in the girdle area; usually spares mucosa	Skin biopsy: subepidermal bullae with neutrophils; DIF: linear pattern IgA at DEJ	
Toxic epidermal necrolysis (TEN; see Ch. 20) or TEN-like GVHD (see Chs 52, 60)	Usually 6 weeks of age or older, except for intrauterine GVHD	Tender erythema, bullae, epidermal sloughing/erosions	Often widespread, evolving rapidly over hours to days; mucosal involvement	Skin biopsy: subepidermal blister with epidermal necrosis (usually full thickness)	Usually associated with Gram-negative sepsis or due to GVHD (maternofetal or transfusion-associated) in infants with severe combined immunodeficiency
Intrauterine epidermal necrosis	Birth	Widespread erosions and ulcerations without vesicles or pustules	Generalized, spares mucous membranes	Skin biopsy: epidermal necrosis and calcification of pilosebaceous units	Prematurity, rapid mortality
Congenital erosive and vesicular dermatosis (Fig. 34.12)	Birth	Erosions, vesicles, crusts, "scalded skin"	Generalized with relative sparing of face, palms/soles	Clinical diagnosis, often retrospective; skin biopsy (nonspecific): epidermal necrosis, neutrophils or mixed infiltrate; must exclude other etiologies (e.g. HSV)	Prematurity; heals with supple reticulated scarring; CNS/developmental abnormalities
Pyoderma gangrenosum (see Ch. 26)	Rare reports of congenital or neonatal disease	Sharply demarcated ulcerations with undermined borders	Any site, especially groin, buttocks	Clinical; exclusion of other etiologies; skin biopsy: infiltration of neutrophils without primary vasculitis or infection	Associations include inflammatory bowel disease, hematologic malignancies
Acrodermatitis enteropathica (see Ch. 51)*	Weeks to months	Sharply demarcated, eroded erythematous plaques with scale-crust; occasionally intact vesicles/bullae	Periorificial (i.e. around mouth, nose, eyes, genitalia), neck folds, hands/feet	Low serum zinc (less than 50 microg/dl) and alkaline phosphatase levels	Irritability, diarrhea, failure to thrive; onset classically after weaning if breastfed; acquired zinc deficiency: low maternal breast milk zinc or prematurity
Methylmalonic acidemia, other organic acidemias/ aminoacidopathies (see Fig. 51.12)*	Days to weeks	Erythema with or without erosions	Periorificial or more widespread	Urine organic acid analysis; plasma isoleucine level (if restricted diet)	Lethargy, hypotonia, neutropenia, metabolic acidosis; in some cases, skin findings are associated with therapeutic restrictions of dietary amino acids
Restrictive dermopathy	Birth	Rigid tense skin with linear erosions, tears	Generalized; skin tears most common in flexural creases	Clinical; distinguish from Neu–Laxova syndrome (intrauterine growth retardation, microcephaly, abnormal brain development, edema, parchment-like or ichthyosiform skin); genetic analysis (*LMNA, ZMPSTE24*)	Joint contractures, micrognathia, fixed facial expression, restrictive pulmonary disease, early mortality
Infantile hemangioma (see Ch. 103)	Birth to first few weeks	Ulceration without initial vesicle or bullae	Any site, but often diaper area or lip	Clinical	Cause often not clinically apparent until hemangioma begins to proliferate
Aplasia cutis congenita (see Ch. 64) (Fig. 34.6)	Birth	"Bullous" form: round/oval, sharply demarcated with overlying membrane; other types with raw, full-thickness ulcer; may occasionally present in newborns as scar	Scalp (especially vertex) or face most common; other sites depending on etiology	Usually clinical; imaging studies to evaluate underlying bone, CNS	Possible associations: sagittal sinus thrombosis, meningitis, CNS defects, trisomy 13, limb-reduction abnormalities
Linear porokeratosis, porokeratotic eccrine ostial and dermal duct nevus (PEODDN) (see Ch. 62)	Rarely evident at birth, usually appears later	Erosions occasionally develop; usually erythema and keratotic border or (in PEODDN) spines	Often extremities, but any site possible	Skin biopsy: cornoid lamella (may not be evident in newborn period)	Risk of squamous cell carcinoma
Erosions overlying large congenital melanocytic nevi (see Ch. 112)	Birth to first few days	Erosions, ulcerations	Superimposed on the congenital melanocytic nevus	Clinical; skin biopsy to exclude melanoma if persistent or other unusual features	In some cases, neurocutaneous melanosis may be present

*An acrodermatitis enteropathica-like eruption (periorificial or more widespread), often associated with edema and hypoalbuminemia, can occur in infants (typically 3–5 months of age) with cystic fibrosis as well as in those with organic acidemias/aminoacidopathies (see Ch. 51).

Table 34.2 Differential diagnosis of bullae, erosions and ulcerations (cont'd). CNS, central nervous system; CSF, cerebrospinal fluid; DEJ, dermal–epidermal junction; DFA, direct fluorescent antibody; DIF, direct immunofluorescence; FDP, fibrin degradation product; GVHD, graft-versus-host-disease; PT, prothrombin time; PTT, partial thromboplastin time. *Adapted from Frieden IJ, Howard R. In: Eichenfield LF, Frieden IJ, Esterly NB (eds). Textbook of Neonatal Dermatology. Philadelphia: WB Saunders, 2008:136–8.*

Continued

DIFFERENTIAL DIAGNOSIS OF BULLAE, EROSIONS AND ULCERATIONS					
Disease	**Usual age**	**Skin: morphology**	**Skin: distribution**	**Diagnostic studies (skin)**	**Comments**
Focal dermal hypoplasia (see Ch. 62)	Birth	Occasional blisters, but more often hypoplasia or aplasia of skin; linear and whorled pattern; also fat "herniation", telangiectasias	Any body region	Clinical; skin biopsy: dermal hypoplasia with fat abutting epidermis; genetic analysis (*PORCN*)	Skeletal, eye and CNS abnormalities to varying degrees
Absent dermal ridges and congenital milia (Basan syndrome; see Ch. 64)	Birth	Bullae; absent dermal ridge patterns, multiple milia	Fingers, plantar surface of feet	Clinical	Family history (autosomal dominant); findings overlap with those of Naegeli–Franceschetti–Jadassohn syndrome (see Ch. 67)
Porphyrias (see Ch. 49)	Days to months	Photosensitive blistering	Sun-exposed areas or more generalized if exposed to phototherapy for hyperbilirubinemia	Transient form: elevated plasma porphyrins; heritable forms: elevated urine, fecal and/or plasma porphyrins ± pink/fluorescent urine	Transient form usually related to hemolytic disease; heritable forms presenting with blistering in infancy (e.g. congenital erythropoietic porphyria) are rare
Perinatal gangrene of the buttock	Days	Sudden-onset erythema and cyanosis, then gangrenous ulcers	Buttocks	Clinical	Umbilical artery catheterization in some cases
Neonatal purpura fulminans	Days	Initially purpura or cellulitis-like areas evolving to necrotic bullae or ulcers	Buttocks, extremities, trunk and scalp	Prolonged PT/PTT, low fibrinogen, elevated FDPs, low protein C or S levels	Related to sepsis or inherited protein C or S deficiency
Ankyloblepharon–ectodermal dysplasia–clefting (AEC) syndrome	Birth	Erythroderma, peeling skin and superficial erosions	Generalized, with prominent scalp involvement	Clinical; genetic analysis (*p63*)	Associated findings include ankyloblepharon, ectodermal dysplasia and cleft lip/palate

Table 34.2 Differential diagnosis of bullae, erosions and ulcerations (cont'd). CNS, central nervous system; PT, prothrombin time; PTT, partial thromboplastin time. *Adapted from Frieden IJ, Howard R. In: Eichenfield LF, Frieden IJ, Esterly NB (eds). Textbook of Neonatal Dermatology. Philadelphia: WB Saunders, 2008:136–8.*

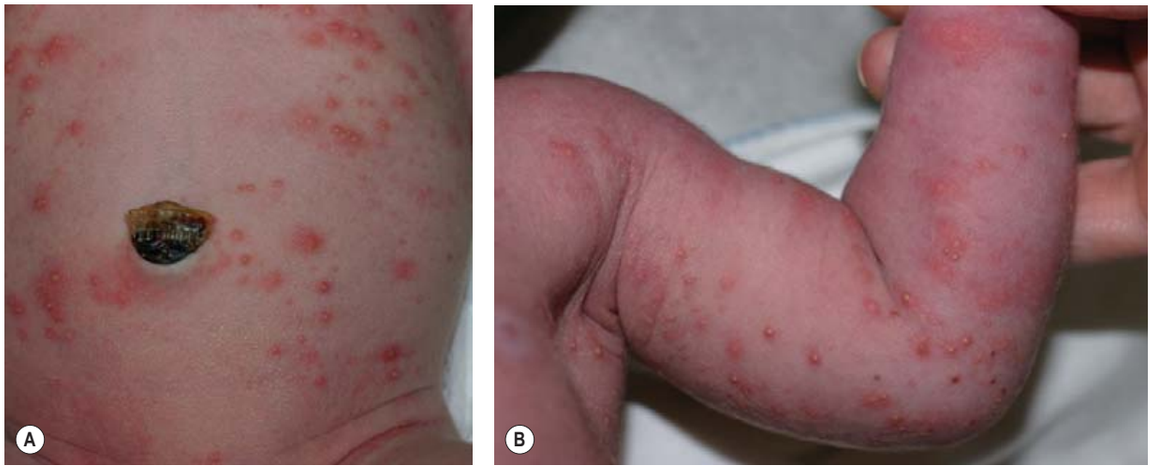


Fig. 34.1 Erythema toxicum neonatorum. Scattered papulovesicles and pustules with an erythematous flare on the abdomen (**A**) and upper extremity (**B**).

Miliaria

Synonyms: ■ Heat rash ■ Miliaria crystallina – "dew drops" ■ Miliaria rubra – prickly heat

Key features

- Three variants: miliaria crystallina, miliaria rubra and miliaria profunda (rare)
- Due to obstruction of eccrine sweat ducts, often in association with increased temperature (exogenous or endogenous)
- Sites of predilection include the forehead, neck, upper trunk and occluded areas
- Spontaneous resolution with cooling
- Prevention consists of avoidance of overheating and limiting excessive swaddling

Miliaria is a common condition, present in up to 15% of newborns, and is seen more frequently in warm climates. Two types of miliaria (see Ch. 39) are typically observed in the newborn period. *Miliaria crystallina*, sometimes present at birth, is due to obstruction of the eccrine sweat duct as it courses through the stratum corneum. Sweat collects beneath the stratum corneum, causing clear, small, flaccid vesicles that are often likened to "dew drops" (Fig. 34.4). *Miliaria rubra*, usually seen after the first week of life, is also caused by a blockage of the sweat ducts, but at a deeper level (the malpighian layer) of the epidermis. The obstructed flow leads to leakage of fluid into the lower epidermis and upper dermis, resulting in an inflammatory response that accounts for the development of erythematous papules and pustules. *Miliaria profunda*, a more inflammatory variant, is related to deeper obstruction of the eccrine duct and is very rare in infants.

Both miliaria crystallina and miliaria rubra may be seen in relation to excessive warming inside an incubator, overswaddling, fever or occlusive dressings. Lesions occur most commonly on the forehead, neck and upper trunk as well as in areas of skin that have been occluded.

In miliaria crystallina, the characteristic histologic features are subcorneal or intracorneal vesicles that are centered on the acrosyringium

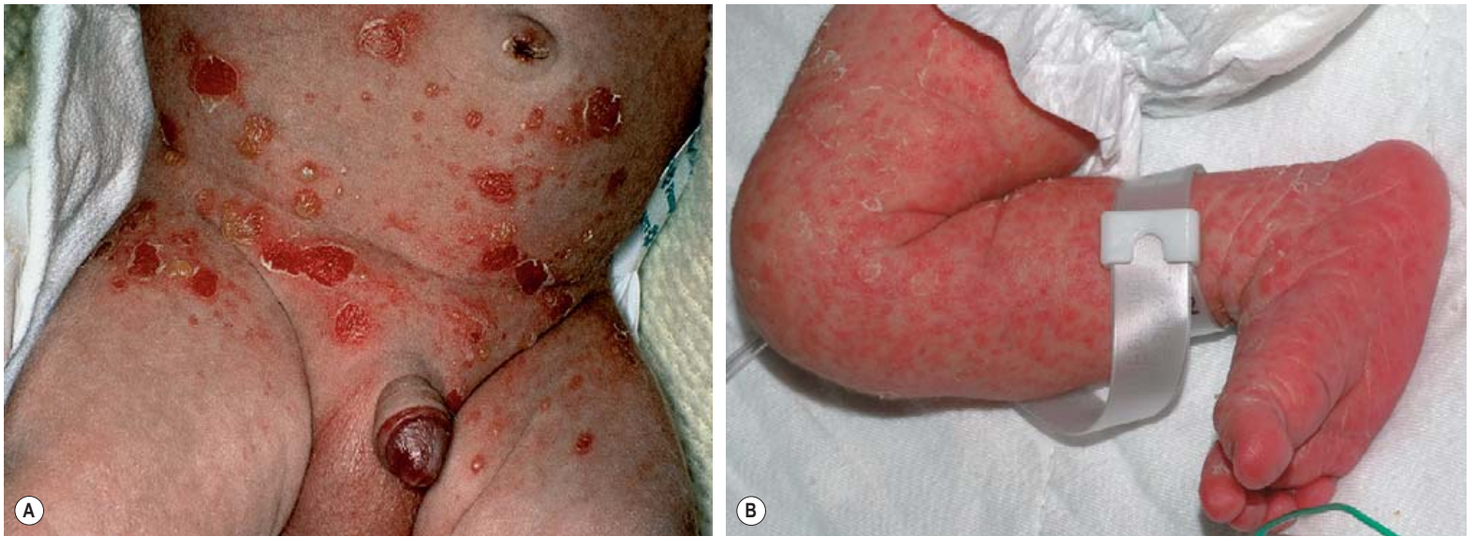


Fig. 34.2 Bullous impetigo versus congenital candidiasis. A Multiple superficial erosions with collarettes of scale in the diaper area in an infant with bullous impetigo. Note the scattered vesiculopustules. **B** Numerous pink papules admixed with small superficial pustules and desquamation due to congenital candidiasis. Note the plantar involvement. *B, Courtesy, Julie V Schaffer, MD.*

Fig. 34.3 Transient neonatal pustular melanosis in an African-American neonate. A One hour after birth, flaccid vesiculopustules and superficial erosions with minimal surrounding erythema are present in the groin. **B** On the 8th day of life, hyperpigmented macules and a few collarettes of scale are evident on the lower leg.

Fig. 34.4 Miliaria crystallina. Tiny, superficial vesicles, seen on the back and neck of this newborn, are characteristic of miliaria crystallina. *From Eichenfield LF, Frieden IJ, Esterly NB, et al. (eds). Textbook of Neonatal Dermatology. © 2001 Saunders.*

with relatively little surrounding inflammation. In miliaria rubra, intraepidermal spongiosis and vesicles are seen along with a chronic inflammatory infiltrate in the dermis[3,8]. The exact cause of miliaria is unknown. A pathophysiologic link to an extracellular polysaccharide produced by *Staphylococcus epidermidis* that blocks sweat ducts has been proposed[9], but this may not explain all cases, particularly congenital forms.

Miliaria resolves without treatment. Prevention is accomplished by avoidance of overheating and overswaddling when feasible.

Neonatal Cephalic Pustulosis

Synonym: ■ Neonatal acne

Key features

- Onset usually within the first 2–3 weeks of life
- Inflammatory non-comedonal pustular eruption, most commonly observed on the cheeks, and less often on the forehead, chin, scalp and chest
- *Malassezia* spp. have been implicated in its etiopathogenesis
- Spontaneous involution over weeks to months

Fig. 34.5 Neonatal cephalic pustulosis. Papulopustules on the forehead and cheeks of a 3-week-old infant. *Courtesy, Julie V Schaffer, MD.*

Historically referred to as "neonatal acne", neonatal cephalic pustulosis lacks several of the features associated with classic acne vulgaris, in particular open and closed comedones and a prolonged course. Young infants with this condition tend to exhibit relatively rapid resolution of lesions within days to weeks and therapy is usually not necessary. Discrete papulopustules are most commonly seen on the cheeks but may also develop on the forehead (Fig. 34.5), chin, eyelids, neck, upper chest and scalp. Onset is usually within the first 2–3 weeks of life, and there is no association with other medical problems.

The results of some studies have suggested that an inflammatory response to *Malassezia (Pityrosporum)* spp. (including *M. furfur, M. sympodialis* and *M. globosa*) may be involved in the etiopathogenesis of neonatal cephalic pustulosis[10–12], but other studies have found no correlation between colonization of neonatal skin with *Malassezia* spp. and the presence or severity of neonatal cephalic pustulosis[13]. While these yeasts have been cultured from lesional skin in affected patients, they are part of the normal skin flora in humans, and thus their exact etiologic role in the condition remains uncertain.

A Giemsa-stained smear of pustular contents may demonstrate yeast forms, neutrophils and other inflammatory cells; culture of *Malassezia* spp. requires specialized media. Treatment with a topical imidazole may improve the condition, but it usually remits spontaneously within several weeks.

While many authors now consider neonatal cephalic pustulosis to be synonymous with neonatal acne, there are some infants (typically 3–6 months of age or older) whose clinical presentation is more reminiscent of classic acne vulgaris, including the presence of comedones as well as inflammatory lesions and a more prolonged course. This is usually referred to as infantile acne (see Ch. 36).

Cutaneous Candidiasis

Key features

- Most commonly due to infection with *Candida albicans* in both term and preterm infants
- Two distinct clinical presentations: *neonatal* candidiasis (due to infection acquired during delivery or postnatally) and *congenital* candidiasis (due to infection acquired *in utero*)
- *Neonatal* candidiasis is characterized by oral thrush as well as pink–red patches with satellite papules and pustules that favor the diaper area, other intertriginous sites and the face
- First-line therapy consists of topical anti-yeast medications (e.g. imidazole creams), unless there is concern for systemic infection

There are two clinical patterns of infection with *Candida albicans* in the newborn period: *neonatal* candidiasis, which is quite common and acquired during delivery or postnatally, and *congenital* candidiasis, which is uncommon and acquired *in utero*.

Neonatal candidiasis typically presents after the first week of life, involving primarily the diaper area and oral mucosa. In some patients, other intertriginous areas as well as the face may be affected. Pink–red patches with satellite papules and pustules are the characteristic findings; pustules and scaling may also be present at the peripheral border. Therapy with topical anti-yeast medications (e.g. an imidazole cream) is usually sufficient. Premature infants and those with very low birthweights should be closely observed and cultures of blood, urine and cerebrospinal fluid obtained as indicated; treatment with parenteral antifungals should be considered if there are signs of systemic infection[3].

In contrast, the relatively uncommon *congenital* candidiasis presents with a more widespread eruption, usually evident at birth but sometimes appearing as late as the 6th day of life. Risk factors include a foreign body in the uterus or cervix (such as a retained intrauterine device or cervical cerclage), premature delivery and a maternal history of vaginal candidiasis[3]. Skin lesions occur on the face, trunk and extremities, while the diaper area and oral mucosa are usually spared. Cutaneous findings vary from erythematous papules and vesiculopustules to diffuse erythema and a "burn-like" dermatitis[14] to fine scaling. Typically, an erythematous papular eruption appears first and is followed by pustules and desquamation (see Fig 34.2B). In contrast to ETN and TNPM, the palms and soles are often involved, and nail dystrophy can be present. In some infants, nail changes (yellow discoloration and transverse ridging) are the only manifestations of congenital candidiasis[14a].

The differential diagnosis includes other infections (e.g. with *Listeria* spp. or HSV) as well as miliaria, ETN and TNPM (see Table 34.1). The presence of budding yeast and pseudohyphae in a KOH preparation points to the correct diagnosis. If the placenta is examined, characteristic yellow–white papules may be found on the umbilical cord[3].

Treatment of *congenital* candidiasis is dependent on the gestational age and weight of the infant. Premature infants (<27 weeks gestational age and <1500 g) are at greater risk for the development of disseminated systemic candidiasis and therefore should be treated with parenteral antifungal agents after cultures have been obtained from the blood, urine and cerebrospinal fluid[14]. Infants of a more advanced gestational age with no evidence of systemic infection can be treated with topical therapy as discussed for *neonatal* candidiasis. However, regardless of gestational age, systemic antifungal therapy should be considered for infants with *congenital* candidiasis who have respiratory distress, an elevated white blood cell count with a left shift, or other signs of systemic infection[14].

Sucking Blisters

Key features

- Caused by vigorous sucking of the affected region *in utero*
- Common locations include the radial forearm, wrist, hands and fingers
- May present with an intact bulla, erosion, callus or superficial ulceration on a non-inflamed base
- Usually an isolated finding without associated abnormalities
- Resolves over days to weeks and therapy is supportive

Sucking blisters are found in 1 of every 250 newborns, although they may be small and go unnoticed. They are an isolated finding caused by sucking *in utero* and are usually seen on the radial forearm, wrist, hand or fingers. The flaccid bullae occur on a non-inflamed base and rupture easily, leading to linear or round erosions. Lesions are usually 5–15 mm in diameter and may be unilateral or bilateral.

The diagnosis of sucking blisters is usually straightforward and suggested by a non-inflammatory and (in most cases) solitary lesion in a typical location and the overall healthy status of the infant. The lesions clear in days to weeks without specific treatment[3].

Fig. 34.6 Aplasia cutis congenita. Ulcerations on the vertex of the scalp may be misdiagnosed as an HSV infection. The angulated appearance of the larger ulceration would not be characteristic of HSV infection.

Exogenous Causes of Erosions

Key features

- There are multiple exogenous causes for erosions, including friction from diapers, fetal scalp electrodes, pulse oximetry probes, "heel stick" phlebotomy and removal of adhesive materials
- A typical location and known exposure to exogenous materials/procedures assist in diagnosis

Neonatal skin is more susceptible to erosions and ulcerations than is the skin of older infants or adults. This fragility is even more pronounced in preterm infants. As a result, there are a number of etiologies, including iatrogenic injury, for erosive skin changes.

Superficial erosions in the diaper area frequently occur within the first 2 weeks of life in full-term infants but become less common in older infants. These erosions are primarily due to friction and irritation from the diaper, urine and feces in the setting of transient neonatal skin fragility. A common cause of skin injury on the scalp is the fetal scalp electrode monitor placed during delivery. These erosions are usually superficial, but occasionally lacerations or frank ulcers may ensue. Differentiation from aplasia cutis congenita (Fig. 34.6) is usually straightforward, but may be more difficult in severe cases.

Pulse oximetry probes may lead to small blisters or erosions related to thermal burns and therefore should not be left in one place for more than 24 hours. Removal of adhesive materials (e.g. tape over dressings and electrode leads) can also cause erosions due to neonatal skin fragility. Puncture wounds from "heel sticks", a common method of phlebotomy utilized in the newborn nursery, are a potential cause of acral erosions; the medial or lateral (versus midline) location and procedural history are clues to the diagnosis[3]. Occasionally, heel-stick sites may develop calcinosis cutis.

UNCOMMON AND RARE CAUSES

Acropustulosis of Infancy

Synonym: ■ Infantile acropustulosis

Key features

- Onset usually between 3 and 6 months of age, occasionally at birth
- Pruritic acral vesiculopustular eruption without burrows
- Recurrences occur in crops, typically every 3–4 weeks, and then decrease in frequency and severity with time, resolving completely by approximately 3 years of age
- Therapy is symptomatic and consists of potent topical corticosteroids and oral antihistamines

Fig. 34.7 Acropustulosis of infancy. Multiple vesiculopustules with an erythematous base on the medial ankle of an infant.

Acropustulosis of infancy (AI) is an uncommon skin condition that more frequently affects darkly pigmented male infants, but occurs in both genders and all races. Onset is usually around 3–6 months of age, although lesions may be present in the neonatal period. Extremely pruritic vesicles and pustules appear on acral sites, including the palms and soles, dorsal aspects of the hands and feet, lateral fingers and toes, and, less often, wrists and ankles (Fig. 34.7). Occasionally, lesions are found on the scalp, torso or proximal extremities. The lesions appear in crops, last 7–14 days, and then recur in 3–4 weeks. The natural history of AI is marked by decreasing frequency and severity of the intermittent flares over time, with spontaneous involution usually occurring by 3 years of age.

A smear of pustular contents reveals numerous neutrophils, occasional eosinophils, and no bacteria or fungal elements. Histologic examination of lesional skin, while generally unnecessary, can help to confirm the diagnosis of AI. Histologic features include intraepidermal (subcorneal) vesicles filled with neutrophils and occasionally eosinophils, focal degeneration of keratinocytes, and, in some cases, dermal edema. Occasionally, peripheral eosinophilia is present.

The major entity in the differential diagnosis of AI is scabies, which can be difficult to differentiate clinically. In some patients, AI may represent a post-scabetic hypersensitivity phenomenon following successful treatment of the infestation. Linear burrows are pathognomonic of active scabies, and genital or more widespread lesions and pruritic eruptions in family members also suggest a diagnosis of scabies. Mineral oil examination of skin scrapings for signs of scabies should be performed when evaluating an infant or a toddler with acral vesicles and pustules; in addition, dermoscopy can be used for *in vivo* visualization of mites. In uncertain cases, empiric treatment for scabies may be warranted.

Other conditions with clinical overlap include dyshidrotic eczema and pustulosis palmaris et plantaris – both of which are extremely rare in infancy. Congenital candidiasis is usually not limited to acral skin, and transient neonatal pustular melanosis is not pruritic, does not favor acral locations, and does not recur.

The etiology of AI is unknown. Some cases have been associated with a personal or family history of atopy. Symptoms can usually be effectively controlled with intermittent application of potent or superpotent topical corticosteroids[15] and administration of oral antihistamines. Dapsone (1–2 mg/kg/day) can be considered when the eruption is especially severe, but the risks of methemoglobinemia and other hematologic side effects usually outweigh the benefits of this form of treatment[3,16].

Eosinophilic Pustular Folliculitis in Infancy

Synonyms: ■ Neonatal eosinophilic pustular folliculitis ■ Infantile eosinophilic pustular folliculitis ■ Eosinophilic pustular folliculitis of infancy

Fig. 34.8 Eosinophilic pustular folliculitis in infancy. Crusted papules and pustules on the scalp of a 1-year-old boy.

Key features

- Recurrent pruritic crops of follicular vesiculopustular lesions
- Favors the scalp and face; rarely involves the trunk and extremities
- Similar natural history as acropustulosis of infancy, exhibiting spontaneous resolution within 3–5 years
- An eosinophilic infiltrate surrounds the hair follicles and invades the outer root sheath
- Therapy is symptomatic
- Rare relationship with HIV infection in infants

Eosinophilic pustular folliculitis (EPF) in infancy is an uncommon entity that presents at birth or during the first few days to weeks of life with sterile pustules on the scalp, face (especially the brow region), and, less commonly, the trunk and extremities. The pruritic pustules often develop hemorrhagic crusts (Fig. 34.8) and recur in crops, occasionally leaving scars. It has been postulated that this condition may be related to acropustulosis of infancy, due to occasional acral involvement and similar cyclical recurrences. The cause of EPF is unknown. It is more frequently seen in male infants, and HIV infection is not commonly associated with this form of EPF as it is in adults. Some authors have suggested that EPF in infancy represents a clinicopathologic reaction pattern with heterogeneous underlying causes rather than a distinctive inflammatory dermatosis.

A smear of pustular contents demonstrates primarily eosinophils, without bacteria or yeast forms. Histologically, a dense eosinophilic and mixed infiltrate is seen around follicles and in the dermal interstitium. The perifollicular cuffing is often associated with invasion of the outer root sheath. Peripheral blood eosinophilia may be present.

The differential diagnosis includes ETN, TNPM, acropustulosis of infancy, bacterial folliculitis, tinea capitis, scabies and reactions to arthropod bites. Since the histologic findings of EPF are quite similar to those of the vesicular and papulopustular lesions seen in association with hyper-IgE syndrome[17] (see below), this diagnosis should also be considered especially in more severe cases.

Symptomatic therapy is the same as that for acropustulosis of infancy and includes potent topical corticosteroids and oral antihistamines[3]. EPF usually resolves spontaneously over 3 to 5 years.

Congenital Langerhans Cell Histiocytosis

Synonyms: ■ Hashimoto–Pritzker disease* ■ Congenital self-healing reticulohistiocytosis*

*Now recognized to be part of Langerhans cell histiocytosis spectrum

Fig. 34.9 Congenital Langerhans cell histiocytosis. Numerous erosions with crusting on the face and trunk of a newborn.

Key features

- Presents at birth and lasts weeks to months
- Crusted papules, vesiculopustules, erosions or nodules; occasionally petechiae or purpura
- May be limited to the skin or, uncommonly, associated with extracutaneous involvement
- Cutaneous infiltrates of $S100^+/CD1a^+$ Langerhans cells; electron microscopy demonstrates characteristic Birbeck granules
- Pure cutaneous form often resolves without treatment
- Both cutaneous and extracutaneous relapses may occur; patients require longitudinal evaluation

Congenital Langerhans cell histiocytosis (LCH) is a rare condition that is virtually always evident at the time of birth. The most typical lesions are crusted papules, pustules and papulovesicles (Fig. 34.9), but nodules may also be present (see Ch. 91). Additional skin findings include petechiae, atrophy, milia and mucosal erosions. Lesions are often widespread but can be solitary, and they may continue to develop and evolve over the first days to weeks of life. Lesions of congenital LCH can develop anywhere on the skin surface, including the palms and soles[3]. The differential diagnosis includes neonatal varicella or HSV infection, congenital candidiasis, congenital syphilis, intrauterine GVHD, and the early-onset form of infantile acropustulosis.

Histologically, a proliferation of Langerhans cells – large, polygonal, histiocytic cells with "coffee bean" nuclei – is present in the superficial dermis and occasionally in the epidermis (epidermotropism). These cells stain positively with S100, CD1a and Langerin immunostains. Ultrastructurally, they contain the characteristic Birbeck granules[18,19].

In an infant diagnosed with congenital cutaneous LCH, a prompt evaluation for systemic involvement is indicated, including a complete physical examination, liver function tests, a complete blood cell count with differential, and a skeletal survey. Distinction between purely cutaneous and multisystem disease is not possible based solely on the skin findings. In fact, the histologic and immunohistochemical features of "congenital self-healing reticulohistiocytosis" and disseminated Langerhans cell histiocytosis are indistinguishable, suggesting that these entities represent different ends of a clinical spectrum[20,21].

In patients whose disease is limited to the skin, lesions usually resolve spontaneously over a period of weeks to months and the prognosis is very good. However, relapses of cutaneous or extracutaneous disease (e.g. diabetes insipidus due to pituitary involvement) may occur months or years later, highlighting the importance of longitudinal evaluation of these patients. The prognosis of multisystem

congenital LCH is less favorable, and systemic therapy is generally required.

Incontinentia Pigmenti

Synonym: ■ Bloch–Sulzberger syndrome

Key features

- X-linked dominant disease, lethal in male fetuses unless mosaic
- Cutaneous lesions are characterized by four distinct phases: vesicular, verrucous, hyperpigmented and hypopigmented/atrophic
- The most common forms of extracutaneous involvement are dental, ophthalmologic and neurologic
- Defect in gene on chromosome Xq28 that encodes NEMO, the NF-κB essential modulator

Incontinentia pigmenti (IP) is an uncommon X-linked dominant multisystem disease that presents within the first 2 weeks of life in 90% of patients. It is usually lethal in male fetuses and is caused by mutations in the *NEMO* gene (NF-κB essential modulator) on Xq28, the protein product of which confers protection against apoptosis induced by the tumor necrosis factor family of cytokines (see Ch. 62).

Cutaneous lesions tend to follow the lines of Blaschko and occur in four classic phases. The vesicular stage is characterized by yellow or clear vesicles in linear and whorled streaks, usually most prominently distributed on the lower extremities (Fig. 34.10A). The verrucous phase of IP consists of hyperkeratotic linear plaques. The third phase, characterized by linear and whorled grayish-brown hyperpigmentation, occurs most often on the trunk and in some patients may be the only cutaneous feature. The first three phases typically resolve during infancy or childhood. The fourth phase, consisting of atrophic, hypopigmented thin streaks favoring the calves, may persist indefinitely. The various clinical stages of IP can overlap, occur *in utero*, or occasionally be skipped entirely. Associated cutaneous findings include patchy scarring alopecia (typically at the vertex), areas of woolly hair, nail dystrophy and anhidrosis within atrophic linear streaks. Extracutaneous features can include dental abnormalities such as hypodontia and conical or peg-shaped teeth; CNS abnormalities manifesting as seizures, delayed psychomotor development and spastic paralysis; and ocular disease characterized by retinal vascular abnormalities that have the potential to lead to blindness. During the vesicular phase, patients often have peripheral blood leukocytosis and eosinophilia.

Histologically, lesions from the vesicular stage of IP demonstrate spongiosis with necrotic keratinocytes, dyskeratosis and infiltrating eosinophils (Fig. 34.10B). A dermal infiltrate composed predominantly of eosinophils is also present[8].

The cutaneous lesions generally do not require therapy. All affected infants should be referred for baseline and longitudinal ophthalmologic examinations and should have periodic neurodevelopmental and dental evaluations. Genetic testing is available.

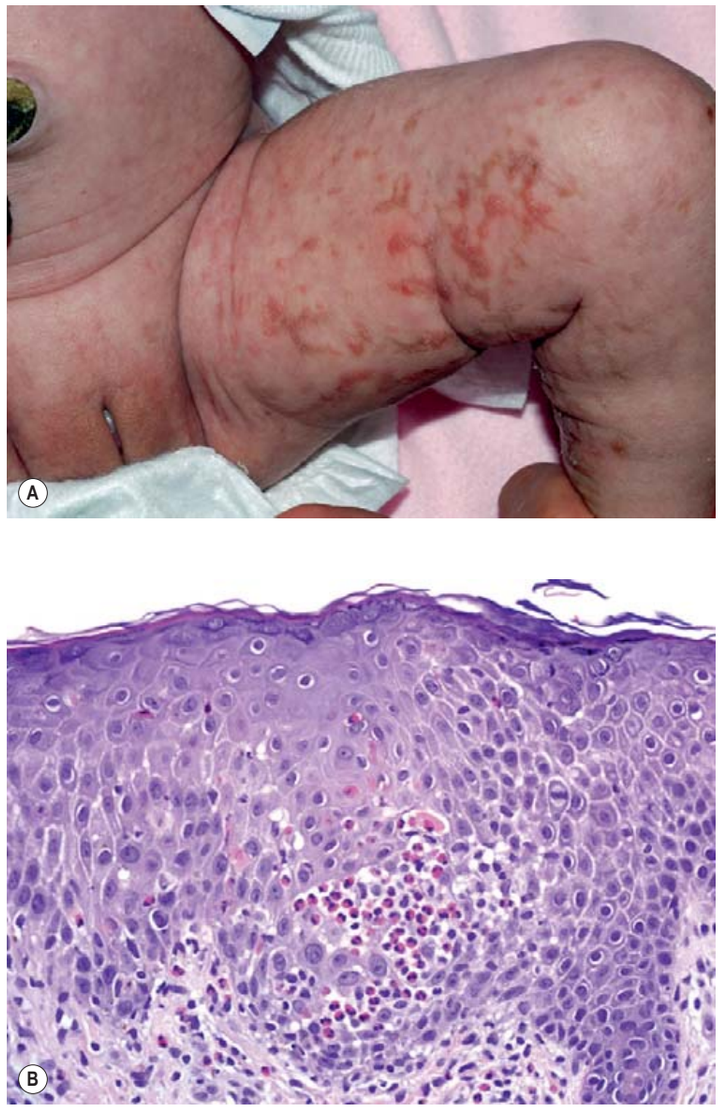


Fig. 34.10 Incontinentia pigmenti stage 1. A Admixture of erythematous streaks containing vesicles and yellow–brown streaks with scale on the lower extremity of a female neonate. **B** Histopathology showing eosinophilic spongiosis and dyskeratotic keratinocytes. *A, Courtesy, Julie V Schaffer, MD. B, Courtesy, Laura B Pincus, MD.*

Hyperimmunoglobulin E (Hyper-IgE) Syndrome

Synonym: ■ Job syndrome

Key features

- A multisystem immunologic disorder
- Papulopustular and vesicular eruption with crusting favoring the face, scalp and neck as well as in the axillae and diaper area
- Peripheral blood eosinophilia
- During the first few months of life, other features such as "cold" abscesses, eczematous dermatitis, recurrent infections and elevated levels of serum IgE are often not present

Hyper-IgE syndrome is a disease of abnormal inflammatory responses that frequently presents at birth or during the first month of life with a vesicular or papulopustular eruption (see Ch. 60). These skin lesions are usually concentrated on the head and shoulders, but they can also affect the axillae and diaper area[22]. Hyper-IgE syndrome is classically associated with high circulating levels of IgE (over 2000 IU/ml) and eosinophilia, but elevated IgE levels may not be evident during early infancy and can fluctuate independently of the severity of the skin disease. Histologic features of the vesicular and papulopustular lesions include intraepidermal vesicles containing eosinophils, perivascular infiltrates of eosinophils, and an eosinophilic folliculitis similar to that seen in eosinophilic pustular folliculitis[17].

Outside of the neonatal period, hyper-IgE syndrome is associated with "cold" abscesses, eczematous dermatitis, recurrent pneumonias with pneumatocele formation, osteopenia, and retention of deciduous teeth. Mutations in the gene encoding signal transducer and activator of transcription 3 (STAT3) are responsible for the classic form of hyper-IgE syndrome, which is inherited in an autosomal dominant manner[23].

VERY RARE DISORDERS

Neonatal Behçet's Disease

Key features

- Most commonly seen in offspring of mothers with known Behçet's disease
- Favorable outcome for most affected infants
- Transient orogenital ulcerations as well as vesiculopustular, purpuric or necrotic skin lesions presenting during the first week of life
- Differential diagnosis includes neonatal HSV infection

Neonatal Behçet's disease has been described in infants born to mothers with active Behçet's disease during pregnancy (see Ch. 26). Cutaneous findings in neonatal Behçet's disease develop during the first week of life and are transient, suggesting pathogenesis involving placental transfer of maternal immunoglobulin. These infants have been described as having ulcerations of the oral and genital mucosae as well as vesiculopustular, purpuric and necrotic skin lesions on the hands and feet and at sites of trauma. Most infants have no other symptoms, although there are isolated reports of life-threatening disease[24]. Intestinal involvement with colitis has also been observed.

The primary differential diagnosis is neonatal HSV infection (Fig. 34.11), which is differentiated by positive direct fluorescent antibody assays, Tzanck smear, viral culture and polymerase chain reaction (PCR).

Fig. 34.11 Neonatal HSV infection. Note the clustering of the vesicles on an erythematous base.

Vesiculopustular Eruption and Transient Myeloproliferative Disorder in Down Syndrome

Key features

- Neonatal vesiculopustular eruption seen in patients with Down syndrome
- Associated with a congenital leukemoid reaction referred to as transient myeloproliferative disorder
- Skin lesions favor the face but may be more extensive; they usually resolve spontaneously

There are a number of reports of a vesiculopustular eruption in neonates with trisomy 21 or mosaicism for trisomy 21. The eruption typically begins during the first few days of life and is associated with transient myeloproliferative disorder, a congenital leukemoid reaction that affects approximately 10% of neonates with Down syndrome. Vesicles and pustules are located most prominently on the face but may also involve the trunk and extremities. Lesions have a predilection for sites of minor trauma or adhesive dressings. Histologically, intraepidermal spongiotic vesiculopustules are present in association with a perivascular infiltrate. The infiltrating cells include immature myeloid cells, which are usually also present in the peripheral blood.

Although the skin lesions tend to resolve spontaneously as the leukemoid reaction subsides, affected patients are at increased risk for the development of acute megakaryocytic leukemia during the first few years of life and thus should be followed by a pediatric oncologist[25,26].

Intrauterine Epidermal Necrosis

Key features

- Reported in premature infants, all of whom died shortly after birth
- Skin erosions and ulcerations only; there are no vesicles or pustules
- No mucous membrane involvement
- Associated with brain infarcts, cardiomegaly and renal tubular necrosis
- Etiology unknown

Four premature infants were reported to have widespread epidermal necrosis at birth, followed by death shortly thereafter. Erosions and ulcerations were noted, but no vesicles or pustules; the mucous membranes were spared. Histologically, the epidermis demonstrated confluent necrosis and the adnexal pilosebaceous structures were calcified. There were brain infarcts with associated leukomalacia as well as cardiomegaly and renal tubular necrosis. The etiology of the findings remains unknown[27,28]. The differential diagnosis includes intrauterine infection, epidermolysis bullosa, acute GVHD, toxic epidermal necrolysis, and congenital erosive and vesicular dermatosis.

Congenital Erosive and Vesicular Dermatosis

Key features

- Widespread vesicles and erosions with "scalded skin"-like areas
- Heals with characteristic reticulated scarring that is also widespread

At least 18 cases of a condition referred to as "congenital erosive and vesicular dermatosis" have been reported[29,30]. At birth, the neonates – almost all premature – have widespread erosions, vesicles, crusting and

Fig. 34.12 Congenital erosive and vesicular dermatosis. **A,B** Widespread bright red, irregularly shaped erosions on the buttocks, thighs and back of a 2-week-old infant. Note the jagged outline of the healing lesion on the back. **C** Residual supple and reticulate scarring in a 9-month-old child. *A,B, Courtesy, Anthony J Mancini, MD. C, Courtesy, Julie V Schaffer, MD.*

Fig. 34.13 Bullous congenital ichthyosiform erythroderma. Diffuse scaling and a large erosion with scale-crust in a neonate. Histologically, epidermolytic hyperkeratosis was seen.

Fig. 34.14 Staphylococcal scalded skin syndrome. Radiating perioral scale-crusts due to exfoliative toxins.

"scalded skin"-like erythematous areas affecting up to 75% of the body surface area (Fig. 34.12A,B). Reported associated findings include a collodion-like membrane, transparent areas of skin, livedo reticularis-like vascular patterns, and ulcerations. The face, palms and soles are usually relatively spared. The lesions heal in 1 to 2 months with characteristic reticulated scars that often cover large areas of the skin (Fig. 34.12C). Later on, scarring alopecia of the scalp and eyelashes, scarring of the tongue, absent or hypoplastic nails, and heat intolerance with hypohidrosis may be seen; mild ongoing blistering is occasionally observed. Mental retardation, brain atrophy, hemiparesis and retinal scars have also been reported.

The cause of congenital erosive and vesicular dermatosis remains unknown, but an unidentified intrauterine infection has been suspected. The diagnosis is often made in retrospect, after other etiologies (most notably HSV infection) have been excluded. Biopsy specimens from the acute phase have demonstrated epidermal necrosis, subepidermal vesiculation, or an eroded epidermis with a neutrophilic or mixed dermal infiltrate and no evidence of vasculitis or thrombosis. Later in the course, biopsy specimens have shown scar formation with loss of eccrine structures.

For affected neonates, the differential diagnosis may include intrauterine infection (especially HSV and varicella), acute intrauterine GVHD, epidermolysis bullosa, bullous congenital ichthyosiform erythroderma (Fig. 34.13) and intrauterine epidermal necrosis. Infants with congenital erosive and vesicular dermatosis should be followed for evidence of diminished sweating and neurologic defects. Treatment is supportive, with no specific therapy available.

Pyoderma Gangrenosum

Key features

- Rare in newborns and infants
- Deep ulcers with undermined borders
- The perineum is the most common location in infants

Rarely reported in infants and newborns, most cases of pyoderma gangrenosum in this age group involve the perineum. Otherwise, the clinical features of the ulcer, including an undermined violaceous border, are similar to those seen in older children and adults[31]. Biopsy specimens show a neutrophilic infiltrate without evidence of infection, but the diagnosis is often one of exclusion after other causes of ulceration such as infection, immunodeficiency, thrombosis and vasculitis are eliminated. The treatment options vary, but intralesional or systemic corticosteroids are usually first-line choices.

Fig. 34.15 Bullous mastocytosis. A Tense bulla on the wrist and flaccid bullae on the dorsal hand as well as pink plaques on the trunk in a 1-month-old infant. **B** Second infant with erosions and diffuse infiltration of the skin with mast cells, leading to a thickened leathery appearance.

Fig. 34.16 Neonatal pemphigoid gestationis. Vesiculobullous lesions in a neonate whose mother had active pemphigoid gestationis. *Courtesy, Jean L. Bolognia, MD.*

Restrictive Dermopathy

Key features

- Rare, fatal laminopathy due to mutations in *LMNA* or *ZMPSTE24* genes that encode lamin A and a zinc metallopeptidase essential for lamin A processing, respectively
- Taut, shiny skin with spontaneous linear splits in flexural creases and prominent vessels
- Intrauterine growth retardation, abnormal facies, flexion contractures of the extremities, restrictive lung disease, bone mineralization defects, and early neonatal death

Restrictive dermopathy is a rare disease characterized by rigid, tense skin with erosions and linear tears that occur most commonly in flexural creases. The disorder results in a fetal akinesia or hypokinesia deformation sequence characterized by multiple joint contractures, dysmorphic facies with a fixed facial expression, and polyhydramnios with reduced fetal movements; the latter results in premature delivery, often at about 31 weeks' gestation. Other features include translucent skin with prominent vessels, micrognathia, sparse/absent eyelashes, natal teeth, large fontanelles, dysplasia of the clavicles, and poorly expanded lungs as a result of the restrictive skin changes. Most affected newborns die from pulmonary disease within the first week of life. Restrictive dermopathy is now known to be a lethal neonatal laminopathy, caused by either dominant *de novo* mutations in *LMNA*, which encodes lamin A, or recessive null mutations in *ZMPSTE24*, which encodes a zinc metallopeptidase essential for lamin A processing[32].

Noma Neonatorum

Key features

- Usually related to *Pseudomonas aeruginosa* septicemia
- Necrotic ulcerations of orofacial and anogenital regions
- Predisposing factors include premature birth, low birthweight and malnutrition

Two forms of noma have been described in the newborn period. The first is a manifestation of infection, usually *Pseudomonas aeruginosa* septicemia, and has been reported almost exclusively in developing countries[33]. Infants present with an abrupt onset of gangrenous ulcerations of the nose, lips, mouth, eyelids, anus and scrotum. In severe cases, the ulcerations can destroy underlying bony structures and cause extensive deformity. Predisposing factors include premature birth, low birthweight, malnutrition and previous illness. Some authors suggest that this form of noma neonatorum may represent a form of neonatal ecthyma gangrenosum[34].

The second form of noma has been seen in Native American infants who present with perineal and oral ulcerations in the setting of severe combined immunodeficiency[35]. The presence of oral and perineal ulcerations in newborns and infants should prompt an evaluation for infection and immunologic deficiencies.

Perinatal Gangrene of the Buttock

Key features

- Erythema of the buttocks that progresses to ulceration and gangrene
- May be related to occlusion or spasm of the internal iliac artery

This rare condition is characterized by the sudden onset of erythema and cyanosis of the buttocks, followed by progressive development of gangrene and ulcerations. Although some cases have been associated with umbilical artery catheter infusions, others have been spontaneous. Occlusion or spasm of the internal iliac artery has been postulated as a potential cause[36]. Other disorders to consider when evaluating a neonate with hemorrhagic bullae and gangrenous soft tissue infarction include purpura fulminans, congenital coagulopathies (including protein C and S deficiency), and disseminated intravascular coagulation due to infection[3].

REFERENCES

1. Berg FJ, Solomon LM. Erythema neonatorum toxicum. Arch Dis Child. 1987;62:327–8.
2. Lucky AW. Transient benign cutaneous lesions in the newborn. In: Eichenfield LF, Frieden IJ, Esterly NB (eds). Textbook of Neonatal Dermatology. Philadelphia: WB Saunders, 2008:85–98.
3. Frieden IJ, Howard R. Vesicles, pustules, bullae, erosions and ulcerations. In: Eichenfield LF, Frieden IJ, Esterly NB (eds). Textbook of Neonatal Dermatology. Philadelphia: WB Saunders, 2008:131–58.
4. Marchini G, Hultenby K, Nelson A, et al. Increased expression of HMGB-1 in the skin lesions of erythema toxicum. Pediatr Dermatol. 2007;24:474–82.
5. Ferraandiz C, Coroleu W, Ribera M, et al. Sterile transient neonatal pustulosis is a precocious form of erythema toxicum neonatorum. Dermatology. 1992;185:18–22.
6. Perrin E, Sutherland J, Balthazar S. Inquiry into the nature of the lentigines neonatorum: demonstration of a statistical relationship with squamous metaplasia of the amnion. Am J Dis Child. 1961;102:648–9.
7. Ramamurthy RS, Reveri M, Esterly NB, et al. Transient neonatal pustular melanosis. J Pediatr. 1976;88:831–5.
8. Maize JC, Burgdorf WHC, Hurt MA, et al. Intraepidermal vesicular and pustular diseases. In: Cutaneous Pathology. Philadelphia: Churchill Livingstone, 1998:245–66.
9. Mowad CM, McGinley KJ, Foglia A, Leyden JJ. The role of extracellular polysaccharide substance produced by *Staphylococcus epidermidis* in miliaria. J Am Acad Dermatol. 1995;33:729–33.
10. Rapelanoro R, Mortureux P, Couprie B, et al. Neonatal *Malassezia furfur* pustulosis. Arch Dermatol. 1996;132: 190–3.
11. Niamba P, Weill FX, Sarlangue J, et al. Is common neonatal cephalic pustulosis (neonatal acne) triggered by *Malassezia sympodialis*? Arch Dermatol. 1998;134: 995–8.
12. Bernier V, Weill FX, Hirigoyen V, et al. Skin colonization by *Malassezia* species in neonates. A prospective study and relationship with neonatal cephalic pustulosis. Arch Dermatol. 2002;138:215–18.
13. Ayhan M, Sancak B, Karaduman A, et al. Colonization of neonate skin by *Malassezia* species: relationship with neonatal cephalic pustulosis. J Am Acad Dermatol. 2007;57:1012–18.
14. Darmstadt GL, Dinulos JG, Miller A. Congenital cutaneous candidiasis: clinical presentation, pathogenesis, and management guidelines. Pediatrics. 2000;105:438–44.

14a. Sánchez-Schmidt JM, Vicente-Villa MA, Viñas-Arenas M, et al. Isolated congenital nail candidiasis: report of 6 cases. Pediatr Infect Dis J. 2010;29:974–6.

15. Mancini AJ, Frieden IJ, Paller AS. Infantile acropustulosis revisited: history of scabies and response to topical corticosteroids. Pediatr Dermatol. 1998;15:337–41.
16. Kahn G, Rywlin AM. Acropustulosis of infancy. Arch Dermatol. 1979;115:831–3.
17. Chamlin SL, McCalmont TH, Cunningham BB, et al. Cutaneous manifestations of hyper-IgE syndrome in infants and children. J Pediatr. 2002;141:572–5.
18. Maize JC, Burgdorf WHC, Hurt MA, et al. Proliferative disorders of mononuclear phagocytes and Langerhans cells. In: Cutaneous Pathology. Philadelphia: Churchill Livingstone, 1998:763–88.
19. Newman B, Hu W, Nigro K, Gilliam AC. Aggressive histiocytic disorders that can involve the skin. J Am Acad Dermatol. 2007;56:302–16.
20. Kapur P, Erickson C, Rakheja D, et al. Congenital self-healing reticulohistiocytosis (Hashimoto-Pritzker disease): ten-year experience at Dallas Children's Medical Center. J Am Acad Dermatol. 2007;56:290–4.
21. Jaffe R. Is there a role for histopathology in predicting the clinical outcome in congenital and infant Langerhans cell disease? Pediatr Blood Cancer. 2009;53:924–5.
22. Kamei R, Honig PJ. Neonatal Job's syndrome featuring a vesicular eruption. Pediatr Dermatol. 1988;5:75–82.
23. Holland SM, DeLeo FR, Elloumi HZ, et al. *STAT3* mutations in the hyper-IgE syndrome. N Engl J Med. 2007;357:1608–19.
24. Stark AC, Bhakta B, Chamberlain MA, et al. Life-threatening transient neonatal Behçet's disease. Br J Rheumatol. 1997;36:700–2.
25. Lerner LH, Wiss K, Gellis S, Barnhill R. An unusual pustular eruption in an infant with Down syndrome and a congenital leukemoid reaction. J Am Acad Dermatol. 1996;35:330–3.
26. Nijhawan A, Baselga E, Gonzalez-Ensenat MA, et al. Vesiculopustular eruptions in Down syndrome neonates with myeloproliferative disorders. Arch Dermatol. 2001;137:760–3.
27. Ruiz-Maldonado R, Duraan-McKinster C, Carrasco-Daza D, et al. Intrauterine epidermal necrosis: report of three cases. J Am Acad Dermatol. 1998;38:712–15.
28. Allee JE, Saria EA, Rosenblum D, et al. Intrauterine epidermal necrosis. J Cutan Pathol. 2001;28:383–6.
29. Metz BJ, Hicks J, Levy M. Congenital erosive and vesicular dermatosis healing with reticulated supple scarring. Pediatr Dermatol. 2005;22:55–9.
30. Gonçalves RV, Pessoa OM, Lowy G. Evaluation of a congenital erosive and vesicular dermatosis healing with reticulated supple scarring. Pediatr Dermatol. 2007;24:384–6.
31. Graham JA, Hansen KK, Rabinowitz LG, Esterly NB. Pyoderma gangrenosum in infants and children. Pediatr Dermatol. 1994;11:10–17.
32. Navarro CL, Cadinanos J, De Sandre-Giovannoli A, et al. Loss of XMPSTE24 (FACE-1) causes autosomal recessive restrictive dermopathy and accumulation of lamin A precursors. Hum Mol Genet. 2005;14:1503–13.
33. Ghosal SP, Sen Gupta PC, Mukherjee AK, et al. Noma neonatorum: its aetiopathogenesis. Lancet. 1978;2:289–91.
34. Freeman AF, Mancini AJ, Yogev R. Is noma neonatorum a presentation of ecthyma gangrenosum in the newborn? Pediatr Infect Dis J. 2002;21:83–5.
35. Rotbart HA, Levin MJ, Jones JF, et al. Noma in children with severe combined immunodeficiency. J Pediatr. 1986;109:596–600.
36. Bonifazi E, Meneghini C. Perinatal gangrene of the buttock: an iatrogenic or spontaneous condition? J Am Acad Dermatol. 1980;3:596–8.

This page intentionally left blank

Acropustulosis of infancy. Multiple vesiculopustules with an erythematous base on the dorsal fingers

Transient neonatal pustular melanosis. Pustules, hyperpigmented macules, and collarettes of scale are seen on the chin and neck of an African-American neonate.

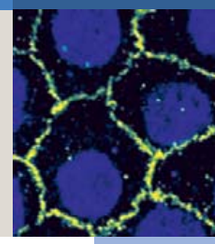
Acropustulosis of infancy. Multiple vesiculopustules with an erythematous base on the plantar surface.

Incontinentia pigmenti stage I. Multiple vesicles and bullae with an erythematous border on the lower extremity. *Courtesy of Anthony J Mancini MD.*

Erythema toxicum neonatorum. Scattered papulovesicles with an erythematous flare. *Courtesy of Kalman Watsky MD.*

Structure and Function of Eccrine, Apocrine and Sebaceous Glands

35



Martin Schaller and Gerd Plewig

Chapter Contents

Eccrine, apocrine and apoeccrine sweat glands 539
Sebaceous glands 542

ECCRINE, APOCRINE AND APOECCRINE SWEAT GLANDS

Key features

- Eccrine sweat glands are activated by emotional and thermal stimuli and are necessary for thermoregulation; they have a generalized distribution, with the highest density on the palms and soles
- The eccrine secretory unit consists of a coiled secretory portion that drains into a long thin duct whose apical portion (acrosyringium) opens to the skin surface
- Innervation of eccrine glands consists of postganglionic sympathetic fibers that have acetylcholine as the principal neurotransmitter
- Apocrine sweat glands are androgen-dependent for their development and have an unclear function in humans; primary locations are the axillae, anogenital region, periumbilical region and nipples
- Apocrine glands, whose apical portion (acrosyringium) drains into terminal hair follicles, continuously secrete a sterile odorless viscous fluid that is rich in precursors of odoriferous substances

INTRODUCTION

The major sweat glands in humans are eccrine and apocrine glands (Table 35.1)[1,2]. They vary in type and density, depending on anatomic location.

Disorders of sweating are common and can be due to dysfunction of central sweat centers; sympathetic ganglia and their pre- and postganglionic fibers; or secretory glands and ducts[3]. Clinical disorders include hyperhidrosis, hypohidrosis and sweat retention. Hyperhidrosis, which can be emotional or secondary to systemic disease, often leads to social stigmatization. Hypohidrosis and anhidrosis may be markers for genodermatoses (see Ch. 63) and can lead to life-threatening hyperthermia. Sweat retention disorders (i.e. miliaria) are typically transient and often occur after extensive sweating[3]. Knowledge of the structure and function of sweat glands is important for proper diagnosis and treatment of sweating disorders (see Chs 39 & 159).

STRUCTURE, FUNCTION AND PATHOPHYSIOLOGY

In humans, there are two main types of sweat glands: eccrine and apocrine. They are distinct from one another structurally, developmentally and functionally (Fig. 35.1). A third type of sweat gland, the apoeccrine gland, was described in 1987 by Sato et al.[4], who found such glands consistently in the axillae of adults but not children. These apoeccrine sweat glands possessed certain morphologic and functional features of eccrine and apocrine glands[4,5]. However, a recent study that examined serial histologic sections of normal axillary skin using routine and immunofluorescent staining found no evidence of apoeccrine glands[6].

Eccrine Sweat Glands

Structure

Approximately 1.5 to 4 million eccrine sweat glands are distributed over the entire cutaneous surface (with the exception of the external auditory canals, vermilion lips, clitoris and labia minora) and are active from birth. The highest density is found on the palms and soles. The eccrine secretory unit consists of a proximal coiled secretory portion in the lower dermis and subcutaneous tissue. This drains into a long thin duct with an apical portion (acrosyringium) that opens directly onto the skin surface (see Fig. 35.1)[7]. The secretory coils contain two cell types interspersed within a single cell layer: (1) large clear cells responsible for the gland's secretion of electrolytes and water; and (2) dark cells, of unknown function, with basophilic granules that are thought to produce sialomucin (Fig. 35.2). Both cell types are surrounded by myoepithelial cells, which probably function to enhance the delivery of sweat to the skin surface[1,2]. The ductal epithelium is composed of two or more layers of cuboidal cells without surrounding myoepithelium. The intraepidermal portion of the duct, the acrosyringium, is twisted like a corkscrew with similar coils in the stratum corneum[8]. Recent investigations revealed expression of stem cell markers (e.g. prominin-1/CD133) in the secretory and ductal portions of eccrine glands[9].

Innervation of the eccrine glands is provided by postganglionic sympathetic fibers that have acetylcholine (not norepinephrine) as their principal terminal neurotransmitter (Table 35.2). These sympathetic fibers are controlled by the hypothalamic sweat center[8]. The sweat center responds to its own temperature (as a reflection of core body temperature) as well as neural stimuli from the periphery.

Development

During embryogenesis, at 3 months' gestation, sweat glands begin to develop as a cord of epithelial cells that buds from the epidermal ridge on the palms and soles. By 5 months' gestation, similar structures have appeared over the remainder of the body. Functional eccrine glands are present at birth and react to thermal and emotional stimuli. Unlike apocrine glands, they have no developmental relationship with the pilosebaceous follicle[2,8].

Function

Eccrine sweat is a sterile, dilute electrolyte solution that contains primarily sodium chloride (NaCl), potassium and bicarbonate. Other components include antimicrobial peptides (e.g. dermcidin)[11], proteolytic enzymes, glucose, pyruvate, lactate, urea, ammonia, calcium, amino acids, epidermal growth factor, cytokines and immunoglobulins. Additional organic compounds and heavy metals are also excreted in sweat.

The quantity and quality of eccrine sweat secretion varies greatly, depending on emotional and environmental stimuli[1–3]. There are several methods for measuring sweat production (Table 35.3). Under maximal

CHARACTERISTICS OF SWEAT GLANDS			
	Eccrine	**Apocrine**	**Apoeccrine***
Localization	Entire body skin, highest density on palms and soles	Axillae, anogenital, periumbilical, nipples and areolae	Axillae
Morphology	Long, thin duct opens to skin surface	Short, thick duct opens into upper part of follicular canal	Duct comparable to eccrine gland duct
	Secretory coil with narrow lumen	Secretory coil with wide lumen	Secretory coil with dilated and non-dilated tubular segments
Cell types in secretory coil	Large secretory clear cells, dark cells, and myoepithelial cells	Epithelial (typically cuboidal) and myoepithelial cells	Eccrine and apocrine morphologic features
Main innervation/neurotransmitter	Sympathetic fibers/acetylcholine	Unclear/possible humoral effects of β-adrenergic receptor agonists	Sympathetic fibers/acetylcholine
Development	Present at birth	Present at birth	Probably not present before adolescence
	No relationship to pilosebaceous follicle	Associated with terminal hair follicle	No relationship to pilosebaceous follicle
Function/pathogenic role	Thermoregulation/role in hyperhidrosis and hypohidrosis	Unclear/some role in olfactory communication; role in follicular apocrine Fox–Fordyce disease	Unclear/possible roles in thermoregulation, axillary hyperhidrosis and non-follicular apoeccrine Fox–Fordyce disease

*Observed in some but not all studies of normal axillary skin.

Table 35.1 Characteristics of sweat glands.

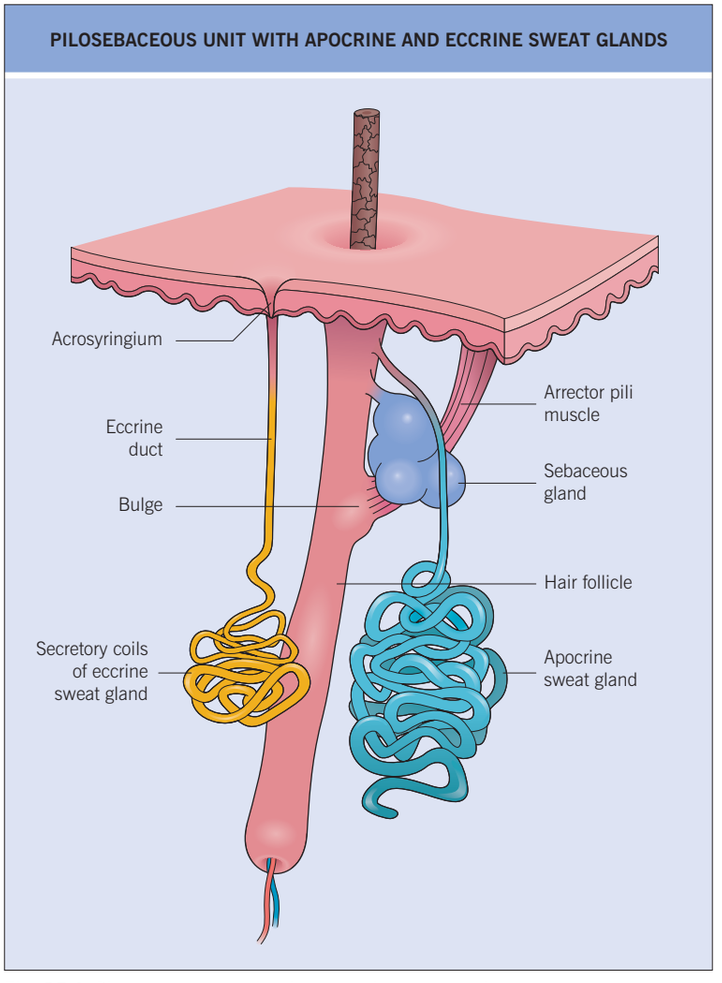


Fig. 35.1 Pilosebaceous unit with apocrine and eccrine sweat glands. Pilosebaceous unit with an associated apocrine sweat gland and a nearby eccrine sweat gland.

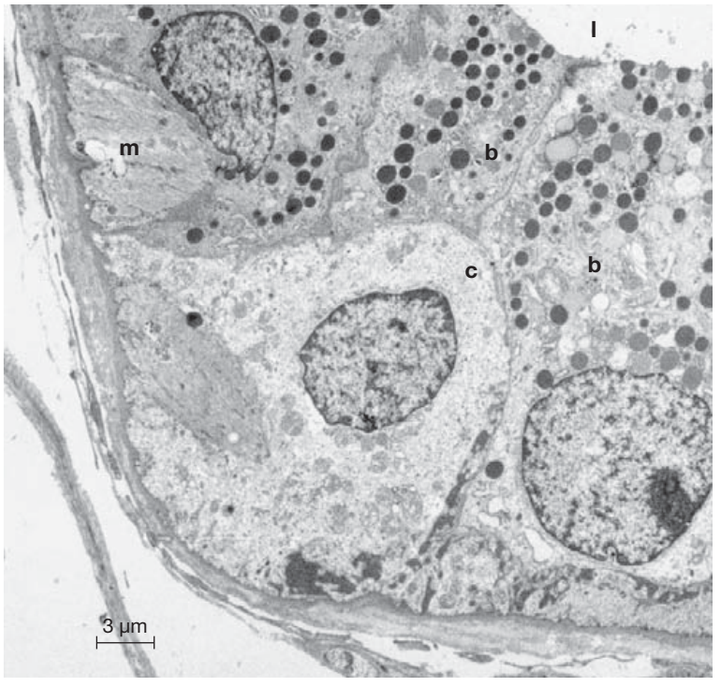


Fig. 35.2 Ultrastructure of the secretory coil of an eccrine gland. A dilated lumen (l), a clear or secretory cell (c), dark cells with basophilic granules (b) and myoepithelial cells (m).

stimulation, the body can produce 3 liters in 1 hour. Sweat is formed in two steps[12]: (1) release of nearly isotonic primary sweat by the secretory coil; and (2) partial reabsorption of NaCl by duct cells, resulting in the delivery of a hypotonic fluid to the skin surface. The final concentration of NaCl may be higher when sweat is produced at a more rapid rate.

Continuous secretion of sweat provides a mechanism for thermoregulation via evaporative heat loss, maintenance of electrolyte balance, and keeping the stratum corneum moist to insure fine tactile skills and pliability of the palms and soles[1–3]. The excretory function of the sweat gland can be instrumental in the delivery of systemically administered drugs to the stratum corneum (e.g. ketoconazole and griseofulvin)[13], and it provides an explanation for cutaneous side effects of certain chemotherapeutic drugs. Botulinum toxin can be used to treat eccrine hyperhidrosis. After dermal injection, botulinum toxin taken up by the nerve terminal interferes with proteins required to release acetylcholine at the neuroglandular junction (see Fig. 159.1).

Pathophysiology

Disorders affecting eccrine function involve modifications of sweat quantity or quality; these can be localized (e.g. Frey's syndrome) or

INNERVATION AND RECEPTOR PROFILES OF SWEAT GLANDS		
	Eccrine	**Apocrine**
Nerve fibers near gland	+	±
Cholinergic muscarinic (M_3) receptors	++	±
α_1-adrenergic receptors	+	–
β_2- > β_3-adrenergic receptors	+	+
Purinergic receptors	+	+

Table 35.2 Innervation and receptor profiles of sweat glands. Apoeccrine glands are thought to have the same innervation and receptor profile as eccrine glands. Based on data from ref. 10.

METHODS FOR EVALUATING SWEAT PRODUCTION
• Visualization of sweat by the starch–iodine reaction or quinizarin method • Measurement of electric potential and resistance of the skin • Measurement of skin temperature (e.g. infrared thermography) • Gravimetry (e.g. weighing filter paper before and after application to the skin) • Measurement of evaporative water loss from the skin

Table 35.3 Methods for evaluating sweat production.

Fig. 35.3 Toxic erythema of chemotherapy (palmar erythrodysesthesia). Erythema and blister formation, most notably on the distal portion of the first and second digits and the digital creases (arrows).

generalized (e.g. hypohidrotic ectodermal dysplasia). The sweat glands are also affected in cystic fibrosis (CF). Individuals with CF lose excessive amounts of salt (NaCl) when they sweat, and the most common screening test for CF measures the amount of Cl^- in the sweat.

Hyper- and hypohidrosis

Excess function of eccrine glands is typically due to enhanced cutaneous sympathetic outflow in response to mental and thermal stimuli. The former results primarily in increased sweating of the palms, soles and axillae[14]. This emotional form of hyperhidrosis can be a major inconvenience, but it is not associated with morphologic or functional abnormalities of the glands, nor with internal diseases[2].

Stimulation of eccrine sweat glands may occur in association with a variety of underlying disorders (see Ch. 39), including neurologic, infectious, neoplastic (e.g. lymphomas) and endocrine diseases, in particular the hypoestrogenemia associated with menopause[1,2,4].

Increased sweating can lead to overhydration and even maceration of the skin. This may be accompanied by secondary bacterial and fungal infections (see Chs 74 & 77). Proteolytic activity by resident and transient skin flora (microbiota) can lead to odor-producing substances (e.g. ammonia and short-chain fatty acids); this is referred to as eccrine bromhidrosis.

Hypohidrosis or anhidrosis may be congenital, e.g. due to a reduced number of eccrine glands in patients with hypohidrotic ectodermal dysplasia (see Ch. 63), or acquired, e.g. due to poral occlusion in patients with scleroderma or administration of medications with anticholinergic effects. Acquired or inherited neuropathies also represent another important cause of hypohidrosis[1,2,4].

Drug-related eccrine disorders

Concentration of drugs in the eccrine glands is well known. Drugs known to be secreted into eccrine sweat include chemotherapeutic agents (e.g. cyclophosphamide, cytarabine), antibiotics (e.g. ciprofloxacin, β-lactam antibiotics) and antifungals. In patients receiving chemotherapy, excretion of toxic components into eccrine sweat is thought to play a role in the production of neutrophilic eccrine hidradenitis and other forms of toxic erythema of chemotherapy (Fig. 35.3). Toxic insult to the eccrine ductal cells from chemotherapy leads to the histologic finding of eccrine squamous syringometaplasia (see Ch. 21)[1,2,4,13].

Disorders of sweat retention

Occlusion of the eccrine ducts can result from a parakeratotic plug of PAS-positive material, which then leads to sweat retention. Miliaria may be triggered by a high environmental or body temperature, excessive sweating (especially under occlusive clothing or dressings) and an increased density of resident bacteria, e.g. *Staphylococcus epidermidis*. Ductal plugs within the stratum corneum lead to superficial miliaria (miliaria crystallina), while intraepidermal and dermal duct occlusion induce miliaria rubra and profunda, respectively (see Ch. 39)[15].

Apocrine Sweat Glands

Structure

Apocrine sweat glands are confined to certain anatomic locations (axillae, anogenital region, periumbilical region, areolae, nipples, vermilion border of the lip) and are larger than eccrine glands[1,2]. Modified forms of apocrine glands are found in the external auditory canals (ceruminous glands) and on the eyelid margins (glands of Moll). Apocrine glands consist of a secretory portion, which is located in the deep dermis and subcutaneous fat, and a stretched duct that opens into the upper portion of the follicular canal, i.e., the apocrine acrosyringium (see Fig. 35.1)[1,2]. The secretory unit is a convoluted tube with a single layer of epithelial cells (typically columnar) surrounded by myoepithelial cells. The duct consists of a double layer of cuboidal cells, as well as myoepithelial cells that support the movement of secretions to the skin surface. Although immunohistochemical staining may help to differentiate between apocrine and eccrine sweat glands (e.g. CD15 staining of apocrine but not eccrine secretory cells), the specificity of several markers (e.g. human milk fat globule-1 [HMFG-1], gross cystic disease fluid protein-15 [GCDFP-15]) has been questioned[6,16] and distinction may require serial routine sectioning or electron microscopy[17].

Apocrine gland secretion increases in response to local or systemic administration of catecholamines and cholinergic agonists, but the mechanisms controlling physiologic secretion are poorly understood. In a recent study of normal axillary skin, secretory coils of apocrine glands were found to have β-adrenergic and purinergic but not cholinergic receptors (see Table 35.2)[10]. Nerve fibers were found near eccrine glands but not apocrine glands, suggesting that catecholamines stimulate the latter through humoral mechanisms[10].

Development

Embryologically, the apocrine sweat gland is derived from the primary epithelial germ layer, which also gives rise to the sebaceous gland and hair follicle. In the embryo, apocrine sweat glands are present over the entire skin surface, but most of them subsequently disappear, resulting in the characteristic distribution found in adults. Enlargement of the glands occurs with the approach of puberty and is due to hormonal stimulation (primarily by androgens).

Function

Apocrine glands continuously secrete very small quantities of an oily fluid. This sweat is sterile, odorless and viscous, with a pH between 5.0 and 6.5. It is rich in precursors of odoriferous substances (cholesterol, triglycerides, fatty acids, cholesterol esters, squalene). It also contains androgens, carbohydrates, ammonia and ferric iron. Apocrine or "decapitation" secretion refers to the "pinching off" and release of the luminal portion of secretory cells; apocrine glands also employ merocrine (exocytosis of vesicles) and holocrine (rupture of the plasma membrane) secretion.

In animals, apocrine glands are the source of pheromones, which act as chemical signals that instigate behavioral responses (e.g. sexual attraction) or mark territorial boundaries. In humans, apocrine glands do not have a clear function but may play some role in olfactory communication[1,2].

Pathophysiology

Although apocrine sweat is initially sterile and odorless, bacteria on the skin surface modify and degrade the secreted substances, resulting in typical, rancid (*Corynebacterium* spp.) or sweaty (*Micrococcus* spp.) body odor termed bromhidrosis. When biopsies from bromhidrosis patients have been compared with controls, the apocrine glands were more abundant and larger with active decapitation. These histologic differences may reflect increased production of apocrine sweat and thus may help explain bromhidrosis[18]. Insufficient body and textile hygiene will worsen the condition. Of note, some androgenic steroids have an odor similar to natural axillary odor.

Apocrine chromhidrosis refers to the secretion of pigmented (yellow, green or black) sweat. It is a reflection of the rich lipofuscin content of apocrine sweat. Pseudo- or extrinsic apocrine chromhidrosis results from staining of the sweat by chromogenic bacteria (especially *Corynebacterium* spp.) or colored garments. Occlusion of apocrine ducts by a keratinous plug influenced by functional hormonal changes underlies follicular apocrine miliaria (Fox–Fordyce disease; see Ch. 39).

Apoeccrine Sweat Glands

Structure

Apoeccrine sweat glands have been found only in the adult axilla[19]. As noted above, there are conflicting data about the existence of this third type of sweat gland, with no evidence of axillary apoeccrine glands in a recent study[6]. The secretory coil of apoeccrine sweat glands has been described as consisting of dilated and non-dilated tubular segments[2,4]. The dilated segments and their secretory cells are ultrastructurally very similar to those of apocrine glands, while the non-dilated segments, which are smaller in diameter, resemble eccrine secretory coils. The apoeccrine duct opens directly onto the skin surface and not via follicular structures; it has the same morphologic features as the eccrine gland duct. The innervation of the apoeccrine gland consists of postganglionic sympathetic fibers with acetylcholine as the principal terminal neurotransmitter[2,4] (see Table 35.1). Adrenergic stimulation also occurs.

Development

Apoeccrine sweat glands are thought to develop during puberty from eccrine-like precursor cells and have been identified only in adult axillae[2,4]. The relative percentage of axillary apoeccrine sweat glands has been noted to be higher in patients with hyperhidrosis as compared to normohidrotic individuals.

Function

Apoeccrine sweat is a clear fluid that is secreted persistently after cholinergic stimulation. The constituents of apoeccrine sweat are not known. The secretory rate can be as much as 10 times that of the eccrine gland[2,4].

Pathophysiology

Epidermal or other growth factors in sweat may be involved in stimulating the differentiation of apoeccrine glands[17]. It has been postulated that these glands play an important role in axillary hyperhidrosis[4,5] and non-follicular apoeccrine Fox–Fordyce disease[20].

SEBACEOUS GLANDS

Key features

- Sebaceous glands produce sebum via holocrine secretion and have multiple biological functions, including hormonal and immune modulation
- Except for ectopic or free sebaceous glands of the vermilion lips, orogenital mucosae, areolae and eyelids, these glands are associated with hair follicles
- Sebum consists of free fatty acids, wax and sterol esters, triglycerides and squalene
- Sebum production is a sensitive indicator of androgenic activity; it increases at the time of puberty and decreases in later adulthood (particularly in postmenopausal women)
- Sebaceous follicles are rich in microorganisms including *Malassezia* spp., *Staphylococcus epidermidis* and *Propionibacterium* spp.

INTRODUCTION

Except for the free sebaceous glands found on the vermilion lips and oral mucosa (Fordyce granules), eyelids (meibomian glands), areolae (Montgomery tubercles), labia minora and prepuce (Tyson glands), sebaceous glands are associated with hair follicles. Sebaceous glands produce sebum, which is released into the infundibular portion of the hair follicle. Sebum production increases at the time of puberty and is a critical factor in the pathogenesis of acne vulgaris[21]. Sebaceous glands also play important roles in cutaneous endocrine function (including the hypothalamus–pituitary–adrenal-like axis of the skin as well as androgen metabolism) and innate immunity, producing neuropeptides, androgens, cytokines and antimicrobial peptides that also contribute to acne pathogenesis (Table 35.4).

STRUCTURE, FUNCTION AND PATHOPHYSIOLOGY

Structure

The distribution of sebaceous glands within the skin is variable. However, they are particularly well developed on the scalp, face, upper back and chest. There are three different types of pilosebaceous units: vellus, sebaceous and terminal (Fig. 35.4).

A sebaceous follicle consists of four parts: the keratinized follicular infundibulum, the hair, the cauliflower-like convoluted sebaceous gland, and the sebaceous duct which connects the gland with the infundibulum (Figs 35.1 & 35.5). The infundibulum is divided into two parts. The distal portion, or acroinfundibulum, is very similar to the adjacent epidermis. It displays keratinization with a granular layer, and corneocytes (squames) are shed into the lumen. The lower part, or infrainfundibulum, is quite different. It shows a distinct pattern of trichilemmal keratinization and no granular layer.

Sebaceous follicles have a rich normal flora (resident microbiota) of bacteria (e.g. *S. epidermidis* and *Propionibacterium* spp. such as *P. acnes*) and fungi (e.g. *Malassezia* spp.) (see Fig. 35.5)[22]. They also harbor *Demodex* mites, which increase in number in older adults and are rarely seen in prepubertal children.

Development

Sebaceous glands are derived from the epidermis as buds from developing hair follicle root sheaths and grow downward into the dermis. Sebaceous glands are present at birth, and sebum production is relatively high at this time. It soon declines and remains low until puberty, at which time it again increases. Androgens, in particular 5α-dihydrotestosterone (DHT), appear to be the major factor that controls the development of the glands and the production of sebum. The level of sebum production at the end of puberty remains constant through mid-adulthood. Sebum production declines in women after menopause, and in men during the sixth to seventh decade of life.

Although stem cells in the hair follicle bulge can regenerate sebaceous glands following injury, under homeostatic conditions bulge cells do

ROLES OF THE SEBACEOUS GLAND IN PATHOGENESIS OF ACNE VULGARIS AND ROSACEA		
SG component	**Actions in SGs**	**Observations in SGs of patients with AV and R**
HYPOTHALAMIC–PITUITARY–ADRENAL-LIKE AXIS		
Corticotropin-releasing hormone (CRH)* and CRH receptors (CRH-Rs)	↑ lipid and androgen synthesis ↑ production of IL-6, IL-8 (CRH-R2)	↑ levels of CRH and (in sebaceous ducts) CRH-R1 in **AV**
α-Melanocyte stimulating hormone (MSH)* and melanocortin-1 & -5 receptors (MC1-R, MC5-R†)	↑ sebocyte differentiation and lipid synthesis (MC5-R)	↑ levels of MC1-R in **AV**
OTHER NEUROPEPTIDES		
Substance P	↑ sebocyte proliferation/ differentiation ↑ production of inflammatory cytokines	↑ substance P-containing nerves in **AV**
ANDROGENS		
Testosterone* and dihydrotestosterone (DHT)*	↑sebocyte proliferation/ differentiation and lipid synthesis (especially DHT) May ↑ infundibular keratinization	↑ conversion of testosterone to DHT in **AV** Association of hyperandrogenic disorders with **AV**‡
SEBUM COMPONENTS AND DERIVATIVES		
Monounsaturated fatty acids (MUFAs), lipoperoxides (LPs), other proinflammatory lipids (e.g. generated via 5-lipoxygenase), linoleic acid (LA)	↑ infundibular keratinization (MUFAs, LPs, *deficient* LA) ↑cytokine production, chemotaxis, and PPAR activation (MUFAs, LPs)	↑ overall sebum production, MUFAs and LPs in **AV** ↑ 5-lipoxygenase in **AV** ↓ linoleic acid in **AV**
INNATE IMMUNE SYSTEM		
Toll-like receptors (TLRs, especially TLR2)	Upon stimulation (e.g. by *P. acnes*), ↑production of IL-1, IL-8, IL-12, TNF-α (TLR2)	↑ expression of TLR2 and TLR4 in **AV** Possible ↑ expression of TLR2 in **R**
Defensins, cathelicidins, MUFAs (e.g. sapienic acid)	Antimicrobial properties ↑ cytokine production and chemotaxis	↑ levels of cathelicidin (especially a proteolytically processed form with ↑ proinflammatory and vasoactive effects) in **R**
ORGANISMS		
Propionibacterium acnes§	↑ production of antimicrobial peptides & inflammatory cytokines/ chemokines (e.g. via TLR2 stimulation) ↑ free fatty acids (e.g. via lipase activity) May ↑ infundibular keratinization	↑ *P. acnes* in **AV**
Demodex folliculorum	May stimulate or carry bacteria (e.g. *Bacillus oleronius*) that stimulate innate and adaptive immune reactions	↑ density of *D. folliculorum* and reactivity to *B. oleronius* in **R**

*Can be produced locally by the SG as well as remotely.
†Marker of sebocyte differentiation.
‡Most AV patients have normal levels of circulating androgens.
§Different phylogenetic clusters of *P. acnes* vary in their ability to induce immune responses.

Table 35.4 Roles of the sebaceous gland (SG) in pathogenesis of acne vulgaris (AV) and rosacea (R). IL, interleukin; PPAR, peroxisome proliferator-activated receptor; TNF, tumor necrosis factor.

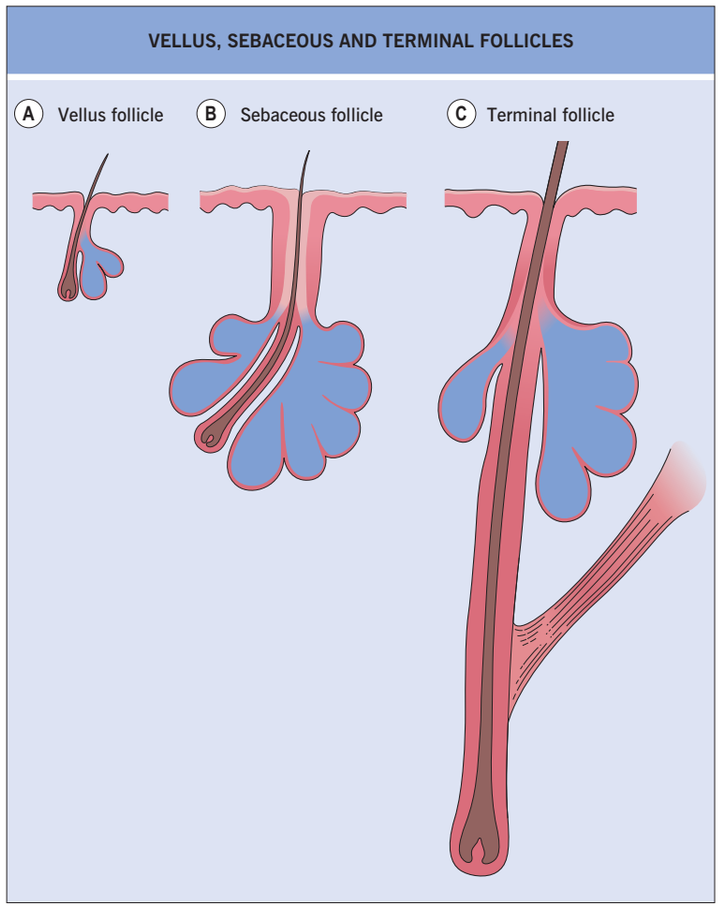


Fig. 35.4 Vellus, sebaceous and terminal follicles. Three different types of pilosebaceous units. **A** Vellus follicle with a small sebaceous gland and short thin hair. **B** Sebaceous follicle with a large multilobular sebaceous gland and mid-sized hair. **C** Terminal follicle with a fairly large sebaceous gland and thicker hair. *Adapted from Plewig G, Kligman AM. Acne and Rosacea, 3rd edn. Berlin: Springer, 2000.*

not appear to contribute to the formation of sebaceous glands[23]. Human sebocytes can differentiate into both sebocytes and interfollicular epidermal cells, suggesting a bipotential stem cell function[21,24]. In cultured human sebocytes and an *in vivo* mouse model, overexpression of c-Myc stimulates *sebaceous* differentiation, whereas overexpression of β-catenin induces *epidermal* differentiation[24]. Expression of the stem cell marker keratin 15 has been observed in human basal sebocytes[23]. Blimp-1 (*B-l*ymphocyte-*i*nduced *m*aturation *p*rotein-1) was found to be a marker for sebocyte progenitor cells in mice, but in humans it is expressed by terminally differentiating cells of the sebaceous gland, hair follicle and interfollicular epidermis[24].

Function

Sebum is a light yellow viscous fluid. It is composed of triglycerides, free fatty acids, squalene, wax and sterol esters, and free sterols. The admixture of ceramides, mostly derived from epidermal lipids, occurs in the acroinfundibulum before the entire sebum mixture reaches the skin surface. Secretion of sebum is holocrine, that is, the sebocytes disintegrate and thereby release their sebum as they migrate towards the central gland and sebaceous duct. Sebocyte turnover time is approximately 14 days, and the flow of sebum is relatively continuous. The amount of sebum produced varies among individuals and races, but the average rate in adults is approximately 1 mg/10 cm^2 every 3 hours[25].

Sebaceous glands contain androgen receptors that bind DHT, which is then translocated to the nucleus[26]. They also express functional receptors for neuropeptides such as corticotropin-releasing hormone (CRH), melanocortins and substance P[21,27]. The latter receptors contribute to proliferation and differentiation of cells in the sebaceous gland (sebocytes) and modulate their production of lipids, androgens and cytokines in response to stimuli such as emotional stress (see Table 35.4).

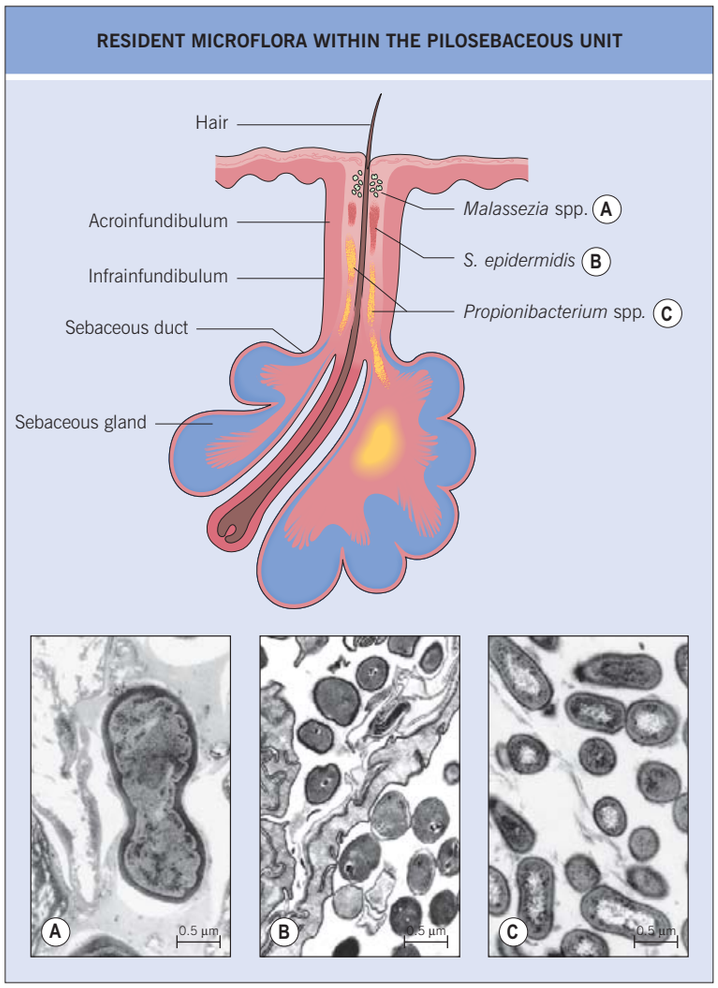


Fig. 35.5 Resident microflora within the pilosebaceous unit. Localization of resident microflora within the pilosebaceous unit and electron microscopic view of organisms: **A** *Malassezia* spp.; **B** *Staphylococcus epidermidis*; **C** *Propionibacterium* spp., including *P. acnes*, *P. granulosum* and (least often) *P. parvum*.

Pathophysiology

Sebum production that is less than 0.5 mg/10 cm^2 every 3 hours is associated with sebostasis or dry skin, and 1.5–4.0 mg/10 cm^2 every 3 hours is considered excessive and results in the clinical condition known as seborrhea. Sebaceous follicles are most commonly found on the face, behind the ears, and on the upper portions of the chest and back – the same distribution as acne vulgaris. Clinically, these areas tend to be oilier than the rest of the body. In general, acne patients have larger sebaceous glands and produce more sebum than do patients with normal skin. The function of sebaceous follicles is influenced by genetic factors and levels of circulating hormones.

Growth of sebaceous glands and increased sebum production are both induced by androgens, particularly DHT. In men, DHT is mainly derived from testosterone, while in women, androstenedione is the main precursor. The conversion of testosterone to DHT is 30 times higher in skin affected by acne than in normal skin. Eunuchs, who lack testicular function, do not get acne. However, increased sebum alone is insufficient to cause acne vulgaris, as witnessed by the fact that patients with Parkinson's disease have marked seborrhea but do not get acne.

Sebaceous glands play several major roles in the pathogenesis of acne vulgaris and may also contribute to the pathogenesis of rosacea (see Table 35.4)[26]. Sebum in sebaceous glands and within the ducts is sterile and contains no free fatty acids, but the microenvironment of the infundibulum favors the growth of *P. acnes* and *S. epidermidis*[28]. In patients with acne vulgaris, the resident microorganisms (especially *P. acnes*) are quantitatively increased in sebaceous follicles. Their lipases split di- and triglycerides, producing free fatty acids that alter the pattern of keratinization within the infundibulum. Abnormal keratinization is one of the first pathogenic steps in acne vulgaris, with increased proliferation and retention of corneocytes in the infundibulum resulting in a microcomedo. Free fatty acids are also chemotactic and attract neutrophils.

The infrainfundibulum of acne patients responds to a variety of physiologic and exogenous stimuli more readily than that in patients without acne. Therefore, comedogenic agents such as halogenated cyclic hydrocarbons, tar products and some cosmetics cause more problems in acne patients than in other individuals[25]. Follicular acneiform eruptions also develop in patients receiving inhibitors of the *e*pidermal growth *f*actor *r*eceptor (EGFR); they occur with antibodies that block the interaction of EGF with its receptor (e.g. cetuximab) as well as with inhibitors of EGFR tyrosine kinase activity (e.g. gefitinib; see Ch. 36). EGFR is strongly expressed in keratinocytes and in cells of eccrine and apocrine glands. Inhibition of the EGFR disturbs the normal differentiation and morphogenesis of hair follicles, inducing excessive follicular hyperkeratosis, follicular plugging, and growth of microorganisms in the dilated infundibula[29].

REFERENCES

1. Sato K, Kang WH, Saga K, Sato KT. Biology of sweat glands and their disorders. I. Normal sweat gland function. J Am Acad Dermatol. 1989;20:537–63.
2. Wilke K, Martin A, Terstegen L, Biel SS. A short history of sweat gland biology. Int J Cosmet Sci. 2007;29:169–79.
3. Sato K, Kang WH, Saga K, Sato KT. Biology of sweat glands and their disorders. II. Disorders of sweat gland function. J Am Acad Dermatol. 1989;20:713–26.
4. Sato K, Leidal R, Sato F. Morphology and development of an apoeccrine sweat gland in human axillae. Am J Physiol. 1987;252:R166–80.
5. Sato K, Sato F. Sweat secretion by human axillary apoeccrine sweat gland in vitro. Am J Physiol. 1987;252:R181–7.
6. Bovell DL, Corbett AD, Holmes S, et al. The absence of apoeccrine glands in the human axilla has disease pathogenetic implications, including axillary hyperhidrosis. Br J Dermatol. 2007;156:1278–86.
7. Christophers E, Plewig G. Formation of the acrosyringium. Arch Dermatol. 1973;107:378–82.
8. Wenzel FG, Horn TD. Nonneoplastic disorders of the eccrine glands. J Am Acad Dermatol. 1998;38:1–17.
9. Karbanova J, Missol-Kolka E, Fonseca AV, et al. The stem cell marker CD133 (Prominin-1) is expressed in various human glandular epithelia. J Histochem Cytochem. 2008;56:977–93.
10. Lindsay SL, Holmes S, Corbett AD, et al. Innervation and receptor profiles of the human apocrine (epitrichial) sweat gland: routes for intervention in bromhidrosis. Br J Dermatol. 2008;159:653–60.
11. Schittek B, Hipfel R, Sauer B, et al. Dermcidin: a novel human antibiotic peptide secreted by sweat glands. Nat Immunol. 2001;2:1133–7.
12. Garty H, Palmer LG. Epithelial sodium channels: function, structure, and regulation. Physiol Rev. 1997;77:359–96.
13. Johnson HL, Maibach HI. Drug excretion in human eccrine sweat. J Invest Dermatol. 1971;56:182–8.
14. Iwase S, Ikeda T, Kitazawa H, et al. Altered response in cutaneous sympathetic outflow to mental and thermal stimuli in primary palmoplantar hyperhidrosis. J Auton Nerv Syst. 1997;64:65–73.
15. Hölzle E, Kligman AM. The pathogenesis of miliaria rubra. Role of the resident microflora. Br J Dermatol. 1978;99:117–37.
16. Jeong KB, Shin DH, Choi JS, et al. The utility of HMFG-1 and GCDFP-15 to discriminate the differentiation of eccrine and apocrine neoplasms. Korean J Dermatol. 2003;41:1583–91.
17. Saga K. Histochemical and immunohistochemical markers for human eccrine and apocrine sweat glands: an aid for histopathologic differentiation of sweat gland tumors. J Investig Dermatol Symp Proc. 2001;6:49–53.
18. Bang YH, Kim JH, Paik SW, et al. Histopathology of apocrine bromhidrosis. Plast Reconstr Surg. 1996;98:288–92.
19. Beer GM, Baumuller S, Zech N, et al. Immunohistochemical differentiation and localization analysis of sweat glands in the adult human axilla. Plast Reconstr Surg. 2006;117:2043–9.
20. Kamada A, Saga K, Jimbow K. Apoeccrine sweat duct obstruction as a cause for Fox-Fordyce disease. J Am Acad Dermatol. 2003;48:453–5.
21. Kurokawa I, Danby FW, Ju Q, et al. New developments in our understanding of acne pathogenesis and treatment. Exp Dermatol. 2009;18:821–32.
22. Wolff HH, Plewig G, Januschke E. Ultrastructure and microflora in follicles and comedones. Hautarzt. 1976;27:432–40.
23. Abbas O, Mahalingam M. Epidermal stem cells: practical perspectives and potential uses. Br J Dermatol. 2009;161:228–36.
24. Lo Celso C, Berta MA, Braun KM, et al. Characterization of bipotential epidermal progenitors derived from human sebaceous gland: contrasting roles of c-Myc and beta-catenin. Stem Cells. 2008;26:1241–52.
25. Plewig G, Kligman A. Acne and Rosacea, 3rd edn. Berlin: Springer, 2000.
26. Zouboulis CC, Baron JM, Bohm M, et al. Frontiers in sebaceous gland biology and pathology. Exp Dermatol. 2008;17:542–51.
27. Ganceviciene R, Graziene V, Fimmel S, et al. Involvement of the corticotropin-releasing hormone system in the pathogenesis of acne vulgaris. Br J Dermatol. 2009;160:345–52.
28. Leyden JJ, McGinley KJ, Vowels B. *Propionibacterium acnes* colonization in acne and nonacne. Dermatology. 1998;196:55–8.
29. Duvic M. EGFR inhibitor-associated acneiform folliculitis: assessment and management. Am J Clin Dermatol. 2008;9:285–94.

Acne Vulgaris 36

Andrea L Zaenglein and Diane M Thiboutot

Synonym: ■ Acne

Key features

- A multifactorial disorder of the pilosebaceous unit
- Significant psychologic and economic impact
- Clinically characterized by comedones, papules, pustules, cysts and scarring

INTRODUCTION

Acne vulgaris is a multifactorial disorder of the pilosebaceous unit. The clinical picture can vary significantly, from mild comedonal acne to fulminant systemic disease. Although all age groups may be affected by its many variants, acne is primarily a disorder of adolescence. Acne has an undeniable psychosocial impact, and affected individuals have an increased likelihood of self-consciousness, social isolation, depression and even suicidal ideation[1]. Recent insights into the pathogenesis of acne have aided significantly in further defining the subtypes of acne and establishing effective treatment regimens.

HISTORY

In the sixth century AD, the term "acne" was first used by the Emperor Justinian's physician, Aetius Amidenus. It was later translated from Greek into Latin, and through these translations confusion arose regarding its original meaning[2]. The debate continues as to whether its origin is from the Greek *acme*, meaning peak, or whether acne was actually the original term. Its use became obsolete until the 1800s, when "acne" regained a place in medical dictionaries. In 1842, Erasmus Wilson separated acne simplex (acne vulgaris) from acne rosacea[3].

EPIDEMIOLOGY

Acne vulgaris affects approximately 40–50 million individuals each year in the US alone, leading to an estimated annual cost in the US of at least $2.5 billion. With a peak incidence during adolescence, acne affects approximately 85% of young people between 12 and 24 years of age and is therefore a physiologic occurrence in this group. Although it is typically thought of as a disease of youth, acne often continues to be problematic well into adulthood. In a recent survey-based study, 35% of women and 20% of men reported having acne in their 30s, while 26% of women and 12% of men were still affected in their 40s[4]. Caucasian boys and men have a tendency to have more severe nodulocystic disease than other groups.

Individuals at increased risk for the development of acne include those with an XYY karyotype or endocrine disorders such as polycystic ovarian syndrome, hyperandrogenism, hypercortisolism and precocious puberty. Patients with these conditions tend to have more severe acne that is less responsive to standard therapy.

PATHOGENESIS

The development of acne involves a complex interaction of multiple factors, both internal and external to the pilosebaceous apparatus. Appreciating the anatomy and physiology of this unique structure is vital to understanding the pathogenesis of acne (Fig. 36.1) and essential for formulating effective treatment regimens. The structure and function of sebaceous glands are reviewed in detail in Chapter 35, and Table 35.4 summarizes their roles in acne.

Genetic Factors

The pathogenesis of acne is multifactorial, and the precise role of genetic predisposition is uncertain. The number, size and activity of sebaceous glands is inherited. In addition, the concordance rate for the prevalence and severity of acne among identical twins is extremely high. It is a widely held belief that acne (including nodulocystic acne) runs in families, and an association between moderate to severe acne and a family history of acne has been observed in several studies[5]. However, because of the extremely high prevalence of acne, it is difficult to attribute its presence exclusively to genetic factors.

Sebum Production

The sebaceous gland is controlled primarily by hormonal stimulation (see below). After the first 6 months of life (when sebum production is relatively high), the rate decreases and remains stable throughout childhood. At adrenarche, sebum production dramatically increases. Although the overall composition of sebum is the same in persons with or without acne, those with acne have variable seborrhea[6].

Comedo Formation

One of the first steps in the production of acne is the formation of the microcomedo. This begins in the keratinized lining of the upper portion of the follicle, the infundibulum (Fig. 36.1A). Comedo formation occurs when the corneocytes, which are normally shed into the lumen of the follicle and extruded through the follicular ostium, are retained and accumulate, leading to hyperkeratosis. Increased cohesiveness of these cells is responsible for this phenomenon. The ultrastructural components of the cell that are responsible for adhesiveness all play a role, including lamellar granules, cell membranes, epidermal lipids, and intercellular cementing substances.

In addition to increased intercellular cohesiveness of the corneocytes, their production is accelerated as well. This combination of increased cellular cohesion and proliferation occurs in the proximal portion of the infundibulum, the infrainfundibulum, and it creates a bottleneck phenomenon and subsequent microcomedo formation. In the underlying follicular epithelium, keratohyaline granules are increased in size and number, whereas lamellar granules and tonofilaments are decreased.

As the comedo expands, the sebaceous lobule undergoes regression (Fig. 36.1B,C). Because of the very narrow opening to the skin surface, there is initially an accumulation of loosely packed shed keratinocytes and sebum. With expansion of the comedo, the contents become closely packed, creating whorled lamellar concretions. As the forces increase, rupture of the comedo wall with extrusion of the immunogenic keratin and sebum occurs, with resultant inflammation (Fig. 36.1C,D).

Inflammatory Responses

Inflammation is not only the result of comedo rupture, as it is also seen early in acne lesion formation. For example, in acne-prone sites, the number of $CD4^+$ T cells and levels of interleukin-1 (IL-1) have been shown to be increased perifollicularly prior to hyperkeratinization[7]. The type of inflammatory response determines the clinical lesion seen. If neutrophils predominate (typical of early lesions), a suppurative pustule is formed. Neutrophils also promote the inflammatory response by releasing lysosomal enzymes and generating reactive oxygen species, and levels of the latter in the skin and plasma may correspond with

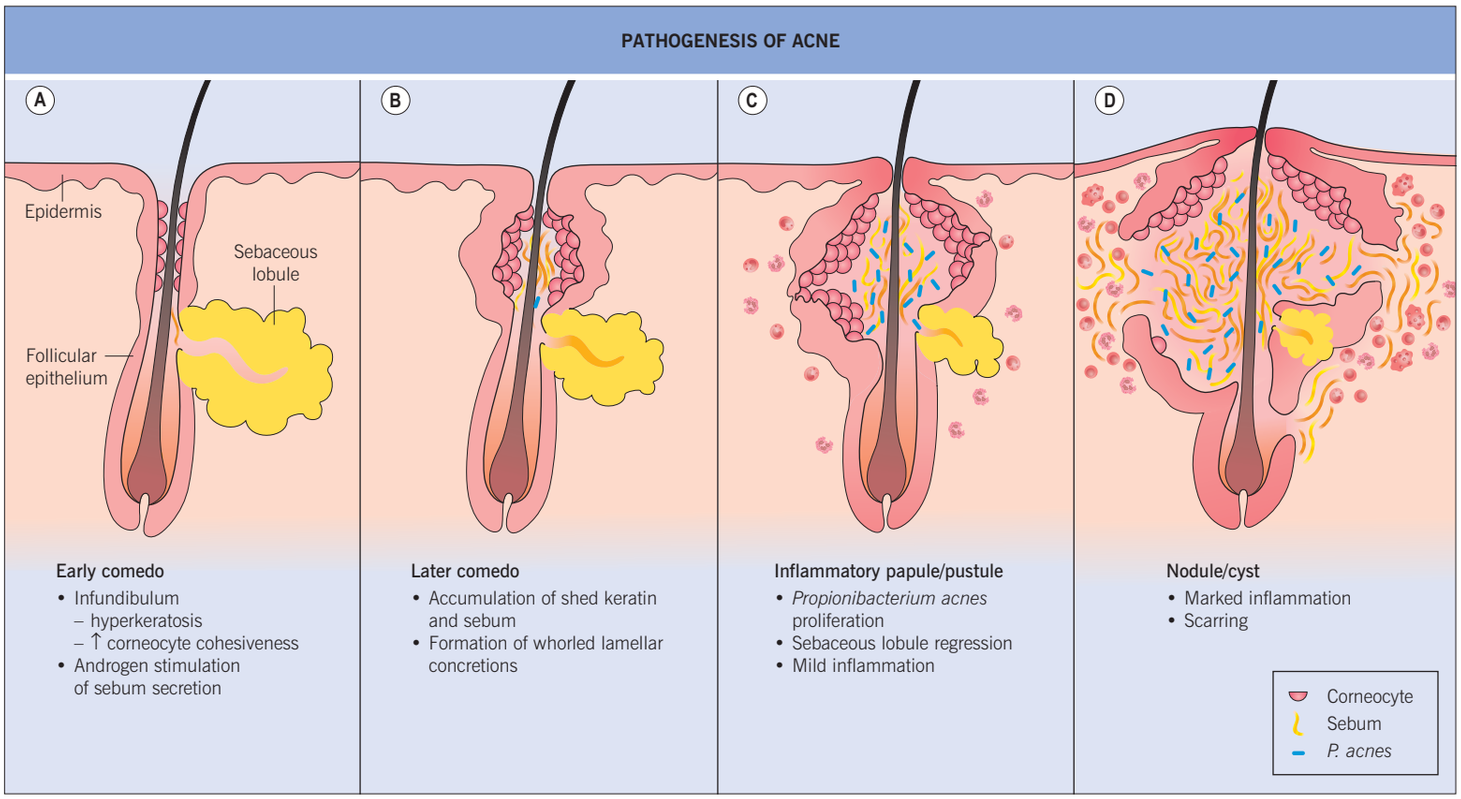


Fig. 36.1 Pathogenesis of acne.

acne severity[8]. Influx of lymphocytes (predominately T-helper [Th] cells) and foreign body-type giant cells, in addition to neutrophils, results in inflamed papules, nodules and cysts. The type of inflammatory response also plays a role in the development of scarring. Early, nonspecific inflammation results in less scarring than does a delayed, specific inflammatory response[9].

Propionibacterium acnes and the Innate Immune System

Propionibacterium acnes contributes significantly to the pathogenesis of acne. These Gram-positive, non-motile rods are found deep within the sebaceous follicle, along with *P. granulosum* and, rarely, *P. parvum*. They are anaerobic/microaerophilic and naturally produce porphyrins (primarily coproporphyrin III) that fluoresce with Wood's lamp illumination. The pathogenicity of these microorganisms stems from several of their properties, including the release of enzymes that contribute to comedo rupture, lipases and chemotactic factors, as well as stimulation of a host response (by inflammatory cells and keratinocytes) that involves production of proinflammatory mediators and reactive oxygen species. Increased numbers of *P. acnes* have been reported in acne patients, but their numbers do not correlate with clinical severity[10]. Different strains of *P. acnes* have been shown to induce varying degrees of sebocyte differentiation and proinflammatory cytokine/chemokine reponses[11].

Interactions between the skin's innate immune system and *P. acnes* play an important role in acne pathogenesis. One mechanism is via Toll-like receptors (TLRs), a class of transmembrane receptors that mediates the recognition of microbial pathogens by immune cells such as monocytes, macrophages and neutrophils as well as by keratinocytes (see Ch. 4). TLR2 (which recognizes lipoproteins and peptidoglycans) is found on the surface of macrophages surrounding acne follicles, and *P. acnes* has been found to increase expression of TLR2 and TLR4 on keratinocytes. *P. acnes* has been shown to stimulate the release of proinflammatory mediators (e.g. IL-1α, IL-8, IL-12, tumor necrosis factor-α [TNF-α], matrix metalloproteinases) through the TLR2 pathway[12–14]. IL-8 results in neutrophil recruitment, the release of lysosomal enzymes and subsequent disruption of the follicular epithelium, whereas IL-12 promotes Th1 responses (see Ch. 4). The degree to which IL-8, IL-12 and interferon-γ production is augmented does not appear to depend upon the strain of *P. acnes* that is present[14,15].

In contrast, certain strains of *P. acnes* may have an increased propensity to upregulate expression of human β-defensin-2 by the pilosebaceous unit via a TLR-dependent mechanism[14,16]. Beta-defensin-2 (production of which is also augmented by sebum free fatty acids), cathelicidins (expressed by sebocytes with upregulation by *P. acnes*), and other antimicrobial peptides such as psoriasin (see Ch. 4) work synergistically to protect the pilosebaceous unit from *P. acnes*[17,18]. Histone H4, which is secreted in a holocrine manner by sebocytes, also directly kills *P. acnes* and may function together with free fatty acids to augment innate immune defenses[19]. Lastly, *P. acnes* can induce monocytes to differentiate into two distinct innate immune cell subsets: (1) $CD209^+$ macrophages (development of which is promoted by tretinoin) that more effectively phagocytose and kill *P. acnes*; and (2) $CD1b^+$ dendritic cells that activate T cells and release proinflammatory cytokines[20].

Hormonal Influences

Hormonal effects on sebum secretion are key to the pathogenesis of acne. Androgens are produced both outside the sebaceous unit, primarily from the gonads and adrenal glands, and locally within the gland via the action of androgen-metabolizing enzymes such as 3β-hydroxysteroid dehydrogenase (HSD), 17β-HSD and 5α-reductase (Fig. 36.2). Androgen receptors, found in the cells of the basal layer of the sebaceous gland and the outer root sheath of the hair follicle, are responsive to testosterone and 5α-dihydrotestosterone (DHT), the most potent androgens. DHT has a 5–10-fold greater affinity than testosterone for the androgen receptor and is thought to be the principal androgen mediating sebum production.

The role of androgens in sebaceous gland activity begins during the neonatal period. From birth until approximately 6–12 months of age, infant boys have elevated levels of luteinizing hormone (LH), which stimulates testicular production of testosterone. In addition, both male and female infants exhibit increased levels of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS) secondary to a large, androgen-producing "fetal zone" in the adrenal gland that involutes over the first

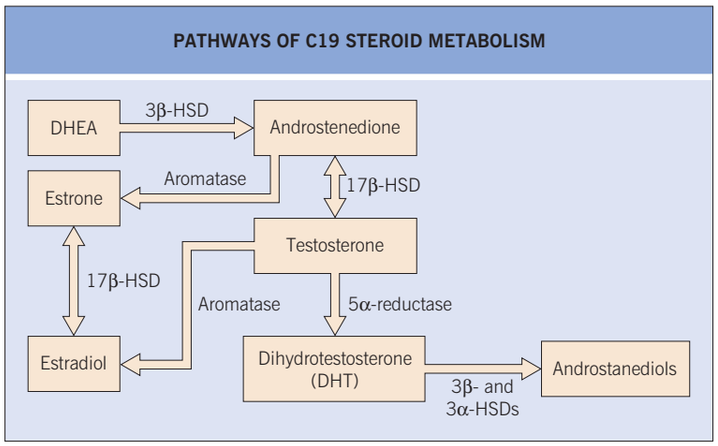


Fig. 36.2 Pathways of C19 steroid metabolism. Dehydroepiandrosterone (DHEA) is a weak androgen that is converted to the more potent testosterone by 3β-hydroxysteroid dehydrogenase (HSD) and 17β-HSD. 5α-reductase then converts testosterone to dihydrotestosterone (DHT), the predominant hormonal effector on the sebaceous gland. Both DHEA and testosterone can be metabolized to estrogens by the enzyme aromatase. The sebaceous gland expresses each of these enzymes.

Fig. 36.3 Comedonal acne vulgaris. On the cheek, there are open and closed comedones as well as postinflammatory hyperpigmentation.

year of life. Of note, sebaceous gland activity in infants is not due to persistent maternal hormonal stimulation, as was previously hypothesized. Both testicular and adrenal androgen production decrease substantially by 1 year of age and remain at a stable nadir until adrenarche.

With the onset of adrenarche (typically at 7–8 years of age, usually heralding menarche by several years), circulating levels of DHEAS begin to rise due to adrenal production. This hormone can serve as a precursor for the synthesis of more potent androgens within the sebaceous gland (see Fig. 36.2). The rise in serum levels of DHEAS in prepubescent children is associated with an increase in sebum production and the initial development of comedonal acne[21].

Little is known about the physiologic role of estrogens in modulating sebum production. Any estrogen given systemically in sufficient amounts will decrease sebum production. However, the dose of estrogen required to suppress sebum production is greater than the dose required to suppress ovulation. Although acne may respond to treatment with lower-dose oral contraceptives containing 0.035–0.050 mg of ethinyl estradiol or its esters, higher doses of estrogen are often required to demonstrate a reduction in sebum secretion[22]. As with androgens, it is not known whether circulating estrogens or locally produced estrogens are important in modulating sebum secretion. Estrogens may act by several mechanisms, including:

- directly opposing the effects of androgens locally within the sebaceous gland
- inhibiting the production of androgens by gonadal tissue via a negative feedback loop whereby pituitary gonadotropin release is inhibited
- regulating genes that negatively influence sebaceous gland growth or lipid production.

Dietary Factors

The relationship between diet and acne remains a subject of controversy. Over the past decade, observational studies have found that milk intake (especially skim milk) is positively associated with acne prevalence and severity, and prospective studies have documented a link between a high glycemic-load diet and acne risk[23].

CLINICAL FEATURES

Acne is typically found in sites with well-developed sebaceous glands, most often the face and upper trunk. Non-inflammatory acne is characterized by open and closed comedones (Fig. 36.3). The histologic features of these follicular-based lesions are reflected in their clinical appearance. Closed comedones (whiteheads) are generally small (~1 mm), skin-colored papules with no apparent follicular opening or associated erythema. These lesions may be subtle and better appreciated upon palpation, stretching or side-lighting of the skin (Fig. 36.4). In contrast, open comedones (blackheads) are dome-shaped papules with a conspicuous dilated follicular opening that is filled with an inspissated core of shed keratin (Fig. 36.5). Melanin deposition and lipid oxidation within the debris may be responsible for the black coloration. "Ice-pick"-type scarring sometimes results from comedones alone.

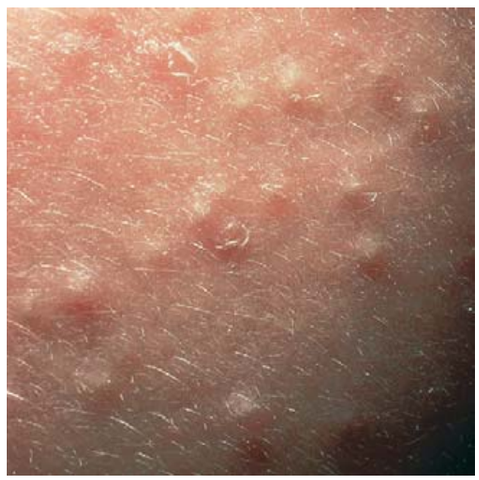


Fig. 36.4 Closed comedones highlighted by side lighting. *Courtesy, Ronald P Rapini, MD.*

Inflammatory acne also originates with (micro)comedo formation, followed by the development of papules, pustules, nodules and cysts of varying severity (Figs 36.6 & 36.7). Erythematous papules typically range from 1 to 5 mm in diameter. Pustules tend to be approximately equal in size and are filled with white pus and normal flora. As the severity of lesions progresses, nodules form and become markedly inflamed, indurated and tender. The cysts of acne are deeper and filled with a combination of pus and serosanguineous fluid. In patients with severe nodulocystic acne, these lesions frequently coalesce to form large, complex inflamed plaques that can include sinus tracts.

Early treatment of acne is essential for the prevention of lasting cosmetic disfigurement due to scarring. Erythema and postinflammatory hyperpigmentation (Fig. 36.8) often persist after resolution of inflammatory acne lesions. Although the pigmentary changes usually fade over many months if the acne is brought under control, occasionally

Fig. 36.5 Open comedones in a patient with scarring cystic acne.

Fig. 36.7 Severe cystic acne. This form is best treated with low doses of isotretinoin initially, to avoid precipitating a flare.

Fig. 36.6 Inflammatory acne vulgaris. Papules, obvious pustules, and atrophic scars are present.

Fig. 36.8 Postinflammatory hyperpigmentation secondary to acne. Such pigmentary changes are most common in patients with darker skin colors.

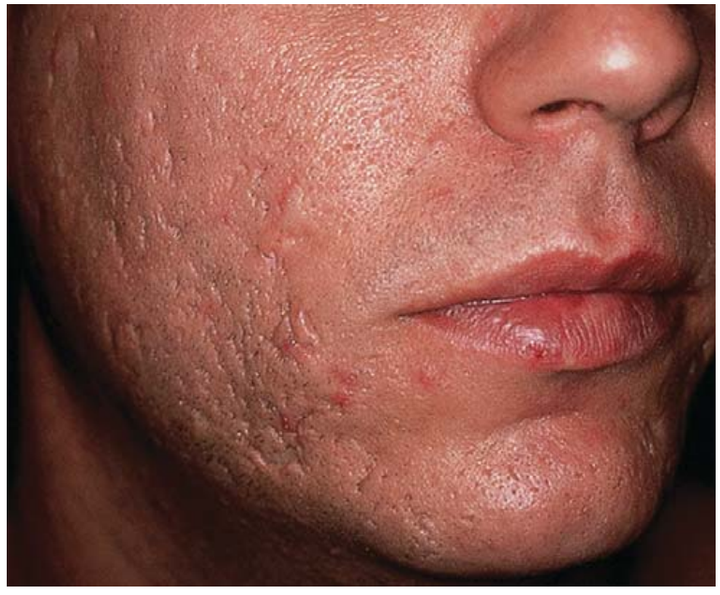


Fig. 36.9 "Ice-pick" scarring secondary to acne.

they can be permanent. Unfortunately, pitted scars (Fig. 36.9) or hypertrophic scars (most commonly on the trunk; see Fig. 98.5) are often sequelae of nodulocystic acne.

Acne Variants

Post-adolescent acne

Inflammatory acne persisting beyond 25 years of age is most common in women, tends to flare during the week prior to menstruation, and typically features tender, deep-seated papulonodules on the lower third of the face, jawline and neck[24]. Approximately one-third of affected women have other signs of hyperandrogenism (see below), but regardless of androgen levels, hormonal therapy is often effective. A predominantly comedonal, adult-onset form of acne that is associated with smoking has also been described[24].

Acne fulminans

Acne fulminans is the most severe form of acne and is characterized by the abrupt development of nodular and suppurative acne lesions in association with systemic manifestations. This uncommon variant primarily affects boys 13–16 years of age. Patients typically have mild to moderate acne prior to the onset of acne fulminans, when numerous microcomedones suddenly erupt and become markedly inflamed. There is rapid coalescence into painful, oozing, friable plaques with hemorrhagic crusts (Fig. 36.10). The face, neck, chest, back and arms are all affected. Lesions tend to ulcerate and can lead to significant scarring.

Osteolytic bone lesions may accompany the cutaneous findings; the clavicle and sternum are most commonly affected, followed by the ankles, humerus and iliosacral joints. Systemic manifestations include fever, arthralgias, myalgias, hepatosplenomegaly and severe malaise. The related *s*ynovitis, *a*cne, *p*ustulosis, *h*yperostosis and *o*steitis (SAPHO) syndrome, which can present with acne fulminans, is discussed in detail in Chapter 26. Erythema nodosum may also arise in association with acne fulminans. Laboratory abnormalities vary and include an elevated ESR, proteinuria, leukocytosis and anemia. Labora-

Fig. 36.10 Acne fulminans. Inflamed, friable papulopustules and plaques with erosions, oozing and formation of granulation tissue. *Courtesy, Julie V Schaffer, MD.*

Fig. 36.11 Solid facial edema due to acne vulgaris. There is soft tissue swelling in the central portion of the face.

tory studies are not required to establish the diagnosis, but their evolution may parallel the clinical course and response to therapy.

Treatment of acne fulminans usually includes oral corticosteroids and oral isotretinoin, often with initiation of the latter at a low dose and/or after the acute inflammation subsides. Paradoxically, an acne fulminans-like flare occasionally develops during the first few weeks of isotretinoin therapy for acne[25], and this may be avoided by starting with a low dose of isotretinoin (see Ch. 126). Additional treatment options for acne fulminans include topical or intralesional corticosteroids, oral antibiotics (generally of limited efficacy), TNF-α inhibitors and immunosuppressive agents (e.g. azathioprine). Dapsone may be particularly beneficial in the treatment of acne fulminans associated with erythema nodosum[26].

Acne conglobata and associated conditions

Acne conglobata is a severe form of nodulocystic acne that may have an eruptive onset but without systemic manifestations. This recalcitrant acne variant is part of the follicular occlusion tetrad, along with dissecting cellulitis of the scalp, hidradenitis suppurativa and pilonidal cysts (see Ch. 38).

The association of sterile *p*yogenic *a*rthritis, *p*yoderma gangrenosum, and *a*cne conglobata can occur in the context of an autosomal dominant autoinflammatory disorder referred to as PAPA syndrome, which is caused by mutations in the gene that encodes *p*roline–*s*erine–*t*hreonine *p*hosphatase *i*nteracting *p*rotein 1 (PSTPIP1; also known as CD2 antigen-binding protein 1 [CD2BP1])[27]. Dysfunction of CD2BP1, which has a role in actin reorganization and interacts with the pyrin protein (defective in familial Mediterranean fever), compromises the physiologic signaling required for maintenance of a proper inflammatory response. The triad of acne conglobata, hidradenitis suppurativa and pyoderma gangrenosum has also been described outside the setting of PAPA syndrome[27a]. Of note, a possible association between nodulocystic acne and inflammatory bowel disease may potentially confound links that have been observed between the latter disorder and acne therapies such as tetracyclines and isotretinoin[27,27b].

Solid facial edema

An unusual and disfiguring complication of acne vulgaris is solid facial edema (Morbihan's disease). Clinically, there is a distortion of the midline face and cheeks due to soft tissue swelling (Fig. 36.11). The woody induration may be accompanied by erythema. Impaired lymphatic drainage and fibrosis (potentially induced by mast cells) in the setting of chronic inflammation are thought to be involved in the pathogenesis of solid facial edema, and a report of its occurrence in identical twins with acne suggests that genetic factors may also have a role. Similar changes have been described in patients with rosacea and Melkersson–Rosenthal syndrome (see Table 36.2). Although fluctuations in severity are common, solid facial edema does not usually resolve spontaneously. Treatment with isotretinoin (0.2–1 mg/kg/day), alone or in combination with ketotifen (1–2 mg/day; not available in the US) or prednisone (10–30 mg/day), for 4–5 months has been reported to be useful[28,29].

Acne mechanica

Acne mechanica occurs secondary to repeated mechanical and frictional obstruction of the pilosebaceous outlet. Comedo formation is the result. Well-described mechanical factors include rubbing by helmets, chin straps, suspenders and collars. A classic example of acne mechanica is fiddler's neck, where repetitive trauma from violin placement on the lateral neck results in a well-defined lichenified, hyperpigmented plaque interspersed with comedones. Linear and geometrically distributed areas of involvement should suggest acne mechanica. Treatment is aimed at eliminating the inciting forces.

Acne excoriée des jeunes filles

Acne excoriée des jeunes filles, as the name implies, occurs primarily in young women. Typical comedones and inflammatory papules are systematically excoriated in a ritualistic manner, leaving crusted erosions that may scar (see Ch. 7). Linear erosions suggest self-manipulation, and an underlying psychiatric component should be considered. Individuals with an anxiety disorder, obsessive–compulsive disorder or personality disorder are particularly at risk. Antidepressants or psychotherapy may be indicated in such patients.

Drug-induced acne

Acne or eruptive acneiform lesions can be seen as a side effect of a number of medications (Table 36.1). An abrupt, monomorphous eruption of inflammatory papules and pustules is often observed in drug-induced acne (Figs 36.12 & 36.13), in contrast to the heterogeneous morphology of lesions seen in acne vulgaris. This explains why some clinicians use the term "folliculitis".

High-dose intravenous or oral corticosteroids commonly induce characteristic acneiform eruptions with a concentration of lesions on the chest and back (see Fig. 36.12). Steroid-induced acne (and rosacea) can also result from the inappropriate use of topical corticosteroids on the face. Inflamed papules and pustules develop on a background of erythema that favors the distribution of corticosteroid application. Lesions eventually resolve following discontinuation of the corticosteroid, although "steroid dependency" can lead to prolonged and severe flares post-withdrawal (see Ch. 37). When a history of prescription medication use is not elicited, a comprehensive review of all over-the-counter medications and supplements, as well as recent medical procedures, may reveal the responsible agent (see Table 36.1).

CAUSES OF DRUG-INDUCED ACNE	
Common	**Uncommon**
• Anabolic steroids (danazol, testosterone) • Bromides* • Corticosteroids (see Fig. 36.12) • Corticotropin • EGFR inhibitors (see Fig. 36.16) • Iodides† • Isoniazid (see Fig. 36.13) • Lithium • Phenytoin • Progestins (see text)	• Azathioprine • Cyclosporine • Disulfiram • Phenobarbital • Propylthiouracil • Psoralen + ultraviolet A • IQuinidine • Vitamins B_6 and B_{12}
*Found in sedatives, analgesics and cold remedies. †Found in contrast dyes, cold/asthma remedies, kelp and combined vitamin–mineral supplements.	

Table 36.1 Causes of drug-induced acne. EGFR, epidermal growth factor receptor.

Fig. 36.12 Acneiform eruption secondary to high-dose dexamethasone. Abrupt eruption of monomorphous follicular papules and pustules on the trunk.

Fig. 36.13 Drug-induced acne due to isoniazid. *Courtesy, Kalman Watsky, MD.*

Occupational acne, acne cosmetica and pomade acne

Exposure to insoluble, follicle-occluding substances in the workplace is responsible for occupational acne (see Ch. 16). Offending agents include cutting oils, petroleum-based products, chlorinated aromatic hydrocarbons, and coal tar derivatives. Comedones dominate the clinical picture, with varying numbers of papules, pustules and cystic lesions distributed in exposed as well as typically covered areas. Primarily comedonal facial acne (with a predominance of closed comedones) can also develop in areas of skin chronically exposed to follicle-occluding cosmetics (*acne cosmetica*) or hair products (*pomade acne*; favors forehead and temples).

Chloracne

Chloracne, the term used to define occupational acne caused by exposure to chlorinated aromatic hydrocarbons, develops after several weeks of exposure. The malar, retroauricular and mandibular regions of the head and neck (see Fig 16.13), as well as the axillae and scrotum, are most commonly afflicted with small cystic papules and nodules. The extremities, buttocks and trunk are variably involved. Cystic lesions can heal with significant scarring, and recurrent outbreaks may occur for many years following exposure. The following agents, found in electrical conductors and insulators, insecticides, fungicides, herbicides and wood preservatives, have all been implicated: polychlorinated naphthalenes, biphenyls, dibenzofurans and dibenzodioxins; polybrominated naphthalenes and biphenyls; tetrachloroazobenzene; and tetrachloroazoxybenzene.

Prevention of exposure is integral to the safety of at-risk employees. Initial management is aimed at vigorous removal of chemical agents at the time of exposure. Topical or oral retinoids and oral antibiotics may be beneficial therapeutic interventions.

Neonatal acne (neonatal cephalic pustulosis)

Neonatal acne occurs in more than 20% of healthy newborns (see Ch. 34). Lesions usually appear at about 2 weeks of age and generally resolve within the first 3 months of life. Small, inflamed papulopustules (but typically not comedones) arise primarily on the cheeks and nasal bridge, but the forehead, chin, neck and upper trunk can also be involved (see Fig. 34.5).

The pathogenesis of neonatal acne has been the subject of debate. An inflammatory response to *Malassezia* spp. (e.g. *sympodialis, furfur*) has been proposed as the etiology by some investigators, leading to renaming of the disorder as "neonatal cephalic pustulosis". Additional support for this view comes from the clinical response to treatment with topical imidazoles (e.g. ketoconazole 2% cream). The active sebaceous glands and high sebum excretion rate in neonates (see Pathogenesis) are also thought to play a role. The substantial decline in sebum production after the first few months of life helps to explain the limited period of susceptibility to neonatal acne. Given the transient and benign nature of this eruption, parental reassurance alone is usually adequate. However, as noted previously, therapy with topical imidazoles can be effective.

Infantile acne

If acne presents at 3–12 months of age (occasionally as late as 18–24 months), it is classified as infantile (Fig. 36.14). In contrast to neonatal acne, comedo formation is prominent and pitted scarring can develop. Deep cystic lesions and suppurative nodules are occasionally seen. The pathogenesis of infantile acne reflects the androgen production intrinsic to this stage of development (see Pathogenesis), including elevated levels of LH stimulating testicular production of testosterone in boys during the first 6–12 months of life (with levels transiently equivalent to those during puberty) and elevated levels of DHEA produced by the infantile adrenal gland in both boys and girls. These androgen levels normally decrease substantially by 12 months of age and remain at nadir levels until adrenarche.

Infantile acne typically resolves within 1–2 years and remains quiescent until around puberty. In unusual cases, however, infantile-onset acne may persist into adolescence. Topical retinoids (e.g. tretinoin, adapalene) and benzoyl peroxide are first-line treatments for infantile acne. Oral antibiotics (e.g. erythromycin, azithromycin) can be helpful for patients with a more severe inflammatory component, and

Fig. 36.14 Infantile acne. Presentations can range from scattered papulopustules (**A**) to multiple coalescing papulonodules and inflammatory cysts (**B**). If the latter child failed to improve with a topical retinoid plus an oral antibiotic, consideration would be given to oral isotretinoin. *Courtesy, Kalman Watsky, MD.*

isotretinoin is occasionally required for recalcitrant or nodulocystic presentations[30].

Endocrinologic abnormalities

Although most patients with acne do not have overt endocrinologic abnormalities, hyperandrogenism should be suspected in female patients with hirsutism (see Ch. 70) or irregular menstrual periods, as well as in children who develop acne between 2 and 7 years of age. Acne in such patients is often severe or more difficult to treat, and the onset can be fairly abrupt. Other signs and symptoms of hyperandrogenism in women and children include coarsening of the voice, a muscular habitus, androgenetic alopecia, clitoromegaly with variable posterior labial fusion, and increased libido. *I*nsulin *r*esistance and *a*canthosis *n*igricans can occur in association with *h*yper*a*ndrogenism in the HAIR-AN syndrome. These patients are at increased risk for accelerated cardiovascular disease and diabetes mellitus, and they should be followed by appropriate medical specialists.

The evaluation of patients suspected of having hyperandrogenism includes a thorough history and physical examination; the age of the patient and pubertal status are also important parameters. Prepubertal boys and girls and postpubertal women with signs of hyperandrogenism should undergo appropriate evaluation. Laboratory studies should not be performed while the patient is taking oral contraceptives. Initial tests should include serum levels of total and free testosterone, DHEAS, and 17-hydroxyprogesterone. Patients with clinical signs and symptoms suggestive of hypercortisolism should also have an AM serum cortisol level, and X-rays of the hand and wrist to evaluate bone age should be obtained in prepubertal children.

Understanding pathways of hormone production is essential in the evaluation of hyperandrogenic states (see Fig. 70.15). For example, an elevated serum DHEAS or 17-hydroxyprogesterone level indicates an adrenal source of excess androgen production. The degree to which levels of these hormones are increased is then useful in discerning an etiology. DHEAS values in the range of 4000–8000 ng/ml or 17-hydroxyprogesterone levels >3 ng/ml may be indicative of congenital adrenal hyperplasia. Defects in adrenal enzymes, most commonly 21-hydroxylase or (less often) 11-hydroxylase, lead to this condition. Patients with severe deficiencies of these enzymes become symptomatic during infancy, whereas those with partial deficiencies present in adolescence. If the serum DHEAS is >8000 ng/ml, with or without an elevated testosterone level, an adrenal tumor should be suspected.

If the testosterone levels (total and free) are elevated and the DHEAS level is relatively normal, an ovarian source is likely. Polycystic ovary syndrome (PCOS) is the most common condition associated with an elevated serum testosterone, with levels typically ranging from 100 to 200 ng/dl. An increased LH/FSH ratio (>2–3) is also commonly observed. Symptoms of PCOS include irregular menstrual periods, hirsutism, obesity, insulin resistance and reduced fertility (see Fig. 70.11). When levels of serum testosterone exceed 200 ng/dl, an ovarian tumor should be considered.

Apert syndrome

Also known as acrocephalosyndactyly type I, Apert syndrome is an autosomal dominant disorder that features disfiguring synostoses of the bones of the hands and feet, vertebral bodies and cranium. Affected individuals have an increased incidence of severe (frequently nodulocystic), early-onset acne with a more widespread distribution than in classic acne, often involving the entire extensor aspects of the arms, buttocks and thighs[31]. Acne in patients with Apert syndrome also tends to be highly resistant to therapy, although isotretinoin has been reported to be beneficial. Other cutaneous findings in this disorder can include marked seborrhea, nail anomalies (e.g. a single nail for the second through fourth digits), and diffuse pigmentary dilution of the hair and skin. Of note, Apert syndrome results from *activating* mutations in the *FGFR2* gene, which encodes fibroblast growth factor receptor 2; mosaicism for the same *FGFR2* mutations has been found to underlie acneiform/comedonal nevi (see Ch. 62). FGFR2 signaling has been shown to have effects on follicular keratinocyte proliferation, sebaceous lipogenesis and inflammatory cytokine production, and it may be associated with a nuclear deficiency of the forkhead box O1 (FoxO1) transcription factor.

Acneiform Eruptions

Epidermal growth factor receptor inhibitor-induced papulopustular eruption

Inhibitors of *e*pidermal *g*rowth *f*actor *r*eceptor (EGFR/HER1) signaling represent an expanding class of therapeutic agents currently being used for the treatment of solid tumors, including head and neck squamous cell carcinoma and lung, colon and breast carcinoma. Inhibitors include gefitinib, cetuximab, erlotinib, lapatinib and panitumumab, with a number of tyrosine kinase inhibitors and monoclonal antibodies in clinical trials or under development (Fig. 36.15). The incidence of acneiform eruptions due to EGFR inhibitors is very high, e.g. up to 95% of patients treated with panitumumab; additional cutaneous side effects of these agents are presented in Table 21.14. In some studies, the presence or severity of the acneiform eruption had a positive correlation with treatment outcomes (e.g. response rate and survival time).

Patients present with an eruption of monomorphous follicular pustules and papules involving the face, scalp and upper trunk, usually 1–3 weeks after beginning treatment with an EGFR inhibitor (Fig 36.16). Secondary infection with *Staphylococcus aureus* often occurs, with oozing and the formation of honey-colored crusts. While frequently described as acneiform, histopathology reveals a pattern of folliculitis, with intrafollicular collections of neutrophils and perifollicular lymphocytes. No comedonal lesions are seen either microscopically or clinically, further differentiating this eruption from acne vulgaris.

In the oncology patient, the differential diagnosis includes corticosteroid-induced acne, various forms of folliculitis (e.g. *Pityrosporum, Demodex* spp.), neutrophilic eccrine hidradenitis and viral-associated trichodysplasia spinulosa. Because discontinuation of the medication is not an option in a patient who is responding to therapy,

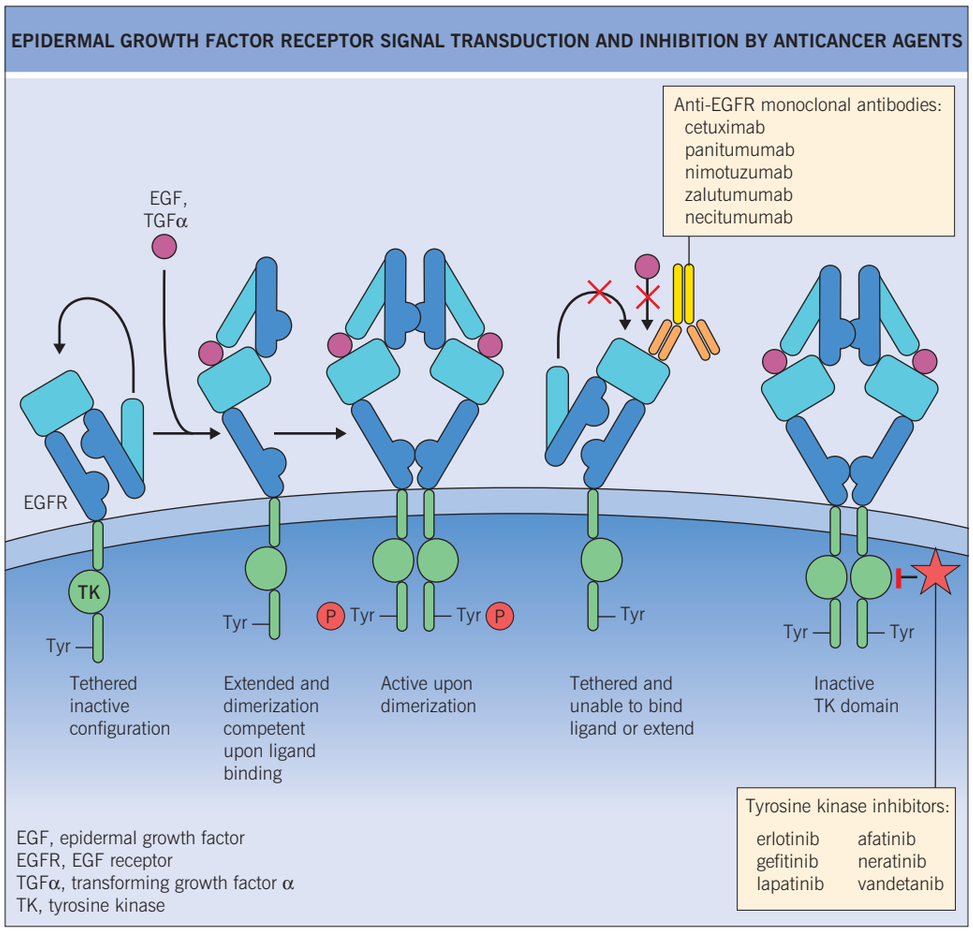


Fig. 36.15 Epidermal growth factor receptor (EGFR) signal transduction and inhibition by anticancer agents.

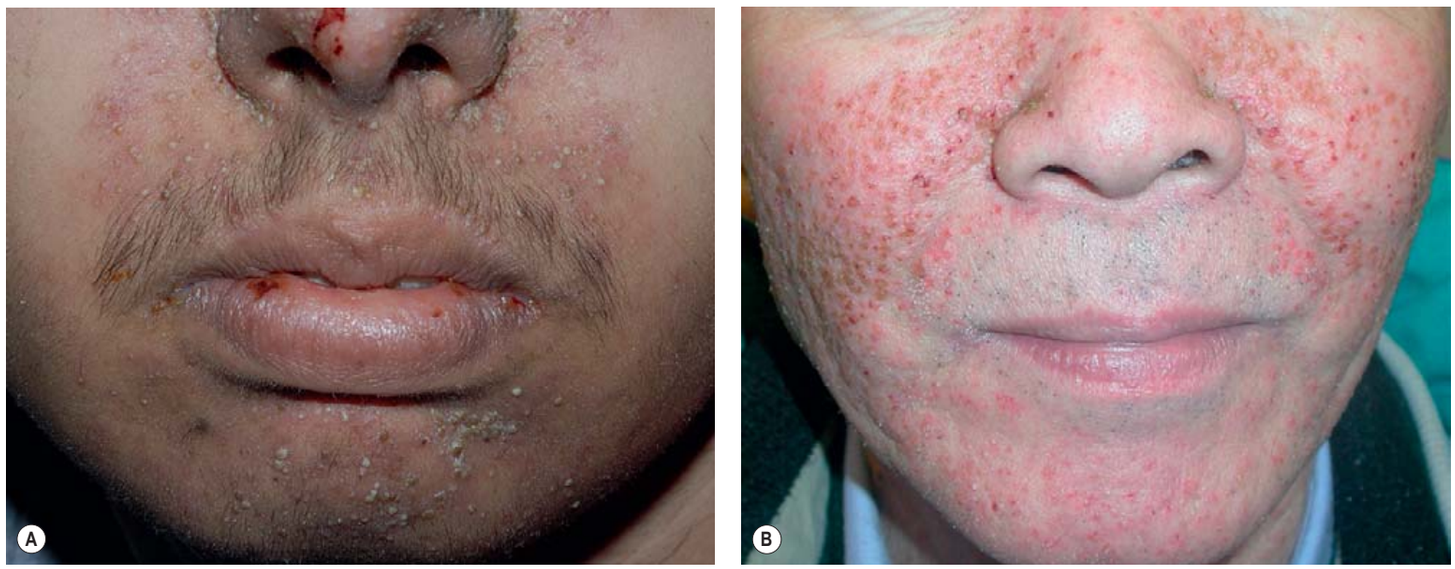


Fig. 36.16 Acneiform eruptions due to epidermal growth factor receptor inhibitors. A,B Numerous monomorphous follicular pustules and crusted papules on the face of two patients treated with erlotinib. *A, Courtesy, Julie V Schaffer, MD.*

multiple treatments have been tried with variable success, including topical and oral antibiotics, topical and (for severe eruptions) oral corticosteroids, and topical and oral retinoids; prophylaxis with oral doxycycline or minocycline may also be of benefit.

Tropical acne

Tropical acne is a follicular acneiform eruption that results from exposure to extreme heat. This can occur in tropical climates or secondary to scorching occupational environments, as in furnace workers. Historically, tropical acne caused significant morbidity among military troops. Markedly inflamed nodulocystic acne involving the trunk and buttocks is typically seen, and secondary staphylococcal infection is a frequent complication. Treatment is often of limited efficacy until the patient returns to a more moderate climate.

Radiation acne

Radiation acne is characterized by comedo-like papules occurring at sites of previous exposure to therapeutic ionizing radiation. The lesions

begin to appear as the acute phase of radiation dermatitis starts to resolve. The ionizing rays induce epithelial metaplasia within the follicle, creating adherent hyperkeratotic plugs that are resistant to expression.

"Pseudoacne" of the transverse nasal crease

The transverse nasal crease is a horizontal anatomical demarcation line found in the lower third of the nose which corresponds to the separation point between the alar cartilage and the triangular cartilage. Milia, cysts and comedones can line up along this fold (Fig. 36.17A)[32]. These acne-like lesions are not hormonally responsive and arise during early childhood prior to the onset of puberty. Treatment consists of surgical expression as needed.

Idiopathic facial aseptic granuloma

This chronic, painless, solitary nodule with an acneiform appearance can develop on the cheeks of young children (mean age, 3.8 years)[33]. Multiple lesions are uncommon. Histopathologic evaluation reveals a dermal lymphohistiocytic infiltrate with foreign body-type giant cells. Cultures are typically negative (70% of patients) and the lesions do not respond to antibiotic therapy. They eventually resolve spontaneously, after an average of 11 months, without treatment[33].

Childhood flexural comedones

This recently described entity is characterized by discrete, double-orifice comedones localized to the axillae and, less commonly, the groin[34]. The majority of patients have a single lesion and the average age at diagnosis is 6 years, with boys and girls equally affected. A small subset of cases are familial. There is no association with other signs of hidradenitis suppurativa, acne vulgaris or precocious puberty. In most cases, the flexural comedones are discovered incidentally in patients presenting with other dermatologic concerns such as molluscum contagiosum.

PATHOLOGY

Histopathologic examination of acne lesions demonstrates the stages of acnegenesis that parallel the clinical findings (see Fig. 36.1). In early lesions, microcomedones are seen. A mildly distended follicle with a narrowed follicular opening is impacted by shed keratinocytes. The granular layer at this stage is prominent. In closed comedones, the degree of follicular distension is increased and a compact cystic structure forms. Within the cystic space, eosinophilic keratinaceous debris, hair, and numerous bacteria are present. Open comedones have broad, expanded follicular ostia and greater overall follicular distension. The sebaceous glands are typically atrophic or absent. A mild perivascular mononuclear cell infiltrate circles the expanding follicle.

As the follicular epithelium distends, the cystic contents inevitably begin to rupture into the dermis (Fig. 36.18). The highly immunogenic cystic contents (keratin, hair and bacteria) induce a marked inflammatory response. Neutrophils first appear, creating a pustule. As the lesion matures, foreign body granulomatous inflammation engulfs the follicle and end-stage scarring can result.

In acne fulminans, there is massive inflammation with varying degrees of overlying necrosis. Comedones are rarely observed. Severe scarring may be seen in resolving lesions.

Fig. 36.17 Disorders in the differential diagnosis of comedonal acne vulgaris. **A** "Pseudoacne" of the transverse nasal crease in a young child. Note the milia and comedones located along this anatomical demarcation line. **B** Trichostasis spinulosa. Multiple vellus hairs and keratinous debris are found within the dilated follicular orifices. *A, Courtesy, Julie V Schaffer, MD. B, Courtesy, Judit Stenn, MD.*

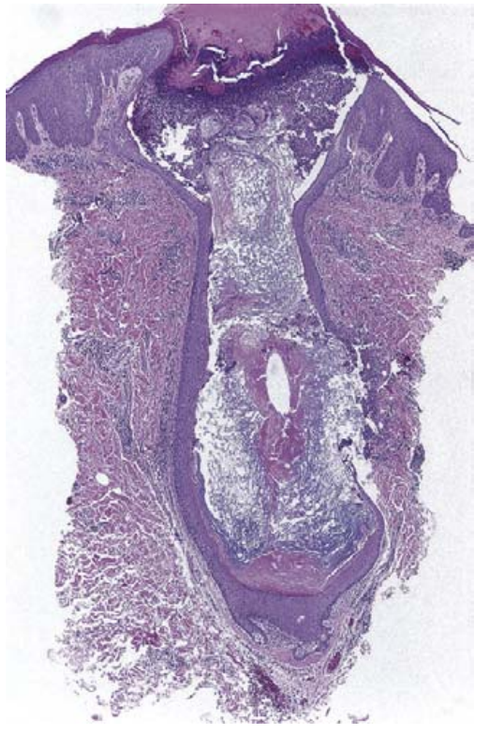


Fig. 36.18 Histology of an inflamed comedo. There is disruption of the pilosebaceous unit and secondary inflammation. *Courtesy, Ronald P Rapini, MD.*

DIFFERENTIAL DIAGNOSIS

Although classic acne vulgaris is usually easily recognized clinically, the differential diagnosis of acneiform eruptions is broad and depends upon the age of onset, lesional morphology and location (Table 36.2). During the neonatal period, acne must be differentiated from other common dermatoses. Sebaceous hyperplasia occurs in the majority of healthy neonates, presenting as transient yellowish papules on the cheeks, nose and forehead. Miliaria rubra is also very common during the neonatal period, when overheating and bundling can cause temporary obstruction of the eccrine ducts that leads to formation of small inflammatory papulopustules. Small, white milia often appear on the cheeks and nose of neonates, but they generally resolve within a few months.

Predominantly comedonal acne vulgaris needs to be differentiated from comedonal eruptions caused by follicular occlusion or friction, including pomade and occupational acne, acne cosmetica and acne mechanica (see above); history as well as location can help to make the diagnosis of these forms of "contact acne". Sebaceous hyperplasia, a very common finding in adults, is relatively uncommon in adolescents. These yellowish, lobulated papules arise primarily on the forehead and cheeks.

A solitary enlarged comedo is better classified as a dilated pore of Winer; rarely it represents a large-pore basal cell carcinoma. Multiple open comedones are clustered in the lateral malar region in Favre–Racouchot disease (see Ch. 87) or appear in a linear array in nevus comedonicus (see Chs 62 and 109). If multiple vellus hairs are seen arising from a dilated follicular orifice (in association with keratinous debris), trichostasis spinulosa is the likely diagnosis (Fig. 36.17B). The most common location is the nose.

Angiofibromas and appendageal tumors of follicular origin, e.g. trichoepitheliomas, trichodiscomas and fibrofolliculomas, often present as multiple facial papules (see Ch. 111). They are typically non-inflammatory, and, in the case of trichoepitheliomas, lesions are concentrated in the nasolabial folds. Non-inflammatory, closed cystic papules and nodules on the central chest and back characterize steatocystoma multiplex (see Ch. 110). This autosomal dominant disorder must be differentiated from a similar clinical condition, eruptive vellus hair cysts. These smaller cysts may become inflamed and, as the name implies, contain multiple vellus hairs that can be easily visualized histologically.

The follicle-based inflammatory papules and pustules of acne vulgaris must be distinguished from the many forms of folliculitis, including staphylococcal, Gram-negative, and eosinophilic variants (see Ch. 38). In folliculitis, the lesions are typically monomorphous and comedones are not present. Gram-negative folliculitis can complicate acne vulgaris treated with oral antibiotics for a prolonged period. The inflammatory

DIFFERENTIAL DIAGNOSIS OF ACNE	
ACNE VULGARIS – COMEDONAL	
Closed	**Open**
• Milia • Osteoma cutis • Sebaceous hyperplasia • Syringomas • Trichoepitheliomas* • Trichodiscomas, fibrofolliculomas • Eruptive vellus hair cysts†, steatocystoma multiplex† • Colloid milia • Acne exacerbated by systemic corticosteroids‡ or anabolic steroids • Contact acne (occupational, pomade, cosmetica, mechanica; chloracne) • Follicular mucinosis	• Contact acne (see above) • Acne exacerbated by systemic corticosteroids‡ or anabolic steroids • Trichostasis spinulosa (see Fig. 36.17B) • Favre–Racouchot disease • Nevus comedonicus • Basaloid follicular hamartoma syndrome • Familial dyskeratotic comedones • Radiation-induced comedones • Dilated pore of Winer (single lesion) • Follicular spines (in settings such as viral-associated trichodysplasia spinulosa§, type VI pityriasis rubra pilaris§, multiple myeloma, demodicosis§, follicular mucinosis and lithium therapy)
ACNE VULGARIS – INFLAMMATORY	
• Rosacea • Perioral dermatitis • Folliculitis – culture-negative (normal flora), staphylococcal, Gram-negative, eosinophilic§, *Pityrosporum, Demodex* spp. (adults > children§) • Acne/acneiform eruptions due to topical or systemic corticosteroids‡, anabolic steroids or other medications (e.g. lithium, EGFR inhibitors; see Table 36.1) • Pseudofolliculitis barbae, acne keloidalis nuchae • Furuncle/carbuncle • Neutrophilic dermatoses and neutrophilic eccrine hidradenitis	• Keratosis pilaris • Viral-associated trichodysplasia spinulosa (also referred to as viral-associated trichodysplasia of immunosuppression)§ • Lupus miliaris disseminatus faciei • Psychogenic (neurotic) excoriations, factitial lesions • Follicular mucinosis, follicular mycosis fungoides • Tinea faciei • Molluscum contagiosum (especially inflamed lesions) • Angiofibromas
NEONATAL ACNE (NEONATAL CEPHALIC PUSTULOSIS)	
• Sebaceous hyperplasia • Milia • Miliaria rubra (especially pustular variant)	• Candidal infections • Papulopustular eruption of hyper-IgE syndrome • Vesiculopustular eruption of transient myeloproliferative disorder
SOLID FACIAL EDEMA SECONDARY TO ACNE VULGARIS	
• Solid facial edema secondary to rosacea • Melkersson–Rosenthal syndrome, sarcoidosis (e.g. Heerfordt's syndrome), lepromatous leprosy • Lymphoma (B- or T-cell), leukemia cutis, angiosarcoma • Scleromyxedema, myxedema, self-healing (juvenile) cutaneous mucinosis • Autoimmune connective tissue disease (e.g. dermatomyositis, lupus erythematosus, Still's disease)	• Angioedema (lasts <24–48 hours), C1 esterase inhibitor deficiency (lasts 42–72 hours), blepharochalasis/Ascher syndrome • Sweet's syndrome or cellulitis – more abrupt onset • Superior vena cava syndrome • Lymphatic malformation • Other – trichinosis, primary systemic amyloidosis, pachydermoperiostosis

*Early or small-sized.
†In the differential diagnosis of cystic lesions of the trunk.
‡Can also lead to rosacea-like picture (see Ch. 38).
§Often in the setting of HIV infection and/or other immunocompromised states.

Table 36.2 Differential diagnosis of acne. EGFR, epidermal growth factor receptor.

lesions typically appear on the central face (including the upper lip) and cheeks as well as on the upper trunk and, in the case of *Pseudomonas* ("hot tub") folliculitis, on the lower trunk. Eosinophilic folliculitis usually occurs in the setting of HIV infection and is markedly pruritic.

Pseudofolliculitis barbae and acne keloidalis nuchae most often affect men of African descent (see Ch. 38). The papular component of rosacea favors the malar region, chin and forehead; the presence of telangiectasias, an absence of comedones and a history of easy flushing can aid in diagnosis (see Ch. 37). Rosacea typically occurs at a later age than acne, but both can develop in a single individual. Prolonged use of topical corticosteroids on the face may lead to rosacea-like lesions or perioral/periorificial dermatitis, and patients treated with oral corticosteroids can develop an eruption of monomorphous papulopustules that favors the trunk ("steroid folliculitis"; see Fig. 36.12). This can occur at any age and resolves upon discontinuation of the corticosteroid. Lastly, psychogenic (neurotic) excoriations and factitial dermatitis concentrated on the face, chest and back can mimic acne, particularly acne excoriée des jeunes filles. Linearity and the lack of a clinically detectable primary lesion are clues.

TREATMENT

A thorough history and physical examination are key to developing an appropriate and maximally effective treatment plan (Table 36.3). The physician should review with the patient all prescription and over-the-counter medications used for acne or other conditions, and note the clinical responsiveness to them. A review of cosmetics, sunscreens, cleansers and moisturizers is also helpful. In female patients, a menstrual and oral contraceptive history is important in determining hormonal influences on acne. On physical examination, careful note should be taken of lesion morphology, including the presence of comedones, inflammatory lesions, nodules and cysts. Secondary changes such as scarring and postinflammatory pigmentary changes are also important clinical findings. The patient's skin color and type can influence the chosen formulation of a topical medication. Patients with oily skin tend to prefer the more drying gels and lotions, whereas those with drier skin types may prefer creams.

Common therapies for the treatment of acne are listed in Tables 36.4 and 36.5.

Topical Treatments

Topical retinoids

The anti-acne activity of topical retinoids involves normalization of follicular keratinization and corneocyte cohesion, which aids in the expulsion of existing comedones and prevents the formation of new ones. Topical retinoids also have significant anti-inflammatory properties and thus may be used as monotherapy for acne with both comedonal and mild inflammatory components. In addition, concurrent use of a topical retinoid can enhance the efficacy of benzoyl peroxide and topical antibiotics by increasing the penetration of the latter medications into the sebaceous follicle. Topical retinoids used for acne include tretinoin, adapalene, tazarotene and (in some countries) isotretinoin (see Ch. 126); topical products that combine tretinoin or adapalene with clindamycin, or adapalene with benzoyl peroxide, are also available.

HISTORY AND PHYSICAL EXAMINATION OF THE ACNE PATIENT

History	Physical examination
Sex Age Motivation Lifestyle/hobbies Occupation Current and previous treatments Use of cosmetics, sunscreens, cleansers, moisturizers Menstrual history Medications • Corticosteroids • Oral contraceptives • Anabolic steroids • Other (e.g. lithium, EGFR inhibitors; see Table 36.1) Concomitant illnesses	Skin type (e.g. oily versus dry) Skin color/phototype Distribution of acne • Face (e.g. "T-zone", cheeks, jawline) • Neck, chest, back, upper arms Overall degree of involvement (mild, moderate or severe) Lesion morphology • Comedones • Inflammatory papules • Pustules • Cysts • Sinus tracts Scarring • Pitted • Hypertrophic • Atrophic Postinflammatory pigmentary changes

Table 36.3 History and physical examination of the acne patient. EGFR, epidermal growth factor receptor.

TREATMENT OF ACNE VULGARIS

	Mild		Moderate		Severe
	Comedonal	Papular/pustular	Papular/pustular	Nodular	Conglobata/fulminans
First line	Topical retinoid	Topical retinoid + topical antimicrobial*	Oral antibiotic† + topical retinoid ± BPO	Oral antibiotic† + topical retinoid ± BPO	Oral isotretinoin (may require concurrent oral corticosteroid, esp. for acne fulminans)
Second line	Alternative topical retinoid Azelaic acid Salicylic acid	Alternative topical retinoid + alt. topical antimicrobial Azelaic acid Salicylic acid Topical dapsone	Alternative oral antibiotic‡ + alt. topical retinoid ± BPO/azelaic acid	Oral isotretinoin Alternative oral antibiotic† + alt. topical retinoid ± BPO/azelaic acid	Dapsone High-dose oral antibiotic + topical retinoid + BPO
Options for female patients			Oral contraceptive/ antiandrogen	Oral contraceptive/ antiandrogen	Oral contraceptive/ antiandrogen
Surgical options	Comedo extraction		Comedo extraction	Comedo extraction Intralesional corticosteroid	Intralesional corticosteroid
Refractory to treatment		Exclude Gram-negative folliculitis	Exclude Gram-negative folliculitis		
			Female patient: exclude adrenal or ovarian dysfunction Exclude use of anabolic steroid or other acne-exacerbating medications		
Maintenance			Topical retinoid ± BPO	Topical retinoid ± BPO	Topical retinoid ± BPO

*Antibiotic (e.g. clindamycin, erythromycin or sodium sulfacetamide) and/or BPO.
†Tetracycline derivatives.
‡e.g. azithromycin or trimethoprim–sulfamethoxazole.

Table 36.4 Treatment of acne vulgaris. Lack of response should also lead the clinician to consider non-compliance with treatment or another diagnosis. In general, monotherapy with a topical or oral antibiotic should be avoided. alt, alternative; BPO, benzoyl peroxide. *Adapted from Gollnick H, Cunliffe W, Berson D, et al. J Am Acad Dermatol. 2003;49(1 Suppl):S1–37.*

COMMON THERAPIES FOR ACNE VULGARIS	
Topical therapy	**Systemic therapy**
Benzoyl peroxide (1) Antibiotics – Clindamycin (1) – Erythromycin (1) – Sodium sulfacetamide/sulfur (1) Retinoids (1) Salicylic acid (2) Azelaic acid (1) Dapsone (1)	Oral minocycline (1) Oral doxycycline (1) Oral tetracycline (1) Oral erythromycin (1) Oral azithromycin (1) Oral contraceptives (1) Oral spironolactone (1) Oral isotretinoin (1)

Table 36.5 Common therapies for acne vulgaris. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

The most common side effect of topical retinoids is local irritation resulting in erythema, dryness, peeling and scaling. Delivery systems have been developed to permit a greater concentration of retinoid while decreasing irritancy, primarily through controlled slow release (e.g. tretinoin impregnated into inert microspheres or incorporated within a polyolprepolymer). A pustular flare of acne occasionally occurs during the initial 3–4 weeks of treatment with a topical retinoid. This resolves spontaneously with continued usage. Thinning of the stratum corneum and irritation may also increase the user's susceptibility to sunburn. Therefore, the use of sunscreens should be advised.

Tretinoin (all-*trans*-retinoic acid), a naturally occurring metabolite of retinol, was the first topical comedolytic agent used for the treatment of acne. Because tretinoin is photolabile, night-time application is recommended to prevent early degradation. To decrease the potential for irritation, treatment is often started with a lower-concentration cream formulation of tretinoin and the strength later increased (or the vehicle changed to a gel). Alternate-night to every-third-night application may be necessary initially, with increased frequency as tolerated. Stepwise increments are typically done at 3–4-week intervals.

Although epidemiologic studies have not shown an increased risk of birth defects in infants of mothers using topical tretinoin during the first trimester, sporadic case reports of birth defects have been published[35,36]. Because of this and the fact that systemic retinoids are known teratogens, the use of topical tretinoin in pregnancy is discouraged. However, dietary intake of vitamin A has been shown to have a greater influence on serum retinoid levels than facial application of tretinoin[37].

The synthetic retinoid *adapalene* is an aromatic naphthoic acid derivative (see Fig. 126.1). In the skin, it primarily binds the retinoic acid receptor γ (RARγ), whereas tretinoin binds to both RARα and RARγ. Although animal studies have shown adapalene to have milder comedolytic properties than tretinoin, it is also less irritating[38]. Unlike tretinoin, adapalene is light-stable and resistant to oxidation by benzoyl peroxide.

Tazarotene is a synthetic acetylenic retinoid that, once applied, is converted into its active metabolite, tazarotenic acid. Like adapalene, this metabolite selectively binds RARγ but not RARα or RXR (see Ch. 126). Both daily overnight application of tazarotene and short contact therapy regimens have been used and shown to be effective in the treatment of comedonal and inflammatory acne. Topical tazarotene has been designated pregnancy category X, so contraceptive counseling should be provided to all women of childbearing age who are prescribed this medication.

Benzoyl peroxide and other topical antibacterial agents

Benzoyl peroxide is a potent bacteriocidal agent that reduces *P. acnes* within the follicle. It also has mild comedolytic properties and is particularly effective when used in combination with other therapies. In contrast to topical antibiotics, microbial resistance to benzoyl peroxide has not been reported. Many preparations for all skin types are available in both over-the-counter and prescription formulations. These include bar soaps, washes, gels, lotions, creams, foams and pads in concentrations ranging from 2.5% to 10% as well as products that combine benzoyl peroxide with clindamycin, erythromycin or adapalene. As benzoyl peroxide is a bleaching agent, whitening of clothing and bedding can occur. Development of contact dermatitis (irritant > allergic) to benzoyl peroxide is also possible, and should be suspected in patients who develop marked erythema with its use.

Topical antibiotics are widely used for the treatment of acne and are available alone as well as in combination with benzoyl peroxide or a retinoid. *Clindamycin* and *erythromycin* represent the two most commonly utilized antibiotics and the formulations vary from creams and gels to solutions and pledgets (see Ch. 127).

Azelaic acid is a naturally occurring dicarboxylic acid found in cereal grains. It is available as a topical cream and gel, which have been shown to be effective in inflammatory and comedonal acne. By inhibiting the growth of *P. acnes*, azelaic acid reduces inflammatory acne. It also reverses the altered keratinization of follicles affected by acne and thus demonstrates comedolytic properties. The activity of azelaic acid against inflammatory lesions may be greater than its activity against comedones. Azelaic acid is applied twice daily and its use is reported to have fewer local side effects than topical retinoids. In addition, it may help to lighten postinflammatory hyperpigmentation.

Sodium sulfacetamide is a well-tolerated topical antibiotic that is thought to restrict the growth of *P. acnes* through competitive inhibition of the condensation of para-aminobenzoic acid with pteridine precursors (see Ch. 127). It is formulated in a 10% lotion, suspension, foam and cleanser, either alone or in combination with 5% sulfur. Tinted formulations are also available.

Topical *dapsone* 5% gel is approved for the treatment of acne vulgaris. Of note, a temporary yellow–orange staining of the skin and hair occasionally occurs with concomitant use of topical dapsone and benzoyl peroxide.

Other topical medications

Salicylic acid is a widely used comedolytic and mild anti-inflammatory agent (see Ch. 153). It is also a mild chemical irritant that works in part by drying up active lesions. Salicylic acid is available over the counter in concentrations of up to 2% in numerous delivery formulations, including gels, creams, lotions, foams, solutions and washes. Side effects of topical salicylic acid include erythema and scaling.

Oral Treatments

Antibiotics

Oral tetracycline derivatives, especially doxycycline and minocycline, and less often macrolides (e.g. erythromycin, azithromycin) are prescribed for moderate to severe inflammatory acne unresponsive to topical combinations. In this setting, the primary mechanism of action of these agents is suppression of the growth of *P. acnes*, thereby reducing bacterial production of inflammatory factors. However, several of these antibiotics also possess intrinsic anti-inflammatory properties.

Details regarding the mechanisms of action, recommended dosages, and side effects of tetracyclines and macrolides are reviewed in Chapter 127. Resistance of *P. acnes* to erythromycin and the three major tetracyclines (tetracycline and doxycycline more so than minocycline) has been reported. The enhanced efficacy of minocycline, a lipophilic derivative of tetracycline, may be due to its greater penetration into the sebaceous follicle; however, it is also associated with a higher incidence of serious adverse events, including a minocycline-induced hypersensitivity syndrome and autoimmune reactions (see Ch. 21). The latter typically develop after many months to years of therapy and can include hepatitis, a lupus erythematosus-like syndrome and cutaneous polyarteritis nodosa (often associated with antineutrophil cytoplasmic antibodies).

Hormonal therapy

Hormonal therapy is an established second-line treatment for female patients with acne and can be very effective, irrespective of whether or not the serum androgen levels are abnormal. Although women and girls with acne may have higher serum levels of androgens than those without acne, the levels in acne patients are often within the normal range. Hormonal therapies seem to work best in adult women with inflammatory papules and nodules that tend to flare in the week prior to menstruation and involve the lower face and neck. These patients often note little improvement in their acne despite multiple courses of various oral antibiotics.

In such patients, hormonal therapy with oral contraceptives, which block both ovarian and adrenal production of androgens, can be initiated

and oral antibiotics discontinued. The use of oral contraceptives is also indicated for women of childbearing potential if treatment with spironolactone is anticipated (see below). Because of the potential risks associated with oral contraceptive use and the need for breast and pelvic examinations, consultation with a gynecologist is recommended.

Most oral contraceptive formulations combine an estrogen with a progestin in order to minimize the risk of endometrial cancer, which is known to occur with unopposed estrogen administration. Although progestins have intrinsic androgenic activity, second-generation, low-androgenic progestins (e.g. ethynodiol diacetate, norethindrone, levonorgestrel) have been developed. Newer, third-generation progestins (e.g. desogestrel, norgestimate, gestodene [Europe]) have even less androgenic activity than their predecessors, and other progestins (e.g. drospirenone, cyproterone acetate, dienogest) have *anti*androgenic properties.

Three oral contraceptives are currently FDA-approved for the treatment of acne, although others also have evidence of efficacy[39] (Table 36.6). The first is a triphasic oral contraceptive composed of a norgestimate–ethinyl estradiol (35 mcg) combination. The second contains a graduated dose of ethinyl estradiol (20–35 mcg) in combination with norethindrone acetate, while the third contains a stable dose of ethinyl estradiol (20 mcg) plus drospirenone (3 mg) with a 24-day dosing regimen. Side effects from oral contraceptives include nausea, vomiting, abnormal menses, weight gain and breast tenderness; agents containing drospirenone can lead to elevations in serum potassium levels, but this is generally not clinically significant in otherwise healthy individuals. Rare but more serious complications include hypertension and thromboembolism (e.g. deep venous thrombosis, pulmonary embolism). The increase in risk of the latter ranges from 2–4-fold with levonorgestrel or norethindrone to 3.5–7-fold with desogestrel, drospirenone and cyproterone acetate[40,41]; it is higher for women over the age of 35 years, smokers and those with other prothrombotic risk factors (e.g. hereditary thrombophilia)[42].

The progestational antiandrogen cyproterone acetate is currently marketed in Europe and Canada but is not available in the US. Its anti-acne effects are mediated primarily through androgen receptor blockade. The standard formulation combines cyproterone acetate (2 mg) with ethinyl estradiol (35 or 50 mcg) in an oral contraceptive formulation. This preparation is widely used in Europe as the treatment of choice for sexually active women with hormonally responsive acne. Singular formulations of cyproterone acetate are also available. Studies have indicated that approximately 75–90% of patients treated with doses of 50–100 mg daily (with or without ethinyl estradiol 50 mcg) show substantial improvement[43]. Although similar efficacy has been reported for the 2 mg cyproterone acetate dose in the oral contraceptive formulation, higher doses (e.g. on days 5–14 of the menstrual cycle) may be helpful in women with severe hyperandrogenism. The most frequent side effects are breast tenderness, headache, nausea and irregular menses; hepatotoxicity or thromboembolism represent uncommon complications.

COMMONLY USED ORAL CONTRACEPTIVES	
Oral contraceptive®	**Estrogen mcg/Progestin mcg**
FDA-APPROVED FOR ACNE VULGARIS	
Ortho Tri-Cyclen	Ethinyl estradiol 35/norgestimate 180, 215, 250
Estrostep	Ethinyl estradiol 20, 30, 35/norethindrone 1000
Yaz, Loryna and Beyaz*	Ethinyl estradiol 20/drospirenone 3000
CLINICAL DATA TO SUPPORT USE	
Alesse	Ethinyl estradiol 20/levonorgestrel 100
Diane-35†	Ethinyl estradiol 35/cyproterone acetate 2000
Yasmin, Syeda, Zarah and Safyral*	Ethinyl estradiol 30/drospirenone 3000
Natazia	Estradiol valerate 1000, 2000, 3000/dienogest 2000, 3000
NO/INSUFFICIENT CLINICAL DATA	
Demulen	Ethinyl estradiol 35, 50/ethynodiol diacetate 1000
Desogen	Ethinyl estradiol 35/desogestrel 150
Mircette	Ethinyl estradiol 20, 10/desogestrel 150
Ortho-Cept	Ethinyl estradiol 35/desogestrel 150
Ortho-Cyclen	Ethinyl estradiol 35/norgestimate 250
Ortho-Novum 7/7/7	Ethinyl estradiol 35/norethindrone 500, 750, 1000
Ortho-Novum 10/11	Ethinyl estradiol 35/norethindrone 500, 1000
Ortho Tri-Cyclen Lo	Ethinyl estradiol 25/norgestimate 180, 215, 250
Ovcon-35	Ethinyl estradiol 35/norethindrone 400
TriPhasil	Ethinyl estradiol 35, 50/levonorgestrel 50, 75, 125

*Also contains levomefolate calcium for protection against neural tube defects.
†Not available in the US.

Table 36.6 Commonly used oral contraceptives.

Spironolactone functions as both an androgen receptor blocker and an inhibitor of 5α-reductase. In doses of 50–100 mg twice daily, it has been shown to reduce sebum production and improve acne[44]. Side effects are dose-related and include potential hyperkalemia, irregular menstrual periods, breast tenderness, headache and fatigue. However, hyperkalemia is rare in young healthy patients. Although breast tumors have been reported in rodent models given spironolactone, this drug has not been directly linked to the development of cancer in humans[45]. Because it is an antiandrogen, there is a risk of feminization of a male fetus if a pregnant woman takes this medication. The potential risk to a fetus and the symptoms of irregular menstrual bleeding can be alleviated by combining spironolactone with an oral contraceptive. Side effects can also be minimized if therapy is initiated with a low dose (25–50 mg/day). Effective maintenance doses range from 25 to 200 mg/day. As with other hormonal therapies, a clinical response may take up to 3 months.

Records were reviewed of 85 women treated with 50–100 mg daily of spironolactone, administered either as a single agent or as an adjunct to standard therapies[46]. The maximum length of treatment was 24 months. Clearing of acne occurred in 33% of women treated with low-dose spironolactone, 33% had marked improvement, 27% showed partial improvement and 7% showed no improvement. The treatment was well tolerated, with 58% reporting no adverse effects. Menstrual irregularities occurred in 17.5%, and symptoms of lethargy, fatigue, dizziness or headache (CNS symptoms) were reported in 16%. Less common side effects included breast tenderness, a diuretic effect, postural hypotension and nausea. Slight elevations in serum potassium (range 4.8–5.3 mEq/l) were identified in 13.7% of the 73 patients examined, but this was not considered to be clinically significant. The following benefits were noted in some patients: an improvement in premenstrual syndrome, decreased facial oiliness, decreased metrorrhagia, reduced endometriosis pain and increased libido. The results of this study suggested that:

- most side effects of spironolactone are dose-dependent, including menstrual irregularities (the most common side effect)
- CNS symptoms are also relatively common, but appear to be unrelated to dose
- hyperkalemia may be measurable but is clinically insignificant in the absence of cardiac or renal disease
- reductions in blood pressure are slight, but rarely can be associated with orthostatic symptoms.

Flutamide, a nonsteroidal androgen receptor blocker that is approved by the FDA for the treatment of prostate cancer, can also be an effective treatment for acne in women at doses of 62.5–500 mg/day. In addition to side effects similar to those of other antiandrogens (e.g. menstrual irregularities, breast tenderness, risk of feminization of a male fetus), severe dose-related hepatotoxicity occasionally occurs.

Isotretinoin

Since 1971, oral isotretinoin (13-*cis*-retinoic acid) has been available in Europe for the treatment of acne. Twelve years later, the FDA approved it for patients with severe, nodulocystic acne refractory to treatment, including oral antibiotics. Over time, other clinical forms of acne have also been shown to benefit greatly from the use of isotretinoin[47]. These include significant acne that is unresponsive to therapy (including oral antibiotics) and/or results in scarring, as well as Gram-negative folliculitis, pyoderma faciale and acne fulminans. The mechanism of action of isotretinoin, as well as dosing regimens, side effects and monitoring protocols, are discussed in detail in Chapter 126.

Patients with acne are typically treated with an isotretinoin dose of 0.5–1 mg/kg/day (taken with a fatty meal to increase gastrointestinal absorption), often with a lower dose during the first month of treatment to prevent an initial acne flare and to allow the patient to adjust to dose-dependent side effects. Reaching a cumulative dose of 120–150 mg/kg (e.g. 4–5 months of treatment with 1 mg/kg/day) has been shown to reduce the risk of relapse. However, a 6-month course of low-dose isotretinoin (e.g. 0.25–0.4 mg/kg/day, 40–70 mg/kg cumulative) can be effective in the treatment of moderate acne, with fewer side effects and improved patient satisfaction[48]. Subsets of patients who are less likely to respond to isotretinoin and/or more likely to require multiple courses of treatment include adolescents under 16 years of age who have nodulocystic acne, individuals with endocrine abnormalities, and women with less severe acne. Considering that improvement may continue for several months after discontinuing isotretinoin, a hiatus of at least 2–3 months is recommended before starting another course of therapy. Scarred nodules and sinus tracts that represent sequelae from previously active cystic acne are not isotretinoin-responsive but may improve with surgical modalities, which are generally delayed at least 6–12 months after completing isotretinoin therapy to avoid the possible risk of atypical healing or scarring responses.

The most common adverse effects of isotretinoin involve the skin and mucous membranes and are dose-dependent. These include cheilitis, dryness of the oral and nasal mucosa, generalized xerosis and skin fragility. With the institution of isotretinoin therapy, induction of an acne fulminans-like flare, formation of excessive granulation tissue, and cutaneous infections (in particular with *Staphylococcus aureus*) can also occur (Fig. 36.19).

Teratogenicity is a serious potential complication (see Table 126.7), and female patients of childbearing potential must have at least one (in the US, two) negative pregnancy test(s) before starting treatment and practice effective contraception for 1 month prior to, during, and for 1 month after completing therapy. In the US, prescription of isotretinoin requires all physicians and patients to register with a pregnancy risk management program (iPLEDGE™), which mandates monthly office visits for all patients (with counseling not to share the medication) and monthly pregnancy testing for female patients with childbearing potential. Isotretinoin therapy leads to elevated serum triglyceride levels in 25–50% of patients and may have side effects involving the musculoskeletal system (most often myalgias), eyes, liver (occasionally elevated transaminases); intestines (controversial link to inflammatory bowel disease) and central nervous system (see Table 126.8 and Ch. 126). To date, no firmly established causal association with depression or suicide attempts has been demonstrated.

Fig. 36.19 Impetigo in a patient treated with isotretinoin. Multiple serous crusts are evident.

Surgical Treatment

Comedo extraction can improve the cosmetic appearance of acne and aid in therapeutic responsiveness to topical comedolytic agents. The keratinous contents of open comedones may be expressed using a comedo extractor. The Schamberg, Unna and Saalfield types of comedo expressers are most commonly used. Nicking the surface of a closed comedo with an 18-gauge needle or a #11 blade allows easier expression. Extraction is especially beneficial for deep, inspissated and persistent comedones. This procedure should be used in conjunction with a topical retinoid or other comedolytic treatment for maximum benefit. Comedo extraction should not be performed on inflamed comedones or pustules because of the risk of scarring. Light electrocautery and electrofulguration (see Ch. 140) have also been reported as effective treatments for comedones. Electrofulguration has the added benefit of not requiring the prior use of a topical anesthetic. In selected patients, cryotherapy represents another surgical option for the treatment of comedonal acne (see Ch. 138).

Photodynamic therapy utilizing topical 5-aminolevulinic acid together with various light sources (e.g. blue, red, intense pulsed) or lasers (e.g. pulsed dye, 635 nm red diode) as well as methyl aminolevulinate plus red light have been successfully used to treat acne (see Ch. 135). In addition, blue or intense pulsed light alone and lasers such as the pulsed dye, the 1320 nm neodymium:YAG and especially the 1450 nm diode may be of therapeutic benefit for inflammatory acne (see Ch. 137).

Intralesional injection of corticosteroid (triamcinolone acetonide 2–5 mg/ml) can quickly improve the appearance and tenderness of deep, inflamed nodules and cysts. Larger cysts may require incision and drainage prior to injection. The maximal amount of corticosteroid used per lesion should not exceed 0.1 ml. The risks of corticosteroid injections include hypopigmentation (particularly in darkly pigmented skin), atrophy, telangiectasias, and needle tract scarring.

Low-concentration chemical peels are also beneficial for the reduction of comedones. The α-hydroxy acids (including glycolic acid), salicylic acid and trichloroacetic acid are the most common peeling agents. These lipid-soluble comedolytic agents act by decreasing corneocyte cohesion at the follicular opening and assist in comedo plug extrusion. Such agents are generally well tolerated by most skin colors and types, and they can be used by the patient at home or in the dermatologist's office. Higher-concentration glycolic acid peels (20–70%, depending on the patient's skin type) and the less predictable phenol peel may also be performed in the office setting. Risks of chemical peels include irritation, pigmentary alteration and scarring.

One of the most distressing consequences of acne vulgaris is scarring. Surgical treatments should be aimed at the type of scarring present. Laser resurfacing (fractional as well as traditional), dermabrasion and deeper chemical peels seek to reduce the variability of the skin surface and smooth out depressed scars that improve when the skin is stretched. For discrete depressed scars, soft tissue augmentation can be temporarily beneficial. Filler substances used include poly-L-lactic acid, calcium hydroxylapatite and autologous fat (see Ch. 158). Punch grafting is an option for patients with "ice-pick" scarring. Surgical subscision is also a commonly used technique in the management of acne scars. For larger hypertrophic scars, aggregated pitted scars and sinus tracts, full-thickness surgical excision may result in improved scar placement and a better cosmetic appearance.

REFERENCES

1. Halvorsen JA, Stern RS, Dalgard F, et al. Suicidal ideation, mental health problems, and social impairment are increased in adolescents with acne: a population-based study. J Invest Dermatol. 2011;131:363–70.
2. Goolamali SK, Andison AC. The origin and use of the word 'acne'. Br J Dermatol. 1977;96:291–4.
3. Waisman M. Concepts of acne of the British School of Dermatology prior to 1860. Int J Dermatol. 1983;22:126–9.
4. Collier CN, Harper JC, Cafardi JA, et al. The prevalence of acne in adults 20 years and older. J Am Acad Dermatol. 2008;58:56–9.
5. Ghodsi SZ, Orawa H, Zouboulis CC. Prevalence, severity, and severity risk factors of acne in high school pupils: a

community-based study. J Invest Dermatol. 2009;129: 2136–41.
6. Powell EW, Beveridge GW. Sebum excretion and sebum composition in adolescent men with and without acne vulgaris. Br J Dermatol. 1970;82:243–9.
7. Jeremy AHT, Holland DB, Roberts SG, et al. Inflammatory events are involved in acne lesion initiation. J Invest Dermatol. 2003;121:20–7.
8. Abdel-Fattah NS, Shaheen MA, Ebrahim AA, El Okda ES. Tissue and blood superoxide dismutase activities and malondialdehyde levels in different clinical severities of acne vulgaris. Br J Dermatol. 2008;159: 1086–91.
9. Holland DB, Jeremy AH, Roberts SG, et al. Inflammation in acne scarring: a comparison of the responses in lesions from patients prone and not prone to scar. Br J Dermatol. 2004;150:72–81.
10. Leyden JJ, McGinley KJ, Mills OH, Kligman AM. *Propionibacterium* levels in patients with and without acne vulgaris. J Invest Dermatol. 1975;65:382–4.
11. Nagy I, Pivarcsi A, Kis K, et al. *Propionibacterium acnes* and lipopolysaccharide induce the expression of antimicrobial peptides and proinflammatory cytokines/ chemokines in human sebocytes. Microbes Infect. 2006; 8:2195–205.
12. Kim J, Ochoa MT, Krutzik SR, et al. Activation of toll-like receptor 2 in acne triggers inflammatory cytokine responses. J Immunol. 2002;169:1535–41.
13. Jalian HR, Liu PT, Kanchanapoomi M, et al. All-trans retinoic acid shifts *Propionibacterium acnes*-induced matrix degradation expression profile toward matrix preservation in human monocytes. J Invest Dermatol. 2008;128:2777–82.
14. Nagy I, Pivarcsi A, Koreck A, et al. Distinct strains of *Propionibacterium acnes* induce selective human beta-defensin-2 and interleukin-8 expression in human keratinocytes through toll-like receptors. J Invest Dermatol. 2005;124:931–8.
15. Sugisaki H, Yamanaka K, Kakeda M, et al. Increased interferon-gamma, interleukin-12p40 and IL-8 production in *Propionibacterium acnes*-treated peripheral blood mononuclear cells from patient with acne vulgaris: host response but not bacterial species is the determinant factor of the disease. J Dermatol Sci. 2009;55:47–52.
16. Chronnell CM, Ghali LR, Ali RS, et al. Human beta defensin-1 and -2 expression in human pilosebaceous units: upregulation in acne vulgaris lesions. J Invest Dermatol. 2001;117:1120–5.
17. Nakatsuji T, Kao MC, Zhang L, et al. Sebum free fatty acids enhance the innate immune defense of human sebocytes by upregulating beta-defensin-2 expression. J Invest Dermatol. 2010;130:985–94.
18. Lee D-Y, Yamasaki K, Rudsil J, et al. Sebocytes express functional cathelicidin antimicrobial peptides and can act to kill *Propionibacterium acnes*. J Invest Dermatol. 2008;128:1863–6.
19. Lee DY, Huang CM, Nakatsuji T, et al. Histone H4 is a major component of the antimicrobial action of human sebocytes. J Invest Dermatol. 2009;129:2489–96.
20. Liu PT, Phan J, Tang D, et al. CD209(+) macrophages mediate host defense against *Propionibacterium acnes*. J Immunol. 2008;180:4919–23.
21. Lucky AW, Biro FM, Huster GA, et al. Acne vulgaris in premenarchal girls. An early sign of puberty associated with rising levels of dehydroepiandrosterone. Arch Dermatol. 1994;130:308–14.
22. Strauss JS, Pochi PE. Effect of cyclic progestin-estrogen therapy on sebum and acne in women. JAMA. 1964;190: 815–19.
23. Bowe WP, Joshi SS, Shalita AR. Diet and acne. J Am Acad Dermatol. 2010;63:124–41.
24. Capitanio B, Sinagra JL, Bordignon V, et al. Underestimated clinical features of postadolescent acne. J Am Acad Dermatol. 2010;63:782–8.
25. Jansen T, Plewig G. Acne fulminans. Int J Dermatol. 1998; 37:254–7.
26. Tan BB, Lear JT, Smith AG. Acne fulminans and erythema nodosum during isotretinoin therapy responding to dapsone. Clin Exp Dermatol. 1997;22:26–7.
27. Wise CA, Gillum JD, Seideman CE, et al. Mutations in *CD2BP1* disrupt binding to PTP PEST and are responsible for PAPA syndrome, an autoinflammatory disorder. Hum Mol Genet. 2002;11:961–9.
27a. Braun-Falco M, Kovnerystyy O, Lohse P, Ruzicka T. Pyoderma gangrenosum, acne, and suppurative hidradenitis (PASH) - a new autoinflammatory syndrome distinct from PAPA syndrome. J Am Acad Dermatol. 2011 Jul 9. [Epub ahead of print]
27b. Alikhan A, Henderson GP, Becker L, Sciallis GF. Acne treatment and inflammatory bowel disease: what is the evidence? J Am Acad Dermatol. 2011;65:650–4.
28. Friedman SJ, Fox BJ, Albert HL. Solid facial edema as a complication of acne vulgaris: treatment with isotretinoin. J Am Acad Dermatol. 1986;15:286–9.
29. Jungfer B, Jansen T, Przybilla B, Plewig G. Solid persistent facial edema of acne: successful treatment with isotretinoin and ketotifen. Dermatology. 1993;187: 34–7.
30. Arbegast KD, Braddock SW, Lamberty LF, Sawka AR. Treatment of infantile cystic acne with oral isotretinoin: a case report. Pediatr Dermatol. 1991;8:166–8.
31. Solomon LM, Fretzin D, Pruzansky S. Pilosebaceous abnormalities in Apert's syndrome. Arch Dermatol. 1970;102:381–5.
32. Risma KA, Lucky AW. Pseudoacne of the nasal crease: a new entity? Pediatr Dermatol. 2004;21:427–31.
33. Boralevi F, Leaute-Labreze C, Lepreux S, et al. Idiopathic facial aseptic granuloma: a multicentre prospective study of 30 cases. Br J Dermatol. 2007;156:705–8.
34. Larralde M, Abad M, Muñoz AS, et al. Childhood flexural comedones: a new entity. Arch Dermatol. 2007;143: 909–11.
35. Johnson EM. A risk assessment of topical tretinoin as a potential human developmental toxin based on animal and comparative human data. J Am Acad Dermatol. 1997;36:S86–90.
36. Navarre-Belhassen C, Blanchet P, Hillaire-Buys D, et al. Multiple congenital malformations associated with topical tretinoin [letter]. Ann Pharmacother. 1998;32: 505–6.
37. Buchan P, Eckhoff C, Caron D, et al. Repeated topical administration of all-*trans*-retinoic acid and plasma levels of retinoic acids in humans. J Am Acad Dermatol. 1994;30:428–34.
38. Cunliffe WJ, Caputo R, Dreno B, et al. Clinical efficacy and safety comparison of adapalene gel and tretinoin gel in the treatment of acne vulgaris: Europe and US multicenter trials. J Am Acad Dermatol. 1997;36: S126–34.
39. Arowojolu A, Gallo M, Lopez L, et al. Combined oral contraceptives for the treatment of acne. Cochrane Database Syst Rev. 2009;3:CD004425.
40. Lidegaard O, Lokkegaard E, Svendsen AL, et al. Hormonal contraception and risk of venous thromboembolism: national follow-up study. BMJ. 2009; 339:b2890.
41. van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, et al. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. BMJ. 2009;339:b2921.
42. Trenor CC 3rd, Chung RJ, Michelson AD, et al. Hormonal contraception and thrombotic risk: a multidisciplinary approach. Pediatrics. 2011;127:347–57.
43. van Wayjen R, van den Ende A. Experience in the long-term treatment of patients with hirsutism and/or acne with cyproterone acetate-containing preparations: efficacy, metabolic and endocrine effects. Exp Clin Endocrinol Diabetes. 1995;103: 241–51.
44. Goodfellow A, Alaghband-Zadeh J, Carter G, et al. Oral spironolactone improves acne vulgaris and reduces sebum excretion. Br J Dermatol. 1984;111: 209–14.
45. Shaw J. Spironolactone in dermatologic therapy. J Am Acad Dermatol. 1991;24:236–43.
46. Shaw JC. Low-dose adjunctive spironolactone in the treatment of acne in women: a retrospective analysis of 85 consecutively treated patients. J Am Acad Dermatol. 2000;43:498–502.
47. Pochi PE, Shalita AR, Strauss JS, et al. Report of the Consensus Conference on Acne Classification. Washington, DC, March 24 and 25, 1990. J Am Acad Dermatol. 1991;24:495–500.
48. Lee JW, Yoo KH, Park KY, et al. Effectiveness of conventional, low-dose and intermittent oral isotretinoin in the treatment of acne: a randomized, controlled comparative study. Br J Dermatol. 2011;164:1369–75.

This page intentionally left blank

Infantile acne. Multiple open and closed comedones, papules and atrophic scarring. *Courtesy of Holly Gunn MD.*

Rosacea and Related Disorders 37

Frank C Powell and *Síona Ní Raghallaigh*

INTRODUCTION

The clinical and histologic parameters of rosacea remain poorly defined despite the fact that it is a relatively common dermatosis. There is no laboratory test that can simply confirm the diagnosis of rosacea. In addition, the concept that certain disorders are "related" to rosacea is not based on scientific evidence but on clinical similarities.

The term *rosacea* is used to encompass a constellation of signs and symptoms. The latter include: persistent facial erythema, telangiectasias, inflammatory papules and pustules, a tendency for frequent facial flushing, non-pitting facial edema, ocular inflammation of various types, and phymatous changes, primarily of the nose, but also of the ears, forehead, chin or eyelids. Some authors also include (as variants of rosacea) *rosacea fulminans*, which is characterized by the explosive onset of inflammatory papules and pustules superimposed on a background of facial erythema and sometimes even accompanied by fever, and *rosacea conglobata* where inflammatory facial cysts with associated scarring are seen[1]. However, inclusion of these variants under the title rosacea is controversial, and some authors regard them related more to acne vulgaris. Persistent red–brown to skin-colored facial papules with a characteristic non-caseating granulomatous histology is referred to as *granulomatous rosacea*, while individuals with frequent facial flushing and easily irritated facial skin have been classified as having "pre-rosacea". In addition to the labeling of certain clinical presentations as "stages" of progression, the inclusion of this diverse spectrum of clinical features under the heading of rosacea has impeded an understanding of the pathogenesis of this disease.

In 2002, a classification of the subtypes of rosacea was published[2] and it has helped to clarify the situation (see Table 37.2). The hope is that this classification scheme will provide a framework for future investigations.

HISTORY

Robert Willan is credited with the earliest medical descriptions of "acne rosacea"[3]. The form of the disease he described would nowadays be classified as papulopustular rosacea. Early on, rosacea was thought by many dermatologists of that time to have a "seborrheic pathogenesis", similar to acne vulgaris. Radcliff-Crocker later postulated that repeated flushing lead to dilated, leaky, facial blood vessels with subsequent inflammatory skin changes. This hypothesis retains its supporters to this day.

EPIDEMIOLOGY

Previously published reports regarding the frequency of rosacea in the population have sometimes suffered from inadequate definitions of disease. In 1989, a study of over 800 Swedish office workers reported a prevalence of rosacea of 10%[4]. However, the majority of these individuals had facial erythema and telangiectasias without inflammatory skin lesions, but these findings can be impossible to distinguish clinically from the facial skin changes induced by chronic exposure to ultraviolet (UV) light (dermatoheliosis). A population study of 1000 individuals in Ireland that used an agreed clinical definition of papulopustular rosacea found a prevalence of 2.7%. This study also showed that papulopustular rosacea was not associated with photodamage[5]. An additional 14% of this study population had skin changes similar to the Swedish group that could be attributed to either erythematotelangiectatic rosacea or dermatoheliosis. These latter changes were associated with photodamage.

PATHOGENESIS

The exact pathogenesis of rosacea is unknown. The disorder which is known today as rosacea will probably be shown in time to comprise several similar, possibly related, but different clinical conditions, each with separate predominant pathogenic mechanisms. Some of the factors currently thought to be relevant are listed in Table 37.1.

Rosacea occurs most frequently in Caucasians and in those with fair sun-sensitive skin, i.e. skin phototypes I and II. There may be a genetic predisposition to the disorder, as 10–20% of patients report a family history of rosacea. Epidemiologic studies suggest that erythematotelangiectatic rosacea may be related to UV exposure and photodamage (see above). UVB exposure has been shown to induce angiogenesis and to increase the secretion of angiogenic factors such as vascular endothelial growth factor (VEGF) from keratinocytes[6]. Evidence suggests that exposure to UV radiation leads to the production of reactive oxygen species, which then induce an upregulation of matrix metalloproteinases[7], leading to damage to blood vessels and the dermal matrix. It may be that these factors are most relevant to those patients with erythematotelangiectatic rosacea.

Histologic examination of papulopustular rosacea demonstrates inflammatory changes that are most pronounced at the pilosebaceous follicle[8,9]. These changes may result from dysfunction of the innate immune response which protects the skin against infection as well as other environmental stimuli such as UV radiation and chemical trauma. Triggering the innate immune system leads to a controlled release of cytokines and antimicrobial molecules such as the peptide cathelicidin. In rosacea, there is an upregulation of cathelicidin and its processing serine protease (kallikrein 5), suggesting dysfunction of the innate immune system[10]. When injected into murine skin, cathelicidin peptides and their associated enzymes induced pro-inflammatory and angiogenic activity, features which may be of greater relevance to papulopustular rosacea[11].

Persistent centrofacial erythema and telangiectasias are common features of rosacea, as is flushing (transient erythema). An elevation in cutaneous blood flow has been observed in skin affected by papulopustular rosacea, when compared with non-affected skin[12]. In addition, there is elevated expression of VEGF, CD31 (a pan-endothelial cell marker) and lymphatic endothelial marker D2-40 (podoplanin) in lesional skin, suggesting stimulation of vascular and lymphatic endothelial cells[13]. Aberrant control of cutaneous thermal mechanisms has also been proposed as a cause of vasodilation. Compared to controls, rosacea patients flush more readily in response to heat, and their heat pain thresholds have been demonstrated to be lower[12].

Patients with rosacea often report symptoms of facial dryness, stinging or burning. Studies have confirmed a lowered threshold for irritancy in the skin of rosacea patients[14]. This may be due to epidermal barrier dysfunction, characterized by increased transepidermal water loss, which has been demonstrated in patients with rosacea[15]. In addition, it has been suggested that disruption or abnormality of the stratum corneum allows penetration of sensory irritants which then leads to a stinging sensation[16]. These findings have practical implications when advising rosacea patients regarding appropriate facial skin care.

Neurogenic inflammation (an inflammatory response induced by sensory nerves which release neuromediators at the site of inflammation) can result in vasodilation, extravasation of plasma proteins and recruitment of inflammatory cells. Environmental triggers are known to activate G protein-coupled receptors and ion channels on sensory nerves (see Ch. 5); upon stimulation, neuropeptides such as calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase activating polypeptide (PACAP) induce vasodilation of arterioles and capillaries[17].

PATHOGENIC HYPOTHESES FOR ROSACEA	
Theory	**Explanation**
Aberrant innate immune system	• The innate immune response protects against microbial infection without requiring specific recognition of the pathogenic stimulus • Activation of innate immunity leads to release of cytokines and antimicrobial molecules such as the peptide cathelicidin • In rosacea, there is upregulation of cathelicidin and its processing serine protease, suggesting dysfunction of the innate immune system
Ultraviolet radiation (UVR)	• UVR exposure has been shown to: – induce angiogenesis – increase production of reactive oxygen species, which then leads to upregulation of matrix metalloproteinases (MMPs) • MMPs result in damage to blood vessels and the dermal matrix
Vascular changes	• An increase in blood flow is seen within affected skin in rosacea • Rosacea patients flush more readily in response to heat as compared with controls • An elevated expression of VEGF and lymphatic endothelial markers is observed, suggesting stimulation of blood vascular and lymphatic endothelial cells
Epidermal barrier dysfunction	• Increased transepidermal water loss • Lowered threshold for skin irritancy • Seen in both erythematotelangiectatic and papulopustular rosacea
Neurogenic inflammation	• Sensory nerves release neuromediators at the site of inflammation, resulting in vasodilation, extravasation of plasma proteins and recruitment of inflammatory cells • Exact mechanisms not well understood
Microbes	• *Demodex* mites (*folliculorum* and *brevis*), which are commensals of normal skin, are found in greater numbers in rosacea patients • *Demodex* infestation is associated with an intense perifollicular infiltrate of predominantly $CD4^+$ helper T cells • Staphylococcal organisms are also thought to play a role in rosacea pathogenesis

Table 37.1 Pathogenic hypotheses for rosacea. VEGF, vascular endothelial growth factor.

Fig. 37.1 Erythematotelangiectatic rosacea. Persistent erythema of the medial and lateral cheeks is seen. In this patient, there are no telangiectasias, indicating mild (grade 1) disease.

Fig. 37.2 Dermatoheliosis in a skin phototype I patient. Telangiectasias and erythema due to chronic actinic damage are particularly marked on the facial prominences. Features of dermatoheliosis overlap with those of erythematotelangiectatic rosacea.

However, these pathways are not well understood and their relevance to rosacea is unclear.

Although *Demodex* mites (*folliculorum* and *brevis*) are facial skin commensals, they are often prominent within the pilosebaceous follicle when rosacea skin is examined histologically. Using the skin surface biopsy technique, several investigators have shown that these mites are present in far greater numbers in rosacea patients than in control subjects[18,19]. Follicular infestation with multiple mites has been shown to be associated with an intense perifollicular infiltrate of predominantly $CD4^+$ helper T cells[20]. Antigenic proteins produced by a bacterium (*Bacillus oleronius*) isolated from *Demodex* mites have been shown to stimulate an inflammatory response in patients with papulopustular rosacea[21]. It has been suggested that *Demodex* mites and their associated bacteria upregulate cutaneous proteases, thereby potentiating the dysregulation of the local innate immune response (see above)[22]. These pathomechanisms are probably most relevant for the papulopustular subtype of rosacea.

Lastly, it seems unlikely, based on current evidence, that *Helicobacter pylori* infection plays an etiologic role in the pathogenesis of rosacea.

CLINICAL FEATURES

Rosacea usually has its onset during middle age, with women being affected somewhat earlier than men. Rosacea has been observed in children, with associated ocular changes and therapeutic responses that are similar to those in adult patients, but the lack of adequate criteria to verify the diagnosis hinders the establishment of childhood rosacea as a specific entity. Although women are said to be more frequently affected by rosacea than men, the evidence for this is unclear. Rhinophyma, however, clearly occurs primarily in men. The prevalence of rosacea in individuals with darker skin phototypes has not been well studied, but it may be greater than was previously assumed. In more darkly pigmented skin, erythema and telangiectasias may be difficult to appreciate clinically, so a history of skin sensitivity and flushing, along with centrofacial or ocular inflammatory lesions, may assist in establishing the diagnosis.

In 2002, a consensus publication provided a classification scheme for rosacea[2] (Table 37.2), and the clinical characteristics of the four major forms will be discussed separately.

- *Erythematotelangiectatic rosacea* includes individuals who have a tendency for flushing, combined with a background of persistent facial erythema (Fig. 37.1) and sometimes telangiectasias. Such patients typically have skin phototypes I or II. The clinical definition of erythematotelangiectatic rosacea can prove challenging because of overlap with the cutaneous findings of chronic actinic damage in fair-skinned individuals (dermatoheliosis) (Fig. 37.2). Patients with dermatoheliosis can also have thermolabile facial skin and may experience flushing, particularly with environmental temperature change. In addition, individuals who complain of flushing as a solitary symptom should not be labeled as having "pre-rosacea" but rather should be investigated for other causes of flushing as listed in Table 106.2.

CLASSIFICATION, CLINICAL FEATURES AND MANAGEMENT OF SUBTYPES OF ROSACEA				
Subtype	**Predominant clinical features**	**Severity**		**Management**
		Grade	**Features**	
Erythematotelangiectatic	• Persistent centrofacial erythema • Flushing • Telangiectasias • Skin sensitivity	1	Occasional mild flushing; faint persistent centrofacial erythema; few telangiectasias	• General recommendations for facial skin care (see Table 37.5) • Reduce flushing • Minimize irritation • Topical treatments used in papulopustular rosacea may cause irritation • Laser therapy of prominent blood vessels in grades 2 and 3 disease
		2	Frequent troublesome flushing; moderate persistent centrofacial erythema; several distinct telangiectasias	
		3	Frequent severe flushing; pronounced persistent centrofacial erythema; many prominent telangiectasias; possible edema	
Papulopustular	• Persistent centrofacial erythema • Papules • Pustules/papulopustules • Overlap with other subtypes may occur	1	Few papules and/or papulopustules; mild persistent centrofacial erythema	• Topical or systemic medications for grades 1 and 2 disease • Systemic medications for grade 3 • May require repeated courses or gradual taper
		2	Several papules and/or papulopustules; moderate persistent centrofacial erythema	
		3	Extensive papules and/or papulopustules; pronounced persistent centrofacial erythema; inflammatory plaques or edema may be present	
Phymatous	• Thickened, nodular skin • Prominent pores • Can affect nose (rhinophyma), chin (gnathophyma), forehead (metophyma), ears (otophyma), eyelids (blepharophyma) • May be associated with other features of rosacea or occur in isolation	1	Puffiness; mildly patulous follicles; no clinically apparent hypertrophy of connective tissue or sebaceous glands; no change in contour	• Surgical or laser therapy for grades 2 and 3 rhinophyma • Other phymas are more difficult to treat but may improve with systemic treatments, if an inflammatory component is present
		2	Moderate swelling; moderately dilated patulous follicles; clinically, mild hypertrophy of the sebaceous glands or connective tissue; change in nasal contour without nodular component	
		3	Marked swelling; large dilated follicles; distortion of contour due to hypertrophy of the sebaceous glands and/or connective tissue, with a nodular component	
Ocular	• Dry, gritty sensation • Blepharitis • Conjunctivitis • Chalazia and hordeola • Keratitis, episcleritis, scleritis, iritis (rare)	1	Mild itch, dryness or grittiness; fine scaling of eyelid margins; telangiectasia of eyelid margins; mild conjunctival injection	• Topical medications for grade 1 • Systemic medications for grade 2 • Refer to ophthalmologist for persistent grade 1 or 2 disease or suspected grade 3 disease
		2	Burning or stinging; crusting, irregularity, erythema and/or edema of eyelid margins; definite conjunctival injection; chalazion or hordeolum	
		3	Pain, photosensitivity, blurred vision; severe eyelid changes with loss of lashes, severe conjunctival inflammation; corneal changes, with potential loss of vision; episcleritis, scleritis; iritis	

Table 37.2 Classification, clinical features and management of subtypes of rosacea. Adapted from ref. 23.

- *Papulopustular rosacea* is characterized by a centrofacial eruption of multiple, small (<3 mm), dome-shaped, erythematous papules, some of which are surmounted by a seropustule (Fig. 37.3). These lesions can appear singly or in crops. The patient may complain of slight tenderness or itch associated with the lesions, but in general the social distress caused by the appearance of the eruption far exceeds the physical symptoms. Individual lesions last about 2 weeks then subside into a blotchy erythema, which gradually fades; resultant scarring is not seen. As some lesions fade, others appear.

  A halo of erythema may surround the larger inflammatory lesions and tiny telangiectatic blood vessels may be visible within this rim. In severely affected skin, slight scaling or a crusted appearance may sometimes be seen (Fig. 37.4). These findings should not be confused with seborrheic dermatitis, which may accompany papulopustular rosacea but is characterized by a greasy, yellowish scale and involvement of the facial creases and the eyebrows.
- The most common expression of *phymatous rosacea* is rhinophyma, which reflects hypertrophy of the sebaceous glands in nasal skin. Rhinophyma is usually seen in patients with other features of rosacea but may occur in patients with acne vulgaris; occasionally it is due to chronic actinic damage or may arise *de novo*. Specifically, rhinophyma does not represent "end-stage" rosacea as many patients have had only mild or no preceding rosacea. Male patients are predominantly affected by rhinophyma[24], and telangiectatic vessels of the distal nose may predispose to subsequent development of hypertrophic changes of rhinophyma (Fig. 37.5A). The earliest clinical sign of rhinophyma is the appearance of dilated pores (patulous follicles) on the distal portions of the nose (Fig. 37.5B). In severe cases of rhinophyma,

Fig. 37.3 Moderate papulopustular rosacea of the forehead. Note the superficial nature of the inflammatory lesions.

Fig. 37.4 Moderate to severe papulopustular rosacea. There is a typical centrofacial distribution of erythema, telangiectasias, papules and pustules. In addition, the skin has a scaly, crusty surface and this is often a sign of more severe disease.

TYPES OF PHYMATOUS ROSACEA	
Phyma	**Clinical features**
Rhinophyma	Apparent initially as dilated patulous follicles at the distal end of the nose When marked, can lead to debilitating nasal deformity
Gnathophyma	Rare occurrence, with central chin typically involved May give rise to asymmetrical swelling
Otophyma	Usually affects the lower half of the helices and lobes of the ears
Mentophyma	Cushion-like, firm swelling of central forehead
Blepharophyma	Swelling of the eyelids Usually seen as a component of edematous rosacea but may accompany severe papulopustular or ocular rosacea

Table 37.3 Types of phymatous rosacea.

there is hypertrophy of tissue with nasal distortion as soft, fleshy, nodular growths increase in size (Fig. 37.5C).

Although basal cell carcinomas have been reported to arise in skin affected by rhinophyma, there is insufficient evidence to suggest that this condition predisposes to malignant change. Other phymatous skin changes are rare (Table 37.3). Of note, the edematous changes sometimes seen in patients with severe inflammatory rosacea (Fig. 37.6) should not be confused with phymatous rosacea, as such changes (unlike those of phymatous rosacea) often subside with successful management of the inflammation.

- *Ocular rosacea* can occur without accompanying cutaneous changes (in which case the diagnosis is difficult to make with certainty) or it may be seen in patients with any of the other subtypes of rosacea. Those with erythematotelangiectatic and papulopustular rosacea appear to be particularly vulnerable to the development of ocular inflammation, with up to 50% of patients affected. Symptoms consist of nonspecific complaints of itching, tearing, dryness, gritty sensations, crusting of eyelids and an inability to wear contact lenses, as well as frequent styes. However, patients may not volunteer these symptoms unless specifically asked.

  The clinical signs of ocular rosacea are diverse and lacking in specificity. There may be tiny concretions at the bases of the cilia (conical dandruff), or mild scaling of the eyelid margins (scurf). More active disease manifests as blepharitis, often with eyelid swelling and conjunctival injection; the latter gives the affected eye a reddish appearance (Fig. 37.7). Cysts arising from the meibomian glands (chalazia) present as firm non-tender swellings of the cutaneous tarsal surface, while hordeola are similar, but are tender swellings often referred to by patients as "styes". Severe ocular disease (keratitis, corneal neovascularization, uveitis, scleritis or iritis) is fortunately rarely seen in patients with rosacea. Patients who complain of pain or photophobia require specialist attention.

Fig. 37.5 Rhinophyma – early versus advanced disease. A Tortuous, telangiectatic vessels on the distal aspect of the nose contribute to its hyperemic appearance; this hyperemia may predispose to the subsequent hypertrophic changes of rhinophyma. Note the early sign of dilated follicles. **B** Prominent follicular openings or patulous follicles with evidence of the early swelling of glandular rhinophyma. **C** Distortion of nasal tissue due to nodular hypertrophy of sebaceous glands. Electrosurgery or laser therapy can be used to debulk and resculpt this nose.

In addition to the four major types of rosacea, there are variants that include granulomatous rosacea and rosacea fulminans, also referred to

Fig. 37.6 Inflammatory rosacea with edematous changes. An intensely erythematous plaque is present on the medial aspect of the cheek. This may improve once the underlying inflammation is treated appropriately.

Fig. 37.7 Ocular rosacea. A Tiny concretions of keratin (conical dandruff) are visible at the bases of some of the eyelashes of the lower eyelid. There is also evidence of blepharitis of the lower eyelid and conjunctival injection. **B** Marked injection of the conjunctivae, leading to the appearance of red eyes. Ectropion is also present.

Fig. 37.8 Variants of rosacea. **A** Discrete skin-colored to brown papules scattered on the face. Histologically, granulomas with central caseation necrosis were observed, which led to the diagnosis of lupus miliaris disseminatus faciei; nowadays this entity is thought to fall within the spectrum of granulomatous rosacea. **B** Rosacea fulminans (pyoderma faciale). Striking plaque on the cheek studded with pustules.

as pyoderma faciale (see Introduction) (Fig. 37.8). Also, rarely extrafacial lesions of rosacea are seen, primarily on the scalp of male patients with androgenic alopecia.

PATHOLOGY

Histologic changes in the erythematotelangiectatic form of rosacea may be subtle and are often limited to vascular ectasia and mild edema (Fig. 37.9A). In the inflammatory papulopustular form, a more prominent perivascular and perifollicular lymphohistiocytic infiltrate appears (Fig. 37.9B). Sebaceous hyperplasia may be prominent in some patients. Comedo formation is notably lacking. In the granulomatous form of rosacea, non-caseating epithelioid granulomas are seen within the dermis (Fig. 37.9C).

DIFFERENTIAL DIAGNOSIS

Acne vulgaris (see Ch. 36) is in the differential diagnosis of the papulopustular subtype of rosacea. However, unlike in acne vulgaris, open and closed comedones are not seen in patients with rosacea. Since both disorders are so common, a patient with rosacea may have features of coexistent or previous acne vulgaris (e.g. scarring). Rosacea-like disorders also need to be considered (see below) – in particular, periorificial dermatitis and steroid-induced rosacea. The differential diagnosis also includes *Demodex* folliculitis.

The erythematotelangiectatic form of rosacea needs to be distinguished from chronic actinic damage (in fair-skinned individuals), seborrheic dermatitis (see Ch. 13), cutaneous lupus (lacks pustules; see Ch. 41), keratosis pilaris rubra and erythromelanosis faciei. The latter two disorders have characteristic tiny follicular white papules (see Ch. 38). The differential diagnosis of the blepharitis of ocular rosacea includes seborrheic dermatitis and allergic contact dermatitis.

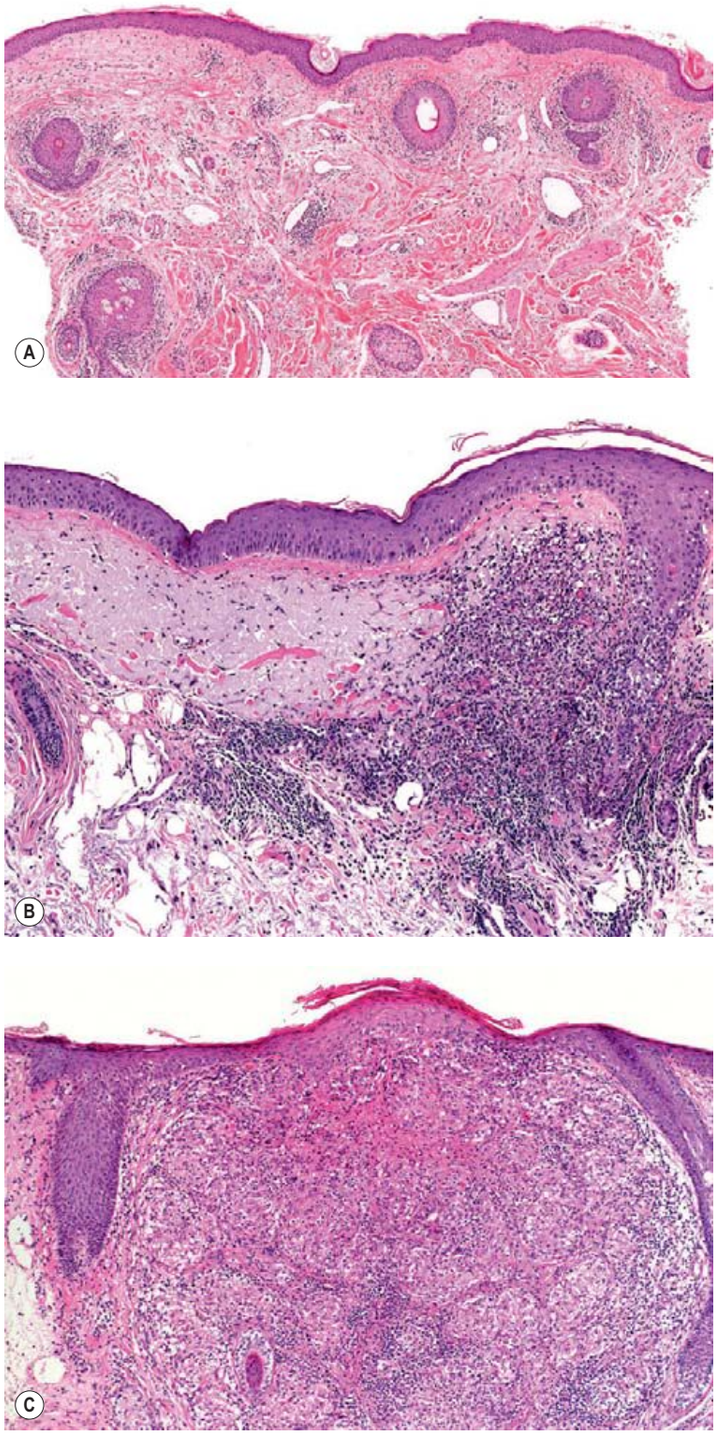


Fig. 37.9 Rosacea – range of histologic findings. A *Erythematotelangiectatic form* with multiple dilated blood vessels within the dermis as well as minimal perifollicular and perivascular lymphocytic infiltrates. **B** *Papulopustular form* with a dense dermal infiltrate of lymphocytes, predominantly surrounding an involved hair follicle. There is also marked solar elastosis. **C** *Granulomatous form* with a nodular granulomatous infiltrate composed of histiocytes, histiocytic giant cells and admixed lymphocytes filling the upper interfollicular dermis. *Courtesy, Lorenzo Cerroni, MD.*

TREATMENT

Categorizing rosacea into subtypes is especially useful when therapeutic options are being considered (Table 37.4). The particular subtype determines the management that will be required, with treatment of acute inflammation different from the therapy necessary to maintain clearance. Grading each subtype into mild, moderate and severe (grades 1–3; see Table 37.2) will also help the physician decide on the most appropriate treatment(s). Grading is also useful for monitoring progress[27].

It is important to educate the patient at the initial consultation as to the chronic relapsing nature of this disorder and the need for a maintenance regimen. Otherwise, the expectation might be that one course of therapy is curative.

Patients with grade 1 erythematotelangiectatic rosacea present with mild fixed facial erythema and intermittent flushing. Frequent flushing with the presence of multiple telangiectatic blood vessels is characteristic of grades 2 and 3 disease (see Table 37.2). Therapy focuses on recommendations for facial skin care (Table 37.5), reduction of the tendency for flushing by avoiding precipitating factors and specific medications, diminishing the facial erythema, and removing the telangiectasias (see Table 37.4). Topical and systemic therapies used to treat papulopustular rosacea are often ineffective in the treatment of erythematotelangiectatic rosacea and may irritate the skin. Avoidance of sun exposure and the constant use of a sunblock cream (SPF ≥15) are important, as a significant component of the patient's skin changes may be due to dermatoheliosis.

Patients with papulopustular rosacea are treated primarily with topical and systemic antibiotics (used separately or in combination), although other agents have also been used to treat this subtype of rosacea (see Table 37.4). Many of the recommended systemic antibiotics are the same as those used for the treatment of acne vulgaris, but the courses for rosacea are usually shorter (4 to 6 weeks as opposed to 4 to 6 months). Sometimes, successful treatment of the inflammatory lesions of papulopustular rosacea reveals background telangiectasias (the PERT phenomenon – "post-erythema-revealed telangiectasias"). It is useful to warn patients of this possibility, as otherwise they might attribute the appearance of these telangiectasias to the prescribed treatment. Following successful treatment of inflammatory lesions, individuals with papulopustular rosacea should continue with maintenance therapy (usually topical); otherwise, relapse is likely 3 to 6 months after discontinuation of treatment. Many patients with moderate to severe (grades 2 and 3) papulopustular rosacea require repeated courses of systemic antibiotic therapy.

Rhinophyma is the most common manifestation of phymatous rosacea and is the phyma most amenable to surgical treatment (see Table 37.4). Mild disease may be responsive to medical treatment with isotretinoin, although conclusive evidence of efficacy is lacking. More severe (grades 2 and 3) disease with marked swelling and deformity responds best to physical modalities such as CO_2 laser therapy, electrosurgery or surgical excision. Other phymatous variants are very rare and therapeutic interventions are based solely on case reports.

Patients with mild ocular rosacea (grade 1 disease) often complain of itch or a dry gritty feeling in the eye(s). Lavage of eyelid margins with a mild shampoo on cotton-tipped applicators and tear replacement therapy are usually sufficient for this grade of ocular rosacea. Burning or stinging of the eyes with crusting of the eyelid margins or the formation of chalazia or hordeola are manifestations of moderate (grade 2) disease and patients require either topical antibiotics (such as metronidazole gel or fucidic acid) or systemic antibiotic therapy as outlined for papulopustular rosacea (see Table 37.4). Symptoms such as pain and photophobia as well as visual disturbances are features of severe (grade 3) disease. Such symptoms or lack of response to treatment requires prompt referral to an ophthalmologist for evaluation.

ROSACEA-LIKE DISORDERS

- *Morbihan's disease* is a rare disorder characterized by progressive then persistent, asymptomatic, non-pitting swelling of the central upper face that is associated with fixed facial erythema (Fig. 37.10). It is a poorly defined clinical entity and the exact etiology is not known. Histologic examination shows dermal edema with prominent mast cells within a mild inflammatory infiltrate. It may represent the endpoint of diverse initiating factors such as injury or allergic contact dermatitis[30] and it is debatable as to whether there is any relationship to rosacea. In general, there is no effective therapy, but prolonged courses of low-dose oral isotretinoin have been reported to be helpful in individual patients, as have systemic antihistamines.
- *Periorifical dermatitis*, also referred to as perioral dermatitis, has a superficial resemblance to rosacea but the morphology of the lesions – grouped tiny superficial papulovesicles or papulopustules

MEDICAL AND SURGICAL THERAPIES FOR ROSACEA	
ERYTHEMATOTELANGIECTATIC ROSACEA	
Treatment	**Comments**
Facial skin care recommendations (see Table 37.5)	Particularly useful as this subtype is prone to skin irritation and "sensitivity"
Photoprotection	UVR may potentiate dermal matrix damage
Topical agents, e.g. azelaic acid, metronidazole	May reduce erythema, but their use is often limited by their irritant effects
Topical oxymetazoline[25]	Selective α_1-agonist that may improve erythema
Laser therapy	Use of lasers (e.g. pulsed dye, potassium-titanyl-phosphate) as well as intense pulsed light may improve grades 2 and 3
PAPULOPUSTULAR ROSACEA	
Topical treatments	**Comments**
Metronidazole (0.75% gel or cream; 1% cream)*,† once or twice daily	Can be used as initial treatment to clear inflammatory lesions or as indefinite maintenance therapy
Azeleic acid (15% gel)*,† twice daily	Appears to be more effective than topical metronidazole but with more side effects, e.g. irritation Azeleic acid (20% cream bid) is a non-FDA-approved alternative dose
Sodium sulfacetamide (10%) and sulphur (5%) in a cream or lotion* once or twice daily	May include 10% urea
Erythromycin (2% solution) twice daily	Alcohol in solution may reduce tolerance
Clindamycin (1% lotion) daily	
Benzoyl peroxide 5% and clindamycin 1% daily	May cause skin irritation
Tretinoin (0.025% cream; 0.05% cream; 0.01% gel) daily	Alters epidermal keratinization and may improve photodamage Poorly tolerated by some patients
Permethrin (5% cream) daily–weekly	Shown to be as effective as topical metronidazole for the treatment of papules and erythema May have future role in combination with antibiotics, but further studies needed
Pimecrolimus (1% cream) twice daily	Some studies have shown improvement in erythema, but there have been case reports of exacerbations, so further studies needed
Systemic treatments	**Dosage and duration**
Doxycycline*,†	40 mg daily (30 mg immediate release and 10 mg delayed release) for 6–12 weeks As effective as the 100 mg dose but with less adverse effects
Doxycycline	50–100 mg once or twice daily for 6–12 weeks
Minocycline	50–100 mg twice daily or sustained action formula (1 mg/kg) daily for 6–12 weeks
Tetracycline	250–500 mg twice daily for 6–12 weeks
Erythromycin	250–500 mg once or twice daily for 6–12 weeks
Azithromycin	250–500 mg (5–10 mg/kg) thrice weekly
Metronidazole	200 mg once or twice daily for 4–6 weeks
Isotretinoin	10–40 mg daily
PHYMATOUS ROSACEA	
Treatment	**Comments**
Isotretinoin	May reduce nasal volume and halt the progression of rhinophyma
Surgical excision	Can effectively debulk and resculpt the nose
Electrosurgery	
CO_2 laser	
OCULAR ROSACEA	
Treatment	**Comments**
Eyelid hygiene and artificial tears	Frequently used to treat mild disease Useful for maintaining remission following treatment of grades 2 and 3 disease with systemic antibiotics
Fuscidic acid	
Metronidazole gel	
Cyclosporine 0.5% ophthalmic emulsion†	More effective than artificial tears in treatment of ocular rosacea
Systemic antibiotics (see above section)	For grade 2–3 disease
*The only FDA-approved treatments for rosacea (evidence-based support = 1) †In a Cochrane review of randomized controlled trials conducted for moderate to severe rosacea, these were the only treatments shown to be effective[26].	

Table 37.4 Medical and surgical therapies for rosacea. UVR, ultraviolet radiation.

GENERAL RECOMMENDATIONS FOR FACIAL SKIN CARE AND EDUCATION IN PATIENTS WITH ROSACEA
FACIAL SKIN CARE
• Wash with lukewarm water and use soap-free cleansers that are pH balanced
• Cleansers are applied gently with fingertips
• Use sunscreens with both UVA and UVB protection and an SPF ≥15
• Sun-blocking creams containing the physical barriers titanium dioxide and/or zinc oxide are usually well tolerated
• Use cosmetics and sunscreens that contain protective silicones
• Water-soluble facial powder containing inert green pigment helps to neutralize the perception of erythema
• Moisturizers containing humectants (e.g. glycerin) and occlusives (e.g. petrolatum) help to repair the epidermal barrier
• Avoid astringents, toners and abrasive exfoliators
• Avoid cosmetics that contain alcohol, menthols, camphor, witch hazel, fragrance, peppermint and eucalyptus oil
• Avoid waterproof cosmetics and heavy foundations that are difficult to remove without irritating solvents or physical scrubbing
• Avoid procedures such as glycolic peels or dermabrasion
PATIENT EDUCATION
• Reassure the patient about the benign nature of the disorder and the rarity of rhinophyma, particularly in women
• Emphasize the chronicity of the disease and the likelihood of exacerbations
• Direct patients to information websites such as those of the National Rosacea Society (www.rosacea.org) or the American Academy of Dermatology (www.aad.org)
• Advise to avoid recognized triggers
• Explain the importance of compliance with topical regimens
• Educate on the importance of sun avoidance

Table 37.5 General recommendations for facial skin care and education in patients with rosacea. Adapted from refs 23, 28 & 29.

Fig. 37.10 Morbihan's disease. Erythematous, firm, non-pitting, non-painful swelling of the upper face. Areas of greatest involvement have acquired a "peau d'orange" appearance.

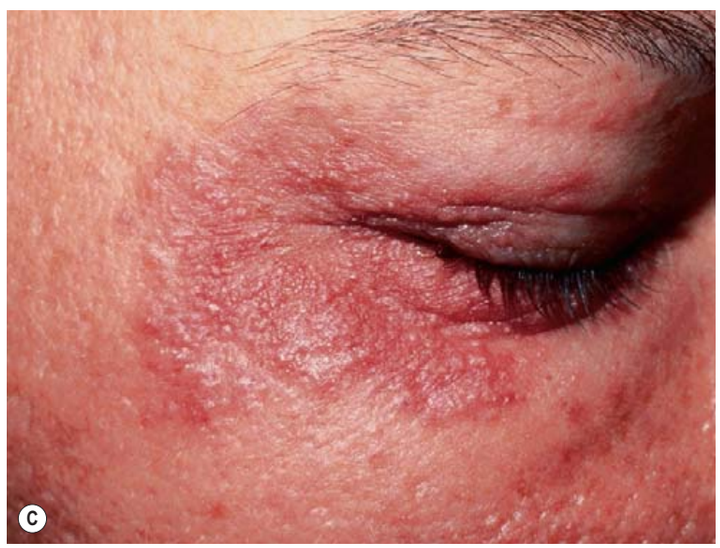


Fig. 37.11 Periorificial dermatitis (also referred to as perioral dermatitis). **A** Accentuation of erythema with superimposed fine superficial papulo-pustules and papulovesicles around orifices, i.e. in a perioral, perinasal and periorbital distribution pattern. The papular lesions are often agminated and, in contrast to papulo-pustular rosacea, are usually all at the same stage of evolution. **B** Granulomatous periorificial dermatitis in a child with mono-morphous pink papules that have become confluent around the mouth. The eruption, which had previously worsened upon treatment with topical and oral corticosteroids, resolved with a 6-week course of azithromycin. **C** Periocular dermatitis with multiple fine papules and pustules superimposed on a pink plaque. *B, Courtesy, Julie V Schaffer, MD. C, Courtesy, Ronald P Rapini, MD.*

in the same stage of development rather than larger crops of papules and pustules in varying stages of development – and the distribution – perioral rather than centrofacial – usually indicate the correct diagnosis (Fig. 37.11). In addition, papules may be superimposed on or admixed with thin plaques that can resemble a nonspecific dermatitis. Sometimes the papules have a granulomatous component. These patients may or may not have a history of topical or inhaled corticosteroid usage. Affected individuals often describe an intolerance of sunlight, cosmetic applications and/or hot water. Systemic antibiotics (tetracycline, doxycycline, minocycline, erythromycin, azithromycin) are prescribed for 4 to 6 weeks. Topical corticosteroid therapy should be discontinued. Unlike rosacea, clearance is not usually followed by a subsequent relapse.

- *Rosaceiform dermatitis* refers to a drug eruption caused by the application of topical calcineurin inhibitors to the face. It is characterized by facial erythema, small papules and numerous pustules. In contrast to the centrofacial eruption of papulopustular rosacea, the distribution is generally more widespread. *Demodex* mites have been found to be abundant on the facial skin of some of these patients and it may be that the immunomodulating effect of these agents facilitates their proliferation on the skin.

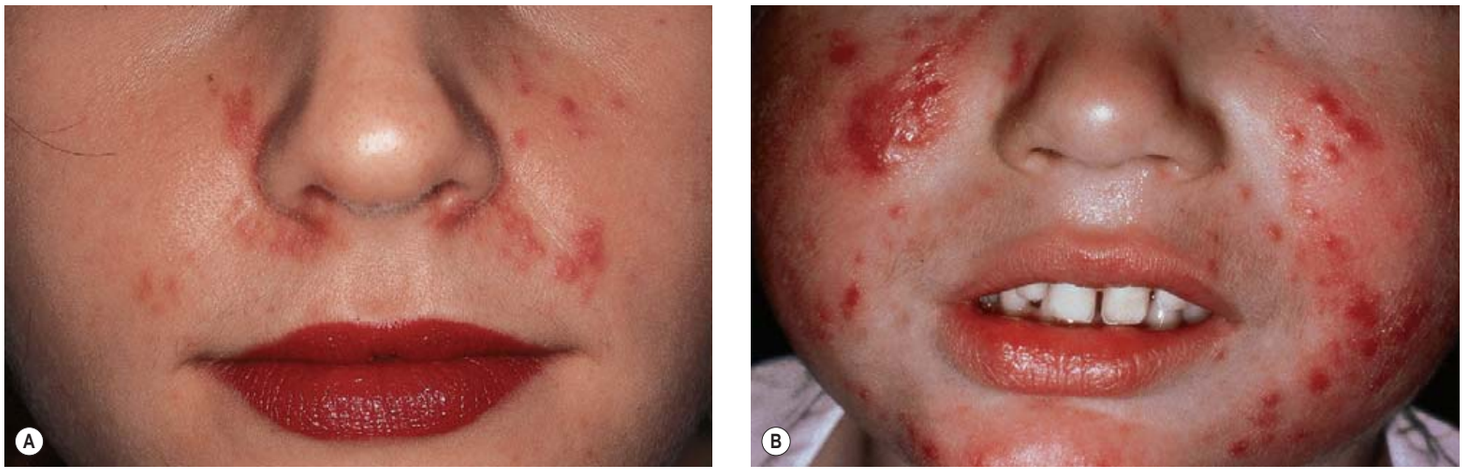


Fig. 37.12 Steroid rosacea. A Milder disease in an adult with scattered erythematous papules and papulopustules. **B** Severe disease in a child with confluence of papulopustules. *A, Courtesy, Kalman Watsky, MD.*

- *Papulopustular eruptions due to epidermal growth factor receptor (EGFR) inhibitors* are increasingly being seen (see Ch. 36). Depending upon the particular inhibitor, up to 90% of patients can develop this side effect. Although perhaps more similar in morphology to rosacea (e.g. lacks the comedones seen in acne vulgaris), inflammatory lesions are often more widespread and can involve the entire face, scalp and trunk. Pre-emptive therapy with doxycycline (100 mg twice daily) as well as topical sunscreens and moisturizers can lead to a reduction in severity. The eruption has been attributed to the importance of EGFR signalling in the skin[31]. Patients with this rosaceiform eruption have also been shown to have an increased density of *Demodex folliculorum*[32].
- *Steroid-induced rosacea* presents with erythema, papules, pustules and sometimes telangiectasias and atrophy due to repeated applications of potent topical corticosteroid preparations to the face (Fig. 37.12). Again, *Demodex* mites are present in high numbers. Reducing the strength of the topical corticosteroid application rather than its abrupt discontinuation is advisable in order to avoid a rebound flare. Systemic antibiotics (tetracycline, doxycycline or minocycline) are usually required for up to 6 weeks to allow the skin to settle.
- *Pityriasis folliculorum* is a poorly recognized disorder that primarily affects young to middle-aged women. These patients rarely, if ever, allow water to contact the skin of their face and continually apply moisturizing creams and cosmetic preparations. The predominant feature is a roughened, whitish, scaling skin surface (referred to as "frosty") superimposed on a background of faint erythema plus scattered fine papules and pustules; the lesions are not limited to the central portion of the face. Often the patient complains of burning or stinging sensations. Gentle scraping of the skin surface with a glass slide reveals the presence of multiple dead and some live *Demodex* mites. Application of a topical sulfur preparation or permethrin 5% cream at night for up to 2 weeks is effective when combined with resumption of facial washing. Complaints of skin irritation (especially during the initial phases) may limit the patient's compliance with these measures and gentle persuasion to persist with treatment is required.
- *Haber's syndrome* is a rare familial genodermatosis characterized by early-onset facial erythema, verrucous papules, truncal keratotic lesions and pitted atrophic scars. Some authors group this disorder with Dowling-Degos disease and reticulate acropigmentation of Kitamura.

REFERENCES

1. Jansen T, Plewig G, Kligman AM. Diagnosis and treatment of rosacea fulminans. Dermatology. 1994;188:251–4.
2. Wilkin J, Dahl M, Detmar M, et al. Standard classification of rosacea: report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. J Am Acad Dermatol. 2002;46:584–7.
3. Powell FC. Rosacea: Diagnosis and Management. New York: Informa Healthcare, 2009.
4. Berg M, Liden S. An epidemiological study of rosacea. Acta Derm Venereol. 1989;69:419–23
5. McAleer MA, Fitzpatrick P, Powell FC. Papulopustular rosacea: prevalence and relationship to photodamage. J Am Acad Dermatol. 2010;63:33–9.
6. Yano K, Kadoya K, Kajiya K, et al. Ultraviolet B irradiation of human skin induces an angiogenic switch that is mediated by upregulation of vascular endothelial growth factor and by downregulation of thrombospondin-1. Br J Dermatol. 2005;152: 115–21.
7. Wlaschek M, Briviba K, Stricklin GP, et al. Singlet oxygen may mediate the ultraviolet A-induced synthesis of interstitial collagenase. J Invest Dermatol. 1995;104:194–8.
8. Powell FC. The histopathology of rosacea: "where's the beef?" Dermatology. 2004;209:173–4.
9. Powell FC. Rosacea and the pilosebaceous follicle. Cutis. 2004;74(3 Suppl):9–12, 32–4.
10. Yamasaki K, Di Nardo A, Barden A, et al. Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea. Nat Med. 2007;13:975–80.
11. Yamakasaki K, Gallo RL. The molecular pathology of rosacea. J Dermatol Sci. 2009;55:77–81.
12. Guzman-Sanchez DA, Ishiuji Y, Patel T, et al. Enhanced blood flow and sensitivity to noxious heat stimuli in papulopustular rosacea. J Am Acad Dermatol. 2007;57:800–5.
13. Gomaa AH, Yaar M, Eyada MM, Bhawan J. Lymphangiogenesis and angiogenesis in non-phymatous rosacea. J Cutan Pathol. 2007;34: 748–53.
14. Lonne-Rahm SB, Fischer T, Berg M. Stinging and rosacea. Acta Derm Venereol (Stockh). 1999;79:460–1.
15. Dirshka T, Tronnier H, Folster-Holst R. Epithelial barrier function and atopic diathesis in rosacea and perioral dermatitis. Br J Dermatol. 2004;150:1136–41.
16. Dahl MV. Pathogenesis of rosacea. Adv Dermatol. 2001;17:29–45.
17. Roosterman D, Goerge T, Schneider SW, et al. Neuronal control of skin function: the skin as a neuroimmunoendocrine organ. Physiol Rev. 2006;86:1309–79.
18. Bonnar E, Eustace P, Powell FC. The *Demodex* mite population in rosacea. J Am Acad Dermatol. 1993;28: 443–8.
19. Forton F, Seys B. Density of *Demodex folliculorum* in rosacea: a case-control study using a standardised skin surface biopsy. Br J Dermatol. 1993;128:650–9.
20. Georgala S, Katoulis AC, Kylafis GD, et al. Increased density of *Demodex folliculorum* and evidence of delayed hypersensitivity reaction in subjects with papulopustular rosacea. J Eur Acad Dermatol Venereol. 2001;15:441–4.
21. Lacey N, Delaney S, Kavanagh K, Powell FC. Mite-related bacterial antigens stimulate inflammatory cells in rosacea. Br J Dermatol. 2007;157:474–81.
22. Lacey N, Ní Raghallaigh S, Powell FC. *Demodex* mites – commensals, parasites or mutualistic organisms? Dermatology. 2011;222:128–30.
23. Powell FC. Rosacea. N Engl J Med. 2005;352:793–803.
24. Roberts JO, Ward CM. Rhinophyma. J R Soc Med. 1985;78:678–81.
25. Shanler SD, Ondo AL. Successful treatment of the erythema and flushing of rosacea using a topically applied selective α1-adrenergic receptor agonist, oxymetazoline. Arch Dermatol. 2007;143:1369–71.
26. van Zuuren EJ, Kramer S, Carter B, et al. Interventions for rosacea. Cochrane Database Syst Rev. 2011;(3):CD003262.
27. Wilkin J, Dahl M, Detmar M, et al. Standard grading system for rosacea: report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. J Am Acad Dermatol. 2004;50:907–12.
28. Pelle MT, Crawford GH, James WD. Rosacea: II. Therapy. J Am Acad Dermatol. 2004;51:499–512.
29. Del Rosso JQ, Baum EW. Comprehensive medical management of rosacea: an interim study report and literature review. J Clin Aesthet Dermatol. 2008;1:20–5.
30. Wohlrab J, Lueftl M, Marsch WC. Persistent erythema and edema of the midthird and upper aspect of the face (morbus morbihan): evidence of hidden immunologic contact urticaria and impaired lymphatic drainage. J Am Acad Dermatol. 2005;52:595–602.
31. Lacouture ME. Mechanisms of cutaneous toxicities to EGFR inhibitors. Nat Rev Cancer. 2006;6:803–12.
32. Gerber PA, Kukova G, Buhren BA, Homey B. Density of *Demodex folliculorum* in patients receiving epidermal growth factor receptor inhibitors. Dermatology. 2011;222:144–7.

This page intentionally left blank

Folliculitis and Other Follicular Disorders

38

Amy McMichael, Ashley R Curtis, Daniela Guzman-Sanchez and A Paul Kelly

Chapter Contents

Superficial folliculitis 571
Disorders of follicular keratinization 577
Deep folliculitis 579
Trichostasis spinulosa 585
Folliculodystrophy of immunosuppression 585

Key features

- Follicular pustules, often arising on an erythematous base
- Favors areas with terminal hairs, such as the scalp and beard, as well as the upper trunk, buttocks and lower extremities
- Bacterial culture of pustular contents most commonly reveals normal flora, followed by *Staphylococcus aureus*
- Treatment depends on the particular type of folliculitis

INTRODUCTION

This chapter will review both superficial and deep forms of folliculitis as well as disorders of follicular keratinization and the follicular occlusion tetrad (acne conglobata, hidradenitis suppurativa, dissecting cellulitis, and pilonidal sinus). Examples of superficial forms of folliculitis include those due to *Staphylococcus aureus* or *Pseudomonas aeruginosa* infections, whereas acne keloidalis and pseudofolliculitis barbae are examples of deep forms. The disorders of follicular keratinization represent a varied group of dermatoses that have in common prominent keratotic follicular plugs. Some of these disorders are reviewed in other chapters, e.g. lichen planopilaris, pityriasis rubra pilaris and keratosis pilaris, while others are discussed here, e.g. lichen spinulosus and erythromelanosis follicularis faciei. Lastly, there are inflammatory disorders that can have a follicular predilection such as GVHD or, in darkly pigmented skin, papular eczema and pityriasis rosea.

SUPERFICIAL FOLLICULITIS

Synonym: ■ Impetigo of Bockhart

Introduction

Folliculitis is a very common disorder and is characterized by follicular pustules. Microbial cultures may fail to identify a pathogen, but, of the infectious etiologies, *Staphylococcus aureus* is the most common. Folliculitis, however, can be due to a wide range of microorganisms (Fig. 38.1).

Clinical features

Follicular pustules are usually accompanied by an erythematous rim (Fig. 38.2). Lesions may be pruritic, especially those on the occipital scalp, or even tender or painful. Occasionally, when there is more widespread involvement, patients can complain of generalized pruritus, a condition sometimes referred to as "itching folliculitis"[1].

Folliculitis occurs most commonly in the head and neck region (especially the scalp and beard area; Fig. 38.3), upper trunk, buttocks and legs, as well as in the axillae and groin. It favors areas that are occluded and/or have terminal hairs. In addition, shaving (e.g. pubic hair) and occlusion can exacerbate folliculitis. If no pustules are present, follicular-based erythematous papules or a superimposed collarette of scale serve as clues to the diagnosis[1].

Pathology

A moderately intense follicular infiltrate of lymphocytes, neutrophils and macrophages is seen, with extension of the neutrophils into the

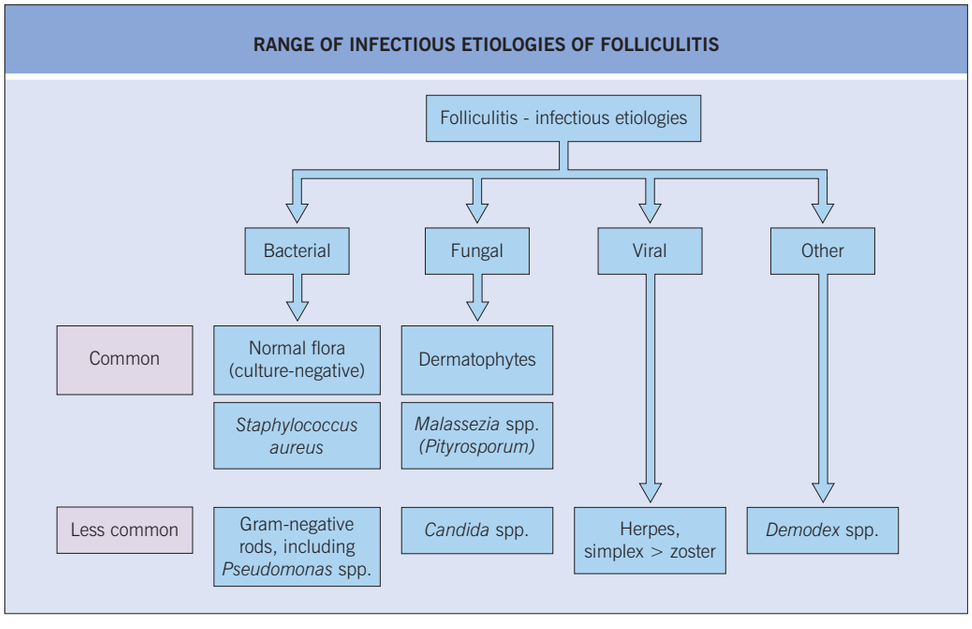


Fig. 38.1 Range of infectious etiologies of folliculitis. Non-infectious causes that need to be considered include eosinophilic folliculitis, drug-induced folliculitis and irritant folliculitis. Edematous lesions of folliculitis are most suggestive of eosinophilic folliculitis, *Demodex* folliculitis and *Pseudomonas* "hot tub" folliculitis. *Courtesy, Jean L Bolognia, MD.*

Fig. 38.2 Folliculitis (culture-negative). Follicular pustules with an erythematous rim are present on the upper back. The differential diagnosis is primarily folliculitis due to *Staphylococcus aureus* and acne.

Fig. 38.3 Folliculitis of the beard area due to *Staphylococcus aureus.* Discrete papulopustules are seen posteriorly. Centrally, there is deeper involvement with plaque formation (sycosis barbae).

follicular epithelium and follicular canal aggregating variably to form an abscess. Late-stage changes include follicular rupture and a granulomatous response. Tissue Gram stain and stains for fungi may reveal pathogenic organisms. Occasionally, cytopathic changes due to herpes simplex viral infection may be seen within the follicular epithelium (see Ch. 80) or multiple *Demodex* organisms within the follicular canal in demodicidosis (see Fig. 38.5D).

Differential diagnosis

The differential diagnosis includes the entities outlined in Table 38.1 as well as acne vulgaris, pseudofolliculitis barbae and, occasionally, rosacea. Microscopic examination of follicular contents may provide a clue to the type of folliculitis as well as microbial cultures and histologic examination. In hospitalized patients who are confined to bed, folliculitis may develop predominantly on the posterior trunk and thus needs to be distinguished from other disorders exacerbated by occlusion including Grover's disease, miliaria rubra and cutaneous candidiasis.

Treatment

The treatment chosen depends upon the culture results and severity (see Chs 74 & 127). For patients whose cultures fail to demonstrate a pathogenic microbe, the treatments, as in acne, include topical benzoyl peroxide, topical antibiotics (e.g. clindamycin) and oral antibiotics (e.g. tetracycline or doxycycline), with the anti-inflammatory properties of these antibiotics probably playing a role. This should be combined with an attempt to reduce overhydration of the skin, occlusion and irritation[1].

Eosinophilic Folliculitis

Three major forms of eosinophilic folliculitis have been described – eosinophilic pustular folliculitis (Ofuji's disease), AIDS (or immunosuppression)-associated eosinophilic folliculitis, and eosinophilic pustular folliculitis in infancy.

Eosinophilic pustular folliculitis

Synonym: ■ Ofuji's disease

Key features

- Follicular papulopustules as well as erythematous patches and plaques with superimposed coalescent pustules; central clearing leads to figurate lesions
- Most commonly involves the face, followed by the upper extremities and trunk
- Moderate to severe pruritus is a frequent symptom
- Recurrent crops of lesions that involute over 7–10 days
- Peripheral blood eosinophilia is also seen
- Histologically, eosinophils predominate around and within the follicular epithelium

Introduction

Eosinophilic pustular folliculitis is characterized by recurrent episodes of eruptive, intensely pruritic, follicular papulopustules. It typically affects "acne-prone" areas of the body such as the face, back and extensor surface of the arms[2]. To date, this disorder has not been associated with systemic disease.

History

In 1965, Ise and Ofuji[3] were the first to report a patient who had repeated episodes of follicular pustules on the face and back with peripheral blood eosinophilia. Five years later, Ofuji et al.[4] described three additional patients and proposed the name "eosinophilic pustular folliculitis" for this new clinical entity.

Epidemiology

Eosinophilic pustular folliculitis is a relatively rare entity, with most of the reported cases emanating from Japan. The majority of patients are adults and the average age of onset is 30 years[2]. The ratio of men to women is approximately 5:1. There have been occasional reports of eosinophilic pustular folliculitis in children, often with clinical features similar to the infantile form (see below).

Pathogenesis

The etiology and pathogenesis of eosinophilic pustular folliculitis is unknown. Perhaps tryptase-positive, chymase-negative mast cells play a role.

Clinical features

Recurrent crops of intensely pruritic, grouped, follicular pustules and papulopustules develop in a somewhat explosive fashion. In addition, there may be erythematous patches and plaques with superimposed coalescent pustules; central clearing and centrifugal extension produce annular and serpiginous lesions. Typically, areas with "sebaceous" follicles, such as the face, back and extensor surface of the arms, are affected. However, the digits, palms and soles may be involved, proving that not all lesions are follicular. Lesions last approximately 7–10 days. Spontaneous involution followed by relapses (on average every 3–4 weeks) is common. The patients have no accompanying systemic symptoms.

Pathology

Involved follicles may show spongiosis, with exocytosis of lymphocytes and eosinophils into the follicular epithelium. These findings can

LESS COMMON FORMS OF FOLLICULITIS		
Etiology/risk factors	**Clinical features**	**Therapy**
IRRITANT FOLLICULITIS		
Usually occurs following the application of topical medications (e.g. tar preparations), ointments Exacerbated by application in a direction opposite that of hair growth	Follicular pustules in the sites of application or exposure to irritant Favors areas with terminal hairs	• Discontinue inciting topical agent • Apply medications in the same direction as hair growth • Topical mid-potency corticosteroid lotion
GRAM-NEGATIVE FOLLICULITIS		
Due to *Klebsiella*, *Enterobacter* and *Proteus* spp. Usually seen in patients with acne vulgaris receiving long-term antibiotic therapy	Pustules in the facial T-zone and in a perinasal distribution Adult men with oily skin	• Topical: gentamicin, benzoyl peroxide • Systemic: quinolones (e.g. ciprofloxacin) • If severe or recurrent: isotretinoin, 0.5–1 mg/kg/day for up to 16 weeks
Hot tub folliculitis due to *Pseudomonas aeruginosa* in the setting of use of a hot tub/whirlpool 12–48 hours prior to onset	Edematous, pink to red follicular papules and pustules, primarily on the trunk (Fig. 38.4) Often pruritic and resolves spontaneously in immunocompetent host May be serious illness in immunocompromised host	• Generally self-limited; can use antibacterial soap • If severe or immunocompromised host: ciprofloxacin, 500 mg po twice daily for 7–14 days • Water in hot tub, whirlpool or swimming pool must be maintained with chlorine (0.4–1.0 ppm, pH 7.2–7.4) and changed every 6–8 weeks to lower organic carbon level
DERMATOPHYTE FOLLICULITIS		
Tinea barbae due to *Trichophyton mentagrophytes* var. *mentagrophytes* or *T. verrucosum* classically occurs in male farm workers	Inflammatory papules and pustules in the beard more often than the mustache areas, with crusting and loosened hairs that can be removed without pain	• Topical antifungals (may be ineffective) • Micronized or ultramicronized griseofulvin, 500–1000 mg/day or 500–700 mg/day po, respectively, for 4–6 weeks • Terbinafine, 250 mg/day po for 2–3 weeks • Itraconazole, 200 mg po twice daily for 1 week per month, for 2 pulses
Majocchi's granuloma, usually due to *T. rubrum*, characteristically develops in women who shave their legs	Follicular pustules and follicular papules or nodules (Fig. 38.5A), most often located on the lower legs Pustules at edges of tinea cruris or corporis	
***PITYROSPORUM* FOLLICULITIS**		
Typically occurs in young adults, with aggravating factors including warm weather, occlusion and excessive sebum production May also develop in association with antibiotic therapy (especially tetracyclines) or iatrogenic immunosuppression (e.g. organ transplant recipients)	Pruritic follicular papules and occasionally pustules, primarily on the back, chest and shoulders Central white–yellow color often represents compact keratin rather than pus A KOH preparation of follicular contents reveals abundant yeast forms	• Topical: antifungals, selenium sulfide shampoo, 50% propylene glycol in water • Systemic: fluconazole 100–200 mg/day for 3 weeks; itraconazole 200 mg/day for 1–3 weeks
***CANDIDA* FOLLICULITIS**		
Primarily in diabetics	Pruritic satellite pustules surrounding areas of intertriginous candidiasis Facial lesions may mimic tinea barbae or acne rosacea	• Prevent skin-to-skin contact in intertriginous areas • If possible, discontinue antibiotics and/or corticosteroid therapy • Mild to moderate disease: topical antifungals • Recalcitrant or severe disease: fluconazole 100 mg daily for 1 week then every other day for 1 month
HERPES SIMPLEX FOLLICULITIS		
Herpetic sycosis is usually seen in men with a history of recurrent localized facial herpes simplex infection who shave with a blade razor Widespread or unusual presentations of herpes simplex folliculitis may be seen in HIV-infected or otherwise immunosuppressed individuals (Fig. 38.5B)	Rapid development of individual and grouped follicular pustules and vesicles on an erythematous base in the beard area A Tzanck smear or biopsy reveals multinucleated giant cells Direct immunofluorescent antibody (DFA) assay+	• Acyclovir 200 mg po 5 times per day for 5–10 days • Famciclovir 500 mg po three times per day for 5–10 days • Valacyclovir 500 mg po three times per day for 5–10 days
***DEMODEX* FOLLICULITIS (DEMODICIDOSIS)**		
May be associated with immune suppression	Erythematous follicular papules and pustules on the face, often with a background of diffuse erythema (Fig. 38.5C) Skin scrapings reveal numerous *Demodex* mites (Fig. 38.5E)	• Topical: 5% permethrin cream • Systemic: single dose of ivermectin 200 microg/kg po
DRUG-INDUCED FOLLICULITIS (ACNEIFORM ERUPTION)		
Most common in acne-prone patients and age groups Corticosteroids, androgenic hormones, EGFRI, iodides, bromides, lithium, isoniazid and anticonvulsants Can develop within 2 weeks of starting the offending agent, but the risk is proportional to the dose and duration of therapy	Acute eruption of monomorphic erythematous follicular papules and pustules on the trunk, shoulders and upper arms Unlike acne vulgaris, comedones are rarely present	• Discontinue the offending drug, if possible • Topical: benzoyl peroxide, clindamycin, erythromycin, retinoids • Systemic: tetracycline, doxycycline, minocycline
ACTINIC FOLLICULITIS		
Seasonal Follows initial summer sun exposure	Development of follicular pustules on the upper trunk and arms 24–30 hours after first sun exposure of the summer Lesions spare the face and are not pruritic	• Sun avoidance; sunscreens will not prevent lesion formation • Topical mid-potency corticosteroids • Isotretinoin 0.35–0.5 mg/kg/day for 3–6 months

Table 38.1 Less common forms of folliculitis. EGFRI, epidermal growth factor receptor inhibitor.

Fig. 38.4 ***Pseudomonas*** **"hot tub" folliculitis. A, B** Edematous follicular papules on the flank that begin to develop 2–3 days following the use of a hot tub. The number and size can vary. *B, Courtesy, Kalman Watsky, MD.*

extend from the sebaceous gland and its duct up to and including the infundibular zone. A dermal infiltrate of lymphocytes and eosinophils may also be present. Micropustular aggregation develops, followed by the hallmark finding, infundibular eosinophilic pustules[5]. Secondary follicular mucinosis is sometimes seen.

Differential diagnosis

Clinically, some of the lesions may resemble other forms of superficial folliculitis (see previous section). However, the explosive crops, annular plaques with central clearing, intense pruritus, peripheral blood eosinophilia, and histologic findings enable differentiation from clinically similar entities.

Treatment

To date, potential treatments are based upon small case series or case reports. Topical antipruritics, oral antihistamines, and topical corticosteroids or tacrolimus ointment can be prescribed for the associated pruritus. Open wet dressings may provide some relief. First-line treatment for eosinophilic pustular folliculitis is oral indomethacin (50 mg/day). Second-line therapies include UVB phototherapy, oral minocycline (100 mg twice daily), oral dapsone (100 to 200 mg/day for ≥2 weeks), systemic corticosteroids and colchicine (0.6 mg twice daily).

AIDS-associated eosinophilic folliculitis

Synonym: ■ Immunosuppression-associated eosinophilic folliculitis

Key features

- Pruritic follicular papules that favor the face, scalp and upper trunk in the setting of HIV infection or other immunosuppressed states
- Usually occurs in HIV-infected patients whose CD4 count is <300 cells/mm^3
- Histologically, lesions are characterized by spongiosis and exocytosis of eosinophils and lymphocytes into the follicular epithelium
- Clinical improvement occurs with elevation of the CD4 count via antiretroviral therapy

Introduction

A pruritic papular eruption with histologic features that are similar to eosinophilic pustular folliculitis (Ofuji's disease) can develop in HIV-infected patients, many of whom fulfill the criteria for AIDS. Eosinophilic folliculitis has also been observed in patients with lymphoma, chronic lymphocytic leukemia, acute myelogenous leukemia and myeloproliferative disorders, as well as those who have undergone allogeneic hematopoietic stem cell transplantation; hence, the use of the term immunosuppression-associated eosinophilic folliculitis. However, in comparison to Ofuji's disease, there are neither large coalescent pustules nor figurate lesions and the individual lesions are more persistent.

History

AIDS-associated eosinophilic folliculitis was first described in 1986 as a pruritic papular dermatosis occurring in HIV-infected individuals[6].

Epidemiology

The disorder is more prevalent in adult men, but this probably reflects the relative proportion of this group amongst the population with AIDS. The possibility of *Demodex* mites triggering an immune reaction in advanced HIV infection has been raised[7], as has a possible association with the use of foscarnet. The development of eosinophilic folliculitis correlates with a low CD4 count (in particular <300/mm^3), and clinical improvement has been observed following antiretroviral-induced increases in CD4 counts. However, in one study of 57 patients, eosinophilic folliculitis developed within 3 to 6 months of initiating different regimens of antiretroviral therapy (that led to a modest increase in CD4 counts), lending support to the conclusion that eosinophilic folliculitis can be part of the immune reconstitution syndrome (see Ch. 78)[8].

Pathogenesis

Little is known about the exact pathogenesis of AIDS-associated eosinophilic folliculitis. However, Amerio et al.[9] found that, as in other eosinophilic diseases, a Th2 pattern can be seen. They found elevated levels of interleukin (IL)-4, IL-5, RANTES and eotaxin mRNA within lesional skin; the latter two are chemokines.

Clinical features

AIDS (or immunosuppression)-associated eosinophilic folliculitis is characterized by a chronic, pruritic, follicular papular eruption of the face, scalp and upper trunk (Fig. 38.6). HIV-infected individuals characteristically have a CD4 count <300 cells/mm^3. The papules may be slightly edematous and there may be no pustules. The associated pruritus can be intense.

Pathology

The histologic features are similar to those of Ofuji's disease (see above)[10].

Differential diagnosis

The differential diagnosis includes more common causes of folliculitis (see above) as well as the entities outlined in Table 38.1, especially *Demodex* folliculitis. Microscopic examination of follicular contents as well as performance of a biopsy may be necessary to establish the diagnosis (see Fig. 38.1). Necrotizing eosinophilic folliculitis is said to be distinguished by its association with atopy and the presence of

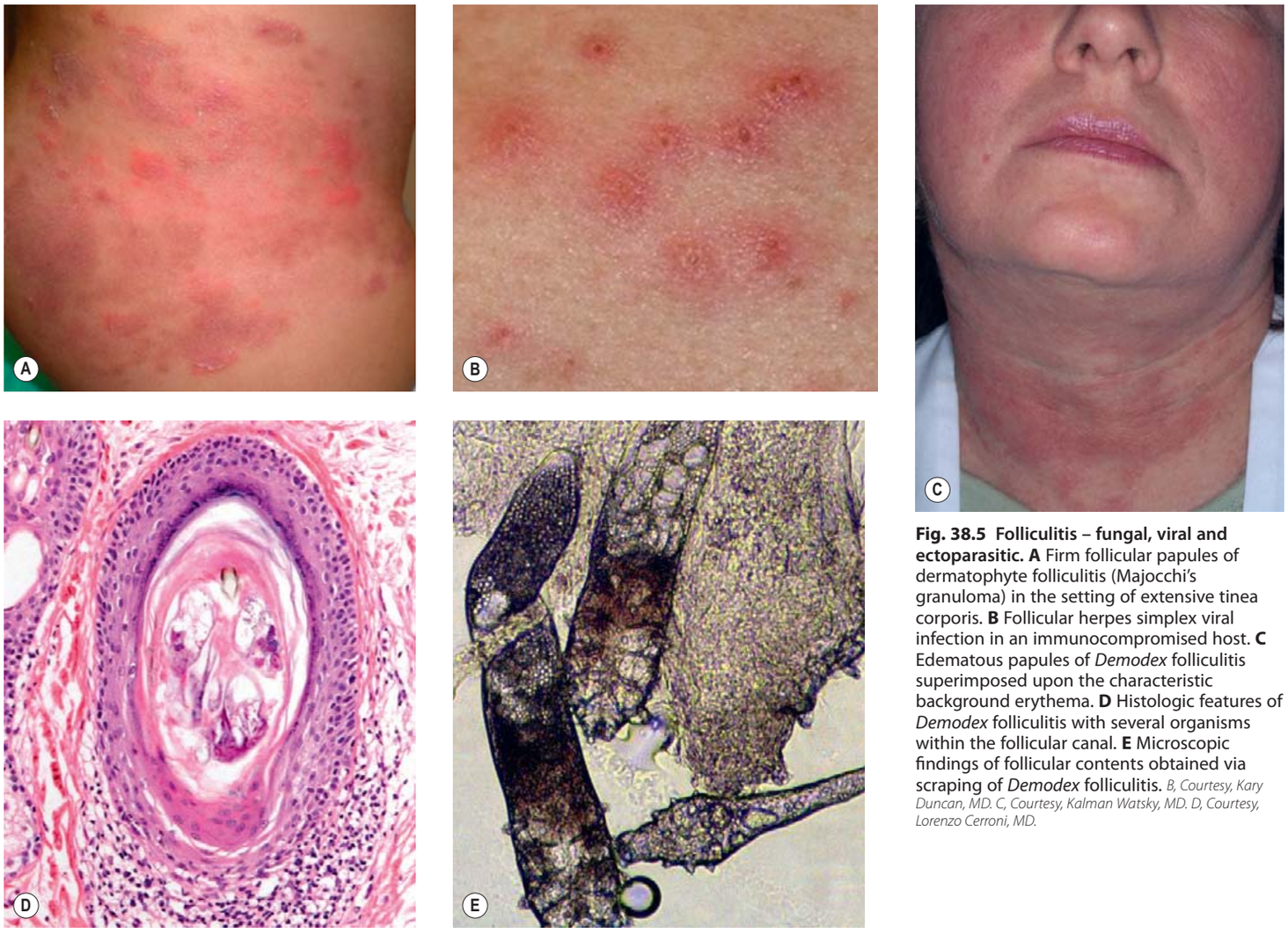


Fig. 38.5 Folliculitis – fungal, viral and ectoparasitic. A Firm follicular papules of dermatophyte folliculitis (Majocchi's granuloma) in the setting of extensive tinea corporis. **B** Follicular herpes simplex viral infection in an immunocompromised host. **C** Edematous papules of *Demodex* folliculitis superimposed upon the characteristic background erythema. **D** Histologic features of *Demodex* folliculitis with several organisms within the follicular canal. **E** Microscopic findings of follicular contents obtained via scraping of *Demodex* folliculitis. *B, Courtesy, Kary Duncan, MD. C, Courtesy, Kalman Watsky, MD. D, Courtesy, Lorenzo Cerroni, MD.*

Fig. 38.6 AIDS-associated eosinophilic folliculitis. Multiple follicular papules on the chest in the setting of AIDS. There are two punch biopsy sites. Note the edematous nature of some of the lesions.

nodules and ulceration, with evidence of follicular necrosis and eosinophilic vasculitis histologically.

Treatment

Treatment of the underlying HIV infection, with a resultant rise in the CD4 cell count, may lead to a resolution of lesions. In patients who have failed antiretroviral therapy or in other immunosuppressed hosts, oral and topical antipruritics in combination with topical corticosteroids may prove inadequate, and UVB phototherapy may be required. Additional therapies include topical permethrin, topical tacrolimus[11], oral itraconazole (100–400 mg daily), oral antibiotics, isotretinoin (0.5–1 mg/kg/day × 1–4 weeks, then taper), and interferon (β and γ).

Eosinophilic pustular folliculitis in infancy

Synonyms: ■ Infantile eosinophilic pustular folliculitis ■ Neonatal eosinophilic pustular folliculitis ■ Eosinophilic pustular folliculitis in childhood ■ Eosinophilic pustulosis (of the scalp) in childhood

Key features

- Unusual, self-limiting disorder that typically appears during early infancy
- Multiple, pruritic, follicular pustules and vesicopustules on an erythematous base
- Seen primarily on the scalp and brow region
- Secondary crusting is common
- Histologically, there is a dense dermal perifollicular infiltrate of eosinophils and lymphocytes, which may spare the sebaceous glands and outer root sheath

Introduction
Eosinophilic pustular folliculitis in infancy is a rare, self-limiting disorder of unknown etiology that occurs during infancy (see Ch. 34). It differs from adult eosinophilic pustular folliculitis by primarily involving the scalp and by frequently developing secondary crusting.

History
In 1984, Lucky et al.[12] first described five infants with this disorder. To date, approximately 40 cases have been reported. In several patients, the eosinophilic folliculitis developed within the first 24 hours of life[13]. However, the lesions typically appear within the first few days to weeks of life. To date, one HIV-related case has been reported in an infant, with an onset at 3 months of age[14].

Epidemiology
Eosinophilic pustular folliculitis in infancy occurs primarily in children less than 1 year of age and is more common in boys. The limited number of reported cases precludes any more detailed epidemiologic analysis.

Pathogenesis
The etiology of this self-limiting disorder is unknown, and the pustules are sterile. The eosinophil clearly plays a role in this disease, and the regulation of its function is reviewed in Chapter 25. Of note, some authors have proposed that eosinophilic pustular folliculitis in infancy is better characterized as a clinicopathologic reaction pattern (with heterogeneous underlying causes such as arthropod bites and dermatophytosis) than as a specific inflammatory dermatosis.

Clinical features
Pruritic follicular-based pustules and vesicopustules with an erythematous rim appear, primarily on the scalp. Involvement of the neck, face and trunk may be seen and, occasionally, lesions develop on the extremities[12,13]. They often have an erythematous base and secondary crusting. The lesions follow a cyclical course for a period of 3 months to up to 5 years.

Pathology
Similar to Ofuji's disease, there is exocytosis of eosinophils into the epidermis in association with spongiosis and subcorneal pustules; a dense dermal perifollicular infiltrate of eosinophils, histiocytes and lymphocytes is seen[12,13]. The infiltrate may not invade the sebaceous glands or outer root sheath of the hair follicles. Peripheral blood eosinophilia is present in some patients.

Differential diagnosis
The differential diagnosis includes erythema toxicum neonatorum, transient neonatal pustular melanosis, acropustulosis of infancy, scabies (which can involve the scalp in infants), Langerhans cell histiocytosis, and the following two rare disorders: papulopustular eruption of hyper-IgE syndrome and vesiculopustular eruption of transient myeloproliferative disorder. Erythema toxicum neonatorum has almost identical histologic features, but its onset is within the first 48 hours of life and the eruption, which has a more widespread distribution pattern, usually resolves within 1 week (see Ch. 34). This natural history easily separates the two entities.

Transient neonatal pustular melanosis occurs in 4–5% of infants with darkly pigmented skin. Lesions are present at the time of birth and favor the face, neck and shins. Neutrophils are the predominant cells. The lesions of acropustulosis of infancy occur more frequently in male infants with darkly pigmented skin, and are seen most often on the hands and feet and less often on the scalp, proximal extremities and trunk. The disorder may occur during the neonatal period, but usually appears at 3–6 months of age. Lesions last 7–10 days and crops occur for months to years, usually resolving completely by the age of 3 years. Given that eosinophilic pustular folliculitis in infancy occasionally involves the extremities and has a similar natural history of cropping, some authors have suggested a relationship between the two entities.

Langerhans cell histiocytosis is a rare disorder that often has cutaneous involvement when it develops during infancy. Papules, pustules, vesicles and crusts are seen, especially on the scalp and in flexural areas. Histologic examination demonstrates the presence of $S100^+$, $CD1a^+$ Langerhans cells.

Treatment
Parents should be reassured regarding the benign, self-limited nature of the disorder. Topical corticosteroids and oral antihistamines can help to relieve pruritus during flares of the disease.

Disseminate and Recurrent Infundibulofolliculitis

Synonyms: ■ Hitch and Lund disease ■ Recurrent disseminated infundibulofolliculitis

Key features
- Seen primarily in adults with darkly pigmented skin
- Hundreds of uniform, skin-colored papules that have been likened to "goose bumps"
- Favored sites of involvement are the trunk, neck and upper extremities
- May last for months to years and can be pruritic
- Histologically, there is mild inflammation of the follicular infundibulum

The first individuals with disseminate and recurrent infundibulofolliculitis were described by Hitch and Lund in 1968[15]. Four years later, they reported an additional two cases, bringing the total to five patients; all were young adults with darkly pigmented skin. Although the lesions may resemble papular eczema, the patients do not have a history of atopy. There seems to be neither seasonal variation nor an association with systemic disease, medications, atopy or contact dermatitis.

The disease is characterized by numerous 1–2 mm, pruritic, skin-colored papules, often pierced by a hair, forming large areas of what looks like "goose bumps" (Fig. 38.7). The trunk is involved most often, followed by the neck, buttocks and arms. The lesions may last for weeks, months or years. Disseminate and recurrent infundibulofolliculitis occurs almost exclusively in individuals with darkly pigmented skin.

Although the lesions most closely resemble papular eczema (and some authors do not separate the two entities), other diseases that may be considered in the differential diagnosis are lichen nitidus and folliculitis (see above), but the follicular pattern and the lack of erythema or pustules exclude these two entities, respectively. The lack of keratotic plugs or spines within the hair follicles distinguishes this disorder from

Fig. 38.7 Disseminate and recurrent infundibulofolliculitis (of Hitch and Lund). Numerous monotonous follicular papules on the chest. *Courtesy, Jean L Bolognia, MD.*

keratosis pilaris, pityriasis rubra pilaris, lichen planopilaris, and the disorders discussed in the next section (e.g. phrynoderma). Careful examination of the primary lesions excludes the diagnosis of Darier disease.

Histologically, the principal findings are in the infundibular portion of the hair follicle. There is perifollicular edema, slight infiltration of lymphocytes with occasional neutrophils, and a slight proliferation of fibroblasts[16].

Topical corticosteroids are sometimes effective, and lactic acid preparations (12%) or 20–40% urea may be helpful. If topical medications prove unsuccessful, PUVA may be tried (three times a week for 3 weeks, followed by maintenance therapy twice a month). Vitamin A (50 000 IU twice daily) and isotretinoin (0.5 mg/kg/day for 16 weeks) have also been tried, but evidence for their efficacy is anecdotal as well.

DISORDERS OF FOLLICULAR KERATINIZATION

Although this group of dermatoses has a wide spectrum of clinical presentations, all are characterized by a prominent plug of keratin within the follicular orifice. For most of these entities, the cause of the abnormal keratinization is unknown. The dermatoses are usually distinguished on the basis of the size, extent and distribution of the keratotic lesions, as well as the presence or absence of perifollicular erythema and associated scarring. Disorders in this group that are discussed in other chapters include keratosis pilaris (Ch. 12), pityriasis rubra pilaris (Ch. 9) and lichen planopilaris (Ch. 11).

Erythromelanosis Follicularis Faciei

Synonym: ■ Erythromelanosis follicularis faciei et colli

Key features

- An uncommon disorder that involves the lateral cheeks and sometimes the lateral aspects of the neck
- Multiple pinpoint follicular papules are superimposed on a red–brown patch; the papules appear relatively hypopigmented
- May be accompanied by keratosis pilaris

Introduction

Erythromelanosis follicularis faciei was first described in 1960 by Kitamura and associates in Japanese men. Six years later, the first patient was described in the English literature by Mishima and Rudner[17]. It can begin during the second decade of life and is characterized by background erythema and hyperpigmentation as well as tiny follicular papules.

Epidemiology

Although the disorder was initially reported in Japanese men, it is now known to affect all races and both sexes[18]. However, it does favor people of Asian ancestry.

Pathogenesis

The pathogenesis is unknown.

Clinical features

On the lateral aspect of the cheeks, and sometimes the lateral aspects of the neck, there is a background of red–brown-colored skin. The latter is due to a combination of vasodilation and hyperpigmentation. However, in skin type I patients, there may be only erythema, leading to significant overlap with keratosis pilaris rubra. Numerous pinhead-sized follicular papules are present within the involved areas, and they appear relatively hypopigmented. Patients may also have keratosis pilaris of the upper outer arms, with a small rim of erythema surrounding the follicular keratotic plug (see Ch. 12).

Pathology

There is slight follicular hyperkeratosis with increased epidermal pigmentation. Diameters of the hair shafts and outer root sheaths are decreased, as is the thickness of the inner root sheath. The adnexa are often surrounded by a lymphocytic infiltrate. Both the thickness and the compactness of the horny layer are usually increased[19]. By quantitative histopathology, an increase in the percent area of superficial blood vessels was observed that correlated with visual grading of the associated erythema[20].

Differential diagnosis

The differential diagnosis of erythromelanosis follicularis faciei includes primarily keratosis pilaris rubra and a combination of melasma plus telangiectatic erythema from photodamage. However, the latter combination lacks tiny follicular papules, while keratosis pilaris rubra of the cheeks lacks hyperpigmentation and favors children (see Ch. 12).

Poikiloderma of Civatte is another entity that is sometimes confused with erythromelanosis follicularis faciei et colli. The former involves the anterolateral aspects of the neck with obvious sparing of the midsubmental region. The areas of erythema are a reflection of multiple interfollicular telangiectasias. Because the telangiectasias spare the immediate thin rim of skin around each follicle, these areas appear relatively hypopigmented. Occasionally, poikiloderma of Civatte extends onto the mandibular region.

Less often, two disorders within the spectrum of keratosis pilaris atrophicans, ulerythema ophryogenes and atrophoderma vermiculatum, may be considered (Table 38.2). Although ulerythema ophryogenes is characterized by small follicular papules, they are erythematous, usually appear during early childhood, and favor the eyebrows (Fig. 38.8). In addition, there is associated follicular atrophy and scarring alopecia of the lateral eyebrows. Atrophoderma vermiculatum affects the cheeks but presents with honeycomb scarring or a worm-eaten appearance (see Ch. 99).

Treatment

Various topical keratolytic agents have been used, including urea cream (10–20%), ammonium lactate lotion (6–12%), tretinoin cream (0.025–0.1%), adapalene (0.1–0.3%) and an ammonium lactate plus hydroquinone (4%) cream combination, but evidence for their use is anecdotal. Both salicylic acid peels (20–30%) and glycolic acid peels have been employed. When severe, limited courses of isotretinoin (0.1–1 mg/kg/day) have been tried. Laser treatment of the background erythema or hyperpigmentation may be attempted, but it requires multiple sessions.

Keratosis Pilaris Atrophicans

Keratosis pilaris atrophicans encompasses a group of disorders in which the abnormality in follicular keratinization is accompanied by atrophy and scarring alopecia. The key features of ulerythema ophryogenes, atrophoderma vermiculatum, keratosis follicularis spinulosa decalvans, and folliculitis spinulosa decalvans are outlined in Table 38.2. Treatment with keratolytics, topical retinoids, topical or intralesional corticosteroids, oral antibiotics and phototherapy has limited efficacy, but

Fig. 38.8 Ulerythema ophryogenes. Alopecia of the eyebrow admixed with tiny follicular papules. *Courtesy, Jean L Bolognia, MD.*

THE SPECTRUM OF KERATOSIS PILARIS ATROPHICANS							
Disorder	**Mode of inheritance**	**Genetic locus**	**Age at onset**	**Distribution**	**Cutaneous features**	**KP***	**Other occasional features and associations**
Keratosis pilaris atrophicans faciei (ulerythema ophryogenes)	AD	18p11.2	Infancy	Eyebrows (particularly the lateral third; see Fig. 38.8) > temples, cheeks, forehead	• Erythematous follicular papules with central keratotic plugs, eventuating in follicular atrophy • Scarring alopecia of the lateral eyebrows	+	• Associated with Noonan syndrome, cardio-facio-cutaneous syndrome, Cornelia de Lange syndrome and woolly hair
Atrophoderma vermiculatum	?AD	?	Childhood (usually 5–12 years)	Cheeks > preauricular area, upper lip	• Pitted, atrophic depressions in a reticulate pattern ("worm-eaten" or "honeycomb" appearance)†	–	• Associated with Rombo, Nicolau–Balus, Tuzun, and Braun–Falco–Marghescu syndromes (see Ch. 99)
Keratosis follicularis spinulosa decalvans (KFSD)	XR	Xp22.11–p22.12; mutations in *MBTPS2*‡	Childhood (inflammation often remits at puberty)	Face, scalp, limbs, trunk	• Erythematous follicular papules with central keratotic plugs, eventuating in follicular atrophy • Scarring alopecia of the scalp, eyebrows, and eyelashes	++	• Palmoplantar keratoderma, facial erythema • Keratitis, photophobia • Aminoaciduria
Folliculitis spinulosa decalvans	?AD	?	Puberty (onset or worsening)	Scalp	• Follicular pustules • Features of KFSD	++	• Palmoplantar keratoderma • Blepharitis, conjunctivitis, keratitis, photophobia

*Associatd keratosis pilaris (KP) on the extremities and trunk, which does not typically eventuate in atrophy.
†May be preceded by erythematous follicular papules.
‡Protein product (membrane-bound transcription factor peptidase, site 2) is required for cleavage of sterol regulatory element-binding proteins (SREBPs) and its dysfunction leads to decreased sterol responsiveness.

Table 38.2 The spectrum of keratosis pilaris atrophicans. AD, autosomal dominant; XR, X-linked recessive; +, mild to moderate; ++, severe.

combination therapy may benefit individual patients and, anecdotally, oral retinoids and intense pulsed light have been reported to lead to improvement. In later stages, dermabrasion, laser resurfacing and dermal fillers may help to improve the appearance of atrophic scarring.

Lichen Spinulosus

Synonym: ■ Keratosis spinulosa

Key features

- Clusters of multiple follicular papules, each with a keratotic spine
- Texture likened to that of a nutmeg grater
- Usually asymptomatic, arises suddenly, and enlarges over a week
- Appears most often in children and adolescents; favors the neck, extensor arms, abdomen and buttocks
- Can persist indefinitely

Introduction, history and epidemiology

Lichen spinulosus is characterized by grouped, skin-colored, keratotic follicular papules. The disorder was first described by Adamson in 1908 as a chronic superficial dermatitis within circumscribed patches in children and adolescents[21]. In one series, the average age at onset was 16 years[22].

Pathogenesis

Although several factors, such as atopy, infections and heredity, have been proposed as playing a role in lichen spinulosus, the exact etiology is unknown and most patients do not have associated systemic abnormalities. There are reports of lichen spinulosus-like lesions arising in the setting of HIV infection[23]. Additional associations reported in the literature (but possibly coincidental) include seborrheic dermatitis, a drug reaction (omeprazole), Hodgkin disease, Crohn's disease, syphilis, and an id reaction to fungal infections.

Fig. 38.9 Lichen spinulosus. Grouped, skin-colored follicular papules on the extensor surface of the arm. Central keratotic plugs can be seen.

Clinical features

Typical lesions measure 2–6 cm in diameter (Fig. 38.9) and are composed of multiple, skin-colored, keratotic follicular papules, each of which has a keratotic spine. Lichen spinulosus favors the neck, shoulders and extensor surfaces of the arms, as well as the abdomen, buttocks and popliteal fossae, and the distribution pattern is often symmetric. The face is usually spared, as are the hands and feet. Lesions often arise suddenly in crops, enlarge over a week, and then remain stationary. Idiopathic lichen spinulosus usually appears during childhood and adolescence and is asymptomatic, although in some patients the lesions are pruritic and the patches may be surrounded by faint erythema. Spinulosis of the face (tiny follicular keratotic spicules of the cheeks) may be a manifestation of lichen spinulosus.

Pathology
Histologically, lichen spinulosus most resembles keratosis pilaris.

Differential diagnosis
The differential diagnosis of lichen spinulosus includes keratosis circumscripta, follicular ichthyosis, and juvenile pityriasis rubra pilaris (especially type IV; see Ch. 9). Keratosis circumscripta, also referred to as psoriasis circumscripta with palmoplantar keratosis, is characterized by well-circumscribed lesions consisting of grouped folliculocentric papules, with or without palmoplantar hyperkeratosis. Lesions favor the nape of the neck, elbows and knees, as well as the hips, sacrum and posterior axillary folds. Onset is usually at age 3–5 years and it has been described primarily in Africans[24,25]. The pathogenesis is unknown, but it may be a variant of psoriasis[24] as the histologic findings are similar to those of plaque-type psoriasis. This entity may be of historical interest, as the most recent published report was in 1979.

Follicular ichthyosis is an unusual disorder characterized by keratotic papules with follicular plugging and prominent follicular ostia and an onset in early childhood[26]. The predominant site of involvement is the head and neck region. Lesions can also occur on the extensor surfaces of the extremities, especially the fingers, elbows and knees. *I*chthyosis *f*ollicularis with *a*trichia and *p*hotophobia (IFAP) syndrome is a rare disorder whose X-linked recessive form is allelic with keratosis follicularis spinulosa decalvans (see Table 38.2). It is characterized by widespread non-inflammatory follicular keratoses, generalized non-scarring alopecia, and photophobia. Hereditary mucoepithelial dysplasia is an autosomal dominant condition that manifests with severe keratitis, erythema of the oral mucosa (characterized by a paucity of desmosomes and dyskeratotic cells with internalized gap junctions) and psoriasiform perineal plaques, as well as widespread follicular keratoses and non-scarring alopecia similar to IFAP.

Less often, lichen spinulosus may be confused with keratosis pilaris (has perifollicular erythema and lacks discrete clusters), lichen planopilaris or phrynoderma (see below). Facial spines can also be seen in pityriasis rubra pilaris (especially that which occurs in HIV-infected individuals with preceding severe acne and/or hidradenitis suppurativa), folliculodystrophy of immunosuppression (trichodysplasia spinulosa), demodicosis, follicular mucinosis, and in patients with multiple myeloma. Some authors group lichen spinulosus in the setting of HIV infection under the term "HIV-associated follicular syndrome". Lastly, widespread follicular plugging has been reported as a side effect of systemic lithium therapy[27].

Treatment
Topical therapies such as 12% lactic acid, 20%–40% urea and 6% salicylic acid may improve the texture. Glycolic acid and salicylic acid peels have also been reported to be beneficial.

Phrynoderma
Phrynoderma, which means "toad skin", is seen primarily in Asia and Africa and is rare in high-income countries, except in settings such as intestinal malabsorption[28], anorexia nervosa or fad diets (see Ch. 51). Phrynoderma is seen most often in association with vitamin A deficiency, but some patients may have measurable deficiencies in other vitamins and/or proven malnutrition[29,30]. Follicular papules of various sizes with conical keratotic plugs favor the extensor surfaces of the extremities (see Fig. 51.7), but may then spread to involve other locations. The face is the last site to become involved, and the hands and feet are spared. Associated systemic findings (e.g. ocular, CNS), histologic features, diagnosis via measurement of serum vitamin A levels, and treatment are discussed in Chapter 51.

DEEP FOLLICULITIS
The major forms of deep folliculitis are furuncles (see Ch. 74), sycosis (barbae, lupoid, mycotic; Table 38.3), pseudofolliculitis barbae, acne keloidalis and hidradenitis suppurativa. The lesions are firm, tender erythematous papules or nodules that measure up to 2 cm in diameter. Deep lesions should never be manipulated (i.e. squeezed) by the patient, because this may cause bacteremia or seeding of the heart valves (endocarditis), brain (abscess) or bones (osteomyelitis).

FORMS OF SYCOSIS

Type	Characteristics
Barbae	• Bacterial folliculitis of the beard and/or mustache areas, usually caused by *Staphylococcus aureus* • Deep-seated, edematous, perifollicular papules and pustules that may coalesce to form plaques studded with pustules and crusts • Subacute to chronic course with frequent relapses
Lupoid	• Scarring form of deep folliculitis, typically affecting the beard area; may be caused by *S. aureus* (although cultures often fail to reveal pathogenic organisms) • Peripheral extension of perifollicular papules and pustules with central atrophic scarring/cicatricial alopecia; granulomatous inflammation can lead to an appearance reminiscent of lupus vulgaris • Chronic course, refractory to treatment
Mycotic	• Dermatophyte folliculitis of the beard area (most often the chin), usually caused by zoophilic organisms • Inflammatory perifollicular papules and pustules coalesce to form nodules and plaques with purulent discharge from patulous follicles, crusting and loose hairs that can be painlessly removed (Fig. 38.10)
Herpetic	• See Table 38.1

Table 38.3 Forms of sycosis.

Fig. 38.10 Mycotic sycosis. Firm plaque of the upper cutaneous lip studded with multiple pustules due to a zoophilic dermatophyte. *Courtesy, Kalman Watsky, MD.*

Pseudofolliculitis Barbae

Synonyms: ■ Shave bumps ■ Razor bumps ■ Barber's itch ■ Folliculitis barbae traumatica ■ Scarring pseudofolliculitis of the beard ■ Chronic sycosis barbae ■ Ingrown hairs

Key features
- A common chronic disorder occurring most often in the beard area of men who shave
- It favors those of African descent with darkly pigmented skin and tightly curled hair
- The etiology is tightly curved hairs curving back into the skin when shaved
- Lesions range from inflammatory papules and pustules to firm papules and keloidal scars
- Although the only way to cure the disease is to stop shaving, shaving techniques can be optimized

Introduction

Pseudofolliculitis barbae is a common chronic inflammatory disorder occurring most often in the beard area of men who shave, especially in men with darkly pigmented skin and tightly curled hair. It may also develop in other shaved areas, in women, and in any racial group.

Epidemiology

Pseudofolliculitis barbae primarily affects men of African descent with darkly pigmented skin. The prevalence ranges from 45% to 80%, depending upon the particular study. Men of all races may develop pseudofolliculitis barbae within the beard area, but it is less common and is usually mild in those with lightly pigmented skin and straight hair. Women who shave may also develop pseudofolliculitis barbae, especially in the groin.

Pathogenesis

The disorder is thought to be caused by intrafollicular and transfollicular penetration of tightly curled, coarse hairs within the beard area. When shaved, tightly curled hair is usually cut at an oblique angle, creating a sharp tip at the distal end of the hair that enables it to penetrate into the skin 1–2 mm from where the hair exits the follicle (Fig. 38.11). Thus, transfollicular penetration occurs when the cut hair grows out of the follicle normally but penetrates the skin as it grows in a spiral fashion back toward the skin surface. Once the hair penetrates the dermis, an inflammatory reaction ensues.

More recently, the presence of a single nucleotide polymorphism in the 1A α-helical subdomain of the hair follicle companion layer-specific keratin K6hf (K75) was reported to be an additional genetic risk factor for pseudofolliculitis barbae[31].

Clinical features

In men who shave, inflammatory papules appear in the beard area and on the anterolateral neck. However, the mustache area, which may also be shaved daily, does not develop pseudofolliculitis barbae. Pustules and even abscesses may be seen. Hyperpigmentation of the resultant firm papules can occur (Fig. 38.12), as can hypertrophic scars and keloids, especially in longstanding disease. Chronic lesions may cause the hair to create grooves in the skin; the anterior neck and submandibular areas are particularly prone to this complication. Once the grooves have formed, shaving becomes extremely difficult.

Pathology

The sharp cut end of the hair initially causes an invagination in the epidermis, which is accompanied by inflammation and frequently by an intralesional microabscess. As the hair penetrates the epidermis, a heavy mixed inflammatory cell infiltrate develops as a reaction to the downgrowth of the epidermis in an attempt to ensheathe the hair[32]. This is accompanied by abscess formation within the pseudofollicle and a foreign body giant cell reaction at the tip of the invading hair[32]. Naked hair shafts surrounded by acute and chronic inflammation or primarily fibrotic dermis are commonly observed.

Differential diagnosis

Facial acne vulgaris is similar in appearance, but differs by having comedones as well as papules and pustules. Histologically, the foreign body reaction needs to be differentiated from cutaneous sarcoidosis.

Treatment

Before therapy is initiated, the patient should be given a candid explanation regarding the cause of pseudofolliculitis barbae. It should be stressed that the only way to cure the disease is to stop shaving, but there are several treatments that may control the process. In those with severe disease, a hiatus of several months without shaving is recommended. Once inflammatory lesions have completely cleared, patients resume shaving; therefore they need to be given advice on shaving methods (Table 38.4).

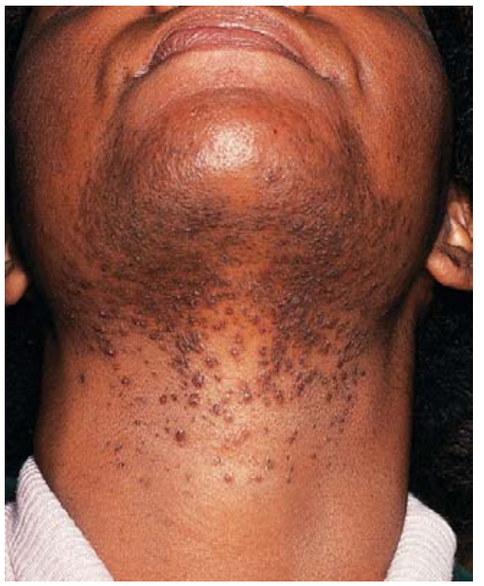


Fig. 38.12 Pseudofolliculitis barbae. Multiple firm hyperpigmented papules on the lower face and neck (beard distribution).

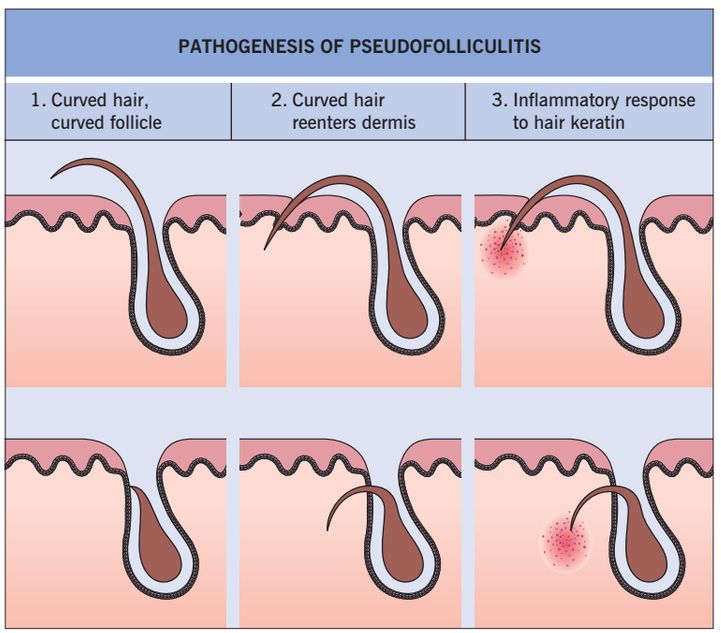


Fig. 38.11 Pathogenesis of pseudofolliculitis. *Courtesy, MA Abdallah, MD.*

ADVICE ON SHAVING METHODS FOR PATIENTS WITH PSEUDOFOLLICULITIS BARBAE

IMPORTANT POINTS

- Do not pull the skin taut
- Do not shave against the grain/direction of hair growth
- Use a sharp razor each time, preferably multi-blade
- Take short strokes (with the grain of the hair) and do not shave over the same areas more than twice

METHOD

1. Remove pre-existing hairs with electric clippers, leaving approximately 1–2 mm of stubble
2. Wash area with non-abrasive acne soap and rough wash-cloth; in areas with "ingrown hairs", gentle massaging with a soft toothbrush may help
3. Rinse area with water, then compress face with warm tap water for several minutes
4. Using shaving cream of your choice, massage moderate amount of lather on area to be shaved (do not allow lather to dry; if it does, reapply it)
5. Use a sharp blade (whichever type seems to cut best but not too close) and shave with the grain of the hair using short even strokes with minimal tension (and no more than twice over one area); in hard-to-shave areas, you may need to shave against the grain
6. After shaving, rinse with tap water and then apply the most soothing aftershave preparation of your choice. If significant burning or itching ensues, a topical corticosteroid cream or lotion (1–2.5% hydrocortisone) can be used as an alternative aftershave preparation

Table 38.4 Advice on shaving methods for patients with pseudofolliculitis barbae.

THERAPEUTIC APPROACH TO PSEUDOFOLLICULITIS BARBAE	
Shaving	• Mild to moderate cases: continue shaving daily, but follow guidelines in Table 38.4 • Severe cases: consider discontinuing shaving, with no resumption of shaving until all inflammatory lesions have cleared and all "ingrown hairs" are released; during this period, the patient can trim his beard to a minimum length of 0.5 cm using scissors or electric clippers
Compresses and release of ingrowing hairs	• Warm tap water, saline or Burow's solution (aluminum acetate) compresses for 10 minutes three times daily to soothe lesions, remove any crusts, reduce drainage secondary to inflammation and/or excoriations, and soften the epidermis to allow easier release of "ingrown hairs"
Topical therapy	• Low-potency topical corticosteroid lotion and/or topical clindamycin should be applied after compresses and freeing of embedded hairs
Secondary bacterial infection	• Appropriate systemic antibiotic should be prescribed, based upon bacterial cultures
Recalcitrant disease	• Prednisone (45–60 mg) or its equivalent every morning for 7–10 days may be necessary • Topical eflornithine cream twice daily may be helpful* • Laser hair removal (utilizing appropriate laser for skin color) with goal of permanent hair reduction (see Ch. 137)
*Based upon case series.	

Table 38.5 Therapeutic approach to pseudofolliculitis barbae.

Except for very mild cases, pseudofolliculitis barbae requires medical intervention during its acute phase, when it is often painful and/or pruritic. Although antibiotics, topical or systemic, are not particularly beneficial (unless secondary infection is present), they may provide some anti-inflammatory effect. The recommended therapeutic approach is outlined in Table 38.5.

Adjunct treatments such as topical tretinoin solution, gel or cream, α-hydroxy acids or benzoyl peroxide (e.g. Benzashave®) may be used in patients with mild to moderate pseudofolliculitis barbae. However, those with severe and chronic disease usually have only slight improvement. These products are thought to work by alleviating hyperkeratosis as well as "toughening" the skin. Initially, tretinoin is applied every other night, and the patient should be told to expect some stinging, burning and peeling. Depending on the individual's response, the concentration and frequency of application may be increased or decreased. Of note, the shaving methods outlined in Table 38.4 still need to be followed.

A more recently developed therapy for pseudofolliculitis barbae is the use of hair removal lasers. For example, the Nd:YAG laser can be used with a long pulse duration and continuous contact cooling, even in patients with skin types V or VI, as can a modified 810 nm superlong-pulse diode laser. Treatment is given at 3- to 4-week intervals for two to three sessions. Of course, care must be taken when selecting the energy settings, especially in patients with deeply pigmented skin[33]. Additional therapeutic options are eflornithine cream[34] and chemical depilatories. With the latter, the beard should be trimmed prior to application of the depilatory and, to avoid irritation, treatments should be limited to, at most, every second or third day.

Acne Keloidalis

Synonyms: ■ Acne keloidalis nuchae ■ Folliculitis keloidis nuchae ■ Nuchal keloid acne ■ Folliculitis keloidalis ■ Dermatitis papillaris capillitii (historical)

Key features

- Begins as a chronic folliculitis of the posterior neck and occipital scalp
- With time, keloidal papules and plaques develop
- Vast majority of affected individuals are men of African descent

Fig. 38.13 Acne keloidalis. An admixture of follicular pustules, crusted papules and firm fibrotic hyperpigmented papules on the posterior neck and occipital scalp. There is associated alopecia.

Introduction

Acne keloidalis refers to the presence of keloid-like papules and plaques on the occipital scalp and posterior neck. This disorder occurs almost exclusively in men of African descent. The patients usually develop a chronic folliculitis and perifolliculitis of the posterior scalp and neck initially, which then heals with keloid-like papules. Over time, these papules may coalesce to form one or several large plaques, which gradually enlarge over a period of years. The lesions are usually pruritic and may also be painful and cosmetically disfiguring. The sooner the condition is treated, the less likely it will become disfiguring.

History

Acne keloidalis was first described by Kaposi in 1869 as "dermatitis papularis capillitii". However, the disorder had been previously recognized in Hebra's clinic and referred to as "sycosis frambroisiformis". Three years after Kaposi's publication (1872), Bazin named the condition "acne keloidalis". Since then, this disorder has been described in the literature under a variety of names (see Synonyms above).

Epidemiology

In the US, acne keloidalis occurs most often in young African-American men, followed in frequency by Hispanics, Asians and, least often, Caucasians. It accounts for less than 1% of dermatologic disorders seen in African-Americans. Acne keloidalis may occur in women, but the male:female ratio is at least 20:1. Development prior to puberty and after the age of 50 years is extremely rare.

Pathogenesis

The cause of acne keloidalis is unknown. In one study, two-thirds of affected patients had concomitant seborrheic dermatitis and one-third had concomitant pseudofolliculitis barbae. No specific genetic factor has been identified. Shaving or cutting short, tightly curled hair (as is found in many individuals with darkly pigmented skin) and then having the new hair curve back and penetrate the skin may be the precipitating event (see Fig. 38.11). Other frequently incriminated etiologies are constant irritation from shirt collars, chronic low-grade folliculitis, and an autoimmune process.

Clinical features

Acne keloidalis often begins as a posterior scalp and/or neck folliculitis, followed by the development of firm, dome-shaped follicular papules that are 2–4 mm in diameter and may or may not be pruritic (Fig. 38.13). Pustules may also be present within the same area but are usually short-lived because they are traumatized when the hair is combed or brushed and they are easily ruptured by scratching. In contrast to acne vulgaris, comedones are not present.

As the disease progresses, more hard papules develop and slowly enlarge. Some coalesce and form keloid-like plaques, which are often

Fig. 38.14 Acne keloidalis. Keloidal papulonodules and a large plaque of the occipital scalp, associated with scarring alopecia. Note the tufts of hair at the superior border of the scar.

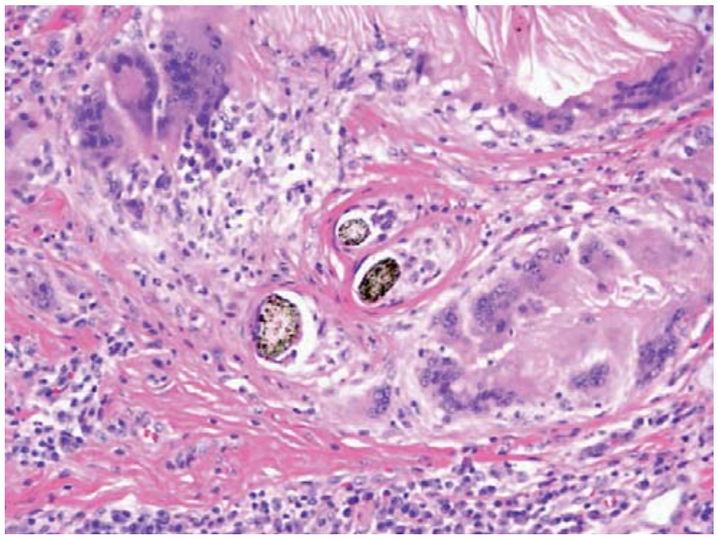


Fig. 38.15 Acne keloidalis – histologic features. Naked hair shafts in the dermis with perifollicular fibrosis and surrounding granulomatous inflammation with multinucleated giant cells.

arranged in a band-like distribution near the posterior hairline (Fig. 38.14). The plaques are usually only a few centimeters in diameter but may grow to more than 10 cm. Even when only papules are present, a large portion of the posterior scalp may be involved.

When the area of involvement is significant, there is usually patchy alopecia or complete hair loss. In occasional patients, the scarring process may extend onto the vertex and/or parietal scalp. Often, the upper borders of large lesions are fringed with tufted hairs that resemble the hair on a doll's head, as in other scarring alopecias such as folliculitis decalvans (see Ch. 69). Occasionally, subcutaneous abscesses with draining sinuses may be present, and they may emit a malodorous discharge.

Pathology

Inflammation begins in the upper one-third of the hair follicle. Descriptions of the initial infiltrate vary from it being composed of neutrophils and lymphocytes to predominantly plasma cells[35]. Sebaceous glands are markedly diminished or absent in all stages of the disease[35]. In the more advanced lesions, hair follicles are disrupted, and fragments of naked hair shafts surrounded by granulomatous inflammation may be seen (Fig. 38.15). Dermal fibrosis is also present at this stage, and the collagen fibers resemble those seen in scar tissue rather than those in keloids. Sometimes, a single follicle may show several different stages of inflammation when viewed throughout its length. The lower portion of the follicle, including the matrix, is usually spared until later in the disease process. Actual keloid formation can be seen in late stages.

Differential diagnosis

Clinically, the initial lesions may resemble more common forms of folliculitis (see above). Although keloids and hypertrophic scars secondary to trauma enter the differential diagnosis, the number, shape and distribution of the lesions usually point to the correct diagnosis. On the neck there may be overlap with pseudofolliculitis barbae, and when there is more extensive or severe scalp involvement, folliculitis decalvans and dissecting cellulitis may enter the differential diagnosis.

Treatment

The first line of defense is prevention. Those who have acne keloidalis should not wear any kind of head-dress or head gear that causes mechanical irritation of the posterior hairline. In addition, they should neither edge their posterior hairline with a razor nor wear shirts or sweaters that irritate the posterior scalp and neck.

The sooner therapy is initiated, the less likely the patient is to develop large lesions. Twice-daily application of a tretinoin gel and a mid- to high-potency corticosteroid gel may be sufficient to relieve all symptoms and flatten existing lesions. Topical or systemic antibiotics, as for acne vulgaris, may clear the folliculitis but do not soften or clear the secondary keloidal lesions. Triamcinolone acetonide (5–20 mg/ml) can be injected into the keloidal papules, but if they persist, one author (PK) prefers to do a punch excision with a hair transplant trephine followed by either a primary closure or healing by second intention (Table 38.6). The punch must extend below the level of the hair follicle to be successful. In addition, a 50:50 mixture of 2% lidocaine (with epinephrine) and triamcinolone acetonide (40 mg/ml) can be used for local anesthesia in order to help prevent recurrence. If the patient sleeps on his or her back or has a short neck, then the lesions can be closed with silk sutures to prevent stiff suture ends from piercing the skin. One week after suture removal, the excision sites are injected with triamcinolone acetonide (40 mg/ml), and this can be performed three more times at 3-week intervals. A bacterial culture should be obtained from any site with oozing or drainage, followed by treatment with the appropriate systemic antibiotic.

For plaques 1.0–1.5 cm in vertical diameter (i.e. superior to inferior border), excision with primary closure is the treatment of choice. Some

THERAPEUTIC OPTIONS FOR ACNE KELOIDALIS	
Non-inflamed papules and plaques	Mixture of tretinoin gel and potent corticosteroid gel twice daily
Inflamed lesions with pustules	Bacterial culture and appropriate systemic antibiotic or a course of oral isotretinoin
Small papules	Punch excision to below level of hair follicles
	Close primarily or allow to heal secondarily
	Laser hair removal for permanent hair reduction
Plaques ≤1.5 cm in vertical diameter	Excise and close primarily
Larger plaques and nodules (>1.5 cm in vertical diameter)	Excise with horizontal ellipse
	Extend excision below posterior hairline and include fascia or deep subcutaneous tissue
	Allow to heal by second intention
	Do not inject corticosteroids into postoperative site
	Laser excision and cryosurgery are sometimes successful
Postoperative care	Topical imiquimod daily for 6 weeks (8 weeks every other day if irritation)
Maintenance	Tretinoin–corticosteroid gel mixture, intermittent intralesional corticosteroids and/or oral or topical antibiotics (when needed)

Table 38.6 Therapeutic options for acne keloidalis.

Fig. 38.16 Pilonidal sinus and abscess formation at the superior portion of the intergluteal cleft. *Courtesy, Kalman Watsky, MD.*

claim that daily topical imiquimod, starting immediately postoperatively and continuing for 6–8 weeks, may prevent recurrence (see Ch. 128). If the imiquimod causes irritation, then it should be discontinued for a few days and subsequently applied every other day for a total of 8 weeks. While controversial, radiation therapy following excision of keloids is discussed in Chapter 98.

Lesions >1.5 cm in vertical diameter should not be closed primarily, because the postoperative scar usually spreads to the width of the excisional defect, producing a non-hair-bearing flat scar. For these lesions, the area of acne keloidalis is excised to the level of the fascia or deep subcutaneous tissue and left to heal secondarily. The excision must include the posterior hairline within the surgical ellipse[36]. It will take 8–12 weeks for the defect to close. Corticosteroids are not injected into these sites because they may prevent wound contracture.

Some patients have been successfully treated with CO_2 laser excision, but it requires postoperative triamcinolone injections (10–40 mg/ml) every 3 weeks for four sessions, starting 2 weeks after the laser procedure. As with pseudofolliculitis barbae, the diode laser has been reported (case series) as being helpful in clearing papular lesions[37]. Cryotherapy is also sometimes useful, but it requires freezing for 30–40 seconds. In individuals with darkly pigmented skin, freezing for more than 25 seconds may cause hypopigmentation (which can last 12–18 weeks) or even depigmentation.

Following surgical procedures, intralesional or potent topical corticosteroids (e.g. gel, foam), alone[38] or in combination with oral or topical antibiotics, can be used, as well as a tretinoin–corticosteroid gel mixture (see Table 38.6). Based upon case reports, a course of oral isotretinoin may prove helpful in recalcitrant inflammatory cases of acne keloidalis.

Follicular Occlusion Tetrad

In 1956, Pillsbury, Shelley and Kligman coined the term "follicular occlusion triad" for the common association of acne conglobata (see Ch. 36), hidradenitis suppurativa, and dissecting cellulitis of the scalp (see Ch. 69). They proposed that the pathologic event unique to each disease was follicular hyperkeratinization[39]. In 1975, a fourth component, pilonidal sinus (further discussion of which is beyond the scope of this text; Fig. 38.16), was added, creating the follicular tetrad. The term "acne inversa" is sometimes used as an all-inclusive term for this group of associated disorders. Systemic retinoids and corticosteroids have been successful in treating all four of these disorders, but specific therapies for each entity are usually more successful.

Hidradenitis Suppurativa

Synonyms: ■ Acne inversa ■ Verneuil's disease ■ Pyoderma fistulans significa

Key features

- Poral occlusion of the pilosebaceous units within intertriginous zones, especially the axillary, anogenital and inframammary regions
- Secondary inflammation of the apocrine glands
- Inflamed nodules and sterile abscesses are followed by sinus tracts, fistulae and hypertrophic scars

Introduction

Hidradenitis suppurativa is a cutaneous disorder that targets apocrine gland-bearing skin sites, in particular the axillae and anogenital region. It is a chronic condition characterized by recurrent "boils" and draining sinus tracts with subsequent scarring.

History

Hidradenitis suppurativa was first conceptualized as a specific disease and then named by Verneuil in 1854. He described its association with sweat glands. Although apocrine gland dysfunction was initially considered to be the underlying cause, it is now known that occlusion of the follicular infundibula followed by rupture of the follicle is the inciting event.

Epidemiology

Hidradenitis suppurativa starts at or soon after puberty. Children are not affected unless they have precocious puberty, and women are affected three times as often as men. In Denmark, 4% of the young adult population and 1% of the general population were said to be affected. In England, the incidence is 1 : 600[40]. People of African descent have a higher incidence than those of European descent.

Pathogenesis

Currently, hidradenitis suppurativa is thought to represent an inflammatory disorder originating from the hair follicle. Primary "apocrinitis" has been observed in only 5% of the patients with the disease[41]. Rupture of the follicle allows introduction of its contents, including keratin and bacteria, into the surrounding dermis[42]. This excites a vigorous chemotactic response and abscess formation. Epithelial strands are generated, possibly from ruptured follicular epithelia, and form sinus tracts[42].

Despite the apparent strong clinical influence of sex hormones, most patients have normal androgen profiles[43]. In addition, apocrine glands (unlike sebaceous glands) are not androgen-sensitive[43]. Although a familial form of hidradenitis suppurativa with autosomal dominant inheritance has been described[44], further studies found no significant associations with specific human leukocyte antigen (HLA)-A, -B or -DR subtypes[45]. Lithium therapy has been reported to exacerbate hidradenitis suppurativa and a role for tumor necrosis factor-α has been suggested by the therapeutic response to TNF-α inhibitors in some studies[45a] as well as increased serum levels of TNF-α in patients with hidradenitis suppurativa[46]. Increased serum levels of interleukin (IL)-2, which correlate with disease activity, have also been observed[47].

Clinical features

Initially, inflammatory nodules and sterile abscesses develop in the axillae, groin, perianal and/or inframammary areas (Fig. 38.17A). These lesions may be very tender and extremely painful. Over time, sinus tracts (Fig. 38.17B) and hypertrophic scars (Fig. 38.17C) may develop. This is accompanied by chronic drainage, leading to a marked degree of frustration, embarrassment, self-consciousness and depression, especially when the discharge is malodorous. The discharged fluid is often a mixture of serous exudate, blood and pus, in varying proportions. There are grading systems for assessment of severity and response to treatment (Table 38.7).

Complications of hidradenitis suppurativa include anemia, secondary amyloidosis, lymphedema, and fistulae to the urethra, bladder, peritoneum and rectum. Other complications include hypoproteinemia, nephrotic syndrome and SAPHO syndrome (see Ch. 26). Squamous cell carcinoma, sometimes with metastasis or humoral hypercalcemia, is an occasional complication of this chronic scarring disease[48,49].

Fig. 38.17 Hidradenitis suppurativa. A Papulopustules, nodules, sinus tracts and scarring in the axilla (Hurley stage II). **B** Superficial sinus tracts that serve as a clue to the diagnosis, even in the absence of active disease. **C** Severe disease (Hurley stage III) with inflammatory nodules, hypertrophic scarring, draining fistulae and sinus tract formation of the perianal region, buttocks and upper thighs. This is the type of patient who is at risk for the development of squamous cell carcinoma and secondary amyloidosis. *A, Courtesy, Kalman Watsky, MD.*

HIDRADENITIS SUPPURATIVA – GRADING SYSTEMS AND TREATMENT APPROACH
HURLEY STAGING SYSTEM
Stage I – one or more abscesses with no sinus tract or scar formation Stage II – one or more widely separated recurrent abscesses, with sinus tract and scar formation Stage III – multiple interconnected tracts and abscesses throughout an affected region
SARTORIUS GRADING SYSTEM[51]
• Anatomical region involved: axilla, groin, gluteal or other region or inframammary region (left and/or right) – 3 points per region involved • Number and scores of lesions: abscesses, nodules, fistulae, scars (points per lesion of all regions involved) – nodules = 2; fistulae = 4; scars = 1; others = 1 • The longest distance between two relevant lesions*, i.e. nodules and fistulae, in each region – <5 cm = 2; <10 cm = 4; >10 cm = 8 • Are all lesions clearly separated by normal skin? In each region – yes 0/no 6
THERAPEUTIC APPROACH
• Weight reduction (if overweight) and smoking cessation • Reduce friction and moisture (loose-fitting clothing and undergarments, absorbent powders, topical aluminum chloride) • Antiseptic soaps and topical antibiotics (e.g. clindamycin may reduce *Staphylococcus aureus* colonization and secondary infection) • Intranasal mupirocin (5-day course for nasal carriers of *S. aureus*) • Intralesional triamcinolone (5 mg/ml) into early inflammatory lesions • Oral antibiotics, alone or in combination (doxycycline, minocycline, clindamycin, rifampin, dapsone, trimethoprim–sulfamethoxazole)[52] • Hormonal therapy (ethinyl estradiol plus cyproterone acetate, finasteride) • Systemic retinoids (disappointing results with isotretinoin, but acitretin has anecdotally been reported as beneficial) • Immunosuppressive and anti-inflammatory agents (prednisone†, mycophenolate mofetil, cyclosporine[53], azathioprine, TNF-α inhibitors[54]) • Surgical excision, followed by primary closure or grafting • CO_2 laser stripping and second intention healing[55]; Nd:YAG laser • Other (botulinum toxin A[56], photodynamic therapy[57])
*Or size if only one lesion. †Disease often flares with taper.

Table 38.7 Hidradenitis suppurativa – grading systems and treatment approach. *From Sartorius K, Lapins J, Emtestam L, Jemec GBE. Suggestions for uniform outcome variables when reporting treatment effects in hidradenitis suppurativa. Br J Dermatol. 2003;149:211–13.*

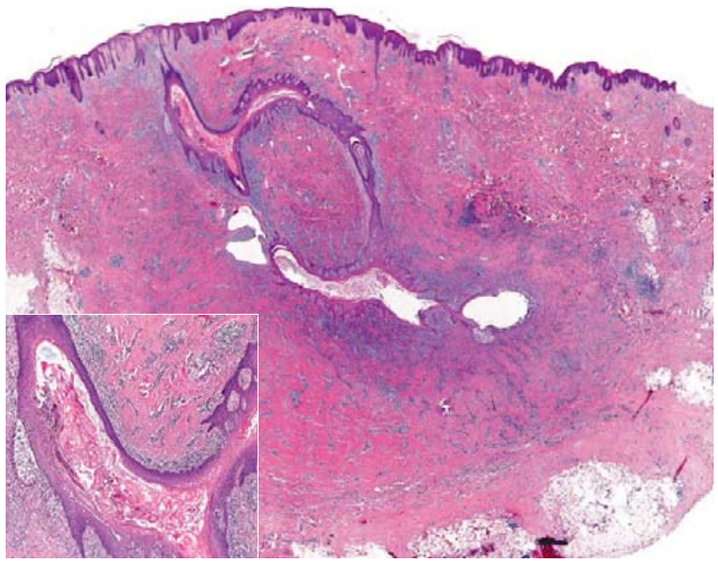


Fig. 38.18 Hidradenitis suppurativa – histologic features. A keratin-filled sinus tract (insert) is seen within the dermis, extending into the subcutaneous fat. It is surrounded by marked fibrosis and mixed inflammatory infiltrates. *Courtesy, Lorenzo Cerroni, MD.*

Pathology

There is a heavy mixed inflammatory cell infiltrate in the lower half of the dermis, usually with extension into the subcutis. Abscesses are present in active cases, and they may connect to the skin surface via a sinus tract[50]. The sinus tracts contain inflammatory cells and keratinous debris (Fig. 38.18). Granulation tissue with inflammatory cells and occasional foreign body giant cells is present in up to 25% of biopsy specimens[50]. In chronic disease, there may be extensive fibrosis with destruction of pilosebaceous follicles and sweat glands.

Differential diagnosis

Initially, hidradenitis suppurativa may resemble staphylococcal furunculosis, but the latter usually has central pointing or ulceration and usually does not form sinus tracts. Crohn's disease, granuloma inguinale, mycetoma and tuberculosis may resemble hidradenitis suppurativa. Elephantiasis nostras verrucosa secondary to recurrent

streptococcal infections accompanied by lymphangitis may cause distortion of the external genitalia and resemble hidradenitis suppurativa.

Treatment

A variety of therapeutic interventions have been described[45a]. Many are successful some of the time, but none are successful all of the time. A therapeutic approach to the patient with hidradenitis suppurativa is outlined in Table 38.7. The clinician must consider the degree of severity and response to previous treatments.

TRICHOSTASIS SPINULOSA

Trichostasis spinulosa is a common but often underdiagnosed follicular disorder of unknown etiology. Asymptomatic comedo-like lesions that contain keratin and multiple vellus hairs are seen, primarily on the face (especially its mid to lower central portion; see Fig. 36.17B) and the trunk, in particular the interscapular region. Histologically, there is follicular hyperkeratosis and multiple vellus hairs in the follicular canal enveloped within a keratotic sheath. Patients seek treatment because of the cosmetic appearance, but options are limited; the latter include keratolytics, depilatories, topical tretinoin and lasers (e.g. long-pulsed alexandrite, pulsed diode, fractional resurfacing)[58].

FOLLICULODYSTROPHY OF IMMUNOSUPPRESSION

Synonym: ■ Trichodysplasia spinulosa ■ Viral-associated trichodysplasia of immunosuppression ■ Viral-associated trichodysplasia spinulosa ■ Cyclosporine-induced follicular dystrophy

Follicular dystrophy of immunosuppression was first described in 1995 in the context of drug-induced immunosuppression in organ transplant recipients, hence its original association with cyclosporine[59]. The etiology of this entity is not known, but a viral etiology has been proposed due to the detection of intranuclear viral particles by electron microscopy[60]. Skin-colored to pink follicular papules and follicular spines favor the central face and they may be accompanied by loss of the eyebrows and eyelashes; extrafacial lesions with associated alopecia may also develop. Histologically, enlarged anagen-type follicles have dilated lumina due to marked hyperkeratosis, with some authors suggesting that the entire machinery of the follicular bulb is devoted to the manufacture of inner root sheath-like keratin[60]. The spicules can be identified by surface microscopy or light microscopy (spicule pull-test)[61]. If immunosuppressive therapy cannot be reduced, topical cidofovir or tazarotene gel or oral valganciclovir (900 mg once or twice daily) may be tried.

REFERENCES

1. Luelmo-Aguilar J, Santandreu MS. Folliculitis: recognition and management. Am J Clin Dermatol. 2004;5:301–10.
2. Ota T, Hata Y, Tanikawa A, et al. Eosinophilic pustular folliculitis (Ofuji's disease): indomethacin as a first choice of treatment. Clin Exp Dermatol. 2001;26:179–81.
3. Ise S, Ofuji S. Subcorneal pustular dermatosis: a follicular variant? Arch Dermatol. 1965;92:169–71.
4. Ofuji S, Ogino A, Horio T, et al. Eosinophilic pustular folliculitis. Acta Derm Venereol. 1970;50:195–203.
5. Ofuji S. Eosinophilic pustular folliculitis. Dermatologica. 1987;174:53–6.
6. Soeprono FF, Schimella RA. Eosinophilic pustular folliculitis in patients with acquired immunodeficiency syndrome. Report of three cases. J Am Acad Dermatol. 1986;14:1020–2.
7. Farina MC, Requena L, Sarasa JL, et al. Spinulosis of the face as a manifestation of demodicidosis. Br J Dermatol. 1998;138:901–3.
8. Rajendran PM, Doler JC, Heaphy MR Jr. Eosinophilic folliculitis: before and after the introduction of antiretroviral therapy. Arch Dermatol. 2005;141:1227–31.
9. Amerio P, Verdolini R, Proietto G, et al. Role of Th2 cytokines, RANTES and eotaxin, in AIDS-associated eosinophilic folliculitis. Acta Dermatol Venereol. 2001;81:92–5.
10. Rosenthal D, LeBoit PE, Klumpp L, Berger TG. Human immunodeficiency virus-associated eosinophilic folliculitis. Arch Dermatol. 1991;127:206–9.
11. Toutus-Trellu L, Abraham SH, Pechere M, et al. Topical tacrolimus for effective treatment of eosinophilic folliculitis associated with human immunodeficiency virus infection. Arch Dermatol. 2005;141:1203–8.
12. Lucky AW, Esterly NB, Heskel N, et al. Eosinophilic pustular folliculitis in infancy. Pediatr Dermatol. 1984;1:202–6.
13. Buckley DA, Munn SE, Higgins EM. Neonatal eosinophilic pustular folliculitis. Clin Exp Dermatol. 2001;26:251–5.
14. Ramdial PD, Morar N, Dlova NC, Aboabaker J. HIV-associated eosinophilic folliculitis in an infant. Am J Dermatopathol. 1999;21:241–6.
15. Hitch JM, Lund HZ. Disseminate and recurrent infundibulo-folliculitis: report of a case. Arch Dermatol. 1968;97:432–5.
16. Owen WR, Wood C. Disseminate and recurrent infundibulofolliculitis. Arch Dermatol. 1979;115:174–5.
17. Mishima Y, Rudner E. Erythromelanosis follicularis faciei et colli. Dermatologica. 1966;132:269–87.
18. Hodak E, Ingber A, Alcalay JT, David M. Erythromelanosis follicularis faciei in women. J Am Acad Dermatol. 1996;34:714.
19. Sodaify M, Baghestani S, Handjani F, Sotoodeh H. Erythromelanosis follicularis faciei et colli. Int J Dermatol. 1994;33:643–4.
20. Kim MG, Hong SJ, Son SJ, et al. Quantitative histopathologic findings of erythromelanosis follicularis faciei et colli. J Cutan Pathol. 2001;28:160–4.
21. Adamson HG. On a form of chronic superficial dermatitis in circumscribed patches with symmetrical distribution occurring in children. Br J Dermatol. 1908;20:109–22.
22. Friedman SJ. Lichen spinulosus. Clinicopathologic review of thirty five cases. J Am Acad Dermatol. 1990;22:261–4.
23. Cohen SJ, Dicken CH. Generalized lichen spinulosus in an HIV-positive man. J Am Acad Dermatol. 1991;25:116–18.
24. Soyinka F, Laja AD. Keratosis circumscripta. A distinct dermatological entity or variant of psoriasis? Dermatologica. 1978;156:341–50.
25. Shrank AB. Keratosis circumscripta. Arch Dermatol. 1966;93:408–10.
26. Hazell M, Marks R. Follicular ichthyosis. Br J Dermatol. 1984;111:101–9.
27. Rifkin A, Kurtin SB, Quitkin F, Klein DF. Lithium-induced folliculitis. Am J Psychiatry. 1973;130:1018–19.
28. Wechsler HL. Vitamin A deficiency following small-bowel bypass surgery for obesity. Arch Dermatol. 1979;115:73–5.
29. Maronn M, Allen DM, Esterly NB. Phrynoderma: a manifestation of vitamin A deficiency? … The rest of the story. Pediatr Dermatol. 2005;22:60–3.
30. Bleasal NR, Stapleton KM, Lee MS, Sullivan J. Vitamin A deficiency phrynoderma: due to malabsorption and inadequate diet. J Am Acad Dermatol. 1999;41:322–4.
31. Winter H, Schissel D, Parry DAD, et al. An unusual Ala12Thr polymorphism in the 1A alpha-helical segment of the companion layer-specific keratin K6hf: evidence for a risk factor in the etiology of the common hair disorder pseudofolliculitis barbae. J Invest Dermatol. 2004;122:652–7.
32. Lucas S. Bacterial diseases. In: Elder D, Elenitsas R, Johnson B, Murphy G (eds). Lever's Histopathology of the Skin. Philadelphia: Lippincott Williams & Wilkins, 2005:465–78.
33. Smith EP, Winstanley D, Ross EV. Modified super-long pulse 810nm diode laser in the treatment of pseudofolliculitis barbae in skin types V and VI. Dermatol Surg. 2005;31:297–301.
34. Garcia-Zuazaga J. Pseudofolliculitis barbae: review and update on new treatment modalities. Mil Med. 2003;168:561–4.
35. Herzberg AJ, Dinehart SM, Kerns BJ, Pollack SV. Acne keloidalis. Transverse microscopy, immunohistochemistry, and electron microscopy. Am J Dermatopathol. 1990;12:109–21.
36. Glenn MJ, Bennett RG, Kelly AP. Acne keloidalis nuchae: treatment with excision and second intention healing. J Am Acad Dermatol. 1995;33:243–6.
37. Shah GK. Efficacy of diode laser for treating acne keloidalis nuchae. Indian J Dermatol Venereol Leprol. 2005;71:31–4.
38. Callender VD, Young CM, Haverstock CL, et al. An open label study of clobetasol propionate 0.05% and betamethasone valerate 0.12% foams in the treatment of mild to moderate acne keloidalis. Cutis. 2005;75:317–21.
39. Pillsbury DM, Shelley WB, Kligman AM. Dermatology. Philadelphia: WB Saunders, 1956.
40. Harrison BJ, Mudge M, Hughes LE. The prevalence of hidradenitis in South Wales. In: Marks R, Plewig G (eds). Acne and Related Disorders. London: Martin Dunitz, 1991:365–6.
41. Jemec GBE, Hansen U. The histology of hidradenitis suppurativa. J Am Acad Dermatol. 1996;34:994–9.
42. Mortimer PS, Lunniss PJ. Hidradenitis suppurativa. J R Soc Med. 2000;93:420–2.
43. Barth JH, Kealey T. Androgen metabolism by isolated human axillary apocrine glands in hidradenitis suppurativa. Br J Dermatol. 1991;125:304–8.
44. Von Der Werth JM, Williams HC, Raeburn JA. The clinical genetics of hidradenitis suppurativa revisited. Br J Dermatol. 2000;142:947–53.
45. Lapins J, Olerup O, Emtestam L. No human leukocyte antigen-A, -B or -DR association in Swedish patients with hidradenitis suppurativa. Acta Derm Venereol. 2001;81:28–30.
45a. Jemec GBE. Hidradenitis suppurativa. N Engl J Med. 2012;366:158–64.
46. Matusiak L, Bieniek A, Szepietowski JC. Increased serum tumour necrosis factor-alpha in hidradenitis suppurativa patients: is there a basis for treatment with anti-tumour necrosis factor-alpha agents? Acta Derm Venereol. 2009;89:601–3.
47. Matusiak Ł, Bieniek A, Szepietowski JC. Soluble interleukin-2 receptor serum level is a useful marker of hidradenitis suppurativa clinical staging. Biomarkers. 2009;14:432–7.
48. Lavogiez C, Delaporte E, Darras-Vercambre S, et al. Clinicopathological study of 13 cases of squamous cell carcinoma complicating hidradenitis suppurativa. Dermatology. 2010;220:147–53.
49. Sparks MK, Kuhlman DS, Prieto A, Callen JP. Hypercalcemia in association with cutaneous squamous cell carcinoma. Occurrence as a late complication of hidradenitis suppurativa. Arch Dermatol. 1985;121:243–6.
50. Weedon D. Skin Pathology. Edinburgh: Churchill Livingstone, 1999:390.
51. Sartorius K, Lapins J, Emtestam L, Jemec GBE. Suggestions for uniform outcome variables when reporting treatment effects in hidradenitis suppurativa. Br J Dermatol. 2003;149:211–13.

52. Gener G, Canoui-Poitrine F, Revuz JE, et al. Combination therapy with clindamycin and rifampicin for hidradenitis suppurativa: a series of 116 consecutive patients. Dermatology. 2009;219:148–54.
53. Rose RF, Goodfield MJD, Clark SM. Treatment of recalcitrant hidradenitis suppurativa with oral ciclosporin. Clin Exp Dermatol. 2006;31:154–5.
54. Haslund P, Lee RA, Jemec GB. Treatment of hidradenitis suppurativa with tumour necrosis factor-alpha inhibitors. Acta Derm Venereol. 2009;89:595–600.
55. Lapins J, Marcusson JA, Entestam L. Surgical treatment of chronic hidradenitis suppurativa: CO_2 laser stripping-secondary intention technique. Br J Dermatol. 1994;131:551–6.
56. O'Reilly DJ, Pleat J, Richards A. Treatment of hidradenitis suppurativa with botulinum toxin A. Plast Reconstr Surg. 2005;116:1575–6.
57. Sotiriou E, Apalla Z, Maliamani F, Ioannides D. Treatment of recalcitrant hidradenitis suppurativa with photodynamic therapy: report of five cases. Clin Exp Dermatol. 2009;34:e235–6.
58. Manuskiatti W, Tantikun N. Treatment of trichostasis spinulosa in skin phototypes III, IV, and V with an 800-nm pulsed diode laser. Dermatol Surg. 2003;29:85–8.
59. Izakovic J, Buchner SA, Duggelin M, et al. [Hair-like hyperkeratosis in patients with kidney transplants. A new cyclosporine side-effect.] Hautarzt. 1995;46:841–6.
60. Sperling LC, Tomaszewski MM, Thomas DA. Viral-associated trichodysplasia in patients who are immunocompromised. J Am Acad Dermatol. 2004;50:318–22.
61. Lee JS-S, Frederiksen P, Kossard S. Progressive trichodysplasia spinulosa in a patient with chronic lymphocytic leukaemia in remission. Australasian J Dermatol. 2008;49:57–60.

Diseases of the Eccrine and Apocrine Sweat Glands

39

Jami L Miller

Chapter Contents

Hyperhidrosis *587*
Hypohidrosis and anhidrosis *594*
Specific diseases of the sweat gland *595*
Sweat as a predisposing influence on skin disease *598*
Apocrine sweat gland disorders *601*

Key features

- 2–5 million eccrine glands are unevenly distributed over the skin surface
- In healthy individuals, eccrine sweat is 99% water
- Sweating is a reflex sympathetic autonomic function mediated by cholinergic neurons

Sweating is an essential thermoregulatory function. There are two main mechanisms to cool the body: radiative cooling via cutaneous vasodilation and evaporative cooling via sweat. Sweat, primarily produced by the eccrine sweat glands, leads to dissipation of heat through evaporation. For the purposes of this discussion, the term "sweat" applies to eccrine glands and their secretory products unless otherwise specified.

While each individual has 2–5 million eccrine glands, none are found on the clitoris, glans penis, labia minora, external auditory canal and lips. Eccrine glands are separate from the apocrine-pilosebaceous apparatus (see Ch. 35). By dermoscopy, eccrine ductal orifices can be seen along the dermatoglyphic ridges. In healthy individuals, eccrine sweat is 99% water. The average adult can produce over 0.5 liters of sweat per hour; athletes or those acclimatized to hot environments can produce up to 3–4 liters per hour[1]. Physically fit or acclimatized persons initiate sweating earlier and conserve sodium, chloride and other electrolytes more efficiently. Thermoregulatory control is similar in men and women and diminishes only slightly with age[2].

Sweating is a reflex function controlled primarily by the sympathetic nervous system. These nerves are anatomically sympathetic but functionally cholinergic, i.e. acetylcholine, rather than norepinephrine, is the principal terminal neurotransmitter. Neural impulses for sweating (sudomotor impulses) travel from the anterior hypothalamus via the reticulospinal tracts to the appropriate level in the spinal cord, out through the rami communicantes to autonomic ganglia, and then within sympathetic cholinergic neurons to the secretory cells of the eccrine glands. Adrenergic innervation has also been demonstrated for the eccrine glands, but it is not believed to be physiologically important[3]. In addition, the sweat glands, via a direct effect on the secretory cells, respond to certain drugs (e.g. cholinergic agonists) as well as to the local application of heat.

HYPERHIDROSIS

Key features

- Excessive sweating
- Primary hyperhidrosis is the most common type, typically affecting the palms, soles and/or axillae
- Secondary hyperhidrosis is due to an underlying condition (e.g. genetic syndrome, infection, tumor) or medication and may be localized or generalized

Hyperhidrosis is estimated to affect 3% of the US population[4]. The most widely used classification system divides it into primary and secondary types. Other classification systems separate hyperhidrosis into categories based on the source of the neural impulses that drive it: cortical (emotional), hypothalamic (thermoregulatory), medullary (gustatory), spinal cord and local axon reflexes.

Primary Hyperhidrosis

Synonym: ■ Primary focal hyperhidrosis

Key features

- Main sites are volar (palms, soles) and axillary skin; the face may also be involved
- Hyperhidrosis arises from increased cortical stimulation and occurs *only* during waking hours (diurnal)
- While other hyperhidroses develop during childhood, axillary hyperhidrosis begins at or following puberty; patients are otherwise healthy
- As many as 80% of affected individuals have a family history of hyperhidrosis

Primary hyperhidrosis, the most common type of hyperhidrosis, is defined as excessive sweating in localized areas (usually the palms, soles and/or axillae) that is not associated with a systemic disorder. Men and women of all races are equally affected and Table 39.1 lists the diagnostic criteria[5]. Between 60% and 80% of patients with primary hyperhidrosis have a family history[6], with a pattern of inheritance suggesting autosomal dominant transmission with incomplete penetrance. A locus for primary palmar hyperhidrosis was mapped to chromosome 14q in three Japanese families[7].

Intense emotion or stress can elicit sweating in anyone. It occurs most often on the palms, soles or axillae and can also affect the face (Fig. 39.1), especially the forehead and the cutaneous upper lip. The post-orgasmic sweating observed with sexual activity[8] may also derive from emotional stimulation.

Clinically significant primary hyperhidrosis occurs in two major forms: volar (palmoplantar) and axillary, which can coexist[1]. However, one of the two forms usually predominates. The onset of volar hyperhidrosis is often during childhood, whereas axillary hyperhidrosis typically develops at or soon after puberty. Primary hyperhidrosis is

CRITERIA FOR THE DIAGNOSIS OF PRIMARY HYPERHIDROSIS
1. Focal, visible excess sweating
2. Present for at least 6 months
3. No apparent secondary causes
4. At least two of the following:
• Bilateral and symmetric
• Impairs activities of daily life
• At least one episode per week
• Age of onset <25 years
• Positive family history
• Stops during sleep

Table 39.1 Criteria for the diagnosis of primary hyperhidrosis. *Adapted from Hornberger J, Grimees K, Naumann M, et al. Recognition, diagnosis and treatment of primary focal hyperhidrosis. J Am Acad Dermatol. 2004;51:274–86.*

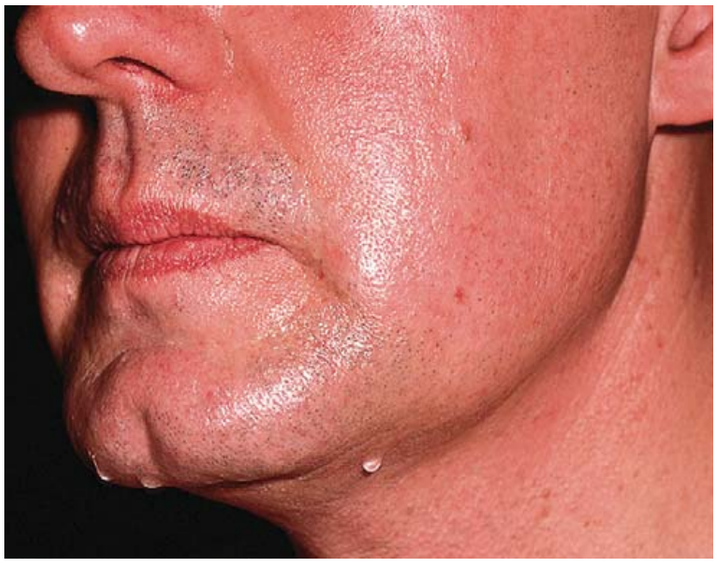


Fig. 39.1 Primary cortical (emotional) hyperhidrosis involving the face. Sweat droplets are evident on the upper cutaneous lip, jawline and chin.
Reproduced from Hurley HJ. Hyperhidrosis. Curr Opin Dermatol. 1997;4:105–14. Philadelphia: Rapid Science Publishers.

Fig. 39.2 Volar hyperhidrosis (primary cortical). The plantar skin is moist and glistening with eccrine sweat.
Courtesy, Jean L Bolognia, MD.

CAUSES OF CORTICAL HYPERHIDROSIS
PRIMARY HYPERHIDROSIS*
SECONDARY HYPERHIDROSIS
Disorders of cornification
• Palmoplantar keratodermas • Pachyonychia congenita • Congenital ichthyosiform erythroderma (bullous and non-bullous forms)
Other genodermatoses
• Epidermolysis bullosa: simplex > junctional • Dermatopathia pigmentosa reticularis • Dyskeratosis congenita • Pachydermoperiostosis (digital clubbing and thick, furrowed skin on the face and scalp) • Apert syndrome (craniosynostosis, digital anomalies, severe acne; *FGFR2* mutations) • Nail–patella syndrome
Hereditary sensory and autonomic neuropathies (HSANs)†
• Familial dysautonomia (Riley–Day syndrome; HSAN type III; blotchy erythema, decreased lacrimation, postural hypotension, and dysautonomic crises [vomiting, hypertension]) • Congenital autonomic dysfunction with universal pain loss • Congenital sensory neuropathy (HSAN type II)
*Synchronous discharge of vasoconstrictor and sudomotor impulses can result in symmetrical lividity of the palms and soles. †Caused by episodes of increased central sympathetic outflow to peripheral sudomotor neurons that are hypersensitive via a compensatory mechanism (in the setting of an overall decrease in sympathetic fibers); hypothalamic (thermal) hyperhidrosis can also occur.

Table 39.2 Causes of cortical hyperhidrosis. *Adapted from Moschella S, Hurley HV. Dermatology. Philadelphia: WB Saunders, 1992.*

seen in both cold and warm environments, but it is usually more problematic in hot weather. A chronic and unremitting course is characteristic, with little or no variation in association with age, disease or hormonal status.

Volar hyperhidrosis is the most common form of primary hyperhidrosis (Fig. 39.2), affecting approximately 50–60% of patients[3,4]. The entire palm and sole, as well as the lateral aspects, tips and distal dorsal skin of the fingers, display sweating. It can clearly have an impact on quality of life.

Axillary hyperhidrosis is the second most common form of primary hyperhidrosis, affecting 30–50% of patients[4]. The right axilla usually produces more sweat than the left (60:40). Exceptionally, one axilla may be hyperhidrotic while the opposite axilla is hypohidrotic or virtually anhidrotic. Odor (axillary bromhidrosis) is usually absent; the excessive quantities of eccrine sweat presumably wash away or dilute odorogenic apocrine sweat droplets and bacteria.

Secondary Hyperhidrosis

Secondary hyperhidrosis is caused by or associated with another systemic disorder. It may be localized or generalized. There are many causes, which can be divided into categories based on the source of the neural impulse driving the response: cortical, hypothalamic, medullary, spinal cord or local.

Disorders associated with cortical hyperhidrosis

Key features

- Several disorders of cornification and other genodermatoses affecting palmoplantar skin are associated with volar hyperhidrosis
- Patients with hereditary autonomic neuropathies can also exhibit cortical hyperhidrosis

Isolated sweating of the palms and soles is due to cortical excitation by emotional or sensory stimuli. Excessive volar sweating associated with certain inherited palmoplantar keratodermas is therefore assumed to be cortical in nature, although the pathogenic relationship between the abnormal keratinization and hyperhidrosis has not been precisely

delineated. Many palmoplantar keratodermas are malodorous, likely related to sweat-induced maceration of the thickened stratum corneum and bacterial degradation of keratin. Other genodermatoses affecting the volar skin, such as epidermolysis bullosa simplex, can also have associated palmoplantar hyperhidrosis.

In familial dysautonomia (Riley–Day syndrome), episodic (often emotionally induced) hyperhidrosis of the face and trunk is accompanied by blotchy erythema. Other hereditary sensory and autonomic neuropathies such as congenital autonomic dysfunction with universal pain loss can present with emotional and thermal hyperhidrosis. Additional causes of cortical hyperhidrosis are listed in Table 39.2.

Hypothalamic (thermal) hyperhidrosis

Key features

- Due to elevated body temperature (e.g. acute febrile illness, lymphoma, chronic infection) or direct hypothalamic stimuli (e.g. pheochromocytoma, medications, toxins)
- May be nocturnal (night sweats) or diurnal

The hypothalamus is responsible for many autonomic activities, including thermoregulation. Elevation of the temperature of the blood by 0.5°F or more excites the hypothalamic nuclei and results in vascular dilation and generalized sweating responses aimed at dissipating body heat[3].

Febrile illnesses are among the more common pathologic states that cause hypothalamic sweating. At the height of the fever, notably with temperatures of 39–40°C (102–104°F) or above, sweating is absent, the apparent result of inhibition of the hypothalamic center for sweating. With defervescence, sweating characteristically ensues. Lymphomas and chronic infections (e.g. tuberculosis) can present with episodic thermoregulatory sweating, which may be described as "night sweats" (that actually follow unperceived mild febrile pulses). Such conditions should be considered in any patient with a fever of undetermined origin.

Generalized sweating of hypothalamic origin can also be seen in a number of metabolic and endocrine disorders (Table 39.3). Patients with diabetes mellitus may exhibit hypohidrosis (e.g. the legs) as well as various forms of hyperhidrosis. For example, hyperhidrosis is a characteristic sign of insulin-induced hypoglycemia (but not diabetic ketoacidosis), and compensatory hyperhidrosis of the trunk can develop in the setting of diabetic neuropathy affecting the extremities (see below). In addition, diabetics may exhibit gustatory hyperhidrosis, primarily of the face and neck. Troublesome sweating of the scalp can also be seen in poorly controlled diabetics, and, with regulation of the hyperglycemia, the hyperhidrosis often improves.

Disorders with vasomotor instability, such as Raynaud's phenomenon, autoimmune connective tissue diseases, frostbite and other cold injuries, and reflex sympathetic dystrophy, may be associated with excessive sweating because of disturbed autonomic function[9]. A synchronous discharge of vasoconstrictor and sudomotor impulses evokes a "cold sweat", usually of the hands and feet, producing macerated, soggy wet, violaceous skin known as symmetrical lividity.

Cerebral cortex lesions, such as a tumor, abscess or cerebrovascular accident, may be associated with a contralateral hyperhidrosis. This apparently results from release of a cortical inhibitory influence that normally exerts a regulatory effect on hypothalamic sudomotor activity[10]. Hypothalamic sweating is also observed in Parkinson's disease and occurs as the "sweating sickness" following encephalitis. Harlequin syndrome, characterized by unilateral flushing and hyperhidrosis in association with contralateral anhidrosis, may be due to peripheral or central nervous system (CNS) abnormalities[11].

Episodic release of catecholamines from pheochromocytomas directly stimulates the hypothalamus and may elicit sweating[12]. Exposures to toxins and medications can also lead to hypothalamic hyperhidrosis, and a number of drugs that act on the CNS have increased sweating as a potential side effect (Table 39.4). Additional causes of hypothalamic hyperhidrosis are presented in Table 39.3.

Pressure and postural hyperhidrosis may be due to hypothalamic or possibly cortical stimulation. With changes in posture or the application of pressure to one side of the supine individual, a variety of sweating patterns have been described, such as lateral hyperhidrosis, horizontal hemihidrosis and crossed hemihidrosis. Idiopathic localized unilateral hyperhidrosis of the face and neck or forearm has been reported as an episodic disorder triggered by heat, emotional or gustatory stimuli[13].

CAUSES OF HYPOTHALAMIC HYPERHIDROSIS

Infection	Tumors	Endocrine/ metabolic	Vasomotor	Neurologic	Drugs/toxins	Miscellaneous
• Acute febrile illnesses (defervescence) • Tuberculosis • Brucellosis • Malaria • Subacute bacterial endocarditis • Other	• Lymphoma • Pheochromocytoma* • Carcinoid*	• Hyperthyroidism • Acromegaly • Hypoglycemia • Obesity • Menopause • Pregnancy • Porphyria (acute intermittent) • Phenylketonuria • Gout	• Congestive heart failure† • Myocardial ischemia • Raynaud's phenomenon • Acrocyanosis • Cold injury • Symmetrical lividity of the palms and soles‡ • Reflex sympathetic dystrophy • Autoimmune connective tissue disease (e.g. rheumatoid arthritis, SLE)	• Tumors • Cerebrovascular accidents • Parkinson's disease • Postencephalitic • Episodic spontaneous hypothermia with hyperhidrosis§ • Cold-induced sweating syndrome‖ • Familial dysautonomia‡	• Alcoholism • Alcohol or opioid withdrawal • Mercury toxicity (acrodynia) • Chronic arsenic toxicity • See Table 39.4	• Compensatory hyperhidrosis (e.g. in association with miliaria, diabetic neuropathy, sympathectomy)¶ • Localized unilateral hyperhidrosis (face and neck, forearm)‡ • POEMS syndrome • Speckled lentiginous nevus syndrome • Mitochondrial disorders • Pressure and postural hyperhidrosis‡

*Via release of catecholamines (pheochromocytoma) and serotonin (carcinoid tumors, usually metastatic).
†Patients have sympathetic activation, with impaired vasodilatory responses to heating but preserved sweating.
‡Also associated with cortical hyperhidrosis.
§Referred to as Hines–Bannick syndrome or, when associated with agenesis of the corpus callosum, Shapiro syndrome.
‖Autosomal recessive condition caused by mutations in the genes encoding cytokine receptor-like factor-1 and cardiotrophin-like cytokine factor-1; additional features include facial dysmorphism, flexion deformities (elbows, fingers) and scoliosis.
¶Compensatory hyperhidrosis is also a feature of Ross' syndrome (segmental anhidrosis, generalized areflexia and tonic pupils).

Table 39.3 Causes of hypothalamic hyperhidrosis. POEMS, polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes; SLE, systemic lupus erythematosus. *Adapted from Moschella S, Hurley HV. Dermatology. Philadelphia: WB Saunders, 1992.*

DRUGS THAT CAN STIMULATE ECCRINE SWEATING	
DIRECT-ACTING CHOLINOMIMETIC AGENTS	
• Acetylcholine • Anti-xerostomia drugs – Cevimeline – Pilocarpine • Methacholine	
CHOLINESTERASE INHIBITORS	
• Anti-Alzheimer's drugs* – Donepezil – Galantamine – Rivastigmine – Tacrine • Anticholinergic antidote – Physostigmine	• Antimyasthenics – Ambenonium – Edrophonium (for diagnosis) – Neostigmine – Pyridostigmine
ADRENOMIMETIC AGENTS	
• Dopamine • Epinephrine • Isoproterenol	• Norepinephrine • Phenylpropanolamine
ANTIDIABETIC (HYPOGLYCEMIC) AGENTS	
• Insulins • Sulfonylureas	
CNS STIMULANTS	
• Amphetamines • Caffeine • Theophylline	
ANTIDEPRESSANTS	
• MAOIs† – Isocarboxazid – Phenelzine – Selegiline – Tranylcypromine • SSRIs† – Citalopram – Duloxetine – Escitalopram – Fluoxetine – Fluvoxamine – Paroxetine – Sertraline	• Tricyclics† – Amitriptyline – Amoxapine – Desipramine – Doxepin – Imipramine – Maprotiline – Nortriptyline – Protriptyline – Trimipramine • Other – Buspirone† – Trazodone†
ANTIPSYCHOTICS	
• Phenothiazines – Chlorpromazine – Fluphenazine – Perphenazine – Thioridazine – Triflupromazine	• Other typical antipsychotics – Chlorprothixene – Haloperidol – Loxapine – Molindone – Thiothixene
ANTIPYRETICS	
• Acetylsalicylic acid • NSAIDs	
OPIOIDS	
• Fentanyl† • Meperidine† • Methadone†	
OTHER DRUGS	
• ACE inhibitors • Amlodipine • Atomoxetine • Dextromethorphan*,† • Ipecac • Pentoxifylline	• Phosphodiesterase inhibitors (e.g. sildenafil) • Sibutramine† • Sumatriptan† • Tramadol† • Yohimbine

*Increased sweating is infrequently observed at pharmacologic doses but represents a sign of overdose.

†Combination of MAOIs (which include linezolid as well as antidepressants) with drugs such as tricyclics, SSRIs, certain opioids and tryptophan can result in the serotonin syndrome, which is characterized by mental status changes, autonomic hyperactivity (including sweating) and neuromuscular abnormalities.

Table 39.4 Drugs that can stimulate eccrine sweating. ACE, angiotensin converting enzyme; CNS, central nervous system; MAOI, monoamine oxidase inhibitor; NSAID, nonsteroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor.

Medullary (gustatory) hyperhidrosis

Key features

- Taste receptors in the mouth are the source of the afferent impulses that stimulate sweating
- Physiologic medullary hyperhidrosis is most commonly triggered by spicy foods, alcohol and citrus fruits
- Pathologic medullary hyperhidrosis occurs when disrupted nerves for sweat aberrantly connect with nerves for salivation; this can be caused by local injury to, or disease of, the parotid gland (Frey's syndrome), trauma to the sympathetic trunk, and CNS disorders (e.g. encephalitis, syringomyelia)

Physiologic medullary hyperhidrosis

Any food or drink that stimulates the taste buds may induce sweating in normal individuals, particularly of the face. This is thought to occur via a variant reflex arc in which afferent impulses from taste bud receptors travel via the glossopharyngeal nerve to nuclei within the medulla oblongata (hence the term "medullary" hyperhidrosis), but lead to provocation of sweating rather than (or in addition to) the usual response of salivation. A few minutes after ingestion of a stimulating food or beverage, sweating and erythema are seen most commonly on the upper cutaneous lip or cheeks. It may be unilateral or bilateral and may be brief or persist as long as the stimulating food or beverage is ingested. Associated vasodilation localized to the areas of sweating causes the erythema, which may be faint. Spicy or sharp-tasting foods and beverages, such as citrus fruits, alcohol and condiments, may elicit the reaction. It is most common in children and young adults and in warmer environments. A familial tendency has been described[14]. There are no other concurrent local or systemic signs or symptoms. A variant of gustatory hyperhidrosis can occur on the face in diabetics. Unusual types of gustatory hyperhidrosis involving the scalp and the knee have also been described and support the concept of a central medullary mechanism for these sweating responses[15].

Pathologic medullary hyperhidrosis

This disorder arises after disruption of nerves. During healing, nerve fibers mediating sweating aberrantly connect to nerves that mediate salivation. Impulses in parasympathetic fibers normally supplying the salivary glands are now misdirected to the sweat glands. As a result, salivary stimulation elicits sweating. Of note, thermal sweating in the areas of affected skin is reduced.

The parotid form appears weeks to months following surgery, trauma, an abscess or other diseases (including herpes zoster) affecting the parotid gland. These patients experience vasodilation and sweating on the cheek and adjacent neck with salivary stimulation produced by eating, drinking or even chewing (Fig. 39.3). Sweating most often occurs in the distribution of the auriculotemporal nerve (see Ch. 142); at times there is also unilateral localized pain.

Auriculotemporal syndrome (Frey's syndrome) is common after parotid surgery, developing in 40% or more of patients, although many are not aware of it. It can also occur during infancy (frequently as a consequence of trauma to the parotid region in a forceps-assisted delivery), presenting with gustatory flushing, but usually no obvious sweating, that is often erroneously attributed to food allergy.

Another variant of gustatory hyperhidrosis, the chorda tympani syndrome, results from transposition of sympathetic sudomotor and parasympathetic secretomotor fibers to the submandibular gland that are carried in the chorda tympani nerve. In this syndrome, salivary stimuli induce sweating on the chin and lower jaw line.

Patients with cluster headaches can have sympathetic deficits that result in impaired thermoregulatory sweating on the affected side of the forehead. However, ipsilateral hyperhidrosis and flushing may occur together with excessive lacrimation during headache attacks. This is due to misdirection of parasympathetic fibers, that normally supply the lacrimal glands, to sweat glands and blood vessels. Patients with Raeder's syndrome (Horner's syndrome [ptosis, meiosis ± anhidrosis] plus unilateral temporofrontal headaches and pain) may also have excessive supraorbital sweating (lacrimal sweating). Gustatory lacrimation, rather than gustatory or lacrimal sweating, is the clinical problem in the

Fig. 39.3 Gustatory sweating in the auriculotemporal (Frey's) syndrome, as a consequence of parotid surgery. The blue–black area represents sweating (starch–iodine technique). Salivary stimulation induced this sweating response.
Reproduced from Hurley HJ. Hyperhidrosis. Curr Opin Dermatol. 1997;4:105–14. Philadelphia: Rapid Science Publishers.

OTHER CAUSES OF SECONDARY HYPERHIDROSIS

Medullary (gustatory)	Spinal cord	Axon reflex	Abnormal blood vessels or eccrine glands (non-neural)
• Physiologic gustatory sweating • Frey's syndrome • Chorda tympani syndrome • Cluster headaches • Sympathectomy • Sympathetic trunk injury (e.g. by lung carcinoma, mesothelioma, thyroidectomy) • Encephalitis • Syringomyelia	• Spinal injury • Syringomyelia • Tabes dorsalis	• Inflammatory skin diseases • Drugs (see Table 39.4)	• Eccrine nevi • Aquagenic palmoplantar keratoderma • Eccrine angiomatous hamartoma • Maffucci syndrome • Arteriovenous fistula • Klippel–Trenaunay syndrome • Glomuvenous malformation • Blue rubber bleb nevus syndrome • Cold erythema • Granulosis rubra nasi • Pretibial myxedema

Table 39.5 Other causes of secondary hyperhidrosis. *Adapted from Moschella S, Hurley HV. Dermatology. Philadelphia: WB Saunders, 1992.*

"crocodile tears" syndrome that can occur due to transposition of autonomic fibers for lacrimation and salivation after facial nerve injury.

Any condition that injures the vagus nerve and sympathetic trunk, as they lie close together in the thorax, may cause a pathologic medullary hyperhidrosis (Table 39.5). Sympathectomy, thyroidectomy, carcinoma of the lung, mesothelioma, osteoma of the spine, and subclavian aneurysm are possible causes[16]. Cholinergic fibers from the vagus nerve sprout into the adjacent sympathetic trunk during the healing process and can result in a gustatory hyperhidrosis with sweating on the face, neck and portions of the trunk and upper extremities.

In patients with syringomyelia or encephalitis, gustatory hyperhidrosis is occasionally seen on the face and upper trunk. It involves the glossopharyngeal and vagus nerves. Disturbances in the brainstem apparently lead to transposition of the central medullary nuclei for salivation and sweating. There is no peripheral crossing of sympathetic and parasympathetic nerve fibers as is seen in other forms of pathologic gustatory hyperhidrosis.

Spinal (cord transection) sweating

Key features
- Spinal disorders may result in a lack of thermal sweating below the injury as well as unusual patterns of hyperhidrosis
- Mass reflex sweating may occur around the injured level

Any injury or disease process that severs or interferes with the reticulospinal tracts of the cord can disrupt the sweating reflex (see Table 39.5). A lack of sweating in response to *thermal* stimulation usually occurs below the level of the injury. Abnormal patterns of segmental sweating may occur in conjunction with other autonomic, sensory and motor alterations. Onset and duration are unpredictable. Sweating can be excessive, drenching the patient in the regions involved. Bouts of "mass reflex sweating" are initiated in the skin below the level of the cord interruption. It is most intense in skin segments close to the level of the transection. Mass reflex sweating does not occur in transections below T8–T10.

Autonomic dysreflexia

Key features
- Direct stimulation (e.g. electrical, physical or drug-induced) of a sympathetic axon can cause sweating
- May be seen with inflammatory skin diseases

Autonomic dysreflexia is a syndrome that may occur with spinal injury at or above T6[17]. Massive episodic sympathetic discharge results in sweating above the level of the transection accompanied by headache, hypertension, facial flushing, bradycardia or tachycardia, piloerection and paresthesias.

Direct stimulation of a cutaneous sympathetic axon can induce sweating in an area approximately 4 cm in diameter[3]. Electrical and physical impulses as well as subcutaneous injection of drugs with nicotine-like effects on autonomic ganglia can incite this local form of hyperhidrosis. Mediators from inflammatory skin conditions (e.g. psoriasis, dermatitis) can also elicit localized hyperhidrosis. Substance P is believed to participate in the mediation of axon reflex sweating, and a number of other mediators, including kinins, dopamine, prostaglandins, angiotensin and adenine, may be involved[18].

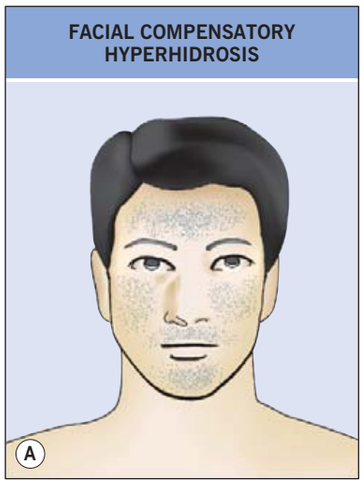
Compensatory hyperhidrosis

Key features
- Anhidrosis in one area may cause hyperhidrosis in another
- Miliaria, diabetic neuropathy and sympathectomy are well-known causes

The coordinated functioning of the body's eccrine sweat glands is illustrated by the phenomenon of compensatory hyperhidrosis, in which the sweat glands of one area become hyperactive in an effort to compensate for hypo- or anhidrosis, caused by denervation or disease, in another. Apparently, a threshold number of sweat glands must be nonfunctional in order for the compensatory response to occur. The nature or type of the underlying process that produces the anhidrosis also appears to be important. For example, compensatory hyperhidrosis does not seem to develop secondary to the anhidrosis produced by lymphomas.

The best-known clinical forms of compensatory hyperhidrosis occur in the following three situations:

- *Miliaria*: longstanding or recurrent miliaria rubra or profunda typically results in numerous non-functional sweat glands within large areas of the trunk. This induces compensatory hyperhidrosis of the face (Fig. 39.4A), especially in response to ambient heat or exercise.
- In *diabetes mellitus*, disturbance of the autonomic nervous system due to peripheral neuropathy and microangiopathy often causes



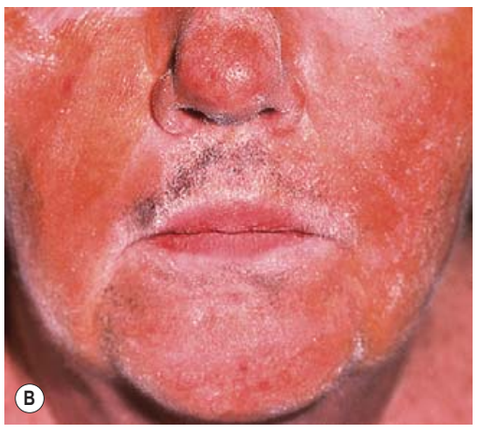


Fig. 39.4 Compensatory hyperhidrosis of the face. A Outline of the sites of facial compensatory hyperhidrosis in patients with extensive miliaria. **B** Facial compensatory hyperhidrosis (upper lip and chin) in a patient with diabetes mellitus (starch–iodine technique). *Courtesy, Harry Hurley, MD.*

Fig. 39.5 Eccrine angiomatous hamartoma. Cluster of painful pink–violet papules and plaques on the thigh and knee that had been present since one year of age. There was associated hyperhidrosis, but not hypertrichosis. Histologically, an increased number of both eccrine glands and small blood vessels is seen. *Courtesy, Julie V Schaffer, MD.*

anhidrosis or hypohidrosis of the affected skin, particularly the legs. With the loss of sweating on the lower extremities, these patients may develop compensatory increases in thermal sweating on the trunk, especially the back. A second type of compensatory hyperhidrosis, gustatory in character and usually on the face and neck (Fig. 39.4B), may also be seen in diabetic patients with peripheral neuropathy of the lower extremities.

- *Post-sympathectomy*: with the loss of sweating that results from cervicothoracic sympathectomy, a thermal hyperhidrosis, usually on the trunk, is common. Sympathectomized patients may also experience gustatory hyperhidrosis.

Non-neural hyperhidrosis

Key features

- Direct stimulation of eccrine glands can cause sweating
- Triggers include local heat, drugs and vascular tumors

Direct stimulation of eccrine sweat glands by heat or sudomimetic drugs can lead to localized sweating. Even denervated skin sweats when heat is applied[3]. Table 39.5 outlines additional non-neural causes of localized hyperhidrosis, including increased activity of eccrine glands overlying vascular lesions such as eccrine angiomatous hamartoma (Fig. 39.5).The rare disorder "cold erythema" affects the skin and gastrointestinal tract – exposure to cold produces local cutaneous erythema and intense pain along with a central area of hyperhidrosis. As with other entities in which local pain is a clinical feature (e.g. glomuvenous malformations), increased blood flow or an axon reflex (secondary to the pain) may be the casual mechanism for this sweating.

Diagnosis of Hyperhidrosis

Key features

- Differentiation between primary and secondary hyperhidrosis is important
- Colorimetric and gravimetric methods document hyperhidrosis

The first step is to differentiate between primary and secondary hyperhidrosis. History will elicit location, duration and specific triggers. Other medical disorders and medications (including over-the-counter products) must be documented. An extensive review of systems should point to any secondary causes.

Patients who do not fit the classic pattern of primary hyperhidrosis (see Table 39.1) should undergo further evaluation, focusing on possible etiologies (see Tables 39.2–39.5) during a complete history and physical examination. Laboratory testing and radiographic studies may be needed (Table 39.6).

Measurement of sweat can be performed. A grading scale for volar disease lists "low" as a moist palm or sole without visible sweat droplets. "Moderate" disease is characterized by sweating toward the fingertips. "Severe" cases drip sweat. Axillary involvement can be measured by the sweat stains on clothing: <5 cm is considered normal; 5–10 cm, mild; 10–20 cm, moderate; and >20 cm, severe.

Colorimetric techniques such as the starch–iodine or quinizarin methods[19] demonstrate the sweating pattern and reveal the location of the most active sweat glands in a given area. In the starch–iodine technique, iodine solution (e.g. 3.5% in alcohol) is applied to clean, shaved skin and allowed to dry, then starch powder (e.g. cornstarch) is brushed onto the area; the mixture turns blue–black in sites with sweating (Fig. 39.6). A combination of paper impregnated with starch and iodine can also be utilized (Fig. 39.7). Although not routinely performed in patients with hyperhidrosis, these tests can be used to plan treatment with botulinum toxin or local surgical ablation.

Additional quantitative assessment methods are available. In order to document amounts of sweat produced, gravimetric (via weighing filter paper before and after application to the skin) and evaporative (via a device that assesses water vapor loss from the skin) measurements can be made in volar or axillary sites[19]. Most patients with axillary hyperhidrosis will produce at least 100–300 mg of sweat in a 5-minute test period with mental arithmetic as a sweating stimulus. Infrared thermography represents another method of evaluating sweat gland

INITIAL PATIENT EVALUATION FOR SECONDARY HYPERHIDROSIS	
Laboratory test	**Disease**
Serum electrolytes, BUN, creatinine	Renal disease (rare)
Fasting blood glucose level and/or HbA1c	Diabetes mellitus
Thyroid function tests	Hyperthyroidism
Skin and/or blood tests for tuberculosis (e.g. PPD, QFTB-G)	Tuberculosis
Chest X-ray	Tuberculosis, neoplasm
Complete blood count	Infection
Sedimentation rate	Infection, neoplasm, inflammatory disease
Antinuclear antibodies	Autoimmune connective tissue disease
Urinary catecholamines*	Pheochromocytoma
*If suggestive signs or symptoms.	

Table 39.6 Initial patient evaluation for secondary hyperhidrosis. Further evaluation depends upon results and consideration of entities in Table 39.3. PPD, (tuberculin) purified protein derivative; QFTB-G, QuantiFERON-TB Gold.

Fig. 39.6 Delineation of area for injections of botulinum toxin A for axillary hyperhidrosis (starch–iodine technique). Blue–black areas represent foci of sweating. In the case of onabotulinumtoxinA, a total of 50–100 U is injected, utilizing 10 to 15 injection sites. *Courtesy, Alastair Carruthers, MD, and Jean Carruthers, MD.*

Fig. 39.7 Palmar hyperhidrosis as assessed by the semiquantitative starch paper–iodine technique. Sweating can also be demonstrated directly on palmar skin by the starch–iodine technique, as shown in Figure 39.6 for axillary hyperhidrosis. *Courtesy, Harry Hurley, MD.*

function, allowing comparison between anatomic areas and even individual glands.

Treatment of Hyperhidrosis

Key feature

- Treatment options for hyperhidrosis include topical aluminum chloride preparations, oral agents (anticholinergics, α- or β-adrenergic blockers, α_2-adrenergic agonists), botulinum toxin A, iontophoresis, biofeedback therapy, and surgical procedures

Treatment options available for hyperhidrosis are outlined in Table 39.7. With the exception of 12% aluminum chloride, over-the-counter antiperspirants are usually not strong enough to significantly improve the problem. More effective topical preparations are available: 6.25% or 20% aluminum chloride hexahydrate (depending upon site and severity) is usually the first-line treatment for localized hyperhidrosis. These solutions should be applied to dry surfaces at night, when sweating is diminished. Occlusion with gloves or plastic film enhances penetration of the drug. Application is recommended for three to five consecutive nights, then one to two times a week as needed to control sweating. Treated skin can be washed the following morning. The salt precipitates in the sweat duct and blocks it. With chronic use, atrophy of secretory cells may develop. Burning and irritant contact dermatitis are common side effects, particularly in women who shave their axillae.

Some patients who sweat significantly at night require a preliminary dose of an anticholinergic (glycopyrrolate 1 mg or propantheline bromide 15 mg) 1 hour before application for the first few applications. This reduces sweating enough to prevent washing away of the topical solution. Topical aldehyde agents such as formaldehyde and glutaraldehyde are effective, especially for volar disease, but allergic sensitization may develop that can result in cross-reactions with aldehydes in the environment (lotions, soaps, shoes). Other side effects include discoloration of the skin.

Tap water iontophoresis over 20 minutes two to three times a week may be helpful. The mechanism of action is unknown but is thought to lead to blockage of the sweat duct in the stratum corneum. Side effects are minimal and include tingling of the skin during treatment. Introduction of anticholinergic medications via iontophoresis is not advised due to potential systemic absorption.

Oral anticholinergics will decrease sweating in most patients. The most commonly used agents are oxybutynin[20] and glycopyrrolate[21] (see Table 39.7 for recommended regimens). When higher doses are required to control the hyperhidrosis, unacceptable side effects can often develop, including dry eyes, dry mouth, insomnia, mental status changes (e.g. confusion, hallucinations), palpitations, seizures, blurred vision, bowel disturbances, urinary retention and hypertension.

Clonidine (an α_2-adrenergic agonist that decreases central sympathetic outflow) and phenoxybenzamine (an α-adrenergic blocker) have been used with some success in anecdotal reports[22,23]. Potential side effects include hypotension, rebound hypertension, sedation, constipation, weakness and headache.

Propranolol, a β-adrenergic blocker, is commonly used for the treatment of performance anxiety and it may improve hyperhidrosis temporarily. However, long-term use may induce hyperhidrosis.

Botulinum toxin type A (BTA) has been approved by the Food and Drug Administration in the US for the treatment of axillary hyperhidrosis (see Fig. 39.6); it is also effective for volar disease. BTA prevents release of acetylcholine from cholinergic neurons (see Ch. 159). Injection into hyperhidrotic skin will produce near anhidrosis for 4 to 6 months. Side effects, if any, are short-lived. Muscle weakness, especially of the intrinsic muscles of the hands or feet, has been reported and resolves spontaneously over 2 to 5 weeks. Compensatory hyperhidrosis has not been observed[24].

Surgical treatment represents the final option after other therapeutic modalities have failed. Excision of the sweat glands is often effective for axillary disease, but resection of the entire axillary skin causes significant scarring. Compensatory hyperhidrosis is not seen with this form of local surgery. Newer methods include removal or destruction of the axillary sweat gland layer by surgical dissection, curettage or liposuction[24,25].

TREATMENT OF HYPERHIDROSIS					
	Therapy	**Frequency & recommended dose**	**Side effects**	**Duration**	**Comments**
First-line	*Topicals* Aluminum chloride hexahydrate – 6.25% (e.g. Xerac AC®), 15% (with 2% SA), 20% (e.g. Drysol®) Aluminum chloride – 12% (e.g. Certain Dri®) Zirconium salts Aldehydes	Use nightly for 3–5 nights, then every few days as needed	Burning Irritant contact dermatitis	Days	Blocks sweat ducts Aldehydes not recommended due to sensitization Zirconium salts may be effective in axillae, but not volar surfaces
Second-line	*Iontophoresis*	2–3 times a week	Discomfort during procedure	Days	Blocks sweat ducts
	Botulinum toxin A	Every 4–6 months	Discomfort during injection Weakness of underlying muscles	Months	Prevents release of acetylcholine
	Oral therapy	As needed		Hours	
	Oxybutynin	1.25–5 mg bid	Dry mouth and urinary retention most common; also confusion and decreased mental status		Anticholinergic
	Glycopyrrolate	1–2 mg bid			Anticholinergic
	Clonidine	0.1–0.3 mg bid	Hypotension, rebound hypertension		α_2-Adrenergic agonist
	Propranolol	10–40 mg bid	Hypotension, bradycardia, hyperhidrosis with long-term use		β-Adrenergic blocker
	Clonazepam	0.25–0.5 mg bid	Sedation		Anxiolytic
Third-line	*Local excision*	Once	Scarring	Permanent	Last resort
	Sympathectomy		Compensatory hyperhidrosis Horner's syndrome	Usually permanent	

Table 39.7 Treatment of hyperhidrosis. bid, twice daily; SA, salicylic acid.

Although sympathectomy is the last resort for patients with volar hyperhidrosis, advances in endoscopic surgery have decreased the morbidity associated with this procedure. Sympathectomy at the T2–T3 level for palmar disease and the lumbar area for plantar disease is effective. Risks of the procedure include Horner's syndrome, hypotension and pneumothorax. Compensatory hyperhidrosis of the trunk or gustatory facial sweating may occur[24] and the hyperhidrosis may gradually recur.

HYPOHIDROSIS AND ANHIDROSIS

Key features

- An inability to sweat can be life-threatening due to the development of heat-related illnesses (see Ch. 88)
- Causes of hypo- and anhidrosis include central or neuropathic disruption of neural impulses, sweat gland abnormalities, and medications

Three major categories of disorders are recognized causes of anhidrosis: (1) central and neuropathic diseases or medications that disrupt stimuli as they track from the anterior hypothalamus to the eccrine gland; (2) peripheral (non-neural) alterations in the gland itself; and (3) conditions of idiopathic origin.

Central and Neuropathic Hypohidrosis

Disturbance or interruption of innervation at any level, from the sweating centers in the brain down through the descending neural tracts to the sweat glands, can result in decreased or absent sweating. Causes are listed in Table 39.8. Pontine or medullary lesions lead to unilateral facial anhidrosis on the ipsilateral side of the face and neck. Fiber tracts carrying sudomotor neurons to lower levels in the spinal cord, however, are both crossed and uncrossed and the resultant anhidrosis of the skin may be ipsilateral or contralateral.

Both peripheral neuropathies and degenerative neurologic disorders can cause anhidrosis. Chronic orthostatic (postural) hypotension may be associated with decreased sympathetic innervation of the sweat glands and syncopal episodes in these patients are not accompanied by sweating (in contrast to the sweating, pallor and nausea seen in common vasodepressor fainting).

CAUSES OF CENTRAL AND NEUROPATHIC HYPOHIDROSIS AND ANHIDROSIS
• Tumors, infarctions and other lesions of the hypothalamus, pons or medulla • Spinal cord tumors and injuries • Degenerative syndromes – Pure autonomic failure – Multiple system atrophy (Shy–Drager syndrome)* – Ross' syndrome • Autoimmune autonomic neuropathy • Congenital insensitivity to pain with anhidrosis • Peripheral neuropathy due to: – Diabetes – Alcoholism – Amyloidosis (immunoglobulin light chain and transthyretin types) – Leprosy
*Progressive autonomic dysfunction, parkinsonism and ataxia.

Table 39.8 Causes of central and neuropathic hypohidrosis and anhidrosis.

Ross' syndrome, which consists of Adie's syndrome (myotonic pupils and absent deep tendon reflexes) plus segmental anhidrosis that is typically associated with compensatory hyperhidrosis, also falls into this group. Congenital insensitivity to pain with anhidrosis (hereditary sensory and autonomic neuropathy type IV) is a rare autosomal recessive disorder which presents with recurrent fevers due to anhidrosis, self-mutilation due to insensitivity to pain and mental retardation. Immunohistochemical staining (e.g. for an axonal marker such as protein gene product 9.5 [PGP 9.5]) of skin biopsy specimens reveals a lack of innervation of eccrine sweat glands.

Disruption of the superior cervical ganglion, an occasional complication of cervicothoracic sympathectomy, results in Horner's syndrome, and chemical blockade of selected sympathetic ganglia will result in regional anhidrosis. Any drug that interrupts synaptic transmission in autonomic ganglia will suppress sweating (Table 39.9).

DRUGS THAT CAUSE HYPOHIDROSIS AND ANHIDROSIS
BLOCKADE OF NEUROTRANSMISSION
• **Nicotinic acetylcholine receptor antagonists (ganglion-blocking agents)**
– Hexamethonium
– Mecamylamine
– Tetraethylammonium
– Trimethaphan
• **Muscarinic acetylcholine receptor antagonists***
– Atropine
– Glycopyrrolate
– Oxybutynin
– Scopolamine
• **Calcium channel blockers**
• **α-Adrenergic blockers**
– Phenoxybenzamine (hypohidrosis occasionally observed)
– Phentolamine†
• **α_2-Adrenergic agonists‡**
– Clonidine
DYSFUNCTION OR DESTRUCTION OF THE ECCRINE GLAND§
– Aldehydes (topical)
– Aluminum salts (topical)
– 5-Fluorouracil
– Quinacrine
– Topiramate¶
– Zirconium salts (topical)
– Zonisamide¶
*Antipsychotic drugs (e.g. phenothiazines), tricyclic antidepressants and some antihistamines can also have anticholinergic effects, especially when administered in combination and at high doses.
†Thought to suppress eccrine sweating by inhibiting ganglionic transmission.
‡Decrease sympathetic outflow from the CNS.
§Eccrine gland necrosis is also a feature of coma bullae, which are classically associated with barbiturate overdose but can also be observed in comas induced by other drugs (see Ch. 33); syringosquamous metaplasia may result from the toxic effects of chemotherapeutic agents (e.g. cytarabine, doxorubicin) on the eccrine glands.
¶Decreased sweating has been attributed to inhibition of carbonic anhydrase isoenzymes in the eccrine glands.

Table 39.9 Drugs that cause hypohidrosis and anhidrosis. Refers to systemic administration unless otherwise indicated.

PERIPHERAL CAUSES OF HYPOHIDROSIS AND ANHIDROSIS DUE TO SWEAT GLAND ABNORMALITIES
GENETIC DISORDERS
• Ectodermal dysplasias
– Hypohidrotic ectodermal dysplasia
– Hypohidrotic ectodermal dysplasia with immune deficiency
– Rapp–Hodgkin syndrome
– Naegeli–Franceschetti–Jadassohn syndrome
• Incontinentia pigmenti
• Bazex syndrome
• Fabry disease*
DESTRUCTION
• Tumors (e.g. lymphoma)
• Burns
• Radiation therapy
• Systemic sclerosis (scleroderma) and morphea
• Sjögren's syndrome†
• Graft-versus-host disease
• Acrodermatitis chronica atrophicans
OBSTRUCTION
• Miliaria
• Ichthyoses
• Psoriasis
• Eczematous dermatoses
• Bullous diseases
• Porokeratosis
*Hyperhidrosis (related to autonomic dysfunction) can also occur.
†Hypohidrosis can also result from peripheral neuropathy.

Table 39.10 Peripheral causes of hypohidrosis and anhidrosis due to sweat gland abnormalities.

Peripheral Anhidrosis

Congenital and acquired alterations or disturbances of the sweat glands result in an absence or significant reduction in sweating (Table 39.10). A near absence of sweat glands is found in male patients with X-linked hypohidrotic ectodermal dysplasia, while female carriers show reduced sweating[26]. Bazex syndrome, also known as Bazex–Dupré–Christol syndrome, is an X-linked dominant disease characterized by hypohidrosis, hypotrichosis, multiple basal cell carcinomas and follicular atrophoderma (see Ch. 99).

The skin of elderly individuals may show some atrophy of the sweat glands, but overall they are preserved and continue to function with advancing age. Toxic and thermal insults to the skin and a variety of inflammatory and neoplastic disorders can destroy or produce atrophy of the sweat glands with resultant anhidrosis (see Table 39.10)[27]. Perhaps the most common causes of anhidrosis are inflammatory and hyperkeratotic disorders that produce sweat duct obstruction.

Diagnosis of Anhidrosis

Heat intolerance may be due to many underlying disorders as well as to personal preference. New symptoms such as drowsiness, fatigue or inability to concentrate in hot environments in association with a decrease in the patient's "normal sweating" point to acquired hypo- or anhidrosis. As with hyperhidrosis, a careful history will yield clues to the diagnosis. Special attention must be given to new medications, recent medical events (e.g. a cerebrovascular accident), the presence of diabetes or other chronic conditions (see Tables 39.8–39.10) and family history.

Examination of the patient's skin may not reveal the presence or extent of anhidrosis. A hot environment or exercise may be required, but excessive overheating must be avoided. Colorimetric or gravimetric testing (as for hyperhidrosis) will demonstrate diminished or absent sweating. Local intradermal injection of cholinergic drugs to stimulate sweating in small areas can also be utilized, but the risk of side effects generally precludes their injection into large areas. Testing for axon reflex sweating with intradermal nicotine sulfate or picrate in appropriate doses (e.g. 0.001 mg) may be performed in patients in whom peripheral neuropathies are suspected.

Finally, a biopsy specimen from an affected area of skin should be obtained in virtually all patients with anhidrosis. Immunohistochemical stains and electron microscopy may be necessary to identify sweat gland abnormalities.

Treatment of Anhidrosis

Unfortunately, treatment options for anhidrosis are limited. Offending medications should be discontinued. Keeping the patient in a cool environment is essential. For disorders due to clogged sweat ducts, gentle exfoliation may be helpful. Disorders of keratinization (e.g. lamellar ichthyosis) associated with overheating should be treated aggressively, with restoration of sweating as a minimal therapeutic endpoint. Use of water-containing spray bottles can prove useful.

SPECIFIC DISEASES OF THE SWEAT GLAND

Miliaria

Key features

- Sweat retention can be caused by obstruction of the eccrine duct at various levels
- Miliaria crystallina or sudamina (superficial ductal occlusion) – clear vesicles
- Miliaria rubra or prickly heat (intermediate ductal occlusion) – erythematous papules or pustules
- Miliaria profunda or mammillaria (deeper ductal occlusion) – white papules
- Common in neonates (whose eccrine sweat ducts are not fully developed) and adults living in hot, humid conditions
- Resolves with relocation to a cool environment

Miliaria is a group of eccrine disorders having in common obstruction of the eccrine sweat duct. Three types, each reflecting obstruction of sweat ducts at different levels, from the stratum corneum to the dermal–epidermal junction, are recognized (Table 39.11). Blockage results in retention of sweat within the duct, causing a sweat retention vesicle to form.

Epidemiology

Miliaria is most common in children, particularly neonates whose eccrine ducts are not fully developed. Congenital miliaria crystallina has been described[27]. It is also common in adults who live or work in very hot, humid environments. There is no racial or sex predisposition and it can be seen in the elderly. Miliaria has not been associated with an underlying systemic disease.

Pathogenesis

Excessive sweating, particularly under occlusive clothing, can lead to maceration of the stratum corneum which is sufficient to cause blockage of the eccrine duct[28]. Keratinous plugs form, causing obstruction.

Clinical features

Each type of miliaria is clinically distinctive (see Table 39.11). Miliaria crystallina presents as small, clear vesicles (Fig. 39.8) that rupture easily. It is most commonly observed on the face and upper trunk of infants and on the trunk in adults, and it poses no systemic risk for the patient.

The most common and clinically important form is miliaria rubra, which is characterized by small, non-follicular, erythematous macules and papules topped by a punctate vesicle (Fig. 39.9). Lesions are usually pruritic and occasionally burn. Onset is within days to weeks of exposure to hot environments. Miliaria rubra may become pustular, especially in chronic, extensive cases. Miliaria pustulosa, as this variant is known, is sterile, although secondary bacterial infection may occur. Miliaria rubra typically occurs on the upper trunk and neck in both children and adults. Extensive cases of miliaria rubra can lead to hyperpyrexia as a result of the obstruction of large numbers of sweat glands and compromise of their thermoregulatory role (see Ch. 88). When miliaria rubra is chronic or recurrent, occlusion may extend to a deeper level and produce miliaria profunda. Because of their deeper location, the sweat retention vesicles of miliaria profunda appear clinically as white papules, 1 to 3 mm in diameter. They start within minutes of initiation of sweating and subside within 1 to 2 hours after the sweating ceases. Since the sweat retention vesicle lies in the upper dermis below the level of the itch receptors, lesions of miliaria profunda are asymptomatic. Only in those patients with concomitant miliaria rubra can pruritus or burning develop. Miliaria profunda is relatively rare and typically occurs on the trunk and proximal extremities. When large numbers of sweat glands are occluded and essentially non-functional, these individuals are at risk for significant thermoregulatory problems and a compensatory hyperhidrosis of the face is routinely observed (see Fig. 39.4). Axillary and inguinal lymphadenopathy can also be seen, with resolution upon clearing of the miliaria. The term "tropical anhidrotic asthenia" has been applied to these patients.

Pathology

Biopsy specimens demonstrate ductal blockage. Keratinous obstruction of sweat ducts at the level appropriate for each type of miliaria may be seen: in the stratum corneum for miliaria crystallina; the mid-epidermis or spinous layer for miliaria rubra; and at the dermal–epidermal junction for miliaria profunda. Sweat retention vesicles may be seen

Fig. 39.8 Miliaria crystallina. Multiple small superficial vesicles with clear fluid.

Fig. 39.9 Miliaria rubra. Multiple erythematous non-follicular papules and papulovesicles on the back.

THREE TYPES OF MILIARIA				
Type	**Location of obstruction**	**Cutaneous lesions**	**Patient population(s)**	**Most common locations**
Crystallina	Stratum corneum	Non-pruritic, clear, fragile, 1 mm vesicles	Neonates <2 weeks of age Children and adults in hot climates	Face and trunk
Rubra	Mid-epidermis	Pruritic, erythematous, 1–3 mm papules; may have pustules	Neonates 1–3 weeks of age Children and adults in hot climates	Neck and upper trunk
Profunda	Dermal–epidermal junction	Non-pruritic, white, 1–3 mm papules	Adults in hot climates; often with multiple bouts of miliaria rubra	Trunk and proximal extremities

Table 39.11 Three types of miliaria.

underlying the respective sites of occlusion. Dermal inflammation is absent in miliaria crystallina, whereas perivascular lymphocytic infiltrates and vasodilation are evident in miliaria rubra. An eosinophilic cast can be seen occluding sweat ducts at the dermal–epidermal junction or intraepidermally in miliaria profunda. Periductal infiltration of lymphocytes is also seen along with mild focal spongiosis of the adjacent epidermis. Special stains may reveal Gram-positive bacteria in both rubra and profunda lesions, but cultures are typically negative unless the lesions are secondarily infected.

Differential diagnosis

Each type of miliaria has such a classic clinical presentation that the diagnosis is usually apparent. A simple diagnostic test involves the puncture of a miliaria vesicle with a fine needle, resulting in release of the trapped clear sweat. In neonates, miliaria rubra must be distinguished from erythema toxicum neonatorum, neonatal cephalic pustulosis (which can involve the upper trunk as well as the face), candidiasis, and (in atypical cases) other vesiculopustular diseases of the newborn (see Table 34.1). In adults, the differential diagnosis for miliaria rubra includes other conditions with a predilection for sites of occlusion and excessive sweating, such as folliculitis (with normal flora or *Staphylococcus aureus*), candidiasis and Grover's disease (see Ch. 87). The regression of miliaria profunda within hours of ceasing physical exertion and/or exposure to high temperatures distinguishes it from other papular eruptions.

Treatment

Management of all types of miliaria requires placement of the patient in a cool environment, in which sweating stops, for several days to weeks. Gradually, the obstructed sweat ducts shed their occluding keratinous plugs and normal sweating is restored. Topical anhydrous lanolin may dissolve the plugs in miliaria profunda[28]. Anecdotally, other topicals (including corticosteroids and antibiotics) as well as oral antibiotics, retinoids, and vitamins A and C have been advocated as therapeutic options.

Altered Composition of Eccrine Sweat

Key features

- Some disorders (e.g. cystic fibrosis) lead to abnormal chemical composition of sweat
- Eccrine bromhidrosis is most commonly caused by maceration of the stratum corneum and bacterial degradation of keratin
- Eccrine chromhidrosis is caused by exogenous chemicals that color the sweat, whereas apocrine chromhidrosis is due to intrinsic causes

Abnormalities of eccrine sweat composition, as evidenced by altered electrolyte content or the presence of other anomalous substances, should be recognized as disorders of eccrine function. Some of these glandular disturbances are not accompanied by clinically distinctive signs or symptoms, whereas others result in well-defined clinical conditions that are associated with profound effects on the general health of the affected individual.

Most notable among this group of disorders are those in which there is altered electrolyte concentration in sweat (Table 39.12). Cystic fibrosis, an autosomal recessive disorder caused by mutations in the *c*ystic *f*ibrosis *t*ransmembrane conductance *r*egulator (*CFTR*) gene, is an important example in which all of the exocrine glands in the body are affected, leading to dysfunction of multiple organs, including the lungs, exocrine pancreas, intestines and liver. Cystic fibrosis patients demonstrate decreased electrolyte reabsorption by the eccrine duct, which results in increased loss of sodium, chloride and (to a lesser extent) potassium in sweat. Increased Cl^- concentration in sweat (>60 mEq/l on two separate occasions) remains the most widely used diagnostic test for this disease (the sweat chloride test). Cystic fibrosis patients still produce sweat in response to heat and most pharmacologic stimuli, but the increased loss of electrolytes poses a systemic risk for them in hot environments. An absent or markedly diminished response of the eccrine glands and other exocrine glands to β-adrenergic agonists is another marker for this disorder. This reflects the underlying pathogenic defect in the CFTR protein, a Cl^- channel that regulates other ion channels and is activated via cyclic adenosine monophosphate (cAMP) via β-adrenergic stimulation.

SYSTEMIC DISORDERS THAT AFFECT THE LEVELS OF ELECTROLYTES IN SWEAT

INCREASED LEVELS OF ELECTROLYTES IN SWEAT*

- Cystic fibrosis
- Endocrine disorders
  - Adrenal insufficiency (e.g. due to Addison's disease or congenital adrenal hyperplasia)
  - Myxedema
  - Nephrogenic diabetes insipidus
- Familial intrahepatic cholestasis
- Malnutrition
- Metabolic disorders
  - Fucosidosis
  - Glycogen storage disease type I
- Unacclimatized individuals exposed to heat

DECREASED LEVELS OF ELECTROLYTES IN SWEAT

- Endocrine disorders
  - Aldosteronism
  - Cushing's syndrome
  - Thyrotoxicosis
- Hypoproteinemic edema (e.g. due to cirrhosis or nephrotic syndrome)

*Elevated sweat electrolytes (which may result in a false-positive chloride sweat test) can also be observed in patients with skin conditions such as widespread atopic dermatitis, ichthyosiform erythroderma or ectodermal dysplasia.

Table 39.12 Systemic disorders that affect the levels of electrolytes in sweat.

Excretion of calcium in eccrine sweat has been demonstrated in patients with widespread idiopathic calcinosis cutis. In uremia, high levels of urea can produce a "uremic frost" on the skin of these seriously ill patients. However, this is rarely seen now that dialysis is a common procedure. Decreased size of the sweat glands, the significance of which is unknown, has also been described in patients with uremia[29]. Many drugs, including opiates (e.g. methadone, morphine), amphetamines, anticonvulsants, antimicrobials (e.g. azole antifungals, griseofulvin, quinolones, cephalosporins) and chemotherapeutic agents (e.g. cytarabine, cyclophosphamide, thiotepa), as well as metals such as copper and mercury have also been shown to be secreted in sweat[30,31].

In healthy individuals, eccrine sweat is odorless when it is secreted. Odor (bromhidrosis) can develop secondary to maceration of the stratum corneum with bacterial degradation of keratin. This may be seen on the feet and in intertriginous areas, especially the inguinal region. The types of bromhidrosis are listed in Table 39.13.

Malodorous sweat can be caused by abnormal secretion of amino acids and their analogues or breakdown products. This occurs in several heritable metabolic disorders (see Table 39.13), with the sweat often having a distinctive smell such as musty or "mousy" in phenylketonuria (see Ch. 63) or a sweet odor in maple syrup urine disease. Odorogenic compounds may also be detected in the saliva and urine of these patients. Some foods, such as garlic and asparagus, can cause eccrine bromhidrosis.

Individuals with an inherited deficiency in the enzyme *f*lavin-containing *m*onoo*x*ygenase-3 (FMO3) excrete large quantities of trimethylamine in their urine, sweat and saliva after ingestion of marine fish (which contains trimethylamine-*N*-oxide) or choline- and lecithin-containing foods (e.g. eggs, kidney and liver)[32]. The resultant "fishy" odor characterizes this disorder, trimethylaminuria. The clinical spectrum of trimethylaminuria ranges from a severe, constant, socially debilitating condition with onset in early childhood (e.g. with a homozygous mutation that abrogates FMO3 function) to mild or intermittent manifestations (often related to dietary factors or overgrowth of intestinal bacteria) that begin during adulthood (e.g. with a heterozygous polymorphism that decreases FMO3 function).

Colored eccrine sweating (*eccrine* chromhidrosis) results from contamination of colorless eccrine sweat by a chromogen such as a dye

TYPES OF BROMHIDROSIS
APOCRINE
• Axillary (no odor from other apocrine areas)
ECCRINE
• Keratinogenic – Plantar – Intertriginous • Metabolic – Phenylketonuria (musty or "mousy" odor) – Maple syrup urine disease (sweet odor) – Methionine adenosyltransferase deficiency ("boiled cabbage" odor) – Methionine malabsorption syndrome (oasthouse syndrome) – Trimethylaminuria ("fishy" odor) – Dimethylglycine dehydrogenase deficiency ("fishy" odor) – Isovaleric acidemia ("sweaty feet" odor) • Exogenous – Foods, e.g. garlic, asparagus, curry – Drugs, e.g. penicillins, bromides – Chemicals, e.g. dimethyl sulfoxide (DMSO)

Table 39.13 Types of bromhidrosis.

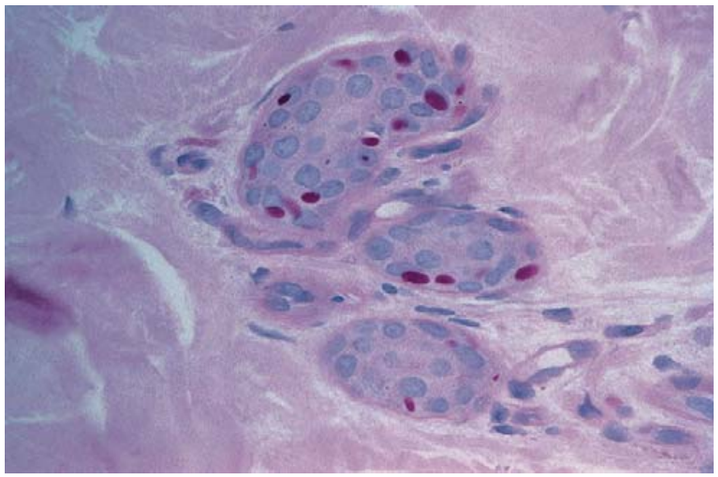


Fig. 39.10 Lafora disease. Large, purplish-red granules in the outer layer of eccrine duct cells (PAS stain). *Courtesy, Harry Hurley, MD.*

(e.g. from clothing), paint, pigment from a microorganism (e.g. *Piedraia* or *Corynebacterium* spp.), or another colored chemical on the surface of the skin. Copper miners or workers in industry often exhibit blue or blue–green skin from external deposits of copper salts that color the sweat. The use of self-tanning products can result in brown sweat. Hematidrosis (bloody sweat) has not been confirmed scientifically. Red sweat has been described in patients receiving clofazimine and rifampin. In contrast, *apocrine* chromhidrosis is usually intrinsic in origin, resulting from the excretion in apocrine sweat of lipofuscin in large amounts or in a highly oxidized state. Chromhidrosis, primarily axillary in location and presumably of apocrine origin, can be seen in alkaptonuria (see Ch. 63) and may be a presenting sign of the disease as the excreted pigment stains the undershirts of these patients.

Cytologic Inclusions and Other Morphologic Changes of Diagnostic Importance in the Sweat Glands

A variety of disorders display diagnostic microscopic findings within the eccrine sweat glands, ranging from intracellular inclusions and degenerative alterations to changes in the size of the glands or their components (Fig. 39.10). Table 39.14 summarizes these distinctive histopathologic features, which may be overlooked in the diagnostic evaluation of patients. Most of the findings listed can be visualized by light microscopy. Of note, viral particles from Ebola virus and severe acute respiratory syndrome (SARS) have been found in eccrine sweat ducts by electron microscopy[33]. Whether the sweat is contagious remains to be proven.

DIAGNOSTIC MICROSCOPIC CHANGES IN ECCRINE GLANDS	
Disorder	**Microscopic changes**
Hypothyroidism	PAS-positive, diastase-resistant granules in secretory cells
Lymphoma Multiple myeloma Heat stroke	Vacuolar degeneration of secretory cells or ducts
Neuronal ceroid lipofuscinoses	Cytoplasmic inclusions in secretory cells
Mucopolysaccharidoses (e.g. Hurler, Hunter, Sanfilippo) Mucolipidoses Acid maltase deficiency Adrenoleukodystrophy	Membrane-bound vacuoles in secretory cells
Sphingolipidoses (e.g. Fabry, Niemann–Pick, Sandhoff)	Lipid inclusions in secretory cells
Lafora disease	PAS-positive granules in outer layer of duct cells
Argyria	Granules in eccrine basement membrane (darkfield)
Trisomy 13, 18 or 21	Differences in duct:secretory coil length
Ebola hemorrhagic fever Severe acute respiratory syndrome (SARS)	Viral particles in lumen of sweat gland tubule
Uremia	Reduced size of sweat glands

Table 39.14 Diagnostic microscopic changes in eccrine glands.

SWEAT AS A PREDISPOSING INFLUENCE ON SKIN DISEASE

Key features

- Wet skin is more permeable than dry skin
- Wet skin is more likely to develop contact allergies than dry skin
- Several diseases are aggravated by sweat, including Hailey–Hailey disease, Grover's disease, folliculitis and pitted keratolysis

That wet skin is more permeable than dry skin has been clearly established, and skin wetted by perspiration is more likely to be sensitized to contact allergens. Sweaty skin is also more susceptible to absorption of toxic chemicals. The macerative effect of sweat is an essential early step in the pathogenesis of sweat retention syndromes, such as miliaria. Sweat-saturated keratin, upon bacterial degradation, gives rise to plantar bromhidrosis and pitted keratolysis. Softening of the skin by sweat facilitates the entry and growth of microorganisms, encouraging the development of flexural candidiasis, bacterial folliculitis, bullous impetigo, superficial dermatophyte infections, tinea versicolor, verrucae and molluscum contagiosum. Grover's disease and Hailey–Hailey disease are clearly aggravated by sweating. Some systemic drugs, such as antifungal agents, are excreted in eccrine sweat and diffuse from the sweat ducts to the surrounding stratum corneum, exerting inhibitory effects on microorganisms. Finally, the decreased electrical skin resistance that occurs with sweating causes increased conductance of electrical currents.

Granulosis Rubra Nasi

Key features

- Hyperhidrosis of the nose is followed by macular erythema; papules and vesicles can also develop
- The process may extend to the cheeks, lips and upper chin
- Onset is during the first decade of life and it usually resolves by puberty
- Autosomal dominant transmission

Granulosis rubra nasi is a rare inherited condition. It generally appears during childhood (peak incidence between ages 7 and 12 years), but adolescent or adult onset is possible. The etiology and pathogenesis of this disorder have not been elucidated. An autosomal dominant inheritance pattern has been described.

The condition starts with hyperhidrosis of the tip of the nose that may be present for years before the characteristic erythema develops on the nose; the latter can extend to the cheeks, chin and upper lip. The entire area of erythema displays excessive sweating. Papules, sweat droplets and vesicles may form at the orifices of the eccrine ducts. Cystic lesions can also develop and the nose may be cold. It may itch but is not painful. Primary hyperhidrosis of the palms and soles is a common concomitant finding, as is poor peripheral circulation with pernio or acrocyanosis. Granulosis rubra nasi usually resolves at puberty but may continue into adulthood.

Histopathologically, dilation of dermal blood and lymphatic vessels with perivascular lymphocytic infiltration and dilation of sweat ducts (at times simulating a hidrocystoma) are seen. The epidermis, connective tissue and pilosebaceous apparatus are otherwise normal and no heterotopic apocrine glands are found. No associated systemic disease or abnormal laboratory findings have been described.

The differential diagnosis includes rosacea, acne vulgaris, periorificial dermatitis, lupus pernio and lupus erythematosus. Treatment is disappointing and limited to drying lotions and reassurance that the disorder typically resolves spontaneously at puberty.

Keratolysis Exfoliativa

Synonyms: ■ Lamellar dyshidrosis ■ Recurrent focal palmar peeling ■ Dyshidrosis lamellosa sicca

Key features

- Superficial desquamation of the palms and occasionally the soles
- Non-inflammatory
- May be associated with primary hyperhidrosis
- Treatment is with keratolytics

Keratolysis exfoliativa is a common, asymptomatic, superficial desquamative process of palmar and (less often) plantar skin; it usually worsens in warm weather and is occasionally associated with hyperhidrosis. Keratolysis exfoliativa is seen in healthy adults and probably reflects low-grade physical or chemical damage to the thick stratum corneum of volar skin. Concurrent irritant dermatitis may also be present. Maceration from imbibition of water by the thick stratum corneum may also be a pathogenic influence, although hyperhidrosis is not a regular feature.

Clinically, it appears as an irregular annular or circinate pattern of scaling, 2 to 15 mm in diameter (Fig. 39.11). There are no antecedent or concurrent vesicles or papules, and no fungi are recoverable from the lesions. Treatment is disappointing. Humectant and keratolytic topical products containing urea, ammonium lactate or salicylic acid (5–6%) may be helpful. Topical corticosteroids are not useful unless there is associated dermatitis.

Fig. 39.11 Keratolyis exfoliativa. Small annular collarettes of scale on the palm. *Courtesy, Jean L Bolognia, MD.*

Multiple Sweat Gland Abscesses

Synonym: ■ Periporitis staphylogenes

Key features

- Rare neonatal disorder that often occurs in the setting of malnourishment or debilitation
- Miliaria lesions become infected and form abscesses
- Most common on the neck, back and buttocks
- May be associated with systemic symptoms

Multiple sweat gland abscesses represent a rare disorder of newborn infants that is likely due to a secondary staphylococcal infection of miliaria lesions. Malnourished or debilitated neonates are preferentially affected.

Clinically, erythematous papules and nodules are distributed on the neck, back, buttocks and occipital skin. They are typically round or oval erythematous swellings that measure 1 to 2 cm in diameter and do not exhibit warmth, tenderness or fluctuance. Lymphangitis and constitutional signs and symptoms such as fever and lassitude may occur with larger or more numerous lesions. Bacterial smears and cultures reveal *S. aureus*. Microscopically, abscess formation involving the sweat glands is seen.

The differential diagnosis includes furuncles or carbuncles and subcutaneous fat necrosis of the newborn. Neutrophil dysfunction, hypogammaglobulinemia and other signs of immunodeficiency have not been reported in neonates with multiple sweat gland abscesses. However, primary immunodeficiencies (e.g. chronic granulomatous disease, hyper-IgE syndrome; see Ch. 60) should be considered in affected infants with recurrent infections (cutaneous or extracutaneous). Systemic antibiotics, correction of the child's nutritional state and elimination of factors encouraging the development of miliaria should be undertaken in the management of this condition.

Neutrophilic Eccrine Hidradenitis

Synonyms: ■ Chemotherapy-associated eccrine hidradenitis ■ Drug-associated eccrine hidradenitis

Key features

- Typically occurs following administration of chemotherapy (most often cytarabine in patients with acute myelogenous leukemia)
- Both children and adults can be affected
- Painful erythematous papules and plaques are classically found on the trunk
- Usually resolves within a few days to weeks

Fig. 39.12 Neutrophilic eccrine hidradenitis. Pink annular plaque on the dorsal hand.

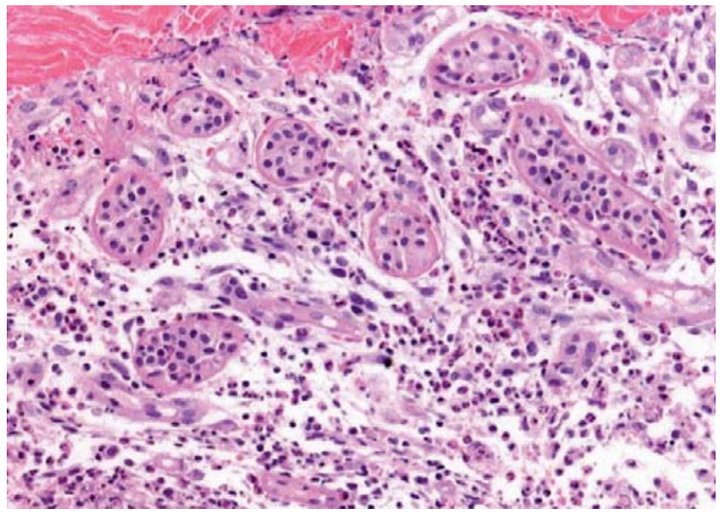


Fig. 39.13 Neutrophilic eccrine hidradenitis – histologic features. The inflammatory infiltrate is composed primarily of neutrophils which surround and are within the eccrine glands and coils. There are slight degenerative changes of primarily secretory cells. *Courtesy, Lorenzo Cerroni, MD.*

Epidemiology and pathogenesis

Neutrophilic eccrine hidradenitis (NEH) is a disorder of the eccrine sweat glands that usually develops 7–14 days after initiating chemotherapy[27]. It is most commonly associated with administration of cytarabine (often in patients with acute myelogenous leukemia); other agents that have been implicated include anthracyclines, mitoxantrone, methotrexate, cyclophosphamide, 5-fluorouracil, bleomycin, vinca alkaloids, and imatinib mesylate. Adults and children are equally affected. It has also been reported after zidovudine treatment in HIV patients and following administration of granulocyte colony-stimulating factor. In a small number of patients, NEH preceded and was believed to herald a new malignancy (usually acute myelogenous leukemia) or its relapse. It is generally regarded as a cytotoxic process directed at the sweat glands, e.g. via a direct toxic effect of chemotherapeutic drugs that are excreted in the sweat.

Clinical features

Clinically, erythematous papules and plaques occur on the trunk and may also affect the extremities (Fig. 39.12) and face. Polymorphic lesions, e.g. linear, annular, erythema multiforme-like, of varying sizes have been described, some of which were purpuric (typically in association with chemotherapy-related thrombocytopenia) or pustular. Patients are often febrile and, as a consequence of chemotherapy, neutropenic.

Pathology

Histopathologic evaluation reveals eccrine sweat glands with degenerative vacuolar changes within secretory and (to a lesser degree) ductal cells; the process usually spares the acrosyringium. A neutrophilic inflammatory infiltrate classically accompanies these changes (Fig. 39.13). However, the infiltrate may be sparse or lymphocytic in the setting of chemotherapy-induced neutropenia. Squamous metaplasia of the cuboidal epithelial cells of the eccrine ducts (eccrine squamous syringometaplasia) is occasionally observed.

Differential diagnosis

The clinical differential diagnosis includes primarily Sweet's syndrome and infection, e.g. cellulitis, bacterial or fungal emboli. An infectious form of NEH has been described; most of the patients were immunocompromised, and the pathogenic organism (e.g. *Serratia, Enterobacter, S. aureus, Nocardia*) was often identified in tissue culture but not via light microscopy plus special stains of lesional specimens.

The clinical presentations of eccrine squamous syringometaplasia vary from vesicles to large erythematous patches, which may occur in a widespread or localized (e.g. major body folds, elbows and knees) distribution. Because such eruptions can be induced by the same group of chemotherapeutic agents implicated in NEH, and eccrine squamous syringometaplasia can be observed histologically in some classic cases of NEH, it has been postulated that the two entities exist on a spectrum of chemotherapy-associated eccrine changes (see Ch. 21). Finally, idiopathic palmoplantar hidradenitis (described below) has distinct clinical features and can easily be differentiated from NEH.

Treatment

The eruption of NEH resolves several days to weeks after cessation of chemotherapy, but may recur in subsequent cycles. Because NEH usually arises in the setting of fever and neutropenia, empiric antimicrobial therapy is frequently administered until the possibility of infection is excluded. Corticosteroids seem to shorten the duration of the lesions and relieve the pain in some patients. Dapsone can be beneficial in treating NEH and preventing recurrences[34].

Idiopathic Palmoplantar Hidradenitis

Synonyms: ■ Palmoplantar eccrine hidradenitis ■ Recurrent palmoplantar hidradenitis

Key features

- Occurs primarily in otherwise healthy children
- Sudden onset of painful nodules on the palms and/or soles
- Likely due to mechanical rupture of eccrine sweat glands
- Resolves spontaneously within a few days to weeks, but may be recurrent

Idiopathic palmoplantar hidradenitis is primarily a disease of children, and it is not associated with underlying medical conditions or drug intake[35]. Onset is often preceded by vigorous physical activity. The proposed pathomechanism involves eccrine gland rupture due to mechanical and thermal trauma.

This disorder is characterized by the sudden onset of multiple, tender, erythematous nodules on the soles and (less often) the palms (Fig. 39.14). Neutrophilic infiltration of the secretory and ductal components of the coiled portion of the sweat glands is seen in biopsy specimens. This infiltrate is distinctly nodular, and neutrophilic abscesses may be observed. The differential diagnosis includes the "pseudomonas hot-foot syndrome", panniculitis (e.g. erythema nodosum), pernio and vasculitis (e.g. polyarteritis nodosa). Several authors have suggested that the entity "traumatic plantar urticaria" belongs within the spectrum of idiopathic palmoplantar hidradenitis. Spontaneous resolution

Fig. 39.14 Idiopathic palmoplantar hidradenitis. Erythematous papulonodules on the plantar surface. *Courtesy, Michael L Smith, MD.*

in a matter of days to weeks is the rule, although recurrent attacks occur in as many as half of affected children.

Grover's Disease

Sweating is one of several factors, along with chronic photodamage, that play a role in Grover's disease. See Chapter 87 for a discussion of this disorder.

APOCRINE SWEAT GLAND DISORDERS

Not all sweat gland disorders involve the eccrine glands. Apocrine sweat glands are confined to the axillae, eyelids (Moll's glands), external auditory meatus, areola and nipple of the breast, periumbilical region, and anogenital region, in particular the mons pubis, labia minora, prepuce, scrotum and circumanal area. Apocrine secretion is a slow, usually continuous process analogous to milk formation in the mammary gland. Bacterial degradation of apocrine sweat yields ammonia and short-chain fatty acids that account for apocrine bromhidrosis (see above).

Fox–Fordyce Disease

Synonym: ■ Apocrine miliaria

Key features

- Caused by plugging of the apocrine sweat glands
- Occurs primarily in women 15–35 years of age
- Skin-colored follicular papules develop in the axillary, anogenital and periareolar areas
- May be intensely pruritic

Fox–Fordyce disease is a chronic, pruritic disorder of the apocrine glands.

Epidemiology

Most commonly affecting women between the ages of 15 and 35 years, it usually remits after menopause.

Pathogenesis

The etiology of Fox–Fordyce disease is unknown, but hormonal factors are thought to play a role. Emotional and physical stimuli may also have a role in the disease course.

Fig. 39.15 Fox–Fordyce disease. Monomorphic skin-colored papules in the axillary vault. Lesions may be intensely pruritic or patients may be unaware of the condition.

Clinical features

Fox–Fordyce disease presents as dome-shaped, skin-colored, discrete perifollicular papules in the axillary (Fig. 39.15), anogenital and periareolar skin. Less common locations include the medial thighs, periumbilical area and sternal region. Loss of hair in affected areas is frequently observed. The condition is often intensely pruritic. Pregnancy and oral contraception may ameliorate the itching, while heat and emotional stress can aggravate symptoms.

Pathology

Early histologic findings of Fox–Fordyce disease include a keratin plug in the follicular infundibulum, which obstructs the entrance of the apocrine duct. This blockage leads to apocrine sweat retention and subsequent rupture of the duct at the level of the epidermis. Epidermal spongiosis and vesiculation are seen. Associated findings include a perifollicular and periadnexal inflammatory infiltrate, consisting of lymphocytes with occasional histiocytes and eosinophils.

Treatment

Treatment of Fox–Fordyce disease is difficult. Topical and intralesional corticosteroids are often a first-line therapy, although their use may be limited by the risk of cutaneous atrophy in naturally occluded sites. Topical calcineurin inhibitors may reduce pruritus and improve the appearance of skin lesions. Topical tretinoin has been shown to reduce pruritus, but has little effect on the clinical appearance of the disease and may produce irritation[36]. Twice-daily clindamycin lotion may also be useful in minimizing symptoms[37]. Some women respond to oral contraceptives[38], while other patients receive temporary relief from oral isotretinoin. Physical interventions that may be beneficial include phototherapy, electrocautery and excision of periareolar skin.

REFERENCES

1. Hurley HJ. The eccrine sweat glands: structure and function. In: Freinkel RK, Woodley DT (eds). The Biology of the Skin. New York: Parthenon Publications, 2001:47–76.
2. Kenney LW, Munce TA. Aging and human temperature regulation. J Appl Physiol. 2003;95:2598–603.
3. Rothman S. Sweat secretion. In: Physiology and Biochemistry of the Skin. Chicago: Chicago University Press, 1954:162–78.
4. Sutton DR, Kowalski JW, Glaswer DA, Stang PE. US prevalence of hyperhidrosis and impact on individuals with axillary hyperhidrosis: results from a national survey. J Am Acad Dermatol. 2004;51:241–8.
5. Hornberger J, Grimes K, Naumann M, et al. Recognition, diagnosis and treatment of primary focal hyperhidrosis. J Am Acad Dermatol. 2004;51:274–86.
6. Hurley HJ, Shelley WB. Axillary hyperhidrosis clinical features and local surgical management. Br J Dermatol. 1966;78:127–41.
7. Higashimoto I, Yoshiura K, Hirakawa N, et al. Primary palmar hyperhidrosis locus maps to 14q11.2–q13. Am J Med Genet. 2006;140:567–72.
8. Masters W, Johnson V. Human Sexual Response. Boston: Little, Brown & Co., 1966:287, 291.
9. Schwartzman RJ, McLellan TL. Reflex sympathetic dystrophy. A review. Arch Neurol. 1987;44:555–61.
10. Linder F. Über den Einfluss der Hirnrinde auf die Schweissekretion (zur Frage der vegetativen Hempilagie). Deutsche Ztschr Nervenh. 1947;157:86–94.
11. Willaert WI, Scheltinga MR, Steenhuisen SF, Hiel JA. Harlequin syndrome: two new cases and a management proposal. Acta Neurol Belg. 2009;109:214–20.
12. Prout BJ, Wardell WM. Sweating and peripheral blood flow in patients with pheochromocytoma. Clin Sci. 1969;36:109–20.
13. Sato K, Kang WH, Saga K, Sato KT. Biology of sweat glands and their disorders. II. Disorders of sweat gland function. J Am Acad Dermatol. 1989;20:713–26.
14. Mailander JC. Heritable gustatory sweating. J Am Med Assoc. 1967;201:203–5.
15. Mellinkoff J, Mellinkoff JL. Gustatory sweating of the left knee. J Am Med Assoc. 1950;142;901–2.
16. Bloor K. Gustatory sweating and other responses after cervico-thoracic sympathectomy. Brain. 1969;92:137–46.
17. Pasquina RF, Houston RM, Belandres PV. Beta-blockade in the treatment of autonomic dysreflexia. A case report and review. Arch Phys Med Rehab. 1998;79:582–4.
18. Hokfelt T, Johansson O, Kellerth JO, et al. Immunohistochemical distribution of substance P. In: von Euler US, Pernow B (eds). Substance P. New York: Raven Press, 1977:117–45.
19. Randall WC. Quantitation of the output of individual sweat glands and their response to stimulation. J Appl Physiol. 1949;2:72–80.
20. LeWitt P. Hyperhidrosis and hypothermia responsive to oxybutynin. Neurology. 1998;39:506–7.
21. Edick CM. Oral glycopyrrolate for the treatment of diabetic gustatory sweating. Ann Pharmacother. 2005;39:1760.
22. Torch EM. Remission of facial and scalp hyperhidrosis with clonidine hydrochloride and topical aluminum chloride. South Med J. 2000;93:68–9.
23. Manusov EG, Nadeau MT. Hyperhidrosis: a management dilemma. J Fam Pract. 1989;28:412–15.
24. Connolly M, de Berker D. Management of primary hyperhidrosis: a summary of the different treatment modalities. Am J Clin Dermatol. 2003;4:861–97.
25. Bechara FG, Sand M, Tomi NS, et al. Repeat liposuction-curettage treatment of axillary hyperhidrosis is safe and effective. Br J Dermatol. 2007;157:739–43.
26. Frias JL, Smith DW. Diminished sweat pores in hypohidrotic ectodermal dysplasia. A new method for assessment. J Pediatr. 1968;72:606–10.
27. Wenzel FG, Horn TD. Nonneoplastic disorders of the eccrine glands. J Am Acad Dermatol. 1998;38:1–17.
28. Kirk JF, Wilson BB, Chun W, Cooper PH. Miliaria profunda. J Am Acad Dermatol. 1996;35:854–6.
29. Cawley EP, Hoch-Legati C, Bond GM. The eccrine sweat glands of patients with uremia. Arch Dermatol. 1961;84:889–97.
30. de la Torre R, Farre M, Navarro M, et al. Clinical pharmacokinetics of amphetamine and related substances: monitoring in conventional and nonconventional matrices. Clin Pharmacokinet. 2004;43;157–85.
31. Cohn JR, Emmett EA. The excretion of trace elements in human sweat. Ann Clin Lab Sci. 1978;8:270–5.
32. Leopold DA, Preti G, Mozell MM, et al. Fish odor syndrome presenting as dysosmia. Arch Otolaryngol Head Neck Surg. 1990;116:354–5.
33. Ding Y, He L, Zhang Q, et al. Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways. J Pathol. 2004;203:622–30.
34. Shear NH, Knowles SR, Shapero L, Poldri P. Dapsone in prevention of recurrent neutrophilic hidradenitis. J Am Acad Dermatol. 1996;35:819–22.
35. Simon M Jr, Cremer H, von den Driesch P. Idiopathic recurrent palmoplantar hidradenitis in children. Report of 22 cases. Arch Dermatol. 1998;134:76–9.
36. Giacobetti R, Caro WA, Roenigk HH. Fox-Fordyce disease: control with tretinoin cream. Arch Dermatol. 1979;115:1365–6.
37. Miller ML, Harford RR, Yeager JK. Fox-Fordyce disease treated with topical clindamycin solution. Arch Dermatol. 1995;131:1112–13.
38. Kronthal HJ, Pomeranz JR, Sitomer G. Fox-Fordyce disease. Treatment with oral contraceptives. Arch Dermatol. 1965;91:243–5.

Sweating pattern in axillary hyperhidrosis. Blue–black areas represent foci of sweating, as demonstrated by the starch–iodine technique: iodine solution (e.g. 3.5% in alcohol) is applied to clean, shaved skin and allowed to dry, then starch powder (e.g. cornstarch) is brushed onto the area.

Autoantibodies Encountered in Patients with Autoimmune Connective Tissue Diseases

40

Heidi T Jacobe, Richard D Sontheimer and Stephanie Saxton-Daniels

Chapter Contents

Autoantibodies encountered in lupus erythematosus *607*
Autoantibodies encountered in idiopathic inflammatory dermatomyopathies *609*
Autoantibodies encountered in systemic sclerosis (scleroderma) and morphea (localized scleroderma) *613*
Autoantibodies encountered in other rheumatic disorders that can affect the skin *613*

Key features

- Autoantibodies can be of significant value in the diagnosis, management and prognosis of the autoimmune connective tissue diseases (AI-CTDs), but their interpretation depends on the type of autoantibody and the specific AI-CTD
- The classic ANA assay remains the entrée into the world of AI-CTD serology, and understanding its limitations is critical to clinical decision-making
- The evolution of clinical immunology laboratory technology has altered the significance of some of the original clinical–serologic correlations reported at the time of discovery of the autoantibodies. Basic understanding of key technical issues related to current laboratory methodologies is therefore important
- There has been a trend toward adopting solid-phase immunoassay techniques (e.g. ELISA) to detect many autoantibodies. For several autoantibodies, including anti-Ro/SS-A and anti-double-stranded (ds) DNA antibodies, this has resulted in some decrease in disease specificity
- Certain autoantibodies have significant disease specificity and thus can be of great diagnostic value: anti-dsDNA and anti-Smith (Sm) for systemic lupus erythematosus (SLE); anti-Mi-2 for classic dermatomyositis; anti-Jo-1 for antisynthetase syndrome; anti-topoisomerase-1 (Scl-70), anti-RNA polymerases (RNAP), and anticentromere for different clinical forms of systemic sclerosis; and cytoplasmic antineutrophil cytoplasmic antibodies (C-ANCA) for Wegener's granulomatosis. However, most autoantibodies fall into the disease-nonspecific category
- The absolute blood levels of a few autoantibodies can correlate positively with underlying autoimmune disease activity (e.g. anti-dsDNA in SLE, C-ANCA in Wegener's granulomatosis), but in most cases the titer does not correlate with disease activity

INTRODUCTION

The autoimmune connective tissue diseases (AI-CTDs) are a group of polygenic clinical disorders often having heterogeneous and overlapping clinical features; the term "rheumatic diseases" can be used synonymously for AI-CTD. It should be noted that the older designation, "collagen vascular diseases", is an obsolete term that should be avoided. Furthermore, the unqualified term "connective tissue diseases" can cause confusion with genetic disorders that involve structural abnormalities of connective tissue, e.g. Ehlers–Danlos syndrome.

A hallmark of these disorders is the production of circulating autoantibodies (aAb) that have been identified by various immunochemical techniques. When the diagnosis of an AI-CTD is being considered, the most commonly requested laboratory test is measurement of antinuclear antibodies (ANA). For the purposes of this chapter, ANA are defined as all aAb that can be detected by indirect immunofluorescence microscopy and are reactive against nuclei (or sometimes the cytoplasm) of human cells. ANA preferentially target cellular structures vital to cellular function (e.g. DNA- and RNA-binding proteins) and they are primarily of the IgG class. These aAb reflect basic inflammatory events in tissue, but rarely carry pathogenic potential (the exception being ANCA).

If used appropriately, clinical laboratory testing for ANA can be useful in the diagnosis and management of AI-CTD patients. In order to maximize the clinical utility of aAb testing in AI-CTD, familiarity with the serologic tests currently used to identify these aAb, as well as the disease associations of the various aAb, is helpful.

When approached comprehensively, serologic testing in the AI-CTDs is a broad and intimidating subject. However, our discussion will focus on the clinical significance of the various aAb associated with AI-CTDs that have expression in the skin (i.e. lupus erythematosus [LE], dermatomyositis [DM], systemic sclerosis [SSc] and ANCA-associated vasculitides). Chapters 41–45 present an in-depth discussion of these disorders. Therefore, the molecular identity of the various autoantigens and their clinical associations are summarized in table form (see Tables 40.2–40.4). For the reader who desires a more comprehensive analysis, several review articles are listed.

An effort will be made to illustrate the often complex relationships that can exist between the presence and relative amounts of these aAb, disease diagnosis, and prognosis. The basic principles of clinical utility as related to the various aAb laboratory tests (e.g. sensitivity, specificity) will be briefly addressed. The related subjects of circulating immune complexes and cryoglobulins are discussed in Chapters 4, 23 and 24.

Chapter Organization

Although the various AI-CTDs are distinct clinical entities, they can have features in common. Consequently, each AI-CTD has aAb specific to that particular disorder as well as other aAb that are shared with the other diseases. In addition, some patients can display overlapping clinical features of several different AI-CTDs and, as a result, an overlap in the pattern of aAb production (Fig. 40.1).

This chapter is organized based upon two major considerations in the use of aAb testing:

- historical and technical aspects of ANA assays
- aAb associated with AI-CTDs that have cutaneous manifestations.

HISTORICAL PERSPECTIVE

One can better appreciate the evolution of thought that has occurred in this area by considering the change in methodology used to identify and measure these aAb over the past 50 years[1]. In 1948, Hargraves, aided by the observations of John Haserik, described the LE cell phenomenon that is still thought to be specific for systemic LE (SLE), but is rarely performed. Approximately 10 years later, Friou and co-workers used the newly described indirect immunofluorescence microscopy technique to establish the classic, cell-based ANA assay.

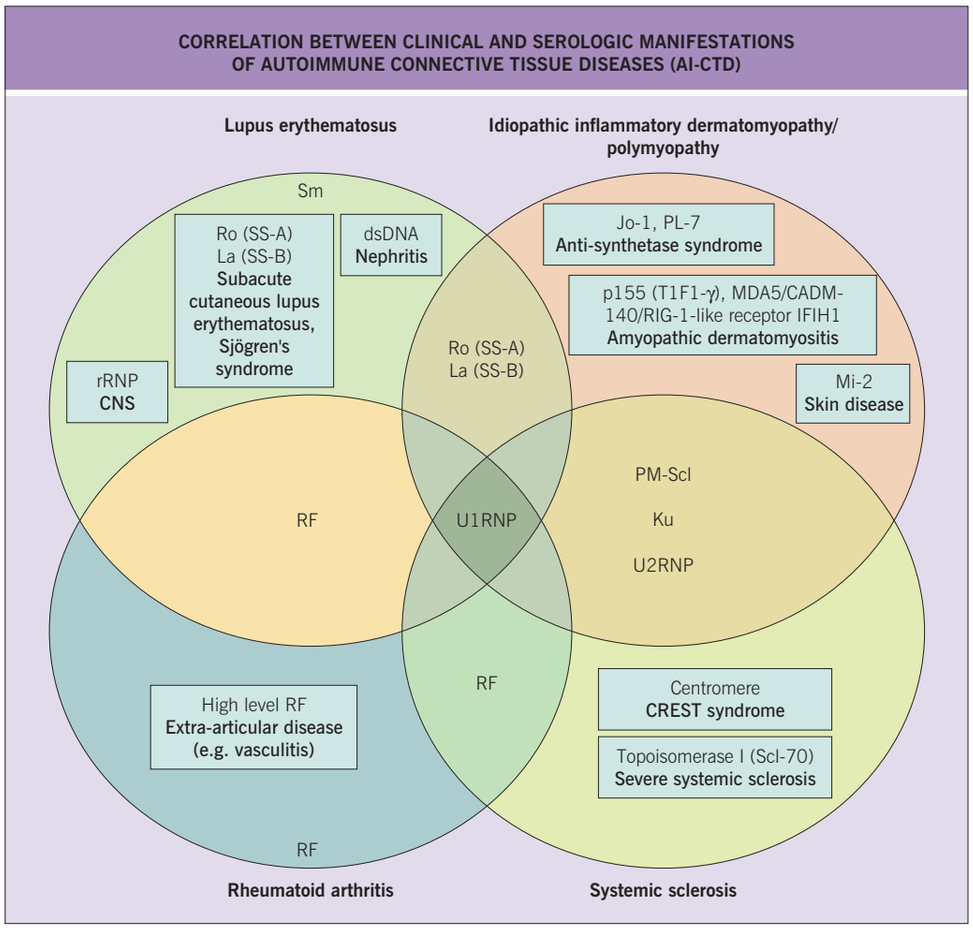


Fig. 40.1 Correlation between clinical and serologic manifestations of autoimmune connective tissue diseases (AI-CTD). Venn diagram representation of major clinico-serologic correlations in the primary AI-CTD that impact the skin. Some targets of autoantibodies are specific (boxed with clinical associations) while others are seen in the context of overlapping clinical features. High levels of U1RNP autoantibody with overlapping features of all four of these AI-CTD defines the concept of mixed connective tissue disease. With thanks to Jan Dutz, MD, for contributory comments. CADM, clinically amyopathic dermatomyositis; IFIH1, interferon induced with helicase C domain-containing protein 1; MDA5, melanoma differentiation-associated gene 5; p155, a 155 kDa polypeptide; RF, rheumatoid factor; RNP, ribonucleoprotein, TIF1-γ, transcriptional intermediary factor 1 gamma.

A decade later, Tan and co-workers (followed shortly by Clark, Reichlin and co-workers) employed the Ouchterlony double immunodiffusion technique to identify and define precipitating serum aAb that reacted with saline extractable nuclear antigens (ENA) such as nuclear ribonucleoprotein (nRNP), Sm, Ro/SS-A and La/SS-B. Unfortunately, the Ouchterlony double immunodiffusion technique is time-consuming and expensive. However, a more efficient adaptation of the double immunodiffusion technique, counterimmunoelectrophoresis, can be used as an alternative to the less expensive solid-phase immunoassays (e.g. *e*nzyme-*l*inked *i*mmuno*s*orbent *a*ssay [ELISA]; see below)[2].

In 1979, the molecularly and genetically defined ANA era began as the result of work by Lerner and Steitz, who employed immunodiffusion and Western blotting (see Chs 3 & 81) to define the molecular identities of the nRNP and Ro : La families of ribonucleoprotein autoantigens. These observations generated the notion that the various AI-CTD aAb might be more efficiently and cost-effectively assayed by using purified and/or recombinant forms of the various autoantigens in solid-phase immunoassays such as the ELISA. While less expensive and more convenient, there are a number of drawbacks to employing the ELISA and related immunoassay techniques to detect ANA such as anti-Ro/SS-A and anti-dsDNA aAb, in particular increased sensitivity and decreased specificity (see below). Newer techniques (e.g. proteasome microarrays, Luminex xMAP® technology) are currently under development and in the future they may allow the simultaneous profiling of all relevant aAb in a given patient.

Understanding the actual immunochemical techniques used to detect and quantify the various types of ANA can be helpful to the clinician, but is beyond the scope of this chapter. The reader is referred to a review by Griesmacher and Peichl[3].

THE CLASSIC ANA ASSAY

Although there is debate about its role in the diagnosis and management of AI-CTD[4,5], the classic ANA indirect immunofluorescence assay is still the most clinically efficient screening test for systemic autoimmune disorders such as SLE. A number of potential pitfalls must be considered when interpreting the results of the ANA assay (Table 40.1). The following discussion will focus on the key aspects of interpreting ANA test results. More detailed discussions are available elsewhere[1,3,6–9].

Importance of Technical Aspects of the ANA Assay

As the name implies, the ANA assay identifies antibodies present in serum that bind to autoantigens present in the nuclei (or cytoplasm) of mammalian cells. The current version of the ANA assay used in almost all clinical laboratories employs a *human* tumor cell line such as Hep-2 for the nucleated cell substrate. aAb are detected with a fluorochrome-conjugated antiserum that is specific for human immunoglobulin (the aAb) that is bound to nuclei in the cell substrate (Fig. 40.2). Earlier versions of the ANA assay utilized rodent cell lines and the latter lacked some of the autoantigens present in human cell nuclei (e.g. Ro/SS-A). Thus, sera from some SLE patients could be negative when assayed on rodent cells, especially if the predominant aAb were anti-Ro/SS-A (i.e. "ANA-negative SLE"). This occurred in up to 15% of certain SLE patient populations, particularly those enriched in anti-Ro/SS-A aAb-associated disorders such as subacute cutaneous LE (SCLE) and Sjögren's syndrome (SjS). Nowadays, because of the use of human

MAJOR ISSUES RELATED TO THE INTERPRETATION OF RESULTS OF ANTINUCLEAR ANTIBODY ASSAYS
• Methods of detecting and reporting ANA
• Subjective nature of ANA assay endpoint
• "Normal" versus "abnormal" ANA levels
• Patient age
• Drug-induced ANA
• ANA can be seen in disorders other than AI-CTDs
• Sontheimer's corollary to Greenwald's Law of Lupus

Table 40.1 Major issues related to the interpretation of results of antinuclear antibody (ANA) assays.

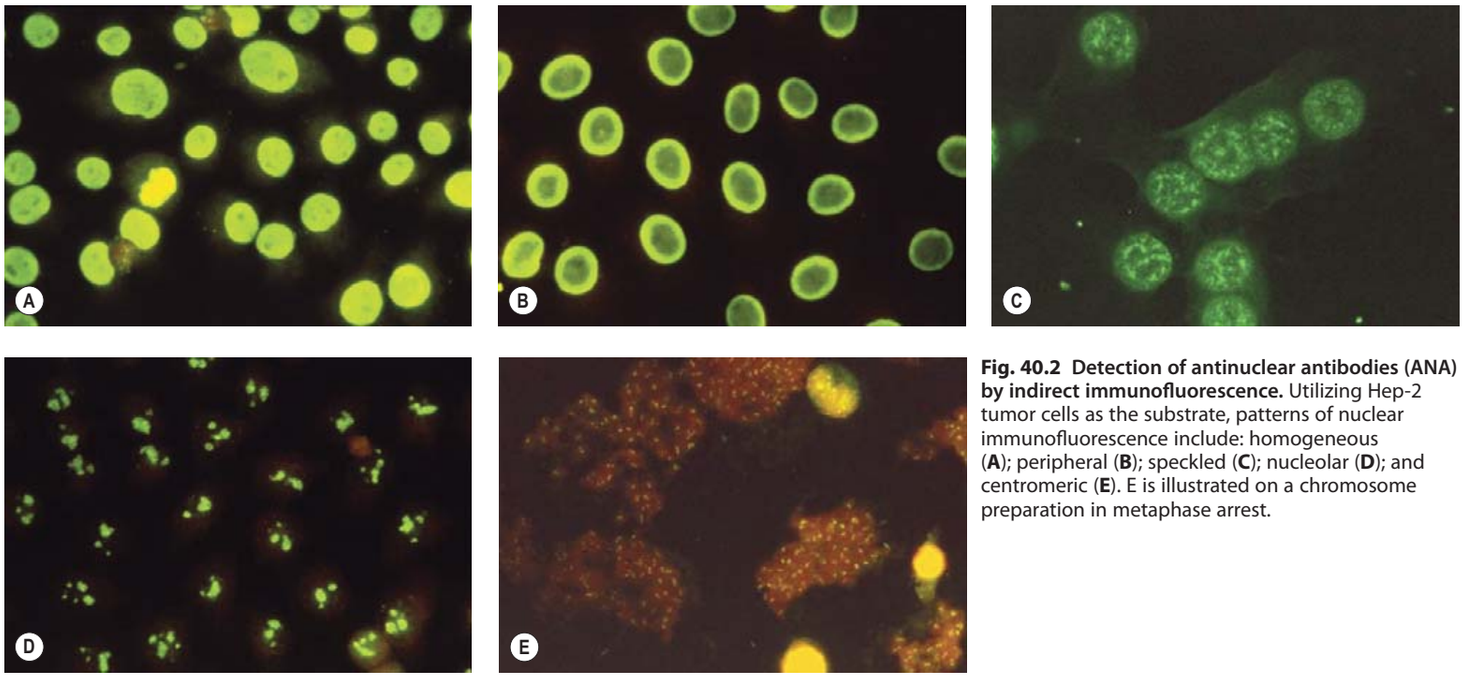


Fig. 40.2 Detection of antinuclear antibodies (ANA) by indirect immunofluorescence. Utilizing Hep-2 tumor cells as the substrate, patterns of nuclear immunofluorescence include: homogeneous (**A**); peripheral (**B**); speckled (**C**); nucleolar (**D**); and centromeric (**E**). E is illustrated on a chromosome preparation in metaphase arrest.

Hep-2 cells, only ~1–2% of SLE patients are ANA-negative. Thus, "ANA-negative SLE" is predominantly an historical phenomenon.

It is also important to remember that determination of the ANA assay *titer* (which reflects the serial serum dilutions necessary for fluorescence to disappear) depends upon subjective interpretation by a laboratory technician. Consequently, even in the same laboratory, a single serum specimen can have an ANA titer result that varies within a two-tube dilution range. In other words, a serum sample reported as having an ANA titer of 1:320 might be read as 1:160 or 1:640 upon repeat testing in the same laboratory within the same timeframe. Such variability is more often encountered when different laboratory technicians read and report ANA results. Although an attempt has been made by the World Health Organization to standardize reporting of ANA results with an international unit system (e.g. 1 IU rather than a titer of 1:160), virtually all clinical laboratories in the US continue to report ANA results using a titer system.

"Normal" Versus "Abnormal" ANA Values

The ANA titer that is considered to be abnormal can vary significantly, depending upon how the assay is performed and interpreted. The commercial ANA kits that are used most commonly in laboratories today usually indicate that an ANA titer of 1:40 or 1:80 is considered abnormal (presumably because accepting such relatively low levels of ANA as being abnormal retains a high degree of *sensitivity* of the ANA assay in detecting systemic AI-CTD). However, using such low ANA titer cut-offs creates a lot of positive, but clinically insignificant, ANA test results, i.e. it reduces specificity. A number of studies that have compared ANA results in SLE populations with those in normal control populations have indicated that a titer of <1:160, using a human tumor cell line substrate, has little clinical utility. For example, in one report based upon 15 international laboratories, the ANA positivity rate in a population of healthy individuals (ages 20–60 years) was 13.3% at 1:80, 5.0% at 1:160, and 3.3% at 1:320[10]. Of note, the elderly, relatives of those with SLE, and patients with other autoimmune disorders (e.g. autoimmune thyroid disease), as well as healthy individuals, may have abnormally elevated ANA titers.

CLINICAL SIGNIFICANCE OF ANA

Immunofluorescence Patterns

Various patterns of nuclear immunofluorescence can be observed in the ANA assay (i.e. homogeneous [syn. diffuse; Fig. 40.2A], peripheral [syn. rim; Fig. 40.2B], speckled [syn. particulate; Fig. 40.2C], nucleolar [Fig. 40.2D], and centromeric [syn. discrete speckled; Fig. 40.2E]). With one exception (see below), these patterns have little disease specificity and are of little value in the management of patients. Furthermore, most commercial laboratories report primarily homogeneous and speckled nucleoplasmic staining patterns. Because these two patterns commonly occur in healthy and older individuals, a higher threshold may need to be set for determining whether a titer is clinically relevant (e.g. ≥1:160).

The exception is the centromeric (discrete speckled) pattern (see Fig. 40.2E), which is a reflection of antibodies binding to the polypeptide components of chromosomal centromeres (e.g. CENP-B); this pattern is associated primarily with the limited form of SSc (see Table 40.4). A peripheral (rim) ANA pattern can be suggestive of the presence of aAb to DNA, including dsDNA (SLE). The nucleolar ANA pattern is due to aAb binding to ribosomal RNA processing molecules such as fibrillarin, and it can be indicative of SSc. A high-titer speckled (particulate) ANA pattern is due to a number of antibodies, including those that recognize Sm, RNP, Ro/SS-A, La/SS-B, Sc1-70 and RNA polymerases (RNAP). In general, however, specific tests for nuclear and cytoplasmic antigens, rather than ANA patterns, are used nowadays to identify specific aAb.

Concept of Clinical Utility as Applied to aAb Testing

A comprehensive discussion of the concept of clinical utility in laboratory testing (i.e. sensitivity, specificity, positive predictive value, negative predictive value) can be found elsewhere[6–9]. However, by way of summary, the key concepts of clinical utility analysis are presented in Figure 40.3. These principles should be kept in mind

CONCEPT OF CLINICAL UTILITY IN LABORATORY TESTING

	Disease present	Disease absent
Positive result	True positive (TP)	False positive (FP)
Negative result	False negative (FN)	True negative (TN)

Sensitivity=TP/(TP+FN)
Specificity=TN/(TN+FP)
Positive predictive value=TP/(TP+FP)
Negative predictive value=TN/(TN+FN)

Fig. 40.3 Concept of clinical utility in laboratory testing. With thanks to Jan Dutz, MD, for contributory comments. *With permission from Ward MM. Laboratory testing for systemic rheumatic diseases. Postgrad Med. 1998;103:93–100.*

at all times when considering the cost–benefit ratio of the various types of laboratory testing currently available for autoimmune diseases.

The ANA test is used most often for the diagnosis of SLE, and in populations of SLE patients, sensitivity is 98% and specificity 90%[7,8]. However, in *unselected populations of individuals*, the positive predictive value of ANA testing for the detection of SLE is 30–40%, while the negative predictive value is 99%. Thus, about two-thirds of positive ANAs seen in a general medical population will be associated with disorders other than SLE and only very rarely will a person with a negative ANA have SLE. It is also important to remember that a positive ANA can be found in a large percentage of patients with other AI-CTDs: SSc (90%), SjS (70%), idiopathic inflammatory dermatomyopathies (DM/PM) (40–65%). There are numerous clinical associations for a positive ANA test[11], and it is very important to realize that often clinically silent systemic autoimmune diseases, such as autoimmune thyroiditis, pernicious anemia or Addison's disease, can contribute to a positive ANA in patients who present with organ-specific autoimmune dermatologic disorders such as vitiligo and alopecia areata.

Clinical Value of aAb in Diagnosis Versus Disease Activity Monitoring

In everyday practice, these laboratory tests can be used to: establish the diagnosis of an AI-CTD; provide prognostic information; and, in specific instances, monitor the level of systemic activity of an AI-CTD[7,8]. For example, the Sm aAb is highly specific for SLE and thus has considerable diagnostic value. However, the absolute amounts of anti-Sm aAb present in the circulation of a patient at different points in time do not correlate strongly enough with SLE disease activity to have practical clinical value in patient management. Likewise, there is not much value in serial determinations of titers of the ANA assay to monitor disease activity in SLE. However, a few aAb can be used for establishing the diagnosis and monitoring systemic activity, e.g. anti-dsDNA in LE nephritis and cytoplasmic antineutrophil cytoplasmic antibodies (C-ANCA) in Wegener's granulomatosis. In the case of providing prognostic information, an example would be the presence of anti-RNAP aAb as a risk factor for the development of renal crisis in scleroderma.

"Sontheimer's Corollary" to Greenwald's Law of Lupus

Robert A Greenwald formulated a law stating that if a patient is diagnosed as having SLE, everything that happens to that patient afterwards, rightly or wrongly, is attributed to SLE. One of us (RDS) formulated a corollary to Greenwald's Law, stating that anything happening to a patient with a positive ANA that is not immediately otherwise explicable will automatically be blamed on SLE[12]. This is especially true in patients presenting with non-lupus photosensitive facial eruptions (e.g. rosacea, polymorphic light eruption, photoallergic contact dermatitis) who might also have a positive ANA test for reasons other than SLE[13].

Phototherapy and the ANA Assay

The question of ANA and anti-Ro/SS-A antibody testing often arises in patients being considered for phototherapy, especially if there is any concern about an underlying photosensitive state. However, when screening patients for a multisystem autoimmune disease such as SLE, it is a good rule to remember that patients having any degree of clinically significant SLE are virtually never asymptomatic. Symptoms such as easy fatigability, malaise and arthralgias are almost always present. In addition, studies have shown that phototherapy protocols such as PUVA do not significantly induce the appearance of ANA and other AI-CTD aAb. Therefore, while a thorough history, review of systems and physical examination are indicated in all patients prior to phototherapy, ANA testing is not, unless there is a consistent history or suggestive physical findings.

How Does One Evaluate a Positive ANA Result in a Patient Suspected of Having SLE?

This question would likely be answered differently by different specialists. Dermatologists usually see a highly selected population of LE patients by virtue of their having some form of cutaneous involvement that at times can be the only significant clinical manifestation of the autoimmune disease process (e.g. chronic or subacute cutaneous LE). Therefore, in comparison to a rheumatologist evaluating a patient with suspected SLE, a more focused approach can be undertaken by a dermatologist evaluating a positive ANA in a patient who has or is suspected of having cutaneous LE (Fig. 40.4).

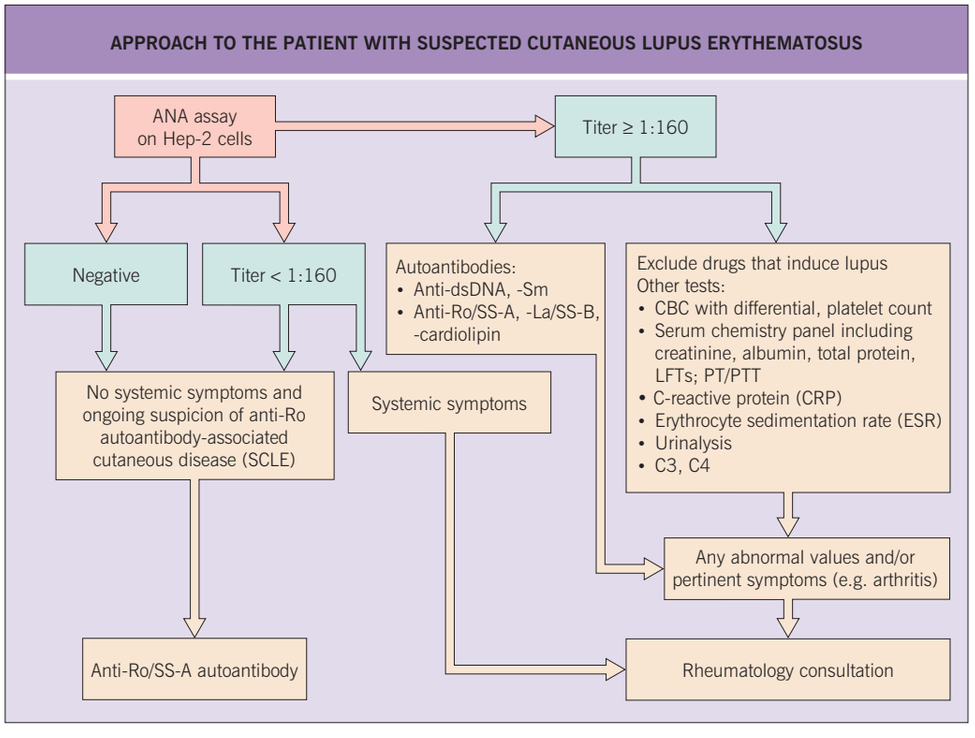


Fig. 40.4 Approach to the patient with suspected cutaneous lupus erythematosus. It should be noted that these recommendations are most relevant within the context of a dermatology practice setting. CBC, complete blood count; LFTS, liver function tests; PT, prothrombin time; PTT, partial thromboplastin time; SCLE, subacute cutaneous lupus erythematosus. With thanks to Jan Dutz, MD, for contributory comments.

AUTOANTIBODIES ENCOUNTERED IN LUPUS ERYTHEMATOSUS

A listing of aAb that can be seen in patients with LE (see Ch. 41) is presented in Table 40.2. In addition, data related to the prevalence with which they are observed, their specific clinical associations, and their molecular specificities are also provided; the latter are addressed in depth in several reviews[1,3,7,8,14,15]. The prevalences of the aAb presented in the tables in this chapter represent the estimated median values reported from different cross-sectional studies where the conventional assay techniques used in most clinical laboratories today were employed (unfortunately, the results of such studies can vary widely). In addition, the various aAb encountered in SLE are subdivided into those that are and are not specific for SLE.

aAb to Sm and dsDNA are specific and prevalent enough to represent one of the 11 ACR classification criteria for SLE (see Ch. 41). aAb to single-stranded (ss) DNA are also seen in LE but are not at all specific for this disorder. Rising levels of anti-dsDNA aAb correlate positively with SLE disease activity, especially when associated with falling complement values. High levels can reflect an increased risk for LE nephritis. Unfortunately, the clinical value of anti-dsDNA aAb measurements is somewhat diluted by the characteristics of modern assay techniques. The popular ELISA assays preferentially detect *low-avidity* anti-dsDNA aAb that are also seen in patients who do not have SLE. It is recommended that all positive anti-dsDNA aAb ELISA results be confirmed by a second assay technique that detects *high-avidity* anti-dsDNA aAb, such as the Farr radioimmunoassay or the *Crithidia luciliae* indirect immunofluorescence assay. Unfortunately, there are similar issues associated with the current assay techniques for a number of the AI-CTD aAb[3,14,16] (see below).

Anti-Ro/SS-A and anti-La/SS-B aAb were originally thought to react exclusively with cytoplasmic RNP and were thus designated as

AUTOANTIBODIES ASSOCIATED WITH LUPUS ERYTHEMATOSUS

Target	Median prevalence*	Molecular specificity	Clinical associations
		HIGH SPECIFICITY FOR SLE	
dsDNA†	60%	Double-stranded (native) DNA	LE nephritis and monitoring activity of nephritis
Sm	10–30% of Caucasians; 30–40% of Asians and African-Americans	Splicesome RNP (ribonucleoprotein particles involved in splicing pre-mRNA)	
rRNP	7–15%; 40% of Asians	Ribosomal P proteins (proteins involved in ribosome function)	Neuropsychiatric LE
		LOW SPECIFICITY FOR SLE	
ANA (most common IF patterns: homogeneous, peripheral)	99%		
ssDNA	70%	Denatured DNA	Possible risk for SLE in DLE patients; also seen in RA, DM/PM, MCTD, SSc, SjS, morphea
C1q	60%	C1q component of complement	Severe SLE, hypocomplementemic urticarial vasculitis syndrome
PCNA	50%	A component of multiprotein complexes involved in cell proliferation	–
U1RNP	50%	Splicesome RNP	Overlapping features with other AI-CTDs; MCTD (100%)
Ro/SS-A	50%	hYRNP (quality control function for misfolded RNA molecules)	SCLE (75–90%), neonatal LE/congenital heart block (99%), SCLE–SjS overlap, primary SjS (70%); associated with vasculitis
La/SS-B	20%	hYRNP	SCLE (30–40%), SCLE–SjS overlap, primary SjS (40%); occurs in conjunction with Ro/SS-A
Cardiolipin	50%	Cardiolipin, a negatively charged phospholipid	Recurrent spontaneous abortions, thrombocytopenia, and hypercoagulable state in SLE (cutaneous manifestations include livedo reticularis, leg ulcers, acral infarction/ulceration, hemorrhagic cutaneous necrosis); similar associations in primary antiphospholipid antibody syndrome; clinical manifestations have strongest association with IgG class of anticardiolipin
β2 glycoprotein I	25%	An important cofactor for cardiolipin in cardiolipin aAb assays	Relatively high risk of thrombosis in SLE and primary antiphospholipid antibody syndrome
Histones	40%	Histones	Drug-induced SLE; also RA, SLE and SSc with pulmonary fibrosis (in conjunction with other aAb)
Rheumatoid factor	25%	Fc portion of IgG	Nonspecific
Ku	10%	DNA end-binding repair protein complex	Overlap with other AI-CTDs such as DM/PM, SSc
Alpha-fodrin	10%	An actin-binding protein found at the periphery of chromaffin cells that may be involved in secretion	SjS

*Based on most common assay techniques currently employed in clinical immunology laboratories. Note that these figures represent the authors' best estimates based on most recently published data.
†Listed in decreasing order of prevalence within categories.

Table 40.2 Autoantibodies associated with lupus erythematosus. aAb, autoantibody; AI-CTDs, autoimmune connective tissue diseases; ANA, antinuclear antibodies; DLE, discoid lupus erythematosus; DM/PM, dermatomyositis/polymyositis; IF, immunofluorescence; LE, lupus erythematosus; MCTD, mixed connective tissue disease; PCNA, proliferating cell nuclear antigen; RA, rheumatoid arthritis; RNP, ribonucleoprotein; SCLE, subacute cutaneous lupus erythematosus; SjS, Sjögren's syndrome; SLE, systemic lupus erythematosus; SSc, systemic sclerosis. Adapted from ref. 1.

cytoplasmic aAb. However, subsequent work has documented that these aAb react with proteins present in human cytoplasmic RNP (hYRNP) that are found in both the cytoplasm and nucleus. The Ro and La proteins are a "linked set" of autoantigens by virtue of their being present in the same RNP particles. As a result, an autoimmune response that develops against one of these autoantigens often spreads to the other. This explains the observation that when one aAb is present in an individual, the other is frequently present as well. (Anti-Ro/SS-A aAb can occur alone; however, it is extremely rare for anti-La/SS-B aAb to occur without anti-Ro/SS-A aAb.)

As with anti-dsDNA aAb assays, it is important to understand certain technical considerations relating to anti-RNP aAb assays, such as those used to measure anti-Ro/SS-A, anti-La/SS-B, anti-U1RNP and anti-Sm aAb (i.e. ENA). A number of these aAb were originally identified by Ouchterlony double immunodiffusion, which is a less sensitive but highly specific technique for identifying such aAb. However, this assay has been replaced by solid-phase immunoassays such as ELISA (see earlier), and the ELISA is more sensitive but less specific for detecting anti-RNP aAb. As a result, some of the original clinical correlations for anti-Ro/SS-A, anti-La/SS-B, anti-Sm and anti-U1RNP aAb that related to the results of immunodiffusion analysis do not hold with regard to the results of modern ELISA.

This issue can be illustrated by the results of studies that examined the measurement of anti-Ro/SS-A and anti-La/SS-B aAb, aAb of importance to dermatologists given their association with idiopathic and drug-induced SCLE, neonatal LE, annular erythema of SjS, and SLE. Lee and colleagues[17] compared the sensitivity of Ouchterlony double immunodiffusion and ELISA assays for the detection of aAb to native forms of the human Ro/SS-A antigen in different clinical settings. In unselected populations of SLE patients, abnormal levels of anti-Ro/SS-A aAb detected by ELISA were twice as prevalent (50%) as those detected by immunodiffusion (25%). Greater than 90% of SCLE patients had anti-Ro/SS-A antibody by ELISA, whereas only 65–75% were positive by immunodiffusion. Sixty percent of DLE patients were positive for anti-Ro/SS-A aAb by ELISA, while fewer than 5% were positive by immunodiffusion. Ten percent of normal individuals had anti-Ro/SS-A antibody by ELISA, with fewer than 0.3% having such antibodies by immunodiffusion. Therefore, the ELISA technique was much more sensitive in detecting anti-Ro/SS-A aAb; however, it was considerably less specific than the Ouchterlony double immunodiffusion assay. The authors of this chapter would support the more recent suggestion that any equivocal anti-RNP aAb results obtained by ELISA should be confirmed with more specific assays such as counterimmunoelectrophoresis[2], given that up to 10% of the population has anti-Ro/SS-A antibodies by ELISA.

As another strategy for ascertaining the clinical value of aAb, some investigators have sought to determine whether specific clinical correlations exist with regard to aAb to individual molecular constituents of autoantigen-containing particles. For example, three polypeptides, 60 kDa Ro, 52 kDa Ro and calreticulin, have been associated with hYRNP. Careful attempts have been made to determine whether aAb to 60 kDa Ro and 52 kDa Ro have differential clinical correlations with respect to anti-Ro/SS-A aAb-associated skin diseases, i.e. SCLE, annular erythema of SjS, and neonatal LE/congenital heart block[18]. However, the results of such studies have been equivocal and today no consensus exists in this area.

As can be seen in Table 40.2, there are a number of nonspecific aAb that can be seen in SLE patients that have additional clinical associations. An in-depth discussion of this group of aAb is available in several recent reviews[3,14].

Drug-Induced ANA/SLE

A number of drugs are capable of triggering a positive ANA and/or a drug-induced SLE syndrome (e.g. procainamide, hydralazine, isoniazid, chlorpromazine, phenytoin, quinidine, methyldopa). An important dermatologic drug, minocycline, has also been added to this list. The predominant clinical manifestations of drug-induced SLE are musculoskeletal symptoms (arthritis, arthralgia, myalgia) and serositis (pleuritis, pericarditis). Skin involvement is seen much less commonly in the drug-induced form of SLE. In a comprehensive review of this subject, only 25% of hydralazine-induced SLE patients had "skin involvement", and fewer than 5% of procainamide-induced SLE patients experienced "skin changes". In the same analysis, 71% of idiopathic SLE patients had some type of skin change[19]. It has been the experience of one of the authors (RDS) that when LE-specific skin disease is present, it manifests as acute cutaneous LE (ACLE; see Ch. 41). Antihistone aAb represent a serologic marker of drug-induced ANA and the classic form of drug-induced SLE (present in 95%). A different set of drugs (e.g. hydrochlorothiazide, terbinafine, diltiazem, naproxen, griseofulvin) has been reported to trigger anti-Ro/SS-A aAb production and the cutaneous lesions of SCLE. Antihistone aAb do not appear to be produced in this setting.

Induction of ANA and Anti-dsDNA Antibodies by Tumor Necrosis Factor-α Inhibitors

TNF-α blockade by recombinant proteins has become an increasingly common therapeutic intervention. This form of immunomodulation is associated with the induction of aAb, especially ANA and anti-dsDNA antibodies. However, the clinical significance of these aAb is less clearly defined, as there is a relatively low incidence of clinically detectable autoimmune disease.

Etanercept, a recombinant human TNF receptor fusion protein composed of a dimer consisting of the extracellular portion of two p75 receptors fused to the Fc portion of human IgG1 (see Ch. 128), is approved for use in several disorders, including psoriasis and psoriatic arthritis. There are multiple reports of etanercept inducing ANA and anti-dsDNA antibodies. In a prospective study of 20 spondyloarthropathy patients treated with etanercept for 1 year, three patients (15%) developed newly positive ANAs and one patient (5%) developed a significantly increased titer; anti-dsDNA aAb were present in 3 of 20 patients (15%). None of these patients developed clinically apparent SLE or cutaneous LE[20]. These observations are similar to those previously reported in rheumatoid arthritis (RA) patients treated with etanercept[21,22]. Of those patients in a French national survey who were treated with etanercept for different indications (3800 patients), 4 developed anti-DNA aAb plus cutaneous lesions while 3 had systemic manifestations and fulfilled the diagnostic criteria for SLE[23].

Cutaneous findings noted in patients treated with etanercept include: a butterfly rash (ACLE), SCLE and DLE as well as small vessel vasculitis and chilblains. Additional findings were phlebitis (with anticardiolipin antibodies), leukopenia, thrombocytopenia, serositis, and general manifestations, e.g. fever, weight loss, asthenia. The signs and symptoms of SLE occurred within a mean of 4 months. Once treatment with etanercept was discontinued, serologic and clinical abnormalities abated in all the patients over several weeks (median, 8 weeks)[22,23]. A few patients did receive oral corticosteroids for the associated systemic illness[23], but none developed nephritis (the latter is rare[24]). Women were preferentially affected[22].

Compared with etanercept, *infliximab* (chimeric monoclonal anti-TNF-α antibody) induces a higher rate of aAb formation, but as with etanercept this can have unclear clinical significance. In a prospective study of 34 patients with spondyloarthropathy and 59 patients with RA treated with infliximab for 2 years, 62% and 41% of the patients, respectively, developed newly positive ANAs after 1 year. High rates of anti-dsDNA aAb were also observed (71% of spondyloarthropathy and 49% of RA patients)[20]. These figures have been corroborated in similar patient groups[25] as well as extended to patients with psoriasis treated with infliximab[26]. Of note, none of the spondyloarthropathy patients were on concomitant immunosuppressive therapy, while all of the RA patients were, perhaps accounting for the difference between the two groups. Similarly, Crohn's disease patients who were on immunosuppressive therapy at baseline developed fewer antibodies[27]. Of note, isolated IgM anti-dsDNA aAb are typically not associated with clinical findings, as opposed to the development of multiple aAb (e.g. IgG anti-dsDNA, antihistone aAb), which are commonly seen in patients with TNF-α inhibitor-induced lupus or lupus-like syndrome.[28,29]

Despite the high rate of aAb development in patients treated with infliximab, reports of SLE are relatively unusual. In the French national survey discussed previously[23], 9 patients were diagnosed as having infliximab-induced SLE. The clinical manifestations observed in the etanercept and infliximab groups were similar (see above). Signs of SLE developed after a mean of 9 months of treatment and resolved after a mean of 6 months. In clinical trials involving 2468 patients with RA who had received *adalimumab*, 12.6% developed newly positive ANA

(titer > 1:40) and 10 patients developed findings consistent with lupus[29a]. Of 29 patients with RA who received adalimumab for 24 weeks, 12 (41%) developed newly positive ANA and 1 anti-dsDNA aAb[29b].

In sum, TNF-α inhibitor-induced lupus differs from typical drug-induced lupus in several ways. Firstly, skin manifestations, including a malar rash, SCLE, DLE, photosensitivity and purpura, are prominent[30]. Secondly, ANA and anti-dsDNA aAb are more common than antihistone antibodies[22]. Although the development of aAb occurs relatively commonly, only occasionally are they of clinical significance. Therefore, in the absence of suggestive clinical signs or symptoms, we do not recommend screening for ANA prior to initiation of TNF-α inhibitors.

AUTOANTIBODIES ENCOUNTERED IN IDIOPATHIC INFLAMMATORY DERMATOMYOPATHIES

aAb that can be encountered in patients with the idiopathic inflammatory dermatomyopathies (syn. DM/polymyositis [PM], idiopathic inflammatory myopathies; see Ch. 42) are presented in Table 40.3. At this time, the clinical utility of routine laboratory testing for these antibodies is not well established. Although some are indicative of internal organ involvement and prognosis, they occur so infrequently that they are not helpful in most clinical settings. The designation for this group of diseases, "idiopathic inflammatory *dermato*-myopathies", has been coined to allow inclusion of cutaneous-only or cutaneous-predominant subsets of DM, such as clinically amyopathic DM (i.e. amyopathic DM and hypomyopathic DM)[31–34].

p155 (TIF1-γ) and MDA5/CADM-140/RIG-I-like receptor IFIH1

Patients with adult-onset, clinically amyopathic DM appear to have a somewhat higher prevalence of ANA (65%) than do patients with classic DM and PM. However, not until recently has the molecular specificity of these ANA been examined.

In a pilot study of 19 patients with adult-onset, clinically amyopathic DM, aAb to a 155 kDa polypeptide were identified in the majority of individuals (via radiolabeled immunoprecipitation and immunoblots)[35]. This same aAb was subsequently detected in 20–30% of patients with the classic form of juvenile-onset or adult-onset DM[36], and the 155 kDa polypeptide was reported to be identical to transcriptional intermediary factor 1 gamma (TIF1-γ)[37]. In adult-onset, classic DM patients, the presence of anti-TIF1-γ aAb has been associated with an increased risk of internal malignancy[38–40].

Utilizing the same immunoprecipitation/immunoblot approach, adult Japanese patients with clinically amyopathic DM and (often severe) interstitial lung disease were noted to have aAb that recognized a 140 kDa molecule[41]. This autoantigen, CADM-140, was subsequently found to be identical to two previously identified gene products, interferon induced with helicase C domain protein 1 (IFIH1) and melanoma differentiation-associated gene 5 (MDA5)[42,43]. Reportedly, it represents one of the RIG-1-like receptors that plays a role in innate immunity. In a recent retrospective series, plasma samples from 77 patients with DM were screened for anti-MDA5 aAb[43a]. The ten patients (13%) with these aAb had a rather distinct clinical phenotype with cutaneous ulcerations and/or tender palmar papules, oral pain

AUTOANTIBODIES ENCOUNTERED IN THE IDIOPATHIC INFLAMMATORY DERMATOMYOPATHIES

Target	Median prevalence*	Molecular specificity	Clinical association
HIGH SPECIFICITY FOR DM/PM			
p155	80% (clinically amyopathic); 20–30% (classic)	Transcriptional intermediary factor 1 gamma (TIF1-γ)	Clinically amyopathic DM; in adult-onset classic DM, increased risk of malignancy
Mi-2	15%	Helicase nuclear proteins	Gottron's papules/sign, shawl sign, periungual telangiectasias, cuticular overgrowth/dystrophy
Jo-1	20%	Histidyl tRNA synthetase	Antisynthetase syndrome
PL-7	5%	Threonyl tRNA synthetase	Antisynthetase syndrome
PL-12	3%	Alanyl tRNA synthetase	Antisynthetase syndrome
OJ	Rare	Isoleucyl tRNA synthetase	Antisynthetase syndrome
EJ	Rare	Glycyl tRNA synthetase	Antisynthetase syndrome, possibly increased frequency of skin changes
SRP	5%	Signal recognition particle (intracytoplasmic protein translocation)	Fulminant DM/PM, cardiac involvement
Fer	Rare	Elongation factor 1-α	–
Mas	Rare	Small RNA	–
MDA5/CADM-140	10–15%	IFN induced with helicase C domain protein 1 (IFIH1)/melanoma differentiation-associated gene 5 (MDA5)	Clinically amyopathic DM, rapidly progressive interstitial lung disease, palmar papules, painful ulcers with associated vasculopathy, gum pain
LOW SPECIFICITY FOR DM/PM			
ANA (most common IF patterns: speckled, nucleolar)	40%		Clinically amyopathic DM (65%)
ssDNA	40%	Single-stranded DNA	SLE, SSc, morphea
PM-Scl (PM-1)	10%	Ribosomal RNA processing enzyme	Overlap with SSc
Ro/SS-A (especially 52 kDa Ro)	15%	hYRNP	Overlap with SjS, SCLE, neonatal LE/CHB, SLE
U1RNP	10%	Splicesome RNP	Overlap with other AI-CTDs
Ku	3%	DNA end-binding repair protein complex	Overlap with SSc
U2RNP	1%	Splicesome RNP	Overlap with SSc

*Using current assay techniques.

Table 40.3 Autoantibodies encountered in the idiopathic inflammatory dermatomyopathies (DM/PM). ANA, antinuclear antibodies; CHB, congenital heart block; DM/PM, dermatomyositis/polymyositis; IF, immunofluorescence; IFN, interferon; LE, lupus erythematosus; RNP, ribonucleoprotein; SCLE, subacute cutaneous lupus erythematosus; SjS, Sjögren's syndrome; SLE, systemic lupus erythematosus; SSc, systemic sclerosis. Adapted from ref. 1.

AUTOANTIBODIES ASSOCIATED WITH SSc AND MORPHEA (LOCALIZED SCLERODERMA)				
Target	**SSc, all**	**SSc with diffuse cutaneous scleroderma**	**SSc with limited cutaneous scleroderma (also referred to as CREST syndrome)**	**Morphea (localized scleroderma)**
ANA (most common IF patterns: speckled, nucleolar, centromere)	95%*			40%
Centromere (CENP-B)		30%	80% (pulmonary hypertension)	
Scl-70 (DNA topoisomerase I, which unwinds DNA)		60% (pulmonary fibrosis)	15%	
Fibrillin-1 (major component of microfibrils in the extracellular matrix)		5%	10%	30%
Histones	40%			35%†
Rheumatoid factor	25%			25%
ssDNA	10–30%			50% (may correlate with disease severity or activity; most prevalent in linear morphea)
Fibrillarin (U3RNP)	5%	Internal organ involvement		
PM-Scl	5%	Polymyositis, SSc overlap		
RNA polymerases	5–20%	45% (aAb levels correlate positively with extent of skin involvement & renal disease)	6%	
Th/To RNP (mitochondrial enzyme) (associated with limited pulmonary fibrosis)		11%	19%	5%
Calpastatin‡	25%			
HMG (a non-histone nucleosomal protein)		30%	40%	
MMP 1 and 3 (degrade ECM proteins; aAb prevents degradation)	52%	71%	33%	
PDGFR (expressed on fibroblasts)§	16–100%§			

*Median prevalence using current assay techniques.
†Higher in patients with linear scleroderma and generalized morphea.
‡Endogenous inhibitor of the calcium-dependent protease, calpain.
§Results vary, depending upon study; evidence that aAb does not activate the receptor; up to 18% of controls may have this aAb.

Table 40.4 Autoantibodies associated with systemic sclerosis (SSc) and morphea (localized scleroderma). A more in-depth discussion of these aAb and autoantigens can be found elsewhere[16,44–48]. The shaded areas represent the hallmark aAb of SSc. Patients with SSc can also develop additional aAb including: anti-endothelial cell aAb which may induce apoptosis of endothelial cells, but are non-specific; anti-NAG-2 aAb which are expressed on vascular endothelial cells and fibroblasts and may also induce endothelial cell apoptosis; and anti-topoisomerase II aAb which are more commonly seen in patients with morphea. ANA, antinuclear antibodies; ECM, extracellular matrix; HMG, high mobility group; IF, immunofluorescence; NAG-2, tetraspan novel antigen-2; PDGFR, platelet-derived growth factor receptor; RNP, ribonucleoprotein. Adapted from ref. 1.

and ulceration, hand swelling, arthritis/arthralgia and diffuse hair loss. Recognition of this subset of patients is clinically important because of the association of anti-MDA5 aAb with rapidly progressive interstitial lung disease.

An enzyme-linked solid-phase immunoassay for detection of CADM-140/IFIH1/MDA aAb5 has recently been developed which will be easier for commercial laboratories to perform[42]. Hopefully, a similar solid-phase immunoassay will be developed for the p155 (TIF1-γ) autoantigen. Then it will be possible to perform larger prospective studies in more ethnically diverse patient populations in order to document disease specificities and the true clinical utility of these two aAb for both classic DM and clinically amyopathic DM.

Jo-1 and Mi-2

Anti-Jo-1 and anti-Mi-2 are better-established, myositis-specific aAb; however, their prevalence is so relatively low that they often have limited utility in a routine clinical setting. Anti-Jo-1 is one of several myositis-specific aAb that are directed against the various individual aminoacyl transfer RNA synthetases that deliver amino acids to the ribosome during protein translation (see Table 40.3). The presence of one or more of these "antisynthetase" aAb correlates positively with a subset of mostly PM and some DM patients who have an increased risk of arthritis, Raynaud's phenomenon, and interstitial lung disease (this clinico-serologic constellation has been referred to as the "antisynthetase syndrome"). The mechanic's hand skin lesion was originally described to occur in this setting. However, it has subsequently been observed in other DM subsets, including clinically amyopathic DM.

Anti-Mi-2 aAb are seen in highest frequency in patients having the hallmark skin lesions of DM (Gottron's papules, Gottron's sign, shawl sign). aAb to the signal recognition particle (SRP) are seen even less commonly than anti-Jo-1 and anti-Mi-2. However, when present, they do signal a risk for fulminant DM/PM with cardiac involvement and a high rate of mortality.

Table 40.3 also lists a number of other aAb that can be seen in DM/PM; however, they are not at all specific for this disease group. Thus, it is not surprising that some of the aAb also appear in Tables 40.2 and 40.4. There are case reports of TNF-α inhibitor-induced dermatomyositis, but some of the patients had anti-Jo-1 aAb prior to therapy, raising the possibility that they were already at risk for the disease.

AUTOANTIBODIES ASSOCIATED WITH OTHER RHEUMATIC DISEASES HAVING CUTANEOUS MANIFESTATIONS			
Autoantibody	**Median prevalence***	**Molecular specificity**	**Clinical associations**
RHEUMATOID ARTHRITIS			
Rheumatoid factor	80%	Fc portion of IgG	Low levels: very nonspecific (healthy elderly individuals, SLE, SSc, MCTD, neoplasia, chronic infections, chronic inflammatory lung diseases, chronic liver disease, sarcoidosis, systemic vasculitides). High levels: associated with erosive, crippling RA (25–90%) and extra-articular manifestations of RA, e.g. systemic vasculitis (i.e. peripheral neuropathy, cutaneous vasculitis); mixed cryoglobulinemia secondary to hepatitis C infection (types II, III; 40–100%); SjS
Anti-cyclic citrullinated protein (CCP) antibodies	70%	Citrullinated proteins in the skin (e.g. filaggrin) and joints	Increased severity of RA, including radiologic progression of erosive arthritic changes; predictor for the development of RA
SJÖGREN'S SYNDROME			
Alpha-fodrin	70%	An actin-binding protein found at the periphery of chromaffin cells that may be involved in secretion	More specific for SjS than anti-Ro aAb; also seen in SLE
Ro/SS-A	60%	hYRNP	SLE, SCLE, neonatal LE/CHB
La/SS-B	20%	hYRNP	SLE, SCLE, neonatal LE/CHB
MIXED CONNECTIVE TISSUE DISEASE (SHARP'S SYDROME)			
U1RNP†	100%‡	Splicesome RNP	Raynaud's phenomenon, swollen hands with sausage-like swelling of digits, polyarthritis, myositis, inverse association with nephritis

*Using current assay techniques.
†In MCTD, associated with high-titer ANA and lack of other aAb.
‡By definition at time of diagnosis.

Table 40.5 Autoantibodies associated with other rheumatic diseases having cutaneous manifestations. More in-depth information concerning clinico-serologic associations can be found elsewhere[3,7,8,16]. aAb, autoantibodies; CHB, congenital heart block; LE, lupus erythematosus; MCTD, mixed connective tissue disease; RA, rheumatoid arthritis; RNP, ribonucleoprotein; SCLE, subacute cutaneous lupus erythematosus; SjS, Sjögren's syndrome; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

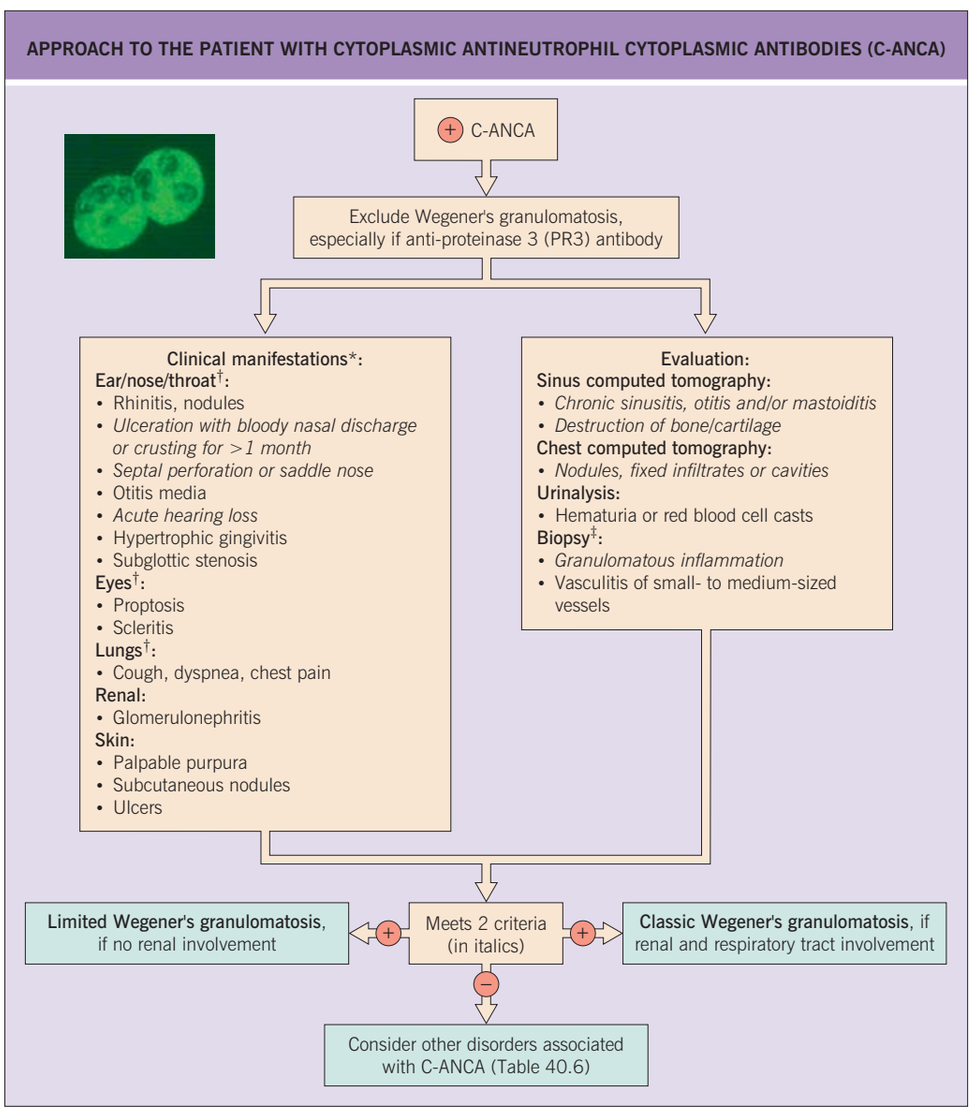


Fig. 40.5 Approach to the patient with cytoplasmic antineutrophil cytoplasmic antibodies (C-ANCA). *Some patients also have gastrointestinal, cardiac and/or neurologic involvement. †Granulomatous inflammation. ‡Of skin, mucosa, respiratory tract (upper/lower) or kidney. *Courtesy, Julie V Schaffer, MD. Photomicrograph from Wiik AS, Fritzler MJ. Laboratory tests in rheumatic disorders. In: Hochberg MC, Silman AJ, Smolen JS, et al. (eds). Rheumatology, 4th edn. London: Mosby Elsevier; 2008.*

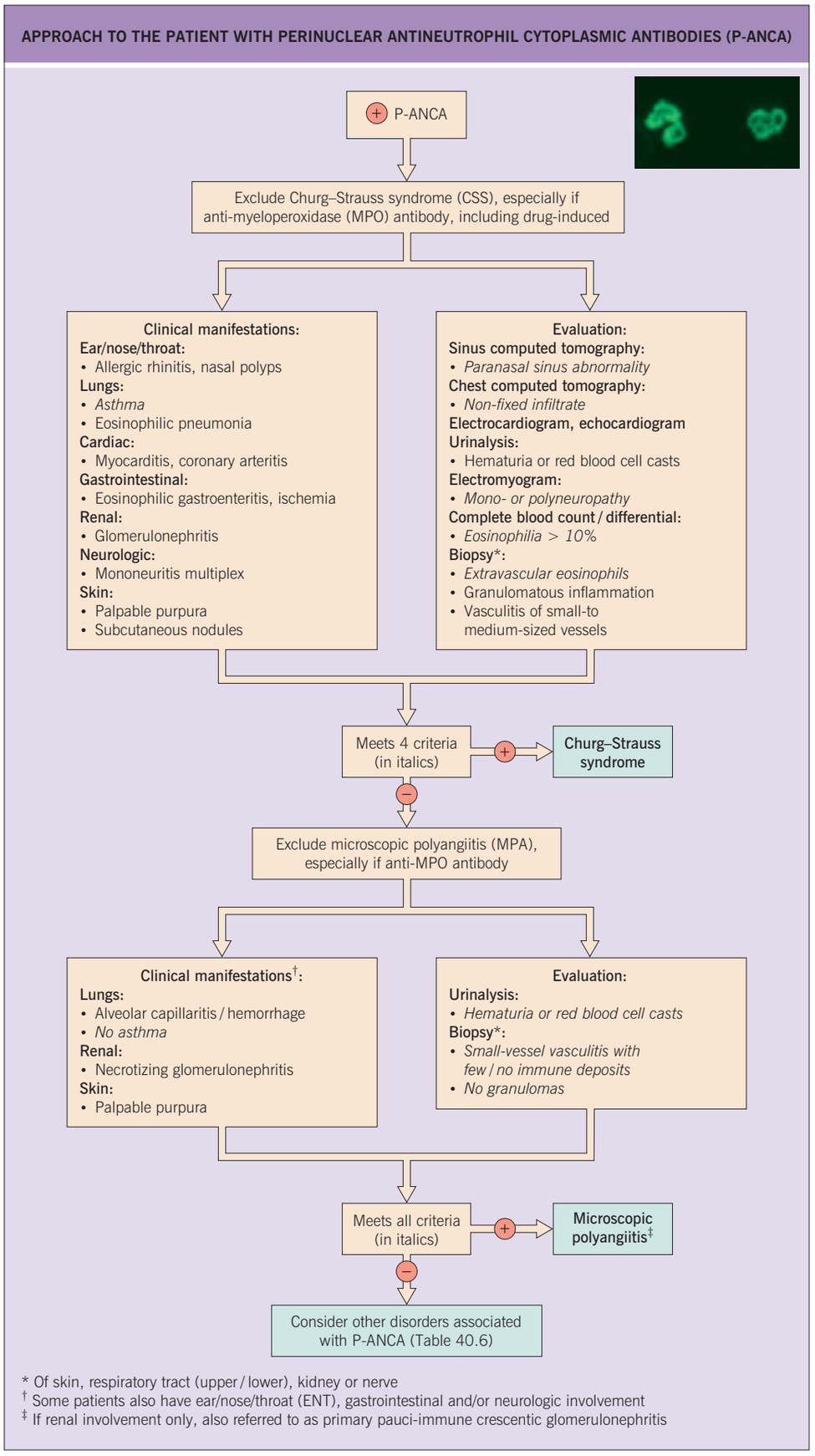


Fig. 40.6 Approach to the patient with perinuclear antineutrophil cytoplasmic antibodies (P-ANCA). Use of leukotriene inhibitors (see Ch. 130) has been associated with the onset of Churg–Strauss syndrome. Whether this represents unmasking of previously undiagnosed CSS is a subject of ongoing debate. *Courtesy, Julie V Schaffer, MD. Photomicrograph from Wiik AS, Fritzler MJ. Laboratory tests in rheumatic disorders. In: Hochberg MC, Silman AJ, Smolen JS, et al. (eds). Rheumatology, 4th edn. London: Mosby Elsevier; 2008.*

AUTOANTIBODIES ENCOUNTERED IN SYSTEMIC SCLEROSIS (SCLERODERMA) AND MORPHEA (LOCALIZED SCLERODERMA)

aAb associated with SSc and morphea (see Chs 43 & 44) are presented in Table 40.4[44–47]. The major scleroderma aAb are those that react with: (1) a centromere protein (CENP-B); (2) a DNA-unwinding enzyme, topoisomerase I (originally named Scl-70); and (3) RNA polymerases (RNAP). Anticentromere aAb correlate most strongly with the limited cutaneous form of SSc (CREST syndrome) while aAb against DNA topoisomerase I and RNAP are seen more commonly in diffuse cutaneous scleroderma; anti-RNAP aAb are also associated with an increased risk of developing scleroderma-associated renal crisis[48]. However, as the data in the table indicate, there can be overlap, e.g. ~30% of diffuse cutaneous scleroderma patients have anti-CENP-B aAb. The latter can also be seen in other clinical disorders such as primary biliary cirrhosis. As with other AI-CTDs, some of the other aAb that can be encountered in scleroderma patients have very little specificity for this group of disorders (i.e. antihistone, anti-ssDNA, anti-PM/Scl).

While there is little clinical overlap between SSc and morphea, some degree of serologic overlap has been described (e.g. anti-fibrillin-1 aAb). aAb to fibrillin-1 (as distinguished from fibrillarin [U3RNP]), histones and ssDNA occur in 30–50% of patients with morphea. As with classic ANA, these antibodies have been observed more often in patients who have the more widespread forms of morphea, such as linear scleroderma and generalized morphea. To date, a morphea-specific aAb has not been identified nor has an aAb that clearly reflects disease activity or prognosis.

AUTOANTIBODIES ENCOUNTERED IN OTHER RHEUMATIC DISORDERS THAT CAN AFFECT THE SKIN

aAb that can be seen in patients with some of the other rheumatic disorders that can have cutaneous manifestations[49,50] are presented in Table 40.5 (see Ch. 45).

Antineutrophil cytoplasmic antibodies (ANCA) are a subgroup of neutrophil-specific aAb. A clinical approach to a patient with either cytoplasmic ANCA (C-ANCA) or perinuclear ANCA (P-ANCA), which are characteristic of systemic vasculitides, is outlined in Figures 40.5 and 40.6. Other disorders associated with ANCA are summarized in Table 40.6. See Chapter 24 for additional clinical details.

OTHER DISORDERS ASSOCIATED WITH ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES (ANCA)

	Type of ANCA*	Major antigen(s)†	Evaluation
INFLAMMATORY BOWEL DISEASE			
Ulcerative colitis (50–70%) > Crohn's disease (20–40%)	P > C	Catalase, BPI, α-enolase, LF, CG, HMG1/2 > MPO, PR3	Colonoscopy
AUTOIMMUNE LIVER DISEASE			
Autoimmune hepatitis (type 1; 80%), primary sclerosing cholangitis (70%) > primary biliary cirrhosis (30%)	P > C	Actin, HMG1/2	LFTs; ANA; anti-smooth muscle Ab; antimitochondrial Ab
AUTOIMMUNE CONNECTIVE TISSUE DISEASE			
Systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis (20–30%) > Sjögren's syndrome, dermatomyositis, reactive arthritis, relapsing polychondritis, antiphospholipid syndrome	P > C	MPO, PR3, BPI, CG, LF, lysozyme, HMGI/2	ANA panel; RF; anticardiolipin Ab
DRUG-INDUCED VASCULITIS/LUPUS/HEPATITIS			
Propylthiouracil (20%), minocycline > levamisole, sulfasalazine Hydralazine, penicillamine > allopurinol‡ TNF-α inhibitors High-dose intravenous immunoglobulin	P > C P P, C C	MPO > PR3, elastase MPO, elastase MPO, PR3 –	Skin biopsy; ANA panel; LFTs; discontinue drug
OTHER CUTANEOUS AND/OR SYSTEMIC VASCULITIDES§			
Mixed cryoglobulinemia, Behçet's disease, paraneoplastic Henoch–Schönlein purpura, Buerger's disease	P > C P	Variable Variable	Skin biopsy; cryoglobulins; hepatitis B, C panels; exclude malignancy
OTHER GLOMERULONEPHRITIDES			
Anti-GBM Ab-associated (30%) > immune complex (15%) > poststreptococcal	P	MPO	UA; BUN/creatinine; ASO; renal biopsy
INFECTIONS			
Respiratory tract infections (bacterial/mycobacterial/ fungal), enteritis, periodontitis, HIV, parvovirus B19, malaria, leprosy	P, C	MPO, others	Cultures; serologies; echocardiogram
Onchocerciasis	P	Defensin	
Hepatitis C virus infection	P, C	CG, BPI, MPO	Serologies
Subacute bacterial endocarditis, chromomycosis, invasive amebiasis	C	PR3	
CYSTIC FIBROSIS (80%)	C > P	BPI	Sweat test
HYPERGAMMAGLOBULINEMIA	P, C	–	Serum protein electrophoresis

*C-ANCA are often atypical; in addition, immunofluorescence testing in some laboratories may not distinguish C-ANCA (atypical) from atypical ANCA.
†P-ANCA often have antigen specificity other than MPO, e.g. LF, elastase, CG, lysozyme, BPI, HMG1/2, α-enolase, catalase, actin, defensin; C-ANCA (atypical) have antigen specificity other than proteinase 3, e.g. BPI, lysozyme or multiple antigens.
‡Other drugs associated with P-ANCA in scattered case reports include cimetidine, cefotaxime, phenytoin, isotretinoin, clozapine and thioridazine.
§Although primarily associated with C-ANCA, 5–15% of patients with Wegener's granulomatosis have P-ANCA; likewise, although primarily associated with P-ANCA, 5–10% of patients with Churg–Strauss syndrome and ~40% of those with microscopic polyangiitis have C-ANCA; ANCA have also been reported in leukocytoclastic vasculitis of unknown etiology and unclassified vasculitis.

Table 40.6 Other disorders associated with antineutrophil cytoplasmic antibodies (ANCA). Ab, antibodies; ANA, antinuclear antibodies; ASO, antistreptolysin O; BPI, bactericidal/permeability-increasing protein; C, cytoplasmic [C-ANCA or C-ANCA (atypical)]; CG, cathepsin G; GBM, glomerular basement membrane; HMG1/2, high mobility group non-histone chromosomal proteins; LF, lactoferrin; LFTs, liver function tests; MPO, myeloperoxidase; P, perinuclear (P-ANCA); RF, rheumatoid factor; UA, urinalysis. *Courtesy, Julie V Schaffer, MD.*

REFERENCES

1. Sontheimer R, McCauliffe D, Targoff I. Antinuclear antibodies: clinical correlations and biologic significance. Adv Dermatol. 1992;7:3–52.
2. Phan T, Ng W, Bird D, et al. High-quality, cost-effective strategy for detection of autoantibodies to extractable nuclear antigens. Clin Diagn Lab Immunol. 2001;8:471–4.
3. Griesmacher A, Peichl P. Autoantibodies associated with rheumatic diseases. Clin Chem Lab Med. 2001;39: 189–208.
4. Nossent H, Rekvig OP. Antinuclear antibody screening in this new millennium: farewell to the microscope? Scand J Rheumatol. 2001;30:123–6.
5. Limburg PC, Kallenberg CGM. Antinuclear antibody screening in this new millennium: farewell to the microscope? Comment on the article. Scand J Rheumatol. 2001;30:127–8.
6. Slater C, Davis R, Shmmerling R. Antinuclear antibody testing. A study of clinical utility. Arch Intern Med. 1996;156:1421–5.
7. Donald F, Ward M. Evaluative laboratory testing practices of United States rheumatologists. Arthritis Rheum. 1998;41:725–9.
8. Ward M. Laboratory testing for systemic rheumatic diseases. Postgrad Med. 1998;103:93–100.
9. Adams B, Mutasim D. The diagnostic value of anti-nuclear antibody testing. Int J Dermatol. 2000;39:887–91.
10. Tan EM, Feltkamp TEW, Smolen JS, et al. Range of antinuclear antibodies in "healthy" individuals. Arthritis Rheum. 1997;40:1601–11.
11. Shiel WC Jr, Jason M. The diagnostic associations of patients with antinuclear antibodies referred to a community rheumatologist. J Rheumatol. 1989;16:782–5.
12. Sontheimer RD. Greenwald's law of lupus: the Sontheimer amendment. J Rheumatol. 1993;20: 1258–9.
13. Black AA, McCauliffe DP, Sontheimer RD. Prevalence of acne rosacea in a rheumatic skin disease subspecialty clinic. Lupus. 1992;1:229–37.
14. Egner W. The use of laboratory tests in the diagnosis of SLE. J Clin Pathol. 2000;53:424–32.
15. Sherer Y, Gorstein A, Fritzler MJ, Shoenfeld Y. Autoantibody explosion in systemic lupus erythematosus: more than 100 different antibodies found in SLE patients. Semin Arthritis Rheum. 2004;34:501–37.
16. Tan EM. Autoantibodies in diagnosis and in identifying autoantigens. Immunologist. 1999;7:85–92.
17. Lee LA, Roberts CM, Frank MB, et al. The autoantibody response to Ro/SSA in cutaneous lupus erythematosus. Arch Dermatol. 1994;130:1262–8.
18. McCauliffe DP, Yin H, Wang LX, Lucas L. Autoimmune sera react with multiple epitopes on recombinant 52 and 60 kDa Ro(SSA) proteins. J Rheumatol. 1994;21: 1073–80.
19. Rubin RL. Drug induced lupus. In: Wallace DJ, Hahn B, Dubois EL (eds). Dubois' Lupus Erythematosus. Philadelphia: Lippincott Williams & Wilkins, 2002:xiii, 1348.
20. De Rycke L, Baeten D, Kruithof E, et al. Infliximab, but not etanercept, induces IgM anti-double-stranded DNA autoantibodies as main antinuclear reactivity: biologic and clinical implications in autoimmune arthritis. Arthritis Rheum. 2005;52:2192–201.
21. Wick MC, Ernestam S, Lindblad S, et al. Adalimumab (Humira) restores clinical response in patients with secondary loss of efficacy from infliximab (Remicade) or etanercept (Enbrel): results from the STURE registry at Karolinska University Hospital. Scand J Rheumatol. 2005;34:353–8.
22. Antonov D, Kazandjieva J, Etugov D, et al. Drug-induced lupus erythematosus. Clin Dermatol. 2004;22:157–66.
23. De Bandt M, Sibilia J, Le Loet X, et al. Systemic lupus erythematosus induced by anti-tumour necrosis factor alpha therapy: a French national survey. Arthritis Res Ther. 2005;7:R545–51.
24. Mor A, Bingham C III, Barisoni L, et al. Proliferative lupus nephritis and leukocytoclastic vasculitis during treatment with etanercept. J Rheumatol. 2005;32:740–3.
25. Eriksson C, Engstrand S, Sundqvist KG, Rantapaa-Dahlqvist S. Autoantibody formation in patients with rheumatoid arthritis treated with anti-TNF alpha. Ann Rheum Dis. 2005;64:403–7.
26. Poulalhon N, Begon E, Lebbe , et al. A follow-up study in 28 patients treated with infliximab for severe recalcitrant psoriasis: evidence for efficacy and high incidence of biological autoimmunity. Br J Dermatol. 2007;156:329–36.
27. Garcia-Planella E, Domenech E, Esteve-Comas M, et al. Development of antinuclear antibodies and its clinical impact in patients with Crohn's disease treated with chimeric monoclonal anti-TNFalpha antibodies (infliximab). Eur J Gastroenterol Hepatol. 2003;15:351–4.
28. Williams EL, Gadola S, Edwards CJ. Anti-TNF-induced lupus. Rheumatology (Oxford). 2009;48:716–20.
29. Saleem G, Li SC, MacPherson BR, Cooper SM. Hepatitis with interface inflammation and IgG, IgM, and IgA anti-double-stranded DNA antibodies following infliximab therapy: comment on the article by Charles et al. Arthritis Rheum. 2001;44:1966–8.

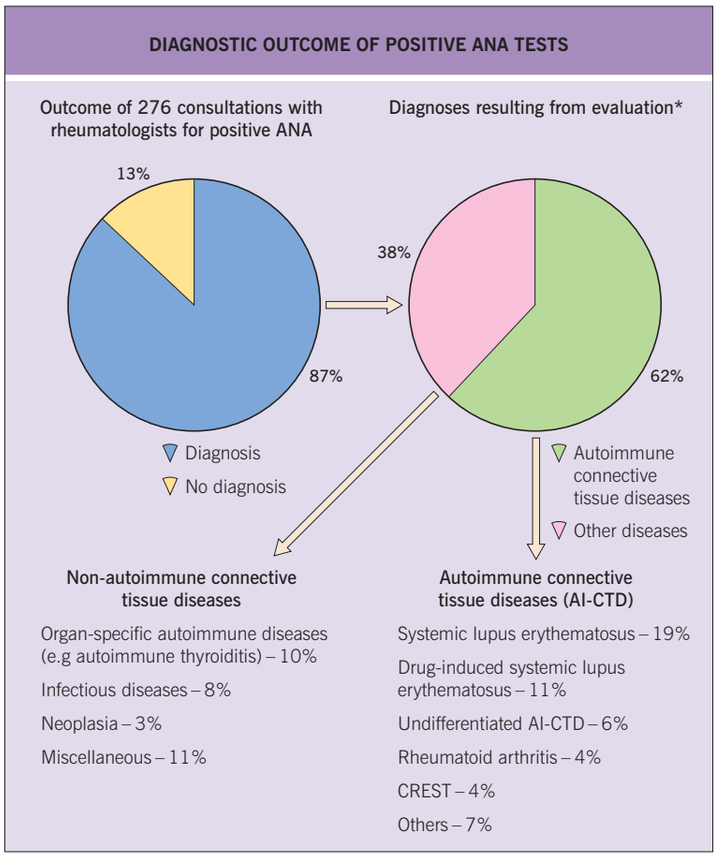
29a. Haraoui B, Keystone E. Musculoskeletal manifestations and autoimmune diseases related to new biologic agents. Curr Opin Rheumatatol. 2006;18:96–100.

29b. Benucci M, Saviola G, Baiardi P, et al. Anti-nucleosome antibodies as prediction factor of development of autoantibodies during therapy with three different TNF alpha blocking agents in rheumatoid arthritis. Clin Rheumatol. 2008;27:91–5.

30. Stratigos AJ, Antoniou C, Stamathioudaki S, et al. Discoid lupus erythematosus-like eruption induced by infliximab. Clin Exp Dermatol. 2004;29:150–3.
31. Euwer RL, Sontheimer RD. Amyopathic dermatomyositis (dermatomyositis sine myositis). Presentation of six new cases and review of the literature. J Am Acad Dermatol. 1991;24:959–66.
32. Euwer RL, Sontheimer RD. Amyopathic dermatomyositis: a review. J Invest Dermatol. 1993;100:124S–7S.
33. Sontheimer RD. Cutaneous features of classic dermatomyositis and amyopathic dermatomyositis. Curr Opin Rheumatol. 1999;11:475–82.
34. Sontheimer RD. Would a new name hasten the acceptance of amyopathic dermatomyositis (dermatomyositis sine myositis) as a distinctive subset within the idiopathic inflammatory dermatomyopathies spectrum of clinical illness? J Am Acad Dermatol. 2002;46:626–36.
35. Sontheimer RD, Targoff I, Trieu E, Racila D. Autoantibodies to 155 kD and Se autoantigens in patients with clinically amyopathic dermatomyositis. [abstract]. J Invest Dermatol. 2001;117:457.
36. Targoff IN, Mamyrova G, Trieu EP, et al. A novel autoantibody to a 155-kd protein is associated with dermatomyositis. Arthritis Rheum. 2006;54:3682–9.
37. Targoff I, Trieu EP, Levy-Neto M, et al. Autoantibodies to transcriptional intermediary factor 1-gamma in dermatomyositis. [abstract]. Arthritis Rheum. 2006;54(suppl):S518.
38. Kaji K, Fujimoto M, Hasegawa M, et al. Identification of a novel autoantibody reactive with 155 and 140 kDa nuclear proteins in patients with dermatomyositis: an association with malignancy. Rheumatology (Oxford). 2007;46:25–8.
39. Fujikawa K, Kawakami A, Kaji K, et al. Association of distinct clinical subsets with myositis-specific autoantibodies towards anti-155/140-kDa polypeptides, anti-140-kDa polypeptides, and anti-aminoacyl tRNA synthetases in Japanese patients with dermatomyositis: a single-centre, cross-sectional study. Scand J Rheumatol. 2009;38:263–7.
40. Chinoy H, Fertig N, Oddis CV, et al. The diagnostic utility of myositis autoantibody testing for predicting the risk of cancer-associated myositis. Ann Rheum Dis. 2007;66: 1345–9.
41. Sato S, Hirakata M, Kuwana M, et al. Autoantibodies to a 140-kd polypeptide, CADM-140, in Japanese patients with clinically amyopathic dermatomyositis. Arthritis Rheum. 2005;52:1571–6.
42. Sato S, Hoshino K, Satoh T, et al. RNA helicase encoded by melanoma differentiation-associated gene 5 is a major autoantigen in patients with clinically amyopathic dermatomyositis: association with rapidly progressive interstitial lung disease. Arthritis Rheum. 2009;60: 2193–200.
43. Nakashima R, Imura Y, Kobayashi S, et al. The RIG-I-like receptor IFIH1/MDA5 is a dermatomyositis-specific autoantigen identified by the anti-CADM-140 antibody. Rheumatology (Oxford). 2010;49:433–40.

43a. Fiorentino D, Chung L, Zwerner J, et al. The mucocutaneous and systemic phenotype of dermatomyositis patients with antibodies to MDA5 (CADM-140): a retrospective study. J Am Acad Dermatol. 2011;65:25–34.

44. Maddison PJ. Autoantibodies and clinical subsets: relevance to scleroderma. Wien Klin Wochenschr. 2000;112:684–6.
45. Greenberg AS, Falanga V. Localized cutaneous sclerosis. In: Sontheimer RD, Provost TT (eds). Cutaneous Manifestations of Rheumatic Diseases. Baltimore: Williams & Wilkins, 1996:141–155.
46. Gabrielli A, Avvedimento E, Krieg T. Scleroderma. N Engl J Med. 2009;360:1989–2003.
47. Arkachaisri T, Fertig N, Pino S, Medsger TJ. Serum autoantibodies and their clinical associations in patients with childhood- and adult-onset linear scleroderma. A single-center study. J Rheumatol. 2008;35:2439–44.
48. Nihtyanova S, Parker J, Black CM, et al. A longitudinal study of anti-RNA polymerase III antibody levels in systemic sclerosis. Rheumatology (Oxford). 2009;48:1218–21.
49. Braverman IM. Skin Signs of Systemic Disease. Philadelphia: Saunders, 1998.
50. Sontheimer RD, Provost TT. Cutaneous Manifestations of Rheumatic Diseases. Baltimore: Williams & Wilkins, 1996.



Diagnostic outcome of positive ANA tests. Outcome of rheumatology evaluations of patients referred for consultations for positive ANA of undetermined clinical significance. Adapted from data presented in ref. 10. With thanks to Jan Dutz MD for contributory comments. *Total number of patients = 276, but number of diagnoses = 284, because 8 patients had more than one diagnosis.

Lupus Erythematosus 41

Lela A Lee and Victoria P Werth

Synonyms/variants: ■ Discoid lupus erythematosus: a subset of chronic cutaneous lupus erythematosus ■ Lupus profundus: a variant of lupus panniculitis ■ Lupus erythematosus tumidus: tumid lupus

Key features

- There are several variants of cutaneous lupus, defined in part by the location and depth of the inflammatory infiltrate
- Acute cutaneous lupus involves primarily the epidermis and upper dermis and is usually associated with systemic disease
- Subacute cutaneous lupus involves primarily the epidermis and upper dermis and is associated with anti-Ro/SSA autoantibodies and photosensitivity; the majority of patients do not have significant systemic disease
- Discoid lesions of lupus involve the epidermis, upper and lower dermis, and adnexal structures, and they can scar; the majority of patients do not have significant systemic disease
- Lupus erythematosus tumidus involves the dermis but there is no prominent epidermal or adnexal involvement
- Lupus panniculitis involves the subcutaneous tissue and may result in disfiguring depressed scars

INTRODUCTION

Lupus erythematosus is a multisystem disorder that prominently affects the skin. Cutaneous lesions are a source of disability and, on many occasions, an indicator of internal disease.

HISTORY

The term "lupus erythemateaux" was first used by Cazenave in the mid-1800s[1]. Cazenave and others helped to articulate the difference between lupus erythematosus (LE) and lupus vulgaris, a clinical variant of cutaneous tuberculosis. Due in part to observations of Hutchinson, Osler and Jadassohn, it was recognized that cutaneous lesions of LE may be associated with significant internal abnormalities, including arthritis, nephritis, serositis, cytopenias and neurologic disease. In 1964 and during the following years, Dubois developed the concept of lupus as a spectrum of disease, ranging from isolated cutaneous lesions to life-threatening, multiorgan disease. Gilliam also developed the concept of a spectrum of disease, and, in 1979, he, Sontheimer and Thomas described a subset of cutaneous disease, which they termed "subacute" cutaneous lupus[2]. The description was virtually identical to that of "ANA-negative" lupus (see Ch. 40), reported by Maddison, Provost and Reichlin in 1981[3].

Important diagnostic advances included discovery of the LE cell phenomenon by Hargraves, Richmond and Morton in 1948[4]; the ANA by Friou in 1957[5]; the lupus band by Burnham, Neblett and Fine in 1963[6]; and the association of specific clinical manifestations of lupus with specific autoantibodies by a variety of investigators[7–9]. With regard to skin disease, the associations of anti-Ro (also known as anti-SSA) autoantibodies with neonatal lupus by Weston et al. in 1981[10] and with subacute cutaneous lupus (SCLE) by Sontheimer et al. in 1982[11] are noteworthy milestones.

Antimalarial therapy in the form of quinine was used for cutaneous lupus by Payne in 1894[12]. By the late 1950s, synthetic antimalarials had become a mainstay of therapy. Systemic corticosteroids and other immunosuppressive agents also came into use during the mid twentieth century.

EPIDEMIOLOGY

Systemic lupus erythematosus (SLE) is a common disease with significant morbidity and mortality. The strongest factor affecting risk for lupus is gender: women with systemic lupus outnumber men by at least 6 to 1[13]. Since lupus occurs most commonly in women during their childbearing years, it is likely that hormonal factors influence susceptibility to lupus. Consistent with the importance of sex steroids in the expression of disease, lupus is rare in prepubertal children. With regard to patients who have only cutaneous lesions, there appears to be a somewhat lower female-to-male ratio (perhaps 3:1) but there is still a female predominance.

Ethnicity is also a major risk factor, and its effect in some populations is almost as strong as that of gender. For example, the prevalence of SLE is fourfold higher in African-American women as compared to Caucasian American women (4 in 1000 vs 1 in 1000)[13]. In addition, African-Americans tend to develop disease at an earlier age and have a higher mortality rate. A long-term study of a multi-ethnic cohort of 587 SLE patients from Texas, Alabama and Puerto Rico found that African-Americans and Hispanics from Texas had more severe disease than Caucasian Americans or Hispanics from Puerto Rico, suggesting that both genetic and non-genetic factors play a role[14].

It is difficult to compare data from different countries, and this is sometimes even a problem with data from within the same country, due in part to differences in case identification and validation (reviewed in ref. 15). It is likely that Caucasian populations in Europe have a similar prevalence of lupus as do Caucasians living in the US. It also appears that the prevalence of lupus among both Asians and Latin Americans is similar to that of Caucasian Americans. A retrospective study from a single county in Minnesota indicated that the incidence of cutaneous LE, excluding patients who also had SLE, was similar to the incidence of SLE[15].

PATHOGENESIS

The pathogenesis of cutaneous LE is complex, and it involves an interaction between genetic and environmental factors. The latter include ultraviolet radiation (UVR), medications, and possibly viruses. This interplay triggers a complex inflammatory cascade of cytokine, chemokine and inflammatory cell responses that include cells residing within as well as recruited to the skin. Overall, the lichenoid tissue reaction, defined as epidermal basal cell damage and a band-like lymphocytic infiltrate in the upper dermis, characterizes most subsets of cutaneous LE. It involves activation of keratinocytes, endothelial cells and skin dendritic cells plus the production of type I interferons (IFNs), followed by the recruitment and activation of $CD4^+$ and $CD8^+$ cytotoxic T cells. The end result is cytotoxic keratinocyte damage.

Genes that can affect overall immunoreactivity include those whose protein products are involved in B- and T-cell function, innate immunity, immune complex clearance, apoptosis, ubiquitination, DNA methylation or cellular adhesion[16]. Examples from all these gene classes, in addition to genes with unknown function, have been implicated in some way in human or animal models of SLE (Table 41.1; see Ch. 4).

Both genetic background based upon ancestry and mutations in specific genes contribute to the clinical heterogeneity in cutaneous LE. For

example, the incidences of photosensitivity and discoid LE (DLE) differ in those of northern versus southern European ancestry[17], and SCLE is associated with the HLA-B8-DR3 extended haplotype (including *TNF2*), as well as C2 and C4 deficiencies[18]. Genes previously associated with SLE, e.g. *TYK2*, *IRF5* and *CTLA4*, also confer an increased risk for developing DLE and SCLE[19], while mutations in *TREX1*, which encodes a DNA exonuclease, are associated with familial chilblain lupus[20]. In the latter patients, dysfunction of the exonuclease leads to an accumulation of IFN-stimulatory nucleic acids.

Autoantibodies clearly play a role in SCLE and neonatal lupus, where anti-Ro (more specifically, anti-Ro60 and anti-Ro52) and anti-La autoantibodies are frequently observed (see Ch. 40); in the case of neonatal lupus, these antibodies are transmitted transplacentally. Blocking the function of either Ro60 or Ro52 presumably predisposes one to these diseases. Of note, Ro60 plays an important role in cell survival following UVR, possibly via binding to misfolded non-coding RNAs and targeting them for degradation, and mice which lack Ro60 develop a lupus-like syndrome[21]. Ro52 has a known regulatory role in inflammation, targeting both interferon regulatory factor 3 (IRF3) and IRF8 for degradation[22]; thus, antibodies to Ro52 may be proinflammatory. Alternatively, or in addition, these autoantibodies could lead to disease via activation of proteins and cells of the immune system, following immune complex formation.

Both ultraviolet B (UVB) and ultraviolet A radiation have been implicated in exacerbation of cutaneous LE, although UVB is a more efficient cause of photo-induced changes in the skin[23]. UVR induces apoptosis, which leads to translocation of cellular and nuclear antigens[24], and there may also be a reduction in the clearance of apoptotic cells[25]. In addition, UVR increases keratinocyte production of Ro52[26].

A number of proinflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-1, HMGB1 (high-mobility group box 1), and IL-18[27–29], are induced by UVR. Following UV irradiation of keratinocytes, a complex array of chemokines, including chemokine (C-C motif) ligand 5 (CCL5), CCL20, CCL22, and chemokine (C-X-C motif) ligand 8 (CXCL8), is produced. Of note, there is an increase in these chemokines within lesions of cutaneous LE, likely leading to leukocyte recruitment to the skin[30]. These effects require adhesion molecules, with activation of endothelial cells (increased expression of ICAM-1, VCAM-1 and E-selectin) and induction of ICAM-1 on basal keratinocytes (Fig. 41.1A)[31,32].

GENES ASSOCIATED WITH SYSTEMIC LUPUS ERYTHEMATOSUS	
B- and T-cell function	***HLA-DR*** – major histocompatibility complex, class II
	BLK – B lymphoid tyrosine kinase
	BANK1 – B-cell scaffold protein (with ankyrin repeats) 1
	CTLA4 – cytotoxic T lymphocyte antigen 4
	FCGR2B – Fc fragment of IgG, low affinity IIb, receptor (CD32)
	LYN v-yes-1 – Yamaguchi sarcoma viral related oncogene homolog
	PTPN22 – protein tyrosine phosphatase, non-receptor type 22 (lymphoid)
	STAT4 – signal transducer and activator of transcription 4
	PDCD1 – programmed cell death 1
	IRAK1 – interleukin-1 receptor-associated kinase 1
	TNFSF4 – tumor necrosis factor (ligand) superfamily, member 4
	IL21 – interleukin 21
Innate immunity	***IRF5*** – interferon regulatory factor 5
	TNFAIP3 – tumor necrosis factor, alpha-induced protein 3
	SPP1 – secreted phosphoprotein 1 (osteopontin)
	TREX1 – three prime repair exonuclease 1 (see text)
	TYK2 – tyrosine kinase 2
	IRAK1 – see above
	STAT4 – see above
Immune complex clearance	*FCGR3A* – Fc fragment of IgG, low affinity IIIa, receptor (CD16a)
	FCGR3B – Fc fragment of IgG, low affinity IIIb, receptor (CD16b)
	CRP – C-reactive protein, pentraxin-related
	ITGAM – integrin, alpha M (complement component 3 receptor 3 subunit; CD11b)
	C4A – complement component 4A
	C4B – complement component 4B
	C2 – complement component 2
	C1Q – complement component 1, q subcomponent
Apoptosis	*ATG5* – autophagy related 5 homolog
	STAT4 – see above
Ubiquitination	*UBE2L3* – ubiquitin-conjugating enzyme E2L 3
	TNFAIP3 – tumor necrosis factor, alpha-induced protein 3
DNA methylation	*MECP2* – methyl CpG binding protein 2 (Rett syndrome)
Cellular adhesion	*ITGAM* – see above
Other/unknown	*PXK* – PX domain containing serine/threonine kinase
	ICA1 – islet cell autoantigen 1
	SCUBE1 – signal peptide, CUB domain, EGF-like 1
	NMNAT2 – nicotinamide nucleotide adenylyltransferase 2
	XKR6 – XK, Kell blood group complex subunit-related family, member 6
	KIAA1542

Table 41.1 Genes associated with systemic lupus erythematosus. For detailed information on the function of these protein products, see www.genecards.org. The most strongly associated genes are in bold. *Adapted from ref. 16.*

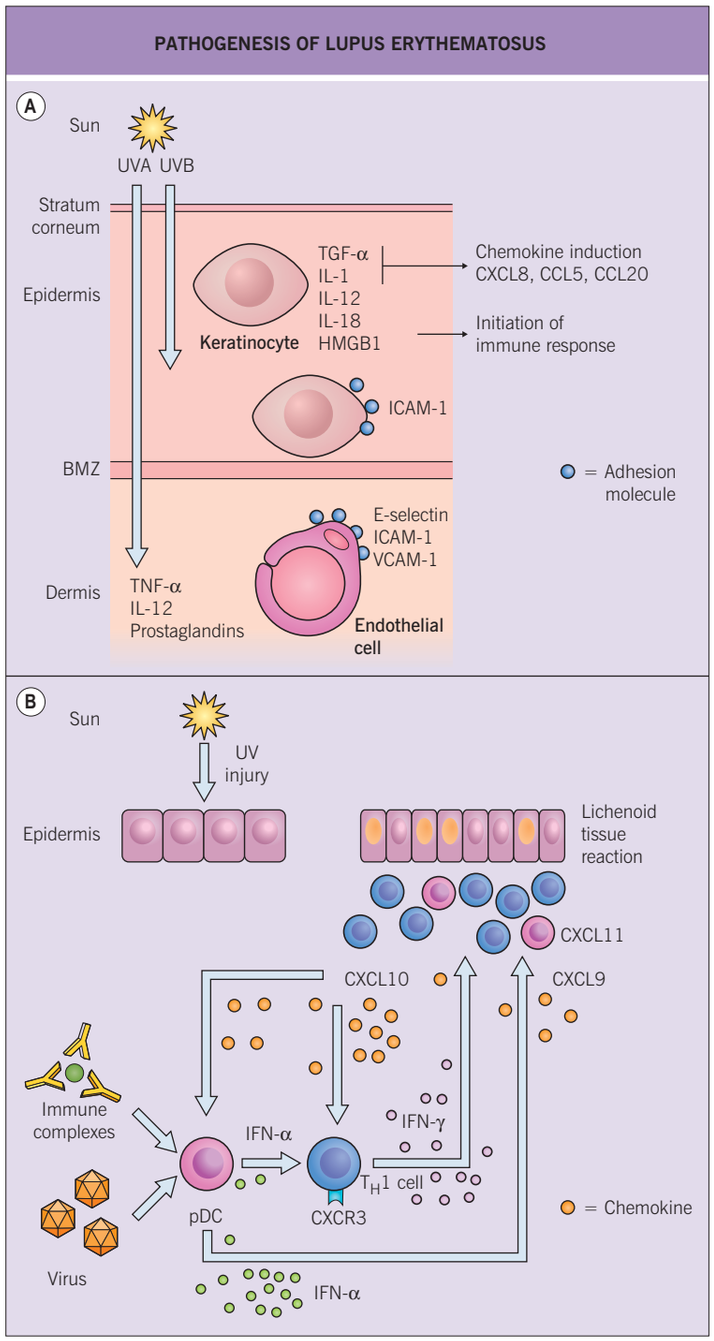


Fig. 41.1 Pathogenesis of lupus erythematosus. A In photosensitive cutaneous LE, ultraviolet radiation (UVA and UVB) triggers cytokine and chemokine production, initiating an immune response. **B** A lichenoid tissue reaction is the endpoint of a complex cascade that includes activation of dendritic cells, release of interferon (IFN), production of chemokines, and activation of T cells. BMZ, basement membrane zone; CCL, chemokine (C-C motif) ligand; CXCL, chemokine (C-X-C motif) ligand; CXCR, chemokine (C-X-C motif) receptor; HMGB1, high-mobility group box 1; IL, interleukin; ICAM, intercellular adhesion molecule; pDC, plasmacytoid dendritic cell; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule. *Adapted from Dutz JP et al., In: Wallace DJ, Hahn BH (eds). Dubois' Lupus Erythematosus, 7th edn. Philadelphia: Lippincott, Williams & Wilkins, 2006, and Meller S, Gilliet M, Homey B. Chemokines in the pathogenesis of lichenoid tissue reactions. J Invest Dermatol. 2009;129:315–19.*

IFN is another cytokine that plays a role in the pathogenesis of cutaneous LE. Increased secretion of IFN can result from binding of apoptotic cells to Fcγ receptors on macrophages; binding of viral pathogens, DNA, RNA or immune complexes to Toll-like receptors on plasmacytoid dendritic cells; and single nucleotide polymorphisms (SNPs) in genes that encode proteins in the IFN pathway[33]. Notably, an increase in proteins upregulated by IFN, including the chemokines CXCL9 and CXCL10, has been observed in the skin of patients with cutaneous LE[30,34] (Fig. 41.1B). IFN-α further drives the differentiation of monocytes to plasmacytoid dendritic cells, which are potent producers of IFN-α/β, thus forming an amplification loop[35]. Increased numbers of plasmacytoid dendritic cells have been found within cutaneous LE lesions[34]. Epidermal and dermal dendritic cells can acquire keratinocyte-derived antigens and prime $CD8^+$ T cells to these antigens within the skin-draining lymph nodes[36]. Corroborating evidence for the role of IFN-α is provided by the induction of cutaneous LE in patients receiving IFN-α for other medical conditions. The increased IFN signature seen in SLE has also been detected in peripheral blood mononuclear cells from patients with DLE and SCLE, but not those with LE tumidus[37].

The IFN-upregulated chemokines can recruit CXCR3-positive $CD4^+$ and $CD8^+$ T cells to the skin, as well as immature plasmacytoid dendritic cells, contributing to the characteristic interface infiltrate of cutaneous LE[30,38]. In addition, via the production of IFN-α, plasmacytoid dendritic cells drive the activation and expansion of T cells. There is also evidence for the presence of granzyme B and TIA1 (poly(A)-binding protein), two cytotoxic granule-associated proteins involved in apoptosis, in the skin of all subsets of cutaneous LE, although somewhat less so in SCLE, suggesting that there are fewer $CD8^+$ T cells in SCLE[38]. In patients with disseminated, scarring DLE, high numbers of circulating $CCR4^+$ cytotoxic T cells were detected[39]. One study found *decreased* numbers of $Foxp3^+CD4^+CD25^+$ T regulatory cells in the skin, but not the blood, of cutaneous LE patients, and Treg cells are known to down-regulate the immune response[40].

A scenario that integrates current theories regarding the pathogenesis of several subsets of cutaneous LE is shown in Figure 41.1. In the proposed model, a response to UVR triggers cytokine and chemokine production by keratinocytes as well as endothelial cell activation, thereby initiating the immune response (see Fig. 41.1A). In the context of genetic risk and environmental factors, a complex cascade ensues that includes activation of dendritic cells, release of IFN, activation of T cells, and production of chemokines; a positive feedback loop ultimately results in a lichenoid tissue reaction (see Fig. 41.1B).

DIFFERENT FORMS OF CUTANEOUS LUPUS AND THEIR ASSOCIATION WITH SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Type of cutaneous lupus	Association with SLE
• Acute cutaneous lupus erythematosus (ACLE)	++++
• Subacute cutaneous lupus erythematosus (SCLE)	++
• Chronic cutaneous lupus erythematosus (CCLE)	
– Discoid lupus erythematosus (DLE)	
▪ Localized (head and neck)	+
▪ Widespread/disseminated	++
▪ Hypertrophic	+
– Lupus erythematosus tumidus (LET)	+/–
– Lupus panniculitis	+
– Chilblain lupus	++
• Other variants	
– Bullous eruption of SLE	++++
– Rowell's syndrome	++ to ++++

Table 41.2 Different forms of cutaneous lupus and their association with systemic lupus erythematosus (SLE).

CLINICAL FEATURES

Cutaneous Lupus – Three Major Forms

Classification

The most commonly used classification of cutaneous lesions in LE is that of the late Professor James Gilliam[41]. He segregated skin lesions into those that are specific and those that are not specific. Within the category of specific cutaneous lesions, he subdivided these into acute, subacute and chronic (Table 41.2). This choice of terms was based upon the observation that three distinct types of cutaneous LE are commonly seen: the often transient acute cutaneous LE (ACLE) typified by malar

erythema; the frequently long-lived, intensely inflammatory discoid lesions which can lead to permanent disfiguring scars (DLE); and a photosensitive eruption characteristically more long-lasting than ACLE but without the potential for scarring, for which the term subacute cutaneous LE (SCLE) was coined. Typically grouped within the chronic cutaneous LE category are not only DLE, but also the less common LE tumidus, lupus panniculitis and chilblain lupus.

Formal studies have not been done comparing duration of disease activity for the various types of cutaneous LE, and there is a considerable range in the duration of activity within each subtype. On occasion, ACLE and SCLE lesions may be chronic, and DLE and LE tumidus lesions may be relatively short-lived. In fact, some authorities have proposed that LE tumidus should be removed from the chronic category and be given its own category, intermittent cutaneous LE[42]. These caveats aside, Gilliam's classification schema has proven utility in the organization of the various types of cutaneous LE and it is the basis for the classification herein, accompanied by a focus on the morphology and histopathology of lesions (Fig. 41.2). The three major forms of cutaneous LE will be discussed first, followed by the remaining entities outlined in Table 41.2.

Discoid lupus erythematosus

Discoid lesions represent one of the most common skin manifestations of lupus, and they are certainly the most common type of cutaneous LE that a dermatologist is requested to evaluate. Discoid lesions are found most often on the face, scalp and ears (Fig. 41.3), but may be present in a widespread distribution (Fig. 41.4). It is unusual for discoid lesions to be present below the neck without lesions also being present above the neck[43]. On occasion, discoid lesions occur on mucosal surfaces, including the lips, nasal mucosa, conjunctivae and genital mucosa.

Some patients with discoid lesions exhibit a photodistribution, and sun exposure appears to have a role in lesional development. However, many patients have discoid lesions in sun-protected skin, and there is no clear association between sun exposure and their development.

Discoid lesions have the potential for scarring, and, with time, a substantial proportion of patients develop disfiguring scarring. Active lesions are intensely inflammatory, with a pronounced inflammatory infiltrate in both the superficial and deep dermis. As a result, active lesions tend to feel indurated on palpation. The adnexa are prominently

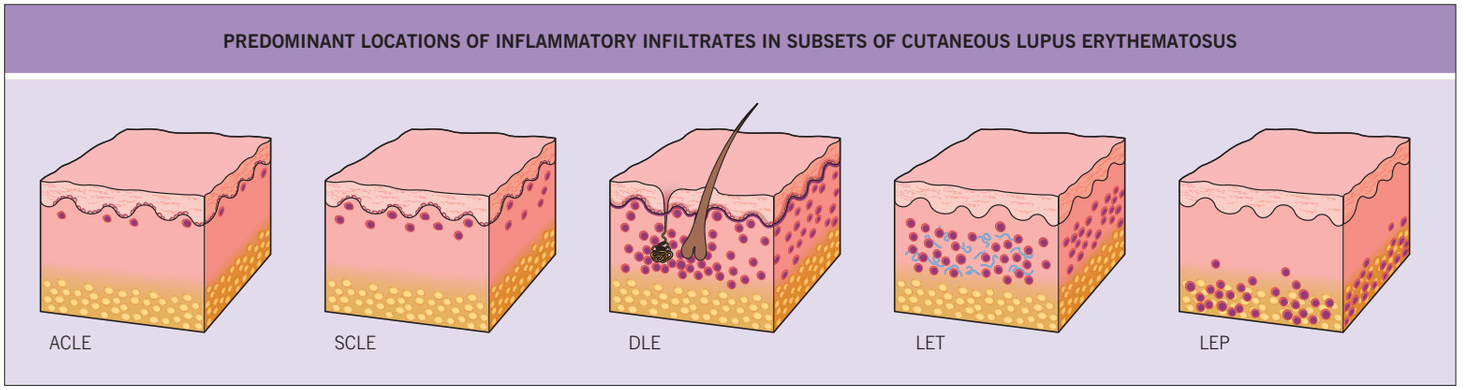


Fig. 41.2 Predominant locations of inflammatory infiltrates in subsets of cutaneous lupus erythematosus. The types of cutaneous lupus erythematosus are: acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE), discoid lupus erythematosus (DLE), lupus erythematosus tumidus (LET) and lupus panniculitis (LEP); the latter three are forms of chronic cutaneous lupus erythematosus (see Table 41.2). The primary locations of the infiltrates are as follows: superficial dermis, ACLE and SCLE; superficial plus deep dermis and periadnexal, DLE; superficial and deep dermis, LET; and subcutaneous fat, LEP. The final diagnosis requires clinicopathologic correlation.

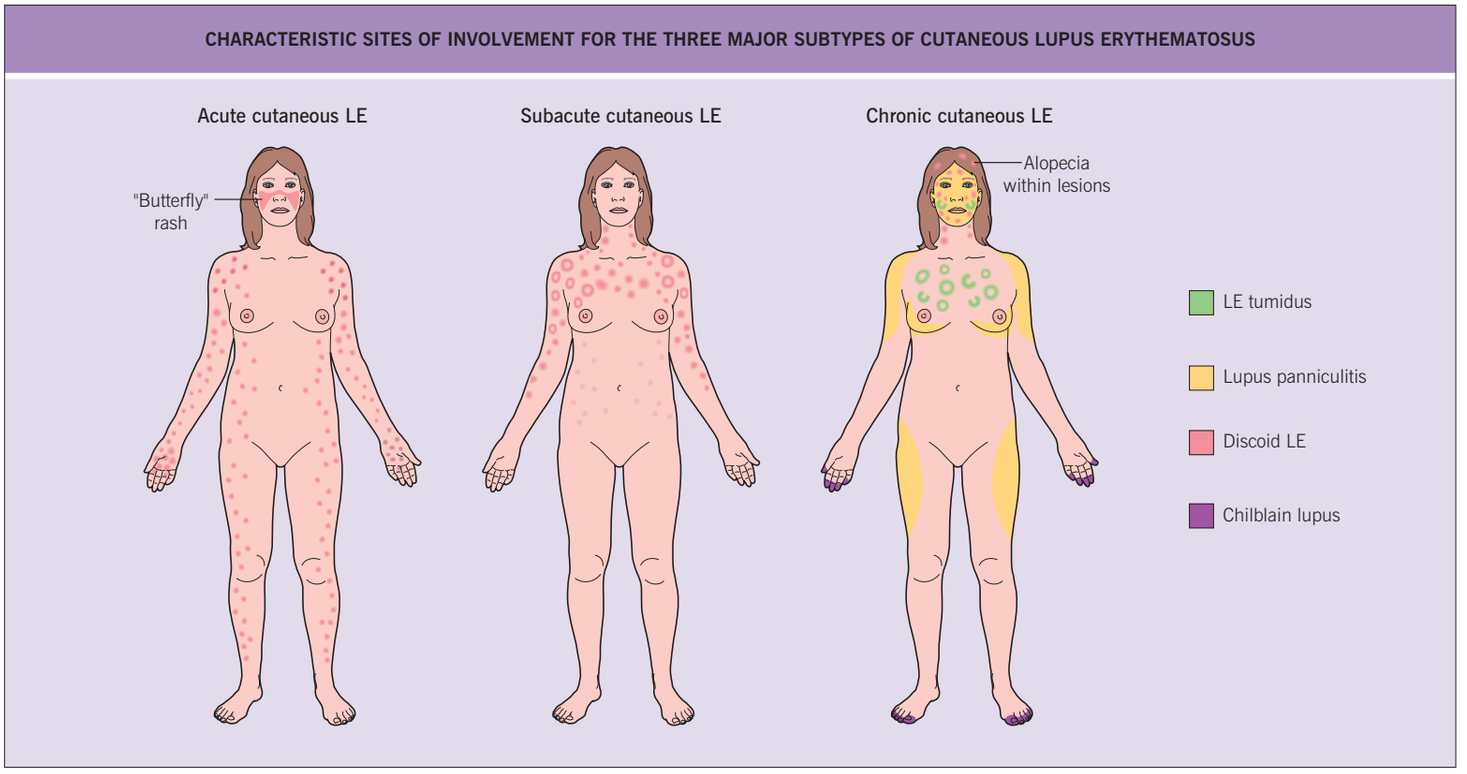


Fig. 41.3 Characteristic sites of involvement for the three major forms of cutaneous lupus erythematosus (LE).

Fig. 41.4 Various presentations of discoid lesions of lupus erythematosus. Lesions, which favor the head and neck region, may show erythema, scaling, atrophy and dyspigmentation in addition to scarring (and alopecia) (**A–D**). The scarring process may be destructive (**E**). Less common sites include the palms (**F**) and soles (**G**), where lesions can be keratotic or ulcerative as in lichen planus. The patients with plantar involvement had systemic lupus erythematosus and responded well to isotretinoin. **H** Occasionally, hypertrophic lesions develop with significant hyperkeratosis. *C, Courtesy, Kalman Watsky, MD; H, Courtesy, Julie V Schaffer, MD.*

involved, with follicular plugging and scarring alopecia commonly observed. Dyspigmentation is to be expected in longstanding lesions, typically with hypopigmentation in the central area and hyperpigmentation at the periphery (Fig. 41.5), but sometimes with vitiligo-like depigmentation. Rarely, squamous cell carcinoma develops in a longstanding discoid lesion.

Of the various forms of chronic cutaneous LE, discoid lesions (often referred to as DLE) are the most common (see Table 41.2). Patients with only discoid lesions may have associated arthralgias, but, over time, only 5–15% of these patients eventually develop clear-cut SLE[44–46a]. The risk may be higher in patients with widespread (disseminated) discoid lesions[43,45,46]. However, it is important to remember that

discoid lesions represent one of the 11 ARA criteria for SLE (see below) and can be a common presenting manifestation of SLE.

An unusual variant of DLE is hypertrophic DLE, characterized by thick scaling overlying the discoid lesion or occurring at the periphery of the discoid lesion. The intensely hyperkeratotic lesions are often prominent on the extensor arms (see Fig. 41.4H), but the face and upper trunk may also be involved. Frequently, there are typical discoid lesions present in other locations.

Subacute cutaneous lupus erythematosus

SCLE is typically photosensitive, with lesions confined to sun-exposed skin. It is notable that the midfacial skin is usually spared, while the sides of the face, upper trunk and extensor aspects of the upper extremities are commonly involved (Fig. 41.6; see Fig. 41.3)[47]. In some patients, the disease may be mild, with only a few small scaly patches appearing after sun exposure.

Lesions of SCLE may have an annular configuration, with raised red borders and central clearing (Fig. 41.7), or a papulosquamous presentation with an eczematous or psoriasiform appearance. SCLE lesions characteristically have a relatively sparse, superficial inflammatory infiltrate, and, consequently, there is usually no induration. Lesions often result in dyspigmentation, particularly hypopigmentation or even depigmentation, but do not scar.

In some instances, lesions of SCLE have appeared in patients receiving certain medications, in particular hydrochlorothiazide and terbinafine, but also calcium channel blockers, nonsteroidal anti-inflammatory drugs (e.g. naproxen), griseofulvin and antihistamines. The lesions may or may not clear once the medication is discontinued.

The long-term prognosis of patients who have SCLE is not completely known, largely because this subset of cutaneous LE only recently has been widely recognized. It is clear that a certain percentage of patients, perhaps 10–15%, will over time develop significant internal disease, including nephritis[44]. Since anti-Ro autoantibodies are associated with Sjögren's syndrome as well as SCLE, it is not surprising that some patients have features of both conditions, and some may have serious internal manifestations of Sjögren's syndrome such as pulmonary or neurologic disease.

An important feature of SCLE, from the standpoint of understanding the pathogenesis of lupus, is its regular association with the anti-Ro autoantibody (see Ch. 40). Although investigators differ in their opinions as to the prevalence of anti-Ro in SCLE, it is likely that a substantial majority of patients with this condition (approximately 70% in a large series, reported range of 60–100%) have anti-Ro antibody[47,48].

Acute cutaneous lupus

The lesions of ACLE are exemplified by the development of bilateral malar erythema ("butterfly rash"; Fig. 41.8). These lesions tend to be transient, follow sun exposure, and resolve without scarring (but sometimes with dyspigmentation). An association with anti-dsDNA

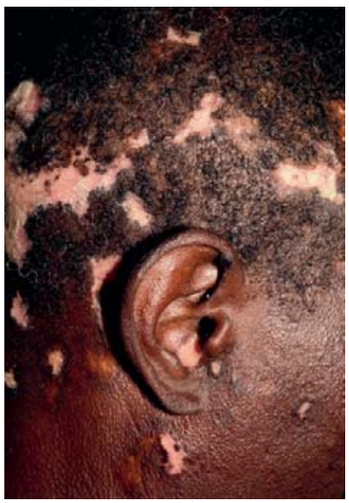


Fig. 41.5 Discoid lupus lesions with dyspigmentation and scarring alopecia. Hypopigmentation often develops centrally with hyperpigmentation at the periphery. *Courtesy, Joyce Rico, MD.*

Fig. 41.6 Subacute cutaneous lupus erythematosus (SCLE). Numerous erythematous annular plaques on the back, some of which have associated white scale. Note the photodistribution. *Courtesy, Kathryn Schwarzenberger, MD.*

Fig. 41.7 Subacute cutaneous lupus erythematosus (SCLE). Lesions are most commonly seen on the sun-exposed aspects of the upper extremities. The margins of the annular lesions may have scale-crust (**A**) or be composed of multiple papules (**B**). *A, Courtesy, Jean L Bolognia, MD.*

antibodies and lupus nephritis has been proposed and is plausible[44], although some patients with a malar rash have neither anti-dsDNA antibodies nor lupus nephritis. Patients presenting with this type of eruption must be evaluated carefully for evidence of internal disease.

The morphology of the lesions ranges from mild erythema to intense edema. The presence of telangiectasias, erosions, dyspigmentation and epidermal atrophy (i.e. poikiloderma) may help to distinguish the malar erythema of ACLE from that of common facial eruptions such as seborrheic dermatitis and the vascular type of rosacea. Occasionally, there is a papular component, and occasionally lesions develop scaling (see Fig. 41.8C). The duration may range from a few hours to several weeks. The face, particularly the malar area, is most commonly affected, but sometimes lesions may be more widespread in distribution (Fig. 41.9; see Fig. 41.3). When lesions occur on the hands, the knuckles are typically spared. It is not unusual for the acute cutaneous eruption to be accompanied by oral ulcerations.

Rarely, patients with lupus develop an acute eruption clinically similar to toxic epidermal necrolysis or erythema multiforme major (Fig. 41.10). The presence of erythema multiforme-like lesions in lupus patients has been termed Rowell's syndrome[49]. These lesions may represent a severe variant of ACLE or, in some cases, SCLE.

The three major types of cutaneous LE are not mutually exclusive. In a given patient, more than one type of cutaneous lesion may occur.

Cutaneous Lupus – Additional Variants

(see Table 41.2)

Lupus erythematosus tumidus

Some patients with cutaneous LE have lesions characterized by induration and erythema but no scale or follicular plugging. The epidermis appears to be uninvolved in the disease process, although there is an intense dermal inflammatory infiltrate. LE tumidus lesions may be the same as the "urticarial plaques" described in lupus patients. However, these fixed plaques should not be confused with urticarial vasculitis (see Ch. 24). Some authors state that the lesions are most common on the face, although they can be quite common on the trunk (Fig. 41.11). Morphologically, the lesions are similar to those of Jessner's lymphocytic infiltrate and may have central clearing (see Ch. 121); some believe that Jessner's lymphocytic infiltrate and LE tumidus are either very closely related or one and the same[50].

Both the very low prevalence of SLE and the relatively low prevalence of immunoglobulin deposition within the cutaneous lesions in patients reported to have LE tumidus have made it difficult to determine whether LE tumidus is actually a variant of LE or an independent entity. However, the presence of LE tumidus lesions in patients with other specific types of cutaneous LE is evidence in favor of its being classified as a form of cutaneous LE. LE tumidus has been reported to be reproducible by phototesting in the majority of patients[51]. The lesions tend to resolve without scarring or atrophy.

Lupus panniculitis

Intense inflammation in the fat leads to indurated plaques that can evolve into disfiguring, depressed areas. Lesions of lupus panniculitis have a distinctive distribution, occurring predominantly on the face, upper arms (Fig. 41.12), upper trunk, breasts, buttocks and thighs (see Fig. 41.3). Some patients have discoid lesions overlying the panniculitis, and, in those cases, the condition is sometimes referred to as lupus profundus. For further discussion of lupus panniculitis, see Chapter 100.

Chilblain lupus

Chilblain lupus (SLE pernio; Fig. 41.13) consists of red or dusky purple papules and plaques on the toes, fingers, and sometimes the nose, elbows, knees and lower legs. The lesions are brought on or exacerbated

Fig. 41.8 Acute cutaneous lupus erythematosus (ACLE). The facial erythema, often referred to as a "butterfly rash" may be variable (**A**), edematous (**B**) or have associated scale (**C**). The presence of small erosions can aid in the clinical differential diagnosis. *A, Courtesy, Kalman Watsky, MD.*

Fig. 41.9 Acute cutaneous lupus erythematosus (ACLE). This patient had ACLE lesions on the arms as well as the face.

Fig. 41.10 Toxic epidermal necrolysis-like eruption of acute lupus erythematosus. This presentation has also been referred to as a form of *a*cute *s*yndrome of *a*poptotic *p*an-epidermolysis (ASAP).

Fig. 41.11 Lupus erythematosus tumidus. Annular pink plaques on the chest (**A**) and pink–violet plaques on the face (**B**). None of the lesions have epidermal change. *B, Courtesy, Julie V Schaffer, MD.*

Fig. 41.12 Lupus panniculitis. Erythematous plaque on the upper arm. The lesions may resolve with lipoatrophy.

Fig. 41.13 Chilblain lupus. Violaceous plaques, some with scale, on toes. If there is a family history of this disorder, the possibility of mutations in *TREX1*, which encodes a DNA exonuclease, can be considered.

by cold, particularly moist cold climates. These lesions may represent the concurrence of ordinary chilblains with LE (see Ch. 88), although, with time, the lesions may develop a gross and microscopic appearance consistent with a discoid lesion.

Neonatal lupus erythematosus

A neonatal form of SCLE may occur in infants whose mothers have anti-Ro autoantibodies. In babies who have neonatal lupus erythematosus (NLE), the SCLE-like lesions are histologically identical to those of SCLE in adults, and there is a strong association with anti-Ro antibodies. Indeed, almost 100% of babies with NLE have anti-Ro antibodies[52]. Unlike SCLE in adults, lesions have a predilection for the face, especially the periorbital region and scalp (Fig. 41.14). Photosensitivity is very common in NLE, but sun exposure is not required for lesions to form, as it is possible for lesions to be present at birth. Neonatal lupus skin lesions typically resolve without scarring, although dyspigmentation may persist for many months, and some children have residual telangiectasias.

Children who have the cutaneous lesions of NLE may also exhibit internal manifestations. The major extracutaneous findings are congenital heart block (with or without cardiomyopathy), hepatobiliary disease and thrombocytopenia. The heart block is almost always present by birth, but on rare occasions has developed after birth. Clinically significant cardiomyopathy occurs concurrently in a small percentage of babies who have heart block. Usually, the cardiomyopathy is apparent in the neonatal period, but it is possible for it to become apparent only after several months have elapsed. Cardiac NLE has a mortality rate of approximately 20%, and about two-thirds of children require pacemakers[53].

Hepatobiliary disease and cytopenias, especially thrombocytopenia, may be present at birth, or they may develop within the first few months of life[54]. Hepatobiliary disease has been reported to present as liver failure during gestation or in the neonatal period, as conjugated hyperbilirubinemia during the first few weeks of life, or with mild elevations of aminotransferases at 2–3 months of life.

It is common for babies with NLE to exhibit only one of the above clinical manifestations, and thus many children with cutaneous NLE have no other significant clinical findings. However, children who have skin signs of NLE should be evaluated for internal manifestations with a physical examination in addition to an electrocardiogram, complete blood count, and liver function tests, when indicated.

Other Variants

In the clinical setting of lupus, bullous lesions may appear for several reasons. On occasion, bullous or crusted lesions occur simply as a result of the intensity of the basal cell damage in lesions of ACLE or SCLE (see Fig. 41.7A) or, possibly, DLE. Rarely, a dramatic, acute eruption similar to erythema multiforme major or toxic epidermal necrolysis (TEN) may occur in patients with preexisting ACLE or SCLE, or it may appear *de novo*. Blisters occurring within ACLE and SCLE lesions and erythema multiforme-like and TEN-like cutaneous lupus fit within the category of lupus-specific skin lesions.

The term bullous eruption of SLE, or bullous SLE, has been used to describe a blistering eruption that consists of vesicles and bullae whose

histopathology often resembles dermatitis herpetiformis, with a primarily neutrophilic infiltrate and microabscesses within the dermal papillae (Fig. 41.15)[55]. In some patients, the clinical and histologic features may resemble bullous pemphigoid or epidermolysis bullosa acquisita. Immunoreactants are often found at the basement membrane zone and antibodies to type VII collagen have been detected in several patients[56]. This eruption may represent the concurrence of lupus with an autoimmune blistering disease due to autoantibodies to a component of the basement membrane zone. There are also a number of case reports of other autoimmune bullous diseases appearing in patients with lupus (reviewed in ref. 57).

A *lupus/lichen planus overlap syndrome* has been described, in which lesions have features of both conditions (see Ch. 11).

Systemic Lupus Erythematosus

Lupus erythematosus is potentially a multiorgan disease, although in individual patients it is often only one or a few organs that are significantly affected. The organ systems most commonly affected are joints, skin, hematologic, pulmonary, renal and the CNS. Many of the internal organ manifestations classically associated with lupus are part of the criteria for the classification of SLE (see Table 41.7), and reference to these criteria may serve as a useful reminder of the possible character of internal organ involvement (e.g. non-erosive arthritis, pleuritis, pericarditis, proteinuria, cellular casts in the urine, seizures, psychosis, hemolytic anemia, leukopenia, lymphopenia, thrombocytopenia). However, it should be remembered that these systemic features have been selected as criteria due to their usefulness in distinguishing SLE from other rheumatic diseases. They are not necessarily the most common systemic features of SLE, and certainly do not represent a comprehensive listing of possible organ involvement. Signs and symptoms such as fever, weight loss, fatigue, myalgias and lymphadenopathy are exceedingly common, if nonspecific, and may be useful indicators of increased risk for SLE in patients who present with cutaneous lesions. Although ACLE is the cutaneous phenotype with the strongest association with systemic disease, patients with any type of cutaneous LE may develop internal involvement.

Fig. 41.14 Neonatal lupus erythematosus. Annular erythematous plaques on the forehead and scalp. Note the resemblance to the annular form of subacute cutaneous lupus erythematosus. *Courtesy, Julie V Schaffer, MD.*

Fig. 41.15 Bullous eruption of systemic lupus erythematosus. Vesicles and bullae due to autoantibodies against type VII collagen can develop in patients with systemic disease.

Nonspecific Cutaneous Lesions

Vascular lesions are common in patients with LE, particularly in those who have systemic disease (Table 41.3). These lesions include Raynaud's phenomenon (see Ch. 43), livedo reticularis, palmar erythema and periungual telangiectasia. Purpura, urticarial papules or ulcerations due to vasculitis may occur, as well as cutaneous infarction resembling Degos' disease or atrophie blanche. Patients with cutaneous LE who have any of these findings should be evaluated for systemic disease. Livedo reticularis, thromboses, ulcerations, and lesions resembling Degos' disease have each been associated with antiphospholipid antibodies[58] (see Ch. 23). The association of livedo reticularis with ischemic CNS disease has been called Sneddon syndrome, and the phenotype of the antiphospholipid syndrome has been called Hughes syndrome[59].

Alopecia often occurs as a result of scarring discoid lesions. However, non-scarring diffuse alopecia can appear in patients with systemic disease. It has been reported that patients with lupus have an increased likelihood of alopecia areata compared with the general population[60].

Sclerodactyly, calcinosis and rheumatoid nodules, findings more consistent with scleroderma or rheumatoid arthritis, have been observed in some patients with lupus, although many of the patients with these findings may have overlap syndromes rather than classic lupus. Other skin findings reported to occur in patients who have lupus include erythromelalgia, papulonodular mucinosis (of Gold; see Ch. 46) and anetoderma (see Ch. 99).

Patients with SLE have more subtle nailfold capillary abnormalities than do patients with scleroderma or dermatomyositis. Prominent large, tortuous capillaries and areas of marked avascularity are not characteristic of SLE.

CUTANEOUS FINDINGS (NONSPECIFIC) THAT SUGGEST THE DIAGNOSIS OF SYSTEMIC LUPUS ERYTHEMATOSUS
Diffuse non-scarring alopecia
Raynaud's phenomenon
Nailfold telangiectasias and erythema
Vasculitis
• Urticarial vasculitis
• Small vessel vasculitis (e.g. palpable purpura)
• Polyarteritis nodosa-like lesions
• Ulcerations
Cutaneous signs of antiphospholipid syndrome
• Livedo reticularis
• Ulcerations
• Acrocyanosis
• Atrophie blanche-like lesions
• Degos'-like lesions
Livedoid vasculopathy
Palmar erythema
Papular and nodular mucinosis

Table 41.3 Cutaneous findings (nonspecific) that suggest the diagnosis of systemic lupus erythematosus. These are in addition to skin signs of other autoimmune connective tissue diseases, which raise the possibility of an overlap syndrome.

PATHOLOGY

Routine Histopathology

Histologic findings in cutaneous LE depend in large part on the subtype (Fig. 41.16; see Fig. 41.2). Characteristic findings in ACLE, SCLE, discoid lesions, LE tumidus, and lupus panniculitis are outlined in Table 41.4. However, in practice, an overlap in histologic findings occurs among the various clinical phenotypes, particularly ACLE, SCLE and discoid lesions. Some of the more distinctive histologic features of cutaneous LE are basal cell damage (also referred to as vacuolar degeneration or hydropic change), lymphohistiocytic inflammatory infiltrates and, primarily in discoid lesions, periadnexal inflammation, follicular plugging, and scarring. In lesions of ACLE, dermal changes can be relatively subtle although basal cell damage may be pronounced. In SCLE, epidermal changes and a superficial lymphocytic infiltrate are common. In contrast to discoid lesions, SCLE lesions tend to have little or no hyperkeratosis, basement membrane thickening, periadnexal infiltrate,

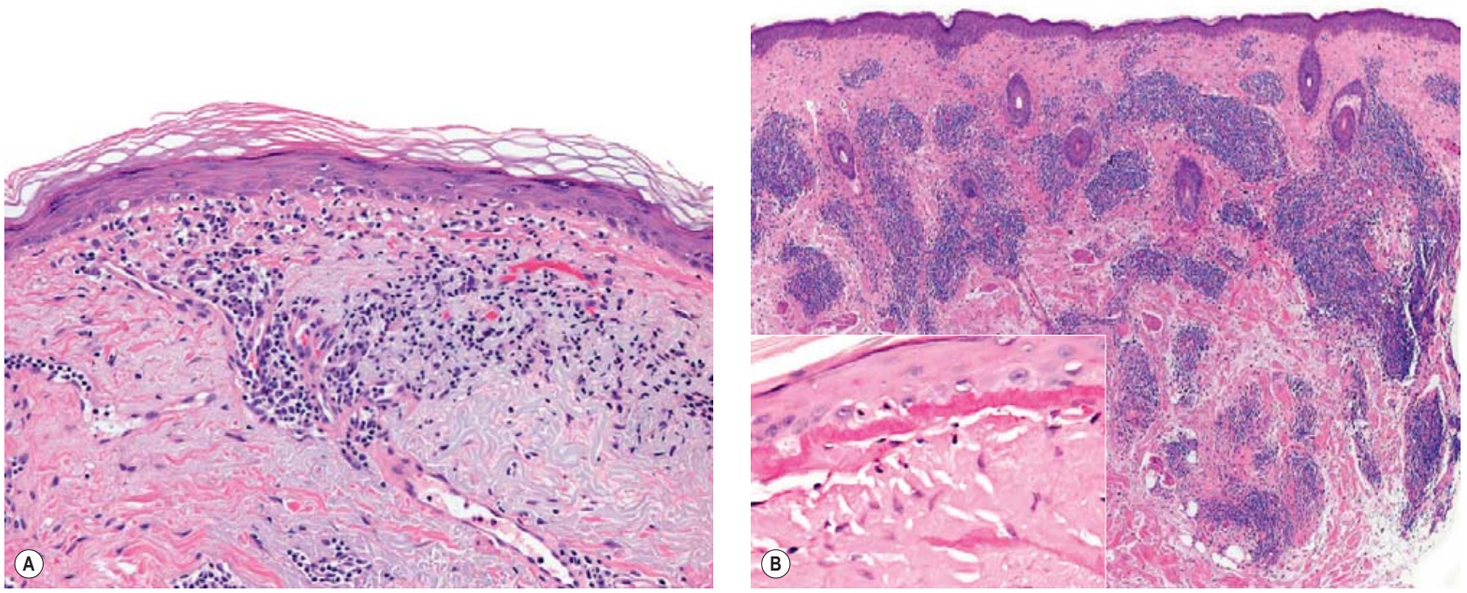


Fig. 41.16 Histologic features of cutaneous lupus erythematosus (LE). A Acute cutaneous LE showing interface dermatitis with vacuolization of basal keratinocytes and sparse superficial lymphoid infiltrates. **B** Chronic discoid LE showing focal interface dermatitis and dense perivascular and periadnexal lymphoid infiltrates throughout the entire dermis. A thickened basement membrane is a characteristic finding and can be highlighted by PAS staining (insert). *Courtesy, Lorenzo Cerroni, MD.*

CHARACTERISTIC HISTOLOGIC FINDINGS IN CUTANEOUS LUPUS ERYTHEMATOSUS (LE)					
Histologic finding	**Acute cutaneous LE**	**Subacute cutaneous LE**	**Discoid lesions of LE**	**LE tumidus**	**Lupus panniculitis**
Vacuolar alteration of basilar layer	++	++	+	–	+/–
Apoptotic keratinocytes	+	++	+	–	+/–
Hyperkeratosis	–	–	+	–	–
Epidermal atrophy	+	++	+	–	+/–
Pilosebaceous atrophy	–	–	++	–	+/–
Follicular plugging	–	+	++	–	+/–
Basement membrane zone thickening	+	+	++	–	–
Lymphocytic infiltrate in the upper dermis	+	+	++	+	+/–
Lymphocytic infiltrate in the lower dermis	–	–	++	+	+
Lymphocytic infiltrate in the subcutis	–	–	+	–	++
Lymphocytic infiltrate, periadnexal	–	+/–	++	+/–	+/–
Dermal edema	++	–	+	+	–
Dermal mucin	+	+/-	+	++	+/–
Dermal fibrosis	–	–	+	–	–
Focal hemorrhage	+	–	–	–	–
Fibrin deposition	+	–	+	–	–

Table 41.4 Characteristic histologic findings in cutaneous lupus erythematosus (LE). The table is intended as a broad overview only. Not every feature will be present in every lesion, some features may be present that are not indicated as characteristic, and overlap exists amongst subtypes. [–], not a defining feature; [+/–], a feature that may be present in some lesions; [+], a feature that is typically present; [++], a defining feature that may be prominent.

follicular plugging, deep dermal infiltrate, or scarring[61]. LE tumidus has prominent dermal mucin deposition and lymphocytic infiltrates with a lack of epidermal change. While changes of lupus panniculitis are most prominent in the subcutis, an overlying discoid lesion can be found in many cases[62].

Immunopathology of Lesional Skin

Examination of the skin for deposits of immunoreactants is called direct immunofluorescence (DIF). DIF of lesional skin does not replace routine histologic staining as the method of choice for establishing a diagnosis of cutaneous LE. DIF is not even necessary as an adjunctive diagnostic test if the histopathology and clinical presentation are definitive. In those cases where the routine histopathology is equivocal, DIF can be a valuable asset in establishing a diagnosis.

The most characteristic DIF finding in cutaneous LE is antibody deposition at the dermal–epidermal junction and around hair follicles[6]. These deposits are typically granular, and they are composed primarily of IgG and/or IgM (Fig. 41.17), although IgA can also occasionally be seen. In addition, deposits of complement proteins are to be expected. Some investigators have reported that in SCLE, granular deposits of IgG and IgM are observed primarily within the epidermis rather than at the dermal–epidermal junction[63]. There is evidence that the epidermal deposits are due to anti-Ro autoantibodies depositing directly within the skin[64].

In ACLE, SCLE and DLE, DIF of lesional skin is positive in the majority of cases. In general, a positive DIF supports the diagnosis of cutaneous LE, but a negative DIF does not exclude the diagnosis. It has been noted that DIF is most likely to be positive in well-established, active lesions. There is relatively little information about the expected frequency of positive DIF in LE tumidus. Many reports have noted nonspecific findings. In lupus panniculitis, DIF may show immunoreactants around dermal vessels, but granular deposits at the dermal–epidermal junction are not uniformly present.

Immunopathology of Normal-Appearing Skin

In normal-appearing skin, the presence of antibody deposits at the dermal–epidermal junction correlates reasonably well with systemic disease. The antibody deposits are sometimes referred to as a "lupus band", and examination for them as the "lupus band test". The terminology is confusing, because some authors use the term "lupus band" to apply to the antibody deposits at the dermal–epidermal junction, whether the skin tested is normal-appearing or lesional, and other authors reserve the term "lupus band" to describe antibody deposits in normal-appearing skin. It has been proposed that, if this terminology is used, the investigator should modify the term "lupus band" by a preceding adjective of "lesional" or "non-lesional", so that the subject of discussion is clearly identified[37]. The antibody and complement deposits at the dermal–epidermal junction are usually described as granular, although some experienced observers have identified subtypes of deposits, variously classified as fibrillar, thready, stippled, shaggy, linear, lumpy-bumpy or homogeneous[65].

Weak, discontinuous deposits may be seen in persons who do not have LE, including healthy adults, particularly when chronically sun-exposed skin is examined. For this reason, many investigators do not consider a non-lesional lupus band test to be positive unless the deposition of immunoreactants is strong and continuous. A true positive non-lesional lupus band test occurs in three-quarters or more of patients with SLE if sun-exposed skin is examined, and in about one-half of patients with SLE if sun-protected skin is examined[66]. A positive non-lesional lupus band test is unlikely to occur in patients who do not have SLE, but there are instances where the non-lesional lupus band test has been positive in patients with other autoimmune diseases.

In most cases, clinical evaluation and serologic testing for specific autoantibodies provides the required information, and the non-lesional lupus band test is superfluous. In cases where the clinical presentation or laboratory findings are atypical, the non-lesional lupus band test may have diagnostic value.

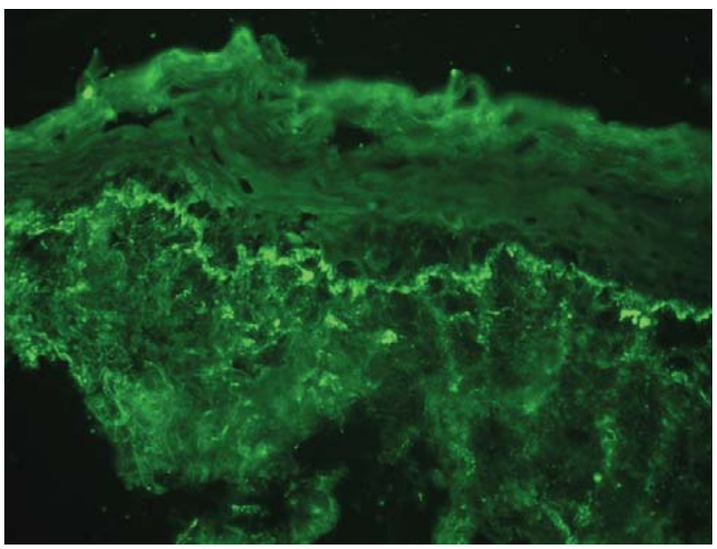


Fig. 41.17 Direct immunofluorescence of cutaneous lupus. Granular deposits of IgM are present at the dermal–epidermal junction within lesional skin. Antibody deposits at the dermal–epidermal junction are the most characteristic immunohistologic finding in lesions of cutaneous lupus and normal skin of patients with systemic lupus erythematosus. *Courtesy, Janet Fairley, MD.*

DIFFERENTIAL DIAGNOSIS

The differential diagnosis varies considerably with the subtype of cutaneous LE under consideration. Some of the major entities in each of the differential diagnoses are outlined in Table 41.5.

In evaluating a patient with cutaneous lesions, lesional biopsy for H&E is, in general, the most valuable diagnostic test. An approach to the diagnosis of cutaneous LE is shown in Figure 41.18. In an occasional situation, such as that of a patient with known SLE who has transient facial lesions that appear to be ACLE, the clinician may forego a biopsy because of the high likelihood of obtaining nonspecific findings and the cosmetic sequela of a scar on the face. Thus, the diagnostic tree presented is not intended to be followed strictly for each situation, but rather is meant as a general overview of the diagnostic approach, to be individualized for each patient.

In evaluating a patient with cutaneous lesions for the presence of systemic disease, the dermatologist can take a directed history, perform a cutaneous examination looking for signs of possible systemic disease (such as vasculitic lesions), and perform blood and urine testing for evidence of hematologic or renal disease, ANA, and SLE-specific autoantibodies (Table 41.6). Many clinicians also obtain an ESR and complement levels. Autoantibodies to dsDNA, Sm and possibly also ribosomal P are relatively specific for SLE, and are, therefore, helpful indicators of a high likelihood of systemic disease (see Ch. 40). Autoantibodies to Ro, La, U1RNP, histones and ssDNA are common in patients with SLE, but they are not disease-specific. An ANA is helpful if negative, as it is quite unusual for patients with SLE to have a negative ANA. It is common for the ANA to be positive in patients with cutaneous lesions, and a positive ANA is neither an indicator of systemic disease nor of LE. Positive ANAs may be found in patients with many other diseases (see Ch. 40) and even in apparently normal individuals. Approximately a third of apparently normal individuals have a positive ANA at a dilution of 1:40, 13% at a dilution of 1:80, and 5% at a dilution of 1:160[67].

In many cases, the decision to make a diagnosis of SLE is done on the basis of whether or not the patient's findings fulfill four or more criteria for the classification of SLE (Table 41.7)[68]. It should be noted that the classification was developed by rheumatologists to help distinguish patients with SLE from patients with other rheumatic diseases. In particular, most of the control subjects evaluated in the study that defined the SLE criteria were patients with rheumatoid arthritis. Therefore, the criteria are especially useful in distinguishing SLE from other conditions that affect joints, and they are quite useful as a means of standardizing patient groups for experimental protocols. However, the criteria should not be used in lieu of clinical judgment, i.e. patients

DIFFERENTIAL DIAGNOSES OF CUTANEOUS LUPUS SUBTYPES
ACUTE CUTANEOUS LUPUS/MALAR RASH
• Rosacea (including corticosteroid-induced) • Seborrheic dermatitis (especially photosensitive form) • Sunburn • Drug-induced photosensitivity (phototoxic and photoallergic) • Dermatomyositis • Erysipelas • Pemphigus erythematosus • Dermatitis, atopic, contact and photocontact • Acne vulgaris (rarely)
SUBACUTE CUTANEOUS LUPUS
• Psoriasis • Dermatophytosis, including tinea incognito • Photolichenoid drug eruption • Granuloma annulare • Figurate erythemas (e.g. erythema annulare centrifugum) • Dermatitis, atopic, contact and photocontact • Pemphigus foliaceus
DISCOID LESIONS
• Facial discoid dermatosis • Tinea faciei, tinea capitis, tinea corporis • Lichen planus and lichen planopilaris • Jessner's lymphocytic infiltrate • Polymorphous light eruption • Sarcoidosis • Lymphocytoma cutis • Lymphoma cutis • Granuloma faciale • Dimorphic fungal infections, lupus vulgaris • When single lesion, non-melanoma skin cancer
TUMID LUPUS LESIONS
• Jessner's lymphocytic infiltrate* • Polymorphous light eruption • Reticular erythematous mucinosis
LUPUS PANNICULITIS
• Other panniculitides (see Ch. 100)
*Some authorities believe that Jessner's lymphocytic infiltrate and LE tumidus are the same condition.

Table 41.5 Differential diagnoses of cutaneous lupus subtypes. Mothers of boys with chronic granulomatous disease and patients with Sjögren's syndrome have an annular erythema similar to annular SCLE; patients with GVHD can develop SCLE-like lesions.

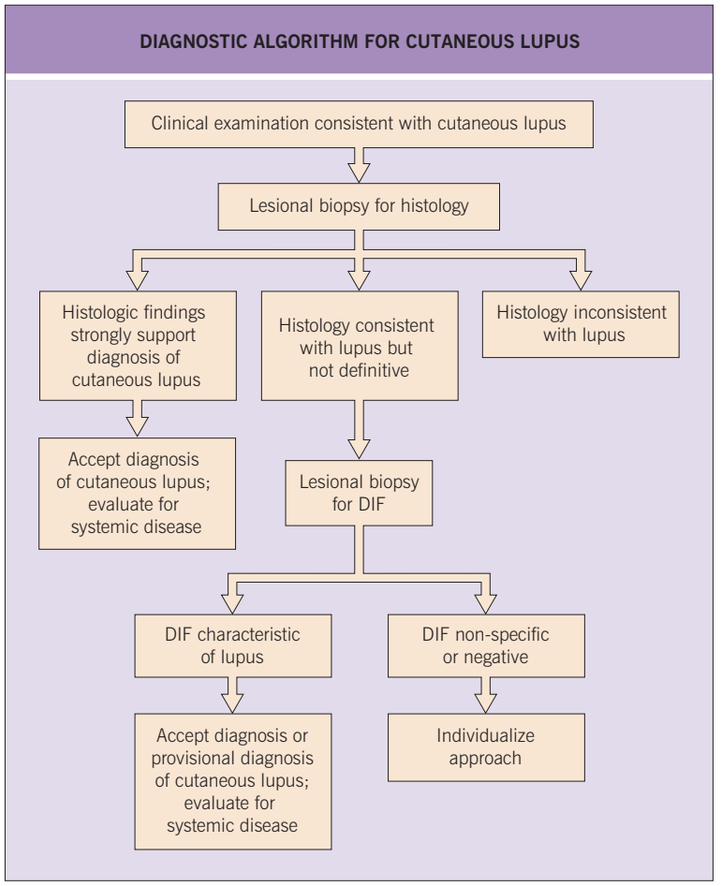


Fig. 41.18 Diagnostic algorithm for cutaneous lupus. This algorithm is intended as a guide to diagnosis and should be individualized for each situation. For example, lesional biopsy for direct immunofluorescence (DIF) may be performed at the same time as a lesional biopsy for routine histology. Less definitive histologic findings might sometimes be acceptable if the patient is already known to have SLE. Whether a diagnosis is clear-cut or provisional may be, on occasion, a subjective determination.

EVALUATION FOR SYSTEMIC LUPUS ERYTHEMATOSUS
HISTORY
PHYSICAL EXAMINATION
• Specific cutaneous lesions (see Table 41.2) • Nonspecific cutaneous lesions (see Table 41.3) • Lymphadenopathy, arthritis
LABORATORY TESTS
• ANA with profile (anti-dsDNA, -Sm) • Urinalysis • CBC with differential, platelet count • Chemistries (BUN, creatinine) • Erythrocyte sedimentation rate • Complement levels (C3, C4)

Table 41.6 Evaluation for systemic lupus erythematosus. ANA, antinuclear antibodies; BUN, blood urea nitrogen; CBC, complete blood count; ds, double-stranded; Sm, Smith.

who do not have four or more criteria may still have SLE, and, conversely, it is possible to meet four criteria and yet not have SLE.

The SLE classification criteria do emphasize the need to exclude drug-induced systemic lupus. The latter presents as a lupus-like systemic illness with arthralgias, myalgias, pleuritis and fever, but lacking nephritis and CNS disease. It is observed in patients who are receiving specific medications, in particular procainamide and hydralazine, and who develop antihistone autoantibodies (although these autoantibodies are nonspecific and are also common in patients with SLE). In contrast to drug-induced SCLE with anti-Ro autoantibodies (see above), patients with drug-induced SLE rarely have specific lesions of cutaneous LE, but they may have nonspecific lesions. Of note, patients receiving TNF inhibitors may develop autoantibodies, particularly ANA and anti-dsDNA, and on occasion develop cutaneous lesions that can resemble ACLE, SCLE or DLE.

TREATMENT

Topical Therapy

Topical or intralesional corticosteroids are a mainstay of therapy (Table 41.8). They offer a high degree of safety as well as the potential for a relatively rapid response. The systemic side effects of corticosteroids are largely avoided, although the cutaneous side effects are not. It is frequently the case that topical corticosteroids need to be of high potency in order for a response to occur, and discoid lesions are one of the few instances where it may be appropriate to use high-potency corticosteroids on the face. Patients should be instructed about the risks and benefits of therapy, the need to limit the application to affected areas, and the need for monitoring for cutaneous side effects.

THE AMERICAN COLLEGE OF RHEUMATOLOGY 1982 REVISED CRITERIA FOR CLASSIFICATION OF SYSTEMIC LUPUS ERYTHEMATOSUS*	
Criterion	**Definition**
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Arthritis	Non-erosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling or effusion
6. Serositis	a) **Pleuritis** – convincing history of pleuritic pain, rubbing heard by a physician, or evidence of pleural effusion *OR* b) **Pericarditis** – documented by ECG, rub or evidence of pericardial effusion
7. Renal disorder	a) Persistent **proteinuria** greater than 0.5 g/day or greater than 3+ if quantitation not performed *OR* b) **Cellular casts** – may be red cell, hemoglobin, granular, tubular or mixed
8. Neurologic disorder	a) **Seizures** – in the absence of offending drugs or known metabolic derangements, e.g. uremia, ketoacidosis or electrolyte imbalance *OR* b) **Psychosis** – in the absence of offending drugs or known metabolic derangements, e.g. uremia, ketoacidosis or electrolyte imbalance
9. Hematologic disorder	a) **Hemolytic anemia** with reticulocytosis *OR* b) **Leukopenia** – less than 4000/mm^3 total WBC on two or more occasions *OR* c) **Lymphopenia** – less than 1500/mm^3 on two or more occasions *OR* d) **Thrombocytopenia** – less than 100 000/mm^3 in the absence of offending drugs
10. Immunologic disorder	a) **Anti-DNA antibody to native DNA** in abnormal titer *OR* b) **Anti-Sm:** presence of antibody to Sm nuclear antigen *OR* c) Positive finding of **antiphospholipid antibodies** based on: (1) an abnormal serum level of IgG or IgM anticardiolipin antibodies; (2) a positive test result for lupus anticoagulant using standard methods; or (3) a false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test (FTA-ABS)
11. Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence (or an equivalent assay) at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

*The proposed classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person shall be said to have systemic lupus erythematosus if any four or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.

Table 41.7 The American College of Rheumatology 1982 revised criteria for classification of systemic lupus erythematosus[69]. ECG, electrocardiogram; Sm, Smith; WBC, white blood cell.

Particularly in active discoid lesions and LE tumidus lesions, intralesional triamcinolone, often given in a concentration of 4–5 mg/ml, can be very effective. The injections may be repeated monthly while the lesions are active. There are anecdotal reports of the use of new topical immunomodulators (e.g. tacrolimus) for cutaneous lesions.

Systemic Therapy

Antimalarial therapy has been used for more than a half-century for cutaneous LE, and it remains the gold standard for systemic therapy. Hydroxychloroquine sulfate is the most commonly chosen antimalarial, as it is usually well tolerated. Chloroquine and quinacrine (mepacrine) are alternatives. In patients who are not responsive to hydroxychloroquine sulfate, quinacrine may be added to the regimen[69a]. Quinacrine can turn the skin yellow, although it does not invariably do so. The dose of hydroxychloroquine sulfate chosen is usually 200 mg once or twice per day. It has been reported that if the dose does not exceed 6.5 mg/kg ideal body weight/day, eye toxicity is quite unlikely[70]. For chloroquine, the usual dose is 125–250 mg/day, with the eye toxicity-minimizing dose being no more than 3.5–4 mg/kg ideal body weight/

THERAPY OF CUTANEOUS LUPUS
LOCAL THERAPY
Sun protection (2)
Topical and intralesional corticosteroids (2)
Topical calcineurin inhibitors (2)
Topical retinoids (3)
SYSTEMIC ANTIMALARIAL THERAPY
Hydroxychloroquine (200 mg po qd–bid in adults; up to 6.5 mg/kg ideal body weight/day) (2)
Chloroquine (125–250 po qd in adults; up to 3.5–4 mg/kg ideal body weight/day) (2)
Quinacrine (100 mg po qd) (2)
Combination of hydroxychloroquine or chloroquine and quinacrine (2)
SYSTEMIC THERAPY FOR ANTIMALARIAL-RESISTANT CUTANEOUS DISEASE
Retinoids (e.g. acitretin, isotretinoin) (2)
Thalidomide (50–100 mg po qd for clearing and, if necessary, 25–50 mg po qd–twice weekly for maintenance) (2)
Dapsone (primarily for bullous eruption of SLE) (2)
Immunosuppressive agents (e.g. mycophenolate mofetil, azathioprine) (2)
Sulfasalazine (2)
Clofazimine (3)
Systemic corticosteroids (3)
Immune response modifiers (e.g., rituximab, abatacept,* belimumab, anti-IL-6 Ab, anti-IL-10 Ab) (3)
*Not more effective than placebo in non life-threatening SLE.

Table 41.8 Therapy of cutaneous lupus. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports. bid, twice daily; qd, daily.

day[70]. Quinacrine is thought by most not to cause eye toxicity. For patients on hydroxychloroquine sulfate or chloroquine, eye examinations should be done by a physician knowledgeable in antimalarial eye toxicity.

The response to antimalarials is relatively slow. It may take 2 or 3 months for efficacy to be appreciated, and sometimes several more months to achieve maximal efficacy. Consequently, for patients who are beginning therapy for cutaneous LE, topical or intralesional therapy should usually be given along with antimalarial therapy. It has been observed that there is a larger than expected percentage of cigarette smokers among patients who present with cutaneous lupus, and that smokers may have more extensive cutaneous disease. It has also been observed that smokers do not respond as well to antimalarial therapy as do non-smokers. Thus, smoking cessation may be a useful adjunctive therapy in some individuals.

Some patients do not respond either to single antimalarial therapy or to the combination of quinacrine with either hydroxychloroquine sulfate or chloroquine. Disease that is refractory to antimalarials is often refractory to other therapies as well. Nonetheless, it is reasonable to seek a therapy that will work well, if the risks of therapy are deemed to be worth the potential benefits. In antimalarial-resistant patients, therapeutic options include oral retinoids, thalidomide, immunosuppressive agents such as mycophenolate mofetil or azathioprine, clofazimine, sulfasalazine and systemic corticosteroids[71]. Dapsone has been used, but usually with little success except in the rare subset of bullous eruption of SLE. Both retinoids and thalidomide are potent teratogens, making them difficult choices in women of childbearing potential. Thalidomide also frequently causes a peripheral neuropathy. For that reason, some clinicians have advocated giving thalidomide in low or intermittent dosing in an attempt to minimize toxicity. In the future, immune response modifiers (such as rituximab, and anti-B-lymphocyte stimulator [BlyS], -IL-6 and -IL-10 antibodies) may play an important role in the treatment of cutaneous LE.

In patients with systemic LE but no major organ involvement (i.e. potentially life-threatening involvement of visceral organs), treatment for mild disease includes NSAIDs, while corticosteroids and immunosuppressives (e.g. azathioprine, leflunomide, mycophenolate mofetil) are usually prescribed for moderate to severe disease. When there is a mild degree of major organ involvement, corticosteroids are the primary treatment, but for moderate to severe involvement, pulse cyclophosphamide +/– pulse corticosteroids are often recommended. Immune response modifiers (biologic therapies) are reserved for refractory disease (see Table 41.8)[72]. For a recent more comprehensive review, the reader is referred to reference 73.

Adjunctive Therapy

Sun protection is a vital part of therapy for many patients because the sun exacerbates or initiates their skin lesions. For others, sun protection is important for cancer prevention, particularly in hypopigmented skin or in chronic discoid lesions, where the risk of skin cancer development may be higher. Cancer prevention is also essential for patients who are on immunosuppressive therapy. Lastly, it has been reported that sun exposure can exacerbate systemic disease in patients who have SLE. Therefore, there are a variety of reasons why sun protection should be emphasized, even in persons whose skin lesions are not induced or exacerbated by sun exposure.

Sunscreens should be applied to exposed skin daily, and more often if sun sensitivity is great or sun exposure is intense or prolonged. Broad-spectrum, high-SPF sunscreens are preferred (see Ch. 132). In some cases, the addition of a physical sunblock such as titanium dioxide or zinc oxide is useful. Protective clothing is important to emphasize, as the proper protective clothing is often significantly more effective than sunscreens. Sun avoidance is even more effective than protective chemicals and clothing. Midday sun is particularly high in UVB, a spectrum of UV radiation to which many patients are susceptible. It is more difficult to minimize UVA exposure, as UVA is present in substantial quantities throughout the day and can penetrate some types of window glass. Education on the optimal use of sunscreens and protective clothing and effective approaches to sun avoidance is important for most patients with lupus. Careful attention should be given to vitamin D and calcium intake.

For some patients, cosmetic cover-up is the most helpful therapeutic intervention (see Ch. 153). Particularly in situations where the disease activity has subsided but dyspigmentation remains, cosmetic camouflage of the hyperpigmentation or hypopigmentation may be the best approach.

REFERENCES

1. Cazenave PLA. Lupus erythemateux (erytheme centrifuge). Ann Malad Peau Syph. 1851;3:297–9.
2. Sontheimer RD, Thomas JR, Gilliam JN. Subacute cutaneous lupus erythematosus: a cutaneous marker for a distinct lupus erythematosus subset. Arch Dermatol. 1979;115:1409–15.
3. Maddison PJ, Provost TT, Reichlin M. Serological findings in patients with "ANA-negative"systemic lupus erythematosus. Medicine (Baltimore). 1981;60:87–94.
4. Hargraves M, Richmond H, Morton R. Presentation of two bone marrow elements: the "tart" cell and the "LE" cell. Mayo Clin Proc. 1948;23:25–8.
5. Friou GJ. Clinical application of lupus serum: nucleoprotein reaction using fluorescent antibody technique [abstract]. J Clin Invest. 1957;36:890.
6. Burnham TK, Neblett TR, Fine G. The application of the fluorescent antibody technique to the investigation of lupus erythematosus and various dermatoses. J Invest Dermatol. 1963;41:451–6.
7. Tan EM, Kunkel HG. Characteristics of a soluble nuclear antigen precipitating with sera of patients with systemic lupus erythematosus. J Immunol. 1966;96:464–71.
8. Clark G, Reichlin M, Tomasi TB. Characterization of a soluble cytoplasmic antigen reactive with sera from patients with systemic lupus erythematosus. J Immunol. 1969;102:117–22.
9. Mattioli M, Reichlin M. Characterization of a soluble nuclear ribonucleoprotein antigen reactive with SLE sera. J Immunol. 1971;107:1281–90.
10. Franco HL, Weston WL, Peebles C, et al. Autoantibodies directed against sicca syndrome antigens in the neonatal lupus syndrome. J Am Acad Dermatol. 1981;4:67–72.
11. Sontheimer RD, Maddison PJ, Reichlin M, et al. Serologic and HLA associations in subacute cutaneous lupus erythematosus, a clinical subset of lupus erythematosus. Ann Intern Med. 1982;97:664–71.
12. Payne JF. A postgraduate lecture on lupus erythematosus. Clin J. 1894;4:222–9.
13. Ruo V, Hochberg MC. The epidemiology of systemic lupus erythematosus. In: Wallace DJ, Hahn BH (eds). Dubois' Lupus Erythematosus, 6th edn. Philadelphia: Lippincott, Williams & Wilkins, 2002:65–83.

14. Uribe AG, McGwin G Jr, Reveille JD, Alarcón GS. What have we learned from a 10-year experience with the LUMINA (Lupus in Minorities; Nature vs. Nurture) cohort? Where are we heading? Autoimmun Rev. 2004;3: 321–9.
15. Durosaro O, Davis MD, Reed KB, Rohlinger AL. Incidence of cutaneous lupus erythematosus, 1965–2005: a population-based study. Arch Dermatol. 2009;145: 249–53.
16. Moser KL, Kelly JA, Lessard CJ, et al. Recent insights into the genetic basis of systemic lupus erythematosus. Genes Immun. 2009;10:373–9.
17. Chung SA, Tian C, Taylor KE, et al. European population substructure is associated with mucocutaneous manifestations and autoantibody production in systemic lupus erythematosus. Arthritis Rheum. 2009;60:2448–56.
18. Provost TT, Arnett F, Reichlin M. Homozygous C2 deficiency, lupus erythematosus, and anti-Ro (SSA) antibodies. Arthritis Rheum. 1983;26:1279–82.
19. Järvinen TM, Hellquist A, Koskenmies S, et al. Tyrosine kinase 2 and interferon regulatory factor 5 polymorphisms are associated with discoid and subacute cutaneous lupus erythematosus. Exp Dermatol. 2010;19:123–31.
20. Rice G, Newman WG, Dean J, et al. Heterozygous mutations in TREX1 cause familial chilblain lupus and dominant Aicardi-Goutieres syndrome. Am J Hum Genet. 2007;80:811–15.
21. Xue D, Shi H, Smith, JD, et al. A lupus-like syndrome develops in mice lacking the Ro 60-kDa protein, a major lupus autoantigen. Proc Natl Acad Sci U S A. 2003;100: 7503–8.
22. Higgs R, Ni Gabhann J, Ben Larbi N, et al. The E3 ubiquitin ligase Ro52 negatively regulates IFN-beta production post-pathogen recognition by polyubiquitin-mediated degradation of IRF3. J Immunol. 2008;181: 1780–6.
23. Kochevar IE. Action spectrum and mechanisms of UV radiation-induced injury in lupus erythematosus. J Invest Dermatol. 1985;85:140s–143s.
24. Casciola-Rosen LA, Anhalt G, Rosen A. Autoantigens targets in systemic lupus erythematosus are clustered in two populations of surface structures on apoptotic keratinocytes. J Exp Med. 1994;179:1317–30.
25. Kuhn A, Herrmann M, Kleber S, et al. Accumulation of apoptotic cells in the epidermis of patients with cutaneous lupus erythematosus after ultraviolet irradiation.[see comment]. Arthritis Rheum. 2007;54:939–50.
26. Oke V, Vassilaki I, Espinosa A, et al. High Ro52 expression in spontaneous and UV-induced cutaneous inflammation. J Invest Dermatol. 2009;129:2000–10.
27. Werth VP, Zhang W. Wavelength-specific synergy between ultraviolet radiation and interleukin-1 alpha in the regulation of matrix-related genes: mechanistic role for tumor necrosis factor-alpha. J Invest Dermatol. 1999;113:196–201.
28. Wang D, Drenker M, Eiz-Vesper B, et al. Evidence for a pathogenetic role of interleukin-18 in cutaneous lupus erythematosus. Arthritis Rheum. 2008;58:3205–15.
29. Popovic K, Ek M, Espinosa A, et al. Increased expression of the novel proinflammatory cytokine high mobility group box chromosomal protein 1 in skin lesions of patients with lupus erthematosus. Arthritis Rheum. 2005:52:3639–45.
30. Meller S, Winterberg F, Gilliet M, et al. Ultraviolet radiation-induced injury, chemokines, and leukocyte recruitment: an amplification cycle triggering cutaneous lupus erythematosus. Arthritis Rheum. 2005;52: 1504–16.
31. Norris P, Poston RN, Thomas DS, et al. The expression of endothelial leukocyte adhesion molecule-1 (ELAM-1), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) in experimental cutaneous inflammation: a comparison of ultraviolet B erythema and delayed hypersensitivity. J Invest Dermatol. 1991;96:763–70.
32. Bennion SD, Middleton MH, David-Bajar KM, et al. In three types of interface dermatitis, different patterns of expression of intercellular adhesion molecule-1 (ICAM-1) indicate different triggers of disease. J Invest Dermatol. 1995;105:71s–79s.
33. Ronnblom L, Eloranta ML, Alm GV. The type I interferon system in systemic lupus erythematosus. Arthritis Rheum. 2006;54:408–420.
34. Farkas L, Beiske K, Lund-Johansen F, et al. Plasmacytoid dendritic cells (natural interferon-alpha/beta-producing cells) accumulate in cutaneous lupus erythematosus lesions. Am J Pathol. 2001;159:237–243.
35. Siegal FP, Kadowaki N, Shodell M, et al. The nature of the principal type 1 interferon-producing cells in human blood. Science. 1999;284:1835–1837.
36. Waithman J, Allan RS, Kosaka H, et al. Skin-derived dendritic cells can mediate deletional tolerance of class I-restricted self-reactive T cells. J Immunol. 2007;179: 4535–4541.
37. Braunstein I, Klein RS, Okawa J, et al. The IFN-inducible gene signature is elevated in SCLE and DLE and correlates with CLASI score. Arthritis Rheum. 2009;60:S551 (Abstract).
38. Wenzel J, Zahn S, Mikus S, et al. The expression pattern of interferon-inducible proteins reflects the characteristic histological distribution of infiltrating immune cells in different cutaneous lupus erythematosus subsets. Br J Dermatol. 2007;157: 752–7.
39. Wenzel J, Henze S, Worenkamper E, et al. Role of chemokine receptor CCR4 and its ligand thymus- and activation-regulated chemokine CCL17 for lymphocyte recruitment in cutaneous lupus erythematosus. J Invest Dermatol. 2005;124:1241–8.
40. Franz B, Fritzsching B, Riehl A, et al. Low number of regulatory T cells in skin lesions of patients with cutaneous lupus erythematosus. Arthritis Rheum. 2007;56:1910–20.
41. Gilliam JN, Sontheimer RD. Distinctive cutaneous subsets in the spectrum of lupus erythematosus. J Am Acad Dermatol. 1981;4:471–5.
42. Specker C, Schneider M. Relationship between cutaneous and systemic lupus erythematosus. In: Kuhn A, Lehmann P, Ruzicka T (eds). Cutaneous Lupus Erythematosus. Berlin: Springer-Verlag, 2005:177–86.
43. Prystowsky SD, Herndon JH Jr, Gilliam JN. Chronic cutaneous lupus erythematosus (DLE) – a clinical and laboratory investigation of 80 patients. Medicine (Baltimore). 1975;55:183–91.
44. Costner MI, Sontheimer RD, Provost TT. Lupus erythematosus. In: Sontheimer RD, Provost TT (eds). Cutaneous Manifestations of Rheumatic Diseases, 2nd edn. Philadelphia: Lippincott, Williams & Wilkins, 2004:15–64.
45. Callen JP. Chronic cutaneous lupus erythematosus. Clinical, laboratory, therapeutic, and prognostic examination of 62 patients. Arch Dermatol. 1982;118:412–16.
46. Millard LG, Rowell NR. Abnormal laboratory test results and their relationship to prognosis in discoid lupus erythematosus: a long-term follow-up study of 92 patients. Arch Dermatol. 1979;115:1055–8.

46a. Grönhagen CM, Fored CM, Granath F, Nyberg F. Cutaneous lupus erythematosus and the association with systemic lupus erythematosus: a population-based cohort of 1088 patients in Sweden. Br J Dermatol. 2011;164:1335–41.

47. Sontheimer RD. Subacute cutaneous lupus erythematosus. Clin Dermatol. 1985;3:58–68.
48. Lee LA, Roberts CM, Frank MB, et al. The autoantibody response to Ro/SSA in cutaneous lupus erythematosus. Arch Dermatol. 1994;130:1262–8.
49. Rowell NR, Beck JS, Anderson JR. Lupus erythematosus and erythema multiforme-like lesions. Arch Dermatol. 1963;88:176–80.
50. Weber F, Schmuth M, Fritsch P, et al. Lymphocytic infiltration of the skin is a photosensitive variant of lupus erythematosus: evidence by phototesting. Br J Dermatol. 2001;144:292–6.
51. Kuhn A, Richter-Hintz D, Oslislo C, et al. Lupus erythematosus tumidus – a neglected subset of cutaneous lupus erythematosus: report of 40 cases. Arch Dermatol. 2000;136:1033–41.
52. Lee LA, Frank MB, McCubbin VR, et al. The autoantibodies of neonatal lupus erythematosus. J Invest Dermatol. 1994;102:963–6.
53. Buyon JP, Hiebert R, Copel J, et al. Autoimmune-associated congenital heart block: demographics, mortality, morbidity and recurrence rates obtained from a national neonatal lupus registry. J Am Coll Cardiol. 1998;31:1658–66.
54. Lee LA. The clinical spectrum of neonatal lupus. Arch Dermatol Res. 2009;301:107–110.
55. Hall RP, Lawley TJ, Smith HR, et al. Bullous eruption of systemic lupus erythematosus. Dramatic response to dapsone therapy. Ann Intern Med. 1982;97:165–70.
56. Gammon WR, Briggaman RA. Bullous SLE: a phenotypically distinctive but immunologically heterogeneous bullous disorder. J Invest Dermatol. 1993;100:285–345.
57. Yell JA, Wojnarowska F. Bullous skin disease in lupus erythematosus. Lupus. 1997;6:112–21.
58. Englert HJ, Hawkes CH, Boey ML, et al. Degos' disease: association with anticardiolipin antibodies and the lupus anticoagulant. Br Med J (Clin Res Ed). 1984;289:576.
59. Frances C, Piette JC. Cutaneous manifestations of Hughes syndrome occurring in the context of lupus erythematosus. Lupus. 1997;6:139–44.
60. Werth VP, White WL, Sanchez MR, et al. Incidence of alopecia areata in lupus erythematosus. Arch Dermatol. 1992;128:368–71.
61. Bangert JL, Freeman RG, Sontheimer RD, Gilliam JN. Subacute cutaneous lupus erythematosus and discoid lupus erythematosus. Comparative histopathologic findings. Arch Dermatol. 1984;120:332–7.
62. Sanchez NP, Peters MS, Winkelmann RK. The histopathology of lupus erythematosus panniculitis. J Am Acad Dermatol. 1981;5:673–80.
63. David-Bajar KM, Bennion SD, DeSpain JD, et al. Clinical, histologic, and immunofluorescent distinctions between subacute cutaneous lupus erythematosus and discoid lupus erythematosus. J Invest Dermatol. 1992;99:251–7.
64. Lee LA, Gaither KK, Coulter SN, et al. Pattern of cutaneous immunoglobulin G deposition in subacute cutaneous lupus erythematosus is reproduced by infusing purified anti-Ro (SSA) autoantibodies into human skin-grafted mice. J Clin Invest. 1989;83:1556–62.
65. Burnham TK, Fine G. The immunofluorescent "band" test for lupus erythematosus. I. Morphologic variations of the band of localized immunoglobulins at the dermal–epidermal junction in lupus erythematosus. Arch Dermatol. 1969;99:413–20.
66. David-Bajar KM, Davis BM. Pathology, immunopathology, and immunohistochemistry in cutaneous lupus erythematosus. Lupus. 1997;6:145–57.
67. Tan EM, Feltkamp TE, Smolen JS, et al. Range of antinuclear antibodies in "healthy" individuals [see comments]. Arthritis Rheum. 1997;40:1601–11.
68. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1982;25:1271–7.
69. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. American College of Rheumatology website. http://www.rheumatology.org/publications/classification/SLE/1982SLEupdate.asp?aud=mem.

69a. Chang AY, Piette EW, Foering KP, et al. Response to antimalarial agents in cutaneous lupus erythematosus: A prospective analysis. Arch Dermatol. Jul 18, 2011. 10.1001/archdermatol.2011.191

70. Ochsendorf FR. Antimalarials. In: Kuhn A, Lehmann P, Ruzicka T (eds). Cutaneous Lupus Erythematosus. Berlin: Springer-Verlag, 2005:347–72.
71. Callen JP. Management of cutaneous lupus erythematosus. In: Kuhn A, Lehmann P, Ruzicka T (eds). Cutaneous Lupus Erythematosus. Berlin: Springer-Verlag, 2005:437–44.
72. Dall'Era M, Wofsy D. Systemic lupus erythematosus clinical trials – an interim analysis. Nat Rev Rheumatol. 2009;5:348–51.
73. Tassiulas IO, Boumpas DT. Clinical features and treatment of systemic lupus erythematosus. In: Firestein GS, Budd RC, Harris ED, et al. (eds). Kelley's Textbook of Rheumatology. Philadelphia: Saunders, 2009:1263–300.

This page intentionally left blank

Dermatomyositis 42

Joseph L Jorizzo and Ruth Ann Vleugels

Synonyms: ■ Dermatomyositis/polymyositis ■ Idiopathic inflammatory myopathies ■ Idiopathic inflammatory dermatomyopathies

Key features

- Autoimmune connective tissue disease of uncertain etiology demonstrating a bimodal age distribution with both juvenile and adult forms
- Clinical and laboratory signs of proximal extensor inflammatory myopathy
- Distinctive, photodistributed, pink–violet poikiloderma favoring the scalp, periocular region, and extensor surfaces, in addition to nail fold telangiectasias
- Histopathologic evidence of interface dermatitis with mucin in skin biopsy specimens and lymphocytic myositis in biopsy specimens from affected muscle
- Therapy includes systemic corticosteroids and possibly immunosuppressive drugs with the prognosis being very good, except for adults with associated advanced malignancy, refractory myositis or systemic involvement

INTRODUCTION

Along with polymyositis and inclusion body myositis, dermatomyositis is classified as one of the idiopathic inflammatory myopathies. Dermatomyositis is a disease of presumed autoimmune pathogenesis that presents with a symmetric, proximal extensor inflammatory myopathy and a characteristic cutaneous eruption. Previously, polymyositis was thought to represent the same disease process, but just limited to the muscle. However, there is now increasing evidence that the pathogenetic mechanisms of polymyositis and dermatomyositis differ significantly. In polymyositis, clonally expanded, autoreactive $CD8^+$ T cells invade myocytes expressing MHC class I antigens and cause necrosis via the perforin pathway. In contrast, there are data to support the theory that autoantigens activate a humoral immune process in dermatomyositis, in which complement is deposited in capillaries causing capillary necrosis and ischemia[1]. Because an appreciation of these pathogenetic differences occurred rather recently, previous studies often pooled cases of dermatomyositis and polymyositis, making interpretation of their data challenging.

Both dermatomyositis and polymyositis can occur in association with other autoimmune connective tissue diseases, including overlap syndromes with additional features of lupus erythematosus (LE), scleroderma, Sjögren's syndrome, rheumatoid arthritis, and mixed connective tissue disease. Dermatomyositis is characterized by a bimodal age distribution, with up to one-quarter of patients in the adult group having an associated occult malignancy. Patients with juvenile dermatomyositis do not have an increased risk of malignancy but do have an increased incidence of calcinosis cutis and associated small vessel vasculitis. There is a subset of patients in whom the cutaneous manifestations of dermatomyositis exist without objective evidence of muscle inflammation, referred to as amyopathic dermatomyositis, and formally known as dermatomyositis sine myositis. For dermatologists, establishing the diagnosis of dermatomyositis is important because it is a serious, treatable, multisystem disease that has a different prognosis and treatment approach from LE. The malignancy association in adults provides the dermatologist with an opportunity to assist medical colleagues in detecting the tumor at an early stage because the skin disease often precedes the onset of symptoms related to the malignancy. The diagnosis is commonly missed, which gives the dermatologist an opportunity to make a very meaningful contribution.

The treatment of dermatomyositis with muscle and/or systemic involvement requires systemic corticosteroids (e.g. prednisone 1 mg/kg/day) with a taper that is slower than in the treatment of systemic LE. If this approach is used, as many as three-quarters of patients may enter a clinically disease-free period without medication, usually within 2–3 years[2].

HISTORY

Polymyositis and dermatomyositis have been recognized as clinical entities for more than 100 years. Although the first adult patients with dermatomyositis and malignancy were described early in the twentieth century, a causal association was not suggested until the 1940s. A major step forward in the understanding of these disorders occurred in 1975, when Bohan and Peter proposed generally accepted clinical criteria for their diagnosis[3,4]. Over the past 15 years, it has become more widely accepted that a subset of patients has skin-limited disease (i.e. amyopathic dermatomyositis). For this reason, Sontheimer[5] has proposed a revised classification of the idiopathic inflammatory myopathies that includes amyopathic forms of dermatomyositis, with muscle involvement no longer required for a definitive diagnosis (Table 42.1).

EPIDEMIOLOGY

Dermatomyositis and polymyositis are relatively rare diseases that occur throughout the world. In adults, both dermatomyositis and polymyositis affect women two to three times more often than men. The incidence of dermatomyositis ranges from 2 to 9 per million amongst various populations[7–9] and seems to be increasing, although this may simply be a result of increased detection, as well as better diagnosis and reporting. Table 42.2 summarizes the findings in four recent studies[9–12].

PATHOGENESIS

Dermatomyositis is believed to result from an immune-mediated process triggered by outside factors (e.g. malignancy, drugs, infectious agents) in genetically predisposed individuals. Table 42.3 illustrates some of the evidence that supports this theory[13–33]. Serum antinuclear autoantibodies are often present, as are other myositis-specific autoantibodies, as summarized in Table 42.4[34,35]. The antisynthetase antibodies are directed against cytoplasmic antigens; therefore the antinuclear antibody test may even be negative. Patients with antisynthetase antibodies often have overlap syndromes. The term antisynthetase syndrome has been coined to refer to patients with these autoantibodies,

fever, erosive polyarthritis, "mechanic's hands", Raynaud's phenomenon, and interstitial lung disease[36].

CLINICAL FEATURES

Cutaneous Disease

The most important diagnostic feature of the cutaneous eruption of dermatomyositis is poikiloderma. This feature occurs both in patients with dermatomyositis, where it is characterized by a pink–violet color, and in patients with lupus erythematosus, where the poikiloderma is red. Poikiloderma includes features of hyperpigmentation, hypopigmentation, telangiectasias and epidermal atrophy, and these features are common to both diseases. If the clinician misses the poikiloderma, the eruption of dermatomyositis may occasionally be misdiagnosed as psoriasis because some lesions can present as well-marginated plaques on the elbows and knees and be covered with fine silvery scale.

Additional clinical clues to the diagnosis of dermatomyositis are a photodistribution and nail fold changes. Photodistributed poikiloderma involving the "V" of the chest and the upper back is often referred to as the "shawl sign". Cuticular dystrophy (i.e. "ragged" cuticles) is quite characteristic, as are nail fold telangiectasias (Fig. 42.1). If the photodistribution and nail fold changes are missed, the eruption may be misdiagnosed as other conditions characterized by poikiloderma, such as cutaneous T-cell lymphoma. Often, the dermatologist correctly notices the photodistribution but thinks first of a photodrug eruption

REVISED CLASSIFICATION SYSTEM FOR THE IDIOPATHIC INFLAMMATORY DERMATOMYOPATHIES
Dermatomyositis
Adult-onset
Classic DM
Classic DM with malignancy
Classic DM as part of an overlapping connective tissue disorder
Clinically amyopathic DM*
Amyopathic DM
Hypomyopathic DM
Juvenile-onset
Classic DM
Clinically amyopathic DM
Amyopathic DM
Hypomyopathic DM
Polymyositis
Isolated polymyositis
Polymyositis as part of an overlapping connective tissue disorder
Polymyositis associated with internal malignancy (?)†
Inclusion body myositis

*Both adult-onset and juvenile-onset amyopathic DM and hypomyopathic DM can be further subcategorized as "provisional" and "confirmed" when patients have biopsy-confirmed hallmark cutaneous manifestations of DM without muscle weakness and with normal muscle enzymes for ≥6 months (provisional) or 24 months (confirmed).
†Although more recent population-based studies have clearly confirmed that adult-onset classic DM is associated with a significant risk for internal malignancy, these same studies have questioned whether such a relationship exists for polymyositis.

Table 42.1 Revised classification system for the idiopathic inflammatory dermatomyopathies. This classification scheme recognizes, with equal weighting, the cutaneous and muscle manifestations of this group of disorders. Adapted from ref. 6

PATHOGENESIS OF DERMATOMYOSITIS
GENETICS[13–15]
• Monozygotic twins affected • Associated human leukocyte antigens (HLA) – HLA-DR3 and -B8 (juvenile dermatomyositis) – HLA-DR52 (patients with anti-Jo-1 antibodies) – HLA-DR7 and -DRw53 (patients with anti-Mi-2 antibodies) – HLA-B14 and -B40 (adults with dermatomyositis overlap) – HLA-DRB1*15021 (Japanese with juvenile dermatomyositis) • TNF-α 308A allele polymorphism
CELLULAR IMMUNITY/APOPTOSIS[16–22]
• Histopathologic findings in skin and muscle ($CD8^+$ lymphocytes) • Lymphocyte-mediated experimental myositis in mice • Increased Ki-67 and p53 expression in keratinocytes after UVB irradiation • Increased CD40 expression on muscle cells • Decreased circulating CD54 (ICAM-1)-positive lymphocytes • Fas ligand on T cells and Fas receptor on muscle cells • MHC class I overexpressed in affected muscle tissues • Elevated expression of COX-1, COX-2 and 5-LOX mRNA in affected muscle tissues
HUMORAL IMMUNITY[23]
• Association with autoimmune diseases (Hashimoto's thyroiditis, Graves' disease, myasthenia gravis, type I diabetes mellitus, primary biliary cirrhosis, dermatitis herpetiformis, vitiligo, and other autoimmune connective tissue diseases) • Myositis-specific antibodies versus antibodies against aminoacyl-tRNA synthetases, non-synthetases, cytoplasmic antigens, and nuclear antigens. Examples include: antisynthetase, anti-Jo-1 (lung disease) and anti-Mi-2 (most specific for dermatomyositis)
INFECTIOUS PRECIPITANTS[24,25]
• Seasonal variation • Picornavirus substrate for aminoacyl-tRNA synthetases • *Escherichia coli*, muscle protein and a capsid protein of a picornavirus that induces mouse myositis all have some homology in amino acid sequences with Jo-1 • Echovirus infection in patients with hypogammaglobulinemia • Coxsackievirus-9 myositis • AIDS myositis
DRUG AND VACCINE PRECIPITANTS[26–31]
• Hydroxyurea, D-penicillamine, TNF-α inhibitors, nonsteroidal anti-inflammatory drugs, lipid-lowering drugs (statins > gemfibrozil), cyclophosphamide, BCG vaccine; single case reports of phenytoin, alfuzosin (α-agonist for BPH), omeprazole, ipecac (repeated exposures), interferon-α-2b, tegafur, etoposide, articaine, sulfacetamide sodium ophthalmic drops
MALIGNANCY ASSOCIATION (ADULTS)[32,33]

Table 42.3 Pathogenesis of dermatomyositis. BCG, Bacillus Calmette-Guérin; BPH, benign prostatic hyperplasia; ICAM, intercellular adhesion molecule; TNF, tumor necrosis factor.

CLINICAL SUBTYPES OF DERMATOMYOSITIS – DEMOGRAPHICS AND ASSOCIATED FINDINGS				
	Clinical subtype			
	Adult-onset classic dermatomyositis[9]	Adult-onset clinically amyopathic dermatomyositis[10]	Juvenile-onset classic dermatomyositis[11]	Juvenile-onset clinically amyopathic dermatomyositis[12]
No. of patients	20	291	120	38
Mean age (years)	51.9	50	7.7	10.5
Malignancy detected	6/20 (30%)	41/291 (14%)	0/120 (0%)	0/38 (0%)
Sex ratio (F:M)	3:1	3:1	2.2:1	3:2

Table 42.2 Clinical subtypes of dermatomyositis – demographics and associated findings.

SERUM AUTOANTIBODIES IN ADULT AND JUVENILE DERMATOMYOSITIS				
Autoantibodies	**Target antigen function**	**Clinical phenotype**	**Autoantibody frequency, %**	
			Adult DM	**Juvenile DM**
Anti-aminoacyl-tRNA synthetases (e.g. anti-Jo-1 [histidyl], anti-PL-7 [threonyl]; see Ch. 40)	Intracytoplasmic protein synthesis	Antisynthetase syndrome (myositis, mechanic's hands, Gottron's papules, arthritis, fever, Raynaud's phenomenon, high frequency of interstitial lung disease)	up to 20%	1–3
Anti-SRP	Protein translocation	Acute-onset necrotizing myopathy (severe weakness, high CK); may be refractory to treatment	5	<1
Anti-Mi-2	Helicase – transcription	Adult DM and juvenile DM (hallmark is cutaneous disease, milder muscle disease with good response to treatment)	15	<10
Anti-p155/140	See Ch. 40	Cancer-associated myositis in adult DM; severe cutaneous disease in adult DM and juvenile DM	80 (amyo); 20–30 (classic)	~25
Anti-p140	Likely NXP-2 – nuclear transcription, RNA metabolism	Juvenile DM with calcinosis	NA	~25
Anti-SAE	Post-translational modification	Adult DM; may present with clinically amyopathic DM	NA	NA
Anti-CADM-140 (MDA5)	Innate immunity	Clinically amyopathic DM; rapidly progressive interstitial lung disease	10–15	NA

Table 42.4 Serum autoantibodies in adult and juvenile dermatomyositis (DM). The autoantigen CADM-140 was subsequently found to be identical to two previously identified gene products, interferon induced with helicase C domain protein 1 (IFIH1) and melanoma differentiation-associated gene 5 (MDA5). CADM, cancer-associated dermatomyositis; CK, creatine kinase; NA, not applicable; NXP-2, nuclear matrix protein NXP2; SAE, small ubiquitin-like modifier activating enzyme; SRP, signal recognition particle. *Adapted from ref. 35.*

Fig. 42.1 Dermatomyositis – cuticular dystrophy and nail fold telangiectasias. The cuticles are "ragged" and within the proximal nail fold, dilated capillary loops alternate with vessel dropout (insert). Atrophy, telangiectasias and hypopigmentation are present on the fingers. *Courtesy, Julie V Schaffer, MD.*

or lupus erythematosus and does not include dermatomyositis in the differential diagnosis.

The features that are most characteristic, and that distinguish dermatomyositis from lupus erythematosus, are the violaceous hue of the poikiloderma and the tendency of lesions to be distributed around the eyes (the heliotrope sign) and on extensor surfaces. However, the heliotrope sign can be quite subtle, with only mild erythema of the eyelids, and it may wax and wane over time. Associated periorbital edema can range from mild to marked (Fig. 42.2). In addition, a more diffuse facial erythema, or even malar erythema, is often present (see Fig. 42.12).

The cutaneous lesions of dermatomyositis are accentuated on extensor surfaces, including the knuckles. When lesions on the knuckles develop a secondary lichenoid quality, they are termed Gottron's papules (Fig. 42.3); violaceous discoloration of the knuckles, elbows and/or knees is known as Gottron's sign (Fig. 42.4). Calcinosis cutis is more prevalent in juvenile dermatomyositis, affecting between 25% and 70% of patients[7,37]. The cutaneous lesions of dermatomyositis are often pruritic (Fig. 42.5), and this can significantly affect the patients' quality of life[38–40]. Of note, pruritus is a feature that can occasionally help distinguish dermatomyositis from LE.

Additional manifestations range from poikiloderma of the scalp to centripetal flagellate erythema (Fig. 42.6A) to erosions and ulcerations (Fig. 42.6B; Table 42.5)[41–43]. It is also important to look for dermatologic signs of other connective tissue diseases in patients with dermatomyositis, because of the frequency of overlap syndromes. The most common cutaneous findings would be signs of overlap with systemic sclerosis, especially limited disease with CREST features (*c*alcinosis, *R*aynaud's phenomenon, *e*sophageal dysmotility, *s*clerodactyly, *t*elangiectasias), annular lesions suggestive of subacute cutaneous lupus erythematosus, or nodules suggestive of rheumatoid arthritis. Cutaneous small vessel vasculitis can occur as an associated finding, especially in patients with juvenile dermatomyositis.

It is important to understand that patients may present with classic cutaneous manifestations of dermatomyositis but no muscle disease. Careful patient evaluation and longitudinal assessment will demonstrate that some of these patients have skin disease alone (amyopathic dermatomyositis) while others eventually evolve into full-blown dermatomyositis (with muscle disease) or they develop hypomyopathic dermatomyositis, i.e. no muscle weakness clinically, but myositis by

Fig. 42.2 Dermatomyositis – eyelid edema and heliotrope sign. **A** Inflammation of the upper eyelid can be more subtle in darkly pigmented skin; note involvement of the lateral nasal root and the cheeks. **B** The characteristic pink–violet color is seen with involvement of the hairline, lower forehead, upper eyelids and cheeks; the edema is striking and involves the nasal root as well as the eyelids. *B, Courtesy, Jean L Bolognia, MD.*

Fig. 42.3 Dermatomyositis – Gottron's papules. **A** The flat-topped (lichenoid) papules overlying the proximal interphalangeal (IP) and metacarpophalangeal (MCP) joints are subtle and were misdiagnosed as verrucae vulgaris in this child. **B** Obvious accentuation of skin lesions over the MCP joints, with coalescence of pink–violet lichenoid papules. **C** Papulosquamous plaques with a somewhat linear configuration proximally; clues against psoriasis are the Gottron's papules of the distal IP joints, cuticular dystrophy and nail fold telangiectasias. *A, B, Courtesy, Julie V Schaffer, MD.*

radiographic or laboratory testing[44]. The clinical characteristics of patients with classic dermatomyositis and with amyopathic dermatomyositis have recently been reviewed[10], in particular with respect to differences in malignancy risk. Although it has generally been thought that the malignancy risk is greater in the setting of classic dermatomyositis, there have been several case series that have observed associated malignancies in patients with amyopathic dermatomyositis, even in those who remain muscle disease-free for years and therefore can be considered confirmed cases of amyopathic disease. Fulminant lung disease has also been reported in patients with amyopathic dermatomyositis. Therefore, both malignancy screening and evaluation for systemic involvement are recommended, irrespective of muscle involvement.

Systemic Disease

Patients with dermatomyositis usually present with complaints of malaise and loss of energy. The dermatologic manifestations precede the onset of objective muscle disease in most patients; however, when the muscle disease begins, it is indistinguishable clinically from that seen in patients with polymyositis. The myopathy affects proximal muscle groups, especially the extensor groups (triceps and quadriceps), in a symmetric fashion. In advanced disease, all muscle groups can be affected. Patients may be unable to complete simple tasks such as combing their hair or rising to their feet from a sitting position. The affected muscle groups are often tender to palpation in more advanced disease. Muscle strength should be graded on sequential visits by

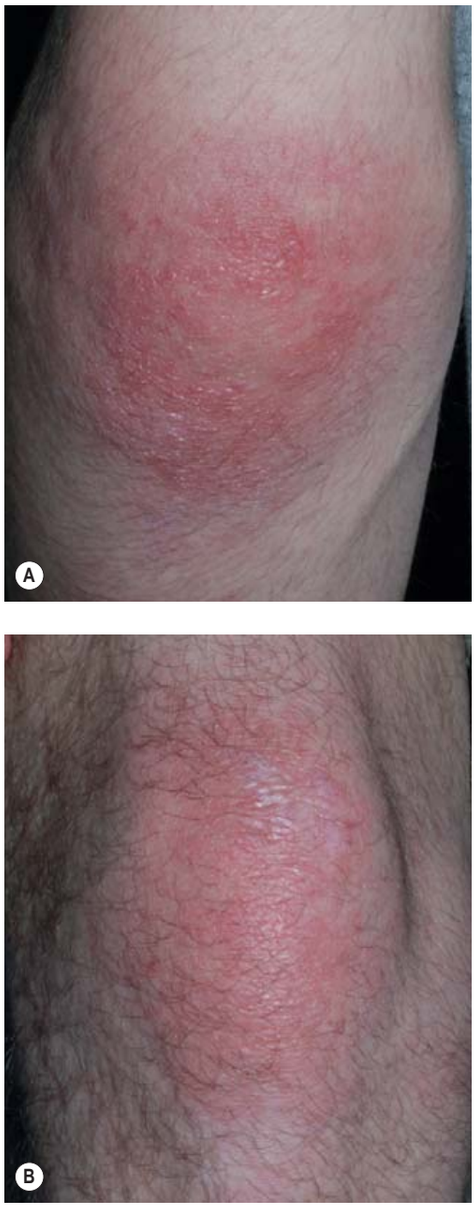


Fig. 42.4 Dermatomyositis – Gottron's sign. Thin pink papules and plaques of the elbow (**A**) and knee (**B**). Some of the papules on the elbow are flat-topped (lichenoid). *Courtesy, Julie V Schaffer, MD.*

Fig. 42.5 Dermatomyositis – involvement of the upper back. The pink–violet plaques, some with associated scale, were very pruritic, as evidenced by multiple excoriations. Linear streaks of erythema are also seen. *Courtesy, Jean L Bolognia, MD.*

muscle groups (e.g. right and left triceps 3/5, right and left quadriceps 4/5, etc.), although other more formal methods of quantification, such as the use of a hand-held pull gauge, have been described[45]. Symptoms of true dysphagia should prompt investigation for overlap with scleroderma, although patients with advanced muscle disease can have cricopharyngeal muscle dysfunction and consequently difficulty initiating swallowing. Distal esophageal involvement can present as gastroesophageal reflux disease.

Calcinosis is more common in patients with juvenile dermatomyositis than in adults and is most often associated with a delay in the institution of systemic corticosteroids or with advanced, therapy-resistant disease. In addition to calcinosis cutis, deposits may occur in the deep fascia and in intramuscular connective tissue. Lesions occur as hard, irregular nodules, which on occasion drain a chalky material via fistulae to the surface. Calcinosis cutis favors sites of trauma, such as the elbows, knees and fingers, but can occur anywhere. The lesions may be painful and can complicate return to normal function.

Pulmonary disease occurs in approximately 15–30% of patients with dermatomyositis, and generally presents as a diffuse interstitial fibrosis that is similar to that seen in patients with rheumatoid arthritis or scleroderma[46]. A recent study suggested that lung disease may be present in as many as 65% of patients[47]; however, this conclusion was based on a small series of patients (n = 17) and methodologic issues were raised[48]. Pulmonary involvement is a particular feature of the antisynthetase syndrome[36]. Patients may also develop acute respiratory distress syndrome (ARDS). Because this disease is resistant to corticosteroid therapy, it follows a course independent from that of the muscle disease and can adversely affect prognosis in much the same way as in patients with mixed connective tissue disease.

Cardiac disease is not commonly symptomatic. When it is, it usually presents as arrhythmias or as conduction defects[49]. Patients with dermatomyositis are often not thoroughly evaluated for possible cardiac disease, and prompt treatment of the muscle disease may mask the true frequency of cardiac disease. In one retrospective review, cardiac involvement was shown to be the major prognostic factor for death in patients with dermatomyositis (not associated with an underlying malignancy)[50]. Additional reported indicators of poor prognosis (other than malignancy) include older age, progressive disease, initiation of therapy after 24 months of muscle weakness, longer duration of symptoms before diagnosis, pulmonary disease, dysphagia, and extensive cutaneous involvement of the trunk[51].

For the patient with dermatomyositis, a thorough review of systems should include a discussion of arthritis, renal disease, gastrointestinal disease, pulmonary disease, cardiac disease, and other manifestations such as neuropathy and Raynaud's phenomenon. Their presence may suggest systemic involvement and/or overlap with other connective tissue diseases – in particular, systemic LE, rheumatoid arthritis and scleroderma. One dermatology-based case series observed a 19% overlap rate in adult patients with dermatomyositis[2].

Malignancy

The reported frequency of an internal malignancy in adults with dermatomyositis varies from less than 10% to over 50%. The malignancy association occurs with adult dermatomyositis, but not with the juvenile form or with polymyositis. Patients with amyopathic dermatomyositis also appear to be at increased risk for an associated malignancy. A disproportionate number of the associated malignancies are carcinomas. Genitourinary malignancies, especially ovarian cancer, and colon cancer may be overrepresented[52,53]; in some Southeast Asian

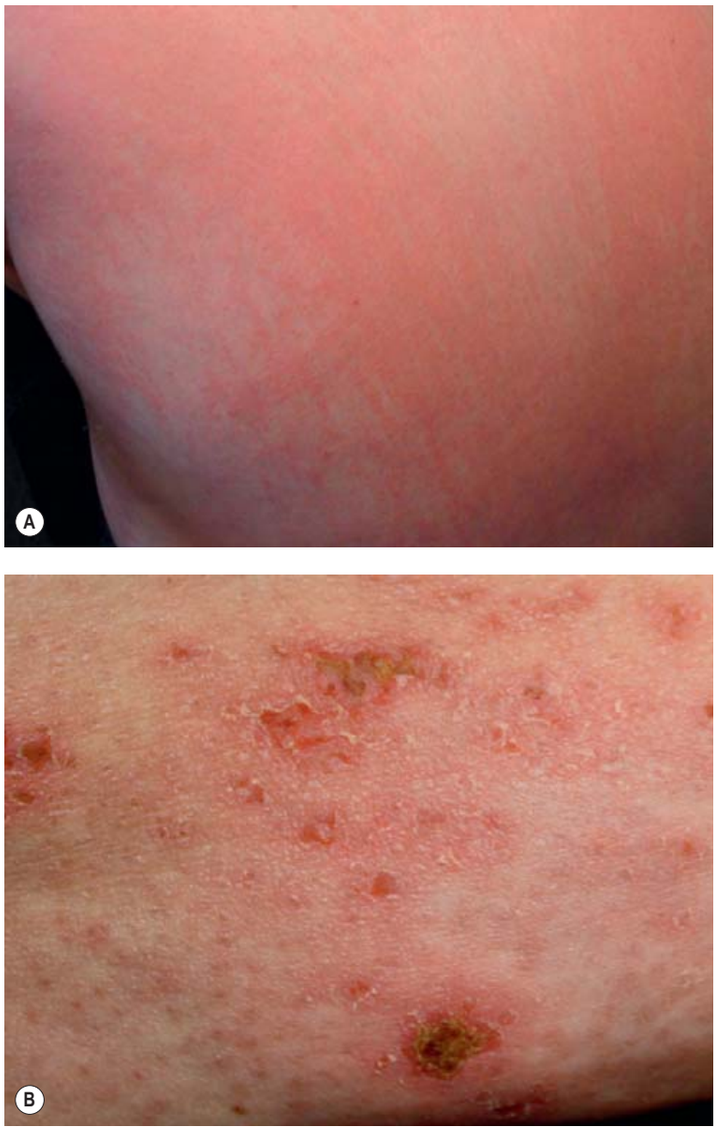


Fig. 42.6 Dermatomyositis – less common presentations. A Flagellate erythema of the posterior trunk. **B** Secondary changes with the lesions include scale, erosions and serous as well as hemorrhagic crusts.

populations, nasopharyngeal carcinoma is overrepresented[54]. Other commonly seen malignancies include breast, lung, gastric, pancreatic, lymphomas (including non-Hodgkin), and other female genital cancers[53,55]. The risk of malignancy may return to normal after 2–5 years[33,53,56]. Callen has suggested that the best approach to patient management in this setting is ongoing vigilance with frequent and thorough medical histories, repeated review of systems, complete physical examinations, and screening laboratory tests.[57] More recently, he has advocated additional investigations, including CT of the chest, abdomen and pelvis, in the malignancy assessment (Table 42.6)[56]. With regard to long-term survival, as expected, patients with cancer-associated inflammatory myopathy (including dermatomyositis) have an inferior survival curve when compared to patients with juvenile or non-cancer-associated adult myopathies[50].

CUTANEOUS MANIFESTATIONS OF DERMATOMYOSITIS

Common	Uncommon
Heliotrope sign (Fig. 42.2)	Cutaneous erosions or ulcerations (Fig. 42.6B)
Eyelid edema (Fig. 42.2)	Holster sign (poikiloderma of the lateral thighs)
Gottron's papules (Fig. 42.3)	Flagellate erythema (Fig. 42.6A)
Gottron's sign (Fig. 42.4)	Vesicobullous lesions
Photodistributed poikiloderma (includes facial erythema, shawl sign) (Fig. 42.12)	Exfoliative erythroderma
Scalp poikiloderma (see Fig. 13.3)	Panniculitis
Non-scarring alopecia	Gingival telangiectasias
Nail fold changes (includes ragged cuticles, nail fold telangiectasias*) (Fig. 42.1)	Pustular eruption of the elbows and knees
Calcinosis cutis (especially in juvenile dermatomyositis)	Lipoatrophy (especially in juvenile dermatomyositis)
	Small vessel vasculitis (especially in juvenile dermatomyositis)

*Dilated capillary loops alternating with vessel dropout.

Table 42.5 Cutaneous manifestations of dermatomyositis.

EVALUATION OF THE PATIENT WITH DERMATOMYOSITIS

- History, including potential triggers (see Table 42.3) and previous malignancies, and a review of systems
- Physical examination – skin, muscle and complete general examination (including, in adults, breast and pelvic* [women], testicular and prostate [men], and rectal [both sexes]); in Southeast-Asian patients, consider full ENT examination
- Laboratory evaluation

• ***Cutaneous –***	Skin biopsy(ies)
• ***Muscle –***	• Serum creatine kinase, serum aldolase, occasionally urine creatine†
	• Electromyography (EMG); muscle biopsy; MRI or U/S (if EMG or muscle biopsy are negative or declined; increasingly, MRI is being done in lieu of EMG and muscle biopsy, if classic cutaneous findings and consistent histology)
• ***Pulmonary –***	• Pulmonary function tests (PFTs) with CO diffusion
	• Chest X-ray and/or high-resolution chest CT
• ***Cardiac –***	• Electrocardiogram (EKG)
	• If symptomatic, echocardiogram and/or Holter monitor
• ***Esophageal –***	• If symptoms, barium swallow
• ***General –***	Complete blood count, comprehensive metabolic panel with fasting levels of glucose and lipids‡, autoantibody panel
• ***Malignancy screen (adults)***§,¶	• Urinalysis, stool occult blood testing
	• Serum prostate-specific antigen (PSA) [men]
	• Serum CA125 [women]
	• Mammogram and transvaginal pelvic U/S [women]
	• CT of chest, abdomen and pelvis
	• Colonoscopy, if age-appropriate, iron deficiency anemia, occult blood in stool, or symptoms
	• Upper endoscopy – if colonoscopy negative in the setting of iron deficiency anemia, occult blood in stool, or symptoms
• If planning chronic systemic corticosteroids	DEXA bone density scan (see Ch. 125)

*Includes Papanicolaou smear.
†Aspartate transaminase (AST), alanine transaminase (ALT), and lactic dehydrogenase (LDH) may also be elevated due to myositis.
‡Fasting levels of glucose and lipids are important in children.
§Malignancy screening should be performed at the time of diagnosis and annually for a minimum of 3 years thereafter; history and physical examination can be performed more frequently.
¶Can also consider serum protein and immunofixation electrophoreses.

Table 42.6 Evaluation of the patient with dermatomyositis. CO, carbon monoxide; CT, computerized tomography; DEXA, dual energy x-ray absorptiometry; ENT, ear, nose and throat; MRI, magnetic resonance imaging; U/S, ultrasound.

PATHOLOGY

The characteristic changes seen in skin biopsy specimens from patients with dermatomyositis can be very subtle (Fig. 42.7) and include epidermal atrophy, basement membrane degeneration, vacuolar alteration of basal keratinocytes, and dermal changes consisting of interstitial mucin deposition and a sparse lymphocytic infiltrate. In some cases, a colloidal iron stain may help to highlight the presence of mucin. The histopathologic changes may be indistinguishable from those seen in specimens from patients with poikilodermatous lesions of LE. Gottron's papules show a lichenoid infiltrate but have acanthosis rather than epidermal atrophy[58].

Muscle biopsy specimens also show characteristic changes. The combination of type II muscle fiber atrophy, necrosis, regeneration, and hypertrophy with centralized sarcolemmal nuclei, plus lymphocytes in both a perifascicular and a perivascular distribution, is classic[59]. It is best for the clinician to request that the surgeon sample triceps muscle rather than the usually biopsied deltoid muscle because the latter is often spared until late in the disease. Another option, especially for patients with mild involvement, is to choose the biopsy site based upon MRI findings (see below).

DIFFERENTIAL DIAGNOSIS AND EVALUATION

Although a detailed differential diagnosis of the patient who presents with proximal muscle weakness in the absence of skin lesions (i.e. the differential diagnosis of polymyositis) is beyond the scope of this dermatologic review, it is the subject of a recent textbook[60]. Two validated instruments, the Dermatomyositis Skin Severity Index (DSSI) and the updated Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI), can be used to classify the severity of the cutaneous disease of dermatomyositis. These indices should be helpful in assessing therapeutic responses in future clinical trials[61,62].

The patient with a characteristic cutaneous eruption should have a skin biopsy performed to confirm the clinical impression of dermatomyositis (Fig. 42.8). Once the presumed diagnosis is confirmed histopathologically, then a search for muscle and/or associated systemic disease must begin, because it is their presence or absence that dictates therapeutic decisions (see Table 42.6). The evaluation for myositis can include: strength testing of proximal extensor muscles and other muscles, serum levels of muscle enzymes, an electromyogram, and/or triceps muscle biopsy. However, increasingly, an MRI (Figs 42.9 & 42.10) or ultrasound (Fig. 42.11) of proximal muscles is obtained prior to, or in lieu of, a muscle biopsy; the latter applies especially to patients with classic cutaneous lesions (both clinically and histologically).

Patients with normal muscle enzyme levels should be followed at regular intervals because these patients can have occult muscle disease, evolve into classic dermatomyositis, or remain as amyopathic dermatomyositis[44]. Additional baseline investigations for pulmonary disease (often predicted by anti-Jo-1 antibodies; see Table 42.6), for cardiac disease, for symptomatic esophageal disease (barium swallow or manometry) and for features of overlap connective tissue disease should be performed at this stage, prior to the institution of systemic therapy unless immediate therapy is warranted to halt rapidly progressive disease. Adult patients should have screening for occult malignancy annually for at least 2–3 years, or more frequently based upon symptoms. A detailed history, review of symptoms, and complete physical examination should be performed at regular intervals of 4–6 months. Adult patients with amyopathic dermatomyositis should have similar evaluations for malignancy and associated systemic disease.

The classic muscle enzymes that should be assessed at baseline and at regular intervals throughout the treatment period are creatine kinase (CK) and aldolase. Aspartate and alanine transaminases and lactate dehydrogenase are often elevated as well, since they also are released from damaged muscle tissue. It has been estimated that 95% of patients with dermatomyositis have an elevated CK at some point during their

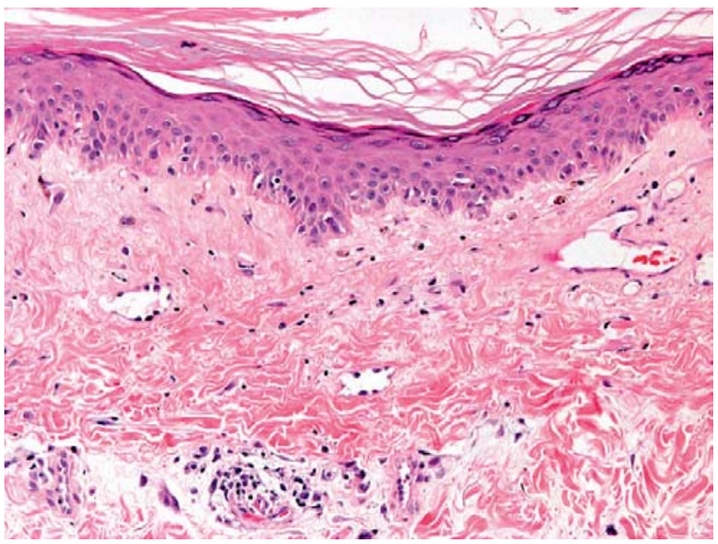


Fig. 42.7 Dermatomyositis – histopathologic features. The vacuolar changes within the basal layer can be subtle. In the dermis, dilated blood vessels and a sparse lymphocytic infiltrate are seen (poikilodermatous changes). *Courtesy, Lorenzo Cerroni, MD.*

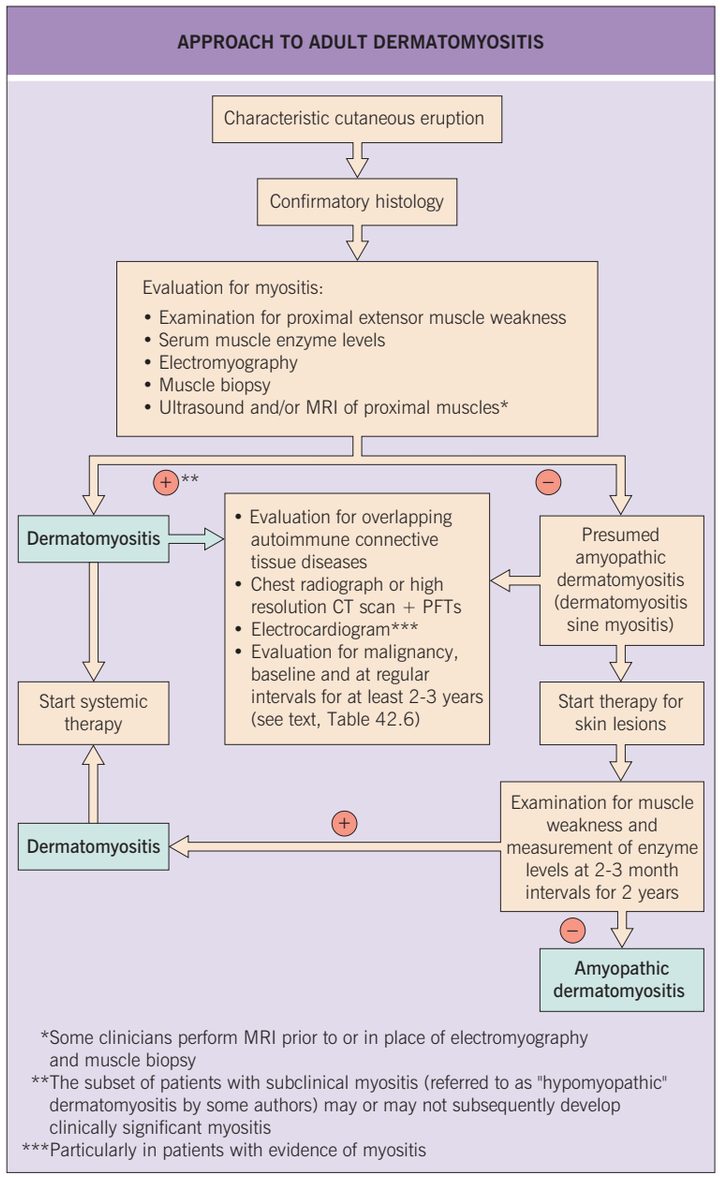


Fig. 42.8 Approach to adult dermatomyositis. The approach for children is similar but without the malignancy evaluation. Some authors classify patients with no evidence of myositis ≥6 months after the onset of skin disease as having amyopathic dermatomyositis, but such individuals may go on to develop muscle disease. PFTs, pulmonary function tests.

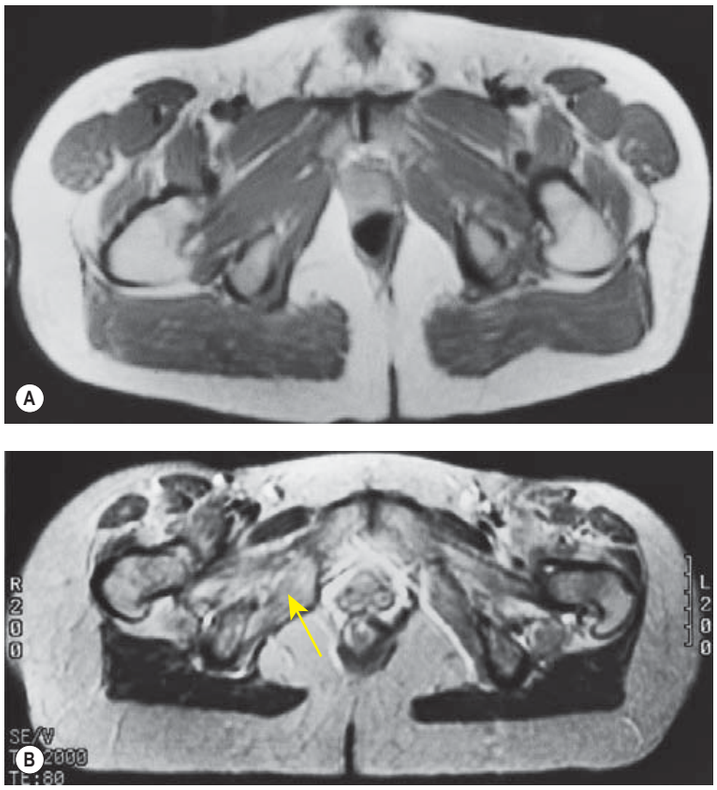


Fig. 42.9 T2-weighted MR images of the pelvic region. A In a normal control patient. **B** In a patient with dermatomyositis. This shows increased signal intensity (white color; arrow) diffusely in multiple muscle groups. The increased signal correlates with inflammation.

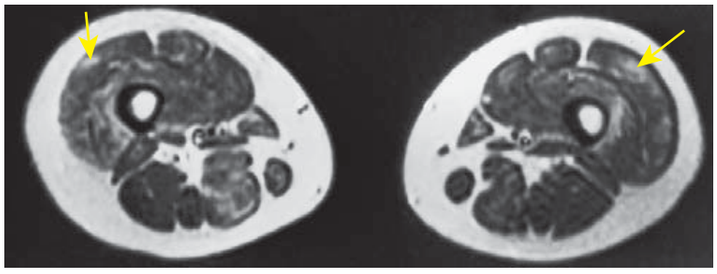


Fig. 42.10 T2-weighted MR images of the proximal thigh in a patient with dermatomyositis. Note the increased signal density, primarily in the extensor muscles (white color, arrows). The increased signal correlates with inflammation.

illness[8]. Urine creatine is elevated in some patients who have a normal serum CK, but this test is not routinely performed. Myoglobin, another protein released by damaged muscle, can be detected in the serum even in patients with mild muscle disease. Its detection in urine is a cause for concern, and, rarely, severe myoglobinuria can result in acute renal failure.

Electromyography (EMG) is a sensitive but nonspecific test in patients with dermatomyositis. Over 90% of patients have abnormal EMG results. The combination of an abnormal electromyogram with classic cutaneous lesions (clinically and histologically) makes the diagnosis of dermatomyositis very likely. EMG findings are less helpful in patients with polymyositis because there is overlap with other myopathies in the differential diagnosis[63].

In the absence of classic cutaneous lesions, the muscle biopsy is a very important test for confirming the diagnosis and excluding other inflammatory myopathies. Surgeons will usually biopsy the deltoid muscle for convenience, but this muscle is relatively spared until late in the disease; therefore, the surgeon should be directed to perform a triceps muscle biopsy.

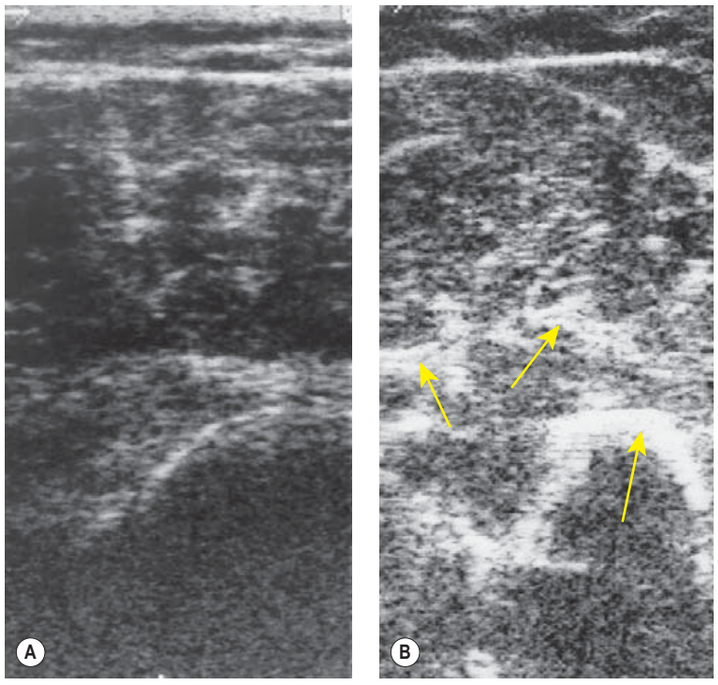


Fig. 42.11 Ultrasound images of the triceps muscle. A Cross-sectional ultrasound image from normal (control) triceps muscle. **B** Ultrasound image from affected triceps muscle in a patient with dermatomyositis. An increase in interstitial echoes is seen (arrows).

MRI (see Figs 42.9 & 42.10) and ultrasound (see Fig. 42.11) of muscles are sensitive tests that can add greatly to patient evaluation. Both can be used to determine the appropriate site for a muscle biopsy[44]. Ultrasound is less expensive and easier to perform sequentially. MRI may be the most sensitive test for muscle disease, but it is more expensive[44,64]. Recent studies suggest that MRI might be useful in evaluating children for soft tissue changes that might precede calcinosis cutis[64].

The differential diagnosis of the dermatologic findings in dermatomyositis is summarized in Table 42.7.

TREATMENT

A therapeutic ladder for the treatment of patients with dermatomyositis is summarized in Table 42.8. As with many rare dermatologic diseases, double-blind, placebo-controlled trials are lacking. However, a dermatology-based case series supported the belief that a number of patients (75–85%) can become muscle disease-free, off treatment, after a period of 24–48 months, utilizing a slow corticosteroid taper[2]. Long-term follow-up of pediatric patients also confirmed this conclusion[65,66]. There is a clear discordance between response of the muscle disease to therapy and response of the skin disease[2]. Available therapy for the skin disease is clearly inadequate, with many patients exprienc-ing persistent cutaneous disease and pruritus, especially of the scalp, which can become a major complaint once the muscle disease is under control. Aggressive topical therapy and systemic therapy (e.g. antimalarials or weekly methotrexate) added specifically for the skin disease often do not provide adequate relief. It is clear however, that, except in adult patients with an advanced malignancy, the prognosis for corticosteroid-treated dermatomyositis in children and in adults is excellent, especially when compared with a mortality of up to 50% in the pre-corticosteroid era[66].

The treatment of dermatomyositis must take into account the discordance between the response of the muscle disease and that of the dermatologic disease to systemic therapy. The search for muscle involvement must be thorough, even in the patient with normal serum muscle enzymes. Two positive objective tests documenting muscle disease (e.g. EMG and muscle biopsy, or one of these plus MRI or muscle ultrasound) should trigger the initiation of systemic corticosteroid therapy in doses aimed at control of the muscle disease (i.e. generally prednisone 1 mg/kg/day). Patients with dermatologic

DIFFERENTIAL DIAGNOSIS OF DERMATOMYOSITIS
SYSTEMIC LUPUS ERYTHEMATOSUS
Physician might notice the nail fold telangiectasias and photodistributed poikiloderma but miss the muscle weakness, heliotrope, extensor distribution, pruritus, and the violaceous hue (true lupus erythematosus might be present in the setting of an overlap syndrome) (Fig. 42.12)
PSORIASIS
Involvement of elbows and knees with papulosquamous lesions can lead to misdiagnosis
AIRBORNE OR ALLERGIC CONTACT DERMATITIS
Eyelid edema can be marked in dermatomyositis; look for additional sites of dermatitis
PHOTODRUG ERUPTION
Photodistribution
CUTANEOUS T-CELL LYMPHOMA
The poikiloderma often begins in intertriginous zones rather than on the scalp, face and extensor surfaces
ATOPIC DERMATITIS
Usually in children, where the physician focuses on the pruritus and secondary lichenification
SCLERODERMA
The nail fold telangiectasias are similar in appearance, but the dyspigmentation is quite different; edema of the hands is an early sign (true scleroderma may be present in the setting of an overlap syndrome)
TRICHINOSIS
Patients have painful muscles and periorbital edema, but not other features
PHOTODISTRIBUTED FORM OF MULTICENTRIC RETICULOHISTIOCYTOSIS
Firm papules have distinct histologic features

Table 42.7 Differential diagnosis of dermatomyositis.

Fig. 42.12 Dermatomyositis. Misdiagnoses include psoriasis, contact dermatitis, and if there is significant facial involvement as in this patient, acute cutaneous lupus erythematosus.

THERAPEUTIC LADDER FOR DERMATOMYOSITIS	
SYSTEMIC THERAPY	
Oral prednisone:	1 mg/kg/day tapered to 50% over 6 months and to zero over 2–3 years (1) Option to use pulse, split-dose, or alternate-day (2)
Methotrexate:	5–20 mg weekly (2)
Azathioprine:	2–3 mg/kg/day (1)
Others:	High-dose IVIg (2 g/kg/month) (1)
	Pulse cyclophosphamide (0.5–1.0 g/m^2 monthly) (2)
	Chlorambucil (4 mg/day) (2)
	Cyclosporine (3–5 mg/kg/day) (2)
	Tacrolimus (0.12 mg/kg/day) (3)
	Mycophenolate mofetil (1 g twice daily) (2)
	Sirolimus (5 mg/day × 2 weeks, 2 mg/day × 2 weeks, then 1 mg/day) (3)
	Infliximab (5–10 mg/kg every 2 weeks initially) (3)
	Etanercept (3)†
	Rituximab (375 mg/m^2/infusion for 4 weekly infusions) (2)
	Fludarabine (3)
	Hematopoietic stem cell transplantation (3)
	Plasmapheresis (3)†
CUTANEOUS LESIONS	
Sunscreens (high sun protection factor including protection against UVA) (3) Topical corticosteroids (3) Topical tacrolimus (3) Hydroxychloroquine (200 mg twice daily; increased frequency of drug eruptions in patients with dermatomyositis) (2) Hydroxychloroquine (200 mg twice daily) plus quinacrine (100 mg/day) (3) Low-dose weekly methotrexate (5–15 mg weekly) (2) Mycophenolate mofetil (3) High-dose IVIg (2 g/kg/month) (1) Retinoids (3) Dapsone (3) Thalidomide (3) Leflunomide (3) Antiestrogens (e.g. tamoxifen, anastrazole) (3) TNF-α inhibitors (e.g. infliximab, etanercept) (3)* Rituximab (3) Tacrolimus (3)	
*Reported cause of drug-induced dermatomyositis. †Double-blind trial showed no benefit.	

Table 42.8 Therapeutic ladder for dermatomyositis. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

manifestations alone can be treated as described below, with repeated clinical muscle examination and enzyme screening (i.e. generally CK and aldolase) at 2–3-month intervals. If muscle disease is confirmed, then systemic corticosteroid therapy is initiated.

If CK and aldolase serum levels are minimally elevated and corticosteroid therapy is initiated early, the disease generally comes under control rapidly over 2–4 weeks and corticosteroids can be used as monotherapy with doses tapered to half the starting dose by 6 months. If the disease is advanced and enzyme levels are high (e.g. CK > 1000 U/1), the disease can be much more difficult to control, requiring pulse prednisone, split-dose prednisone in doses above 1 mg/kg/day, and/or initiation of a steroid-sparing agent such as low-dose weekly methotrexate at the onset. Again, an attempt is made to taper the prednisone to 0.5 mg/kg/day in a single morning dose by 6–8 months.

Attention to general health maintenance principles and osteoporosis prevention is a key element of patient management (see Ch. 125). This can be accomplished by joint longitudinal care with an internist or pediatrician. Adults also need frequent (e.g. every 4–6 months for at least 2–3 years) complete physical examinations for malignancy.

Children with juvenile dermatomyositis should be followed by a pediatrician comfortable with monitoring their developmental milestones while on immunosuppressive therapy (e.g. at least every 6 months). In addition, lipodystrophy and metabolic abnormalities, including hypertriglyceridemia and insulin resistance, have become increasingly recognized as potential complications of juvenile dermatomyositis[67,68].

There is support for steroid-sparing therapies (especially in the setting of severe or recalcitrant disease), including IVIg[69], methotrexate[70], chlorambucil[71], pulse cyclophosphamide[72,73], cyclosporine (also for lung disease)[74,75], fludarabine[76], mycophenolate mofetil[77,78], azathioprine[79], tacrolimus[80], siroliumus[81], infliximab[82], etanercept[83], rituximab[84] and hematopoietic stem cell transplantation[85]. A placebo-controlled study showed no benefit from plasmapheresis or leukapheresis in dermatomyositis[86]. In children with severe or refractory disease, IVIg is often administered[86a]. Adjunctive physical therapy is also very important in improving muscle strength and endurance[87]. Benefits of exercise and rehabilitation have been demonstrated, even in the course of active disease and without inducing flares of the myositis[88].

Dermatologic disease can be particularly challenging therapeutically, and not all patients clear their cutaneous manifestations when their muscle disease remits on systemic corticosteroids. Patients with dermatologic disease without active muscle disease are generally not treated with systemic corticosteroids as a mainstay of their therapy, and they often present a unique therapeutic challenge. As a result, the treatment of amyopathic dermatomyositis often differs significantly from the treatment of classic dermatomyositis in that systemic corticosteroids are not traditionally utilized.

For cutaneous disease, anecdotal reports and small case series support the use of topical corticosteroids (which are especially useful when there is lichenification due to chronic pruritus as a component of the illness), topical tacrolimus[89], antimalarial therapy[90,91] (either as monotherapy or in combination, which is less dramatic in its effect than when used for LE lesions), low-dose weekly methotrexate, mycophenolate mofetil[92], IVIg[93], dapsone[94] and thalidomide[95], as well as additional agents listed in Table 42.8. Calcinosis cutis may respond to diltiazem and/or surgical excision; other therapies include low-dose warfarin, bisphosphonates, probenecid, aluminum hydroxide, and electric shock wave lithotripsy (ESWL). Early and aggressive therapy of juvenile dermatomyositis does seem to reduce the risk of calcinosis cutis, which can be extremely challenging to treat. The rare panniculitis associated with dermatomyositis may respond to antimalarial therapy[96].

REFERENCES

1. Dalakas MC, Hohlfeld R. Polymyositis and dermatomyositis. Lancet. 2003;362:971–82.
2. Dawkins MA, Jorizzo JL, Walker FO, et al. Dermatomyositis: a dermatology-based case series. J Am Acad Dermatol. 1998;38:397–404.
3. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med. 1975;292:344–7.
4. Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). N Engl J Med. 1975;292:403–7.
5. Sontheimer RD. Cutaneous features of classical dermatomyositis and amyopathic dermatomyositis. Curr Opin Rheumatol. 1999;11:475–82.
6. Sontheimer RD. Would a new name hasten the acceptance of amyopathic dermatomyositis (dermatomyositis sine myositis) as a distinctive subset within the idiopathic inflammatory dermatomyopathies spectrum of clinical illness? J Am Acad Dermatol. 2002;46:626–36.
7. Dalakas MC. Polymyositis, dermatomyositis and inclusion-body myositis. N Engl J Med. 1991;325:1487–98.
8. Jorizzo JL. Dermatomyositis: practical aspects. Arch Dermatol. 2002;138:114–16.
9. Bendewald MJ, Wetter DA, Li X, Davis MD. Incidence of dermatomyositis and clinically amyopathic dermatomyositis: a population-based study in Olmsted County, Minnesota. Arch Dermatol. 2010;146:26–30.
10. Gerami P, Schope JM, McDonald L, et al. A systematic review of adult-onset clinically amyopathic dermatomyositis (dermatomyositis sine myositis): a missing link within the spectrum of the idiopathic inflammatory myopathies. J Am Acad Dermatol. 2006;54:597–613.
11. McCann LJ, Juggins AD, Maillard SM, et al. The Juvenile Dermatomyositis National Registry and Repository (UK and Ireland) – clinical characteristics of children within the first 5 yr. Rheumatology (Oxford). 2006;45:1255–60.
12. Gerami P, Walling HW, Lewis J, et al. A systematic review of juvenile-onset clinically amyopathic dermatomyositis. Br J Dermatol. 2007;157:637–44.
13. Goldstein R, Duvic M, Targoff IN, et al. HLA-D region genes associated with autoantibody responses to histidyl-transfer RNA synthetase (Jo-1) and other translation-related factors in myositis. Arthritis Rheum. 1990;33:1240–8.
14. Werth VP, Callen JP, Ang G, Sullivan KE. Associations of tumor necrosis factor alpha and HLA polymorphisms with adult dermatomyositis: implications for a unique pathogenesis. J Invest Dermatol. 2002;119:617–20.
15. Tomono N, Mori M, Nakajima S, et al. HLA-DRB1*15021 is the predominant allele in Japanese patients with juvenile dermatomyositis. J Rheumatol. 2004;31:1847–50.
16. Miller FW, Love LA, Barbieri SA, et al. Lymphocyte activation markers in idiopathic myositis: changes with disease activity and differences among clinical and autoantibody subgroups. Clin Exp Immunol. 1990;81:373–9.
17. Pablos JL, Santiago B, Galindo M, et al. Keratinocyte apoptosis and p53 expression in cutaneous lupus and dermatomyositis. J Pathol. 1999;188:63–8.
18. O'Gorman MR, Bianchi L, Zaas D, et al. Decreased levels of CD54 (ICAM-1)-positive lymphocytes in the peripheral blood in untreated patients with active juvenile dermatomyositis. Clin Diagn Lab Immunol. 2000;7:693–7.
19. Sugiura T, Kawaguchi Y, Harigai M, et al. Increased CD40 expression on muscle cells of polymyositis and dermatomyositis: role of CD40-CD40 ligand interaction in IL-6, IL-8, IL-15, and monocyte chemoattractant protein-1 production. J Immunol. 2000;164: 6593–600.
20. Civatte M, Schleinitz N, Krammer P, et al. Class I MHC detection as a diagnostic tool in noninformative muscle biopsies of patients suffering from dermatomyositis (DM). Neuropathol Appl Neurobiol. 2003;29:546–52.
21. Li CK, Varsani H, Holton JL, et al. MHC Class I overexpression on muscles in early juvenile dermatomyositis. J Rheumatol. 2004;31:605–9.
22. Studynkova JT, Kuchen S, Jeisy E, et al. The expression of cyclooxygenase-1, cyclooxygenase-2 and 5-lipoxygenase in inflammatory muscle tissue of patients with polymyositis and dermatomyositis. Clin Exp Rheumatol. 2004;22:395–402.
23. Targoff IN. Autoantibodies. In: Wortman RL (ed.). Clinical Disorders of Skeletal Muscle. Philadelphia: Lippincott, Williams & Wilkins, 2000:268–9.
24. Pachman LM, Litt DL, Rowley AH, et al. Lack of detection of enteroviral RNA or bacterial DNA in magnetic resonance imaging-directed muscle biopsies from twenty children with active untreated juvenile dermatomyositis. Arthritis Rheum. 1995;38:1513–18.
25. Dalakas MC, Pezeshkpour GH, Gravell M, Sever JL. Polymyositis associated with AIDS retrovirus. JAMA. 1986;256:2381–3.
26. Dourmishev AL, Dourmishev LA. Dermatomyositis and drugs. Adv Exp Med Biol. 1999;455:187–91.
27. Flendrie M, Vissers WH, Creemers MC, et al. Dermatological conditions during TNF-alpha-blocking therapy in patients with rheumatoid arthritis: a prospective study. Arthritis Res Ther. 2005;7: R666–76.
28. Vasconcelos OM, Campbell WW. Dermatomyositis-like syndrome and HMG-CoA reductase inhibitor (statin) intake. Muscle Nerve. 2004;30:803–7.
29. Vela-Casasempere P, Borras-Blasco J, Navarro-Ruiz A. Alfuzosin-associated dermatomyositis. Br J Rheumatol. 1998;37:1135–6.
30. Dimachkie MM, Vriesendorp FJ, Heck KA. Phenytoin-induced dermatomyositis: case report and literature review. J Child Neurol. 1998;13:577–80.
31. Seidler AM, Gottlieb AB. Dermatomyositis induced by drug therapy: a review of case reports. J Am Acad Dermatol. 2008;59;5:872–80.
32. Sigurgeirsson B, Lindelof B, Edhag O, Allander E. Risk of cancer in patients with dermatomyositis or polymyositis. A population-based study. N Engl J Med. 1992;326:363–7.
33. Chow WH, Gridley G, Mellemkjaer L, et al. Cancer risk following polymyositis and dermatomyositis: a nationwide cohort study in Denmark. Cancer Causes Control. 1995;6:9–13.
34. Sontheimer RD, McCauliffe DP, Zappi E, Targoff I. Antinuclear antibodies: clinical correlations and biologic significance. Adv Dermatol. 1992;7:3–52.
35. Gunawardena H, Betteridge ZE, McHugh NJ. Myositis-specific autoantibodies: their clinical and pathogenic significance in disease expression. Rheumatology (Oxford). 2009;48:607–12.
36. Oddis CV, Medsger TA Jr, Cooperstein LA. A subluxing arthropathy associated with the anti-Jo-1 antibody in polymyositis/dermatomyositis. Arthritis Rheum. 1990;33:1640–5.
37. Fisler RE, Liang MG, Fuhlbrigge RC, et al. Aggressive management of juvenile dermatomyositis results in improved outcome and decreased incidence of calcinosis. J Am Acad Dermatol. 2002;47:505–11.
38. Shirani Z, Kucenic MJ, Carroll CL, et al. Pruritus in adult dermatomyositis. Clin Exp Dermatol. 2004;29:273–6.
39. Hundley JL, Carroll CL, Lang W, et al. Cutaneous symptoms of dermatomyositis significantly impact patients' quality of life. J Am Acad Dermatol. 2006;54:217–20.
40. Hundley JL, Carroll CL, Lang W, et al. Cutaneous symptoms of dermatomyositis significantly impact patients' quality of life. J Am Acad Dermatol. 2006;54:217–20.
41. Kasteler JS, Callen JP. Scalp involvement in dermatomyositis. Often overlooked or misdiagnosed. JAMA. 1994;272:1939–41.
42. Chao YY, Yang LJ. Dermatomyositis presenting as panniculitis. Int J Dermatol. 2000;39:141–4.
43. Quecedo E, Febrer I, Serrano G, et al. Partial lipodystrophy associated with juvenile dermatomyositis: report of two cases. Pediatr Dermatol. 1996;13:477–82.
44. Stonecipher MR, Jorizzo JL, Monu J, et al. Dermatomyositis with normal muscle enzyme concentrations. A single-blind study of the diagnostic value of magnetic resonance imaging and ultrasound. Arch Dermatol. 1994;130:1294–9.
45. Stoll T, Bruhlmann P, Stucki G, et al. Muscle strength assessment in polymyositis and dermatomyositis: evaluation of the reliability and clinical use of a new, quantitative, easily applicable method. J Rheumatol. 1995;22:473–7.
46. Tazelaar HD, Viggiano RW, Pickersgill J, Colby TV. Interstitial lung disease in polymyositis and dermatomyositis. Clinical features and prognosis as correlated with histologic findings. Am Rev Respir Dis. 1990;141:727–33.
47. Fathi M, Dastmalchi M, Rasmussen E, et al. Interstitial lung disease, a common manifestation of newly diagnosed polymyositis and dermatomyositis. Ann Rheum Dis. 2004;63:297–301.
48. Rozman B, Bozic B, Kveder T. Interstitial lung disease, a common manifestation of newly diagnosed polymyositis and dermatomyositis. Ann Rheum Dis. 2004;63:1005–6.
49. Askari AD, Huettner TL. Cardiac abnormalities in polymyositis/dermatomyositis. Semin Arthritis Rheum. 1982;12:208–19.
50. Danko K, Ponyi A, Constantin T, et al. Long-term survival of patients with idiopathic inflammatory myopathies

according to clinical features: a longitudinal study of 162 cases. Medicine (Baltimore). 2004;83:35–42.
51. Iorizzo LJ, Jorizzo JL. The treatment and prognosis of dermatomyositis: an updated review. J Am Acad Dermatol. 2008;59:99–112.
52. Marie I, Hatron PY, Levesque H, et al. Influence of age on characteristics of polymyositis and dermatomyositis in adults. Medicine (Baltimore). 1999;78:139–47.
53. Hill CL, Zhang Y, Sigurgeirsson B, et al. Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. Lancet. 2001;357:96–100.
54. Huang YL, Chrn YJ, Lin MW, et al. Malignancies associated with dermatomyositis and polymyositis in Taiwan: a nationwide population-based study. Br J Dermatol. 2009;161:854–60.
55. Barnes BE, Mawr B. Dermatomyositis and malignancy. A review of the literature. Ann Intern Med. 1976;84:68–76.
56. Callen JP. Collagen vascular diseases. J Am Acad Dermatol. 2004;51:427–39.
57. Callen JP. Myositis and malignancy. Curr Opin Rheumatol. 1994;6:590–4.
58. Hanno R, Callen JP. Histopathology of Gottron's papules. J Cutan Pathol. 1985;12:389–94.
59. Schwarz HA, Slavin G, Ward P, Ansell BM. Muscle biopsy in polymyositis and dermatomyositis: a clinicopathological study. Ann Rheum Dis. 1980;39:500–7.
60. Wortman RL. Diseases of skeletal muscle. In: Wortman RL (ed.). Clinical Disorders of Skeletal Muscle. Philadelphia: Lippincott, Williams & Wilkins, 2000.
61. Carroll CL, Lang W, Snively B, et al. Development and validation of the Dermatomyositis Skin and Severity Index. Br J Dermatol. 2008;158:345–50.
62. Yassaee M, Fiorentino D, Okawa J, et al. Modification of the cutaneous Dermatomyositis Disease Area and Severity Index, an outcome instrument. Br J Dermatol. 2010;162:669–73.
63. Bromberg MB, Albers JW. Electromyography in idiopathic myositis. Mt Sinai J Med. 1988;55:459–64.
64. Kimball AB, Summers RM, Turner M, et al. Magnetic resonance imaging detection of occult skin and subcutaneous abnormalities in juvenile dermatomyositis. Implications for diagnosis and therapy. Arthritis Rheum. 2000;43:1866–73.
65. Collison CH, Sinal SH, Jorizzo JL, et al. Juvenile dermatomyositis and polymyositis: a follow-up study of long-term sequelae. South Med J. 1998;91:17–22.
66. Fisler RE, Liang MG, Fuhlbrigge RC, et al. Aggressive management of juvenile dermatomyositis results in improved outcome and decreased incidence of calcinosis. J Am Acad Dermatol. 2002;47:505–11.
67. Huemer C, Kitson H, Malleson PN, et al. Lipodystrophy in patients with juvenile dermatomyositis – evaluation of clinical and metabolic abnormalities. J Rheumatol. 2001;28:610–15.
68. Bingham A, Mamyrova G, Rother KI, et al. Predictors of acquired lipodystrophy in juvenile-onset dermatomyositis and a gradient of severity. Medicine (Baltimore). 2008;87:70–86.
69. Dalakas MC. Controlled studies with high-dose intravenous immunoglobulin in the treatment of dermatomyositis, inclusion body myositis, and polymyositis. Neurology. 1998;51(6 suppl. 5): S37–45.
70. Al-Mayouf S, Al-Mazyed A, Bahabri S. Efficacy of early treatment of severe juvenile dermatomyositis with intravenous methylprednisolone and methotrexate. Clin Rheumatol. 2000;19:138–41.
71. Sinoway PA, Callen JP. Chlorambucil. An effective corticosteroid-sparing agent for patients with recalcitrant dermatomyositis. Arthritis Rheum. 1993;36:319–24.
72. Riley P, Maillard SM, Wedderburn LR, et al. Intravenous cyclophosphamide pulse therapy in juvenile dermatomyositis. A review of efficacy and safety. Rheumatology (Oxford). 2004;43:491–6.
73. al-Janadi M, Smith CD, Karsh J. Cyclophosphamide treatment of interstitial pulmonary fibrosis in polymyositis/dermatomyositis. J Rheumatol. 1989;16:1592–6.
74. Nawata Y, Kurasawa K, Takabayashi K, et al. Corticosteroid resistant interstitial pneumonitis in dermatomyositis/polymyositis: prediction and treatment with cyclosporine. J Rheumatol. 1999;26:1527–33.
75. Kobayashi I, Yamada M, Takahashi Y, et al. Interstitial lung disease associated with juvenile dermatomyositis: clinical features and efficacy of cyclosporin A. Rheumatology (Oxford). 2003;42:371–4.
76. Adams EM, Pucino F, Yarboro C, et al. A pilot study: use of fludarabine for refractory dermatomyositis and polymyositis, and examination of endpoint measures. J Rheumatol. 1999;26:352–60.
77. Gelber AC, Nousari HC, Wigley FM. Mycophenolate mofetil in the treatment of severe skin manifestations of dermatomyositis: a series of 4 cases. J Rheumatol. 2000;27:1542–5.
78. Majithia V, Harisdangkul V. Mycophenolate mofetil (CellCept): an alternative therapy for autoimmune inflammatory myopathy. Rheumatology (Oxford). 2005;44:386–9.
79. Bunch TW. Prednisone and azathioprine for polymyositis: long-term followup. Arthritis Rheum. 1981;24:45–8.
80. Yamada A, Ohshima Y, Omata N, et al. Steroid-sparing effect of tacrolimus in a patient with juvenile dermatomyositis presenting poor bioavailability of cyclosporine A. Eur J Pediatr. 2004;163:561–2.
81. Nadiminti U, Arbiser JL. Rapamycin (sirolimus) as a steroid-sparing agent in dermatomyositis. J Am Acad Dermatol. 2005;52(2 suppl. 1):17–19.
82. Hengstman GJ, van den Hoogen FH, Barrera P, et al. Successful treatment of dermatomyositis and polymyositis with anti-tumor-necrosis-factor-alpha: preliminary observations. Eur Neurol. 2003;50:10–15.
83. Norman R, Greenberg RG, Jackson JM. Case reports of etanercept in inflammatory dermatoses. J Am Acad Dermatol. 2006;54:S139–42.
84. Levine TD. Rituximab in the treatment of dermatomyositis: an open-label pilot study. Arthritis Rheum. 2005;52:601–7.
85. Saccardi R, Di Gioia M, Bosi A. Haematopoietic stem cell transplantation for autoimmune disorders. Curr Opin Hematol. 2008;15:594–600.
86. Miller FW, Leitman SF, Cronin ME, et al. Controlled trial of plasma exchange and leukapheresis in polymyositis and dermatomyositis. N Engl J Med. 1992;326: 1380–4.
86a. Stringer E, Bohnsack J, Bowyer SL, et al. Treatment approaches to juvenile dermatomyositis (JDM) across North America: The Childhood Arthritis and Rheumatology Research Alliance (CARRA) JDM Treatment Survey. J Rheumatol. 2010;37:1953–61.
87. Alexanderson H, Stenstrom CH, Lundberg I. Safety of a home exercise programme in patients with polymyositis and dermatomyositis: a pilot study. Rheumatology (Oxford). 1999;38:608–11.
88. De Salles Painelli V, Gualano B, Artioli GG, et al. The possible role of physical exercise on the treatment of idiopathic inflammatory myopathies. Autoimmun Rev. 2009;8:355–9.
89. Hollar CB, Jorizzo JL. Topical tacrolimus 0.1% ointment for refractory skin disease in dermatomyositis: a pilot study. J Dermatolog Treat. 2004;15:35–9.
90. Ang GC, Werth VP. Combination antimalarials in the treatment of cutaneous dermatomyositis: a retrospective study. Arch Dermatol. 2005;141:855–9.
91. Woo TY, Callen JP, Voorhees JJ, et al. Cutaneous lesions of dermatomyositis are improved by hydroxychloroquine. J Am Acad Dermatol. 1984;10:592–600.
92. Gelber AC, Nousari HC, Wigley FM. Mycophenolate mofetil in the treatment of severe skin manifestations of dermatomyositis: a series of 4 cases. J Rheumatol. 2000;27:1542–5.
93. Dalakas MC, Illa I, Dambrosia JM, et al. A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. N Engl J Med. 1993;329:1993–2000.
94. Cohen JB. Cutaneous involvement of dermatomyositis can respond to dapsone therapy. Int J Dermatol. 2002;41:182–4.
95. Stirling DI. Thalidomide and its impact in dermatology. Semin Cutan Med Surg. 1998;17:231–42.
96. Oddis CV, Medsger TA. Polymyositis-dermatomyositis. In: Bellamy N (ed). Prognosis in Rheumatic Disease. Lancaster: Kluwer Academic, 1991:233–49.

This page intentionally left blank

Systemic Sclerosis (Scleroderma) and Related Disorders

43

M Kari Connolly

Chapter Contents

Systemic sclerosis *643*
Eosinophilic fasciitis *651*
Nephrogenic systemic fibrosis *652*
Stiff skin syndrome *654*
Sclerodermoid syndromes induced by exogenous substances ... *654*

SYSTEMIC SCLEROSIS

Synonyms: Systemic sclerosis: ■ Scleroderma ■ Progressive systemic sclerosis

Subtypes of clinical involvement: ■ Diffuse ■ Limited (includes CREST syndrome)

Key features

- An autoimmune connective tissue disease of unknown etiology
- Characterized by symmetric hardening of the skin of the fingers, hands and face that may generalize
- Raynaud's phenomenon is common and digital ulcers develop
- Internal organ involvement is frequent and affects the lungs, gastrointestinal tract, heart and kidneys; lung involvement is the leading cause of death
- Treatment focuses on internal organ involvement; effective therapy for cutaneous fibrosis remains inadequate

Introduction

Systemic sclerosis (SSc, scleroderma) is an autoimmune connective tissue disease (AI-CTD) of unknown etiology that affects the skin, blood vessels and internal organs. The name *systemic sclerosis* is meant to convey the systemic nature of the disease, which has two major clinical subtypes: *limited* and *diffuse*. Limited SSc is characterized by fibrotic skin changes that are limited to the fingers, hands and face and includes the CREST syndrome. In diffuse SSc, generalized fibrotic skin changes are seen and they usually start in the fingers and hands but spread to involve the forearms, arms, trunk, face and lower extremities. Because SSc is not invariably progressive, the word "progressive" has been dropped from the terminology for this condition.

The diagnosis of SSc is based on clinical findings and laboratory abnormalities[1]. The differential diagnosis of symmetric and widespread cutaneous induration includes SSc as well as generalized morphea, eosinophilic fasciitis, scleromyxedema, nephrogenic systemic fibrosis, and scleredema (favors neck and upper trunk) (Table 43.1).

History

The first reported case of SSc (in 1754) was a young Italian woman who developed progressive induration of her skin. From the clinical description, it is impossible to determine whether she had true SSc or another sclerodermoid disorder.

Epidemiology

SSc has a worldwide distribution and affects all races. The annual incidence and prevalence rates in the US are approximately 20 and 250 cases per million population, respectively[1]. Women are affected three to four times as often as men are. Although SSc can occur in children and the elderly, the onset is typically between the ages of 30 and 50 years. Black patients have an earlier mean age of onset and a higher likelihood of diffuse disease[2]. Approximately 1.5% of SSc patients have one or more affected first-degree relatives, representing a 10- to 15-fold higher risk of SSc in family members than in the general population[3]. SSc is associated with a significant mortality rate, with an overall 10-year survival of less than 70%[1]. Parameters that predict a worse prognosis include male sex, black race, older age at diagnosis, internal organ involvement at diagnosis, skin fibrosis affecting the trunk, and elevated erythrocyte sedimentation rate (ESR)[1].

Pathogenesis

The pathogenesis of SSc is unknown. Key pathogenic abnormalities in the skin and internal organs are vascular dysfunction, immune activation with autoantibody production, and tissue fibrosis characterized by deposition of collagen and other extracellular matrix proteins (Fig. 43.1)[4–6].

Vascular dysregulation

Vascular dysfunction in the form of impaired angiogenesis is an early event in the pathogenesis of SSc[6]. The blood vessels affected range from the smallest capillaries within the proximal nail fold to the large pulmonary arteries. Endothelial cell injury occurs early (before fibrosis is evident), based on changes seen by electron microscopy, such as perivascular leak and edema[7]. Surrounding smooth muscle cells are also affected and have altered production of and responsiveness to vasoconstrictive (e.g. cold, endothelin) and vasodilatory (e.g. nitric oxide) factors. Structural abnormalities such as intimal proliferation leading to luminal occlusion develop and lead to hypoxia which induces synthesis of profibrotic cytokines, fibroblast activation and collagen production[8]. Raynaud's phenomenon and digital ulcers are caused by reversible vasospasm as well as irreversible arterial damage with intimal proliferation and luminal obstruction. Scleroderma renal crisis and pulmonary artery hypertension are manifestations of large vessel dysregulation.

Immune dysregulation

Patients with SSc produce specific, and therefore diagnostic, autoantibodies (e.g. anticentromere, anti-topoisomerase I [Scl-70]; see Ch. 40), and these autoantibodies also have prognostic implications[9,10]. Complexes containing topoisomerase I autoantibody, when bound to the surface of fibroblasts, have been found to stimulate monocyte adhesion and activation. In addition, anti-endothelial cell antibodies from SSc patient sera can trigger endothelial cell apoptosis. One group described *stimulatory* autoantibodies against the platelet-derived growth factor (PDGF) receptor in SSc sera which induced reactive oxygen species and expression of type I collagen by normal human fibroblasts[11]. However, two subsequent studies were unable to confirm these findings[12].

Lymphocytic infiltrates have been observed in both the skin and lungs of SSc patients before the development of fibrosis. Oligoclonal T-cell expansion has been identified in lesional skin, indicating an antigen-driven response, and T cells demonstrate a Th2-predominant profile with increased production of profibrotic cytokines such as interleukin (IL)-4 and IL-13. More recently, Th17 cells and IL-17 have been implicated as playing a role in SSc, as have the innate immune system and

MAJOR CLINICAL AND LABORATORY MANIFESTATIONS OF SYSTEMIC SCLEROSIS AND OTHER SELECTED CONDITIONS CHARACTERIZED BY CUTANEOUS INDURATION

	Systemic sclerosis	Morphea	Eosinophilic fasciitis	Scleredema	Scleromyxedema	NSF
Major clinical variants	• Limited • Diffuse	• Plaque-type morphea • Linear morphea • Generalized morphea		• Post-infectious (type I) • Monoclonal gammopathy-associated (type II) • Diabetes mellitus-associated (type III)		
Raynaud's phenomenon	++	–	–	–	–	–
Symmetric induration	++*	–	++*	++	++	+
Sclerodactyly	++	–	–	–	–	–
Facial involvement	+	– plaque-type and generalized + linear (en coup de sabre)	–	± types I and II – type III	+	–
Systemic involvement	++	–	+	–	++	+
Antinuclear antibodies	++	± generalized and linear – plaque-type	–	–	–	–
Anticentromere antibodies	+ limited	–	–	–	–	–
Anti-topoisomerase I (Scl-70) antibodies	+ diffuse	–	–	–	–	–
Monoclonal gammopathy	–	–		+ type II	++	–
Spontaneous remission	–	++ plaque-type + generalized ± linear	++	++ type I ± types II and III	–	±†

*May be preceded by edematous phase.
†With improved renal function.

Table 43.1 Major clinical and laboratory manifestations of systemic sclerosis and other selected conditions characterized by cutaneous induration. NSF, nephrogenic systemic fibrosis; ++, almost always; +, common; ±, sometimes; –, rare or unusual. *Courtesy, Vincent Falanga, MD.*

INTERACTIONS BETWEEN ENDOTHELIAL CELLS, LEUKOCYTES AND FIBROBLASTS IN SCLERODERMA PATHOGENESIS

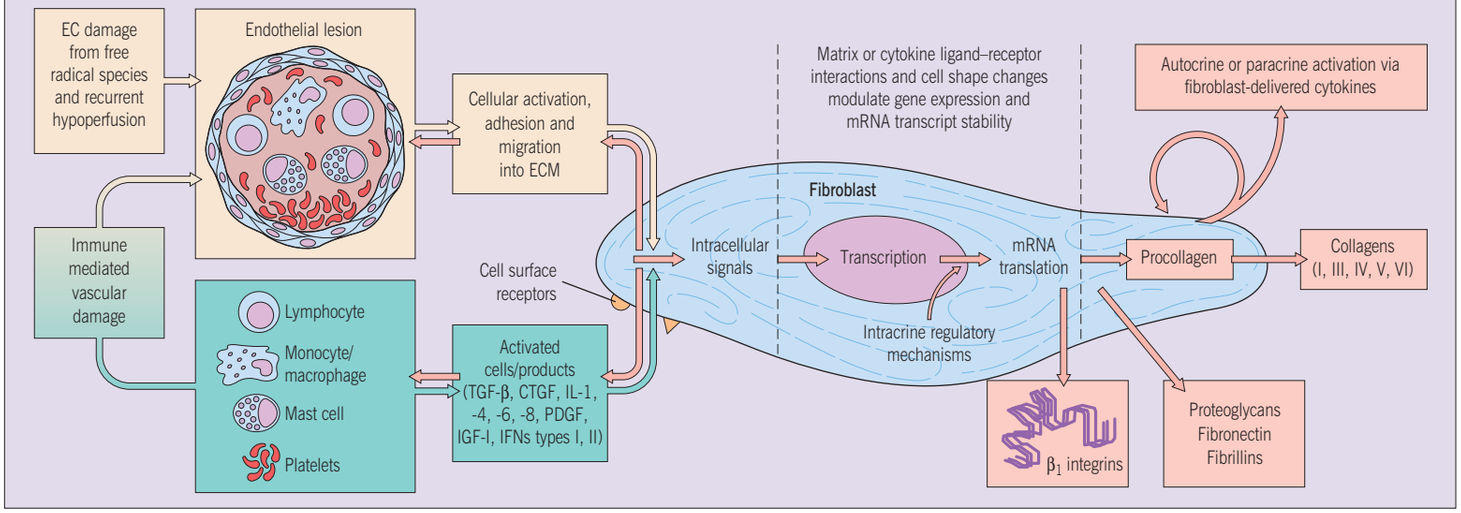


Fig. 43.1 Interactions between endothelial cells, leukocytes and fibroblasts in scleroderma pathogenesis. CTGF, connective tissue growth factor; EC, endothelial cell; ECM, extracellular matrix; IFN, interferon; IGF, insulin-like growth factor; PDGF, platelet-derived growth factor; TGF, transforming growth factor. Genetic susceptibility loci that may increase the risk of developing scleroderma include a region on chromosome 15q (which contains the fibrillin-1 gene) as well as polymorphisms in *STAT4* and the promotor for CTGF. *Adapted from Hochberg MC, Silman AJ, Smolen JS, et al (eds). Rheumatology, 3rd edn. Edinburgh: Mosby, 2003.*

types I (α,β) and II (γ) interferons. SSc patients also have expansion of naive B cells and chronic activation, but a decreased number, of memory B cells.

Fibrosis

Fibrosis represents the final common pathway in SSc. There is excessive deposition of collagens, proteoglycans, fibronectin, fibrillins and adhesion molecules (e.g. β_1-integrins), which sequester cytokines and growth factors (see Fig. 43.1). Attention has focused on transforming growth factor-β (TGF-β) and connective tissue growth factor (CTGF). The latter is induced by TGF-β and may be responsible for maintenance of collagen synthesis.

Given the complex extracellular matrix changes seen in SSc[13], both the fibroblast and the myofibroblast have been a focus of attention. Some evidence suggests that there is an inherent defect, an autocrine loop, or a hypersensitivity to growth factors in SSc fibroblasts. However, the possibility exists that SSc fibroblasts actually have a normal phenotype, but are exposed to an abnormal microenvironment with enhanced activity of growth factors or ischemic mediators. The accumulation of collagen in SSc seems to be primarily the result of increased synthesis, rather than decreased degradation.

Fig. 43.2 Late stage of systemic sclerosis with diffuse cutaneous scleroderma. Note the fixed flexion contractures, sclerodactyly, and the digital ulceration overlying the third proximal interphalangeal joint.

Fig. 43.3 Pitted scars of the digital pulp in a patient with systemic sclerosis. *Courtesy, Kalman Watsky, MD.*

Clinical Features

Diagnostic criteria and classification

For the purposes of clinical trials, the classification scheme of the American College of Rheumatology has been helpful, with either the one major criterion – symmetric cutaneous sclerosis proximal to the metacarpophalangeal (MCP) or metatarsophalangeal (MTP) joints – or two or more minor criteria – sclerodactyly (Fig. 43.2); digital pitted scars or loss of substance from finger pads (Fig. 43.3); bibasilar pulmonary fibrosis – considered diagnostic of SSc[1,2].

Based upon the degree of skin involvement, there are two major clinical subtypes: limited and diffuse[1]. When the skin disease involves the distal and proximal portions of the extremities plus the trunk and face, it is considered diffuse disease, but when the induration is limited to the distal extremities and face, it is considered limited disease[1]. While both subtypes represent systemic diseases, there are variable degrees of internal organ involvement (Table 43.2). Typically, diffuse SSc is associated with early internal organ involvement (within 5 years of disease onset) and a worse prognosis[1], whereas patients with limited SSc tend to develop internal involvement later in the disease course, occasionally after decades.

The acronym *CREST syndrome* describes the clinical features in a subset of patients with limited SSc: *c*alcinosis, *R*aynaud's phenomenon, *e*sophageal involvement, *s*clerodactyly and *t*elangiectasia. Rarely, patients present with characteristic internal organ involvement, Raynaud's phenomenon and positive serologies but no cutaneous involvement, which is referred to as *systemic sclerosis sine scleroderma*.

Cutaneous features

Many patients with SSc experience an early edematous phase, which often features pitting edema of the digits (Fig. 43.4). The skin

COMPARISON OF CLINICAL AND LABORATORY FEATURES OF DIFFUSE AND LIMITED SYSTEMIC SCLEROSIS

	Diffuse SSc (%)	Limited SSc (%)
Raynaud's phenomenon	90	99
Finger swelling	95	90
Tendon friction rubs	70	5
Arthralgia	98	90
Proximal weakness	80	60
Calcinosis	20	40
Mat telangiectasias*	60	90
Esophageal dysmotility	80	90
Small bowel involvement	40	60
Interstitial lung disease	70	35
Pulmonary hypertension	15–20	20–25
Cardiomyopathy	15	10
Renal crisis	20†	1
Sicca syndrome	15	35
Antinuclear antibodies	90	90
Anticentromere antibody	5–30	50–90
Anti-topoisomerase I (Scl-70) antibody	20–60	10–15
Cumulative survival (5 years)	70	90
(10 years)	50	70

*In addition, nail fold capillary abnormalities are observed in >90% of SSc patients.
†Has decreased with the use of angiotensin-converting enzyme (ACE) inhibitors.

Table 43.2 Comparison of clinical and laboratory features of diffuse and limited systemic sclerosis (SSc). *Adapted from Hochberg MC, Silman AJ, Smolen JS, et al. (eds). Rheumatology, 3rd edn. Edinburgh: Mosby, 2003. © Elsevier 2003.*

Fig. 43.4 Early, edematous phase of systemic sclerosis. Note the demonstration of pitting edema on two of the digits. *Courtesy, Jean L Bolognia, MD.*

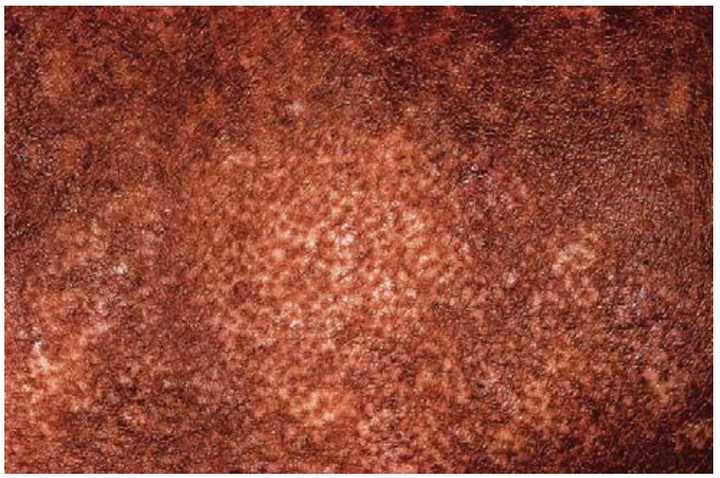


Fig. 43.5 The "salt and pepper" sign. Leukoderma with retention of perifollicular pigmentation in a patient with systemic sclerosis.

Fig. 43.6 Mat/matted (squared-off) telangiectasias in two patients with systemic sclerosis. The first patient (**A**) had CREST syndrome (limited-disease subtype) while the second patient (**B**) presented with diffuse hyperpigmentation and had interstitial lung disease. *B, Courtesy, Jean L Bolognia, MD.*

Fig. 43.7 Calcinosis cutis of the finger in a patient with systemic sclerosis.

subsequently hardens and develops a taut, shiny appearance (indurated phase). Eventually, there may be gradual thinning of the skin (late atrophic phase). The fingers can develop flexion contractures and ulcers (see Fig. 43.2) while involvement of the face can lead to a beaked nose, microstomia and a somewhat youthful appearance.

There are a number of cutaneous changes other than fibrosis in patients with SSc. Dyspigmentation in areas of sclerosis is commonly observed. Some patients develop diffuse hyperpigmentation, with accentuation in sun-exposed areas and sites of pressure. The "leukoderma of scleroderma" is characterized by localized areas of depigmentation with sparing of the perifollicular skin; this helpful diagnostic finding is sometimes referred to as the "salt and pepper" sign (Fig. 43.5). Pigment may also be retained in the skin overlying superficial veins. This leukoderma favors the upper trunk and central face and may overlie uninvolved or sclerotic skin.

Telangiectasias are more common in patients with limited SSc but also occur in patients with diffuse disease (see Table 43.2). The telangiectasias most often involve the face, lips and palms. These telangiectatic macules are matted or squared-off (Fig. 43.6). Capillary abnormalities in the proximal nail fold are present in more than 90% of SSc patients and can be useful in supporting the diagnosis[14]. Use of an ophthalmoscope or dermatoscope may enhance appreciation of the changes. A distinct pattern of capillary loss ("drop out") alternating with dilated loops is characteristic of SSc.

Dystrophic calcinosis cutis most commonly develops on the extremities, usually near joints and in distal locations (Fig. 43.7). In addition, the skin is often dry due to decreased sweating, and pruritus can be quite marked. Fibrotic skin in SSc may show diminished hair growth, but this is variable; hypertrichosis can also occur, particularly during the recovery phase. Overall, the cutaneous changes are extremely troublesome to patients with SSc. For example, in a questionnaire-based study involving 300 patients with SSc, facial involvement and microstomia were the patients' greatest concerns[15].

CLINICAL AND LABORATORY FEATURES OF PRIMARY AND SECONDARY RAYNAUD'S PHENOMENON		
Feature	**Primary Raynaud's**	**Secondary Raynaud's**
Sex	F:M 20:1	F:M 4:1
Age at onset	Puberty	>25 years
Frequency of attacks	Usually <5 per day	5–10+ per day
Precipitants	Cold, emotional stress	Cold
Ischemic injury	Absent	Present
Abnormal capillaroscopy	Absent	>95%
Other vasomotor phenomena	Yes	Yes
Antinuclear antibodies	Absent/low titer	90–95%
Anticentromere antibody	Absent	50–60%
Anti-topoisomerase I (Scl-70) antibody	Absent	20–30%
In vivo platelet activation	Absent	>75%

Table 43.3 Clinical and laboratory features of primary and secondary Raynaud's phenomenon. *Adapted from Hochberg MC, Silman AJ, Smolen JS, et al. (eds). Rheumatology, 3rd edn. Edinburgh: Mosby, 2003. © Elsevier 2003.*

Fig. 43.8 Raynaud's phenomenon in a patient with severe sclerodermoid chronic graft-versus-host disease. The fingers have a violaceous hue as well as areas of blanching (white) and digital ulceration. Oral sildenafil led to a significant improvement.

Raynaud's phenomenon is characterized by episodic vasospasm of the digital arteries resulting in white, blue and red discoloration of the fingers secondary to cold stimuli. Raynaud's phenomenon occurs in two settings (Table 43.3). *Primary Raynaud's phenomenon (Raynaud's disease)* typically develops in adolescent girls and young women and is not associated with any underlying medical problems[16]. Primary Raynaud's phenomenon is common and estimated to affect 3% to 5% of the population. In contrast, *secondary Raynaud's phenomenon* is uncommon and is associated with an underlying medical problem (Fig. 43.8; Table 43.4). Notably, SSc represents one of the leading causes of secondary Raynaud's phenomenon. An approach to differentiating primary from secondary Raynaud's phenomenon is presented in Figure 43.9.

Cutaneous ulcers are common in patients with SSc (Fig. 43.10). Whereas ulcers on the tips of the digits are probably due to ischemia, those on the interphalangeal joints are more likely to persist because of continued trauma (see Fig. 43.2). Ulcers can lead to osteomyelitis and even amputation (autoamputation or surgical intervention).

Extracutaneous features

The majority of patients with SSc have internal organ involvement (Table 43.5), which is the cause of significant morbidity and mortality in this disease[1,2]. Occasionally, a patient with SSc will present with internal organ involvement before skin involvement is evident. The most commonly affected organs are the gastrointestinal tract, lungs, heart and kidneys. However, renal crisis is no longer the leading cause of death in SSc, having been replaced by pulmonary disease. There are two major forms of pulmonary involvement in SSc[1,2]. The first is interstitial lung disease (alveolitis) that eventuates into pulmonary fibrosis. The second form of involvement is pulmonary arterial hypertension. Screening tests for both disorders are outlined in Table 43.5.

Autoantibodies

Autoantibody testing is useful in confirming the diagnosis of SSc (see Ch. 40). Most patients have elevated titers of antinuclear antibodies (ANA)[1,9], with the nucleolar and discrete speckled patterns being relatively specific for SSc. Patients with antibodies to topoisomerase I (Scl-70) are more likely to have diffuse disease with an increased risk of interstitial lung disease. In contrast, patients with anticentromere antibodies are more likely to have limited disease. Autoantibodies to RNA polymerase are usually associated with diffuse disease.

DIFFERENTIAL DIAGNOSIS OF RAYNAUD'S PHENOMENON
STRUCTURAL VASCULOPATHIES
Large and medium-sized arteries
Thoracic outlet syndrome
Brachiocephalic trunk disease (atherosclerosis, Takayasu's arteritis)
Buerger's disease (thromboangiitis obliterans)*
Crutch pressure
Small arteries and arterioles
Systemic sclerosis
Systemic lupus erythematosus
Dermatomyositis
Overlap syndromes
Cold injury
Vibration disease (hand-arm vibration syndrome, hypothenar hammer syndrome)
Chemotherapy (bleomycin, vinca alkaloids, cisplatin, carboplatin)
Vinyl chloride disease
Arsenic poisoning
NORMAL BLOOD VESSELS – ABNORMAL BLOOD ELEMENTS
Cryoglobulinemia (monoclonal or mixed)
Cryofibrinogenemia
Cold agglutinin disease
Myeloproliferative disorders (e.g. essential thrombocythemia)
NORMAL BLOOD VESSELS – ABNORMAL VASOMOTION
Primary (idiopathic) Raynaud's phenomenon
Drug-induced (ergot alkaloids, bromocriptine, interferon, estrogen, cyclosporine, sympathomimetic agents, clonidine, cocaine, nicotine)
Carpal tunnel syndrome
Pheochromocytoma
Carcinoid syndrome
Reflex sympathetic dystrophy
Other vasospastic disorders (migraine, Prinzmetal)
*Can also affect small arteries.

Table 43.4 Differential diagnosis of Raynaud's phenomenon. Paraneoplastic acral vascular syndrome, which can present with Raynaud's phenomenon as well as acrocyanosis and gangrene, has been observed in patients with various solid tumors (e.g. lung or ovarian carcinoma). *Adapted from Hochberg MC, Silman AJ, Smolen JS, et al. (eds). Rheumatology, 3rd edn. Edinburgh: Mosby, 2003. © Elsevier 2003.*

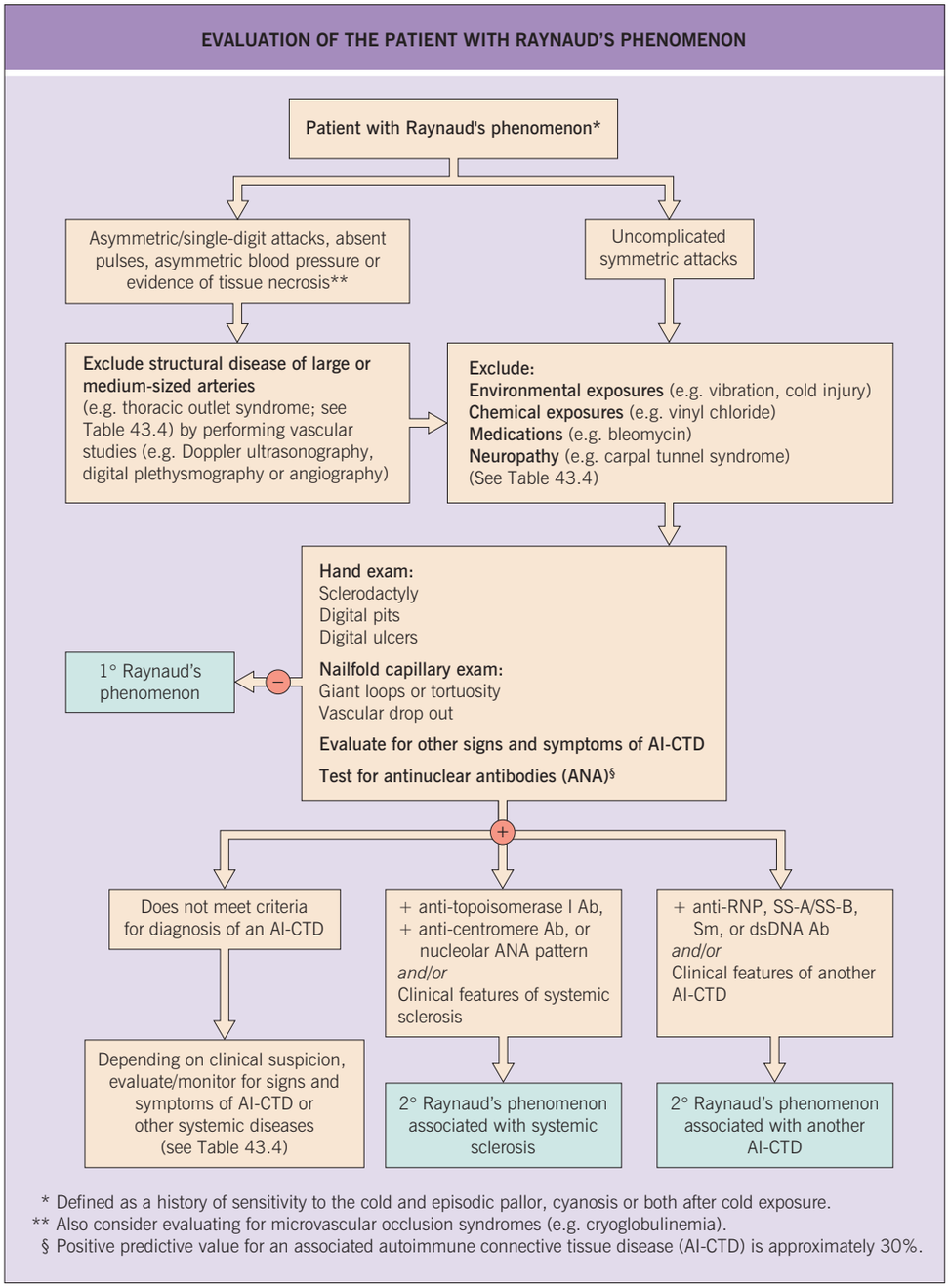


Fig. 43.9 Evaluation of the patient with Raynaud's phenomenon. RNP, ribonucleoprotein; Sm, Smith; ds, double-stranded.

Fig. 43.10 Ulceration of the elbow in a patient with systemic sclerosis. *Courtesy, Joyce Rico, MD.*

EVALUATION AND TREATMENT OF INTERNAL ORGAN INVOLVEMENT IN PATIENTS WITH SYSTEMIC SCLEROSIS			
	Symptoms/signs*	**Studies**	**Treatment**
Pulmonary: • Interstitial lung disease • Pulmonary artery hypertension	Shortness of breath, dyspnea on exertion, dry cough Tachypnea, bibasilar rales, signs of right-sided CHF (e.g. peripheral edema, hepatomegaly, dilated neck veins)	• Interstitial lung disease: Pulmonary function tests, including DLCO† High-resolution CT† • Pulmonary artery hypertension: Echocardiogram Right heart catheterization	• Interstitial lung disease: immunosuppression, primarily cyclophosphamide or mycophenolate mofetil • Pulmonary artery hypertension: vasodilators including endothelin receptor antagonists (bosentan, sitaxsentan, ambrisentan), prostacyclin analogues (iloprost [inhaled], epoprostenol [IV], trepostinil [sc]), and PDE5 inhibitors (sildenafil, tadalafil)
Cardiac	Shortness of breath, dyspnea on exertion, palpitations Signs of right- or left-sided CHF (e.g. tachypnea, rales, peripheral edema [see above])	Electrocardiogram Right heart catheterization	Diuretics, ACE inhibitors, β-blockers (unless contraindicated), angiotensin II receptor blockers, aldosterone antagonists May need to consider withdrawal of calcium channel blockers
Renal, including scleroderma renal crisis‡	Headache, blurry vision Hypertension	Blood pressure BUN, creatinine, urinalysis	Blood pressure control, in particular the use of ACE inhibitors
Gastrointestinal	Dyspepsia, dysphagia, postprandial bloating, constipation, diarrhea Signs of malnutrition	Upper gastrointestinal series (barium swallow) with small bowel follow-through Manometry Endoscopy Malabsorption evaluation	Proton-pump inhibitors for gastroesophageal reflux Domperidone or metoclopramide to improve motility and bloating

*Patients may be asymptomatic.
†At baseline and every 6–12 months for first five years after initial diagnosis, then yearly.
‡Suspected if, compared to baseline, the systolic pressure is elevated >20 mmHg or the diastolic pressure is elevated >10 mmHg.

Table 43.5 Evaluation and treatment of internal organ involvement in patients with systemic sclerosis. ACE, angiotensin-converting enzyme; BUN, blood urea nitrogen; CHF, congestive heart failure; CT, computerized tomography; DLCO, diffusion capacity of carbon monoxide; IV, intravenous; PDE5, phosphodiesterase type 5; sc, subcutaneous.

Antifibrillarin antibodies (present in <10% of SSc patients) are associated with diffuse SSc but can also occur in other AI-CTDs such as systemic lupus erythematosus (SLE)[10].

Pathology

Histologically, areas of cutaneous induration are characterized by compact or hyalinized collagen, excessive deposition of collagen, atrophic eccrine and pilosebaceous glands, loss of subcutaneous fat, and a sparse lymphocytic infiltrate in the dermis and subcutis (Fig. 43.11). Adnexal structures, especially eccrine glands, may be "trapped" by the excessive deposition of collagen. However, the different subsets of SSc cannot be distinguished histologically[17].

Direct immunofluorescence studies are usually negative in patients with SSc. While endothelial damage can occur in cutaneous blood vessels, this finding is only seen at the ultrastructural level[7]; reduplication of the basement membrane is also observed. It should be noted that, in its end stage, areas of sclerosis may be indistinguishable histologically from other diseases characterized by collagen deposition, such as morphea (which tends to have a more robust inflammatory infiltrate than SSc in its earlier stages).

Differential Diagnosis

The differential diagnosis of dermal sclerosis is extensive[18]. Table 43.1 compares the features of SSc to those of morphea, eosinophilic fasciitis, scleredema, scleromyxedema and nephrogenic systemic fibrosis. SSc can be distinguished by the characteristic symmetric induration of the skin of the distal extremities (especially the upper extremity), nail fold capillary findings, association with Raynaud's phenomenon, autoantibody profile, and internal organ involvement. Some patients with SSc also have features of another AI-CTD (e.g. overlap syndromes). Additional entities in the sclerodermoid differential diagnosis are presented in Table 43.6. Localized forms of scleroderma (e.g. morphea) are discussed in Chapter 44. Chronic GVHD can mimic certain features of SSc. The cutaneous sclerosis of chronic GVHD typically begins as circumscribed morpheaform plaques that favor the trunk (which may eventually coalesce and become more reminiscent of scleroderma) as well as lesions that resemble lichen sclerosus or eosinophilic fasciitis (see Ch. 52). Patients with chronic GVHD can also have pulmonary (e.g. bronchiolitis obliterans) and gastrointestinal involvement.

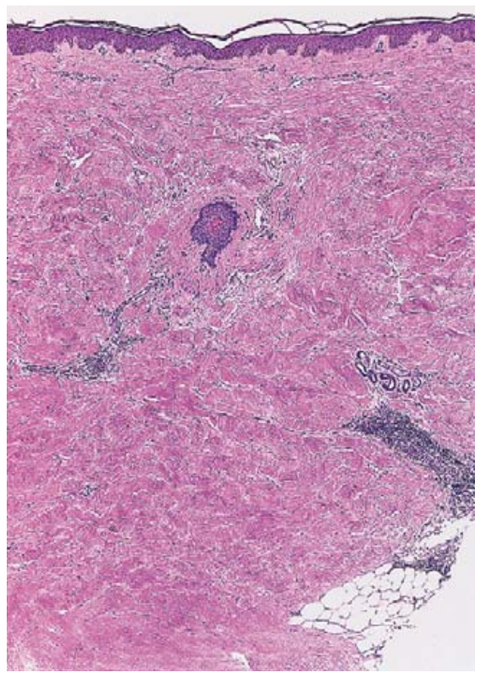


Fig. 43.11 Systemic sclerosis – histologic features. There is a dense sclerosis of the dermis with decreased adnexal structures and "trapping" of remaining adnexal structures that are encased by collagen. Sparse perivascular infiltrates of lymphocytes are present. *Courtesy, Ronald P Rapini, MD.*

DIFFERENTIAL DIAGNOSIS OF SCLERODERMOID CONDITIONS	
	Clinical features
MUCINOSES	
• Scleredema	Induration of the upper back, neck and face; occasional internal involvement (see Ch. 46)
• Scleromyxedema	Waxy papules (often in a linear array); diffuse induration favoring the face, upper trunk, arms and thighs; monoclonal gammopathy; neurologic, gastrointestinal and pulmonary involvement (see Ch. 46)
IMMUNOLOGIC	
• Chronic GVHD*	Morpheaform plaques favoring the trunk, which may become generalized; eosinophilic fasciitis (see Ch. 52)
• Eosinophilic fasciitis	Symmetric induration with a "pseudo-cellulite" appearance on the extremities (sparing hands and feet) (see text)
• Generalized morphea*	Expansion and coalescence of morphea plaques to involve a large portion of the trunk and extremities (see Ch. 44)
• Fibroblastic rheumatism	Sclerodactyly; fibrotic nodules on the hands
PARANEOPLASTIC	
• POEMS syndrome	Sclerotic skin on the extremities (see Ch. 114)
• Amyloidosis (primary systemic)†	Diffuse induration favoring the face, distal extremities and trunk (see Ch. 47)
• Carcinoid syndrome	Sclerotic skin on the legs (see Table 53.3)
NEOPLASTIC	
• Carcinoma *en cuirasse**	Sclerodermoid encasement of the chest by metastatic carcinoma (usually breast cancer)
METABOLIC	
• Diabetic cheiroarthropathy	Thickened skin and limited mobility of the hands (see Table 53.4)
• Porphyria cutanea tarda*,‡	Morpheaform plaques in sun-exposed areas (see Chs 44 & 49)
NEUROLOGIC	
• Reflex sympathetic dystrophy*	Painful, cold, swollen extremity eventually develops cutaneous sclerosis (see Ch. 6)
• Spinal cord injury	Sclerotic skin in affected areas
TOXIN-MEDIATED	
• Nephrogenic systemic fibrosis*	Associated with exposure to gadolinium-based contrast agents (US, 1997–present; now worldwide) (see text)
• Eosinophilia–myalgia syndrome	Associated with L-tryptophan ingestion (US, 1989) (see text)
• Toxic oil syndrome*	Associated with toxic oil ingestion (Spain, 1981) (see text)
DRUG- OR CHEMICAL-INDUCED (SEE TEXT)	
• Bleomycin*	Acrosclerosis, Raynaud's phenomenon; pulmonary fibrosis (more common, usually no concurrent skin lesions)
• Taxanes*	Edema followed by sclerosis of the lower extremities; acrosclerosis
• Vinyl chloride, chlorinated hydrocarbons*	Acrosclerosis, acral fibrotic papulonodules, Raynaud's phenomenon, acro-osteolysis; pulmonary fibrosis
VENOUS INSUFFICIENCY	
• Lipodermatosclerosis*	Woody induration and hemosiderin pigmentation on the lower legs; may also involve the pannus (see Ch. 100)
GENETIC DISORDERS	
• Restrictive dermopathy§	Tight, thin skin over the entire body; joint contractures; *LMNA* or *ZMPSTE24* mutations
• Hutchinson–Gilford progeria	Sclerotic skin on the lower trunk, buttocks and thighs; *LMNA* mutations (see Ch. 63)
• Werner syndrome	Tight, sclerotic skin on the distal extremities; *RECQL2* mutations (see Ch. 63)
• Stiff skin syndrome*	Fibrosis of the skin/fascia of the buttocks and thighs with hip contractures (see text)
• Phenylketonuria	Sclerotic skin on the thighs and buttocks with hip contractures (see Ch. 63)
• Winchester syndrome*	Diffuse, symmetric, leathery skin thickening; fibrotic plaques or bands; *MMP2* mutations (see Table 70.2)
• Ataxia–telangiectasia	Tight, sclerotic facial skin (see Ch. 60)
• Huriez syndrome	Sclerodactyly; atrophic skin on dorsal surfaces of hands and feet; palmoplantar keratoderma (see Ch. 58)
• H syndrome	*H*ypertrichosis in association with areas of hyperpigmentation and induration (primarily lower trunk and lower extremities), sensorineural *h*earing loss, short *h*eight, *h*eart anomalies, *h*epatosplenomegaly, scrotal masses, hypergonadotropic *h*ypogonadism, antibody-negative insulin-dependent diabetes mellitus, facial telangiectasias; mutations in *SLC29A3* which encodes nucleoside transporter hENT3

*Can overlap with morpheaform disorders, which are listed in Table 44.1.
†Primary cutaneous amyloidosis can also occur in patients with systemic sclerosis and generalized morphea.
‡May also be observed in patients with congenital erythropoietic porphyria and hepatoerythropoietic porphyria.
§Sclerodermoid changes are typically present at birth.

Table 43.6 Differential diagnosis of sclerodermoid conditions. Disorders with a clinical presentation similar to systemic sclerosis are referred to as *sclerodermoid*, while those reminiscent of morphea are referred to as *morpheaform* (see Ch. 44).

Treatment

SSc is a challenging disease to treat. Therapeutic interventions focus primarily on internal organ involvement, but unfortunately most of these treatments have had no significant impact on cutaneous manifestations[19].

Raynaud's phenomenon

First-line therapy for Raynaud's phenomenon is behavioral and involves educating patients to keep warm and avoid smoking to minimize the frequency and severity of attacks.

Second-line therapy is pharmacologic, starting with vasodilators[16]. Calcium channel blockers (e.g. nifedipine) have been the most widely used medications. Angiotensin II receptor blockers (e.g. losartan) may also be effective, and combinations of these medications can be used. More recently, phosphodiesterase type 5 inhibitors (e.g. sildenafil, tadalafil) that target the nitric oxide-mediated vasodilation pathway have been employed, and results have been mixed[20–22]. Care must be taken so that the vasodilators do not excessively lower systemic blood pressure. In addition, calcium channel blockers may exacerbate gastroesophageal reflux disease.

Oral antiplatelet agents (e.g. low-dose aspirin) and/or pentoxifylline may theoretically provide additional blood flow to compromised distal sites and may be used empirically. While biofeedback can also be helpful, topical preparations in general have been ineffective.

Cutaneous ulcers

Digital ulcers on the fingers are difficult to treat and a source of great morbidity. The approach to digital ulcers includes the treatments for Raynaud's phenomenon outlined above. Detailed occupational and recreational histories are important to identify risk factors and sources of injury. Based upon two randomized controlled trials, bosentan, an oral endothelin receptor antagonist, has been approved in Europe, but not the US, for the prevention of new digital ulcers in SSc patients[23]. While disappointing results were observed in a double-blind randomized trial of oral iloprost (a prostacyclin analogue)[24], when administered intravenously, it resulted in a reduction in digital ulcers and improved healing[25]. More limited studies of the subcutaneous prostacyclin analogue treprostinil suggest that it may also be effective. In refractory cases, nerve blocks and sympathectomies may be considered.

In patients with SSc, autolytic debridement of ulcers via occlusive dressings is thought to be safer than mechanical debridement. In general, moist hydrocolloid dressings provide a better wound healing environment than dry or wet-to-dry dressings. Enzymatic debriding agents (e.g. collagenase) and topically applied growth factors (e.g. PDGF) have been utilized in a few SSc patients. Skin equivalents or grafts can also be used to stimulate the wound bed and decrease wound pain.

Cutaneous sclerosis

In the early stage of SSc, cutaneous and subcutaneous edema develops rapidly, but during the indurated and atrophic stages, the cutaneous involvement progresses more slowly and tends to gradually improve, independent of treatment. Unfortunately, objective, quantitative measurements of cutaneous fibrosis that are sensitive to change over short periods of time are currently lacking for SSc. The traditional instrument for measuring skin involvement in SSc is the modified Rodnan skin score[1]. Although this is a validated outcome measure, it is not ideal and is relatively insensitive to small changes over short periods of time. An adapted engineering tool, the durometer, may be more suitable for assessing cutaneous induration and hardness in patients with SSc[26].

In a trial of D-penicillamine in 134 patients with diffuse disease, there was no difference between the low-dose and the high-dose treatment groups[27]. Although minocycline looked promising in a pilot study, a larger follow-up study failed to show a benefit[28]. Methotrexate can be helpful in SSc patients with overlap polymyositis. However, in a randomized, placebo-controlled trial (involving 71 patients with early SSc) where methotrexate was administered for 1 year, there was a trend in favor of methotrexate but it did not reach statistical significance[29].

A long list exists of additional agents that have been tried in SSc, but ultimately most have been shown to be ineffective. For example, interferons were abandoned due to lack of benefit. Relaxin, a hormone that relaxes ligatures, did decrease skin scores, but it had no benefit systemically and is no longer used. Photopheresis has been shown to have a marginal effect on skin scores. PUVA and UVA1 may also have a role in SSc therapy[29a,29b].

Other cutaneous complications

Calcinosis cutis represents a serious problem for which no effective medical therapy exists. Low-dose warfarin (i.e. a dose that does not alter the prothrombin time) can decrease the inflammatory reaction associated with calcium deposits. Although there were case reports of the effectiveness of calcium channel blockers for calcinosis, this was not observed in larger patient series. In certain situations, surgical removal of the calcium deposits may be necessary. Treatment with extracorporeal shock wave lithotripsy has also been reported. Telangiectasias can be treated cosmetically with pulsed dye laser therapy.

Internal organ involvement

Treatment of specific internal organ involvement is outlined in Table 43.5. Detailed discussions of these therapeutic approaches are available in other texts[1,2]. Of note, the use of ACE inhibitors to treat scleroderma renal crisis has been a major therapeutic advance[1].

In several retrospective studies, immunosuppression with cyclophosphamide was reported to be beneficial in the treatment of interstitial lung disease. A prospective, randomized, controlled trial showed a modest benefit with oral cyclophosphamide (1 to 2 mg/kg/day for 1 year) compared to placebo[30]. There are significant potential side effects, such as cytopenias, hemorrhagic cystitis and an increased risk of bladder carcinoma. Other immunosuppressive agents such as mycophenolate mofetil, azathioprine, chlorambucil, 5-fluorouracil, cyclosporine and systemic corticosteroids may also be beneficial for certain patients, but their use has not been well studied.

Advances in the treatment of pulmonary artery hypertension have also occurred, in particular the use of oral vasoactive compounds, some of which are also used for Raynaud's phenomenon and digital ulcers. These include endothelin receptor antagonists (bosentan[31], sitaxsentan, ambrisentan) and phosphodiesterase type 5 inhibitors (sildenafil, tadalafil). Prostacyclin analogues (iloprost [inhaled], epoprostenol [intravenous], treprostinil [subcutaneous]) are approved for pulmonary arterial hypertension in SSc patients[32], but are no longer sole or first-line therapy.

Autologous hematopoietic stem cell transplantation is currently being studied in both Europe and the US. The "SCOT" trial, "scleroderma cyclophosphamide or transplant", is underway in the US and should help clarify how effective high-dose immunosuppression is in treating SSc patients. Lastly, treatment with the tyrosine kinase inhibitor imatinib has shown some promise in small studies[33] and warrants further investigation for SSc as well as for other fibrosing disorders such as chronic GVHD and nephrogenic systemic fibrosis.

EOSINOPHILIC FASCIITIS

Synonyms: ■ Shulman's syndrome ■ Diffuse fasciitis with eosinophilia

History

Eosinophilic fasciitis was first reported in 1975 by Shulman, who described a fibrosing disorder characterized by the rapid onset of woody induration of the extremities in association with peripheral eosinophilia[34].

Clinical Features

A history of strenuous physical activity precedes the clinical findings in about 30% of patients with eosinophilic fasciitis. Initial manifestations include edema and pain of the involved extremities, which quickly progresses to fibrosis and a dimpled or "pseudo-cellulite" appearance (Fig. 43.12). The distribution is symmetric, but usually spares the

Fig. 43.12 Eosinophilic fasciitis – clinical features. Induration of the skin with a dimpled or "pseudo-cellulite" appearance, also referred to as rippling or puckering. *Courtesy, Joyce Rico, MD.*

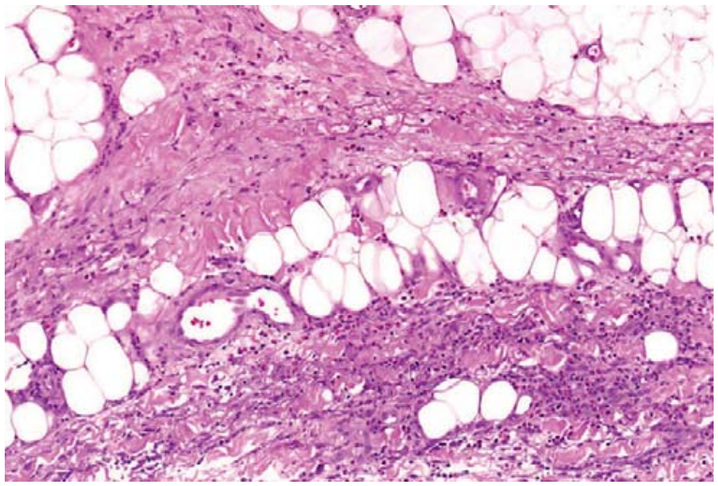


Fig. 43.13 Eosinophilic fasciitis – histologic features. Thickening of the deep fascia and septae of the subcutis with an inflammatory infiltrate comprised of lymphocytes, histiocytes and eosinophils. *Courtesy, Philip E LeBoit, MD.*

hands, feet and face. The "groove sign" refers to linear depressions where veins appear to be sunken within the indurated skin.

Laboratory findings include an elevated ESR, hypergammaglobulinemia and a striking peripheral eosinophilia[35]. Antinuclear antibodies are not elevated (compared to controls) and complement levels are normal. Pancytopenia, anemia, thrombocytopenia and myeloproliferative disorders have been reported in association with this disease. Some authors have advocated that patients with eosinophilic fasciitis and unexplained anemia undergo bone marrow biopsy to evaluate for a hematologic malignancy. Patients with chronic GVHD can develop eosinophilic fasciitis (see Ch. 52).

Pathology

Histologically, there is a thickening of the deep fascia, which may be 10 to 50 times the normal width (Fig. 43.13). Within the fascia and subfascial muscle, a patchy infiltrate composed of lymphocytes and plasma cells is seen. Eosinophils and mast cells may be present, and dermal fibrosis is a feature[36].

Treatment

Once the diagnosis of eosinophilic fasciitis is established via fascial biopsy and/or MRI (see Fig. 52.7), prompt treatment is essential to preserve mobility and function. Therapy is usually initiated with oral corticosteroids. Response is typically noted within the first few weeks, and clinical improvement may be seen over several months. The dose of prednisone is tapered over 6–24 months as tolerated. If an inadequate response is observed, hydroxychloroquine, cyclosporine, dapsone, methotrexate, PUVA or infliximab may be used alone or in combination with prednisone. UVA1, alone or in combination with a retinoid, can also be considered.

PROPOSED DIAGNOSTIC CRITERIA FOR NEPHROGENIC SYSTEMIC FIBROSIS – CLINICAL AND HISTOPATHOLOGIC	
Clinical	**Histologic**
MAJOR CRITERIA • Patterned plaques • Joint contractures • "Cobblestoning" • Marked induration/*peau d'orange* appearance	• Increased dermal cellularity (score +1) • $CD34^+$ cells (score +1) • Thick and thin collagen bundles (score +1) • Preserved elastic fibers (score –1 if *absent*) • Septal involvement (score +1) • Osseous metaplasia (score +3)
MINOR CRITERIA • Puckering/linear banding • Superficial plaque/patch • Dermal papules • Scleral plaques (age < 45 years)	

Interpretation	Clinical	Histologic score
Highly consistent with NSF	2 or more major criteria	4
Consistent with NSF	1 major criterion	3
Suggestive of NSF	2 or more minor criteria	2
Inconsistent with NSF	1 or no minor criteria	1
NSF excluded	Diagnostic of another entity	0

Table 43.7 Proposed diagnostic criteria for nephrogenic systemic fibrosis – clinical and histopathologic. *Adapted from Girardi M, Kay, J, Elston DM, et al. Nephrogenic systemic fibrosis: clinicopathological definition and work-up recommendations J Am Acad Dermatol. www.ncbi.nlm.nih.gov/pubmed/21724294*

NEPHROGENIC SYSTEMIC FIBROSIS

Synonym: ■ Nephrogenic fibrosing dermopathy

History

Nephrogenic systemic fibrosis (NSF) is a relatively new entity in the differential diagnosis of scleroderma-like disorders that affects both the skin and internal organs (see Table 43.1)[37]. Acute kidney injury or chronic severe renal insufficiency, together with exposure to gadolinium-based contrast agents used in medical imaging, are now known to be the underlying causative factors in this disorder[38]. In addition to a strengthening of black box warnings, the FDA in 2010 stated that three contrast agents – gadopentetate dimeglumine (Magnevist™), gadodiamide (Omniscan™) and gadoversetamide (OptiMARK™) – were contradicted in patients with acute kidney injury or chronic severe kidney disease.

Epidemiology and Pathogenesis

NSF is most often observed in middle-aged adults but has been described in children and elderly patients. It has no sex or race predilection. Since the recognition of the causal link between renal dysfunction and exposure to gadolinium-based contrast medium, the number of new cases per year has markedly decreased. Exposure to a greater amount of contrast material as is used in magnetic resonance angiography is thought to increase the risk of developing NSF.

Although the evidence that gadolinium is present in affected tissue in NSF patients is irrefutable, the mechanisms by which the fibrosis develops is unknown. One hypothesis involves aberrant tissue targeting

Fig. 43.14 Nephrogenic systemic fibrosis (NSF) – clinical features. Thickening and induration of the skin can be obvious (**A**), or lesions may present as purple–brown plaques (**B**). Scleral plaques (**C**) in a patient less than 45 years of age is a minor criterion for NSF. *A, Courtesy, Jean L Bolognia, MD. B, Courtesy, Kalman Watsky, MD.*

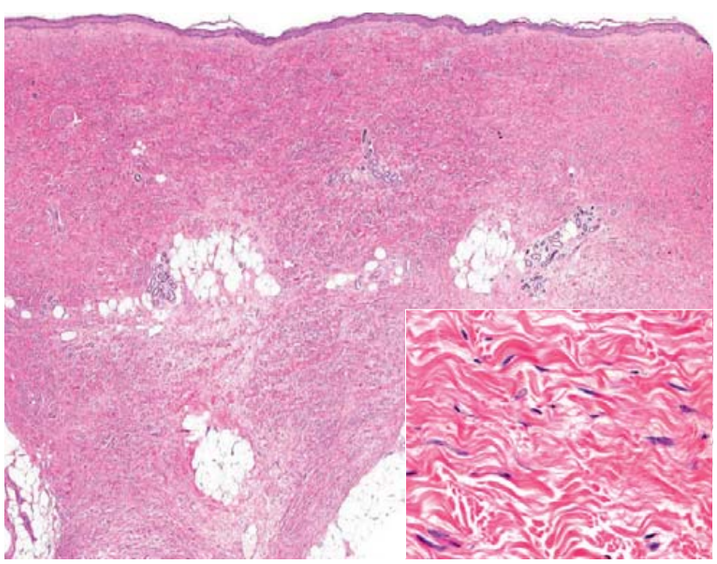


Fig. 43.15 Nephrogenic systemic fibrosis – histologic features. There is an increase in the cellularity and amount of collagen in the dermis and within the septae of the panniculus. The spindle cells (insert) stain positively for CD34 and procollagen I. *Courtesy, Lorenzo Cerroni, MD.*

of the "circulating fibrocyte", a bone marrow-derived leukocyte that is normally recruited to injured tissues, where it participates in matrix deposition and remodeling.

Clinical Features

NSF presents with patterned, thick, indurated plaques distributed symmetrically on the extremities (Fig. 43.14A,B) and trunk. The plaques are erythematous to hyperpigmented and can have an irregular advancing edge with an "amoeboid" appearance. Confluent involvement on the extremities often results in joint contractures. The condition is frequently associated with considerable pain and loss of mobility. Extracutaneous manifestations include yellow scleral plaques (Fig. 43.14C) and systemic fibrosis affecting the heart, lungs and skeletal muscle. Proposed diagnostic clinical criteria are outlined in Table 43.7.

Pathology

Because the disease process typically extends along fibrous septa into the subcutis, a deep biopsy specimen is required for diagnosis (Fig. 43.15). Histologic features include a haphazard arrangement of thickened collagen bundles and increased dermal fibroblast-like cells that stain positively for CD34 and procollagen I (an immunohistochemical profile identical to that of the circulating fibrocyte). Vascular proliferation, mucin deposition and an increased number of dendritic cells can also be observed in NSF, but there is no significant lymphoplasmacytic infiltrate. By energy dispersive spectroscopy, particles of gadolinium can be detected within involved tissues[39].

Treatment

The lesions of NSF are refractory to treatment with corticosteroids and other immunosuppressive drugs. There have been anecdotal reports of improvement with imatinib, rapamycin, UVA1 phototherapy, extracorporeal photochemotherapy, photodynamic therapy, plasmapheresis, high-dose IVIg, and discontinuation of erythropoietin.

STIFF SKIN SYNDROME

Synonym: ■ Congenital fascial dystrophy

History

Stiff skin syndrome was first described by Esterly and McKusick in 1971[40].

Epidemiology

This condition may be congenital or develop during early childhood. Familial occurrences have been described, but the mode of inheritance has not been established.

Pathogenesis

The underlying genetic defect is not definite but mutations in the fibrillin-1 gene have been implicated. The presence of giant "amianthoid-like" collagen fibrils in affected fascia has been postulated to reflect a disturbance in the organization of collagen and glycosaminoglycans in the extracellular matrix.

Clinical Features

Stiff skin syndrome is characterized by "rock hard" induration and thickening of the skin and subcutaneous tissues, which is most pronounced on the buttocks and thighs, with characteristic sparing of the inguinal folds[41]. The hands and feet are not involved. Mild hypertrichosis is often observed in affected areas. Restricted joint mobility leads to a characteristic posture of hip and knee flexion and prominent lumbar lordosis while standing, and patients may have short stature. The condition is stable or slowly progressive, and abnormalities of internal organs are not typically observed. Patients with unilateral involvement have been reported, some with features that overlapped with scleredema, deep morphea and linear melorheostotic scleroderma.

Pathology

Histologic examination demonstrates markedly thickened, hyalinized fascia without an associated inflammatory infiltrate. Thickened collagen bundles and mucin deposition may or may not be present in the overlying dermis.

Treatment

Stiff skin syndrome has a chronic course, and no effective treatments have been reported. Physical therapy can help to prevent progressive joint contractures.

SCLERODERMOID SYNDROMES INDUCED BY EXOGENOUS SUBSTANCES

Exposure to drugs, chemicals and other exogenous substances can lead to cutaneous and extracutaneous sclerosis (see Table 43.6)[42]. The clinical presentation may be similar to that of SSc, including acrosclerosis, Raynaud's phenomenon and pulmonary fibrosis. Other exposures to exogenous agents can result in the development of circumscribed sclerotic plaques resembling morphea. Exogenous substances that induce sclerodermoid conditions are discussed below, and those responsible for morpheaform lesions are discussed in Chapter 44.

Toxic Oil Syndrome

In 1981, the toxic oil syndrome affected more than 25 000 people in Spain; 600 died and approximately 300 remained permanently disabled. It resulted from the ingestion of aniline-degraded and reprocessed rapeseed oil, which led to a specific immune response in genetically susceptible individuals. New cases are no longer seen, as exposure to these contaminated cooking oils was halted. Many of the manifestations of toxic oil syndrome have been reproduced in experimental animal models, and clinical symptoms and severity in mice were shown to be dependent on the genetic background. In humans, toxic oil syndrome started with a morbilliform eruption and flu-like symptoms such as fever and headache; peripheral eosinophilia was observed in half of affected individuals. The inflammatory process subsequently affected the CNS, lungs and salivary glands. Skin involvement either resolved, evolved into a lichen planus-like eruption, or progressed to a morpheaform or sclerodermoid picture.

Eosinophilia–Myalgia Syndrome

In 1989, a contaminated preparation of L-tryptophan led to an outbreak of "eosinophilia–myalgia syndrome", which affected more than 1500 people in the US and led to at least 30 fatalities. The acute phase of the condition was characterized by severe myalgias, fever, dyspnea, edema, a macular exanthem and peripheral eosinophilia. Despite the discontinuation of L-tryptophan intake, approximately half of patients went on to a chronic phase that featured diffuse, deep sclerodermoid induration of the extremities (with acral sparing), progressive peripheral neuropathy and myopathy.

Sclerodermoid Syndromes Induced by Drugs

Several drugs, particularly bleomycin and the taxanes (see Table 43.6), can induce cutaneous sclerosis and pulmonary fibrosis mimicking SSc. Additional medications that have been associated with sclerodermoid changes include other chemotherapeutic agents such as peplomycin (a bleomycin analogue), cisplatin, carboplatin, gemcitabine, uracil-tegafur and topotecan, as well as ergot alkaloids, L-5-hydroxytryptophan ± carbidopa, penicillamine, appetite suppressants and cocaine. Specific autoantibodies are usually absent, and the sclerosis often (but not always) regresses upon withdrawal of the drug.

Sclerodermoid Syndromes Induced by Chemicals

Exposure to certain organic chemicals can lead to a clinical picture that resembles SSc (see Table 43.6). In contrast to the acute onset of the toxic oil and eosinophilia–myalgia syndromes, exposure to vinyl chloride (typically by individuals who clean the autoclaves used to polymerize the monomer), organic solvents (e.g. trichloroethylene, trichloroethane, perchloroethylene), pesticides or epoxy resins induces a slowly progressive process of sclerosis. It typically begins with insidious acrosclerosis and Raynaud's phenomenon (especially with vinyl chloride exposure), but morpheaform plaques and fibrotic nodules can also develop. Acral osteolysis, hepatic toxicity and pulmonary involvement are often observed. In addition, patients experience fatigue, weight loss, arthralgias and myalgias. Autoantibodies are absent, and cessation or reversal of the disease process follows removal of the exposure.

Silicosis

The incidence of SSc is approximately 20-fold higher in individuals with occupational exposure to silica, such as miners and foundry workers, than in the general population. In an epidemiologic study from Germany, three-quarters of men with typical SSc had been exposed to silica dust in the workplace. The mean duration of exposure was 14 years, with a mean delay in onset of the disease of 24 years from the first exposure. Quartz is absorbed via inhalation and percutaneously, and silicosis is caused by particles with a diameter less than 5 microns. Once absorbed, silica cannot be removed from the body. Although silica has nonspecific proinflammatory and profibrotic effects, HLA and TNF-α subtype associations suggest the need for a specific pre-existing immunophenotype for disease progression to occur. SSc associated with pulmonary silicosis is clinically, serologically and immunologically indistinguishable from the idiopathic form of the disease. Silica exposure has also been associated with the development of other AI-CTD, including Sjögren's syndrome, SLE and rheumatoid arthritis.

REFERENCES

1. Silver RM, Medsger TA Jr, Bolster MB. Systemic sclerosis and scleroderma variants. In: Koopman WJ, Moreland LW (eds). Arthritis and Allied Conditions, 15th edn. Baltimore: Lippincott Williams & Wilkins, 2005:1633–80.
2. Mayes MD, Varga J, Buch MH, Seibold JR. Systemic sclerosis. In: Klippel JH, Stone JH, Crofford LJ, White PH (eds). Primer on the Rheumatic Diseases, 13th edn. New York: Springer Verlag, 2008:343–62.
3. Arnett FC, Cho M, Chatterjee S, et al. Familial occurrence frequencies and relative risks for systemic sclerosis (scleroderma) in three United States cohorts. Arthritis Rheum. 2001;44:1359–62.
4. Katsumoto TR, Whitfield ML, Connolly MK. The pathogenesis of systemic sclerosis. Ann Rev Pathol Mech Dis. 2011;6:509–37.
5. Jimenez SA, Derk CT. Following the molecular pathways toward an understanding of the pathogenesis of systemic sclerosis. Ann Intern Med. 2004;140:37–50.
6. Gabrielli A, Avvedimento EV, Krieg T. Scleroderma: mechanisms of disease. N Engl J Med. 2009;360:1989–2003.
7. Prescott RJ, Freemont AJ, Jones CJ, et al. Sequential dermal microvascular and perivascular changes in the development of scleroderma. J Pathol. 1992;166:255–63.
8. Falanga V, Zhou L, Yufit T. Low oxygen tension stimulates collagen synthesis and COL1A1 transcription through the action of TGF-β1. J Cell Physiol. 2002;191:42–50.
9. Steen VD. Autoantibodies in systemic sclerosis. Semin Arthritis Rheum. 2005;35:35–42.
10. Cepeda EJ, Reveille, JD. Autoantibodies in systemic sclerosis and fibrosing syndromes: clinical indications and relevance. Curr Opin Rheumatol. 2004;16: 723–32.
11. Baroni SS, Santillo M, Bevilacqua F, et al. Stimulatory autoantibodies to the PDGF receptor in systemic sclerosis. N Engl J Med. 2006;354:2667–76.
12. Classen JF, Henrohn D, Rorsman F, et al. Lack of evidence of stimulatory autoantibodies to platelet-derived growth factor receptor in patients with systemic sclerosis. Arthritis Rheum. 2009;60:1137–44.
13. Sargent JL, Milano A, Bhattacharyya S, et al. A TGFbeta-responsive gene signature is associated with a subset of diffuse scleroderma and increased disease severity. J Invest Dermatol. 2010;130:694–705.
14. Grassi W, Medico PD, Izzo F, Cervini C. Microvascular involvement in systemic sclerosis: capillaroscopic findings. Semin Arthritis Rheum. 2001;30:397–402.
15. Paquette D, Falanga V. The psychosocial dimensions of scleroderma: a survey. Arthritis Rheum. 2000;43:1522.
16. Wigley FM. Raynaud's phenomenon. N Engl J Med. 2002;347:1001–8.
17. Weedon D. Disorders of collagen. In: Skin Pathology, 2nd edn. Edinburgh: Churchill Livingstone, 2002: 345–80.
18. Jablonska S, Blaszczyk M. Differential diagnosis of systemic sclerosis-like disorders. In: Clements PJ, Furst DE (eds). Systemic Sclerosis, 2nd edn. Philadelphia: Lippincott Williams & Wilkins, 2004:99–119.
19. Korn JH. Scleroderma: a treatable disease. Cleve Clin J Med. 2003;70:954–68.
20. Fries R, Shariat K, von Wilmowsky H, Bohm M. Sildenafil in the treatment of Raynaud's phenomenon resistant to vasodilatory therapy. Circulation. 2005;112:2980–5.
21. Ramos-Casal M, Fonollosa-Pia V, Brito-Zerón P, Sisó-Almirall A. Targeted therapy for systemic sclerosis: How close are we? Nat Rev Rheumatol. 2010;6:269–78.
22. Schiopu E, Hsu VM, Impens AJ, et al. Randomized placebo-controlled crossover trial of tadalafil in Raynaud's phenomenon secondary to systemic sclerosis. J Rheumatol. 2009;36:2264–8.
23. Korn JH, Mayes M, Matucci Cerinic M, et al. Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelin receptor antagonist. Arthritis Rheum. 2004;50:3985–93.
24. Belch JJ, Capell HA, Cooke ED, et al. Oral iloprost as a treatment for Raynaud's syndrome: a double-blind multicentre placebo-controlled study. Ann Rheum Dis. 1995;54:197–200.
25. Wigley FM, Wise RA, Seibold RJ, et al. Intravenous iloprost infusion in patients with Raynaud phenomenon secondary to systemic sclerosis. Ann Intern Med. 1994;120:199–206.
26. Falanga V, Bucalo B. Use of a durometer to assess skin hardness. J Am Acad Dermatol. 1993;29:47–51.
27. Clements PJ, Furst DE, Wong WK, et al. High-dose versus low-dose D-penicillamine in early diffuse systemic sclerosis: analysis of a two-year, double-blind, randomized, controlled clinical trial. Arthritis Rheum. 1999;42:1194–203.
28. Mayes MD, O'Donnell D, Rothfield NF, et al. Minocycline is not effective in systemic sclerosis: results of an open-label multicenter trial. Arthritis Rheum. 2004;50:553–7.
29. Pope JE, Bellamy N, Seibold JR, et al. A randomized, controlled trial of methotrexate versus placebo in early diffuse scleroderma. Arthritis Rheum. 2001;44:1351–8.

29a. Kreuter A, Gambichler T. UV-A1 phototherapy for sclerotic skin diseases. Arch Dermatol. 2008;144:912–5.

29b. Su O, Onsun N, Onay HK, et al. Effectiveness of medium-dose ultraviolet A1 phototherapy in localized scleroderma. Int J Dermatol. 2011;50:1006–13.

30. Tashkin DP, Elashoff R, Clements PJ, et al. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med. 2006;354:2655–66.
31. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy of pulmonary artery hypertension. N Engl J Med. 2002;346:896–903.
32. Badesch DB, Tapson VJ, McGoon MD, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to scleroderma spectrum of disease. A randomized, controlled trial. Ann Intern Med. 2000;132:425–34.
33. Chung L, Fiorentino DF, Benbarak MJ, et al. Molecular framework for response to imatinib mesylate in systemic sclerosis. Arthritis Rheum. 2009;60:584–91.
34. Shulman LE. Diffuse fasciitis with eosinophilia: a new syndrome? Trans Assoc Am Physicians. 1975;88: 70–86.
35. Lakhanpal S, Ginsburg WW, Michet CJ, et al. Eosinophilic fasciitis: clinical spectrum and therapeutic response in 52 cases. Semin Arthritis Rheum. 1998;17:221–31.
36. Barnes L, Rodnam GP, Medsger TA, Short D. Eosinophilic fasciitis. A pathologic study of twenty cases. Am J Pathol. 1979;96:493–517.
37. Cowper SE, Robin HS, Steinberg SM, et al. Scleromyxedema-like cutaneous diseases in renal-dialysis patients. Lancet 2000;356: 1000–1.
38. Marckmann P, Skov L, Rossen K, et al. Nephrogenic systemic fibrosis: suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. J Am Soc Nephrol. 2006;17: 2359–62.
39. High WA, Ayers RA, Chandler J, et al. Gadolinium is detectable within the tissue of patients with nephrogenic systemic fibrosis. J Am Acad Dermatol. 2007;56:21–6.
40. Esterly NB, McKusick VA. Stiff skin syndrome. Pediatrics. 1971;47:360–9.
41. Lu T, McCalmont TH, Frieden IJ, et al. The stiff skin syndrome: case series, differential diagnosis of the stiff skin phenotype, and review of the literature. Arch Dermatol. 2008;144:1351–9.
42. Haustein UF. Scleroderma and pseudoscleroderma: uncommon presentations. Clin Dermatol. 2005;23:480–90.

This page intentionally left blank

Morphea and Lichen Sclerosus

44

Martin Röcken and Kamran Ghoreschi

Morphea and lichen sclerosus are inflammatory skin diseases that ultimately evolve into two distinct modes of scar formation. Morphea affects primarily the dermis and may extend to subcutaneous structures. Lichen sclerosus is most often a disease of the genital mucosa (but may also involve extragenital sites) and it affects both the epidermis and the superficial dermis. Neither one leads to involvement of internal organs other than occasionally the underlying muscle or bone. While an individual patient may have both disorders simultaneously, they are addressed separately because of their multiple dissimilarities. Therapy of these two diseases will be discussed together.

MORPHEA

Subtypes/synonyms: ■ Plaque-type morphea – localized scleroderma, circumscribed scleroderma ■ Linear morphea – linear scleroderma ■ Morphea *en coup de sabre* – scleroderma *en coup de sabre* ■ Deep morphea – morphea profundus

Key features

- Asymmetric sclerotic plaques, usually 2–15 cm in diameter
- Active lesions can have a lilac border with central hypo- or dyspigmentation, while inactive lesions often become hyperpigmented
- The sclerosis may extend deeply into the fat or underlying structures (e.g. fascia, muscle, bone), causing disability
- There is no associated systemic disease
- Often progresses for several years, then regresses; the linear subtype is usually persistent

INTRODUCTION

Morphea is a clinically distinct inflammatory disease, primarily of the dermis and subcutaneous fat, which ultimately leads to a scar-like sclerosis. The small vessel changes, the inflammatory infiltrate and the ultimate structural modifications are identical in morphea and systemic sclerosis, but the two diseases are distinct entities that can easily be distinguished clinically. Morphea has an asymmetric patchy or linear distribution, whereas systemic sclerosis usually begins as symmetric tightening of the hands and fingers that extends progressively toward the proximal upper extremities. Although generalized morphea may resemble early diffuse scleroderma, the presence in the latter condition of Raynaud's phenomenon, digital sclerosis, and involvement of the gastrointestinal tract and the lung generally allows separation of systemic sclerosis from morphea. Distinguishing between deep morphea and eosinophilic fasciitis can prove more difficult.

Morphea has associated morbidity and impacts quality of life as a result of symptoms such as pain, skin tightness or decreased range of motion of joints[1]. In ~10% of patients, scar formation may lead not just to the usual disfigurement but also to significant contractures or growth retardation, handicapping the affected individual for life[2]. Thus, prompt treatment (e.g. UVA1, PUVA) is indicated when morphea affects more than the superficial dermis.

HISTORY

A condition of thickened skin was first mentioned by Hippocrates around 400 BC. The term "scleroderma" is derived from the Greek words *skleros* (hard or indurated) and *derma* (skin). The first description of a generalized "hardness" of the skin in a young woman was by an Italian physician, Carlo Curzio, in 1753, and the French physician Gintrac coined the term "sclérodermie" in 1847. Thomas Addison has been credited with the first detailed description (in 1854) of morphea, which he referred to as Alibert's keloid syndrome[3]. In 1924, Matsui described the typical histopathologic changes of scleroderma, including the increase in collagen and thickening of vessel walls in involved skin. O'Leary and Nomland[4] elaborated the distinctive features of systemic sclerosis versus morphea in 1930.

EPIDEMIOLOGY

Even though morphea has been long recognized as a well-defined entity, few population-based studies have been published. One of the best analyses is a survey from Olmsted County, Minnesota, that attempted to register all patients with the disorder from 1960 to 1993[5]. During this period, the annual incidence rate was 27 per million inhabitants. According to this study, 56% of patients had plaque-type, 20% linear, 13% generalized, and 11% deep morphea. Overall, the incidence appears to be increasing slightly[2].

The prevalence of morphea increases with age. It is approximately 500 and 2200 per million at ages 18 and 80 years, respectively[2]. The disease is more prevalent in women than in men (2.6 to 1), with the exception of linear morphea, which has no gender preference. Data published on the incidence and prevalence of morphea probably reflect an underestimation, as they critically depend on clinical recognition and diagnosis.

Morphea is very rarely life-threatening. In the Olmsted County study, the survival rate of patients with morphea was not significantly different from that of the general population[5]. However, in 11% of the patients, substantial disability occurred. This is of particular concern since disability occurs primarily with linear morphea, and the latter often has its onset before age 18 years (approximately two-thirds of patients)[5].

PATHOGENESIS

Autoantibodies are usually as prevalent in morphea as in the general population, with two exceptions: (1) an increased prevalence of anti-single strand DNA (ssDNA), -topoisomerase IIα, -phospholipid, -fibrillin-1 and -histone antibodies in patients with morphea (see Ch. 40); and (2) high titers of antinuclear antibodies (ANA) in juvenile patients with linear morphea and individuals with generalized morphea. Autoantibodies that activate receptors on fibroblasts, in particular the platelet-derived growth factor receptor (PDGFR), and presumably trigger a cascade that leads to increased collagen synthesis have not been described in patients with morphea (see Ch. 43).

Neither histology nor immunohistology of a single lesion will distinguish between morphea and systemic sclerosis. In most clinicopathologic reviews, it is assumed that the two diseases are triggered by distinct events. However, the development of sclerosis following the initiating event seems to follow a common pathway. It is therefore

assumed that pathogenic steps leading to systemic sclerosis also contribute to the development of morphea, so they will be included in this discussion.

Currently, sclerosis of the skin is thought to involve three major, closely connected components: vascular damage, activated T cells, and altered connective tissue production by fibroblasts (Fig. 44.1)[6].

Vascular Changes

A prominent feature of advanced sclerosis is a reduction in the number of capillaries. Studies performed in systemic sclerosis suggest that microvascular injury is a very early – and perhaps even the primary – event. Endothelial cell markers such as soluble adhesion molecules and vascular endothelial growth factor (VEGF) are elevated in the sera of patients with systemic sclerosis, indicating endothelial activation. The morphologic changes principally affect capillaries and small arterioles 50–500 microns in diameter. The initial changes include expression of adhesion molecules and endothelial swelling, followed by thickening of the basement membrane and intimal hyperplasia. An extrapolation is that similar changes may be occurring in patients with morphea.

Control of Fibroblast Function by T-Cell-Derived Cytokines

Pioneering work by Leroy[7] showed that fibroblasts isolated from sclerotic tissue produce increased amounts of collagen (types I, II and III) and other extracellular matrix proteins when they are cultured *in vitro*. These fibroblasts can maintain this phenotype for weeks over several passages. This raised the question as to whether scleroderma results from an inborn or an acquired error in collagen metabolism within fibroblasts. Today, most data favor the concept that abnormal collagen production is due to instructions from surrounding cells. T cells in particular have the capacity to modify collagen synthesis by fibroblasts and they are regularly present, at least in a perivascular location and especially at the leading edge of developing sclerosis (see Fig. 44.1).

Pathologically enhanced production of collagen and other extracellular matrix proteins is induced by T-cell-derived cytokines, especially interleukin (IL)-4, IL-13 and transforming growth factor-β (TGF-β). IL-4 is produced by $CD4^+$ T helper type 2 (Th2) lymphocytes (see Ch. 4) and can directly enhance TGF-β production[8]. In contrast, pathologic production of collagen (types I, II, III) and other extracellular matrix proteins can be significantly suppressed by interferon-α (IFN-α) or IFN-γ. IFN-γ is produced by $CD4^+$ Th1 lymphocytes and IFN-α is capable of promoting Th1 responses[8]. Th1 differentiation also implicates IL-12 signaling via the transcription factor STAT4. An association between *STAT4* polymorphisms (e.g. rs7574865) and an increased susceptibility to systemic sclerosis, especially the limited subtype, was recently reported[9,10].

While IL-4 is the most potent force in driving Th2-cell differentiation (see Fig. 4.10)[11], it is also produced by Th2 lymphocytes. Because IL-4 enhances pathologic collagen production by fibroblasts and induces recruitment of eosinophils, it is believed that immune responses dominated by IL-4- as well as IL-13- and TGF-β-producing cells are critically involved in the development of skin sclerosis. This concept is supported by clinical and experimental data:

- *In situ* analysis of progressing inflammatory margins of skin sclerosis has revealed predominantly IL-4 expression[12].
- Th2-associated cytokines IL-13 and IL-33 have been shown to promote skin fibrosis experimentally in mice and early treatment of scleroderma-developing mice with anti-IL-4 antibodies prevented scleroderma[13,14].
- Systemic retinoids (which interact with TGF-β signaling) appear to reduce pathologic collagen synthesis by fibroblasts and case series suggest that retinoids can improve sclerosis in patients with sclerodermoid GVHD[15,16].

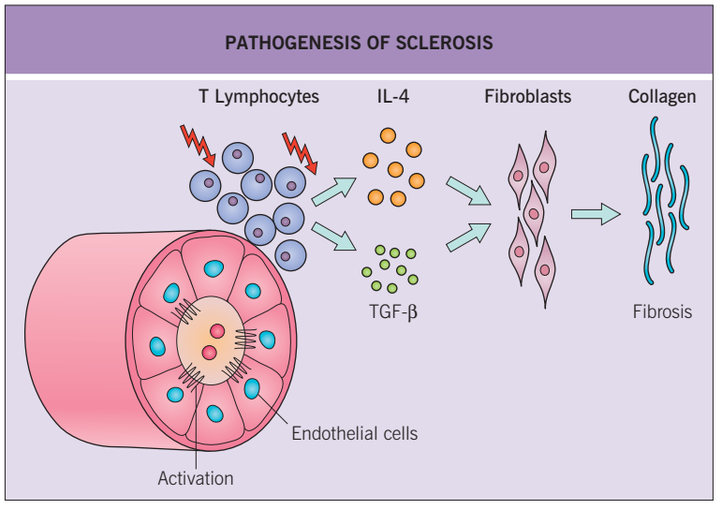


Fig. 44.1 Pathogenesis of sclerosis. Three components are involved during the formation of sclerosis: vascular damage, lymphocyte activation, and altered connective tissue production. IL, interleukin; TGF, transforming growth factor.

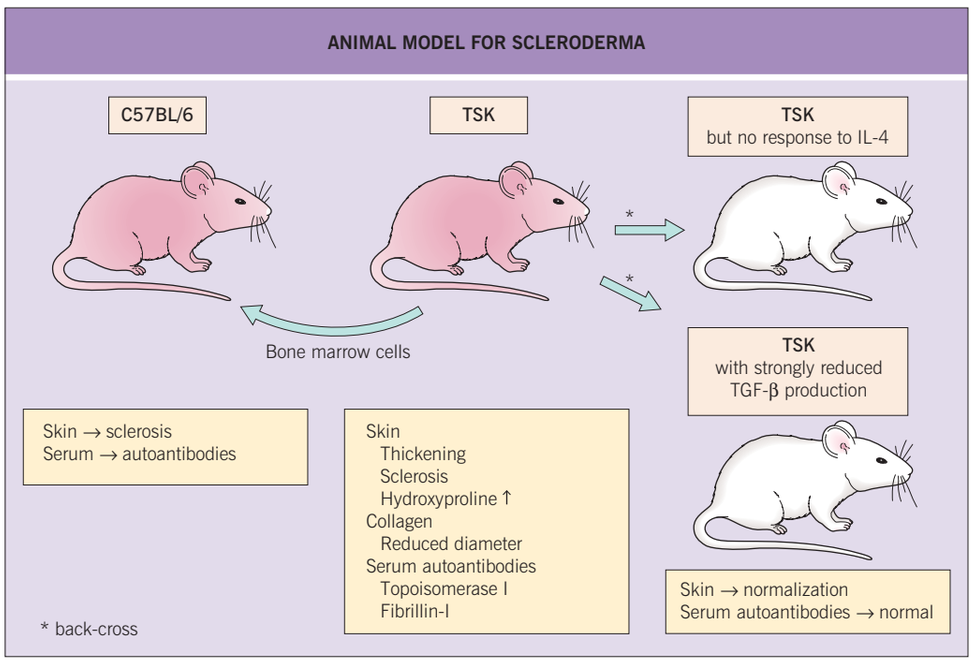


Fig. 44.2 Animal model for scleroderma. Transfer of scleroderma phenotype from diseased animals (TSK mice) to healthy syngeneic mice (C57BL/6) by bone marrow cells. Lack of tight skin and autoantibody production by back-crossing TSK mice with mice that cannot respond to IL-4 or mice that produce minimal amounts of TGF-β. IL, interleukin; TGF, transforming growth factor; TSK, tight skin strain of mice.

Fig. 44.3 Early inflammatory plaque-type morphea of the trunk. Early-stage lesion presenting as an erythematous edematous plaque.

One therapeutic approach for morphea would be to shift from Th2 responses to Th1 responses. However, a series of placebo-controlled clinical trials that tested the efficacy of IFN-γ or IFN-α in morphea had negative results[17]. Perhaps establishment of more effective cytokine-based therapies for skin sclerosis requires a more detailed understanding of cytokine actions *in vivo*.

Lastly, when scleroderma fibroblasts are compared to control fibroblasts, there are differences in intracellular signaling proteins. Examples include activation of p38 mitogen-activated protein kinase and higher levels of both Ha-Ras protein and reactive oxygen species (ROS)[18,19]. These findings and data from animal studies demonstrating the development of skin fibrosis after injections of pro-oxidative agents point to a role for oxidative stress in the pathogenesis of skin sclerosis[20].

Animal Model and Genetics

Currently, the best animal model for studying pathogenic events in scleroderma is the tight skin (TSK) mouse (Fig. 44.2). A partial duplication of the fibrillin-1 gene may be responsible for the increased synthesis and accumulation of collagen in the skin and internal organs of TSK mice. TSK mice not only have increased collagen deposits, but also the collagen fibers are reduced in length and the amounts of hydroxyproline are increased in the dermis, as is the case in morphea and systemic sclerosis. Moreover, the mice have high antibody titers against topoisomerase I and fibrillin-1, similar to patients with systemic sclerosis and morphea, respectively. One major difference is that blood vessels remain uninvolved in TSK mice, demonstrating that sclerosis of the skin can develop in the presence of apparently normal vessels[21]. The phenotype can be transferred from diseased animals to healthy syngeneic mice via bone marrow cells (see Fig. 44.2).

Fibroblasts from TSK mice have elevated IL-4 receptor α expression and back-crossing the TSK mice onto a genetic background that either can not respond to IL-4 or is deficient in producing TGF-β prevents skin sclerosis. Moreover, this back-cross normalizes collagen length, skin thickness and hydroxyproline content and prevents antibody formation to topoisomerase I (see Fig. 44.2)[21]. Promising therapeutic interventions include CpG motif-containing oligodeoxynucleotides that promote Th1 responses (and suppress IL-4 production) and PDGFR-targeting kinase inhibitors (e.g. imatinib), both of which reduce dermal thickening and fibrosis in TSK mice[22]. Of note, in case series, imatinib has led to improvement of cutaneous sclerosis in both fibrotic chronic GVHD and nephrogenic systemic fibrosis.

Besides the phenotypic similarities, the genetic locus associated with the TSK phenotype appears to be related to risk of developing scleroderma. In humans, this susceptibility locus is on chromosome 15q in a region of 2-cM that contains the fibrillin-1 gene (mutations in the fibrillin-1 gene have been implicated in stiff skin syndrome)[23]. Other genetic variations reported to be associated with scleroderma include polymorphisms in both *STAT4* (see above) and the promotor region of the gene encoding connective-tissue growth factor (CTGF)[9,10,24].

Fig. 44.4 Plaque-type morphea of the back. Multiple, large hyperpigmented plaques, several of which have an inflammatory border.

Triggering Events

Most immunologic and metabolic studies were designed to understand systemic sclerosis, and the question remains as to whether they can also explain focal, asymmetric inflammation and sclerosis of the skin. The major discriminating factor between morphea and systemic sclerosis might be the triggering event, with morphea being caused by a local trigger within the skin and systemic sclerosis being initiated by triggers with systemic effects.

These questions initiated the search for potential triggers and studies of diseases that share clinical features with morphea and scleroderma. One intensively investigated area was the potential role of infection with *Borrelia burgdorferi*. The isolation of *B. burgdorferi* from the skin of some selected patients with morphea originally supported this speculation. However, larger studies by several groups from different countries found that morphea lesions normally do not contain mRNA for *B. burgdorferi* or related strains and the prevalence of antibodies against *B. burgdorferi* is similar in patients with and without morphea[25]. Thus, this theory has been abandoned.

CLINICAL FEATURES

Morphea can be subdivided into several subgroups: plaque-type morphea, linear morphea, generalized morphea, and other less common variants (e.g. deep, guttate, nodular). There are also inflammatory syndromes leading to superficial or deep sclerosis of the skin that resemble morphea (i.e. morpheaform; see below). Patients with morphea do not have Raynaud's phenomenon or involvement of internal organs, except for underlying fascia, muscle and bone in some patients with linear morphea. In rare patients with presumptive morphea, clinically insignificant fibrosis of the lung or slightly reduced esophageal motility has been detected radiographically or by scintigraphy. Clinically relevant involvement of internal organs is only observed in certain types of pseudoscleroderma (see Ch. 43).

Clinical Manifestations

Plaque-type morphea, the most frequent variant, is characterized by the insidious onset of a slightly elevated, erythematous or violaceous, somewhat edematous plaque that undergoes centrifugal expansion (Fig. 44.3). It is generally asymptomatic and therefore frequently goes unnoticed by the patient. The central portion of the progressing lesion starts to transform into sclerotic, scar-like tissue. Depending on the depth of the sclerosis, the skin becomes progressively indurated.

Fig. 44.5 Comparison of deep morphea and eosinophilic fasciitis. **A** Note the "pseudocellulite" appearance of the involved skin of the thigh in deep morphea. **B** In eosinophilic fasciitis, the level of fibrosis is also deep, resulting in a similar clinical appearance.

Centrally, it can acquire a shiny white color, and peripherally, a violaceous or "lilac" ring. Postinflammatory hyperpigmentation often dominates over the white sclerosis as the lesions mature (Fig. 44.4).

Skin structures such as hairs and sweat glands are frequently lost. Some patients complain of itch, perhaps due to associated xerosis. Once the "lilac" ring vanishes, the lesion's progression also halts. Although this inflammatory margin may be difficult to appreciate, especially in linear sclerosis, it is an important component of the physical examination as it is an indicator of clinical activity.

The plaques of morphea most commonly develop on the trunk and are between 2 and 15 cm in diameter. They are usually multiple and asymmetric, but marked variation exists. Individual lesions may enlarge significantly or remain stable in size.

The course of morphea is also variable. In most patients, morphea progresses over 3–5 years, then arrests and eventually resolves spontaneously. However, residual atrophy and/or dyspigmentation are commonly observed. Rarely, patients have relapsing disease for more than 5 years. Because many patients are lost to follow-up, no definitive long-term statistical data have been published.

Fig. 44.6 Nodular (keloidal) morphea. Elevated, firm pink papulonodules arising within an area of hyperpigmented induration. *Courtesy, Jean L Bolognia, MD.*

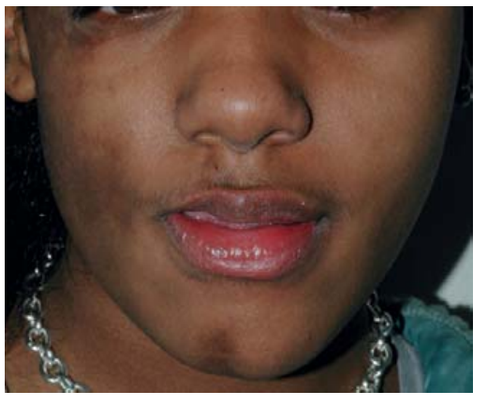


Fig. 44. 7 Parry–Romberg syndrome. Hyperpigmentation and loss of subcutaneous fat, leading to facial asymmetry. *Courtesy, Julie V Schaffer, MD.*

Variants

Various manifestations of morphea have become associated with specific names. They do not really reflect unique entities, but rather different morphologic features, distribution patterns or depth of involvement. In most patients, morphea seems to be randomly distributed. However, in some patients, the lesions are unilateral, and they may follow dermatomes or Blaschko's lines.

- **Guttate morphea** presents primarily as multiple, rather superficial, nummular plaques. Even though relatively small, they may become deeply indurated.
- **Atrophoderma of Pasini and Pierini** is considered by some to be a very superficial variant of plaque-type morphea, while others consider it to be a separate entity in the differential diagnosis of "burnt-out" morphea (see Ch. 99). Hyperpigmented patches are seen most commonly on the posterior trunk; occasionally, lesions follow Blaschko's lines (linear atrophoderma of Moulin).
- **Deep morphea** reflects an inflammation and sclerosing process that affects primarily the deep dermis and subcutaneous fat and may even involve underlying structures (e.g. the fascia) (Fig. 44.5A). Patients normally develop a single or few hard deep plaques that may impair motility of the skin; ultimately, lesions may calcify, leading to deep osteoma cutis. Because of the location of the sclerosis, individual lesions can share some clinical features with eosinophilic fasciitis (Fig. 44.5B and see Ch. 43).
- In **nodular or keloidal morphea**, inflammation within the dermis leads to thick, keloid-like nodules (Fig. 44.6) or streaks. It is clinically indistinguishable from indurated keloids.
- In rare patients, especially those where sclerosis of the skin is associated with diffuse, rapidly progressive edema, lymphoceles

Fig. 44.8 Linear morphea of the leg. The differential diagnosis includes linear melorheostosis which is often associated with underlying candlewax-like linear hyperostosis.

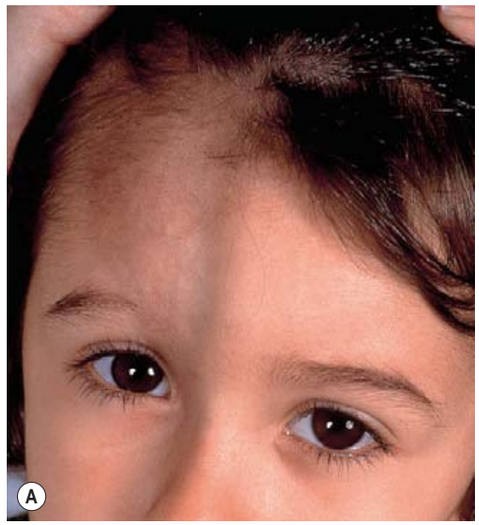


Fig. 44.9 Morphea *en coup de sabre*. Linear depressions and sclerosis are more frequently paramedian (rather than midline) and can be wide **(A)** or narrow **(B).** Note the prominent veins and loss of the medial eyebrow in A. *B, Courtesy, Julie V Schaffer, MD.*

may result from stasis of lymphatic fluid. When the latter develop into bullae, this is referred to as **bullous morphea**. It is more frequently observed in generalized morphea or sclerodermoid GVHD and is rarely a feature of plaque-type morphea. Bullous morphea has to be distinguished from mechanical blisters that may occur in the central scar and are secondary to impaired mechanical stability of the dermal–epidermal junction.

Linear Morphea and Parry–Romberg Syndrome

Linear morphea is different from plaque morphea, with respect to age of onset, distribution, clinical outcome and serologies. Morphea *en coup de sabre* (meaning stroke or blow with a single-edged sword) is a term used for linear morphea of the forehead and scalp. Hemifacial atrophy, or Parry–Romberg syndrome, is probably a very severe variant of linear morphea, but it may be a phenotype for more than one entity. There is a progressive loss of subcutaneous fat, but little or no sclerosis (Fig. 44.7). The entire distribution of the trigeminal nerve, including the eye and the tongue, may be affected.

Linear morphea may present initially as a linear, erythematous (inflammatory) streak, but more frequently it begins as a harmless-appearing lesion of plaque-type morphea that extends longitudinally as a series of plaques that then join to form a scar-like band (Fig. 44.8). This band may severely impair the mobility of the affected limb. Linear morphea tends to involve the underlying fascia, muscle and tendons. This leads not only to muscle weakness but also to a shortening of the muscles and fascia that impairs joint motility. Linear morphea is especially dangerous when extending over joints, as this almost invariably results in disabling joint immobilization. In some patients, involvement is circular rather than linear and results in progressive atrophy of the limb similar to the Parry–Romberg variant of facial morphea.

The *en coup de sabre* type of morphea represents linear morphea of the head (Fig. 44.9). It is normally unilateral and extends from the forehead into the frontal scalp. It may start either as a linear streak or as a row of small plaques that coalesce. A paramedian location is more common than a median location. Like plaque morphea, it may initially be surrounded by a discrete lilac ring that extends longitudinally and may reach the eyebrows, nose and even the cheeks. The waning inflammation leaves a linear, hairless crevice that in some patients is more sclerotic, while in others is more atrophic.

En coup de sabre morphea can also involve the underlying muscles and osseous structures. Rarely, the inflammation and sclerosis progress to involve the meninges and even the brain, creating a potential focus for seizures. Alternatively, very slowly progressing inflammation, indistinguishable from the inflammatory process of linear morphea, leads to gradual involution of the skin, fatty tissues and underlying bones.

Generalized Morphea

Rarely, plaque-type morphea is rapidly progressive, where multiple enlarging plaques appear simultaneously and coalesce until they involve nearly the entire integument. Rather, this variant normally begins insidiously on the trunk as plaque morphea. An individual lesion is indistinguishable from classic plaque morphea, except that it does not stop expanding. Just as in the diffuse form of systemic sclerosis, the plaques rapidly coalesce and affect the entire trunk, often only sparing the nipples. The sclerosis may involve the extremities down to the hands (presenting initially as puffy edema). As the cutaneous sclerosis progresses, it may result in disabling constrictions that even cause difficulty in breathing due to impaired thorax mobility and inflammation of the intercostal muscles. Although an aggressive therapeutic approach is recommended, the disease is usually persistent given its often limited response.

Morphea in Childhood

About 20% of those with morphea are children and teenagers. The female-to-male ratio for plaque-type morphea is about 2:1, with a mean age of disease onset of 7 years[26]. Linear morphea is more of a problem, as two-thirds of all patients with this variant are younger than 18 years of age when it develops. Also, in young children and adolescents, linear morphea often leads to growth retardation of the affected limb. Thus, if left untreated, linear morphea may result not only in decreased range of motion of joints but also in permanent limb asymmetry from

Fig. 44.10 Linear morphea of the leg in two adolescents. A Extensive induration of the left leg with hypoplasia and an obvious flexion contracture of the knee; there is also involvement of the right foot. **B** Linear distribution of coalescing sclerotic plaques on the thigh; note the lilac-colored border. *B, Courtesy, Julie V Schaffer, MD.*

unilateral hypoplasia (Fig. 44.10). Linear morphea that is indistinguishable from the idiopathic variant can also follow allogeneic hematopoietic stem cell transplantation.

Disabling pansclerotic morphea of children is similar to generalized morphea of the adult. It usually starts before 14 years of age and tends to cause lifelong severe disability due to persistent atrophy of the underlying muscles and contractures of the involved joints. The disease tends to extend from the trunk to the hands and feet. Periodontal atrophy may occur, but there is only slight involvement of the esophagus and lung. Distinction from systemic sclerosis may prove challenging.

Importantly, in a large multicenter study of children with morphea (85% of whom had linear morphea or Parry–Romberg syndrome [PRS]), 22% had extracutaneous findings that were primarily articular (11%), neurologic (4%) and ocular (2%)[26]. The latter were seen primarily in those with linear morphea of the head or PRS.

LABORATORY FINDINGS

Laboratory abnormalities are not a prominent feature of morphea, except for generalized and linear morphea. The ESR and serum protein levels are usually normal, but eosinophilia may occur, especially during early active phases of the disease. The presence of ANA or antibodies to ssDNA and histones are unusual in patients with plaque-type morphea (see Ch. 40). They are more frequent in linear and generalized morphea, where ANA can be found in high titers in 40–80% of patients. About 40% of children and adolescents with morphea have elevated ANA titers[26,27].

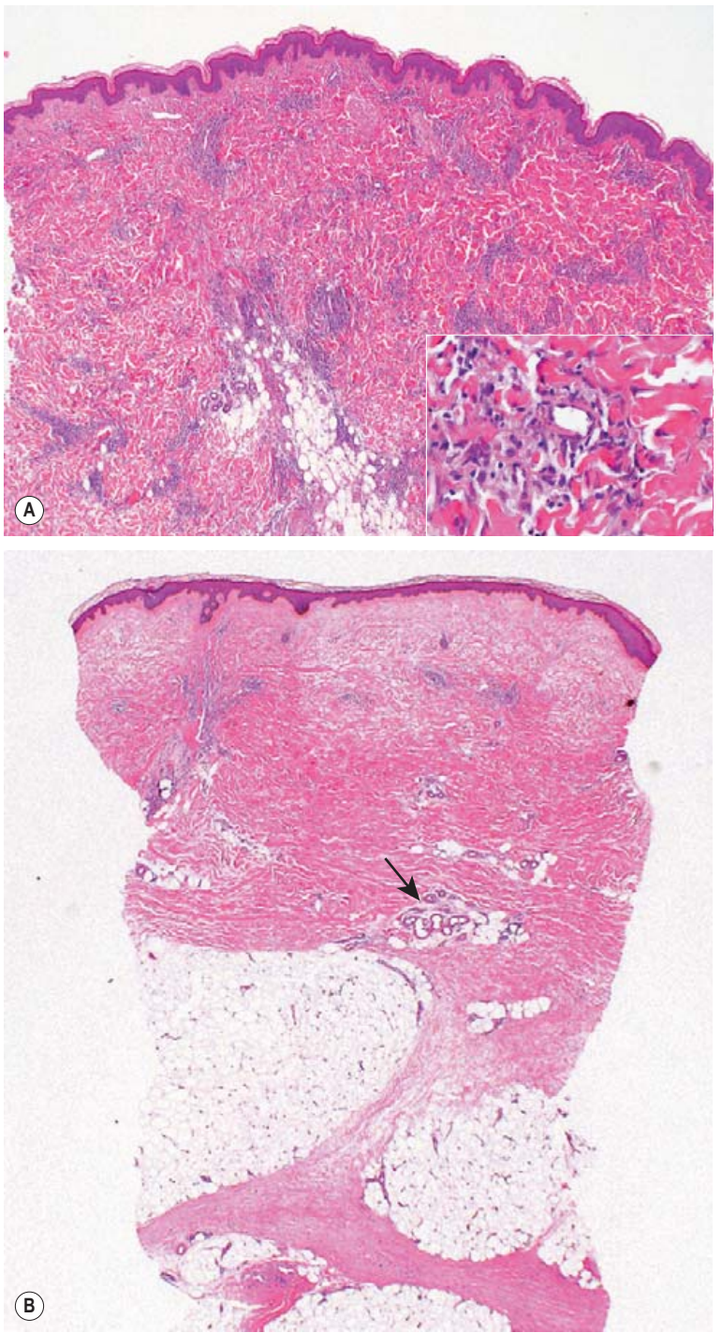


Fig. 44.11 Morphea – histologic features. A Overview with thickening of the dermis and perivascular infiltrates of lymphocytes and plasma cells (insert). **B** Advanced sclerosis of the entire dermis extending into the fat with thickened collagen bundles and "trapped" eccrine glands (arrow).

PATHOLOGY

The histology of scleroderma depends on two factors: the stage and area of the lesion sampled (early inflammatory margin or central sclerosis) and the depth to which the disease extends. In most situations, morphologic changes are best seen at the border between the dermis and subcutaneous fat. Specimens for histology must include subcutaneous fat and it is important to note whether the biopsy specimen is taken from the inflammatory border or from the fibrotic center.

At the inflammatory border, vascular changes are relatively discrete by light microscopy. Vessel walls show endothelial swelling and edema. Capillaries and small arterioles are surrounded by an infiltrate that contains primarily $CD4^+$ T cells and sometimes eosinophils, plasma cells and mast cells (Fig. 44.11A).

In later stages, the inflammatory infiltrate wanes and ultimately disappears completely, except in some areas of the subcutaneous fat.

The epidermis is basically normal in appearance, but the rete ridges may be diminished, leaving a flattened dermal–epidermal junction. Edema is no longer visible in the dermis and upper subcutis. Capillaries and small vessels are significantly reduced in number, and homogeneous collagen bundles with decreased space between the bundles replace most structures. At this stage, collagen bundles in the reticular dermis appear densely packed, as evidenced by a more intense eosinophilic staining, and are aligned parallel to the dermal–epidermal junction (Fig. 44.11B). Eccrine glands appear atrophic and "trapped" within the thickened dermis. The underlying subcutis is homogenized and hyalinized.

Deep morphea affects primarily the deep subcutaneous tissue. Following the inflammatory phase, extensive sclerosis and hyalinization extend into the underlying fascia. Involvement of the underlying fascia is obligatory in deep morphea and is also frequently observed in linear and generalized types of morphea. In these patients, the fascia and even the underlying muscle (frequently vacuolated) are involved in the process of progressive sclerosis, characterized by replacement of the differentiated tissue by collagen bundles.

MORPHEAFORM (AND SCLERODERMOID) INFLAMMATORY SYNDROMES

Some entities (e.g. sclerosis secondary to exposure to bleomycin, vinyl chloride or epoxy resin) that are characterized by acrosclerosis and Raynaud's phenomenon have a clinical presentation similar to scleroderma (i.e. sclerodermoid or pseudoscleroderma), while others present with circumscribed plaques similar to morphea (i.e. morpheaform). The former are discussed in Chapter 43 and the latter are discussed below and presented in Table 44.1. There are also clinical disorders that may have either type of clinical presentation, such as toxic oil syndrome.

DIFFERENTIAL DIAGNOSIS OF MORPHEAFORM SKIN LESIONS
Morphea (plaque-type, linear, generalized* or deep*)
Chronic graft-versus-host disease*
Lichen sclerosus (may coexist with morphea)
Lipodermatosclerosis*
Sclerosis at injection sites†
• Vitamin K_1 (Texier's disease) or vitamin B_{12}
• Silicone or paraffin implants
• Interferon-β
• Glatiramer
• Enfuvirtide
• Bleomycin (intralesional therapy)
• Opioids (e.g. pentazocine, ketobemidone, methadone)
Chemical/toxin exposures
• Aromatic/chlorinated hydrocarbons (e.g. benzene or toluene at sites of contact with skin)*
• Nephrogenic systemic fibrosis (induced by gadolinium-containing contrast media)*
• Toxic oil syndrome (historical)*
Radiation-induced morphea
Porphyria (porphyria cutanea tarda, hepatoerythropoietic porphyria, congenital erythropoietic porphyria)
Muckle–Wells syndrome
Winchester syndrome*
Asymmetric childhood scleredema/stiff skin syndrome*
Linear melorheostosis
Reflex sympathetic dystrophy*
Morpheaform sarcoidosis
Sclerosing congenital melanocytic nevus
Dermatofibrosarcoma protuberans
Cutaneous metastases (e.g. carcinoma *en cuirasse*)
*Can overlap with sclerodermoid disorders, which are outlined in Table 43.6; in particular, deep morphea and eosinophilic fasciitis may have a similar appearance.
†Systemic medications for which there have been reports of an association with morpheaform lesions include bleomycin, taxanes (e.g. paclitaxel, docetaxel), bromocriptine, ethosuximide, valproic acid, appetite suppressants and penicillamine.

Table 44.1 Differential diagnosis of morpheaform skin lesions.

While a variety of inflammatory diseases ultimately lead to superficial or deep sclerosis of the skin, their exact relationship to morphea is enigmatic. Some of these diseases are preceded by or associated with eosinophilia in blood or tissue. Infiltration by eosinophils may be of unknown etiology, as in eosinophilic fasciitis, or it may reflect an immune reaction to a defined toxic insult or antigenic stimulus, as in the L-tryptophan syndrome (eosinophilia–myalgia syndrome), toxic oil syndrome, or GVHD following hematopoietic stem cell transplantation. Lastly, since certain exogenous drugs or chemicals, endogenous metabolites or X-ray irradiation induce sclerosis at the site of tissue injury in only a subset of individuals, this suggests that unique metabolic events and innate or adaptive immune responses to these compounds determine the individual's susceptibility to develop sclerosis.

- **Lipodermatosclerosis**. Chronic venous insufficiency that persists for many years leads to sclerosis in association with chronic hypoxia. Lipodermatosclerosis favors the lower extremities, but can also involve the pannus; it is discussed in Chapter 100.
- **Injections of vitamin K_1 (Texier's disease)**. Injection of oil-soluble vitamin K_1 rarely causes a strictly localized, deep eosinophilic fasciitis that is indistinguishable from deep morphea. It may ultimately resolve with atrophy of the dermis and/or subcutis.
- **Paraffin and silicone injections or implants**. It is suspected that injection of silicone or liquid paraffin during reconstructive surgery or leakage of silicone implants may cause chronic inflammation that results in localized morphea-like sclerosis. The belief that these substances can cause more generalized inflammation and trigger systemic diseases such as systemic sclerosis, eosinophilic fasciitis or mixed connective tissue disease was not substantiated when meta-analyses were performed[28].
- **Porphyrias**. In adults, porphyria cutanea tarda can lead to morphea-like sclerosis in UV-exposed sites, such as the face, hairless scalp, dorsal aspects of the hands, and the upper chest. Histology and electron microscopy findings may resemble morphea except for the presence of PAS-positive deposits around dermal blood vessels. Other rare forms of porphyria can also lead to scarring in UV-exposed sites (see Ch. 49).
- **Radiation-induced morphea**. This disorder is characterized by marked sclerosis, erythema and pigmentary changes occurring within the radiation field or even beyond it. The incidence of radiation-induced morphea is about 1 in 500 patients and it is seen primarily in patients treated for breast carcinoma. Predictive risk factors for the development of radiation-induced morphea are unknown and disease onset can even occur several years after radiation therapy. In addition to the changes of radiation dermatitis, histopathology demonstrates perivascular and subcutaneous inflammation together with dermal fibrosis and collagen deposition.
- **Chronic GVHD**. Patients with chronic GVHD develop lesions that resemble morphea and lichen sclerosus as well as eosinophilic fasciitis (see Ch. 52).
- **Nephrogenic systemic fibrosis**. This entity is discussed in detail in Chapter 43.

DIFFERENTIAL DIAGNOSIS

In addition to the other morpheaform and sclerodermoid conditions discussed above, the most important entity in the differential diagnosis is systemic sclerosis (see Ch. 43). Absence of Raynaud's phenomenon and lung or esophageal involvement is characteristic of morphea. The other common considerations are lichen sclerosus and keloids; however, the former can coexist with morphea. Dupuytren's contracture and camptodactyly, a benign ulnar deviation of the fourth and fifth finger, can be clinically distinguished from linear morphea.

Scleredema leads to diffuse woody induration of the upper back and neck. Symmetric tightness and induration of acral sites can be seen in insulin-dependent diabetes with cheiroarthropathy, also referred to as waxy skin and stiff joints. In children, progeria and premature aging syndromes need to be distinguished from Parry–Romberg syndrome, but the latter is unilateral. Additional entities in the sclerodermoid differential diagnosis (e.g. scleromyxedema) are listed in Table 43.6.

LICHEN SCLEROSUS

Synonyms: ■ Lichen sclerosus et atrophicus ■ Kraurosis vulvae ■ Balanitis xerotica obliterans (lichen sclerosus of the penis)

Key features

- Sclerotic, ivory-white, flat papules and plaques with epidermal atrophy and, in extramucosal sites, follicular plugging
- Most commonly affects female or male genitalia, less often extragenital skin
- May cause scarring of the vaginal introitus or phimosis
- Severe pruritus may occur
- No systemic manifestations

INTRODUCTION

Lichen sclerosus is a clinically distinct inflammatory disease primarily of the superficial dermis or submucosa that leads to ivory-white scar-like atrophy. Extragenital lichen sclerosus may itch and be cosmetically disturbing. Genital lichen sclerosus causes both dryness and severe, persistent pruritus, and it often leads to progressive atrophy and functional impairment. Phimosis or scarring of the vaginal introitus are the most frequent complications.

HISTORY

Francois Henri Hallopeau's report on a "lichen plan atrophique" in 1887 is considered to be the first description of lichen sclerosus. The typical histopathologic changes of lichen sclerosus et atrophicus were published by Ferdinand Jean Darier in 1892. Unna, Westberg, von Zumbusch and others elucidated the clinical features of lichen sclerosus in various case reports[29–31]. This contributed to the panoply of terms, such as white spot disease or lichen albus, an aspect that complicates any literature survey. Lichen sclerosus in the genital area was first described in women by Breisky as kraurosis vulvae[32] and 40 years later in men by Stühmer as balanitis xerotica obliterans[33]. Today, lichen sclerosus, the term proposed by the International Society for the Study of Vulvar Disease, is most frequently used[34,35].

EPIDEMIOLOGY

Lichen sclerosus is relatively uncommon, although the exact prevalence is unknown. It occurs at all ages and seems to have a similar incidence in all races; the reported female-to male-ratio varies widely, depending upon the study, from 10:1 to 1:1[34,35].

In both sexes, the anogenital area is affected in at least 85% of patients. However, the best epidemiologic studies concentrate on vulvar disease. Since lichen sclerosus of non-genital skin frequently causes no symptoms, it is likely that the prevalence of extragenital lichen sclerosus is underestimated.

Prospective and retrospective studies in adult patients suggest that lichen sclerosus is one of the most common causes of symptomatic vulvar disease. In two large series, lichen sclerosus was diagnosed in 13% to 19% of patients[36] presenting with symptomatic vulvar disease. In women, the peak incidence is during the fifth and sixth decades, and a second peak occurs in girls between 8 and 13 years of age. Among prepubertal girls with vulvar disease, the relative frequency of lichen sclerosus is similar to that in adults. Extragenital lichen sclerosus is rare in children. In boys and men, lichen sclerosus frequently leads to phimosis (seen in 14 of 100 prepubertal boys undergoing circumcision for phimosis). Of 357 male patients attending a dermatology clinic with genital skin disease, 14% had lichen sclerosus[37].

PATHOGENESIS

As in most inflammatory diseases, genetic predisposition contributes to the development of lichen sclerosus, as it may be found in monozygotic and fraternal twins. In addition, association with the MHC class II antigen HLA-DQ7 was observed in a relatively large study[38]. The existence of a susceptibility gene for sclerosis within this region of the MHC is underlined by the finding that the same region is associated with an increased risk of autoimmune diseases. Even though inflammation seems essential for initiation and progression of lichen sclerosus, the mechanisms leading to subsequent sclerosis remain speculative.

Perhaps with the exception of autoantibodies against extracellular matrix protein 1 (ECM-1), no specific immunologic parameters have been identified in patients' sera that clearly correlate with either risk of disease or disease activity. IgG autoantibodies against ECM-1 are found in 80% of patients with lichen sclerosus and the latter may act as an autoantigen[39]. Oxidative stress may also play a role in the pathogenesis of lichen sclerosus, based upon analysis of lesional skin that showed lipid peroxidation of epidermal basal cell layers, oxidative DNA damage and oxidative protein damage.

CLINICAL FEATURES

Lichen sclerosus is a disease that can affect both extragenital skin and the anogenital region. Lichen sclerosus of the oral cavity, the palms or soles is rare. In the oral mucosa, bluish white papules up to 5 mm in diameter may occur on the buccal mucosa or under the tongue. They can lead to superficial scar-like atrophy or erosions.

Extragenital lichen sclerosus normally does not cause symptoms except for dryness and associated pruritus. Lesions favor the trunk (Fig. 44.12A) and the proximal extremities. More specific predilection sites include the neck (Fig. 44.12B), shoulders, flexor surfaces of the wrists, and sites of physical trauma or continuous pressure (e.g. the shoulder or hip). The periorbital area and scalp are rarely affected.

It is unusual to see extragenital disease during its early phases when single lesions begin as polygonal, bluish-white, shiny, slightly elevated, interfollicular papules. Over time, these papules often enlarge or coalesce into larger plaques. Most patients present with slightly sclerotic, scar-like papules and plaques that are usually ivory in color and have a shiny and/or wrinkled surface. Occasionally, lesions have a pink or light violet hue. At sites of continuous pressure, the surface may acquire a parchment-like appearance.

In more advanced stages, telangiectasias or follicular plugging can be seen (Fig. 44.13A). The flattened interface between the epidermis and dermis results in fragility of the dermal–epidermal junction; as a result, lichen sclerosus is occasionally complicated by the development of bullae that tend to become hemorrhagic (Fig. 44.13B).

In women, the vulva and the perianal region are commonly involved, often in a figure-of-eight configuration (see Ch. 73). Although the disease may be symptom-free, it frequently causes severe pruritus and soreness. These symptoms may be considerable and lead to dysuria, dyspareunia, or pain upon defecation (often manifesting as constipation in children). Lichen sclerosus often begins as a slightly elevated, sharply demarcated area of erythema, which can be slightly eroded (Fig. 44.14). Over time, the involved skin becomes shiny, hypopigmented and sclerotic, and fissures may develop. Associated scarring can lead to burying of the clitoris and fusion of the labia minora to the labia majora. With severe disease, loss of the labia minora and significant narrowing of the introitus can occur. Sexual intercourse may become impossible.

Areas of purpura often develop within lesions of anogenital lichen sclerosus and can even aid in clinical diagnosis. However, the hemorrhage combined with erosions may be misdiagnosed as sexual abuse. Careful examination, perhaps with confirmation of the diagnosis by histology, is mandatory. The two disorders can coexist and sexual abuse may (although rarely) trigger the onset of lichen sclerosus as a Koebner phenomenon. False accusations can be as problematic or traumatic to the child and family as overlooking sexual abuse.

In boys and men, acquired phimosis or recurrent balanitis are the primary presenting features, and perianal involvement is very rare. Itching and soreness are common. On the glans and the inner aspect of the foreskin, lichen sclerosus starts as sharply demarcated, sometimes slightly blue–red lesions, occasionally with erosions. This inflammation tends to evolve into an atrophic white sclerotic scar (Fig. 44.15). The constriction may cause pain on erection and, at advanced stages, dysuria and urinary obstruction. If the foreskin is affected,

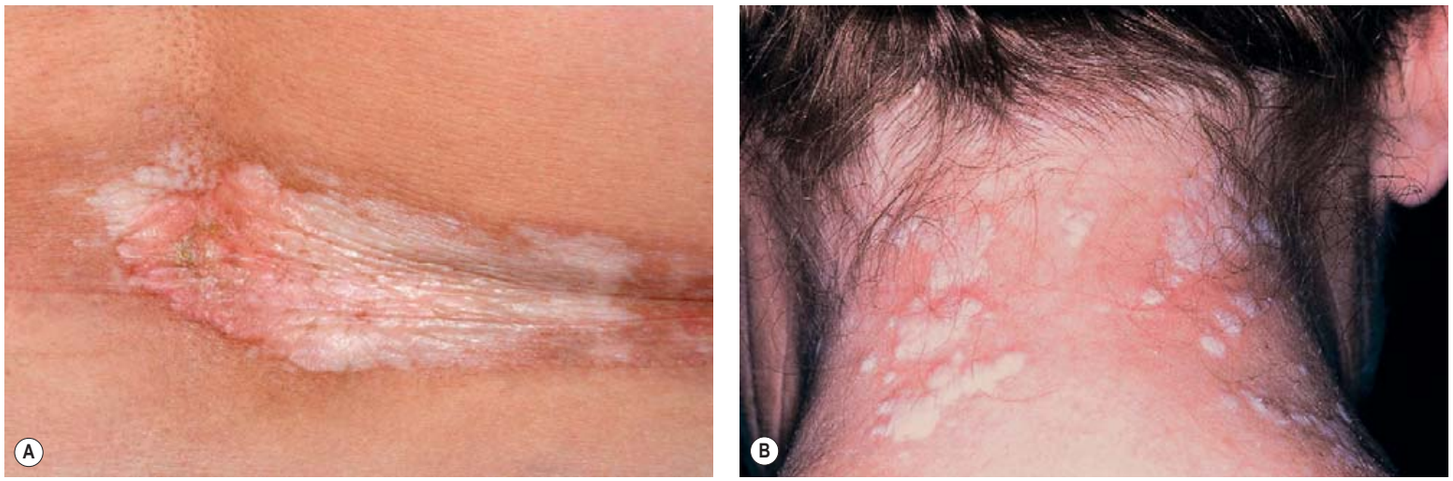


Fig. 44.12 Lichen sclerosus. A large shiny, ivory-colored plaque of the lower back (**A**) and white papules and small plaques on the neck (**B**).

Fig. 44.13 Lichen sclerosus. **A** Follicular plugging in a plaque of lichen sclerosus on the back of a patient with chronic GVHD. **B** Hemorrhagic bullae on the leg. *A, Courtesy, Jean L Bolognia, MD.*

Fig. 44.14 Vulvar lichen sclerosus. Centrally, there is erythema with superficial erosion and purpura. More peripherally, white plaques with a wrinkled surface are seen. Note fissuring of the perineum.

Fig. 44.15 Lichen sclerosus of the penis (balanitis xerotic obliterans). Note the ivory color, erosion and scarring.

lichen sclerosus invariably leads to phimosis (difficulty in retracting the foreskin to uncover the glans), with the additional risk of paraphimosis (when a foreskin retracted behind the glans can not be returned to its original position); the latter represents a urologic emergency. Many boys and men first present when the phimosis impairs repositioning of the foreskin; in these situations, diagnosis depends on histology. Progressive disease can be associated with poorly healing ulcers of the glans. While circumcision is clearly a first-line therapy, lichen sclerosus may recur at the site of a circumcision.

An open question is whether genital lichen sclerosus is a precancerous condition. Interpretation and comparison of the data are complicated by two factors: some of the patients reported as developing cancer had previously received X-ray therapy for the disease or had previous dysplasia due to human papillomavirus (HPV) infection. It is therefore very difficult to establish a useful meta-analysis. Most data suggest that lichen sclerosus is not intrinsically precancerous, but that it has to be considered as a chronic scar continuously exposed to a humid milieu, where carcinogenesis may be promoted[34,35].

PATHOLOGY

Lichen sclerosus has a specific histologic pattern. Initially, superficial dermal edema is associated with a band-like lymphocytic infiltrate (Fig. 44.16A). The epidermis is thinned, with orthohyperkeratosis and vacuolar degeneration of the basal layer. Hyperkeratosis is especially pronounced at follicular openings and may lead to plugging. The vacuolar degeneration at the dermal–epidermal interface and the flattening of the rete ridges predisposes to the development of blisters, which may become hemorrhagic. The most important changes are found in the superficial dermis, where the pale staining reflects homogenized dermal collagen (Fig. 44.16B) or edema (early stage). Loss of elastic fibers is typical for lichen sclerosus but is not observed in morphea. Clefting and hemorrhage within the homogenized papillary dermis is often seen.

During the early phases, the inflammatory infiltrate is especially pronounced along the zone of hyalinization and consists of lymphocytes ($CD3^+$, $CD4^+$, $CD8^+$), macrophages and mast cells. In older lesions, the mononuclear infiltrate is reduced and sparse, and patchy islands of mononuclear cells are dispersed within the hyalinized dermis. Ultrastructural studies reveal shortened collagen fibers.

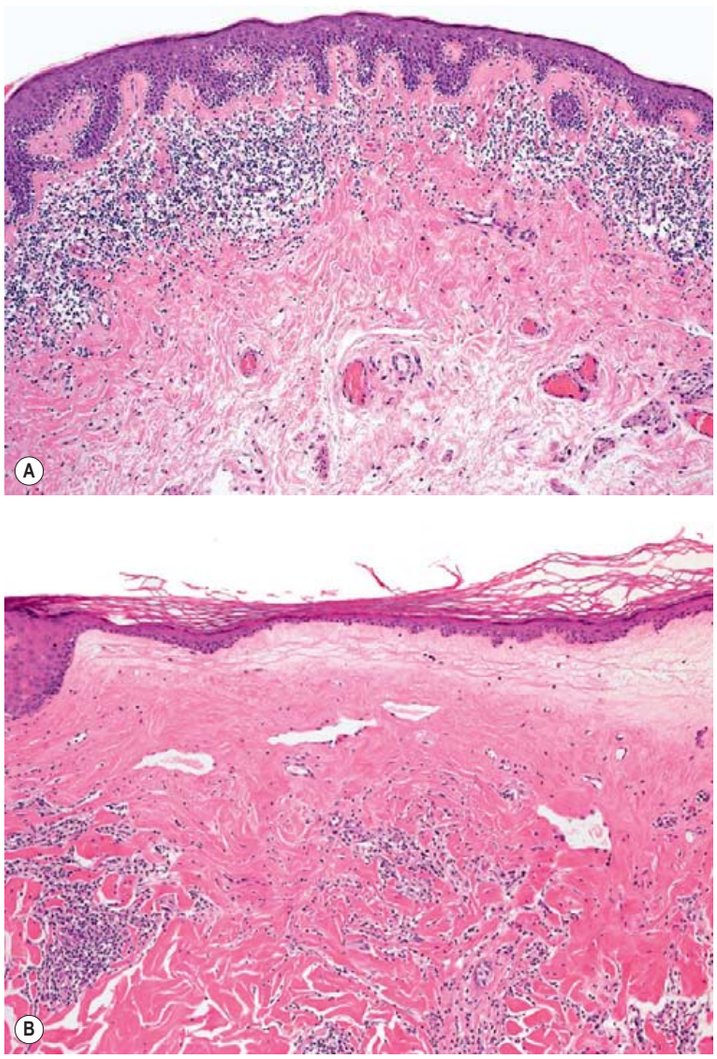


Fig. 44.16 Lichen sclerosus – histologic features. A Early lesion with band-like infiltrate of lymphocytes in the upper dermis and vacuolar change at the dermal–epidermal junction. Mild homogenization of the papillary dermis is present. **B** Late lesion with orthohyperkeratosis, thinning of the epidermis and homogenization of the upper dermis. There is also hyalinization and sclerosis of the papillary dermis, telangiectasias and an interstitial lymphocytic infiltrate. *Courtesy, Lorenzo Cerroni, MD.*

DIFFERENTIAL DIAGNOSIS

The most important entity in the differential diagnosis of extragenital lichen sclerosus is morphea, and for genital lichen sclerosus in girls and boys, it is sexual abuse[40]. In adults, genital lichen sclerosus may mimic erythroplasia of Queyrat or erosive lichen planus (see Ch. 73). Distinction often requires histologic examination. Biopsies may also be needed to exclude malignant transformation, especially when there is a superimposed infection with potentially carcinogenic HPV-16 or HPV-18. Histologically, lichen sclerosus-associated pseudoepitheliomatous hyperplasia has to be distinguished from squamous cell carcinoma (SCC). A past history of allogeneic hematopoietic stem cell transplant points to chronic GVHD.

TREATMENT OF MORPHEA AND LICHEN SCLEROSUS

Various therapeutic modalities have been reported for lichen sclerosus and morphea (Table 44.2). Most reports are based on single or limited observations or, occasionally, larger numbers of patients but without controls. Well-designed, randomized controlled trials are rare. Meta-analysis of the literature suggests that some treatments are well established and effective in a majority of patients while others seem to be effective in only a small number of patients. Well-established treatment options should not be confused with therapeutic suggestions based on a single observation or those that require more substantial investigation.

A major problem has been the lack of standardized outcome measures for assessing the efficacy of various therapies for morphea and lichen sclerosus. However, there has been a recent attempt to devise a reproducible severity index score for morphea[41]. In addition, 20 MHz ultrasound measurements of individual plaques (pre- and post-therapy) can prove helpful.

Phototherapies

Phototherapy for morphea was first described in 1994[42], and since then, the efficacy has been confirmed by more than 30 publications[43,44]. Due to the nature of phototherapy, placebo-controlled studies can not be performed. Nonetheless, little doubt exists as to the efficacy of this therapy, as untreated morphea normally progresses over 3–5 years and then regresses very slowly over years. More rapid spontaneous improvement only occurs in a small minority of patients[2]. The clinical course is definitely different in patients receiving either bath PUVA therapy or UVA1. If 30–36 treatments of bath PUVA therapy (at slightly suberythematous doses) or 30–36 treatments of UVA1 (30–60 J/cm^2) are given, morphea either completely resolves or markedly improves in at least 60% of patients[45] (Fig. 44.17). Further advantages of phototherapy, and especially UVA1, include clinical improvement in all skin types[46] and long periods of remission[47].

Both photochemotherapy and UVA1 induce expression of matrix metalloproteinase 1, a collagenase that reduces procollagen and collagen within the skin. The regression of morphea can be objectively documented by measuring skin thickness and skin density by 20 MHz ultrasound (Fig. 44.18) or by histology[44,48,49]. Both phototherapies seem

TREATMENT OF MORPHEA AND LICHEN SCLEROSUS					
	Treatment modalities	**Morphea**		**Lichen sclerosus**	
		Efficacy	**Level of evidence**	**Efficacy**	**Level of evidence**
Local	Topical corticosteroids	+	3	+++ (ultrapotent)	1
	Intralesional corticosteroids	+	3	++	2
	Topical calcineurin inhibitors	+ (early lesions)	2	++	2
	Vitamin A analogues	+	3	+	2
	Vitamin D analogues	+	3	+	3
	Testosterone	No experience		0	1
	Progesterone	No experience		0	1
	Intralesional interferon-γ	0	1	No experience	
Systemic	Penicillin	++ (approx. 5% of patients)	3	No experience	
	Hydroxy-/chloroquine	No experience		+	3
	Corticosteroids	+	3	+	3
	Vitamin A analogues*	+	3	++	1
	Vitamin D analogues	0	1	+	3
	Cyclosporine	0	3	No experience	
	Penicillamine	++	3	No experience	
	Methotrexate	++	2	No experience	
Phototherapy	Oral photochemotherapy	++	3	+	3
	Bath photochemotherapy	+++	2	++	3
	Cream photochemotherapy	++	3	+	3
	UVA1	+++	2	++	2
	Photodynamic therapy	+	3	++	3
	Extracorporeal photopheresis	+	3	No experience	
Others	CO_2 laser	No experience		++	3
	Surgery	Selected patients		Selected patients	
	Physical therapy	Important		–	–

*e.g. acetretin.

Table 44.2 Treatment of morphea and lichen sclerosus. +++, Highly effective; ++, effective; +, moderately effective; 0, low efficacy or ineffective. 1, prospective controlled trial; 2, retrospective study or large case series; 3, small case series or individual case reports.

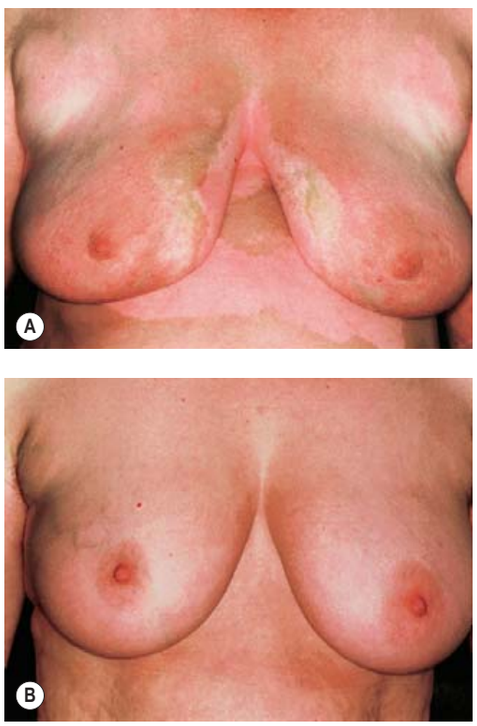


Fig. 44.17 Phototherapy of morphea. Disseminated morphea on the trunk before (**A**) and after PUVA bath photochemotherapy (**B**).

to be effective in all types of morphea except for morphea profunda. There is less experience with extensive linear or pansclerotic morphea, but these subtypes may also improve with either mode of phototherapy[50]. In the case of photochemotherapy, it has been administered primarily as bath PUVA therapy[16,51] (few reports exist on the use of cream PUVA or systemic PUVA[50]).

Another open question is the ideal dose for UVA1 therapy. Most initial studies were performed with either low (20 J/cm^2) or medium doses (30–70 J/cm^2) of UVA1 and reported similar efficacy. A recent study that utilized 20 MHz ultrasound rather than clinical assessment of morphea lesions reported a better response (after 30 treatments) with medium-dose (70 J/cm^2) than with low-dose (20 J/cm^2) UVA1[48]. In agreement with these reports, we have observed that 36 treatments with 30 J/cm^2 of UVA1 markedly improved morphea in the majority of patients[45]. Importantly, in responding patients, lesions of morphea continue to improve beyond the end of the therapy. Thus, therapy can be terminated after 36 treatments, even if the sclerosis has not yet completely resolved. The only exception appears to be linear morphea, which may require significantly more treatments. In our experience, selected patients who fail to respond to one mode of phototherapy may benefit from a switch to the other, i.e. if a patient does not improve within 4 months with one type of phototherapy (e.g. bath PUVA), a new therapy cycle should be initiated utilizing another mode of phototherapy (e.g. UVA1). Patients may also benefit from phototherapy plus low-dose systemic retinoids as this combination has led to improvement of sclerodermoid GVHD and plaque-type morphea[16,52].

Much less experience exists with regard to phototherapy for lichen sclerosus. Based upon observations in a small number of patients with extragenital lichen sclerosus, bath or cream PUVA therapy or UVA1 therapy may improve lesions in some selected patients; similar results have been reported for genital lichen sclerosus. For example, a preliminary study reported clinical improvement in 10 patients with extragenital lichen sclerosus following 40 treatments with low-dose UVA1 (20 J/cm^2)[53]. Based upon our experience with extragenital lichen sclerosus, phototherapy seems less effective than in morphea. More detailed studies are required and phototherapy may be an alternative for selected patients with extensive lichen sclerosus who respond poorly to topical corticosteroids and/or calcineurin inhibitors.

There are no consistent results from the use of extracorporeal photophoresis. The associated costs and the invasiveness are very high, and the efficacy of UVA1 or photochemotherapy clearly appears to be superior. Although preliminary data from a prospective study of

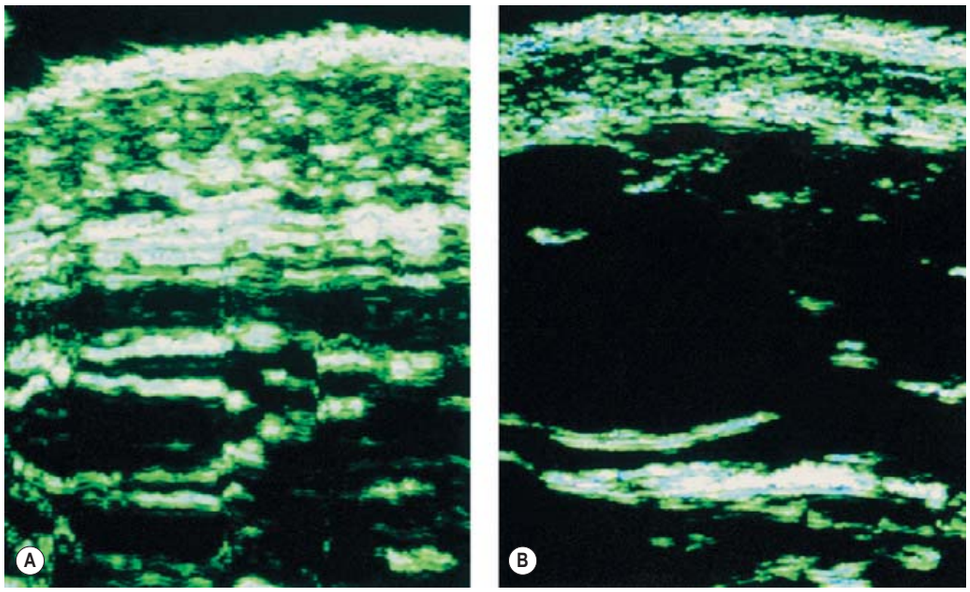


Fig. 44.18 High-frequency ultrasound (20 MHz) of a morphea plaque. Before (**A**) and after PUVA bath photochemotherapy (**B**), showing reduction of corium thickness and hyperechoic bands of connective tissue.

Fig. 44.19 Ultrapotent topical corticosteroids in the treatment of lichen sclerosus in a 12-year-old girl. Before (**A**) and after topical application of clobetasol propionate 0.05% cream daily for 5 months (**B**).

photodynamic therapy for vulvar lichen sclerosus pointed to significant relief of symptoms, similar results were not observed in more recent studies.

Topical Therapies

Corticosteroids

Retrospective and prospective studies have clearly documented that ultrapotent topical corticosteroids are highly effective in the treatment of genital lichen sclerosus. In the majority of these studies, clobetasol propionate 0.05% cream was applied for 12–24 weeks[54]. Clinical improvement was confirmed by histopathology. Both safety and efficacy of clobetasol in the treatment of genital lichen sclerosus were documented for all age groups and in both sexes. Nearly all the patients with vulvar lichen sclerosus responded to ultrapotent topical corticosteroids, and amongst those who improved, about 20% experienced complete clearance[55]. However, topical corticosteroids do not cure the disease and relapses may occur.

Major side effects were not reported, even with long-term and maintenance use of clobetasol. Therefore, potent topical corticosteroids represent first-line therapy for genital lichen sclerosus, including in children (Fig. 44.19). Alternatively, corticosteroids such as triamcinolone can be injected intralesionally. Of note, vulvar SCC appeared to develop primarily in untreated or irregularly treated lesions of vulvar lichen sclerosus.

The benefit of topical corticosteroids in the treatment of morphea is questionable. Ultrapotent topical corticosteroids may be useful for reducing inflammation in superficial active lesions. Similarly, intralesional injection of triamcinolone into the margins may reduce or prevent progression. Topical corticosteroids are ineffective in resolving sclerosis.

Calcineurin inhibitors

The macrolide immunosuppressants pimecrolimus (1% cream) and tacrolimus (0.1% ointment) have been used as topical treatments for vulvar lichen sclerosus. Several case reports and initial trials involving limited numbers of patients suggest that these therapies are effective[56]. Concerns have been raised as to the possibility of increasing the risk of developing SCC or reactivating HPV following the use of topical calcineurin inhibitors for vulvar lichen sclerosus. Long-term safety and efficacy studies as well as randomized trials comparing these agents with clobetasol are needed. With regard to morphea, improvement following topical tacrolimus (0.1% ointment) has been reported in case series, especially in patients with early inflammatory lesions[57,58]. Again, prospective, double-blind, randomized trials are needed.

Vitamin derivatives

Derivatives of vitamin D and vitamin A are still under study in morphea. *In vitro*, calcipotriol inhibits the proliferation of cultured fibroblasts and topical calcipotriene (0.005% ointment) has been used for the treatment of morphea[59]. Single reports have described improvement of both vulvar lichen sclerosus and morphea when treated with topical vitamin A derivatives. All of these observations require confirmation by controlled studies.

Hormones

For years, topical testosterone or progesterone preparations were frequently used for the treatment of genital lichen sclerosus. In sharp contrast to ultrapotent topical corticosteroids, there is no evidence to support the efficacy of these agents. Controlled clinical studies have clearly shown that hormone preparations have no clinical benefit in lichen sclerosus[60]. In one study, 2% testosterone propionate was even less effective than petrolatum ointment[61].

Systemic Treatments

Immunosuppression

Oral corticosteroids (methylprednisolone or prednisone 1–2 mg/kg/day) may be helpful during the inflammatory stages of morphea, especially in those patients with rapidly progressive linear or disabling morphea. However, systemic corticosteroids do not improve established sclerosis and disease activity may rebound following discontinuation.

Alternatively, 15–20 mg/week of methotrexate seems to be helpful in the acute phase of morphea[62]. Based on experience with other autoimmune diseases, some authors favor the combination of methotrexate plus corticosteroids, especially in rapidly progressive disabling types of morphea[63]. Clinical data from a prospective pilot study confirmed the therapeutic effectiveness of methotrexate (15 mg/week) combined with pulsed high-dose intravenous methylprednisolone (1 g 3 days per month)[64]. Placebo-controlled studies are still lacking, but the potential benefit documented in systemic sclerosis suggests that this mode of immunosuppression, administered for several months to up to 1 year, may be indicated in selected patients with disabling morphea.

In contrast, cyclosporine has not been shown to be effective. Furthermore, cyclosporine should not be combined with any form of phototherapy.

Although systemic immunosuppression is normally not indicated for lichen sclerosus, there is a subset of patients with recalcitrant generalized disease. In a small series of such patients, a combination of pulsed high-dose intravenous corticosteroids plus low-dose oral methotrexate led to improvement[65].

Penicillin and its derivatives

Regression of morphea or systemic sclerosis during prolonged treatment with penicillin or penicillamine has been observed in adults and in children[66]. Penicillin in the range of 30×10^6 IU/day for 3–4 weeks is helpful in about 5% of patients, as documented by several authors. In addition, the response is reproducible in those individuals who relapse following previously successful penicillin regimens. Penicillamine seems to be similarly effective but is used less often because of its potential side effects.

In lichen sclerosus, neither penicillin nor other antibiotics nor penicillamine are helpful.

Vitamin derivatives

Treatment with the oral vitamin A derivatives etretinate or acitretin at doses of 10–50 mg/day is effective in morphea and lichen sclerosus[67,68]. Importantly, the response can only be assessed after several months of therapy. The exact mechanism by which retinoids improve sclerosis is unclear. However, in cultured scleroderma fibroblasts, retinoids can induce COX-2 and PGE_2 while inhibiting the profibrotic factor CTGF and collagen production (types I and III)[69]. Moreover, retinoids interact with TGF-β signaling, one of the key cytokine pathways for promoting collagen synthesis by fibroblasts (see Fig. 44.1). Retinoids (e.g. etretinate, isotretinoin) are also effective in certain pseudoscleroderma disorders such as "sclerodermoid" GVHD[15,16].

The other vitamin derivative investigated for the treatment of morphea is calcitriol. 1,25-Dihydroxyvitamin D_3 has pronounced anti-inflammatory effects, and it modulates fibroblast growth as well as TGF-β[70]. Despite promising case reports, a double-blind, placebo-controlled study did not confirm the clinical efficacy of oral calcitriol in morphea[71].

Cytokines, TNF-α inhibitors, multi-kinase inhibitors

As IFN-γ and IFN-α normalize pathogenic collagen production by fibroblasts *in vitro*, both cytokines have been tested for the treatment of morphea. However, in controlled studies, neither cytokine reversed cutaneous sclerosis[17]. Whether TNF-α has a pathogenic role in morphea and systemic sclerosis is unclear. In a pilot study of patients with systemic sclerosis, infliximab did not improve skin sclerosis[72].

The signaling pathways of growth factors such as TGF-β and PDGF, which play a role in generating cutaneous sclerosis, represent potential therapeutic targets. Imatinib is an example of a multi-kinase inhibitor that can inhibit the PDGF receptor (hence its effect on dermatofibrosarcoma protuberans). In case series, systemic administration of imatinib reduced skin sclerosis in patients with systemic sclerosis[22,73].

Surgery

In the case of persistent contractures, reconstructive surgery may be needed. Similarly, surgical revision may be required in linear or *en coup de sabre* morphea. Autologous fat transplantation has been used successfully for the latter as well as for Parry–Romberg syndrome.

Circumcision is the treatment of choice for genital lichen sclerosus complicated by phimosis or paraphimosis.

Physical Therapy

Expert and longstanding physiotherapy is obligatory for patients in whom morphea threatens to impair mobility.

REFERENCES

1. Kroft EB, de Jong EM, Evers AW. Psychological distress in patients with morphea and eosinophilic fasciitis. Arch Dermatol. 2009;145:1017–22.
2. Mayes MD. Classification and epidemiology of scleroderma. Semin Cutan Med Surg. 1998;17:22–6.
3. Addison T. On the keloid of Alibert, and on true keloid. Med Chirurg Trans. 1854;37:27.
4. O'Leary PA, Nomland R. A clinical study of one hundred and three cases of scleroderma. Am J Med Sci. 1930;180:95.
5. Peterson LS, Nelson AM, Su WP, et al. The epidemiology of morphea (localized scleroderma) in Olmsted County 1960–1993. J Rheumatol. 1997;24:73–80.
6. Abraham DJ, Varga J. Scleroderma: from cell and molecular mechanisms to disease models. Trends Immunol. 2005;26:587–95.
7. Leroy EC. Connective tissue synthesis by scleroderma skin fibroblasts in cell culture. J Exp Med. 1972;135:1351–62.
8. Röcken M, Racke M, Shevach EM. IL-4-induced immune deviation as antigen-specific therapy for inflammatory autoimmune disease. Immunol Today. 1996;17:225–31.
9. Rueda B, Broen J, Simeon C, et al. The STAT4 gene influences the genetic predisposition to systemic sclerosis phenotype. Hum Mol Genet. 2009;18:2071–7.
10. Dieudé P, Guedj M, Wipff J, et al. STAT4 is a genetic risk factor for systemic sclerosis having additive effects with IRF5 on disease susceptibility and related pulmonary fibrosis. Arthritis Rheum. 2009;60:2472–9.
11. Ghoreschi K, Thomas P, Breit S, et al. Interleukin-4 therapy of psoriasis induces Th2 responses and improves human autoimmune disease. Nat Med. 2003;9:40–6.
12. Salmon-Ehr V, Serpier H, Nawrocki B, et al. Expression of interleukin-4 in scleroderma skin specimens and scleroderma fibroblast cultures. Potential role in fibrosis. Arch Dermatol. 1996;132:802–6.
13. Rankin AL, Mumm JB, Murphy E, et al. IL-33 induces IL-13-dependent cutaneous fibrosis. J Immunol. 2010;184:1526–35.
14. Ong C, Wong C, Roberts CR, et al. Anti-IL-4 treatment prevents dermal collagen deposition in the tight-skin mouse model of scleroderma. Eur J Immunol. 1998;28:2619–29.
15. Marcellus DC, Altomonte VL, Farmer ER, et al. Etretinate therapy for refractory sclerodermatous chronic graft-versus-host disease. Blood. 1999;93:66–70.
16. Ghoreschi K, Thomas P, Penovici M, et al. PUVA-bath photochemotherapy and isotretinoin in sclerodermatous graft-versus-host disease. Eur J Dermatol. 2008;18:667–70.
17. Hunzelmann N, Anders S, Fierlbeck G, et al. Double-blind, placebo-controlled study of intralesional interferon gamma for the treatment of localized scleroderma. J Am Acad Dermatol. 1997;36:433–5.
18. Ihn H, Yamane K, Tamaki K. Increased phosphorylation and activation of mitogen-activated protein kinase p38 in scleroderma fibroblasts. J Invest Dermatol. 2005;125:247–55.
19. Svegliati S, Cancello R, Sambo P, et al. Platelet-derived growth factor and reactive oxygen species (ROS) regulate Ras protein levels in primary human fibroblasts via ERK1/2: amplification of ROS and Ras in systemic sclerosis fibroblasts. J Biol Chem. 2005;280:36474–82.
20. Servettaz A, Goulvestre C, Kavian N, et al. Selective oxidation of DNA topoisomerase 1 induces systemic sclerosis in the mouse. J Immunol. 2009;182:5855–64.

21. McGaha T, Saito S, Phelps RG, et al. Lack of skin fibrosis in tight skin (TSK) mice with targeted mutation in the interleukin-4R alpha and transforming growth factor-beta genes. J Invest Dermatol. 2001;116:136–43.
22. Akhmetshina A, Venalis P, Dees C, et al. Treatment with imatinib prevents fibrosis in different preclinical models of systemic sclerosis and induces regression of established fibrosis. Arthritis Rheum. 2009;60:219–24.
23. Loeys BL, Gerber EE, Riegert-Johnson D, et al. Mutations in fibrillin-1 cause congenital scleroderma: stiff skin syndrome. Sci Transl Med. 2010;2:1–10.
24. Fonseca C, Lindahl GE, Ponticos M, et al. A polymorphism in the CTGF promotor region associated with systemic sclerosis. N Engl J Med. 2007;357:1210–20.
25. Weide B, Schittek B, Klyscz T, et al. Morphoea is neither associated with features of *Borrelia burgdorferi* infection, nor is this agent detectable in lesional skin by polymerase chain reaction. Br J Dermatol. 2000;143:780–5.
26. Zulian F, Vallongo C, Woo P, et al. Localized scleroderma in childhood is not just a skin disease. Arthritis Rheum. 2005;52:2873–81.
27. Zulian F, Athreya BH, Laxer R, et al. Juvenile localized scleroderma: clinical and epidemiological features in 750 children. An international study. Rheumatology (Oxford). 2006;45:614–20.
28. Janowsky EC, Kupper LL, Hulka BS. Meta-analyses of the relation between silicone breast implants and the risk of connective-tissue diseases. N Engl J Med. 2000;342:781–90.
29. Unna PG. Karenblattförmige Sklerodermie. Lehrbuch der speziellen path Anatomie. Berlin: A Hirschwald, 1894:112.
30. Westberg F. Ein Fall mit weissen Flecken einhergehender, bisher nicht bekannter Dermatose. Monatschr Prakt Dermatol. 1901;33:355.
31. von Zumbusch LR. Über lichen albus, eine bisher unbeschriebene Erkrankung. Arch Dermatol Syph. 1906;82:339.
32. Breisky A. Über kraurosis vulvae. Z Heilkd. 1885;6:69–80.
33. Stühmer A. Balanitis xerotica obliterans (post operationem) und ihre Beziehungen zur Kraurosis glandis et praeputii penis. Arch Derm Syph. 1928;156:613.
34. Meffert JJ, Davis BM, Grimwood RE. Lichen sclerosus. J Am Acad Dermatol. 1995;32:393–416.
35. Powell JJ, Wojnarowska F. Lichen sclerosus. Lancet. 1999;353:1777–83.
36. Heller DS, Randolph P, Young A, et al. The cutaneous-vulvar clinic revisited: a 5-year experience of the Columbia Presbyterian Medical Center Cutaneous-Vulvar Service. Dermatology. 1997;195:26–9.
37. Mallon E, Hawkins D, Dinneen M, et al. Circumcision and genital dermatoses. Arch Dermatol. 2000;136:350–4.
38. Marren P, Yell J, Charnock FM, et al. The association between lichen sclerosus and antigens of the HLA system. Br J Dermatol. 1995;132:197–203.
39. Oyama N, Chan I, Neill SM, et al. Autoantibodies to extracellular matrix protein 1 in lichen sclerosus. Lancet. 2003;362:118–23.
40. Powell J, Wojnarowska F. Childhood vulval lichen sclerosus and sexual abuse are not mutually exclusive diagnoses. BMJ. 2000;320:311.
41. Arkachaisri T, Vilaiyuk S, Torok KS, et al. Development and initial validation of the localized scleroderma skin damage index physician global assessment of disease damage: a proof-of-concept study. Rheumatology (Oxford). 2010;49:373–81.
42. Kerscher M, Volkenandt M, Meurer M, et al. Treatment of localised scleroderma with PUVA bath photochemotherapy. Lancet. 1994;343:1233.
43. Kerscher M, Dirschka T, Volkenandt M. Treatment of localised scleroderma by UVA1 phototherapy. Lancet. 1995;346:1166.
44. Kerscher M, Meurer M, Sander C, et al. PUVA bath photochemotherapy for localized scleroderma. Evaluation of 17 consecutive patients. Arch Dermatol. 1996;132:1280–2.
45. Ghoreschi K, Rocken M. Phototherapy of sclerosing skin diseases. Dermatology. 2002;205:219–20.
46. Jacobe HT, Cayce R, Nguyen J. UVA1 phototherapy is effective in darker skin: a review of 101 patients of Fitzpatrick skin types I-V. Br J Dermatol. 2008;159: 691–6.
47. Kroft EB, van de Kerkhof PC, Gerritsen MJ, et al. Period of remission after treatment with UVA-1 in sclerodermic skin diseases. J Eur Acad Dermatol Venereol. 2008;22:839–44.
48. Sator PG, Radakovic S, Schulmeister K, et al. Medium-dose is more effective than low-dose ultraviolet A1 phototherapy for localized scleroderma as shown by 20-MHz ultrasound assessment. J Am Acad Dermatol. 2009;60:786–91.
49. Gruss C, Reed JA, Altmeyer P, et al. Induction of interstitial collagenase (MMP-1) by UVA-1 phototherapy in morphea fibroblasts. Lancet. 1997;350:1295–6.
50. Scharffetter-Kochanek K, Goldermann R, Lehmann P, et al. PUVA therapy in disabling pansclerotic morphoea of children. Br J Dermatol. 1995;132:830–1.
51. Lüftl M, Degitz K, Plewig G, Röcken M. Psoralen bath plus UV-A therapy. Possibilities and limitations. Arch Dermatol. 1997;133:1597–603.
52. Ozdemir M, Engin B, Toy H, Mevlitoglu I. Treatment of plaque-type localized scleroderma with retinoic acid and ultraviolet A plus the photosensitizer psoralen: a case series. J Eur Acad Dermatol Venereol. 2008;22:519–21.
53. Kreuter A, Gambichler T, Avermaete A, et al. Low-dose ultraviolet Al phototherapy for extragenital lichen sclerosus: results of a preliminary study. J Am Acad Dermatol. 2002;46:251–5.
54. Lorenz B, Kaufman RH, Kutzner SK Lichen sclerosus. Therapy with clobetasol propionate. J Reprod Med. 1998;43:790–4.
55. Cooper SM, Gao XH, Powell JJ, Wojnarowska F. Does treatment of vulvar lichen sclerosus influence its prognosis? Arch Dermatol. 2004;140:702–6.
56. Hengge UR, Krause W, Hofmann H, et al. Multicentre, phase II trial on the safety and efficacy of topical tacrolimus ointment for the treatment of lichen sclerosus. Br J Dermatol. 2006;155:1021–8.
57. Stefanaki C, Stefanaki K, Kontochristopoulos G, et al. Topical tacrolimus 0.1% ointment in the treatment of localized scleroderma. An open label clinical and histological study. J Dermatol. 2008;35: 712–18.
58. Kroft EB, Groeneveld TJ, Seyger MM, et al. Efficacy of topical tacrolimus 0.1% in active plaque morphea: randomized, double-blind, emollient-controlled pilot study. Am J Clin Dermatol. 2009;10:181–7.
59. Cunningham BB, Landells ID, Langman C, et al. Topical calcipotriene for morphea/linear scleroderma. J Am Acad Dermatol. 1998;39:211–15.
60. Cattaneo A, De Marco A, Sonni L, et al. Clobetasol vs. testosterone in the treatment of lichen sclerosus of the vulvar region. Minerva Ginecol. 1992;44:567–71.
61. Sideri M, Origoni M, Spinaci L, Ferrari A. Topical testosterone in the treatment of vulvar lichen sclerosus. Int J Gynaecol Obstet. 1994;46:53–6.
62. Seyger MM, van den Hoogen FH, van Vlijmen-Willems IM, et al. Localized and systemic scleroderma show different histological responses to methotrexate therapy. J Pathol. 2001;193:511–16.
63. Uziel Y, Feldman BM, Krafchik BR, et al. Methotrexate and corticosteroid therapy for pediatric localized scleroderma. J Pediatr. 2000;136:91–5.
64. Kreuter A, Gambichler T, Breuckmann F, et al. Pulsed high-dose corticosteroids combined with low-dose methotrexate in severe localized scleroderma. Arch Dermatol. 2005;141:847–52.
65. Kreuter A, Tigges C, Gaifullina R, et al. Pulsed high-dose corticosteroids combined with low-dose methotrexate treatment in patients with refractory generalized extragenital lichen sclerosus. Arch Dermatol. 2009;145:1303–8.
66. Falanga V, Medsger TA Jr. D-penicillamine in the treatment of localized scleroderma. Arch Dermatol. 1990;126:609–12.
67. Samsonov VA, Gareginian SA. Tigazon in the therapy of patients with circumscribed scleroderma. Vestn Dermatol Venerol. 1990;11:17–20.
68. Bousema MT, Romppanen U, Geiger JM, et al. Acitretin in the treatment of severe lichen sclerosus et atrophicus of the vulva: a double-blind, placebo-controlled study. J Am Acad Dermatol. 1994;30:225–31.
69. Xiao R, Kanekura T, Yoshida N, et al. 9-Cis-retinoic acid exhibits antifibrotic activity via the induction of cyclooxygenase-2 expression and prostaglandin E2 production in scleroderma fibroblasts. Clin Exp Dermatol. 2008;33:484–90.
70. Oyama N, Iwatsuki K, Satoh M, et al. Dermal fibroblasts are one of the therapeutic targets for topical application of 1 alpha, 25-dihydroxyvitamin D3: the possible involvement of transforming growth factor-beta induction. Br J Dermatol. 2000;143:1140–8.
71. Hulshof MM, Bouwes Bavinck JN, Bergman W, et al. Double-blind, placebo-controlled study of oral calcitriol for the treatment of localized and systemic scleroderma. J Am Acad Dermatol. 2000;43:1017–23.
72. Denton CP, Engelhart M, Tvede N, et al. An open-label pilot study of infliximab therapy in diffuse cutaneous systemic sclerosis. Ann Rheum Dis. 2009;68: 1433–9.
73. Chung L, Fiorentino DF, Benbarak MJ, et al. Molecular framework for response to imatinib mesylate in systemic sclerosis. Arthritis Rheum. 2009;60:584–91.

Other Rheumatologic Diseases 45

Jennie T Clarke

Chapter Contents

Systemic-onset juvenile idiopathic arthritis (Still's disease) 671
Adult-onset Still's disease 672
Relapsing polychondritis 675
Sjögren's syndrome 677
Mixed connective tissue disease 679
Extra-articular manifestations of rheumatoid arthritis 680
Interstitial granulomatous dermatitis and palisaded neutrophilic and granulomatous dermatitis 683

SYSTEMIC-ONSET JUVENILE IDIOPATHIC ARTHRITIS (STILL'S DISEASE)

Synonyms: ■ Juvenile idiopathic arthritis: juvenile rheumatoid arthritis (JRA); juvenile chronic arthritis

Key features

- There are several types of juvenile idiopathic arthritis, including systemic-onset, polyarticular (either rheumatoid factor [RF]-positive or RF-negative) and oligoarticular
- Systemic-onset juvenile idiopathic arthritis, also known as Still's disease, is characterized by high spiking fevers, lymphadenopathy, hepatosplenomegaly, transient cutaneous eruptions of erythematous macules and papules (often accompanying the fevers and associated with Koebner phenomena), and arthritis

Introduction

Juvenile idiopathic arthritis (JIA) is classified into seven major types (Table 45.1)[1], including systemic-onset, rheumatoid factor (RF)-positive polyarticular, RF-negative polyarticular, and oligoarticular. Systemic-onset JIA (SoJIA), also known as Still's disease, is characterized by an evanescent, erythematous eruption that typically accompanies spiking fevers. Cutaneous manifestations are less common in the other types, although the RF-positive subgroup of polyarticular JIA can present with rheumatoid nodules and other skin findings similar to those of adult rheumatoid arthritis (see below), and nearly all patients with psoriatic arthritis have cutaneous and/or nail psoriasis (see Ch. 8).

History

In 1897, George Still, an English pediatrician, first described a chronic arthritis in children that was associated with fever, lymphadenopathy and organomegaly.

Epidemiology

JIA is the most common rheumatic disease in childhood, and its overall prevalence is estimated to be 0.2–1 per 1000 children (by definition ≤16 years of age)[2]. SoJIA comprises 15–20% of all cases of JIA and can occur at any time from infancy through adolescence, with a mean age at onset of 6 years. Whereas most other types of JIA have a female predominance, SoJIA affects both sexes equally.

Pathogenesis

Recent insight into the pathogenesis of SoJIA suggests that it is better classified as an autoinflammatory rather than an autoimmune disease. The inflammation characteristic of this disease appears to result from activation of *innate* immune responses rather than adaptive phenomena characterized by antigen-specific, lymphocyte-driven immune responses. Dysregulated production of interleukin (IL)-1 appears to play a critical role in the pathogenesis of SoJIA. When peripheral blood mononuclear cells (PBMCs) from healthy individuals are exposed to sera from patients with SoJIA, there is upregulation of gene expression for the innate inflammatory cytokines IL-1α and IL-1β (as well as upregulation of other innate immunity genes)[3]. The PBMCs of SoJIA patients produce an excess of IL-1β upon activation, and administration of IL-1 receptor antagonists (e.g. anakinra, rilonacept) can reduce disease activity (see below). The dysregulated IL-1 production may be due to inflammasome activation[4] (Fig. 45.1) and/or dysregulation of the alternative secretory pathway downstream of caspase-1 that is responsible for the production of the calcium-binding proteins S100A8, S100A9 and S100A12; the latter are secreted during activation of neutrophils and monocytes[5]. Patients with SoJIA have exceptionally high serum levels of S100A8, S100A9 and S100A12, and these proteins do exhibit proinflammatory effects on endothelial cells and leukocytes.

At the onset and during flares of SoJIA, vascular endothelial cells express leukocyte adhesion molecules, leading to a perivascular infiltrate of neutrophils and activated monocytes that secrete proinflammatory cytokines including tumor necrosis factor-α (TNF-α), IL-1 and IL-6[5]. Many of the clinical features of SoJIA can be explained by the effects of these cytokines. For example, IL-1 stimulates granulopoiesis in the bone marrow and activates thermoregulatory functions of the hypothalamus to cause fever. The chronic overexpression of IL-6 observed in SoJIA increases osteoclastogenesis and reduces osteoblast activity. IL-6 also stimulates hepatocytes and induces the production of acute phase reactants such as C-reactive protein.

Clinical Features

Daily high fevers (usually above 38.9°C) that typically occur in the late afternoon or early evening are characteristic of SoJIA. The arthritis is frequently polyarticular, and the joints most commonly affected are the knees, ankles and hips, followed by the small joints of the hands. A subgroup of patients may develop destructive joint disease similar to that seen in RF-positive polyarticular arthritis (see Table 45.1).

An exanthem is present in up to 90% of patients with the acute febrile presentation of SoJIA[6], and it is often preceded or accompanied by arthralgias. Although arthritis usually develops during the first few months of the disease course, in approximately one-quarter of patients the exanthem begins prior to the onset of arthritis, occasionally predating joint involvement by several years. The eruption is typically transient, non-pruritic and erythematous, and it coincides with fevers (Fig. 45.2). There is a predilection for the axillae and waist, and linear lesions secondary to the Koebner phenomenon are often observed. Other less common cutaneous features include persistent plaques (which also may be linear) and periorbital edema and erythema[7]. Rheumatoid nodule-like lesions that favor extensor surfaces have been described in the setting of methotrexate therapy for SoJIA[8]. Additional systemic features of SoJIA are outlined in Table 45.1. Although there are no laboratory findings specific for SoJIA, leukocytosis, granulocytosis, thrombocytosis, elevated hepatic enzymes, an elevated ESR, extremely high serum

CLASSIFICATION OF JUVENILE IDIOPATHIC ARTHRITIS	
Systemic onset (20%) (Still's disease)	**Features required for diagnosis** • High episodic fevers – daily for ≥2 weeks and documented to be quotidian for ≥3 days • At least one of the following: *evanescent eruption*, generalized lymphadenopathy, hepatomegaly or splenomegaly, serositis • Symmetric polyarthritis > oligoarthritis (erosive in 20%)* ***Other features*** • Leukocytosis with neutrophilia, anemia (often severe), thrombocytosis, elevated ESR, elevated ferritin and C-reactive protein levels • Occasionally myocarditis, pneumonitis, anterior uveitis (<1%), CNS involvement, macrophage activation syndrome (6–13%); rarely amyloidosis • RF- and ANA- negative in >95% of patients
RF-negative polyarthritis (5%)	• 3–9 years of age • ≥5 joints in the first 6 months • Small joints of the hands & feet > knees, wrists, ankles; erosive arthritis (15%) • RF-negative; ANA-negative
RF-positive polyarthritis (15%)	• 10–16 years of age • ≥5 joints in the first 6 months • Small joints of the hands & feet > knees, wrists, ankles; erosive arthritis (>50%) • *Rheumatoid nodules*, low-grade fever, mild anemia, weight loss • RF-positive (100%); ANA-positive (70%)
Oligo/pauciarticular arthritis (60%): • type I – 50% • type II – 10%	• ≤4 joints in the first 6 months† • Knees > ankles, wrists; often asymmetric • Type I: 1–8 years of age; uveitis 30–50%; ANA-positive 60%; RF-negative • Type II: 9–16 years of age; HLA-B27; RF-negative; ANA-negative
Enthesitis-related arthritis	• Arthritis *and* enthesitis - or - • Arthritis *or* enthesitis plus ≥2 of the following: sacroiliac joint tenderness/spinal pain, HLA-B27, family history of HLA-B27-associated disease in first- or second-degree relative, anterior uveitis, onset of arthritis in a boy after age 8 years
Psoriatic arthritis	• Arthritis and *psoriasis* - or - • Arthritis and ≥2 of the following: dactylitis, *nail abnormalities* (see Ch. 71), family history of psoriasis in ≥1 first-degree relative • Other features: anterior uveitis, ANA-negative
Other arthritis	• Children with arthritis of unknown cause persisting ≥6 weeks that does not fulfill criteria for any other categories or fulfills criteria for more than one category

*Onset may be delayed for months to years.
†The persistent oligoarthritis subtype never affects more than 4 joints, whereas the extended oligoarthritis subtype affects a cumulative total of ≥5 joints after the first 6 months of disease.

Table 45.1 Classification of juvenile idiopathic arthritis. The previous term was juvenile rheumatoid arthritis. Enthesitis is inflammation at the site of insertion of muscles. For all the types, diagnosis requires onset before 16 years of age and duration of arthritis for ≥6 weeks in at least one joint. ANA, antinuclear antibody; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor.

ferritin levels, and a polyclonal gammopathy are commonly observed; ANA and RF are rarely present.

Pathology

Histologic features of the transient exanthem include edema of the superficial dermis and a mild mixed perivascular infiltrate (including neutrophils), but leukocytoclastic vasculitis is not seen. Persistent plaques are characterized by parakeratosis, necrotic keratinocytes within the epidermis, and a dermal infiltrate similar to that of the evanescent eruption.

Differential Diagnosis

The differential diagnosis of a transient exanthem associated with fever and arthritis includes rheumatic fever, urticarial vasculitis, and periodic fever syndromes (Table 45.2). The characteristic cutaneous findings in rheumatic fever are erythema marginatum (see Ch. 19) and urticarial lesions; rheumatic fever nodules are unusual. Patients with urticarial vasculitis may have arthralgias and fever; however, the urticarial lesions persist for greater than 24 hours, and they often resolve with purpura or postinflammatory hyperpigmentation. Histologic examination of recent-onset lesions demonstrates leukocytoclastic vasculitis.

Additional disorders to consider include other autoimmune connective tissue diseases, leukemia (which may present with fevers and musculoskeletal complaints prior to the development of diagnostic abnormalities in the peripheral blood), and infections such as parvovirus B19 and malaria.

Treatment

The course and prognosis of SoJIA is variable. In approximately 40–50% of patients, the arthritis resolves completely. However, approximately one-half of the children may have a chronic course that includes persistent arthritis and systemic complications such as macrophage activation syndrome (non-remitting fevers, leukopenia, thrombocytopenia), hepatitis, pericarditis and rarely amyloidosis (see Table 45.1)[9]. Patients with symptoms that persist for longer than 6 months carry a worse prognosis[9].

Mild articular or extra-articular disease can be treated with nonsteroidal anti-inflammatory drugs (NSAIDs) with or without hydroxychloroquine. Moderate or severe disease often requires the use of systemic corticosteroids with or without adjuvant drugs such as methotrexate. Inhibitors of TNF-α have been increasingly used as adjuvant or monotherapy; however, these agents are less effective in patients with SoJIA than in those with other types of JIA[10]. Potent corticosteroid-sparing or immunomodulating agents, such as abetacept, azathioprine and leflunomide, are required infrequently[10]. Thalidomide is also a therapeutic option for children with SoJIA. It suppresses the activity of cytokines (e.g. TNF-α and IL-6) that have been shown to play a role in the fever and malaise associated with SoJIA. Trials of biologic agents that are antagonists of the IL-1 receptor (e.g. anakinra, rilonacept, canakinumab) or the IL-6 receptor (e.g. tocilizumab) have demonstrated promising results in patients with SoJIA, and they will likely figure prominently in the treatment of refractory disease[10]. Hematopoietic stem cell transplantation has been successfully performed in children who have failed to respond to combinations of medications[10].

ADULT-ONSET STILL'S DISEASE

Synonyms:
- Still's disease in the adult
- Adult Still's disease

Key features

- A characteristic feature is recurrent episodes of high spiking fevers that often occur in the late afternoon
- An asymptomatic macular exanthem accompanies the fevers, is salmon-pink in color, and frequently demonstrates the Koebner phenomenon
- Arthritis with subsequent carpal ankylosis is a distinctive feature

Introduction

Adult-onset Still's disease can be a severe debilitating systemic illness that is often difficult to diagnose. The vast majority of these patients have an exanthem, and this can be the most distinctive sign of the disorder.

Epidemiology

Adult-onset Still's disease primarily affects young adults, with an onset before the age of 30 years in the majority of patients. Rarely it occurs

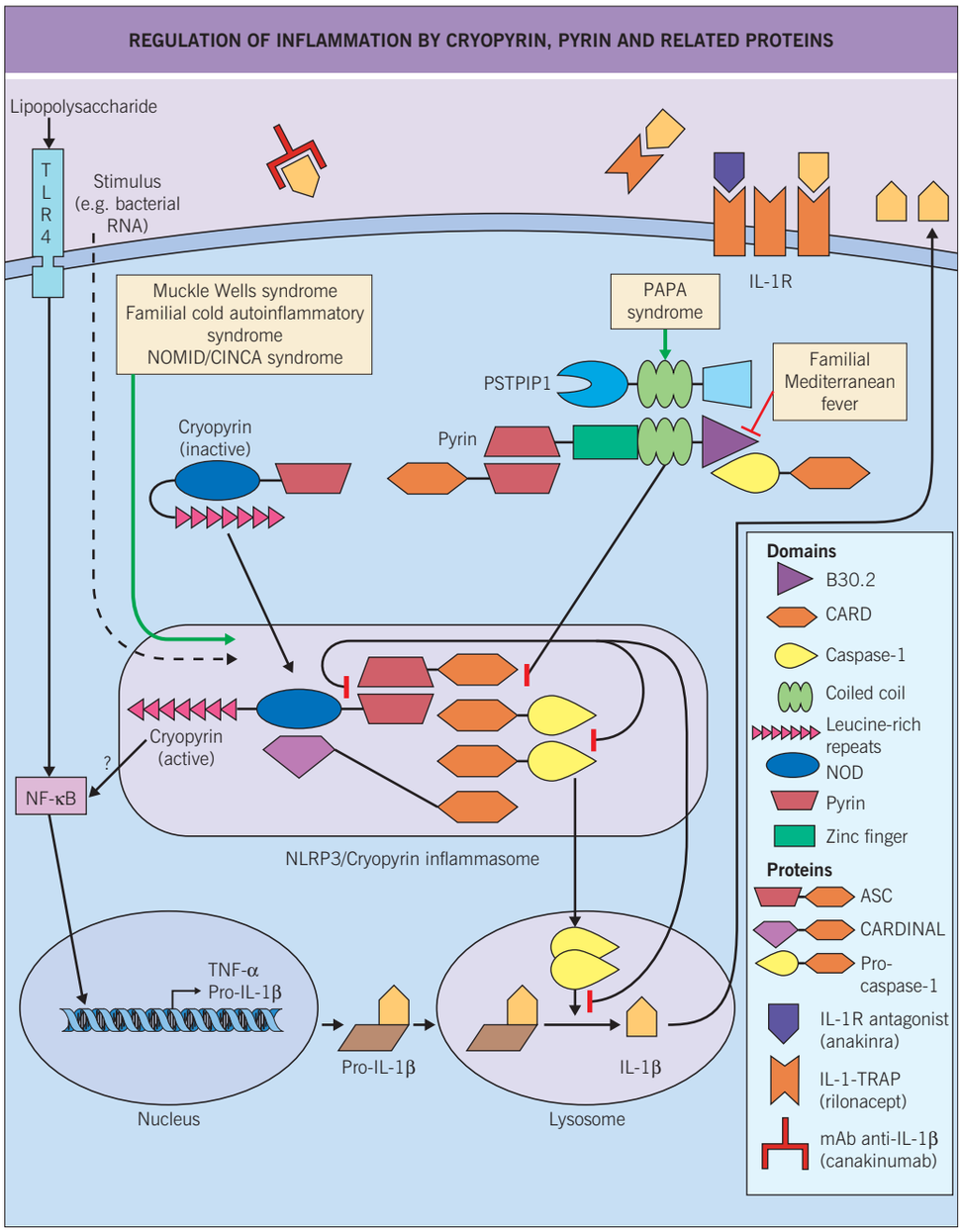


Fig. 45.1 Regulation of inflammation by cryopyrin, pyrin and related proteins. Upon release of autoinhibition, cryopyrin interacts with apoptosis-associated speck-like protein with a CARD domain (ASC) and *CARD-i*nhibitor of *N*F-κB-*a*ctivating *l*igand (CARDINAL) in an "inflammasome", leading to activation of caspase-1 (and perhaps NF-κB) and generation of mature interleukin (IL)-1β. Pyrin can competitively bind ASC and (pro)-caspase-1, thereby preventing them from being incorporated into the cryopyrin inflammasome; the formation of a separate pyrin inflammasome leading to IL-1β activation has also been postulated. *P*roline-*s*erine-*t*hreonine *p*hosphatase-*i*nteracting *p*rotein 1 (PSTPIP1) binds (and perhaps inhibits) pyrin, and this interaction is strengthened by the *PSTPIP1* mutations that underlie PAPA syndrome. CARD, *ca*spase-*r*ecruitment *d*omain; CINCA, *c*hronic *i*nfantile *n*eurologic, *c*utaneous and *a*rticular syndrome; IL-1R, interleukin-1 receptor; NF-κB, nuclear factor-κB; NLRP3, *N*OD-*l*ike *r*eceptor *p*yrin domain-containing protein 3; NOD, *n*ucleotide-binding *o*ligomerization *d*omain; NOMID, *n*eonatal-*o*nset *m*ultisystem *i*nflammatory *d*isease; PAPA, *p*yogenic *a*rthritis, *p*yoderma gangrenosum and *a*cne; RIP2, *r*eceptor-*i*nteracting *p*rotein-2; TLR, Toll-like receptor; TNF, tumor necrosis factor. *Courtesy, Julie V Schaffer, MD.*

Fig. 45.2 Systemic-onset juvenile idiopathic arthritis (Still's disease). Evanescent pink papules and plaques in a child. Note the linear array of some of the lesions. *Courtesy, Carlos H Nousari, MD.*

in individuals over the age of 60 years. Women are affected slightly more often than men.

Pathogenesis

The etiology of adult-onset Still's disease is unknown. The disease has been linked with a number of HLA antigens, including HLA-B14, -B17, -B18, -B35, -Bw35, -Cw4, -DR2, -DR7, -DR4, and -Dw6, suggesting a genetic component[11]. It has been hypothesized to occur in a susceptible individual as a reactive condition triggered by a variety of infectious agents, including viruses (rubella, mumps, echovirus 7, cytomegalovirus, EBV, parainfluenza, influenza A, coxsackievirus B4, adenovirus, human herpesvirus 6, parvovirus B19, hepatitis B, hepatitis C) and bacteria (*Mycoplasma pneumoniae*, *Chlamydophila* [*Chlamydia*] *pneumoniae*, *Yersinia enterocolitica* 3 and 9, *Brucella abortus*, *Borrelia burgdorferi*)[11]. To date, however, no infectious agent has been implicated consistently.

The role of Th1 cytokines in the pathogenesis of adult-onset Still's disease has been the subject of more recent investigation. Of note, serum levels of IL-2, IL-6, IL-18, TNF-α and IFN-γ are elevated in patients with the disease[11,12].

Clinical Features

The onset of the disease is frequently heralded by a sore throat and constitutional symptoms including arthralgias and myalgias. Fever is a prominent feature; it is usually above 39°C and has a spiking pattern, often occurring in the late afternoon or early evening and resolving within several hours. The skin eruption is asymptomatic and transient, occurring in association with the fever spikes. It is most often macular with a characteristic salmon-pink color (Fig. 45.3A), favors sites of

HEREDITARY PERIODIC FEVER SYNDROMES						
	FMF	**HIDS**	**TRAPS***	**Cryopyrin-associated periodic syndromes (CAPS)**		
				MWS	**FCAS†**	**NOMID (CINCA)**
Ethnicity	Jewish, Arab, Turkish, Italian, Armenian	Predominantly Dutch, northern European	Any ethnic group	Any ethnic group	Any ethnic group	Any ethnic group
Inheritance	AR	AR	AD	AD	AD	AD
Gene	*MEFV*	*MVK*‡	*TNFRSF1A*	*NLRP3 (CIAS1)*	*NLRP3 (CIAS1)*	*NLRP3 (CIAS1)*
Chromosome	16p13.3	12q24	12p13	1q44	1q44	1q44
Protein	Pyrin	Mevalonate kinase	TNF receptor-1	Cryopyrin	Cryopyrin	Cryopyrin
Attack length	1–3 days	3–7 days	Often >7 days	1–2 days	Minutes–3 days	Continuous + flares
Mucocutaneous lesions	Erysipeloid erythema and edema	Erythematous macules and edematous papules, which may become purpuric; occasional oral and vaginal ulcers	Erythematous patches and edematous plaques (often annular or serpiginous); later ecchymotic in appearance; rarely oral ulcers	Urticarial papules and plaques	Cold-induced urticarial papules and plaques	Urticarial papules and plaques; occasional oral ulcers
Distribution of skin lesions	Favor lower leg, foot	Widespread on face, trunk and extremities	Migrate distally on an extremity with underlying myalgia; may be more widespread	Widespread on face, trunk and extremities	Extremities > trunk, face	Widespread on face, trunk and extremities
Abdominal pain and serositis	Peritonitis > pleuritis > pericarditis	Abdominal pain, but rarely serositis	Peritonitis > pleuritis, pericarditis	Abdominal pain, but rarely serositis	Rare	Rare
Musculoskeletal findings	Monoarthritis > exercise-induced myalgia	Arthralgia > oligoarthritis > myalgia	Migratory myalgia > arthralgia > monoarthritis	Myalgia ("lancing limb pain"), arthralgia > large-joint oligoarthritis	Arthralgia > myalgia	Epiphyseal and patellar overgrowth, arthritis, deforming arthropathy
Ocular findings	Uncommon	Uncommon	Periorbital edema, conjunctivitis, rarely uveitis	Conjunctivitis, episcleritis, optic disc edema	Conjunctivitis	Conjunctivitis, uveitis, optic disc edema, blindness
Neurologic findings	Rarely aseptic meningitis	Headache	Headache	Sensorineural hearing loss; headache	Headache	Sensorineural hearing loss; aseptic meningitis, seizures
Other clinical findings	Acute scrotal swelling; splenomegaly	Cervical LAN, HSM	Scrotal pain; splenomegaly, occasional LAN			LAN, HSM; dysmorphic facies – frontal bossing, protruding eyes
Amyloidosis	Most common in M694V homozygotes	Rare	~15% of cases	~25% of cases	Uncommon	Late complication
Dermal infiltrate in typical skin lesions	Neutrophils	Neutrophils and/or lymphocytes; mild vasculitis common	Lymphocytes, monocytes and a few neutrophils	Neutrophils and/or lymphocytes (sparse)	Neutrophils (perivascular)	Neutrophils (perivascular + periadnexal)
Cutaneous vasculitis	LCV/HSP (5–10%), PAN (~1%)	LCV/HSP	Lymphocytic small vessel (rare)			
Laboratory abnormalities§	Low C5a inhibitor in serosal fluids	High serum IgD‖ (>100 IU/ml) and IgA1; mevalonate in urine during attacks; low lymphocyte mevalonate kinase	Low serum soluble TNF receptor-1 (<1 ng/ml between attacks)			
Treatment	Colchicine prophylaxis; TNF inhibitors, thalidomide, herbal remedies	TNF inhibitors (e.g. etanercept); simvastatin; anakinra¶	Glucocorticoids; TNF inhibitors (e.g. etanercept)	Glucocorticoids; rilonacept, canakinumab, anakinra¶	Rilonacept, canakinumab, anakinra¶	Rilonacept, canakinumab, anakinra¶

*Includes familial Hibernian fever.
†Also referred to as familial cold urticaria.
‡Allelic with mevalonic aciduria, which is characterized by dysmorphology, psychomotor retardation and progressive cerebellar ataxia as well as periodic fevers and other features of HIDS.
§Genetic analysis can be performed to confirm the diagnosis.
‖IgD levels are occasionally normal; elevated IgD may also be observed in FMF and TRAPS.
¶IL-1 antagonists.

Table 45.2 Hereditary periodic fever syndromes. AD, autosomal dominant; AR, autosomal recessive; CINCA, chronic infantile neurologic, cutaneous and articular syndrome; FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulinemia D with periodic fever syndrome; HSM, hepatosplenomegaly; HSP, Henoch–Schönlein purpura; LAN, lymphadenopathy; LCV, leukocytoclastic vasculitis; MWS, Muckle–Wells syndrome; NOMID, neonatal-onset multisystem inflammatory disease; PAN, polyarteritis nodosa; TNF, tumor necrosis factor; TRAPS, TNF receptor-associated periodic syndrome. *Courtesy, Julie V Schaffer, MD.*

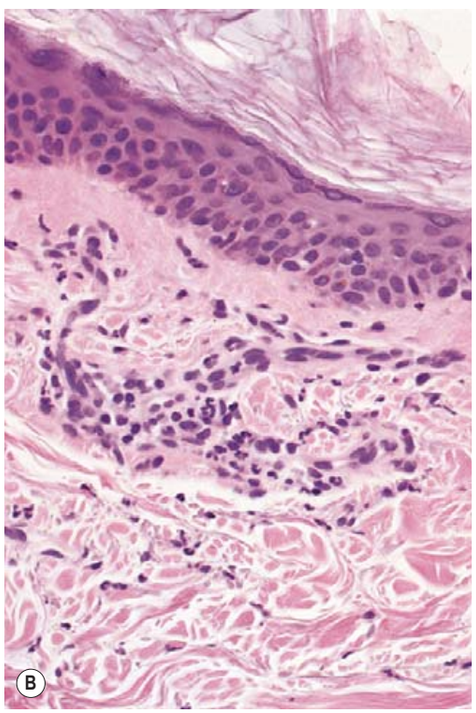


Fig. 45.3 Adult-onset Still's disease. A Multiple pink macules and urticarial papules that were accompanied by a fever spike. The patient also had markedly elevated serum ferritin levels. **B** Histologic features of a mixed perivascular and interstitial infiltrate with neutrophils and lymphocytes. *A, Courtesy, Diane Davidson, MD; B, Courtesy, Jean L Bolognia, MD.*

pressure, and can exhibit the Koebner phenomenon. Although the trunk is most commonly involved, lesions can appear on the extremities, including the palms and soles. Violaceous to reddish brown, scaly, persistent papules and plaques can also occur, and were observed in more than half of patients with adult-onset Still's disease in a recent Taiwanese series[13].

Depending upon the series, arthritis occurs in 65–100% of patients, and most often it affects the knees, wrists and ankles, although other joints may also be involved. The pattern is usually symmetric, and most patients ultimately develop joint pain associated with the fever spikes. A distinctive feature of the arthritis of adult-onset Still's disease is carpal ankylosis, which results in minimal pain but a limited range of motion in the carpal joints. Similar ankylosis may occur in the proximal and distal interphalangeal joints as well as the cervical spine. The metacarpophalangeal (MCP) joints are usually spared.

There may be hepatomegaly, but splenomegaly is less common. Involvement of the lungs (pleuritis, pleural effusions, pulmonary fibrosis), heart (pericarditis, myocarditis, cardiac tamponade), and kidneys (nephritis) is rare.

Laboratory findings in adult-onset Still's disease are similar to those of SoJIA and include elevations in the C-reactive protein level, ESR, and platelet count. Leukocytosis and anemia are common, as are abnormalities in hepatic function tests. There are often significant elevations in serum ferritin levels, sometimes >4000 mg/ml, and ferritin levels may correlate with disease activity[11]. Titers of ANA and RF are usually low or negative.

Pathology

Histologic examination of the exanthem reveals an interstitial and perivascular neutrophil-dominant mixed infiltrate without vasculitis (Fig. 45.3B). Immunofluorescence microscopy findings are nonspecific. As in SoJIA, persistent plaques demonstrate necrotic keratinocytes within the epidermis and a dermal infiltrate of neutrophils.

Adult-onset Still's disease should always be considered in an adult with fever of unknown origin (defined as fever >38.3°C on several occasions over a period of at least 3 weeks or uncertain diagnosis after 1 week of hospitalization). The differential diagnosis is similar to that of SoJIA (see above). Additionally, Schnitzler's syndrome should be considered in an adult patient with recurrent fevers, arthralgia and an urticarial eruption. In addition to non-pruritic urticaria, patients have recurrent fevers, bone pain (lower extremity, iliac and vertebral due to hyperostosis), and a monoclonal IgM gammopathy. Angioedema is observed in about 15% of patients with Schnitzler's syndrome, and lymphoplasmacytic malignancies in 10–15%[11]. Histologically, a neutrophil-predominant dermal infiltrate is seen, and, occasionally, urticarial vasculitis.

Treatment

Although some patients respond to high-dose aspirin or NSAIDs, the majority require oral corticosteroids (e.g. 40–60 mg prednisone daily) to control acute systemic features. When corticosteroids cannot be tapered, methotrexate is the most commonly employed second-line therapy. As in SoJIA, biologic agents that inhibit the IL-1 receptor or IL-6 receptor (e.g. tocilizumab) appear to be promising[14,14a]. A therapeutic response to TNF-α inhibitors has also been reported.

RELAPSING POLYCHONDRITIS

Synonyms: ■ Atrophic polychondritis ■ Systemic chondromalacia

Key features

- A prominent clinical feature is erythema, swelling and pain of the cartilaginous portion of the ear, followed by destruction of the cartilage
- Additional findings include nasal chondritis (which may result in a saddle nose deformity) and arthritis of the joints of the central chest
- The most serious complications result from ocular, renal and respiratory tract involvement

Introduction

Relapsing polychondritis is an uncommon inflammatory disorder with a suspected autoimmune origin that primarily affects cartilaginous structures. The diagnosis is usually established based upon the presence of: (1) histologically confirmed chondritis in *two* of the following three sites: auricular, nasal and laryngotracheal cartilage; or (2) chondritis in *one* of the aforementioned sites plus at least *two* other features, including: ocular inflammation, audiovestibular damage and inflammatory arthritis. Relapsing polychondritis has been associated with other autoimmune disorders (25–30%) and with myelodysplastic syndromes. Dermatologic manifestations may be the initial presenting sign and early diagnosis and treatment can prevent later complications (e.g. ascending aortitis, glomerulonephritis).

History

The disease was first described in 1923 by Jaksch-Wartenhorst and was called "polychondropathia". It was later renamed "relapsing polychondritis" due to its episodic nature[15].

Epidemiology

Relapsing polychondritis is most common in Caucasians, but has been reported in other races. In 80% of cases, the onset is between the ages of 20 and 60 years. Men and women are equally affected.

Pathogenesis

Although the etiology of relapsing polychondritis is unknown, the pathogenesis seems to involve an immunologic reaction against type II collagen[16]. However, circulating antibodies against type II collagen are present in fewer than half of affected individuals, and antibodies against types IX and XI collagen have also been described[17]. The clinical usefulness of these antibodies in the diagnosis, prognosis or monitoring of disease activity or the response to therapy is unclear. That said, transmission of relapsing polychondritis to a neonate from an affected mother has been reported (with subsequent recovery of the infant), lending support to an antibody-mediated pathogenesis. Antibodies to matrilin-1, an extracellular matrix protein located in auricular, septal, tracheal and sternal cartilage, may also play a role in the immune response seen in relapsing polychondritis[18]. Additionally, there is a positive association with HLA-DR4, while the extent of organ involvement has been negatively associated with HLA-DR6[17].

Clinical Features

The most prominent clinical feature is erythema, swelling and pain of the cartilaginous portion of the auricle, sparing the earlobe (Fig. 45.4). Symptoms can persist for several days to weeks and may encroach on the external auditory meatus, compromising hearing. Chronic inflammation leads to destruction of the cartilage, leaving the ear unsupported and scarred. During the course of their disease, 90% of patients will develop auricular involvement, and in at least 25% it is a presenting sign.

Nasal chondritis eventually develops in up to 70% of patients and may result in a saddle nose deformity. Symptoms include pain, stuffiness, crusting, rhinorrhea, epistaxis and compromise of olfaction. Nasal chondritis is typically less recurrent than the auricular chondritis, and the saddle nose deformity is more common in men[16].

Involvement of the cartilage of the respiratory tract (larynx, trachea, bronchi) and/or costochondral joints occurs in approximately 50% of patients and can be the most serious complication. Signs and symptoms include cough, hoarseness, choking, dyspnea, wheezing or tenderness to palpation of the anterior neck overlying the larynx or trachea. Complications include airway obstruction or collapse, flail chest and secondary pulmonary infections.

Fig. 45.4 Relapsing polychondritis. Erythema and swelling of the ear with sparing of the earlobe. *Courtesy, Kalman Watsky, MD.*

Arthritis is common (50–80% of patients) and it is the presenting symptom in one-third of patients. An episodic, migratory, asymmetric, non-erosive oligo- or polyarthritis can affect any joint, although the knees and MCP and proximal interphalangeal joints are those most commonly affected. There may also be involvement of the sternoclavicular and sternomanubrial joints.

Ocular inflammation develops in approximately 65% of patients. It can involve virtually any component of the eye, leading to conjunctivitis, scleritis, corneal ulcerations, uveitis or optic neuritis[16]. A variety of reactive cutaneous lesions are seen in patients with relapsing polychondritis[19], including aphthae, small vessel vasculitis, annular urticarial plaques[19a] livedo reticularis, erythema elevatum diutinum and erythema nodosum. None is pathognomonic and some may be coincidental or due to a coexisting disease. The presence of cutaneous small vessel vasculitis and/or aphthae is reported to increase the likelihood of an associated myelodysplastic syndrome (see Ch. 24). In addition, an overlap between relapsing polychondritis and Behçet's disease, termed *m*outh *a*nd *g*enital ulcers and *i*nflamed *c*artilage (MAGIC) syndrome, has been reported[20].

Less common systemic features include audiovestibular damage, cardiovascular disease (aortitis, valvular dysfunction, pericarditis, conduction system abnormalities, myocarditis), renal dysfunction (glomerulonephritis, glomerulosclerosis, tubulointerstitial disease), and neurologic sequelae (cranial nerve palsies, vasculitis of the central or peripheral nervous system).

Pathology

Histopathologically, there is breakdown of the normal lacunar structure of the cartilage, with neutrophilic infiltrates initially, followed by lym-

DIFFERENTIAL DIAGNOSIS OF NASAL DEFORMITY OR DESTRUCTION
NEOPLASTIC DISORDERS
Nasal natural killer/T-cell lymphoma*
Squamous cell and basal cell carcinomas
Olfactory neuroblastoma, salivary gland tumors
Rhabdomyosarcoma, chondrosarcoma, other sarcomas
INFLAMMATORY DISORDERS
Relapsing polychondritis
Wegener's granulomatosis
Sarcoidosis
INFECTIOUS DISORDERS
Bacterial
Rhinoscleroma
Glanders
Noma
Syphilis (late congenital and tertiary)
Yaws (gangosa)
Mycobacterial
Leprosy
Tuberculosis (lupus vulgaris)
Fungal
Paracoccidioidomycosis > other dimorphic fungal infections
Zygomycosis (mucormycosis and entomophthoramycosis)
Aspergillosis
Parasitic
Mucocutaneous leishmaniasis (espundia)
Amebiasis due to free-living organisms†
Rhinosporidiosis‡
OTHER ETIOLOGIES
Substance abuse (e.g. cocaine)
Nasal myiasis
Factitious/traumatic
*Previously referred to as angiocentric T-cell lymphoma and lethal midline granuloma.
†Include *Acanthamoeba* spp. and *Balamuthia mandrillaris*; granulomatous centrofacial skin lesions may lead to fatal amebic encephalitis.
‡Characterized by nasal polyps; recent molecular studies have classified the causative organism, *Rhinosporidium seeberi*, as an aquatic protistan parasite, phylogenetically at the animal–fungus boundary.

Table 45.3 Differential diagnosis of nasal deformity or destruction.

phoplasmacytic infiltrates. In late stages there is replacement of cartilage by granulation tissue and fibrosis.

Differential Diagnosis

In the early inflammatory phase, the erythema and pain may be misdiagnosed as erysipelas or cellulitis. Infectious chondritis, traumatic chondritis, Wegener's granulomatosis, and congenital syphilis may mimic the cartilage destruction seen in relapsing polychondritis (Table 45.3). Wegener's granulomatosis can be distinguished from relapsing polychondritis by the presence of anti-proteinase 3 antibodies (C-ANCA; see Ch. 40) and the absence of auricular involvement.

Treatment

Although relapsing polychondritis has traditionally been associated with significant morbidity and mortality, it is a treatable disease (with survival rates of 94% at 8 years). A comprehensive evaluation for systemic involvement should be performed prior to initiation of therapy, as systemic disease requires more aggressive treatment. The most common causes of death are pneumonia, systemic vasculitis, airway collapse and renal failure[16].

The initial treatment is with prednisone (0.5–1 mg/kg/day; higher doses are given if there is visceral involvement), which improves acute flares and decreases the number and severity of recurrences. NSAIDs and colchicine may be employed to decrease fever, auricular chondritis and arthralgias. Dapsone (50–150 mg/day) can also be used. Hydroxychloroquine and immunosuppressive agents (e.g. methotrexate, cyclosporine, azathioprine, 6-mercaptopurine, cyclophosphamide, mycophenolate mofetil) have been tried alone or in conjunction with corticosteroids, with variable responses. More recently, successful results with infliximab and the IL-1 receptor antagonist anakinra have been reported, while a retrospective series of nine patients treated with the anti-CD20 antibody rituximab failed to demonstrate significant clinical improvement[21]. Surgery is sometimes performed to repair damage to cartilaginous structures after the inflammation has been controlled.

SJÖGREN'S SYNDROME

Synonyms: ■ Mikulicz disease ■ Sicca syndrome

Key features

- This autoimmune disorder primarily affects secretory glands
- The most common features are xerostomia, xerophthalmia and arthritis
- Cutaneous manifestations include xerosis, petechiae, purpura (palpable and non-palpable), urticarial vasculitis and annular erythema
- Serious complications include B-cell lymphomas – in particular, extranodal marginal zone lymphomas of the MALT (mucosa-associated lymphoid tissue) type, peripheral neuropathy and systemic vasculitis
- Factors associated with a poorer prognosis include hypocomplementemia, vasculitis and/or cryoglobulinemia

Introduction

Sjögren's syndrome (SjS) is an autoimmune disorder that affects secretory glands, in particular the lacrimal and salivary glands. In addition to exocrine gland dysfunction, patients may develop a range of systemic manifestations due to autoimmune-mediated insults to multiple organ systems. This disease can be difficult to diagnose due to its insidious onset and initially nonspecific symptomatology. Mucocutaneous manifestations are prominent and may be the initial presenting signs. SjS may exist as a primary disorder or in association with other autoimmune diseases (secondary SjS), including rheumatoid arthritis, systemic lupus erythematosus (LE) and scleroderma.

EUROPEAN–AMERICAN CONSENSUS GROUP MODIFICATION OF THE EUROPEAN COMMUNITY CRITERIA FOR THE DIAGNOSIS OF SJÖGREN'S SYNDROME

- Symptoms of xerophthalmia
- Signs of xerophthalmia (Schirmer test, Rose Bengal test)
- Symptoms of xerostomia
- Signs of impaired salivary gland function (sialogram, scintigraphy)
- Positive salivary gland biopsy (see text)
- Presence of autoantibodies (anti-Ro/SS-A or anti-La/SS-B)

Table 45.4 European-American Consensus Group modification of the European community criteria for the diagnosis of Sjögren's syndrome. Patients must have either a positive salivary gland biopsy or positive autoantibodies (anti-Ro/SS-A or anti-La/SS-B) plus fulfill ≥3 of the additional criteria. A positive salivary gland biopsy or the presence of autoantibodies (in addition to the first four criteria) is associated with a diagnostic sensitivity of 97% and a specificity of 90%[22].

History

The first description of SjS was by Hadden in 1888. Four years later, Mikulicz described a patient with bilateral enlargement of the parotid glands and associated lymphocytic infiltrates. However, it was not until 1933 that Henrik Sjögren described the triad of keratoconjunctivitis sicca, xerostomia and arthritis. Castleman and Morgan determined that the histopathology of Sjögren's syndrome and Mikulicz disease were identical. Over the past several decades, the diagnostic criteria for SjS have been debated and revised, and the currently accepted criteria are the European–American Consensus Group modification of the European community criteria for SjS (Table 45.4)[22].

Epidemiology

Although SjS most commonly presents during the fourth and fifth decades, pediatric cases have been reported. The female : male ratio is 9 : 1 and men with this syndrome tend to have a less aggressive disease course with fewer extraglandular manifestations. SjS is one of the most common autoimmune disorders, affecting approximately 0.3–0.6% of the total population[23]. The overall mortality rate in primary SjS is comparable to that in the normal population[23].

Pathogenesis

The pathogenesis of SjS is unknown. As in other autoimmune diseases, environmental factors likely trigger inflammatory events in a genetically susceptible host, resulting in the autoimmune phenomena characteristic of the disease. In SjS, it has been proposed that abnormalities intrinsic to glandular epithelial, dendritic and/or stromal cells may initiate the lymphocytic infiltration and aberrant signaling. Viral infection of the glands may stimulate the innate immune system via Toll-like receptors, leading to autoimmune destruction of glandular cells due to molecular mimicry[24]. While no single virus has been consistently or reproducibly demonstrated as a predominant trigger, EBV, coxsackievirus, human T-cell lymphotropic virus-1 (human T-cell leukemia virus), and hepatitis C virus have all been implicated in various populations[23]. There is upregulation of type I and II interferon gene expression, possibly related to viral infection and perpetuated by immune complexes such as anti-SS-A or anti-SS-B antibodies complexed with hYRNA. Activation of the Th17/IL-23 system has also recently been described in SjS patients[25].

Serum levels of B-cell activating factor are elevated in patients with SjS. It is possible that this protein allows autoreactive B cells to escape apoptosis and have autoimmune potential. Patients with SjS frequently have hypergammaglobulinemia and autoantibodies that recognize Ro/

SS-A and La/SS-B; presence of these autoantibodies increases the risk of developing cutaneous small vessel vasculitis, both in patients with SjS and in those with systemic LE. In lymphocytes infiltrating the salivary glands, increased levels of costimulatory molecules CD40 and CD40 ligand (CD154) have been noted, as has increased expression of the genes that encode the antiapoptotic proteins bcl-2 and bcl-x[26]. This could play a role in the development of marginal zone B-cell lymphoma in the salivary gland.

Clinical Features

The most prominent feature of SjS is xerosis of the mucous membranes, particularly of the eyes, mouth and vagina. Keratoconjunctivitis sicca occurs as a result of destruction of the lacrimal gland, and patients may experience ocular dryness, a foreign body sensation, pain or photophobia. Objective tests to verify decreased tear production and assess the integrity of the corneal surface, such as the Schirmer test and Rose Bengal dye test, respectively, should be performed by an ophthalmologist[24]. In the Schirmer test, a piece of Whatman paper wick is folded over the lower eyelid for 5 minutes, and if the aqueous component of the tear film migrates <5 mm, there is lacrimal gland dysfunction. Complications of xerophthalmia include keratitis, corneal thinning and ulceration, and recurrent infections[24].

Xerostomia due to destruction of the major and minor salivary glands may present as a dry, sore, burning mouth and lips. Patients may have difficulty swallowing or require frequent ingestion of fluids during conversations. On examination, the infralingual salivary pool may be absent and the saliva cloudy and stringy. Although the major salivary glands (parotid and submandibular) may become transiently enlarged (~20% of patients), persistent swelling of these salivary glands or lymphadenopathy should prompt an evaluation for lymphoma. Of note, patients with SjS have a 16-fold greater risk of developing lymphoma (as compared to the general population)[23]; these B-cell lymphomas are often extranodal and can originate in salivary as well as lacrimal glands.

Xerostomia may be assessed functionally by salivary gland scintigraphy, sialometry or parotid sialography, but these tests are not commonly employed. On the other hand, salivary gland biopsy is a readily available procedure and represents an important component of the diagnosis of SjS (see Table 45.4). Perlèche or thrush can result from candidal overgrowth, and should be suspected when patients report a sudden increase in pain. Dental caries are a common problem, particularly along the gingival margin, and scrupulous dental hygiene with frequent dental examinations is crucial. Because saliva has an elevated pH that neutralizes gastric acid, patients with SjS may experience more severe gastroesophageal reflux disease or gastro-tracheal reflux (which can mimic upper respiratory tract infections), and aggressive reflux treatment is warranted[24]. Assessment for *Helicobacter pylori* infection is also performed, because the presence of this organism has been associated with MALT lymphomas in patients with SjS[24].

Vaginal xerosis is common, and since many patients are perimenopausal or postmenopausal, it may be multifactorial. It may present as dryness, burning and/or dyspareunia. Candidal and bacterial overgrowth are common complications.

The most common skin finding is xerosis, usually presenting as pruritus. Other cutaneous manifestations include palpable and nonpalpable purpura, urticarial vasculitis, erythema nodosum, nodular amyloidosis and Sweet's syndrome. Lesions of annular erythema, clinically reminiscent of subacute cutaneous LE or LE tumidus, have been reported primarily in Japanese patients with SjS. Whether or not these patients have an LE/SjS overlap is a matter of debate. Raynaud's phenomenon has been reported in 30% of patients with primary SjS.

Vasculitis is the most important cutaneous finding in SjS, as it is associated with an increased risk of morbidity and mortality[27]. Patients with cutaneous small vessel vasculitis may present with palpable purpura (Fig. 45.5) or with urticarial lesions (the latter either in the setting of hypo- or normo-complementemia; see Ch. 24). Some patients develop lesions of pigmented purpura (capillaritis) or macular hemorrhage which can be identical to the lesions seen in patients with hypergammaglobulinemic purpura of Waldenström (see Ch. 22). Of note, many of the patients with the latter disorder have evidence of an autoimmune connective tissue disease (including SjS). The presence of purpura should prompt an evaluation for cryoglobulinemia. Patients found to have vasculitis, cryoglobulinemia and/or hypocomplementemia have an increased mortality rate and an increased risk of developing B-cell lymphomas[28].

Fig. 45.5 Cutaneous small vessel vasculitis in a patient with Sjögren's syndrome. Patients can also develop lesions of pigmented purpura (capillaritis). *Courtesy, Penn State Department of Dermatology.*

Extraglandular and extracutaneous involvement may present with a diverse array of symptoms due to involvement of a variety of tissues including the lungs (interstitial pneumonitis, often subclinical), kidneys (interstitial nephritis, tubular dysfunction), bone marrow, and peripheral and central nervous systems (peripheral neuropathy, short-term memory loss, depression, immune-mediated hearing loss, multiple sclerosis-like presentation)[24]. Arthritis is a common finding; it is usually polyarticular, non-erosive , chronic and progressive, and it can be asymmetric. The most frequently involved joints are the knees and ankles.

As discussed above, the risk of developing B-cell lymphomas is increased in patients with SjS. The lymphomas are often extranodal in origin (e.g. salivary glands, lacrimal glands) and usually marginal zone lymphomas of the MALT type[29]. In a series of 380 patients with primary SjS, approximately 3% developed lymphoma during 9 years of observation[30].

Laboratory Findings

Primary SjS is associated with anti-Ro/SS-A (~60–80%), and anti-La/SS-B (~40–60%) autoantibodies. Patients with secondary SjS may have additional autoantibodies, depending upon the specific autoimmune connective tissue disease (see Ch. 40). Because both specificity and sensitivity of anti-Ro antibodies depend upon the diagnostic assay utilized (e.g. an ELISA is more sensitive but less specific), a rather wide range of "Ro-positivity" exists. This topic is discussed in detail in Chapter 40.

Other laboratory abnormalities often observed in patients with SjS include an elevated ESR and a positive RF.

Pathology

To confirm the diagnosis of SjS, a biopsy of the minor salivary glands is often performed. The presence of two or more aggregates of inflammatory cells (50 or more lymphocytes) in 4 mm^2 of salivary gland tissue is required for the diagnosis. A mixture of T and B cells (with a normal CD4:CD8 ratio) is usually seen.

The typical histopathologic features of pigmented purpuric eruptions, cutaneous small vessel vasculitis, cryoglobulinemic vasculitis, and

urticarial vasculitis are seen in the vasculopathies associated with SjS; however, none of the histologic findings is specific for SjS.

Differential Diagnosis

Sicca symptoms are common in the elderly in part due to age-related atrophy of secretory glands. Xerostomia is a common side effect of drugs with anticholinergic properties and it may also result from previous irradiation, salivary gland stones, and chronic viral infections. Xerophthalmia can be a symptom of ocular rosacea (see Ch. 37), infiltration of the lacrimal glands (e.g. sarcoidosis, amyloidosis), irradiation, estrogen deficiency, and hypovitaminosis A. It may reflect impaired blinking (e.g. Parkinson's disease) or herald the onset of mucous membrane (cicatricial) pemphigoid. In addition, patients with chronic graft versus host disease can have both xerophthalmia and xerostomia.

Early in the disease course, it may be difficult to distinguish SjS from other autoimmune connective tissue diseases. Complaints such as arthralgias and myalgias are often nonspecific. Because 50% of the salivary glands must be destroyed before symptoms arise, sicca symptoms may not be a prominent complaint initially. Patients with SjS/LE overlap can pose a diagnostic challenge. They are often anti-Ro-positive and may have prominent cutaneous disease or they may be asymptomatic but give birth to a child with neonatal LE (anti-Ro antibodies are associated with subacute cutaneous LE as well as with neonatal LE). Overlap patients may initially present with only symptoms of LE but subsequently develop SjS, or vice versa, and some may have late-onset disease (age >50 years).

Treatment

Therapy for most manifestations of SjS is symptomatic. Xerophthalmia may be treated with preservative-free artificial tears and lubricating ointments. The placement of punctual plugs that occlude the nasolacrimal ducts may increase accumulation of tear film. Home humidifiers may help relieve symptoms of xerophthalmia. Cyclosporine (0.05%) eyedrops may prove helpful, but it can take several months to achieve a therapeutic effect.

Xerostomia can be treated with methylcellulose drops (artificial saliva), but this is often unpalatable. Frequent ingestion of water or sugarless fluids and chewing sugar-free gum are generally the most acceptable forms of therapy. Use of a cool mist vaporizer at bedtime may also help. Prevention of dental caries is essential; scrupulous dental hygiene and topical fluoride treatments are recommended. Antifungal medications to treat and prevent candidiasis as well as chlorhexidine rinses (0.12%) can improve oral symptoms. Salivary gland massage to prevent inspissation of mucous plugs and promote salivary flow can be helpful. Muscarinic receptor agonists (e.g. pilocarpine, cevimeline) are systemic secretagogues that may alleviate xerostomia and xerophthalmia, but their use may be limited by unwanted side effects such as excessive sweating.

Dryness of the skin can be treated with emollients. Vaginal dryness may be improved with artificial lubricants. Frequent monitoring for and treatment of candidal and bacterial overgrowth is recommended; prophylactic use of vaginal antifungal agents is an option. In postmenopausal women, estrogen replacement therapy may be a helpful supplemental therapy.

In general, immunosuppressive agents should be reserved for patients with cutaneous vasculitis or involvement of the nervous system and internal organs. Systemic corticosteroids, hydroxychloroquine and steroid-sparing immunosuppressants (e.g. methotrexate, azathioprine, mycophenolate mofetil) are used in patients with serious internal manifestations. Therapy with TNF-α inhibitors has not proven to be very useful overall[24]. In initial small series, B-cell depletion with the anti-CD20 antibody rituximab led to conflicting results[31,32], but in a more recent randomized, double-blind, placebo-controlled trial, rituximab led to a significant improvement in saliva flow rate[32a].

MIXED CONNECTIVE TISSUE DISEASE

Synonyms: ■ Undifferentiated connective tissue disease ■ Sharp's syndrome

Key features

- The existence of mixed connective tissue disease (MCTD) as a distinct entity is controversial, as patients often have overlapping clinical and serologic features of various combinations of rheumatoid arthritis, systemic sclerosis, systemic LE and polymyositis
- Major disease features include: high-titer IgG anti-U1 ribonuclear protein (U1RNP) antibodies, Raynaud's phenomenon, swollen hands or sclerodactyly, myositis, esophageal dysmotility and arthritis
- Compared with systemic LE, there is a lower incidence of renal disease and a higher incidence of pulmonary disease
- Pulmonary hypertension is the most serious complication

Introduction

The designation of mixed connective tissue disease (MCTD) as a distinct disease entity continues to be debated. However, there is little argument that there exists a group of patients with a constellation of serologic and clinical manifestations for whom MCTD is a useful label. These patients have high titers of antibodies to U1RNP and certain clinical features observed in other autoimmune connective tissue diseases, including arthritis, pulmonary hypertension, esophageal dysmotility, myopathy, digital swelling and constitutional symptoms. Over time, some patients with MCTD develop manifestations more consistent with the diagnosis of systemic LE or systemic sclerosis.

History

MCTD was first described by Sharp et al.[33] in 1972, including its clinical features and the presence of an antibody to an extractable nuclear antigen.

Epidemiology

MCTD is much more common in women than in men (9:1), with most patients presenting during the second or third decade of life. The exact incidence of MCTD is unclear, especially since some authors do not consider it to be a separate entity. A number of patients would be more appropriately classified as having an overlap syndrome, and others may actually have systemic LE, systemic sclerosis, or dermatomyositis/polymyositis. It is believed that "classic" MCTD is the least common of the autoimmune connective tissue diseases. In the past, the prognosis of MCTD was thought to be better than that of systemic LE; however, long-term evaluation of patients with MCTD has found their prognosis to be poorer than that expected in patients with systemic LE. The majority of deaths in MCTD have been attributable to pulmonary hypertension[34,35].

Pathogenesis

Although the pathogenesis is not clear, there appears to be an immune response to U1RNP. U1RNP plays an essential role in the splicing of pre-mRNA into mRNA. The U1RNP molecule consists of three polypeptides (U1-A, U1-C, U1-70kD) that associate with U1RNA as well as a series of proteins that are common to multiple U-RNA and RNA-splicing molecules, including Smith (Sm) and splicing factors (SR proteins). Although anti-U1RNP IgG antibodies may be seen in LE, systemic sclerosis and polymyositis, titers of anti-U1RNP tend to be higher in MCTD. Another distinct autoantigen often recognized by MCTD sera is hnRNP-A2, which is another spliceosome component. Of note, antibodies to EBV and cytomegalovirus cross-react with components of U1RNP, suggesting that molecular mimicry related to prior exposure to these viruses may be involved in the development of anti-U1RNP autoimmunity[36]. Genetic studies have demonstrated an association of HLA-DR4, -DR1 and -DR2 in patients with MCTD[37].

Clinical Features

MCTD often presents with prominent cutaneous symptoms, including Raynaud's phenomenon and edematous erythematous digits. Raynaud's phenomenon is often an early manifestation, and it eventually

develops in almost all patients; "ice-pick" digital infarcts or even gangrenous digits can be observed. The patients often have periungual telangiectasias with dropout areas, and the hands and fingers may feel sclerodermatous and tight due to increased dermal collagen deposition as well as edema. Calcinosis cutis can also occur.

Poikilodermatous areas on the upper trunk and proximal extremities are common, in addition to the sclerodermoid changes of the distal extremities. However, the diffuse involvement of the face, upper trunk or extremities observed in patients with progressive systemic sclerosis is usually not seen. Photosensitivity and lesions indistinguishable clinically and histopathologically from acute systemic LE (e.g. malar rash) or subacute cutaneous LE may also occur. Cutaneous small vessel vasculitis and livedoid vasculopathy may develop as well[38]. Rheumatoid nodules and orogenital mucosal lesions such as buccal ulcers and nasal septal perforation have been described[38,39].

An inflammatory myopathy is common in patients with MCTD. However, dermatomyositis-specific findings such as Gottron's papules, a periorbital heliotrope eruption, and erythema and scaling of the scalp are not usually seen. Arthralgias or polyarthritis occur in 50–70% of patients with MCTD, often early in the disease course[38]. The arthritis ranges from mild to erosive.

Pulmonary hypertension is the most serious complication of MCTD (occurring in up to 25% of patients), and it may be associated with the presence of antiphospholipid antibodies[34]. Pulmonary fibrosis, often mild, may also occur, and, like pulmonary hypertension, is frequently asymptomatic early during its course. Pleurisy and pericarditis occur in ~60% of patients[35]. Periodic pulmonary examinations, chest radiographs, high-resolution CT scans, echocardiography, and pulmonary function tests are warranted. Esophageal dysmotility is common, occurring in up to 85% of patients; it can be asymptomatic, but most commonly manifests as reflux esophagitis and dysphagia[38].

Pathology

There are no histopathologic features pathognomonic for MCTD. The histologic findings vary depending upon the type of skin lesion examined. In general, cutaneous manifestations clinically resembling acute or subacute cutaneous LE, leukocytoclastic vasculitis or livedoid vasculopathy will have the histologic features characteristic of these entities.

Differential Diagnosis

The differential diagnosis of MCTD consists primarily of systemic LE, systemic sclerosis, dermatomyositis/polymyositis, and overlap syndromes. Some patients initially diagnosed with MCTD may over time develop a preponderance of clinical and serologic features of one of these diseases, requiring a change in diagnosis. The absence of hypocomplementemia or anti-dsDNA and anti-Sm antibodies helps to distinguish MCTD from systemic LE, while the more severe arthritis and the myositis help distinguish MCTD from systemic sclerosis. The inflammatory myopathies usually manifest with more severe myositis than is encountered in MCTD, and the former do not usually feature the lower esophageal dysmotility common in MCTD. The presence of Raynaud's phenomenon plus coarse periungual telangiectasias excludes other sclerodermoid disorders such as POEMS syndrome and porphyria cutanea tarda (see Ch. 43).

Treatment

The goal of therapy in MCTD is to control symptoms and maintain function. Therapy should be tailored to the specific organ involvement and disease severity. Patients with pulmonary hypertension require longitudinal care with a pulmonologist or rheumatologist experienced in managing pulmonary complications.

In general, manifestations of MCTD that often overlap with LE or polymyositis, such as serositis, cutaneous lesions, arthritis and myositis, usually respond to corticosteroids, while scleroderma-like features such as Raynaud's phenomenon and pulmonary hypertension generally do not[40]. Topical corticosteroids and systemic antimalarials are often helpful for LE-like dermatoses. Raynaud's phenomenon can be treated with vasodilators in addition to non-pharmacologic measures (avoidance of cold, gloves, etc.). For severe systemic disease, a variety of therapies have been evaluated, including immunosuppressive agents (e.g. methotrexate, cyclosporine, azathioprine, mycophenolate mofetil and cyclophosphamide), plasmapheresis and autologous hematopoietic stem cell transplantation. It is difficult to evaluate the efficacy of these treatments since there are no prospective large-scale studies, and most are based on single cases or small case series.

EXTRA-ARTICULAR MANIFESTATIONS OF RHEUMATOID ARTHRITIS

Key features

- In addition to deforming arthritis, patients can develop rheumatoid nodules, pyoderma gangrenosum, and small and medium-sized vessel vasculitis
- Other cutaneous manifestations include rheumatoid neutrophilic dermatitis and palisaded neutrophilic and granulomatous dermatitis

Introduction

Rheumatoid arthritis (RA) is a systemic disease where the primary manifestation is arthritis but in which there can be cutaneous manifestations (see Table 53.1). Several of these can serve as helpful diagnostic clues or, in the case of rheumatoid vasculitis, point to serious illness.

Epidemiology

RA is common, affecting 1–3% of the adult population in the US. Women are affected two to three times more often than men, and although it may develop in any age group, the peak onset is between 30 and 55 years of age.

Pathogenesis

The cause of RA is unknown, but, as with other autoimmune diseases, it is thought to result from a complex interaction between genetic susceptibility and environmental factors, particularly infectious agents. The concordance rate for RA in monozygotic twins is 34%, whereas in dizygotic twins it is only 3%. As in other autoimmune diseases, a complex interplay between innate and acquired immune responses appears to be involved. Initiating events in RA may involve the binding of extracellular matrix constituents in the synovium to Toll-like receptors, leading to the subsequent induction of inflammatory responses (increased TNF-α, IL-6, chemokines and angiogenic factors) and maturation of antigen-presenting cells[41]. A gain-of-function polymorphism in the *PTPN22* gene, which encodes a lymphoid-specific protein tyrosine phosphatase that serves as a negative regulator of T-cell activation, confers susceptibility to RA and JIA, as well as other autoimmune disorders such as systemic LE, Graves disease and type 1 diabetes mellitus (perhaps by impairing thymic negative selection or regulatory T cells). Of note, there is a reduction in the number of regulatory T cells in RA[42].

RA is also associated with HLA-DR1 and -DR4. The HLA-DRB1 shared epitope allele, a highly significant genetic risk factor for RA, contributes to its pathogenesis primarily by increasing the propensity to develop antibodies that target citrullinated proteins (which are found in the skin and joints). Such antibodies represent specific and predictive serologic markers for RA, and they have been shown to bind the synovium and enhance tissue injury in animal models of autoimmune arthritis. A variety of infectious agents, including particular proteins produced by EBV and *Escherichia coli*, have been thought to play a role due to molecular mimicry of the hypervariable domain of HLA-DRB1*0401 or induction of anti-citrullinated protein antibody production.

Clinical Features

Rheumatoid nodules

Rheumatoid nodules are present in 20% of patients with RA, and they occur in patients with moderate to high titers of RF (IgG, IgM or IgA). Most, if not all, of the cases of seronegative RA with "rheumatoid nodule"-like lesions were proven to be subcutaneous granuloma

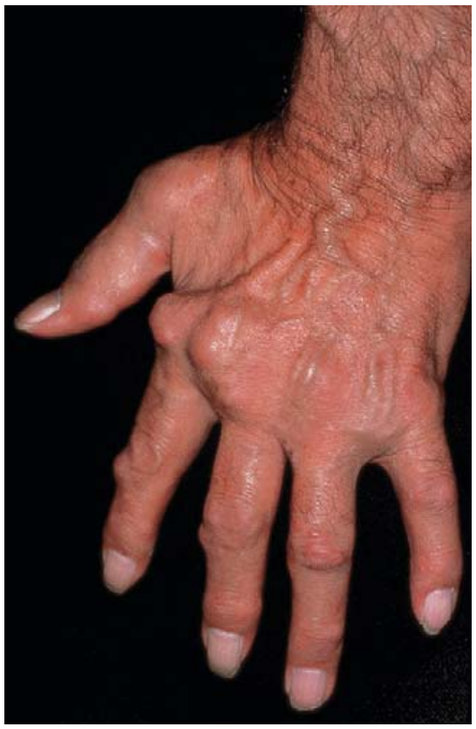


Fig. 45.6 Rheumatoid arthritis and rheumatoid nodules. Note the periarticular location of the skin-colored nodules. *Courtesy, Kalman Watsky, MD.*

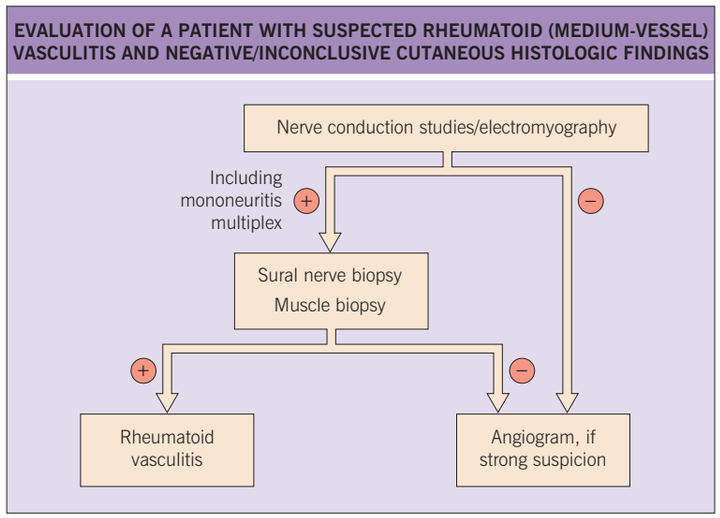


Fig. 45.8 Evaluation of a patient with suspected rheumatoid vasculitis (involving medium-sized vessels) in whom cutaneous histologic findings are negative or inconclusive.

Fig. 45.7 Methotrexate-induced nodulosis in a patient with rheumatoid arthritis. *Courtesy, Jean L Bolognia, MD.*

annulare or other entities with palisading granulomas histologically (see below). Rheumatoid nodules are firm, semi-mobile papulonodules that occur most commonly in periarticular locations over extensor surfaces (Fig. 45.6), and in areas subject to pressure or trauma. They range from several millimeters to as much as 5 cm in diameter and are typically asymptomatic. Occasionally the nodules are tender or painful, especially if there is associated trauma or ulceration. Rheumatoid nodules may also occur in visceral organs.

Accelerated rheumatoid nodulosis is characterized by the sudden appearance of multiple rheumatoid nodules (Fig. 45.7). Lesions usually appear following the initiation of methotrexate therapy, but can also be seen after the initial administration of TNF-α inhibitors. In some of these patients, there had also been a tapering of systemic corticosteroids.

Rheumatoid vasculitis

Rheumatoid vasculitis is a rare and typically late complication of RA. It is thought to occur in only 2–5% of those with RA, but, at autopsy, vasculitis has been found in up to a third of patients. Rheumatoid vasculitis typically occurs in the context of high-titer RF, rheumatoid nodules, and a history of severe erosive arthritis. The vasculitis may affect vessels of any size, and the clinical presentations reflect this, with palpable and non-palpable purpura in small vessel disease versus nodules, ulcerations, necrotizing livedo reticularis and/or digital infarcts in medium-sized vessel disease. Systemic manifestations of rheumatoid vasculitis can include neuropathies, cerebral infarction, scleritis, alveolitis, carditis, intestinal ulcers and proteinuria. Clinicopathologic correlation and serologic assessment should be performed when rheumatoid vasculitis is suspected. For example, if an ulcer is biopsied, a wedge perpendicular to the edge of the ulcer which includes both surrounding non-ulcerated skin as well as the ulcer base should be obtained. In up to 40% of patients with RA and medium-sized vessel vasculitis, there is evidence of a peripheral neuropathy (subclinical or clinical) that often presents as mononeuritis multiplex. This incidence seems to be even higher in patients with extensive cutaneous disease. Therefore, if vasculitis cannot be identified after multiple deep skin biopsies but the diagnosis is still suspected, nerve conduction studies followed by sural nerve biopsy (or a muscle biopsy) can be performed (Fig. 45.8). Mortality may be as high as 43%[43], and, therefore, aggressive intervention and rheumatologic consultation is warranted.

Bywater's lesions

Bywater's lesions include nailfold thromboses and purpuric papules on the distal digits (especially the digital pulp; see Fig. 53.4). Histologically, there is a small vessel leukocytoclastic vasculitis. Typically these lesions are not associated with systemic vasculitis[44].

Felty syndrome

Felty syndrome represents an uncommon but severe subset of seropositive RA that is characterized by granulocytopenia, splenomegaly and therapy-resistant leg ulcers (often pretibial). These patients are predisposed to cutaneous and systemic infections that can be refractory to standard treatment, and they are at increased risk of lymphomas and leukemias[45]. The ulcers are likely multifactorial and may be secondary to pyoderma gangrenosum, medium-sized vessel vasculitis (although vasculitis is often not confirmed histologically), venous hypertension, neuropathy, or perhaps an ulcerating form of palisaded neutrophilic and granulomatous dermatitis (PNGD)[46].

Neutrophilic dermatoses

Sterile infiltration of the skin by neutrophils can occur in patients with RA. The primary disorders are pyoderma gangrenosum, Sweet's syndrome, and rheumatoid neutrophilic dermatitis (see Chs 26 & 53), but there may be overlap and the term "neutrophilic dermatosis" is often used.

Pyoderma gangrenosum (PG) (Fig. 45.9) occurs at a higher frequency in patients with RA than in the general population. Although PG

Fig. 45.9 Pyoderma gangrenosum in a patient with rheumatoid arthritis. The chronic relapsing ulcerations involved the lower extremities. *Courtesy, Carlos H Nousari, MD.*

frequently occurs as a single, painful lesion on the lower extremities, the presence of chronic relapsing lesions in unusual sites such as the face, upper extremities and abdomen should raise the suspicion of an underlying disease, especially rheumatologic and hematologic disorders or inflammatory bowel disease. Sweet's syndrome classically presents with erythematous, edematous, tender plaques that favor the head and neck region and the upper extremities. As with PG, the presence of bullous lesions or involvement of atypical locations should prompt the exclusion of an underlying rheumatologic or hematologic disorder.

Rheumatoid neutrophilic dermatitis (also referred to as rheumatoid neutrophilic dermatosis) resembles Sweet's syndrome, both clinically and histologically. It occurs in patients with severe and usually seropositive RA, and it is characterized by erythematous urticarial papules and plaques that are persistent and asymptomatic, but occasionally ulcerate. Lesions are symmetrically distributed, most commonly on the extensor forearms and hands, but they can occur elsewhere.

Other

Patients with RA may also develop erythema elevatum diutinum (see Ch. 24) and PNGD (see below) as well as a number of cutaneous side effects from medications used to treat the arthritis (see Table 53.1).

Pathology

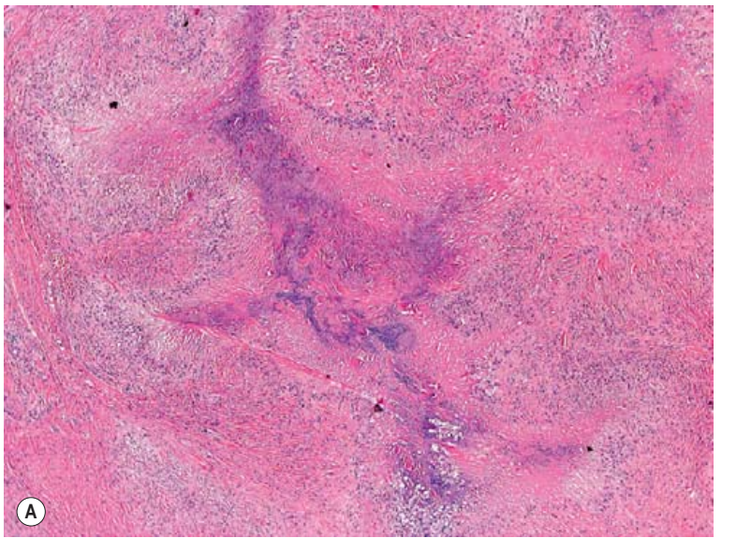
Rheumatoid nodules are typically located in the deep dermis or subcutis and are composed of a central zone of brightly eosinophilic fibrin surrounded by a palisaded layer of histiocytes and granulation tissue (Fig. 45.10). Acute or early lesions may show leukocytoclastic vasculitis and/or an interstitial neutrophilic infiltrate.

The histologic findings of PG, Sweet's syndrome, and small, medium-sized and large vessel vasculitis are discussed in Chapters 24 and 26. When rheumatoid vasculitis affects medium-sized vessels, it can be histologically indistinguishable from polyarteritis nodosa. Direct immunofluorescence in rheumatoid vasculitis shows prominent deposition of IgM as well as C3 in small and medium-sized vessels, whereas in polyarteritis nodosa the IgM and C3 vascular deposits are weaker and sparse and limited to medium-sized vessels.

Differential Diagnosis

Although rheumatoid nodules share several histologic features with PNGD, in the latter the clinical lesions are more polymorphous, with papules and plaques rather than periarticular skin-colored nodules. Because both the clinical and histologic findings can be similar, subcutaneous granuloma annulare may be misdiagnosed as rheumatoid nodules. However, individuals with subcutaneous granuloma annulare are otherwise healthy and are usually children. Occasionally, gouty tophi may be mistaken for rheumatoid nodules.

The differential diagnosis of cutaneous vasculitis is discussed in detail in Chapter 24. Specifically, rheumatoid vasculitis may be confused with mixed cryoglobulinemia given the presence of arthritis, RF, and complement activation in both entities. However, in the former



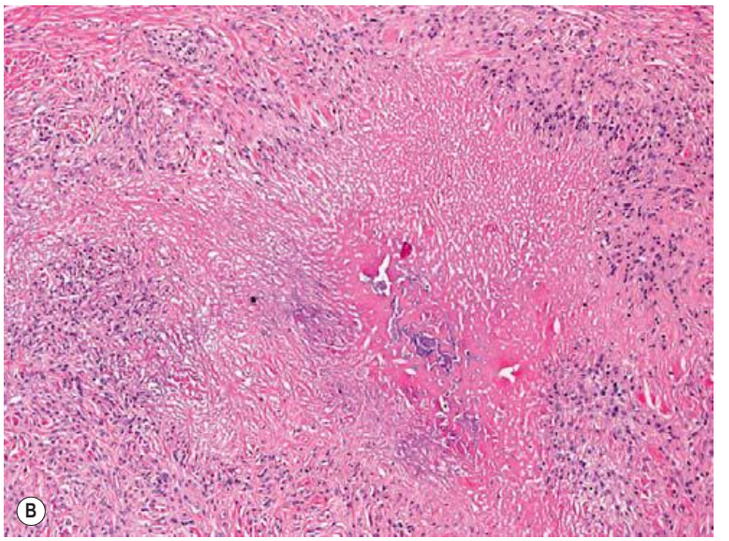


Fig. 45.10 Rheumatoid nodule – histiologic features. A Large, irregular area of necrobiosis surrounded by a palisade of histiocytes. **B** Details of necrobiosis and palisade of histiocytes with elongated nuclei. *Courtesy, Lorenzo Cerroni, MD.*

the titer of RF is significantly higher and levels of both C3 and C4 are decreased, whereas in cryoglobulinemia C4 levels are low with relatively normal levels of C3. Bywater's lesions may resemble septic emboli, traumatic lesions and, less often, pernio.

As previously mentioned, rheumatoid neutrophilic dermatitis strongly resembles Sweet's syndrome, but could also be mistaken for urticaria or urticarial vasculitis. Ulcerations in RA and Felty syndrome may have a variety of causes, including PG, rheumatoid vasculitis, superficial ulcerating rheumatoid necrobiosis (see Ch. 53) and secondary antiphospholipid syndrome, as well as infections (especially in patients receiving immunosuppressives), lymphoma (particularly angiocentric variants) and thromboembolic disorders.

Treatment

RA therapy is aimed at improving symptoms and preventing end-organ damage. Some of the cutaneous manifestations may improve with treatment of the joint disease, while others (e.g. rheumatoid nodules) often persist. Rheumatoid nodules can be excised, but recurrence is common. Intralesional corticosteroid injections may decrease the size of the nodules, but do not lead to complete resolution. Rheumatoid neutrophilic dermatitis is treated with oral corticosteroids or antineutrophilic agents such as dapsone or colchicine, while Felty syndrome may be treated with recombinant granulocyte colony-stimulating factor (G-CSF) and/or splenectomy.

Rheumatoid vasculitis involving medium-sized and large vessels requires aggressive treatment as it can be rapidly progressive and life-threatening. Intravenous methylprednisolone (500–1500 mg/day for 3 days) followed by prednisone (1 mg/kg/day) plus cyclophosphamide (daily or monthly) and plasmapheresis should be considered.

In less severe cases, including the small vessel variant of rheumatoid vasculitis, azathioprine and mycophenolate mofetil may be considered; methotrexate does not have a consistent effect in this complication of RA. Although there are reports of vasculitis developing in patients with RA after the initiation of TNF-α inhibitors, there are also multiple reports documenting the beneficial effects of this class of drugs in the treatment of rheumatoid vasculitis as well[46]. Several reports have also documented improvement in rheumatoid vasculitis after rituximab therapy[46]. Recurrences of rheumatoid vasculitis are less likely to occur when a stable, long-term regimen re-establishes control of the underlying RA.

For the treatment of RA-associated PG, systemic corticosteroids and cyclosporine are highly effective. Excellent results have also been reported with TNF-α inhibitors. Additional treatments are reviewed in Chapter 26.

INTERSTITIAL GRANULOMATOUS DERMATITIS AND PALISADED NEUTROPHILIC AND GRANULOMATOUS DERMATITIS

Synonyms:
Interstitial granulomatous dermatitis (IGD) with arthritis:
■ IGD with plaques and arthritis ■ IGD with plaques ■ IGD with cutaneous cords and arthritis

Palisaded neutrophilic and granulomatous dermatitis (PNGD):
■ Rheumatoid papules ■ Churg–Strauss granuloma ■ Cutaneous extravascular necrotizing granuloma ■ Superficial ulcerating rheumatoid necrobiosis

Key features

- Granulomatous dermatitis presenting in the context of autoimmune disease occurs in two major clinicopathologic patterns
- In *interstitial granulomatous dermatitis (IGD) with arthritis*, annular plaques or linear cords favor the trunk, axillae and medial thighs in patients with RA or seronegative arthritis; histologically, rosettes of palisading histiocytes surround tiny foci of degenerated collagen, often accompanied by neutrophils but without evidence of vasculitis
- In *palisaded neutrophilic and granulomatous dermatitis (PNGD)*, symmetrically distributed, umbilicated papules favor the elbows and extensor surfaces of the digits in patients with disorders such as RA, systemic LE and Wegener's granulomatosis; the histologic findings range from small vessel vasculitis with prominent neutrophils and leukocytoclasis (early lesions) to palisading granulomas (fully developed lesions), and both stages demonstrate basophilic degenerated collagen
- Interstitial granulomatous drug eruptions may mimic IGD or PNGD

Introduction

Palisaded neutrophilic and granulomatous dermatitis (PNGD) and interstitial granulomatous dermatitis (IGD) with arthritis represent two clinicopathologic patterns of granulomatous dermatitis that occur in patients with RA and other autoimmune disorders. These entities may exist on a spectrum.

History

In 1994, Chu and colleagues[47] proposed the term "palisaded neutrophilic and granulomatous dermatitis" for the histologic reaction pattern that characterizes papular eruptions on the extensor extremities that present in the context of autoimmune connective tissue disease and other conditions characterized by immune complex generation. Such skin lesions were originally described in the setting of Churg–Strauss syndrome, and their association with a broad spectrum of autoimmune and inflammatory disorders was first recognized by Winkelmann in 1978 (cutaneous extravascular necrotizing granuloma). Some authors include "interstitial granulomatous dermatitis with arthritis", a term coined by Ackerman in 1993, within the PNGD spectrum. Others argue that the former represents a separate entity with distinct clinical (annular plaques and cords favoring the lateral trunk and skin folds) and histologic (histiocytic rosettes without evidence of vasculitis) features.

Pathogenesis

It is thought that the initiating insult in PNGD and IGD is immune complex deposition on or around the walls of small dermal blood vessels as a result of the underlying disease, which leads to a subacute or chronic neutrophil-rich small vessel vasculitis (more prominent in PNGD). This then impairs blood flow to the area in a smoldering fashion, as opposed to the abrupt vascular occlusion of classic vasculitis; consequently, there is degeneration of the local collagen rather than acute necrosis. The degenerated collagen incites an immune response resulting in a palisading lymphohistiocytic infiltrate. Moderate but persistent levels of immune complexes may contribute to this phenomenon. The cascade of events is likely aggravated or precipitated by exogenous trauma, which explains the predilection of PNGD lesions for the extensor surfaces. Variable sizes, amounts and sites of immune complex deposition (e.g. dermal venules versus the interstitial dermis) as well as different triggers and underlying systemic inflammatory disorders may account for the distinct clinical and histologic features of PNGD and IGD.

Clinical Features

PNGD typically presents as skin-colored to erythematous papules that appear symmetrically on extensor surfaces, particularly the elbows and fingers. Central umbilication with crusts or perforation (with extrusion of necrobiotic collagen) may be present (see Fig. 53.1), and ulceration occasionally occurs. These lesions are observed most often in patients with RA, systemic LE or systemic vasculitis, particularly Wegener's granulomatosis.

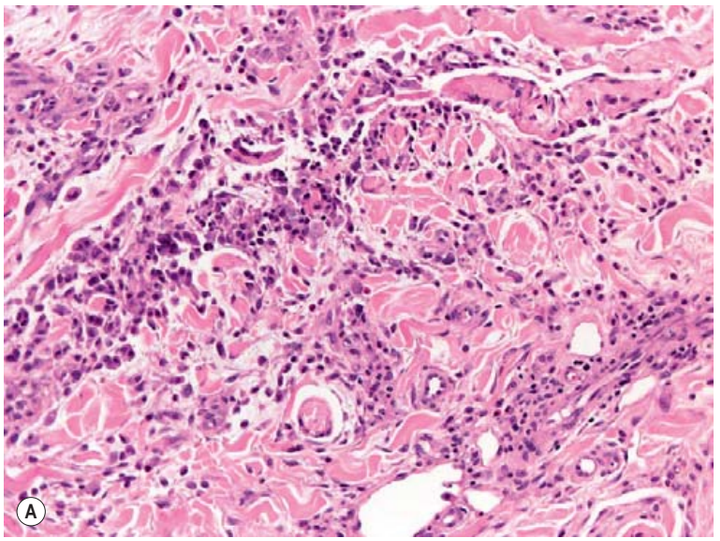
IGD with arthritis is characterized by erythematous plaques (often with an annular configuration) or linear cords (the "rope sign"; Fig. 45.11A) that favor the lateral trunk, axillae, buttocks, medial thighs (see Fig. 53.3), and groin. Large areas of involvement can be seen (Fig. 45.11B). It usually occurs in women with RA, seronegative arthritis or polyarthralgias and is often associated with autoimmune thyroiditis.

Pathology

The histopathologic features of PNGD and IGD exist on a spectrum and vary depending on the stage of evolution of the lesion that is biopsied. Early lesions of PNGD often show a pandermal infiltrate of neutrophils and focal leukocytoclastic vasculitis. Classic, fully developed lesions are characterized by zones of basophilic degenerated collagen surrounded by palisades of histiocytes, neutrophils and nuclear debris (Fig. 45.12). "Incomplete" early lesions may display focal basophilic collagen necrosis and histiocytes without orderly palisading in association with prominent neutrophils, whereas late lesions can exhibit well-developed palisading granulomas with only a sparse complement of neutrophils.

The histologic pattern of IGD features smaller "rosettes" of palisading histiocytes surrounding tiny, discrete foci of degenerated collagen (piecemeal fragmentation) within a dense, "bottom-heavy" dermal interstitial infiltrate that contains variable numbers of neutrophils and eosinophils. There is no evidence of vasculitis, and dermal mucin is usually absent.

Fig 45.11 Interstitial granulomatous dermatitis – clinical features. A Firm, linear subcutaneous cord along the axillary line (arrows) in a patient with rheumatoid arthritis. **B** Large symmetric pink patches and thin plaques that often resemble inflammatory patch-type granuloma annulare. *A, Courtesy, Kathryn Schwarzenberger, MD.*



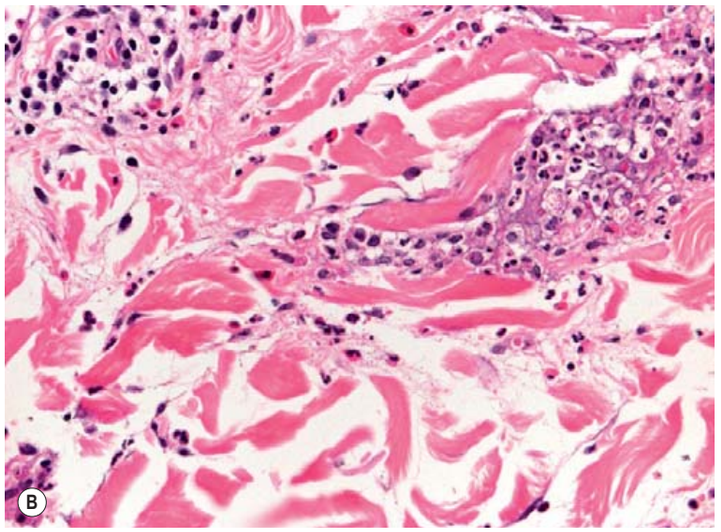


Fig 45.12 Interstitial granulomatous dermatitis – histologic features. A Fully developed lesions usually demonstrate neutrophils and histiocytes in association with basophilic degenerating collagen bundles; some eosinophils may be present as well. **B** Details of histiocytes admixed with lymphocytes, neutrophils and eosinophils. *Courtesy, Lorenzo Cerroni, MD.*

Differential Diagnosis

The clinical differential for PNGD includes perforating disorders, early rheumatoid nodules, accelerated rheumatoid nodulosis, and papular granuloma annulare (GA). The interstitial granulomatous drug reaction, which is most often caused by calcium channel blockers and angiotensin-converting enzyme inhibitors (Table 45.5), can mimic PNGD and IGD, both clinically and histologically. Onset typically occurs after months to years of therapy with the culprit medication. In addition, the development of IGD- and PNGD-like lesions has been associated with TNF inhibitor therapy in patients with RA. The clinical presentation of IGD with plaques may resemble patch-type GA, the inflammatory stage of morphea, erythema migrans or mycosis fungoides.

The histologic differential diagnosis includes other palisaded granulomatous dermatitides such as GA, necrobiosis lipoidica (see Ch. 93) and rheumatoid nodules. GA is more likely to have a patchy infiltrate concentrated in the upper dermis ("top heavy") and abundant mucin deposition. A relative paucity of neutrophils and leukocytoclasis distinguishes GA from PNGD, whereas the presence of either larger palisades or a lack of palisades (e.g. in the interstitial pattern seen in patch-type GA) differentiates GA from IGD. Rheumatoid nodules can be recognized by their central eosinophilia (rather than basophilia) and predominantly subcutaneous location. All of these entities may show transepidermal elimination of degenerated collagen. Additional diagnostic considerations for an interstitial granulomatous infiltrate with variable neutrophils may include dimorphic fungal or atypical mycobacterial infections, Lyme disease and leprosy. Histologic features that favor an interstitial granulomatous drug reaction over IGD include a vacuolar interface dermatitis, atypical lymphocytes, prominent eosinophils, a lack of neutrophils and minimal collagen degeneration.

The evaluation of a patient with palisaded necrotizing granulomas and a suspected rheumatologic disorder is outlined in Figure 45.13, and the relationship of PNGD and IGD with other dermatoses that have granulomatous, neutrophilic or vasculitic components and affect this patient population is depicted in Figure 45.14.

Treatment

No specific therapy is required for these skin conditions, although improvement has been reported with the use of high-potency topical or intralesional corticosteroids, dapsone and hydroxychloroquine. Treatment of the underlying disease can also lead to resolution of existing lesions and prevent recurrences.

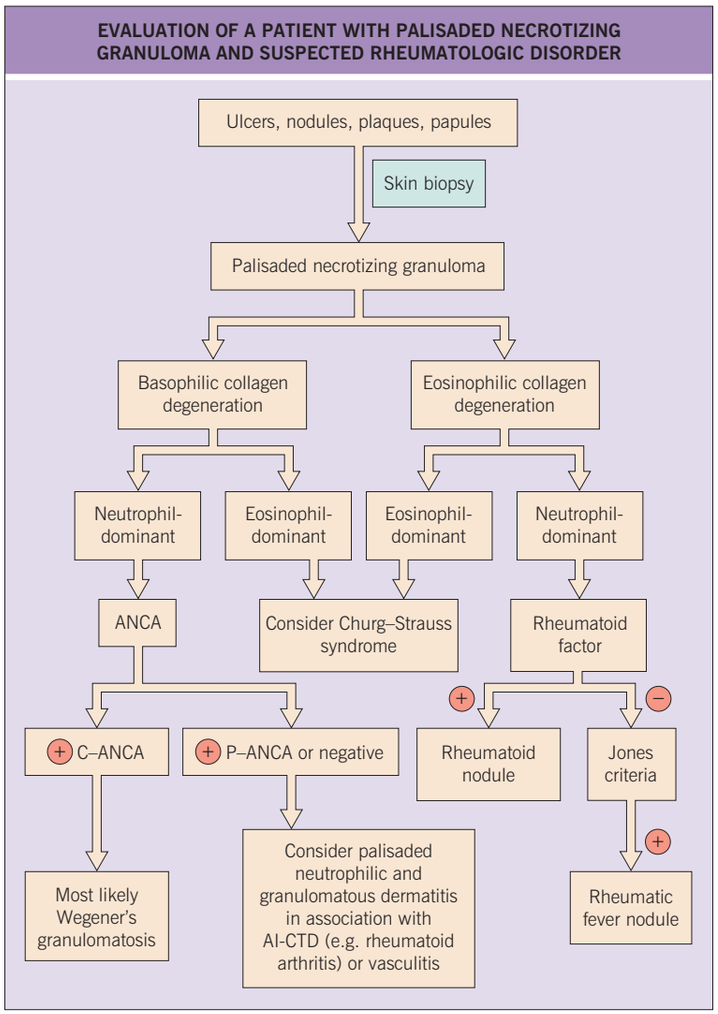


Fig. 45.13 Evaluation of a patient with palisaded necrotizing granuloma and suspected rheumatologic disorder. Jones criteria for rheumatic fever are reviewed in Ch. 19. AI-CTD, autoimmune connective tissue disease.

CAUSES OF INTERSTITIAL GRANULOMATOUS DRUG REACTION

COMMON

- Calcium channel blockers: diltiazem, verapamil, nifedipine
- HMG-CoA reductase inhibitors: simvastatin, pravastatin, lovastatin
- Furosemide
- Beta-blockers: labetalol, metoprolol, atenolol, propranolol
- Antihistamines (H_1 or H_2 blockers): famotidine, cimetidine, ranitidine, brompheniramine
- Angiotensin-converting enzyme inhibitors: enalapril, lisinopril
- TNF-α inhibitors: infliximab, etanercept, adalimumab; lenalidomide, thalidomide
- Anakinra

UNCOMMON

- Hydrochlorothiazide (HCTZ)
- Carbamazepine
- Diazepam
- Bupropion
- Darifenacin
- Sennoside
- Ganciclovir

Table 45.5 Causes of interstitial granulomatous drug reaction. HMG, β-hydroxy-β-methylglutaryl; TNF, tissue necrosis factor.

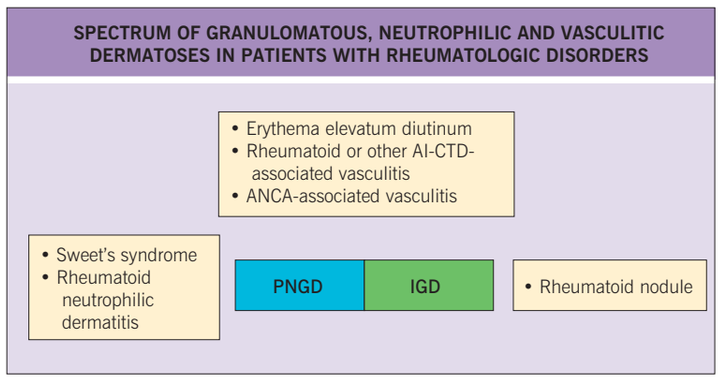


Fig. 45.14 Spectrum of granulomatous, neutrophilic and vasculitic dermatoses in patients with rheumatologic disorders. AI-CTD, autoimmune connective tissue disease; ANCA, antineutrophil cytoplasmic antibodies; IGD, interstitial granulomatous dermatitis; PNGD, palisaded neutrophilic and granulomatous dermatitis. *Courtesy, Julie V Schaffer, MD.*

REFERENCES

1. Petty RE, Southwood TR, Baum J, et al. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. J Rheumatol. 1998;25:1991–4.
2. Andersson GB. Juvenile arthritis: who gets it, where and when? A review of current data on incidence and prevalence. Clin Exp Rheumatol. 1999;17:367–74.
3. Pascual V, Allantaz F, Patel P, et al. How the study of children with rheumatic diseases identified interferon-α and interleukin-1 as novel therapeutic targets. Immunol Rev. 2008:223;39–59.
4. Sidiropoulos PI, Goulielmos G, Voloudakis GK, et al. Inflammasomes and rheumatic diseases: evolving concepts. Ann Rheum Dis. 2008;67:1382 –9.
5. Frosch M, Roth J. New insights in systemic juvenile idiopathic arthritis – from pathophysiology to treatment. Rheumatology. 2008;47:121–5.
6. Calabro JJ, Marchesano JM. Rash associated with juvenile rheumatoid arthritis. J Pediatr. 1968;72:611–19.
7. Prendiville JS, Tucker LB, Cabral DA, Crawford RI. A pruritic linear urticarial rash, fever, and systemic inflammatory disease in five adolescents: adult-onset Still disease or systemic juvenile idiopathic arthritis sine arthritis? Pediatr Dermatol. 2004;21:580–8.
8. Falcini F, Taccetti G, Ermini M. Methotrexate-associated appearance and rapid progression of rheumatoid nodules in systemic-onset juvenile rheumatoid arthritis. Arthritis Rheum. 1997;40:175–8.
9. Wagner-Weiner L. Pediatric rheumatology for the adult rheumatologist. J Clin Rheumatol. 2008;14:109–19.
10. Hayward K, Wallace CA. Recent developments in anti-rheumatic drugs in pediatrics: treatment of juvenile idiopathic arthritis. Arthr Res Ther. 2009;11:216.
11. Efthimiou P, Paik PK, Bielory L. Diagnosis and management of adult onset Still's disease. Ann Rheum Dis. 2006;564–72.
12. Efthimiou P, Georgy S. Pathogenesis and management of adult-onset Still's disease. Semin Arthritis Rheum. 2006;36:144–52.
13. Lee JY, Yang CC, Hsu MM. Histopathology of persistent papules and plaques in adult-onset Still's disease. J Am Acad Dermatol. 2005;52:1003–8.
14. Kötter I, Wacker A, Koch S, et al. Anakinra in patients with treatment-resistant adult-onset Still's disease. Semin Arthritis Rheum. 2007;37:189–97.

14a. Puechal X, DeBandt M, Berthelot JM, et al. Tocilizumab in refractory adult Still's disease. Arthritis Care Res. 2011;63:155–9.

15. Pearson CM, Kline HM, Newcomer VD. Relapsing polychondritis. N Engl J Med. 1960;263:51–8.
16. Letko E, Zafirakis P, Baltatzis A, et al. Relapsing polychondritis: a clinical review. Semin Arthritis Rheum. 2002;31:384–95.
17. Kent PD, Michet CJ, Luthra HS. Relapsing polychondritis. Curr Opin Rheumatol. 2003;16:56–61.
18. Hansson AS, Johannesson M, Svensson L, et al. Relapsing polychondritis, induced in mice with matrilin 1, is an antibody- and complement-dependent disease. Am J Pathol. 2004;164:959–66.
19. Frances C, el Rassi R, Laporte JL, et al. Dermatologic manifestations of relapsing polychondritis. A study of 200 cases at a single center. Medicine (Baltimore). 2001;80:173–9.

19a. Tronquoy AF, de Quatrebarbes J, Picard D, et al. Papular and annular fixed urticarial eruption: A characteristic skin manifestation in patients with relapsing polychondritis. J Am Acad Dermatol. 2011; May 17 [Epub ahead of print]

20. Firestein GS, Gruber HE, Weisman MH, et al. Mouth and genital ulcers with inflamed cartilage: MAGIC syndrome. Am J Med. 1985;79:65–72.
21. Leroux G, Costedoat-Chalumeau N, Brihaye B, et al. Treatment of relapsing polychondritis with rituximab: a retrospective study of nine patients. Arthritis Rheum. 2009;61:577–82.
22. Vitali C, Bombardieri S, Jonssson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis. 2002;61:554–8.
23. Delaleu N, Jonsson MV, Appel S, Jonsson R. New concepts in the pathogenesis of Sjogren's syndrome. Rheum Dis Clin North Am. 2008;34:833–45.

24. Fox RI, Liu AY. Sjogren's syndrome in dermatology. Clin Dermatol. 2006;24:393–413.
25. Nguyen CQ, Hu MH, Li Y, et al. Salivary gland tissue expression of interleukin-23 and interleukin-17 in Sjogren's syndrome: findings in humans and mice. Arthritis Rheum. 2008;58:734–43.
26. Nakamura H, Kawakami A, Tominaga M, et al. Expression of CD-40/CD-40 ligand and Bcl-2 family proteins in labial salivary glands of patients with Sjögren's syndrome. Lab Invest. 1999;79:261–9.
27. Ramos-Casals M, Anaya JM, Garcia-Carrasco M, et al. Cutaneous vasculitis in primary Sjögren syndrome: classification and clinical significance of 52 patients. Medicine (Baltimore). 2004;83:96–106.
28. Brito-Zero P, Ramos-Casals M, Bove A, et al. Predicting adverse outcomes in primary Sjögren's syndrome: identification of prognostic factors. Rheumatology. 2007;46:1359–62.
29. Voulgarelis M, Moutsopoulos HM. Mucosa-associated lymphoid tissue lymphoma in Sjögren's syndrome: risks, management, and prognosis. Rheum Dis Clin North Am. 2008;34:921–33.
30. Ramos-Casals M, Font J, Carcia-Carrasco M, et al. Primary Sjögren syndrome: hematologic patterns of disease expression. Medicine (Baltimore). 2002;81:281–92.
31. Coca A, Sanz I. B cell depletion in lupus and Sjögren's syndrome: an update. Curr Opin Rheumatol. 2009;21:483–8.
32. Thanou-Stavraki T, James JA. Primary Sjögren's syndrome: current and prospective therapies. Semin Arthritis Rheum. 2008;37:273–92.

32a. Meijer JM, Meiners PM, Vissink A, et al. Effectiveness of rituximab treatment in primary Sjögren's syndrome: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2010;62:960–8.

33. Sharp GC, Irvin WS, Tan EM, et al. Mixed connective tissue disease: an apparently distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antigen (ENA). Am J Med. 1972;52: 148–59.
34. Lundberg IE. The prognosis of mixed connective tissue disease. Rheum Dis Clin North Am. 2005;31:535–47.
35. Venables PJW. Mixed connective tissue disease. Lupus. 2006;15:132–7.
36. Greidinger EL, Hoffman RW. Autoantibodies in the pathogenesis of mixed connective tissue disease. Rheum Dis Clin North Am. 2005;31:437–50.
37. Ariner M, Steiner G, Smolen JS. Does mixed connective tissue disease exist? Yes. Rheum Dis Clin North Am. 2005;31:411–20.
38. Pope JE. Other manifestations of mixed connective tissue disease. Rheum Dis Clin North Am. 2005;31: 519–33.
39. Hamza M. Orogenital ulcerations in mixed connective tissue disease (letter). J Rheumatol. 1985;12:643–4.
40. Kim P, Grossman JM. Treatment of mixed connective tissue disease. Rheum Dis Clin North Am. 2005;31:549–65.
41. Sanchez-Pernaute O, Ospelt C, Neidhart M, Steffen G. Epigenetic clues to rheumatoid arthritis. J Autoimm. 2008;30:12–20.
42. Smolen JS, Aletaha A, Koeller M, et al. New therapies for treatment of rheumatoid arthritis. Lancet. 2007;370: 1861–74.
43. Sayah A, English JC III. Rheumatoid arthritis: a review of the cutaneous manifestations. J Am Acad Dermatol. 2005;53:191–209.
44. Craig SD, Jorizzo JL, White WL, et al. Cutaneous signs of rheumatic disease: acral purpuric papules in a patient with clinical rheumatoid arthritis. Arthritis Rheum. 1994;37:957–9.
45. Rosenstein ED, Kramer N. Felty's and pseudo-Felty's syndromes. Semin Arthritis Rheum. 1991;21:129–42.
46. Turesson C, Matteson EL. Vasculitis in rheumatoid arthritis. Curr Opin Rheumatol. 2009;21:35–40.
47. Chu P, Connolly MK, LeBoit PE. The histopathologic spectrum of palisaded neutrophilic and granulomatous dermatitis in patients with collagen vascular disease. Arch Dermatol. 1994;130:1278–83.

Mucinoses 46

Franco Rongioletti and Alfredo Rebora

Key features

- The cutaneous mucinoses are a heterogeneous group of disorders in which an abnormal amount of mucin accumulates in the skin
- The etiopathogenesis of cutaneous mucinoses is unknown
- The cutaneous mucinoses are divided into two groups: (1) primary cutaneous mucinoses, in which the mucin deposition leads to clinically distinctive lesions and is the major histologic feature; and (2) secondary mucinoses, in which the mucin deposition is simply an associated finding
- Primary cutaneous mucinoses are further divided into degenerative–inflammatory forms (which may be dermal or follicular) and hamartomatous–neoplastic forms
- Associated disorders include paraproteinemia (scleromyxedema, scleredema), diabetes mellitus (scleredema), thyroid disease (pretibial myxedema, myxedema) and autoimmune connective tissue disease (lupus erythematosus, dermatomyositis)

INTRODUCTION

The cutaneous mucinoses are a heterogeneous group of disorders in which an abnormal amount of mucin accumulates in the skin, either diffusely or focally[1].

Mucin is a component of the dermal extracellular matrix and is normally produced in small amounts by fibroblasts. It is a jelly-like, amorphous mixture of acid glycosaminoglycans (formerly referred to as acid mucopolysaccharides), which are complex carbohydrates composed of multiple repeating polysaccharide units (see Ch. 95). The acid glycosaminoglycans may be attached to both sides of a protein core (proteoglycan monomer), as in the case of dermatan sulfate and chondroitin sulfate, or they may be free, as in the case of hyaluronic acid, which is the most important component of dermal mucin.

Mucin is capable of absorbing 1000 times its own weight in water, playing a major role in maintaining the salt and water balance of the dermis. In routinely stained sections, the presence of either a blue-staining material between separated collagen bundles or empty spaces within the dermis is a good clue that there is mucin deposition. For confirmation, special stains can be used, such as Alcian blue, colloidal iron or toluidine blue (Table 46.1). Furthermore, dermal mucin is PAS-negative and, if composed of hyaluronic acid, hyaluronidase-sensitive. Fixation of biopsy specimens in absolute alcohol (rather than formalin) may improve its detection, and monoclonal antibodies have been used to detect sulfated acid glycosaminoglycans[2]. An alternative approach is to utilize biotinylated hyaluronan (HA)-binding proteins coupled to an avidin-peroxidase reaction[3].

Why mucin abnormally accumulates within the skin of some individuals is unclear. Certain "serum factors", e.g. immunoglobulins and/or cytokines, could promote the upregulation of glycosaminoglycan synthesis[4]. For example, increased serum immunoglobulin levels (monoclonal or polyclonal) and circulating autoantibodies can be found in association with cutaneous mucinoses such as scleromyxedema, Graves disease-associated pretibial myxedema, and papulonodular mucinosis of lupus erythematosus. However, the serum from these patients stimulates mucin production even *after* the elution of either the IgG paraprotein in those with scleromyxedema or the autoantibodies in those with Graves disease-associated pretibial myxedema. Circulating cytokines such as interleukin (IL)-1, TNF-α and TGF-β, which are known to stimulate glycosaminoglycan synthesis in the skin, could play a role in excess mucin deposition. A reduction in the normal catabolic degradation of mucin could also be a factor.

This chapter focuses on the disorders characterized by abnormal dermal deposits of mucin, composed primarily of hyaluronic acid (Fig. 46.1). The mucopolysaccharidoses (MPS), in which the predominant dermal mucin is dermatan sulfate or heparan sulfate (e.g. Hunter syndrome), are discussed in Chapter 48.

STAINING CHARACTERISTICS OF ACID GLYCOSAMINOGLYCANS (MUCOPOLYSACCHARIDES)

Histologic stain	Acid glycosaminoglycans (mucopolysaccharides)	
	Non-sulfated (hyaluronic acid*)	Sulfated (heparan sulfate, dermatan sulfate, chondroitin sulfate†)
Colloidal iron	⊕	⊕
Alcian blue		
pH 2.5	⊕	⊕
pH 0.5	⊖	⊕
Metachromasia with toluidine blue		
pH 4.0	⊕	⊕
pH < 2.0	⊖	⊕
PAS‡	⊖	⊖
Hyaluronidase-sensitive	⊕	⊖

*Major GAG in the disorders discussed in this chapter; not bound to protein core.
†Major GAGs in the mucopolysaccharidoses, e.g., Hunter syndrome, Hurler syndrome; bound to protein core (proteoglycan).
‡Stains neutral mucopolysaccharides.

Table 46.1 Staining characteristics of acid glycosaminoglycans (mucopolysaccharides). GAG, glycosaminoglycan.

CLASSIFICATION

The cutaneous mucinoses may be classified as primary, in which mucin deposition is the major histologic feature resulting in clinically distinctive lesions (Table 46.2), and secondary, in which mucin simply represents an associated histologic finding (Table 46.3). Primary mucinoses can then be divided into degenerative–inflammatory forms and hamartomatous–neoplastic types. The former are further subdivided into dermal and follicular forms, based upon the location of the mucin (see Table 46.2).

PRIMARY DEGENERATIVE–INFLAMMATORY MUCINOSES

Dermal Mucinoses

Scleromyxedema

Synonyms: ■ Papular mucinosis ■ Generalized and sclerodermoid lichen myxedematosus

CLASSIFICATION OF THE PRIMARY CUTANEOUS MUCINOSES
DEGENERATIVE–INFLAMMATORY MUCINOSES
Dermal
Scleromyxedema or papular mucinosis*
Lichen myxedematosus (localized variants)
• Discrete papular form†
• Acral persistent papular mucinosis†
• Cutaneous mucinosis of infancy
• Nodular form
Self-healing cutaneous mucinosis
• Juvenile type
• Adult type
Scleredema
Mucinoses associated with altered thyroid function
• Localized (pretibial) myxedema
• Generalized myxedema
Reticular erythematous mucinosis
Papulonodular mucinosis associated with autoimmune connective tissue diseases (most commonly LE)
Cutaneous focal mucinosis
Digital mucous cyst (myxoid cyst)
Miscellaneous mucinoses
Follicular
Follicular mucinosis (Pinkus)
Urticaria-like follicular mucinosis
HAMARTOMATOUS–NEOPLASTIC MUCINOSES
Mucinous nevus
(Angio)myxoma
*Also referred to as generalized and sclerodermoid lichen myxedematosus.
†Also seen in HIV-infected individuals.

Table 46.2 Classification of the primary cutaneous mucinoses. LE, lupus erythematosus.

DISORDERS ASSOCIATED WITH HISTOLOGIC DEPOSITION OF MUCIN (SECONDARY MUCINOSES)
EPITHELIAL MUCINOSIS
• Basal cell carcinoma
• Rare – squamous cell carcinoma, keratoacanthoma, verruca, seborrheic keratosis, mycosis fungoides
DERMAL MUCINOSIS
• Granuloma annulare
• Lupus erythematosus, dermatomyositis >> scleroderma
• Mesenchymal tumors (e.g. myxosarcoma, myxoid lipoblastoma, DFSP)
• Neural tumors (e.g. neurofibroma, lobular neuromyxoma)
• Epithelial tumors (e.g. basal cell carcinoma, eccrine carcinoma)
• Other tumors (e.g. cutaneous metastases, mucinous carcinoma of the eyelid)
• Obesity-associated lymphedema
• Hypertrophic scar
• Rare – chronic GVHD, cutaneous reactions to interferon, herpes zoster, venous insufficiency, hereditary progressive mucinous histiocytosis
FOLLICULAR MUCINOSIS
• Lymphoma, T-cell
• Eczematous dermatoses
• Rare – lupus erythematosus, insect bites (including in the setting of CLL), side effect of imatinib, familial reticuloendotheliosis

Table 46.3 Disorders associated with histologic deposition of mucin (secondary mucinoses). A limited amount of dermal mucin can occasionally be observed in virtually all cutaneous disorders. CLL, chronic lymphocytic leukemia; DFSP, dermatofibrosarcoma protuberans.

DIAGNOSTIC CRITERIA OF SCLEROMYXEDEMA VERSUS LOCALIZED VARIANTS OF LICHEN MYXEDEMATOSUS	
Scleromyxedema	**Localized variants of lichen myxedematosus**
Generalized papular eruption and sclerodermoid features	Papular eruption (or nodules and/or plaques due to confluence of papules)
Microscopic triad (mucin deposition, fibroblast proliferation, fibrosis)	Mucin deposition with variable fibroblast proliferation
Monoclonal gammopathy	Absence of monoclonal gammopathy
Absence of thyroid disorder	Absence of thyroid disorder

Table 46.4 Diagnostic criteria of scleromyxedema versus localized variants of lichen myxedematosus.

Introduction and definition

Scleromyxedema is a chronic idiopathic disorder characterized by numerous firm papules and areas of induration that are due to dermal mucin deposition in association with an increase in dermal collagen[4]. Patients also have a monoclonal gammopathy and systemic, even lethal, manifestations. This entity must be distinguished from localized variants of lichen myxedematosus where the skin is the sole site of involvement (Table 46.4). There are, however, occasional patients who have an atypical constellation of findings and fall between scleromyxedema and localized lichen myxedematosus (atypical forms; see below).

History

Although the first descriptions of scleromyxedema were attributed to Dubreuilh in 1906 and Reitman in 1908, it was not until the review of Montgomery and Underwood in 1953 that the disease was distinguished from scleroderma and generalized myxedema. A year later, Gottron and his colleagues gave the name "scleromyxedema" to the generalized and sclerotic form. The association of a monoclonal gammopathy with scleromyxedema was first described in 1963.

Epidemiology and pathogenesis

Scleromyxedema is a fairly uncommon disease, affecting middle-aged adults of both sexes equally. The pathogenesis of scleromyxedema is unknown. The role of the associated monoclonal gammopathy remains a matter of debate. While patients have evidence of a plasma cell dyscrasia, paraprotein levels do not correlate with either the extent or the progression of the disease. In addition, sera from patients with scleromyxedema enhanced fibroblast proliferation *in vitro*, but an immunoglobulin purified from paraprotein-containing sera failed to do so, suggesting a pathogenetic role for circulating factors other than the paraprotein. Clinical remission of scleromyxedema (and reduction of the M-protein) following autologous hematopoietic stem cell transplantation points to the bone marrow as a source of these circulating factors. Lastly, the development of scleromyxedema following a cutaneous granulomatous reaction to intradermal injections of hyaluronic gel suggests the possibility of a human adjuvant disease[5].

Clinical features

In scleromyxedema, numerous, 2–3 mm, firm, waxy, closely spaced papules develop in a widespread symmetrical distribution pattern. The most common sites of involvement are the head and neck region (Fig. 46.2), upper trunk, hands, forearms and thighs. Papules are often arranged in a strikingly linear array. The surrounding skin is shiny and indurated, i.e. sclerodermoid in appearance, and the glabella is typically involved with deep longitudinal furrowing. Severe involvement of the face can result in a leonine facies (Fig. 46.3). Erythema, edema and a brownish discoloration may also be seen in the involved areas; pruritus is not rare. The mucous membranes and scalp are spared. As the condition progresses, erythematous and infiltrated plaques may appear with skin stiffening, sclerodactyly and decreased motility of the mouth and joints. Overlying the proximal interphalangeal joints, a central depression surrounded by an elevated rim (due to skin thickening) can be seen and is referred to as the "doughnut sign". Mat and cuticular telangiectasias and calcinosis, as seen in systemic sclerosis, are absent.

Scleromyxedema is almost always associated with paraproteinemia. The monoclonal gammopathy is usually IgG and the light chains are

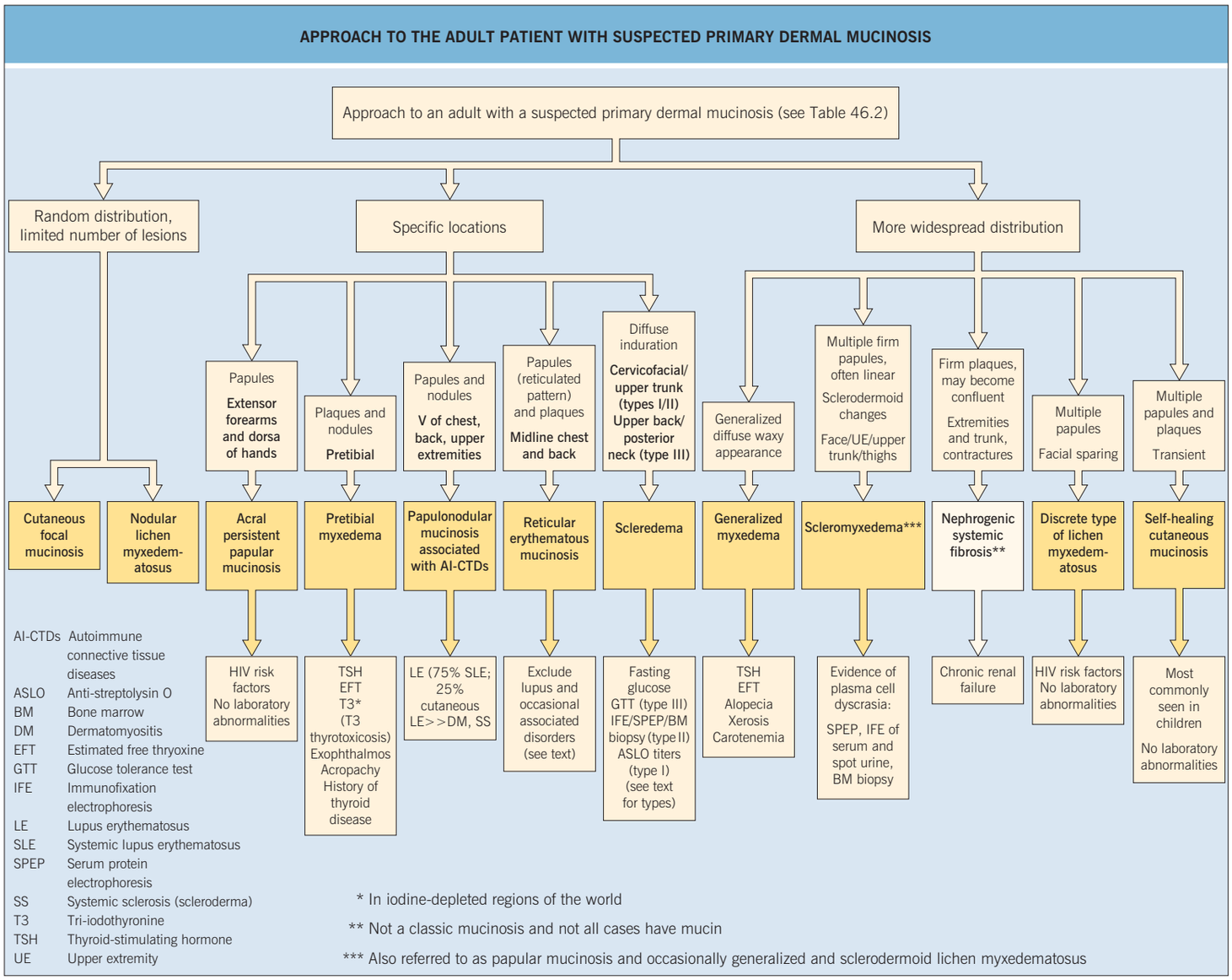


Fig. 46.1 Approach to the patient with suspected primary dermal mucinosis. Pretibial myxedema must be distinguished from obesity-associated lymphedematous mucinosis.

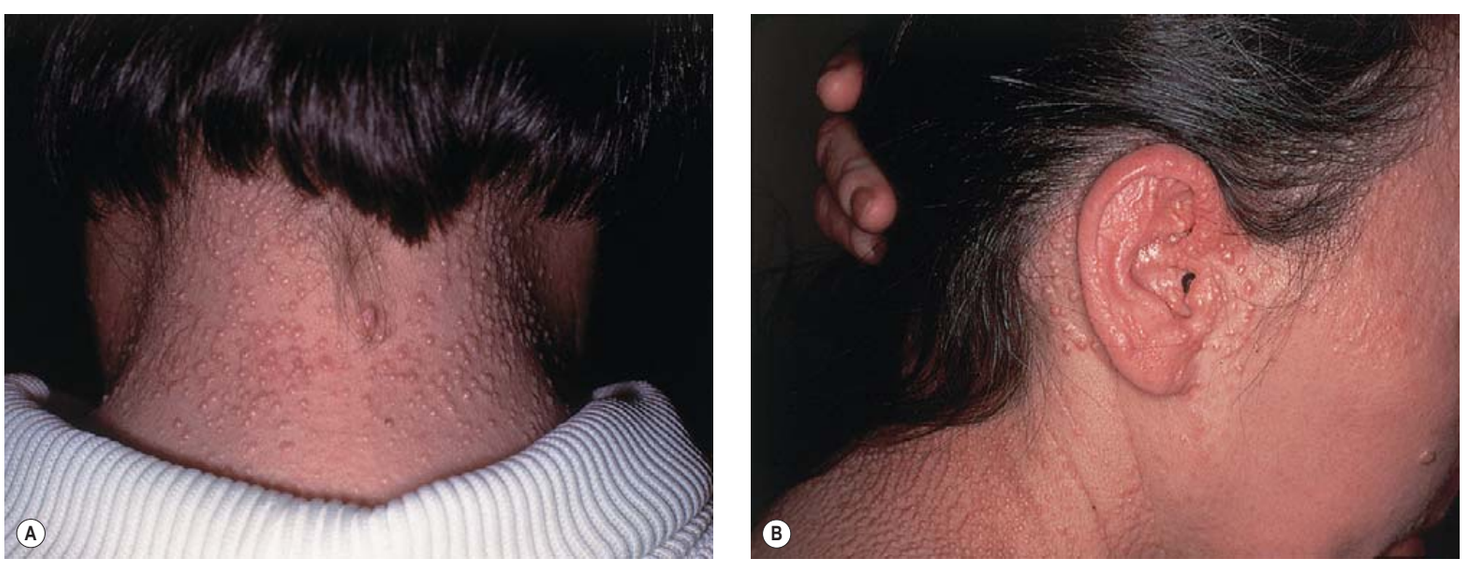


Fig. 46.2 Scleromyxedema. A,B Numerous monomorphic, firm, skin-colored to pink papules which can have a linear arrangement (most obvious on the left neck [**A**] and the upper back [**B**]).

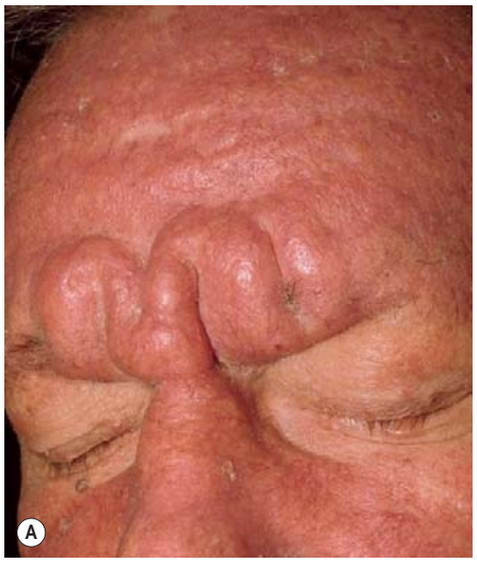


Fig. 46.3 Scleromyxedema. Thickening of the skin of the forehead (**A**) and trunk (**B**), leading to deep furrows and folds. Scleromyxedema is one of the causes of leonine facies. *Courtesy, Joyce Rico, MD.*

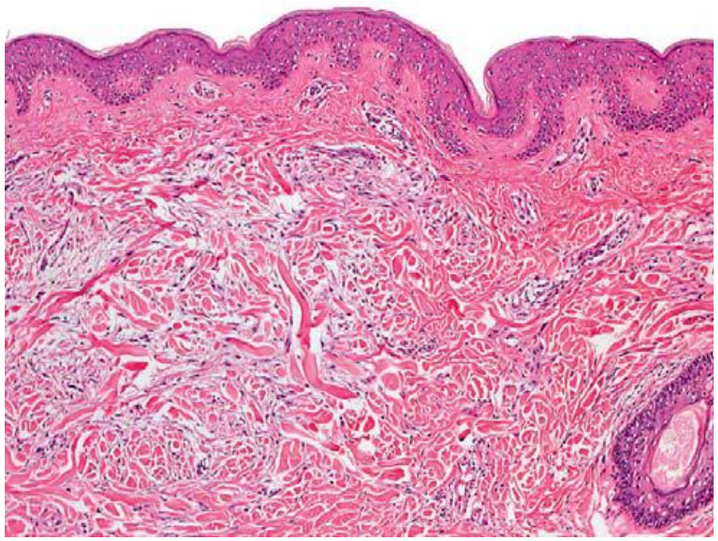


Fig. 46.4 Histopathology of scleromyxedema. Typical triad of fibrosis, an increased number of irregularly arranged fibroblasts, and interstitial deposits of mucin in the upper and mid reticular dermis. *Courtesy, Lorenzo Cerroni, MD.*

more commonly lambda. Although a mild plasmacytosis may be observed in bone marrow biopsies, less than 10% of patients with scleromyxedema progress to multiple myeloma. Patients with scleromyxedema can have a number of internal manifestations, in particular muscular, neurologic, rheumatologic, pulmonary, renal and cardiovascular. Dysphagia, proximal muscle weakness due to myositis, disturbances of the CNS leading to unexplained coma[6], peripheral neuropathy, arthropathies, carpal tunnel syndrome, restrictive or obstructive lung disease, and a scleroderma-like renal disease may accompany or follow the cutaneous manifestations. While the predominantly sensory peripheral neuropathy typically affects older men and has an insidious onset, the dermato-neuro syndrome is a potentially life-threatening encephalopathy. This syndrome begins abruptly with a worsening of skin lesions, a flu-like prodrome, fever and seizures, and it can eventuate in an unexplained coma[6].

Pathology

Scleromyxedema is characterized by a triad of microscopic features[7]:

- a diffuse deposit of mucin in the upper and mid reticular dermis
- an increase in collagen deposition
- a marked proliferation of irregularly arranged fibroblasts (Fig. 46.4).

The epidermis may be normal or thinned by the pressure of the underlying mucin and fibrosis; the hair follicles may be atrophic. A slight superficial, perivascular, lymphoplasmacytic infiltrate is often present. The elastic fibers are fragmented and decreased in number. Mucin may fill the walls of myocardial blood vessels as well as the interstitium of the kidney, pancreas, adrenal glands and nerves. In the dermato-neuro syndrome, autopsy findings have not proved helpful in elucidating its underlying pathogenesis.

Differential diagnosis

The primary differential diagnosis for scleromyxedema is scleroderma (systemic sclerosis) and scleredema. The presence of papules, especially in linear arrays, is a very helpful clinical sign in distinguishing scleromyxedema. Additional entities in the sclerodermoid differential diagnosis should be excluded (see Ch. 43). In particular, nephrogenic systemic fibrosis, which develops in individuals with renal dysfunction, may have mucin in biopsy specimens, but patients lack both facial involvement (commonly seen in scleromyxedema) and paraproteinemia. Criteria for diagnosing scleromyxedema versus localized variants of lichen myxedematosus are summarized in Table 46.4 and the dermatologic disorders in which leonine facies can develop are outlined in Table 46.5.

Treatment

The treatment of scleromyxedema can be disappointing. In the past, monthly courses of melphalan were often the therapy of choice, targeting the plasma cell dyscrasia. However, while this alkylating agent can result in some clinical improvement, it has also been implicated in 30% of the deaths secondary to its induction of hematologic malignancies and septic complications[8]. Other chemotherapeutic agents (e.g. cyclophosphamide, methotrexate, chlorambucil, 2-chlorodesoxyadenosine) have been tried, but with no better results and the risk of similar side effects.

Nowadays, therapeutic regimens are based primarily upon those used to treat myeloma and include various combinations of melphalan, dexamethasone or prednisone, thalidomide (100–200 mg daily long term, with higher doses initially), lenalidomide, and bortezomib (a proteasome inhibitor)[9]. As in myeloma, corticosteroids are usually not administered as monotherapy due to more limited sustained responses. In appropriate candidates who have disabling or potentially life-threatening disease, autologous hematopoietic stem cell transplantation is an option[9a,9b]. Of note, there is increasing evidence that IVIg may represent an effective and relatively safe treatment for both cutaneous and extracutaneous manifestations of scleromyxedema, including the dermato-neuro syndrome[10].

Additional therapies include intralesional and topical corticosteroids, but they are of limited value. Primarily in case series, topical and intralesional hyaluronidase, PUVA, UVA1, systemic retinoids, electron beam radiation, plasmapheresis[10a], extracorporeal photochemotherapy, dermabrasion, and topical dimethyl sulfoxide have all produced some improvement without treating the underlying disease. Granulocyte

LEONINE FACIES – ASSOCIATED DERMATOLOGIC DISEASES
Scleromyxedema
Systemic amyloidosis
Lipoid proteinosis
Lepromatous leprosy
Leishmaniasis
Cutaneous lymphoma (T-cell, B-cell)
Actinic reticuloid form of chronic actinic dermatitis
Leukemia cutis
Mastocytosis (nodular)
Sarcoidosis
Multicentric reticulohistiocytosis
Progressive nodular histiocytosis
Pachydermoperiostosis

Table 46.5 Leonine facies – associated dermatologic diseases. Leonine facies can also be seen in patients with Paget's disease of the bone. *Insert, Courtesy, Joyce Rico, MD.*

colony-stimulating factor proved beneficial in one patient with idiopathic neutropenia, as did cyclosporine in a second patient. Interferon-α has led to paradoxical effects, with both improvement and worsening of the disease[11].

Dysarthria and a flu-like illness may herald the life-threatening coma, and the patient should be promptly admitted to the hospital for close observation. Occasionally, spontaneous improvement and clinical resolution, even after 15 years, have been described[4].

Lichen myxedematosus (localized variants)

Introduction

In the localized variants of lichen myxedematosus, patients develop small, firm, waxy papules (or nodules and plaques produced by the confluence of papules) that are limited to only a few sites – usually the upper and lower limbs and/or trunk. The skin is the only site of involvement and these variants, in contrast to scleromyxedema, are not associated with sclerosis, paraproteinemia or systemic involvement nor are they associated with thyroid disease (see Fig. 46.1)[4]. While most dermatologists equate lichen myxedematosus with localized, skin-limited disease, a source of potential confusion is the uncommon and more historical use of the term "generalized and sclerodermoid lichen myxedematosus" to describe scleromyxedema.

The localized variants of lichen myxedematosus are subdivided into four subtypes:

- a discrete papular form
- acral persistent papular mucinosis
- cutaneous mucinosis of infancy
- a pure nodular form.

Localized variants of lichen myxedematosus may be observed in association with HIV infection, exposure to toxic oil or L-tryptophan (historical), and hepatitis C viral (HCV) infection.

Epidemiology

Exact incidence and prevalence rates for the localized variants of lichen myxedematosus are not known.

Clinical features

Discrete papular lichen myxedematosus is characterized by 2–5 mm papules, numbering from just a few to hundreds and involving the limbs and trunk in a symmetrical pattern[12] (Fig. 46.5). The affected skin is not indurated and the face is spared. The lesions progress slowly without systemic involvement. However, they rarely resolve spontaneously. Progression to scleromyxedema has never been proven.

In **acral persistent papular mucinosis**, first described in 1986 by Rongioletti et al.[13], multiple ivory to skin-colored papules develop exclusively on the dorsal aspect of the hands and extensor surface of the distal forearms (Fig. 46.6). A female predominance (female : male ratio of 3 : 1) has been noted. The lesions persist without systemic manifestations[14].

In **cutaneous mucinosis of infancy** (syn. papular mucinosis of infancy), first described by Lum in 1980, firm opalescent papules appear on the neck (Fig. 46. 7), upper arms (especially the elbows), and trunk[4].

Fig. 46.5 Localized lichen myxedematosus – discrete papular type. Persistent whitish papules on the arms.

Fig. 46.6 Acral persistent papular mucinosis. Skin-colored papules on the dorsal aspect of the hands.

Neither systemic symptoms nor spontaneous resolution are observed. Of the handful of patients described to date, at least two have had a congenital linear variant, which might be better categorized as an example of a mucinous nevus[15].

Nodular lichen myxedematosus is characterized by multiple nodules on the limbs and trunk, with a mild or absent papular component.

Localized lichen myxedematosus in HIV-infected patients has been described in HIV-positive men who have either had sex with other men or abused illicit drugs. The majority developed the discrete papular form of lichen myxedematosus on the limbs and trunk, while the remainder had acral persistent papular mucinosis. All became infected with HIV before the onset of the lichen myxedematosus. Most of them had hypergammaglobulinemia, which is a well-recognized manifestation of HIV infection, and to date only two had a paraproteinemia. Of note, up to 10% of HIV-infected individuals can have a monoclonal gammopathy of undetermined significance (MGUS) and how this relates to the mucinosis remains to be determined. None of the patients had visceral involvement due to mucin deposition[16].

Fig. 46.7 Cutaneous mucinosis of infancy. Skin-colored papules on the back of the neck in a young girl.

Localized lichen myxedematosus in "toxic" syndromes. Multiple papules due to mucin deposition with a clinical appearance similar to the discrete form of lichen myxedematosus have also been described in the setting of toxic oil syndrome and L-tryptophan-associated eosinophilia–myalgia syndrome. Although unrelated epidemiologically and both of historical interest, toxic oil syndrome (due to the ingestion of adulterated rapeseed oil in Spain in the early 1980s) and L-tryptophan-associated eosinophilia–myalgia (related to a contaminant in L-tryptophan-containing products used as sedatives during the late 1980s) share several clinical features, including constitutional symptoms, peripheral eosinophilia, hyperpigmentation and a sclerodermoid appearance[17], in addition to this mucinous papular eruption. Usually 1–5 months after the onset of the illness, white or skin-colored papules (1–5 mm in diameter) appeared, primarily on the limbs. The lesions resolved slowly after exposure to the toxic substance ceased.

Localized lichen myxedematosus and HCV infection. An association of lichen myxedematosus with chronic hepatitis due to HCV infection has been reported[18], especially from Japan[19], but this relationship needs to be confirmed by more extensive studies.

Atypical forms of lichen myxedematosus. Occasional patients with lichen myxedematosus have atypical features or features intermediate between scleromyxedema and localized lichen myxedematosus[4]. This group includes patients with scleromyxedema who lack a monoclonal gammopathy as well as individuals with localized forms of lichen myxedematosus who also have a monoclonal gammopathy and/or systemic symptoms. One possible explanation for the former group is performance of just a serum protein electrophoresis (SPEP), rather than a SPEP plus an immunofixation electrophoresis of serum and urine; the latter is a more sensitive assay.

Pathology

In the localized forms of lichen myxedematosus, the histologic changes are less characteristic than in scleromyxedema. Mucin accumulates in the upper and mid reticular dermis and fibroblast proliferation is variable; fibrosis is not marked and may even be absent. In acral persistent papular mucinosis, mucin accumulates focally in the upper reticular dermis (sparing a subepidermal zone) and fibroblasts are not increased in number. In cutaneous mucinosis of infancy, the mucin may be so superficial as to look as if it were "enclosed" by epidermis[7].

Differential diagnosis

Histologic examination of the skin helps to distinguish localized variants of lichen myxedematosus from several papular eruptions that can have a similar appearance, such as granuloma annulare, lichen amyloidosus, lichen planus and other lichenoid eruptions, papular elastorrhexis and eruptive collagenomas. It is also important to differentiate these entities from scleromyxedema and the cutaneous mucinosis that can occur in the setting of autoimmune connective tissue diseases (see below).

Treatment

Localized lichen myxedematosus does not require therapy, and a wait-and-see approach is recommended. Topical application of corticosteroids, pimecrolimus or tacrolimus may be of some benefit[12]. One patient with associated HIV infection had a complete remission after treatment with oral isotretinoin. However, spontaneous resolution may occur[20], even in the setting of HIV infection[16].

Self-healing cutaneous mucinosis

Although previously considered a subtype of localized lichen myxedematosus, self-healing cutaneous mucinosis is best regarded as a distinct rare form of primary dermal mucinosis. It was initially described in children, with ages of reported patients ranging from 1 to 15 years[21]. However, the same disorder was subsequently observed in a few adults, but in the authors' opinion, some of the adult patients were actually examples of localized lichen myxedematosus with spontaneous resolution[22].

Self-healing cutaneous mucinosis is characterized by the following clinical presentations: (1) an acute eruption of multiple papules, sometimes coalescing into linear infiltrated plaques, on the face, neck, scalp, abdomen and thighs; and (2) mucinous subcutaneous nodules in periarticular areas and on the face, with periorbital swelling. In addition, systemic symptoms (e.g. fever, arthralgias and muscle tenderness) may accompany the cutaneous lesions, but paraproteinemia, bone marrow plasmacytosis and thyroid dysfunction are not observed. Spontaneous resolution over a period of a few weeks to several (i.e. 2 to 8) months is characteristic, hence the name. Histologically, papular lesions show dermal mucin deposition with mild inflammation and a small increase in the number of fibroblasts, whereas nodules have deep mucinous deposits associated with bands of fibrosis and a prominent proliferation of fibroblasts[21].

Scleredema

Synonyms: ■ Scleredema adultorum of Buschke ■ Scleredema diabeticorum

Introduction

Scleredema is a symmetrical diffuse induration of the upper part of the body due to a thickened dermis and deposition of mucin.

History

Although Buschke has been credited with first describing scleredema, the original description dates back to Pitford in 1876. A relationship with diabetes mellitus was only established in 1970.

Epidemiology and pathogenesis

Scleredema is an unusual disease that affects all races. Diabetes mellitus is considered to be a pathogenetic factor. The form that is associated with diabetes is more prevalent in men, while other forms are seen more commonly in women. Irreversible glycosylation of collagen and resistance to degradation by collagenase may lead to an accumulation of collagen. Alternatively, excess stimulation by insulin, microvascular damage and hypoxia may increase the synthesis of collagen and mucin. Streptococcal hypersensitivity (type I), injury to lymphatics, and paraproteinemia (type II) may also play a role.

Clinical features

Classically, there are three types of scleredema, although a simpler division into those with and those without diabetes has been suggested[23]. The *first type* affects primarily middle-aged women, but also children. It is preceded by fever, malaise and an infection (usually streptococcal) of the upper or lower respiratory tract. The skin of the cervicofacial region suddenly hardens with extension to the trunk and proximal upper limbs. The face is expressionless and opening of the mouth and swallowing are difficult because of the involvement of the tongue and pharynx. This type usually resolves in a few months.

The *second type* shares the same clinical features as the first but has a more subtle onset, without a preceding illness; it persists for years. This type is more frequently associated with a monoclonal gammopathy[23].

Fig. 46.8 Scleredema in association with diabetes mellitus. Diffuse induration of the upper part of the body with overlying erythema.

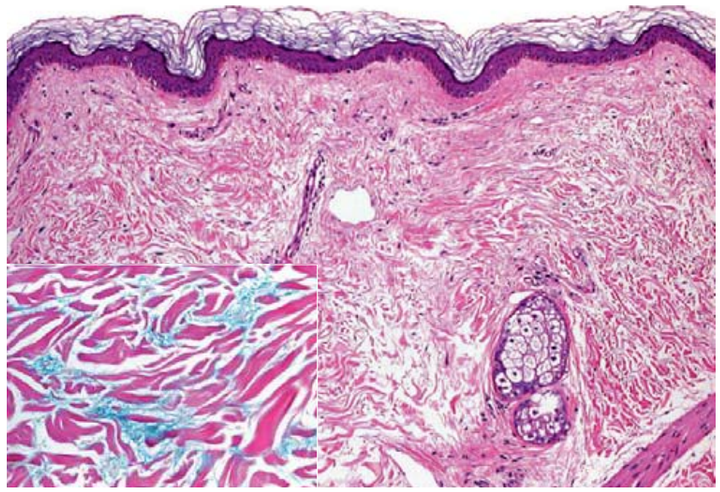


Fig. 46.9 Histopathology of scleredema. Slightly separated collagen bundles and normal dermal cellularity. Insert: Mucin deposits between collagen bundles. *Courtesy, Lorenzo Cerroni, MD.*

The *third type* occurs primarily in obese middle-aged men with insulin-dependent diabetes *(scleredema diabeticorum)*. The onset is subtle and the involvement persistent. Erythema and induration of the posterior neck and the back are commonly observed (Fig. 46.8), as is a *peau d'orange* appearance of the skin. In those patients who also have cheiroarthropathy, the skin of the distal extremities may appear waxy (presumably due to increased amounts of glycosylated collagen).

Unusual cases with limited site involvement, e.g. periorbital skin, have also been reported[24]. Systemic manifestations (in all three forms) include serositis, dysarthria, dysphagia, myositis, parotitis, and ocular and cardiac abnormalities (e.g. ophthalmoplegia, congestive heart failure). Reported associations include hyperparathyroidism, rheumatoid arthritis, Sjögren's syndrome, malignant insulinoma, multiple myeloma, gall bladder carcinoma, carcinoid[25] and HIV infection[16]. Except for limitation of movement, scleredema usually causes little morbidity. Type 1 may clear in 6 months to 2 years, whereas the other types last longer. Type 3 scleredema has even proved fatal when there was internal involvement.

Pathology

The principal alteration in scleredema is the thickening of the reticular dermis, with large collagen bundles separated from one another by clear spaces filled with mucin, resulting in fenestration of the dermis (Fig. 46.9). There is no increase in the number of fibroblasts, but the elastic fibers are reduced in number. At times, the mucin deposition can be so slight that multiple biopsies or staining of unfixed frozen sections are required to detect it. There is often a sparse perivascular lymphocytic infiltrate. Direct immunofluorescence is usually negative, but deposits of IgG and C3 have been found at the dermal–epidermal junction. Mucin also accumulates within skeletal muscle and the heart.

Differential diagnosis

Scleredema may be confused with scleroderma, but the absence of Raynaud's phenomenon and cuticular and mat telangiectasias points to scleredema. Patients with scleromyxedema also have firm papules (often in a linear array) in addition to dermal induration as well as a proliferation of fibroblasts histologically. The other types of cutaneous mucinoses are usually distinguished on the basis of clinical findings. Additional entities in the sclerodermoid differential diagnosis should be excluded (see Ch. 43). Occasionally, because of associated erythema, patients with diabetes-associated scleredema are sometimes misdiagnosed as having cellulitis (usually by non-dermatologists).

Treatment

Therapy is unnecessary for scleredema associated with streptococcal infections because it is self-limited. Regression of scleredema associated with diabetes or monoclonal gammopathy is uncommon and no specific treatment is available. Unfortunately, control of the hyperglycemia does not have any influence on the skin. Based upon case series and case reports, PUVA, UVA1, narrowband UVB, pulse therapy with cyclophosphamide plus oral corticosteroids, cyclosporine, factor XIII infusion, IVIg and electron beam therapy have all been reported to be of benefit[26,27]. Systemic and intralesional corticosteroids, intralesional hyaluronidase, methotrexate, antibiotics and penicillamine have not proved helpful. Because several of these therapies have been used for scleromyxedema, they were tried in patients with gammopathy-associated scleredema, with mixed results. Aggressive therapies, however, should be limited to individuals with disabling disease or systemic manifestations.

Mucinoses associated with altered thyroid function

Localized (pretibial) myxedema

Definition

Localized or pretibial myxedema is characterized by cutaneous induration of the shins due to mucin deposition. It is often associated with hyperthyroidism (most commonly due to Graves disease), but may appear following treatment of the thyroid disease.

Epidemiology and pathogenesis

Graves disease is seven times more common in women than in men and its onset is usually during the third or fourth decade. Pretibial myxedema is one of the signs of Graves disease, along with goiter, exophthalmus, thyroid acropachy, and thyroid-stimulating immunoglobulins that recognize the thyroid-stimulating hormone (TSH) receptor. Overall, it is found in 1–5% of patients with Graves disease, but in up to 25% of those patients with exophthalmus[28]. It can also appear in the setting of hypothyroidism following the treatment of Graves disease. Rarely, localized myxedema occurs in Hashimoto's thyroiditis without thyrotoxicosis, and even in euthyroid patients.

A serum factor (unrelated to thyroid-stimulating immunoglobulins) may incite fibroblasts to produce mucin. Fibroblasts from the dermis of the lower extremities have been found to be more sensitive to such a factor than are fibroblasts from other areas of the body. An insulin-like growth factor, trauma, and lymphatic obstruction due to mucin may also play a role[29].

Clinical features

Localized myxedema presents as erythematous to skin-colored, sometimes purple–brown or yellowish, waxy indurated nodules or plaques; they characteristically have a *peau d'orange* appearance[28] (Fig. 46.10). Usually, the lesions are located on the anterolateral aspect of the lower legs or feet. Localized myxedema can also present as a diffuse non-pitting edema of the shins or feet that evolves into elephantiasis. Even more rarely, localized myxedema affects the face, shoulders, upper extremities, lower abdomen, scars or donor graft sites. Large plaques are often painful and pruritic. When present, hypertrichosis and hyperhidrosis are confined to pretibial myxedematous skin.

Apart from appearance, associated morbidity is usually minimal. Entrapment of peroneal nerves by mucinous connective tissue may cause foot drop or faulty dorsiflexion.

Fig. 46.10 Pretibial myxedema. Purple–brown plaques on the shins of a patient with Graves disease. A *peau d'orange* appearance is present.

Pathology
Large quantities of mucin are deposited within the reticular dermis, causing collagen bundles to separate and the dermis to thicken[7]. A grenz zone of normal collagen is also observed. A perivascular and periadnexal lymphocytic infiltrate with mast cells is seen, as well as large stellate fibroblasts. Elastic fibers are reduced in number. There is often hyperkeratosis in addition to papillomatosis and hyperplasia of the epidermis.

Differential diagnosis
In addition to lichen simplex chronicus and hypertrophic lichen planus, pretibial myxedema should be distinguished from lymphedema, lipedema and obesity-associated lymphedematous mucinosis. In the latter disorder, semi-translucent papules, plaques with woody induration and occasionally vesicles develop on the shins of euthyroid, morbidly obese individuals with significant lower extremity edema. Histologically, in addition to epidermal atrophy (with effacement of the rete ridge pattern), vertically oriented capillaries and deposits of hemosiderin, mucin deposition is present within the superficial papillary dermis and around vessels[29].

Treatment
Corticosteroids, either applied under occlusive dressings or delivered by intralesional injection, may lead to improvement and provide symptomatic relief, especially if there is associated pruritus and superimposed dermatitis. Usually, skin grafting is followed by relapses. Plasmapheresis, gradient pneumatic compression, IVIg and octreotide (synthetic eight-amino acid peptide with somatostatin-like properties including inhibition of growth hormone and insulin secretion), with or without surgical shave removal, have been of some benefit[30]. Therapy for the associated hyperthyroidism does not improve the cutaneous lesions and, often, localized myxedema develops after treatment has been instituted. Localized myxedema may clear spontaneously (after an average of 3.5 years).

Generalized myxedema

Definition
Generalized myxedema is a manifestation of severe hypothyroidism in which mucin is deposited in the dermis, leading to waxiness of the skin.

Pathogenesis
Generalized myxedema is due to a quantitative or functional deficiency of thyroxine. Impaired degradation, rather than increased synthesis, of mucin has been suggested.

Fig. 46.11 Generalized myxedema in an adult with hypothyroidism. The face is puffy with a dull expression and the hair is dry.

Clinical features
Hypothyroidism may be congenital (with sequelae formerly referred to as cretinism) or of juvenile or adult onset.

Congenital hypothyroidism affects 1 in 5000 neonates and may cause a distinctive syndrome of dwarfism, mental retardation, and systemic and cutaneous findings. Somnolence, constipation, poor feeding, low muscle tone, persistence of jaundice, and respiratory distress all suggest the diagnosis. However, more than a third of infants have no symptoms. Periorbital tissues and the tongue, lips, hands and genitals are puffy. The skin is dry, cold and pale. Nails and hair are dry and brittle, and there can be patchy alopecia. The presence of a clavicular pad is diagnostic.

Juvenile hypothyroidism develops in a previously euthyroid child. Clinical features include short stature, abnormal physical and mental development, retardation of sexual maturity, and poor performance at school. Hypertrichosis may develop on the shoulders and upper back.

Adult hypothyroidism is the most common form of the disease. It is seen primarily in women 40–60 years of age, often as a result of autoimmune disease (usually Hashimoto's thyroiditis), therapy of hyperthyroidism (usually Graves disease) or, rarely, pituitary or hypothalamic failure. Rarely, the ingestion of large quantities of foodstuffs that contain inhibitors of iodine uptake by the thyroid gland, e.g. raw bok choy, can lead to myxedema.

The initial symptoms are subtle and include mental and physical sluggishness, weight gain, constipation, leg cramps, loss of appetite, and cold intolerance. The face has a dull expression. The eyelids, lips, tongue and hands are puffy, the nose is broad (Fig. 46.11), and the speech becomes hoarse and slurred. The skin is pale, cool, waxy and dry; an absence of sweating can lead to acquired ichthyosis or eczema craquelé. A yellowish discoloration of the palms and soles due to carotenemia may appear. Hair and nails are dry and brittle, and a diffuse non-scarring alopecia is common; alopecia of the lateral third of the eyebrows can also be seen. Purpura involving the extremities, blue telangiectatic fingertips, delayed wound healing, and xanthomas may be seen. Systemic manifestations include cardiomegaly, megacolon or bowel obstruction, psychiatric symptoms mimicking Alzheimer's disease, serositis, carpal tunnel syndrome, and seventh nerve paralysis[29].

Pathology
Mucin deposits, mainly perivascular and perifollicular, splay collagen bundles and may extend into the subcutaneous fat and nerves. Fibroblasts are not increased in number, but elastic fibers are reduced. Mucin deposits in the brain probably cause the psychiatric symptoms.

Diagnosis and differential diagnosis
The diagnosis is suspected clinically. Low levels of circulating free T_4 confirm the diagnosis. The serum TSH level is high in primary hypothyroidism and low in secondary hypothyroidism. Myxedema does not seem to occur in secondary hypothyroidism.

Treatment
Early treatment is crucial for proper mental development of neonates with hypothyroidism, but it is also critical for the juvenile and adult forms. Measurement of serum levels of T_4 and/or TSH is performed between 2 and 4 days of age in newborn screening panels, and

treatment should be initiated within the first 2 weeks of life. Usually, symptoms subside with thyroxine administration and recur if it is discontinued. Even areas of hair loss regrow with proper treatment. If untreated, patients can die as a result of "myxedema coma".

Reticular erythematous mucinosis

Synonyms: ■ Plaque-like cutaneous mucinosis ■ Reticular erythematous mucinosis syndrome ■ Midline mucinosis

Introduction and definition

Reticular erythematous mucinosis (REM) is a photoaggravated disorder in which persistent, erythematous papules or plaques develop in the midline of the back or chest. The papules often have a reticular or net-like configuration. This disorder has some overlap with lupus erythematosus (LE) tumidus.

History

Steigleder and colleagues coined the term "reticular erythematous mucinosis" in 1974. However, the initial description of similar cases appeared in 1960, when Perry and colleagues described three patients with plaque-like cutaneous mucinosis. Some authors regard these two entities as identical, while others view them as being on a continuum[31].

Epidemiology and pathogenesis

REM is a rare disorder that occurs most often in middle-aged women, although men and children are not spared. It is seen worldwide, and sunlight may be a causal or promoting factor. Familial cases, suggesting a genetic predisposition, have been reported[32] . Within endothelial cells and pericytes of lesional skin, tubuloreticular inclusions have been detected. Although these inclusions occur in viral infections, they can also be produced by high levels of interferon and are also found within endothelial cells in LE. Lastly, the fibroblasts of REM patients exhibit an abnormal overstimulation induced by exogenous IL-1.

Clinical features

Plaque-like cutaneous mucinosis and REM are probably different clinical presentations of the same rare syndrome. On the mid back or chest, pink to red macules and papules merge into reticulated and annular patterns (Fig. 46.12) or plaque-like lesions. They may be slightly pruritic and sometimes lesions spread to the abdomen. Sun exposure usually worsens the eruption, but it has occasionally been reported to be beneficial. Provocative phototests (UVA and/or UVB) can sometimes reproduce REM lesions. In general, REM is not associated with systemic diseases or abnormal laboratory tests. However, LE, breast and colon carcinoma, diabetes, myxedema, hypothyroidism, Hashimoto's thyroiditis, thrombocytopenia, monoclonal gammopathies and HIV infection have been reported in patients with REM[16,31]. Oral contraceptives, menses, pregnancy, heat, X-ray therapy and perspiration may promote or exacerbate REM.

Fig. 46.12 Reticular erythematous mucinosis. Grouped pink papules on the central chest with no surface changes; there is a subtle annular and reticulated configuration. Note the significant tan.

Pathology

The epidermis is normal. Interstitial deposits of small amounts of mucin are seen in the upper dermis, along with a perivascular and, at times, perifollicular T-cell infiltrate[7]. Vascular dilation is present. Usually, direct immunofluorescence is negative, but, rarely, granular deposits of IgM, IgA and C3 have been seen at the dermal–epidermal junction[31].

Differential diagnosis

In biopsy specimens of discoid lesions of LE, there is involvement of the epidermis and deposits of IgG and C3 are found at the dermal–epidermal junction, and in lymphocytic infiltrate of Jessner, there is minimal, if any, dermal mucin. LE tumidus can be impossible to distinguish microscopically from REM, and some authors group REM with LE tumidus. Seborrheic dermatitis and tinea versicolor may involve the central chest, but they have associated scale and can be diagnosed clinically, as can confluent and reticulated papillomatosis.

Treatment

Antimalarials (e.g. hydroxychloroquine) are usually effective in clearing the lesions within 4–8 weeks. Broad-spectrum sunscreens should also be used. Results from other treatments such as topical and systemic corticosteroids, topical calcineurin inhibitors, oral antihistamines, tetracycline, cyclosporine, UVB irradiation and pulsed dye laser are quite variable. Despite the potential for an exacerbation, successful results with UVA1 irradiation have been reported[33]. The lesions may clear spontaneously, even after 15 years.

Papulonodular mucinosis associated with autoimmune connective tissue diseases

Synonyms (when associated with LE): ■ Cutaneous lupus mucinosis ■ Papulonodular mucinosis in (systemic) lupus erythematosus ■ Papular and nodular mucinosis of Gold

Papules, nodules and plaques secondary to mucin deposition may accompany or even antedate an autoimmune connective tissue disease, most commonly LE and, rarely, dermatomyositis or scleroderma. Cutaneous lupus mucinosis occurs in 1.5% of patients with LE[34]. Only in Japan has a male predominance been observed. The lesions present as asymptomatic skin-colored, at times erythematous, 0.5–2 cm papules and nodules (Fig. 46.13); rarely will they merge into large plaques. Tangential illumination can be used to enhance detection of the lesions. A central depression and pigmentation may be additional features. The back, V of the chest, and the upper extremities are the most common sites of involvement. In only a few reported patients was there a flare of the papulonodules after sun exposure.

Fig. 46.13 Lupus cutaneous mucinosis. Skin-colored papules and nodules leading to a "lumpy" appearance of the chest.

Cutaneous lupus mucinosis can antedate LE or begin concurrently. The clinical course may correlate, in some patients, with underlying disease activity. Approximately 75% of patients with LE who develop papular and nodular mucinosis have systemic involvement, primarily renal and articular. The minority have only skin involvement, usually discoid or subacute cutaneous LE lesions.

Histologically, mucin abounds in the upper and mid dermis but may involve the subcutaneous fat as well. Sometimes, it is accompanied by a slight perivascular lymphocytic infiltrate. The epidermal changes of LE are absent, but linear or granular deposits of immunoglobulin and/or C3 are detected at the dermal–epidermal junction.

Cutaneous lesions of dermatomyositis often have dermal mucin histologically; rarely, patients develop erythematous nodules and plaques due to mucin deposition. The latter appear primarily on the trunk[35] and usually follow the myositis. Papular and nodular mucinosis can also occur in association with scleroderma, both systemic and cutaneous forms[36].

Treatment

Therapies for papular and nodular mucinosis are similar to those used for LE and dermatomyositis, i.e. sunscreens, topical corticosteroids and oral antimalarials. For unresponsive cases, systemic corticosteroids can be prescribed. Intralesional corticosteroids may prove useful for reducing the size of large nodules and plaques.

Cutaneous focal mucinosis

Cutaneous focal mucinosis presents as an asymptomatic skin-colored papule or nodule, less than 1 cm in diameter. The lesion can occur anywhere on the body or in the oral cavity. Cutaneous focal mucinosis favors adults and only rarely has it been linked to thyroid disorders (without myxedema), REM or scleromyxedema[37]. The diagnosis is based upon histologic findings.

Histologically, mucin is dispersed throughout the upper and mid dermis, sparing the subcutaneous fat. Cleft-like spaces, but no cysts, are seen. Spindle-shaped or stellate, vimentin-positive fibroblasts are present[38]. There is also a minor population of dermal dendrocytes that are partially factor XIIIa-positive and partially CD34-positive. The elastic and reticulum fibers are absent, but capillaries are normal in number.

Cutaneous focal mucinosis results from a "muciparous" reaction of the connective tissue to nonspecific stimuli and should be distinguished from a digital mucous cyst as well as an angiomyxoma, which represents a true neoplasm. Cutaneous focal mucinosis can be surgically excised, and relapses are uncommon.

Digital mucous cyst (myxoid cyst) is discussed in Chapter 110.

Miscellaneous mucinoses

There are other degenerative–inflammatory mucinoses that are not easily assigned to any of the entities previously described.

Neuropathia mucinosa cutanea was described only once, in a young man who had livedo reticularis on his legs and hyperesthesia. Hypertrophic (onion-like) intradermal nerves were encased by mucin[1].

Atypical tuberous myxedema (Jadassohn–Dosseker) probably represents a pure nodular variant of lichen myxedematosus[1].

Perifollicular mucinosis and **eccrine mucinosis**, which have been described in HIV-infected patients, appear to basically represent a histologic epiphenomenon (secondary mucinosis) that reflects a "muciparous" reactive tendency in HIV-infected individuals. This tendency manifests itself not only in the skin (see above), but also in the bone marrow[16].

Familial forms of "papular mucinosis" have also been described, but whether they represent a distinct entity or a familial form of localized lichen myxedematosus[39] is uncertain.

Secondary dermal mucinoses are outlined in Table 46.3[40].

Primary Follicular Mucinoses

Mucin accumulates within the follicular epithelium in two distinctive primary disorders: Pinkus' follicular mucinosis and urticaria-like follicular mucinosis. Otherwise, follicular mucinosis is considered a histologic epiphenomenon (i.e. secondary mucinosis), most often associated with cutaneous T-cell lymphoma (in particular mycosis fungoides and Sézary syndrome) or other skin diseases (e.g. atopic dermatitis; see Table 46.3).

Follicular mucinosis

Synonyms: ■ Alopecia mucinosa ■ Mucinosis follicularis ■ Pinkus' follicular mucinosis – benign primary form

History, epidemiology and pathogenesis

This uncommon inflammatory disorder, described in 1957 by Pinkus, has a predilection for children and for adults in the third and fourth decades of life. It is far from clear why dermal-type mucin is deposited selectively within an epithelial structure. Although follicular keratinocytes have been considered to be the source of the mucin, an etiologic role for cell-mediated immune mechanisms has been proposed[41], including a reaction to persistent antigens such as *Staphylococcus aureus*.

Clinical features

Primary follicular mucinosis is an idiopathic benign form of the disease, apparently not linked to lymphoma[42]. Clinically, it presents as an acute or subacute eruption in children and young adults and is characterized by one or several pink plaques (that sometimes have associated scale) or plaques composed of grouped follicular papules. Lesions are limited to the face (Fig. 46.14A) and scalp and are associated with alopecia. Papulonodules (Fig. 46.14B), annular plaques, folliculitis, follicular spines and acneiform eruptions have also been described[43]. A second type of follicular mucinosis, characterized by: (1) a more generalized distribution (extremities, trunk and face; Fig. 46.14C); (2) larger and more numerous plaques; (3) a chronic clinical course; and (4) occurrence in a slightly older age group[41], is probably best regarded as a secondary follicular mucinosis associated with atopic dermatitis or cutaneous T-cell lymphoma, rather than a primary condition.

Pathology

Mucin accumulates within the follicular epithelium and sebaceous glands, causing keratinocytes to disconnect (Fig. 46.14D). In more advanced lesions, the follicles are converted into cystic spaces containing mucin, inflammatory cells and altered keratinocytes. A perifollicular infiltrate of lymphocytes, histiocytes and eosinophils is seen[7].

Differential diagnosis

The differentiation between primary follicular mucinosis and mycosis fungoides-associated follicular mucinosis is very difficult[7], and there is no single reliable criterion. Although the existence of a primary form of follicular mucinosis has been questioned by some authors (who consider it an "indolent" localized form of cutaneous T-cell lymphoma[41]), features in favor of a primary form are the young age of the patient, a solitary plaque or limited number of lesions in the head and neck region, spontaneous resolution, and the absence histologically of epidermotropism and atypical lymphocytes. Detection of clonal T-cell gene rearrangements does not seem to help differentiate the two types[41].

Treatment

There is no specific treatment. A wait-and-see approach is recommended for primary follicular mucinosis as many cases resolve spontaneously within 2–24 months. Based upon case series and case reports, topical, intralesional and systemic corticosteroids, PUVA, dapsone, antimalarials, indomethacin, minocycline, oral isotretinoin, interferon-α-2b, orthovoltage irradiation, and UVA1 phototherapy[44] have been reported to be beneficial. For secondary forms, treatment of the underlying disease is indicated. Longitudinal evaluation and assessment for cutaneous T-cell lymphoma is recommended for patients with presumed primary follicular mucinosis that is persistent or becomes more extensive.

Urticaria-like follicular mucinosis

Urticaria-like follicular mucinosis is a very rare disorder that occurs primarily in middle-aged men. Pruritic urticarial papules or plaques appear on the head and neck within an erythematous "seborrheic" background. As lesions resolve, red macules persist for a few weeks. Hair-bearing regions may be involved, but neither follicular plugging nor alopecia is seen. Urticaria-like follicular mucinosis waxes and wanes irregularly over a period that can vary from a few months to 15 years. There are no associated systemic diseases. Response to natural

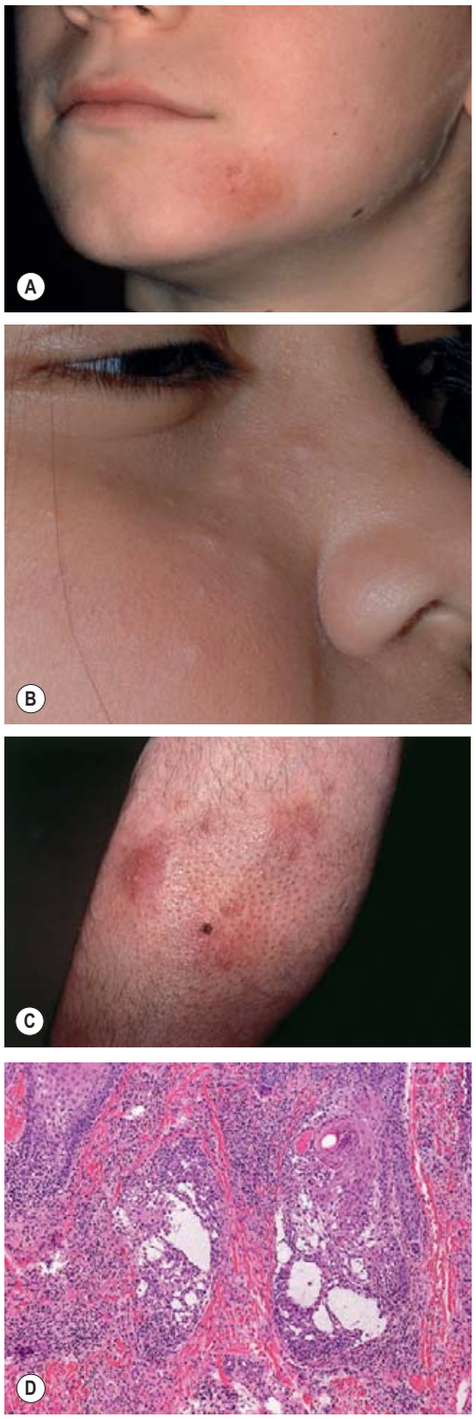


Fig. 46.14 Follicular mucinosis. A Pink plaque containing multiple follicular papules in a young boy. **B** Skin-colored papules on the cheek of a child. **C** Grouped follicular papules on the leg of an older adult in association with erythematous plaques. Note the associated alopecia. The hemorrhagic crust is the site of a previous biopsy. **D** Histology of follicular mucinosis (patient in A). Mucin deposition (wispy) within the follicular epithelia. *A,D, Courtesy, Lorenzo Cerroni, MD; B, Courtesy, Julie V Schaffer, MD.*

sunlight has been inconsistent, but it has been beneficial in a small number of cases.

As in primary follicular mucinosis, mucin-filled cystic spaces occupy hair follicles. In the upper dermis, lymphocytes and eosinophils are seen around blood vessels and hair follicles. In only a single patient to date were vascular C3 deposits seen by direct immunofluorescence. The prognosis is good, and, based upon a limited number of case reports, antimalarials and dapsone were reportedly beneficial[45].

PRIMARY HAMARTOMATOUS–NEOPLASTIC MUCINOSES

Although stromal mucin deposition may be found in a variety of cutaneous tumors as an additional finding (e.g. basal cell carcinomas and neurofibromas), only in mucinous nevus and (angio)myxoma is the mucin deposition a distinctive feature.

Mucinous Nevus

A mucinous nevus (nevus mucinosus) is a benign hamartoma that can be congenital or acquired. It consists of a plaque that usually has a unilateral linear nevoid pattern[46]. Histologically, a diffuse deposit of mucin is seen in the upper dermis, and collagen and elastic fibers are absent within the mucinous area. The epidermis can be normal or it may be acanthotic with elongation of the rete ridges and hyperkeratosis, as in an epidermal nevus. The latter set of findings points to a combined hamartoma, in which features of an epidermal nevus are associated with those of a connective nevus of the proteoglycan type. The cellular component of a mucinous nevus consists of CD34-positive fibroblasts and scarce factor XIIIa-positive dendritic cells[47].

The term "familial multiple acral mucinous fibrokeratomas" has been used to describe a patient with multiple, hereditary keratotic and mucinous lesions of the hands[48].

(Angio)myxoma

A cutaneous myxoma is an acquired benign neoplasm that is usually nodular and measures 1–5 cm in diameter. It favors the trunk, head and neck, and genital region; rarely, cutaneous myxomas have an acral location[49]. These tumors can be solitary, without any systemic abnormalities, or multiple. When multiple, they may be a manifestation of Carney complex (cutaneous myxomas, cardiac myxomas, numerous lentigines, multiple blue nevi, endocrine overactivity).

Histologically, a cutaneous myxoma is a lobulated, well-defined lesion characterized by a mucinous matrix within the dermis and the subcutis, with variably shaped fibroblasts, mast cells, and a few collagen and reticulin fibers. Bizarre multinucleated cells and regular mitotic figures can be seen. The stromal cells are smooth muscle actin (SMA)-positive and factor XIII-negative. Myxomas must be distinguished from cutaneous focal mucinosis, a reactive lesion which is usually <1 cm and ill-defined histologically; the latter does not have an epithelial component and the mucin deposits are in the dermis but not the subcutis. This differentiation is important as myxomas are true neoplasms, although benign, which can recur after incomplete excision.

REFERENCES

1. Rongioletti F, Rebora A. The new cutaneous mucinoses: a review with an up-to-date classification of cutaneous mucinoses. J Am Acad Dermatol. 1991;24:265–70.
2. Warner TF, Wrone DA, Williams EC, et al. Heparan sulphate proteoglycan in scleromyxedema promotes FGF-2 activity. Pathol Res Pract. 2002;198:701–7.
3. Neudecker BA, Stern R, Mark LA, Steinberg S. Scleromyxedema-like lesions of patients in renal failure contain hyaluronan: a possible pathophysiological mechanism. J Cutan Pathol. 2005;32:612–15.
4. Rongioletti F, Rebora A. Updated classification of papular mucinosis, lichen myxedematosus, and scleromyxedema. J Am Acad Dermatol. 2001;44:273–81.
5. Rongioletti F, Cattarini G, Sottofattori E, Rebora A. Granulomatous reaction after intradermal injections of hyaluronic acid gel. Arch Dermatol. 2003;139:815–16.
6. Rongioletti F, Hazini A, Rebora A. Coma associated with scleromyxedema and interferon alfa therapy. Full recovery after steroids and cyclophosphamide combined with plasmapheresis. Br J Dermatol. 2001;144:1283–4.
7. Rongioletti F, Rebora A. Cutaneous mucinoses: microscopic criteria for diagnosis. Am J Dermatopathol. 2001;23:257–67.
8. Dinneen AM, Dicken CH. Scleromyxedema. J Am Acad Dermatol. 1995;33:37–43.
9. Sansbury JC, Cocuroccia B, Jorizzo JL, et al. Treatment of recalcitrant scleromyxedema with thalidomide in 3 patients. J Am Acad Dermatol. 2004;51:126–31.

9a. Donato ML, Feasel AM, Weber DM, et al. Scleromyxedema: role of high-dose melphalan with autologous stem cell transplantation. Blood. 2006;107:463–6.

9b. Bos R, de Waal EGM, Kuiper H, et al. Thalidomide and dexametasone followed by autologous stem cell transplantation for scleromyxedema. Rheumatol. 2011; doi:10.1093/rheumatology/ker209.

10. Rey JB, Luria RB. Treatment of scleromyxedema and the dermatoneuro syndrome with intravenous immunoglobulin. J Am Acad Dermatol. 2009;60: 1037–40.

10a. Defaveri do Prado A, Schmoeller D, Bisi MC, et al. Scleromyxedema with monoclonal gammopathy and neurological involvement: recovery from coma after plasmapheresis. Int J Dermatol. 2011; doi: 10.1111/j.1365-4632.2010.04691.x.

11. Rongioletti F, Rebora A. Paradoxical effect of interferon alfa on lichen myxedematosus. J Am Acad Dermatol. 2000;43:730.
12. Rongioletti F, Zaccaria E, Cozzani E, Parodi A. Treatment of localized lichen myxedematosus of discrete type with tacrolimus ointment. J Am Acad Dermatol. 2008;5: 530–2.
13. Rongioletti F, Rebora A, Crovato F. Acral persistent papular mucinosis: a new entity. Arch Dermatol. 1986; 122:1237–9.
14. Harris JE, Purcell SM, Griffin TD. Acral persistent papular mucinosis. J Am Acad Dermatol. 2004;51:982–8.
15. Podda M, Rongioletti F, Greiner D, et al. Cutaneous mucinosis of infancy: is it a real entity or the paediatric form of lichen myxoedematosus (papular mucinosis)? Br J Dermatol. 2001;144:590–3.
16. Rongioletti F, Ghigliotti G, De Marchi R, et al. Cutaneous mucinoses and HIV infection. Br J Dermatol. 1998;139: 1077–80.
17. Rongioletti F, Rebora A. Cutaneous toxic mucinoses. J Am Acad Dermatol. 1992;26:789–90.
18. Rongioletti F, Rebora A. Worsening of lichen myxedematosus during interferon alfa-2a therapy for chronic active hepatitis. J Am Acad Dermatol. 1998;38: 760–1.
19. Banno H, Takama H, Nitta Y, et al. Lichen myxedematosus associated with chronic hepatitis C. Int J Dermatol. 2000;39:212–14.
20. Kwon OS, Moon SE, Kim JA, Cho KH. Lichen myxedematosus with rapid spontaneous regression. Br J Dermatol. 1997;136:295–6.
21. Cowen EW, Scott GA, Mercurio MG. Self-healing juvenile cutaneous mucinosis. J Am Acad Dermatol. 2004;50: S97–100.
22. Sperber BR, Allee J, James WD. Self-healing papular mucinosis in an adult. J Am Acad Dermatol. 2004;50: 121–3.
23. Beers WH, Ince A, Moore TL. Scleredema adultorum of Buschke: a case report and review of the literature. Semin Arthritis Rheum. 2006;35:355–9.
24. Ioannidou D, Krasagakis K, Stefanidou MR, et al. Scleredema adultorum of Buschke presenting as periorbital edema: a diagnostic challenge. J Am Acad Dermatol. 2005;52(suppl.):41–4.
25. Yu JI, Park W, Lee KK, Park W. Scleredema adultorum of Buschke associated with a carcinoid tumor. Int J Dermatol. 2009;48:784–6.
26. Bowen AR, Smith L, Zone JJ. Scleredema adultorum of Buschke treated with radiation. Arch Dermatol. 2003; 139:780–4.
27. Kroft EB, de Jong EM. Scleredema diabeticorum case series: successful treatment with UV-A1. Arch Dermatol. 2008;144:947–8.
28. Burman KD, McKinley-Grant L. Dermatologic aspects of thyroid disease. Clin Dermatol. 2006;24:247–55.
29. Rongioletti F, Donati P, Amantea A, et al. Obesity-associated lymphedematous mucinosis J Cutan Pathol. 2009;36:1089–94.
30. Felton J, Derrick EK, Prince ML. Successful combined surgical and octreotide treatment of severe pretibial myxoedema reviewed after 9 years. Br J Dermatol. 2003;148:825–6.
31. Braddock SW, Davis CS, Davis RB. Reticular erythematous mucinosis and thrombocytopenic purpura: report of a case and review of the world literature, including plaque-like cutaneous mucinosis. J Am Acad Dermatol. 1988;19:859–68.
32. Caputo R, Marzano AV, Tourlaki A, Marchini M. Reticular erythematous mucinosis occurring in a brother and sister. Dermatology. 2006;212:385–7.
33. Meewes C, Henrich A, Krieg T, Hunzelmann N. Treatment of reticular erythematous mucinosis with UV-A1 radiation. Arch Dermatol. 2004;140:660–2.
34. Shekari AM, Ghiasi M, Ghasemi E, Kani ZA. Papulonodular mucinosis indicating systemic lupus erythematosus. Clin Exp Dermatol. 2009;34:558–60.
35. Tan E, Tan SH, Ng SK. Cutaneous mucinosis in dermatomyositis associated with a malignant tumor. J Am Acad Dermatol. 2003;48(Suppl 5):S97–100.
36. Van Zander J, Shaw JC. Papular and nodular mucinosis as a presenting sign of progressive systemic sclerosis. J Am Acad Dermatol. 2002;46:304–6.
37. Rongioletti F, Amantea A, Balus L, et al. Cutaneous focal mucinosis associated with reticular erythematous mucinosis and scleromyxedema. J Am Acad Dermatol. 1991;24:656–7.
38. Nebrida ML, Tay YK. Cutaneous focal mucinosis: a case report. Pediatr Dermatol. 2002;19:33–5.
39. Scheidegger EP, Itin P, Kempf W. Familial occurrence of axillary papular mucinosis. Eur J Dermatol. 2005;15:70–2.
40. Siewert E, Weyers W, Dietrich CG, et al. Cutaneous mucinosis and skin necrosis complicates interferon alfacon-1 (consensus interferon) treatment of chronic hepatitis C. Eur J Med Res. 2005;28:63–7.
41. Rongioletti F, De Lucchi S, Meyes D, et al. Follicular mucinosis: a clinicopathologic, histochemical, immunohistochemical and molecular study comparing the primary benign form and the mycosis fungoides-associated follicular mucinosis. J Cutan Pathol. 2010;37:15–9.
42. Brown HA, Gibson LE, Pujol RM, et al. Primary follicular mucinosis: long term follow-up of patients younger than 40 years with and without clonal T-cell receptor gene rearrangement. J Am Acad Dermatol. 2002;47: 856–62.
43. Wittenberg GP, Gibson LE, Pittelkow MR, et al. Follicular mucinosis presenting as an acneiform eruption: report of four cases. J Am Acad Dermatol. 1998;38: 849–51.
44. von Kobyletzki G, Kreuter JA, Nordmeier R, et al. Treatment of idiopathic mucinosis follicularis with UVA1 cold light phototherapy. Dermatology. 2000;201: 76–7.
45. Harthi FA, Kudwah A, Allan A, et al. Urticaria-like follicular mucinosis responding to dapsone. Acta Derm Venereol. 2003;83:389–90.
46. Rongioletti F, Rebora A. Mucinous nevus. Arch Dermatol. 1996;132:1522–3.
47. Tardío JC, Granados R. The cellular component of the mucinous nevus consists of CD34-positive fibroblasts. J Cutan Pathol. 2010;37:1019–20.
48. Moulin G, Balme B, Thomas L. Familial multiple acral mucinous fibrokeratomas J Am Acad Dermatol. 1998; 38:999–1001.
49. Misago N, Mori T, Yoshioka M, Narisawa Y. Digital superficial angiomyxoma. Clin Exp Dermatol. 2007;32: 536–8.

47 Amyloidosis

Richard W Groves and Martin M Black

Chapter Contents

Primary (localized) cutaneous amyloidosis *702*
Secondary cutaneous amyloidosis *705*
Systemic amyloidosis *705*

Synonyms: ■ Primary systemic amyloidosis – AL amyloidosis ■ Secondary systemic amyloidosis – AA amyloidosis

Subtypes: ■ Primary cutaneous amyloidosis – macular amyloidosis, friction amyloidosis, lichen amyloidosis (lichen amyloidosus), biphasic amyloidosis, dyschromic amyloidosis, nodular amyloidosis

Key features

- Characteristic properties of amyloid include congophilia and green birefringence under polarized light, distinctive fibrillar ultrastructure, and cross-β-pleated sheet configuration by X-ray crystallography
- The three major forms of primary cutaneous amyloidosis are:
  - macular amyloidosis: confluent or rippled hyperpigmentation, often on the upper arm and back
  - lichen amyloidosis: hyperpigmented papules, often in a rippled pattern; favors the extensor surfaces of the extremities and back
  - nodular amyloidosis: waxy skin-colored to pink nodules
- Biphasic amyloidosis has features of both macular amyloidosis and lichen amyloidosis
- The amyloid deposits in macular amyloidosis and lichen amyloidosis are keratinocyte-derived, whereas those in nodular amyloidosis are composed of immunoglobulin light chains and are often accompanied by an infiltrate of plasma cells
- Mucocutaneous lesions are seen in 30–40% of patients with primary systemic (AL) amyloidosis and include waxy papulonodules and plaques, ecchymoses, pinch purpura, and macroglossia; carpal tunnel syndrome in association with the latter is a classic presentation
- In the absence of specific mucocutaneous lesions, aspiration of abdominal fat can be performed as amyloid deposits may be detected in some patients with primary systemic amyloidosis
- Once the diagnosis of AL amyloidosis is established, evaluation for systemic involvement is indicated

INTRODUCTION

Amyloidosis is not a single disease; rather, the term is used to refer to several diseases that share the common feature of abnormal extracellular deposition of amyloid, a fibrillar proteinaceous material, within tissues[1]. Amyloidosis can therefore occur in a wide variety of clinical settings, which may be as diverse as multiple myeloma, Alzheimer's disease, familial polyneuropathies and primary cutaneous lichen amyloidosis.

Amyloid itself is not a single chemically distinct substance, and several types of amyloid have been described. However, regardless of the source, pathogenetic mechanisms or the disease process involved, amyloid material does share some common tinctorial and other physicochemical properties, e.g. the cross-β-pleated sheet configuration[2].

The two clinical settings in which dermatologists are likely to encounter amyloidoses are: (1) the more common, primary cutaneous forms of amyloidosis; and (2) the less common systemic amyloidosis with cutaneous manifestations.

History

Virchow, in 1854, introduced the term "amyloid"[3]. He believed that the substance resembled starch or cellulose because, like starch, it turned blue when stained with iodine followed by dilute sulfuric acid. In 1928, Gutmann first described a patient with clinical features of lichen amyloidosis, while Freudenthal, in 1930, introduced the term "lichen amyloidosus"[3].

Epidemiology

The precise epidemiology of systemic amyloidosis is not known, as the disease is often undiagnosed or misdiagnosed[4]. In the US, the incidence of primary systemic amyloidosis is estimated to be approximately 1275 to 3200 new cases per year[4]. Amyloidosis has been estimated to occur in ~6–15% of patients with multiple myeloma (primary systemic

CLINICAL CLASSIFICATION OF AMYLOIDOSIS
SYSTEMIC AMYLOIDOSIS
Primary systemic amyloidosis (AL >> AH amyloid protein) • Plasma cell dyscrasias (more common) • Multiple myeloma-associated
Secondary systemic amyloidosis (reactive; AA amyloid protein) • Chronic inflammation (e.g. rheumatoid arthritis) • Chronic infection (e.g. tuberculosis)
Hemodialysis-associated amyloidosis
Genetic (inherited) forms of amyloidosis (various amyloid proteins) • Familial amyloid polyneuropathy (AD) • Muckle–Wells syndrome and other cryopyrin-associated periodic syndromes (AD) • Familial Mediterranean fever (AR) • TNF receptor-associated periodic syndrome (TRAPS; AD) • Familial amyloidosis, Finnish type (AD)
ORGAN-LIMITED (LOCALIZED) AMYLOIDOSIS
Cutaneous • Primary: macular*, lichen*, biphasic*, dyschromic, nodular • Secondary: incidental finding within various skin tumors (e.g. dermatofibromas, intradermal melanocytic nevi, seborrheic keratoses, adnexal tumors, basal cell carcinomas, Bowen's disease, porokeratosis); following PUVA therapy
Endocrine • Medullary carcinoma of the thyroid, insulinoma, type 2 diabetes
Cerebral • Alzheimer's disease
*Seen in patients with Sipple syndrome.

Table 47.1 Clinical classification of amyloidosis. Familial amyloid polyneuropathy is also known as familial amyloidotic polyneuropathy. See Table 45.2 for details on several of the genetic forms of amyloidosis. AD, autosomal dominant; AR, autosomal recessive.

CHEMICAL CLASSIFICATION OF AMYLOIDOSES		
Precursor protein	**Amyloid protein**	**Clinical syndrome**
(Apo) serum AA*	AA	Secondary systemic amyloidosis, hereditary periodic fever syndromes (e.g. familial Mediterranean fever, Muckle–Wells syndrome, TRAPS; see Ch. 45)
Apolipoprotein AI	AApoAI	Familial amyloid polyneuropathy
Calcitonin	ACal	Medullary carcinoma of the thyroid
Cystatin C	ACys	Hereditary cystatin C amyloid angiopathy†
Gelsolin	Agel	Familial amyloidosis, Finnish type
Immunoglobulin heavy chain (very rare)‡	AH	Primary systemic amyloidosis
Keratin	Aker	Primary (localized) cutaneous amyloidosis
Immunoglobulin light chain	AL	Primary systemic amyloidosis (associated with plasma cell dyscrasia§ >> multiple myeloma), primary cutaneous nodular amyloidosis
Transthyretin	ATTR	Familial amyloid polyneuropathy, senile systemic amyloidosis
Aβ precursor protein (AβPP)	Aβ	Alzheimer's disease, aging
β_2-microglobulin	$A\beta_2M$	Chronic hemodialysis
Corneodesmosin	–	Hypotrichosis simplex of the scalp

*Amyloid-associated protein synthesized by the liver.
†Detection of deposits within clinically normal skin allows diagnosis prior to clinical symptoms (cerebral hemorrhage).
‡More commonly, heavy chains produce a non-amyloid type deposit termed heavy chain deposition disease.
§Monoclonal gammopathy; progression depends upon risk factors (see Ch. 119).

Table 47.2 Chemical classification of amyloidoses. Adapted from ref. 10.

amyloidosis) and in ~5–11% of patients with rheumatoid arthritis (secondary systemic amyloidosis)[5]. However, better control of the inflammatory response in rheumatoid arthritis appears to have led to a marked decline in the incidence of renal replacement therapy (i.e. dialysis or transplantation) for associated secondary systemic amyloidosis[6].

Primary cutaneous amyloidosis also has a worldwide prevalence. It is commonly observed in Southeast Asian countries, including Singapore, Taiwan and Thailand[7]. Lichen amyloidosis appears to be more common in those of Chinese descent. Macular amyloidosis is also commonly seen in Central and South American countries, especially those close to the equator[8]. In general, macular amyloidosis and lichen amyloidosis occur more frequently in individuals with skin phototypes III and IV.

Classification

Amyloidosis can be classified clinically into systemic (generalized) forms, with involvement of several organ systems, and organ-limited (localized) forms, in which deposits are limited to a single organ such as the skin (Table 47.1). In the localized forms, amyloid deposition occurs at or near the site of synthesis, while, in the systemic forms, the precursors are secreted into the circulation and amyloid is usually deposited at distant sites[9]. Amyloidosis can also be classified on the basis of the specific precursor protein (Table 47.2; see next section).

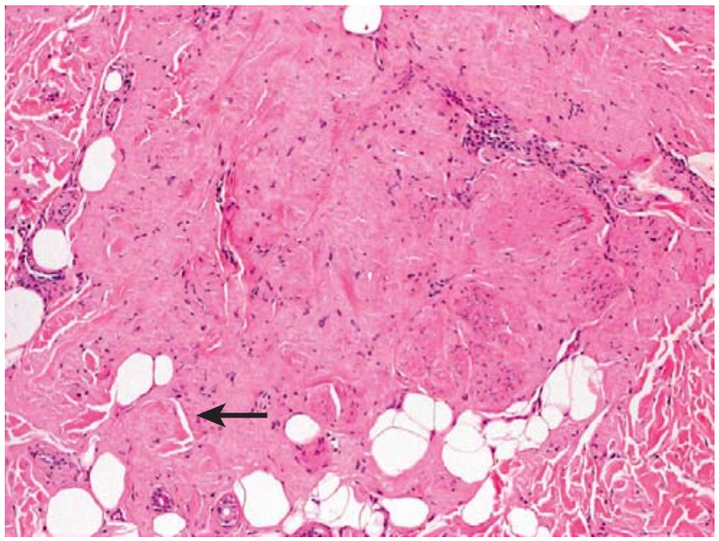


Fig. 47.1 Histologic features of amyloid deposits within the skin. In this example of nodular amyloidosis, the dermal deposits are eosinophilic, amorphous and contain fissures (arrow). *Courtesy, Lorenzo Cerroni, MD.*

HISTOLOGIC CRITERIA USED TO DEFINE AMYLOID
• Homogeneous, hyaline, eosinophilic deposits in H&E-stained sections (Fig. 47.1)
• Crystal violet metachromasia
• Positive staining with alkaline Congo red
• Apple-green birefringence under polarized light after Congo red staining; also dichroic (Fig. 47.2)
• Fibrillar structure on electron microscopy (Fig. 47.3)
• Stains brightly by ultraviolet fluorescence microscopy after Thioflavin T staining (Fig. 47.2)
• Staining with antibodies to amyloid P component
• Staining with antibodies directed against specific precursors (e.g. keratin)

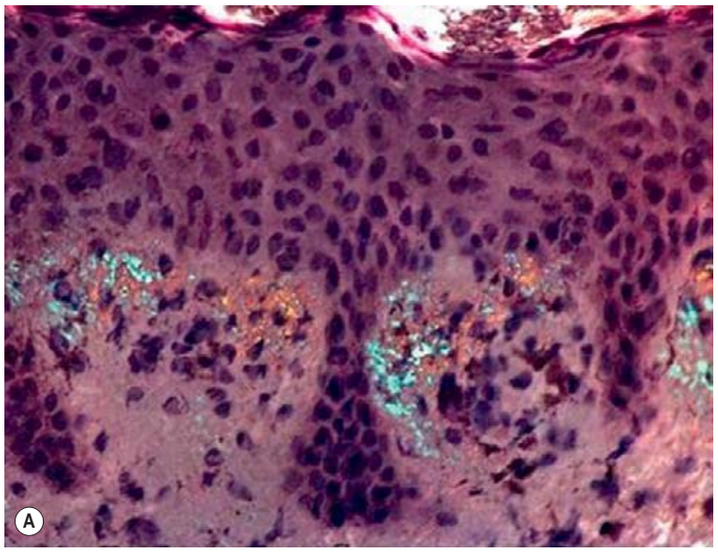
Table 47.3 Histologic criteria used to define amyloid[2].

Pathogenesis

The major component of amyloid is the fibril protein; the minor components are amyloid P component, glycosaminoglycans and apoE lipoprotein. Amyloid P is a glycoprotein derived from serum amyloid P protein (SAP) and it has a specific calcium-dependent binding affinity for amyloid. Approximately 18 distinct forms of amyloid fibril proteins and their precursors have been identified, including: AL (amyloid light chains), containing immunoglobulin light chains; AA (amyloid-associated), a protein synthesized by the liver; Aβ amyloid, found in cerebral lesions of Alzheimer's disease; and ATTR (transthyretin-associated), found in some forms of familial amyloidosis[9]. Each condition is associated with a specific precursor protein, many of which are listed in Table 47.2. The precursor proteins[10] are initially soluble proteins. They then undergo changes leading to aggregation, polymerization, fibril formation, and, finally, extracellular deposition in tissues as insoluble amyloid.

The process by which this transformation takes place is multifactorial and differs amongst the various types of amyloidoses. In primary systemic amyloidosis, substitution of amino acids in specific positions in the variable region of the immunoglobulin light chain potentially destabilizes the light chains and increases their likelihood of being converted to amyloid fibrils. Similarly, mutations in the transthyretin gene have been shown to alter significantly the stability of the transthyretin protein and increase its amyloidogenicity[2,4]. The accumulation of these relatively inert amyloid fibrils within vital organs leads to pressure atrophy and eventually interferes with the normal functioning of the organ.

The precise pathogenesis of primary cutaneous amyloidosis is not yet fully understood. Prolonged friction, genetic predisposition, Epstein-Barr virus and environmental factors have all been proposed as possible etiologic factors. The precursor protein involved has not been fully characterized; however, the amyloid of macular and lichenoid variants



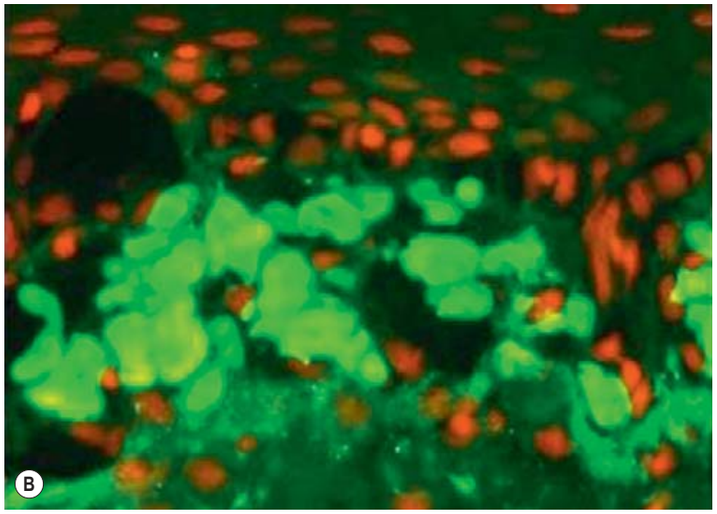


Fig. 47.2 Use of special stains to identify amyloid deposits within the papillary dermis in lichenoid amyloidosis. A With a Congo red stain, there is characteristic green birefringence with polarized light; the color can vary from yellow-green to blue-green. **B** With a Thioflavin T stain, amyloid deposits stain brightly with ultraviolet fluorescence microscopy. *Courtesy, St John's Institute of Dermatology.*

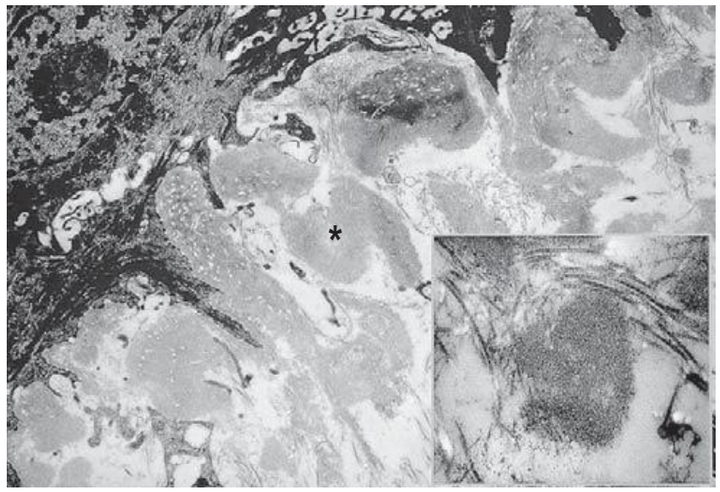


Fig. 47.3 Electron microscopy of cutaneous amyloid deposits. There are clusters of filamentous deposits (*) and 7–10-nm non-branching fibrils (insert). *Courtesy, St John's Institute of Dermatology.*

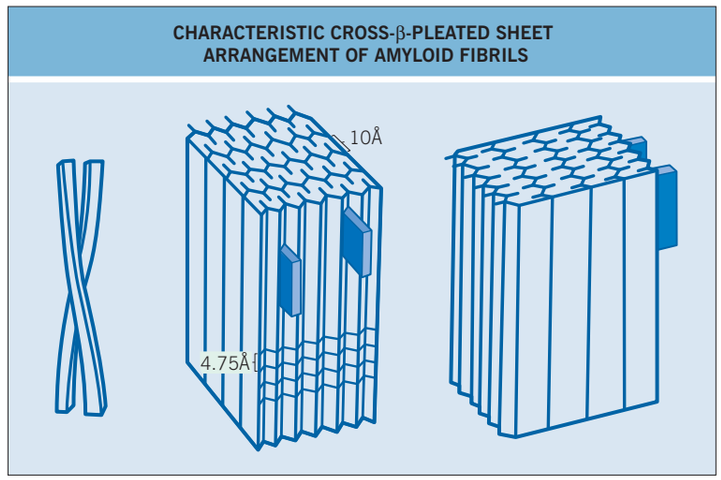


Fig. 47.4 Characteristic cross-β-pleated sheet arrangement of amyloid fibrils. Schematic representation of findings seen by X-ray crystallography. There is an antiparallel configuration of paired filaments, and sites of binding of the planar Congo red dye are indicated by the solid blue blocks. *Adapted from Cooper JH. Selective amyloid staining as a function of amyloid composition and structure: histochemical analysis of the alkaline Congo red, standardized toluidine blue, and iodine methods. Lab Invest. 1974;31:232–8.*

of primary cutaneous amyloidosis is thought to be keratinocyte-derived[11]. This has been supported by ultrastructural studies demonstrating transitional forms between viable keratinocytes and amyloid, as well as by positive reactions with monoclonal antibodies directed against keratins of basal keratinocytes. The fibrillar theory proposes that the tonofilaments of keratinocytes undergo filamentous degeneration and pass into the dermis, where, presumably, they are modified by histiocytes and fibroblasts into amyloid material. An alternative theory suggests that the material is produced at the epidermo-dermal interface, with precursor proteins being secreted by basal keratinocytes. This hypothesis has also been supported by both ultrastructural findings and demonstration of basement membrane antigens such as type IV collagen and laminin within amyloid deposits[12]. These cutaneous amyloid deposits stain positively with anti-human antibodies directed against IgG, IgM and IgA immunoglobulins, but this staining is thought to be the result of nonspecific absorption of the immunoglobulins rather than being an indicator of immunoglobulin as the precursor protein. Apolipoprotein E4 has also been shown to be associated with this type of cutaneous amyloid deposit and may be synthesized locally by epidermal keratinocytes[13].

In nodular amyloidosis, there is no specific staining with antikeratin antibodies. The amyloid deposits are composed of immunoglobulin light chains, suggesting plasma cell derivation akin to the nodular cutaneous lesions of primary systemic amyloidosis. Thus, its origin is very different from that of either macular or lichen amyloidosis[11,12]. However, in nodular amyloidosis, presumably there is local production of light chains, whereas in primary systemic amyloidosis, the light chains are present in the systemic circulation.

Amyloid characteristics

In H&E-stained sections, amyloid appears as amorphous, eosinophilic fissured masses (Fig. 47.1 & Table 47.3). With Congo red staining, amyloid has an orange–red color by light microscopy, and it has a characteristic green birefringence under polarized light (Fig. 47.2A). Other special stains that can be used to detect amyloid deposits include crystal violet, methyl violet, periodic acid–Schiff (PAS), Sirius red, pagoda red, Dylon stain and Thioflavin T (Fig. 47.2B)[1,11]. AA (but not AL) amyloid loses its affinity for Congo red after exposure to potassium permanganate.

By electron microscopy, amyloid appears as 7 to 10 nm wide, non-branching, non-anastomosing fibrils (Fig. 47.3). X-ray crystallography and infrared spectroscopy reveal a characteristic cross-β-pleated sheet conformation (Fig. 47.4). These findings are identical in all types of amyloid, regardless of clinical setting or chemical composition[1]. The cross-β-pleated sheet configuration of amyloid is believed to be responsible for the staining and birefringence with Congo red.

Immunohistochemical stains utilizing antibodies directed against the amyloid fibril proteins (e.g. immunoglobulin γ light chain, transthyretin, keratin, AA protein) can help to differentiate between the types of amyloid. However, these immunohistochemical stains do have limitations. For precise identification of the nature of an amyloid protein, especially AL amyloid, tandem mass spectrometry (MS/MS) can be done, and the latter can be performed on formalin-fixed, paraffin-embedded sections or subcutaneous fat aspirates[14].

PRIMARY (LOCALIZED) CUTANEOUS AMYLOIDOSIS

Primary cutaneous amyloidosis is associated with the deposition of amyloid in apparently normal skin without associated deposits in internal organs (see Table 47.1). The most common variants are macular amyloidosis, lichen amyloidosis and biphasic amyloidosis.

Clinical features

Although primary cutaneous amyloidosis is classically divided into macular (macular amyloidosis), papular (lichen amyloidosis) and nodular (nodular amyloidosis) forms, the first two entities actually represent the ends of a clinical spectrum. In some patients and even some lesions, both forms can be present, and the term "biphasic amyloidosis" is used to describe this situation[15,16].

Macular amyloidosis is often pruritic but it may be asymptomatic. The lesions of macular amyloidosis are hyperpigmented, either in a confluent manner or a characteristic rippled pattern. The latter can be best appreciated by stretching the skin. The most common site of involvement is the upper back, especially over the scapular area, followed by the extensor surfaces of the extremities. Extensive involvement can be seen in an occasional patient. Macular amyloidosis usually presents in early adulthood, and women may be affected more often than men[1,17]. In biphasic amyloidosis, fine papular lesions are superimposed upon a background of hyperpigmentation (Fig. 47.5A).

The term "friction amyloidosis" has been used to describe a subgroup of patients in whom local friction from nylon brushes, towels and other rough materials contributes to the production of macular and lichenoid lesions. There is also significant clinical overlap between macular amyloidosis and the pigmented type of notalgia paresthetica, where pruritus of the scapular areas leads to rubbing and scratching[11] (see Ch. 7).

Lichen amyloidosis is the most common form of primary cutaneous amyloidosis and usually presents as persistent, pruritic plaques on the shins or other extensor surfaces of the extremities, e.g. the anterior thighs or forearms (Fig. 47.6)[10,15]. Initial lesions are discrete, firm, scaly, skin-colored or hyperpigmented papules, which later coalesce into plaques that often have a rippled or ridged pattern. At the onset, lesions are usually unilateral, but a bilateral, symmetrical distribution can develop[11,15].

Primary cutaneous amyloidosis manifesting as pigmentation and lichenification of the anal and sacral regions has been described as an ano-sacral variant, but these patients often have lichen amyloidosis or biphasic amyloidosis elsewhere[15,16]. Bullous lesions have also been described in the setting of lichen amyloidosis, but they are more commonly associated with systemic amyloidosis. Dyschromic amyloidosis is a rare variant in which a guttate leukoderma is superimposed upon a background of hyperpigmentation and admixed with characteristic lesions of macular and lichenoid amyloidosis (see Ch. 67).

Macular and/or lichenoid amyloidosis has also been described in association with autoimmune connective tissue disorders (e.g. scleroderma [Fig. 47.7], systemic lupus erythematosus, dermatomyositis) and primary biliary cirrhosis[1]. In one series of patients with scleroderma, 9% had hyperpigmentation of the upper back in association with dermal deposits that stained positively with antikeratin antibodies[18]. Lastly, one patient was observed to have sparing of lichen amyloidosis lesions in areas with higher cutaneous temperatures (such as along the course of large superficial veins), suggesting that amyloid fibril formation may be a temperature-dependent process *in vivo*[19].

Familial forms of macular and lichenoid amyloidosis are unusual. Included in this group are families with Sipple syndrome, which is due to mutations in the *RET* oncogene (see below). In addition, several families with primary localized cutaneous amyloidosis have been

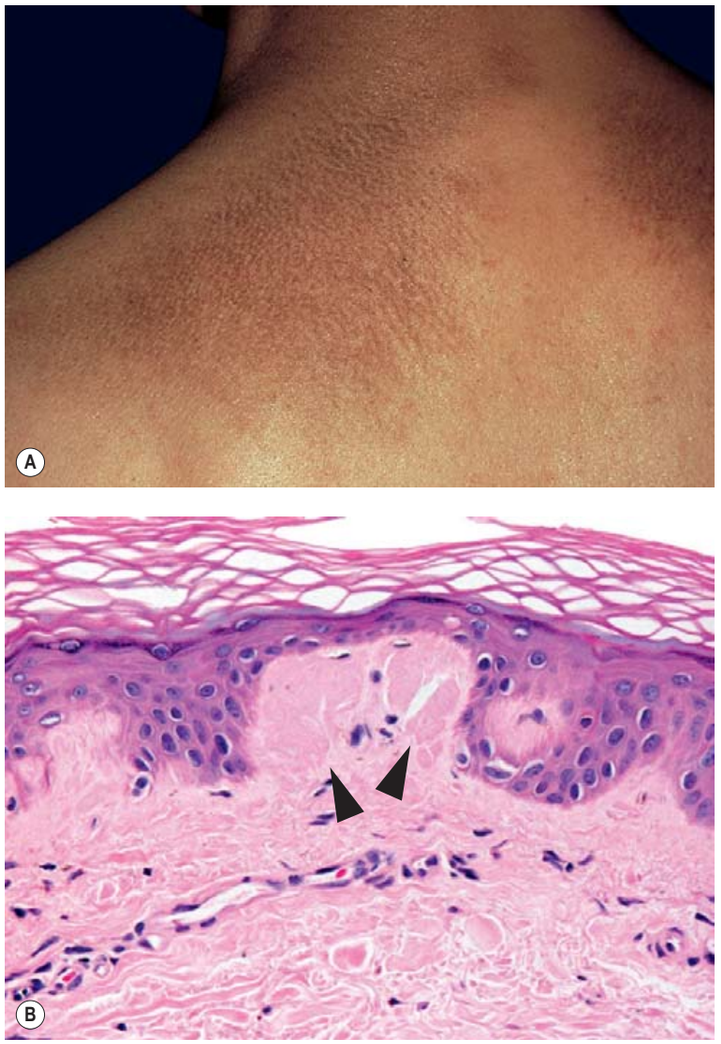


Fig. 47.5 Biphasic amyloidosis. A Characteristic rippled hyperpigmentation of macular amyloidosis (superiorly) as well as papules of lichenoid amyloidosis (inferiorly). **B** Histologically, deposits of amyloid within the dermal papillae (arrowheads) as well as melanophages within the papillary dermis; note the characteristic fissure in the amyloid deposit. These deposits may be subtle. *B, Courtesy, Lorenzo Cerroni, MD.*

Fig. 47.6 Lichen amyloidosis. Keratotic, hyperpigmented plaques on the legs. Insert: Closer view of individual keratotic papules. *Courtesy, St John's Institute of Dermatology.*

Fig. 47.7 Primary cutaneous amyloidosis in a patient with systemic scleroderma. Note the numerous papules, some of which are in a linear array.

shown to have mutations in the genes that encode either oncostatin M receptor β (OSMRβ)[20] or the alpha subunit of the interleukin (IL)-31 receptor (IL-31RA)[21]. OSMRβ is a component of both the OSM type II receptor and the IL-31 receptor whose ligands are OSM and IL-31, respectively; IL-31RA combines with OSMRβ to form the IL-31 receptor[22]. Of note, IL-31 has been shown to be of importance in pruritic skin conditions (e.g. dermatitis, prurigo nodularis), and in some animal models, anti-IL-31 antibodies can alleviate itch. Primary cutaneous amyloidosis has also been reported in association with pachyonychia congenita, dyskeratosis congenita and familial palmoplantar keratoderma[1].

Nodular amyloidosis is rare, and it presents as single or multiple waxy nodules or infiltrated plaques, most commonly on the trunk or extremities (Fig. 47.8A,B). Immunoglobulin γ light chains as well as β_2-microglobulin have been demonstrated within the deposits in this type of cutaneous amyloidosis, and both are thought to be produced by plasma cells in the vicinity of the deposits (see Fig. 47.8D)[23]. In two patients, gene rearrangement studies identified a clone of amyloid-producing plasma cells in the skin of a nodular lesion while there was no evidence of a clonal plasma cell proliferation in the bone marrow of one patient[24,25]. There may be an association between Sjögren's syndrome and nodular amyloidosis of the skin or lung.

The nodular variant has been reported to progress to systemic involvement, hence long-term follow-up is necessary. However, recent observations suggest that this risk is approximately 7%, much less than the previously quoted 50%. Although 40% of patients in this long-term study had a paraproteinemia at presentation, the gammopathy remained static during the follow-up period and progression to systemic involvement was observed in only 1 of 15 patients, 23 years after the initial presentation[26]. A similar study of 16 patients with nodular amyloidosis found a near equal sex distribution, with a tendency for an acral distribution. There was one patient who subsequently died from systemic amyloidosis[27].

Pathology

In macular and lichenoid forms of amyloidosis, amyloid deposits are restricted to the upper dermis, particularly the papillary dermis (see Fig. 47.5B). In lichen amyloidosis, the deposits may expand the papillae and displace the elongated rete ridges laterally, and the overlying epidermis is often acanthotic and hyperkeratotic. Melanophages and a sparse perivascular lymphohistiocytic infiltrate can be seen in both forms. Antikeratin antibodies (such as LP34, MNF 116 and RCK 102) may be useful in identifying these two forms of primary cutaneous amyloidosis.

In contrast, in the nodular variant, the dermis, subcutis and blood vessel walls are diffusely infiltrated with amyloid (Fig. 47.8C). A perivascular infiltrate of plasma cells may also be seen (Fig. 47.8D)[26]. Immunostaining for light chain deposition can aid in the diagnosis of nodular amyloidosis.

TREATMENT OF MACULAR AND LICHENOID AMYLOIDOSIS
Potent topical corticosteroids, including under occlusion (2)
Topical calcineurin inhibitors (3)
Intralesional corticosteroids (3)
Occlusive dressings (e.g. hydrocolloid) or wraps (e.g. zinc oxide-impregnated) (3)
UVB phototherapy (2)
PUVA phototherapy (2)
Systemic retinoids (2)
Dermabrasion (2)
CO_2 laser therapy (2)
Low-dose cyclophosphamide (3)
Cyclosporine (3)

Table 47.4 Treatment of macular and lichensoid amyloidosis. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports. PUVA, psoralen plus UVA; UVB, ultraviolet B.

Differential diagnosis

The diagnosis of primary cutaneous amyloidosis is based upon the morphology of the lesions and on the histologic demonstration of the cutaneous amyloid deposits (see Table 47.3).

There is significant overlap in the appearance of macular amyloidosis and notalgia paresthetica. The latter is also seen on the upper back and can have rippled hyperpigmentation. Biopsy specimens of notalgia paresthetica contain melanophages but no amyloid deposits. When macular amyloidosis is more diffuse or confluent, it has to be differentiated from postinflammatory hyperpigmentation. Other entities in the differential diagnosis may include pityriasis versicolor, atrophic lichen planus, erythema dyschromicum perstans (ashy dermatosis), and drug-induced pigmentation.

The primary differential diagnosis for lichen amyloidosis includes lichen simplex chronicus (LSC) and hypertrophic lichen planus (LP). Both of these are characterized by chronic pruritic plaques, often on the shins. Histologically, both have hyperkeratosis, acanthosis and a mild to moderate lymphohistiocytic inflammatory infiltrate but no amyloid deposits. In LSC, lichenification is often prominent, while hypertrophic LP lesions may have a violaceous hue and, on histologic examination, a lichenoid infiltrate with vacuolar degeneration. Other entities that may be considered in the differential diagnosis include papular mucinosis, pretibial myxedema, prurigo simplex/nodularis, pemphigoid nodularis, lichen ruber moniliformis, colloid milium and epidermolysis bullosa pruriginosa.

Nodular amyloidosis may resemble the cutaneous lesions of primary systemic amyloidosis and the latter should be excluded (see above). The clinical differential diagnosis also includes lymphoma cutis, cutaneous lymphoid hyperplasia (pseudolymphoma), pretibial myxedema, sarcoidosis, granuloma annulare, reticulohistiocytosis and granuloma faciale, all of which have rather distinctive histopathologic features and therefore can be easily differentiated.

Treatment

To date, none of the treatment modalities described (Table 47.4) has proven to be curative or uniformly effective in patients with macular and lichenoid amyloidosis. Treatment must be directed at breaking the itch–scratch–itch cycle usually present in these patients. Chronic friction, scratching and rubbing, for example with towels and nylon brushes, can serve as possible precipitating or aggravating factors, and patients should be advised of this. Potent topical corticosteroids are useful to some extent, especially in mild cases, and their use under occlusion or in combination with a mild keratolytic agent such as salicylic acid (particularly in lichen amyloidosis) may have added benefit. Access to the involved sites can be limited by occlusive dressings such as hydrocolloid dressings or gauze wraps impregnated with zinc oxide for weeks to months, but recurrence rates may be high. A trial of topical dimethyl sulfoxide (DMSO; 50% or 100% solution) in 25 patients has been reported to have little beneficial effect[28]. Based upon case reports, topical calcineurin inhibitors may play an adjunctive role.

A study that compared the efficacy of topical corticosteroids with either UVB phototherapy or topical PUVA phototherapy in patients

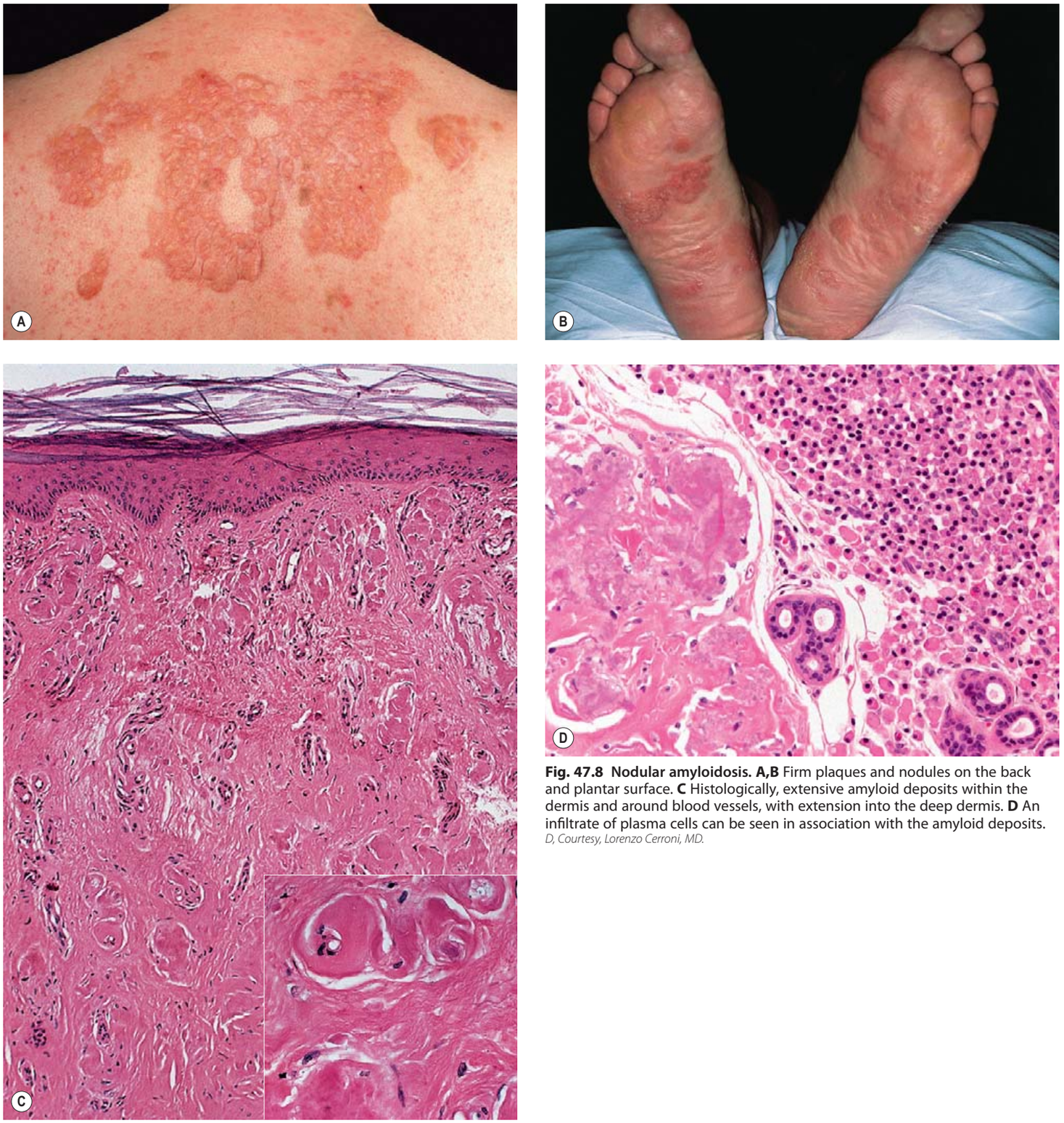


Fig. 47.8 Nodular amyloidosis. A,B Firm plaques and nodules on the back and plantar surface. **C** Histologically, extensive amyloid deposits within the dermis and around blood vessels, with extension into the deep dermis. **D** An infiltrate of plasma cells can be seen in association with the amyloid deposits.
D, Courtesy, Lorenzo Cerroni, MD.

with lichen amyloidosis found the pruritus and roughness scores to be better on the sides treated with either form of phototherapy, with PUVA being marginally better in reducing pruritus[29]. Dermabrasion was shown to be beneficial in lichen amyloidosis involving the limbs: the epidermis and part of the papillary dermis along with some of the amyloid was removed, permitting re-epithelialization to occur from the adnexal structures[30]. After more than 5 years of follow-up, there was significant improvement in symptoms and appearance without recurrence. Postinflammatory hypo- and hyperpigmentation did occur but usually improved over time.

Oral retinoids such as etretinate (1 mg/kg/day) have been reported to improve pruritus and result in flattening of lesions. Acitretin (0.5 mg/kg/day) produced similar results with some clearance of the associated hyperpigmentation[31]. In a preliminary study, low-dose cyclophosphamide (50 mg daily) was reported to be effective in reducing pruritus and papules in lichen amyloidosis[11]. However, the side effects of these systemic medications (see Chs 126 & 130) must be weighed against the possible benefits.

Surgical excision, cryotherapy, electrodesiccation and CO_2 laser can be used to treat nodular amyloidosis, but local recurrences are

common[30]. Strategies for the future treatment of amyloidosis include the depletion of the ubiquitous amyloid P component via complexes with the experimental agent R-1-[6-[R-2-carboxypyrrolidin-1-yl]-6-oxohexanoyl]pyrrolidine-2-carboxylic acid (CPHPC) and immunotherapy to promote clearance of amyloid using specific antibodies[32,33].

SECONDARY CUTANEOUS AMYLOIDOSIS

Secondary cutaneous amyloidosis refers to clinically inapparent amyloid deposits that are seen histopathologically within skin tumors, including dermatofibromas, intradermal melanocytic nevi, seborrheic keratoses, pilomatricomas, trichoepitheliomas, sweat gland tumors, basal cell carcinomas, Bowen's disease and porokeratosis[1,11]. The argument has been made that deposits in this setting represent a histologic epiphenomenon without obvious clinical implications. It has also been reported following PUVA therapy.

SYSTEMIC AMYLOIDOSIS

Primary Systemic Amyloidosis

Primary systemic amyloidosis is a manifestation of an underlying plasma cell dyscrasia, although patients usually do not fulfill the criteria for multiple myeloma (e.g. hypercalcemia, osteolytic lesions; see Ch. 119). The fibrils are composed of AL protein, which consists of immunoglobulin light chains, usually λ chains (75–80%).

Clinical features

Primary systemic amyloidosis is associated with a wide spectrum of organ involvement. The presenting symptoms are often varied and nonspecific, such as fatigue, weight loss, paresthesias, dyspnea, and syncopal attacks due to orthostatic hypotension[4,34].

In the oral cavity, amyloid deposits appear as soft rubbery swellings and an infiltration of the mucosa. An associated hemorrhagic component is frequently seen. The tongue can be uniformly enlarged and firm (Fig. 47.9A), or it may have hemorrhagic papules, plaques and blisters on its surface (Fig. 47.9B); the latter may vary from translucent to yellow–brown in color. Xerostomia can result from infiltration of the salivary glands.

Following minor trauma, petechiae, purpura and ecchymoses are often observed, especially on the eyelids and neck and in the axillae and anogenital region (due to infiltration of vessel walls with amyloid; Fig. 47.10). Characteristically, periorbital purpura (the "raccoon eyes" sign) may be precipitated by coughing, the Valsalva maneuver, or proctoscopy for a rectal biopsy, as well as after pinching or rubbing the skin (pinch purpura).

Clinically evident skin involvement occurs in approximately 25% of individuals with primary systemic amyloidosis. Skin infiltration by amyloid presents as waxy, translucent or purpuric papules (Fig. 47.11A,B), nodules and plaques that resemble nodular amyloidosis. A smooth erythematous waxy infiltration can appear on the palms and volar aspect of the fingertips. Smooth, skin-colored papules, a few millimeters in diameter, may be seen on the face, neck and scalp and in the anogenital region.

Less often, diffuse cutaneous infiltration may result in an infiltrated sclerodermoid appearance and cause the scalp skin to be thrown into folds resembling cutis verticis gyrata with associated alopecia. Bullous lesions, especially hemorrhagic blisters resembling those of porphyria cutanea tarda and epidermolysis bullosa acquisita, may be the initial sign of the disease. In addition, nail dystrophy due to amyloid deposits around blood vessels and in the dermis of the nail bed can be observed. Rarely, patients also have evidence of acquired acral cutis laxa. The presence of macroglossia together with carpal tunnel syndrome is a classic presentation and should trigger an investigation for amyloidosis.

Other signs and symptoms of primary systemic amyloidosis depend upon the organs involved. Renal involvement manifests as proteinuria (albuminuria), and consequently hypoalbuminemia and edema (i.e. nephrotic syndrome). Cardiac involvement may eventually lead to a restrictive cardiomyopathy and congestive heart failure, resulting in dyspnea, hepatomegaly and bilateral lower extremity as well as presacral edema. Autonomic and sensory neuropathies are common.

Fig. 47.9 Primary systemic amyloidosis. A Macroglossia with dental impressions on the tongue. **B** Papulonodues of the tongue and external nares; some are purpuric while others are translucent with a yellowish hue. *B, Courtesy, Dennis Cooper, MD.*

Fig. 47.10 Primary systemic amyloidosis. Purpura and yellow–brown plaques in a periorbital distribution. *Courtesy, Joyce Rico, MD.*

Fig. 47.11 Primary systemic amyloidosis. A Numerous waxy translucent facial papules. Some have a yellow to yellow–brown color. **B** Some of the waxy papules have become purpuric, but this can be more difficult to appreciate because of the pigmentation of the skin (compare to Fig. 47. 10). The periorbital region is a characteristic site of involvement. *A, Courtesy, Jean L Bolognia, MD. B, Courtesy, Judith Stenn, MD.*

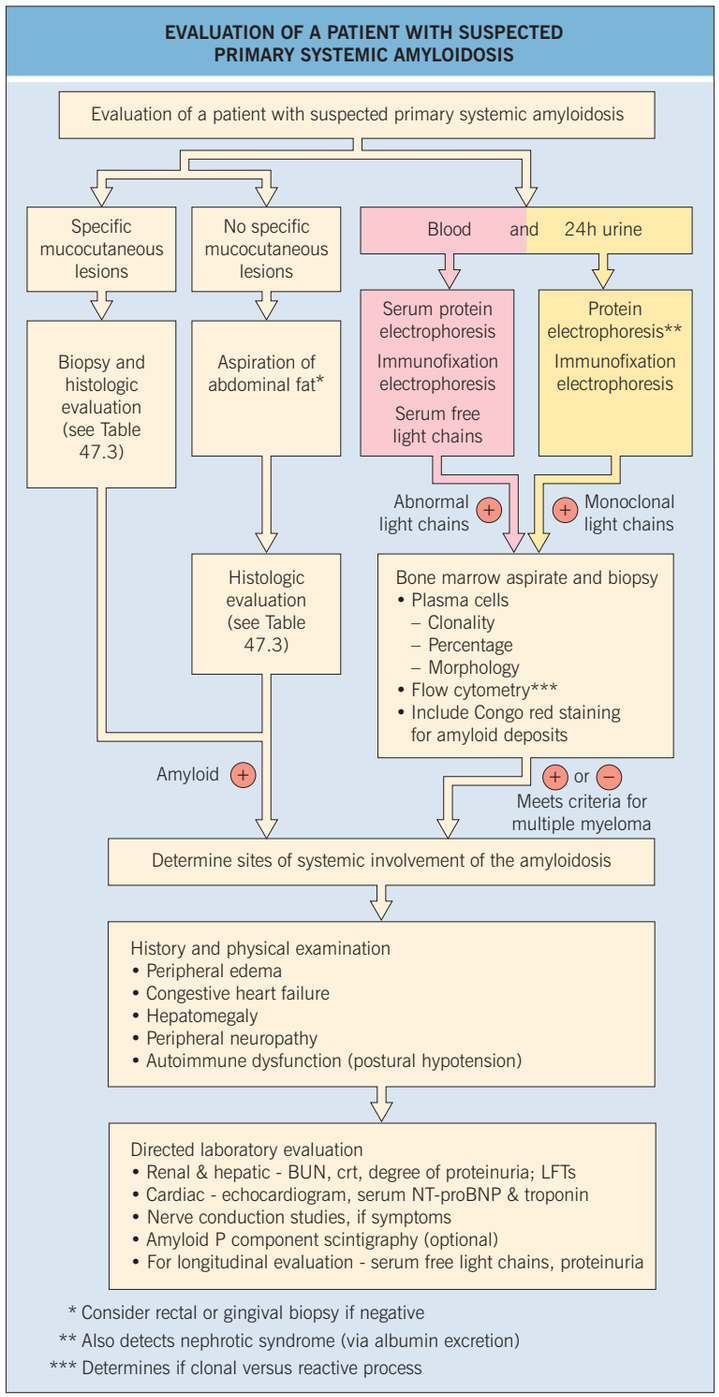


Fig. 47.12 Evaluation of a patient with suspected primary systemic amyloidosis. Because the amyloid is formed from immunoglobulin light chains, an abnormality of light chains in the blood or urine (e.g. increased concentration or abnormal ratio in the blood, positive immunofixation electrophoresis [IFE] of the urine) is required for diagnosis. BUN, blood urea nitrogen; crt, creatinine; LFTs, liver function tests; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Sensory involvement is usually bilateral and symmetrical, while autonomic involvement can result in postural hypotension, impotence and disturbances in gastrointestinal motility (e.g. gastroparesis). Hepatomegaly due to amyloid infiltration or congestive heart failure may be present.

In up to 80–90% of patients with primary systemic amyloidosis, amyloid deposits can be demonstrated in random rectal mucosal biopsies or in abdominal subcutaneous fat aspirates; the latter is favored because of the potential risk for bleeding with the former. Gingival or tongue biopsies may also be obtained to demonstrate the presence of amyloid, but in the absence of involvement clinically, they are less sensitive. In addition, bone marrow biopsies are examined for the presence of amyloid deposits. Based upon the finding that all of these amyloid deposits contain amyloid P (which is derived from serum amyloid protein [SAP]), SAP scintigraphy is also employed, primarily outside the US. It utilizes radioiodine-labeled SAP and is a sensitive, non-invasive method for locating amyloid deposits and monitoring disease. A more practical method for assessing response to therapy is measurement of serum free light chains.

The approach to a patient with suspected primary systemic amyloidosis as well as the evaluation of a patient with confirmed primary systemic amyloidosis is outlined in Figure 47.12.

Pathology

In primary systemic amyloidosis, cutaneous lesions are characterized by amyloid deposits in the dermis and subcutis. Amyloid is also often found around sweat glands and within blood vessel walls (Fig. 47.13). In the kidneys, deposits are seen primarily in the glomeruli; arteries and arterioles may also be affected. In the liver, amyloid is first deposited in the space of Disse between endothelial and parenchymal cells. It then progressively encroaches upon adjacent hepatocytes and sinusoids, leading to atrophy and replacement of large areas of liver parenchyma with amyloid material.

Differential diagnosis

The differential diagnosis of the waxy papules includes papular mucinosis, nodular amyloidosis and lipoid proteinosis, and when the lesions are primarily on the face, they could be confused with adnexal tumors (see Ch. 111). Entities in the sclerodermoid differential diagnosis (see Ch. 43) need to be considered when there is diffuse infiltration of the skin.

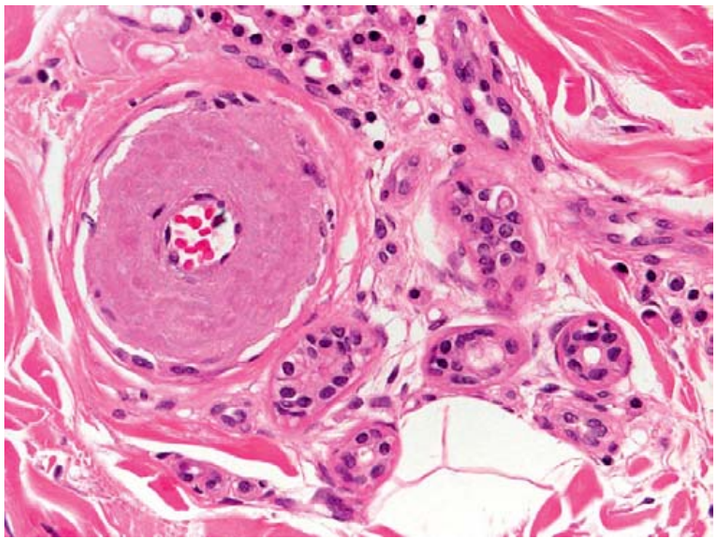


Fig. 47.13 Primary systemic amyloidosis – histologic features. Amyloid deposits are seen in a perivascular location. *Courtesy, Lorenzo Cerroni, MD.*

Treatment

Without therapy, the prognosis for primary systemic amyloidosis is poor: median survival is ~13 months[34], especially if there is cardiac involvement. Treatment strategies have paralleled those for multiple myeloma, including melphalan and systemic corticosteroids[4,35,36]. Nowadays, the treatment of choice for younger patients with minimal cardiac involvement is high-dose melphalan followed by autologous peripheral blood stem cell transplantation. In one study with an 8-year follow-up period, a complete hematologic response was observed in 40% of transplanted patients and was associated with a prolonged survival. A survival benefit and clinical improvement in organ function was also seen in those who did not achieve a complete hematologic response[37]. For older patients or those with cardiac involvement, newer targeted agents (e.g. lenalidomide, bortezomib) are used alone or in combination with systemic corticosteroids and melphalan.

Supportive measures are administered according to the organs affected and the consequent manifestations. Nephrotic syndrome and congestive heart failure require diuretic therapy and treatment of associated arrhythmias. Neuropathy and gastrointestinal involvement are treated symptomatically.

Secondary Systemic Amyloidosis

Secondary systemic amyloidosis occurs as a complication of severe chronic inflammatory diseases of an infectious or non-infectious nature, such as tuberculosis, lepromatous leprosy, rheumatoid arthritis and ankylosing spondylitis. It has also been observed in patients with hidradenitis suppurativa, dystrophic epidermolysis bullosa, generalized psoriasis, chronic pustular psoriasis, scleroderma, dermatomyositis and systemic lupus erythematosus. Secondary systemic amyloidosis is characterized by the deposition of a distinctive non-immunoglobulin protein designated AA (amyloid A protein). The precursor is an acute phase protein which is synthesized by the liver and appears to have a regulatory function in lipoprotein metabolism during inflammation. AA amyloidosis usually affects the kidneys, liver, spleen, adrenals and heart. Cutaneous lesions due to amyloid deposits are rarely seen in this type of amyloidosis (however, amyloid can sometimes be detected within aspirates of subcutaneous fat)[1,11].

Successful treatment of the underlying infectious or inflammatory disease may halt the progression of the reactive amyloidosis. For example, the use of systemic immunomodulators ("biologic agents") such as TNF-α inhibitors in rheumatoid arthritis and ankylosing spondylitis patients with secondary amyloidosis has been shown to be clinically beneficial, resulting in a significant reduction in acute phase reactants and proteinuria[38]. Recently, a controlled clinical study found that eprodisate may slow the loss of renal function in AA amyloidosis. Interestingly, this oral drug acts by changing the conformational configuration of the amyloid protein, rather than by affecting its production[39].

Hemodialysis-Associated Amyloidosis

Hemodialysis-associated amyloidosis results from decreased excretion of β_2-microglobulin and is seen in patients receiving long-term hemodialysis for renal failure. Beta$_2$-microglobulin is retained in the circulation as it fails to be filtered through the dialysis membranes, and it has a tendency to deposit in the synovial membranes. Thus, the predominant manifestations are musculoskeletal, including carpal tunnel syndrome, bone cysts and a destructive spondylo-arthropathy[4]. Occasionally, skin lesions, in particular subcutaneous nodules, have been reported[40,41].

Inherited Amyloidoses

The genetic bases of primary (localized) cutaneous amyloidosis have been previously discussed (see above). Additional inherited forms of amyloidosis have either an autosomal dominant or autosomal recessive inheritance pattern (see Table 47.1). Several of the diseases in this group, such as familial amyloid polyneuropathy and senile systemic amyloidosis, are associated with mutations in the transthyretin gene on chromosome 18; its protein product is a single polypeptide chain of 127 amino acid residues. Transthyretin is synthesized in the liver, choroid plexus and eye, and it is a serum transport protein for thyroxine and retinol-binding protein[9]. The predominant clinical features are due to the peripheral sensorimotor and autonomic neuropathy, with paresthesias, trophic ulcers, carpal tunnel syndrome, postural hypotension, impotence, and disturbances of gastrointestinal motility. Orthotopic liver transplantation removes the major supply of transthyretin and is an effective treatment for this form of amyloidosis[32].

Patients with the extremely rare disorder familial amyloidosis, Finnish type, which is due to mutations in the gene that encodes gelsolin, present with a characteristic triad of corneal lattice dystrophy, cranial neuropathies and skin findings. The latter include cutis laxa-like changes and skin fragility[42].

Muckle–Wells syndrome

Muckle–Wells syndrome can present as familial urticaria during early childhood (see Chs 18 and 45). The symptoms include periodic attacks of fever, lancinating limb pains and an urticarial eruption, with the development of progressive perceptive deafness over time. There may be an associated AA amyloid nephropathy (see Table 45.2)[43].

Familial Mediterranean fever

Familial Mediterranean fever (FMF) is inherited in an autosomal recessive fashion and is characterized by recurrent febrile episodes lasting for 1 or 2 days, with recurrent painful self-limiting episodes of pleuritis, peritonitis or synovitis (see Ch. 45). It tends to affect certain ethnic groups, including Arabs, Sephardic Jews and Armenians. Cutaneous manifestations include an erysipelas-like erythema that develops over the joints, lower legs and dorsal aspect of the feet, in addition to small vessel vasculitis and nonspecific purpuric lesions[44]. FMF is due to mutations in the gene that encodes pyrin, which plays a role in the regulation of the NLRP3/cryopyrin inflammasome (see Fig. 45.1). Colchicine is used prophylactically to prevent polyserositis and AA amyloid deposition.

Sipple syndrome or multiple endocrine neoplasia (MEN) type 2A

Sipple syndrome is an autosomal dominant disorder with the triad of medullary carcinoma of the thyroid, pheochromocytomas and hyperparathyroidism (see Ch. 63). Increased serum levels of calcitonin are a reflection of hyperplasia or carcinoma of the parafollicular calcitonin-producing C cells of the thyroid. Multiple endocrine neoplasia (MEN) type 2A is associated with pruritic areas of hyperpigmentation on the upper back. The lesions have been described as notalgia paresthetica, macular amyloidosis and lichen amyloidosis, depending upon the observer. The unusual finding is the early age of onset, often before the age of 10 years. Recognition of this skin sign of systemic disease can lead to a preventive thyroidectomy once the diagnosis is established[45]. A recent study of 10 families with MEN 2A found an incidence of lichen amyloidosis of 36%; moreover, all those with cutaneous amyloidosis had a specific mutation in codon 634 of the *RET* proto-oncogene[46].

Hypotrichosis simplex of the scalp

Hypotrichosis simplex of the scalp is an uncommon autosomal dominant disorder in which patients have normal hair at birth, but then progressively lose almost all scalp hair by the third decade. Eyebrows, beard and axillary hair, nails and teeth develop normally. Mutations in the gene that encodes corneodesmosin, a glycoprotein expressed in the epidermis and inner root sheath, lead to truncated proteins. Deposits of the truncated protein accumulate as amorphous amyloid deposits around hair follicles and in the papillary dermis[47].

X-Linked Reticulate Pigmentary Disorder (Partington Amyloidosis)

Partington and colleagues described a family with an X-linked disease in which adult women had linear streaks of hyperpigmentation and male patients manifested a reticulated mottled brown pigmentation of the skin, which, on biopsy, demonstrated dermal deposits of amyloid (in adults but not children). In women, the involvement was limited to the skin, but in male patients, recurrent respiratory infections, corneal dystrophy and photophobia were seen (see Ch. 67). As in macular amyloidosis, the amyloid deposits are keratin-positive and amyloid deposits have not been found in other tissues[48]. The gene for this disorder has been localized by linkage analysis to Xp21–p22[48].

APPENDIX

Tandem mass spectrometry (MS/MS) for precise identification of an amyloid protein: Mayo Clinic Medical Laboratories, Rochester, MN, USA. University of Tennessee Health Science Center, Knoxville, TN, USA.

REFERENCES

1. Breathnach SM. Amyloid and amyloidosis. J Am Acad Dermatol. 1988;18:1–16.
2. Buxbaum J. The amyloidoses. Mt Sinai J Med. 1996;63:16–23.
3. Wong CK. Amyloid. History and modern concepts. Clin Dermatol. 1990;8:1–6.
4. Falk RH, Comenzo RL, Skinner M. The systemic amyloidoses. N Engl J Med. 1997;337:898–909.
5. Glenner GG. Amyloid deposits and amyloidosis. The beta-fibrilloses (first of two parts). N Engl J Med. 1980;302:1283–92.
6. Immonen K, Finne P, Grönhagen-Riska C. A marked decline in the incidence of renal replacement therapy for amyloidosis associated with inflammatory rheumatic diseases – data from nationwide registries in Finland. Amyloid. 2011;18:25–8.
7. Tan T. Epidemiology of primary cutaneous amyloidoses in southeast Asia. Clin Dermatol. 1990;8:20–4.
8. Ollague W, Ollague J, Ferretti H. Epidemiology of primary cutaneous amyloidoses in South America. Clin Dermatol. 1990;8:25–9.
9. Buxbaum JN, Tagoe CE. The genetics of the amyloidoses. Annu Rev Med. 2000;51:543–69.
10. Sipe JD, Benson MD, Buxbaum JN, et al. Amyloid fibril protein nomenclature: 2010 recommendations from the nomenclature committee of the International Society of Amyloidosis. Amyloid. 2010;17:101–4.
11. Black MM. Amyloidosis. In: Champion RH, Burton JL, Burns AD, Breathnach SM (eds). Rook/Wilkinson/Ebling Textbook of Dermatology, 6th edn. Oxford: Blackwell Science, 1998:2626–37.
12. Hashimoto K, Ito K, Taniguchi Y, et al. Keratin in cutaneous amyloidoses. Clin Dermatol. 1990;8:55–65.
13. Furumoto H, Hashimoto Y, Muto M, et al. Apolipoprotein E4 is associated with primary localized cutaneous amyloidosis. J Invest Dermatol. 2002;119:532–3.
14. Solomon A, Murphy CL, Westermark CL, et al: Misclassification of amyloidosis is unwarranted. Blood. 2006;108:776–7.
15. Wang WJ. Clinical features of cutaneous amyloidoses. Clin Dermatol. 1990;8:13–9.
16. Wang WJ, Chang YT, Huang CY, et al. Clinical and histopathological characteristics of primary cutaneous amyloidosis in 794 Chinese patients. Zhonghua Yi Xue Za Zhi (Taipei). 2001;64:101–7.
17. Rasi A, Khatami A, Javaheri SM. Macular amyloidosis: an assessment of prevalence, sex, and age. Int J Dermatol. 2004;43:898–9.
18. Ogiyama Y, Hayashi Y, Kou C, et al. Cutaneous amyloidosis in patients with progressive systemic sclerosis. Cutis. 1996;57:28–32.
19. Parsi K, Kossard S. Thermosensitive lichen amyloidosis. Int J Dermatol. 2004;43:925–8.
20. Arita K, South AP, Hans-Filho G, et al. Oncostatin M receptor-beta mutations underlie familial primary localized cutaneous amyloidosis Am J Hum Genet. 2008;82:73–80.
21. Lin M, Lee D, Liu T, et al. Novel IL31RA gene mutation and ancestral OSMR mutant allele in familial primary cutaneous amyloidosis. Eur J Hum Genet. 2010;18:26–32.
22. Tanaka A, Lai-Cheong JE, van den Akker PC, et al. The molecular skin pathology of familial primary localized cutaneous amyloidosis. Exp Dermatol. 2010;19:416–23.
23. Fujimoto N, Yajima M, Ohnishi Y, et al. Advanced glycation end product-modified beta2-microglobulin is a component of amyloid fibrils of primary localized cutaneous nodular amyloidosis. J Invest Dermatol. 2002;118:479–84.
24. Grünewald K, Sepp N, Weyrer K, et al. Gene rearrangement studies in the diagnosis of primary systemic and nodular primary localized cutaneous amyloidosis. J Invest Dermatol. 1991;97:693–6.
25. Hagari Y, Mihara M, Hagari S. Nodular localized cutaneous amyloidosis: detection of monoclonality of infiltrating plasma cells by polymerase chain reaction. Br J Dermatol. 1996;135:630–3.
26. Woollons A, Black MM. Nodular localized primary cutaneous amyloidosis: a long-term follow-up study. Br J Dermatol. 2001;145:105–9.
27. Moon AO, Calamia KT, Walsh JS. Nodular amyloidosis: review and long-term follow-up of 16 cases. Arch Dermatol. 2003;139:1157–9.
28. Pandhi R, Kaur I, Kumar B. Lack of effect of dimethylsulphoxide in cutaneous amyloidosis. J Dermatolog Treat. 2002;13:11–4.
29. Jin AG, Por A, Wee LK, et al. Comparative study of phototherapy (UVB) vs. photochemotherapy (PUVA) vs. topical steroids in the treatment of primary cutaneous lichen amyloidosis. Photodermatol Photoimmunol Photomed. 2001;17:42–3.
30. Wong CK. Amyloid treatment. Clin Dermatol. 1990;8:108–11.
31. Hernandez-Nunez A, Dauden E, Moreno de Vega MJ, et al. Widespread biphasic amyloidosis: response to acitretin. Clin Exp Dermatol. 2001;26:256–9.
32. Hirschfield GM, Hawkins PN. Amyloidosis: new strategies for treatment. Int J Biochem Cell Biol. 2003;35:1608–13.
33. Pepys MB, Herbert J, Hutchinson WL, et al. Targeted pharmacological depletion of serum amyloid P component for treatment of human amyloidosis. Nature. 2002;417:254–9.
34. Kyle RA, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. Semin Hematol. 1995;32:45–59.
35. Kyle RA, Gertz MA, Greipp PR, et al. A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine. N Engl J Med. 1997;336:1202–7.
36. Skinner M, Anderson J, Simms R, et al. Treatment of 100 patients with primary amyloidosis: a randomized trial of melphalan, prednisone, and colchicine versus colchicine only. Am J Med. 1996;100:290–8.
37. Skinner M, Sanchorawala V, Seldin DC, et al. High-dose melphalan and autologous stem-cell transplantation in patients with AL amyloidosis: an 8-year study. Ann Intern Med. 2004;140:85–93.
38. Fernandez-Nebro A, Tomero E, Ortiz-Santamaria V, et al. Treatment of rheumatic inflammatory disease in 25 patients with secondary amyloidosis using tumor necrosis factor alpha antagonists. Am J Med. 2005;118:552–6.
39. Dember LM, Hawkins PN, Hazenberg BPC, et al. Eprodisate for the treatment of renal disease in AA amyloidosis. N Engl J Med. 2007;356:2349–60.
40. Shimizu S, Yasui C, Yasukawa K, et al. Subcutaneous nodules on the buttocks as a manifestation of dialysis-related amyloidosis: a clinicopathological entity. Br J Dermatol. 2003;149:400–4.
41. Uenotsuchi T, Imafuku S, Nagata M, et al. Cutaneous and lingual papules as a sign of beta 2 microglobulin-derived amyloidosis in a long-term hemodialysis patient. Eur J Dermatol. 2003;13:393–5.
42. Kiuru-Enari S, Keski-Oja J, Haltia M. Cutis laxa in hereditary gelsolin amyloidosis. Br J Dermatol. 2005;152:250–7.
43. Muckle TJ. The 'Muckle-Wells' syndrome. Br J Dermatol. 1979;100:87–92.
44. Majeed HA, Quabazard Z, Hijazi Z, et al. The cutaneous manifestations in children with familial Mediterranean fever (recurrent hereditary polyserositis). A six-year study. Q J Med. 1990;75:607–16.
45. Kousseff BG. Multiple endocrine neoplasia 2 (MEN 2)/MEN 2A (Sipple syndrome). Dermatol Clin. 1995;13:91–7.
46. Verga U, Fugazzola L, Cambiaghi S, et al. Frequent association between MEN 2A and cutaneous lichen amyloidosis. Clin Endocrinol (Oxf). 2003;59:156–61.
47. Caubet C, Bousset L, Clemmensen O, et al. A new amyloidosis caused by fibrillar aggregates of mutated corneodesmosin. FASEB J. 2010;24:3416–26.
48. Partington MW, Prentice RS. X-linked cutaneous amyloidosis: further clinical and pathological observations. Am J Med Genet. 1989;32:115–19.

Deposition Diseases 48

Jennifer Quist, Sven Quist and Harald Gollnick

Chapter Contents

Gout 709
Pseudogout 711
Lipoid proteinosis 712
Colloid milium 713
Mucopolysaccharidoses 714

INTRODUCTION

The cutaneous deposition disorders are a heterogeneous group of conditions characterized by the presence of primarily endogenous substances within the dermis or the subcutis. Deposition disorders can be associated with localized or generalized cutaneous findings, and skin involvement is sometimes the earliest sign of a deposition disease. Histologic examination of cutaneous lesions, with the use of special stains, is the most specific diagnostic tool (Table 48.1). In addition, specific enzymatic assays or genetic mutational analysis can then be performed to establish the precise diagnosis.

This chapter will focus on gout, pseudogout, lipoid proteinosis, colloid milium and the mucopolysaccharidoses. Additional deposition disorders such as papular mucinosis, amyloidosis, porphyria and calcinosis cutis are reviewed in Chapters 46, 47, 49 and 50.

GOUT

Synonyms: ■ Urate crystal arthropathy ■ Podagra ■ Urate deposition disease

Key features

- Gout is a metabolic disease in which the underlying abnormality is hyperuricemia
- Deposits of needle-like crystals of monosodium urate are found in several sites, most commonly the skin (as tophi) and the joints
- In fresh preparations of synovial fluid and expressed material from tophi, the crystals exhibit negative birefringence when examined by polarized light
- In routinely fixed histologic sections, amorphous deposits that contain needle-like clefts are seen in the dermis and subcutis

DISORDERS WITH DERMAL DEPOSITS – HISTOLOGIC FEATURES

Disease	Microscopic findings	Histochemical stains	Special processing
Gout	Dermal deposits of amorphous material with needle-like clefts surrounded by giant cells Polarizing light/fresh preparation – fine, needle-like crystals; negative birefringence	20% silver nitrate solution: urate crystals appear black and the surrounding tissue yellow De Galantha stain: crystals brown–black	Best fixative to preserve crystals: ethanol-based (Carnoy's fluid)
Lipoid proteinosis	Masses of amorphous or laminated hyalin-like material Also surrounds capillaries in the papillary dermis and appendages	Contains type IV collagen and laminin PAS-positive and diastase-resistant ⊕ Alcian blue, hyaluronidase-sensitive Sudan III (+/–) Congo red (usually –)	
Colloid milium (adult form)	Nodules of amorphous eosinophilic material Artifactual clefts Solar elastosis	Stains similarly to amyloid ⊕ Congo red ⊕ Thioflavin T ⊕ Crystal violet	
Mucopolysaccharidoses	Granules within fibroblasts Large vacuolated cells in sweat glands and the external root sheath of hair follicles (gargoyle cells)	Granules within fibroblasts: ⊕ Metachromasia with toluidine blue and Giemsa ⊕ Alcian blue ⊕ Colloidal iron (see Table 46.1)	Fixation in absolute alcohol better than in formalin (consider when clinical diagnosis not supported by histologic findings)
Mucinoses, e.g. papular mucinosis, scleredema, pretibial myxedema (Ch. 46)	Mucin between collagen and variable fibroblast proliferation	⊕ Metachromasia with toluidine blue ⊕ Alcian blue ⊕ Colloidal iron (see Table 46.1)	Fixation in absolute alcohol better than in formalin
Amyloidosis (Ch. 47)	Fractured, amorphous, faintly eosinophilic material in dermis	⊕ Congo red ⊕ Thioflavin T ⊕ Crystal violet	In glutaraldehyde for electron microscopy
Ochronosis (Ch. 67)	Sausage- or banana-shaped brown/yellow structures	Black staining with methylene blue or cresyl violet	
Calcinosis cutis (Ch. 50)	Irregular masses of deeply basophilic material Variable granulomatous inflammation	⊕ von Kossa ⊕ Alizarin red is more specific	May fracture microtome blade May need decalcification solution first
Porphyrias, in particular EPP (Ch. 49)	Perivascular rim of delicate eosinophilic fibrillar material In chronic lesions, also dense homogeneous deposits	PAS-positive and diastase-resistant Immunohistochemistry for BMZ components (type IV collagen)	

Table 48.1 Disorders with dermal deposits – histologic features. BMZ, basement membrane zone; EPP, erythropoietic protoporphyria.

Introduction

Gout is a metabolic disease in which needle-like crystals of monosodium urate (the ionized form of uric acid) from supersaturated fluids are deposited in tissue. Clinical manifestations include gouty arthritis, accumulation of crystals in connective tissue (tophi), uric acid nephrolithiasis and renal impairment[1,2].

Epidemiology

Gout is the most common form of crystal-induced arthritis, and its prevalence seems to have increased over the past few decades. Men 40–50 years of age are most commonly affected. The male-to-female ratio is 9:1, and most women with gout are postmenopausal. In England, gout is found in up to 1.6% of adults and approximately 20% of patients have a family history of gout[2,3].

Pathogenesis

Gout is a consequence of deposits of urate crystals that have precipitated from supersaturated body fluids. Uric acid is the end product of the catabolism of purines. When the body increases its production of uric acid or if the kidneys do not excrete sufficient amounts, the result is hyperuricemia (Table 48.2).

Urate crystals can activate the NLRP3 inflammasome (see Fig. 45.1) and stimulate the production of the proinflammatory cytokine interleukin-1 by monocytes and macrophages[4]. The subsequent migration and activation of neutrophils as well as complement activation initiate a vicious cycle. The ingestion of crystals by neutrophils triggers cell damage and leakage of lysosomes, which then result in further inflammation and tissue damage.

Clinical Features

The typical patient with gout is a middle-aged or older man, who may have a family history of the disease. Risk factors include obesity, excessive alcohol intake, renal insufficiency and certain medications, most commonly diuretics. The natural history of gout involves four clinical stages[1]: (1) asymptomatic hyperuricemia; (2) acute gouty arthritis; (3) intercritical gout (the intervals between attacks, which progressively become shorter in duration); and (4) chronic tophaceous gout.

Acute gouty arthritis

The most common symptom of gout is the development of severe joint pain over a period of 6–12 hours, accompanied by tenderness, erythema, warmth and swelling. Usually, initial attacks are monoarticular, but in up to 40% of patients they may be polyarticular[5]. In 75% of patients, the first metatarsophalangeal joint is involved (referred to as podagra); additional sites include the knee, ankle and foot, and, less commonly, the hand, wrist and elbow. Fever and systemic symptoms may accompany an acute attack of gout. As the swelling subsides, the skin acquires a violaceous hue and this is often followed by desquamation.

Chronic tophaceous gout

Cutaneous deposits of monosodium urate, known as "tophi", usually appear an average of 10 years after the onset of gout. These tophi present as firm dermal or subcutaneous papules and nodules or as a fusiform swelling. Their contours may be smooth or multilobulated (Fig. 48.1) and the lesions can vary from skin-colored to white–yellow to red (Fig. 48.2). The surface may be ulcerated and there may be associated drainage of material (varies from clear fluid with white flecks to a thick chalky material).

The most common locations for tophi are the skin overlying joints and the helix of the ear. Unusual sites include the eyes, nose, larynx, breast and heart valves. However, tophi develop in fewer than 10% of patients with gout. Depending upon the size and location of the tophi,

CLASSIFICATION OF HYPERURICEMIA	
Overproduction of uric acid	• Primary idiopathic • Excessive dietary purine intake and obesity • Increased nucleotide turnover – High-grade lymphomas (e.g. Burkitt's) and myeloma – Myeloproliferative disorders, esp. acute myelogenous leukemia – Tumor lysis syndrome – Hemolysis – Psoriasis (severe) • Accelerated ATP degradation – Alcohol abuse – Severe muscle exertion • Hypoxanthine–guanine phosphoribosyl transferase deficiency (Lesch–Nyhan syndrome) • Phosphoribosyl pyrophosphatase synthetase overactivity
Decreased excretion of uric acid	• Primary idiopathic • Renal insufficiency • Enhanced tubular urate reabsorption (e.g. diuretics, dehydration) • Drug ingestion (e.g. cyclosporine > tacrolimus, pyrazinamide, low-dose salicylates) • Toxins (e.g. lead-induced nephropathy) • Miscellaneous – lactic acidosis, hypertension, hyperparathyroidism, hypothyroidism

Table 48.2 Classification of hyperuricemia.

Fig. 48.1 Tophaceous gout of a digit. The deposits create a multilobulated appearance. A small incision over the yellow–white areas followed by microscopic examination of the expressed material would allow a bedside diagnosis.

Fig. 48.2 Tophaceous gout of the tragus. The erythema reflects surrounding inflammation.

complete, partial or minimal resolution can occur when the serum uric acid level is normalized[2,6].

Elevated levels of uric acid in the urine can lead to uric acid nephrolithiasis and even acute renal failure when uric acid precipitates in the renal tubules and collecting ducts. The most common setting for the latter is the tumor lysis syndrome in which chemotherapy is given for a rapidly dividing chemosensitive malignancy, e.g. leukemias, lymphomas.

The initial diagnosis of gout is usually made in the setting of acute arthritis, based upon the presence of urate crystals in an aspirate of joint fluid. Hyperuricemia is usually present, but alone it is insufficient for establishing the definitive diagnosis of gout. Additional laboratory abnormalities during an acute attack include an elevated white blood cell count (in the joint fluid and blood) and an elevated ESR.

When examined by polarized light microscopy, the needle-shaped urate crystals change color from yellow to blue based upon their alignment relative to the axis of the "red plate" compensator, i.e. they exhibit negative birefringence. In patients with recurrent attacks, radiographs of involved joints often show "punched-out" erosions with sclerotic "overhanging" margins, but no osteophytes. A 24-hour urine collection for uric acid allows the identification of patients at risk for nephrolithiasis (see Table 48.2).

Pathology

In gouty tophi, the key histologic feature is the presence of deposits of amorphous material within the dermis and subcutis. These deposits contain needle-like clefts (which represent dissolved urate crystals) and are surrounded by an infiltrate composed of histiocytes and multinucleated giant cells as well as lymphocytes (Fig. 48.3). Secondary calcification or even ossification can occasionally be seen.

In order to preserve the crystals, the biopsy specimen needs to be placed in an ethanol-based fixative, such as Carnoy's fluid. Then, under regular or polarized light, brightly refractile brown sheaths of fine needle-like crystals can be seen. Upon staining with 20% silver nitrate solution, the crystals appear black and the surrounding tissue yellow, whereas with the De Galantha stain, the crystals appear brown to black[7].

Differential Diagnosis

The differential diagnosis of acute gouty arthritis includes pseudogout (see below), osteoarthritis, psoriatic arthritis, reactive arthritis (previously referred to as Reiter's disease) and septic arthritis. Given its destructive nature, septic arthritis needs to be considered even in patients in whom the diagnosis of gout has been previously established. The presence of needle-shaped crystals with negative birefringence in an aspirate of joint fluid is diagnostic of gout, while Gram stain and culture exclude septic arthritis.

The differential diagnosis of cutaneous gouty tophi includes xanthomas, rheumatoid nodules and calcinosis cutis. Examination of expressed fluid or chalky material by polarized light can provide a "bedside" diagnosis. By ultrasonography, central clear spaces are seen within tophi whereas rheumatoid nodules contain central echodense areas[6].

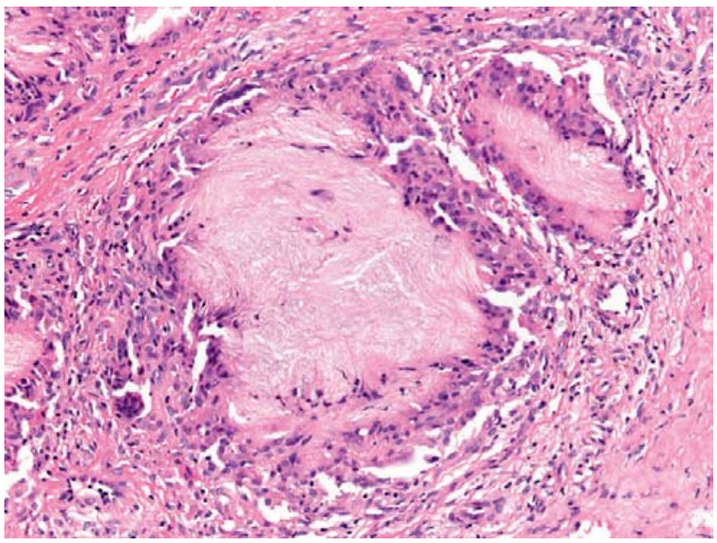


Fig. 48.3 Tophaceous gout – histologic features. Deposits of amorphous, acellular material within the dermis. Needle-like spaces are present within the amorphous deposits and histiocytes and multinucleated giant cells surround the deposits. *Courtesy, Lorenzo Cerroni, MD.*

Treatment

In acute gout, short-acting nonsteroidal anti-inflammatory drugs (*NSAIDs*) are taken orally at the highest safe dosage as long as symptoms persist, e.g. indomethacin 50 mg three times daily for several days. Contraindications include peptic ulceration, renal insufficiency and anticoagulation[6,8].

Colchicine, a derivative of the autumn crocus, has been used to treat gout for centuries. This drug relieves pain and swelling and can help to prevent future attacks. The primary effect of colchicine is an inhibition of the transport of phagocytized urate crystals to lysosomes within neutrophils via its binding to microtubules. Colchicine also interferes with leukocyte migration, chemotaxis and adhesion. For patients with normal renal function who are not receiving strong CYP3A4 inhibitors, the Food and Drug Administration (FDA)-recommended dosage for acute gout flares is 1.2 mg orally followed by 0.6 mg 1 hour later. Prophylaxis in such patients consists of colchicine 0.6 mg once or twice daily. Even at these lower doses, gastrointestinal toxicity is still a concern. Systemic *corticosteroids* may be used for a period of 1–3 weeks if NSAIDs and colchicine are ineffective or contraindicated[6,8].

The xanthine oxidase inhibitor *allopurinol* blocks uric acid production and is often used for chronic therapy of gout, including those with high levels of excreted uric acid (overproducers and hyperexcretors) as well as those who are poor excretors. Side effects include diarrhea, thrombocytopenia, hepatitis, and skin eruptions that can range from morbilliform to erythroderma or toxic epidermal necrolysis (see Ch. 21). More recently, *febuxostat*, an oral non-purine xanthine oxidase inhibitor, was approved for the chronic treatment of gout; its major side effects are liver enzyme elevations and cardiovascular thromboembolic events[9]. Drug–drug interactions, e.g. with azathioprine, can occur with both of these medications (see Fig. 130.3). Uricosuric agents such as oral *probenecid* and *sulfinpyrazone* can be used as second-line therapy for patients with normal renal function and no renal stones.

Some patients may benefit from a reduction in purine-rich foods (e.g. organ meats [liver, heart], fish), alcohol consumption and body weight[6]. In the setting of potential tumor lysis syndrome, intravenous *rasburicase* can be administered, which rapidly converts uric acid to the more soluble allantoin. Bimonthly intravenous *pegloticase*, which has the same mechanism of action, is now approved for patients with chronic gout refractory to conventional therapy, and improvement in tophi has been observed. Lastly, given the evidence for inflammasome activation, *anakinra* has been used for refractory gout and *rilonacept* for prevention of gout flares in patients on allopurinol.

PSEUDOGOUT

Synonyms: ■ Chondrocalcinosis ■ Calcium pyrophosphate disease ■ Calcium gout

Key features

- Pseudogout is a form of arthritis that is due to deposits of calcium pyrophosphate dihydrate (CPPD) crystals within the joint
- It most commonly affects the knee and other large joints of older persons with osteoarthritis
- In aspirates of joint fluid, rhomboid CPPD crystals are seen and they exhibit weakly positive birefringence under polarized light

Pseudogout, which may be clinically indistinguishable from gout, was recognized as a distinct disease entity in 1962[10]. It results when calcium pyrophosphate dihydrate (CPPD) crystals (produced by nucleo-

side triphosphate pyrophosphohydrolase, a catalytic enzyme found in osteoarthritic cartilage) form within joint fluid and then lead to lysis of neutrophils that have ingested the crystals. Although pseudogout is often related to osteoarthritis, it has also been associated with metabolic abnormalities such as hyperparathyroidism and hemochromatosis.

Symptoms of pseudogout include intermittent attacks of pain and swelling of affected joints, most commonly the knee, wrist and shoulder. The onset of symptoms in pseudogout is usually more insidious than in gout. Occasionally, extra-articular CPPD deposition (tophaceous pseudogout) may present as a hard subcutaneous nodule overlying joints primarily of the head (especially the temporomandibular joint), neck or distal extremities[11].

Microscopically, CPPD crystals appear shorter than urate crystals and are often rhomboidal in shape. Polarizing microscopy of sections stained with a non-aqueous alcoholic eosin stain (NAES)[12] allows the demonstration of CPPD crystals with positive birefringence (in contrast to urate crystals with negative birefringence [see above] and calcium hydroxyapatite crystals without birefringence [in tumoral calcinosis]). Treatment of the acute phase of pseudogout is identical to that of gout[11]. In patients with chronic renal failure, the interleukin-1 receptor antagonist anakinra may be considered (see Fig. 45.1)[13].

LIPOID PROTEINOSIS

Synonyms: ■ Hyalinosis cutis et mucosae ■ Urbach–Wiethe disease

Key features

- A rare autosomal recessive deposition disorder due to mutations in the extracellular matrix protein 1 *(ECM1)* gene
- Hyalin-like material is deposited in multiple organs, including the skin, oral mucosa, larynx and brain
- Papules and nodules favor the face, as do pitted scars; diffuse waxy thickening of the skin can be associated with verrucous changes, especially on the elbows, knees and hands

History

Lipoid proteinosis was first described by Siebenmann in 1908. Twenty years later, it was established as a distinct entity by two Viennese physicians, Erich Urbach, a dermatologist, and Camillo Wiethe, an otorhinolaryngologist.

Epidemiology

Most patients are of European ancestry, including descendants of Dutch immigrants who settled in South Africa in the middle of the seventeenth century[14]. Not only do Afrikaners have the highest incidence of this genetic disease, they also exhibit a founder effect, i.e. the population shares a common mutation.

Pathogenesis

In 2002, lipoid proteinosis was shown to be due to loss-of-function mutations in the extracellular matrix protein 1 *(ECM1)* gene[15]. The latter encodes a secretory glycoprotein that can act as a negative regulator of endochondral bone formation and a promoter of angiogenesis. In addition, ECM1a (see below) is found within the basement membrane zone and can enhance the binding of collagen IV to laminin 332. It also interacts with components of the extracellular matrix such as fibronectin and glycosaminoglycans (e.g. hyaluronic acid, chondroitin sulfate)[16].

The *ECM1* gene has three splice variants that result in three isoforms: (1) ECM1a, a protein of 540 amino acids encoded by a 10-exon gene; (2) ECM1b, a protein of 415 amino acids reflecting a lack of exon 7; and (3) ECM1c, a protein of 559 amino acids due to an additional exon 5a within intron 5. Patients with mutations in exon 7 still express the ECM1b isoform and tend to have milder disease as compared to those with mutations in exon 6, who tend to have more severe disease and reduced expression of all three isoforms. Approximately one-third of pathogenic mutations reported to date occur in each of these two exons[15]. The degree of cutaneous immunofluorescent staining (utilizing an anti-ECM1 antibody) points to the location; reduced staining suggests mutations in exon 7, while an absence of staining suggests mutations in exon 6[16].

Clinical Features

The first clinical sign of lipoid proteinosis is often a weak cry or hoarseness due to infiltration of the laryngeal mucosa. Hoarseness remains throughout life. Cutaneous lesions usually appear during the first 2 years of life, in two overlapping stages. The first stage consists of vesicles and hemorrhagic crusts on the skin of the face and extremities and in the mouth, often in association with trauma. The skin lesions may resolve with scarring including "ice-pick"-like scars.

In the second stage, there is an increase in the hyalin deposits within the dermis (Fig. 48.4). The skin becomes diffusely thickened and waxy and develops a yellow discoloration. Papules, plaques and nodules appear on the face (including the eyelid margin) as well as in the axillae and on the scrotum. Verrucous lesions may develop on the extensor surfaces, especially the elbows (see Fig. 48.4C), knees and hands. Generalized scaling has also been observed[17] as has alopecia of the eyebrows and eyelashes. Corneal ulcers may occur due to infiltration of the eyelids.

In addition to involvement of the tongue (diffuse infiltration), the frenulum (restricted motion of the tongue) and the oropharynx, recurrent parotitis can occur due to occlusion of the salivary duct. Dental anomalies include hyperplasia or aplasia of the upper incisors, premolars or molars. Patients usually lose their teeth at an early age. Neurologic manifestations are common and consist primarily of seizures, and, less often, abnormal behavior[18]. A pathognomonic radiographic finding is bilateral, intracranial, sickle-shaped calcification within the temporal lobes.

In general, the disease has a stable or slowly progressive course that is compatible with a normal lifespan, except for the risk of respiratory obstruction in infancy. An elevated ESR may be seen due to increased α- or γ-globulins.

Pathology

The major clinical manifestations are related to the deposition of an amorphous or laminated material around blood vessels and in the connective tissues. The amorphous deposits consist primarily of non-collagen proteins, while the concentric layers of basement membrane-like material contain collagen (types II and IV) and laminin. In addition, the deposits are PAS-positive and diastase-resistant, indicating the presence of neutral mucopolysaccharides.

H&E-stained sections of early lesions reveal pink, hyalin-like thickening of the capillaries within the papillary dermis, and in one patient, vesicles were due to non-dyskeratotic acantholysis. Older lesions are characterized by hyperkeratosis, occasionally papillomatosis, and a thickened dermis in which bundles of pink hyalin deposits are found in a diffuse pattern (Fig. 48.5); the bundles are often oriented perpendicularly to the dermal–epidermal junction. There are smaller scattered deposits of hyalin in the lower dermis. Hyalin mantles can surround the eccrine glands as well as the hair follicles, sebaceous glands and, rarely, arrector pili muscles.

In addition to type IV collagen, laminin and neutral mucopolysaccharides, hyaluronic acid is also present in the dermis, as demonstrated by Alcian blue and hyaluronidase staining (see Ch. 46). Fat stains (e.g. Sudan III) give inconsistent results, and, rarely, the deposits stain with Congo red. Ultrastructurally, reduplication of the basement membrane of vessels and, occasionally, the dermal–epidermal junction is seen; the deposits appear to be composed of small granules and short filaments of low electron density that measure 3–5 nm in diameter.

Differential Diagnosis

The clinical differential diagnosis includes erythropoietic protoporphyria (EPP), amyloidosis, papular mucinosis (scleromyxedema), colloid milium and non-X histiocytoses. In infants, the possibility of juvenile hyaline fibromatosis and infantile systemic hyalinosis need to be considered, both of which are due to mutations in the gene that encodes

Fig. 48.4 Lipoid proteinosis – clinical features. A Beaded eyelid papules, hemorrhagic crusts, and confluent waxy papules of the glabella leading to an early leonine facies. **B** Skin-colored papulonodules of the elbow as well as irregular hypopigmented scars of the extensor forearm. **C** Characteristic verrucous changes of the elbow. **D** A firm tongue with numerous tiny papules on the dorsal surface. **E** Multiple, round hypopigmented and depressed scars on the shoulder. **F** Waxy, yellowish plaque on the back. *B,D,E, Courtesy, Julie V Schaffer, MD. C, Courtesy, Judit Stenn, MD.*

capillary morphogenesis protein 2 (see Ch. 98). Histologically, the differential diagnosis includes EPP and colloid milium. In cutaneous lesions of EPP, colloid milium and amyloidosis (see Table 48.1), the hyalinization is milder, more focal and superficial, and it rarely involves the eccrine glands. The deposits in colloid milium do not have the striking perivascular pattern seen in lipoid proteinosis.

Treatment

Currently, there is no known cure or effective treatment for lipoid proteinosis. Topical glucocorticoids have been used with some beneficial effect, as have humectants. Plastic surgery and dermabrasion have also been successfully performed in selected patients[19], and there are scattered reports of the use of systemic retinoids[20], D-penicillamine and oral dimethyl sulfoxide (DMSO)[21].

COLLOID MILIUM

Synonyms: ■ Colloid degeneration of the skin ■ Elastosis colloidalis conglomerata ■ Miliary colloidoma

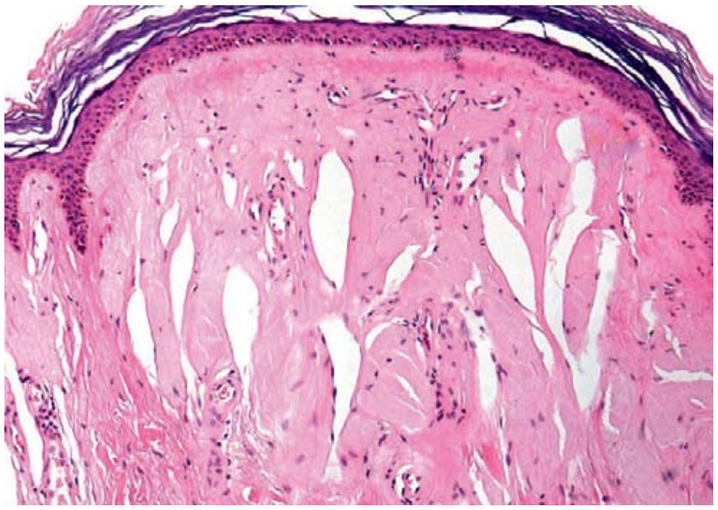


Fig. 48.5 Lipoid proteinosis – histologic features. Hyperkeratosis, a flattened epidermis and vertically oriented eosinophilic deposits in the dermis. Note the cleft formation. *Courtesy, Lorenzo Cerroni, MD.*

Key features

- A rare disorder in which dome-shaped, translucent papules develop in sun-exposed skin
- Four variants are recognized: adult, juvenile, pigmented and nodular colloid degeneration
- Histologically, amorphous, eosinophilic, granular deposits within the superficial dermis

Introduction/Epidemiology

Adult colloid milium is the most common form of the disease. It usually occurs in middle-aged, fair-skinned individuals who have had significant cumulative sun exposure, with a male-to-female ratio of 4:1. The adult form has also been observed in outdoor oil refinery workers, suggesting an additional effect of petrochemicals. In general, *juvenile* colloid milium develops before puberty and both an autosomal recessive and an autosomal dominant inheritance pattern have been reported[22].

Pathogenesis

Although excessive sun exposure clearly plays a role in *adult* colloid milium, the precise pathogenesis is not known. Photoinduced damage to dermal elastic fibers, as in solar elastosis, has been suggested. In *juvenile* colloid milium, ultraviolet light-induced damage to epidermal keratinocytes has been observed and this may reflect an inherited susceptibility. *Pigmented* colloid milium is a variant of the adult form in which there is a combination of excessive sun exposure plus topical application of hydroquinone or phenols[23].

Clinical Features

In both the adult and juvenile forms, multiple, dome-shaped, translucent to yellow or yellow–brown papules are seen in areas of chronic sun exposure, e.g. the face (especially periorbitally), ears, posterolateral neck, and the dorsal aspect of the hands and forearms. With minor trauma, lesions can become hemorrhagic. In *pigmented* colloid milium, grouped to confluent gray–brown papules are present on the face, whereas in *nodular colloid degeneration*, skin-colored to yellowish nodules or plaques develop, often on the face[22,23].

Pathology

In *adult* colloid milium, nodules composed of homogeneous eosinophilic colloid material are seen in the papillary dermis. Within the nodules, there may be clefts and fissures. A grenz zone is often present, as is evidence of solar elastosis beneath the nodules. Although the colloid masses contain degenerated elastic fibers, they often exhibit a staining profile similar to amyloidosis, i.e. positive staining with crystal violet, Congo red and thioflavin T stains. In addition, PAS staining is positive.

In *juvenile* colloid milium, amorphous eosinophilic deposits are also found within the papillary dermis, but when compared to the adult form, there is less clefting and no grenz zone. As with colloid bodies (which are also keratinocyte-derived), nonspecific staining for immunoglobulins, complement and fibrin is seen. In addition, staining for keratin is positive.

In *pigmented* colloid milium, lightly pigmented islands of colloid material are found in the upper dermis. In *nodular colloid degeneration*, homogenized amorphous dermal collagen with small fissures and clefts are found. Whether this entity is a variant of nodular amyloidosis is still under debate. Ultrastructurally, colloid milium is characterized by amorphous and granular material which lacks the straight, nonbranching filaments seen in amyloidosis.

Differential Diagnosis

Clinically, the differential diagnosis of juvenile and adult forms of colloid milium includes erythropoietic protoporphyria (EPP), mucinoses (e.g. papular, self-healing), lipoid proteinosis, adnexal tumors and primary systemic amyloidosis (adults). Pigmented colloid milium needs to be distinguished from exogenous ochronosis. Histologically, colloid milium must be distinguished from EPP, lipoid proteinosis and amyloidosis. In cutaneous lesions of EPP, there are hyaline deposits around and within the superficial blood vessel walls, whereas the dermal deposits of lipoid proteinosis are accentuated around the blood vessels. Cutaneous amyloidosis may be indistinguishable from the juvenile type of colloid milium, as both stain positively for keratin; some authors consider juvenile colloid milium to be a variant of lichen amyloidosis. Unlike lipoid proteinosis and lichen amyloidosis, the dermal deposits of adult colloid milium do not stain positively for laminin and type IV collagen or cytokeratin, respectively.

Treatment

Treatment modalities are limited and include laser therapy (e.g. long-pulsed Er:YAG, fractional photothermolysis), dermabrasion, intense pulsed light, cryotherapy and chemical peels[24].

MUCOPOLYSACCHARIDOSES

Key features

- A group of inherited disorders, primarily autosomal recessive, characterized by deficiencies of specific lysosomal enzymes involved in the catabolism of glycosaminoglycans (GAGs), also referred to as mucopolysaccharides
- Excessive amounts of the GAGs are found in various tissues and lead to coarse facies, mental retardation, hepatosplenomegaly, skeletal abnormalities and corneal clouding
- One of the mucopolysaccharidoses, Hunter syndrome (X-linked recessive), has distinctive skin-colored to white papules over the scapulae (pebbling)
- Screening tests include examination of the urine, peripheral leukocytes and dermal fibroblasts for the presence of excessive GAGs

Clinical Features and Pathology

The mucopolysaccharidoses are due to mutations in several genes that encode the enzymes involved in the catabolism of glycosaminoglycans (GAGs)[25]. Examples of GAGs include dermatan sulfate, heparan sulfate and chondroitin sulfate. The storage of excessive amounts of the GAGs in various tissues leads to a constellation of findings; the most common manifestations are coarse facies, mental retardation, hepatosplenomegaly, skeletal abnormalities (dysostosis multiplex), joint stiffness, cardiovascular disease and corneal clouding (Table 48.3). Depending upon the

THE MUCOPOLYSACCHARIDOSES										
Disorder	**Enzyme deficiency**	**Stored material**	**Clinical types (onset)**	**Inheritance**	**Clinical features**					
					Neurologic	**Liver and/or spleen enlargement**	**Skeletal disease**	**Ophthalmologic**	**Hematologic**	**Other features**
MPS 1 H, Hurler	α-L-Iduronidase	Dermatan sulfate Heparan sulfate	Infancy	AR	Mental retardation	+++	++++	Corneal clouding	Vacuolated lymphocytes	Coarse facies, cardiovascular involvement, respiratory compromise, joint stiffness, dermal melanocytosis*
MPS I H/S, Hurler/ Scheie	α-L-Iduronidase	Dermatan sulfate Heparan sulfate	Childhood	AR	Mild mental retardation	++	++	Corneal clouding	Vacuolated lymphocytes	Severity intermediate between Hurler and Scheie
MPS I S, Scheie	α-L-Iduronidase	Dermatan sulfate Heparan sulfate	Late childhood/ early adulthood	AR	None	+	+	Corneal clouding	Vacuolated lymphocytes	Normal stature, valvular heart disease, joint stiffness, carpal tunnel syndrome
MPS II, Hunter	Iduronate 2-sulfatase	Dermatan sulfate Heparan sulfate	Severe – infancy Mild – late childhood	X-linked recessive	Mental retardation, less in mild form	++ to +++	++ to ++++	Retinal degeneration, no corneal clouding	Granulated lymphocytes	Coarse facies, cardiovascular involvement, joint stiffness, distinctive pebbly skin lesions
MPS III A–D, Sanfilippo A–D	A: Heparan-*N*-sulfatase B: *N*-acetyl-α-glucosaminidase C: Acetyl-CoA: α-glucosaminide *N*-acetyltransferase D: *N*-acetyl-glucosamine-6-sulfatase	Heparan sulfate	Early childhood	AR	Severe mental retardation, with deterioration during early childhood	+	+	None	Granulated lymphocytes	Mild coarse facies, usually normal stature, severe behavioral problems
MPS IV A, Morquio A	*N*-acetylgalactosamine-6-sulfatase	Keratan sulfate Chondroitin-6 sulfate	Childhood	AR	None	+	++++	Corneal clouding	Granulated neutrophils	Distinctive skeletal deformity, odontoid hypoplasia, aortic valve disease
MPS IV B, Morquio B	β-Galactosidase†	Keratan sulfate Chondroitin-6 sulfate	Childhood	AR	None	±	++++	Corneal clouding	Granulated neutrophils	See above, Morquio A
MPS VI, Maroteaux–Lamy	Arylsulfatase B (*N*-acetylgalactosamine-4-sulfatase)	Dermatan sulfate	Late infancy/ childhood	AR	None	++	++++	Corneal clouding	Granulated neutrophils and lymphocytes (most prominent of all MPS)	Coarse facies, valvular heart disease, upper airway obstruction
MPS VII, Sly	β-Glucuronidase	Dermatan sulfate Heparan sulfate Chondroitin-4 and -6 sulfate	Wide range Severe – neonatal Mild – adolescence	AR	Mental retardation, absent in some adults	+ to +++	+ to +++	Corneal clouding	Granulated neutrophils	Coarse facies, cardiovascular involvement, hydrops fetalis in neonatal form

*Persistent and extensive, often involving the anterior as well as posterior trunk; has also been described in patients with GM1-gangliosidosis (see Ch. 63).
†Allelic with GM1-gangliosidosis.

Table 48.3 The mucopolysaccharidoses (MPS). AR, autosomal recessive. *Adapted with permission from Hopkin R, Grabowski GA. Lysosomal storage diseases. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J (eds). Harrison's Principles of Internal Medicine, 18th edn. New York:McGraw-Hill, 2011.*

specific type of mucopolysaccharidosis (MPS), the presence and severity of the clinical findings varies.

Cutaneous manifestations are nonspecific (e.g. hypertrichosis, thickening of the skin), except for the presence of skin-colored to white papules or nodules over the scapulae ("pebbling") in patients with Hunter syndrome[26], which is inherited in an X-linked recessive fashion. The lesions measure 1–10 mm in diameter and may become confluent; they can extend from the posterior axillary line to the midline. Less common sites of involvement are the arms, the lateral upper chest and the buttocks. Extensive dermal melanocytosis has also been reported in patients with Hurler syndrome as well as those with GM1 gangliosidosis type 1.

Screening tests include examination of the urine for excessive amounts of GAGs and examination of circulating leukocytes (usually lymphocytes; see Table 48.3) or dermal fibroblasts for vacuoles or granules. The latter contain sulfated acid GAGs that can be demonstrated via special stains (see Table 46.1). The peripheral blood smear should be fixed in absolute methanol and fixation of the skin biopsy specimen in absolute alcohol is preferred. Specific enzyme assays or genetic mutational analysis can then be performed; prenatal diagnosis is also possible.

In addition to the presence of vacuoles or granules within fibroblasts, the cutaneous papules of Hunter syndrome have extracellular deposits of metachromatic material[26]. Biopsy specimens from all types of MPS can have vacuolated cells within sweat glands and the external root sheath of hair follicles. Keratinocytes may develop a pale distended cytoplasm which displaces the nucleus to one side. Biopsy specimens of diffusely thickened skin demonstrate fragmentation and hyalinization of collagen and increased amounts of mucin. By electron microscopy, fibrillogranular material is seen within lysosomes in all types of MPS.

Treatment

Although symptomatic and supportive interventions (e.g. home oxygen, physical therapy for joint stiffness, and cardiac valve replacement) still play an important role in the treatment of mucopolysaccharidoses, nowadays there are additional therapeutic options – in particular, enzyme replacement and hematopoietic stem cell transplantation[27]. The mucopolysaccharidoses are ideal candidates for enzyme replacement therapy because there is a high-affinity uptake mechanism for lysosomal enzymes. Currently available enzymes include α-L-iduronidase (laronidase; Aldurazyme™) for MPS I, *N*-acetylgalactosamine 4-sulfatase (galsulfase; Naglazyme™) for MPS VI, and iduronate-2-sulfatase (idursulfase; Elaprase™) for MPS II. For example, a reduction in hepatic lysosomal storage was observed with laronidase, while an improvement in walking and stair-climbing abilities were observed with galsulfase[28].

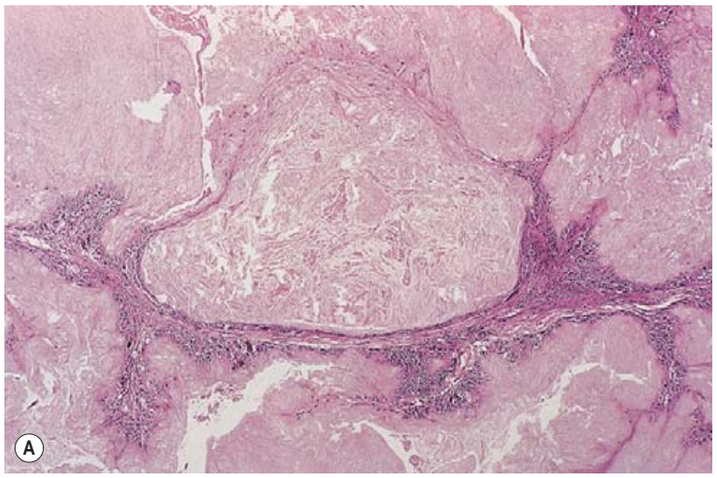
Since 1981, bone marrow transplants have been attempted with varying degrees of success. More recently, results of allogeneic hematopoietic stem cell transplants and cord-blood transplants from unrelated donors have been more encouraging, particularly in patients with MPS I H, II, III and VI.

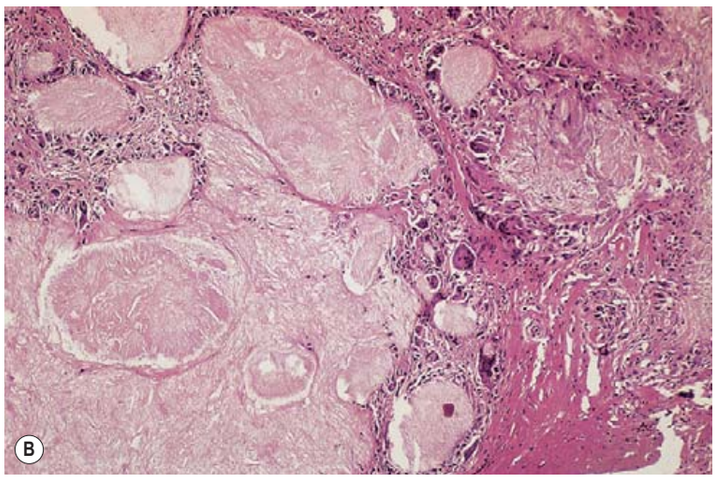
REFERENCES

1. Touart DM, Sau P. Cutaneous deposition diseases. Part II. J Am Acad Dermatol. 1998;39:527–44.
2. Richette P, Bardin T. Gout. Lancet. 2010;375:318–28.
3. Harris CM, Lloyd DC, Lewis J. The prevalence and prophylaxis of gout in England. J Clin Epidemiol. 1995;48:1153–8.
4. Punzi L, Calo L, Plebani M. Clinical significance of cytokine determination in synovial fluid. Crit Rev Clin Lab Sci. 2002;39:63–88.
5. Lawrence RC, Helmick CG, Arnett FC. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis Rheum. 1998;41:778–99.
6. Keith MP, Gilliland WR. Updates in the management of gout. Am J Med. 2007;120:221–4.
7. Smoller, BR, Horn TD. Dermatopathology in Systemic Disease. Oxford: Oxford University Press, 2001:31–2.
8. Zhang W, Doherty M, Bardin T, et al. EULAR evidence based recommendations for gout. Part II: management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis. 2006;65:1312–24.
9. Becker MA, Schumacher HR Jr, Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med. 2005;353:2450–61.
10. McCarty DJ, Kohn NN, Faire JS. The significance of calcium phosphate crystals in the synovial fluid of arthritic patients: the "pseudogout" syndrome. Clinical aspects. Ann Intern Med. 1962;56:711–37.
11. Joseph J, McGrath H. Gout or "pseudogout": how to differentiate crystal-induced arthropathies. Geriatrics. 1995;50:33–9.
12. Shidham V, Chivukula M, Basir Z, Shidham G. Evaluation of crystals in formalin-fixed, paraffin-embedded tissue sections for the differential diagnosis of pseudogout, gout, and tumoral calcinosis. Mod Pathol. 2001;14:806–10.
13. Announ N, Palmer G, Guerne PA, Gabay C. Anakinra is a possible alternative in the treatment and prevention of acute attacks of pseudogout in end-stage renal failure. Joint Bone Spine. 2009;76:424–6.
14. Heyl T. Lipoid proteinosis in South Africa. Dermatologica. 1971;142:129–32.
15. Hamada T, McLean WH, Ramsay M, et al. Lipoid proteinosis maps to 1q21 and is caused by mutations in the extracellular matrix protein 1 gene (*ECM1*). Hum Mol Genet. 2002;11:833–40.
16. Sercu S, Zhang M, Oyama N, et al. Interaction of extracellular matrix protein 1 with extracellular matrix components: ECM1 is a basement membrane protein of the Skin. J Invest Dermatol. 2008;128:1397–408.
17. Touart DM, Sau P. Cutaneous deposition diseases. Part I. J Am Acad Dermatol. 1998;39:149–71.
18. Emsley RA, Paster L. Lipoid proteinosis presenting with neuropsychiatric manifestations. J Neurol Neurosurg Psychiatry. 1985;48:1290–2.
19. Buchan NG, Kemble JV. Successful surgical treatment of lipoid proteinosis. Br J Dermatol. 1974;90:561–6.
20. Dowlati A, Dowlati Y, Mansauri P. Lipoid proteinosis and its response to etretinate therapy. In: Pierard GE, Pierard-Franchimont C (eds). The Dermis: From Biology to Diseases. Liège, Belgium: Service de Dermatopathologie, 1989:135–42.
21. Wong CK, Lin CS. Remarkable response of lipoid proteinosis to oral dimethyl sulphoxide. Br J Dermatol. 1988;119:541–4.
22. Lewis AT, Le EH, Quan LT, et al. Unilateral colloid milium of the arm. J Am Acad Dermatol. 2002;46:S5–7.
23. Findlay GH, Morrison JG, Simon IW. Exogenous ochronosis and pigmented colloid milium from hydroquinone bleaching creams. Br J Dermatol. 1975;93:613–22.
24. Marra DE, Pourrabbani S, Fincher EF, et al. Fractional photothermolysis for the treatment of adult colloid milium. Arch Dermatol. 2007;143:572–4.
25. Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Scriver CR, Beaudet AL, Sly WS, et al. (eds). The Metabolic and Molecular Basis of Inherited Disease, 7th edn. New York: McGraw-Hill, 1995:2465–94.
26. Freeman RG. A pathological basis for the cutaneous papules of mucopolysaccharidosis II (the Hunter syndrome). J Cutan Pathol. 1977;4:318–28.
27. Muenzer J, Fisher A. Advances in the treatment of mucopolysaccharidosis type I. N Engl J Med. 2004;350:1932–4.
28. Kakkis ED, Muenzer J, Tiller GE, et al. Enzyme-replacement therapy in mucopolysaccharidosis. N Engl J Med. 2001;344:182–8.

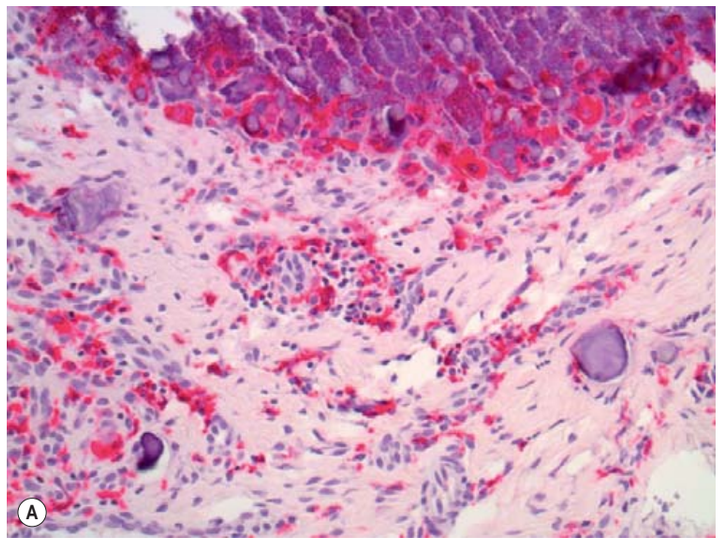
Tophaceous gout. The deposits create a multilobulated appearance.

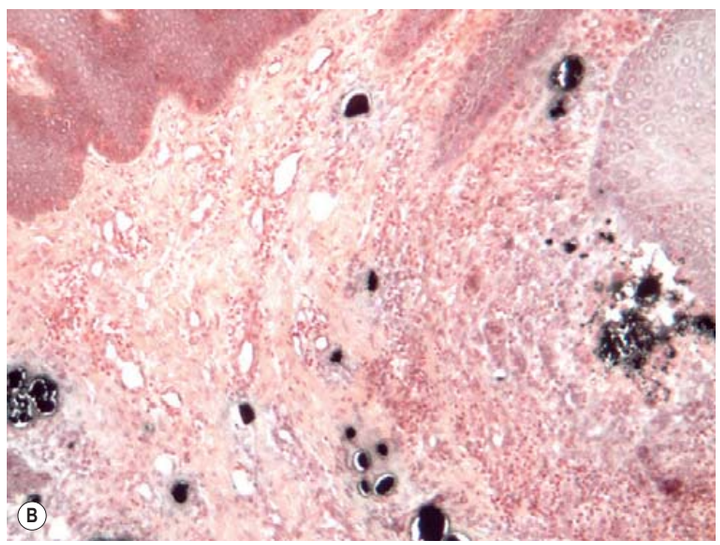
Type VI mucopolysaccharidosis. A 3-year-old with coarse features and stunted growth.





Histologic features of gout. A Deposits of amorphous, acellular material within the dermis. **B** Higher magnification. Needle-like spaces are present within the amorphous deposits, and histiocytes and multinucleated giant cells surround the deposits.





Histological features of pseudogout. A Calcium deposits in the upper dermis **B** van Giesson staining.

49 Porphyria

Jorge Frank and Pamela A Poblete-Gutiérrez

Key features

- The porphyrias result from dysfunction of enzymes involved in heme biosynthesis
- The different types can be classified into either acute versus non-acute or cutaneous versus non-cutaneous forms
- Cutaneous symptoms exclusively involve sun-exposed areas of the body
- Life-threatening neurologic attacks can occur in the acute porphyrias
- Diagnosis of specific types of porphyria may at times be difficult because clinical symptoms are often nonspecific and biochemical findings can overlap
- The genetic bases of the porphyrias have been well characterized, facilitating accurate molecular diagnosis and genetic counseling

INTRODUCTION

The porphyrias are metabolic disorders, each arising from a predominantly hereditary deficiency of one of the eight enzymes of the porphyrin-heme biosynthetic pathway (Fig. 49.1)[1]. Traditionally, these disorders are subdivided into erythropoietic and hepatic forms, according to the major site of expression of the enzyme deficiency. From a dermatologist's perspective, the porphyrias can be classified into cutaneous versus non-cutaneous forms (Table 49.1). However, from a general clinician's point of view, it is more appropriate to classify the porphyrias into acute and non-acute forms, thereby emphasizing the presence or absence of potentially life-threatening acute neurologic attacks (Table 49.2)[2]. Therefore, we will adhere to the latter classification throughout this chapter.

The porphyrias are of particular dermatologic interest because most forms have distinct cutaneous manifestations that allow a presumptive diagnosis. Laboratory tests are then used to confirm the suspected diagnosis. The genetic defects underlying the porphyrias have been well characterized (Table 49.3), facilitating molecular diagnosis and genetic counseling for affected families.

HISTORY

In 1874, Schultz described a man with a history of cutaneous photosensitivity, accompanied by the excretion of wine-red urine[3]. Subsequently, Baumstark detected urinary pigments, which he named "urorubrohaematin" and "urofuscohaematin"[4]. Günther established the first classification of the porphyrias in 1911, recognizing them as hereditary metabolic disorders characterized by increased porphyrin excretion. He distinguished between two different forms: (1) haematoporphyria acuta, characterized by acute neurovisceral attacks without skin lesions; and (2) haematoporphyria congenita and chronica, both disorders having cutaneous findings in sun-exposed areas of the body[5]. In 1937, the terms "acute intermittent porphyria" and "porphyria cutanea tarda" were introduced. Over the next four decades, variegate porphyria (in 1953), hereditary coproporphyria (in 1955), erythropoietic protoporphyria (in 1961), hepatoerythropoietic porphyria (in 1969) and δ-aminolevulinic acid (ALA) dehydratase deficiency porphyria (in 1979) were described[6]. Most recently, X-linked dominant protoporphyria was recognized[7].

EPIDEMIOLOGY

The porphyrias are rare disorders, occurring in all races and both sexes. Whereas some forms appear during infancy, other variants usually do not present until puberty or adulthood. Prevalence rates vary from 0.1 to 10 per 100 000 individuals (see Table 49.2)[1]. However, the precise prevalence of the various porphyrias is not known, due primarily to geographic differences, the likelihood of underdiagnosis, and the incomplete penetrance of the dominantly inherited porphyrias.

PATHOGENESIS

Mutations in any of the genes encoding the enzymes in the heme biosynthetic pathway can lead to a pathologic accumulation and measurable excretion of porphyrins and/or porphyrin precursors, as a result of enzyme dysfunction[1]. Except for patients with acquired porphyria cutanea tarda, all forms of porphyria are inherited as monogenetic traits (see Table 49.3).

Cutaneous Findings

To date, no single factor can explain the photosensitization evoked by porphyrins plus UV radiation. Nonetheless, there are a number of cellular and soluble factors that are thought to be involved, among them reactive oxygen species, particular cell types (e.g. erythrocytes, mast cells, polymorphonuclear cells, fibroblasts), and soluble mediators (e.g. components of the complement system or factor XII-dependent pathways, eicosanoids), as well as matrix metalloproteinases[6]. Most likely, interactions between these factors contribute to the development of cutaneous lesions. Porphyrins absorb light energy intensely in the Soret band (major absorption peak between 400 and 410 nm). As a result, they enter into an excited state and can then transfer this absorbed energy to oxygen molecules, thus creating reactive oxygen species. Cellular and tissue damage induced by photoactivated porphyrins is believed to result primarily from the formation of reactive singlet oxygen and free radicals, with subsequent lipid peroxidation and protein cross-linking[8,9]. The type of cellular damage depends on the solubility and tissue distribution of the porphyrins. Accumulation of water-soluble uro- and coproporphyrins leads to blistering, as is seen in most of the cutaneous porphyrias (e.g. porphyria cutanea tarda, variegate porphyria). In contrast, accumulation of lipophilic protoporphyrins leads to an immediate cutaneous burning sensation after exposure to the appropriate wavelengths of light, accompanied by erythema and edema, as is seen in erythropoietic protoporphyria[9].

Acute Porphyric Attack

Two porphyria variants, acute intermittent porphyria and ALA dehydratase deficiency porphyria, are not associated with cutaneous findings. The dysfunctional enzymes in these two porphyrias act early in heme biosynthesis, and their substrates, ALA and porphobilinogen (PBG), are non-phototoxic porphyrin precursors (see Fig. 49.1). However, both acute intermittent porphyria and ALA dehydratase deficiency

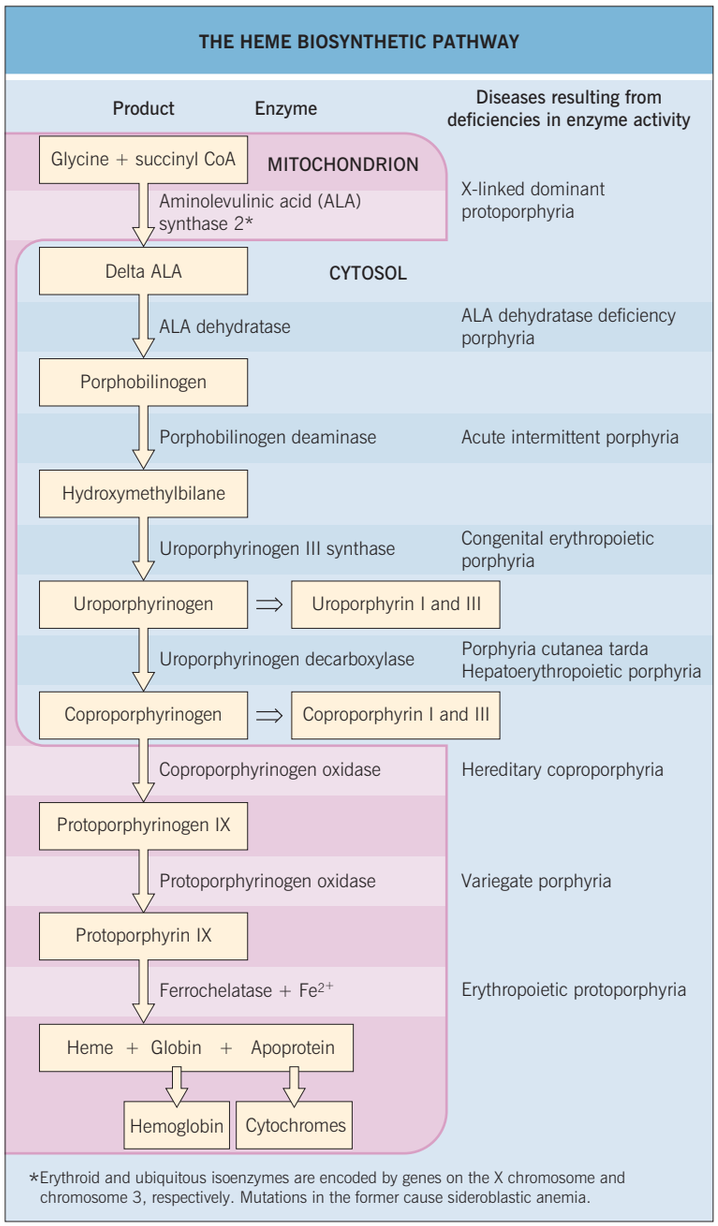


Fig. 49.1 The heme biosynthetic pathway. ALA, aminolevulinic acid. δ-aminolevulinic acid is also referred to as 5-aminolevulinic acid.

CLASSIFICATION OF THE PORPHYRIAS INTO CUTANEOUS AND NON-CUTANEOUS FORMS

Cutaneous	Non-cutaneous
Porphyria cutanea tarda	Acute intermittent porphyria
Erythropoietic protoporphyria	ALA dehydratase deficiency porphyria
Variegate porphyria	
Hereditary coproporphyria	
Congenital erythropoietic porphyria	
Hepatoerythropoietic porphyria	
X-linked dominant protoporphyria	

Table 49.1 Classification of the porphyrias into cutaneous and non-cutaneous forms. ALA, aminolevulinic acid.

porphyria can manifest with life-threatening acute neurologic attacks (see Table 49.2). It appears that ALA and PBG, which are excreted in massive amounts from the liver during an acute attack, are extremely neurotoxic. Lacking appropriate barrier protection, the autonomic and peripheral nervous systems are particularly susceptible to the toxic effects[10].

Of note, porphyrin abnormalities are also observed in the setting of lead poisoning, sideroblastic and hemolytic anemia, iron deficiency, renal failure, cholestasis, liver disease and gastrointestinal hemorrhage. However, associated photosensitivity has only been documented in rare cases of sideroblastic anemia[6].

CLINICAL AND LABORATORY INVESTIGATION

In establishing the diagnosis of a specific type of porphyria, the medical evaluation involves up to four steps:

- a thorough clinical assessment that includes a family history and physical examination, with particular reference to sun-exposed sites
- biochemical measurement of porphyrins and porphyrin precursors in urine, feces, blood and/or plasma (Table 49.4)
- determination of the activity of specific enzymes (specialized laboratories)
- DNA mutational analysis (specialized laboratories).

Difficulties in obtaining a definitive diagnosis are primarily a result of the different types of porphyria having overlapping clinical and/or biochemical features (Fig. 49.2). This is especially true of variegate porphyria and hereditary coproporphyria, which may present with cutaneous lesions similar to those observed in porphyria cutanea tarda and/or neurologic and visceral findings resembling those encountered in acute intermittent porphyria.

With regard to biochemical analyses, markedly elevated urinary levels of the porphyrin precursors ALA and PBG can be found during an acute attack. However, asymptomatic "carriers" (who harbor mutations) are rarely detected via measurement of urinary porphyrin precursors because the latter can exhibit significant variability and levels may be only slightly elevated or even normal during the intervals between acute attacks. In addition, diagnoses based upon measurements of enzymatic activity in fibroblasts or lymphocytes are not always conclusive. This is because an overlap exists between the values obtained in patients, asymptomatic carriers, and normal control individuals[11].

Therefore, the ability to detect specific genetic mutations has made a significant impact on the precise diagnosis of porphyrias and the ability to provide accurate genetic counseling[6,10].

THE NON-ACUTE PORPHYRIAS

The non-acute porphyrias consist of porphyria cutanea tarda (PCT), erythropoietic protoporphyria (EPP), X-linked dominant protoporphyria (XLDPP), congenital erythropoietic porphyria (CEP), and hepatoerythropoietic porphyria (HEP). All these porphyrias present primarily with cutaneous findings (see Tables 49.1 & 49.2)[1,6]. While histologic examination of involved skin is not required to confirm a presumptive diagnosis of any of the cutaneous porphyrias, a biopsy specimen may have been obtained to exclude other entities in the differential diagnosis. Occasionally, the pathologist may suggest the diagnosis of a cutaneous porphyria (based upon histologic findings) even though the clinician suspected another disorder, e.g. epidermolysis bullosa acquisita.

Porphyria Cutanea Tarda (PCT)

Worldwide, PCT is the most common type of porphyria. It results from decreased catalytic activity of uroporphyrinogen decarboxylase, the fifth enzyme in heme biosynthesis (see Fig. 49.1)[1,6].

At least two types of PCT can be distinguished: (1) a sporadic (acquired) variant, designated type I PCT, in which the dysfunctional enzyme is exclusively expressed in the liver; and (2) an autosomal dominant familial (hereditary) variant, designated type II PCT, in which the catalytic enzymatic defect is detected in all tissues (see Table 49.3). In most countries, the ratio of type I to type II PCT is currently estimated to be approximately 3:1 to 4:1[12]. Interestingly, Elder[13] reported several families with typical clinical and biochemical features of overt PCT but with normal uroporphyrinogen decarboxylase activity in their red blood cells. This variant of the disease has been designated type III PCT.

CLASSIFICATION OF THE PORPHYRIAS INTO ACUTE AND NON-ACUTE FORMS			
	Incidence	**Age of onset**	**Important aspects**
ACUTE PORPHYRIAS			
Acute intermittent porphyria	0.5–1 per 100 000	Second to fourth decade of life; rarely before puberty	Most common acute porphyria in the world; acute neurologic attacks but no photosensitivity/cutaneous manifestations
Variegate porphyria	~1 per 300 in South Africa; relatively rare elsewhere	Second to third decade of life; usually not before puberty	Cutaneous manifestations similar to porphyria cutanea tarda, and acute attacks similar to acute intermittent porphyria can occur (neurocutaneous porphyria); founder mutations identified in South Africa and Chile
Hereditary coproporphyria	Very rare (<75 cases reported)	Usually not before puberty	Acute attacks similar to acute intermittent porphyria, and cutaneous manifestations including erythema and blistering in sun-exposed areas can occur (neurocutaneous porphyria)
ALA-D deficiency porphyria	Extremely rare (<10 cases reported)	Early and late onset have been described	Neurologic symptoms similar to acute intermittent porphyria can occur; no photosensitivity/cutaneous manifestations
NON-ACUTE PORPHYRIAS			
Porphyria cutanea tarda	Most common porphyria worldwide	Third to fourth decade of life; usually not before puberty	Acquired and hereditary variants exist; moderate to severe photosensitivity; cutaneous findings in sun-exposed areas include skin fragility, erosions, crusts, vesicles and bullae, milia, scarring, hyperpigmentation and hypertrichosis; indistinguishable from variegate porphyria
Erythropoietic protoporphyria	Second-highest incidence of the cutaneous porphyrias	Early childhood (1 to 4 years); late onset extremely rare	Cutaneous manifestations include erythema, edema, crusts, purpura, skin thickening, and waxy scars, primarily on the dorsal hands and face; usually no blistering; in ~5% of patients, severe liver disease can occur; cholelithiasis; palmar keratoderma in rare AR form
Congenital erythropoietic porphyria	Very rare (~170 cases reported)	Infancy/first decade of life	Very severe clinical course; in sun-exposed sites, vesicles and bullae, erosions, ulcerations, crusts, milia, scarring, hyperpigmentation and hypertrichosis; mutilation; hemolytic anemia; hepatosplenomegaly; porphyrin deposition in bones and teeth (erythrodontia); pink, red or violet staining of diapers
Hepatoerythropoietic porphyria	Extremely rare (~35 cases reported)	Early infancy	Recessive variant of porphyria cutanea tarda; markedly increased photosensitivity and severe clinical course possible; in sun-exposed sites, vesicles and bullae, skin fragility, erosions, crusts, milia, scarring and hypertrichosis; mutilation can occur; diapers stained by darkly colored urine
X-linked dominant protoporphyria	Very rare	Early childhood	Skin symptoms indistinguishable from erythropoietic protoporphyria; most recent type of porphyria to be recognized; liver disease appears to occur more frequently than in erythropoietic protoporphyria

Table 49.2 Classification of the porphyrias into acute and non-acute forms. Important clinical and epidemiological aspects are highlighted. ALA-D, aminolevulinic acid dehydratase; AR, autosomal recessive.

GENETIC ASPECTS OF THE PORPHYRIAS			
	Gene locus	**Protein product and gene symbol**	**Mode of inheritance**
ACUTE PORPHYRIAS			
Acute intermittent porphyria	11q23.3	Porphobilinogen deaminase; *PBGD*	AD
Variegate porphyria	1q22–23	Protoporphyrinogen oxidase; *PPOX*	AD
Hereditary coproporphyria	3q12	Coproporphyrinogen oxidase; *CPO*	AD
ALA-D deficiency porphyria	9q34	δ-Aminolevulinic acid dehydratase; *ALAD*	AR
NON-ACUTE PORPHYRIAS			
Porphyria cutanea tarda	1p34	Uroporphyrinogen decarboxylase; *UROD*	AD (up to 25% of cases); otherwise acquired
Erythropoietic protoporphyria	18q21.3	Ferrochelatase; *FECH*	AD*; rarely, AR
Congenital erythropoietic porphyria	10q25.2–q26.3	Uroporphyrinogen III synthase; *UROS*	AR
Hepatoerythropoietic porphyria	1p34	Uroporphyrinogen decarboxylase; *UROD*	AR
X-linked dominant protoporphyria	Xp11.21	δ-Aminolevulinic acid synthase 2; *ALAS2*	XLD

*Actually semi-dominant inheritance with a mutation in one allele and a specific intronic polymorphism in the second allele ("hypomorphic" allele; see text).

Table 49.3 Genetic aspects of the porphyrias. ALA-D, aminolevulinic acid dehydratase; AD, autosomal dominant; AR, autosomal recessive; XLD, X-linked dominant.

CHARACTERISTIC BIOCHEMICAL FINDINGS IN THE PORPHYRIAS											
Type of porphyria	**Urine**				**Feces**			**Erythrocytes**			**Plasma**
	ALA	**PBG**	**URO**	**COPRO**	**URO**	**COPRO**	**PROTO**	**URO**	**COPRO**	**PROTO**	
ACUTE PORPHYRIAS											
Acute intermittent porphyria	++ to ++++	++ to ++++	+++	++	N to +	N to +	N to +	N	N	N	N
Variegate porphyria	++ to +++	++ to +++	+++	+++	N	+++	++++	N	N	N	624–626 nm*
Hereditary coproporphyria	N to ++	N to ++	++	++++	++	++++	N to +	N	N	N	619 nm*
ALA-D deficiency porphyria	+++	N	+	++	N	+	+	N	N	++	ALA, COPRO & PROTO ↑
NON-ACUTE PORPHYRIAS											
Porphyria cutanea tarda	N	N	++++	++	++	ISOCOPRO	+	N	N	N	URO ↑
Erythropoietic protoporphyria	N	N	N	N	N	++	++ to ++++	N	N to +	+++	PROTO ↑
Congenital erythropoietic porphyria	N	N	++++	++	+	+++	+	++++	+++	+++	URO & COPRO ↑
Hepatoerythropoietic porphyria	N	N	+++	ISOCOPRO	N	ISOCOPRO	N	N	+	++++	URO ↑
X-linked dominant protoporphyria	N	N	N	N	NA	NA	NA	NA	NA	++++†	PROTO ↑

*Peak fluorometric emission.
†Approximately 40% zinc protoporphyrin.

Table 49.4 Characteristic biochemical findings in the porphyrias. In patients with variegate porphyria or hereditary coproporphyria who have no symptoms (cutaneous or systemic), urine porphyrins may not be elevated (shaded areas). ALA, aminolevulinic acid; ALA-D, aminolevulinic acid dehydratase; COPRO, coproporphyrin; ISOCOPRO, isocoproporphyrin; PBG, porphobilinogen; PROTO, protoporphyrin; URO, uroporphyrin. N = normal; NA, not available; + = above normal range; ++ = slightly elevated; +++ = highly elevated; ++++ = very highly elevated; ↑ = increase.

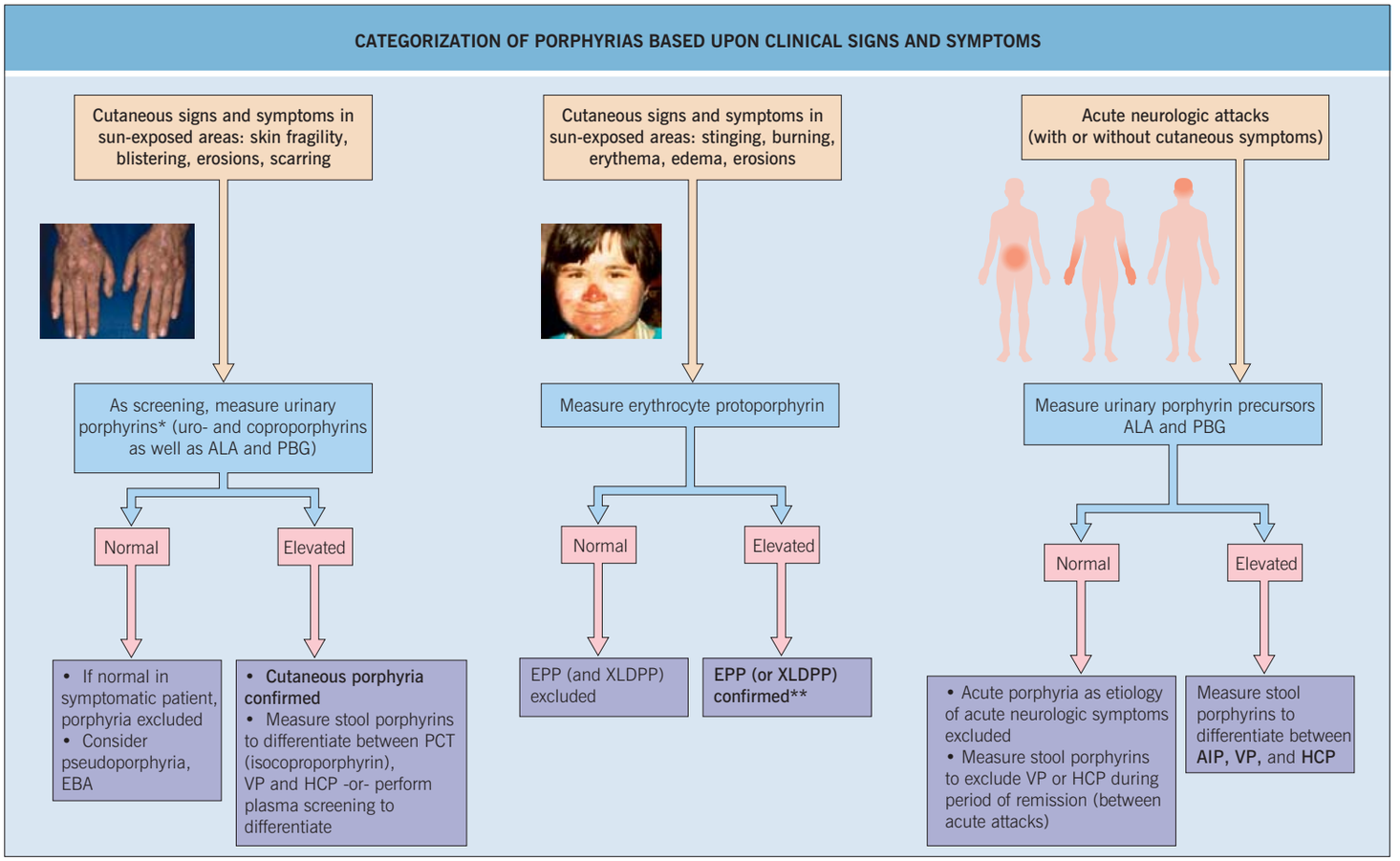


Fig. 49.2 Categorization of porphyrias based upon clinical signs and symptoms. AIP, acute intermittent porphyria; ALA, aminolevulinic acid; EBA, epidermolysis bullosa acquisita; EPP, erythropoietic protoporphyria; HCP, hereditary coproporphyria; PBG, porphobilinogen; VP, variegate porphyria; XLDPP, X-linked dominant protoporphyria. *24-hour collection. **To confirm diagnosis of XLDPP, measure zinc-chelated protoporphyrin.

Fig. 49.3 Porphyria cutanea tarda. A Marked fragility with multiple hemorrhagic crusts, erosions and milia as well as scars. **B** Flaccid hemorrhagic bulla and tense vesicle with clear fluid on the forefinger, accompanied by crusts and scars.

Fig. 49.4 Porphyria cutanea tarda. Hypertrichosis of the malar region of the cheek. *Courtesy, Judit Stenn, MD.*

Fig. 49.5 Porphyria cutanea tarda presenting as yellow–brown morpheaform plaques. The plaques were in sun-exposed areas in this patient with a history of alcohol abuse.

Indeed, there is increasing evidence that some facets of the etiology of PCT have yet to be completely elucidated.

The cutaneous manifestations of PCT include increased photosensitivity and skin fragility as well as blistering, erosions, crusts, milia and scars in sun-exposed sites (Fig. 49.3; see Table 49.2). Additionally, postinflammatory hyperpigmentation, hypertrichosis (Fig. 49.4), scarring alopecia, and morpheaform and sclerodermoid changes (Fig. 49.5) can be observed.

Histologic examination of vesiculobullae commonly reveals subepidermal cell-poor blisters with a characteristic festooning of dermal papillae; the latter is most likely due to the deposition of PAS-positive glycoproteins in and around the wall of vessels localized in the upper dermis (Fig. 49.6). Direct immunofluorescence microscopy often demonstrates immunoglobulins (mainly IgG; less commonly IgM), complement and fibrinogen at the dermal–epidermal junction and around blood vessels of the papillary dermis. In sclerotic lesions, there is dermal fibrosis as well as PAS-positive deposits around blood vessels.

Biochemically, increased urinary excretion of uroporphyrin (type I isomers > type III isomers), hepta-carboxylated porphyrins (type III isomers > type I isomers), and coproporphyrin can be detected, as well as increased excretion of isocoproporphyrin in the feces; the latter finding being exclusive to PCT and hepatoerythropoietic porphyria. Historically, a presumptive clinical diagnosis of PCT was followed by an examination of the patient's urine, both under Wood's lamp illumination (in the dark) and after exposure to natural light. Due to the excessive excretion of porphyrins, the urine of PCT patients turns red to brown after several hours of exposure to natural light and it has a pink to red fluorescence when exposed to a UVA light source. However, it has to be borne in mind that these bedside observations are neither sensitive nor specific diagnostic tests.

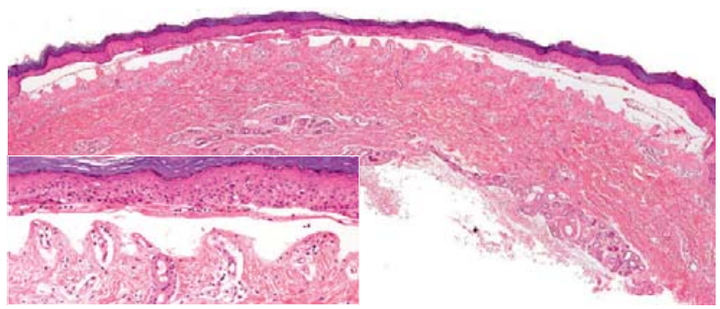


Fig. 49.6 Porphyria cutanea tarda – histologic features. Subepidermal blister of acral skin with a minimal ("cell-poor") dermal inflammatory infiltrate. Festooning of the dermal papillae is seen (insert). *Courtesy, Lorenzo Cerroni, MD.*

A wide variety of triggering factors (including hepatotoxins) have been reported to precipitate the clinical manifestations of PCT, among them alcohol, estrogens, polychlorinated hydrocarbons, dialysis in patients with renal failure, iron, inheritance of specific mutations in the *HFE* gene which underlie classic hemochromatosis, and viral infections such as hepatitis C and HIV. Interestingly, homozygosity for the *HFE* gene mutation C282Y has been found to be associated with an earlier onset of disease in both sporadic and familial PCT, with the effect being more marked in familial PCT[14]. PCT patients appear to have a higher risk of developing hepatocellular carcinoma[1,6].

Erythropoietic Protoporphyria (EPP)

EPP is due to a semi-dominantly inherited deficiency of ferrochelatase, the last enzyme in the heme biosynthetic pathway (see Fig. 49.1)[1,6].

Clinically, EPP is characterized by cutaneous photosensitivity that manifests early in life, i.e. during early childhood. Acute photosensitivity episodes are characterized by intense burning, stinging and pruritus of sun-exposed skin, particularly on the nose, cheeks and dorsal aspects of the hands, followed by erythema, edema, crusts, petechiae and then wax-like scarring (Figs 49.7 & 49.8; see Table 49.2). Skin symptoms can occur within minutes of sun exposure, often starting early in the springtime, continuing throughout the summer, and diminishing during fall and winter. Window glass does not protect the patient. Patients suffering from EPP often report that the only way to relieve the burning and stinging sensations is to cool the affected skin under cold water. In patients with EPP who have not had recent sun exposure, the only detectable cutaneous findings may be scars on the nose and lips (see Fig. 49.8). In rare patients with recessively inherited EPP, palmar keratoderma can be seen[15].

Histologically, vacuolization of epidermal cells is seen in acute lesions. Intercellular edema may also be present, as well as vacuolization and lysis of endothelial cells within superficial dermal blood vessels. In older lesions (e.g. areas of waxy scarring), eosinophilic PAS-positive deposits are observed around blood vessels (Fig. 49.9). There can be a resemblance to the amorphous protein depositions seen in lipoid proteinosis. Ultrastructurally, thickening and degeneration of capillary basement membranes is seen.

Biochemically, EPP is characterized by an increase in free protoporphyrin levels in erythrocytes, plasma, feces, and other tissues such as the liver (see Table 49.4)[1,6]. Historically, microscopic examination of a blood smear via UV illumination was performed to detect erythrocyte fluorescence. However, this test is not particularly sensitive or specific. The greatest concern in patients with EPP is a rapid accumulation of protoporphyrin within the liver and biliary system, with the development of cholestasis. This can lead to hepatic damage and progressive (even fatal) liver failure. Of note, liver function tests may remain normal until late in the course of the disease[16].

The genetic basis for the development of cutaneous symptoms in EPP has been elucidated. Only those individuals who inherit a heterozygous ferrochelatase gene mutation involving one parental allele (allele A) *and* a specific intronic polymorphism (IVS3–48T/C) of the other parental allele (allele B) develop skin symptoms. This latter specific polymorphism *in trans* constitutes a "hypomorphic" allele and leads to abnormal modulation of splicing. As a result, the aberrantly spliced mRNA is degraded by a nonsense-mediated decay mechanism, producing a decreased steady-state level of mRNA. Combined, a mutation in allele A plus the polymorphism in allele B lead to a marked reduction in ferrochelatase activity that is ~15–25% of normal[17].

Certainly, the identification of the molecular mechanisms underlying the photosensitivity observed in EPP has to be considered a milestone in porphyria research. Still, the development of protoporphyrin-induced hepatic disease and the molecular mechanisms underlying the phenotype associated with severe liver injury are not yet well understood.

Fig. 49.7 Erythropoietic protoporphyria. Erythema, edema and hemorrhagic crusts on the nose as well as the fingers in a young girl.

X-linked Dominant Protoporphyria (XLDPP)

XLDPP is characterized by a deficiency of the erythroid tissue-specific isoform of the first enzyme in the heme biosynthetic pathway, δ-aminolevulinic acid synthase 2. It is encoded by the *ALAS2* gene on the X chromosome.

Fig. 49.8 Erythropoietic protoporphyria. Subtle scarring on the nose and linear scars on the upper cutaneous lip in a 6-year-old child. *Courtesy, Gillian Murphy, MD.*

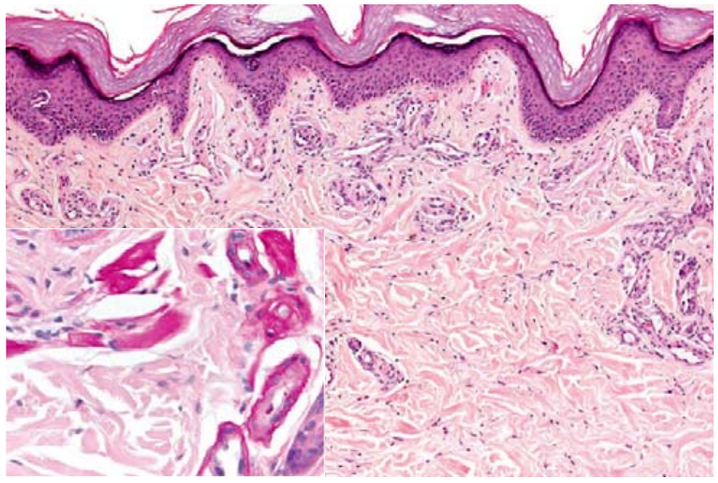


Fig. 49.9 Erythropoietic protoporphyria – histologic features. Eosinophilic deposits around blood vessels are more pronounced than in porphyria cutanea tarda. These deposits are highlighted by a PAS stain (insert). *Courtesy, Lorenzo Cerroni, MD.*

Clinically, this variant of protoporphyria is indistinguishable from EPP. However, the percentage of patients at risk for potentially fatal liver disease appears to be higher than in classic EPP. Biochemical profiling demonstrates higher total protoporphyrin levels in erythrocytes (as compared to EPP due to ferrochelatase deficiency), with approximately 40% being zinc-protoporphyrin[7].

Congenital Erythropoietic Porphyria (CEP)

Synonym: ■ Günther disease

With approximately 170 cases reported to date, CEP is a very rare, autosomal recessively inherited disorder that results from markedly decreased catalytic activity of uroporphyrinogen III synthase, the fourth enzyme in heme biosynthesis (see Fig. 49.1). CEP manifests shortly after birth with severe cutaneous photosensitivity, blistering, erosions, crusts and ulcerations, followed by extensive scarring and deformation, primarily of the hands (Fig. 49.10A; see Table 49.2). On the face, a loss of eyebrows and eyelashes, as well as severe mutilation of cartilaginous structures (e.g. the nose), are frequently observed. Furthermore, erythrodontia (Fig. 49.10B), acro-osteolysis and skeletal abnormalities (e.g. demineralization) are common clinical features. In addition, a variable degree of hematologic involvement, ranging from mild forms of hemolytic anemia to intrauterine hydrops fetalis and hepatosplenomegaly, can be observed. Pink, red or violet staining of diapers can serve as an early clue to the diagnosis. Biochemically, there is increased urinary excretion of uroporphyrin I and coproporphyrin I plus elevated levels of coproporphyrin I in the stool (see Table 49.4)[18].

Hepatoerythropoietic Porphyria (HEP)

HEP, the homozygous (or compound heterozygous) variant of hereditary PCT, is an extremely rare disease that is due to a pronounced decrease in uroporphyrinogen decarboxylase activity (see Table 49.3). Clinically, HEP usually presents during early childhood, with dark urine in the diapers often the initial clinical finding. Subsequently, severe cutaneous photosensitivity develops, associated with blistering, pruritus, hypertrichosis, hyperpigmentation and scleroderma-like scarring (Fig. 49.11; see Table 49.2). If the clinical course is severe, the symptoms closely resemble those observed in CEP. However, unlike the latter, HEP is not usually associated with hematologic abnormalities (e.g. severe anemia).

Urinary levels of uroporphyrin and hepta-carboxylated porphyrins are elevated, as are fecal levels of coproporphyrin and isocoproporphyrin. Increased levels of zinc-chelated protoporphyrin within erythrocytes can also be seen (see Table 49.4)[1,19].

Pseudoporphyria

Pseudoporphyria (also referred to as pseudoporphyria cutanea tarda or bullous dermatosis of dialysis) encompasses those conditions that closely resemble PCT. However, in contrast to PCT, no biochemical abnormalities in porphyrin metabolism are detected (see Fig. 49.2). Skin fragility, erosions, blisters, and scarring have a predilection for the dorsal aspect of the hands (Fig. 49.12), the face, and the extensor surfaces of the legs. Pseudoporphyria is commonly encountered in patients suffering from chronic renal insufficiency or in those undergoing renal dialysis (hemodialysis more often than peritoneal dialysis). It is also seen in association with the ingestion of specific drugs, including

Fig. 49.10 Congenital erythropoietic porphyria. A Severe mutilation of the hands due to scarring. **B** Erythrodontia due to massive protoporphyrin deposition in the teeth. *A, Courtesy, José Mascaro, MD.*

Fig. 49.11 Hepatoerythropoietic porphyria. Hypertrichosis and severe scarring are seen, resulting in a clinical appearance similar to congenital erythropoietic porphyria. *Courtesy, José Mascaro, MD.*

Fig. 49.12 Dialysis-associated pseudoporphyria. Vesicles formed on the dorsal aspects of the hands in this patient with chronic renal failure. *Courtesy, Kalman Watsky, MD.*

DRUG-INDUCED PSEUDOPORPHYRIA
NSAIDS*
Naproxen (propionic acid derivative) – NSAID most frequently implicated
Nabumetone
Oxaprozin (propionic acid derivative)
Ketoprofen (propionic acid derivative)
Mefenamic acid
Diflunisal
Celecoxib
Rofecoxib (currently off the market)
ANTIBIOTICS
Nalidixic acid
Tetracycline, doxycycline
Ciprofloxacin
Ampicillin/sulbactam combined with cefepime
DIURETICS
Furosemide
Hydrochlorothiazide/triamterene
Chlorthalidone
Bumetanide
RETINOIDS
Isotretinoin
Etretinate
MISCELLANEOUS
Amiodarone
Carisoprodol/aspirin – attributed to the carisoprodol
Cyclosporine
Dapsone
5-Fluorouracil (intravenous)
Flutamide
Leflunomide
Oral contraceptive pill (estrogens, progestins)
Pyridoxine (vitamin B_6)
Voriconazole
*When caused by NSAIDs, consider prescribing diclofenac, indomethacin or sulindac.

Table 49.5 Drug-induced pseudoporphyria. The most common causes are in bold. NSAID, nonsteroidal anti-inflammatory drug. *Courtesy, Misty Sharp, MD.*

nonsteroidal anti-inflammatory drugs (e.g. naproxen, nabumetone, ketoprofen), furosemide, antibiotics (e.g. nalidixic acid, tetracycline) and retinoids (Table 49.5), and it can occur in association with the use of tanning beds. In the latter situation, vesicles may be seen on the palms.

Histologic findings are indistinguishable from those found in lesions of PCT. Patients who require renal dialysis may develop PCT or pseudoporphyria. Even if they are anuric, it is important to remember that the diagnosis of PCT can be established via plasma or stool studies (see Table 49.4). Treatment is easier for drug-induced pseudoporphyria, as the major recommendation is discontinuation of exposure to the suspected precipitant[20]. Sun protection is advised for all patients.

Differential Diagnosis

PCT must be distinguished from other types of cutaneous porphyria that manifest with blistering. These include mild variants of CEP and HEP and importantly (since they can be associated with life-threatening acute attacks), VP and HCP. Furthermore, pseudoporphyria (see above), epidermolysis bullosa acquisita, polymorphous light eruption, and phototoxic and bullous drug eruptions have to be excluded. All aforementioned diseases can easily be differentiated from PCT by porphyrin analysis[1,6,14,21]. If no porphyrin abnormalities are detected, histologic examination of lesional skin (routine and immunofluoresence) can aid in establishing the diagnosis.

In ***EPP***, the differential diagnosis consists of solar urticaria, phototoxic or photoallergic contact dermatitis and drug reactions, polymorphous light eruption, hydroa vacciniforme and lipoid proteinosis[1,6,15,21].

CEP has to be differentiated from HEP and the rare homozygous (or compound heterozygous) variants of VP and HCP. Mild variants can sometimes mimic PCT. Likewise, the most important entities in the differential diagnosis of ***HEP*** are CEP and the rare aforementioned homozygous variants of VP and HCP.

Treatment

A causal therapeutic strategy would consist of either enzyme replacement therapy or gene therapy. However, such therapeutic modalities are not currently available.

The avoidance of UV light exposure, sun-protective clothing, and regular application of broad-spectrum sunscreens are crucial, both prophylactically and therapeutically. Because the wavelengths that induce the porphyrias are in the 400–410 nm range, sunscreens are limited in their therapeutic effectiveness, with the exception of titanium dioxide and zinc oxide (see Ch. 132).

Patients with PCT should be encouraged to eliminate triggering factors such as alcohol ingestion and estrogen therapy. In patients with iron overload, successful treatment can be achieved by repeated phlebotomy (venesection) of approximately 500 ml blood every 2 weeks, as tolerated by the patient; some authors recommend weekly venesections of 300 ml blood. When required, maintenance phlebotomy is performed at less frequent intervals.

Therapeutic phlebotomy reduces iron stores, thereby improving heme synthesis by reducing iron-induced inhibition of uroporphyrinogen decarboxylase activity. While the therapeutic goal is to reduce serum ferritin levels to the lower limit of the reference range, care should be taken to not induce anemia. Phlebotomy usually leads to resolution of skin fragility and blistering within 2–4 months. However, normalization of urinary porphyrin concentrations will usually take longer (about 12 months).

Another therapeutic option is low-dose hydroxychloroquine or chloroquine. These antimalarials are thought to work by accelerating the secretion of porphyrins, and they may also inhibit porphyrin synthesis. Standard therapy consists of 200 mg of hydroxychloroquine or 125 mg of chloroquine *twice weekly*, and complete remission can be expected within 6–9 months (Table 49.6). Administration of higher doses of these antimalarials (as are used in cutaneous lupus erythematosus) can lead to hepatotoxicity. The antimalarials can be used in combination with phlebotomy to induce a remission more rapidly[1,6,15].

The genetic background of PCT patients, with respect to the presence of *HFE* gene mutations, appears to play a critical role in the outcome of chloroquine or hydroxychloroquine treatment. Whereas heterozygosity for mutation C282Y and compound heterozygosity for *HFE* mutations did not compromise the therapeutic response, PCT patients homozygous for C282Y failed to respond to antimalarial therapy and retained high serum iron and ferritin levels as well as transferrin saturation[22].

In some patients with EPP, β-carotene minimizes burning, stinging and photosensitivity reactions. Although β-carotene has no effect on the protoporphyrin levels in erythrocytes, it reduces photosensitivity by quenching the formation of free radicals that occurs during the cutaneous photoreaction. The administered doses range from 30 to 90 mg/day in children and from 60 to 180 mg/day in adults, with desired maximum plasma levels of 600–800 mcg/dl. In five patients treated with afamelanotide ([Nle^4, $D\text{-}Phe^7$]-α-MSH; 20 mg every 60 days as a resorbable implant) in an open-label study, increased tolerance to artificial light (11×) was observed at day 120[23]. Afamelanotide has been designated an orphan drug for the treatment of EPP. Single reports of cysteine therapy or narrowband UVB phototherapy exist, but the usefulness of these treatments has not been demonstrated convincingly. Cholestyramine or charcoal can be considered in order to reduce enterohepatic recirculation of porphyrins and bile acids. Overall, current therapeutic options for EPP are more limited than for PCT[1,6,10,15].

Patients with CEP require surveillance for anemia and skin infections. Frequent blood transfusions can suppress erythropoiesis, thereby decreasing porphyrin production and photosensitivity. Concomitant administration of deferoxamine or deferasirox can reduce the resulting iron overload. Bone marrow or hematopoietic stem cell transplantation leads to marked reduction of porphyrin levels and photosensitivity and has been reported to be curative[1,10,18].

No specific treatment options are currently available for patients with HEP and XLDPP. Careful patient education regarding sun protection is very important.

THERAPEUTIC APPROACHES TO THE ACUTE AND NON-ACUTE PORPHYRIAS	
Acute porphyrias	**Therapy strategies**
Acute intermittent porphyria; variegate porphyria; hereditary coproporphyria; ALA-dehydratase deficiency porphyria	**Acute attacks** 1. Identification and elimination of precipitating factors (porphyrinogenic drugs; alcohol; hormones) 2. Monitoring in intensive care unit and input from porphyria specialists 3. Adequate pain therapy, e.g. with opioid analgesics 4. Adequate therapy of nausea and vomiting, e.g. with promethazine, ondansetron 5. Intravenous administration of either: (1) heme arginate (Normosang®; Europe only), 3 mg/kg once daily for 4 consecutive days; or (2) hemin (Panhematin®; FDA-approved), usually 1–4 mg/kg/day (over 10–15 min) for 3–14 days *versus* 3-4 mg/kg once daily for 4 days with more extended treatment for severe cases 6. If necessary, until heme preparations become available, intravenous glucose infusions 7. Measurement of urinary porphyrin excretion during the acute attack (daily, if possible) **Cutaneous symptoms (variegate porphyria; hereditary coproporphyria)** 1. Photoprotection, e.g. broad-spectrum sunscreens and/or protective clothing 2. Avoidance of sunlight exposure and trauma
Non-acute porphyrias	**Therapy strategies**
Porphyria cutanea tarda	1. Photoprotection, e.g. broad-spectrum sunscreens and/or protective clothing 2. Avoidance of sunlight exposure and trauma 3. Cease alcohol ingestion; stop estrogen therapy 4. Phlebotomy: 400–500 ml every 2 weeks over ~3–6 months 5. Low-dose hydroxychloroquine or chloroquine: 200 mg or 125 mg twice weekly (e.g. on Monday and Thursday), respectively, over 6–12 months, until porphyrin excretion is within normal range 6. Measurement of urinary porphyrin excretion to monitor therapeutic outcome
Erythropoietic protoporphyria/ X-linked dominant protoporphyria	1. Photoprotection, e.g. broad-spectrum sunscreens and/or protective clothing 2. Avoidance of sunlight exposure (common window glass does not provide protection) 3. Oral β-carotene: 30–90 mg/day in children; 60–180 mg/day in adults. Desirable maximum plasma level: 600–800 mcg/dl. Administration during the spring, summer and fall, with a hiatus during the winter in higher latitudes 4. Afamelanotide ([Nle^4, D-Phe^7]-α-MSH; 20 mg every 60 days as a resorbable implant) may increase tolerance to light exposure 5. Consider cholestyramine or charcoal to reduce enterohepatic recirculation of porphyrins and bile acids in order to enhance hepatic porphyrin excretion; results vary
Congenital erythropoietic porphyria	1. Photoprotection, e.g. broad-spectrum sunscreens and/or protective clothing 2. Strict avoidance of sunlight exposure 3. Change day–night rhythm 4. Splenectomy (reduces hemolysis and platelet consumption) 5. Bone marrow or hematopoietic stem cell transplantation
Hepatoerythropoietic porphyria	1. Photoprotection, e.g. broad-spectrum sunscreens and/or protective clothing 2. Strict avoidance of sunlight exposure and trauma 3. Change day–night rhythm 4. Of note, therapeutic approaches used in porphyria cutanea tarda (e.g. phlebotomy, antimalarials) are not effective

Table 49.6 Therapeutic approaches to the acute and non-acute porphyrias. While the therapeutic measures for an acute porphyric attack are the same for each of the acute porphyrias, different treatment strategies are recommended for each of the non-acute porphyrias, depending upon the prevailing manifestations and the respective form of porphyria. ALA, aminolevulinic acid.

THE ACUTE PORPHYRIAS

The acute porphyrias consist of acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP), and δ-aminolevulinic acid dehydratase (ALA-D) deficiency porphyria (see Tables 49.1 & 49.2)[2,6].

Patients with acute porphyrias can present with a broad range of clinical findings, including persistent colicky abdominal pain, nausea and vomiting, obstipation, tachycardia, hypertension, seizures, paresthesias, para- and tetraplegia, and acute psychosis (Table 49.7). Unfortunately, this spectrum of fairly nonspecific symptoms can mimic a number of other diseases and the porphyrias are often not included in the differential diagnosis, especially if neurologic symptoms prevail[2,24]. Acute attacks can be precipitated by a variety of factors, including porphyrinogenic drugs (e.g. antimalarials, tetracyclines, sulfonamides), alcohol, hormonal changes, recurrent or chronic infections, and reduced caloric intake due to fasting or diets. The latter may be a result of enhanced expression of the transcriptional coactivator PGC-1α[25].

In addition to the manifestations outlined in Table 49.7, patients with VP and HCP may have cutaneous findings that are clinically indistinguishable from those of PCT. As a result, VP and HCP are also referred to as neurocutaneous porphyrias[1,2].

A consortium of porphyria specialists from several European porphyria centers has recently established the European Porphyria Initiative (EPI). The goals of the EPI are to set standards and provide guidelines for the diagnosis and treatment of porphyrias. On the EPI (www.porphyria-europe.org) and the American Porphyria Foundation (www.porphyriafoundation.com) websites, important information is available for both patients and physicians.

Acute Intermittent Porphyria (AIP)

Worldwide, AIP is the most common type of acute porphyria. This autosomal dominantly inherited disorder is characterized by a deficiency of porphobilinogen deaminase, the third enzyme in heme biosynthesis (see Fig. 49.1).

AIP will not be discussed in detail here because patients do not have skin manifestations. It usually presents after puberty with acute porphyric attacks (see Table 49.7) that may be precipitated by the various trigger factors outlined above. Elevated urinary levels of the porphyrin precursors ALA and PBG can be detected during an acute attack: ALA levels range from 5 to 20 times normal and PBG levels are increased to as high as 20- to 50-fold normal[1,26].

Variegate Porphyria (VP)

Synonyms: ■ South African porphyria ■ Mixed porphyria

POSSIBLE MANIFESTATIONS OF AN ACUTE PORPHYRIC ATTACK		
Gastrointestinal and metabolic	**Neurologic**	**Cardiac and pulmonary**
Colicky abdominal pain	**Paresthesias**	**Tachycardia**
Nausea and vomiting	**Motor and sensory peripheral neuropathy (para- and tetraplegia)**	Hypertension
Constipation	Seizures	Respiratory paralysis
Obstipation	Muscle pain, back pain	
Hyponatremia	Encephalopathy	
	Paralysis	
	Anxiety	
	Acute psychosis	
	Coma	

Table 49.7 Possible manifestations of an acute porphyric attack. The more prevalent symptoms are in bold.

VP is characterized by an autosomal dominantly inherited deficiency of protoporphyrinogen oxidase, the seventh enzyme in the pathway of heme biosynthesis (see Fig. 49.1).

Cutaneous and neuropsychiatric symptoms can occur separately or simultaneously in affected individuals. Clinically, the skin findings in VP cannot be differentiated from those observed in PCT. Likewise, the acute attacks observed in VP are identical to those encountered in AIP.

During acute attacks, elevated urinary levels of ALA and PBG are encountered. However, during periods of remission, urinary ALA and PBG levels may be within normal range. Therefore, additional biochemical analyses of fecal porphyrins are mandatory in order to establish the diagnosis of VP. Elevated levels of stool protoporphyrin and coproporphyrin can be detected, with the concentration of protoporphyrin usually being higher than that of coproporphyrin. It is noteworthy that this abnormal biochemical stool profile can also be detected during periods of remission between attacks[1,27]. On the other hand, a plasma fluorescence emission peak of 624–626 nm is seen only in symptomatic patients, including those with cutaneous involvement.

Hereditary Coproporphyria (HCP)

HCP is a very rare autosomal dominantly inherited disease, characterized by a deficiency of coproporphyrinogen oxidase, the sixth enzyme in the porphyrin-heme biosynthetic pathway (see Fig. 49.1). The clinical symptoms are similar to those encountered in VP. However, in contrast to the latter, the concentrations of coproporphyrin in the stool are usually higher than those of protoporphyrin (see above)[1,28].

δ-Aminolevulinic Acid Dehydratase (ALA-D) Deficiency Porphyria

Synonyms: ■ Plumboporphyria ■ Doss porphyria

This autosomal recessively inherited porphyria variant is extremely rare. As fewer than 10 cases have been reported worldwide, ALA-D deficiency porphyria does not have an important clinical presence. The disease can present during early childhood (as well as in adulthood) with acute neurologic symptoms that resemble those encountered in AIP[1,7].

Differential Diagnosis

When patients with VP or HCP present with cutaneous manifestations, the differential diagnosis is identical to that of PCT (see above). If acute neurologic attacks prevail, a broad range of gastrointestinal, neurologic and psychiatric diseases have to be excluded, including an "acute abdomen", peripheral neuropathies and viral infections[1,2,6]. A more detailed discussion can be found in textbooks of internal medicine.

Treatment

Cutaneous symptoms

Patients with VP or HCP must minimize UV light exposure by wearing sun-protective clothing and applying broad-spectrum sunscreens. In contrast to in PCT, phlebotomy seems to be of no benefit. Although it is conceivable that chloroquine and hydroxychloroquine might be helpful in decreasing the associated photodermatoses (see PCT), these antimalarials belong to the group of drugs considered to be potential inducers of acute porphyric attacks. Thus, their use is not recommended.

Acute porphyric attack

An acute porphyric attack is a potentially life-threatening event associated with a significant mortality rate (up to 5%). It requires rapid therapeutic intervention to prevent complications such as paralysis, respiratory failure and coma. Treatment should consist of the following consecutive measures (see Table 49.6)[2].

1. Precipitating factors, e.g. porphyrinogenic drugs, must be identified and eliminated. If necessary, patients should be initially monitored in an intensive care unit.
2. Systemic symptoms such as abdominal pain, nausea and vomiting should be treated symptomatically, e.g. by administration of opioid analgesics and promethazine or ondansetron, respectively.
3. The most important therapeutic step is prompt intravenous administration of heme preparations such as heme arginate (Normosang® [Orphan Europe]) or hemin (FDA-approved; Panhematin® [Lundbeck])[29]. Heme arginate reduces the overproduction of porphyrin precursors via a negative feedback mechanism in that it represses the increased activity of the rate-limiting enzyme in heme biosynthesis, ALA synthase. Of note, heme preparations have the disadvantage of being unstable, and thrombophlebitis is a fairly common side effect[30–32].

Historically, acute attacks were treated primarily with glucose infusions. However, given the availability of effective heme preparations (see above), glucose should only be administered adjunctively or as a temporary measure if heme arginate or hematin are not immediately available.

REFERENCES

1. Puy H, Gouya L, Deybach JC. Porphyrias. Lancet. 2010;375:924–37.
2. Poblete Gutiérrez P, Kunitz O, Wolff C, Frank J. Diagnosis and treatment of the acute porphyrias: an interdisciplinary challenge. Skin Pharmacol Appl Skin Physiol. 2001;14:393–400.
3. Schultz JH. Ein fall von pemphigus leprosus, kompliziert durch lepra visceralis. Inaugural Dissertation, Greifswald, 1874.
4. Baumstark F. Zwei pathologische harnfarbstoffe. Pflügers Archiv für Gestinale Physiologie. 1874;9:568–84.
5. Günther H. Die haematoporphyrie. Deutsches Archiv für Klinische Medizin. 1911;105:89–146.
6. Bickers DR, Frank J. The porphyrias. In: Wolff K, Goldsmith LA, Katz SI, et al. (eds). Dermatology in General Medicine, 7th edn. New York: McGraw-Hill, 2007:1228–56.
7. Whatley SD, Ducamp S, Gouya L, et al. C-terminal deletions in the *ALAS2* gene lead to gain of function and cause X-linked dominant protoporphyria without anemia or iron overload. Am J Hum Genet. 2008;83:408–14.
8. Kessel D. Determinants of hematoporphyrin-catalyzed photosensitization. Photochem Photobiol. 1982;36:99–101.
9. Sandberg S, Romslo I. Porphyrin-induced photodamage at the cellular and the subcellular level as related to the solubility of the porphyrin. Clin Chim Acta. 1981;109:193–201.
10. Kauppinen R. Porphyrias. Lancet. 2005;365:241–52.
11. Grandchamp B, Puy H, Lamoril J, et al. Review: molecular pathogenesis of hepatic acute porphyrias. Gastroenterol Hepatol. 1996;11:1046–52.
12. Méndez M, Poblete-Gutiérrez P, García-Bravo M, et al. Molecular heterogeneity of familial porphyria cutanea tarda in Spain: characterization of 10 novel mutations in the *UROD* gene. Br J Dermatol. 2007;157:501–7.
13. Elder GH. Human URO-D defects. In: Orfanos CE, Stadler R, Gollnick H (eds). Dermatology in Five Continents. Berlin: Springer-Verlag, 1988:857–60.
14. Brady JJ, Jackson HA, Roberts AG, et al. Co-inheritance of mutations in the uroporphyrinogen decarboxylase and hemochromatosis genes accelerates the onset of porphyria cutanea tarda. J Invest Dermatol. 2000;115:868–74.

15. Holme SA, Whatley SD, Roberts AG, et al. Seasonal palmar keratoderma in erythropoietic protoporphyria indicates autosomal recessive inheritance. J Invest Dermatol. 2009;129:599–605.
16. Frank M, Doss MO. Severe liver disease in protoporphyria. Curr Probl Dermatol. 1991;20:160–7.
17. Gouya L, Puy H, Robreau AM, et al. The penetrance of dominant erythropoietic protoporphyria is modulated by expression of wildtype *FECH*. Nat Med. 2002; 30:27–8.
18. Desnick RJ, Astrin KH. Congenital erythropoietic porphyria: advances in pathogenesis and treatment. Br J Haematol. 2002;117:779–95.
19. Roberts AG, Elder GH, de Salamanca RE, et al. A mutation (G281E) of the human uroporphyrinogen decarboxylase gene causes both hepatoerythropoietic porphyria and overt familial porphyria cutanea tarda: biochemical and genetic studies on Spanish patients. J Invest Dermatol. 1995;104:500–2.
20. Green JJ, Manders SM. Pseudoporphyria. J Am Acad Dermatol. 2001;44:100–8.
21. Murphy GM. Diseases associated with photosensitivity. J Photochem Photobiol B. 2001;64:93–8.
22. Stölzel U, Köstler E, Schuppan D, et al. Hemochromatosis (*HFE*) gene mutations and response to chloroquine in porphyria cutanea tarda. Arch Dermatol. 2003;139:309–13.
23. Harms J, Lautenschlager S, Minder CE, Minder EI. An alpha-melanocyte-stimulating hormone analogue in erythropoietic protoporphyria. N Engl J Med. 2009;360:306–7.
24. Crimlisk HL. The little imitator-porphyria: a neuropsychiatric disorder. J Neurol Neurosurg Psychiatry. 1997;62:319–28.
25. Handschin C, Lin J, Rhee J, et al. Nutritional regulation of hepatic heme biosynthesis and porphyria through PGC-1alpha. Cell. 2005;122:505–15.
26. Kauppinen R, von und zu Fraunberg M. Molecular and biochemical studies of acute intermittent porphyria in 196 patients and their families. Clin Chem. 2002;48:1891–900.
27. Frank J, Christiano AM. Variegate porphyria: past, present and future. Skin Pharmacol Appl Skin Physiol. 1998;11:310–20.
28. Kühnel A, Gross U, Doss MO. Hereditary coproporphyria in Germany: clinical-biochemical studies in 53 patients. Clin Biochem. 2000;33:465–73.
29. Dhar GJ, Bossenmaier I, Petryka ZJ, et al. Effects of hematin in hepatic porphyria. Further studies. Ann Intern Med. 1975;83:20–30.
30. Goetsch CA, Bissell DM. Instability of hematin used in the treatment of acute hepatic porphyria. N Engl J Med. 1986;315:235–8.
31. Tenhunen R, Mustajoki P. Acute porphyria: treatment with heme. Semin Liver Dis. 1998;18:53–5.
32. Mustajoki P, Nordmann Y. Early administration of heme arginate for acute porphyric attacks. Arch Intern Med. 1993;153:2004–8.

This page intentionally left blank

Calcifying and Ossifying Disorders of the Skin 50

Janet A Fairley

Chapter Contents

Cutaneous calcification *729*
Cutaneous ossification (osteoma cutis) *733*

Synonyms: ■ Calcinosis cutis: cutaneous calcification ■ Osteoma cutis: cutaneous ossification ■ Calciphylaxis: calcific uremic arteriolopathy; calcifying panniculitis; uremic gangrene syndrome ■ Subepidermal calcified nodule: solitary congenital nodular calcification; Winer's nodular calcinosis

Key features

- Calcium regulates several key physiologic events in the skin, including epidermal proliferation, differentiation and cell–cell adhesion
- Disruption of normal calcium regulatory pathways can lead to calcification and/or ossification of the skin
- Four major types of cutaneous calcification are seen: dystrophic, in which pre-existing damage to the skin results in calcium deposits; metastatic, where systemic metabolic disorders lead to calcium deposits in the skin and often other tissues; iatrogenic, as a result of medical therapy or testing; and idiopathic, in which no cause can be identified
- Ossification can occur in conjunction with calcification or it may occur primarily in a number of genetic syndromes
- A careful evaluation of parameters of calcium-phosphate metabolism, combined with an assessment for associated systemic abnormalities, is necessary for the correct classification of calcifying disorders
- Therapy of calcifying disorders is difficult. Treatment of any associated disorder, such as hyperparathyroidism, is essential to prevent further calcification. Agents that modify calcium metabolism may be tried, but evidence of efficacy is often based upon case series. Surgical excision may be useful in circumscribed disease that interferes with function

INTRODUCTION

Calcium plays a vital role in regulating key physiologic events in many tissues, including the skin. In the epidermis, calcium shares in the control of major functions, including proliferation, differentiation and cell–cell adhesion. While the full range of pumps, channels and regulatory factors in the skin is still being elucidated, control of intra- and extracellular calcium concentrations and maintenance of gradients is known to be essential for its regulatory role. When factors that regulate calcium in the skin are disrupted, by either local or systemic events, the result can be cutaneous calcification or ossification as well as acantholysis and dyskeratosis.

Calcification represents the deposition of amorphous, insoluble calcium salts, while ossification is the deposition of calcium and phosphorus in a proteinaceous matrix as hydroxyapatite crystals. Ossification may follow pre-existing calcification in the skin, but in most disorders one mode of calcium deposition predominates. Each of the calcifying and ossifying disorders of the skin is rare. In aggregate, however, the finding of calcium deposition within the skin is not rare.

CUTANEOUS CALCIFICATION

Calcifying disorders of the skin are generally divided into four broad categories: dystrophic, metastatic, idiopathic and iatrogenic calcification[1]. Dystrophic calcification is calcification that occurs in the setting of localized tissue damage without systemic metabolic abnormalities in calcium regulation. Theoretically, dystrophic calcification occurs because the underlying disease process damages cell membranes, allowing calcium influx and subsequent intracellular crystallization. Alternatively, the acidity that accompanies cell damage may disrupt normal processes that inhibit calcification. In contrast, metastatic calcification occurs in normal tissue when there is dysfunction of the calcium regulatory systems. When no known local or systemic factors can be identified, the calcification is categorized as idiopathic, and that related to medical therapy or testing is iatrogenic.

DYSTROPHIC CALCIFICATION

Autoimmune Connective Tissue Disease

Autoimmune connective tissue diseases (AI-CTDs) represent some of the more common disorders in which one sees dystrophic calcification. While cutaneous calcification may be seen in any of the AI-CTDs, it is most commonly observed in the CREST form of scleroderma and in childhood dermatomyositis. Approximately 50–70% of children with dermatomyositis develop some degree of cutaneous calcification, while the latter occurs in ~20% of patients with the adult form of the disease[2]. Small deposits may occur in the skin or larger firm masses may begin in the muscle groups most severely affected; it is most frequently seen on the elbows, knees, buttocks and shoulders. Extrusion of calcium through the skin causes significant morbidity with pain and secondary infection.

In calcinosis universalis, the most severe form of dystrophic calcification, there is diffuse involvement with sheet-like masses of calcium. The calcification occurs along fascial planes, often leading to severe functional impairment. Aggressive treatment of dermatomyositis with immunosuppressive agents and/or IVIg may be warranted to try to avoid this serious complication (see Ch. 42). However, once calcification has developed, the effectiveness of these therapies can be quite variable.

The CREST (*c*alcification, *R*aynaud's phenomenon, *e*sophageal dysmotility, *s*clerodactyly and *t*elangiectasia) variant of scleroderma is the other AI-CTD in which cutaneous calcification is frequently seen. Calcification is usually less severe than in dermatomyositis and is usually restricted to the hands and upper extremities (Fig. 50.1); it is also seen over bony prominences and tendons. Extrusion of white chalky material is sometimes followed by localized ulceration, often at sites of trauma such as the digits. Calcinosis universalis can occur in scleroderma, but much less frequently than in dermatomyositis.

Dystrophic calcification has occasionally been reported in chronic cutaneous, acute systemic and subacute cutaneous lupus erythematosus as well as generalized morphea (Fig. 50.2)[3–5]. The calcification may occur within lesions of lupus panniculitis or elsewhere. In systemic lupus erythematosus, calcification is most often an asymptomatic radiologic finding.

Fig. 50.1 Dystrophic calcification in a patient with CREST syndrome.

Fig. 50.2 Radiograph of calcinosis cutis in a patient with generalized morphea. Areas that were previously firm became rock-hard and lesions of perforating calcinosis cutis (transepidermal elimination) developed on both legs. *Courtesy, Jean L Bolognia, MD.*

Treatment of dystrophic calcification

Therapies that have been tried for dystrophic calcification include a low calcium and phosphate diet, aluminum hydroxide and bisphosphonates, though no controlled trials have convincingly shown clinical improvement. Colchicine, probenecid and sodium thiosulfate have been described as helpful in a small number of patients. Long-term treatment with diltiazem was reported to decrease the size of calcium deposits, presumably through its effect on calcium transport into cells[6,7]. Months to years of treatment may be required if the calcification is extensive. Surgical excision is appropriate in selected patients with localized masses that are painful or interfere with function.

Panniculitis

Lobular panniculitis may also result in dystrophic calcification. Patients with pancreatitis or pancreatic cancer release pancreatic enzymes that cause lipolysis of subcutaneous fat (see Ch.100). Fatty acids formed in this process combine with calcium to form calcium soaps. Clinically, crops of nodules appear on the lower extremities and, less often, on the trunk, which may ulcerate and drain. Histologically, calcium deposits are seen both intra- and extracellularly within the areas of fat necrosis. Other forms of panniculitis that may calcify include subcutaneous fat necrosis of the newborn and lupus profundus. In subcutaneous fat necrosis of the newborn, there are erythematous nodules and plaques on the cheeks, back, buttocks and extremities. The nodules usually clear spontaneously, but, in some patients, symptomatic and even dramatic hypercalcemia may occur. Generally, the calcium deposits are small and are most easily noted radiologically; occasionally, more widespread deposits may be seen.

Genetic Disorders

A number of genetic disorders may be accompanied by cutaneous calcification. Pseudoxanthoma elasticum (PXE) is characterized by calcification of the elastic fibers of the skin (see Ch. 97). The coexistence of typical elastic fiber calcification along with small discrete foci of cutaneous calcification or ossification has also been reported[8,9]. In addition, progressive calcification of elastic tissue in Bruch's membrane of the retina and in the cardiovascular system may occur in these patients. Mutations in the *ABCC6* gene (ATP-binding cassette) that encodes a membrane transporter system have been identified in PXE patients[10,11]. Serum levels of fetuin-A, a major anti-mineralization protein, are significantly reduced in PXE patients and this may allow unchecked calcification of elastic fibers in affected tissues[12].

Ehlers–Danlos syndrome encompasses multiple disorders in which genetic mutations lead to abnormal collagen synthesis, metabolism or function (see Ch. 95). In Ehlers–Danlos syndrome, patients develop hard subcutaneous nodules known as spheroids or spherules, which are thought to represent herniated fat lobules that have become calcified (see Ch. 97).

Dystrophic calcification may also occur in patients with porphyria cutanea tarda[13] (PCT; see Ch. 49). It is most often seen in patients with longstanding disease who develop sclerodermoid changes and secondary calcification within these areas. As is the case with other lesions of PCT, the calcification appears most commonly in the head and neck region or on the dorsal surface of the hands. Ulceration has also been reported, although rarely, in association with these lesions.

Other rare genetic syndromes in which cutaneous calcification may be seen include Werner syndrome and Rothmund–Thompson syndrome (see Ch. 63). Cerebral amyloid angiopathy, an autosomal dominant condition due to mutations in the gene encoding the amyloid precursor protein, can present with dementia, patchy leukoencephalopathy, hemorrhagic strokes, external carotid artery dysplasia and occipital calcifications[14]. Biopsy specimens of the skin may show microcalcification of the dermal blood vessels. While the latter is asymptomatic, dermatologists might be called upon to biopsy the skin as a diagnostic measure.

Infections

Infections, particularly parasitic, can lead to dystrophic calcification. Calcified cysts form around larvae or worms, including *Onchocerca volvulus* and the tapeworm, *Taenia solium*. Intrauterine herpes simplex has also been reported to cause unusual annular plaques of calcinosis cutis in newborns.

Fig. 50.3 Dystrophic calcification in an infant at the site of a previous "heel stick" for obtaining blood. *Courtesy, Julie V Schaffer, MD.*

Neoplasms

Incidental calcification has been noted in a large number of benign and malignant tumors of the skin. Up to 75% of pilomatricomas develop calcification and in 15–20% there is evidence of ossification. A chalky, calcium-containing material may drain from the surface of these tumors. Activating mutations in the β-catenin gene have been demonstrated in sporadic pilomatricomas[15]. Other calcifying adnexal tumors or cysts include basal cell carcinomas, pilar cysts, epidermoid inclusion cysts and chondroid syringomas[16,17]. Rarely, melanocytic nevi, atypical fibroxanthomas, pyogenic granulomas, trichoepitheliomas and seborrheic keratoses have been reported to calcify.

Other

Trauma, "heel sticks" (for obtaining blood in neonates; Fig. 50.3), subcutaneous or intramuscular injections sites, surgical and burn scars, and keloids have also been reported as triggers of dystrophic calcification.

METASTATIC CALCIFICATION

Renal Disease

The most common cause of metastatic calcification is chronic renal failure (Fig. 50.4). In patients with renal failure, there are two major factors that lead to calcifications in the skin and soft tissues. First, patients with renal disease have an impaired ability to clear phosphate. Secondly, there is impaired synthesis of 1,25-dihydroxyvitamin D_3, since 1-α hydroxylation, which is necessary for activation of vitamin D_3, takes place in the kidney. This impaired production of 1,25-dihydroxyvitamin D_3 leads to decreased absorption of calcium from the intestine and hypocalcemia. Hypocalcemia, in turn, induces increased levels of parathyroid hormone (PTH) and increased mobilization of calcium and phosphate. The serum calcium concentration is normalized, but significant hyperphosphatemia may develop, and, if the solubility product of calcium and phosphate is exceeded, metastatic calcification can result. This metastatic calcification may take one of two forms: benign nodular calcification or calciphylaxis.

Benign nodular calcification usually develops in the setting of chronic renal failure with prolonged secondary hyperparathyroidism. Clinically, there are large deposits of calcium in the skin and subcutaneous tissue, often in periarticular sites. The number and size correlate with the severity of the hyperphosphatemia. The lesions are usually asymptomatic except for the pressure they can place on surrounding structures. Normalization of serum calcium and phosphate levels may result in resorption of the lesions; however, if larger deposits interfere with function, surgical removal is recommended.

More recently, deposition of calcium in the skin was reported following subcutaneous administration of low-molecular-weight heparin in two renal transplant patients. Both patients developed nodules with ulceration at the sites of the heparin injections. Histologic evaluation confirmed the diagnosis of calcinosis cutis. The process was self-limited and resolved following discontinuation of nadroparin. The calcium content of the nadroparin in combination with hyperphosphatemia due to renal dysfunction was hypothesized as the underlying pathogenic mechanism[18].

Calciphylaxis (synonyms: uremic gangrene syndrome, calcific uremic arteriolopathy, calcifying panniculitis) is characterized by progressive vascular calcification as well as ischemic necrosis of the skin and soft tissues. Early lesions are violaceous reticulated patches (Fig. 50.5A,B). Bullae or a gray color may develop within the lesions, signifying imminent tissue necrosis and ulcer formation (Fig. 50.5C). The lesions are extremely painful even at the earliest stages of development. Death is often due to gangrene and sepsis.

Patients who develop calciphylaxis are predominantly female and often have diabetes mellitus[19–21]. Obesity and poor nutritional status are also risk factors for calciphylaxis. A case–control study showed no statistical differences in the serum levels of calcium, phosphate, PTH

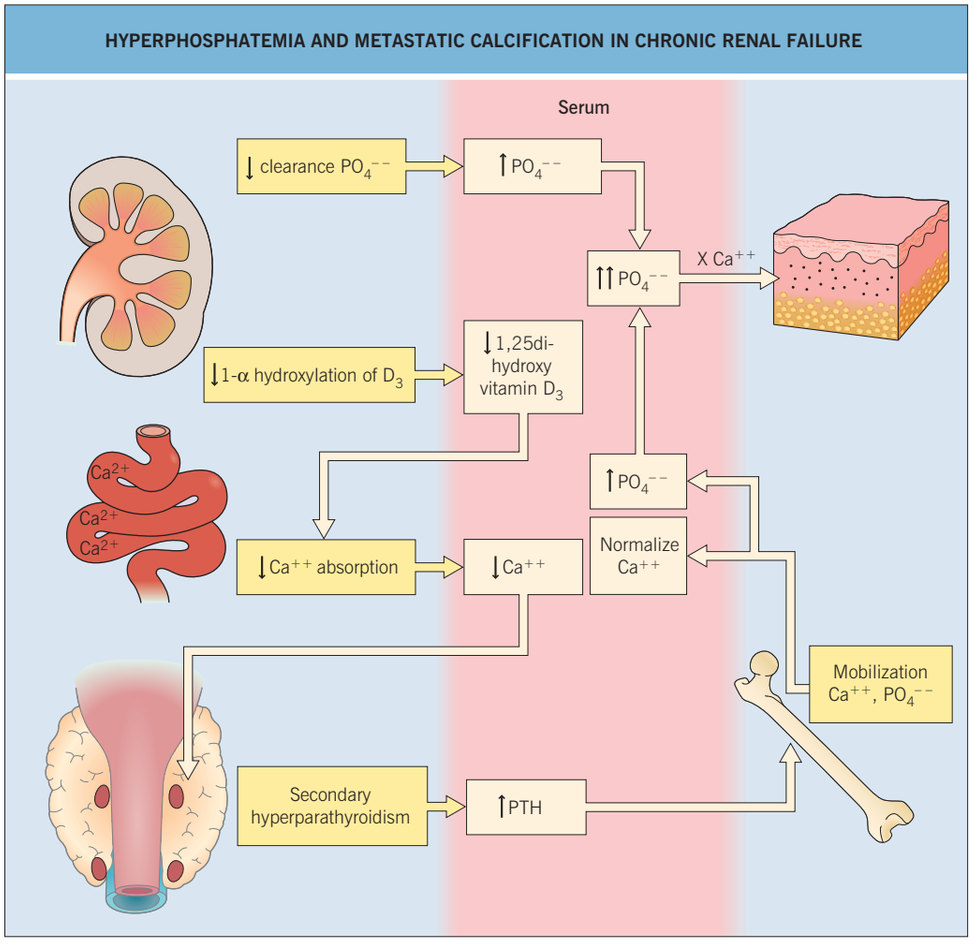


Fig. 50.4 Mechanisms of hyperphosphatemia and metastatic calcification in patients with chronic renal failure.

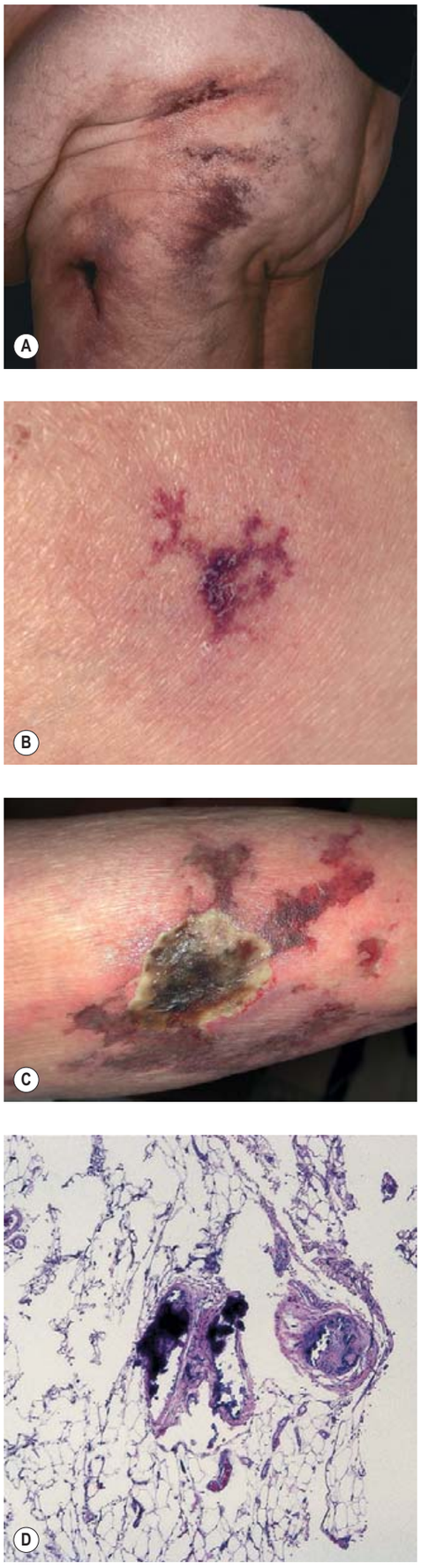


Fig. 50.5 Calciphylaxis in three patients with chronic renal failure. **A,B** Typical reticulated, violaceous plaques that usually precede ulceration. **C** Ulceration of the leg with surrounding retiform purpura and ischemia. **D** Perivascular deposition of calcium is seen within the walls of blood vessels in the subcutaneous fat. Of note, even when the clinical lesions are impressive, the degree of calcification seen histologically may be subtle. *B, Courtesy, Kalman Watsky, MD.*

or the calcium-phosphate product in patients with calciphylaxis as compared to control dialysis patients. The use of calcium salts as phosphate binders was the only risk factor that could be identified; however, the number of patients in the study was small[19].

The cause of calciphylaxis remains unclear. Animal studies have suggested that exposure to a "sensitizing" agent such as PTH followed by exposure to a "challenging" agent such as metal salts could cause precipitation of calcium in tissues[22]. The relevance of this work to the clinical disorder, however, remains unproven. Protein C dysfunction has been identified in a number of calciphylaxis patients, but is not consistently found in all patients. Since functional or quantitative abnormalities in protein C lead to a hypercoagulable state (see Ch. 23), it is possible that alterations in protein C function may contribute to the tissue necrosis in that subset of patients. While the majority of patients who develop calciphylaxis have end-stage renal disease, occasionally it is seen in the setting of severe primary hyperparathyroidism and, less often, in the absence of a clearly identifiable trigger.

For vascular calcification to occur, one important step is the conversion of vascular smooth muscle cells into osteoblast-like cells. Phosphates, inflammatory mediators in the vessel wall and bone morphogenic protein (BMP)-2 have all been proposed as potential stimuli for this conversion. In addition, BMP-7, matrix gla protein, fetuin-A (see above), osteoprotegerin and phosphatonins are currently being investigated as positive or negative regulators of the process[23].

Treatment of calciphylaxis

In patients with calciphylaxis, the overall mortality is as high as 85%, though it is hoped that early recognition and better treatments may improve the outcome. Proximal involvement in particular is associated with a worse prognosis. The current standard management of calciphylaxis includes normalization of the calcium-phosphate product by low calcium dialysis, use of phosphate binders, and parathyroidectomy (if medical management of hypercalcemia fails), along with aggressive wound care. Phosphate binders containing a combination of calcium acetate and magnesium carbonate have been shown to be more beneficial than calcium carbonate-containing binders[24], and parathyroid resection can normalize serum calcium, phosphate and PTH levels in calciphylaxis patients. A recent multivariate analysis suggested that overall survival is improved by surgical debridement and aggressive management of wound infections[25]. There was no clear benefit from parathyroidectomy, but a trend towards improved survival was observed when debridement and parathyroidectomy were combined.

Other proposed treatment modalities include sodium thiosulfate[26], pamidronate, cinacalcet (a calcimimetic), hyperbaric oxygen and low-dose tissue plasminogen activator[27,28]. Most of these treatment suggestions are based on small case series of patients.

Milk–Alkali Syndrome

Ingestion of excessive amounts of calcium-containing foods or antacids can lead to hypercalcemia and the milk–alkali syndrome. Patients with milk–alkali syndrome have acute manifestations including nephrocalcinosis, irreversible renal failure and diffuse subcutaneous calcification.

Hypervitaminosis D

Chronic ingestion of supraphysiologic doses of vitamin D can lead to hypercalcemia and hypercalciuria. Clinical signs include weakness and lethargy, nausea, headache and polyuria. Nephrolithiasis and calcinosis cutis may occur. Hypercalcemia is also seen in patients with sarcoidosis secondary to increased calcium absorption due to 1,25-dihydroxyvitamin D production by the granulomas. For other causes of metastatic cutaneous calcification, see Table 50.1.

IDIOPATHIC CALCIFICATION

Idiopathic Calcified Nodules of the Scrotum

The term "idiopathic calcified nodules of the scrotum" is used to describe firm, whitish nodules that develop on the scrotum. There are

DISORDERS OF CUTANEOUS CALCIFICATION
DYSTROPHIC
• Autoimmune connective tissue diseases, especially dermatomyositis, CREST • Cutaneous tumors or cysts, e.g. pilomatricomas, pilar cysts • Infections, especially parasitic • Trauma, including "heel sticks" in neonates, injection sites, surgical scars • Panniculitis • Genetic disorders, e.g. pseudoxanthoma elasticum, Ehlers–Danlos syndrome
METASTATIC
• Chronic renal failure Calciphylaxis* Benign nodular calcification of renal disease • Hypervitaminosis D • Milk–alkali syndrome • Sarcoidosis • Tumoral calcinosis (familial) • Hyperparathyroidism • Neoplasms (e.g. multiple myeloma, adult T-cell leukemia/lymphoma, SCC of the lung or head and neck)
IDIOPATHIC
• Idiopathic calcified nodules of the scrotum • Subepidermal calcified nodule • Tumoral calcinosis (sporadic) • Milia-like calcinosis
IATROGENIC
• Extravasation of intravenous solutions containing calcium or phosphate • Application of calcium-containing electrode paste for EMGs and EEGs • Application of calcium alginate dressings to denuded skin • Organ transplantation, especially liver
*Can occasionally occur in the setting of severe primary hyperparathyroidism and, less often, in the absence of a clearly identifiable trigger.

Table 50.1 Disorders of cutaneous calcification. CREST, *c*alcification, *R*aynaud's phenomenon, *e*sophageal dysmotility, *s*clerodactyly and *t*elangiectasia; EEG, electroencephalogram; EMG, electromyography; SCC, squamous cell carcinoma.

often multiple lesions. Histologically, some of them seem to represent calcified epidermoid inclusion cysts; however, in some lesions, no precursor cyst can be identified[29]. Based upon a recent study of 100 scrotal nodules, a spectrum of disease emerged – from epidermoid cysts with foci of calcification, to calcification with degeneration of some to most of the cyst wall, to unencapsulated calcium. The authors concluded that pre-existing epidermoid cysts may account for most of these calcified nodules[30]. A female equivalent, idiopathic calcinosis of the vulva, has also been described[31].

Subepidermal Calcified Nodule

Subepidermal calcified nodule (synonyms: solitary congenital nodular calcification, Winer's nodular calcinosis) is a solitary firm nodule that favors the head and neck region, most commonly the ears. They are also seen on the lateral aspects of the digits. Subepidermal calcified nodules usually develop in children but have been observed in all age groups. Trauma, perhaps *in utero*, or calcification of a pre-existing milium, eccrine duct hamartoma or hair follicle nevus has been hypothesized as the cause. Histologically, focal amorphous masses of calcium with a surrounding inflammatory infiltrate are seen. Epidermal ulceration and transepidermal elimination of the calcium deposits occur frequently. Surgical removal is recommended if the lesions are symptomatic.

Tumoral Calcinosis

Tumoral calcinosis may be either sporadic or familial. In both forms, patients develop large, often painful, deposits of calcium-phosphate in the dermis and subcutaneous tissues around large joints. Ulceration of the overlying skin may occur in larger lesions. The familial form is associated with either hyperphosphatemia or a normophosphatemic state. The former is inherited as an autosomal recessive trait and these patients have primary hyperphosphatemia due to increased reabsorption of phosphate in the renal tubule[32]. Mutations in the *GALNT3* gene, which encodes N-acetylgalactosaminyltransferase 3 (ppGalNAc-T3) which initiates mucin-type O-glycosylation, have been identified in a number of these families[33]. It is hypothesized that this glycosylation is important in regulating a class of proteins called "phosphatonins" that modulate circulating phosphate levels. Hyperphosphatemic familial tumoral calcinosis can also be caused by loss-of-function mutations in the genes that encode fibroblast growth factor 23 (FGF23, a phosphaturic protein that is glycosylated by ppGalNAc-T3) and klotho (a co-receptor for FGF23).

A homozygous mutation in the *SAMD9* (*s*terile *a*lpha *m*otif *d*omain containing 9) gene, which encodes a protein involved in the regulation of extraosseous calcification, has been found to underlie normophosphatemic familial tumoral calcinosis in families of Jewish Yemenite origin[34]. Dietary phosphate restriction and antacids that inhibit phosphate absorption may be of some benefit, but surgical excision of symptomatic lesions remains the treatment of choice.

Milia-like Calcinosis

Idiopathic calcinosis may sometimes take the form of small, milia-like lesions that develop on the dorsal surface of the hands and the face. Most commonly, these lesions appear in the setting of Down syndrome, although rarely they have been reported in patients with no other abnormalities[35]. In some patients, the calcinosis appears to result from calcification of pre-existing syringomas, but usually no precursor lesions can be found.

IATROGENIC CALCIFICATION

Iatrogenic calcification is due to the rapid precipitation of calcium salts within the skin. When the tissue concentration of calcium rises and exceeds the solubility product, calcium precipitates within the tissue, resulting in firm nodules in the dermis and/or subcutaneous tissue. A secondary inflammatory response is elicited and, over a period of weeks to months, the calcium is either absorbed or is transepidermally eliminated, depending on the depth of the deposit.

Iatrogenic calcification most commonly occurs with extravasation of calcium gluconate, calcium chloride or phosphate-containing intravenous solutions[36–38]. In a rabbit model of iatrogenic calcification, intralesional injections of triamcinolone into sites of extravasation decreased inflammation and ulceration. This treatment appeared to be most helpful when given immediately after the initial extravasation. Iatrogenic calcification has also been reported following prolonged electroencephalograms, electromyography and brainstem auditory evoked potential testing when a high-calcium electrode paste is employed[39]. Several patients were noted to develop calcification in split-thickness skin graft donor sites following the use of calcium alginate dressings[40].

Transient cutaneous calcifications have been observed in patients following liver transplantation[41,42]. They are generally small deposits in the skin that appear shortly after the transplant. They are hypothesized to arise as a consequence of the large amounts of calcium and blood products containing citrate required during surgery, combined with metabolic abnormalities during the perioperative period. In addition to the skin, calcinosis has been reported in the lungs, grafted liver, kidneys, vascular walls and colon. Calcinosis cutis has also been observed in a patient following lung transplantation[43].

CUTANEOUS OSSIFICATION (OSTEOMA CUTIS)

There are four genetic disorders that regularly have cutaneous or subcutaneous ossification as a clinical feature: fibrodysplasia ossificans progressiva, progressive osseous heteroplasia, plate-like osteoma cutis, and Albright hereditary osteodystrophy. Of these disorders, *fibrodysplasia ossificans progressiva* differs from the others in that the mechanism of bone formation is endochondral and involvement of the skin and subcutaneous tissue is only via extension from deeper tissues. These

patients have extreme morbidity and often die at an early age due to restriction in movement of the chest. Fibrodysplasia ossificans progressiva is an autosomal dominant disorder with dysregulation of the bone morphogenic protein (BMP) signaling pathway. Heterozygosity for mutations in the *ACVR1* gene, which encodes the activin A receptor (a BMP type I receptor), has been observed in both inherited and sporadic forms of the disease. Of note, an arginine (R) to histidine (H) substitution at position 206 (R206H) was found not only in affected family members (i.e. the inherited form of the disease), but also in 30 of 32 *de novo* cases of fibrodysplasia ossificans progressiva, leading the authors to suggest that the R206H-associated mutation may represent one of the most specific codons in the human genome to be associated with a disease phenotype[44,45]. These patients are unlikely to present to a dermatologist due to their limited and late skin involvement.

The three entities progressive osseous heteroplasia (Fig. 50.6), plate-like osteoma cutis, and Albright hereditary osteodystrophy are all characterized by intramembranous ossification that begins in the dermis.

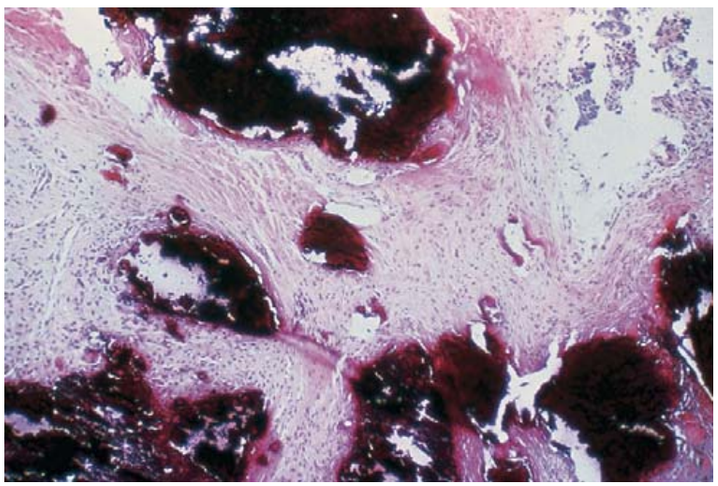


Fig. 50.6 Progressive osseous heteroplasia – histologic features. Deposits of calcium are seen more superficially, often with foci of cartilage and bone formation in the subcutaneous tissue.

While distinctive features are seen in each of these entities, there is also considerable clinical overlap. The cutaneous lesions in *progressive osseous heteroplasia* are asymptomatic papules and nodules. Some are more plaque-like and studded with papules that give rise to a "rice-grain" texture. The lesions generally appear shortly after birth and may be rapidly progressive[46,47]. The location and extent of the ossification determines the associated morbidity; in general, there are no associated developmental or endocrine abnormalities. Initially, progressive osseous heteroplasia was thought to be limited to female patients, but this later proved not to be the case. Unilateral involvement has also been described.

The lesions of *plate-like osteoma cutis* often have an appearance that is similar to those of progressive osseous heteroplasia, but there will only be a single or limited number of sites of involvement, leading to the suggestion that the former represents a more limited form of the latter. *Albright hereditary osteodystrophy* is distinguished from these two entities by its associated findings such as pseudohypoparathyroidism or pseudo-pseudohypoparathyroidism plus brachydactyly, obesity, short stature and round facies. The algorithm in Figure 50.7 demonstrates how clinical features may be used to classify these genetic disorders of cutaneous ossification.

The argument that progressive osseous heteroplasia and plate-like osteoma cutis may represent related disorders is strengthened by the report of a family in which two members had plate-like osteoma cutis and one had progressive osseous heteroplasia[48]. Genetic analysis has provided further evidence of the pathogenic relationship of these disorders – patients with progressive osseous heteroplasia, plate-like osteoma cutis, and Albright hereditary osteodystrophy all have mutations in the gene (*GNAS1*) that encodes the α-subunit of the stimulatory G protein which regulates adenyl cyclase activity[49–51]. The latter is believed to be a negative regulator of bone formation. In a study of 18 patients with progressive osseous heteroplasia, heterozygous inactivating mutations were found in 13 of the probands. While the defective allele was inherited from the *father* in almost all cases of progressive osseous heteroplasia[52,53], in some of these families, inheritance of a defective *GNAS1* from the *mother* resulted in Albright hereditary osteodystrophy. This indicates that the *GNAS1* locus is subject to imprinting (see Ch. 54); more recent data demonstrate that different splice variants are expressed solely by maternal or paternal alleles[54].

Therapy for most forms of cutaneous ossification is difficult. Underlying abnormalities in calcium and/or phosphorus should be addressed; however, when complete ossification develops, the only therapeutic

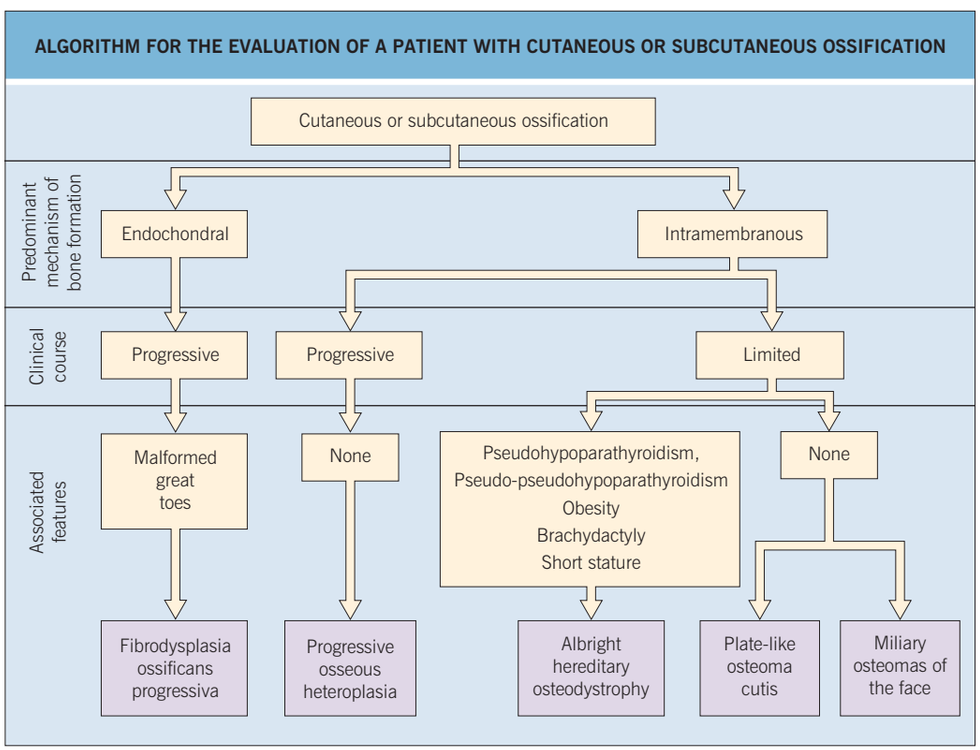


Fig. 50.7 Algorithm for the evaluation of a patient with cutaneous or subcutaneous ossification.

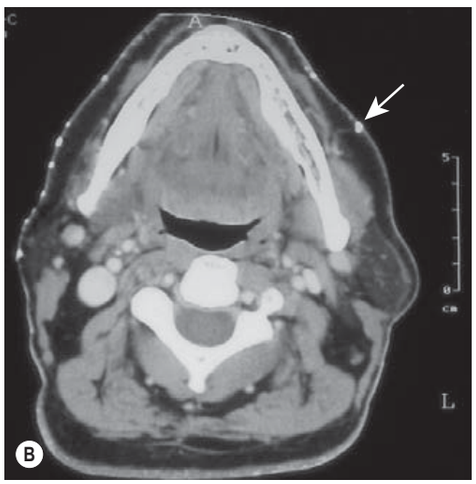


Fig. 50.8 Miliary osteoma cutis. **A** Multiple discrete whitish papules developed on the face of a patient with no previous history of acne. **B** The foci of ossification are readily apparent on CT scan (arrow). **C,D** In contrast, many of the papules in these patients with a history of acne are skin-colored or blue.

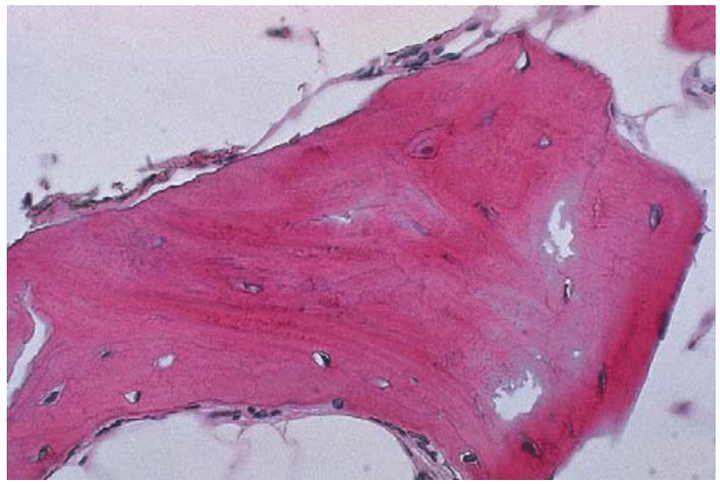


Fig. 50.9 Osteoma cutis – histologic features. Islands of bone formation are present within the dermis. Occasionally, osteoblasts and bone marrow elements can also be seen.

intervention is excision of neoformed bone. Even with surgical removal, recurrence of the bony deposits is common in the genetic disorders that lead to cutaneous ossification.

Miliary osteomas of the face is a fairly common entity characterized by multiple, scattered foci of cutaneous ossification. Small, firm papules appear on the face of adults and they can be skin-colored, white or bluish (Fig. 50.8)[55]. Although these osteomas are often observed in the setting of chronic acne vulgaris, a number of patients with identical clinical findings (but without predisposing acne) have also been reported. The unusual appearance of these osteomas on CT scan is shown in Figure 50.8B. Histologically, islands of bone formation are seen in the dermis (Fig. 50.9).

Treatment of miliary osteoma cutis is primarily surgical. An incision over each lesion followed by gentle curettage of the bony material with the edge of a surgical blade and then suture closure has been recommended. When lesions are numerous, however, this may not be practical. Laser resurfacing with curettage of exposed osseous fragments has been employed in this situation. Topical tretinoin gel has also been reported to have a beneficial effect on miliary osteomas[56].

"SECONDARY" CUTANEOUS OSSIFICATION

Ossification may also develop as a secondary event. Most disorders in which calcification can be seen have also been reported to ossify. Ossification occurs as a result of inflammatory or neoplastic processes and is often preceded by calcification. Secondary ossification has been described in melanocytic nevi and other benign tumors such as pilomatricomas as well as in pilar and epidermoid cysts and basal cell carcinomas.

LABORATORY EVALUATION OF PATIENTS WITH CUTANEOUS CALCIFICATION AND OSSIFICATION

In addition to a thorough history and physical examination focusing on the associated features that have been described, some selected laboratory investigations may be helpful in the evaluation of calcifying and ossifying disorders. A summary of this evaluation is outlined in Table 50.2. Abnormalities are expected most often in association with metastatic causes of calcification rather than in the other categories (see Table 50.1). Serum calcium and phosphate levels should be obtained and the calcium-phosphate product determined. While this may give a general clue about the patient's metabolic status with regard to calcium and phosphate, a normal value does not necessarily exclude these disorders. Rare reports of patients with calcinosis cutis and a normal serum calcium level but abnormally low urinary excretion of calcium have appeared; thus, an assessment of the 24-hour urinary calcium excretion may be warranted in some patients.

LABORATORY EVALUATION OF PATIENTS WITH CUTANEOUS CALCIFICATION/OSSIFICATION
Special histologic stains for calcium: • von Kossa • Alizarin red S Serum levels of: • Calcium • Phosphate • Parathyroid hormone (PTH) • Vitamin D_3 24-hour urinary calcium excretion Protein C activity and function (if calciphylaxis suspected) Genetic analysis (if hereditary disorder suspected; see text and Table 55.12)

Table 50.2 Laboratory evaluation of patients with cutaneous calcification/ossification.

REFERENCES

1. Walsh JS, Fairley JA. Calcifying disorders of the skin. J Am Acad Dermatol. 1995;33:693–706.
2. Bowyer SL, Blane CE, Sullivan DB, Cassidy JT. Childhood dermatomyositis. Factors predicting functional outcome and development of dystrophic calcification. J Pediatr. 1983;103:882–8.
3. Rothe MJ, Grant-Kels JM, Rothfield NF. Extensive calcinosis cutis with systemic lupus erythematosus. Arch Dermatol. 1990;126:1060–3.
4. Ueki H, Takei Y, Nakagawa S. Cutaneous calcinosis in localized discoid lupus erythematosus. Arch Dermatol. 1980;116:196–7.
5. Marzano AV, Kolesnikova LV, Gasparini G, Alessi E. Dystrophic calcinosis cutis in subacute lupus. Dermatology. 1999;198:90–2.
6. Dolan AL, Kassimos D, Gibson T, Kingsley GH. Diltiazem induces remission of calcinosis in scleroderma. Br J Rheumatol. 1995;34:576–8.
7. Palmieri GM, Sebes JI, Aelion JA, et al. Treatment of calcinosis with diltiazem. Arthritis Rheum. 1995;38:1646–54.
8. Buka R, Wei H, Sapadin A, et al. Pseudoxanthoma elasticum and calcinosis cutis. J Am Acad Dermatol. 2000;43:312–15.
9. Choi GS, Kang DS, Chung JJ, Lee MG. Osteoma cutis coexisting with cutis laxa-like pseudoxanthoma elasticum. J Am Acad Dermatol. 2000;43:337–9.
10. Ringpfeil F, Lebwohl MG, Christiano AM, Uitto J. Pseudoxanthoma elasticum: mutations in the *MRP6* gene encoding a transmembrane ATP-binding cassette (ABC) transporter. Proc Natl Acad Sci U S A. 2000;97:6001–6.
11. Bergen AA, Plomp AS, Schuurman EJ, et al. Mutations in *ABCC6* cause pseudoxanthoma elasticum. Nat Genet. 2000;25:228–31.
12. Hendig D, Schulz V, Arndt M, et al. Role of serum fetuin-A, a major inhibitor of systemic calcification, in pseudoxanthoma elasticum. Clin Chem. 2006;52:227–34.
13. Wilson PR. Porphyria cutanea tarda with cutaneous "scleroderma" and calcification. Australas J Dermatol. 1989;30:93–6.
14. Iglesias S, Chapon F, Baron JC. Familial occipital calcifications, hemorrhagic strokes, leukoencephalopathy, dementia, and external carotid dysplasia. Neurology. 2000;55:1661–7.
15. Chan EF. Pilomatricomas contain activating mutations in beta-catenin. J Am Acad Dermatol. 2000;43:701–2.
16. Walsh JS, Perniciario C, Randle HW. Calcifying basal cell carcinomas. Dermatol Surg. 1999;25:49–51.
17. Roth SI, Stowell RD, Helwig EB. Cutaneous ossification. Report of 120 cases and review of the literature. Arch Pathol. 1963;76:44–54.
18. van Haren FM, Ruiter DJ, Hilbrands LB. Nadroparin-induced calcinosis cutis in renal transplant recipients. Nephron. 2001;87:279–82.
19. Zacharias JM, Fontaine B, Fine A. Calcium use increases risk of calciphylaxis: a case-control study. Perit Dial Int. 1999;19:248–52.
20. Weenig RH, Sewell LD, Davis MDP, et al. Calciphylaxis: natural history, risk factor analysis and outcome. J Am Acad Dermatol. 2007;56:569–79.
21. Walsh JS, Fairley JA. Calciphylaxis. J Am Acad Dermatol. 1996;35:786–7.
22. Selye H. Calciphylaxis. Chicago: University of Chicago Press, 1962:1–16.
23. Stompor T. An overview of the pathophysiology of vascular calcification in chronic kidney diseases. Perit Dial Int. 2007;27:S215–22.
24. Duebner HJ. Combined use of calcium acetate and magnesium carbonate as phosphate binder. Neiren-und Hochdruckkrankheiten. 2004;33:403–8.
25. Lal G, Nowell AG, Liao J, et al. Determinants of survival in patients with calciphylaxis: a multivariate analysis. Surgery. 2009;146:1028–34.
26. Meissner M, Kaufmann R, Gille J. Sodium thiosulphate: a new way of treatment for calciphylaxis? Dermatology. 2007;214:278–82.
27. Velasco N, MacGregor MS, Innes A, MacKay IG. Successful treatment of calciphylaxis with cinacalcet – an alternative to parathyroidectomy? Nephrol Dial Transplant. 2006;21:1999–2004.
28. Robinson MR, Augustine JJ, Korman NJ. Cinacalcet for the treatment of calciphylaxis. Arch Dermatol. 2007;143:152–4.
29. Shah V, Shet T. Scrotal calcinosis results from calcification of cysts derived from hair follicles: a series of 20 cases evaluating the spectrum of changes resulting in scrotal calcinosis. Am J Dermatopathol. 2007;29:172–5.
30. Dubey S, Sharma R, Maheshwari V. Scrotal calcinosis: idiopathic or dystrophic. Dermatol Online J. 2010;16:5.
31. Bernardo BD, Huettner PC, Merritt DF, Ratts VS. Idiopathic calcinosis cutis presenting as labial lesions in children: report of two cases with literature review. J Pediatr Adolesc Gynecol. 1999;12:157–60.
32. Topaz O, Bergman R, Mandel U, et al. Absence of intraepidermal glycosyltransferase ppGalNAc-T3 expression in familial tumoral calcinosis. Am J Dermatopathol. 2005;27:211–15.
33. Topaz O, Shurman DI, Bergman R, et al. Mutations in *GALNT3*, encoding a protein involved in O-linked glycosylation, cause familial tumoral calcinosis. Nat Genet. 2004;36:579–81.
34. Sprecher E. Familial tumoral calcinosis: from characterization of a rare phenotype to the pathogenesis of ectopic calcification. J Invest Dermatol. 2010;130:652–60.
35. Kim DH, Kang H, Cho SH, Park YM. Solitary milialike idiopathic calcinosis cutis unassociated with Down's syndrome: two case reports. Acta Derm Venereol. 2000;80:151–2.
36. Goldminz D, Barnhill R, McGuire J, Stenn KS. Calcinosis cutis following extravasation of calcium chloride. Arch Dermatol. 1988;124:922–5.
37. Wheeland RG, Roundtree JM. Calcinosis cutis resulting from percutaneous penetration and deposition of calcium. J Am Acad Dermatol. 1985;12:172–5.
38. Clendenning WE, Auerbach R. Traumatic calcium deposition in the skin. Arch Dermatol. 1964;89:360–3.
39. Schoenfeld RJ, Grekin JN, Mehregan A. Calcium deposition in the skin. A report of four cases following electroencephalography. Neurology. 1965;15:477–80.
40. Davey RB, Sparnon AL, Byard RW. Unusual donor site reactions to calcium alginate dressings. Burns. 2000;26:393–8.
41. Munoz SJ, Nagelberg SB, Green PJ, et al. Ectopic soft tissue calcium deposition following liver transplantation. Hepatology. 1988;8:476–83.
42. Ehsani AH, Ghiasi M, Hoseini MS. Calcinosis cutis complicating liver transplantation. Dermatol Online J. 2006;12:23.
43. Friedman JS, Walters RF. Woolsey J, Fine JA. A unique presentation of calcinosis cutis in a patient with cystic fibrosis after double lung transplants. J Am Acad Dermatol. 2003;49:1131–6.
44. Shore EM, Xu M, Feldman GJ, et al. A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressiva. Nat Genet. 2006;38:525–7.
45. Kaplan FS, Le Merrer M, Glaser DL, et al. Fibrodysplasia ossificans progressiva. Best Pract Res Clin Rheumatol. 2008;22:191–205.
46. Miller ES, Esterly NB, Fairley JA. Progressive osseous heteroplasia: report of two cases. Arch Dermatol. 1996;132:787–91.
47. Kaplan FS, Shore EM. Progressive osseous heteroplasia. J Bone Miner Res. 2000;15:2084–94.
48. Urtizberea JA, Testart H, Cartault F, et al. Progressive osseous heteroplasia. Report of a family. J Bone Joint Surg Br. 1998;80:768–71.
49. Eddy MC, De Beur SM, Yandow SM, et al. Deficiency of the alpha-subunit of the stimulatory G protein and severe extraskeletal ossification. J Bone Miner Res. 2000;15:2074–83.
50. Yeh GL, Mathur S, Wivel A, et al. *GNAS1* mutation and *Cbfa1* misexpression in a child with severe congenital platelike osteoma cutis. J Bone Miner Res. 2000;15:2063–73.
51. Bastepe M, Juppner H. Identification and characterization of two new, highly polymorphic loci adjacent to *GNAS1* on chromosome 20q13.3. Mol Cell Probes. 2000;14:261–4.
52. Shore EM, Ahn J, deBeur J, et al. Paternally inherited inactivating mutations of the *GNAS1* gene in progressive osseous heteroplasia. N Engl J Med. 2002;346:99–106.
53. Lebrun M, Abeguile G, David A, et al. Progressive osseous heteroplasia; a model for the imprinting effects of GNAS inactivating mutations in humans. J Clin Endocrinol Metab. 2010;95:3028–38.
54. Weinstein LS. The stimulatory G protein α-subunit gene: mutations and imprinting lead to complex phenotypes. J Clin Endocrinol Metab. 2001;86:4622–6.
55. Goldminz D, Greenberg RD. Multiple miliary osteoma cutis. J Am Acad Dermatol. 1991;24:878–81.
56. Smith CG, Glaser DA. Treatment of multiple miliary osteoma cutis with tretinoin gel. J Am Acad Dermatol. 1999;41:550.

Nutritional Diseases 51

Stephanie McLeish Schaefer and Chad M Hivnor

Key features

- Nutritional deficiencies may affect any organ system, including the skin, which may provide clues to the diagnosis
- The two classic protein–energy malnutrition syndromes are kwashiorkor and marasmus
- In addition to inadequate oral intake, there are secondary causes of nutritional deficiencies, e.g. intestinal malabsorption due to medical conditions or surgical procedures
- Vitamin and trace element deficiencies can lead to a wide range of mucocutaneous findings, from follicular keratoses to periorificial erosions and glossitis
- Insufficient and deficient levels of vitamin D have been noted worldwide, in both low-income and high-income countries
- Obesity can be associated with high-calorie malnutrition and a number of skin changes, from acanthosis nigricans to lipodermatosclerosis

INTRODUCTION

Both isolated nutritional deficiencies and general malnutrition due to inadequate intake and/or abnormalities in the metabolism of nutrients necessary to sustain life can result in multisystem disorders. Deficiency of one isolated nutrient is rare, as individuals are usually deficient in multiple nutrients at the same time. In general, nutrients are categorized as macronutrients (carbohydrates, proteins and fats) or micronutrients (vitamins and minerals). Most people who suffer from nutritional deficiencies live in low-income countries. However, there are certain conditions that predispose individuals from high-income countries to develop nutritional deficiencies, such as alcoholism, intestinal malabsorption, bulimia and fad diets.

Nutrients must follow an orderly process of ingestion, digestion, absorption and circulation plus subsequent metabolism in order to be beneficial. When any one of these processes is disrupted, clinical manifestations may appear.

EPIDEMIOLOGY AND PATHOGENESIS

In low-income countries, malnutrition stems primarily from inadequate ingestion of all macronutrients as well as many micronutrients (Fig. 51.1). The World Health Organization (WHO) has estimated that worldwide in 2001, 54% of childhood deaths were due directly or indirectly to the multisystem ramifications of malnutrition. In industrialized regions of the world, malnutrition is directly linked to the per capita gross national product; if a country has a per capita income that is less than US$300 per year, endemic malnutrition is likely, especially in infants and young children.

The incidence of primary malnutrition in high-income countries is unknown, but the pathogenesis is thought to be at least twofold. Firstly, excessive consumption of foods high in calories but low in nutrients can lead to obese patients who lack essential vitamins and minerals. This is supported by a study in which 57% of morbidly obese patients undergoing preoperative assessment for bariatric surgery were found to have a deficiency in at least one micronutrient[1]. A second etiology involves various restrictive diets, including those based upon real or perceived need (e.g. food allergies), psychiatric illness (e.g. anorexia nervosa) or mental impairment (e.g. illicit drug abuse), all of which disrupt the intake of appropriate nutrients and can result in malnutrition.

In addition to a diet inadequate in the quantity and/or quality of macro- and micronutrients (i.e. primary causes), there are medical

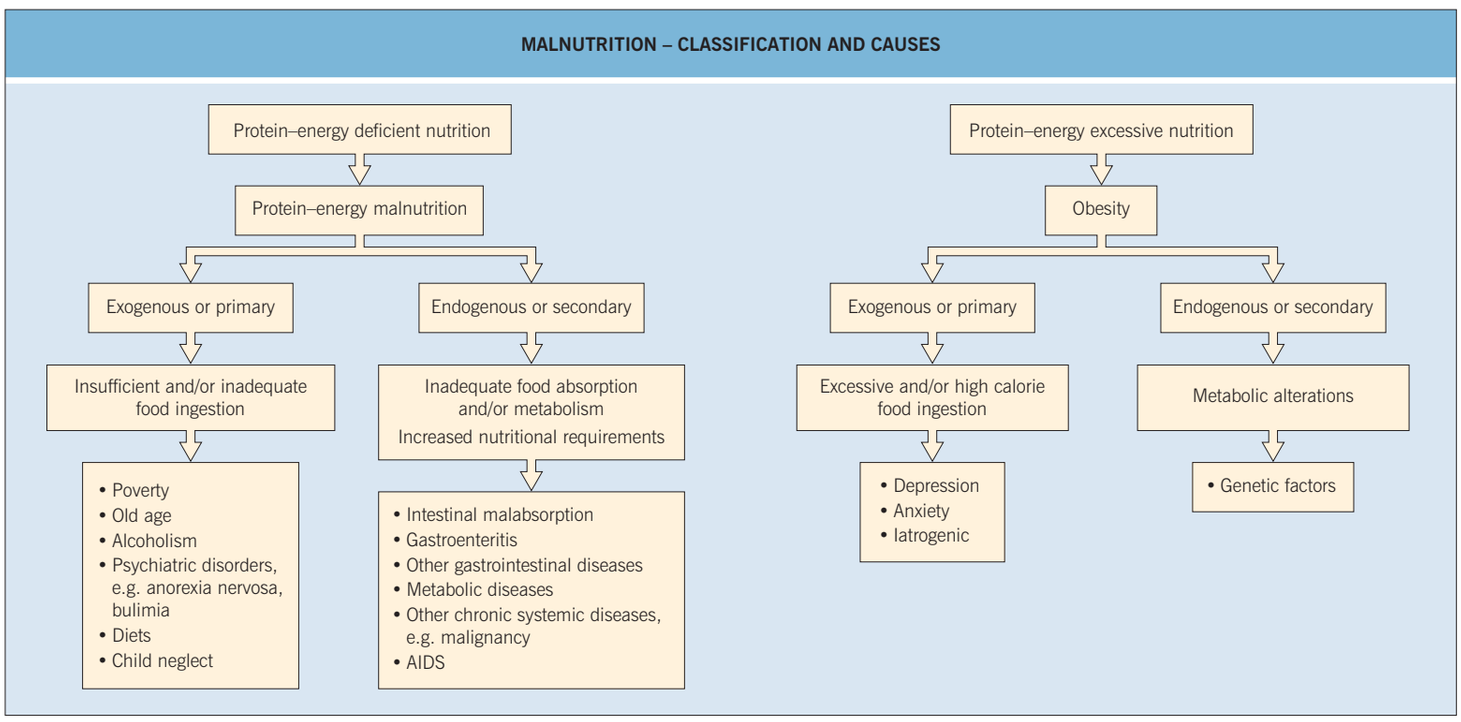


Fig. 51.1 Malnutrition – classification and causes. *Courtesy, Ramón Ruiz-Maldonado, MD.*

CHARACTERISTICS OF PROTEIN–ENERGY MALNUTRITION AND ESSENTIAL FATTY ACID DEFICIENCY			
	Protein–energy malnutrition		Essential fatty acid deficiency[2,3]
	Marasmus	Kwashiorkor	
Causes	• Decreased energy intake over months to years • Other primary causes: alcoholism, psychiatric disorders (anorexia nervosa, bulimia), diets for treatment of diseases or "allergic disorders", child neglect/abuse • Secondary causes: intestinal malabsorption, chronic diarrhea, malignancies, chronic systemic diseases (e.g. hepatic failure), AIDS*, metabolic disorders	• Decreased protein intake during periods of stress lasting a few weeks or more • Can result from diets consisting primarily of rice or rice-based beverages (e.g. "rice milk") for perceived milk intolerance • Other causes: protein-losing enteropathies, extensive gastrointestinal surgeries, HIV disease*	• Protein–energy malnutrition • Gastrointestinal disorders/surgeries causing severe fat malabsorption • Long-term parenteral nutrition without lipid supplementation • Diets extremely low in fat • Nephrotic syndrome
Cutaneous features	• Dry, thin, pale, lax and wrinkled skin • Occasionally, fine scaling and hyperpigmentation (Fig. 51.2) • Follicular hyperkeratosis and folliculitis in adults • Ulcerations • Excess of lanugo-like hair • Thin hair that grows slowly and falls out readily • Impaired growth of nails and fissured nails • Purpura (Fig. 51.3)	• Dyschromia is a common finding • Pallor due to distention of the skin and loss of pigment • Hypopigmentation following abrasions, and ulcerations and hyperpigmentation in areas subject to trauma • Superficial desquamation in mild cases ("enamel paint spots"), but in severe cases large areas of erosion ("flaky paint") (Fig. 51.5) • Other cutaneous signs include erythema, thinning, petechiae, ecchymoses and purpura • Hair is sparse, dry, lusterless and brittle with a reddish tinge; bands of light and dark coloration ("flag sign") reflect intermittent periods of malnutrition; positive gentle hair pull test • Nails are soft and thin • Mucosal lesions: cheilitis, xerophthalmia and vulvovaginitis	• The skin is dry, scaly, and leathery with underlying erythema • Intertriginous erosions • Alopecia and more lightly pigmented hair • Increase in transepidermal water loss • Petechiae
Systemic features	• Starved appearance but alert • Reasonably preserved responsiveness to short-term stress • Loss of subcutaneous fat and muscle (Fig. 51.2) • "Monkey facies" or an aged appearance (due to loss of buccal fat pads) • Suppression of growth	• Relatively well-nourished appearance • Edema or even anasarca (Fig. 51.4) • Apathy, anorexia, irritability • Failure to thrive (retardation of growth and mental development) • Superimposed bacterial and fungal (e.g. candidal) infections • Bilateral parotitis, hepatomegaly, diarrhea, loss of muscle mass	• Growth failure • Poor wound healing • Impaired reproduction • Abnormal liver and kidney function tests • Capillary fragility • Increased susceptibility to infections • Neurologic damage
Lab findings and diagnostic criteria	• Triceps skin-fold <3 mm • Mid-arm muscle circumference <15 cm • Creatinine-height index <60% of standard • Low zinc levels • Epidermal acanthosis or atrophy (depending upon the stage), hyperkeratosis • Most hair bulbs are in the telogen phase • Abundant broken hairs	• At least one of the following: poor wound healing, decubitus ulcers or skin breakdown • Anergy • Hypoalbuminemia (<2.5 g/dl) • Total iron-binding capacity <200 microg/dl • Peripheral lymphocyte count <1500/microl • Steatohepatitis • In "enamel paint spots", thickened, pigmented stratum corneum with an underlying stratum lucidum • Decreased number of anagen hair follicles and increased number of telogen follicles • Structural abnormalities in anagen follicles – severe atrophy, shaft constriction, depletion of pigment • Exclude nephrotic syndrome	• Low plasma levels of linoleic, linolenic and arachidonic acids • Accumulation of 5,8,11-eicosatrienoic acid • Elevated levels of palmitoleic and oleic acids • Anemia, thrombocytopenia • Orthokeratotic hyperkeratosis, acanthosis with hypergranulosis, atrophic sebaceous glands, and papillary dermal vasodilation with a mixed cell infiltrate (in rat models) • Steatohepatitis
Treatment	• Treat cautiously, slowly replacing proteins and calories, allowing readaptation of metabolic and intestinal functions • Supplementation with linoleic acid and zinc • Monitor for hypophosphatemia and cardiorespiratory failure (associated with overly aggressive nutritional replacement) • Treatment of underlying diseases if possible	• Aggressive nutritional support is indicated to rapidly restore metabolic balance; correction of any electrolyte disturbances or hypoglycemia • Institute diet with adequate protein and caloric intake; supplementation with minerals and vitamins is required as patients often have multiple nutritional deficiencies • Identify and attempt to treat underlying cause(s), including bacterial and parasitic diseases • Topical moisturizers as needed	• Essential fatty acid replacement, depending upon severity: – topical – oral – intravenous • Correction of coexisting nutritional deficiencies
Prognosis	• 10% mortality, often secondary to diarrhea or pneumonia • Mortality rate related to underlying disease(s)	• Prognosis in adult patients is poor, even with aggressive nutritional support • In children, a lesser degree of stress is required to precipitate the disorder, so it is less foreboding • Severe, relapsing cases and those with coexistent HIV disease have a high mortality rate • Death usually occurs due to overwhelming infection despite antibiotic treatment	• Prognosis depends on the severity and coexistence of other nutritional deficiencies • Depends on awareness of this entity

*HIV infection is more often associated with marasmus than with kwashiorkor.

Table 51.1 Characteristics of protein–energy malnutrition and essential fatty acid deficiency.

conditions that can lead to a functional malnutrition (i.e. secondary causes). The latter include an increase in metabolic requirements (e.g. severe infections) and/or a decrease in the transport and utilization of nutrients (e.g. intestinal malabsorption, bariatric surgery). Malnutrition is also seen in individuals with late-stage internal malignancies and advanced AIDS (Table 51.1).

CLINICAL FEATURES

Clinically, the signs and symptoms of nutritional deficiencies are often due to a lack of multiple nutrients. Cutaneous manifestations in part reflect the fact that epidermal maturation (from basal cell layer to stratum corneum) occurs over a period of 10–14 days. Deficiencies, especially of macronutrients, can interfere with this process, resulting in skin that is dry and thin in appearance with associated epidermal atrophy sometimes leading to wrinkling. Prolonged deficiencies can reduce both protein production, including that of dermal collagen and muscle, and the amount of subcutaneous fat. As a result, patients may develop dermal atrophy, muscle wasting and/or lax skin.

Additional clinical findings of marasmus and kwashiorkor, such as dyschromia (hypo- and hyperpigmentation), desquamation and erosions (Fig. 51.2), are reviewed in Table 51.1. Patients may also have cutaneous manifestations from a deficiency in one or more micronutrients, and these are outlined in Table 51.2.

Protein–Energy Malnutrition

Worldwide, protein–energy malnutrition is the most prevalent nutritional deficiency and there are two major forms: marasmus and kwashiorkor. According to the WHO, on a global basis, *marasmus* affects more than 50 million children who are less than 5 years of age (Fig. 51.3). However, it can occur in individuals of all ages as marasmus results from a prolonged inadequate intake of calories and energy. Based on the Waterlow classification of protein–energy malnutrition in children (which accounts for the degree of stunted growth in children), marasmus represents a reduction in body weight that is >60% of expected weight for height[4]. These patients frequently develop recurrent infections due to their inability to mount a normal immune response.

Kwashiorkor is a more acute form of childhood and adult protein–energy malnutrition (see Table 51.1). A characteristic finding is peripheral edema or even anasarca in association with hypoalbuminemia (Fig. 51.4). One consequence of this edema is a body weight that is 60–80% of expected, in contrast to marasmus. However, some patients will have overlapping features of both disorders[4]. In at-risk populations, kwashiorkor can develop after a child is weaned from breast milk and begins a diet rich in carbohydrates but deficient in proteins.

Based upon this and other clinical observations, it was thought that kwashiorkor was due to a relative deficiency in protein *intake*. However, more recently, this proposed pathogenesis has been questioned based upon several observations. For example, protein intakes were found to be similar in a group of children, irrespective of whether they had marasmus or kwashiorkor[5]. In addition, kwashiorkor can develop within just a few weeks of an acute, life-threatening illness. A current theory is that kwashiorkor is related to physiologic stresses, caused by an acute or chronic illness (including infections), which increase protein and energy requirements at a time when intake is frequently limited[6]. This would help to explain why kwashiorkor has a higher mortality rate as well as the observation that kwashiorkor often occurs in the setting of an acute illness superimposed upon on a chronic state of milder malnutrition. It is hypothesized that the stress of the former blocks the protein-sparing response that is normally in effect during states of starvation.

In addition to peripheral edema, patients with kwashiorkor also develop desquamation and erosions that have been likened to "enamel paint" and "flaky paint" (Fig. 51.5). Both kwashiorkor and marasmus can have secondary causes such as "rice milk" diets or chronic diarrhea and these are outlined in Table 51.1. The cutaneous and systemic abnormalities associated with primary protein–energy malnutrition are

Fig. 51.2 Marasmus. This child is emaciated and has obvious hyperpigmentation. Both erosions and desquamation are present on the scalp. *Courtesy, Ramón Ruiz-Maldonado, MD.*

Fig. 51.3 Marasmus. Multiple purpuric lesions are seen. *Courtesy, Ramón Ruiz-Maldonado, MD.*

Fig. 51.4 Kwashiorkor. There is intense edema of the buttocks and lower extremities in addition to areas of erythema with erosions and desquamation. *Courtesy, Ramón Ruiz-Maldonado, MD.*

often reversible following nutritional therapy. However, if the malnutrition is prolonged, this may preclude normal physical and/or mental development[4].

Essential Fatty Acid Deficiency

Essential fatty acids (EFAs) are unsaturated fatty acids that must be obtained from an exogenous source because they cannot be synthesized by the human body. Linoleic, linolenic and arachidonic acids are the major EFAs, although arachidonic acid can be metabolized from linoleic acid. EFAs have multiple functions, both structural and synthetic, including being a precursor to prostaglandins, reducing fluidity within phospholipid membranes, energy storage and proper lamellar granule formation. They constitute between 13% and 30% of the skin's fatty acids.

While isolated deficiencies of EFAs are uncommon, this can occur in patients receiving parenteral nutrition without lipid supplementation and with overly aggressive low-fat diets. In most instances, however, EFA deficiency is associated with other nutritional deficiencies (see Table 51.1). The presence of decreased plasma levels of linoleic and arachidonic acids plus increased levels of eicosatrienoic acid (normally undetectable) establishes the diagnosis of EFA deficiency (see Fig. 51.12).

Fig. 51.5 Kwashiorkor. This child's arm has edema and superficial epidermal necrosis with an "enamel paint" appearance. *Courtesy, Ramón Ruiz-Maldonado, MD.*

Vitamins and Trace Elements

Micronutrients represent a diverse array of dietary components necessary to sustain health. The physiologic roles of micronutrients are as varied as their composition. Several micronutrients function as cofactors for enzymes, while others act as biochemical substrates or hormones; in addition, there are some whose function has not been well defined[7].

VITAMIN DEFICIENCIES IN ADULTS AND CHILDREN

Vitamin	Clinical manifestations			Reference values*	Replacement therapy
	Mucocutaneous	Systemic	Other		
FAT-SOLUBLE VITAMINS – CAN EASILY ACCUMULATE AND LEAD TO TOXICITY IF REPLACED IN HIGH DOSES FOR PROLONGED PERIODS					
A (retinol)	• Phrynoderma – follicular papules with central keratotic plug; favors extensor surfaces of extremities (Fig. 51.6) & buttocks • Generalized xerosis • Sparse, fragile hair	• Night blindness • Xerophthalmia (dryness of the cornea & conjunctivae) • Bitot spots (gray–white patches on the conjunctivae) • Keratomalacia (softness of the cornea, sometimes with ulceration)[12] • Stunted growth	• Increase in measles-related mortality • Increased susceptibility to and mortality from respiratory and diarrheal illnesses[12]	• Conventional: 30–100 microg/dl (<20 microg/dl only when hepatic stores depleted) • IU: 1.05–3.50 micromol/l	• Based on severity of ophthalmologic impairment • 10 000–50 000 IU/day PO or IM in infants on days 1, 2 & 14 • 200 000 IU/day PO or IM in children and adults on days 1, 2 & 14 • Higher doses given if keratomalacia
D: **D_2:** ergocalciferol **D_3:** cholecalciferol	• None	• Muscle weakness • Rickets in children • Osteomalacia in adults	• Possible decrease in innate immunity (see Table 51.3) • Possible increase in internal malignancies (e.g. colon, prostate)	• Total serum or plasma 25(OH) vitamin D is measured (D_2 plus D_3) • Deficiency: <20 ng/ml (IU: <50 nmol/l) • Insufficiency: 20–29 ng/ml (IU: 51–75 nmol/l)[13]	• For deficiency, 20 000 IU of vitamin D_3 or 50 000 IU of vitamin D_2 orally once weekly × 8 weeks; repeat for another 8 weeks if 25(OH) vitamin D still <30 ng/ml[14] • Plus 1 g/day of oral calcium if deficient
E (tocopherol)	• None	• Ophthalmoplegia, ptosis • Muscle weakness, ataxia • Pigmentary retinopathy			• 600 IU BID orally[15]
K **K_1:** phytanodione **K_2:** menaquinone	• Purpura, ecchymoses	• If severe hypoprothrombinemia, extensive hemorrhage at any body site • Hemorrhagic disease of the newborn – infants not given vitamin K at birth plus inadequate diet or mother on medications which inhibit vitamin K function[12,†]		• Elevated prothrombin time & INR • Serum or plasma vitamin K is measured • Conventional: 80–1160 pg/ml	• Newborns: 0.5–1 mg sc or IM • Children: 2 mg • Adults: 5–10 mg • Orally if asymptomatic • Intravenously in emergencies (risk of anaphylaxis) • Fresh frozen plasma • Doses for K_1 and K_2 similar

*In laboratory medicine, there has been a movement toward expressing values in international units (IU) rather than conventional units, e.g. mg/dl, but because this is not done universally, both values are provided in this table.

†Medications that inhibit hepatic vitamin K epoxide reductase: warfarin, anticonvulsants, certain cephalosporins (containing side chains of N-methylthiotetrazole or methylthiadiazole), high-dose salicylates and rifampin.

Table 51.2 Vitamin deficiencies in adults and children. Adapted in part from refs 7, 9,10 & 11. BID, twice daily; GI, gastrointestinal; GU, genitourinary; IM, intramuscularly; IV, intravenously; INR, international normalized ratio; PO, orally; RBCs, red blood cells; TID, three times daily; sc, subcutaneously.

Continued

VITAMIN DEFICIENCIES IN ADULTS AND CHILDREN					
Vitamin	**Clinical manifestations**			**Reference values***	**Replacement therapy**
	Mucocutaneous	**Systemic**	**Other**		
WATER SOLUBLE VITAMINS – LESS LIKELY TO ACCUMULATE & LEAD TO TOXICITY, BUT IN HIGH DOSES CAN LEAD TO SIDE EFFECTS, E.G. NEPHROLITHIASIS (VITAMIN C), HEPATITIS (NIACIN)					
C (ascorbic acid)	• Spongy gingivae with bleeding & erosions • Petechiae, ecchymoses • Follicular hyperkeratosis, especially forearms, abdomen & legs • Corkscrew hairs (flattened & curled) with perifollicular erythema or hemorrhage (Fig. 51.7)	• Subperiosteal hemorrhage with "pseudoparalysis", especially in children • Arthralgias, joint swelling, edema • Loose teeth • Impaired wound healing • Weakness, malaise, depression • Vasomotor instability[12] • In infants, hemorrhage into GI and GU tracts • Anemia • Impeded growth • Cerebral & femoral sheath hemorrhages	• Many of the signs of *scurvy* are related to impaired collagen synthesis • Fractures of cartilaginous matrix • Positive Rumpel–Leede capillary fragility test (>20 petechiae/inch^2)‡	• Conventional: 0.5–1.5 mg/dl (plasma) • IU: 28–85 mmol/l (plasma) • Absence of vitamin C in urine	• Adults: 800 mg/day orally • Children: 150 mg/day orally
B_1 (thiamine)	• Skin breakdown may be seen in "wet" beriberi due to edema • Glossitis and glossodynia	• Early – fatigue, apathy, irritability, depression, drowsiness, anorexia, nausea, abdominal pain • Late – peripheral neuropathy, weakness, cardiac failure, mental alterations, growth retardation • Prolonged deprivation – meningismus, coma	• *Beriberi* is divided into "wet" and "dry" forms§ • Korsakoff's syndrome – amnesia, confabulation & peripheral neuropathy • Wernicke's encephalopathy – ophthalmoplegia, horizontal nystagmus, ataxia, confusion	• Measurement of the RBC transketolase activity coefficient is recommended‖ • Circulating thiamine levels – Conventional: 0.2–2 microg/dl (plasma); 1.8–4.8 microg/dl (whole blood) • IU: 7.5–75 nmol/l (plasma); 70–180 nmol/l (whole blood)	• 100 mg TID IV × several days, followed by 100 mg/day orally until complete recovery[15] • Infantile beriberi – 5–20 mg IV[15]
B_2 (riboflavin, lactoflavin)	• Angular cheilitis • Glossitis – pebbly appearance, then atrophic with irregular denudation of papillae • In periorificial sites (head & neck, anogenital region) – painless scaly papules, ulcers, indolent fissures & seborrheic dermatitis-like lesions • Conjunctivitis	• Superficial keratitis • Photophobia • Changes in iris (pigment clumping) • Anemia due to bone marrow hypoplasia • Mental retardation in newborns	• In adults, *oro-oculo-genital syndrome* can occur, especially if there are additional B vitamin deficiencies	• Conventional: 4–24 microg/dl • IU: 106–638 nmol/l • Elevation of the activation coefficient for RBC glutathione reductase confirms diagnosis • Urinary or RBC riboflavin concentration also useful	• Riboflavin 3–10 mg/day orally • In refractory cases, 2 mg IM TID
B_3 (niacin, nicotinic acid)	• Photodistributed erythema that becomes scarlet or hyperpigmented, with scale-crust; surface has shellac-like appearance (Fig. 51.8) • "Casal's necklace" – well-demarcated band around the neck • Painful fissures of the palms & soles • Peri-anal & oral inflammation & erosions • Cheilitis & glossitis (atrophic, red) • Vaginitis with ulceration	• Peripheral neuropathy with dysesthesias, including burning • Esophagitis • Anorexia • Lassitude • Dizziness • Irritability, disorientation • Abdominal pain • Late – irritability, anxiety, apathy, diarrhea, nausea, dementia	• The classic triad of *pellagra* is dermatitis, diarrhea & dementia, with the fourth "d" possibly death • Because of large tissue stores, symptoms develop after months of niacin or tryptophan deficiency • Other causes of pellagra include carcinoid syndrome, Hartnup disease, and medications, e.g. isoniazid¶	• No sensitive or specific serum assays • Most reliable test is urinary excretion of niacin metabolites: N′-methylnicotinamide and its 2-pyridone derivative (N′-methyl-2-pyridone-5-carboxamide)[15]	• Mild cases – nicotinic acid 50 mg TID orally[15] • If symptomatic, nicotinic acid 25 mg TID IV[15] • Advanced stages – nicotinic acid 50–100 mg IM TID × 3–4 days, followed by similar quantities PO[15]

*In laboratory medicine, there has been a movement toward expressing values in international units (IU) rather than conventional units, e.g. mg/dl, but because this is not done universally, both values are provided in this table.
‡Following inflation of blood pressure cuff to a point between systolic and diastolic blood pressure for 5 minutes.
§"Wet" beriberi derives its name from the edema that occurs secondary to cardiac failure, which can be high-output. In "dry" beriberi, neurologic manifestations predominate, e.g. peripheral neuropathy (sensory and motor), confusion and nystagmus.
‖Transketolase activity coefficient measures enzyme activity before and after the addition of exogenous thiamine pyrophosphate; RBCs from a deficient individual express a substantial increase in enzyme activity with the addition of thiamine pyrophosphate[7]
¶Tryptophan (an essential fatty acid) is a precursor of niacin. In carcinoid syndrome, tryptophan is preferentially converted to serotonin instead of niacin, and in Hartnup disease, niacin deficiency is due to decreased intestinal absorption of tryptophan.

Table 51.2 Vitamin deficiencies in adults and children (cont'd). Adapted in part from refs 7, 9,10 & 11. BID, twice daily; GI, gastrointestinal; GU, genitourinary; IM, intramuscularly; IV, intravenously; INR, international normalized ratio; PO, orally; RBCs, red blood cells; TID, three times daily; sc, subcutaneously.

Continued

VITAMIN DEFICIENCIES IN ADULTS AND CHILDREN					
Vitamin	**Clinical manifestations**			**Reference values***	**Replacement therapy**
	Mucocutaneous	**Systemic**	**Other**		
B_5 (pantothenic acid)	• None	• Fatigue, headache & vomiting • Hypoglycemia • Paresthesias	• Rare		
B_6 (pyridoxine, pyridoxamine, pyridoxal)	• Periorificial seborrheic dermatitis-like lesions • Angular cheilitis, stomatitis • Glossitis – atrophic with ulceration • Conjunctivitis • Intertrigo	• Anorexia, nausea, vomiting • Neurologic symptoms including peripheral neuropathy, somnolence, confusion & seizures • Sideroblastic anemia, eosinophilia, lymphopenia		• Plasma pyridoxal phosphate levels are measured • Conventional: 5–30 ng/ml • IU: 10–121 nmol/L	• Pyridoxine 50–100 mg/day PO to prevent neuropathy[15] • 100 mg/day IV in those with seizures[15]
B_7 (biotin)	• Alopecia • Seborrheic dermatitis of the scalp, face, flexures & perianal region • Nummular eczema[12] • Blepharitis, conjunctivitis • Erythroderma in neonatal form • Juvenile form may resemble acrodermatitis enteropathica	• Depression, lassitude • Anorexia, nausea & vomiting • Paresthesias & hyperesthesias • Hypotonia, muscle pain • Developmental delay, hearing loss • Seizures, ataxia • Both forms fatal if not treated	• Neonatal form – holocarboxylase synthetase deficiency (see Fig. 51.12) • Juvenile form – biotinidase deficiency • Two forms have overlap; both autosomal recessive • Metabolic acidosis, lactic acidosis, hyperammonemia	• Measurement of plasma levels of biotin is unreliable • Increased urinary excretion of organic acids (e.g. 3-hydroxy-isovaleric acid) • Additional diagnostic tests include enzyme activity and genetic analysis (see Fig. 51.12)	• Infants & children – 5–20 mg/day PO or IM • Adults – 10–40 mg/day PO or IM
B_9 (folic acid)	• Cheilitis, glossitis, mucosal erosions • Diffuse hyperpigmentation, with accentuation in sun-exposed sites	• Megaloblastic anemia (macrocytosis plus hypersegmented neutrophils is pathognomonic)[12] • Weakness secondary to anemia • Neuropsychiatric symptoms due to impaired synthesis of myelin	• While folate can reverse the megaloblastic anemia of B_{12} deficiency, it cannot reverse the neurologic degeneration	• Conventional: 140–628 ng/ml in packed RBCs • IU: 317–1422 nmol/l in packed RBCs	• Replace folate and exclude B_{12} deficiency • Folate 1 mg TID PO, followed by 1 mg/day • Folate 1–5 mg/day IV if acutely ill[15]
B_{12} (cyanocobalamin [CNCbl])	• Cutaneous findings are uncommon • Diffuse or patchy hyperpigmentation, including flexural areas, palms, soles, nails, oral cavity • Glossitis with fissures of the oral mucosa (early sign prior to anemia)[16] • Painful, red, swollen tongue	• Megaloblastic anemia due to altered folic acid metabolism • Peripheral neuropathy, ataxia	• Pernicious anemia – decrease in gastric intrinsic factor • Juvenile form – normal gastric acid secretion (in contrast to adult form) • Use of Schilling test has been supplanted by serologic testing for anti-parietal cell and anti-intrinsic factor antibodies • As an autoimmune endocrinopathy, associated with vitiligo, alopecia areata	• Megaloblastic anemia with decreased serum B_{12} levels • Conventional: 200–835 pg/ml • IU: 148–616 pmol/l • More sensitive assay is serum levels of methylmalonic acid and homocysteine**	• CNCbl 1 mg IM twice weekly × 2 weeks then weekly × 2 months then monthly[15] • Oral route is now felt to be appropriate, even in pernicious anemia or in states of abnormal absorption – 500 microg/day of CNCbl

*In laboratory medicine, there has been a movement toward expressing values in international units (IU) rather than conventional units, e.g. mg/dl, but because this is not done universally, both values are provided in this table.

**These levels are increased early in vitamin B_{12} deficiency.

Table 51.2 Vitamin deficiencies in adults and children (cont'd). Adapted in part from refs 7, 9,10 & 11. BID, twice daily; GI, gastrointestinal; GU, genitourinary; IM, intramuscularly; IV, intravenously; INR, international normalized ratio; PO, orally; RBCs, red blood cells; TID, three times daily; sc, subcutaneously.

Fig. 51.6 Phrynoderma of vitamin A deficiency. Multiple clusters of follicular papules with central keratotic plugs. Histologically, keratinous plugs within follicles, hyperkeratosis and atrophy of sebaceous glands are seen. It must be differentiated from pityriasis rubra pilaris and keratosis pilaris.

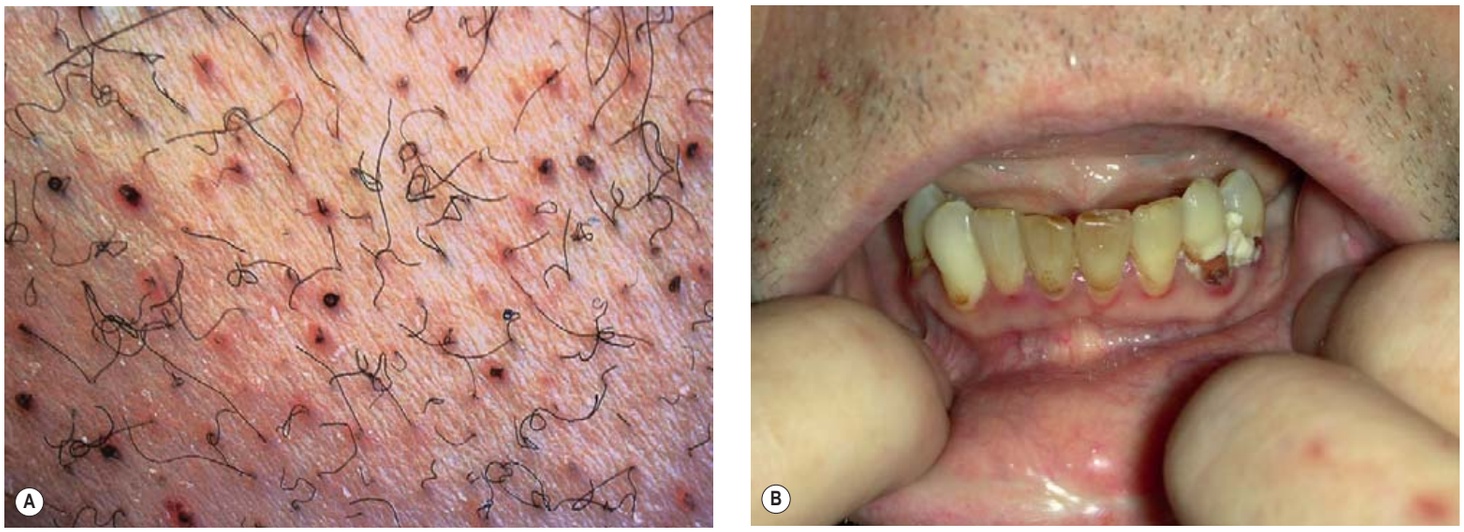


Fig. 51.7 Scurvy. A Corkscrew hairs and perifollicular hemorrhage on the lower extremities. **B** Gingivitis and gingival erosions. *B, Courtesy, Jeffrey Callen, MD.*

Under normal circumstances, the recommended average daily dietary intake for each micronutrient is measured in milligrams or even smaller quantities. This distinguishes micronutrients from macronutrients (carbohydrates, fats, proteins) as well as the macrominerals (calcium, magnesium, phosphorus)[7].

Vitamins

Vitamins are required constituents of the human diet as they are essential for development and maintenance of bodily functions. However, they do not have a direct role as an energy source. Vitamins are categorized as either fat-soluble (A, D, E, K) or water-soluble (all the others), as outlined in Table 51.2. This categorization is physiologically meaningful since none of the fat-soluble vitamins appear to serve as cofactors for enzymes, whereas most of the water-soluble vitamins do[7]. In addition, symptomatic vitamin excess is more likely with fat-soluble vitamins (see below). Lastly, the use of vitamins as therapeutic interventions in dermatology includes topical vitamin D analogues for psoriasis[8] (see Ch. 129) and oral or topical retinoids to treat acne and disorders of cornification (see Ch. 126).

Tables 51.2 and 51.3 review the major fat- and water-soluble vitamins, including their functions and the causes as well as signs and symptoms of associated deficiencies. Current standards for diagnosing these deficiencies, recommendations for daily supplements, and replacement therapies are also included.

Vitamin excess

Excessive ingestion of vitamins most commonly occurs in individuals seeking potential (and often unproven) "anti-aging" or antineoplastic effects. Toxicity due to high doses of water-soluble vitamins is rarely seen, as these compounds are rapidly excreted via the urine. In contrast, high doses of fat-soluble vitamins may lead to harmful side effects, including hepatic toxicity, nephrolithiasis and peripheral neuropathy (Table 51.4). They may also have unanticipated effects at high doses in certain populations. For example, in the β-Carotene and Retinol Efficacy Trial (CARET), a large cancer prevention trial, patients at high risk for lung cancer were given supplements containing β-carotene and vitamin A. Not only did these supplements fail to prevent lung cancer, they were actually associated with increased rates of lung cancer[19]. The reported association of oral isotretinoin and topical tretinoin (more controversial) with increased mortality in smokers remains to be corroborated[20].

Vitamin D

The signs and symptoms of vitamin D deficiency, none of which are cutaneous, are outlined in Table 51.2. The preferred method for assessing vitamin D status (and excluding deficiency) is measurement of total serum levels of 25-hydroxyvitamin D. While secondary hyperparathyroidism can influence the 1,25-dihydroxyvitamin D assay, this is not the case with the 25-hydroxyvitamin D assay. In addition,

Fig. 51.8 Pellagra. A Hyperpigmentation with desquamation of the dorsal aspects of the hands and forearms. **B** Hyperpigmented desquamation of the distal lower extremity. Note the shiny shellac-like appearance on the lateral ankle. *B, Courtesy, Jeffrey Callen, MD.*

VITAMINS – SOURCES, FUNCTIONS AND RECOMMENDED PROPHYLACTIC DOSES

Vitamin	Natural sources	Functions	Underlying etiologies/risk factors	Recommended prophylactic doses
A	• Animal fats, liver, milk, green leafy vegetables	• Normal vision • Embryogenic development • Physical growth • Immune function • Keratinocyte proliferation and differentiation • Squamous metaplasia of sebaceous and eccrine glands	• Minimal, if any, animal fats in diet – Poverty – Alcoholism – Anorexia nervosa – Fad diets • Fat malabsorption	• Infants & children: 100 000–200 000 IU every 4–6 months from age 6 months to 5 years • In measles: 200 000 IU once daily × 2 days • Postpartum women: 200 000 IU within 6 weeks of delivery
D	• UVB irradiation of the skin • Cod liver oil, fish (salmon, mackerel), fortified milk or yogurt • Estimates of sources – 10% from food & 90% from UVB	• Induces antimicrobial peptide gene expression in keratinocytes, monocytes, NK cells, T cells, B cells & neutrophils[8] • Induces cathelicidins via the vitamin D receptor • Helps absorption of ~85% of calcium and 40% of phosphorus via the gut • Decreases proliferation of malignant cells & induces terminal differentiation[8]	• Risk factors include: breastfed infants, individuals with darkly pigmented skin or limited sun exposure, advanced age, BMI >30 (fat sequesters vitamin D), living at extreme degrees of latitude[8] • Generalized disorders of cornification	• Vitamin D_3 is three times more effective than D_2 • Currently, the recommendation for adults is 600–1000 IU of vitamin D_3 per day* • The American Academy of Pediatrics has recommended 400 IU of vitamin D per day until age 18 years[17]
E	• Ubiquitous in foods, so deficiency is rare	• Possible role in cellular homeostasis • Antioxidant • Interferes with vitamin K-dependent coagulation via unknown mechanism	• Chronic cholestasis & pancreatic insufficiency (absorption requires biliary and pancreatic secretions)[15] • Long-term fat malabsorption	• No clearly proven medical benefits of daily vitamin E supplementation beyond the recommended daily allowance ingested in food
K	• K_1: green leafy vegetables & meat • K_2: fermented foods & grass-fed animals • Diet: ~50% • Bacteria within large bowel: ~50%	• K_1: hepatic synthesis of coagulation factors II, VII, IX & X and proteins C & S • K_2: regulates mineral localization (e.g. calcium)[18]	• Broad-spectrum antibiotics (reduce intestinal bacteria) • Malabsorption syndromes • Low-birthweight infants (inadequate intake, non-colonized colon, low hepatic stores, maternal medications†) • Liver diseases, biliary atresia, cystic fibrosis • Medications: cholestyramine, colestipol, orlistat and inhibitors of vitamin K epoxide reductase†	• Newborns: 0.5–1 mg sc or IM routinely administered prophylactically at birth
C	• Fresh fruits & vegetables	• Collagen formation • Cofactor for several enzymes, e.g. lysyl hydroxylase • Antioxidant • Iron absorption • Folate metabolism (folic acid to active form folinic acid)	• Alcoholism, chronic drug abuse • Fad diets • Deficient intake for as few as 3 months can lead to scurvy[12] • Increased requirements in the setting of febrile illnesses, diarrhea, iron deficiency	• Children: 40–50 mg/day • Adults: 60–100 mg/day
B_1 (thiamine)	• Yeast, cereals, liver, meat, eggs, vegetables	• Role in pyruvate metabolism (a source of energy generation) • Cofactor in metabolism of carbohydrates, lipids, branched-chain amino acids[15]	• Starvation, alcoholism • Polished rice diet • Hyperemesis gravidarum • B_1-deficient diet (IV hyperalimentation or parenteral nutrition) followed by high-carbohydrate diet exacerbates symptoms[15,‡] • Hemodialysis, leukemia, rapidly growing carcinoma	• Infants: 0.05 mg/day • Children and adults: 0.05–1.5 mg/day
B_2 (riboflavin)	• Milk and nutrients listed for vitamin B_1 (see above)	• Intracellular oxidation–reduction reactions	• Achlorhydria & GI malabsorption • Alcoholism • Hypothyroidism • Neonatal phototherapy for hyperbilirubinemia • Medications: chlorpromazine, probenecid, tricyclic antidepressants • Exacerbated by respiratory infections	• Infants: 0.6 mg/day • Children and adults: 1–2 mg/day
B_3 (niacin)	• Liver, lean pork, salmon, poultry and red meat • Humans are able to synthesize niacin from tryptophan (an essential amino acid)	• Vital oxidation–reduction reactions • Biosynthesis of epidermal lipids, e.g. ceramides	• Malnutrition • Intestinal malabsorption • Alcoholism • Diet limited to tryptophan-deficient maize[§] • Carcinoid syndrome[§] • Hartnup disease[§] • Medications: isoniazid	• Infants: 8 mg/day • Children and adults: 9–20 mg/day

*Many countries and institutions have their own recommendations regarding the appropriate dose of oral vitamin D per day. Over the past several years, there has been a trend toward higher doses. Currently, the NIM-recommended daily allowances for vitamin D are: 400 IU/day (0–12 months of age), 600 IU/day (1–70 years of age), and 800 IU/day (>70 years of age), whereas the American Academy of Dermatology has recommended 1000 IU/day for adults at risk for deficiency.

†Medications which inhibit vitamin K epoxide reductase in the liver: warfarin, anticonvulsants, certain cephalosporins (containing side chains of N-methylthiotetrazole or methylthiadiazole), high-dose salicylates, isoniazid and rifampin.

‡Pyruvate and lactate, which interfere with carbohydrate metabolism, accumulate in a B_1-deficient state. A high-carbohydrate diet accentuates the pre-existing vitamin-deficient state, often precipitating a Wernicke's or Korsakoff's syndrome.

§Tryptophan (an essential fatty acid) is a precursor of niacin. Tryptophan is deficient in maize, and millet interferes with tryptophan metabolism as it is high in leucine. In carcinoid syndrome, tryptophan is preferentially converted to serotonin instead of niacin, and in Hartnup disease, niacin deficiency is due to decreased intestinal absorption of tryptophan.

Table 51.3 Vitamins – sources, functions and recommended prophylactic doses. Adapted in part from refs 7, 9 & 10. GI, gastrointestinal; IM, intramuscular; IV, intravenous; sc, subcutaneous; UVB, ultraviolet B radiation.

Continued

VITAMINS – SOURCES, FUNCTIONS AND RECOMMENDED PROPHYLACTIC DOSES				
Vitamin	**Natural sources**	**Functions**	**Underlying etiologies/risk factors**	**Recommended prophylactic doses**
B_5	• Synthesized in gut by bacterial flora	• Component of coenzyme A which plays major role in metabolism	• Protein–energy malnutrition	• Not well studied as deficiency is extremely rare
B_6	• Widely distributed in nature • Pyridoxine in plant food • Pyridoxal and pyridoxamine in animal products • All forms convert to the active form pyridoxal phosphate	• Cofactor for multiple enzymes involved in amino acid metabolism and conversion of linoleic acid to arachidonic acid • Ceramide synthesis • Gluconeogenesis & heme biosynthesis[15]	• Other vitamin or trace element deficiencies (metabolism of B_6 is dependent on riboflavin, niacin & zinc) • Medications: isoniazid, anticonvulsants, penicillamine, hydralazine, oral contraceptives, corticosteroids[15] • Inflammatory bowel disease, uremia & cirrhosis	• 0.5–2 mg per day • Supplementation required in those taking isoniazid
B_7 (biotin)	• Liver is best source • Other meats, egg yolks, yeast, tomatoes • Probably synthesized in gut by bacterial flora	• Essential cofactor for several carboxylases involved in cellular metabolism, e.g. of fatty acids • Plays role in gluconeogenesis[12]	• Inborn error of metabolism • Inadequate diet • Excessive raw egg white consumption‖ • Chronic anticonvulsant therapy	• Normal intake: – Infants: 5 microg/day – Children: 8–20 microg/day – Adults: 30 microg/day • Supplementation: – Children: 200 microg/day – Adults: 300 microg/day
B_9 (folate)	• Liver, green leaves, meat, milk, yeast • Easily destroyed with cooking[12] • Body stores are limited, so anemia can result after 4–5 months of deficient intake	• DNA synthesis	• Deficient diets • Medications (which interfere with folate metabolism): methotrexate, sulfasalazine, pyrimethamine	• Infants: 65–80 microg/day • Children: 150–300 microg/day • Adults: 400 microg/day • During breastfeeding: 500 microg/day • Prenatal and 1st trimester: 600 microg/day • If taking methotrexate: 1000 microg (1 mg)/day; maximum of 5000 microg (5 mg)/day
B_{12}	• Fish, shellfish, meat, dairy products • Body stores are large, so development of deficiency requires 3–6 years of a deficient state	• DNA synthesis	• Strict vegetarianism/veganism • Decrease in gastric intrinsic factor (pernicious anemia) • Gastrectomy, surgical resection of terminal ileum • Overgrowth of intestinal bacteria • Medications: metformin	• For the normal population on a regular diet, no need for supplementation

‖Excessive consumption of raw egg whites (>20 eggs/day) leads to high levels of the protein avidin, which binds to biotin, rendering it biologically unavailable. Avidin is deactivated by cooking, while biotin remains intact.

Table 51.3 Vitamins – sources, functions and recommended prophylactic doses (cont'd). Adapted in part from refs 7, 9 & 10. GI, gastrointestinal; IM, intramuscular; IV, intravenous; sc, subcutaneous; UVB, ultraviolet B radiation.

25-hydroxyvitamin D has a longer half-life (2 weeks) and therefore is thought to better reflect body stores[8,14]. Currently, although a consensus is lacking, vitamin D deficiency is defined by most experts as a serum level of 25-hydroxyvitamin D that is <20 ng/ml (50 nmol/l), and vitamin D insufficiency as circulating levels of 20–29 ng/ml (51–75 nmol/l) (see Table 51.2).

Based upon these levels, it is estimated that one billion people worldwide have either deficient or insufficient levels of vitamin D[13]. Depending upon the study, from 40% to 100% of elderly men and women in the US and Europe (excluding those in nursing homes) are deficient in vitamin D[13]. However, vitamin D deficiency is not limited to the elderly. Recently, it was reported that 52% of Hispanic and black adolescents and 48% of white preadolescent girls in the US had 25-hydroxyvitamin D levels <20 ng/ml[14].

As a result of these and other studies, concern has been raised that the recommended daily intake of 400 IU of vitamin D_3 is inadequate. Because the 25-hydroxyvitamin D assay is expensive and universal testing is not feasible, there has been a call to simply revise the current recommendations. While some have advocated 800–1000 IU of oral vitamin D_3 daily for children and adults (unless there are contraindications)[8,14,17], others such as the National Institute of Medicine has recommended: 400 U/day (0–12 months of age), 600 IU/day (1–70 years of age), and 800 IU/day (>70 years of age). All of these doses are below the age-dependent, tolerable, upper daily limits of 1000 IU for infants and children (up to 18 years old) and of 2000 IU for adults[17]. Vitamin D_3 (cholecalciferol; animal diet as source) is viewed as nutritionally superior to vitamin D_2 (ergocalciferol; source is plants) and therefore is regarded as the best form for supplementation and for fortifying foods. Of note, unless a person frequently eats foods rich in fish oils, it is very difficult to obtain enough vitamin D_3 from dietary sources alone[17].

Dermatologists in particular are well aware that there is also an endogenous source of vitamin D production, initiated with the conversion of 7-dehydrocholesterol to provitamin D_3 when skin is exposed to ultraviolet B radiation (Fig. 51.10). It is thought that typically over 90% of vitamin D is produced in this manner. Obviously, the balance between sun protection (to prevent photodamage and cutaneous malignancies) and increasing the risk of vitamin D deficiency has become a matter of debate. As effects of vitamin D, beyond calcium homeostasis and bone mineralization, have become increasingly recognized, the debate has intensified. For example, immunomodulatory effects via the innate immune system have been reported, as has an association between vitamin D deficiency and an increased risk of several internal malignancies[14]. While there are studies that refute the latter as well as no direct evidence linking sunscreen use with vitamin D deficiency[8,21], it is prudent to recommend supplementation to patients who are limiting sun exposure and/or have risk factors for the development of vitamin D deficiency (see Tables 51.2 & 51.3).

Trace elements

Trace elements and minerals constitute ~3% of body weight at birth and 4% in adults. Based upon animal studies, 15 trace elements have

VITAMIN EXCESS IN ADULTS AND CHILDREN				
Vitamin	**Mechanism of toxicity**	**Clinical manifestations**		**Comments**
		Cutaneous	**Systemic**	
A	• Chronic intake of >25 000 IU vitamin A per day • Ingestion of polar bear liver • Co-administration with other retinoids	• Cheilitis • Xerosis with pruritus • Dermatitis • Alopecia	• Painful swelling of the long bones in young children • Elevated hepatic enzymes • Skeletal hyperostosis • Calcification of extraspinal tendons and ligaments • Pseudotumor cerebri • Lethargy, anorexia	• Assessment by serum concentrations – unreliable • Similar side effects as oral retinoids (see Ch. 126) • Treatment – immediate discontinuation
Beta-carotene (natural provitamin of vitamin A)	• Carotenemia – high intake of carrots & yellow squash, including as baby food • Lycopenia – high intake of tomatoes, gac, papaya, pink guava & other fruits • Inability to convert β-carotene to vitamin A (e.g. hypothyroidism, diabetes, anorexia nervosa)	• Yellow–orange discoloration (Fig. 51.9) due to deposition of carotenes/lycopenes in areas with: – the thickest layer of stratum corneum (palms & soles) – abundant sebaceous glands (nasolabial folds, forehead) • Carotenoderma usually appears when carotene levels are 3–4× normal	• None	• Skin discoloration slowly disappears after altering diet • Measurement of serum carotenoids (normal range: 0.4–1.5 mg/l) differentiates this disorder from jaundice, in which mucous membranes have a yellow color (most apparent in sclerae)
D	• >50 000 IU/day of oral supplementation	• None	• Nausea, vomiting • Poor appetite • Diarrhea, constipation • Weakness • Nephrolithiasis, nephrocalcinosis • Hypercalcemia, hypercalciuria, hyperphosphatemia	• NOT caused by excessive UV exposure (previtamin D_3 and vitamin D_3 inactivated by sustained exposure of skin to heat) • Tolerable upper limit for adults is 2000 IU/day[17]
E	• High supplement doses	• Petechiae, ecchymoses	• May reduce platelet aggregation • Interferes with function of vitamin K	• Drug–drug interaction with warfarin (see Ch. 133)
K	• None	• None	• None	• Side effects at sc injection sites: – early – erythematous plaque, often annular (see Ch. 21) – late – morpheaform plaque (Texier's disease)
C	• Excessively high doses of oral supplements	• None	• GI upset • Osmotic diarrhea • Nephrolithiasis	• Abrupt discontinuation of excessive vitamin C intake can also lead to scurvy
B_3	• Excessively high doses of oral supplements	• Flushing, pruritus, xerosis • Acanthosis nigricans	• Dyspepsia • Hepatic failure • Hyper- or hypoglycemia • Hyperuricemia	
B_6	• Long-term oral doses of >200 mg/day	• Photosensitivity	• Loss of proprioception • Painful sensory neuropathy	

Table 51.4 Vitamin excess in adults and children. Adapted in part from refs 7, 9 & 10. GI, gastrointestinal; sc, subcutaneous; UV, ultraviolet.

Fig. 51.9 Carotenemia. The patient's legs are noticeably orange when compared to the photographer's hand.

been identified as essential for health: *iron*, *zinc*, *copper*, *chromium*, *selenium*, *iodine*, *fluoride*, *manganese*, *molybdenum*, *cobalt*, nickel, tin, silicon, vanadium and arsenic (in very small doses). As for being essential nutrients in humans, there is compelling evidence for just the first 10 (in italics). They serve multiple cellular functions including as cofactors for enzymes and as prosthetic groups in metalloproteins. An example of the latter is the complexing of iron and protoporphyrin IX via ferrochelatase to form heme[7]. Deficiency syndromes related to essential trace elements, other than iron, zinc, copper, iodine or cobalt, were not recognized until recently. Explanations include the exceedingly small requirements for these trace elements, their ubiquitous nature in foodstuffs[7], and the lack of routine laboratory assays. Only trace elements of dermatologic importance will be discussed in this chapter.

Zinc

Zinc is one of the most important trace elements in humans, playing a critical role in the function of more than 200 zinc-dependent metalloenzymes that regulate lipid, protein and nucleic acid synthesis and degradation. Zinc can be found in human breast milk, animal-based foods, shellfish, legumes and green leafy vegetables. There is evidence to suggest that zinc plays a role in enhancing wound healing and improving immune function[22] and this may explain the poor wound

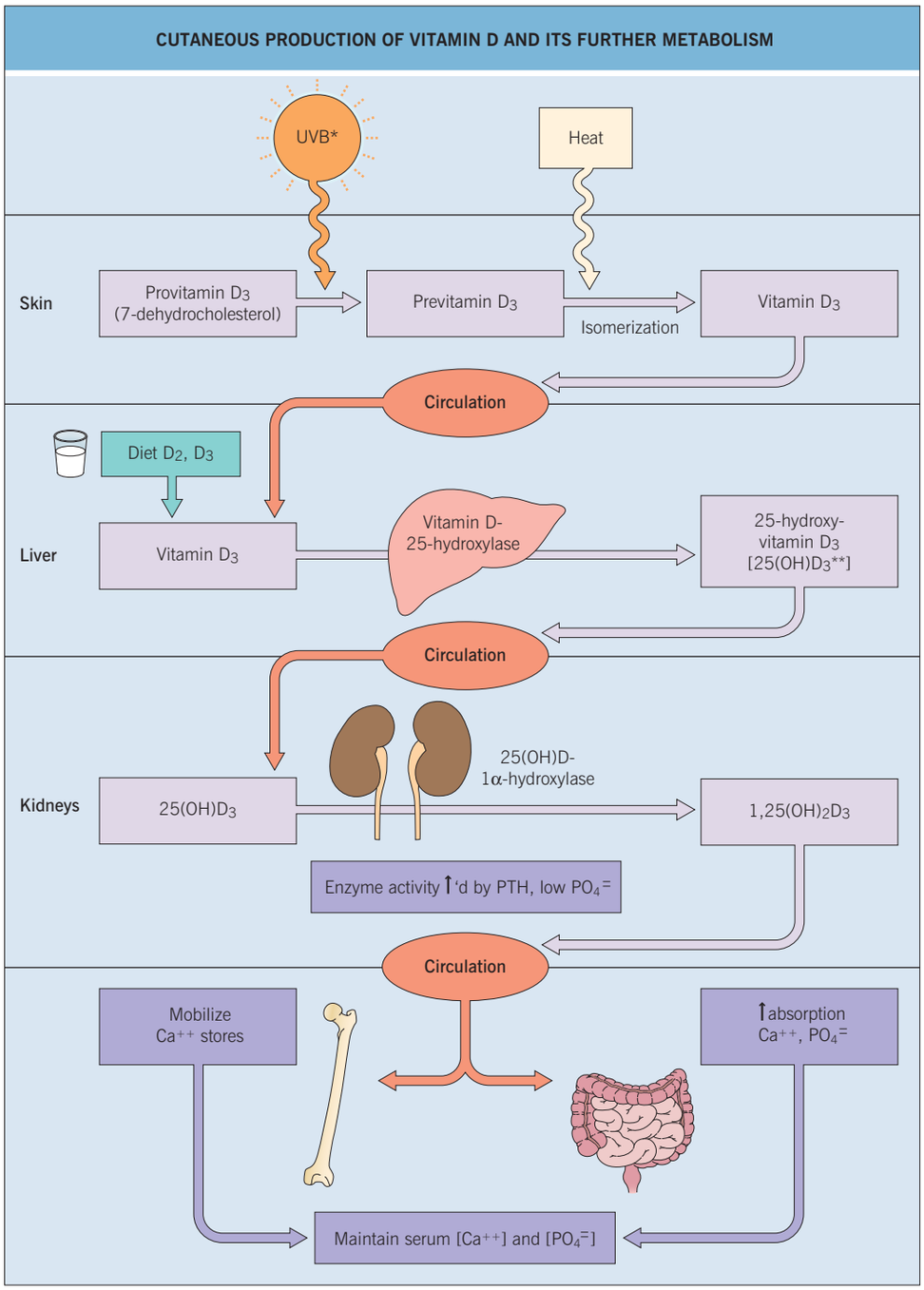


Fig. 51.10 Cutaneous production of vitamin D and its further metabolism. During exposure to ultraviolet B radiation, 7-dehydrocholesterol within the skin is converted to previtamin D_3, which is then immediately converted to vitamin D_3 in a heat-dependent process[14]. Of note, the heat from excessive sunlight exposure can degrade previtamin D_3 and vitamin D_3 into inactive photoproducts. Both forms of vitamin D (D_3 and D_2) are biologically inactive and they require activation in the liver and then the kidney. After binding to carrier proteins, vitamin D is transported to the liver, where it is enzymatically hydroxylated to 25-hydroxyvitamin D [25(OH)D], the major circulating form of vitamin D. 25-hydroxyvitamin D is then converted into its active form, 1,25-dihydroxyvitmain D [$1,25(OH)_2D$], within the kidney by the enzyme 1α-hydroxylase. Of interest, this final hydroxylation step can also occur in keratinocytes when the enzyme CYP27B1 is upregulated in response to wounding or by Toll-like receptor (TLR) activation from microbial-derived ligands[8].

Serum levels of phosphorus, calcium and fibroblast growth factor 23 can either increase or decrease renal production of $1,25(OH)_2D$. $1,25(OH)_2D$ decreases its own synthesis via feedback inhibition and decreases the synthesis and secretion of parathyroid hormone by the parathyroid glands. $1,25(OH)_2D$ also enhances intestinal calcium absorption in the small intestine by interacting with the vitamin D receptor–retinoic acid X receptor complex (VDR-RXR) to enhance the expression of the epithelial calcium channel and calbindin-D 9K, a calcium-binding protein. In addition, $1,25(OH)_2D$ is recognized by its receptor in osteoblasts, leading to a series of events that maintain calcium and phosphorus levels in the blood which in turn promotes mineralization of the skeleton. *Most effective wavelength = 300 ± 5 nm. **Measurement of this form most commonly done to assess vitamin D status.

healing and increased susceptibility to cutaneous infections that can be seen in patients with chronic zinc deficiency. Due to its antioxidant properties, zinc might protect the skin against UV-induced damage[23].

Patients with zinc deficiency can develop erythema, scale-crusts and erosions, especially in the following sites – perioral, acral and perineal (Fig. 51.11); occasionally, vesicles or bullae are seen as well as psoriasiform plaques. Zinc deficiency may also lead to alopecia, paronychia, onychodystrophy, blepharitis, conjunctivitis, stomatitis and angular cheilitis. Diarrhea, depression (apathy) and dermatitis (erosive) are sometimes considered the triad of zinc deficiency, but the triad is seen in only 20% of patients. Superimposed cutaneous infections with *Candida* spp. and staphylococci are very common. Patients are typically irritable and sleep poorly; children with chronic zinc deficiency may experience growth retardation and/or develop hypogonadism. If treatment is not initiated, death may ensue.

Zinc deficiency can be either acquired or inherited as an autosomal recessive disorder, acrodermatitis enteropathica (AE). The latter is due to mutations in the gene that encodes the zinc transporter SLC39A4 which is expressed in the intestine and kidney. Clinical manifestations usually appear within 1 to 2 weeks after weaning from breast milk, or at 4 to 10 weeks of age if bottle-fed. However, there are reports of zinc deficiency in breastfed babies where the breast milk contained low levels of zinc. Of note, infants and children with cystic fibrosis can also develop zinc deficiency (Fig. 51.12). This deficiency should be considered in patients who have treatment-resistant seborrheic dermatitis or anogenital dermatitis.

There are several risk factors for developing acquired zinc deficiency, including alcoholism, anorexia nervosa, diets high in mineral-binding phytate (Middle Eastern diets), and vegan diets. Of note, vegan diets can also lead to low levels of long-chain n-3 (omega-3) fatty acids, calcium, vitamin D and vitamin B_{12}[24]. In addition, intestinal malabsorption often results in multiple deficiencies, including zinc. Lastly, zinc deficiency can be seen in association with pregnancy, HIV infection, chronic renal failure and drugs (e.g. penicillamine).

The histologic finding of epidermal necrosis (see below) plus low serum alkaline phosphatase and zinc levels point to the diagnosis; the normal reference range for zinc is 70–150 microg/dl (10.7–22.9 micromol/l). An explanation for the abnormal alkaline phosphatase

Fig. 51.11 Zinc deficiency. Genetic (**A, B**) and acquired (**C, D**) forms. Both have erythema with erosions (**A, C**) as well as crusting and desquamation. Lesions favor acral and periorificial sites.

level is that for this enzyme, zinc is an essential trace element. Special trace element tubes should be used for blood collection in order to avoid metal contamination and EDTA-containing tubes should be avoided.

Cutaneous and other systemic manifestations respond dramatically to zinc sulfate or zinc gluconate (1–2 mg/kg/day in the acquired forms and 3 mg/kg/day for AE). The commercially available 220 mg zinc sulfate tablets contain 50 mg of elemental zinc. Patients with persistent malabsorption syndromes and AE require lifelong zinc supplementation, with repeated serum zinc determinations. Lastly, hypozincemia has been described in some patients with necrolytic acral erythema and treatment with zinc sulfate 220 mg orally twice daily resulted in resolution of the lesions.

Copper

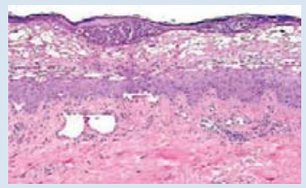
Copper is an essential trace element that is required for the function of a number of enzymes, e.g. tyrosinase, lysyl oxidase. The average adult body contains ~80 mg of copper. In the bloodstream, 90% of copper is associated with ceruloplasmin, and the remainder is bound to other plasma proteins, primarily albumin. Acquired copper deficiency is rare. It has been reported in infants receiving milk low in copper, in protein–energy malnutrition, and as a consequence of excessive zinc intake. Symptoms include anemia, neutropenia and failure to thrive, but cutaneous findings are limited to rare reports of pigmentary dilution of the skin and hair.

Menkes disease, also known as kinky hair disease, represents an inherited form of copper deficiency. It is an X-linked recessive condition characterized clinically by defective copper absorption with low copper levels in the blood, liver and hair. Affected infants may appear normal and develop normally until 2 to 3 months of age, when they gradually manifest failure to thrive, lethargy, hypothermia and hypotonia. In addition to seizures and developmental delay, patients may also have anemia and bony abnormalities (similar to those in scurvy). Arteriography demonstrates tortuosity and elongation of arteries, a reflection of immature elastin (as detected by ultrastructural studies)[25]. Decreased activity of several enzymes, including cytochrome C oxidase (in the brain), lysyl oxidase (in connective tissues and blood vessels) and ascorbic acid oxidase (in bones), may account for the associated clinical findings.

Pudgy cheeks, a cupid's bow of the upper lip, and horizontal eyebrows comprise the typical facies in Menkes disease[26]. However, a more obvious and characteristic finding is alopecia with abnormal hair shafts. There are 180° twists of the hair (pili torti), segmental shaft narrowing (monilethrix) and brush-like swellings of the hair shaft (trichorrhexis nodosa). The hairs appear to be light in color, sparse (Fig. 51.13), fragile and kinky. Patients may also have diffuse cutaneous pigmentary dilution due to decreased activity of tyrosinase, a copper-dependent enzyme. In addition, obligate female carriers may have patches of swirled hypopigmentation or pili torti along Blaschko's lines, as a result of lyonization.

DIFFERENTIAL DIAGNOSIS OF "NUTRITIONAL DERMATITIS"

Evaluation of the infant/child* with periorificial and acral erythema and erosions



Zinc deficiency	Essential fatty acid deficiency	Biotin deficiency	Organic acidurias**	Cystic fibrosis
Acrodermatitis enteropathica (genetic form): • Onset days to weeks after birth if bottle-fed, or after weaning if breast-fed **Acquired forms:** • Low zinc level in maternal milk • Parenteral nutrition without zinc supplementation • Gastrointestinal disorders/ surgeries or high-fiber diets (high phytate content) causing poor absorption • HIV infection	• Parenteral nutrition without lipid supplementation • Gastrointestinal disorders/ surgeries causing severe fat malabsorption • Nephrotic syndrome	**Biotinidase deficiency:** onset age 3 months to 2 years (juvenile form) **Holocarboxylase synthetase deficiency:** onset days to months after birth (neonatal form) **Acquired forms:** • Parenteral nutrition without biotin supplementation • Gastrointestinal disorders/ surgeries causing severe malabsorption • Excessive intake of raw egg whites • Chronic anticonvulsant therapy (e.g. phenytoin, carbamazepine, valproic acid)	**Propionic acidemia** (propionyl CoA carboxylase deficiency) **Methylmalonic acidemia** (methylmalonyl CoA mutase deficiency or lack of vitamin B_{12} activity) **Maple syrup urine disease** (branched-chain α-ketoacid dehydrogenase deficiency) **Citrullinemia** (argininosuccinic acid synthetase deficiency)	Onset typically at age 3–5 months (precedes respiratory symptoms)
Signs: • Stomatitis, glossitis • Alopecia • Secondary infections (e.g. candidiasis) • Photophobia • Diarrhea • Irritability • Failure to thrive	**Signs:** • Diffusely xerotic skin • Alopecia and lightly pigmented hair • Failure to thrive • Thrombocytopenia	**Signs:** • Alopecia • Blepharitis, conjunctivitis • Secondary infections (e.g. candidiasis) • Vomiting • Metabolic acidosis • Hypotonia, lethargy, seizures, developmental delay • Optic atrophy, hearing loss, ataxia (with biotinidase deficiency)	**Signs:** • Alopecia • Secondary infections (e.g. candidiasis) • Vomiting • Metabolic acidosis • Hypotonia, lethargy, developmental delay • Failure to thrive • Pancytopenia	**Signs:** • Eruption often involves the trunk • +/– Alopecia • No mucous membrane involvement • Diarrhea • Edema • Irritability • Failure to thrive
Laboratory: • Plasma zinc level • Serum alkaline phosphatase level (low) • +/– Zinc level of maternal milk • Genetic analysis	**Laboratory:** • Plasma linoleic, arachidonic and eicosatrienoic acid levels (eicosatrienoic:arachidonic ratio > 0.4)	**Laboratory:** • Plasma ammonia and lactate levels • Urine organic acid analysis • Biotinidase activity in serum • Holocarboxylase synthetase activity in skin fibroblasts or peripheral blood lymphocytes • Genetic analysis	**Laboratory:** • Plasma ammonia and glycine levels • Urine organic acid analysis • Plasma isoleucine level (if on low branched-chain amino acid diet)	**Laboratory:** • Serum albumin level • Plasma zinc level • Sweat test • Genetic analysis

* In older patients, the differential diagnosis includes necrolytic migratory erythema (as seen in glucagonoma syndrome) and necrolytic acral erythema (in association with hepatitis C infection); periorificial (oral and perineal) erythema and erosions can also be seen in niacin (pellagra) and riboflavin deficiencies, with a characteristic photodistributed eruption found in the former; severe infantile seborrheic dermatitis typically involves other intertriginous sites such as the neck as well as the diaper area, scalp and face

** Cutaneous eruptions may be associated with adherence to a therapeutic diet low in branched-chain amino acids (e.g. isoleucine deficiency)

Fig. 51.12 Differential diagnosis of "nutritional dermatitis" (in addition to exogenous protein–energy malnutrition). *Courtesy, Julie V Schaffer, MD. Photomicrograph, courtesy, Earl Glusac, MD.*

Fig. 51.13 Menkes disease. This child has the characteristic pale skin and sparse kinky hair. *Courtesy, Ramón Ruiz-Maldonado, MD.*

The clinical features, low serum levels of copper and ceruloplasmin, and microscopic hair shaft findings establish the diagnosis. Infants with Menkes disease have a poor prognosis, with a life expectancy of 3 to 5 years and progressive deterioration leading to death. Treatment with copper histidine is usually unsuccessful. Mutations in *ATP7A*, which encodes a copper-transporting ATPase, lead to Menkes disease (as well as occipital horn syndrome; see Ch. 95); therefore, prenatal diagnosis is possible.

Copper toxicity can be acquired or inherited. The acquired form usually results from the ingestion of excessive amounts of copper (e.g. milk boiled in eroded copper pots) and it leads to gastrointestinal symptoms and occasionally (in predisposed individuals) childhood cirrhosis. The inherited form is Wilson disease, an autosomal recessive disorder characterized by an accumulation of copper within internal organs (in particular the liver, cornea and brain). Affected individuals have mutations in the gene *ATP7B* which also encodes a copper-transporting P-type ATPase. Dysfunction of this protein leads to an impairment of both intrahepatic trafficking and biliary excretion of copper[26].

Because daily copper intake exceeds the body's requirements, an effective means of excreting excess copper is crucial. This is accomplished by ATP7B, which mediates both copper secretion into plasma (coupled with ceruloplasmin synthesis) and its excretion into bile. The presence of excess copper within tissues (due to dysfunction of ATP7B) induces free-radical reactions and lipid peroxidation. Resultant hepatic damage leads to steatosis, inflammation, cirrhosis and, finally, liver failure[27].

The diagnosis of Wilson disease is established by the detection of low serum ceruloplasmin, increased urinary copper excretion, increased hepatic copper content, and/or genetic testing. The clinical hallmarks of Wilson disease are hepatomegaly, cirrhosis, Kayser–Fleischer corneal rings, and neurologic symptoms (dysarthria, dyspraxia, ataxia, and parkinsonian-like extrapyramidal signs).

Chelating agents, in particular penicillamine, are used to treat Wilson disease. Oral zinc can be prescribed for pre-symptomatic patients or as maintenance therapy, as it induces a negative copper balance.

Selenium

Selenium, in the form of selenocysteine, is an essential component of several enzymes, including those involved in thyroid hormone metabolism and protection against oxidative damage (e.g. glutathione peroxidase). Deficiency of selenium typically results in a cardiomyopathy as well as muscle pain and weakness due to muscle degeneration. Cutaneous manifestations include hypopigmentation of the skin and hair (considered early signs), leukonychia and xerosis, all of which respond to selenium replacement[28]. There was also a report of erythematous scaly papules and plaques involving the cheeks, hips, thighs and popliteal fossae, along with erosions in the diaper area[29]. Elevated serum levels of creatine kinase and transaminases are often present in selenium deficiency as well.

Selenium deficiency has been reported in patients receiving total parenteral nutrition and in those who live in areas where the soil content of selenium is poor[30]. Low serum levels of selenium and glutathione peroxidase activity are indicative of selenium deficiency. The recommended replacement dosage in selenium-deficient patients is a maximum of 100–200 microg per day, with the Recommended Daily Allowance (RDA) being 70 microg per day for adults and 20 microg for infants.

Although controversial, over-supplementation can occur due to reported beneficial cardiovascular and anti-cancer effects[31]. If supplements are taken, they should not exceed 200 microg per day. Excessive selenium ingestion can produce selenosis in humans, leading to a peripheral neuropathy, dermatitis, alopecia, abnormal nails, nausea and vomiting as well as a garlic-like breath odor. The use of selenium sulfide shampoo in large areas of eroded or ulcerated skin may lead to excessive absorption, with loss of appetite and tremor.

Anorexia Nervosa and Bulimia (Nervosa)

Anorexia nervosa and bulimia nervosa are eating disorders characterized by starvation, excessive exercise, self-induced vomiting and/or abuse of medications (e.g. laxatives, diuretics). Both can result in primary and secondary nutritional deficiencies. Anorexia nervosa is a persistent unwillingness or inability to maintain adequate body weight, whereas patients with bulimia typically binge-eat then purge or fast. These disorders occur most commonly in adolescent girls and young adult women, but can affect both genders and all age groups. Skin disorders, either real or perceived, are common in these patients and women in particular report a greater dissatisfaction with the appearance of their skin when compared to a similar cohort[32].

The dietary changes and starvation associated with anorexia nervosa and bulimia can lead to a number of cutaneous findings, including telogen effluvium, lanugo-like hair, xerosis, generalized pruritus, carotenoderma and hyperpigmentation. In addition, these patients can develop acrocyanosis, perniosis and livedo reticularis. Signs of specific nutritional deficiencies (e.g. pellagra, scurvy, acrodermatitis enteropathica) may be present, as well as poor wound healing, seborrheic dermatitis and edema[33]. Additional clues to the diagnosis include petechiae, interdigital intertrigo, paronychia, and particularly calluses or scars on the knuckles or dorsal surface of the hand (Russell's sign) due to repeated self-induced vomiting over prolonged periods of time. Patients with bulimia may also have enlarged salivary glands and erosion of their tooth enamel. Psychiatric and nutritional support must be instituted as severe malnutrition is common.

Obesity

Obesity, whether acquired or inherited, is defined as a body mass index (BMI) over 30; the latter has been found to correlate with high levels of the adipokine leptin[34]. Genetic disorders such as Prader–Willi, Bardet–Biedl, Alström and Wilson–Turner syndromes have been associated with childhood-onset obesity. In addition, endocrine disorders such as Cushing's disease, Cushing's syndrome, and insulin resistance include obesity amongst their clinical manifestations.

Acquired obesity is at epidemic proportions in both adults and children in industrialized nations. Although paradoxical, it is a functional malnutrition due to the consumption of high-caloric foods that are low in nutrients. Obesity is a systemic disease, as evidenced by an increased incidence of hypertension, hyperglycemia and hyperlipidemia, components of the metabolic syndrome (see Table 53.5), as well as atherosclerotic cardiovascular disease and premature death. Cutaneous manifestations are nonspecific, but some of the more common findings, such as acanthosis nigricans, appear to be related to insulin resistance (Table 51.5)[35]. One speculation is that the insulin resistance may be related to the relative zinc deficiency observed in obese patients (zinc is thought to promote insulin-induced glucose uptake in peripheral tissues)[36].

Bariatric Surgery and Gastrointestinal Malabsorption

The increase in acquired obesity has led to an increase in the number and types of bariatric surgery performed. Due to subsequent alterations in gastrointestinal absorption, some post-bariatric surgery patients can develop nutritional deficiencies. Two of the more commonly performed surgeries are laparoscopic adjustable banding and the Roux-en-Y gastric bypass. Because the normal absorptive surface is left intact with the former, nutrient deficiencies in these patients are rare. On the other hand, the Roux-en-Y gastric bypass procedure reduces stomach size and, as a result, there are lower levels of intrinsic factor, gastrin, hydrochloric acid and pepsinogen, which lead to a reduction in protein digestion. The Roux-en-Y procedure also decreases the physical grinding of food

DERMATOSES OBSERVED IN OBESE INDIVIDUALS
• Plantar hyperkeratosis (presumably pressure-related)
• Acanthosis nigricans (insulin resistance*)
• Skin tags
• Striae distensae
• Intertrigo (*Candida* spp. and bacteria; related to increased temperature and humidity of permanent semi-occlusive skin folds)
• Hyperpigmentation (frictional; favors inner thighs and under bra straps)
• Hyperhidrosis
• Stasis dermatitis
• Leg ulcers, most commonly venous
• Lipodermatosclerosis, lower extremities and abdominal pannus
• Lymphedema, lower extremities and abdominal pannus
• Obesity-associated lymphoedematous mucinosis, lower extremities and pannus
*Perhaps due to excess insulin binding to insulin-like growth factor receptors on keratinocytes.

Table 51.5 Dermatoses observed in obese individuals. Individuals with psoriasis have an increased prevalence of obesity.

that typically helps to release vitamins and minerals. Abnormally low levels of micronutrients, such as iron, zinc, copper and vitamins A, E, B_9 (folate) and B_{12}, may be seen in these patients, and long-term monitoring is required, as it may take months or years for signs and symptoms to appear[37].

In disorders such as Crohn's disease that are associated with gastrointestinal malabsorption, at least 50% of patients may have low plasma concentrations of vitamin C, copper, niacin and zinc[38].

PATHOLOGY

Nutritional deficiencies generally occur in combination; therefore, the resultant pathologic changes are often very variable. Although nutritional diseases have been better studied biochemically than structurally, there are several helpful histologic clues, including necrosis of the upper one-third of the epidermis (see Fig. 51.12). This distinctive reaction pattern has been reported in pellagra, acrodermatitis enteropathica, acquired zinc deficiency, glucagonoma and pseudoglucagonoma syndromes. In the early stages, there is vacuolar degeneration of the upper half of the epidermis. This stage is followed by the development of acanthosis, with hyperkeratosis and an increase in pigment throughout the epidermis. The late stage is characterized by epidermal atrophy (with flattening of the rete ridges) and dermal fibrosis[39]. In protein–energy malnutrition, nonspecific histologic features are seen, such as epidermal atrophy and hyperkeratosis.

Hair is a superb model of growth and differentiation. The histologic study of the hair matrix and hair shaft may be useful in detecting moderate to severe degrees of protein–energy malnutrition[40].

DIFFERENTIAL DIAGNOSIS

Nutritional diseases rarely result from the deficiency of a single nutrient, element or vitamin. Therefore, clinical manifestations are often nonspecific and, in mild to moderate deficiencies, somewhat subtle. A few specific deficiencies have characteristic mucocutaneous and systemic features that are easily recognized by the experienced clinician. Most suspected deficiencies are easily confirmed via laboratory analysis (see Table 51.2), and readily respond to the administration of the deficient nutrient, element and/or vitamin.

TREATMENT

The treatment of nutritional diseases must be individualized, taking into account the likelihood of multiple deficiencies of both macro- and micronutrients. The recommended treatment for specific nutritional diseases is reviewed in this chapter, but management frequently requires a multidisciplinary approach.

REFERENCES

1. Gehrer S, Kern B, Peters T, et al. Fewer nutritional deficiencies after laparoscopic sleeve gastrectomy (LSG) than after laparoscopic Roux-Y-gastric bypass (LRYGB) – a prospective trial. Obes Surg. 2010;20:447–53.
2. Prottey C. Essential fatty acid and the skin. Br J Dermatol. 1976;94:579–85.
3. Abushufa R, Reed P, Weinkove C, et al. Essential fatty acid status in patients on long term home parental nutrition. JEPN J Parenter Enteral Nutr. 1995;19:286–90.
4. Klein S. Protein energy malnutrition. In: Ausielo D, Goldman L (eds). Cecil Textbook of Medicine, 23rd edn. Philadelphia: Saunders, 2007:1613–17.
5. Lin C, Boslaugh S, Ciliberto H, et al. A prospective assessment of food and nutrient intake in a population of Malawian children at risk for kwashiorkor. J Pediatr Gastroenterol Nutr. 2007;44:487–93.
6. Jahoor F, Badaloo A, Reid M, Forrester T. Protein metabolism in severe childhood malnutrition. Ann Trop Paediatr. 2008;28:87–101.
7. Mason J. Vitamins, trace minerals and other micronutrients. In: Ausielo D, Goldman L (eds). Cecil Textbook of Medicine, 23rd edn. Philadelphia: Saunders, 2007:1626–40.
8. Miller J, Gallo R. Vitamin D and innate immunity. Dermatol Ther. 2010;23:13–22.
9. Lucky A, Powell J. Cutaneous manifestations of endocrine, metabolic and nutritional disorders. In: Schachner L, Hansen R (eds). Textbook of Pediatric Dermatology, 3rd edn. London: Elsevier, 2004:935–941.
10. Russel R, Suter P. Vitamin and trace mineral deficiency and excess. In: Fauci AS, Braunwald E, Kasper DL, et al. (eds). Harrison's Principles of Internal Medicine, 17th edn. New York: McGraw-Hill, 2008:441–50.
11. Nieves D, Goldsmith L. Cutaneous changes in nutritional disease. In: Freedberg I, Eisen A, Wolff F (eds). Fitzpatrick's Dermatology in General Medicine, 6th edn. New York: McGraw-Hill, 2003:1399–1412.
12. Suskind, S. Nutritional deficiencies during normal growth. Pediatr Clin North Am. 2009;56:1035–53.
13. Holick M, Garabedian M. Vitamin D: photobiology, metabolism, mechanism of action, and clinical applications. In: Favus MF (ed.). Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 6th edn. Washington, DC: American Society for Bone and Mineral Research, 2006:129–37.
14. Holick M. Vitamin D deficiency. N Engl J Med. 2007;357:266–81.
15. Kumar, M. Presentations of nutritional deficiencies. Neurol Clin. 2010;28:107–70.
16. Graells J, Ojeda R, Muniesa C, et al. Glossitis with linear lesions: an early sign of vitamin B12 deficiency. J Am Acad Dermatol. 2009;60:498–500.
17. Lehmann B, Meurer M. Vitamin D metabolism. Dermatol Ther. 2010;23:2–12.
18. Masterjohn C. On the Trail of the Elusive X-Factor: A Sixty-Two-Year-Old Mystery Finally Solved. Washington, DC: The Weston A Price Foundation, 2008.
19. Omenn G, Goodman G, Thornquist M, et al. Risk factors for lung cancer and for intervention effects in CARET, the Beta-Carotene and Retinol Efficacy Trial. J Natl Cancer Inst. 1996;21:1550–9.
20. Weinstock M, Bingham F, Lew R, et al. Topical tretinoin therapy and all-cause mortality. Arch Dermatol. 2009;145:18–24.
21. Wolpowitz D, Gilchrest B. The vitamin D questions: how much do you need and how should you get it? J Am Acad Dermatol. 2006;54:301–17.
22. Schwartz J, Marsh R, Draelos Z. Zinc and skin health: overview of physiology and pharmacology. Dermatol Surg. 2005;31:837–47.
23. Rostan E, DeBuys H, Madey D, Pinnell S. Evidence supporting zinc as an important antioxidant for skin. Int J Dermatol. 2002;41:606–11.
24. Craig W. Health effects of vegan diets. Am J Clin Nutr. 2009;89:1627S–33S.
25. Oakes B, Danks D, Campbell D. Human copper deficiency: ultrastructural studies of the aorta and skin in a child with Menkes' syndrome. Exp Mol Pathol. 1976;25:82–98.
26. Spitz J. Genodermatoses, 2nd edn. New York: Lippincott Williams & Wilkins, 2005:274–327.
27. Ferenci P. Pathophysiology and clinical features of Wilson disease. Metab Brain Dis. 2004;19:229–39.
28. Vinton NE, Dahlstrom KA, Strobel CT, Ament ME. Macrocytosis and pseudoalbinism: manifestations of selenium deficiency. J Pediatr. 1987;111:711–17.
29. Kanekura T, Yotsumoto S, Maeno N, et al. Selenium deficiency: report of a case. Clin Exp Dermatol. 2005;30:346–8.
30. Prendiville JS, Manfredi LN. Skin signs of nutritional disorders. Semin Dermatol. 1992;11:88–97.
31. Beckett G, Arthur J. Selenium and endocrine systems. J Endocrinol. 2005;184:455–65.
32. Gupta M, Gupta A. Dissatisfaction with skin appearance among patients with eating disorders and non-clinical controls. Br J Dermatol. 2001;145:110–13.
33. Glorio R, Allevato M, De Pablo A. Prevalence of cutaneous manifestations in 200 patients with eating disorders. Int J Dermatol. 2000;39:348–53.
34. Maffei M, Halaas J, Ravussin E, et al. Leptin levels in human and rodent: measurement of plasma leptin and OB RNA in obese and weight-reduced subjects. Nat Med. 1995;1:1155–61.
35. Garcia-Hidalgo L, Orozco-Topete R, Gonzalez-Barranco J, et al. Dermatoses in 156 obese adults. Obes Res. 1999;7:299–302.
36. Marreiro D, Fisberg M, Cozzolino S. Zinc nutritional status and its relationships with hyperinsulinemia in obese children and adolescents. Biol Trace Elem Res. 2004;100:137–49.
37. von Drygalski A, Andris D. Anemia after bariatric surgery: more than just iron deficiency. Nutr Clin Pract. 2009;24:217–26.
38. Filippi J, Al-Jaouni R, Wiroth J, et al. Nutritional deficiencies in patients with Crohn's disease in remission. Inflamm Bowel Dis. 2006;12:185–91.
39. Caputo R, Ackerman A, Sison-Torre E. Pediatric Dermatology and Dermatopathology: A Text and Atlas. New York: Lea & Febiger, 1999:65–80.
40. McLaren, D. Skin in protein energy malnutrition. Arch Dermatol. 1987;123:1674–6.

This page intentionally left blank

Scurvy. Hemorrhage beneath the buccal mucosa.

Graft-versus-Host Disease 52

Edward W Cowen

Key features

- Currently, 25 000 allogeneic hematopoietic stem cell transplants (HSCTs) are performed worldwide each year
- Trends in the use of unrelated donors, non-myeloablative conditioning protocols, and donor lymphocyte infusions are impacting the incidence and presentation of graft-versus-host disease (GVHD)
- Acute GVHD is a major complication of allogeneic HSCT; severe skin involvement is associated with a high mortality rate
- Chronic cutaneous GVHD is a polymorphous condition with features resembling lichen planus, lichen sclerosus, morphea and eosinophilic fasciitis
- Chronic cutaneous GVHD is difficult to treat and the aggressiveness of treatment must be balanced against the complications of chronic immunosuppression

INTRODUCTION

Graft-versus-host disease (GVHD) is a multiorgan disease most commonly due to the transfer of foreign donor hematopoietic stem cells into a host recipient via an allogeneic hematopoietic stem cell transplant (HSCT). GVHD may also occur following transfusion of non-irradiated blood products (to immunocompromised hosts) by maternal–fetal transmission or in the setting of solid organ transplantation. Despite several decades of experience with HSCT for a broadening array of disorders (Table 52.1), GVHD remains a treatment dilemma and a significant cause of non-relapse-related morbidity and mortality. Acute GVHD (aGVHD) often presents in a more dramatic fashion and requires prompt diagnosis and treatment. Management of chronic GVHD (cGVHD), particularly in patients who are refractory to first-line therapy, remains challenging.

HISTORY

The first successful allogeneic bone marrow transplant was performed in 1968. Subsequent advances in histocompatibility antigen testing increased safety while establishment of bone marrow donor registries made HSCT accessible to thousands of patients each year who lacked a suitable related donor. However, use of matched unrelated donor (MUD) transplants carries a greater likelihood of a mismatch of minor human leukocyte antigen (HLA) loci compared to matched related donors, which may be partially responsible for the rising incidence of cGVHD. More recently, the use of umbilical cord blood and reduced-intensity conditioning regimens (which raise the age of eligibility) has led to a further increase in the number of transplants.

EPIDEMIOLOGY

Currently, 25 000 allogeneic HSCTs are performed worldwide each year. Although a variety of donor and recipient factors ultimately impact GVHD incidence (Table 52.2), the most important predictor of GVHD remains HLA compatibility between donor and recipient. Approximately 40% of HLA-identical HSCT recipients and 60–70% of HLA-mismatched HSCT recipients will develop GVHD.

Over the past decade, umbilical cord blood and especially peripheral blood have been increasingly utilized as the stem cell source in place of bone marrow. Cord blood transplantation is associated with a

PRIMARY DISORDERS TREATED WITH ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION
Leukemias (e.g. acute myelogenous, acute lymphoblastic > chronic myelogenous, chronic lymphocytic)
Lymphomas (e.g. non-Hodgkin)
Bone marrow failure (e.g. aplastic anemia, dyskeratosis congenita, Fanconi anemia)
High-risk myelodysplasia
Immunodeficiencies (e.g. severe combined immunodeficiency, Griscelli syndrome [type 2], Chédiak–Higashi syndrome, Wiskott-Aldrich syndrome, ataxia–telangiectasia syndrome, chronic granulomatous disease, DiGeorge syndrome, familial hemophagocytic lymphohistiocytosis)
Other myeloproliferative disorders (e.g. myelofibrosis, essential thrombocytosis, polycythemia vera)
Other hematologic disorders (e.g. plasma cell dyscrasias, hypereosinophilic syndrome, paroxysmal nocturnal hemoglobinuria, sickle cell disease, thalassemia)
Metabolic disorders (e.g. fucosidosis, Gaucher disease, mucopolysaccharidoses)
Autoimmune diseases (e.g. ALPS, IPEX syndrome)
Miscellaneous (e.g. congenital erythropoietic porphyria [Günther disease], histiocytoses)

Table 52.1 Primary disorders treated with allogeneic hematopoietic cell transplantation. ALPS, autoimmune lymphoproliferative syndrome; IPEX, immune dysregulation, polyendocrinopathy, X-linked.

RISK FACTORS ASSOCIATED WITH THE DEVELOPMENT OF GRAFT-VERSUS-HOST DISEASE
DONOR
HLA incompatibility with recipient Unrelated to recipient Female (especially multiparous) with male recipient
RECIPIENT
Age (older-aged > middle-aged > pediatric)
STEM CELL SOURCE
Peripheral blood > bone marrow > cord blood T-cell-replete graft
OTHER
Myeloablative conditioning regimen*
*Associated with higher rate of aGVHD compared with non-myeloablative HSCT, but does not affect incidence of cGVHD.

Table 52.2 Risk factors associated with the development of graft-versus-host disease (GVHD). a, acute; c, chronic; HSCT, hematopoietic stem cell transplant.

decreased incidence of GVHD, but higher rates of non-engraftment. In addition, because the number of stem cells present in cord blood is limited, two cord blood units are often required for successful engraftment into an adult recipient. Peripheral blood has clearly emerged as a preferred stem cell source at many major transplant centers. In peripheral blood HSCTs, the donor is treated with a colony-stimulating factor (e.g. filgrastim) which mobilizes the donor stem cells from the marrow into the circulation. Cells are then collected via apheresis and infused into the recipient. Peripheral blood HSCT avoids general anesthesia for the donor and is associated with more rapid engraftment when compared to bone marrow HSCT; however, there is an increased risk of cGVHD[1].

Several other trends in HSCT are also affecting the natural history of GVHD. Removal of donor T cells ("T-cell depletion") prior to transplantation through *ex vivo* graft manipulation (e.g. cell separation), or *in vivo* treatment of the recipient (e.g. antithymocyte globulin, alemtuzumab), significantly decreases the risk of GVHD, but at the expense of increased cancer relapse due to abrogation of donor T-cell graft-versus-tumor (GVT) effect. Recognition of the key role of GVT effect (rather than the conditioning chemotherapy) in cancer remission has also led to the proliferation of non-myeloablative, reduced-intensity conditioning regimens ("mini-transplants"). Although lower doses of chemotherapy and/or radiation are utilized, they are sufficiently immunosuppressive to allow engraftment. This minimizes conditioning-related toxicities (e.g. mucositis) and allows for HSCT in older patients and those with comorbidities. While these regimens appear to decrease the risk of aGVHD, they may also delay the appearance of "classic" aGVHD manifestations. Finally, donor lymphocyte infusions (DLI), administered to the recipient post-HSCT to augment the GVT effect, have altered the traditional timing of both "acute" and "chronic" disease. For

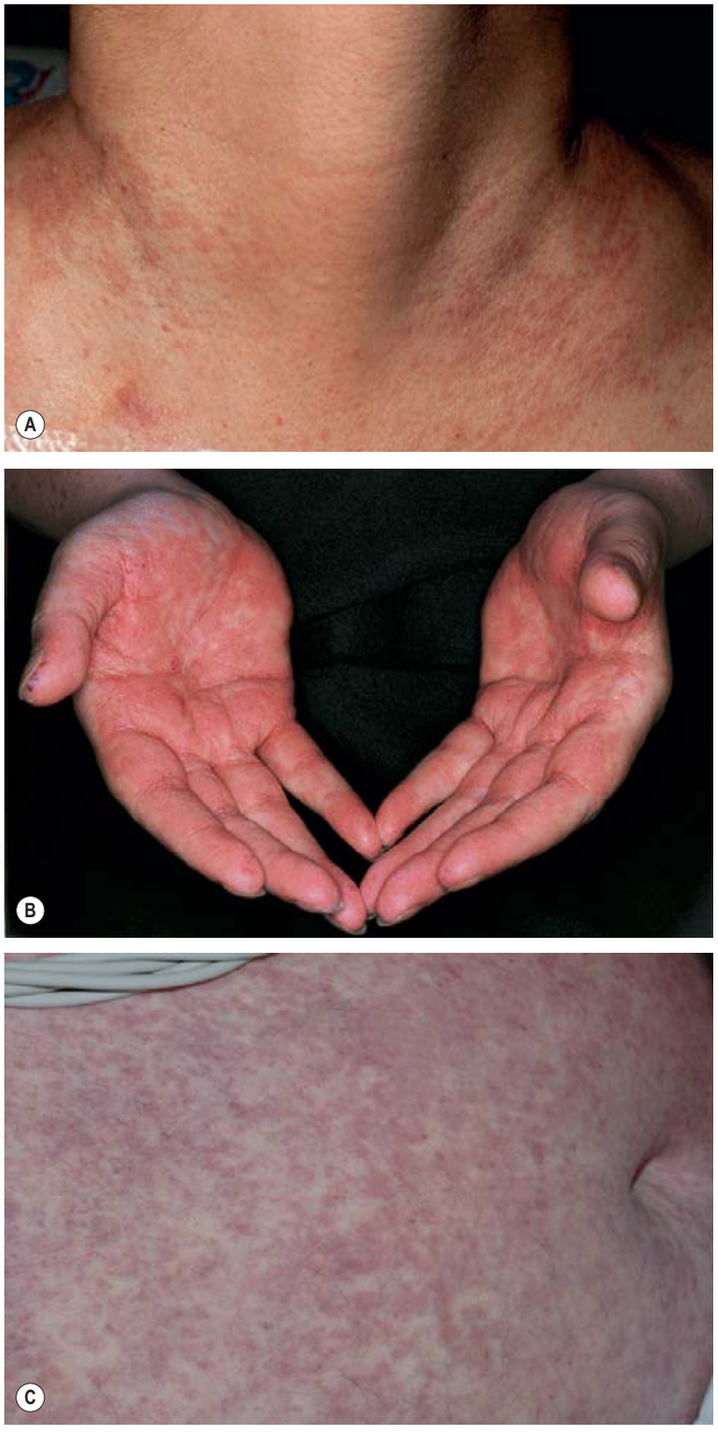


Fig. 52.1 Clinical spectrum of acute cutaneous graft-versus-host disease. A *Stage I* – discrete and coalescing small pink papules on the upper chest and neck of a woman 6 weeks following allogeneic bone marrow transplant. **B, C** *Stage II* – pink macules and papules of the palms that are becoming confluent 14 weeks post allogeneic bone marrow transplant and pink–violet macules and minimally elevated papules on the abdomen in a liver transplant recipient **D** *Stage III* – diffuse erythema with desquamation, but without bullae formation. **E** *Stage IV* – coalescence of bullae plus epidermal necrosis leading to large areas of denudation in a patient who had received an allogeneic bone marrow transplant; note the resemblance to toxic epidermal necrolysis. *B, Courtesy, Dennis Cooper, MD. C, Courtesy, Julie V Schaffer, MD.*

CLINICAL STAGING AND HISTOLOGIC GRADING OF ACUTE GRAFT-VERSUS-HOST DISEASE					
Stage	**Skin**	**Liver**	**Gut**	**Grade**	**Histologic**
1	Erythematous macules and papules, <25% BSA	Bilirubin 2 to <3 mg/dl	Diarrhea, 500–1000 ml/day, or persistent nausea	I	Focal vacuolar change of basal keratinocytes
2	Erythematous macules and papules, 25–50% BSA	Bilirubin 3–6 mg/dl	Diarrhea, 1000–1500 ml/day	II	Grade 1 *plus* necrotic keratinocytes in the epidermis and/or hair follicle and a dermal lymphocytic infiltrate
3	Erythematous macules and papules (>50% BSA) to generalized erythroderma	Bilirubin 6–15 mg/dl	Diarrhea, >1500 ml/day	III	Grade 2 *plus* fusion of basilar vacuoles to form clefts and microvesicles
4	Generalized erythroderma with bulla formation	Bilirubin >15 mg/dl	Severe abdominal pain with or without ileus	IV	Grade 3 *plus* large areas of separation of epidermis from dermis

Table 52.3 Clinical staging and histologic grading of acute graft-versus-host disease (GVHD). Overall, grade 1 GVHD represents stage 1 or 2 cutaneous GVHD but no liver or gut involvement, while grades II–IV require internal involvement. BSA, body surface area.

MUCOCUTANEOUS MANIFESTATIONS OF CHRONIC GRAFT-VERSUS-HOST DISEASE
SKIN
Alopecia
Angiomatous papules
Bullae
Eczema craquelé
Edema
Erythema
Hypo- or hyperpigmentation
Ichthyosis-like
Keratosis pilaris-like
Lichen planus-like (see Fig. 52.2A)
Lichen sclerosus-like (see Fig. 52.2B,C)
Morbilliform (maculopapular)
Morphea-like (see Fig. 52.2D)
Poikiloderma
Scleroderma-like (see Fig. 52.2E)
Sweat impairment
Ulceration
NAILS
Brittleness
Longitudinal ridging or splitting
Onycholysis
Pterygium unguis (dorsal)
SUBCUTANEOUS TISSUE
Fasciitis (see Fig. 52.3)
Panniculitis
ORAL MUCOSA
Erythema
Gingivitis
Keratotic plaques
Lichen planus-like (see Fig. 52.4B)
Mucocele
Mucosal atrophy
Mucositis
Pseudomembranes
Restriction of oral opening from sclerosis
Ulceration
Xerostomia
GENITAL MUCOSA
Lichen planus-like (see Fig. 52.4A)
Vaginal scarring and/or stenosis
Vulvar erosions and/or fissures (see Fig. 52.4C)

Table 52.4 Mucocutaneous manifestations of chronic graft-versus-host disease. Diagnostic features (based on NIH Consensus Criteria[7]) are in bold; the other signs and symptoms listed are not considered sufficient to establish a diagnosis of chronic GVHD without further testing or evidence of other organ system involvement. For involvement of other organs, see text and ref. 7.

instance, DLI may induce classic aGVHD manifestations even when administered after the 100-day time period.

The skin is the most frequently affected organ in both aGVHD and cGVHD. Approximately 80% of patients who develop aGVHD have skin involvement at the time of diagnosis[2]; however, prevalence rates vary dramatically between HSCT protocols, and differentiation of sclerotic versus non-sclerotic features are often not reported, rendering estimates of specific manifestations difficult. In the cGVHD setting, non-sclerotic skin disease generally presents earlier than sclerotic disease. However, neither antecedent aGVHD nor antecedent "lichenoid" skin involvement is a prerequisite to the later development of sclerotic disease. In one institutional review of 270 consecutive patients following HLA-identical HSCT, only 7 (13%) of 53 patients with cGVHD manifested sclerotic features[3]. In contrast, in a review of 110 NIH patients with primarily refractory cGVHD evaluated in a referral setting, sclerotic features were detected in 58 (53%)[4].

PATHOGENESIS

The pathogenesis of aGVHD can be summarized in a three-step process. First, HSCT conditioning and consequent damage to host tissues leads to activation of *host* antigen-presenting cells (APC). Second, *donor* T cells proliferate in response to contact with activated APC. Finally, destruction of target tissues (skin, liver, gastrointestinal tract) occurs via cytotoxic T lymphocytes, natural killer cells, and soluble factors (TNF-α, INF-γ, IL-1, nitric oxide)[5].

By contrast, a clear understanding of cGVHD is still lacking and available murine models recapitulate only select features of human disease (e.g. sclerotic skin involvement, autoantibodies). Alloreactive T cells are again thought to play a central role, but a number of other immune mediators have been increasingly implicated. Many cGVHD manifestations resemble autoimmune disease, suggesting a role for B cells in the disease process. Indeed, rituximab (anti-CD20 antibody) is a beneficial salvage therapy in some patients. B cells appear to prime T cells to minor histocompatibility antigens, and levels of *B*-cell *a*ctivating *f*actor of the TNF *f*amily (BAFF), a marker of B-cell activation, correlate with cGVHD. Multiple autoantibodies are often present in patients with cGVHD, including antinuclear anti-dsDNA, and anti-smooth muscle antibodies, although, to date, they have not been shown to correlate with specific disease manifestations. Recently, activating antibodies against the platelet-derived growth factor receptor (PDGFR) were reported in patients with cGVHD and patients with systemic sclerosis, suggesting that blockage of this profibrotic pathway with agents such as imatinib mesylate may have potential efficacy.

Characterization of immunologic differences between "early" and "late" cGVHD may soon provide important insight into the phenotypic variety of cGVHD. Early-onset cGVHD (3–9 months) is associated with IFN-γ, increased regulatory T cells, and a T-cell cytokine response (IL-2Rα). By contrast, late cGVHD (>9 months) is characterized by lack of a Th2 shift, B-cell activation via soluble BAFF, induction of Toll-like

Fig. 52.2 Clinical spectrum of chronic cutaneous graft-versus-host disease. **A** Lichen planus-like – thin pink–violet papules and plaques with scale, admixed with postinflammatory hyperpigmentation. **B** Lichen sclerosus-like (early) – multiple gray–white thin plaques with obvious wrinkling are present on the mid back. **C** Lichen sclerosus-like (late) – thicker shiny white plaques on the upper back admixed with erosions. **D** Morphea-like (morpheaform) – shiny, hyperpigmented, sclerotic plaque extending circumferentially around the beltline and into the inguinal area. **E** Scleroderma-like (sclerodermoid) – the skin is shiny and bound-down with dyspigmentation, hair loss and multiple erosions; nail loss, small angiomatous nodules and marked reduction in range of motion of the ankles are also present. *B, Courtesy, Dennis Cooper, MD. C, Courtesy Joyce Rico, MD.*

Fig. 52.3 Eosinophilic fasciitis-like presentation of chronic cutaneous graft-versus-host disease. A rippled appearance and irregular nodular texture to the skin is indicative of involvement of subcutaneous tissues; extension of the elbow is limited. Especially in the earlier, more edematous phase, the presence of hypereosinophilia is a clue to the diagnosis.

receptor 9 (TLR9) highly-expressing B cells, and autoantibody formation[6]. Careful definitions of disease states, in particular distinction between sclerotic and non-sclerotic skin manifestations, will be invaluable for validation of this hypothesis.

CLINICAL FEATURES

Acute GVHD

Acute GVHD presents in the skin as a morbilliform exanthem (Fig. 52.1), with an initial predilection for acral areas (e.g. dorsal hands and feet, palms, soles, forearms, ears, as well as the upper trunk). Lesions most commonly appear 4–6 weeks following HSCT despite prophylactic immunosuppressive therapy. Pruritus is variable and a follicular pattern may be observed. Patients may be thrombocytopenic, which can give the eruption a hemorrhagic appearance. The gastrointestinal tract (nausea, voluminous diarrhea, abdominal pain) and the liver (transaminitis, cholestasis, bilirubin elevation) are the two other primary organ systems affected by aGVHD. Together with body surface area of skin involvement, these manifestations are used for staging and grading of disease severity (Table 52.3). Stage IV acute skin disease consists of generalized involvement with bullae formation which may lead to skin sloughing resembling toxic epidermal necrolysis, and it portends a very low likelihood of survival.

Chronic GVHD

In contrast to aGVHD, cGVHD may manifest in nearly any organ system. Skin and mucosal involvement are exceedingly common, and there is remarkable variability in both presentation and severity (Table 52.4). Other sites of involvement include the eyes (keratoconjunctivitis sicca, blepharitis, corneal erosions), salivary glands (sicca syndrome), esophagus (strictures, webs), liver, pancreas (exocrine insufficiency) and lungs (bronchiolitis obliterans).

In the past, differentiation of aGVHD and cGVHD was linked to time of onset following HSCT (≤ or > 100 days); however, this is a somewhat arbitrary distinction and changing HSCT regimens have altered the onset of classic aGVHD and cGVHD manifestations (see above). For instance, features of both aGVHD and cGVHD may occur simultaneously (overlap chronic GVHD), or acute features may first present after day 100 (delayed acute GVHD). The NIH Consensus Project proposed a new classification of cGVHD using organ-specific criteria[7]. "Diagnostic" skin criteria, i.e. those manifestations sufficient to make a clinical diagnosis of cGVHD, are provided in Table 52.4 (bold type). "Distinctive" cGVHD criteria are those which require biopsy confirmation as well as exclusion of other possible etiologies in order for a diagnosis of cGVHD to be established.

The most characteristic manifestation of epidermal cGVHD involvement is reticulate pink to violet papules and plaques with overlying scale, which in some patients resembles lichen planus (LP; Fig. 52.2A). Lesions often initially involve the dorsal aspects of the hands and feet, the forearms and trunk, but they can become widespread. In the past, the term

Fig. 52.4 Orogenital involvement in chronic cutaneous graft-versus-host disease. A, B Lichen planus-like – flat-topped violet papules on the penis and several ulcers on the tongue with a lacy white pattern on the upper vermilion lip and the distal dorsal tongue. **C** Severe erosive disease of the vulva, with nearly total resorption of the labia minora and agglutination of the lips of the clitoral hood. The vulvar introitus is also markedly narrowed.
B, Courtesy, Jean L Bolognia, MD.

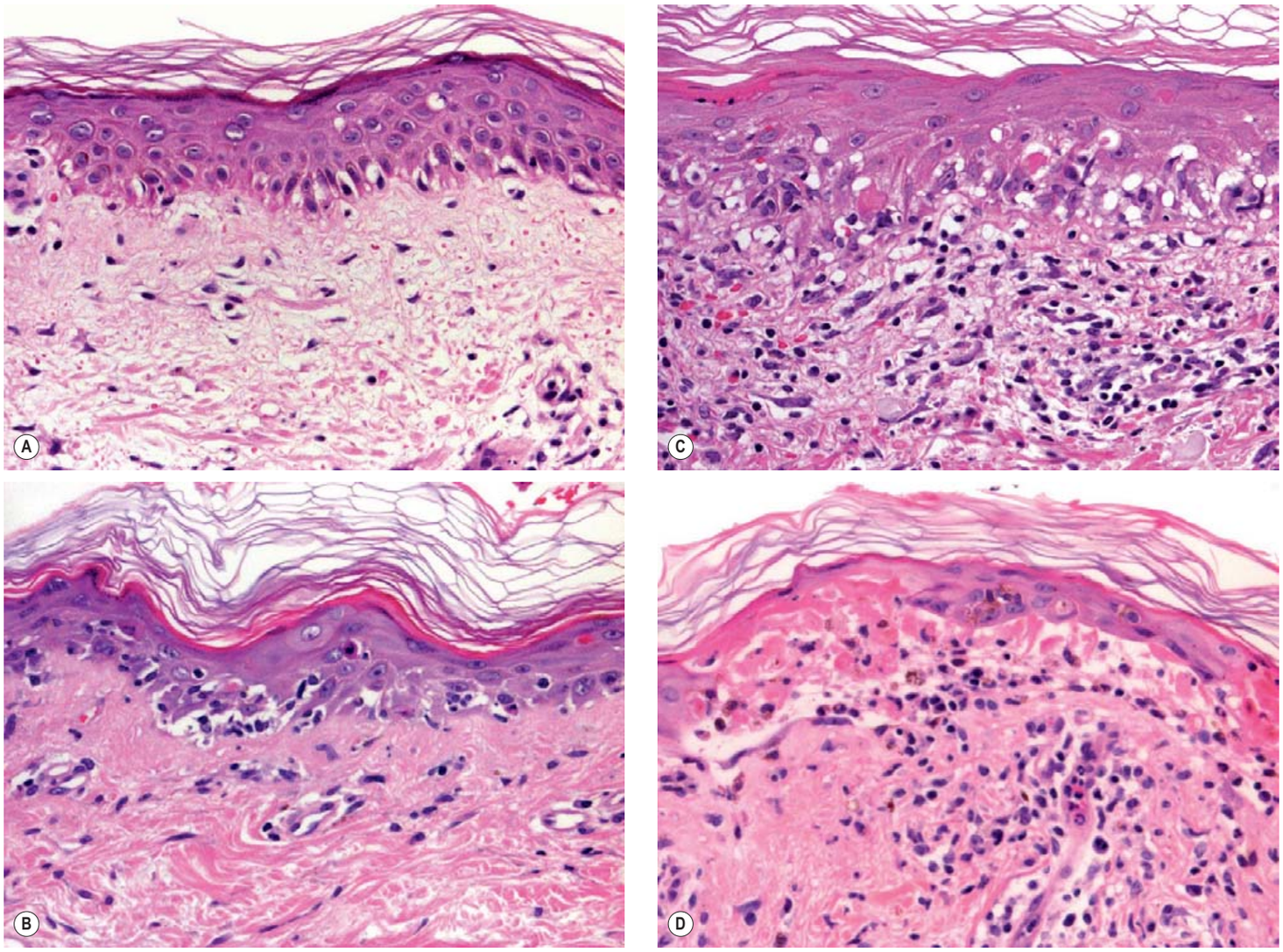


Fig. 52.5 Acute cutaneous graft-versus-host disease – histologic grades. A Grade I – focal vacuolar changes of the basal layer of the epidermis and sparse lymphocytic infiltrate. **B** Grade II – necrosis of keratinocytes and more obvious vacuolar degeneration of the basal layer. **C** Grade III – apoptosis of keratinocytes and blurring of the dermal–epidermal junction due to marked vacuolar degeneration and a lichenoid infiltrate of lymphocytes. **D** Grade IV – full-thickness necrosis of the epidermis with separation of the epidermis from the dermis. Of note, stage I changes are rather nonspecific and are also seen with autoimmune disorders showing the histopathologic pattern of an interface dermatitis (e.g. lupus erythematosus). *Courtesy, Lorenzo Cerroni, MD.*

"lichenoid" was used as a broad term which encompassed this presentation as well as all other non-sclerotic cGVHD skin eruptions. In light of the greater appreciation for the breadth of clinical presentations of cutaneous cGVHD and to utilize more precise diagnostic terminology, the term "lichenoid" should be reserved for histologic description rather than as designation of a GVHD phenotype. In addition to LP-like lesions, psoriasiform plaques, keratosis pilaris-like follicular erythema, a subacute cutaneous LE-like eruption, or poikiloderma may develop. Epidermal cGVHD involvement often leaves a remarkable patterned hyperpigmentation which resolves very slowly over several months.

Similar to the use of "lichenoid", the single designation "sclerodermoid" cGVHD is inadequate to describe the spectrum of sclerotic skin and subcutaneous tissue presentations. Sclerotic involvement includes superficial lichen sclerosus-like plaques, localized or widespread morphea-like involvement, and subcutaneous rippling of the skin with joint contractures resembling eosinophilic fasciitis[8]. Lichen sclerosus-like involvement commonly presents as shiny, wrinkled, gray–white plaques on the upper back (Fig. 52.2B,C); there may be associated follicular plugging. Morphea-like (morpheaform) areas of sclerosis may occur anywhere on the body, but frequently localize to sites of previous skin injury (e.g. port placement sites) as well as areas of friction (e.g. the waistband; Fig. 52.2D). Unlike systemic sclerosis, involvement is more patchy and diffuse symmetric induration with sclerodactyly and pinched facies is rare. Deep-seated fibrosis of the subcutaneous tissue and fascia may present with insidious loss of joint range-of-motion or as nonspecific myalgias and cramping. Subtle rippling of the overlying skin may be present with a firm, nodular texture noted with deep palpation (Fig. 52.3). Linear depressions within sites of fascial involvement (groove sign) demarcate the path of vascular structures or fascial bundles. Longstanding fibrosis may result in skin ulceration, particularly of the legs and frictional surfaces, and the proliferation of benign angiomatous nodules (Fig. 52.2E).

The mucosal surfaces are frequently affected by cGVHD (Fig. 52.4). Oral involvement is second only to skin involvement in disease prevalence. Oral involvement resembles LP with lacy white plaques on the non-attached mucosa, ulceration and gingivitis. Mucocele development is frequently seen. Genital involvement may affect as many as 50% of female patients, but may not be reported by the patient without specific questioning[9]. Symptoms of burning, pruritus and dyspareunia are common. Manifestations range from erythema and fissuring to labial resorption and fusion. Scarring of the vagina may lead to shortening and narrowing of the vaginal canal and risk of hematocolpos in menstruating women.

Nail changes are common and range from thin, brittle nails with distal splitting to anonychia (see Fig. 52.2E). Dorsal pterygium formation can be seen. Additional cutaneous findings include facial milia, nodular fibromas, scarring alopecia, alopecia areata, and vitiligo-like changes.

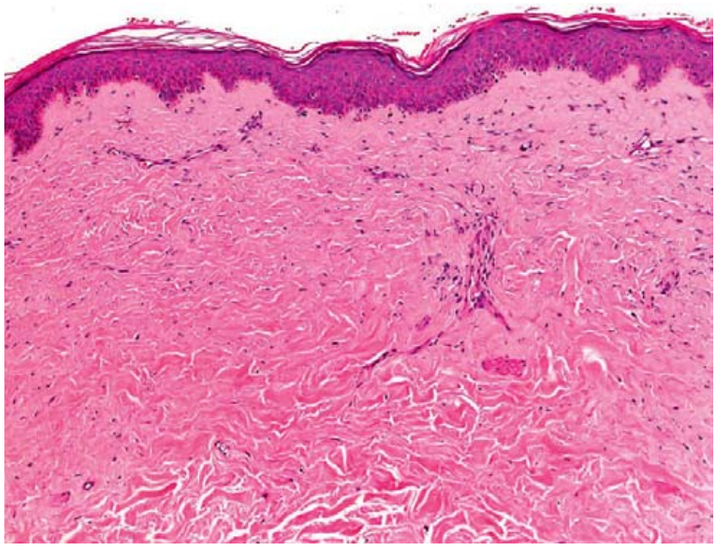


Fig. 52.6 Chronic cutaneous graft-versus-host disease (morpheaform type) – histologic features. There is sclerosis of the dermis with thickening of collagen bundles. These same histologic features can be seen in morphea and systemic sclerosis (scleroderma). Pigmentary incontinence, with a few melanophages within the papillary dermis can also be seen in this form of chronic GVHD. *Courtesy, Lorenzo Cerroni, MD.*

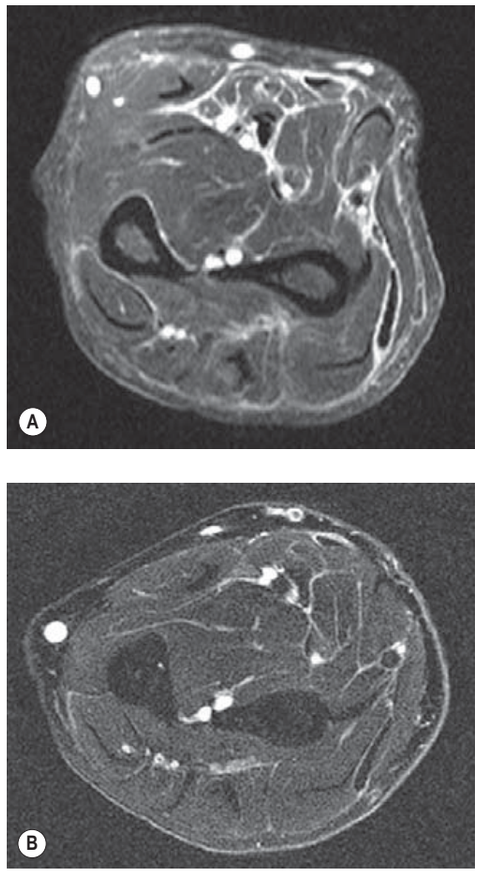


Fig. 52.7 Magnetic resonance imaging of the eosinophilic fasciitis-like presentation of chronic cutaneous graft-versus-host disease. A Prior to treatment (systemic corticosteroids), with a lace-like white pattern representing edema of the fascia. **B** After treatment, with marked diminution of edema. The round white circles represent blood vessels. *Courtesy, Dennis Cooper, MD.*

PATHOLOGY

Histologically, aGVHD is characterized by widespread keratinocyte necrosis, basal layer hydropic degeneration and a band-like lymphohistiocytic infiltrate in the upper dermis (Fig. 52.5); however, skin biopsies obtained shortly after disease onset may display more subtle findings, and early on the features of aGVHD may be limited to the hair follicle. In addition, these histologic features overlap with those of viral exanthems and drug eruptions, making a definitive diagnosis difficult to render in some patients. Because of the mortality associated with acute severe involvement, empiric treatment may be needed despite equivocal histologic results if there is a high level of clinical suspicion, particularly concurrent GI or hepatic manifestations.

The histology of cGVHD reflects the variable skin manifestations of the condition. cGVHD with epidermal involvement may resemble aGVHD with additional features of epidermal orthokeratosis and hypergranulosis. The sclerotic subtypes of cGVHD may have concurrent epidermal features or may just demonstrate fibrosis of the dermis (Fig. 52.6), subcutaneous tissue and/or fascia. While the location and extent of collagen thickening and fibrosis can vary, a panniculitis with thickening of subcutaneous fat septae is often seen. However, for the diagnosis of fasciitis, magnetic resonance imaging can often supplant the need for a deep fascial biopsy procedure (Fig. 52.7).

DIFFERENTIAL DIAGNOSIS

The primary differential diagnosis of aGVHD is a viral or drug exanthem and engraftment syndrome. Engraftment syndrome is a poorly understood phenomenon associated with a nonspecific erythematous skin eruption, fever, and pulmonary edema at the time of neutrophil engraftment; the pulmonary edema is associated with increased levels of B-type natriuretic peptide (BNP). When there is palmoplantar involvement during the first 2–6 weeks following HSCT, the possibility of toxic erythema of chemotherapy should be considered. Because of its clinical variability, the differential diagnosis of cGVHD is much broader, and includes lichenoid drug eruptions, autoimmune connective tissue diseases (lupus, dermatomyositis, morphea, systemic sclerosis), and papulosquamous disorders. Recent reports of transient acantholytic dermatosis[10] and voriconazole-associated photosensitivity[11] misdiagnosed as cGVHD emphasizes the value of biopsy confirmation when non-diagnostic features are encountered[12].

TREATMENT

Acute GVHD

Limited cutaneous aGVHD (without other organ involvement) may initially be managed with topical corticosteroids; however, most patients require systemic corticosteroids. First-line therapy consists of oral prednisone or IV methylprednisolone (1 mg/kg twice daily) and is typically added to ongoing prophylactic GVHD therapy with a systemic calcineurin inhibitor (tacrolimus, cyclosporine). This results in disease control in approximately 50% of patients. Patients who do not respond to corticosteroid therapy are at high risk of mortality, but a number of second-line therapies, including other immunosuppressive agents such as mycophenolate mofetil and TNF-α inhibitors (e.g. etanercept, infliximab), can be tried.

Chronic GVHD

Chronic GVHD continues to be a major therapeutic challenge because no single therapy with proven superiority has emerged. Skin-directed therapies play an important adjunctive role in select patients with cutaneous cGVHD disease. In addition to the severity of skin disease, the rate of symptom progression should be considered when choosing between a topical versus systemic regimen. For local control of the LP-like eruption or pruritus, medium- to high-potency topical corticosteroids and topical calcineurin inhibitors (pimecrolimus, tacrolimus) are appropriate. Unfortunately, topical medications are limited by the percentage of body surface area that is involved and may only provide partial relief. Phototherapy with PUVA, UVB and UVA1 have all shown some benefit in small series, however, controlled trial data are needed. The potential for increased skin malignancies in the setting of concurrent immunosuppressive therapy must also be weighed against the benefit of UV therapy.

As with aGVHD, first-line systemic therapy of cGVHD is systemic corticosteroids, but the dose and duration of treatment is

highly variable. Approximately 50% of cGVHD patients will not respond adequately to corticosteroid therapy, and for this group there is no standard salvage therapy of proven superiority. Options include hydroxychloroquine, mycophenolate mofetil, imatinib mesylate[12a], rituxumab[13], acitretin, basiliximab and extracorporeal photophoresis. In patients with ocular symptoms, site-specific therapies such as special contact lenses can prove very helpful. Referral to physical therapy is recommended when there is evidence of a decrease in the range of motion of joints.

Long term, the importance of sun protection should be emphasized, as patients are typically prescribed one or more photosensitizing agents, including trimethoprim/sulfamethoxazole, levofloxacin and voriconazole. In addition, the latter drug can increase the risk of developing cutaneous malignancies. Patients, especially those with significant photodamage and/or a previous history of cutaneous carcinomas, should be educated regarding skin cancer risk in the setting of immunosuppression, and they should receive regular surveillance for skin cancer.

REFERENCES

1. Pidala J, Anasetti C, Kharfan-Dabaja MA, et al. Decision analysis of peripheral blood versus bone marrow hematopoietic stem cells for allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2009;15:1415–21.
2. Martin PJ, Schoch G, Fisher L, et al. A retrospective analysis of therapy for acute graft-versus-host disease: initial treatment. Blood. 1990;76:1464–72.
3. Chosidow O, Bagot M, Vernant JP, et al. Sclerodermatous chronic graft-versus-host disease. Analysis of seven cases. J Am Acad Dermatol. 1992;26:49–55.
4. Patel AR, Pavletic SZ, Turner ML, Cowen EW. The isomorphic response in morphealike chronic graft-vs-host disease. Arch Dermatol. 2008;144:1229–31.
5. Ferrara JLM, Levine JE, Reddy P, Holler E. Graft-versus-host disease. Lancet. 2009;373:1550–61.
6. Schultz K. Pathophysiology of Chronic Graft-versus-Host Disease: Interdisciplinary Management. Cambridge: Cambridge University Press, 2009.
7. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant. 2005;11:945–56.
8. Schaffer JV, McNiff JM, Seropian S, et al. Lichen sclerosus and eosinophilic fasciitis as manifestations of chronic graft-versus-host disease: expanding the sclerodermoid spectrum. J Am Acad Dermatol. 2005;53:591–601.
9. Zantomio D, Grigg AP, MacGregor L, et al. Female genital tract graft-versus-host disease: incidence, risk factors and recommendations for management. Bone Marrow Transplant. 2006;38:567–72.
10. Bolanos-Meade J, Anders V, Wisell J, et al. Grover's disease after bone marrow transplantation. Biol Blood Marrow Transplant. 2007;13:1116–17.
11. Patel AR, Turner ML, Baird K, et al. Voriconazole-induced phototoxicity masquerading as chronic graft-versus-host disease of the skin in allogeneic hematopoietic cell transplant recipients. Biol Blood Marrow Transplant. 2009;15:370–6.
12. Nishio N, Yagasaki H, Takahashi Y, et al. Engraftment syndrome following allogeneic hematopoietic stem cell transplantation in children. Pediatr Transplant. 2009;13:831–7.

12a. Olivieri A, Locatelli F, Zecca M, et al. Imatinib for refractory chronic graft-versus-host disease with fibrotic features. Blood. 2009;114:709–18.

13. Cutler C, Miklos D, Kim HT, et al. Rituximab for steroid-refractory chronic graft-versus-host disease. Blood. 2006;108:756–62.

Chronic GVHD. A Lacy white pattern on the mucosal surface of the lower lip in the lichenoid form. Note the Beau's lines of the fingernails reflecting the time of the transplant. **B** Morpheaform plaque with a healing ulceration on the shoulder in the sclerodermoid form.

	Sclerotic-type cGVHD	Systemic sclerosis
Autoantibodies	Variable, non-specific	Yes, associated with specific clinical subtypes
Cardiac involvement	Rare	Yes, conduction system abnormalities
GI dysmotility/strictures	Yes	Yes
Pulmonary hypertension	No	Yes
Pulmonary fibrosis	Yes*	Yes
Renal disease	Rare, nephrotic syndrome	Yes, scleroderma renal crises (in diffuse subtype)
Raynaud's disease	Rare	Yes
Sclerodactyly	Rare	Yes
Skin manifestations		
Fibrosis	Dermis, subcutaneous tissue, and/or fascia	Dermis
Natural history	Patchy involvement, variable course	Symmetric, acral to proximal progression
Facial involvement	Rare, usually patchy involvement	Common, diffuse skin tightening (scleroderma facies)

*In setting of bronchiolitis obliterans

Comparison of clinical and laboratory features of sclerotic-type cGVHD and systemic sclerosis

PATIENT HANDOUT General dermatologic recommendations for patients with cutaneous graft-versus-host disease (GVHD).

Dry skin and pruritus
Use moisturizing, non-scented soaps
Apply emollients frequently, in particular ointments and thicker creams
Avoid tight-fitting or abrasive clothing; wear cool, breathable fabrics
Avoid antihistamines if there is dryness of the eyes or mouth (sicca syndrome)

Nail dystrophy
Keep nails trimmed or filed to prevent breakage and pain
A clear nail lacquer can be used as a nail hardener

Signs of skin sclerosis (hardening)
Early signs of skin sclerosis (hardening) include darkening or tightening of the skin at the waistband or bra line, rippling or dimpling of the skin, and decreased joint range of motion of joints

Skin ulcers
Sites where there is breakdown of the skin serve as potential sites where bacteria can enter the body; these areas need to be kept clean and covered

Recommendations regarding sun exposure and skin cancer
The risk of skin cancer is increased in patients with GVHD, and the risk is potentiated by iatrogenic immunosuppression and/or phototherapy (e.g. UVB, PUVA)
Exposure to ultraviolet radiation (UVR) may also induce a flare of GVHD or exacerbate drug-induced photosensitivity
Several of the frequently prescribed medications can increase sun sensitivity; they include sulfamethoxasole/trimethoprim (Septra®, Bactrim®) and voriconazole (Vorinastat®)
If possible, avoid outdoor activities during peak hours of UVR (10am-4pm)
Apply broad-spectrum sunblock on sun-exposed sites on a regular basis
Use a broad-brimmed hat and protective clothing; consider using a laundry additive that increases the UV protective factor of clothing (e.g. Sun Guard™)
Perform self-skin examination on a regular basis

Residual dyspigmentation from chronic cutaneous graft-versus-host disease (GVHD). Extensive hyper- and hypopigmentation in an African-American child with a history of epidermal involvement of cGVHD.

Lichen sclerosus-like chronic cutaneous graft-versus-host disease. Gray-white ovoid plaques on the back.

Dermatologic Manifestations in Patients with Systemic Disease

53

Kathryn Schwarzenberger and Jeffrey P Callen

Chapter Contents

Cutaneous rheumatology *761*
Cutaneous hematology and oncology *763*
Cutaneous endocrinology and metabolic disease *768*
Cutaneous gastroenterology *771*

Key features

- Cutaneous manifestations of systemic disease are frequently encountered in the practice of medicine
- Dermatologic disease may be the initial sign of an internal disease
- Skin disease may complicate therapy directed at internal disorders

Dermatologic disease is frequently associated with internal manifestations[1,2], and there are many cutaneous disorders that are traditionally associated with systemic disease, e.g. the autoimmune connective tissue diseases and sarcoidosis. In addition, most endocrinopathies have dermatologic manifestations, as do many infectious diseases. When one begins to closely examine many of the disorders that are discussed elsewhere in this text, it becomes clear that isolated dermatologic disease is relatively uncommon. Many of the conditions have associated systemic manifestations, the potential for such manifestations, or the potential to be treated with drugs that have systemic implications. Therefore, a detailed review of all dermatologic signs of internal disease is beyond the scope of this chapter. Rather, some of the disorders will be discussed specifically, while many others will be reviewed via the use of tables that present an overview of data relevant to these topics. The approach utilized is by organ system.

CUTANEOUS RHEUMATOLOGY

Topics traditionally included as cutaneous rheumatology[3] are as follows: lupus erythematosus (Ch. 41); dermatomyositis (Ch. 42); scleroderma, Raynaud's phenomenon, and related conditions (Ch. 43); vasculitides (Ch. 24); and miscellaneous disorders. Miscellaneous disorders usually include: rheumatoid arthritis (Ch. 45), pyoderma gangrenosum (Ch. 26), psoriatic arthritis (Ch. 8), Behçet's disease (Ch. 26), Sweet's syndrome (Ch. 26), bowel-associated dermatosis–arthritis syndrome (Ch. 26), reactive arthritis (formerly Reiter's disease) (Ch. 8), Kawasaki disease (Ch. 81), and relapsing polychondritis (Ch. 45).

Cutaneous conditions reported in patients with rheumatoid arthritis are summarized in Table 53.1 (Figs 53.1–53.6)[4,5]. Dermatologists should be particularly careful in this group of patients to couple laboratory evaluation with a complete cutaneous examination, including all mucosal surfaces, nails and nail folds, hair, and the entire cutaneous surface. Clinical criteria are published for the diagnosis of many of these disorders; dermatologists should be familiar with the criteria and should incorporate them into a focused, thorough history, including relevant negatives. It is very helpful to think of the clinicopathologic basis and pathogenesis of lesions. For example, in patients with systemic lupus erythematosus, photodistributed lesions with an interface histopathology, i.e. discoid lesions, subacute lesions and poikilodermatous lesions, have different implications and are treated differently than vessel-based lesions, such as those due to small or larger vessel vasculitis.

Sjögren's syndrome is characterized by the occurrence of keratoconjunctivitis sicca and xerostomia in association with an autoimmune disorder. Frequently, the skin can be involved in primary Sjögren's syndrome with vascular inflammation (e.g. small vessel vasculitis, hypergammaglobulinemic purpura) even before the clinical diagnosis has been made. Some patients from the Far East, including Japan and the Philippines, have been described with what has been called the

CUTANEOUS CONDITIONS ASSOCIATED WITH RHEUMATOID ARTHRITIS	
PALISADING GRANULOMAS	
• Rheumatoid nodules • Palisaded neutrophilic and granulomatous dermatitis – Rheumatoid papules (Fig. 53.1) – Interstitial granulomatous dermatitis (with plaques or cutaneous cords; Fig. 53.2) – Superficial ulcerating rheumatoid necrobiosis (Fig. 53.3)	
VASCULAR REACTIONS	
• Pigmented purpuric eruptions (capillaritis) • Bywater's lesions (purpuric papules of the distal digits due to small vessel vasculitis; Fig. 53.4) • Small, medium-sized and large vessel vasculitis • Erythema elevatum diutinum • Intravascular or intralymphatic histiocytosis (erythema, induration and papules in a reticular pattern overlying swollen joints, most often the elbows)	
NEUTROPHILIC DERMATOSES	
• Pyoderma gangrenosum • Rheumatoid neutrophilic dermatitis (rheumatoid neutrophilic dermatosis) • Sweet's syndrome • Pyoderma gangrenosum-like leg ulcers in Felty's syndrome • Neutrophilic lobular panniculitis	
COMPLICATIONS OF THERAPIES FOR RHEUMATOID ARTHRITIS	
• NSAIDs (naproxen, oxaprozin and others)	• Pseudoporphyria (Fig. 53.5) • Toxic epidermal necrolysis
• Penicillamine	• Pemphigus • Lichenoid drug reaction • Elastosis perforans serpiginosa • Pseudoxanthoma elasticum-like changes
• Gold	• Pityriasis rosea-like eruption • Lichenoid drug reaction
• Methotrexate	• Accelerated nodulosis* – most often on the hands; rarely involves heart & lung • Methotrexate-induced papular eruption – favors extremities
• Tumor necrosis factor-α inhibitors (see Ch. 128)	• Local injection site reaction (etanercept, adalimumab, golimumab) • Urticaria, angioedema, anaphylaxis (infliximab > adalimumab) • Urticarial eruption • Vasculitis (small or larger vessel vasculitis) • Interstitial granulomatous dermatitis • Lupus erythematosus – systemic or cutaneous (Fig. 53.6) • New-onset psoriasiform eruption and palmoplantar pustulosis (see Ch. 21) • Accelerated nodulosis* • Dermatomyositis
*Also referred to as accelerated rheumatoid nodulosis and accelerated cutaneous nodulosis.	

Table 53.1 Cutaneous conditions associated with rheumatoid arthritis. An evanescent erythematous eruption and persistent plaques also can develop in patients with Still's disease (see Ch. 45).

Fig. 53.1 Rheumatoid papules. Multiple red–brown papules, some with scale-crust, on the lower extremity. This entity is within the spectrum of palisaded neutrophilic and granulomatous dermatitis (see Table 53.1).

Fig. 53.2 Annular variant of interstitial granulomatous dermatitis (IGD). This clinical presentation with annular plaques on the medial thighs is often seen in the setting of rheumatoid arthritis. Of note, IGD has also been implicated as a side effect of medications, including calcium channel blockers , TNF-α inhibitors, and HMG-CoA reductase inhibitors ("statins").

Fig. 53.3 Superficial ulcerating rheumatoid necrobiosis. Shiny, yellow plaques with red–brown edges and areas of ulceration that clinically resemble necrobiosis lipoidica. This patient had active rheumatoid vasculitis.

Fig. 53.4 Bywater's lesions. Tender, purpuric papules on the distal fingers in a patient with rheumatoid vasculitis. Histologically, leukocytoclastic vasculitis is seen.

Fig. 53.5 Pseudoporphyria in a patient with rheumatoid arthritis. The cause was a nonsteroidal anti-inflammatory drug. *Courtesy, Kalman Watsky, MD.*

Fig. 53.6 Annular lupus-like lesions in a patient receiving etanercept. This is a potential side effect of the entire group of tumor necrosis factor-α inhibitors.

"annular erythema of Sjögren's syndrome". The original descriptions suggested that this was a distinct entity; however, we now believe that this represents a form of subacute cutaneous lupus erythematosus, and that it might be better classified as a form of secondary Sjögren's syndrome. Secondary Sjögren's syndrome may also occur in patients with other rheumatologic diseases, including rheumatoid arthritis, dermatomyositis and scleroderma. It is necessary to remember that the diagnosis of Sjögren's syndrome is a diagnosis of exclusion, and that it must be differentiated from conditions that might cause xerostomia/xerophthalmia, including GVHD, sarcoidosis, hepatitis C viral infection, and HIV disease.

CUTANEOUS HEMATOLOGY AND ONCOLOGY

Disorders of interest to the dermatologist and to hematologists or oncologists are also well covered in the following chapters of this textbook: metastatic disease (Ch. 122), leukemia/lymphoma (Chs 119–121), dysproteinemias (Ch. 119), histiocytoses (Ch. 91), vascular neoplasms (Ch. 114), cutaneous T-cell lymphoma (Ch. 120), pigmented lesions (Chs 112 & 113), and cutaneous reactions to chemotherapeutic agents (Ch. 21).

Skin signs of internal malignancy are summarized in Tables 53.2 and 53.3. Table 53.2 summarizes the criteria for the association of dermatoses and neoplasia that were first proposed by Helen O Curth, and Table 53.3 represents the application of these criteria to some of the specific associations (Figs 53.7–53.12)[6–10]. The use of "Curth's criteria" is important to establish whether a given criterion is a chance occurrence or truly a malignancy-associated event. In addition, an eczematous or psoriasiform plaque of the nipple and surrounding skin can be seen in Paget's disease due to epidermal extension of an underlying ductal adenocarcinoma of the breast (Fig. 53.13). While extramammary Paget's disease (EMPD) most commonly represents a primary intraepithelial adenocarcinoma (>75% of patients; Fig. 53.14), secondary EMPD can be due to an underlying visceral malignancy, e.g. colon, bladder.

Acanthosis nigricans is characterized by velvety hyperpigmentation of the intertriginous surfaces and, less often, extensor surfaces. Although this disorder is traditionally associated with internal malignancy (most frequently gastric adenocarcinoma), it is more often associated with an endocrinopathy, particularly insulin resistance[11] (Figs 53.15 & 53.16). The areas most often affected are the neck and axillae, but any fold, including that of the lower lip and chin, can be affected. Malignancy-associated acanthosis nigricans is usually rapid in onset and may be accompanied by skin tags, multiple seborrheic keratoses or tripe palms. The patients may even manifest changes on the lips, and weight loss is common. In contrast, acanthosis nigricans associated with endocrine dysfunction is more insidious in its onset, is less widespread, and the patients are often overweight or obese. In either instance, there are probably one or more circulating factors that stimulate the epidermal proliferation (i.e. papillomatosis) that is observed histopathologically. An approach to the patient with acanthosis nigricans in outlined in Figure 53.17. Treatment of the underlying malignancy, or effective treatment of the endocrinopathy, including weight loss and insulin sensitizers, will often result in improvement or disappearance of the acanthosis nigricans. Recurrence of malignancy-associated acanthosis nigricans requires a search for recurrent cancer.

CRITERIA USED TO ASSOCIATE A DERMATOSIS AND MALIGNANCY (CURTH'S POSTULATES)	
Concurrent onset	The neoplasm is discovered at the time of diagnosis of the dermatosis, or shortly following diagnosis
Parallel course	Therapy of the malignancy results in disappearance of the dermatosis, and, if the malignancy recurs, then the dermatosis relapses
Uniform site or type of neoplasm	The neoplasm is of a specific cell type within a specific organ or tissue
Statistical association	
Genetic linkage	

Table 53.2 Criteria used to associate a dermatosis and malignancy (Curth's postulates).

Fig. 53.7 Bazex syndrome (acrokeratosis paraneoplastica). The patient had a squamous cell carcinoma of the tonsillar pillar.

Fig. 53.8 Erythema gyratum repens. This patient had cancer of the breast.

Fig. 53.9 Paraneoplastic pemphigus. This patient had no history of malignancy, nor was one discovered with careful assessment, yet he had clinical features and immunopathologic confirmation for this immunobullous disorder.

PARANEOPLASTIC DERMATOSES		
Dermatoses	**Cutaneous findings**	**Comments**
DISORDERS THAT ARE ASSOCIATED WITH CANCER IN MOST OR ALL CASES		
Bazex syndrome (acrokeratosis paraneoplastica)	Acral psoriasiform plaques, typically with involvement of the nose and helices; often the lesions are violaceous (Fig. 53.7). Longitudinal and horizontal ridging of the nails occurs in 75% of patients	By definition, this condition is linked to malignancy, generally occurring in the upper aerodigestive tract (pharynx, larynx or esophagus)
Carcinoid syndrome	Flushing and erythema of the head and neck. Pellagra-like dermatitis and sclerodermoid changes may develop in advanced disease	Flushing associated with ~10% of mid-gut tumors (small intestine, appendix, proximal colon) and liver metastases are required; type III gastric and bronchial carcinoid tumors are also associated with flushing (liver metastases are not required)
Erythema gyratum repens	Concentric erythematous lesions, often giving the appearance of grains of wood (Fig. 53.8; see Ch. 19)	Variable sites and types of malignancy
Acquired hypertrichosis lanuginosa (malignant down)	Growth of fine lanugo hairs in a generalized distribution or localized to the face. With time, these hairs may become coarser (see Ch. 70)	Associated with a variety of internal malignancies, most often carcinoma of the lung, colon or breast
AESOP syndrome	Large red to violet–brown patch	Patch overlies a plasmacytoma
Ectopic adrenocorticotropic hormone (ACTH) syndrome	Generalized hyperpigmentation	Production of ACTH by a tumor (often a small cell carcinoma of the lung) may result in hyperpigmentation and features of Cushing's syndrome
Glucagonoma syndrome	Necrolytic migratory erythema, angular cheilitis, glossitis	Due to a glucagon-secreting tumor of the pancreas. Patients are often treated for intertrigo before the syndrome is diagnosed. Weight loss and diabetes mellitus accompany the dermatosis
Paraneoplastic pemphigus	Erosive disease of the mucous membranes (Fig. 53.9) and erythema multiforme-like, bullous pemphigoid-like or lichenoid skin lesions (see Ch. 29)	Most often associated with non-Hodgkin lymphoma, chronic lymphocytic leukemia or Castleman's disease (with the latter accounting for the majority of cases in children and Asian populations). Castleman's tumors have been shown to produce the autoantibodies responsible for paraneoplastic pemphigus, and their resection can lead to remission of mucocutaneous lesions. Bronchiolitis obliterans is a common complication
POEMS syndrome (*p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *M*-protein and *s*kin changes)	Although the glomeruloid hemangioma (Fig. 53.10) is considered to be pathognomonic, it is present in a minority of patients. Other skin findings include cherry angiomas, hyperpigmentation, hypertrichosis, sclerodermatous thickening, hyperhidrosis, digital clubbing, plethora, acrocyanosis and leukonychia	Osteosclerotic myeloma, Castleman's disease and plasmacytomas have been reported in patients with POEMS. In addition to the findings designated in the acronym, patients may have peripheral edema, ascites, pulmonary effusions, papilledema, thrombocytosis, polycythemia and increased serum levels of VEGF
Sign of Leser-Trélat	Rapid appearance or growth of multiple seborrheic keratoses; keratoses may be inflamed	Often these patients have acanthosis nigricans and generalized pruritus. Controversy continues regarding the existence of this sign in the absence of generalized pruritus and acanthosis nigricans, in part because determining whether seborrheic keratoses are eruptive can be difficult. Eruptive seborrheic keratoses can also develop in erythrodermic patients who do not have an underlying malignancy
Tripe palms	Ridged velvety lesions on the palms	May or may not be accompanied by acanthosis nigricans
DISORDERS THAT ARE STRONGLY ASSOCIATED WITH CANCER IN A SUBSET OF CASES		
Acanthosis nigricans	Rapid onset of hyperpigmented velvety changes of the flexural surfaces (e.g. neck, axillae and groin). May also involve extensor surfaces (e.g. elbows, knees and knuckles) and, in malignancy-associated cases, the lips, oral mucosa and palms (see above, tripe palms). Glossitis is also frequently present in malignancy-associated acanthosis nigricans	Association with adenocarcinoma of the stomach or other sites within the GI or GU tracts; in this setting, acanthosis nigricans is often accompanied by weight loss. Acanthosis nigricans is more commonly associated with endocrinologic abnormalities, particularly insulin resistance (Figs 53.15 & 53.16); such patients are typically overweight, and the onset of the condition is usually insidious
Anti-epiligrin cicatricial pemphigoid (AECP)*	Oral ulcerations, conjunctival erosions and scarring. Tense blisters and erosions of the skin may also develop	Roughly one-third of patients with AECP have or develop cancer within the first year following diagnosis. The cancer is usually an adenocarcinoma and is often at an advanced stage at the time of diagnosis, possibly accounting for the high mortality rate of AECP
Dermatomyositis (adult)*	Heliotrope, Gottron's papules, photodistributed poikiloderma, nailfold overgrowth with dilated capillary loops, pruritic diffuse scaly alopecia of the scalp (see Ch. 42)	Population-based studies demonstrate an over-representation of ovarian, lung, colorectal and pancreatic carcinomas and non-Hodgkin lymphoma in Caucasians
Neutrophilic dermatoses	Sweet's syndrome (Fig. 53.11) or pyoderma gangrenosum (particularly the atypical bullous form) (see Ch. 26)	Approximately 10–20% of cases are associated with hematologic disorders such as acute myelogenous leukemia or plasma cell dyscrasia (IgA). Underlying solid tumors are rare

Table 53.3 Paraneoplastic dermatoses. AESOP syndrome – *a*denopathy, *e*xtensive *s*kin patch *o*verlying (a) *p*lasmacytoma. GI, gastrointestinal; GU, genitourinary; VEGF, vascular endothelial growth factor. *Statistical association.

Continued

PARANEOPLASTIC DERMATOSES		
Dermatoses	**Cutaneous findings**	**Comments**
DERMATOSES THAT MAY BE ASSOCIATED WITH CANCER IN A SUBSET OF PATIENTS		
Acquired angioedema due to C1 esterase inhibitor dysfunction	Acquired angioedema without associated wheals	Associated with B-cell lymphoproliferative disorders, including lymphomas, as well as monoclonal gammopathy of undetermined significance (MGUS)
Acquired ichthyosis	Resembles ichthyosis vulgaris; most often located on the legs	Lymphoma typically predates the diagnosis of the ichthyosis
Amyloidosis, primary systemic	Waxy, translucent or purpuric papules; periorbital and pinch purpura; macroglossia	Monoclonal gammopathy due to plasma cell dyscrasia >> multiple myeloma; deposits composed of immunoglobulin light chain (AL)
Cryoglobulinemia, type I	Retiform purpura and necrosis that favors cooler acral sites; acral cyanosis; livedo reticularis	Monoclonal gammopathy due to lymphoplasmocytic disorders
Cutaneous small vessel vasculitis	Palpable purpura	Less than 1% of patients with vasculitis have an associated malignancy, most commonly hairy cell leukemia and chronic lymphocytic leukemia
Dermatitis herpetiformis (DH)	Pruritic erosions and blisters on extensor surfaces, scalp and/or buttocks	Through the association of DH with gluten-sensitive enteropathy, enteropathy-associated T-cell lymphoma occasionally occurs
Exfoliative erythroderma	Diffuse, scaly, erythematous skin	May be associated with cutaneous T-cell lymphoma or, occasionally, with a systemic lymphoma or leukemia
Juvenile xanthogranulomas (JXGs) in the setting of neurofibromatosis 1 (NF1)	Pink–yellow to red–brown, dome-shaped papules and nodules, most often located on the head and neck	A triple association between JXGs, NF1 and JMML has been described
Multicentric reticulohistiocytosis	Nodular lesions, most often on the dorsal aspects of the hands (Fig. 53.12)	A variety of associated malignancies have been reported, developing in approximately one-quarter of adult patients
Mycosis fungoides	Patch, plaque or nodular disease	Some studies have demonstrated an increased risk of second malignancies
Necrobiotic xanthogranuloma	Indurated xanthomatous plaques with necrosis and ulceration, usually in a periorbital location	Paraproteinemia (>80% of cases, most often IgG with κ light chains); multiple myeloma or a lymphoproliferative disorder develop in a minority of patients
Normolipemic plane xanthoma	Yellowish patches and thin plaques that favor the skin folds, upper trunk and periorbital area	Paraproteinemia, due to a plasma cell dyscrasia or lymphoproliferative disorder
Porphyria cutanea tarda (PCT)	Erosions, blisters and scars on the dorsal aspect of the hands, hyperpigmentation, hypertrichosis, milia	Through its association with hepatitis C virus, PCT may also be associated with primary hepatocellular carcinoma (hepatoma)
Schnitzler's syndrome	Chronic urticaria	Associated with an IgM κ paraproteinemia; lymphoplasmacytic malignancies develop in approximately 15% of patients. Additional manifestations include fevers, arthralgias and bone pain
Scleromyxedema	Sclerodermoid induration and a widespread eruption of firm, waxy papules arranged in linear arrays	Almost always associated with paraproteinemia (usually IgG with λ light chains); multiple myeloma develops in <10% of cases
DERMATOSES THAT HAVE BEEN PROVEN NOT TO BE ASSOCIATED WITH CANCER		
Bowen's disease	Erythematous scaly plaque	The results of early studies that suggested an association with internal malignancy were likely explained by arsenic exposure in affected individuals and have not been replicated
FAMILIAL CANCER SYNDROMES AND THE SKIN		
• Cowden disease (breast, thyroid and GI carcinomas), Muir–Torre syndrome (GI carcinoma), Gardner syndrome (GI carcinoma), Peutz–Jeghers syndrome (various malignancies) – see Table 53.11 • Costello syndrome (rhabdomyosarcoma, bladder carcinoma), Werner syndrome (sarcomas and other malignancies) – see Table 53.13 • Birt–Hogg–Dubé syndrome, familial cutaneous leiomyomatosis (renal carcinoma) – see Table 53.14 • Howel–Evans syndrome (esophageal carcinoma) – see Ch. 58 • Ataxia–telangiectasia (leukemia, lymphoma, breast cancer) – see Ch. 60 • Neurofibromatosis (malignant peripheral nerve sheath tumors, JMML, rhabdomyosarcoma, pheochromocytoma, carcinoid), tuberous sclerosis (renal carcinoma) – see Ch. 61 • Multiple endocrine neoplasia syndromes – see Table 63.2 • Dyskeratosis congenita (leukemia, Hodgkin disease) – see Ch. 67 • Nevoid basal cell carcinoma syndrome (medulloblastoma, fibrosarcoma) – see Table 108.5 • Bloom syndrome (lymphoproliferative and GI malignancies), Rothmund–Thomson syndrome (osteosarcoma), xeroderma pigmentosum (sarcomas, leukemia, GI and lung carcinomas) – see Table 87.4 • Familial atypical mole and multiple melanoma syndrome (pancreatic carcinoma in a subset) – see Ch. 113		

Table 53.3 Paraneoplastic dermatoses (cont'd). GI, gastrointestinal; JMML, juvenile myelomonocytic leukemia.

Fig. 53.10 POEMS syndrome. This patient had multiple angiomas on his trunk as well as his face and scalp. All the angiomas that were examined histologically were glomeruloid hemangiomas. In addition, he reported a recent 10 lb weight loss, impotence and fatigue, and was found to have a neuropathy, adult-onset diabetes, hypothyroidism and peripheral edema. His underlying disorder was an osteosclerotic myeloma.

Fig. 53.11 Acute febrile neutrophilic dermatosis (Sweet's syndrome) associated with acute myelogenous leukemia. The hemorrhagic component is secondary to severe thrombocytopenia.

Fig. 53.12 Multicentric reticulohistiocytosis. Multiple nodules are present on the dorsal hands in this adolescent. This patient did not have a malignancy.

Fig. 53.13 Paget's disease of the breast. A chronic, erythematous plaque surrounds the nipple. *Courtesy, Robert Hartman, MD.*

Fig. 53.14 Extramammary Paget's disease. Note the well-demarcated border of the erythematous plaque. The patient had no underlying internal malignancy.

Fig. 53.15 Acanthosis nigricans and acrochordons of the neck in a patient with insulin resistance and obesity. Note the velvety texture of the skin.

Fig. 53.16 Acanthosis nigricans over the knuckles in a patient with insulin resistance and obesity. Acanthosis nigricans can involve extensor surfaces as well as flexural areas. *Courtesy, Jean L Bolognia, MD.*

The glucagonoma syndrome is characterized by the development of necrolytic migratory erythema, adult-onset diabetes mellitus, weight loss and glossitis. These patients also are frequently anemic, and may have alterations of their personality. Skin lesions of necrolytic migratory erythema are eroded, erythematous patches and plaques that characteristically involve intertriginous areas, the face (especially around the mouth), and distal extremities. Blisters may occur and lead to erythematous erosions. The eruption, which can be painful or pruritic, remits and recurs over the course of several weeks to months. It is frequently misdiagnosed as intertrigo or as seborrheic dermatitis.

Biopsy specimens reveal characteristic features of an abrupt necrolysis of the upper epidermis. Most, but not all, patients have a glucagon-secreting tumor of the pancreas. There have been patients with zinc deficiency, fatty acid deficiency, or biotin deficiency who have developed similar cutaneous findings (see Ch. 51). An occasional patient has had severe liver disease and necrolytic migratory erythema-like lesions. Effective treatment of the tumor will result in a disappearance of the disease, or, in the case of necrolytic migratory erythema associated with a deficiency state, replacement therapy will lead to resolution of the cutaneous findings. The differential diagnosis includes necrolytic acral erythema (see below).

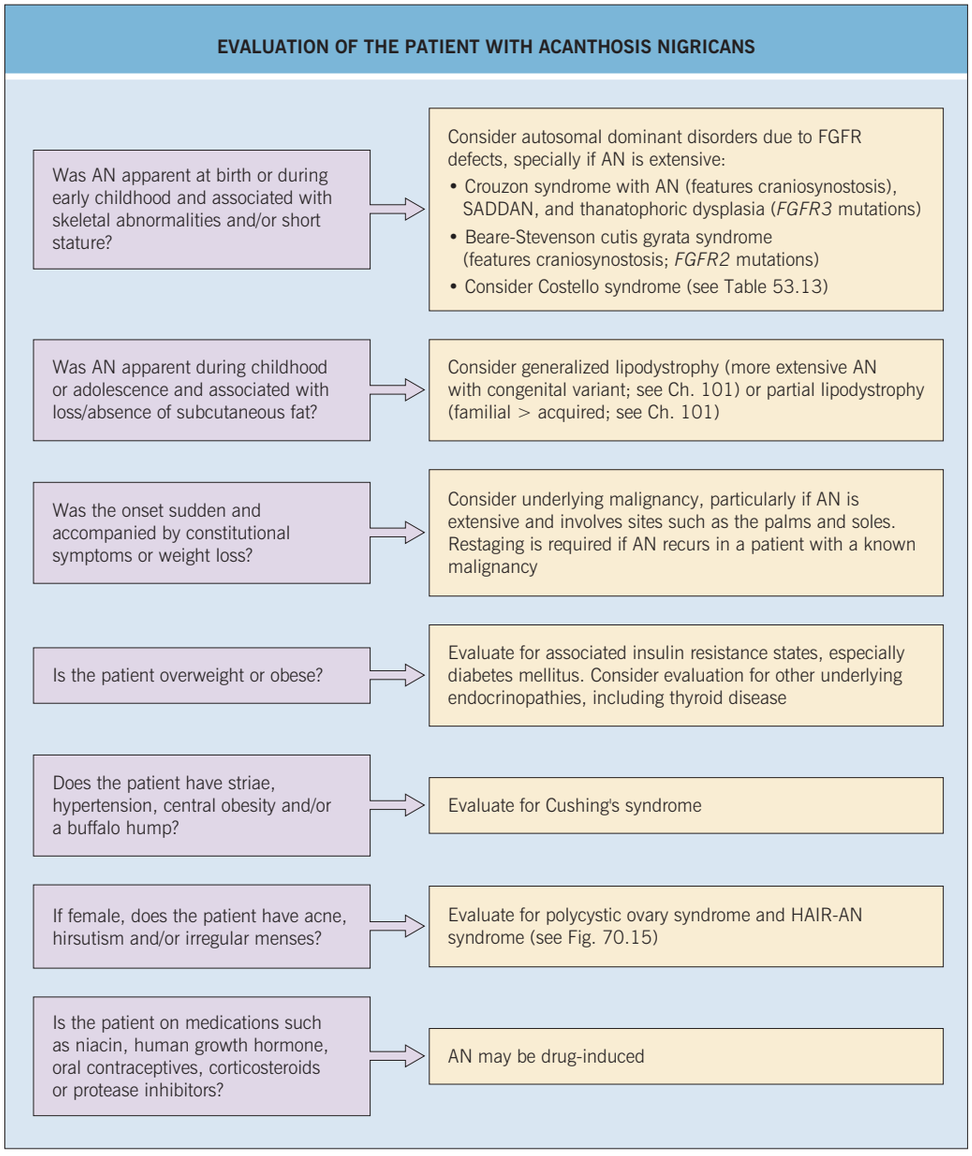


Fig. 53.17 Evaluation of the patient with acanthosis nigricans (AN). FGFR, fibroblast growth factor receptor; HAIR-AN, hyperandrogenemia, insulin resistance, acanthosis nigricans; SADDAN, severe achrondroplasia with developmental delay and AN.

CUTANEOUS ENDOCRINOLOGY AND METABOLIC DISEASE

Endocrine diseases, particularly diabetes mellitus, represent an area in which cutaneous manifestations may be important clues to diagnosis. Patients with endocrine diseases are especially susceptible to a number of associated mucocutaneous disorders.

Diabetes mellitus is a very common medical disease with sequelae that affect almost every organ system. The skin is no exception. Table 53.4 summarizes cutaneous manifestations of diabetes mellitus (Figs 53.18–53.22). Several recent reviews have been published on this topic[11].

The metabolic syndrome, previously known as syndrome X, is a common disorder in which there are multiple phenotypes with primary characteristics that include central obesity, hypertension, dyslipidemia, and type 2 diabetes. Almost all patients with this disorder have insulin resistance, and it is associated with a high risk of cardiovascular disease. Clinical criteria for the diagnosis of metabolic syndrome are outlined in Table 53.5. Women with polycystic ovary syndrome have a greater frequency of the metabolic syndrome and are often found to have cutaneous abnormalities including acanthosis nigricans, acne vulgaris and hirsutism[14]. An association between psoriasis vulgaris and the metabolic syndrome has also been identified. Patients with moderate to severe psoriasis are at increased risk of atherosclerotic cardiovascular disease, which is linked to their propensity for the metabolic syndrome. The components of the metabolic syndrome – hyperlipidemia, diabetes mellitus, hypertension and obesity – are established risk factors[15].

Fig. 53.18 Bullosis diabeticorum (diabetic bullae). Non-inflammatory bullae on the lower extremity in a patient with diabetes mellitus.

SELECTED DERMATOLOGIC ASSOCIATIONS OF DIABETES MELLITUS

Dermatosis	Clinical description	Comments
Acanthosis nigricans (AN)	Velvety hyperpigmentation of the intertriginous/flexural areas (Fig. 53.15) and, less often, extensor surfaces (Fig. 53.16)	Commonly associated with insulin resistance and most of the patients are obese. More common in Hispanics and individuals of African descent. Recent evidence strongly links AN in children with insulin resistance and diabetes
Acral dry gangrene	Necrosis of the fingertips or toes	Due to vascular disease in larger vessels
Acral erythema	Erysipelas-like erythema of the hands and/or feet	May be due to small vessel occlusive disease with compensatory hyperemia
Carotenemia	Diffuse orange–yellow skin color	Related to an increase in serum carotene level
Diabetic bullae (bullosis diabeticorum)	Tense non-inflammatory bullae on the lower extremities (Fig. 53.18)	Unknown pathogenesis
Diabetic cheiroarthropathy	Thickened skin and limited joint mobility of the hands and fingers, leading to flexion contractures (starting with the fifth digit and progressing radially) and an inability to approximate the palmar surfaces of the hands and fingers (prayer sign)	Postulated to result from increased glycosylation of collagen in the skin. Associated with retinopathy, nephropathy, and duration (but not control) of the DM
Diabetic dermopathy	Brown atrophic macules and patches on the legs (Fig. 53.19)	Possibly precipitated by trauma
Disseminated granuloma annulare	Erythematous annular lesions composed of papules	There is controversy about the exact relationship of disseminated granuloma annulare and DM (see Ch. 93)
Eruptive xanthomas	Red–yellow papules that appear over a period of weeks to months (Fig. 53.20)	Associated with elevated serum triglycerides in patients with poorly controlled diabetes. Control of the DM results in a disappearance of the xanthomas (see Ch. 92)
Hemochromatosis	Bronzing of the skin due to an increase in melanin rather than iron	Excess of iron stores associated with cirrhosis and cardiac dysfunction as well as DM. Due to mutations in *HFE*, most commonly C282Y. Also risk factor for porphyria cutanea tarda
Necrobiosis lipoidica	Yellow atrophic patches, most often on the shins. A red–brown rim may indicate activity at the border (Fig. 53.21). Ulceration can occur and is often slow to heal	Intralesional triamcinolone, aspirin, dipyridamole and/or pentoxyfylline are possibly helpful. Not all patients have DM (see Ch. 93)
Neuropathic leg ulcers	Non-painful ulcerations at sites of pressure, most commonly on the foot (Fig. 53.22); a keratotic rim is characteristic	Associated with sensory neuropathy (see Ch. 105)
Perforating disorders (e.g. acquired perforating dermatosis)	Keratotic papules, primarily on the extremities	Often occurs in African-American diabetic patients with chronic kidney disease on dialysis (see Ch. 96)
Rubeosis	Chronic, flushed appearance of the face, neck and upper extremities	Improved by dietary diabetic control. Flares with vasodilator therapies
Scleredema (adultorum of Buschke)	Erythematous induration of the upper back and nape due to glycosaminoglycan deposition	Unknown etiology. No relationship to control of the DM

Table 53.4 Selected dermatologic associations of diabetes mellitus (DM). Additional cutaneous conditions associated with DM include hirsutism (e.g. related to polycystic ovary syndrome or HAIR-AN – *h*yperandrogenemia, *i*nsulin *r*esistance, *a*canthosis *n*igricans; see Ch. 70), necrolytic migratory erythema (in the setting of DM due to a glucagon-secreting pancreatic tumor; see Table 53.3), and infections such as mucocutaneous candidiasis, erythrasma (especially the disciform variant), cellulitis and necrotizing fasciitis. Adapted from ref. 12.

Fig. 53.19 Diabetic dermopathy. Note the brown macules and patches on the shins. *Courtesy, Jean L Bolognia, MD.*

Fig. 53.21 Necrobiosis lipoidica. Controversy exists about the exact risk of diabetes mellitus in such patients, but it is much more strongly associated with diabetes than is granuloma annulare.

Fig. 53.20 Eruptive xanthomas are frequently associated with poorly controlled diabetes mellitus. This patient was first discovered to have diabetes following the appearance of these yellow–red papules.

Fig. 53.22 Neuropathic ulcers on the toes of a patient with diabetic sensory neuropathy.

CRITERIA FOR THE CLINICAL DIAGNOSIS OF THE METABOLIC SYNDROME
• Elevated waist circumference (population- and country-specific definitions)
• Elevated triglycerides (≥150 mg/dl)
• Reduced HDL (<40 mg/dl in males; <50 mg/dl in females)
• Elevated blood pressure (systolic ≥130 and/or diastolic ≥85 mm/Hg)
• Elevated fasting blood glucose (≥100 mg/dl)

Table 53.5 Criteria for the clinical diagnosis of the metabolic syndrome. Metabolic syndrome is identified by the presence of three of these five criteria. Drug treatment for dyslipidemia, hypertension or hyperglycemia also fulfills the corresponding criterion. Most patients with type 2 diabetes mellitus meet criteria for metabolic syndrome. Adapted from ref. 13.

Thyroid disease is also associated with a significant number of dermatologic disorders. Current reviews have highlighted these dermatologic manifestations and associations[16]. Table 53.6 summarizes the dermatologic manifestations of thyroid disease.

Adrenal disease classically manifests as excessive glucocorticoid activity (Cushing's syndrome) (Figs 53.23 & 53.24) or as insufficient glucocorticoid activity (Addison's disease) (Fig. 53.25), but there can also be excessive production of adrenal androgens (see Ch. 70). Features of these syndromes are outlined in Tables 53.7 and 53.8, respectively (see Ch. 125).

DERMATOLOGIC MANIFESTATIONS OF THYROID DISEASE		
	Hyperthyroidism	**Hypothyroidism**
Cutaneous changes	Fine, velvety, smooth skin Warm and moist due to increased sweating Hyperpigmentation – localized or generalized Pruritus	Dry, rough, coarse skin Cold and pale Boggy and edematous skin (myxedema) Yellow discoloration as a result of carotenemia Easy bruising (capillary fragility)
Cutaneous diseases	Pretibial myxedema*, thyroid acropachy Urticaria, dermatographism Increased incidence of vitiligo	Acquired ichthyosis and palmoplantar keratoderma Eruptive and/or tuberous xanthomas Increased incidence of vitiligo
Hair changes/diseases	Fine, thin Mild, diffuse alopecia Increased incidence of alopecia areata	Dull, coarse, brittle Slow growth (increase in telogen hair phase) Alopecia of the lateral third of the eyebrows Increased incidence of alopecia areata
Nail changes	Onycholysis Koilonychia Clubbing from thyroid acropachy	Thin, brittle, striated Slow growth Onycholysis (rare)

*Can persist when patient is treated and becomes euthyroid or can be associated with euthyroid Graves' disease.

Table 53.6 Dermatologic manifestations of thyroid disease. A serum thyroid-stimulating hormone (TSH) level is the most reliable test of thyroid function, and it is usually markedly suppressed in patients with hyperthyroidism. Additional laboratory findings in hyperthyroid patients include elevated free T_3 and/or free T_4 levels. Patients with primary hypothyroidism have elevated TSH levels and decreased free T_4 levels. The detection of anti-thyroid peroxidase and/or antithyroglobulin antibodies points to autoimmune thyroid disease (Hashimoto's thyroiditis, Graves' disease) while the presence of anti-TSH receptor antibodies points to Graves' disease. Ascher's syndrome consists of blepharochalasis, double lip and goiter.

DERMATOLOGIC MANIFESTATIONS OF CUSHING'S SYNDROME
ALTERED SUBCUTANEOUS FAT DISTRIBUTION
• Rounded facies • Fullness of the cheeks ("moon" facies) • Dorsal cervical vertebral fat deposition ("buffalo hump") (Fig. 53.23)* • Pelvic girdle fat deposition* • Reduced fat in the arms and legs*
SKIN ATROPHY
• Global atrophy with epidermal and dermal components affected • Multiple striae on abdomen, flanks, arms and thighs (Fig. 53.24) • Cutaneous fragility and prolonged wound healing • Purpura with minor trauma due to reduced connective tissue support
CUTANEOUS INFECTIONS
• Pityriasis (tinea) versicolor • Dermatophytosis and onychomycosis • Candidiasis
ADNEXAL EFFECTS
• Corticosteroid-related acne • Hirsutism
*This same change is indicative of insulin resistance and occurs in HIV-associated lipodystrophy.

Table 53.7 Dermatologic manifestations of Cushing's syndrome. An overnight dexamethasone suppression test (8 a.m. plasma cortisol >140 nmol/l after receiving 1 mg at midnight) or 24-hour urine free cortisol determination (>140 nmol/24 h) can be used as a screen for Cushing's syndrome due to endogenous cortisol production. Elevated plasma adrenocorticotropic hormone (ACTH) levels are found in Cushing's disease (pituitary overproduction of ACTH) and ectopic ACTH syndrome, whereas ACTH levels are suppressed in patients with adrenal tumors.

Fig. 53.23 "Buffalo hump" of Cushing's syndrome due to fat redistribution. The patient also has evidence of hirsutism. *Courtesy, Judit Stenn, MD.*

Fig. 53.24 Cushing's syndrome with multiple striae. *Courtesy, Judit Stenn, MD.*

Fig. 53.25 Diffuse hyperpigmentation of Addison's disease. The hyperpigmentation (shown in contrast to the physician's hand) is accentuated in sun-exposed skin and can also involve sites of trauma, skin creases and mucosae.

SELECTED DERMATOLOGIC MANIFESTATIONS OF ADDISON'S DISEASE
• Hyperpigmentation (MSH-like effect due to secretion of ACTH) – Diffuse with accentuation in sun-exposed areas (Fig. 53.25) – Sites of trauma – Axillae, perineum and nipples – Palmar creases – Melanocytic nevi – Mucous membranes – Hair – Nails • Loss of ambisexual hair in postpubertal women • Fibrosis and calcification of cartilage including the ear (rare) • Associated findings in candidiasis endocrinopathy syndrome – Vitiligo – Chronic mucocutaneous candidiasis

Table 53.8 Selected dermatologic manifestations of Addison's disease. The rapid adrenocorticotropic hormone (ACTH) stimulation test (which assesses adrenal reserve) should be performed when adrenal insufficiency is suspected, as basal serum cortisol levels may be normal in patients with partial deficiencies. Plasma ACTH levels are elevated in primary adrenocortical insufficiency (Addison's disease) and suppressed in secondary adrenocortical insufficiency (e.g. due to exogenous glucocorticoid therapy). MSH, melanocyte-stimulating hormone.

SKIN FINDINGS IN CROHN'S DISEASE AND ULCERATIVE COLITIS
• Erythema nodosum – often reflective of active bowel disease • Urticaria • Cutaneous small vessel vasculitis • Cutaneous polyarteritis nodosa • "Pustular" vasculitis or bowel-associated dermatosis–arthritis syndrome-like lesions • Pyoderma gangrenosum – primarily the classic (typical) ulcerative form (Fig. 53.26) or peristomal lesions (Fig. 53.27); a vegetative pustular variant (pyoderma vegetans) occasionally occurs. These lesions may or may not reflect activity of the bowel disease • Other neutrophilic dermatoses, ranging from acneiform lesions to Sweet's syndrome to panniculitis • Oral lesions – Granulomatous infiltrates (with Crohn's disease only) – Aphthosis – Angular cheilitis – Pyostomatitis vegetans (mucosal variant of pyoderma gangrenosum) • Contiguous (anogenital) and "metastatic" Crohn's disease (Fig. 53.28) • Fistulae (perianal and abdominal) • Acquired acrodermatitis enteropathica-like lesions (patients with zinc deficiency and/or essential fatty acid deficiency) • Epidermolysis bullosa acquisita • Psoriasis

Table 53.9 Skin findings in Crohn's disease and ulcerative colitis.

Fig. 53.26 Pyoderma gangrenosum associated with inflammatory bowel disease. The ulcer has typical features of pyoderma gangrenosum, including a ragged edge, undermined violet border and surrounding inflammation.

Fig. 53.27 Peristomal pyoderma gangrenosum in the setting of inflammatory bowel disease. Patients with ostomies, particularly ileostomies, are at risk for peristomal dermatoses, including pyoderma gangrenosum.

Fig. 53.28 "Metastatic" Crohn's disease. Non-contiguous granulomatous inflammation of the skin is often manifested by deep inflammatory fissures in the inguinal folds.

CUTANEOUS GASTROENTEROLOGY

With the exception of Table 26.12, cutaneous aspects of gastroenterologic or hepatic disease are not specifically discussed elsewhere in this text[17–19]. Table 53.9 is a list of selected cutaneous associations of Crohn's disease and ulcerative colitis (Figs 53.26–53.28). Patients with ostomies, particularly those with an ileostomy, are at risk for developing peristomal dermatoses, the most common of which are listed in Table 53.10. Table 53.11 lists dermatologic conditions associated with gastrointestinal bleeding or hemorrhage (Figs 53.29–53.32)[18].

Cutaneous hepatology has been the subject of recent reviews[19] and Table 53.12 is a list of selected dermatologic aspects of liver disease. An interesting disease that has been described in association with hepatitis C viral infection is necrolytic acral erythema. This entity is histologically similar to necrolytic migratory erythema (see above), but is clinically distinct as it primarily involves acral sites. The lesions present as painful or pruritic, pink to violet–brown plaques with hyperkeratosis (Fig. 53.33). Blisters and erosions are common, and disease activity tends to wax and wane. Almost all reported cases have been associated with hepatitis C viral infection, and variable success has resulted from treatment with interferon (alone or plus ribavirin) or oral zinc supplementation.

PERISTOMAL SKIN DISORDERS	
Skin disorder	**Comments**
Irritant contact dermatitis	Most common cause of peristomal dermatitis, especially in patients with an ileostomy. Primarily attributed to exposure to feces or urine
Pre-existing skin disease (e.g. psoriasis, seborrheic dermatitis, atopic dermatitis)	Exclude primary contact dermatitis or infection or superimposed contact dermatitis
Cutaneous infection (*Candida* spp. dermatophyte, herpes virus [primarily simplex], bacteria [especially *Staphylococcus aureus*])	Colonization with bacteria and/or yeast is common. Recent treatment with antibiotics predisposes to candidiasis. May initially improve then worsen if treated inappropriately with topical corticosteroids
Allergic contact dermatitis	Relatively uncommon. Potential allergens include: adhesive pastes, adhesive ring or wafer of stoma bag, ostomy bag, epoxy resin, rubber, lanolin and fragrances. Patch test with both standardized allergens and patient's own products
Pyoderma gangrenosum	Infrequent cause of peristomal dermatitis; most common in patients with inflammatory bowel disease (Fig. 53.27)
Pseudo-verrucous papules and nodules	Seen more commonly in association with urostomies; may be misdiagnosed as verrucae

Table 53.10 Peristomal skin disorders. Peristomal skin disorders are common and may limit use and efficacy of the stoma appliance. When the etiology is uncertain, evaluation can include KOH examination, microbial cultures, patch testing and histologic examination. Adapted from ref. 20.

Fig. 53.30 Blue rubber bleb nevus syndrome. Several venous malformations are evident on this patient's tongue.

Fig. 53.32 Gingival cobblestoning in Cowden disease. This patient also had trichilemmomas and a "Cowden's nodule" or sclerotic fibroma on the neck.

Fig. 53.29 Hereditary hemorrhagic telangiectasia. Multiple small bright red macules and papules on the tongue and lips.

Fig. 53.31 Peutz–Jeghers syndrome. Multiple brown macules on the lips and oral mucosa.

Fig. 53.33 Necrolytic acral erythema. This is a manifestation of hepatitis C viral infection.

CUTANEOUS DISEASES ASSOCIATED WITH GASTROINTESTINAL BLEEDING OR HEMORRHAGE				
Disorder	**Cutaneous findings**	**Gastrointestinal features**	**Other pertinent findings**	**Treatment and comments**
GENETIC (ESPECIALLY THOSE ASSOCIATED WITH VASCULAR MALFORMATIONS AND GI POLYPS)				
Hereditary hemorrhagic telangiectasia	Macular and papular telangiectasias on facial and acral skin (Fig. 53.29) as well as the oral mucosa	Recurrent hemorrhage in the upper GI tract	Epistaxis is often the initial manifestation. Arteriovenous malformations (AVMs) of the lungs, liver and CNS	Autosomal dominant; most commonly due to mutations in *ENG* and *ACVRL1*, which encode endoglin and ALK, TGF-β receptors. Treatment consists of surgical resection, embolization or laser therapy of AVM causing hemorrhage
Blue rubber bleb nevus syndrome	Subcutaneous blue to purple venous malformations (Fig. 53.30)	GI vascular malformations	Possible vascular malformations in other organs (e.g. CNS, lungs)	Autosomal dominant or sporadic
Pseudoxanthoma elasticum	Yellow papules and plaques in intertriginous zones, redundant lax skin	Upper or lower GI hemorrhage	Angioid streaks in the eye, hypertension, premature atherosclerosis, uterine hemorrhage, vascular calcification	Autosomal recessive disorder due to mutations in the *ABCC6* gene. Perhaps a diet high in magnesium is helpful
Ehlers–Danlos syndrome, vascular type (type IV)	Translucent fragile skin with extensive bruising	GI hemorrhage due to arterial rupture or intestinal perforation	Minimal joint hyperextensibility (limited to digits), rupture of other arteries or the uterus, acrogeric facies	Autosomal dominant, deficiency of type III collagen
Gardner syndrome	Epidermoid cysts, pilomatricomas, lipomas, fibromas and desmoid tumors	Hemorrhage from adenomatous colonic polyps. Adenocarcinoma of the colon is universal if the colon is not removed	Mandibular and maxillary osteomas and cysts, *c*ongenital *h*ypertrophy of the *r*etinal *p*igment *e*pithelium (CHRPE)	Autosomal dominant due to mutations in the *APC* gene. Colectomy must be appropriately timed
Peutz–Jeghers syndrome	Melanotic macules on mucosal surfaces (Fig. 53.31) and, less often, on acral or perioral skin	Hamartomatous polyps throughout the GI tract. Intussusception or hemorrhage may occur	Possibly increased incidence of breast, ovarian and GI cancer	Autosomal dominant due to mutations in *STK11*, which encodes a serine/threonine kinase. Remove symptomatic areas of the bowel
Cowden disease (multiple hamartoma syndrome; PTEN hamartoma syndrome)	Multiple facial or periorificial papules (trichilemmomas), perioral lentigines, cobblestoning of the oral mucosal surface (Fig. 53.32), acral keratotic papules, sclerotic fibromas, lipomas	Hamartomatous polyps throughout the GI tract. Bleeding is rare	Fibrocystic breast disease along with frequent cancers of the breast, often bilateral. Thyroid tumors including cancer	Autosomal dominant due to mutations in the *PTEN* tumor suppressor gene, which encodes a phosphatase
Muir–Torre syndrome	Sebaceous neoplasia and multiple keratoacanthomas	Multiple GI malignancies are possible	Cancer also may occur in the larynx and GU tract, as well as lymphomas	Autosomal dominant due to mutations in one of several mismatch repair genes, including *MSH2* (~90%), *MLH1* and *MSH6*
INFLAMMATORY/AUTOIMMUNE				
Cronkhite–Canada syndrome	Circumscribed areas of lentiginous hypermelanosis, alopecia, generalized nail thinning	Adenomatous GI polyps, diarrhea, abdominal pain	Weight loss due to malabsorption	Malignant degeneration is unusual
Vasculitis	Palpable purpura, necrotizing livedo reticularis, nodules, or ulcers	Ulcerations secondary to vasculitis of the vessels in the bowel. May be more common in IgA-associated vasculitis (Henoch–Schönlein purpura)	Arthritis and nephritis are two additional features of Henoch–Schönlein purpura	Corticosteroids and/or immunosuppressive agents may or may not be effective
Malignant atrophic papulosis (Degos disease)	Early lesions – pale red papules with central necrosis Late lesions – atrophic ivory scars	Similar lesions of the GI mucosa. Hemorrhage may result in death	CNS involvement, pleuritis, pericarditis	May be related to lupus erythematosus or to the antiphospholipid antibody syndrome
Ulcerative colitis	Erythema nodosum, vasculitis, pyoderma gangrenosum See Table 53.9	Uniform and continuous inflammation of the large bowel. Rectal involvement is present in majority (>95%) of patients. Toxic megacolon may develop	Aphthous stomatitis is common. Malignant degeneration in the large intestine is frequent in patients with uncontrolled, longstanding disease	Treatment options include sulfonamides, immunosuppressives, corticosteroids and total colectomy

Table 53.11 Cutaneous diseases associated with gastrointestinal bleeding or hemorrhage. CNS, central nervous system; GI, gastrointestinal; GU, genitourinary. Adapted from refs 12 & 21.

Continued

CUTANEOUS DISEASES ASSOCIATED WITH GASTROINTESTINAL BLEEDING OR HEMORRHAGE				
Disorder	**Cutaneous findings**	**Gastrointestinal features**	**Other pertinent findings**	**Treatment and comments**
Crohn's disease	Erythema nodosum, vasculitis, pyoderma gangrenosum, perianal fistulae and metastatic Crohn's disease See Table 53.9	Chronic inflammation, often granulomatous, of the bowel. Skip areas occur	Aphthous stomatitis, arthritis, chronic blood loss	Treatment options include sulfonamides, metronidazole, corticosteroids and other immunosuppressives, including TNF-α inhibitors
NUTRITIONAL				
Scurvy	Perifollicular purpura, corkscrew hairs	Collagen degeneration in the vasculature due to vitamin C deficiency. GI blood loss results in anemia	Gingivitis with friable gums and easy bleeding, conjunctival hemorrhage, difficulty walking	Vitamin C replacement
NEOPLASTIC				
Kaposi sarcoma	Violaceous macules, papules, and nodules of the skin and oral mucosa	Similar tumors may occur in the GI tract	Includes HIV-related, "African"and classic subtypes, with the latter favoring elderly men of Mediterranean heritage; related to HHV-8 infection	Chemotherapy or radiation therapy may be helpful

Table 53.11 Cutaneous diseases associated with gastrointestinal bleeding or hemorrhage (cont'd). GI, gastrointestinal; HHV, human herpesvirus. Adapted from refs 12 & 21.

DERMATOLOGIC ASPECTS OF LIVER DISEASE		
Liver disease	**Dermatologic manifestations/associations**	**Other features, treatment, and comments**
Cirrhosis	• Spider angiomas and other telangiectasias • Palmar erythema • Dilated abdominal wall veins • Terry's nails (white nail bed) • Muehrcke's nails (transverse white bands) • Sparse axillary, pubic and pectoral hair • Pruritus • Jaundice	• Gynecomastia • Parotid enlargement
Primary biliary cirrhosis (PBC)	• Jaundice • Diffuse hyperpigmentation • Xanthomas – eruptive, planar and, occasionally, tuberous • Pruritus • May coexist with scleroderma	Cholestyramine, rifampin, ursodiol and naloxone may help to relieve the pruritus. Osteoporosis is a common complication. Treatment options for PBC include ursodiol, colchicine, methotrexate and liver transplantation
Hemochromatosis ("bronze diabetes")	• Generalized hyperpigmentation	Due to mutations in *HFE*, most commonly C282Y. Phlebotomy to reduce iron stores is first-line therapy; also chelation (e.g. deferasirox)
Wilson disease (hepatolenticular degeneration)	• Kayser-Fleischer ring – golden brown or greenish circle of pigment in Descemet's membrane at the periphery of the cornea • Blue lunulae • Pretibial hyperpigmentation	Autosomal recessive; due to mutations in *ATP7B* which encodes a copper-transporting ATPase. Treatment with penicillamine, trientine or liver transplantation
Hepatitis B and C viruses	• Cutaneous small vessel vasculitis (B,C) • Cryoglobulinemic vasculitis (C>>B) • Urticarial vasculitis (B,C) • Polyarteritis nodosa (classic – B, cutaneous – C) • Necrotizing livedo reticularis (C) • Urticaria (B,C) • Porphyria cutanea tarda (C>B) • Pruritus (B,C) • Lichen planus – particularly erosive oral disease (C) • Sarcoidosis (following therapy with interferon and/or ribavirin) (C>B) • Necrolytic acral erythema (Fig. 53.33) (C) • Gianotti–Crosti syndrome (B>C) • Erythema multiforme (B,C) • Erythema nodosum (B>C)	Interferon and ribavirin are useful for hepatitis C viral infections and may prevent cirrhosis and hepatocellular cancer; telaprevir, an NS3/4A protease inhibitor, was recently FDA-approved for the treatment of genotype 1 chronic hepatitis C infection

Table 53.12 Dermatologic aspects of liver disease.

OTHER SYSTEMIC DISEASES WITH CUTANEOUS MANIFESTATIONS

Sarcoidosis is a multisystem disease with major cutaneous manifestations (see Ch. 93)[22]. Cardiovascular diseases and the skin are not specifically discussed elsewhere in this text. Table 53.13 is a review of cardiac and dermatologic abnormalities that are features of multisystem disorders (Figs 53.34 & 53.35)[23,24]. Pulmonary disorders are listed in Table 53.14 (Fig. 53.36).

Cutaneous aspects of renal disease are discussed in various chapters, but are not considered as a group elsewhere in this textbook. Table 53.15 is an overview of cutaneous changes that are particularly prevalent in patients with renal disease (Figs 53.37 & 53.38)[25–30].

Pruritus is a feature of uremia, but it can occur in non-uremic patients on hemodialysis. It is still unclear why patients with chronic kidney disease on dialysis experience itching. The pruritus may be localized or generalized. It is usually worse during dialysis, but may occur "round the clock" (see Ch. 6).

Patients who undergo renal transplantation usually receive immunosuppressive agents, including cyclosporine, tacrolimus, sirolimus, azathioprine, and/or corticosteroids, in order to prevent rejection. The combination of these drugs predisposes the patient to two major problems: infection (e.g. HPV, CMV) and malignancy (e.g. squamous cell carcinoma, Kaposi sarcoma, Merkel cell carcinoma).

Fig. 53.34 Antiphospholipid antibody syndrome. In addition to bland thromboses, these patients may have cardiac valvular vegetations.

Fig. 53.36 Periorificial and facial papules of sarcoidosis. The presence of lesions on the nasal rim is often associated with granulomatous inflammation of the upper respiratory tract.

Fig. 53.35 Relapsing polychondritis. The inflammation spares the earlobes, which lack cartilage.

Fig. 53.37 Calciphylaxis. This patient presented with these necrotic skin lesions and was found to have severe end-stage renal disease due to amyloidosis of the kidney.

CARDIOCUTANEOUS ABNORMALITIES IN MULTISYSTEM DISORDERS			
Disease	**Cutaneous features**	**Cardiovascular findings**	**Comments**
		GENETIC	
Cardio-facio-cutaneous syndrome	Generalized ichthyosis-like scaling, keratosis pilaris, café-au-lait macules, sparse curly hair	Pulmonic stenosis, atrial septal defects, hypertrophic cardiomyopathy	Autosomal dominant condition due to mutations in four genes in the mitogen-activated protein kinase (MAPK) pathway – *BRAF* > *KRAS, MEK1/2*. Patients also have characteristic facies, short stature and developmental delay
Costello syndrome	Lax skin on the hands and feet, deep palmoplantar creases, periorificial papillomas, acanthosis nigricans, curly hair	Pulmonic stenosis, hypertrophic cardiomyopathy, arrhythmias	Autosomal dominant condition due to *HRAS* > *KRAS* mutations. Patients also have mental and growth retardation and an increased risk of rhabdomyosarcoma and bladder carcinoma
Carvajal syndrome	Striate epidermolytic palmoplantar keratoderma, woolly scalp hair	Dilated left ventricular cardiomyopathy	Autosomal recessive disorder due to desmoplakin mutations
Cutis laxa	Looseness of the skin	Aortic dilation and rupture, pulmonary artery stenosis, right-sided heart failure	Autosomal dominant (AD) and recessive (AR) forms due to mutations in the elastin (AD > AR), fibulin-4 (AR) and fibulin-5 (AR > AD) genes; systemic involvement is more common in the AR form
Ehlers–Danlos syndrome (EDS)	Variable degree of skin hyperelasticity and fragility (e.g. "cigarette" paper scars, ecchymoses)	Classic and hypermobility types (I–III): aortic root dilation, mitral and tricuspid valve regurgitation or prolapse Vascular type (IV): arterial aneurysms, dissection and rupture Cardiac valvular type: valvular abnormalities	Due to mutations in the genes encoding collagen V (classic type), tenascin X (subset of classic and hypermobility types), collagen III (vascular type) and collagen I (cardiac valvular type)
Fabry disease	Angiokeratoma corporis diffusum, hypohidrosis	Hypertrophic cardiomyopathy, valvular abnormalities, conduction defects, progressive atherosclerotic disease of the coronary and cerebral arteries	α-Galactosidase A deficiency, X-linked recessive disorder. Cardiac and cerebrovascular disease and renal failure are the usual causes of death
Hemochromatosis	Generalized bronze hyperpigmentation	Congestive heart failure, supraventricular arrhythmias	Diabetes, cirrhosis. Genetic testing is available for *HFE* gene mutations
Homocystinuria	Livedo reticularis, malar rash, tissue-paper scars, diffuse pigmentary dilution	Atherosclerosis, arterial and venous thrombosis	Autosomal recessive disorder due to homozygous cystathionine β-synthase (CBS) deficiency. Patients also exhibit marfanoid characteristics and ectopia lentis. Hyperhomocysteinemia (due to homozygous methylenetetrahydrofolate reductase deficiency >> heterozygous CBS deficiency) also increases risk of arterial and venous thrombosis
LEOPARD syndrome	Multiple lentigines, café-au-lait and café-noir macules	ECG abnormalities, pulmonary artery stenosis	*L* – lentigines, *E* – ECG abnormality, *O* – ocular hypertelorism, *P* – pulmonary stenosis, *A* – abnormalities of the genitalia, *R* – retardation of growth, *D* – deafness. Autosomal dominant disorder due to mutations in the *PTPN11* gene
Loeys–Dietz syndrome	Translucent skin, easy bruising, atrophic scarring	Aortic aneurysms, arterial tortuosity; significant risk of aortic dissection and rupture, even at an early age	Autosomal dominant disorder due to mutations in the genes that encode TGF-β receptor 1 and 2. Overlapping clinical features with Marfan syndrome and vascular type (IV) EDS. Craniofacial anomalies are seen primarily in type I
Marfan syndrome	Striae, decreased subcutaneous fat	Dilation and dissection of the ascending aorta, mitral valve prolapse and regurgitation	Autosomal dominant disorder due to mutations in the gene that encodes fibrillin-1. Characterized by tall stature with long limbs, arachnodactyly, dolichocephaly, myopia and ectopia lentis. In addition to β-blockers, angiotensin II receptor blockers (e.g. losartan), which antagonize pathogenic TGF-β signaling, can prevent aortic root dilation
Multiple endocrine neoplasia (MEN) types 2A (Sipple syndrome) and 2B (multiple mucosal neuroma syndrome)	MEN 2A – notalgia paresthetica, macular or lichen amyloidosis, often with childhood onset MEN 2B – neuromas of the eyelids, lips, tongue and other mucosal sites; GI ganglioneuromatosis also occurs	Hypertensive crises due to pheochromocytomas (often bilateral)	Autosomal dominant conditions due to mutations in the *RET* proto-oncogene. Also manifest with medullary cell carcinoma of the thyroid (MEN 2A and 2B), parathyroid adenomas (MEN 2A) and a marfanoid habitus (MEN 2B)
Carney complex (NAME and LAMB syndromes)	Cutaneous myxomas, blue nevi, lentigines	Atrial myxoma	Endocrine neoplasia of the adrenal glands, pituitary gland, and/or testes. Autosomal dominant disorder due to mutations in the *PRKAR1A* gene
Naxos disease	Diffuse non-epidermolytic palmoplantar keratoderma, woolly scalp hair	Arrhythmogenic right ventricular cardiomyopathy	Autosomal recessive condition due primarily to mutations in the gene that encodes plakoglobin (rarely desmocollin 1)

Table 53.13 Cardiocutaneous abnormalities in multisystem disorders. ECG, electrocardiogram; GI, gastrointestinal; TGF, transforming growth factor. Adapted from ref. 12.

Continued

CARDIOCUTANEOUS ABNORMALITIES IN MULTISYSTEM DISORDERS			
Disease	**Cutaneous features**	**Cardiovascular findings**	**Comments**
Neurofibromatosis 1	Café-au-lait macules, neurofibromas, intertriginous freckling	Hypertension, essential or due to pheochromocytoma or renal artery stenosis	Due to mutations in the *NF1* gene, which encodes neurofibromin
Progeria	Sclerodermoid changes, mottled hyperpigmentation, loss of subcutaneous fat, alopecia	Premature atherosclerosis	Autosomal dominant premature aging syndrome due to mutations in the gene encoding lamins A and C
Pseudoxanthoma elasticum	Yellow papules and plaques in intertriginous areas, redundant lax skin	Premature atherosclerotic vascular disease, aortic aneurysm, hypertension	Upper or lower GI hemorrhage, angioid streaks in the eye, uterine hemorrhage. Autosomal recessive disorder due to mutations in the *ABCC6* gene
Tuberous sclerosis complex (TSC)	Facial angiofibromas, periungual and subungual fibromas, ash leaf macules, shagreen patch	Cardiac rhabdomyomas, arrhythmias	Renal angiomyolipomas, CNS tumors, mental retardation, seizures. Due to mutations in *TSC1* or *TSC2*, which encode hamartin and tuberin
Werner syndrome	Premature graying, alopecia, sclerodermoid changes, loss of subcutaneous fat, ankle ulcerations	Premature atherosclerosis	Myocardial infarction is usually responsible for death by the fifth decade. Autosomal recessive disorder due to mutations in the *RECQL2* gene, which encodes a helicase. Other features include cataracts and malignancy
		INFLAMMATORY/AUTOIMMUNE	
Behçet's disease	Oral and genital aphthae, pathergy, pustular vasculitis, pyoderma gangrenosum-like lesions, erythema nodosum-like lesions	Pericarditis, coronary arteritis, myocarditis, arrhythmias, valvular disease; vasculitis of the vasa vasorum, primarily of large blood vessels	Ocular and CNS involvement. Inflammatory bowel disease should be excluded
Dermatomyositis	Gottron's papules, heliotrope rash, photodistributed poikiloderma	Nonspecific ECG changes, pericarditis and congestive heart failure are rare	Cardiac involvement is a poor prognostic sign
DRESS/DIHS (drug hypersensitivity with eosinophilia and systemic symptoms/ drug-induced hypersensitivity syndrome)	Widespread morbilliform or urticarial eruption or erythroderma; facial edema often present	ECG changes may simulate acute myocardial infarction; acute myocardial dysfunction and hypotension	Hepatitis, polyarthritis and eosinophilia common. Symptoms suggestive of cholecystitis sometimes present. Treatment consists of discontinuation of offending drug and corticosteroids. Can follow levels of N-terminal pro-brain natriuretic peptide (NT-proBNP)
Kawasaki disease (mucocutaneous lymph node syndrome)	Glossitis, cheilitis, acral erythema, edema and desquamation, polymorphous eruption, conjunctival injection	Coronary arteritis, coronary artery aneurysms	High fever, lymphadenopathy. Treatment with intravenous immunoglobulin and aspirin is beneficial
Neonatal lupus erythematosus	Transient, non-scarring annular lesions of LE (SCLE-like) that favor the periorbital region	Congenital heart block	Presumed to be due to transplacental passage of autoantibodies, most commonly Ro (SS-A). May have transient cytopenias and hepatitis. Rash and cardiac disease rarely occur in the same patient; subsequent pregnancies may manifest either. Mothers often have or develop an autoimmune connective tissue disease
Systemic lupus erythematosus	Malar erythema, photosensitivity, lupus skin lesions. Patients with antiphospholipid antibodies may have necrotizing livedo reticularis, leg ulcers or widespread cutaneous necrosis (Fig. 53.34)	Pericarditis, verrucous endocarditis (Libman–Sacks), coronary artery disease	Anticardiolipin antibody may play a role. Treatment of LE with corticosteroids may predispose to coronary artery disease
Multicentric reticulohistiocytosis	Erythematous nodules of the hands and, less often, the extremities and the face (Fig. 53.12)	Pericarditis, congestive heart failure, coronary artery disease, cardiomegaly	Deforming arthritis is frequent
Psoriasis	Well-demarcated, pink-to-red plaques with silvery scale on the elbows, knees and scalp, around the umbilicus and in the gluteal cleft	Increased risk of cardiovascular disease, including cerebrovascular and peripheral artery disease. In patients with moderate to severe psoriasis, possible increased risk of death from atherosclerotic cardiovascular disease	High incidence of metabolic syndrome in patients with moderate to severe psoriasis (see Table 53.5)
Relapsing polychondritis	Beefy, red ears (sparing the lobes); inflammation in other tissues with cartilage (e.g. the nose). Late findings include floppy ears and weakness in other areas where the cartilage was affected (Fig. 53.35)	Aortic insufficiency, dissecting aortic aneurysm	Arthritis, tracheal collapse. Dapsone may be helpful. Corticosteroids and/or other immunosuppressive agents are also used
Rheumatic fever	Erythema marginatum, subcutaneous nodules	Pancarditis in the acute phase. Late manifestations include mitral and/or aortic valve dysfunction	Rare in US. Follows pharyngitis due to group A β-hemolytic streptococcal infection. Polyarthritis, chorea, fever

Table 53.13 Cardiocutaneous abnormalities in multisystem disorders (cont'd). CNS, central nervous system; ECG, electrocardiogram; GI, gastrointestinal; LAMB, lentigines, atrial myxoma, mucocutaneous myxoma, blue nevi; LE, lupus erythematosus; NAME, nevi, atrial myxoma, myxoma of the skin, ephelides. Adapted from ref. 12.

Continued

CARDIOCUTANEOUS ABNORMALITIES IN MULTISYSTEM DISORDERS			
Disease	**Cutaneous features**	**Cardiovascular findings**	**Comments**
Sarcoidosis	Papules, nodules, plaques and/or lesions in scars	Conduction defects, congestive heart failure	Pulmonary disease, lymphadenopathy, hepatic involvement, hypercalcemia. Cardiac involvement denotes a poor prognosis
Scleroderma	Cutaneous sclerosis, Raynaud's phenomenon	Pulmonary artery hypertension, conduction defects, pericarditis, visceral Raynaud's phenomenon	Cardiac involvement denotes a poor prognosis. May also have interstitial lung disease
Vasculitis	Palpable purpura, nodules, livedo reticularis, ulcerations	Coronary artery vasculitis	Arthritis, GI colic or bleeding. Cardiac involvement is uncommon
		NEOPLASTIC	
Primary systemic amyloidosis (AL)	Pinch purpura, waxy skin, translucent papules, macroglossia	Restrictive cardiomyopathy, conduction disturbances	Proteinuria, urinary light chains, association with plasma cell dyscrasia >> multiple myeloma
Carcinoid syndrome	Flushing; pellagra-like dermatitis and sclerodermoid features may occur as late manifestations	Endocardial plaques – tricuspid insufficiency, conduction defects	Flushing associated with approx. 10% of mid-gut tumors (small intestine, appendix, proximal colon) and liver metastases are required; type III gastric and bronchial carcinoid tumors are also associated with flushing (liver metastases are not required)
		INFECTIOUS	
Endocarditis – bacterial or fungal	Purpura, nailfold infarction, Janeway lesions, Osler's nodes	Vegetations and dysfunction of the valves	Fever. May simulate vasculitis or cryoglobulinemia
		METABOLIC/ENDOCRINE	
Diabetes mellitus	See Table 53.4	Coronary artery and peripheral artery disease	–
Hyperlipidemia	Xanthomas of multiple types	Coronary artery disease	see Ch. 92
		OTHER	
Exfoliative erythroderma	Exfoliative dermatitis	High-output cardiac failure	The eruption may be due to dermatitis, psoriasis, cutaneous T-cell lymphoma, a drug eruption or other causes
PHACES syndrome	Segmental infantile hemangioma, most often of the face and neck	Coarctation of the aorta, atrial and ventricular septal defects, anomalous cervical and cerebral arteries	*P* – posterior fossa malformations, *H* – hemangioma, *A* – arterial anomalies, *C* – cardiac defects and coarctation of the aorta, *E* – eye anomalies, *S* – sternal defects and supraumbilical raphe

Table 53.13 Cardiocutaneous abnormalities in multisystem disorders (cont'd). GI, gastrointestinal. Adapted from ref. 12.

PULMONARY DISEASE AND THE SKIN				
Disorder	**Cutaneous findings**	**Pulmonary disease**	**Other features**	**Treatment and comments**
		GENETIC		
Birt–Hogg–Dubé syndrome	Classic triad of fibrofolliculomas, trichodiscomas and acrochordons	Lung cysts, spontaneous pneumothoraces	Increased risk of renal carcinoma. Due to mutations in the gene encoding folliculin	Surveillance for renal tumors
Hereditary hemorrhagic telangiectasia	Mucosal, facial and acral telangiectatic macules and papules	Pulmonary AVMs	Epistaxis, recurrent GI bleeding, AVMs in other organs including the CNS	No therapy has been proven to be effective. Surgical correction of AVMs or excision of bleeding areas
Yellow nail syndrome	Thickened, slow-growing, excessively curved, yellow-to-green nails with onycholysis, transverse ridging, onychomadesis and absent cuticles and lunulae	Pleural effusions, bronchiectasis	Lymphedema, sinusitis	Complete triad of yellow nails, lymphedema and respiratory tract involvement seen in only one-third of patients; 2 of 3 findings needed for diagnosis
		INFLAMMATORY/AUTOIMMUNE		
Sarcoidosis – chronic	Papules, nodules (Fig. 53.36), plaques, lupus pernio, lesions in scars and tattoos	Fibrosis due to granulomatous inflammation	Hypercalcemia, ocular disease, CNS disease, bone cysts	Hydroxychloroquine may be useful for the skin lesions. Prednisone, methotrexate, or other immunosuppressive agents (e.g. oral tacrolimus, TNF-α inhibitors) may lead to improvement
Sarcoidosis – acute	Erythema nodosum	Bilateral hilar lymphadenopathy	Arthritis, anterior uveitis	Self-limiting. NSAIDs or potassium iodide may provide symptomatic relief
Wegener's granulomatosis	Vasculitic lesions (e.g. palpable purpura or nodules), cutaneous granulomas, pyoderma gangrenosum-like ulcers	Cavitating pulmonary nodules, vasculitis	Glomerulonephritis, upper respiratory tract inflammation, mucosal ulceration, friable hypertrophic gingiva	The presence of antineutrophil cytoplasmic antibody may aid in diagnosis. Cyclophosphamide, corticosteroids, sulfonamides, methotrexate

Table 53.14 Pulmonary disease and the skin. AVMs, arteriovenous malformations; CNS, central nervous system; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs; TNF, tumor necrosis factor.

Continued

PULMONARY DISEASE AND THE SKIN				
Disorder	**Cutaneous findings**	**Pulmonary disease**	**Other features**	**Treatment and comments**
Churg–Strauss syndrome	Palpable purpura, urticarial plaques, nodules	Asthma	Allergic rhinitis, peripheral eosinophilia, neuropathy, systemic vasculitis	The presence of antineutrophil cytoplasmic antibody may aid in diagnosis. Systemic corticosteroids, methotrexate, cyclophosphamide, rituximab
Dermatomyositis	Gottron's papules, heliotrope, photodistributed poikiloderma	Interstitial lung disease, aspiration pneumonitis, hypoventilation	Proximal, symmetric muscle weakness	Corticosteroids, immunosuppressive agents, IVIg
Scleroderma	Sclerosis, Raynaud's phenomenon	Interstitial lung disease, pulmonary artery hypertension	Esophageal dysmotility, arthritis	Cyclophosphamide for neutrophilic alveolitis, endothelin receptor antagonists
Urticarial vasculitis	Urticarial papules and plaques, often with a subtle purpuric component	Chronic obstructive pulmonary disease	The hypocomplementemic variant may involve the joints, GI tract, kidneys and eyes as well as the lungs; patients may have systemic lupus erythematosus	Oral corticosteroids, hydroxychloroquine, dapsone, colchicine
NEOPLASTIC/PARANEOPLASTIC				
Kaposi sarcoma	Red–violet to dark purple plaques and/or nodules of the skin and oral mucosa; in the classic form, most commonly seen on the lower extremities	Multifocal involvement can be asymptomatic or lead to dyspnea, cough, hemoptysis and/or chest pain	Lymphedema of the lower extremities. Gastrointestinal involvement common	Related to HHV-8 infection. Four major forms (see Ch. 114). Treatment includes antiretroviral therapy (HIV-related form), radiotherapy, taxanes and liposomal doxorubicin
Lymphomatoid granulomatosis	Nodules or plaques or papules	Angiocentric, angiodestructive infiltrate of atypical lymphocytes	Systemic lymphoma	Immunosuppressive or cytotoxic therapy
Paraneoplastic pemphigus	Erosive disease of the mucous membranes (see Fig. 53.9) and erythema multiforme-like, bullous pemphigoid-like or lichenoid skin lesions	Bronchiolitis obliterans	Most often associated with non-Hodgkin lymphoma, chronic lymphocytic leukemia or Castleman's disease	Immunosuppressive/cytotoxic medications (including prednisone), plasmapheresis, IVIg, rituximab (alone or in combination). Resection of Castleman's disease can lead to remission of mucocutaneous lesions
INFECTIOUS				
Tuberculosis	Lupus vulgaris, scrofuloderma (see Table 75.5)	Apical infiltrates, cavitating infiltrates; non-productive or productive cough	Fever, weight loss	Triple-drug antituberculous therapy
Blastomycosis*	Verrucous, ulcerated plaques or nodules. May be studded with pustules, especially at the periphery	Patchy infiltrates or normal chest X-ray	Bone and GU involvement, including testes	Inhalation followed by dissemination, including to skin; treatment includes itraconazole, amphotericin B
Cryptococcosis	Variable cutaneous findings, from papulonodules and plaques to molluscum contagiosum-like lesions and cellulitis	Varies from asymptomatic infection to severe pneumonia and acute respiratory distress syndrome	Meningeal involvement (needs to be excluded via lumbar puncture)	Severe infections favor immunocompromised hosts. Depending upon severity, fluconazole, amphotericin B
Aspergillosis	Primary cutaneous lesions – plaques with black crusts Secondary cutaneous emboli – necrotic papules and plaques, often with ulceration and rapidly progressive	In those with disseminated cutaneous emboli, cavitating infiltrates and nodules	In immunocompromised hosts, can disseminate widely	Disseminated disease affects primarily patients who are neutropenic and immunosuppressed (e.g. chronic corticosteroids)
Varicella	Lesions in various stages of development, including papules, papulovesicles, pustules and hemorrhagic crusts; cephalocaudal progression	Pulmonary involvement correlates with severity of skin involvement. Interstitial infiltrates or patchy airway disease leads to cough and dyspnea	Liver and CNS additional sites of infection. Reye's syndrome associated with use of aspirin.	Adults, pregnant or postpartum women and immunocompromised individuals at highest risk for pulmonary disease. Systemic antiviral medications recommended
OTHER				
Toxic epidermal necrolysis	Widespread necrosis and detachment	Acute respiratory distress syndrome	Erosions of the oropharyngeal, nasal, conjunctival, esophageal and genitourinary mucosa	Prompt discontinuation of all potential culprit drugs, IVIg therapy, admission to an intensive care or burn unit

*Primary pulmonary infection also occurs in other systemic mycoses due to dimorphic pathogens, including coccidioidomycosis, histoplasmosis and paracoccidioidomycosis.

Table 53.14 Pulmonary disease and the skin (cont'd). CNS, central nervous system; GI, gastrointestinal; HHV, human herpesvirus; IVIg, intravenous immunoglobulin.

RENAL DISEASE AND THE SKIN				
Disorder	**Cutaneous findings**	**Renal abnormality**	**Other findings**	**Treatment and comments**
		GENETIC		
Tuberous sclerosis complex (TSC)	Facial angiofibromas, ash leaf macules, shagreen patch, periungual or subungual fibromas	Renal hamartomas (angiomyolipomas). Polycystic kidney disease may occur in a contiguous gene syndrome with *TSC2*	CNS tumors, mental retardation, cardiac rhabdomyomas, seizures	Autosomal dominant. Due to mutations in *TSC1* or *TSC2*, which encode hamartin and tuberin
Fabry disease	Angiokeratoma corporis diffusum	Proteinuria, renal failure due to accumulation of ceramide trihexoside	Acral pain and paresthesias, hypohidrosis, corneal and lenticular opacities. Hypertrophic cardiomyopathy, coronary artery disease, CVAs	Renal transplantation, replacement therapy with the deficient enzyme, α-galactosidase A. X-linked recessive disorder
Nail–patella syndrome	Hypoplasia of the nails, with greatest involvement of medial digits; triangular lunulae	Congenital nephrosis, glomerulonephritis	Absence or hypoplasia of the patella, iliac horns	Autosomal dominant disorder due to mutations in *LMX1B*
Birt–Hogg–Dubé syndrome	Classic triad of fibrofolliculomas, trichodiscomas and acrochordons	Renal tumors, particularly chromophobe and hybrid oncocytic carcinomas	Spontaneous pneumothoraces	Due to mutations in the gene encoding folliculin. Surveillance for renal tumors
Familial cutaneous leiomyomatosis	Multiple cutaneous leiomyomas	Predisposition to develop renal carcinoma	Uterine leiomyomas	Due to mutations in the gene encoding fumarate hydratase. Surveillance for renal tumors
		INFLAMMATORY/AUTOIMMUNE		
Systemic lupus erythematosus	Malar erythema, cutaneous LE lesions, photosensitivity, diffuse alopecia, vasculitis	Glomerulonephritis – focal, membranous or proliferative	Arthritis, serositis, cytopenias, multiple autoantibodies, hypocomplementemia	Varies, depending upon the organ system involved and the severity or type of involvement
Scleroderma	Raynaud's phenomenon, acral or diffuse sclerosis, CREST syndrome	Malignant hypertension, rapidly progressive renal failure	Esophageal dysmotility, arthritis, pulmonary fibrosis, pulmonary hypertension	Angiotensin-converting enzyme inhibitors, dialysis, cytotoxic agents
Henoch–Schönlein purpura	Palpable purpura	IgA-associated glomerulonephritis	Arthritis, GI vasculitis	Symptomatic therapy; systemic corticosteroids, and possibly other immunosuppressive agents, may be beneficial for nephritis and severe GI involvement
Polyarteritis nodosa	Nodules, livedo reticularis	Renal artery aneurysms, hypertension	Arthritis, mononeuritis multiplex, abdominal pain, serositis, fever	Corticosteroids with or without cytotoxic agents (e.g. cyclophosphamide)
Wegener's granulomatosis	Palpable purpura, nodules, cutaneous granulomas	Glomerulonephritis	Upper and lower respiratory tract inflammation	Cyclophosphamide, corticosteroids, sulfonamides, methotrexate
Cutaneous small vessel vasculitis	Palpable purpura	Glomerulonephritis may occur, but is less common than in the vasculitides mentioned above	Arthritis	Drug-induced and hepatitis C virus are possible etiologies. Symptomatic therapy or corticosteroids, with or without immunosuppressive agents
Sarcoidosis	Papules, nodules, plaques	Hypercalciuria, nephrolithiasis	Lymphadenopathy, uveitis, pulmonary fibrosis, hepatosplenomegaly, hypercalcemia	Corticosteroids, immunosuppressive agents
		NEOPLASTIC		
Primary systemic amyloidosis (AL)	Pinch purpura, translucent papules, macroglossia	Proteinuria, including nephrotic syndrome, and renal insufficiency	Restrictive cardiomyopathy, paraproteinemia due to plasma cell dyscrasia	Corticosteroids, melphalan, bortezomib, hematopoietic stem cell transplant
		OTHER		
Cutaneous changes of end-stage renal disease	1. Pale color, sallowness 2. Xerosis or acquired ichthyosis 3. Pruritus 4. Acquired perforating dermatosis 5. Pseudoporphyria 6. Calciphylaxis (Fig. 53.37) 7. Uremic frost	End-stage renal disease of various causes. 1–6 are more common in dialysis patients. 7 is rarely observed	1. Anemia of chronic disease 2. – 3. Possible increase in tissue mast cells 4. Related to pruritus 5. Porphyrins may be borderline elevated or within normal limits 6. Obese women are more often affected. Increased $Ca^{2+} \times PO_4^{2-}$ product, increased PTH level. Calcification of the vessel walls	1. Erythropoietin, transplantation 2. Emollients, lactic acid or urea preparations 3. UV light 4. See Table 96.4 5. Erythropoietin, N-acetylcysteine 6. Phosphate binders (non-calcium), surgical debridement, parathyroidectomy may be helpful 7. Dialysis

Table 53.15 Renal disease and the skin. CNS, central nervous system; CREST, *c*alcinosis, *R*aynaud's, *e*sophageal dysmotility, *s*clerodactyly and *t*elangiectasias; CVA, cerebrovascular accident; GI, gastrointestinal; LE, lupus erythematosus; PTH, parathyroid hormone.

Continued

RENAL DISEASE AND THE SKIN				
Disorder	**Cutaneous findings**	**Renal abnormality**	**Other findings**	**Treatment and comments**
Cutaneous diseases associated with long-term immunosuppression	1. Infections – mycobacterial, viral, bacterial, fungal 2. Neoplasia – porokeratosis, squamous cell carcinoma, Kaposi sarcoma	End-stage renal disease of various causes	–	Reduction in level of immune suppression. Treat infections with appropriate antimicrobials. Treat carcinomas with removal of lesions
Nephrogenic systemic fibrosis (NSF) – formerly nephrogenic fibrosing dermopathy (NFD)	Woody indurated plaques on the extremities > trunk, often becoming confluent and limiting motion of the joints. Peau d'orange appearance is common (Fig. 53.38)	Occurs primarily in patients with chronic renal failure on dialysis, but has also been described in renal transplant recipients and patients with acute renal failure	Systemic fibrosis (e.g. of the heart, lungs and skeletal muscle) has been observed. Linked to administration of gadolinium-containing contrast media. Hypercoagulable state also a risk factor	Prevention via assessment of renal function pre-MRI. Renal transplantation, and, based upon small case series, imatinib, rapamycin, UVA1 phototherapy

Table 53.15 Renal disease and the skin (cont'd).

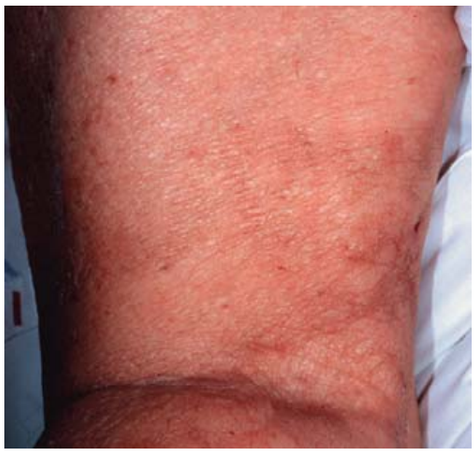


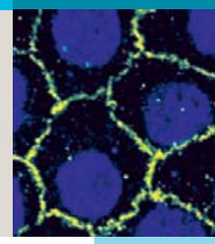
Fig. 53.38 Nephrogenic systemic fibrosis. This sclerosing disorder is seen almost exclusively in patients with renal failure who have received gadolinium-containing contrast media. In addition to the peau d'orange appearance of the skin, this patient had severe restriction of the movement of his hands, wrists and feet.

Pregnancy is an important physiologic state that is associated with its own specific dermatoses and with modification of other dermatoses (see Ch. 27)[31]. Mast cell disease is the subject of Chapter 118. Internal disease can produce profound effects on the nails, hair and mucous membranes, and the reader is referred to the chapters that review these structures in detail. Leg ulcers are also potential dermatologic clues to underlying disease and are discussed in Chapter 105.

REFERENCES

1. Callen JP, Jorizzo JL, Bolognia JB, et al. Dermatological Signs of Internal Disease, 4th edn. Philadelphia: WB Saunders, 2009.
2. Lebwohl MG. The Skin and Systemic Disease. A Color Atlas and Text. New York: Churchill Livingstone, 2004.
3. Sontheimer RD, Provost TT. Cutaneous Manifestations of Rheumatic Diseases, 2nd edn. Philadelphia: Lippincott Williams & Wilkins, 2003.
4. Jorizzo JL, Daniels JC. Dermatologic conditions reported in patients with rheumatoid arthritis. J Am Acad Dermatol. 1983;8:439–53.
5. Sangueza OP, Caudell MD, Menghesha YM, et al . Palisaded neutrophilic granulomatous dermatitis in rheumatoid arthritis. J Am Acad Dermatol. 2002;47:251–7.
6. Thiers BH, Sahn RE, Callen JP. Cutaneous manifestations of internal malignancy. CA Cancer J Clin. 2009;59:73–98.
7. Stone SP, Buescher LS. Life-threatening paraneoplastic cutaneous syndromes. Clin Dermatol. 2005;23: 301–6.
8. Wang J, Zhu X, Li R, et al. Paraneoplastic pemphigus associated with Castleman tumor. A commonly reported subtype of paraneoplastic pemphigus in China. Arch Dermatol. 2005;141:1285–93.
9. Tsao H. Update on familial cancer syndromes and the skin. J Am Acad Dermatol. 2000;42:939–69.
10. Rultak SJ, Brentnall TA, Lynch HT, Austin MA. Characterization of the neoplastic phenotype in the familial atypical multiple-mole melanoma-pancreatic carcinoma syndrome. Cancer. 2003;98:798–804.
11. Köstler E, Porst H, Wollina U. Cutaneous manifestations of metabolic diseases: uncommon presentations. Clin Dermatol. 2005;23:457–64.
12. Jorizzo JL, Callen JP. Dermatologic manifestations of internal disease. In: Arndt KA, Robinson JK, LeBoit PE, et al. (eds). Cutaneous Medicine and Surgery, Philadelphia: WB Saunders, 1996:1863–89.
13. Alberti KGMM, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120:1640–5.
14. Apridonidze T, Essah PA, Iuorno MJ, Nestler JE. Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2005;90:1929–35.
15. Friedewald VE, Cather JC, Gelfand JM, et al. AJC editor's consensus: psoriasis and coronary artery disease. Am J Cardiol. 2008;102:1631–43.
16. Leonardt JM, Heymann WR. Thyroid disease and the skin. Dermatol Clin. 2002;20:473–8.
17. Zone JJ. Skin manifestations of celiac disease. Gastroenterology. 2005;128(4 suppl. 1):S87–91.
18. Boh EE, Al-Smadi RMF. Gastrointestinal disease and the skin. Dermatol Clin. 2002;20:523–46.
19. Bonkovsky HL, Mehta S. Hepatitis C: a review and update. J Am Acad Dermatol. 2001;44:159–81.
20. Lyon CC, Smith AJ, Griffiths CE, Back MH. The spectrum of skin disorders in abdominal stoma patients. Br J Dermatol. 2000;143:1248–60.
21. Callen JP, Fabre VC. Cutaneous manifestations of systemic disease. In: Moschella SL, Hurley HJ (eds). Dermatology, Philadelphia: WB Saunders, 1992:1682–71.
22. Judson MA. Sarcoidosis: clinical presentation, diagnosis and approach to treatment. Am J Med Sci. 2008;335:26–33.
23. Adelmalek NF, Gerber TL, Menter A. Cardiocutaneous syndromes and associations. J Am Acad Dermatol. 2002;46:161–83.
24. McDonnell JK. Cardiac diseases and the skin. Dermatol Clin. 2002;20:503–11.
25. Cordova KB, Oberg TJ, Malik M, Robinson-Bostom L. Dermatologic conditions seen in end-stage renal disease. Semin Dialysis. 2009;22:45–55.
26. Robinson-Bostom L, DiGiovanna JJ. Cutaneous manifestations of end-stage renal disease. J Am Acad Dermatol. 2000;43:975–89.
27. Goldsmith DJA, Black MM. Skin disorders in the setting of renal failure: invited editorial. J Eur Acad Dermatol Venereol. 2001;15:392–8.
28. Knable AL. Cutaneous nephrology. Dermatol Clin. 2002;20:513–21.
29. Cowper SE. Nephrogenic systemic fibrosis: the nosological and conceptual evolution of nephrogenic fibrosing dermopathy. Am J Kidney Dis. 2005;46: 763–5.
30. Center for Disease Control and Prevention (CDC). Nephrogenic fibrosing dermopathy associated with exposure to gadolinium-containing contrast agents – St. Louis, Missouri, 2002–2006. MMWR Morb Mortal Wkly Rep. 2007;56:137–41.
31. Kroumpouzos G, Cohen LM. Dermatoses of pregnancy. J Am Acad Dermatol. 2001;45:1–22.

This page intentionally left blank



54 Basic Principles of Genetics

Maija Kiuru, Amalia Martinez-Mir and Angela M Christiano

'Everything is genetic (except trauma)'
Francis Collins, MD, PhD, meeting of the American Academy of Dermatology, 1995

Key features

- Genetic disease may be caused by defects in one gene (Mendelian or monogenic diseases) or more than one gene (polygenic diseases), but it can also be a result of the interaction of environmental and genetic factors (complex or multifactorial traits)
- The major Mendelian patterns of inheritance are autosomal recessive (e.g. oculocutaneous albinism), autosomal dominant (e.g. Darier disease), X-linked recessive (e.g. hypohidrotic ectodermal dysplasia), and X-linked dominant (e.g. incontinentia pigmenti)
- Factors modifying the basic Mendelian pattern of inheritance include incomplete penetrance, age-dependent penetrance, variable expression, *de novo* mutations, pseudodominant inheritance, genomic imprinting and mitochondrial inheritance
- Chromosomal anomalies can consist of abnormalities in the number (e.g. polyploidy, aneuploidy) or structure (e.g. translocations, inversions) of the chromosomes
- Methods of disease gene identification include functional cloning, linkage analysis followed by positional cloning, and a combination of the two, known as the positional candidate approach
- Genetic variants associated with complex traits can be identified by genome-wide association studies (GWAS), which utilize detailed maps of human sequence variation (single nucleotide polymorphisms, SNPs)

INTRODUCTION

The completion of the human genome sequence, with an estimated size of 3.2 gigabases (gb) and containing approximately 20 000–25 000 genes[1], represents a powerful tool in medicine that facilitates the identification of disease-associated genes. Detailed information on human sequence variation and advanced technologies for its detection have broadened our knowledge of the genetic basis of human disease. It is also becoming clear that epigenetics (heritable changes in phenotype and/or gene expression that do not result from changes in the DNA sequence) are involved in the pathogenesis of medical disorders.

Rapid advances in the development of molecular biology techniques (see Ch. 3), together with the continuing flow of information and tools derived from the human genome, puts the physician in a privileged position, having direct access to clinically relevant genetic information. Consequently, it is important for physicians in general, and dermatologists in particular, to understand basic concepts of genetics (Table 54.1) and become familiar with new technology in order to apply them appropriately in caring for patients and interpret the results of studies that are performed. The wealth of new information also emphasizes the necessity of combined efforts between the clinical and research arms of dermatology.

Access to patients with genetic disorders and accurate clinical descriptions are essential for investigations aimed at the identification of disease-causing genes, which can in turn provide benefits to affected individuals. Such insights have importance in genetic counseling and prenatal diagnosis, and they can also contribute to the identification of at-risk individuals and families (e.g. in population-based screenings), presymptomatic diagnosis, prediction of possible complications and course of a disease, determination of response to pharmacologic interventions and even the development of treatments that target the underlying defect.

Since the early 1980s, the molecular bases of numerous cutaneous genetic disorders have been identified, including many forms of epidermolysis bullosa (EB; see Ch. 32), ectodermal dysplasia (ED; see Ch. 63), ichthyosis (see Ch. 57), and hypotrichosis (see Ch. 69). Although such conditions do not account for the majority of patients in a dermatologist's practice, understanding these diseases has helped to set the stage for the study of more common disorders, such as atopic dermatitis and psoriasis, that have more complex etiologies. The gene identification strategies developed for genetically simpler diseases, and the genes identified, have played a major role in determining the underlying causes of common complex disorders. In recent years, advances in mapping and detecting human sequence variation have led to insights into the genetic bases of complex diseases via genome-wide association studies. The clinician has played, and will continue to play, a key role in the feasibility of such investigations, which are completely dependent on a well-characterized collection of patient samples.

GENETIC DISEASES

Key features

- Accurate information about phenotype and family history is essential in identifying the pattern of inheritance of a particular genetic disease
- Single-gene disorders can follow several different inheritance patterns
- The phenotype can vary based on incomplete penetrance, variable expression and X inactivation
- Heterogeneity at the locus or allelic level can make identification of a gene defect challenging

Although genetic diseases can manifest in several members of a family, this is not the case for all genetic disorders. Likewise, it is not true that any disease present in more than one family member is genetic. Pedigrees in which a genetic disease is transmitted (i.e. segregates or is inherited) can range from a single affected member all the way to multiple generations with many affected members in each generation.

Genetic diseases may be caused by defects in one gene (Mendelian or monogenic diseases) or more than one gene (polygenic diseases), but they can also be the result of the interaction of environmental and genetic factors (multifactorial diseases). In other instances, an aberrant structure or number of one or more chromosomes or a differential parental chromosomal contribution can be the cause of the disease.

In the following sections, we provide an overview of the different types of genetic diseases.

MENDELIAN DISEASES: PATTERNS OF INHERITANCE

A key initial step in the assessment of the risk for each individual in a family with a particular inherited disease is the establishment of the mode of inheritance of the condition. For this purpose, it is essential to collect accurate information on the clinical phenotype and to examine as many family members as possible to define their status

BASIC CONCEPTS IN GENETICS	
Nuclear DNA	• Deoxyribonucleic acid (DNA) contained within nuclei of eukaryotic organisms • Packed into chromosomes • Selectively folded and unfolded to allow the expression of hundreds of genes at different times and in different cell types • Each somatic cell contains approximately 2 meters of DNA[2]
Chromosome	• Organized structures of DNA and proteins that are found within the nucleus • Each diploid organism (including humans) has two sets of chromosomes, one from its father and one from its mother • Each pair of chromosomes is composed of two homologous chromosomes, one from each parent • Humans normally have 23 pairs of chromosomes: 22 pairs of autosomes and one pair of sex chromosomes (XX in females and XY in males) • Chromosomes X and Y share only two small regions, known as the pseudoautosomal regions
Karyotype	• Describes the chromosomal constitution of an individual (e.g. 46, XY or 46, XX)
Haploid cell	• Contains only one chromosome complement or "n" (for humans, n = 23) • Gametes (paternal and maternal) are haploid cells
Diploid cell	• Contains two chromosome complements or "2n" (for humans, 2n = 46) • Human cells (other than gametes) are diploid
Centromere	• A site of constriction in a chromosome that is essential for correct cell division • Depending on the position of the centromere, chromosomes can be: – *Metacentric*: centromere near the middle, two "arms" of similar length – *Submetacentric*: centromere between the center and end, two "arms" of somewhat different lengths – *Acrocentric*: centromere near the end, two "arms" of very different lengths • Composed of a series of proteins (called histones) and repetitive DNA sequences (several thousand kilobases) • Divides the chromosome into two arms: the short (petite) arm or p, and the long arm or q
Telomere	• A region of repetitive DNA (TTAGGG sequence) and proteins at the ends of each chromosome • Plays a key role in the maintenance of chromosomal integrity and ensuring correct replication
Meiosis	• The process of cell division by which a diploid cell from the germline gives rise to haploid gametes via segregation and random assortment of homologous chromosomes • Results in combinations of chromosomes in the daughter cells that are different than that in the parental cell
Mitosis	• The process of somatic cell division of proliferating cells by which the genetic material of a cell is duplicated and equally distributed between the two resulting daughter cells • To achieve this duplication of genetic material, the chromosome replicates itself and forms two *sister chromatids*, which will each become the chromosome of a daughter cell
Locus	• The location of a particular sequence of DNA (a gene or any fragment of DNA) on a chromosome • Since we have two copies of each chromosome, we also have two copies of each locus, which can be identical or different
Gene	• A segment of DNA that encodes a protein (or occasionally an RNA chain) that serves a function
Allele	• Alternative forms of a particular gene or DNA sequence at a given locus • An individual has two alleles at each autosomal locus (one from each parent), and the locus/individual is referred to as: – *Homozygous* if the alleles are identical – *Heterozygous* if the alleles are different (Fig. 54.1) • Since males have only one copy of the X and Y chromosomes, they are *hemizygous* for loci on these two chromosomes
Polymorphic locus	• Exhibits at least two alleles with a frequency in the general population of >1% (see Fig. 54.1) • Can be located within or outside of a gene
Single nucleotide polymorphism (SNP)	• A single nucleotide in a particular location within the genome that has at least two different forms with a frequency of >1% in the general population • Occurs on average every 1000 nucleotides[3]
Mutation	• A change in the DNA sequence • Refers to variation resulting in a disease phenotype • Although any change in the DNA is technically a mutation, the term is often used to refer to a pathogenic variant that results in a disease phenotype
Genotype	• The alleles present at a specific locus (or in the whole genome) of an individual
Phenotype	• The manifestation of a particular genotype (in the context of the environment in which it is expressed) • Different genotypes are not always recognizable as distinct phenotypes • A change in a phenotype can be caused by variant alleles that are present in the general population (normal variation) or by pathogenetic variation that leads to a disease

Table 54.1 Basic concepts in genetics.

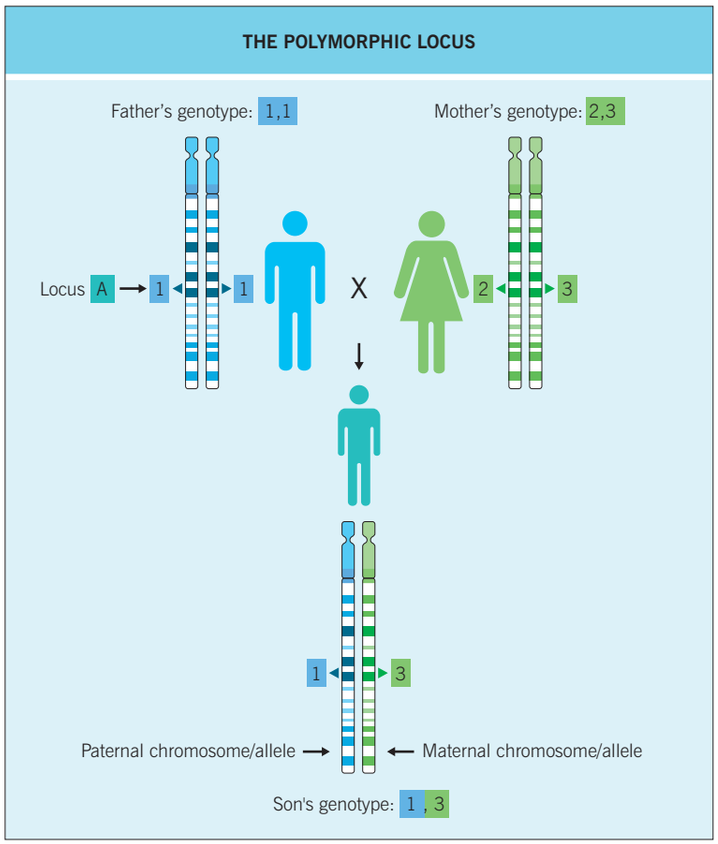


Fig. 54.1 The polymorphic locus. Locus *A* represents a polymorphic locus with three different alleles. The example shows a family in which the father is homozygous for allele 1 and the mother is heterozygous for alleles 2 and 3. The son of this family has inherited allele 1 from the father and allele 3 from the mother, and is thus heterozygous (1,3).

– affected or unaffected. The family is usually ascertained through one family member, the *proband*, around whom the pedigree is built with information on the phenotypes and relationships between different individuals.

Even when a single-gene defect is enough to cause a disease phenotype (monogenic disorders), its expression can be highly variable (see below for incomplete penetrance and variable expression). Genes are expressed on a particular genetic background, which is different in every individual, and genes and their products interact with other genes and proteins. Thus, one can expect that even monogenic disorders may show some degree of variability. If a gene can be subject to different genetic background effects in different individuals, and if this genetic background can modify its expression, then slightly or even considerably different clinical entities can be due to mutations in the same gene; this phenomenon is known as *allelic heterogeneity* (Table 54.2)[4–13]. This term also refers to separate diseases caused by different mutations in the same gene. On the other hand, defects in different genes can result in the same phenotype, known as *genetic or locus heterogeneity* (Table 54.3)[14–21]. Thus, a diagnosis based purely on clinical signs and symptoms can lead to misclassification of a patient on a genetic level, which underscores the relevance of the identification of disease genes.

There are several examples of both allelic and locus heterogeneity in dermatology. As an example of allelic heterogeneity, mutations in the *GJB3* gene that encodes connexin 31 can result in autosomal dominant erythrokeratodermia variabilis as well as autosomal dominant or recessive deafness. In contrast, EB simplex of the localized (Weber–Cockayne) type can result from heterozygous mutations in the keratin 14 or keratin 5 gene. Tables 54.2 and 54.3 list examples of cutaneous disorders with allelic and locus heterogeneity, respectively. Some diseases, such as EB simplex, display both allelic and locus heterogeneity.

Once a phenotype is defined, including its range of variability, the disease phenotype can be followed within the pedigree. The transmission of the trait in the pedigree will define the pattern of inheritance of the disease. The genes responsible for monogenic traits can be located either on autosomes, defining an autosomal phenotype, or on the X chromosome in the case of an X-linked phenotype. Irrespective of the location of the gene, when a mutation in one of two alleles is sufficient to produce the phenotype, the trait is *dominant*. On the contrary, when both alleles of a gene (or, in the case of hemizygotes, one allele) must be altered in order to produce the phenotype, the condition is called *recessive*. Therefore, a phenotype can be inherited as an autosomal dominant or recessive trait or as an X-linked dominant or recessive trait (Table 54.4). There are also Y-linked genes, normally affecting male fertility[22], although their relevance in more general diseases is possible.

EXAMPLES OF ALLELIC HETEROGENEITY IN GENODERMATOSES	
Gene	**Phenotype**
GJB3	Erythrokeratodermia variabilis
	AD non-syndromic sensorineural deafness
	AR non-syndromic hearing loss
	AD deafness with peripheral neuropathy
Desmoplakin	Striate palmoplantar keratoderma
	Dilated cardiomyopathy with woolly hair and keratoderma
	Arrhythmogenic right ventricular cardiomyopathy
Plectin	EBS and limb-girdle muscular dystrophy
	EBS of the Ogna type
	EBS with pyloric atresia
ATP7A	Menkes disease
	Occipital horn syndrome

Table 54.2 Examples of allelic heterogeneity in genodermatoses[4–13]. AD, autosomal dominant; AR, autosomal recessive; *ATP7A*, gene for ATPase, Cu^{2+}-transporting, α-polypeptide; EBS, epidermolysis bullosa simplex; *GJB3*, gene for connexin 31.

EXAMPLES OF GENODERMATOSES WITH GENETIC OR LOCUS HETEROGENEITY				
Phenotype	**Gene**			
EB simplex (Dowling–Meara, Koebner, and Weber–Cockayne variants)	*KRT5* *KRT14*			
Bullous congenital ichthyosiform erythroderma (epidermolytic hyperkeratosis)	*KRT1* *KRT10*			
Hermansky-Pudlak syndrome	*HPS1* *HPS5*	*AP3B1* *HPS6*	*HPS3* *DTNBP1*	*HPS4* *BLOC1S3*
Tuberous sclerosis	*TSC1* *TSC2*			
Hereditary hemorrhagic telangiectasia	*ENG* (endoglin) *ACVRL1*			
Hypohidrotic ectodermal dysplasia	*EDA* (ectodysplasin A) *EDAR* (ectodysplasin A receptor) *EDARADD* (EDAR-associated death domain)			

*Mutations in different genes result in X-linked recessive (EDA), autosomal recessive (EDAR, EDARADD) and autosomal dominant (EDAR, EDARADD) forms of the disorder.

Table 54.3 Examples of genodermatoses with genetic or locus heterogeneity[14–24]. *ACVRL1*, gene for activin A receptor type II-like 1; *AP3B1*, gene for beta-3A subunit of AP3; *BLOC1S3*, gene for biogenesis of lysosome-related organelles complex-1, subunit 3; *DTNBP1*, gene for dystrobrevin binding protein 1 (dysbindin); EB, epidermolysis bullosa; *HPS*, genes for Hermansky–Pudlak syndrome; *KRT*, genes for keratins; *TSC*, genes for tuberous sclerosis complex.

PATTERNS OF INHERITANCE					
Pattern	**Parents affected**	**Gender affected**	**Transmission**	**Recurrence risk**	**Risk factors**
Autosomal recessive	No (carriers)	Both equally	Disease seen in siblings of proband, not in parents or offspring Usually seen in one generation	1 in 4	Consanguinity, isolated population (e.g. geographically, linguistically)
Autosomal dominant	Yes	Both equally	Disease seen in every generation	1 in 2	*De novo* mutations
X-linked recessive	Mother a "carrier"	Males have the "full" disease Female "carriers" may have mild manifestations (e.g. in a mosaic pattern)	No male-to-male transmission (but all daughters of an affected male are "carriers")	1 in 2 male children born to a female "carrier" will be affected (and 1 in 2 of her female children will be carriers)	*De novo* mutations
X-linked dominant	Yes	Predominantly females if lethal in males during embryonic development; otherwise milder in females (often with a mosaic pattern of skin lesions) than in males	Affected males have: (1) no affected sons; and (2) all daughters affected No male-to-male transmission	1 in 2 children born to affected female (may spontaneously abort male fetuses if "male lethal" condition)	*De novo* mutations; tend to be lethal in males

*Unless the proband has a *de novo* mutation and is therefore the first generation affected.

Table 54.4 Patterns of inheritance.

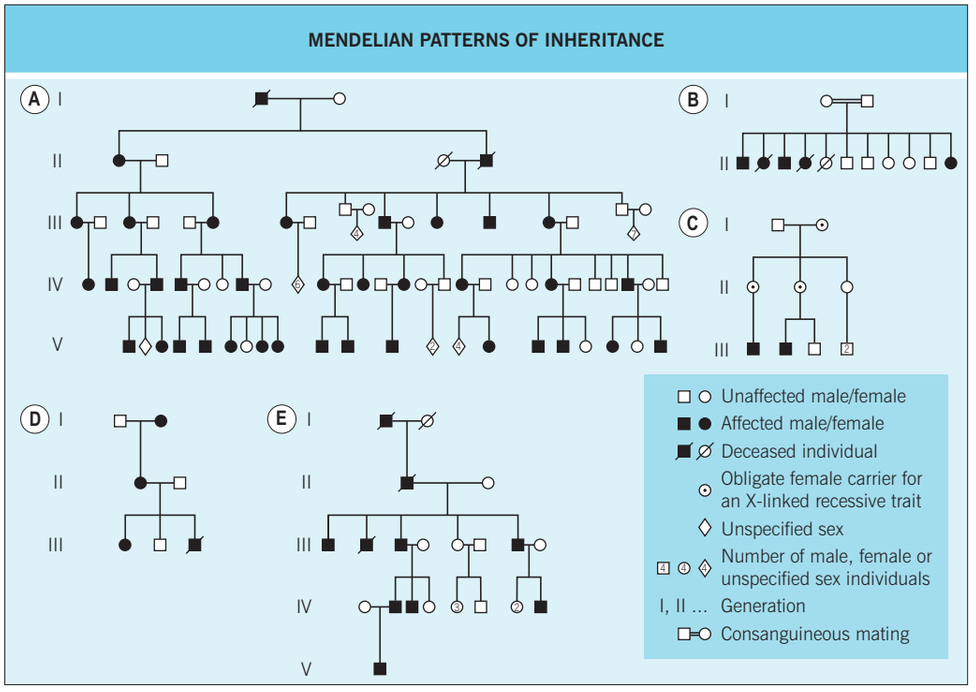


Fig. 54.2 Mendelian patterns of inheritance. **A** Autosomal dominant epidermolysis bullosa simplex superficialis (adapted from ref. 27). **B** Autosomal recessive woolly hair, palmoplantar keratoderma and cardiomyopathy (adapted from ref. 26). **C** X-linked recessive immune deficiency and hypohidrotic ectodermal dysplasia (adapted from ref. 24). **D** X-linked dominant incontinentia pigmenti (adapted from ref. 25). **E** Y-linked retinitis pigmentosa (adapted from ref. 23).

Of note, although this chapter focuses on genodermatoses, this information regarding Mendelian or complex traits applies to extracutaneous diseases.

Autosomal Dominant Inheritance

In a pedigree of an autosomal dominant disease, each affected person (other than the first affected family member, who has a *de novo* mutation) has an affected parent, both sexes are equally affected and can transmit the trait, and there is transmission from generation to generation (Fig. 54.2A)[23–27]. A single mutant allele is enough to give rise to the phenotype. Thus, each offspring of an individual with an autosomal dominant disorder has a 50% risk of inheriting the mutant allele.

An autosomal dominant trait can be transmitted from father to son, and it cannot be transmitted by an unaffected individual (see below for a discussion on incomplete penetrance). Examples of autosomal dominant genodermatoses are EB simplex, Darier and Hailey–Hailey diseases and nail–patella syndrome.

A patient with an autosomal dominant disease is usually heterozygous for the disease-causing mutation. Although infrequent, homozygotes for autosomal dominant diseases have been reported, and they usually exhibit a more severe phenotype compared with heterozygotes. An example of this would be a family with a mutation in the *KRT14* gene, which in heterozygous form gives rise to EB simplex of the localized type and in homozygous form results in more severe EB simplex of the generalized (Koebner) type[28].

There are, however, exceptions to the rules, mainly due to incomplete penetrance, variable expression or *de novo* mutations (see below).

Autosomal Recessive Inheritance

In a pedigree of an autosomal recessive disease, an affected individual has clinically unaffected parents, both sexes are equally affected, and there is no transmission from generation to generation (Fig. 54.2B). Both alleles of a given gene must be mutated for the disease to develop. For each offspring, the chance of inheriting the disorder is 25%.

Type I oculocutaneous albinism and atrichia with papular lesions (a rare form of total alopecia) are examples of autosomal recessive genodermatoses.

There is often an increased frequency of *consanguinity* (sharing a common ancestor) in families with recessive conditions. Consanguineous matings increase the probability that a mutated allele present in the common ancestor will become homozygous in the offspring of the related parents (homozygosity by descent). When more than one affected family member with an autosomal recessive disease is present in a single pedigree, they are usually part of the same generation. However, the presence of consanguinity (inbreeding) can also explain some pedigrees in which an autosomal recessive trait is observed in more than one generation. For example, matings between unaffected carriers and affected patients give rise to affected family members in two consecutive generations (pseudo-dominant inheritance; see below).

A patient with an autosomal recessive disease has inherited two copies of the disease-causing mutation, while both parents are heterozygotes for the mutant gene (i.e. they are carriers of one mutant copy as well as having one normal copy). Both parents can carry the same mutation, thus the patient will be homozygous for the disease-causing mutation, or the parents can carry two different mutations affecting the same gene, and the patient will be *compound heterozygous*.

X-linked Recessive Inheritance

Patients with an X-linked recessive disease are typically male; they usually have unaffected parents, but their mother may have some evidence of the condition due to functional mosaicism (see Ch. 62). There is no male-to-male transmission, since an affected male will transmit the Y chromosome and not the mutant X chromosome to his son, and (excluding mosaic manifestations in women, which remove the condition from the "true" X-linked recessive category) the trait does not appear in successive generations (Fig. 54.2C).

The inheritance risk for the offspring will depend on the parent transmitting the disease allele. An affected father will transmit the mutated allele (but not the complete disease) to all his daughters, but to none of his sons. All the daughters of an affected man will be obligate carriers, since they will all inherit the mutated allele from the father. An obligate female carrier will transmit the mutated allele to 50% of her children. Thus, sons and daughters of a carrier mother will have a 50% chance of being affected or carriers, respectively.

The two main characteristics of an X-linked recessive trait are the absence of male-to-male transmission and female carriers being asymptomatic. Regarding the former, one clearcut exception is the offspring of an affected male and a female carrier. In some instances, female "carriers" may have clinical manifestations in a mosaic pattern; with variable skewing of X-inactivation (see below), the spectrum of disease can range from absent to severe. As a result, the distinction between "recessive" and "dominant" may be blurred in this group of patients.

Examples of recessive X-linked diseases in dermatology are X-linked ichthyosis (steroid sulfatase deficiency; see Ch. 57), hypohidrotic ectodermal dysplasia, and Menkes disease.

X-linked Dominant Inheritance

In a pedigree of an X-linked dominant disease, affected individuals (other than the first affected family member, who has a *de novo* mutation) have at least one affected parent and (unless male-lethal) the disorder occurs in both males and females. However, females (who are heterozygous rather than hemizygous) generally have a milder and/or mosaic phenotype (see below). There is no male-to-male transmission, and the trait appears in successive generations (Fig. 54.2D). The risk of the offspring inheriting the disease depends on the transmitting parent. An affected father will transmit the trait to all his daughters, but to none of his sons. An affected mother, on the other hand, will transmit the trait to 50% of her children, regardless of the sex of the offspring. Some X-linked dominant diseases are lethal in males during early intrauterine development. In this situation, the disorder is seen almost exclusively in females (who may have an increased frequency of spontaneous abortions when they become pregnant). Occasional male patients can be explained by mosaicism, either functional in the setting of Klinefelter syndrome (47, XXY karyotype) or genomic due to mosaicism secondary to a *de novo* half-chromatid or postzygotic mutation (see Ch. 62).

Because of lyonization (the random epigenetic inactivation of one of the two X chromosomes in each cell in female embryos; see below), female patients with X-linked dominant skin diseases typically have a mosaic pattern of cutaneous lesions. Non-random patterns of X inactivation in these patients may reflect preferential survival of cells expressing the normal X chromosome. Examples of X-linked dominant diseases in which girls present with a mosaic pattern of skin findings are focal dermal hypoplasia (Goltz syndrome)[29] and incontinentia pigmenti[30]. Girls with both disorders present with cutaneous, dental and ocular abnormalities, whereas for boys, lethality *in utero* is presumed.

Y-linked Inheritance

In a pedigree with a Y-linked disease (holandric inheritance), affected boys always have affected fathers and only males are affected. All sons of affected fathers are affected (Fig. 54.2E).

There are relatively few Y-linked disorders, and most of them affect male fertility[22]. Possible examples affecting other organs have been described[23], but their Y-linked inheritance cannot be proven.

EXCEPTIONS TO BASIC MENDELIAN PATTERNS OF HERITANCE

By definition, Mendelian diseases are the result of mutations in a single gene. But, as mentioned previously, this gene can modify and be modified by other genes as well as by epigenetic factors and the environment. Thus, although the presence of the genotype at a single locus is still responsible for having the disease phenotype, the final manifestation of phenotype can be subject to variation in its expression. The following sections describe single-gene defects that, by means of variability in the expression of the mutant allele or by the location of the mutant gene, constitute apparent or real deviations from the basic Mendelian patterns of inheritance outlined above.

Incomplete or Reduced Penetrance and Late-Onset Diseases

As defined above, a carrier of a dominant mutation or a homozygote (or compound heterozygote) for recessive mutations will manifest the disease phenotype. This is true for many genetic traits, but there are some exceptions to this rule. In terms of genetic counseling, these exceptions can present a dilemma.

Incomplete or reduced penetrance refers to situations where not all the individuals who carry the disease genotype manifest the condition. The degree of penetrance indicates the probability of an individual with the disease genotype developing the disease phenotype. Penetrance is an "all-or-nothing" phenomenon, in which some individuals who have inherited the disease genotype do not express the disease phenotype at all. An example of the result of incomplete penetrance would be an autosomal dominant pedigree with an affected individual, unaffected parents, but an affected grandparent. As a consequence, the trait appears to skip a generation (Fig. 54.3A)[31,32].

A particular type of incomplete penetrance is the so-called late-onset diseases, characterized by age-dependent penetrance. Some diseases exhibit complete penetrance, but only starting from a certain age. The trait is manifest from birth in congenital diseases, but there are many other disorders where the symptoms appear later in life. Darier and Hailey–Hailey diseases are good examples of age-dependent penetrance, in which the main features of the disease usually develop in the second to fourth decades[33,34]. Age-dependent penetrance presents a challenge for genetic counseling and the establishment of the inheritance pattern of a trait, since some individuals may be too young to know whether or not they are affected.

Variable Expression

Not only can a disease genotype completely fail to appear (reduced penetrance), but there may be variation in the severity of the findings that develop. This variation can be interfamilial (between families) or even intrafamilial (within a family). Different degrees of phenotypic

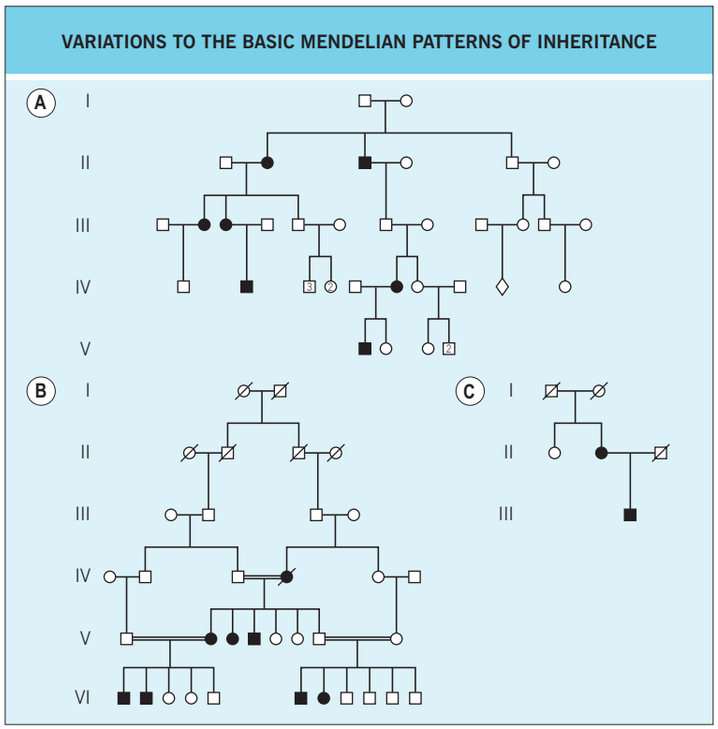


Fig. 54.3 Variations to the basic Mendelian patterns of inheritance. **A** Reduced penetrance in a pedigree with autosomal dominant retinitis pigmentosa (adapted from ref. 31). **B** High degree of consanguinity in a family with hypotrichosis, with affected family members in several generations. **C** Pseudodominant inheritance in autosomal recessive atrichia with papular lesions (APL). The inheritance of APL in this pedigree mimics an autosomal dominant pattern of inheritance resulting from the mating between a patient homozygous for the causative genetic mutation (II:2) and an unaffected carrier (adapted from ref. 32). The key for symbols commonly used for pedigree drawing is indicated at the bottom of Figure 54.2.

manifestation of a particular genotype is called *variable expression* (variable expressivity). Darier disease and neurofibromatosis type 1, for example, display complete penetrance in adults, but they have a broad range of severity[35].

The variable expression of some traits manifests as a tendency to increase in severity and decrease in the age of onset through successive generations. This phenomenon is referred to as *genetic anticipation*, and it presents an additional challenge in genetic counseling. Most of these disorders are neurologic or muscular diseases, such as Huntington disease and Friedreich ataxia. The molecular basis of genetic anticipation is now known. Certain genes contain a variable number of repeats of a three-nucleotide sequence, known as a trinucleotide. There is a range in the number of these repeats in the general population, as a part of normal variation. Through an unknown mechanism (DNA polymerase "slippage" has been hypothesized), the number of these repeats can increase dramatically and enter the disease-associated range. In general, the number of repeats within this range tends to increase through generations (although it can also decrease). The severity and age of onset of the resulting phenotype correlates with the length of the repeat. The paradigm of genetic anticipation is myotonic dystrophy, with a "cascade of mild, adult, childhood, and then congenital disease" in successive generations[36].

X Inactivation

Although women have a double dose of the X chromosome compared with men, for most of the X-linked genes (with one exception being those in the pseudoautosomal region), any particular cell in a woman's body has only a single active X chromosome. The mechanism of *X inactivation (lyonization)* is responsible for this dosage compensation in women. During embryonic development, one of the two X chromosomes in each cell is randomly inactivated via epigenetic mechanisms. From this stage on, all the derived ("daughter") cells have the same inactivated X chromosome as their progenitor cell. As a result, a woman has two alleles for every gene located within the X chromosome, but a given cell expresses only one of them. If one of these alleles contains a disease-causing mutation, the resulting phenotype will depend on the proportion of cells expressing that mutated allele in a particular tissue. As noted above, this explains why female "carriers" of X-linked recessive conditions can manifest some symptoms of the disease, and an X-linked dominant phenotype in girls is usually milder than in boys (where it may even be lethal).

On average, each allele of an X-linked gene is active in half of the cells in a woman. But this proportion varies, and in some instances a particular X chromosome is active in a large proportion of cells, which is known as skewed or non-random X inactivation. For example, girls with incontinentia pigmenti (due to mutations in the *NEMO* gene; see Ch. 62) have highly skewed X inactivation, suggesting a negative selection against cells with an active mutant allele[30]. Non-random X inactivation has also been observed in hematopoietic cells of female carriers of X-linked dyskeratosis congenita[37].

Balanced X;autosome translocations also result in non-random X inactivation, usually of the normal (not translocated) X chromosome. This is thought to explain fully affected females in some X-linked recessive diseases. Such is the case for hypohidrotic ectodermal dysplasia in carriers of a t(X;9) translocation[38].

De novo Mutations

In a population, the different alleles of a genetic locus responsible for both normal variation and disease phenotypes arise by mutational events in the DNA. An example is when a fully penetrant autosomal dominant genetic disease appears in a child with no previous family history of that condition. In such instances, the underlying *de novo* mutation usually occurred during meiosis in one of the parents. *De novo* mutations account for a higher proportion of affected individuals in dominant diseases that are severe or otherwise decrease reproductive fitness than in milder dominant conditions.

The identification of *de novo* mutations can have a profound impact on genetic counseling. A recessive condition commonly presents with a single affected child born to unaffected parents; future children born to these parents each have a risk of 25% of the disease, but (in the absence of further consanguinity) the likelihood of the child eventually having affected offspring will reflect the prevalence of the mutant allele in the general population. In contrast, if a single affected child born to unaffected parents has a *de novo* dominant mutation, there is no recurrence risk for the future offspring of the parents, since a second *de novo* mutation at the same gene would be highly unlikely. However, the affected child will transmit the mutation to 50% of his or her offspring, as typically seen for an autosomal dominant trait. An exception to the extremely low recurrence risk for the parents in the second scenario is the situation of gonadal mosaicism (see below).

De novo mutations occur with varying frequencies in different disorders. Up to 50% of patients with neurofibromatosis type 1 or tuberous sclerosis (both autosomal dominant conditions with very high penetrance) have a *de novo* mutation. As another example, in dominant dystrophic EB, the same *de novo* mutation, Gly2043Arg, in the type VII collagen gene *(COL7A1)* has occurred independently throughout the world[39].

Mosaicism and Chimerism

X inactivation represents a *functional* form of mosaicism, with each cell expressing the genes from only one of the two X chromosomes. *Genomic* mosaicism characterized by an alteration in the DNA sequence (affecting genes or chromosomes) can also occur, giving rise to a genetically heterogeneous organism and potentially causing disease. When a mutation or chromosomal abnormality occurs in a cell during embryonic development (referred to as a postzygotic or somatic mutation), its descendent cells carry the same mutation. The rest of the cells, not affected by the mutation, carry the wild-type (non-mutant) allele. The result is a mosaic individual with two different cell populations. The location of the cell and the timing of the mutational event during development determine both the distribution and extent of the cells carrying the mutation in the affected individual, and the potential for passing on the trait to future generations (see Ch. 62).

As noted above, when an individual has a *de novo* dominant mutation, the risk of the parents of that individual having a second

affected child is normally extremely low. But there are some instances in which a second child is unexpectedly affected, although a *de novo* mutation was initially suspected. This is usually due to *gonadal (germline) mosaicism* in one of the parents (see Ch. 62). If a dominant postzygotic mutation occurs after the separation of the gonadal and somatic cell lineages and it affects the latter, the risk for transmitting the trait to the offspring of that individual is zero. However, if the mutation took place in a gonadal cell or precursor, a proportion of that individual's gametes will carry the mutated allele. In the first affected generation, the inheritance pattern will mimic that of an autosomal recessive trait, since affected children will be born to unaffected parents. But inheritance will follow a classic autosomal dominant pattern in subsequent generations. The key information for genetic counseling is whether the mutation is present in the gondads of the mosaic individual. The extent of involvement of the gonads will determine the recurrence risk for the offspring.

Gonadal mosaicism has been documented in several disorders, including neurofibromatosis type 1 and dominant dystrophic EB. In one report involving dominant dystrophic EB, a mutation was identified in an affected child born to unaffected parents[40]. Although a *de novo* mutation was the most likely explanation, the possibility of gonadal mosaicism was considered and prenatal diagnosis was performed during the parents' next pregnancy. The results indicated that the fetus had an identical mutation to that of the affected child, indicating gonadal mosaicism in one of the parents.

When mosaicism affects the skin, it can become evident by the appearance of skin changes (e.g. hypo- or hyperpigmentation, scaling, inflammation) following the lines of Blaschko or in other segmental patterns (e.g. a block-like distribution) (see Ch. 62)[41]. Mosaic involvement of the skin in autosomal dominant disorders has been classified into two types (see Fig. 62.2). In *type 1*, the "segmental" affected skin carries a heterozygous mutant allele, while the genotype of the skin outside the affected areas (which is normal in appearance) bears two wild-type alleles. Examples include epidermal nevi and segmental forms of Darier disease. In *type 2*, the segmental disease occurs in the setting of milder, more diffuse involvement with the same phenotype. These individuals have one mutant allele in all the cells of the body (giving rise to the diffuse phenotype), and a "second hit" mutation that inactivates or deletes the wild-type allele (e.g. loss of heterozygosity; see below) in the more severely affected segment. Examples include linear porokeratosis superimposed on disseminated superficial actinic porokeratosis, segmental leiomyomas in individuals with hereditary leiomyomatosis (see below), and segmental Hailey–Hailey disease in the setting of milder classic symmetric disease[42–44]. In patients with type 1 segmental skin disease, the possibility of gonadal (in addition to somatic) mosaicism must be considered. An example would be a parent with an epidermolytic nevus having a child with epidermolytic ichthyosis (bullous congenital ichthyosiform erythroderma).

In *revertant mosaicism*, a postzygotic mutation leads to recovery of the wild-type phenotype (either partially or completely) within a subpopulation of cells in an individual who has a genetic disease[45]. Mechanisms for revertant mosaicism include a "back" mutation (i.e. reversing the original point mutation), mitotic recombination (with crossing-over of homologous chromosomes leading to homozygous mutant and homozygous normal daughter cells), gene conversion (where the donating chromosome is unchanged), and a second site mutation (e.g. that silences a dominant negative allele). Revertant mosaicism affecting the skin has been documented in ichthyosis en confetti and several types of EB[45].

Finally, the different populations of cells present in a mosaic derive from a single, homogenous zygote. In contrast, there are examples of individuals with cell populations that have completely different genetic composition. They are known as *chimeras,* and the different cell populations are thought to result from fusion of two zygotes (i.e. fused dizygotic twins) or fertilization of one egg by two sperm.

Inbreeding

Inbreeding is one of the factors that can modify the frequency of alleles in a population, increasing the number of homozygotes. Mating between two individuals who share a common ancestor is referred to as *consanguineous*.

A recessive mutation can pass undetected through generations in the heterozygous state. If a carrier of a recessive mutation has children with a carrier of another (or the same) recessive mutation in the same gene, each of their offspring has a 25% likelihood of inheriting both mutant alleles and therefore manifesting with the disease. The overall incidence of a recessive disorder depends upon the frequency of recessive mutant alleles of the affected gene in the general population. However, in inbred populations, the probability that two carriers of a mutation (typically the same mutation originating from a common ancestor) will mate is significantly higher. This explains the increased prevalence of consanguinity that is observed in families with autosomal recessive diseases. Consanguinity is especially frequent in diseases where the mutant alleles are extremely rare within the general population.

Affected offspring from a consanguineous mating are homozygous not only for the pathogenic mutation but also for the region surrounding that mutated gene, which reflects two copies of the same chromosomal region traveling from the common ancestor through different branches of the family and coming together again in the consanguineous mating. The affected offspring are called *homozygous by descent*, indicating that both mutant alleles originate from the same ancestral mutant allele. When there is only one affected family member, the presence of consanguinity in that individual's parents makes an autosomal recessive condition more likely. When analyzing a pedigree, it is important to consider the possibility of consanguinity (even if unknown to the parents), especially if unaffected parents of an affected child originate from the same geographic area or belong to the same small ethnic group.

Since there is a higher probability that any two persons are related in an inbred population, it is also possible that consanguineous matings can occur more than once in the same pedigree. In these situations, one can find affected individuals in different generations of a kindred, simulating an autosomal dominant trait (Fig. 54.3B).

Most of the considerations discussed previously for consanguineous matings can also be applied to populations derived from a small group of ancestors and subjected to geographic or linguistic isolation (e.g. Finnish, Icelandic and French-Canadian populations). If one of the ancestors carried a particular recessive mutation, it would be overrepresented in that "isolated" population. Known as the *founder effect*, this explains much higher incidences of certain diseases in isolated populations compared with other groups. For example, a large proportion of the current Caucasian population in South Africa descends from a small number of Dutch settlers, and the high incidence of porphyria variegata (see Ch. 49) in South Africans today has been traced back to a few of these settlers in the seventeenth century[46].

Quasidominant (Pseudodominant) Inheritance

The inheritance of an autosomal recessive trait can also mimic an autosomal dominant pattern (Fig. 54.3C) when an individual with an autosomal recessive disorder mates with a carrier of a recessive mutation in the same gene. In these situations, each child has a 50% probability of inheriting two mutant alleles. Although this is the same risk as for an autosomal dominant trait, this parent-to-child transmission does not occur in successive generations, unless the unlikely event of a mating between a homozygote and a heterozygote occurs a second time. Instead, the subsequent risk of having an affected child reflects the prevalence of the mutant allele in the general population. These situations can happen in both inbred and "outbred" populations, although the probability of such matings is increased in the former.

An example of pseudodominant inheritance was reported in a family in which a mother and her son had atrichia with papular lesions (suggesting dominant inheritance), even though this disorder is typically inherited in an autosomal recessive manner. Molecular analysis revealed that both the affected mother and son were homozygous for mutations in the same gene, in accordance with the recessive nature of the disease (see Fig. 54.3C)[32].

Loss of Heterozygosity

There are some disorders in which susceptibility to the development of certain tumors is inherited as a Mendelian trait. In these cases, affected individuals usually carry a heterozygous germline mutation in a tumor suppressor gene that is involved in the regulation of cell

growth. Inactivating (loss-of-function) mutations in both alleles of a tumor suppressor gene can contribute to tumor formation (see Ch. 107). Individuals in these families are at higher risk of developing a tumor, since a single somatic mutation inactivating the second (normal) allele of the same gene can trigger tumor formation. For this reason, inherited forms of cancer susceptibility often result in the development of multiple tumors in the same individual, as opposed to the single tumors typically found in sporadic cases. When the former tumors are analyzed, two mutations are identified in the tumor suppressor gene: (1) the germline mutation; and (2) a new somatic mutation, which is referred to as a "second hit"[47].

One type of somatic mutational event that commonly occurs in tumors is known as *loss of heterozygosity (LOH)*. When analyzing the DNA of tumor samples from an individual heterozygous for specific polymorphisms (usually microsatellites; see below), the results from the tumor may show homozygosity for a single allele instead of the heterozygosity seen in their constitutional DNA. Known as LOH, this phenomenon may result from a deletion that encompasses the normal allele or gene conversion that leads to two copies of the mutant allele (known as copy neutral LOH). Advanced tumor cells can show extensive LOH throughout the genome. Certain regions for which LOH is frequently observed have been shown to represent the locations of tumor suppressor genes.

Examples of inherited tumor susceptibility syndromes involving the skin include hereditary leiomyomatosis and renal cell cancer (HLRCC)[48] and the nevoid basal cell carcinoma syndrome (Gorlin syndrome)[49]. HLRCC is caused by a heterozygous germline mutation in the fumarate hydratase tumor suppressor gene (*FH*), and tumors (including cutaneous leiomyomas) display LOH or a second loss-of-function mutation in *FH*[48]. Gorlin syndrome (characterized by multiple basal cell carcinomas, medulloblastomas and jaw cysts) is caused by a germline mutation in the patched 1 gene (*PTCH1*)[49]. The tumors that develop in affected individuals typically display LOH in the *PTCH1* locus, also following the "two-hit" model of carcinogenesis.

Mitochondrial Inheritance

Mitochondrial inheritance is an example of a single-gene defect that does not follow a classic Mendelian pattern of inheritance (see Ch. 63). Every cell has many mitochondria, each containing one or more copies of the mitochondrial genome, a 16 kb circular DNA molecule. Only females pass mitochondria to their offspring, so there is no paternal complement. During cell division, mitochondria segregate randomly to each of the two daughter cells. Thus, if a mother carries a mutation in one gene located on the mitochondrial chromosome in only some of her mitochondria, the daughter cells can inherit a variable number of organelles carrying the mutation. A situation where all mitochondria carry the mutation is known as *homoplasmy*, and a mixture of mitochondria carrying the normal or the mutant version of the gene is known as *heteroplasmy*. The resulting phenotype will depend on the proportion of mutant versus normal mitochondria in a specific tissue.

Mitochondrial inheritance leads to a pedigree where both women and men can be affected, but only women transmit the disease trait. The proportion of affected children seems to be random, and there is a high degree of variability in the expression of the phenotype.

As an example, a transition from adenine (A) to guanine (G) at position 7445 of the mitochondrial DNA, affecting the gene encoding the tRNA for serine, has been identified as the cause of a form of palmoplantar keratoderma with or without associated sensorineural deafness. In these pedigrees, the disease presents with incomplete penetrance and with varying severity[50,51].

Phenocopy

A phenocopy refers to clinical findings caused by environmental factors that mimic the phenotype of a genetic disorder. Porphyria cutanea tarda (PCT), for example, is an autosomal dominant disorder caused by mutations in the *UROD* gene that encodes uroporphyrinogen decarboxylase. Affected patients are predisposed to fragility and bullae in sun-exposed areas. A similar phenotype can be caused by exposure to certain chemicals. Between 1955 and 1961, approximately 3000 patients developed PCT in Turkey because of exposure to hexachlorobenzene, which is used to preserve wheat seeds. PCT has also been reported in individuals with industrial exposure to certain hydrocarbons[52] and pesticides[53].

Epigenetics and Imprinting

Epigenetics refers to heritable changes affecting gene expression that do not result from alterations in the DNA sequence[54]. Epigenetic changes can involve DNA methylation or modification of histones (e.g. acetylation and deacetylation) and chromatin. RNA-dependent gene silencing can also occur under the influence of small and large RNA species, including small interfering RNAs (siRNAs)[55], microRNAs (miRNAs)[56] and large intervening non-coding RNAs (lincRNAs)[57].

Imprinting is an epigenetic phenomenon in which the sex of the transmitting parent determines whether particular genes are expressed in the offspring (Fig. 54.4). For example, mating of a male lion with a female tiger results in the giant "liger" (due to inheritance of a growth gene from the lion father that is "turned on"), whereas a male tiger and female lion produce a considerably smaller "tigon" (due to inheritance of a growth gene from the lion mother that is "turned off").

The effect of imprinting is especially apparent in the case of *uniparental disomy (UPD)*, where both homologous chromosomes are derived from the same parent, instead of one from each parent. In *heterodisomy* two different homologues are inherited from the same parent, and in *isodisomy* a single chromosome from one parent is duplicated. UPD can go undetected for some chromosomes, while it results in a disease phenotype for others. An example of the latter is UPD for chromosome 15 in Prader–Willi and Angelman syndromes (Fig. 54.5).

Uniparental isodisomy that affects a recessive mutant allele can result in homozygosity. The Herlitz type of junctional EB, (JEB-H; also an example of locus heterogeneity) is an autosomal recessive disorder

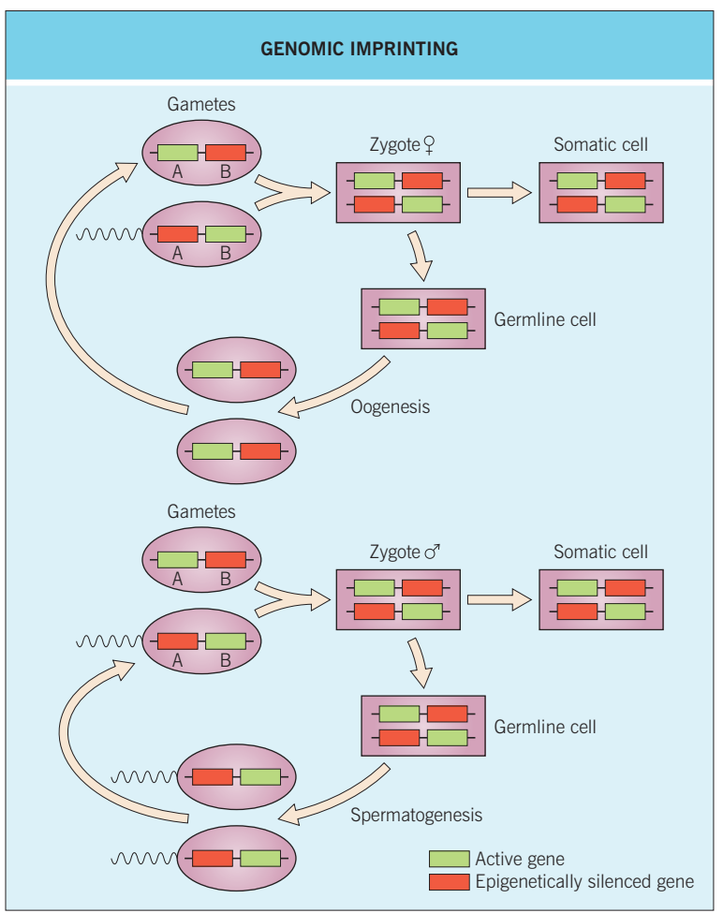


Fig. 54.4 Genomic imprinting. Genes A and B are epigenetically silenced in male and female gametes, respectively. Somatic cells in males and females will maintain the imprinting pattern present in the gametes. In the germline, on the contrary, the imprinting will be erased and the corresponding sex-specific imprint established.

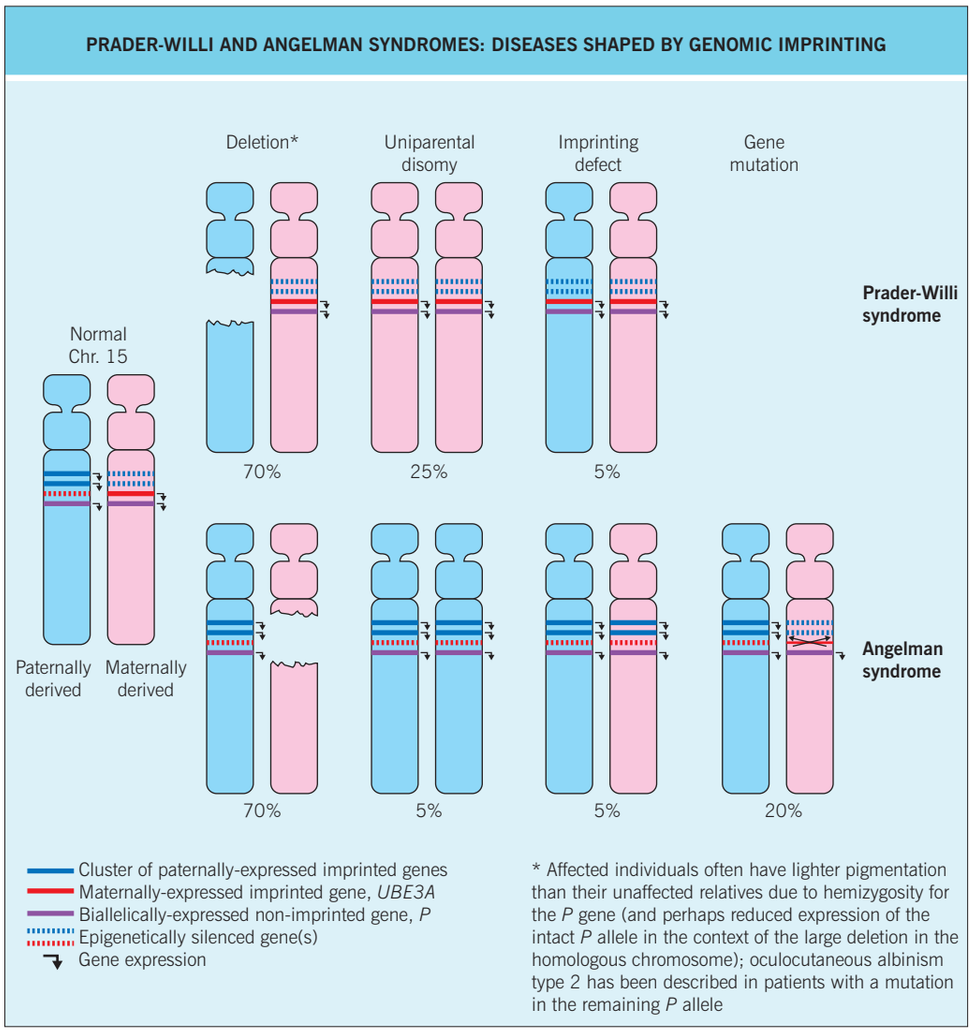


Fig. 54.5 Prader–Willi and Angelman syndromes: diseases shaped by genomic imprinting.

that can be caused by mutations in one of three genes encoding subunits of laminin – *LAMA3*, *LAMB3* and *LAMC2*. Both paternal and maternal UPD have been described in JEB-H patients[58]. For example, paternal uniparental isodisomy was found to underlie homozygosity for a paternal *LAMC2* mutation in one patient[59]. Similarly, maternal isodisomy has been reported to result in homozygosity for a maternal *COL7A* mutation in children with recessive dystrophic EB[60].

In addition to their roles in monogenic diseases, epigenetic changes are involved in cancer. Cancer is typically characterized by global hypomethylation and site-specific hypermethylation. The hypomethylation activates growth-promoting genes such as *HRAS*, cyclin D1 (*CCND1*) and those in the melanoma antigen family (*MAGE*)[54]. By contrast, hypermethylation silences tumor suppressor genes such as retinoblastoma 1 (*RB1*), von Hippel-Lindau (*VHL*), and adenomatosis polyposis coli (*APC*)[54]. Epigenetic alterations can also contribute to inflammatory disorders such as systemic lupus erythematosus.

CHROMOSOMAL DISORDERS

Key features

- Chromosomal abnormalities account for >50% of spontaneous abortions
- Defects in chromosomal number or structure can result in disease
- Chromosomal rearrangements can be useful in identifying disease genes located near breakpoints

The above sections discuss disease-causing mutations that affect a single gene, but this is not always the case. For example, the majority of spontaneous abortuses exhibit chromosomal anomalies[61], which typically involve multiple genes contained in the affected region.

Chromosomal anomalies can affect the number or structure of chromosomes. The differences in DNA composition along a chromosome have allowed the development of banding techniques that distinguish each chromosome in a karyotype; chromosomal anomalies, both numerical and structural, can also be recognized. In addition, the use of fluorescence *in situ* hybridization (FISH), which detects DNA sequences as short as 1 kb[2], allows the identification of very small changes in the chromosomal constitution that are not visible by the use of conventional banding techniques. Furthermore, advances in microarray technology have enabled the use of array-based comparative genomic hybridization for detection of genomic copy number variations at a considerably higher level of resolution than chromosome-based methods.

Chromosomal numerical abnormalities can involve the whole genome (polyploidy) or just one pair of homologues (aneuploidy). The only forms of polyploidy observed in humans are triploidy with three complete sets of chromosomes (3*n*), and tetraploidy with four chromosome complements (4*n*). However, unless mosaic, polyploidy results in a spontaneous abortion or death soon after birth. Aneuploidy refers to extra or missing chromosome(s). The only observed aneuploidies are trisomies, with three copies of a single chromosome, and, less often, monosomies. Trisomies for a whole chromosome that are compatible with extrauterine life (outside the setting of mosaicism) involve chromosomes 21 (Down syndrome), 18 (Edwards syndrome), 13 (Patau syndrome) and 23 (XXY, Klinefelter syndrome; XYY). Monosomy for

the X chromosome (Turner syndrome) can also occur. Other trisomies and monosomies may be observed in mosaic or partial (e.g. due to translocations) forms.

Structural abnormalities involve breakage of chromosomes. They are *balanced* if there is no net gain or loss of genetic material, or *unbalanced* when they are accompanied by additional or missing genetic information. The stability of the resulting rearranged chromosome through cell division will depend on the presence of a centromere and two telomeres, the necessary elements for the correct segregation of chromosomes.

Balanced chromosomal abnormalities include some types of translocations and inversions. In a reciprocal translocation, two breaks in two non-homologous chromosomes occur and the chromosomal segments distal to the breaks are exchanged. The total number of chromosomes remains the same. If the translocation breakpoint affects a gene or its regulatory sequence, or otherwise places a gene under the control of novel regulatory elements (e.g. the Philadelphia chromosome), it can result in an observable phenotype (e.g. chronic myelogenous leukemia). The major problem with reciprocal translocations arises in the offspring of the carriers. Depending on the combination of parental chromosomes inherited, they can result in partial trisomy or monosomy for the chromosomal regions involved in the translocation (i.e. an unbalanced chromosomal anomaly in the child).

Inversions are balanced rearrangements in which two breaks occur in the same chromosome and the intervening segment is inverted before the chromosome is reconstituted. In a *pericentric inversion*, the inverted segment includes the centromere, whereas in a *paracentric inversion*, the two breaks occur in the same chromosome arm, without involvement of the centromere.

Classic examples of skin conditions associated with chromosomal anomalies are "hypomelanosis of Ito" and "linear and whorled nevoid hypomelanosis", where streaks and swirls of hypo- or hyperpigmentation following Blaschko's lines are a reflection of mosaicism, and a chromosomal anomaly can often be identified in affected skin. Other genodermatoses are occasionally caused by chromosomal abnormalities. Hypohidrotic ectodermal dysplasia, for example, has been diagnosed in several patients with rearranged X chromosomes, such as X;autosome translocations or genomic deletions involving the *EDA* gene[62]. Another example is Ambras syndrome, a form of congenital universal hypertrichosis. Several cases have been reported with cytogenetic abnormalities involving one common chromosomal region, 8q22. One of the patients had a balanced pericentric inversion denoted (8) (p11.2, q22)[63] and a second patient had the paracentric inversion (8) (q12, q22)[64]. The fact that two independent chromosomal abnormalities involved the same chromosomal region in unrelated patients with the same rare disease suggests that the chromosomal region 8q22 contains a candidate gene or regulatory region responsible for the Ambras syndrome phenotype[65]. Recently, a position effect resulting in decreased expression of the trichorhinophalangeal syndrome I gene (*TRPS1*) at 8q23 was reported in Ambras syndrome patients[66].

IDENTIFICATION OF DISEASE GENES

Key features

- Functional cloning relies upon knowledge of the gene's function but not its location within the genome
- Positional cloning involves linking a particular disease gene to a region of a chromosome using genetic markers
- Positional candidate gene approaches to gene identification utilize both positional and functional information

In general, two major approaches, functional and/or positional cloning, are utilized for the identification of the gene responsible for a Mendelian (monogenic) disorder. The approach usually depends on the type of information available regarding the particular trait.

Functional cloning requires some previous knowledge about the defective function, but no positional information is needed. When the abnormal function leading to the disease phenotype is known, such as the biochemical defect or the defective protein itself, several approaches can be applied to clone the corresponding gene. However, even though functional cloning has facilitated the cloning of genes in the past, its application is very limited, since there are only a few disorders that feature an obvious biochemical defect, e.g. tyrosinase activity in oculocutaneous albinism.

The *candidate gene* approach uses information on the defective pathway, function, structure or tissue underlying the phenotype. The expression of a gene in the same tissues as those affected by the disease phenotype, its function (e.g. role in a given metabolic pathway or cellular structure), and its homology or relationship to mutated genes responsible for closely related phenotypes can be good starting points for choosing a candidate gene. Additional and very helpful sources of information are animal models. There are many examples, although also some exceptions, where closely related phenotypes in mice and humans were caused by mutations in orthologous genes (homologous genes in different species). By means of the candidate gene approach, two separate groups identified mutations in the transglutaminase 1 gene (*TGM1*) as the molecular basis for lamellar ichthyosis (LI; see Ch. 57), an autosomal recessive disorder of cornification[67,68]. Huber et al.[67] examined the *TGM1* gene following analyses that showed decreased or absent activity and expression of this protein in LI patients. On the other hand, Russell et al.[68] studied *TGM1* and other genes on the basis of the known role of their encoded proteins in the formation of the cornified envelope.

Positional cloning starts with the chromosomal assignment of the region containing the defective gene by means of linkage analysis. Positional cloning has been a powerful tool in disease-gene identification, since, for most diseases, the only information available is the observable phenotype segregating in pedigrees. The identification of the gene responsible for hypohidrotic ectodermal dysplasia is an example of positional cloning. The genetic locus was mapped to the chromosomal region Xq12–q13.1 by means of linkage analysis and translocations in female patients. After finding putative new genes in the disease interval, Kere et al.[69] identified the *EDA* gene, which encodes ectodysplasin (see Ch. 63).

The approach that has yielded most results, however, uses a combination of both functional and positional information. In the *positional candidate approach*, once the chromosomal location of the disease locus is known, functional information is utilized to directly analyze the candidate genes contained in that particular chromosomal region (see below). A positional cloning approach[70] as well as a candidate gene approach[71] were utilized by independent groups to identify *ABCA12* as the gene underlying harlequin ichthyosis.

Previous information on the location of the gene, such as the presence of chromosomal abnormalities or LOH in a patient, can considerably accelerate the identification of disease genes. These chromosomal abnormalities are usually translocations, inversions, deletions or duplications. The occurrence of X;autosome translocations involving the same breakpoint on the X chromosome in several women with hypohidrotic ectodermal dysplasia helped to indicate the location of the causative gene. Together with linkage analysis and observations of small deletions in affected patients, this led to the identification of the *EDA* gene[69].

In the same way, LOH can provide hints as to where the disease gene might be. This has proven to be particularly useful in the identification of tumor suppressor genes. Familial cylindromatosis is inherited as an autosomal dominant trait, and >70% of the tumors show LOH in the vicinity of the gene that causes the disease; in all cases, the allele lost in the tumors is the wild-type allele. Moreover, the tumors show no other regions of LOH within the genome. Linkage analysis combined with the presence of LOH led to the identification of the underlying mutated tumor suppressor gene, *CYLD*[72,73].

Linkage Analysis

For many disorders, there is no previous information on the defective function or possible location of the disease gene. In such situations, positional cloning by a linkage analysis approach is performed to map the location of the disease gene. The aim of linkage analysis is the

identification of a chromosomal region that is transmitted along with the disease phenotype (co-segregates). When this region is found, the disease is said to be linked to that genetic locus.

The requirements for performing a linkage analysis include a thorough definition of the phenotype, the availability of pedigrees with enough linkage information (power), a "dense" map of highly polymorphic markers, and the application of statistical analysis. When defining the phenotype to be studied, it must be kept in mind that the correspondence between a gene and a disease is not always linear. There are numerous examples of allelic heterogeneity, with mutations in the same gene resulting in different phenotypes (see Table 54.2), and locus heterogeneity, in which the same or very similar phenotypes are caused by mutations in different genes (see Table 54.3). Furthermore, since the disease gene is unknown and the phenotype itself will be used to track the disease gene along the pedigree, it is essential to know if special circumstances such as incomplete penetrance, age-dependent penetrance or phenocopies might be expected.

Once the phenotype has been clearly established, a large enough sample must be chosen to achieve statistically significant results. Linkage studies are usually performed either on a single large pedigree or on several smaller ones. The first approach ensures genetic homogeneity of the sample, but it may not be available for every disease, whereas the second approach introduces the unwanted possibility of locus heterogeneity.

With a well-characterized, large enough collection of samples, the linkage analysis itself can be performed. Linkage analysis, and genetic mapping methods in general, rely on genetic recombination or crossing-over. The rationale is that the closer together the two loci are, the less frequently they will be separated by recombination during meiosis. Loci very close together are rarely separated by recombination, while recombination occurs more often between loci on the same chromosome that are separated by a greater distance; the larger the distance, the higher the frequency of recombination. A particular combination of alleles for several loci close to one another on the same chromosome is known as a *haplotype* (Fig. 54.6). Due to the independent assortment of maternal and paternal homologous chromosomes during meiosis, loci located on different chromosomes segregate independently.

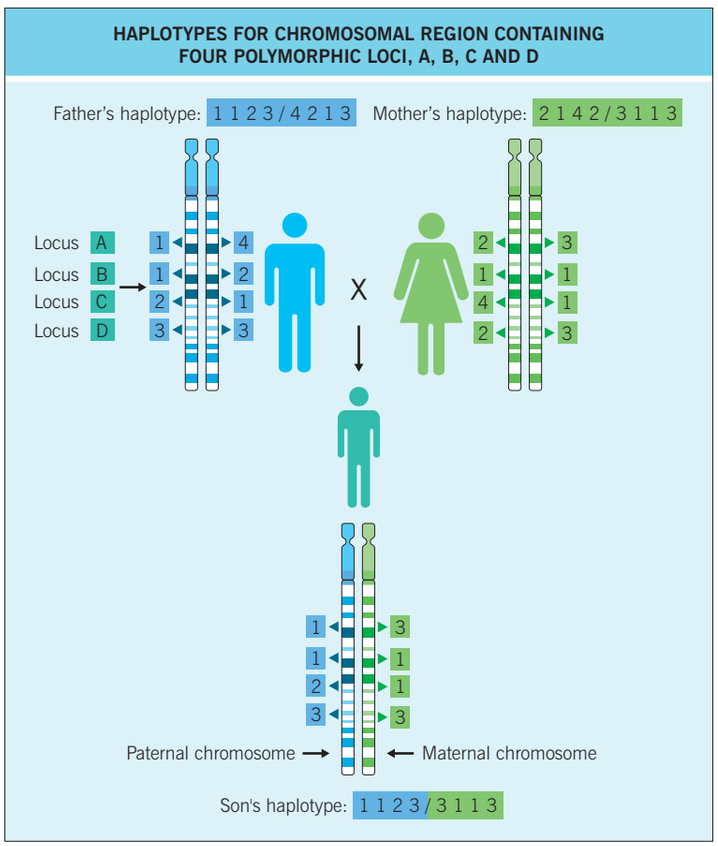


Fig. 54.6 Haplotypes for a chromosomal region containing four polymorphic loci, A, B, C and D. Loci very close together will rarely be separated by recombination.

The frequency of recombination (θ) between two loci reflects the genetic and physical distance between them. A recombination fraction of 1% or 0.01 is equivalent to approximately 1 centimorgan (cM), which is a unit of genetic distance.

When linkage analysis is performed, the disease gene is unknown. The inheritance of the disease phenotype is compared with the inheritance of polymorphic loci along the genome that serve as markers. The goal is to find one or more polymorphisms that are inherited in the same manner as would be expected for the disease gene. The disease locus is then said to be linked to this marker, which allows investigators to follow the disease gene through the pedigree until it is actually identified. It is important to note that the linked marker is not necessarily the disease gene itself, but simply a closely linked locus.

There are many types of DNA polymorphisms, but not all of them are useful markers for a linkage analysis. The two requirements are: (1) the informativeness, which reflects the number and frequency of different alleles at a locus (which increase the likelihood that an individual will be heterozygous); and (2) the distribution (density) of the polymorphisms, with shorter distances between loci allowing linkage to be detected with smaller samples.

Although microsatellites (tandem repeats of two to four nucleotides, e.g. $[CA]_n$) were used for linkage analysis in the past, genome-wide linkage analysis using single nucleotide polymorphism (SNP; Fig. 54.7) DNA microarrays has become the method of choice. SNPs refer to the presence of different nucleotides at a particular position (see Fig. 54.7 A,B)[3], whereas microsatellites vary in length due to different numbers of the repeated sequence[74] (see Fig. 54.7C). DNA microarrays used for linkage analysis enable genotyping of more than 1 million SNPs in a single experiment and also provide information on copy number variation and LOH.

Once the data from a genome-wide scan are gathered, statistical analyses are performed to determine the significance of the results. The possibility of false positives must be considered, since more than one region that mimics the inheritance of the disease gene in a particular pedigree can be found by chance. The statistical value used is the LOD score (Z), which is the logarithm of the odds in favor of linkage. The LOD score tests the linkage between two loci (one marker and the disease locus, or two polymorphic markers) in what is known as a two-point analysis. By convention, a LOD score of ≥3 (meaning ≥1000 : 1 odds that the observed linkage did not occur by chance) is interpreted as indicating linkage between two loci, whereas a LOD score of ≤–2 excludes linkage. The values between 3 and –2 are inconclusive (i.e. not sufficient to prove or disprove linkage). Calculations of LOD scores are performed using specialized statistical computer software. These calculations are done assuming a particular inheritance pattern, disease allele frequency, penetrance, possibility of phenocopies, etc. This type of analysis, where the model under study is specified, is known as parametric analysis.

The use of more than one marker can be helpful, since a particular pedigree can be informative for different markers. The analysis of data from different markers at one time is called multipoint analysis, as opposed to the two-point analysis described above.

Refinement of the Linkage Interval

The identification of the linkage interval gives an idea of the most likely location for the disease gene, but these intervals are often too large to work with (5–10 cM or even larger), containing hundreds of genes. Unless an obvious candidate gene maps to the interval that is initially identified, an additional step of narrowing down the disease locus is necessary. This refinement of the disease locus can be achieved by different means. Finding LOH or a chromosomal abnormality in a subset of patients is helpful, but such additional information is usually not available. For most genetic diseases, narrowing the linkage interval requires increasing the number of individuals studied and/or the number of markers analyzed within the defined region. When several close markers are analyzed, the disease gene is linked to a certain haplotype rather than a single marker.

In this step of the study, the analysis of haplotypes (see Fig. 54.6) is essential to find recombinations that narrow the linkage interval. The goal is to identify the boundaries of the smallest possible interval,

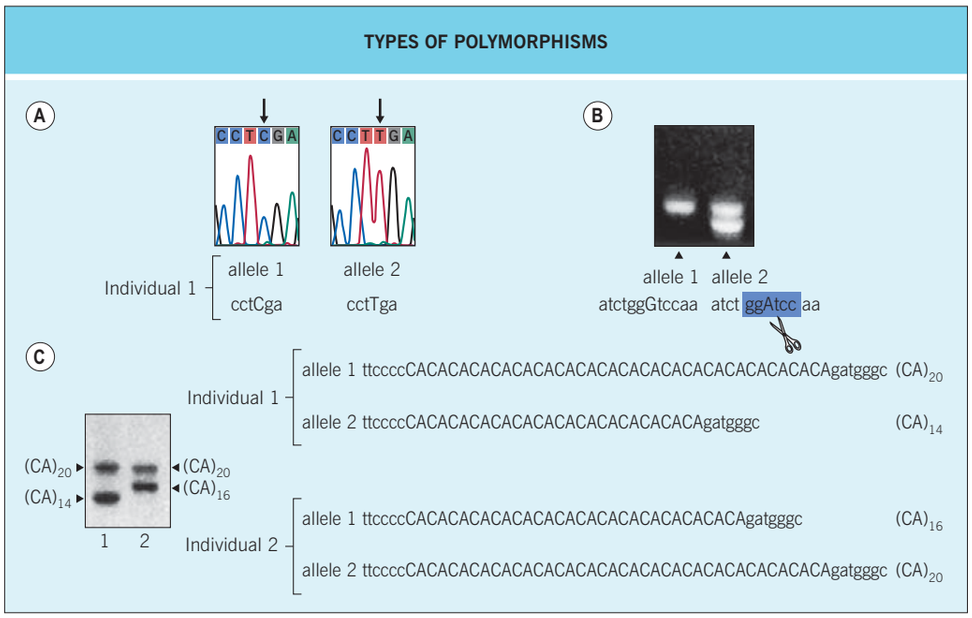


Fig. 54.7 Types of polymorphisms: single nucleotide polymorphisms (SNPs) and microsatellites. SNPs consist of single base substitutions and can be detected via DNA sequencing (**A**) and restriction enzyme cleavage (**B**). **A** Point substitution (arrows) replacing a cytosine (C) with a thymidine (T) identified by DNA sequencing. **B** The sequence *ggAtcc* is the target site for the restriction enzyme *BamH1*. In the presence of this particular sequence, the enzyme will cut the DNA into two fragments, detected as two bands in an agarose gel (allele 2). If this sequence is altered by a base substitution and, therefore, not recognized by the enzyme, no cleavage occurs (allele 1). A polymorphism that affects the recognition site for a restriction enzyme is referred to as an RFLP (restriction fragment length polymorphism). **C** Example of microsatellites. The repeat unit of the microsatellites shown here is the dinucleotide (CA). The number of tandem repeats of the (CA) unit can vary in each allele. The figure shows two individuals heterozygous for the number of repeats of this dinucleotide. The differences in length between these three alleles appear as bands of DNA of different sizes in a polyacrylamide gel.

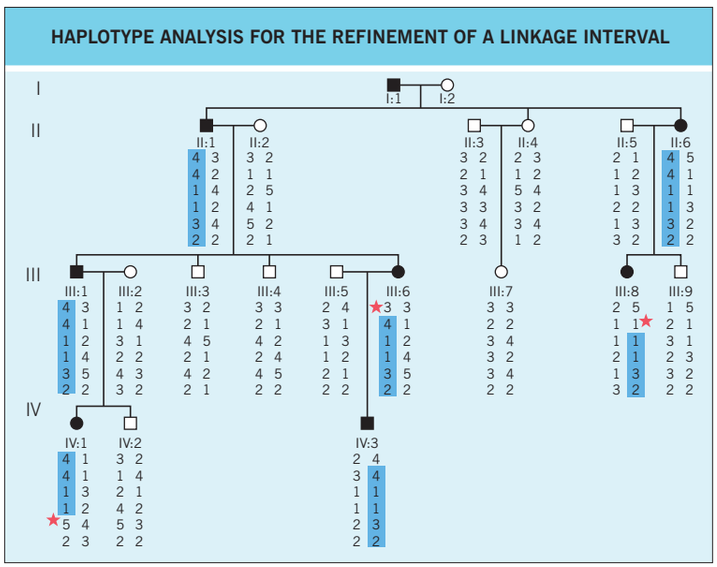


Fig. 54.8 Haplotype analysis for the refinement of a linkage interval. The disease-associated haplotype, 4 4 1 1 3 2 (shaded in blue), has been broken by genetic recombination in three family members (stars). The two key recombinant individuals, III:8 and IV:1, have allowed the narrowing of the disease interval. The key for symbols commonly used for pedigree drawing is indicated at the bottom of Figure 54.2.

defined by the closest markers that show recombination with the disease phenotype. Recombination events can 'break' the shared haplotype in different members/generations of the pedigree. Identification of an individual in whom recombination has occurred *inside* the disease-associated haplotype, known as a key recombination event, reduces the region where the disease gene is presumed to be located (Fig. 54.8). By identifying different key recombination events, the linkage interval can be progressively narrowed.

Positional Candidate Genes

When the linkage interval cannot be further reduced, attempts to identify the actual disease gene begin. The information now available on the human genome have made the positional candidate approach the most powerful disease-gene cloning strategy. Sequence data can be obtained through internet resources such as the National Center for Biotechnology Information (NCBI; www.ncbi.nlm.nih.gov) and Ensembl (www.ensembl.org/), where the user can browse integrated maps of polymorphic markers, known genes and predicted genes.

The process by which the genes responsible for Darier and Hailey–Hailey diseases were identified exemplify the positional candidate approach. The gene underlying Darier disease was localized to chromosome 12 by linkage analysis[75,76]. After refinement of the region, several genes were identified in the linkage interval. Among them, the *ATP2A2* gene encoding the calcium pump SERCA2 was considered a good candidate due to the role of calcium in epithelial junctions (defective in the epidermis of patients with Darier disease) and cell differentiation. Indeed, *ATP2A2* was found to be mutated in these patients.

In a separate study, linkage to chromosome 3 was established for the similar Hailey–Hailey disease phenotype[77]. Fortunately, one gene in the critical linkage interval, *ATP2C1*, showed homology to calcium ATPases and, consequently, was postulated to have a function related to SERCA2. As expected, this gene was mutated in Hailey–Hailey patients[78].

Mouse models represent another powerful tool in the identification of disease genes. This approach relies on the existence of chromosomal regions that share the same origin in evolution, known as syntenic regions. Once the genetic interval in humans is determined, the syntenic interval in mice can be analyzed to identify additional candidate genes. Also, if a similar phenotype in the mouse has been mapped to this region and the mutated gene is known, this becomes an excellent candidate for the human disease counterpart, and vice versa. This comparative genomic approach was used to identify mutations in the hairless gene in patients with atrichia with papular lesions[79] and mutations in the desmoglein 4 gene in patients with localized autosomal recessive hypotrichosis[80], as defects in these genes lead to similar phenotypes in mice (in which mutations were first discovered) and humans.

Identification of Mutations

Once a candidate gene is identified, its involvement in the disease must be proven. This involves the identification of pathogenic mutations, which are DNA variants present in affected patients and absent in a control population. There are several different types of mutations. Point mutations consist of the substitution of a single nucleotide position. This change can lead to an amino acid substitution (missense mutation), the generation of a termination codon (nonsense mutation), or no change in the protein sequence (silent mutation). There can also be small duplications, insertions or deletions. If they affect a piece of the protein-coding sequence in a manner that is not a multiple of three nucleotides (a codon), this will lead to a frameshift in the protein sequence and often the generation of a premature termination codon. These types of mutations can affect both coding and non-coding sequences, e.g. the promoter region, consensus splicing signals, and

other key intronic positions. Large rearrangements, such as partial or complete deletions of the entire gene, can also occur. It is important to recognize that some mutations, especially missense and silent substitutions, can be non-pathogenic variants present in the general population as polymorphisms.

COMPLEX TRAITS

Classic Mendelian diseases, where a defect in a single gene is sufficient to cause the disorder, represent only a small proportion of genetic diseases. There are many common conditions that, although heritable, are not due to a single-gene defect. Instead, they develop as a consequence of multiple genetic factors that confer disease susceptibility, interacting among themselves and with the environment. Such traits are referred to as complex or multifactorial traits. They tend to cluster or aggregate in families, but they do not follow Mendelian pattern of inheritance.

In contrast to the relatively clearcut recurrence risk for Mendelian traits, the risks for multifactorial traits are estimated based on epidemiologic data. Some examples of complex traits in dermatology include atopic dermatitis, vitiligo, psoriasis and alopecia areata. The absence of a Mendelian inheritance pattern can be observed when a collection of pedigrees with the same complex trait is analyzed (Fig. 54.9).

The goal in the study of complex traits is the identification of DNA variants in multiple different genes, each with a contribution to the final phenotype and conferring a degree of susceptibility to the carrier. Until recently, the identification of genetic variants contributing to complex traits was slow and challenging. However, the characterization of normal human genome variation and development of microarray-based technologies now enable genome-wide association studies (GWAS) in which several hundred thousand SNPs can be analyzed in thousands of individuals to determine the genetic architecture of complex diseases. The steps involved in GWAS are depicted in Fig. 54.10[81].

Although useful and extremely popular, GWAS pose significant challenges, primarily related to selecting a disease suitable for analysis and obtaining a large sample size of both cases and controls. A successful investigation requires that the phenotype of interest can be sensitively and specifically diagnosed or measured. Furthermore, extremely large collections of patients need to be studied in order to identify a statistically significant contribution for a given genetic factor.

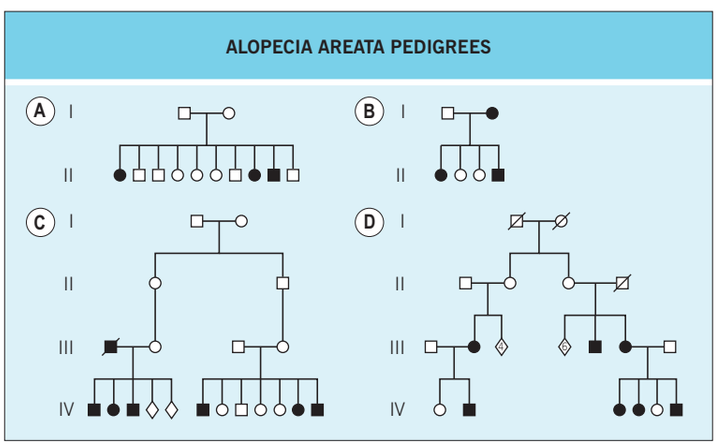


Fig. 54.9 Pedigrees with alopecia areata as an example of multifactorial dermatologic disease. Although some of the pedigrees individually can mimic Mendelian patterns of inheritance (**A, B**), others show a more complex pattern (**C,D**). In some cases, the disease can be inherited through two unrelated branches of the family (**C**). A single mode of inheritance cannot be established for the disease as a group. The key for symbols commonly used for pedigree drawing is indicated at the bottom of Figure 54.2.

The rationale for GWAS is that common diseases are attributable to common allelic variants present in more than 1–5% of the population[82]. With a few exceptions (e.g. age-related macular degeneration) in which heritability is explained by a small number of common variants with a large effect, the proportion of heritability explained by the identified variants is typically relatively small (e.g. 20%)[82]. The "missing heritability" is thought to be explained by large numbers of variants with small effects, rare variants, structural variants such as copy number alterations, gene–gene interactions, and the role of the shared environment among relatives.

Examples of GWAS in dermatology include those investigating susceptibility to psoriasis, atopic dermatitis, vitiligo, alopecia areata, melanocytic nevi, melanoma and basal cell carcinoma as well as variation in pigmentation of the skin and hair[83–91]. Studies of psoriasis have revealed several susceptibility loci, including major histocompatibility complex (MHC) and late cornified envelope gene clusters as well as genes involved in interleukin, tumor necrosis factor-α and nuclear factor-κB signaling[89,90]. GWAS in patients with alopecia areata have implicated genes involved in innate and adaptive immunity (e.g. controlling activation of natural killer cells and regulatory T cells) as well as those expressed specifically in the hair follicle[91]. Skin and hair pigmentation have been linked to variants in the melanocortin 1 receptor (*MC1R*), tyrosinase (*TYR*), two-pore segment channel 2 (*TPCN2*), solute carrier family 24 member 4 (*SLC24A4*), agouti signaling protein (*ASIP*) and Kit ligand (*KITLG*)[84]. Several of these loci (e.g. *MC1R*, *TYR*, *ASIP*) have also been associated with melanoma susceptibility[85,87].

In addition to GWAS, the knowledge gathered from Mendelian disorders has provided important clues to the etiology of more common related complex traits. As an example, loss-of-function mutations in the filaggrin gene (*FLG)* were first identified in patients with ichthyosis vulgaris, who also have a high incidence of atopic dermatitis[92,93]. The same loss-of-function alleles in the *FLG* gene were subsequently found to represent a strong predisposing factor for atopic dermatitis, with at least one allele present in 20–50% of affected children and adults in European and Asian populations[92]. Another gene associated with atopic dermatitis is *SPINK5*, loss-of-function mutations in which cause Netherton syndrome, an autosomal recessive ichthyosiform disorder with atopic manifestations[94]. A significant association has been observed between a particular *SPINK5* variant (Glu420Lys) and atopic dermatitis[94], providing potential insights into the pathogenesis of this multifactorial disorder.

Homozygosity for the mutation W185X in the *PVLR1* gene, has been shown to cause autosomal recessive cleft lip/palate (CLP) with ectodermal dysplasia, seen very frequently on Margarita Island, north of Venezuela[87]. This same mutation has been shown to be over-represented among individuals with the multifactorial isolated CLP in northern Venezuela (5.8%) when compared with control individuals from the same population (0.4%). Although these results are highly significant, they constitute only a moderate genetic risk factor, since just a small number of CLP patients carry the mutation[95].

The identification of genetic factors that increase susceptibility to complex traits can reveal pathways for the development of targeted therapies and ways to modify key environmental factors that contribute to common health issues. Disease-gene identification is thus of crucial importance not only for genetic counseling and prenatal diagnosis, but also as a step toward the elucidation of the mechanisms underlying a wide variety of diseases (from rare genodermatoses to common multifactorial conditions) and the eventual development of successful treatments.

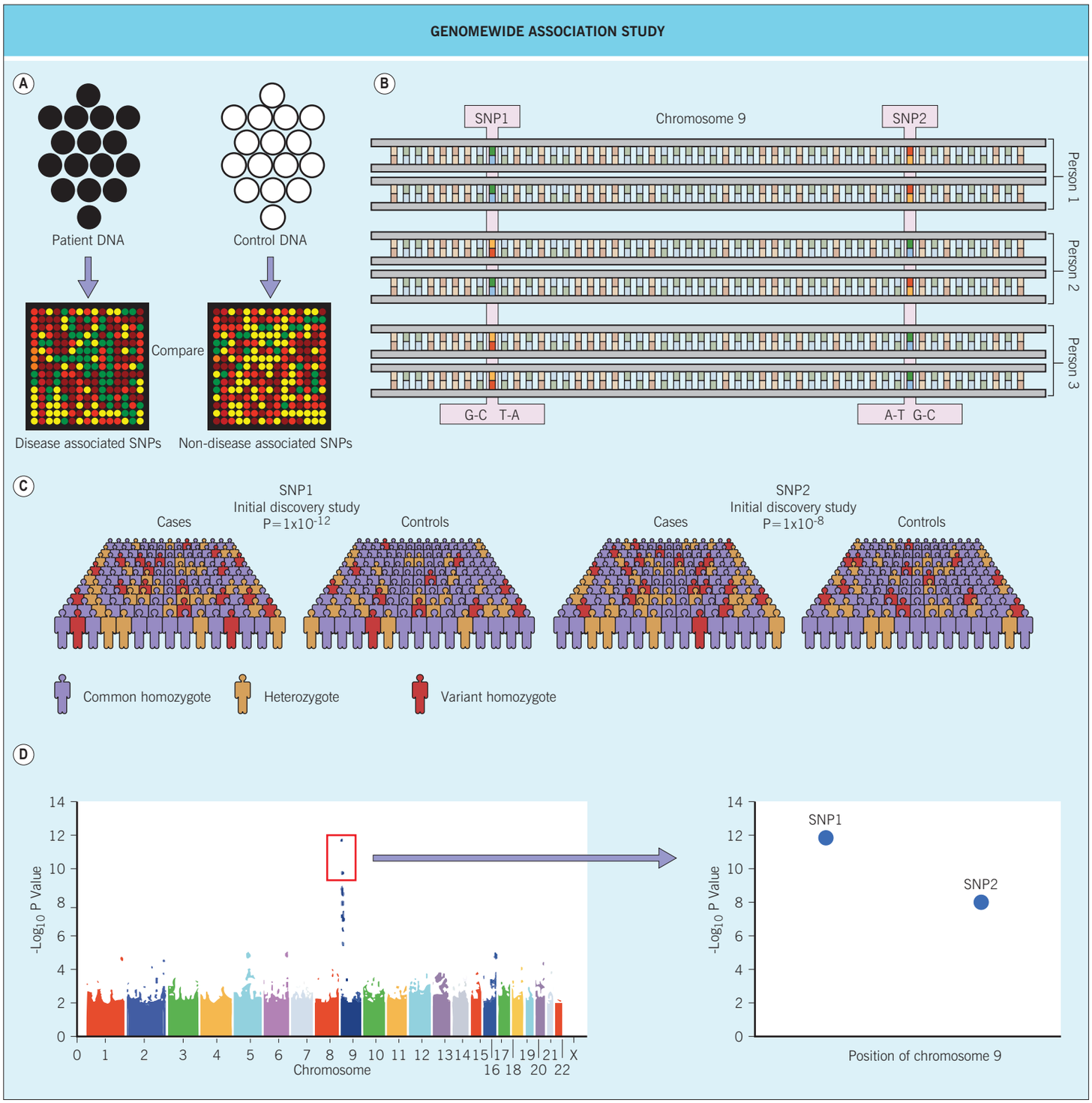
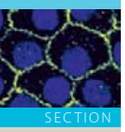


Fig. 54.10 Genome-wide association study (GWAS). A In a GWAS with a case–control design, single-nucleotide polymorphisms (SNPs; markers of genetic variation) across the human genome are genotyped using DNA microarrays in a large group of individuals with a certain disease and compared to controls from the general population. **B** A small locus on chromosome 9 (representing a tiny fragment of the genome) containing two SNPs is depicted as an example. **C** The strength of the association between each SNP and the disease is calculated based on that SNP's prevalence in cases versus controls. Because of the large number of statistical tests that are performed and the resulting high false-positive rate, statistical significance is typically set a P value of 10^{-8}. In this example, SNPs 1 and 2 on chromosome 9 are associated with the disease, with P values of 10^{-12} and 10^{-8}, respectively. **D** For all genotyped SNPs that have survived a quality-control screen, the chromosomal location is plotted on the x-axis and the negative logarithm of the P value on the y-axis (a Manhattan plot). Each chromosome is shown in a different color. The results implicate a locus on chromosome 9, marked by SNPs 1 and 2, which are adjacent to each other (graph at right), and other neighboring SNPs. *Adapted with permission from Manolio TA. Genomewide association studies and assessment of the risk of disease. N Engl J Med. 2010;363:166–76.*

REFERENCES

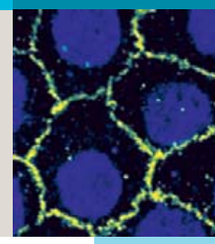
1. Stein LD. Human genome: end of the beginning. Nature. 2004;431:915–16.
2. Miller OJ, Therman, E. Human Chromosomes, 4th edn. New York: Springer-Verlag, 2001:13–74.
3. Frazer KA, Ballinger DG, Cox DR, et al. A second generation human haplotype map of over 3.1 million SNPs. Nature. 2007;449:851–61.
4. Pulkkinen L, Smith FJ, Shimizu H, et al. Homozygous deletion mutations in the plectin gene (PLEC1) in patients with epidermolysis bullosa simplex associated with late-onset muscular dystrophy. Hum Mol Genet. 1996;5:1539–46.
5. Smith FJ, Eady RA, Leigh IM, et al. Plectin deficiency results in muscular dystrophy with epidermolysis bullosa. Nat Genet. 1996;13:450–7.
6. Richard G, Smith LE, Bailey RA, et al. Mutations in the human connexin gene GJB3 cause erythrokeratodermia variabilis. Nat Genet. 1998;20:366–9.
7. Xia JH, Liu CY, Tang BS, et al. Mutations in the gene encoding gap junction protein beta-3 associated with autosomal dominant hearing impairment. Nat Genet. 1998;20:370–3.
8. Armstrong DK, McKenna KE, Purkis PE, et al. Haploinsufficiency of desmoplakin causes a striate subtype of palmoplantar keratoderma. Hum Mol Genet. 1999;8:143–8.
9. Liu XZ, Xia XJ, Xu LR, et al. Mutations in connexin31 underlie recessive as well as dominant non-syndromic hearing loss. Hum Mol Genet. 2000;9:63–7.
10. Norgett EE, Hatsell SJ, Carvajal-Huerta L, et al. Recessive mutation in desmoplakin disrupts desmoplakin-intermediate filament interactions and causes dilated cardiomyopathy, woolly hair and keratoderma. Hum Mol Genet. 2000;9:2761–6.
11. Lopez-Bigas N, Olive M, Rabionet R, et al. Connexin 31 (GJB3) is expressed in the peripheral and auditory nerves and causes neuropathy and hearing impairment. Hum Mol Genet. 2001;10:947–52.
12. Koss-Harnes D, Hoyheim B, Anton-Lamprecht I, et al. A site-specific plectin mutation causes dominant epidermolysis bullosa simplex Ogna: two identical de novo mutations. J Invest Dermatol. 2002;118:87–93.
13. Rampazzo A, Nava A, Malacrida S, et al. Mutation in human desmoplakin domain binding to plakoglobin causes a dominant form of arrhythmogenic right ventricular cardiomyopathy. Am J Hum Genet. 2002;71:1200–6.
14. Bonifas JM, Rothman AL, Epstein EH Jr. Epidermolysis bullosa simplex: evidence in two families for keratin gene abnormalities. Science. 1991;254:1202–5.
15. Coulombe PA, Hutton ME, Letai A, et al. Point mutations in human keratin 14 genes of epidermolysis bullosa simplex patients: genetic and functional analyses. Cell. 1991;66:1301–11.
16. Lane EB, Rugg EL, Navsaria H, et al. A mutation in the conserved helix termination peptide of keratin 5 in hereditary skin blistering. Nature. 1992;356:244–6.
17. Chan YM, Yu QC, Fine JD, et al. The genetic basis of Weber-Cockayne epidermolysis bullosa simplex. Proc Natl Acad Sci USA. 1993;90:7414–18.
18. Dong W, Ryynanen M, Uitto J. Identification of a leucine-to-proline mutation in the keratin 5 gene in a family with the generalized Kobner type of epidermolysis bullosa simplex. Hum Mutat. 1993;2:94–102.
19. Dell'Angelica EC, Shotelersuk V, Aguilar RC, et al. Altered trafficking of lysosomal proteins in Hermansky-Pudlak syndrome due to mutations in the beta 3A subunit of the AP-3 adaptor. Mol Cell. 1999;3:11–21.
20. Anikster Y, Huizing M, White J, et al. Mutation of a new gene causes a unique form of Hermansky-Pudlak syndrome in a genetic isolate of central Puerto Rico. Nat Genet. 2001;28:376–80.
21. Suzuki T, Li W, Zhang Q, et al. Hermansky-Pudlak syndrome is caused by mutations in HPS4, the human homolog of the mouse light-ear gene. Nat Genet. 2002;30:321–4.
22. McElreavey K, Krausz C. Sex chromosome genetics '99. Male infertility and the Y chromosome. Am J Hum Genet. 1999;64:928–33.
23. Zhao G, Xia H, Xia Y. A pedigree of Y-linked retinitis pigmentosa. Investigation report of a family. Chin Med J (Engl). 1995;108:631–3.
24. Zonana J, Elder ME, Schneider LC, et al. A novel X-linked disorder of immune deficiency and hypohidrotic ectodermal dysplasia is allelic to incontinentia pigmenti and due to mutations in IKK-gamma (NEMO). Am J Hum Genet. 2000;67:1555–62.
25. Kenwrick S, Woffendin H, Jakins T, et al. Survival of male patients with incontinentia pigmenti carrying a lethal mutation can be explained by somatic mosaicism or Klinefelter syndrome. Am J Hum Genet. 2001;69:1210–17.
26. Djabali K, Martinez-Mir A, Horev L, et al. Evidence for extensive locus heterogeneity in Naxos disease. J Invest Dermatol. 2002;118:557–60.
27. Martinez-Mir A, Liu J, Gordon D, et al. EB simplex superficialis resulting from a mutation in the type VII collagen gene. J Invest Dermatol. 2002;118:547–9.
28. Hu ZL, Smith L, Martins S, et al. Partial dominance of a keratin 14 mutation in epidermolysis bullosa simplex – increased severity of disease in a homozygote. J Invest Dermatol. 1997;109:360–4.
29. Goltz RW. Focal dermal hypoplasia syndrome. An update. Arch Dermatol. 1992;128:1108–11.
30. Smahi A, Courtois G, Vabres P, et al. Genomic rearrangement in NEMO impairs NF-kappaB activation and is a cause of incontinentia pigmenti. The International Incontinentia Pigmenti (IP) Consortium. Nature. 2000;405:466–72.
31. McGee TL, Devoto M, Ott J, et al. Evidence that the penetrance of mutations at the RP11 locus causing dominant retinitis pigmentosa is influenced by a gene linked to the homologous RP11 allele. Am J Hum Genet. 1997;61:1059–66.
32. Zlotogorski A, Martinez-Mir A, Green J et al. Evidence for pseudodominant inheritance of atrichia with papular lesions. J Invest Dermatol. 2002;118:881–6.
33. Burge SM. Hailey-Hailey disease: the clinical features, response to treatment and prognosis. Br J Dermatol. 1992;126:275–82.
34. Burge SM, Wilkinson JD. Darier-White disease: a review of the clinical features in 163 patients. J Am Acad Dermatol. 1992;27:40–50.
35. Munro CS. The phenotype of Darier's disease: penetrance and expressivity in adults and children. Br J Dermatol. 1992;127:126–30.
36. de Die-Smulders CE, Howeler CJ, Mirandolle JF, et al. Anticipation resulting in elimination of the myotonic dystrophy gene: a follow up study of one extended family. J Med Genet. 1994;31:595–601.
37. Ferraris AM, Forni GL, Mangerini R, et al. Nonrandom X-chromosome inactivation in hemopoietic cells from carriers of dyskeratosis congenita. Am J Hum Genet. 1997;61:458–61.
38. Zankl A, Addor MC, Cousin P, et al. Fatal outcome in a female monozygotic twin with X-linked hypohydrotic ectodermal dysplasia (XLHED) due to a de novo t(X;9) translocation with probable disruption of the EDA gene. Eur J Pediatr. 2001;160:296–9.
39. Wessagowit V, Ashton GH, Mohammedi R, et al. Three cases of de novo dominant dystrophic epidermolysis bullosa associated with the mutation G2043R in COL7A1. Clin Exp Dermatol. 2001;26:97–9.
40. Cserhalmi-Friedman PB, Garzon MC, Guzman E, et al. Maternal germline mosaicism in dominant dystrophic epidermolysis bullosa. J Invest Dermatol. 2001;117:1327–8.
41. Happle R. Mosaicism in human skin. Understanding the patterns and mechanisms. Arch Dermatol. 1993;129:1460–70.
42. Freyschmidt-Paul P, Hoffmann R, Konig A, et al. Linear porokeratosis superimposed on disseminated superficial actinic porokeratosis: report of two cases exemplifying the concept of type 2 segmental manifestation of autosomal dominant skin disorders. J Am Acad Dermatol. 1999;41:644–7.
43. Konig A, Happle R. Two cases of type 2 segmental manifestation in a family with cutaneous leiomyomatosis. Eur J Dermatol. 2000;10:590–2.
44. Poblete-Gutierrez P, Wiederholt T, Konig A, et al. Allelic loss underlies type 2 segmental Hailey-Hailey disease, providing molecular confirmation of a novel genetic concept. J Clin Invest. 2004;114:1467–74.
45. Jonkman MF, Castellanos Nuijts M, van Essen AJ. Natural repair mechanisms in correcting pathogenic mutations in inherited skin disorders. Clin Exp Dermatol. 2003;28:625–31.
46. Dean G. Porphyria variegata. Acta Derm Venereol Suppl (Stockh). 1982;100:81–5.
47. Knudson AG Jr. Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci USA. 1971;68:820–3.
48. Tomlinson IP, Alam NA, Rowan AJ, et al. Germline mutations in FH predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer. Nat Genet. 2002;30:406–10.
49. High A, Zedan W. Basal cell nevus syndrome. Curr Opin Oncol. 2005;17:160–6.
50. Reid FM, Vernham GA, Jacobs HT. A novel mitochondrial point mutation in a maternal pedigree with sensorineural deafness. Hum Mutat. 1994;3:243–7.
51. Martin L, Toutain A, Guillen C, et al. Inherited palmoplantar keratoderma and sensorineural deafness associated with A7445G point mutation in the mitochondrial genome. Br J Dermatol. 2000;143:876–83.
52. Bleasel NR, Varigos GA. Porphyria cutanea tarda. Australas J Dermatol. 2000;41:197–206.
53. Spiewak R. Pesticides as a cause of occupational skin diseases in farmers. Ann Agric Environ Med. 2001;8:1–5.
54. Feinberg AP. Phenotypic plasticity and the epigenetics of human disease. Nature. 2007;447:433–40.
55. Hamilton AJ, Baulcombe DC. A species of small antisense RNA in posttranscriptional gene silencing in plants. Science. 1999;286:950–2.
56. Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell. 1993;75:843–54.
57. Guttman M, Amit I, Garber M, et al. Chromatin signature reveals over a thousand highly conserved large non-coding RNAs in mammals. Nature. 2009;458:223–7.
58. Pulkkinen L, Bullrich F, Czarnecki P, et al. Maternal uniparental disomy of chromosome 1 with reduction to homozygosity of the LAMB3 locus in a patient with Herlitz junctional epidermolysis bullosa. Am J Hum Genet. 1997;61:611–19.
59. Takizawa Y, Pulkkinen L, Chao SC, et al. Mutation report: complete paternal uniparental isodisomy of chromosome 1: a novel mechanism for Herlitz junctional epidermolysis bullosa. J Invest Dermatol. 2000;115:307–11.
60. Fassihi H, Lu L, Wessagowit V, et al. Complete maternal isodisomy of chromosome 3 in a child with recessive dystrophic epidermolysis bullosa but no other phenotypic abnormalities. J Invest Dermatol. 2006;126:2039–43.
61. Ladda RL. Genetic Disorders of the Skin. Chicago: Year Book Medical, 1991:1–30.
62. Thomas NS, Chelly J, Zonana J, et al. Characterisation of molecular DNA rearrangements within the Xq12-q13.1 region, in three patients with X-linked hypohidrotic ectodermal dysplasia (EDA). Hum Mol Genet. 1993;2:1679–85.
63. Baumeister FA, Egger J, Schildhauer MT, et al. Ambras syndrome: delineation of a unique hypertrichosis universalis congenita and association with a balanced pericentric inversion (8) (p11.2; q22). Clin Genet. 1993;44:121–8.
64. Balducci R, Toscano V, Tedeschi B, et al. A new case of Ambras syndrome associated with a paracentric inversion (8) (q12; q22). Clin Genet. 1998;53:466–8.
65. Tadin M, Braverman E, Cianfarani S, et al. Complex cytogenetic rearrangement of chromosome 8q in a case of Ambras syndrome. Am J Med Genet. 2001;102:100–4.
66. Fantauzzo KA, Tadin-Strapps M, You Y, et al. A position effect on TRPS1 is associated with Ambras syndrome in humans and the Koala phenotype in mice. Hum Mol Genet. 2008;17:3539–51.
67. Huber M, Rettler I, Bernasconi K, et al. Mutations of keratinocyte transglutaminase in lamellar ichthyosis. Science. 1995;267:525–8.
68. Russell LJ, DiGiovanna JJ, Rogers GR, et al. Mutations in the gene for transglutaminase 1 in autosomal recessive lamellar ichthyosis. Nat Genet. 1995;9:279–83.
69. Kere J, Srivastava AK, Montonen O, et al. X-linked anhidrotic (hypohidrotic) ectodermal dysplasia is caused by mutation in a novel transmembrane protein. Nat Genet. 1996;13:409–16.
70. Kelsell DP, Norgett EE, Unsworth H, et al. Mutations in ABCA12 underlie the severe congenital skin disease harlequin ichthyosis. Am J Hum Genet. 2005;76:794–803.
71. Akiyama M, Sugiyama-Nakagiri Y, Sakai K, et al. Mutations in lipid transporter ABCA12 in harlequin ichthyosis and functional recovery by corrective gene transfer. J Clin Invest. 2005;115:1777–84.
72. Bignell GR, Warren W, Seal S, et al. Identification of the familial cylindromatosis tumour-suppressor gene. Nat Genet. 2000;25:160–5.
73. Takahashi M, Rapley E, Biggs PJ, et al. Linkage and LOH studies in 19 cylindromatosis families show no evidence of genetic heterogeneity and refine the CYLD locus on chromosome 16q12-q13. Hum Genet. 2000;106:58–65.



74. Lander ES, Linton LM, Birren B, et al. Initial sequencing and analysis of the human genome. Nature. 2001;409:860–921.
75. Bashir R, Munro CS, Mason S, et al. Localisation of a gene for Darier's disease. Hum Mol Genet. 1993;2:1937–9.
76. Craddock N, Dawson E, Burge S, et al. The gene for Darier's disease maps to chromosome 12q23-q24.1. Hum Mol Genet. 1993;2:1941–3.
77. Ikeda S, Welsh EA, Peluso AM, et al. Localization of the gene whose mutations underlie Hailey-Hailey disease to chromosome 3q. Hum Mol Genet. 1994;3:1147–50.
78. Hu Z, Bonifas JM, Beech J, et al. Mutations in ATP2C1, encoding a calcium pump, cause Hailey-Hailey disease. Nat Genet. 2000;24:61–5.
79. Ahmad W, Faiyaz ul Haque M, Brancolini V, et al. Alopecia universalis associated with a mutation in the human hairless gene. Science. 1998;279:720–4.
80. Kljuic A, Bazzi H, Sundberg JP, et al. Desmoglein 4 in hair follicle differentiation and epidermal adhesion: evidence from inherited hypotrichosis and acquired pemphigus vulgaris. Cell. 2003;113:249–60.
81. Hardy J, Singleton A. Genomewide association studies and human disease. N Engl J Med. 2009;360:1759–68.
82. Manolio TA, Collins FS, Cox NJ, et al. Finding the missing heritability of complex diseases. Nature. 2009;461:747–53.
83. Birlea SA, Gowan K, Fain PR, et al. Genome-wide association study of generalized vitiligo in an isolated European founder population identifies SMOC2, in close proximity to IDDM8. J Invest Dermatol. 2010;130:798–803.
84. Sulem P, Gudbjartsson DF, Stacey SN, et al. Genetic determinants of hair, eye and skin pigmentation in Europeans. Nat Genet. 2007;39:1443–52.
85. Brown KM, Macgregor S, Montgomery GW, et al. Common sequence variants on 20q11.22 confer melanoma susceptibility. Nat Genet. 2008;40:838–40.
86. Stacey SN, Gudbjartsson DF, Sulem P, et al. Common variants on 1p36 and 1q42 are associated with cutaneous basal cell carcinoma but not with melanoma or pigmentation traits. Nat Genet. 2008;40:1313–18.
87. Bishop DT, Demenais F, Iles MM, et al. Genome-wide association study identifies three loci associated with melanoma risk. Nat Genet. 2009;41:920–5.
88. Falchi M, Bataille V, Hayward NK, et al. Genome-wide association study identifies variants at 9p21 and 22q13 associated with development of cutaneous nevi. Nat Genet. 2009;41:915–19.
89. Nair RP, Duffin KC, Helms C, et al. Genome-wide scan reveals association of psoriasis with IL-23 and NF-kappaB pathways. Nat Genet. 2009;41:199–204.
90. Zhang XJ, Huang W, Yang S, et al. Psoriasis genome-wide association study identifies susceptibility variants within LCE gene cluster at 1q21. Nat Genet. 2009;41:205–10.
91. Petukhova L, Duvic M, Hordinsky M, et al. Genome-wide association study in alopecia areata implicates both innate and adaptive immunity. Nature. 2010;466:113–17.
92. Palmer CN, Irvine AD, Terron-Kwiatkowski A, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nat Genet. 2006;38:441–6.
93. Smith FJ, Irvine AD, Terron-Kwiatkowski A, et al. Loss-of-function mutations in the gene encoding filaggrin cause ichthyosis vulgaris. Nat Genet. 2006;38:337–42.
94. Walley AJ, Chavanas S, Moffatt MF, et al. Gene polymorphism in Netherton and common atopic disease. Nat Genet. 2001;29:175–8.
95. Sozen MA, Suzuki K, Tolarova MM, et al. Mutation of PVRL1 is associated with sporadic, non-syndromic cleft lip/palate in northern Venezuela. Nat Genet. 2001;29:141–2.

Genetic Basis of Cutaneous Diseases

55



Vered Molho-Pessach and Julie V Schaffer

Key features

- Advances in molecular technology have led to elucidation of the genetic bases of the majority of single-gene inherited skin disorders, greatly improving our understanding of these conditions
- McKusick's Online Mendelian Inheritance in Man (OMIM) database provides easily accessible, up-to-date information on human genes and genetic diseases; each gene or phenotype entry is assigned a specific six-digit MIM number
- Genotype–phenotype correlations in genodermatoses are often complex, with multiple examples of allelic heterogeneity (mutations in a single gene causing more than one disorder) and locus heterogeneity (mutations in different genes causing the same disorder)
- Molecular classification of genodermatoses into categories such as keratin defects and nuclear envelope defects complements traditional morphologic classification, providing insights into pathomechanisms and relationships between conditions
- Certain syndromic associations actually represent contiguous gene syndromes caused by large deletions that affect two or more neighboring genes
- Types 1 and 2 mosaicism in autosomal dominant disorders have been confirmed on a molecular level, and functional X-chromosome mosaicism can lead to a mosaic distribution of skin lesions in female patients heterozygous for X-linked disorders
- Determining the molecular basis of a monogenic skin disorder (such as non-Herlitz junctional epidermolysis bullosa) may help us to understand the pathogenesis of an acquired skin disease (such as bullous pemphigoid)
- Molecular research has begun to pave the way to the ultimate goal of gene therapy for severe inherited skin disorders such as dystrophic or junctional epidermolysis bullosa

Abbreviations:
AD, autosomal dominant; AR, autosomal recessive; XD, X-linked dominant; XR, X-linked recessive.

INTRODUCTION

In 1987, deletions in the steroid sulfatase gene were found to underlie X-linked recessive ichthyosis[1]. This heralded an era of tremendous progress in the elucidation of the genetic bases of inherited skin disorders, made possible by rapid advances in molecular technology (including the recent development of next-generation sequencing), discovery of candidate genes, utilization of animal models, and sequencing of the human genome (including single nucleotide polymorphisms [SNPs] useful for linkage analysis and homozygosity mapping; see Ch. 54)[2–4]. Better understanding of signaling pathways, molecules involved in cell–cell communication and adhesion, and mechanisms of cutaneous differentiation have also contributed to the momentum.

As a result of this explosion in research, more than 1000 genes were recognized to be responsible for a particular human phenotype by the year 2000, with approximately 300 of these conditions including cutaneous abnormalities[5]; by 2012, these numbers had increased to over 3500 and 1000, respectively[6–8]. Currently, the molecular genetic bases of the majority of single-gene inherited skin disorders have been established[9,10]. The emergence of new genomic and proteomic databases has transformed laborious positional cloning approaches and traditional functional studies, circumventing previous obstacles to the study of rare conditions and facilitating identification of candidate genes. For example, microarray (see Ch. 3)-based SNP genotyping enabled the identification of *ABCA12* mutations as the cause of harlequin ichthyosis; although classic linkage analysis was not possible due to the limited size of the pedigrees, homozygosity mapping (utilizing the aforementioned technology) linked this autosomal recessive condition to a region of homozygosity shared by affected individuals from diverse ethnic backgrounds[11]. With whole-exome (the transcribed portion of the genome) and even whole-genome sequencing now feasible and relatively affordable, disease-causing genes (especially in recessive disorders) can potentially be identified without genetic mapping[8].

In the past, diagnosis of genodermatoses was complicated by the existence of multiple complex classification systems based on various combinations of clinical, histologic, radiographic and biochemical criteria. Inconsistent nomenclature laden with descriptive terms, eponyms and synonyms added to the confusion and potential for misdiagnosis[12]. As the genetic bases of genodermatoses have been determined, integration of molecular and clinical data has helped to simplify disease categorization and eliminate redundant terminology. This has been successfully accomplished for disorders such as epidermolysis bullosa (EB) and ichthyoses, but it represents a work in progress, to be continually refined as additional genotype–phenotype correlations are established[13,14]. In addition, grouping hereditary skin disorders according to their molecular bases (Table 55.1) can supplement traditional morphologic classification, clarifying pathomechanisms and the relationships between conditions.

As the "morbid anatomy of the dermatologic genome" continues to be established, new challenges will arise and additional questions will be answered[15]. Because of the rarity of many genodermatoses, their full clinical spectra have yet to be elucidated. However, with the increasing availability of genetic and biochemical testing (www.genetests.org), dermatologists can establish the diagnosis in patients with mild or atypical presentations, thereby expanding the range of phenotypes. Continuing to decipher heritable skin disorders will require close interactions between basic scientists and clinicians. Hopefully, such translational research will continue to lead to better understanding of cutaneous structure and function; insights into the pathogenesis of common multifactorial disorders; and effective therapies as well as diagnostic and prognostic information, improved genetic counseling and DNA-based prenatal/preimplantation testing for patients with genodermatoses.

In this chapter, Tables 55.3 to 55.12 divide monogenic skin disorders with a known genetic basis (as well as selected diseases where the locus but not gene has been defined) into categories according to their primary clinical features; groups of monogenic conditions similarly listed in tables elsewhere in the book (rather than in this chapter) are noted in Table 55.2. Groups of diseases with major findings that fit into more than one table (e.g. disorders of keratinization and ectodermal dysplasias that are characterized by prominent hair abnormalities) are indicated, but additional overlap is inevitable.

MOLECULAR CLASSIFICATION OF HEREDITARY SKIN DISORDERS	
Molecular defect	**Skin disorders that result**
Keratin defects	See Table 56.5
Defects in structural proteins of the cornified cell envelope	Ichthyosis vulgaris, loricrin keratoderma (variant Vohwinkel syndrome)
Lipid metabolism defects	Various ichthyoses, including CHILD syndrome, Conradi–Hünermann–Happle syndrome, neutral lipid storage disease, lamellar ichthyosis/congenital ichthyosiform erythroderma spectrum (e.g. defective lipoxygenase 3 or 12R, cytochrome p450 4F22), self-healing collodion baby (defective lipoxygenase 3 or 12R), late-onset autosomal recessive congenital ichthyosis, Refsum disease, rhizomelic chondrodysplasia punctata, Sjögren–Larsson syndrome, X-linked recessive ichthyosis and ichthyosis, intellectual disability and spastic quadriplegia; various hyperlipidemias; Farber lipogranulomatosis, Gaucher disease type 2, hyperimmunoglobulinemia D syndrome, localized autosomal recessive hypotrichosis II/autosomal recessive woolly hair, Niemann–Pick disease, psoriasiform dermatitis-microcephaly-developmental delay syndrome
Transglutaminase defects	Lamellar ichthyosis/congenital ichthyosiform erythroderma spectrum (defective transglutaminase 1), acral peeling skin syndrome
Protease/proteasome defects	Dermatosparaxis, familial hidradenitis suppurativa, hereditary angioedema (type III), ichthyosis–hypotrichosis syndrome, IFAP (*i*chthyosis *f*ollicularis–*a*trichia–*p*hotophobia) syndrome, KLICK (*k*eratosis *l*inearis–*i*chthyosis *c*ongenita–sclerosing *k*eratoderma) syndrome, Papillon–Lefèvre and Haim–Munk syndromes, prolidase deficiency, restrictive dermopathy (defective zinc metallopeptidase), hereditary thrombotic thrombocytopenic purpura, Torg–Winchester syndrome (including the nodulosis–arthropathy–osteolysis variant)
Protease inhibitor defects	Antithrombin III deficiency, hereditary angioedema (types I & II), Netherton syndrome
Desmosomal defects (see Table 56.3)	Acantholytic ectodermal dysplasia, arrhythmogenic right ventricular dysplasia/cardiomyopathy + palmoplantar keratoderma + woolly hair; Carvajal syndrome, hypotrichosis and skin lesions, hypotrichosis simplex of the scalp, lethal acantholytic epidermolysis bullosa, lethal congenital epidermolysis bullosa, localized autosomal recessive hypotrichosis I, monilethrix (autosomal recessive), Naxos disease, generalized inflammatory peeling skin syndrome, plakophilin deficiency, skin fragility/woolly hair syndrome, striate palmoplantar keratoderma
Connexin defects (see Table 58.3)	Bart–Pumphrey syndrome, erythrokeratodermia variabilis, hidrotic ectodermal dysplasia, hereditary lymphedema type IC, KID (*k*eratitis–*i*chthyosis–*d*eafness) syndrome, oculodentodigital dysplasia, palmoplantar keratoderma with deafness, Vohwinkel syndrome (classic)
Other defects in cell-to-cell adhesion	Ichthyosis–hypotrichosis–sclerosing cholangitis syndrome, cleft lip/palate–ectodermal dysplasia syndrome, ectodermal dysplasia–syndactyly syndrome, ectodermal dysplasia–ectrodactyly–macular dystrophy, hypotrichosis with juvenile macular dystrophy, leukocyte adhesion deficiency type I
Defects in keratinocyte–extracellular matrix (ECM) adhesion	Various forms of epidermolysis bullosa (EB) simplex, junctional EB and dystrophic EB (keratin–ECM linkage); Kindler syndrome (actin–ECM linkage)
ATP-binding cassette (ABC) transporter defects	Harlequin ichthyosis, lamellar ichthyosis/congenital ichthyosiform erythroderma spectrum (defective ABCA12), pseudoxanthoma elasticum, sitosterolemia, Tangier disease/familial hypoalphaproteinemia
Calcium pump defects	Darier disease, Hailey–Hailey disease
Copper transporter defects	Menkes disease, occipital horn syndrome, Wilson disease
Defects in other transporters	Acrodermatitis enteropathica (zinc transporter), arterial tortuosity syndrome (glucose transporter), autosomal dominant hemochromatosis (iron-regulated transporter), Ehlers-Danlos syndrome-like spondylocheirodysplasia (zinc transporter), H syndrome (nucleoside transporter), Hartnup disease (neutral amino acid transporter), ichthyosis–prematurity syndrome (fatty acid transporter), oculocutaneous albinism (transporters on lysosome-related organelles)
Collagen defects	Various types of dystrophic EB, various types of Ehlers–Danlos syndrome, Ullrich muscular dystrophy, lysyl hydroxylase 3 deficiency
Defects in other ECM proteins	Autosomal dominant cutis laxa, autosomal recessive cutis laxa type I, cutis laxa with severe pulmonary/gastrointestinal/urinary abnormalities, Ehlers–Danlos syndrome hypermobility type/due to tenascin-X deficiency, juvenile hyaline fibromatosis/infantile systemic hyalinosis, lipoid proteinosis, Marfan syndrome, stiff skin syndrome
Nuclear membrane defects (see Table 63.9)	Buschke–Ollendorff syndrome/melorheostosis, Néstor-Guillermo progeria syndrome, Hutchinson–Gilford progeria syndrome, mandibuloacral dysplasia, partial > generalized lipodystrophy (familial and "acquired" forms), restrictive dermopathy
Defects in pyrin/NOD-family members and related proteins (see Fig. 45.1)	Blau syndrome, CINCA syndrome, familial cold autoinflammatory syndrome, familial Mediterranean fever, Muckle–Wells syndrome, PAPA syndrome
RecQ DNA helicase defects	Bloom syndrome, Rothmund–Thomson syndrome, Werner syndrome
Classic DNA repair defects	Various subtypes of xeroderma pigmentosum, trichothiodystrophy and Cockayne syndrome; Muir–Torre syndrome, constitutional mismatch repair deficiency syndrome
Cell cycle checkpoint defects	Ataxia telangiectasia, familial atypical mole–malignant melanoma (FAMMM) syndrome, multiple endocrine neoplasia (MEN) 4
Defects in telomere maintenance	Dyskeratosis congenita (seven genes implicated to date)
Protein-tyrosine phosphatase (PTP) defects	Bannayan–Riley–Ruvalcaba syndrome*, Cowden disease*, LEOPARD syndrome†, Noonan syndrome†, lymphedema and choanal atresia

*The defective proteins also have a role in the phosphatidylinositol 3-kinase (PI3K)/AKT pathway (see Fig. 55.4).
†The protein-tyrosine phosphatase that is defective in LEOPARD and Noonan syndromes has a role in the RAS–MAPK pathway (see Fig. 55.6).

Table 55.1 Molecular classification of hereditary skin disorders. cAMP, cyclic adenosine monophosphate; CHILD, congenital *h*emidysplasia with *i*chthyosiform nevus and *l*imb *d*efects; CINCA, *c*hronic *i*nfantile *n*eurologic, cutaneous and *a*rticular syndrome; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; NOD, nucleotide-binding oligomerization domain; PAPA, *p*yogenic *a*rthritis, *p*yoderma gangrenosum, and *a*cne; SCC, squamous cell carcinoma; STAT, signal transduction and activation of transcription; WNT, wingless-type integration site.

Continued

MOLECULAR CLASSIFICATION OF HEREDITARY SKIN DISORDERS	
Molecular defect	**Skin disorders that result**
RAS-MAPK pathway defects (see Fig. 55.5)	Capillary malformation–arteriovenous malformation, cerebral capillary malformations (familial), cardio-facio-cutaneous syndrome, Costello syndrome, Legius syndrome, LEOPARD syndrome, neurofibromatosis type 1, Noonan syndrome, Noonan-like disorder with loose anagen hair
cAMP and AMP-activated protein kinase pathway defects (see Fig. 55.4)	Albright hereditary osteodystrophy, Carney complex, McCune–Albright syndrome, Peutz–Jeghers syndrome*, tuberous sclerosis*
Defects in WNT/β-catenin signaling (see Fig. 55.7)	Anonychia congenita, ectodermal dysplasia–neoplastic syndrome, Gardner syndrome, Goltz syndrome (focal dermal hypoplasia), hereditary hypotrichosis simplex, palmoplantar keratoderma with cutaneous SCC and sex reversal, WNT10A-related ectodermal dysplasias (including odonto-onycho-dermal dysplasia and Schöpf–Schulz–Passarge syndrome)
Defects in transforming growth factor (TGF)-β signaling	Buschke–Ollendorff syndrome/melorheostosis, Ferguson–Smith multiple self-healing squamous epitheliomas, hereditary hemorrhagic telangiectasia, Loeys–Dietz syndrome, Marfan syndrome, stiff skin syndrome
Defective vesicle assembly/protein sorting to vesicles	ARC (*a*rthrogryposis–*r*enal *d*ysfunction–cholestasis) syndrome, Hermansky–Pudlak syndrome, MEDNIK (*m*ental retardation, *e*nteropathy, *d*eafness, *n*europathy, *i*chthyosis, *k*eratodermia) syndrome
Defective vesicle trafficking or transport	Autosomal recessive cutis laxa type IIA, CEDNIK (*ce*rebral *d*ysgenesis, *n*europathy, *i*chthyosis and *k*eratoderma) syndrome, Chédiak–Higashi syndrome, gerodermia osteodysplastica, Griscelli syndrome, ocular albinism type 1, wrinkly skin syndrome, MACS (*m*acroecphaly, *a*lopecia, *c*utis laxa and *s*coliosis) syndrome
*The defective proteins also have a role in the phosphatidylinositol 3-kinase (PI3K)/AKT pathway (see Fig. 55.4).	

Table 55.1 Molecular classification of hereditary skin disorders (cont'd). cAMP, cyclic adenosine monophosphate; SCC, squamous cell carcinoma; WNT, wingless-type integration site.

McKUSICK' S MENDELIAN INHERITANCE IN MAN

McKusick's Mendelian Inheritance in Man (MIM) database was first published in 1966 as "Catalogs of Autosomal Dominant, Autosomal Recessive and X-linked Phenotypes". In the 1994 edition, the subtitle was changed to "A Catalog of Human Genes and Genetic Disorders", reflecting the progress that had been made in the field. Online MIM (OMIM; www.ncbi.nlm.nih.gov/omim) has been widely available on the Internet for over 25 years, providing immediate access to current information on human genes and genetic diseases[6,7]. This database is updated continuously and can be searched by entering a constellation of clinical features as well as the name of a gene or syndrome.

A particular six-digit number (MIM number) is assigned to each OMIM entry. The first digit of the MIM number indicates the mode of inheritance of the corresponding genetic defect: 1 for autosomal dominant (entries before May 1994); 2 for autosomal recessive (entries before May 1994); 3 for X-linked; 4 for Y-linked; 5 for mitochondrial; and 6 for autosomal dominant or recessive (entries after May 1994). *Phenotype entries* describe the clinical and biochemical features, inheritance, mapping and molecular genetics of a given disease or trait; a "*#*" is used to designate those for which the molecular basis is known. *Gene entries* are marked by a "*", while *gene plus phenotype* entries are indicated with a "+"; both are appended with important disease-causing allelic variants (each of which is given a four-digit extension, beginning with .0001).

GENOTYPE–PHENOTYPE CORRELATIONS

Genotype–phenotype correlations in genodermatoses are often complex. Mutations in a single gene can cause more than one clinical disorder, a phenomenon referred to as *allelic* or *clinical heterogeneity* (see Table 53.1). This can result either from the same mutation occurring in patients with different genetic backgrounds or ages at presentation (e.g. identical *PTEN* mutations leading to Cowden disease and Bannayan–Riley–Ruvalcaba syndrome) or from different mutations (e.g. distinct mutations in the gene encoding lamin A/C leading to Hutchinson–Gilford progeria and familial partial lipodystrophy). Mutations that affect different domains of a protein can produce divergent phenotypes; for example, mutations in the sterile alpha motif (SAM) domain of the p63 protein typically cause AEC (*a*nkyloblepharon, *e*ctodermal dysplasia and *c*left lip/palate) syndrome, while those in the DNA-binding domain give rise to EEC (*e*ctrodactyly, *e*ctodermal dysplasia and *c*left lip/palate) syndrome. Various mutations in a particular gene can even lead to disorders with different modes of inheritance, such as X-linked dominant incontinentia pigmenti (a male-lethal condition due to a genomic rearrangement resulting in a partial deletion of the *n*uclear factor-κB *e*ssential *mo*dulator *[NEMO]* gene) and X-linked recessive hypohidrotic ectodermal dysplasia with immunodeficiency (due to milder, "hypomorphic" mutations in the *NEMO* gene). Conditions recently found to represent unexpected examples of allelic heterogeneity in the transforming growth factor-β (TGF-β) signaling pathway include mutations in the TGF-β receptor 1 gene (*TGFBR1*) in Ferguson–Smith multiple self-healing squamous epithelioma (loss-of-function) as well as Loeys–Dietz syndrome (gain-of-function), and fibrillin 1 gene (*FBN1*) mutations in stiff skin syndrome as well as Marfan syndrome.

The type of mutation can also affect the severity of a genodermatosis. The potentially lethal Herlitz type of junctional EB (JEB, an autosomal recessive disorder) is typically caused by mutations in the *LAMB3* gene that lead to a premature termination codon (resulting in a complete absence of the LAMB3 protein), whereas milder non-Herlitz forms of JEB are produced by missense or splice-site mutations in the same gene (resulting in a LAMB3 protein with decreased function). In contrast, in autosomal dominant conditions where there is dimerization of the mutated protein product (e.g. the KIT tyrosine kinase receptor that is defective in piebaldism), dominant negative missense mutations often result in more severe disease (via abnormal proteins binding to and disrupting normal proteins) than do mutations that lead to premature termination codons and thereby result in haploinsufficiency (complete loss of half of the proteins).

In other instances, mutations in different genes produce the same clinical disorder; this is referred to as *locus* or *genetic heterogeneity*. Locus heterogeneity can occur when mutated proteins serve a similar function (e.g. components of various *b*iogenesis of *l*ysosome-related *o*rganelle *c*omplexes [BLOCs] in Hermansky–Pudlak syndrome) or interact with one another in a complex (e.g. hamartin and tuberin in tuberous sclerosis), as a ligand and receptor (e.g. endothelin-3 and the endothelin-B receptor in type 4 Waardenburg syndrome) or in a signaling pathway (e.g. various RAS–mitogen-activated protein kinase [MAPK] pathway proteins in cardio-facio-cutaneous syndrome; see below). However, phenotypic differences can arise when these proteins also have distinct functions and/or tissue distributions; for example, the neurologic abnormalities in Griscelli syndrome 1 result from myosin Va expression in neurons, and the immunodeficiency and hemophagocytic syndrome that characterize Griscelli syndrome 2 reflect RAB27A expression in hematopoietic cells.

MOLECULAR CLASSIFICATION OF HEREDITARY SKIN DISORDERS

Molecular classification (see Table 55.1) represents a useful approach to the categorization of genodermatoses. Based on the pathogenetic

GROUPS OF MONOGENIC SKIN DISORDERS LISTED IN TABLES ELSEWHERE IN THE BOOK	
Category	**Table(s)**
Epidermolysis bullosa	32.1
Desmosomal disorders and keratinopathies	56.3 & 5
Connexin disorders	58.3
Nuclear membrane disorders	63.9
Disorders of hypopigmentation (diffuse or circumscribed)	66.3, 5 & 6
Hair disorders	69.7
Ehlers-Danlos syndrome, cutis laxa and other extracellular matrix disorders	95.5, 97.2 & 97.6
Vascular anomalies	104.2

Table 55.2 Groups of monogenic skin disorders listed in tables elsewhere in the book. In addition, other chapters (especially in the genodermatosis section) have tables that present more detailed information on monogenic skin disorders.

Fig. 55.1 Autosomal recessive monilethrix due to desmoglein 4 mutations. Sparse short hairs, stubble and follicular papules on the scalp. Insert: Trichogram showing alternating elliptical nodes and constrictions.

defect rather than the clinical presentation, it can highlight similarities between conditions with seemingly disparate phenotypes (e.g. classic ichthyoses and metabolic disorders such as Gaucher disease, both caused by defects in lipid metabolism) and facilitate better understanding of important cellular pathways (e.g. RAS signaling) and responses to external stimuli (e.g. pyrin/NOD family members that function in innate immunity). Several groups of genodermatoses for which molecular classification has been instructive are discussed below.

Keratin Defects

In 1991, EB simplex (EBS) became the first human disease shown to be caused by intermediate filament mutations. Since that time, molecular defects in keratins have been identified in a diverse group of hereditary disorders affecting the skin, leading to mechanical fragility and/or abnormal keratinization, depending on the layer of the epidermis in which the defective protein is expressed; the hair, nails and oral mucosa may also be involved (see Table 55.2)[16]. Dowling–Degos disease and Naegeli–Franceschetti–Jadassohn (NFJ) syndrome, which are characterized by reticulated pigmentation and (for NFJ) ectodermal dysplasia, represent entities more recently recognized as belonging to the keratin disorder category.

Keratin intermediate filaments, which are expressed in a tissue- and differentiation-specific fashion, are composed of heterodimeric subunits formed by the specific pairing of a type I (acidic; K9–20, 25–28 [inner root sheath], 31–40 [hair]) and type II (basic–neutral; K1–8, 71–75 [inner root sheath], 81–86 [hair]) keratin (see Ch. 56). Keratin genes are clustered at two loci in the human genome, 17q21 (type I keratins) and 12q13 (type II keratins). Many keratin disorders can be caused by mutations (often dominant negative) in either the type I or type II component of a particular keratin pair, thus exhibiting locus heterogeneity (e.g. K10 or K1 for epidermolytic ichthyosis; K14 or K5 for EBS). Allelic heterogeneity is also observed, with mutations in the highly conserved helix initiation and termination motifs leading to more severe phenotypes than those in other regions (e.g. the Dowling–Meara type of EBS versus localized EBS) (see Fig. 56.5).

Defects in Intercellular Junctions

Mutations in genes encoding components of desmosomes and gap junctions underlie a variety of genodermatoses, several of which have prominent extracutaneous manifestations.

Desmosomal defects

Desmosomes are intercellular junctions that provide mechanical integrity to tissues by anchoring intermediate filaments to the cell surface and mediating strong cell–cell adhesion (see Ch. 56). They are particularly important in stratified squamous epithelia and the myocardium, tissues that are subjected to substantial mechanical stress[17]. It is therefore not surprising that impaired keratinization, skin fragility and cardiomyopathy represent features of disorders caused by defects in desmosomal proteins such as desmoplakin, plakoglobin and plakophilin 1 (see Fig. 56.8 and Tables 55.3, 55.5 & 56.3). Abnormal hair (oftentimes woolly in nature) can also result from abnormalities in these proteins, and defects in other desmosomal components such as desmoglein 4 and corneodesmosin (which are highly expressed within the hair follicle) can lead to hypotrichosis and (for desmoglein 4) an autosomal recessive form of monilethrix (Fig. 55.1; see Table 55.6).

Connexin defects

Gap junctions are intercellular channels that connect the cytoplasm of neighboring cells, facilitating communication that coordinates cellular growth, differentiation and responses to stimuli as well as tissue morphogenesis and homeostasis (see Ch. 58). Transmembrane connexin proteins undergo oligomerization to form the connexons that compose gap junctions. Connexin proteins such as Cx26, Cx30, Cx31 and Cx43 are preferentially expressed in ectoderm-derived epithelia of the inner ear and cornea as well as in the epidermis and its appendages[18]. This accounts for the sensorineural deafness, keratitis and cutaneous abnormalities (ranging from keratoderma to erythrokeratoderma to ectodermal dysplasias affecting the hair and nails) that are observed in various connexin disorders (see Tables 55.1, 55.3 & 55.5). Several connexins are expressed in lymphatic cells, and mutations in the gene encoding Cx47 were recently found to cause a hereditary type of lymphedema[19].

Defects in Keratinocyte–Extracellular Matrix Adhesion

The hemidesmosome links keratin intermediate filaments (K5, K14) within basal keratinocytes to proteins within the lamina densa (basement membrane proper) and sublamina densa regions of the epidermal basement membrane zone (see Ch. 28). Defects in protein components of these structures lead to various forms of EB (simplex, junctional and dystrophic; see Ch. 32)[20]. The basement membranes of epithelia in other sites such as the eye, oral cavity, gastrointestinal tract and genitourinary tract may also be affected in patients with EB. Additional clinical manifestations can result when the abnormal protein has important functions in extraepithelial tissues, such as the skeletal muscle for plectin (leading to EBS with muscular dystrophy).

HEREDITARY DISORDERS OF KERATINIZATION					
Disorder	**Mode of inheritance**	**Gene or gene product**	**Gene symbol**	**Gene locus**	**MIM number(s)**
COMMON ICHTHYOSES					
Ichthyosis vulgaris	AsD	Filaggrin	*FLG*	1q21.3	146700, 135940
X-linked recessive ichthyosis	XR	Steroid sulfatase	*STS*	Xp22.32	308100
NON-SYNDROMIC AUTOSOMAL RECESSIVE CONGENITAL ICHTHYOSES					
Lamellar ichthyosis (LI) and congenital ichthyosiform erythroderma (CIE) spectrum	AR	Transglutaminase 1*	*TGM1*	14q11.2	242100, 242300, 190195
	AR	Epidermal lipoxygenase 3 (CIE>LI)*	*ALOXE3*	17p13.1	242100, 607206
	AR	12(R)-Lipoxygenase (CIE>LI)*	*ALOX12B*	17p13.1	242100, 603741
	AR	ATP-binding cassette (ABC), subfamily A, member 12 (LI>CIE)	*ABCA12*	2q34	601277, 607800
	AR	Cytochrome P450, family 4, subfamily F, polypeptide 22 (LI>CIE)	*CYP4F22*	19p12	604777
	AR	Ichthyin (CIE>LI)	*NIPAL4 (ICHTHYIN)*	5q33	609383, 612281
	AR	Patatin-like phospholipase domain containing 1 (CIE>LI)	*PNPLA1*	6p21.31	612121
Harlequin ichthyosis	AR	ATP-binding cassette (ABC), subfamily A, member 12	*ABCA12*	2q34	242500, 607800
Late-onset autosomal recessive congenital ichthyosis	AR	Lipase N	*LIPN*	10q23.31	613924, 613943
KERATINOPATHIC ICHTHYOSES					
Epidermolytic ichthyosis (bullous congenital ichthyosiform erythroderma)	AD	Keratin 1	*KRT1*	12q11–q13	113800, 139350
	AD	Keratin 10	*KRT10*	17q21–q22	113800, 148080
Superficial epidermolytic ichthyosis (ichthyosis bullosa of Siemens)	AD	Keratin 2	*KRT2*	12q11–q13	146800, 600194
Ichthyosis en confetti	AD	Keratin 10	*KRT10*	17q21–q22	148080
Ichthyosis (hystrix) Curth–Macklin	AD	Keratin 1	*KRT1*	12q11–q13	146590, 139350
OTHER NON-SYNDROMIC ICHTHYOSES AND ERYTHROKERATODERMAS					
Erythrokeratodermia variabilis†	AD	Connexin 31 (gap junction protein β3)	*GJB3*	1p35.1	133200, 603324
	AD	Connexin 30.3 (gap junction protein β4)	*GJB4*	1p35.1	133200, 605425
Generalized inflammatory peeling skin syndrome	AR	Corneodesmosin	*CDSN*	6p21.3	270300, 602593
KLICK (*k*eratosis *l*inearis–*i*chthyosis *c*ongenita–sclerosing *k*eratoderma) syndrome	AR	Proteasome maturation protein	*POMP*	13q12.3	601952, 613386
SYNDROMIC ICHTHYOSES AND ERYTHROKERATODERMAS					
ARC (*a*rthrogryposis–*r*enal dysfunction–cholestasis) syndrome	AR	Vacuolar protein sorting 33 homolog B	*VPS33B*	15q26.1	208085, 608552
CEDNIK (*c*erebral *d*ysgenesis, *n*europathy, *i*chthyosis and *k*eratoderma) syndrome	AR	Synaptosomal-associated protein, 29kDa	*SNAP29*	22q11.2	609528, 604202
CHILD syndrome	XD	3β-hydroxysteroid dehydrogenase	*NSDHL*	Xq28	308050, 300275
Conradi–Hünermann–Happle syndrome	XD	Δ^8–Δ^7 sterol isomerase (emopamil-binding protein)	*EBP*	Xp11.23–p11.22	302960, 300205
Dolichol kinase deficiency	AR	Dolichol kinase	*DOLK*	9q34.11	610768, 610746
Gaucher syndrome type 2	AR	Acid beta-glucosidase	*GBA*	1q21	606463, 230900
Ichthyosis–hypotrichosis syndrome	AR	Matriptase (serine protease)	*ST14*	11q24.3–q25	610765, 606797
Ichthyosis–hypotrichosis–sclerosing cholangitis syndrome	AR	Claudin 1	*CLDN1*	3q27–q29	607626, 603718
Ichthyosis, intellectual disability and spastic quadriplegia	AR	Elongase of very long chain fatty acids 4	*ELOVL4*	6q14	605512
Ichthyosis prematurity syndrome	AR	Fatty acid transport protein 4	*SLC27A4*	9q334	608649, 604194
IFAP (*i*chthyosis *f*ollicularis–*a*trichia–*p*hotophobia) syndrome	XR	Membrane-bound transcription factor protease, site 2	*MBTPS2*	Xp22.12–p22.11	300294, 308205

*Biallelic mutations in these genes have also been associated with a self-healing (or self-improving) collodion baby phenotype.

†A subset of patients with a progressive symmetric erythrokeratoderma phenotype also have mutations in the gene encoding connexin 30.3.

Table 55.3 Hereditary disorders of keratinization. These disorders are covered primarily in Chapters 57 and 58. AsD, autosomal semidominant; CHILD, *c*ongenital *h*emidysplasia with *i*chthyosiform nevus and *l*imb *d*efects; ERCC, excision repair cross-complementing; mt, mitochondrial inheritance; XP, xeroderma pigmentosum.

Continued

HEREDITARY DISORDERS OF KERATINIZATION					
Disorder	**Mode of inheritance**	**Gene or gene product**	**Gene symbol**	**Gene locus**	**MIM number(s)**
KID (*k*eratitis–*i*chthyosis–*d*eafness) syndrome‡	AD	Connexin 26 (gap junction protein β2)	*GJB2*	13q11–q13	148210, 121011
MEDNIK (*m*ental retardation, *e*nteropathy, *d*eafness, *n*europathy, *i*chthyosis, *k*eratodermia) syndrome	AR	Adaptor-related protein complex 1, sigma-1 subunit	*AP1S1*	7q22.1	603531
Multiple sulfatase deficiency	AR	Sulfatase-modifying factor 1	*SUMF1*	3p26	272200, 607939
Netherton syndrome	AR	Serine protease inhibitor, Kazal-type 5 (lymphoepithelial Kazal-type-related inhibitor, LEKTI)	*SPINK5*	5q32	256500, 605010
Neutral lipid storage disease with ichthyosis (Chanarin–Dorfman syndrome)	AR	Abhydrolase domain-containing 5 (comparative gene identification 58, esterase-lipase-thioesterase subfamily)	*ABHD5 (CGI-58)*	3p21	275630, 604780
Refsum disease	AR	Phytanoyl-CoA 2-hydroxylase	*PHYH (PAHX)*	10p15.3–p12.2	266500, 602026
	AR	Peroxin-7	*PEX7*	6q21–q22.2	266500, 601757
Rhizomelic chondrodysplasia punctata, type 1	AR	Peroxin-7	*PEX7*	6q21–q22.2	215100, 601757
Sjögren–Larsson syndrome	AR	Aldehyde dehydrogenase family 3, member A2 (fatty aldehyde dehydrogenase)	*ALDH3A2 (FALDH)*	17p11.2	270200, 609523
Trichothiodystrophy	AR	General transcription factor IIH polypeptide 5 (TTDA)	*GTF2H5*	6q25.3	608780, 601675
	AR	Excision repair cross-complementing group 3 (XPB)	*ERCC3*	2q21	133510, 610651
	AR	Excision repair cross-complementing group 2 (XPD)	*ERCC2*	19p13.2–q13.3	126340, 278730
	AR	Chromosome 7 open reading frame 11 (patients usually lack ichthyosis)	*C7Orf11*	7p14	609188, 234050
PALMOPLANTAR KERATODERMAS					
Diffuse palmoplantar keratoderma, epidermolytic (Vörner)	AD	Keratin 1	*KRT1*	12q11–q13	139350
	AD	Keratin 9	*KRT9*	17q21.1–q21.2	144200, 607606
Diffuse palmoplantar keratoderma, non-epidermolytic (Unna–Thost)	AD	Keratin 1	*KRT1*	12q11–q13	600962, 139350
Focal palmoplantar keratoderma, non-epidermolytic	AD	Keratin 16	*KRT16*	17q21.2	600962, 148067
	AD	Keratin 6c	*KRT6C*	12q13.13	612315
Palmoplantar keratoderma with deafness	mt	Mitochondrial tRNA-serine 1	*MT-TS1*		148350, 590080
	AD	Connexin 26 (gap junction protein β2)	*GJB2*	13q11–q12	148350, 121011
Bart–Pumphrey syndrome	AD	Connexin 26 (gap junction protein β2)	*GJB2*	13q11–q12	149200, 121011
Mal de Meleda	AR	Secreted leukocyte antigen-6 (Ly6)/urokinase-type plasminogen activator (uPAR)-related protein 1	*SLURP1*	8q24.3	248300, 606119
Oculodentodigital dysplasia	AD	Connexin 43 (gap junction protein α1)	*GJA1*	6q22–q23	164200, 121014
Papillon–Lefèvre syndrome	AR	Cathepsin C	*CTSC*	11q14.2	245000, 602365
Haim–Munk syndrome	AR	Cathepsin C	*CTSC*	11q14.2	245010, 602365
Tyrosinemia type 2 (Richner–Hanhart syndrome)	AR	Tyrosine aminotransferase	*TAT*	16q22.1–q22.3	276600
Vohwinkel syndrome, classic form	AD	Connexin 26 (gap junction protein β2)	*GJB2*	13q11–q12	124500, 121011
Loricrin keratoderma (Vohwinkel syndrome, variant form)	AD	Loricrin	*LOR*	1q21	604117, 152445
Naxos disease	AR	Plakoglobin	*JUP (PKGB)*	17q21	601214, 173325
Carvajal syndrome	AR	Desmoplakin	*DSP*	6p24	605676, 125647
Arrhythmogenic right ventricular dysplasia/cardiomyopathy + palmoplantar keratoderma + woolly hair	AR	Desmocollin 2	*DSC2*	18q12.1	125645
Striate palmoplantar keratoderma	AD	Desmoplakin	*DSP*	6p21	148700, 125647
	AD	Desmoglein 1	*DSG1*	18q12.1–q12.2	148700, 125670
	AD	Keratin 1	*KRT1*	12q11–q13	148700, 139350

‡Includes the HID (hystrix-like ichthyosis–deafness) syndrome variant; a mutation in *GJB6* has also been reported in a single patient to date with a KID syndrome phenotype.

Table 55.3 Hereditary disorders of keratinization (cont'd). These disorders are covered primarily in Chapters 57 and 58. CHILD, *c*ongenital *h*emidysplasia with *i*chthyosiform nevus and *l*imb *d*efects; ERCC, excision repair cross-complementing; XP, xeroderma pigmentosum.

Continued

HEREDITARY DISORDERS OF KERATINIZATION					
Disorder	**Mode of inheritance**	**Gene or gene product**	**Gene symbol**	**Gene locus**	**MIM number(s)**
Palmoplantar keratoderma with cutaneous SCC and sex reversal	AR	R-spondin 1	*RSPO1*	1p34.3	610644, 609595
OTHER DISORDERS					
Acral peeling skin syndrome	AR	Transglutaminase 5	*TGM5*	15q15.2	609796, 603805
Cardio-facio-cutaneous syndrome	AD	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog	*KRAS*	12p12.1	115150, 190070
	AD	v-Raf murine sarcoma viral oncogene homolog B1	*BRAF*	7q34	115150, 164757
	AD	Mitogen-activated protein kinase kinase 1	*MAP2K1 (MEK1)*	15q22.1–q22.33	115150, 176872
	AD	Mitogen-activated protein kinase kinase 2	*MAP2K2 (MEK2)*	19p13.3	115150, 601263
Darier disease	AD	Sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase 2 (SERCA2)	*ATP2A2*	12q23–q24.1	124200, 108740
Hailey–Hailey disease	AD	Human secretory pathway Ca^{2+} ATPase 1 (hSPCA1)	*ATP2C1*	3q21–q24	169600, 604384
Keratosis follicularis spinulosa decalvans[§]	XR	Membrane-bound transcription factor peptidase, site 2	*MBTPS2*	Xp22.12–p22.11	308800, 300294
Noonan syndrome	AD	Protein tyrosine phosphatase, non-receptor type 11	*PTPN11*	12q24	163950, 176876
	AD	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog	*KRAS*	12p12.1	609942, 190070
	AD	v-Raf-1 murine leukemia viral oncogene homolog	*RAF1*	3p25	164760
	AD	Son of sevenless homolog 1 (guanine nucleotide exchange factor)	*SOS1*	2p22–p21	610733, 182530
	AD	Neuroblastoma RAS viral (v-ras) oncogene homolog	*NRAS*	1p13.2	164790, 613224
Noonan syndrome-like disorder	AD	Cas-Br-M (murine) ecotropic retroviral transforming sequence	*CBL*	11q23.3	165360, 613563
Noonan syndrome-like disorder with loose anagen hair	AD	Suppressor of clear homolog	*SHOC2*	10q25	602775, 607721
Porokeratosis, disseminated superficial actinic	AD	(Squamous cell carcinoma antigen recognized by T cells 3)[¶]	*(SART3)*	12q24.1	611684, 175900
	AD			15q25.1–q26.1, 18p11.3, 1p31.3–p31.1	607728, 612353, 612293
Psoriasiform dermatitis–microcephaly–developmental delay	AR	Sterol-C4-methyl oxidase-like	*SC4MOL*	4q32–q34	607545
Seborrhea-like dermatitis with psoriasiform elements	AD	Zinc finger protein 750	*ZNF750*	17q25.3	610227, 610226
White sponge nevus	AD	Keratin 4	*KRT4*	12q13	193900, 123940
	AD	Keratin 13	*KRT13*	17q21–q22	193900, 148065

[§]Phenotypic overlap with IFAP syndrome, which is also caused by mutations in *MBTPS2*. In addition, a duplication involving the *SAT1* gene has been reported in a single patient to date with keratosis follicularis spinulosa decalvans.
[¶]To date, reported in a single Chinese family and not confirmed in subsequent studies.

Table 55.3 Hereditary disorders of keratinization (cont'd). These disorders are covered primarily in Chapters 57 and 58. CHILD, *c*ongenital *h*emidysplasia with *i*chthyosiform nevus and *l*imb *d*efects; ERCC, excision repair cross-complementing; XP, xeroderma pigmentosum.

Focal adhesions are structurally defined sites of linkage between the intracellular actin cytoskeleton and the extracellular matrix (ECM). Mutations in the gene encoding the focal adhesion protein kindlin-1 cause Kindler syndrome, an autosomal recessive disorder characterized by acral blistering and photosensitivity early in life, progressive poikiloderma and erosive periodontal disease (see Ch. 63). Kindlin-1 is found within basal keratinocytes along the cell surface that faces the basement membrane, and it has roles in keratinocyte adhesion, polarity, proliferation and motility. To date, Kindler syndrome represents the only skin fragility disorder known to be caused by disruption of linkage between actin microfilaments (rather than keratin intermediate filaments) and the ECM[20].

Transmembrane Transporter Defects

Abnormalities in transmembrane transporters underlie a variety of genodermatoses, ranging from occipital horn syndrome and Menkes disease (both due to mutations in the gene encoding the ATP7A copper transporter) to oculocutaneous albinism types 2 and 4 (due to defective transporters on lysosome-related organelles) to metabolic disorders such as acrodermatitis enteropathica, Hartnup disease and hemochromatosis. Recent additions to this list include implication of a fatty acid transporter in ichthyosis prematurity syndrome[21] and an intracellular nucleoside transporter in H syndrome (Fig. 55.2)[22]. Disorders of calcium pumps and ATP-binding cassette (ABC) transporters, which underscore the important roles of transmembrane transporters in cutaneous homeostasis, are discussed below.

Calcium pump defects

Darier disease and Hailey–Hailey disease are distinct autosomal dominant disorders that share the histologic feature of epidermal acantholysis leading to suprabasal cleft formation; on an ultrastructural level, this corresponds to disruption of the desmosome–keratin intermediate

Fig. 55.2 H syndrome. This autosomal recessive disorder due to mutations in the *SLC29A3* gene (which encodes a nucleoside transporter) presents with *h*yperpigmentation, *h*ypertrichosis, induration and varicose veins in a characteristic distribution pattern on the thighs with sparing of the knees (**A**). Additional features include *h*allus valgus and flexion contractures of the toes (**B**), *h*epatosplenomegaly, *h*eart anomalies, *h*earing loss, *h*ypogonadism, low *h*eight and *h*yperglycemia/diabetes mellitus.

filament complex. The two conditions also have some clinical similarities, including intertriginous involvement, vesiculobullous lesions (relatively uncommon in Darier disease), nail changes, exacerbation with heat, and frequent superinfections. As a result of these overlapping features, it was initially postulated that Darier disease and Hailey–Hailey disease were allelic disorders caused by defects in a gene encoding a structural component of the epidermis. However, linkage studies mapped Darier disease to chromosome 12 and Hailey–Hailey disease to chromosome 3, and no candidate structural genes were found in these regions.

In 1999, pathogenetic mutations in the *ATP2A2* gene, which encodes a sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase, were identified in patients with Darier disease. Subsequently, mutations in the *ATP2C1* gene on chromosome 3, which encodes a Ca^{2+} ATPase localized to the Golgi apparatus, were shown to cause Hailey–Hailey disease. Determining the molecular bases of these genodermatoses thus demonstrated the pivotal role of calcium homeostasis in epidermal differentiation and cell–cell adhesion[23].

ATP-binding cassette transporter defects

Members of the ABC transporter superfamily bind and hydrolyze adenosine triphosphate (ATP) in order to transport various molecules across a cell membrane or into a vesicle. Well-known examples include the cystic fibrosis transmembrane conductance regulator (CFTR, ABCC7; the chloride ion channel that is defective in patients with cystic fibrosis) and the P glycoprotein (ABCB1; an important cellular mechanism of multidrug resistance). Several phenotypically diverse genodermatoses are also caused by mutations in ABC transporters (see Table 55.1)[24].

Because fragmentation and calcification of elastic fibers in the skin, eyes and cardiovascular system are major features of pseudoxanthoma elasticum (PXE), the latter was initially thought to represent a heritable connective tissue disorder that (presumably) resulted from mutations in a gene encoding an extracellular matrix protein. Surprisingly, PXE was instead found to be caused by mutations in the *ABCC6* gene, which encodes an organic acid transporter (based on *in-vitro* studies) that is expressed almost exclusively in the liver and kidneys. Together with evidence that metabolites present in the sera of PXE patients interfere with the normal assembly of elastic fibers *in vitro*, this suggests that PXE is actually better characterized as a metabolic disorder with secondary connective tissue manifestations.

Biallelic mutations in *ABCA12*, which encodes a transporter that secretes lipids into lamellar granules, cause both harlequin ichthyosis and a form of lamellar ichthyosis[25] (see Fig. 56.2). Patients with harlequin ichthyosis tend to have nonsense mutations, whereas those with lamellar ichthyosis typically have missense mutations. This represents one of the most clearcut genotype–phenotype correlations observed to date for non-syndromic autosomal recessive ichthyoses. Defective formation of intercellular lipid layers, which are essential for epidermal barrier function, due to genetic defects in lipid metabolism also represents the pathomechanism of an expanding list of other ichthyosiform disorders (see Table 55.1 and Fig. 56.2)[25].

Nuclear Envelope Defects

"Nuclear envelopathies" represent a recently defined, clinically heterogeneous group of inherited disorders caused by defects in structural components of the nuclear envelope (see Table 63.9). In addition to a variety of extracutaneous findings (e.g. skeletal dysplasia, muscular dystrophy, cardiomyopathy and neuropathy), dermatologic manifestations include premature aging of the skin (e.g. in progeria and "atypical Werner syndrome" due to *LMNA* mutations), cutaneous fibrosis (e.g. in restrictive dermopathy and Buschke–Ollendorff syndrome/melorheostosis due to *LMNA* and *LEMD3* mutations, respectively) and partial lipodystrophy (e.g. familial Dunnigan and "acquired" Barraquer–Simons types due to *LMNA* and *LMNB2* mutations, respectively).

"Laminopathies" represent the largest subgroup of envelopathies and result from mutations in the genes that encode the lamin A/C and lamin B2 proteins of the nuclear membrane lamina, which lies just inside the inner nuclear membrane[26]. The *LEMD3* gene encodes MAN1, an inner nuclear membrane protein that associates with lamin A. In addition to "true" envelopathies, mutations in the *ZMPSTE24* gene, which encodes a zinc metallopeptidase involved in the processing of prelamin A into mature lamin A, can result in restrictive dermopathy and mandibuloacral dysplasia (characterized by lipodystrophy, premature aging and skeletal defects; can also be caused by *LMNA* mutations). The study of patients with envelopathies has provided insight into the importance of lamins and other nuclear envelope proteins to the structural integrity of the nucleus, chromatin organization, transcriptional regulation, control of differentiation, and mechanisms of aging[26].

Defects in Pyrin/NOD Family Members and Related Proteins

Over the past decade, the molecular bases of several hereditary periodic fever syndromes and other autoinflammatory disorders have been found to be due to defects in proteins containing *n*ucleotide-binding *o*ligomerization *d*omains (NODs) and/or pyrin domains (see Table 45.2)[27]. This has drawn attention to the NOD and pyrin families and related proteins (see Fig. 45.1), helping to uncover their importance in innate immune responses and acquired inflammatory disorders. Defects in such proteins lead to diverse cutaneous phenotypes, ranging from urticarial papules in cryopyrin-related disorders and erysipeloid erythema in familial Mediterranean fever to nodulocystic acne and pyoderma gangrenosum in PAPA syndrome to granulomatous dermatitis (together with arthritis and uveitis) in Blau syndrome (Fig. 55.3). Upon uncovering *NOD2* mutations as the defect in Blau syndrome, it was also established that this autosomal dominant disorder and

HEREDITARY CONNECTIVE TISSUE DISORDERS					
Disorder	**Mode of inheritance**	**Gene or gene product**	**Gene symbol**	**Gene locus**	**MIM number(s)**
DISORDERS CHARACTERIZED BY LAX SKIN (SEE CH. 97, WITH OVERVIEWS IN TABLES 95.5 & 97.6)					
EHLERS–DANLOS SYNDROME (SEE CH. 97, WITH OVERVIEWS IN TABLES 95.5 & 97.2)					
DISORDERS CHARACTERIZED BY EXCESSIVE EXTRACELLULAR MATRIX PROTEIN DEPOSITION (SEE CHS 48, 98 & 116; TABLE 43.6)					
Buschke–Ollendorff syndrome (± melorheostosis)	AD	LEM domain-containing 3 (Man 1, an inner nuclear membrane protein)	*LEMD3 (MAN1)*	12q14	166700, 607844
Inherited systemic hyalinosis (juvenile hyaline fibromatosis, infantile systemic hyalinosis)	AR	Anthrax toxin receptor 2 (capillary morphogenesis protein 2)	*ANTXR2*	4q21	228600, 236490, 608041
Lipoid proteinosis	AR	Extracellular matrix protein 1	*ECM1*	1q21	247100, 602201
Stiff skin syndrome	AD	Fibrillin 1	*FBN1*	15q21.1	184900, 134797
Torg–Winchester syndrome (including the nodulosis–arthropathy–osteolysis variant)	AR	Matrix metalloproteinase 2	*MMP2*	16q13	259600, 120360
OTHER DISORDERS (SEE CHS 62 & 97; TABLES 43.6, 64.4 & 95.5)					
Adams–Oliver syndrome	AD AR	Rho GTPase activating protein 31 Dedicator of cytokinesis 6	*ARHGAP31* *DOCK6*	3q13.33 19p13.2	100300, 610911 614194, 614219
Goltz syndrome (focal dermal hypoplasia)	XD	Porcupine homolog	*PORCN*	Xp11.23	305600, 300651
Loeys–Dietz syndrome (type 1A, 2A)	AD	TGF-β receptor 1 (gain-of-function mutations)	*TGFRB1*	9q22	609192, 608967, 190181
Loeys–Dietz syndrome (type 1B, 2B)	AD	TGF-β receptor 2 (gain-of-function mutations)	*TGFRB2*	3p22	610168, 610380, 190182
Marfan syndrome	AD	Fibrillin 1	*FBN1*	15q21.1	134797, 154700
MIDAS syndrome	XD	Holocytochrome c synthase	*HCCS*	Xp22	309801, 300056
Multiple pterygium syndrome	AR	Cholinergic receptor, nicotinic γ	*CHRNG*	2q33–q34	253290, 265000
Popliteal pterygium syndrome	AD	Interferon regulatory factor-6	*IRF6*	1q32–q41	119500, 607199
Van der Woude syndrome	AD	Interferon regulatory factor-6	*IRF6*	1q32	119300, 607199
Restrictive dermopathy*	AD>>AR AR	Lamin A/C Zinc metallopeptidase (STE24 homolog)	*LMNA* *ZMPSTE24*	1q22 1p34	275210, 150330 275210, 606480
Setleis syndrome	AR	Twist homolog 2	*TWIST2*	2q37.3	227250
Ullrich disease	AR AR AR	Collagen VI, α1 chain Collagen VI, α2 chain Collagen VI, α3 chain	*COL6A1* *COL6A2* *COL6A3*	21q22.3 21q22.3 2q37	254090, 120220 254090, 120240 254090, 120250

*Allelic with familial partial lipodystrophy, mandibuloacral dysplasia, Hutchinson–Gilford progeria syndrome and atypical Werner syndrome (see Tables 55.12 & 63.9); an autosomal recessive form of restrictive dermopathy due to LMNA mutations has been reported in only one patient to date.

Table 55.4 Hereditary connective tissue disorders. MIDAS, *mi*crophthalmia, *d*ermal *a*plasia and *s*clerocornea.

Fig. 55.3 Blau syndrome. Granulomatous dermatitis presenting as numerous pinkish-tan, flat-topped papules in a generalized distribution in a 1-year-old boy. Patients also develop epidermal atrophy and arthritis with non-tender, boggy synovial swelling.

ECTODERMAL DYSPLASIAS					
Disorder	**Mode of inheritance**	**Gene or gene product**	**Gene symbol**	**Gene locus**	**MIM number(s)**
Acantholytic ectodermal dysplasia	AR	Plakoglobin	*JUP (PKGB)*	17q21	173325
AEC syndrome (including Rapp–Hodgkin syndrome)	AD	Tumor protein p63, sterile alpha motif (SAM) domain and elsewhere in the tail region	*p63 (TP63)*	3q27	106260, 129400, 603273
EEC syndrome	AD	Tumor protein p63, DNA-binding domain	*p63 (TP63)*	3q27	604292, 603273
ADULT (*a*cro-*d*ermato-*u*ngual-*l*acrimal-*t*ooth) syndrome	AD	Tumor protein p63, hotspot at end of DNA-binding domain	*p63 (TP63)*	3q27	103285, 603273
Limb–mammary syndrome	AD	Tumor protein p63, often truncating in C-terminal region	*p63 (TP63)*	3q27	603543, 603273
Cleft lip/palate–ED syndrome	AR	Nectin-1 (poliovirus receptor-related 1)	*PVRL1*	11q23–q24	225000, 225060, 600644
Cranioectodermal dysplasia 1	AR	Intraflagellar transport 122 homolog	*IFT122*	3q21	218330, 60045
Cranioectodermal dysplasia 2	AR	WD repeat domain 35	*WDR35*	2p24.3	613610, 13602
ED–neoplastic syndrome	AD	Axis inhibitor 2	*AXIN2*	17q23–q24	608615, 602024
ED–syndactyly syndrome 1	AR	Nectin-4 (poliovirus receptor-related 4)	*PVRL4*	1q22–q23.2	613573, 609607
EEM syndrome	AR	Cadherin 3 (P-cadherin)	*CDH3*	16q22.1	225280, 114021
Ellis–van Creveld (EVC) syndrome	AR AR	EVC EVC2 (limbin)	*EVC* *EVC2*	4p16 4p16	225500, 604831 225500, 607261
Hidrotic ED (Clouston syndrome)	AD	Connexin 30 (gap junction protein β6)	*GJB6*	13q12	129500, 604418
Hypohidrotic ED	AD, AR AD, AR XR	Ectodysplasin A receptor (EDAR) EDAR-associated death domain Ectodysplasin A (Tabby protein)	*EDAR* *EDARADD* *EDA*	2q11–q13 1q42.3 Xq12–q13.1	129490, 224900. 604095 129490, 224900, 606603 305100, 300451
Hypohidrotic ED with immunodeficiency	XR	Inhibitor of κ light polypeptide gene enhancer in B cells, kinase γ (nuclear factor-κB essential modulator)	*IKBKG (NEMO)*	Xq28	300291, 300301, 300248
	AD	Nuclear factor of κ light polypeptide gene enhancer in B cells inhibitor-α	*NFKBIA*	14q13	612132, 164008
Immunodeficiency, myopathy and ED	AR	ORAI calcium release-activated calcium modulator 1	*ORAI1*	12q24.31	612782, 610277
Odonto-onycho-dermal dysplasia and other WNT10A-related EDs (including Schöpf–Schulz–Passarge syndrome)	AR	Wingless-type MMTV integration site family, member 10A	*WNT10A*	2q35	224750, 257980, 606268
Plakophilin deficiency (ED/skin fragility syndrome)	AR	Plakophilin 1	*PKP1*	1q32	604536, 601975
"Pure" hair–nail type ED	AR	Keratin 85	*KRT85*	12q11–q13	602032, 602767
Tooth and nail (Witkop) syndrome	AD	Muscle segment homeobox 1	*MSX1*	4p16.1	189500, 142983
Tricho-dento-osseous syndrome	AD	Distal-related homeobox 3	*DLX3*	17q21.2–q22	190320, 600525

Table 55.5 Ectodermal dysplasias. Ectodermal dysplasias (EDs), genetic disorders characterized by abnormalities in two or more of the major structures derived from the ectoderm (e.g. hair, teeth, nails and sweat glands), are discussed in Chapter 63. See Table 55.7 for Naegeli–Franceschetti–Jadassohn syndrome and dermatopathia pigmentosa reticularis. AEC, *a*nkyloblepharon, *e*ctodermal defects, cleft lip/palate; EEC, *e*ctodermal dysplasia, *e*ctrodactyly, *c*left lip/palate; EEM, *e*ctodermal dysplasia, *e*ctrodactyly, *m*acular dystrophy.

"early-onset sarcoidosis" are identical on a genetic as well as phenotypic level (with the latter resulting from *de novo NOD2* mutations), thus representing a single disease entity. However, different *NOD2* variants have been implicated in Crohn's disease and susceptibility to leprosy.

Defects in DNA Repair Genes, Tumor Suppressor Genes and Oncogenes

Hereditary cancer syndromes that affect the skin can be divided into groups based upon whether the associated malignancies are primarily cutaneous (e.g. Gorlin syndrome; see Table 55.10) or extracutaneous (see Table 55.11); individuals in the latter group may have either benign cutaneous neoplasms (e.g. Cowden disease) or non-neoplastic skin lesions (e.g. ataxia–telangiectasia)[28]. To complement this clinical approach, molecular classification of such syndromes can help to explain relationships among disorders and understand the disrupted pathway or process, perhaps suggesting candidate genes for patients with similar phenotypes for which the underlying molecular defect has not yet been identified. In addition to characterization based on the specific pathomechanism (e.g. RAS-ERK pathway activation[29]; see below), hereditary cancer syndromes can be separated into three general categories: (1) defective DNA repair and protection of genomic integrity

HEREDITARY DISORDERS OF THE HAIR AND NAILS					
Disorder	**Mode of inheritance**	**Gene or gene product**	**Gene symbol**	**Gene locus**	**MIM number(s)**
DISORDERS WITH HYPOTRICHOSIS AND/OR HAIR SHAFT ABNORMALITIES (SEE CH. 69, WITH AN OVERVIEW IN TABLE 69.7)					
DISORDERS WITH HYPERTRICHOSIS (SEE TABLES 70.1 & 70.2)					
Congenital generalized hypertrichosis, X-linked	XR		Interchromosomal insertion mediated by a palindromic sequence	Xq27.1	307150
Congenital generalized hypertrichosis terminalis with or without gingival hyperplasia	AD		Microdeletion involving *ABCA5, ABCA6, ABCA10* and *MAP2K6*	17q24.2–q24.3	135400
Hypertrichosis universalis congenita (Ambras syndrome)	AD	(Tricho-rhino-phalangeal syndrome I)	(Chromosomal anomalies affect *TRPS1* expression)	8q22	145701
Leigh syndrome	mt	Various components of mitochondrial respiratory chain complexes			256000
	AR	Surfeit 1	*SURF1*	9q33–q34	256000, 185620
NAIL DISORDERS (SEE CH. 71)					
Anonychia congenita	AR	R-spondin family, member 4	*RSPO4*	20p13	206800, 610573
Isolated AR nail dysplasia	AR	Frizzled 6	*FZD6*	8q22.3	614157, 603409
Isolated congenital nail clubbing	AR	Hydroxyprostaglandin dehydrogenase 15-(NAD)	*HPGD*	4q34–q35	119900, 601688
Isolated toenail dystrophy	AD	Collagen VII, α1 chain	*COL7A1*	3p21.3	607523, 120120
Nail–patella syndrome	AD	LIM homeobox transcription factor 1β	*LMX1B*	9q34.1	161200, 602575
Pachyonychia congenita-6a	AD	Keratin 6a	*KRT6A*	12q13	167200, 148041
Pachyonychia congenita-16	AD	Keratin 16	*KRT 16*	17q12–q21	167200, 148067
Pachyonychia congenita-6b	AD	Keratin 6b	*KRT6B*	12q13	167210, 148042
Pachonychia congenita-17	AD	Keratin 17	*KRT17*	17q12–q21	167210, 148069
Tricho-rhino-phalangeal syndrome 1	AD	TRPS1 (zinc finger protein)	*TRPS1*	8q24.12	190350, 604386

Table 55.6 Hereditary disorders of the hair and nails. Hair and/or nail abnormalities can also be observed in patients with disorders of keratinization and ectodermal dysplasias (see Tables 55.3 & 55.5). Pachydermoperiostosis is included in Table 55.12. mt, mitochondrial inheritance.

("caretaker" genes); (2) defective tumor suppressor ("gatekeeper") genes; and (3) activated oncogenes.

Defective DNA repair and protection of genomic integrity

Inactivation of caretaker genes causes an increased mutation rate in all genes, including gatekeeper genes with critical roles in controlling tumor growth (see below). Classic examples of caretaker dysfunction include defects in various nucleotide excision repair proteins (required for correction of UV-induced DNA damage) in xeroderma pigmentosum and abnormal mismatch repair in Muir–Torre syndrome (a subtype of the hereditary non-polyposis colorectal cancer syndrome). Defects in RecQ helicases, which function in DNA replication, recombination and repair, underlie Bloom, Rothmund–Thomson and Werner syndromes. This leads to genomic instability, as evidenced by findings such as accumulation of chromosomal aberrations, increased sister chromatid exchange (Bloom syndrome) and shortened telomeres (Werner syndrome). The compromised telomere maintenance observed in dyskeratosis congenita can result from defects in telomerase subunits (RNA and reverse transcriptase) or associated proteins (e.g. dyskerin, a Cajal body protein, ribonucleoprotein analogs, a shelterin complex component).

Defective tumor suppressor genes

In hereditary cancer syndromes caused by a defective tumor suppressor gene, there is classically a heterozygous germline loss-of-function mutation followed by a somatic "second hit" that leads to loss of heterozygosity and abrogation of protein function in affected tissues. Examples include *PTCH* (encoding patched) in Gorlin syndrome (see Ch. 107), *CDKN2A* (encoding $p16^{INK4a}$ and $p14^{ARF}$, which maintain activity of the retinoblastoma [Rb] and p53 tumor suppressor proteins, respectively) in the familial atypical mole-malignant melanoma syndrome (see Ch. 113), and *PTEN* in the PTEN hamartoma tumor syndrome (see Ch. 63). The PTEN protein negatively regulates the phosphatidylinositol 3-kinase (PI3K)/AKT cascade, the same pathway that is positively regulated by the RET oncogene (Fig. 55.4; see below). Proteus syndrome is caused by mosaicism for an activating mutation in the *AKT1* oncogene, explaining its clinical similarity to type 2 mosaic PTEN hamartoma tumor syndrome (see below).

Activated oncogenes

Germline gain-of-function mutations in oncogenes have been identified in some autosomal dominant hereditary tumor syndromes, including *RET* in multiple endocrine neoplasia (MEN) 2A/2B (see Fig. 55.4), *KIT* in familial mastocytosis plus gastrointestinal stromal tumors, and those encoding RAS-MAPK pathway components in certain "RASopathies" (Fig. 55.5). The latter include Costello (Fig. 55.6), Noonan, cardio-facio-cutaneous (CFC) and LEOPARD syndromes[30]. In addition, neurofibromatosis type 1 (NF1) and Legius syndrome (previously referred to as NF1-like syndrome) represent RASopathies due to germline *loss*-of-function mutations in tumor suppressor genes that normally downregulate RAS-MAPK signaling[29].

RASopathies share extracutaneous features such as ocular hypertelorism, macrocephaly, cardiac defects (especially pulmonary stenosis) and developmental delay, as well as a spectrum of skin findings that includes hair abnormalities (e.g. curly, woolly, loose anagen), pigmented lesions (e.g. lentigines, melanocytic nevi, café-au-lait macules)[31], keratosis pilaris, acanthosis nigricans and distal phalangeal transverse creases (see Fig. 55.6B&C). Some RASopathies also have more specific cutaneous manifestations (e.g. neurofibromas in NF1, lax acral skin in Costello syndrome; see Fig. 55.6B).

HEREDITARY DISORDERS OF PIGMENTATION					
Disorder	**Mode of inheritance**	**Gene or gene product**	**Gene symbol**	**Gene locus**	**MIM number(s)**
DISORDERS WITH DIFFUSE PIGMENTARY DILUTION OR CIRCUMSCRIBED LEUKODERMA (SEE CH. 66, WITH OVERVIEWS IN TABLES 66.3, 66.5 & 66.6)					
DISORDERS WITH HYPERPIGMENTATION (SEE CH. 67)					
Dermatopathia pigmentosa reticularis	AD	Keratin 14	*KRT14*	17q12–q21	125595, 148066
Naegeli–Franceschetti–Jadassohn syndrome	AD	Keratin 14	*KRT14*	17q12–q21	161000, 148066
Dowling–Degos disease (including Galli–Galli disease)	AD	Keratin 5	*KRT5*	12q13	179850, 148040
Incontinentia pigmenti	XD	Inhibitor of κ light polypeptide gene enhancer in B cells, kinase γ (nuclear factor-κB essential modulator)	*IKBKG (NEMO)*	Xq28	308300, 300248
McCune–Albright syndrome	Postzygotic mutation	Stimulatory G protein, α-subunit (G, α; activating mutations)	*GNAS*	20q13.2	174800, 139320
X-linked reticulate pigmentary disorder, Partington type	XR			Xp22.11–p21.3	301220
Progressive familial hyperpigmentation	AD	Kit ligand	*KITLG*	12q22	145250, 184745
Terminal osseous dysplasia with pigmentary defects	XD	Filamin A	*FLNA*	Xq28	300244, 300017
DYSCHROMATOSES (SEE CH. 67)					
Dyschromatosis symmetrica hereditaria	AD	Adenosine deaminase, RNA-specific	*ADAR*	1q21.3	127400, 601059
Dyschromatosis universalis hereditaria	AD AR			6q24.2–q25.2 12q21–q23	127500 612715
Progressive familial hyper- and hypopigmentation	AD	Kit ligand	*KITLG*	12q22	184745

Table 55.7 Hereditary disorders of pigmentation.

HEREDITARY METABOLIC SKIN DISORDERS					
Disorder	**Mode of inheritance**	**Gene or gene product**	**Gene symbol**	**Gene locus**	**MIM number(s)**
DISORDERS DUE TO ENZYME DEFICIENCIES (SEE CH. 63)					
Alkaptonuria	AR	Homogentisate 1,2-dioxygenase (homogentisate oxidase)	*HGD*	3q21–q23	203500, 607474
Biotinidase deficiency	AR	Biotinidase	*BTD*	3p25	253260, 609019
Holocarboxylase synthetase deficiency	AR	Holocarboxylase synthetase	*HLCS*	21q22.1	253270, 609018
Fabry disease*	XR	α-Galactosidase A	*GLA*	Xq22.1	301500, 300644
Fucosidosis*	AR	α-L-Fucosidase	*FUCA1*	1p34	230000
Farber lipogranulomatosis	AR	Acid ceramidase	*ASAH*	8p22–p21.3	228000
Gaucher disease types I–III	AR	Acid β-glucosidase (glucocerebrosidase)	*GBA*	1q21	230800, 230900, 231000, 606463
Hereditary angioedema Types I & II	AD	Serpin peptidase inhibitor, clade G, member 1 (C1 inhibitor)	*SERPING1*	11q11–q13.1	106100, 606860
Type III	AD (only females affected)	Factor XII (Hageman factor)	*F12*	5q33–qter	610618, 610619
Homocystinuria	AR	Cystathionine β-synthase†	*CBS*	21q22.3	236200
Niemann–Pick disease type A	AR	Acid sphingomyelinase	*SMPD1*	11p15.4–p15.1	257200, 607608
Phenylketonuria	AR AR AR	Phenylalanine hydroxylase Quinoid dihydropteridine reductase 6-Pyruvoyltetrahydropterin synthase	*PAH* *QDPR* *PTS*	12q24.1 4p15 11q22.3	261600 261630 261640
Prolidase deficiency	AR	Prolidase (peptidase D)	*PEPD*	19q13.11	170100

*Additional metabolic disorders that can present with angiokeratoma corporis diffusum include aspartylglycosaminuria (208400), galactosialidosis (256540), GM1 gangliosidosis (230500), Kanzaki disease (609242) and β-mannosidosis (248510) (see Table 63.6).
†Defects in this gene represent the most common cause of homocystinuria.

Table 55.8 Hereditary metabolic skin disorders.

Continued

HEREDITARY METABOLIC SKIN DISORDERS					
Disorder	**Mode of inheritance**	**Gene or gene product**	**Gene symbol**	**Gene locus**	**MIM number(s)**
DISORDERS DUE TO DEFECTIVE TRANSPORTERS/RELATED PROTEINS					
Acrodermatitis enteropathica	AR	Solute carrier family 39, member 4 (zinc transporter)	*SLC39A4*	8q24.3	201100, 607059
H syndrome‡	AR	Solute carrier family 29, member 3 (nucleoside transporter)	*SLC29A3*	10q22.2	612391, 612373
Hartnup disease	AR	Solute carrier family 6, member 19 (neutral amino acid transporter)	*SLC6A19*	5p15	234500, 608893
Hemochromatosis	AR AR AD	Hemochromatosis Transferrin receptor 2 Solute carrier family 40, member 1 (ferroportin)	*HFE* *TFR2* *SLC40A1*	6p21.3 7q22 2q32	235200, 604250 235200, 604720 606069, 604653
Hemochromatosis, juvenile	AR AR	Hepcidin antimicrobial peptide Hemojuvelin	*HAMP* *HFE2*	19q13 1q21	602390, 606464 602390, 608374
Wilson disease	AR	Cu^{2+}-transporting P-type ATPase 7B	*ATP7B*	13q14.3–q21.1	277900, 606882
HYPERLIPIDEMIAS (SEE CH. 92)					
Lipoprotein lipase deficiency (type I hyperlipoproteinemia)	AR	Lipoprotein lipase	*LPL*	8p22	238600, 609708
Apolipoprotein C-II deficiency (type I hyperlipoproteinemia)	AR	Apolipoprotein C-II	*APOC2*	19q13.2	207750, 608083
Familial chylomicronemia (type I hyperlipoproteinemia)	AR	Glycosyl-phosphatidylinositol-anchored high-density lipoprotein-binding protein 1	*GPIHBP1*	8q24.3	612757
Familial hypercholesterolemia (type II hyperlipoproteinemia)	AD AD AD AR	LDL receptor Apolipoprotein B-100, LDL receptor-binding domain Proprotein convertase subtilisin/kexin type 9 Low-density-lipoprotein receptor adaptor protein 1	*LDLR* *APOB* *PCSK9* *LDLRAP1*	19p13.2 2p24 1p34.1–p32 1p36–p35	143890, 606945 144010, 107730 603776, 607786 603813, 605747
Dysbetalipoproteinemia (type III hyperlipoproteinemia)	AR	Apolipoprotein E	*APOE*	19q13.2	107741
Familial hypertriglyceridemia (type IV/V hyperlipoproteinemia)	AD AD	Lipase, member I Apolipoprotein A-V	*LIPI* *APOA5*	21q11.2 11q23	145750, 609252 144650, 145750, 606368
Cerebrotendinous xanthomatosis	AR	Cytochrome P450, subfamily 27A, polypeptide 1 (sterol-27-hydroxylase)	*CYP27*	2q33-qter	213700, 606530
Hypoalphalipoproteinemia	AD AD	Apolipoprotein A-I ATP-binding cassette-1, sub-family A, member 1 (cholesterol efflux regulatory protein)	*APOA1* *ABCA1*	11q23.3 9q31	604091, 107680 604091, 600046
Tangier disease	AR	ATP-binding cassette-1, sub-family A, member 1 (cholesterol efflux regulatory protein)	*ABCA1*	9q31	205400, 600046
Sitosterolemia	AR AR	ATP-binding cassette, sub-family G, member 5 (sterolin 1) ATP-binding cassette, sub-family G, member 8 (sterolin 2)	*ABCG5* *ABCG8*	2p21 2p21	210250, 605459 210250, 605460
PORPHYRIAS (SEE CH. 49)					
Congenital erythropoietic porphyria (Günther disease)	AR	Uroporphyrinogen-III synthase	*UROS*	10q25.2–q26.3	263700, 606938
Hepatoerythropoietic porphyria	AR	Uroporphyrinogen-III decarboxylase	*UROD*	1p34	176100, 613521
Porphyria cutanea tarda§	AD	Uroporphyrinogen-III decarboxylase	*UROD*	1p34	176100, 613521
Hereditary coproporphyria	AD	Coproporphyrinogen oxidase	*CPOX*	3q12	121300, 612732
Variegate porphyria	AD	Protoporphyrinogen oxidase	*PPOX*	1q22	176200, 600923
Erythropoietic protoporphyria	AD	Ferrochelatase	*FECH*	18q21.3	177000, 612386

‡Including cases reported as pigmented hypertrichotic insulin-dependent diabetes mellitus syndrome and familial histiocytosis syndrome.
§Approximately 25% of affected individuals have an underlying *UROD* mutation, often together with additional genetic (e.g. mutations in the *HFE* gene that underlie hemochromatosis) or exogenous (e.g. alcohol, hepatitis C viral infection) factors.

Table 55.8 Hereditary metabolic skin disorders (cont'd).

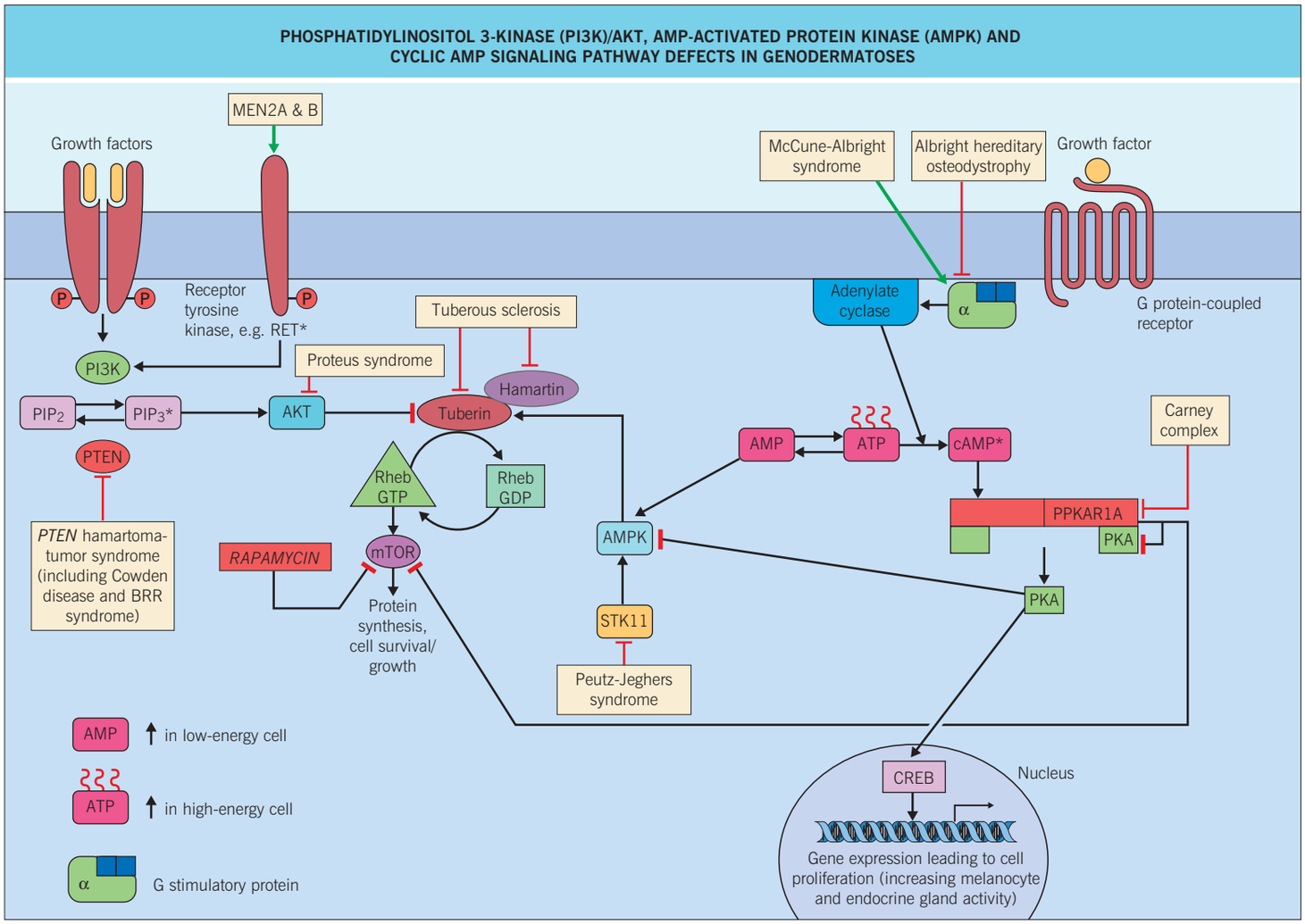


Fig. 55.4 Phosphatidylinositol 3-kinase (PI3K)/AKT, AMP-activated protein kinase (AMPK) and cyclic AMP signaling pathway defects in genodermatoses. The PI3K/AKT pathway is negatively regulated by the PTEN tumor suppressor protein and can be stimulated by a variety of receptor tyrosine kinases as well as by RAS (via cross-talk with the RAS-ERK pathway; see Fig. 55.3). AKT (protein kinase B) inhibits the GTPase activating-protein tuberin, which leads to increased *m*ammalian *t*arget *o*f *r*apamycin (mTOR) activity and resultant cell growth. During periods of nutrient depletion (high AMP/low ATP), serine-threonine kinase 11 (STK11) promotes AMPK-mediated activation of tuberin, which results in decreased mTOR activity and less protein synthesis. Ligand binding to G protein-coupled receptors activates adenylate cyclase, producing increased intracellular cAMP and activation of protein kinase A catalytic subunits (PKA; via release from *p*rotein *k*inase *A* *r*egulatory subunit 1α [PRKAR1A]); this leads to transcription of *c*AMP *r*esponse *e*lement *b*inding protein (CREB)-controlled genes as well as inhibition of AMPK (which is also negatively regulated by AKT). *Other effector pathways include activation of RAS-ERK (see Fig. 55.3). AMP, adenosine monophosphate; ATP, adenosine triphosphate; BRR, Bannayan–Riley–Ruvalcaba; ERK, *e*xtracellular signal-*r*egulated *k*inase; GDP, guanosine diphosphate; GTP, guanosine triphosphate; PIP2, phosphatidylinositol diphosphate; PIP3, phosphatidylinositol triphosphate; PTEN, phosphatase and tensin homolog deleted on chromosome 10.

These disorders are associated with variably increased risks for the development of benign (e.g. neurofibromas in NF1, infantile hemangiomas in CFC syndrome) and malignant (e.g. rhabdomyosarcoma in Costello syndrome) tumors. Targeted drugs aimed at proteins in the RAS-MAPK pathway hold promise for the treatment of sporadic cancers (e.g. BRAF inhibitors for melanoma) as well as RASopathies themselves.

Defects in WNT/β-Catenin Signaling

WNT (*w*ingless-type *int*egration site) family members are lipid-modified, secreted signaling proteins that play important roles in numerous physiologic and pathologic processes, ranging from stem cell differentiation, cell polarity/adhesion and tissue morphogenesis/maintenance (including hair follicle development) to wound repair, inflammation, oncogenesis and aging. WNT signaling can be divided into canonical (β-catenin-dependent) and non-canonical (β-catenin-independent) pathways. Several genodermatoses result from defects in proteins that function in the WNT/β-catenin pathway (Fig. 55.7). Goltz syndrome (focal dermal hypoplasia; see Ch. 62) (Fig. 55.8) is caused by mutations in the *PORCN* gene, which encodes an O-acyltransferase in the endoplasmic reticulum that palmitoylates and thereby facilitates secretion of WNT proteins. Mutations in the *WNT10A* gene produce several relatively common forms of ectodermal dysplasia as well as Schöpf–Schulz–Passarge syndrome (featuring hidrocystomas and palmoplantar keratoderma with eccrine syringofibroadenomatosis). Gardner syndrome (a variant of *a*denomatous *p*olyposis *c*oli) is due to mutations in the *APC* tumor suppressor gene that encodes an inhibitor of WNT/β-catenin signaling[32], and mutations in the APC downregulated 1 gene (*APCDD1*) were recently found to underlie hereditary hypotrichosis simplex. Lastly, anonychia congenita and "palmoplantar keratoderma with cutaneous SCC and sex reversal" are caused by mutations in genes encoding R-spondins that activate WNT/β-catenin signaling.

CONTIGUOUS GENE SYNDROMES

Certain syndromic associations actually represent contiguous gene syndromes caused by large deletions that affect two or more neighboring genes. For example, deletions in the Xp22.3 region can give rise to X-linked recessive ichthyosis, X-linked recessive chondrodysplasia

HEREDITARY SKIN DISORDERS CHARACTERIZED BY BENIGN TUMORS OR VASCULAR ANOMALIES					
Disorder	**Mode of inheritance**	**Gene or gene product**	**Gene symbol**	**Gene locus**	**MIM number(s)**
DISORDERS WITH BENIGN TUMORS (SEE CHS 61, 62, 104, 117 & 118)					
Familial cylindromatosis; Brooke–Spiegler syndrome; multiple familial trichoepitheliomas	AD	CYLD (deubiquitinating enzyme)	*CYLD*	16q12–q13	132700, 601606, 605041, 605018
Familial mastocytosis ± gastrointestinal stromal tumors*	AD	KIT proto-oncogene (stem cell factor receptor)	*KIT*	4q12	606764, 164920
Infantile hemangiomas, hereditary	AD			5q31–q33	602089
Leiomyomatosis, cutaneous and uterine (Reed syndrome)†	AD	Fumarate hydratase	*FH*	1q42.1	150800, 136850
Lipomatosis, familial multiple	AD			12q15	151900
Lipomatosis, benign symmetric (Madelung disease)‡	mt	Mitochondrial tRNA-lysine	*MT-TK*		151800, 590060
Ferguson–Smith multiple self-healing squamous epitheliomas	AD	Transforming growth factor-β receptor 1 (loss-of-function mutations)	*TGFBR1*	9q22	132800
Neurofibromatosis type 1	AD	Neurofibromin 1 (GTPase activating protein)	*NF1*	17q11.2	162200, 613113
Legius syndrome	AD	Sprouty-related, EVH1 domain-containing 1	*SPRED1*	15q14	611431, 609291
Watson syndrome; neurofibromatosis–Noonan syndrome	AD	Neurofibromin 1 (GTPase activating protein)	*NF1*	17q11.2	193520, 601321, 162200, 613113
Neurofibromatosis type 2	AD	Neurofibromin 2 (merlin)	*NF2*	22q12.2	101000, 607379
Proteus syndrome	Postzygotic mutation	AKT1 oncogene	*AKT1*	14q32.33	164730, 176920
Steatocystoma multiplex	AD	Keratin 17	*KRT17*	17q12–q21	148069, 184500
Tuberous sclerosis	AD AD	Hamartin Tuberin	*TSC1* *TSC2*	9q34 16p13.3	191100, 605284 191100, 191092

*Occasionally malignant.
†Also associated with renal cell carcinoma.
‡In cases of benign symmetric lipomatosis associated with MERRF (myoclonic epilepsy with ragged red fibers) syndrome.

Table 55.9 Hereditary skin disorders characterized by benign tumors or vascular anomalies. GTP, guanine triphosphate; mt, mitochondrial inheritance; TGF, transforming growth factor.

HEREDITARY DISORDERS ASSOCIATED WITH CUTANEOUS CANCER					
Disorder	**Mode of inheritance**	**Gene or gene product**	**Gene symbol**	**Gene locus**	**MIM number(s)**
Bazex–Dupré–Christol syndrome	XD			Xq25–q27.1	301845
Epidermodysplasia verruciformis	AR AR	Transmembrane channel-like 6 Transmembrane channel-like 8	*TMC6* *TMC8*	17q25 17q25	226400, 605828 226400, 605829
Familial atypical mole–malignant melanoma (FAMMM) syndrome	AD AD	Cyclin-dependent kinase inhibitor 2A* Cyclin-dependent kinase 4	*CDKN2A* *CDK4*	9p21 12q24	155600, 600160 155600, 123829
Gorlin (nevoid basal cell carcinoma) syndrome	AD AD AD	Patched 1 Patched 2 Suppressor of fused homolog (Drosophila)	*PTCH1* *PTCH2* *SUFU*	9q22.3 1p34.1 10q24.32	109400, 601309 109400, 603673 109400, 607035
Huriez syndrome (sclerotylosis)	AD			4q23	181600
Palmoplantar keratoderma with cutaneous SCC and sex reversal	AR	R-spondin 1	*RSPO1*	1p34.3	610644, 609595
Xeroderma pigmentosum (XP) XPA	AR	(DNA damage-binding protein and progressivity factor in nucleotide excision repair)	*XPA*	9q22.3	278700, 611153
XPB	AR	ERCC3 (TFIIH subunit, 3′→5′ DNA helicase in nucleotide excision repair)	*ERCC3*	2q21	610651, 133510
XPC	AR	(DNA damage-binding protein in nucleotide excision repair)	*XPC*	3p25	278720, 613208
XPD	AR	ERCC2 (TFIIH subunit, 5′→3′ DNA helicase in nucleotide excision repair)	*ERCC2*	19q13.2–q13.3	278730, 126340
XPE	AR	DNA damage-binding protein 2	*DDB2*	11p12–p11	278740, 600811
XPF	AR	ERCC4 (5′-endonuclease in nucleotide excision repair)	*ERCC4*	16p13.2–p13.1	278760, 133520
XPG	AR	ERCC5 (3′-endonuclease in nucleotide excision repair)	*ERCCS*	13q33	278780, 133530
XP variant	AR	DNA polymerase-η	*POLH*	6p21.1–p12	278750, 603968

*Also associated with increased risk of developing pancreatic cancer.

Table 55.10 Hereditary disorders associated with cutaneous cancer. These conditions are discussed in Chapters 79, 87, 99, 108 and 112. ERCC, excision repair cross-complementing; SCC, squamous cell carcinoma; TFIIH, transcription factor IIH.

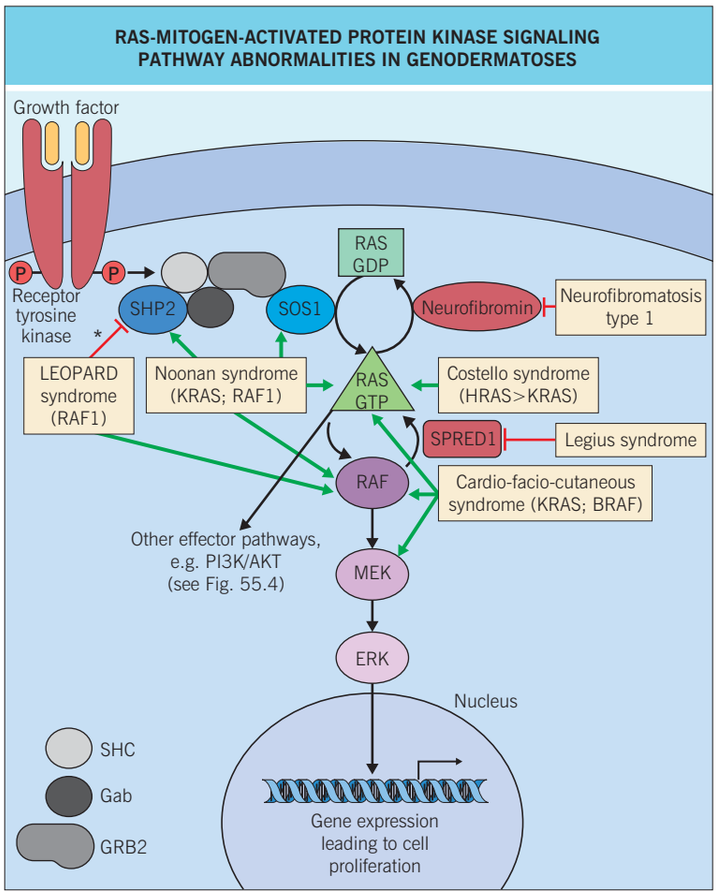


Fig. 55.5 RAS–mitogen-activated protein kinase (MAPK) signaling pathway abnormalities in genodermatoses. The phenotypic overlap among neurofibromatosis type 1 and Legius, Noonan, cardio-facio-cutaneous, Costello and LEOPARD syndromes is explained by underlying germline mutations in different components of the RAS-MAPK pathway that lead to activation of this signaling cascade. Of note, similar *somatic* activating mutations are found in a variety of benign and malignant tumors (e.g. *BRAF* or *NRAS* mutations in the majority of melanocytic nevi and melanomas; see Ch. 113). Growth factor binding to receptor tyrosine kinases results in activated receptor complexes containing adapters such as Src *h*omology 2 (SH2) domain-*c*ontaining (SHC), *g*rowth factor *r*eceptor-*b*ound 2 (GRB2) and *G*RB2-*a*ssociated *b*inding (Gab) proteins as well as SHP2, a SH2 domain-containing non-receptor protein tyrosine phosphatase that relays signals from activated receptors to RAS and deactivates negative regulators of RAS (e.g. Sprouty). The activated receptor complex recruits son of sevenless homolog 1 (SOS1), a guanine nucleotide exchange factor that increases levels of active RAS-guanosine triphosphate (GTP). In contrast, neurofibromin is a GTPase activating protein that promotes hydrolysis of RAS-GTP to RAS-guanosine diphosphate (GDP), which terminates signaling. **In vitro* studies suggest a dominant negative effect, but the consequences could vary depending on the substrate, cell type or developmental stage.

Fig. 55.6 Costello syndrome due to a heterozygous activating *HRAS* mutation in a 3-year-old girl. A Verrucous periorificial (periocular, perinasal) plaques. **B** Loose acral skin with deep palmoplantar creases. Note the distal phalangeal transverse crease on the thumb. **C** Acanthosis nigricans.

punctata, Kallmann syndrome (hypogonadotrophic hypogonadism with anosmia), ocular albinism type 1, short stature and mental retardation. Of note, more than 90% of patients with X-linked recessive ichthyosis have complete deletion of the *STS* gene and flanking sequences, which represents one of the highest incidences of chromosomal deletions among all genetic disorders. Additional genodermatoses that can present as contiguous gene syndromes include Ehlers–Danlos syndrome (due to tenascin-X deficiency) plus congenital adrenal hyperplasia (due to 21-hydroxylase deficiency), tricho-rhino-phalangeal syndrome plus multiple cartilaginous exostoses (together referred to as Langer–Giedion syndrome), and MIDAS (*mi*crophthalmia, *d*ermal *a*plasia and *s*clerocornea) syndrome plus Aicardi syndrome (agenesis of the corpus callosum with a chorioretinal abnormality).

CUTANEOUS MOSAICISM

A mosaic is defined as an organism composed of at least two genetically different populations of cells that originate from a genetically homogeneous zygote (see Ch. 62). As a uniquely accessible organ, the skin provides an excellent opportunity to visualize and study mosaicism, which can present with skin lesions that follow Blaschko's lines or have a checkerboard, phylloid (see below) or lateralized pattern of distribution.

Mosaic forms of autosomal dominant genodermatoses include: (1) a heterozygous postzygotic mutation occurring on a wild-type ("normal") background (type 1); and (2) a postzygotic "second hit" leading to loss-of-heterozygosity in the setting of a heterozygous constitutional mutation (type 2). The latter manifests clinically as a localized area or streaks of more severe disease on a background of milder disease (e.g. linear porokeratosis in a patient with disseminated superficial actinic porokeratosis). Examples of type 1 mosaicism that have been confirmed on a

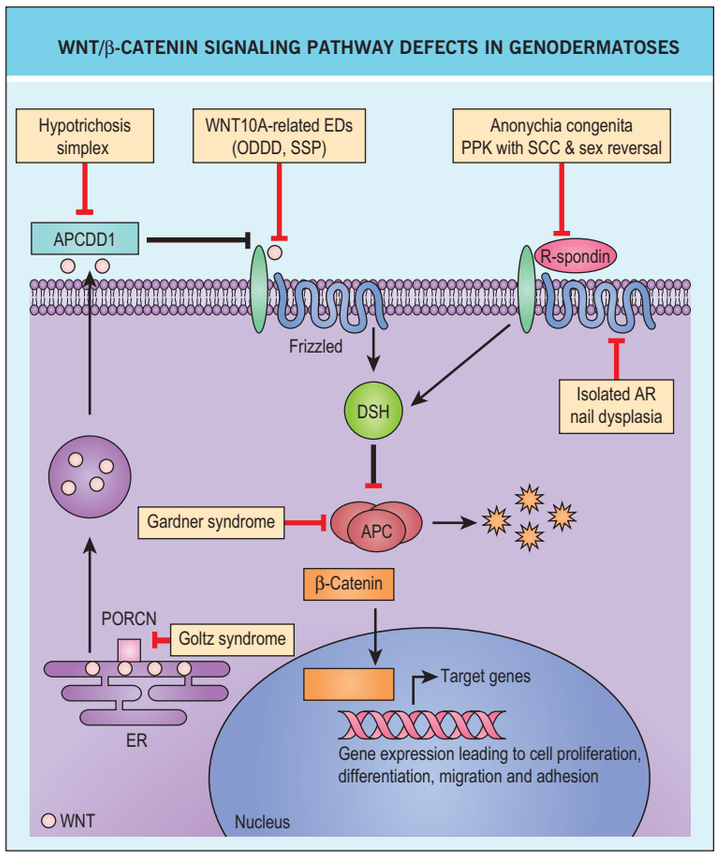


Fig. 55.7 WNT/β-catenin signaling pathway defects in genodermatoses. The porcupine homolog (PORCN) O-acyltransferase in the endoplasmic reticulum (ER) palmitoylates WNT proteins, facilitating their secretion. Extracellular WNT binds to the frizzled transmembrane receptor, which activates dishevelled (DSH), a cytosolic protein that inhibits the "destruction complex" (containing the adenomatous polyposis coli [APC] tumor suppressor protein) that mediates proteasomal degradation of β-catenin. As a result, β-catenin accumulates and is translocated to the nucleus, where it induces the transcription of genes that lead to cell proliferation, differentiation, migration and adhesion. APC downregulated 1 (APCDD1) can inhibit WNT signaling. R-spondins are other secreted proteins that bind to frizzled and activate the WNT/β-catenin pathway. AR, autosomal recessive; EDs, ectodermal dysplasias; ODDD, odonto-onycho-dermal dysplasia; PPK, palmoplantar keratoderma; SCC, squamous cell carcinoma; SSP, Schöpf–Schulz–Passarge syndrome.

Fig. 55.8 Goltz syndrome (focal dermal hypoplasia). **A** Hyperpigmented macules and dermal atrophy with fat "herniation" on the posterior thigh. **B** Raspberry-like papillomas on the lower lip. **C** Ectrodactyly.

molecular level include linear Darier disease *(ATP2A2* mutations), epidermolytic epidermal nevi *(K1* or *K10* mutations) and non-epidermolytic epidermal nevi (fibroblast growth factor receptor 3 *[FGFR3]* mutations); constitutional mutations in the latter gene produce craniosynostosis syndromes associated with severe acanthosis nigricans (Fig. 55.9). On a molecular level, type 2 mosaicism has been documented for Hailey–Hailey disease *(ATP2C1* mutations) (Fig. 55.10), Darier disease (*ATP2A2*), glomuvenous malformations (*GLMN* mutations), and *PTEN* hamartoma tumor syndrome (referred to as "SOLAMEN" [segmental *o*vergrowth, *l*ipomatosis, *a*rteriovenous *m*alformation and *e*pidermal *n*evus] or "Proteus-like" syndrome).

All women and girls are functional mosaics due to the random, irreversible, stably inherited inactivation of one of the two X chromosomes that occurs in each cell during early embryonic development (lyonization). However, 15% of genes on the human X chromosome escape lyonization and 10% are variably inactivated. In women heterozygous for X-linked disorders, functional mosaicism can result in skin lesions that follow Blaschko's lines or have other mosaic distribution patterns. This occurs in female patients with X-linked dominant, male-lethal disorders such as incontinentia pigmenti (*NEMO* mutations), CHILD (*c*ongenital *h*emidysplasia with *i*chthyosiform nevus and *l*imb *d*efects) syndrome (*NSDHL* mutations), Conradi–Hünermann–Happle syndrome (*EBP* mutations) and Goltz syndrome (*PORCN* mutations; see Fig. 55.8) as well as in female "carriers" of X-linked dermatoses such as hypohidrotic ectodermal dysplasia (*EDA* mutations; Fig 55.11) and *i*chthyosis *f*ollicularis-*a*trichia-*p*hotophobia (IFAP) syndrome (*MBTPS2*; Fig. 55.12). The gene encoding steroid sulfatase escapes lyonization, explaining why skin lesions in a mosaic pattern are not observed in female carriers of X-linked recessive ichthyosis.

HEREDITARY SKIN DISORDERS ASSOCIATED WITH EXTRACUTANEOUS CANCER					
Disorder	**Mode of inheritance**	**Gene or gene product**	**Gene symbol**	**Gene locus**	**MIM number(s)**
Ataxia–telangiectasia	AR	Ataxia–telangiectasia mutated (phosphatidylinositol 3-kinase-like serine/threonine protein kinase)	*ATM*	11q22.3	208900, 607585
Birt–Hogg–Dubé syndrome	AD	Folliculin	*FLCN*	17p11.2	135150, 607273
Bloom syndrome	AR	RecQ protein-like 3 (DNA helicase)	*BLM (RECQL3)*	15q26.1	210900, 604610
Costello syndrome (see text)	AD	v-Ha-ras Harvey rat sarcoma viral oncogene homolog	*HRAS*	11p15.5	218040, 190020
	AD	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog	*KRAS*	12p12.1	218040, 190070
Cowden-like syndrome	AD	Succinate dehydrogenase complex, subunit B, iron sulfur	*SDHB*	1p36.1-p35	612359, 185470
	AD	Succinate dehydrogenase complex, subunit D, integral membrane protein	*SDHD*	11q23	612359, 602690
Dyskeratosis congenita	XR	Dyskerin	*DKC1*	Xq28	305000, 300126
	AD	Telomerase RNA component	*TERC*	3q26.2	127550, 602322
	AD	Telomere repeat binding factor 1-interacting nuclear factor 2	*TINF2*	14q12	127550, 604319
	AD, AR	Telomerase reverse transcriptase	*TERT*	5p15.33	187270
	AR	Telomerase Cajal body protein 1	*TCAB1 (WRAP53)*	17p13	612661
	AR	NOP10 ribonucleoprotein homolog	*NOP10*	15q14	224230, 606471
	AR	NHP2 ribonucleoprotein homolog	*NHP2*	5q35.3	224230, 606470
Gardner syndrome	AD	Adenomatous polyposis coli	*APC*	5q21–q22	175100
Howel–Evans syndrome (tylosis–esophageal carcinoma)	AD			17q25	148500
Muir–Torre syndrome	AD	MutS homolog 2 (mismatch repair enzyme)	*MSH2*	2p22	158320, 609309
	AD	MutS homolog 6 (mismatch repair enzyme)	*MSH6*	2p16	158320, 600678
	AD	MutL homolog 1 (mismatch repair enzyme)	*MLH1*	3p21	158320, 120436
MUTYH-associated polyposis	AR	MutY homolog	*MUTYH*	1p34.3–p32.1	608456, 604933
Constitutional mismatch repair deficiency syndrome (childhood tumor syndrome with neurofibromatosis type 1 phenotype)	AR	MutS homolog 2 (mismatch repair enzyme)	*MSH2*	2p22	276300, 609309
	AR	MutS homolog 6 (mismatch repair enzyme)	*MSH6*	2p16	276300, 600678
	AR	MutL homolog 1 (mismatch repair enzyme)	*MLH1*	3p21	276300, 120436
	AR	Postmeiotic segregation increased 2 (mismatch repair enzyme)	*PMS2*	7p22	276300, 600259
Multiple endocrine neoplasia (MEN) MEN 1	AD	Menin	*MEN1*	11q13	131100
MEN 2A	AD	Ret proto-oncogene (cysteine-rich extracellular domain)	*RET*	10q11.2	171400, 164761
MEN 2B	AD	Ret proto-oncogene (particularly Met918Thr in substrate recognition pocket)	*RET*	10q11.2	162300, 164761
MEN 4	AD	Cyclin-dependent kinase inhibitor 1B (p27, Kip1)	*CDKN1B*	12p13.1–p12	610755, 600778
		Cyclin-dependent kinase inhibitor 2C (p18, inhibits CDK4)*	*CDKN2C*	1p32.3	603369
PTEN hamartoma tumor syndrome (including Cowden disease and Bannayan–Riley–Ruvalcaba syndrome)	AD	Phosphatase and tensin homolog	*PTEN*	10q23.31	153480, 601728
Rothmund–Thomson syndrome	AR	RecQ protein-like 4 (DNA helicase)	*RECQ4*	8q24.3	268400, 603780

*Reported in only one patient to date.

Table 55.11 Hereditary skin disorders associated with extracutaneous cancer. These conditions are discussed in Chapters 60, 63, 67 and 87. CNS, central system.

TWIN SPOTTING

Twin spotting (didymosis) is a concept that may explain the coexistence of discrete areas of skin (usually near one another) that differ clinically and genetically from each other and from the background skin. This form of mosaicism can potentially occur in an embryo that has two different mutant alleles at the *same locus* (*allelic*; e.g. one encoding darker and the other lighter pigmentation) or at *nearby loci* (*non-allelic*; both heterozygous, one on each of a pair of homologous chromosomes). In these scenarios, mitotic recombination can give rise to two different homozygous populations of daughter cells that each manifest with a distinct phenotype (Fig. 55.13). Possible examples of *allelic twin spotting* include cutis tricolor (hyperpigmented and hypopigmented spots on background skin with intermediate pigmentation) and vascular twin nevi (port-wine stain and nevus anemicus; see Fig. 55.13), whereas phakomatosis pigmentokeratotica (papular SLN plus sebaceous/"organoid" epidermal nevus) and phakomatosis pigmentovascularis (see Table 104.4) may reflect *non-allelic twin spotting*.

REVERTANT MOSAICISM

Revertant mosaicism is a means of "natural gene therapy" in which a spontaneous secondary genetic phenomenon leads to rescue of a disease-causing mutation, allowing a mosaic clone of heterozygous cells to regain wild-type ("normal") function[33]. It has been described most often in patients with EB (see Ch. 32), potentially explaining the tendency of some forms of this condition to improve with age. A growth

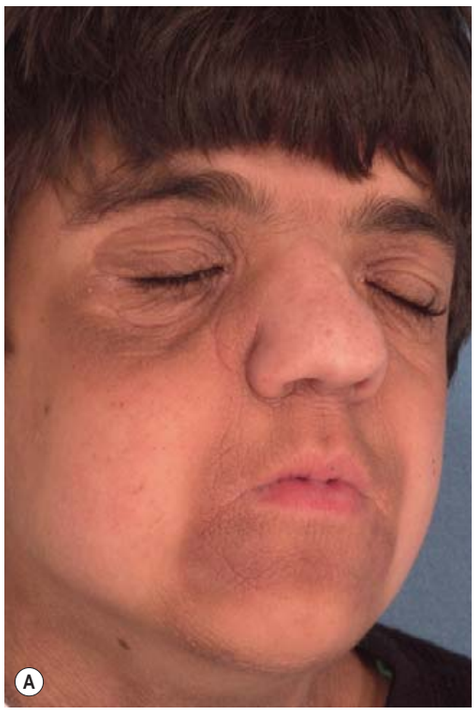


Fig. 55.9 Skin disease due to fibroblast growth factor receptor 3 (FGFR3) defects. **A** Severe acanthosis nigricans in a patient with the Crouzon craniosynostosis syndrome. **B** Systematized epidermal nevus in a young boy who had developmental delay. These conditions can be caused by germline and mosaic *FGFR3* mutations, respectively. *A, Courtesy, Seth J Orlow, MD, PhD.*

Fig. 55.10 Type 2 segmental Hailey–Hailey disease. This 7-year-old girl had a history of recurrent blistering on the right abdomen, groin and thigh since infancy.

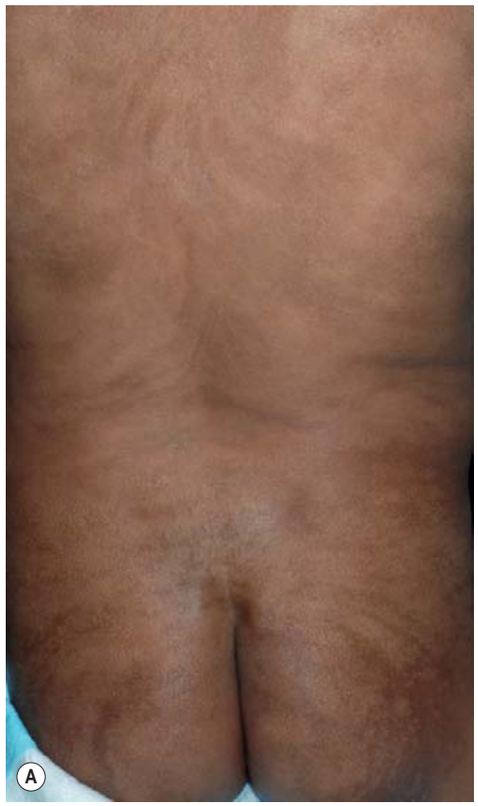
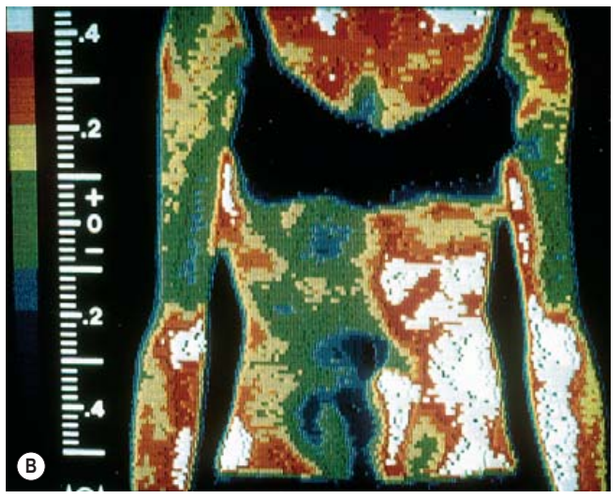


Fig. 55.11 Female "carriers" of X-linked hypohidrotic ectodermal dysplasia. **A** The skin within hyperpigmented streaks and swirls following Blaschko's lines is slightly depressed and very smooth, in contrast to follicular prominence in the surrounding areas. Starch-iodine testing on the back disclosed a patchy distribution of active sweat glands. This 2-year-old girl also had whorled areas of sparse hair on the posterior scalp and several cone-shaped teeth. **B** A color thermogram demonstrates an asymmetric distribution of skin temperature on the anterior trunk. *B, From Clark RP, Goff MR, MacDermot KD. Identification of functioning sweat pores and visualization of skin temperature patterns in X-linked hypohidrotic ectodermal dysplasia by whole body thermography. Hum Genet. 1990;86:7–13.*



advantage and selective pressures (e.g. blistering) may help to increase the number of revertant cells over time. Recently, revertant mosaicism via mitotic recombination was found to account for the numerous small "islands" of normal skin in a background of ichthyosiform erythroderma that characterize ichthyosis en confetti[34]. Affected individuals have specific frameshift mutations in the *KRT10* gene, which produce mutant proteins with an arginine-rich C-terminus that redirects them to the nucleolus; this mislocalization may have a role in promoting the reversion.

CHROMOSOMAL DISORDERS

Chromosomal disorders represent abnormalities in the number or structure of chromosomes. Aneuploidy refers to having an additional or missing chromosome; examples that are compatible with postnatal survival include complete trisomies for chromosomes 21 (Down syndrome; Fig. 55.14), 18 (Edwards syndrome) and 13 (Patau syndrome) as well as monosomy for the X chromosome (Turner syndrome) and XXY (Klinefelter syndrome) or XYY karyotypes.

OTHER INHERITED SKIN DISORDERS					
Disorder	**Mode of inheritance**	**Gene or gene product**	**Gene symbol**	**Gene locus**	**MIM number**
CRANIOSYNOSTOSIS/SKELETAL DYSPLASIA SYNDROMES					
Apert syndrome	AD	Fibroblast growth factor receptor 2	*FGFR2*	10q26	101200, 176943
Beare–Stevenson cutis gyrata syndrome	AD	Fibroblast growth factor receptor 2	*FGFR2*	10q26	123790, 176943
Crouzon syndrome with acanthosis nigricans; SADDAN; thanatophoric dysplasia	AD	Fibroblast growth factor receptor 3*	*FGFR3*	4p16.3	123500, 187600, 134934
Oral–facial–digital syndrome	XD	Oral–facial–digital syndrome 1	*OFD1*	Xp22.3–p22.2	311200, 300170
DISORDERS WITH PROMINENT NEUROLOGIC ABNORMALITIES					
Cockayne syndrome† CSA CSB	AR AR	ERCC8 (transcription-coupled repair protein) ERCC6 (transcription-coupled repair protein)	*ERCC8* *ERCC6*	5 10q11	216400, 609412 133540, 609413
Cold-induced sweating syndrome	AR AR	Cytokine receptor-like factor 1 Cardiotrophin-like cytokine factor 1	*CRLF1* *CLCF1*	19p12 11q13.3	272430, 604237 272430, 607672
Primary erythromelalgia	AD	Sodium channel, voltage-gated, type IX, α-subunit	*SCN9A*	2q24	133020, 603415
Familial dysautonomia (Riley–Day syndrome)	AR	Inhibitor of κ light polypeptide gene enhancer in B cells, kinase complex-associated protein	*IKBKAP*	9q31	223900, 603722
Insensitivity to pain with anhidrosis	AR	Neurotrophic tyrosine kinase receptor type 1	*NTRK1*	1q21–q22	256800, 191315
Familial primary localized cutaneous amyloidosis	AD AD	Oncostatin M receptor Interleukin-31 receptor A	*OSMR* *IL31RA*	5p13.1 5q11.2	105250, 601743 609510, 613955
DEFECTS IN COAGULATION OR PLATELET PLUGGING (SEE CH. 23, TABLE 105.10)					
Activated protein C resistance (factor V Leiden)	AD	Factor V	*F5*	1q23	188055, 227400
Protein C deficiency	AD	Protein C	*PROC*	2q13–q14	176860
Protein S deficiency	AD	Protein S	*PROS1*	3p11.1–q11.2	176880
Antithrombin III deficiency	AD	Serpin peptidase inhibitor C1 (antithrombin III)	*SERPINO*	1q23–q25	107300
Hyperprothrombinemia	AD	Prothrombin, G20210A polymorphism	*F2*	11p11–q12	176930
Thrombotic thrombocytopenic purpura, familial	AR	ADAM metallopeptidase with thrombospondin type 1 motif, 13 (von Willebrand factor-cleaving protease)	*ADAMTS13*	9q34	604134, 274150
DISORDERS OF PREMATURE AGING (SEE CH. 63)					
Branchio-oculo-facial syndrome	AD	Transcription factor AP-2α	*TFAP2A*	6p24	113620, 107580
Néstor-Guillermo progeria syndrome	AR	Barrier to autointegration factor 1	*BANF1*	11q13.1	603811
Hutchinson–Gilford progeria‡	AD>>AR	Lamin A/C	*LMNA*	1q21.2	176670, 150330
Mandibuloacral dysplasia‡	AR AR	Lamin A/C Zinc metallopeptidase (STE24 homolog)	*LMNA* *ZMPSTE24*	1q21.2 1p34	248370, 150330 608612, 606480
"Atypical Werner syndrome"‡	AD	Lamin A/C	*LMNA*	1q21.2	277700, 150330
Werner syndrome§	AR	RecQ protein-like 2 (DNA helicase)	*WRN (RECQL2)*	8p12–p11.2	277700, 604611
LIPODYSTROPHY SYNDROMES (SEE CH. 101)					
Leprechaunism (Rabson–Mendenhall syndrome)	AR	Insulin receptor	*INSR*	19p13.2	246200, 262190, 147670
Lipodystrophy, congenital generalized (Berardinelli–Seip)	AR AR AR AR	Seipin 1-Acylglycerol-3-phosphate O-acyl transferase-2 Caveolin 1 Polymerase I and transcript release factor	*BSCL2* *AGPAT2* *CAV1* *PTRF*	11q13 9q34.3 7q31.1 17q21.31	269700, 606158 608594, 603100 612526, 601047 613327, 603198
Lipodystrophy, familial partial‡	AD AD AD	Lamin A/C Peroxisome proliferator-activated receptor-γ Perilipin 1	*LMNA* *PPARG* *PLIN1*	1q21.2 3p25 15q26.1	151660, 150330 604367, 601487 613877, 170290
Lipodystrophy, "acquired" partial (Barraquer–Simons syndrome)	AD	Lamin B2	*LMNB2*	19p13.3	608709, 150341

*Somatic *FGFR3* mutations have been found to underlie a subset of epidermal nevi.
†Patients with mutations in *ERCC3* (XPB), *ERCC2* (XPD) and *ERCC5* (XPG) may have phenotypes with features of both xeroderma pigmentosum and Cockayne syndrome (XP/CS; see Table 55.10).
‡Familial partial lipodystrophy, mandibuloacral dysplasia, Hutchinson–Gilford progeria, restrictive dermopathy and "atypical Werner syndrome" are allelic disorders (see Tables 55.4 & 63.9).
§Increased risk of malignancies, especially sarcomas.

Table 55.12 Other inherited skin disorders. ERCC, excision repair cross-complementing; SADDAN, *s*evere *a*chondroplasia with *d*evelopmental *d*elay and *a*canthosis *n*igricans.

Continued

OTHER INHERITED SKIN DISORDERS					
Disorder	**Mode of inheritance**	**Gene or gene product**	**Gene symbol**	**Gene locus**	**MIM number**
DISORDERS WITH CUTANEOUS CALCIFICATION OR OSSIFICATION (SEE CH. 50)					
Albright hereditary osteodystrophy	AD	Stimulatory G protein, α-subunit ($G_s\alpha$; inactivating mutations)	*GNAS*	20q13.2	103580, 139320
Progressive osseous heteroplasia	AD	Stimulatory G protein, α-subunit ($G_s\alpha$; inactivating mutations)	*GNAS*	20q13.2	166350, 139320
Fibrodysplasia ossificans progressiva	AD	Activin A receptor, type 1	*ACVR1*	2q23–q24	135100, 102576
Hyperphosphatemic familial tumoral calcinosis	AR	UDP-N-acetyl-αD-galactosamine:polypeptide N-acetylgalactosaminyltransferase 3	*GALNT3*	2q24–q31	211900, 601756
	AR	Fibroblast growth factor 23	*FGF23*	12p13.3	211900, 605380
	AR	Klotho	*KL*	13q12	604824
Normophosphatemic familial tumoral calcinosis	AR	Sterile alpha motif domain-containing 9	*SAMD9*	7q21	610455, 610456
Pachydermoperiostosis	AR	15-hydroxyprostaglandin dehydrogenase	*HPGD*	4q34.1	259100, 601688
	AR	Solute carrier organic anion transporter, member 2A1	*SLCO2A1*	3q22.1	614441, 601460
DISORDERS ASSOCIATED WITH MULTIPLE LENTIGINES[¶] (SEE CH. 112)					
Carney complex (LAMB/NAME syndrome)	AD	Protein kinase A regulatory subunit 1α	*PRKAR1A*	17q24	160980, 188830
Familial generalized lentiginosis	AD			4q21.1–q22.3	151001
LEOPARD syndrome**	AD	Protein tyrosine phosphatase, nonreceptor type 11	*PTPN11 (SHP2)*	12q24	151100, 176876
	AD	v-Raf-1 murine leukemia viral oncogene homolog	*RAF1*	3p25	164760
Peutz–Jeghers syndrome	AD	Serine-threonine kinase 11	*STK11 (LKB1)*	19p13.3	175200, 602216
AUTOINFLAMMATORY SYNDROMES (SEE TABLE 45.2 AND CH. 26)					
Blau syndrome (familial granulomatous arthritis, dermatitis and uveitis)	AD	Nucleotide-binding oligomerization domain-containing 2	*NOD2 (CARD15)*	16q12	186580, 609464, 605956
CINCA (*c*hronic *i*nfantile *n*eurologic, *c*utaneous and *a*rticular) syndrome	AD	NLR family, pyrin domain-containing 3 (cryopyrin)	*NLRP3 (CIAS1)*	1q44	607115, 606416
Familial cold autoinflammatory syndrome	AD	NLR family, pyrin domain-containing 3 (cryopyrin)	*NLRP3 (CIAS1)*	1q44	120100, 606416
	AD	NLRP12	*NLRP12*	19q13.42	611762, 609648
	AD	Phospholipase C, γ2	*PLCG2*	16q23.3	614468, 600220
Muckle–Wells syndrome	AD	NLR family, pyrin domain-containing 3 (cryopyrin)	*NLRP3 (CIAS1)*	1q44	191900, 606416
Cyclic neutropenia	AD	Neutrophil elastase	*ELA2*	19p13.3	162800, 130130
DIRA (*d*eficiency of the *i*nterleukin-1 *r*eceptor *a*ntagonist)	AR	Interleukin-1 receptor antagonist	*IL1RN*	2q14.2	612852, 147679
Generalized pustular psoriasis	AR	Interleukin-36 receptor antagonist	*IL36RN*	2q13	605507, 614204
Familial Hibernian fever (tumor necrosis factor receptor-associated periodic syndrome; TRAPS)	AD	Tumor necrosis factor receptor superfamily, member 1A	*TNFRSF1A*	12p13.2	142680, 191190
Familial Mediterranean fever	AR	Pyrin (marenostrin)	*MEFV*	16p13	249100, 608107
Hyperimmunoglobulinemia-D syndrome	AR	Mevalonate kinase	*MVK*	12q24	260920, 251170
Majeed syndrome	AR	Lipin 2	*LPIN2*	18p	609628, 605519
PAPA (*p*yogenic *a*rthritis–*p*yoderma gangrenosum–*a*cne) syndrome	AD	Proline-serine-threonine phosphatase-interacting protein 1	*PSTPIP1*	15q24–q26.1	604416, 606347
Familial chilblain lupus/autosomal dominant Aicardi–Goutières syndrome***	AD	3′ repair exonuclease 1	*TREX1*	3p21.31	610448, 606609
	AD	SAM- and HD-domain-containing protein 1	*SAMHD1*	20q11.23	614415, 606754
Familial hidradenitis suppurativa	AD	Nicastrin	*NCSTN*	1q22-q23	142690, 605254
	AD	Presenilin enhancer 2 homolog	*PSENEN*	19q13.12	613736, 607632
	AD	Presenilin 1	*PSEN1*	14q24.3	613737, 104311
Neonatal–onset inflammatory skin and bowel disease	AR	A disintegrin & metalloproteinase 17	*ADAM17*	2p25.1	603639, 614328

[¶]Neurofibromatosis type 1 and PTEN hamartoma tumor syndrome are listed in Table 55.9 and 55.11, respectively.
**A mutation in the *BRAF* gene has also been reported in two patients with a LEOPARD syndrome phenotype.
***Mutations in several other genes have been found to cause autosomal recessive forms of Aicardi–Goutières syndrome associated with variable manifestations of lupus erythematosus (cutaneous and/or systemic).

Table 55.12 Other inherited skin disorders (cont'd). LAMB, *l*entigines, *a*trial myxomas, *m*ucocutaneous myxomas, *b*lue nevi; LEOPARD, *l*entigines, *E*CG changes, *o*cular hypertelorism, *p*ulmonary stenosis, *a*bnormal genitalia, *r*etardation of growth, *d*eafness; NAME, *n*evi, *a*trial myxomas, *m*yxoid neurofibromas, *e*phelides.

Continued

OTHER INHERITED SKIN DISORDERS						
Disorder		**Mode of inheritance**	**Gene or gene product**	**Gene symbol**	**Gene locus**	**MIM number**
DISORDERS ASSOCIATED WITH IMMUNODEFICIENCY (SEE CH. 60 FOR DISCUSSION OF THESE AND ADDITIONAL DISORDERS)						
*A*utoimmune *p*olyendocrinopathy–*c*andidiasis–*e*ctodermal *d*ystrophy (APECED)		AR	Autoimmune regulator	*AIRE*	21q22.3	240300, 607358
Chronic mucocutaneous candidiasis		AD	Interleukin 17F	*IL17F*	6p12	114580
		AD	Signal transducer and activator of transcription 1	*STAT1*	2q32.2	600555, 614162
		AR	Caspase recruitment domain family, member 9	*CARD9*	9q34	212050, 607212
		AR	C-type lectin domain family 7, member A (dectin-1)	*CLEC7A*	12p13.2–p12.3	613108, 606264
		AR	Interleukin 17 receptor A	*IL17RA*	22q11.1	
Chronic granulomatous disease		XR	Cytochrome b_{245} β-polypeptide (gp91-phox)	*CYBB*	Xp21.1	306400, 300481
		AR	Cytochrome b_{245} α-polypeptide (p22-phox)	*CYBA*	16q24	233690, 608508
		AR	Neutrophil cytosolic factor 1 (p47-phox; component of NADPH oxidase)	*NCF1*	7q11.23	233700, 608512
		AR	Neutrophil cytosolic factor 2 (p67-phox, component of NADPH oxidase)	*NCF2*	1q25	233710, 608515
		AR	Neutrophil cytosolic factor 4 (p40-phox, component of NADPH oxidase)	*NCF4*	22q13.1	601488
Clericuzio-type poikiloderma with neutropenia		AR	Chromosome 16 open reading frame 57	*C16orf57*	16q13	604173, 613276
Hyperimmunoglobulinemia-E (Job) syndrome		AD	Signal transducer and activator of transcription 3	*STAT3*	17q21	147060, 102582
		AR	Dedicator of cytokinesis 8	*DOCK8*	9p24.3	243700, 611432
IPEX (*i*mmune dysregulation, *p*olyendocrinopathy, *e*nteropathy, *X*-linked) syndrome		XR	Forkhead box P3	*FOXP3*	Xp11.23	304790, 300292
Leukocyte adhesion deficiency	Type I	AR	β_2 Integrin	*ITGB2*	21q22.3	116920, 600065
	Type II	AR	Solute carrier family 35, member C1 (GDP-fucose transporter 1)	*SLC35C1*	11p11.2	266265, 605881
	Type III	AR	Fermitin family member 3 (kindlin 3)	*FERMT3*	11q13.1	612840, 607901
Omenn syndrome (see Ch. 60 for other conditions that can present with an Omenn phenotype)		AR	Recombination activating gene 1	*RAG1*	11p13	603554, 179615
		AR	Recombination activating gene 2	*RAG2*	11p13	603554, 179616
		AR	DNA cross-link repair 1C (Artemis)	*DCLRE1C*	10p	603554, 605988
WHIM (*w*arts, *h*ypogammaglobulinemia, *i*nfections and *m*yelokathexis) syndrome		AD	Chemokine (C-X-C motif) receptor 4	CXCR4	2q21	193670, 162643
Wiskott–Aldrich syndrome		XR	WAS protein	*WAS*	Xp11.23–p11.22	301000, 300392

Table 55.12 Other inherited skin disorders (cont'd).

Fig. 55.12 Ichthyosis follicularis with atrichia and photophobia (IFAP) syndrome. Note the confluent psoriasiform plaques on the scalp.

Mosaic aneuploidies or partial trisomies and monosomies due to duplications, deletions or translocations of portions of chromosomes can also occur. The cutaneous and extracutaneous features of several relatively common chromosomal disorders are presented in Table 55.13.

Phylloid hypomelanosis, characterized by leaf-like hypopigmented patches (Fig. 55.15), usually results from mosaic trisomy 13. In contrast, hypomelanotic streaks and swirls that follow Blaschko's lines (so-called "hypomelanosis of Ito") can be caused by mosaicism for a wide variety of chromosomal aberrations (see Ch. 62).

INSIGHT INTO ACQUIRED SKIN DISORDERS PROVIDED BY THE STUDY OF GENODERMATOSES

Inherited monogenic skin disorders can serve as models to improve our understanding of the pathogenesis of common acquired skin diseases. For example, basement membrane proteins that are defective in JEB (e.g. type XVII collagen [bullous pemphigoid antigen 2], laminin 332 [5] subunits) and dystrophic EB (type VII collagen) are also targeted in autoimmune blistering diseases such as bullous pemphigoid, mucous membrane (cicatricial) pemphigoid, and EB acquisita (see Ch. 28). In addition, the excessive granulation tissue that develops due to a truncated laminin α3 subunit in patients with laryngo-onycho-cutaneous syndrome has provided clues to the role of this protein in regulating

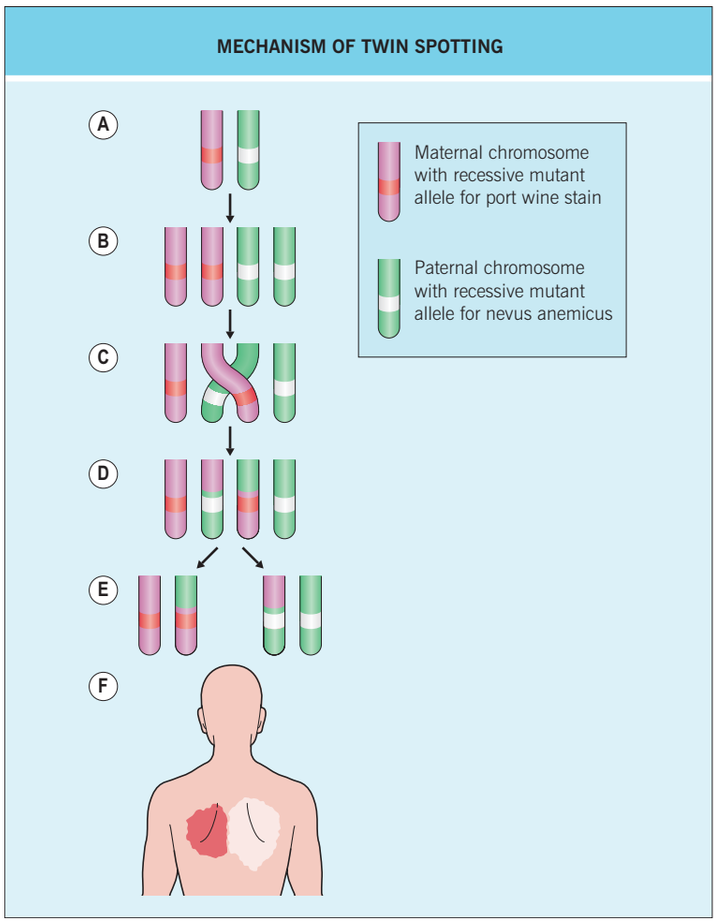


Fig. 55.13 Mechanism of twin spotting. This embryo has two different recessive mutant alleles at a *single locus* (the background of *allelic* twin spotting) that encodes a protein affecting the cutaneous vasculature. **A** The pair of homologous chromosomes containing this locus. **B** Semiconservative replication during mitosis. **C** Crossing over occurs, with exchange of the region carrying the two mutations. **D** As a result, each duplicated chromosome is composed of two different chromatid segments distal to the point of crossing over. **E** Random assortment of the chromatids during mitosis may result in two different daughter cells that are each homozygous for one of the mutations. **F** Population of the skin by these two lineages leads to a port wine stain adjacent to a nevus anemicus. The same phenomenon could occur with two different recessive mutant alleles at *neighboring loci* (both heterozygous), one on each of a pair of homologous chromosomes (the background of *non-allelic* twin spotting). Of note, gene conversion (where the "donating" chromosome is unchanged) occurs more frequently than mitotic crossing over.

Fig. 55.14 Cutaneous manifestations of Down syndrome (trisomy 21). **A** Full lips with cheilitis and a protruding, fissured tongue. **B** Multiple facial syringomas.

Fig. 55.15 Phylloid hypomelanosis due to mosaic trisomy 13. This condition is characterized by leaf-like and oblong patches of hypopigmentation in a pattern reminiscent of a floral ornament. *Courtesy, Arne König, MD, and Rudolf Happle, MD.*

angiogenesis and granulation tissue formation during normal wound healing. Likewise, observation of similar dermal hyalinization in the rare genodermatosis lipoid proteinosis and lichen sclerosus led to the discovery of autoantibodies against extracellular matrix protein 1, the protein that is defective in the former disorder, in the majority of patients with lichen sclerosus[35].

Loss-of-function variants in the gene that encodes filaggrin (the protein that aggregates keratin filaments during keratinocyte terminal differentiation; see Ch. 56) not only cause ichthyosis vulgaris but also represent a major predisposing factor for atopic dermatitis, with a significantly higher prevalence (20–50%) in individuals with atopic dermatitis compared to the general population (<5–10%). Defective filaggrin also represents a predisposing factor for asthma, but specifically that occurring in individuals with pre-existing atopic dermatitis. Barrier dysfunction due to abnormalities in the serine protease inhibitor (SPINK5) involved in Netherton syndrome may also play a role in the pathogenesis of atopic dermatitis, and polymorphisms in the *SPINK5* gene have been shown to be associated with this common acquired skin disease.

SKIN FINDINGS ASSOCIATED WITH CHROMOSOMAL ABERRATIONS				
Disorder	**Chromosomal aberration**	**Mucocutaneous anomalies**	**Extracutaneous anomalies**	**Comments**
Turner syndrome	45, XO	Congenital lymphedema (usually resolves by age 2 years), low posterior hairline, numerous melanocytic nevi, small hyperconvex nails, tendency to form keloids	Short stature, webbed neck, "shield-like" chest with widely spaced nipples, absence of sexual development, cardiovascular defects, renal malformations, sensorineural hearing loss, autoimmune hypothyroidism	Mosaicism (e.g. 45, XO/46, XX or 45, XO/46, XY) in ~40% of patients
Klinefelter syndrome	47, XXY	Varicose veins, leg ulcers	Tall stature, gynecomastia, small testes, infertility	Mosaicism 46, XY/47, XXY in ~20% of patients; uncommon variants include 48, XXXY and 48, XXYY
Trisomy 21 (Down syndrome)	47, XY, +21 47, XX, +21	Single palmar crease, protruding scrotal tongue, cheilitis (see Fig. 55.14A), multiple syringomas (often with calcification; see Fig. 55.14B), alopecia areata, ichthyosiform hyperkeratosis, keratosis pilaris, milia-like calcinosis cutis, elastosis perforans serpiginosa, multiple collagenomas, cutis marmorata/acrocyanosis; a predisposition to developing folliculitis, dermatophyte infections and Norwegian scabies; vesiculopustular eruptions associated with neonatal transient myeloproliferative disorder	Brachycephaly, characteristic facial appearance (e.g. epicanthal folds, flat nasal bridge), Brushfield spots (speckled irides), broad hands, brachydactyly, atlantoaxial instability, mental retardation, immunodeficiency, congenital heart defects, duodenal atresia, leukemia (especially acute myeloid leukemia), hearing loss, autoimmune hypothyroidism	
Phylloid hypomelanosis (see Fig. 55.15)	Mosaic trisomy 13	Round, oval or oblong hypopigmented macules resembling floral ornaments	Absence of corpus callosum, retinal coloboma, craniofacial defects, brachydactyly, clinodactyly, camptodactyly, conductive hearing loss	
Pallister–Killian syndrome	Mosaic tetrasomy 12p (isochromosome 12p)	Hypopigmented streaks and swirls following Blaschko's lines; fine, sparse hair during infancy	Postnatal growth deficiency, characteristic facies (anteverted nostrils, down-turned mouth with thin upper lip), mental retardation	

Table 55.13 Skin findings associated with chromosomal aberrations.

PRENATAL AND PREIMPLANTATION GENETIC DIAGNOSIS

In the past, prenatal diagnosis was based on techniques such as ultrastructural and immunohistochemical analysis of fetal skin biopsy specimens obtained between 18 and 22 weeks' gestational age (GA). Today, such methods have been largely replaced by DNA-based testing that is less invasive and more reliable. The diagnosis of genodermatoses for which the molecular basis is known can be established prenatally by performing chorionic villus sampling (at 10–12 weeks' GA) or amniocentesis (at 14–16 weeks' GA) and analyzing fetal DNA (after determining the underlying genetic defect in family members)[36]. Non-invasive prenatal diagnostic techniques that utilize fetal cells or cell-free genetic material from the maternal circulation are being developed and may become standard practices in the future[37]. Preimplantation genetic diagnosis can also be performed for a variety of severe genetic skin diseases. This involves analysis of DNA from single cells (blastomeres) extracted from late cleavage stage embryos following *in vitro* fertilization[38]. In this way, knowing the genetic bases of heritable skin conditions may be of tremendous value to affected families.

TREATMENT FOR HEREDITARY SKIN DISORDERS

Gene Therapy

The accessibility of the skin makes it an excellent target for gene therapy. Although the routine application of this treatment modality is not currently possible, steps have been taken to study its feasibility, particularly in patients with EB. For example, *ex vivo* gene therapy led to full functional correction of the skin fragility phenotype (stable after a several-year follow-up period) in a man with JEB due to *LAMB3* mutations, demonstrating for the first time successful gene therapy for a disease of solid tissue[38]. The technique that was utilized involved retroviral-mediated transduction of autologous epidermal stem cells with a wild-type copy of the *LAMB3* gene, followed by reconstitution of the patient's skin on the anterior thighs with epithelial sheets grown from the genetically corrected cells. A disadvantage of this *ex vivo* approach is the relatively small surface area that can be treated with each graft. Possible delivery methods to surmount the epidermal barrier in order to perform *in vivo* gene transfer into the skin include utilization of viral vectors as well as direct injection of naked plasmid DNA, microinjection of DNA, electroporation and lipofection of DNA-lipid complexes. However, limited long-term stability of the transferred genes represents a potential problem.

There are serious safety concerns regarding the use of retroviral vectors for gene therapy because of their uncontrolled insertion into the human genome[39]. Several patients with X-linked severe combined immunodeficiency who were treated with retroviral-mediated *ex vivo* gene transfer developed T-cell leukemias related to activation of a proto-oncogene via integration of the retroviral vector into its 5′ untranslated region. This has led to protocol modifications and investigation of alternative approaches such as use of other vectors based on lentiviruses (which tend to integrate into transcribed regions of genes).

For gene therapy of dominant-negative keratin disorders such as EBS and pachyonychia congenita, another strategy is to use small interfering RNA to specifically "knock down" expression of the mutant keratin.

Cell Therapy

Systemic administration of either genetically corrected autologous fibroblasts or the collagen VII protein has been shown to result in the appearance of this collagen in the basement membrane zone of wounded skin (with subsequent healing) in a mouse model of recessive dystrophic EB (RDEB). In patients with RDEB, intradermal injections of allogeneic fibroblasts have been found to result in the generation of new collagen VII and anchoring fibrils at the dermal–epidermal junction[40,41]. A systemic approach to cell therapy that has shown some promise for RDEB is transplantation of bone marrow-derived allogeneic stem cells following total or partial myeloablation. In an initial report, this resulted

in the sustained presence of donor cells in the skin, increased deposition of collagen VII at the dermal–epidermal junction, and variably decreased blistering in children with RDEB[42].

Therapy Targeting Affected Molecular Signaling Pathways

Loss-of-function mutations in different tumor suppressor genes that negatively regulate the mammalian target of rapamycin (mTOR) signaling pathway (which stimulates cell growth/proliferation when activated) underlie several hamartoma syndromes, including tuberous sclerosis, the PTEN hamartoma tumor syndrome, and Peutz–Jeghers syndrome (see Fig. 55.4). Recognition of the mTOR overactivation common to these disorders has led to successful treatment of affected individuals with the mTOR inhibitors rapamycin (sirolimus) and everolimus. For example, use of these agents in patients with tuberous sclerosis has resulted in regression of subependymal giant cell astrocytomas, renal angiomyolipomas, pulmonary lymphangioleiomyomatosis and (with topical as well as oral therapy) facial angiofibromas[43].

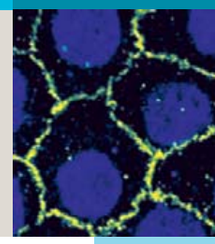
This illustrates how understanding the molecular pathway that is affected in a group of genodermatoses can translate into effective therapy. Another example of molecular advances resulting in novel approaches to treatment is targeted therapy of plexiform neurofibromas via inhibition of KIT signaling by imatinib mesylate upon recognition of the critical role of activated mast cells in the tumor microenvironment to neurofibroma formation in NF1.

REFERENCES

1. Bonifas JM, Morley BJ, Oake RE, et al. Cloning of a cDNA for steroid sulfatase. Proc Natl Acad Sci USA. 1987;84:9248–51.
2. Lander LS, Linton LM, Birren B, et al. Initial sequencing and analysis of the human genome. Nature. 2001;409:860–921.
3. Venter JC, Adams M, Meyers E, et al. The sequence of the human genome. Science. 2001;291:1304–51.
4. Bale SJ. The morbid anatomy of the dermatologic genome: an update for the third millennium. J Cutan Med Surg. 2001;5:117–25.
5. Antonarakis SE, McKusick VA. OMIM passes the 1,000-disease-gene mark. Nat Genet. 2000;25:11.
6. McKusick VA. Mendelian inheritance in man and its online version, OMIM. Am J Hum Genet. 2007;80;588–604.
7. Online Mendelian Inheritance in Man, OMIM™ McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD), June 2011. World Wide Web URL: http://www.ncbi.nlm.nih.gov/omim/.
8. Lander ES. Initial impact of the sequencing of the human genome. Nature. 2011;470:187–97.
9. Irvine AD, McLean WH. The molecular genetics of the genodermatoses: progress to date and future directions. Br J Dermatol. 2003;148:1–13.
10. Richard G. Molecular genetics in dermatology. Clin Dermatol. 2005;23:1.
11. Kelsell DP, Norgett EE, Unsworth H, et al. Mutations in *ABCA12* underlie the severe congenital skin disease harlequin ichthyosis. Am J Hum Genet. 2005;76:794–803.
12. Uitto J, Richard G. Progress in epidermolysis bullosa: from eponyms to molecular genetic classification. Clin Dermatol. 2005;23:33–40.
13. Fine JD, Eady RAJ, Bauer EA, et al. The classification of inherited epidermolysis bullosa (EB): report of the Third International Consensus Meeting on diagnosis and classification of EB. J Am Acad Dermatol. 2008;58:931–50.
14. Oji V, Tadini G, Akiyama M, et al. Revised nomenclature and classification of inherited ichthyoses: results of the first ichthyosis consensus conference in Soreze 2009. J Am Acad Dermatol. 2010;63:607–41.
15. Der Kaloustian VM, Happle R. Genetic diseases of the skin: progress and perspectives. Am J Med Genet. 2004;131C:1–3.
16. Irvine AD. Inherited defects in keratins. Clin Dermatol. 2005;23:6–14.
17. Kottke MD, Delva E, Kowalczyk AP. The desmosome: cell science lessons from human diseases. J Cell Sci. 2006;119:797–806.
18. Richard G. Connexin disorders of the skin. Clin Dermatol. 2005;23:23–32.
19. Ferrell RE, Baty CJ, Kimak MA, et al. GJC2 missense mutations cause human lymphedema. Am J Hum Genet. 2010;86:943–8.
20. Has C, Bruckner-Tuderman L. Molecular and diagnostic aspects of genetic skin fragility. J Dermatol Sci. 2006;44:129–44.
21. Klar J, Schweiger M, Zimmerman R. Mutations in the fatty acid transport protein 4 gene cause the ichthyosis prematurity syndrome. Am J Hum Genet. 2009;85:248–53.
22. Molho-Pessach V, Lerer I, Abeliovich D et al. The H syndrome is caused by mutations in the nucleoside transporter hENT3. Am J Hum Genet. 2008;83:529–34.
23. Szigeti R, Kellermayer R. Autosomal-dominant calcium ATPase disorders. J Invest Dermatol. 2006;126:2370–6.
24. Uitto J. The gene family of ABC transporters – novel mutations, new phenotypes. Trends Molec Med. 2005;11:341–3.
25. Akiyama M. Harlequin ichthyosis and other autosomal recessive congenital ichthyoses: the underlying genetic defects and pathomechanisms. J Dermatol Sci. 2006;42:83–9.
26. Capell BC, Collins FS. Human laminopathies: nuclei gone genetically awry. Nat Rev Genet. 2006;7:940–52.
27. Simon A, van der Meer JW. Pathogenesis of familial periodic fever syndromes or hereditary autoinflammatory syndromes. Am J Physiol Regul Integr Comp Physiol. 2007;292:R86–98.
28. Somoano B, Niendorf KB, Tsao H. Hereditary cancer syndromes of the skin. Clin Dermatol. 2005;23:85–106.
29. Schubbert S, Shannon K, Bollag G. Hyperactive Ras in developmental disorders and cancer. Nat Rev Cancer. 2007;7:295–308.
30. Rauen KA, Schoyer L, McCormick F, et al. Proceedings from the 2009 genetic syndromes of the Ras/MAPK pathway: from bedside to bench and back. Am J Med Genet. 2010;152A:4–24.
31. Messiaen L, Yao S, Brems H, et al. Clinical and mutational spectrum of neurofibromatosis type 1–like syndrome. JAMA. 2009;302:2111–18.
32. Chien AJ, Conrad WH, Moon RT. A Wnt survival guide: from flies to human disease. J Invest Dermatol. 2009;129:1614–27.
33. Jonkman MF, Castellanos Nuijts M, van Essen AJ. Natural repair mechanisms in correcting pathogenic mutations in inherited skin disorders. Clin Exp Dermatol. 2003;28:625–31.
34. Choate KA, Lu Y, Zhou J, et al. Mitotic recombination in patients with ichthyosis causes reversion of dominant mutations in *KRT10*. Science. 2010;330:94–7.
35. McGrath JA. Translational benefits from research on rare genodermatoses. Australas J Dermatol. 2004;45:89–93.
36. Fassihi H, Eady RA, Mellerio JE, et al. Prenatal diagnosis for severe inherited skin disorders: 25 years' experience. Br J Dermatol. 2006;154:106–13.
37. Huang Z, Fong CY, Gauthaman K, et al. Novel approaches to manipulating foetal cells in the maternal circulation for non-invasive prenatal diagnosis of the unborn child. J Cell Biochem. 2011;112:1475–85.
38. Bick DP, Lau EC. Preimplantation genetic diagnosis. Pediatr Clin North Am. 2006;53:559–77.
39. Hacein-Gay-Abina S, Garrigue A, Wang GP, et al. Insertional oncogenesis in 4 patients alter retrovirus-mediated gene therapy of SCID-XL. J Clin Invest. 2008;117:132–42.
40. Wong T, Gammon L, Liu L, et al. Potential of fibroblast cell therapy for recessive dystrophic epidermolysis bullosa. J Invest Dermatol. 2008;128:2179–89.
41. Uitto J. Epidermolysis bullosa: prospects for cell-based therapies. J Invest Dermatol. 2008;128:2140–2.
42. Wagner JE, Ishida-Yamamoto A, McGrath JA , et al. Bone marrow transplantation for recessive dystrophic epidermolysis bullosa. N Engl J Med. 2010;363:629–39.
43. Haemel AK, O'Brian AL, Teng JM. Topical rapamycin: a novel approach to facial angiofibromas in tuberous sclerosis. Arch Dermatol. 2010;146:715–18.

This page intentionally left blank

56 Biology of Keratinocytes



Meral J Arin, Dennis R Roop, Peter J Koch and Maranke I Koster

Chapter Contents

The epidermis: structure and function 825
Keratin intermediate filaments 827
Epidermal differentiation 830
Keratinocyte adhesion 831
Keratinocyte–matrix interactions 834
Related diseases 834

Key features

- The epidermis functions as a barrier that provides protection against harmful substances and water loss
- Through a complex terminal differentiation program, the progeny of epidermal stem cells undergo molecular and biochemical changes that generate the morphologically different strata of the epidermis
- Keratinocyte terminal differentiation culminates in the replacement of the plasma membrane with the cornified cell envelope
- Keratin intermediate filaments, which are expressed by keratinocytes in a differentiation-specific manner, are required to maintain epidermal integrity and have additional roles in the regulation of basic cell functions
- Desmosomes, which integrate the keratin cytoskeleton into the cell membrane and establish adhesive points between opposing cells, are necessary for epidermal stability and stress resistance; these cell–cell junctions also function as signaling centers in epidermal morphogenesis and homeostasis
- Other cell–cell junctions that are found in keratinocytes include adherens junctions and tight junctions
- A variety of inherited skin diseases are caused by a failure of normal epidermal differentiation and function

INTRODUCTION

The main function of the epidermis is to provide a barrier between the organism and the environment. This barrier is the result of a complex terminal differentiation program in which the progeny of epidermal stem cells undergo a series of molecular and biochemical changes that lead to generation of the morphologically different strata of the epidermis (Fig. 56.1). This chapter reviews key signaling pathways that control this terminal differentiation program, with discussion of inherited skin diseases that are caused by a failure of normal epidermal differentiation.

THE EPIDERMIS: STRUCTURE AND FUNCTION

The epidermis, the outermost layer of the skin, functions as a barrier that provides the organism with protection against harmful substances and water loss. This barrier function is established during embryogenesis and maintained in mature epidermis through a continuous program of self-renewal. This self-renewal is mediated by epidermal stem cells, which are located in the basal layer of the interfollicular epidermis as well as in the bulge region of hair follicles (see Ch. 2). Although either of these stem cell types can regenerate both epidermal and hair follicle lineages in response to injury, under homeostatic conditions they only contribute to their own lineage. Through asymmetric cell division, interfollicular epidermal stem cells give rise to a daughter stem cell and a transit amplifying cell. Transit amplifying cells undergo a few cell divisions before beginning a terminal differentiation program, which is associated with an irreversible withdrawal from the cell cycle. Such committed cells detach from the basement membrane and move suprabasally, a process that is mediated by the inactivation of integrins, extracellular matrix receptors that anchor basal cells to the basement membrane (see Ch. 28). Newly formed spinous keratinocytes thus occupy the first suprabasal layer of the epidermis.

Keratinocyte terminal differentiation culminates in the replacement of the plasma membrane with the *cornified cell envelope* (CE), a composite of several covalently cross-linked proteins (Fig. 56.2)[1], most of which are encoded by genes located in the epidermal differentiation cluster on chromosome 1. Examples of CE components include

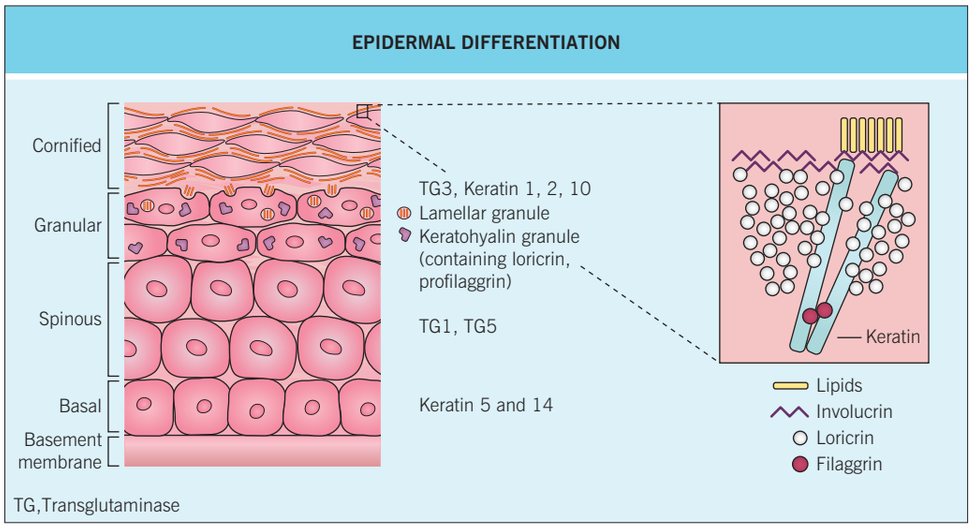


Fig. 56.1 Epidermal differentiation. As keratinocytes are transformed from mitotically active cells in the basal layer to fully differentiated, enucleated squames in the cornified layer, specific proteins are expressed at particular locations within the epidermis. Keratohyalin (profilaggrin- and loricrin-containing) and lamellar (lipid-containing) granules extrude their contents in the granular layer, leading to bundling of keratin filaments and replacement of the plasma membrane with the highly cross-linked, lipid-covered cornified cell envelope (see insert and Fig. 56.2). *Courtesy, Julie V Schaffer, MD.*

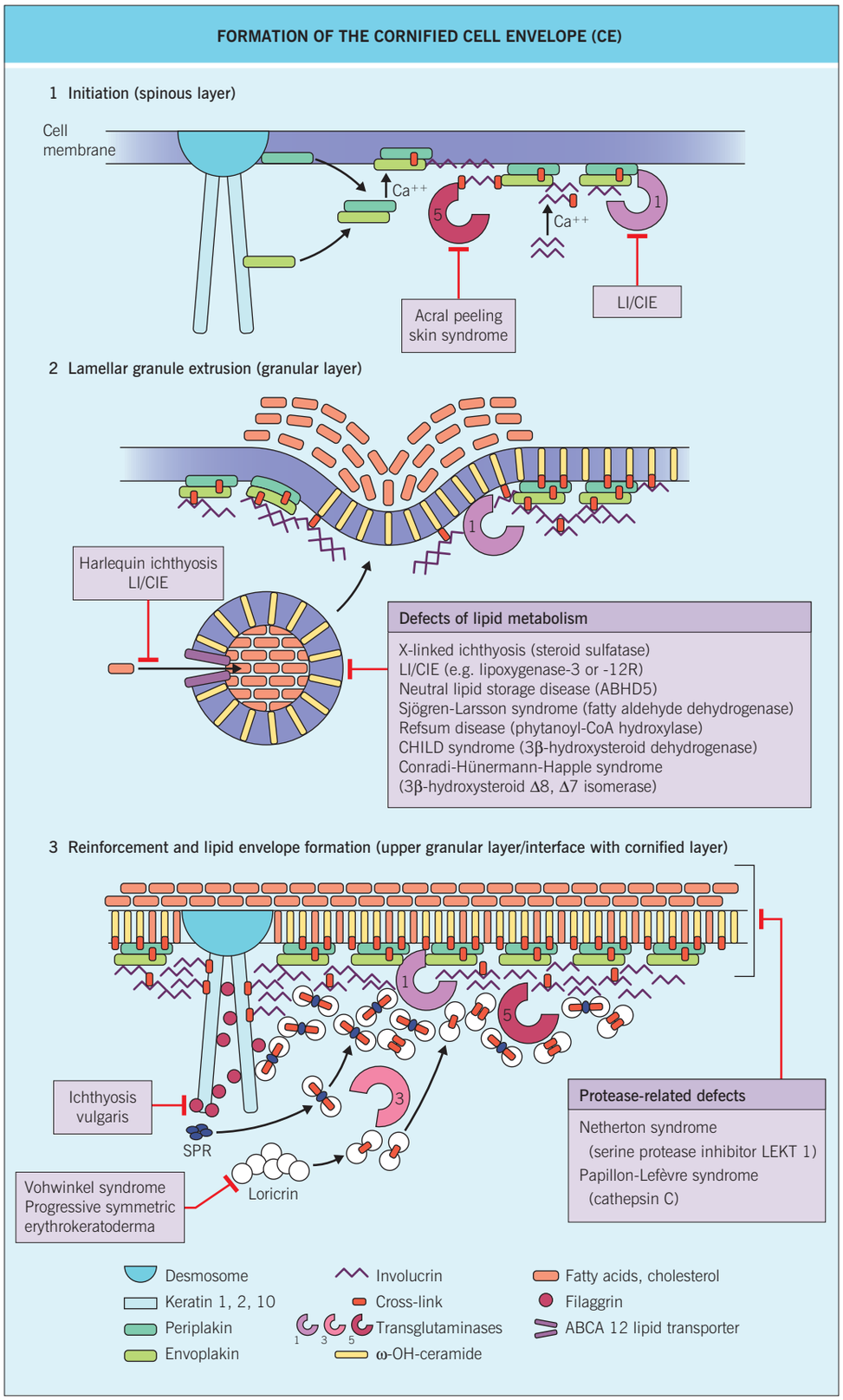


Fig. 56.2 Formation of the cornified cell envelope (CE). Terminal differentiation of keratinocytes is triggered by an increase in the intracellular Ca^{2+} concentration of the suprabasal epidermis. CE assembly is initiated in the upper spinous layer via formation of a cross-linked scaffold composed of envoplakin, periplakin and involucrin along the inner surface of the cell membrane (**1**). This is followed by (or perhaps coincident with) extrusion of lamellar granules into the extracellular space (**2**). Specialized ω-hydroxyceramides are delivered to and eventually replace the cell membrane, where they become linked to scaffold proteins. Reinforcement occurs via cross-linking and translocation to the cell periphery of loricrin (which accounts for >80% of the mass of the CE) and small proline-rich proteins (SPRs) (**3**). Complexes of keratin and filaggrin also become cross-linked to the CE. In addition, proteases play important roles in processing of CE proteins and the proteolysis of corneodesmosomes that is required for desquamation. A mature, terminally differentiated cornified cell thus consists of keratin filaments covalently attached to the CE, which is composed of protein and lipid envelope components and imbedded in extracellular lipid lamellae. Defects in transglutaminases, lipid metabolism, CE structural proteins and proteases lead to a variety of diseases characterized by ichthyosis and/or keratoderma (**1–3**). CHILD, congenital *h*emidysplasia with *i*chthyosiform erythroderma and *l*imb *d*efects; LI, lamellar ichthyosis; CIE, congenital ichthyosiform erythroderma. *Courtesy, Julie V Schaffer, MD.*

involucrin, small proline-rich proteins (SPR), XP-5/late envelope proteins (LEP), loricrin, cystatin, envoplakin, periplakin, elafin, repetin, filaggrin, S100 proteins, keratins and desmosomal proteins. Note that mutations in some of the genes that encode these proteins can lead to skin disorders. For example, mutations in the loricrin and filaggrin genes give rise to palmoplantar keratoderma (PPK) and ichthyosis vulgaris (see below), respectively.

The extracellular surface of the CE is covered by lipids, which form the *cornified lipid envelope* (CLE) (see Ch. 124). Keratinocytes that have assembled the CE/CLE and that have lost their nucleus and cell organelles are termed corneocytes. These cell remnants constitute the stratum corneum, which serves to cover the body surface of terrestrial mammals.

Both the CE and the CLE are required for establishing a cutaneous water barrier. Failure or impairment of the water barrier leads to increased transcutaneous water loss and an increased susceptibility to infections, a major problem in premature infants, and disorders such as Netherton syndrome.

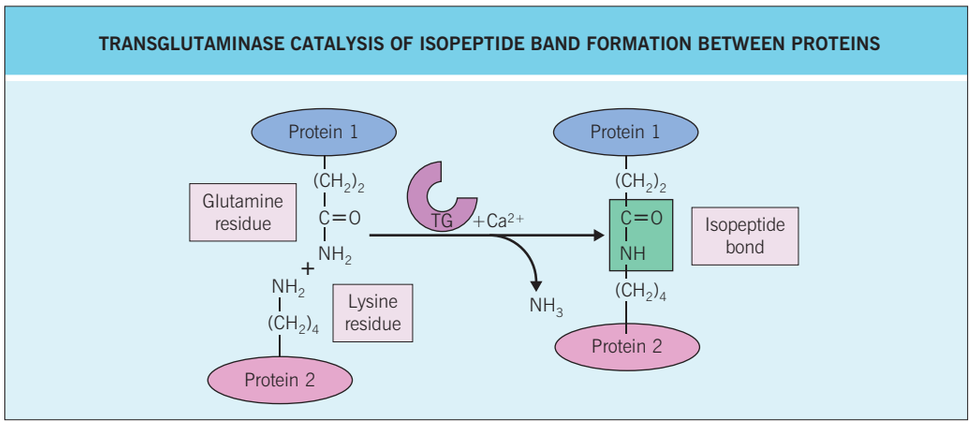


Fig. 56.3 Transglutaminase catalysis of isopeptide bond formation between proteins. Transglutaminases (TGs) are calcium-dependent enzymes that catalyze the formation of γ-glutamyl lysine isopeptide bonds between proteins. TGs also have a role in the creation of ester bonds between proteins and ω-hydroxyceramides. Such cross-linking is essential for assembly of the CE. Four TGs are expressed in the epidermis: TG1 (keratinocyte TG; membrane-bound), TG2 (tissue TG; basal layer), TG3 (epidermal TG; hair follicle and terminally differentiating keratinocytes) and TG5 (upper epidermis). *Courtesy, Julie V Schaffer, MD.*

CE assembly begins within the upper spinous and granular cell layers, where a growing list of proteins is chemically cross-linked, primarily by ε-(γ-glutamyl) lysine isopeptide bonds (Fig. 56.3). This reaction is catalyzed by a class of enzymes termed transglutaminases (TGases). Loss-of-function mutations in the gene that encodes TGase 1 lead to lamellar ichthyosis and congenital ichthyosiform erythroderma, generalized skin disorders resulting from a failure to form proper CEs.

Because the CE is highly resistant to chemical attack, very harsh conditions (e.g. boiling the epidermal cells in buffers containing high concentrations of detergents) are required to isolate and purify CE proteins. One surprising finding is that a loss of *individual* CE components in knockout mice does not necessarily have a major impact on barrier function. One possible explanation for this unexpected result is the presence of compensatory gene regulatory pathways that maintain barrier function even in the absence of major CE components[2]. Better characterization of these regulatory pathways will provide insights into how the barrier is established and maintained, hopefully leading to the development of new strategies for the treatment of diseases caused by impaired barrier function (see Ch. 124).

KERATIN INTERMEDIATE FILAMENTS

Keratin intermediate filaments provide resilience to keratinocytes, the most abundant cell type in the epidermis. Keratins represent the largest group of intermediate filament proteins (Table 56.1), with more than 50 individual members. Based upon their biochemical properties (e.g. isoelectric point, molecular weight), keratins are classified as either type I (K9–K28, K31–K40) or type II (K1–K8, K71–K86) (Table 56.2). Type I and type II keratins form obligatory heteropolymers (i.e. pairs composed of one keratin from each group) that become the basic building blocks of epithelial intermediate filaments (Fig. 56.4). The continuing identification of novel keratin genes plus the increasing number of keratins that have been recognized in mammalian species other than mice and humans made it necessary to revise the keratin nomenclature[3] (see Table 56.2). The new classification system divides the 54 human keratin genes into three categories: (1) epithelial keratin genes; (2) hair keratin genes; and (3) keratin pseudogenes.

Keratins have a common domain structure that they share with other intermediate filament proteins[4]. The central α-helical rod domain consists of 310 amino acid residues and is divided into four segments (1A, 1B, 2A, 2B), which are interrupted by three non-helical segments of variable lengths, termed linkers (Fig. 56.5). The rod domain is composed of seven-residue amino acid sequence repeats $(a\text{-}b\text{-}c\text{-}d\text{-}e\text{-}f\text{-}g)_n$ termed "heptad repeats", where positions "a" and "d" represent hydrophobic residues that are considered crucial for stabilization of the heterodimer. In the middle of the 2B domain, the heptad pattern is interrupted, giving rise to the "stutter". This helical segment is highly conserved among intermediate filaments and does not participate in the formation of the coiled-coil dimer that forms the basic building block of intermediate filaments (see Fig. 56.4).

The beginning and end of the α-helical rod domain, referred to as the helix initiation and helix termination motifs, are highly conserved among the different keratins and play a pivotal role in keratin intermediate filament assembly (e.g. filament elongation). These helix boundary peptides represent genetic "hot spots" for mutations in many of the hereditary keratin disorders (see Fig. 56.5). The severity and other phenotypic features of genodermatoses caused by a keratin defects often correlate with the position of the underlying mutation, with more severe disease resulting from mutations in the helix initiation and termination motifs (see Table 56.5).

The head and tail regions that flank the rod domain are subdivided into extreme end (E), variable (V) and (in type II keratins) homologous (H) domains. Whereas epithelial keratins possess glycine- and serine-rich head and tail domains, these regions have a high content of cysteine and proline in hair keratins. Variations in the head and tail domains account for much of the diversity among different keratin proteins, which suggests that these domains play an important role in cell type-specific functions.

Keratins and Signaling

Keratins are markers for keratinocyte differentiation and are required to maintain epidermal integrity. However, intermediate filaments may also influence other basic cell functions, such as cell cycle progression, metabolic activity and apoptosis. The mechanisms by which keratins regulate these processes are not well understood. However, accumulating evidence suggests that intermediate filaments can bind signaling proteins, thereby controlling the cytoplasmic and, indirectly, nuclear pools of these molecules[5–9]. Interestingly, deletion of the entire type II keratin gene cluster from the mouse genome (which completely prevented the assembly of keratin intermediate filaments) resulted in an early embryonic lethal phenotype associated with growth retardation and defects in yolk sac hematopoiesis and vasculogenesis, underscoring the importance of keratins to cellular signaling and differentiation of a non-epithelial cell lineage[10].

Hair Keratins

The mature hair is the differentiation product of trichocytes and is found within the central core of the hair follicle. The anagen (growing) follicle is a complex structure consisting of eight distinct, concentrically arranged cell layers (see Ch. 68). The innermost compartment is the hair shaft, which is composed of a medulla, cortex and one-layered cuticle; the latter serves as a protective coat for the hair shaft. The innermost living cell layer of the hair follicle (which surrounds the growing hair shaft) is the inner root sheath (IRS); it consists of the IRS cuticle as well as Huxley and Henle layers. The outermost compartment is the outer root sheath (ORS), which is continuous with the interfollicular epidermis. The companion layer is located between the IRS and the ORS.

The medulla contains a mixture of epithelial (K17, K75) and hair keratins (K33, K34, K36, K37, K81), whereas the cortex contains type I hair keratins (K31–K38) and type II hair keratins (K81, K83, K85 and K86) (Fig. 56.6). Hair keratins K32 and K35 and their partners K82 and K85 are found in the cuticle, and the three IRS layers can be detected with antibodies against K71, K74 and K73. The epithelial keratins K5 and K14 are found throughout the full thickness of the ORS, while expression of K6, K16 and K17 is limited to the isthmus and the lower ORS. Additional keratins expressed in the ORS are K15 and K19.

TYPES OF INTERMEDIATE FILAMENTS					
Type I	**Type II**	**Type III**	**Type IV**	**Type V**	**Others**
Keratins (acidic)	Keratins (basic)	Vimentin Desmin GFAP Peripherin	Neurofilament-L Neurofilament-M Neurofilament-H α-Internexin Syncoilin Nestin Synemin	Lamin A/C Lamin B1 Lamin B2	Filensin Phakinin

Table 56.1 Types of intermediate filaments. GFAP, glial fibrillary acidic protein; L, M and H, low-, medium- and high-molecular weight.

PREVIOUS AND NEW HUMAN KERATIN NOMENCLATURE							
Type I				**Type II**			
Previous name	**New name**	**Previous name**	**New name**	**Previous name**	**New name**	**Previous name**	**New name**
K9	K9	K25irs1	K25	K1	K1	K6hf	K75
K10	K10	K25irs2	K26	K2e	K2	K2p	K76
K12	K12	K25irs3	K27	K3	K3	K1b	K77
K13	K13	K25irs4	K28	K4	K4	K5b	K78
K14	K14	Ha1	K31	K5	K5	K6l	K79
K15	K15	Ha2	K32	K6a	K6a	Kb20	K80
K16	K16	Ha3-I	K33a	K6b	K6b	Hb1	K81
K17	K17	Ha3-II	K33b	K6e/h	K6c	Hb2	K82
K18	K18	Ha4	K34	K7	K7	Hb3	K83
K19	K19	Ha5	K35	K8	K8	Hb4	K84
K20	K20	Ha6	K36	K6irs1	K71	Hb5	K85
K23	K23	Ha7	K37	K6irs2	K72	Hb6	K86
K24	K24	Ha8	K38	K6irs3	K73	–	–
–	–	Ka35	K39	K6irs4	K74	–	–
–	–	Ka36	K40	–	–	–	–

Table 56.2 Previous and new human keratin nomenclature. Darker shading indicates keratins with names that were changed. irs, inner root sheath; Ha, type I hair keratins; Hb, type II hair keratins. *From Schweizer J, Bowden PE, Coulombe PA, et al. J Cell Biol. 2006;174:169–74.*

ALIGNMENT AND ASSEMBLY OF KERATIN MOLECULES AND KERATIN FILAMENT PACKING

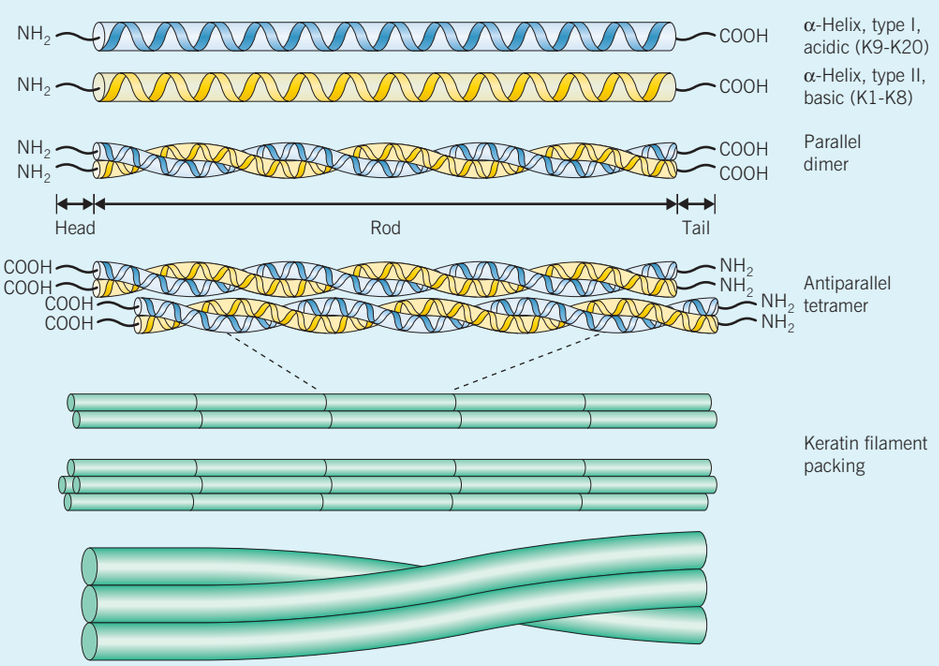


Fig. 56.4 Alignment and assembly of keratin molecules and keratin filament packing. Intermediate filament assembly takes place in several stages and begins with the heterodimerization of one type I and one type II keratin protein in a coiled-coil fashion. Two heterodimers then associate to form a tetramer. Lateral aggregation of tetramers yields higher-order polymers which eventually make up the filament network of the keratinocyte. *Courtesy, Julie V Schaffer, MD.*

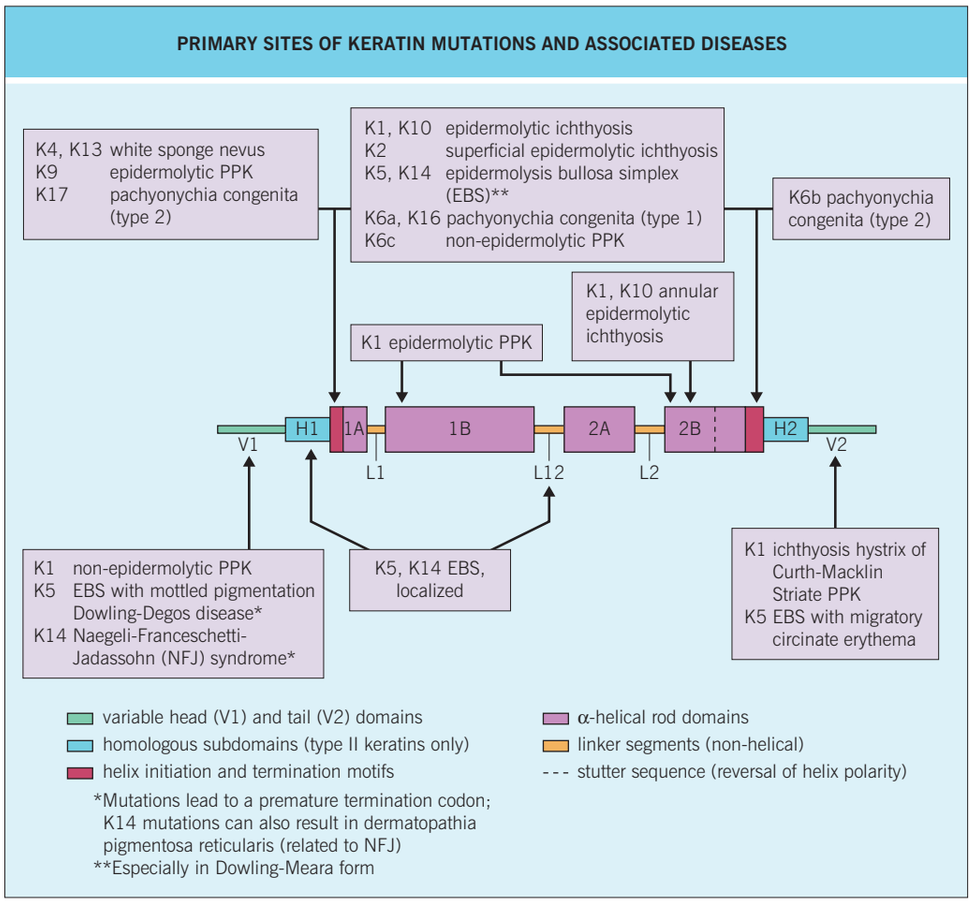


Fig. 56.5 Primary sites of keratin mutations and associated diseases. PPK, palmoplantar keratoderma. *Courtesy, Julie V Schaffer, MD.*

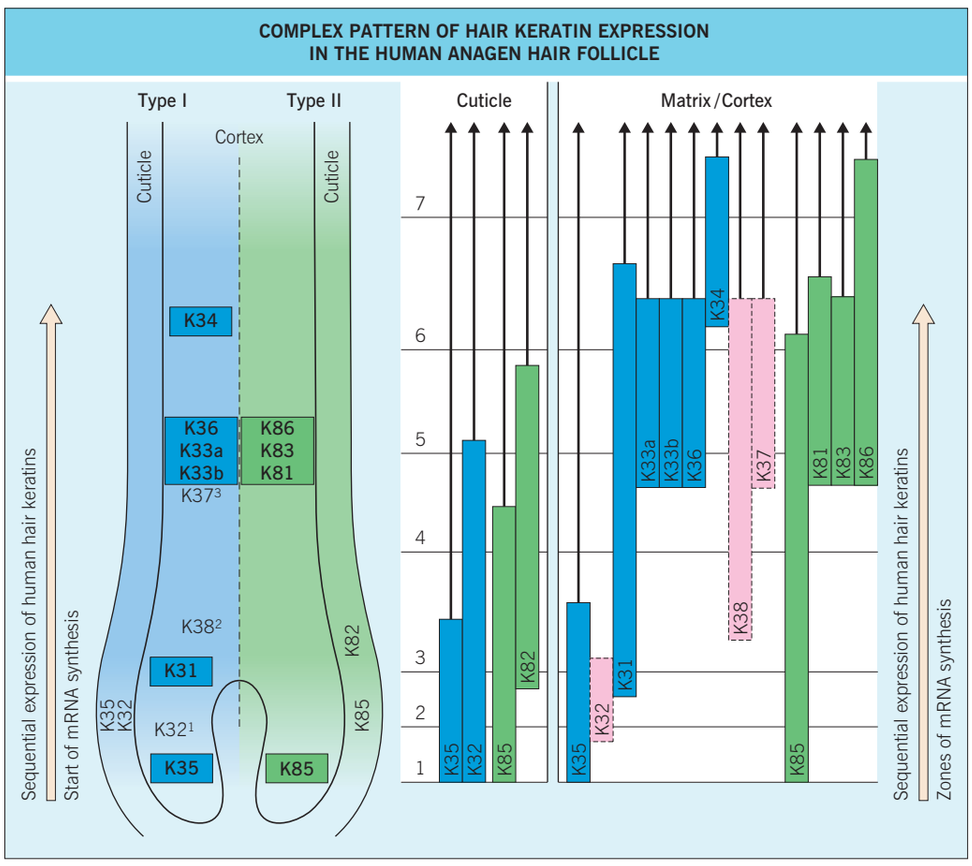


Fig. 56.6 Complex pattern of hair keratin expression in the human anagen hair follicle. Major type I hair keratins are in blue, and major type II hair keratins are in green. Minor hair keratins are in pink. [1]This protein is weakly expressed at this site. [2]To date, expression of this protein has only been detected in single cortex cells. [3]To date, this protein has only been detected in vellus hairs. Autosomal dominant monilethrix is caused by mutations in K81, K83, and K86. *Redrawn from Langbein L, et al. The catalog of human hair keratins. J Biol Chem. 2001;276:35123–32.*

EPIDERMAL DIFFERENTIATION

Epidermal differentiation is a tightly regulated process that involves the transformation of proliferating cells in the basal layer into the dead corneocytes of the stratum corneum. During this process, the keratins that are expressed are highly specific for the state of differentiation (Fig. 56.7). The mitotically active keratinocytes in the basal compartment of the epidermis express the keratin pair K5 and K14. In addition, but less abundantly, K15 is expressed. In the absence of K14, K15 can assemble with K5, thereby providing mechanical stability to the keratinocyte.

As keratinocytes move suprabasally to the spinous layer, they withdraw from the cell cycle. This process is associated with a down-regulation of K5 and K14 and an induction of the differentiation-specific keratins, K1 and K10. Further maturation of spinous keratinocytes into granular keratinocytes results in expression of K2, a reinforcement keratin. With further maturation, filaments containing the suprabasal keratins are bundled parallel to the surface and, eventually, keratinocytes lose their cytoplasmic organelles and differentiate into lifeless corneocytes that are shed into the environment.

Interestingly, a number of epidermal keratins have a more restricted anatomic distribution pattern. For example, K9 is specifically expressed in the suprabasal cells of palmoplantar skin. Another subset of keratins, K6, K16 and K17, are expressed not only in palmoplantar epidermis, but also in keratinocytes of the nail bed, hair follicle, and sebaceous and sweat glands. In addition, this group of keratins is rapidly induced by injury, ultraviolet radiation and wounding, as well as in hyperproliferative conditions[11].

Regulatory Pathways Involved in Epidermal Development and Differentiation

The regulatory pathways necessary for normal keratinocyte differentiation include those that: (1) establish and maintain basal keratinocytes; (2) initiate and execute terminal differentiation; (3) form the stratum corneum. Examples of these pathways are discussed in more detail below.

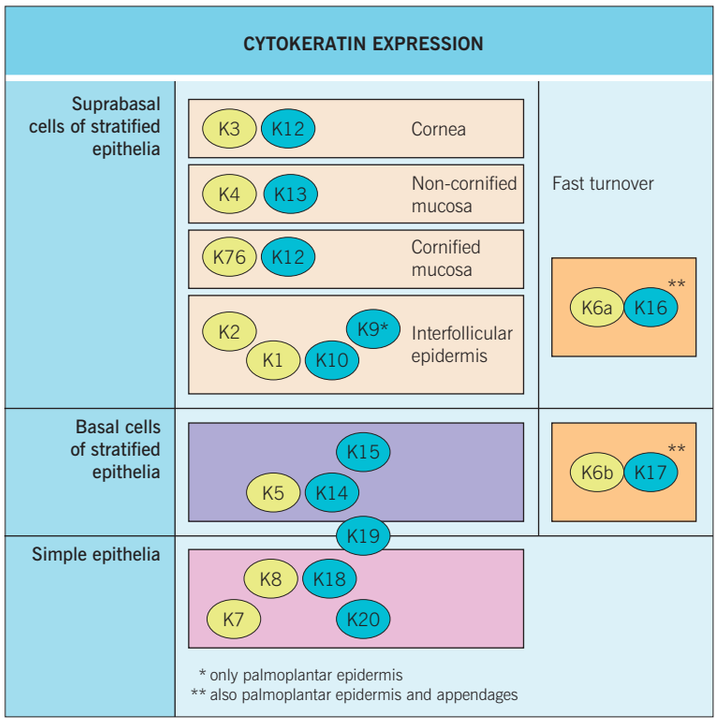


Fig. 56.7 Cytokeratin expression. Type II (basic) keratins are in yellow (K1–K8; K76) and type I (acidic) keratins are in blue (K9–K20). Keratin disorders are presented in Fig. 56.5 and Tables 56.3 & 56.5.

Genes required for establishing/maintaining basal keratinocytes

An example of a transcription factor whose importance in epidermal development and differentiation became apparent following the generation of a knockout mouse model is p63[12]. The *p63* gene encodes six different proteins, each of which can function as a transcriptional activator or repressor. Strikingly, completely p63-deficient mice fail to initiate epidermal morphogenesis, and they are born with a single-layered epithelium covering their bodies rather than a stratified epidermis. After birth, exposure of these mice to the environment leads to a rapid death due to dehydration. The failure of p63-deficient epithelial cells to adopt an epidermal fate suggests that p63 may play an important role in specifying the epidermal lineage.

Consistent with this hypothesis, ectopic p63 expression was shown to induce expression of the epidermal keratins K5 and K14. Subsequent studies demonstrated that p63 is required for both the initial induction of K5/K14 expression in embryonic basal keratinocytes and the maintenance of K5/K14 expression in the basal layer of mature epidermis. Besides regulating epidermal keratin expression, p63 is important for maintaining the proliferative state of basal keratinocytes. The latter is accomplished, in part, by the ability of p63 to repress the expression of cell cycle inhibitors. Thus, one role of p63 is to maintain basal keratinocytes in a proliferative state and to prevent the onset of terminal differentiation.

Genes required for terminal differentiation in mature epidermis

After basal keratinocytes have undergone a few rounds of cell division, they irreversibly withdraw from the cell cycle, move suprabasally, and become spinous keratinocytes. Surprisingly, this process is also controlled, in part, by an isoform of p63, ΔNp63α[12]. ΔNp63α synergizes with Notch signaling to induce K1 expression. In addition, ΔNp63α mediates cell cycle exit by inducing cell cycle inhibitors and by repressing genes required for cell cycle progression. The importance of p63 for normal epidermal development and differentiation is further underscored by the finding that *p63* mutations underlie a subset of ectodermal dysplasias, which are characterized by abnormalities in the skin and skin appendages (see Ch. 63).

The Notch signaling pathway is also required for the formation of the spinous layer[13]. *In vitro* studies initially suggested such a role for Notch signaling, and this was confirmed by the use of mouse models in which Notch signaling was altered. For example, ablation of Notch signaling resulted in the development of an extremely thin spinous layer, whereas constitutively active Notch signaling resulted in an expansion of the spinous layer. Notch activity promotes terminal differentiation by inducing K1 expression and mediating cell cycle withdrawal.

Ca^{2+} in epidermal differentiation

In addition to signaling via p63 and Notch, an important trigger of keratinocyte differentiation is an increase in extracellular Ca^{2+} concentration[14]. In mature epidermis, there is a gradient of increasing extracellular Ca^{2+} concentration from the basal layer to the cornified layers. Ca^{2+} plays an important role in keratinocyte differentiation. Increasing the Ca^{2+} concentration in the media of cultured keratinocytes can induce a differentiation program indistinguishable from that of keratinocytes *in vivo*, with successive expression of markers of keratinocyte terminal differentiation[15].

The importance of Ca^{2+} for keratinocyte differentiation has led to the identification of several Ca^{2+}-responsive proteins in the epidermis that are involved in the formation of the granular cell layer[16]. The protein kinase C (PKC) family of proteins is activated by Ca^{2+} signaling and functions specifically in the transition from spinous to granular cells. PKC proteins have a dual role, contributing to the down-regulation of K1 and K10 expression as well as to the induction of markers of granular keratinocytes, including loricrin, filaggrin and transglutaminases.

In addition to the PKC family, several proteins that undergo conformational changes upon binding to Ca^{2+} are expressed in mouse and human epidermis. Of these, the calcium-sensing receptor is specifically expressed in granular keratinocytes. Interestingly, mice lacking the full-length form of the calcium-sensing receptor fail to properly form a

granular layer, while overexpression of the calcium-sensing receptor in basal keratinocytes causes expanded spinous and granular cell layers[17].

Genes required for terminal differentiation in embryonic epidermis

Whereas the signaling pathways discussed above are critical for the formation of the spinous layer in postnatal skin, the molecular mechanisms that underlie the development of a spinous layer during epidermal morphogenesis appear to be different[18]. One reason for this distinction is that during epidermal morphogenesis, basal keratinocytes do not directly differentiate into spinous keratinocytes. Instead, basal keratinocytes initially differentiate into intermediate keratinocytes. Like spinous cells, intermediate cells express K1. However, unlike spinous keratinocytes, they still undergo proliferation. The intermediate cell layer exists only transiently during epidermal morphogenesis, and intermediate cells ultimately differentiate into spinous and granular cells, which then undergo further terminal differentiation.

The importance of the intermediate cell layer for normal epidermal development has been demonstrated by mouse models in which intermediate cells fail to mature into spinous and granular cells. Such a block in differentiation occurs in mice lacking expression of inhibitor of κB kinase-α (IKKα), interferon regulatory factor 6 (IRF6) or ovo-like 1 (Ovol1), as well as in mice expressing a mutant form of 14–3–3σ[18]. The latter mutant protein was identified in repeated epilation *(Er)* mutant mice. In all instances, an expanded intermediate cell layer develops, further terminal differentiation is disrupted, and the consequent failure to establish barrier function results in neonatal lethality.

KERATINOCYTE ADHESION

Desmosomes

Desmosomes are multi-protein complexes that function as cell–cell adhesion structures (junctions) in epidermal cells[19] (Fig. 56.8). They also provide attachment sites for the keratin intermediate filament cytoskeleton of keratinocytes. Consequently, these junctions are critical components of a supracellular filament network that traverses the interfollicular epidermis and the epithelia of skin appendages, such as hair follicles[20].

Although the biochemical composition of desmosomes varies from tissue to tissue, the core of the desmosome is formed mainly by transmembrane glycoproteins that belong to the desmoglein (Dsg) and desmocollin (Dsc) subfamilies of Ca^{2+}-dependent cell adhesion proteins (cadherins). The current hypothesis is that heterophilic and homophilic interactions between Dsg and Dsc proteins are required to establish cell–cell coupling (see Ch. 29)[21,22]. Another protein, termed "Perp", is also crucial for this process[23]. The transmembrane proteins are linked to the keratin intermediate filament network via a complex of several proteins, including desmoplakin, plakoglobin, one of several plakophilin (Pkp) isoforms, and often additional accessory proteins[24,25].

To complicate matters, several desmosomal components are encoded by multigene families. In humans, for example, there are four *Dsg* genes *(Dsg1–4)*, three *Dsc* genes, and three *Pkp* genes. In the epidermis, several Dsg and Dsc isoforms can be present in the same cell and even in the same desmosome. It is assumed that the specific composition of the desmosome affects its adhesive properties. Regulating adhesiveness of junctions (via changes in the protein composition or through protein modifications) is considered to be a crucial prerequisite for regulating cell migration, cell sorting and the formation of the proper tissue histo-architecture during embryonic development.

One example of differential regulation of desmosomes within the context of tissue/organ development is the formation of skin appendages, such as hair follicles and mammary glands. Regardless of the type of appendage that is being formed, the initial steps are very similar. First, keratinocytes from the basal cell layer change their polarity and down-regulate desmosomal proteins[26]. Next, these cells break through the basement membrane and invade the underlying dermal tissue. Eventually, the cells begin to differentiate in order to form the various cell layers and tissues that constitute the new appendage. During this process, desmosomal adhesion is re-established. The molecular pathways that control differential expression of desmosomal genes during such developmental processes are not yet known. However, based on work focusing on the regulation of classical cadherins (e.g. E-cadherin),

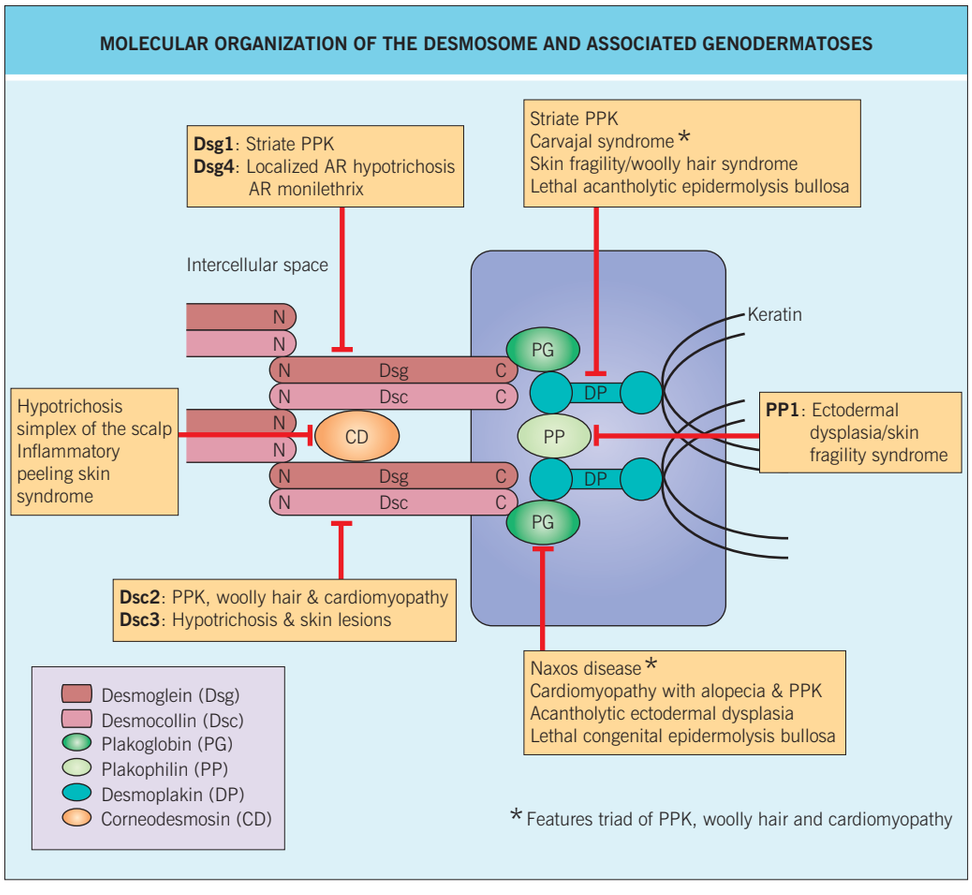


Fig. 56.8 Molecular organization of the desmosome and associated genodermatoses. Type 1 transmembrane glycoproteins from the cadherin family (desmogleins and desmocollins) are linked to intermediate filaments via a complex that contains catenins (plakoglobin, plakophilins) and plakin proteins (desmoplakin). Both homophilic and heterophilic interactions have been postulated to participate in establishing desmosomal adhesion. Examples of inherited skin diseases affecting the components of desmosomes are shown. AR, autosomal recessive; PPK, palmoplantar keratoderma.

it is likely that major epidermal signaling pathways, such as the Wnt and NF-κB cascades, are involved.

Of note, the phenomenon of local proliferation of keratinocytes followed by invasion into dermal tissue also occurs in cutaneous wound healing and the initial stages of cancer progression. It is therefore likely that the same gene regulatory pathways that govern adnexal development also control these biological processes.

What happens when desmosomes do not function properly?

Tissues that are exposed to a significant amount of mechanical stress, such as the skin and its appendages, mucous membranes (e.g. in the oral cavity) and the heart, are often affected by desmosomal defects. The clinical symptoms of desmosomal diseases can usually be ascribed to tissue fragility, with mucocutaneous blistering, abnormal hair and cardiomyopathy being the major manifestations of desmosomal defects[19,27]. In fact, dysfunction of more than 10 desmosomal proteins has been linked to either skin or heart diseases, including Dsc1, Dsc2, Dsg1, Dsg2, Dsg3, Dsg4, desmoplakin, plakoglobin, plakophilin1, plakophilin2 and corneodesmosin (Table 56.3). Most of the associated disorders represent genodermatoses, i.e. skin diseases caused by gene mutations. However, there are also acquired desmosomal diseases, such as pemphigus vulgaris (PV) and pemphigus foliaceus (PF) (with disruption due to autoantibodies) and staphylococcal scalded skin syndrome (with disruption due to bacterial toxins)[28].

The first mucocutaneous disorders linked to a desmosomal defect were PV and PF (see Ch. 29). In these diseases, autoantibodies bind to Dsg and induce epidermal and/or mucous membrane blistering via acantholysis, a process thought to be caused by loss of Dsg. In contrast to the blisters observed in patients with keratin mutations (e.g. individuals with epidermolysis bullosa simplex), PV and PF blisters are caused by cell–cell separation, not cytolysis. Nevertheless, both groups of diseases illustrate the point that desmosomes and the associated keratin intermediate filaments must function properly in order to maintain tissue integrity.

Besides their ability to stabilize tissues, desmosomes also function as signaling centers, for example, by controlling the cytoplasmic pool of signaling molecules. In fact, certain features of pemphigus are caused by abnormal signaling through the desmosomes that are targeted by autoantibodies[19]. This finding further supports the notion that desmosomes are more than merely cellular glue. The emerging picture is one of a highly dynamic structure that actively participates in signal transduction.

Plakoglobin is a core component of desmosomes that is involved in relaying signals to the nucleus. This protein belongs to the armadillo protein family, the prototype of which is β-catenin. Plakoglobin binds desmosomal cadherins (Dsg, Dsc) at the plasma membrane (see

MUTATIONS IN STRUCTURAL AND DESMOSOMAL PROTEINS FOUND WITHIN STRATIFIED SQUAMOUS EPITHELIA: ASSOCIATED HUMAN DISEASES AND MOUSE MODELS

Gene/protein	Disease association	Phenotype of mouse models
	STRUCTURAL PROTEINS	
K5	Epidermolysis bullosa simplex (including with mottled pigmentation, with migratory circinate erythema) Dowling–Degos disease	ND
K14	Epidermolysis bullosa simplex Naegeli–Franscheschetti–Jadassohn syndrome & dermatopathia pigmentosa reticularis	Blistering due to collapse of keratin network in basal keratinocytes
K1	Epidermolytic ichthyosis Ichthyosis hystrix of Curth–Macklin Diffuse non-epidermolytic palmoplantar keratoderma (PPK) Diffuse epidermolytic PPK	Blistering due to collapse of keratin network in suprabasal keratinocytes
K10	Epidermolytic ichthyosis Ichthyosis en confetti	Blistering due to collapse of keratin network in suprabasal keratinocytes ND
K2	Ichthyosis bullosa of Siemens	ND
K9	Epidermolytic PPK	ND
K4, K13	White sponge nevus	ND
K6a	Pachyonychia congenita-6a (formerly type 1)	Intraepidermal blisters, hyperkeratosis
K6b	Pachyonychia congenita-6b (formerly type 2)	ND
K6c	Focal or diffuse non-epidermolytic PPK	ND
K16	Pachyonychia congenita-16 (formerly type 1)	ND
K17	Pachyonychia congenita-17 (formerly type 2) Steatocystoma multiplex	Alopecia
K74	Autosomal dominant woolly hair/hypotrichosis	ND
K75	Increased risk of pseudofolliculitis barbae	ND
K81, K83, K86	Monilethrix	ND
K85	"Pure" hair–nail type ectodermal dysplasia	ND
K3, K12	Meesmann corneal dystrophy	ND
K8	Familial cirrhosis	ND
K8, K18	Increased risk of inflammatory bowel disease	ND
Loricrin	Vohwinkel syndrome Progressive symmetric erythrokeratoderma (subset of patients)	Epidermal barrier defect
Filaggrin	Ichthyosis vulgaris Atopic dermatitis	ND

Table 56.3 Mutations in structural and desmosomal proteins found within stratified squamous epithelia: associated human diseases and mouse models.
ND, not determined.

Continued

MUTATIONS IN STRUCTURAL AND DESMOSOMAL PROTEINS FOUND WITHIN STRATIFIED SQUAMOUS EPITHELIA: ASSOCIATED HUMAN DISEASES AND MOUSE MODELS		
Gene/protein	**Disease association**	**Phenotype of mouse models**
	DESMOSOMAL PROTEINS	
Dsc1	Subcorneal pustular dermatosis	Skin fragility, localized hair loss
Dsc2	Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) ARVD/C, PPK & woolly hair*	ND
Dsc3	Hypotrichosis and skin lesions*	Skin blistering with PV-like histopathology and telogen hair loss in conditional Dsc3 null skin
Dsg1	Pemphigus foliaceus Bullous impetigo & staphylococcal scalded skin syndrome Striate PPK	ND
Dsg2	ARVD/C	Embryonic lethality
Dsg3	Pemphigus vulgaris	Mucous membrane blistering and hair loss
Dsg4	Localized autosomal recessive hypotrichosis Autosomal recessive monilethrix	Hair defects
Desmoplakin	Striate PPK Carvajal syndrome Skin fragility/woolly hair syndrome Lethal acantholytic epidermolysis bullosa ARVD/C	Embryonic lethality Heart defects in tetraploid rescued mice
Plakoglobin	Naxos disease Cardiomyopathy with alopecia and PPK Acantholytic ectodermal dysplasia Lethal congenital epidermolysis bullosa ARVD/C	Embryonic lethality, heart defects
Plakophilin1	Ectodermal dysplasia/skin fragility syndrome	ND
Plakophilin2	ARVD/C	Embryonic lethality, heart defects
Plakophilin3	ND	Hair abnormalities
Corneodesmosin	Hypotrichosis simplex of the scalp Inflammatory peeling skin syndrome	Loss of adhesion between granular and cornified cell layers, skin water barrier defects, hair loss in conditional corneodesmosin null epidermis
*To date, reported in a single family.		

Table 56.3 Mutations in structural and desmosomal proteins found within stratified squamous epithelia: associated human diseases and mouse models (cont'd). Dsc, desmocollin; Dsg, desmoglein; ND, not determined.

Fig. 56.8). However, it can also form complexes with Tcf/Lef transcription factors and thus control gene expression within the nucleus. Furthermore, plakoglobin can influence other biological properties of a cell, such as proliferation, migration and apoptosis[19]. Plakophilins can also affect cytoplasmic signaling pathways, and at least two isoforms (Pkp1, Pkp2) have nuclear functions[24].

Other Types of Cell Junctions

In addition to desmosomes, several other morphologically and biochemically defined cell junctions are found in keratinocytes, including adherens junctions and tight junctions[20].

Adherens junctions

Adherens junctions consist of classical cadherins, in particular E- and P-cadherin, as well as a complex of cytoplasmic plaque proteins (α-catenin, β-catenin, γ-catenin [also known as plakoglobin]) that connect the transmembrane proteins to the actin microfilament cytoskeleton. Note that the armadillo protein plakoglobin can bind to both desmosomal and classical cadherins (see above).

P-cadherin is expressed primarily in the basal layer of mouse epidermis (the preferred experimental model of skin biologists), whereas E-cadherin is expressed throughout the interfollicular epidermis. A genetically engineered loss of P-cadherin in mice has little effect on the interfollicular epidermis, although it does affect the mammary gland. On the other hand, loss of E-cadherin in epidermis-specific (conditional) null mice can lead to severe defects in the homeostasis and function of the epidermis. Most interestingly, it appears that loss of E-cadherin can affect tight junctions (see below) and thus the skin barrier function of the epidermis. Based on an analysis of genetically engineered mice, it has become evident that normal expression of the plaque proteins α-catenin, β-catenin and plakoglobin is also required for normal epidermal function.

Similar to desmosomal cadherins, classical cadherins are differentially regulated during development of skin appendages[29]. For example, E-cadherin is down-regulated in keratinocytes that invade the underlying dermis. A failure to down-regulate cadherin-based adhesion appears to suppress invasive growth of keratinocytes and thus appendage formation.

As indicated above, armadillo proteins (e.g. β-catenin and plakoglobin) are involved in signaling from cell junctions to the nucleus. While β-catenin is a downstream effector of the classical (canonical) Wnt pathway, plakoglobin appears to be able to signal either via Wnt components or independently. Interestingly, in at least two cell types, plakoglobin counteracts classical Wnt signaling[30].

Signaling through adhesive junctions (i.e. adherens junctions and desmosomes) is still a new area in cutaneous research, and we can expect significant progress in our understanding of how these junctions affect skin and skin appendage development in the next few years.

Tight junctions

Together, tight junctions *(zonula occludens)*, adherens junctions and desmosomes form the apical junctional complex in polarized epithelial cells. Tight junctions are thought to "seal" the intercellular space, thus preventing the free diffusion of macromolecules. Consequently, these junctions are crucial for maintaining a barrier between two compartments. Surprisingly, until a few years ago, tight junctions were thought to be absent from the epidermis, but their presence has been demonstrated by several investigators. In the granular layer of the

KERATINOCYTE INTEGRIN RECEPTORS	
Integrin	**Ligand**
	β_1 FAMILY
$\alpha_1\beta_1$	Fibrillar collagen, laminin
$\alpha_2\beta_1$	Fibrillar collagen, laminin
$\alpha_3\beta_1$	Fibronectin, laminin 5, denatured collagen
$\alpha_5\beta_1$	Fibronectin
$\alpha_6\beta_1$	Laminin
	β_4 FAMILY
$\alpha_6\beta_4$	Laminin 5
	α_v FAMILY
$\alpha_v\beta_1$	Fibronectin, vitronectin
$\alpha_v\beta_3$	Vitronectin, fibronectin, fibrinogen, denatured collagen
$\alpha_v\beta_5$	Vitronectin
$\alpha_v\beta_6$	Fibronectin, tenascin

Table 56.4 Keratinocyte integrin receptors. *Courtesy, Irene M Leigh, MD.*

epidermis, they form a seal that is required for maintaining the water barrier function of the epidermis[31].

KERATINOCYTE–MATRIX INTERACTIONS

The epidermis is separated from the underlying dermis by a basement membrane (see Ch. 28), which consists of proteins secreted by epidermal keratinocytes and dermal fibroblasts[32]. Glycoproteins, including laminins, collagens, proteoglycans and fibronectin, constitute the main components of the skin basement membrane. Keratinocytes are anchored to the basement membrane through integrins, transmembrane receptors for extracellular matrix proteins (Table 56.4). In addition to their structural role, integrins function by transducing signals from the extracellular matrix to the epidermal keratinocytes.

Recently, another family of proteins that is required for basement membrane integrity during embryogenesis has been identified. This family consists of the protein products of *Fras1, Frem1* and *Frem2* genes, three proteins that form a complex within the basement membrane. Loss-of-function mutations in any of these three genes result in a destabilization of the protein complex, causing aberrant basement membrane formation and consequent skin blistering in mouse models; in humans, loss-of-function mutations in the *FRAS1* or *FREM2* genes underlie Fraser syndrome, a multisystem autosomal recessive disorder characterized by embryonic (but not postnatal) blistering of the skin, cutaneous syndactyly, cryptophthalmos and renal defects[33].

RELATED DISEASES

Keratin Disorders

Mutations in keratin genes cause a variety of disorders of the skin and other epithelia, usually with an autosomal dominant pattern of inheritance. The underlying mutations typically act in a dominant-negative fashion, interfering with normal intermediate filament assembly. This causes aggregation of disorganized keratin bundles, which often leads to clinically evident cell fragility. As noted above, mutations in the helix initiation and termination motifs are generally associated with relatively severe disease phenotypes, whereas mutations affecting other keratin domains usually cause milder disease (see Fig. 56.5). Specific genotype–phenotype correlations in skin disorders caused by mutations in keratin genes are presented in Table 56.5.

Epidermolysis bullosa simplex

Epidermolysis bullosa (EB) comprises a group of heritable skin fragility disorders characterized by skin blistering following minor mechanical trauma (see Ch. 32). In the simplex form of EB (EBS), tissue separation is within the epidermis. According to a revised classification, EBS is divided into two major subtypes: (1) *suprabasal*, which can be caused by mutations in genes encoding desmosomal components (see above and Table 56.3) and often features acantholysis histologically; and (2) *basal*, where the cleavage plane is within basal keratinocytes[34]. Genotype–phenotype correlations are well established for basal EBS due to *KRT5* and *KRT14* mutations (see Table 56.5). The clinical severity is related to the location of the mutations and the degree to which they perturb keratin structure[35]. Interestingly, hyperpigmentation is a major feature of Dowling–Degos disease, Naegeli–Franceschetti–Jadassohn syndrome and dermatopathia pigmentosa reticularis (which do not feature prominent blistering; see Ch. 67) as well as EBS with mottled pigmentation, demonstrating that mutations in keratin genes expressed in the basal epidermis can lead to pigmentary changes in addition to skin fragility.

Epidermolytic ichthyosis and palmoplantar keratoderma

Epidermolytic ichthyosis (bullous congenital ichthyosiform erythroderma) is a disorder of keratinization caused by mutations in *KRT1* or *KRT10*[36] (see Ch. 57). It is usually inherited in an autosomal dominant fashion due to heterozygous missense mutations (typically involving the helix initiation and termination motifs) that lead to clumping of keratin filaments in the suprabasal layers of the epidermis and subsequent cytolysis. A form of epidermolytic ichthyosis associated with PPK (mainly due to *KRT1* mutations) can be distinguished from a form where palmoplantar involvement is absent (mainly due to *KRT10* mutations). *KRT1* mutations (outside of the critical helix initiation and termination regions) have also been identified in epidermolytic and non-epidermolytic variants of isolated PPK, which is more commonly caused by mutations in *KRT9*[37] (Table 56.5). A recessive form of epidermolytic ichthyosis characterized by a complete absence of the K10 protein in the epidermis has also been described in several families. Mutations in *KRT1* or *KRT10* that occur during embryogenesis can cause a mosaic form of epidermolytic ichthyosis, which presents as an epidermolytic epidermal nevus (see Ch. 62). Vertical transmission of the mutation is possible if the gondads are involved, causing generalized disease in affected offspring. Genotype–phenotype correlations in other disorders of cornification caused by mutations in keratin genes are outlined in Table 56.5.

White sponge nevus of Cannon

White sponge nevus is characterized by white plaques involving the oral mucosa, with occasional involvement of other mucosal surfaces such as the esophagus, vagina, rectum and nasal cavity. The plaques may wax and wane over time, and suprabasal cytolysis and keratin clumping are observed histologically. Mutations in the genes encoding K4 and K13, which are specifically expressed in mucosal keratinocytes, cause this condition.

Gastrointestinal disorders

K8 and K18 are the major keratins that are expressed in gastrointestinal epithelia, including the liver, pancreas and gut. Mutations in these simple keratins are typically located within the head and tail domains and do not involve the highly conserved helix boundary regions. K8 and K18 mutations are considered as risk factors for developing liver and gastrointestinal disorders (e.g. cirrhosis, inflammatory bowel disease), with additional genetic and environmental alterations likely required for disease development[38]. The mutation-associated predisposition to tissue injury is likely related to mechanical and non-mechanical keratin functions, including maintenance of cell integrity and protection from oxidative injury and apoptosis.

Filaggrin Disorders

Filaggrin is a component of the cornified cell envelope and is responsible for aggregating keratins. It represents the processed product of profilaggrin, which is cleaved into individual filaggrin polypeptides by caspase 14. Loss-of-function mutations in filaggrin underlie ichthyosis vulgaris (Fig. 56.9), a semidominant condition with incomplete penetrance (~90% in homozygotes and ~60% in heterozygotes)[39] (see Ch. 57). Whereas patients with a heterozygous filaggrin mutation display

GENOTYPE–PHENOTYPE CORRELATIONS IN MUCOCUTANEOUS DISORDERS CAUSED BY MUTATIONS IN KERATIN GENES					
Disorder	**Inheritance**	**Gene**	**Type/location of mutation(s)**	**Clinical features**	**Chapter where covered**
EBS, localized (Weber–Cockayne)	AD	*KRT5, KRT14*	L12; H1 of *KRT5*	Blistering limited to palms/soles	32
EBS, generalized non-Dowling–Meara	AD		L12, L2; central portions of 1A & 2B	Generalized blistering, variable severity	
EBS, Dowling–Meara	AD		Helix initiation & termination motifs; "hotspot" Arg125Cys/His in *KRT14*	Severe, herpetiform generalized blistering; PPK	
EBS, autosomal recessive	AR		Truncating or splice-site mutations	Blistering, variable distribution and severity	
EBS with mottled pigmentation	AD	*KRT5 >> KRT14*	Pro25Leu in V1 of *KRT5*	Blistering, palmoplantar or generalized; "mottled" hypo- & hyperpigmentation or reticulated hyperpigmentation	
EBS with migratory circinate erythema	AD	*KRT5*	Frameshift mutation leading to extended V2 region	Migrating annular areas of erythema and vesiculation	
Dowling–Degos disease	AD		V1 – truncating (leading to haploinsufficiency)	Hyperpigmented macules in reticulated array in intertriginous sites	67
Naegeli–Franceschetti–Jadassohn syndrome & dermatopathia pigmentosa reticularis	AD	*KRT14*	V1 – truncating (leading to haploinsufficiency)	Reticulated hyperpigmentation; lack of dermatoglyphs, PPK; variable hypotrichosis, hypohidrosis, nail dystrophy, dental abnormalities	
Epidermolytic ichthyosis	AD	*KRT1, KRT10*	Helix initiation & termination motifs; "hotspot" Arg156 in KRT10	Erythroderma and blistering in neonates; later, corrugated hyperkeratosis; variable PPK (esp. with KRT1)	57
	AR	*KRT10*	2B – truncating		
Annular/cyclic epidermolytic ichthyosis	AD	*KRT1, KRT10*	2B		
Ichthyosis hystrix Curth–Macklin	AD	*KRT1*	V2 – truncated tail	Spiked/ridged hyperkeratosis; PPK	
Ichthyosis en confetti	AD	*KRT10*	Frameshift mutations leading to arginine-rich tail; revertant clones via mitotic recombination	Ichthyosiform erythroderma with progressive development of small islands of normal skin	
Superficial epidermolytic ichthyosis (ichthyosis bullosa of Siemens)	AD	*KRT2*	Helix termination > initiation motifs	Superficial blistering/molting; variable hyperkeratosis; no PPK	
Epidermolytic PPK	AD	*KRT1*	1B (diffuse with "tonotubular" keratin), 2B (mild diffuse/focal)	Focal/striate or diffuse epidermolytic PPK	58
		KRT9	Helix initiation > termination motifs, with "hotspot" Arg163		
Non-epidermolytic PPK	AD	*KRT1*	V1 (diffuse), V2 (striate)	Focal/striate or diffuse non-epidermolytic PPK	
		KRT6C	Helix initiation & termination motifs (focal > diffuse; with blistering)		
Pachyonychia congenita-6a/16 (type 1)	AD	*KRT6A, KRT16*	Helix initiation > termination motifs	Painful focal PPK; hypertrophic nail dystrophy; oral leukokeratosis; variable cysts	58, 71
Pachyonychia congenita-6b/16 (type 2)	AD	*KRT6B, KRT17*	Helix termination motif of *KRT6B*; helix initiation motif with "hotspots" Asn92 & Arg94 in *KRT17*	As above; frequently steatocystoma multiplex; also natal teeth	
Pseudofolliculitis barbae	Risk factor	*KRT75*	1A	Inflammatory papules due to short curled hairs penetrating back into skin	38
Monilethrix	AD	*KRT81, KRT83, KRT86*	Helix termination (*KRT86* > *KRT81* > *KRT83*) & initiation (*KRT86*) motifs	Fragile, "beaded" hairs; perifollicular hyperkeratosis	69
"Pure" hair–nail type ectodermal dysplasia	AR	*KRT85*	V1 (more severe phenotype), V2	Hypotrichosis; nail dystrophy	63
White sponge nevus	AD	*KRT4, KRT13*	Helix initiation > termination motifs	White plaques of the oral mucosa > other epithelia	

Table 56.5 Genotype–phenotype correlations in mucocutaneous disorders caused by mutations in keratin genes. Also see Fig. 56.5. AD, autosomal dominant; AR, autosomal recessive; EBS, epidermolysis bullosa simplex; H1, homologous subdomain 1; KRT, keratin; L12/L2, linker segments (non-helical); PPK, palmoplantar keratoderma; V1, variable head domain; V2, variable tail domain; 1A/1B/2A/2B, α-helical rod domain segments.

mild scaling or no phenotype, those with homozygous or compound heterozygous mutations have more severe ichthyosis vulgaris with dry, scaly skin and a substantially altered cutaneous barrier.

In addition to ichthyosis vulgaris, loss-of-function mutations in filaggrin are also a major predisposing factor for atopic dermatitis. Approximately 20–50% of patients with atopic dermatitis have at least one filaggrin null allele. Furthermore, individuals who carry filaggrin mutations and develop atopic dermatitis are also predisposed to the subsequent onset of asthma. This suggests that epicutaneous sensitization and inflammation of the skin in the context of an abnormal epidermal barrier may play a role in later development of airway hyperreactivity (see Ch. 12).

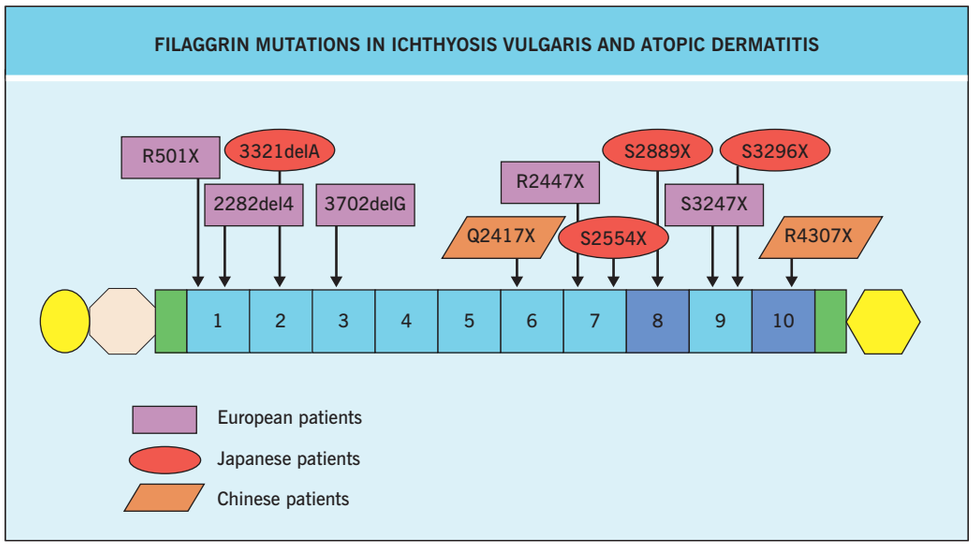


Fig. 56.9 Filaggrin loss-of-function variants in ichthyosis vulgaris and atopic dermatitis. The filaggrin protein consists of several domains: an S100 Ca^{2+}-binding domain (yellow oval), a B-domain (beige octagon), two imperfect filaggrin repeats (green rectangles), 10 filaggrin repeats (blue numbered rectangles; some individuals have two copies of repeat 8 and/or 10), and a C-terminal domain (yellow hexagon). Mutations in filaggrin that have been identified in patients with ichthyosis vulgaris and atopic dermatitis are indicated.

CONCLUSION

In recent years, we have made great progress towards understanding the structure and function of the epidermis. The challenge is now to better elucidate the gene regulatory mechanisms and cell signaling pathways that are required for the development and maintenance of this organ. The identification of epigenetic factors and modifier genes will help to explain phenotypic variations and establish more precise genotype–phenotype correlations. This knowledge will also form the foundation for the development of new therapeutic strategies for the treatment of acquired and inherited diseases of the skin.

REFERENCES

1. Steinert PM. The complexity and redundancy of epithelial barrier function. J Cell Biol. 2000;151:F5–8.
2. Segre J. Complex redundancy to build a simple epidermal permeability barrier. Curr Opin Cell Biol. 2003;15:776–82.
3. Schweizer J, Bowden PE, Coulombe PA, et al. New consensus nomenclature for mammalian keratins. J Cell Biol. 2006;174:169–74.
4. Steinert PM. Structure, function, and dynamics of keratin intermediate filaments. J Invest Dermatol. 1993;100:729–34.
5. Tong X, Coulombe PA. Keratin 17 modulates hair follicle cycling in a TNFalpha-dependent fashion. Genes Dev. 2006;20:1353–64.
6. Chen J, Cheng X, Merched-Sauvage M, et al. An unexpected role for keratin 10 end domains in susceptibility to skin cancer. J Cell Sci. 2006;119:5067–76.
7. Meng Y, Wu Z, Yin X, et al. Keratin 18 attenuates estrogen receptor alpha-mediated signaling by sequestering LRP16 in cytoplasm. BMC Cell Biol. 2009;10:96.
8. Russell D, Ross H, Lane EB. ERK involvement in resistance to apoptosis in keratinocytes with mutant keratin. J Invest Dermatol. 2010;130:671–81.
9. Gilbert S, Ruel A, Loranger A, et al. Switch in Fas-activated death signaling pathway as result of keratin 8/18-intermediate filament loss. Apoptosis. 2008;13:1479–93.
10. Vijayaraj P, Kroeger C, Reuter U, et al. Keratins regulate yolk sac hematopoiesis and vasculogenesis through reduced BMP-4 signaling. Eur J Cell Biol. 2010;89:299–306.
11. Swensson O, Langbein L, McMillan JR, et al. Specialized keratin expression pattern in human ridged skin as an adaptation to high physical stress. Br J Dermatol. 1998;139:767–75.
12. Koster MI, Roop DR. Sorting out the p63 signaling network. J Invest Dermatol. 2008;128:1617–19.
13. Watt FM, Estrach S, Ambler CA. Epidermal Notch signalling: differentiation, cancer and adhesion. Curr Opin Cell Biol.2008;20:171–9.
14. Bikle DD, Oda Y, Xie Z. Calcium and 1,25(OH)2D: interacting drivers of epidermal differentiation. J Steroid Biochem Mol Biol. 2004;89–90:355–60.
15. Yuspa SH, Kilkenny AE, Steinert PM, et al. Expression of murine epidermal differentiation markers is tightly regulated by restricted extracellular calcium concentrations in vitro. J Cell Biol. 1989;109:1207–17.
16. Denning MF. Epidermal keratinocytes: regulation of multiple cell phenotypes by multiple protein kinase C isoforms. Int J Biochem Cell Biol. 2004;36:1141–6.
17. Tu CL, Oda Y, Komuves L, et al. The role of the calcium-sensing receptor in epidermal differentiation. Cell Calcium. 2004;35:265–73.
18. Koster MI, Roop DR. Mechanisms regulating epithelial stratification. Annu Rev Cell Dev Biol. 2007;23:93–113.
19. Schmidt A, Koch PJ. Desmosomes: just cell adhesion or is there more? Cell Adh Migr. 2007;1:28–32.
20. Franke WW. Discovering the molecular components of intercellular junctions – a historical view. Cold Spring Harb Perspect Biol. 2009;1:a003061.
21. Chitaev NA, Troyanovsky SM. Direct Ca2+-dependent heterophilic interaction between desmosomal cadherins, desmoglein and desmocollin, contributes to cell-cell adhesion. J Cell Biol. 1997;138:193–201.
22. Spindler V, Heupel WM, Efthymiadis A, et al. Desmocollin 3-mediated binding is crucial for keratinocyte cohesion and is impaired in pemphigus. J Biol Chem. 2009;284:30556–64.
23. Ihrie RA, Marques MR, Nguyen BT, et al. Perp is a p63-regulated gene essential for epithelial integrity. Cell. 2005;120:843–56.
24. Bass-Zubek AE, Godsel LM, Delmar M, et al. Plakophilins: multifunctional scaffolds for adhesion and signaling. Curr Opin Cell Biol. 2009;21:708–16.
25. Garrod D, Chidgey M. Desmosome structure, composition and function. Biochim Biophys Acta. 2008;1778:572–87.
26. Nanba D, Hieda Y, Nakanishi Y. Remodeling of desmosomal and hemidesmosomal adhesion systems during early morphogenesis of mouse pelage hair follicles. J Invest Dermatol. 2000;114:171–7.
27. Bolling MC, Jonkman MF. Skin and heart: une liaison dangereuse. Exp Dermatol. 2009;18:658–68.
28. Stanley JR, Amagai M. Pemphigus, bullous impetigo, and the staphylococcal scalded-skin syndrome. N Engl J Med. 2006;355:1800–10.
29. Hardy MH, Vielkind U. Changing patterns of cell adhesion molecules during mouse pelage hair follicle development. 1. Follicle morphogenesis in wild-type mice. Acta Anat (Basel). 1996;157:169–82.
30. Garcia-Gras E, Lombardi R, Giocondo MJ, et al. Suppression of canonical Wnt/beta-catenin signaling by nuclear plakoglobin recapitulates phenotype of arrhythmogenic right ventricular cardiomyopathy. J Clin Invest. 2006;116:2012–21.
31. Schluter H, Moll I, Wolburg H, et al. The different structures containing tight junction proteins in epidermal and other stratified epithelial cells, including squamous cell metaplasia. Eur J Cell Biol. 2007;86:645–55.
32. McMillan JR, Akiyama M, Shimizu H. Epidermal basement membrane zone components: ultrastructural distribution and molecular interactions. J Dermatol Sci. 2003;31:169–77.
33. Short K, Wiradjaja F, Smyth I. Let's stick together: the role of the Fras1 and Frem proteins in epidermal adhesion. IUBMB Life. 2007;59:427–35.
34. Fine JD, Eady RA, Bauer EA, et al. The classification of inherited epidermolysis bullosa (EB): Report of the Third International Consensus Meeting on Diagnosis and Classification of EB. J Am Acad Dermatol. 2008;58:931–50.
35. Muller FB, Kuster W, Wodecki K, et al. Novel and recurrent mutations in keratin KRT5 and KRT14 genes in epidermolysis bullosa simplex: implications for disease phenotype and keratin filament assembly. Hum Mutat. 2006;27:719–20.
36. Oji V, Tadini G, Akiyama M. Revised nomenclature and classification of inherited ichthyoses: Results of the First Ichthyosis Consensus Conference in Sorèze 2009. J Am Acad dermatol. 2010;63:607–41.
37. Smith F. The molecular genetics of keratin disorders. Am J Clin Dermatol. 2003;4:347–64.
38 Omary MB, Ku NO, Strnad P, et al. Toward unraveling the complexity of simple epithelial keratins in human disease. J Clin Invest. 2009;119:1794–805.
39. McGrath JA, Uitto J. The filaggrin story: novel insights into skin-barrier function and disease. Trends Mol Med. 2008;14:20–7.

Ichthyoses, Erythrokeratodermas and Related Disorders

57

Gabriele Richard and *Franziska Ringpfeil*

Chapter Contents

Ichthyoses 840
- Ichthyosis vulgaris 840
- Steroid sulfatase deficiency 843
- Epidermolytic ichthyosis 845
- Superficial epidermolytic ichthyosis 847
- Ichthyosis en confetti 848
- Ichthyosis hystrix Curth–Macklin 848
- Ichthyosis hystrix 848
- Collodion baby 849
- Lamellar ichthyosis 850
- Congenital ichthyosiform erythroderma 851
- Harlequin ichthyosis 855
- Comèl–Netherton syndrome 857
- Sjögren–Larsson syndrome 859
- Neutral lipid storage disease with ichthyosis 860
- Trichothiodystrophy with ichthyosis 861
- Refsum disease 862
- Other ichthyoses 862

Erythrokeratodermas 862
- Erythrokeratodermia variabilis 862
- Progressive symmetric erythrokeratoderma 863
- Keratitis– ichthyosis–deafness syndrome 864

X-linked dominant ichthyosiform disorders 866
- CHILD syndrome 866
- Conradi–Hünermann–Happle syndrome 867

Key features

- Ichthyoses and erythrokeratodermas are clinically and etiologically heterogeneous groups of disorders of cornification
- Ichthyoses are characterized by scaling of the skin in a widespread distribution
- Erythrokeratodermas feature discrete areas of erythema and hyperkeratosis, usually without substantial scale
- Most inherited ichthyoses and erythrokeratodermas are evident at birth or manifest in infancy
- Clinical features, pattern of inheritance and structural, biochemical and molecular abnormalities help to differentiate these disorders
- Therapy is symptomatic and primarily aimed at reducing hyperkeratosis. Topical management consists of emollients, keratolytics and retinoids
- Many, but not all, disorders respond well to oral retinoids. Treatment is initiated at low doses and titrated to response. Benefits and side effects must be carefully considered because of the chronic nature of these conditions

Ichthyoses and erythrokeratodermas are disorders of cornification in which abnormal differentiation and desquamation of the epidermis result in a defective epidermal barrier. Ichthyoses represent a large clinically and etiologically heterogeneous group of conditions that feature generalized scaling of the skin (Table 57.1). Erythrokeratodermas are characterized by circumscribed areas of erythema and hyperkeratosis without obvious scaling. Willan introduced the term "ichthyosis", derived from the Greek root "*ichthy*" meaning fish, in his textbook of dermatology in 1808[1]. Since then, nomenclature and nosology of congenital ichthyoses has continuously evolved, including a confusing medley of different terms (e.g. descriptive names, eponyms, synonyms) and classification systems.

Milestones in recognizing distinct entities include the description of harlequin ichthyosis in the nineteenth century, separation of the bullous and non-bullous types of ichthyosis by Brocq (who also coined the name "congenital ichthyosiform erythroderma") in the early 20th century[2], and differentiation between autosomal dominant "epidermolytic hyperkeratosis" and autosomal recessive "lamellar ichthyosis" by Frost and Van Scott in 1966[3]. Alibert mentioned the autosomal dominant inheritance of ichthyosis vulgaris as early as 1806[4]. X-linked ichthyosis, despite several earlier reports, was only fully recognized in Wells and Kerr's study in 1966[5], followed by the identification of steroid sulfatase deficiency in the 1970s[6]. Advances in the molecular etiology and biology of ichthyoses and erythrokeratodermas have provided tools to categorize these disorders of cornification, at least in part, on the basis of their underlying genetic defects. An international group of clinical and research experts recently developed a revised nomenclature and classification system for ichthyoses and other disorders of cornification, incorporating molecular causes as well as functional aspects of disease pathogenesis[7].

Establishing the correct diagnosis in a patient with ichthyosis is a prerequisite for making prognostic predictions, planning therapy and offering genetic counseling. This may pose a considerable challenge, as these disorders are uncommon and have overlapping clinical spectra. However, a variety of clinical and laboratory-based clues can aid in making the diagnosis (Table 57.2).

In general, it is helpful to determine whether an ichthyosis presented at birth (e.g. as a collodion baby) or later in life and whether manifestations are limited to the skin or are part of a multisystem disorder. The quality and distribution of the scale as well as the presence or absence of erythroderma, blistering and abnormalities of cutaneous adnexa are other useful clinical features. A thorough family history is essential for recognizing the inheritance pattern, and examination of both parents (even in a seemingly sporadic case) may reveal valuable diagnostic hints such as an epidermal nevus representing a mosaic presentation of epidermolytic ichthyosis. Patients whose parents are clinically unaffected may have a recessive ichthyosis (especially in the setting of consanguinity and/or affected siblings), a dominant ichthyosis due to a "new" mutation, or (for male patients) an X-linked recessive ichthyosis (where their mother may be an asymptomatic carrier and male relatives could potentially be affected). A few disorders can be recognized based on characteristic histopathologic and ultrastructural features, such as epidermolytic ichthyosis and ichthyosis hystrix Curth–Macklin. Laboratory studies suggest the diagnosis in other conditions, including steroid sulfatase deficiency (steroid sulfatase enzyme analysis) and neutral lipid storage disease (lipid vacuoles in circulating leukocytes) (see Table 57.2).

This diagnostic approach allows the clinician to identify many ichthyoses based on their key features. For conditions with a known molecular etiology, genetic testing can confirm the diagnosis, allow more precise genetic counseling and provide the basis for prenatal testing.

FEATURES OF SELECTED ICHTHYOSES AND ERYTHROKERATODERMAS								
Diagnosis	**Gene**	**Chromosomal location**	**Mode of inheritance**	**Incidence**	**Onset**	**Primary cutaneous features**	**Associated features**	**Diagnosis**
COMMON ICHTHYOSES								
Ichthyosis vulgaris	*FLG*	1q21.3	Autosomal semi-dominant	1:250	Infancy/ childhood	Fine, adherent scales on extremities and trunk with sparing of flexures; larger scale on lower legs; hyperlinear palms/soles, furrowed heels	Keratosis pilaris; atopic diathesis	Clinical; diminished/ absent stratum granulosum; absent/ reduced FLG immunostaining; molecular testing
Steroid sulfatase deficiency (X-linked recessive ichthyosis)	*STS*	Xp22.31	X-linked recessive	1:2000–1:6000 boys/men	Infancy	Fine to large, dark, adherent scales on extremities, trunk, neck and lateral face	Corneal opacities; cryptorchidism *Female carriers*: corneal opacities; prolonged labor with affected child	Lipoprotein electrophoresis (increased mobility of β-fraction); plasma cholesterol sulfate increased; decreased steroid sulfatase activity in leukocytes; FISH, array CGH, other molecular testing
NONSYNDROMIC AUTOSOMAL RECESSIVE CONGENITAL ICHTHYOSES								
Lamellar ichthyosis (LI)	*TGM1* *ABCA12** *CYP4F22**	14q12 2q35 19p13.12	Autosomal recessive†	1:200 000–1:300 000	Birth	Frequently collodion membrane at birth; large, thick, plate-like brown scales in generalized distribution; absent or mild erythroderma; variable palm/sole involvement	Heat intolerance; frequent scarring alopecia, ectropion, eclabium	Clinical; electron microscopy; *in situ* transglutaminase-1 expression and activity assay; molecular testing
Congenital ichthyosiform erythroderma (CIE)	*TGM1* *ALOXE3*‡ *ALOX12B*‡ *NIPAL4 (ICHTHYIN)*‡ *PNPLA1*‡	14q12 17p13.1 17p13.1 5q33.3 6p21.31	Autosomal recessive†	1:100 000–1:200 000	Birth	Frequently collodion membrane at birth; fine, white scale in generalized distribution; erythroderma; variable palm/sole involvement	Heat intolerance; variable scarring alopecia, ectropion	See lamellar ichthyosis; molecular testing
Harlequin ichthyosis	*ABCA12*	2q35	Autosomal recessive	Rare	Birth	Very thick, yellow–brown plates of scale that tightly encase the neonate; large, deep, bright red fissures; extreme ectropion, eclabium and ear deformities; survivors develop severe CIE-like phenotype	Premature delivery; often neonatal death due to sepsis or respiratory insufficiency	Clinical; molecular testing
KERATINOPATHIC ICHTHYOSES (also include ichthyosis en confetti – see text)								
Epidermolytic ichthyosis (bullous CIE)	*KRT1* *KRT10*	12q13.13 17q21.2	Autosomal dominant (very rarely autosomal recessive)	1:300 000	Birth	*At birth:* erythroderma, blistering and erosions *Later:* hyperkeratosis with cobblestone pattern (most prominent over joints), ridging of the flexures; generalized or localized; variable degree of erythroderma, palmoplantar involvement and blistering	Frequent skin infections; malodor; gait and posture abnormalities	Clinical; histopathology; molecular testing
Superficial epidermolytic ichthyosis (ichthyosis bullosa of Siemens)	*KRT2*	12q13.13	Autosomal dominant	Rare	Birth	Erythroderma and blistering at birth; later, hyperkeratosis with flexural accentuation, 'molting' of the skin; palms and soles spared		Clinical; histopathology; molecular testing
Ichthyosis hystrix Curth–Macklin	*KRT1*	12q13.13	Autosomal dominant	Rare	Birth	Mild to severe, mutilating palmoplantar keratoderma; hyperkeratosis with verrucous, cobblestone or hystrix-like pattern on extremities and trunk	Pseudoainhum; digital contractures	Clinical; electron microscopy; molecular testing

*Also occasionally associated with CIE or intermediate LI/CIE phenotypes; a CIE-like phenotype is also seen in harlequin ichthyosis survivors.
†There are also rare reports of autosomal dominant inheritance of LI or CIE phenotypes (occasionally with a collodion membrane at birth) with unknown genetic bases.
‡Also occasionally associated with mild LI or intermediate LI/CIE phenotypes.

Table 57.1 Features of selected ichthyoses and erythrokeratodermas. CGH, comparative genomic hybridization; FISH, fluorescence *in situ* hybridization.

Continued

FEATURES OF SELECTED ICHTHYOSES AND ERYTHROKERATODERMAS								
Diagnosis	**Gene**	**Chromosomal location**	**Mode of inheritance**	**Incidence**	**Onset**	**Primary cutaneous features**	**Associated features**	**Diagnosis**
SYNDROMIC ICHTHYOSES								
Comèl–Netherton syndrome	*SPINK5*	5q33.1	Autosomal recessive	1:50 000–1:300 000	Birth/infancy	Congenital erythroderma and peeling; two principal phenotypes: ichthyosis linearis circumflexa and CIE-like; pruritus and eczematous plaques are common	Trichorrhexis invaginata and other hair shaft abnormalities; highly elevated serum IgE; neonatal temperature instability, electrolyte imbalance, failure to thrive; recurrent infections; food and other allergies; nonspecific aminoaciduria	Clinical; psoriasiform histopathology; light microscopic hair shaft analysis; serum IgE measurement; electron microscopy (ruthenium tetroxide); molecular testing
Sjögren–Larsson syndrome	*ALDH3A2*	17p11.2	Autosomal recessive	1:250 000	Birth	Fine to plate-like scaling or non-scaling hyperkeratosis; favors abdomen, neck, flexures; lichenification; pruritus	Spastic di- and tetraplegia; mental retardation; perifoveal glistening white dots; white matter disease of the brain	Fatty aldehyde hydrogenase activity assay in cultured fibroblasts; molecular testing (preferred method)
Neutral lipid storage disease with ichthyosis	*ABHD5 (CGI-58)*	3p21.33	Autosomal recessive	Rare	Birth	Generalized fine, white scales with variable erythema	Developmental delay; hepatomegaly; myopathy; hearing impairment; cataracts; lipid-containing vacuoles in leukocytes	Peripheral blood smear to detect lipid vacuoles; oil stains of frozen skin biopsy specimens; molecular testing
Trichothiodystrophy (Tay syndrome, (P) IBIDS)	*ERCC2* *ERCC3* *GTF2H5* *C70RF11***	19q13.32 2q14.3 6q25.3 7p14.1	Autosomal recessive	Rare	Birth	Generalized scaling with absent or minimal erythroderma, except during infancy	Ichthyosis; brittle hair and nails; intellectual impairment; decreased fertility; short stature; photosensitivity	Clinical; microscopic hair shaft examination under polarizing light; analysis of hair sulfur/cysteine content
Refsum disease	*PHYH* *PEX7*	10p13 6q23.3	Autosomal recessive	Rare	Childhood to adulthood	Fine, white scales on extremities and trunk, resembling ichthyosis vulgaris	Peripheral neuropathy; cranial nerve dysfunction (deafness, anosmia); cerebellar ataxia; atypical retinitis pigmentosa; cardiomyopathy	Increased plasma phytanic acid; phytanoyl-CoA hydroxylase activity assay in cultured fibroblasts; molecular testing
ERYTHROKERATODERMAS								
Erythrokeratodermia variabilis	*GJB3* *GJB4*	1p34.3 1p34.3	Autosomal dominant (very rarely autosomal recessive)	Rare	Birth/infancy	Transient, variable erythematous patches; more stable, geographic, hyperkeratotic plaques over knees, elbows, Achilles tendons, extremities, buttocks, lateral trunk; face and scalp often spared; less common generalized hyperkeratosis; palmoplantar keratoderma in ~50% of patients	Burning or stinging sensation preceding or accompanying erythema	Clinical, particularly history or presence of transient erythema; molecular testing
Progressive symmetric erythrokeratoderma	(*LOR*) (*GJB4*)	(1q21.3) (1p34.3)	Autosomal dominant or recessive	Rare	Infancy/childhood	Fixed, slowly progressive, erythematous, hyperkeratotic plaques with sharp, figurate borders; on cheeks, over knees, elbows, extremities, rarely trunk; palmoplantar keratoderma common		Clinical

**Mutations in this gene are not associated with ichthyosis or photosensitivity.

Table 57.1 Features of selected ichthyoses and erythrokeratodermas (cont'd).

Continued

FEATURES OF SELECTED ICHTHYOSES AND ERYTHROKERATODERMAS								
Diagnosis	**Gene**	**Chromosomal location**	**Mode of inheritance**	**Incidence**	**Onset**	**Primary cutaneous features**	**Associated features**	**Diagnosis**
Keratitis–ichthyosis–deafness syndrome	*GJB2 (GJB6)*	13q12.11 (13q12.11)	Autosomal dominant	Rare	Birth/ infancy	Transient neonatal erythroderma; erythematous, hyperkeratotic plaques with well-demarcated, borders on face and extremities; follicular keratoses; thickening of the skin with an appearance of "coarse-grained leather"; stippled palmoplantar keratoderma	Congenital sensorineural hearing impairment; progressive keratitis with corneal neovascularization, conjunctivitis; recurrent mucocutaneous infections, especially with *Candida albicans*; increased susceptibility to oral and cutaneous squamous cell carcinoma; nail, hair and dental anomalies	Clinical; molecular testing
SYNDROMIC X-LINKED DOMINANT ICHTHYOSIFORM CONDITIONS								
CHILD syndrome	*NSDHL*	Xq28	X-linked dominant	Rare	Birth	At birth, unilateral erythema and waxy, yellowish adherent scale; later, verrucous; hyperkeratosis of variable extent, with affinity for skin folds	Ipsilateral skeletal hemidysplasia, organ hypoplasia	Clinical; molecular testing
Conradi–Hünermann–Happle syndrome	*EBP*	Xp11.23	X-linked dominant	Rare	Birth	At birth, ichthyosiform erythroderma with feathery, adherent scale along Blaschko's lines; later, follicular atrophoderma along Blaschko's lines	Unilateral cataracts; chondrodysplasia punctata (during infancy); asymmetric skeletal abnormalities; patchy scarring alopecia	Clinical; epiphyseal stippling on X-rays during infancy; accumulation of plasma 8(9) cholesterol; molecular testing

Table 57.1 Features of selected ichthyoses and erythrokeratodermas (cont'd).

Despite advances in our understanding of the pathomechanisms underlying ichthyoses, effective therapies are available for only a small subset of these conditions. Hopefully, ongoing research will lead to the development of targeted treatments that will be of greater benefit to ichthyosis patients. Patient organizations such as the Foundation for Ichthyosis and Related Skin Types (FIRST; www.scalyskin.org) can provide valuable support to affected individuals and their families.

ICHTHYOSES

ICHTHYOSIS VULGARIS

Synonyms: ■ Ichthyosis simplex ■ Autosomal dominant ichthyosis

History

In 1806, Alibert[4] described "ichthyose nacrée", which represented the first well-documented report of ichthyosis vulgaris. In 1966, Wells and Kerr[5] separated autosomal dominant and X-linked recessive forms of ichthyosis and delineated their clinical and epidemiological features.

Epidemiology

Ichthyosis vulgaris is the most common disorder of cornification, with an estimated prevalence of 1 in 250 individuals[5]. It is inherited in an autosomal semidominant manner, with mild ichthyosis in individuals with heterozygous filaggrin mutations and more severe ichthyosis in those with mutations in both filaggrin alleles. There is incomplete penetrance in heterozygotes and variable phenotypic expression between and within families.

Pathogenesis

Loss-of-function mutations in the filaggrin gene (*FLG*) underlie ichthyosis vulgaris (see Fig. 56.9)[8]. *FLG* encodes profilaggrin, a major component of the keratohyalin granules located in the granular layer of the epidermis. During keratinocyte terminal differentiation, profilaggrin is cleaved into filaggrin peptides, which aggregate keratin intermediate filaments. These complexes are cross-linked to the cornified cell envelope (see Figs 56.1 & 56.2) and are responsible for proper formation of compact squamous cells. Filaggrin is eventually degraded into water-retaining amino acids that serve as a natural moisturizer. Filaggrin deficiency results in impaired squamous cell formation, transepidermal water loss, and a propensity to develop inflammatory responses upon exposure to allergens and haptens; this explains the association of *FLG* mutations with atopic dermatitis as well as ichthyosis vulgaris (see Ch. 12). The flaky-tail mouse (caused by loss-of-function mutations in the murine *Flg* gene) is an animal model that serves as a tool for the study of ichthyosis vulgaris.

Clinical Features

Ichthyosis vulgaris is usually not evident at birth. Dry skin and mild to moderate scaling appear during infancy or early childhood. Fine, white, flaky scales develop on the extremities (Fig. 57.1), especially the extensor surfaces. The groin and flexural areas are spared because of increased humidity in those regions. On the lower legs, the scales are usually larger with an adherent center and detached, outward-turning edges. Mild hyperkeratosis of the palms and soles leading to accentuated skin markings (hyperlinearity) is common (Fig. 57.2).

In more severe disease, scaling occurs on the trunk, scalp, forehead and cheeks. Palmoplantar involvement is also more pronounced and often results in furrows or painful fissures of the heels.

CLUES IN THE DIAGNOSIS OF ICHTHYOSES AND ERYTHROKERATODERMAS

Initial evaluation of a neonate/young infant with a collodion membrane/ichthyosis may include the following*:

- Complete blood count, electrolytes, hepatic panel, immunoglobulin levels (including IgE)
- Peripheral blood smear (to evaluate for vacuoles in leukocytes)
- Light microscopic examination of clipped hairs (including eyebrow hairs)
- Hearing screen (e.g. via the auditory brainstem response or otoacoustic emission test)
- Ophthalmologic examination
- Consider skin biopsy, especially if bullae (to assess for epidermolysis) or following resolution of a collodion membrane (e.g. for transglutaminase-1 immunostaining)
- Consider X-rays to evaluate epiphyses, especially if ichthyosiform lesions are in a mosaic distribution pattern

Feature	Disorder
Anosmia	• Refsum disease • Steroid sulfatase deficiency in a contiguous gene deletion syndrome on Xp (X-linked ichthyosis + Kallmann syndrome)
Arthrogryposis†	• Gaucher syndrome type 2 • Arthrogryposis–renal dysfunction–cholestasis (ARC) syndrome
Ataxia	• Refsum disease • Neutral lipid storage disease • Erythrokeratodermia with ataxia
Bullae/blisters†	• Epidermolytic ichthyosis • Superficial epidermolytic ichthyosis (ichthyosis bullosa of Siemens)
Di- or tetraplegia	• Sjögren–Larsson syndrome • Rhizomelic chondrodysplasia punctata
Diarrhea, chronic†	• MEDNIK syndrome
Elevated serum IgE†	• Netherton syndrome • Generalized inflammatory peeling skin syndrome
Erythroderma†	• Congenital ichthyosiform erythroderma • Lamellar ichthyosis (mild) • Harlequin ichthyosis (survivors) • Netherton syndrome • Generalized inflammatory peeling skin syndrome • Trichothiodystrophy • CHILD syndrome (unilateral) • Conradi–Hünermann–Happle syndrome • Neutral lipid storage disease • Sjögren–Larsson syndrome • Epidermolytic ichthyosis (during infancy) • Steroid sulfatase deficiency (mild during infancy)
Fast-moving β-lipoprotein fraction on electrophoresis†	• Steroid sulfatase deficiency
Hair shaft abnormalities†	
"Tiger-tail" hair‡	• Trichothiodystrophy
Trichorrhexis invaginata	• Netherton syndrome
Trichorrhexis nodosa	• Trichothiodystrophy • Netherton syndrome
Pili torti	• Arthrogryposis–renal dysfunction–cholestasis (ARC) syndrome
Hyperlinear palms and soles	• Ichthyosis vulgaris • Refsum disease • CYP4F22-related congenital ichthyosis
Hypernatremic dehydration in neonates†	• Netherton syndrome • Harlequin ichthyosis • Collodion babies (with various underlying disorders)
Hypogonadism/cryptorchidism†	• Steroid sulfatase deficiency • Multiple sulfatase deficiency • Trichothiodystrophy without photosensitivity
Hypotrichosis†	• KID syndrome (occasionally atrichia) • Ichthyosis–hypotrichosis syndrome • Ichthyosis–hypotrichosis–sclerosing cholangitis syndrome • IFAP syndrome (often atrichia) • Trichothiodystrophy • Netherton syndrome • Arthrogryposis–renal dysfunction–cholestasis (ARC) syndrome

*With additional studies as indicated based on the clinical presentation; see Figure 10.10 for other considerations in an erythrodermic infant.
†Finding often evident in the neonatal period or early infancy.
‡Also seen in normal infants, but usually not in all hairs.

Table 57.2 Clues in the diagnosis of ichthyoses and erythrokeratodermas. CHILD, congenital hemidysplasia with ichthyosiform erythroderma and limb defects; IFAP, ichthyosis follicularis with atrichia and photophobia; KID, keratitis–ichthyosis–deafness; MEDNIK, mental retardation, enteropathy, deafness, peripheral neuropathy, ichthyosis, and keratodermia.

Continued

CLUES IN THE DIAGNOSIS OF ICHTHYOSES AND ERYTHROKERATODERMAS	
Feature	**Disorder**
Hystrix-like hyperkeratoses	• Epidermolytic ichthyosis • Ichthyosis hystrix Curth–Macklin • Erythrokeratodermia variabilis • KID syndrome
Increased susceptibility to infections†	• Netherton syndrome • Generalized inflammatory peeling skin syndrome • KID syndrome • Trichothiodystrophy
Increased susceptibility to malignancies	
Testicular cancer > acute lymphoblastic leukemia	• Steroid sulfatase deficiency
Squamous cell carcinoma	• KID syndrome (cutaneous and oral) • (Congenital ichthyosiform erythroderma) • (Netherton syndrome)
Malignant proliferating pilar tumors	• KID syndrome
Linear distribution along Blaschko's lines† (see also Ch. 62)	• Epidermolytic nevus • CHILD syndrome • Conradi–Hünermann–Happle syndrome
Liver dysfunction, hepatomegaly†	• Neutral lipid storage disease • Ichthyosis–hypotrichosis–sclerosing cholangitis syndrome • Gaucher disease • Arthrogryposis–renal dysfunction–cholestasis (ARC) syndrome
Mental retardation	• Sjögren–Larsson syndrome • Trichothiodystrophy • Multiple sulfatase deficiency • Rhizomelic chondrodysplasia punctata • CEDNIK syndrome • MEDNIK syndrome • Arthrogryposis–renal dysfunction–cholestasis (ARC) syndrome
Neuropathy	• Refsum disease • CEDNIK syndrome • MEDNIK syndrome
Ocular findings	
Cataracts† (variable onset)	• Refsum disease • Trichothiodystrophy • Rhizomelic chondrodysplasia punctata • Conradi–Hünermann–Happle syndrome (unilateral) • Neutral lipid storage disease
Corneal opacities	• Steroid sulfatase deficiency • Arthrogryposis–renal dysfunction–cholestasis (ARC) syndrome
Keratitis† (variable onset)	• KID syndrome • IFAP syndrome • Hereditary mucoepithelial dysplasia
Perifoveal glistening white dots† (variable onset)	• Sjögren–Larsson syndrome
Retinitis pigmentosa	• Refsum disease
Peeling skin	• Netherton syndrome • Superficial epidermolytic ichthyosis (ichthyosis bullosa of Siemens) • Generalized inflammatory peeling skin syndrome • Autosomal recessive exfoliative ichthyosis • Acral peeling skin syndrome
Photosensitivity	• Trichothiodystrophy
Sensorineural hearing impairment	• KID syndrome • Refsum disease • Neutral lipid storage disease • CHILD syndrome • Arthrogryposis–renal dysfunction–cholestasis (ARC) syndrome • CEDNIK syndrome • MEDNIK syndrome
Stippled epiphyses	• CHILD syndrome • Rhizomelic chondrodysplasia punctata • Conradi–Hünermann–Happle syndrome
Vacuoles in circulating blood cells	• Neutral lipid storage disease (leukocytes, especially neutrophils) • Ichthyosis–hypotrichosis–sclerosing cholangitis syndrome (eosinophils)

†Finding often evident in the neonatal period or early infancy.

Table 57.2 Clues in the diagnosis of ichthyoses and erythrokeratodermas (Cont'd). CEDNIK, cerebral dysgenesis, neuropathy, ichthyosis and keratoderma; CHILD, congenital hemidysplasia with ichthyosiform erythroderma and limb defects; IFAP, ichthyosis follicularis with atrichia and photophobia; KID, keratitis–ichthyosis–deafness; MEDNIK, mental retardation, enteropathy, deafness, peripheral neuropathy, ichthyosis, and keratodermia.

Fig. 57.1 Ichthyosis vulgaris. Fine white scales on the leg. *Courtesy, Julie V Schaffer, MD.*

Fig. 57.2 Hyperlinear palms in ichthyosis vulgaris. *Courtesy, SJ Bale, PhD, and JJ DiGiovanna, MD.*

Clinical symptoms (e.g. pruritus) and severity depend on season and climate, improving during the summer and with higher humidity, and worsening in a dry, cold environment. Although the ichthyosis may be progressive during childhood, it usually improves with age.

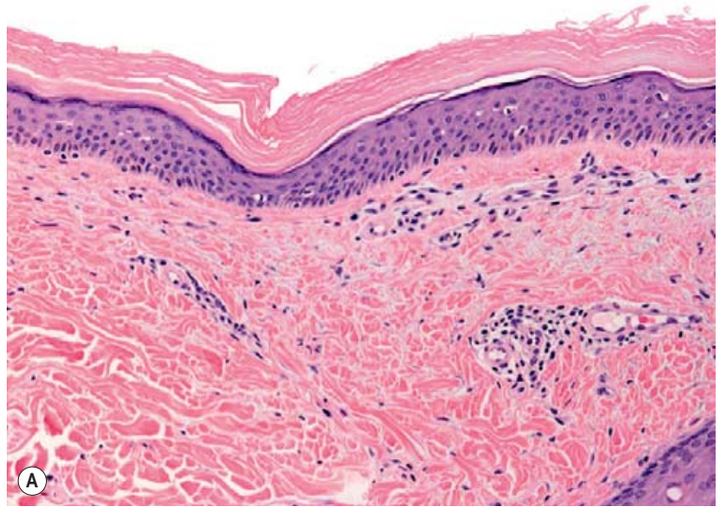
Ichthyosis vulgaris is frequently associated with keratosis pilaris and the atopic triad of asthma, hay fever and atopic dermatitis. The latter is encountered in at least 25–50% of patients with ichthyosis vulgaris and can obscure the characteristic sparing of the flexures. Conversely, approximately 10–15% of individuals with atopic dermatitis also have moderate to severe ichthyosis vulgaris.

Pathology

Mild orthokeratotic hyperkeratosis is seen and many (but not all) patients have an attenuated or diminished granular layer (Fig. 57.3A). Approximately 30–50% of affected individuals have no detectable granular layer and no keratohyalin granules by electron microscopy[9], while others have structural abnormalities in keratohyalin granules. Immunohistochemistry demonstrates diminished or absent filaggrin staining in most patients (Fig. 57.3B & C).

Differential Diagnosis

The border between dry skin (xerosis) and mild ichthyosis vulgaris is not clear-cut, and both can be associated with atopic dermatitis. In male patients, X-linked ichthyosis may be differentiated by larger, darker scales and involvement of the neck and other flexures; a maternal history of delayed or prolonged labor, cryptorchidism and the inheritance pattern can represent additional clues. Biochemical, array comparative genomic hybridization (CGH) or fluorescent *in situ* hybridization (FISH) testing can exclude steroid sulfatase deficiency. Acquired ichthyosis is distinguished by its development later in life and association with conditions such as malnutrition, infections (e.g. leprosy), neoplasms (e.g. lymphoma) and inflammatory disorders (e.g. sarcoidosis).



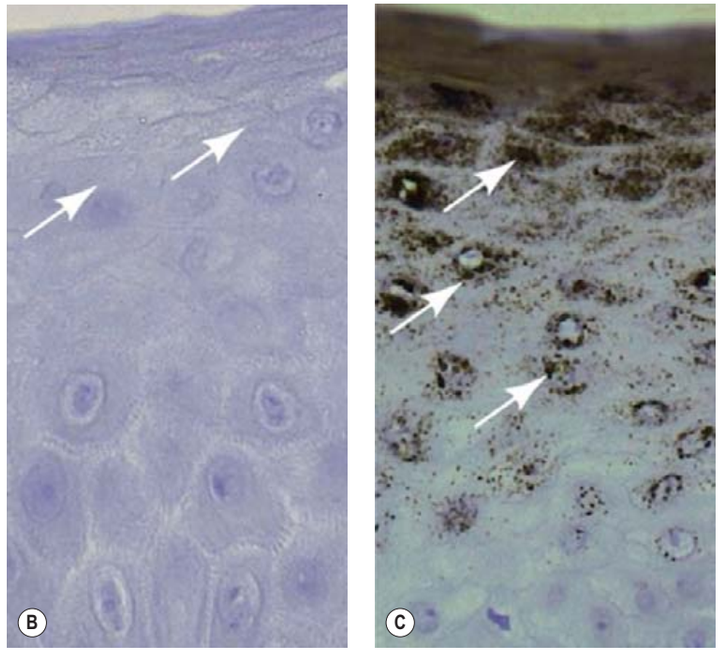


Fig. 57.3 Histologic features of ichthyosis vulgaris (IV). A Orthokeratotic hyperkeratosis and a diminished granular layer are evident. Immunostaining with an anti-filaggrin antibody demonstrates a complete absence of filaggrin in an IV patient homozygous for a deleterious *FLG* mutation (**B**), while filaggrin is strongly expressed throughout the granular layer in normal skin (**C**). *A, Courtesy, Lorenzo Cerroni, MD. B & C, Courtesy, WH Irwin McLean, PhD.*

Treatment

The mainstay of treatment is reduction of scaling through the use of emollients and humectants, and those containing ceramides together with other lipids may be especially effective. Preparations that contain urea or keratolytics such as α-hydroxy, lactic and salicylic acids are beneficial; with the latter, care must be taken to prevent salicylate toxicity. Topical retinoids may decrease scaling, but irritation of the skin limits their use. Vitamin D analogues seem ineffective. Systemic treatment with acitretin or isotretinoin is possible but rarely necessary. The use of moisturizing cleansers and humidifiers may also be helpful.

STEROID SULFATASE DEFICIENCY

Synonym: ▪ X-linked recessive ichthyosis

History

The first report of a type of ichthyosis occurring only in boys and men dates back to the beginning of the nineteenth century, but it was not until the 1920s that its X-linked recessive inheritance was clearly recognized. In 1966, the clinical features of this entity were distinguished from those of ichthyosis vulgaris[5]. The underlying steroid sulfatase deficiency was identified in the late 1970s.

Epidemiology

The worldwide incidence is between 1 in 2000 and 1 in 9500 male births. It is an X-linked recessive disorder that is transmitted by asymptomatic female carriers and almost exclusively affects boys and men.

Pathogenesis

Diminution or complete absence of steroid sulfatase activity is caused by a deletion of the entire *STS* gene on chromosome Xp22.31 in 90% of patients and inactivating mutations in others[10]. Steroid sulfatase deficiency results in impaired hydrolysis of cholesterol sulfate and dehydroepiandrosterone sulfate (DHEAS), with subsequent accumulation of cholesterol 3-sulfate in the epidermis. High levels of this metabolite can inhibit transglutaminase-1, explaining the partial overlap with lamellar ichthyosis and underscoring the pivotal role of transglutaminase-1 in formation of the cornified envelope and epidermal barrier.

In women pregnant with an affected fetus, steroid sulfatase deficiency in the fetal placenta causes low or absent levels of estrogen in the urine and amniotic fluid because of inadequate deconjugation of DHEAS (which is necessary for estrogen synthesis). As a result, labor often fails to initiate spontaneously or progress, due to insufficient dilation of the cervix. This can only be partially overcome by oxytocin administration, often necessitating cesarean section.

Clinical Features

In ~90% of affected boys, X-linked ichthyosis presents during the neonatal period with mild erythroderma and generalized peeling, often with exfoliation of large, translucent scales. The typical polygonal, dark-brown, adherent scales develop later during infancy and are distributed symmetrically on the extremities, trunk and neck (Fig. 57.4). The scales are occasionally grayish or white, and they tend to be larger on the lower extremities. The neck is almost invariably involved, which has resulted in the descriptive term "dirty neck disease" (Fig. 57.4D); other flexural areas may or may not be affected. Fine scaling of the scalp is frequently seen during early childhood but diminishes over time. The palms, soles and face are characteristically spared, with the exception of the preauricular area; some clinicians consider the latter to be a

Fig. 57.4 Steroid sulfatase deficiency. Large light-brown (**A**) and more prominent dark-brown (**B**) scales on the lower legs. **C** Smaller dark-brown scales on the trunk, with sparing of the skin folds. **D** Dark scales on the neck, sometimes referred to as a "dirty neck". *A–C, Courtesy, Julie V Schaffer, MD.*

pathognomonic feature[11]. The ichthyosis tends to improve in the summer, but (in contrast to ichthyosis vulgaris) does not significantly subside with age.

Asymptomatic corneal opacities occur in 10–50% of male patients and in some female carriers, but other ocular abnormalities such as deuteranopia (green color-blindness) are rare. Male patients have a 20-fold increased incidence of cryptorchidism and, independent of testicular maldescent, are thought to be at higher risk for developing testicular cancer and hypogonadism[12]. There have been rare reports of seizures, reactive psychological disorders, attention deficit disorder, developmental delay, pyloric hypertrophy, a congenital defect in the abdominal wall and acute lymphoblastic leukemia in patients with steroid sulfatase deficiency. Although steroid sulfatase activity is measurably reduced in 85% of female carriers, the remaining activity seems sufficient to prevent any skin manifestations.

Pathology

Histopathologic findings include hyperkeratosis or parakeratosis overlying a normal or slightly thickened granular layer. Follicular hyperkeratosis may be present. Electron microscopy shows an increased size and number of keratohyalin granules. In the stratum corneum, desmosomes are retained and cells contain a large number of melanosomes. Biochemical and cell kinetic studies show normal epidermal cell turnover and water homeostasis.

Other diagnostic tests

Array CGH, FISH, Southern blot and PCR-based analysis are available through many diagnostic laboratories and are useful for detecting the underlying genetic defect, which, when known in a female carrier, may also be utilized for prenatal diagnosis (via chorionic villi or amniotic fluid samples). However, non-invasive prenatal diagnosis through decreased serum estriol levels and the presence of non-hydrolyzed sulfated steroids in maternal urine is preferred. Accumulation of cholesterol sulfate can be detected indirectly by increased migration of the β-fraction in serum lipoprotein electrophoresis. It can also be measured directly by chromatography or spectrophotometry using epidermal scale, placental tissue or amniotic fluid. In addition, a biochemical assay is available to measure steroid sulfatase enzymatic activity in leukocytes, fibroblasts, keratinocytes or placental tissue.

Differential Diagnosis

Clinically, ichthyosis vulgaris is distinguished by sparing of flexural areas (including the neck) and an association with hyperlinear palms and keratosis pilaris. An identical cutaneous phenotype can be associated with X-linked recessive chondrodysplasia punctata and hypogonadotropic hypogonadism with anosmia (Kallmann syndrome) in male patients with a contiguous Xp microdeletion syndrome. Ichthyosis with hypogonadism (Rud syndrome) is probably not a distinct disorder but may result from submicroscopic deletions in the telomeric portion of the short arm of the X chromosome. Refined karyotyping, FISH or array CGH analysis is essential for detecting X;Y translocations and X chromosome deletions in patients who present with these additional findings.

Treatment

Topical humectants (in particular propylene glycol), keratolytics and retinoids are effective alone or in combination, whereas vitamin D analogues are disappointing and cause significant irritation. Systemic retinoids are rarely necessary.

EPIDERMOLYTIC ICHTHYOSIS

Synonyms: ■ Bullous congenital ichthyosiform erythroderma (Brocq) ■ Epidermolytic hyperkeratosis ■ Bullous ichthyosis

History

Nikolsky first recognized the characteristic histopathology of the bullous form of congenital ichthyosis in 1897[13], and Brocq differentiated between dry (non-bullous) and wet (bullous) forms of congenital ichthyosiform erythroderma in 1902[2]. Based on the distinctive histopathologic features of the epidermis, Frost and Van Scott[3] introduced the name "epidermolytic hyperkeratosis" for this autosomal dominant blistering form of congenital ichthyosis in 1966.

Epidemiology

Epidermolytic ichthyosis (EI) has an estimated worldwide prevalence of 1 in 200 000 to 1 in 300 000. It is generally an autosomal dominant disorder with complete penetrance, with rare reports of autosomal recessive inheritance. Both genders are affected equally. About 50% of all cases occur sporadically (reflecting new mutations).

Pathogenesis

EI is caused by heterozygous mutations in the genes encoding keratin 1 *(KRT1)* and keratin 10 *(KRT10)*[14]. These keratins are expressed in the differentiated spinous and granular layers of the epidermis, which are the sites of disease pathology in this disorder. *KRT1* mutations are usually associated with severe palmoplantar keratoderma, whereas *KRT10* mutations spare the palms and soles because this gene is not expressed in these locations[15]. Pathogenic mutations leading to non-conservative amino acid substitutions cluster at the boundaries of the α-helical rod region (mutational "hot spots" in the helix initiation and termination motifs; see Fig. 56.5)[14]. Mutations in other sites are uncommon and generally associated with a milder or unusual phenotype[14].

Mutations perturb keratin alignment, oligomerization and filament assembly, thus weakening the cytoskeleton, compromising the mechanical strength and cellular integrity of the epidermis, and leading to cytolysis and blistering. Epidermal acanthosis and hyperkeratosis result from hyperproliferation, decreased desquamation and other factors. The barrier function of the skin is markedly disturbed, leading to increased transepidermal water loss and bacterial colonization of the stratum corneum.

Clinical Features

EI presents at birth with erythroderma, peeling, erosions and widespread areas of denuded skin (Fig. 57.5A; see Ch. 34). Hyperkeratosis may be present, but it often develops later during infancy. Skin fragility, blistering and erythema decrease over time, and severe hyperkeratosis prevails (Fig. 57.5B–D). However, patients may still periodically shed large plates of superficial epidermis, revealing a tender, erythematous base. Ridges along skin lines are common in flexures (see Fig. 57.5D), while hyperkeratosis over the extensor surfaces of the joints often forms a cobblestone pattern (see Fig. 57.5C).

The clinical presentation varies considerably among patients and families, and six characteristic clinical patterns with or without palmoplantar involvement have been described[15]. Unusual clinical variants of EI include "cyclic ichthyosis with epidermolytic hyperkeratosis" and "annular epidermolytic ichthyosis", which are caused by distinct mutations outside the helix boundary regions of *KRT1* and *KRT10*, respectively[14].

EI is disfiguring and has tremendous impact on patients' quality of life and social interactions. Sepsis as well as fluid and electrolyte imbalances can be life-threatening in the neonatal period. Episodes of blistering and secondary skin infections are also problematic later in life. The disorder is accompanied by a pungent body odor, and it is occasionally associated with posture and gait abnormalities. Angular cheilitis and severe scalp involvement leading to encasement of hair shafts and hair loss are additional associated findings.

Epidermolytic nevi (mosaic epidermolytic ichthyosis)

The mosaic form of EI is characterized by unilateral or bilateral streaks of hyperkeratosis that follow the lines of Blaschko[16]. Extensive involvement with marked hyperkeratosis leading to protruding, porcupine-like spines has been referred to as "ichthyosis hystrix", but this is a descriptive term rather than the name of a distinct disorder. Epidermolytic nevi are caused by a postzygotic mutation in *KRT1* or *KRT10* that arises during embryogenesis. If this mutation involves gonadal cells, it can potentially be transmitted to the patient's offspring, resulting in full-blown, generalized disease[16]. Examination of both parents of a child with sporadic EI is therefore recommended.

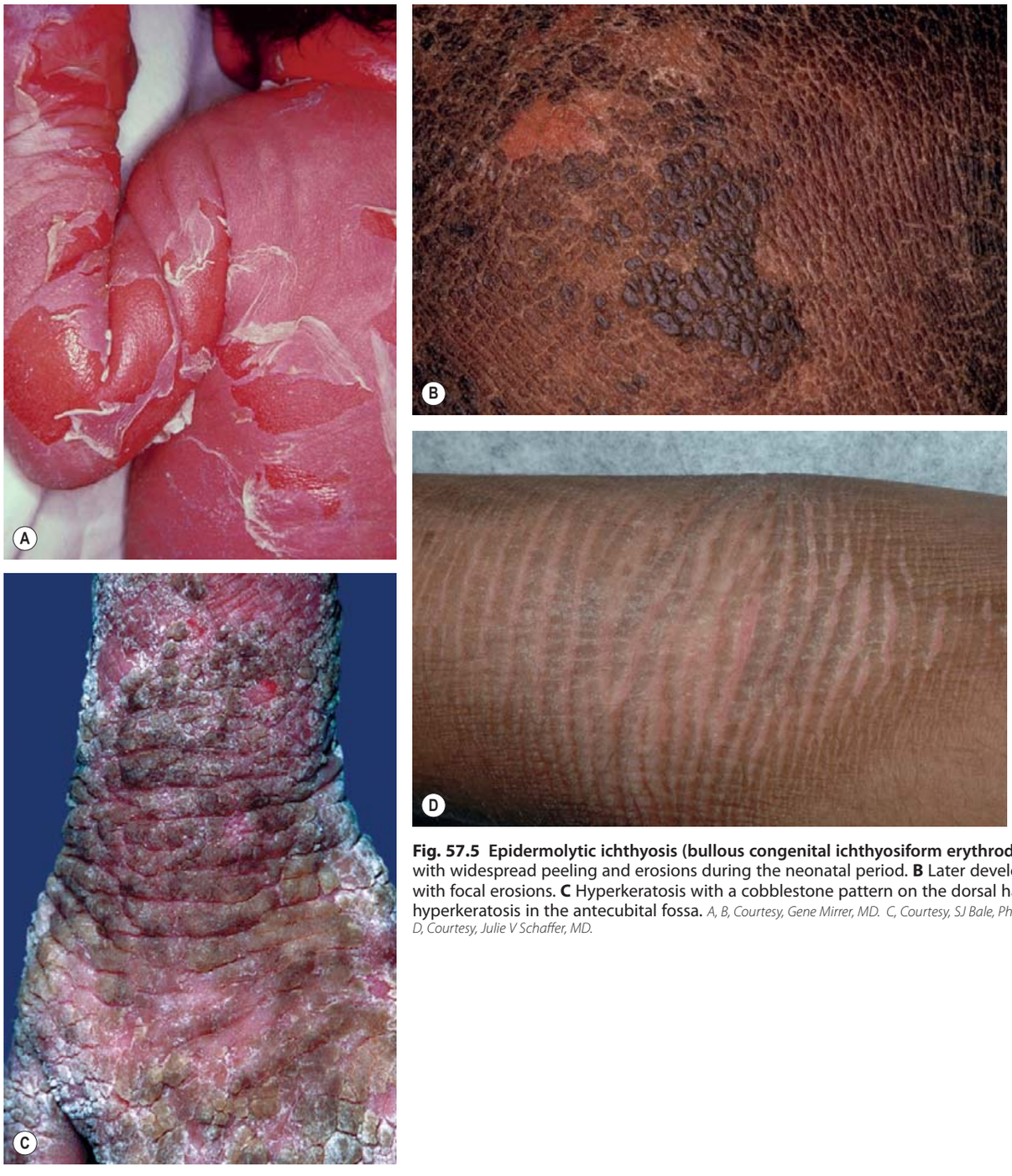


Fig. 57.5 Epidermolytic ichthyosis (bullous congenital ichthyosiform erythroderma). A Erythroderma with widespread peeling and erosions during the neonatal period. **B** Later development of hyperkeratosis with focal erosions. **C** Hyperkeratosis with a cobblestone pattern on the dorsal hand. **D** Corrugated hyperkeratosis in the antecubital fossa. *A, B, Courtesy, Gene Mirrer, MD. C, Courtesy, SJ Bale, PhD, and JJ DiGiovanna, MD. D, Courtesy, Julie V Schaffer, MD.*

Pathology

Highly characteristic structural and ultrastructural abnormalities allow EI to be distinguished from other congenital ichthyoses. Key features on routine histologic examination are dense orthokeratotic hyperkeratosis, prominent acanthosis, hypergranulosis, and cytolysis of the suprabasal and granular layers leading to small intraepidermal blisters (Fig. 57.6). Keratinocytes exhibit marked intracellular vacuolization and dense clumps of keratin intermediate filaments (KIFs). Collectively, these histopathologic changes are described as "epidermolytic hyperkeratosis". A mild perivascular lymphohistiocytic infiltrate is usually present in the upper dermis. Ultrastructural analysis reveals fragmented, clumped KIFs in the lower epidermis and perinuclear KIF shells in the upper epidermis.

Other diagnostic tests

Mutation screening and complete sequencing of *KRT1* and *KRT10* is commercially available. Prenatal diagnosis can be performed when

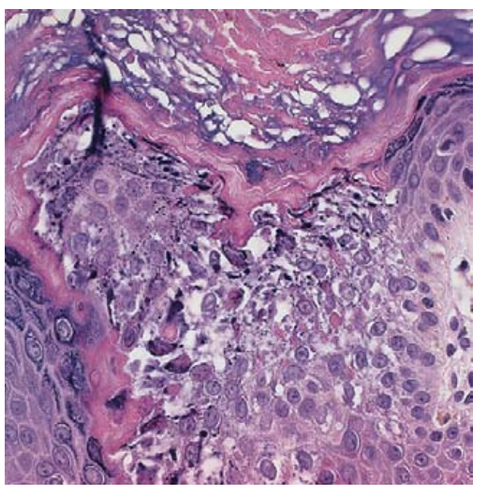


Fig. 57.6 Histology of epidermolytic ichthyosis. Striking ortho-hyperkeratosis, intracellular vacuolization of keratinocytes, and a prominent granular layer with clumped keratin filaments are seen.

NEONATAL PRESENTATION OF SELECTED ICHTHYOSES AND RELATED DISORDERS					
Disorder	**Collodion membrane**	**Bullae/blisters/erosions**	**Erythroderma**	**Generalized ichthyosis**	**Peeling/exfoliation**
Epidermolytic ichthyosis		+	(+)	+	(+)
Superficial epidermolytic ichthyosis (ichthyosis bullosa of Siemens)		+		+	+
Lamellar ichthyosis	+		(+)	+	
Congenital ichthyosiform erythroderma	+		+	+	
Self-healing/self-improving collodion baby	+				
Sjögren–Larsson syndrome	(+)		+	+	
Neutral lipid storage disease	(+)		+	+	
Trichothiodystrophy	(+)		+	+	
Netherton syndrome			+	+	+
Steroid sulfatase deficiency				+	
Peeling skin syndromes (see Table 57.6)				(+)	+
Conradi–Hünermann–Happle syndrome	(+)		+ (Blaschko's lines)	+ (Blaschko's lines)	
CHILD syndrome			Unilateral	Unilateral*	
KID syndrome			+	(+)	

*Some attenuated or band-like involvement may occasionally be appreciated on the contralateral side.

Table 57.3 Neonatal presentation of selected ichthyoses and related disorders. Parentheses indicate inconsistent or occasional findings.

the underlying mutation has been identified in affected family members[17].

Differential Diagnosis

In the neonatal period, the presence of blisters and erosions differentiates EI from non-bullous congenital ichthyoses (Table 57.3). Clinical distinction from the various forms of epidermolysis bullosa, staphylococcal scalded skin syndrome, and other vesiculobullous and erosive disorders that can present in neonates may require skin biopsy specimens and cultures (see Chs 32 & 34).

Later during infancy and childhood, EI can be distinguished from other congenital ichthyoses by the history of blistering (at birth and focal recurrences) and cutaneous superinfections as well as the distinctive histologic features. Although the latter may also be seen in epidermolytic palmoplantar keratoderma (see Ch. 58), hyperkeratosis in this autosomal dominant disorder is limited to the palms and soles. Superficial EI (ichthyosis bullosa of Siemens) lacks erythroderma and shows "molting" of the superficial epidermis due to epidermolysis within the granular layer. Ichthyosis hystrix Curth–Macklin sometimes resembles EI, with ridged, verrucous hyperkeratosis over joints and in flexures, but many patients have only palmoplantar keratoderma (see below). In contrast to EI, there is no clinical or histologic evidence of either blister formation or epidermolysis, and specific ultrastructural abnormalities of the KIFs are present.

Treatment

The disfigurement and malodor often affect psychosocial functioning. Treatment is symptomatic and should be adapted to the age of the patient and clinical issues. In the neonatal period, patients require management in an intensive care nursery to provide protective isolation and prevent or treat dehydration, electrolyte imbalance and cutaneous superinfection. Sepsis should be treated with broad-spectrum antibiotics. When the neonate is handled carefully and protective padding and lubricants are used, erosions and denuded skin usually heal rapidly.

In children and adults, therapy is aimed at reducing hyperkeratosis, removing scale and softening the skin. Keratolytic creams and lotions containing urea, salicylic acid and α-hydroxy acids are effective but often not well tolerated, especially in children, because of burning and stinging. Widespread topical application of higher-concentration salicylic acid preparations should be avoided because of the risk of systemic salicylism. Topical tretinoin and vitamin D preparations may be beneficial but often cause skin irritation. Frequent use of emollients and humectants can be combined with hydration (e.g. soaking of the skin during bathing) and mechanical abrasion of keratotic skin (e.g. gentle scrubbing with a soft brush or sponges).

Bacterial skin infections are common and often trigger blistering; they require topical or systemic antibiotic treatment. Use of antiseptics such as antibacterial soaps, chlorhexidine or dilute sodium hypochlorite baths may help to control bacterial colonization. Continuous preventive therapy (oral or topical antibiotics) should be avoided because of the risk of developing antibiotic resistance. Because of the increased skin fragility, it is also important to prevent mechanical trauma (e.g. by wearing comfortable clothing and shoes). Oral retinoids may drastically reduce hyperkeratosis and the frequency of infections in patients with generalized EI, but they also increase epidermal fragility and blistering. Low initial doses with gradual increase and careful monitoring are advisable, with use of the lowest effective maintenance dose[18].

SUPERFICIAL EPIDERMOLYTIC ICHTHYOSIS

Synonyms: ▪ Ichthyosis bullosa of Siemens ▪ Ichthyosis exfoliativa

History

In 1937, Siemens[19] first recognized this congenital ichthyosis as a distinct entity and differentiated it from classic EI.

Epidemiology

This is a rare autosomal dominant ichthyosis.

Pathogenesis

Superficial EI is caused by heterozygous mutations in the gene for keratin 2 (*KRT2*), which is expressed only in the uppermost spinous and granular cell layers of the epidermis. Mutations cluster in the boundaries of the rod region of *KRT2;* Glu487Lys in the helix termination motif is most frequently identified[20].

Clinical Features

The phenotype is milder than in classic EI. At birth, the skin may appear normal or show mild blistering. Trauma-induced small blisters on the extremities occur during infancy but usually subside by early childhood, while hyperkeratosis develops. Predilection sites are the skin overlying the joints, the flexures and the dorsa of the hands and feet (Fig. 57.7), always sparing the palms and soles. The skin may appear

Fig. 57.7 Superficial epidermolytic ichthyosis (ichthyosis bullosa of Siemens). Increased skin markings and "collarettes" where the skin has been superficially shed ("Mauserung"). *Courtesy, Anthony J Mancini, MD.*

ridged, shiny or lichenified. A characteristic feature is superficially denuded areas with collarette-like borders, described as "molting" or "Mauserung", which develop due to superficial blistering and shedding of the stratum corneum.

Pathology

Histopathologic abnormalities include orthokeratotic hyperkeratosis, acanthosis and vacuolization of the granular cell layer, occasionally leading to superficial intraepidermal separation. By electron microscopy, clumping of tonofilaments is present but limited to the upper spinous and granular cell layers.

Differential Diagnosis

Infants usually do not present with the marked erythroderma and widespread blistering seen in classic EI, and later in life there is a milder course with skin shedding that is more superficial and a lack of erythema. Peeling skin syndromes can have a similar clinical appearance but do not feature vacuolization of the granular layer. Recurrent blistering is also a feature of epidermolysis bullosa simplex, but this disorder does not have associated hyperkeratosis (with the exception of occasional palmoplantar keratoderma) and can be differentiated based on deeper blisters due to basal epidermolysis.

Treatment

The management is similar to that of EI.

ICHTHYOSIS EN CONFETTI

Synonyms: ■ Confetti ichthyosis ■ Congenital reticular ichthyosiform erythroderma ■ Ichthyosis with confetti ■ Ichthyosis variegata

Ichthyosis en confetti is a rare autosomal dominant disorder in which affected individuals are born with an ichthyosiform erythroderma and palmoplantar keratoderma[21]. During infancy and childhood, hundreds to thousands of small, confetti-like "islands" of normal skin appear in a widespread distribution, increasing in number and size over time. Histologic findings in ichthyotic skin include acanthosis, perinuclear vacuolization of keratinocytes in the upper epidermis, and parakeratotic hyperkeratosis.

This condition was recently found to be caused by heterozygous frameshift mutations in the *KRT10* gene[21]. The mutant keratin 10 protein has an arginine-rich C-terminus that redirects it from its normal location in the keratin intermediate filament network to the nucleolus. Each island of normal skin represents a revertant clone that arises via mitotic recombination (i.e. crossing-over that leads to homozygous mutant and homozygous normal daughter cells). The exact role of the frameshift mutations in the markedly elevated rate of mitotic recombination remains to be determined.

ICHTHYOSIS HYSTRIX CURTH–MACKLIN

History

In 1954, Ollendorff-Curth and Macklin[22] described a family with hystrix-like hyperkeratosis and palmoplantar keratoderma. Electron microscopic examinations by Anton-Lamprecht et al.[23] revealed peculiar ultrastructural abnormalities of the keratinocyte cytoskeleton. Since the initial description, only a few large families and sporadic cases have been reported.

Epidemiology

This is a rare disorder with autosomal dominant inheritance.

Pathogenesis

In two unrelated families with ichthyosis hystrix Curth–Macklin, heterozygous mutations in the keratin 1 gene (*KRT1*) have been demonstrated. In contrast to EI, the mutations were small nucleotide deletions/insertions leading to a frameshift and production of a keratin 1 protein with an aberrant tail domain lacking the usual glycine loop motifs[24]. In another family without palmoplantar keratoderma, the disorder was not linked to the keratin gene loci on chromosomes 12q13.3 and 17q21.2, suggesting clinical or genetic heterogeneity[25].

Clinical Features

The hyperkeratotic areas in ichthyosis hystrix Curth–Macklin can clinically mimic EI, but there is no skin fragility. Clinical expression varies even within families, ranging from palmoplantar keratoderma (which may be severe and mutilating) to localized hyperkeratotic plaques to generalized hystrix-like hyperkeratosis (i.e. horny, rigid spikes). Hyperkeratosis is present at birth or develops during early childhood. It has a cobblestone-like or ridged surface over large joints and in skin folds. Circular constriction bands (pseudoainhum), starfish-like keratoses, knuckle pads, digital flexion contractures and secondary bacterial infections have been described.

Pathology

Most histopathologic features, including orthokeratotic hyperkeratosis, hypergranulosis, acanthosis and church spire-like papillomatosis, are nonspecific. Cells in the differentiated cell layers may be vacuolated or binucleated. Ultrastructural abnormalities in the upper epidermis are diagnostic, with a shell-like, interspersed network of tangled KIFs, often associated with perinuclear vacuolization and formation of binucleated cells. In contrast to EI, there is no epidermolysis or keratin clumping.

Differential Diagnosis

Ichthyosis hystrix Curth–Macklin can be differentiated from EI and epidermolytic palmoplantar keratoderma by the absence of blistering and skin fragility as well as electron microscopic findings.

Treatment

The most effective treatments are systemic retinoids and topical keratolytic agents (see EI above).

ICHTHYOSIS HYSTRIX

Synonyms: ■ "Porcupine man" ■ Ichthyosis hystrix gravior type Lambert ■ Ichthyosis hystrix gravior type Rheydt (the initial term for hystrix-like ichthyosis with deafness [HID] syndrome) ■ Systematized verrucous nevus

Ichthyosis hystrix is a descriptive term for massive hyperkeratosis that has a verrucous surface or forms protruding, porcupine-like spines; it does not represent a distinct clinical entity. This phenotype is most commonly observed in patients with EI, but it can also be seen in clinically and genetically heterogeneous disorders ranging from verrucous epidermolytic nevi to ichthyosis hystrix Curth-Macklin to hystrix-like ichthyosis with deafness (HID) syndrome (a variant of keratitis–ichthyosis–deafness [KID] syndrome due to mutations in the *GJB2* gene)[26,27]. A well-known example of the ichthyosis hystrix phenotype is the "porcupine men" of the Lambert family from Suffolk, England[28]. Since no blister formation was mentioned in the records of this kindred, it remains unclear if they had a form of EI.

COLLODION BABY

Synonyms: ■ Collodion fetus ■ Ichthyosis congenita ■ Self-healing collodion baby – lamellar exfoliation of the newborn, desquamation of the newborn, self-improving collodion baby

Epidemiology

The collodion baby is a shared presentation of several congenital ichthyoses, most with autosomal recessive inheritance. It is not a distinct disorder.

Pathogenesis

The pathomechanisms leading to formation of a collodion membrane are not completely understood, but this presentation points to disturbed adaptation of the fetal epidermis to postnatal life. Collodion babies who eventually develop lamellar ichthyosis have been shown to harbor mutations in the transglutaminase-1 gene, leading to deficiency of this crucial cross-linking enzyme of the epidermis[29,30]. Transglutaminase-1 deficiency perturbs formation of the cornified cell envelope, resulting in hyperkeratosis, profoundly impaired barrier function and transepidermal water loss. Defects in multiple lipid-processing enzymes or lipid transporters have been demonstrated in other congenital ichthyoses with a collodion membrane presentation, such as lipoxygenase deficiency in congenital ichthyosiform erythroderma, ABCA12 deficiency in lamellar ichthyosis, fatty aldehyde dehydrogenase deficiency in Sjögren–Larsson syndrome, abhydrolase 5 deficiency in neutral lipid storage disease, and β-glucocerebrosidase deficiency in Gaucher disease. These findings underscore the importance of lipids to epidermal barrier function.

A milder phenotype of a self-healing (or self-improving) collodion baby has been reported in association with *TGM1, ALOX12B* or *ALOXE3* mutations, which were shown to fully inactivate the encoded protein only *in utero* but not after birth[31–33]. It has been postulated that the self-healing collodion baby has a "dynamic" phenotype that is dependent on environmental conditions, which influence the stability of the mutant protein. A self-healing collodion baby with membranes localized to acral areas due to compound heterozygous *TGM1* mutations has also been reported[34].

Clinical Features

Collodion babies are often born prematurely and have increased perinatal morbidity and mortality. At birth, the neonate is covered with a taut, shiny, transparent membrane formed by the thickened stratum corneum, which resembles a plastic wrap (Fig. 57.8). Its tautness often leads to ectropion, eclabium and hypoplasia of nasal and auricular cartilage. Sucking and pulmonary ventilation may also be impaired, resulting in dehydration, malnutrition, hypoxia and pneumonia. After birth, the parchment-like membrane gradually dries, cracks and breaks up. In the process, fissures develop that impair epidermal barrier function, which can lead to percutaneous loss of water and permit the entry of microorganisms; fluid and electrolyte imbalances, skin infections and sepsis may follow. In addition, circular bands of hardened skin can lead to vascular constriction and distal edema.

Within two weeks, the membrane peels off in sheets and a transition to the underlying disease phenotype takes place. Most commonly, congenital ichthyosiform erythroderma or lamellar ichthyosis ensue. Sjögren–Larsson syndrome, trichothiodystrophy, neutral lipid storage disease, infantile Gaucher disease, Conradi–Hünermann–Happle syndrome and ectodermal dysplasias may rarely present as collodion baby (Table 57.4). In self-healing or self-improving phenotypes, desquamation of the collodion membrane leaves normal skin or an extremely mild generalized ichthyosis.

Pathology

Light microscopic and electron microscopic abnormalities of the collodion membrane are nonspecific and reveal mostly an excessively thickened, orthokeratotic stratum corneum. Therefore, it is usually preferable to defer a skin biopsy until after transition to the underlying disease phenotype occurs. At that time, immunostaining can demonstrate the presence or absence of transglutaminase-1 protein in the upper epidermis[35]. *In situ* assays of transglutaminase activity can be performed on skin biopsy sections and allow rapid identification of patients with transglutaminase-1 deficiency, even as a collodion

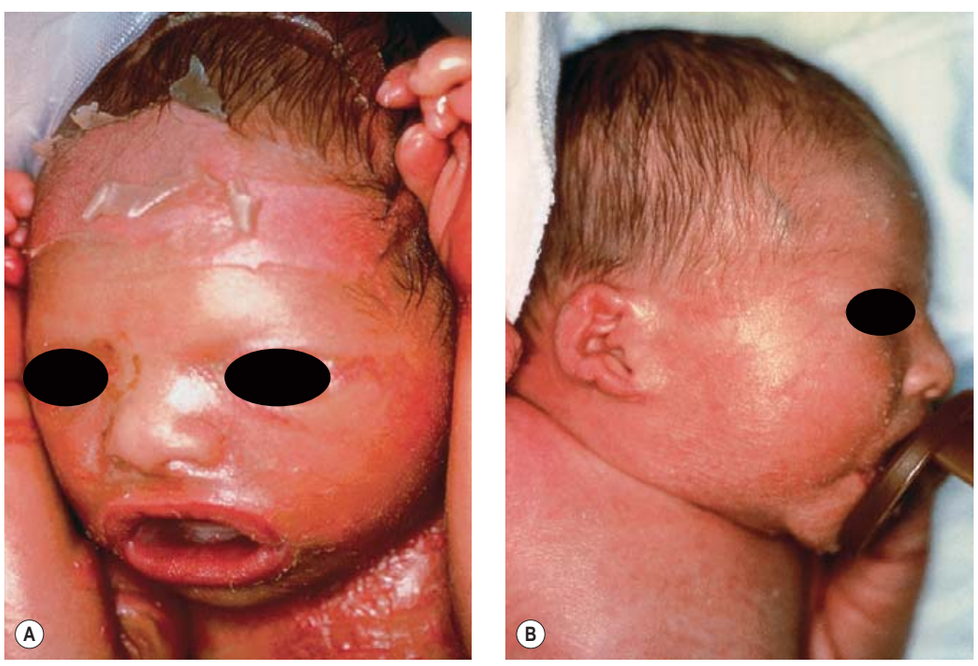


Fig. 57.8 Collodion baby. A Day 1 with eclabium. **B** Day 8 with erythema and diffuse mild scaling and misshapen ears.

DIFFERENTIAL DIAGNOSIS OF A COLLODION BABY	
Disorder	**Frequency**
Self-healing/self-improving collodion baby	Always
Lamellar ichthyosis	Common
Congenital ichthyosiform erythroderma	Common
Autosomal dominant lamellar ichthyosis	Rare
Autosomal dominant congenital ichthyosiform erythroderma	Rare
Sjögren–Larssen syndrome	Rare
Trichothiodystrophy	Rare
Infantile Gaucher disease	Rare
Ectodermal dysplasias (EDs)*	Very rare
Neutral lipid storage disease	Very rare
Conradi–Hünermann–Happle syndrome	Very rare
*E.g. hypohidrotic ED or ankyloblepharon-ED-clefting (AEC) syndrome.	

Table 57.4 Differential diagnosis of a collodion baby.

baby[32,35]. However, interpretation of the transglutaminase activity assay requires experience, and this test is not widely available.

Differential Diagnosis

The phenotype of harlequin ichthyosis is much more severe and so striking that a clinical distinction between the two disorders is, in most circumstances, not difficult.

Treatment

Collodion babies are at risk for thermoinstability, hypernatremic dehydration, skin infections and sepsis. It is therefore essential to keep them in a controlled environment and to carefully monitor for fluid and electrolyte imbalances. Collodion babies are also at risk for pneumonia secondary to restricted ventilation and aspiration of amniotic fluid containing scales. To facilitate gradual desquamation of the collodion membrane, it is generally recommended that infants be placed in a humidified incubator and the skin treated with wet compresses and light emollients to increase its elasticity and pliability. Manual removal of the collodion membrane and use of topical keratolytic agents are not advisable, because of the increased risk of infections and percutaneous absorption.

LAMELLAR ICHTHYOSIS

Synonyms: ■ Ichthyosis congenita type 2 ■ Non-erythrodermic autosomal recessive lamellar ichthyosis

History

In 1966, Frost and Van Scott[3] coined the term "lamellar ichthyosis" for all autosomal recessive forms of non-bullous congenital ichthyosis. Williams and Elias[36] further separated this group into two distinct phenotypes, lamellar ichthyosis (LI) and (non-bullous) congenital ichthyosiform erythroderma (CIE), which now have been recognized as part of a continuum with intermediate phenotypes. In the current classification system, the LI–CIE spectrum (as well as harlequin ichthyosis) falls within the non-syndromic autosomal recessive congenital ichthyosis (ARCI) category[7]. However, a rare autosomal dominant form of LI with almost indistinguishable clinical features has also been identified[37].

Epidemiology

LI occurs worldwide with an estimated prevalence of 1 in 200 000 to 1 in 300 000 live births, but it may be more common in certain regions such as Norway (1 in 90 000) or in inbred populations. LI is genetically heterogeneous and in most families is inherited as an autosomal recessive trait, although there are rare reports of autosomal dominant transmission.

Pathogenesis

Transglutaminase-1 deficiency due to deleterious mutations in both copies of the *TGM1* gene accounts for 38–55% of all patients with an ARCI on the LI–CIE spectrum and 65–90% of those with classic LI[29,30,38,39]. LI–CIE spectrum patients with a collodion membrane at birth, plate-like scale, ectropion and/or alopecia are approximately four times more likely to have *TGM1* mutations than those without at least one of these features[38]. Many patients of northern European descent share a mutation (thought to originate from a German predecessor) that leads to alternative splicing of *TGM1* mRNA[40].

Transglutaminase-1 catalyzes the calcium-dependent cross-linking of proteins through the formation of ε-(γ-glutamyl) lysine isopeptide bonds; it also creates ester bonds between proteins and ω-hydroxyceramides (see Fig. 56.3). This enzyme is expressed in the upper differentiated layers of the epidermis, where it facilitates the formation of the cornified cell envelope by cross-linking numerous structural proteins (e.g. involucrin, small proline-rich proteins, loricrin, keratins and desmosomal proteins) to one another as well as to the lipid envelope. Hence, pathogenic *TGM1* mutations seriously perturb the complex process of cornification and desquamation.

Transgenic mice deficient in transglutaminase-1 exhibit a phenotype similar to LI, with impaired barrier function leading to tremendous transepidermal water loss and abnormal percutaneous absorption. In mice, the lack of transglutaminase-1 results in complete loss of the cornified cell envelope, disturbed degradation of nuclei and keratohyalin granules, and cytoplasmic accumulation of loricrin. These observations emphasize the essential role of transglutaminase-1 in the development and maturation of the stratum corneum and for postnatal adaptation of the skin to a dry environment.

Biallelic missense mutations in the ATP-binding cassette subfamily A member 12 gene (*ABCA12*) have been reported primarily in LI patients of Northern African decent (Morocco, Mali, Algeria)[41]. These mutations cluster within the five exons (28–32) that encode the first nucleotide binding fold of this ABC transporter, which is responsible for the energy-dependent transport of lipid substrates across membranes and is found in lamellar bodies. Of note, more deleterious mutations in the *ABCA12* gene cause harlequin ichthyosis (see below).

Mutations in the *CYP4F22* gene, which encodes a cytochrome P450 enzyme thought to function in lipoxygenase pathways (see below), underlie a form of LI associated with hyperlinear palms (but usually no collodion membrane) that has been described in consanguineous families from Algeria, France, Italy and Lebanon[42]. Mutations in the *ALOX12B* and *ALOXE3* genes, which encode lipoxygenases, and the *NIPAL4* (*ICHTHYIN*) gene (see CIE section below) are occasionally associated with mild LI or intermediate LI/CIE phenotypes.

Clinical Features

Classic LI is a severe disorder that is apparent at birth and persists throughout life, although milder variants also occur. Most affected neonates are encased in a collodion membrane (see previous section). Over the first weeks of life, the collodion membrane is gradually replaced by generalized large scales. LI is characterized by large, brown, plate-like scales that form a mosaic or bark-like pattern with minimal to no associated erythroderma (Fig. 57.9A). The scales are centrally attached and have raised borders, often leading to superficial fissures. South African "bathing suit ichthyosis" represents a form of LI (caused by a particular *TGM1* mutation) that affects only the trunk and scalp.

Tautness of facial skin commonly results in ectropion (Fig. 57.9B), eclabium, and significant hypoplasia of nasal and auricular cartilage. Severe ectropion may lead to madarosis, conjunctivitis and incomplete lid closure with ensuing keratitis. Traction and compression exerted by the taut skin can cause scarring alopecia, especially at the periphery of the scalp. Hair shafts are normal but often encased by the thickened stratum corneum. The degree of palmoplantar keratoderma is variable and can range from accentuated skin markings to severe thickening with cracking and fissuring. Secondary nail dystrophy with thickened nail plates and ridging is not uncommon. Intraepidermal constriction of sweat ducts often results in severe heat

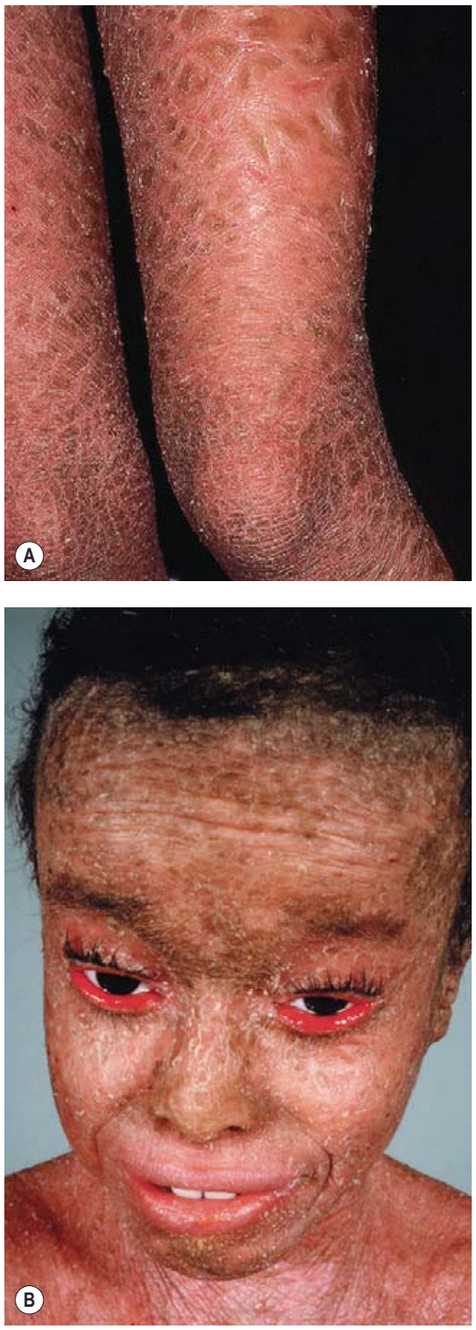


Fig. 57.9 Lamellar ichthyosis. A Large, plate-like scales on the lower extremities forming a mosaic pattern. **B** Obvious ectropion as well as plate-like scales.

intolerance, while accumulation of scale in the external ear canals can lead to occlusion, bacterial colonization and recurrent infections.

Pathology

The histologic abnormalities are not diagnostic. Massive orthokeratotic hyperkeratosis covers an acanthotic epidermis, sometimes with psoriasiform or papillomatous hyperplasia. In contrast to CIE, the epidermal proliferation rate is normal or only slightly elevated. Elongated cholesterol clefts, variable numbers of translucent lipid droplets in the stratum corneum, and a thin or absent cornified cell envelope have been observed by electron microscopy, although these findings overlap with those of CIE[43].

Other diagnostic tests

In addition to measuring transglutaminase-1 activity in cultured keratinocytes, screening procedures to detect transglutaminase-1 deficiency in skin biopsy specimens include immunostaining with anti-transglutaminase-1 antibodies, *in situ* measurement of transglutaminase-1 activity (e.g. covalent incorporation of biotinylated substrate peptides into skin cryostat sections)[32,35] and testing for the presence of cross-linked cell envelopes[44]. Although these assays are not widely available for diagnostic purposes, genetic testing is commercially available for detecting pathogenic mutations in *TGM1* and *ABCA12* (as well as *ALOX12B, ALOXE3* and *NIPAL4*); *CYP4F22* testing is offered mainly in research laboratories. Prenatal diagnosis can be performed in families with known mutations from chorionic villus sampling (CVS) or amniocentesis material obtained at an early gestational age[45]. Molecular testing has now largely replaced light and electron microscopic examination of fetal skin biopsy specimens or skin cells sloughed into the amniotic fluid, which must be obtained after 20 weeks of gestation to reliably show characteristic findings (e.g. hyperkeratinization of hair follicles, which can be difficult to interpret)[46].

Differential Diagnosis

In the neonatal period, there is considerable clinical overlap with other congenital ichthyoses that present with a collodion membrane, especially CIE and the self-healing collodion baby (see Tables 57.4 & 57.5). Later in life, the large, dark, plate-like scales, ectropion and no discernible erythroderma of LI can be readily distinguished from most other ichthyoses. Although classic CIE is differentiated by marked erythroderma and small white scales, some patients exhibit intermediate LI/CIE phenotypes with variable degrees of erythroderma as well as quality and size of scales. Autosomal dominant LI is extremely rare, and it remains to be determined whether the presence of a transformation zone between the stratum granulosum and stratum corneum and an abnormal lipid profile in the scales represent distinct characteristics of this entity.

Treatment

Neonatal care is detailed in the section describing collodion babies. Severe disease often necessitates systemic therapy with oral retinoids from early childhood. Acitretin can be very effective in alleviating hyperkeratosis and scaling. Treatment is usually initiated at a low dose and then titrated to the minimal effective dose, which is dictated by the course and severity of the disease[18]. The therapeutic benefits may also include an improvement of the ectropion, thus avoiding eye complications and reconstructive eyelid surgery. However, the benefits of long-term systemic retinoid therapy must be weighed against the potential toxicities. A randomized controlled study in patients with LI and other moderate to severe forms of ichthyosis found that liarozole (a retinoic acid metabolism blocking agent; currently not available in the US) was equally effective as acitretin but showed a trend towards a more favorable tolerability profile.

Topical management should always take into consideration the severely impaired desquamation and barrier function of the skin. The use of keratolytics is often limited due to skin irritation and an increased risk of systemic absorption, especially in children. Topical vitamin D_3 derivatives, tazarotene[47], and formulations containing lactic acid and propylene glycol in a lipophilic cream base[48] have been effective. Heat intolerance can be ameliorated by frequent moistening of the skin with water or the use of air conditioning and humidifiers. Severe ectropion requires longitudinal ophthalmologic evaluation; surgical repair is sometimes necessary to prevent irreversible corneal damage.

LI and other severe forms of ARCI are often disfiguring, which may hinder the psychosocial development of affected children and adolescents. Families and patients need support in dealing with these issues, and patient advocacy groups such as FIRST (www.scalyskin.org) are excellent resources.

CONGENITAL ICHTHYOSIFORM ERYTHRODERMA

Synonyms: ■ Non-bullous congenital ichthyosiform erythroderma ■ Ichthyosis congenita type 1 ■ Erythrodermic autosomal recessive lamellar ichthyosis

Epidemiology

CIE appears to be slightly more common than LI, affecting 1 in 100 000 to 1 in 200 000 people. In the vast majority of families, CIE is inherited

as an autosomal recessive trait, although there are rare reports of autosomal dominant transmission. This type of ARCI is clinically and genetically very heterogeneous.

Pathogenesis

To date, mutations in at least five genes have been shown to cause CIE: *TGM1*, *ALOXE3*, *ALOX12B*, *NIPAL4* (*ICHTHYIN*) and *ABCA12*. Two additional CIE loci on chromosome 12p11.2–q13 have been identified, and ARCI without erythema has been mapped to 19p13.1–p13.2. In contrast to LI, only a minority of CIE patients carry recessive mutations in the *TGM1* gene, which lead to transglutaminase-1 deficiency with resulting abnormal formation of the cornified cell envelope and perturbed barrier function of the skin[29,40].

Approximately 10–15% of CIE patients from diverse ethnic backgrounds without *TGM1* mutations harbor inactivating mutations in two lipoxygenase (LOX) genes, *ALOX12B* and *ALOXE3*, each accounting for about half of the cases[31,49]. The majority of these individuals are born with a collodion membrane, with subsequent development of mild to moderate CIE. The enzymes 12R-LOX and eLOX are preferentially synthesized in the epidermis and function in sequence to generate epoxy alcohol metabolites, which are crucial for formation of the epidermal lipid barrier. 12R-LOX is responsible for generating fatty acid hydroperoxide, while eLOX functions as hydroperoxide isomerase to produce epoxy alcohols.

The *NIPAL4* (*ICHTHYIN*) gene has been found to underlie CIE in families from the Mediterranean basin, Iran, South America and Northern Europe[50,51]. In a Scandinavian study, this gene was mutated in 16 of 18 kindreds with an ARCI characterized ultrastructurally by abnormal lamellar bodies and elongated perinuclear membranes in the stratum granulosum[51]. Affected individuals have widespread congenital ichthyosis with variable associated erythema and usually no collodion

ADDITIONAL RARE ICHTHYOSES FOR WHICH THE GENETIC BASIS OR CHROMOSOMAL LOCUS IS KNOWN

Disorder	Gene (protein)	Chromosomal location	Mode of inheritance	Dermatologic features	Associated features	Diagnosis*
			GENERALIZED ICHTHYOSIS			
Arthrogryposis–renal dysfunction–cholestasis (ARC) syndrome	*VPS33B* (vacuolar protein sorting 33 homolog B)	15q26.1	AR	Generalized fine to large scales on trunk and extremities with sparing of skin folds	Arthrogryposis, metabolic acidosis and aminoaciduria due to renal tubular dysfunction, cholestasis, sensorineural deafness, CNS abnormalities, lethal within first year of life	Clinical; molecular testing
*C*erebral *d*ysgenesis, *n*europathy, *i*chthyosis and *k*eratoderma (CEDNIK) syndrome	*SNAP29* (SNARE protein involved in vesicle fusion)	22q11.2	AR	Normal skin in infancy, later widespread large scale with variable erythema; palmoplantar keratoderma	Dysmorphic facies, microcephaly, neuropathy, delayed psychomotor development, hearing impairment, optic nerve atrophy, cachexia, fatal within first decade of life	MRI showing cortical dysplasia and abnormal corpus callosum; electron microscopy showing clear vesicles within the epidermis
Ichthyosis, intellectual disability and spastic quadriplegia	*ELOVL4* (elongase of very long chain fatty acids 4)	6q14	AR	Generalized fine scale and variable erythema with involvement of skin folds; variable collodion membrane	Seizures, mental and growth retardation, spastic tetraplegia	Clinical
Ichthyosis–hypotrichosis syndrome	*ST14* (matriptase, a transmembrane serine protease)	11q24.3–q25	AR	Large scales on trunk, extensor extremities and scalp; curly, sparse, brittle scalp hair with pili torti and pili bifurcate, absent eyebrows and eyelashes; improvement in adulthood	Photophobia, corneal opacities, pitted or conical teeth	Clinical
Ichthyosis–hypotrichosis–sclerosing cholangitis syndrome	*CLDN1* (claudin 1, a tight junction protein)	3q28	AR	Fine to large scales on trunk and extremities with sparing of flexures; hypotrichosis, coarse hair, scarring alopecia of scalp (frontal, temporal) and eyebrows	Neonatal jaundice and hepatomegaly due to sclerosing cholangitis or congenital paucity of biliary ducts; hypodontia and enamel dysplasia	Clinical; peripheral blood smear to detect eosinophil vacuoles
Ichthyosis prematurity syndrome	*SLC27A4* (solute carrier family 27 member 4, a fatty acid transporter)	9q34.11	AR (Scandinavian families)	Thick, caseous, desquamating scale at premature birth; widespread perifollicular hyperkeratosis, larger scale on distal extremities	Polyhydramnios, premature birth, neonatal respiratory distress, peripheral eosinophilia, atopy	Clinical; electron microscopy showing membrane aggregations within upper epidermis
Late-onset autosomal recessive ichthyosis	*LIPN* (lipase N, involved in epidermal triglyceride metabolism)	10q23	AR	Onset in childhood of generalized ichthyosis with fine white scales or (especially on legs) larger brown scales; little associated erythema	None	Clinical

*Although the disease-causing genes have been identified for most of these disorders, unless noted otherwise, molecular testing is currently available only through research laboratories.

Table 57.5 Additional rare ichthyoses and related disorders for which the genetic basis or chromosomal locus is known. Ichthyosis may also occur in autosomal recessive congenital disorders of glycosylation due to deficiency in dolichol kinase (also features alopecia, microcephaly and cardiomyopathy) or steroid 5-α-reductase 3 (also features lax skin, colobomas and cerebellar hypoplasia). AD, autosomal dominant; AR, autosomal recessive; ER, endoplasmic reticulum.

Continued

ADDITIONAL RARE ICHTHYOSES FOR WHICH THE GENETIC BASIS OR CHROMOSOMAL LOCUS IS KNOWN						
Disorder	**Gene (protein)**	**Chromosomal location**	**Mode of inheritance**	**Dermatologic features**	**Associated features**	**Diagnosis***
Multiple sulfatase deficiency (mucosulfatidosis, Austin disease)	*SUMF1* (sulfatase-modifying factor 1, responsible for post-translational modification of a cysteine residue at the active site of all sulfatases, including steroid sulfatase)[108]	3p26.2	AR	Similar to steroid sulfatase deficiency, but often less severe	Findings depend upon residual sulfatase activity; may resemble metachromatic leukodystrophy or various mucopolysaccharidoses (see Ch. 48); coarse facies; broad great toes, chondrodysplasia calcificans, dysostosis multiplex; deafness; hypotonia, hydrocephalus, developmental delay, neurologic deterioration	Reduced arylsulfatase A/B/C, heparan sulfatase and iduronate-2 sulfatase activity/ levels in fibroblasts (cultured), leukocytes, plasma or chorionic villi; tandem mass spectrometry profile in amniotic fluid for prenatal diagnosis[109,110]
Rhizomelic chondrodysplasia punctata (autosomal recessive chondrodysplasia punctata type 1; chondrodystrophia calcificans punctata)	*PEX7* (peroxisomal type 2 targeting signal receptor; functions in peroxisomal biogenesis[111])	6q23.3	AR	Ichthyosis and alopecia occur in ~25% of patients; at birth, erythroderma and thick, sticky vernix with underlying adherent scale; diffuse or patchy scales with feather-like edges in infancy; later, follicular atrophoderma, scarring alopecia of the scalp, sparse or absent eyebrows and eyelashes *Histologic findings*: (during infancy) hyperkeratosis, focal parakeratosis, follicular plugging	Symmetric skeletal anomalies with rhizomelia (shortening of the proximal limbs), scoliosis, chondrodysplasia punctata (in infancy)[112]; facial dysmorphism (frontal bossing, flat nasal bridge); bilateral congenital cataracts; progressive psychomotor retardation usually results in death by 2 years of age; occasional survival with spastic tetraplegia	Stippled epiphyses (punctate calcifications) on X-rays prenatally and during infancy; in plasma/RBCs: low plasmalogen in first month of life, later increased phytanic acid; electron microscopy shows small vacuoles with needle-like calcium inclusions in keratinocytes; peroxisomal dysfunction in cultured chorionic villous or amniotic fluid cells[113]; molecular testing (not available in the US)
ERYTHROKERATODERMA OR FOCAL ICHTHYOSIFORM LESIONS						
Ichthyosis follicularis, atrichia and photophobia (IFAP) syndrome	*MBTPS2* (membrane-bound transcription factor peptidase site 2, a zinc metalloprotease with roles in cholesterol homeostasis and the ER stress response[114])	Xp22.12-p22.11	X-linked "recessive"	*Affected males*: congenital atrichia with absence of eyebrows and lashes; follicular keratoses ("nutmeg grater" skin); psoriasiform plaques; occasionally lamellar scaling or hyperkeratosis of the palms and soles; nail dystrophy; increased susceptibility to mucocutaneous bacterial and fungal infections *"Carrier" females*: linear streaks with follicular keratoses or scaling; patchy hypotrichosis *Histologic findings*: hyperkeratosis, absent/ poorly developed hair follicles and sebaceous glands	Vascularizing keratitis; short stature; variable intellectual disability, cerebral atrophy, temporal lobe malformation, hypoplasia of the corpus callosum, seizures; inguinal hernias; occasional urogenital, renal and vertebral malformations or Hirschsprung disease	Clinical
*M*ental retardation, *e*nteropathy, *d*eafness, *n*europathy, *i*chthyosis, *k*eratodermia (MEDNIK) syndrome	*AP1S1* (adaptor-related protein complex 1 sigma 1 subunit, involved in vesicular protein trafficking)[115]	7q22.1	AR	Erythematous patches and hyperkeratotic plaques of variable sizes and shapes; mucosal involvement	Chronic diarrhea; sensorineural deafness; peripheral neuropathy; mental and growth retardation	Clinical; elevated plasma very-long-chain fatty acids

*Although the disease-causing genes have been identified for most of these disorders, unless noted otherwise, molecular testing is currently available only through research laboratories.

Table 57.5 Additional rare ichthyoses and related disorders for which the genetic basis or chromosomal locus is known (cont'd). AD, autosomal dominant; AR, autosomal recessive; ER, endoplasmic reticulum.

Continued

ADDITIONAL RARE ICHTHYOSES FOR WHICH THE GENETIC BASIS OR CHROMOSOMAL LOCUS IS KNOWN						
Disorder	**Gene (protein)**	**Chromosomal location**	**Mode of inheritance**	**Dermatologic features**	**Associated features**	**Diagnosis***
Erythrokeratodermia with ataxia (Giroux–Barbeau syndrome)	Unknown	1p34–35.1	AD (French-Canadian family)	Erythematous, hyperkeratotic plaques with fine, white, adherent scales on extremities (knees, ankles, elbows, wrists); diminish or disappear during adulthood[116] *Histologic findings*: acanthosis, hyperkeratosis, focal parakeratosis, perinuclear vacuolization, clumped keratohyalin granules	Progressive neurologic symptoms develop during 4th–5th decades of life, including nystagmus, ataxia, dysarthria and hyporeflexia	Clinical
*K*eratosis *l*inearis with *i*chthyosis congenita and sclerosing *k*eratoderma (KLICK) syndrome	*POMP* (proteasome maturation protein)	13q12.13	AR	Mild generalized ichthyosiform scaling, linear distribution of keratotic papules in flexural sites; hyperkeratotic plaques on knees, palmoplantar keratoderma with constriction bands	Digital flexion contractures	Clinical
PEELING SKIN						
Generalized inflammatory peeling skin syndrome†	*CDSN* (corneodesmosin, a desmosomal protein)[79]	6p21.3	AR	Erythroderma with fine white scales; widespread, patchy superficial (subcorneal) peeling of the skin; pruritus; fine hair during infancy	Mild failure to thrive and staphylococcal skin infections during infancy; atopic manifestations (e.g. asthma, food allergies); elevated serum IgE	Clinical
Autosomal recessive exfoliative ichthyosis	*CSTA* (cystatin A, a protease inhibitor)	3q21	AR	Peeling skin on palms, soles, elbows and knees; fine white scale on trunk and extremities; no histologic evidence of epidermolysis	None	Clinical; electron microscopy showing widened intercellular spaces and aggregates of keratin filaments in basal keratinocytes
Generalized peeling skin syndrome	*CHST8* (carbohydrate sulfotransferase 8)	19q13.1	AR	Generalized peeling skin, especially on the extremities	None	Clinical
Acral peeling skin syndrome	*TGM5* (transglutaminase 5)[117]	15q15.2	AR	Superficial (subcorneal) skin peeling on acral extremities with associated erythema (Fig. 57.18); exacerbated by elevated ambient temperature and humidity	None	Clinical
Erythrokeratolysis hiemalis (keratolytic winter erythema, Oudtshoorn disease)	Unknown	8p23–p22	AD (South African families)	Episodic/seasonal development of circinate erythematous plaques with scaling and centrifugal peeling; predominantly on palms/soles with occasional extension to legs > arms (rarely on trunk and face); occasional blisters in center of new plaques; triggered by viral infection or fever; improves with age[118] or with tar + UV therapy or topical 5-fluorouracil	None	Clinical; histologic findings of parakeratosis, necrosis in the stratum spinosum and basaloid proliferation

*Although the disease-causing genes have been identified for most of these disorders, unless noted otherwise, molecular testing is currently available only through research laboratories.
†Netherton syndrome can also present with a phenotype of generalized peeling skin and erythroderma.

Table 57.5 Additional rare ichthyoses and related disorders for which the genetic basis or chromosomal locus is known (cont'd). AD, autosomal dominant; AR, autosomal recessive; ER, endoplasmic reticulum.

membrane at birth[51]. Ichthyin is a transmembrane protein with homologies to both transporters and G-protein-coupled receptors, and it is hypothesized to represent a membrane receptor for ligands (trioxilins A3 and B3) from the hepoxilin pathway[50].

Homozygous mutations in the patatin-like phospholipase domain-containing 1 gene (*PNPLA1*) were recently found to cause CIE with a collodion membrane presentation in families from northern Africa[51a]. The PNPLA1 protein has a role in epidermal lipid barrier formation. Patients with CIE resulting from biallelic *ABCA12* mutations (at least one of which is missense) have been reported, but they tend to have somewhat larger scales than in classic CIE[52]. In addition, individuals with harlequin ichthyosis (which generally results from truncating

mutations and/or deletions in *ABCA12*) who survive the neonatal period typically develop a very severe CIE-like phenotype.

Clinical Features

CIE usually presents at birth with a collodion membrane, with subsequent evolution into generalized erythroderma and scaling that remain throughout life. The clinical features of CIE tend to be milder than those of classic LI, but there is variability in the intensity of erythema as well as the size and type of scale. In severely affected patients, CIE is characterized by an intense, bright red erythroderma; generalized white, small scales with a "powdery" consistency (Fig. 57.10); and additional findings such as ectropion and scarring alopecia. Scales may become larger, darker or plate-like, especially on the extensor surface of the lower extremities. The palms and soles are usually severely affected with a diffuse, fissuring keratoderma that contrasts with the fine, translucent scales elsewhere on the body. Patients with milder disease exhibit less intense erythroderma and scaling (although the latter still tends to be generalized) and have variable palmoplantar involvement.

The obstruction of sweat ducts and pores often results in hypohidrosis and heat intolerance. Secondary nail dystrophy, onychomycosis and digital flexion contractures are not uncommon. Severe exfoliative erythroderma can cause metabolic stress in growing children, including substantial energy expenditure through evaporation in the setting of increased transepidermal water loss and failure to meet their high caloric needs can lead to growth retardation[53]. However, most children with CIE have normal growth and development. Adults with CIE may have an increased risk of developing cutaneous squamous cell carcinoma (SCC), so longitudinal skin surveillance should be considered[54].

Pathology

The histopathologic and ultrastructural features of CIE are nondiagnostic. Compared to LI, there is more parakeratosis (focal or extensive) and the acanthosis is typically more pronounced and accompanied by hypergranulosis. Unlike LI, the epidermal cell turnover rate in CIE is markedly increased. Ultrastructural abnormalities in CIE include an increased number of lamellar bodies, an accumulation of lipid droplets in the stratum corneum (often more prominent than in LI)[55,56] and disorganized intercellular lipid lamellae[55]; although characteristic of CIE, these findings overlap with those seen in LI and other hyperproliferative disorders.

Other diagnostic tests

As in LI, transglutaminase-1 deficiency can be detected by immunostaining for and/or assessing the activity of this enzyme in skin biopsy specimens. Prenatal molecular diagnosis is possible when disease-causing mutations have been identified in family members. Interpretation of ultrastructural findings in fetal skin biopsy specimens is difficult, and diagnostic features may not be present before the 21st week of gestation.

Differential Diagnosis

A collodion membrane at birth requires consideration of LI, a self-healing collodion baby and other forms of ichthyosis (see Tables 57.4 & 57.5). After transition to the ichthyosis phenotype, pronounced erythroderma and fine white scales in classic CIE differentiate it from classic LI, which is characterized by less erythema, large dark scales and more frequent ectropion, eclabium and scarring alopecia. However, many intermediate phenotypes with variable degrees of erythema and size and quality of scale exist. As noted above, harlequin ichthyosis survivors typically develop an extremely severe CIE-like phenotype. A variety of clinical, histologic and laboratory findings differentiate CIE from other erythrodermic forms of ichthyosis, including syndromic as well as non-syndromic conditions (see Tables 57.1 & 57.2).

Treatment

A summary of therapeutic strategies is provided above in the section on LI. Erythrodermic patients have a special need for increased intake of fluids, calories, iron and protein to balance substantial loss through the skin, which can be 3–10 times higher than normal[53]. Therapy with oral retinoids can reduce scaling, but it is less beneficial in suppressing the erythroderma.

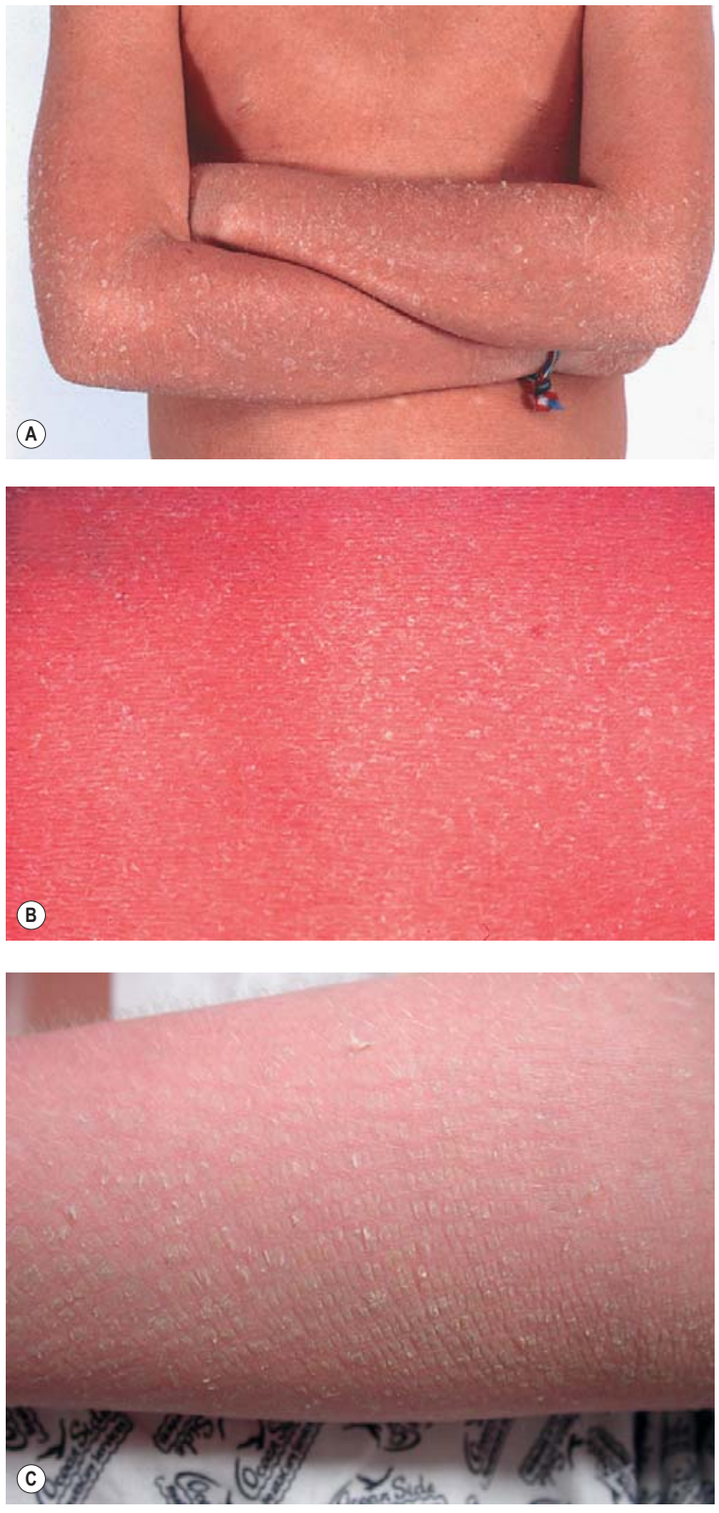


Fig. 57.10 Congenital ichthyosiform erythroderma. A Intense redness and fine, flaky, white scale on the trunk and arms. Close-up of fine white (**B**) and coarser yellowish (**C**) scale in a background of prominent erythema. *A, Courtesy, SJ Bale, PhD, and JJ DiGiovanna, MD.*

HARLEQUIN ICHTHYOSIS

Synonyms: ■ Harlequin baby ■ Harlequin fetus ■ Ichthyosis congenita gravior

History

This most extreme and distinct form of ARCI was described as early as 1750 by the Reverend Oliver Hart. In 1900, Riecke recognized the histopathologic features of dramatic thickening of the stratum corneum and follicular hyperkeratosis, and he distinguished this disorder from other types of congenital ichthyosis. "Harlequin" refers to the resemblance of the facial features and diamond-shaped scales in affected neonates to the costume of the comic servant character with this name. Initially called a "harlequin fetus" because of the premature delivery and fatal outcome, increasing survival rates due to improved neonatal care and systemic retinoid treatment have resulted in evolution to the terms "harlequin baby" and (currently) "harlequin ichthyosis" (HI).

Epidemiology

This rare disorder is inherited in an autosomal recessive manner and has been reported in patients with a wide variety of ethnic backgrounds.

Pathogenesis

In 2005, biallelic loss-of-function mutations in the ABC transporter gene *ABCA12* were identified as the cause of HI[57,58]. Truncating mutations and deletions in this gene are usually associated with severe HI, whereas missense mutations may cause a somewhat milder phenotype that overlaps with CIE/LI[59,60]. *ABCA12* encodes a membrane protein of epidermal lamellar bodies that is involved in energy-dependent lipid transport.

Lamellar bodies are absent or improperly formed in patients with HI[61], and essential epidermal lipids (e.g. glucosylceramide) are abnormally processed and incompletely secreted (or not secreted at all) into intercellular spaces. These changes prevent the formation of lipid bilayers in the stratum corneum and result in massive hyperkeratosis and a severe breakdown of the permeability barrier. Akiyama et al.[57] demonstrated that *in vitro* correction of the ABCA12 deficiency in HI keratinocytes restores normal production and distribution of glucosylceramide and the formation of lamellar bodies.

Clinical Features

Individuals with HI are usually born prematurely (mean gestational age, 35 weeks) and often die within a few days or weeks because of respiratory insufficiency or sepsis[62]. Affected neonates are encased in a hard, armor-like, tremendously thickened stratum corneum that results in severe immobilization and restricts ventilation. Shortly after birth, the hyperkeratotic cast cracks and forms large, yellow, adherent plates separated by broad, deep, intensely red fissures (Fig. 57.11). Increased transcutaneous loss of water and heat results in dehydration, electrolyte imbalances (e.g. hypernatremia) and temperature instability. The latter may impede recognition of skin infections or sepsis, which are promoted by the large fissures.

The tautness of the skin results in marked eversion of the eyelids (ectropion) and lips (eclabium), rudimentary development of ear and nasal cartilage, and sometimes microcephaly, giving the face an extremely distorted appearance. The hands and feet are edematous and swollen, often covered by a mitten-like casing. Although the digits are well developed, autoamputation due to constricting skin bands occasionally occurs. Eyelashes and eyebrows are usually missing, while scalp hair may be present. Eclabium and taut facial skin prohibit effective suckling by the infant.

Over the past two decades, improved prenatal care and oral retinoid therapy have led to prolonged survival in an increasing number of HI patients. More than half of affected individuals now live beyond the neonatal period, with the oldest HI patient to date being 25 years of age[58,59,62]. All survivors develop a severe, exfoliative ichthyosiform erythroderma, and half have a painful palmoplantar keratoderma; dystrophic nails (e.g. small, thickened) and poor hair growth are also common. Complications in these patients include recurrent skin infections, reduced sweating with heat intolerance, ocular problems related to persistent ectropion, chronic constipation and joint contractures[62]. Although affected children often have delayed growth and development (especially of motor skills), intelligence is typically normal.

Fig. 57.11 Harlequin ichthyosis. Severe hyperkeratosis with fissuring as well as eclabion and ectropion. *Reproduced from Morillo M, Novo R, Torrelo A, et al. Feto arlequin. Actas Dermosifiliogr. 1999;90:185–7.*

Pathology

The histologic hallmark is an extraordinarily thickened and compact orthokeratotic stratum corneum, although parakeratosis is occasionally observed. Hair follicles and sweat ducts have prominent hyperkeratotic plugging. Ultrastructural features include abnormal or missing lamellar bodies in the granular layer, absent extracellular lipid lamellae, and the presence of lipid inclusions or remnant organelles in the stratum corneum[61]. However, similar findings have been described in patients with CIE without transglutaminase-1 deficiency. Hair follicles show concentric accumulation of keratotic material around hair shafts, a highly characteristic feature that was historically used to establish the diagnosis based on prenatal skin biopsy specimens obtained in the second trimester[63,64].

Other diagnostic tests

Prenatal molecular testing (as early as the 10th week of gestation with CVS) is available for HI families.

Differential Diagnosis

The clinical presentation of harlequin ichthyosis at birth is striking and highly characteristic. Hyperkeratosis and associated abnormalities, such as ectropion and eclabium, are usually much milder in collodion babies. However, the clinical findings in children and adults with HI overlap with severe forms of CIE. The facial features and taut, scaling skin in Neu–Laxova syndrome may be reminiscent of HI, but this rare autosomal recessive disorder also features microcephaly, lissencephaly (few and shallow convolutions of the brain), syndactyly and a variety of other congenital malformations.

Treatment

HI remains a life-threatening and often fatal disorder, and survivors require long-term multidisciplinary management. During the neonatal period, intensive care is needed to provide sufficient nutrition, monitor and manage body temperature, correct fluid and electrolyte imbalances, and prevent and treat respiratory dysfunction, pneumonia or sepsis. Severe ectropion necessitates ophthalmologic care. Infants should be kept in humidified incubators and treated topically with light emollients. Early administration of systemic retinoids, in particular acitretin (usually with an initial dose of 1 mg/kg/day)[65], has been shown to result in shedding of the large, keratotic plates within weeks as well as improvement of the ectropion and eclabium. It is important to discuss

the overall prognosis, therapeutic options and potential side effects with each family before beginning treatment.

COMÈL–NETHERTON SYNDROME

Synonyms: ■ Netherton syndrome ■ Ichthyosis linearis circumflexa ■ Trichorrhexis invaginata

History

This disorder is named after Comèl, an Italian who first described the clinical features of ichthyosis linearis circumflexa, and Netherton, an American who discovered an unusual hair shaft abnormality that he termed "bamboo hair" in a child with a CIE phenotype. Wilkinson et al.[66] delineated the triad of congenital ichthyosis, trichorrhexis invaginata and atopy as "Netherton's syndrome" in 1964. It was later recognized that this disorder encompasses different cutaneous presentations, such as ichthyosiform erythroderma, localized ichthyosis linearis circumflexa and continuous skin peeling[12,67].

Epidemiology

Comèl–Netherton syndrome (NTS) is an autosomal recessive disorder that occurs worldwide, with a higher prevalence in inbred populations. Considering the phenotypic variability and clinical overlap with atopic dermatitis as well as other forms of ichthyosis, it has been estimated that the incidence of NTS might be as high as 1 in 50 000[12]. In one series, 18% of patients who presented with erythroderma during the neonatal period had NTS[68].

Pathogenesis

NTS is caused by biallelic mutations in the serine protease inhibitor Kazal type 5 gene (*SPINK5*)[69,70]. More than 50 *SPINK5* mutations have been identified, with small deletions, insertions or nonsense mutations that result in premature termination of translation in ~65% of cases and missense mutations that compromise enzyme function in the remainder.

SPINK5 encodes the multi-domain serine protease inhibitor LEKTI, which is predominantly expressed in the lamellar granules of epithelia and lymphoid tissues. A lack of functional LEKTI leads to uncontrolled activity of serine proteases, and a significant increase (up to five-fold) of trypsin-like proteolytic activity in the stratum corneum has been documented in NTS patients[71]. This disturbs the regulation of lipid-processing enzymes that is critical to proper formation of the lamellar lipid bilayer system in the stratum corneum. Hastened degradation of desmoglein 1 results in disintegration and shedding of horny cells, ultimately producing superficial clefts within the stratum corneum and severely disrupted skin barrier function[72]. In addition, LEKTI deficiency leads to a loss of crucial anti-inflammatory and antimicrobial mechanisms in the skin.

Histochemical analysis of hair shafts in NTS demonstrates a reduced number of disulfide bonds, which is suggestive of diminished cross-linkage of hair keratin structures and a weaker coherence of cortical cells. Such focal softening of the hair shaft may allow intussusception of the distal shaft into the dilated proximal cup.

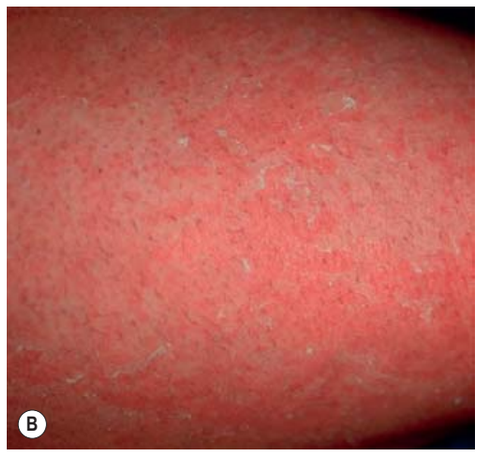


Fig. 57.12 Netherton syndrome. A Generalized involvement with features of congenital ichthyosiform erythroderma. **B** Close-up showing "peeling" quality of the scale. **C** Short, thin hair on the scalp, sparse eyebrows and a lack of eyelashes.

Clinical Features

NTS presents in most (but not all) patients at or soon after birth with generalized erythroderma and scaling (resembling CIE) or continuous peeling of the skin. A collodion membrane is not a feature of NTS. Approximately 20% of neonates develop potentially fatal complications such as hypernatremic dehydration, electrolyte imbalances, perturbed thermoregulation, failure to thrive, pneumonia and sepsis. In patients with severe disease, generalized ichthyosis and erythroderma persist throughout life (Fig. 57.12).

In the majority of patients, the ichthyosis gradually evolves into serpiginous or circinate scaling and erythematous plaques, which are bordered by a peculiar double-edged scale and descriptively named "ichthyosis linearis circumflexa" (Fig. 57.13). The plaques are usually distributed on the trunk and extremities and change over time in size, shape and location, reflecting the undulating course of NTS. The lesions are pruritic, and many patients develop eczematous plaques and/or lichenification in flexural sites, especially the wrists and antecubital and popliteal fossae. Scalp involvement with thick scale is common.

Hair shaft abnormalities usually develop during infancy and early childhood and improve with age, but they vary tremendously in age of onset, extent, severity and type. While in some patients the scalp hair grows slowly and is sparse, thin and fragile, it has a normal appearance in others. Light microscopic examination of clipped hair from the scalp and (of particularly high yield) the eyebrows[73] often reveals trichorrhexis invaginata (bamboo hair) with a ball-and-socket appearance (Fig. 57.14) or nodular thickening of the distal end of broken hair shafts ("golf tee"). Multiple additional abnormalities may be observed, including pili torti,

Fig. 57.13 Ichthyosis linearis circumflexa. Note the double-edged scale.

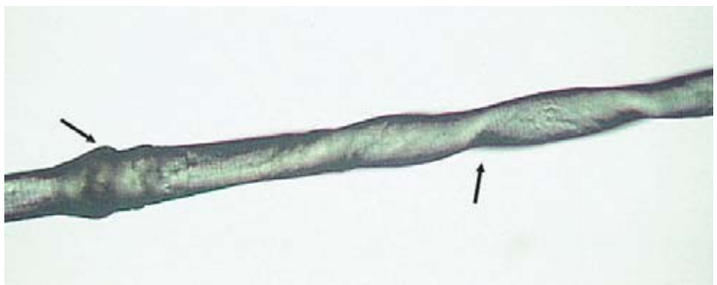


Fig. 57.14 Abnormal hair shaft in Netherton syndrome. Trichorrhexis invaginata with its ball-and-socket appearance (left arrow) and twist in the hair shaft (right arrow).

trichorrhexis nodosa and "helical" hair. Eyelashes and secondary sexual hair can also be affected.

The third characteristic feature of NTS is immune imbalance. Serum levels of IgE are usually markedly elevated, ranging from 100 to >10 000 IU/ml. Eosinophilia and allergic reactions to various foods (e.g. nuts, eggs, fish) and other antigens are common, with clinical manifestations ranging from an exacerbation of eczematous skin lesions to urticaria and angioedema to anaphylactic shock. Children have an increased susceptibility to cutaneous, respiratory and systemic infections, which might reflect defective production of antibodies against protein and polysaccharide antigens. Human papilloma virus (HPV) infections are relatively common and can result from epidermodysplasia verruciformis-associated HPV types. HPV infections may increase the incidence of SCC (e.g. of the vulva or skin) in patients with NTS.

During infancy and early childhood, patients with generalized skin involvement often continue to experience failure to thrive, which may be related to enteropathy with villus atrophy and malnutrition (especially considering the increased caloric needs associated with erythroderma); this often results in short stature[74]. Intermittent aminoaciduria is not uncommon. A few patients with substantial developmental delay have been reported. Although this could be due to consanguinity in these families, in one patient, persistent, mild diffuse volume loss indicative of a permanent injury of brain tissue was documented by MRI[75].

Pathology

On light microscopic examination, the epidermis shows pronounced parakeratotic hyperkeratosis with a diminished or absent granular layer, acanthosis and papillomatosis. There are often dense, almost band-like, lymphohistiocytic perivascular infiltrates in the papillary dermis. Subcorneal clefting, spongiosis, exocytosis and Munro's microabscesses can occur. The stratum corneum may be strongly eosinophilic on PAS stain. Trichorrhexis invaginata, in which the distal hair shaft is telescoped into the proximal segment, is a highly characteristic light microscopic finding in clipped hairs; other hair shaft abnormalities may also be evident (see above).

Ultrastructural abnormalities in the epidermal lipid system that are not present in other erythrodermic disorders may assist in differentiating NTS from CIE and erythrodermic psoriasis. In particular, premature secretion of lamellar body contents in the upper epidermis as well as the presence of intercellular electron-dense accumulations and abnormal splitting in the superficial stratum corneum seem specific for NTS[72,76]. Other ultrastructural abnormalities that are not consistently found include round cytoplasmic inclusion bodies in the upper cell layers (potentially representing lysosomes), a decreased tonofilament–desmosome system and a lack of lamellar bodies. Transmission electron microscopy of hair shafts reveals faulty keratinization, cleavage and electron-dense depositions in the cortex.

Other diagnostic tests

Molecular testing of the *SPINK5* gene is available and can facilitate diagnosis of NTS. Prenatal diagnosis can be performed in families with known *SPINK5* mutations from CVS (as early as the 10th gestational week) or amniocentesis material[70]. In addition, immunostaining of skin biopsy specimens with LEKTI antibodies can be used to determine absence or aberrant distribution of LEKTI protein in the epidermis of affected patients[77,78].

Differential Diagnosis

During infancy, NTS often presents a diagnostic challenge due to its clinical overlap with CIE, erythrodermic psoriasis, and disorders of the immune system (e.g. Omenn syndrome). Although the presence of trichorrhexis invaginata and other hair shaft abnormalities can distinguish NTS from these conditions, characteristic hair shaft abnormalities may not be present at birth or in early infancy, and their detection requires repeated microscopic analysis of many hairs from different locations (e.g. scalp, eyebrows). Elevated serum IgE levels can also help to differentiate NTS from CIE and psoriasis.

In addition to Omenn syndrome, hyper-IgE syndrome may represent a diagnostic consideration; the latter is characterized by elevated IgE levels in association with recurrent bacterial and candidal infections and a neonatal papulopustular eruption that is followed by the development of atopic-like dermatitis. However, the facial, dental and skeletal anomalies observed in classic hyper-IgE syndrome are not seen in NTS. To differentiate among these and other primary immunodeficiencies, including Wiskott–Aldrich syndrome (see Ch. 60), infants with failure to thrive and generalized eczematous or scaling skin require a comprehensive immunologic evaluation.

In acrodermatitis enteropathica (see Ch. 51), erythematous, sometimes figurate plaques with scale-crust are usually restricted to periorificial areas and the distal extremities. If zinc deficiency cannot be excluded with certainty, an empirical trial of zinc treatment is indicated. The migratory, serpiginous plaques of ichthyosis linearis circumflexa can also resemble those seen in erythrokeratodermia variabilis. Prominent borders with a double-edged scale and associated hair shaft abnormalities are specific for NTS, while transient, variable erythematous patches are characteristic of erythrokeratodermia variabilis.

Peeling skin syndromes (PSSs) are clinically and genetically heterogeneous disorders characterized by perpetual peeling and desquamation of the skin with variable associated erythema. They share many features with NTS, including congenital erythroderma (in the generalized inflammatory subtype of PSS), pruritus, and histologic and ultrastructural abnormalities. Although mutations in the corneodesmosin gene (*CDSN*) were recently found to cause generalized inflammatory PSS[79], *SPINK5* mutations have been identified in some patients with erythroderma and generalized skin peeling[75].

Treatment

Treatment is symptomatic and should be adjusted to the patient's specific needs. Neonates with exfoliative erythroderma and severe impairment of skin barrier function often require management in an intensive care nursery. Patients who develop failure to thrive and enteropathy may need nutritional support to ensure sufficient intake of calories and protein.

Topical emollients, keratolytics, tretinoin, calcipotriene (calcipotriol) and corticosteroids (alone or in combination) are variably effective.

Although the skin lesions of NTS may respond well to topical tacrolimus, dramatically increased percutaneous absorption of this medication has been described in NTS patients, presumably due to their severe skin barrier dysfunction[80]. Use of topical tacrolimus in NTS patients therefore requires monitoring of plasma drug levels. Topical pimecrolimus has also been successfully used in NTS patients, with considerably less systemic absorption[81]. Topical or systemic antimicrobial agents are often required to treat bacterial and fungal skin infections, but continuous preventive antibiotic therapy (oral or topical) should be avoided because of the risk of developing antibiotic resistance. Oral antihistamines may be helpful in controlling pruritus. Systemic retinoids have variable efficacy, leading to dramatic improvement in some patients and exacerbation of the disease in others. Benefit from treatment with psoralen plus UVA (PUVA), UVA1 and balneophototherapy (broadband UVB plus salt water baths) has been reported.

SJÖGREN–LARSSON SYNDROME

History

In 1957, Sjögren and Larsson[82] defined the clinical triad of congenital ichthyosis, gradually developing di- or tetraplegia, and mental retardation as a distinct disorder in 28 Swedish patients. In 1988, Rizzo et al.[83] discovered an underlying deficiency in the oxidation of long-chain fatty acids due to malfunction of the fatty alcohol dehydrogenase : fatty aldehyde dehydrogenase enzyme complex. Subsequently, De Laurenzi et al.[84] identified the underlying defect in the fatty aldehyde dehydrogenase gene (*ALDH3A2/FALDH*).

Epidemiology

Sjögren–Larsson syndrome (SLS) is an autosomal recessive neurocutaneous disorder. It occurs worldwide with an estimated prevalence of less than 1 in 100 000. It is most common in northern Sweden, where it is estimated that 1.3% of the population are heterozygous carriers[82].

Pathogenesis

SLS is caused by a deficiency of the microsomal fatty aldehyde dehydrogenase enzyme due to recessive inactivating mutations in the *ALDH3A2* (*FALDH*) gene[84]. More than 80 distinct mutations have been identified to date, and sequence analysis of the *ALDH3A2* gene has almost 100% sensitivity in patients with a clinical diagnosis of SJS. In a group of 121 SLS families, 38% had missense, 16% splice site and 5% nonsense mutations, with deletions, insertions and complex mutations in the remainder[85]. A few mutations have a high allelic frequency in northern European and Middle Eastern populations due to a founder effect[85].

The microsomal fatty aldehyde dehydrogenase enzyme (FALDH) catalyzes NAD-dependent oxidation of long-chain aliphatic aldehydes (derived from metabolism of 16- to 18-carbon straight-chain fatty alcohols and ether glycerolipids) into fatty acids. This pathway is important for the synthesis of epidermal lipids as well as the catabolism of ether phospholipids and sphingolipids in the brain[86]. The symptoms of SLS are thought to stem from membrane alterations due to accumulation of fatty alcohol- or fatty aldehyde-modified lipids and proteins. Retarded myelination and a variable degree of dysmyelination probably result from the accumulation of free lipids in the periventricular white matter. In addition, FALDH catalyzes steps downstream of lipoxygenases (12R-LOX and eLOX) in the hepoxilin pathway of arachidonic acid metabolism (which is also modulated by ichthyin). FALDH also degrades leukotriene B_4, and the accumulation of leukotrienes may contribute to pruritus in SLS patients.

Clinical Features

SLS presents at birth with varying degrees of erythema, hyperkeratosis and scaling. A collodion membrane and ectropion are rare. After infancy, the erythema tends to fade, while hyperkeratosis and scaling become more prominent and darker in color. The ichthyosis varies from fine, white scales to larger, plate-like scales to non-scaling, yellowish hyperkeratosis (Fig. 57.15). Predilection sites include the lower abdomen (especially around the umbilicus), the neck (especially the sides and nape) and flexural areas. Approximately 70% of patients develop palmoplantar keratoderma. Accentuated skin markings and lichenification of flexural areas are common. In contrast to most other ichthyoses, SLS is associated with persistent pruritus, which often leads to visible excoriations.

Fig. 57.15 Sjögren–Larsson syndrome. Yellowish-brown hyperkeratosis, accentuated skin markings and areas of scaling on the lower back and buttocks. *Courtesy, Julie V Schaffer, MD.*

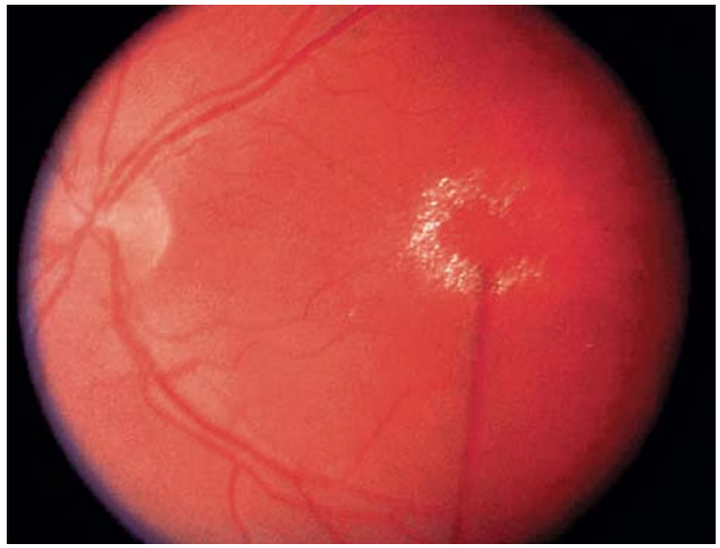


Fig. 57.16 Sjögren–Larsson syndrome. Perifoveal glistening white dots of the ocular fundus. *Courtesy, WB Rizzo, MD.*

An important diagnostic and almost pathognomonic finding in SLS is the presence of perifoveal glistening white dots in the ocular fundus, which represents a form of juvenile macular dystrophy (Fig. 57.16)[87]. These dots can be detected in many, but not all, patients during the first year of life, and they increase in number over time. Involvement of the CNS usually manifests at the end of the first year of life with delayed motor development, an abnormal gait, pyramidal signs, spasticity and contractures. The lower extremities are usually more severely affected than the arms. The di-or tetraplegia is gradually progressive and accompanied by speech defects and mental retardation. Seizures are present in almost 40% of affected individuals, and MRI of the brain shows white matter disease in most patients. Other variable clinical features of SLS include superficial corneal defects and photophobia, dental and/or osseous dysplasia, and hypertelorism.

Pathology

The histopathologic features are nonspecific and include primarily orthokeratotic hyperkeratosis, papillomatosis and moderate acanthosis

with a well-developed granular layer. Similarly, the ultrastructural abnormalities are not diagnostic. Keratinocytes may show mitochondrial proliferation and a prominent Golgi apparatus, with lamellar membranous inclusions and clefts in corneocytes.

Other diagnostic tests

Cultured skin fibroblasts, keratinocytes or leukocytes have drastically reduced or absent FALDH activity. Biochemical analysis has proven to be a reliable diagnostic tool that also allows detection of unaffected carriers, who exhibit half of the normal levels[88]. Another sensitive marker for the enzyme deficiency in SLS is the detection of elevated free fatty alcohols in cultured fibroblasts and plasma. However, the preferred method for confirming the diagnosis of SLS is DNA-based molecular testing. Prenatal molecular diagnosis from CVS or amniocentesis material can also be performed[85,88].

Differential Diagnosis

Clinically, the combination of congenital ichthyosis with spasticity and/or retinal glistening dots is diagnostic for SLS. The skin findings can overlap with those of steroid sulfatase deficiency, severe ichthyosis vulgaris and mild forms of CIE or lamellar ichthyosis. In contrast to the latter two disorders, ectropion, eclabium and alopecia are usually not seen in SLS.

Treatment

Management of SLS patients requires a multidisciplinary approach, including dermatologic, neurologic, ophthalmologic and orthopedic care as well as social support. Topical keratolytics and vitamin D preparations in combination with hydration of the skin are helpful in reducing hyperkeratosis and scaling. Systemic retinoids, especially acitretin, are effective and relatively safe even in children when a minimal effective dose is maintained and patients are monitored for side effects. The 5-lipoxygenase inhibitors (e.g. zileuton) block the synthesis of leukotriene B_4 and have been shown to decrease pruritus in a subset of SLS patients, but a beneficial effect on the ichthyosis and CNS symptoms has not been demonstrated. Treatment of neurologic abnormalities is symptomatic, including anticonvulsive agents for seizures as well as aggressive physical therapy and (if indicated) surgical intervention to improve mobility. Various forms of a fat-reduced diet have yet to provide consistent and reproducible results.

NEUTRAL LIPID STORAGE DISEASE WITH ICHTHYOSIS

Synonym: ▪ Chanarin–Dorfman syndrome

History

This disorder of lipid metabolism was first recognized as a distinct entity by Dorfman et al.[89] in 1974, and Chanarin et al.[90] coined the name in 1975.

Epidemiology

This is a rare autosomal recessive disorder. Most cases have been observed in consanguineous families from the Middle East and Mediterranean basin (e.g. Sicily, Greece, Turkey, Algeria and Morocco).

Pathogenesis

Neutral lipid storage disease with ichthyosis is an inborn error of lipid metabolism with accumulation of triglycerides in the skin and other organs. The disorder is caused by deleterious germline mutations in the abhydrolase domain containing 5 gene (*ABHD5*; previously known as *CGI-58*), which encodes a protein in the esterase/lipase/thioesterase subfamily[91]. This lipid droplet-associated protein facilitates lipolysis in cooperation with triglyceride lipases, perilipin and other factors[92]. Cytoplasmic accumulation of triglyceride droplets presumably results from a block in the degradation of endogenously produced diacylglycerols[93]. Hydrolyzed fatty acids and the acylated glycerol backbone of triglycerides cannot be properly incorporated into phospholipids, and they are instead re-esterified to form triglycerides. Hydrolysis of triglycerides of exogenous origin (serum lipoproteins) via liposomal acid lipase as well as endogenous triglycerides via cytosolic lipase is normal. In the skin, deficiency of the ABHD5 protein is thought to result in defective lipid production within lamellar granules[94].

Clinical Features

The disorder presents at birth with generalized, fine, white scaling of the skin and a variable degree of erythema, thus resembling CIE[90,91,93]. At least one patient with a collodion membrane has been reported and several patients have had ectropion, eclabium and alopecia[93]. On the lower extremities and scalp, the scales may be grayish, larger and plate-like with detached borders.

The widespread tissue deposition of neutral lipids results in a broad array of systemic manifestations during childhood. Serum liver enzymes and muscle phosphocreatine kinase are usually elevated, although the myopathy may be mild and detectable only by neurologic examination. Hepatomegaly is common, and liver biopsy often reveals severe fatty degeneration and fibrosis, which may not be reflected in liver function studies.

Cataracts, neurosensory deafness and developmental delay are frequent features, while growth retardation, ataxia, microcephaly, splenomegaly and intestinal malabsorption have been observed only in a subset of patients. The prognosis of neutral lipid storage disease with ichthyosis depends primarily on the course of the liver disease and extent of hepatic fibrosis.

Pathology

A diagnostic feature is the presence of numerous lipid-containing vacuoles in circulating granulocytes (Jordan's anomaly), eosinophils and monocytes, a finding detectable on a fresh peripheral blood smear but not by automated blood counting methods (Fig. 57.17). Similar findings (but to a lesser extent) may be seen in heterozygous carriers of the disease. Using lipid stains (oil red O, Sudan III), cytoplasmic lipid droplets can be also detected in fresh frozen skin sections, particularly in the epithelium of eccrine sweat glands and ducts but also in fibroblasts and basal and sometimes suprabasal keratinocytes. Ultrastructural abnormalities of the epidermis include globular electron-lucent inclusions, which disrupt the normal structure of lamellar bodies in the cells of the granular layer and change the conformation of intercellular lipid lamellae throughout the stratum corneum[95].

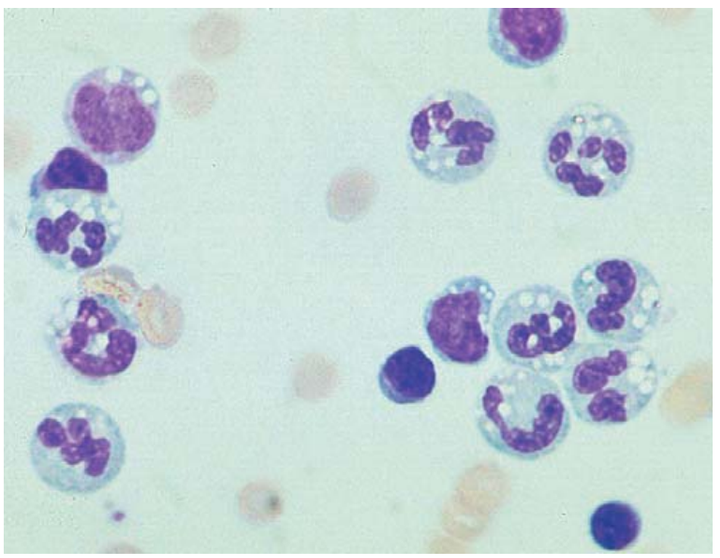


Fig. 57.17 Neutral lipid storage disease. Lipid droplets in circulating granulocytes and monocytes but not lymphocytes or erythrocytes. *Courtesy, ML Williams, MD.*

Fig. 57.18 Acral peeling skin syndrome. Superficial peeling of the skin on the ankle and dorsal aspect of the foot. *Courtesy, E Sprecher, MD, PhD.*

Differential Diagnosis

The associated ichthyosis is clinically similar to CIE, but the microscopic detection of lipid vacuoles in circulating white blood cells is diagnostic for neutral lipid storage disease with ichthyosis. In Refsum disease, a peroxisomal disorder characterized by accumulation of phytanic acid, the ichthyosis is not congenital and is more reminiscent of ichthyosis vulgaris. Although cytoplasmic lipid accumulations in basal keratinocytes may be found in both disorders, lipid droplets on a peripheral blood smear are not seen in Refsum disease.

Treatment

Therapy is symptomatic. Topical emollients and keratolytics as well as systemic retinoids have been shown to improve the ichthyosis. A fat-restricted diet (e.g. low in long-chain but enriched in medium-chain fatty acids) has been reported to be beneficial in a few patients, but data are too limited to determine if systemic complications can be prevented.

TRICHOTHIODYSTROPHY WITH ICHTHYOSIS

Synonyms: ■ IBIDS: ichthyosis, brittle hair, infertility, developmental delay, short stature ■ Tay syndrome ■ PIBIDS: photosensitivity + IBIDS ■ Sulfur-deficient brittle hair syndrome

History

The first description of this disorder was in 1968, when Pollitt et al.[96] reported siblings with brittle hair, trichorrhexis nodosa, short stature and mental retardation. In 1971, Tay[97] described three siblings with similar features and additional skin involvement resembling CIE. Several years later, the term "trichothiodystrophy" was proposed to encompass a heterogeneous group of neuroectodermal disorders that share the finding of sulfur-deficient, short, brittle hair.

Epidemiology

With the exception of one reported case with possible X-linked transmission, the disorder is inherited in an autosomal recessive fashion, affecting both genders equally.

Pathogenesis

Trichothiodystrophies are a heterogeneous group of neuroectodermal disorders. In types that are associated with photosensitivity, there is reduced stability or altered function of the large transcription factor IIH (TFIIH) (see Ch. 86). This can be due to recessive mutations in two genes that encode its helicase subunits, *ERCC2*/XPD and, less frequently, *ERCC3*/XPB. These genes are also mutated in patients with xeroderma pigmentosum (XP; complementation groups D and B, respectively) and combined Cockayne syndrome–XP. Mutations in the *GTF2H5* gene, which encodes the TFIIH subunit TTD-A, have also been implicated in a small subset of patients with photosensitive trichothiodystrophy[98]. In addition, mutations in *C7ORF11*, which encodes a protein with a potential role in regulating mitosis and cytokinesis, have been identified in patients with a non-photosensitive form of trichothiodystrophy that typically lacks ichthyosis.

The TFIIH deficiency in patients with trichothiodystrophy due to abnormal XPD or XPB results in impaired DNA repair, thus leading to photosensitivity, as well as repression of the basal transcription of genes that are highly expressed in differentiated cells of various tissues. The latter mechanism might explain defective synthesis of high-sulfur matrix proteins in hair and nails, growth retardation, short stature and neurologic abnormalities, and it is supported by findings in transgenic animals[99]. In contrast, the TFIIH defect in XP profoundly impairs global genome nucleotide excision repair (which is particularly important for UV-induced DNA damage) and thereby leads to cancer formation as well as photosensitivity, while abnormal transcription-coupled repair in Cockayne syndrome results in apoptosis of metabolically active cells (e.g. neurons) rather than carcinogenesis. This lack of carcinogenesis in trichothiodystrophy might be attributed to the fact that the TFIIH defects in these patients do not completely abolish its nucleotide excision repair function[100]. Analysis of the steady-state level of TFIIH in fibroblast strains of trichothiodystrophy patients with *ERCC2*/XPD mutations revealed a substantial and specific reduction (up to 70%) in the cellular concentration of TFIIH complex[101].

Clinical Features

The obligatory finding in all types of trichothiodystrophy is short, unruly, fragile hair of the scalp, eyebrows and eyelashes due to abnormally low sulfur content (i.e. deficient cysteine and/or methionine). Body, axillary and pubic hair may also be affected. Nail changes are common and can include thinning, longitudinal ridging, yellow discoloration, splitting and onychogryphosis. Patients with trichothiodystrophy may present at birth or in the neonatal period with erythroderma and generalized fine scaling similar to that seen in CIE. A collodion membrane presentation is rare and not associated with ectropion or eclabium. The erythema usually resolves during infancy. The size and color of the associated scale is variable, ranging from fine and translucent to large and dark.

Photosensitivity occurs in half of patients, but (similar to Cockayne syndrome) there is no propensity to develop cutaneous malignancies[99]. Additional cutaneous findings that have been described in trichothiodystrophy patients include follicular keratoses, folliculitis, erythema, atopic-like dermatitis, cheilitis, hypohidrosis, pruritus, hyperpigmentation of the eyelids, lentigines, hypopigmented macules, telangiectasias, poikiloderma, "hemangiomas", lipoatrophy, pyoderma and palmar pustules. Other associated abnormalities depend upon the type of trichothiodystrophy and include short stature, mental retardation, hypogonadism, progeria-like features (e.g. decreased subcutaneous fat), cataracts, joint contractures and (very rarely) osteosclerosis.

Pathology

By light microscopy, hair shafts show transverse fractures (trichoschisis) in conjunction with an irregular surface and diameter. Occasionally, a nodal appearance similar to trichorrhexis nodosa or 180° twists as in pili torti may be observed. Polarizing light microscopy is the gold standard for detecting the characteristic light and dark bands, the so-called "tiger-tail" or "zigzag" pattern (see Ch. 69), which has been incorrectly referred to as alternating birefringence[99]. On transmission electron microscopy, an abnormal arrangement of microfibers as well as an absence of the exocuticle and cuticular A-layer may be seen. If ichthyosis is present, histopathologic changes are typically similar to those found in ichthyosis vulgaris (see above). Occasionally, perinuclear vacuoles are seen.

Other diagnostic tests

Hair sulfur content can be semi-quantitatively analyzed by scanning electron microscopy. Determination of cysteine content through amino acid analysis of hydrolyzed hair is also possible.

Differential Diagnosis

Although Cockayne syndrome shares several features with the photosensitive form of trichothiodystrophy, the former lacks ichthyosis and

tiger-tail hairs. Likewise, the characteristic findings on microscopic hair analysis distinguish trichothiodystrophy from other conditions that feature congenital alopecia or hypotrichosis, including Menkes disease. Polarized hairs can also have a tiger-tail pattern in healthy infants, but this is usually not prominent in all hairs as it is in trichothiodystrophy. Hair shaft abnormalities (including trichorrhexis nodosa), ichthyosiform erythroderma and failure to thrive are also seen in NTS; although differentiation from trichothiodystrophy can be difficult in the neonatal period, elevated serum IgE levels are suggestive of NTS. Patients with Sjögren–Larsson syndrome, lamellar ichthyosis and CIE have no hair shaft abnormalities.

Treatment

If photosensitivity is present, sun protection is essential. Treatment of the ichthyosis should be tailored to its severity. Symptomatic relief is best achieved with humectants or (in more severe cases) systemic retinoids.

REFSUM DISEASE

Synonyms: ■ Heredopathia atactica polyneuritiformis ■ Phytanic acid storage disease

Refsum disease is a rare autosomal recessive neurocutaneous disorder that results from abnormal lipid metabolism. It is caused by mutations in the phytanoyl-CoA hydroxylase (*PHYH*) or peroxisome biogenesis factor 7 (*PEX7*) genes, which lead to impaired degradation of phytanic acid[102–104]. As a result, this 20-carbon, saturated, branched-chain fatty acid (exclusively derived from exogenous sources) accumulates in multiple tissues and body fluids.

During childhood or adolescence, half of patients with Refsum disease develop ichthyosis of mild to moderate severity that is characterized by small white scales on the extremities and trunk, often resembling ichthyosis vulgaris. Larger, adherent scales and hyperlinear or hyperkeratotic palms and soles may also be seen. Histologic examination of affected skin shows orthokeratotic hyperkeratosis and lipid-containing vacuoles in basal keratinocytes.

Adolescents with Refsum disease present with the insidious onset of neurologic symptoms such as weakness, difficulty walking and poor night vision. Cardinal features are atypical retinitis pigmentosa, hypo- or anosmia, peripheral polyneuropathy of a mixed motor and sensory type, cerebellar dysfunction and elevated protein levels in the cerebrospinal fluid. Other findings can include sensorineural deafness, cataracts, renal tubular dysfunction, cardiomyopathy and skeletal hyperostosis.

Refsum disease typically follows a progressive but undulating course and results in gradual neurologic deterioration. However, drastic reduction of dietary phytanic acid intake (<5 mg daily; found mainly in dairy products and animal fats) can both prevent acute attacks and arrest neurologic progression, although retinal changes are usually irreversible[105–107]. LDL apheresis can be performed to eliminate (V)LDL-bound phytanic acid in settings of acute toxicity[105–107].

OTHER ICHTHYOSES

Additional rare ichthyoses for which the genetic basis or chromosomal locus is known are presented in Table 57.5.

ERYTHROKERATODERMAS

ERYTHROKERATODERMIA VARIABILIS

Synonyms: ■ Erythrokeratoderma variabilis ■ Erythrokeratodermia figurata variabilis ■ Mendes da Costa disease

History

De Buy Wenninger published the first description of this entity in 1907[119]. Eighteen years later, Mendes da Costa presented a detailed clinical description of the disease in a mother and daughter, reviewed eight previously reported cases, and coined the name "erythroet keratodermia variabilis"[120]. Over the next several decades, large Dutch and Swiss kindreds with this condition were described. The first case in the American literature was reported by Barsky and Bernstein in 1964[121].

Epidemiology

Erythrokeratodermia variabilis (EKV) is a rare disorder, predominantly inherited in an autosomal dominant fashion with nearly complete penetrance but considerable intra- and interfamilial variability. More than 200 cases have been reported, the majority of which were in Caucasians, although EKV has also been observed in African-Americans and Asians. In a few families, autosomal recessive inheritance has been documented.

Pathogenesis

Most, but not all, cases of EKV are caused by dominant mutations in the connexin genes *GJB3* and *GJB4*[122,123] (see Table 58.3). These genes encode the gap junction proteins β3 (connexin 31) and β4 (connexin 30.3), which belong to a large family of transmembrane proteins that form intercellular channels (see Ch. 58). To date, 14 dominant and 2 recessive mutations have been reported in *GJB3* or *GJB4* in >20 unrelated families and sporadic cases with EKV. All mutations result in amino acid substitutions of conserved residues in connexin 31 or connexin 30.3, which have been shown to alter the structure or function of gap junction channels, impair cytoplasmic trafficking of the mutant gap junction proteins to the cell membrane and/or induce cell death, thereby impairing normal epidermal differentiation[124].

Clinical Features

The hallmark of EKV is the coexistence of transient erythematous patches and more stable hyperkeratotic plaques. One of these features frequently predominates, and occasionally one is missing. The erythematous component is most prevalent during childhood and later slowly subsides. More than 50% of patients present at birth or in the neonatal period, and 90% within the first year of life, with transient erythematous patches that can involve any part of the integument. These lesions are well demarcated with a geographic, circinate or target-like appearance, and they can coalesce into large figurate patches (Fig. 57.19). Circinate or gyrate erythematous patches have been associated predominantly with mutations in *GJB4*, and this variant might be identical to the previously described "erythrokeratodermia en cocarde". The erythema is of variable intensity and is sometimes surrounded by a blanched halo. Individual lesions usually persist for only minutes to hours, although they may last for days. In about 35% of patients, the erythema is preceded or accompanied by a burning sensation, which

Fig. 57.19 Erythrokeratodermia variabilis. Transient erythematous patches and generalized brownish hyperkeratosis.

Fig. 57.20 Erythrokeratodermia variabilis. A Symmetrically distributed hyperkeratotic plaques with hypertrichosis. **B** Brown hyperkeratotic plaques with geographic borders in a 7-year-old child. *B, Courtesy, Julie V Schaffer, MD.*

may cause discomfort. The remarkable variability in number, size, shape, location and duration of erythematous patches is reflected in the name of the disease.

Hyperkeratosis evolves simultaneously with or following the appearance of transient erythematous lesions. Sharply demarcated, yellow–brown to pink–brown thickened plaques with geographic borders progressively develop on the limbs, buttocks and trunk in an almost symmetric distribution (Fig. 57.20). In approximately half of all patients, the thickening of the skin extends onto the palms and soles, while the flexures, face and scalp tend to be spared. The surface can be ridged, verrucous or velvety, and it may have collarette-like peeling or fine, adherent scales. Lesions on the elbows, knees, Achilles tendons, dorsal aspect of the feet, and waistline are particularly common and tend to persist for months to years. In a subset of patients with severe disease, hyperkeratosis is generalized and persistent, with a yellow–brown–gray thickening of the skin and accentuated skin markings. Fine scaling, peeling and hypertrichosis may be observed. Some patients develop thick, dark plates of hyperkeratosis with a spiny, hystrix-like appearance, especially on the lower extremities.

After gradual progression throughout infancy and childhood, EKV tends to stabilize after puberty. Improvement over time and periodic clearing of the skin are not unusual. Skin lesions may be triggered by factors such as emotional stress, sudden temperature changes, mechanical friction and sun exposure.

Pathology

Histopathologic features are orthokeratotic, basket-weave hyperkeratosis, moderate to severe acanthosis with a prominent granular layer, and papillomatosis. There are dilated, elongated capillaries with minimal perivascular inflammation in the papillary dermis. Severe papillomatosis with suprapapillary thinning may result in a "church spire" configuration of the epidermis. Ultrastructural studies have had variable results, including a reduced number of lamellar bodies in the granular layer.

Differential Diagnosis

EKV shares many clinical features with progressive symmetric erythrokeratoderma (PSEK), making it difficult to distinguish these disorders. In contrast to EKV, hyperkeratotic plaques in PSEK usually develop on an erythematous base and there are no additional "migrating" red patches. However, transient erythematous patches are subtle or absent in some EKV patients, especially during adulthood. Although a *GJB4* mutation has been identified in some patients with a PSEK phenotype, the absence of pathogenic mutations in *GJB3* or *GJB4* in at least six patients/families with PSEK suggests that it also exists as a genetically distinct entity[122,125]. More thorough genotype-phenotype correlations are needed to better understand the phenotypic spectra of EKV and PSEK and the relationship between these conditions.

The migratory, serpiginous erythematous plaques of ichthyosis linearis circumflexa (a presentation of NTS) are typically bordered by a double-edged scale, and patients usually have additional manifestations such as hair shaft abnormalities, eczematous lesions and pruritus. The micaceous scale and histopathologic findings of psoriasis distinguish it from EKV. Patients with erythrokeratolysis hiemalis (see Table 57.5) develop erythematous circinate plaques with centrifugal peeling that primarily affect the palms and soles but occasionally extend to the arms and legs. Sharply demarcated hyperkeratotic plaques that wax and wane may also be seen in rare cyclic and annular subtypes of epidermolytic ichthyosis (due to *KRT1* and *KRT10* mutations, respectively; see above). Greither syndrome (see Ch. 58) is another condition due to *KRT1* mutations that features a transgredient palmoplantar keratoderma as well as hyperkeratotic plaques that can resemble lesions in EKV and PSEK, but no transient erythema. Lastly, MEDNIK syndrome (*m*ental retardation, *e*nteropathy, *d*eafness, peripheral *n*europathy, *i*chthyosis, *k*eratoderma) has skin findings (erythematous patches and hyperkeratotic plaques) similar to EKV (see Table 57.5).

Treatment

Therapy is symptomatic and depends on the severity and extent of hyperkeratosis, which varies over time and from patient to patient. Topical management with keratolytic agents (e.g. lactic acid, urea, α-hydroxy acids) and/or retinoids (e.g. tretinoin, tazarotene) may be sufficient for mild disease. Systemic retinoids such as acitretin and isotretinoin are the treatment of choice for more extensive or severe EKV. These agents often produce dramatic improvement or complete clearing of hyperkeratosis and significant reduction in the development of erythematous lesions, although the latter cannot be completely suppressed. The minimal maintenance dose for patients with EKV is usually considerably lower than that required for other disorders of cornification. Nevertheless, the use of retinoids should always be considered carefully, since chronic therapy is necessary to avoid relapse and long-term side effects, especially in children, may ensue. The red patches in EKV often result in cosmetic concerns, which can be limited by masking uncovered skin with camouflaging makeup. Avoidance of sudden temperature changes and trauma to the skin (e.g. friction or irritation) may be beneficial.

PROGRESSIVE SYMMETRIC ERYTHROKERATODERMA

Synonyms: ■ Erythrokeratoderma progressiva symmetrica ■ Gottron syndrome

History

The original description of PSEK dates back to Darier in 1911[126], and Gottron coined the name in 1922[127].

Epidemiology

PSEK is a rare disorder that appears to be genetically heterogeneous. Autosomal dominant and, less frequently, autosomal recessive transmission have been reported.

Pathogenesis

This disorder of cornification is characterized by increased epidermal cell proliferation in lesional skin. Two patients reported to have PSEK were found to have a dominant mutation in the *GJB4* gene (as seen in EKV)[125]. In a single Japanese family with PSEK-like features associated with mutilating palmoplantar keratoderma including pseudoainhum (which is usually not seen in PSEK), Ishida-Yamamoto et al.[128] detected a frameshift mutation in the loricrin gene. However, in one study, none of six PSEK patients/families from different ethnic backgrounds harbored disease-causing mutations in either the loricrin gene or the connexin genes implicated in EKV, indicating that additional genes must be causally involved[122]. A locus for PSEK on chromosome 21q11.2–q21.2 has been identified in a five-generation Chinese family[129].

Clinical Features

PSEK usually begins during infancy or early childhood with the development of fixed, sharply demarcated, polycyclic hyperkeratotic plaques on an erythematous base covered by fine scale or with a rough, verrucous surface, especially over joints. They are symmetrically distributed on the extremities (Fig. 57.21), buttocks, face (especially the cheeks) and, occasionally, the trunk. A subset of patients initially presents with bright red, progressively thickening plaques on the cheeks. Diffuse, erythematous palmoplantar keratoderma has been observed in at least half of the patients. The hyperkeratotic plaques slowly increase in number and size during childhood, but they tend to stabilize after puberty.

Pathology

Acanthosis of the epidermis with basket-weave and often patchy parakeratotic hyperkeratosis is seen. The granular layer is prominent and sometimes shows intracellular vacuolization. Follicular plugging is not uncommon. Dilated capillaries and sparse lymphocytic perivascular infiltrates are found in the papillary dermis. Electron microscopic examination reveals perinuclear vacuolization and lipid-like vacuoles or laminated inclusions in the stratum corneum, but these features are not diagnostic. Occasionally, swollen mitochondria and irregular keratohyalin granules may be observed.

Fig. 57.21 Progressive symmetric erythrokeratoderma. Well-demarcated, symmetrically distributed hyperkeratotic plaques on the lower extremities with underlying erythema and fine, white scale; the patient also had a plantar keratoderma.

Differential Diagnosis

The skin findings in PSEK, EKV and erythrokeratodermia associated with ataxia (see Table 57.5) overlap considerably, although the occurrence of transient erythema and relative sparing of the face can differentiate EKV. Diffuse palmoplantar keratodermas, especially the transgredient type described by Greither, may be associated with hyperkeratotic plaques on the knees, elbows and other extensor surfaces. The presence of perifollicular papules, islands of sparing and a salmon color distinguish pityriasis rubra pilaris, while psoriasis has characteristic micaceous scale and distinctive histopathologic findings.

Treatment

Topical keratolytics (urea, α-hydroxy acids, salicylic acid), propylene glycol and emollients are usually not very helpful. The use of topical retinoids or vitamin D preparations has not yet been reported. Several PSEK patients have been noted to respond well to systemic treatment with retinoids (isotretinoin, acitretin), while others did not. There are also anecdotal reports of successful PUVA therapy.

KERATITIS–ICHTHYOSIS–DEAFNESS SYNDROME

Synonyms: ▪ KID syndrome ▪ Erythrokeratodermia progressiva Burns

History

In 1915, Frederick Burns provided a detailed clinical description delineating all the key features of this syndrome[130]. Subsequently, several case reports emerged in the literature using different names to describe the skin involvement, such as "atypical erythrokeratodermia with deafness", "atypical ichthyosiform erythroderma", "ichthyosiform dermatosis" and others. In 1981, Skinner summarized the previous reports and coined the acronym "KID" (keratitis–ichthyosis–deafness) syndrome[131]. Although several authors[12,132] argued that the skin findings represent erythrokeratoderma rather then ichthyosis, the widely used acronym prevailed. KID syndrome presents an overlap between disorders of cornification and ectodermal dysplasias.

Epidemiology

KID syndrome is a rare disorder, with about 200 published cases. Although it is inherited in an autosomal dominant manner, the majority (>90%) of reported cases have been sporadic.

Pathogenesis

The vast majority of KID syndrome patients harbor mutations in *GJB2*, which encodes connexin 26, a β-type gap junction protein[133,134]. In a single patient with features of KID syndrome and congenital atrichia, a causative mutation was identified in the *GJB6* gene encoding connexin 30[135]. All pathogenic mutations identified to date have been heterozygous missense mutations. A *GJB2* mutation substituting aspartic acid with asparagine in codon 50 (D50N) is particularly common and accounts for almost 80% of KID patients[133,134]; it is likely due to a mutational "hot spot" (CpG island). D50N usually results in "classic" KID syndrome, but the follicular occlusion triad and the allelic hystrix-like–ichthyosis–deafness (HID) syndrome have also been described in patients with this mutation[27]. Other *GJB2* mutations affecting the amino terminus or transmembrane domains of connexin 26 have been associated with atypical clinical features such as lack of palmoplantar keratoderma or corneal involvement, generalized spiny or verrucous keratoses, mucosal involvement and the follicular occlusion triad.

ADDITIONAL MUCOCUTANEOUS MANIFESTATIONS OF KID SYNDROME
INFLAMMATORY
• Follicular occlusion triad (onset usually at puberty): acne conglobata, dissecting cellulitis of the scalp, hidradenitis suppurativa • Folliculitis • Cheilitis with red, "chapped", fissured lips (especially at the angles of the mouth*) • Stomatitis with erythematous patches, adherent white plaques and erosions*
INFECTIOUS
• Recurrent or chronic mucocutaneous bacterial (e.g. *Staphylococcus aureus*), fungal (e.g. *Candida* spp.) and viral infections • Sepsis in the neonatal period (may be fatal)
NEOPLASTIC
• Cutaneous and oral squamous cell carcinoma (10–20% of patients) • Epidermoid and pilar cysts • Proliferating pilar tumors, benign or malignant (the latter aggressive/metastasizing)
*May have candidal superinfection.

Table 57.6 Additional mucocutaneous manifestations of KID syndrome. The spectrum of hyperkeratotic manifestations is described in the text.

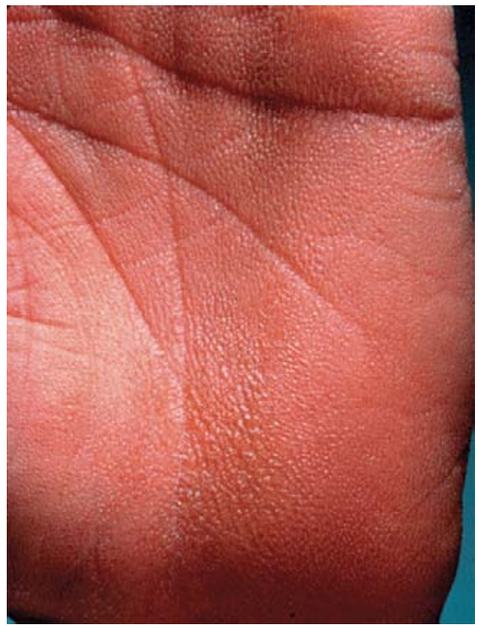


Fig. 57.23 KID syndrome. Palmar keratoderma with a grainy surface.

Fig. 57.22 KID syndrome. In addition to the erythematous plaques, characteristic radial furrows are seen. *Courtesy, L Russell, MD, and SJ Bale, PhD.*

Clinical Features

There is considerable variability in the type, extent and severity of cutaneous features in patients with KID syndrome (Table 57.6). The first manifestation is often transient erythroderma at birth or during infancy. Later, most patients develop symmetrically distributed, well-demarcated, hyperkeratotic plaques with an erythematous base and a rough, ridged or verrucous surface (i.e. erythrokeratoderma) (Fig. 57.22); psoriasiform plaques have also been described. The plaques are predominantly localized to the knees, elbows and face (often with radial furrows around the mouth), although the helices, scalp, groin and other skin folds, skin overlying small joints and other parts of the extremities, and, rarely, trunk may be affected. A plaque-like or diffuse palmoplantar keratoderma with a grainy, reticulated or stippled-appearing surface pattern (reminiscent of Vohwinkel syndrome) is almost always present (Fig. 57.23). Prominent follicular keratoses and cheilitis (especially perlèche) are common. Some patients develop diffuse thickening of the skin with a coarse-grained appearance, which may also lead to deep facial furrows. Nails may be dystrophic and show leukonychia. Although most patients have normal hair, some affected individuals have lusterless hair or alopecia of the scalp, eyelashes and eyebrows. Heat intolerance rarely occurs.

The spectrum of cutaneous lesions in KID syndrome also includes folliculitis, the follicular occlusion triad, cysts and proliferating pilar tumors (with rare reports of malignant lesions) (see Table 57.6). Another serious complication is the development of SCC of the skin and oral mucosa, which occurs in 10–20% of patients at a median age of 25 years (but as early as the first decade of life)[132]. KID syndrome is also associated with increased susceptibility to mucocutaneous bacterial, viral and fungal infections, in particular with *Candida albicans*.

All KID patients have congenital sensorineural hearing impairment that (in contrast to the keratitis) is not progressive. Hearing loss is generally severe and bilateral, although unilateral or moderate hearing impairment has been observed. Approximately 95% of patients have ocular involvement, which typically presents at birth, during infancy or in early childhood with photophobia and blepharitis. Vascularizing keratitis, chronic blepharitis and conjunctivitis develop and worsen with age. Scarring and neovascularization often cause a progressive decline in visual acuity and may eventuate in blindness. Dental abnormalities such as small or absent teeth, delayed eruption or excessive caries have been described in patients with KID syndrome. The Dandy–Walker malformation (a congenital anomaly of the cerebellar vermis and fourth ventricle), short heel cords, facial dysmorphism and other developmental abnormalities have also been reported.

Pathology

Histologically, there are no uniform findings, even if multiple biopsy specimens are obtained from the same patient. Acanthosis and papillomatosis of the epidermis with basket-weave hyperkeratosis and follicular plugging are the most consistent features. Vacuolization of the cells in the granular layer has also been described. Two ultrastructural studies did not reveal any significant skin abnormalities. The corneal epithelium may be dyskeratotic, atrophic or absent centrally and Bowman's membrane may be absent. In the inner ear, the organ of Corti is immature or atrophic.

Differential Diagnosis

There have been a few reports of *Desmons (Senter) syndrome*, an autosomal recessive metabolic disorder characterized by skin changes similar to KID syndrome and hearing impairment (but no keratitis) together with glycogen deposition leading to hepatomegaly, cirrhosis, growth failure and mental retardation. Other erythrokeratodermas, such as EKV and PSEK, are not associated with impaired hearing and keratitis. *Ichthyosis follicularis with atrichia and photophobia (IFAP)* syndrome (X-linked due to *MBTPS2* mutations; see Table 57.5) and *hereditary mucoepithelial dysplasia* (autosomal dominant) are both characterized by follicular keratoses, psoriasiform plaques, alopecia, keratitis and susceptibility to mucocutaneous infections (but not hearing impairment); in the latter disorder, the plaques favor the perineal area and fiery red oral mucosal patches are present. *Keratosis follicularis spinulosa decalvans* (allelic to IFAP; see Ch. 38) also features follicular keratoses and keratitis, but it progresses to scarring alopecia and does not manifest with hyperkeratotic plaques, palmoplantar keratoderma or hearing impairment.

Hystrix-like–ichthyosis–deafness (HID) syndrome (also referred to as ichthyosis hystrix type Rheydt) shares all the features of KID syndrome and is also caused by *GJB2* mutations[27]. Compared to KID syndrome, skin involvement is more severe and keratitis is milder in HID syndrome.

Treatment

Skin treatment consists of emollients and keratolytics; topical retinoids may be beneficial. Oral retinoid therapy yields mixed results: the hyperkeratosis may or may not respond, the palmoplantar keratoderma is recalcitrant, and ocular side effects may aggravate the keratitis and neovascularization. Corneal transplants, although often the only possibility for improving vision, are usually not very successful because of revascularization[132]. Hearing aids and cochlear implants have been used successfully to improve communication. Mucocutaneous infections often require systemic therapy. Surveillance for the development of SCC and other tumors via periodic examination of the mucous membranes as well as the skin (including the scalp) is required.

X-LINKED DOMINANT ICHTHYOSIFORM DISORDERS

CHILD SYNDROME

Synonyms: ▪ Congenital hemidysplasia with ichthyosiform erythroderma (or nevus) and limb defects ▪ CHILD nevus

History

The first description of this condition in 1948[136] was followed by 17 case reports before Happle delineated the key features and proposed the acronym CHILD syndrome in 1980[137].

Epidemiology

This is a rare X-linked dominant disorder that is generally lethal in affected male embryos. However, two affected boys, one of who was known to have a normal karyotype (and presumably a postzygotic rather than germline *NSDHL* mutation), have been reported[136,138].

Pathogenesis

CHILD syndrome is a disorder of lipid metabolism that results in disturbed cholesterol biosynthesis. Inactivating mutations in *NSDHL*, which encodes the enzyme 3β-hydroxysteroid-dehydrogenase, were initially identified in five families with right-sided skin and skeletal involvement[139]; such mutations were subsequently described in additional patients with left-sided involvement. The striking hemilateral phenotype has been postulated to result from deficient sonic hedgehog signaling (which helps to confer left–right asymmetry during embryogenesis) in cells expressing the X-chromosome with a *NSDHL* mutation, resulting in selection against these cells on one side of the body. Cholesterol has critical roles in mammalian development (including its importance in hedgehog signaling), and inborn errors in cholesterol biosynthesis have been found to cause several other malformation syndromes.

Clinical Features

CHILD syndrome classically presents at birth or in the neonatal period with a striking unilateral distribution of erythema and thickened skin with a waxy surface or yellowish adherent scale (Fig. 57.24). The erythema most often involves the right side of the body and is sharply demarcated at the anterior and posterior midline of the trunk. The face is typically spared. Occasionally, there is partial spontaneous resolution or periodic exacerbation of the cutaneous inflammation[137]. During infancy, the erythema lessens, while hyperkeratotic plaques or bands with a verrucous surface prevail and often become more pronounced. They may follow Blaschko's lines or uniformly affect large areas on half of the body, with affinity for the skin folds (ptychotropism). Because of the clinical resemblance to inflammatory linear verrucous epidermal nevus (ILVEN), the terms "CHILD nevus" and "psoriasiform epidermal nevus" have been used. The contralateral side of the body may have mild skin involvement in a mosaic pattern, but symmetric distribution is extremely rare. Linear alopecia (on the affected side of the scalp and/or body) and claw-like nail dystrophy or onychorrhexis are common.

Fig. 57.24 CHILD syndrome. Note the sharp midline demarcation on the trunk. *From Happle R, Mittag H, Kuster W. Dermatology. 1995;191:210–6, with permission. Courtesy, R Happle, MD.*

Ipsilateral skeletal abnormalities range from hypoplasia of digits or ribs to complete amelia; congenital or secondary scoliosis may also occur. Stippled epiphyses can be identified on radiologic examination in early infancy but tend to resolve during childhood. The teeth are typically normal. Asymmetric organ hypoplasia commonly affects the brain, kidneys, heart and lungs on the (severely) affected side of the body. Mild hearing loss and cleft palate may be present. Analogous with the cutaneous manifestations, minor organ anomalies may be observed on the contralateral side.

Pathology

Histopathologic changes include an acanthotic and papillomatous epidermis with marked ortho- and parakeratosis, overlying a mild superficial perivascular infiltrate. Numerous vacuoles are present within the cells of the lower stratum corneum. Multiple layers of granular cells surround the sweat ducts, while the granular zone in the surrounding epidermis may be absent, normal or thickened[138]. Occasionally, foamy histiocytes have been noted in dermal papillae. Ultrastructural abnormalities include abundant pale-staining mitochondria, cytoplasmic glycogen, lipid retention in the stratum corneum, and altered lamellar granular content, both intracellularly and intercellularly.

Other diagnostic tests

Molecular analysis of the *NSDHL* gene is available. Plasma cholesterol is normal despite defective cholesterol biosynthesis.

Differential Diagnosis

Sebaceous nevus syndrome may resemble CHILD syndrome but can be clinically differentiated by its distribution pattern and the lack of erythema and scaling. ILVEN is a less extensive condition that is not associated with visceral abnormalities. Punctate epiphyseal calcifications and asymmetric limb shortening together with congenital ichthyosiform erythroderma in a distribution following Blaschko's lines may be seen in X-linked dominant chondrodysplasia punctata (see below). However, the skin manifestations are not unilateral and are replaced by atrophoderma by 2 years of age; in addition, skeletal defects are usually less severe than in CHILD syndrome[139].

Treatment

Cosmetically and functionally satisfactory results from dermabrasion of affected skin followed by placement of split-thickness skin grafts

obtained from the clinically normal contralateral side of the body have been described[140]. Single case reports have noted successful treatment of skin lesions with topical tretinoin or systemic retinoids. Emollients and corticosteroids are ineffective. Requirements for multidisciplinary care depend on the extent of associated organ involvement.

CONRADI–HÜNERMANN–HAPPLE SYNDROME

Synonyms: ■ X-linked dominant chondrodysplasia punctata ■ Chondrodysplasia punctata type 2 (CDPX2) ■ Conradi–Hünermann syndrome ■ Happle syndrome

History

In 1971, the dominant Conradi–Hünermann type of chondrodysplasia was differentiated from the more severe, autosomal recessive, rhizomelic form. Happle subsequently reviewed the literature and established that the Conradi–Hünermann type has an X-linked dominant mode of inheritance[141].

Epidemiology

Conradi–Hünermann–Happle syndrome (CHHS) is a rare X-linked dominant disorder. It is lethal in male embryos outside the setting of an XXY karyotype or mosaicism due to a postzygotic mutation in the *EBP* gene. However, an X-linked recessive multiple congenital anomaly syndrome (with male patients who die by early childhood and unaffected female carriers) caused by a less severe germline mutation in the *EBP* gene was recently described[142].

Pathogenesis

Conradi–Hünermann–Happle syndrome is due to a defect in cholesterol biosynthesis that is caused by mutations in the *EBP* gene, which encodes emopamil-binding protein (EBP)[143,144]. The resulting deficiency of EBP, a widely expressed integral membrane protein with Δ8-Δ7-sterol isomerase activity, leads to accumulation of 8-dehydrocholesterol and 8(9)cholesterol[144], which can be detected in plasma and cultured fibroblasts. However, levels of the end product cholesterol sulfate are normal in plasma and fibroblasts because of X-inactivation[143,144]. Impaired cholesterol synthesis during a critical period of mammalian development is thought to be responsible for the phenotype. A particular hemizygous missense mutation affecting the first transmembrane domain of EBP (presumably with less deleterious effects on enzyme function) and accumulation of the aforementioned cholesterol precursors have been found in boys with an allelic multiple congenital anomaly syndrome[142].

Clinical Features

At birth, the majority of CHH syndrome patients have generalized erythema with thick, adherent, feathery scale; streaks and whorls of hyperkeratosis following Blaschko's lines are often observed (Fig. 57.25A). The erythroderma resolves substantially, if not completely, within the first weeks or months of life. In older children, hyperkeratosis is largely replaced (with residual mild scaling) by linear or patchy follicular atrophoderma with dilated follicular openings and ice-pick-like scars. The atrophoderma is most pronounced on the forearms and dorsal hands, whereas the palms and soles are usually spared. Hyper- or hypopigmentation along Blaschko's lines may coexist separately from atrophodermic areas[141]. Scalp involvement results in patchy scarring alopecia. In addition, hair may be sparse, coarse or lusterless. Nail changes include onychoschizia and flattening of the nail plate, while the teeth are normal.

Skeletal anomalies are usually asymmetric. They include frontal bossing, malar hypoplasia, a flat nasal bridge, a short neck, rhizomelic shortening of the limbs, and scoliosis. Widespread premature calcifications manifesting as stippled epiphyses (chondrodysplasia punctata) typically involve the trachea and vertebrae and can be detected on radiographs during infancy (Fig. 57.25B). These are not apparent once bone maturation progresses. Unilateral cataracts, which are present at birth or develop within the first months of life, are the most common ocular abnormality and may be accompanied by microphthalmia or microcornea. Occasionally, other features may be associated and include congenital heart defects, sensorineural deafness, CNS malformations and congenital renal anomalies. Intellect is usually not impaired and life expectancy is normal.

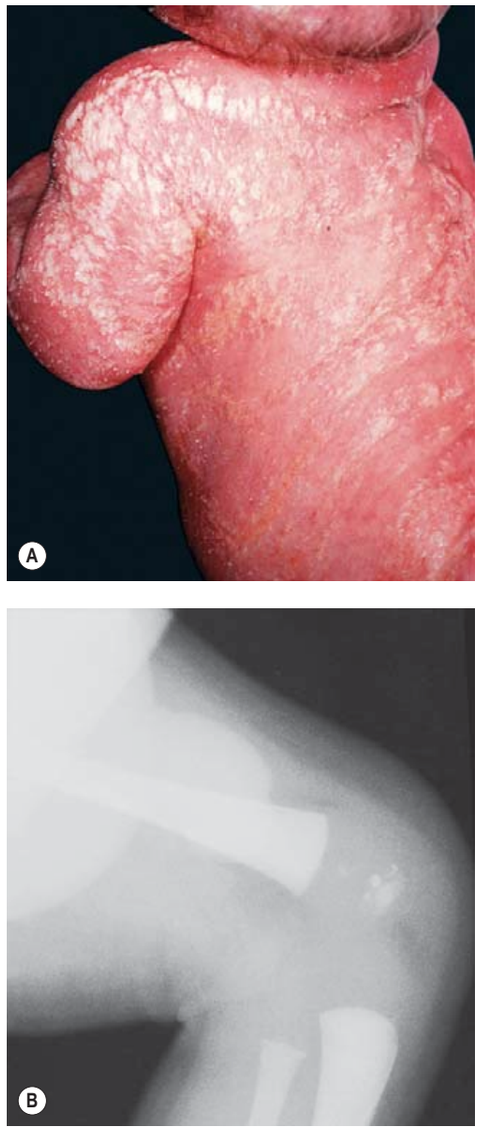


Fig. 57.25 Conradi–Hünermann–Happle syndrome.
A Erythroderma and linear streaks and whorls of hyperkeratosis.
B Epiphyseal stippling at the knee. *A, Courtesy, R Happle, MD. B, Courtesy, Jean L Bolognia, MD.*

Boys with the allelic X-linked recessive syndrome have a collodion-like presentation at birth and evolution to variable ichthyosis phenotype[142]. Additional features include a Dandy-Walker malformation, hydrocephalus, cataracts, cryptorchidism, and cardiovascular, craniofacial and skeletal anomalies.

Pathology

Hyperkeratosis with focal parakeratosis is common and most prominent in follicular ostia, where dystrophic calcification may be observed within keratotic plugs. The granular layer is diminished and keratinocytes contain small vacuoles with needle-like calcium inclusions on electron microscopy.

Other diagnostic tests

Radiographs reveal premature calcifications in the cartilage of the trachea, spine and long bones during the first year of life (see Fig. 57.25B). Accumulation of 8(9)cholesterol in plasma can be detected by mass spectrophotometry and often confirms the diagnosis. Molecular analysis of the *EBP* gene is also available.

Differential Diagnosis

Stippled epiphyses during infancy and asymmetric limb shortening are also seen in girls with CHILD syndrome, but the skin involvement

usually shows striking lateralization and does not fade completely. However, some overlap in the clinical findings of CHILD and CHH syndromes is not surprising, since both represent disorders of cholesterol biosynthesis. Ichthyosis linearis circumflexa in Netherton syndrome is readily distinguished by its double-edged scale, and the lesions do not follow Blaschko's lines. Cutaneous manifestations in congenital ichthyosiform erythroderma are more generalized. Hyper- and hypopigmentation in "pigmentary mosaicism", incontinentia pigmenti and epidermal nevi (including epidermolytic variants) follow Blaschko's lines but lack follicular atrophoderma.

Treatment

Although the erythema gradually resolves, residual mild scaling may benefit from application of emollients, and products containing urea or lactic acid. Orthopedic and ophthalmologic care are essential.

REFERENCES

1. Willan R. Ichthyosis. On Cutaneous Diseases, vol. 1. London: Barnard, 1808:197–212.
2. Brocq L. Erythrodermie congenitale ichthyosiforme avec hyperepidermotrophie. Ann Dermatol Syphiligre (Paris). 1902;4:1.
3. Frost P, Van Scott EJ. Ichthyosiform dermatoses. Classification based on anatomic and biometric observations. Arch Dermatol. 1966;94:113–26.
4. Alibert L. Les icthyoses. In: Description des maladies de la peau, observes a l'hospital Saint-Luis et exposition meilleurs methodes pour leur traitement. Paris, 1806:167–84.
5. Wells RS, Kerr CB. Ichthyosis. Br Med J. 1966;2: 1504–6.
6. Webster D, France JT, Shapiro LJ, Weiss R. X-linked ichthyosis due to steroid-sulphatase deficiency. Lancet. 1978;1:70–2.
7. Oji V, Tadini G, Akiyama M, et al. Revised nomenclature and classification of inherited ichthyoses: results of the First Ichthyosis Consensus Conference in Sorèze 2009. J Am Acad Dermatol. 2010;63:607–41.
8. Smith FJ, Irvine AD, Terron-Kwiatkowski A, et al. Loss-of-function mutations in the gene encoding filaggrin cause ichthyosis vulgaris. Nat Genet. 2006;38:337–42.
9. Fleckman P, Brumbaugh SG. Absence of the granular layer and keratohyalin define a morphologically distinct subset of individuals with ichthyosis vulgaris. Exp Dermatol. 2002;11:327–36.
10. Bonifas JM, Morley BJ, Oakey RE, et al. Cloning of a cDNA for steroid sulfatase: frequent occurrence of gene deletions in patients with recessive X chromosome-linked ichthyosis. Proc Natl Acad Sci U SA. 1987;84:9248–51.
11. Wells RS, Jennings MC. X-linked ichthyosis and ichthyosis vulgaris. Clinical and genetic distinctions in a second series of families. J Am Med Assoc. 1967;202:485–8.
12. Traupe H. The Ichthyoses. A Guide to Clinical Diagnosis, Genetic Counseling, and Therapy. Berlin: Springer Verlag, 1989.
13. Nikolsky P. Contribution à l'étude des anomalies congénitales de kératinisation. Comptes-Rendus du XII Congres International de Medicine, Moscuo. 1897;IV:433–42.
14. Irvine AD, McLean WH. Human keratin diseases: the increasing spectrum of disease and subtlety of the phenotype-genotype correlation. Br J Dermatol. 1999;140:815–28.
15. DiGiovanna JJ, Bale SJ. Clinical heterogeneity in epidermolytic hyperkeratosis. Arch Dermatol. 1994;130:1026–35.
16. Paller AS, Syder AJ, Chan YM, et al. Genetic and clinical mosaicism in a type of epidermal nevus. N Engl J Med. 1994;331:1408–15.
17. Rothnagel JA, Lin MT, Longley MA, et al. Prenatal diagnosis for keratin mutations to exclude transmission of epidermolytic hyperkeratosis. Prenat Diagn. 1998;18:826–30.
18. Lacour M, Mehta-Nikhar B, Atherton DJ, Harper JI. An appraisal of acitretin therapy in children with inherited disorders of keratinization. Br J Dermatol. 1996;134:1023–9.
19. Siemens HW. Dichtung und Wahrheit ueber die ichthyosis bullosa, mit Bemerkungen zur Systematik der Epidermolysen. Derm Syph. 1937;175:590–608.
20. Basarab T, Smith FJ, Jolliffe VM, et al. Ichthyosis bullosa of Siemens: report of a family with evidence of a keratin 2e mutation, and a review of the literature. Br J Dermatol. 1999;140:689–95.
21. Choate KA, Lu Y, Zhou J, et al. Mitotic recombination in patients with ichthyosis causes reversion of dominant mutations in KRT10. Science. 2010;330:94–7.
22. Curth HO, Macklin MT. The genetic basis of various types of ichthyosis in a family group. Am J Hum Genet. 1954;6:371–82.
23. Anton-Lamprecht I, Curth HO, Schnyder UW. Ultrastructure of inborn errors of keratinization. II. Ichthyosis hystrix type Curth–Macklin. Arch Dermatol Forsch. 1973;246:77–91.
24. Sprecher E, Ishida-Yamamoto A, Becker OM, et al. Evidence for novel functions of the keratin tail emerging from a mutation causing ichthyosis hystrix. J Invest Dermatol. 2001;116:511–19.
25. Bonifas JM, Bare JW, Chen MA, et al. Evidence against keratin gene mutations in a family with ichthyosis hystrix Curth-Macklin. J Invest Dermatol. 1993;101:890–1.
26. Schnyder UW. Ichthyosis hystrix typus Rheydt (Ichthyosis hystrix gravior mit praktischer Taubheit). Z Hautkr. 1977;52:763–6.
27. van Geel M, van Steensel MA, Kuster W, et al. HID and KID syndromes are associated with the same connexin 26 mutation. Br J Dermatol. 2002;146:938–42.
28. Penrose LS, Stern C. Reconsideration of the Lambert pedigree (ichthyosis hystrix gravior). Ann Hum Genet. 1958;22:258–83.
29. Huber M, Rettler I, Bernasconi K, et al. Mutations of keratinocyte transglutaminase in lamellar ichthyosis. Science. 1995;267:525–8.
30. Russell LJ, DiGiovani JJ, Rogers GR, et al. Mutations in the gene for transglutaminase 1 in autosomal recessive lamellar ichthyosis. Nat Genet. 1995;9:279–83.
31. Eckl KM, Krieg P, Kuster W, et al. Mutation spectrum and functional analysis of epidermis-type lipoxygenases in patients with autosomal recessive congenital ichthyosis. Hum Mutat. 2005;26:351–61.
32. Raghunath M, Hennies HC, Velten F, et al. A novel in situ method for the detection of deficient transglutaminase activity in the skin. Arch Dermatol Res. 1998;290:621–7.
33. Vahlquist A, Bygum A, Gånemo A, et al. Genotypic and clinical spectrum of self-improving collodion ichthyosis: ALOX12B, ALOXE3, and TGM1 mutations in Scandinavian patients. J Invest Dermatol. 2009;130:438–43.
34. Mazereeuw-Hautier J, Aufenvenne K, Deraison C, et al. Acral self-healing collodion baby: report of a new clinical phenotype caused by a novel TGM1 mutation. Br J Dermatol. 2009;161:456–63.
35. Hohl D, Aeschlimann D, Huber M. In vitro and rapid in situ transglutaminase assays for congenital ichthyoses – a comparative study. J Invest Dermatol. 1998;110:268–71.
36. Williams ML, Elias PM. Heterogeneity in autosomal recessive ichthyosis. Clinical and biochemical differentiation of lamellar ichthyosis and nonbullous congenital ichthyosiform erythroderma. Arch Dermatol. 1985;121:477–88.
37. Traupe H, Kolde G, Happle R. Autosomal dominant lamellar ichthyosis: a new skin disorder. Clin Genet. 1984;26:457–61.
38. Farasat S, Wei M-H, Liewehr D, et al. Novel transglutaminase-1 mutations and genotype-phenotype investigations of 104 patients with autosomal recessive congenital ichthyosis in the USA. J Med Genet. 2009;46:103–11.
39. Eckl KM, de Juanes S, Kurtenbach S, et al. Molecular analysis of 250 patients with autosomal recessive congenital ichthyosis: evidence for mutation hotspots in ALOXE3 and allelic heterogeneity in ALOX12B. J Invest Dermatol. 2009;129:1421–8.
40. Shevchenko YO, Compton JG, Toro JR, et al. Splice-site mutation in TGM1 in congenital recessive ichthyosis in American families: molecular, genetic, genealogic, and clinical studies. Hum Genet. 2000;106:492–9.
41. Lefevre C, Audebert S, Jobard F, et al. Mutations in the transporter ABCA12 are associated with lamellar ichthyosis type 2. Hum Mol Genet. 2003;12:2369–78.
42. Lefèvre C, Bouadjar B, Ferrand V, et al. Mutations in a new cytochrome P450 gene in lamellar ichthyosis type 3. Hum Mol Genet. 2006;15:767–76.
43. Kanerva L, Lauharanta J, Niemi KM, Lassus A. New observations on the fine structure of lamellar ichthyosis and the effect of treatment with etretinate. Am J Dermatopathol. 1983;5:555–68.
44. Jeon S, Djian P, Green H. Inability of keratinocytes lacking their specific transglutaminase to form crosslinked envelopes: absence of envelopes as a simple diagnostic test for lamellar ichthyosis. Proc Natl Acad Sci U S A. 1998;95:687–90.
45. Schorderet DF, Huber M, Laurini RN, et al. Prenatal diagnosis of lamellar ichthyosis by direct mutational analysis of the keratinocyte transglutaminase gene. Prenat Diagn. 1997;17:483–6.
46. Akiyama M, Holbrook KA. Analysis of skin-derived amniotic fluid cells in the second trimester; detection of severe genodermatoses expressed in the fetal period. J Invest Dermatol. 1994;103:674–7.
47. Hofmann B, Stege H, Ruzicka T, Lehmann P. Effect of topical tazarotene in the treatment of congenital ichthyoses. Br J Dermatol. 1999;141:642–6.
48. Ganemo A, Virtanen M, Vahlquist A. Improved topical treatment of lamellar ichthyosis: a double-blind study of four different cream formulations. Br J Dermatol. 1999;141:1027–32.
49. Jobard F, Lefevre C, Karaduman A, et al. Lipoxygenase-3 (ALOXE3) and 12(R)-lipoxygenase (ALOX12B) are mutated in non-bullous congenital ichthyosiform erythroderma (NCIE) linked to chromosome 17p13.1. Hum Mol Genet. 2002;11:107–13.
50. Lefevre C, Bouadjar B, Karaduman A, et al. Mutations in ichthyin a new gene on chromosome 5q33 in a new form of autosomal recessive congenital ichthyosis. Hum Mol Genet. 2004;13:2473–82.
51. Dahlqvist J, Klar J, Hausser I, et al. Congenital ichthyosis: mutations in ichthyin associated with specific structural abnormalities in the granular layer of epidermis. J Med Genet. 2007;44:615–20.

51a. Grall A, Guaguère E, Planchais S, et al. *PNPLA1* mutations cause autosomal recessive congenital ichthyosis in golden retriever dogs and humans. Nat Genet. 2012;44:140–7.

52. Akiyama M. ABCA12 mutations and autosomal recessive congenital ichthyosis: a review of genotype/phenotype correlations and of pathogenetic concepts. Hum Mutat. 2010;31:1090–6.
53. Moskowitz DG, Fowler AJ, Heyman MB et al. Pathophysiologic basis for growth failure in children with ichthyosis: an evaluation of cutaneous ultrastructure, epidermal permeability barrier function, and energy expenditure. J Pediatr. 2004;145:82–92.
54. Brown VL, Farrant PB, Turner RJ, et al. Multiple aggressive squamous skin cancers in association with nonbullous congenital ichthyosiform erythroderma. Br J Dermatol. 2008;158:1125–8.
55. Ghadially R, Williams ML, Hou SY, Elias PM. Membrane structural abnormalities in the stratum corneum of the autosomal recessive ichthyoses. J Invest Dermatol. 1992;99:755–63.
56. Niemi KM, Kanerva L, Kuokkanen K, Ignatius J. Clinical, light and electron microscopic features of recessive congenital ichthyosis type I. Br J Dermatol. 1994;130:626–33.
57. Akiyama M, Sugiyama-Nakagiri Y, Sakai K, et al. Mutations in lipid transporter ABCA12 in harlequin ichthyosis and functional recovery by corrective gene transfer. J Clin Invest. 2005;115:1777–84.

58. Kelsell DP, Norgett EE, Unsworth H, et al. Mutations in ABCA12 underlie the severe congenital skin disease harlequin ichthyosis. Am J Hum Genet. 2005;76:794–803.
59. Thomas AC, Cullup Y, Norgett E, et al. ABCA12 is the major harlequin ichthyosis gene. J Invest Dermatol. 2006;126:2408–13.
60. Thomas AC, Sinclair C, Mahmud N et al. Novel and recurring ABCA12 mutations associated with harlequin ichthyosis: implications for prenatal diagnosis. Br J Dermatol. 2008;158:611–13.
61. Milner ME, O'Guin WM, Holbrook KA, Dale BA. Abnormal lamellar granules in harlequin ichthyosis. J Invest Dermatol. 1992;99:824–9.
62. Rajpopat S, Moss C, Mellerio J, et al. Harlequin ichthyosis: a review of clinical and molecular findings in 45 cases. Arch Dermatol. 2011;147:681–6.
63. Akiyama M, Dale BA, Smith LT, et al. Regional difference in expression of characteristic abnormality of harlequin ichthyosis in affected fetuses. Prenat Diagn. 1998;18:425–36.
64. Akiyama M, Suzumori K, Shimizu H. Prenatal diagnosis of harlequin ichthyosis by the examination of keratinized hair canals and amniotic fluid cells at 19 weeks' estimated gestational age. Prenat Diagn. 1999;19:167–71.
65. Singh S, Bhura M, Maheshwari A, et al. Successful treatment of harlequin ichthyosis with acitretin. Int J Dermatol. 2001;40:472–3.
66. Wilkinson RD, Curtis GH, Hawks WA. Netherton's disease. Arch Dermatol. 1964;89:46–54.
67. Schneider I, Sebok B, Kosztolanyi G, Szekeres G. Comel-Netherton syndrome: evolution of manifestation in a 20-year follow-up and phenotypic overlap with peeling skin syndrome type B. Acta Derm Venereol. 2000;80:209–10.
68. Pruszkowski A, Bodemer C, Fraitag S, et al. Neonatal and infantile erythrodermas: a retrospective study of 51 patients. Arch Dermatol. 2000;136:875–80.
69. Chavanas S, Bodemer C, Rochat A, et al. Mutations in SPINK5, encoding a serine protease inhibitor, cause Netherton syndrome. Nat Genet. 2000;25:141–2.
70. Sprecher E, Chavanas S, DiGiovanna JJ, et al. The spectrum of pathogenic mutations in SPINK5 in 19 families with Netherton syndrome: implications for mutation detection and first case of prenatal diagnosis. J Invest Dermatol. 2001;117:179–87.
71. Komatsu N, Takata M, Otsuki N, et al. Elevated stratum corneum hydrolytic activity in Netherton syndrome suggests an inhibitory regulation of desquamation by SPINK5-derived peptides. J Invest Dermatol. 2002;118:436–43.
72. Ishida-Yamamoto A, Deraison C, Bonnart C, et al. LEKTI is localized in lamellar granules, separated from KLK5 and KLK7, and is secreted in the extracellular spaces of the superficial stratum granulosum. J Invest Dermatol. 2005;124:360–6.
73. Powell J, Dawber RP, Ferguson DJ, Griffiths WA. Netherton's syndrome: increased likelihood of diagnosis by examining eyebrow hairs. Br J Dermatol. 1999;141:544–6.
74. Pradeaux L, Olives JP, Bonafe JL, et al. Digestive and nutritional manifestations of Netherton's syndrome. Arch Fr Pediatr. 1991;48:95–8.
75. Geyer AS, Ratajczak P, Pol-Rodriguez M, et al. Netherton syndrome with extensive skin peeling and failure to thrive due to a homozygous frameshift mutation in SPINK5. Dermatology. 2005;210:308–14.
76. Fartasch M, Williams ML, Elias PM. Altered lamellar body secretion and stratum corneum membrane structure in Netherton syndrome: differentiation from other infantile erythrodermas and pathogenic implications. Arch Dermatol. 1999;135:823–32.
77. Bitoun E, Micheloni A, Lamant L, et al. LEKTI proteolytic processing in human primary keratinocytes, tissue distribution and defective expression in Netherton syndrome. Hum Mol Genet. 2003;12:2417–30.
78. Raghunath M, Tontsidou L, Oji V, et al. SPINK5 and Netherton syndrome: novel mutations, demonstration of missing LEKTI, and differential expression of transglutaminases. J Invest Dermatol. 2004;123: 474–83.
79. Oji V, Eckl KM, Aufenvenne K, et al. Loss of corneodesmosin leads to severe skin barrier defect, pruritus, and atopy: unraveling the peeling skin disease. Am J Hum Genet. 2010;87:274–81.
80. Allen A, Siegfried E, Silverman R, et al. Significant absorption of topical tacrolimus in 3 patients with Netherton syndrome. Arch Dermatol. 2001;137: 747–50.
81. Yan AC, Honig PJ, Ming ME, et al. The safety and efficacy of pimecrolimus 1% cream for the treatment of Netherton syndrome: results from an exploratory study. Arch Dermatol. 2010;146:57–62.
82. Sjögren T, Larsson T. Oligophrenia in combination with congenital ichthyosis and spastic disorder. Acta Psychiatr Neurol Scand. 1957;32:1–112.
83. Rizzo WB, Dammann AL, Craft DA. Sjögren-Larsson syndrome. Impaired fatty alcohol oxidation in cultured fibroblasts due to deficient fatty alcohol: nicotinamide adenine dinucleotide oxidoreductase activity. J Clin Invest. 1988;81:738–44.
84. De Laurenzi V, Rogers GR, Hamrock DJ, et al. Sjögren-Larsson syndrome is caused by mutations in the fatty aldehyde dehydrogenase gene. Nat Genet. 1996;12:52–7.
85. Rizzo WB, Carney G. Sjögren-Larsson syndrome: diversity of mutations and polymorphisms in the fatty aldehyde dehydrogenase gene (ALDH3A2). Hum Mutat. 2005;26:1–10.
86. Rizzo WB, Craft DA. Sjögren–Larsson syndrome. Deficient activity of the fatty aldehyde dehydrogenase component of fatty alcohol: NAD+ oxidoreductase in cultured fibroblasts. J Clin Invest. 1991;88:1643–8.
87. Jagell S, Polland W, Sandgren O. Specific changes in the fundus typical for the Sjögren-Larsson syndrome. An ophthalmological study of 35 patients. Acta Ophthalmol (Copenh). 1980;58:321–30.
88. Sillen A, Holmgren G, Wadelius C. First prenatal diagnosis by mutation analysis in a family with Sjögren- Larsson syndrome. Prenat Diagn. 1997;17:1147–9.
89. Dorfman ML, Hershko C, Eisenberg S, Sagher F. Ichthyosiform dermatosis with systemic lipidosis. Arch Dermatol. 1974;110:261–6.
90. Chanarin I, Patel A, Slavin G, et al. Neutral-lipid storage disease: a new disorder of lipid metabolism. Br Med J. 1975;1:553–5.
91. Lefevre C, Jobard F, Caux F, et al. Mutations in CGI-58, the gene encoding a new protein of the esterase/ lipase/thioesterase subfamily, in Chanarin-Dorfman syndrome. Am J Hum Genet. 2001;69:1002–12.
92. Yamaguchi T, Omatsu N, Morimoto E, et al. CGI-58 facilitates lipolysis on lipid droplets but is not involved in the vesiculation of lipid droplets caused by hormonal stimulation. J Lipid Res. 2007;48:1078–9.
93. Williams ML, Coleman RA, Placezk D, Grunfeld C. Neutral lipid storage disease: a possible functional defect in phospholipid-linked triacylglycerol metabolism. Biochim Biophys Acta. 1991;1096: 162–9.
94. Akiyama M, Sawamura D, Nomura Y, et al. Truncation of CGI-58 protein causes malformation of lamellar granules resulting in ichthyosis in Dorfman-Chanarin syndrome. J Invest Dermatol. 2003;121:1029–34.
95. Elias PM, Williams ML. Neutral lipid storage disease with ichthyosis. Defective lamellar body contents and intracellular dispersion. Arch Dermatol. 1985;121:1000–8.
96. Pollitt RJ, Jenner FA, Davies M. Sibs with mental and physical retardation and trichorrhexis nodosa with abnormal amino acid composition of the hair. Arch Dis Child. 1968;43:211–6.
97. Tay CH. Ichthyosiform erythroderma, hair shaft abnormalities, and mental and growth retardation. A new recessive disorder. Arch Dermatol. 1971;104: 4–13.
98. Giglia-Mari G, Coin F, Ranish JA, et al. A new, tenth subunit of TFIIH is responsible for the DNA repair syndrome trichothiodystrophy group A. Nat Genet. 2004;36:714–19.
99. Itin PH, Sarasin A, Pittelkow MR. Trichothiodystrophy: update on the sulfur-deficient brittle hair syndromes. J Am Acad Dermatol. 2001;44:891–920.
100. Cleaver JE. Cancer in xeroderma pigmentosum and related disorders of DNA repair. Nat Rev Cancer. 2005;5:564–73.
101. Botta E, Nardo T, Lehmann AR, et al. Reduced level of the repair/transcription factor TFIIH in trichothiodystrophy. Hum Mol Genet. 2002;11: 2919–28.
102. Jansen GA, Ofman R, Ferdinandusse S, et al. Refsum disease is caused by mutations in the phytanoyl-CoA hydroxylase gene. Nat Genet. 1997;17:190–3.
103. Mihalik SJ, Morrell JC, Kim D, et al. Identification of PAHX, a Refsum disease gene. Nat Genet. 1997;17: 185–9.
104. Van den Brink DM, Brites P, Haasjes J, et al. Identification of PEX7 as the second gene involved in Refsum disease. Am J Hum Genet. 2003;72:471–7.
105. Lou JS, Snyder R, Griggs RC. Refsum's disease: long term treatment preserves sensory nerve action potentials and motor function. J Neurol Neurosurg Psychiatry. 1997;62:671–2.
106. Weinstein R. Phytanic acid storage disease (Refsum's disease): clinical characteristics, pathophysiology and the role of therapeutic apheresis in its management. J Clin Apheresis. 1999;14:181–4.
107. Straube R, Gackler D, Thiele A, et al. Membrane differential filtration is safe and effective for the long-term treatment of Refsum syndrome – an update of treatment modalities and pathophysiological cognition. Transfus Apher Sci. 2003;29:85–91.
108. Dierks T, Schmidt B, Borissenko LV, et al. Multiple sulfatase deficiency is caused by mutations in the gene encoding the human C(alpha)-formylglycine generating enzyme. Cell. 2003;113:435–44.
109. Patrick AD, Young E, Ellis C, Rodeck CH. Multiple sulphatase deficiency: prenatal diagnosis using chorionic villi. Prenat Diagn. 1988;8:303–6.
110. Ramsay SL, Maire I, Bindloss C, et al. Determination of oligosaccharides and glycolipids in amniotic fluid by electrospray ionisation tandem mass spectrometry: in utero indicators of lysosomal storage diseases. Mol Genet Metab. 2004;83:231–8.
111. Braverman N, Steel G, Obie C, et al. Human PEX7 encodes the peroxisomal PTS2 receptor and is responsible for rhizomelic chondrodysplasia punctata. Nat Genet. 1997;15:369–76.
112. Basbug M, Serin IS, Ozcelik B, et al. Prenatal ultrasonographic diagnosis of rhizomelic chondrodysplasia punctata by detection of rhizomelic shortening and bilateral cataracts. Fetal Diagn Ther. 2005;20:171–4.
113. Gould SJ, Raymond GV, Valle D. The peroxisome biogenesis disorders. In: Scriver CR (ed). The Metabolic and Molecular Bases of Inherited Disorders, New York: McGraw-Hill, 2001:3181–217.
114. Vera-Casano A, Weirich C, Grzeschik KH. IFAP syndrome is caused by deficiency in MBTPS2, an intramembrane zinc metalloprotease essential for cholesterol homeostasis and ER stress response. Am J Hum Genet. 2009;84:459–67.
115. Montpetit A, Côté S, Brustein E, et al. Disruption of AP1S1, causing a novel neurocutaneous syndrome, perturbs development of the skin and spinal cord. PLoS Genet. 2008;4:e1000296.
116. Giroux JM, Barbeau A. Erythrokeratodermia with ataxia. Arch Dermatol. 1972;106:183–8.
117. Cassidy AJ, van Steensel MAM, Steijlen PM, et al. A homozygous missense mutation in TGM5 abolishes epidermal transglutaminase 5 activity and causes acral peeling skin syndrome. Am J Hum Genet. 2005;77:909–17.
118. Findlay GH, Nurse GT, Heyl T, et al. Keratolytic winter erythema or 'Oudtshoorn skin': a newly recognized inherited dermatosis prevalent in South Africa. S Afr Med J. 1977;52:871–4.
119. de Buy Wenninger LM. Erythrokeratodermie congenitale ichthyosiforme avec hyperepidermotrophie in Verslagen van vereeningingene. Nederl Tijdschr Geneesk. 1907;1A:510–15.
120. Mendes da Costa S. Erythro- et keratodermia variabilis in a mother and a daughter. Acta Derm Venerol. 1925;6:255–61.
121. Barsky S, Bernstein G. Keratosis rubra figurata. Arch Dermatol. 1964;90:373–4.
122. Richard G, Brown N, Smith LE, et al. The spectrum of mutations in erythrokeratodermias – novel and de novo mutations in GJB3. Hum Genet. 2000;106:321–9.
123. Macari F, Landau M, Cousin P, et al. Mutation in the gene for connexin 30.3 in a family with erythrokeratodermia variabilis. Am J Hum Genet. 2000;67:1296–301.
124. Richard G. Connexin disorders of the skin. Clin Dermatol. 2005;23:23–32.
125. van Steensel MAM, Oranje AP, van der Schroeff JG, et al. The missense mutation G12D in connexin 30.3 can cause both erythrokeratodermia variabilis of Mendes da Costa and progressive symmetric erythrokeratodermia of Gottron. Am J Med Genet A. 2009;149A:657–61.
126. Darier MJ. Verrucose erythro-keratoderma in symmetrical and progressive layers. Bull Soc Fr Dermatol. 1911;22:252–64.
127. Gottron HA. Congenital angelegte symmetrische progressive Erythrokeratodermie. Zentbl Haut-Geschl Krankh. 1922;4:493–4.
128. Ishida-Yamamoto A, McGrath JA, Lam H, et al. The molecular pathology of progressive symmetric

erythrokeratoderma: a frameshift mutation in the loricrin gene and perturbations in the cornified cell envelope. Am J Hum Genet. 1997;61:581–9.
129. Cui Y, Yang S, Gao M, et al. Identification of a novel locus for progressive symmetric erythrokeratodermia to a 19.02-cM interval at 21q1 1.2–21q21.2. J Invest Dermatol. 2006;126:2136–9.
130. Burns FS. A case of generalized keratoderma with unusual involvement of the eyes and nasal and buccal mucosa. J Cutan Dis. 1915;33:255–60.
131. Skinner BA, Greist MC, Norins AL. The keratitis, ichthyosis, and deafness (KID) syndrome. Arch Dermatol. 1981;117:285–9.
132. Caceres-Rios H, Tamayo-Sanchez L, Duran-Mckinster C, et al. Keratitis, ichthyosis, and deafness (KID syndrome): review of the literature and proposal of a new terminology. Pediatr Dermatol. 1996;13:105–13.
133. Richard G, Rouan F, Willoughby CE, et al. Missense mutations in GJB2 encoding connexin-26 cause the ectodermal dysplasia keratitis-ichthyosis-deafness syndrome. Am J Hum Genet. 2002;70:1341–8.
134. van Steensel MA, van Geel M, Nahuys M, et al. A novel connexin 26 mutation in a patient diagnosed with keratitis- ichthyosis-deafness syndrome. J Invest Dermatol. 2002;118:724–7.
135. Jan AY, Amin S, Ratajczak P, et al. Genetic heterogeneity of KID syndrome: identification of a Cx30 gene (GJB6) mutation in a patient with KID syndrome and congenital atrichia. J Invest Dermatol. 2004;122:1108–13.
136. Zellweger H, Uehlinger EE. Fall von halbseitiger Knochenchondromatose (Ollier) mit Naevus ichthyosiformis. Helv Paediatr Acta. 1948;2: 153–63.
137. Happle R, Koch H, Lenz W. The CHILD syndrome. Congenital hemidysplasia with ichthyosiform erythroderma and limb defects. Eur J Pediatr. 1980;134:27–33.
138. Happle R, Effendy I, Megahed M, et al. CHILD syndrome in a boy. Am J Med Genet. 1996;62:192–4.
139. Konig A, Happle R, Bornholdt D, et al. Mutations in the NSDHL gene, encoding a 3beta-hydroxysteroid dehydrogenase, cause CHILD syndrome. Am J Med Genet. 2000;90:339–46.
140. König A, Skrzypek J, Löffler H, et al. Donor dominance cures CHILD nevus. Dermatology. 2010;220:340–5.
141. Happle R. X-linked dominant chondrodysplasia punctata. Review of literature and report of a case. Hum Genet. 1979;53:65–73.
142. Furtado LV, Bayrak-Toydemir P, Hulinsky B, et al. A novel X-linked multiple congenital anomaly syndrome associated with an EBP mutation. Am J Med Genet A. 2010;152A:2838–44.
143. Braverman N, Lin P, Moebius FF, et al. Mutations in the gene encoding 3 beta-hydroxysteroid-delta 8, delta 7-isomerase cause X-linked dominant Conradi-Hunermann syndrome. Nat Genet. 1999;22: 291–4.
144. Derry JM, Gormally E, Means GD, et al. Mutations in a delta 8-delta 7 sterol isomerase in the tattered mouse and X-linked dominant chondrodysplasia punctata. Nat Genet. 1999;22:286–90.

58 Keratodermas

Alfons L Krol and Dawn Siegel

Key features

- Palmoplantar keratodermas can be inherited or acquired
- The three major patterns of involvement are diffuse, focal and punctate
- Additional distinguishing features include an erythematous border, associated hyperhidrosis and transmigration to areas beyond the palmoplantar skin
- It is important to determine whether other features are present, e.g. impaired hearing, cardiomyopathy (in patients with woolly hair), starfish keratoses, pseudoainhum, knuckle pads, atrophy, oral lesions, nail changes, blisters
- Histologic examination can determine whether or not epidermolytic hyperkeratosis is present

INTRODUCTION

Palmoplantar keratodermas (PPKs) represent a diverse group of hereditary and acquired disorders characterized by hyperkeratosis of the skin on the palms and soles (Table 58.1). Progress in our knowledge of keratins and the keratinocyte cytoskeleton as well as desmosomes and gap junctions has increased our understanding of the pathogenesis of these conditions (Table 58.2). Conversely, essential biologic functions of widely expressed proteins have been discovered from the study of PPKs[1].

Keratins are heteropolymeric proteins that form the intermediate filament cytoskeleton of keratinocytes. Keratin proteins directly associate with a number of subcellular structures, including desmosomes, hemidesmosomes and protein complexes within the cornified cell envelope (see Ch. 56). Keratins interact with these structures in a highly regulated and complex manner in order to maintain the integrity of the skin.

There are two types of keratins: (1) acidic or type I (encoded on chromosome 17q), which encompass K9 to K28 and K31 to K40 (including those formerly referred to as Ha trichocyte keratins); and (2) basic or type II (encoded on chromosome 12q), which encompass K1 to K8 and K71 to K86 (including those formerly referred to as Hb trichocyte keratins) (see Table 56.2). Type I keratins partner with type II keratins in a tissue- and differentiation-specific manner (see Fig. 56.7). Keratin pairs expressed in the epidermis include K1/K10 in suprabasal keratinocytes, K5/K14 in basal keratinocytes (also in mucosa), and K6a/K16 as well as K6b/K17 in keratinocytes of the palms/soles, epidermal appendages and hyperproliferative skin (also in mucosa). K9 is highly expressed only in suprabasal keratinocytes of the palmoplantar epidermis[2], and its partner is thought to be K1. Keratin intermediate filaments represent heteropolymers assembled from coiled-coil keratin heterodimers (see Fig. 56.4).

The molecular structure of keratins and other intermediate filaments consists of a central α-helical rod domain composed of four segments (1A, 1B, 2A, 2B) that are interrupted by non-helical linker segments (see Fig. 56.5). The amino (1A) and carboxy (2B) terminal regions of the central α-helical rod domain are most critical for keratin function. Keratin gene mutations are responsible for several types of inherited PPK[3].

Desmosomes are cell–cell junctions that integrate the intermediate filament cytoskeleton into the cell membrane and establish adhesive points between opposing cells (see Fig. 56.8). Desmosomes are vital to the maintenance of mechanical integrity and stress resistance of individual cells and multicellular sheets, functions that are particularly critical in the epidermis and heart. Desmosomes also have important roles in the regulation of tissue morphogenesis and homeostasis.

Desmoglein and desmocollin proteins belong to the cadherin superfamily of cell–cell adhesion mediators and form the core of the desmosome (see Ch. 56). Each of these type I membrane glycoproteins exists as multiple isoforms (desmoglein 1–4 and desmocollin 1–3), which are products of different genes and are expressed in a cell type- and differentiation-specific manner[4]. The intracellular portions of desmogleins and desmocollins bind to plakoglobin (an armadillo protein/catenin family member). Plakoglobin in turn binds directly to the N-terminus of desmoplakin, a plakin protein. Desmoplakin forms a bridge between the desmosomal cadherin/catenin complex and the intermediate filament cytoskeleton, which interacts with the desmoplakin C terminus[5]. Striate PPK has been shown to be due to mutations in the genes that encode desmoplakin and desmoglein 1[6], whereas PPK plus woolly hair and cardiomyopathy can result from mutations in the genes for desmoplakin and plakoglobin[7] (see Table 58.2 and Fig. 56.8).

Gap junctions are specialized transmembrane channels that connect the cytoplasm of neighboring cells, facilitating cell-to-cell communication[8]. The status of the channels (i.e. open or closed) is controlled by several mechanisms, including voltage, calcium concentration, pH and phosphorylation. Each gap junction channel is composed of integral membrane proteins called connexins. Six connexin monomers oligomerize to form an annular hemichannel called a connexon; connexons then cluster at the plasma membrane to dock with the connexons of an apposing cell to form functional channels (Fig. 58.1). The half-life of each connexin is short (i.e. a matter of hours), which results in a constant state of assembly and degradation of channels. Different connexins are expressed in a tissue- and differentiation-specific manner as well as in response to stimuli.

The first human disorder shown to be due to a connexin defect was X-linked dominant Charcot–Marie–Tooth disease, where loss of connexin 32 (Cx32) was found to result in impaired diffusion of nutrients and signaling molecules into peripheral nerves. In 1997, the association of defects in several connexins with hearing impairment was demonstrated, and it is now known that recessive mutations in the gene that encodes Cx26 are the single most important cause of non-syndromic congenital hearing impairment (with carrier frequencies ranging from 3% to 10% in the general population)[9]. In addition to peripheral neuropathy and hearing impairment, the clinical manifestations of connexin disorders can involve the skin, cutaneous appendages and eyes (Table 58.3)[10]. The phenotypic spectrum of autosomal dominant disorders caused by defects in Cx26 range from Vohwinkel syndrome (mutilating PPK with deafness)[11] to keratitis–ichthyosis–deafness (KID) syndrome (which also features a "stippled" PPK; see Ch. 57). Hidrotic ectodermal dysplasia (due to mutations in the gene that encodes Cx30)[12] and erythrokeratodermia variabilis (EKV; due to mutations in the genes that encode Cx31 and Cx30)[13] are other connexin disorders that can manifest with a PPK. For example, a patchy or diffuse PPK, often associated with peeling, affects approximately half of families with EKV (see Ch. 57).

The inherited PPKs are uncommon disorders, and reports of individual families have resulted in non-uniform nomenclature that includes many eponyms. Several attempts have been made to classify keratodermas, none of which is entirely satisfactory. However, a straightforward working classification[14] divides PPKs into three broad types based on the pattern of palmoplantar involvement:

- ***diffuse PPK*** – involvement of the entire palmoplantar surface (Fig. 58.2)

PALMOPLANTAR KERATODERMAS	
HEREDITARY	**ERYTHROKERATODERMAS (SEE CH. 57)**
Diffuse type Unna–Thost type: non-epidermolytic PPK Vörner type: epidermolytic PPK Meleda type: Mal de Meleda Greither type: transgrediens and progrediens PPK Gamborg–Nielsen (Norrbotten) type Sybert type	Keratitis–ichthyosis–deafness (KID) syndrome* Hystrix-like ichthyosis–deafness (HID) syndrome* Erythrokeratodermia variabilis* Progressive symmetric erythrokeratoderma*
Diffuse type with associated features Vohwinkel syndrome: mutilating PPK PPK with sensorineural deafness due to mitochondrial or *GJB2* gene defect Bart–Pumphrey syndrome: knuckle pads, leukonychia, and sensorineural deafness Huriez syndrome: PPK with scleroatrophy PPK with sex reversal and squamous cell carcinoma Hidrotic ectodermal dysplasia: Clouston syndrome Olmsted syndrome: mutilating PPK with periorificial plaques Papillon–Lefèvre syndrome: PPK with periodontitis Haim–Munk syndrome: PPK with periodontitis, arachnodactyly and acro-osteolysis Naxos disease: diffuse PPK with woolly hair and arrhythmogenic cardiomyopathy	**ICHTHYOSES WITH ASSOCIATED KERATODERMA (SEE CH. 57)** Epidermolytic ichthyosis (bullous congenital ichthyosiform erythroderma)* Ichthyosis hystrix Curth–Macklin* Congenital ichthyosiform erythroderma* Lamellar ichthyosis Harlequin ichthyosis Sjögren–Larsson syndrome* Refsum syndrome CEDNIK (*c*erebral *d*ysgenesis, *n*europathy, *i*chthyosis and *k*eratoderma) syndrome* MEDNIK (*m*ental retardation, *e*nteropathy, *d*eafness, *n*europathy, *i*chthyosis and *k*eratoderma) syndrome* KLICK syndrome (*k*eratosis *l*inearis with *i*chthyosis *c*ongenita and *s*clerosing *k*eratoderma) Netherton syndrome (rarely)
Focal type PPK striata/areata type: striate PPK, focal non-epidermolytic PPK, Wachters type, Brünauer–Fuhs–Siemens type Hereditary painful callosities: nummular epidermolytic PPK, focal epidermolytic PPK	**OTHER ECTODERMAL DYSPLASIAS WITH ASSOCIATED KERATODERMA** Ectodermal dysplasia with skin fragility* Acantholytic ectodermal dysplasia* Schöpf–Schulz–Passarge syndrome*: PPK with hidrocystomas, hypodontia and hypotrichosis Odonto-onycho-dermal dysplasia* Ectodermal dysplasia–ectrodactyly–clefting (EEC) syndrome Cleft lip/palate ectodermal dysplasia Oculo-dento-digital dysplasia Naegeli–Franceschetti–Jadassohn syndrome, dermatopathia pigmentosa reticularis
Focal type with associated features Howel–Evans syndrome: non-epidermolytic PPK with carcinoma of the esophagus Richner–Hanhart syndrome: oculocutaneous tyrosinemia Pachyonychia congenita-6a/16: type 1, Jadassohn–Lewandowsky type Pachyonychia congenita-6b/17: type 2, Jackson–Lawler type Carvajal syndrome: striate PPK with woolly hair and dilated cardiomyopathy Focal palmoplantar and gingival keratosis	**OTHER** Epidermolysis bullosa: simplex (Dowling–Meara, with mottled pigmentation >> Weber–Cockayne), non-Herlitz junctional (occasionally) Kindler syndrome Erythropoietic protoporphyria Familial pityriasis rubra pilaris* Linear PPK associated with epidermal nevus* Dyskeratosis congenita Darier disease (typically punctate) Cowden disease (punctate) Porokeratotic eccrine ostial and dermal duct nevus (PEODDN; porokeratotic adnexal ostial nevus)* Cardio-facio-cutaneous syndrome HOPP (*h*ypotrichosis, acro-*o*steolysis/*o*nychogryphosis, *p*almoplantar keratoderma and *p*eriodontitis) syndrome* Cantu syndrome*: hyperkeratosis–hyperpigmentation syndrome Cole disease*: guttate hypopigmentation with punctate PPK
Punctate type Punctate palmoplantar keratoderma: keratosis punctata palmaris et plantaris, Buschke–Fischer–Brauer type Acrokeratoelastoidosis Focal acral hyperkeratosis Porokeratosis punctata palmaris et plantaris	
ACQUIRED	
Keratoderma climactericum Spiny keratoderma Keratoderma associated with hypothyroidism/myxedema Keratoderma associated with cancer Aquagenic PPK Drug-induced keratoderma (e.g. lithium, verapamil, venlafaxine, tegafur, imatinib, glucan, capecitabine)	

*PPK is a major feature of the disorder.

Table 58.1 Palmoplantar keratodermas (PPKs). Progrediens means progressive, referring to the tendency to involve additional sites (e.g. the elbows and knees) over time.

- ***focal PPK*** – localized areas of hyperkeratosis, located mainly over pressure points. There are two patterns of focal PPK: (a) the areata/nummular type, which is characterized by oval lesions, usually on the plantar surface; and (b) the striate type, which presents as linear hyperkeratotic lesions, most commonly extending from the palms to the volar surface of the fingers (Fig. 58.3)
- ***punctate PPK*** – small (1 mm to 1 cm) keratotic papules on the palms and soles (Fig. 58.4).

Of note, focal involvement sometimes evolves to a diffuse PPK over time (e.g. from infancy to adulthood). Further classification depends upon the presence or absence of: (1) associated cutaneous and/or extracutaneous findings; and (2) epidermolytic hyperkeratosis on histologic evaluation (see Table 58.1)[14]. Another feature that has been used to characterize PPKs is whether or not *transgrediens* is evident; this term refers to extension of hyperkeratosis across the "line of transgredience" onto the dorsal aspects of the fingers, toes, hands and feet as well as the flexor aspects of the wrists and heels. In the future, as our knowledge of the genetic bases of specific clinical syndromes improves, keratodermas may be classified by their molecular pathology (see Table 58.2).

HEREDITARY KERATODERMAS

DIFFUSE PALMOPLANTAR KERATODERMA (ISOLATED)

Diffuse Non-epidermolytic and Epidermolytic Palmoplantar Keratoderma

Synonyms: ■ Unna–Thost type: non-epidermolytic PPK ■ Vörner type: epidermolytic PPK

History

In 1880, Thost described a family with diffuse non-transgrediens PPK. This was followed by Unna's description of a clinically identical, autosomal dominant PPK in two families. Although "Unna–Thost type" is used to designate non-epidermolytic PPK (NEPPK), in 1992,

HEREDITARY PALMOPLANTAR KERATODERMAS WITH KNOWN GENETIC BASES								
Type	**Protein product of mutated gene**	**Synonyms**	**Inheritance**	**Onset**	**Hyperhidrosis**	**Extensor surfaces of extremities involved?**	**Erythematous border**	**Comments**
				DIFFUSE				
Unna–Thost	K1* K6c*	Non-epidermolytic PPK (NEPPK)	AD	2–5 years, sometimes later	++	No	Yes	Second most common type of diffuse PPK (after EPPK)
Vörner	K9 K1	Epidermolytic PPK (EPPK)	AD	0–3 years	+	No	Yes	Clinically identical to diffuse NEPPK, but histology shows epidermolytic hyperkeratosis
Meleda	SLURP-1	Mal de Meleda	AR	0–3 years	+	Yes	Yes	Atopic dermatitis, often infected
Greither	K1 (in some families)	Transgrediens and progrediens PPK	AD	Infancy	Yes	Yes	Yes	
Mutilating	Loricrin (+ ichthyosis) Connexin 26 (+ deafness)	Vohwinkel syndrome, keratoderma hereditaria mutilans	AD	Infancy	No	Yes	Yes	Honeycomb palms, pseudoainhum, starfish keratoses on the knuckles, sensorineural deafness (Cx26)
With deafness	Mitochondrial tRNA for serine		Mitochondrial	Variable	No	No	No	Deafness
With sex reversal & SCC	R-spondin 1		AR	Infancy	No	No	No	Acral SCC, XX sex reversal (i.e. female-to-male)
Papillon–Lefèvre syndrome	Cathepsin C	PPK with periodontitis	AR	Birth to early infancy	Yes	Yes	Yes	Periodontitis, premature loss of teeth, psoriasiform lesions on extremities, pyogenic infections
Naxos disease	Plakoglobin Desmocollin 2*	Diffuse NEPPK with woolly hair and cardiomyopathy	AR	Infancy	No	No	Yes	Woolly hair; arrhythmias and right ventricular cardiomyopathy develops during adolescence
				FOCAL				
Striate/areata type	Desmoglein 1 Desmoplakin K1 K16† & K6c	Wachters type, Brünauer–Fuhs–Siemens type	AD	4–10 years	+/–	No	No	Striate on palms, islands on feet, variable phenotype
Richner–Hanhart syndrome	Tyrosine amino-transferase	Tyrosinemia type II, oculocutaneous tyrosinemia	AR	Infancy (ocular) Early childhood to adolescence (skin)	Yes	Yes	Yes	Dendritic keratitis, corneal ulcers, mental retardation
Pachyonychia congenita (PC)	K16 & K6a K17 & K6b	PC1, Jadassohn–Lewandowsky type PC2, Jackson–Lawler type	AD	Infancy to early childhood	Yes	No	Yes	PC1: more severe NEPPK PC2: steatocystoma multiplex & eruptive vellus hair cysts more common, natal teeth
Carvajal syndrome	Desmoplakin	Striate PPK with woolly hair and cardiomyopathy	AR > AD	Infancy	No	No	Yes	Woolly hair; dilated cardiomyopathy (variable onset); occasionally skin fragility, nail dystrophy, hypodontia

*Single family reported to date.
†Less confirmed.

Table 58.2 Hereditary palmoplantar keratodermas (PPKs) with known genetic bases. Those due to connexin mutations are listed in Table 58.3. AD, autosomal dominant; AR, autosomal recessive; SCC, squamous cell carcinoma.

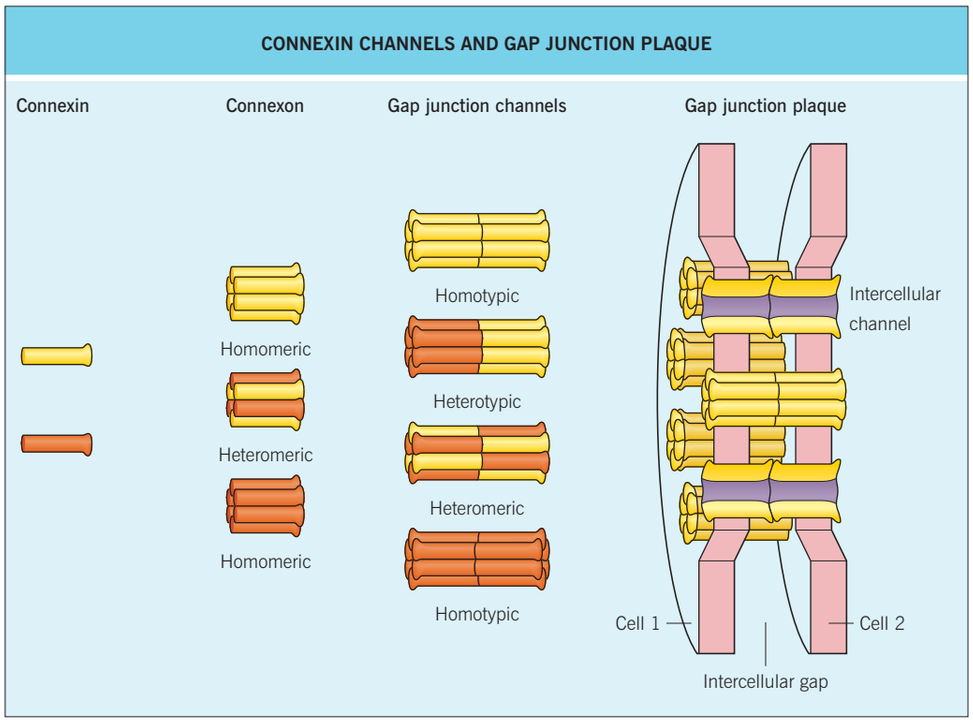


Fig. 58.1 Connexin channels and gap junction plaque. Six connexin molecules oligomerize to form a connexon hemichannel with a central pore that has a maximum diameter of 2 nm. Connexons may be homomeric if all the participating molecules are of the same connexin species, or heteromeric if they differ. Connexons of adjacent cells dock in the intercellular gap to form a complete gap junction intercellular channel. *Redrawn with permission from Richard G, Smith LE, Bailey RA, et al. Mutations in the human connexin gene* GJB3 *cause erythrokeratoderma variabilis. Nat Genet. 1998;20:366–9.*

HUMAN CONNEXIN DISORDERS

Disorder	Inheritance	Connexin	Gene	Major organ distribution
Non-syndromic hearing impairment (DFNB1)	AR	Cx26	*GJB2*	Ubiquitous, including liver, cochlea, mammary gland, skin and appendages, mucous membranes, pancreas, kidney, intestine, lung
Non-syndromic hearing impairment (DFNA3)	AD	Cx26	*GJB2*	
Palmoplantar keratoderma and hearing impairment, including Vohwinkel syndrome	AD	Cx26	*GJB2*	
Bart–Pumphrey syndrome	AD	Cx26	*GJB2*	
Keratitis–ichthyosis–deafness (KID) syndrome & hystrix-like–ichthyosis–deafness (HID) syndrome	AD	Cx26 (Cx30)*	*GJB2 (GJB6)**	
Non-syndromic hearing impairment (DFNA3)	AD	Cx30	*GJB6*	Brain, cochlea, skin
Hidrotic ectodermal dysplasia (Clouston syndrome)	AD	Cx30	*GJB6*	
Erythrokeratodermia variabilis	AD>>AR	Cx30.3	*GJB4*	Skin, kidney
Erythrokeratodermia variabilis	AD>>AR	Cx31	*GJB3*	Skin, eye, placenta, kidney, testes, cochlea, Schwann cells
Non-syndromic hearing impairment	AR>>AD	Cx31	*GJB3*	
Peripheral sensory neuropathy and hearing impairment	AD	Cx31	*GJB3*	
Charcot–Marie–Tooth disease	X-linked dominant	Cx32	*GJB1*	Brain, Schwann cells, liver, thyroid, kidney, pancreas, uterus
Polymorphism may be a marker for atherosclerotic plaque development		Cx37	*GJA4*	Gonads, lung, endothelium, heart, skin
Oculo-dento-digital dysplasia	AD	Cx43	*GJA1*	Ubiquitous, including eyes, teeth, musculoskeletal, brain, heart, skin
Hypoplastic left heart syndrome	Oligogenic	Cx43	*GJA1*	
Cataract, zonular pulverulent-3	AD	Cx46	*GJA3*	Lens, heart, kidney, peripheral nervous system
Hereditary lymphedema	AD	Cx47	*GJC2*	Lymphatic vessels, CNS
Hypomyelinating leukodystrophy	AR	Cx47	*GJC2*	
Cataract, zonular pulverulent-1	AD	Cx50	*GJA8*	Lens, cornea, heart

*Reported in a single patient.

Table 58.3 Human connexin disorders. Disorders in bold feature palmoplantar keratoderma. AD, autosomal dominant; AR, autosomal recessive; CNS, central nervous system. Adapted from ref. 10 with permission.

Fig. 58.2 Diffuse non-epidermolytic palmoplantar keratoderma. Note the sharp demarcation at the wrist and side of the thumb **(A)** and the greater thickness in sites of pressure **(B).** *A, Courtesy, Julie V Schaffer, MD.*

Fig. 58.3 Focal palmoplantar keratoderma. A Striate type on the palm. **B** Areata type on the soles.

Küster et al.[15] reviewed the family described by Thost and found the histologic features of epidermolytic hyperkeratosis, which characterize the "Vörner type" of PPK. Subsequently, after K9 mutations were reported in epidermolytic PPK (EPPK)[16], identical mutations were found in the descendants of the family studied by Thost. These findings brought into question the previously held belief that the non-epidermolytic type was the most common form of PPK, as multiple biopsies may be required to identify epidermolytic hyperkeratosis.

Epidemiology

EPPK is one of the more common keratin disorders, with an estimated incidence of at least 4.4 per 100 000 in Northern Ireland[15]. The incidence of NEPPK is unknown.

Pathogenesis

The expression of *keratin 9* is limited to the suprabasal cell layers of palmar and plantar skin. In patients with the diffuse form of EPPK (Vörner type), the majority of K9 mutations are localized to a very small area of this type I keratin gene that encodes the helix initiation motif in the 1A domain (see Ch. 56). Such mutations are highly disruptive to keratin filament assembly, causing tonofilament aggregation and cytolysis.

Within palmoplantar skin, keratin 9 is thought to partner with *keratin 1*. Of note, mutations in K1 and K10 are associated with epidermolytic ichthyosis (EI; bullous congenital ichthyosiform erythroderma) in which epidermolytic hyperkeratosis is seen histologically (see Ch. 57). As might be expected, patients with EI caused by K1 mutations often have severe PPK, whereas those with K10 mutations typically lack palmoplantar involvement because the latter gene is usually not expressed in these sites. The majority of mutations reported in EI patients have been in the critical 1A and 2B domains of the keratin molecule. However, families with diffuse EPPK alone caused by K1 mutations (often in the beginning of the 1B domain) have also been described[17].

Kimonis et al.[18] reported a pedigree with a K1 mutation that resulted in diffuse NEPPK rather than the expected EI or EPPK. The mutation was in a non-critical portion of the *K1* gene and thus had less of an effect on the K1 protein. This may be analogous to the situation in epidermolysis bullosa simplex (EBS), where the Weber–Cockayne type, due to mutations in non-critical portions of the *K5* and *K14* genes, is characterized by a milder, acrolocalized form of the disorder[19]. Of note, *K1* mutations have also been identified in patients with focal forms of PPK (see below). However, the gene(s) responsible for most cases of diffuse NEPPK remain to be determined. Linkage analysis, based upon three pedigrees from England, identified a diffuse NEPPK locus proximal to the type II keratin gene cluster on chromosome 12q[20].

Some patients with EBS (especially the Dowling–Meara type) develop diffuse (or focal) keratoderma. Interestingly, mutations in the *K5* gene

Fig. 58.4 Punctate palmoplantar keratoderma. Keratotic papules, some coalescing to form plaques, on the palm (**A**) and sole (**B**).

Fig. 58.5 Diffuse epidermolytic palmoplantar keratoderma. **A,B** Diffuse hyperkeratosis with involvement of the lateral aspect of the foot; note the erythema at the border with uninvolved skin. **C** Erythema is present at the border on the flexor wrist as well as in areas where there is reduced hyperkeratosis.

that result in the production of a truncated *keratin 5* protein have been associated with severe diffuse PPK as well as the skin fragility and blistering of EBS, suggesting that the K5 tail domain may have a function that is particularly important in palmoplantar skin[19].

Until patients who have been assigned separate eponyms, such as Gamborg–Nielsen (Norrbotten) or Sybert types of keratoderma, have had molecular screening of appropriate keratin genes and other genes implicated in PPKs, these entities are best thought of as variants of the diffuse type of EPPK or NEPPK.

Clinical features

The clinical features of EPPK and NEPPK are identical. The palmoplantar skin is initially red, followed by the appearance of thick, yellow hyperkeratosis that expands to involve the lateral aspects of the hands and feet. The surface can be smooth and waxy (see Fig. 58.2) or irregular and verrucous. The condition may present during the first few months of life and is usually well developed by 3–4 years of age. Both epidermolytic and non-epidermolytic forms are typically non-transgredient, with a sharp demarcation of the lesions at the wrists and no tendency to involve the extensor surfaces. The border of the hyperkeratosis tends to be erythematous (Fig. 58.5).

Hyperhidrosis, secondary dermatophyte infections and pitted keratolysis are observed more frequently in NEPPK than EPPK. Blisters are occasionally reported in EPPK, in particular during childhood; however, the etiology may be a secondary dermatophyte infection rather than the underlying genetic defect. Constriction of the pulps of the distal fingertips, knuckle pads and thickened nails without dystrophy are occasionally seen[14].

Pathology

EPPK is characterized by the histologic findings of epidermolytic hyperkeratosis. Clumping of tonofilaments leading to perinuclear vacuolization is seen, as are large keratohyalin granules and cellular degeneration in the spinous and granular cell layers (see Ch. 57). A careful search of several biopsy specimens may be required to identify these changes, which are often subtle and patchy. NEPPK shows nonspecific changes, with orthohyperkeratosis, acanthosis, and either thickening or a reduction of the granular cell layer (Fig. 58.6).

Differential diagnosis

Diffuse NEPPK and EPPK are distinguished from one another histologically. Analysis of the *K9* (if epidermolytic) or *K1* gene can further characterize diffuse PPK without associated features in some affected individuals. The possibility of associated sensorineural deafness (suggesting an underlying Cx26 or mitochondrial defect) should be investigated, and a cardiac evaluation is indicated for individuals with woolly

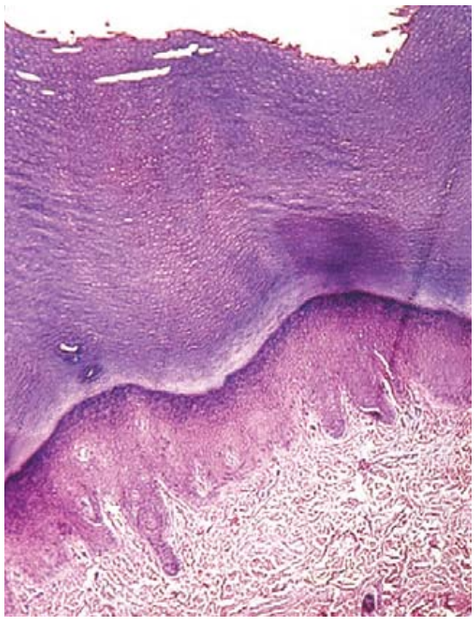


Fig. 58.6 Histologic features of non-epidermolytic palmoplantar keratoderma. Note the massive hyperkeratosis, acanthosis and hypergranulosis.

hair in addition to a diffuse PPK to exclude Naxos disease and related conditions. Patients with hidrotic ectodermal dysplasia also have hypotrichosis and nail dystrophy, individuals with Huriez syndrome display scleroatrophic changes on the dorsal aspect of the hands and hypoplastic nails, and those with Papillon–Lefèvre syndrome develop psoriasiform lesions and destructive periodontitis. Both Mal de Meleda and Olmsted syndrome present with a diffuse transgredient PPK together with periorificial lesions, which are more severe in the latter disorder. Vohwinkel syndrome is characterized by transgredient mutilating PPK associated with starfish keratoses on the knuckles and pseudoainhum (as well as deafness in patients with Cx26 defects).

Treatment

Factors to consider in selecting a local treatment for diffuse PPK include the severity of symptoms, the degree of hyperkeratosis and the age of the patient. Salicylic acid 4–6% in petrolatum may be helpful in reducing the degree of hyperkeratosis but must be used with caution in children. Application of 50% propylene glycol in water under plastic occlusion several nights per week can also be beneficial, and lactic acid- and urea-containing creams and lotions represent additional keratolytic options. Mechanical debridement with a blade or dental drill may be useful for troublesome areas. Secondary fungal and bacterial infections often require systemic therapy for eradication.

Oral retinoid therapy can have variable effects. It may improve the hyperkeratosis but also tends to increase the fragility of the skin. In a study of patients with EI, those with *K1* mutations and associated PPK did not benefit from treatment with oral acitretin or topical retinoids (tazarotene or tretinoin), whereas most individuals with *K10* mutations improved[21]. The epidermis of non-responders had reduced expression of *K2* mRNA, which may function as a substitute for the mutated protein in those with K1 defects. Further studies on genotype/phenotype correlations in PPKs and their response to treatment are needed.

Mal de Meleda

Mal de Meleda is a rare autosomal recessive disorder that was first described in inhabitants of the island of Mljet (Meleda) off the Dalmatian coast. Shortly after birth, patients have the onset of diffuse palmar and plantar thickening with an erythematous border. The disease is progressive and transgredient, with lesions present on the dorsal surfaces of the hands and feet as well as the elbows and knees. Severe hyperhidrosis accompanied by malodor is characteristic of this PPK. It is often complicated by fissuring and secondary fungal or bacterial infections, and there are reports of melanoma arising in affected acral sites[22]. Periorificial lesions reminiscent of those seen in Olmsted syndrome also develop. Thickened nails with koilonychia or subungual hyperkeratosis are common, and constricting bands of the digits may occur. Histologically, palmoplantar skin displays orthohyperkeratosis with a normal granular layer.

Mal de Meleda is caused by mutations in the *s*ecreted *l*eukocyte antigen-*6*/*u*rokinase-type plasminogen activator *r*elated *p*rotein-1 gene (*SLURP1*)[23]. The SLURP-1 protein is an allosteric agonist of the nicotinic acetylcholine receptor with pro-apoptotic activity and roles in keratinocyte differentiation and T-cell activation[22].

Greither Syndrome

Greither syndrome (transgrediens and progrediens PPK), originally described in 1952, is characterized by a diffuse transgredient PPK with onset in early infancy. The severity of the PPK is variable and it is accompanied by hyperhidrosis. There are usually hyperkeratotic plaques on the knees and elbows, and, in some patients, in flexural regions. Histologically, epidermolytic changes of the granular layer are seen.

The disease is inherited in an autosomal dominant fashion. Two large families with features of Greither syndrome (and a history of neonatal blistering) were shown to have a missense mutation in their *K1* gene[24], emphasizing the variability of the clinical phenotype seen in patients with *K1* mutations.

DIFFUSE PALMOPLANTAR KERATODERMA WITH ASSOCIATED FEATURES

Mutilating Palmoplantar Keratoderma

Synonyms: ■ Vohwinkel syndrome ■ Keratoderma hereditaria mutilans ■ Subtype due to loricrin mutations: loricrin keratoderma, variant Vohwinkel syndrome, Vohwinkel syndrome with ichthyosis ■ Subtype due to connexin 26 mutations: classic Vohwinkel syndrome, Vohwinkel syndrome with deafness

Fig. 58.7 Mutilating palmoplantar keratoderma (Vohwinkel syndrome). A Diffuse honeycombed keratoderma of the sole. **B** Pseudoainhum formation.

Vohwinkel first described this autosomal dominant disorder in 1929. Honeycombed, diffuse hyperkeratosis of the palms and soles appears in infancy (Fig. 58.7A) and then becomes transgredient. This is followed by the development of constricting bands of the digits during early childhood, which may lead to digital autoamputation, i.e. pseudoainhum (Fig. 58.7B). Peculiar starfish-shaped keratoses appear over the knuckles of the fingers and toes and are said to be characteristic of the disorder. Hearing loss of at least a moderate degree is seen in many patients (see below). Additional reported findings are alopecia and ichthyosis. Histologic features include hyperkeratosis, acanthosis and a thickened granular cell layer with retained nuclei in the stratum corneum.

The disorder was originally mapped to the epidermal differentiation complex on chromosome 1q21 and associated with a mutation in the gene that encodes *loricrin,* a major cornified envelope protein (see Ch. 56). The family that was analyzed also displayed mild generalized ichthyosis but had normal hearing. It has since been shown that the subtype of Vohwinkel syndrome associated with deafness is caused by mutations in the gap junction β2 gene (*GJB2*) encoding ***Cx26***[11], in particular a heterozygous substitution (D66H) affecting the first extracellular domain of this protein. Notably, different mutations in the *GJB2* gene have been found to underlie other forms of PPK associated with hearing impairment[10] (see Table 58.3). Mutilating PPK without hearing impairment associated with ichthyosis hystrix (Curth–Macklin type; see Ch. 57) is caused by mutations in the variable tail region of K1[25]. One patient with the latter condition had previously been reported in the literature as having Vohwinkel syndrome in association with ichthyosis, stressing the necessity of combining clinical, histologic, ultrastructural and molecular data to properly categorize patients with mutilating PPK.

Bart–Pumphrey Syndrome

Synonym: ▪ PPK with knuckle pads, leukonychia and deafness

Bart, a dermatologist, and Pumphrey, an otolaryngologist, described this autosomal dominant syndrome in 1967[26]. All patients reported to date have been profoundly hearing impaired from birth, and during early childhood they developed a diffuse PPK together with hyperkeratoses (knuckle pads) over the metacarpophalangeal and proximal and distal interphalangeal joints (Fig. 58.8). Leukonychia is variable and tends to improve with age. The keratoderma may have a pitted or stippled surface reminiscent of the "honeycomb" appearance seen in Vohwinkel syndrome. Bart–Pumphrey syndrome has been shown to be caused by mutations in the *GJB2* gene encoding Cx26[27], providing an explanation for its clinical overlap with Vohwinkel syndrome.

Huriez Syndrome

Synonyms: ▪ Palmoplantar keratoderma with scleroatrophy ▪ Sclerotylosis

Fig. 58.8 Bart–Pumphrey syndrome. Leukonychia and knuckle pads in a patient with sensorineural deafness.

This rare syndrome has an autosomal dominant inheritance pattern. At birth, red, atrophic skin is present on the dorsal aspect of the hands and feet. The associated diffuse keratoderma is mild and more evident on palmar skin than plantar skin. With time, sclerodactyly and nail changes appear, including ridging, koilonychia, fissuring and hypoplasia. Affected patients have an increased risk of developing squamous cell carcinoma (SCC) in areas of atrophic skin[28]. The differential diagnosis of Huriez syndrome includes PPK with sex reversal and SCC (see below).

Histologic features of the keratoderma include orthohyperkeratosis, acanthosis and an increased granular layer. By electron microscopy, dense bundles of tonofilaments are seen throughout the epidermis and coarse clumped keratohyalin granules are evident in the granular layer. A characteristic finding is an almost complete absence of Langerhans cells in the affected skin. The gene responsible for Huriez syndrome has been mapped to 4q23[29].

Palmoplantar Keratoderma with Sex Reversal and Squamous Cell Carcinoma

This rare autosomal recessive syndrome, thus far described in several consanguineous Italian kindreds[30,31], features a diffuse NEPPK with onset in infancy and marked predisposition to the development of acral SCC. In addition, affected individuals with an XX genotype have either (1) a male phenotype (i.e. female-to-male sex reversal), often associated with hypospadias and hypogonadism; or (2) ambiguous genitalia, sometimes with hermaphroditism (existence of both male and female gonadal structures). Other manifestations include sclerodactyly with variable cutaneous atrophy (causing some patients to initially be reported as having Huriez syndrome), nail dystrophy (e.g. hypoplasia, longitudinal ridging, skin growth over the nail plate) and periodontitis leading to early loss of teeth.

In 2006, this condition was found to be due to mutations in the R-spondin1 gene (*RSPO1*), which encodes a protein that activates β-catenin signaling and has important roles in gonadal development[32]. *RSPO1* mutations represent the only known cause of XX sex reversal or XX hermaphroditism other than translocation of the testis-determining gene (*SRY*; normally on the Y chromosome) to the X chromosome or an autosome.

Hidrotic Ectodermal Dysplasia

Synonym: ▪ Clouston syndrome

Hidrotic ectodermal dysplasia is an autosomal dominant disorder in which a diffuse PPK occurs in conjunction with hypotrichosis and nail dystrophy. The condition is most common in individuals of French-Canadian ancestry, where large kindreds have been described[33], but it has been reported in individuals with a variety of ethnic backgrounds. Patients have hypotrichosis involving the scalp, eyebrows, eyelashes, and axillary and genital regions. Alopecia may be severe, even in infancy, although usually its onset is gradual, becoming more pronounced after puberty. The nails, which may be normal at birth, gradually become thickened and dystrophic, displaying short nail plates that are easily shed (Fig. 58.9; see Fig. 63.16). The nail abnormalities may mimic those of pachyonychia congenita or other syndromes of "hair–nail hypoplasia", resulting in misdiagnosis of these patients[34]. The PPK initially develops over pressure points and then increases with age. Thickened skin with a "pebbled" appearance may also be evident on the dorsal aspects of the digits (see Fig. 58.9), knees and elbows.

Histologic evaluation of thickened palms and soles shows orthohyperkeratosis with a normal granular layer. Papular lesions may demonstrate proliferation of ductal structures within a fibrovascular stroma, which is referred to as eccrine syringofibroadenomatosis. Ultrastructural examination of the hair shows disorganization of the hair fibers, with a loss of the hair shaft cuticle.

Hidrotic ectodermal dysplasia is caused by missense mutations in the *GJB6* gene, which encodes Cx30[12]. To date, four mutations in this gene have been found to underlie hidrotic ectodermal dysplasia; two of these are recurrent and account for the majority of affected families, and one was also identified in a boy with clinical features of keratitis–ichthyosis–deafness (KID) syndrome plus atrichia. The dysfunctional

Fig. 58.9 Hidrotic ectodermal dysplasia (Clouston syndrome). Note the "pebbled" skin on the dorsal aspect of the toes as well as the dystrophic nail plates. *Courtesy, D Sasseville, MD, and R Wilkinson, MD.*

Cx30 interferes with normal function of epithelial cells by disturbing their cell-to-cell communication[10].

Olmsted Syndrome

Synonym: ▪ Mutilating PPK with periorificial plaques

More than 45 patients with Olmsted syndrome have been described to date in the literature, and approximately two-thirds of them were male. The mode of inheritance has not been clearly established, although both autosomal dominant and X-linked recessive modalities have been proposed. During the first year of life, well-defined erythematous, hyperkeratotic plaques appear in the perioral and often the inguinal, genital and intergluteal areas. Keratoderma also begins during infancy, often initially focal and then becoming diffuse and severe. This leads to flexion deformities and constriction of the digits, and autoamputation may eventually occur. SCC and melanoma have been observed in the areas of keratoderma[35]. Thus far, investigation of a single patient failed to detect mutations in the genes for K1, Cx26, loricrin and SLURP-1[36].

Diffuse NEPPK with Sensorineural Deafness

Diffuse (or occasionally focal) NEPPK, sometimes with a "stippled" texture, together with impaired hearing can be caused by dominant-negative mutations in the *GJB2* gene that encodes Cx26. In addition, diffuse NEPPK and sensorineural hearing loss have been associated with a particular mutation (A7445G) in the mitochondrially encoded tRNA for serine (*MT-TS1)* in several kindreds[37].

Papillon–Lefèvre Syndrome

This syndrome, which is inherited in an autosomal recessive fashion, is characterized by diffuse, transgredient PPK (Fig. 58.10) in association with destructive periodontitis (beginning in childhood) and premature loss of teeth. Scaly psoriasiform lesions may be seen on the extremities. Frequent cutaneous and systemic pyogenic infections may occur, including hepatic abscesses[38]. Acral melanomas have also been reported in several affected individuals.

Loss-of-function mutations in the cathepsin C gene (*CTSC*) are responsible for Papillon–Lefèvre syndrome[39]. *Haim–Munk syndrome*, which features arachnodactyly, acro-osteolysis and atrophic nail changes in addition to PPK and periodontitis, is also due to mutations in cathepsin C[40]. Cathepsin C (dipeptidyl peptidase I) is a physiologic activator of groups of serine proteases found in inflammatory cells that are vital to the body's immune defenses[41]. An adult with a late-onset Papillon–Lefèvre syndrome phenotype was noted to have no alterations in the cathepsin C gene[42], suggesting that such patients have a different underlying genetic defect.

Fig. 58.10 Papillion–Lefèvre syndrome. Plantar keratoderma.

Naxos Disease

Synonym: ▪ Diffuse non-epidermolytic PPK with woolly hair and cardiomyopathy

This autosomal recessive disorder is prevalent on the Greek island of Naxos. It is characterized by arrhythmogenic right ventricular cardiomyopathy, mild NEPPK, and woolly hair[7]. The keratoderma appears during the first year of life, is diffuse in nature (with an erythematous border), and is non-transgredient. Woolly scalp hair is present at birth. Cardiac disease, manifested by arrhythmias, heart failure and/or sudden death, is usually not evident until after puberty.

In 2000, a homozygous two-base pair deletion in the plakoglobin gene (which leads to a truncated protein) was found to cause Naxos disease[43]. Plakoglobin is an important component of both desmosomes and adherens junctions in the skin and cardiac myocytes. A member or the armadillo protein family, plakoglobin links the inner and outer portions of the desmosomal plaque by binding tightly to the cytoplasmic domain of cadherins (e.g. desmoglein, desmocollin) (see Ch. 56). Dysfunction of the plakoglobin protein may lead to detachment of cardiac myocytes and ultimately to their death. Plakoglobin defects may also lead to desmosomal junction fragility in the hair follicle and shaft, explaining the woolly hair. Alopecia (rather than woolly hair) associated with focal PPK and cardiomyopathy due to a homozygous missense mutation in the plakoglobin gene has also been described[43a]. Homozygous truncating or splice-site plakoglobin mutations have also been identified in patients with *"acantholytic ectodermal dysplasia"* (featuring skin fragility and dystrophic nails as well as PPK and woolly hair) and *"lethal congenital epidermolysis bullosa"*, neither of which is associated with cardiac abnormalities[44,45].

A similar condition characterized by striate EPPK, dilated cardiomyopathy and woolly hair is caused by mutations in the gene that encodes desmoplakin[46,47] (Carvajal syndrome; see below). A homozygous mutation in the gene encoding desmocollin 2 has also been shown to cause the triad of a mild diffuse PPK, arrhythmogenic right ventricular cardiomyopathy and woolly hair[48]. Clinicians must be aware of these associations, and any patient with a PPK and woolly hair (or alopecia) should be sent for a cardiac evaluation.

FOCAL PALMOPLANTAR KERATODERMA (ISOLATED)

Synonyms: ▪ PPK striata/areata: striate PPK, focal non-epidermolytic PPK, Wachters PPK, Brünauer–Fuhs–Siemens PPK ▪ Hereditary painful callosities: nummular epidermolytic PPK, focal epidermolytic PPK

Focal areas of keratoderma can occur as localized circular lesions (areata/nummular) corresponding to sites of friction or pressure points (typically on the plantar surface) or as linear (striate) lesions extending from the palms onto the fingers (see Fig. 58.3). Repetitive trauma (e.g. from manual labor) increases the severity, and affected individuals with sedentary occupations tend to have milder changes. The major histologic features are acanthosis and an increased granular layer.

Focal isolated PPK can be inherited in an autosomal dominant fashion due to mutations in several genes encoding desmosomal components or keratins (which bind to the desmosomal plaque) (see Fig. 56.8). Desmosomal function is particularly important on the palms and soles, which are subject to friction and mechanical trauma on a regular basis. Heterozygous mutations in the *desmoglein 1* gene (*DSG1*) can cause isolated focal PPK. The majority of these are truncating mutations that are thought to lead to haploinsufficiency. Isolated focal PPK can also result from mutations in the gene that encodes the desmosomal plaque protein *desmoplakin*[49], with haploinsufficiency due to a heterozygous null mutation underlying the disorder.

Heterozygous mutations in the *K6c* or *K16* genes have been identified in patients with a focal NEPPK but no other features of pachyonychia congenita[50,51]; a combination of diffuse (on the feet) and focal (on the hands) PPK due to a K6c mutation has also been described in a single patient to date[51a].

However, individuals in some of these families also displayed dystrophic nails, oral leukokeratosis and/or follicular keratoses, suggesting a forme fruste of pachyonychia congenita. A kindred with striate PPK caused by a frameshift mutation within the variable tail domain of *K1* has also been reported. Lastly, focal PPK (striate in one patient) and sensorineural hearing loss have been described in individuals with mutations in the gene encoding *Cx26*[52].

Hereditary painful callosities (nummular EPPK) differ in that changes are localized to pressure points on the plantar surface, and histology shows epidermolytic hyperkeratosis. The underlying genetic abnormalities have not yet been identified.

FOCAL PALMOPLANTAR KERATODERMA WITH ASSOCIATED FEATURES

Howel–Evans Syndrome

Synonyms: ■ Focal non-epidermolytic PPK with carcinoma of the esophagus ■ Tylosis–esophageal carcinoma

This autosomal dominant disorder has been reported in several families over many generations. Two types have been described: type A, with a late onset of the PPK and higher risk of esophageal carcinoma, and type B, with an early onset of PPK and benign course. The designation may be artificial in that type B families who never develop esophageal carcinoma may actually have other variants of focal PPK. Type A families develop focal PPK by 5 to 10 years of age, often limited to the pressure areas of the balls of the feet, with milder involvement of the palms (Fig. 58.11). Manual labor aggravates the lesions. Keratosis pilaris, dry rough skin, and oral leukokeratosis are often present. In affected individuals, carcinoma of the esophagus typically develops during the fifth decade. The gene responsible for this condition has been mapped to a small region on chromosome 17q25 distal to the keratin gene cluster. Loss of heterozygosity in this region has been shown to occur in a variety of human cancers, including esophageal cancer, suggesting that it contains one or more tumor suppressor genes[53].

Richner–Hanhart Syndrome

Synonyms: ■ Tyrosinemia type II ■ Oculocutaneous tyrosinemia

This is a rare autosomal recessive disorder of tyrosine metabolism, and many of the reported families are of Italian origin. Photophobia and dendritic keratitis with corneal ulcerations often appear in the first year of life (Fig. 58.12). Tyrosine crystal deposition is seen on slit-lamp examination, and serum and urinary tyrosine levels are elevated. Painful, focal hyperkeratotic plaques on the palms and soles represent the characteristic cutaneous finding (Fig. 58.13). The skin changes can appear during early childhood or be delayed until adolescence; blistering and hyperhidrosis may be seen. Progressive mental retardation occurs if the patient is not treated with a restrictive diet.

Histologic features of hyperkeratotic lesions are usually nonspecific: acanthosis with hypergranulosis and hyperkeratosis. However, electron microscopy reveals aggregations of tonofilaments, and needle-shaped tyrosine crystalline inclusions are found within the keratinocytes.

Richner–Hanhart syndrome is caused by mutations in the gene that encodes hepatic tyrosine aminotransferase (TAT)[54]. A diet restricted in tyrosine and phenylalanine will clear the keratitis and the skin lesions, and it may delay or prevent cognitive impairment[55].

Fig. 58.11 Howel–Evans syndrome. Focal palmoplantar keratoderma in association with carcinoma of the esophagus.

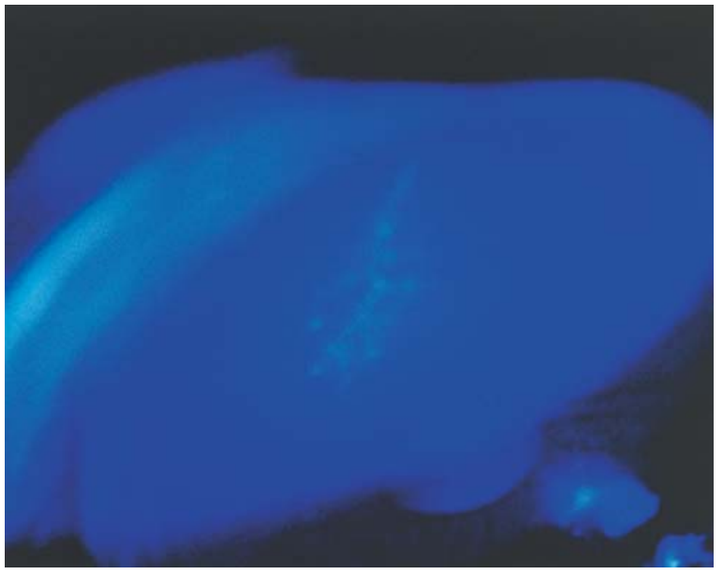


Fig. 58.12 Richner–Hanhart syndrome (tyrosinemia II). Dendritic keratitis detected by slit-lamp examination.

Fig. 58.13 Richner–Hanhart syndrome (tyrosinemia II). Focal painful keratoses on the plantar surface in a patient with corneal ulcers and mental retardation. *Courtesy, Jean L Bolognia, MD.*

CLINICAL FEATURES OF PACHYONYCHIA CONGENITA		
Feature	**PC-6a/16 (formerly PC-1)**	**PC-6b/17 (formerly PC-2)**
Painful focal palmoplantar keratoderma	++	++
Hypertrophic nail dystrophy	++	++
Oral leukokeratosis	++	+
Follicular keratoses	++	++
Steatocystoma multiplex & vellus hair cysts	+ (uncommon)	++
Other cysts (e.g. epidermoid)	+	++
Natal/prenatal teeth	-	+ (primarily in PC-17)
Pili torti/other hair abnormalities*	+ (uncommon)	+

*E.g. coarse, brittle, and/or curly hair.

Table 58.4 Clinical features of pachyonychia congenita (PC). PC-6a tends to be more severe than PC-16. ++, present in majority of patients; + present in minority of patients.

Pachyonychia Congenita

Synonyms: ■ Pachyonychia congenita type 1: Jadassohn–Lewandowsky type ■ Pachyonychia congenita type 2: Jackson–Lawler type

The cardinal features of pachyonychia congenita (PC) include a focal NEPPK (predominantly plantar) as well as hypertrophic nail dystrophy, oral leukokeratosis, and (in a subset of patients) pilosebaceous cysts. The disorder is inherited in an autosomal dominant manner, and two major variants have classically been described: (1) PC1 (Jadassohn–Lewandowsky type), associated with a more severe PPK; and (2) PC2 (Jackson–Lawler type), associated with steatocystoma multiplex and natal teeth. However, there is considerable overlap between these groups, and classification based on the affected gene has recently been established (Table 58.4)[56,57].

The focal NEPPK is often extremely painful and typically develops on the soles in areas of friction and pressure; spread to the dorsal feet is occasionally observed, usually in association with trauma, excessive friction or infection[58]. Hyperhidrosis is common, and acral blistering (clinical or subclinical underlying hyperkeratotic skin) may occur. Multiple pilosebaceous cysts (characteristically steatocystoma multiplex or eruptive vellus hair cysts but also epidermoid and trichilemmal cysts) develop in some patients (see Table 58.4), usually after puberty. Other features include follicular keratoses, angular cheilitis, oral leukokeratosis, and hoarseness secondary to laryngeal involvement[1].

The hypertrophic nail dystrophy of PC presents as wedge-shaped thickening of the nail bed due to subungual hyperkeratosis; this leads to elevation of the nail plate, which can be marked (Fig. 58.14). The nail plates are frequently thickened, darkened and friable, and they may assume an omega shape. Overall, involvement of the nail apparatus is greater distally than proximally. All 20 nails may or may not be involved, and changes tend to be more severe in the toenails and nails of the thumb and index fingers. During infancy, erythema of the nail bed may be the only visible sign, preceding the characteristic nail changes[59].

Histologically, the areas of focal NEPPK show hyperkeratosis with patchy hypergranulosis. Large misformed keratohyalin granules are present, which, on electron microscopy, appear as perinuclear keratin aggregates.

PC results from heterozygous mutations in the genes encoding the following proteins: (1) K6a (~50% of cases; associated with more severe disease) and its partner K16 (~30% of cases), classically the causes of PC1; and (2) K6b (~5% of cases) and its partner K17 (~15% of cases), classically the causes of PC2[57,60,61]. Most PC patients have a dominant-negative missense mutation in the helix initiation or termination motif of one of these keratins[56,57] (see Fig. 56.5). Individuals with identical missense mutations in K17 can have the classic nail findings of PC or steatocystoma multiplex but little or no nail dystrophy[61,62].

Fig. 58.14 Pachyonychia congenita. **A** Thickening of palmar skin and hypertrophic nail dystrophy with wedge-shaped subungual hyperkeratosis. **B** Painful focal plantar keratoderma with associated erythema and blistering.

Treatment with emollients and keratolytics may be helpful in milder cases of PC[63]. Attempts should be made to minimize repeated trauma and friction. Systemic retinoids have led to some improvement of the nails and skin, and botulinum toxin-A injections can reduce hyperhidrosis and pain[64]. Surgical excision of severely deformed nails (with matrix ablation) is usually followed by recurrence, as the keratins

involved in PC are expressed in the nail bed. K17 is also expressed in the nail matrix, and this may explain the occasional patient who improves with simple matrix ablation. Treatment with small interfering RNAs (siRNAs) that specifically target and silence expression of dominant-negative mutant *K6a* is currently being investigated[65], including the development of novel delivery methods to avoid the pain of intradermal injection. Another possible therapeutic approach is oral or topical administration of statins (e.g. simvastatin), which down-regulate *K6a* promoter activity, to patients with K6a defects (considering that loss of expression of this keratin is likely tolerated due to the functional redundancy of K6a, K6b and K6c)[66].

Carvajal syndrome

Synonym: ▪ Striate EPPK with woolly hair and dilated cardiomyopathy

Classic Carvajal syndrome has autosomal recessive inheritance and was first described in families from Ecuador[67]; variants (some with dominant inheritance) were subsequently recognized in other ethnic groups. This disorder features the triad of focal/striate EPPK, dilated cardiomyopathy and woolly hair. As with Naxos disease (see above), the PPK appears during early infancy and hair abnormalities are present at birth. The cardiac disease may begin during adolescence or have onset in early childhood; although it involved the left ventricle in the original kindreds, the right or both ventricles can be affected[46,47]. In addition to the core triad, scaly plaques and keratoses can develop on the elbows and knees or in flexural sites. Skin fragility with intraepidermal blistering (and acantholysis histologically), nail dystrophy and dental enamel defects have been observed in a Carvajal syndrome variant[68].

Histologic features of the PPK include spongiform edema with widened intercellular spaces in the epidermis and a variable degree of epidermolytic hyperkeratosis. The keratinocytes are abnormal, with dense eosinophilic cytoplasm surrounding a pyknotic nucleus. Immunohistochemistry demonstrates perinuclear localization of keratin in suprabasal keratinocytes, suggesting a collapsed intermediate filament network.

Carvajal syndrome is due to mutations in the gene that encodes desmoplakin, classically in both alleles and affecting the protein's carboxy-terminal tail (which binds to intermediate filaments and is important in cardiac myocytes)[67]. However, the same triad of findings (with the additional feature of hypodontia) has been reported in individuals with dominant-negative mutations in the desmoplakin gene[47]. As noted above, desmoplakin mutations also cause *isolated focal/striate PPK* with autosomal dominant inheritance. Other autosomal recessive conditions due to desmoplakin defects include *skin fragility/woolly hair syndrome* (also features PPK and nail dystrophy but not cardiac abnormalities) and *lethal acantholytic epidermolysis bullosa* (also features total alopecia, anonychia and [variably] cardiomyopathy).

PUNCTATE PALMOPLANTAR KERATODERMA AND RELATED CONDITIONS

Punctate Palmoplantar Keratoderma

Synonyms: ▪ Keratosis punctata palmaris et plantaris ▪ Buschke–Fischer–Brauer type

Over the last century, multiple variants of punctate PPK (PPPK) have been described in the medical literature. However, imprecise terms and redundant nomenclature have hampered classification. Lack of linkage of PPPK to the keratin gene cluster has led to the suggestion that molecular aberrations in non-keratin structural proteins involved in keratin filament assembly and function may be responsible[69]. Although to date no specific genes have been identified, linkage analyses in three large kindreds with PPPK mapped the disease locus to the region between 15q22.2 and 15q22.31[70].

This disorder is inherited as an autosomal dominant trait with an equal sex ratio; sporadic cases are also seen. The incidence is approximately 1 per 100 000. Unlike other forms of PPK, lesions are uncommon in childhood, usually beginning to appear during adolescence or early adulthood.

Punctate keratodermas are characterized by multiple keratoses, 2–9 mm in diameter, which vary in appearance (see Fig. 58.4). The lesions begin as pinhead-sized, firm, translucent papules, which may remain translucent or become opaque and verrucous over time. Sometimes there is a central keratotic core, which leaves a depression when removed. The papules can enlarge to form callus-like lesions, and they are aggravated by manual work; large lesions may be painful. In patients of African ancestry, punctate keratoses frequently occur in the palmar creases[71] (Fig. 58.15).

Histologically, PPPK lesions show compact columns of massive hyperkeratosis over a sharply limited area of the epidermis. There is increased thickness of the granular cell layer, and the dermis is devoid of inflammation.

PPPK is commonly misdiagnosed as verrucae vulgaris, but the papules do not demonstrate multiple bleeding points upon paring. Punctate porokeratosis of the palms and soles can have a similar clinical appearance to PPPK and is distinguished by the presence of a cornoid lamella histologically (rather than a column of orthohyperkeratosis). A parakeratotic column is also seen in spiny keratoderma, but the lesions in

Fig. 58.15 Punctate keratoses of the palmar creases in an African-American.

DIFFERENTIAL DIAGNOSIS OF PALMOPLANTAR PITS
HEREDITARY DISORDERS
Nevoid basal cell carcinoma syndrome
Basaloid follicular hamartoma syndrome
Darier disease
Reticulate acropigmentation of Kitamura
Punctate PPK (including punctate keratoses of the palmar creases)*
Cowden disease*
Porokeratotic eccrine ostial & dermal duct nevus (PEODDN)*
ACQUIRED DISORDERS
Pitted keratolysis
Associated with Dupuytren's contracture
Punctate porokeratoses*
*Characterized primarily by keratoses, which may leave a pit upon removal of the keratotic plug.

Table 58.5 Differential diagnosis of palmoplantar pits. They are rarely seen in alkaptonuria, epidermodysplasia verruciformis, Blau syndrome, and lesions of lichen nitidus, lichen planus or psoriasis. Occasionally, lesions of circumscribed palmar or plantar hypokeratosis can be multiple and <5 mm. PPK, palmoplantar keratoderma.

this disorder resemble music box spines. Multiple punctate palmoplantar keratoses can also be seen in patients with Darier disease and Cowden disease, and a search for other mucocutaneous signs of these disorders should be performed. Arsenical keratoses tend to appear later in life and can be distinguished by their histologic appearance. Because the palmoplantar pits of nevoid basal cell carcinoma syndrome and plantar pitted keratolysis are characterized by foci of absent or reduced stratum corneum, they are usually not confused with PPPK. Additional conditions that can present with palmoplantar pits are listed in Table 58.5.

Treatment is symptomatic, and keratolytics can help to soften individual lesions. Both topical and systemic retinoids have been used, with variable success.

Acrokeratoelastoidosis and Focal Acral Hyperkeratosis

Synonyms: ▪ Acrokeratoelastoidosis of Costa ▪ Keratoelastoidosis marginalis

These two entities are characterized by 2–4 mm skin-colored papules that occur on the marginal borders of the hands, digits and/or feet (Fig. 58.16). Some of the papules may be umbilicated[72]. Both disorders can have an autosomal dominant inheritance pattern. Histologic features represent the major difference between these two conditions: only hyperkeratosis is seen in focal acral hyperkeratosis, while the additional finding of fragmentation and degeneration of dermal elastic fibers characterizes acrokeratoelastoidosis.

In addition to whether or not they represent separate entities, areas of debate with regard to these disorders include: (1) whether the term focal acral hyperkeratosis should be reserved for the clinical scenario described by Dowd et al.[72], i.e. an onset prior to the age of 20 years and predilection for female patients with African ancestry; and (2) if the term acrokeratoelastoidosis should be used to describe the band of solar elastosis found on the inner thumb and index finger of patients with severe solar damage.

ACQUIRED KERATODERMAS AND RELATED CONDITIONS

Keratoderma Climactericum

This disorder was first described by Haxthausen in 1934. Hyperkeratosis begins over pressure points on the heels in women over the age of 45 years. There is no preceding history of skin disorders, including eczema or psoriasis. As the hyperkeratosis extends, fissures form and make walking painful. Obesity and cold dry climates aggravate the condition, as can wearing backless shoes, e.g. sandals. If present, involvement of the hands is much milder and more discrete. Deschamps et al.[73] investigated 10 patients with keratoderma climactericum, measuring serum levels of sex hormones and vitamin A levels as well as performing fungal scrapings and patch tests, all of which were normal or negative. Others have reported similar changes following oophorectomy in young women that responded to estrogen replacement. Low-dose oral retinoid treatment has produced improvement over a period of several weeks. Topical estradiol 0.05% ointment[74] or preparations containing 25–40% urea may prove useful.

Aquagenic Palmoplantar Keratoderma

Synonyms: ▪ Acquired aquagenic palmoplantar keratoderma ▪ Aquagenic wrinkling of the palms and soles ▪ Transient reactive papulotranslucent acrokeratoderma ▪ Aquagenic syringeal acrokeratoderma

Patients with aquagenic PPK develop thickening and white to translucent, "pebbly" changes on their palms shortly after immersion in water (e.g. within 3 minutes) (Fig. 58.17), often in association with edema and burning pain[75,76]. Plantar involvement is less frequently observed. Onset is typically during the second decade of life, with a predilection for girls and women; familial occurrence has been described (in a parent plus child or in siblings). Aquagenic PPK is common in patients with cystic fibrosis (CF), with studies documenting characteristic findings on the hands in approximately 40–80% of CF patients, 25% of CF carriers and no controls following 3 minutes of immersion in room-temperature water[77,78].

Histologically, normal skin or dilated eccrine ostia and a mildly hyperkeratotic stratum corneum may be seen. Treatment with 20% aluminum chloride hexahydrate has been reported to decrease the frequency of skin changes and symptoms.

Palmoplantar Keratoderma Associated with Hypothyroidism/Myxedema

There are at least 10 reports in the literature of diffuse or focal PPK developing in association with hypothyroidism, often in the setting of myxedema. The PPK improved or resolved with thyroid replacement in these patients.

Keratoderma and Cancer

Esophageal carcinoma in association with focal PPK (Howel–Evans syndrome) as well as the increased risk of acral SCC in patients with

Fig. 58.16 Focal acrokeratoelastoidosis. Multiple skin-colored papules at the margin of the palmar skin.

Fig. 58.17 Aquagenic keratoderma. White "pebbly" changes on the palm following immersion in water. *Courtesy, Julie V Schaffer, MD.*

Huriez syndrome and "PPK with sex reversal" are discussed above. Epithelioma cuniculatum and acral melanoma have also been reported in individuals with mutilating forms of PPK. Acquired diffuse PPK has been described in patients with carcinomas of the lung, breast, kidney and colon. "Tripe palms" refers to velvety, thickened palmar skin with exaggerated ridges. It is often associated with acanthosis nigricans and may herald malignancies of the lung, stomach or genitourinary tract[79].

Arsenical keratoses present as small, corn-like areas of hyperkeratosis on the palms and soles. Over time, the lesions enlarge, thicken and increase in number, spreading to the dorsal surfaces of the hands and feet. Ulceration often occurs when SCC develops. On histologic examination, epidermal changes vary from benign hyperplasia to moderate atypia or frank SCC. The latent period between ingestion of inorganic arsenic and onset of keratoses is 10 to 30 years or longer[80]. Visceral malignancies, particularly of the lung and genitourinary tract, usually develop after the onset of skin tumors.

Circumscribed Palmar or Plantar Hypokeratosis

This entity, which was first described in 2002[81], presents as a well-circumscribed, mildly erythematous, circular depression on the palm (favoring the thenar and hypothenar regions) or medial side of the sole. Lesions are solitary or few in number, and they typically develop in middle-aged or older women. Histologically, a sharp drop-off is evident between involved and adjacent skin, and the lesional epidermis has an extremely thin stratum corneum and diminished granular layer (Fig. 58.18). The clinical differential diagnosis may include a porokeratosis or Bowen's disease, but neither a cornoid lamella nor atypical keratinocytes are observed. Although the etiology remains unknown, aberrant keratin expression (e.g. diminished K9) has been documented, and a localized loss in the ability of keratinocytes to undergo palmoplantar differentiation has been postulated[82].

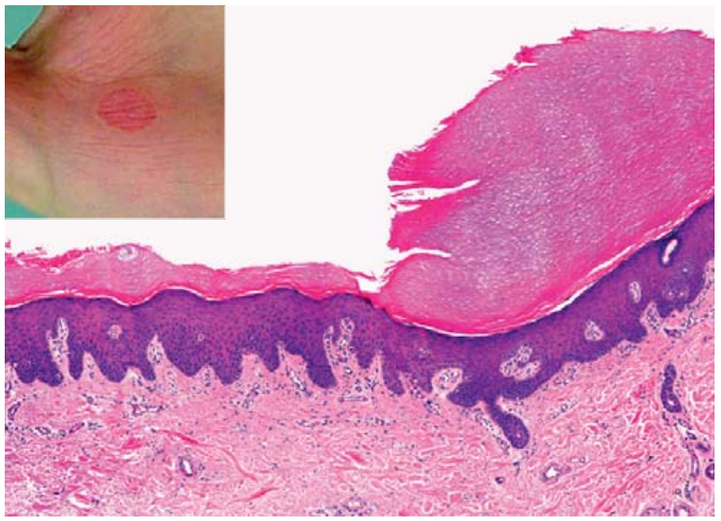


Fig. 58.18 Circumscribed palmar hypokeratosis. A sharp drop-off is seen between the lesional epidermis, which has a very thin stratum corneum, and the surrounding skin. Clinically, a pink depression is seen (see insert).

REFERENCES

1. Lane EB, McLean WHI. Keratins and skin disorders. J Pathol. 2004;204:355–66.
2. McLean WHI. Genetic disorders of palm skin and nail. J Anat. 2003;202:133–42.
3. Kelsell DP, Stevens HP. The palmoplantar keratodermas: much more than palms and soles. Mol Med Today. 1999;5:107–13.
4. Angst B, Marcozzi C, Magee A. The cadherin superfamily: diversity in form and function. J Cell Sci. 2001;114:629–41.
5. Green K, Gaudry C. Are desmosomes more than tethers for intermediate filaments? Nat Rev Mol Cell Biol. 2000;1:208–12.
6. Rickman L, Simrak D, Stevens HP, et al. N-terminal deletion in a desmosomal cadherin causes the autosomal dominant skin disease striate palmoplantar keratoderma. Hum Mol Genet. 1999;8:971–6.
7. Protonotarios N, Tsatsopoulou A, Anastasakis A, et al. Genotype–phenotype assessment in autosomal recessive arrhythmogenic right-ventricular cardiomyopathy (Naxos disease) caused by a deletion in plakoglobin. J Am Coll Cardiol. 2001;38:1477–84.
8. Unger VM, Kumar NM, Gilula NB, et al. Three-dimensional structure of a recombinant gap junction membrane channel. Science. 1999;283:1176–80.
9. Cohn ES, Kelly PM. Clinical phenotype and mutations in connexin 26 (DFNB1/GJB2), the most common cause of childhood hearing loss. Am J Med Genet. 1999;89:130–6.
10. Richard G. Connexin disorders of the skin. Adv Dermatol. 2001;17:243–77.
11. Maestrini E, Korge BP, Ocana-Sierra J, et al. A missense mutation in connexin 26, D66H, causes mutilating keratodermas with sensorineural deafness (Vohwinkel's syndrome) in three unrelated families. Hum Mol Genet. 1999;8:1237–43.
12. Lamartine J, Munhoz Essenfelder G, Kibar Z, et al. Mutations in GJB6 cause hidrotic ectodermal dysplasia. Nat Genet. 2000;26:142–4.
13. Richard G, Smith LE, Bailey RA, et al. Mutations in the human connexin gene GJB3 cause erythrokeratoderma variabilis. Nat Genet. 1998;20:366–9.
14. Ratnavel RC, Griffiths WAD. The inherited palmoplantar keratodermas. Br J Dermatol. 1997;137:485–90.
15. Küster W, Becker A. Indication for the identity of palmoplantar keratoderma type Unna-Thost with type Vörner. Thost's family revisited 110 years later. Acta Dermatol Venereol (Stockh). 1992;72:120–2.
16. Reis A, Hennies HC, Langbein L, et al. Keratin 9 gene mutations in epidermolytic palmoplantar keratoderma (EPPK). Nat Genet. 1994;6:174–9.
17. Terron-Kwiatkowski A, van Steensel MAM, van Geel M, et al. Mutation S233L in the 1B domain of keratin 1 causes epidermolytic palmoplantar keratoderma with "tonotubular" keratin. J Invest Dermatol. 2006;126:607–13.
18. Kimonis V, DiGiovanna JJ, Yang JM, et al. A mutation in the VI end domain of keratin 1 in non-epidermolytic palmar-plantar keratoderma. J Invest Dermatol. 1994;103:764–9.
19. Livingstone RJ, Sybert VP, Smith LT, et al. Expression of a truncated keratin 5 may contribute to severe palmar-plantar hyperkeratosis in epidermolysis bullosa simplex patients. J Invest Dermatol. 2001;116:970–4.
20. Kelsell DP, Stevens HP, Purkis PE, et al. Fine genetic mapping of diffuse non-epidermolytic palmoplantar keratoderma to chromosome 12q11–q13: exclusion of the mapped type II keratins. Exp Dermatol. 1999;8:388–91.
21. Virtanen M, Gedde-Dahl T, Mork NJ, et al. Phenotypic/genotypic correlations in patients with epidermolytic hyperkeratosis and the effects of retinoid therapy on keratin expression. Acta Dermatol Venereol. 2001;81:163–70.
22. Tjiu JW, Lin PJ, Wu WH, et al. SLURP1 mutation-impaired T-cell activation in a family with mal de Meleda. Br J Dermatol. 2011;164:47–53.
23. Fischer J, Bouadjar B, Heilig R, et al. Mutations in the gene encoding SLURP-1 in mal de Meleda. Hum Mol Genet. 2001;10:875–80.
24. Gach JE, Munro CS, Lane EB, et al. Two families with Greither's syndrome caused by keratin 1 mutation. J Am Acad Dermatol. 2005;53:S225–30.
25. Sprecher E, Ishida-Yamamoto A, Becker OM, et al. Evidence for novel functions of the keratin tail emerging from a mutation causing ichthyosis hystrix. J Invest Dermatol. 2001;116:511–19.
26. Bart RS, Pumphrey RE. Knuckle pads, leukonychia and deafness. A dominantly inherited syndrome. N Engl J Med. 1967;276:202–7.
27. Richard G, Brown N, Ishida-Yamamoto A, et al. Expanding the phenotype of Cx26 disorders – Bart-Pumphrey syndrome is caused by a novel missense mutation in *GJB2*. J Invest Dermatol. 2004;123:856–63.
28. Delaporte E, N'guyen-Mailfer C, Janin A, et al. Keratoderma with scleroatrophy of the extremities or sclerotylosis (Huriez syndrome): a reappraisal. Br J Dermatol. 1995;133:409–16.
29. Lee YA, Stevens HP, Delaporte E, et al. A gene for an autosomal dominant scleroatrophic syndrome predisposing to skin cancer (Huriez syndrome) maps to chromosome 4q23. Am J Hum Genet. 2000;66:326–30.
30. Vernole P, Terrinoni A, Didona B, et al. An SRY-negative XX male with Huriez syndrome. Clin Genet. 2000;57:61–6.
31. Radi O, Parma P, Imbeaud S, et al. XX sex reversal, palmoplantar keratoderma, and predisposition to squamous cell carcinoma: genetic analysis in one family. Am J Med Genet A. 2005;138A:241–6.
32. Parma P, Radi O, Vidal V, et al. R-spondin1 is essential in sex determination, skin differentiation and malignancy. Nat Genet. 2006;38:1304–9.
33. Clouston HR. A hereditary ectodermal dystrophy. Can Med Assoc J. 1929;21:18–31.
34. van Steensel MAM, Jonkman MF, van Geel M, et al. Clouston syndrome can mimic pachyonychia congenita. J Invest Dermatol. 2003;121:1035–8.
35. Dessureault J, Poulin Y, Bourcier M, et al. Olmsted syndrome – palmoplantar and periorifical keratodermas: association with malignant melanoma. J Cutan Med Surg. 2003;7:236–42.
36. Mevorah B, Goldberg I, Sprecher E, et al. Olmsted syndrome. J Am Acad Dermatol. 2005;53:S266–S272.
37. Martin L, Toutain A, Guillen C, et al. Inherited palmoplantar keratoderma and sensorineural deafness associated with A7445G point mutation in the mitochondrial genome. Br J Dermatol. 2000;143:876–83.
38. Almuneef M, Al Khenaizan S, Al Ajaji S, et al. Pyogenic liver abscess and Papillon-Lefèvre syndrome: not a rare association. Pediatrics. 2003;111:e85–8.
39. Hart PS, Zhang Y, Firatli E, et al. Identification of cathepsin C mutations in ethnically diverse Papillon-Lefèvre syndrome patients. J Med Genet. 2000;37:927–32.

40. Hart TC, Hart PS, Michalec MD, et al. Haim-Munk syndrome and Papillon-Lefèvre syndrome are allelic mutations in cathepsin C. J Med Genet. 2000;37:81–2.
41. Turk D, Janjic V, Stern I, et al. Structure of human dipeptidyl peptidase I (cathepsin C): exclusion domain added to an endopeptidase framework creates the machine for activation of granular serine proteases. EMBO J. 2001;20:6570–82.
42. Pilger U, Hennies C, Truschnegg A, et al. Late-onset Papillon-Lefèvre syndrome without alteration of the cathepsin C gene. J Am Acad Dermatol. 2003;49:S240–3.
43. McKoy G, Protonotarios N, Crosby A, et al. Identification of a deletion in plakoglobin in arrhythmogenic right ventricular cardiomyopathy with palmoplantar keratoderma and woolly hair (Naxos disease). Lancet. 2000;335:2119–24.

43a. Erken H, Yariz KO, Duman D, et al. Cardiomyopathy with alopecia and palmoplantar keratoderma (CAPK) is caused by a JUP mutation. Br J Dermatol. 2011;165: 917–21.

44. Winik BC, Asial RA, McGrath JA, et al. Acantholytic ectodermal dysplasia: clinicopathological study of a new desmosomal disorder. Br J Dermatol. 2009;160:868–74.
45. Cabral RM, Liu L, Hogan C, et al. Homozygous mutations in the 5′ region of the JUP gene result in cutaneous disease but normal heart development in children. J Invest Dermatol. 2010;130:1543–50.
46. Uzumcu A, Norgett EE, Dindar A, et al. Loss of desmoplakin isoform 1 causes early onset cardiomyopathy and heart failure in a Naxos-like syndrome. J Med Genet. 2006;43:e5.
47. Norgett EA, Lucke TW, Bowers B, et al. Early death from cardiomyopathy in a family with autosomal dominant striate palmoplantar keratoderma and wooly hair associated with a novel insertion mutation in desmoplakin. J Invest Dermatol. 2006;126:1651–4.
48. Simpson MA, Mansour S, Ahnood D, et al. Homozygous mutation of desmocollin-2 in arrhythmogenic right ventricular cardiomyopathy with mild palmoplantar keratoderma and woolly hair. Cardiology. 2009;113:28–34.
49. Whittock NV, Ashton GHS, Dopping-Hepenstal PJC, et al. Striate palmoplantar keratoderma resulting from desmoplakin haploinsufficiency. J Invest Dermatol. 1999;113:940–6.
50. Smith FJ, Fisher MP, Healy E, et al. Novel keratin 16 mutations and protein expression studies in pachyonychia congenita type 1 and focal palmoplantar keratoderma. Exp Dermatol. 2000;9:170–7.
51. Wilson NJ, Messenger AG, Leachman SA, et al. Keratin K6c mutations cause focal palmoplantar keratoderma. J Invest Dermatol. 2010;130:425–9.

51a. Akasaka E, Nakano H, Nakano A, et al. Diffuse and focal palmoplantar keratoderma can be caused by a keratin 6c mutation. Br J Dermatol. 2011;165:1290–2.

52. Leonard NJ, Krol AL, Bleoo S, et al. Sensorineural hearing loss, striate palmoplantar hyperkeratosis, and knuckle pads in a patient with a novel connexin 26 (*GJB2*) mutation. J Med Genet. 2005;42:e2.
53. Harada H, Nagai H, Tsuneizumi M, et al. Identification of *DMC1*, a novel gene in the TOC region on 17q25.1 that shows loss of expression in multiple human cancers. J Hum Genet. 2001;46:90–5.
54. Scott CR. The genetic tyrosinemias. Am J Med Genet Part C. 2006;142C:121–6.
55. Macsai MS, Schwartz TL, Hinkle D, et al. Tyrosinemia II: nine cases of ocular signs and symptoms. Am J Ophthalmol. 2001;132:522–7.
56. McLean WH, Hansen CD, Eliason MJ, et al. The phenotypic and molecular genetic features of pachyonychia congenita. J Invest Dermatol. 2011;131:1015–17.
57. Wilson NJ, Leachman SA, Hansen CD, et al. A large mutational study in pachyonychia congenita. J Invest Dermatol. 2011;131:1018–24.
58. Harris K, Hull PR, Hansen CD, et al. Transgrediens pachyonychia congenita (PC): case series of a nonclassical PC presentation. Br J Dermatol. 2012;166:124–8.
59. Su WP, Chun SI, Hammond DE, et al. Pachyonychia congenita: a clinical study of 12 cases and a review of the literature. Pediatr Dermatol. 1990; 7:33–8.
60. McLean WH, Rugg EL, Lunny DP, et al. Keratin 16 and 17 mutations cause pachyonychia congenita. Nat Genet. 1995;9:273–8.
61. Smith FJD, Liao H, Cassidy AJ, et al. The genetic basis of pachyonychia congenita. J Invest Dermatol Symp Proc 2005;10:21–30.
62. Covello SP, Smith FJ, Sillevis Smitt JH, et al. Keratin 17 mutations cause either steatocystoma multiplex or pachyonychia congenita type 2. Br J Dermatol. 1998;139:475–80.
63. Milstone LM, Fleckman P, Leachman SA, et al. Treatment of pachyonychia congenita. J Invest Dermatol Symp Proc. 2005;10:18–20.
64. Swartling C, Vahlquist A. Treatment of pachyonychia congenita with plantar injections of botulinum toxin. Br J Dermatol. 2006;154:763–5.
65. Leachman SA, Hickerson RP, Schwartz ME, et al. First-in-human mutation-targeted siRNA phase Ib trial of an inherited skin disorder. Mol Ther. 2010;18:442–6.
66. Zhao Y, Gartner U, Smith FJ, et al. Statins downregulate K6a promoter activity: a possible therapeutic avenue for pachyonychia congenita. J Invest Dermatol. 2011;131:1045–52.
67. Norgett EE, Hatsell SJ, Carvajal-Huerta L, et al. Recessive mutation in desmoplakin disrupts desmoplakin-intermediate filament interactions and causes dilated cardiomyopathy, woolly hair and keratoderma. Hum Mol Genet. 2000;9:2761–6.
68. Mahoney MG, Sadowski S, Brennan D, et al. Compound heterozygous desmoplakin mutations result in a phenotype with a combination of myocardial, skin, hair, and enamel abnormalities. J Invest Dermatol. 2010;130:968–78.
69. Kelsell DP, Stevens HP, Ratnavel R, et al. Genetic linkage studies in non-epidermolytic palmoplantar keratoderma: evidence for heterogeneity. Hum Mol Genet. 1995;4:1021–5.
70. Gao M, Yang M, Li KL, et al. Refined localization of a punctate palmoplantar keratoderma gene to a 5.06-cM region of 15q22.2–15q22.31. Br J Dermatol. 2005;152:874–8.
71. Bourrat E, Cabotin PP, Baccard M, et al. Palmoplantar keratodermas in black patients (Fitzpatrick skin phototype 5-6) of African descent: a multicenter comparative and descriptive series. Br J Dermatol. 2011;165:219–21.
72. Dowd PM, Harman RRM, Black MM. Focal acral hyperkeratosis. Br J Dermatol. 1983;109:97–103.
73. Deschamps P, Leroy D, Pedailles S, et al. Keratoderma climactericum (Haxthausen's disease): clinical signs, laboratory findings and etretinate treatment in 10 patients. Dermatologica. 1986;172:258–62.
74. Zultak M, Bedeaux C, Blanc D. Keratoderma climacterium treatment with topical estrogen. Dermatologica. 1988;176:151–2.
75. English JC, McCollagh ML. Transient reactive papulotranslucent acrokeratoderma. J Am Acad Dermatol. 1996;34:686–7.
76. Yan AC, Aasi SM, Alms WJ, et al. Aquagenic palmoplantar keratoderma. J Am Acad Dermatol. 2001;44:696–9.
77. Berk DR, Ciliberto HM, Sweet SC, et al. Aquagenic wrinkling of the palms in cystic fibrosis: comparison with controls and genotype-phenotype correlations. Arch Dermatol. 2009;145:1296–9.
78. Gild R, Clay CD, Morey S. Aquagenic wrinkling of the palms in cystic fibrosis and the cystic fibrosis carrier state: a case–control study. Br J Dermatol. 2010;163:1082–4.
79. Mullans EA, Cohen PR. Tripe palms: a cutaneous paraneoplastic syndrome. South Med J. 1996;89:626–7.
80. Wong SS, Kong CT, Chee LG. Cutaneous manifestations of chronic arsenicism: review of seventeen cases. J Am Acad Dermatol. 1998;38:179–85.
81. Pérez A, Rütten A, Gold R, et al. Circumscribed palmar or plantar hypokeratosis: a distinctive epidermal malformation of the palms or soles. J Am Acad Dermatol. 2002;47:21–7.
82. Yasuda M, Abe M, Suto M, et al. Circumscribed palmar hypokeratosis on both hands: distinct keratin expression in multiple depressed lesions. Br J Dermatol. 2011;164:211–13.

This page intentionally left blank

Darier Disease and Hailey–Hailey Disease

59

Daniel Hohl

Chapter Contents

Darier disease 887
Hailey–Hailey disease 893

DARIER DISEASE

Synonyms: ■ Darier–White disease ■ Keratosis follicularis ■ Dyskeratosis follicularis

Key features

- An uncommon autosomal dominant disorder in which mutations in the *ATP2A2* gene result in dysfunction of an endoplasmic reticulum Ca^{2+} ATPase (SERCA2), thus interfering with intracellular Ca^{2+} signaling
- Keratotic and crusted papules and plaques favor seborrheic areas; additional features include palmoplantar papules, variable nail changes, and whitish oral mucosal papules
- Clinical subtypes include an acral hemorrhagic variant and segmental forms (types 1 and 2)
- Histologically, acantholytic dyskeratosis is seen with suprabasilar clefting, "corps ronds" and "grains"

Introduction

Darier disease is an autosomal dominant genodermatosis with characteristic mucocutaneous findings such as keratotic papules on the upper trunk and longitudinal erythronychia. Insufficient function of the 2b isoform of the sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA2b) leads to abnormal intracellular Ca^{2+} signaling, notably involving the endoplasmic reticulum. The result is a loss of suprabasilar cell adhesion (acantholysis) and an induction of apoptosis (dyskeratosis).

History

In 1889, the French dermatologist Jean Darier[1], at the Hôpital Saint-Louis in Paris, and James C White[2], Professor of Dermatology at Harvard University, independently reported a skin disease characterized by brown, crusted, malodorous lesions with a follicular distribution. Darier called the disease "psorospermose folliculaire végétante" because of his histopathologic studies, where throughout the malpighian layer he saw a large number of round bodies surrounded by a double-layered membrane. He and others thought that these bodies represented psorosperms, a type of parasitic protozoa now referred to as coccidia, which they postulated were the causative agents for the disease. However, attempts to culture or inoculate the supposed parasites failed, and the histologic changes were subsequently recognized as sequelae of abnormal keratinization[3]. The supposed follicular origin of the disease could not be confirmed either, as lesions were noted to occur outside the pilosebaceous unit[4]. It was White who first suggested the hereditary character of the disorder, when the daughter of his initially described patient developed similar skin lesions[5].

Epidemiology

In different studies, the prevalence of Darier disease has ranged from 1 in 100 000 in Denmark[6] to 1 in 55 000 or 1 in 36 000 in England[7], and the estimated incidence is 4 per million per 10 years. Men and women are equally affected. Darier disease has an autosomal dominant mode of inheritance with complete penetrance and variable expressivity. For example, in a series of 42 patients with Darier disease, 7 of 18 affected individuals who recalled no family history were found to be members of known Darier kindreds with mildly affected parents[7]. The clinical severity varies greatly among different families carrying identical mutations and even among members of the same family. Indeed, subtle changes of the skin or nails may remain unnoticed by affected persons.

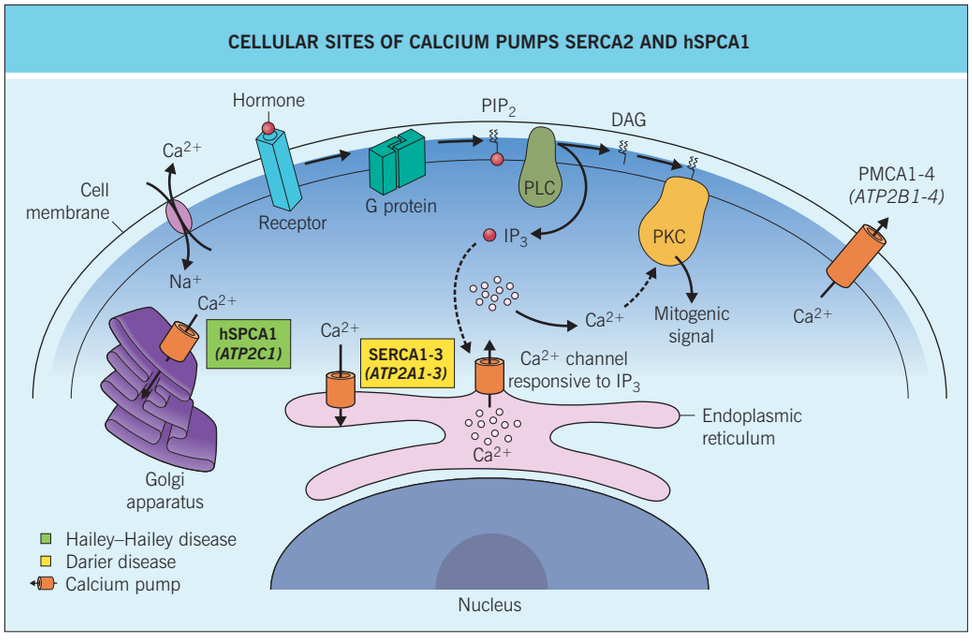


Fig. 59.1 Cellular sites of calcium pumps SERCA2 and hSPCA1. Darier disease is due to mutations in *ATP2A2* which encodes SERCA2. PIP_2, phosphoinositol diphosphate; IP_3, inositol triphosphate; PLC, phospholipase C; DAG, diacylglycerol; PKC, protein kinase C.

Pathogenesis

Mutations in the endoplasmic reticulum Ca^{2+} ATPase *ATP2A2* (protein product SERCA2) cause both acantholysis and apoptosis (accounting for the histologic finding of acantholytic dyskeratosis in Darier disease), most likely through haploinsufficiency[8]. More than 120 distinct *ATP2A2* mutations have been identified, and in general there is no clear genotype–phenotype correlation. Possible exceptions include particular *ATP2A2* mutations associated with acrokeratosis verruciformis of Hopf[9] and the acral hemorrhagic subtype of Darier disease[10,11].

ATP2A2 mutations result in high cytosolic Ca^{2+} concentrations due to inadequate filling of the endoplasmic reticulum (ER) Ca^{2+} stores (Fig. 59.1)[12]. Although both SERCA2a and SERCA2b isoforms are found in the epidermis, SERCA2b is the major product and its dysfunction alone can produce Darier disease[13]. SERCA2 is ubiquitously expressed, but a lack of compensatory SERCA3 expression in keratinocytes may explain the particular vulnerability of these cells to SERCA2 deficiency.

Several pathogenic mechanisms have been proposed for the acantholytic dyskeratosis of Darier disease. Defects in Ca^{2+} sequestration into the ER may produce acantholysis by impairing the normal synthesis, processing, folding and trafficking of junctional proteins (e.g. desmoplakin)[14]. In contrast to Golgi Ca^{2+} stores, keratinocyte ER Ca^{2+} depletion is also associated with apoptosis. The latter may be mediated by accumulation of unfolded proteins within the ER, which can lead to two highly conserved stress responses: the "unfolded protein response" and the "ER overload response" (reviewed in ref. 15). Alternatively, Ca^{2+} dysregulation may result in impaired control of cell cycle checkpoints and a lower threshold for skin trauma to trigger keratinocyte apoptosis. ATP receptors, which are thought to have roles in apoptosis as well as calcium signaling, have been found to localize abnormally in lesional Darier disease epidermis, with decreased P2Y2 (a G protein-coupled receptor) but increased P2X7 (a death receptor) in the plasma membrane of acantholytic cells[16].

Clinical Features

Onset and clinical pattern

In approximately 70% of patients, the disease begins between the ages of 6 and 20 years, with a peak onset during puberty (ages 11–15 years)[17]. The primary lesions are keratotic, sometimes crusted, red to brown papules, which develop preferentially in a "seborrheic" distribution involving the trunk (Fig. 59.2), scalp (especially its margins; Fig. 59.3), face and lateral aspects of the neck (Fig. 59.4). Despite its initial description as follicular dyskeratosis, the papules are not limited to a perifollicular location. The lesions tend to become confluent and may form papillomatous masses (Fig. 59.2B,D). Small (2–3 mm) hypomelanotic macules may be admixed with the keratotic papules and occasionally are the predominant feature (Fig. 59.5). Rarely, sterile vesicles or

Fig. 59.2 Darier disease. Truncal involvement with a predilection for seborrheic areas. Keratotic papules can vary from red (**A, B**) to brown (**C, D**) in color and may become confluent. *A & C, Courtesy, Julie V Schaffer, MD.*

bullae are prominent, and, in these cases, herpetic infection (Kaposi's varicelliform eruption) must be excluded[18].

In approximately 50% of patients, flat-topped, skin-colored or brownish, 2–4 mm papules reminiscent of flat warts are found on the dorsal aspects of the hands (Fig. 59.6) and feet, and, less often, on the forearms and legs (also see below for the acral hemorrhagic type). Most patients have lesions in the axillae, groin (Fig. 59.7) and/or inframammary area. Although these intertriginous lesions are usually mild, they are occasionally the predominant finding and may result in the misdiagnosis of Hailey–Hailey disease (HHD)[19]. Occasionally, macerated, fungating masses are seen in the axillae or groin. In Darier disease, malodor is a frequent and distressing associated finding.

Palmoplantar papules, many of which are keratotic, and keratin-filled depressions are almost invariably found (Fig. 59.8). Subtle changes can be detected by obtaining finger or palm prints, which show interruption of the dermatoglyphic pattern. Nail changes (Fig. 59.9) include longitudinal red and/or white lines, longitudinal ridging and fissuring, and wedge-shaped subungual hyperkeratosis. The nails are brittle and tend to break distally, forming V-shaped notches[19].

The prevalence of oral manifestations has varied in different cohorts. In one study, painless whitish papules of varying severity were present in 50% (12/24) of patients with Darier disease; the palate was the most common site of involvement (Fig. 59.10), followed by the gingiva, buccal mucosa and tongue[20]. In another series, mucosal lesions were found in only 15% (24/163) of Darier disease patients[17].

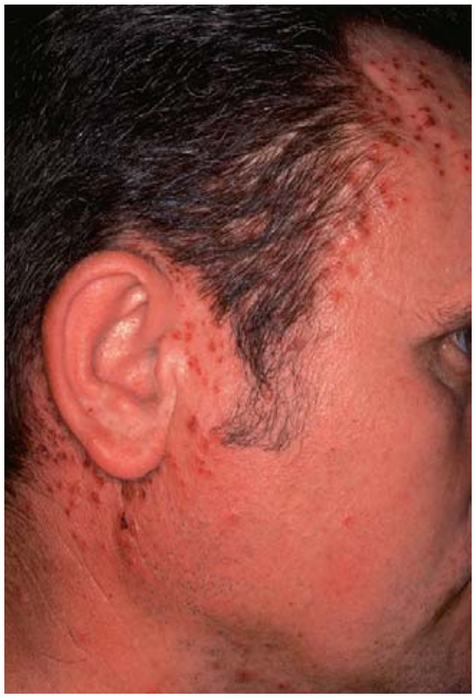


Fig. 59.3 Darier disease. Crusted papules at the hairline on the face and in the posterior auricular area.

Fig. 59.5 Darier disease. Observed most commonly in individuals with darkly pigmented skin, a guttate leukoderma may be seen in patients with Darier disease, including the segmental form. *Courtesy, Julie V Schaffer, MD.*

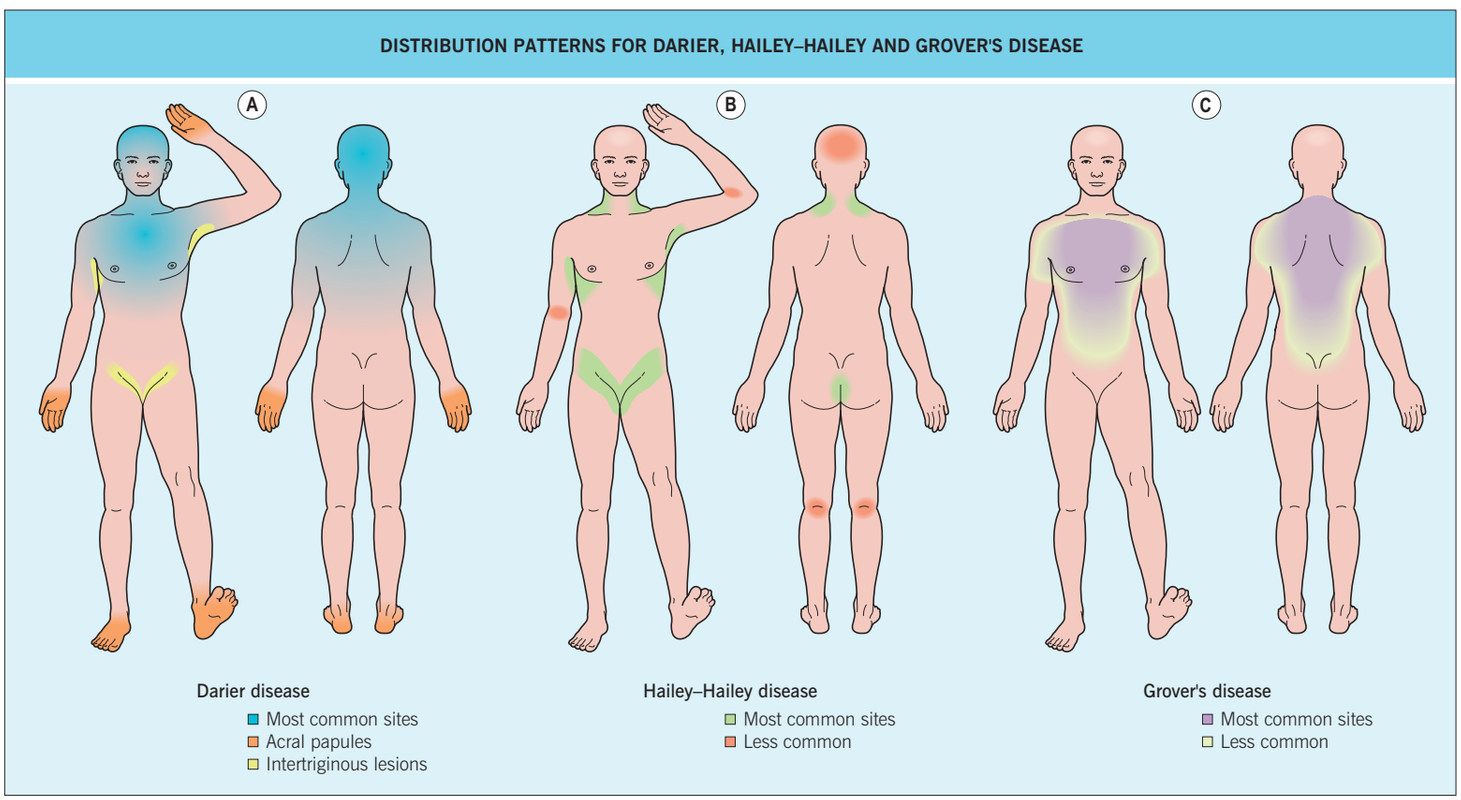


Fig. 59.4 Distribution patterns for Darier, Hailey–Hailey and Grover's disease.

Fig. 59.6 Darier disease. Multiple flat-topped papules on the dorsal aspect of the hand.

Fig. 59.7 Darier disease. Severe involvement in intertriginous zones, including the abdominal fold and groin.

Fig. 59.8 Palmar involvement in Darier disease. A Both keratotic papules and keratin-filled depressions are seen. **B** Less commonly, a thick, spiked focal keratoderma is observed. *A, Courtesy, Kalman Watsky, MD. B, Courtesy, Julie V Schaffer, MD.*

Symptoms

Most patients complain of moderate itching. Equally distressing are the appearance and the odor, which can lead to social isolation.

Modifying factors

The disease frequently worsens in the summer. Darier disease has been experimentally induced in uninvolved skin by UV irradiation[21]. However, sweating, heat and occlusion appear to be equally important exacerbating factors, since lesions occur primarily in covered areas and flares often develop without UV exposure (e.g. after long airplane flights). Lithium carbonate (commonly used to treat bipolar disorder) can provoke skin lesions in patients with Darier disease and should be avoided[22].

Course of the disease

Darier disease follows a chronic course without spontaneous remission. Disease severity can fluctuate, with some patients reporting improvement and others deterioration over time[17].

Infectious complications

The keratotic and papillomatous lesions of Darier disease are prone to secondary infections with bacteria, yeast and dermatophytes[17], often leading to vegetating, malodorous plaques. In addition, patients occasionally develop widespread skin infections with human papillomaviruses (HPV) and herpesviruses. Kaposi's varicelliform eruption due to rapid cutaneous spread of a herpes simplex viral (HSV) infection (Fig. 59.11) is a potentially serious complication that must be suspected when there is a sudden onset of vesicular and crusted lesions accompanied by fever and malaise[23]. Systemic antiviral therapy (e.g. acyclovir, valacyclovir) is necessary, and oral antibiotic treatment of secondary bacterial infections may also be indicated. Immunologic studies in patients with Darier disease have shown no consistent abnormalities[24–26]. Thus, the increased frequency of skin infections is likely caused by disruption of the epidermal barrier.

Fig. 59.9 Darier disease. Alternating longitudinal red and white streaks as well as notching of the free edge of the nail plate. *Courtesy, Antonella Tosti, MD.*

Salivary glands

Oral salivary gland obstruction with painful swelling may occur in some patients. Darier-like histologic changes are responsible for the obstruction of the salivary ducts[26].

Fig. 59.10 Oral mucosal Darier disease. Whitish papules on the palate.

Fig. 59.11 Darier disease with superimposed HSV infection (Kaposi's varicelliform eruption). Multiple hemorrhagic crusts of a similar size are seen.

Neuropsychiatric disorders

Various neuropsychiatric conditions such as epilepsy, intellectual impairment and mood disorders have been reported in association with Darier disease[17,27]. In a recent study, neuropsychiatric assessment of 100 Darier disease patients revealed higher lifetime rates of major depression (30%), suicide attempts (13%), bipolar disorder (4%) and epilepsy (3%) than in the general population[28]. Such findings, however, have not been consistently observed; for example, in a study of 75 Darier disease patients, significant neuropsychiatric abnormalities were not identified[7]. Although a predominance of missense mutations and clustering of mutations in the 3′ portion of the *ATP2A2* gene were reported to be associated with neuropsychiatric features in some families[29], this correlation could not be substantiated by others[10]. More recent analysis of the same families speaks against a neuropsychiatric role of the *ATP2A2* mutation itself, but for the existence of a closely linked susceptibility gene for bipolar disorder[30]. Disfigurement and social isolation associated with severe skin diseases are known to cause psychiatric and social morbidity[31]. Therefore, developmental disorders, depression and increased suicidal ideation in patients with Darier disease might be explained, at least in part, by non-genetic factors[19].

Others

Ocular complications, e.g. corneal ulcerations or staphylococcal endophthalmitis, occur very rarely. There have been a few reports of squamous cell carcinomas arising in cutaneous or mucosal sites chronically affected by Darier disease[32]. Malignant transformation is a rare event and may be related to infection with oncogenic types of HPV or changes in keratinocyte adhesion and proliferation secondary to SERCA2 haploinsufficiency, which has been associated with squamous cell carcinomas of the skin and upper gastrointestinal tract in mice. Observations of bone cysts, renal agenesis and autoimmune thyroiditis in patients with Darier disease are thought to represent chance associations.

Fig. 59.12 Type 1 segmental Darier disease. Note the distribution of the papules along Blaschko's lines.

Clinical subtypes of Darier disease (Table 59.1)

Acral hemorrhagic type

In addition to the classic clinical features, patients with Darier disease can develop red to blue–black, irregularly shaped, sharply demarcated macules on the palms and soles as well as the dorsal aspects of the hands[17]. The lesions represent hemorrhage into acantholytic vesicles. Specific missense mutations were found in several non-related families with the acral hemorrhagic type of Darier disease[10,11]. Further studies are needed to confirm this genotype–phenotype correlation; if true, it might provide insight into the pathogenesis of intraepidermal hemorrhage.

Segmental types 1 and 2

Two types of segmental Darier disease have been described, both with a distribution of lesions along Blaschko's lines (see Ch. 62). In the more common type 1 (Fig. 59.12), the age of onset, severity, and histologic findings within the streaks are similar to those of generalized Darier disease. Type 1 segmental Darier disease results from a postzygotic mutation in the *ATP2A2* gene during embryogenesis, which leads to a mosaic pattern of skin involvement. Heterozygous *ATP2A2* mutations in affected but not background skin have been documented in patients with this form of segmental Darier disease[33]. If there are mutant cells in the gonads, a patient with type 1 segmental manifestations may have offspring with generalized Darier disease.

In the type 2 segmental variant, patients with generalized Darier disease have linear streak(s) with increased severity[34]. Type 2 segmental manifestations of autosomal dominant disorders occur when patients with a heterozygous germline mutation also have a postzygotic inactivating mutation in the *other* allele of the same gene (i.e. a "second hit" causing loss of heterozygosity), which leads to more severe manifestations in a mosaic distribution. A second hit in the *ATP2A2* gene was recently identified in skin from erosive patches following Blaschko's lines in a 1-year-old boy with a family history of Darier disease[34a]. This molecular mechanism is well known from tumor suppressor

LESS COMMON PRESENTATIONS OF DARIER DISEASE
MORPHOLOGIC VARIANTS
• Guttate hypopigmentation (see Fig. 59.5) > hyperpigmented flat-topped papules and macules ("freckle-like")*
• Vesiculobullous lesions
• Acral hemorrhagic lesions
• Keratoderma (spiked; see Fig. 59.8B)
• "Cornifying" (e.g. with cutaneous horns)
• Comedones†, facial cysts, acne conglobata
• Periocular nodulocystic lesions
• Alopecia, cutis verticis gyrata
DISTRIBUTION PATTERNS
• Predominantly involving intertriginous areas, sun-exposed skin, the extremities, acral sites, or the scalp (pityriasis amiantacea-like)
• Segmental (type 1 > 2) (Fig. 59.12)
EXTRACUTANEOUS
• Oral mucosal erosions
• Corneal opacities or ulcers
• Salivary gland obstruction
• Laryngeal involvement
*A persistent acantholytic dermatosis and extensive lentiginous "freckling" without an underlying *ATP2A2* mutation has also been described.
†The differential diagnosis may include familial dyskeratotic comedones.

Table 59.1 Less common presentations of Darier disease.

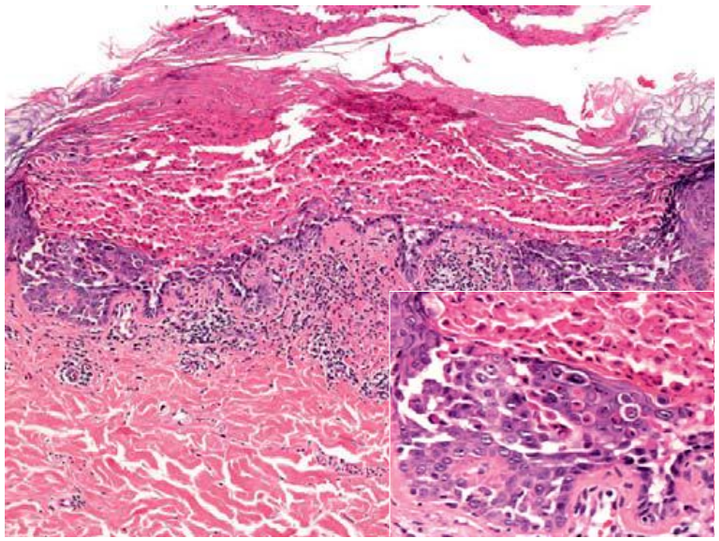


Fig. 59.13 Histopathology of Darier disease. Hyperkeratosis, grains and corp ronds (insert) are seen in addition to acantholysis leading to suprabasilar clefting. *Courtesy, Lorenzo Cerroni, MD.*

Fig. 59.14 Acrokeratosis verruciformis of Hopf. Involvement of the dorsal aspect of the foot with flat-topped papules.

gene syndromes, e.g. nevoid basal cell carcinoma syndrome, where loss of heterozygosity results in tumor formation.

Pathology

There are two prominent histologic features in Darier disease, acantholysis and dyskeratosis (Fig. 59.13). Acantholysis is due to a disturbance in cell adhesion that leads to suprabasilar cleft formation. At the ultrastructural level, this corresponds to a loss of desmosomes and detachment of keratin filaments from the desmosomes[35]. Dyskeratosis is due to apoptosis of keratinocytes and is characterized by nuclear condensation and perinuclear keratin clumping. Two types of dyskeratotic cells are observed in Darier disease[36]:

- "Corps ronds" – acantholytic enlarged keratinocytes in the malpighian layer with darkly staining and partially fragmented nuclei surrounded by a clear cytoplasm and encircled by a bright ring of collapsed keratin bundles.
- "Grains" – small, oval cells in the stratum corneum characterized by an intensely eosinophilic cytoplasm composed of collapsed keratin bundles containing shrunken parakeratotic nuclear remnants. "Grains" are likely derived from "corps ronds", but formal proof that they indeed represent different stages of the same pathologic process has not been provided.

The epidermis overlying acantholytic and dyskeratotic foci is thickened and shows papillomatosis and hyperkeratosis. In the superficial dermis, there is a mild to moderate perivascular inflammatory infiltrate. Diagnostic histologic changes are often focal, necessitating a careful search. Similar histologic features may be observed in Grover's disease, but in the latter there tends to be more acantholysis, less dyskeratosis, and fewer "corps ronds" or "grains". The two conditions can be histologically indistinguishable, but the findings are typically more pronounced, widespread and follicularly based in Darier disease.

Differential Diagnosis

Acrokeratosis verruciformis of Hopf

Flat-topped, wart-like papules on the dorsal aspects of the extremities are a common manifestation of Darier disease. They are clinically indistinguishable from the lesions in the autosomal dominant disorder described by Hopf as "acrokeratosis verruciformis" (Fig. 59.14)[37]. There has been debate as to whether acrokeratosis verruciformis is a separate entity or an allelic forme fruste of Darier disease, and reports of an underlying *ATP2A2* mutation in some but not all patients with acrokeratosis verruciformis suggest genetic heterogeneity[9,38]. Acrokeratosis verruciformis and Darier disease have traditionally been separated on the basis of their histologic features, with the former lacking acantholysis and dyskeratosis. However, serial sectioning is often required to find foci of acantholysis and dyskeratosis in acral skin biopsy specimens from patients with Darier disease[39].

Hopf actually described nail changes and palmoplantar keratotic papules in his initial report, and there have been subsequent observations of patients who had the classic skin findings of Darier disease as well as acrokeratosis verruciformis[40]. Because patients with Darier disease often develop warty lesions on the extremities before keratotic papules appear in a seborrheic distribution[7], it is possible that some patients who present with acrokeratosis verruciformis could later be diagnosed with classic Darier disease. Of note, a particular *ATP2A2* mutation (P602L) was identified in a British family with acrokeratosis verruciformis alone[9] and a Swiss kindred with acrokeratosis verruciformis together with a forme fruste of Darier disease appearing only after intense UV exposure (author's unpublished observation).

Others

Although the clinical differential diagnosis may include severe seborrheic dermatitis and Grover's disease (transient acantholytic dermatosis; see Fig. 59.4 and Ch. 87), Darier disease is readily distinguished by involvement of acral skin, the nails and the oral mucosa. A family history may also be a clue to the diagnosis of Darier disease, and histologic findings differentiate it from seborrheic dermatitis. In Grover's disease, the pruritic crusted papules are not confluent, and they typically develop after occlusion and/or sweating. However, in a persistent form of acantholytic dermatosis that affects patients with significant actinic damage, the papules are scalier and the histologic features closely resemble those of Darier disease[41].

In patients with predominantly flexural involvement, pemphigus vegetans (Hallopeau type), blastomycosis-like pyoderma (pyoderma vegetans) and HHD may represent diagnostic considerations. Pemphigus vegetans usually develops at an older age and is characterized histologically by exocytosis of eosinophils as well as acantholysis; direct immunofluorescence (DIF) shows the intercellular pattern of the pemphigus group, and anti-desmoglein antibodies can be detected by ELISA. Pyoderma vegetans features a neutrophilic infiltrate, and acantholysis is not observed. HHD is sometimes difficult to separate clinically from primarily intertriginous Darier disease. The presence of palmoplantar papules, longitudinal erythronychia, distal notching of the nails, mucosal lesions and prominent dyskeratosis as well as acantholysis histologically can serve as clues to the diagnosis of Darier disease. Occasionally, a sporadic disorder referred to as "papular acantholytic dyskeratosis" may be localized to the vulvocrural area.

Treatment

General measures

Lightweight clothes and sunscreen help prevent aggravation due to heat, sweating and sun exposure. Daily skin care includes the use of antimicrobial cleansers to prevent malodorous bacterial colonization and keratolytic emollients to reduce scaling and irritation.

Topical therapy

Topical corticosteroids (see Ch. 125) are usually less effective as monotherapy than are topical retinoids (see Ch. 126). However, retinoid-associated irritation is common and can be reduced by alternate-day application, liberal use of emollients[42,43], and combination therapy with mid-potency topical corticosteroids. Intermittent use of topical antibiotics and antifungal agents is helpful in treating malodor due to microbial colonization and mild secondary infections. Several reports have suggested that topical 5-fluorouracil (1% or 5%) may be efficacious[44], but calcipotriene (calcipotriol) had no clear benefit in a small randomized controlled study[45].

Systemic therapy

Isotretinoin and acitretin are very effective treatments for Darier disease, with significant improvement and control of the disease in approximately 90% of patients[19,46]. Unfortunately, the use of these agents is limited by their side effects and patients relapse after cessation of therapy. Thus, systemic retinoids should be reserved for patients with severe disease unresponsive to topical treatment. Because of the teratogenic potential of systemic retinoids, contraception is mandatory for women of childbearing potential (see Ch. 126). Individual dose titration is important to ensure maximal therapeutic effect with minimal dose-related side effects, such as mucosal dryness (cheilitis, epistaxis, conjunctivitis) and elevation of serum lipids and liver enzymes. Intermittent therapy to prevent exacerbations during the summer months is a useful approach. In patients with predominantly bullous or intertriginous lesions, oral retinoids may aggravate the disease and are not recommended[47].

A small subset of female patients with Darier disease report premenstrual exacerbations of their skin condition. In these cases, oral contraceptives can mitigate symptoms[48]. There are case reports of cyclosporine being used to control severe Darier disease[49], and it may be helpful for patients who cannot tolerate or do not respond to oral retinoids.

Surgical therapy

Surgical therapy may be an effective alternative for focal recalcitrant lesions, particularly in the flexural and gluteal areas. Excision followed by split-thickness grafting, dermabrasion or laser removal (CO_2 or erbium:YAG) may yield a long-term remission[50,51]. Destructive treatment must include the follicular infundibulum in order to prevent recurrences. Experience is necessary to avoid scarring, particularly in body areas at risk for hypertrophic scar or keloid formation. From this standpoint, the erbium:YAG laser might have an advantage over the CO_2 laser[52]. Small series also describe successful pulsed dye laser and photodynamic therapy[53,54].

HAILEY–HAILEY DISEASE

Synonym: ■ Familial benign chronic pemphigus

Key features

- An uncommon autosomal dominant disorder in which mutations in the *ATP2C1* gene result in dysfunction of a Golgi-associated Ca^{2+} ATPase, thus interfering with intracellular Ca^{2+} signaling
- Clinically, flaccid blisters and erosions are seen on the neck and in intertriginous areas, especially the axillae and groin; moist malodorous vegetations and fissures can develop
- Segmental variants (types 1 and 2) can occur
- The major histologic finding is acantholysis throughout the spinous layer, sometimes referred to as a "dilapidated brick wall"

Introduction

HHD is an autosomal dominant genodermatosis characterized by vesicular and erosive lesions that favor the intertriginous areas, especially the axillae and groin. Mutations in the *ATP2C1* gene that encodes the Golgi-associated Ca^{2+} ATPase hSPCA1 lead to abnormal intracellular Ca^{2+} signaling, resulting primarily in a loss of cellular adhesion (acantholysis) in the stratum spinosum.

History

In 1939, Howard and Hugh Hailey, brothers working in the Department of Dermatology at Emory University School of Medicine in Atlanta, Georgia, described a chronic dermatosis in two sets of brothers. The disorder was characterized by recurrent blisters and erosive, crusted lesions on the neck (in one pair of brothers) and in the axillae and groin (in the second pair)[55]. Histologic sections from all four patients showed similar features – intraepidermal vesicles, mild dyskeratosis, hyperkeratosis and a moderate dermal lymphocytic infiltrate. Different dermatopathologists interpreted these findings variably as pemphigus, pemphigus-like or Darier disease. The authors themselves believed that they were dealing with a novel entity unrelated to Darier disease and coined the name "familial benign chronic pemphigus".

A disease called "pemphigus congénital familiale héréditaire" had been described 6 years prior to the report by the Hailey brothers. Therefore, some believe that HHD should also bear the name of the French dermatologists Gougerot and Allée. However, they did not perform a biopsy, and the early onset and initial localization on pressure points suggest that their patients may have actually suffered from epidermolysis bullosa simplex[56]. The subsequent controversy as to whether "familial benign chronic pemphigus" was a unique disease or a phenotypic variant of Darier disease was finally solved by our understanding of the molecular genetics of both disorders.

Epidemiology

There are no data regarding the exact prevalence of HHD. Based upon clinical experience, HHD is seen approximately as frequently as Darier disease. The mode of inheritance is autosomal dominant with complete penetrance, but the age of onset and expressivity varies greatly among the affected members of a family[57]. In one series, 9 of 58 patients had no family history[57]. However, very mild forms of the disease may go unnoticed in patients carrying the same mutated *ATP2C1* gene as their more severely affected relatives. Thus, the proportion of cases caused

by sporadic mutations may be lower than previously assumed. There is no evidence to date of a correlation between the phenotype and the underlying *ATP2C1* mutation[58].

Pathogenesis

HHD is caused by mutations in the *ATP2C1* gene[59,60], which encodes a Ca^{2+} ATPase, hSPCA1, that is localized to the Golgi apparatus[61,62] (see Fig. 59.1). hSPCA1 transports Ca^{2+} and Mn^{2+}, and it sequesters Ca^{2+} within the Golgi lumen. Like Darier disease, HHD is likely caused by haploinsufficiency[63]. Acantholysis due to *ATP2C1* mutations appears to be mediated through impaired Ca^{2+} sequestration, resulting in the observed depletion of Ca^{2+} within the Golgi lumen[61], via one or more of the following mechanisms. First, normal Golgi Ca^{2+} levels are required for complete processing of proteins through the Golgi apparatus[64], and Golgi Ca^{2+} depletion may impair processing of junctional proteins. Indeed, junctional proteins required for normal cell-to-cell adhesion are reduced in epidermal biopsies from HHD patients[65]. In addition, HHD keratinocytes and epidermis demonstrate altered ATP signaling, possibly leading to lower calcium content of basal keratinocytes and abnormal transition from keratin 14 to keratin 10 expression[16]. Reduced cellular ATP levels may result in impaired actin reorganization and abnormal formation of the adherens junctions required for normal keratinocyte cell-to-cell adhesion[66].

Clinical Features

Onset and clinical pattern

The initial lesions and associated symptoms usually develop during the second or third decade of life but may be delayed until the fourth or fifth decade[57]. HHD has a predilection for intertriginous sites, such as the axillae (Fig. 59.15), groin, lateral aspects of the neck, and perianal region (see Fig. 59.4). The scalp, antecubital and popliteal fossae, and trunk are less frequently involved. Inframammary (Fig. 59.16) and vulvar lesions are common in women, and female patients occasionally present with isolated vulvar disease[67].

The primary lesion is a flaccid vesicle on erythematous or normal-appearing skin, which ruptures easily and therefore is often overlooked (see Fig. 59.15). The blisters give rise to macerated or crusted erosions (see Fig. 59.16), which tend to spread peripherally, producing a circinate border with crusts and small vesicles when examined carefully (Fig. 59.17). Development of chronic, moist, malodorous vegetations and painful fissures is common. Healing occurs without scarring, leaving postinflammatory hyperpigmentation.

Asymptomatic, longitudinal white bands in the fingernails (longitudinal leukonychia) may serve as a subtle diagnostic clue in patients with limited or atypical disease[68]. Involvement of the buccal[69], vaginal[70] or conjunctival[71] mucosa is rare.

Symptoms

Painful intertriginous erosions and crusting may interfere with physical and professional activities. Fetid odor and pruritus add to the psychosocial distress of the patients.

Modifying factors

Given the abnormal cell–cell adhesion within the epidermis, friction can induce new lesions. Heat and sweating can also exacerbate this disease, and patients often note worsening during the summer months. UV irradiation does not appear to influence the course of the disease[57]; however, recent data reveal that *ATP2C1* mRNA expression is suppressed by UVB[72]. Microbial colonization and secondary infections are important modifying factors, as discussed below. In particular, staphylococcal infection potentiates acantholysis and may lead to severe and widespread blistering[73].

Course of the disease

Complete remissions as well as flares are common, and the clinical course in an individual patient is difficult to predict. Some patients report attenuation of the disease at an older age, whereas others state that there is no change or worsening with aging. Life expectancy is not altered.

Fig. 59.16 Hailey–Hailey disease. Chronic submammary lesion with erosions in a worm-eaten pattern.

Fig. 59.15 Hailey–Hailey disease. Erythematous, eroded plaque in the axilla. Note the intact flaccid vesicles at 2 and 7 o'clock.

Fig. 59.17 Hailey-Hailey disease. Circinate plaques on the back with erosions and crusting in the active borders.
Courtesy, Louis A Fragola, Jr, MD.

Complications

Infections

As in Darier disease, colonization and secondary bacterial, fungal and viral infections play an important role in disease exacerbation and persistence[74]. Vegetating lesions and malodor suggest bacterial and/or fungal overgrowth. Topical and, sometimes, systemic antimicrobial agents may be required to induce a clinical remission.

Recalcitrant intertriginous lesions have been described in association with HSV infections[74]. Direct fluorescent antibody assays, viral cultures or PCR-based testing of infected keratinocytes can confirm this diagnosis; occasionally, a skin biopsy is required. Kaposi's varicelliform eruption due to HSV is a rare complication of HHD[75]. It is characterized by fever and a rapidly spreading vesicular eruption, and should be promptly treated with an oral antiviral medication (e.g. acyclovir, valacyclovir). Generalized cowpox infection in a patient with Darier disease has also been reported.

Malignant transformation

There are a few case reports of cutaneous squamous cell carcinoma developing within chronic lesions of HHD in the anogenital region[76]. It is possible that impairment of the structural integrity of the epidermis may predispose patients to infection with oncogenic strains of HPV (see Ch. 79).

Clinical subtypes of Hailey–Hailey disease

Segmental type 1

Segmental type 1 HHD is caused by a heterozygous postzygotic mutation in an otherwise normal embryo, resulting in a mosaic distribution of disease with age of onset and severity similar to the non-mosaic phenotype. Only a few cases of segmental type 1 involvement in HHD have been reported.

Segmental type 2

There are rare patients with generalized HHD who also have a segmental area of more pronounced involvement with earlier onset (analogous to type 2 segmental lesions described above for Darier disease). This results from postzygotic inactivation of the normal *ATP2C1* allele (loss of heterozygosity), which leads to more severe disease in a mosaic pattern[77]. Unlike HHD due to a heterozygous mutation, the affected segments display acantholysis within adnexal structures, which might make it impossible to eradicate foci of blistering using superficial surgical methods (see below).

Pathology

Whereas acantholysis in Darier disease occurs primarily in discrete foci, the loss of intercellular bridges in HHD is generally more widespread within the epidermis. Thus, larger areas of dyscohesion with single or groups of acantholytic cells are seen, which have been likened to a "dilapidated brick wall". Dermal papillae, lined by a single layer of basal cells, protrude into the blister cavities and are referred to as "villi" (Fig. 59.18). In contrast to Darier disease, necrotic keratinocytes are uncommon, and only rare acantholytic dyskeratotic cells, i.e. "corps ronds" as in Darier disease, may be observed. In more chronic lesions, epidermal hyperplasia, parakeratosis and focal crusts are found. A moderate perivascular lymphocytic infiltrate is observed in the superficial dermis. DIF is negative, thus excluding pemphigus vulgaris. Ultrastructurally, the disturbance of cellular adhesion is reflected in the dissolution of the desmosome–tonofilament complex and formation of perinuclear tonofilament aggregates[78].

Histologically, Grover's disease may be indistinguishable from HHD, but these two entities are readily distinguished on the basis of clinical features.

Differential Diagnosis

The blisters in HHD are typically fragile and rupture easily. Therefore, clinical experience and a high index of suspicion may be necessary to diagnose this disorder, especially in patients with limited disease. Lesions confined to the axillae or groin may be mistaken for intertrigo or candidiasis. Isolated perianal maceration is easily misdiagnosed as irritant dermatitis, and vulvar involvement may resemble lichen simplex chronicus[67]. Histologic examination of affected skin is often the key to the diagnosis.

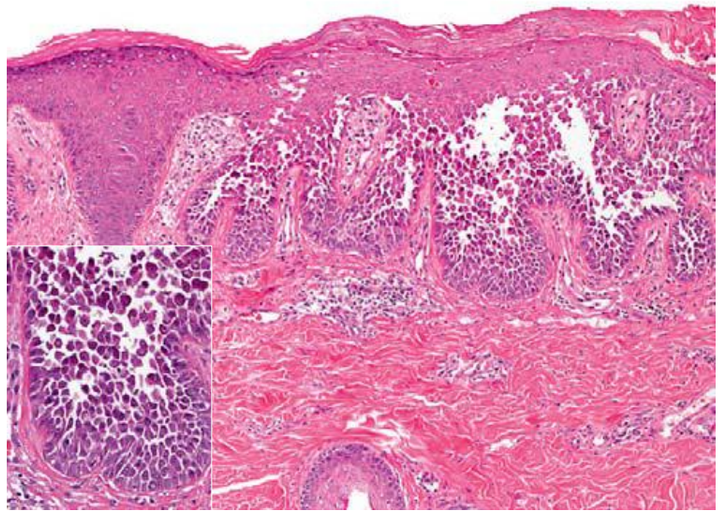


Fig. 59.18 Histopathology of Hailey–Hailey disease. Focal crusting and acantholysis beginning in the suprabasilar area and extending throughout the epidermis. The latter has been likened to a "dilapidated brick wall". *Courtesy, Lorenzo Cerroni, MD.*

The lesions of inverse psoriasis have sharper borders, fewer erosions and less crusting. A total skin examination, looking for additional sites of involvement and associated signs, e.g. nail pitting, will aid in the diagnosis. Vegetating intertriginous lesions in HHD may be identical to those of pemphigus vegetans (Hallopeau type), but the latter can be differentiated by positive DIF of perilesional skin.

The cutaneous features of HHD and Darier disease may overlap. Older reports described patients with characteristic skin findings of both genodermatoses who therefore carried two diagnoses[79], but genetic analysis can now establish a single diagnosis in such individuals. In general, the two disorders have different patterns of distribution that are fairly easily distinguished (see Fig. 59.4). Moreover, a predominantly vesicular eruption in patients with Darier disease is rare[18]. Palmar pits were previously reported in a woman with HHD, but she may have been misdiagnosed[80]. Additional features such as V-shaped notches in the distal free edge of the nail plate, longitudinal erythronychia, and oral papules point to the diagnosis of Darier disease.

Treatment

General measures

Wearing lightweight clothes is recommended to avoid friction and sweating. Colonization and secondary bacterial, fungal and viral infections should be prevented with antimicrobial cleansers and treated with appropriate topical and/or systemic antimicrobial agents.

Topical therapy

Topical corticosteroids are an effective treatment in many patients and are often combined with topical antimicrobials and cleansers. Early application of corticosteroids can ameliorate developing lesions[57]. When the disease is refractory to topical preparations, it may respond to intralesional corticosteroids. In order to minimize the potential side effects of topical corticosteroids in intertriginous zones (e.g. atrophy, striae, telangiectasias; see Ch. 125), the lowest potency that is effective should be used; these medications can be applied intermittently and/or steroid-sparing agents can be substituted.

Anecdotal reports have described a therapeutic benefit from topical application of tacrolimus[81], cyclosporine, 5-fluorouracil[82], calcitriol and tacalcitol[83]. Improvement of axillary disease after chemodenervation of sweat glands with botulinum toxin has also been observed[84].

Surgical therapy

Surgical therapy should be considered for disease unresponsive to general measures and topical treatments. Wide excision and grafting

have been reported to be successful[85], but this aggressive approach has been replaced by more superficial ablative techniques. The most well-documented method is dermabrasion[86], but vaporization of the epidermis with a scanned CO_2 or erbium:YAG laser[52] and photodynamic therapy with 5-aminolevulinic acid[87] seem to be equally effective. These approaches remove diseased epidermis and their dermal niche of fibroblasts to the level of the mid-dermis. Re-epithelialization (from the spared adnexal structures) occurs within 7–14 days.

Systemic therapy

With the exception of antimicrobial agents for superinfections, there is no strong evidence to support the use of any particular systemic therapy in HHD. Oral retinoids are not clearly effective[57], and there are only anecdotal reports of severely affected individuals improving with the use of immunomodulatory drugs, e.g. prednisone, cyclosporine, methotrexate, dapsone and alefacept[88–90].

REFERENCES

1. Darier J. De la psorospermose folliculaire végétante. Ann Dermatol Syphiligr. 1889;10:597–612.
2. White J. A case of keratosis (ichthyosis) follicularis. J Cutan Genito-Urinary Dis. 1889;7:201–9.
3. Boeck C. Four cases of Darier's disease. Arch Dermatol Syph. 1891;23:827.
4. Ellis F. Keratosis follicularis is not primarily a follicular disease. Arch Dermatol Syph. 1944;50:27–30.
5. White J. Keratosis follicularis (psorospermose folliculaire végétante). A second case. J Cutan Genito-Urinary Dis. 1890;8:13–20.
6. Svendsen I, Abrectsen B. The prevalence of dyskeratosis follicularis (Darier's disease) in Denmark. Acta Derm Venereol. 1959;39:256–69.
7. Munro CS. The phenotype of Darier's disease: penetrance and expressivity in adults and children. Br J Dermatol. 1992;127:126–30.
8. Foggia L, Hovnanian A. Calcium pump disorders of the skin. Am J Med Genet C Semin Med Genet. 2004;131C:20–31.
9. Dhitavat J, Macfarlane S, Dode L, et al. Acrokeratosis verruciformis of Hopf is caused by mutation in *ATP2A2*: evidence that it is allelic to Darier's disease. J Invest Dermatol. 2003;120:229–32.
10. Ruiz-Perez VL, Carter SA, Healy E, et al. *ATP2A2* mutations in Darier's disease: variant cutaneous phenotypes are associated with missense mutations, but neuropsychiatric features are independent of mutation class. Hum Mol Genet. 1999;8:1621–30.
11. Hamada T, Yasumoto S, Karashima T, et al. Recurrent p.N767S mutation in the *ATP2A2* gene in a Japanese family with haemorrhagic Darier disease clinically mimicking epidermolysis bullosa simplex with mottled pigmentation. Br J Dermatol. 2007;157:605–8.
12. Foggia L, Aronchik I, Aberg K, et al. Activity of the hSPCA1 Golgi Ca^{2+} pump is essential for Ca^{2+}-mediated Ca^{2+} response and cell viability in Darier disease. J Cell Sci. 2006;119:671–9.
13. Dhitavat J, Dode L, Leslie N, et al. Mutations in the sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase isoform cause Darier's disease. J Invest Dermatol. 2003;121:486–9.
14. Dhitavat J, Cobbold C, Leslie N, et al. Impaired trafficking of the desmoplakins in cultured Darier's disease keratinocytes. J Invest Dermatol. 2003;121:1349–55.
15. Paschen W. Dependence of vital cell function on endoplasmic reticulum calcium levels: implications for the mechanisms underlying neuronal cell injury in different pathological states. Cell Calcium. 2001;29:1–11.
16. Leinonen PT, Hagg PM, Peltonen S, et al. Reevaluation of the normal epidermal calcium gradient, and analysis of calcium levels and ATP receptors in Hailey-Hailey and Darier epidermis. J Invest Dermatol. 2009;129:1379–87.
17. Burge SM, Wilkinson JD. Darier-White disease: a review of the clinical features in 163 patients. J Am Acad Dermatol. 1992;27:40–50.
18. Telfer NR, Burge SM, Ryan TJ. Vesiculo-bullous Darier's disease. Br J Dermatol. 1990;122:831–4.
19. Burge S. Darier's disease – the clinical features and pathogenesis. Clin Exp Dermatol. 1994;19:193–205.
20. Macleod RI, Munro CS. The incidence and distribution of oral lesions in patients with Darier's disease. Br Dent J. 1991;171:133–6.
21. Hedblad MA, Nakatani T, Beitner H. Ultrastructural changes in Darier's disease induced by ultraviolet irradiation. Acta Derm Venereol. 1991;71:108–12.
22. Ehrt U, Brieger P. Comorbidity of keratosis follicularis (Darier's disease) and bipolar affective disorder: an indication for valproate instead of lithium. Gen Hosp Psychiatry. 2000;22:128–9.
23. Verner E, Shteinfeld M, Zuckerman F. Eczema herpeticum in a patient with Darier's disease during treatment with etretinate. J Am Acad Dermatol. 1985;13:678–80.
24. Jegasothy BV, Humeniuk JM. Darier's disease: a partially immunodeficient state. J Invest Dermatol. 1981;76:129–32.
25. Patrizi A, Ricci G, Neri I, et al. Immunological parameters in Darier's disease. Dermatologica. 1989;178:138–40.
26. Rand R, Baden HP. Commentary: Darier-White disease. Arch Dermatol. 1983;119:81–3.
27. Craddock N, Owen M, Burge S, et al. Familial cosegregation of major affective disorder and Darier's disease (keratosis follicularis). Br J Psychiatry. 1994;164:355–8.
28. Gordon-Smith K, Jones LA, Burge SM, et al. The neuropsychiatric phenotype in Darier disease. Br J Dermatol. 2010;163:515–22.
29. Jacobsen NJ, Lyons I, Hoogendoorn B, et al. *ATP2A2* mutations in Darier's disease and their relationship to neuropsychiatric phenotypes. Hum Mol Genet. 1999;8:1631–6.
30. Jones I, Jacobsen N, Green EK, et al. Evidence for familial cosegregation of major affective disorder and genetic markers flanking the gene for Darier's disease. Mol Psychiatry. 2002;7:424–7.
31. Denicoff KD, Lehman ZA, Rubinow DR, et al. Suicidal ideation in Darier's disease. J Am Acad Dermatol. 1990;22:196–8.
32. Alexandrescu DT, Dasanu CA, Farzanmehr H, et al. Development of squamous cell carcinomas in Darier disease: a new model for skin carcinogenesis? Br J Dermatol. 2008;159:1378–80.
33. Sakuntabhai A, Dhitavat J, Burge S, et al. Mosaicism for *ATP2A2* mutations causes segmental Darier's disease. J Invest Dermatol. 2000;115:1144–7.
34. Happle R, Itin PH, Brun AM. Type 2 segmental Darier disease. Eur J Dermatol. 1999;9:449–51.

34a. Fölster-Holst R, Nellen RG, Jensen JM, et al. Molecular genetic support for the rule of dichotomy in type 2 segmental Darier disease. Br J Dermatol. 2011 Sep 6. [Epub ahead of print]

35. Sato A, Anton-Lamprecht I, Schnyder UW. Ultrastructure of dyskeratosis in morbus Darier. J Cutan Pathol. 1977;4:173–84.
36. Douwes FR. On the histology and histochemistry of Darier's disease. Arch Klin Exp Dermatol. 1968;233:309–22.
37. Hopf G. Über eine bisher noch nicht beschriebene disseminierte Keratose (Acrokeratosis verruciformis). Dermatol Z. 1931;60:227–50.
38. Wang PG, Gao M, Lin GS, et al. Genetic heterogeneity in acrokeratosis verruciformis of Hopf. Clin Exp Dermatol. 2006;31:558–63.
39. Hafner O, Vakilzadeh F. Acrokeratosis verruciformis-like changes in Darier disease. Hautarzt. 1997;4 8:572–6.
40. Herndon JH, Wilson JD. Acrokeratosis verruciformis (Hopf) and Darier's disease: genetic evidence for a unitary origin. Arch Dermatol. 1966;93:305–10.
41. Fawcett HA, Miller JA. Persistent acantholytic dermatosis related to actinic damage. Br J Dermatol. 1983;109:349–54.
42. Burge SM, Buxton PK. Topical isotretinoin in Darier's disease. Br J Dermatol. 1995;133:924–8.
43. Burkhart CG, Burkhart CN. Tazarotene gel for Darier's disease. J Am Acad Dermatol. 1998;38:1001–2.
44. Schmidt H, Ochsendorf FR, Wolter M, et al. Topical 5-fluorouracil in Darier disease. Br J Dermatol. 2008;158:1393–6.
45. Kragballe K, Steijlen PM, Ibsen HH, et al. Efficacy, tolerability, and safety of calcipotriol ointment in disorders of keratinization. Results of a randomized, double-blind, vehicle-controlled, right/left comparative study. Arch Dermatol. 1995;131:556–60.
46. Christophersen J, Geiger JM, Danneskiold-Samsoe P, et al. A double-blind comparison of acitretin and etretinate in the treatment of Darier's disease. Acta Derm Venereol. 1992;72:150–2.
47. Bleiker T, Bourke J, Graham-Brown R, Hutchinson P. Etretinate may work where acitretin fails. Br J Dermatol. 1997;136:368–70.
48. Oostenbrink JH, Cohen EB, Steijlen PM, van de Kerkhof PC. Oral contraceptives in the treatment of Darier-White disease – a case report and review of the literature. Clin Exp Dermatol. 1996;21:442–4.
49. Martini P, Peonia G, Benedetti A, Lorenzi S. Darier-White syndrome and cyclosporin. Dermatology. 1995;190:174–5.
50. McElroy JA, Mehregan DA, Roenigk RK. Carbon dioxide laser vaporization of recalcitrant symptomatic plaques of Hailey-Hailey disease and Darier's disease. J Am Acad Dermatol. 1990;23:893–7.
51. Zachariae H. Dermabrasion in Darier's disease. Acta Derm Venereol. 1979;59:184–6.
52. Beier C, Kaufmann R. Efficacy of erbium:YAG laser ablation in Darier disease and Hailey-Hailey disease. Arch Dermatol. 1999;135:423–7.
53. Roos S, Karsai S, Ockenfel HM, et al. Successful treatment of Darier disease with the flashlamp-pumped pulsed-dye laser. Arch Dermatol. 2008;144:1073–5.
54. Exadaktylou D, Kurwa HA, Calonje E, et al. Treatment of Darier's disease with photodynamic therapy. Br J Dermatol. 2003;149:606–10.
55. Hailey H, Hailey H. Familial benign chronic pemphigus. Arch Dermatol. 1939;39:679–85.
56. Steffen C, Thomas D. Was Henri Gougerot the first to describe "Hailey-Hailey" disease? Am J Dermatopathol. 2003;25:256–9.
57. Burge SM. Hailey-Hailey disease: the clinical features, response to treatment and prognosis. Br J Dermatol. 1992;126:275–82.
58. Ikeda S, Shigihara T, Mayuzumi N, et al. Mutations of *ATP2C1* in Japanese patients with Hailey-Hailey disease: intrafamilial and interfamilial phenotype variations and lack of correlation with mutation patterns. J Invest Dermatol. 2001;117:1654–6.
59. Hu Z, Bonifas JM, Beech J, et al. Mutations in *ATP2C1*, encoding a calcium pump, cause Hailey-Hailey disease. Nat Genet. 2000;24:61–5.
60. Sudbrak R, Brown J, Dobson-Stone C, et al. Hailey-Hailey disease is caused by mutations in *ATP2C1* encoding a novel Ca^{2+} pump. Hum Mol Genet. 2000;9:1131–40.
61. Behne MJ, Tu CL, Aronchik I, et al. Human keratinocyte *ATP2C1* localizes to the Golgi and controls Golgi Ca^{2+} stores. J Invest Dermatol. 2003;121:688–94.
62. Vanoevelen J, Dode L, Van Baelen K, et al. The secretory pathway Ca^{2+}/Mn^{2+}-ATPase 2 is a Golgi-localized pump with high affinity for Ca^{2+} ions. J Biol Chem. 2005;280:22800–8.
63. Fairclough RJ, Lonie L, Van Baelen K, et al. Hailey-Hailey disease: identification of novel mutations in *ATP2C1* and effect of missense mutation A528P on protein expression levels. J Invest Dermatol. 2004;123: 67–71.
64. Durr G, Strayle J, Plemper R, et al. The medial-Golgi ion pump Pmr1 supplies the yeast secretory pathway with Ca^{2+} and Mn^{2+} required for glycosylation, sorting, and endoplasmic reticulum-associated protein degradation. Mol Biol Cell. 1998;9:1149–62.
65. Hakuno M, Shimizu H, Akiyama M, et al. Dissociation of intra- and extracellular domains of desmosomal cadherins and E-cadherin in Hailey-Hailey disease and Darier's disease. Br J Dermatol. 2000;142: 702–11.
66. Aronchik I, Behne MJ, Leypoldt L, et al. Actin reorganization is abnormal and cellular ATP is decreased

in Hailey-Hailey keratinocytes. J Invest Dermatol. 2003;121:681–7.
67. Wieselthier JS, Pincus SH. Hailey-Hailey disease of the vulva. Arch Dermatol. 1993;129:1344–5.
68. Kirtschig G, Effendy I, Happle R. Leukonychia longitudinalis as the primary symptom of Hailey-Hailey disease. Hautarzt. 1992;43:451–2.
69. Fischer H, Nikolowski W. Die Mundschleimhaut beim Pemphigus benignus familiaris chronicus. Arch Klin Exp Dermatol. 1962;214:261–73.
70. Vaclavinkova V, Neumann E. Vaginal involvement in familial benign chronic pemphigus (Morbus Hailey-Hailey). Acta Derm Venereol. 1982;62:80–1.
71. Oguz O, Gokler G, Ocakoglu O, et al. Conjunctival involvement in familial chronic benign pemphigus (Hailey-Hailey disease). Int J Dermatol. 1997;36:282–5.
72. Mayuzumi N, Ikeda S, Kawada H, et al. Effects of ultraviolet B irradiation, proinflammatory cytokines and raised extracellular calcium concentration on the expression of *ATP2A2* and *ATP2C1*. Br J Dermatol. 2005;152:697–701.
73. Chave TA, Milligan A. Acute generalized Hailey-Hailey disease. Clin Exp Dermatol. 2002;27:290–2.
74. Zaim MT, Bickers DR. Herpes simplex associated with Hailey-Hailey disease. J Am Acad Dermatol. 1987;17:701–2.
75. Stallmann D, Schmoeckel C. Hailey-Hailey disease with dissemination and eczema herpeticatum in therapy with etretinate. Hautarzt. 1988;39:454–6.
76. Cockayne SE, Rassl DM, Thomas SE. Squamous cell carcinoma arising in Hailey-Hailey disease of the vulva. Br J Dermatol. 2000;142:540–2.
77. Poblete-Gutierrez P, Wiederholt T, Konig A, et al. Allelic loss underlies type 2 segmental Hailey-Hailey disease, providing molecular confirmation of a novel genetic concept. J Clin Invest. 2004;114:1467–74.
78. Burge SM, Millard PR, Wojnarowska F. Hailey-Hailey disease: a widespread abnormality of cell adhesion. Br J Dermatol. 1991;124:329–32.
79. Nicolis G, Tosca A, Marouli O, Stratigos J. Keratosis follicularis and familial benign chronic pemphigus in the same patient. Dermatologica. 1979;159:346–51.
80. Verbov J. Palmar lesions in familial benign pemphigus. Br J Dermatol. 1969;81:77.
81. Rabeni EJ, Cunningham NM. Effective treatment of Hailey-Hailey disease with topical tacrolimus. J Am Acad Dermatol. 2002;47:797–8.
82. Dammak A, Camus M, Anyfantakis V, et al. Successful treatment of Hailey-Hailey disease with topical 5-fluorouracil. Br J Dermatol. 2009;161:967–8.
83. Aoki T, Hashimoto H, Koseki S, et al. 1alpha,24-dihydroxyvitamin D3 (tacalcitol) is effective against Hailey- Hailey disease both in vivo and in vitro. Br J Dermatol. 1998;139:897–901.
84. Lapiere JC, Hirsh A, Gordon KB, et al. Botulinum toxin type A for the treatment of axillary Hailey-Hailey disease. Dermatol Surg. 2000;26:371–4.
85. Menz P, Jackson IT, Connolly S. Surgical control of Hailey-Hailey disease. Br J Plast Surg. 1987;40:557–61.
86. Hamm H, Metze D, Brocker EB. Hailey-Hailey disease. Eradication by dermabrasion. Arch Dermatol. 1994;130:1143–9.
87. Ruiz-Rodriguez R, Alvarez JG, Jaen P, et al. Photodynamic therapy with 5-aminolevulinic acid for recalcitrant familial benign pemphigus (Hailey-Hailey disease). J Am Acad Dermatol. 2002;47:740–2.
88. Fairris GM, White JE, Leppard BJ, Goodwin PG. Methotrexate for intractable benign familial chronic pemphigus. Br J Dermatol. 1986;115:640.
89. Berth-Jones J, Smith SG, Graham-Brown RA. Benign familial chronic pemphigus (Hailey-Hailey disease) responds to cyclosporin. Clin Exp Dermatol. 1995;20:70–2.
90. Hurd D, Johnston C, Bevins A. A case report of Hailey-Hailey disease treated with alefacept (Amevive). Br J Dermatol. 2008;158:399–401.

This page intentionally left blank

Primary Immunodeficiencies 60

Julie V Schaffer and Amy S Paller

Chapter Contents

Ataxia–telangiectasia 899
Chronic mucocutaneous candidiasis 902
Cartilage–hair hypoplasia syndrome 904
Chédiak–Higashi syndrome 904
Complement disorders 905
Chronic granulomatous disease 908
Hyperimmunoglobulin E syndromes 911
Immunoglobulin deficiencies 915
IPEX syndrome 915
Leukocyte adhesion deficiency 915
Severe combined immunodeficiency 919
Wiskott–Aldrich syndrome 921

INTRODUCTION

Primary immunodeficiencies represent a heterogeneous group of inherited disorders characterized by immune system defects that result in susceptibility to infections as well as additional manifestations such as autoimmunity, allergy and malignancy. The molecular bases have been defined for more than 150 monogenic primary immunodeficiency diseases, providing valuable insight into the function of the human immune system[1,2].

Patients with genetic immunodeficiency disorders often manifest with cutaneous abnormalities[1,3]. Some of these skin findings are highly characteristic of a particular disorder, while others, such as eczematous or granulomatous dermatitis, are shared by other immunodeficiencies[4] (Table 60.1). Screening laboratory tests for a patient with recurrent cutaneous infections that raise suspicion of a primary immunodeficiency[5] are listed in Table 60.2.

ATAXIA–TELANGIECTASIA

Synonym: ■ Louis–Bar syndrome

Key features

- Progressive cerebellar ataxia
- Oculocutaneous telangiectasias, initially of the bulbar conjunctivae
- Selective deficiency of humoral and cell-mediated immunity, leading to sinopulmonary infections
- Increased sensitivity to ionizing radiation
- Leukemias and lymphomas

Introduction

Ataxia–telangiectasia (AT) is characterized by oculocutaneous telangiectasias, progressive cerebellar ataxia beginning in infancy, a variable immunodeficiency with a tendency to develop sinopulmonary infections, and chromosomal instability with persistent DNA damage after exposure to ionizing radiation.

Epidemiology

AT is an autosomal recessive disorder that occurs in 1:40 000 to 1:100 000 live births, with a carrier rate of up to 1% of the population.

Pathogenesis

AT results from mutations in the ataxia–telangiectasia mutated gene (*ATM*), which encodes a phosphatidylinositol 3-kinase-like serine/threonine protein kinase that plays a central role in activating apoptotic and cell cycle responses to DNA damage, particularly double-stranded breaks[6]. These DNA breaks are sensed directly by the MRE11–RAD50–NBS1 (MRN) complex, which recruits ATM and triggers its dissociation from inactive multimers to active monomers[7]. Autophosphorylated ATM monomers subsequently activate (via phosphorylation) a variety of targets, including p53, BRCA1, FANCD2, and Artemis in addition to NBS1 and MRE11. The result is cell cycle arrest and facilitation of DNA repair, both in the setting of external insults (e.g. ionizing radiation) and in the processing of physiologic DNA breaks that occur during V(D)J recombination in lymphocytes, telomere maintenance and meiosis[6]. This provides an explanation for the sensitivity to ionizing radiation, immunodeficiency, premature aging, and defective spermatogenesis that are observed in patients with AT. Progressive neurologic deterioration in affected individuals likely reflects defective DNA repair in a cell population that cannot replicate. Oxidative stress related to ATM dysfunction has also been implicated in the pathogenesis of the disease.

Of note, mutations in the *MRE11* and *NBS1* genes cause two related conditions, AT-like disorder (featuring radiosensitivity and neurologic manifestations similar to AT, but no telangiectasias) and Nijmegen breakage syndrome (characterized by microcephaly, immunodeficiency, chromosomal instability and cancer predisposition), respectively.

Clinical Features

The first manifestation of AT is usually ataxia, which typically appears when the affected child begins to walk. However, the diagnosis is often not recognized until the oculocutaneous telangiectasias are well developed, at a median age of 6 years[8]. The telangiectasias first appear at 3–6 years of age on the lateral and medial bulbar conjunctivae as red, symmetric horizontal streaks (Fig. 60.1A). Telangiectasias subsequently develop on the ears, eyelids, malar prominences, antecubital and popliteal fossae and presternal area, and less commonly on the dorsal aspects of the hands and feet and the hard and soft palate. The nonfacial cutaneous telangiectasias are often subtle, resembling fine petechiae (Fig. 60.1B).

Progeric changes of the skin and hair are noted in almost 90% of patients. Subcutaneous fat is lost early and the facial skin tends to become atrophic and sclerotic. Gray hairs frequently appear in young children, and diffuse graying of the hair may occur by adolescence. Non-infectious cutaneous granulomas are another common cutaneous manifestation of AT[9] (Fig. 60.2). These granulomatous plaques tend to be persistent and ulcerate, leading to significant discomfort. Nevoid hyper- and/or hypopigmentation (particularly large segmental café-au-lait lesions) are often observed in children with AT, with chromosomal instability likely explaining this pigmentary mosaicism. Other dermatologic findings that have been described in individuals with AT include poikiloderma, eczematous dermatitis, seborrheic dermatitis

CUTANEOUS FINDINGS IN PRIMARY IMMUNODEFICIENCY DISORDERS										
Disorder	***S. aureus* infections**		**CMC**	**Warts**	**Eczematous dermatitis**	**Granulomatous dermatitis* (non-infectious)**	**LE**	**SVV**	**Ulcers (PG-like)**	**Other findings**
	Superficial pyodermas	**Abscesses**								
Ataxia–telangiectasia	+	+			+	+ (often ulcerate)				Oculocutaneous telangiectasias, progeric changes, CALM, BCC
Chédiak–Higashi syndrome	+	+							+	Pigmentary dilution, hyperpigmentation in sun-exposed sites, silvery hair, bleeding diathesis, gingivitis
Chronic granulomatous disease	++	++	+		+	++ (nodular, necrotic)	+		+	DLE in female carriers, Sweet's syndrome, oral ulcers
Chronic mucocutaneous candidiasis			++			(++) (candidal)				Dermatophyte infections, vitiligo, alopecia areata
Common variable immunodeficiency	+	+	+	+	+	++	+	+	+	Dermatophyte infections, vitiligo, alopecia areata
Complement deficiencies	+	+	+				++	+	+	Dermatomyositis, urticaria, lipodystrophy (C3), JIA
DiGeorge syndrome†			+		+	+				
Hyper-IgE syndrome	++	++ (cold)	+	‡	++					Neonatal papulopustular eruption
Hyper-IgM syndrome	+	+		+		+	+		+	Oral ulcers
Idiopathic CD4+ lymphocytopenia			+	++			+			
IgA deficiency	+	+	+		+		+	+	+	Vitiligo, lipodystrophia centrifugalis abdominalis
IgM deficiency	+	+		+	+		+			
IL-1 receptor-associated kinase-4 (IRAK-4) deficiency	++	++ (cold)	+							
Leukocyte adhesion deficiency		++ (necrotic)							++	Poor wound healing, delayed separation of the umbilical stump, gingivitis
SCID	+	+	+	+	+	+*				GVHD, erythroderma (Omenn syndrome)
TAP deficiency						++		+	+	
WHIM syndrome	+	+		++						
Wiskott–Aldrich syndrome	++	+			++	+		+		Bleeding diathesis
X-linked agammaglobulinemia	+	++			+	+				Dermatomyositis-like eruption (due to echovirus); ecthyma gangrenosum

*Extensive cutaneous and extracutaneous granulomatous disease (including destructive midfacial granulomas) has been described in children with hypomorphic *RAG1* or *RAG2* mutations.
†Defective thymic function, hypocalcemia secondary to hypoparathyroidism, congenital heart defects, and craniofacial anomalies; due to 21q11 deletions.
‡Patients with the autosomal recessive form of hyper-IgE syndrome are also at increased risk of developing mucocutaneous squamous cell carcinoma and severe warts, molluscum contagiosum and herpes simplex or varicella–zoster viral infections.

Table 60.1 Cutaneous findings in primary immunodeficiency disorders. +, occasional finding; ++, common finding; BCC, basal cell carcinoma; CALM, café-au-lait macules; CMC, chronic mucocutaneous candidiasis; DLE, discoid lupus erythematosus; GVHD, graft-versus-host disease; IL, interleukin; JIA, juvenile idiopathic arthritis; LE, lupus erythematosus; PG, pyoderma gangrenosum; SCID, severe combined immunodeficiency; SVV, small vessel vasculitis; TAP, transporter associated with antigen processing; WHIM, warts, hypogammaglobulinemia, infections and myelokathexis.

with blepharitis, keratosis pilaris, vitiligo, warts, hirsutism and acanthosis nigricans.

Cerebellar ataxia usually begins during infancy and is characterized by swaying of the head and trunk. Choreoathetosis, dysarthric speech, oculomotor abnormalities and myoclonic jerks often become prominent during childhood. Despite good muscle strength, patients are typically confined to a wheelchair by 11 years of age. The facies become dull and hypotonic, with mask-like changes developing concurrently with progressive progeric features. Of note, milder AT with onset of neurologic manifestations in adulthood has been described in individuals with *ATM* mutations that result in residual kinase activity.

Chronic or recurrent sinopulmonary infections occur in more than 80% of AT patients[10]. The most common cause of death is bronchiectasis with respiratory failure. Mildly elevated hepatic transaminase levels are noted in approximately half of patients, and the majority of affected individuals have evidence of glucose intolerance, hyperinsulinemia and insulin resistance. Other manifestations of AT include growth retardation (70%), developmental delay (33%) and hypogonadism.

Although lymphoid malignancy has been reported as the presenting sign of AT during infancy, most neoplasias occur in young adults. Patients who survive into their late teenage years have an up to 40% risk of developing a malignancy, especially leukemia (70-fold increase compared to unaffected individuals) and lymphoma (200-fold increase). Occasionally, patients develop basal cell carcinomas during the third decade of life.

SCREENING LABORATORY TESTS FOR A PATIENT WITH RECURRENT CUTANEOUS INFECTIONS		
Test	**Finding**	**Immunodeficiency identified**
Complete blood count with differential, platelet count, and examination of smear	• Giant granules within neutrophils, ± neutropenia • Neutrophilia • Small platelets, thrombocytopenia	Chédiak–Higashi syndrome Leukocyte adhesion deficiency Wiskott–Aldrich syndrome
Hair shaft examination	• Small, regular clumps of melanin • Large, irregular clumps of melanin	Chédiak–Higashi syndrome Griscelli syndrome (type 2; *RAB27A*)
Quantitative immunoglobulins	• All Ig ↓ • IgA ↓, IgG ↓, ± IgM ↓ • IgA ↓ or IgM ↓ • IgM ↑, all other Ig ↓ • IgM ↑, ± IgA ↑, ± IgG ↓ • IgA ↓, IgE ↓, $IgG_{2,4}$ ↓ • IgE ↑↑ • IgM ↓, ± IgG ↓, IgA ↑, IgE ↑	X-linked agammaglobulinemia Common variable immunodeficiency Selective IgA or IgM deficiency Hyper-IgM syndrome Hypohidrotic ectodermal dysplasia with immunodeficiency Ataxia–telangiectasia Hyper-IgE syndrome Wiskott–Aldrich syndrome
Total hemolytic complement (CH50)	• Marked ↓	Various complement deficiencies
Nitroblue tetrazolium (NBT) reduction assay	• <10% of normal NBT reduction	Chronic granulomatous disease
T- and B-cell analysis by flow cytometry	• Lack of T cells ± B cells	Severe combined immunodeficiency

Table 60.2 Screening laboratory tests for a patient with recurrent cutaneous infections (including staphylococcal) when there is suspicion of a primary immunodeficiency.

Fig. 60.1 Ataxia–telangiectasia. Linear telangiectasias on the bulbar conjunctivae (**A**) and extensive telangiectasias on the neck (**B**) of young women with ataxia–telangiectasia. *A, Courtesy, Jean L Bolognia, MD.*

Fig. 60.2 Persistent granulomatous plaques on the leg of a child with ataxia–telangiectasia. These lesions often ulcerate and are difficult to manage.

Carriers of heterozygous ATM mutations have a two- to threefold increase in both the risk of developing breast cancer and the likelihood of death from cancer (e.g. malignancies of the stomach, colon and lung as well as breast), with greater excess mortality in individuals less than 50 years of age[11].

Pathology

Immunologic defects in patients with AT include: (1) decreased serum levels of IgA (in 70% of patients), IgE (in up to 80% of patients) and IgG (especially IgG_2 and IgG_4; in 60% of patients); (2) low-molecular-weight (8S) IgM (in 80% of patients) and increased serum levels of IgM (in a minority of patients); (3) defects in cell-mediated immunity such as lymphopenia (in 70% of patients) and deficient *in vitro* responses to antigens and mitogens[10]. Affected individuals tend to have a relative deficiency of $CD4^+$ T cells, an excess of γ/δ T cells and elevated serum levels of interleukin-8 (IL-8; a chemokine that may contribute to pathogenic inflammation in AT). The majority of patients have an absent or abnormal thymus. Individuals with no ATM activity have more severe immunologic deficits that those with low levels of ATM activity[12].

Spontaneous chromosomal abnormalities (fragments, breaks, gaps and translocations) occur 2–18 times more frequently in patients with AT than in unaffected individuals, and an increased rate of telomeric shortening is also observed. Rearrangements of chromosomes 7 and 14 are particularly common and may predict the development of lymphoma. Fibroblast DNA from both patients and carriers is extremely sensitive to ionizing radiation and to radiomimetic agents such as bleomycin.

Almost all patients with AT have elevated levels of α-fetoprotein and carcinoembryonic antigen, and measuring the former can aid in establishing the diagnosis in individuals older than 2 years of age. MRI demonstrating cerebellar atrophy represents another clue to the diagnosis in patients older than 2 years. Radiosensitivity testing with the colony survival assay, analysis of radioresistant DNA synthesis (which demonstrates an abnormal S phase checkpoint), immunoblotting for the ATM protein, assessment of ATM kinase activity, karyotyping to identify 7;14 translocations, and sequencing the *ATM* gene may be utilized to confirm the diagnosis. Prenatal diagnosis of AT can be performed when parental mutations have been identified.

Differential Diagnosis

Children with AT may be thought to have Friedreich's ataxia until the ocular telangiectasias become apparent. The conjunctival telangiectasias are occasionally misdiagnosed as conjunctivitis, but the chronicity and size of the telangiectatic vessels distinguish AT. Bloom syndrome (see Ch. 87) can present with facial and occasionally conjunctival telangiectasias, café-au-lait macules, decreased immunoglobulin levels, recurrent respiratory infections and hematologic malignancies, but patients do not have neurologic abnormalities. RIDDLE syndrome is a recently described autosomal recessive condition that features *r*adiosensitivity, *i*mmunodeficiency, facial *d*ysmorphism, *d*ifficulty *le*arning, abnormal motor control and short stature due to mutations in the *RNF168* gene, which encodes a protein that mediates ubiquitin-dependent signaling at sites of DNA double-stranded breaks.

Treatment

The median lifespan in patients with AT is 20 to 25 years. More than half of patients die from chronic sinopulmonary disease and up to a third succumb to malignancy or complications of cancer treatment. Some of the patients who survive into adulthood show improvement in neurologic and immunologic status.

Therapy is supportive:

- antibiotics for infections; prophylactic antibiotics and IVIg replacement therapy for patients with severe immunodeficiency
- avoidance of sun exposure and use of sunscreens
- early physiotherapy for patients with bronchiectasis and consideration of systemic corticosteroid therapy for interstitial lung disease
- physical therapy to prevent contractures related to neurologic dysfunction
- screening for the development of malignancy.

If malignancy occurs, chemotherapy is typically necessary; radiation and radiomimetic chemotherapeutic agents, especially bleomycin, should be avoided. AT patients have a decreased threshold for postradiation erythema, tissue necrosis and radiation-induced cutaneous malignancy. If radiation is necessary, restriction of the fractions to 1 Gy and total radiation to less than 20 Gy is recommended. Bone marrow and fetothymic transplants, transfer factor administration and levamisole therapy have not resulted in clinical improvement. In patients with truncating *ATM* mutations, treatment with aminoglycosides can induce read-through of premature termination codons and restore production of functional ATM protein, providing the basis for a potential therapeutic approach[13].

CHRONIC MUCOCUTANEOUS CANDIDIASIS

Key features

- Recurrent and progressive candidal infections of skin, nails and mucosae
- Variable immunodeficiency, with a particular inability to mount a response against *Candida albicans*
- May be associated with autoimmune endocrinopathies

Introduction

Chronic mucocutaneous candidiasis (CMC) represents a heterogeneous group of disorders characterized by progressive and recurrent infections of the skin, nails and mucous membranes with *Candida albicans*[14]. Affected individuals demonstrate an ineffective immune response against this organism, and patients with an earlier onset and greater severity of candidal infections typically have more severe underlying immunologic abnormalities.

Epidemiology

Many patients with CMC do not have a family history of candidal infections or immunodeficiency. However, patients with the candidiasis endocrinopathy syndrome (*a*utoimmune *p*olyendocrinopathy–*c*andidiasis–*e*ctodermal *d*ystrophy syndrome, APECED[15]) often have similarly affected relatives. Inheritance of APECED and other familial forms of CMC is usually autosomal recessive (Table 60.3).

Pathogenesis

Patients with CMC have a T-cell deficiency that prevents effective handling of candidal organisms, although T-cell deficits are not always detectable *in vitro*. In some patients, the defect is specific to *Candida* spp. in others, the immunologic response to other organisms is also abnormal.

APECED results from mutations in the *AIRE* (*a*uto*i*mmune *re*gulator) gene, which encodes a transcription factor[16]. The AIRE protein regulates the ectopic expression of self antigens in the thymus, which allows the development of peripheral tolerance via negative selection of autoreactive T cells and the generation of antigen-specific regulatory T cells[17]. In APECED patients, failure to delete autoreactive T cells leads to autoimmune disease.

Recent investigations have implicated defective maturation of dendritic cells and impaired Th17 responses in the predisposition to *Candida* infections that characterizes APECED and other forms of CMC[18,19]. "Pure" forms of CMC with autosomal dominant inheritance can be caused by either *IL17F* mutations that lead to IL-17F deficiency or gain-of-function signal transducer and activator of transcription 1 (*STAT1*) mutations that impair IL-17 immunity, and an autosomal recessive CMC variant results from *IL17RA* mutations that abolish function of the IL-17 receptor A[19a,19b]. Neutralizing autoantibodies targeting Th17-associated cytokines (e.g. IL-17A/F, IL-22) have been identified in APECED patients and individuals with thymoma-associated CMC[20]. CMC can result from defects in the genes encoding dectin-1 (a pattern-recognition receptor that binds to β-glucan in the *Candida* cell wall) and caspase recruitment domain family member-9 (CARD9) (see Table 60.3), proteins that act together to activate a Th17 response[21,22]. In other types of CMC, inadequate production of IL-23 and overproduction of IL-6, which result in an inefficient IL-17 response, have been observed.

Clinical Features

The clinical severity of CMC ranges from recurrent, treatment-resistant thrush (Fig. 60.3) or a few erythematous scaly plaques and dystrophic nails to severe, generalized, crusted granulomatous plaques. The cutaneous plaques occur most frequently on the scalp and in perioricial and intertriginous sites. Scalp infections may lead to scarring alopecia. Affected nails are thickened, brittle and discolored, with associated paronychia (Fig. 60.4). Although mucosal involvement is usually limited to oral thrush with hyperkeratotic plaques, chronic lesions on esophageal, genital and laryngeal mucosae with resultant stricture formation may occur. Systemic candidiasis is rare, but cutaneous dermatophyte infections are common. Up to 80% of patients with childhood-onset CMC develop recurrent or severe infections with organisms other than *Candida*, including bacterial septicemia.

Subgroups of CMC in children and adolescents include those described in Table 60.3. An association of CMC with abnormalities of iron metabolism or (as noted above) thymoma has also been described in adult patients.

Fig. 60.3 Chronic mucocutaneous candidiasis. Extensive, recalcitrant thrush on the tongue of a 5-year-old child with chronic mucocutaneous candidiasis.

SUBGROUPS OF CHRONIC MUCOCUTANEOUS CANDIDIASIS IN CHILDREN AND ADOLESCENTS	
Subgroup	**Features**
Familial "pure" CMC	• Autosomal dominant form due to mutations in the *STAT1* gene (which lead to impaired IL-17 immunity) or IL-17F gene (*IL17F*), and autosomal recessive form due to mutations in the IL-17 receptor A gene (*IL17RA*) • Oral candidiasis usually begins by age 2 years • Cutaneous and ungual candidiasis also common • No associated endocrinopathy
Chronic localized candidiasis ("candidal granuloma")	• Majority have cutaneous lesions by age 5 years • Thick, adherent crusts, most commonly on the face and scalp • Usually concomitant oral candidiasis • Histologically, epidermal hyperkeratosis and acanthosis; dermal infiltrates of lymphocytes, plasma cells and, sometimes, giant cells
Autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy syndrome (APECED)*	• Caused by mutations in the *AIRE* gene, usually with autosomal recessive inheritance • Increased prevalence among Finns, Iranian Jews, and Sardinians • Candidal infections usually begin by age 5 years • Candidal granulomas, especially of the face and scalp • Endocrinologic dysfunction may not be apparent until teenage or even adult years • Associated autoimmune endocrinopathies – hypoparathyroidism (90%) – hypoadrenocorticism (60%) – both of the above (30%) – hypogonadism (45%) – thyroid disease (15%) – type 1 diabetes mellitus – hypopituitarism • Cutaneous autoimmune disorders – alopecia areata (20%) – vitiligo – lupus-like panniculitis • Other autoimmune disorders – pernicious anemia (15%) – chronic active hepatitis/juvenile cirrhosis (10%) • Chronic diarrhea and malabsorption (usually associated with hypoparathyroidism; 25%), pulmonary fibrosis, keratoconjunctivitis, splenic atrophy, dental enamel hypoplasia • Antithyroglobulin, antimicrosomal, antiparietal cell and antiadrenal antibodies; rheumatoid factor • An autosomal dominant form of CMC associated with autoimmune thyroid disease may occur due to dominant-negative *AIRE* mutations and has also been linked to chromosome 2p in one family
CARD9-associated CMC	• Autosomal recessive form of CMC due to mutations in the *CARD9* gene • Chronic oral and vulvovaginal candidiasis; also dermatophytosis • Fatal candidal infections of the brain during the second decade of life in some affected individuals
Dectin-1 deficiency	• Due to biallelic polymorphisms that result in a truncated dectin-1 protein • Chronic/recurrent vulvovaginal candidiasis and onychomycosis
Late-onset CMC	• Initial infections in late childhood or early teenage years • Milder involvement than in other subgroups • Responses against *Candida albicans* may normalize after effective therapy
Familial chronic nail candidiasis	• Autosomal dominant form of CMC mapped to the pericentromeric region of chromosome 11 in a five-generation Italian family • Onset in infancy of candidiasis limited to the nails of the hands and feet • Association with low serum levels of intercellular adhesion molecule-1 (ICAM-1)
CMC associated with keratitis	• A family with CMC (oral and vaginal), alopecia and keratitis has been described – photophobia developed by age 2 years, and the remainder of the findings by age 5 years – inheritance pattern appeared to be autosomal dominant • Keratitis can be a feature of APECED • CMC can occur in patients with keratitis–ichthyosis–deafness (KID) syndrome
CMC associated with other immunodeficiency disorders	• Severe combined immunodeficiency • DiGeorge syndrome • Hyper-IgE syndrome
CMC associated with predominantly non-immunologic conditions	• KID syndrome • Multiple carboxylase deficiency • Acrodermatitis enteropathica • Ectodermal dysplasia–ectrodactyly–clefting syndrome
*The latter refers primarily to dental enamel hypoplasia; also known as autoimmune polyendocrine syndrome type 1.	

Table 60.3 Subgroups of chronic mucocutaneous candidiasis (CMC) in children and adolescents. CARD9, caspase recruitment domain family member-9; IL, interleukin; STAT1, signal transducer and activator of transcription 1.

Pathology

Candidal organisms are confined to the stratum corneum and are demonstrable in scrapings and cultures. Approximately 70% of patients have direct evidence of an immunologic defect, including decreased lymphocyte proliferation *in vitro*, impaired cytokine production and absent delayed-type hypersensitivity (DTH) in response to *Candida*, as well as nonspecific findings such as abnormal leukocyte chemotaxis or phagocytosis, depressed IgA levels, and complement dysfunction. These heterogeneous immune abnormalities reflect the variety of underlying clinical disorders. Candidal polysaccharides may act as serum factors

Fig. 60.4 Chronic mucocutaneous candidiasis. **A,B** Marked onychodystrophy with significant paronychial swelling and erythema (**A**) and crusted plaques on the palm (**B**) in patients with chronic mucocutaneous candidiasis. **C** Recurrent cutaneous candidiasis presenting as erythema, pustules and scale-crust near the site of an intravenous line on the arm in an infant with DiGeorge syndrome.

that inhibit the immune response, and, in some patients, DTH to candidal antigens has been restored after antifungal therapy[16].

Differential Diagnosis

Candidal infections, particularly thrush, are fairly common in infants. Recurrent thrush in young children with frequent otitis media may reflect alterations in bacterial flora caused by the administration of systemic antibiotics; this is seen much more often than CMC or other immunodeficiencies. Recurrent or recalcitrant candidal infections should prompt consideration of HIV infection. Clearance after traditional therapy helps to distinguish secondary candidal infections from mild CMC.

The IPEX (*i*mmune dysregulation, *p*oly-endocrinopathy, *e*nteropathy, *X*-linked) syndrome (see below) can present with autoimmune skin conditions and endocrinopathies together with recurrent infections, but the latter are typically bacterial rather than candidal. Autoimmune endocrinopathies, enteropathy, eczematous dermatitis, and a predisposition to bacterial, viral and fungal infections have also been described in patients with IL-2 receptor α-chain deficiency (see Table 60.5).

Treatment

Patients with CMC do not respond well to standard topical medications, and the cutaneous granulomas are especially difficult to treat. Most patients benefit from long-term therapy with systemic antifungal agents such as itraconazole, fluconazole and terbinafine. Attempts at immune enhancement are usually ineffective, although transfer factor administration may be beneficial to some patients with defective cell-mediated immunity. Hematopoietic stem cell transplantation, fetal thymus grafts, and leukocyte infusions have been utilized in patients with severe immunologic deficiencies. Patients should be evaluated at least annually for the development of endocrinopathies, particularly if there is a family history of CMC or APECED.

CARTILAGE–HAIR HYPOPLASIA SYNDROME

Synonym: ■ MuKusick-type metaphyseal chondrodysplasia

Key features

- Fine, sparse, hypopigmented hair
- Short-limbed dwarfism with metaphyseal dysostosis
- Doughy skin with abnormal elastic tissue
- Defective cell-mediated and (in a minority of patients) humoral immunity

Cartilage–hair hypoplasia (CHH) syndrome is a pleiotropic autosomal recessive disorder that occurs most commonly in Amish individuals and Finns. The condition results from mutations in the *RMRP* gene that encodes the RNA component of a ribonucleoprotein endoribonuclease, RNase MRP, which cleaves RNA primers responsible for DNA replication in mitochondria and processes pre-rRNA in the nucleolus[23].

Affected individuals are most likely to visit the dermatologist for their fine, sparse, hypopigmented hair, although they may also have soft, doughy skin with degenerated elastic tissue[24]. The short-limbed dwarfism results from metaphyseal dysostosis, and ligamentous laxity is often observed. Most patients have some degree of defective cell-mediated immunity, which predisposes them to severe varicella and herpes simplex viral infections. Approximately a third of patients also have abnormal humoral immunity, most frequently an IgA or IgG deficiency, which increases their susceptibility to recurrent respiratory tract infections that can lead to bronchiectasis. Severe combined immunodeficiency and an Omenn syndrome-like phenotype (e.g. erythroderma, eosinophilia, chronic diarrhea, lymphadenopathy, hepatosplenomegaly; see below) occasionally occur in affected individuals. Neutropenia and anemia can develop due to autoimmunity or bone marrow hypoplasia. Hirschsprung disease, other autoimmune disorders and impaired spermatogenesis represent additional manifestations of CHH. Patients also have an increased risk of developing non-Hodgkin lymphoma and basal cell carcinomas. Hematopoietic stem cell transplantation, which can restore function of the immune system and bone marrow, should be considered in patients with severe immunodeficiency or cytopenias.

CHÉDIAK–HIGASHI SYNDROME

Synonyms: ■ Béguez César–Steinbrinck syndrome ■ Chédiak–Higashi disease ■ Chédiak–Steinbrinck–Higashi syndrome ■ Chédiak–Steinbrinck anomaly

Key features

- Autosomal recessive disorder of vesicle trafficking that results in giant organelles, including melanosomes, leukocyte granules and platelet-dense granules
- Silvery hair, mild diffuse pigmentary dilution (often with an admixture of hyper- and hypopigmentation in sun-exposed sites), and a variable degree of photophobia and nystagmus
- Recurrent pyogenic infections and a mild bleeding diathesis
- An "accelerated phase" with pancytopenia and organomegaly due to lymphohistiocytic infiltration, which is fatal without hematopoietic stem cell transplantation
- Progressive neurologic deterioration in survivors

Epidemiology

Chédiak–Higashi syndrome (CHS) is a rare autosomal recessive disease reported most often in individuals of Northern European, Spanish, Middle Eastern and Japanese ancestry[25]. Patients of African descent have also been described[26].

Pathogenesis

CHS represents a disorder of vesicle trafficking and is caused by mutations in the *lys*osomal *t*rafficking regulator gene (*LYST*)[27]. Most patients have frameshift or nonsense mutations that result in a truncated protein and lead to a severe phenotype with progression to a fatal lymphoproliferative "accelerated phase" during childhood, but 10–15% of affected individuals have missense mutations that are associated with a milder phenotype and survival to adulthood[28].

The giant intracytoplasmic granules that characterize CHS result from dysregulated fission/fusion of lysosome-related organelles, which include melanosomes, platelet-dense granules and leukocyte cytolytic granules[25]. The latter granules cannot effectively migrate or discharge their peroxidative and proteolytic enzymes, leading to defective target cell killing. The localization of cytotoxic T lymphocyte-associated antigen (CTLA-4) to enlarged vesicles rather than the cell surface may play a role in the development of lymphoproliferative disease. In addition, abnormal antigen presentation by B cells and generalized impairment in plasma membrane repair may contribute to the pathogenesis of CHS.

Clinical Features

Patients with CHS usually present in infancy with mild diffuse pigmentary dilution of the skin, hair and eyes. In individuals with relatively dark constitutive pigmentation, areas of bronze to slate-gray hyperpigmentation may be evident in sun-exposed sites, often admixed with guttate hypopigmented macules. Hair color is variable, but a silvery, metallic sheen is characteristic. Decreased ocular pigment can result in photophobia, nystagmus and strabismus, but visual acuity is usually normal.

Infections primarily involve the skin and respiratory tract, and they are typically caused by *Staphylococcus aureus*, *Streptococcus pyogenes* and *Streptococcus pneumoniae*. The skin infections are most often superficial pyodermas. Cutaneous ulcerations resembling pyoderma gangrenosum, gingivitis and ulceration of the oral mucosa have also been described. Although the bleeding diathesis of CHS is generally mild, patients may report easy bruising, petechiae and epistaxis.

Approximately 85% of patients with CHS enter a lymphoproliferative "accelerated phase" characterized by pancytopenia and lymphohistiocytic infiltration of the liver, spleen, lymph nodes, oral mucosa and other internal organs. This "hemophagocytic syndrome" results from uncontrolled T-cell and macrophage activation, possibly associated with EBV infection, and typically leads to death by age 10 years (usually from overwhelming infection or hemorrhage) unless hematopoietic stem cell transplantation is performed.

Patients with CHS who survive the first decade of life experience progressive neurologic deterioration, with clumsiness, abnormal gait and paresthesias. Peripheral and cranial neuropathies, spinocerebellar degeneration, parkinsonism and dementia can manifest in adult patients who were treated with hematopoietic stem cell transplantation as children as well as in those with otherwise mild disease.

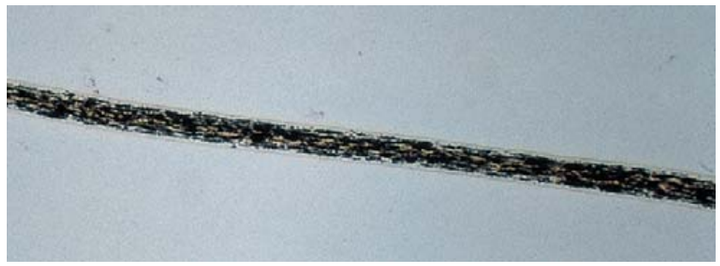


Fig. 60.5 Chédiak–Higashi syndrome. Light microscopic examination of hair shows small, regularly spaced clumps of melanin in patients with Chédiak–Higashi syndrome.

Pathology

The silvery hair of patients with CHS is characterized by clumps of melanin microscopically (Fig. 60.5), and giant melanosomes may be evident within melanocytes in skin biopsy specimens. A peripheral blood smear demonstrating abnormally large granules in the perinuclear area of granulocytes can assist in establishing the diagnosis. Immunologic defects in CHS include neutropenia, diminished leukocyte chemotaxis, impaired antibody-dependent cell-mediated cytotoxicity, reduced cytotoxic and regulatory T-cell activity, and markedly decreased natural killer (NK) cell function.

Differential Diagnosis

The features of CHS and the three types of Griscelli syndrome (GS), another autosomal recessive disorder that can present with immune dysfunction and silvery hair (but with a different pattern of pigment clumping), are compared in Table 60.4 (see also Ch. 66). Although leukocytes have a normal appearance in GS, hypogammaglobulinemia can be observed. Hermansky–Pudlak syndrome type 2 (*AP3B1* mutations) can manifest with recurrent infections due to neutropenia and abnormal cytotoxic T-cell function as well as a bleeding diathesis and diffuse pigmentary dilution, but not silvery hair. Tricho-hepato-enteric syndrome (phenotypic diarrhea of infancy), an autosomal recessive disorder caused by mutations in the tetratricopeptide repeat domain 37 gene (*TTC37*), can present with diffuse pigmentary dilution of the skin and hair, immunodeficiency and platelet abnormalities; unlike CHS, it is also characterized by brittle hair with trichorrhexis nodosa, intractable diarrhea during infancy, primary liver disease, facial dysmorphism and cardiac defects. Other inherited disorders characterized by lymphoproliferation due to immune dysregulation are presented in Table 60.5.

Treatment

Hematopoietic stem cell transplantation may reverse the immunodeficiency of CHS and prevent or (following immunochemotherapy with etoposide, corticosteroids and cyclosporine) abrogate the lymphoproliferative accelerated phase. However, it has no effect on pigmentary alteration and does not halt neurologic degeneration. Management of the CHS is otherwise largely supportive, with administration of prophylactic antibiotics to prevent recurrent infections.

COMPLEMENT DISORDERS

Key features

- Deficiency or dysfunction of early complement components increases susceptibility to pyogenic infections caused by encapsulated bacteria and autoimmune disorders, especially systemic lupus erythematosus
- Deficiency of late complement components leads to a markedly increased risk of neisserial infections

Introduction

The complement system represents an important effector of the innate immune response (see Ch. 4). An enzymatic cascade of complement

FEATURES OF CHÉDIAK–HIGASHI SYNDROME AND GRISCELLI SYNDROME					
	CHS	**GS1***		**GS2**	**GS3**
Gene defect	*LYST*	*MYO5A*		*RAB27A*	*MLPH*
Major sites of gene expression	Melanocytes, platelets, granulocytes, CNS	Melanocytes, CNS		Melanocytes, cytotoxic T cells	Melanocytes
Cellular defect	Vesicle trafficking (e.g. fission/fusion)	Vesicle movement/transfer		As in GS1	As in GS1
Pigmentary dilution of the skin†	+	+	+		+
Silvery/metallic hair	+	+	+		+
Hair microscopy: clumps of melanin	Small, regularly spaced	Larger, irregularly distributed			
Melanocytes	Giant melanosomes	"Stuffed" with melanosomes			
Neutrophils	Giant granules	Normal-appearing granules			
Ocular findings	+	–	–		–
Bleeding diathesis	+	–	–		–
Recurrent infections	+	–	+		–
Accelerated phase	+	–	+		–
Primary neurologic abnormalities	+	+	–‡		–

*Elejalde syndrome (neuroectodermal melanolysosomal disease), which presents with pigmentary features of GS plus severe neurologic dysfunction, likely represents a variant of GS1. Elejalde syndrome is not associated with immunodeficiency. A form of GS with manifestations limited to the skin and hair can result from deletion of the MYO5A F-exon, which is only expressed in melanocytes.
†Often accompanied by hyperpigmentation ± guttate hypopigmented macules in acral and sun-exposed sites.
‡May develop neurologic symptoms secondary to the hemophagocytic syndrome of the accelerated phase.

Table 60.4 Features of Chédiak–Higashi syndrome (CHS) and Griscelli syndrome (GS). The latter is caused by defective attachment of organelles to the actin cytoskeleton (see Ch. 64). CNS, central nervous system.

INHERITED DISORDERS CHARACTERIZED BY LYMPHOPROLIFERATION DUE TO IMMUNE DYSREGULATION				
Disorder	**Inh**	**Gene**	**Protein (function)**	**Clinical features**
Chédiak–Higashi syndrome	AR	*LYST*	See Table 60.4	See Table 60.4
Griscelli syndrome type 2	AR	*RAB27A*		
Familial hemophagocytic lymphohistiocytosis	AR	*PRF1*	Perforin (major cytolytic granule protein of CTL and NK cells)	• Hemophagocytic syndrome • Absent NK cell cytotoxicity • Fatal during early childhood unless hematopoietic stem cell transplantation is performed
	AR	*UNC13D*	Munc13–4 (primes cytolytic granules for secretion)	
	AR	*STX11*	Syntaxin 11 (involved in cytolytic granule trafficking and fusion)	
	AR	*STXBP2*	Syntaxin-binding protein 2 (regulates cytolytic granule trafficking)	
X-linked lymphoproliferative syndrome (Duncan disease)	XR	*SH2D1A*	Signaling lymphocyte activation molecule-associated protein (adaptor protein that regulates B-, T- and NK-cell function; particularly important for immune responses to EBV)	• Severe EBV-related infectious mononucleosis in childhood or adolescence (e.g. fever, pharyngitis, LAN, HSM), often associated with morbilliform eruptions, purpura and/or jaundice • ± Hypogammaglobulinemia • Fatal EBV-related B-cell lymphoma (70%) • Lymphocytic vasculitis
	XR	*XIAP*	X-linked inhibitor of apoptosis	
EBV-associated lymphoproliferative syndrome	AR	*ITK*	IL-2-inducible T-cell kinase	
Autoimmune lymphoproliferative syndrome (Canale–Smith syndrome) (see Fig. 20.6)	AD >AR	*TNFRSF6*	CD95 (Fas; cell-surface apoptosis receptor)	• Massive LAN and/or splenomegaly • Increased $CD4^-/CD8^-$ α/β T cells • Autoimmune cytopenias, LE, small vessel vasculitis • Recurrent bacterial and viral infections (*CASP8*) • Increased risk of lymphoma
	AD >AR	*TNFSF6*	CD95L (Fas ligand)	
	AD > AR	*CASP10*	Caspase 8 and 10 (proteases in intracellular apoptosis cascade)	
	AR	*CASP8*		
	AD	*NRAS*	NRAS (gain of function leads to decreased lymphocyte apoptosis)	
Immunodeficiency with lymphoid proliferation	AR	*IL2RA*	IL-2 receptor α-chain (apoptosis of developing T cells in the thymus)	• Bacterial, viral and fungal infections • Extensive lymphocytic infiltration of the liver, lung, gut and bones • Eczematous dermatitis; autoimmune polyendocrinopathy, cytopenias and enteropathy

Table 60.5 Inherited disorders characterized by lymphoproliferation due to immune dysregulation. Hemophagocytic syndromes result from uncontrolled T-cell and macrophage activation, manifesting with fever, pancytopenia, hepatosplenomegaly (HSM) and lymphadenopathy (LAN) (due to lymphohistiocytic infiltration), hypertriglyceridemia and hypofibrinogenemia. AD, autosomal dominant; AR, autosomal recessive; CTL, cytotoxic T lymphocytes; Inh, inheritance; LE, lupus erythematosus; NK, natural killer; XR, X-linked recessive.

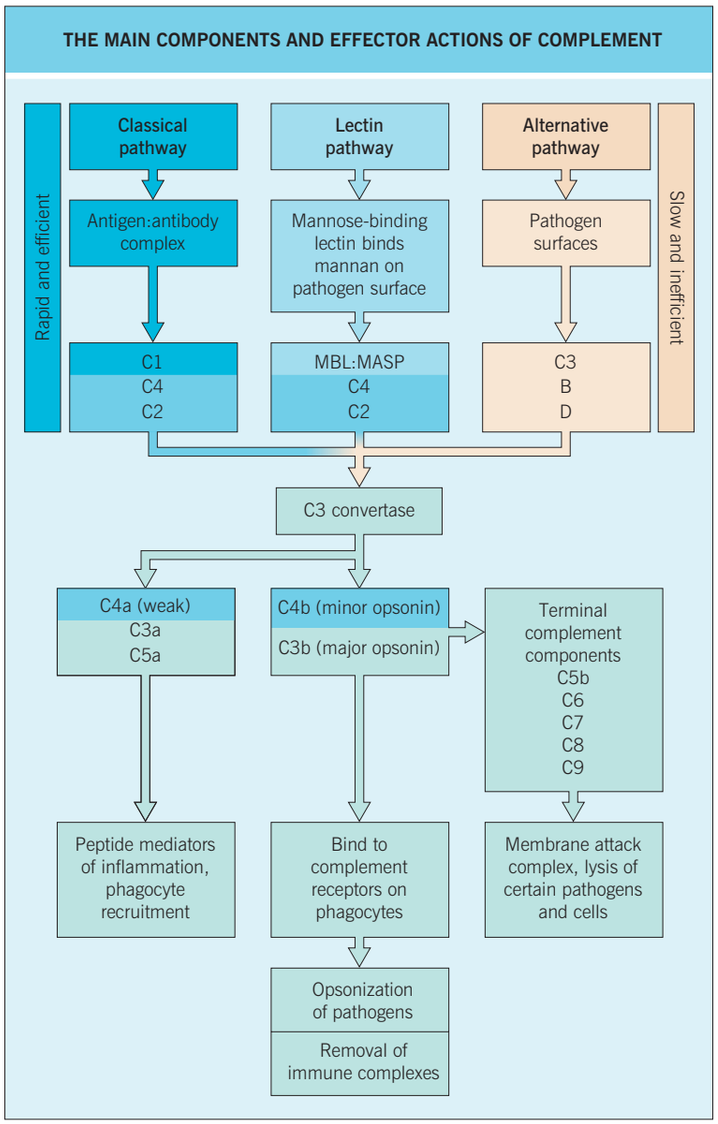


Fig. 60.6 The main components and effector actions of complement. The C3b bound to the C3 convertase binds C5, allowing the C3 convertase to generate C5b, which associates with the bacterial membrane and triggers the late events. MBL, mannose-binding lectin; MASP, MBL-associated serine protease. *Copyright © 2005 from Immunobiology by Charles A. Janeway et al. Adapted with permission of Garland Science/Taylor & Francis Books, Inc.*

activation can be triggered by three different pathways: classical, alternative and lectin (Fig. 60.6). In addition to their roles in killing microbial pathogens, complement proteins (Table 60.6) serve as regulators of a variety of humoral and cellular immune functions. As a result, clinical manifestations of complement deficiency include autoimmune diseases as well as increased susceptibility to infection[29].

Epidemiology

Deficiency of C2 represents the most common hereditary complement disorder[29]. Homozygous C2 deficiency occurs in approximately 1 : 20 000 individuals, and 1–2% of the population has the heterozygous form. Homozygous deficiencies of C1q, C1r, C1s and C4 are rare, but affected individuals manifest with autoimmune disease more frequently than those with homozygous C2 deficiency. Heterozygotes usually make enough protein to ensure function and are in general asymptomatic, so most of the complement disorders are inherited as autosomal recessive traits. One exception is hereditary angioedema (HAE), an autosomal dominant condition due to deficiency or dysfunction of the C1 inhibitor (see Ch. 18).

In contrast to the low prevalence of deficiencies in components of the classical complement pathway, 5–10% of the population is homozygous or compound heterozygous for alleles that lead to a lack of functional mannose-binding lectin (MBL), the major recognition factor of the lectin pathway of complement activation[30]. Although the clinical penetrance of MBL deficiency is low, it may have a substantial impact on immunity and autoimmunity at the population level. In addition, approximately 1 : 10 000 individuals has a homozygous deficiency in the MBL-associated serum protease (MASP) that functions in this pathway.

Pathogenesis

Deficiency of C2 can result from a defect in either protein synthesis (type 1) or secretion (type 2). Defects involving the early components of the classical complement pathway (C1, C4, C2) manifest with an increased risk of autoimmune disorders, especially systemic lupus erythematosus (SLE) (Table 60.7). The genes that encode these complement components, including four highly polymorphic genes for C4 (two each for C4A and C4B), are located within the HLA region on chromosome 6. C4-null alleles have been linked with SLE, and the C4A gene is deleted in the Caucasoid extended haplotype (HLA A1, B8, DR3) that is strongly associated with SLE.

The pathogenesis of SLE in the setting of complement deficiency may also be related to impaired physiologic clearance of autoantigen-containing apoptotic cells[31]. Epidermal keratinocytes undergoing UVB-induced apoptosis preferentially display autoantigens such as Ro in plasma membrane blebs. Binding of C1q to the blebs results in activation of the classical complement pathway and removal of the apoptotic cells by phagocytes; in the absence of C1q, autoantibodies have the opportunity to bind to Ro, leading to activation of B and T cells and loss of immune tolerance. Decreased MBL-mediated clearance of apoptotic debris and DNA might likewise explain the predisposition to SLE associated with MBL deficiency. Furthermore, the complement system may enhance the elimination of self-reactive B cells during lymphocyte development, with complement deficiency leading to a lack of B-cell self-tolerance. Complement components are also important for handling immune complexes and regulating production of cytokines (e.g. type I interferons) that have a key role in SLE pathogenesis.

The variety of recurrent infections associated with complement deficiencies underscores the central role of complement in bacterial clearance. Patients deficient in the early classical components, especially C2, have increased susceptibility to infections with encapsulated bacteria, especially *Str. pneumoniae*. Opsonization of bacteria and fungi may be ineffective in disorders of the classical pathway because of the slow, inadequate formation of C3b. However, because the lectin and alternative pathways can bypass early classical components to intersect with the cascade at the level of C3 (see Table 60.6 & Fig. 60.6), these deficiencies do not usually lead to overwhelming infections. C5 deficiencies result in impaired generation of chemotactic factors, which may lead to inadequate neutrophil function. Individuals with C5 to C9 (membrane attack complex), properdin and factor D deficiencies develop recurrent neisserial infections in their teenage years. This underscores the importance of the bactericidal MAC complex and the alternative complement pathway (which requires properdin and factor D) in the destruction of these organisms. However, because a lack of lytic activity limits release of bacterial products (e.g. lipopolysaccharide) that stimulate a damaging cytokine response, the mortality of meningococcal infections in patients with MAC deficiency is actually lower than that in immunocompetent individuals. In contrast, patients with a properdin or factor D deficiency are unable to eradicate *Neisseria* spp. via opsonophagocytosis and have severe disease that is often fatal.

Clinical Features

Individuals with homozygous deficiencies in the early components of the classical complement pathway (C1, C4, C2) have a risk of SLE that ranges from >90% for C1q to 10–20% for C2. Among those with C2 deficiency, features of lupus erythematosus (especially photosensitivity and subacute cutaneous lupus erythematosus) are most common in women, with the age at onset ranging from early childhood to adulthood (median 30 years). Other manifestations of C2 deficiency-associated SLE are presented in Table 60.8. SLE in the setting of C1q/r/s or C4 deficiency usually develops during childhood, affects boys and girls equally, and is often associated with renal disease and palmoplantar keratoses as well as photosensitivity. Other autoimmune and/or inflammatory disorders and susceptibilities to infection associated

COMPLEMENT SPLIT PRODUCTS AND COMPLEXES			
Split product	**Function**	**Complex**	**Function**
C1q	Recognition factor of CP (binds Ag-Ab complexes) Activates C1r	C1inh-C1r-C1s	Formed during C1 activation
C1r	Cleaves C1s to an active protease		
C1s	Cleaves C4 and C2		
C4a	Anaphylatoxin (weak)	C4b2a	CP C3 convertase
C4b	Part of the CP C3 and C5 convertases Opsonization		
C2a	Part of the CP C3 and C5 convertases		
C2b	Unknown		
C3(H_2O)	Recognition factor of AP (binds bacterial surfaces, including lipopolysaccharide)	C3bBb	AP C3 convertase
C3a	Anaphylatoxin Chemotaxis (eosinophils) Direct antimicrobial effect	C4b2a3b	CP C5 convertase
C3b	Part of CP C5 and AP C3/C5 convertases Opsonization	$C3b_{(n)}Bb$	AP C5 convertase
C5a	Anaphylatoxin (strong) Chemotaxis (neutrophils and monocytes) Regulation of apoptosis		
C5b	Part of membrane attack complex	$C5b\text{-}9_n$ SC5b-9	Membrane attack complex Soluble terminal complement complex

Table 60.6 Complement split products and complexes. Dark blue, classical pathway (CP); medium blue, CP and lectin pathway; yellow, alternative pathway (AP); green, all three pathways. Anaphylatoxins are inflammatory mediators that increase vascular permeability and cause mast cell degranulation. Opsonization represents binding of a protein to the pathogen surface in order to target it for destruction. C1 inh, C1 esterase inhibitor; SC, soluble complex.

with complement deficiencies are listed in Table 60.7. C2 deficiency may coexist with common variable immunodeficiency, and the development of Hodgkin disease has occasionally been reported.

MBL deficiency may confer an increased risk of acute respiratory infections in children aged 6–18 months, who no longer have maternal antibodies but are not yet able to mount an efficient antibody response to the carbohydrate antigens of encapsulated bacteria[30]. Several studies have shown that MBL deficiency is associated with an increased risk of developing SLE or dermatomyositis and a higher incidence of infections in the setting of immunosuppressive therapy.

Pathology

The total hemolytic complement (CH50) is markedly decreased or undetectable in complement deficiencies other than hereditary angioedema. The alternative pathway lytic test (AP50) can be used to screen for deficiencies in components of this pathway, although it is less sensitive than the CH50. Immunoprecipitation assays (e.g. radial immunodiffusion or ELISA) can determine the levels of specific complement components and MBL[32], and functional studies of individual components may be informative when antigen levels are normal.

Differential Diagnosis

Complement components may be specific targets of autoimmune responses; for example, anti-C1q antibodies are found in 30–50% of patients with SLE (often with renal involvement) and virtually all of those with hypocomplementemic urticarial vasculitis. The "*Leiner phenotype*" of exfoliative dermatitis, failure to thrive, chronic diarrhea and recurrent infections has been observed in infants with C3 or C5 deficiency or C5 dysfunction. However, this constellation of findings can also develop in patients with other disorders such as X-linked agammaglobulinemia, hyper-IgE syndrome and severe combined immunodeficiency. Low complement levels related to bacterial and viral infections should also be differentiated from primary complement deficiencies.

Treatment

Conservative therapy is often effective for patients with autoimmune manifestations of complement deficiency. The use of topical corticosteroids and sun protection may be sufficient to treat cutaneous lupus erythematosus in these individuals. Antimalarial drugs, systemic corticosteroids, and other immunosuppressive medications are typically required in more severe cases, with consideration of the increased risk of infections in patients with complement deficiencies. The use of plasma transfusions to replace the deficient components may actually activate the cascade and accelerate immune complex deposition. Infections should be treated with early, aggressive antibiotic therapy.

CHRONIC GRANULOMATOUS DISEASE

Synonyms: ■ Chronic granulomatous disorder ■ Bridges–Good syndrome ■ Quie syndrome

Key features

- Inability to kill intracellular organisms through generation of oxidative metabolites
- X-linked recessive or autosomal recessive inheritance
- Recurrent pneumonias and cutaneous infections, lymphadenopathy and hepatosplenomegaly
- Patients develop granulomas as a compensatory effort to confine organisms

Introduction

Chronic granulomatous disease (CGD) is a group of disorders characterized by severe, recurrent infections due to an inability of leukocytes to kill phagocytosed bacteria and fungi by generating oxidative metabolites. The activity of the nicotinamide dinucleotide phosphate (NADPH) oxidase complex is reduced in all forms of CGD.

Epidemiology

The incidence of CGD is approximately 1:200 000 live births[33,34]. Ninety percent of patients are boys. Approximately three-quarters of

COMPLEMENT DISORDERS		
Complement component	**Common infectious agents**	**Autoimmune/inflammatory disorders**
CLASSICAL PATHWAY		
C1q	Encapsulated bacteria, *Candida* spp.	SLE*, GN
C1r	Encapsulated bacteria	SLE*, GN
C1s	Encapsulated bacteria	SLE*
C1 inhibitor		Hereditary angioedema, SLE, GN, partial lipodystrophy, vasculitis
C4	Encapsulated bacteria	SLE* with PPK and scars, HSP, GN, urticaria, JIA‡
C2†	Encapsulated bacteria, especially *Streptococcus pneumoniae*	SLE*, SCLE, DLE, dermatomyositis, HSP, other vasculitides, atrophoderma, cold urticaria, JIA‡, IBD, atherosclerosis
LECTIN PATHWAY		
MBL§	Encapsulated bacteria, especially *N. meningitides*	SLE, dermatomyositis, atherosclerosis, chronic pulmonary disease
MASP-2	Encapsulated bacteria, especially *S. pneumoniae*	SLE, IBD
C3 AND ALTERNATIVE PATHWAY		
C3	Encapsulated bacteria (severe infections)	SLE, vasculitis, lipodystrophy (partial [cephalo]thoracic), GN, "Leiner phenotype"
Factor H	Encapsulated bacteria	SLE, HUS, GN, age-related macular degeneration
Factor I (C3b inactivator)	Encapsulated bacteria	SLE, HUS, aquagenic urticaria, angioedema
Properdin¶	*Neisseria* spp. (fulminant infections)	
Factor D	*Neisseria* spp.	
MEMBRANE ATTACK COMPLEX		
C5 dysfunction	Gram-negative bacteria	"Leiner phenotype"
C5 deficiency	*Neisseria* spp. *S. pneumoniae*	SLE
C6	*Neisseria, Brucella, Toxoplasma* spp.	SLE, JIA, GN
C7	*Neisseria* spp.	SLE, CREST syndrome, ankylosing spondylitis
C8α	*Neisseria* spp.	SLE, fever with HSM, eosinophilia, hypergammaglobulinemia
C8β	*Neisseria* spp.	SLE, JIA
C9	*Neisseria* spp.	

*Hierarchy of SLE risk with homozygous mutations: C1q (~90%) > C1r/s > C4 > C2 (~10–20%).
†Most common of the homozygous complement deficiencies.
‡Especially in heterozygous girls.
§Very low penetrance.
¶X-linked recessive.

Table 60.7 Complement disorders. Unless otherwise specified, affected individuals usually have biallelic defects. Pyogenic infections caused by encapsulated organisms (e.g. *Streptococcus pneumoniae, Haemophilus influenzae* and *Streptococcus pyogenes*) in individuals with classical pathway component deficiencies are not as frequent as neisserial infections in those with membrane attack complex component deficiencies. CREST: *c*alcinosis, *R*aynaud's phenomenon, *e*sophageal dysmotility, *s*clerodactyly, *t*elangiectasias; DLE, discoid lupus erythematosus; GN, glomerulonephritis; HSM, hepatosplenomegaly; HSP, Henoch–Schönlein purpura; HUS, hemolytic uremic syndrome; IBD, inflammatory bowel disease; INH, inhibitor; JIA, juvenile idiopathic arthritis; MBL, mannose-binding lectin; MASP, MBL-associated serum protease; PPK, palmoplantar keratoderma; SCLE, subacute cutaneous lupus erythematosus; SLE, systemic lupus erythematosus. *Adapted with permission from Schachner L, Hansen R, eds. Pediatric Dermatology, 4th edn. London: Mosby, 2011.*

FEATURES OF SYSTEMIC LUPUS ERYTHEMATOSUS IN C2 DEFICIENCY	
Common features	**Features more suggestive of C2 deficiency-associated SLE than classic SLE**
Photosensitivity*	Childhood onset
SCLE*, ACLE, or DLE	Extensive, treatment-resistant skin lesions
Cicatricial alopecia	Mild or absent renal disease
Oral ulcerations (50%)	Absent or low-titer ANA and anti-dsDNA
Fever (>50%)	Antibodies
Arthralgias and/or arthritis (80%)	Negative lupus band test
Leukopenia (50%)	Less severe disease overall
Anti-Ro antibody (75%)	Pyogenic infections with encapsulated
Rheumatoid factor (40%)	bacteria, e.g. *Streptococcus pneumoniae*
	Increased risk of atherosclerosis

*Most common cutaneous manifestations.

Table 60.8 Features of systemic lupus erythematosus (SLE) in C2 deficiency. Less frequent manifestations include central nervous system vasculitis, pleuritis, pericarditis, Raynaud's phenomenon, thrombocytopenia, anti-Sm or anti-RNP antibodies, circulating immune complexes and a positive RPR. ACLE, acute cutaneous lupus erythematosus; DLE, discoid lupus erythematosus; SCLE, subacute cutaneous lupus erythematosus. *Adapted with permission from Schachner L, Hansen R, eds. Pediatric Dermatology, 4th edn. London: Mosby, 2011.*

cases have X-linked recessive transmission, while the remainder are autosomal recessive.

Pathogenesis

The defects in CGD involve five subunits of the phagocyte NADPH oxidase: the membrane-bound gp91^{phox} (phagocyte oxidase) and p22^{phox}; and the cytoplasmic p47^{phox}, p67^{phox} and p40^{phox} (Table 60.9). The failure of microbial killing that characterizes CGD results from an inability of the NADPH oxidase system to rapidly generate toxic reactive oxygen species (ROS) by transferring electrons from NADPH to molecular O_2 (the "respiratory burst") after phagocytosis of a pathogen. Regardless of the gene affected in patients with CGD, having residual NADPH oxidase activity and the resultant ability to generate ROS is associated with less severe disease and longer survival[35].

NADPH oxidase activity results in the activation of antimicrobial proteases within the phagosome and the formation of microbicidal "neutrophil extracellular traps" (NETs)[36,37]. In addition to killing and degrading microorganisms, ROS produced by the NADPH oxidase system have roles in the induction of neutrophil apoptosis (which prevents tissue damage at sites of inflammation) and regulation of cytokine synthesis. Animal models of CGD have shown that a lack of ROS leads to excess inflammation via decreased regulatory T-cell activity,

GENETIC DEFECTS AFFECTING COMPONENTS OF THE PHAGOCYTE NADPH OXIDASE					
Disorder	**Gene**	**Protein**	**Location within NADPH oxidase**		**% of CGD patients**
			Resting state	**Active state**	
X-linked recessive chronic granulomatous disease	*CYBB*	gp91^{phox}	Membrane-bound subunits of flavocytochrome b_{558}	Same	70
Autosomal recessive chronic granulomatous disease	*CYBA*	p22^{phox}			≤5
	NCF1	p47^{phox}	Cytosolic complex	Associated with flavocytochrome b_{558}	20
	NCF2	p67^{phox}			≤5
	NCF4	p40^{phox}			Rare
Neutrophil immunodeficiency syndrome	*RAC2*	Rac2 GTPase*	Cytosolic complex with RhoGDI	Membrane- and GTP-bound	–

*Also has a role in actin cytoskeletal dynamics, integrin-dependent adhesion and neutrophil migration; see Table 60.12.

Table 60.9 Genetic defects affecting components of the phagocyte NADPH oxidase. CGD, chronic granulomatous disease; *NCF*, neutrophil cytosolic factor; RhoGDI, Rho GDP-dissociation inhibitor.

ORGANISMS THAT CAUSE INFECTIONS IN PATIENTS WITH CHRONIC GRANULOMATOUS DISEASE		
Type of organism	**Common causes**	**Less frequent causes**
Gram-positive bacteria	*Staphylococcus aureus**	*Propionibacterium* spp.
	Nocardia spp.	
Gram-negative bacteria	*Burkholderia cepacia*	*Acinetobacter* spp.
	Klebsiella spp.	Other *Burkholderia* spp.
	Serratia marcescens†	*Chromobacterium violaceum*
		Enterobacter spp.
		Escherichia coli
		Granulobacter bethesdensis
		Proteus spp.
		Pseudomonas spp.
		Salmonella spp.
Mycobacteria		*Mycobacterium tuberculosis*
		Atypical mycobacteria
Fungi	*Candida* spp.	*Paecilomyces* spp.
	Aspergillus spp.‡	*Penicillium* spp.
		Phaeohyphomycetes
		Trichosporon spp.

*Most common cause of cutaneous infections, abscesses and suppurative adenitis.
†Most common cause of osteomyelitis; also a frequent cause of cutaneous abscesses and ulcers.
‡Most common cause of pneumonia.

Table 60.10 Organisms that cause infections in patients with chronic granulomatous disease.

Fig. 60.7 Lupus erythematosus-like skin lesions in chronic granulomatous disease due to p47^{phox} deficiency. A biopsy specimen from an annular plaque showed findings typical of cutaneous lupus erythematosus. *Courtesy, Edward Cowen, MD.*

unrestrained γ/δ T-cell activity and augmented production of cytokines such as IL-8 and IL-17. Increased inflammasome activity leading to IL-1β production has also been identified in cells from CGD patients.

Clinical Features

The skin, perianal area, lymph nodes and lungs are the sites most often affected by CGD. In general, the X-linked form tends to be more severe than the autosomal recessive forms, with a younger mean age at diagnosis (3 years versus 8 years)[33]. Organisms that commonly cause infections in patients with CGD are listed in Table 60.10. Most carriers of CGD do not have an increased susceptibility to infections.

The earliest manifestations of CGD are usually staphylococcal infections of the skin around the ears and nose, which may begin in the neonatal period and progress to extensive purulent dermatitis with regional lymphadenopathy during infancy. Cutaneous abscesses occur in 40% of patients, usually due to *S. aureus* but also caused by *Serratia marcescens* infection, which can also present with large, poorly healing cutaneous ulcers[38]. Purulent inflammatory reactions may develop at sites of minor cutaneous trauma or regional lymph node drainage and heal slowly with scarring. Cutaneous granulomas, which are often nodular and necrotic, occur less frequently than infections. Seborrheic dermatitis, scalp folliculitis, acute or chronic cutaneous lupus erythematosus-like skin lesions (Fig. 60.7; especially discoid lesions), Sweet's syndrome, and ulcers involving the oral mucosa (resembling aphthous stomatitis), the perioral area and other cutaneous sites have also been described in patients with CGD. Female carriers of X-linked CGD occasionally present with discoid lesions, Jessner's lymphocytic infiltrate, photosensitivity, Raynaud's phenomenon, severe aphthous stomatitis and granulomatous cheilitis.

The extracutaneous organs most frequently involved in CGD are the lymph nodes, lungs, liver, spleen and gastrointestinal tract (Table 60.11). Suppurative lymphadenitis develops in half of patients, most often affecting cervical nodes and leading to abscess and fistula formation. Granulomas of the lungs, liver, spleen, and gastrointestinal and genitourinary tracts occur more frequently than those of the skin. These granulomas can lead to obstruction of the gastric outlet or urinary tract. Excessive inflammatory responses may also lead to wound dehiscence, pneumonitis, and clinical presentations that mimic inflammatory bowel disease, sarcoidosis, rheumatoid arthritis and IgA nephropathy[34,39].

Pathology

Common nonspecific abnormalities in CGD include leukocytosis, anemia, elevated ESR, hypergammaglobulinemia, a decreased number of T cells, and an abnormal chest radiograph. Skin testing for delayed-type hypersensitivity is normal, as are studies of phagocytosis and chemotaxis.

FREQUENCY OF SIGNS AND SYMPTOMS IN PATIENTS WITH CHRONIC GRANULOMATOUS DISEASE	
Symptom	**Percentage of patients**
Lymphadenopathy	90
Hepatosplenomegaly	85
Pneumonia	80
Underweight	75
Short stature	50
Persistent diarrhea and/or abdominal pain	40
Hepatic/perihepatic abscess	35
Pleuritis/empyema	35
Septicemia or meningitis	35
Osteomyelitis	25
Conjunctivitis and/or chorioretinitis	25
Facial periorificial dermatitis	20
Perianal abscess	15
Lung abscess	15
Ulcerative stomatitis	15
Peritonitis	10
Onset by age 1 year	65
Onset with lymphadenitis	25

Table 60.11 Frequency of signs and symptoms in patients with chronic granulomatous disease.

Biopsy specimens from cutaneous granulomas that develop in CGD patients demonstrate histiocytic infiltrates associated with foreign body giant cells and accumulation of neutrophils with necrosis. Lupus erythematosus-like skin lesions in CGD patients and carriers may have histologic features similar to classic discoid lesions, but they sometimes lack vacuolar degeneration of basal keratinocytes; immunofluorescence examination of lesional skin is negative in the majority of cases.

The screening test for CGD is the nitroblue tetrazolium (NBT) reduction assay. NBT is yellow in its soluble, oxidized form; when reduced, the dye precipitates and becomes blue (formazan precipitate). Only 5–10% of leukocytes from patients with CGD are able to reduce NBT during phagocytosis, compared to 80–90% of leukocytes from unaffected individuals and approximately 50% of leukocytes from carriers of X-linked CGD. The ferricytochrome c reduction and dihydrorhodamine 123 assays are more accurate and quantitative in measuring the respiratory burst, and they can be performed to verify the diagnosis of CGD[40]. Immunoblot analysis may demonstrate lack of the $gp91^{phox}$ and $p22^{phox}$ proteins; however, gene sequencing must still be done to ascertain which gene is affected, since mutations resulting in the absence of one protein lead to the absence of the other. A lack of the $p47^{phox}$, $p67^{phox}$, or $p40^{phox}$ protein by immunoblot analysis indicates the affected gene.

Differential Diagnosis

Laboratory tests allow differentiation of CGD from other immunodeficiency disorders characterized by increased susceptibility to bacterial infections. Additional inherited phagocyte disorders are listed in Table 60.12.

Treatment

The use of antibiotics has markedly reduced the morbidity and mortality rates of CGD. Although cutaneous and nodal infections are often readily apparent, localized foci of internal infection, (which may or may not be associated with fever) can be difficult to detect. Thorough periodic evaluation of the lungs, liver and bones by routine radiographs, ultrasounds or CT, MRI, positron emission tomography (PET) and bone scans often uncovers occult foci of inflammation or infection. Cultures should be performed to identify the infectious agent, and invasive procedures may be necessary to obtain adequate tissue samples. While awaiting culture results or in situations where material from the affected site cannot be obtained, patients with evidence of infection should be treated empirically with broad-spectrum parenteral antibiotics that cover *S. aureus* as well as Gram-negative bacteria. Intravenous therapy should be continued for at least 10–14 days, followed by a several-week course of oral antibiotics. Surgical interventions such as debridement, irrigation and prolonged drainage are important for deeper infections.

Chronic prophylaxis with trimethoprim–sulfamethoxazole has been shown to decrease the incidence of bacterial infection in CGD patients without increasing the incidence of fungal infections. The rate of *Aspergillus* spp. infections has been reduced by prophylaxis with itraconazole[41]. Patients with CGD have shown clinical improvement after administration of interferon-γ, which likely augments oxidant-independent antimicrobial pathways. Leukocyte transfusions have been used for rapidly progressive, life-threatening infections. Short courses of systemic corticosteroids have also been helpful for patients with obstructive granulomas of the bronchopulmonary, gastrointestinal or genitourinary tract[31].

Hematopoietic stem cell transplantation represents a potentially curative treatment for CGD, and its use for this condition has increased in recent years. Although younger patients without infection at the time of transplantation have the best outcomes (survival >90–95%), use of reduced-intensity conditioning regimens has enabled high-risk adults with recalcitrant fungal infections to be successfully transplanted. In children with a history of recurrent severe infections or corticosteroid-dependent inflammatory disease, especially those who have an HLA-identical family member, transplantation should be considered before irreversible organ damage occurs.

Gene therapy was initially performed in five adults with the $p47^{phox}$-deficient form of CGD, and a single infusion of transduced $CD34^+$ peripheral blood stem cells led to peak levels of corrected granulocytes in 3–6 weeks with persistence for as long as 6 months[42]. More recently, two young men with X-linked recessive CGD were treated with non-myeloablative conditioning prior to the infusion of $CD34^+$ peripheral blood stem cells transduced *ex vivo* with a retroviral vector expressing $gp91^{phox}$; this led to sustained engraftment of functionally corrected phagocytes. However, following initial resolution of infections, the transgene was silenced due to methylation of the viral promoter in both patients, and within 3 years they developed myelodysplasia with monosomy 7 as a result of insertional activation of ecotropic viral integration site 1 (*EVI1*)[43].

Dihydrorhodamine 123 flow cytometric studies may be utilized in determining the carrier status of the sisters and other female relatives of patients with X-linked CGD, which is important for genetic counseling prior to pregnancy. Prenatal diagnosis of CGD is also possible.

HYPERIMMUNOGLOBULIN E SYNDROMES

Synonyms: ■ Hyper-IgE syndromes ■ Job syndrome ■ Buckley syndrome

Key features

- Classic form is an autosomal dominant disorder characterized by extremely high immunoglobulin E levels
- Recurrent infections of the skin (particularly "cold abscesses") and sinopulmonary tract with S. *aureus* and, especially during infancy, *C. albicans*
- A neonatal papulopustular eruption is followed by severe atopic-like dermatitis
- Coarse facial features, osteopenia with fractures, scoliosis and dental abnormalities
- An autosomal recessive form with a broader spectrum of infectious complications also exists

Introduction

Hyperimmunoglobulin E syndrome (HIES) is characterized by recurrent cutaneous and sinopulmonary infections, dermatitis beginning in

OTHER INHERITED PHAGOCYTE DEFECTS				
Disorder	**Inh**	**Gene**	**Protein (defect or function)**	**Clinical features**
DISORDERS FEATURING NEUTROPENIA OR NEUTROPHIL DEFECTS				
Severe congenital neutropenia	AD	*ELA2*	Neutrophil elastase (abnormal elastase trafficking and accumulation)	• Neutropenia • MDS, AML
	AD	*GFI1*	Transcriptional repressor of elastase (abnormal elastase accumulation)	• Neutropenia, lymphopenia • Circulating myeloid progenitors
	AR	*HAX1*	Mitochondrial HS1-associated protein X1 (protects against apoptosis in myeloid cells)	• Neutropenia • Increased apoptosis of myeloid cells
	AD	*CSF3R*	Granulocyte colony-stimulating factor receptor	• Neutropenia • Severe myeloid hypoplasia
	AR	*G6PC3*	Glucose 6 phosphatase catalytic subunit 3 (glucose metabolism)	• Neutropenia, thrombocytopenia • Urogenital and cardiac malformations • Ectatic veins on trunk/extremities
Cyclic neutropenia	AD	*ELA2*	Neutrophil elastase	• Alternating 21-day cycles of neutropenia & monocytopenia • Fever and oral ulcers at nadir
X-linked neutropenia	XR	*WASP*	WASP (gain of function; see text, Wiskott–Aldrich syndrome)	• Neutropenia
p14 deficiency	AR	*MAPBPIP*	MAP binding partner 1-interacting protein (p14; endosomal biogenesis)	• Neutropenia • Pneumococcal infections • Diffuse pigmentary dilution of the skin and hair • Short stature, coarse facies
Shwachmann–Bodian–Diamond syndrome	AR	*SBDS*	SBDS protein (ribosomal RNA metabolism)	• Neutropenia > pancytopenia • MDS, AML • Exocrine pancreatic insufficiency • Chondrodysplasia
Specific granule deficiency	AR	*CEBPE*	C/EBPε transcription factor (granulocyte differentiation)	• Bilobed neutrophils • Recurrent bacterial infections
Myeloperoxidase deficiency	AR	*MPO*	Myeloperoxidase (microbial killing by granulocytes)	• *Candida* spp. and *S. aureus* infections • Often asymptomatic
LEUKOCYTE ADHESION DEFICIENCIES (LADS) AND RELATED CONDITIONS				
LAD-I	AR	*ITGB2*	β_2-integrin subunit of LFA-1, CR3, and p150 (see text)	• Neutrophilia; ↓ tissue neutrophils • Necrotic abscesses, ulcers • Poor wound healing, delayed umbilical stump separation • Gingivitis • Bleeding diathesis (LAD-III)
LAD-II	AR	*SLC35C1 (FUCT1)*	GDP-fucose transporter 1 (sialyl-Lewis X expression; see text)	
LAD-III	AR	*FERMT3*	Kindlin-3 (defective integrin activation; see text)	
Rac2 deficiency	AD	*RAC2*	Rac2 GTPase (NADPH oxidase, integrin-dependent adhesion, and neutrophil migration; see Table 60.9)	
DEFECTS RESULTING IN PREDISPOSITION TO SPECIFIC INFECTIONS				
Defects of the interleukin-12/interferon-γ axis	AR	*IL12B*	Subunit of IL-12 and IL-23 (stimulation of IFN-γ production)	• Severe mycobacterial and *Salmonella* infections • Disseminated BCG infection** • Viral infections (*STAT1, TYK2*) • Hyper-IgE syndrome (*TYK2*; see text)
	AR	*IL12RB1*	IL-12 and IL-23 receptor β1 chain	
	AR, AD	*IFNGR1*	IFN-γ receptor (ligand binding)	
	AR	*IFNGR2*	IFN-γ receptor (signaling)	
	AR, AD	*STAT1**	Signal transducer and activator of transcription 1 (STAT1)* (IFN receptor signaling is impaired by loss-of-function mutations)	
	AR	*TYK2*	Tyrosine kinase 2 (IFN/IL-12/other cytokine receptor signaling)	
Defects in Toll-like receptor (TLR) signaling	AD	*TLR3*	TLR3 (signals IFN-α/β production)	• Herpes simplex encephalitis
	AR	*UNC93B1*	UNC-93B (endoplasmic reticulum protein required for TLR3 signaling)	
	AR	*IRAK4*	IL-1 receptor associated kinase-4 (IL-1 receptor & TLR signaling)	• Recurrent pyogenic sinopulmonary and skin infections with *Streptococcus pneumoniae* and *S. aureus*, respectively
	AR	*MYD88*	Myeloid differentiation primary response gene 88 (recruits IRAK4 to the IL-1 receptor and TLRs)	

*Gain-of-function STAT1 mutations impair IL-17 immunity and lead to chronic mucocutaneous candidiasis; defects in STAT3 underlie AD hyper-IgE syndrome (see text), and defects in STAT5B (involved in IL-2 and growth hormone receptor signaling) lead to an AR syndrome of growth hormone insensitivity, decreased $CD4^+/CD25^+$ regulatory T cells, viral infections and eczematous dermatitis.

**Disseminated BCG infections have also been associated with mutations in the interferon regulatory factor 8 gene (*IRF8*; AD or AR inheritance), which impair the development of monocytes and dendritic cells. In addition, a deficiency in B and natural killer cells as well as monocytes and dendritic cells caused by heterozygous mutations in the *GATA2* gene (which encodes a transcription factor expressed in hematopoietic cells) is associated with susceptibility to mycobacterial infections and predisposition to leukemia/myelodysplasia.

Table 60.12 Other inherited phagocyte defects. See text and Tables 60.4 and 60.9 for Chédiak–Higashi syndrome and chronic granulomatous disease. AD, autosomal dominant; AML, acute myeloid leukemia; AR, autosomal recessive; BCG, bacillus Calmette-Guérin; IFN, interferon; IL, interleukin; Inh, inheritance; MAP, mitogen-activated protein kinase kinase 1; MDS, myelodysplastic syndrome; LFA-1, lymphocyte function-associated antigen-1; WASP, Wiskott–Aldrich syndrome protein; XR, X-linked recessive.

infancy or early childhood, and extremely elevated IgE levels[44]. Job syndrome is a subgroup of HIES that was originally described in female patients with fair skin, red hair and hyperextensible joints as well as the typical features of HIES.

Epidemiology

The classic form of HIES is inherited in an autosomal dominant fashion with variable expressivity. Many patients show a partial phenotype. Clinically distinct autosomal recessive forms of HIES (AR-HIES) have also been described[45–47].

Pathogenesis

Heterozygous mutations in the gene encoding *s*ignal *t*ransducer and *a*ctivator of *t*ranscription 3 (STAT3) cause autosomal dominant HIES[48,49]. Cytokine signals are transduced by different combinations of receptor-associated Janus kinases (JAKs) and STAT proteins; upon phosphorylation by JAKs, the latter dimerize, translocate to the nucleus and activate target genes. Susceptibility to bacterial and candidal infections in HIES reflects the roles of STAT3-dependent cytokines (e.g. IL-6, IL-21, IL-23) in the differentiation of IL-17-producing $CD4^+$ T cells (which help to defend against these organisms)[50]. A lack of stimulation of β-defensin production by IL-22 (which is produced by Th17 cells and signals via STAT3) may contribute to the development of infections at epithelial surfaces (e.g. skin, lungs) in HIES.

Because STAT3 is critical to the signaling pathways for IL-6 (which promotes acute phase responses and acts as a pyrogen) and IL-10 (an anti-inflammatory cytokine), STAT3 dysfunction can explain the "cold" abscesses and destructive inflammation (e.g. in the lung) that characterize HIES. Defective generation of IL-10-induced tolerogenic dendritic cells and $FOXP3^+$-induced regulatory T cells may contribute to other inflammatory features of HIES, such as the atopic-like dermatitis and high IgE levels[51]. STAT3 also down-regulates differentiation of osteoclasts, and osteoporosis represents a feature of STAT3 deficiency in mice as well as HIES. Lastly, leukocytes from both STAT3-deficient animals and patients with HIES produce higher levels of interferon-γ and tumor necrosis factor (TNF)-α upon stimulation with IL-12 and lipopolysaccharide/interferon-γ, respectively, than do leukocytes from unaffected controls[48,49].

Homozygous mutations in the gene encoding tyrosine kinase 2 (TYK2), a member of the JAK family, were identified in a patient with a form of AR-HIES characterized by defects in signaling pathways for IL-12 and interferon-α/β (see Table 60.12) as well as IL-6 and IL-10[52]. This patient presented with elevated serum IgE levels, eczematous dermatitis and recurrent bacterial (including *Salmonella*), mycobacterial, fungal and viral infections. Biallelic mutations in the dedicator of cytokinesis 8 protein (*DOCK8*) gene cause another type of AR-HIES (see below)[46,47]. The DOCK8 protein, a member of the DOCK180-related family of atypical guanine nucleotide exchange factors, is thought to regulate cytoskeletal rearrangements that have important roles in immune functions such T-cell expansion and antibody responses.

The dermatitis of HIES shares several immunopathologic features with atopic dermatitis, including reactivity against *S. aureus*, abnormal cytokine responses and increased levels of IgE. The expression of IgE in patients with HIES is maximally activated and does not increase further upon IL-4 administration; in contrast, IL-4 has a stimulatory effect on IgE production in both atopic dermatitis patients and normal individuals.

Clinical Features

Patients with classic HIES typically present during the first month of life with a non-infectious, folliculocentric papulopustular eruption involving the face, scalp, neck, axillae and diaper area[53,54]. Chronic candidiasis of the oral mucosa, periungual areas and nails occurs in approximately 80% of HIES patients and may represent the initial infectious manifestation during infancy.

Cutaneous staphylococcal infections include impetiginized plaques and retroauricular fissures, folliculitis, furunculosis, abscesses, cellulitis, lymphangitis, and paronychia leading to nail dystrophy[54]. The cutaneous abscesses are often large, and they most commonly involve the neck, scalp (Fig. 60.8), periorbital area, axillae and groin. Such lesions are referred to as "cold abscesses" because they are not as red or tender as those that develop in healthy individuals. Patients are often afebrile or have only a low-grade fever. Although the abscesses tend to be staphylococcal, many patients have recurrent skin infections with other organisms, including *Str. pyogenes* as well as *C. albicans.*

Fig. 60.8 Hyperimmunoglobulin E syndrome. Several erythematous, slightly purulent "cold" abscesses are apparent on the forehead and scalp of this infant.

The eczematous rash of HIES shares many clinical features with atopic dermatitis, including severe pruritus, lichenification and staphylococcal superinfection[54]. It is virtually always present in young children with classic HIES but frequently clears by adolescence. Unlike individuals with atopic dermatitis, patients with HIES do not commonly exhibit allergic rhinitis, asthma or other cutaneous signs of atopy.

Although some HIES patients have only cutaneous manifestations, most also develop recurrent bronchitis and pneumonias. Pulmonary infections are usually caused by *S. aureus* and *Haemophilus influenzae*, and they may result in empyema, bronchiectasis and pneumatocele formation. The pneumatoceles tend to persist and become the site of further infections with bacterial or fungal organisms, particularly *Aspergillus* spp. Massive hemoptysis occasionally ensues. *Pneumocystis jiroveci* pneumonia can also occur in infants and children with HIES. Other common sites of infection include the ears, oral mucosa, sinuses and eyes. Visceral infections other than pneumonia are unusual.

Due to both bony defects and the deforming effects of chronic facial abscesses, HIES patients develop progressive facial coarsening with thickened doughy skin, large follicular ostia, pitted scarring, a broad nasal bridge, a wide fleshy nasal tip, deep-set eyes, a prominent forehead, and irregularly proportioned cheeks and jaw. Osteopenia is frequently present and is associated with an increased risk of fractures of the long bones, ribs and pelvis. More than half of adolescents and adults with HIES have had at least three fractures, often due to unrecognized or minor trauma. Scoliosis occurs in 75% of patients 16 years of age or older, and hyperextensibility of joints has been reported in 70% of patients. Approximately half of individuals with HIES have a high-arched palate, and dental abnormalities associated with HIES include retention of primary teeth (due to failure of root resorption) and lack of eruption of secondary teeth. Additional manifestations include brain abnormalities (e.g. Chiari malformations, lacunar infarctions, focal hyperintensities in white matter on T2-weighted MRI sequences) and the development of coronary artery aneurysms in adulthood. HIES is associated with an increased risk of non-Hodgkin lymphoma of B-cell origin

AR-HIES due to *DOCK8* mutations shares some features with classic HIES, including highly elevated serum IgE levels, peripheral eosinophilia, chronic eczematous dermatitis (Fig. 60.9A), and recurrent staphylococcal and candidal infections of the skin (including cold abscesses) and respiratory tract[45–47]. However, these AR-HIES patients do not present with skeletal and dental abnormalities or pneumatoceles, but instead develop severe viral (e.g. warts, herpes simplex, varicella–zoster and molluscum contagiosum; Fig. 60.9B) and opportunistic infections, asthma, allergies resulting in anaphylaxis,

Fig. 60.9 Autosomal recessive hyperimmunoglobulin E syndrome due to DOCK8 deficiency. A Widespread eczematous dermatitis. **B** Extensive molluscum contagiosum. *Courtesy, Edward Cowen, MD.*

autoimmunity, central nervous system vasculitis, mucocutaneous squamous cell carcinomas and lymphomas.

Pathology

All HIES patients, by definition, have markedly elevated serum levels of polyclonal IgE, usually peaking at >2000 IU/ml and sometimes declining during adulthood. Patients develop particularly high levels of anti-staphylococcal and anti-candidal IgE antibodies and often have immediate wheal-and-flare reactions to a variety of foods and environmental allergens. Many affected individuals also have eosinophilia of the peripheral blood and sputum. Cell-mediated immunity is often abnormal, as manifested by anergy to skin testing and impaired *in vitro* lymphoproliferative responses to specific antigens. Serum levels of IgG, IgA and IgM are usually normal in classic HIES, as are lymphocyte subsets. In contrast, AR-HIES due to DOCK8 deficiency features a combined immunodeficiency that is characterized by lymphopenia (deficiency of $CD4^+$ T cells > $CD8^+$ T cells > B cells), low IgM levels and variable IgG levels as well as elevated IgE levels and peripheral eosinophilia[46,47].

The infantile papulopustular eruption of HIES is characterized histologically by eosinophilic folliculitis, eosinophilic spongiosis, and a superficial and deep perivascular infiltrate with abundant eosinophils[53,54].

Differential Diagnosis

Diagnostic guidelines for classic HIES have recently been proposed[55], with criteria including IgE >1000 IU/ml and a weighted score of five clinical features (Table 60.13); these characteristics plus a lack of Th17 cells or the detection of a heterozygous *STAT3* mutation allow for a probable or definitive diagnosis, respectively.

HIES must be differentiated from a number of other disorders that feature elevated IgE levels and a cutaneous eruption, including atopic dermatitis, Wiskott–Aldrich syndrome, Netherton syndrome, Omenn syndrome, DiGeorge syndrome, IPEX syndrome and GVHD. Atopic dermatitis and Wiskott–Aldrich syndrome are most easily confused with HIES because they present with eczematous dermatitis and staphylococcal infections. However, the development of cold abscesses, recurrent pneumonia, coarse facial features and osteopenia help to differentiate HIES from these disorders, and Wiskott–Aldrich syndrome can be distinguished by the associated platelet abnormalities. In a recent series of pediatric patients who had a serum IgE level of >2000 IU/ml, 69% (48/70) had atopic dermatitis and only 8% (6/70) had HIES; no correlation was observed between the IgE level and diagnosis of HIES[56]. Elevated IgE levels, susceptibility to pyogenic infections and eczematous dermatitis have also been described in patients with prolidase deficiency, an autosomal recessive condition due to *PEPD* mutations that also features chronic leg ulcers, facial dysmorphism and mental retardation. Lastly, patients with chronic granulomatous disease

DIAGNOSTIC GUIDELINES FOR HYPERIMMUNOGLOBULIN E SYNDROME DUE TO *STAT3* MUTATIONS							
Clinical finding	**Points**						**Multiplication factor**
	0	**2**	**4**	**5**	**6**	**8**	
Pneumonias (X-ray proven, total #)	none	1	2	–	3	>3	2.5
Newborn papulopustular eruption*	absent	–	present	–	–	–	2.1
Pathologic bone fractures	none	–	1–2	–	–	>2	3.3
Characteristic facies	absent	mild	–	present	–	–	3.3
High-arched palate	absent	present	–	–	–	–	2.5
Possible HIES: IgE >1000 IU/ml *plus* weighted score of >30 **Probable HIES**: As above plus lack of Th17 cells† or a family history of definitive HIES **Definitive HIES:** As above plus a dominant-negative heterozygous mutation in *STAT3*							
*In the first 3 weeks of life. †IL-17-producing $CD4^+$ T cells; in the peripheral blood by flow cytometry.							

Table 60.13 Diagnostic guidelines for hyperimmunoglobulin E syndrome (HIES) due to *STAT3* mutations[55].

and myeloperoxidase deficiency develop bacterial and candidal abscesses, but they do not typically have markedly elevated levels of IgE.

Treatment

Treatment of the infectious complications of HIES includes incision and drainage of abscesses as well as therapeutic and prophylactic administration of antibiotics. Interferon-γ has been shown to help control infections, and IVIg may improve the dermatitis, prevent infections and lower IgE levels. In anecdotal reports, treatment with omalizumab (a monoclonal antibody that targets IgE) improved the eczematous dermatitis of HIES.

IMMUNOGLOBULIN DEFICIENCIES

Synonyms: ■ X-linked agammaglobulinemia ■ Bruton agammaglobulinemia ■ Bruton–Gitlin syndrome ■ Congenital hypogammaglobulinemia ■ X-linked hypogammaglobulinemia

Key features

Agammaglobulinemia

- The inheritance pattern is X-linked recessive in 90% of patients and autosomal recessive in 10%
- Recurrent bacterial infections begin in the first few years of life

Common variable immunodeficiency (CVID)

- Heterogeneous group of disorders with defects in both humoral and cell-mediated immunity
- May manifest during childhood or adulthood, with clinical onset at an average age of 30 years
- Variable severity of infectious and autoimmune complications

Selective IgA deficiency

- Most common immunoglobulin deficiency, but usually asymptomatic, with clinical manifestations in only 10–15% of affected individuals
- Bacterial sinopulmonary infections and autoimmune disorders may occur

Hyper-IgM syndromes

- Usually has an X-linked recessive inheritance pattern, but autosomal recessive forms also exist
- Recurrent sinopulmonary and gastrointestinal infections with pyogenic bacteria and opportunistic organisms
- Oral ulcerations and verrucae may develop

The most common immunoglobulin deficiency is selective IgA deficiency, found in 1:500 persons with an equal sex distribution. Panhypogammaglobulinemia has a prevalence of 1:25 000, with X-linked agammaglobulinemia[54] (affecting primarily boys) and common variable immunodeficiency[57] (CVID; no sexual predilection) representing the most frequent forms. The clinical onset of CVID (average age 30 years) is typically later than that of X-linked agammaglobulinemia (often during the first few years of life, after levels of maternal antibodies wane at ~6 months of age). Approximately 15% of patients with CVID have family members with selective IgA deficiency. The pathogenesis and clinical features of immunoglobulin deficiencies[57–62] are presented in Figure 60.10 and Table 60.14.

The treatment of hypogammaglobulinemia is antibody replacement by IVIg or subcutaneous immunoglobulins and antibiotic therapy for infections. However, IVIg and other blood products containing IgA should be avoided in individuals with profound IgA deficiency, who may develop anti-IgA antibodies; fatal anaphylactic reactions have been reported. Recalcitrant non-infectious granulomas (cutaneous and extracutaneous) in patients with CVID may respond to treatment with TNF-α inhibitors.

Female carriers of X-linked agammaglobulinemia may be detected via examination of B-cell X-inactivation patterns, which show skewing towards cells with inactivation of the mutated X chromosome. DNA-based prenatal diagnosis is possible when the genetic defect in affected family members has been identified.

IPEX SYNDROME

Key features

- X-linked recessive disorder due to mutations in the *FOXP3* gene
- Cutaneous findings include a widespread eczematous dermatitis during infancy and a variety of autoimmune skin conditions
- Also features enteropathy and endocrinopathies with autoimmune etiologies

IPEX (*i*mmune dysregulation, *p*olyendocrinopathy, *e*nteropathy, *X*-linked) syndrome is an X-linked recessive disorder caused by *FOXP3* gene mutations that result in abnormal development of regulatory T cells. Affected individuals typically present during infancy with severe diarrhea secondary to autoimmune enteropathy and develop a variety of autoimmune endocrinopathies (e.g. early-onset type 1 diabetes mellitus, thyroiditis, cytopenias). Most IPEX patients have a widespread eczematous dermatitis and elevated IgE levels during early infancy, and this is often complicated by staphylococcal superinfections and sepsis. Cutaneous manifestations of IPEX can also include psoriasiform dermatitis, cheilitis, nail dystrophy, and autoimmune skin conditions such as alopecia areata, chronic urticaria and bullous pemphigoid[63]. Autoimmune endocrinopathies, enteropathy and eczematous dermatitis have also been described in patients with IL-2 receptor α-chain (CD25) deficiency[64] (see Table 60.3) In addition, an autosomal recessive disorder due to mutations in the *ADAM17* gene encoding the TNF-α converting enzyme features a widespread psoriasiform dermatitis with pustular flares, brittle hair, staphylococcal skin infections and chronic diarrhea[64a].

LEUKOCYTE ADHESION DEFICIENCY

Key features

- Gingivitis and periodontitis
- Necrotic ulcerations clinically resembling pyoderma gangrenosum
- Poor wound healing; delayed separation of the umbilical stump
- Life-threatening bacterial and fungal infections

Introduction

Leukocyte adhesion deficiency (LAD) comprises three autosomal recessive disorders that affect the ability of neutrophils, monocytes and lymphocytes to adhere to the vascular endothelium and migrate to sites of infection and tissue injury[65,66].

Pathogenesis

Leukocyte adhesion requires a group of integrins (cell surface glycoproteins) that share a common 95 kDa β_2-subunit known as CD18. The β_2-subunit can be linked to different a chains to form three distinct cell surface glycoproteins: (1) lymphocyte function antigen 1 (LFA-1; CD11a); (2) complement receptor type 3 (CR3; $iC3_b$ receptor; Mac-1, CD11b); and (3) p150,95 (complement receptor type 4; CD11c). The primary ligand for these glycoproteins is intercellular adhesion molecule-1 (ICAM-1), which participates in the initiation and evolution of localized inflammation in the skin and other tissues. LAD-I is caused by mutations in the *ITGB2* gene that encodes CD18, and it manifests with dysfunction of all three glycoproteins. This leads to profound impairment of leukocyte firm adhesion to the vascular endothelium and mobilization into extravascular sites of inflammation, as well as defective neutrophil and monocyte chemotaxis and phagocytosis.

LAD-II is due to mutations in the *FUCT1* gene, which encodes a GDP-fucose transporter that is required for formation of sialyl-Lewis X

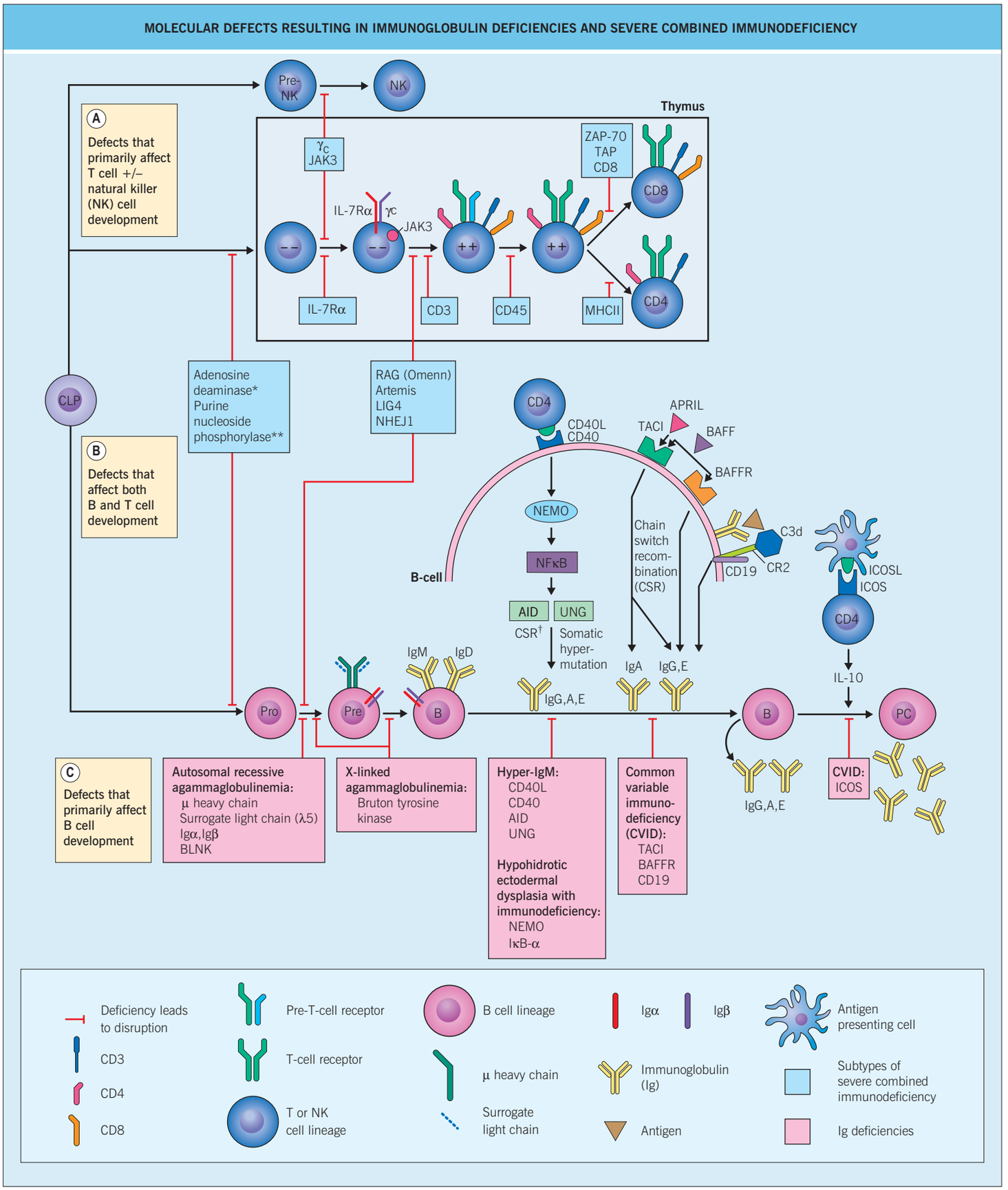


Fig. 60.10 Molecular defects resulting in immunoglobulin deficiencies and severe combined immunodeficiency (SCID). *Also important for B-cell maturation in germinal centers. **Affects T cells more than B cells. †Switch from IgM to IgG, IgA or IgE. AID, activation-induced cytidine deaminase; APRIL, *a pro*liferation-*i*nducing *l*igand; BAFF(R), B-cell activating factor (receptor); BLNK, B-cell linker protein (binds Bruton tyrosine kinase); CD40L, CD40 ligand; CLP, common lymphoid precursor; CR2, complement receptor 2; γ_c, common γ chain; ICOS(L), inducible costimulator on activated T cells (ligand); IκB-α, inhibitor of κB-α; IL, interleukin; IL-7Rα, IL-7 receptor α-chain; MHC, major histocompatibility complex; NEMO, NF-κB essential modulator; NHEJ1, non-homologous end-joining 1; NK, natural killer cell; PC, plasma cell; TACI, transmembrane activator and CAML interactor; TAP, transporter associated with antigen processing; UNG, uracil-DNA glycosylase; –, double-negative thymocyte; ++, double-positive thymocyte.

PRIMARY IMMUNOGLOBULIN DEFICIENCY DISORDERS						
Disorder	**Gene**	**Protein (function)**	**Ig levels**	**B cells**	**Infectious and systemic manifestations**	**Cutaneous manifestations**
BLOCK IN B-CELL DIFFERENTIATION AT THE PRO-B- TO PRE-B-CELL TRANSITION						
X-linked agammaglobulinemia	*BTK*	Bruton tyrosine kinase (pre-B-cell receptor [BCR] signaling)	All ↓	↓↓	• Recurrent infections with *Staphylococcus, Streptococcus, Pneumococcus, Haemophilus* and *Pseudomonas* spp. • Hepatitis B and enteroviral infections • Lymphomas (~5%)	• The skin is the most common site of infection – Furuncles and cellulitis – Ecthyma gangrenosum • Eczematous dermatitis • Papular dermatitis due to lymphohistiocytic infiltration • Non-infectious granulomas • Dermatomyositis-like disorder associated with chronic echoviral meningoencephalitis
AR agammaglobulinemia	*IGHM*	μ heavy chain of IgM (component of pre-BCR)				
	CD79A, CD79B	Igα chain, Igβ chain (bind μ heavy chain)				
	IGLL1	λ5 (surrogate light chain of pre-BCR)				
	BLNK	B-cell linker protein (binds Bruton tyrosine kinase)				
AD agammaglobulinemia	*LRRC8A*	Leucine-rich repeat-containing 8 family member A				
DEFECTIVE CLASS SWITCH RECOMBINATION (E.G. FROM IGM TO IGG, IGA OR IGE) AND SOMATIC HYPERMUTATION*						
Common variable immunodeficiency (CVID)†	*ICOS*	Inducible co-stimulator on activated T cells (T-cell help for B-cell differentiation)	IgG,A ↓; ± IgM ↓	NI or ↓	• Bacterial sinopulmonary infections (organisms similar to X-linked agammaglobulinemia) • *Giardia* spp. gastroenteritis • Autoimmune diseases, especially hemolytic anemia and idiopathic thrombocytopenic purpura • Increased risk of cancer (10-fold overall) and lymphoma (400-fold)	• Pyodermas and mucocutaneous candidiasis • Extensive warts and dermatophyte infections • Eczematous dermatitis • Non-infectious granulomas (may also involve the lungs, liver and spleen) • Autoimmune conditions such as vitiligo, alopecia areata and vasculitis • Clonal $CD8^+$ lymphocytic infiltration of the skin
	TNFRSF13B (AD or AR)	Transmembrane activator and CAML interactor (TACI; B-cell isotype switching)				
	TNFRSF13C	B-cell activating factor receptor (BAFFR; B-cell isotype switching)				
	CD19‡	CD19 antigen (B-cell survival and differentiation)				
	MSH5 (AD)	Mismatch repair protein (regulates class switch recombination)				
Selective IgA deficiency	*TNFRSF13B* (AD)	See above section	IgA ↓§; anti-IgA antibodies in ~half	NI	• Clinical manifestations in 10–15% • Similar to CVID	• Mucocutaneous candidiasis • Eczematous dermatitis • Autoimmune conditions such as SLE, vitiligo and lipodystrophia centrifugalis abdominalis
	MSH5 (AD)					
Selective IgM deficiency	?	?	IgM ↓	NI	• Recurrent bacterial infections • Autoimmune diseases	• Extensive warts • Eczematous dermatitis • SLE
X-linked hyper-IgM syndrome	*CD40LG*	CD40 ligand (on T cells)	IgM ↑; isohemagglutinins ↑; IgA,E,G ↓↓	NI	• Recurrent sinopulmonary and GI infections with pyogenic bacteria and opportunistic organisms (e.g. PCP)	• Pyodermas • Extensive warts • Oral (Fig. 60.11) and anogenital ulcers
AR hyper-IgM syndromes	*CD40*	CD40 (on B cells)				
	AICDA	Activation-induced cytidine deaminase			• As above, but massive LAN (with germinal centers), HSM and no	• Pyodermas
	UNG	Uracil-DNA glycosylase				

†Heterogeneous group of disorders with defects primarily in humoral but also involving cell-mediated immunity; TNFRSF13b is the most common of the underlying genetic defects identified to date, accounting for approximately 10% of CVID.
‡*CD81* is required for CD19 expression, and a homozygous mutation in the CD81 gene was reported in a patient with hypogammaglobulinemia and autoimmune vasculitis. Of note, a homozygous loss-of-function mutation in the *MS4A1* gene that encodes CD20 can result in recurrent sinopulmonary infections associated with low IgG levels, a normal total number of B cells, decreased memory B cells and poor T cell-independent antibody responses.
§Symptomatic patients often develop the immunodeficiency pattern of CVID.

Table 60.14 Primary immunoglobulin deficiency disorders. Autosomal recessive (AR) unless otherwise specified. AD, autosomal dominant; CAML, calcium-modulating cyclophilin ligand; GI, gastrointestinal; HSM, hepatosplenomegaly; Ig, immunoglobulin; *IKBKG*, inhibitor of κ light polypeptide gene enhancer in B cells, kinase γ; LAN, lymphadenopathy; MR, mental retardation; NI, normal; PCP, *Pneumocystis jiroveci* pneumonia; SLE, systemic lupus erythematosus.

Continued

Disorder	Gene	Protein (function)	Ig levels	B cells	Infectious and systemic manifestations	Cutaneous manifestations
PRIMARY IMMUNOGLOBULIN DEFICIENCY DISORDERS						
Hypohidrotic ectodermal dysplasia with immunodeficiency	*IKBKG (NEMO)* (X-linked recessive)	NF-κB essential modulator (activates NF-κB, which is involved in CD40 signaling)	IgM ↑; ± IgA ↑; ± IgG ↓	NI	• Pyogenic bacterial and opportunistic infections • Subset of *NEMO* patients with osteopetrosis and lymphedema	• Pyodermas • Ectodermal dysplasia (see Ch. 62)
	IKBA (*NFKBIA*; AD, gain of function)	Inhibitor of κB-α (inhibits NF-κB)				
ABNORMAL DNA METHYLATION LEADING TO DEFECTIVE B-CELL NEGATIVE SELECTION AND TERMINAL DIFFERENTIATION						
*I*mmunodeficiency, centromeric instability, and *f*acial anomalies (ICF) syndrome	*DNMT3B*	DNA methyltransferase 3β	All ↓	NI or ↓	• Bacterial sinopulmonary and GI infections • Abnormal facies, MR	• Telangiectasias (uncommon) • Nevoid hyperpigmentation
ABERRANT CHEMOKINE SIGNALING						
WHIM syndrome[¶]	*CXCR4* (AD, gain-of-function)	CXC chemokine receptor 4 (binds CXCL12; key role in bone marrow homeostasis and lymphocyte trafficking)	IgG ↓; ± IgA,M ↓	↓	• Recurrent bacterial sinopulmonary infections • Myelokathexis (mature neutrophils fail to exit the bone marrow)	• Cellulitis and pyodermas • Extensive verruca vulgaris and condyloma acuminata (Fig. 60.12)
DELAYED MATURATION OF HELPER T-CELL FUNCTION						
Transient hypogammaglobulinemia of infancy	?	?	IgG,A ↓ (resolves by age 3 y)	NI	• Failure to thrive in infancy • Recurrent sinopulmonary and GI infections	• Recurrent pyodermas and abscesses

[*]T-cell priming may also be defective, particularly in CD40–CD40L disorders (leading some authors to classify the latter as subtypes of severe combined immunodeficiency).
[¶]Warts, hypogammaglobulinemia, infections and myelokathexis; treatment with plerixafor (AMD 3100) , a CXCR4 antagonist, is under investigation.

Table 60.14 Primary immunoglobulin deficiency disorders (cont'd). Autosomal recessive (AR) unless otherwise specified. AD, autosomal dominant; GI, gastrointestinal; Ig, immunoglobulin; *IKBKG*, inhibitor of κ light polypeptide gene enhancer in B cells, kinase γ; MR, mental retardation; NI, normal.

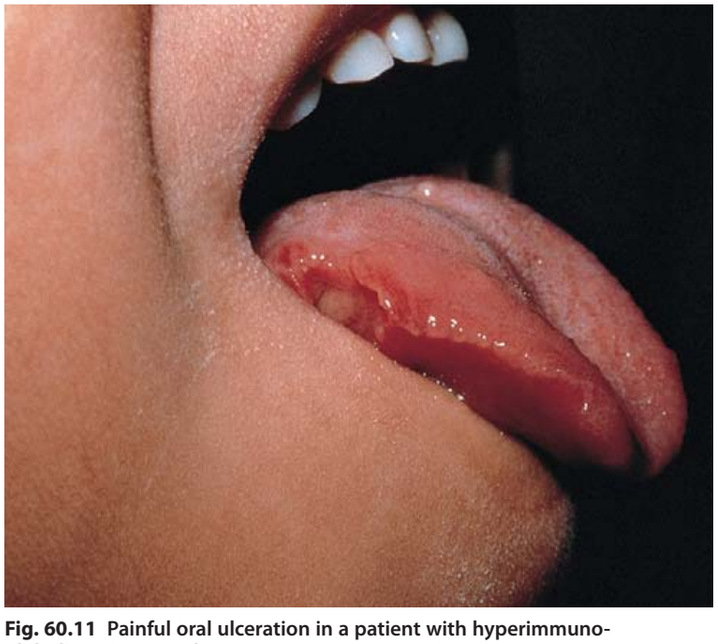


Fig. 60.11 Painful oral ulceration in a patient with hyperimmunoglobulinemia M syndrome. *Reprinted with permission from Schachner L, Hansen R, eds. Pediatric Dermatology, 4th edn. London: Mosby, 2011.*

Fig. 60.12 Extensive, recalcitrant perianal warts in a child with WHIM syndrome. *Courtesy, Edward Cowen, MD.*

(the fucosylated ligand for selectins) on the surface of leukocytes[67]. This causes a defect in the initial steps of tethering and rolling of leukocytes on the endothelial cell surface (via interaction of sialyl-Lewis X on leukocytes with E- or P-selectin on endothelial cells) that are required for their targeting to sites of infection and inflammation.

In order to undergo firm adhesion and subsequently extravasate from the bloodstream, circulating leukocytes must activate integrins *in situ* to rapidly increase their affinity and avidity for endothelial ligands. Patients with LAD-III have impaired integrin activation in hematopoietic cells, which leads to impaired leukocyte β_1- and platelet β_3-integrins in addition to leukocyte β_2-integrins as in LAD-I. It is caused by loss-of-function mutations in the *FERMT3* gene that encodes kindlin-3, an effector of integrin activation in hematopoietic cells[68].

Clinical Features

The most common manifestation of LAD is gingivitis with periodontitis, which often leads to the loss of teeth. Minor injuries to the skin

Fig. 60.13 A 7-year-old boy with leukocyte adhesion deficiency type I was scratched by his sister, resulting in a large gaping wound that healed poorly. *Reprinted with permission from Schachner L, Hansen R, eds. Pediatric Dermatology, 4th edn. London: Mosby, 2011.*

may rapidly expand to form large, chronic ulcerations (Fig. 60.13) that can resemble "burnt out" pyoderma gangrenosum. Poor wound healing also results in paper-thin, atrophic scars. A history of delayed separation of the umbilical stump represents a clue to the diagnosis.

Patients with LAD develop recurrent otitis media, pneumonia and cutaneous infections caused by pyogenic bacteria. The latter often present as cellulitis and necrotic abscesses with relatively little production of purulent material, typically located in the perianal area or on the face. Life-threatening bacterial, fungal or (less frequently) viral infections may also occur. More than three-quarters of patients with severe LAD-I (<1% of normal CD18 levels) die within the first 5 years of life, whereas approximately half of patients with moderate disease (1–10% of normal CD18 levels) live to age 30 years[66].

Additional clinical manifestations of LAD-II include mental retardation, microcephaly, hypotonia, short stature and distinctive facies[67]. Patients with LAD-III often present with a bleeding tendency, developmental delay, osteopetrosis and hepatosplenomegaly. Dermal hematopoiesis with a "blueberry muffin" appearance secondary to myelodysplastic syndrome has been described in infants and children with LAD-III[69].

Pathology

Individuals with LAD have marked *peripheral blood neutrophilia* (5–20 times normal levels). Although cutaneous ulcerations may resemble pyoderma gangrenosum clinically, histologic examination reveals a relative *paucity of tissue neutrophils*. Flow cytometric analysis reveals markedly decreased leukocyte CD18 expression in individuals with LAD-I. Patients with LAD-II have the Bombay red blood cell type due to a lack of the H blood group antigen, and those with LAD-III have abnormal platelet aggregation (reflecting defective activation of β_3-integrin) and (less often) anemia.

Differential Diagnosis

A mutation in the gene encoding the Rac2 GTPase, which has a role in phagocyte NADPH oxidase activation as well as integrin-dependent adhesion and neutrophil migration, can lead to clinical features similar to those of LAD, including delayed separation of the umbilical stump, poor wound healing, neutrophilia, and recurrent perirectal abscesses with an absence of pus (see Tables 60.9 & 60.12).

Treatment

Soft tissue infections in LAD patients require prolonged courses of antimicrobial therapy and, in some cases, surgical debridement. Meticulous dental hygiene is important in reducing the severity of the periodontitis. Oral administration of fucose may improve immune function in patients with LAD-II[67], and healing of chronic ulcers following IVIg administration to a patient with LAD-I has been reported. Hematopoietic stem cell transplantation represents the only definitive therapy for LAD, but it is limited by infectious complications and GVHD. Two patients with severe LAD-I were treated without prior conditioning with an infusion of autologous hematopoietic stem cells that had been corrected *ex vivo* with a retroviral vector encoding CD18, but circulating $CD18^+$ cells persisted for less than 2 months[66]. However, canine LAD-I has been successfully treated with non-myeloablative conditioning followed by infusion of autologous hematopoietic stem cells transduced *ex vivo* by a CD18-expressing foamy virus vector (which has less potential for genotoxicity than a retroviral vector); this led to complete reversal of the LAD phenotype that was sustained for more than 2 years[70].

SEVERE COMBINED IMMUNODEFICIENCY

Synonyms: ■ Severe combined immunodeficiency (SCID) syndrome ■ Severe mixed immunodeficiency syndrome ■ Glanzmann–Riniker syndrome ■ Alymphocytosis ■ Thymic alymphoplasia

Key features

- Recurrent infections, diarrhea and failure to thrive within the first 3–6 months of life
- Risk of GVHD, especially from unirradiated blood products
- Lack of lymphoid tissue
- Deficiencies of T, B and/or NK cells

Introduction

Severe combined immunodeficiency (SCID) is a heterogeneous group of disorders that share clinical manifestations related to defective function of both cell-mediated and humoral immunity[71,72] (Table 60.15).

Epidemiology

SCID occurs in 1:30 000 to 1:100 000 live births. Three-quarters of affected patients are boys. More than 40% of cases have X-linked recessive inheritance, most due to defects in the gene encoding the common γ (γ_c) chain of the IL-2 receptor, and the remainder are autosomal recessive. Approximately 20% of cases occur because of adenosine deaminase (ADA) deficiency, and 6% result from *JAK3* mutations.

Pathogenesis

Molecular defects that can lead to the SCID phenotype are presented in Figure 60.10 and Table 60.15.

Clinical Features

Infants with SCID may present with widespread seborrheic-like dermatitis or morbilliform eruptions, often reflecting maternofetal GVHD. Cutaneous eruptions may also resemble lichen planus, acrodermatitis enteropathica, Langerhans cell histiocytosis, ichthyosiform erythroderma and scleroderma. Extensive eczematous dermatitis or erythroderma, often with alopecia, may occur outside the setting of GVHD in infants with Omenn syndrome, which also features hepatosplenomegaly and peripheral eosinophilia.

Recurrent infections, chronic diarrhea and failure to thrive are apparent within the first few months of life. Common early infections include mucocutaneous candidiasis, persistent viral gastroenteritis, and pneumonias due to bacteria, viruses or *Pneumocystis jiroveci*. Cutaneous infections are most often caused by *C. albicans, S. aureus* and *Str. pyogenes*. Despite recurrent infections, patients with SCID typically lack tonsillar buds and palpable lymphoid tissue. SCID due to ADA deficiency is associated with an increased risk of developing dermatofibrosarcoma protuberans (often multiple and morpheaform) during the first two decades of life[72a].

CLASSIFICATION OF SEVERE COMBINED IMMUNODEFICIENCY			
Disorder	**Gene**	**Protein function**	**Cells**
DEFECTS IN CYTOKINE RECEPTORS AND THEIR SIGNALING			
X-linked SCID*	*IL2RG*	Common γ chain (γ_c) of the receptors for IL-2, 4, 7, 9, 15 and 21	$T^-/B^+/NK^-$
JAK3 deficiency	*JAK3*	Tyrosine kinase with a role in signal transduction via the receptors for IL-2, 4, 7, 9, 15, and 21	$T^-/B^+/NK^-$
Interleukin-7 receptor deficiency†	*IL7R*	α-chain of the IL-7 receptor; critical for development and differentiation of T cells	$T^-/B^+/NK^+$
INCREASED APOPTOSIS OF LYMPHOCYTES ± OTHER HEMATOPOIETIC CELLS			
Defects in purine pathway enzymes that result in the build-up of toxic metabolites			
Adenosine deaminase (ADA) deficiency*	*ADA*	Enzyme in the purine salvage pathway‡	$T^-/B^-/NK^-$
Purine nucleoside phosphorylase (PNP) deficiency	*PNP*	Enzyme in the purine salvage pathway (downstream of ADA)‡	$T^-/B^-/NK^-$
Defects disrupting mitochondrial energy production			
Reticular dysgenesis (aleukocytosis)	*AK2*	Adenylate kinase 2, a mitochondrial enzyme that regulates ADP levels in leukocytes; profound neutropenia and sensorineural deafness	$T^-/B^-/NK^-$
Defects disrupting actin polymerization			
Coronin 1A deficiency	*CORO1A*	Actin regulator expressed in T-cell precursors	$T^-/B^+/NK^+$
DEFECTS IN (PRE-)T-CELL RECEPTORS (TCRS) ± B-CELL RECEPTORS (BCRS) AND THEIR SIGNALING			
Omenn syndrome†	*RAG1* and *RAG2*	Mediate V(D)J recombination of the genes that encode BCRs (immunoglobulins) and TCRs§	$T^-/B^-/NK^+$
Artemis deficiency†	*DCLRE1C (Artemis)*	Repairs the DNA double-stranded breaks that occur during V(D)J recombination and upon exposure to ionizing radiation§	$T^-/B^-/NK^+$
PRKDC deficiency	*PRKDC*	DNA-activated protein kinase catalytic subunit critical for V(D)J recombination§	$T^-/B^-/NK^+$
LIG4 syndrome	*LIG4*	Ligase component of the DNA non-homologous end-joining (NHEJ) machinery required for the repair of DNA double-stranded breaks§	$T^-/B^-/NK^+$
NHEJ1 deficiency	*NHEJ1*	NHEJ factor required for the repair of DNA double-stranded breaks§	$T^-/B^-/NK^+$
T-cell receptor deficiencies	*CD3γ*, *CD3δ*, *CD3ε* and *CD3ζ*	TCR-associated proteins required for cell surface expression of and signal transduction by the TCR; most severe with defective CD3δ	$T^-/B^+/NK^+$
	TRAC	TCR-α constant region; relatively mild immunodeficiency	
CD45 deficiency	*PTPRC*	Transmembrane tyrosine phosphatase with a role in TCR signaling	$T^-/B^+/NK^+$
ZAP-70 deficiency	*ZAP-70*	Tyrosine kinase with a role in TCR signaling	$CD4^+CD8^-/B^+/NK^+$
CD8 deficiency	*CD8A*	Co-receptor for TCRs recognizing MHC class I-associated peptides; role in TCR signaling¶	$CD4^+CD8^-/B^+/NK^+$
Calcium channel deficiency	*ORAI1*	Pore-forming subunit of calcium channel with a role in TCR signaling; hypohidrotic ectodermal dysplasia and myopathy	$T^+/B^+/NK^+$
	STIM1	Calcium channel component with a role in TCR signaling; hepatosplenomegaly, lymphadenopathy, autoimmune cytopenias, dental dysplasia, myopathy	$T^+/B^+/NK^+$
ANTIGEN PRESENTATION DEFECTS (BARE LYMPHOCYTE SYNDROMES)			
MHC class II deficiency	*CIITA, RFXANK, RFX5 and RFXAP*	Transactivate the MHC class II promoter; MHC class II molecules are required for the positive selection of $CD4^+$ T cells in the thymus as well as for antigen presentation to $CD4^+$T cells	$T^+/B^+/NK^+$, but fewer and dysfunctional $CD4^+$T cells
MHC class I deficiency	*TAP1* and *TAP2*	*T*ransporter associated with *a*ntigen *p*rocessing; translocates peptides from the cytosol to MHC class I molecules in the endoplasmic reticulum¶	$CD4^+CD8^-/B^+/NK^+$
DEFECTIVE THYMIC DEVELOPMENT			
Winged helix nude (forkhead box N1) deficiency	*WHN (FOXN1)*	Transcription factor important to thymic development; defect leads to complete congenital alopecia and nail dystrophy (human equivalent of "nude" mice)	$T^-/B^+/NK^+$

*Two most common forms, accounting for approximately two-thirds of cases.
†Artemis and interleukin-7 receptor deficiencies can also lead to an Omenn syndrome phenotype (see text).
‡Defective ADA or PNP activity results in accumulation of (deoxy)adenosine or deoxyguanosine triphosphate metabolites, respectively, which are particularly toxic to developing lymphocytes; measuring red blood cell levels of the enzymes and/or metabolites can help establish the diagnosis.
§Patients are unable to produce the diversity of B- and T-cell receptors that are required for adaptive immunity; Artemis, PRKDC, LIG4 and NHEJ1 defects lead to sensitivity to ionizing radiation; both of the latter two conditions are associated with microcephaly and bird-like facies, and photosensitivity and telangiectasias have been described in patients with LIG4 syndrome.
¶Not true SCID; present with bacterial sinopulmonary infections and, in TAP deficiency, cutaneous granulomas; a milder form of bare lymphocyte syndrome can result from TAP binding protein (tapasin) deficiency.

Table 60.15 Classification of severe combined immunodeficiency (SCID). Cartilage–hair hypoplasia (see text) occasionally presents as SCID with an Omenn-like phenotype. *DCLRE1C*, DNA cross-link repair protein 1C; MHC, major histocompatibility complex; V(D)J, variable/diversity/joining.

Pathology

Nearly all patients with SCID have a profound T-cell deficiency and a low absolute lymphocyte count. Patients are further classified by the results of fluorescent activated cell sorter (FACS) analysis into those with and without B lymphocytes and NK cells. The laboratory abnormalities observed in different types of SCID are noted in Table 60.15. Certain forms of SCID show distinctive radiographic manifestations; for example, patients with ADA deficiency demonstrate cupping and flaring of the costochondral junction on chest radiographs. Flow cytometric analysis of peripheral blood mononuclear cells with antibodies directed against a particular protein that is missing from the cell surface (e.g. γ_c or JAK3) as well as direct gene analysis can help to establish a specific diagnosis.

Maternal T-cell engraftment is detectable (e.g. maternal T cells representing ≥1% of peripheral blood leukocytes) in approximately half of infants with SCID. The presence of maternal T cells is asymptomatic in the majority of cases, and a third of patients have mild changes such as cutaneous erythema and scale, a morbilliform eruption, elevated hepatic transaminases, and eosinophilia. Skin biopsy specimens show the histopathologic features of GVHD. Maternofetal GVHD is typically less severe than that resulting from postnatal inoculation of allogeneic lymphocytes (e.g. from unirradiated blood product transfusions), which can be fatal.

Differential Diagnosis

SCID must be differentiated from other immunodeficiency disorders, especially HIV infection. The latter is distinguished by normal to increased immunoglobulin levels, a relative decrease in $CD4^+$ T cells, and the presence of anti-HIV antibodies.

Treatment

Without intervention, the outcome for SCID patients is death by 1 year of age. Early diagnosis of SCID is critical, preferably before the administration of live vaccines or unirradiated blood products. A blood screening test for T-cell lymphopenia has been developed and was recently implemented in population-wide pilot programs for the detection of SCID in newborns in the US. Infants with SCID should be kept in protective isolation and monitored for the development of infections, which should be treated aggressively.

Hematopoietic stem cell transplantation during infancy is the treatment of choice for SCID. Because the patient's immune system is unable to reject the transplanted cells, myeloablative therapy is not required. The result is engraftment of donor T and NK cells, but usually not B cells. With an HLA-identical sibling donor, T-cell reconstitution typically occurs within 3–4 months, GVHD is uncommon and the long-term survival rate is >90%. Transplantation of haploidentical parental stem cells, which can be depleted of post-thymic T cells to reduce the risk of GVHD, often requires some chemotherapeutic conditioning to facilitate engraftment and results in ≤80% survival. *In utero* injection of haploidentical $CD34^+$ cells has also been used to treat X-linked SCID. SCID patients often require IVIg replacement therapy for persistent B-cell deficiency following hematopoietic stem cell transplantation, and T-cell function may decline over time.

Enzyme replacement via injection of polyethylene glycol-conjugated ADA can lead to improved immune function in children with ADA deficiency. Gene therapy has been successfully performed in more than 50 children with X-linked SCID or ADA deficiency via retroviral-mediated *ex vivo* gene transfer into $CD34^+$ cells[73,74]. Follow-up studies on 19 of these patients (4 months–4 years after treatment) showed that transcriptional start sites and coding regions of active genes were the preferred retroviral integration sites in circulating T cells as well as in pre-infusion transduced $CD34^+$ cells; in the former cells, ~25% of all integrations were clustered at common sites, suggesting *in vivo* selection of transduced cells with a higher capacity for engraftment, survival and proliferation[75]. Although T- and NK-cell function was restored, at least five patients with X-linked SCID have developed T-cell leukemias (2–6 years after treatment) related to activation of proto-oncogenes such as *LMO2* by the retroviral vector[76]. These complications raised serious concerns regarding the safety of gene therapy, and this has led to protocol modifications and investigation of alternative approaches such as lentiviral vectors and *in situ* gene transfer.

Prenatal diagnosis of SCID can be performed by fetal DNA analysis in families with a known genetic defect; ADA assays and examination of maternal X-chromosome inactivation may also be utilized for specific types of SCID.

WISKOTT–ALDRICH SYNDROME

Synonyms: ■ Wiskott–Aldrich–Huntley syndrome ■ Eczema–thrombocytopenia–immunodeficiency syndrome

Key features

- X-linked recessive immunodeficiency disorder characterized by the classic triad of atopic-like dermatitis, a bleeding tendency due to microthrombocytopenia, and recurrent sinopulmonary infections
- Onset of bacterial infections is early in life, with later development of viral and *Pneumocystis* spp. infections
- Hepatosplenomegaly, lymphadenopathy and autoimmune diseases often develop
- Lymphomas occur in approximately one-quarter of survivors

Introduction

Wiskott–Aldrich syndrome (WAS) is characterized by recurrent pyogenic infections, bleeding due to thrombocytopenia and platelet dysfunction, and recalcitrant eczematous dermatitis[77]. The full triad develops in a minority of patients, with platelet abnormalities representing the most constant feature.

Epidemiology

Most patients with this X-linked recessive immunodeficiency are boys, but girls are occasionally affected in the setting of non-random X-chromosome inactivation or homozygosity for a mild mutation. WAS has an incidence of approximately 1 : 250 000 live male births in European populations; it is less common in blacks and Asians.

Pathogenesis

WAS is caused by loss-of-function mutations in the *WASP* gene, which is constitutively expressed in all hematopoietic cell lineages. The WAS protein (WASP) controls the assembly of actin filaments, which are required for microvesicle and pro-platelet formation as well as T-cell activation and polarization toward antigen-presenting cells[78]. Loss-of-function *WASP* mutations also cause X-linked recessive thrombocytopenia, an allelic disorder with a phenotype limited to platelet abnormalities, while gain-of-function *WASP* mutations can lead to X-linked congenital neutropenia.

Abnormal T-cell function is central to the immunologic defect in WAS, with resultant diminution of both cell-mediated and humoral responses[78]. Although the number of T cells in WAS patients has been observed to decrease with age, affected infants also have reduced numbers of T cells (especially naive T cells) and B cells[79]. This suggests that impaired lymphocyte maturation and output from the thymus are central to the immunodeficiency of WAS. WASP function is required for the activation of regulatory T cells, helping to explain the autoimmune manifestations of WAS. Defects in B-cell migration, differentiation and organization into germinal centers have roles in the impaired humoral immunity of WAS, with reduced expression of CD21 and CD35 (complement receptors involved in antigen capture and presentation) also potentially contributing to autoimmunity[79]. Although NK cells are not decreased in number, their cytolytic activity is abnormal in WAS. Lastly, small, structurally abnormal platelets with a reduced half-life (due in part to splenic destruction) account for the thrombocytopenia of WAS[78].

Clinical Features

Because thrombocytopenia and platelet dysfunction are present from birth, the first clinical signs of WAS are usually petechiae and ecchymoses of the skin and oral mucosa. Spontaneous bleeding from the oral

Fig. 60.14 Severe atopic dermatitis in an infant with Wiskott–Aldrich syndrome. The boy was successfully treated with bone marrow transplantation, and his dermatitis virtually cleared owing to the T-cell engraftment. *Reprinted with permission from Schachner L, Hansen R, eds. Pediatric Dermatology, 4th edn. London: Mosby, 2011.*

cavity, epistaxis, hematemesis, melena and hematuria are commonly observed.

The dermatitis of WAS typically develops during the first few months of life, and it fulfills the diagnostic criteria for atopic dermatitis (see Tables 12.1 & 12.2). The face, scalp and flexural areas are most severely affected, although patients often have widespread involvement with progressive lichenification. Exfoliative dermatitis occasionally develops. Excoriated areas frequently have serosanguineous crusts and petechiae (Fig. 60.14). Secondary bacterial infections are common, as are eczema herpeticum and molluscum contagiosum.

Recurrent bacterial infections begin during the first 3 months of life, coincident with diminishing levels of placentally transmitted maternal antibodies. These infections include otitis externa and media, pneumonia, sinusitis, conjunctivitis, furunculosis, meningitis and septicemia. Encapsulated bacteria such as *Str. pneumoniae, H. influenzae* and *Neisseria meningitides* are the predominant organisms. With advancing age, there is increased susceptibility to infections with viruses (e.g. herpes simplex) and *P. jiroveci*.

The majority of children with WAS develop at least one autoimmune disease, most commonly cutaneous small vessel vasculitis (often associated with painful edema), autoimmune hemolytic anemia or neutropenia, arthritis, inflammatory bowel disease and cerebral vasculitis[80]. IgE-mediated conditions such as urticaria, food allergies and asthma also occur with increased frequency. Hepatosplenomegaly and lymphadenopathy are additional features of WAS. Lymphomas develop in up to a quarter of WAS patients 20 years of age and older, especially those with a history of autoimmune disease. Non-Hodgkin lymphomas predominate, and are most often diffuse large B-cell in type with extranodal and brain involvement (similar to AIDS-related lymphomas).

The median survival for WAS patients is now approximately 15 years. The most common causes of death (outside the setting of transplantation) are infection (50%), bleeding (25%) and malignancy (25%).

Pathology

The most frequent laboratory abnormalities in WAS are persistent thrombocytopenia (platelet counts <80 000/mm^3) and low mean platelet volume (<5.0 fl). WAS patients may also have lymphopenia and eosinophilia. Serum IgM and IgG_2 levels are typically low, while IgA, IgE and IgD levels tend to be elevated. Antibody responses to polysaccharide antigens are markedly diminished. Delayed-type hypersensitivity skin test reactions are usually absent, and responses to mitogens are often depressed, especially in older patients. Monocyte and neutrophil chemotaxis may also be defective.

Assessment of WASP expression in peripheral blood mononuclear cells by flow cytometry-based assays or immunoblot analysis can be performed in suspected cases prior to mutational analysis. Patients with a complete lack of WASP expression in circulating cells tend to have a more severe phenotype.

Differential Diagnosis

The cutaneous and laboratory features of other immunodeficiency syndromes characterized by eczematous dermatitis are summarized in Tables 60.1 and 60.2, and an approach to the differential diagnosis of infantile erythroderma is presented in Figure 10.10.

Treatment

Hematopoietic stem cell transplantation is the treatment of choice for patients with WAS. Full engraftment results in normal platelet numbers and function, restoration of immunologic status, and clearance of the dermatitis. Affected children who receive a hematopoietic stem cell transplant now have an overall survival rate of >85%, with lower rates (~70%) in those transplanted at >5 years of age with an unrelated donor[80a]. Gene therapy using retrovirally transduced, WASP-reconstituted, autologous $CD34^+$ cells has also been successfully performed[81].

Appropriate prophylactic use of antibiotics and antivirals can decrease the risk of fatal infections in WAS patients[82]. IVIg therapy has a role in preventing infections (considering patients' lack of antibodies to polysaccharide antigens) and may potentially improve the dermatitis. Topical corticosteroid preparations remain a mainstay of treatment for the latter. Splenectomy can help to reduce bleeding complications in patients with recurrent severe hemorrhage; unfortunately, splenectomy further increases the risk of infections with encapsulated organisms. Platelet transfusions may be given prior to surgery and in the setting of life-threatening hemorrhage.

Genetic counseling is important for the sisters and other female relatives of WAS patients. Female carriers may be detected by genetic analysis or detection of selective inactivation of the abnormal X chromosome in lymphocytes and platelets. Prenatal diagnosis can be performed by direct mutational analysis.

REFERENCES

1. Fischer A. Human primary immunodeficiency diseases: a perspective. Nat Immunol. 2004;5: 23–30.
2. Piirila H, Valiaho J, Vihinen M. Immunodeficiency mutation databases (IDbases). Hum Mutat. 2006;27:1200–8.
3. International Union of Immunological Societies Expert Committee on Primary Immunodeficiencies, Notarangelo L, Fischer A, et al. Primary immunodeficiencies: 2009 update. J Allergy Clin Immunol. 2009;124:1161–78.
4. Mitra A, Pollock B, Gooi J. Cutaneous granulomas associated with primary immunodeficiency disorders. Br J Dermatol. 2005;153:194–9.
5. Bonilla FA, Bernstein L, Khan DA, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol. 2005;94:S1–63.
6. Lavin MF. Ataxia-telangiectasia: from a rare disorder to a paradigm for cell signalling and cancer. Nat Rev Mol Cell Biol. 2008;9:759–69.
7. Lee JH, Paull TT. ATM activation by DNA double-stranded breaks through the Mre11-Rad50-Nbs1 complex. Science. 2005;308:551–4.
8. Cabana MD, Crawford RO, Winkelstein JA, et al. Consequences of the delayed diagnosis of ataxia-telangiectasia. Pediatrics. 1998;102:98–100.
9. Paller AS, Massey RB, Curtis MA, et al. Cutaneous granulomatous lesions in patients with ataxia-telangiectasia. J Pediatr. 1991;119:917–22.
10. Nowak-Wegrzyn A, Crawford TO, Winkelstein JA, et al. Immunodeficiency and infections in ataxia-telangiectasia. J Pediatr. 2004;144:505–11.
11. Thompson D, Duedal S, Kirner J, et al. Cancer risks and mortality in heterozygous ATM mutation carriers. J Natl Cancer Inst. 2005;97:813–22.
12. Staples ER, McDermott EM, Reiman A, et al. Immunodeficiency in ataxia telangiectasia is correlated strongly with the presence of two null mutations in the ataxia telangiectasia mutated gene. Clin Exp Immunol. 2008;153:214–20.
13. Lai C-H, Chun HH, Nahas SA, et al. Correction of ATM gene function by aminoglycoside-induced read-through of premature termination codons. Proc Natl Acad Sci U S A. 2004;101:15676–81.
14. Kirkpatrick CH. Chronic mucocutaneous candidiasis. Pediatr Infect Dis J. 2001;20:197–206.
15. Ahonen P, Myllárniemi S, Sipilá I, et al. Clinical variation of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) in a series of 68 patients. N Engl J Med. 1990;322:1829–36.
16. [Anonymous]. An autoimmune disease, APECED, is caused by mutations in a novel gene featuring two PHD-type zinc-finger domains. The Finnish-German

APECED Consortium. Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. Nat Genet. 1997;17:399–403.
17. Liston A, Lesage S, Wilson J, et al. Aire regulates negative selection of organ-specific T cells. Nat Immunol. 2003;4:350–4.
18. Ryan KR, Hong M, Arkwright PD, et al. Impaired dendritic cell maturation and cytokine production in patients with chronic mucocutaneous candidiasis with or without APECED. Clin Exp Immunol. 2008;154:406–14.
19. Ng WF, von Delwig A, Carmichael AJ, et al. Impaired T(H)17 responses in patients with chronic mucocutaneous candidiasis with and without autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. J Allergy Clin Immunol. 2010;126:1006–15.
19a. van de Veerdonk FL, Plantinga TS, et al. STAT1 mutations in autosomal dominant chronic mucocutaneous candidiasis. N Engl J Med. 2011;365:54–61.
19b. Puel A, Cypowyj S, Bustamante J, et al. Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. Science. 2011;332:65–8.
20. Kisand K, Boe Wolff AS, Podkrajsek KT, et al. Chronic mucocutaneous candidiasis in APECED or thymoma patients correlates with autoimmunity to Th17-associated cytokines. J Exp Med. 2010:207:299–308.
21. Glocker EO, Hennigs A, Nabavi M, et al. A homozygous CARD9 mutation in a family with susceptibility to fungal infections. N Engl J Med. 2009;361:1727–35.
22. Ferwerda B, Ferwerda G, Plantinga TS, et al. Human dectin-1 deficiency and mucocutaneous fungal infections. N Engl J Med. 2009;361:1760-7.
23. Ridanpaa M, Van Eenennaam H, Pelin K, et al. Mutations in the RNA component of RNase MRP cause a pleiotropic human disease, cartilage-hair hypoplasia. Cell. 2001;104:195–203.
24. Brennan T, Pearson R. Abnormal elastic tissue in cartilage-hair hypoplasia. Arch Dermatol. 1988;124:1411–14.
25. Shiflett SL, Kaplan J, Ward DM. Chédiak-Higashi syndrome: a rare disorder of lysosomes and lysosome related organelles. Pigment Cell Res. 2002;15:251–7.
26. Anderson LL, Paller AS, Malpass D, et al. Chédiak-Higashi syndrome in a black child. Pediatr Dermatol. 1992; 9:31–6.
27. Barbosa MD, Nyugen QA, Tchernev VT, et al. Identification of the homologous beige and Chédiak-Higashi syndrome genes. Nature. 1996;382:262–5.
28. Karim MA, Suzuki K, Fukai K, et al. Apparent genotype-phenotype correlation in childhood, adolescent, and adult Chédiak-Higashi syndrome. Am J Med Genet. 2002;108:1–22.
29. Sjöholm AG, Jönsson G, Braconier JH, et al. Complement deficiency and disease: an update. Molec Immunol. 2006;43:78–85.
30. Casanova JL, Abel L. Human mannose-binding lectin in immunity: friend, foe, or both? J Exp Med. 2004; 199:1295–9.
31. Sontheimer RD, Racila E, Racila DM. C1q: its functions within the innate and adaptive immune responses and its role in lupus autoimmunity. J Invest Dermatol. 2005;125:14–23.
32. Wen L, Atkinson JP, Giclas PC. Clinical and laboratory evaluation of complement deficiency. J Allergy Clin Immunol. 2004;113:585–93.
33. Winkelstein JA, Marino MC, Johnston RB Jr, et al. Chronic granulomatous disease. Report on a national registry of 368 patients. Medicine (Baltimore). 2000;79:155–69.
34. Segal BH, Leto TL, Gallin JI, et al. Genetic, biochemical, and clinical features of the chronic granulomatous disease. Medicine (Baltimore). 2000;79:170–200.
35. Kuhns DB, Alvord WG, Heller T, et al. Residual NADPH oxidase and survival in chronic granulomatous disease. N Engl J Med. 2010;363:2600–10.
36. Rada BK, Geiszt M, Kaldi K et al. Dual role of phagocytic NADPH oxidase in bacterial killing. Blood. 2004;104:2947–53.
37. Brinkmann V, Zychlinsky A. Beneficial suicide: why neutrophils die to make NETs. Nat Rev Microbiol. 2007;5:577–82.
38. Friend JC, Hilligoss DM, Marquesen M, et al. Skin ulcers and disseminated abscesses are characteristic of *Serratia marcescens* infection in older patients with chronic granulomatous disease. J Allergy Clin Immunol. 2009;124:164–6.
39. De Ravin SS, Naumann N, Cowen EW, et al. Chronic granulomatous disease as a risk factor for autoimmune disease. J Allergy Clin Immunol. 2008;122;1097–103.
40. Jirapongsananuruk O, Malech HL, Kuhns DB, et al. Diagnostic paradigm for evaluation of male patients with chronic granulomatous disease, based on the dihydrorhodamine 123 assay. J Allergy Clin Immunol. 2003;111:374–9.
41. Gallin JI, Alling DW, Malech HL. Itraconazole to prevent fungal infections in chronic granulomatous disease. N Engl J Med. 2003;348:2416–22.
42. Malech HL, Maples PB, Whiting-Theobald N, et al. Prolonged production of NADPH oxidase-corrected granulocytes after gene therapy of chronic granulomatous disease. Proc Natl Acad Sci U S A. 1997;94:12133–8.
43. Stein S, Ott MG, Schultze-Strasser S, et al. Genomic instability and myelodysplasia with monosomy 7 consequent to EVI1 activation after gene therapy for chronic granulomatous disease. Nat Med. 2010;16:198–204.
44. Grimbacher B, Holland SM, Gallin JI, et al. Hyper-IgE syndrome with recurrent infections – an autosomal dominant multisystem disorder. N Engl J Med. 1999;340:692–702.
45. Renner ED, Puck JM, Holland SM, et al. Autosomal recessive hyperimmunoglobulin E syndrome: a distinct disease entity. J Pediatr. 2004;144:93–9.
46. Zhang Q, Davis JC, Lamborn IT, et al. Combined immunodeficiency associated with *DOCK8* mutations. N Engl J Med. 2009;361:2046–55.
47. Engelhardt KR, McGhee S, Winkler S, et al. Large deletions and point mutations involving the dedicator of cytokinesis 8 (*DOCK8*) in the autosomal-recessive form of hyper-IgE syndrome. J Allergy Clin Immunol 2009;124:1289–302.
48. Holland SM, DeLeo FR, Elloumi HZ, et al. *STAT3* mutations in the hyper-IgE syndrome. N Engl J Med. 2007;357:1608–19.
49. Minegishi Y, Saito M, Tsuchiya S, et al. Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. Nature. 2007;448:1058–62.
50. Milner JD, Brenchley JM, Laurence A, et al. Impaired TH17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. Nature. 2008;452: 773–6.
51. Saito M, Nagasawa M, Takada H, et al. Defective IL-10 signaling in hyper-IgE syndrome results in impaired generation of tolerogenic dendritic cells and induced regulatory T cells. J Exp Med. 2011;208:235–49.
52. Minegishi Y, Saito M, Morio T, et al. Human tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity. Immunity. 2006;25:745–55.
53. Chamlin SL, McCalmont TH, Cunningham BB, et al. Cutaneous manifestations of hyper-IgE syndrome in infants and children. J Pediatr. 2002;141:572–5.
54. Eberting CL, Davis J, Puck JM, et al. Dermatitis and the newborn rash of hyper-IgE syndrome. Arch Dermatol. 2004;140:1119–25.
55. Woellner C, Gertz EM, Schäffer AA, et al. Mutations in *STAT3* and diagnostic guidelines for hyper-IgE syndrome. J Allergy Clin Immunol. 2010;125:424–32.
56. Joshi AY, Iyer VN, Boyce TG, et al. Elevated serum immunoglobulin E (IgE): when to suspect hyper-IgE syndrome – a 10-year pediatric tertiary care center experience. Allergy Asthma Proc. 2009;30:23–7.
57. Conley ME. Genes required for B cell development. J Clin Invest. 2003;112:1636–8.
58. Di Renzo M, Pasqui AL, Auteri A. Common variable immunodeficiency: a review. Clin Exp Med. 2004;3:211–17.
59. Chang MW, Romero R, Scholl PR, et al. Mucocutaneous manifestations of the hyper-IgM immunodeficiency syndrome. J Am Acad Dermatol. 1998;38:191–6.
60. Etzioni A, Ochs HD. The hyper IgM syndrome – an evolving story. Pediatr Res. 2004;56:519–25.
61. Grimbacher B, Schäffer AA, Peter HH. The genetics of hypogammaglobulinemia. Curr Allergy Asthma Rep. 2004;4:349–58.
62. Castigli E, Wilson SA, Garibyan L, et al. *TACI* is mutant in common variable immunodeficiency and IgA deficiency. Nat Genet. 2005;37:829–34.
63. Halabi-Tawil M, Ruemmele FM, Fraitag S, et al. Cutaneous manifestations of immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome. Br J Dermatol. 2009;160:645–51.
64. Caudy AA, Reddy ST, Chatila T, et al. CD25 deficiency causes an immune dysregulation, polyendocrinopathy, enteropathy, X-linked-like syndrome, and defective IL-10 expression from CD4 lymphocytes. J Allergy Clin Immunol. 2007;119;482–7.
64a. Blaydon DC, Biancheri P, Di WL, et al. Inflammatory skin and bowel disease linked to ADAM17 deletion. N Engl J Med. 2011;365:1502–8.
65. Bunting M, Harris ES, McIntyre TM, et al. Leukocyte adhesion deficiency syndromes: adhesion and tethering defects involving β2 integrins and selectin ligands. Curr Opin Hematol. 2002;9:30–5.
66. Bauer TR, Gu YC, Creevy KE, et al. Leukocyte adhesion deficiency in children and Irish setter dogs. Pediatr Res. 2004;55:363–7.
67. Wild MK, Lühn K, Marquardt T, et al. Leukocyte adhesion deficiency II: therapy and genetic defect. Cells Tissues Organs. 2002;172:161–73.
68. Svensson L, Howarth K, McDowall A, et al. Leukocyte adhesion deficiency-III is caused by mutations in *KINDLIN3* affecting integrin activation. Nat Med. 2009;15:306–12.
69. Kilic SS, Etzioni A. The clinical spectrum of leukocyte adhesion deficiency (LAD) III due to defective CalDAG-GEF1. J Clin Immunol. 2009;29:117–22.
70. Bauer TR, Allen JM, Hai M, et al. Successful treatment of canine leukocyte adhesion deficiency by foamy virus vectors. Nat Med. 2008;14:93–7.
71. Buckley RH. The multiple causes of human SCID. J Clin Invest. 2004;10:1409–11.
72. Kalman L, Lindegren ML, Kobrynski L, et al. Mutations in genes required for T-cell development: *IL7R, CD45, IL2RG, JAK3, RAG1, RAG2, ARTEMIS*, and *ADA* and severe combined immunodeficiency. Genet Med. 2004;6:16–26.
72a. Kesserwan C, Sokolic R, Cowen EW, et al. Multicentric dermatofibrosarcoma protuberans in patients with adenosine deaminase-deficient severe combined immune deficiency. J Allergy Clin Immunol. 2011. [epub ahead of print]
73. Aiuti A, Cattaneo F, Galimberti S, et al. Gene therapy for immunodeficiency due to adenosine deaminase deficiency. N Engl J Med. 2009;360:447–58.
74. Hacein-Bey-Abina S, Le Deist F, Carlier F, et al. Sustained correction of X-linked severe combined immunodeficiency by ex vivo gene therapy. N Engl J Med. 2002;346:1185–93.
75. Bushman FD. Retroviral integration and human gene therapy. J Clin Invest. 2007;117:2083–6.
76. Hacein-Bey-Abina S, Garrigue A, Wang GP, et al. Insertional oncogenesis in 4 patients after retrovirus-mediated gene therapy of SCID-X1. J Clin Invest. 2008;117:3132–42.
77. Orange JS, Stone KD, Turvey SE, et al. The Wiskott-Aldrich syndrome. Cell Mol Life Sci. 2004;61:2361–85.
78. Burns S, Cory GO, Vainchenker W, et al. Mechanisms of WASp-mediated hematologic and immunologic diseases. Blood. 2004;104:3454–62.
79. Ochs HD, Notarangelo LD. Structure and function of the Wiskott-Aldrich syndrome protein. Curr Opin Hematol. 2005;12:284–91.
80. Dupuis-Girod S, Medioni J, Haddad E, et al. Autoimmunity in Wiskott-Aldrich syndrome: risk factors, clinical features, and outcome in a single-center cohort of 55 patients. Pediatrics. 2003;111:e622–e627.
80a. Moratto D, Giliani S, Bonfim C, et al. Long-term outcome and lineage-specific chimerism in 194 patients with Wiskott-Aldrich syndrome treated by hematopoietic cell transplantation in the period 1980–2009: an international collaborative study. Blood. 2011;118:1675–84.
81. Boztug K, Schmidt M, Schwarzer A, et al. Stem-cell gene therapy for the Wiskott-Aldrich syndrome. N Engl J Med. 2010;363:1918–27.
82. Conley ME, Saragoussi D, Notarangelo L, et al. An international study examining therapeutic options used in treatment of Wiskott-Aldrich syndrome. Clin Immunol. 2003;109:272–7.

This page intentionally left blank

Neurofibromatosis and Tuberous Sclerosis 61

Hensin Tsao and Su Luo

Chapter Contents

Neurofibromatosis type 1 925
Tuberous sclerosis 933

INTRODUCTION

Neurofibromatosis (NF) and tuberous sclerosis (TS) are neurocutaneous disorders, or phakomatoses. They are characterized by cutaneous lesions as well as peripheral and/or central nervous system neoplasms. Like most hereditary cancer syndromes, NF and TS are autosomal dominant in inheritance. Despite a high penetrance for both diseases, new cases of NF type 1 (NF1) and TS frequently represent *de novo* mutations. The pleiotropic nature of these two neurocutaneous syndromes has led to complex schemes for their classification and diagnosis. Dermatologists are frequently asked to participate in the clinical diagnosis of patients with NF1 and TS due to the early appearance of cutaneous, especially pigmentary, findings. Advances in the molecular characterization of these disorders have revealed related, but distinct, pathogenic mechanisms.

In 1982, Riccardi proposed a classification scheme for patients with NF (Table 61.1). Elucidation of the molecular bases of NF1, NF2, segmental/mosaic NF1 (formerly known as NF5), and "NF1-like" syndromes has further refined the categorization of patients. Among these conditions, NF1 has the most well-characterized and diagnostic skin findings and is the main focus in this chapter.

NEUROFIBROMATOSIS TYPE 1

Synonym: ■ von Recklinghausen disease

Key features

- NF1 is an autosomal dominant disorder with an incidence of approximately 1 in 3000 births
- Clinical characteristics include café-au-lait macules, neurofibromas, freckling in the axillae and groin, Lisch nodules, and bony defects
- Patients with NF1 have an increased risk of developing juvenile myelomonocytic leukemia and a variety of extracutaneous tumors, including optic gliomas, malignant peripheral nerve sheath tumors, pheochromocytomas and CNS tumors
- Up to 50% of patients with NF1 have a new spontaneous mutation rather than an inherited mutation
- The protein product of the *NF1* gene (neurofibromin) is involved in the negative regulation of Ras signaling
- Other well-characterized forms of NF include segmental/mosaic NF1 and NF2 (vestibular schwannomas)

History

Individuals with NF1 have been described throughout history[1,2]. In 1882, von Recklinghausen[3] provided the first in-depth report of the clinical and pathologic nature of the neurofibromas. Fifty years later, the Viennese ophthalmologist Lisch described the iris nodules that were more recently recognized as an important criterion in the clinical diagnosis of NF. In the mid twentieth century, Crowe, Schull and Neel compiled a landmark monograph with a comprehensive description of the manifestations of this disease[4].

Epidemiology

NF1 has been reported worldwide. Its incidence is approximately 1 in 3000 births[4–6].

Pathogenesis

NF1 is inherited in an autosomal dominant manner. Most large series have found that 30–50% of patients have no affected relatives and thus likely harbor new spontaneous mutations[4–6]. There is also the possibility of germline mosaicism in a parent, especially when two siblings develop NF1 in the absence of a family history. The penetrance of NF1 approaches 100% in carefully examined adults[7], but expressivity is variable. A wide range of clinical findings and complications can develop among individuals with the same underlying mutation. The specific *NF1* mutation is therefore not the only factor that determines phenotype.

In 1987, an international consortium found evidence of linkage to the pericentromeric region of chromosome 17 in families with NF1[8]. Subsequent descriptions of two NF1 patients with balanced translocations involving the long arm of chromosome 17 (17q11.2) further refined the position of the *NF1* locus[9,10]. The localization data derived from these studies led to the cloning of the *NF1* gene[11–13].

The *NF1* gene spans over 350 kilobases (kb) of genomic DNA, with at least 59 exons encoding a 327 kDa protein (neurofibromin) that consists of 2818 amino acids (Fig. 61.1)[14]. Over 80% of NF1 patients have a mutation that predicts truncation of the neurofibromin protein, and approximately 5% of patients have a large deletion ("microdeletion") that encompasses the entire *NF1* gene plus a variable number of flanking genes[15]. Although there is usually no clear genotype–phenotype correlation, exceptions include: (1) a 3-base pair in-frame deletion (AAT in exon 17) that is associated with an absence of cutaneous neurofibromas[16]; and (2) a recurrent 1.4-mega-base pair deletion ("type 1 microdeletion") that results in a more severe phenotype[17,18]. The latter can include an earlier onset and larger number of neurofibromas, an increased risk of malignant peripheral nerve sheath tumors, marked

RICCARDI'S CLASSIFICATION OF NEUROFIBROMATOSIS

Category	Description
NF1	von Recklinghausen disease
NF2	Acoustic schwannoma
NF3*	Mixed (central and peripheral neurofibromas)
NF4*	Variant
NF5*,†	Segmental café-au-lait macules, neurofibromas, or both, affecting one or more dermatomes
NF6*,‡	Café-au-lait macules only
NF7*	Late onset
NF-NOS	Not otherwise specified

*Primarily of historical/conceptual interest.
†Now referred to as segmental NF1.
‡Includes Legius (NF1-like) syndrome.

Table 61.1 Riccardi's classification of neurofibromatosis.

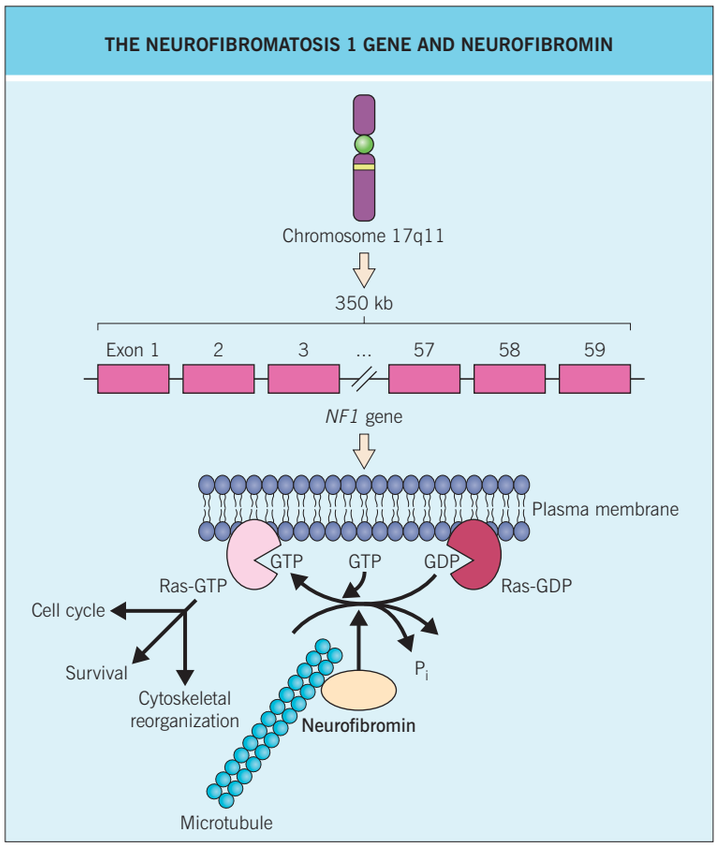


Fig. 61.1 The neurofibromatosis 1 gene and neurofibromin. *NF1* is located on chromosome 17q11.2 and encodes the *G*TPase-*a*ctivating *p*rotein (GAP)-related protein neurofibromin. One of the functions of neurofibromin is to negatively regulate the activity of Ras proteins. Ras, like other related G proteins, is dependent upon GTP binding for its full activity, and GAP proteins shut off the signal by accelerating the hydrolysis of GTP to GDP.

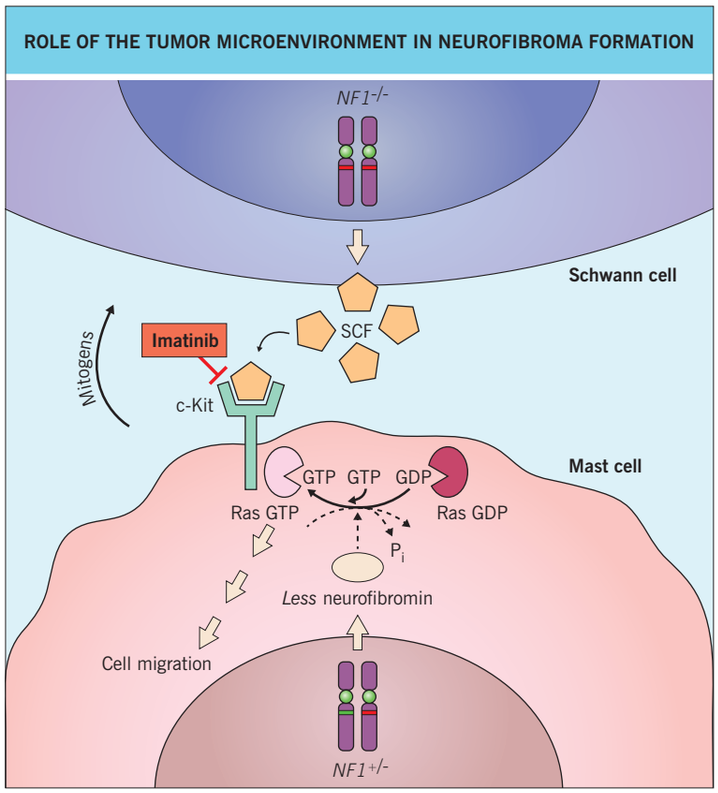


Fig. 61.2 Role of the tumor microenvironment in neurofibroma formation. *NF1* nullizygous (*Nf1*$^{-/-}$) Schwann cells oversecrete stem cell factor (SCF), which binds the Kit receptor on *NF1* heterozygous (*Nf1*$^{+/-}$) mast cells. This leads to mast cell recruitment and their activation to produce growth factors that stimulate neurofibroma development. Inhibition of KIT signaling by imatinib mesylate can block neurofibroma formation and progression.

cognitive deficiencies, facial dysmorphism, overgrowth and connective tissue dysplasia (e.g. hyperextensible skin, joint laxity, mitral valve prolapse)[17,18].

Sequence similarities between a central 300–400 amino acid domain within neurofibromin and *G*TPase-*a*ctivating *p*roteins (GAPs) led to recognition of neurofibromin's role in the negative regulation of the Ras–*m*itogen-*a*ctivated *p*rotein *k*inase (MAPK) pathway that promotes cell survival and proliferation (see Fig. 61.1 and Fig. 55.6)[19]. Like all G proteins, Ras activity requires GTP. Neurofibromin and other GAPs accelerate the hydrolysis of GTP to GDP, thereby terminating the Ras signal and functioning as tumor suppressor proteins. Neurofibromin has also been shown to associate with microtubules[20], although the consequences of this interaction remain unclear.

As observed in other autosomal dominant genodermatoses (e.g. nevoid basal cell carcinoma syndrome) caused by a defective tumor suppressor gene, a *somatic* mutation inactivating the remaining allele of the gene (i.e. a "second hit" causing loss of heterozygosity [LOH]) can be found within skin lesions of NF1. Biallelic *NF1* inactivation has been identified in Schwann cells from neurofibromas as well as melanocytes from café-au-lait macules in patients with NF1[21,22]. In a mouse model, *Nf1* nullizygosity (*Nf1*$^{-/-}$) in Schwann cells was shown to be necessary, but not sufficient, for neurofibroma formation[23]; however, plexiform neurofibromas did arise from *Nf1*$^{-/-}$ Schwann cells when the microenvironment included *Nf1*$^{+/-}$ (rather than wild-type) mast cells[24]. The latter cells appear early in neurofibroma development and are hypermotile in response to the c-Kit ligand (stem cell factor), which is oversecreted by *Nf1*$^{-/-}$ Schwann cells. Once recruited, mast cells produce growth factors that likely promote neurofibroma tumorigenesis (Fig. 61.2). Of note, genetic or pharmacologic attenuation of kit signaling in *Nf1*$^{+/-}$ mast cells has been found to diminish neurofibroma initiation and progression (see Treatment section below).

Clinical Features

The clinical features of NF1 (Table 61.2) are myriad, although some occur with greater frequency than others[4–6,25–35].Through decades of careful study, almost every organ system has been found to be involved in NF1. However, the cutaneous manifestations of NF1 represent particularly important clinical features and have a central role in the diagnosis of the condition.

Oculocutaneous manifestations

Café-au-lait macules (CALMs) are tan to dark brown (depending on the degree of pigmentation of uninvolved skin), uniformly pigmented macules and patches that are randomly distributed on the body (except for the scalp, palms and soles). They are sharply demarcated with regular borders and often have an oval shape (Fig. 61.3); the diameter can vary from a few millimeters to over 4 cm. CALMs may not be apparent at birth and frequently become more noticeable during the first year of life; fading of these lesions during later adulthood has also been described[35a]. When located within areas of dermal melanocytosis, CALMs are usually surrounded by a rim of normally pigmented skin (see Ch. 112). Larger CALMs, especially those with associated hypertrichosis, should be palpated to exclude the possibility of an underlying plexiform neurofibroma (see below).

Crowe et al.[4] reported that 10% of the normal population has one to five CALMs, and Burwell et al.[36] found that 26% of 732 white schoolchildren had at least one CALM greater than 1 cm in diameter. In the latter study, only three children (0.4%) had six or more CALMs and all three were siblings with a family history of NF1. For the clinical diagnosis of NF1, a minimum of six CALMs is required to meet the specificity of this criterion (Table 61.3). Although the distinction between CALMs and freckles is generally straightforward, larger lentigines, especially in younger children and infants, can mimic CALMs. Thus, CALMs must be >5 mm in prepubertal individuals and >15 mm in

MAJOR CLINICAL FEATURES OF NEUROFIBROMATOSIS TYPE 1
CUTANEOUS
• Neurofibromas (60–90%) • Café-au-lait macules (>90%) • Axillary and/or inguinal freckling (~80%) • Plexiform neurofibroma (25%)
OCULAR
• Lisch nodules (>90%) • Hypertelorism (25%) • Glaucoma
SKELETAL

• *Cranial*
  • Macrocephaly (20–50%)
  • Sphenoid wing dysplasia (<5%)
• *Spinal*
  • Scoliosis (5–10%)
  • Spina bifida
• *Limbs*
  • Pseudarthrosis (2%)
  • Thinning of long bone cortex
  • Local bony overgrowth
  • Absent patellae

TUMORS
• Optic glioma (10–15%) (with or without precocious puberty) • Malignant peripheral nerve sheath tumors (3–15%) • Pheochromocytoma (~1%) • Juvenile myelomonocytic leukemia (especially in patients with concomitant JXGs) • CNS tumors other than optic gliomas (~5%) • Rhabdomyosarcoma, especially of the genitourinary tract • Duodenal carcinoid • Somatostatinoma • Parathyroid adenoma • Gastrointestinal stromal tumors (GIST) • Breast cancer (~5-fold increased risk in women <50 years of age)
NEUROLOGIC
• Unidentified bright objects (UBO) on MRI (50–75%) • Learning difficulties (30–50%) • Seizures (~5%) • Mental retardation (severe in <5%) • Aqueductal stenosis and hydrocephalus (~2%)
CARDIOVASCULAR
• Hypertension (~30%), mostly essential, some from renal artery stenosis or pheochromocytoma • Pulmonic stenosis (~1%) • Renal artery stenosis (~2%) • Cerebrovascular anomalies (2–5%), including vascular stenoses and aneurysms

Table 61.2 Major clinical features of neurofibromatosis type 1. JXGs, juvenile xanthogranulomas.

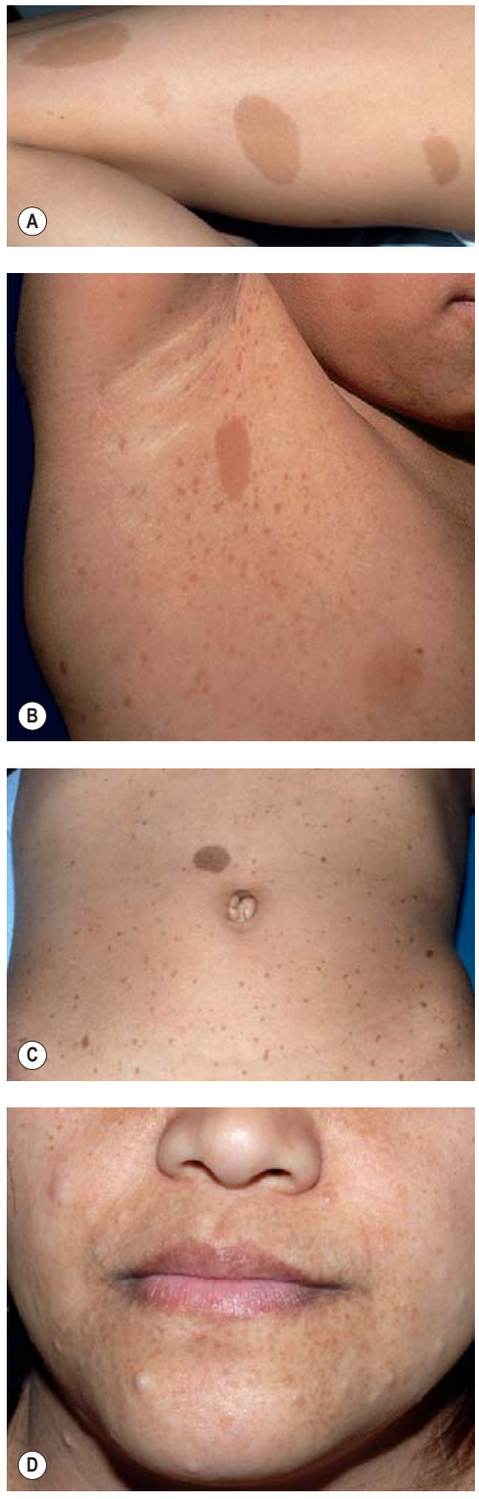


Fig. 61.3 Café-au-lait macules and "freckling". Oval-shaped, light- to medium-brown patches with regular borders and uniform pigmentation (**A**–**C**). Numerous 1–3 mm lentigines are most commonly found in the axillae (Crowe's sign) (**B**) but can also develop in other locations such as the abdomen (**C**) and perioral region (**D**). *A–D, Courtesy, Julie V Schaffer, MD.*

DIAGNOSTIC CRITERIA FOR NEUROFIBROMATOSIS TYPE 1
Two or more of the following must be present: • Six or more café-au-lait macules >5 mm in prepubertal individuals and >15 mm in postpubertal individuals • Two or more neurofibromas of any type or one plexiform neurofibroma • "Freckling" in the axillary or inguinal regions • Optic gliomas • Two or more Lisch nodules (iris hamartomas) • Osseous lesion, such as sphenoid wing dysplasia or thinning of long bone cortex, with or without pseudarthrosis • First-degree relative (parent, sibling or offspring) with NF1 by the above criteria

Table 61.3 Diagnostic criteria for neurofibromatosis type 1.

postpubertal individuals in order to satisfy the diagnostic criterion for NF1.

In its fullest expression, NF1 can manifest as thousands of neurofibromas in an affected individual, hence the appellation *neurofibromatosis* (Fig. 61.4). Several variants of neurofibromas are observed in NF1. Most commonly, proliferations of spindle cells occur within the dermis, leading to *cutaneous* neurofibromas (CNFs). CNFs are skin-colored to pink, tan or brown, dome-shaped or pedunculated papulonodules that are soft or slightly rubbery in texture and can range from a few millimeters to several centimeters in diameter; early lesions, however, may be barely elevated. They invaginate easily with gentle pressure, thereby exhibiting the pathognomonic "buttonhole" sign. Although usually asymptomatic, these soft nodules may become pruritic or, occasionally, irritated. CNFs appear as early as 4–5 years of age but more typically develop around puberty, with occasional acceleration during pregnancy.

Subcutaneous neurofibromas (SNFs) occur deeper in the dermis and subcutis, tending to be firmer and less well-circumscribed than CNFs. Nearly one-fifth of NF1 patients have at least one SNF[37] and

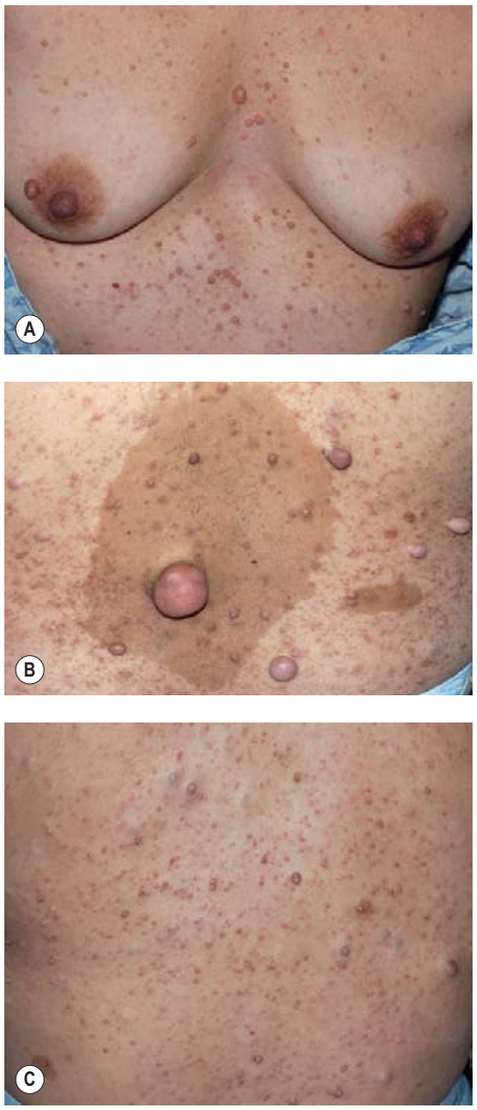


Fig. 61.4 Multiple cutaneous neurofibromas. Soft, skin-colored to pinkish-tan, dome-shaped or polypoid, well-demarcated papules and nodules of various sizes (**A**–**C**) as well as ill-defined violaceous lesions (**C**) can occur in patients with NF1. Neurofibromas may be superimposed on café-au-lait macules and lentigines (**B**, **C**). *A–C, Courtesy, Julie V Schaffer, MD.*

Fig. 61.5 Spectrum of cutaneous neurofibromas. Lesions range from subtle blue–red macules (**A**) to exophytic nodules with associated hypertrichosis (**B**). *Courtesy, Julie V Schaffer, MD.*

one-quarter of these individuals develop tumor-related local complications. Less common cutaneous presentations of neurofibromas in patients with NF1 include: (1) *blue–red macules* due to thick-walled blood vessels as well as neurofibromatous tissue in the papillary dermis (Fig. 61.5); and (2) *pseudo-atrophic macules* due to replacement of collagen in the reticular dermis with neurofibromatous tissue[38].

Plexiform neurofibromas (PNFs) (Fig. 61.6) may track along nerves to create tender, firm nodules or masses (classically resembling a "bag of worms" upon palpation) in the subcutaneous tissue, or they can infiltrate diffusely to involve all layers of the skin, fascia, muscle, or even internal structures. Approximately 25% of NF1 patients have clinically apparent PNFs. These lesions often cause soft tissue and bony hypertrophy, and massive distortion of the head, neck or extremities may result. Impingement upon nerves may lead to neurologic deficits.

Unlike other neurofibromas, PNFs are probably all congenital in origin. Superficial and/or diffuse lesions usually become clinically apparent by the age of 4 or 5 years[25], while deep/internal nodular lesions may remain undetected even in adulthood unless a full-body MRI is performed[39]. Older children without evidence of soft tissue overgrowth related to a PNF are unlikely to develop this finding later in life. Both hyperpigmentation and hypertrichosis can overlie PNFs[40], sometimes leading to misdiagnosis as a congenital melanocytic nevus (see Fig. 61.6).

The transformation of PNFs into malignant peripheral nerve sheath tumors (MPNSTs, also known as "neurofibrosarcomas") occurs in 3–15% of patients with NF1[6,37], with a peak incidence in young adults. The onset of rapid growth, increased firmness or persistent pain within an established PNF or the development of a new neurologic deficit may herald malignant degeneration (see Management section). MPNSTs can be very aggressive and are often fatal[41].

"Freckling" in the axillae (see Fig. 61.3) and groin in NF1 patients was first noted by Crowe[4] and is therefore referred to as "Crowe's sign". Numerous 1–3 mm brown macules (more akin to lentigines than ephelides) typically populate these intertriginous zones, the neck, and, occasionally, the majority of the skin surface (see Figs 61.3 & 61.4). Involvement of the axillae is most common, occurring in about 80% of NF1 patients[37,42]. The lesions usually arise by 4–6 years of age, following the emergence of CALMs but preceding the development of neurofibromas. As a result, intertriginous "freckling" is a useful clinical sign in the evaluation of a young child with multiple CALMs[43].

There are numerous reports of patients with NF1, juvenile myelomonocytic leukemia (JML) and juvenile xanthogranulomas (JXGs). As many as 18% of children with NF1 are diagnosed with one or more JXGs during the first 3 years of life[44], and young children with NF1 also have a 200- to 500-fold greater risk of developing JML (incidence 1/2000–1/5000) compared to the general pediatric population. In 1995, Zvulunov et al.[45] reviewed the world literature and calculated a 30–40-fold higher-than-expected rate of a triple association between NF1, JML and JXG. Based on this, they estimated that the risk of JML in children with NF1 is 20 to 30 times higher if JXGs are present; however, these authors' assumptions and statistical methods have been criticized[44]. Although neurofibromin is known to regulate the proliferation of myeloid cells, the exact etiopathogenesis of the "triple association" remains unclear.

Glomus tumors of the fingers and toes have recently been recognized as a manifestation of NF1, and bialleic inactivation of the *NF1* gene

Fig. 61.6 Plexiform neurofibromas. Clinical presentations include: a hyperpigmented plaque that may be misdiagnosed as a congenital melanocytic nevus or (if not palpated) a café-au-lait macule (**A**); a sharply demarcated reddish-brown plaque (**B**); and a poorly circumscribed, sagging pink mass (**C**). *A–C, Courtesy, Julie V Schaffer, MD.*

Fig. 61.7 Lisch nodules. Multiple yellow–brown papules of the iris.

Fig. 61.8 Segmental neurofibromatosis. A cluster of soft, pink to pink–brown papules limited to the thigh. There were no associated café-au-lait macules. *Courtesy, Jean L Bolognia, MD.*

has been documented within these lesions in NF1 patients[46]. The tumors are often multiple and, like their sporadic counterpart, present with localized tenderness, paroxysmal pain, and sensitivity to cold (see Ch. 114). Focal swelling, ill-defined reddish discoloration (often of the nail bed) and nail dystrophy may be observed.

Pigmented iris hamartomas, or Lisch nodules, begin to develop at about the age of 3 years and occur, in about 90% of NF1 patients who are 20 years of age and older[31,37,47,48]. The lesions are 1–2 mm, dome-shaped, yellow–brown papules that are best seen on slit-lamp examination (Fig. 61.7). Although Lisch nodules are useful in diagnosing NF1, they rarely lead to symptoms or complications.

In segmental NF1 (formerly known as NF5), cutaneous neurofibromas, CALMs and/or "freckling" are present in one or more dermatomes (especially for neurofibromas; Fig. 61.8) or in other mosaic distribution patterns such as along the lines of Blaschko (especially for CALMs and freckling; see Ch. 62). This form of NF1 is a reflection of mosaicism due to a postzygotic mutation in the *NF1* gene. If the mutation involves the gonads (germline mosaicism) as well as the skin, there is a chance of full-blown NF1 in the patient's offspring.

Neurologic manifestations

Optic gliomas occur in up to 15% of children with NF1[49]. The behavior of these CNS neoplasms is variable, ranging from asymptomatic enlargement to progressive visual compromise and proptosis associated with tumor expansion[50]. Precocious puberty occurs in about 3% of children with NF1, most of whom have optic gliomas[51,52]. Non-optic CNS tumors occur in about 5%[42] and pheochromocytomas in about 1% of NF1 patients[25,53].

In MRI studies of the brain, T_2-weighted unidentified bright objects (UBOs) can be observed in 50–75% of children with NF1[54]. These are most commonly seen in the basal ganglia, brainstem and cerebellum. UBOs have been shown to evolve over time[55], and they may contribute to cognitive impairment via thalamocortical dysfunction[56].

Although severe mental retardation is uncommon, learning difficulties occur in 30–50% of affected children[37,57]; there is also an increased likelihood of attention deficit disorder and sleep disturbances. Seizures develop in about 5% of NF1 patients, although no specific cortical lesions have been linked to the abnormal electroencephalographic (EEG) activity[30].

Skeletal manifestations

Macrocephaly[26] and scoliosis[34,57] are the most common skeletal abnormalities seen in individuals with NF1. A highly distinctive but less common finding is pseudarthrosis of the long bones. This is a congenital defect that begins as bowing, especially of the tibia. Eventually, the process erodes the cortex of the bone, leading to pathologic fractures and false joint formation, or pseudarthrosis[25,37]. Sphenoid wing dysplasia is a congenital, typically unilateral, bony defect in the posterior wall of the orbit[37]. This abnormality usually presents with pulsating exophthalmos.

Cardiovascular manifestations

Hypertension is a common finding in NF1 patients. Although essential hypertension is most frequent, renovascular stenosis[58] (especially in children) and unsuspected pheochromocytomas[59] may be the etiology in some patients.

Timing of onset of clinical manifestations

The prevalence of various clinical features in patients with NF1 evolves over the first two decades of life (Fig. 61.9). PNFs and skeletal defects are probably congenital, whereas the CALMs are congenital or become apparent in the first few years of life. Intertriginous "freckling", Lisch nodules, and optic gliomas begin to occur by the school-age years, and multiple CNFs typically start to develop closer to puberty. The National Institutes of Health (NIH) criteria for NF1 are met in 97% of affected individuals by age 8 years and in 100% by age 20 years (see Table 61.3)[31].

Pathology

The CALMs, CNFs and MPNSTs associated with NF1 are histologically similar to their sporadic counterparts. CALMs from affected individuals are characterized primarily by increased epidermal melanin; other nonspecific findings may include a higher number of melanocytes compared to the surrounding skin and giant melanosomes[60].

CNFs feature a well-circumscribed but unencapsulated dermal collection of small nerve fibers and loosely arranged spindle cells; the latter have scanty pale cytoplasm and elongated wavy nuclei (see Ch. 115). These spindle cells represent a mixture of fibroblasts, Schwann cells and perineural cells, and they are set in a collagenous stroma with varying amounts of mucin and scattered mast cells. The nuclei are relatively banal, and mitotic activity should raise a suspicion of malignancy.

PNFs are specific to NF1. Histologically, they are composed of large hypertrophied nerves surrounded by spindle-shaped fibroblasts and Schwann cells embedded in a myxoid matrix (see Ch. 115). In some PNFs, neurofibromatous changes extend diffusely into the papillary and reticular dermis. The stroma may be more collagenous than myxoid, and organoid differentiation may occur, forming structures resembling Meissner's corpuscles.

MPNSTs are comprised of alternating cellular and myxoid areas. The cells (as in neurofibromas) stain positively with S100, but they are much more pleomorphic, with wavy and hyperchromatic nuclei (see Ch. 115). Increased mitotic activity and perivascular whorling of tumor cells are often observed. Areas of bony or cartilaginous differentiation may also be present, along with hyalinized nodules.

Differential Diagnosis

In an affected individual with complete expression of NF1, the criteria set by the NIH Consensus Conference are met[61] (see Table 61.3) and the diagnosis is usually straightforward. In infants, establishing the diagnosis can sometimes be difficult because of the lack of age-dependent features. This is particularly true for children with six or more CALMs but no other findings (NF1 suspect)[62]. An approach to this clinical situation is outlined in Figure 61.10. In a recent series of 110 children (median age 3 years; range, 1 month to 17 years) who presented to a NF1 clinic with CALMs but no other features of NF1, 34/44 (77%) of those with six or more "typical" CALMs (distinct regular borders, uniform pigmentation) eventually met criteria for NF1 (almost all before age 6 years), compared to 2/15 (15%) of those with six or more "atypical" CALMs (smudgy irregular borders, non-homogeneous pigmentation) and 0/51 of those with fewer than six CALMs[63].

Comprehensive testing of the *NF1* gene via a multistep approach (including reverse transcriptase–polymerase chain reaction [RT-PCR], direct sequencing, microsatellite marker analysis, multiplex ligation-dependent probe amplification [MLPA] and interphase fluorescence *in situ* hybridization [FISH]) is clinically available and can identify the underlying mutation in ≥95% of non-founder patients who fulfill the NIH diagnostic criteria, detecting pathogenic splice-site mutations and deletions that are missed by genomic DNA-based sequencing. This allows an accurate diagnosis to be established in young children who do not (yet) meet diagnostic criteria and individuals with atypical clinical presentations. It also makes prenatal or preimplantation diagnosis an option for affected families.

In addition to segmental NF1 (see above), unilateral lentigines in the axilla or groin may be seen in patients with partial unilateral lentiginosis (PUL) or a large speckled lentiginous nevus (nevus spilus)[64]. These segmental conditions are characteristically sharply demarcated at the midline, but bilateral involvement occasionally occurs. PUL and

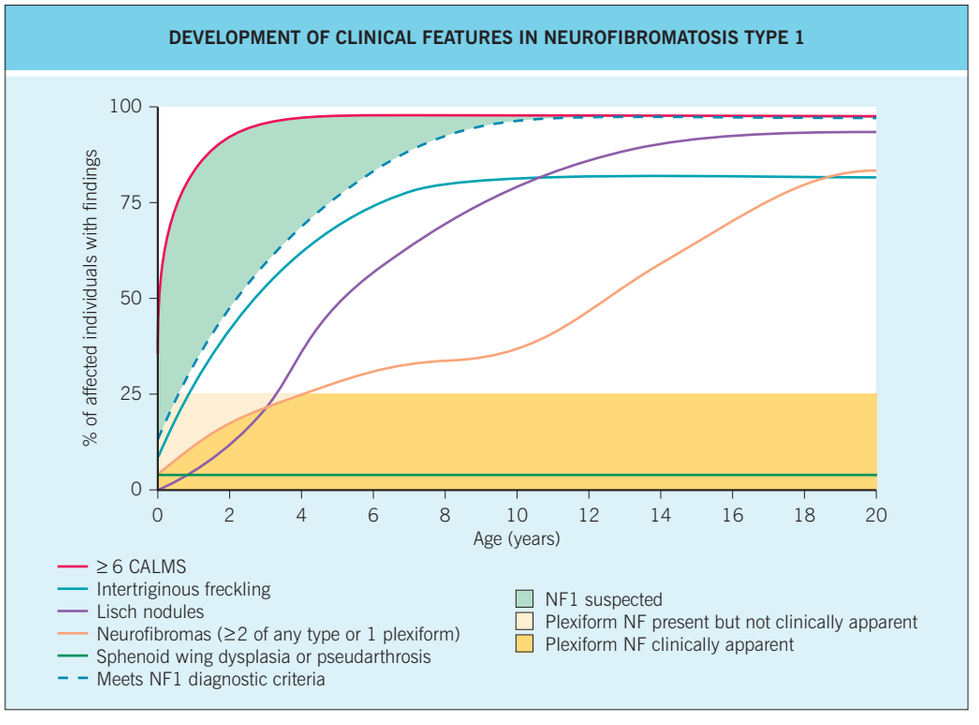


Fig. 61.9 Development of clinical features in neurofibromatosis type 1. The time course of major diagnostic lesions that develop in NF1. During the first few years of life, a child may have only café-au-lait macules. *Adapted from DeBella K, Szudek J, Friedman JM. Use of the National Institutes of Health criteria for diagnosis of neurofibromatosis 1 in children. Pediatrics 2000;105:608–14.*

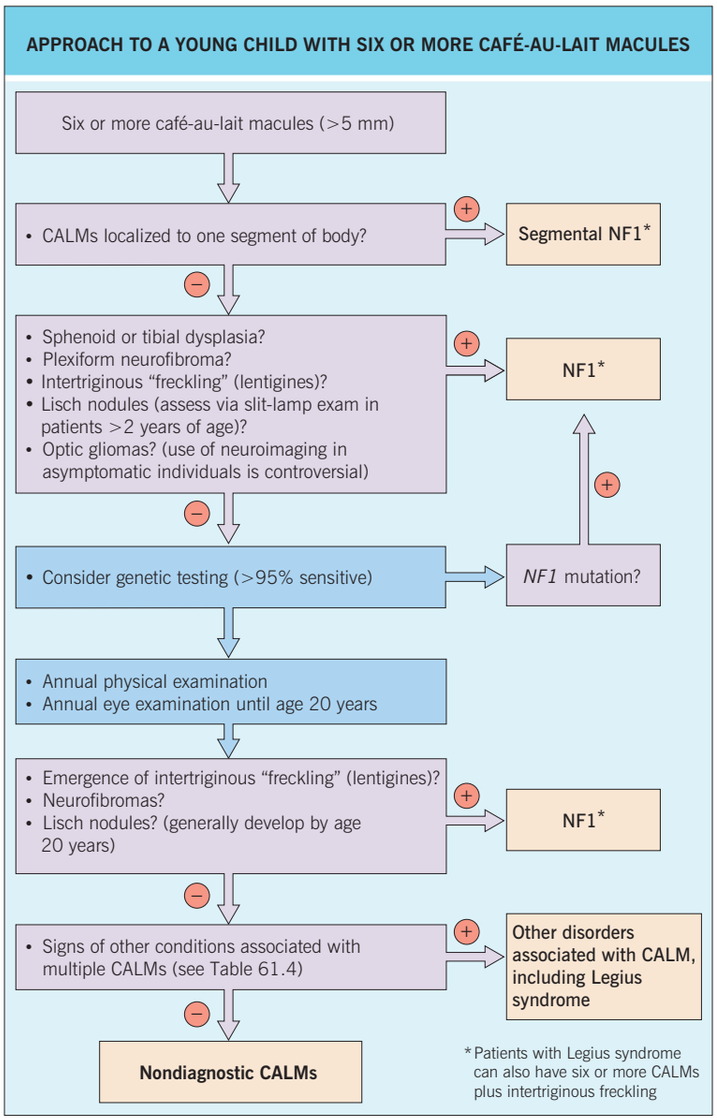


Fig. 61.10 Approach to a young child with six or more café-au-lait macules. More than half of these patients will eventually prove to have NF1 or, less often, one of the other CALM-associated syndromes (see Table 61.4). Although uncommon, the latter should be considered if other NF1 signs do not develop. Genetic analysis for NF1 is commercially available (www.genetics.uab.edu/medgenomics/#testservice).

segmental NF1 can coexist in the same patient[65]. The presence of CALMs in addition to lentigines increases the likelihood of segmental NF1. When individuals suspected of having segmental NF1 do not have a detectable mutation in the peripheral blood, the diagnosis can be confirmed by analyzing the *NF1* gene in melanocytes or Schwann cells cultured from a lesional skin biopsy specimen (e.g. of a CALM or neurofibroma, respectively).

Some patients with a familial tendency to develop multiple "typical" NF1-like CALMs, often in association with intertriginous "freckling", do not develop neurofibromas or Lisch nodules and lack an underlying *NF1* mutation. Recent studies have demonstrated that >70% of such individuals have a heterozygous germline mutation that inactivates the *SPRED1* gene, which encodes a protein that inhibits Ras–Raf interaction and thereby (like neurofibromin) negatively regulates MAPK signaling[66,67]. This autosomal dominant condition, known as *NF1-like syndrome* or *Legius syndrome*, accounts for ~2% of all patients who meet NF1 criteria[67]. Additional disorders associated with multiple CALMs, some caused by other genetic defects that lead to increased MAPK signaling, are presented in Table 61.4.

Historically, neurofibromatosis type 2 (NF2) has been discussed in the context of NF1. However, the clinical manifestations and molecular genetics of NF2 are distinct from those of NF1 (Table 61.5). NF2 is less common and has a lower frequency of cutaneous findings than NF1; Lisch nodules are not a feature of NF2. The tumor upon which a diagnosis of NF2 typically rests is the vestibular schwannoma. In the 1990 diagnostic criteria for NF2, neurofibromas were included as one of the index tumors[68]. However, in a 1997 update, neurofibromas were excluded from the diagnostic criteria for NF2[69]. Mautner et al.[70] found that 60% of NF2 patients had skin tumors, usually schwannomas appearing as flat or spherical nodular subcutaneous tumors of the peripheral nerves on the limbs and trunk. Although one-third of the affected individuals in this series had CALMs, only 2 of 88 patients had six or more CALMs.

McCune–Albright syndrome also features CALMs that are present at birth or become apparent during infancy. Additional manifestations of this sporadic disorder (thought to be lethal unless in a mosaic state) include polyostotic fibrous dysplasia and endocrine hyperfunction (most commonly precocious puberty). Affected tissues harbor an *activating* mutation in the gene encoding $G_s\alpha$ (i.e. the α-subunit of the G protein that stimulates adenylate cyclase), which leads to increased intracellular levels of cyclic AMP. Compared to the CALMs that occur in NF1, those of McCune–Albright syndrome and other forms of "pigmentary mosaicism" are generally larger, have a linear (e.g. broad bands along Blaschko's lines) or segmental distribution pattern, usually do not cross the midline, and have an irregular border that may resemble the "coast of Maine". The most common sites are the head, neck, trunk and buttocks.

PNFs need to be distinguished from congenital melanocytic nevi, especially when they are hyperpigmented with hypertrichosis. It is equally important not to misdiagnose patients with large congenital melanocytic nevi with smaller "satellite" lesions and prominent neurotization as having NF1.

Management

Management of NF1 patients requires a multidisciplinary approach[61,69]; if available, a multispecialty NF clinic can help to optimize care. Dermatologists are often consulted to assist in establishing the diagnosis in affected children. Evaluation of individuals newly diagnosed with NF1 should include a thorough history (personal and family) and physical examination, with particular attention to signs and symptoms of disease manifestations (see Table 61.2). As part of the initial care of NF1 patients, an in-depth educational discussion should include the natural history of the condition, possible medical complications and neurodevelopmental sequelae, and psychosocial considerations; genetic counseling should also be provided. Table 61.6 summarizes recommendations for the evaluation and management of NF1 patients[71,72]. Goals of longitudinal care include early recognition and treatment of complications, maximization of academic and vocational achievement, and minimization of the disease's psychosocial impact.

The cutaneous lesions of NF1 can lead to a variety of age-dependent management issues. PNFs may grow into large, bulky tumors during early childhood. Multidisciplinary teams are often required to excise deep and extensive neurofibromatous tissue, and the lesions tend to recur following surgery. CALMs do not need or respond well to treatment, although it may be desired for cosmetic purposes. When laser therapy is performed, CALMs tend to persist or recur (see Ch. 137). During adolescence and adulthood, removal of CNFs may be indicated for functional or cosmetic reasons. Simple surgical excision is the treatment of choice for selected bothersome lesions; laser ablation or electrocautery can be used to remove numerous small CNFs[73,74], but recurrences are common and hypertrophic scarring may develop.

Lifelong surveillance for the development of MPNSTs is essential, particularly for patients at increased risk of this malignancy due to the known presence of PNFs, polyneuropathy secondary to multiple nerve root tumors, a history of radiation therapy (with reports of MPNSTs arising in the radiation field), or a germline *NF1* microdeletion[39]. An increase in the growth rate, firmness, pain or neurologic symptoms associated with a PNF merits further evaluation. ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) can aid in the early detection of malignant change within PNFs[75]. Based on the largest study to date, histologic evaluation has been recommended for symptomatic lesions with a maximum standardized uptake value (SUVmax) of ≥3.5 on delayed imaging (4 hours after ^{18}F-FDG injection)[76].

Targeted medical treatments that are currently under investigation in NF1 patients include imatinib mesylate (a potent inhibitor of the

DISORDERS ASSOCIATED WITH MULTIPLE CAFÉ-AU-LAIT MACULES	
Disorder	**Notes**
NEUROFIBROMATOSIS AND RELATED DISORDERS	
Neurofibromatosis 1 (NF1)	AD; six or more CALMs in >90% of patients; mutations in *NF1* gene; see text
Neurofibromatosis 2	AD; six or more CALMs in minority of patients; mutations in *NF2* gene; see Table 61.5
Segmental NF1 (neurofibromatosis 5)	CALMs ± "freckling" in a block-like distribution or following Blaschko's lines; occasionally also neurofibromas; reflects mosaicism due to a postzygotic *NF1* mutation, which may involve the gonads in some patients
Legius (NF1-like) syndrome	AD; six or more CALMs in >80% and intertriginous "freckling" in ~50% of patients; lack neurofibromas, Lisch nodules, optic gliomas and typical osseous lesions of NF1; macrocephaly and learning disabilities are common; lipomas, hypopigmented macules and vascular anomalies in small minority; loss-of-function mutations in *SPRED1* gene, the protein product of which inhibits MAPK signaling
Watson syndrome	AD; short stature; pulmonic valve stenosis; MR; may also have Lisch nodules, axillary/inguinal freckling, and neurofibromas; allelic with NF1; 60/100*
Noonan syndrome	AD; short stature; pterygium colli; characteristic facies; cardiac defects, esp. pulmonic valve stenosis; skeletal and testicular abnormalities; keratosis pilaris atrophicans; lymphedema; nevi; activating mutations in *PTPN11* (allelic with LEOPARD syndrome) > *SOS1, RAF1* > *KRAS, NRAS*; patients with an NF1–Noonan overlap phenotype have mutations in *NF1* gene
Cardio-facio-cutaneous syndrome	AD; short stature; characteristic facies; low-set ears; cardiac defects; MR; sparse curly hair; dry skin to generalized ichthyosiform eruption; activating mutations in MAPK pathway genes – *BRAF* > *MEK1, MEK2* > *KRAS*
Jaffe–Campanacci syndrome	Disseminated non-ossifying fibromas of long and jaw bones; hypogonadism or cryptorchidism; MR; giant cell granulomas (jaws)
Juvenile xanthogranulomas + multiple CALMs	Juvenile myelomonocytic leukemia in some patients; association usually (but not always) occurs in the setting of NF1
Constitutional mismatch repair deficiency syndrome (childhood tumor syndrome with NF1 phenotype; Turcot syndrome type 1)	AR; multiple CALMs, axillary freckling, neurofibromas and/or CNS gliomas (i.e. features similar to NF1) as well as hypopigmented macules, hematologic malignancies and colorectal carcinoma; patients have mutations in both copies of a DNA mismatch repair gene, e.g. *MLH1, MSH2, MSH6, PMS2*; hereditary non-polyposis colorectal cancer (HNPCC) syndrome can occur in heterozygotes
McCune–Albright syndrome	Not inherited; presumably lethal unless in mosaic state; polyostotic fibrous dysplasia; hyperfunction of endocrine glands, esp. gonads (e.g. precocious puberty); CALMs usually appear during infancy and can overlie bony changes; CALMs classically end at midline, but so can larger CALMs of NF; CALMs may follow Blaschko's lines; activating mutations in the *GNAS1* gene that encodes $G_s\alpha$; 35/100*
DISORDERS WITH ADDITIONAL CUTANEOUS FINDINGS	
Tuberous sclerosis (TS)	AD; MR; seizures; hypopigmented macules; angiofibromas; fibrous plaques; mutations in *TSC1* and *TSC2* genes; see text
Westerhof syndrome†	AD; congenital hypopigmented macules; MR; growth retardation; ?forme fruste of TS
Piebaldism	AD; CALMs in involved as well as uninvolved skin; mutations in *KIT* proto-oncogene
Familial progressive hyper- and hypopigmentation	AD; CALMs of variable sizes admixed and overlapping with lentigines and hypopigmented macules and patches; activating mutations in *KITLG* gene
Mukamel syndrome	AR; premature graying (infancy); lentigines; depigmented macules; MR; spastic paraparesis, microcephaly, scoliosis
LEOPARD syndrome	Called café noir macules because of dark color; mutations in *PTPN11*; 38/100*
Partial unilateral lentiginosis	Agminated lentigines; debatable if associated neurologic or psychiatric problems; unilateral axillary freckling and Lisch nodules have been described (such patients may actually have segmental NF1)
Bannayan–Riley–Ruvalcaba syndrome‡	AD; penile lentigines; vascular malformations; lipomas; intestinal hamartomas; macrocephaly; mutations in *PTEN* gene; ≤10% of patients have CALMs
Cowden disease‡	AD; multiple trichilemmomas; cobblestoning of oral mucosa; palmoplantar keratoses; sclerotic fibromas, hamartomas and carcinoma of breast, thyroid, colon; mutations in *PTEN* gene; ≤10% of patients have CALMs
Gastrocutaneous syndrome†	AD; peptic ulcer/hiatal hernia; multiple lentigines; hypertelorism; myopia
Ataxia–telangiectasia	AR; telangiectasias of conjunctivae, head/neck, and acral sites; premature canities; cerebellar ataxia; abnormal DNA repair; lymphomas and leukemias; immunodeficiency; sinopulmonary infections; mutations in *ATM* gene; 20/100*
Bloom syndrome	AR; telangiectatic erythema of face; photosensitivity; growth retardation; increased sister chromatid exchanges; malignancies; hypogonadism; mutations in *BLM* gene that encodes the RecQ protein-like-3 DNA helicase
Fanconi anemia	AR; generalized hyperpigmentation, esp. flexural ± guttate "hypopigmented" macules; pancytopenia; skeletal malformations, e.g. aplasia radii; chromosomal fragility and malignancies, e.g. acute myelogenous leukemia
Chromosomal anomalies/ mosaicism	In particular, ring chromosomes (7, 11, 12, 15, 17); rearrangements of 7 and 14; ring 7 also associated with vascular lesions (hemangiomas and capillary malformations) and congenital melanocytic nevi
Extensive epidermal and sebaceous nevi	Sporadic; "syndrome" includes seizures, MR, musculoskeletal and ocular abnormalities; hypophosphatemic vitamin D-resistant rickets
Multiple endocrine neoplasia 1	AD; tumors of the pituitary, parathyroid, and pancreatic islet cells; multiple facial angiofibromas, collagenomas, lipomas; *MEN1* gene
Multiple endocrine neoplasia 2B	AD; mucosal neuromas; marfanoid habitus; medullary thyroid carcinoma; intestinal ganglioneuromatosis; pheochromocytoma; mutations in *RET* proto-oncogene
Johnson–McMillin syndrome	Probable AD; alopecia; anosmia; deafness; hypogonadism; microtia

*Estimates of prevalence of CALMs[62].
†To date, observed in a single family.
‡Overlapping conditions collectively referred to as PTEN hamartoma-tumor syndrome.
§Single case reports of multiple CALMs in association with X-linked hypohidrotic ectodermal dysplasia, woolly hair, and osteoma cutis.

Table 61.4 Disorders associated with multiple café-au-lait macules (CALMs). Multiple CALMs may also be seen in patients with segmental pigmentation disorder (see Ch. 67). AD, autosomal dominant; AR, autosomal recessive; *KITLG*; KIT ligand; LEOPARD, lentigines/ECG abnormalities/ocular hypertelorism/pulmonary stenosis/ abnormalities of genitalia/retardation of growth/deafness syndrome; MAPK, mitogen-activated protein kinase; MR, mental retardation.

Continued

DISORDERS ASSOCIATED WITH MULTIPLE CAFÉ-AU-LAIT MACULES	
Disorder	**Notes**
Tay syndrome[†]	?AR; growth retardation; MR; triangular face; cirrhosis; trident hands; CALMs; premature canities; vitiligo
OTHER DISORDERS[§]	
Silver–Russell syndrome	Growth retardation; triangular face; clinodactyly 5th finger; hemihypertrophy; epigenetic changes on chromosome 15p13 or maternal uniparental disomy of chromosome 7; 45/100*
Leschke syndrome	Growth retardation; MR; diabetes mellitus; genital hypoplasia; hypothyroidism

*Estimates of prevalence of CALMs[62].
[†]To date, observed in a single family.
[§]Single case reports of multiple CALMs in association with X-linked hypohidrotic ectodermal dysplasia, woolly hair, and osteoma cutis.

Table 61.4 Disorders associated with multiple café-au-lait macules (CALMs) (cont'd). Multiple CALMs may also be seen in patients with segmental pigmentation disorder (see Ch. 67). AR, autosomal recessive;. MR, mental retardation.

KEY FEATURES OF NEUROFIBROMATOSIS 2
• Autosomal dominant transmission; affects approximately 1 in 40 000 individuals • Approximately half of the cases are due to *de novo* mutations rather than inherited germline mutations (similar to NF1) • Bilateral vestibular schwannomas, meningiomas and spinal tumors • Two-thirds of patients develop cutaneous schwannomas, and approximately 50% develop café-au-lait macules (CALMs), but fewer in number compared to NF1* • No Lisch nodules or mental retardation/learning disabilities • *NF2* gene is located on chromosome 22q12 and encodes a cytoskeleton-associated protein of ~600 amino acids named merlin/neurofibromin 2, which is structurally related to the ERM (ezrin-radixin-moesin) protein family of membrane-cytoskeleton linkers
*In two large series of patients with NF2 (n = 161), only two individuals had more than five CALMs of the required size to meet NF1 criteria and over half of those with any CALMs had only one (41 of 72).

Table 61.5 Key features of neurofibromatosis 2 (NF2).

c-Kit receptor on mast cells; see Pathogenesis section and Fig. 61.2) for PNFs and dual inhibition of mammalian target of rapamycin (mTOR) and upstream *p*hosphatidyl*i*nositol *3-k*inase (PI3K)/AKT signaling for MPNSTs[24,77].

Resources for patients and families include Neurofibromatosis, Inc. (www.nfinc.org), the Neurofibromatosis Clinics Association (www.nfpittsburgh.org), the Children's Tumor Foundation (www.ctf.org), and the Neurofibromatosis Association UK (www.nfauk.org).

TUBEROUS SCLEROSIS

Synonyms: ■ Tuberous sclerosis complex (TSC) ■ Bourneville disease ■ Epiloia (*e*pilepsy, *l*ow *i*ntelligence, *a*ngiofibroma)

Key features

- Tuberous sclerosis is an autosomal dominant disorder with an incidence of approximately 1 in 10 000 births
- Key cutaneous features include hypopigmented macules, facial angiofibromas, collagenomas, and periungual fibromas
- The characteristic oral findings are gingival fibromas and dental enamel pits
- Hamartomas can be found in the eye as well as several internal organs, including the brain, kidneys, heart and lungs
- Seizures, mental deficits and neuropsychiatric disturbances are common
- Up to 75% of cases are due to new spontaneous mutations
- Mutations have been identified in two genes: *TSC1* and *TSC2*; their protein products are hamartin and tuberin, respectively

EVALUATION AND MANAGEMENT OF NEUROFIBROMATOSIS 1 (NF1) PATIENTS
AT TIME OF DIAGNOSIS AND ANNUALLY DURING CHILDHOOD AND ADOLESCENCE (UNLESS OTHERWISE INDICATED)
Dermatologic examination (especially if a plexiform neurofibroma [PNF] is present) • Surgical consultation if painful or disfiguring neurofibromas • PET/CT if rapid growth, increased firmness or persistent pain within an established PNF or the development of a new neurologic deficit* Ophthalmologic examination with visual assessment (prior to age 8 years) • Orbital/brain MRI if signs/symptoms of optic glioma Evaluation for scoliosis (also initial evaluation for tibial bowing) • Referral to orthopedics if scoliosis develops Neurologic examination, developmental/behavioral evaluation, and (in young children) measurement of head circumference • Orbital/brain and/or spinal MRI if neurologic signs/symptoms develop[†] • Comprehensive developmental assessment prior to starting school and if problems arise Cardiac assessment and measurement of blood pressure • Referral to cardiology if murmur is detected • Renal arteriography and 24-hour urine collection for catecholamines and metanephrines if hypertension develops Assessment for pubertal development • Orbital/brain MRI and referral to endocrinology if precocious puberty develops
MINIMUM ANNUAL EVALUATION FOR ADULTS WITH UNCOMPLICATED DISEASE
Dermatologic evaluation if PNF is present • PET/CT for indications described above Neurologic examination (especially if a PNF is present) • MRI and/or other studies as indicated if neurologic signs/symptoms develop Measurement of blood pressure • Evaluation as described above if hypertension develops In women, screening for breast cancer with clinical examination + mammography ± MRI (beginning by age 40 years)
POTENTIALLY AFFECTED FAMILY MEMBERS
Dermatologic examination for cutaneous manifestations of NF1 Ophthalmologic examination for Lisch nodules Consider genetic testing if a mutation has been identified in the proband
*Immediate assessment is required for any of these findings. [†]The role of neuroimaging in asymptomatic patients is controversial.

Table 61.6 Evaluation and management of neurofibromatosis 1 (NF1) patients. CT, computed tomography; MRI, magnetic resonance imaging; PET/CT, positron emission tomography/computed tomography.

Introduction

Tuberous sclerosis (TS) is an autosomal dominant disorder characterized by seizures, mental retardation and skin findings, including congenital hypomelanotic macules and facial angiofibromas. As with NF1, cutaneous lesions are often the initial clinical features, and, dermatologists are routinely called upon to assist in the diagnosis of TS.

History

During the mid-1800s, Virchow recognized scleromas in the brain and von Recklinghausen described a similar patient with both scleromas and myomata in the heart[37]. Between 1880 and 1900, Bourneville provided the first systematic descriptions of the disease, including neural and cutaneous findings. Vogt posited the classic triad of epilepsy, low intelligence and angiofibromas (termed the Vogt triad) in 1908, and Sherlock coined the term "epiloia" a few years later. In 1920, van der Hoeve described the significance of retinal hamartomas, which he termed "phakomas" (hence the designation "phakomatosis")[78]. At that time, examination of the ocular fundi was the only external access to the CNS before death.

Epidemiology

TS has an incidence of approximately 1 in 10 000 births, and the overall prevalence is estimated to be between 1 in 10 000 and 1 in 30 000[79,80].

Pathogenesis

TS is a hamartomatous condition characterized by disordered cellular proliferation, migration and differentiation. It has an autosomal dominant pattern of inheritance. However, the majority of affected individuals have new spontaneous mutations.

In the 1980s, TS kindreds from around the world were analyzed and the disease locus was mapped to chromosome 9q34 in a subset of affected families. Further study led to the discovery of a second disease locus on chromosome 16p13[81]. In 1994, Povey et al.[82] studied 32 TS families and found that about half demonstrated linkage to chromosome 9q34 (*TSC1*), whereas the other half showed linkage to chromosome 16p13 (*TSC2*).

In 1993, the *TSC2* gene on chromosome 16 was identified and found to be deleted or mutated in the subset of TS families linked to this region[83]. *TSC2* is composed of 41 small exons that encode an 1807 amino acid, 200 kDa protein referred to as tuberin. Like neurofibromin, tuberin contains a GAP domain (Fig. 61.11). Tuberin stimulates the GTPase activities of Rab5, a protein involved in endocytosis[84], and Rheb, a Ras-related protein that activates the mTOR pathway. By "turning off" Rheb, tuberin inhibits the cell growth and proliferation that result from mTOR signaling. The latter is a central regulator of cellular responses to nutrition, energy levels, and a variety of growth factors.

Despite its earlier localization, the *TSC1* gene was identified after *TSC2*[85]. The *TSC1* gene consists of 23 exons that encode a 130 kDa protein termed hamartin. Hamartin shares no sequence homology with tuberin or any other known tumor suppressor gene. However, hamartin interacts with tuberin[86] and other cytoskeletal components, and it functions together with tuberin to negatively regulate mTOR signaling (see Fig. 61.11)[87,88].

In large series of TS patients, *TSC2* mutations have been identified more frequently than *TSC1* mutations, with an overall ratio of approximately 3 : 1[89,90]. Individuals with *TSC2* mutations tend to have a more severe phenotype than those with *TSC1* mutations. There is a more equal proportion of *TSC2* and *TSC1* mutations in familial cases of TS, and among patients with *TSC2* mutations, familial cases tend to have a milder phenotype than *de novo* cases[89,90]; these findings may reflect a decreased likelihood of reproduction in more severely affected individuals. Some patients with mild sporadic TS are mosaics for a mutation in *TSC1* or *TSC2*. If such patients have gonadal involvement, they may pass on more severe disease to their offspring.

In mouse models, heterozygous Tsc1 mutant ($Tsc1^{+/-}$) mice develop renal and extrarenal tumors such as hepatic hemangiomas with loss of the wild-type *Tsc1* allele. Homozygous Tsc1 mutants ($Tsc1^{-/-}$) die during the embryonic period, frequently with evidence of lack of closure of the neural tube[91]. Heterozygous Tsc2 mice ($Tsc2^{+/-}$) display a high incidence of multiple bilateral renal cystadenomas, liver hemangiomas and lung adenomas. Progression to renal carcinoma, fatal bleeding from the liver hemangiomas, and angiosarcomas are occasionally observed. Like *Tsc1*-null mice, *Tsc2*-null ($Tsc2^{-/-}$) mice die during the embryonic period, but the cause is hepatic hypoplasia[92]. More recently, $Tsc2^{+/-}$ mice were shown to have abnormalities in learning and memory that were associated with hyperactive hippocampal mTOR signaling. Treatment of adult mice with the mTOR inhibitor rapamycin resulted in improved cognitive function. Whether similar results would be observed in humans awaits further study[93].

Clinical Features

As with NF1, the diagnosis of TS often involves a dermatologist, as some of the earliest findings of TS appear on the skin (Table 61.7).

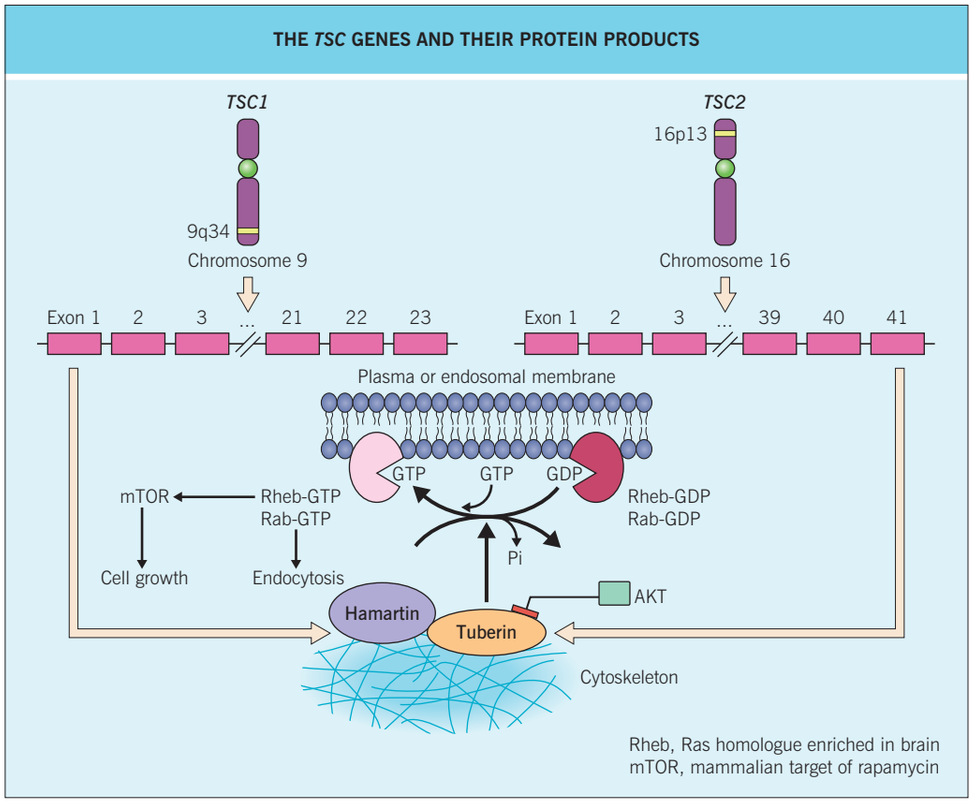


Fig. 61.11 The *TSC* genes and their protein products. *TSC1* and *TSC2* are located on chromosomes 9q34 and 16p13, respectively. The *TSC1* product, hamartin, interacts with the *TSC2* product, tuberin, and negatively regulates signaling by the small GTPases Rab and Rheb. Like Ras, the activity of Rab and Rheb is dependent upon bound GTP, and tuberin (like neurofibromin) accelerates hydrolysis of GTP to GDP in order to turn off Rab and Rheb. AKT, human homologue of the murine AKT8 retrovirus transforming sequence.

MAJOR CLINICAL FEATURES OF TUBEROUS SCLEROSIS
CUTANEOUS
• Facial angiofibromas (~80%) and fibrous plaque of the forehead (~20%)
• Hypomelanotic macules (90–100%) – polygonal; lance-ovate (ash leaf); confetti
• Shagreen patch (40–50%)
• Periungual fibromas (30–60%)
• Molluscum pendulum
• Café-au-lait macules
OCULAR
• Retinal hamartomas (~40%)
• Achromatic retinal patches (~40%)
• Retinal astrocytoma
SKELETAL
• Cystic areas of bone rarefaction, especially phalanges
DENTAL
• Pitted enamel (>90%)
• Gingival fibromas (up to 70%)
PULMONARY
• Lymphangioleiomyomatosis (~30% of women)
RENAL
• Multiple bilateral angiomyolipomas (75–90%)
• Cysts
• Carcinoma
ENDOCRINE
• Precocious puberty
• Hypothyroidism
NEUROLOGIC
• Seizures (70–95%)*
• Subependymal nodules (>80%)†
• Cortical tubers (>90%)
• Infantile spasms (~70%)
• Mental retardation
• Intracranial calcification on plain radiography or CT
• Giant cell astrocytoma
CARDIOVASCULAR
• Myocardial rhabdomyoma‡ (80%)
• Wolff–Parkinson–White syndrome
*Includes infantile spasms.
†Nearly all patients by puberty.
‡Increasingly difficult to distinguish from normal myocardium as patient ages.

Table 61.7 Major clinical features of tuberous sclerosis.

Oculocutaneous manifestations

The time course for developing the cutaneous findings of TS is shown in Figure 61.12. The hypomelanotic macules are not depigmented (as in vitiligo) but instead are hypopigmented (Fig. 61.13). A Wood's light can help to diagnose these lesions, which may be very subtle in children with lightly pigmented skin. The macules are usually present at birth or within the first few months of life, although their appearance is sometimes delayed until early childhood in individuals with fair skin). They may adopt several configurations, and small (<2 cm) polygonal or "thumbprint"-shaped macules are most common[94]. The lance-ovate hypopigmented macule or "ash leaf spot" (named after the Eastern Mountain ash tree) is rounded at one end and tapered at the other, and it can range from 1 to 12 cm in size. Although less frequent than polygonal macules, ash leaf spots are quite characteristic of TS.

More than 90% of TS patients have more than one hypomelanotic macule[95], and some have over 100 lesions. Scores of small (1–2 mm), "guttate" hypopigmented macules (also known as "white freckles" or "confetti" macules) may also be seen, especially on the extremities (Fig. 61.14). Although these guttate lesions occur in less than 5% of affected infants, they are probably the most specific pigmentary manifestation of TS[94,95]. Areas of poliosis are also occasionally observed in infants with TS.

Approximately 1–4% of healthy infants and children have a circumscribed hypopigmented macule or patch, i.e. a nevus depigmentosus[94,96,97]. Debard and Richardet[96] examined the skin of 9737 infants aged 1–18 months and found that 0.7% had one or two white spots that were larger than 1 cm; however, no unaffected infant had more than three spots. Thus, three or more hypomelanotic macules was chosen as a major criterion for the clinical diagnosis of TS (Table 61.8).

Café-au-lait macules (CALMs) have been reported in up to 30% of patients with TS and are usually present within the first few months of life[94,95]. Most TS patients, however, have fewer than the six CALMs required to diagnose NF1.

Angiofibromas (previously referred to as "adenoma sebaceum"), which are not typically present at birth, start to appear in the centrofacial area as early as the first 2 years of life and develop by adolescence in approximately 80% of TS patients. The lesions may begin with mild erythema of the cheeks and forehead and then mature into pink to red or red–brown papules or papulonodules, which may coalesce into plaques. The papules are often dome-shaped and have a smooth, shiny surface (Fig. 61.15). With the exception of individuals with mosaic TS, facial angiofibromas have a bilateral and symmetric distribution.

A larger variant of the angiofibroma, the fibrous plaque of the forehead, can be seen in about 20% of TS patients[95]. The forehead plaques are usually firm and yellow–brown to pink–tan in color (see Fig. 61.15). They grow very slowly over time.

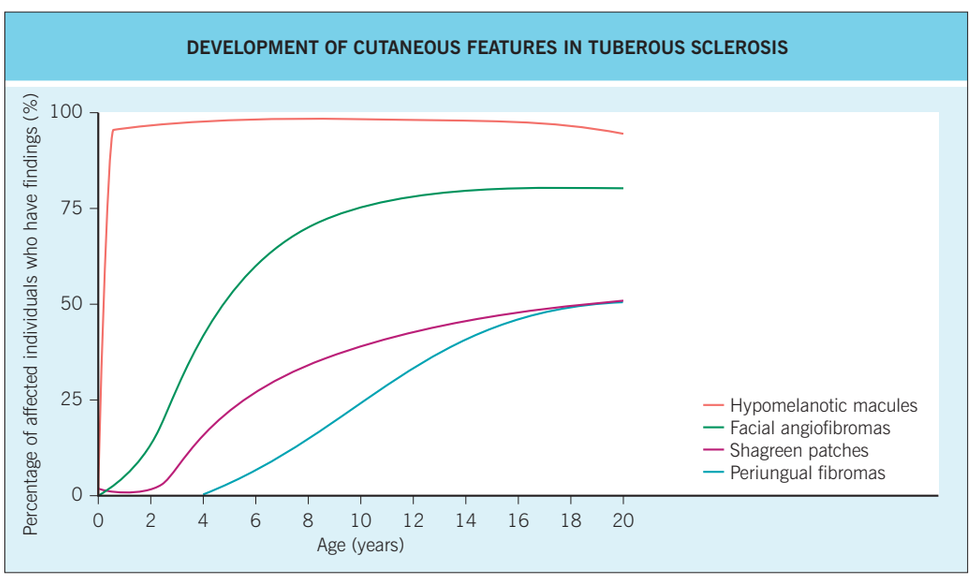


Fig. 61.12 Development of cutaneous features in tuberous sclerosis. Hypomelanotic macules are usually the only cutaneous finding at birth.

DIAGNOSTIC CRITERIA FOR TUBEROUS SCLEROSIS COMPLEX
MAJOR FEATURES
Facial angiofibromas or forehead plaque
Non-traumatic ungual or periungual fibromas
Hypomelanotic macules (three or more)
Shagreen patch (connective tissue nevus)
Multiple retinal nodular hamartomas
Cortical tubers
Subependymal nodules
Subependymal giant cell astrocytoma
Renal angiomyolipoma
Cardiac rhabdomyoma, single or multiple
Lymphangioleiomyomatosis
MINOR FEATURES
"Confetti" hypopigmented skin lesions
Multiple, randomly distributed pits in dental enamel
Gingival fibromas
Retinal achromic patch
Cerebral white matter radial migration lines
Multiple renal cysts
Hamartomatous rectal polyps
Bone cysts
Non-renal hamartoma
Definite tuberous sclerosis
• Either two major features *or* one major feature plus two minor features
Probable tuberous sclerosis
• One major plus one minor feature
Possible tuberous sclerosis
• Either one major feature *or* two or more minor features
Key:
Cutaneous *Extracutaneous*

Table 61.8 Diagnostic criteria for tuberous sclerosis complex[98].

Fig. 61.13 Ash leaf macule in a child with tuberous sclerosis.

Fig. 61.14 Guttate leukoderma of tuberous sclerosis. Multiple 1–2 mm hypopigmented "confetti" macules.
Courtesy, Jean L Bolognia, MD.

Fig. 61.15 Facial angiofibromas and fibrous plaques. Multiple shiny, dome-shaped papules on the cheeks and nose of two adolescents. Fibrous plaques can occur on the cheek (**A**) as well as on the forehead (**B**).
B, Courtesy, Julie V Schaffer, MD.

A characteristic truncal lesion is the shagreen ("leather") patch, which represents a connective tissue nevus. These occur most commonly in the lumbosacral area and typically begin to develop at around 2 years of age (although they occasionally become apparent earlier), eventually affecting approximately half of TS patients[95]. Clinically, they appear as skin-colored, hyperpigmented or (occasionally) hypopigmented plaques that can reach up to 10 cm in diameter and often have an uneven surface (Fig. 61.16). Multiple lesions may be present. A distinctive feature is prominent, but slightly depressed, follicular openings, giving rise to a pigskin-like appearance.

Periungual papules or nodules (Koenen tumors; Fig. 61.17) begin to develop later in childhood and can continue to form throughout adulthood. These fibromas are seen more commonly around the toenails than the fingernails, and some lesions lead to distortion of the nail plate (e.g. a longitudinal groove) without a visible tumor. Soft, pedunculated, skin-colored papules and nodules (molluscum pendulum) can also be seen in some TS patients. These lesions favor flexural areas, such as the neck, axillae and groin, and resemble large acrochordons.

Fig. 61.16 Connective tissue nevi (shagreen patches) in tuberous sclerosis. These plaques can be hyperpigmented (**A**) or hypopigmented (**B**) relative to the patient's background skin. The surface is said to resemble leather or pigskin. *A, Courtesy, Julie V Schaffer, MD.*

Fig. 61.17 Periungual fibromas of tuberous sclerosis. Multiple fibromas of the toes arising in a periungual location.

Fig. 61.18 Retinal hamartomas of tuberous sclerosis. *Courtesy, Jean L Bolognia, MD.*

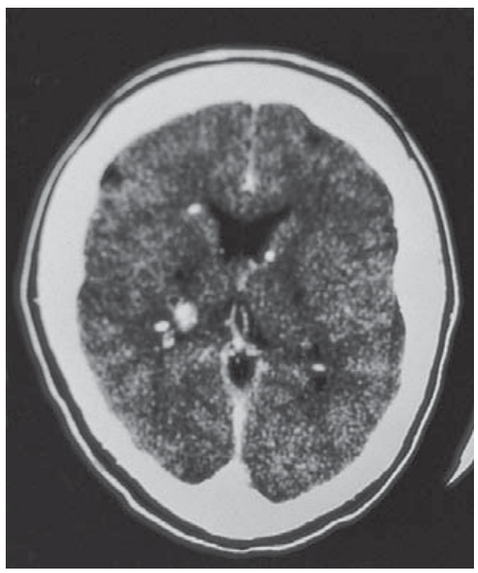


Fig. 61.19 Cranial CT demonstrating multiple calcified subependymal nodules in a paraventricular location. *Courtesy, Jean L Bolognia, MD.*

Gingival fibromas have been described in 10–70% of affected individuals[94,99]. Enamel pits are seen in nearly all TS patients and (upon close examination) in 70% of unaffected individuals; however, in one study, 70% of TS patients had more than 14 pits, compared with less than 5% of controls[100]. Thus, the presence of many enamel pits is suggestive of TS.

Retinal lesions are present in about half of TS patients, with retinal hamartomas seen in approximately 40% (Fig. 61.18). The most common morphologic type of hamartoma is the flat, translucent lesion (70%), followed by the multinodular "mulberry" lesion (55%) and the transitional-type lesion (9%). Punched-out areas of retinal depigmentation can also be found in about 40% of affected individuals[101]. Most ocular lesions in TS patients do not lead to visual loss.

Neurologic manifestations

Infantile spasms occur in approximately 70% of infants with TS. They are characterized by massive flexion or extension of the limbs, trunk and head lasting from a fraction of a second to 3 seconds, occurring in series separated by intervals of a few seconds, for periods of several minutes. These spasms typically begin at about 3 months of age, as opposed to other types of TS-associated seizures, which usually develop after 1 year of age[102]. The EEG changes seen in this setting have been termed hypsarrhythmia[102,103].

Mental deficits occur with a high frequency in children and adults with TS[102,103]. Other neuropsychiatric disturbances, including autism, attention deficit disorders and psychoses, are also common[104–106].

Multiple calcified subependymal nodules along the ventricular surface can be seen on CT scan (Fig. 61.19) in over 80% of TS patients under the age of 2 years. These nodules can be found in essentially all patients by puberty[107]. Occasionally, subependymal giant cell astrocytomas develop that can resemble these more benign nodules. However, additional radiographic characteristics and clinical behavior over time (astrocytomas tend to enlarge, whereas nodules remain stable) are helpful in distinguishing between the two types of lesions[98]. Multiple cortical tubers (an abnormal growth of neuronal and glial cells), which were once thought to be pathognomonic for TS, can also be detected by neuroimaging (e.g. MRI) in the vast majority of patients[107].

Cardiovascular manifestations

Cardiac rhabdomyomas, which can be detected prenatally as well as after birth by echocardiography or MRI, are found in over 80% of infants with TS[107]. However, cardiac rhabdomyomas tend to involute during the first 3 years of life[108], and they often disappear altogether by adulthood. Arrhythmias, especially Wolff–Parkinson–White syndrome, appear to be more common in affected individuals[109].

Renal manifestations

Multiple bilateral angiomyolipomas are frequently noted on routine renal ultrasounds of TS patients. Most of these lesions are asymptomatic, especially during childhood and when they measure less than 4 cm in diameter[108]. Children with TS who develop severe renal cysts often have a contiguous gene syndrome in which both *TSC2* and the polycystic kidney disease (*PKD*) genes are lost in a single large chromosomal deletion[110]. Occasionally, renal cell carcinomas develop in TS patients.

Other manifestations

Although once thought to be rare, pulmonary lymphangioleiomyomatosis is often asymptomatic and occurs in up to one-third of women with TS. On high-resolution CT scan, these lesions appear as cysts. Men rarely develop this manifestation of TS[111], and estrogen is suspected to be involved in stimulating growth of smooth muscle cells in the lung. Hamartomatous polyps in the gastrointestinal tract have also been reported in affected individuals[112,113].

Pathology

Hypopigmented macules have a reduction in the amount of epidermal melanin but a normal number of melanocytes. The melanocytes have poorly developed dendrites[114]. On electron microscopy, small, immature melanosomes are seen whose number, degree of melanization and transfer to keratinocytes are reduced[114–116].

Angiofibromas consist of an irregular proliferation of fibrous tissue and blood vessels. Expansion of the hamartomatous process can lead to compression of adnexae. Characteristically, there is perifollicular concentric fibrosis. Sebaceous glands are normal in size and number but are often prominent in the background facial skin, especially after puberty.

The *shagreen patch* (Fig. 61.20) and *periungual fibromas* represent collagenomas. The dermis is replaced by thick bundles of collagen, and elastin fibers are typically absent. The fibroblasts may be large and morphologically atypical.

Differential Diagnosis

Prior to 1998, a diagnosis of TS could be rendered with a single primary feature (facial angiofibromas, periungual fibromas, cortical tubers, subependymal nodule or astrocytoma, multiple calcified subependymal nodules, or multiple retinal hamartomas). However, debate regarding the specificity of TS-related findings led to a revision of the diagnostic criteria for TS complex in 1998 (see Table 61.8)[98]. Four of the major features are cutaneous, and a thorough dermatologic examination frequently helps to establish the diagnosis. Although seizures occur in the majority of affected infants, the possibility of TS is often considered in asymptomatic infants with multiple hypomelanotic macules. An approach to this clinical situation is outlined in Figure 61.21. Echocardiography can be helpful in establishing the diagnosis in infants and is easier to perform in this age group than cranial CT or MRI studies to detect CNS lesions.

Comprehensive genetic testing (including sequencing and duplication/deletion analysis) is clinically available and can identify a mutation in the *TSC1* or *TSC2* gene in approximately 85% of individuals who meet criteria for TS. TS patients without a detectable mutation may be mosaics or have an unusual mutation in a non-coding region, and they tend to have relatively mild disease.

Multiple facial angiofibromas, collagenomas, gingival papules, confetti-like hypomelanotic macules and CALMs can occur in patients with multiple endocrine neoplasia type 1 (MEN 1; see Ch. 63)[117]. The overlap in cutaneous phenotype suggests that the protein product of the *MEN1* gene may affect the same pathways (e.g. mTOR signaling) as tuberin and hamartin. Multiple facial angiofibromas have also been observed in adults with Birt–Hogg–Dubé syndrome (see Ch. 111).

As discussed above, a nevus depigmentosus represents a common cause of a congenital hypopigmented macule or patch, and some infants have more than one of these lesions. A larger nevus depigmentosus that has a segmental distribution (also referred to as segmental pigmentation disorder) or follows Blaschko's lines may be composed of multiple hypopigmented macules and patches but in one region of the body. Piebaldism presents with congenital leukoderma, and vitiligo occasionally develops soon after birth. Piebaldism can usually be easily distinguished by its distribution (midportions of the extremities and mid-abdomen), the presence of normal and hyperpigmented "islands" within the areas of leukoderma, and chalk-white depigmentation (rather than hypopigmentation as in TS) due to an absence of melanocytes within affected areas. In vitiligo there is also depigmentation due to an absence of melanocytes. Postinflammatory hypopigmentation (e.g. from atopic or seborrheic dermatitis) is a frequent cause of acquired hypopigmented macules in infants; a history of preceding erythema or roughness can usually be elicited. Idiopathic guttate hypomelanosis

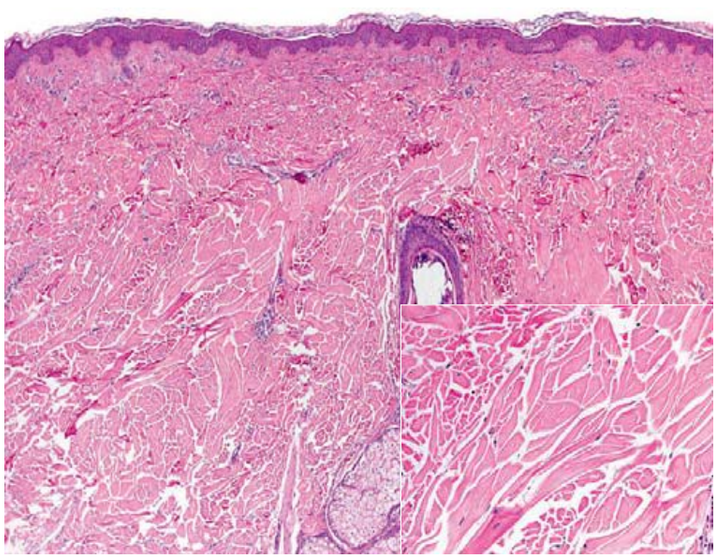


Fig. 61.20 Histology of a shagreen patch. Increased collagen forming thickened bundles in the dermis. *Courtesy, Lorenzo Cerroni, MD.*

EVALUATION AND MANAGEMENT OF TUBEROUS SCLEROSIS (TS) PATIENTS
NEWLY DIAGNOSED
Neurodevelopmental and behavioral evaluation (especially for children)
Ophthalmologic examination
Cranial CT or MRI*
Electroencephalogram (EEG; only if history of seizures)
Electrocardiogram (ECG)
Echocardiography (if cardiac symptoms or ECG abnormalities; also generally done in children <5 years of age)
Renal ultrasonography to detect polycystic kidney disease (and angiomyolipomas)
Chest CT to detect lymphangioleiomyomatosis (adult women only)
ESTABLISHED (TO MONITOR FOR COMPLICATIONS)
Comprehensive developmental assessment at school entry and as needed for educational/behavioral concerns
Ophthalmologic examination (as needed)
Cranial CT or MRI every 1–3 years during childhood and adolescence*,†
EEG (only to monitor seizure treatment or if new-onset seizures or cognitive performance declines)
Echocardiography (only if cardiac symptoms occur)
Renal ultrasonography every 1–3 years if no history of renal lesions, twice yearly if known angiomyolipomas‡
Chest CT (to screen adult women for lymphangioleiomyomatosis; thereafter, if pulmonary symptoms develop)
POTENTIALLY AFFECTED FAMILY MEMBERS
Dermatologic and (if skin findings not diagnostic) ophthalmologic examinations for manifestations of TS
Consider cranial CT, renal ultrasonography or (for infants only) echocardiography
Consider genetic testing if a mutation has been identified in the proband
*Findings have correlated with seizure activity and cognitive deficits in some but not all studies.
†Assess for enlarging lesions suggestive of subependymal giant cell astrocytomas, which are most common during childhood.
‡Angiomyolipomas >3.5–4 cm in diameter have a greater risk of hemorrhage and should be assessed with CT or MRI; prophylactic renal arterial embolization or kidney-sparing surgery is recommended for symptomatic lesions of this size.

Table 61.9 Evaluation and management of tuberous sclerosis (TS) patients. CT, computed tomography; MRI, magnetic resonance imaging.

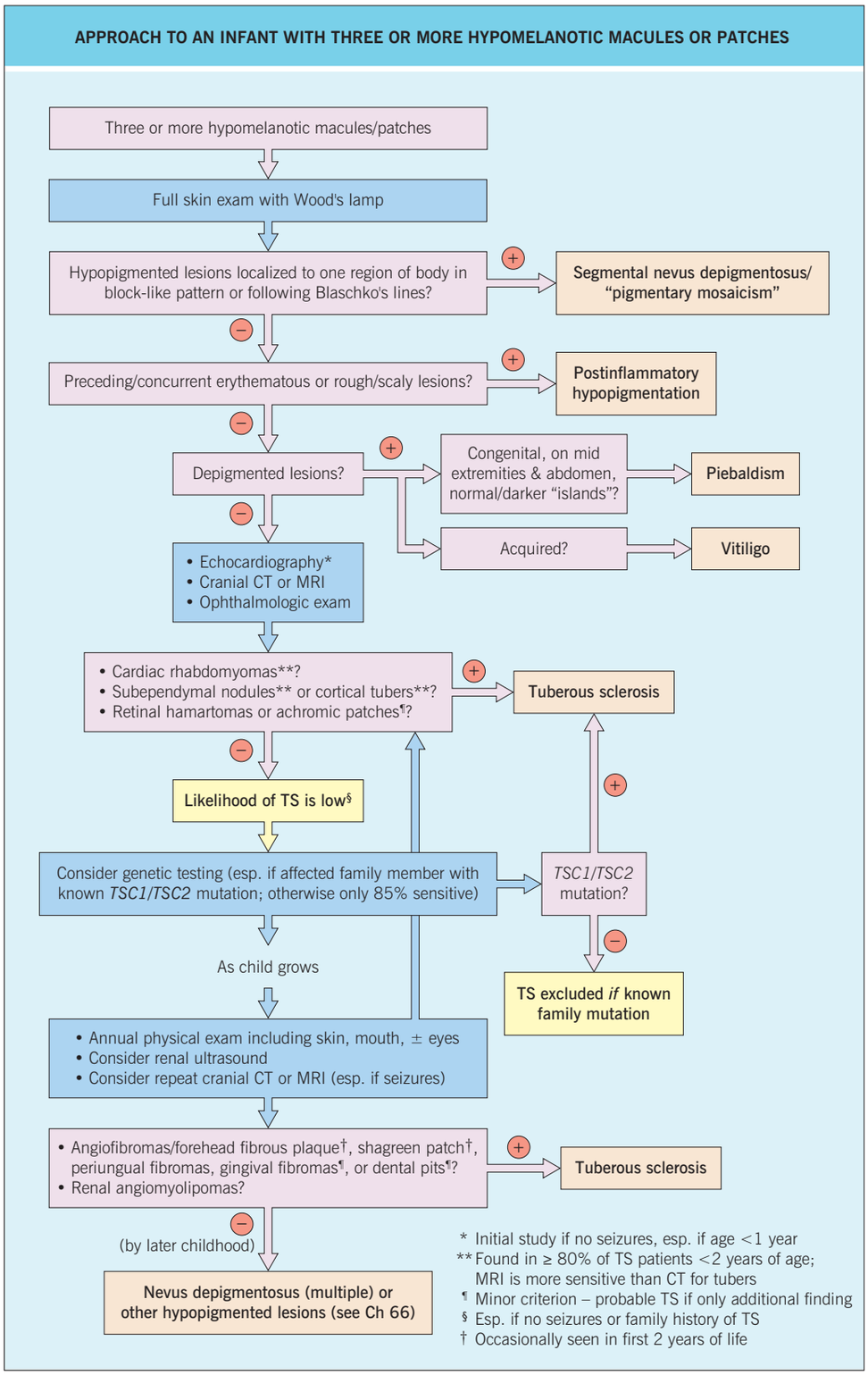


Fig. 61.21 Approach to an infant with three or more hypomelanotic macules or patches. A child with fewer than three macules and no family history of tuberous sclerosis (TS) has an extremely low likelihood of having this disease.

(IGH) may resemble the confetti-like leukoderma of TS; however, IGH is an acquired disorder with a preference for the shins and extensor forearms of older adults.

A congenital smooth muscle hamartoma can present during infancy as a firm, skin-colored to hyperpigmented plaque that may resemble a shagreen patch, but often it contains follicular papules (due to hyperplastic arrector pili muscles), accentuates with rubbing (pseudo-Darier's sign), and has associated hypertrichosis rather than prominent but depressed follicular orifices. Histologically, smooth muscle hamartomas are characterized by numerous intradermal bundles of smooth muscle rather than collagen.

The differential diagnosis for facial angiofibromas may include acne vulgaris and trichoepitheliomas. Individual acneiform lesions should resolve over a period of weeks. Trichoepitheliomas are clinically less red in color, although a biopsy is often indicated to ascertain a definitive diagnosis. Additional causes of multiple facial papules are listed in Table 36.1 and Figure 111.4.

Management

Nearly every organ can be affected by TS, and clinical findings vary tremendously even within families. Certain signs and complications typically appear at birth, whereas others develop much later in life. The NIH-sponsored Tuberous Sclerosis Consensus Conference subcommittee's recommendations for the evaluation and management of individuals newly diagnosed with TS, established patients, and potentially affected family members are presented in Table 61.9[108,108a].

Investigations in TS patients should focus on detecting disease manifestations and complications that are potentially significant and treatable, and it is important to provide genetic counseling to affected individuals and families.

Increasing numbers and sizes of facial angiofibromas may become a cosmetic concern as the patient grows older. Techniques such as dermabrasion, electrosurgery and treatment with ablative (including fractional resurfacing) and pulsed dye (for thinner erythematous lesions) lasers have been used with variable efficacy. Patients should understand that the lesions often recur after treatment.

In clinical trials, targeted therapy with the mTOR inhibitor rapamycin in TS patients has led to reduction in the size of renal angiomyolipomas and (in two of three trials to date) improvement of lung function in women with lymphangioleiomyomatosis[118,118a]. Rapamycin-induced regression of TS-associated subependymal giant cell astrocytomas has also been reported. In addition, improvement of facial angiofibromas with oral or topical administration of rapamycin (e.g. in a 1% solution or ointment) has been described[119,120,121]. Further studies (including large randomized control trials) of mTOR inhibitors for the treatment of renal, pulmonary, neurologic and cutaneous manifestations of TS are underway.

Resources for patients and families include the Tuberous Sclerosis Alliance (www.tsalliance.org), the National Institutes of Neurological Disorders and Stroke (www.ninds.nih.gov/disorders/tuberous_sclerosis/tuberous_sclerosis.htm) and the Tuberous Sclerosis Association (www.tuberous-sclerosis.org).

REFERENCES

1. Zanca A. Antique illustrations of neurofibromatosis. Int J Dermatol. 1980;19:55–8.
2. Ragge NK, Munier FL. Ancient neurofibromatosis. Nature. 1994;368:815.
3. von Recklinghausen FD. Ueber die multiplen Fibrome der Haut und ihre Beziehung zu den multiplen Neuromen. Berlin: August Hirschwald, 1882.
4. Crowe FW, Schull WJ, Neel JV. A Clinical, Pathological and Genetic Study of Multiple Neurofibromatosis. Springfield, IL: Charles C Thomas, 1956.
5. Samuelsson B, Axelsson R. Neurofibromatosis. A clinical and genetic study of 96 cases in Gothenburg, Sweden. Acta Derm Venereol Suppl (Stockh). 1981;95:67–71.
6. Huson SM, Compston DA, Clark P, Harper PS. A genetic study of von Recklinghausen neurofibromatosis in south east Wales. I. Prevalence, fitness, mutation rate, and effect of parental transmission on severity. J Med Genet. 1989;26:704–11.
7. Ritter JL, Riccardi VM. Von Recklinghausen neurofibromatosis (NF-I): an argument for very high penetrance and a comparison of sporadic and inherited cases. Am J Hum Genet. 1985;37:A135.
8. Skolnick MH, Ponder B, Seizinger B. Linkage of NF1 to 12 chromosome 17 markers: a summary of eight concurrent reports. Genomics. 1987;1:382–3.
9. Fountain JW, Wallace MR, Bruce MA, et al. Physical mapping of a translocation breakpoint in neurofibromatosis. Science. 1989;244:1085–7.
10. Ledbetter DH, Rich DC, O'Connell P, et al. Precise localization of NF1 to 17q11.2 by balanced translocation. Am J Hum Genet. 1989;44:20–4.
11. Wallace MR, Marchuk DA, Anderson LB, et al. Type 1 neurofibromatosis gene: identification of a large transcript disrupted in three NF 1 patients. Science. 1990;249:181–6.
12. Cawthon RM, Weiss R, Xu G, et al. A major segment of the neurofibromatosis type 1 gene: cDNA sequence, genomic structure, and point mutations. Cell. 1990;62:193–201.
13. Viskochil D, Buchberg AM, Xu G, et al. Deletions and a translocation interrupt a cloned gene at the neurofibromatosis type 1 locus. Cell. 1990;62:187–92.
14. Shen MH, Harper PS, Upadhyaya M. Molecular genetics of neurofibromatosis type 1 (NF1). J Med Genet. 1996;33:2–17.
15. Kluwe L, Siebert R, Gesk S, et al. Screening 500 unselected neurofibromatosis 1 patients for deletions of the NF1 gene. Hum Mutat. 2004;23:111–16.
16. Upadhyaya M, Huson SM, Davies M, et al. An absence of cutaneous neurofibromas associated with a 3-bp inframe deletion in exon 17 of the NF1 gene (c.2970-2972 delAAT): evidence of a clinically significant NF1 genotype-phenotype correlation. Am J Hum Genet. 2007;80:140–51.
17. Pasmant E, Sabbagh A, Spurlock G, et al. NF1 microdeletions in neurofibromatosis type 1: from genotype to phenotype. Hum Mutat. 2010;31:E1506–18.
18. Mautner VF, Kluwe L, Friedrich RE, et al. Clinical characterisation of 29 neurofibromatosis type-1 patients with molecularly ascertained 1.4 Mb type-1 NF1 deletions. J Med Genet. 2010;47:623–30.
19. Wigler MH. Oncoproteins. GAPs in understanding Ras. Nature. 1990;346:696–7.
20. Gregory PE, Gutmann DH, Mitchell A, et al. Neurofibromatosis type 1 gene product (neurofibromin) associates with microtubules. Somat Cell Mol Genet. 1993;19:265–74.
21. Colman SD, Williams CA, Wallace MR. Benign neurofibromas in type 1 neurofibromatosis (NF1) show somatic deletions of the NF1 gene. Nat Genet. 1995;11:90–2.
22. De Schepper S, Maertens O, Callens T, et al. Somatic mutation analysis in NF1 café au lait spots reveals two NF1 hits in the melanocytes. J Invest Dermatol. 2008;128:1050–3.
23. Zhu Y, Ghosh P, Charnay P, et al. Neurofibromas in NF1: Schwann cell origin and role of tumor environment. Science. 2002;296:920–2.
24. Yang FC, Ingram DA, Chen S, et al. Nf1-dependent tumors require a microenvironment containing Nf1+/- and c-kit-dependent bone marrow. Cell. 2008;135:437–48.
25. Gutmann DH, Collins FS. Neurofibromatosis type 1. In: Vogelstein B, Kinzler KW (eds). The Genetic Basis of Human Cancer. New York: McGraw-Hill, 1998:423–42.
26. White AK, Smith RJ, Bigler CR, et al. Head and neck manifestations of neurofibromatosis. Laryngoscope. 1986;96:732–7.
27. Szudek J, Birch P, Friedman JM. Growth in North American white children with neurofibromatosis 1 (NF1). J Med Genet. 2000;37:933–8.
28. Listernick R, Charrow J, Greenwald MJ, Esterly NB. Optic gliomas in children with neurofibromatosis type 1. J Pediatr. 1989;114:788–92.
29. Listernick R, Darling C, Greenwald M, et al. Optic pathway tumors in children: the effect of neurofibromatosis type 1 on clinical manifestations and natural history. J Pediatr. 1995;127:718–22.
30. Kulkantrakorn K, Geller TJ. Seizures in neurofibromatosis 1. Pediatr Neurol. 1998;19:347–50.
31. DeBella K, Szudek J, Friedman JM. Use of the National Institutes of Health criteria for diagnosis of neurofibromatosis 1 in children. Pediatrics. 2000;105:608–14.
32. Cnossen MH, Moons KG, Garssen MP, et al. Minor disease features in neurofibromatosis type 1 (NF1) and their possible value in diagnosis of NF1 in children < or = 6 years and clinically suspected of having NF1. Neurofibromatosis team of Sophia Children's Hospital. J Med Genet. 1998;35:624–7.
33. Blatt J, Jaffe R, Deutsch M, Adkins JC. Neurofibromatosis and childhood tumors. Cancer. 1986;57:1225–9.
34. Akbarnia BA, Gabriel KR, Beckman E, Chalk D. Prevalence of scoliosis in neurofibromatosis. Spine. 1992;17:S244–8.
35. Riccardi VM, Powell PP. Neurofibrosarcoma as a complication of von Recklinghausen neurofibromatosis. Neurofibromatosis. 1989;2:152–65.
35a. Duong TA, Bastuji-Garin S, Valeyrie-Allanore L, et al. Evolving pattern with age of cutaneous signs in neurofibromatosis type 1: a cross-sectional study of 728 patients. Dermatology. 2011;222:269–73.
36. Burwell RG, James NJ, Johnston DI. Café-au-lait spots in schoolchildren. Arch Dis Child. 1982;57:631–2.
37. Pivnick EK, Riccardi VM. The neurofibromatoses. In: Freedberg IM, Eisen AZ, Wolff K, et al. Fitzpatrick's Dermatology in General Medicine, 6th edn. New York: McGraw-Hill, 2003:1825–33.
38. Westerhof W, Konrad K. Blue-red macules and pseudoatrophic macules: additional cutaneous signs in neurofibromatosis. Arch Dermatol. 1982;118:577–81.
39. Mautner VF, Asuagbor FA, Dombi E, et al. Assessment of benign tumor burden by whole-body MRI in patients with neurofibromatosis 1. Neuro Oncol. 2008;10:593–8.
40. Riccardi VM. Pathophysiology of neurofibromatosis. IV. Dermatologic insights into heterogeneity and pathogenesis. J Am Acad Dermatol. 1980;3:157–66.
41. Storm FK, Eilber FR, Mirra J, Morton DL. Neurofibrosarcoma. Cancer. 1980;45:126–9.
42. McGaughran JM, Harris DI, Donnai D, et al. A clinical study of type 1 neurofibromatosis in north west England. J Med Genet. 1999;36:197–203.
43. Korf BR. Diagnostic outcome in children with multiple café au lait spots. Pediatrics. 1992;90:924–7.
44. Cambiaghi S, Restano L, Caputo R. Juvenile xanthogranuloma associated with neurofibromatosis 1: 14 patients without evidence of hematologic malignancies. Pediatr Dermatol. 2004;21:97–101.
45. Zvulunov A, Barak Y, Metzker A. Juvenile xanthogranuloma, neurofibromatosis, and juvenile chronic myelogenous leukemia. World statistical analysis. Arch Dermatol. 1995;131:904–8.
46. Brems H, Park C, Maertens O, et al. Glomus tumors in neurofibromatosis type 1: genetic, functional, and clinical evidence of a novel association. Cancer Res. 2009;69:7393–401.
47. Lewis RA, Riccardi VM. Von Recklinghausen neurofibromatosis. Incidence of iris hamartomata. Ophthalmology. 1981;88:348–54.
48. Otsuka F, Kawashima T, Imakado S, et al. Lisch nodules and skin manifestation in neurofibromatosis type 1. Arch Dermatol. 2001;137:232–3.
49. Lewis RA, Gerson LP, Axelson KA, et al. von Recklinghausen neurofibromatosis. II. Incidence of optic gliomata. Ophthalmology. 1984;91:929–35.
50. Packer RJ, Bilaniuk LT, Cohen BH, et al. Intracranial visual pathway gliomas in children with neurofibromatosis. Neurofibromatosis. 1988;1:212–22.
51. Habiby R, Silverman B, Listernick R, Charrow J. Precocious puberty in children with neurofibromatosis type 1. J Pediatr. 1995;126:364–7.
52. Cnossen MH, Stam EN, Cooiman LC, et al. Endocrinologic disorders and optic pathway gliomas in children with neurofibromatosis type 1. Pediatrics. 1997;100:667–70.
53. Sorensen SA, Mulvihill JJ, Nielsen A. Long-term follow-up of von Recklinghausen neurofibromatosis. Survival and malignant neoplasms. N Engl J Med. 1986;314:1010–15.
54. Duffner PK, Cohen ME, Seidel FG, Shucard DW. The significance of MRI abnormalities in children with neurofibromatosis. Neurology. 1989;39:373–8.
55. Kraut MA, Gerring JP, Cooper KL, et al. Longitudinal evolution of unidentified bright objects in children with neurofibromatosis-1. Am J Med Genet A. 2004;129A:113–19.
56. Chabernaud C, Sirinelli D, Barbier C, et al. Thalamo-striatal T2-weighted hyperintensities (unidentified bright objects) correlate with cognitive impairments in neurofibromatosis type 1 during childhood. Dev Neuropsychol. 2009;34:736–48.
57. Riccardi VM, Eichner JE. Neurofibromatosis: Phenotype, Natural History, and Pathogenesis. Baltimore, MD: Johns Hopkins University Press, 1986.
58. Walther MM, Herring J, Enquist E, et al. von Recklinghausen's disease and pheochromocytomas. J Urol. 1999;162:1582–6.

59. Fossali E, Signorini E, Intermite RC, et al. Renovascular disease and hypertension in children with neurofibromatosis. Pediatr Nephrol. 2000;14: 806–10.
60. Johnson BL, Charneco DR. Café au lait spot in neurofibromatosis and in normal individuals. Arch Dermatol. 1970;102:442–6.
61. Neurofibromatosis – conference statement. National Institutes of Health Consensus Development Conference. Arch Neurol. 1988;45:575–8.
62. Ortonne J-P, Brocard E, Floret D, et al. Valeur diagnostique des taches café-au-lait (TCL). Ann Dermatol Venereol. 1980;107:313–27.
63. Nunley KS, Gao F, Albers AC, et al. Predictive value of café au lait macules at initial consultation in the diagnosis of neurofibromatosis type 1. Arch Dermatol. 2009;145:883–7.
64. Langenbach N, Pfau A, Landthaler M, Stolz W. Naevi spili, café-au-lait spots and melanocytic naevi aggregated alongside Blaschko's lines, with a review of segmental melanocytic lesions. Acta Derm Venereol. 1998;78:378–80.
65. Lee WS, Yoo MS, Ahn SK, Won JH. Partial unilateral lentiginosis associated with segmental neurofibromatosis. J Dermatol. 1995;22:958–9.
66. Brems H, Chmara M, Sahbatou M, et al. Germline loss-of-function mutations in SPRED1 cause a neurofibromatosis 1-like phenotype. Nat Genet. 2007;39:1120–6.
67. Messiaen L, Yao S, Brems H, et al. Clinical and mutational spectrum of neurofibromatosis type 1-like syndrome. JAMA. 2009;302:2111–18.
68. Mulvihill JJ, Parry DM, Sherman JL, et al. NIH conference. Neurofibromatosis 1 (Recklinghausen disease) and neurofibromatosis 2 (bilateral acoustic neurofibromatosis). An update. Ann Intern Med. 1990; 113:39–52.
69. Gutmann DH, Aylsworth A, Carey JC, et al. The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. JAMA. 1997;278:51–7.
70. Mautner VF, Lindenau M, Baser ME, et al. Skin abnormalities in neurofibromatosis 2. Arch Dermatol. 1997;133:1539–43.
71. Ferner RE, Huson SM, Thomas N, et al. Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. J Med Genet. 2007;44:81–8.
72. Williams VC, Lucas J, Babcock MA, et al. Neurofibromatosis type 1 revisited. Pediatrics. 2009;123: 124–33.
73. Becker DW Jr. Use of the carbon dioxide laser in treating multiple cutaneous neurofibromas. Ann Plast Surg. 1991;26:582–6.
74. Levine SM, Levine E, Taub PJ, et al. Electrosurgical excision technique for the treatment of multiple cutaneous lesions in neurofibromatosis type I. J Plast Reconstr Aesthet Surg. 2008;61:958–62.
75. Ferner RE, Golding JF, Smith M, et al. [18F]2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG PET) as a diagnostic tool for neurofibromatosis 1 (NF1) associated malignant peripheral nerve sheath tumours (MPNSTs): a long-term clinical study. Ann Oncol. 2008;19:390–4.
76. Warbey VS, Ferner RE, Dunn JT, et al. [18F]FDG PET/CT in the diagnosis of malignant peripheral nerve sheath tumours in neurofibromatosis type-1. Eur J Nucl Med Mol Imaging. 2009;36:751–7.
77. Zou CY, Smith KD, Zhu QS, et al. Dual targeting of AKT and mammalian target of rapamycin: a potential therapeutic approach for malignant peripheral nerve sheath tumor. Mol Cancer Ther. 2009;8:1157–68.
78. Gomez MR. Phenotypes of the tuberous sclerosis complex with a revision of diagnostic criteria. Ann N Y Acad Sci. 1991;615:1–7.
79. Osborne JP, Fryer A, Webb D. Epidemiology of tuberous sclerosis. Ann N Y Acad Sci. 1991;615:125–7.
80. Wiederholt WC, Gomez MR, Kurland LT. Incidence and prevalence of tuberous sclerosis in Rochester, Minnesota, 1950 through 1982. Neurology. 1985;35: 600–3.
81. Kandt RS, Haines JL, Smith M, et al. Linkage of an important gene locus for tuberous sclerosis to a chromosome 16 marker for polycystic kidney disease. Nat Genet. 1992;2:37–41.
82. Povey S, Burley MW, Attwood J, et al. Two loci for tuberous sclerosis: one on 9q34 and one on 16p13. Ann Hum Genet. 1994;58:107–27.
83. European Chromosome 16 Tuberous Sclerosis Consortium. Identification and characterization of the tuberous sclerosis gene on chromosome 16. Cell. 1993; 75:1305–15.
84. Xiao GH, Shoarinejad F, Jin F, et al. The tuberous sclerosis 2 gene product, tuberin, functions as a Rab5 GTPase activating protein (GAP) in modulating endocytosis. J Biol Chem. 1997;272:6097–100.
85. van Slegtenhorst M, de Hoogt R, Hermans C, et al. Identification of the tuberous sclerosis gene TSC1 on chromosome 9q34. Science. 1997;277:805–8.
86. van Slegtenhorst M, Nellist M, Nagelkerken B, et al. Interaction between hamartin and tuberin, the TSC1 and TSC2 gene products. Hum Mol Genet. 1998;7:1053–7.
87. Lamb RF, Roy C, Diefenbach TJ, et al. The TSC1 tumour suppressor hamartin regulates cell adhesion through ERM proteins and the GTPase Rho. Nat Cell Biol. 2000;2:281–7.
88. Tee AR, Fingar DC, Manning BD, et al. Tuberous sclerosis complex-1 and -2 gene products function together to inhibit mammalian target of rapamycin (mTOR)-mediated downstream signaling. Proc Natl Acad Sci U S A. 2002;99:13571–6.
89. Sancak O, Nellist M, Goedbloed M, et al. Mutational analysis of the TSC1 and TSC2 genes in a diagnostic setting: genotype–phenotype correlations and comparison of diagnostic DNA techniques in tuberous sclerosis complex. Eur J Hum Genet. 2005;13:731–41.
90. Au KS, Williams AT, Roach ES, et al. Genotype/phenotype correlation in 325 individuals referred for a diagnosis of tuberous sclerosis complex in the United States. Genet Med. 2007;9:88–100.
91. Kobayashi T, Minowa O, Sugitani Y, et al. A germ-line Tsc1 mutation causes tumor development and embryonic lethality that are similar, but not identical to, those caused by Tsc2 mutation in mice. Proc Natl Acad Sci U S A. 2001;98:8762–7.
92. Onda H, Lueck A, Marks PW, et al. Tsc2(+/-) mice develop tumors in multiple sites that express gelsolin and are influenced by genetic background. J Clin Invest. 1999;104:687–95.
93. Ehninger D, Han S, Shilyansky C, et al. Reversal of learning deficits in a Tsc2+/- mouse model of tuberous sclerosis. Nat Med. 2008;14:843–8.
94. Hurwitz S, Braverman IM. White spots in tuberous sclerosis. J Pediatr. 1970;77:587–94.
95. Jozwiak S, Schwartz RA, Janniger CK, et al. Skin lesions in children with tuberous sclerosis complex: their prevalence, natural course, and diagnostic significance. Int J Dermatol. 1998;37:911–17.
96. Debard A, Richardet JM. [Letter: Significance of achromic spots in the infant]. Nouv Presse Med. 1975;4:2405.
97. Vanderhooft SL, Francis JS, Pagon RA, et al. Prevalence of hypopigmented macules in a healthy population. J Pediatr. 1996;129:355–61.
98. Roach ES, Gomez MR, Northrup H. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. J Child Neurol. 1998;13:624–8.
99. Sparling JD, Hong CH, Brahim JS, et al. Oral findings in 58 adults with tuberous sclerosis complex. J Am Acad Dermatol. 2007;56:786–90.
100. Flanagan N, O'Connor WJ, McCartan B, et al. Developmental enamel defects in tuberous sclerosis: a clinical genetic marker? J Med Genet. 1997;34 :637–9.
101. Rowley SA, O'Callaghan FJ, Osborne JP. Ophthalmic manifestations of tuberous sclerosis: a population based study. Br J Ophthalmol. 2001;85:420–3.
102. Pampiglione G, Moynahan EJ. The tuberous sclerosis syndrome: clinical and EEG studies in 100 children. J Neurol Neurosurg Psychiatry. 1976;39:663–73.
103. Friedman E, Pampiglione G. Prognostic implications of electroencephalographic findings of hypsarrhythmia in first year of life. Br Med J. 1971;4:323–5.
104. Curatolo P, Cusmai R, Cortesi F, et al. Neuropsychiatric aspects of tuberous sclerosis. Ann N Y Acad Sci. 1991; 615:8–16.
105. Hunt A, Dennis J. Psychiatric disorder among children with tuberous sclerosis. Dev Med Child Neurol. 1987;29: 190–8.
106. Smalley SL, Tanguay PE, Smith M, Gutierrez G. Autism and tuberous sclerosis. J Autism Dev Disord. 1992;22: 339–55.
107. Jozwiak S, Schwartz RA, Janniger CK, Bielicka-Cymerman J. Usefulness of diagnostic criteria of tuberous sclerosis complex in pediatric patients. J Child Neurol. 2000;15:652–9.
108. Roach ES, DiMario FJ, Kandt RS, Northrup H. Tuberous Sclerosis Consensus Conference: recommendations for diagnostic evaluation. National Tuberous Sclerosis Association. J Child Neurol. 1999;14:401–7.
108a. Yates JR, Maclean C, Higgins JN, et al. The Tuberous Sclerosis 2000 Study: presentation, initial assessments and implications for diagnosis and management. The Tuberous Sclerosis 2000 Study Group. Arch Dis Child. 2011;96:1020–5.
109. O'Callaghan FJ, Clarke AC, Joffe H, et al. Tuberous sclerosis complex and Wolff-Parkinson-White syndrome. Arch Dis Child. 1998;78:159–62.
110. Brook-Carter PT, Peral B, Ward CJ, et al. Deletion of the TSC2 and PKD1 genes associated with severe infantile polycystic kidney disease – a contiguous gene syndrome. Nat Genet. 1994;8:328–32.
111. Moss J, Avila NA, Barnes PM, et al. Prevalence and clinical characteristics of lymphangioleiomyomatosis (LAM) in patients with tuberous sclerosis complex. Am J Respir Crit Care Med. 2001;164:669–71.
112. Hizawa K, Iida M, Matsumoto T, et al. Gastrointestinal involvement in tuberous sclerosis. Two case reports. J Clin Gastroenterol. 1994;19:46–9.
113. Devroede G, Lemieux B, Masse S, et al. Colonic hamartomas in tuberous sclerosis. Gastroenterology. 1988;94:182–8.
114. Jimbow K. Tuberous sclerosis and guttate leukodermas. Semin Cutan Med Surg. 1997;16:30–5.
115. Fitzpatrick TB. History and significance of white macules, earliest visible sign of tuberous sclerosis. Ann N Y Acad Sci. 1991;615:26–35.
116. Fitzpatrick TB, Szabo G, Hori Y, et al. White leaf-shaped macules. Earliest visible sign of tuberous sclerosis. Arch Dermatol. 1968;98:1–6.
117. Darling TN, Skarulis MC, Steinberg SM, et al. Multiple facial angiofibromas and collagenomas in patients with multiple endocrine neoplasia type 1. Arch Dermatol. 1997;133:853–7.
118. Bissler JJ, McCormack FX, Young LR, et al. Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. N Engl J Med. 2008;358: 140–51.
118a. McCormack FX, Inoue Y, Moss J, et al. Efficacy and safety of sirolimus in lymphangioleiomyomatosis. N Engl J Med. 2011;364:1595–606.
119. Hofbauer GF, Marcollo-Pini A, Corsenca A, et al. The mTOR inhibitor rapamycin significantly improves facial angiofibroma lesions in a patient with tuberous sclerosis. Br J Dermatol. 2008;159:473–5.
120. Haemel AK, O'Brian AL, Teng JM. Topical rapamycin: a novel approach to facial angiofibromas in tuberous sclerosis. Arch Dermatol. 2010;146:715–18.
121. Mutizwa MM, Berk DR, Anadkat MJ. Treatment of facial angiofibromas with topical application of oral rapamycin solution (1 mg/mL) in two patients with tuberous sclerosis. Br J Dermatol. 2011;165:922–3.

This page intentionally left blank

Mosaicism and Linear Lesions

62

Celia Moss

Chapter Contents

Mosaicism in X-linked conditions *947*
Mosaicism for autosomal dominant conditions *952*
Linear inflammatory disorders *955*
Lethal disorders rescued by mosaicism *956*
Chromosomal mosaicism *959*
Chimerism *960*

Key features

- In the skin, mosaicism (genomic or functional) classically appears as cutaneous findings that follow Blaschko's lines
- The pattern may vary according to cell type and timing of mosaicism
- Diagnostically, it helps to consider what the differential diagnosis would be if the lesions were generalized
- If there is also gonadal mosaicism, offspring may have the generalized condition

INTRODUCTION

The term "mosaic" is used to describe individuals composed of cells of different genotypes that are derived from a genetically homogeneous zygote. For example patients with mosaic Turner syndrome have both 45,XO and 46,XX cells. The skin provides an ideal canvas to visualize patterns of mosaicism.

In 1901, Alfred Blaschko[1] documented the characteristic lines and whorls that are followed by epidermal nevi and other skin conditions now known to result from mosaicism (Fig. 62.1A). In 1961, Mary Lyon postulated that similar striped patterns in female mice heterozygous for coat color genes on the X chromosome reflected two populations of cells, one expressing the maternal X chromosome and one the paternal X chromosome. She hypothesized that all women are functional mosaics with regard to the X chromosome. In 1965, Curth and Warburton[2] used the Lyon hypothesis to explain the linear pattern of skin findings in the X-linked disorder incontinentia pigmenti. A decade later, Happle[3] recognized lyonization as the reason that skin lesions follow Blaschko's lines in heterozygous female patients with other X-linked genodermatoses.

We now know that cutaneous findings along Blaschko's lines and with other mosaic distribution patterns can result from: (1) *genomic*

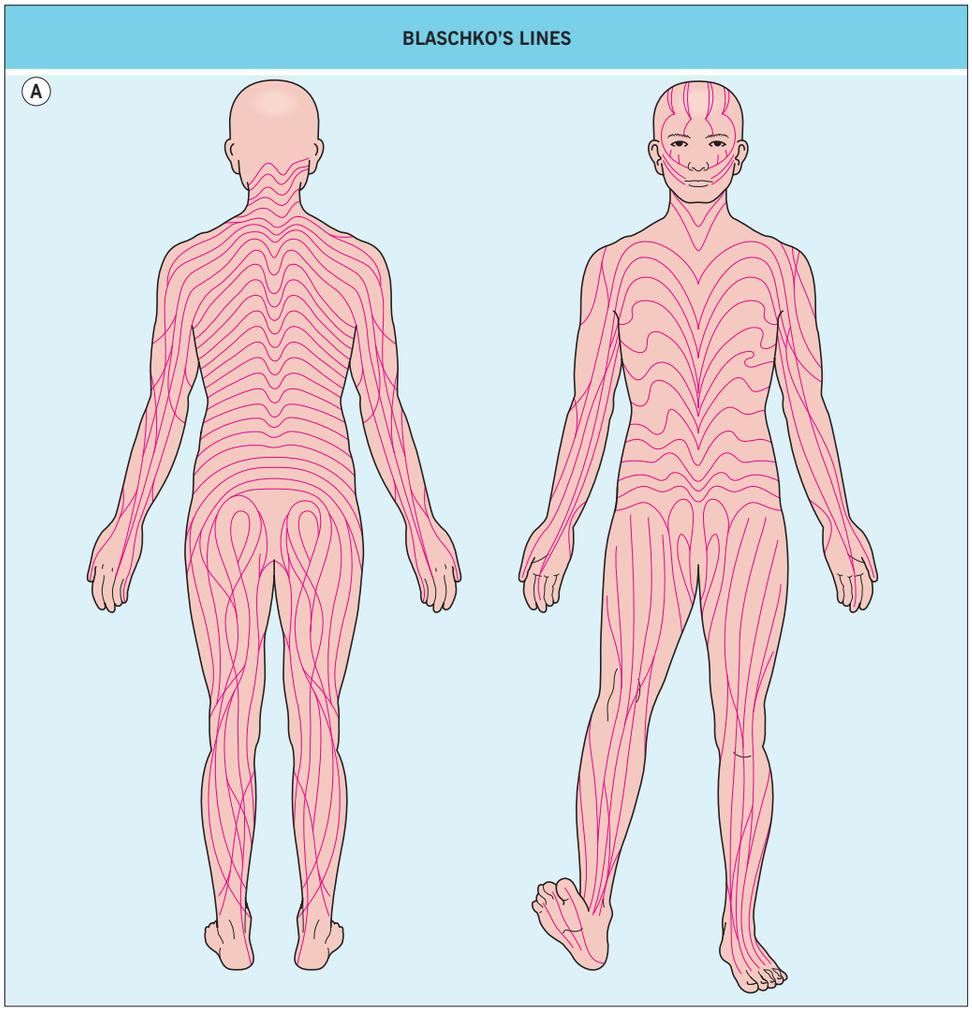


Fig. 62.1 Blaschko's lines. A These diagrams are taken from Blaschko's original drawings[1]. Note the S-shape of the abdominal lines and the V-shape on the central back.

Continued

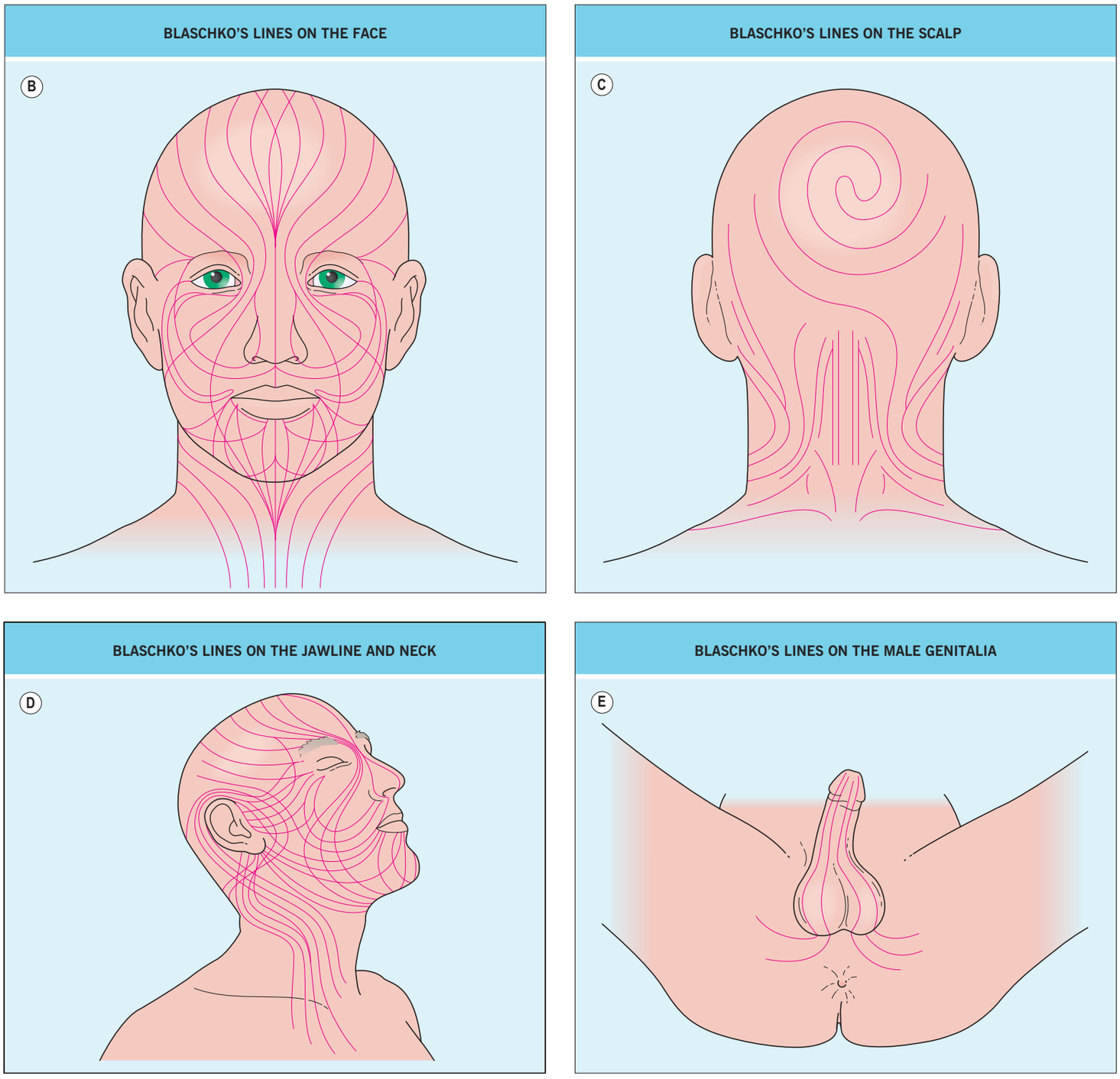


Fig. 62.1 Blaschko's lines (cont'd). **B** Blaschko's lines on the face, based on personal observations and ref. 8. **C** Blaschko's lines on the scalp, based on ref. 8. **D** Blaschko's lines on the jawline and neck, based on personal observations and ref. 8. **E** Blaschko's lines on the male genitalia, based on ref. 1.

(genetic) mosaicism due to changes in the DNA sequence (e.g. mutations or chromosomal alterations); and (2) *functional (epigenetic) mosaicism* due to changes in gene expression that are passed on to subsequent cell generations (e.g. lyonization[4]) (Table 62.1). Epigenetic mosaicism due to autosomally inherited retrotransposons (elements of retroviral origin that can affect the activity of neighboring genes) may explain occasional familial aggregation of non-X-linked disorders with a mosaic distribution pattern[5]. Mosaic skin conditions can be categorized based upon the nature of the corresponding generalized condition (Table 62.2).

The idea that Blaschko's lines represent the embryonic migration pathways of skin cells was first expressed by Douglass Montgomery, who concluded that the linear patterns of epidermal nevi "may be due to the streams or trend of growth of the tissues"[6]. Intriguingly, Montgomery presented his work to the American Dermatological Association in the same month (May 1901) that Blaschko presented his to the Deutschen Dermatologischen Gesellschaft in Breslau. Although both of these dermatologists published their findings, Montgomery's remarkable contribution was eclipsed by that of his German contemporary. In fact, the now widely held theory that Blaschko's lines reflect routes of embryonic cell migration did not surface again until the late 1970s[3,7].

Blaschko's original diagram (see Fig. 62.1A) omitted the midface, scalp, lateral neck, and genital area. The trajectories of Blaschko's lines in these areas have now been established[8] (Fig. 62.1B–E), as have analogous patterns in the eyes, teeth and oral mucosa. Considerable variability occurs in the degree of whorling on the flanks and the directions of lines on the face; the posterior midline may be shifted to the left or right, but the anterior midline tends to be sharply centered from the upper sternum to the pubis.

CAUSES OF MOSAICISM AND THE CORRESPONDING PATHOGENESIS	
Cause of mosaicism	**Pathogenesis**
GENOMIC (GENETIC)	
Half-chromatid mutation	A mistake during the first meiotic division of gametogenesis whereby an incorrect base is added. When the resulting mismatched double strand separates in mitosis, it will provide two templates that are not exactly complementary, giving rise to two different lines of daughter cells
Postzygotic (somatic) mutation	A mutation occurring after fertilization
Chromosomal non-disjunction	The failure of chromosomes to separate correctly during either meiosis or mitosis, resulting in daughter cells with aberrations of chromosome number or structure
Chimerism*	Fertilization of one egg by two sperm, or fusion of two zygotes, resulting in an individual composed of two genetically different cell lines
FUNCTIONAL (EPIGENETIC)	
Lyonization	Random inactivation of one of the two X chromosomes (which forms the Barr body) in each female cell during early embryonic development. Whether the paternal or maternal X chromosome is inactivated is random, but once the choice has been made, it is the same in all daughter cells
Epigenetic modification of autosomal gene(s)	A change in gene expression, passed from one cell generation to the next, but not resulting from an alteration in the DNA sequence, that affects some cells in an otherwise genetically homogeneous individual

*Because the clones originate from distinct organisms, chimerism differs from true mosaicism.

Table 62.1 Causes of mosaicism and the corresponding pathogenesis.

MOSAIC SKIN CONDITIONS CLASSIFIED ACCORDING TO THE NATURE OF THE CORRESPONDING GENERALIZED CONDITION	
Nature of the generalized condition	**Linear condition**
X-linked dominant single-gene disorder, lethal in males and mosaic manifestations in females	• Incontinentia pigmenti (*NEMO*) • Goltz syndrome (*PORCN*) • Conradi–Hünermann–Happle syndrome (*EBP*) • CHILD syndrome (*NSDHL*) • MIDAS syndrome (*HCCS*) • Oral–facial–digital syndrome type 1 (*OFD1*) • Terminal osseous dysplasia with pigmentary defects (*FLNA*)*
X-linked single-gene disorder, diffuse disease in males and variable mosaic manifestations in females	Female "carriers" of the following disorders: • Hypohidrotic ectodermal dysplasia (*EDA*) • Hypohidrotic ectodermal dysplasia with immune deficiency (*NEMO*) • X-linked reticulate pigmentary disorder • X-linked dyskeratosis congenita (*DKC1*) • Menkes disease (*ATP7A*) • Ichthyosis follicularis with atrichia and photophobia/keratosis follicularis spinulosa decalvans (*MBTPS2*) • X-linked congenital generalized hypertrichosis
Autosomal dominant single-gene disorder	• Epidermolytic verrucous epidermal nevus (*KRT1*, *KRT10*) [epidermolytic ichthyosis] • Non-epidermolytic verrucous epidermal nevus† (*FGFR3*) [acanthosis nigricans of thanatophoric dysplasia] • PTEN ("Cowden") epidermal nevus/segmental hamartomas (*PTEN*) [PTEN hamartoma tumor syndrome] • Palmoplantar verrucous epidermal nevus (*KRT16*) [pachyonychia congenita] • Acneiform nevus (*FGFR2*) [acne of Apert syndrome] • Linear Darier disease (*ATP2A2*) • Linear Hailey–Hailey disease (*ATP2C1*) • Linear porokeratosis • Linear basal cell carcinomas and basaloid follicular hamartomas • Segmental neurofibromatosis type 1 (*NF1*) • Linear/segmental angiofibromas (likely *TSC1* or *TSC2*) [tuberous sclerosis complex] • Segmental venous malformations (*TEK*) [cutaneous and mucosal venous malformation syndrome] • Segmental plaque-type glomuvenous malformations (*GLMN*) [hereditary glomuvenous malformations] • Parkes Weber syndrome (*RASA1*) [familial CM-AVM] • Segmental leiomyomas (*FH*) [multiple cutaneous and uterine leiomyomatosis]

*Features hyperpigmented, atrophic (with dermal hypoplasia) facial macules and digital fibromas.

Table 62.2 Mosaic skin conditions classified according to the nature of the corresponding generalized condition. The (gene) and [generalized condition] are noted when not evident from the name of the linear variant. *ATP7A*, ATPase, copper-transporting, α polypeptide; CHILD, congenital *h*emidysplasia with *i*chthyosiform erythroderma/nevus and *l*imb *d*efects; *EBP*, emopamil binding protein; *EDA*, ectodysplasin A; *FLNA*, filamin A; *HCCS*, holocytochrome c synthase; *MBTPS2*, membrane-bound transcription factor peptidase, site 2; MIDAS, *mi*crophthalmia, *d*ermal *a*plasia and *s*clerocornea; *NEMO*, NF-κB essential modulator; *NSDHL*, NAD(P)-dependent steroid dehydrogenase like.

Continued

MOSAIC SKIN CONDITIONS CLASSIFIED ACCORDING TO THE NATURE OF THE CORRESPONDING GENERALIZED CONDITION	
Nature of the generalized condition	**Linear condition**
Possible autosomal dominant single-gene disorder	• Linear seborrheic keratoses (possibly *FGFR3*) [thanatophoric dysplasia/related disorders] • Nevoid telangiectasia, angioma serpiginosum and angiokeratoma circumscriptum (possibly *RASA1* or *KRIT1*) [familial CM-AVM or CCM] • Maffucci syndrome • Linear syringomas • Linear trichoepitheliomas, spiradenomas and/or cylindromas (likely *CYLD*) [multiple familial trichoepitheliomas, Brooke-Spiegler syndrome and cylindromatosis] • Segmental agminated acquired melanocytic nevi • "Zosteriform" speckled lentiginous nevus‡
Multifactorial inflammatory disorder (genetic susceptibility + environmental contributions)	• Linear psoriasis • Linear lichen planus • Linear lichenoid GVHD • Linear lupus erythematosus and dermatomyositis • Linear fixed and lichenoid drug eruptions • Linear lichen nitidus • Lichen striatus • "Blaschkitis" • Linear morphea • Linear atrophoderma of Moulin • Segmental vitiligo
Presumed autosomal dominant lethal disorder rescued by mosaicism (never seen in a generalized form)	• Non-epidermolytic verrucous epidermal nevus or linear seborrheic keratoses (*PIK3CA*) • Sebaceous nevus • PEODDN (porokeratotic eccrine ostial and dermal duct nevus) • Proteus syndrome (*AKT1*) • ILVEN (inflammatory linear verrucous epidermal nevus) • Nevus lipomatosis superficialis • Encephalocraniocutaneous lipomatosis • Oculocerebrocutaneous syndrome • McCune–Albright syndrome (*GNAS*) • Segmental vascular malformations§ • Linear fibromatosis
Chromosomal anomalies (may be lethal in a generalized form)	• Hypomelanosis of Ito • Nevus depigmentosus • Linear and whorled nevoid hypermelanosis • Pallister–Killian syndrome (tetrasomy 12p)
Chimerism	• Segmental hyper- and hypopigmentation

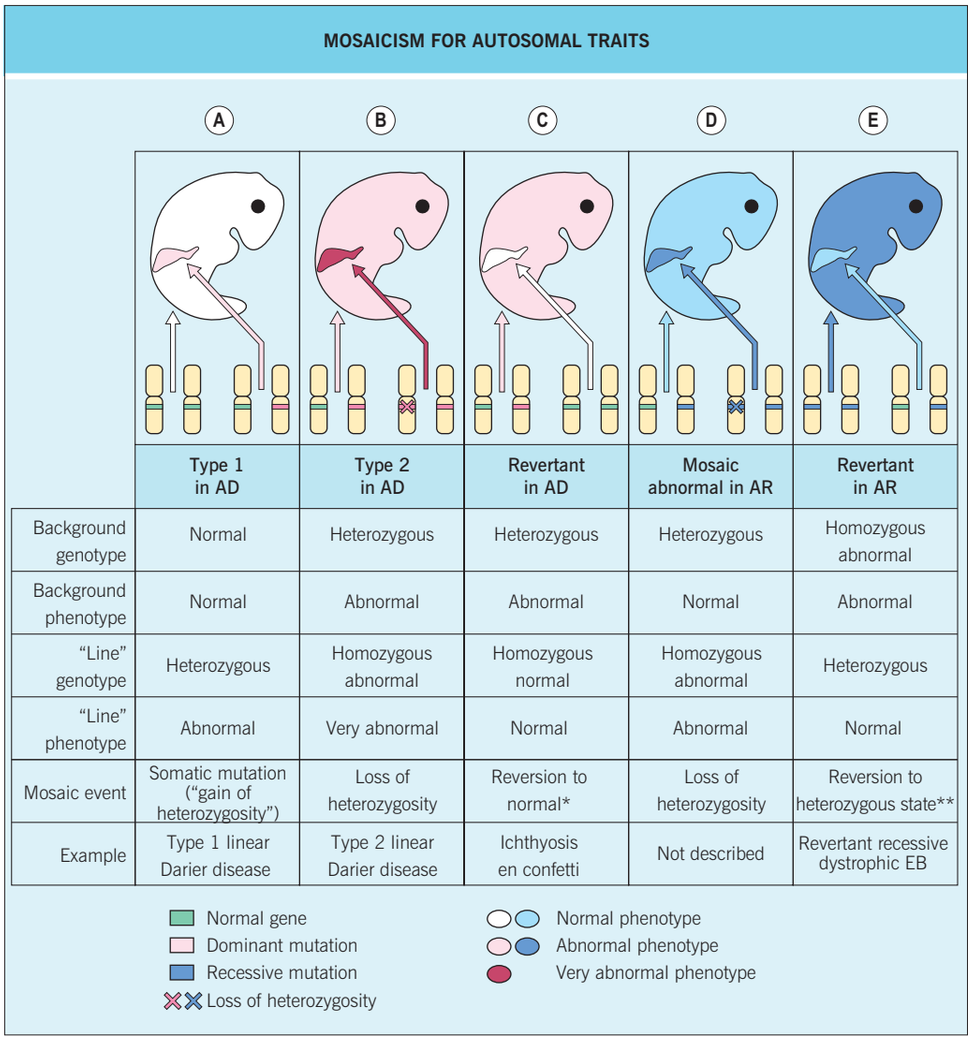
†Also (*KRAS*) [cardiofaciocutaneous syndrome, which is occasionally associated with acanthosis nigricans]; mosaicism for an activating mutation reported in one patient to date.
‡Candidates include genes for autosomal dominant lentiginosis syndromes, e.g. LEOPARD (*PTPN11*), Carney complex (*PRKAR1A*) and neurofibromatosis type 1 (*NF1*).
§Possible examples include those associated with Klippel–Trenaunay and Sturge–Weber syndromes as well as cutis marmorata telangiectatica congenita and "lymphangioma circumscriptum" (microcystic lymphatic malformations).

Table 62.2 Mosaic skin conditions classified according to the nature of the corresponding generalized condition (cont'd). The (gene) and [generalized condition] are noted when not evident from the name of the linear variant. *ATP2A2* and *APT2C1*, ATPase, calcium-transporting; CCM, cerebral capillary malformation (sometimes associated with hyperkeratotic cutaneous capillary–venous malformations); CM-AVM, capillary malformation–arteriovenous malformation; *FGFR*, fibroblast growth factor receptor; *FH*, fumarate hydratase; *GLMN*, glomulin; *GNAS*, guanine nucleotide binding protein (G protein), alpha stimulating polypeptide 1; GVHD, graft-versus-host disease; *KRT*, keratin gene (e.g. *KRT16*); *NF1*, neurofibromin 1; *PIK3CA*, phosphatidylinositol 3-kinase catalytic subunit alpha.

EXPECTED PATTERN OF CUTANEOUS MOSAICISM ACCORDING TO ITS TIMING OF ONSET				
Timing	**Configuration/shape of skin lesions**	**Number of skin lesions**	**Laterality**	**Organs affected**
Meiosis	Linear	Multiple	Bilateral	Multiorgan
Very early blastocyst (includes lyonization)	Linear	Multiple	Bilateral	Multiorgan
Later blastocyst	Linear	Fewer	Uni- or bilateral	Multiorgan
Later in first trimester, pre-organogenesis	Linear or oval	Fewer	Uni- or bilateral	Multiorgan
First trimester, post-organogenesis	Linear or oval	Few or single	Uni- or bilateral	Skin only
Second/third trimester	Oval or round	Single	Unilateral	Skin only
Postnatal	Round (smaller)	Single	Unilateral	Skin only

Table 62.3 Expected pattern of cutaneous mosaicism according to its timing of onset.

Mosaic skin conditions do not always follow Blaschko's lines[9]. Assuming that the pattern is determined by cell migration, it depends on the stage of development at which mosaicism arises (Table 62.3) and the cell type affected (Table 62.4). The classic pattern defined by Blaschko is seen in disorders of epidermal cells, which is not surprising since Blaschko based his diagrams on epidermal nevi[10]. Embryonic keratinocytes move outwards from the neural crest by directional proliferation, in more-or-less continuous lines that are deflected by the complex interplay between cell migration and surface remodeling. In contrast, melanoblasts are thought to migrate individually to the skin, where they then proliferate antenatally. This explains the block-like, patchy and phylloid patterns seen in some pigmentary conditions that



	Type 1 in AD	Type 2 in AD	Revertant in AD	Mosaic abnormal in AR	Revertant in AR
Background genotype	Normal	Heterozygous	Heterozygous	Heterozygous	Homozygous abnormal
Background phenotype	Normal	Abnormal	Abnormal	Normal	Abnormal
"Line" genotype	Heterozygous	Homozygous abnormal	Homozygous normal	Homozygous abnormal	Heterozygous
"Line" phenotype	Abnormal	Very abnormal	Normal	Abnormal	Normal
Mosaic event	Somatic mutation ("gain of heterozygosity")	Loss of heterozygosity	Reversion to normal*	Loss of heterozygosity	Reversion to heterozygous state**
Example	Type 1 linear Darier disease	Type 2 linear Darier disease	Ichthyosis en confetti	Not described	Revertant recessive dystrophic EB

Fig. 62.2 Mosaicism for autosomal traits. With revertant mosaicism (**C** and **E**), the phenotype depends on the degree of gene reversion (complete or partial), the timing of the revertant mutation (large segment or multiple bands if during embryogenesis versus smaller spot if postnatally), and a selective advantage of revertant cells (e.g. blistering of non-revertant skin in epidermolysis bullosa, EB). AD, autosomal dominant; AR, autosomal recessive. *Additional mechanisms include mitotic recombination (with crossing over of homologous chromosomes leading to homozygous mutant and homozygous normal daughter cells) and a second-site mutation (e.g. that silences a dominant negative allele). **Additional mechanisms include gene conversion (where the donating chromosome is unchanged) and a second-site mutation (e.g. that restores the reading frame, prevents a termination codon or affects RNA splicing). *Courtesy, Julie V Schaffer, MD.*

EXPECTED PATTERN OF CUTANEOUS MOSAICISM ACCORDING TO CELL OR TISSUE TYPE		
Cell affected	**Embryonic movement**	**Expected pattern**
Melanoblast	Single cell migration	Blaschko's lines, block-like or phylloid
Keratinocyte	Directional proliferation following surface forces	Blaschko's lines
Fibroblast, fat cell, other mesodermal cells	Multidirectional proliferation following growth of segment	Segmental
Nerve cell	Along future dermatomes	Dermatomal
Endothelial and other blood vessel cells	Within segments/future dermatomes	Segmental/dermatomal

Table 62.4 Expected pattern of cutaneous mosaicism according to cell or tissue type.

result from mosaicism. Cutaneous blood vessels, fibroblasts and other mesodermal derivatives take different routes; mosaic disorders involving these tissues are rarely distributed along Blaschko's lines, more often displaying patterns that correspond to embryonic segments or dermatomes. The distribution of skin lesions along Blaschko's lines in Goltz syndrome (focal *dermal* hypoplasia) and linear morphea are postulated to reflect mutated genes that are expressed in the epidermis but lead to changes in the underlying dermis.

Sometimes, a more severe linear lesion is superimposed upon the background of a generalized autosomal dominant disease, with or without a family history of the same generalized condition. This phenomenon, referred to as *type 2 mosaicism*, occurs when an individual with a germline mutation in one allele of a gene (which leads to the autosomal dominant disorder) also has a postzygotic mutation affecting the other allele (a "second hit" causing loss of heterozygosity), resulting in a linear area where the genetic burden is doubled (Fig. 62.2B). Type 2 mosaicism has been proven on a molecular level for conditions including Hailey–Hailey disease,[11] Darier disease[11a] and PTEN hamartoma tumor syndrome (which encompasses Cowden disease and Bannayan–Riley–Ruvalcaba syndrome)[12,13]. Other patients have a linear distribution of the skin lesions that characterize an autosomal dominant genodermatosis (e.g. Darier disease) in the absence of background lesions. Such lesions vary in severity and can also be dense or confluent. In these patients, there is a localized region with a postzygotic mutation in one allele of a gene that is normal in the remainder of the affected individual; this is referred to as *type 1 mosaicism* (Fig. 62.2A).

Theoretically, linear autosomal recessive skin disease could also develop through clonal loss of heterozygosity in a carrier (Fig. 62.2D). While this has not been reported, the opposite phenomenon – regional absence of skin disease attributed to a back/correcting mutation (revertant mosaicism) – has been shown in patients with autosomal recessive as well as autosomal dominant forms of epidermolysis bullosa (where revertant cells have a particular advantage due to the selective pressure of blistering) and in ichthyosis en confetti[14,15] (Fig. 62.2C,E).

Figure 62.3 provides an approach to the differential diagnosis of skin lesions that follow Blaschko's lines. Selected mosaic disorders will be discussed in more detail below.

MOSAICISM IN X-LINKED CONDITIONS

In women heterozygous for X-linked disorders, functional mosaicism due to random X-chromosome inactivation (lyonization) may produce skin lesions following Blaschko's lines. Sons who inherit the abnormal

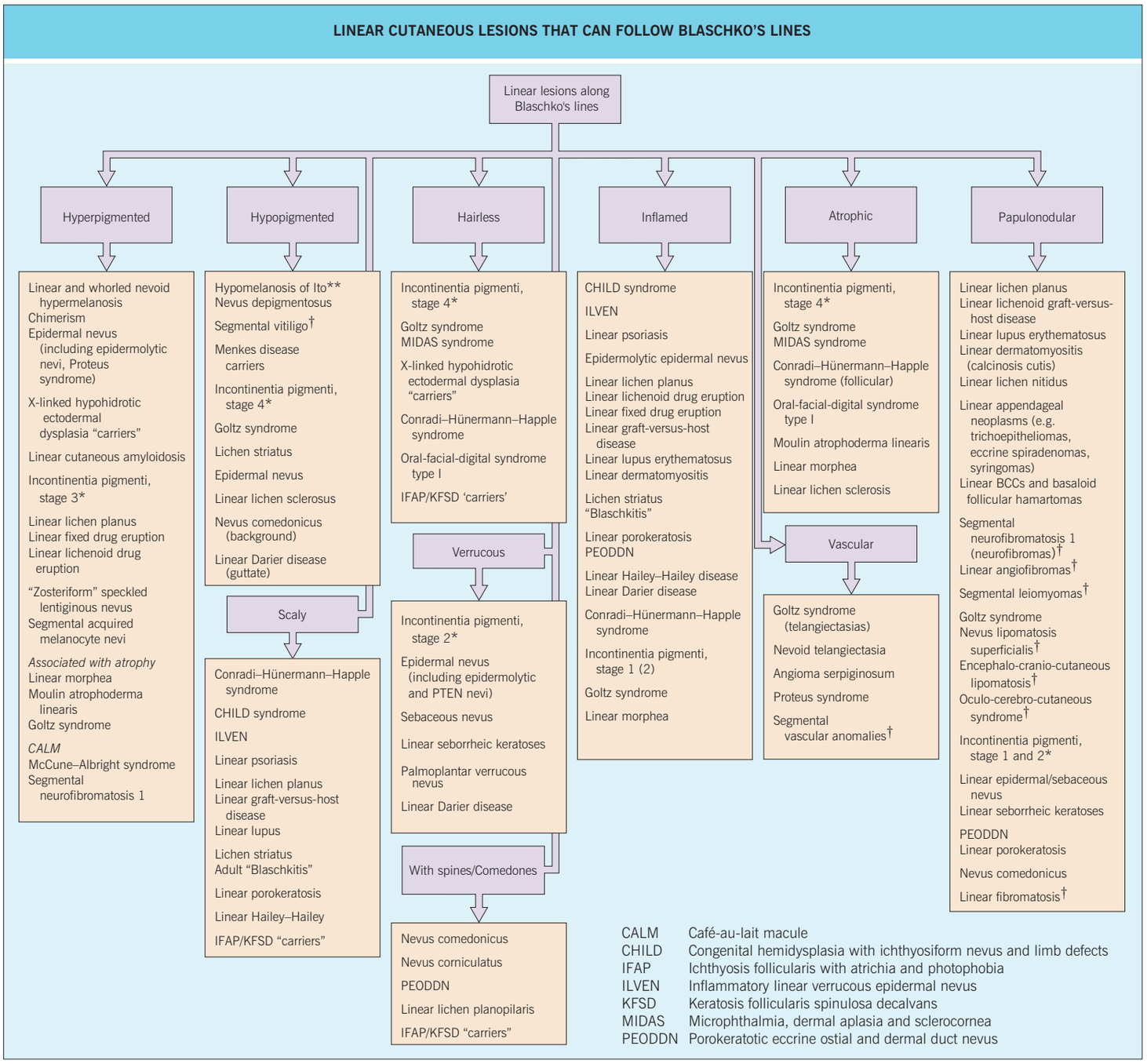


Fig. 62.3 Linear cutaneous lesions that can follow Blaschko's lines. *Also female "carriers" of hypohidrotic ectodermal dysplasia with immune deficiency. **Including Pallister–Killian syndrome. †More often have a segmental or (for neural and vascular lesions) dermatomal pattern.

X chromosome carry and express the mutation in all cells; if recessive, the disorder is usually compatible with survival (e.g. hypohidrotic ectodermal dysplasia), but if dominant, the disorder is generally so severe that males die before birth (e.g. incontinentia pigmenti and Goltz syndrome) because this lethal phenotype can only be rescued by mosaicism (see below). Occasionally, male patients present with the female skin phenotype because they themselves are mosaic, and, therefore, protected by the presence of some normal X chromosomes. X-chromosome mosaicism in boys and men can result from Klinefelter syndrome (where the extra X chromosome permits lyonization), a half-chromatid mutation (see Table 62.1) or a postzygotic mutation (see Table 62.5). These mosaic men can pass on the mutation to their daughters if it is present in their sperm (gonadal mosaicism).

Lyonization occurs synchronously in all cells at about the 1000-cell stage, so the two clones are intimately mixed from the beginning. Female patients with X-linked genodermatoses typically have numerous skin lesions that follow Blaschko's lines in narrow bands. A curious exception is CHILD (*c*ongenital *h*emidysplasia with *i*chthyosiform nevus and *l*imb *d*efects) syndrome, which characteristically shows large unilateral blocks of abnormal skin. This lateralization pattern may reflect the effects of expression of the mutant versus normal X-chromosome in organizer cells that control large developmental fields. Alternatively, a deficiency in sonic hedgehog signaling (which normally helps to confer left–right asymmetry) in cells expressing the *NSDHL* mutation, may result in selection against these cells on one side of the body.

Not all X-linked skin disorders follow Blaschko's lines. For example, women who are heterozygous for the gene defects that underlie Fabry disease, Wiskott–Aldrich syndrome and chronic granulomatous disease have either no lesions or scattered lesions in a non-linear pattern. This is likely because the cells that express the mutated gene are circulating leukocytes or non-epidermal cells (e.g. endothelial cells) for which lyonization does not produce a clinically apparent pattern. In the case of steroid sulfatase-deficient ichthyosis, where the defect is epidermal

but not evident in female carriers, the steroid sulfatase gene is on a part of the X chromosome that does not undergo lyonization.

Incontinentia Pigmenti

Synonym: ■ Bloch–Sulzberger syndrome

Key features

- A disorder with X-linked dominant inheritance and skin lesions that follow Blaschko's lines
- Four stages: (1) inflammatory/vesicular; (2) verrucous; (3) hyperpigmented; and (4) hypopigmented/atrophic
- Other ectodermal abnormalities may be present (e.g. alopecia, nail dystrophy, pegged or missing teeth)
- Occasional involvement of the eyes and central nervous system
- Caused by mutations in the *NEMO* gene

Introduction

Incontinentia pigmenti (IP) is a rare multisystem disorder that may present to neonatologists, neurologists, ophthalmologists or dentists as well as dermatologists. However, the diagnosis rests on the cutaneous findings. The name refers to the pathologic finding of pigmentary incontinence (i.e. dermal melanophages) in the third stage of the disease. The linear skin lesions reflect mosaicism secondary to X inactivation (lyonization).

History

Although Garrod probably first described IP in 1906, Bloch's 1926 report of a "previously unreported pigment disorder" and that 2 years later by Sulzberger are remembered eponymously. In the 1990s, "IP1" (a sporadic condition) was differentiated from "IP2" (classic inherited IP). In 2000, the International Incontinentia Pigmenti Consortium established that "IP2" (now referred to simply as IP) is caused by mutations in the *NEMO* (*N*F-κB *e*ssential *mo*dulator) gene. The condition previously known as "IP1", which is characterized by X/autosome translocations (often involving Xp11) and pigmentary abnormalities along Blaschko's lines without a preceding inflammatory phase, is now recognized as a form of pigmentary mosaicism (see below).

Genetics

IP is an X-linked dominant disorder, usually antenatally lethal in boys, that is caused by mutations in the *NEMO* (also known as *IKBKG*) gene at Xq28[16]. Approximately two-thirds of patients have a particular large deletion that tends to arise during paternal meiosis (male gametogenesis). Occasional occurrences of clinically typical IP in boys are attributed to Klinefelter syndrome (8 of 72 male patients reported to date) or to genomic mosaicism due to a half-chromatid or postzygotic *NEMO* mutation (Table 62.5)[17]. In the latter patients, the distribution of the skin lesions may be relatively limited.

Pathogenesis

The NEMO protein is a subunit of a kinase that activates NF-κB, a transcription factor that protects against TNF-α-induced apoptosis (Fig. 62.4). The idea of IP as a pro-apoptotic state explains male lethality, destruction of epidermal cells, and progressive replacement of cells expressing the mutant X chromosome by those expressing the normal allele[16]. In one report, a liveborn boy whose mother had classic IP died hours after birth due to lethal hematopoietic and immunologic disturbances[18]. Milder *NEMO* mutations are responsible for hypohidrotic ectodermal dysplasia with immune deficiency (HED-ID) in boys, whose mothers often have relatively subtle features of IP (see Table 62.5 and Ch. 63)[19].

Clinical features[20]

IP typically presents with linear erythema and blisters (stage 1) during the first few months of life in an otherwise well baby girl (see Fig. 34.10). Vesiculobullous lesions are most common on the limbs and scalp, frequent on the trunk, and rare on the face. They resolve within days to weeks and are often replaced by verrucous linear plaques (stage 2) that favor the extremities (Fig. 62.5A) and disappear later in infancy. Streaks and swirls of reticulate grayish-brown hyperpigmentation (stage 3) develop next and have a predilection for the trunk and intertriginous sites, with scalloped edges that are thought to reflect the growth of normal keratinocytes into affected skin (Fig. 62.5B). The inflammatory sequence sometimes recurs within pigmented areas during infancy or later in childhood together with intercurrent febrile illnesses. In addition, acral keratotic nodules (including subungual lesions) occasionally arise after puberty. The hyperpigmented streaks tend to fade by adolescence, although a few areas of slate-gray pigmentation may persist lifelong. From the teen years onward, linear hypopigmented bands lacking hair and sweat glands (stage 4) appear on the posterior aspects of the limbs (especially the calves; Fig. 62.5C) and may be the only stigmata of the disease during adulthood[21]. Individual stages of IP may

FINDINGS IN GIRLS AND BOYS WITH NEMO MUTATIONS

	Girl with IP	Boy with IP + Klinefelter syndrome	Son of mother with classic IP	Somatic mosaic boy with IP	Boy with HED-ID†
Karyotype	XX	XXY	XY	XY	XY
***NEMO* genotype**	Heterozygous for typical mutation*	Heterozygous for typical mutation*	Hemizygous for typical mutation*	Mosaic hemizygous for typical mutation* (half-chromatid or postzygotic)	Hemizygous for milder ("hypomorphic") mutation that does not abolish activity
Skin findings	Classic IP	Classic IP	NA	Classic IP, although may have a more limited distribution (e.g. unilateral or localized)	Hypotrichosis, hypohidrosis, recurrent pyogenic infections, extensive seborrheic- or atopic-like dermatitis, reticulated hyperpigmentation (less common)
Immunodeficiency	No	No	Yes, extremely severe	No	Yes, with dysgammaglobulinemia (↑IgM, ↓IgG)
Life expectancy	Normal	Normal	Usually lethal before birth	Normal	Typically shortened due to pyogenic and opportunistic infections; may improve with hematopoietic stem cell transplantation

*A particular large deletion that removes exons 4–10 is found in ~65% of female patients with IP; a *NEMO* mutation may be difficult to detect in peripheral blood samples from mosaic male patients (since mutant leukocytes are prone to apoptosis), so analysis of DNA from lesional skin may be required.
†Mother may have a mild variant of IP; affected boys typically have missing/conical teeth. An allelic variant features osteopetrosis and lymphedema, and an autosomal dominant condition with a similar phenotype can result from mutations in the inhibitor of κBα gene (*IKBA*).

Table 62.5 Findings in girls and boys with *NEMO* mutations. HED-ED, hypohidrotic ectodermal dysplasia with immune deficiency; IP, incontinentia pigmenti; NA, not applicable; *NEMO*, NF-κB essential modulator.

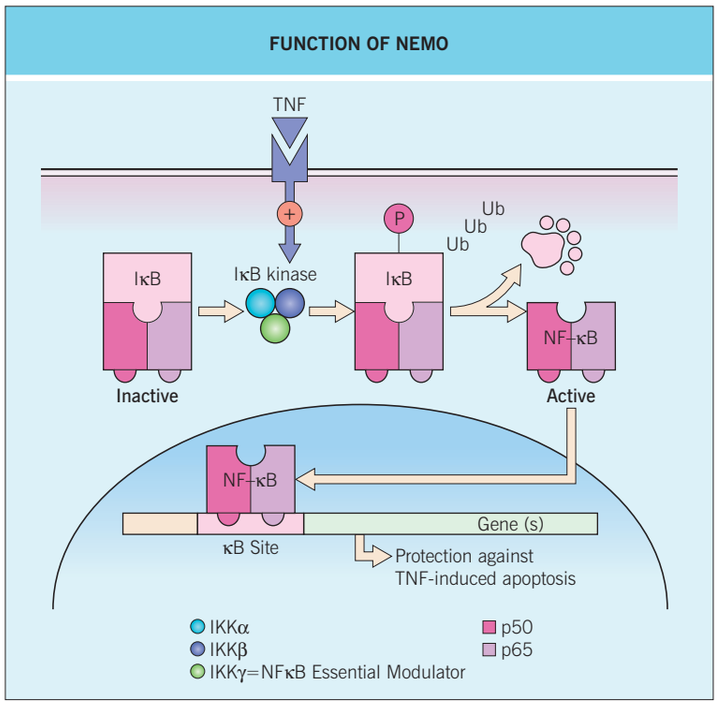


Fig. 62.4 Function of NEMO. In incontinentia pigmenti, lack of NF-κB essential modulator (NEMO; also known as *i*nhibitor of κ light polypeptide gene enhancer in *B* cells, *k*inase γ [IKBKG]) results in failure to activate NF-κB, which normally protects against tumor necrosis factor (TNF)-α-induced apoptosis.

ADDITIONAL MANIFESTATIONS OF INCONTINENTIA PIGMENTI
SURFACE ECTODERMAL DEFECTS
• Missing and conical *teeth* (60–80% of patients) • Linear absence of *hair* (swirled at the vertex in 30–40% of patients) and *sweat glands* • Dystrophic *nails* (ridging, pitting > subungual keratoses; 10–30% of patients) • Asymmetric *breast* development or supernumerary *nipples*
EYE ANOMALIES (20–40% OF PATIENTS)
• Retinal vascular abnormalities • Strabismus • Cataracts • Microphthalmia • Optic atrophy
CENTRAL NERVOUS SYSTEM ABNORMALITIES (20–30% OF PATIENTS)
• Seizures • Developmental delay • Spastic hemi/di/tetraplegia
SKELETAL DEFECTS (UNCOMMON)
• Skull anomalies • Scoliosis
OTHER ORGANS (UNCOMMON)
• Pulmonary hypertension

Table 62.6 Additional manifestations of incontinentia pigmenti.

be absent or overlap. Additional manifestations of this condition are listed in Table 62.6.

Pathology

The early inflammatory phase of IP demonstrates eosinophilic spongiosis and scattered dyskeratotic keratinocytes. The epidermis of verrucous lesions is acanthotic with hyperkeratosis and foci of dyskeratosis. In stage 3, there is pigmentary incontinence as well as variable vacuolization of basal keratinocytes, whereas stage 4 is characterized by a thinned epidermis and dermis devoid of adnexa[21].

Fig. 62.5 Incontinentia pigmenti. A, B Stages 2 (verrucous) and 3 (hyperpigmented). Note the erythematous background of the keratotic papules and plaques on the leg (**A**) and the remaining keratotic lesions on the toes (**B**). The scalloped edges of the hyperpigmented streaks are thought to reflect growth of normal keratinocytes into areas of apoptosis. **C** Stage 4 (atrophic and hypopigmented). Note absence of hairs within the streaks on the calf. *A & B, Courtesy, Julie V Schaffer, MD.*

Differential diagnosis

Neonatal IP can usually be distinguished from infectious conditions (e.g. herpes zoster, varicella or herpes simplex viral infections) by the wellbeing of the child and characteristic patterning of the skin lesions. Peripheral eosinophilia and leukocytosis are common in neonates with

IP, and histologic examination provides confirmation of the diagnosis. There is no preceding inflammatory phase in linear and whorled nevoid hypermelanosis or hypomelanosis of Ito, and adnexa are typically normal. Biopsy specimens of the former condition show predominantly epidermal hyperpigmentation rather than dermal melanophages (see Ch. 67).

Treatment

Baseline and longitudinal ophthalmologic (especially important during infancy) and neurologic evaluations are recommended, as are dental assessments and early intervention when anomalies are present. The mother should be examined and genetic counseling provided; genetic analysis is available. The Incontinentia Pigmenti International Foundation (www.ipif.org) is a good resource for families.

Hypohidrotic Ectodermal Dysplasia with Immune Deficiency

This condition is discussed in detail in Chapter 63.

Goltz Syndrome

Synonyms: ■ Focal dermal hypoplasia ■ Goltz–Gorlin syndrome

Key features

- X-linked dominant condition in which skin lesions follow Blaschko's lines and consist of dermal atrophy in association with telangiectasias, hypopigmentation and/or hyperpigmentation
- Approximately half of patients have areas of fat "herniation" within the streaks
- Raspberry-like papillomas favor the perioral and anogenital regions
- The characteristic digital anomaly is ectrodactyly (lobster-claw deformity)
- Additional findings include hypodontia and ocular defects
- Caused by mutations in the *PORCN* gene

Introduction

Goltz syndrome, an uncommon genetic disorder first described by Goltz in 1962, affects ectodermal and mesodermal structures – primarily the skin, bones, teeth and eyes – in a mosaic pattern.

Genetics

Goltz syndrome is an X-linked dominant condition caused by mutations in the *PORCN* gene. The mosaic distribution of skin lesions in female patients reflects lyonization. Although Goltz syndrome is antenatally lethal in boys with non-mosaic hemizygous mutations (as in IP; see Table 62.5), male patients with genomic (e.g. due to a postzygotic mutation) or functional (in the setting of Klinefelter syndrome) mosaicism account for 10% of affected individuals.

Approximately 95% of all Goltz syndrome cases are sporadic, which likely reflects both a decreased likelihood of reproduction by severely affected women and the lethality of *PORCN* mutations with widespread expression. Some authors have postulated that either preferential inactivation of the mutant X chromosome or a postzygotic mutation is required for survival of affected female fetuses[22]. Patients with the most deleterious mutations (deletions) have more extreme skewing in favor of wild-type[22]. Rare familial cases show anticipation, with the offspring being much more severely affected than the parent and having a higher proportion of mutant cells. Therefore the possibility that an apparently normal mother is a carrier must be considered when counseling families.

Pathogenesis

PORCN belongs to the evolutionarily conserved porcupine gene family and is expressed in the skin, craniofacial and long bones, tooth buds and eyes – structures affected in Goltz syndrome. The PORCN protein has multiple transmembrane domains and is located in the endoplasmic reticulum. It functions as an O-acyltransferase involved in palmitoylation and secretion of Wnt, a morphogen important in ectomesodermal tissue development[22,23]. Wnt signaling stimulates fibroblast proliferation, inhibits adipogenesis and induces osteogenesis, explaining the dermal hypoplasia, fat "herniations" and osteopathia striata (streaks of decreased bone density) observed in Goltz syndrome. Wnt also has key roles in early limb patterning and tooth formation.

Although the primary cutaneous abnormality in Goltz syndrome is in the dermis, the distribution of skin lesions along Blaschko's lines reflects embryonic migration pathways of epidermal cells. Ectoderm-specific deletion of *PORCN* in mice has shown that expression of this gene in the epidermis and resultant Wnt signaling regulate development of the underlying dermis and fat[23a]. Of note, patients with Goltz syndrome have a thin epidermis (as well as dermis) and abnormal adnexal structures. This is not surprising considering that Wnt signaling, including β-catenin-dependent pathways, is known to have critical roles in epidermal regeneration and adnexal morphogenesis/maintenance.

In 3 of 24 patients in one series, a microdeletion affected both the *PORCN* gene and the adjacent *EBP* gene responsible for Conradi–Hünermann–Happle syndrome (see below). Curiously, however, these patients showed no features of the latter disorder. This implies that the *PORCN* hypoplastic skin phenotype predominates over the ichthyosis and follicular changes of Conradi-Hünermann-Happle syndrome[22].

Clinical features[23]

The phenotype of Goltz syndrome varies depending on the proportion and distribution of cells expressing a mutant X chromosome. Streaks of vermiculate dermal atrophy and/or telangiectasias are often present from birth (Fig. 62.6A,B). Later, hypo- and hyperpigmentation as well as outpouchings of fat develop. Although raspberry-like papillomas may appear in any location, they favor the anogenital region as well as the lips (Fig. 62.6C), larynx and acral sites. Bony reduction deformities of the hands are common, particularly ectrodactyly (split-hand/foot or "lobster-claw" malformation). Radiographs of the mid portion of the lower extremities characteristically show osteopathia striata. Eye abnormalities, often unilateral, include coloboma, aniridia, microphthalmia and anophthalmia. Dystrophic nails (e.g. longitudinal fissures, hypoplasia), sparse hair, abnormal teeth (e.g. vertical grooving, hypodontia) and dysmorphic facies (e.g. notched nasal alae, pointed chin, large malformed ears) may be observed. Other occasional features include aplasia cutis congenita, myelomeningocele, cleft lip/palate, deafness, urinary tract anomalies and gastrointestinal maldevelopment.

Pathology

Affected skin shows a reduction in dermal collagen, which can be marked[23], with telangiectasias and a decreased number of adnexal structures. Fat cells of varying sizes are often present in the upper dermis. By electron microscopy, the basement membrane zone can be seen to contain multiple layers of lamina densa-like material, a change consistent with keratinocyte damage. Dermal microfibrils are also increased in the upper dermis.

Differential diagnosis

The distinctive cutaneous and extracutaneous findings of Goltz syndrome, especially dermal atrophy/fat "herniations" and osteopathia striata, distinguish it from other X-linked dominant genodermatoses. Examples of such conditions include MIDAS (which does not involve the distal extremities), Conradi–Hünermann–Happle and oral–facial–digital type 1 syndromes. Although an inflammatory component is occasionally observed, the skin lesions of Goltz syndrome are relatively static in comparison to the evolving lesions of IP.

Treatment

Treatment is supportive, with appropriate subspecialist referral based on the associated abnormalities. The telangiectasias may be improved by pulsed dye laser treatment. Troublesome exophytic papillomas can be treated with curettage or photodynamic therapy.

Fig. 62.6 Goltz syndrome. A Streaks of vermiculate atrophy (hypopigmented) and fat herniation/hamartoma in a girl with Goltz syndrome. **B** Streaks of telangiectasias plus erosions on the leg. **C** Several erythematous, raspberry-like papules on the lips. The most prominent lesion is at the angle of the mouth. Similar lesions can occur in the anogenital region and may be confused with warts.

Conradi–Hünermann–Happle syndrome (X-linked dominant chondrodysplasia punctata)

This rare X-linked dominant disorder presents in female neonates with ichthyosiform erythroderma characterized by feathery, adherent scale and a distribution along Blaschko's lines (see Ch. 57). Extracutaneous findings include rhizomelic limb shortening with epiphyseal stippling (chondrodysplasia punctata) and ocular anomalies such as sectorial cataracts and microphthalmia. Patients often have swirled alopecia following Blaschko's lines and coarse, lusterless hair. After infancy, the skin changes evolve into follicular atrophoderma. Conradi–Hünermann–Happle syndrome is caused by mutations in the *emopamil binding protein* (*EBP*) gene[24], which lies on the X chromosome adjacent to the *PORCN* gene and encodes an isomerase essential for cholesterol biosynthesis. Of note, chondrodysplasia punctata occurs in a variety of other genetic and non-genetic disorders.

CHILD Syndrome (Congenital *H*emidysplasia with *I*chthyosiform Erythroderma [or Nevus] and *L*imb *D*efects)

CHILD syndrome is a rare X-linked dominant congenital disorder that, in its full-blown form, affects half the body with severe limb reductions, scoliosis, diffuse erythema with scale, chondrodysplasia punctata and, occasionally, defects in internal organs (see Ch. 57). Less complete forms show affected areas following Blaschko's lines, sometimes bilaterally, or have a predilection for skin folds. Some authors have postulated that ILVEN (*i*nflammatory *l*inear *v*errucous *e*pidermal *n*evus) may represent a limited form of CHILD syndrome, but this has not been proven on a molecular level. Most cases of CHILD syndrome, including those with bilateral involvement, are caused by mutations in the *NSDHL* gene located on Xq28, which encodes a 3β-hydroxysteroid dehydrogenase enzyme involved in cholesterol biosynthesis[25].

MIDAS Syndrome

MIDAS syndrome is an X-linked dominant condition, antenatally lethal in males, characterized by *mi*crophthalmia, *d*ermal *a*plasia (see Table 64.4), *s*clerocornea and, sometimes, cardiac arrhthymias[26]; it is also known as MLS syndrome (*m*icrophthalmia with *l*inear *s*kin defects). MIDAS is caused by mutation or deletion of the *HCCS* gene on Xp22, which encodes mitochondrial holocytochrome c synthase[27].

Oral–Facial–Digital Syndrome Type I

Oral–facial–digital syndrome type I is an X-linked dominant condition characterized by cleft (or pseudocleft) lip/palate, lobulations and hamartomas of the tongue, hypertrophic oral frenula (associated with alveolar clefts), malformations of the digits, structural brain abnormalities, intellectual disability, polycystic kidneys, facial milia (primarily during infancy) and patchy alopecia that is typically whorled at the vertex. This disorder is caused by mutations in the *OFD1* (*CXORF5*) gene at Xp22.3–p22.2[28], which encodes a centrosomal protein located at the base of primary (non-motile) cilia. The latter structures are present on most cells and mediate signaling pathways such as hedgehog and Wnt during embryonic development.

X-linked Hypohidrotic Ectodermal Dysplasia (Female Patients)

Female patients ("carriers") with the X-linked form of hypohidrotic ectodermal dysplasia may have mild dental anomalies, patchy alopecia and variable degrees of reduced sweating, with a lack of adnexa and sometimes hyperpigmentation in a distribution corresponding to Blaschko's lines (see Ch. 63 and Fig. 55.12).

Menkes Disease (Female Carriers)

Menkes disease, an X-linked recessive disorder caused by dysfunction of a Cu^{2+}-transporting ATPase (α-polypeptide), is described elsewhere (see Ch. 69). Female carriers may have patchy pili torti and hypopigmentation along Blaschko's lines, attributable to functional mosaicism for cells with abnormal copper metabolism.

X-linked Reticulate Pigmentary Disorder

X-linked reticulate pigmentary disorder (initially described by Partington as "familial cutaneous amyloidosis") has been mapped to Xp22–p21. Female patients have hyperpigmented streaks following Blaschko's lines, whereas male patients have generalized reticulated hyperpigmentation and systemic manifestations (see Ch. 67). Histologic findings, which are similar in both sexes, include increased epidermal melanin, dermal melanophages, necrotic keratinocytes and (in some adult patients) cutaneous amyloid in the papillary dermis.

MOSAICISM FOR AUTOSOMAL DOMINANT CONDITIONS

When examining a linear skin disorder, it is helpful to consider what the diagnosis might be if the condition affected the whole skin surface, as some classic autosomal dominant skin disorders occasionally occur in a mosaic pattern. While the lesional morphology and histology are similar in the mosaic and generalized forms, the diagnosis may not be immediately obvious without clues provided by distribution and overall appearance of the generalized disorder. If no generalized disorder exists to match the linear lesions, then it could represent a dominant lethal mutation only survivable in the mosaic form; the latter can be either X-linked (see above) or autosomal.

Mosaicism for autosomal dominant disorders arises either during gametogenesis (half-chromatid mutation) or after fertilization (postzygotic/somatic mutation) (see Table 62.1). Forms of mosaicism in autosomal dominant skin conditions, including type 1 and type 2 as well as revertant mosaicism, are discussed above and summarized in Figure 62.2. For a *de novo* heterozygous mutation, there is generally no antecedent family history. However, there is a risk of passing on the full-blown disorder to the next generation, because mutant cells may be present in the gonads (gonadal mosaicism) as well as in the skin. An unstable premutation or epigenetic mosaicism[5] may explain rare instances of linear skin conditions with autosomal dominant inheritance.

Verrucous epidermal nevi represent a heterogeneous group. Although mosaicism for mutations in genes that cause autosomal dominant disorders have been shown to underlie a subset of verrucous epidermal nevi (Table 62.7), others have no known counterpart in a generalized form and may possibly result from a lethal genetic defect rescued by mosaicism (see below).

Epidermolytic Verrucous Epidermal Nevus

Verrucous epidermal nevi are tan to brown, warty lesions that are distributed along Blaschko's lines and often present from birth (see Ch. 109 and below). They are occasionally referred to as ichthyosis hystrix, a less specific, descriptive term that has been used for generalized as well as mosaic conditions characterized by thick, spiny hyperkeratosis (see Ch. 57). Some verrucous epidermal nevi have the histologic finding of epidermolytic hyperkeratosis and represent a type 1 mosaic form of the autosomal dominant disorder epidermolytic ichthyosis (previously referred to as bullous congenital ichthyosiform erythroderma; see Ch. 57) caused by mutations in keratin 1 or 10 (Fig. 62.7). In patients with epidermolytic epidermal nevi, a heterozygous mutation is present in keratinocytes within the nevus but not in adjacent uninvolved skin. Patients with generalized epidermolytic ichthyosis sometimes inherit their disorder from a parent with the mosaic form[29], presumably because the parent had gonadal as well as cutaneous mosaicism. It is noteworthy that neurologic and other systemic manifestations (epidermal nevus syndrome; see below), occasionally associated with non-epidermolytic verrucous epidermal nevi, are *not* seen with epidermolytic nevi caused by mutant keratin genes, which are not expressed in the brain.

Unilateral Palmoplantar Verrucous Epidermal Nevus due to Keratin 16 Mosaicism

Mosaicism for a heterozygous *keratin 16* (*KRT16*) mutation was reported in a patient with *unilateral* palmoplantar keratotic streaks that followed Blaschko's lines[30]. This condition can be considered to represent a type 1 mosaic form of pachyonychia congenita. It is distinct from striate palmoplantar keratoderma, which features keratotic bands that radiate up the flexor aspects of the digits bilaterally and is often inherited in an autosomal dominant manner due to germline mutations in the genes encoding desmoglein 1, desmoplakin or keratin 1 (see Ch. 58).

Non-epidermolytic Verrucous Epidermal Nevus due to Fibroblast Growth Factor Receptor 3 Pathway Mosaicism

Non-epidermolytic verrucous epidermal nevi often share clinicopathologic features with acanthosis nigricans, including hyperpigmentation,

Fig. 62.7 Epidermolytic verrucous epidermal nevus. Note the shedding of scale and associated relative hypopigmentation within several of the lesions.

EPIDERMAL NEVI: CANDIDATE GENES AND POTENTIAL SYNDROMIC ASSOCIATIONS

Type of nevus	Genes	Potential syndromic associations
Epidermolytic verrucous epidermal nevus	*KRT1, KRT10*	None
Unilateral palmoplantar verrucous epidermal nevus	*KRT16*	Features of pachyonychia congenita
Verrucous epidermal nevus (non-epidermolytic)	*FGFR3* (R248C mutation)	Features of thanatophoric dysplasia (skeletal, CNS abnormalities)
	PIK3CA	?
	KRAS	Features of cardiofaciocutaneous and Noonan syndromes (include skeletal, CNS abnormalities)
	Epidermal differentiation genes at 1q23?	?
Acneiform/comedonal nevus	*FGFR2*	Features of Apert syndrome (skeletal > CNS abnormalities)
PTEN ("Cowden") epidermal nevus	*PTEN* (germline + 2nd hit in affected tissues)	"Proteus-like" features: *s*egmental *o*vergrowth, *l*ipomatosis, *a*rteriovenous *m*alformations, *e*pidermal *n*evi (SOLAMEN); macrocephaly and other features of Cowden disease/Bannayan–Riley–Ruvalcaba syndrome (see Ch. 63)
Proteus nevus	*AKT1*	Feature of Proteus syndrome (see text)
Woolly hair nevus	?	Skeletal and CNS abnormalities
Nevus sebaceous	*PTCH?*	Schimmelpenning syndrome (skeletal, CNS, ocular); phakomatosis pigmentokeratotica (association with papular speckled lentiginous nevus; occasionally neurologic abnormalities, hypophosphatemic vitamin D-resistant rickets)
Inflammatory linear verrucous epidermal nevus (ILVEN)	*NSDHL?*	Ipsilateral limb reductions
CHILD nevus	*NSDHL*	CHILD syndrome

Table 62.7 Epidermal nevi: candidate genes and potential syndromic associations. CHILD, *c*ongenital *h*emidysplasia with *i*chthyosiform erythroderma/nevus and *l*imb *d*efects; CNS, central nervous system; *FGFR*, fibroblast growth factor receptor; *KRT*, keratin; *PIK3CA*, phosphatidylinositol 3-kinase catalytic subunit alpha; PTEN, phosphatase and tensin homolog.

Fig 62.8 Epidermal nevus due to *FGFR3* mutation and seborrheic keratoses following Blaschko's lines. **A** This lesion represents a mosaic counterpart of the acanthosis nigricans in patients with thanatophoric dysplasia, perhaps reflected in its flexural prominence. **B** Unilateral seborrheic keratoses in bands following Blaschko's lines. Seborrheic keratoses often have a somatic activating mutation in *FGFR3* or *PIK3CA*. *B, Courtesy, Luis Requena, MD.*

a "velvety" texture, flexural accentuation (Fig. 62.8A) and histologic findings of acanthosis and papillomatosis[31]. Approximately one-third of non-epidermolytic keratinocytic (i.e. non-organoid, meaning no sebaceous/other adnexal involvement) epidermal nevi are caused by mosaicism for a particular heterozygous activating mutation (R248C) in the *fibroblast growth factor receptor 3* gene (*FGFR3*), which has been found in lesional but not adjacent skin of affected individuals[32]. When present in all of the cells in the body, the same heterozygous mutation causes *thanatophoric dysplasia*, a disorder characterized by widespread acanthosis nigricans as well as short-limbed dwarfism, severe craniofacial malformations, CNS defects and perinatal lethality. This explains reports of craniofacial anomalies[33] and mental retardation[34] in patients with extensive epidermal nevi associated with mosaicism (presumably affecting extracutaneous tissues) for the R248C *FGFR3* mutation.

Mosaic activating mutations in the *PIK3CA* gene, which encodes a phosphatidylinositol-3-kinase subunit that functions downstream of FGFR3, have been identified in other non-epidermolytic verrucous epidermal nevi (see Table 62.7 and below)[35]. A substantial proportion of seborrheic keratoses and related acquired lesions have a somatic activating mutation in *FGFR3* or *PIK3CA*[35,36], and adult onset of seborrheic keratoses distributed along Blaschko's lines (Fig. 62.8B) has been described[37]. In addition, an activating mutation in the *KRAS* gene was identified in an epidermal nevus and rhabdomyosarcoma but not in peripheral blood or unaffected skin from an infant who also had polycystic kidneys and growth retardation (see Table 62.2 and Fig. 55.6)[38]. Of note, some patients with an extensive non-epidermolytic verrucous epidermal nevus develop vitamin D-resistant rickets due to overproduction of fibroblast growth factor 23 (see below, Epidermal nevus syndromes).

Acneiform/Comedonal Nevus due to Fibroblast Growth Factor Receptor 2 Mosaicism

Comedonal nevi, which are often evident at birth but become more prominent at puberty, consist of numerous keratin-filled pits in a linear distribution. Additional findings may include associated inflammatory acne lesions; hypopigmentation of lesional interfollicular epidermis and/or hairs; digital anomalies such as syndactyly and a broad thumb; and CNS defects[39]. A particular activating mutation (S252W) in the *fibroblast growth factor receptor 2* gene (*FGFR2*) has been found in the affected epidermis but not normal skin of patients with acneiform nevi characterized by numerous comedones, inflammatory lesions and (in one individual) hypopigmentation[40,41]. The same *FGFR2* mutation causes most cases of the autosomal dominant disorder Apert syndrome, which features craniosynostosis, digital anomalies (syndactyly, broad thumbs), severe acne, diffuse pigmentary dilution, and (occasionally) brain malformations. The proportion of acneiform/comedonal nevi (with or without "syndromal" associated findings) that represent a type 1 mosaic form of Apert syndrome remains to be determined.

Non-epidermolytic Verrucous Epidermal Nevus and Additional "Proteus-like" Manifestations due to PTEN Mosaicism

In some patients, non-epidermolytic verrucous epidermal nevi, most often thick papillomatous lesions, are associated with macrocephaly and additional segmental manifestations. The latter can include lipomatosis, fibromas, vascular malformations (frequently with an arteriovenous component) and asymmetric overgrowth of the soft tissues and bones. Heterozygous germline mutations in the *PTEN* gene cause the autosomal dominant PTEN hamartoma tumor syndrome, and a "second hit"/loss of *PTEN* heterozygosity has been found within tissue from segmental lesions including epidermal nevi, lipomas, fibromas and vascular malformations in these individuals. Such patients have *type 2 segmental PTEN hamartoma tumor syndrome*[12,13]. This mosaic "Proteus-like" (see below) entity has also been referred to as "SOLAMEN syndrome" (*s*egmental *o*vergrowth, *l*ipomatosis, *a*rteriovenous *m*alformation and *e*pidermal *n*evus) and "type 2 segmental Cowden disease" featuring the "linear Cowden nevus", but more appropriately termed the "PTEN epidermal nevus" to evoke the full spectrum of the PTEN hamartoma tumor syndrome[13,42].

PTEN negatively regulates PIK3CA/AKT signaling and, further downstream, the mammalian target of rapamycin (mTOR) pathway. The mTOR inhibitor rapamycin was reported to slow overgrowth in a boy with type 2 segmental PTEN hamartoma tumor syndrome[43].

Linear Darier Disease (Acantholytic Dyskeratotic Epidermal Nevus)

Morphologically, linear Darier disease (Fig. 62.9) is usually identical to the generalized form (see Ch. 59). Heterozygous mutations in the *ATP2A2* gene have been found in lesional but not normal-appearing skin, documenting type 1 mosaic Darier disease on a molecular level[44]. Less commonly, linear streaks with earlier onset and increased severity due to a "second hit" in the *ATP2A2* gene are found in patients with generalized Darier disease, reflecting type 2 mosaicism[11a].

Linear Hailey–Hailey Disease (Relapsing Linear Acantholytic Dermatosis)

Linear Hailey–Hailey disease is characterized by relapsing erosions and crusting within a particular segmental area; histologically, acantholysis resembling a "dilapidated brick wall" is observed (see Ch. 59). Inactivation of the second *ATP2C1* allele (loss of heterozygosity) was found in linear regions with earlier and more severe involvement in a patient with generalized Hailey–Hailey disease, confirming type 2 mosaicism[11].

Fig. 62.9 Linear Darier disease with hyperpigmented, keratotic papules.

Linear Porokeratosis

Linear porokeratosis is composed of multiple plaques with keratotic borders (cornoid lamellae). It is often congenital, usually persists throughout life, and likely represents a mosaic form of porokeratosis variant(s) with autosomal dominant inheritance, such as porokeratosis of Mibelli, disseminated superficial actinic porokeratosis, and porokeratosis palmaris, plantaris et disseminata. Linear porokeratosis may occur in a background of disseminated lesions, reflecting type 2 mosaicism. Linear lesions are associated with a higher risk of squamous cell carcinomas than are other porokeratosis variants[45], with a postzygotic "second hit" in the underlying gene presumably contributing to cancer development. Although possible chromosomal loci and candidate genes have been identified, the genetic bases of the porokeratosis variants remain unknown. Interestingly, a patchy unilateral distribution of porokeratoses, hyperpigmentation, hypertrichosis, telangiectasias and skeletal anomalies was observed in a man with mosaic trisomy 16[46].

Linear Basal Cell Carcinomas or Basaloid Follicular Hamartomas

Basal cell carcinomas (BCCs) occasionally develop in a linear distribution in an otherwise normal individual. It has been hypothesized that this might represent a mosaic form of nevoid BCC syndrome or nonsyndromic hereditary multiple BCCs, both of which have autosomal dominant inheritance. To date, mutations in the *PTCH* gene have not been identified in linear BCCs.

A linear distribution of basaloid follicular hamartomas (sometimes referred to as basal cell nevi) may occur as a mosaic form of generalized basaloid follicular hamartoma syndrome, an autosomal dominant condition of unknown etiology that presents with skin-colored to hyperpigmented papules, milia-like lesions, comedo-like plugs, palmoplantar pits and hypotrichosis[47,48]. In Happle–Tinschert syndrome, linear or segmental basaloid follicular hamartomas (variably accompanied by hyperpigmentation, hypopigmentation, atrophoderma, hypertrichosis and/or hypotrichosis) are associated with skeletal, dental and cerebral anomalies[48].

Segmental Neurofibromatosis Type 1

Patients with café-au-lait macules and/or neurofibromas limited to a segmental distribution may have a type 1 mosaic form of neurofibromatosis type 1 (NF1; see Ch. 61) due to a postzygotic mutation in the gene encoding neurofibromin[49]. The distribution of café-au-lait macules, which are often accompanied by lentigines, may be block-like or follow Blaschko's lines, whereas neurofibromas usually occur in a dermatomal pattern (see Table 62.4). Like other type 1 mosaic conditions, segmental NF1 usually has no antecedent family history, but offspring may have full-blown NF1[50]. In addition, large segmental plexiform neurofibromas or café-au-lait macules may also occur as a manifestation of type 2 mosaicism (i.e. due to a postzygotic "second hit" in the *NF1* gene) in patients with generalized NF1.

Linear or Segmental Angiofibromas and Mosaicism in Tuberous Sclerosis

Linear or segmental angiofibromas might represent a mosaic form of tuberous sclerosis (TS; see Ch. 61). Although additional manifestations of TS have been described in a subset of such patients, mosaicism for an underlying mutation has not been proven. However, there have been reports of families where somatic or gonadal mosaicism was found in mildly affected (without an obvious segmental distribution of skin lesions) or clinically unaffected parents of children with TS[51].

Venous and Glomuvenous Malformations (see Ch. 104)

A heterozygous postzygotic mutation in the *TEK* gene can be found in approximately half of sporadic venous malformations. These mutations cause constitutive activation of the TIE-2 endothelial cell tyrosine kinase receptor. This therefore represents a type 1 mosaic form of the autosomal dominant cutaneous and mucosal venous malformation syndrome caused by germline *TEK* mutations[52]. Large segmental plaque-type glomuvenous malformations, which are typically congenital, can occur as a type 2 mosaic manifestation of hereditary glomuvenous malformations due to *GLMN* mutations.

Nevoid Telangiectasia

Unilateral nevoid telangiectasia often appears at puberty and usually affects women (see Ch. 106). It has been postulated to represent a mosaic form of hereditary benign telangiectasia or the autosomal dominant capillary malformation–arteriovenous malformation syndrome caused by *RASA1* mutations (see Ch. 104). The *KRIT1* gene that is mutated in patients with the autosomal dominant cerebral capillary malformation and hyperkeratotic cutaneous capillary–venous malformation syndrome represents another candidate gene for segmental telangiectatic or angiokeratoma-like lesions.

"Zosteriform" Speckled Lentiginous Nevus or Segmental Agminated Melanocytic Nevi

It is possible that some speckled lentiginous nevi (SLN; especially macular lesions) represent a type 1 mosaic form of an autosomal dominant lentiginosis syndrome (e.g. LEOPARD)[53,54]. A patchy distribution of affected and spared areas of skin was described in a boy with LEOPARD syndrome due to a germline *PTPN11* mutation inherited from his father (who had classic LEOPARD syndrome) plus sex chromosome mosaicism; the authors postulated that revertant mosaicism represented one of several possible explanations[54]. Of note, segmental NF1 can also present with lentigines (typically together with café-au-lait macules) and background hyperpigmentation reminiscent of a macular SLN. Development of numerous acquired melanocytic nevi in a segmental distribution without the background hyperpigmentation of a SLN has also been described, suggesting mosaicism for a mutation in a nevus-susceptibility gene[55].

Other Linear Benign Tumors

Trichoepitheliomas, spiradenomas and/or cylindromas occasionally occur in a linear distribution. These may represent mosaic forms of autosomal dominant conditions such as multiple familial trichoepitheliomas, Brooke–Spiegler syndrome, and cylindromatosis caused by heterozygous germline mutations in the *CYLD* gene. Likewise, both sporadic linear syringomas and autosomal dominant inheritance of multiple syringomas with a non-linear distribution have been reported[56]. Leiomyomas often occur in a segmental pattern as a type 2 mosaic manifestation of autosomal dominant multiple cutaneous and uterine leiomyomatosis due to fumarate hydratase mutations (i.e. with a "second hit" in the affected segment).

LINEAR INFLAMMATORY DISORDERS

Several inflammatory skin conditions are occasionally distributed along Blaschko's lines. When generalized, these disorders are multifactorial,

Fig. 62.10 Linear psoriasis. Erythema and scale are seen within the streak as well as in small scattered lesions.

Fig. 62.11 Linear lichen planus. More active lesions are seen on the calf, while postinflammatory hyperpigmentation predominates on the thigh. *Courtesy, Anthony J Mancini, MD.*

typically with both a familial susceptibility and environmental contributions. Some display the Koebner phenomenon as well, implying triggering factors localized to the skin. Linear presentations likely result from mosaicism for a "susceptibility" mutation. In some cases, a streak of more severe disease is superimposed on a generalized background of the same condition, perhaps reflecting clonal loss of heterozygosity[57].

Linear Psoriasis

Linear psoriasis[58] is rare (Fig. 62.10), and some reported cases have subsequently been reclassified as ILVEN (see below). Psoriasis following Blaschko's lines may be confused with the Koebner phenomenon where linearity is imposed by exogenous injury (see Ch. 8). However, both can occur in the presence of generalized psoriasis, as can psoriasis superimposed on an epidermal nevus. It may be that the linear clone is characterized by a susceptibility mutation (see above).

Linear Lichen Planus

Linear lichen planus (LP) is more common than linear psoriasis and is seen at all ages. It presents as typical LP lesions in a linear distribution (Fig. 62.11), and postinflammatory hyperpigmentation is often the most prominent feature. Histology may be required to distinguish this disorder from other causes of linear pigmentation (see Fig. 62.3). If the LP lesions extend to the end of a digit, the nail is often affected.

Lichen Striatus

This self-limited linear inflammatory condition usually occurs during childhood (see Ch. 11), most commonly on an extremity in an atopic individual[59]. The condition is not particularly itchy, but it has histologic features of both eczema and lichen planus. Postinflammatory hypopigmentation points to the diagnosis of lichen striatus rather than linear lichen planus; both can be associated with nail dystrophy. Lichen striatus may reflect a susceptibility mutation or loss of heterozygosity in an atopy gene.

Segmental Vitiligo

Vitiligo (see Ch. 66) is another multifactorial disorder that occasionally occurs in a segmental distribution. Compared with symmetric vitiligo, the segmental type is earlier in onset, less likely to spread to other areas of the body, and less frequently associated with other autoimmune diseases. The lesions tend to be broad bands, patches or blocks, less often following Blaschko's lines. The occasional association of segmental with non-segmental vitiligo is in keeping with a polygenic disorder, with loss of heterozygosity for a vitiligo gene expressed in the skin[60].

Segmental vitiligo may occasionally be confused with nevus depigmentosus, but the latter is characterized by hypopigmentation rather than depigmentation, a stable size and shape relative to the growth of the child, and presence at birth or soon thereafter. A congenital linear band with complete absence of pigment raises the possibility of mosaicism for piebaldism.

Blaschkitis

Blaschkitis is a rare inflammatory dermatosis that typically presents as pruritic papules and vesicles along multiple lines of Blaschko, particularly on the trunk. More common in adults than children[61], it follows a relapsing course, with episodes often resolving spontaneously within days. It bears some resemblance to lichen striatus, but the histology is more eczematous and less lichenoid.

Other Linear Inflammatory Disorders

Several other inflammatory disorders occasionally occur in a distribution along Blaschko's lines, suggesting mosaicism for a susceptibility mutation. These conditions include lupus erythematosus (with scleroderma features in one variant)[62,63], dermatomyositis, lichenoid and fixed drug eruptions[64,65], lichenoid GVHD[66], morphea[67], and atrophoderma of Pasini and Pierini (linear atrophoderma of Moulin[68]).

LETHAL DISORDERS RESCUED BY MOSAICISM

For some linear or segmental disorders, no generalized counterpart can be recognized. These cases probably represent mosaicism for an autosomal mutation that would be incompatible with life if it involved all cells in the body. Such conditions occur sporadically.

Non-epidermolytic Epidermal Nevus (Including Sebaceous Nevus)

A linear epidermal nevus may be warty, smooth or barely palpable; brown (Fig. 62.12), pink, yellow or tan (Fig. 62.13); localized or extensive; unilateral or systematized; and isolated or associated with systemic abnormalities. The appearance is affected by both the age of the patient and the site of the lesion. Epidermal nevi are often white and velvety at birth, due to maceration by amniotic fluid. They may first become evident later in infancy or extend over time, a phenomenon parents find worrisome and hard to reconcile with the term "birthmark". Epidermal nevi are more likely to show sebaceous differentiation if they occur on the face or scalp, and this element becomes more prominent after puberty. Epidermal nevi on the scalp tend to have overlying alopecia or hair with an abnormal (e.g. woolly) texture.

This is a heterogeneous group (see Table 62.7); some associated genes are already known and undoubtedly more will be identified. Genes responsible for both generalized autosomal dominant disorders and epidermal nevi are discussed above. Activating mutations in the *PIK3CA* oncogene, which encodes a protein that functions in FGFR signaling, are associated with seborrheic keratoses as well as epidermal nevi[35,36]. There are no known generalized disorders caused by *PIK3CA* mutations, which may be survivable only in a mosaic state. Two patients have been reported with isolated epidermal nevi and mosaicism for a chromosomal break at 1q23, a major locus for genes involved in epidermal differentiation[69]. Mosaic trisomy 6 has also been associated with epidermal nevi[70].

Despite considerable evidence that they are variants of the same condition, smooth round sebaceous nevi of the scalp behave differently from linear sebaceous nevi. Linear lesions are more likely to be associated with neurologic abnormalities; this may relate to the fact that linear lesions arise earlier than round lesions and are more likely to involve multiple organs (see Table 62.3). However, round lesions are more tumor-prone, occasionally developing basal cell carcinoma in adult life, perhaps due to loss of heterozygosity. Deletion of *PTCH* (the Gorlin syndrome gene) has been reported in a nevus sebaceus.

Epidermal Nevus Syndromes

Synonyms/variants: ■ Nevus sebaceus syndrome ■ Schimmelpenning–Feuerstein–Mims syndrome ■ Solomon syndrome ■ Jadassohn syndrome

Key features

- The term encompasses a heterogeneous group of disorders
- The linear lesions are most commonly non-epidermolytic verrucous epidermal nevi, sebaceous nevi, or organoid nevi (with variable combinations of epidermal and adnexal elements)
- Systemic abnormalities involve primarily the skeleton, eyes and CNS

Introduction

Epidermal nevus syndromes (ENSs) are heterogeneous disorders in which epidermal nevi of various types are associated with musculoskeletal, ocular and/or neurologic abnormalities[71,72]. The phenotype is determined not only by the nature of the underlying mutation but also by the timing of origin and distribution of the mosaic clone. A vast array of systemic abnormalities, some of which may have occurred by chance, have been described in patients with epidermal nevi.

History

Reports of epidermal nevi together with abnormalities in other organ systems date back over a century. Various authors are credited with descriptions of these associations, including Jadassohn, Schimmelpenning, Feuerstein and Mims. Solomon and Esterly reviewed the syndrome in 1975[73], and Solomon is often credited with naming the disorder. In 1995, Happle[74] suggested that no one "ENS" exists, but rather that this term encompasses multiple, more specific entities such as Schimmelpenning, Proteus and CHILD syndromes. The term "ENS" is restricted here to sebaceous or verrucous epidermal nevi with associated features that do not fit into other specific disorders.

Genetics

Like epidermal nevi in general, ENSs typically occur in a sporadic fashion and may represent lethal disorders rescued by mosaicism.

Pathogenesis

ENSs are genetically heterogeneous. The diverse abnormalities of the skin and other organs in ENSs suggest basic underlying defects in regulation of cellular growth and differentiation. Among the genes known to be associated with epidermal nevi, *FGFR3* and *PTEN* mutations can also result in musculoskeletal and CNS anomalies (see Table 62.7 and above).

Fig. 62.12 Extensive epidermal nevus. The lesions on the neck are more verrucous.

Fig. 62.13 Epidermal nevus with the classic V-shaped pattern seen on the mid-back.

Clinical features

Other skin findings described in association with verrucous epidermal or sebaceous nevi include hypo- or hyperpigmentation (e.g. café-au-lait macules) in a mosaic distribution, woolly hair nevi, "hemangiomas" or vascular malformations, lipomatous overgrowth, aplasia cutis congenita and melanocytic nevi.

Systemic abnormalities most often involve the CNS (e.g. hemimegalencephaly, seizures, hemiparesis, developmental delay)[75], eye (e.g. lipodermoids, coloboma, choristoma) and skeleton (e.g. asymmetry, abnormal skull shape, kyphoscoliosis, limb hypertrophy). Other reported associations include cardiac and genitourinary anomalies. Hypophosphatemic vitamin D-resistant rickets has been observed in patients with extensive epidermal nevi, especially sebaceous nevi in the setting of phakomatosis pigmentokeratotica (a form of "twin spotting" [see Ch. 55] that also features papular SLN). This phenomenon has been associated with overproduction of fibroblast growth factor 23, a phosphaturic protein that causes oncogenic hypophosphatemic osteomalacia when secreted by various tumors. There is a suggestion that epidermal nevi involving the head are more likely to be associated with cerebral defects, although this observation has not been systematically evaluated.

Pathology

The histopathologic findings depend on the type of epidermal nevus.

Differential diagnosis

Although the clinical and histologic features of various types of epidermal nevi are often distinctive (see above), the clinician also needs to determine whether or not the patient has associated systemic abnormalities. In general, the older the child, the easier the task. The possibility that the epidermal nevus is a component of another multisystem disorder, such as Proteus syndrome or type 2 segmental PTEN hamartoma tumor syndrome, also needs to be considered.

Treatment

There is no specific treatment, so therapy is supportive. Neurologic, ophthalmologic and orthopedic referrals are often required.

Porokeratotic Eccrine Ostial and Dermal Duct Nevus

Porokeratotic eccrine ostial and dermal duct nevus (PEODDN) features keratotic spines and/or punctate pits with keratotic plugs. It can resemble a comedonal nevus but favors the palms and soles (see Fig. 111.39), where pilosebaceous follicles are absent; widespread involvement along Blaschko's lines can also occur[76]. Neonatal erosions, coexisting linear psoriasis, and associated squamous cell carcinomas have been described[76,77].

Proteus Syndrome

Key features

- Asymmetric overgrowth that is progressive and disproportionate
- Non-epidermolytic keratinocytic epidermal nevi and vascular malformations
- Areas of dermal atrophy with prominent venous patterns
- Palmoplantar cerebriform hyperplasia
- Lipomas and regional lipohypoplasia

Introduction

This syndrome, named after the Greek god of many forms, is a mosaic disorder characterized by asymmetric overgrowth of a variety of tissues.

History

Before Proteus syndrome was defined in 1983, patients with this condition were often classified as having ENS, Klippel–Trenaunay syndrome or NF1. Diagnostic criteria for Proteus syndrome were established in 1999, emphasizing the mosaic distribution of lesions, progressive course (particularly during childhood), and disproportionate nature of the overgrowth[78].

Genetics

Proteus syndrome occurs sporadically and is caused by mosaic activating mutations in the *AKT1* gene[78a].

Pathogenesis

The involvement of multiple organ systems in Proteus syndrome is consistent with the expression of AKT1, a serine-threonine protein kinase that promotes cell growth and survival, in many tissues. Although *PTEN* mutations have not been identified in patients with classic Proteus syndrome, some patients with Proteus-like phenotypes have a type 2 segmental form of PTEN hamartoma tumor syndrome (see above)[12,13,42]. This is not surprising considering that PTEN negatively regulates the growth-promoting PIK3CA/AKT pathway that is activated in affected tissues of Proteus syndrome patients.

Clinical features

Epidermal nevi in Proteus patients tend to be relatively thin and "soft"[72]. Other cutaneous manifestations include slow-flow vascular malformations (particularly port-wine stains), cerebriform palmar or plantar connective tissue nevi, patchy dermal hypoplasia resulting in prominent subcutaneous veins, and abnormal fat deposition producing lipomas and lipoatrophy (Fig. 62.14). Disproportionate overgrowth typically results in asymmetric macrodactyly or limb gigantism, usually with abnormal bones and deficient soft tissue, and scoliosis related to megaspondylodysplasia. Visceral overgrowth, especially of the spleen, can also occur.

Pathology

Histopathologic examination of epidermal nevi reveals hyperkeratosis, papillomatosis and acanthosis without adnexal differentiation or epidermolytic hyperkeratosis.

Differential diagnosis

Several other disorders feature epidermal nevi and vascular malformations together with asymmetric overgrowth. However the latter to be relatively proportionate, leading to a "ballooning" effect but normal structure, and less progressive than that of Proteus syndrome. Type 2 segmental PTEN hamartoma tumor syndrome (also known as SOLAMEN syndrome; see above) is characterized by macrocephaly, thicker and more verrucous epidermal nevi, vascular malformations

Fig. 62.14 Proteus syndrome. Epidermal nevus, vascular malformations and localized fatty infiltration of the thigh.

with a fast-flow component, and a lack of truly "cerebriform" palmoplantar connective tissue nevi. Another entity in the differential diagnosis is CLOVE(S) syndrome – *c*ongenital *l*ipomatous *o*vergrowth, *v*ascular anomalies, *e*pidermal nevi and *s*coliosis/other *s*keletal abnormalities (especially broad hands and feet)[79]. Epidermal nevi are an occasional feature of macrocephaly–capillary malformation syndrome (see Ch. 104). Although the association of an epidermal nevus with a port-wine stain was originally included as a form of phakomatosis pigmentovascularis (PPV type I), this variant was removed from more recent versions of the PPV classification scheme (see Table 104.4) because epidermal nevi are not melanocytic lesions. The disfiguring plexiform neurofibromas of NF1 can be distinguished from Proteus syndrome by the clinicopathologic features and presence of café-au-lait macules and other stigmata of NF1. Unlike Proteus syndrome, the overgrowth in Klippel–Trenaunay syndrome (KTS) is spatially associated with a vascular malformation.

Treatment

Management is symptomatic and organ-specific. Individual hamartomas and localized overgrowth can sometimes be treated surgically. Limb gigantism usually requires vascular imaging, with selective embolization sometimes providing an alternative or adjunct to surgery. Patients with Proteus syndrome (like those with KTS) are susceptible to deep venous thrombosis and pulmonary embolism.

ILVEN (Inflammatory Linear Verrucous Epidermal Nevus)

ILVEN is a linear, erythematous, scaly plaque that follows Blaschko's lines and is characteristically pruritic (Fig. 62.15; see Ch. 109). While occasionally present at birth, it usually appears during childhood (or, less often, adult life) and extends over months to years. It responds temporarily, if at all, to topical anti-inflammatory agents and rarely remits spontaneously. There are anecdotal reports of improvement with etanercept. Surgical excision is an option, but possible complications related to scarring need to be considered. This entity has been confused in the past with linear psoriasis.

Unlike the non-inflammatory epidermal nevi, ILVEN is not associated with neurologic defects. Rarely, there are ipsilateral skeletal abnormalities, usually reduction deformities, suggesting that ILVEN is possibly a forme fruste of CHILD syndrome. An alternative acronym is PEN/PENCIL (*p*soriasiform *e*pidermal *n*evus + *c*ongenital *i*psilateral *l*imb defects)[80].

Fig. 62.15 Inflammatory linear verrucous epidermal nevus. Scaly psoriasiform plaques distributed in a linear array.

Encephalocraniocutaneous Lipomatosis (Haberland Syndrome)

Encephalocraniocutaneous lipomatosis (ECCL) is a rare condition characterized by cerebral malformations with ipsilateral eye abnormalities (usually choristomas) and papulonodular skin lesions including lipomas, fibromas, fibrolipomas and angiolipomas. These lesions favor the eyelids and scalp, and alopecia overlying scalp lipomas, referred to as nevus psiloliparus, is occasionally associated with aplasia cutis congenita[81]. The cranial and eye lesions are usually unilateral, but lipomas occasionally occur on both sides of the scalp. Of note, Blaschko's lines cross the cranial midline in a spiral pattern (see Fig. 62.1C). Oculoectodermal syndrome, which also features aplasia cutis congenita (see Table 64.4), may represent a milder variant of ECCL[82].

Oculocerebrocutaneous Syndrome (Delleman–Oorthuys Syndrome)

The primary features of this syndrome are CNS malformations (e.g. cysts, cerebellar hypoplasia, absent corpus callosum), orbital cysts, microphthalmia, finger-like cutaneous appendages representing striated muscle hamartomas (especially around the eye), and aplasia cutis congenita above the ear[83].

McCune–Albright Syndrome

McCune–Albright syndrome is characterized by large blocks of café-au-lait pigmentation, demarcated at the midline and sometimes following Blaschko's lines in broad bands, together with polyostotic fibrous dysplasia of the bone and/or endocrine hyperfunction (classically precocious puberty). It is due to a postzygotic activating mutation in *GNAS*, the gene encoding the α-subunit of the G protein that stimulates adenylate cyclase activity. This results in increased signaling in pathways where cyclic AMP acts as a "second messenger", explaining endocrine overactivities and increased pigmentation due to stimulation of tyrosinase. Large café-au-lait patches in otherwise healthy individuals may represent more limited involvement due to a *GNAS* mutation later in embryonic development. It has proved more difficult to identify the mutation in skin than in other affected tissues[84].

Vascular Malformations

Vascular malformations, including those associated with Klippel–Trenaunay and Sturge–Weber syndromes as well as cutis marmorata telangiectatica congenita and microcystic lymphatic malformations ("lymphangioma circumscriptum"), may also be due to mosaicism for otherwise lethal mutations.

CHROMOSOMAL MOSAICISM

Hypomelanosis of Ito

Synonyms: ■ Linear nevoid hypopigmentation ■ Pigmentary mosaicism ■ Incontinentia pigmenti achromians (historical)

Key features

- A descriptive term rather than a diagnosis
- Hypopigmentation following Blaschko's lines, which can be evident at birth or appear later and may extend over time
- Variable extracutaneous involvement, which can include CNS, musculoskeletal and ocular abnormalities
- The underlying mosaic defect (often a chromosomal aberration) varies

Introduction

Hypomelanosis of Ito represents a description rather than a diagnosis. It refers to hypopigmentation in a distribution following Blaschko's lines due to a clone of skin cells with decreased ability to produce

pigment. Extracutaneous findings are highly variable and are found in a minority of individuals with hypopigmentation along Blaschko's lines. The author reserves the term "hypomelanosis of Ito" for patients with extracutaneous manifestations.

History

Ito, when describing this condition in 1952, interpreted the appearance as a negative image of incontinentia pigmenti, with markings following the same pattern of Blaschko's lines but lighter than the normal skin rather than darker.

Epidemiology

HI affects both sexes and all races, but it is easier to see in darkly pigmented skin.

Genetics

HI is almost always sporadic. There are a few published reports of possible familial occurrence.

Pathogenesis

Chromosomal mosaicism can be identified in the blood by standard cytogenetic analysis in about a third of HI patients. In other cases, the clonal abnormality may be too subtle to be detected cytogenetically or only expressed in tissues other than blood. Fibroblasts cultured from lesional skin show chromosomal mosaicism in some patients with normal blood karyotypes. The yield is increased further by studying cultured keratinocytes (since the mosaic abnormality may be confined to the epidermis; however, keratinocyte cultures are not routinely performed at most cytogenetic laboratories)[85] and by the use of array-comparative genomic hybridization (CGH), which can detect structural variations with much higher resolution[86].

HI can be caused by mosaicism for a wide variety of abnormalities in the structure (e.g. unbalanced translocations) or number (aneuploidies) of autosomes and X chromosomes. Approximately 90% of the chromosomal aberrations that have been reported in patients with HI or linear and whorled nevoid hypermelanosis (LWNH; see below) overlapped with the locations of genes known to be involved in pigmentation[87]. Extracutaneous findings depend upon the particular chromosomal defect and the tissues affected. Diploid/triploid mosaicism, mosaic tetrasomy 12p (Pallister–Killian syndrome; mental retardation, seizures and facial dysmorphism as well as hypo- or hyperpigmentation along Blaschko's lines)[88], and mosaic trisomy (or tetrasomy) 13q (phylloid hypomelanosis rather than hypopigmentation along Blaschko's lines)[89] are specific subtypes.

Clinical features

Streaks and swirls of hypopigmentation along Blaschko's lines can occur anywhere on the cutaneous surface and may be apparent at birth or (especially in those with fair skin) become evident during childhood. Occasional associated skin findings include lentigines, hypertrichosis and alopecia. Approximately one-third of children with hypopigmentation along Blaschko's lines who present to a pediatric dermatologist at a tertiary referral center have extracutaneous abnormalities, which generally became apparent during infancy. The extracutaneous abnormalities are highly variable, most often affecting the CNS, eyes and musculoskeletal system.

Pathology

Lesional skin may appear normal or show reduced numbers of melanocytes.

Differential diagnosis

Figure 62.3 shows the differential diagnosis of hypopigmented lesions following Blaschko's lines. Some patients with chromosomal mosaicism may have linear streaks of both hypo- and hyperpigmentation or a combination of linear and block-like hypopigmentation (see below).

Treatment

Therapy is symptomatic and organ-specific.

Nevus Depigmentosus

A nevus depigmentosus is a hypopigmented skin condition that (like HI) is thought to reflect cutaneous mosaicism. However, it is generally more limited in extent and usually lacks extracutaneous associations. The most common presentation is a localized patch that breaks apart into smaller macules at its periphery (resembling a splash of paint). A segmental variant (block-like; hypopigmented form of "segmental pigmentation disorder"[90]) typically features midline demarcation and less distinct lateral borders, and a linear or "systematized" variant has been described that overlaps with the cutaneous findings in HI[90a]. Although classically evident at birth, a nevus depigmentosus sometimes becomes apparent later in childhood, especially in lightly pigmented individuals.

Linear and Whorled Nevoid Hypermelanosis

LWNH is characterized by hyperpigmentation along Blaschko's lines due to a clone of skin cells with increased (rather than decreased as in HI) pigment production. Similar to HI, a variety of underlying mosaic chromosomal anomalies have been reported. The term "pigmentary mosaicism" therefore describes both HI and LWNH. Although LWNH (like HI) is usually sporadic, epigenetic mosaicism due to autosomally inherited retrotransposons may explain occasional familial aggregation[5]. The skin findings in LWNH typically appear at or soon after birth. Approximately a quarter of patients with LWNH who present to a pediatric dermatologist have extracutaneous findings, which can involve the CNS, musculoskeletal system and (occasionally) heart. Skin histology shows primarily increased epidermal pigmentation in affected skin.

CHIMERISM

Block-like Hyper- and Hypopigmentation due to Chimerism

Chimerism differs from mosaicism in that the different clones originate from different organisms. Human chimeras can result from fusion of two zygotes (i.e. fused dizygotic twins) or fertilization of one egg by two sperm. Usually detected by hematologists as anomalous blood groups, chimerism is exceedingly rare. Findlay and Moores[91] studied more than a million routine blood samples and found evidence of chimerism in only two. Pigmentary variation in chimerism typically presents in a checkerboard pattern; however, streaks along Blaschko's lines and mixtures of light and dark skin that do not correspond to recognized patterns of mosaicism have also been described[92]. In cases of XX/XY chimerism, the karyotype of dermal fibroblasts does not necessarily correspond to the overlying skin color, probably reflecting the different embryonic migration routes in the dermis and epidermis[10].

REFERENCES

1. Blaschko A. Die Nervenverteilung in der Haut in ihrer Beziehung zu den Erkrankungen der Haut. Beilage zu den Verhandlungen der Deutschen Dermatologischen Gesellschaft VII Congress. Breslau; Braumuller, Wien, 1901.
2. Curth HO, Warburton D. The genetics of incontinentia pigmenti. Arch Dermatol. 1965;92:229–35.
3. Happle R. Genetische Bedeutung der Blaschkoschen Linien. Z Hautkr. 1977;52:935–44.
4. Sun BK, Tsao H. X-chromosome inactivation and skin disease. J Invest Dermatol. 2008;128:2753–9.
5. Happle R. Monoallelic expression on autosomes may explain an unusual heritable form of pigmentary mosaicism: a historical case revisited. Clin Exp Dermatol. 2009;34:834–7.
6. Montgomery DW. The cause of the streaks in naevus linearis. J Cutan Genito-urinary Dis. 1901;19:455–64.
7. Shuster S. The skin as a diseased organ. In: Dermatology in Internal Medicine. Oxford: Oxford University Press, 1978:21.
8. Happle R, Assim A. The lines of Blaschko on the head and neck. J Am Acad Dermatol. 2001;44:612–15.
9. Happle R. Mosaicism in human skin. Understanding the patterns and mechanisms. Arch Dermatol. 1993;129:1460–70.

10. Moss C. Cytogenetic and molecular evidence for cutaneous mosaicism: the ectodermal origin of Blaschko lines. Am J Med Genet. 1999;85:330–3.
11. Poblete-Gutierrez P, Wiederholt T, Konig A, et al. Allelic loss underlies type 2 segmental Hailey-Hailey disease, providing molecular confirmation of a novel genetic concept. J Clin Invest. 2004;114:1407–9.
11a. Fölster-Holst R, Nellen RG, Jensen JM, et al. Molecular genetic support for the rule of dichotomy in type 2 segmental Darier disease. Br J Dermatol. 2011. doi: 10.1111/j.1365-2133.2011.10593.x.
12. Loffeld A, McLellan NJ, Cole T, et al. Epidermal naevus in Proteus syndrome showing loss of heterozygosity for an inherited *PTEN* mutation. Br J Dermatol. 2006;154:1194–8.
13. Caux F, Plauchu H, Chibon F, et al. Segmental overgrowth, lipomatosis, arteriovenous malformation and epidermal nevus (SOLAMEN) syndrome is related to mosaic *PTEN* nullizygosity. Eur J Hum Genet. 2007;15:767–73.
14. Jonkman MF, Pasmooij AM. Revertant mosaicism – patchwork in the skin. N Engl J Med. 2009;360:1680–2.
15. Choate KA, Lu Y, Zhou J, et al. Mitotic recombination in patients with ichthyosis causes reversion of dominant mutations in *KRT10*. Science. 2010;330:94–7.
16. Fusco F, Bardaro T, Fimiani G, et al. Molecular analysis of the genetic defect in a large cohort of IP patients and identification of novel *NEMO* mutations interfering with NF-kappaB activation. Hum Mol Genet. 2004;13:1763–73.
17. Pacheco TR, Levy M, Collyer JC, et al. Incontinentia pigmenti in male patients. J Am Acad Dermatol. 2006;55:251–5.
18. Roberts JL, Morrow B, Bega-Rich C, et al. Incontinentia pigmenti in a newborn male infant with DNA confirmation. Am J Med Genet. 1998;75:159–63.
19. Mansour S, Woffendin H, Mitton S, et al. Incontinentia pigmenti in a surviving male is accompanied by hypohidrotic ectodermal dysplasia and recurrent infection. Am J Med Genet. 2001;99:172–7.
20. Hadj-Rabia S, Froidevaux D, Bodak N, et al. Clinical study of 40 cases of incontinentia pigmenti. Arch Dermatol. 2003;139:1206–8.
21. Moss C, Ince P. Anhidrotic and achromians lesions in incontinentia pigmenti. Br J Dermatol. 1987;116:839–49.
22. Bornholdt D, Oeffner F, König A, et al. *PORCN* mutations in focal dermal hypoplasia: coping with lethality. Hum Mutat. 2009;30:E618–28.
23. Clements SE, Mellerio JE, Holden ST, et al. *PORCN* gene mutations and the protean nature of focal dermal hypoplasia. Br J Dermatol. 2009;160:1103–9.
23a. Barrott JJ, Cash GM, Smith AP, et al. Deletion of mouse Porcn blocks Wnt ligand secretion and reveals an ectodermal etiology of human focal dermal hypoplasia/Goltz syndrome. Proc Natl Acad Sci U S A. 2011;108:12752–7.
24. Steijlen PM, van Geel M, Vreeburg M, et al. Novel *EBP* gene mutations in Conradi-Hünermann-Happle syndrome. Br J Dermatol. 2007;157:1225–9.
25. Konig A, Happle R, Fink-Puches R, et al. A novel missense mutation of *NSDHL* in an unusual case of CHILD syndrome showing bilateral, almost symmetric involvement. J Am Acad Dermatol. 2002;46:594–6.
26. Sharma VM, Ruiz de Luzuriaga AM, Waggoner D, et al. Microphthalmia with linear skin defects: a case report and review. Pediatr Dermatol. 2008;25:548–52.
27. Wimplinger I, Morleo M, Rosenberger G, et al. Mutations of the mitochondrial holocytochrome c-type synthase in X-linked dominant microphthalmia with linear skin defects syndrome. Am J Hum Genet. 2006;79:878–89.
28. Thauvin-Robinet C, Cossee M, Cormier-Daire V, et al. Clinical, molecular, and genotype-phenotype correlation studies from 25 cases of oral-facial-digital syndrome type 1: a French and Belgian collaborative study. J Med Genet. 2006;43:54–61.
29. Paller A, Syder AJ, Chan Y-M, et al. Genetic and clinical mosaicism in a type of epidermal nevus. N Engl J Med. 1994;331:1408–15.
30. Terrinoni A, Puddu P, Didona B, et al. A mutation in the VI domain of *K16* is responsible for unilateral palmoplantar verrucous nevus. J Invest Dermatol. 2000;114:1136–40.
31. Ersoy-Evans S, Sahin S, Mancini AJ, et al. The acanthosis nigricans form of epidermal nevus. J Am Acad Dermatol. 2006;55:696–8.
32. Hafner C, van Oers JMM, Vogt T, et al. Mosaicism of activating *FGFR3* mutations in human skin causes epidermal nevi. J Clin Invest. 2006;116:2201–2206.
33. Collin B, Taylor IB, Wilkie AO, Moss C. Fibroblast growth factor receptor 3 (*FGFR3*) mutation in a verrucous epidermal naevus associated with mild facial dysmorphism. Br J Dermatol. 2007;156:1353–6.
34. García-Vargas A, Hafner C, Pérez-Rodríguez AG, et al. An epidermal nevus syndrome with cerebral involvement caused by a mosaic *FGFR3* mutation. Am J Med Genet A. 2008;146A:2275–9.
35. Hafner C, López-Knowles E, Luis NM, et al. Oncogenic *PIK3CA* mutations occur in epidermal nevi and seborrheic keratoses with a characteristic mutation pattern. Proc Natl Acad Sci U S A. 2007;104:13450–4.
36. Hafner C, Vogt T, Landthaler M, Müsebeck J. Somatic *FGFR3* and *PIK3CA* mutations are present in familial seborrhoeic keratoses. Br J Dermatol. 2008;159:214–17.
37. Mabuchi T, Akasaka E, Kondoh A, et al. Seborrheic keratosis that follows Blaschko's lines. J Dermatol. 2008;35:301–3.
38. Bourdeaut F, Hérault A, Gentien D, et al. Mosaicism for oncogenic G12D *KRAS* mutation associated with epidermal nevus, polycystic kidneys and rhabdomyosarcoma. J Med Genet. 2010;47:859–62.
39. Patrizi A, Neri I, Fiorentini C, Marzaduri S. Nevus comedonicus syndrome: a new pediatric case. Pediatr Dermatol. 1998;15:304–6.
40. Munro CS, Wilkie AO. Epidermal mosaicism producing localised acne: somatic mutation in *FGFR2*. Lancet. 1998;352:704–5.
41. Melnik BC, Vakilzadeh F, Aslanidis C, et al. Unilateral segmental acneiform naevus: a model disorder towards understanding fibroblast growth factor receptor 2 function in acne? Br J Dermatol. 2008;158:1397–9.
42. Loffeld A, McLellan NJ, Cole T, Moss C. Type 2 segmental Cowden disease vs. Proteus syndrome: reply from authors. Br J Dermatol. 2008;158:410–1.
43. Marsh DJ, Trahair TN, Martin JL, et al. Rapamycin treatment for a child with germline *PTEN* mutation. Nat Clin Pract Oncol. 2008;5:357–61.
44. Sanderson EA, Killoran CE, Pedvis-Leftick A, Wilkel CS. Localized Darier's disease in a Blaschkoid distribution: two cases of phenotypic mosaicism and a review of mosaic Darier's disease. J Dermatol. 2007;34:761–4.
45. Murata Y, Kumano K, Takai T. Type 2 segmental manifestation of disseminated superficial porokeratosis showing a systematized pattern of involvement and pronounced cancer proneness. Eur J Dermatol. 2001;11:191–4.
46. Ousager LB, Brandrup F, Brasch-Andersen C, Erlendsson A. Skin manifestations in a case of trisomy 16 mosaicism. Br J Dermatol. 2006;154:172–6.
47. Wheeler CE Jr, Carroll MA, Groben PA, et al. Autosomal dominantly inherited generalized basaloid follicular hamartoma syndrome: report of a new disease in a North Carolina family. J Am Acad Dermatol. 2000;43:189–206.
48. Happle R, Tinschert S. Segmentally arranged basaloid follicular hamartomas with osseous, dental and cerebral anomalies: a distinct syndrome. Acta Derm Venereol. 2008;88:382–7.
49. Maertens O, De Schepper S, Vandesompele J, et al. Molecular dissection of isolated disease features in mosaic neurofibromatosis type 1. Am J Hum Genet. 2007;81:243–51.
50. Consoli C, Moss C, Green SH, et al. Gonosomal mosaicism for a nonsense mutation (R1947X) in the *NF1* gene in segmental neurofibromatosis type 1. J Invest Dermatol. 2005;125:463–6.
51. Verhoef S, Bakker L, Tempelaars AM, et al. High rate of mosaicism in tuberous sclerosis complex. Am J Hum Genet. 1999;64:1632–7.
52. Limaye N, Wouters V, Uebelhoer M, et al. Somatic mutations in angiopoietin receptor gene *TEK* cause solitary and multiple sporadic venous malformations. Nat Genet. 2009;41:118–24.
53. Toelle SP, Boltshauser E, Wirth MG, Itin P. Association of lentiginous mosaicism and congenital cataract in a girl. Eur J Dermatol. 2006;16:360–2.
54. Writzl K, Hoovers J, Sistermans EA, Hennekam RC. LEOPARD syndrome with partly normal skin and sex chromosome mosaicism. Am J Med Genet A. 2007;143A:2612–15.
55. Yu X, Nagai H, Nishigori C, Horikawa T. Acquired unilateral melanocytic nevi in otherwise normal skin. Dermatology. 2008;217:63–5.
56. Ceulen RP, Van Marion AM, Steijlen PM, et al. Multiple unilateral skin tumors suggest type 1 segmental manifestation of familial syringoma. Eur J Dermatol. 2008;18:285–8.
57. Happle R. Superimposed segmental manifestation of polygenic skin disorders. J Am Acad Dermatol. 2007;57:690–9.
58. Saraswat A, Sandhu K, Shukla R, Handa S. Unilateral linear psoriasis with palmoplantar, nail, and scalp involvement. Pediatr Dermatol. 2004;21:70–3.
59. Patrizi A, Neri I, Fiorentini C, et al. Lichen striatus: clinical and laboratory features of 115 children. Pediatr Dermatol. 2004;21:197–204.
60. Taïeb A, Morice-Picard F, Jouary T, et al. Segmental vitiligo as the possible expression of cutaneous somatic mosaicism: implications for common non-segmental vitiligo. Pigment Cell Melanoma Res. 2008;21:646–52.
61. Keegan BR, Kamino H, Fangman W, et al. "Pediatric blaschkitis": expanding the spectrum of childhood acquired Blaschko-linear dermatoses. Pediatr Dermatol. 2007;24:621–7.
62. Lee MW, Choi JH, Sung KJ, et al. Linear cutaneous lupus erythematosus in the lines of Blaschko. Pediatr Dermatol. 2001;18:396–9.
63. Julià M, Mascaró JM Jr, Guilabert A, et al. Sclerodermiform linear lupus erythematosus: a distinct entity or coexistence of two autoimmune diseases? J Am Acad Dermatol. 2008;58:665–7.
64. Ozkaya-Bayazit E, Baykal C. Trimethoprim-induced linear fixed drug eruption. Br J Dermatol. 1997;137:1028–9.
65. Happle R, Effendy I. Coexisting linear and disseminated drug eruption: a clinical clue to the understanding of the genetic basis of drug eruptions. Eur J Dermatol. 2001;11:89.
66. Kikuchi A, Okamoto S, Takahashi S. Linear chronic cutaneous graft-versus-host disease. J Am Acad Dermatol. 1997;37:1004–6.
67. Weibel L, Harper JI. Linear morphoea follows Blaschko's lines. Br J Dermatol. 2008;159:175–81.
68. Danarti R, Bittar M, Happle R, Konig A. Linear atrophoderma of Moulin: postulation of mosaicism for a predisposing gene. J Am Acad Dermatol. 2003;49:492–8.
69. Stosiek N, Ulmer R, von den Driesch P, et al. Chromosomal mosaicism in two patients with epidermal verrucous nevus. J Am Acad Dermatol. 1994;30:622–5.
70. Sobey GJ, Quarrell OW, Williams S, McGrath HM. Mosaic chromosome 6 trisomy in an epidermal nevus. Pediatr Dermatol. 2007;24:144–6.
71. Vujevich JJ, Mancini AJ. The epidermal nevus syndromes: multisystem disorders. J Am Acad Dermatol. 2004;50:957–61.
72. Happle R. The group of epidermal nevus syndromes Part I. Well defined phenotypes. J Am Acad Dermatol. 2010;63:1–22.
73. Solomon L, Esterly N. Epidermal and other congenital organoid nevi. Curr Probl Pediatr. 1975;6:3–56.
74. Happle R. Epidermal nevus syndromes. Semin Dermatol. 1995;14:111–21.
75. Menascu S, Donner EJ. Linear nevus sebaceous syndrome: case reports and review of the literature. Pediatr Neurol. 2008;38:207–10.
76. Goddard DS, Rogers M, Frieden IJ, et al. Widespread porokeratotic adnexal ostial nevus: clinical features and proposal of a new name unifying porokeratotic eccrine ostial and dermal duct nevus and porokeratotic eccrine and hair follicle nevus. J Am Acad Dermatol. 2009;61:e1–14.
77. Yu HJ, Ko JY, Kwon HM, Kim JS. Linear psoriasis with porokeratotic eccrine ostial and dermal duct nevus. J Am Acad Dermatol. 2004;50(5 suppl.):S81–3.
78. Turner JT, Cohen MM Jr, Biesecker LG. Reassessment of the Proteus syndrome literature: application of diagnostic criteria to published cases. Am J Med Genet A. 2004;130:111–22.
78a. Johnston JJ, Finn EM, Peters K, et al. A mosaic activating mutation in AKT1 associated with the Proteus syndrome. N Engl J Med. 2011;365:611–19.
79. Sapp JC, Turner JT, van de Kamp JM, et al. Newly delineated syndrome of congenital lipomatous overgrowth, vascular malformations, and epidermal nevi (CLOVE syndrome) in seven patients. Am J Med Genet A. 2007;143A:2944–58.
80. Moss C, Burn J. CHILD + ILVEN = PEN or PENCIL. J Med Genet. 1990;27:390–1.
81. Moog U. Encephalocraniocutaneous lipomatosis. J Med Genet. 2009;46:721–9.
82. Ardinger HH, Horii KA, Begleiter ML. Expanding the phenotype of oculoectodermal syndrome: possible relationship to encephalocraniocutaneous lipomatosis. Am J Med Genet A. 2007;143A:2959–62.
83. Hunter AG. Oculocerebrocutaneous and encephalocraniocutaneous lipomatosis syndromes: blind men and an elephant or separate syndromes? Am J Med Genet A. 2006;140:709–26.
84. Lumbroso S, Paris F, Sultan C. Activating Gsalpha mutations: analysis of 113 patients with signs of McCune-Albright syndrome – a European

Collaborative Study. J Clin Endocrinol Metab. 2004;89:2107–13.
85. Taibjee SM, Hall D, Balderson D, et al. Keratinocyte cytogenetics in pigmentary mosaicism including hypomelanosis of Ito: study of 10 patients including one with trisomy 20 mosaicism. Clin Exp Dermatol. 2009;34:823–9.
86. Gimelli G, Giorda R, Beri S, et al. A large analphoid invdup(3)(q22.3qter) marker chromosome characterized by array-CGH in a child with malformations, mental retardation, ambiguous genitalia and Blaschko's lines. Eur J Med Genet. 2007;50:264–73.
87. Taibjee SM, Bennett DC, Moss C. Abnormal pigmentation in hypomelanosis of Ito and pigmentary mosaicism: the role of pigmentary genes. Br J Dermatol. 2004;151:269–82.
88. Theisen A, Rosenfeld JA, Farrell SA, et al. aCGH detects partial tetrasomy of 12p in blood from Pallister-Killian syndrome cases without invasive skin biopsy. Am J Med Genet A. 2009;149A:914–18.
89. Dhar SU, Robbins-Furman P, Levy ML, et al. Tetrasomy 13q mosaicism associated with phylloid hypomelanosis and precocious puberty. Am J Med Genet A. 2009;149A:993–6.
90. Hogeling M, Frieden IJ. Segmental pigmentation disorder. Br J Dermatol. 2010;162:1337–41.
90a. Browne F, Taijbee SM, Moss C. Segmental pigmentation disorder – response. Br J Dermatol. 2011;164:225–6.
91. Findlay GH, Moores PP. Pigment anomalies of the skin in human chimaera: their relation to systematised naevi. Br J Dermatol. 1980;103:489–98.
92. Lipsker D, Flory E, Wiesel ML, et al. Between light and dark, the chimera comes out. Arch Dermatol. 2008;144:327–30.

Other Genodermatoses 63

Susan J Bayliss and David R Berk; Barbara K Burton; Bernard A Cohen; Alanna F Bree and Virginia P Sybert

Chapter Contents

Disorders featuring tumorigenesis ... 963
Multiple endocrine neoplasia ... 963
Cowden disease ... 963
Gardner syndrome ... 967
Muir–Torre syndrome ... 968
Enzyme deficiency diseases ... 970
Alkaptonuria ... 970
Biotinidase and holocarboxylase synthetase deficiencies ... 970
Fabry disease ... 971
Fucosidosis ... 972
Gaucher disease ... 973
Hartnup disease ... 973
Mitochondrial disorders ... 974
Niemann–Pick disease ... 974
Phenylketonuria ... 975
Premature aging syndromes and poikilodermas ... 975
Hutchinson–Gilford progeria syndrome ... 975
Werner syndrome ... 980
Kindler syndrome ... 981
Ectodermal dysplasias ... 982
Hypohidrotic ectodermal dysplasia ... 984
Hypohidrotic ectodermal dysplasia with immune deficiency ... 985
Hidrotic ectodermal dysplasia ... 986
Witkop tooth and nail syndrome ... 987
Ankyloblepharon–ectodermal dysplasia–clefting syndrome ... 988
Ectodermal dysplasia–ectrodactyly–clefting syndrome ... 989

Introduction

In this chapter, a number of genodermatoses are discussed that are not covered in other chapters of this textbook (Table 63.1).

Disorders characterized by cutaneous or mucosal tumors in conjunction with a variety of extracutaneous neoplasias (both benign and malignant) as well as endocrine abnormalities are the focus of the first section. It includes multiple endocrine neoplasia types 1, 2A and 2B in addition to Cowden disease, Gardner syndrome and Muir–Torre syndrome. This is followed by enzyme deficiencies, premature aging syndromes, poikilodermas and, lastly, ectodermal dysplasias.

DISORDERS FEATURING TUMORIGENESIS

Susan J Bayliss and David R Berk

MULTIPLE ENDOCRINE NEOPLASIA

Multiple endocrine neoplasia (MEN) refers to a group of disorders marked by the presence of neoplasia or hyperplasia in two or more endocrine organs, often in association with mucocutaneous findings. Three major MEN syndromes, termed types 1, 2A and 2B, have been clinically and genetically defined and are described in Table 63.2.

Mucocutaneous features are most notable in MEN types 1 and 2B. In type 1, facial angiofibromas (previously considered pathognomonic for tuberous sclerosis) are seen, in addition to collagenomas (Fig. 63.1), lipomas and hypopigmented macules[1]. Compared to those in tuberous sclerosis, angiofibromas in MEN 1 tend to be smaller and fewer in number, and they are more likely to arise on the upper lip and its vermilion border (in addition to the nose and medial cheeks). Although melanoma has been reported in patients with MEN 1 and the *MEN1* gene is affected in a small subset of sporadic melanomas[2], it remains unclear whether individuals with this syndrome have an increased risk of melanoma.

MEN 2B is notable for multiple mucosal neuromas (especially of the conjunctivae, lips and tongue; Fig. 63.2), which may be present at birth or develop during childhood. They are considered relatively specific for this diagnosis, although mucosal neuromas are occasionally observed in patients with the PTEN hamartoma tumor syndrome (see below)[3]. Cutaneous neuromas are rare and when present are usually in a perinasal location.

COWDEN DISEASE

Synonyms: ■ Multiple hamartoma syndrome ■ Cowden syndrome

Key features

- Autosomal dominant disorder characterized by multiple hamartomatous tumors of ectodermal, mesodermal and endodermal origin
- Mucocutaneous findings include trichilemmomas, acral keratoses, oral papillomas and sclerotic fibromas
- Two major sites of involvement are the thyroid (e.g. adenomas, follicular carcinoma) and the breast (e.g. fibrocystic disease, carcinoma)
- Caused by mutations in the *PTEN* gene

Introduction

Cowden disease (CD) is an uncommon genetic disorder that is characterized by multiple hamartomas of ectodermal, mesodermal and endodermal origin. Mucocutaneous lesions (trichilemmomas, acral keratoses and oral papillomas) are the most constant and characteristic features[4,5]. Neoplasms (benign and malignant) of the breast and thyroid occur in up to two-thirds of patients[6].

History

In 1963, Lloyd and Dennis reported a multisystem disorder with characteristic mucocutaneous lesions and tumors of the breast, thyroid and gastrointestinal tract[4]. They named the disorder "Cowden disease" after their first patient.

Epidemiology

CD is probably more common than is reflected by the number of cases reported, because the clinical findings can be subtle. It is inherited as an autosomal dominant trait with variable expressivity; a female predominance has been noted in some series[7]. Most of the reported patients have been Caucasian, and it is estimated to affect 1 in 200 000 individuals[8].

GENODERMATOSES
Hereditary connective tissue disorders
Disorders of keratinization
Hereditary epidermolysis bullosa
Hereditary disorders of hair and nails
Hereditary disorders of pigmentation
Metabolic skin disorders (including enzyme deficiencies; see below)
Disorders featuring cutaneous cancer
Disorders featuring benign tumors
Skin disorders associated with extracutaneous cancer
• MEN 1, 2A, 2B*
• Cowden disease*
• Gardner syndrome*
• Muir–Torre syndrome*
• Birt–Hogg–Dubé syndrome
• Reed syndrome
Ectodermal dysplasias*
Premature aging syndromes*
Poikilodermas*
Enzyme deficiencies*
• Alkaptonuria
• Biotinidase & holocarboxylase synthetase deficiencies
• Fabry disease & fucosidosis
• Gaucher disease
• Hartnup disease
• Mitochondrial respiratory chain defects
• Niemann–Pick disease
• Phenylketonuria
*Discussed in this chapter.

Table 63.1 Genodermatoses. See also Chapter 54.

Fig. 63.1 Multiple endocrine neoplasia (MEN) type 1. Multiple collagenomas in a patient with MEN type 1.

Fig. 63.2 Multiple endocrine neoplasia type 2B. Enlarged nodular lips and multiple mucosal neuromas on the tongue.

Pathogenesis

Germline mutations in the tumor suppressor gene *PTEN*, located on chromosome 10q22–23, are found in most patients with CD[9]. Mutations in this gene have also been observed in patients with Bannayan–Riley–Ruvalcaba syndrome (BRRS), Lhermitte–Duclos disease (LDD; hamartomatous overgrowth of cerebellar ganglion cells), and autism/macrocephaly syndrome. Of note, there is significant overlap in the clinical findings in patients with CD and BRRS (Table 63.3). Identical mutations have been found in patients with CD and BRRS, and in some families both CD and BRRS phenotypes are observed. As a result these disorders are grouped as PTEN hamartoma tumor syndrome

The primary defect in CD is thought to be an abnormality in the regulation of cellular proliferation[6]. The protein product of the *PTEN* gene is a lipid and protein phosphatase that plays a role in cell-cycle regulation and apoptosis. In particular, PTEN downregulates the phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway (see Fig. 55.5). PTEN also helps to promote chromosomal stability. Importation of the PTEN protein into the nucleus (via monoubiquitination) is essential for its tumor suppressor activity, and some mutations have been shown to disrupt major monoubiquitination sites[10]. Affected tissues include those with physiologic proliferation, such as the epidermis, oral and gastrointestinal mucosa, and thyroid and breast epithelium.

Clinical Features

In 1995, the International Cowden Syndrome Consortium developed operational diagnostic criteria that have since been updated multiple times. The most recent criteria are outlined in Table 63.4. Cutaneous involvement occurs in >80% of patients, and the characteristic mucocutaneous lesions usually begin to appear during the second to third decades of life (average, 22 years; range, birth to 75 years). The facial trichilemmomas present as multiple skin-colored or yellowish-tan verrucous papules that resemble common warts (Fig. 63.3)[5,11]. Other nonspecific cutaneous papules show a predilection for the face and distal extremities, and they may coalesce around facial orifices and the ears.

Multiple sclerotic fibromas of the skin are another relatively specific cutaneous marker of CD[12]. These lesions present as sharply circumscribed dermal papules with a strikingly uniform storiform pattern of collagen bundles on histologic examination (see Ch. 116). Punctate palmoplantar keratoses, often with a central depression, are present in more than half of patients[13] (Fig. 63.4). Keratotic papules can also be seen on the heels, the dorsal aspects of the hands and feet, and the extensor surfaces of the forearms and lower legs.

Other cutaneous lesions observed in patients with CD include lipomas, angiolipomas, vascular anomalies[14,15], acrochordons, and inverted follicular keratoses[5]. Oral lesions of CD appear as 1–3 mm skin-colored papules that often lead to a cobblestone appearance; there can be extensive involvement of the entire oral cavity, including the tongue[13]. The vascular anomalies of CD and BRRS tend to be multifocal, fast-flow lesions with intramuscular involvement and prominent associated ectopic fat. Intracranial developmental venous anomalies are also common (see Ch. 104)[15].

Thyroid disease occurs in approximately two-thirds of patients with CD and can include goiter, adenomas, and carcinoma (follicular > papillary; lifetime risk 5% to 10%)[4,8]. Fibrocystic disease and fibroadenomas of the breast affect three-quarters of female patients. Ductal papillomas and virginal hypertrophy may also be seen. Breast carcinoma develops in 25% to 50% of female patients with CD (at a mean age of approximately 40 years)[8,16], and it has also been reported in affected men[17].

Multiple hamartomatous polyps, usually less than 5 mm in diameter, may be found anywhere in the gastrointestinal tract, including the esophagus, stomach, small intestine, colon and anus. The polyps may involve the entire gastrointestinal tract, but they are most common in the colon. These lesions are usually asymptomatic and their malignant degenerative potential is small, with a recent review identifying only five published cases of colorectal carcinoma in patients with CD[8].

Benign ovarian cysts and uterine leiomyomas commonly develop and endometrial carcinoma occurs in 5–10% of women with CD[8]. Less frequent tumors include teratomas, other genitourinary carcinomas (urethral, cervical, renal cell, and transitional cell of the renal pelvis, ureter or bladder), cysts (Gartner's duct [vaginal], epidermoid, apocrine

TYPES OF MULTIPLE ENDOCRINE NEOPLASIA (MEN)							
MEN type (synonyms)	**Mode of inheritance**	**Gene locus**	**Gene**	**Protein product**	**Location and type of mutations**	**Clinical manifestations**	
						Systemic	**Mucocutaneous**
1 (Wermer syndrome, multiple endocrine adenomatosis)	AD	11q13	*MEN1** [*MENIN*]	Menin (a nuclear protein)	Variable; truncating mutations in >70%	**Pituitary**: prolactinoma > acromegaly, Cushing syndrome **Parathyroid**: hyperplasia or adenoma, hyperparathyroidism **Pancreas**: islet cell hyperplasia, adenoma or carcinoma, e.g. gastrinoma, insulinoma, glucagonoma Less common: foregut carcinoid tumors, adrenal (cortical) tumors, follicular adenomas (thyroid) Uncommon: pheochromocytoma	Multiple facial angiofibromas Collagenomas Lipomas (cutaneous and visceral) Less common: multiple gingival papules, confetti-like hypopigmented macules, possibly CALM
2A (MEN type 2, Sipple syndrome, pheochromocytoma and amyloid-producing medullary thyroid carcinoma, PTC syndrome)	AD	10q11.2	*RET*†	Tyrosine kinase receptor	Point mutations in the cysteine-rich extracellular domain, especially codon 634‡	**Parathyroid**: hyperplasia or adenoma; hyperparathyroidism (less frequent than in MEN 1) **Thyroid**: C-cell hyperplasia, medullary carcinoma§ **Adrenal**: pheochromocytoma (50% bilateral) Unusual: Cushing syndrome	Pruritus¶ Lichen amyloidosis¶ Notalgia paresthetica¶ Macular amyloidosis¶
2B (MEN type 3, multiple mucosal neuroma syndrome, mucosal neuromata with endocrine tumors, Wagenmann–Froboese syndrome)	AD	10q11.2	*RET*†	Tyrosine kinase receptor	>95% of patients have missense mutation (Met^{918}Thr) in substrate-recognition pocket	**Thyroid**: medullary carcinoma§ **Adrenal**: pheochromocytoma (50% bilateral) **GI**: Diffuse ganglioneuromatosis (megacolon, diverticulosis) Medullated corneal nerve fibers Proximal myopathy Marfanoid habitus Reduced subcutaneous fat High-arched palate Flat nasal bridge Pectus excavatum Other: Bilateral pes cavus, high patella, scoliosis, kyphosis, lordosis, joint laxity Rare: Cushing syndrome	Multiple mucosal neuromas, especially eyelid margins, conjunctivae, lips, anterior tongue > gingiva, palate, nasal and laryngeal mucosa Increased nerve fibers in normal skin Prominent, everted lips Everted eyelids Hyperpigmentation around mouth and overlying small joints of hands and feet CALM Circumoral lentigines Hypertrichosis, synophrys Rare: multiple neuromas of perinasal skin

*A tumor suppressor gene.
†Rearranged during transfection of proto-oncogene; mutations in the same gene can be responsible for Hirschsprung disease and familial medullary thyroid carcinoma.
‡Induce dimerization and activation of receptor in the absence of its ligand.
§Screen via measurement of serum calcitonin level after calcium or pentagastrin injection.
¶Onset usually prior to medullary thyroid carcinoma.

Table 63.2 Types of multiple endocrine neoplasia (MEN). A rare fourth type of MEN (MEN 4), caused by mutations in cyclin-dependent kinase inhibitor 1B (CDKN1B) and characterized by pituitary and parathyroid tumors, has been described; familial medullary thyroid carcinoma can result from *NTRK1* mutations as well as *RET* mutations. A woman with medullary thyroid carcinoma, macular amyloidosis, and multiple cutaneous neuromas in a widespread distribution (overlapping features of MEN 2A and MEN 2B) with a RET mutation in codon 768 has also been reported. AD, autosomal dominant; CALM, café-au-lait macules; NTRK1, neurotrophic tyrosine kinase receptor type 1.

hidrocystomas), and benign urethral polyps. Menstrual irregularities may also be present.

Craniomegaly is the most common skeletal manifestation, occurring in 80–100% of patients[7]. One-third of patients with CD have additional skeletal abnormalities, including adenoid facies, a high-arched palate, thoracic kyphosis or kyphoscoliosis, pectus excavatum, bone cysts, large hands and feet, syndactyly and other digital anomalies[11]. Ocular abnormalities have been reported in 13% of patients and include myopia, angioid streaks and retinal vascular anomalies[18].

Lhermitte–Duclos disease (LDD) is characterized by hamartomatous overgrowth of cerebellar ganglion cells, which can lead to elevated intracranial pressure, ataxia and seizures. LDD may be an isolated finding or occur in association with CD[19]. Patients with adult-onset LDD usually have a mutation in the *PTEN* gene.

Pathology

Histologically, trichilemmomas are characterized by a lobular proliferation of pale keratinocytes, often in association with a hair follicle. Basal keratinocytes are oriented to form a palisade, and hyperkeratosis can lead to a cutaneous horn. Histologically, some facial papules in patients with CD may simply be squamous papillomas, while others show follicular infundibular hyperplasia. Oral lesions often represent fibromatous nodules with collagen fibers arranged in whorls. On biopsy, extrafacial and palmoplantar papules tend to be hyperkeratotic papillomas, and they may have changes reminiscent of verrucae or acrokeratosis verruciformis[20].

Differential Diagnosis

The clinical differential diagnosis of the oral papillomas of CD includes verrucae, focal epithelial hyperplasia (Heck's disease), traumatic fibromas, mucosal neuromas of MEN 2B, papillomas of Goltz syndrome, and papular lesions of lipoid proteinosis. A combination of acral keratoses (including palmoplantar) plus oral and facial papules can also be seen in Darier disease, whereas multiple facial angiofibromas and gingival fibromas are characteristic of tuberous sclerosis. These disorders can usually be differentiated from CD by other characteristic features as well as histologic evaluation.

The clinical differential diagnosis of multiple facial trichilemmomas may include angiofibromas (as seen in tuberous sclerosis or MEN 1), trichoepitheliomas, and fibrofolliculomas (Birt–Hogg–Dubé syndrome); in addition to their histologic features, the tendency of trichilemmomas to have a verrucous appearance clinically can help to distinguish them from these lesions. Common warts, seborrheic keratoses, basaloid follicular hamartoma syndrome, and epidermodysplasia verruciformis

CLINICAL MANIFESTATIONS OF PTEN HAMARTOMA TUMOR SYNDROME			
	Onset typically at birth or in childhood	**Onset typically in adolescence or adulthood**	**Variable onset**
Mucocutaneous	Pigmented macules of genitalia (glans and shaft of penis, vulva) Lipomas Vascular anomalies* Neuromas (facial, acral, mucosal) Epidermal nevi Café-au-lait macules	Multiple facial papules† Multiple oral papillomas (lips, tongue)‡ Sclerotic fibromas Inverted follicular keratoses Multiple acrochordons Acanthosis nigricans	Acral/palmoplantar keratoses Scrotal tongue Perioral pigmented macules (rare)
Craniofacial and skeletal	Macrocephaly Down-slanting palpebral fissures Frontal bossing High-arched palate, long philtrum Pectus excavatum Joint hyperextensibility Hand and foot abnormalities§		Scoliosis, kyphoscoliosis
Thyroid		Goiter and/or adenomas Carcinoma (follicular > papillary)	
Breast		Fibrocystic disease Fibroadenomas Adenocarcinoma	
Gastrointestinal tract	Hepatic vascular anomalies	Adenocarcinoma (rare)	Hamartomatous polyps Ganglioneuromas Glycogenic acanthosis of esophagus
Genitourinary system		Ovarian cysts Uterine leiomyomas Menstrual irregularities Testicular lipomatosis Endometrial carcinoma Renal cell carcinoma Testicular tumors (e.g. seminoma)	
Central nervous system	Developmental delay, autism Seizures Hypotonia Developmental venous anomalies	Lhermitte–Duclos disease	Meningioma Spinal neurinoma
Ocular	Prominent corneal nerves Prominent Schwalbe lines Strabismus, amblyopia Retinal vascular anomalies Pseudopapilledema		Cataracts Myopia Angioid streaks
Muscular	Lipoid storage myopathy		
Other	Neonatal macrosomia Persistent drooling		

*Typically multifocal lesions with fast-flow channels, intramuscular involvement and associated ectopic fat; may have capillary, venous and/or lymphatic components.
†Includes trichilemmomas, lesions with histologic features of verrucae and very rarely tumors of the follicular infundibulum.
‡May represent epithelial hyperplasia, sclerotic fibromas or (less often) glycogenic acanthosis.
§Includes accelerated growth of the first metacarpal and first and second middle phalanges, syndactyly and brachydactyly.

Table 63.3 Clinical manifestations of PTEN hamartoma tumor syndrome. In general, the clinical manifestations that are usually evident at birth or during childhood have classically been associated with Bannayan–Riley–Ruvalcaba syndrome and those that usually develop during adolescence or adulthood have classically been associated with Cowden disease.

may represent additional diagnostic possibilities. Less commonly, multiple syringomas or the nevoid basal cell carcinoma syndrome might be considered (see Fig. 111.4).

Mutations in the *SDHB* or *SDHD* genes, which encode subunits of mitochondrial succinate *deh*ydrogenase, can cause an autosomal dominant "Cowden-like" syndrome that is characterized by a predisposition to the development of breast, thyroid and renal carcinomas; to date, cutaneous manifestations have not been described[21].

Treatment

Because approximately one-third of women with CD develop breast cancer, periodic mammograms and magnetic resonance imaging (annually, starting at 30–35 years of age or 5–10 years before the youngest breast cancer diagnosis in the patient's family) are recommended, along with biannual clinical examinations (beginning by age 25 years) and monthly self-examinations. Prophylactic mastectomies can be considered on an individual basis[22]. Thyroid function studies and thyroid ultrasound should be performed at baseline, and current guidelines recommend an annual thyroid ultrasound beginning at age 18 years.

Surveillance for endometrial cancer (annual blind endometrial biopsies beginning at 35–40 years of age or 5 years prior to the earliest endometrial cancer diagnosis in that family) and renal cancer (annual renal ultrasounds and urinalysis with urine cytology) are recommended for individuals with a family history of these malignancies. Evaluation of the gastrointestinal tract should be based on symptomatology; because hamartomatous polyps have little potential for malignant degeneration, screening examinations beyond those recommended for the general population are generally not indicated. Due to the substantial genotypic and phenotypic overlap of CD and BRRS, many authors recommend that patients with BRRS follow the same cancer surveillance protocol.

Although the recognition of CD is based upon clinical and histologic evaluation, genetic testing may be helpful to confirm the diagnosis and to facilitate identification of affected family members[23]. Agents that downregulate the mTOR pathway, such as rapamycin, represent promising therapeutic approaches for CD that are currently under investigation[24]. The facial papules of CD respond variably to topical 5-fluorouracil, oral isotretinoin, curettage, laser ablation or surgical excision[11,25].

COWDEN DISEASE CRITERIA, NATIONAL COMPREHENSIVE CANCER NETWORK 2011
MAJOR CRITERIA
Mucocutaneous lesions – One biopsy-proven trichilemmoma, *or* – Multiple palmoplantar keratoses, *or* – Multifocal or extensive oral mucosal papillomatosis, *or* – Multiple cutaneous facial papules (often verrucous), *or* – Pigmented macules on the glans penis
Macrocephaly (>97th percentile; 58 cm in adult woman, 60 cm in adult man)
Breast carcinoma
Thyroid carcinoma (non-medullary; especially follicular)
Endometrial carcinoma
Multiple gastrointestinal hamartomas or ganglioneuromas
MINOR CRITERIA
Fibromas
Lipomas
Fibrocystic breast disease
Other thyroid lesions (e.g. adenoma, nodules, goiter)
Uterine leiomyomas (fibroids)
Single gastrointestinal hamartoma or ganglioneuroma
Renal cell carcinoma
Mental retardation (IQ ≤75)
Autism spectrum disorder
INDICATIONS FOR *PTEN* GENE TESTING/PROVISIONAL DIAGNOSIS (A, B, *OR* C)
(A) Individual from a family with a known *PTEN* mutation
(B) Individual with a personal history of: • Bannayan–Riley–Ruvalcaba syndrome (BRRS), *or* • Adult Lhermitte–Duclos disease, *or* • Autism spectrum disorder + macrocephaly, *or* • Two or more biopsy-proven trichilemmomas, *or* • Two major criteria, including macrocephaly, *or* • Three major criteria, without macrocephaly, *or* • Two major criteria + two minor criteria, *or* • One major criterion + three minor criteria, *or* • Four minor criteria
(C) Individual with a first-degree relative with a clinical diagnosis of Cowden disease or BRRS plus a personal history of: • One major criterion, *or* • Two minor criteria

Table 63.4 Cowden Disease Criteria, National Comprehensive Cancer Network 2011. Now considered as criteria for *PTEN* gene testing rather than clinical diagnostic criteria; however, patients who meet criteria but do not undergo genetic testing should be managed as though they have Cowden disease. www.nccn.org/professionals/physician_gls/PDF/genetics_screening.pdf.

Fig. 63.3 Cowden disease. Multiple skin-colored papules on the face, especially the nose, some of which are verrucous. *Courtesy, Kalman Watsky, MD.*

Fig. 63.4 Cowden disease. Multiple palmar keratoses, many of which have a glassy appearance. A few have a central depression. *Courtesy, Joyce Rico, MD.*

GARDNER SYNDROME

Synonym: ■ Familial polyposis of the colon

Key features

- Autosomal dominant disorder characterized by premalignant intestinal polyposis and adenocarcinoma of the gastrointestinal tract
- Extraintestinal manifestations include epidermoid cysts, osteomas, desmoid tumors and fibrous tumors (skin, mesentery, retroperitoneum)
- Congenital hyperpigmentation of the retinal pigment epithelium (CHRPE) is an early sign
- Caused by mutations in the *APC* (adenomatous polyposis coli) gene

Introduction

The main features of Gardner syndrome (GS) are premalignant intestinal polyposis, epidermoid cysts, osteomas, and desmoid or fibrous tumors of the skin and other sites[26]. It is considered to represent a phenotypic variant of the familial adenomatous polyposis syndrome with prominent extraintestinal involvement[27].

History

In 1953, Gardner and Stephens described a large family in which many individuals had multiple cutaneous lesions, osteomatosis and fatal bowel cancer. The syndrome now bears Gardner's name.

Epidemiology

The incidence of GS is approximately 1 in 8000 to 1 in 16000 births. It is inherited as an autosomal dominant trait with high penetrance and variable expressivity, affecting men and women equally[28].

Pathogenesis

GS is caused by heterozygous germline mutations in the adenomatous polyposis coli (*APC*) tumor suppressor gene, which resides on chromosome 5q21–22. The *APC* gene encodes a protein that downregulates the Wnt/β-catenin signaling pathway, which has important functions in cellular proliferation, differentiation and adhesion.

Clinical Features

Skin lesions and bony abnormalities appear during childhood and adolescence, frequently occurring before the polyposis develops. Cutaneous

epidermoid cysts affect approximately one-third of patients with GS. These lesions are commonly found on the head and neck, may be present at birth, and tend to increase in size and number and then stabilize.

Osteomas occur in approximately 80% of patients and favor the mandible and maxilla, although they can develop in other bones of the skull and in long bones. Seen in children as young as 8 years of age, osteomas are painless and may grow large enough to be clinically obvious or be detectable only by radiographic studies. Other skeletal lesions include exostoses, endostoses and cortical thickening of the long bones. Dental anomalies are seen in approximately 20% of patients with GS and include supernumerary teeth, odontomas, unerupted teeth and multiple caries.

Desmoid tumors are non-encapsulated, non-metastasizing, locally aggressive benign tumors that occur in 3% to 17% of patients with GS. There is a marked female predominance (70% to 85%). Desmoid tumors may occur spontaneously or at incision sites, arising from musculo-aponeurotic soft tissues. They commonly develop after colectomy and can occur within the abdominal wall or intra-abdominally, with the latter causing greater morbidity via obstruction of the small bowel and/or ureters. Although cytologically benign, desmoid tumors can be invasive, recur, and even cause death. Hereditary desmoid disease characterized by multiple desmoid tumors, often at unusual sites, in patients with few or no colonic polyps has been described in association with *APC* mutations[29].

Fibromas may occur in the skin, subcutaneous tissues, mesentery or retroperitoneum. The "Gardner fibroma" often arises in the first decade of life, favors the back and paraspinal region, and can serve as a desmoid precursor. Lipomas, leiomyomas, trichoepitheliomas, neurofibromas and ovarian cysts are observed less commonly.

Congenital hypertrophy of the retinal pigment epithelium (CHRPE) is seen in an estimated two-thirds of patients with GS and can be an early sign of the disorder (Fig. 63.5)[30]. Because CHRPE is present at birth and easily detected by ophthalmologic examination, it is a useful finding in patients who do not yet have other manifestations. While unilateral solitary CHRPE may occur in unaffected individuals, multiple and bilateral lesions represent a sensitive and specific marker for GS. There are rare reports of adenocarcinoma arising from CHRPE.

Patients with GS are at increased risk for the development of other tumors, including papillary carcinoma of the thyroid (particularly in women), hepatoblastoma (usually affecting children less than 3 years of age), pancreatic and biliary tract carcinomas, adrenal adenomas (and occasionally carcinomas) and various sarcomas (e.g. fibrosarcoma, osteosarcoma). The association of brain tumors (most often medulloblastomas) with adenomatous polyposis in patients with heterozygous *APC* mutations has been referred to as Turcot syndrome type 2, while brain tumors (primarily glioblastomas) plus colonic polyposis in patients with *biallelic* mutations in mismatch repair genes (see below) is known as Turcot syndrome type 1; the latter may also present with multiple café-au-lait spots and hematologic malignancies[31].

Gastrointestinal lesions

In adults, the diagnosis of GS is commonly made when the patient presents with gastrointestinal bleeding secondary to adenomatous polyps. Other findings may include anemia, abdominal pain, diarrhea or constipation, and weight loss. Premalignant adenomatous polyps most commonly occur in the colon but are also found in the small intestine and stomach in over half of patients. Polyps are typically <1 cm in diameter and are rarely seen before the age of 10 years. By the age of 20 years, 50% of patients with GS have demonstrable polyps. Without surgical intervention, colorectal carcinoma is inevitable; it usually develops before age 40 years and arises by early adolescence in approximately 5% of affected individuals[32,33]. Carcinomas of the small intestine (especially the duodenum) can also occur[32].

Fig. 63.5 Congenital hypertrophy of the retinal pigment epithelium. *Courtesy, L Tychsen, MD.*

Pathology

Histologically, intestinal polyps show adenomatous hyperplasia of the mucosa[33]. Cutaneous cysts in patients with GS usually demonstrate the same microscopic changes as ordinary epidermoid cysts, with a lining of keratinizing epithelium that includes a granular layer. Pilomatricoma-like changes, with characteristic basophilic and shadow cell populations, have also been noted in the cysts of GS.

Differential Diagnosis

Epidermoid cysts usually occur in the absence of a particular syndrome, but multiple lesions should prompt a thorough family history and evaluation for other findings of GS (e.g. osteomas, CHRPE). In Peutz–Jeghers syndrome, mucocutaneous lentigines (intraoral, perioral and acral) are seen and the gastrointestinal polyps are hamartomatous rather than adenomatous. Hamartomatous gastrointestinal polyps are also found in juvenile polyposis syndromes (which may be associated with a hereditary hemorrhagic telangiectasia phenotype; see Table 104.2) and PTEN hamartoma tumor syndrome. Additional manifestations such as osteomas, CHRPE and desmoid tumors distinguish GS from these conditions. Of note, mutations in the *MUTYH* base excision repair gene can cause an autosomal recessive form of colorectal adenomatous polyposis, with osteomas, CHRPE, desmoid tumors, pilomatricomas and sebaceous neoplasms (see below) having been described in affected individuals[34].

Treatment

Because of the inevitable development of colorectal carcinoma, prophylactic colectomy is recommended when polyp formation becomes evident, and it is usually performed between 15 and 25 years of age. Initially, children with GS should be monitored with annual sigmoidoscopy beginning at 10–12 years of age. Once polyps are detected, patients should undergo annual colonoscopy until a colectomy is done. Upper gastrointestinal endoscopy is recommended every 1–3 years (depending on polyp burden), with careful inspection of the ampulla of Vater because of the increased risk of cancer in this area. Barium studies or (preferably) capsule endoscopy can be utilized periodically to evaluate the remainder of the small bowel. Because of the increased risk of hepatoblastoma, some experts recommend annual abdominal ultrasounds and measurement of serum α-fetoprotein levels during the first 5 years of life.

Symptomatic epidermoid cysts can be surgically excised. Desmoid tumors are also treated by surgical excision, although there tends to be a high recurrence rate. Preoperative MRI of the abdomen can demonstrate the origin of the tumor and the extent of involvement. If wide surgical excision fails, radiotherapy, hormonal therapy (e.g. tamoxifen, raloxifene), chemotherapy or a combination thereof can be tried. The osteomas of GS may or may not be amenable to surgical intervention. Medications that affect prostaglandin metabolism, such as nonsteroidal anti-inflammatory drugs (NSAIDs), may reduce the risk of colorectal cancer and desmoids[35].

Genetic counseling is imperative, and family members should be evaluated for extraintestinal and intestinal signs of the disorder. Molecular testing for *APC* mutations is commercially available.

MUIR–TORRE SYNDROME

Synonym: ▪ Cutaneous sebaceous neoplasms and keratoacanthomas, with gastrointestinal and other carcinomas

Key features

- An autosomal dominant disorder associated most commonly with adenocarcinoma of the colon, followed by genitourinary carcinomas
- The cutaneous manifestations are sebaceous neoplasms and keratoacanthomas
- Caused by mutations in three DNA mismatch repair genes (*MSH2*, *MLH1*, *MSH6*)

Introduction

Muir–Torre syndrome (MTS) is a rare autosomal dominant genodermatosis that is characterized by sebaceous neoplasms (adenoma, epithelioma or carcinoma), keratoacanthomas and internal malignancies. It is considered to represent a subtype of the hereditary non-polyposis colorectal cancer (HNPCC) syndrome (Lynch syndrome).

History

Muir in 1967 and Torre in 1968 independently reported the syndrome that bears their names. Their two patients had malignancies in several organs plus either keratoacanthoma-like lesions or multiple tumors of sebaceous origin.

Epidemiology

The male:female ratio of MTS is 3:2; affected individuals present with cutaneous manifestations at a mean age of 55 years. In a recent study, MTS was observed in 28% (14/50) of families and 9% (14/152) of individuals with HNPCC (all confirmed to have a germline mismatch repair gene mutation)[36].

Pathogenesis

MTS is caused by heterozygous germline mutations in one of several DNA mismatch repair genes, including *MSH2* (approximately 90% of MTS cases), *MLH1* and *MSH6*[37]. In patients with MTS, somatic loss of heterozygosity (due to inactivation of the other allele of the affected gene) results in microsatellite instability (increased variability in the lengths of repetitive "microsatellite" sequences in the genome that are prone to replication errors) and tumor formation[38].

Clinical Features

Sebaceous tumors can present prior to (~30%), concurrently with (~10%), or after (~60%) the diagnosis of a visceral malignancy. The skin tumors sometimes appear decades before or after a visceral malignancy develops. In general, sebaceous tumors favor the head and neck region (Fig. 63.6) and sebaceous carcinomas tend to affect the periocular area; however, in patients with MTS, these neoplasms often occur in other locations (trunk > extremities)[39]. Sebaceous adenomas are the most common tumor type, and they present as yellow papules or nodules numbering from one to hundreds[40,41]. Keratoacanthomas, which are keratotic skin-colored to erythematous papules or nodules that arise quickly, are seen in approximately 25% of patients with MTS and may exhibit sebaceous differentiation.

Fig. 63.6 Muir–Torre syndrome with multiple sebaceous neoplasms. *Courtesy, Dan Ring, MD.*

The most frequently observed malignancies are colorectal (61%) and genitourinary (22%) carcinomas[42]. Colorectal carcinoma in MTS most often involves the proximal colon and develops at a median age of 50 years, about one decade before colorectal carcinoma typically occurs in the general population. In addition, MTS patients can develop breast carcinomas (6%), hematologic malignancies (11%), head and neck cancers (5%), and neoplasms of the small intestine (3%) or stomach[43].

The diagnosis of MTS is based on the presence of at least one sebaceous tumor (or keratoacanthoma with sebaceous differentiation) and a visceral malignancy in the absence of any known predisposing factor. In the absence of a sebaceous tumor, the diagnosis can be made in a patient with multiple keratoacanthomas, multiple visceral malignancies and a family history of MTS. Findings that suggest a higher or lower likelihood of MTS in patients with sebaceous neoplasms are summarized in Table 63.5.

Pathology

Skin tumors arising as part of MTS fall into two general categories: sebaceous neoplasms and keratoacanthomas. Sebaceous adenomas (with a predominance of mature sebocytes), sebaceomas (vertically oriented with a predominance of basaloid seboblastic cells), so-called sebaceous epitheliomas (inconsistently defined term used for various lesions with seboblastic differentiation) and sebaceous carcinomas may occur (see Ch. 111). A type of sebaceous adenoma that may be specific to this syndrome has been called a seboacanthoma; it has the architecture of a keratoacanthoma but contains well-differentiated sebaceous lobules[44]. In addition, cystic sebaceous tumors, which are well-circumscribed, deep sebaceous lesions with a cystic growth pattern, have been identified in some MTS patients[45].

Immunohistochemical staining for MSH2, MSH6, MLH1 and PMS2 can be a valuable screening tool for MTS-associated tumors, which

RISK ASSESSMENT FOR MUIR–TORRE SYNDROME (MTS)	
Higher likelihood of MTS	**Lower likelihood of MTS**
CLINICOPATHOLOGIC CHARACTERISTICS OF SKIN LESIONS	
• Multiple sebaceous neoplasms • Located outside of the head and neck region • Sebaceous neoplasm with high specificity for MTS, e.g. seboacanthoma	• Single sebaceous neoplasm • Located in photodamaged facial skin • Sebaceous hyperplasia
CHARACTERISTICS OF PATIENT	
• History of colorectal cancer, especially if before 50 years of age or with high MSI histology* • History of other HNPCC-related malignancies† (e.g. small bowel, gastric, endometrial, bladder, ureteral, renal, biliary, pancreatic, glioblastoma), especially if more than one	• Elderly patient with no history of an HNPCC-related malignancy
FAMILY HISTORY	
• Multiple diagnoses of colorectal cancer and/or other HNPCC-related malignancies in family member(s), especially if before 50 years of age and in first-degree relative(s)	• No first-degree relatives with colorectal cancer/other HNPCC-related malignancies, or diagnosis in a single elderly relative
ADDITIONAL ANALYSIS OF SEBACEOUS NEOPLASMS	
• Loss of MSH2, MLH1, MLH6, and/or PMS2 expression shown by immunohistochemical staining‡ • Evidence of MSI in lesional tissue§	• Expression of MLH1, MSH2, MSH6, and PMS2 shown by immunohistochemical staining • No evidence of MSI in lesional tissue§

*Characterized by tumor-infiltrating lymphocytes, Crohn's disease-like lymphocytic reaction, medullary growth pattern, or signet ring/mucinous differentiation.
†Patients with MTS may also have an increased risk of breast, head and neck, and hematologic malignancies.
‡MSH2 and MSH6 proteins form a heterodimer, so lack of one can lead to the absence of the other; likewise, PMS2 is unstable without a functional MLH1 protein.
§Testing can be performed on paraffin-embedded tissue.

Table 63.5 Risk assessment for Muir–Torre syndrome (MTS). HNPCC, hereditary non-polyposis colorectal cancer; MSI, microsatellite instability.

typically show a lack of expression of one or more of these proteins (see Table 63.5)[40,42]. In addition, polymerase chain reaction (PCR)-based assays can be used to demonstrate microsatellite instability in tissue from MTS-associated neoplasms.

Differential Diagnosis

Sebaceous hyperplasia is a common finding in normal individuals and sebaceous adenomas and carcinomas can occur in patients without MTS. Sebaceous adenomas and carcinomas as well as colorectal carcinomas and other malignancies have been described in patients with autosomal recessive colorectal adenomatous polyposis caused by mutations in the *MUTYH* base excision repair gene[34]. Multiple keratoacanthomas may occur as an isolated finding (i.e. without visceral malignancy), especially in patients with the Ferguson–Smith (multiple self-healing) or Grzybowski (generalized eruptive) types of keratoacanthomas. However, these patients should be evaluated to exclude the possibility of MTS.

Treatment

Patients with an internal malignancy require appropriate oncologic referral and management. High-risk individuals (see Table 63.5) should undergo biennial screening colonoscopy beginning at age 20–25 years, as well as serial renal ultrasounds, urinalyses and complete blood counts. For women, routine gynecologic evaluations including yearly breast and pelvic examinations and Pap smears should begin by age 30 years. If indicated, endometrial biopsy and transvaginal ovarian ultrasound can be performed.

Treatment options for the benign sebaceous tumors include curettage, excision, cryosurgery and radiotherapy. Mohs micrographic surgery is recommended for sebaceous carcinomas on the face. Oral retinoids with or without interferon-α may be useful in the prevention of new sebaceous neoplasms.

Molecular testing of mismatch repair genes is commercially available, and identification of the underlying mutation can facilitate early diagnosis and surveillance of affected family members.

ENZYME DEFICIENCY DISEASES

Barbara K Burton

ALKAPTONURIA

Synonym: ■ Ochronosis

Key features

- An autosomal recessive disorder due to deficiency of homogentisic acid oxidase
- Clinical signs include pigmentation of cartilage (e.g. the helices), sclerae and skin (e.g. the axillae)
- Extracutaneous findings include urine that darkens on standing and arthritis

Alkaptonuria is a rare inborn error of metabolism in which homogentisic acid, an intermediate in phenylalanine and tyrosine metabolism, cannot be further metabolized and therefore accumulates in body fluids and tissues. The disorder results from a deficiency of the enzyme homogentisic acid oxidase and is inherited in an autosomal recessive fashion. The cardinal clinical features of the disorder (Fig. 63.7) include urine that turns dark on standing, pigmentation of cartilage and other connective tissues, and arthritis. The arthritis often presents in the fourth decade of life with chronic back pain and stiffness[46], with radiographs showing flattened and calcified intervertebral discs. Later involvement of large peripheral joints can resemble rheumatoid arthritis clinically but osteoarthritis radiographically. Renal complications, including an increased incidence of calculi and occasionally kidney failure, and valvular heart disease may also occur. Life expectancy is normal.

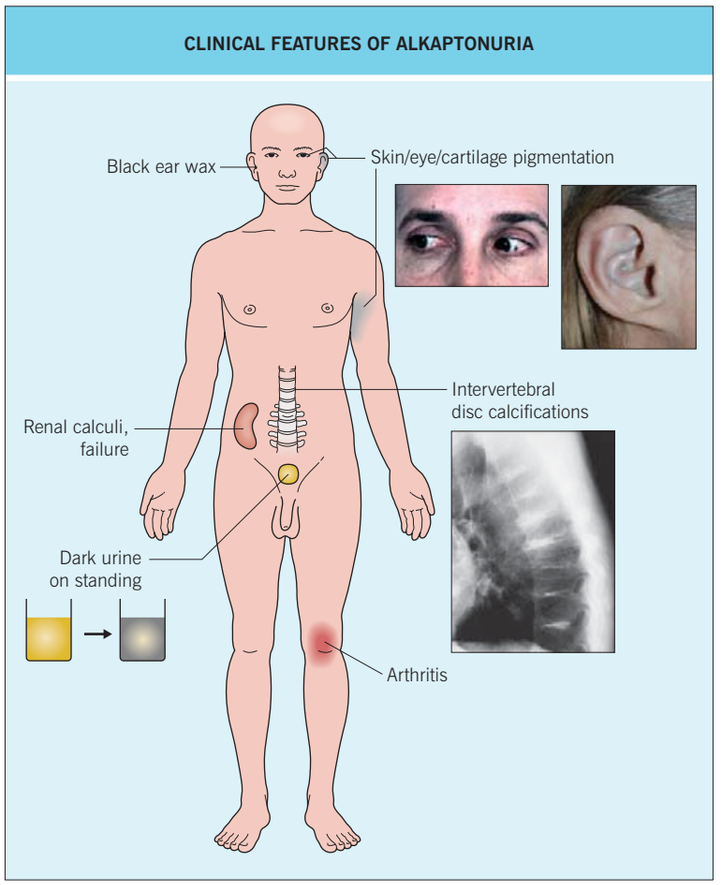


Fig. 63.7 Clinical features of alkaptonuria. *Eyes, courtesy, William Gahl, MD PhD; ear, courtesy, Julie V Schaffer, MD; radiograph, courtesy, Jean L Bolognia, MD.*

The dermatologic features of alkaptonuria are rarely noted prior to 10–15 years of age and typically become apparent during adulthood (often in the fourth decade of life). Axillary skin may be one of the initial sites to develop discoloration, which can range in color from blue to yellow to brown. The classic blue–grey pigmentation associated with this disorder is often first noted in the helices of the ear and sclerae (see Fig. 63.7). Later, it may affect the entire face as well as the palmar and plantar surfaces. Features that may present early in life include brownish discoloration of diapers (due to the dark urine) and cerumen that is more brown to black in color than normal. Diagnosis of alkaptonuria can be confirmed by urine organic acid analysis. There is no definitive treatment, although administration of nitisinone (an inhibitor of homogentisic acid production) or 1 g/day of ascorbic acid in divided doses may be beneficial[47].

BIOTINIDASE AND HOLOCARBOXYLASE SYNTHETASE DEFICIENCIES

Synonyms: ■ Late- and early-onset forms of multiple carboxylase deficiency

Key features

- As biotin is an essential cofactor for carboxylases, there is overlap in the two autosomal recessive disorders
- Cutaneous findings include alopecia and periorificial erythema and erosions (features of "nutritional dermatitis")
- Metabolic acidosis is seen in both disorders
- Biotinidase deficiency is associated with developmental delay, hearing loss and seizures (classically during childhood), while patients with holocarboxylase synthetase deficiency develop encephalopathy and hypotonia (classically during early infancy)

Biotinidase deficiency and holocarboxylase synthetase deficiency are genetically distinct disorders that result in late- and early-onset multiple carboxylase deficiency, respectively. Both disorders are inherited in an autosomal recessive fashion. Biotinidase deficiency, a pan-ethnic disorder with an incidence of approximately 1 in 60 000 births, represents a defect in biotin recycling. Patients with this disorder become functionally biotin-deficient under conditions of normal dietary biotin intake. Since biotin is an essential cofactor for the activity of carboxylases, multiple carboxylase deficiency ensues. The clinical manifestations of the disorder, although entirely preventable with the administration of 5–20 mg of biotin daily, are highly variable and may go unrecognized. This has led to the inclusion of biotinidase deficiency in the newborn screening panel of a number of countries, including the US. Common extracutaneous features of the disorder include developmental delay, hearing loss, seizures, conjunctivitis and metabolic acidosis. Abnormalities on urine organic acid analysis are commonly, but not invariably, noted. The definitive diagnosis is established by an assay of biotinidase activity in blood; prenatal diagnosis is possible via enzymatic and molecular analyses.

Holocarboxylase synthetase deficiency is significantly less common than biotinidase deficiency, although the precise incidence has not been determined. It represents a defect in biotinylation of the apocarboxylases, leading to a failure in synthesis of intact functional holocarboxylases. Patients typically present within the first 3 months of life with symptoms of a metabolic encephalopathy, including poor feeding, lethargy, respiratory distress and hypotonia. Metabolic acidosis, hyperammonemia and organic aciduria are often observed. Definitive diagnosis is established by assays of carboxylases in leukocytes or cultured skin fibroblasts. Most patients exhibit significant improvement when treated with 10 mg of biotin daily. Prenatal diagnosis via enzymatic assay is possible by chorionic villus sampling (CVS) or amniocentesis.

The dermatologic features of biotinidase deficiency and holocarboxylase synthetase deficiency are similar. They occur in over 50% of patients with the former and a smaller proportion of patients with the latter[48,49]. Characteristic findings include alopecia (sometimes evolving to alopecia totalis) and a scaly dermatitis which often begins in the perioral and perianal regions but can become generalized. This periorificial-predominant eruption is notable for its markedly erythematous and, at times, erosive quality. It is similar to the eruptions seen with other nutritional deficiencies, e.g. zinc (see Figs 51.11 & 51.12). Fissures may be prominent on the feet, face and in the perianal area, and cutaneous candidiasis may also be present.

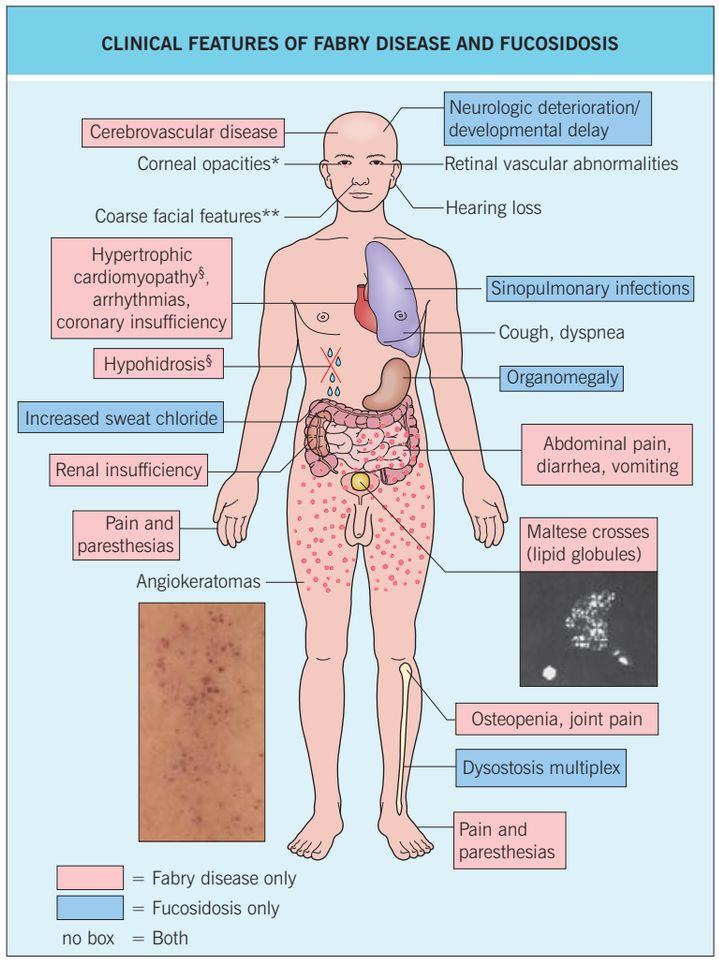


Fig. 63.8 Clinical features of Fabry disease and fucosidosis. *Also lenticular in Fabry disease. **Milder in Fabry disease. §Occasionally observed in fucosidosis. *Angiokeratomas of Fabry disease, courtesy, Anthony J Mancini, MD; photomicrograph of urinary sediment demonstrating Maltese crosses (via polarization), courtesy, Robert J Desnick, MD PhD.*

FABRY DISEASE

Synonym: ■ Anderson–Fabry disease

Key features

- X-linked disorder due to a deficiency of α-galactosidase A
- Characteristic mucocutaneous finding is multiple angiokeratomas
- Additional features include pain and paresthesias of the extremities, hypohidrosis, and renal and coronary insufficiency

Fabry disease is an X-linked lysosomal storage disorder resulting from a defect in glycosphingolipid metabolism[50]. It is a pan-ethnic disorder affecting an estimated 1 in 40 000 men. Female heterozygotes are also often affected, although their clinical manifestations are more variable than those in male hemizygotes and often have later onset. The defect in Fabry disease is deficiency of α-galactosidase A due to mutations in the *GLA* gene that encodes this enzyme. This leads to systemic deposition of glycosphingolipids, predominantly globotriaosylceramide, galabiosylceramide and blood group B substances. The clinical manifestations of the condition result primarily from the accumulation of glycosphingolipids in the vascular endothelium.

The cardinal clinical features of Fabry disease in the first two to three decades of life are pain and paresthesias of the extremities often with onset during childhood or adolescence), angiokeratomas of the skin and mucous membranes, and hypohidrosis (see below; Fig. 63.8). Characteristic corneal opacities (classically whorled "cornea verticillata") are evident in approximately 75% of male hemizygotes and female heterozygotes (including children and adolescents); posterior lenticular opacities and tortuous retinal or conjunctival vessels may also be observed. With increasing age, progressive renal insufficiency develops, leading to the need for dialysis or transplantation. Cardiac sequelae include hypertrophic cardiomyopathy, arrhythmias and coronary insufficiency. Patients may also have cerebrovascular (transient ischemic attacks, strokes), gastrointestinal (abdominal pain, diarrhea, vomiting), pulmonary (chronic cough, dyspnea, wheezing) and musculoskeletal (joint pain, osteopenia) manifestations[50,51]. Characteristic facial features such as periorbital fullness, bushy eyebrows, a broad forehead and nasal bridge, thick lips, prognathism and prominent ear lobes have been noted in men with Fabry disease.

Angiokeratomas are one of the earliest signs of Fabry disease, typically beginning to appear during childhood or adolescence, and may lead to diagnosis of the disorder[52]. In addition to appearing in most male patients, they are observed in approximately 30% of heterozygous girls and women. Angiokeratomas classically develop slowly as individual punctate, dark-red to blue–black macules or slightly elevated papules. The lesions do not blanch with pressure and may become slightly keratotic as they enlarge. The angiokeratomas of Fabry disease tend to be clustered between the umbilicus and the knees but can be present anywhere. Involvement of the oral mucosa and conjunctiva is common. Less frequent vascular findings include linear telangiectasias (favoring the face, lips and oral mucosa), episodic acral vasospasm resembling Raynaud's phenomenon (typically accompanied by pain and paresthesias), peripheral edema and lymphedema[53]. In addition to vascular lesions, hypohidrosis is an early and almost

constant feature of Fabry disease. Decreased body hair has also been described.

Histologically, angiokeratomas are composed of dilated capillaries in the uppermost dermis, partially enclosed by elongated rete ridges (see Ch. 114); hyperkeratosis is seen in older lesions. In the skin, there is evidence of lipid storage in the endothelium, pericytes and smooth muscle of capillaries, venules and arterioles, as well as in arrector pili muscles. This can be detected by a lipid stain such as Sudan black B, or highlighted by periodic acid-Schiff (PAS) staining. Lipid accumulation may also be observed in sweat gland epithelium (see Ch. 39) and perineural cells. Ultrastructural examination of eccrine sweat glands reveals characteristic cytoplasmic inclusions in the clear cells of the secretory coil, coiled duct and basal cells of the straight duct[54]. Inclusions are also seen in the unmyelinated axons innervating the sweat glands.

A definitive diagnosis of Fabry disease is established by demonstration of deficient α-galactosidase A activity in plasma or leukocytes (or, for prenatal testing, cultured amniocytes or chorionic villi), but enzyme activity is within the normal range in up to a third of female heterozygotes. Analysis of the *GLA* gene is clinically available and can be helpful in determining the disease status of girls and women as well as in prenatal/preimplantation diagnosis. Polarizing microscopy of urine reveals birefringent lipid globules ("Maltese crosses") (see Fig. 63.8). Although most commonly seen in association with Fabry disease, it is important to recognize that angiokeratomas are not unique to this condition. They are also observed in a number of other lysosomal storage disorders, as outlined in Table 63.6.

Until recently, treatment for Fabry disease was largely symptomatic. Oral administration of phenytoin, gabapentin or carbamazepine can alleviate the debilitating limb pain experienced by patients with this disorder. Angiotensin-converting enzyme inhibitors are helpful in reducing proteinuria, and end-stage renal disease has historically been treated with dialysis and renal transplantation. Enzyme replacement therapy is now available for Fabry disease and is administered biweekly by intravenous infusion. Accumulated data indicate that it is effective in arresting progression of the disorder[62,63].

FUCOSIDOSIS

Key features

- Autosomal recessive disorder due to deficiency of α-fucosidase
- Multiple angiokeratomas of the skin and oral mucosa
- Extracutaneous findings include coarse facial features, growth retardation, dysostosis multiplex and mental retardation

Fucosidosis is a rare autosomal recessive oligosaccharide storage disorder resulting from deficiency of the lysosomal enzyme α-fucosidase. The precise incidence of the disorder is unknown. The severity of clinical manifestations in affected patients varies across a wide spectrum. In the past, patients were classified into two groups: type I, the more severe form of the disorder with onset in the first year of life; and type II, the milder form with onset in the second year or later[58]. The characteristic extracutaneous manifestations of fucosidosis type I include coarse facial features, growth

INHERITED METABOLIC DISORDERS ASSOCIATED WITH ANGIOKERATOMA CORPORIS DIFFUSUM

Disorder	Enzyme deficiency	Other clinical features	Inheritance pattern	Diagnostic tests	Reference
Aspartylglycosaminuria	Aspartylglycosaminidase	MR, coarse facial features, frequent respiratory infections	AR	Urine oligosaccharides; enzyme assay in leukocytes or fibroblasts*	55
Galactosialidosis	β-Galactosidase and sialidase (neuraminidase) secondary to a defect in the protective protein/ cathepsin A (PPCA)	Coarse facial features, dysostosis multiplex, myoclonus, ataxia, neurologic deterioration, cherry red macular spots	AR	Urine oligosaccharides; enzyme assay in leukocytes or fibroblasts	56
GM1 gangliosidosis	β-Galactosidase	Coarse facial features, dysostosis multiplex, neurologic deterioration, organomegaly, dermal melanocytosis	AR	Urine oligosaccharides; enzyme assay in leukocytes or fibroblasts*	57
Fabry disease	α-Galactosidase A	Pain and paresthesias of extremities, hypohidrosis, corneal and lenticular opacities, renal insufficiency, cardiac and cerebrovascular disease	X-L	Enzyme assay in plasma or leukocytes*	52
Fucosidosis	α-Fucosidase	Coarse facial features, developmental regression, organomegaly, dysostosis multiplex	AR	Urine oligosaccharides; enzyme assay in leukocytes or fibroblasts*	58
Kanzaki disease	α-*N*-Acetylgalactosaminidase	Highly variable, ranging from no other findings to lymphedema, hearing loss and cardiomegaly; normal intelligence	AR	Urine oligosaccharides; enzyme assay in plasma or leukocytes	59
β-Mannosidosis	β-Mannosidase	MR, mild facial dysmorphism, hearing loss	AR	Urine oligosaccharides; enzyme assay in leukocytes or fibroblasts*	60
Sialidosis	Sialidase (neuraminidase)	Coarse facial features, dysostosis multiplex, MR, myoclonus, cherry red macular spots	AR	Urine oligosaccharides and sialic acid; enzyme assay in fibroblasts*	61

*Genetic testing is also available.

Table 63.6 Inherited metabolic disorders associated with angiokeratoma corporis diffusum. AR, autosomal recessive; MR, mental retardation; X-L, X-linked (variable manifestations in female heterozygotes).

retardation, organomegaly, dysostosis multiplex and neurologic deterioration (see Fig. 63.8). An elevated sweat chloride concentration is usually observed. In type II, developmental delay is typically the first finding noted, with the other features of type I often present but less prominent. Sweat chloride is normal in patients with type II. Patients with fucosidosis may also have corneal opacities, retinal vascular abnormalities and a propensity towards frequent sinopulmonary infections.

With increasing age, angiokeratomas virtually indistinguishable from those associated with Fabry disease are observed in patients with fucosidosis. Such lesions are found in about one-third of patients <10 years of age and 85% of those <20 years of age; they are distributed primarily on the trunk and lower extremities. Angiokeratomas can also develop within the oral mucosa. Other reported cutaneous findings include xerosis, thin skin, acrocyanosis and nevus anemicus. The light microscopy findings of the angiokeratomas are similar to those seen in Fabry disease. Electron microscopic examination of clinically normal skin may reveal empty-appearing storage vesicles in endothelial cells, melanocytes, eccrine glands and fibroblasts.

The diagnosis of fucosidosis is supported by demonstration of characteristic abnormalities on urine oligosaccharide analysis and established definitively by assay of α-fucosidase in leukocytes or cultured skin fibroblasts. Prenatal diagnosis is possible by CVS or amniocentesis via enzyme analysis and (when the underlying mutation has been identified in affected family members) genetic testing.

There is no definitive treatment for fucosidosis, and the mortality rate is high, especially after the second decade of life. Bone marrow transplantation has been attempted in the past, with some evidence of clinical improvement[64].

GAUCHER DISEASE

Key features

- Autosomal recessive disorder due to a deficiency of β-glucosidase (glucocerebrosidase)
- Hepatosplenomegaly and bone pain can be seen in all three types of the disease
- Cutaneous manifestations of type 1 disease include yellow–brown pigmentation, easy tanning and petechiae
- A subset of patients with type 2 (acute neuronopathic) Gaucher disease have severe congenital ichthyosis

Gaucher disease is a relatively common autosomal recessive lysosomal storage disorder in which the glycolipid glucocerebroside accumulates as a result of a deficiency of the enzyme β-glucosidase (glucocerebrosidase). There are three distinct clinical subtypes of the disorder, although phenotypic variability is observed in each form. Hepatosplenomegaly and lytic bone lesions occur in all of the subtypes. Type 1 Gaucher disease is most common in individuals of Ashkenazi Jewish descent. Indeed, it is the most common of the so-called "Jewish genetic disorders", occurring with an incidence of 1 in 850 births in this population. The incidence is much lower in other populations and has not been precisely defined. Gaucher disease types 2 and 3 are pan-ethnic disorders; there are no reliable incidence figures.

Type 1, by far the most common variant, is distinguished from types 2 and 3 by a lack of CNS involvement. Presenting findings in type 1 may include hepatosplenomegaly; bruising or bleeding secondary to thrombocytopenia; anemia; and bone pain, which can be very severe and reminiscent of the bone crises associated with sickle cell disease. The cutaneous manifestations of type 1 Gaucher disease are infrequent and relatively nonspecific[65]. They include diffuse brown or yellow–brown pigmentation of the skin and easy tanning. In addition, petechiae and ecchymoses may be observed as a result of the thrombocytopenia that results from infiltration of the bone marrow with glycolipid-filled macrophages (Gaucher cells) or from hypersplenism.

Type 2 Gaucher disease, also referred to as the acute neuronopathic form of the disorder, is a severe and rapidly progressive condition that usually results in death before 2 years of age. Clinical manifestations are present at the time of birth or develop within the first few months of life. They include hepatosplenomegaly, muscle tone abnormalities (e.g. severe spasticity, opisthotonus), oculomotor apraxia and progressive neurologic deterioration. A subgroup of patients with this disorder has severe congenital ichthyosis with a collodion baby phenotype[66,67]. Occasionally, these findings may precede the development of neurologic or visceral abnormalities, suggesting that Gaucher disease should be considered in the differential diagnosis of congenital ichthyosis.

Studies in a mouse model of type 2 Gaucher disease indicate that glucocerebrosidase is required to generate functionally competent membranes for normal epidermal barrier function. The low levels of residual enzymatic activity present in patients with types 1 and 3 Gaucher disease are apparently adequate to protect them, since similar epidermal abnormalities are not observed in patients with these forms. In fact, no specific cutaneous abnormalities have been described in patients with type 3 Gaucher disease, also referred to as the chronic neuronopathic form of the disorder.

The diagnosis of Gaucher disease is established by demonstration of a deficiency of β-glucosidase in leukocytes or cultured skin fibroblasts. Carrier detection is possible by DNA analysis, and prenatal diagnosis can be accomplished by CVS or amniocentesis.

The treatment of symptomatic patients with type 1 Gaucher disease involves intravenous enzyme replacement therapy using a recombinant product. Infusions are typically administered biweekly, and treatment results in an arrest of the progression of the disorder, gradual resolution of organomegaly and some improvement in the bone disease[68]. Experience with enzyme replacement therapy in the neuronopathic forms of Gaucher disease is limited, but it does not ameliorate the CNS manifestations of the disorder. Encouraging results have been reported from bone marrow or peripheral blood stem cell transplantation in patients with type 3 Gaucher disease, so this may be an option for some affected individuals.

HARTNUP DISEASE

Key features

- An autosomal recessive disorder associated with defective renal and intestinal neutral amino acid transport
- Marked aminoaciduria and tryptophan deficiency
- A pellagra-like dermatosis associated with photosensitivity
- Systemic manifestations include ataxia and tremors

Hartnup disease is an autosomal recessive disorder caused by mutations in the *SLC6A19* gene, which encodes a transporter that mediates epithelial uptake of neutral amino acids in the kidneys and intestines[69]. The hallmark of the disorder is a specific hyperaminoaciduria due to diminished renal reabsorption of neutral amino acids. In most affected individuals, there is also reduced intestinal absorption of at least some neutral amino acids, most notably tryptophan. Hartnup disease is one of the most common amino acid disorders, occurring in about 1 in 30 000 births. Most affected individuals, particularly those in high-income countries, remain asymptomatic throughout life, although symptoms can occur when certain exacerbating factors are present, e.g. poor nutrition or persistent diarrhea. Modifying genes may also play a role in producing clinical symptoms.

When clinical features develop, the most common finding is a "pellagra-like" dermatosis[70]. This photosensitive eruption may be related to a relative niacin deficiency, as tryptophan is a precursor in niacin synthesis. It typically appears in patients <13 years of age, resembles a severe sunburn, and is distributed primarily on exposed areas of the body. After the development of erythema following sun exposure, the affected skin becomes dry and scaly with well-defined margins, at times resembling chronic eczema; later findings include desquamation and hypopigmentation. The lesions on the face may resemble acute cutaneous lupus erythematosus. The dermatosis is occasionally pruritic, and blistering may occur, at times resulting in a hydroa vacciniforme-like presentation. The second major manifestation of symptomatic Hartnup disease is intermittent ataxia, which may be accompanied by nystagmus and tremors. Psychiatric disturbances

and other nonspecific neurologic abnormalities have been reported in some patients, but mental retardation is not a feature.

Despite the resemblance of the clinical features of Hartnup disease to pellagra, the disorder is not associated with a demonstrable niacin deficiency. Nonetheless, some patients have responded clinically to administration of oral nicotinamide in doses of 50–300 mg/day. Reversibility of both the dermatologic and neurologic findings has been reported, although there is no change in the aminoaciduria or intestinal transport defect. In addition to nicotinamide, a high protein diet or protein supplementation may be beneficial in some patients. The efficacy of various treatment modalities is difficult to assess in individual cases because of the intermittent nature of the clinical findings in untreated patients.

The definitive diagnosis of Hartnup disease is readily established by urine amino acid analysis, which reveals marked aminoaciduria.

MITOCHONDRIAL DISORDERS

Synonyms: ■ Respiratory chain defects ■ Oxidative phosphorylation defects

Key features

- Marked phenotypic heterogeneity
- 5–10% of patients have pigmentary changes, alopecia, hypertrichosis and hair shaft anomalies
- Neuromuscular dysfunction (e.g. seizures, hypotonia, mental retardation) is common
- Multisystem involvement (e.g. cardiac, renal, hepatic) is characteristic

Mitochondrial respiratory chain defects result in clinically and biochemically heterogeneous metabolic disorders affecting intracellular energy production[71]. The spectrum of clinical phenotypes associated with respiratory chain defects is rapidly expanding and the true incidence of these disorders is unclear. They can present at any age and may potentially affect any organ system. Indeed, one of the hallmarks of these disorders is multisystem involvement. Neuromuscular manifestations are common and can include mental retardation, seizures, stroke, weakness, hypotonia, and absent or excessive sweating. Cardiomyopathy, hearing loss, proximal renal tubular defects, hepatic dysfunction, poor growth, and fatigue are other frequent findings. The clinical course and progression are highly variable, even in patients with similar biochemical abnormalities[72].

The respiratory chain, which is responsible for producing much of the adenosine triphosphate (ATP) required for cellular functioning, is composed of over 100 individual subunits whose genes are located in either the nuclear DNA or the mitochondrial DNA. Mutations in a number of these genes have been identified in patients with various mitochondrial disorders. Depending on the subunit involved, inheritance of a respiratory chain defect can be either Mendelian (usually autosomal recessive) or mitochondrial (maternal). The subunits are organized into five respiratory chain enzyme complexes (complexes I–V), the activity of which can be measured in muscle or in other tissues to aid in the diagnosis of mitochondrial disorders. Although some mitochondrial syndromes are characterized by a particular constellation of clinical findings, there is often poor correlation between the enzyme complex involved and the clinical phenotype.

A wide range of hair and skin abnormalities has been described in association with mitochondrial disorders (Table 63.7)[73]. Such findings have been reported in about 5–10% of patients with documented mitochondrial disorders and can be present in the early stages of these diseases. When such findings are noted in conjunction with seemingly unrelated abnormalities in other organ systems, the possibility of a mitochondrial disorder should be considered.

Biochemical and/or molecular genetic confirmation of the diagnosis of a mitochondrial disorder is rarely straightforward. Measurement of plasma lactate, plasma amino acids and urine organic acids can be helpful in assessing mitochondrial function. Other components of the evaluation may include muscle biopsy for histologic and histochemical evaluation, assays of respiratory chain enzyme complexes in muscle tissue or cultured skin fibroblasts, and (as indicated by clinical and/or biochemical findings) genetic analysis.

Treatment of patients with mitochondrial disorders is problematic and largely symptomatic. A variety of dietary modifications have been tried and may be helpful for some patients. Coenzyme Q10, L-carnitine and riboflavin supplementation are commonly used and may be beneficial. A wide range of other vitamins and cofactors have also been administered, although the benefits are largely unproven.

CUTANEOUS MANIFESTATIONS OF MITOCHONDRIAL RESPIRATORY CHAIN DISORDERS

- Alopecia
- Hair shaft abnormalities – trichoschisis, pili torti, longitudinal grooving, trichorrhexis nodosa, trichothiodystrophy
- Hypertrichosis
- Pigmentary abnormalities – mottled or reticulated pigmentation
- Palmoplantar keratoderma (linked with deafness)
- Hypoplastic nails
- Lipomas
- Acrocyanosis

Table 63.7 Cutaneous manifestations of mitochondrial respiratory chain disorders.

NIEMANN–PICK DISEASE

Key features

- An autosomal recessive disorder due to deficiency of sphingomyelinase
- Rare skin involvement in type A consists of yellow–brown discoloration and facial papules
- Failure to thrive, hepatosplenomegaly and neurologic deterioration (type A)
- Minimal neurologic involvement and milder disease (type B)

Niemann–Pick disease is an autosomal recessive lysosomal storage disorder with several subtypes. Type A is most common in the Ashkenazi Jewish population, where it occurs with an incidence of 1 in 40 000 births. Type B is much less common in this ethnic group and is the predominant phenotype in non-Jewish patients, although precise estimates of its incidence are not available. Types A and B are allelic disorders, both associated with accumulation of sphingomyelin as a result of a deficiency of the enzyme sphingomyelinase. Type A is a severe disorder associated with failure to thrive, hepatosplenomegaly and rapid neurologic degeneration leading to death by 2 to 3 years of age. Type B is characterized by little or no neurologic involvement and survival into adult life. Progressive pulmonary infiltration may occur in either subtype and is associated with significant morbidity in type B. More recently, a third type (type C) has been described that is associated with an accumulation of unesterified cholesterol.

Cutaneous manifestations are typically observed only in patients with Niemann–Pick disease type A[74]. The skin may exhibit a generalized ochre or brownish-yellow discoloration. Papular lesions, most commonly located on the face and upper extremities, may also be present. Histologically, the papules of Niemann–Pick disease consist of foamy histiocytes, multinucleated cells and a variable infiltrate of lymphocytes.

Diagnosis of Niemann–Pick disease type A or B is established by demonstration of deficient sphingomyelinase activity in leukocytes or cultured skin fibroblasts. Prenatal diagnosis is available by CVS or amniocentesis. Carrier detection for type A is possible in the Ashkenazi Jewish population, using DNA analysis.

There is no effective therapy for Niemann–Pick disease type A. Bone marrow transplantation has reversed the clinical manifestations of type B disease.

PHENYLKETONURIA

Key features

- Autosomal recessive disorder due to a deficiency of phenylalanine hydroxylase
- Pigmentary dilution of the skin, eyes and hair
- Atopic-like dermatitis and sclerodermatous skin changes
- Progressive developmental delay/mental retardation if not treated

Phenylketonuria (PKU) is one of the most common inborn errors of metabolism, occurring worldwide with an incidence of approximately 1 in 10 000 births. It is an autosomal recessive disorder resulting from a deficiency of the enzyme phenylalanine hydroxylase that is responsible for conversion of phenylalanine to tyrosine. As a result of this enzyme deficiency, phenylalanine levels rise in blood and tissues of the untreated patient on a phenylalanine-containing diet, and high levels of this amino acid are extremely toxic to the CNS. Progressive developmental delay leading ultimately to moderate to profound mental retardation occurs and may be accompanied by seizures, behavioral problems and psychiatric symptoms.

A relative deficiency of tyrosine in patients with PKU (versus competitive inhibition of tyrosinase by excess L-phenylalanine) leads to diminished melanin production and resultant diffuse pigmentary dilution. The classic patient is described as blonde and blue-eyed, although pigmentation varies depending on the family and ethnic background. Sweat with a musty or "mousy" odor can represent a clue to the diagnosis. Nonspecific dermatitis occurs with increased frequency, and early-onset atopic dermatitis seems particularly common in patients with PKU. Scleroderma-like skin changes that favor the proximal extremities may also be observed[75] (Fig. 63.9) and often have their onset in the first year of life[76], in contrast to the acral predilection and older age of onset in systemic sclerosis.

The classic PKU phenotype is now primarily of historical interest in high-income countries where newborn screening is almost uniformly practiced. The diagnosis is established by plasma amino acid analysis. Identification of affected infants at birth with early institution of a phenylalanine-restricted diet and careful control of blood phenylalanine levels prevents the development of mental retardation and skin changes, although subtle neurocognitive consequences may be observed. Unfortunately, untreated patients are still encountered among children from low-income countries, and despite recommendations that dietary therapy be continued for life, some adolescents and adults in developed countries are not compliant with the dietary restrictions. In such cases, dermatologic manifestations may develop. In patients who resume treatment in later childhood or adult life, the hair color often darkens and sclerodermatous changes may regress. Dietary therapy involves not only restriction of phenylalanine, but also supplementation of tyrosine and other amino acids in the form of special medical foods. Close monitoring by an experienced nutritionist is vital.

Fig. 63.9 Phenylketonuria (PKU). Infant with PKU and sclerodermoid skin changes. *Courtesy, New York Medical College.*

PREMATURE AGING SYNDROMES AND POIKILODERMAS

Bernard A Cohen

The study of rare progeroid syndromes has led to better understanding of the normal aging process. These disorders can be distinguished by their time courses, associated clinical findings, and biochemical and genetic markers (Table 63.8). The inherited congenital and childhood poikilodermas (Fig. 63.10) can also demonstrate some of the features associated with premature aging and may be confused with progeria.

HUTCHINSON–GILFORD PROGERIA SYNDROME

Synonyms: ■ Progeria ■ Hutchinson–Gilford syndrome

Key features

- Rare, occurring in 1 in 8 million to 1 in 4 million births
- Due to mutations in the *LMNA* gene, which encodes nuclear lamins A and C
- Normal motor and mental development
- Characteristic facies with prominent scalp veins and beaked nose
- Wrinkled as well as scleroderma-like skin, alopecia and poor growth
- Generalized atherosclerosis with premature death from cardiovascular and cerebrovascular disease at a median age of 12 years
- Clinical trials using farnesyltransferase inhibitors to prevent accumulation of farnesylated mutant prelamin A ("progerin") are ongoing

Introduction

Hutchinson–Gilford progeria syndrome (HGPS) is a genetic disease characterized by accelerated aging that begins during infancy[77,78]. The term "progeria" originates from the Greek word for old age, "*geras*",

Fig. 63.10 Facial poikiloderma in a 3-year-old boy with Rothmund–Thomson syndrome. This child also had short stature and photosensitivity. *Courtesy, Sarah Chamlin, MD.*

PROGEROID SYNDROMES AND INHERITED POIKILODERMAS										
	Hutchinson–Gilford progeria syndrome	**Werner syndrome**	**Néstor-Guillermo progeria syndrome**	**Acrogeria (Gottron syndrome)***	**Metageria**	**Kindler syndrome**	**Cockayne syndrome**	**Rothmund–Thomson syndrome**	**Poikiloderma with neutropenia, Clericuzi type ("Navajo poikiloderma")**	**Ataxia–telangiectasia**
Inheritance/ gene (if known)	Sporadic AD/*LMNA*	AR/*RECQL2* (*WRN*) Atypical variant – AD/*LMNA*	AR/*BANF1*	AD, AR	AR	AR/*FERMT1 (KIND1)*	AR/*ERCC8 (CSA), ERCC6 (CSB)*	AR/*RECQL4*	AR/*C16orf57*	AR/*ATM*
Gender ratio	M:F = 1.2:1	M = F	M = F	Mostly female	M = F	M = F	M = F	M = F	M = F	M = F
Onset	First year	Second decade	Third year	Birth	Birth	Birth	After first year	First year	First year	Childhood
Stature	Short stature, low weight for height	Short stature, central obesity	Short stature, generalized lipoatrophy	Normal	Tall, thin	Normal	Dwarfism, low weight for height	Short stature	Short stature	Short stature
Facial features	Prominent scalp veins and eyes, perioral cyanosis, frontal bossing, micrognathia, thin beaked nose, small mouth, thin lips	Thin beaked nose, prominent eyes, circumoral furrows, protuberant teeth, micrognathia	Prominent scalp veins and eyes, micrognathia, thin nose, mid facial hypoplasia, thin lips	Micrognathia, thin nose with atrophic tip, proptosis	Beaked nose, prominent eyes	Normal	Sunken eyes due to periorbital fat atrophy; senile 'bird-like' facies, beak-like nose, prognathism	Frontal bossing, saddle nose, prognathism	Midfacial hypoplasia	Normal
Cutaneous features	Dryness, wrinkling, scleroderma-like tautness, mottled hyperpigmentation, loss of subcutaneous fat	Atrophy (epidermal, dermal, subcutaneous), mottled hyperpigmentation, scleroderma-like tautness, keratoses and ulcers over pressure points, subcutaneous calcifications	Atrophy, mottled hyperpigmentation, red swollen skin on phalanges	Poikiloderma, marked skin atrophy on hands and feet, easy bruising, prominent veins on trunk	Poikiloderma with mottled hyperpigmentation, atrophy on extremities, rarely leg ulcers	Congenital acral blistering and photosensitivity; later poikiloderma, atrophy, acral hyperkeratosis; occasional eczematous dermatitis	At presentation: acute photosensitivity, healing with hyperpigmentation; later: wrinkling, loss of subcutaneous fat, poikiloderma	At presentation: acute eruption with erythema and edema, especially on face, ± photosensitivity; later: poikiloderma (Fig. 63.10), acral keratoses	At presentation: erythematous papular or ichthyosiform dermatitis on the extremities and face, ± photosensitivity; later: evolution to poikiloderma, PPK, keratotic papules on face and forearms, recurrent skin infections	Skin and subcutaneous fat atrophy; telangiectasias on bulbar conjunctiva, cheeks, nose and ears; café-au-lait macules, granulomatous plaques
Nails	±Dystrophy, hypoplasia	±Dystrophy	Dystrophy	Dystrophy, thickening	Normal	±Dystrophy	±Dystrophy	±Dystrophy	Dystrophy (especially first toenails) with subungual hyperkeratosis (pachyonychia-like)	Normal

*An acrogeric phenotype also characterizes vascular Ehlers–Danlos syndrome, which is caused by mutations in the gene encoding type III collagen.

Table 63.8 Progeroid syndromes and inherited poikilodermas. Autosomal recessive forms of cutis laxa (due to mutations in the *PYCR1* gene encoding pyrroline-5-carboxylate reductase 1) and Ehlers–Danlos syndrome (due to mutations in the *B4GALT7* gene encoding galactosyltransferase 1) with progeroid features are discussed in Chapter 97. AD, autosomal dominant; AR, autosomal recessive; *BANF1*, barrier-to-autointegration factor 1; *C16orf57*, chromosome 16 open reading frame 57; *FERMT1*, fermitin family homolog 1; PPK, palmoplantar keratoderma.

PROGEROID SYNDROMES AND INHERITED POIKILODERMAS										
	Hutchinson–Gilford progeria syndrome	**Werner syndrome**	**Néstor-Guillermo progeria syndrome**	**Acrogeria (Gottron syndrome)***	**Metageria**	**Kindler syndrome**	**Cockayne syndrome**	**Rothmund–Thomson syndrome**	**Poikiloderma with neutropenia, Clericuzi type ("Navajo poikiloderma")**	**Ataxia–telangiectasia**
Scalp hair	Thin and lightly pigmented, progressing to diffuse alopecia	Premature canities, thinning over time	Progressive alopecia during late childhood	Normal	Fine and thin	Normal	Dry, thin; premature canities	Fine and thin, alopecia	Normal	Premature canities
Musculoskeletal	Thin with narrow thorax, prominent joints, thoracic kyphosis, coxa valga, short clavicles	Spindly extremities, osteoporosis, osteosclerosis of phalanges	Marked acro-osteolysis, resorption of mandible and clavicles, severe osteoporosis, scoliosis	Short phalanges, acro-osteolysis	Generalized loss of subcutaneous fat	Webbing of the fingers, toes	Long limbs, disproportionately large hands and feet, joint contractures, microcephaly	Radial ray defects, metaphyseal chondrodysplasia, delayed bone formation	Normal	Generalized muscle weakness (secondary to neurologic abnormalities)
Metabolic/ malignancy	Growth failure, insulin resistance	Lack of growth spurt at puberty; diabetes mellitus; increased risk of malignancies – soft tissue sarcomas, osteosarcoma	None	None	Early-onset diabetes mellitus	Possible increased malignancy risk	Cellular sensitivity to sunlight and defective DNA repair, but no increase in neoplasia	Increased risk of malignancy, especially osteosarcoma and squamous cell carcinoma	None	Elevated α-fetoprotein, insulin resistance; increased incidence of lymphoma, leukemia and other malignancies
Cardiovascular	Premature atherosclerosis, myocardial fibrosis	Premature atherosclerosis, calcified aortic valve	Normal	Normal	Premature atherosclerosis	Normal	Normal	Normal	Normal	Normal
Prognosis	Average survival 12 years	Average survival ~50 years	Survival into early adulthood	Normal lifespan	Depends on severity of diabetes and atherosclerosis	Normal lifespan	Death by age of 30 years from neurologic degeneration	Normal to shortened life expectancy (if malignancy)	Normal lifespan	Early death from malignancy, infection
Other	High-pitched voice, delayed and abnormal dentition, large open anterior fontanelle, sparse or absent eyebrows and eyelashes	Cataracts, glaucoma, thymic atrophy, high-pitched voice, hypogonadism	Delayed closure of anterior fontanel			Mucous membrane involvement with stenoses (e.g. urethral), ectropion and erosive gingivitis resulting in poor dentition	Optic atrophy, deafness, unsteady gait, demyelination	Cataracts, hypogonadism, hypodontia	Neutropenia (sometimes cyclical), recurrent sinopulmonary infections, lacrimal duct obstruction, carious teeth, ± developmental delay	Cerebellar ataxia, nystagmus, recurrent sinopulmonary infections

*An acrogeric phenotype also characterizes vascular Ehlers–Danlos syndrome, which is caused by mutations in the gene encoding type III collagen.

Table 63.8 Progeroid syndromes and inherited poikilodermas (cont'd).

and was proposed by Gilford when he described several patients with the disorder in 1904.

History

The syndrome was first reported in 1886 by Hutchinson, who described a young boy with an absence of hair and an aged appearance. Nine years later, Gilford reported a second patient and documented the postmortem features. In 1972, DeBusk[77] summarized 60 cases from the world literature plus four new cases.

Epidemiology

DeBusk[77] estimated that HGPS occurred in 1 in 8 million births, and an incidence of 1 in 4 million was observed in the Netherlands from 1900 to 2005[79]. The male:female ratio is 1.2:1[79], and approximately 90% of the patients reported to date have been Caucasian.

In the cases reviewed by DeBusk[77], median and mean paternal ages were advanced, consanguinity was uncommon, and the abortion rate in affected families was normal. These observations favored a sporadic dominant mutation, which was later confirmed by genetic studies (see below). Since HGPS patients usually do not become sexually mature and typically succumb to the disease early in the second decade of life, familial occurrence is rare; however, it can occur in the setting of gonadal mosaicism[77,78]. Consanguineous families with an autosomal recessive variant of HGPS have been described, but additional clinical features such as clavicular aplasia/hypoplasia in affected individuals suggest an overlap with mandibuloacral dysplasia (which is caused by biallelic mutations in *LMNA*; Table 63.9)[80].

Pathogenesis

The vast majority of patients with HGPS have *de novo* point mutations in the lamin A gene (*LMNA*)[81,82]. This gene encodes two protein products (lamin A and lamin C) that represent major components of the nuclear membrane lamina and contribute to the structural scaffolding of the nucleus. In patients with classic HGPS, there is a common mutation within exon 11 that activates a cryptic splice site and leads to an internal deletion of 50 amino acids; this deletion includes a cleavage site that is necessary for the conversion of prelamin A to mature lamin A[83] (Fig. 63.11). As a result, the cells contain a dominant mutant prelamin A ("progerin") that disrupts the nuclear scaffolding. In the patients' cells, including lymphocytes and fibroblasts, there is evidence of altered nuclear sizes and shapes, as well as lobulation of the nuclei, extrusion of chromatin, and nucleolar alterations. Such structural changes presumably lead to functional defects[84] and the premature aging phenotype.

In families with the autosomal recessive progeria–mandibuloacral dysplasia overlap syndrome described above, homozygous missense mutations have been found in the *LMNA* gene[80]. Interestingly, mice with a homozygous mutation in *Lmna* display a progeroid phenotype with many similarities to HGPS, including abnormalities of bone, muscle and skin, as well as early death[85].

Several cellular and biochemical abnormalities have also been described[77,78,86], including short telomeres in progeria cells; of note, progressively decreasing telomere length is seen with normal aging and is associated with low levels of telomerase activity. In a telomerase knockout mouse model (see Ch. 4), some of the clinical features of accelerated aging have been observed.

End-organ growth hormone resistance and/or structurally defective growth hormone have also been observed in some patients with HGPS. A dramatic increase in linear growth may occur in some of these patients after exogenous growth hormone replacement. Additional abnormalities associated with the normal aging process, such as insulin resistance and decreased survival of fibroblast cultures, are also seen in patients with HGPS.

Clinical Features

Although affected children usually appear normal at birth, growth failure and other clinical features appear rather abruptly some time during the first year of life[77,78,87]. Weight gain is very slow, with marked loss during episodes of illness. Linear growth proceeds at half the normal pace and does not undergo the normal acceleration around puberty. Sexual maturation is absent in most patients. Consequently, affected individuals remain sexually immature with short stature and a low weight for height.

Following the development of growth failure, the skin becomes thin and dry, with fewer hairs than normal. Some areas may appear taut and shiny, whereas others (especially the fingers and toes) appear lax and wrinkled. At birth or during early infancy, some patients have thick, inelastic, scleroderma-like skin, usually on the lower abdomen, flanks, thighs and buttocks. Infantile fat is rapidly lost with the onset of growth failure, resulting in prominent superficial veins and the appearance of perioral cyanosis. As the aged appearance progresses, irregular brown pigmentation becomes evident in sun-exposed areas.

At the onset of growth failure, patients begin to develop characteristic facial features, including a disproportionately large cranium, frontal

NUCLEAR ENVELOPATHIES	
Primary feature and associated diseases	**Inheritance**
LAMINOPATHIES – due to mutations in the *LMNA* gene which encodes the lamin A and C proteins of the nuclear membrane lamina*	
Premature aging and/or cutaneous sclerosis	
Hutchinson–Gilford progeria syndrome	AD
Restrictive dermopathy†	AD
"Atypical Werner syndrome"	AD
Other progeroid laminopathies	AD > AR
Skeletal dysplasia and/or arthropathy	
Mandibuloacral dysplasia†	AR
Arthropathy, tendinous calcinosis and progeroid features	AR
Lipodystrophy	
Dunnigan familial partial lipodystrophy	AD
Generalized lipodystrophy with pubertal onset‡	AD
Muscular dystrophy	
Emery–Dreifuss muscular dystrophy	AD > AR
Limb-girdle muscular dystrophy type 1B	AD
Early-onset myopathy with progeroid features	AD
Cardiomyopathy	
Dilated cardiomyopathy type 1A	AD
"Heart–hand syndrome"	AD
Neuropathy	
Charcot–Marie–Tooth type 2B1	AR
CUTANEOUS DISORDERS WITH INNER NUCLEAR MEMBRANE DYSFUNCTION – due to mutations in the *LEMD3* gene, whose protein product associates with lamin A	
Cutaneous sclerosis and/or skeletal dysplasia	
Buschke–Ollendorff syndrome	AD
Osteopoikilosis	AD
Melorheostosis	Type 2 segmental§

*Heterozygous mutations in the *LMNB2* gene, which encodes the lamin B2 protein of the nuclear membrane lamina, can cause "acquired" partial lipodystrophy (Barraquer–Simons syndrome).

†Can also result from recessive mutations in the *ZMPSTE24* gene, which encodes a zinc metalloproteinase involved in the processing of prelamin A into mature lamin A; mandibuloacral dysplasia often presents with progeroid features and lipodystrophy.

‡Overlaps with atypical Werner syndrome; numerous whitish, fibrotic papules on a background of diffuse hyperpigmentation have been described in some patients.

§Germline heterozygous mutation (resulting in Buschke–Ollendorff syndrome or osteopoikilosis) with a presumed second hit in area of melorheostosis.

Table 63.9 Nuclear envelopathies. A heterogeneous group of genetic disorders that share the common findings of cutaneous fibrosis and bone dysplasia. Néstor-Guillermo progeria syndrome (see Table 63.8) is also characterized by abnormalities in the nuclear membrane lamina; this autosomal recessive disorder results from mutations in the barrier-to-autointegration factor 1 gene (*BANF1*), which encodes a protein that interacts with prelamin A (and progerin). AD, autosomal dominant; AR, autosomal recessive.

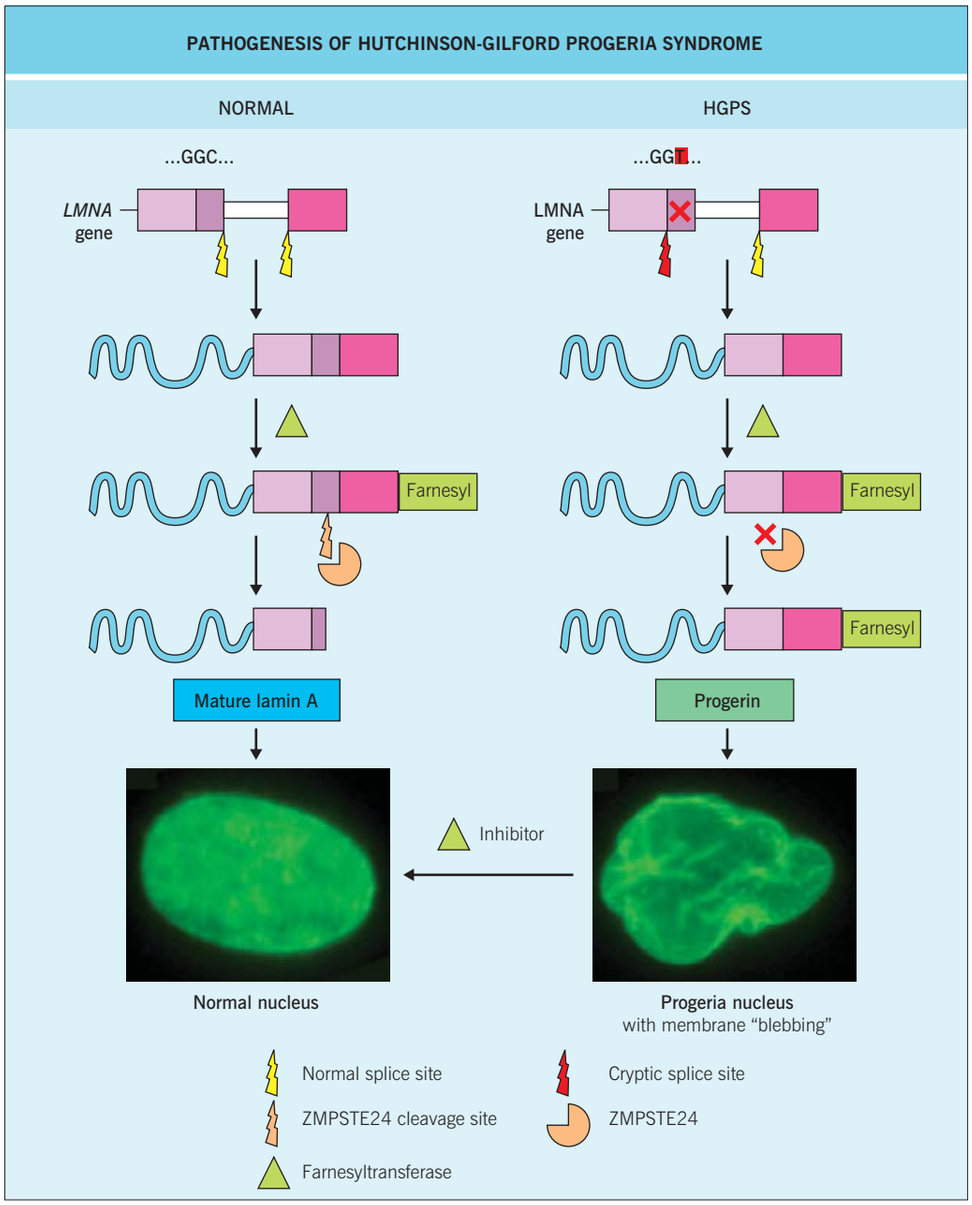


Fig. 63.11 Pathogenesis of Hutchinson-Gilford progeria syndrome (HGPS). Most patients with classic HGPS have a C-to-T point mutation that activates a cryptic splice site and leads to an internal in-frame deletion of 50 amino acids. The deleted region includes a cleavage site for the ZMPSTE24 zinc metalloproteinase, so removal of a farnesylated portion of prelamin A by this enzyme to produce mature lamin A does not occur in HGPS patients. Mutant "progerin" therefore remains farnesylated and, as a result, anchored to the nuclear membrane, where it disrupts nuclear scaffolding and causes blebbing. Administration of farnesyltransferase inhibitors can prevent this disruption of nuclear structure and function by progerin.

bossing, a large open anterior fontanelle, pronounced scalp veins, prominent eyes (due to relatively slow growth of the facial bones), a thin beaked nose with a sculpted appearance, and micrognathia. The facial stigmata tend to become marked by age 2 to 3 years, giving a "plucked-bird" appearance.

Alopecia develops during the first year of life and becomes diffuse and generalized, with later hair growth tending to be fine and lightly pigmented. Eyebrows and eyelashes are often sparse or absent. Although the nails may be normal, dystrophy in the form of small, short and thin nails is common. Marked delay in the eruption of primary and secondary dentition has also been noted in most patients. Teeth may be crowded, rotated, overlapped and maloccluded, and the voice tends to be high-pitched and piping.

Truncal features include a narrow pyriform thorax, shoulders with thin and short clavicles, and prominent thoracic kyphosis giving a stooped appearance. Prominence of the abdomen (relative to the chest) and hypoplastic nipples also contribute to the peculiar habitus. The limbs are usually proportionate and become progressively thinner with increasing prominence of the joints, especially the knees, elbows and small joints of the hand. Coxa valga is usually present by age 2 to 3 years and, in combination with increasing joint stiffness, contributes to a wide-based gait.

Patients are of normal intelligence, and many appear shy and aware of their unusual appearance. Early onset of progressive coronary and cerebral atherosclerosis results in a median lifespan of 12 years.

Pathology and Laboratory Findings

Cutaneous histopathology varies with the site and the age of the patient, and it is usually not helpful in diagnosing the condition[88,89]. The epidermis is fairly normal with minimal hyperkeratosis and a slight increase in melanin in the basal cell layer. Although dermal elastic tissue is normal, dermal collagen tends to be thickened and hyalinized. Adnexal structures are normal or decreased in density and arrector pili muscles are usually prominent.

Radiographic findings include hypoplasia of the facial bones, thinned cranial bones, open fontanelles, and hypoplasia of the mandible with crowding of the teeth. Progressive resorption of bone from the distal phalanges of the fingers and toes is also characteristic, but not diagnostic, of HGPS.

Differential Diagnosis

The differential diagnosis is outlined in Table 63.8 and includes Werner syndrome, "atypical Werner syndrome", Néstor-Guillermo progeria

syndrome, metageria and acrogeria[90]. In distinction to HGPS, patients with Werner syndrome have premature canities, cataracts and an increased incidence of malignancy.

HGPS should also be distinguished from the following disorders: Cockayne syndrome (Ch. 87), Rothmund–Thomson syndrome (Ch. 87), ataxia–telangiectasia (Ch. 60), Kindler syndrome (see below), and Wiedemann–Rautenstrauch syndrome (neonatal progeroid syndrome with premature aging already noted at birth). Lastly, clinical overlap may be seen with other disorders that are due to mutations in the *LMNA* gene (see Table 63.9), such as early-onset myopathy with progeroid features, restrictive dermopathy (see Ch. 34) and mandibuloacral dysplasia.

Treatment

Treatment is directed toward known complications, particularly cardiovascular and cerebrovascular. Although recommended by some investigators, to date, no dietary regimen has been shown to decrease the risk of these complications. Some patients may benefit from administration of exogenous growth hormone. Patients distressed by their unusual physical appearance may benefit from psychiatric counseling. Genetic counseling is also indicated for affected families.

Based upon the finding that the dominant mutant form of prelamin A ("progerin"; see above) contains a persistent abnormal C-terminus that has undergone farnesylation (leading it to be permanently anchored to the nuclear membrane), human HGPS fibroblasts were treated with inhibitors of farnesylation. The result was reversal of the abnormal nuclear morphology[83], and in a mouse model of progeria, treatment with a protein farnesyltransferase inhibitor led to improved body weight, strength and survival, as well as a decrease in osteoporosis[91]. As a result, clinical trials are underway to evaluate a farnesyltransferase inhibitor (lonafarnib) in HGPS patients[92].

Treatment with a combination of a bisphosphonate and statin (which inhibit farnesylation and a related modification, geranylgeranylation) increased survival and prevented premature aging in mice deficient in the Zmpste24 metalloproteinase that processes prelamin A, and these agents are being administered together with lonafarnib (a farnesyltransferase inhibitor; see Fig. 63.11) in some human HGPS studies. Of note, *ZMPSTE24* mutations underlie some human cases of restrictive dermopathy and mandibuloacral dysplasia (see Table 63.9). Lastly, the possibility of targeting mutant mRNAs via RNA interference or the activated cryptic splice site (see above) via modified oligonucleotides is also being explored.

WERNER SYNDROME

Synonym: ■ Progeria of the adult

Key features

- Occurs in 1 in 1 million births, with a higher incidence in Japan
- Autosomal recessive disorder due to mutations in the gene *RECQL2 (WRN)* that encodes a DNA helicase
- Premature aging with the appearance of canities, cataracts, osteoporosis, diabetes mellitus and atherosclerosis during the second decade
- Additional features include sclerodermoid changes, keratoses and ulcerations over bony prominences, short stature, and vascular and soft tissue calcification
- Similar facies to progeria patients, with a pinched appearance and micrognathia
- Increased risk of malignancy

Introduction

Werner syndrome is a genetic disorder of accelerated aging with an onset in the second decade of life. This rare progeroid syndrome has a higher incidence in select populations in Japan[93–97]. Although it is often referred to as progeria of the adult, Werner syndrome has some distinctive clinical findings not typically associated with the normal maturational process (e.g. hypogonadism, laryngeal atrophy, osteosclerosis of the distal extremities)[93–96]. The discovery of underlying mutations in the *RECQL2 (WRN)* gene has allowed investigation into the molecular aspects of Werner syndrome[94,96].

History

In 1904, Werner described a family with two brothers and two sisters between the ages 36 and 40 years who displayed clinical features of premature aging. In 1934, Oppenheimer and Kugel reported two similar cases and established the eponym Werner syndrome.

Epidemiology

Werner syndrome is a rare autosomal recessive disorder with an overall incidence of 1 in 1 million births. However, its incidence in Japan is higher and may approach 1 in 3500 in some communities owing to high rates of consanguinity. It was the study of several large Japanese families that led to identification of the gene responsible for this disorder.

Werner syndrome has been reported in all races and affects both sexes equally. Mild clinical findings have been noted in heterozygote relatives of affected patients.

Pathogenesis

Werner syndrome is caused by mutations in the *RECQL2 (WRN)* gene, which encodes a homolog of the *Escherichia coli* RecQ DNA helicase. Almost all of the mutations identified to date predict a truncated protein, and over half of Japanese patients are homozygous for a specific splice-site mutation[94,96].

The Werner protein (WRN) has both exonuclease and helicase activities, and it plays a role in optimizing DNA repair (particularly base excision repair) and in suppressing illegitimate recombination. Therefore, loss of RecQ helicase results in genomic instability. The accumulation of senescent cells with decreasing replicative capacity and an increasing number of mutations is thought to lead to the clinical findings of premature aging and an increased risk of malignancy. Loss of function of the *RECQL2* gene may occur in the normal population as a function of age[94].

A subset of patients have "atypical Werner syndrome" and lack pathogenic changes in the *RECQL2* gene. Rather, they have heterozygous missense mutations in the *LMNA* gene (see HGPS section) that affect the heptad repeat region and are predicted to interfere with protein–protein interactions[98]. Compared to patients with *RECQL2* mutations, those with atypical Werner syndrome tend to have an earlier onset of disease and more severe age-related manifestations. The latter patients may be better classified as having late-onset HGPS.

Clinical Features

In most affected individuals, growth progresses normally until the beginning of the second decade, when short stature and thin limbs become noticeable. Graying of the hair may begin during childhood but characteristically appears in late adolescence or the early twenties. Other findings of Werner syndrome become evident during the second and third decades of life[93–96].

The typical patient is short, with an average height of 5 ft (1.5 m), and has spindly limbs but central obesity. The hands and feet are small, and the face is thin with a pinched appearance, prominent eyes, beaked nose, circumoral radial furrows, taut lips, protuberant teeth and micrognathia (Fig. 63.12). The voice is high-pitched and raspy.

Cutaneous changes, including atrophy (epidermal, dermal and subcutaneous), scale, mottled hyperpigmentation and tightness reminiscent of scleroderma, are most prominent on the face, forearms, hands, legs and feet. Nails may be dystrophic, hypoplastic or absent, and plantar hyperkeratosis is common. Thick keratoses develop over pressure points such as the fingers, toes, ankles, elbows and, occasionally, the ears. Removal of these keratoses by accidental or deliberate trauma leaves painful progressive ulcers. Ulcers may be resistant to therapy and prone to infection because of ischemia related to peripheral vascular disease. Dystrophic soft tissue calcification and osteomyelitis can also complicate chronic ulcers.

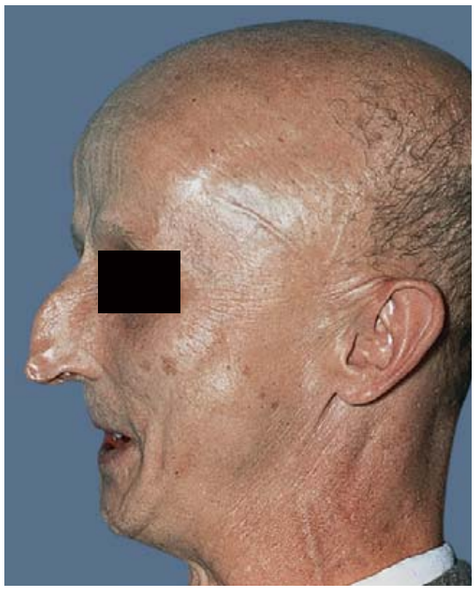


Fig. 63.12 Werner syndrome. Characteristic features include a beaked nose, tautness of the skin, prominent veins, and micrognathia. *Courtesy, Ronald P Rapini, MD.*

Other characteristic findings in Werner syndrome that reflect accelerated aging include cataracts, diabetes mellitus, hyperlipidemia, generalized atherosclerosis, osteoporosis, cerebral cortical atrophy, thymic atrophy and lymphoid depletion. Additional features not usually associated with normal aging include hypogonadism, laryngeal atrophy, osteosclerosis of the extremities, an increased risk of certain malignancies (e.g. soft tissue sarcomas, osteosarcoma), and meningiomas. In the Japanese population, there may be an increased risk of thyroid carcinoma and melanoma.

The average lifespan is approximately 50 years, and death is usually related to cardiovascular and cerebrovascular disease. Of interest, otherwise healthy heterozygotes in families of affected individuals tend to have higher rates of malignancy and myocardial infarction than the general population[94–97].

Pathology and Laboratory Findings

The epidermis is hyperkeratotic and atrophic, with focal hypermelanosis of the basal layer. Appendages are decreased in number and atrophic, and there is fibrosis and variable hyalinization of the dermis. The fat is also atrophic and often replaced by hyalinized connective tissue. Vessels may show changes typical of diabetic angiopathy.

Differential Diagnosis

As with HGPS, the clinical diagnosis is easily made when the characteristic premature canities, dysmorphic facies, and body habitus are recognized. In addition to the other premature aging syndromes outlined in Table 63.8, Werner syndrome must be distinguished from ataxia–telangiectasia as well as disorders associated with plantar keratoderma and scleroderma-like skin changes (e.g. Huriez syndrome).

Treatment

Genetic counseling should be provided, and prenatal diagnosis can be offered to affected families. Identification of heterozygotes in affected families may allow preventive measures and screening protocols to be implemented.

Skin ulcers may prove resistant to therapy and should be treated aggressively and early, with skin grafting occasionally necessary. Case reports have suggested that etidronate may ameliorate painful soft tissue calcifications. Management of diabetes mellitus and hyperlipidemia with proper diet and appropriate medications (e.g. pioglitazone and lipid-lowering agents) can help to reduce complications, including atherosclerosis. Of note, a recent study found that vitamin C supplementation increased the lifespan and reversed age-related metabolic abnormalities in a mouse model of Werner syndrome, suggesting that vitamin C might be beneficial for Werner syndrome patients[99].

KINDLER SYNDROME

Synonyms: ■ Kindler–Weary syndrome ■ Bullous acrokeratotic poikiloderma of Kindler and Weary ■ Congenital poikiloderma with bullae and progressive cutaneous atrophy ■ Hereditary acrokeratotic poikiloderma ■ Congenital poikiloderma with blisters and keratoses

Key features

- Due to loss-of-function mutations in *FERMT1 (KIND1)*, which encodes a protein that mediates anchorage between the actin cytoskeleton and the extracellular matrix via focal adhesions
- Congenital/infantile onset of trauma-induced acral bullae and skin fragility that improves during childhood
- Progressive poikiloderma and diffuse cutaneous atrophy
- Photosensitivity that decreases with age
- Variable features include palmoplantar hyperkeratosis, webbing of the fingers and toes, and mucosal involvement leading to gingivitis, colitis, stenoses and ectropion

Introduction

Now classified as a subtype of epidermolysis bullosa (see Ch. 32), Kindler syndrome is a rare genodermatosis that features progressive poikiloderma, cutaneous atrophy and mucosal inflammation in addition to trauma-induced blistering[100–103].

History

In 1954, Theresa Kindler described a patient with acral blistering and photosensitivity during infancy, followed later in life by progressive poikiloderma and atrophy. Twenty years later, Weary reported 10 members of a single family with similar findings in addition to widespread atopic dermatitis during early childhood and keratotic papules over the joints of the arms and legs that appeared in childhood and persisted indefinitely. Oral involvement was emphasized in subsequent cases[100–102,104,105].

Epidemiology

Cases of Kindler syndrome have been described worldwide, and it has an autosomal recessive inheritance pattern.

Pathogenesis

Kindler syndrome is caused by loss-of-function mutations in the *FERMT1* (*KIND1*) gene, which encodes the fermitin family homolog 1 (kindlin-1) protein that plays a role in linking the actin cytoskeleton to the extracellular matrix[106]. This protein represents the human homolog of the *Caenorhabditis elegans* unc-112 protein. FERMT1 is found throughout the epidermis, especially in basal keratinocytes, and it co-localizes with actin and vinculin in focal adhesions[107–109]. Through integrin-mediated signaling, FERMT1 affects the shape, polarity, adhesion, proliferation, and motility of keratinocytes.

Clinical Features

Characteristic features include congenital or neonatal blistering and photosensitivity, both of which improve during early childhood, and progressive poikiloderma with marked cutaneous atrophy[100–103]. Blistering and skin fragility are most prominent in trauma-prone areas of the arms and legs, particularly the hands and feet (Fig. 63.13A). Bullae usually heal without scarring, but milia and scarring sometimes develop. Occasionally, multiple erosions are present on the extremities (especially the shins and forearms) at birth, producing a clinical picture of aplasia cutis congenita similar to that observed in other forms of epidermolysis bullosa ("Bart syndrome"; see Ch. 64). Photosensitivity, manifested as an increased susceptibility to sunburn, tends to be a problem primarily during early childhood.

In prepubertal children, progressive reticulated hyperpigmentation and telangiectasias develop in sun-exposed areas, and after puberty

Fig. 63.13 Kindler syndrome. A Atrophy, erosions and fusion of the toes in an infant. **B** Poikiloderma of the face and neck with "skip" areas. **C** Wrinkling due to atrophy and fusion between the fourth and fifth toes. *C, Courtesy, Jean L Bolognia, MD.*

these findings spread to sun-protected sites as well. The predominant feature in adult patients with Kindler syndrome is poikiloderma (Fig. 63.13B), which persists throughout life. Diffuse cigarette paper-like atrophy is often present (Fig. 63.13C), particularly on the dorsal surfaces of the hands and feet. Webbing of the fingers and toes (see Fig. 63.13C) and palmoplantar hyperkeratosis may also be evident. Eczematous dermatitis, typically beginning during infancy and resolving by 5 years of age, is occasionally observed.

Patients with Kindler syndrome frequently have erosive gingivitis and poor dentition[104,105]. Mucosal involvement can also lead to ectropion, colitis, and stenoses of the urethral meatus, anus, vagina and esophagus. Malignancies have occasionally been reported, including squamous cell carcinoma of the lip, hard palate and acral skin, as well as transitional cell carcinoma of the bladder[110].

Pathology

In older patients, skin biopsy specimens show the typical changes of poikiloderma, including epidermal atrophy, vacuolization of the basal cell layer, variable epidermal melanin content, dermal melanophages and capillary dilation. Ultrastructural features of blistered skin vary and can include cleavage within basal keratinocytes, through the lamina lucida, and/or below the lamina densa. Clumping of tonofilaments may be observed in keratinocytes adjacent to blistered areas[102], but hemidesmosomes and anchoring fibrils are usually intact[111]. Ultrastructural analysis of non-blistered skin typically demonstrates duplication of the lamina densa and clefting at sites of focal interruption of the lamina densa; these basement membrane changes may also be evident via light microscopy with immunohistochemical staining for type IV or type VII collagen (e.g. broad, patchy staining at the dermal–epidermal junction). Immunostaining of skin biopsy specimens with anti-kindlin-1 antibodies often shows a marked reduction or absence of this protein.

Differential Diagnosis

In infants, the differential diagnosis of Kindler syndrome consists primarily of other forms of epidermolysis bullosa. The predominantly acral distribution of the blisters and associated atrophy are findings that point to Kindler syndrome. Additional causes of blisters in newborns and infants are reviewed in Chapter 34. As poikiloderma becomes a prominent feature (usually by the age of 5 years), the differential diagnosis may include Rothmund–Thomson syndrome, Cockayne syndrome, and other entities outlined in Table 63.8.

Treatment

Treatment is supportive. In infants with bullae and erosions, meticulous wound care is indicated in an effort to prevent infection and minimize scarring. Emollients are useful for dry pruritic skin, and diligent sun avoidance and protection may impede the progression of the cutaneous poikiloderma, particularly the atrophic component. Periodic examination of the skin and oral mucosa can aid in early detection of squamous cell carcinomas. Stenoses occasionally require procedures such as esophageal dilation or surgical intervention, and elective cesarean section should be considered for pregnant women with vaginal stenoses. Regular dental care is important to manage erosive gingivitis and periodontitis. Hemorrhagic colitis can lead to iron deficiency anemia, and bowel resection may be necessary in severe cases[108].

ECTODERMAL DYSPLASIAS

Alanna F Bree and Virginia P Sybert

Key features

- Genetic disorders resulting in structural or functional abnormalities in two or more of the major structures derived from the ectoderm
- Ectodermal structures affected include hair, teeth, nails, sweat glands, mucous glands and sebaceous glands
- Ectodermal dysplasia syndromes are often associated with abnormalities in non-ectodermally derived structures
- Differentiation among the different disorders is based on the types of ectodermal defects, associated non-ectodermal anomalies and mode of inheritance, as well as the underlying genetic defect
- Inherited abnormalities limited to one ectodermal structure (e.g. hair, nails) are not categorized as ectodermal dysplasias

CLASSIC ECTODERMAL DYSPLASIAS				
	Hypohidrotic ED	**Hypohidrotic ED–immune deficiency**	**Hidrotic ED**	**Witkop tooth and nail syndrome**
Inheritance (associated gene)	XLR (*EDA*); AD, AR (*EDAR*); AD, AR (*EDARADD*)	XLR (*NEMO*); AD (*NFKBIA*)	AD (*GJB6*)	AD (*MSX1*)
Protein product	Ectodysplasin A; EDAR; EDARADD	NF-κB essential modulator; NF-κB inhibitor-α	Connexin 30	Muscle segment homeobox 1
Scalp hair	Sparse to absent; often lightly pigmented in children	Sparse	Wiry, brittle; patchy alopecia; often lightly pigmented	Normal to thin
Teeth	Hypodontia, conical	Hypodontia, conical	Normal	Hypo- or anodontia of secondary teeth; primary teeth normal or small
Sweating	Markedly decreased	Mildly decreased	Normal	Normal
Nails	Normal	Normal	White during infancy; thickened, distal separation	Koilonychia improves with age; toenails worse than fingernails
Other	Characteristic facies; neonates may have collodion-like membrane; eczema common; frequent respiratory tract infections; variable phenotype, including mosaic pattern, in female patients with XLR form	Intertrigo, seborrheic-like dermatitis, erythroderma; colitis; recurrent infections (pyogenic or opportunistic); ↑ IgM and IgA, ↓ IgG; rare osteopetrosis, lymphedema	Palmoplantar keratoderma; blepharitis, conjunctivitis	Prolonged retention of primary teeth

Table 63.10 Classic ectodermal dysplasias. AD, autosomal dominant; AR, autosomal recessive; ED, ectodermal dysplasia; EDAR, EDA receptor; EDARADD, EDAR-associated death domain; *GJB6*, gap junction β6; XLR, X-linked recessive.

p63-RELATED ECTODERMAL DYSPLASIA SYNDROMES				
	AEC*	**EEC**	**Limb–mammary**	**ADULT**
Inheritance	AD	AD	AD	AD
Typical *p63* mutations	Missense in SAM domain	Missense in DNA-binding domain	Truncating in C-terminal region†	Missense in hotspot at end of DNA-binding domain†,‡
Scalp hair	Lightly pigmented, wiry, coarse; patchy alopecia	Lightly pigmented, coarse; may be sparse	Normal	Lightly pigmented, sparse; frontal alopecia
Teeth	Hypodontia, misshapen (e.g. conical) teeth	Hypodontia, premature loss of teeth	Hypodontia	Hypodontia, small teeth, premature loss of teeth
Sweating	Hypohidrosis in some patients	Usually normal	Hypohidrosis in some patients	Usually normal
Nails	Hyperconvex, thickened or absent	Transverse ridges, pitting	Variable dystrophy	Ridges, pitting
Cleft lip/palate	~80%; palate ± lip	~50%; usually lip + palate	~30%; palate only	None
Digital anomalies	Syndactyly in some patients; rarely ectrodactyly	Ectrodactyly > syndactyly	Ectrodactyly > syndactyly	Ectrodactyly, syndactyly
Skin findings	Neonatal erythroderma; erosive dermatitis (esp. of scalp)	Xerosis, palmoplantar keratoderma	None	Xerosis, photosensitivity, freckling
Other	Ankyloblepharon; lacrimal duct defects; ectopic breast tissue; hypospadias; GER	Lacrimal duct defects; GU anomalies	Lacrimal duct defects, hypoplastic nipples/breasts; GU anomalies	Lacrimal duct defects; hypoplastic nipples/breasts

*Rapp-Hodgkin syndrome is now included within the AEC spectrum.
†May also be caused by missense mutations in the proline-rich domain.
‡This mutation is thought to constitutively activate a transactivation domain.

Table 63.11 p63-related ectodermal dysplasia syndromes. *p63* mutations also occur in a subset of patients with autosomal dominant non-syndromic split-hand/foot malformation (SHFM). AD, autosomal dominant; ADULT, *a*cro-*d*ermato-*u*ngual-*l*acrimal-*t*ooth; AEC, ankyloblepharon–ectodermal dysplasia–clefting; EEC, ectrodactyly–ectodermal dysplasia–clefting; GER, gastroesophageal reflux; GU, genitourinary; SAM, sterile alpha motif.

Ectodermal dysplasias have long been recognized as distinct inherited entities. For example, affected individuals were described by Wedderburn in 1838 and Darwin in 1875. While these disorders are uncommon, their features are so distinctive that they have received a great deal of medical attention. For over 200 years, they have been defined by their clinical characteristics and mode of inheritance. More than one hundred single-gene disorders qualify as ectodermal dysplasias by having abnormalities in two or more major ectodermal structures (hair, teeth, nails, and sweat glands); other ectodermal structures (e.g. sebaceous glands, mucous glands) can also be affected[112]. Some of these conditions have not been traditionally thought of as ectodermal dysplasias, such as Ellis–van Creveld syndrome, because they are recognized and diagnosed by their prominent involvement of non-ectodermal structures.

There have been many classification schemes proposed over the years, including a descriptive categorization by Pinheiro and Freire-Maia[113], a clinical–genetic model by Priolo and Lagana[114], and a functional classification by Lamartine[115]. In the past decade, the molecular basis of many ectodermal dysplasias has been elucidated, and we are beginning to understand the processes of cell signaling involved in the induction and development of ectodermal structures as well as their interactions with mesodermal structures[116,117]. An international

LESS COMMON ECTODERMAL DYSPLASIAS WITH CUTANEOUS MANIFESTATIONS AND A KNOWN MOLECULAR BASIS								
	Tricho-dento-osseous syndrome	**Ellis–van Creveld syndrome**	**Nectinopathies: cleft lip/palate ED, (CLPED[§]), ED-syndactyly (EDS)**	**ED, ectrodactyly and macular dystrophy (EEM)**	**Odonto-onycho-dermal dysplasia***	**ED/skin fragility syndrome[†] (EDSF) & acantholytic ED (AED)**	**"Pure" hair–nail type ED**	**Immunodeficiency, myopathy and ED**
Inheritance (associated gene)	AD (*DLX3*)	AR (*EVC* or *EVC2*)	AR (*PVRL1* [CLPED], *PVRL4* [EDS])	AR (*CDH3*)	AR, AD* (*WNT10A*)	AR (*PKP1* [EDSF]; *JUP* [AED])	AR (*KRT85*)	AR (*ORAI1*)
Protein product	Distal-related homeobox 3	EVC and EVC2 (limbin)	Nectin 1 (CLPED), nectin 4 (EDS)	Cadherin 3 (P-cadherin)	Wnt10A	Plakophilin 1 (EDSF), plakoglobin (AED)	Keratin 85	ORAI calcium release-activated calcium modulator 1
Scalp hair	Kinky (may straighten with age)	Normal	Brittle, sparse; involves eyebrows and eyelashes; pili torti; progressive alopecia	Sparse; involves eyebrows and eyelashes	Thin, sparse; involves eyebrows and eyelashes	Sparse or woolly	Sparse to absent; fragile; involves eyebrows and eyelashes	Normal
Teeth	Small, widely spaced; thin enamel with pits; taurodontism (elongated pulp chamber)	Neonatal teeth; hypodontia; delayed eruption	Hypodontia; peg-shaped teeth	Small, widely spaced	Hypodontia	Usually normal	Normal	Defective enamel
Sweating	Normal	Normal	Normal	Normal	Hyperhidrosis of palms and soles; occasionally hypohidrosis	Occasionally decreased	Normal	Hypohidrosis
Nails	Brittle	Dystrophic	Dystrophic (variable)	Normal	Dystrophic or absent	Dystrophic	Dystrophic; fragile, irregular distal ends	Normal
Other	Dolicho-cephaly, frontal bossing, increased bone density	Short-limbed dwarfism, skeletal dysplasia	Cleft lip/palate (CLPED); PPK (esp. CLPED); syndactyly; (partial cutaneous of 2–3 & 4–5; EDS > CLPED)	Macular dystrophy; syndactyly, ectrodactyly	Facial telangiectasias, reticulated erythema, "atrophy"; xerosis, follicular keratoses; PPK; smooth tongue	Trauma-induced blisters and erosions (esp. perioral and acral) with acantholysis histologically; PPK	Follicular papules on scalp	Recurrent severe infections, myopathy

*Allelic with Schöpf–Schulz–Passarge syndrome, which has an overlapping phenotype but also features eyelid hidrocystomas and PPK with histologic evidence of eccrine syringofibroadenomas. In a recent study, 10% of previously unclassified ED patients had *WNT10A* mutations, with milder manifestations in heterozygotes. Multiple milia, adnexal neoplasms (e.g. poromas, tumors of the follicular infundibulum), basal cell carcinomas and pili annulati have also been described in patients with *WNT10A* mutations.

Table 63.12 Less common ectodermal dysplasias with cutaneous manifestations and a known molecular basis. Naegeli–Franceschetti–Jadassohn syndrome and dermatopathia pigmentosa reticularis are discussed in Ch. 67. AD, autosomal dominant; AR, autosomal recessive; ED, ectodermal dysplasia; *PVRL1*, poliovirus receptor-related 1; PPK, palmoplantar keratoderma.

conference was held in 2008 with the aim of developing a classification system for ectodermal dysplasias that integrates clinical and molecular data[118].

Tables 63.10, 63.11 and 63.12 summarize the key clinical and genetic features of ectodermal dysplasias with a known molecular basis and/or prominent cutaneous manifestations. Several classic ectodermal dysplasias are discussed in detail in this chapter.

HYPOHIDROTIC ECTODERMAL DYSPLASIA

Synonyms: ■ Anhidrotic ectodermal dysplasia ■ Christ–Siemens–Touraine syndrome

Hypohidrotic ectodermal dysplasia (HED) refers to a group of disorders that share the following features: sparse or absent hair; missing or peg-shaped teeth; and decreased ability to sweat. The most common form is X-linked, and traditionally the term HED has referred to this condition. However, both autosomal dominant and autosomal recessive inheritance of clinically similar conditions have been documented and the underlying molecular defects defined.

Epidemiology

The X-linked form of HED occurs in approximately 1 in 10 000 live-born boys and can affect all racial and ethnic groups. The autosomal dominant and recessive forms are much less common.

Pathogenesis

HED is caused by genetic defects that affect the ectodysplasin signal transduction pathway (Fig. 63.14)[119]. Epithelial cells in the developing tooth, hair follicle and eccrine gland utilize this pathway during morphogenesis, and errors in signaling result in aplasia, hypoplasia or dysplasia of these structures. The pathway is activated at a critical time during development. With activation, a transcription factor, NF-κB, is translocated into the nucleus of these cells and alters the expression of a variety of target genes. The change in gene expression likely has an effect on both cellular proliferation and survival[120].

The gene that is defective in the X-linked form of HED (*EDA*) codes for a soluble ligand, ectodysplasin A. It is secreted by a subset of epithelial cells and binds to its receptor (*ecto*dysplasin-*A* receptor; EDAR) on another group of epithelial cells. Mutations in *EDAR* cause either autosomal recessive or autosomal dominant HED[121]. Autosomal recessive and autosomal dominant HED can also be caused by mutations

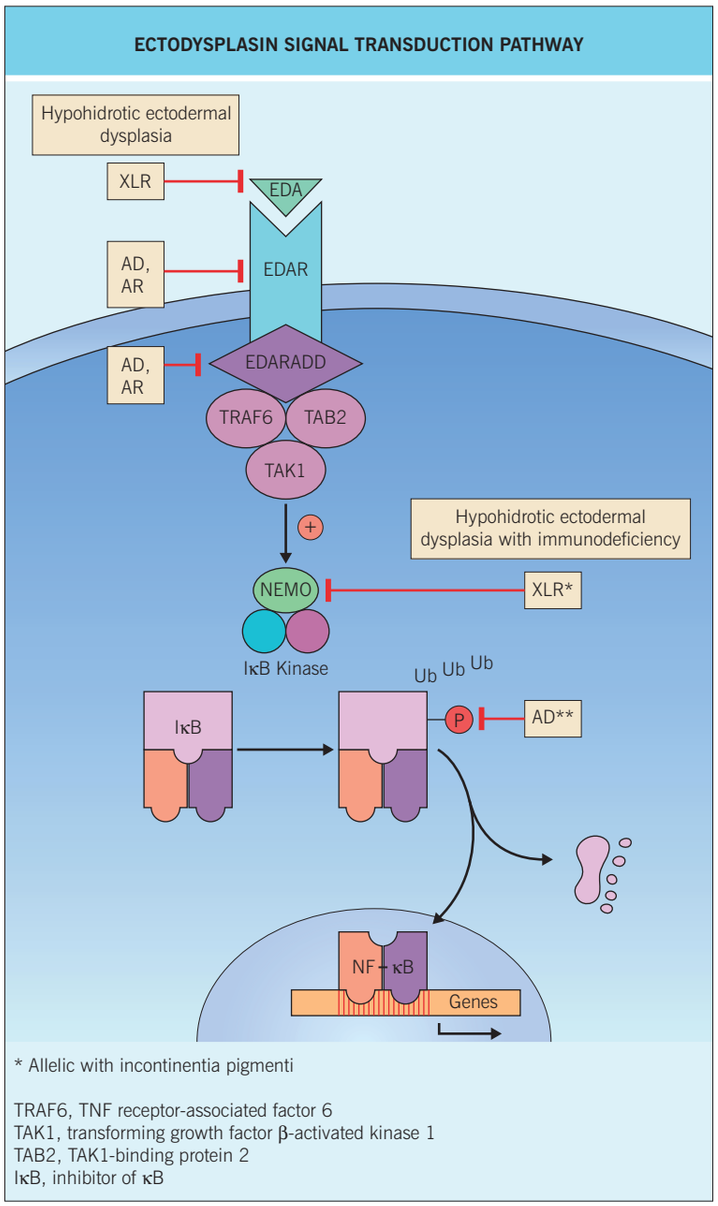


Fig. 63.14 The ectodysplasin signal transduction pathway. **A hypermorphic mutation in the gene encoding IκBα that prevents this protein's phosphorylation (and subsequent ubiquitination/degradation) can result in continued inhibition of NF-κB and a phenotype of hypohidrotic ectodermal dysplasia with immunodeficiency. AD, autosomal dominant; AR, autosomal recessive; EDA, ectodysplasin A; EDAR, EDA receptor; EDARADD, EDAR-associated death domain adapter protein; NEMO, NF-κB essential modulator; XLR, X-linked recessive. Additional details of NEMO function are in Figure 62.4.

in the *EDARADD* (EDAR-associated death domain) gene, which encodes an intracellular adapter protein that assists in transducing the signal from the activated receptor to the nucleus[122]. Molecular analysis of the *EDA* and *EDAR* genes is available in commercial laboratories, but *EDARADD* gene testing is currently available on a research basis only[123].

Clinical Features

Affected newborns may present with a collodion-like membrane or with marked skin scaling. Scalp hair is sparse to absent (Fig. 63.15), and, when present, is usually blonde. Hair may darken at puberty and secondary sexual hairs are typically normal, although body hair is usually sparse or absent. Affected male patients are unable to sweat to a detectable degree[124]. This leads to an inability to maintain core temperature in warm environments, and hyperpyrexia is a major problem. Affected infants often present with fever of unknown origin. The skin is smooth and dermatoglyphics may be effaced because of absent eccrine pores. Atopy is a major problem in these individuals, with eczema affecting nearly two-thirds of patients. Periorbital wrinkling and hyperpigmentation are common. Sebaceous hyperplasia of the face, clinically resembling milia, can develop over time (see Fig. 63.15D). The nails are usually normal.

Both the primary and secondary dentition are affected. Teeth may be absent or reduced in number and abnormally shaped (e.g. peg-shaped). Affected individuals typically have an alteration in their facial appearance characterized by a saddle nose, full everted lips and frontal bossing (see Fig. 63.15). Nasal secretions and cerumen are thick and viscous, and recurrent respiratory tract infections are common. The voice is frequently hoarse or raspy. Affected infants often develop gastroesophageal reflux and feeding problems.

Female patients (Fig. 63.16) with the X-linked form of HED fall into one of three categories: (1) carriers with no detectable clinical features; (2) limited involvement with findings such as decreased hair density, one or more peg-shaped or missing teeth, and patchy distribution of sweat glands along Blaschko's lines (sometimes with relative hyperpigmentation of the skin that lacks adnexa); or (3) full-blown features of the disorder. This variability results from the random nature of X-inactivation (see Ch. 62).

Pathology

A skin biopsy is usually not necessary, but a scalp or palmar biopsy specimen lacking eccrine structures is considered diagnostic of HED[125].

Differential Diagnosis

The majority of affected individuals, either male or female, have the X-linked form. In sporadic cases, molecular diagnosis may be helpful. At birth, HED can be confused with an ichthyosis if a collodion-like membrane is present (see Ch. 57; Table 57.5). Recurrent fevers in an infant may lead to consideration of infectious diseases before the features of HED are recognized. HED with immune deficiency (HED-ID) due to mutations in the *NEMO* gene can be differentiated by the clinical and laboratory features of the associated immune system abnormalities (see below).

Treatment

Controlling ambient temperatures to prevent high fever and external methods of cooling, e.g. wet T-shirts, wet headbands and cooling vests, are important in the care of children with HED. Dentures can be fitted in children as young as 3 years of age, and dental restoration through implants should be employed for older patients. Multidisciplinary care is often required for treatment of other manifestations, which range from nasal concretions, asthma and recurrent respiratory infections to weight deficits and reduced salivary secretion. Referral to the National Foundation for Ectodermal Dysplasias is also an important aspect of care. This organization publishes booklets for patients and physicians and provides yearly conferences and a bimonthly newsletter for member education (http://www.nfed.org/).

The potential for gene or protein therapy for HED is on the horizon[126]. In Tabby mice (the murine form of X-linked recessive HED), the administration of recombinant EDA protein *in utero* or in the immediate postnatal period can completely or partially correct the phenotype[127]. Neonatal administration of recombinant EDA in a canine model of X-linked HED has also led to significant correction of ectodermal defects[128,129].

HYPOHIDROTIC ECTODERMAL DYSPLASIA WITH IMMUNE DEFICIENCY

HED-ID is a rare condition that shares many features with classic HED but is differentiated by the associated immune abnormalities (see Ch. 60).

Pathogenesis

HED-ID is most commonly inherited in an X-linked recessive pattern due to mutations in the *NEMO* (*n*uclear factor-κB *e*ssential *mo*dulator)

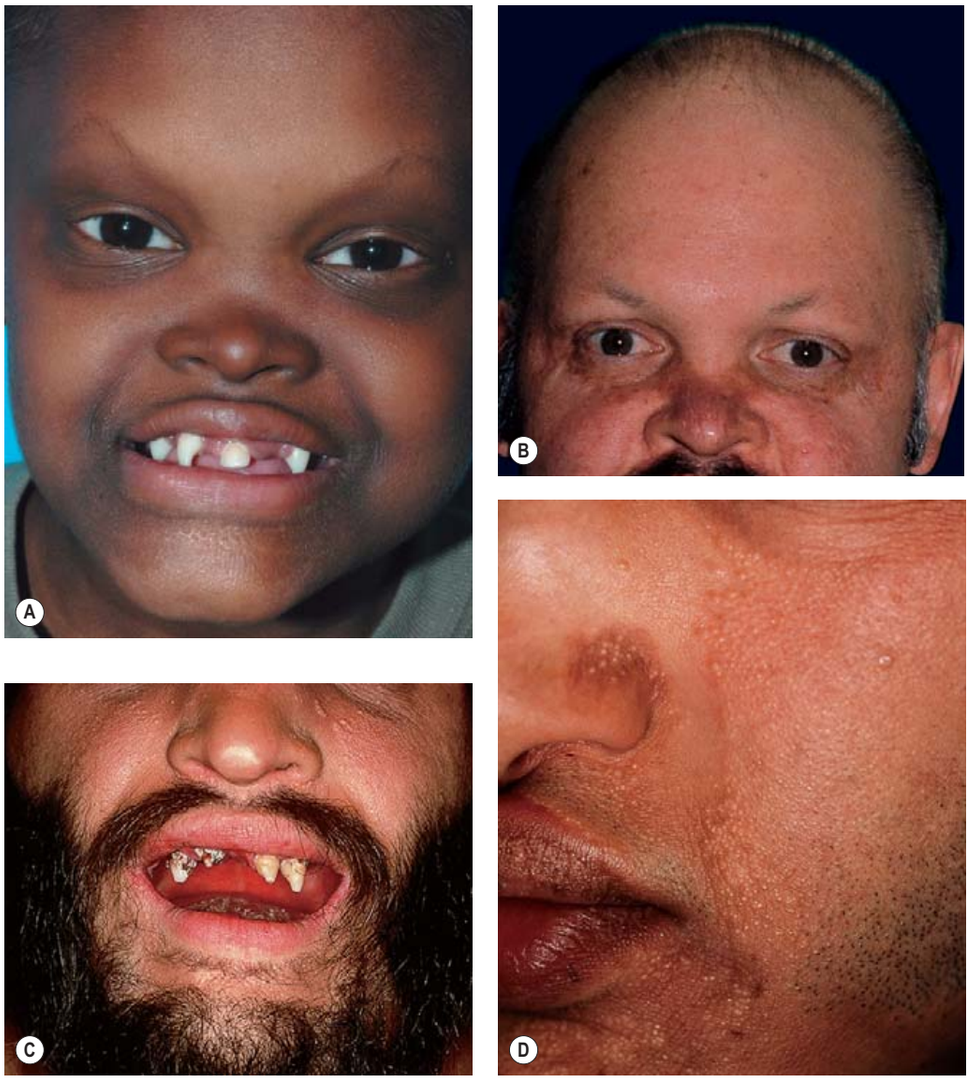


Fig. 63.15 Male patients with hypohidrotic ectodermal dysplasia. Note the flat nasal bridge, depressed nasal tip, sparse hair (scalp, eyebrows, eyelashes), peg-shaped teeth, full lips and sebaceous hyperplasia. Also note the normal secondary hair in adults. *A, Courtesy, Julie V Schaffer, MD; B & D, Courtesy, Mary Williams, MD.*

gene; the latter encodes a subunit of a regulatory kinase that activates NF-κB downstream in the ectodysplasin (see Fig. 63.14) and tumor necrosis factor-α (TNF-α) pathways[130]. The condition is allelic to incontinentia pigmenti, which is caused by more severe *NEMO* mutations that are lethal in male embryos unless rescued by mosaicism (see Ch. 62). An autosomal dominant form of HED-ID due to mutations in the *NFKBIA* gene has also been described. These patients have decreased NF-κB signaling because the mutated α-component of the NF-κB inhibitor is resistant to degradation (see Fig. 63.14).

Clinical Features

Individuals with HED-ID often have milder abnormalities of ectodermal structures than do patients with classic HED. The findings can include hypodontia, conical teeth, hypotrichosis and a reduced ability to sweat; frontal bossing, periorbital wrinkling and everted lips may also be seen. Extensive intertrigo, seborrheic or atopic-like dermatitis that develops into erythroderma, and inflammatory colitis may represent clues to the diagnosis[131], and reticulated hyperpigmentation is occasionally observed. The immunodeficiency results in recurrent pyogenic bacterial (especially of the skin and respiratory tract) and opportunistic infections, and it is characterized by a poor antibody response to polysaccharide antigens, dysgammaglobulinemia (typically with elevated IgM and IgA but decreased IgG levels), and defective natural killer cell activity. Patients with the autosomal dominant form of HED-ID also have a severe T-cell deficiency. Occasionally, infants with X-linked HED-ID present with osteopetrosis (abnormally dense bones) and lymphedema[130,132]. Female carriers may have mild features of incontinentia pigmenti (see Ch. 62).

Treatment

Intravenous immunoglobulin (IVIg) administration does not typically decrease affected individuals' propensity to develop infections. Allogeneic hematopoietic stem cell transplantation has resulted in correction of the immune abnormalities and (in one patient to date) resolution of erythroderma, but reported recipients have had difficulty achieving engraftment and experienced post-transplant complications such as worsening colitis[131,133].

HIDROTIC ECTODERMAL DYSPLASIA

Synonym: ▪ Clouston syndrome

Hidrotic ectodermal dysplasia was first described in a French-Canadian kindred[134] and the ancestry of many affected individuals was traced to a single founder. Subsequently, the disorder has been reported in individuals of varying racial and ethnic backgrounds[135].

Pathogenesis

Hidrotic ectodermal dysplasia is an autosomal dominant condition that is caused by missense mutations in the *GJB6* gene, which encodes the connexin 30 protein[136]. Connexins oligomerize to form gap junctions that are important for communication between cells (see Ch. 58), and *GJB6* is expressed in keratinocytes. Mutations in genes that encode other connexins cause skin disorders ranging from Vohwinkel

Fig. 63.16 Female patients with X-linked hypohidrotic ectodermal dysplasia. Note the peg-shaped teeth, hypodontia, full lips, and sparse eyelashes (**A**) as well as periorbital hyperpigmentation (**B**) and sebaceous hyperplasia (**C**). *A, Courtesy, Julie V Schaffer, MD.*

and keratitis–ichthyosis–deafness (KID) syndromes (*GJB2*) to erythrokeratodermia variabilis (*GJB3* and *GJB4*) (see Table 58.3). Mutations in *GJB6* can also cause non-syndromic autosomal dominant, digenic (together with a *GJB2* mutation) and (less often) recessive deafness, with normal teeth and hair in affected individuals. To date, a *GJB6* mutation has been described in a single patient with KID syndrome (associated with congenital atrichia). Molecular testing of the *GJB6* gene is available in clinical laboratories.

Clinical Features

This condition primarily affects the hair and nails. The teeth and sweating are normal. The hair is wiry, brittle and pale; patchy alopecia is common. Both hair loss and nail changes may progress over time. In affected infants, the nails are typically milky white, gradually thickening throughout childhood. In adults, the nail plates grow slowly, are thick, and separate from the nail bed distally (Fig. 63.17). Hyperkeratosis with stippling of the palms and soles can also be progressive (see Ch. 58). Tiny papules in a grid-like array (corresponding to eccrine acrosyringia) or larger papules coalescing in a cobblestone-like pattern may extend from the palms and soles onto the dorsal surface of the digits, especially distally (see Fig. 63.17 and Fig. 58.9), or even affect other extensor surfaces of the extremities. Oral leukoplakia has been described. Sparse eyelashes may predispose patients to conjunctivitis and blepharitis.

Fig. 63.17 Hidrotic ectodermal dysplasia (Clouston syndrome). Note the thickened, shortened nails with distal separation and tiny papules in a regular distribution on the fingertips.

Fig. 63.18 Witkop tooth and nail syndrome. Small primary teeth, some conical, in a 7-year-old boy. Radiographs showed an absence of nearly all of the secondary teeth. *Courtesy, Julie V Schaffer, MD.*

Pathology

Histologic evaluation of thickened palms and soles shows orthohyperkeratosis with a normal granular layer. Eccrine syringofibroadenomatosis, which is characterized by proliferation of ductal structures within a fibrovascular stroma, may be observed when papular lesions are biopsied. By electron microscopy, there is an increased number of desmosomes in the stratum corneum. The hair does not have specific microscopic changes.

Differential Diagnosis

The hair abnormalities in hidrotic ectodermal dysplasia distinguish it from pachyonychia congenita, which has similar hair findings. A hidrotic ectodermal dysplasia-like phenotype plus deafness has been reported in a patient with a *GJB2* mutation.

Treatment

The National Foundation for Ectodermal Dysplasias can provide support to affected individuals and families. Ablation of the nail matrix is occasionally necessary for pain relief, and patients with substantial alopecia may choose to use hairpieces. Management of hyperkeratotic palms and soles is difficult; similar strategies to those used for the palmoplantar keratodermas, e.g. α-hydroxy acids, urea, soaking and paring, can be employed.

WITKOP TOOTH AND NAIL SYNDROME

Synonyms: ■ Tooth and nail syndrome ■ Witkop syndrome ■ Hypodontia with nail dysgenesis

First described in 1965, this autosomal dominant disorder is probably more common than suggested by the relatively small number of reports in the literature[137]. Affected individuals have small, thin, brittle nail plates, and koilonychia may be evident at birth. The toenails are usually more prominently involved than the fingernails, and nail abnormalities tend to improve with age. Thin, fine scalp hair is an occasional feature. The primary teeth may be normal or small and (in some patients) peg-shaped (Fig. 63.18). There is usually partially or totally absent secondary dentition with prolonged retention of primary teeth.

A mutation in the *MSX1* (muscle segment homeobox 1) gene, which is expressed in developing teeth and nail beds in mice, has been identified in a family with Witkop tooth and nail syndrome[138]. Mutations in *MSX1* have also been described in families with isolated tooth agenesis or non-syndromic cleft lip and/or palate. MSX1 is a transcription factor that has roles in the development of teeth and presumably nails. Fried tooth and nail syndrome represents a similar condition with autosomal recessive inheritance.

ANKYLOBLEPHARON–ECTODERMAL DYSPLASIA–CLEFTING SYNDROME

Synonyms: ■ Hay–Wells syndrome ■ Rapp–Hodgkin syndrome

This autosomal dominant ectodermal dysplasia, first described in 1976[139], has been reported in ethnically and geographically distinct individuals and families[140].

Pathogenesis

The ankyloblepharon–ectodermal dysplasia–clefting (AEC) syndrome is caused by mutations in the sterile alpha motif (SAM) region of the *p63* gene[141]. p63, a transcription factor, is expressed within basal keratinocytes of the skin, which have a high proliferative capacity that is lost in differentiated keratinocytes. The p63 protein has multiple isotypes, with the protein domain present in only some forms. This helps to explain the phenotypic differences between AEC syndrome and ectodermal dysplasia–ectrodactyly–clefting (EEC) syndrome (see Table 63.11 and below), which is due to mutations within the DNA-binding domain of *p63*[141,142].

Clinical Features

This disorder is evident at birth. Up to 90% of affected infants present with erythroderma, peeling skin or erosions, which can result in life-threatening infectious complications (Fig. 63.19A). The scalp is almost always involved (Fig. 63. 19B), and a chronic, erosive scalp dermatitis is common. Patients often develop abnormal granulation tissue and recurrent bacterial infections of the skin. Progressive reticulated hyperpigmentation frequently appears in intertriginous areas, and hypopigmentation of the scalp and face may be seen in children with darkly pigmented skin.

Cribriform and stellate scarring tends to occur in a shawl-like distribution on the shoulders and upper trunk[143]. Patchy alopecia on the scalp is typical and the hairs are wiry, coarse and light-colored; body hair is decreased or absent. Some degree of nail dystrophy is usually evident, with findings ranging from hyperconvex, thickened nail plates to anonychia. Patients may have decreased sweating and heat intolerance[143,144].

Congenital strands of tissue between the eyelids (ankyloblepharon adnatum filiforme) are observed in approximately three-quarters of affected individuals (Fig. 63.19C). These may lyse spontaneously, even prior to birth, or require surgical correction. The lacrimal ducts may be atretic. Approximately 80% of patients with AEC syndrome are born with a cleft palate with or without a cleft lip. Malformed external ears

Fig. 63.19 Ankyloblepharon–ectodermal dysplasia–clefting syndrome. A Extensive erosions in an infant who succumbed to sepsis. **B** Thick scale-crust and alopecia of the scalp. **C** Strands of tissue between the eyelids (ankyloblepharon adnatum filiforme). **D** Digital abnormalities (including syndactyly, brachydactyly) and nail dystrophy (yellowing and thickening of the nail plate). *B, Courtesy, Jean L Bolognia, MD.*

and recurrent otitis media with secondary conductive hearing loss are common[145]. Dental abnormalities include hypodontia and misshapen (e.g. conical) teeth, and many patients have maxillary hypoplasia.

Gastroesophageal reflux affects the majority of AEC patients, while one-quarter of affected children fail to thrive and require gastrostomy placement[146]. Supernumerary nipples, ectopic breast tissue and hypospadias have been described[147]. Limb abnormalities are more common in AEC syndrome than once thought[143,144,148]; these malformations, which are typically less severe than the defects seen in EEC syndrome (see below), can include syndactyly (partial or complete), camptodactyly, brachydactyly and even ectrodactyly (Fig. 63.19D)[147].

Pathology

Hair shaft abnormalities such as pili torti and pili trianguli et canaliculi may be observed. Histopathologic changes are nonspecific and often include mild epidermal atrophy and dermal melanophages[149].

Differential Diagnosis

Rapp–Hodgkin syndrome, once considered to be a distinct entity, is now thought to fall within the AEC spectrum. Affected individuals have heterozygous mutations in the SAM domain of *p63* and clinical findings (including maxillary hypoplasia, cleft palate ± lip, nail dystrophy, and abnormalities of the teeth and hair) that overlap with those of AEC syndrome but do *not* include ankyloblepharon[150]. The clinical features of *c*urly *h*air–*a*nkyloblepharon–*n*ail *d*ysplasia *s*yndrome (CHANDS) also overlap with those of AEC syndrome, but the molecular basis of CHANDS has not yet been determined. The peeling erythroderma of neonates with AEC syndrome can lead to a misdiagnosis of epidermolysis bullosa or congenital ichthyosis.

Treatment

Treatment should be individualized. Surgical repair of oral clefting is usually necessary. Treatment for the erosive scalp dermatitis should be gentle and non-occlusive, with surveillance for and treatment of secondary infections. Debridement and grafting should be avoided as they typically fail or lead to worsening of erosions. Ulceration and granulation tissue may be very difficult to treat, and healing of erosions tends to be slow.

ECTODERMAL DYSPLASIA–ECTRODACTYLY–CLEFTING SYNDROME

Synonym: ▪ Split hand–split foot–ectodermal dysplasia–clefting syndrome

Described by Cockayne in 1936, this disorder occurs in all ethnic groups and has been reported worldwide[151].

Pathogenesis

Ectodermal dysplasia–ectrodactyly–clefting (EEC) syndrome is an autosomal dominant disorder caused by mutations in the *p63* gene[152]. These mutations disrupt the DNA-binding ability of the p63 transcription factor, which is expressed in proliferating epidermal basal cells. *p63* mutations also occur in several related autosomal dominant disorders, including non-syndromic split hand/foot malformation (minority of affected families), limb–mammary syndrome and ADULT (*a*cro-*d*ermato-*u*ngual-*l*acrimal-*t*ooth) syndrome, as well as in AEC syndrome (see Table 63.11 and above). Patients with EEC syndrome typically have missense mutations within the DNA-binding domain that differ from those seen in the other disorders[153]. Molecular testing for *p63* mutations is commercially available.

Clinical Features

The ectodermal changes in this highly variable condition may be quite mild[154]. The scalp hair is usually light in color and coarse. It may be sparse and grow slowly. The secondary sexual hair may also be affected. Scalp folliculitis and dermatitis are rare[155,156]. Approximately 80% of affected individuals have transverse ridging, pitting and slow growth of the nail plates. Xerotic skin and palmoplantar hyperkeratosis can occur, and sweating is usually normal.

Clefting of the palate/lip occurs in approximately 50% of affected individuals, and additional oral abnormalities include enamel hypoplasia, hypodontia and premature loss of secondary teeth. Lacrimal duct defects leading to blepharitis and dacryocystitis are frequently present. Secondary conductive hearing loss is also common.

Ectrodactyly (more specifically referred to as a split-hand/foot malformation) due to failure of normal development of the central digits represents a defining feature of EEC syndrome (Fig. 63.20). The ectrodactyly is frequently asymmetric, usually with more severe involvement of the feet than the hands. Intrafamilial variability is marked. Genitourinary abnormalities are an under-appreciated manifestation of EEC syndrome; renal and urogenital malformations (often resulting in hydronephrosis) affect more than one-third of patients.

Pathology

Histologic features are neither diagnostic nor specific.

Differential Diagnosis

The presence of split-hand/foot malformations and the absence of ankyloblepharon or cutaneous erosions help to distinguish EEC syndrome from AEC syndrome. The findings that differentiate limb–mammary syndrome and ADULT syndrome from EEC are presented in Table 63.11. Other ectodermal dysplasias that feature digital abnormalities include ectodermal dysplasia–ectrodactyly–macular dystrophy (EEM) syndrome, cleft lip/palate ectodermal dysplasia, oculodentodigital dysplasia and ulnar–mammary syndrome (see Tables 63.12 and 64.6). Although Goltz syndrome (focal dermal hypoplasia) can present with split-hand/foot and other digital malformations, nail dystrophy, sparse hair, dental anomalies and (occasionally) cleft lip/palate, it is easily recognized based on the highly characteristic skin findings as well as ocular and additional skeletal (e.g. osteopathia striata) defects (see Ch. 62).

Treatment

As for the other ectodermal dysplasias with oral clefting and lacrimal abnormalities, management involves a multidisciplinary approach. Limb defects may or may not be ameliorated by surgical interventions. All affected individuals should be screened with a renal ultrasound.

Fig. 63.20 Ectodermal dysplasia–ectrodactyly–clefting syndrome. Note the characteristic split-hand/foot deformities in three children.

REFERENCES

1. Darling TN, Skarulis MC, Steinberg SM, et al. Multiple facial angiofibromas and collagenomas in patients with multiple endocrine neoplasia type 1. Arch Dermatol. 1997;133:853–7.
2. Nord B, Platz A, Smoczynski K, et al. Malignant melanoma in patients with multiple endocrine neoplasia type 1 and involvement of the *MEN1* gene in sporadic melanoma. Int J Cancer. 2000;87;463–7.
3. Wells SA, Donis-Keller H. Current perspectives on the diagnosis and management of patients with multiple endocrine neoplasia type 2 syndromes. Endocrinol Metab Clin North Am. 1994;23:215–28.
4. Starink TM. Cowden's disease: analysis of fourteen new cases. J Am Acad Dermatol. 1984;11:1127–41.
5. Ruhoy SM, Thomas D, Nuovo GJ. Multiple inverted follicular keratoses as a presenting sign of Cowden's syndrome: case report with human papillomavirus studies. J Am Acad Dermatol. 2004;51:411–15.
6. Eng C. Will the real Cowden syndrome please stand up: revised diagnostic criteria. J Med Genet. 2000;37: 828–30.
7. Starink TM, Van Der Veen JPW, Arwert F, et al. The Cowden syndrome: a clinical and genetic study in 21 patients. Clin Genet. 1986;29:222–3.
8. Pilarski R. Cowden syndrome: a critical review of the clinical literature. J Genet Couns. 2009;18:13–27.
9. DiCristofano A, Pesce B, Cordon-Cardo C, Pandolfi PP. Pten is essential for embryonic development and tumour suppression. Nat Genet. 1998;19:348–55.
10. Trotman LC, Wang X, Alimonti A, et al. Ubiquitination regulates PTEN nuclear import and tumor suppression. Cell. 2007;128:141–56.
11. Salem OS, Steck WD. Cowden's disease (multiple hamartoma and neoplasia syndrome). J Am Acad Dermatol. 1983;8:686–96.
12. Requena L, Guiterrez J, Yus ES. Multiple sclerotic fibromas of the skin, a cutaneous marker of Cowden's disease. J Cutan Pathol. 1992;19:346–51.
13. Wade TR, Kopf AW. Cowden's disease: a case report and review of the literature. J Dermatol Surg Oncol. 1978;4: 459–64.
14. Barax CN, Lebwohl M, Phelps RG. Multiple hamartoma syndrome. J Am Acad Dermatol. 1987;17:342–6.
15. Tan WH, Baris HN, Burrows PE, et al. The spectrum of vascular anomalies in patients with PTEN mutations: implications for diagnosis and management. J Med Genet. 2007;44:594–602.
16. Brownstein MH, Wolf M, Bikowski JB. Cowden's disease. A cutaneous marker of breast cancer. Cancer. 1978;41: 2393–8.
17. Fackenthal JD, Marsh DJ, Richardson AL, et al. Male breast cancer in Cowden syndrome patients with germline PTEN mutations. J Med Genet. 2001;38: 159–64.
18. Gicquel JJ, Vabres P, Bonneau D, et al. Retinal angioma in a patient with Cowden disease. Am J Ophthalmol. 2003;135:400–2.
19. Perez-Nunez A, Lagares A, Benitez J, et al. Lhermitte-Duclos disease and Cowden disease: clinical and genetic study in five patients with Lhermitte-Duclos disease and literature review. Acta Neurochir (Wien). 2004;146:679–90.
20. Starink TM, Hausman R. The cutaneous pathology of facial lesions in Cowden's disease. J Cutan Pathol. 1984;11:331–7.
21. Ni Y, Zbuk KM, Sadler T, et al. Germline mutations and variants in the succinate dehydrogenase genes in Cowden and Cowden-like syndromes. Am J Hum Genet. 2008;83:261–8.
22. Williard W, Borgen P, Bol R, et al. Cowden's disease, a case report with analyses at the molecular level. Cancer. 1992;69:2969–74.
23. Schreibman IR, Baker M, Amos C, McGarrity TJ. The hamartomatous polyposis syndromes: a clinical and molecular review. Am J Gastroenterol. 2005; 100:476–90.
24. Squarize CH, Castilho RM, Gutkind JS. Chemoprevention and treatment of experimental Cowden's disease by mTOR inhibition with papamycin. Cancer Res. 2008;68:7066–72.
25. Wheeland RG, McGillis ST. Cowden's disease – treatment of cutaneous lesions using carbon dioxide laser vaporization: a comparison of conventional and super pulsed techniques. J Dermatol Surg Oncol. 1989;15:1055–9.
26. Bilkay U, Erdem O, Ozek C, et al. Benign osteoma with Gardner syndrome: review of the literature and report of a case. J Craniofac Surg. 2004;15:506–9.
27. Ballhausen WG. Genetic testing for familial adenomatous polyposis. Ann NY Acad Sci. 2000;910:36–47.
28. Naylor EW, Lebenthal E. Gardner's syndrome. Recent developments in research and management. Dig Dis Sci. 1980;25:945–59.
29. Eccles DM, van der Luijt R, Breukel C, et al. Hereditary desmoid disease due to a frameshift mutation at codon 1924 of the APC gene. Am J Hum Genet. 1996;59:1193–201.
30. Shields JA, Shields CL, Shah PG, et al. Lack of association among typical congenital hypertrophy of the retinal pigment epithelium, adenomatous polyposis and Gardner syndrome. Ophthalmology. 1992;99:1709–13.
31. Wimmer K, Etzler J. Constitutional mismatch repair-deficiency syndrome: have we so far seen only the tip of an iceberg? Hum Genet. 2008;124:105–22.
32. Galiatsatos P, Foulkes WD. Familial adenomatous polyposis. Am J Gastroenterol. 2006;101:385–98.
33. Naylor EW, Lebenthal E. Early detection of adenomatous polyposis coli in the Gardner's syndrome. Pediatrics. 1979;63:222–7.
34. Vogt S, Jones N, Christian D, et al. Expanded extracolonic tumor spectrum in MUTYH-associated polyposis. Gastroenterology. 2009;137:1976–85.
35. Hughes-Fulford M, Boman B. Growth regulation of Gardner's syndrome colorectal cancer cells by NSAIDs. Adv Exp Med Biol. 1997;407:433–41.
36. South CD, Hampel H, Comeras I, et al. The frequency of Muir-Torre syndrome among Lynch syndrome families. J Natl Cancer Inst. 2008;100:277–81.
37. Mangold E, Rahner N, Friedrichs N, et al. MSH6 mutation in Muir-Torre syndrome: could this be a rare finding? Br J Dermatol. 2007;156:158–62.
38. Lynch HT, Fusaro RM. The Muir-Torre syndrome in kindreds with hereditary nonpolyposis colorectal cancer (Lynch syndrome): a classic obligation in preventive medicine. J Am Acad Dermatol. 1999;41:797–9.
39. Dores GM, Curtis RE, Toro JR, et al. Incidence of cutaneous sebaceous carcinoma and risk of associated neoplasms: insight into Muir-Torre syndrome. Cancer. 2008;113:3372–81.
40. Eisen DB, Michael DJ. Sebaceous lesions and their associated syndromes: part II. J Am Acad Dermatol. 2009;61:563–78.
41. Eisen DB, Michael DJ. Sebaceous lesions and their associated syndromes: part I. J Am Acad Dermatol. 2009;61:549–60.
42. Curry ML, Eng W, Lund K, et al. Muir-Torre syndrome: role of the dermatopathologist in diagnosis. Am J Dermatopathol. 2004:26:217–21.
43. Cohen PR. Muir-Torre syndrome in patients with hematologic malignancies. Am J Hematol. 1992;40:64–5.
44. Schwartz RA, Torre DP. The Muir-Torre syndrome: a 25-year retrospect. J Am Acad Dermatol. 1995;33:90–104.
45. Rutten A, Burgdorf W, Hugel H, et al. Cystic sebaceous tumors as marker lesions for the Muir-Torre syndrome: a histopathologic and molecular genetic study. Am J Dermatopathol. 1999;21:405–13.
46. Capkin E, Karkucak M, Yayli S, et al. Ochronosis in differential diagnosis of patients with chronic backache: a review of the literature. Rheumatol Int. 2007;28:61–4.
47. Wolff JA, Barshop B, Nyhan WL, et al. Effects of ascorbic acid in alkaptonuria: alterations in benzoquinone acetic acid and an ontogenic effect in infancy. Pediatr Res. 1989;26:140–4.
48. Wolf B. Disorders of biotin metabolism. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds). The Metabolic and Molecular Bases of Inherited Disease, 8th edn. New York: McGraw-Hill, 2001:3935–64.
49. Nyhan WL. Inborn errors of biotin metabolism. Arch Dermatol. 1987;123:1696–8.
50. Zarate YA, Hopkin RJ. Fabry's disease. Lancet. 2008;372: 1427–35.
51. Martins AM, D'Almeida V, Kyosen SO, et al. Guidelines to diagnosis and monitoring of Fabry disease and review of treatment experiences. J Pediatr. 2009;155:S19–31.
52. Sagebiel RW, Parker F. Cutaneous lesions of Fabry's disease: glycolipid lipidosis: light and electron microscopic findings. J Invest Dermatol. 1968;50:208–13.
53. Orteu CH, Jansen T, Lidove O, et al. Fabry disease and the skin: data from FOS, the Fabry outcome survey. Br J Dermatol. 2007;157:331–7.
54. Lao LM, Kumakiri M, Mima H, et al. The ultrastructural characteristics of eccrine sweat glands in a Fabry disease patient with hypohidrosis. J Dermatol Sci. 1998;18:109–17.
55. Arvio M, Autio S, Louhiala P. Early clinical symptoms and incidence of aspartylglucosaminuria in Finland. Acta Paediatr. 1993;82:587–9.
56. d'Azzo A, Andria G, Strisciuglio P, Galjaard H. Galactosialidosis. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds). The Metabolic and Molecular Bases of Inherited Disease, 8th edn. New York: McGraw-Hill, 2001:3811–26.
57. Beratis NG, Varvarigou-Frimas A, Beratis S, et al. Angiokeratoma corporis diffusum in GM1 gangliosidosis, type 1. Clin Genet. 1989;36:59–64.
58. Willems PJ, Gatti R, Darby JK, et al. Fucosidosis revisited: a review of 77 patients. Am J Med Genet. 1991;38:111–31.
59. Kodama K, Kobayashi H, Abe R, et al. A new case of alpha-N-acetylgalactosaminidase deficiency with angiokeratoma corporis diffusum, with Meniere's syndrome and without mental retardation. Br J Dermatol. 2001;144:363–8.
60. Wenger DA, Sujansky E, Fennessey PV, et al. Human beta-mannosidase deficiency. N Engl J Med. 1986;315:1201–5.
61. Lowden JA, O'Brien JS. Sialidosis: a review of human neuraminidase deficiency. Am J Hum Genet. 1979;31:1–18.
62. Eng CM, Guffon N, Wilcox CR, et al. International Collaborative Fabry Disease Study Group. Safety and efficacy of recombinant human alpha-galactosidase A replacement therapy in Fabry's disease. N Engl J Med. 2001;345:9–16.
63. Desnick RJ, Banikazemi M. Fabry disease: clinical spectrum and evidence-based enzyme replacement therapy. Nephrol Ther. 2006;2(Suppl 2):S172–85.
64. Miano M, Lanina E, Gatti R, et al. Four year follow-up of a case of fucosidosis treated with unrelated donor bone marrow transplantation. Bone Marrow Transplant. 2001; 27:747–51.
65. Goldblatt J, Beieghton P. Cutaneous manifestations of Gaucher disease. Br J Dermatol. 1984;111:331–4.
66. Finn LS, Zhang M, Chen SH, et al. Severe type II Gaucher disease with ichthyosis, arthrogryposis and neuronal apoptosis: molecular and pathological analyses. Am J Med Genet. 2000;91:222–6.
67. Fujimoto A, Tayebi N, Sidransky E. Congenital ichthyosis preceding neurologic symptoms in two sibs with type 2 Gaucher disease. Am J Med Genet. 1995;59:356–8.
68. Martins AM, Valadares ER, Porta G, et al. Recommendations on diagnosis, treatment and monitoring for Gaucher disease. J Pediatr. 2009;155:S10–18.
69. Scriver CR, Mahon B, Levy HL, et al. The Hartnup phenotype: Mendelian transport disorder, multifactorial disease. Am J Hum Genet. 1987;40:401–12.
70. Haim S, Gilhar A, Cohen A. Cutaneous manifestations associated with aminoaciduria. Report of two cases. Dermatologica. 1978;156:244–50.
71. Munnich A, Rustin P. Clinical spectrum and diagnosis of mitochondrial disorders. Am J Med Genet. 2001;106:4–17.
72. Debray F-G, Lambert M, Chevalier I, et al. Long-term outcome and clinical spectrum of 73 pediatric patients with mitochondrial diseases. Pediatrics. 2007;119:722–33.
73. Bodemer C, Rotig A, Rustin P, et al. Hair and skin disorders as signs of mitochondrial disease. Pediatrics. 1999;103:428–33.
74. Schuchman EH, Miranda SR. Niemann-Pick disease: mutation update, genotype/phenotype correlations and prospects for genetic testing. Genet Test. 1997;1:13–19.
75. Nova MP, Kaufman M, Halperin A. Scleroderma-like skin indurations in a child with phenylketonuria: a clinicopathologic correlation and review of the literature. J Am Acad Dermatol. 1992;26:329–33.
76. Al-Mayouf SM, Al-Owain MA. Progressive sclerodermatous skin changes in a child with phenylketonuria. Pediatr Dermatol. 2006;23: 136–8.
77. DeBusk FL. The Hutchinson-Gilford progeria syndrome. Report of 4 cases and review of the literature. J Pediatr. 1972;80:697–724.
78. Sarkar PK, Shinton RA. Hutchinson-Guilford progeria syndrome. Postgrad Med J. 2001;77:312–17.

79. Hennekam RC. Hutchinson-Guilford progeria syndrome: review of the phenotype. Am J Med Genet. 2006;140A: 2603–24.
80. Plasilova M, Chattopadhyay C, Pal P, et al. Homozygous missense mutation in the lamin A/C gene causes autosomal recessive Hutchinson-Gilford progeria syndrome. J Med Genet. 2004;41:609–14.
81. Eriksson M, Brown WT, Gordon LB, et al. Recurrent de novo point mutations in lamin A cause Hutchinson-Gilford progeria syndrome. Nature. 2003;423:293–7.
82. Worman HJ, Ostlund C, Wang Y. Diseases of the nuclear envelope. Cold Spring Harb Perspect Biol. 2010;2:a000760.
83. Capell BC, Erdos MR, Madigan JP, et al. Inhibiting farnesylation of progerin prevents the characteristic nuclear blebbing of Hutchinson-Gilford progeria syndrome. Proc Natl Acad Sci U S A. 2005;102:12879–84.
84. Cao K, Capell BC, Erdos MR, et al. A lamin A protein isoform overexpression in Hutchinson-Gilford progeria syndrome interferes with mitosis in progeria and normal cells. Proc Natl Acad Sci U S A. 2007;104:4949–54.
85. Mounkes LC, Kozlov S, Hernandez L, et al. A progeroid syndrome in mice is caused by defects in A-type lamins. Nature. 2003;423:298–301.
86. Miki T, Morishima A, Nakura J. The genes responsible for the human progeroid syndromes. Intern Med. 2000;39:327–8.
87. Mazereeuw-Hautier J, Wilson LC, Mohammed S, et al. Hutchinson-Gilford progeria syndrome: clinical findings in 3 patients carrying the G608G mutation in *LMNA* and a review of the literature. Br J Dermatol. 2007;156:1308–14.
88. Gabr M, Hashem N, Hashem M, et al. Progeria: a pathologic study. J Pediatr. 1960;57:70–7.
89. Atkins L. Progeria, report of a case with post-mortem findings. N Engl J Med. 1954;250:1065.
90. Greally JM, Boone SG, Lenkey SL, Steele MW. Acrometageria: a spectrum of premature aging syndromes. Am J Med Genet. 1992;44:334–9.
91. Fong LG, Frost D, Meta M, et al. A protein farnesyltransferase inhibitor ameliorates disease in a mouse model of progeria. Science. 2006;311:1621–3.
92. Mehta IS, Bridger JM, Kill IR. Progeria, the nucleolus and farnesyltransferase inhibitors. Biochem Soc Trans. 2010;38:287–91.
93. Epstein CJ, Martin GM, Schultz AL, Motulsky AG. Werner's syndrome: a review of its symptomatology, natural history, pathologic features, genetics and relationship to the natural aging process. Medicine (Baltimore). 1966;45:177–222.
94. Lebel M. Werner syndrome: genetic and molecular basis of a premature aging disorder. Cell Mol Life Sci. 2001;58:857–67.
95. Goto M, Tanimoto K, Horiuchi Y, Sasazuki T. Family analysis of Werner's syndrome: a survey of 42 Japanese families with a review of the literature. Clin Genet. 1981;19:8–15.
96. Nehlin JO, Skovgaard GL, Bohr VA. The Werner syndrome, a model for the study of human aging. Ann NY Acad Sci. 2000;908:167–79.
97. Goto M, Miller RW, Ishikawa Y, Sugano H. Excess of rare cancers in Werner syndrome (adult progeria). Cancer Epidemiol Biomarkers Prev. 1996;5:239–46.
98. Chen L, Lee L, Kudlow BA, et al. *LMNA* mutations in atypical Werner's syndrome. Lancet. 2003;362:440–5.
99. Massip L, Garand C, Paquet ER, et al. Vitamin C restores healthy aging in a mouse model for Werner syndrome. FASEB J. 2010;24:158–72.
100. Haber RM, Hanna WM. Kindler syndrome. Clinical and ultrastructural findings. Arch Dermatol. 1996;132:1487–90.
101. Patrizi A, Pauluzzi P, Neri I, et al. Kindler syndrome: report of a case with ultrastructural study and review of the literature. Pediatr Dermatol. 1996;13:397–402.
102. Forman AB, Prendiville JS, Esterly NB, et al. Kindler syndrome: report of two cases and review of the literature. Pediatr Dermatol. 1989;6:91–101.
103. Penagos H, Jaen M, Sancho MT, et al. Kindler syndrome in native Americans from Panama: report of 26 cases. Arch Dermatol. 2004;140:939–44.
104. Ricketts DN, Morgan CL. Kindler syndrome: a rare case of desquamative lesions of the gingival. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1997;84:488–91.
105. Wiebe CB, Silver JG, Larjava HS. Early-onset periodontitis associated with Weary-Kindler syndrome: a case report. J Periodontol. 1996;67:1004–10.
106. Jobard F, Bouadjar B, Caux F, et al. Identification of mutations in a new gene encoding a FERM family protein with a pleckstrin homology domain in Kindler syndrome. Hum Mol Genet. 2003;12:925–35.
107. Siegel DH, Ashton GHS, Penagos HG, et al. Loss of kindlin-1, a human homolog of the *Caenorhabditis elegans* actin-extracellular-matrix linker protein UNC-112, causes Kindler syndrome. Am J Hum Genet. 2003;73:174–87.
108. Lai-Cheong JE, McGrath JA. Kindler syndrome. Dermatol Clin. 2010;28:119–24.
109. D'Souza MA, Kimble RM, McMillan JR. Kindler syndrome pathogenesis and fermitin family homologue 1 (kindlin-1) function. Dermatol Clin. 2010;28:115–18.
110. Lotem M, Raben M, Zeltser R, et al. Kindler syndrome complicated by squamous cell carcinoma of the hard palate: successful treatment with high dose radiation therapy and granulocyte-macrophage-colony stimulating factor. Br J Dermatol. 2001;144:1284–6.
111. Shimizu H, Sato M, Ban M, et al. Immunohistochemical, ultrastructural, and molecular features of Kindler syndrome distinguish it from dystrophic epidermolysis bullosa. Arch Dermatol. 1997;133:1111–17.
112. Freire-Maia N, Pinheiro M. Ectodermal Dysplasias: a Clinical and Genetic Study. New York: Liss, 1984.
113. Pinheiro M, Freire-Maia N. Ectodermal dysplasias: a clinical classification and a causal review. Am J Med Genet. 1994;53:153–62.
114. Priolo M, Lagana C. Ectodermal dysplasias: a new clinical-genetic classification. J Med Genet. 2001;38:579–85.
115. Lamartine J. Towards a new classification of ectodermal dysplasias. Clin Exp Dermatol. 2003;28:351–5.
116. Visinoni AF, Lisoba-Costa T, Pagnan NAB, et al. Ectodermal dysplasia: clinical and molecular review. Am J Med Genet A. 2009;149A:1980–2002.
117. Priolo M. Ectodermal dysplasias: an overview and update of clinical and molecular-functional mechanisms. Am J Med Genet A. 2009;149A:2003–13.
118. Salinas CF, Jorgenson RJ, Wright JG et al. 2008 International Conference on Ectodermal Dysplasias Classification: conference report. Am J Med Genet A. 2009;149A:1958–69.
119. Mikkola ML. Molecular aspects of hypohidrotic ectodermal dysplasia. Am J Med Genet A. 2009;149A: 2031–6.
120. Schmidt-Ullrich R, Aebischer T, Hulsken J, et al. Requirement of NF-kappaB/Rel for the development of hair follicles and other epidermal appendices. Development. 2001;128:3843–53.
121. Monreal AW, Ferguson BM, Headon DJ, et al. Mutations in the human homologue of mouse *dl* cause autosomal recessive and dominant hypohidrotic ectodermal dysplasia. Nat Genet. 1999;22:366–9.
122. Headon DJ, Emmal SA, Ferguson BM, et al. Gene defect in ectodermal dysplasia implicates a death domain adapter in development. Nature. 2001;414:913–16.
123. Bale SJ, Mitchell AG. Genetic testing in ectodermal dysplasia: availability, clinical utility, and the nuts and bolts of ordering a genetic test. Am J Med Genet A. 2009;149A:2052–6.
124. Clarke A, Phillips DI, Brown R, et al. Clinical aspects of X-linked hypohidrotic ectodermal dysplasia. Arch Dis Child. 1987;62:989–96.
125. Rouse C, Siegfried E, Breer W, et al. Hair and sweat glands in families with hypohidrotic ectodermal dysplasia: further characterization. Arch Dermatol. 2004;140:850–5.
126. Gaide O. Gene therapy and protein therapy of ectodermal dysplasias: a perspective. Am J Med Genet A. 2009;149A:2042–4.
127. Gaide O, Schneider P. Permanent correction of an inherited ectodermal dysplasia with recombinant EDA. Nat Med. 2003;5:614–18.
128. Casal ML, Lewis JR, Mauldin EA, et al. Significant correction of disease after postnatal administration of recombinant ectodysplasin A in canine X-linked ectodermal dysplasia. Am J Hum Genet. 2007;81:1050–6.
129. Mauldin EA, Gaide O, Schneider P, et al. Neonatal treatment with recombinant ectodysplasin prevents respiratory disease in dogs with X-linked ectodermal dysplasia. Am J Med Genet A. 2009;149A:2045–9.
130. Zonana J, Elder ME, Schneider LC, et al. A novel X-linked disorder of immune deficiency and hypohidrotic ectodermal dysplasia is allelic to incontinentia pigmenti and due to mutations in IKK-gamma (NEMO). Am J Hum Genet. 2000;67:1555–62.
131. Mancini AJ, Lawley LP, Uzel G. X-linked ectodermal dysplasia with immunodeficiency caused by *NEMO* mutation. Arch Dermatol. 2008;144:342–6.
132. Doffinger R, Smahi A, Bessia C, et al. X-linked anhidrotic ectodermal dysplasia with immunodeficiency is caused by impaired NF-kappaB signaling. Nat Genet. 2001;27: 277–85.
133. Fish JD, Duerst RE, Gelfand EW, et al. Challenges in the use of allogeneic hematopoietic SCT for ectodermal dysplasia with immune deficiency. Bone Marrow Transplant. 2009;43:217–21.
134. Clouston HR. A hereditary ectodermal dysplasia. Can Med Assoc J. 1929;21:18–31.
135. Kibar Z, Dube MP, Powell J, et al. Clouston hidrotic ectodermal dysplasia (HED): genetic homogeneity, presence of a founder effect in the French Canadian population and fine genetic mapping. Eur J Hum Genet. 2000;8:372–80.
136. Lamartine J, Munhoz Essenfelder G, Kibar Z, et al. Mutations in *GJB6* cause hidrotic ectodermal dysplasia. Nat Genet. 2000;26:142–4.
137. Hudson CD, Witkop CJ Jr. Autosomal dominant hypodontia with nail dysgenesis. Report of 29 cases in six families. Oral Pathol. 1975;39:409–23.
138. Jumlongras D, Bei M, Stimson JM, et al. A nonsense mutation in *MSX1* causes Witkop syndrome. Am J Hum Genet. 2001;69:67–74.
139. Hay RJ, Wells RS. The syndrome of ankyloblepharon, ectodermal defects and cleft lip and palate: an autosomal dominant condition. Br J Dermatol. 1976;94: 277–89.
140. Fete M, vanBokhowen H, Clements SE, et al. International research symposium on ankyloblepharon-ectodermal defects-cleft lip/palate (AEC) syndrome. Am J Med Genet A. 2009;149A:1885–93.
141. McGrath JA, Duijf PH, Doetsch V, et al. Hay-Wells syndrome is caused by heterozygous missense mutations in the SAM domain of *p63*. Hum Mol Genet. 2001;10:221–9.
142. Rinne T, Brunner HG, van Bokhoven H. p63-associated disorders. Cell Cycle. 2007;6:262–8.
143. Julapalli MR, Scher RK, Sybert VP, et al. Dermatologic findings in ankyloblepharon-ectodermal defects-cleft lip/palate (AEC) syndrome. Am J Med Genet A. 2009; 149A:1900–6.
144. Bree AF. Clinical lessons learned from the international research symposium on ankyloblepharon-ectodermal defects-cleft lip/palate (AEC) syndrome. Am J Med Genet A. 2009;149A:1894–9.
145. Cole P, Hatef DA, Kaufman Y, et al. Facial clefting and oroauditory pathway manifestations in ankyloblepharon-ectodermal defects-cleft lip/palate (AEC) syndrome. Am J Med Genet A. 2009;149A:1910–15.
146. Motil KJ, Fete TJ. Growth, nutritional, and gastrointestinal aspects of ankyloblepharon-ectodermal defect-cleft lip and/or palate (AEC) syndrome. Am J Med Genet A. 2009; 149A:1922–5.
147. Sutton VR, Plunkett K, Dang DX, et al. Craniofacial and anthropometric phenotype in ankyloblepharon-ectodermal defects-cleft lip/palate syndrome (Hay-Wells syndrome) in a cohort of 17 patients. Am J Med Genet A. 2009;149A:1916–21.
148. Chiu YE, Drolet BA, Duffy KJ, et al. A case of ankyloblepharon, ectodermal dysplasia, and cleft lip/palate syndrome with ectrodactyly: are the p63 syndromes distinct after all? Pediatr Dermatol. 2011;28:15–19.
149. Dishop MK, Bree AF, Hicks MJ. Pathologic changes of skin and hair in ankyloblepharon-ectodermal defects-cleft lip/palate (AEC) syndrome. Am J Med Genet A. 2009;149A:1935–41.
150. Kannu P, Savarirayan R, Ozoemena L, et al. Rapp-Hodgkin ectodermal dysplasia syndrome: the clinical and molecular overlap with Hay-Wells syndrome. Am J Med Genet A. 2006;140A:887–91.
151. Roelfsema NM, Cobben JM. The EEC syndrome: a literature study. Clin Dysmorphol. 1996;5:115–27.
152. Celli J, Duijf P, Hamel BC, et al. Heterozygous germline mutations in the *p53* homolog *p63* are the cause of EEC syndrome. Cell. 1999;99:143–53.
153. van Bokhoven H, Hamel BC, Bamshad M, et al. p63 Gene mutations in EEC syndrome, limb-mammary syndrome, and isolated split hand-split foot malformation suggest a genotype-phenotype correlation. Am J Hum Genet. 2001;69:481–92.
154. Rinne T, Hamel B, van Bokhoven H, Brunner HG. Pattern of p63 mutations and their phenotypes: update. Am J Med Genet A. 2006;140A:1396–406.
155. Trueb RM, Bruckner-Tuderman L, Wyss M, et al. Scalp dermatitis, distinctive hair abnormalities and atopic dermatitis in the ectrodactyly-ectodermal dysplasia-clefting syndrome. Br J Dermatol. 1995;132:621–5.
156. Trueb RM, Tsambaos D, Spycher MA, et al. Scarring folliculitis in the ectrodactyly-ectodermal dysplasia-clefting syndrome. Dermatology. 1997;194:191–4.

This page intentionally left blank

Developmental Anomalies 64

Richard Antaya and Julie V Schaffer

Chapter Contents

The midline lesion 993
Aplasia cutis congenita 1000
Other developmental anomalies 1004

Key features

- The human neural tube is thought to close in an intermittent, multisite pattern, and neural tube defects that present as midline cutaneous lesions (e.g. cephaloceles, heterotopic brain tissue, rudimentary meningoceles) typically occur at the junction between two closure sites
- Midline lesions of the nose and scalp have a high likelihood of representing developmental defects with a potential intracranial connection, and an evaluation with CT or MRI prior to surgical intervention is critical
- The presence of a "hair collar" surrounding a lesion on the scalp is a sign of ectopic neural tissue or membranous aplasia cutis; the latter is thought to represent a forme fruste of a neural tube defect
- Cutaneous lesions overlying the spinal axis can serve as a marker for spinal dysraphism, and their presence is often an indication for radiologic evaluation
- Aplasia cutis congenita, a physical finding reflecting a disruption of intrauterine skin development, can be approached clinically based on the morphology and distribution of lesions as well as the presence or absence of associated abnormalities
- A number of other developmental anomalies affect the skin; although they usually represent isolated defects, it is important to be aware of potential associated conditions

INTRODUCTION

Developmental anomalies are a diverse group of congenital disorders that result from faulty morphogenesis. They include both *malformations*, defined as structural defects arising due to errors in embryologic development, and *disruptions*, which occur when a structure programmed to develop normally is damaged before it is fully formed. A classic example of the former is incomplete closure of the neural tube resulting in an encephalocele, while the latter process is illustrated by the anomalies associated with varicella embryopathy. Although developmental anomalies that affect the skin are often recognized at birth or during infancy, occasionally diagnosis is delayed until later in life. The cutaneous abnormalities range in severity from isolated, minor physical findings (e.g. rudimentary supernumerary digits) to deforming, potentially life-threatening defects (e.g. deep, irregular scalp aplasia cutis congenita in Adams–Oliver syndrome). Furthermore, some skin lesions that themselves appear to be innocuous may serve as important clues to the presence of a multiple congenital anomaly syndrome or, particularly when involving the midline, the existence of a serious defect of the underlying tissues. Such associations reflect the complex interactions between various ectodermal and mesodermal elements that occur during the intricate processes of morphogenesis and differentiation.

This chapter begins with an overview of the midline lesion and its relationship to closure of the neural tube. A discussion of specific issues pertaining to midline lesions of the nose, scalp and spine follows, including a review of the different types of anomalies that can present in these sites. An overview of aplasia cutis congenita is followed by presentation of a clinical approach based on the morphology and distribution of lesions and the presence or absence of associated abnormalities. Finally, a variety of non-midline developmental anomalies are discussed, including lip pits, accessory tragi, supernumerary nipples, skin dimples, malformations of the dermatoglyphs, rudimentary supernumerary digits, and the amniotic band syndrome. Some cysts that represent developmental anomalies (e.g. branchial cleft cyst, thyroglossal cyst) are covered in Chapter 110.

THE MIDLINE LESION

A number of critical events occur during the third to fifth weeks of embryologic development (see Ch. 2). These include formation of the neural tube, separation of neuroectoderm from surface ectoderm, and interposition of mesodermal elements. Inherent in such a complicated process is the potential for error, which spans a spectrum from obvious, fulminant neural tube defects to subtle cutaneous anomalies. However, the latter may represent a sign of a significant underlying malformation.

Classically, closure of the human neural tube was thought to be a continuous process, beginning at a single focus in the cervical region and progressing bidirectionally in a "zipper-like" fashion to culminate in the closure of the anterior and subsequently posterior neuropores. However, evidence suggests that in humans as well as other mammals, the cranial segment of the neural tube closes in an intermittent or multisite pattern. Four distinct initiation sites of neural tube closure have been identified in the mouse, and a similar pattern of closure has been proposed for humans, with an additional caudal site (Fig. 64.1)[1].

In support of the multisite closure model, major neural tube defects (e.g. partial anencephaly, encephaloceles, myelomeningoceles) have been observed to cluster in discrete regions, either entirely within one closure site or at the junction of two sites[1]. Individuals with two independent cranial neural tube defects have also been described. The multisite model is of particular importance in understanding the etiology of midline cutaneous lesions. For example, the root of the nose (fronto-ethmoidal region) and the vertex of the skull – frequent locations of cephaloceles as well as more subtle neural tube defects such as heterotopic brain tissue (e.g. nasal gliomas) and rudimentary meningoceles – both correspond to the junction of two closure sites (see Fig. 64.1). Interestingly, neural tube closure in the posterior cranial area is thought to occur via a membrane rather than a midline fusion of folds, and the appearance of this site during embryologic development in animals resembles that of membranous aplasia cutis in human neonates[2]. Lastly, it has been suggested that specific genes may control individual closure sites, explaining repetitive events within families.

Midline Lesions of the Head and Neck

The pathogenesis, differential diagnosis and management of midline lesions of the nose (Fig. 64.2) and scalp are discussed below, followed by a review of the individual developmental anomalies that may present with a midline lesion on the head or neck. Midline cysts of this region (e.g. thyroglossal duct cysts, bronchogenic cysts) are discussed in detail in Chapter 110.

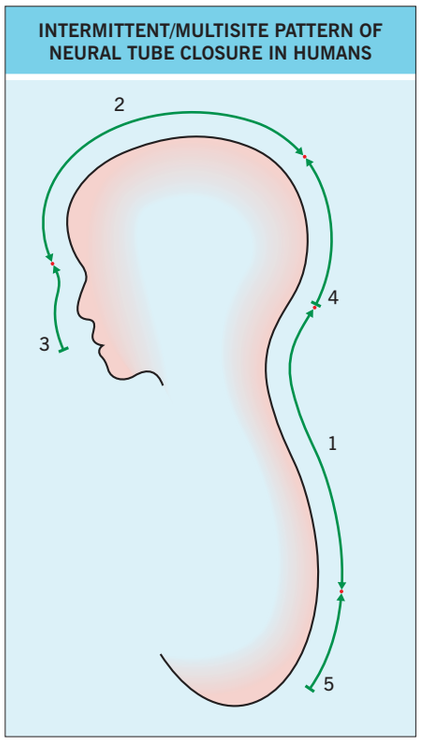


Fig. 64.1 Intermittent/multisite pattern of neural tube closure in humans. The five separate initiation sites are labeled (in chronological order, 1–5), the direction of neural tube closure is indicated by the arrows, and the junctions (where defects tend to occur) designated with dots. The 2–3 junction corresponds to the location of frontoethmoidal neural tube defects, the 2–4 junction to parietal defects, and the 1–4 junction to occipital defects. Closure in region 4 is thought to occur via membranous growth, proceeding in a superior direction; incomplete closure at this site could therefore result in a membranous defect at the 2–4 junction (i.e. the vertex).

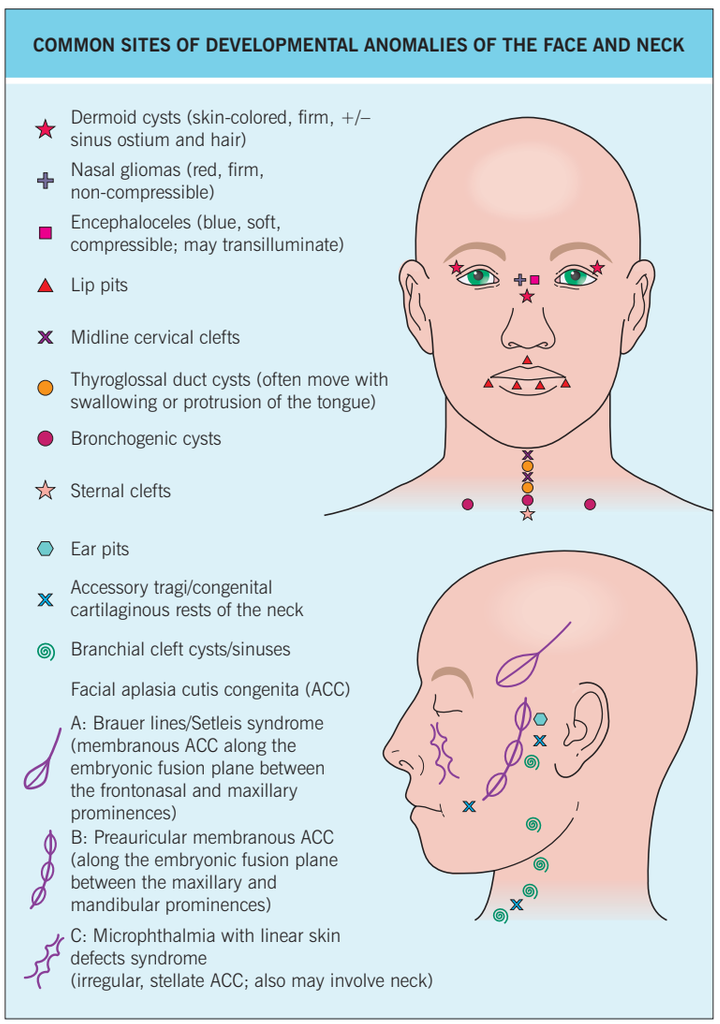


Fig. 64.2 Common sites of developmental anomalies of the face and neck.

Midline nasal lesions

Although most physicians recognize that a midline cutaneous lesion over the spine may be a marker of an underlying defect, the potential intracranial connection of a midline nasal mass or pit is less widely appreciated[3]. Dermoid cysts, dermal sinuses, cephaloceles and heterotopic brain tissue (nasal gliomas) resulting from faulty embryologic development of the frontobasal skull and/or adjacent ectodermal/neuroectodermal tissues all may present as congenital nasal lesions (Table 64.1). As a group, these midline nasal masses occur in only 2–5 per 100 000 live births. They are often misdiagnosed as more familiar entities such as epidermoid cysts and infantile hemangiomas, and patients may present with a history of recurrent cutaneous infections or meningitis.

The various congenital midline nasal masses have similar developmental origins. As the bones of the skull form during the second month of gestation, diverticula of dura mater project: (1) inferiorly into the prenasal space that extends from the base of the skull to the nasal tip, deep to the nasal bone and skin but superficial to the nasal cartilage; and (2) anteriorly through the nasofrontal fontanelle into the glabellar area. These diverticula may make connections with the overlying dermis, but usually they regress completely, with subsequent bony fusion to form the base of the skull and the cribriform plate. However, if the dura mater does not separate, an ectodermal residue with or without a patent intracranial connection can persist; furthermore, if faulty neural tube closure results in a bony defect, there may be herniation of brain tissue. Such ectopic elements can occur either within the prenasal space (nasoethmoidal, "intranasal") or superiorly at the glabella (nasofrontal, "extranasal")[4]. Depending on the contents of the lesion (e.g. cutaneous versus neural tissue, cyst versus tract only) and the patency of the intracranial connection, a dermoid cyst, dermal sinus, cephalocele or nasal glioma results (see below).

It is important to recognize that many of these midline nasal lesions have the potential for intracranial communication, and, consequently, present a risk for the development of serious CNS infections (e.g. meningoencephalitis, a frontal lobe abscess). In addition, recurrent inflammation and progressive expansion of the mass may result in bony atrophy and nasal distortion. Early and complete surgical excision

THE DIFFERENTIAL DIAGNOSIS OF NASAL MASSES PRESENTING AT BIRTH OR DURING INFANCY

DEVELOPMENTAL DEFECTS
• Dermoid cyst*,†
• Cephalocele (encephalocele > meningocele)*
• Nasal glioma*
• Lymphatic malformation
• Nasolacrimal duct cyst
OTHER CYSTS
• Epidermoid cyst
• Pilomatricoma
• Ethmoid mucocele
BENIGN NEOPLASMS AND HAMARTOMAS
• Infantile hemangioma
• Hemangiopericytoma
• Neurofibroma
• Melanotic neuroectodermal tumor of infancy
• Hamartomas: chondromesenchymal, chondroid, lipomatous or angiomatous
• Teratoma‡
MALIGNANT NEOPLASMS
• Rhabdomyosarcoma
• Fibrosarcoma
• Osteosarcoma
• Neuroblastoma

*Midline lesions.
†The most common cause of a congenital midline nasal mass.
‡May also be malignant.

Table 64.1 The differential diagnosis of nasal masses presenting at birth or during infancy.

with repair of associated bony and dural defects is imperative, and this often requires a multidisciplinary approach. In order to prevent ascending infections, biopsy, needle aspiration or other preoperative manipulations should be avoided. A thorough radiologic evaluation prior to surgery is mandatory. While CT is the most accurate method in defining bony defects of the skull, false-positive studies are common, particularly in young children undergoing the process of bone maturation. MRI is superior in demonstrating intracranial masses and other soft tissue changes, and images in multiple planes may aid in planning surgical approaches[5]. In some instances, a combination of CT and MRI findings may be required to adequately complete the preoperative evaluation. In addition, surgical exploration is necessary to definitively exclude the presence of an intracranial connection, as small fibrous tracts may not be detectable with imaging studies.

Midline lesions of the scalp

Subcutaneous nodules of the scalp are common, and in adults they are usually acquired lesions, such as epidermoid and trichilemmal cysts. However, midline scalp lesions that are noted at birth or in early childhood have a high likelihood of representing developmental defects, such as dermoid cysts, cephaloceles, heterotopic brain or meningeal tissue, and aplasia cutis congenita. In one series of 70 children presenting with a solitary, non-traumatic scalp nodule[6], 61% of the lesions were dermoid cysts and 4% cephaloceles. More importantly, 37% of the lesions were found to extend intracranially to the dura or brain.

In the evaluation of a patient with a subcutaneous nodule on the scalp, there are a number of clinical clues that heighten suspicion of a developmental anomaly with potential intracranial extension[7]. These include:

- a patient who is an infant or child
- a lesion first noted at birth or during early childhood
- a family history of neural tube defects
- a history of meningitis
- the presence of neurologic signs or symptoms
- location of the lesion along the midline or over the suture lines of the scalp
- lesions that pulsate, fluctuate in size with crying or straining, transilluminate, or have a central pore (the latter particularly in children, in whom epidermoid cysts are uncommon)
- an overlying capillary malformation (port-wine stain)
- a positive hair collar sign (see below).

A congenital midline lesion, or a scalp nodule with other concerning features, requires a thorough evaluation prior to surgical excision or biopsy. The work-up includes CT or MRI to help determine whether an intracranial connection is present. If a bony defect is detected by CT, a follow-up MRI may be indicated to better evaluate whether there is extension of soft tissue transcranially. A neurosurgical referral is indicated if imaging studies are positive, and, as small communications may be missed, complete surgical removal may be prudent even if they are negative[8].

The *hair collar sign* consists of a ring of long, dark, coarse hair surrounding a congenital scalp nodule. The presence of a hair collar is a relatively specific marker for ectopic neural tissue[8,9]. Hair collars are also seen in membranous aplasia cutis (Figs 64.3 & 64.4), a disorder thought to represent a forme fruste of a neural tube defect (i.e. without the presence of ectopic neural tissue)[2]. Drolet et al.[8] hypothesized that cerebral herniation produces aberrant shearing forces during the formation of hair follicles early in development, causing them to point outward from the defect. The proximity of neuroectoderm expressing neural adhesion molecules may also alter normal epidermal–dermal interactions, thereby inducing the development of large, abnormal follicles[2]. These speculations correlate with the histologic finding of numerous horizontally oriented, hypertrophic follicles emerging from the edge of scalp lesions to form the hair collar[9,10]. The differential diagnosis and evaluation of a positive hair collar sign is presented in Figure 64.5.

Other developmental anomalies of the scalp

Sinus pericranii is a rare disorder characterized by a congenital (or, occasionally, acquired) epicranial venous malformation of the scalp that communicates with an intracranial dural sinus through dilated diploic cranial veins[11]. The lesion is usually located near the midline, especially in the frontal region. Most are asymptomatic and appear as a compressible, fluctuant mass that varies in size with changes in intracranial pressure (Fig. 64.6). The differential diagnosis includes a simple venous or arteriovenous malformation, meningocele or encephalocele.

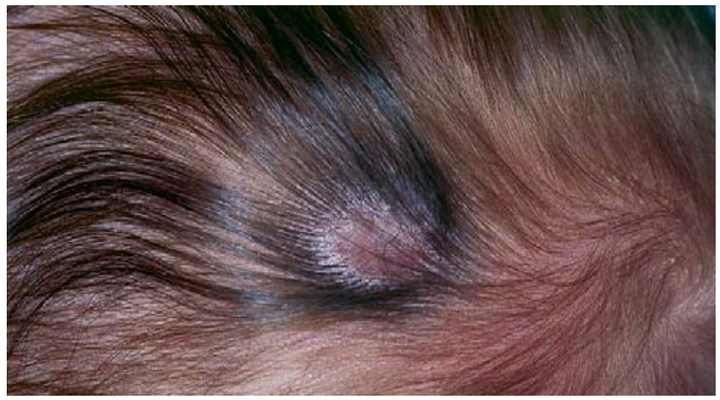


Fig. 64.3 Hair collar sign. Membranous aplasia cutis congenita with a hair collar and an associated capillary malformation. *Courtesy, Kalman Watsky, MD.*

Fig. 64.4 Hair collar sign. Membranous aplasia cutis congenita with a bullous appearance and a surrounding hair collar.

Nevus psiloliparus, a rare scalp anomaly characterized by a variable degree of alopecia and an excessive amount of adipose tissue, is the hallmark of encephalocraniocutaneous lipomatosis (see Ch. 62)[12]. The latter disorder also features papules and nodules, which represent fibromas and fibrolipomas, in a unilateral distribution on the face (especially the eyelids) and scalp; extracutaneous findings include ipsilateral ocular (usually choristomas) and intracranial abnormalities. Nevus psiloliparus presents as a skin-colored, round to oval, smooth, hairless patch or soft plaque located unilaterally on the parietal or frontoparietal scalp.

Dermoid cysts

Dermoid cysts result from sequestration of ectodermal tissue along embryonic fusion planes during development. They are a separate entity from benign cystic teratomas, neoplasms that are also referred to as dermoids. Although dermoid cysts are congenital defects and may be recognized at birth, these lesions often escape notice until they become enlarged, inflamed or infected. This typically occurs by early childhood, but diagnosis may be delayed until as late as the sixth decade of life. Dermoid cysts present as firm, non-compressible, non-pulsatile subcutaneous nodules that often reach a size of 1–4 cm in diameter. The lesions usually do not transilluminate. They are most commonly located around the eyes, particularly the lateral eyebrow (Fig. 64.7), but may also be found on the nose, scalp (often over the anterior fontanelle or the midline occiput), neck, sternum, sacrum and scrotum.

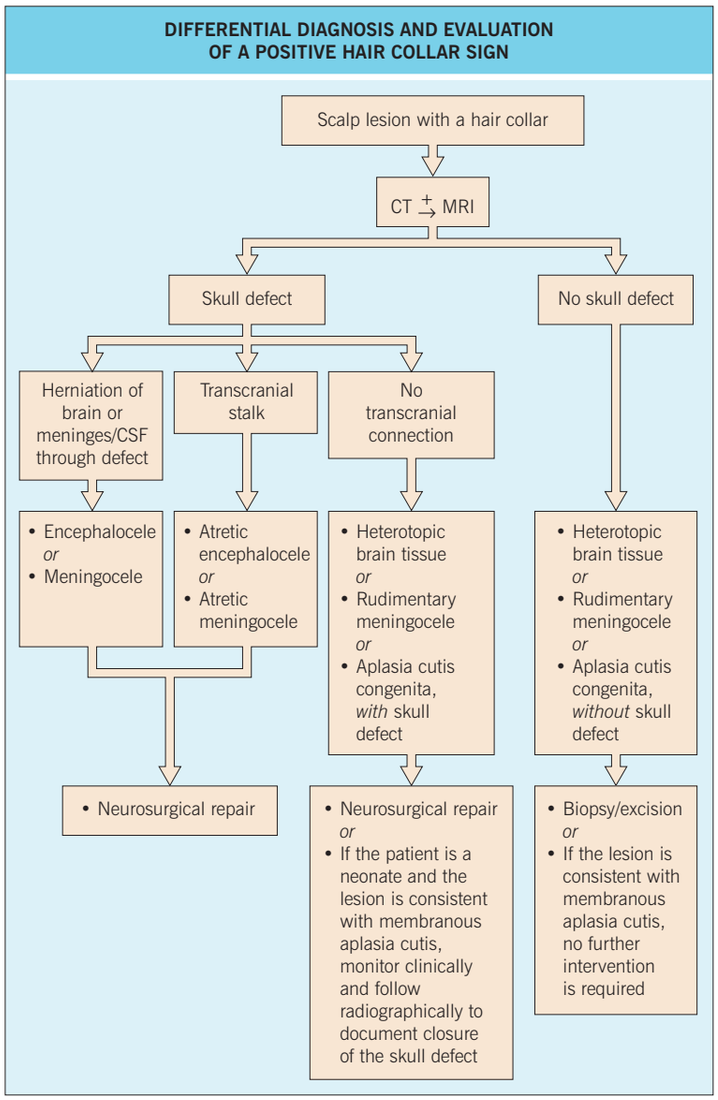


Fig. 64.5 Differential diagnosis and evaluation of a positive hair collar sign. In general, CT is the most accurate method of detecting skull defects. However, if a bony defect is detected by CT, a follow-up evaluation by MRI may be indicated to better determine whether there is extension of soft tissue transcranially.

Fig. 64.6 Sinus pericranii. This venous malformation involving the midline forehead and communicating with an intracranial dermal sinus was evident at birth. Fluctuations in fullness occurred with crying. *Courtesy, Susan Psaila, MD.*

Fig. 64.7 Dermoid cyst. This dermoid cyst presented in an infant as a firm subcutaneous nodule superior to the lateral left eyebrow. *Courtesy, Kalman Watsky, MD.*

Dermoid cysts on the nose or midline scalp have a much higher likelihood of intracranial extension than those in a periocular location[13]. Nasal lesions account for <10% of cervicofacial dermoids. They can occur anywhere from the glabella to the tip of the nose (see above, Midline nasal lesions), and they may result in a widened nasal bridge. The presence of a sinus ostium, which may be heralded by protruding hairs or a sebaceous discharge, increases the risk of intracranial involvement of a nasal dermoid to almost 50%, versus approximately 25% overall[3]. A dermal sinus tract without an associated subcutaneous mass sometimes connects with an intracranial dermoid cyst; this is seen most often on the midline occipital scalp, where especially long hairs may mark the sinus ostium[7]. In addition to infectious complications, a chemical meningitis or even hydrocephalus due to release of keratinous and sebaceous material into the cerebrospinal fluid (CSF) can occur with intracranial dermoid cysts. Lastly, dermoid cysts and dermal sinuses overlying the spine may be associated with occult dysraphism (see below), and, if a tract connects with the subarachnoid space, an increased risk of meningitis.

Histologically, dermoid cysts are lined by keratinizing stratified squamous epithelium and contain mature adnexal structures (see Ch. 110). Malignant degeneration in adulthood is extremely rare. Treatment is by excision, and preoperative imaging studies are required for lesions on the nose, midline scalp or posterior axis in order to exclude a connection to the CNS.

Cephaloceles

Cephalocele is a general term for congenital herniation of intracranial structures through a defect in the skull. *Cranial meningoceles* are herniations in which the sac contains meninges and CSF, while *encephaloceles* contain both meninges and brain (Fig. 64.8). Therefore, by definition, all cephaloceles have an intracranial connection. These lesions result from faulty closure of the cephalic portion of the neural tube during development, and they are much less common than their caudal counterparts (e.g. myelomeningoceles). Cephaloceles occur in approximately 1–3 per 10 000 live births, with a higher incidence in those with a family history of neural tube defects and an approximately 5% risk of neural tube defects in subsequent siblings. They are usually midline or paramedian, occurring most frequently at the occiput or vertex (75%) (see Fig. 64.1), followed by extranasal (e.g. glabella or medial orbit; 15%) and intranasal or pharyngeal (10%) locations[4].

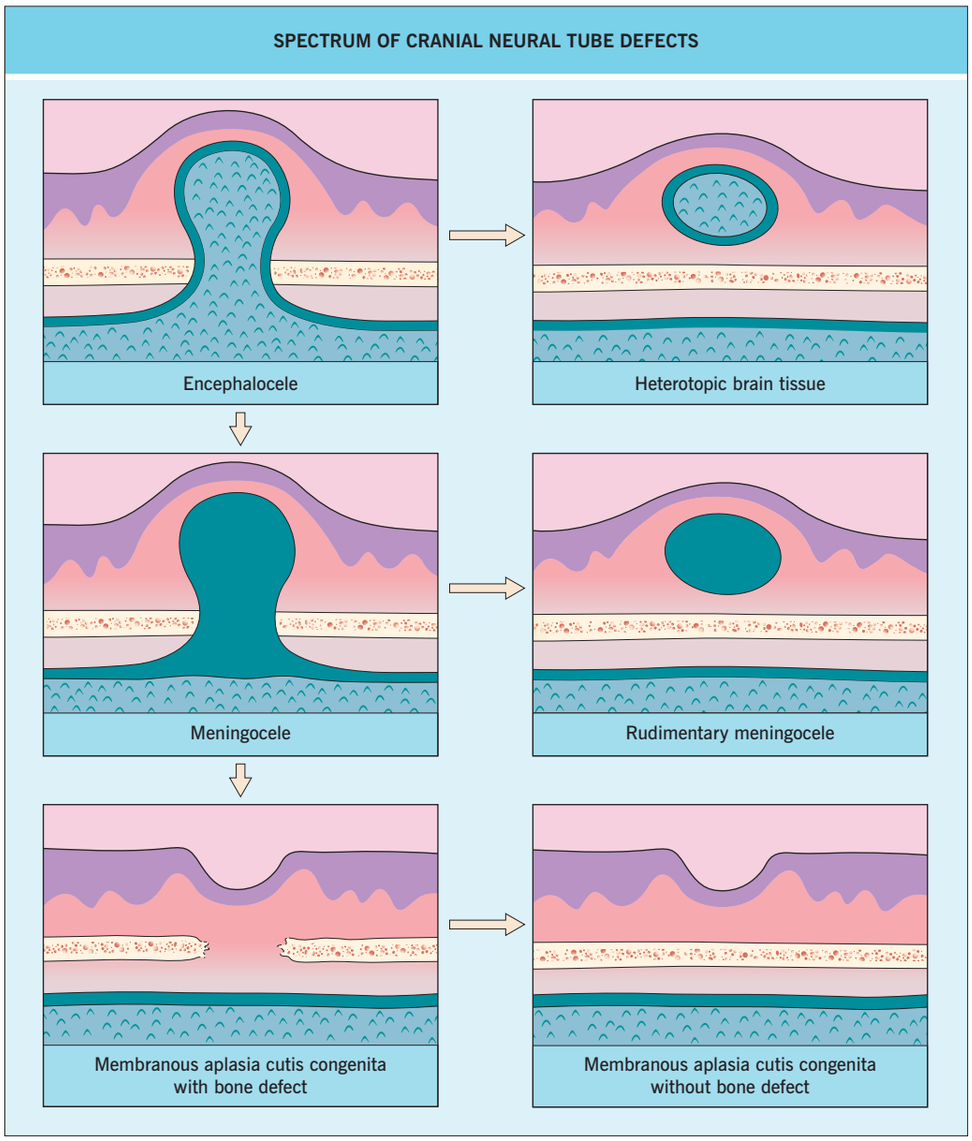


Fig. 64.8 Spectrum of cranial neural tube defects.

Encephaloceles are generally noted early in life due to the resultant deformity. Occasionally, small frontal lesions are misdiagnosed as deep infantile hemangiomas, vascular malformations, hypertelorism or nasal polyps[3,4]; of note, the latter are almost never seen in children younger than 3 years of age.

Cephaloceles typically appear as a soft, compressible, pulsatile mass with a bluish color. They may be covered with either normal skin or a thin, glistening epithelial membrane. The size of cephaloceles varies tremendously, from 1 cm nodules to lesions containing nearly half of the brain, and the size does not necessarily correlate with the extent of the underlying bony defect. Clinical manifestations vary by location. For example, patients with intranasal cephaloceles often present with a broadened nasal bridge but no palpable mass, whereas lesions on the scalp may have an overlying capillary malformation and/or a surrounding hair collar (see above, Midline lesions of the scalp)[8]. Transillumination frequently indicates the presence of CSF; in addition, increased flow of CSF into lesions with crying, the Valsalva maneuver or compression of the jugular veins (Furstenberg test) may result in transient expansion. Leaks of CSF can occur (e.g. CSF rhinorrhea), and patients may have a history of meningitis. Nasal cephaloceles may develop in conjunction with facial clefts and other midline defects, while encephaloceles in particular are often associated with neurologic abnormalities.

On histologic examination, encephaloceles show mature neuroglial tissue embedded in varying amounts of fibrous stroma. Heterotopic brain tissue (see Fig. 64.8) demonstrates similar features, and these lesions cannot be reliably distinguished histologically. When a patient is suspected of having a cephalocele, imaging studies and subsequent neurosurgical repair should be performed as soon as possible.

Nasal gliomas

Synonyms: ■ Nasal cerebral heterotopia ■ Nasal heterotopic brain tissue

Nasal gliomas are masses of heterotopic brain tissue that are located extranasally (e.g. at the nasal root or glabella; 60%), intranasally (30%) or both (10%)[14]. Of note, the nasal glioma, a developmental anomaly with no malignant potential, is an entirely separate entity from the similarly named glioma, a malignant brain tumor. Nasal gliomas result when herniated brain tissue (i.e. an encephalocele) is sequestered extracranially by the bony fusion that forms the base of the skull during development (see Fig. 64.8; see above, Midline nasal lesions). Although a vestigial fibrous stalk connecting with the intracranial space persists in 15–25% of cases[14], unlike encephaloceles, there is no communication with the intracranial leptomeninges or the CSF of the subarachnoid space. Nasal gliomas are present at birth, accounting for <5% of congenital nasal midline masses[3,15], and they typically enlarge in proportion to the growth of the child. Diagnosis is occasionally delayed until adulthood.

An extranasal glioma typically presents as a firm, non-compressible, non-pulsatile, non-transilluminating mass at or just lateral to the nasal

Fig. 64.9 Nasal glioma. A mass was noted on prenatal ultrasound, and this reddish, slightly pedunculated, rubbery nodule was evident at birth. *Courtesy, Mary Chang, MD.*

root (see Fig. 64.9 and Fig. 115.21). The overlying skin is often red with prominent telangiectasias, which may result in misdiagnosis as an infantile hemangioma; however, nasal gliomas do not undergo the proliferative and involutional phases that characterize the latter lesions. Intranasal gliomas may manifest as a widened nasal bridge or a polypoid nodule within the nasal cavity, sometimes protruding from a nostril. They occasionally cause nasal obstruction resulting in respiratory distress, and lesions involving the nasopharynx may be associated with a cleft palate[16]. Excessive lacrimation may occur ipsilateral to nasal gliomas.

Histologically, nasal gliomas demonstrate strands of astrocytes, other glial cells and loosely textured intercellular glial substance interwoven with fibrous tissue. Neurons may or may not be present focally, and there are often prominent dilated blood vessels in the lesion and overlying skin. Immunoperoxidase staining for S100 protein and glial fibrillary acidic protein (GFAP) is positive. After imaging studies to determine whether an intracranial extension is present, nasal gliomas should be surgically excised.

Heterotopic brain tissue and rudimentary meningoceles

Synonyms: ▪ Rudimentary meningoceles – heterotopic meningeal tissue, sequestrated meningoceles, meningeal hamartomas

Heterotopic brain or meningeal tissue is thought to represent an encephalocele or meningocele that has lost its intracranial attachment (see Fig. 64.8). The term *rudimentary meningocele* is preferred for the latter to emphasize its developmental origin and the lack of associated brain tissue[8,17]. The bone underlying heterotopic brain tissue and rudimentary meningoceles is usually intact. However, the spectrum of cranial neural tube defects also includes intermediate forms in which a stalk that connects intracranially remains, but becomes fibrotic with some degree of luminal ablation; these entities are referred to as *atretic encephaloceles* and *atretic meningoceles*[8]. Heterotopic brain tissue may be located in the scalp, orbit, lip and oropharynx, as well as in the nasal area (see above, Nasal glioma); rudimentary meningoceles are usually found on the scalp or overlying the spine[10,17]. These are uncommon congenital anomalies that are diagnosed much less frequently than more fulminant neural tube defects such as encephaloceles.

Heterotopic brain tissue and rudimentary meningoceles typically present as a 1–4 cm solid or cystic subcutaneous nodule, often with a blue–red hue. Occasionally, rudimentary meningoceles have a bullous appearance and are clinically indistinguishable from membranous aplasia cutis[17]. Lesions are often located in the midline occipital or parietal scalp, where they can manifest with alopecia of the overlying skin and/or a surrounding hair collar. An overlying capillary malformation also may be present.

Histologic features of heterotopic brain tissue are as described for nasal glioma. Although classic findings such as cystic cavities lined by meningothelial cells are present in some cases of rudimentary meningocele, the histologic features are often subtle, with meningeal elements simulating the appearance of vascular or loose connective tissue. While signs such as the tendency of meningocytes to encircle collagen bundles and the presence of psammoma bodies may be helpful, immunohistochemical staining for epithelial membrane antigen (EMA) and vimentin are critical in establishing the diagnosis[17]. Because the presence or absence of an intracranial connection cannot be reliably determined by clinical examination, lesions suspected of representing heterotopic neural tissue should be evaluated with imaging studies prior to surgical excision.

Midline cervical clefts

A midline cervical cleft is a rare congenital anomaly resulting from incomplete fusion of the branchial arches in the ventral midline of the neck. Approximately 80 cases have been reported to date in the English-language literature, with a female-to-male ratio of 2 : 1[18]. Midline cervical clefts may be isolated or found in association with a spectrum of other defects, including midline clefts of the lower lip, tongue or mandible, and thyroglossal, branchial cleft or bronchogenic cysts.

Patients present at birth with a vertically oriented, linear cleft on the midline neck at any point between the inferior edge of the mandible and sternum. The lesion is covered with atrophic skin, which is often weeping in the neonatal period. Additional features may include a blind mucosal sinus tract originating from the inferior portion and a skin protuberance at the superior tip. A subcutaneous fibrous cord arising deep to the latter and extending upward to the chin may result in progressive cervical contracture and/or webbing of the neck with extension (pterygium colli medianum).

Histologically, midline cervical clefts consist of parakeratotic stratified squamous epithelium without normal adnexal structures. The subcutis often contains dense connective tissue, and fibrous cords may include bundles of skeletal muscle. In order to prevent progressive deformity, it is recommended that complete surgical excision and closure via multiple Z-plasties be performed within the first year of life. Vertical primary closure is avoided to reduce the risk of cicatricial contracture.

Sternal clefts and supraumbilical raphae

Sternal clefts are rare congenital malformations that result from defective embryologic fusion of paired mesodermal bands in the ventral midline. These lesions most frequently involve the superior sternum, but inferior clefts and a complete bifid sternum can also occur. The skin overlying sternal clefts may be atrophic (Fig. 64.10), scarred or ulcerated, and a dermal sinus tract is occasionally present. Approximately 40% of sternal clefts are associated with large cervicofacial hemangiomas, representing a presentation of the PHACE(S) syndrome (*p*osterior fossa malformations; *h*emangiomas; *a*rterial, *c*ardiac and *e*ye anomalies; *s*ternal cleft/supraumbilical raphe)[19]. Predominantly affecting female infants (female-to-male ratio: 9 : 1), this spectrum of malformations is thought to result from a developmental field defect that occurs between the eighth and tenth weeks of gestation. Of note, the sternal abnormality in PHACE(S) syndrome may be limited to cutaneous atrophy or a pit in the presternal area, with intact underlying bone[20]. For sternal clefts associated with a substantial bony defect, surgical repair can be performed to protect the mediastinal organs and improve respiration as well as cosmesis. A supraumbilical raphe is a midline abdominal defect that presents as a firm, scar-like, linear protuberance extending from the umbilicus cephalad for a few centimeters. Supraumbilical raphae often occur in association with sternal clefts, with or without other features of PHACE(S) syndrome.

Midline Lesions of the Spine

Spinal dysraphism refers to abnormal fusion of dorsal midline structures during embryologic development[21]. This term encompasses a wide variety of congenital spinal defects, ranging from myelomeningoceles

Fig. 64.10 Sternal cleft. Note the atrophic skin overlying the defect and prominent veins in the midline chest. Generalized desquamation is also evident in this 1-day-old post-term neonate. She did not develop an infantile hemangioma and had no cardiac defects or other features of PHACE(S) syndrome.

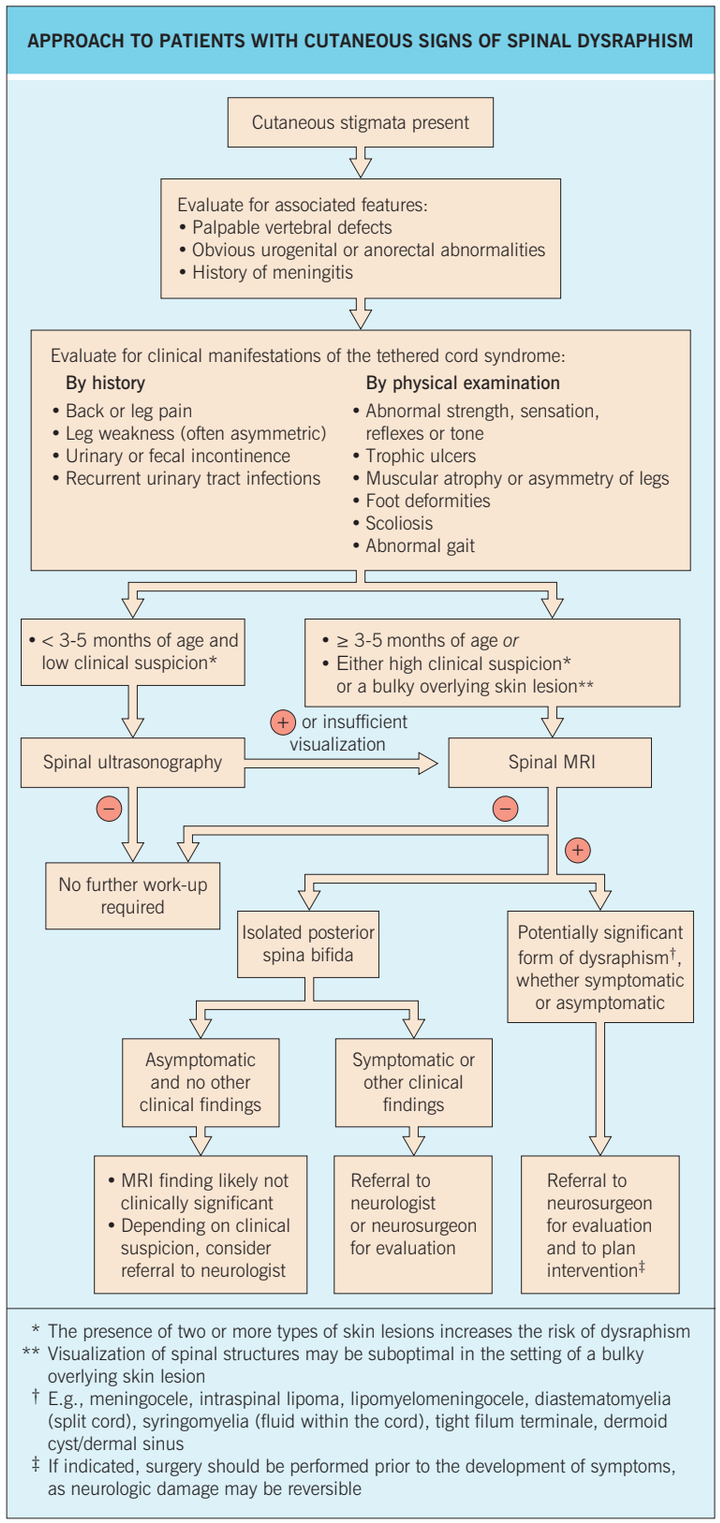


Fig. 64.11 Approach to patients with cutaneous signs of spinal dysraphism.

(protrusion of the spinal cord and meninges with no overlying skin) and other overt anomalies in which neural tissue is exposed (*open spinal dysraphism*) to less obvious, skin-covered malformations (*closed* or *"occult" spinal dysraphism*). The latter include diastematomyelia (a split in the spinal cord), meningoceles, intraspinal lipomas, lipomyelomeningoceles (protrusion of the cord extraspinally into an attached lipoma), tight or fatty filum terminale, dermoid cysts, dermal sinuses and isolated posterior spina bifida[22].

The degree of neurologic impairment associated with closed spinal dysraphism is variable. Any lesion that produces traction and/or pressure can cause progressive damage to the spinal cord, resulting in neurologic symptoms. Whereas isolated posterior spina bifida, an incidental radiographic finding in 15–25% of the general population, is not clinically significant, other forms of dysraphism may become symptomatic by childhood or adolescence. Some patients, however, do not present until adulthood. When diagnosis is delayed, many of the aforementioned malformations can result in the tethered cord syndrome, which occurs when the conus medullaris (normally at the adult position of L1–L2 by 3 months of age) is low-lying and/or immobile. This syndrome is characterized clinically by back pain, urinary incontinence, motor and sensory deficits of the lower extremities, and orthopedic deformities (Fig. 64.11). Occasionally, an acute onset of symptoms is precipitated by childbirth, heavy lifting or spinal trauma. Although neurosurgical intervention can halt progression, neurologic damage is often irreversible. Diagnosis and treatment prior to the development of symptoms is, therefore, critical.

Because the skin and the nervous system share an ectodermal origin, concurrent anomalies of these tissues are common. Midline cutaneous lesions thus serve as a valuable marker for spinal dysraphism, and, in the majority of patients, they are the finding that leads to the diagnosis. Approximately 80% of individuals with closed spinal dysraphism have paraspinal skin abnormalities (with more than one type of skin lesion in the majority of cases)[23,24], compared with <3% of all neonates[25]. Shallow coccygeal dimples and deep gluteal clefts occur in an additional 4% of infants; however, in contrast to dimples located superior to the gluteal cleft (Fig. 64.12), these are considered as normal variants rather than a sign of an underlying malformation[25–27]. Most of the cutaneous lesions associated with spinal dysraphism are located in the lumbosacral area, reflecting the relative rarity of neural tube defects in the cervicothoracic region[28].

Hypertrichosis is the cutaneous marker of spinal dysraphism most often evident at birth. Affected individuals may be born with a V-shaped lumbosacral patch of long, coarse or silky hair on the dorsal midline (Fig. 64.13) known as a "faun tail"[29]. Overall, however, lumbosacral lipomas are the skin lesions most commonly associated with spinal dysraphism[23]. An intraspinal lipoma or lipomyelomeningocele often represents a portion of a larger subcutaneous lipoma, typically presenting as a soft mass located above the gluteal cleft and extending asymmetrically into one buttock. A curved gluteal cleft is suggestive of such a lesion, but clinical findings may be subtle initially, becoming more noticeable with time.

Infantile hemangiomas and vascular malformations located on or near the dorsal midline may also be signs of dysraphism. Infantile hemangiomas associated with spinal anomalies typically span the midline (usually in the lumbosacral area), are superficial (sometimes

Fig. 64.12 Midline deep sacral dimple. The dimple was located above the gluteal cleft in association with a small tail. In contrast, a shallow dimple within the gluteal cleft is a common finding and not a sign of spinal dysraphism. *Courtesy, Seth J Orlow, MD, PhD.*

Fig. 64.13 Hypertrichosis associated with spinal dysraphism. A Circumscribed midline hypertrichosis overlying the lower thoracic spine in an adult with occult dysraphism. The patient periodically trims the hairs. **B** V-shaped patch of long, coarse hair on the mid back in a boy born with a large thoracic myelomeningocele. Severe scoliosis remains after multiple surgeries. *A, Courtesy, Jean L Bolognia, MD.*

with minimal growth beyond reticular erythema and telangiectasias), and tend to have a segmental pattern (Fig. 64.14; see Ch. 103)[30–32]. A patient with an isolated midline lumbosacral hemangioma >2.5 cm in diameter has an approximately 35% risk of having spinal dysraphism, which is higher if the hemangioma is larger, ulcerated or associated with additional cutaneous markers[32]. Several acronyms have been proposed for the constellation of regional extracutaneous anomalies that can occur in individuals with segmental hemangiomas of the lower body, and the most inclusive is ***LUMBAR*** *syndrome*: ***L***, *l*ower body/*l*umbosacral hemangioma and *l*ipomas or other cutaneous anomalies (e.g. "skin tags"); ***U***, *u*rogenital anomalies and *u*lceration; ***M***, *m*yelopathy (spinal dysraphism); ***B***, *b*ony deformities; ***A***, *a*norectal and *a*rterial anomalies; ***R***, *r*enal anomalies. Of note, a telangiectatic patch overlying a spinal defect may actually represent an early or "minimal growth" hemangioma (when found in a neonate or infant/young child, respectively) or the residua after involution of a hemangioma (when found in an older patient).

Vascular malformations are most often an indicator of dysraphism when they occur together with other midline cutaneous lesions (most notably lipomas). In Cobb syndrome (cutaneomeningospinal angiomatosis), capillary malformation- or angiokeratoma-like lesions found in a dermatomal distribution are contiguous with an arteriovenous malformation in the corresponding segment of the spinal cord, and neurologic manifestations of cord compression can develop (see Ch. 104). Lastly, the common occipital capillary stain ("stork bite"), a form of nevus simplex (salmon patch), is *not* a marker for a spinal defect. Lumbosacral capillary stains often have rhomboidal or triangular shapes ("butterfly-like") and are frequently associated with additional nevus simplex lesions of the head, neck and (occasionally) upper back. Many authors feel that regardless of spinal level, capillary stains alone are rarely a sign of dysraphism[26,28]. A prospective study of 3623 neonates found that 1 of the 25 individuals noted to have a sacral capillary stain in the absence of other lumbosacral skin lesions had a spinal abnormality revealed by imaging studies[33].

Cutaneous lesions of the spinal axis that should alert the clinician to the possibility of dysraphism are summarized in Table 64.2. In one study[27], 39% (22/56) of neonates with "high-risk" stigmata (e.g. hypertrichosis, subcutaneous masses, hemangiomas, tails, or dimples above the gluteal cleft) were found to have spinal dysraphism (see Figs 64.13 & 64.14). The presence of two or more skin lesions is a particularly strong sign; in another series, 61% (11/18) of such patients had spinal dysraphism, compared to 8% (3/36) of those with only one skin lesion[34].

High-risk cutaneous stigmata overlying the spine represent an indication for radiologic evaluation, and superficial removal for cosmetic reasons is contraindicated until an underlying abnormality is excluded. The most sensitive modality is MRI, which is the study of choice in patients ≥3–5 months of age. As the vertebrae are not yet completely ossified in infants <3–5 months of age, ultrasonography may serve as a rapid, relatively inexpensive screening tool, allowing sufficient visualization of the spinal cord and canal to exclude dysraphism in many unaffected patients. However, MRI is required preoperatively to better define any positive ultrasonographic findings and to confirm a negative study when visualization of spinal structures is suboptimal, which often occurs in the setting of bulky overlying skin lesions (e.g. lipomas, tags and hemangiomas)[35]. In infants found to have anomalies with the potential to cause traction and/or pressure on the spinal cord, neurosurgical intervention during infancy may be recommended. Figure 64.11 provides an algorithm for the approach to patients with cutaneous signs of spinal dysraphism.

APLASIA CUTIS CONGENITA

Synonyms: ■ Cutis aplasia ■ Congenital absence of skin ■ Congenital scars

Fig. 64.14 Multiple midline cutaneous stigmata overlying the sacral spine. This infant with a segmental distribution of infantile hemangiomas in the lumbosacral area, a dimple, a pseudotail and a deviated gluteal cleft had an underlying lipomeningomyelocele.

SKIN LESIONS OF THE SPINAL AXIS ASSOCIATED WITH DYSRAPHISM	
Lesion	**Features**
Hypertrichosis	A V-shaped patch of long, coarse or silky hair ("faun tail") (Fig. 64.13)
Lipomas	Soft subcutaneous mass, asymmetric buttocks, curved gluteal cleft (Fig. 64.14)
Dimples	Above the gluteal cleft or >2.5 cm from the anal verge in neonates (Figs 64.12 & 64.14); >0.5 cm in size or deep*
Dermal sinuses	Hair may be present at the ostium*
Acrochordons	May be associated with a dimple or dermal sinus
Pseudotails	Caudal protrusion due to prolonged vertebrae or hamartomatous elements, e.g. adipose tissue or cartilage (Fig. 64.14)
True tails	Persistent vestigial appendage with a central core of mature adipose tissue, muscle, blood vessels and nerves
	May be capable of spontaneous or reflex motion
Infantile hemangiomas	Superficial, usually segmental pattern (Fig. 64.14), often ulcerated
Telangiectasias	May represent an early, minimal/arrested growth or regressed infantile hemangioma
Capillary malformations (CM)	Typically found together with other skin lesions
	Cobb syndrome: CM- or angiokeratoma-like lesions in a dermatomal distribution associated with a spinal arteriovenous malformation
Aplasia cutis congenita (ACC)	Ulcer, scar, or atrophic skin
Connective tissue nevus	Typically found together with other skin lesions
Hypo/depigmentation	May represent a nevus depigmentosus (typically found together with other skin lesions) or the residua of ACC
Hyperpigmentation	Typically found together with other skin lesions
Congenital melanocytic nevi	Spinal dysraphism has been reported in patients with neurocutaneous melanosis
Subcutaneous masses	May represent meningoceles, lipomyelomeningoceles, teratomas, ependymomas or plexiform neurofibromas

*Due to a potential risk of meningitis, these lesions should not be probed.

Table 64.2 Skin lesions of the spinal axis associated with dysraphism. The presence of two or more types of lesions increases the risk of a spinal anomaly.

Fig. 64.15 Facial aplasia cutis congenita. Atrophic cutaneous defect extending from the lateral eyebrow to the anterior hairline in a patient with Setleis syndrome. Note the upward-slanting eyebrows and "leonine" facial appearance. *Courtesy, Seth Orlow, MD, PhD.*

Fig. 64.16 Preauricular skin defects. Multiple discrete, round, atrophic skin defects in an infant, extending from the scalp line toward the angle of the mouth in a strikingly linear arrangement (arrows). *Courtesy, Jean L Bolognia, MD.*

Aplasia cutis congenita (ACC) is a condition in which localized or widespread areas of skin are absent or scarred at birth. It may occur as an isolated defect, in association with other developmental anomalies, or as a feature of a variety of disorders (Tables 64.3 & 64.4). There is no single underlying cause of ACC, which simply represents a physical finding that reflects an abnormality in intrauterine skin development. The many possible etiologies include genetic factors, vascular compromise, trauma, teratogens and intrauterine infections[36].

As a result of its causal heterogeneity, the clinical appearance of ACC at birth is extremely variable, ranging from an erosion or deep ulceration to a scar (as a consequence of healing *in utero*) to a discrete ovoid defect covered by a membrane. The latter, referred to as *membranous aplasia cutis*, is the most common form. Occurring primarily on the scalp and often surrounded by a "hair collar" (see Figs 64.3 & 64.4; see above, Midline lesions of the scalp), such lesions may represent a forme fruste of a neural tube defect[2]. However, membranous aplasia cutis can also be seen along the embryonic fusion lines of the face (Table 64.4; Figs 64.2, 64.15 & 64.16)[37,38]. Membranous aplasia cutis typically presents at birth as a sharply marginated ("punched-out"), oval or round defect covered by a thin, translucent, glistening epithelial membrane. Lesions may contain serous fluid in the neonatal period, resulting in a bullous appearance (see Fig. 64.4). Eventually, they flatten and transform into an atrophic scar (Fig. 64.17A).

A second major type of ACC consists of stellate or angulated lesions, which are thought to result from vascular abnormalities and/or intrauterine ischemic events. Examples include irregular midline scalp defects in Adams–Oliver syndrome[39,39a] and extensive, symmetric lesions on

CLASSIFICATION SCHEME FOR APLASIA CUTIS CONGENITA (ACC)			
	Inheritance	**Features**	**Associated abnormalities**
Group 1: Scalp ACC without multiple anomalies	Sporadic > AD	Usually at the vertex Membranous Hair collar	**No associated abnormalities** **Isolated abnormalities** (most often associated with membranous ACC): cleft lip and/or palate, tracheoesophageal fistula, high myopia and cone-rod dysfunction, patent ductus arteriosus, intestinal lymphangiectasia, omphalocele, polycystic kidneys, double cervix and uterus, mental retardation, temporal triangular alopecia
	Often AD	Usually at the vertex Irregular and scar-like	
Group 2: Scalp ACC associated with Adams–Oliver syndrome	AD > AR	Midline scalp Often large, irregular lesions Skull defect Dilated scalp veins	**Adams–Oliver syndrome**: terminal transverse limb defects (e.g. reductions, syndactyly, nail dystrophy), cutis marmorata telangiectatica congenita, cardiac malformations, CNS abnormalities; caused by dominant mutations in the Rho GTPase activating protein 31 gene (*ARHGAP31*) or recessive mutations in the dedicator of cytokinesis 6 gene (*DOCK6*); both of these genes encode proteins with roles in organizing the actin cytoskeleton via regulation of Rho GTPases
Group 3: Scalp ACC associated with epidermal and organoid nevi (and, occasionally, large congenital melanocytic nevi)	Sporadic (may represent a form of twin spotting; see Ch. 55)	Scalp, often unilateral Membranous	**Epidermal nevus or nevus sebaceus**, usually in proximity to the ACC **Large congenital melanocytic nevus**: in a few reports* **Ipsilateral ophthalmologic abnormalities**: corneal opacities, scleral dermoids, eyelid colobomas, retinal dystrophy **CNS abnormalities**: psychomotor retardation, seizures
Group 4: ACC overlying embryologic malformations	Variable	Scalp, often with a hair collar if overlying a neural tube defect Lumbosacral Chest, abdomen	**Cranial malformations**: cephalocele, heterotopic brain or meningeal tissue, congenital midline porencephaly, holoprosencephaly, cranial stenosis, leptomeningeal vascular malformation, posterior fossa arteriovenous fistula **Spinal malformations**: occult dysraphism, myelomeningocele **Thoracic malformations**: sternal cleft **Abdominal malformations**: omphalocele, gastroschisis **Multiple malformations associated with generalized, lethal ACC ('systemic' ACC)**: corneal opacities, choanal atresia, hypoplastic lungs, absent greater omentum, intestinal malrotation & atresias, hepatosplenomegaly, skull defects, syndactyly, anonychia
Group 5: ACC associated with fetus papyraceus, placental infarcts or other ischemic events	Sporadic	Scalp, chest, flanks, axillae and/or extremities (see Fig. 64.18) Multiple, symmetric Stellate/angulated configuration	**Associated fetus papyraceus** due to second-trimester death of twin/triplet or fetal reduction of higher-order pregnancies **Placental infarction**, single umbilical artery **Duodenal, ileal and/or biliary atresias with intestinal infarction** Volkmann ischemic contracture of the forearm Intracranial hemorrhage/CNS abnormalities Amniotic bands, clubbed hands/feet, nail dystrophy
Group 6: ACC associated with EB	AD or AR, depending on EB type	Lower extremities ("Bart syndrome") or large areas of the trunk and extremities	**Simplex, junctional and dystrophic types of EB**: blistering of skin and/or mucous membranes, skin fragility, nail dystrophy **In more severe cases (most associated with junctional EB)**: pyloric atresia, ureteral stenosis, renal abnormalities, arthrogryposis, abnormal ears and nose, amniotic bands
Group 7: ACC localized to extremities without blistering	AD or AR	Pretibial areas, extensor forearms, dorsal hands and feet	**Radial dysplasia** (associated with ACC on the extensor forearm)
Group 8: ACC caused by specific teratogens, maternal conditions or intrauterine infections	Not inherited	Scalp with drugs Any site with congenital infections	**Methimazole (thiamazole), carbimazole**: imperforate anus, urachal malformations **Misoprostol** **Low-molecular-weight heparin** **Valproic acid** **Maternal antiphospholipid syndrome** **Intrauterine varicella, herpes simplex or rubella infection**: signs of these infections
Group 9: ACC associated with malformation syndromes	Variable	Variable	See Table 64.4 **Amniotic band sequence and disorganization syndrome** (see text)

*Referred to as "SCALP" syndrome (*s*ebaceous nevus, *C*NS malformations, *A*CC, *l*imbal dermoid, *p*igmented nevus).

Table 64.3 Classification scheme for aplasia cutis congenita (ACC). Bold text in column 4 signifies main topics, followed by details. AD, autosomal dominant; AR, autosomal recessive; CNS, central nervous system; EB, epidermolysis bullosa. *Adapted from Frieden IJ. J Am Acad Dermatol. 1986;14:646–60, with permission.*

the trunk and/or extremities associated with fetus papyraceus, placental infarction and other forms of vascular insufficiency (Fig. 64.18)[40]. These defects usually appear as ulcers of variable depth with a raw, hemorrhagic or granulating base (Fig. 64.17B,C).

Other patterns of ACC include a lack of skin overlying embryologic malformations, either obvious or occult, and large erosions with jagged borders on the extremities of neonates with epidermolysis bullosa. The latter likely result from the mechanical trauma of fetal movements in a setting of increased skin fragility. The morphology and distribution of the skin defects (see Fig. 64.18) as well as the presence or absence of associated abnormalities represent important clues to the etiology of ACC. Table 64.3 presents a classification scheme for ACC based on these features, and Table 64.4 describes several syndromes associated with ACC. However, because ACC is a physical finding that may result from *any* intrauterine event that disrupts skin development, not all cases can be neatly categorized. Unusual presentations of ACC range from an isolated defect on the ventral penis to an extreme form with absence of skin and subcutaneous tissue over >90% of the body surface area associated with extracutaneous anomalies ("systemic" ACC; see Table 64.3).

The scalp is the most common site for ACC, accounting for >85% of solitary lesions. The majority of cases of scalp ACC, whether membranous or irregular and scar-like, are located at or near the vertex, in proximity to the parietal hair whorl[41]. Approximately 25% of patients

SYNDROMES ASSOCIATED WITH APLASIA CUTIS CONGENITA (ACC, GROUP 9)			
	Inheritance	**Features of ACC**	**Other features**
		FACIAL ACC (SEE FIG. 64.2)	
Brauer lines & Setleis syndrome (bitemporal ACC, focal facial dermal dysplasia)	**Brauer lines:** AD, variable penetrance and expressivity **Setleis syndrome:** AR	Bilateral temples, from lateral eyebrow to anterior hairline* Round or oval, membranous Linear arrangement	**Brauer lines:** no additional abnormalities **Setleis syndrome**: *TWIST2* gene (encoding a transcription factor); abnormal eyelashes, upward-slanting eyebrows, "leonine" facies (Fig. 64.15)
Preauricular skin defects (focal facial dermal dysplasia)	?	Bilateral, from preauricular cheek to angle of mouth† Round or oval, membranous, often with a hair collar Linear arrangement (Fig. 64.16)	No additional abnormalities
Microphthalmia with linear skin defects syndrome (MIDAS syndrome	X-linked dominant	Mid-cheek to bridge of nose Also may occur on neck Stellate erosions that heal with reticulolinear scarring	*HCCS* gene (holocytochrome c synthase); microphthalmia, sclerocornea, agenesis of the corpus callosum, genital anomalies, short stature
		SCALP ACC	
Adams–Oliver syndrome (see Table 64.3, ACC group 2)			
Oculocerebrocutaneous syndrome (Delleman syndrome)	Sporadic or AD	Membranous on supra-auricular scalp (often crescentic shape) Also may occur on neck and lumbosacral area	Orbital cysts, microphthalmia, giant tectum-absent vermis, agenesis of the corpus callosum, facial appendages composed of skeletal muscle
Oculoectodermal syndrome	?AD	Membranous	Epibulbar dermoids, macrocephaly, truncal hyperpigmentation
Johanson–Blizzard syndrome	AR	Stellate or membranous	*UBRI* gene (ubiquitin-protein ligase); dwarfism, hypoplastic nasal alae, hypodontia/peg-like teeth, deafness, microcephaly, hypothyroidism, pancreatic insufficiency
Scalp–ear–nipple syndrome (Finlay–Marks syndrome)	AD	May heal with hypertrophic scarring	Nipple/breast hypo- or aplasia, abnormal ears and teeth, nail dystrophy, syndactyly, reduced apocrine secretion
Trisomy 13 (Patau syndrome)	Sporadic	Membranous Large defects	Holoprosencephaly, ocular abnormalities, deafness, cleft lip/palate, cardiac malformations, polydactyly, narrow and convex nails; early death
4p- (Wolf–Hirschhorn) syndrome	Sporadic	Midline	Microcephaly, ocular abnormalities, cleft lip/palate, preauricular pits and accessory tragi; often early death

*Along the embryonic fusion line between the frontonasal prominence and the maxillary prominence of the first branchial arch.
†Along the embryonic fusion line between the maxillary and mandibular prominences of the first branchial arch.

Table 64.4 Syndromes associated with aplasia cutis congenita (ACC, group 9). ACC also may be found in patients with Goltz syndrome (focal dermal hypoplasia), branchio-oculo-facial syndrome, and several types of ectodermal dysplasias, including the EEC syndrome (*e*ctrodactyly, *e*ctodermal dysplasia, *c*lefting), AEC syndrome (*a*nkyloblepharon, *e*ctodermal dysplasia, *c*left lip/palate) and tricho-odonto-onychial dysplasia. In addition, there have been reports of scalp ACC in patients with Pallister–Killian syndrome (tetrasomy 12p), Opitz syndrome, popliteal pterygium syndrome, Marshall syndrome, and hereditary sensory and motor neuropathy type I (www.ncbi.nlm.nih.gov/omim). AD, autosomal dominant; AR, autosomal recessive; MIDAS, microphthalmia, dermal aplasia and sclerocornea.

have more than one lesion, and multiple membranous lesions may occur in a linear arrangement. Most defects are 1–2 cm in diameter, although the size can range from 0.5 to >10 cm. Scalp ACC involves the underlying skull in 20–30% of cases[42]. Large, irregular lesions are more likely to extend to deeper structures and may affect the dura and/or leptomeninges. Dilated scalp veins may also be seen in association with ACC, especially in patients with Adams–Oliver syndrome (see Table 64.3)[39].

Histologic features of membranous aplasia cutis include an atrophic, flattened epidermis, replacement of the dermis by loose connective tissue, and an absence of adnexal structures. Findings in other types of ACC vary but lesions that have healed generally show scarring and a lack of adnexa. Although histologic examination may be helpful in some instances, the diagnosis of ACC is primarily clinical.

Cutaneous defects noted at birth may be erroneously attributed to obstetric trauma, such as injuries from forceps or fetal scalp electrodes. In many cases, particularly in the setting of affected family members, the diagnosis is made retrospectively when characteristic scarring is observed later in life. Evaluation of a patient with ACC is directed by the history (including obstetric and family history) and physical examination, and, in a neonate, it may include specific investigations such as examination of the placenta and viral studies for herpes simplex and varicella zoster (Fig. 64.17D)[43]. In patients with large, deep, irregular or membranous lesions of the scalp (Fig. 64.17B,E), imaging studies are indicated to assess for underlying bone defects, vascular anomalies or brain malformations. Lastly, elevated α-fetoprotein in midtrimester maternal serum and amniotic fluid as well as elevated acetylcholinesterase in the amniotic fluid may represent early signs of ACC, although they are neither sensitive nor specific for this condition.

Most small lesions of ACC heal within the first few months of life, leaving an atrophic (see Fig. 64.17A) or, less often, hypertrophic ("lumpy") scar. In such instances, daily cleansing and application of a topical antibiotic ointment until healing is complete are often the only interventions required. Underlying skull defects also tend to resolve spontaneously during infancy. However, potential complications of deep ACC of the scalp include life-threatening sagittal sinus hemorrhage/thrombosis and meningitis. Because the risk of complications increases if the period of healing is prolonged, early surgical repair of large stellate scalp lesions or those associated with a dural defect or exposure of the sagittal sinus is recommended. Preoperative imaging studies are required to identify underlying vascular structures. Even without surgical intervention, residual scarred, hairless areas generally become less conspicuous as the child grows. If desired for cosmetic reasons, excision or hair transplants can be performed later in life.

Fig. 64.17 Aplasia cutis congenita (ACC). A This hairless, round, scarred plaque on the scalp of a 6-month-old was present at birth. **B** Stellate ACC on the midline scalp of a neonate. This hemorrhagic lesion was associated with an underlying skull defect and cerebrovascular anomalies. **C** Stellate ACC on the lateral trunk of a neonate born of an initial sextuplet gestation for which fetal reduction was performed. The lesions had a bilateral, symmetric distribution. **D** ACC resulting from congenital varicella. Note the sharply demarcated, deep ulcer on the lower abdominal wall. **E** Membranous ACC associated with a large defect of the underlying skull in a patient with Goltz syndrome. *A, Courtesy, Anthony J Mancini, MD.*

OTHER DEVELOPMENTAL ANOMALIES

Congenital Lip Pits

Synonyms: ■ Lip sinuses ■ Congenital sinuses of the lower lip ■ Midline sinuses of the upper lip

Congenital lip pits are divided into three types based on their location: (1) commissural; (2) upper lip; and (3) lower lip. Commissural lip pits are by far the most common, occurring in 1–2% of newborns. Lip pits likely result from defective embryologic fusion of facial processes with epithelial entrapment. They usually represent the opening of a blind sinus tract, which can extend inward through the orbicularis oris muscle to a depth of >10 mm. This tract occasionally communicates with the ducts of underlying minor salivary glands, and saliva or mucus may drain from the ostium. Lesions are sometimes associated with swelling of the lip or, particularly if located on the philtrum, recurrent infection.

Commissural lip pits are typically found bilaterally in the mucosal surface at the angles of the mouth (Fig. 64.19A). Although most often an isolated anomaly, they may be inherited in an autosomal dominant fashion along with preauricular pits and hearing impairment in patients with a form of branchio-otic syndrome linked to chromosome 1q31[44].

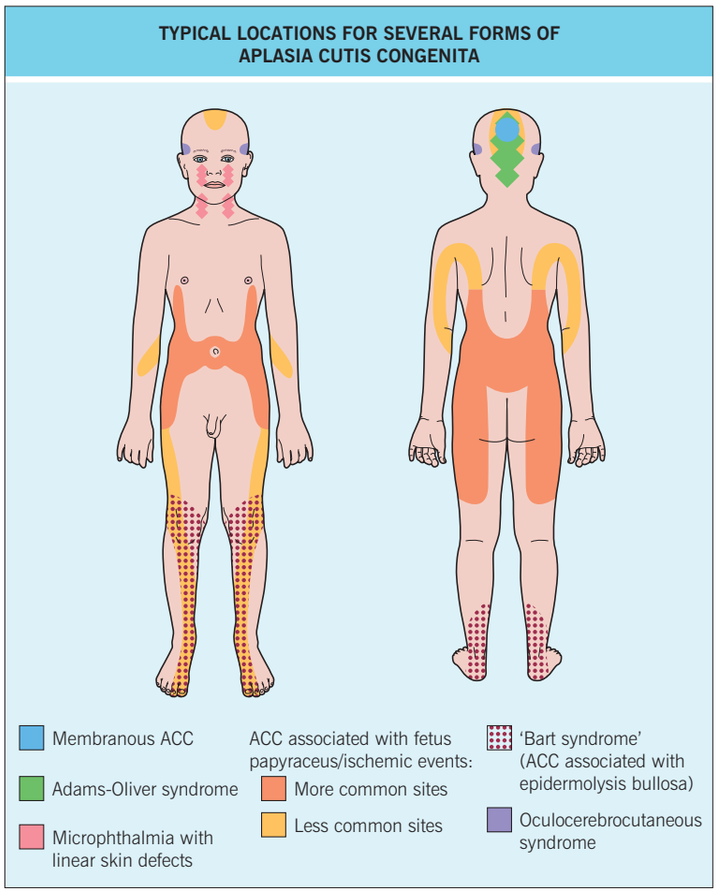


Fig. 64.18 Typical locations for several forms of aplasia cutis congenita (ACC). See Figure 64.2 for Brauer lines/Setleis syndrome, preauricular membranous ACC and another depiction of microphthalmia with linear skin defects.

DISEASES AFFECTING THE SKIN THAT ARE ASSOCIATED WITH CLEFT LIP AND/OR PALATE	
Syndrome	**Other features**
Ectodermal dysplasias (see Ch. 63)	
• EEC syndrome	AD, *p63* gene; *e*ctodermal dysplasia, *e*ctrodactyly, *c*left lip/palate
• AEC syndrome	AD, *p63* gene; *a*nkyloblepharon, *e*ctodermal dysplasia, *c*left lip/palate
• Cleft lip/palate– ectodermal dysplasia*	AR, nectin-1 (*PVRL1*) gene; ectodermal dysplasia, pili torti, syndactyly
Branchio-oculo-facial syndrome	See text – branchial cleft sinuses
Oral–facial–digital syndrome, type 1	X-D, *OFD1* gene; lobulated tongue, hypertrophic oral frenula, digital malformations, whorled alopecia of the vertex, transient facial milia, polycystic kidneys, CNS anomalies
Oculocerebrocutaneous syndrome	See Table 64.4
4p- syndrome (Wolf–Hirschhorn syndrome)	See Table 64.4
Pai syndrome	Facial skin tags, nasal polyps, CNS lipomas
Nevoid basal cell carcinoma syndrome	See Ch. 107
Goltz syndrome (focal dermal hypoplasia)	See Ch. 62
Waardenburg syndrome, type 1 or 3	See Ch. 66
Van der Woude syndrome†	See text – congenital lip pits
Popliteal pterygium syndrome†	See text – congenital lip pits
Nail–patella syndrome	See Ch. 71
Beare–Stevenson cutis gyrata syndrome	AD, *FGFR2* gene; craniosynostosis, cutis gyrata, acanthosis nigricans
LOCAL LESIONS	
Dermal melanocytosis	
Encephaloceles or nasal gliomas	

*Includes Zlotogora–Ogur syndrome, Rosselli–Gulienetti syndrome, and Margarita Island ectodermal dysplasia.
†Allelic disorders.

Table 64.5 Diseases affecting the skin that are associated with cleft lip and/or palate. Other disorders associated with cleft lip/palate that also can affect the skin include Cornelia de Lange, Roberts, Simpson–Golabi–Behmel, Pallister–Hall and CHIME (colobomas [ocular], *h*eart defects, *i*chthyosis, *m*ental retardation and *e*ar anomalies) syndromes, hemifacial microsomia, Meige disease (familial lymphedema praecox) and trisomy 13. AD, autosomal dominant; AR, autosomal recessive; CNS, central nervous system; *PVRL1*, poliovirus receptor-related 1; X-D, X-linked dominant.

Fig. 64.19 Lip pits.
A Bilateral commissural lip pits, representing an incidental finding.
B Bilateral paramedian lower lip pits, each located on the apex of a conical elevation. This was an isolated, asymptomatic anomaly.

Commissural lip pits also have been described in association with alveolar synechiae, ankyloblepharon filiforme adnatum (congenital adhesions between the upper and lower eyelids and ectodermal defects.

Upper lip pits, also known as midline sinuses of the upper lip, are rare. These lesions are typically located along the philtrum. They usually occur as an isolated defect, but they may be associated with hypertelorism and other dysmorphic facial features. In addition, bilateral paramedian upper lip pits may be found in patients with the branchio-oculo-facial syndrome (see below, Branchial cleft sinuses and fistulae).

Lower lip pits may be an isolated finding or seen as a part of Van der Woude syndrome, which is characterized by paramedian pits in the vermilion portion of the lower lip, cleft lip and/or palate, and hypodontia. The lip pits are usually bilateral, and they may be located on the apex of a conical elevation (Fig. 64.19B). Van der Woude syndrome occurs in approximately 1–3 per 100 000 live births, is inherited in an autosomal dominant fashion, and is caused by mutations in the interferon regulatory factor 6 gene (*IRF6*)[45]. Another condition in which lower lip pits are a feature, the popliteal pterygium syndrome, is allelic with Van der Woude syndrome. Additional findings in the popliteal

Fig. 64.20 Accessory tragi. Multiple skin-colored papulonodules in a typical preauricular location as well as on the mandibular cheek.

pterygium syndrome include cleft lip and/or palate, syngnathia, popliteal webbing, nail dysplasia, syndactyly and genital anomalies. Lastly, lower lip pits are occasionally seen in oral–facial–digital syndrome type I (see Table 64.5) and Kabuki syndrome (www.ncbi.nlm.nih.gov/omim).

Histologically, the sinus tracts associated with lip pits are lined by stratified squamous epithelium; associated salivary or mucous glands are occasionally observed. The evaluation of patients with lip pits should include a family history and a physical examination to exclude associated anomalies. If lip pits of any type are symptomatic or cosmetically undesirable, surgical excision is the treatment of choice. The extent of the sinus can be estimated preoperatively by injection of a radiopaque contrast medium.

Accessory Tragi

Synonyms: ▪ Preauricular tags ▪ Preauricular appendages

Accessory tragi are relatively common congenital anomalies of the first branchial arch, and they are found in approximately 3–6 per 1000 live births. Familial occurrence has been reported, sometimes with a consistent anatomic site within kindreds. During development, the external ear is formed by the fusion of six tubercles, three each from the first and second branchial arches; the tragus and anterior crus of the helix are the only portions of the ear derived from the former[46]. Whereas preauricular pits and cysts reflect defective fusion of the tubercles (see Ch. 110), accessory tragi represent remnants of and/or extra tubercles originating from the first branchial arch.

Accessory tragi typically manifest as skin-colored papules or nodules in the preauricular area, but they also may be found on the mandibular cheek (Fig. 64.20) or on the neck along the anterior border of the sternocleidomastoid muscle (also referred to as congenital cartilaginous rests of the neck, see below)[47]. The latter locations reflect the embryologic migration of the external ear from the neck to the side of the head as the mandible develops. Although most often solitary, accessory tragi may be multiple (see Fig. 64.20), and they are bilateral in approximately 10% of cases. They can be either soft or firm due to a cartilaginous core, and they are commonly covered by vellus hairs[46].

Although they usually represent an isolated malformation, accessory tragi are sometimes associated with other developmental anomalies of the first branchial arch, such as cleft lip and palate[48]. Together with ipsilateral facial hypoplasia, ear deformities, epibulbar dermoids and vertebral abnormalities, accessory tragi are a cardinal feature of hemifacial microsomia (Goldenhar syndrome). Accessory tragi may be seen in a number of other multiple congenital anomaly syndromes, including Nager acrofacial dysostosis, Townes–Brocks syndrome, Treacher Collins–Franceschetti syndrome, VACTERL association, Wildervanck syndrome and Wolf–Hirschhorn syndrome (www.ncbi.nlm.nih.gov/omim). Isolated accessory tragi may be associated with an increased risk of hearing impairment, but recent large controlled studies have failed to confirm a purported association between isolated accessory tragi and urinary tract abnormalities.

Histologically, accessory tragi show numerous tiny, mature hair follicles, a prominent connective tissue framework within abundant subcutaneous fat, and often a central plate of elastic cartilage. When accessory tragi are surgically excised for cosmetic reasons, care must be taken to remove any protruding portion of underlying cartilage[47]. Evaluation of an infant with an accessory tragus should include assessment of hearing and examination for other dysmorphic features.

Congenital Cartilaginous Rests of the Neck

Synonyms: ▪ Wattles ▪ Cervical accessory tragi

Congenital cartilaginous rests of the neck are branchial arch remnants that are considered to be the cervical variant of accessory tragi (see above). The alternative term "wattle" refers to the fleshy appendage that hangs from the throat of certain animals, such as turkeys and goats. Typically located over the lower anterior border of the sternocleidomastoid muscle, these asymptomatic lesions may be unilateral or bilateral, and they are not cystic or fistulous. They may be attached to the underlying fascia by a fibrous band, which can be safely transected if excision is desired[49].

Branchial Cleft Sinuses and Fistulae

Synonym: ▪ Lateral cervical sinuses and fistulae

Branchial cleft sinuses most often represent remnants of the second branchial cleft. Unlike the more common branchial cleft cysts that lack a primary cutaneous opening and typically present in older children and adults (see Ch. 110), these lesions are usually detected at birth or during the first few years of life. In the majority of cases, a sinus ostium (frequently with discharge of mucus) is noted on the lateral lower third of the neck along the anterior border of the sternocleidomastoid muscle; the associated tract extends superiorly in the subcutis, and it may be palpable. The less common first branchial cleft sinus can manifest with a cutaneous opening located higher on the neck or in the periauricular region. Approximately 70% of branchial cleft sinuses are located on the right neck and 5–10% are bilateral. There may be a history of recurrent infection, and a skin tag, sometimes with a cartilaginous component, can mark the ostium. Most branchial sinus tracts end blindly, but occasionally there is a fistulous connection with the tonsillar fossa of the pharynx or the external auditory canal[50].

Although usually an isolated malformation, branchial cleft sinuses and fistulae are also features of several multiple congenital anomaly syndromes. These include the branchio-otic and branchio-oto-renal syndromes, autosomal dominant disorders that are further characterized by ear pits, hearing loss, and, in the latter, renal anomalies. These syndromes can be caused by mutations in the *EYA1* (both conditions), *SIX1* (branchio-otic) and *SIX5* (branchio-oto-renal) genes, which encode transcription factors that interact within a complex. Atrophic, eroded or "hemangiomatous" skin overlying branchial cleft sinuses on the neck or in the periauricular area is a distinctive feature of the branchio-oculo-facial syndrome, which is caused by mutations in the gene encoding transcription factor AP2-α. Additional manifestations of this disorder include cleft lip/palate, imperforate nasolacrimal ducts, eye and ear anomalies, and early graying of the hair.

Histologically, a branchial sinus may be lined by stratified squamous or pseudostratified ciliated columnar epithelium. In order to prevent infectious complications, complete surgical excision of branchial sinuses and fistulae is indicated. Imaging may be helpful in delineating the course and extent of the lesion, although recommendations vary among otolaryngologists. Preoperative options include CT fistulography and MRI; in addition, intraoperative contrast fistulography and/or injection of methylene blue dye can be considered[50,51].

Supernumerary Nipples and Other Forms of Accessory Mammary Tissue

Synonyms: ■ Accessory nipples ■ Polythelia ■ Pseudomamma ■ Supernumerary breasts ■ Polymastia

Supernumerary nipples and other forms of accessory mammary tissue are remnants of the embryologic mammary ridges or "milk lines", symmetric ectodermal thickenings that extend from the anterior axillary fold to the upper medial thigh (Fig. 64.21). Normally, there is further development in the pectoral region to form the nipples, while the remainder of the milk line regresses; focal areas of persistence result in accessory mammary tissue. Supernumerary nipples, the most common type of accessory mammary tissue, are found in 1–6% of the population[52]. They usually represent a sporadic developmental anomaly, although approximately 10% of cases are familial. The incidence of supernumerary nipples is similar in men and women. However, accessory mammary tissue in women often becomes prominent at puberty or during pregnancy, and it is then more easily recognized. Conversely, changes in supernumerary nipples may actually represent an early cutaneous sign of pregnancy.

Supernumerary nipples are most commonly seen on the inframammary chest, but they may be located anywhere along the milk lines (including on the vulva) and occasionally in other sites such as the upper back, shoulder, posterior thigh, face, neck or even foot. In addition, supernumerary nipples sometimes overlie the primary nipple or areola. Lesions are most often single, but they may be multiple and/or bilateral. Supernumerary nipples typically present as a small, soft, pink or brown papule, either with a surrounding areola (Fig. 64.22) or without (referred to as pseudomamma and polythelia, respectively). An areola also can develop in the absence of a nipple (polythelia areolaris), and ectopic glandular breast tissue can be found either associated with a nipple and/or areola (supernumerary breasts, polymastia) or alone. In the latter situation, tissue is most often located in the axilla or vulva, and it may demonstrate all of the functional changes of normal breasts, from tenderness and swelling related to the menstrual cycle to lactation through pores in the overlying skin. Of note, a patch of hair located along the milk lines may be a marker of underlying mammary tissue (polythelia pilosa)[53].

A number of other abnormalities have been described in patients with supernumerary nipples. The association between supernumerary nipples and malformations of the kidneys and urinary tract is controversial. Although early reports supported the existence of a "supernumerary nipple/renal field defect", several controlled studies failed to confirm this association[54]. However, a few studies have found supernumerary nipples to be significantly more common in patients with urogenital or renal malignancies than in control groups[55]. An increased incidence of predominantly ipsilateral Becker's nevi has also been noted in patients with supernumerary nipples. Supernumerary nipples are found in several multiple congenital anomaly syndromes, including Simpson–Golabi–Behmel syndrome, cleft lip/palate–ectodermal dysplasia syndrome and tricho-odonto-onychial dysplasia (www.ncbi.nlm.nih.gov/omim).

Histologic features of accessory mammary tissue are similar to those of normal breasts. For example, supernumerary nipples show acanthosis, pilosebaceous structures, smooth muscle, and, in many cases, mammary glands. Fine-needle aspiration cytology can be helpful for evaluation of an axillary or vulvar mass suspected to represent breast tissue, although an incisional or excisional biopsy may be required for definitive diagnosis. Ectopic glandular breast tissue can develop any of the disorders that occur in normally positioned breasts, including fibrocystic changes, mastitis, fibroadenomas and carcinoma. Although such tissue does not have an increased malignant potential compared with the normal breast and prophylactic excision for cancer prevention is not required, routine screening should be performed with periodic physical examination and radiologic studies such as mammography or ultrasonography. Complete surgical excision is the treatment of choice for accessory mammary tissue that is symptomatic or cosmetically undesirable. Most authors do not recommend imaging studies to exclude an associated urinary tract malformation in asymptomatic individuals with accessory mammary tissue as an isolated anomaly.

Absent, Hypoplastic or Anomalous Nipples

Synonyms: ■ Athelia ■ Amastia ■ Hypomastia

Absence or hypoplasia of the nipples may occur either as an isolated developmental abnormality or together with other malformations in a variety of congenital syndromes. The Poland anomaly is a

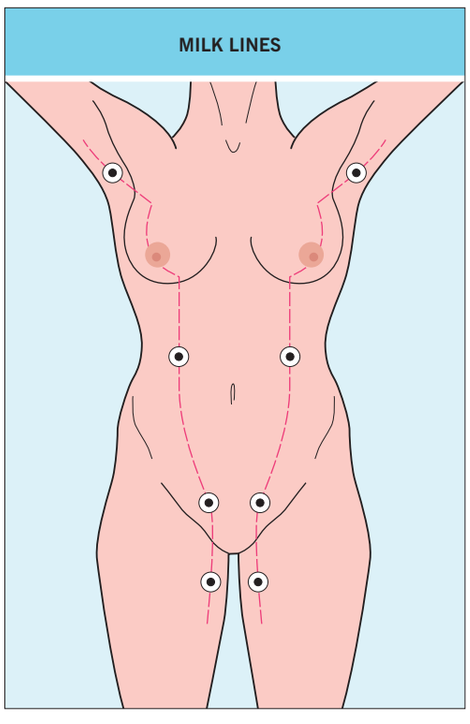


Fig. 64.21 "Milk lines". Supernumerary nipples and other forms of accessory mammary tissue represent focal remnants of the embryologic mammary ridges that extend from the anterior axillary fold to the upper medial thigh bilaterally.

Fig. 64.22 Supernumerary nipple. Note the supernumerary nipple with a surrounding areola in a typical location on the inframammary chest. *Courtesy, Jean L Bolognia, MD.*

predominantly sporadic developmental field defect in which hypoplasia or absence of the nipple and/or breast is associated with ipsilateral aplasia of the sternal head of the pectoralis major muscle, patchy absence of axillary hair, and symbrachydactyly. The Becker's nevus syndrome may also include hypoplasia of the ipsilateral nipple and breast, pectoralis major muscle and/or arm. In addition, nipple and breast hypoplasia or aplasia may occur in X-linked hypohidrotic, tricho-odonto-onychial type and various other ectodermal dysplasias as well as the scalp–ear–nipple syndrome (see Table 64.4), limb–mammary syndrome (ectrodactyly, other hand/foot anomalies and nail dysplasia), ulnar–mammary syndrome (ulnar ray defects, apocrine gland hypoplasia, genital anomalies and abnormal canine teeth; caused by mutations in the *TBX3* gene; see Table 64.6) and ablepharon–macrostomia syndrome. In a rare, lethal form of dwarfism known as Blomstrand chondrodysplasia, loss-of-function mutations in the gene encoding parathyroid hormone receptor 1 result in lack of nipples. Interestingly, during embryonic development, mammary bud epithelium produces a parathyroid hormone-related protein that is required for formation of the nipple and mammary ducts[56].

Inverted nipples are most often inherited as an isolated autosomal dominant trait, but they may also be found in congenital syndromes. For example, inverted nipples occur together with psychomotor retardation, hypotonia, cerebellar hypoplasia, strabismus and abnormal fat distribution as a part of the congenital disorder of glycosylation type Ia. Widely spaced nipples are a feature of a number of congenital disorders, including Turner syndrome, Noonan syndrome, cerebro-oculo-facio-skeletal syndrome, renal hypoplasia syndromes and various chromosomal abnormalities (www.ncbi.nlm.nih.gov/omim).

Skin Dimples

Synonym: ▪ Skin fossae

DISEASES AFFECTING THE SKIN THAT ARE ASSOCIATED WITH CONGENITAL DIGITAL ANOMALIES

Syndrome	Digital anomaly (-dactyly)					Other features
	Syn-	Ectro-	Poly-	Clino-	Brachy-	
Ectodermal dysplasias (see Ch. 63)						
• EEC syndrome*	x	x				AD; *e*ctodermal dysplasia, *e*ctrodactyly, cleft lip/palate
• EEM syndrome	x	x				AR, P-cadherin gene; *e*ctodermal dysplasia, *e*ctrodactyly, *m*acular dystrophy
• Cleft lip/palate–ectodermal dysplasia	x					See Table 64.5
• ED–syndactyly	x					AR, nectin 4 (*PVRL4*) gene; hypotrichosis with pili torti, hypodontia, PPK
• Oculodentodigital dysplasia	x				x	AD, *GJA1* gene; small eyes, enamel hypoplasia, midphalangeal hypoplasia, PPK, hypotrichosis
• Scalp–ear–nipple syndrome	x					See Table 64.4
• Ulnar–mammary syndrome		x	x			See text – absent/hypoplastic nipples
Oral–facial–digital syndrome, type 1	x		x			See Table 64.5
Goltz syndrome (focal dermal hypoplasia)	x	x	x			See Ch. 62
Terminal osseous dysplasia with pigmentary defects				x	x	X-D, filamin A gene; hyperpigmented, atrophic facial macules representing focal dermal hypoplasia, digital fibromas, multiple frenula, hypertelorism
Happle–Tinschert syndrome	x		x			Basaloid follicular hamartomas in a mosaic distribution; dental, skeletal and cerebral anomalies
Epidermal/sebaceous nevus "syndromes"	x		x	x		See Ch. 62
Mosaicism/hypomelanosis of Ito	x		x	x		See Ch. 62
Klippel–Trenaunay syndrome†	x		x			See Ch. 104
Proteus syndrome†	x					See Ch. 62
Adams–Oliver syndrome	x				x	See Table 64.3
Macrocephaly–capillary malformation	x		x			See Ch. 104
Waardenburg syndrome, type 3	x					See Ch. 66
Apert syndrome	x					AD, *FGFR2* gene; craniosynostosis, severe acne, diffuse pigmentary dilution
Nevoid basal cell carcinoma syndrome			x		x	See Ch. 107
Popliteal pterygium syndrome	x					See text – congenital lip pits
Trichorhinophalangeal syndrome					x	AD, *TRPS1* gene; cone-shaped epiphyses, pear-shaped nose, sparse hair
Congenital anonychia–onychodysplasia	x			x	x	See Ch. 71

*Caused by mutations in the *p63* gene; allelic disorders with overlapping manifestations (e.g. ectrodactyly, nipple hypo-/aplasia) include ADULT (acro-dermato-ungual-lacrimal-tooth) syndrome and limb-mammary syndrome.
†Patients often have macrodactyly.

Table 64.6 Diseases affecting the skin that are associated with congenital digital anomalies. Other disorders associated with digital anomalies that also may affect the skin include Cornelia de Lange, Roberts, Simpson–Golabi–Behmel, Pallister–Hall, Russell–Silver, Rubinstein–Taybi and Hurler syndromes, trisomy 13, Fanconi anemia and the Poland anomaly. **Syndactyly**, fused digits; **ectrodactyly**, absent digits resulting in a split hand–foot deformity ("lobster claw"); **polydactyly**, extra digits; **clinodactyly**, laterally or medially "bent" digits; **brachydactyly**, short digits. AD, autosomal dominant; AR, autosomal recessive; PPK, palmoplantar keratoderma; *PVRL4*, poliovirus receptor-related 4; X-D, X-linked dominant.

Skin dimples are deep cutaneous depressions that are seen most commonly on the cheeks or chin, occurring in a familial pattern suggestive of autosomal dominant inheritance. Unilateral or bilateral dimples also may be found in a variety of other locations, most often overlying bony prominences, such as the acromion process of the scapula, elbow, patella, tibia and sacrum. These represent regions in which there is close proximity of the skin to the underlying bone during fetal development, and the dimples are thought to result from early fixation of the skin and deficient formation of the subcutaneous tissue.

Bilateral skin dimples on the shoulders overlying the acromion processes can be inherited in an autosomal dominant fashion as an isolated anomaly. This finding is thought to be more common than the scarcity of reports in the literature would suggest. In addition, bilateral acromial dimples are a feature of several congenital malformation syndromes, including the 18q deletion syndrome, trisomy 9p syndrome, Say syndrome and Russell–Silver dwarfism[57]. Skin dimples also may be seen in association with skeletal abnormalities. For example, dimpling may be found overlying the tibial bend in patients with camptomelic dysplasia and over bowing convexities or exostoses of long bones in those with hypophosphatasia. A characteristic H-shaped dimple on the chin is seen in the whistling face syndrome. Dimples located on the lumbosacral midline may represent a cutaneous sign of spinal dysraphism, and they are also associated with a number of malformation syndromes[57]. In contrast, shallow coccygeal dimples are a relatively common finding in normal newborns[25–27]. Lastly, skin dimples overlying the knees and/or elbows have been reported in association with congenital rubella, Joubert syndrome, limb–mammary syndrome, ulnar–mammary syndrome and multiple pterygium syndrome (www.ncbi.nlm.nih.gov/omim). In other sites, an enlarging dimple in a young child may indicate a nascent lipoblastoma (see Ch. 117).

Congenital Malformations of the Dermatoglyphs

Congenital malformations of the dermatoglyphs (fingerprints) are divided into four main categories based on the appearance of the dermal ridges of which they are composed: (1) ridge aplasia (absent); (2) ridge hypoplasia (poorly formed); (3) ridge dissociation (discontinuous pattern with short segments); and (4) ridges-off-the-end (run off the end of the fingertip rather than looping around). Embryologic development of the dermal ridges occurs in conjunction with that of the eccrine glands of the palms and soles, and the sweat pores are found on the ridges. The lack of eccrine ducts and glands in the palmar skin of patients with ridge aplasia reflects this close relationship[58].

Congenital dermatoglyph malformations types 2–4 can be inherited in an autosomal dominant fashion as an isolated defect. They may also occur in association with conditions such as chromosomal abnormalities, malformations of the distal limbs, and ectodermal dysplasias. The latter, which may feature ridge aplasia as well, include hypohidrotic ectodermal dysplasia, AEC syndrome (*a*nkyloblepharon, *e*ctodermal dysplasia, *c*left lip/palate), dermatopathia pigmentosa reticularis and Naegeli–Franceschetti–Jadassohn (NFJ) syndrome (see Chs 63 & 67). Autosomal dominant inheritance of ridge aplasia together with acral hypohidrosis, neonatal acral blistering (with occasional later recurrences), palmoplantar keratoderma, and variable hypotrichosis and dental anomalies has been described in a few families; although referred to as Basan syndrome, the features overlap with those of NFJ syndrome. Ridge dissociation also may be seen in patients with Rosenthal–Kloepfer syndrome (acromegaloid changes, cutis verticis gyrata, and corneal leukoma) and cystic fibrosis. The differential diagnosis of abnormal dermatoglyphs may also include acquired loss as seen in Kindler syndrome (see Ch. 63).

Rudimentary Supernumerary Digits

Synonym: ▪ Rudimentary polydactyly

Rudimentary supernumerary digits are soft-tissue duplications without a skeletal component that typically arise from the lateral surface of a normal digit, most often the ulnar side of the fifth finger (postaxial; those arising from the thumb are termed preaxial). Such lesions are found in approximately 0.5–1 per 1000 live births in white populations and 3–10 per 1000 live births in black populations. They usually occur as an isolated malformation with a familial pattern suggestive of autosomal dominant inheritance. In some cases, rudimentary supernumerary digits represent the stump remaining after intrauterine amputation of a larger structure. Present at birth and frequently bilateral, lesions range from small, fleshy or wart-like papules (Fig. 64.23) to larger, often pedunculated nodules that may contain cartilage or a vestigial nail. Congenital ectopic nails located on the tips of the fifth fingers also have been described, and these are regarded as a separate entity.

Histologically, rudimentary supernumerary digits often show fascicles of nerve fibers in a pattern similar to that of an acquired neuroma. When removal is desired, surgical excision is the method of choice[59]. Removal via ligation with suture material increases the risk of infection and often leaves a residual papule, which may result in a painful neuroma later in life.

Amniotic Band Sequence and Disorganization Syndrome

Synonyms: ▪ Amniotic band syndrome ▪ Congenital constriction bands ▪ ADAM (*a*mniotic *d*eformity, *a*dhesions and *m*utilations) complex

The amniotic band sequence (ABS) encompasses a variety of congenital anomalies of the limbs, head, body wall and viscera with asymmetric, seemingly random distribution patterns that do not correspond to embryonic fusion planes. Characteristic findings include constriction rings and amputations of the limbs and digits that are associated with fibrous bands. Occurring in approximately 1–10 per 10 000 live births, ABS is primarily a sporadic disorder, although familial cases have been reported.

There are two classic hypotheses for the pathogenesis of ABS. The *extrinsic theory* postulates that early rupture of the amniotic membrane is followed by loss of amniotic fluid and entanglement of fetal parts in fibrous strands of torn amnion, which form rings that encircle and constrict the limbs, portions of the face or even the entire trunk. The *intrinsic theory* proposes that an abnormal endogenous developmental process leads to production of fibrous bands as well as other anomalies (e.g. internal malformations, duplicated structures) not explained by bands alone. Although the former theory has traditionally been more widely accepted, the substantial overlap between ABS and the "disorganization syndrome" (the human equivalent of the mouse disorganization mutant, which has autosomal dominant inheritance) provides support for an intrinsic mechanism[60,61]. The disorganization syndrome features a haphazard pattern of defects, most often limb anomalies (including duplications as well as reductions/circumferential constrictions with attached fibrous bands), craniofacial > truncal clefts, and hamartomatous digit-like appendages.

Fig. 64.23 Bilateral rudimentary supernumerary digits. The ulnar side of the fifth digit is the most common location (referred to as postaxial).

The clinical spectrum of ABS is broad, ranging from isolated minor limb anomalies to major craniofacial and visceral defects. It includes the limb–body wall complex, which is characterized by body wall defects with evisceration of thoracic and/or abdominal organs, irregular anencephaly/encephaloceles and bizarre facial clefting[62]. Variations in severity may depend upon differences in the timing of amniotic rupture or variable expressivity of genetic trait(s). Constriction rings present as circumferential grooves of variable depth on the digits, extremities, neck or trunk. Deep lesions located on an extremity may be associated with distal lymphedema, nerve compression, deformity or intrauterine amputation. Acrosyndactyly can result from a constriction band that encircles adjacent digits. In addition to the distinctive fibrofatty appendages of the disorganization syndrome, other cutaneous manifestations of ABS may include aplasia cutis congenita, often with a stellate morphology, and abnormal dermatoglyphs.

Plastic surgery with wound closure via Z-plasty is indicated for release of constriction bands that restrict growth, compress underlying nerves, or interfere with vascular and/or lymphatic circulation.

Other Developmental Anomalies Associated with Cutaneous Diseases

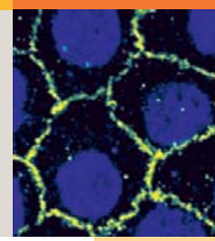
Skin disorders that are associated with cleft lip/palate or congenital digital anomalies are presented in Tables 64.5 and 64.6, respectively.

REFERENCES

1. Van Allen MI, Kalousek DK, Chernoff GF, et al. Evidence for multi-site closure of the neural tube in humans. Am J Med Genet. 1993;47:723–43.
2. Drolet B, Prendiville J, Golden J, et al. 'Membranous aplasia cutis' with hair collars: congenital absence of skin or neuroectodermal defect? Arch Dermatol. 1995;131: 1427–31.
3. Paller AS, Pensler JM, Tomita T. Nasal midline masses in infants and children: dermoids, encephaloceles, and gliomas. Arch Dermatol. 1991;127:362–6.
4. Kennard CD, Rasmussen JE. Congenital midline nasal masses: diagnosis and management. J Dermatol Surg Oncol. 1990;16:1025–36.
5. Barkovich AJ, Vandermarck P, Edwards MS, Cogen PH. Congenital nasal masses: CT and MR imaging features in 16 cases. Am J Neuroradiol. 1991;12:105–16.
6. Ruge JR, Tomita T, Naidich TP, et al. Scalp and calvarial masses of infants and children. Neurosurgery. 1988; 22:1037–42.
7. Baldwin HE, Berck CM, Lynfield YL. Subcutaneous nodules of the scalp: preoperative management. J Am Acad Dermatol. 1991;25:819–30.
8. Drolet BA, Clowry L Jr, McTigue MK, Esterly NB. The hair collar sign: marker for cranial dysraphism. Pediatrics. 1995;96:309–13.
9. Commens C, Rogers M, Kan A. Heterotropic brain tissue presenting as bald cysts with a collar of hypertrophic hair: the 'hair collar' sign. Arch Dermatol. 1989;125: 1253–6.
10. Khallouf R, Fétissof F, Machet MC, et al. Sequestrated meningocele of the scalp: diagnostic value of hair anomalies. Pediatr Dermatol. 1994;11:315–18.
11. Sheu M, Fauteux G, Chang H, et al. Sinus pericranii: dermatologic considerations and literature review. J Am Acad Dermatol. 2002;46:934–41.
12. Torrelo A, Boente Mdel C, Nieto O, et al. Nevus psiloliparus and aplasia cutis: a further possible example of didymosis. Pediatr Dermatol. 2005;22:206–9.
13. Bartlett SP, Lin KY, Grossman R, Katowitz J. The surgical management of orbitofacial dermoids in the pediatric patient. Plast Reconstr Surg. 1993;91:1208–15.
14. Karma P, Rasanen O, Karja J. Nasal gliomas: a review and report of two cases. Laryngoscope. 1977;87:1169–79.
15. Bradley PJ, Singh SD. Congenital nasal masses: diagnosis and management. Clin Otolaryngol Allied Sci. 1982;7: 87–97.
16. Puppala B, Mangurten HH, McFadden J, et al. Nasal glioma presenting as neonatal respiratory distress: definition of the tumor mass by MRI. Clin Pediatr. 1990; 29:49–52.
17. El Shabrawi-Caelen L, White WL, Soyer HP, et al. Rudimentary meningocele: remnant of a neural tube defect? Arch Dermatol. 2001;137:45–50.
18. Eastlack JP, Howard RM, Frieden IJ. Congenital midline cervical cleft: case report and review of the English language literature. Pediatr Dermatol. 2000;17:118–22.
19. Frieden IJ, Reese V, Cohen D. PHACE syndrome: the association of posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities. Arch Dermatol. 1996;132:307–11.
20. Boulinguez S, Teillac-Hamel D, Bedane C, et al. Cervicofacial hemangioma and a minor sternal malformation: inclusion in PHACES syndrome? Pediatr Dermatol. 1998;15:119–21.
21. Lichtenstein BW. Spinal dysraphism: spina bifida and myelodysplasia. Arch Neurosurg Psychiatr. 1940;44: 792–809.
22. Tortori-Donati P, Rossi A, Cama A. Spinal dysraphism: a review of neuroradiological features with embryological correlations and proposal for a new classification. Neuroradiology. 2000;42:471–91.
23. McAtee-Smith J, Hebert AA, Rapini RP, Goldberg NS. Skin lesions of the spinal axis and spinal dysraphism: fifteen cases and a review of the literature. Arch Pediatr Adolesc Med. 1994;148:740–8.
24. Schropp C, Sörensen N, Collmann H, Krauss J. Cutaneous lesions in occult spinal dysraphism – correlation with intraspinal findings. Childs Nerv Syst. 2006;22:125–31.
25. Powell KR, Cherry JD, Hougen TJ, et al. A prospective search for congenital dermal abnormalities of the craniospinal axis. J Pediatr. 1975;87:744–50.
26. Drolet B. Birthmarks to worry about: cutaneous markers of dysraphism. Dermatol Clin. 1998;16:447–53.
27. Kriss VM, Desai NS. Occult spinal dysraphism in neonates: assessment of high-risk cutaneous stigmata on sonography. Am J Roentgenol. 1998;171:1687–92.
28. Enjolras O, Boukobza M, Jdid R. Cervical occult spinal dysraphism: MRI findings and the value of a vascular birthmark. Pediatr Dermatol. 1995;12:256–9.
29. Tavafoghi V, Ghandchi A, Hambrick GW Jr, Udverhelyi GB. Cutaneous signs of spinal dysraphism: report of a patient with a tail-like lipoma and review of 200 cases in the literature. Arch Dermatol. 1978;114:573–7.
30. Iacobas I, Burrows PE, Frieden IJ, et al. LUMBAR: association between cutaneous infantile hemangiomas of the lower body and regional cutaneous anomalies. J Pediatr. 2010;157:795–801.
31. Albright AL, Gartner JC, Wiener ES. Lumbar cutaneous hemangiomas as indicators of tethered spinal cords. Pediatrics. 1989;83:977–80.
32. Drolet BA, Chamlin SA, Garzon MC, et al. Prospective study of spinal anomalies in children with infantile hemangiomas of the lumbosacral skin. J Pediatr. 2010; 157:789–94.
33. Ben-Amitai D, Davidson S, Schwartz M, et al. Sacral nevus flammeus simplex: the role of imaging. Pediatr Dermatol. 2000;17:469–71.
34. Guggisberg D, Hadj-Rabia S, Viney C, et al. Skin markers of occult spinal dysraphism in children: a review of 54 cases. Arch Dermatol. 2004;140:1109–15.
35. Rohrschneider WK, Forsting M, Darge K, Troger J. Diagnostic value of spinal US: comparative study with MR imaging in pediatric patients. Radiology. 1996;200: 383–8.
36. Frieden IJ. Aplasia cutis congenita: a clinical review and proposal for classification. J Am Acad Dermatol. 1986; 14:646–60.
37. Drolet BA, Baselga E, Gosain AK, et al. Preauricular skin defects: a consequence of a persistent ectodermal groove. Arch Dermatol. 1997;133:1551–4.
38. McGaughran J, Aftimos S. Setleis syndrome: three new cases and a review of the literature. Am J Med Genet. 2002;111:376–80.
39. Mempel M, Abeck D, Lange I, et al. The wide spectrum of clinical expression in Adams-Oliver syndrome: a report of two cases. Br J Dermatol. 1999;140:1157–60.

39a. Shaheen R, Faqeih E, Sunker A, et al. Recessive mutations in *DOCK6*, encoding the guanidine nucleotide exchange factor DOCK6, lead to abnormal actin cytoskeleton organization and Adams-Oliver syndrome. Am J Hum Genet. 2011;89:328–33.

40. Lane W, Zanol K. Duodenal atresia, biliary atresia and intestinal infarct in truncal aplasia cutis congenita. Pediatr Dermatol. 2000;17:290–2.
41. Baselga E, Torrelo A, Drolet B, et al. Familial nonmembranous aplasia cutis of the scalp. Pediatr Dermatol. 2005;22:213–17.
42. Demmel U. Clinical aspects of congenital skin defects I: congenital skin defects on the head of the newborn. Eur J Pediatr. 1975;121:21–50.
43. Evers ME, Steijlen PM, Hamel BC. Aplasia cutis congenita and associated disorders: an update. Clin Genet. 1995; 47:295–301.
44. Kumar S, Deffenbacher K, Marres HA, et al. Genomewide search and genetic localization of a second gene associated with autosomal dominant branchio-oto-renal syndrome: clinical and genetic implications. Am J Hum Genet. 2000;60:1715–20.
45. Kondo S, Schutte BC, Richardson RJ, et al. Mutations in *IRF6* cause Van der Woude and popliteal pterygium syndromes. Nat Genet. 2002;32:285–9.
46. Jansen T, Romiti R, Altmeyer P. Accessory tragus: report of two cases and review of the literature. Pediatr Dermatol. 2000;17:391–4.
47. Sebben JE. The accessory tragus – no ordinary skin tag. J Dermatol Surg Oncol. 1989;15:304–7.
48. Brownstein MH, Wanger N, Helwig EB. Accessory tragi. Arch Dermatol. 1971;104:625–31.
49. Vaughan TK, Sperling LC. Diagnosis and surgical treatment of congenital cartilaginous rests of the neck. Arch Dermatol. 1991;127:1309–10.
50. Black CJ, O'Hara JT, Berry J, et al. Magnetic resonance imaging of branchial cleft abnormalities: illustrated cases and literature review. J Laryngol Otol. 2010;124: 213–15.
51. Guarisco JL, Fatakia A. Intraoperative fistulograms in the management of branchial apparatus abnormalities in children. Int J Pediatr Otorhinolaryngol. 2008;72: 1777–82.
52. Grossl NA. Supernumerary breast tissue: historical perspectives and clinical features. South Med J. 2000; 93:29–32.
53. Camacho F, González-Cámpora R. Polythelia pilosa: a particular form of accessory mammary tissue. Dermatology. 1998;196:295–8.
54. Grotto I, Browner-Elhanan K, Mimouni D, et al. Occurrence of supernumerary nipples in children with kidney and urinary tract malformations. Pediatr Dermatol. 2001;18:291–4.
55. Ferrara P, Giorgio V, Vitelli O, et al. Polythelia: still a marker of urinary tract anomalies in children? Scand J Urol Nephrol. 2009;43:47–50.
56. Foley J, Dann P, Hong J, et al. Parathyroid hormone-related protein maintains mammary epithelial fate and triggers nipple skin differentiation during embryonic breast development. Development. 2001;128:513–25.
57. Spencer JM, Schneiderman PI, Grossman ME. Bilateral skin dimples on the shoulders. Pediatr Dermatol. 1993: 10:16–8.
58. Limová M, Blacker KL, LeBoit PE. Congenital absence of dermatoglyphs. J Am Acad Dermatol. 1993;29:355–8.
59. Leber GE, Gosain AK. Surgical excision of pedunculated supernumerary digits prevents traumatic amputation neuromas. Pediatr Dermatol. 2003;20:108–12.
60. Purandare SM, Ernst L, Medne L, et al. Developmental anomalies with features of disorganization (Ds) and amniotic band sequence (ABS): a report of four cases. Am J Med Genet A. 2009;149A:1740–8.
61. Wax JR, Pinette MG, Smith R, et al. Prenatal sonographic findings in human disorganization syndrome. J Ultrasound Med. 2010;29:301–5.
62. Martinez-Frias ML, Bermejo E, Rodriguez-Pinilla E. Body stalk defects, body wall defects, amniotic bands with and without body wall defects, and gastroschisis: comparative epidemiology. Am J Med Genet. 2000;92: 13–8.



Melanocyte Biology 65

Jean L Bolognia and Seth J Orlow

Key features

- The major determinant of normal skin color is the activity of melanocytes, i.e. the quantity and quality of pigment production, not the density of melanocytes
- Melanocytes contain a unique intracytoplasmic organelle, the melanosome, which is the site of melanin synthesis and deposition
- Compared with lightly pigmented skin, darkly pigmented skin has melanosomes that contain more melanin and are larger; once transferred to keratinocytes, the melanosomes are singly dispersed and degraded more slowly
- Tyrosinase is the key enzyme in the melanin biosynthetic pathway
- Two major forms of melanin are produced in melanocytes: brown–black eumelanin and yellow–red pheomelanin
- The production of eumelanin versus pheomelanin is influenced by the binding of melanocyte stimulating hormone to the melanocortin-1 receptor

INTRODUCTION

In order to understand the underlying pathophysiology of cutaneous disorders of hypopigmentation and hyperpigmentation, as well as the process of normal physiologic pigment production, an appreciation of the structure and function of the melanocyte is required. A classic example of basic pathogenesis is type 1 oculocutaneous albinism (OCA), in which pigmentary dilution of the skin, hair and eyes is due to a reduction or absence of tyrosinase activity secondary to mutations in both copies of the tyrosinase gene. Within the realm of physiologic pigmentation, melanocytes in individuals with red hair often express variants of the melanocortin-1 receptor (MC1-R)[1] and population genetics also implicate the *OCA2* (*P*), *ASIP* and *SLC24A5* genes in normal pigment variation (see Table 65.5)[2–4]. As a consequence of the altered amino acid sequences of the variant MC1-Rs, their cell surface expression and interactions with melanocyte stimulating hormone (MSH) can be affected, leading to an increase in the production of pheomelanin as opposed to eumelanin.

The major sections in this chapter are:

- the origin and function of the melanocyte
- the formation and function of the melanosome
- the regulation of melanin biosynthesis.

ORIGIN AND FUNCTION OF THE MELANOCYTE

The melanocyte is a neural crest-derived cell, and during embryogenesis precursor cells (melanoblasts) migrate along a dorsolateral pathway via the mesenchyme to reach the epidermis and hair follicles. Additional sites of melanocyte migration include the uveal tract of the eye (choroid, ciliary body and iris), the leptomeninges and the inner ear (cochlea) (Fig. 65.1). Presumably, the death of melanocytes within the leptomeninges, inner ear and skin is responsible for the aseptic meningitis, auditory symptoms and areas of vitiligo, respectively, seen in patients with the Vogt–Koyanagi–Harada syndrome (see Ch. 66). Recently, it was shown that cutaneous melanocytes can also arise from neural crest-derived Schwann cell precursors that are found along nerves within the skin, having migrated there by a ventral pathway[5].

In the inner ear, particularly in the stria vascularis, melanocytes are thought to play a role in the development of the ability to hear. Aberrant migration or survival of melanocytes within the inner ear, the iris, and mid portions of the forehead and extremities explains the presence of congenital deafness, heterochromia irides, and patches of leukoderma, respectively, in patients with Waardenburg syndrome, the classic neurocristopathy. Also, aberrant migration or survival of enteric ganglion cells, another neural crest-derived cell population, provides an explanation for the association of congenital megacolon (Hirschsprung disease) with either piebaldism or Waardenburg syndrome.

The survival and migration of neural crest-derived cells during embryogenesis depends upon interactions between specific receptors on their cell surface and extracellular ligands. For example, KIT ligand (also known as steel factor or stem cell growth factor) binds to the transmembrane KIT receptor on melanocytes and melanocyte precursors (melanoblasts) (Figs 65.2 & 65.3). Heterozygous germline

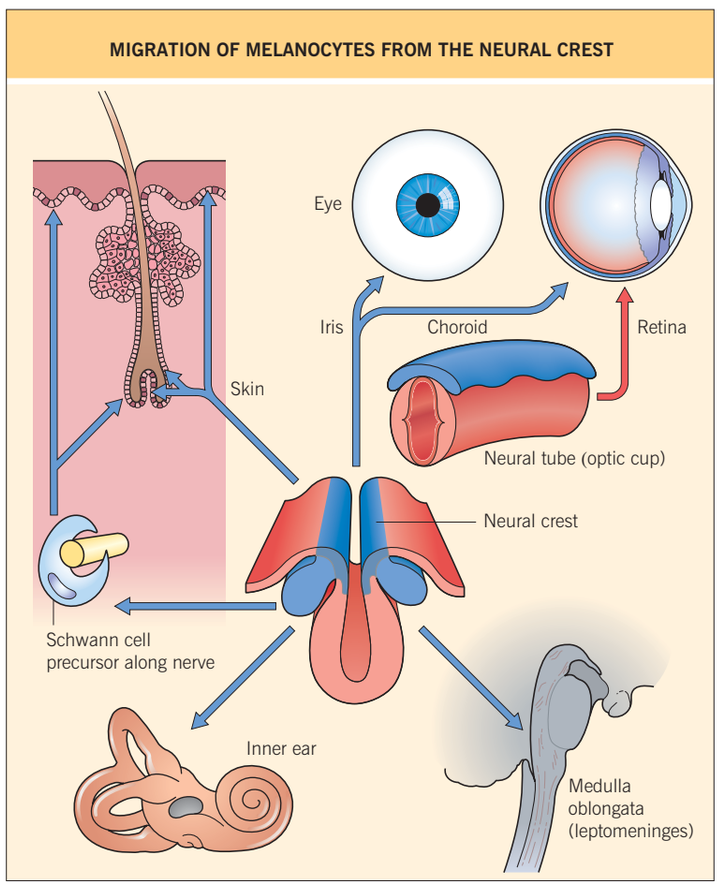


Fig. 65.1 Migration of melanocytes from the neural crest. Melanocytes migrate to the uveal tract of the eye (iris and choroid), the leptomeninges and the cochlea of the inner ear, as well as to the epidermis and hair follicle. Cutaneous melanocytes can also arise from Schwann cell precursors located along nerves in the skin, which also originate from the neural crest. The retina actually represents an outpouching of the neural tube.

mutations in the *KIT* gene that decrease the ability of the KIT receptor to be activated by KIT ligand are responsible for human piebaldism, whereas in mice, mutations in either the *kit* gene or the *steel* gene can lead to white spotting. In the developing CNS, interactions occur between endothelin-3 (ET3 [EDN3]) and the endothelin B receptors (EDNRB) found on melanoblast-ganglion cell precursors (see Fig. 65.3). Mutations in one or both copies of the *EDN3* gene or the *EDNRB* gene can result in Waardenburg syndrome plus congenital megacolon (see Ch. 66).

Transcription factors represent another group of proteins that play an essential role during embryogenesis. Because transcription factors can bind DNA and influence the activity of other genes, they are able to regulate the complex interplay of various sets of genes that is required for embryonic development. Several of the genes that, when mutated, give rise to Waardenburg syndrome encode transcription factors (e.g. *PAX3, MITF, SOX10*; see Table 66.5). Figure 65.4 demonstrates some of these interactions (e.g. PAX3 and SOX10 can control expression of MITF)[7,8].

During embryogenesis, melanin-producing melanocytes are found diffusely throughout the dermis. They first appear in the head and neck region at approximately 10 weeks of gestation. However, by the end of gestation, active dermal melanocytes have "disappeared", except in

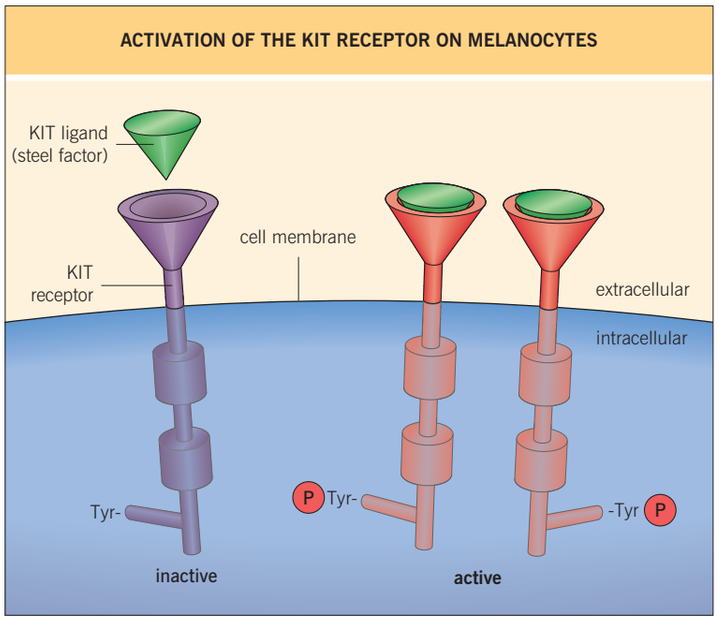


Fig. 65.2 Activation of the KIT receptor on melanocytes. Because the KIT receptor is a tyrosine kinase receptor, it has the ability to place phosphate groups on the tyrosine residues of other proteins (as well as autophosphorylation). Heterozygous germline mutations in the *KIT* gene that prevent the activation of the KIT receptor by KIT ligand, also referred to as steel factor, lead to piebaldism, whereas somatic activating mutations in the *KIT* gene are seen in patients with mastocytosis as well as melanomas arising in acral sites, mucosa and chronically photodamaged skin. A form of familial progressive hyperpigmentation can result from heterozygous gain-of-function germline mutations in the gene that encodes KIT ligand[6].

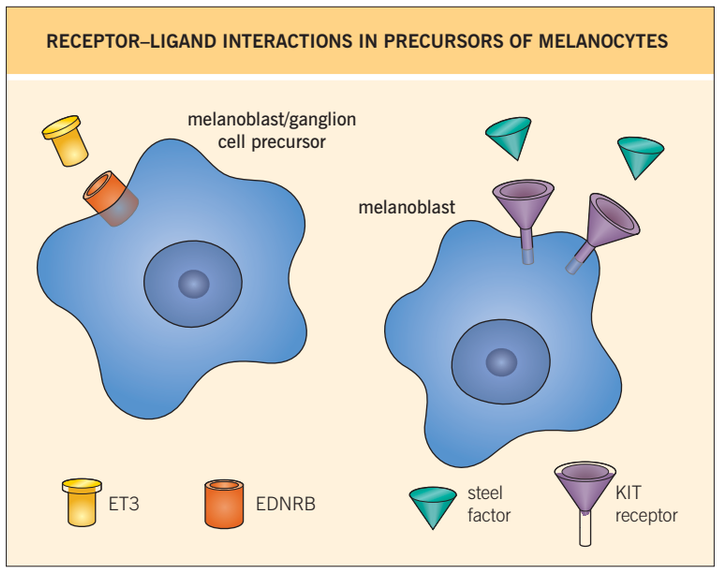


Fig. 65.3 Receptor–ligand interactions in precursors of melanocytes. In the developing CNS, endothelin B receptors (EDNRB) on melanoblast-ganglion cell precursors interact with endothelin-3 (ET3), and in the mesenchyme and final destination sites, KIT receptors on melanoblasts and melanocytes interact with KIT ligand (steel factor).

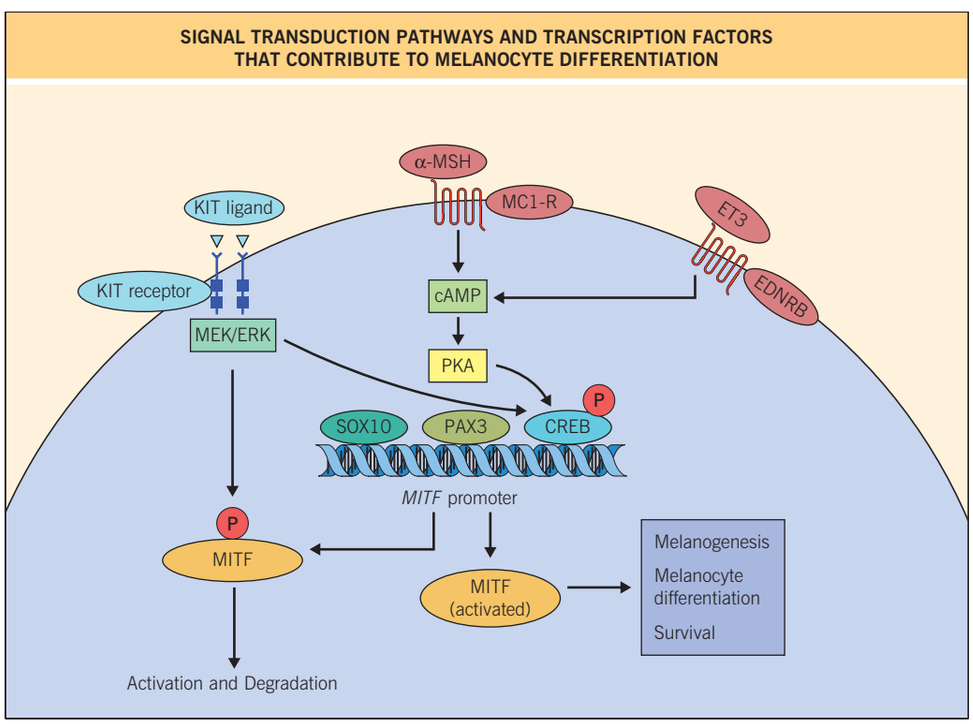


Fig. 65.4 Signal transduction pathways and transcription factors that contribute to melanocyte differentiation. MITF expression is activated early on during the transition from pluripotent neural crest cells to melanoblasts and is required for melanoblast survival[7]. MITF also regulates the expression of multiple pigment genes including those that encode tyrosinase, TYRP1, TYRP2, gp100/Pmel17 and MART-1/Melan-A. Additional transcriptional targets are *CDK2*, *CDKN2A* and *BCL-2* (whose protein product is an inhibitor of apoptosis)[8]. Beyond the role of SOX10, PAX3 and CREB, the T-cell factor/lymphoid enhancer factor (TCF/LEF) family of transcription factors can enable MITF expression to be regulated by Wnt; in mice, Wnt signaling in melanocyte stem cells is critical for hair pigmentation[8a]. Details of how activation of G-protein-coupled receptors leads to an increase in intracellular cAMP is shown in Fig. 65.15. MEK and ERK are key kinases in the mitogen-activated protein kinase (MAPK) pathway (see Fig. 113.2). cAMP, cyclic adenosine monophosphate; CREB, cAMP response-element binding protein; ET3, endothelin-3; EDNRB, endothelin B receptor; MC1-R, melanocortin 1 receptor; MITF, microphthalmia-associated transcription factor; MSH, melanoctye stimulating hormone; PKA, protein kinase A; SOX10, SRY-box containing gene 10.

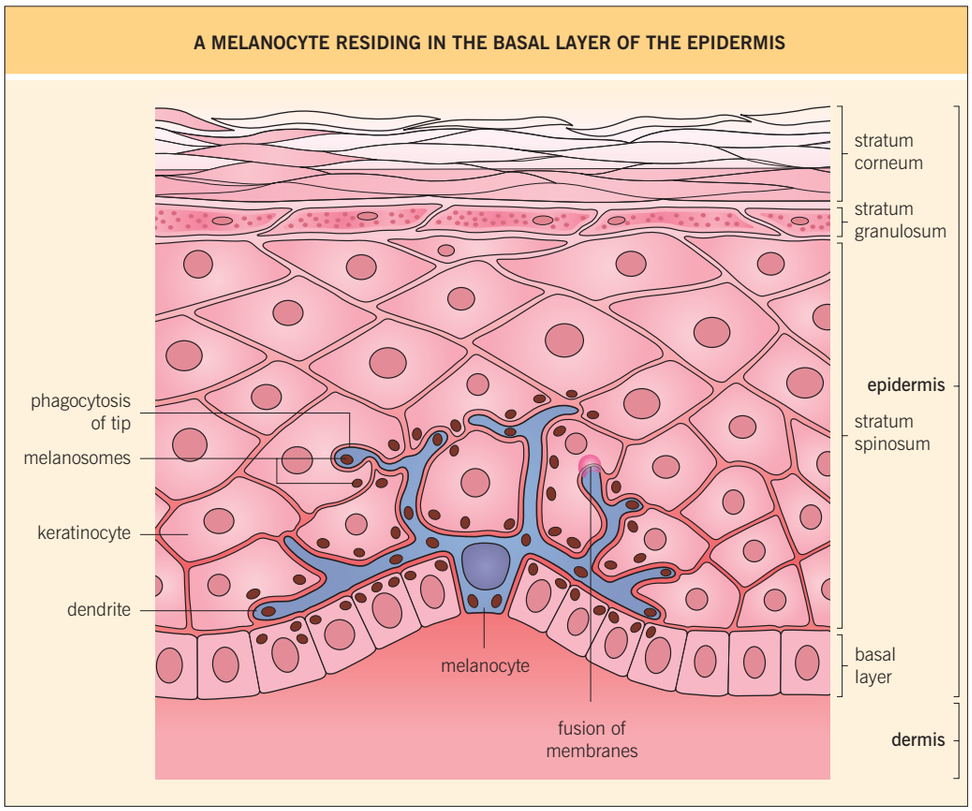


Fig. 65.5 A melanocyte residing in the basal layer of the epidermis. In normal skin, approximately every tenth cell in the basal layer is a melanocyte. Melanosomes are transferred from the dendrites of the melanocyte into neighboring keratinocytes of the epidermis, hair matrices and mucous membranes; no transfer occurs in the pigment epithelium of the retina.

three anatomic locations – the head and neck, the dorsal aspects of the distal extremities, and the presacral area[9]. Some of the dermal melanocytes have clearly migrated into the epidermis, but, given the absolute numbers of cells in the two compartments, death (presumably programmed) of pigment cells has also occurred. The three sites where active dermal melanocytes are still present at the time of birth coincide with the most common sites for dermal melanocytoses and dermal melanocytomas (blue nevi). Hepatocyte growth factor may play a role in the survival and proliferation of these dermal melanocytes as well as somatic activating mutations in *GNA11* and *GNAQ*, which encode G proteins (see Ch. 112).

As depicted in Figure 65.1, melanocytes also migrate to the basal layer of the hair matrix and the outer root sheath of hair follicles. Cells that are actively producing melanin are easily recognized in the matrices of pigmented anagen hairs, whereas melanocytes in the outer root sheath are usually amelanotic and more difficult to identify[10]. It has been hypothesized that there are two populations of melanocytes in the skin, one in the interfollicular epidermis and the second in the hair follicle[11]. Based upon antigen expression and clinical observations, it is the former that is more sensitive to the destructive forces of vitiligo. As a result, repigmentation of patches of vitiligo in which the hairs are still pigmented relies upon activation and subsequent upward migration of the melanocytes present in the outer root sheath[10]. Of note, melanocyte stem cells have been identified within the hair follicle and are discussed in Chapter 2.

By immunohistochemical staining, melanocytes are identified within the fetal epidermis as early as 50 days of gestation[12]. Melanin-containing melanosomes are recognizable by electron microscopy during the fourth month of gestation. Except in benign and malignant neoplasms, melanocytes reside within the basal layer of the epidermis, a location they maintain throughout life (Fig. 65.5). Although the cell body of the melanocyte sits on a specialized region of basal lamina, its dendrites come into contact with keratinocytes as far away as the mid stratum spinosum. This association of a melanocyte with approximately 30–40 surrounding keratinocytes to which it transfers melanosomes has been called the epidermal melanin unit[13]. However, as intruders into the epidermis, melanocytes fail to form desmosomal connections with neighboring keratinocytes; their interactions with keratinocytes are via cadherins.

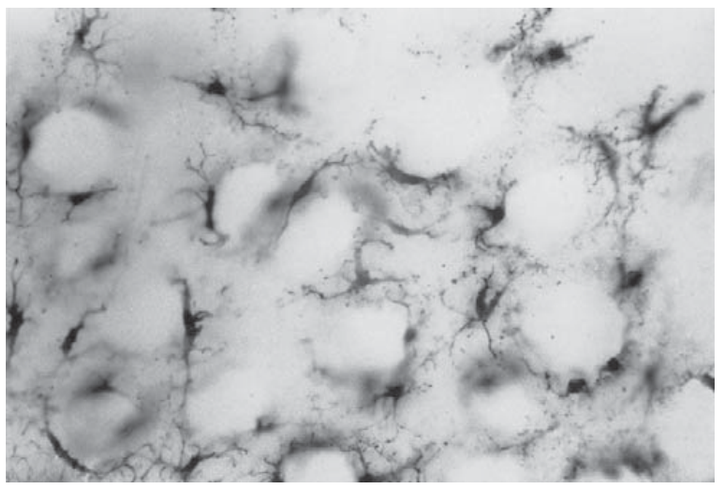


Fig. 65.6 Dihydroxyphenylalanine (DOPA)-stained epidermal sheet. Following incubation with 5 mM L-DOPA for 4–5 hours, the epidermal melanocytes turn black because they contain the enzyme tyrosinase, which converts DOPA to black DOPA-melanin. Note the multiple dendrites and regular spacing of the melanocytes.

Although there is variation in the density of epidermal melanocytes per square millimeter when different regions of the body are analyzed via DOPA-stained epidermal sheets (Fig. 65.6), e.g. the density of melanocytes is greater in the genital region (~1500/mm^2) compared with the back (~900/mm^2), there are smaller differences between individuals when the same anatomic site is examined. This is despite the wide variation in pigmentation seen within the human race. In other words, a person who has minimal baseline pigmentation and an inability to tan has a similar density of melanocytes when compared with a person whose skin is dark brown to black in color. Indeed, even patients with the most severe form of OCA, OCA type 1A, have a normal complement of epidermal melanocytes.

The major determinant of normal skin color is the activity of the melanocytes, i.e. the quantity and quality of pigment production, not

the density of melanocytes[14]. Several factors play a role in determining the level of melanocyte activity; they include specific characteristics of the individual melanosomes (e.g. the dimensions) as well as both baseline (constitutive) and stimulated (facultative) levels of activity of the enzymes involved in the melanin biosynthetic pathway. The latter are influenced by receptor-mediated interactions with extracellular ligands, e.g. MSH (see below).

FORMATION AND FUNCTION OF THE MELANOSOME

Within the cytoplasm of melanocytes is a unique organelle known as the melanosome, in which melanin pigments are synthesized, deposited and transported. The melanosome is most closely related to the lysosome[15]. Through compartmentalization, both organelles provide protection for the remainder of the cell; lysosomes protect against proenzymes such as proteases, and melanosomes protect against melanin precursors (e.g. phenols, quinones) that can oxidize lipid membranes.

The melanosome contains both matrix proteins (e.g. gp100/Pmel17), which form a scaffolding upon which the melanin is deposited, and proteins (primarily enzymes) that regulate the biosynthesis of melanin. Following their formation via ribosomes, all these proteins are found within the lumen of the rough endoplasmic reticulum (RER, Fig. 65.7). In patients with OCA1 and OCA3 (Table 65.1), misfolded tyrosinase or aberrant tyrosinase-related protein 1 (TYRP1) plus tyrosinase polypeptides, respectively, are retained too long within the lumen of the endoplasmic reticulum (ER; see Fig. 65.7 insert)[16]. As a result of ER quality control, these proteins become targets for destruction by proteasomes and therefore are not incorporated into melanosomes.

Several of the enzymes in the melanin biosynthetic pathway are glycoproteins that require the attachment of sugars in order to gain full function. For this reason, they undergo post-translational modification in the ER and the Golgi apparatus and then join up with the matrix proteins (e.g. gp100/Pmel17) to initiate melanogenesis. The targeting of proteins to the plasma membrane versus intracytoplasmic organelles and the targeting of specific proteins to the correct type of organelle are complicated processes. This triaging requires the equivalent of traffic police within the cell, an example of which is adaptor protein 3 (AP-3). Mutations in the gene that encodes the β3A subunit of AP-3 are responsible for a subset of patients with Hermansky–Pudlak syndrome (HPS2)[17]. Other forms of HPS are due to dysfunction of the proteins that serve as components of *b*iogenesis of *l*ysosome-related *o*rganelles *c*omplexes (BLOCs; Fig. 65.8)[18]. It then follows that these patients have dysfunction of more than one intracytoplasmic organelle (see Table 65.1). The associated hypopigmentation can be explained by the failure to efficiently deliver melanogenic proteins, e.g. tyrosinase, TYRP1, to the melanosomes.

The progression of a melanosome from an organelle that lacks melanin to one that is fully melanized is arbitrarily divided, for convenience, into four stages (Fig. 65.9). Proteins that play a key role in the biogenesis of early-stage melanosomes are gp100/Pmel17, MART-1/Melan-A and the ocular albinism type 1 (OA1) G-protein-coupled receptor[19]. Cleavage and processing of gp100/Pmel17, an amyloidogenic protein, leads to a fibrillar matrix that acts as a scaffold upon which melanin is deposited[20]. As melanin is deposited within the melanosome, the organelle migrates via microtubules into the

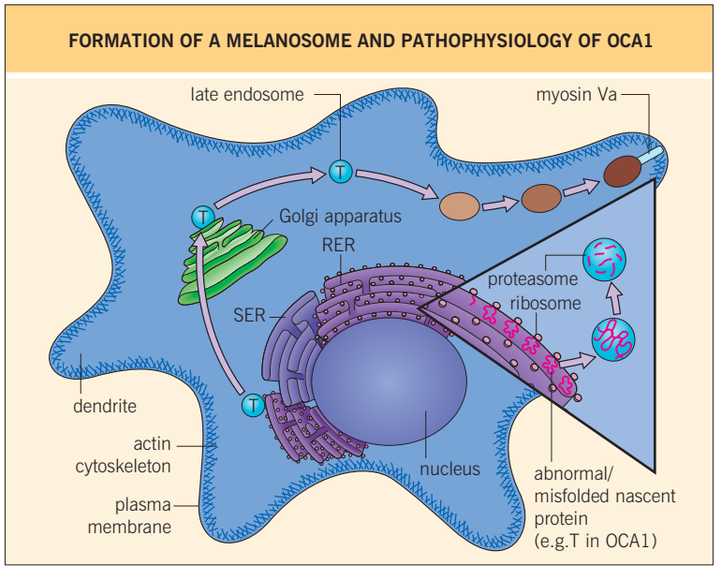


Fig. 65.7 Formation of a melanosome and pathophysiology of oculocutaneous albinism type 1 (OCA1). After glycosylation and processing within the endoplasmic reticulum and Golgi apparatus, several of the enzymes involved in the formation of melanin (including tyrosinase) are packaged in vesicles and then combine with the matrix proteins (e.g. gp100/Pmel17). As more melanin is deposited within the melanosomes, they migrate into the dendrites in preparation for their transfer into neighboring keratinocytes. In patients with OCA1 and OCA3 (triangular insert), tyrosinase polypeptides are retained too long within the lumen of the RER and then become targets for destruction within proteasomes. Thus, they are not incorporated into melanosomes. The primary matrix protein is gp100/Pmel17/silver protein (recognized by HMB45 antibody); formation of the matrix fibers requires cleavage of this protein by a proprotein convertase[15a]. Sorting of proteins to the correct organelles is a complex process and it requires regulators such as adaptor protein 3 (AP-3; see Fig. 65.8); in the case of tyrosinase, specific dileucine residues in its cytoplasmic tail aid in the sorting. RER, rough endoplasmic reticulum; SER, smooth endoplasmic reticulum; T, tyrosinase.

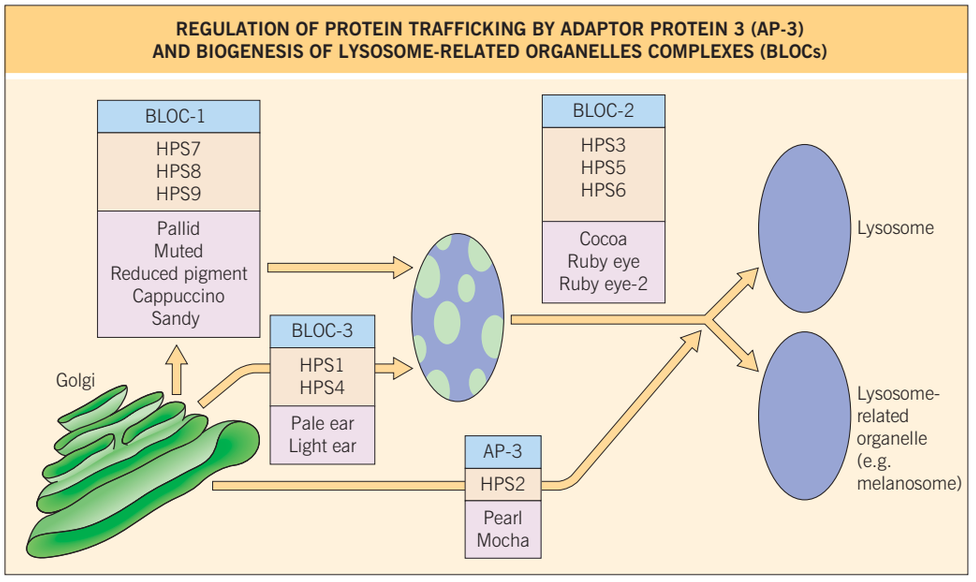


Fig. 65.8 Regulation of protein trafficking by adaptor protein 3 (AP-3) and biogenesis of lysosome-related organelles complexes (BLOCs). The various mouse phenotypes are in light purple-colored boxes. Lysosome-related organelles include melanosomes, platelet dense granules, and lytic granules of cytotoxic lymphocytes and natural killer cells. HPS, Hermansky–Pudlak syndrome. Subtypes of HPS that are associated with a particular BLOC can have similar clinical findings, e.g. patients with HPS1 and HPS4, both members of BLOC-3, develop pulmonary fibrosis and granulomatous colitis.

DISORDERS CHARACTERIZED BY DIFFUSE PIGMENTARY DILUTION IN WHICH THE GENETIC DEFECT IS KNOWN			
Disorder	**Gene**	**Protein product**	**Comments**
		OCULOCUTANEOUS ALBINISM (OCA)	
Type 1A	*TYR*	Tyrosinase	• Complete absence of tyrosinase activity and melanin production • Retention of tyrosinase protein within the ER
Type 1B	*TYR*	Tyrosinase	• Decreased tyrosinase activity; can produce pheomelanin • Retention of tyrosinase protein within the ER • Variant with temperature-sensitive tyrosinase (normal activity at 35°C, but diminished at 37°C)
Type 2	*OCA2* (*P*)	P protein	• Transmembrane protein found in the ER and melanosomes • Possible functions include regulating organelle pH, facilitating vacuolar accumulation of glutathione, and processing/trafficking of tyrosinase
Type 3 (rufous)	*TYRP1*	Tyrosinase-related protein 1*	• TYRP1 stabilizes tyrosinase in mice and humans, and it also functions as a DHICA oxidase in mice • Both "mutant" TYRP1 and tyrosinase are retained in the ER and then degraded
Type 4	*SLC45A2* (*MATP*)	Membrane-associated transporter protein	• Variable phenotype, with hair ranging from white to yellow–brown; most common in Asians • Transmembrane transporter with a role in tyrosinase processing and intracellular trafficking of proteins to the melanosome
		HERMANSKY–PUDLAK SYNDROME†	
1	*HPS1*	HPS1	• Defective trafficking of organelle-specific proteins to melanosomes, lysosomes and cytoplasmic granules (including platelet dense granules and lytic granules in cytotoxic T lymphocytes) • Component of BLOC-3 (see Fig. 65.8)
2	*AP3B1*	β3A subunit of AP-3	• AP-3 is involved in the trafficking of proteins from the trans-Golgi network to appropriate organelles (see Fig. 65.7) • Abnormal binding of AP-3 to CD1 may play a role in associated immunodeficiency
3	*HPS3*	HPS3	• Component of BLOC-2
4	*HPS4*	HPS4	• Component of BLOC-3
5	*HPS5*	Ruby-eye 2 (ru2)	• Component of BLOC-2
6	*HPS6*	Ruby-eye (ru)	• Component of BLOC-2
7	*DTNBP1*	Dysbindin	• Component of BLOC-1
8	*BLOC1S3*	BLOC1S3	• Component (subunit 3) of BLOC-1
9	*PLDN*	Pallidin	• Component of BLOC-1
		CHÉDIAK–HIGASHI SYNDROME	
	CHS1 (*LYST*)	Lysosomal trafficking regulator	• Abnormal vesicle trafficking and fission/fusion of lysosome-related organelles result in giant organelles (e.g. melanosomes, neutrophil granules [lysosomes], platelet dense granules)
		GRISCELLI SYNDROME	
1	*MYO5A*	Myosin Va (attaches melanosomes to actin filaments)	• In all three forms, melanosomes are retained in the body of the melanocyte rather than trafficking to the tips of dendrites for transfer to keratinocytes • Myosin Va expressed in neurons (as well as melanocytes) and dysfunction leads to neurologic abnormalities
2	*RAB27A*	RAB27A (melanosomal membrane GTPase that binds melanophilin)	• GTPase also expressed in hematopoietic cells; defective release of cytotoxic granule contents leads to recurrent infections and hemophagocytic syndrome
3	*MLPH*	Melanophilin (links myosin Va and RAB27A)	• Melanophilin only expressed in melanocytes, so only pigmentary dilution in type 3
	MYO5A	Myosin Va F-exon deletion	• F-exon only expressed in melanocytes

*Recognized by Mel-5 antibody.
†In mice, there are 15 inherited models of Hermansky–Pudlak syndrome; additional genes may be discovered in humans with the condition. Individuals of Puerto Rican origin have HPS1 and 3 (3:1 ratio, respectively); non-Puerto Ricans most commonly have HPS1, followed by 3 and 4.

Table 65.1 Disorders characterized by diffuse pigmentary dilution in which the genetic defect is known. See Chapter 66 for details of clinical findings. AP-3, adaptor protein 3; BLOC, biogenesis of lysosome-related organelles complex (see Fig. 65.8); DHICA, 5,6-dihydroxyindole-2-carboxylic acid; ER, endoplasmic reticulum; TYRP, tyrosinase-related protein.

FOUR MAJOR STAGES OF EUMELANIN MELANOSOMES

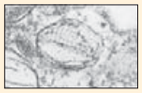
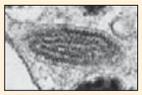
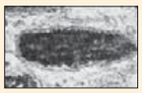
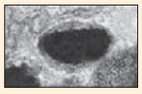
Stage	Description	Electron micrographs
I	Spherical; no melanin deposition	
II	Oval; obvious matrix in the form of parallel longitudinal filaments; minimal deposition of melanin; high tyrosinase activity	
III	Oval; moderate deposition of melanin; high tyrosinase activity	
IV	Oval; heavy deposition of melanin; electron-opaque; minimum tyrosinase activity	

Fig. 65.9 Four major stages of eumelanin melanosomes. *Courtesy, Raymond Boissy, PhD.*

MOVEMENT OF MELANOSOMES WITHIN MELANOCYTE DENDRITES

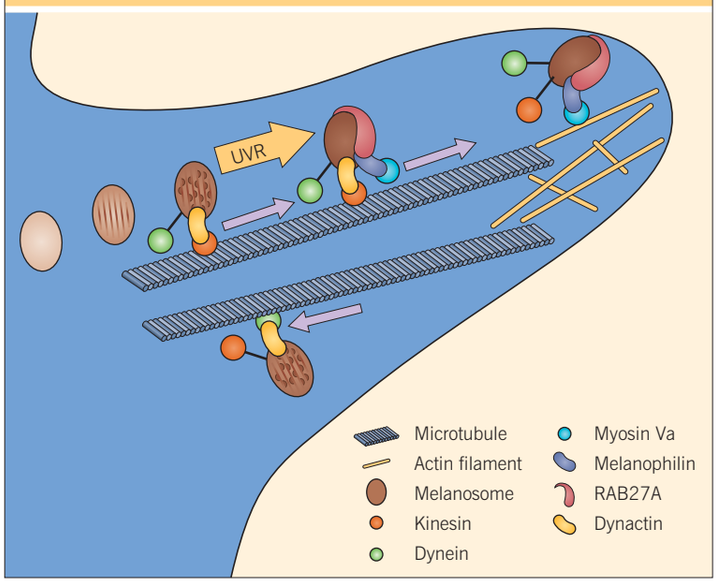


Fig. 65.10 Movement of melanosomes within melanocyte dendrites. As melanin is deposited within melanosomes, they migrate along microtubules from the cell body into dendrites in preparation for transfer to keratinocytes. Kinesin and dynein serve as molecular motors for microtubule-associated anterograde and retrograde melanosomal transport, respectively, and UVR results in augmented anterograde transport via increased kinesin and decreased dynein activity. Myosin Va, which is linked to the melanosomal RAB27A GTPase by melanophilin, captures mature melanosomes when they reach the cell periphery and attaches them to the actin cytoskeleton.

dendrites in preparation for transfer into the neighboring keratinocytes, either within the epidermis or within the anagen hair matrix. In addition to microtubules, proteins such as kinesin and dynein are involved in the movement of melanosomes (Fig. 65.10)[21].

Within the dendrites, there is a specialized myosin (Va) protein that aids in the process of melanosome transfer by assisting attachment between the actin cytoskeleton beneath the plasma membrane and the organelle itself (via RAB27A and melanophilin). The importance of the interactions between these three proteins – myosin Va, RAB27A and melanophilin – is illustrated by the three different forms of Griscelli syndrome in which there are mutations in the respective genes (see Table 65.1)[22,23]. The associated diffuse pigmentary dilution is a reflection of a lack of transfer of melanosomes from the melanocytes to nearby keratinocytes. Histologically, numerous melanosomes are seen to congregate within the center of the melanocytes.

VARIATION OF PREDOMINANT MELANOSOMAL STAGES WITH LEVEL OF CUTANEOUS PIGMENTATION

	Predominant melanosomal stages	
Pigmentation of skin	Melanocytes	Keratinocytes
Fair	II, III	Occasional III
Medium	II, III, IV	III, IV
Dark	IV > III	IV

Table 65.2 Variation of predominant melanosomal stages with level of cutaneous pigmentation.

MELANOSOMES IN LIGHTLY PIGMENTED VERSUS DARKLY PIGMENTED SKIN

	Lightly pigmented skin	Darkly pigmented skin
Melanization	Stages II, III	Stage IV
Size (diameter)	0.3–0.5 microns	0.5–0.8 microns
Number per cell	<20	>200
Distribution of melanosomes within the lysosomes of keratinocytes	Groups of 2–10	Single
Degradation	Fast	Slow

Table 65.3 Melanosomes in lightly pigmented versus darkly pigmented skin.

To reiterate, normal pigmentation of the skin is dependent on an orderly transfer of melanosomes from melanocytes to keratinocytes. When this transfer is disrupted, either in inherited diseases such as Chédiak–Higashi and Griscelli syndromes or in acquired diseases such as atopic dermatitis, the result is hypopigmentation. In the former there is diffuse pigmentary dilution, whereas in the latter the hypopigmentation is circumscribed. Phagocytosis of melanosomes by keratinocytes can be triggered by activation of the keratinocyte growth factor (KGF) receptor (KGFR/FGFR2b) by KGF, also referred to as fibroblast growth factor 7[24], as well as by activation of protease-activated receptor 2 (PAR-2). Inhibitors of PAR-2 receptor–ligand interactions (e.g. inhibitors of serine proteases) have led to cutaneous hypopigmentation in animal models[25] and in the future may be used to treat disorders of hyperpigmentation.

In summary, it is the activity of the melanocytes and their interactions with neighboring keratinocytes, not their density, that is the major determinant of normal skin color. The activity of a melanocyte is reflected in the number of melanized melanosomes it produces as well as in its efficiency at transferring those melanosomes to keratinocytes. For example, primarily stage II and stage III melanosomes are seen in lightly pigmented skin, whereas primarily stage IV melanosomes are seen in darkly pigmented skin (Table 65.2). An additional factor is the rate of degradation of the melanosomes once they are transferred to the surrounding keratinocytes and this is related in part to the size of the individual melanosomes. The smaller melanosomes of lightly pigmented skin are clustered in groups of two to ten within secondary lysosomes in the keratinocytes and are degraded by the mid stratum spinosum (Table 65.3)[14]. In darkly pigmented skin, the melanosomes are larger and singly dispersed within lysosomes of the keratinocytes; they are degraded more slowly, such that melanin granules can still be found in the stratum corneum.

REGULATION OF MELANIN BIOSYNTHESIS

This section will begin with a review of the melanin biosynthetic pathway and then examine the factors, both external and internal, that

can influence the level of melanin production. The "starting material" for the production of melanin, both the brown–black eumelanin and the yellow–red pheomelanin, is the amino acid tyrosine. The key regulatory enzyme in the pathway is tyrosinase, which controls the initial biochemical reaction in this pathway, tyrosine hydroxylation. Tyrosinase also catalyzes additional steps in the biosynthesis of melanin, e.g. the oxidation of dihydroxyindole (Fig. 65.11). It should then come as no surprise that the initial investigations into the molecular basis of OCA focused on the gene that encodes tyrosinase.

In OCA1A, the form of OCA where mutations in both copies of the tyrosinase gene lead to complete loss of enzyme activity, no melanin is found in the hair, skin or eyes (see Table 65.1). However, in OCA1B, where there is decreased enzyme activity, pheomelanin is produced, especially in the hair as the patient ages. As a result, patients with this form of OCA were previously referred to as yellow mutants, a name that has fallen out of favor for obvious reasons. The formation of pheomelanin requires less tyrosinase activity than does the formation of eumelanin (see Fig. 65.11) and therefore the formation of pheomelanin can be thought of as a default pathway.

The activity of tyrosinase is enhanced by DOPA and is stabilized by tyrosinase-related protein 1 (TYRP1) (see below). Competitive inhibitors of tyrosinase activity include hydroquinone, which is used to treat disorders of hyperpigmentation such as melasma, and L-phenylalanine. In patients with phenylketonuria (PKU), there is a diffuse pigmentary dilution due to elevated levels of L-phenylalanine resulting from a deficiency in the enzyme L-phenylalanine hydroxylase that converts L-phenylalanine to L-tyrosine[14]. The characteristic blonde hair of PKU can undergo darkening when the patient is on a low-phenylalanine diet. Of note, tyrosinase is a copper-requiring enzyme and it has two putative copper-binding sites. Rare cases of copper deficiency can lead to diffuse cutaneous pigmentary dilution, and in patients with Menkes kinky hair disease, where a transmembrane Cu^{2+}-transporting ATPase that delivers copper to melanosomes is dysfunctional[26], the kinky hair is hypopigmented.

In a test tube, L-DOPA can spontaneously oxidize to form melanin, an insoluble biopolymer. For this reason, original descriptions of the melanin biosynthetic pathway had tyrosinase as its sole enzyme. However, by the late 1970s, it was becoming clear that there were additional control points in the pathway (see Fig. 65.11). For example, tyrosinase-related protein 2 (TYRP2), so named because its amino acid sequence is similar to that of tyrosinase, converts DOPAchrome to 5,6-dihydroxyindole-2-carboxylic acid (DHICA), hence its initial name DOPAchrome tautomerase. In mice and humans, TYRP1 stabilizes tyrosinase[27] and mutations in both copies of the *TYRP1* gene lead to OCA3 (rufous OCA; see Table 65.1).

Decreased function of yet another transmembrane protein, the P protein (Fig. 65.12), leads to OCA2[28] (see Table 65.1). Based upon its amino acid sequence, a prediction was made that the P protein was involved in the transport of small molecules across the membrane of the melanosome. Tyrosine, the initial precursor in the melanin biosynthetic pathway, was considered the most likely candidate for transmembrane transport. However, this appears not to be the case. More recent data suggest that the P protein regulates processing and trafficking of tyrosinase, possibly via control of pH or glutathione content within intracellular compartments[29].

Melanins represent a group of complex polymers whose functions vary from camouflage to the quenching of oxidative free radicals generated via exposure to UV radiation (UVR). The level and type of melanin production is a complex interplay of the activity of the various enzymes involved in the biosynthetic pathway as well as the activity of proteins such as the P protein and those that stabilize the activity of tyrosinase (e.g. TYRP1). Several factors are known to influence the activity of

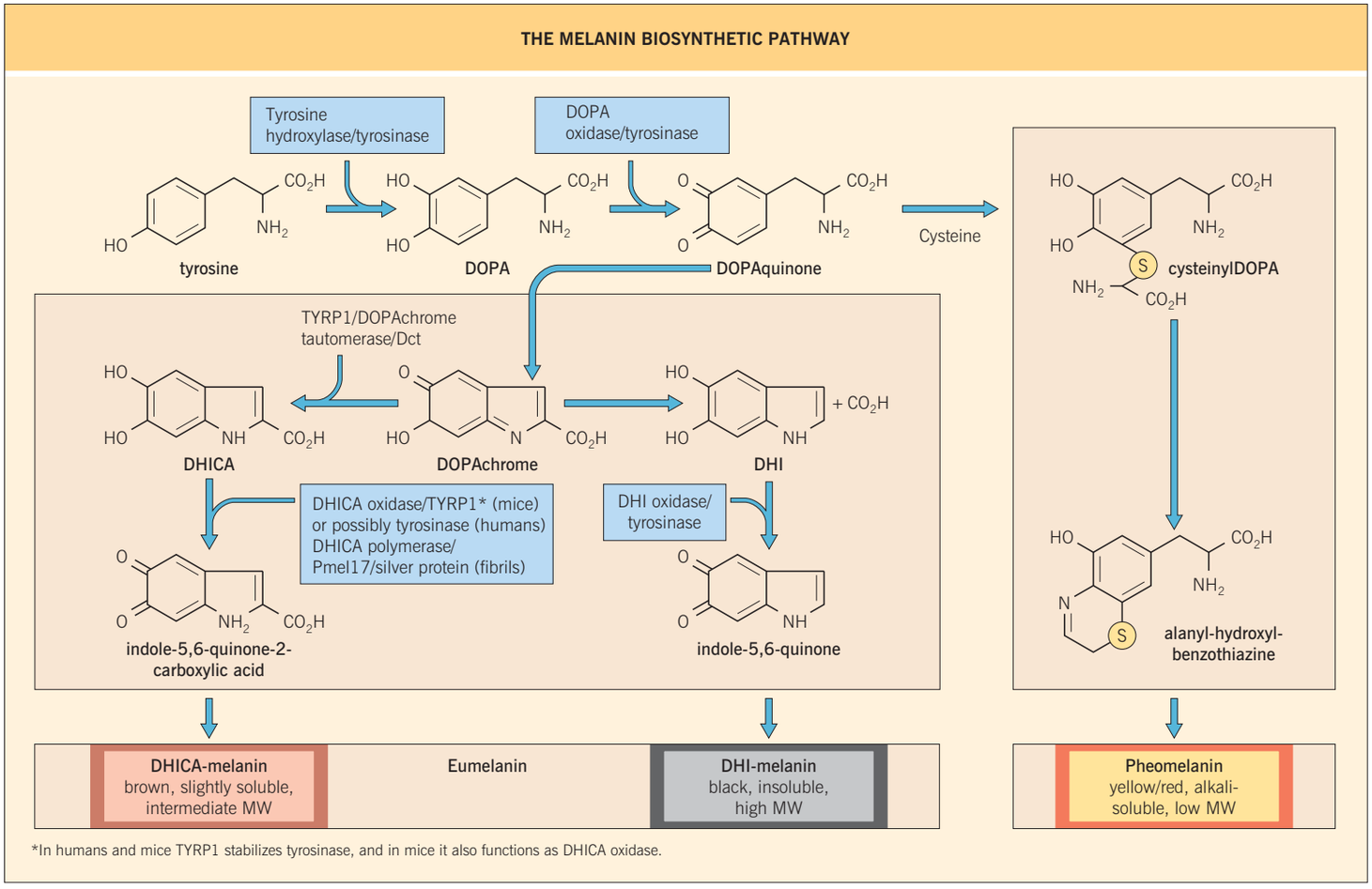


Fig. 65.11 The melanin biosynthetic pathway. The pathway includes the sites of dysfunction in OCA1 (tyrosinase) and OCA3 (TYRP1). The two major forms of melanin in the skin and hair are brown–black eumelanin and yellow–red pheomelanin. The enzymes are transmembrane proteins located within the melanosome. DHI, 5,6-dihydroxyindole; DHICA, 5,6-dihydroxyindole-2-carboxylic acid; DOPA, dihydroxyphenylalanine; MW, molecular weight; TRP, tyrosinase-related protein.
Courtesy, Vincent Hearing, PhD.

these key proteins of melanogenesis, and they include MSH, basic fibroblast growth factor (bFGF), endothelin-1 and UV light (see below).

Among the multiple protein products of the proopiomelanocortin (*POMC*) gene are adrenocorticotropic hormone (ACTH), β-endorphin, and the three forms of MSH (α, β and γ) (Fig. 65.13); in humans, α-MSH represents the major biologically active form of MSH. The primary site of expression of the *POMC* gene is the pituitary gland; however, other sites of expression include the testis, the endothelium, and, of particular importance, the epidermis (keratinocytes). Although MSH is classically associated with the pigmentary system, this peptide has a wide range of biologic properties, including suppression of inflammation and regulation of body weight. For example, mutations in the *POMC* gene can result in severe early-onset obesity, adrenal insufficiency and red hair[30]. It should then come as no surprise that mutations in the genes that encode the receptors to which the protein products of the *POMC* gene bind can lead to similar clinical findings; for example, mutations in the *MC4-R* gene are associated with morbid obesity and "mutations" (variants) in the *MC1-R* gene are associated with red hair (see below). Of note, afamelanotide (4-norleucyl-7-phenylalanine-α-MSH), which has enhanced binding to MC1-R, can lead to cutaneous hyperpigmentation when administered subcutaneously; patients with erythropoietic protoporphyria treated with a subcutaneous implant of afamelanotide experienced less phototoxic reactions and could tolerate more direct sunlight without pain.

As outlined in Table 65.4, there are five major melanocortin receptors, all of which have seven transmembrane domains (Fig. 65.14). Although the MC1-R is present on a variety of cells found within the

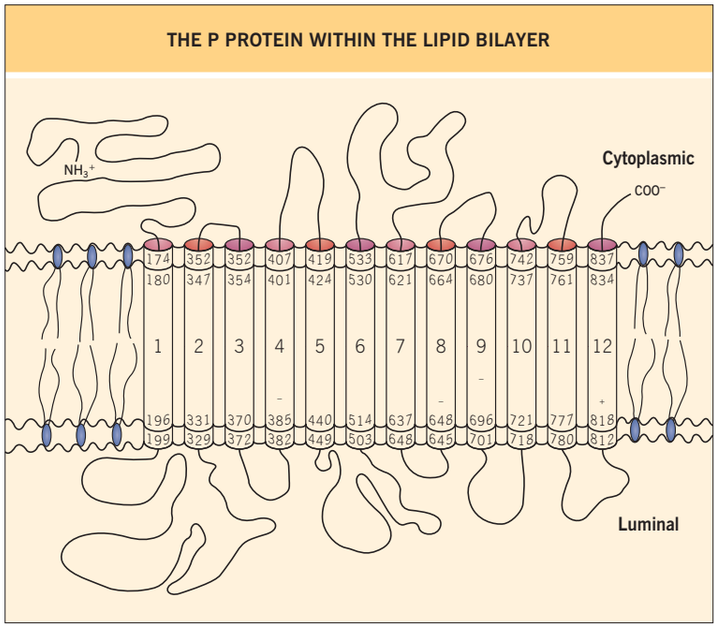


Fig. 65.12 The P protein within the lipid bilayer. The polypeptide has 12 putative transmembrane domains. The membrane-associated transporter protein (MATP) which is dysfunctional in OCA4 has a similar configuration within the plasma membrane. *Adapted from Rinchik EM, Bultman SJ, Horsthemke B, et al. A gene for the mouse pink-eyed dilution locus and for human type II oculocutaneous albinism. Nature. 1993;361:72–6.*

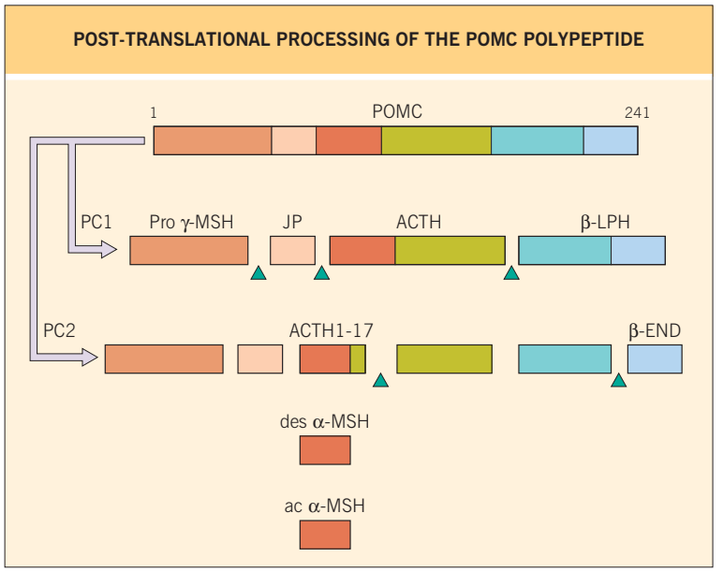


Fig. 65.13 Post-translational processing of the POMC polypeptide. Pituitary hypersecretion of ACTH and/or α-MSH can lead to generalized hyperpigmentation in patients with Addison's disease. ac, acetylated; ACTH, adrenocorticotropic hormone; des, desacetyl; END, endorphin; JP, joining peptide; LPH, lipotropic hormone; MSH, melanocyte stimulating hormone; PC, prohormone-converting enzyme; POMC, proopiomelanocortin.

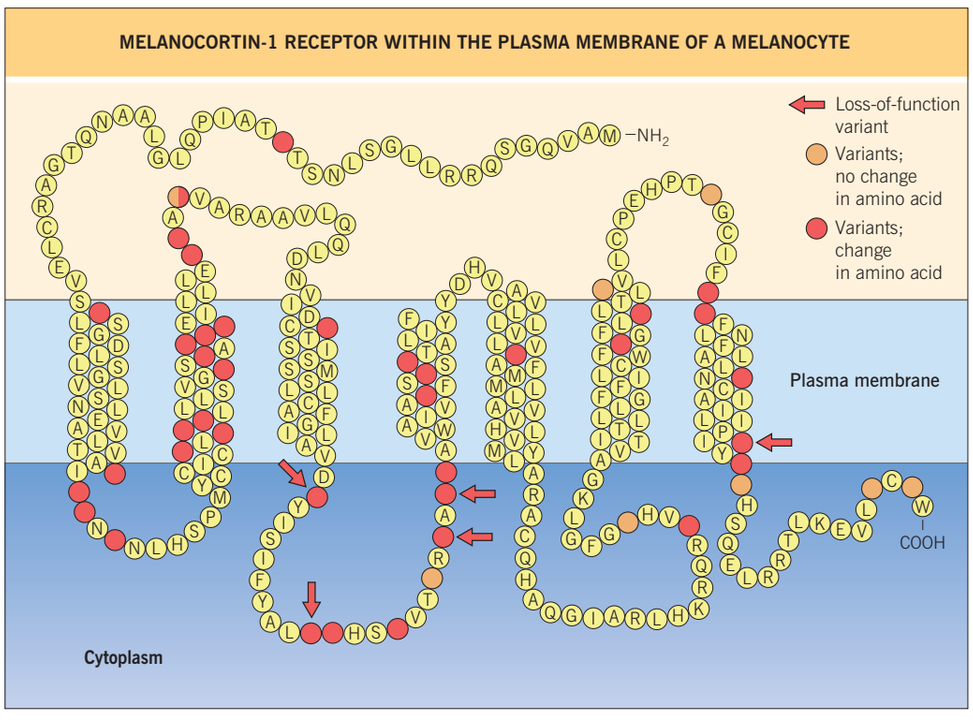


Fig. 65.14 Melanocortin-1 receptor within the plasma membrane of a melanocyte. The red dots represent alterations in the amino acid sequence (variants) compared with the wild type. Some of the variants are due to loss-of-function mutations, i.e. the expected increase in intracellular cAMP is not observed following the binding of MSH, whereas others have no effect on function or lead to decreased function. Loss-of-function variants, e.g. Arg151Cys, Arg160Trp and Asp294His, have been associated with red hair as well as cutaneous melanoma (see Table 65.5). The tan dots represent synonymous variants where there is no change in amino acid sequence.

MAJOR FORMS OF THE MELANOCORTIN RECEPTOR		
Receptor	**Distribution, major (minor)**	**Ligands**
MC1-R*	Melanocytes (keratinocytes, fibroblasts, endothelial cells, antigen-presenting cells)	α-MSH, ACTH > β-MSH
MC2-R	Adrenal cortex (adipocytes)	ACTH
MC3-R†	Brain (gut, placenta)	α-, β-, γ–MSH, ACTH
MC4-R†	Brain	α-, β-MSH, ACTH
MC5-R	Peripheral tissues (sebaceous glands, fibroblasts, adipocytes)	α-, β-MSH, ACTH

*Antagonistic ligands – agouti protein (mouse) and agouti signaling protein (ASIP; human).
†Antagonistic ligand – agouti-related protein (AGRP).

Table 65.4 Major forms of the melanocortin receptor (MCR). ACTH, adrenocorticotropic hormone; MSH, melanocyte stimulating hormone.

skin, from endothelial cells to fibroblasts, the highest density of this receptor is seen on melanocytes[31]. As in the case of the β-adrenergic receptor, the MC1-R is a G-protein-coupled receptor, i.e. it uses proteins that bind guanosine triphosphate (GTP) and guanosine diphosphate (GDP) as intermediary messengers (Fig. 65.15). Following the binding of MSH to the MC1-R, the protein pair interacts with a complex of G proteins. The GTP-$G_s\alpha$ subunit then activates adenylate cyclase, leading to increased production of cyclic adenosine monophosphate (cAMP) within the melanocyte. An increase in the intracellular concentration of cAMP leads to an increase in tyrosinase activity and eumelanin production via MITF (see Fig. 65.4). If the MC1-R is dysfunctional and fails to initiate a significant rise in the intracellular level of cAMP, then pheomelanogenesis is favored (Fig. 65.16). Of note, the majority of individuals with red hair are compound heterozygotes or homozygotes for a loss-of-function mutation in the gene that encodes the MC1-R[1,32] (see Fig. 65.14).

MC1-R also interacts with a protein known as the agouti protein (mouse) or agouti signaling protein (ASIP; human). Agouti is a term

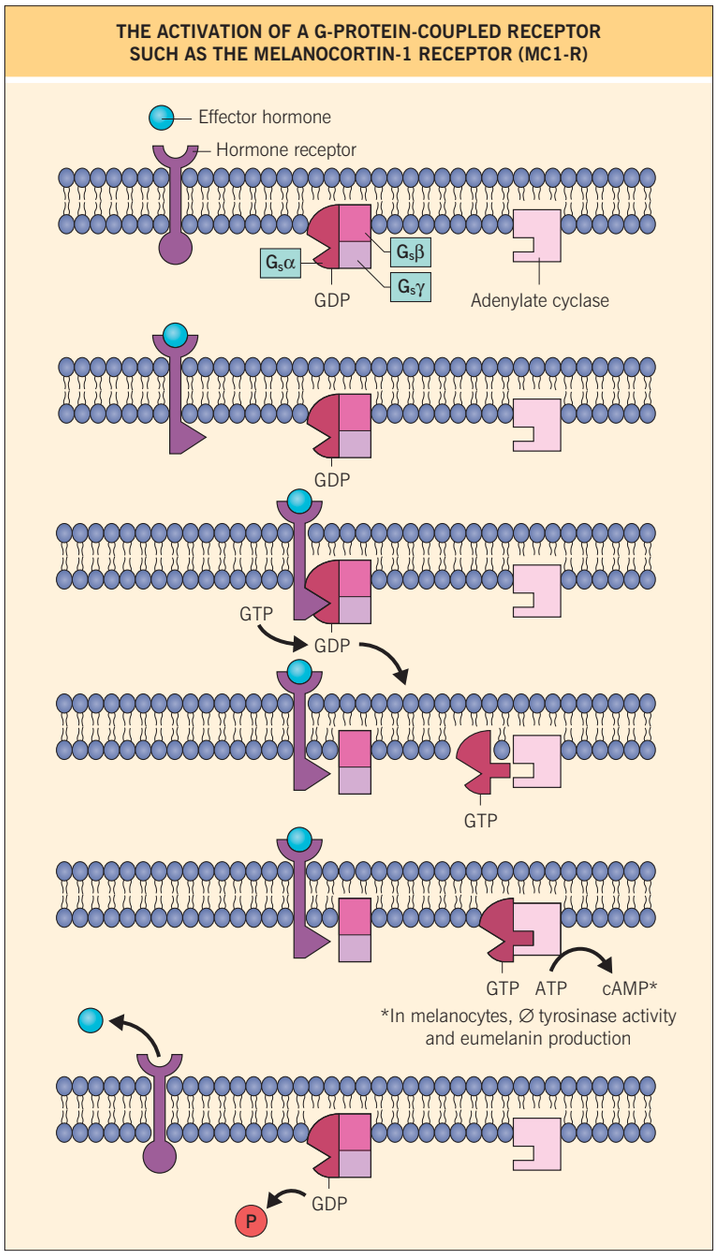


Fig. 65.15 Activation of a G-protein-coupled receptor such as the melanocortin-1 receptor (MC1-R). In the case of the MC1-R, the increase in the intracellular concentration of cAMP leads to an increase in tyrosinase activity and eumelanin production. GDP, guanosine diphosphate; GTP, guanosine triphosphate; P, phosphate group; S, stimulatory. *Adapted from Alberts B. Molecular Biology of the Cell. Garland Publishing; 1989.*

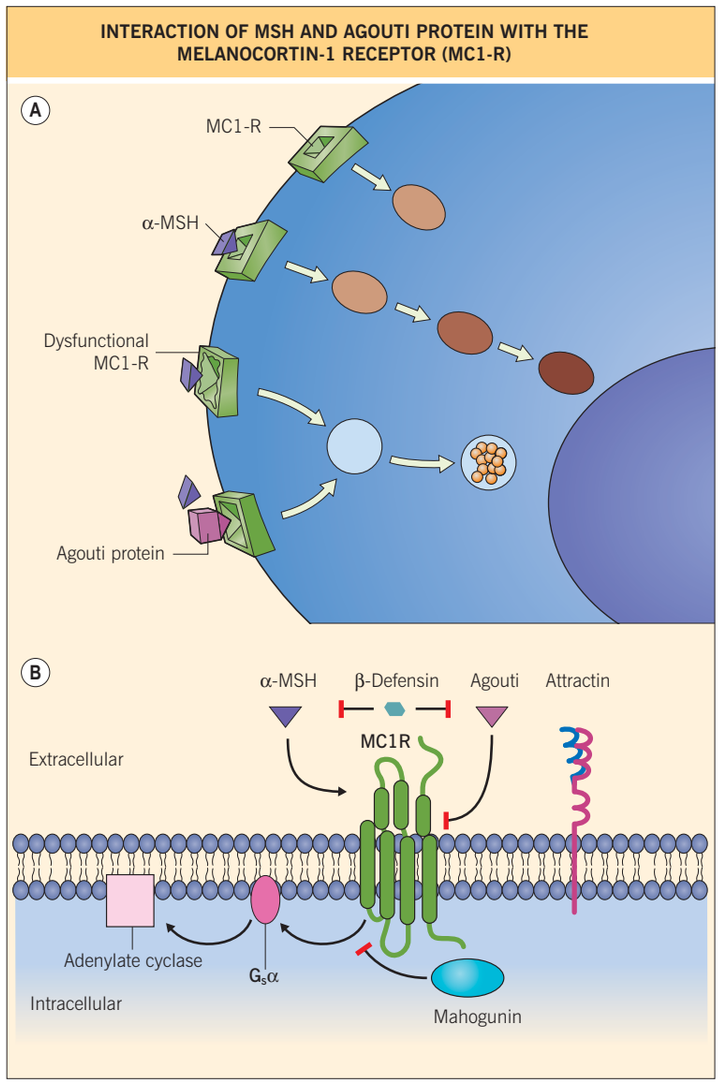


Fig. 65.16 Interaction of melanocyte stimulating hormone (MSH) and agouti protein with the melanocortin-1 receptor (MC1-R). A There is baseline activity of the MC1-R, enhanced by binding with MSH. Agouti protein represents an antagonist ligand for the MC1-R whose binding can lead to pheomelanogenesis. Dysfunction of the MC1-R can also lead to pheomelanogenesis, as in the case of humans with red hair. **B** Interactions are actually more complex, in that to be fully effective, agouti requires attractin and mahogunin; the former aids in the binding of agouti to MC1-R while the latter acts on the cytosolic side. There is also a neutral agonist, β-defensin, which interferes with both agonist and antagonist binding. *Adapted from Schiaffino MV. Signaling pathways in melanosome biogenesis and pathology. Int J Biochem Cell Biol. 2010;42:1094–104.*

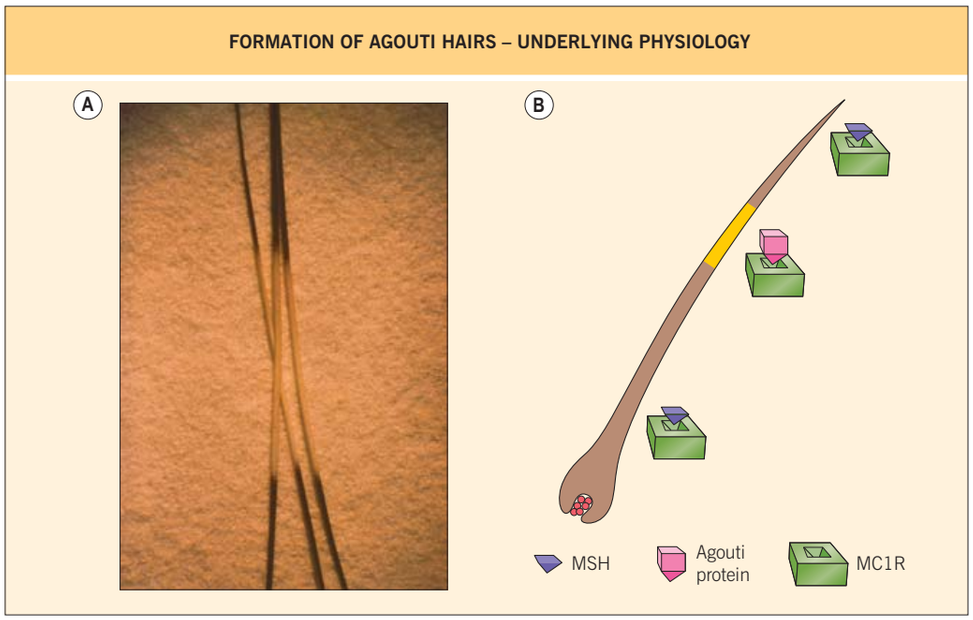


Fig. 65.17 Formation of agouti hairs – underlying physiology. A Fox hairs with alternating eumelanin and pheomelanin production within individual hairs, a pattern referred to as agouti. **B** Explanation for the agouti pattern based on different ligands interacting with the melanocortin 1 receptor (MC1-R). Both gain-of-function mutations at the agouti locus and loss-of-function of MC1-R can lead to yellow-haired mice. In the CNS, an abundance of agouti protein leads to obesity, and yellow mice with gain-of-function mutations at the agouti locus are also obese[33].

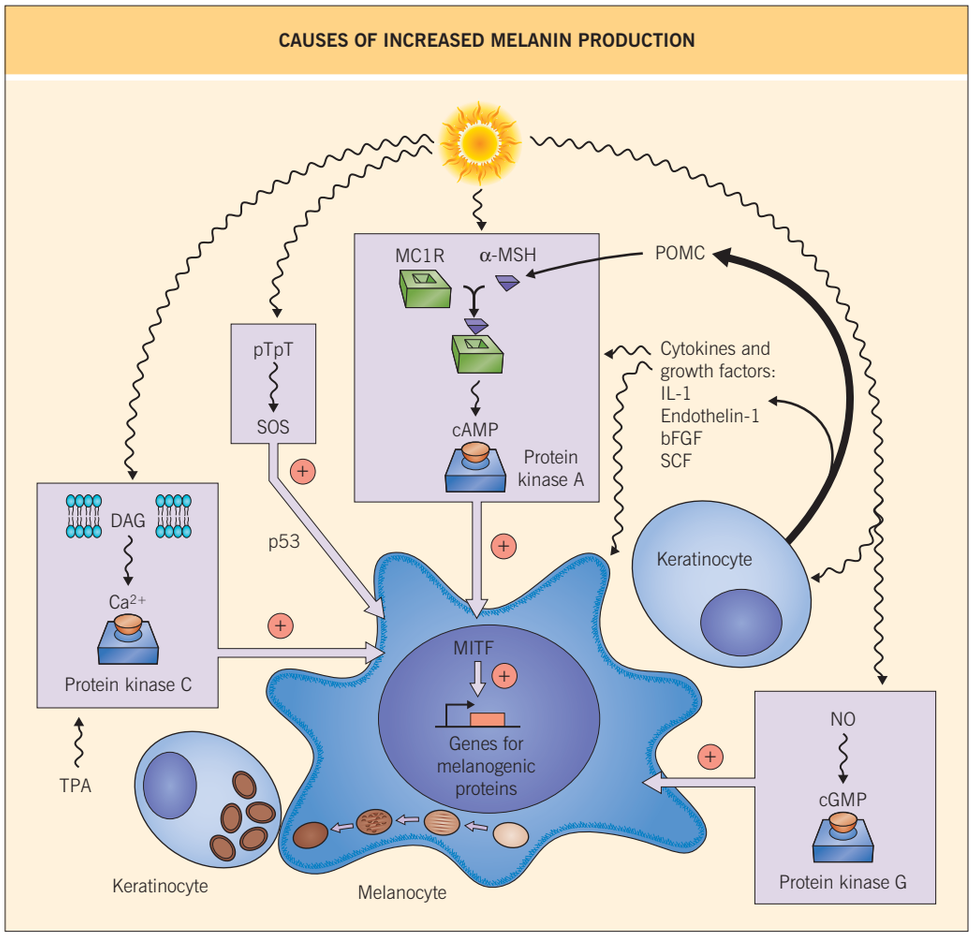


Fig. 65.18 Causes of increased melanin production. These include an increase in one or more of the following: (1) expression of proopiomelanocortin (POMC) and its derivative peptides by cells within the skin, in particular keratinocytes; (2) the number of melanocortin-1 receptors (MC1-R) on melanocytes; (3) the release of diacylglycerol (DAG) from the plasma membrane, which activates protein kinase C; (4) the induction of an SOS response to UVR-induced DNA damage; (5) nitric oxide (NO) production, which activates the cGMP pathway; and (6) production of cytokines and growth factors by keratinocytes. As a result, there is enhanced transcription of the genes that encode microphthalmia-associated transcription factor (MITF) and melanogenic proteins including tyrosinase, tyrosinase-related protein 1 (TYRP1), TYRP2, gp100/Pmel17, and P. In addition, melanocyte dendricity and transfer of melanosomes to keratinocytes is stimulated via increased activity of Rac1 (involved in dendrite formation), the ratio of kinesin to dynein, and expression of protease-activated receptor-2 (PAR2; involved in melanosome transfer). TPA, tetradecanoyl phorbol acetate.

used to describe the banding of hairs seen in some mammals, e.g. dogs, foxes and mice, which is due to alternating production of eumelanin and pheomelanin (Fig. 65.17). The production of agouti protein by the cells in the hair papillae is cyclic, and, when the agouti protein is present, it effectively competes with MSH and the formation of pheomelanin within pheomelanosomes is favored[34,35] (see Fig. 65.16); the latter are characterized by a more spherical shape (compared with eumelanosomes) and the presence of an unstructured matrix with vesicular bodies.

An enhancement of pigment production can be seen following exposure of melanocytes to agents that increase intracytoplasmic levels of cAMP (see Fig. 65.15) such as cholera toxin, forskolin[36], dibutyryl cAMP and MSH. The activation of protein kinase A (PKA) by cAMP leads to the placement of phosphate groups on other proteins, which leads to their activation. One of the proteins that is phosphorylated by PKA is the *c*AMP *r*esponse-*e*lement *b*inding protein (CREB), which functions as a transcription factor, regulating the expression of other genes, including *MITF* (see Fig. 65.4). Patients with the

McCune–Albright syndrome (polyostotic fibrous dysplasia) are mosaics for an activating mutation in the gene that encodes the G protein $G_s\alpha$ (see Fig. 65.15). As a result, the cAMP cascade is permanently "turned on" and, with continued transcription of the CREB-controlled genes, there is hyperplasia of the bones and endocrine organs, albeit in a mosaic pattern. Presumably within the segmental café-au-lait macules typical of this disorder, the increase in intracellular cAMP leads to increased tyrosinase activity and eumelanin production.

Exposure of melanocytes to phorbol esters, e.g. tetradecanoyl phorbol acetate (TPA), can lead to increased melanin formation via the activation of protein kinase C (PKC) (Fig. 65.18). Growth factors, in particular bFGF, can also lead to an increase in the pigment content within melanocytes. Endothelin-1, a small peptide originally isolated from endothelial cells, is produced by keratinocytes and can lead to an increase in tyrosinase activity followed by an increase in melanin production.

Multiple genes have been implicated as playing a role in normal pigment variation in humans, including *MC1-R*, *SLC24A5*, *ASIP* and *OCA2 (P)* (Table 65.5)[2,3]. For example, the presence of a variant (rather than the African ancestral) allele of *SLC24A5*, whose protein product is a putative cation exchanger in the melanosomal membrane, correlates with lighter skin color[4]. In addition, variants in the *OCA2 (P)* gene are thought, at least in part, to determine the normal phenotypic variation in human eye color[2]. A haplotype with several polymorphisms in *ASIP* (and presumably a gain of ASIP function) has been associated with red or blonde hair, freckling and a tendency to burn, while variants that lead to destabilized *ASIP* mRNA have been associated with darker skin phototypes[3,37,38]. Of note, some loss-of-function mutations in *MC1-R* confer a risk for developing cutaneous melanoma, independent of pigmentary phenotype (see Table 65.5)[32].

Ultraviolet Irradiation

Following a single exposure to UVR, an increase in the size of melanocytes can be observed, along with an increase in tyrosinase activity[14]. Repeated exposures to UVR lead to an increase in the number of stage IV melanosomes transferred to keratinocytes, as well as an increase in the number of active melanocytes. When chronically sun-exposed sites (e.g. the upper outer arm) are compared with non-sun-exposed sites

GENES ASSOCIATED WITH PHYSIOLOGIC VARIATION IN HUMAN PIGMENTATION

Gene	Protein	Selected variant(s): amino acid alteration (if applicable) or SNP	Skin color, sun sensitivity, and freckles	Hair color	Eye color	Skin cancer risk*	Population frequencies of variant haplotype		
							European	East Asian	African
TYR	Tyrosinase	Ser192Tyr	Freckles	–	–	SCC	0.4	0	0
		Arg402Gln	Fair, sun-sensitive	Light (weak)	Blue (vs green)	Melanoma, BCC	0.4	0	0.07
TYRP1	TYRP1	rs1408799 C>T	Sun-sensitive	Light	Blue	Melanoma	0.7	0.02	0.2
		rs2733832 C>T	–	Light	Blue	–	0.6	0.02	0.07
OCA2 (P)	P protein	Arg305Trp	–	–	Brown	–	0.07	0.04	0.02
		Arg419Gln	–	–	Green/hazel	Melanoma, BCC	0.07	–	0
		His615Arg	–	–	Brown	–	0	0.5	0
		rs12913832 T>C in *HERC2*†	Fair	Light	Blue	Melanoma (weak)	0.75	–	–
SLC45A2	MATP	Glu272Lys	Dark	Dark	Non-blue	–	0	0.4	0.05
		Leu374Phe	Fair	Light	Blue	Melanoma, NMSC	0.95	0.01	0
SLC24A5	NCKX5	Ala111Thr	Light	–	–	–	0.99	0.01	0.02
SLC24A4	SLC24A4	rs12896399 G>T	Sun-sensitive	Light	Blue (vs green)	–	0.6	0.5	0.01
MC1R	MC1R	R alleles‡	Fair, sun-sensitive, freckles	Red/light	–	Melanoma, NMSC	0.3	0	0
		r alleles§	Variable	Variable	–	Melanoma, NMSC	0.3	0.4	0.01
ASIP	ASIP	g.8818 A>G	Dark	Dark	Brown	–	0.15	–	0.6
		ASIP haplotype‖	Fair, sun-sensitive, freckles	Red/light	Light	Melanoma, NMSC	0.1–0.3	0–0.2	0–0.1
KITLG	KIT ligand	rs642742 A>G	Fair	–	–	–	0.85	0.8	0.07
		rs12821256 T>C	–	Light	–	–	0.15	0	0
TPCN2	TPCN2	Met484Leu	–	Light	–	–	0.2	0	0
		Gly734Gln	–	Light	–	–	0.4	0.2	0.02
IRF4	Interferon regulatory factor 4	rs12203592 C>T	Fair, sun-sensitive	Dark	Blue	–	0.8	0	0
		rs1540771 G>A	Sun-sensitive, freckles	Dark (weak)	–	–	0.5	0.2	0.05

*Independent of pigmentary phenotype.
†Intronic regulatory region that determines expression of the *OCA2* gene; other intronic polymorphisms in the *HERC2* gene have also been linked to decreased pigmentation, with the same proposed mechanism.
‡High-penetrance, loss-of-function "red hair color" alleles, e.g. Asp84Glu, Arg151Cys, Arg160Trp, and Asp294His.
§Low-penetrance alleles, e.g. Val60Leu, Val92Met, and (especially in East Asians) Arg163Gln.
‖Single long (~1.8 Mb) haplotype that includes multiple single nucleotide polymorphisms (SNPs; e.g. rs4911414 G>T and rs4911442 A>G) and encompasses several smaller haplotype blocks.

Table 65.5 Genes associated with physiologic variation in human pigmentation[44–49]. Gray highlight = polymorphism associated with darker pigmentation. The genes in the first four rows are those responsible for OCA types 1 to 4. ASIP, agouti signaling protein; BCC, basal cell carcinoma; MATP, membrane-associated transporter protein; MC1R, melanocortin-1 receptor; NCKX5, Na-Ca-K exchanger 5; NMSC, non-melanoma skin cancer; SCC, squamous cell carcinoma; SLC24A4/5, solute carrier family 24, member 4/5; SLC45A2, solute carrier family 45, member 2; TPCN2, two-pore segment channel 2; TYRP1, tyrosinase-related protein 1. *From Schaffer JV, Bolognia JL. The biology of the melanocyte. In: Cancer of the Skin. Rigel DS, et al. (eds). 2nd ed. St Louis, MI: Elsevier, 2011:23–39.*

(e.g. the upper inner arm), the density of melanocytes is up to two times greater in sun-exposed sites[39]. Melanocytes, like other neural-derived tissues, have a low mitotic rate, and whether this increase in number represents an increase in mitotic rate or an activation of "inactive" melanocytes or melanocyte precursors is not known.

Following exposure to UVA irradiation, an *immediate pigmentary darkening* can be observed, which occurs within minutes and fades over 6–8 hours. It is clinically most obvious in darkly pigmented skin and is thought to represent oxidation of pre-existing melanin or melanin precursors. *Delayed tanning* is visible within 48–72 hours of exposure to UVB and UVA radiation and represents new pigment production via an increase in tyrosinase activity. In addition to an increase in melanocyte size and number, tyrosinase activity, and transfer of melanosomes to keratinocytes, the response to PUVA includes an alteration in size and aggregation pattern of melanosomes, i.e. from smaller and grouped to larger and singly dispersed (see Table 65.3).

UVR may work by increasing one or more of the following:

- transcription of the tyrosinase gene (via MITF)
- the number or activity of MC1-R on melanocytes
- the expression of POMC and its derivative peptides by keratinocytes and other cells within the dermis
- the release of diacylglycerol from the plasma membrane, which activates protein kinase C
- an activation of the nitrous oxide/cGMP pathway
- the production of cytokines and growth factors (e.g. endothelin-1) by keratinocytes
- the induction of an SOS response to UVR-induced DNA damage[31,40,41]
- transactivation of the *POMC* promoter by p53[42,43]
- the ratio of kinesin to dynein (see Fig. 65.10).

The inability of the majority of red-haired individuals to develop a tan following exposure to UVR can be explained, at least in part, by dysfunction of the MC1-R on their melanocytes. This phenomenon, along with the production of oxygen radicals following the UV irradiation of pheomelanins, probably contributes to the increased incidence of both cutaneous melanoma and non-melanoma skin cancers in persons with red hair.

REFERENCES

1. Valverde P, Healy E, Jackson I, et al. Variants of the melanocyte-stimulating hormone receptor gene are associated with red hair and fair skin in humans. Nat Genet. 1995;11:328–30.
2. Sturm RA. Molecular genetics of human pigmentation diversity. Hum Mol Genet. 2009;18:R9–17.
3. Nan H, Kraft P, Hunter DJ, Han J. Genetic variants in pigmentation genes, pigmentary phenotypes, and risk of skin cancer in Caucasians. Int J Cancer. 2009;125:909–17.
4. Lamason RL, Mohideen MA, Mest JR, et al. SLC24A5, a putative cation exchanger, affects pigmentation in zebrafish and humans. Science. 2005;310:1782–6.
5. Adameyko I, Lallemend F, Aquino JB, et al. Schwann cell precursors from nerve innervations are a cellular origin of melanocytes in skin. Cell. 2009;139:366–79.
6. Wang ZQ, Si L, Tang Q, et al. Gain-of-function mutation of KIT ligand on melanin synthesis causes familial progressive hyperpigmentation. Am J Hum Genet. 2009;84:672–7.
7. Lin JY, Fisher DE. Melanocyte biology and skin pigmentation. Nature. 2007;445:843–50.
8. Cheli Y, Ohanna M, Ballotti R, Bertolotto C. Fifteen-year quest for microphthalmia-associated transcription factor target genes. Pigment Cell Melanoma Res. 2010;23: 27–40.

8a. Rabbani P, Takeo M, Chou WC, et al. Coordinated activation of Wnt in epithelial and melanocyte stem cells initiates pigmented hair regeneration. Cell. 2011;145: 941–55.

9. Zimmerman AA, Becker SW Jr. Precursors of epidermal melanocytes in the Negro fetus. In: Gordon M (ed). Pigment Cell Biology. New York: Academic Press, 1959: 159–70.
10. Horikawa T, Norris DA, Johnson TW, et al. DOPA-negative melanocytes in the outer root sheath of human hair follicles express premelanosomal antigens but not a melanosomal antigen or the melanosomeassociated glycoproteins tyrosinase, TRP-1, and TRP-2. J Invest Dermatol. 1996;106:28–35.
11. Tobin DJ, Bystryn JC. Different populations of melanocytes are present in hair follicles and epidermis. Pigment Cell Res. 1996;9:304–10.
12. Holbrook KA, Underwood RA, Vogel AM, et al. The appearance, density and distribution of melanocytes in human embryonic and fetal skin revealed by the antimelanoma monoclonal antibody, HMB-45. Anat Embryol. 1989;180:443–55.
13. Jimbow K, Quevedo WC Jr, Fitzpatrick TB, et al. Some aspects of melanin biology: 1950–1975. J Invest Dermatol. 1976;67:72–89.
14. Bolognia JL, Pawelek JM. Biology of hypopigmentation. J Am Acad Dermatol. 1988;19:217–55.
15. Orlow SJ. Melanosomes are specialized members of the lysosomal lineage of organelles. J Invest Dermatol. 1995;105:3–7.

15a. Leonhardt RM, Vigneron N, Rahner C, Cresswell P. Proprotein convertases process Pmel17 during secretion. J Biol Chem. 2011;286:9321–37.

16. Halaban R, Svedine S, Cheng E, et al. Endoplasmic reticulum retention is a common defect associated with tyrosinase-negative albinism. Proc Natl Acad Sci USA. 2000;97:5889–94.
17. Dell' Angelica EC, Shotelersuk V, Aguilar RC, et al. Altered trafficking of lysosomal proteins in Hermansky-Pudlak syndrome due to mutations in the beta 3A subunit of the AP-3 adaptor. Mol Cell. 1999;3:11–21.
18. Wei ML. Hermansky-Pudlak syndrome: a disease of protein trafficking and organelle function. Pigment Cell Res. 2006;19:19–42.
19. Giordano F, Bonetti C, Surace EM, et al. The ocular albinism type 1 (OA1) G-protein-coupled receptor functions with MART-1 at early stages of melanogenesis to control melanosome identity and composition. Hum Mol Genet. 2009;18:4530–45.
20. McGlinchey RP, Shewmaker F, McPhie P, et al. The repeat domain of the melanosome fibril protein Pmel17 forms the amyloid core promoting melanin synthesis. Proc Natl Acad Sci USA. 2009;106:13731–6.
21. Hara M, Yaar M, Byers HR, et al. Kinesin participates in melanosomal movement along melanocyte dendrites. J Invest Dermatol. 2000;114:438–43.
22. Pastural E, Barrat FJ, Dufourcq-Lagelouse R, et al. Griscelli disease maps to chromosome 15q21 and is associated with mutations in the myosin-Va gene. Nat Genet. 1997;16:289–92.
23. Ménashché G, Ho CH, Sanal O, et al. Griscelli syndrome restricted to hypopigmentation results from a melanophilin defect (GS3) or a *MYO5A* F-exon deletion (GS1). J Clin Invest. 2003;112:450–6.
24. Belleudi F, Purpura V, Scrofani C, et al. Expression and signaling of the tyrosine kinase FGFR2b/KGFR regulates phagocytosis and melanosome uptake in human keratinocytes. FASEB J. 2011;25:170–81.
25. Seiberg M, Paine C, Sharlow E, et al. Inhibition of melanosome transfer results in skin lightening. J Invest Dermatol. 2000;115:162–7.
26. Setty SR, Tenza D, Sviderskaya EV, et al. Cell-specific ATP7A transport sustains copper-dependent tyrosinase activity in melanosomes. Nature. 2008;454:1142–6.
27. Boissy RE, Sakai C, Zhao H, et al. Human tyrosinase related protein-1 (TRP-1) does not function as a DHICA oxidase activity in contrast to murine TRP-1. Exp Dermatol. 1998;7:198–204.
28. Rinchik EM, Bultman SJ, Horsthemke B, et al. A gene for the mouse pink-eyed dilution locus and for human type II oculocutaneous albinism. Nature. 1993; 361:72–6.
29. Puri N, Gardner JM, Brilliant MH. Aberrant pH of melanosomes in pink-eyed dilution (p) mutant melanocytes. J Invest Dermatol. 2000;115:607–13.
30. Krude H, Biebermann H, Luck W, et al. Severe early onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. Nat Genet. 1998;19:155–7.
31. Luger TA, Scholzen T, Grabbe S. The role of alpha melanocyte-stimulating hormone in cutaneous biology. J Invest Dermatol Symp Proc. 1997;2:87–93.
32. Raimondi S, Sera F, Gandini S, et al. MC1R variants, melanoma and red hair color phenotype. Int J Cancer. 2008;122:2753–60.
33. Barsh G. From agouti to POMC – 100 years of fat blonde mice. Nat Med. 1999;5:984–5.
34. Lu D, Willard D, Patel IR, et al. Agouti protein is an antagonist of the melanocyte-stimulating-hormone receptor. Nature. 1994;371:799–802.
35. Suzuki I, Tada A, Ollman MM, et al. Agouti signaling protein inhibits melanogenesis and the response of human melanocytes to alpha-melanotropin. J Invest Dermatol. 1997;108:838–42.
36. D'Orazio JA, Nobuhisa T, Cui R, et al. Topical drug rescue strategy and skin protection based on the role of Mc1r in UV-induced tanning. Nature. 2006;443:340–4.
37. Gudbjartsson DF, Sulem P, Stacey SN, et al. *ASIP* and *TYR* pigmentation variants associate with cutaneous melanoma and basal cell carcinoma. Nat Genet. 2008;40:886–91.
38. Duffy DL, Zhao ZZ, Sturm RA, et al. Multiple pigmentation gene polymorphisms account for a substantial proportion of risk of cutaneous malignant melanoma. J Invest Dermatol. 2010;130:520–8.
39. Gilchrest BA, Blog FB, Szabo G. Effects of aging and chronic sun exposure on melanocytes in human skin. J Invest Dermatol. 1979;73:141–3.
40. Gilchrest BA, Park HY, Eller MS, et al. Mechanisms of ultraviolet light-induced pigmentation. Photochem Photobiol. 1996;63:1–10.
41. Luger TA. Immunomodulation by UV light: role of neuropeptides. Eur J Dermatol. 1998;8:198–9.
42. Cui R, Widlund HR, Feige E, et al. Central role of p53 in the suntan response and pathologic hyperpigmentation. Cell. 2007;128:853–64.
43. Oren M, Bartek J. The sunny side of p53. Cell. 2007;128:826–8.
44. Sturm RA. Molecular genetics of human pigmentation diversity. Hum Mol Genet. 2009;18:R9–R17.
45. Gudbjartsson DF, Sulem P, Stacey SN, et al. *ASIP* and *TYR* pigmentation variants associate with cutaneous melanoma and basal cell carcinoma. Nat Genet. 2008;40:886–91.
46. Nan H, Kraft P, Hunter DJ, et al. Genetic variants in pigmentation genes, pigmentary phenotypes, and risk of skin cancer in Caucasians. Int J Cancer. 2009;125:909–17.
47. Duffy DL, Zhao ZZ, Sturm RA, et al. Multiple pigmentation gene polymorphisms account for a substantial proportion of risk of cutaneous malignant melanoma. J Invest Dermatol. 2010;130:520–8.
48. Landi MT, Bauer J, Pfeiffer RM, et al. MCIR germline variants confer risk for BRAF-mutant melanoma. Science. 2006;313:521–2.
49. Chatzinasiou F, Lill CM, Kypreou K, et al. Comprehensive field synopsis and systematic meta-analyses of genetic association studies in cutaneous melanoma. J Natl Cancer Inst. 2011;103:1127–35.

Vitiligo and Other Disorders of Hypopigmentation

66

Jean-Paul Ortonne and *Thierry Passeron*

Chapter Contents

Vitiligo 1023
Hereditary hypomelanosis 1030
Nutritional hypomelanosis 1038
Postinflammatory hypomelanosis 1038
Infectious and parasitic hypomelanosis 1041
Halo nevus and melanoma-associated leukoderma 1042
Chemical and pharmacologic hypomelanosis 1044
Hypomelanosis from physical agents 1045

INTRODUCTION

Leukoderma and hypopigmentation are general terms used to designate disorders characterized by lightening of the skin. They are classically the result of decreased epidermal melanin content (melanin-related), but they may be secondary to a decreased blood supply to the skin (hemoglobin-related). Hypomelanosis is a more specific term that denotes an absence or reduction of melanin within the skin; amelanosis signifies the total absence of melanin. Depigmentation usually implies a total loss of skin color, most commonly due to disappearance of pre-existing melanin pigmentation, as in vitiligo. The term pigmentary dilution is used to describe a generalized lightening of the skin and hair, as in oculocutaneous albinism; this may be apparent only if affected individuals are compared with unaffected relatives.

Cutaneous hypomelanosis is often classified into two groups:

- *melanocytopenic hypomelanosis*, caused by a partial or total absence of epidermal and/or follicular melanocytes
- *melanopenic hypomelanosis*, in which the number of epidermal and/or follicular melanocytes is normal but the pigment cells fail to synthesize normal amounts of melanin and/or transfer it to surrounding keratinocytes.

Melanocytopenic hypomelanosis may be hereditary and/or congenital due to a defect in melanoblast differentiation, proliferation, migration and/or survival, or it may be acquired. In the latter case, functional melanocytes often disappear as a result of their destruction (e.g. via external trauma, such as cryosurgery, or an autoimmune attack). The factors controlling melanocyte survival may also play a role in the postnatal disappearance of dermal melanocytes. Melanopenic hypomelanosis may result from a number of complex pathologic mechanisms, including abnormalities in melanosomes (e.g. their biogenesis, melanization, transfer or degradation) or melanin removal.

DIAGNOSIS OF LEUKODERMAS[1]

Any patient with a leukoderma should be fully examined under both visible and UVA light (i.e. ~365 nm wavelength in a Wood's lamp). The latter is particularly useful in circumscribed leukodermas, individuals who have very lightly pigmented skin (types I or II), and neonates. Under visible light, it is sometimes difficult to distinguish between hypomelanosis and amelanosis, but the greater the loss of epidermal pigmentation, the more marked the contrast on Wood's lamp examination. This technique is also helpful in differentiating hypomelanotic macules from hemoglobin-related leukodermas; for example, nevus anemicus becomes inapparent.

Most leukodermas are diagnosed clinically following a complete history and physical examination. Histologic examination of involved skin is most helpful for hypomelanoses associated with inflammatory processes (e.g. sarcoidosis, lichen sclerosis). Occasionally, quantification of the epidermal melanocyte density is performed via incubation of biopsy specimens with dihydroxyphenylalanine (DOPA; detects melanocytes with tyrosine activity) or melanocyte-specific immunohistochemical stains such as Mel-5 and Melan-A/MART-1. Ultrastructural studies are performed primarily for research purposes to characterize the subcellular events of melanogenesis (see Ch. 65) because very few hypomelanotic disorders have specific ultrastructural findings.

VITILIGO

Vitiligo is an acquired disorder characterized by circumscribed depigmented macules and patches that result from a progressive loss of functional melanocytes.

Epidemiology

Vitiligo affects approximately 0.5–2% of the general population worldwide[2], and it may appear any time from shortly after birth to late adulthood. The average age of onset is approximately 20 years. Although patients with vitiligo often attribute the onset of their disease to specific life events (e.g. physical injury, sunburn, emotional distress, illness or pregnancy), with the exception of the Koebner phenomenon, there is no proof that these factors cause or precipitate vitiligo.

Pathogenesis

Vitiligo is a multifactorial disorder related to both genetic and non-genetic factors. It is generally agreed that there is an absence of functional melanocytes in vitiligo skin and that the loss of immunohistochemically recognizable melanocytes is the result of their destruction.

In addition to the typical "absolute" type of vitiligo in which there are no DOPA-positive melanocytes (see Fig. 65.6), "relative" types of vitiligo in which melanocytes remain within the lesions but have decreased DOPA-positivity have been observed. It is possible that relative types of vitiligo are forerunners of the absolute type. In general, immunohistochemical evaluation of the epidermis from vitiligo lesions with antibodies to melanocyte markers (related and unrelated to melanogenic activity) cannot detect melanocytes[3]. In addition, the KIT receptor, a protein expressed early in melanocyte differentiation, is undetectable in vitiligo skin, suggesting that putative melanocyte precursors are no longer present. It is therefore thought that melanocytes are absent or present in very small numbers in lesions of vitiligo.

With regard to the epidermal milieu, cytoplasmic vacuolization of keratinocytes and the presence of extracellular granular material (which may be derived from the cytoplasm of altered keratinocytes) have been noted; these findings are most prominent in adjacent normal-appearing skin but may also be evident at the border between lesional and adjacent skin and, occasionally, in lesional skin. Keratinocyte-derived cytokines such as stem cell factor (SCF; KIT ligand), tumor necrosis factor-α (TNF-α) and interleukin (IL)-1 could play a role in the disappearance of the melanocytes[4]. Indeed, levels of SCF are decreased and levels of TNF-α and IL-1 are increased in lesional vitiligo skin compared to non-lesional skin[5–8]. Of note, topical tacrolimus, which has been found to be an effective treatment for vitiligo (see below), decreases TNF-α expression when applied to affected skin[9].

The Langerhans cell density of vitiligo skin, evaluated either by histochemical techniques (ATPase) or by monoclonal antibodies

SELECTED SUSCEPTIBILITY LOCI AND CANDIDATE GENES FOR VITILIGO		
Chromosomal location	**Candidate gene**	**Defective protein**
1p13	*PTPN22*	Protein tyrosine phosphatase, non-receptor type 22
1p31.3	*FOXD3**	Forkhead box D3*
1p36.23	*RERE*	Arginine–glutamic acid dipeptide (RE) repeats
3p14.1	*FOXP1*	Forkhead box P1
3q27–q28	*LPP*	LIM domain containing preferred translocation partner in lipoma
5q22.1	*TSLP*	Thymic stromal lymphopoietin
6p21.3	*HLA* (various genes)	Major histocompatibility complex classes I, II and III
6q27	*CCR6*	Chemokine (C-C motif) receptor 6
	SMOC2	SPARC related modular calcium binding 2
10p15–p14	*IL2RA*	Interleukin 2 receptor α
11q14–q21	*TYR*	Tyrosinase
14q11.2	*GZMB*	Granzyme B
17p13	*NLRP1* (formerly *NALP1*)	Nod-like receptor family, pyrin domain containing 1 (Fig. 66.1)
21q22.3	*UBASH3A*	Ubiquitin associated and SH3 domain containing A
22q12.1	*XBP1*	X-box binding protein 1
22q13.1	*C1QTNF6*	C1q and tumor necrosis factor related protein 6
Xp11.23	*FOXP3*	Forkhead box P3

*In one family to date, a functional variant in the promoter of the *FOXD3* melanoblast developmental regulator gene was associated with autosomal dominant inheritance of an atypical vitiligo phenotype (early onset, widespread, progressive depigmentation).

Table 66.1 Selected susceptibility loci and candidate genes for vitiligo. Virtually all of these genes encode immunoregulatory proteins, with the notable exception of tyrosinase. Genome-wide association studies have identified other susceptibility loci, including 7p13, 7q11, 9q22 and (in Chinese patients) 4q13–q21. HLA, human leukocyte antigen.

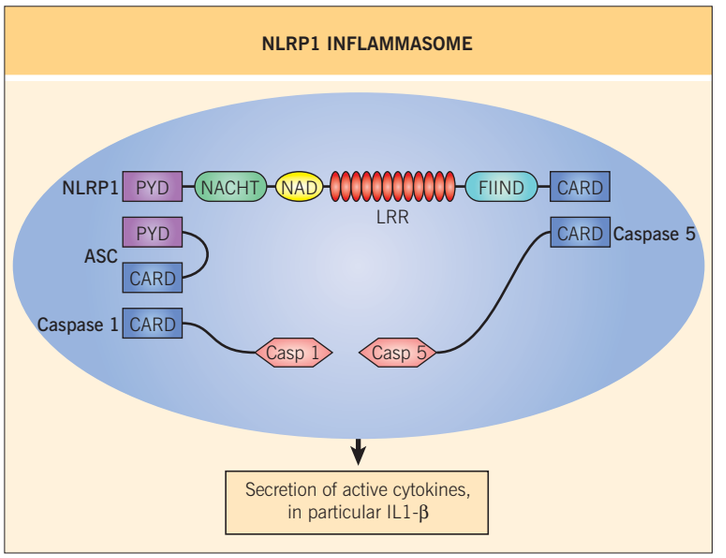


Fig. 66.1 NLRP1 inflammasome. NLRP1 (NOD-like receptor family, pyrin domain containing 1; previously known as NALP1 [NACHT, leucine rich repeat and pyrin domain containing 1]) is an intracellular pattern recognition receptor that stimulates the innate immune system in response to pathogen-associated molecular patterns (e.g. bacterial peptides) and host-derived danger signals. It functions in a cytoplasmic complex, referred to as the NLRP1 inflammasome, that activates caspase-1 and converts proinflammatory interleukins (e.g. pro–IL-1β, pro–IL-18) into their active forms. Variants in the *NLRP1* gene have been associated with vitiligo and other autoimmune diseases. CARD, caspase-recruitment domain; LRR, leucine-rich repeats; NAD, NACHT-associated domain; PYD, pyrin domain.

(anti-CD1a and HLA-DR), has been variably reported as decreased, normal or increased. Functional impairment and degenerative changes (particularly in marginal areas where they are more plump and have shorter dendrites) in Langerhans cells have also been observed. These findings suggest that vitiligo affects the entire keratinocyte–Langerhans cell–melanocyte unit[10].

Genetics of vitiligo

Both twin and family studies indicate the importance of genetic factors in the development of vitiligo, which represents a heterogeneous and complex genetic disease with environmental influences[11,12]. Genome-wide linkage analyses have been performed in multiple patient populations with non-segmental vitiligo, resulting in the identification of a number of susceptibility loci and candidate genes (Table 66.1)[13–18]. Most of these genes are associated with other autoimmune disorders and play a key role in the immune system.

Pathogenic hypotheses for vitiligo

Many pathogenic hypotheses have been proposed for vitiligo, reflecting the complex nature of this condition. A primary challenge is the fact that vitiligo most likely represents a heterogeneous group of disorders with different genetic backgrounds as well as exogenous and intrinsic triggers. Indeed, there is increasing evidence that non-segmental and segmental forms of vitiligo (see below) do not have the same genetic influences and may be distinct entities. For non-segmental vitiligo, accumulated data strongly support an autoimmune etiology in genetically predisposed individuals. Intrinsic defects in melanocytes and exogenous triggers may also play a role in the development of vitiligo. The relative contributions of these factors, and potentially others, in precipitating vitiligo remain to be elucidated. The various hypotheses are not mutually exclusive, and a "convergence theory" has also been proposed[19]. Arguments for and against proposed theories for the pathogenesis of vitiligo are summarized in Table 66.2.

Is there a reliable animal model for vitiligo?

A wide variety of animals (e.g. chickens, mice, cats, dogs, pigs and horses) develop vitiligo, as manifested by progressive depigmentation with a loss of active melanocytes. Circulating anti-melanocyte autoantibodies have been detected in some affected animals. Grafting of human vitiligo skin onto nude mice has also been used as a model for vitiligo, with repigmentation of the grafts in these studies suggesting an important role for systemic factors in the pathogenesis of vitiligo.

Recently, a T-cell receptor (TCR) transgenic mouse that recognizes an epitope of tyrosinase was found to progressively develop vitiligo in a pattern similar to that of human disease, initially involving the face in a symmetric periorificial distribution and later arising on the body. The vitiligo in this model is entirely dependent upon $CD8^+$ T cells, requiring both interferon-γ (IFN-γ) and the chemokine C-X-C motif receptor 3 (CXCR3). However, $CD8^+$ T cells were also present in clinically unaffected skin, suggesting spatial and temporal differences in melanocyte susceptibility and immunologic effector mechanisms[20].

Clinical Features

The most common presentation of vitiligo is totally amelanotic (i.e. milk- or chalk-white) macules or patches surrounded by normal skin. The lesions characteristically have discrete margins, and they can be round, oval, irregular or linear in shape. The borders are usually convex, as if the depigmenting process were "invading" the surrounding normally pigmented skin. Lesions enlarge centrifugally over time, and the rate may be slow or rapid. Vitiligo macules and patches range from millimeters to centimeters in diameter and often vary in size within areas of involvement. In lightly pigmented individuals, the lesions may be subtle or inapparent without the use of a Wood's lamp. In darkly pigmented individuals or after tanning of uninvolved skin, the contrast between vitiliginous areas and the surrounding skin is

PATHOGENIC HYPOTHESES FOR VITILIGO		
Hypothesis	**Evidence for hypothesis**	**Evidence against hypothesis**
Autoimmune destruction of melanocytes	• Epidemiologic association with several autoimmune disorders (see text) • Variants in immunoregulatory genes linked with vitiligo and associated autoimmune disorders (see Table 66.1) • Detection of antibodies against melanocyte proteins (e.g. TYR, TYRP1, DCT, MCHR1, SOX10) in the sera of patients with vitiligo • Destruction of melanocytes in normal human skin engrafted onto nude mice after injection with vitiligo patient sera • Infiltration of $CD8^+$ T cells into perilesional vitiligo skin • Skin-homing, melanocyte-specific cytotoxic T cells (e.g. against surface proteins such as Melan-A/MART-1) frequently detectable in the peripheral blood of vitiligo patients • Reports of generalized vitiligo following bone marrow transplantation from donors with vitiligo • T-cell receptor transgenic mice that recognize an epitope of tyrosinase develop depigmented lesions with characteristics similar to human vitiligo	• Limited evidence for autoimmune pathogenesis of segmental vitiligo • Although there is strong evidence for an autoimmune etiology of generalized vitiligo, it is unclear whether a primary immune attack targets normal melanocytes or if immune activation is triggered by damage to melanocytes by an exogenous or endogenous factor
An intrinsic defect in melanocytes, their adhesive properties and/or factors critical to their survival	• Abnormalities of cultured vitiligo melanocytes: – Dilation of the rough endoplasmic reticulum – Abnormal synthesis/processing of TYRP1 – Increased sensitivity to oxidative stress (e.g. UVB) • Evidence for *transepidermal melanocytorrhagy* due to defective melanocyte adhesion: – Detachment and transepidermal loss of melanocytes observed in *in vivo* studies of vitiligo skin – Induction of detachment by mechanical stress, which could explain the Koebner phenomenon – Decreased adhesion to collagen type IV and "stubby" dendrites in melanocytes cultured from perilesional skin of unstable vitiligo • Evidence for reduced melanocyte survival and dysregulation of melanocyte apoptosis in vitiligo: – The progressive loss of hair follicle melanocytes observed in *bcl-2*$^{-/-}$ mice provides a model of apoptotic loss of melanocytes – Deficiency of factors important for melanocyte maintenance (e.g. SCF, KIT, MITF) in vitiligo skin – Vitiligo-like depigmentation and hair graying observed in patients treated with tyrosine kinase inhibitors that target KIT	• Melanocytorrhagy is observed only in lesional and perilesional areas of vitiligo and appears to be a secondary process • No alteration in the expression of apoptosis regulatory molecules in vitiligo melanocytes compared with normal melanocytes
Defective defense against oxidative stress leading to destruction of melanocytes	• Detection of high *in vivo* levels of epidermal H_2O_2 in vitiligo skin, with potential sources including: – Accumulation of oxidized pteridines, e.g. 6-biopterin (bluish fluorescence) and 7-biopterin (yellow/green fluorescence) – Increased catecholamine biosynthesis in association with increased monoamine oxidase A activity – Inhibition of thioredoxin/thioredoxin reductase by calcium in the setting of defective calcium transfer/homeostasis in vitiligo epidermis • Oxidative degradation of catalase resulting in low levels of this protective enzyme in vitiligo skin	• Whether these abnormalities are the cause of vitiligo lesions, versus secondary consequences of immune attack or an intrinsic defect in melanocytes has not been determined • No conclusive evidence of benefit from therapeutic approaches using pseudocatalase or systemic antioxidant agents in clinical studies

Table 66.2 Pathogenic hypotheses for vitiligo. A "convergence theory" that vitiligo results from a combination of several of these pathogenic mechanisms has also been proposed. Hypotheses with less support include destruction of melanocytes by neurochemical substances or a viral infection (e.g. cytomegalovirus). DCT, dopachrome tautomerase; MCHR1, melanin-concentrating hormone receptor 1; MITF, microphthalmia-associated transcription factor; SCF, stem cell factor; TYR, tyrosinase; TYRP1, tyrosinase-related protein 1; UVB, ultraviolet B.

striking (Fig. 66.2). Vitiligo is usually asymptomatic, but pruritus is sometimes noted.

Vitiligo can develop anywhere on the body. Interestingly, it has a predilection for sites that are normally relatively hyperpigmented, such as the face, dorsal aspect of the hands, nipples, axillae, umbilicus, and sacral, inguinal and anogenital regions (see Fig. 66.2). Facial vitiligo typically occurs around the eyes and mouth (i.e. periorificial), and on the extremities it favors the elbows, knees, digits, flexor wrists (Fig. 66.3), dorsal ankles and shins (Fig. 66.4). Many of the common sites of involvement are subjected to repeated trauma, pressure or friction. Vitiligo on the palms, soles, lips and oral mucosa in lightly pigmented individuals may not be evident without Wood's lamp examination. In acrofacial vitiligo, periungual involvement of one or more digits may be associated with lip depigmentation; however, either can be an isolated finding.

The incidence of body leukotrichia varies from 10% to >60%, as follicular melanocytes are often spared in vitiligo. The occurrence of leukotrichia does not correlate with disease activity, but it is rarely, if ever, seen in the absence of depigmentation of the surrounding epidermis (Fig. 66.5). Vitiligo of the scalp most often presents as one or several localized patches of white or gray hair (poliosis), but scattered

Fig. 66.2 Vitiligo. Complete loss of pigment of the glans penis. Note the lack of any secondary changes. *Courtesy, Jean L Bolognia, MD.*

white hairs due to involvement of individual follicles or even total depigmentation of all the scalp hair can also occur. Isolated early graying or whitening before 30 years of age has been suggested to represent a form of vitiligo. In general, spontaneous repigmentation of depigmented hair in vitiligo does not occur.

Clinical variants

Vitiligo ponctué, an unusual clinical presentation of vitiligo, is characterized by multiple small (confetti-like), discrete amelanotic macules, sometimes superimposed upon a hyperpigmented macule. Although a *hyperpigmented margin* around a macule of leukoderma has been said to be specific for vitiligo, this is not a common feature. Erythema is occasionally observed at the margins of vitiligo lesions, which is referred to as *inflammatory vitiligo* or *"vitiligo with raised inflammatory borders"* (Fig. 66.6); a figurate papulosquamous variant has also been described. *Blue vitiligo* can result when vitiligo develops in areas already affected by postinflammatory hyperpigmentation.

Fig. 66.3 Vitiligo. Depigmentation of the volar wrists as well as the palmar surfaces. *Courtesy, Jean L Bolognia, MD.*

Trichrome vitiligo features a hypopigmented zone between normal and totally depigmented skin. The intermediate zone does not have a gradation of color from white to normal, but rather a fairly uniform hue. The number of melanocytes is also intermediate in this zone, suggesting slower centrifugal progression than in typical vitiligo[21]. In *quadrichrome vitiligo*, a fourth darker color is present at sites of perifollicular repigmentation. *Pentachrome vitiligo* with five shades of color (black, dark brown, medium brown [unaffected skin], tan and white) has also been described.

One of the manifestations of vitiligo is the isomorphic Koebner phenomenon (IKP), characterized by the development of vitiligo in sites of trauma (e.g. a laceration, burn or abrasion). The IKP is more common in patients with progressive non-segmental vitiligo, but it can also affect those with segmental vitiligo. There appears to be a minimal threshold of injury required for the IKP to occur, bringing into question the hypothesis that minor trauma, such as friction from clothes (in the absence of true injury), can induce vitiligo lesions.

Clinical classification of vitiligo

Multiple classification systems for vitiligo have been proposed, leading to confusing terminology. Two major forms are generally recognized: (1) the *segmental* form, which usually does not cross the midline; and (2) the *non-segmental form*, also called vitiligo vulgaris[22]. Segmental and non-segmental vitiligo are occasionally seen in the same patient, with involvement of >1% of the body surface area and the presence of leukotrichia or halo nevi representing possible predictors of the evolution from the former to the latter[22a]. However, genetic and clinical data strongly suggest that they represent two distinct forms of vitiligo.

The following classification scheme divides vitiligo into three general types (see Fig. 66.4): localized, generalized and universal.

Localized:

- *Focal*: one or more macules in one area, but not clearly in a segmental distribution
- *Unilateral/segmental*: one or more macules involving a unilateral segment of the body (Fig. 66.7); lesions usually stop abruptly at the midline
- *Mucosal*: mucous membranes alone

Generalized:

- *Vulgaris*: scattered patches that are widely distributed
- *Acrofacial*: distal extremities and face
- *Mixed*: various combinations of segmental, acrofacial and/or vulgaris

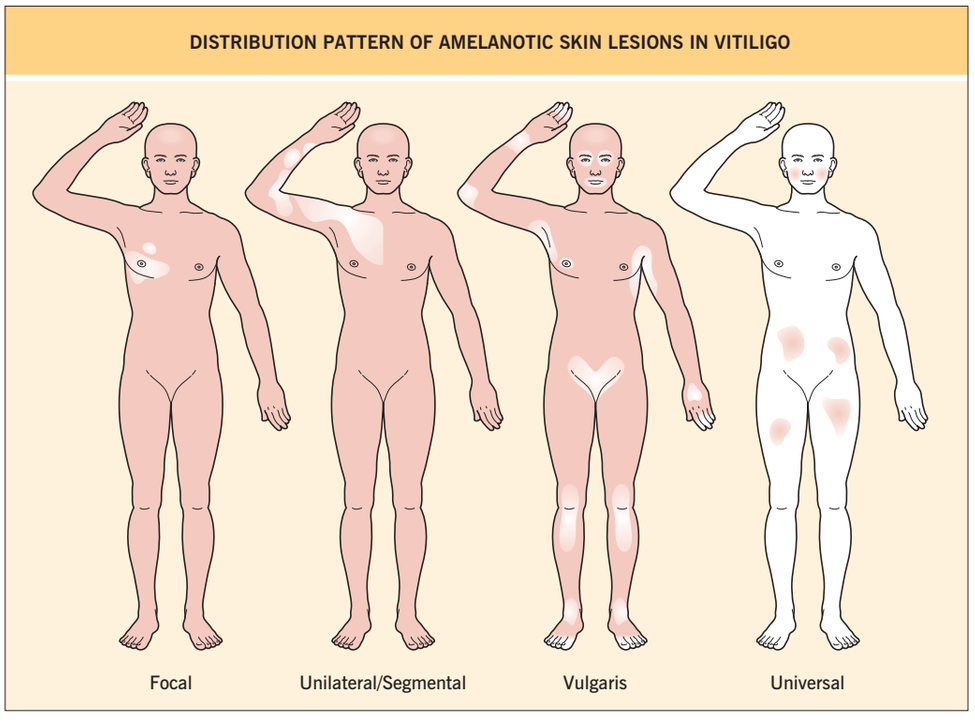


Fig. 66.4 Distribution of amelanotic skin lesions in vitiligo. *Adapted with permission from Le Poole C, Boissy RE. Vitiligo. Semin Cutan Med Surg. 1997;16:3–14.*

Fig. 66.5 Segmental vitiligo. Under normal light, vitiligo can be subtle in lightly pigmented individuals. The clue to the diagnosis is the poliosis of the eyelashes. *Courtesy, Jean L Bolognia, MD.*

Fig. 66.6 Inflammatory vitiligo. There is a figurate outline to the inflammatory border, which is sometimes misdiagnosed as tinea corporis.

Fig. 66.7 Segmental vitiligo. Unilateral band of depigmentation on the face, the most common location for segmental vitiligo. Note the pigmented and depigmented hairs within the affected area. *Courtesy, Kalman Watsky, MD.*

Universal:

- Complete or nearly complete depigmentation.

In our experience, over 90% of vitiligo patients have the generalized type. In the remainder, localized vitiligo is more common than universal vitiligo. Segmental vitiligo is more common in children than adults, accounting for ~15–30% of vitiligo in pediatric patients (see below).

Course of the disease

The onset of vitiligo is usually insidious. Many patients become aware of the depigmented patches, especially in sun-exposed areas, during the summer, when tanning increases the contrast between involved and uninvolved skin. The exact evolutionary appearance of early lesions is unknown, but it is postulated that there is progressive, uniform loss of pigment until a discrete white macule is apparent, which is followed by centrifugal enlargement. Clinical erythema rarely precedes vitiligo.

The course of vitiligo on a case-by-case basis is unpredictable. It becomes more extensive by the appearance of new depigmented macules, enlargement of pre-existing lesions, or both processes. The natural course of the disease is usually one of slow progression, but it may stabilize for a long period of time or spread rapidly. Total body involvement that develops within a few weeks or even a few days is known to occur. Some degree of sun-induced or spontaneous repigmentation is not uncommon in vitiligo, but complete and stable spontaneous repigmentation is rare.

The definitions for active and stable vitiligo are not universally accepted. Furthermore, there is no validated scoring system available to assess vitiligo activity. The *vi*tiligo *d*isease *a*ctivity (VIDA) score and a scoring system that was recently proposed by the Vitiligo European Task Force[22] have yet to be validated.

Vitiligo and ocular disease

The uveal tract (iris, ciliary body and choroid) and retinal pigment epithelium contain pigment cells. Uveitis is the most significant ocular abnormality associated with vitiligo. The most severe form of uveitis is seen in the *Vogt–Koyanagi–Harada (VKH) syndrome*. This is a multisystem disorder characterized by uveitis, aseptic meningitis and otic involvement (e.g. dysacousia), together with vitiligo, especially of the head and neck region, and associated poliosis. Histologic examination of amelanotic skin (which often appears after the systemic symptoms) demonstrates a mononuclear infiltrate consisting primarily of $CD4^+$ lymphocytes, suggesting a prominent role for cell-mediated immunity.

Non-inflammatory depigmented lesions of the ocular fundus are present in some patients with vitiligo, presumably representing focal areas of melanocyte loss. Although sensory hearing loss has been described in a few vitiligo patients (possibly reflecting impairment of cochlear melanocytes), clearcut evidence of otic abnormalities remains to be demonstrated.

Alezzandrini syndrome is a rare disorder characterized by whitening of scalp hair, eyebrows and eyelashes as well as depigmentation of the skin on the forehead, nose, cheek, upper lip and chin in association with ipsilateral visual changes. In the affected eye, there is decreased visual acuity and an atrophic iris. The pathogenesis of Alezzandrini syndrome is unknown, but it is believed to be closely related to VKH syndrome.

Associated disorders

Although most vitiligo patients are otherwise healthy, generalized vitiligo is epidemiologically associated with a number of other autoimmune diseases, especially in patients with a family history of vitiligo or other forms of autoimmunity. The associated conditions include autoimmune thyroid disease, pernicious anemia, Addison's disease, lupus erythematosus, rheumatoid arthritis, and adult-onset autoimmune diabetes mellitus[23,24]. An increased risk of developing these conditions is not surprising considering that they have been linked to the same autoimmunity predisposition genes (e.g. *PTPN22*, *NLRP1*) that have been implicated in the pathogenesis of vitiligo (see Table 66.1).

Patients with the autosomal recessive *a*utoimmune *p*oly*e*ndocrinopathy–*c*andidiasis–*e*ctodermal *d*ystrophy (APECED) syndrome are predisposed to the development of vitiligo as well as the autoimmune destruction of endocrine cells. The gene responsible for

APECED, *AIRE* (*a*uto*i*mmune *re*gulator), encodes a transcription factor that regulates the ectopic expression of self antigens in the thymus, which allows the development of peripheral tolerance. In APECED patients, failure to delete autoreactive T cells leads to autoimmune disease.

Halo melanocytic nevi (see below), alopecia areata and lichen sclerosus are additional autoimmune disorders that may be associated with vitiligo. An increased prevalence of vitiligo in patients with the *m*itochondrial *e*ncephalomyopathy, *l*actic *a*cidosis, and *s*troke-like episodes (MELAS) syndrome was noted in one small study, but whether this represents a true association has not been confirmed.

Childhood vitiligo

Although vitiligo vulgaris is the most common clinical type observed in children, the frequency of segmental vitiligo is significantly increased in children compared to adults (~15–30% versus ≤5–10%, respectively)[25]. The incidence of associated endocrinopathies is significantly less than in the adult vitiligo population. A family history of vitiligo is associated with an earlier age of onset[24]; among pediatric patients, those with a positive family history are more likely to develop vitiligo before 7 years of age.

Pathology

The pathology of vitiligo is described above (see Pathogenesis).

Differential Diagnosis

When there is complete depigmentation, the differential diagnosis includes chemical or drug-induced (e.g. imatinib) leukoderma, postinflammatory depigmentation, the leukodermas associated with melanoma and scleroderma, and the late stages of treponematosis and onchocerciasis. If there is a single circular lesion on the trunk of a young person, a stage III halo nevus should be considered (see below). Early lesions or those with a partial loss of pigment need to be distinguished from postinflammatory hypopigmentation, pityriasis versicolor and other cutaneous infections (e.g. leprosy). A nevus depigmentosus can be distinguished by its early onset (although lesions may not be clinically apparent until mid-childhood in lightly pigmented individuals) as well as hypopigmentation rather than depigmentation. Treatment with potent topical corticosteroids may also lead to hypomelanosis.

Treatment

The aims of vitiligo treatment are repigmentation and stabilization of the depigmentation process. Although there is still no therapeutic panacea for vitiligo, the available options lead to satisfactory results in a substantial number of patients. The choice of therapy depends on the extent, location, and activity of disease as well as the patient's age, skin type, and motivation to undergo treatment. In general, a period of at least 2–3 months is required to determine whether a particular treatment is effective. The areas of the body that typically have the best response to medical therapy are the face, neck, mid extremities and trunk, while the distal extremities and lips are the most resistant to treatment. Repigmentation usually appears in a perifollicular pattern (Fig. 66.8) and/or from the periphery of the lesions. When the hairs within an area of vitiligo are depigmented, the former pattern is not observed.

Corticosteroids

Topical corticosteroids are useful for localized areas of vitiligo. A meta-analysis showed that approximately half of patients with vitiligo affecting ≤20% of the body surface area achieved >75% repigmentation with either class 1 (superpotent) or class 2–3 (high-potency) topical corticosteroids; cutaneous atrophy was observed in 14% and 2% of these groups, respectively[26]. To minimize side effects, class 1 corticosteroids can be used in 6–8-week cycles or on a twice-weekly basis, alternating with topical tacrolimus or a less potent topical corticosteroid; treatment should be discontinued if there is no visible improvement after 2 months.

In general, intralesional corticosteroids should be avoided because of the pain associated with injection and the risk of cutaneous atrophy, which occurs in approximately one-third of vitiligo patients who receive this treatment. Systemic corticosteroids (high-dose pulsed therapy, mini-pulsed regimens or a low daily oral dose) have been reported to arrest rapidly spreading vitiligo and induce repigmentation[27]. However, given the potential for serious side effects, the role of systemic corticosteroids in the treatment of vitiligo remains controversial.

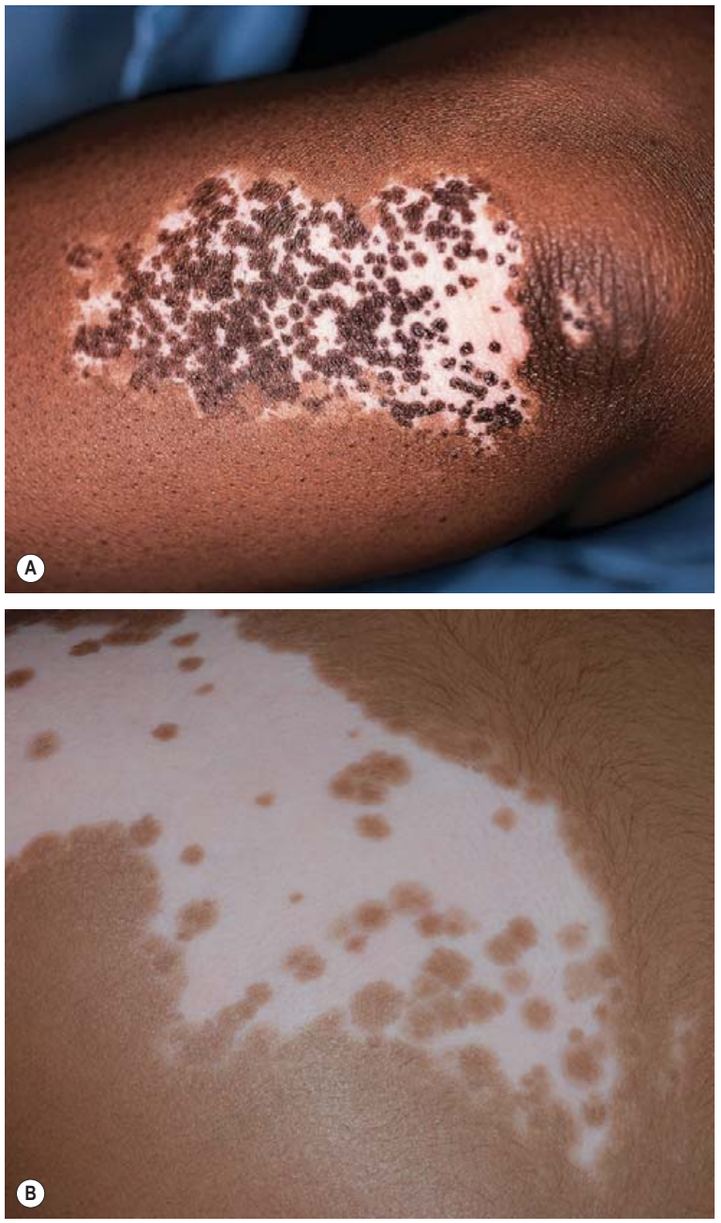


Fig. 66.8 Perifollicular repigmentation. Vitiligo on the elbow (**A**) and segmental vitiligo on the back (**B**) responding to PUVA and narrowband UVB therapy, respectively, with repigmentation in a prominent perifollicular pattern as well as from the periphery. The areas of repigmentation are darker in color than the uninvolved skin in (**A**) and have two shades (darker where well established and lighter at the expanding edge) in (**B**). *A, Courtesy, Jean L Bolognia, MD. B, Courtesy, Julie V Schaffer, MD.*

Topical calcineurin inhibitors

Multiple studies have shown that topical application of tacrolimus 0.1% ointment or pimecrolimus 1% cream twice daily can lead to repigmentation of vitiligo, with response rates in pediatric patients similar to those achieved with topical corticosteroids. The best results are obtained when these agents are used for facial lesions and/or combined with sun exposure, with the latter suggesting a synergistic effect. In addition, topical calcineurin inhibitors (TCIs) have been shown to enhance repigmentation when used together with narrowband UVB phototherapy or the 308 nm excimer laser[28,29]. Of note, avoidance of UV light is suggested by the package insert for TCIs, and the risk : benefit ratio needs to be discussed with patients and further studied (especially

in children). Topical tacrolimus can also be used in conjunction with topical corticosteroids, as discussed above.

Photo(chemo)therapy

Narrowband UVB

In general, narrowband UVB (NB-UVB) is considered to be more effective than broadband UVB in the treatment of vitiligo (see Ch. 134). Several studies have demonstrated the efficacy of NB-UVB monotherapy[30,31]. The starting dose ranges from 100 to 250 mJ/cm^2, which is increased in increments of 10–20% at each subsequent exposure until mild asymptomatic erythema is achieved within the lesions. Treatments are administered two to three times per week, but not on two consecutive days[30]. Short-term side effects include pruritus and xerosis; long-term side effects (e.g. cutaneous carcinogenesis) have not been described. The advantages of NB-UVB over psoralen plus UVA (PUVA) therapy include shorter treatment times, a lack of gastrointestinal side effects, reduced phototoxic reactions and no need for post-treatment photoprotection; in addition, NB-UVB can be used in children, pregnant or lactating women, and individuals with hepatic or kidney dysfunction. Furthermore, NB-UVB produces less accentuation of the contrast between depigmented and normally pigmented skin[32]. NB-UVB has become the first choice of therapy for adults and children with generalized vitiligo, especially if it involves ≥20% of the body surface area or cosmetically sensitive areas that normally respond to treatment.

Psoralen plus UVA

Psoralen photochemotherapy involves the use of psoralens combined with UVA light (see Ch. 134). The psoralen most commonly utilized is 8-methoxypsoralen (8-MOP, methoxsalen). 5-methoxypsoralen (5-MOP, bergapten) is not approved for use in the US and 4,5′,8-trimethylpsoralen (TMP, trioxsalen) is no longer commercially available. Psoralens can be administered orally (oral PUVA) or applied topically (topical PUVA), followed by exposure to either artificial UVA light or natural sunlight (PUVASOL).

Oral PUVA treatments using 8-MOP (0.4–0.6 mg/kg) are typically administered two times weekly. For patients with vitiligo, the initial dose of UVA is usually 0.5–1.0 J/cm^2, which is gradually increased until minimal asymptomatic erythema of the involved skin occurs. To reduce the risk of the Koebner phenomenon, significant erythema (phototoxicity) is avoided. 5-MOP has about the same response rate as 8-MOP in repigmenting vitiligo, but a lower incidence of adverse effects, including reduced phototoxicity as well as less nausea and vomiting.

The response rate of PUVA is variable; although the majority of patients obtain cosmetically acceptable improvement, complete repigmentation is achieved in only a few patients. The total number of PUVA treatments required is generally between 50 and 300. The absolute and relative contraindications, as well as the short- and long-term side effects, of oral PUVA therapy are reviewed in Chapter 134. To date, only a few vitiligo patients with PUVA-induced cutaneous carcinomas have been reported. Although this probably reflects a smaller cumulative UVA dose than in patients treated for other disorders such as psoriasis, large follow-up studies have not yet been done in PUVA-treated vitiligo patients. Until more data are available, it seems wise to recommend that vitiligo patients receive a maximum cumulative UVA dose of 1000 J/cm^2 and a maximum number of 300 treatments.

Topical (paint) PUVA is more difficult to perform because of the high risk of phototoxicity (e.g. blistering, koebnerization) from topical psoralen formulations. Low concentrations (≤0.1%) should be used, which necessitates dilution of the commercially available preparation. Approximately 20–30 minutes after applying the topical preparation (cream or ointment) onto the lesions, the patient should be exposed to initial UVA doses of no more than 0.25 J/cm^2, with the same fractional increments until mild erythema is achieved in the treated sites.

PUVASOL (psoralens + natural sunlight) can be used in sunnier climates, according to the same principles as for PUVA. Less phototoxic oral psoralens such as 5-MOP are preferred, to avoid phototoxic reactions.

Other forms of phototherapy

There have been conflicting reports regarding the efficacy of *oral khellin plus UVA* and *oral phenylalanine plus UVA* for the treatment of vitiligo, and concern has been raised about the hepatic toxicity of khellin. As a result, these modalities are not recommended. *Topical khellin plus UVA* has a relatively low risk of phototoxicity, but it requires a longer duration of treatment and higher UVA doses than oral PUVA to provide the same degree of repigmentation[33].

Focused microphototherapy has the advantage of irradiating only the affected skin. A directed beam of broadband or narrowband UVB light is applied to areas of vitiligo. Treatments are administered from several times weekly to twice monthly, sometimes with an initial boost of daily treatments for 5 days. In one large study, 70% of patients who received a mean of 24 treatments over a 12-month period achieved >75% repigmentation.

Lasers and related light devices

Excimer laser and lamp

The operational wavelength of the 308 nm excimer laser and lamp is close to that of NB-UVB[34]. The therapeutic benefit of the excimer laser for vitiligo has been investigated in multiple studies, and, overall, 20–50% of lesions achieve ≥75% repigmentation[35,36]; the excimer lamp appears to have similar efficacy[37]. Localized patches of vitiligo are treated one to three times weekly for an average of 24 to 48 sessions, with the repigmentation rate depending on the total number of sessions, not their frequency[36]. Erythema and (rarely) blistering represent potential side effects[35].

Helium–neon laser

The helium–neon laser emits a wavelength (632.8 nm) in the red visible light range that can enhance melanocyte proliferation and melanogenesis *in vitro*[38]. In a study performed in 30 patients with segmental vitiligo, 20% of lesions achieved ≥75% repigmentation after a mean of 79 treatment sessions, which were administered once or twice weekly[39].

Surgical therapies

For vitiligo patients who fail to respond to medical therapy, surgical treatment with autologous transplantation techniques may be an option[40]. The general selection criteria for autologous transplantation are stable disease for at least 6 months, an unsatisfactory response to medical therapy, absence of the Koebner phenomenon, a positive minigrafting test (retention/spread of pigment at the recipient site and no koebnerization at the donor site after 2–3 months), no tendency for scar or keloid formation, and age above 12 years[41].

Several methods of surgical repigmentation have been successfully utilized. *Minigrafting* is the simplest technique. Small punch grafts (1–2 mm) from uninvolved skin are implanted within achromic areas, separated from each other by 5–8 mm. A cobblestone effect, a variegated appearance of the grafts, and sinking pits represent potential unfavorable outcomes. Because scarring and dyspigmentation may occur at the donor sites, cosmetically insensitive areas are chosen. The advantages of *suction blister epidermal grafting* are the absence of scarring at the donor site and the possibility of reusing this area. However, failure of the graft to take and koebnerization may occur. *Grafting of cultured autologous melanocytes* is an expensive technique that requires specialized laboratory expertise; grafts consist of pure melanocytes or melanocytes admixed with keratinocytes[42]. To avoid the need for *in vitro* culture (which involves mitogens to enhance cell growth), *grafting of non-cultured epidermal cell suspensions* that include melanocytes has been advocated[43]. *Grafting of individual hairs* to repigment vitiligo leukotrichia has also been successfully performed. Most of these techniques require clinical expertise, and candidates should be carefully selected.

Combination therapy

Combination therapy may produce higher rates of repigmentation compared to traditional monotherapies. Examples include phototherapy following surgical procedures and TCIs or topical corticosteroids together with each other, NB-UVB or excimer laser therapy[44–48]. Although topical vitamin D derivatives are relatively ineffective as monotherapy, these agents may result in additional repigmentation when used in conjunction with phototherapy.

Micropigmentation

The technique of permanent dermal micropigmentation utilizes a nonallergenic iron oxide pigment to camouflage recalcitrant areas of vitiligo. This tattooing method is especially useful for sites known to have

a poor rate of repigmentation with currently available treatments (e.g. the lips, nipples and distal fingers). Although the color may not match perfectly with the normal surrounding skin, the result is immediate and can represent a dramatic aesthetic improvement. However, the color may fade slightly over a period of years.

Depigmentation

Depigmentation represents a treatment option for patients who have widespread vitiligo with only a few areas of normally pigmented skin in exposed sites. The patients must be carefully chosen, i.e. adults who recognize that their appearance will be altered significantly and who understand that depigmentation requires lifelong strict photoprotection (e.g. sunscreens, clothing, umbrellas). The most commonly used agent is 20% monobenzyl ether of hydroquinone (MBEH), applied once to twice daily to the affected areas for 9–12 months or longer[49]. MBEH is a potent irritant and allergen, and an open use test should be performed before more widespread application. It typically takes 1–3 months to initiate a response, and a loss of pigment can occur at distant sites. Although depigmentation from MBEH is considered permanent, repigmentation (especially perifollicular in areas with pigmented hairs) can be seen following a sunburn or even intense sun exposure. Monomethyl ether of hydroquinone in a 20% cream can be used as an alternative to MBEH[50]. Side effects include contact dermatitis, exogenous ochronosis and leukomelanoderma en confetti. Depigmentation via Q-switched ruby laser therapy was reported to achieve faster depigmentation than that achieved with a bleaching agent[50], and this laser has also been used in combination with topical 4-methoxyphenol to induce depigmentation[51]. Depigmentation with the Q-switched alexandrite laser has also been described[52].

Psychological support

The impact of vitiligo on quality of life is severe in many affected individuals, and it is critical for physicians to recognize this aspect of the condition and address their patients' psychological needs. Although a "magic" treatment is not yet available, there is always something beneficial that can be done for vitiligo patients. They first need to know what their skin disorder is. Explaining the nature of the disease process and the potential and limits of available therapies is important and more productive than a fatalistic attitude that there is no cure and vitiligo is "only" a cosmetic disorder. Even helping patients to conceal the condition so that it is not visible can be part of the management plan. The use of support groups and, if indicated, psychological counseling are important supplementary therapies.

Additional controversial therapies

Pseudocatalase with narrowband UVB

The rationale for this treatment is based on the hypothesis that accumulation of hydrogen peroxide leads to pathogenic inactivation of catalase in the skin of patients with vitiligo (see Table 66.2). In an open uncontrolled study, complete repigmentation of lesions on the face and hands was observed in 90% of patients (30 of 33) treated with topical pseudocatalase and calcium twice daily plus UVB twice weekly, with initial repigmentation at 2–4 months[53]. A recent controlled trial, however, showed no additional benefit of pseudocatalase compared to UVB alone[54].

Systemic antioxidant therapy

The rationale for this approach rests on the hypothesis that vitiligo results from a deficiency of natural antioxidant mechanisms. Although to date not validated by a controlled clinical trial, selenium, methionine, tocopherols, ascorbic acid and ubiquinone are prescribed by some physicians.

Potential emerging treatments

Dermabrasion followed by topical 5-fluorouracil and narrowband UVB

Erbium:YAG laser ablation of vitiligo lesions followed by topical application of 5-fluorouracil and NB-UVB therapy twice weekly for 4 months was found to lead to ≥75% repigmentation in ~45% of patients, compared with a rate of 8% for lesions on the opposite side of the body that were treated with NB-UVB alone[55].

Topical prostaglandins

A preliminary study suggested the utility of topical prostaglandin E_2 in the treatment of vitiligo[56]. Although interesting, these results require confirmation.

HEREDITARY HYPOMELANOSIS[57]

Oculocutaneous Albinism

Oculocutaneous albinism (OCA) consists of a group of genetic disorders characterized by diffuse pigmentary dilution due to a partial or total absence of melanin pigment within melanocytes of the skin, hair follicles and eyes[57]. The number of epidermal and follicular melanocytes is normal. Hypopigmentation involving primarily the retinal pigment epithelium is termed ocular albinism (OA).

Epidemiology

OCA is the most common inherited disorder that leads to diffuse hypomelanosis. In most populations, the estimated frequency is 1:20 000; however, it is as high as 1:1500 in some African tribes.

Pathogenesis

All well-characterized types of OCA have an autosomal recessive inheritance pattern, although a few rare families with autosomal dominant OCA have been described[58]. Based upon molecular studies, four types of OCA have been defined (Table 66.3). OCA type 1 (OCA1) results

CLASSIFICATION OF OCULOCUTANEOUS AND OCULAR ALBINISM

Type	Gene	Phenotype	Function of protein
OCA1A] ~40%	*TYR*	Tyrosinase-negative OCA	Melanogenic enzyme (inactive/missing in OCA1A)
OCA1B]	*TYR*	Minimal pigment OCA Platinum OCA Yellow OCA Temperature-sensitive OCA	Melanogenic enzyme (partially active in OCA1B)
OCA2 (~50%)	*OCA2* (previously known as *P*, pink-eyed dilution)	Tyrosinase-positive OCA African brown OCA	Transmembrane transporter with roles in vacuolar glutathione accumulation, regulation of organelle pH and tyrosinase processing/trafficking
OCA3	*TYRP1*	Rufous OCA	Stabilizes tyrosinase
OCA4	*SLC45A2* (formerly *MATP*)	OCA	Transmembrane transporter with roles in tyrosinase processing and trafficking of proteins to the melanosome
OA1	*GPR143*	Nettleship–Falls type OA X-linked OA + macromelanosomes (skin, eyes)	Pigment cell-specific intracellular G protein-coupled receptor that regulates melanosome formation and transport

Table 66.3 Classification of oculocutaneous and ocular albinism. *GPR143*, G protein-coupled receptor 143; *MATP*, membrane-associated transporter protein; OA, ocular albinism; OCA, oculocutaneous albinism; *SLC45A2,* solute carrier family 45 member 2; *TYR*, tyrosinase; *TYRP1*, tyrosinase-related protein-1.

from reduced (OCA1B) or absent (OCA1A) tyrosinase activity (see Ch. 65); at least 230 distinct mutations in the tyrosinase gene (*TYR*) have been identified in patients with OCA1[59]. OCA type 2 (OCA2) is due to mutations in the *P* gene (pink-eyed dilution; now referred to as *OCA2*)[60]. Although the function of the P protein is still debated, more recent studies have pointed to its role in regulating organelle pH and facilitating vacuolar accumulation of glutathione.

OCA type 3 (OCA3) results from mutations in the tyrosinase-related protein 1 (*TYRP1*) gene[61]. TYRP1 protein is a melanocyte-specific gene product involved in eumelanin synthesis (see Fig. 65.11), probably via stabilization of tyrosinase. Both OCA1 and OCA3 appear to be endoplasmic reticulum (ER) retention diseases wherein the abnormal proteins (tyrosinase or TYRP1) never leave the ER to become incorporated into melanosomes[62] (see Fig. 65.7). Of note, dysfunction of the P protein can also lead to abnormal processing and trafficking of tyrosinase. A fourth type of OCA (OCA4) was identified more recently[63]. The gene involved, solute carrier family 45 member 2 (*SLC45A2*; formerly *MATP*, membrane-associated transporter protein), encodes a transmembrane transporter protein with roles in tyrosinase processing and intracellular trafficking of proteins to the melanosome.

Autosomal recessive OA (AROA) is genetically heterogeneous. Some cases of AROA actually represent OCA1B or OCA2, but with subtle cutaneous findings. The most common form of OA is an X-linked recessive disorder caused by mutations in the G protein-coupled receptor 143 gene (*GPR143*; formerly *OA1*), which encodes a pigment cell-specific intracellular G protein-coupled receptor that regulates melanosome formation and transport within melanocytes and cells of the retinal pigment epithelium[64]. Mutations in *GPR143* that lead to ocular albinism can result in retention of the aberrant protein within the ER.

Clinical features

Ocular manifestations

The many ocular manifestations of OA and OCA reflect a reduction in melanin within eye structures or misrouting of optic nerve fibers during development. The former leads to a translucent iris that transmits light upon globe transillumination, as well as a relatively hypopigmented retina and fovea that are associated with photophobia and reduced visual acuity; the severity of these findings correlates with the amount of reduction in melanin pigment. Misrouting of the optic fibers is thought to be responsible for the characteristic strabismus, nystagmus and lack of binocular vision.

OCA1

There are two clinical subtypes of OCA1, based upon whether tyrosinase activity is reduced (OCA1B) or absent (OCA1A).

OCA1A

OCA1A corresponds to the classic "tyrosinase-negative" OCA. The melanocytes of the skin, hair and eyes synthesize no melanin. The characteristic phenotype includes white hair, milky white skin, and blue–gray eyes at birth. With age, the skin color remains white and melanocytic nevi amelanotic, but the hair may develop a slight yellow tint due to denaturing of hair keratins. These patients have an extreme sensitivity to UV light and a strong predisposition to skin cancer. Reduced visual acuity is most severe in OCA1A, and some patients are legally blind.

OCA1B

Because the decrease in tyrosinase activity can vary, the phenotype ranges from obvious to subtle pigmentary dilution when compared with first-degree relatives. One of the original OCA1B phenotypes was called "yellow albinism" because of the eventual color of the patient's hair (the formation of yellow pheomelanin requires less tyrosinase activity). Other clinical types of OCA1B have been referred to as "minimal pigment OCA", "platinum OCA" and "temperature-sensitive OCA". All of these patients have little or no pigment at birth, but they develop some pigmentation of the hair and skin during the first and second decades of life. The majority burn without tanning after sun exposure, and some degree of iris translucency is often present. Amelanotic or pigmented melanocytic nevi can develop.

In the temperature-sensitive OCA1B phenotype, patients are born with white hair and skin and blue eyes. During puberty, scalp and axillary hairs remain white, but arm hairs turn light reddish brown and leg hairs turns dark brown. The abnormal tyrosinase enzyme is temperature-sensitive, losing its activity above 35°C. As a result, melanin synthesis does not occur in warmer areas of the body, akin to the phenotype of a Siamese cat, which also has temperature-sensitive tyrosinase activity.

Fig. 66.9 Oculocutaneous albinism type 2 (OCA2). African patient with obvious squamous cell carcinomas on the cheek as well as multiple pigmented lentigines. *Courtesy, James Nordlund, MD.*

Fig. 66.10 Oculocutaneous albinism type 2 (OCA2). African patient with hypopigmented hair and large pigmented lentigines. *Courtesy, James Nordlund, MD.*

OCA2

The OCA2 phenotype (in addition to OCA1B) corresponds to the classic "tyrosinase-positive" OCA. The clinical spectrum of OCA2 is broad, ranging from minimal to moderate pigmentary dilution of the hair, skin and iris, with little to no ability to tan. The vast majority of individuals of African descent who have "tyrosinase-positive" OCA have OCA2. With time, pigmented melanocytic nevi and lentigines may develop in sun-exposed areas (Fig. 66.9); the latter can become rather large and darkly colored (Fig. 66.10). Another phenotype called "brown OCA" in African and African-American populations results primarily from mutations in the *P* gene. In these individuals, the hair and skin are light brown, the irides are gray to tan at birth, and sunburns are unusual.

The hypopigmentation seen in a subset of patients with Prader–Willi syndrome (PWS) and Angelman syndrome (AS) represents a form of OCA2. PWS features hyperphagia, obesity, hypogonadism and mental retardation, whereas AS is characterized by severe mental retardation, microcephaly, ataxic movements and inappropriate laughter. Due to genomic imprinting (see Ch. 54), deletions of the 15q region (which includes the *P* gene) in the paternal chromosome lead to PWS, while deletions in the maternal chromosome give rise to AS. Approximately 1% of patients with AS or PWS also have OCA2, which occurs when deletion of one copy of the *P* gene is accompanied by a mutation in the second copy.

OCA3

The phenotypes of individuals with OCA3 are classified as "rufous" (vast majority of OCA3 patients) and "brown" (more often seen

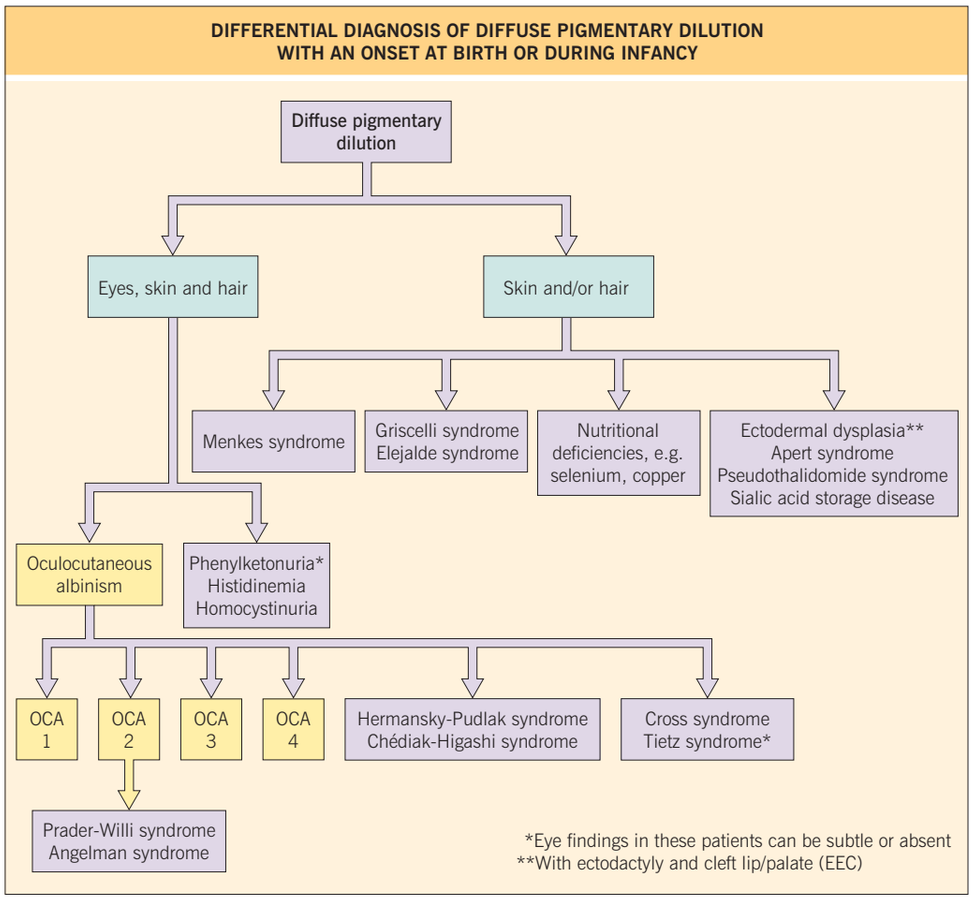


Fig. 66.11 Differential diagnosis of diffuse pigmentary dilution with onset at birth or during infancy. *Adapted from Bolognia JL. A clinical approach to leukoderma. Int J Dermatol. 1999;38:568–72.*

in OCA2). Rufous OCA has been identified in individuals with type III–V skin color, and the phenotype includes a red–bronze skin color, ginger-red hair, and blue or brown irides. Rufous OCA is associated with mutations in the *TYRP1* gene. A patient with the brown OCA phenotype due to mutations in both copies of the *TYRP1* gene has also been described: an African-American child with light brown skin, light brown hair and blue–grey irides.

OCA4

OCA4 is most common among individuals with albinism who are from Japan (~25% of patients), China (10–20% of patients) and India (~10% of patients), and it accounts for ~5% of albinism in Caucasians[65]. The phenotype of OCA4 is variable; hair color ranges from white to yellow–brown, and patients may or may not develop increased pigmentation of the skin and hair over time.

Ocular albinism type 1 (OA1)

Ocular albinism type 1 is characterized by a substantial reduction in visual acuity, hypopigmentation of the retina, and the presence of macromelanosomes in the eyes. Affected boys have nystagmus, photophobia and foveal hypoplasia[64]. Their skin is usually clinically normal without notable pigmentary dilution, although hypopigmented macules have been described in affected individuals who have darkly pigmented skin. Macromelanosomes are evident on histologic examination of the skin.

Pathology

Although there is a reduction in melanin content, a normal number of melanocytes are present within the epidermis.

Differential diagnosis

This is outlined in Figure 66.11. Occasionally, patients with total body vitiligo may be thought to have OCA, but their epidermis lacks melanocytes.

Treatment

No specific treatment is available. Photoprotection (sunscreens, hats, clothing, sun avoidance) is mandatory in patients who have minimal or no pigmentation, in order to avoid cutaneous photocarcinogenesis, in particular the development of squamous cell carcinomas. The latter are a significant cause of morbidity and mortality, especially in tropical regions (see Fig. 66.9). All patients should undergo ophthalmologic evaluation early in life, with longitudinal care as required.

Piebaldism

Piebaldism is an uncommon autosomal dominant disorder characterized by poliosis and congenital, stable, circumscribed areas of leukoderma due to an absence of melanocytes within involved sites.

Epidemiology

The exact prevalence of this condition is not known, but it is estimated to occur in approximately 1 in 40 000 Caucasians.

Pathogenesis

Piebaldism usually results from mutations in the *KIT* proto-oncogene[66], which encodes a member of the tyrosine kinase family of transmembrane receptors that is found on the surface of melanocytes (see Fig. 65.2). A functioning KIT receptor is required for the normal development of melanocytes, both immediately before melanoblast migration from the neural crest and postnatally. Heterozygous deletion of the *SNAI2* gene, which encodes a transcription factor important to melanocyte development, has been found to cause piebaldism in a few patients.

Clinical features

The leukoderma has a characteristic distribution pattern that favors the central anterior trunk, mid extremities, central forehead, and mid-frontal portion of the scalp; the latter results in a white forelock (Fig. 66.12). The lesions are present at birth and classically spare the posterior midline. The white forelock, which is present in 80–90% of patients, is the most familiar feature of piebaldism. However, its absence does not exclude the diagnosis. All the hairs of the forelock are white, and the underlying skin is also amelanotic. This depigmented patch is midline in location, triangular or diamond-shaped, and often symmetrical. The apex can reach the vertex posteriorly, and the affected

Fig. 66.12 Piebaldism. White forelock and characteristic triangular amelanotic patch on the mid-forehead. Note the normally pigmented macules of varying sizes within the leukoderma, primarily at the periphery. *Courtesy, Diane Davidson, MD.*

Fig. 66.13 Piebaldism. Mother and son with the characteristic involvement of the mid extremities. Note the normally pigmented macules within the leukoderma. *Courtesy, Jean L. Bolognia, MD.*

DIFFERENTIAL DIAGNOSIS OF CIRCUMSCRIBED SCALP POLIOSIS
INFLAMMATORY OR AUTOIMMUNE
• Vitiligo • Halo nevus • Alopecia areata (primarily initial cycle of growth) • Postinflammatory (e.g. discoid lupus) • Post-traumatic • Vogt–Koyanagi–Harada syndrome • Alezzandrini syndrome
INHERITED
• Tuberous sclerosis* • Piebaldism (midline frontal) • Waardenburg syndrome (primarily midline frontal) • Isolated white forelock† • Isolated occipital white lock (X-linked recessive) • White forelock with osteopathia striata (autosomal or X-linked dominant) • White forelock with multiple malformations (autosomal or X-linked recessive)
NEVOID
• Associated with nevus comedonicus • Angora hair nevus • Scalp heterochromia secondary to mosaicism*
IDIOPATHIC
*May be lighter than surrounding hair rather than white (e.g. blond streaks in a patient with brown hair). †Separate entity vs possible forme fruste of piebaldism.

Table 66.4 Differential diagnosis of circumscribed scalp poliosis. *Adapted from Bolognia JL, Shapiro PE. Albinism and other disorders of hypopigmentation. In: Arndt KA, et al (eds). Cutaneous Medicine and Surgery. Philadelphia: WB Saunders, 1995.*

area may extend to the root of the nose and include the medial third of the eyebrows; involvement of the nose is rare.

The areas of leukoderma are distinctive and can establish the diagnosis of piebaldism, even in the absence of a white forelock. They are irregular in shape, well-circumscribed and milk-white in color. Normally pigmented and hyperpigmented macules and patches (ranging from a few millimeters to several centimeters in diameter) are typically apparent within the leukodermic patches (Fig. 66.13). Hyperpigmented patches also occur within uninvolved skin and should not be misinterpreted as evidence of neurofibromatosis 1. Poliosis of the eyebrows and eyelashes is a common finding, as are white hairs within areas of leukoderma. Limited contraction of the areas of involvement over time is occasionally observed, and premature graying of the hair is not uncommon.

Pathology

By light and electron microscopy, no melanocytes can be identified in either the interfollicular epidermis or the hair follicles of amelanotic skin[67]. The hyperpigmented macules are characterized by an abundance of melanosomes in the melanocytes and keratinocytes.

Differential diagnosis

The presence of stable amelanotic patches since birth, the characteristic distribution pattern, and the distinctive normally pigmented or hyperpigmented macules within the areas of leukoderma allow the differentiation of piebaldism from vitiligo. The differential diagnosis of circumscribed poliosis of scalp hairs is broad (Table 66.4) and includes both inherited (autosomal dominant and X-linked recessive) and acquired causes. Of note, an isolated white forelock can also be inherited as an autosomal dominant trait. The diagnosis of piebaldism should prompt the clinician to exclude the possibility of Waardenburg syndrome via an ocular examination and evaluation of hearing.

Treatment

Autografts of normal skin into amelanotic areas, including grafting of autologous melanocytes, are a therapeutic option, but this typically requires multiple procedures. Cosmetic products can be used to camouflage affected areas; protection against sunburn is also necessary.

Waardenburg Syndrome

Waardenburg syndrome (WS) is a rare autosomal dominant or autosomal recessive disorder that is characterized by various combinations of the following features[68]:

- achromia of the hair, skin or both in the same pattern as piebaldism (see above)
- congenital deafness
- partial or total heterochromia irides (including isohypochromia)
- medial eyebrow hyperplasia (synophrys)
- a broad nasal root
- dystopia canthorum (an increase in the distance between the inner canthi, with a normal inter-pupillary distance).

Four clinical subtypes of WS have been described (Table 66.5): WS type I, the classic form (WS1); WS type II, which lacks dystopia canthorum (WS2); WS type III, with associated limb abnormalities (WS3, Klein–Waardenburg syndrome); and WS type IV, with Hirschsprung disease (WS4, Shah–Waardenburg syndrome).

Epidemiology

The incidence of WS in the Netherlands has been estimated as approximately 1 in 200 000. In the US, deafness in the setting of WS afflicts 1 in 50 000. WS has been observed in various races and from all regions of the world. Men and women are equally affected.

DISORDERS OF MELANOCYTE DEVELOPMENT					
Human disease		**Mouse model**	**Inheritance**	**Gene**	**Protein**
Piebaldism		Dominant spotting	AD AD	*KIT* *SNAI2*	KIT tyrosine kinase Snail homolog 2 transcription factor
WAARDENBURG SYNDROME					
WS1		Sploch	AD	*PAX3*	Paired box 3 transcription factor
WS2*	A D E	Microphthalmia	AD AR AD	*MITF* *SNAI2* *SOX10*	Microphthalmia-associated transcription factor Snail homolog 2 transcription factor SRY-box 10 transcription factor
WS3†		Sploch	AD	*PAX3*	Paired box 3 transcription factor
WS4	A B C	Piebald spotting Lethal spotting Dominant megacolon	AD, AR AD, AR AD	*EDNRB* *EDN3* *SOX10*	Endothelin B receptor Endothelin-3 SRY-box containing 10
Tietz syndrome			AD	*MITF*	Microphthalmia-associated transcription factor
Albinism, black lock, cell migration disorder of the neurocytes of the gut, and deafness (ABCD) syndrome			AR	*EDNRB*	Endothelin receptor type B

*Other forms of WS2 have been linked to 1p21–p13.3 (WS2B) and 8p23 (WS2C).
†Homozygous *PAX3* mutations have been described in individuals with WS3 whose parents were affected with WS1.

Table 66.5 Disorders of melanocyte development. AD, autosomal dominant; AR, autosomal recessive.

Pathogenesis

The facial dysmorphism seen in WS points to abnormalities during fetal development. It should therefore come as no surprise that several of the genes responsible for WS (*PAX3, MITF, SNAI2, SOX10*; see Table 66.5) encode transcription factors that (by binding DNA and regulating the expression of other genes) have important functions during embryogenesis (see Fig. 65.4). The neural crest is the source of the connective tissues of the head and neck and intestinal ganglion cells as well as melanoblasts, explaining the manifestations of this neurocristopathy. Presumably, the deafness in WS reflects the role of melanocytes in the development of the inner ear.

The PAX3 transcription factor that is mutated in WS1 and WS3 activates melanoblasts and other cells to proliferate and then migrate from the neural crest. The abnormalities of the upper extremities that characterize WS3 imply that PAX3 also regulates limb development[69]. Mutations in the *mi*crophthalmia-associated *t*ranscription *f*actor gene (*MITF*; expression of which is regulated by PAX3 and SOX10), which encodes a helix-loop-helix/leucine zipper transcription factor, can result in WS2. Of note, a mutation in the *MITF* gene that affects the nuclear localization of this protein underlies Tietz syndrome (see below)[70]. In addition to its critical role in melanocyte development, MITF regulates the expression of a number of melanocyte-specific genes (e.g. tyrosinase; see Ch. 65). Homozygous deletion of the *SNAI2* gene (the expression of which is regulated by MITF) has also been identified as a cause of WS2. SNAI2 is a zinc finger transcription factor that has an essential role in the development of neural crest-derived cells, and its complete absence leads to both auditory and pigmentary abnormalities[71].

The SOX10 transcription factor plays an essential role in the development of melanoblasts and ganglion cells, and mutations in this gene can cause WS4 or (if milder) WS2[72]. WS4 can also be caused by mutations in the genes encoding the endothelin B receptor and its endothelin-3 ligand[73]. The endothelin B receptor is found on melanoblast-ganglion cell precursors in the developing neural crest, and its binding to endothelin-3 is essential for the generation of these cell types (see Fig. 65.3).

Clinical features

Waardenburg syndrome type 1 (WS1)

A white forelock, generally similar to that of piebaldism, is the most frequently observed pigmentary abnormality in WS (20–60% of patients). Although the forelock is usually white, patches of red, brown or black hair have been described. A few patients have additional areas of poliosis (e.g. frontoparietal or occipital scalp). Premature graying can involve the scalp hair, eyebrows and body hair, and the onset may be as early as the teens. Areas of leukoderma with an appearance, distribution pattern and natural history similar to piebaldism have been observed in approximately 15% of patients. The prevalence of hearing impairment ranges from 9% to more than 37%[74], and it may be bilateral or unilateral and severe or moderate.

Fig. 66.14 Waardenburg syndrome type 2. Heterochromia irides in the absence of dystopia canthorum. The white forelock is seen in the upper left corner. *Courtesy, Daniel Albert, MD.*

Heterochromia irides, partial (sectorial) or complete, is found in >20% of patients (Fig. 66.14). Complete heterochromia irides gives rise to irides of different colors, one being whitish blue. Bilateral involvement results in bilateral pale blue eyes (isohypochromia). Hypomelanotic fundi may be present.

The eyebrows may be confluent (synophrys) or show hyperplasia of their medial portions (15–70% of patients). The characteristic dystopia canthorum represents an increase in the distance between the inner canthi, with normal distances between the pupils and between the outer canthi. This is accompanied by a shortening in the length of the palpebral fissure (blepharophimosis) and a lateral displacement of the inferior lacrimal points, which are then situated in front of the cornea. The dystopia is usually symmetric but may be asymmetric. Dystopia canthorum is a characteristic feature of WS1 and WS3.

Waardenburg syndrome type 2 (WS2)
WS2 differs from WS1 primarily by the absence of dystopia canthorum. In addition, deafness is probably more common in patients with WS2.

Klein–Waardenburg syndrome (WS3)
WS3 is similar to WS1 but is also associated with upper limb abnormalities (e.g. hypoplasia, syndactyly).

Shah–Waardenburg syndrome (WS4)
In WS4, the characteristic findings of WS occur in association with Hirschsprung disease. In many patients, a white forelock, amelanotic macules and heterochromia irides are present. Deafness is fairly common, but dystopia canthorum and a broad nasal root are uncommon. Additional rare manifestations (associated with *SOX10* mutations) include central nervous system dysfunction, neonatal hypotonia and arthrogryposis.

Tietz syndrome
Tietz syndrome is a rare autosomal dominant disorder characterized by diffuse pigmentary dilution of the skin and hair together with deafness and hypoplasia of the eyebrows. Although the eyes are blue, affected individuals do not have photophobia or nystagmus and the fundi are normal. The clinical phenotype is significantly different from WS2, despite being allelic.

Pathology
As in piebaldism, the areas of involvement in WS have an absence or minimal number of melanocytes when examined by light or electron microscopy.

Diagnosis
In patients with the complete WS phenotype, the diagnosis is clear. However, there is significant clinical heterogeneity, and in some forme fruste cases the diagnosis can be difficult to establish. Examination of family members can be helpful as they may have other features of the disease.

Treatment
No specific treatment is available. However, early diagnosis permits appropriate management of the deafness.

Disorders of Melanosome Biogenesis
Melanosomes are considered members of the lysosome-related organelle family, which includes platelet dense granules and the lytic granules of cytotoxic lymphocytes and natural killer (NK) cells. When the biogenesis of these organelles is disrupted, affected individuals present with the clinical findings of OCA due to their defective melanosomes together with additional symptoms (e.g. bleeding diathesis, immunodeficiency) that reflect abnormalities in other lysosome-related organelles[75,76]. These genetic diseases include Hermansky–Pudlak syndrome (HPS) and Chédiak–Higashi syndrome (CHS).

Hermansky–Pudlak syndrome
To date, nine subtypes of HPS have been identified, each of which is inherited in an autosomal recessive manner (Table 66.6)[77].

Pathogenesis
Most forms of HPS result from mutations in genes that encode components of the *b*iogenesis of *l*ysosome-related *o*rganelles *c*omplexes 1–3 (BLOC1/2/3; see Table 66.6 & Fig. 65.8). These complexes are involved in the formation of lysosome-related organelles, including melanosomes, by a mechanism distinct from that of the adaptor protein 3 (AP-3) complex. The exception is HPS2, which is caused by mutations in the *AP3B1* gene. *AP3B1* encodes the β3A subunit of the AP-3

DISORDERS OF MELANOSOME TRANSPORT AND TRANSFER				
Human disease	**Mouse model**	**Gene mutated**	**Protein function**	**Patient population**
			HERMANSKY–PUDLAK SYNDROME (HPS)	
HPS1	Pale ear	*HPS1*	Trafficking of organelle-specific proteins; component of BLOC-3 (see Fig. 65.8)	Puerto Rico, Arecibo region
HPS2	Pearl	*AP3B1*	β3A (also known as β1) subunit of adaptor protein 3 (AP-3); formation of vesicles from the trans-Golgi network and protein trafficking (see Fig. 65.8)	
HPS3	Cocoa	*HPS3*	Component of BLOC-2	Puerto Rico
HPS4	Light ear	*HPS4*	Component of BLOC-3	
HPS5	Ruby eye 2	*HPS5*	Component of BLOC-2	
HPS6	Ruby eye	*HPS6*	Component of BLOC-2	
HPS7	Sandy	*DTNBP1*	Encodes dysbindin*, a component of BLOC-1	
HPS8	Reduced pigmentation	*BLOC1S3*	Component of BLOC-1 (subunit 3)	
HPS9	Pallid	*PLDN*	Encodes pallidin, a component of BLOC-1	
			CHÉDIAK–HIGASHI SYNDROME (CHS)	
CHS	Beige	*LYST*	Lysosomal trafficking regulator protein that controls fission/fusion of lysosome-related organelles	
			GRISCELLI SYNDROME (GS)	
GS1	Myosin Va dilute	*MYO5A*	Captures melanosomes when they reach the cell periphery within dendrites and attaches them to the actin cytoskeleton; also expressed in neurons	
GS2	Rab27A	*RAB27A*	Melanosomal membrane GTPase that binds to melanophilin and takes part in melanosome attachment at the cell periphery; also functions in granule secretion from cytotoxic T-cells	
GS3	Leaden	*MLPH*	Links myosin Va to Rab27a, enabling docking of melanosomes at the cell periphery	
		Deletion of the *MYO5A* F-exon	The F-exon of myosin Va is only expressed in melanocytes	

*Dysbindin also binds to α- and β-dystrobrevins, components of the dystrophin-associated protein complex in both muscle and non-muscle cells.

Table 66.6 Disorders of melanosome transport and transfer. BLOC, biogenesis of lysosome-related organelles complex; CTL, cytotoxic T lymphocytes; *DTNBP1*, dystrobrevin binding protein 1.

complex, which is involved in protein sorting to lysosomes and lysosome-related organelles (see Fig. 65.8). AP-3 also functions in CD1b-associated antigen presentation and secretion of lytic granules from cytotoxic T cells, explaining the additional clinical feature of immunodeficiency in patients with HPS2.

Clinical features

Compared to unaffected first-degree relatives, patients with HPS have pigmentary dilution of the skin, hair and eyes. The degree varies, depending upon the underlying mutations and the patient's ethnic origin. With age, an increase in pigmentation is usually seen, but patients still have difficulty tanning. Ocular manifestations of albinism, such as nystagmus and reduced visual acuity, are also present.

Systemic manifestations due to organelle dysfunction include a bleeding tendency (e.g. with tooth extraction or childbirth) as well as interstitial pulmonary fibrosis and granulomatous colitis secondary to ceroid lipofuscin accumulation within lysosomes. Less often, renal failure and cardiomyopathy develop, usually during adulthood. Patients with HPS2 experience recurrent bacterial infections due to neutropenia and abnormal cytotoxic T-cell function.

Laboratory findings and pathology

Laboratory evaluation is notable for the presence of hair bulb tyrosinase as well as stage I to III (rarely stage IV) melanosomes and macromelanosomes by electron microscopy. Although the platelet count is normal, the bleeding time and platelet function analyzer (PFA)-100 time are prolonged due to platelet dysfunction. Ultrastructurally, there is an absence of dense bodies within platelets. Ceroid deposits, derived from the degradation of lipids and glycoproteins, are found within lysosomes in affected internal organs, including the lungs and gastrointestinal tract. Presumably, this reflects a defect in lysosomal function.

Treatment

The development of progressive pulmonary fibrosis often leads to premature death in patients with HPS, who have an average lifespan of only 30–50 years. Although the antifibrotic agent pirfenidone appeared to slow the progression of pulmonary fibrosis in HPS1 patients in an initial controlled study, a more recent controlled trial found no benefit of this agent in HPS1 patients with mild to moderate pulmonary disease[78]. Platelet transfusions can be administered prior to surgical procedures in HPS patients.

Cross syndrome

Cross syndrome is characterized by diffuse pigmentary dilution, silvery hair, ocular anomalies, and neurologic abnormalities (e.g. psychomotor retardation, ataxia and spasticity). A family with overlapping features of HPS and Cross syndrome has raised the possibility that this latter syndrome may be a clinical variant of HPS[79].

Chédiak–Higashi syndrome

Chédiak–Higashi syndrome (CHS) is a rare autosomal recessive disorder characterized by OCA with a silvery-gray cast to the hair, photophobia, nystagmus and ocular hypopigmentation; an admixture of hyper- and hypopigmentation may be evident in chronically sun-exposed skin, especially in patients with relatively dark constitutive pigmentation. Additional findings include a bleeding diathesis due to diminished function of platelet dense granules, progressive neurologic dysfunction, and severe immunodeficiency due to abnormal lytic granules in lymphocytes, NK cells and neutrophils (see Ch. 60). A hallmark of the disorder is the presence of giant lysosome-related organelles, including melanosomes, platelet dense granules and neutrophil granules. Examination of a peripheral blood smear for the latter represents a simple method of screening for this condition. CHS is caused by mutations in the *lys*osomal *t*rafficking regulator gene (*LYST*), which encodes a cytoplasmic protein that regulates fission/fusion of lysosome-related organelles[80].

Tricho-hepato-enteric syndrome (phenotypic diarrhea of infancy)

This autosomal recessive disorder caused by mutations in the tetratricopeptide repeat domain 37 gene (*TTC37*) can present with diffuse pigmentary dilution of the skin and hair, platelet defects (including abnormal granules) and immunodeficiency. Unlike CHS, it is also characterized by brittle hair with trichorrhexis nodosa, intractable diarrhea during infancy, primary liver disease, facial dysmorphism and cardiac defects.

Disorders of Melanosome Transport and/or Transfer

Identification of the defective proteins in various forms of Griscelli syndrome (GS) has led to better understanding of processes of melanosome transport.

Epidemiology

Griscelli syndrome and the related Elejalde syndrome (neuroectodermal melanolysosomal disease) are rare autosomal recessive disorders.

Pathogenesis

On the basis of molecular genetics (as well as clinical findings), GS has been separated into three entities, GS1, GS2 and GS3 (see Table 66.6). GS1 is due to mutations in the gene that encodes myosin Va[81]. One end of the myosin Va protein binds the actin cytoskeleton, while the other can bind an organelle, e.g. a melanosome. This linkage plays a key role in the transfer of melanosomes from melanocytes to keratinocytes. GS2 is associated with mutations in *RAB27A*[82], which encodes a small Ras-like GTPase (belonging to the Rab family) that is present in melanosomes. GS3 is due to mutations in *MLPH*, whose protein product, melanophilin, serves to link myosin Va to Rab27a[83] (see Fig. 65.10). Because *MLPH* is expressed only in melanocytes, the associated phenotype is limited to diffuse pigmentary dilution and silvery hair. On the other hand, expression of *MYO5A* in neurons explains the associated neurologic abnormalities in GS1, and expression of *RAB27A* in hematopoietic cells accounts for the immunodeficiency and hemophagocytic syndrome observed in GS2. Elejalde syndrome may represent a variant of GS1, but its molecular basis is not yet known.

Clinical features

All three types of GS are characterized by pigmentary dilution of the skin and silvery-gray hair due to pigment clumping within melanocytes. As noted above, patients with GS1 exhibit primarily neurologic impairment[81], while those with GS2 have immune abnormalities due to defective release of cytotoxic lysosomal contents from hematopoietic cells. A hemophagocytic syndrome can also occur in GS2, with uncontrolled T-lymphocyte and macrophage activation leading to death[82]; this process can involve the CNS in a secondary manner.

Elejalde syndrome presents with the pigmentary findings of GS plus severe neurologic dysfunction.

Treatment

Hematopoietic stem cell transplantation is indicated for the treatment for GS2 (but not GS1 or GS3).

Tuberous Sclerosis Complex

The tuberous sclerosis complex (TSC) represents an autosomal dominant disorder characterized by hamartomas in multiple organs, most commonly the skin, brain, eye, heart and kidney (see Ch. 61).

Clinical features

The classic TSC triad of facial angiofibromas ("adenoma sebaceum"), seizures and mental deficits is preceded by the appearance of white macules. In one study utilizing Wood's lamp examination, hypomelanotic macules were found in 64 of 65 patients with TSC (although this high figure may be an artifact of referral selection).

Hypomelanotic macules are often evident at birth or during the neonatal period. In fact, all lesions are probably present at birth, but they may be inapparent, particularly in lightly pigmented infants, until the skin is exposed to UV light or the patient is examined with a Wood's lamp. The number of lesions varies from one to >100 per patient. The great majority of patients have 2–20 hypomelanotic macules, with 50% having fewer than six and 50% having six or more macules. Lesions may be polygonal, lance-ovate, "thumbprint-like", guttate ("confetti-like") or (rarely) segmental (Fig. 66.15). The most characteristic, but not the most frequent, configuration is lance-ovate

Fig. 66.15 Tuberous sclerosis. Two types of hypomelanotic macules – lance-ovate and confetti (idiopathic guttate hypomelanosis-like). *Courtesy, Dr Strobel.*

DIFFERENTIAL DIAGNOSIS OF GUTTATE LEUKODERMA
Idiopathic guttate hypomelanosis
Pityriasis lichenoides chronica
Lichen sclerosus
Achromic verrucae plana*
Leukoderma punctata (after PUVA therapy)
Vitiligo ponctué
Darier disease (usually admixed with keratotic lesions)
Confetti-like lesions of tuberous sclerosis
Xeroderma pigmentosum
In association with punctate palmoplantar keratoderma
In association with chromosomal abnormalities
Disseminated hypopigmented keratoses (after PUVA therapy)*
Frictional lichenoid dermatitis*
Pityriasis alba
Pityriasis versicolor (especially on the face of children)
Clear cell papulosis*
*Minimally elevated flat-topped papules.

Table 66.7 Differential diagnosis of guttate leukoderma. Guttate hypopigmentation may also be seen in the setting of dyschromatoses (see Table 67.8). *Adapted from Bolognia JL, Shapiro PE. Albinism and other disorders of hypopigmentation. In: Arndt KA, et al (eds). Cutaneous Medicine and Surgery. Philadelphia: WB Saunders, 1995.*

(rounded at one end, pointed at the other), which resembles the leaflet of the mountain ash tree, hence the name "ash leaf spot".

Hypomelanotic macules are usually found on the trunk, particularly posteriorly, but they can be found on any cutaneous surface. They occur more commonly on the lower extremities than on the upper extremities or the head and neck; lesions on the scalp are often associated with more lightly pigmented hairs. The long axis of the lance-ovate (ash leaf) macules is predominantly in the cephalocaudal direction on the extremities and in the transverse direction on the trunk. The margins of the lesions are usually smooth but may be irregular. The macules and patches are a dull white color (hypomelanotic), not the "pure-white" color (amelanotic) of vitiligo. As a result, they may be inapparent on casual examination of lightly pigmented skin. Wood's lamp examination reveals a reduction, but not an absence, of pigmentation. The relative size and number of hypomelanotic macules do not change with age, and spontaneous disappearance does not occur. Café-au-lait macules are seen in some patients.

Pathogenesis

Circumscribed hypomelanosis in TSC does not appear to result from a reduction in the number of melanocytes but rather from decreased size and poor melanization of melanosomes, which (regardless of racial background) are grouped within the lysosomes of keratinocytes (see Table 65.3). Of note, decreased melanosome size is not a feature of other circumscribed congenital hypomelanoses. TSC is caused by mutations in two tumor suppressor genes, *TSC1* and *TSC2*, which encode the hamartin and tuberin proteins, respectively (see Ch. 61). These proteins associate physically *in vivo*, functioning together to negatively regulate mammalian target of rapamycin (mTOR) signaling.

Diagnosis

If an infant has three or more hypopigmented macules, a diagnosis of TSC should be considered and (if there is no history of seizures) echocardiography performed as an initial investigation (see Fig. 61.21). The presence of three or more hypomelanotic macules, especially if lance-ovate in shape, raises the possibility of TSC. The combination of white macules and seizures increases the likelihood of TSC. Although the presence of only one or two hypopigmented macules or patches in an otherwise healthy infant does not completely exclude TSC, the diagnosis of nevus depigmentosus is much more likely.

It is usually fairly easy to distinguish vitiligo, given its characteristic distribution pattern and the pure-white color. Postinflammatory hypopigmentation is typically easily excluded by the lack of preceding or concurrent inflammatory or trauma-induced lesions. Nevus anemicus is readily distinguished by its "disappearance" upon diascopy; in addition, vigorous rubbing or application of ice produces erythema in the hypopigmented lesions of TSC but not in nevus anemicus. Hypomelanotic macules may be observed in patients with ataxia telangiectasia (likely reflecting "pigmentary mosaicism"). Westerhof syndrome is characterized by hypo- and hyperpigmented macules, possibly in association with growth retardation; autosomal dominant inheritance has been proposed, but the etiology is not known. Familial progressive hyper- and hypopigmentation, which also has autosomal dominant inheritance and features lesions ranging from small macules to large patches, was recently found to be caused by heterozygous activating mutations in the KIT ligand gene (*KITLG*)[83a].

Rarely, the hypopigmentation in TSC has a segmental pattern, for which the differential diagnosis includes segmental vitiligo (which progresses over a few months to 2 years and is amelanotic) and "pigmentary mosaicism" (see below). Idiopathic guttate hypomelanosis (IGH) may resemble the confetti lesions of TSC, but IGH is an acquired disorder that usually develops in adults. The diagnosis of TSC should be considered in any child or infant with a guttate leukoderma. Other causes of a guttate leukoderma are outlined in Table 66.7.

"Pigmentary Mosaicism": Hypomelanosis of Ito, Segmental Pigmentation Disorder and Nevus Depigmentosus

Hypomelanosis of Ito (HI) is a descriptive term for hypopigmentation along Blaschko's lines (also referred to as "linear nevoid hypopigmentation"), which reflects mosaicism characterized by a clone of skin cells with a decreased ability to make pigment ("pigmentary mosaicism"; see Ch. 62). Although cytogenetic data are less substantial, "segmental pigmentation disorder" and nevus depigmentosus are also considered to represent manifestations of cutaneous mosaicism[84].

Clinical features

HI may be apparent at birth or become evident during infancy or early childhood. The characteristic pattern of streaks and whorls (Table 66.8) can occur unilaterally or bilaterally and is seen most commonly on the trunk and limbs (Fig. 66.16)[84]. Abnormalities of the CNS, eye or musculoskeletal system are found in approximately 30% of patients with hypopigmentation along Blaschko's lines who present to a pediatric dermatologist at a tertiary referral center.

Nevus depigmentosus occurs in 1 in 50–75 individuals. The name is a bit of a misnomer, as the areas of leukoderma are actually hypomelanotic rather than amelanotic. Most lesions measure a few centimeters in diameter and have irregular but well-defined borders, often breaking apart into smaller macules at the periphery (Fig. 66.17). A block-like variant of nevus depigmentosus, also referred to as the hypopigmented form of the "segmental pigmentation disorder", typically features midline demarcation and less distinct lateral borders[85].

Phylloid hypomelanosis is a distinctive pattern of hypomelanosis that occurs in patients with mosaic forms of trisomy (or tetrasomy) 13 or 13q. The hypomelanosis consists of: (1) round or oval lesions; (2) large

DISORDERS WITH LINEAR HYPOPIGMENTATION
LESIONS USUALLY FOLLOW BLASCHKO'S LINES
• Hypomelanosis of Ito/"linear nevoid hypopigmentation"*
• Lichen striatus
• Focal dermal hypoplasia (Goltz syndrome)
• Menkes kinky hair disease (female carrier)
• Conradi–Hünermann–Happle syndrome
• Epidermal nevus
• In association with nevus comedonicus
• Linear lichen sclerosus
• Guttate macules in linear keratosis follicularis and linear basaloid follicular hamartoma
LESIONS MAY FOLLOW BLASCHKO'S LINES
• Segmental vitiligo
• Segmental ash leaf spot
• Fourth stage of incontinentia pigmenti
LESIONS DO NOT FOLLOW BLASCHKO'S LINES
• Linear hypopigmentation secondary to intralesional corticosteroids
• Pigmentary demarcation lines, type C
*Block-like hypopigmentation represents another pattern of "pigmentary mosaicism" and may coexist with linear lesions; overlaps with a "systematized" nevus depigmentosus with a linear configuration.

Table 66.8 Disorders with linear hypopigmentation. *Adapted from Bolognia JL, Shapiro PE. Albinism and other disorders of hypopigmentation. In: Arndt KA, et al (eds). Cutaneous Medicine and Surgery. Philadelphia: WB Saunders, 1995.*

Fig. 66.16 Hypomelanosis of Ito. Note the S-shaped pattern of the hypopigmented streaks along Blaschko's lines on the flank and abdomen.

asymmetric areas reminiscent of the leaves of a begonia; and (3) pear-shaped or oblong macules. Additional features may include telangiectatic macules, hypertrichosis, CNS defects (especially absence of the corpus callosum), conductive hearing loss, choroidal and retinal colobomas, craniofacial anomalies and digital malformations[86].

Pathology

Light and electron microscopy of involved skin in HI may reveal a decreased number of melanocytes and melanosomes[87]. A wide variety of cytogenetic abnormalities in lymphocytes and/or lesional fibroblasts have been detected in patients with HI (see Ch. 62).

Diagnosis

The differential diagnosis of linear leukoderma is presented in Figure 66.18. Diagnostic considerations for the common type of nevus depigmentosus are discussed above (see TSC).

Fig. 66.17 Nevus depigmentosus. Hypomelanotic patch with a decrease, but not absence, of pigmentation.

OTHER GENETIC FORMS OF HYPOMELANOSIS

Albinism–deafness syndrome, also called Ziprkowski–Margolis syndrome or Woolf syndrome, is an X-linked disorder that has been mapped to Xq26.3–q27.1[88]. Affected boys have congenital sensorineural deafness and a severe piebald-like phenotype with extensive areas of hypopigmentation.

NUTRITIONAL HYPOMELANOSIS

In *kwashiorkor*, which is due to severe protein deficiency, the skin initially becomes erythematous to red–brown in color with marked desquamation (see Ch. 51). Both hypomelanosis and patchy postinflammatory hypermelanosis can be seen, with striking pigmentary changes in florid cases. The hypomelanosis usually begins on the face. The hair is dry and lusterless, and it may become light red–brown in color. Upon resumption of dietary protein intake, the skin repigments slowly. Diffuse pigmentary dilution due to *deficiencies of copper* or *selenium* have also been reported (see Fig. 66.11).

POSTINFLAMMATORY HYPOMELANOSIS

Epidemiology

Postinflammatory hypomelanosis (PIH) represents a very common skin disorder that is more obvious in darkly pigmented or tanned individuals. A large number of dermatoses can lead to PIH[89], including psoriasis, seborrheic dermatitis, atopic dermatitis, sarcoidosis, lichen sclerosus, lichen striatus, pityriasis lichenoides chronica, mycosis fungoides and lupus erythematosus (Fig. 66.19). In some patients, repeated examinations are required to identify primary inflammatory lesions.

Pathogenesis

The various steps that determine skin color, including melanogenesis, are controlled by multiple factors (e.g. growth factors, cytokines) that exert their actions directly or indirectly on keratinocytes and melanocytes. Dysregulation of these processes can induce abnormal melanocyte–keratinocyte interactions. Cutaneous inflammation, for example, is able to alter melanosome biogenesis, melanin production, melanosome transport, and especially transfer of melanosomes to keratinocytes. Severe local inflammation can lead to a loss of functional melanocytes or even melanocyte death.

Clinical features

Hypomelanosis usually follows or coexists with inflammatory lesions, but, occasionally, only hypopigmented lesions are seen, e.g. in sarcoidosis or mycosis fungoides. PIH, either localized or widespread, is usually associated with a decrease, but not absence, of pigment.

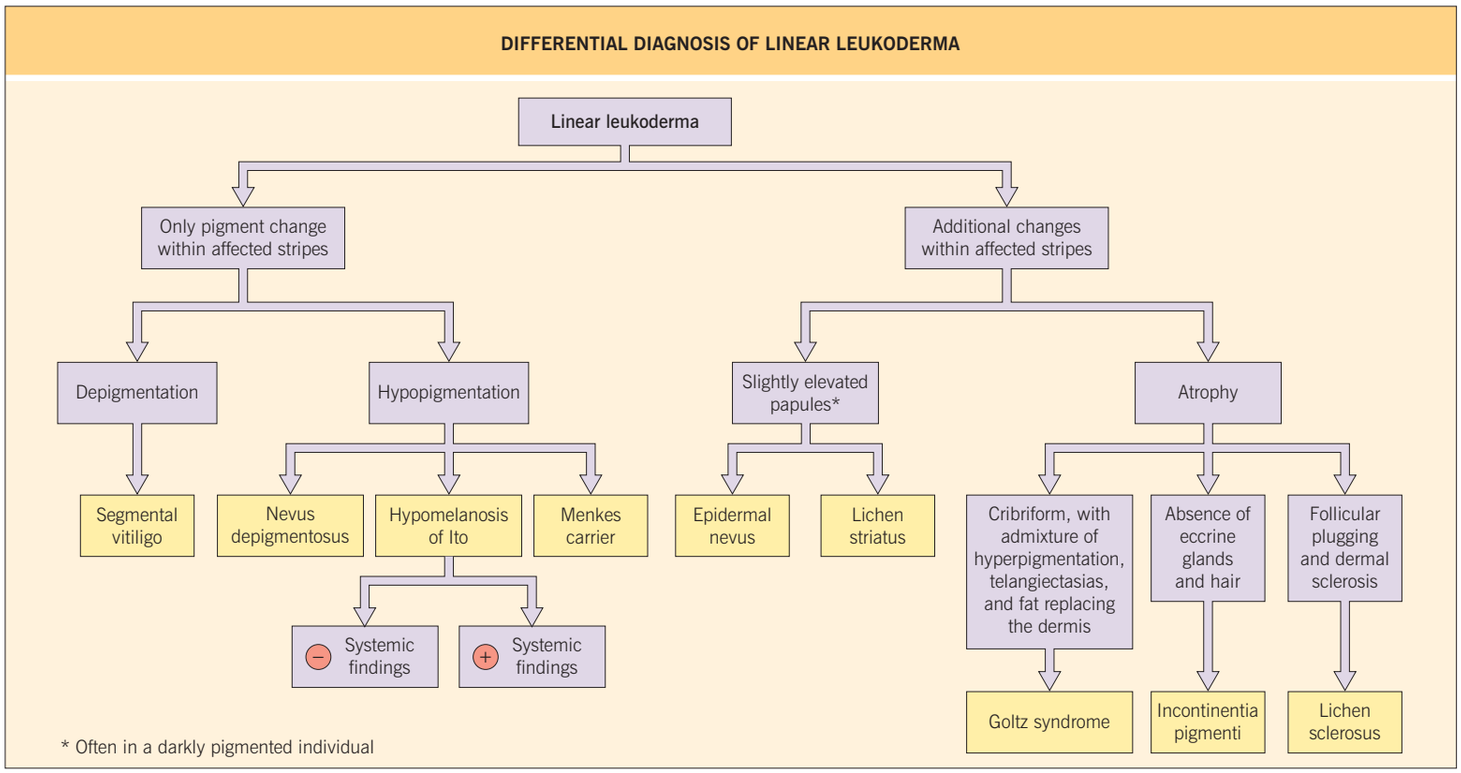


Fig. 66.18 Differential diagnosis of linear leukoderma.

Complete depigmentation is most commonly seen in the setting of severe atopic dermatitis and discoid lupus erythematosus (see Fig. 66.19E,F). Whether this lack of pigment represents koebnerization of vitiligo into areas of inflammation versus the consequence of severe inflammation is debatable.

Pathology

In certain forms of PIH (e.g. sarcoidosis, mycosis fungoides), histologic examination of hypopigmented lesions can aid in establishing the diagnosis, whereas in others (e.g. pityriasis lichenoides chronica) the findings are often nonspecific.

Treatment

Once the underlying inflammatory disorder is effectively treated, the PIH usually gradually resolves. Sun exposure or UVB phototherapy may be helpful. In amelanotic lesions with complete loss of melanocytes, epidermal or melanocyte grafting may be considered (see above).

Pityriasis Alba

Pityriasis alba is a very common condition, consisting of slightly scaly, round to oval, ill-defined macules and patches with mild to moderate hypopigmentation (see Ch. 12). Although it occurs in all races, pityriasis alba is more noticeable in darkly pigmented individuals. It is generally a disorder of childhood and adolescence, and it becomes more apparent during the summer months when the surrounding skin is tanned. The lesions usually vary in size from 0.5 to 3 cm, but larger lesions can also occur.

The earliest lesions may be pink in color, but after a few weeks, the erythema fades and the cutaneous surface assumes a whitish, dry, powdery appearance, sometimes with a slightly raised, pinkish border. The face, especially the malar region, is the most frequent site of involvement. Occasionally, lesions of pityriasis alba are seen on the neck, trunk and extremities. This dermatosis is generally asymptomatic, but some patients complain of itching and burning. With Wood's lamp examination, more lesions may become apparent and a decrease in pigment is confirmed (as opposed to an absence of pigment as in vitiligo). Although the patches of hypomelanosis often remain stationary and unchanged for several years, they usually (but not always) clear spontaneously after puberty.

Light and electron microscopy reveal reduced numbers of active melanocytes and a decrease in the number and size of melanosomes in the affected skin.

The differential diagnosis includes pityriasis versicolor, vitiligo (see above) and other forms of PIH, in particular pityriasis lichenoides chronica when the lesions are extrafacial.

Topical hydrocortisone may be helpful, but emollients seem to be equally effective.

Sarcoidosis

The true incidence of leukoderma in sarcoidosis is unknown. In one series, hypopigmentation was observed in 6% of sarcoidosis patients. The female-to-male ratio is ~2:1. The lesions are described as circumscribed or poorly marginated papules or plaques that vary from one to a few centimeters in diameter, and they may or may not be indurated. In addition, dermal nodules surrounded by hypomelanosis may be seen[90]. The lesions appear most commonly on the extremities, are asymptomatic, and have no other secondary changes. They appear to carry no specific prognostic significance, and spontaneous repigmentation may occur.

Histologically, non-caseating granulomas are seen in the dermis. By electron microscopy, some melanocytes appear normal, while others have abnormalities such as cytoplasmic vacuolation, dilation of the rough endoplasmic reticulum, and degenerative changes within mitochondria. The melanosomes appear morphologically normal, but their number within keratinocytes is decreased. The clinical and histologic features of leprosy differ enough to allow a distinction.

Hypopigmented Mycosis Fungoides

Hypomelanotic mycosis fungoides (MF) is a variant of early-stage MF that is most frequently observed in darkly pigmented individuals (Fig. 66.20), probably because it is more clinically obvious in darker skin. The hypomelanotic lesions occur on the trunk or extremities and may be pruritic. Erythema and slight infiltration are usually, but not always, present. Although the most common age range at the time of diagnosis is 30–40 years, it can develop in children and adolescents. Treatment with photo(chemo)therapy or topical nitrogen mustard (mechlorethamine) can result in repigmentation. Routine histology shows the typical features of MF and electron microscopy demonstrates decreased

Fig. 66.19 Postinflammatory hypomelanosis. Hypopigmentation secondary to psoriasis (**A**), seborrheic dermatitis in an infant (**B**), pityriasis lichenoides chronica (**C**), and lichen striatus (**D**). Note the flat-topped papules in the latter. Complete pigment loss in patients with severe atopic dermatitis (**E**), discoid lupus erythematosus (**F**) and neonatal lupus erythematosus (**G**). *B, Courtesy, Jean L Bolognia, MD. G, Courtesy, Julie V Schaffer, MD.*

numbers of melanosomes within epidermal keratinocytes. Numerous morphologically normal melanosomes are present in melanocytes. These observations suggest a defect in melanosomal transfer, a change seen in most postinflammatory hypomelanoses.

Scleroderma and Lichen Sclerosus

Patients with scleroderma can develop diffuse hypermelanosis[91] with accentuation in sun-exposed sites, a mixture of hypo- and hyperpigmentation in areas of chronic sclerosis (e.g. the hands), and a characteristic leukoderma in both sclerotic and non-sclerotic skin. The latter features circumscribed areas of complete pigment loss except for perifollicular and supravenous retention of pigment (Fig. 66.21). When this peculiar leukoderma is seen, scleroderma must be excluded, as it is only known to occur in two other settings: overlap syndromes (i.e. those that include scleroderma) and scleromyxedema. The origin and pathogenesis of the pigmentary disturbances in scleroderma are unknown.

Genital and extragenital lesions of lichen sclerosus are often hypomelanotic. Additional changes include epidermal atrophy, follicular plugging and, in the anogenital region, purpura. Occasionally, extragenital lichen sclerosus presents as a guttate leukoderma (see Table 66.7; Fig. 66.22). Electron microscopy reveals a loss of pigment cells or decreased number of melanocytes with degenerative changes.

Lupus Erythematosus

In discoid lupus erythematosus (DLE), hypomelanosis or amelanosis is almost always associated with cutaneous atrophy and scarring (see Fig. 66.19F). Hypomelanosis favors the center of the lesions, and it is often accompanied by a rim of hyperpigmentation. In chronic scarring DLE, the pigmentary changes are persistent. Histologically, in addition to a decreased number of epidermal melanocytes, there is epidermal atrophy, vacuolar degeneration of the basal layer, pigmentary incontinence and fibrosis, changes that help to establish the correct diagnosis.

Fig. 66.20 Hypopigmented mycosis fungoides. This condition is most often observed in individuals with darkly pigmented skin.

Fig. 66.21 Leukoderma of scleroderma. Uniform retention of perifollicular pigment within areas of leukoderma. Hyperpigmentation is also seen overlying a superficial vein.

Hypomelanosis is also frequently seen in the center of annular lesions of subacute cutaneous LE, but this is usually reversible.

INFECTIOUS AND PARASITIC HYPOMELANOSIS

Pityriasis (Tinea) Versicolor

The primary lesion is round to oval, hypomelanotic, and usually measures several millimeters to 1–3 cm in diameter (Fig. 66.23). Within the areas of involvement, the lesions are often coalescent centrally. Associated fine scale may be obvious or only apparent upon scratching or stretching the skin. The distribution is usually symmetric and favors the upper trunk and shoulders; lesions sometimes develop on the lower trunk, neck and face (see Ch. 77). While the contrast between the hypomelanotic infected skin and the surrounding normal skin is striking in darkly pigmented patients, or following a tan in lightly pigmented patients, Wood's lamp examination may be required to locate all the lesions.

Fig. 66.22 Guttate lichen sclerosus involving the areola.

Fig. 66.23 Pityriasis (tinea) versicolor. A Hypopigmented variant with obvious scale. **B** Guttate hypopigmented lesions on the cheek; note the classic scaly lesions in the posterior auricular area. *B, Courtesy, Julie V Schaffer, MD.*

Fig. 66.24 Tuberculoid leprosy. Large, thin hypopigmented plaque on the elbow with a raised light pink border.

Fig. 66.25 Onchocerciasis (leopard skin). Depigmentation of the shin with follicular repigmentation or retention of perifollicular pigment, a common site for the associated leukoderma.

In the hypopigmented skin, there is a decreased density of melanosomes within keratinocytes, but no change in the melanocyte density. Abnormal melanosome production, decreased melanin synthesis, and a partial block in melanosome transfer to keratinocytes have all been suggested as underlying defects. Azelaic acid, a competitive inhibitor of tyrosinase produced by *Malassezia furfur*, may play a role in the decreased melanin synthesis. Although the differential diagnosis includes postinflammatory hypopigmentation (e.g. secondary to parapsoriasis), progressive macular hypomelanosis or early vitiligo, the diagnosis of pityriasis versicolor is easily confirmed by examination of the associated scale in a potassium hydroxide preparation.

Hypomelanosis without any scaling may remain for months after spontaneous or treatment-induced eradication of the hyphal form of the organism.

Leprosy

Hypomelanotic macules may be the earliest expression of *lepromatous leprosy*. The lesions are usually small, multiple, subtle and ill-defined; they may be difficult to recognize, particularly in lightly pigmented skin. The face, extremities and buttocks are favored, and the warmer parts of the body are usually spared. There is little or no anhidrosis or loss of sensation. Later, plaques, nodules or diffuse infiltration of the skin appear (see Ch. 75).

The hypopigmented patches of *tuberculoid leprosy* are much different from those of lepromatous leprosy. Tuberculoid lesions have discrete edges and can be quite large, up to 30 cm in diameter (Fig. 66.24). A raised border, uniform infiltration or a characteristic pebbled appearance may be observed. The surface can be slightly scaly, dry or minimally atrophic. The lesions are asymmetrically distributed on the posterolateral aspects of the extremities, back, buttocks and face. There is associated alopecia, anhidrosis, and loss of tactile and heat sensations.

In *borderline (dimorphous) leprosy*, plaques and annular lesions are more common than hypomelanotic macules; the latter, if present, have ill-defined borders. A "Swiss cheese" appearance with erythematous annular lesions and hypomelanotic areas, all bound by vague outer borders, characterizes this form of leprosy. In *indeterminate leprosy*, the macules are usually hypomelanotic, but they may also be erythematous; hypoesthesia may be present. They are asymmetrically distributed and favor exposed sites.

The mechanism of hypopigmentation in leprosy is unknown, and there are no histologic or ultrastructural alterations in the melanocytes. Treatment usually, but not always, results in repigmentation of the hypomelanotic macules.

Treponematoses

In *pinta*, hypomelanotic lesions occur during the late phase of the disease, a few months to several years after the appearance of secondary lesions. Irregular, vitiligo-like areas of depigmentation favor skin overlying bony prominences and are often surrounded by brown to blue–gray hyperpigmentation. Atrophy, xerosis and alopecia may be evident. Longstanding amelanotic lesions do not typically repigment.

Hypomelanosis occasionally develops in untreated tertiary *yaws*. Symmetric hypomelanotic macules enlarge until an entire area is affected. The most common sites are the dorsal aspects of the wrists and hands and over the metacarpophalangeal and interphalangeal joints.

Hypomelanosis may occur in the late stages of *bejel (endemic syphilis)*. Hypomelanotic macules have well-defined borders and may be admixed with pigmented macules. The lesions are usually symmetrically distributed on the extremities, genitalia, areolae and trunk. Early penicillin G treatment results in satisfactory repigmentation.

In *secondary syphilis*, hypomelanosis is an occasional finding that is called "leukoderma syphiliticum". In the "necklace of Venus", small (1–2 mm) hypomelanotic macules are scattered within a larger area of hyperpigmentation on the neck. Hypopigmentation may also develop at sites of previous inflamed lesions, which favor the neck, proximal extremities, upper trunk, abdomen, axillae and groin. Leukoderma syphiliticum regresses with treatment and usually disappears completely within several months to a year.

Onchocerciasis

Initially, small (punctate), yellow–brown hypomelanotic macules appear on the middle third of the shin medial to the tibial crest. Later, the macules enlarge, coalesce and undergo progressive lightening until there is amelanosis (Fig. 66.25). Pigmented macules persist within the hypopigmented patches, hence the designation "leopard skin" (see Ch. 83). Other sites of involvement may include the lateral aspects of the legs, groin and skin overlying the bony prominences of the pelvis.

Post-kala-azar Dermal Leishmaniasis

Small hypomelanotic macules in a symmetric distribution that favors the upper trunk and arms constitute the prenodular stage of the disease. The lesions become elevated over a period of months to years. Total repigmentation following systemic treatment with antimonials is almost impossible to achieve.

Herpes Zoster

Hypo- or depigmentation is sometimes seen in the sites of previous herpes zoster. Amelanosis can result from melanocyte destruction during the inflammatory and healing process, which may also lead to atrophy and fibrosis.

HALO NEVUS AND MELANOMA-ASSOCIATED LEUKODERMA

Halo Nevus

The halo nevus phenomenon (see Ch. 112) most often occurs in children and young adults with multiple melanocytic nevi; it is unusual in

adults over 40 years of age. A central melanocytic nevus is surrounded by a round or oval amelanotic annulus. The lesions are asymptomatic and the most common site is the trunk, particularly the back. There are four stages in the evolution of a halo nevus: (1) appearance of the halo; (2) loss of pigment within the central nevus; (3) disappearance of the nevus; and (4) disappearance of the halo.

Some patients develop multiple halo nevi and/or associated vitiligo. The exact relationship between halo nevi and vitiligo has been the subject of controversy.

Both nevus cells and epidermal melanocytes in the surrounding skin are destroyed, as demonstrated by histologic and ultrastructural studies. Both $CD4^+$ and $CD8^+$ T cells infiltrate halo nevi. Peripheral T cells from a patient with halo nevi were shown to lyse *in vitro* melanocytes obtained from normal nevus, implicating T cells in the pathogenesis of halo nevi. Oligoclonality of the T-cell response in patients with halo nevi further suggests that the destruction of melanocytes could represent the lysis of a distinctive cell type through an immune process mediated by a limited number of T-cell clones[92].

The clinical diagnosis of halo nevus is usually fairly straightforward, but Wood's lamp examination may occasionally be required to detect the halo. The halo phenomenon can occur with a variety of types of melanocytic nevi (e.g. neurotized, blue, congenital) and melanoma. Careful examination of the central lesion is therefore required. Typical halo nevi require no treatment other than reassurance. Individuals beyond 40 years of age with halo nevi should be examined carefully for melanoma (ocular and cutaneous).

Melanoma-Associated Leukoderma

Vitiligo-like depigmentation can occur in patients with cutaneous or ocular melanoma. At least three types of leukoderma are associated with melanoma: hypomelanosis within tumors (primary or metastatic) due to regression (see Ch. 113), amelanosis around tumors (see above; Fig. 66.26), and vitiligo-like depigmentation remote from the tumors. In the latter, involvement of ocular melanocytes (e.g. uveitis, retinopathy, VKH-like changes) has also been reported.

Increasing evidence suggests that melanoma-associated, vitiligo-like leukoderma results from an immune reaction directed against antigenic determinants shared by normal and malignant melanocytes. Although antibodies to pigment cells are commonly found in patients with melanoma, growing evidence points towards an important role for cellular immune responses (Fig. 66.27). Vitiligo-like lesions have been observed in melanoma patients following successful immunotherapy with anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibodies (e.g. ipilimumab) (Fig. 66.28); IL-2; tumor-infiltrating lymphocytes specific for tyrosinase-, gp100- or TYRP1-derived antigens; or peptide vaccines based upon these antigens. In addition, cytotoxic T-lymphocyte clones derived from melanoma patients efficiently lyse cultured human melanocytes.

Clonally expanded T cells with identical Vp regions have been identified in a primary melanoma and a depigmented halo surrounding the tumor, again suggesting a role for a T-cell-mediated antitumoral

Fig. 66.26 Melanoma-associated leukoderma. In a patient with stage IV melanoma, amelanotic, vitiligo-like patches developed at multiple sites, including this excision site. *Courtesy, Jean L Bolognia, MD.*

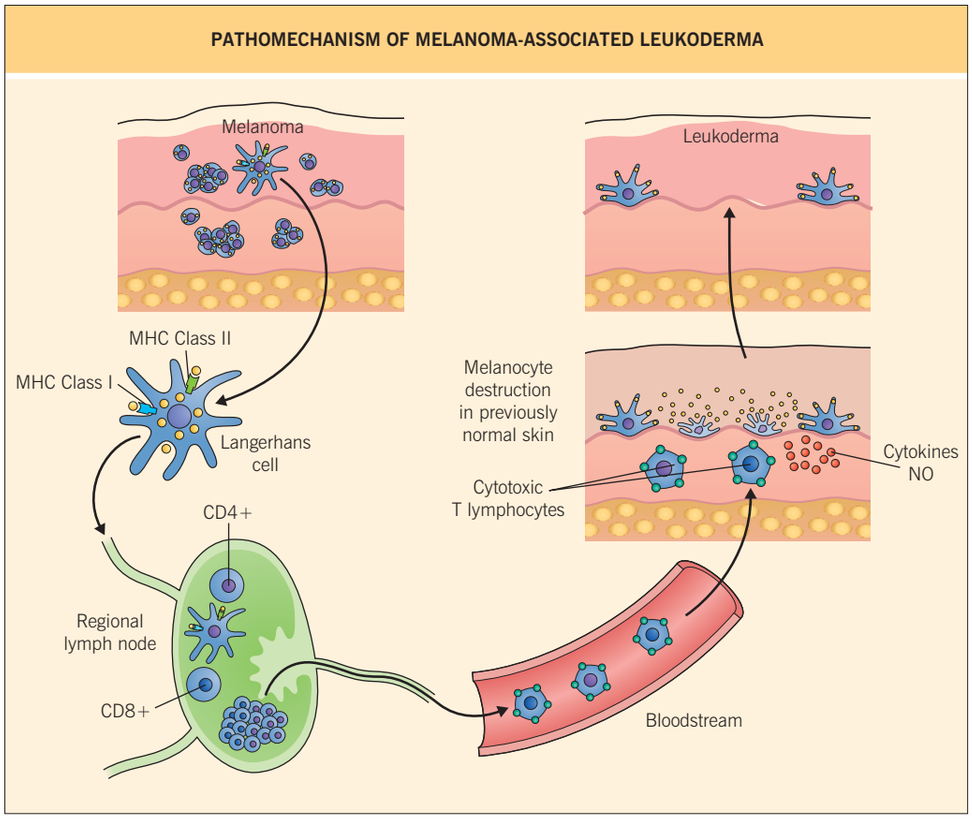


Fig. 66.27 Pathomechanism of melanoma-associated leukoderma. NO, nitric oxide. *From Schaffer JV, Bolognia JL. The biology of the melanocyte. In: Rigel DS et al (eds). Cancer of the Skin, 2nd edn. Philadelphia: Elsevier Saunders, 2011.*

Fig. 66.28 Vitiligo-like leukoderma associated with anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) therapy for metastatic melanoma. *Courtesy, Jean L Bolognia, MD.*

response in the development of melanoma-associated, vitiligo-like leukoderma. Melan-A/MART-1-specific $CD8^+$ T cells have been identified in inflammatory hypomelanotic skin lesions following the infusion of Melan-A/MART-1-specific $CD8^+$ T-cell clones in a patient with metastatic melanoma[93]. Thus, in melanoma patients, "vitiligo" may be a visible effect of a spontaneous (or therapy-induced) antitumoral immune response against melanocyte differentiation antigens (see Ch. 113). Several studies using mouse models have shown that vitiligo-like depigmentation and rejection of B16 melanomas can be accomplished via vaccine strategies targeting melanocyte differentiation antigens. This, plus the occasional observation of spontaneous resolution of metastatic melanoma following the development of vitiligo-like leukoderma, holds hope for the future of immunotherapy.

CHEMICAL AND PHARMACOLOGIC HYPOMELANOSIS

A large number of chemical and pharmacologic agents can cause hypomelanosis of skin and hair[94,95]. The three major groups of depigmenting compounds (Table 66.9) are:

- phenols/catechols
- sulfhydryls
- miscellaneous.

Hydroquinone (HQ) and its derivatives (MMEH, MBEH) are the most widely used "bleaching" agents. HQ induces a reversible hypopigmentation of the skin, and it is used to treat disorders such as melasma. In contrast, depigmentation from MBEH is often permanent and occurs not only in the areas of application but also in distant sites; as a result, its only indication is as depigmentation therapy for widespread vitiligo (see above). Of note, MMEH and MBEH were identified as depigmenting agents after outbreaks of occupational leukoderma in workers exposed to these chemicals in rubber products.

Hypomelanosis can follow the use of either topical or intralesional corticosteroids, particularly in darkly pigmented individuals. Potent topical corticosteroids are unfortunately widely used as lightening agents in many areas of the world (especially Africa and Asia). In most cases, the hypomelanosis is incomplete, but the risk of significant side effects (e.g. acne, atrophy, striae) is high. Hypomelanosis induced by intralesional or intra-articular corticosteroids can be stellate or linear, has an irregular outline, and is often ill-defined (Fig. 66.29). The

SELECTED CHEMICALS ASSOCIATED WITH LEUKODERMA
PHENOL/CATECHOL DERIVATIVES
Monobenzyl ether of hydroquinone (MBEH)
Monomethyl ether of hydroquinone (MMEH) (*p*-methoxyphenol; *p*-hydroxyanisole)
Monoethyl ether of hydroquinone (MEEH) (*p*-ethoxyphenol)
Hydroquinone (HQ) (1,4-dihydroxybenzene; 1,4-benzenediol; quinol; *p*-hydroxyphenol)
p-tert-butylcatechol (PTBC)
p-tert-butylphenol (PTBP)
p-tert-amylphenol (PTAP)
p-phenylphenol
p-octylphenol
p-nonylphenol
p-isopropylcatechol
p-methylcatechol
Butylated hydroxytoluene (BHT)*
Butylated hydroxyanisole (BHA)*
Pyrocatechol (1,2-benzenediol)
p-cresol
SULFHYDRYLS
β-mercaptoethylamine hydrochloride (MEA) (cysteamine)
N-(2-mercaptoethyl)-dimethylamine hydrochloride (MEDA)
Methimazole (1-methyl-2-mercaptoimidazole – MMI)
Sulfanilic acid
Cysteamine dihydrochloride
3-mercaptopropylamine hydrochloride
MISCELLANEOUS
Mercurials
Arsenic
Cinnamic aldehyde
p-phenylenediamine (PPD)
Benzyl alcohol
Azelaic acid
Corticosteroids
Optic preparations
• Physostigmine (eserine)
• Diisopropyl fluorophosphates
• Thiotepa (N,N′,N″-triethylenethiophosphoramide)
• Guanonitrofuracin
Systemic medications
• Chloroquine
• Fluphenazine (Prolixin®)
• Tyrosine kinase inhibitors (e.g. imatinib mesylate, pazopanib)
*Depigmentation weak or not known.

Table 66.9 Selected chemicals associated with leukoderma.

Fig. 66.29 Hypopigmentation due to injection of corticosteroids into the anatomic snuff box. The outline is both stellate and linear.

Fig. 66.30 Chemical leukoderma. Depigmentation developed at sites of contact with rubber swimming goggles. *Courtesy, Kalman Watsky, MD.*

cutaneous hypopigmentation appears several weeks to months after the injection. In most instances, repigmentation occurs within 1 year after discontinuation of the injections.

In any patient, particularly adults, presenting with new-onset "vitiligo" (Fig. 66.30), a detailed history to detect exposure to known depigmenting agents (see Table 66.9) is mandatory. Patch testing can be useful for confirming the diagnosis of chemical leukodermas, but delayed readings are essential (e.g. at 2 weeks, then again at 4–6 weeks). Spontaneous repigmentation may occur following avoidance of the causative agent, but treatment, as for vitiligo, is usually required (see above).

In chemical leukoderma induced by HQ and its derivatives, melanocytes are decreased in number or absent. Other depigmenting agents inhibit tyrosinase (thus blocking melanogenesis) or prevent melanosome transfer.

Patients treated with imatinib mesylate (Gleevec®) have been noted to develop various forms of hypomelanosis, including generalized lightening of the skin, hypopigmentation of the distal digits, difficulty in maintaining a suntan, and progression of vitiligo. These changes appear to be reversible and potentially dose-dependent, and they have been observed more commonly in darkly pigmented individuals[96]. Imatinib mesylate is a tyrosine kinase inhibitor that targets the bcr-abl fusion protein that is characteristic of chronic myelogenous leukemia; it also inhibits three other tyrosine kinases – platelet-derived growth factor (PDGF) receptor-α, PDGF receptor-β and the KIT receptor. Imatinib mesylate-induced inhibition of the KIT receptor, which is involved in melanogenesis and melanocyte homeostasis, is the most likely explanation for the hypopigmentation. Loss of hair color has been noted in patients receiving sunitinib malate, another inhibitor of tyrosine kinase receptors (including the KIT receptor). Sunitinib-induced hair depigmentation appears to be reversible with cessation of treatment[97].

HYPOMELANOSIS FROM PHYSICAL AGENTS

Various types of physical injuries can induce cutaneous hypomelanosis or amelanosis, including thermal burns, freezing, UV radiation, lasers, ionizing radiation, and physical trauma from surgical procedures. The combination of the history of an insult, the shape of the hypopigmentation, and associated findings usually makes the diagnosis relatively straightforward.

Repigmentation is based on a host of factors, including the type and depth of the insult or injury, the anatomic location, and the presence of hair follicles and pigmented hairs.

MISCELLANEOUS

Idiopathic Guttate Hypomelanosis

Idiopathic guttate hypomelanosis (IGH) is a very common disorder, the incidence of which increases with age. It is seen in up to 80% of patients over the age of 70 years. IGH occurs in all races and skin types, but it is more striking in darkly pigmented skin. In Caucasians, IGH may favor those with brown eyes and brown hair. An apparent female predominance is probably the result of heightened perception of a cosmetic problem.

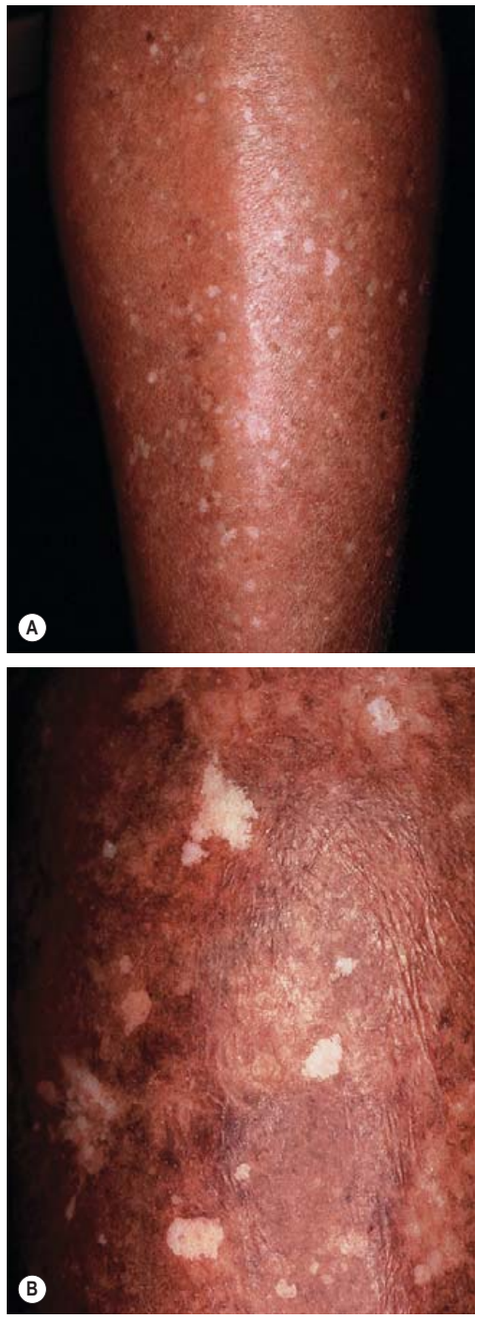


Fig. 66.31 Idiopathic guttate hypomelanosis. **A** Typical 1–5 mm macules on the shin. **B** Occasionally there is admixture of larger lesions.

The typical IGH lesion is a circumscribed, sharply defined, asymptomatic porcelain white macule[98]. The lesions are usually 0.5–6 mm in diameter and often delineated by the skin furrows; occasionally, lesions are up to 2.5 cm in size (Fig. 66.31). Once present, they do not change in size or coalesce; their surface is smooth but not atrophic. Spontaneous repigmentation has not been reported. Hairs within the lesions usually retain their pigment. In most patients, there are multiple lesions on the extensor forearms and shins; the remainder of the extremities can be affected, but rarely the face.

The most consistent histologic features of IGH are a flattening of the dermal–epidermal junction, moderate to marked reduction or focal absence of melanin granules in the basal and suprabasal layers, and a basket-weave hyperkeratosis. There is a moderate to relatively marked reduction in the number of DOPA-positive epidermal melanocytes (10–50% compared with normal skin), but these cells are never totally absent. At the ultrastructural level, some melanocytes have normal melanogenic activity, while others lack mature melanosomes. The

Fig. 66.32 Disseminated hypopigmented keratoses. Over 200 guttate minimally elevated hypopigmented papules developed after several months of PUVA therapy. Histologically, there was no evidence of verruca plana. *Courtesy, Jean L Bolognia, MD*

Fig. 66.33 Clear cell papulosis. Multiple hypopigmented, barely elevated flat-topped papules and macules in the suprapubic area and on the abdomen along the "milk lines" in a 2-year-old boy. Histologically , these lesions are characterized by large clear cells in the lower epidermis that have a pattern of immunohistochemical staining similar to clear cells of Toker and extramammary Paget's disease. *Courtesy, Julie V Schaffer, MD.*

keratinocytes show marked variation in their content of melanin, which may be absent or markedly decreased.

The diagnosis of IGH is usually made clinically; the differential diagnosis of guttate leukoderma is shown in Table 66.7 and includes achromic verrucae plana, pityriasis lichenoides chronica, disseminated hypopigmented keratoses that follow PUVA therapy (Fig. 66.32) and clear cell papulosis (Fig. 66.33). Although lesions of atrophie blanche favor the distal shins and ankles, these porcelain white scars are usually depressed and encircled by papular telangiectasias. The cause of IGH is unknown, but sun exposure probably plays a role.

Cryotherapy with liquid nitrogen has been described as a possible therapy for IGH. As sunlight is most likely a precipitating factor, use of sunscreens and physical barriers should be recommended.

Vagabond's Leukomelanoderma

This skin disorder occurs in older persons in whom dietary deficiency is combined with lack of cleanliness and heavy infestation with *Pediculus humanus* var. *corporis*. These patients have small macules of hypomelanosis (related to scratching) superimposed on a background of diffuse hypermelanosis, especially of the wrists, axillae, groin, inner thighs and posterior neck.

Fig. 66.34 Progressive macular hypomelanosis. Note the coalescence of the non-scaly hypopigmented macules on the center of the back.

DISORDERS ASSOCIATED WITH PREMATURE GRAYING OF SCALP HAIR

- Piebaldism
- Waardenburg syndrome
- Vitiligo
- Sudden whitening of hair
- Hereditary premature canities
- "Bird-headed" dwarfism
- Progeria
- Werner syndrome
- Ataxia telangiectasia
- Rothmund–Thomson syndrome
- Fisch syndrome
- Myotonic dystrophy
- Prolidase deficiency (also in Table 66.11)
- Oasthouse disease

Table 66.10 Disorders associated with premature graying of scalp hair.

Progressive Macular Hypomelanosis

Progressive macular hypomelanosis (PMH) is a fairly common skin disorder, observed more frequently in young women with darkly pigmented skin who originate from or reside in tropical climates. The disorder is characterized by poorly defined, nummular, non-scaly hypopigmented macules and small patches on the trunk, with rare extension onto the proximal extremities or head and neck region; confluence of lesions may occur centrally (Fig. 66.34)[99]. Another variant of PMH features large circular lesions. There is no associated pruritus or preceding inflammation, and patients are sometimes misdiagnosed as having residual hypopigmentation related to pityriasis versicolor. Histologically, there is decreased pigment in the epidermis and a normal-appearing dermis. Electron microscopy demonstrates a shift from large melanosomes in uninvolved skin to small aggregated membrane-bound melanosomes in hypopigmented skin. *Propionibacterium acnes* residing within hair follicles may play a role in PMH. One proposed treatment regimen consists of topical 1% clindamycin and 5% benzoyl peroxide plus UVA irradiation (three times per week for 12 weeks).

Hair Hypomelanosis

Poliosis refers to a circumscribed hypomelanosis of hair (see Table 66.4), whereas canities implies a more generalized depigmentation of hair. Graying of hair, localized or generalized, is characterized by an admixture of normally pigmented, hypomelanotic and amelanotic hairs. Whitening of hair is the endpoint of canities and graying of hair. The graying and whitening of human hair that occurs with aging is due to defective maintenance of melanocyte stem cells[100,101].

A number of genetic disorders are associated with premature graying of hair (Table 66.10), while there are both hereditary and acquired causes of diffuse hypomelanosis of hair (Table 66.11). In Chédiak-Higashi, Griscelli and Elejalde syndromes, the scalp hairs have a silvery hue due to pigment clumping.

DISORDERS ASSOCIATED WITH DIFFUSE HYPOMELANOSIS OF SCALP HAIR

- Fanconi syndrome
- Book syndrome
- Down syndrome
- Hallerman–Streiff syndrome
- Treacher–Collins syndrome
- Prolidase deficiency (also in Table 66.10)
- Hyperthyroidism
- Chronic protein loss or deficiency (e.g. due to kwashiorkor, nephrosis, ulcerative colitis, malabsorption)
- Vitamin B_{12} deficiency
- Tyrosine kinase inhibitors
- Antimalarials (chloroquine > hydroxychloroquine)

Table 66.11 Disorders associated with diffuse hypomelanosis of scalp hair. See also Figure 66.11.

Leukodermas without Hypomelanosis

Woronoff's ring

Woronoff's ring is a blanched halo of fairly uniform width surrounding psoriatic lesions after phototherapy or topical treatments. There is an element of vasoconstriction, but it is uncertain whether there is any decrease in pigmentation.

Nevus anemicus

Nevus anemicus (see Ch. 106) presents as a pale area of variable size (often 3–6 cm) with an irregular, "broken up" outline. It is usually unilateral and located on the trunk. Present since birth, the lesion is most commonly detected later in life, and it is most noticeable when there is surrounding vasodilation due to heat or emotional stress. On diascopy, the lesion becomes indistinguishable from surrounding skin. Histologically, there are no abnormalities in the melanocytes or melanin content. Nevus anemicus is caused by decreased blood flow through the capillaries in the dermal papillae, due to a localized hypersensitivity of the blood vessels to catecholamines.

Cutaneous edema and anemia

Cutaneous edema and anemia also produce lightening of the skin and mucous membranes. In the case of anemia, it is due to decreased hemoglobin levels in the skin.

Angiospastic macules (Bier spots)

Pale macules, usually 3–6 mm in diameter, are seen on the extremities (often more noticeable on the legs) (see Ch. 106). They are due to localized vasoconstriction and are seen most often in young women. Their appearance may be induced by a dependent position or placing a tourniquet on the limb.

REFERENCES

1. Nordlund JJ, Boissy RE, Hearing VJ, et al. The Pigmentary System: Physiology and Pathophysiology. Edinburgh: Blackwell Science, 2006:1–1200.
2. Alikhan A, Felsten LM, Daly M, et al. Vitiligo: a comprehensive overview Part I. Introduction, epidemiology, quality of life, diagnosis, differential diagnosis, associations, histopathology, etiology, and work-up. J Am Acad Dermatol. 2011;65:473–91.
3. LePoole C, van den Wijngaard RMJGJ, Westerhof W, et al. Presence or absence of melanocytes in vitiligo lesions: an immunohistochemical investigation. J.Invest. Dermatol. 1993;100:816–822.
4. Lan CC, Ko YC, Tu HP, et al. Association study between keratinocyte-derived growth factor gene polymorphisms and susceptibility to vitiligo vulgaris in a Taiwanese population: potential involvement of stem cell factor. Br J Dermatol. 2009;160:1180–1187.
5. Moretti S, Spallanzani A, Amato L, et al. Vitiligo and epidermal microenvironment: possible involvement of keratinocyte-derived cytokines. Arch Dermatol. 2002;138:273–274.
6. Moretti S, Spallanzani A, Amato L, et al. New insights into the pathogenesis of vitiligo: imbalance of epidermal cytokines at sites of lesions. Pigment Cell Res. 2002;15:87–92.
7. Kim NH, Jeon S, Lee HJ, Lee AY. Impaired PI3K/Akt activation-mediated NF-kappaB inactivation under elevated TNF-alpha is more vulnerable to apoptosis in vitiliginous keratinocytes. J Invest Dermatol. 2007;127:2612–2617.
8. Birol A, Kisa U, Kurtipek GS, et al. Increased tumor necrosis factor alpha (TNF-alpha) and interleukin 1 alpha (IL1-alpha) levels in the lesional skin of patients with nonsegmental vitiligo. Int J Dermatol. 2006;45:992–993.
9. Grimes PE, Morris R, Avaniss-Aghajani E, et al. Topical tacrolimus therapy for vitiligo: therapeutic responses and skin messenger RNA expression of proinflammatory cytokines. J Am Acad Dermatol. 2004;51:52–61.
10. Nordlund JJ, Ortonne JP. Vitiligo and depigmentation. In: Weston WL (ed.) Current Problems in Dermatology, Vol. 4. St-Louis: Mosby Year Book, 1992:3–30.
11. Passeron T, Ortonne JP. Physiopathology and genetics of vitiligo. J Autoimmun. 2005;25 Suppl:63–68.
12. Zhang XJ, Chen JJ, Liu JB. The genetic concept of vitiligo. J Dermatol Sci. 2005;39:137–146.
13. Fain PR, Gowan K, LaBerge GS, et al. A genomewide screen for generalized vitiligo: confirmation of AIS1 on chromosome 1p31 and evidence for additional susceptibility loci. Am J Hum Genet. 2003;72: 1560–1564.
14. Jin Y, Riccardi SL, Gowan K, et al. Fine-mapping of vitiligo susceptibility loci on chromosomes 7 and 9 and interactions with NLRP1 (NALP1). J Invest Dermatol. 2010;130:774–783.
15. Jin Y, Mailloux CM, Gowan K, et al. NALP1 in vitiligo-associated multiple autoimmune disease. N Engl J Med. 2007;356:1216–1225.
16. LaBerge GS, Bennett DC, Fain PR, Spritz RA. PTPN22 is genetically associated with risk of generalized vitiligo, but CTLA4 is not. J Invest Dermatol. 2008;128:1757–1762.
17. Birlea SA, Gowan K, Fain PR, Spritz RA. Genome-wide association study of generalized vitiligo in an isolated European founder population identifies SMOC2, in close proximity to IDDM8. J Invest Dermatol. 2010;130:798–803.
18. Jin Y, Birlea SA, Fain PR, et al. Variant of TYR and autoimmunity susceptibility loci in generalized vitiligo. N Engl J Med. 2010;362:1686–1697.
19. Westerhof W, d'Ischia M. Vitiligo puzzle: the pieces fall in place. Pigment Cell Res. 2007;20:345–359.
20. Gregg RK, Nichols L, Chen Y, et al. Mechanisms of spatial and temporal development of autoimmune vitiligo in tyrosinase-specific TCR transgenic mice. J Immunol. 2010;184:1909–1917.
21. Hann SK, Kim YS, Yoo JH, Chun YS. Clinical and histopathologic characteristics of trichrome vitiligo. J Am Acad Dermatol. 2000;42:589–596.
22. Taieb A, Picardo M. The definition and assessment of vitiligo: a consensus report of the Vitiligo European Task Force. Pigment Cell Res. 2007;20:27–35.

22a. Ezzedine K, Diallo A, Léauté-Labrèze C, et al. Halo nevi and leukotrichia are strong predictors of the passage to mixed vitiligo in a subgroup of segmental vitiligo. Br J Dermatol. 2011. [epub ahead of press]

23. Alkhateeb A, Fain PR, Thody A, et al. Epidemiology of vitiligo and associated autoimmune diseases in Caucasian probands and their families. Pigment Cell Res. 2003;16:208–214.
24. Laberge G, Mailloux CM, Gowan K, et al. Early disease onset and increased risk of other autoimmune diseases in familial generalized vitiligo. Pigment Cell Res. 2005;18:300–305.
25. Halder RM, Grimes PE, Cowan CA, et al. Childhood vitiligo. J Am Acad Dermatol. 1987;16:948–954.
26. Njoo MD, Spuls PI, Bos JD, et al. Nonsurgical repigmentation therapies in vitiligo: meta-analysis of the literature. Arch Dermatol. 1998;134:1532–1540.
27. Radakovic-Fijan S, Furnsinn-Friedl AM, Honigsmann H, Tanew A. Oral dexamethasone pulse treatment for vitiligo. J Am Acad Dermatol. 2001;44:814–817.
28. Passeron T, Ortonne JP. Use of the 308-nm excimer laser for psoriasis and vitiligo. Clin Dermatol. 2006;24:33–42.
29. Ortonne JP, Passeron T. Melanin pigmentary disorders: treatment update. Dermatol Clin. 2005;23:209–226.
30. Westerhof W, Nieuweboer-Krobotova L. Treatment of vitiligo with UV-B radiation vs topical psoralen plus UV-A. Arch Dermatol. 1997;133:1525–1528.
31. Scherschun L, Kim JJ, Lim HW. Narrow-band ultraviolet B is a useful and well-tolerated treatment for vitiligo. J Am Acad Dermatol. 2001;44:999–1003.
32. Njoo MD, Westerhof W. Vitiligo. Pathogenesis and treatment. Am J Clin Dermatol. 2001;2:167–181.
33. Valkova S, Trashlieva M, Christova P. Treatment of vitiligo with local khellin and UVA: comparison with systemic PUVA. Clin Exp Dermatol. 2004;29:180–184.
34. Baltas E, Nagy P, Bonis B, et al. Repigmentation of localized vitiligo with the xenon chloride laser. Br J Dermatol. 2001;144:1266–1267.
35. Hofer A, Hassan AS, Legat FJ, et al. The efficacy of excimer laser (308 nm) for vitiligo at different body sites. J Eur Acad Dermatol Venereol. 2006;20:558–564.
36. Hofer A, Hassan AS, Legat FJ, et al. Optimal weekly frequency of 308-nm excimer laser treatment in vitiligo patients. Br J Dermatol. 2005;152:981–985.
37. Le Duff F, Fontas E, Giacchero D, et al. 308 nm excimer lamp versus 308 nm excimer laser for treating vitiligo: a randomized study. Br J Dermatol. 2010;163:188–192.
38. Lan CC, Wu CS, Chiou MH, et al. Low-energy helium-neon laser induces locomotion of the immature melanoblasts and promotes melanogenesis of the more differentiated melanoblasts: recapitulation of vitiligo repigmentation in vitro. J Invest Dermatol. 2006;126:2119–2126.
39. Yu HS, Wu CS, Yu CL, et al. Helium-neon laser irradiation stimulates migration and proliferation in melanocytes and induces repigmentation in segmental-type vitiligo. J.Invest.Dermatol. 2003;120:56–64.
40. Gupta S, Olson, M, Kanwar AJ, Ortonne JP. Surgical management of vitiligo. In: Passeron T, Ortonne JP (eds). Medical Treatment of Vitiligo. Oxford: Blackwell, 2007:31–38.
41. Falabella R, Arrunategui A, Barona MI, Alzate A. The minigrafting test for vitiligo: detection of stable lesions for melanocyte transplantation. J Am Acad Dermatol. 1995;32:228–232.
42. Guerra L, Capurro S, Melchi F, et al. Treatment of "stable" vitiligo by Timedsurgery and transplantation of cultured epidermal autografts. Arch Dermatol. 2000;136:1380–1389.
43. Gauthier Y, Surleve-Bazeille JE. Autologous grafting with noncultured melanocytes: a simplified method for treatment of depigmented lesions. J Am Acad Dermatol. 1992;26:191–194.
44. van Geel N, Ongenae K, De Mil M, et al. Double-blind placebo-controlled study of autologous transplanted

epidermal cell suspensions for repigmenting vitiligo. Arch Dermatol. 2004;140:1203–1208.
45. Passeron T, Ostovari N, Zakaria W, et al. Topical tacrolimus and the 308-nm excimer laser: a synergistic combination for the treatment of vitiligo. Arch Dermatol. 2004;140:1065–1069.
46. Kawalek AZ, Spencer JM, Phelps RG. Combined excimer laser and topical tacrolimus for the treatment of vitiligo: a pilot study. Dermatol Surg. 2004;30:130–135.
47. Fai D, Cassano N, Vena GA. Narrow-band UVB phototherapy combined with tacrolimus ointment in vitiligo: a review of 110 patients. J Eur Acad Dermatol Venereol. 2007;21:916–920.
48. Sassi F, Cazzaniga S, Tessari G, et al. Randomized controlled trial comparing the effectiveness of 308-nm excimer laser alone or in combination with topical hydrocortisone 17-butyrate cream in the treatment of vitiligo of the face and neck. Br J Dermatol. 2008;159:1186–1191.
49. Mosher DB, Parrish JA, Fitzpatrick TB. Monobenzylether of hydroquinone. A retrospective study of treatment of 18 vitiligo patients and a review of the literature. Br J Dermatol. 1977;97:669–679.
50. Thissen M, Westerhof W. Laser treatment for further depigmentation in vitiligo. Int J Dermatol. 1997;36:386–388.
51. Njoo MD, Vodegel RM, Westerhof W. Depigmentation therapy in vitiligo universalis with topical 4-methoxyphenol and the Q-switched ruby laser. J Am Acad Dermatol. 2000;42:760–769.
52. Rao J, Fitzpatrick RE. Use of the Q-switched 755-nm alexandrite laser to treat recalcitrant pigment after depigmentation therapy for vitiligo. Dermatol Surg. 2004;30:1043–1045.
53. Schallreuter KU, Wood JM, Lemke KR, Levenig C. Treatment of vitiligo with a topical application of pseudocatalase and calcium in combination with short-term UVB exposure: a case study on 33 patients. Dermatology. 1995;190:223–229.
54. Bakis-Petsoglou S, Le Guay JL, Wittal R. A randomized, double-blinded, placebo-controlled trial of pseudocatalase cream and narrowband ultraviolet B in the treatment of vitiligo. Br J Dermatol. 2009;161:910–917.
55. Anbar TS, Westerhof W, Abdel-Rahman AT, et al. Effect of one session of ER:YAG laser ablation plus topical 5Fluorouracil on the outcome of short-term NB-UVB phototherapy in the treatment of non-segmental vitiligo: a left-right comparative study. Photodermatol Photoimmunol Photomed. 2008;24:322–329.
56. Kapoor R, Phiske MM, Jerajani HR. Evaluation of safety and efficacy of topical prostaglandin E2 in treatment of vitiligo. Br J Dermatol. 2009;160:861–863.
57. Passeron T, Mantoux F, Ortonne JP. Genetic disorders of pigmentation. Clin Dermatol. 2005;23:56–67.
58. King RA, Oetting WS. Oculocutaneous albinism. In: Nordlund JJ, Ortonne JP (eds). The Pigmentary System, 2nd edn. Oxford: Blackwell, 2006:599–613.
59. Toyofuku K, Wada I, Spritz RA, Hearing VJ. The molecular basis of oculocutaneous albinism type 1 (OCA1): sorting failure and degradation of mutant tyrosinase results in a lack of pigmentation. Biochem J. 2001;355:259–269.
60. Brilliant MH. The mouse p (pink-eyed dilution) and human P genes, oculocutaneous albinism type 2 (OCA2), and melanosomal pH. Pigment Cell Res. 2001;14:86–93.
61. Sarangarajan R, Boissy RE. Tyrp1 and oculocutaneous albinism type 3. Pigment Cell Res. 2001;14:437–444.
62. Toyofuku K, Wada I, Valencia JC, et al. Oculocutaneous albinism types 1 and 3 are ER retention diseases: mutation of tyrosinase or Tyrp1 can affect the processing of both mutant and wild-type proteins. Faseb J. 2001;15:2149–2161.
63. Newton JM, Cohen-Barak O, Hagiwara N, et al. Mutations in the human orthologue of the mouse underwhite gene (uw) underlie a new form of oculocutaneous albinism, OCA4. Am J Hum Genet. 2001;69:981–988.
64. Shen B, Orlow SJ. The ocular albinism type 1 gene product is an N-glycoprotein but glycosylation is not required for its subcellular distribution. Pigment Cell Res. 2001;14:485–490.
65. Inagaki K, Suzuki T, Shimizu H, et al. Oculocutaneous albinism type 4 is one of the most common types of albinism in Japan. Am J Hum Genet. 2004;74:466–471.
66. Spritz RA. The molecular basis of human piebaldism. Pigment Cell Res. 1992;5:340–343.
67. Jimbow K, Fitzpatrick TB, Szabo G, Hori Y. Congenital circumscribed hypomelanosis: a characterization based on electron microscopic study of tuberous sclerosis, nevus depigmentosus, and piebaldism. J Invest Dermatol. 1975;64:50–62.
68. Spritz RA. Piebaldism, Waardenburg syndrome, and related disorders of melanocyte development. Semin. Cutan.Med.Surg. 1997;16:15–23.
69. Hoth CF, Milunsky A, Lipsky N. Mutations in the paired domain of the human PAX3 gene cause Klein-Waardenburg syndrome (WS-III) as well as Waardenburg syndrome type I (WS-I). Am J Hum Genet. 1993;52:455–462.
70. Smith SD, Kelley PM, Kenyon JB, Hoover D. Tietz syndrome (hypopigmentation/deafness) caused by mutation of MITF. J Med Genet. 2000;37:446–448.
71. Sanchez-Martin M, Rodriguez-Garcia A, Perez-Losada J, et al. SLUG (SNAI2) deletions in patients with Waardenburg disease. Hum Mol Genet. 2002;11:3231–3236.
72. Pingault V, Bondurand N, Kuhlbrodt K, et al. SOX10 mutations in patients with Waardenburg-Hirschsprung disease. Nat Genet. 1998;18:171–173.
73. Edery P, Attie T, Amiel J, et al. Mutation of the endothelin-3 gene in the Waardenburg-Hirschsprung disease (Shah-Waardenburg syndrome). Nat Genet. 1996;12:442–444.
74. Ortonne JP, Mosher DB, Fitzpatrick TB. Vitiligo and other hypomelanosis of hair and skin. In: Parrish JA, Fitzpatrick TB (eds). Monograph in topics in dermatology. New York: Plenum Press, 1983:1–683.
75. Huizing M, Anikster Y, Gahl WA. Hermansky-Pudlak syndrome and related disorders of organelle formation. Traffic. 2000;1:823–835.
76. Stinchcombe J, Bossi G, Griffiths GM. Linking albinism and immunity: the secrets of secretory lysosomes. Science. 2004;305:55–59.
77. Morgan NV, Pasha S, Johnson CA, et al. A germline mutation in BLOC1S3/reduced pigmentation causes a novel variant of Hermansky-Pudlak syndrome (HPS8). Am J Hum Genet. 2006;78:160–166.
78. O'Brien K, Troendle J, Gochuico BR, et al. Pirfenidone for the treatment of Hermansky-Pudlak syndrome pulmonary fibrosis. Mol Genet Metab. 2011;103:128–134.
79. Tezcan I, Demir E, Asan E, et al. A new case of oculocerebral hypopigmentation syndrome (Cross syndrome) with additional findings. Clin Genet. 1997;51:118–121.
80. Faigle W, Raposo G, Tenza D, et al. Deficient peptide loading and MHC class II endosomal sorting in a human genetic immunodeficiency disease: the Chediak-Higashi syndrome. J Cell Biol. 1998;141:1121–1134.
81. Pastural E, Barrat FJ, Dufourcq-Lagelouse R, et al. Griscelli disease maps to chromosome 15q21 and is associated with mutations in the myosin-Va gene. Nat Genet. 1997;16:289–292.
82. Menasche G, Pastural E, Feldmann J, et al. Mutations in RAB27A cause Griscelli syndrome associated with haemophagocytic syndrome. Nat Genet. 2000;25:173–176.
83. Menasche G, Ho CH, Sanal O, et al. Griscelli syndrome restricted to hypopigmentation results from a melanophilin defect (GS3) or a MYO5A F-exon deletion (GS1). J Clin Invest. 2003;112:450–456.
83a. Amyere M, Vogt T, Hoo J, et al. *KITLG* mutations cause familial progressive hyper- and hypopigmentation. J Invest Dermatol. 2011;131:1234–39.
84. Loomis CA. Linear hypopigmentation and hyperpigmentation, including mosaicism. Semin Cutan Med Surg. 1997;16:44–53.
85. Hogeling M, Frieden IJ. Segmental pigmentation disorder. Br J Dermatol. 2010;162:1337–1341.
86. Happle R. [Phylloid hypomelanosis and mosaic trisomy 13: a new etiologically defined neurocutaneous syndrome]. Hautarzt. 2001;52:3–5.
87. Ruiz-Maldonado R, Toussaint S, Tamayo L, et al. Hypomelanosis of Ito: diagnostic criteria and report of 41 cases. Pediatr Dermatol. 1992;9:1–10.
88. Shiloh Y, Litvak G, Ziv Y, et al. Genetic mapping of X-linked albinism-deafness syndrome (ADFN) to Xq26.3-q27.I. Am J Hum Genet. 1990;47:20–27.
89. Ruiz-Maldonado R, Orozco-Covarrubias ML. Postinflammatory hypopigmentation and hyperpigmentation. Semin Cutan Med Surg. 1997;16:36–43.
90. Mitchell IC, Sweatman MC, Rustin MH, Wilson R. Ulcerative and hypopigmented sarcoidosis. J Am Acad Dermatol. 1986;15:1062–1065.
91. Ortonne JP, Perrot H. Scleroderma: ultrastructural study of the melanin pigmentary disturbances of the skin. Clin Exp Dermatol. 1980;5:13–25.
92. Musette P, Bachelez H, Flageul B, et al. Immune-mediated destruction of melanocytes in halo nevi is associated with the local expansion of a limited number of T cell clones. J Immunol. 1999;162:1789–1794.
93. Yee C, Thompson JA, Roche P, et al. Melanocyte destruction after antigen-specific immunotherapy of melanoma: direct evidence of T cell-mediated vitiligo. J Exp Med. 2000;192:1637–1643.
94. Briganti S, Camera E, Picardo M. Chemical and instrumental approaches to treat hyperpigmentation. Pigment Cell Res. 2003;16:101–110.
95. Solano F, Briganti S, Picardo M, Ghanem G. Hypopigmenting agents: an updated review on biological, chemical and clinical aspects. Pigment Cell Res. 2006;19:550–571.
96. Tsao AS, Kantarjian H, Cortes J, et al. Imatinib mesylate causes hypopigmentation in the skin. Cancer. 2003;98:2483–2487.
97. Moss KG, Toner GC, Cherrington JM, et al. Hair depigmentation is a biological readout for pharmacological inhibition of KIT in mice and humans. J Pharmacol Exp Ther. 2003;307:476–480.
98. Ortonne JP, Perrot H. Idiopathic guttate hypomelanosis. Ultrastructural study. Arch Dermatol. 1980;116: 664–668.
99. Relyveld GN, Menke HE, Westerhof W. Progressive macular hypomelanosis: an overview. Am J Clin Dermatol. 2007;8:13–19.
100. Nishimura E, Granter SR, Fisher DE. Mechanisms of hair graying: incomplete melanocyte stem cell maintenance in the niche. Science. 2005;307:720–724.
101. Steingrimsson E, Copeland NG, Jenkins NA. Melanocyte stem cell maintenance and hair graying. Cell. 2005;121:9–12.

Disorders of Hyperpigmentation 67

Mary Wu Chang

Chapter Contents

Diffuse and circumscribed hyperpigmentation 1049
- Postinflammatory hyperpigmentation 1049
- Erythema dyschromicum perstans 1050
- Lichen planus pigmentosus 1052
- Melasma 1052
- Drug-induced hyperpigmentation or discoloration 1055

Linear hyperpigmentation 1058
- Pigmentary demarcation lines 1058
- Linear postinflammatory hyperpigmentation 1059
- Flagellate pigmentation from bleomycin 1061
- Flagellate mushroom dermatitis 1062
- Hyperpigmentation along the lines of Blaschko 1062

Reticulated hyperpigmentation 1064
- Prurigo pigmentosa 1064
- Dyskeratosis congenita 1066
- Naegeli–Franceschetti–Jadassohn syndrome 1068
- Dermatopathia pigmentosa reticularis 1069
- X-linked reticulate pigmentary disorder 1069
- Dowling–Degos disease 1070
- Reticulate acropigmentation of Kitamura 1071

Dyschromatoses 1071
- Dyschromatosis symmetrica hereditaria 1073
- Dyschromatosis universalis hereditaria 1073
- Acquired brachial cutaneous dyschromatosis 1074

The color of the skin depends upon the amount and distribution of melanin and other chromophores such as hemoglobin, with factors including their effects on light absorption, reflection and scattering. Disorders of hyperpigmentation usually result from an increase in melanin production and, on occasion, from an increase in the density of active melanocytes. Discoloration of the skin may also be caused by deposition of exogenous substances such as drugs, drug complexes (e.g. with melanin or iron) or heavy metals within the dermis.

To aid in the clinical approach, disorders of hyperpigmentation can be divided into diffuse, circumscribed, linear and reticulated subsets. A review of each of these categories is followed by a discussion of dyschromatoses, disorders characterized by both hypo- and hyperpigmentation. Benign melanocytic neoplasms are covered in Chapter 112.

DIFFUSE AND CIRCUMSCRIBED HYPERPIGMENTATION

Introduction

Diffuse and circumscribed hyperpigmentation are discussed together because both postinflammatory hyperpigmentation (PIH) and reactions to systemic drugs, two major causes of hyperpigmentation, can assume either of these patterns. PIH most often presents as circumscribed lesions, and the size, shape and distribution pattern provide clues to the etiology. Melasma is another common cause of circumscribed hypermelanosis. Additional causes of diffuse hyperpigmentation include metabolic diseases, sclerodermoid disorders, nutritional deficiencies and, occasionally, HIV infection.

POSTINFLAMMATORY HYPERPIGMENTATION

Synonym: ■ Postinflammatory hypermelanosis

Key features

- Extremely common, especially in individuals with more darkly pigmented skin
- Develops after inflammation or injury to the skin, but preceding inflammation may be transient or subclinical
- The increased melanin may be primarily within the dermis (e.g. following lichen planus) or in the epidermis (e.g. following acne or atopic dermatitis)
- Epidermal hyperpigmentation fades more readily than dermal hyperpigmentation

Introduction

PIH represents an acquired excess of melanin pigment following cutaneous inflammation or injury. It can occur anywhere on the skin surface, including the mucous membranes and the nail unit. PIH is extremely common and can have significant cosmetic and psychosocial consequences.

Epidemiology

PIH can occur at any age and there is no gender preference. Individuals with darkly pigmented skin tend to have a greater frequency, severity and duration of PIH than those with lighter complexions.

Pathogenesis

In the *epidermal* form of PIH, there is increased melanin production and/or transfer to keratinocytes. Inflammatory mediators (e.g. prostaglandins E_2 and D_2) that enhance pigment production may play a role in this process. In *dermal* hyperpigmentation, melanin enters ("falls into") the dermis via a damaged basement membrane, where it is phagocytosed by and subsequently resides within dermal macrophages (referred to as melanophages). Macrophages may also migrate into the epidermis, phagocytose melanosomes, and then return to the dermis[1]. Melanin within dermal melanophages tends to persist for long periods of time (e.g. years).

Clinical Features

Asymptomatic hyperpigmented macules and patches range in color from either tan to dark brown (epidermal melanin) or gray–blue to gray–brown (dermal melanin). Primary lesions of the underlying inflammatory disorder may or may not be evident admixed with the hyperpigmentation or elsewhere. When primary lesions are absent, the size, shape and distribution pattern of the hyperpigmented lesions can provide clues to the underlying etiology (Table 67.1). PIH can be exacerbated by continued inflammation, trauma or exposure to ultraviolet (UV) irradiation.

DISORDERS ASSOCIATED WITH POSTINFLAMMATORY HYPERPIGMENTATION	
Inflammatory disease	**Clinical clues**
	COMMON
Acne vulgaris	Head/neck region, upper trunk; <1 cm; perifollicular
Atopic dermatitis	Atopic diathesis; face and extensor extremities in infants, then later flexural involvement; excoriations; atopic pleats; xerosis; lichenification; transverse nasal crease ("allergic salute")
Lichen simplex chronicus	Common locations: posterior neck, ankle, scrotum
Transient neonatal pustular melanosis	Black newborns; pustules precede pigmentation
Impetigo	Favors face; most common in children
Insect bites	Favor exposed areas; usually <1 cm; lower extremities common with flea bites; clustered and sometimes linear patterns ("breakfast–lunch–dinner")
	LESS COMMON
Irritant and allergic contact and photocontact dermatitis	Sites determined by etiologic agent and form of exposure; phytophotodermatitis associated with linear hyperpigmentation in sun-exposed areas
Pityriasis rosea	Favors trunk and proximal extremities; lesions follow skin cleavage lines; oval-shaped
Psoriasis	Scalp/nail involvement; knees/elbows most common sites
Polymorphous light eruption	Extensor upper extremities, mid upper chest, face; seasonal (e.g. spring or early summer)
Discoid lupus erythematosus	Face and conchal bowls, with follicular plugging in latter site; oral lesions; in scarred lesions, central hypopigmentation with rim of hyperpigmentation
Lichen planus	Wrists, shins, presacral; nail/oral involvement
Erythema dyschromicum perstans (ashy dermatosis)	Neck, proximal upper extremities, trunk; round or oval in shape with gray–brown to blue–gray color; long axis can follow skin cleavage lines (similar to pityriasis rosea); less commonly observed in fair-skinned individuals
Fixed drug eruption	Circular; favors perioral, acral and genital sites; recurrence at same site(s) with repeated exposure
Morbilliform drug eruption	Widespread; usually discrete lesions, history of drug exposure
Viral exanthem	Widespread; usually discrete lesions; history of associated symptoms
Morphea	Trunk or extremities; large-sized except in guttate variant; may be linear; associated induration and later dermal atrophy
Atrophoderma of Pasini and Pierini	Trunk; large-sized; depressed with "cliff sign" at periphery no induration
Neurotic (psychogenic) excoriation, acne excoriée	Favors face, scalp, extensor surface of arms, upper back (reachable areas); linear or angular shapes; multiple stages of evolution, from erosions/ulcerations to scars

Table 67.1 Disorders associated with postinflammatory hyperpigmentation. *Adapted from Bolognia JL. Disorders of hypopigmentation and hyperpigmentation. In: Harper J, Oranje A, Prose N (eds). Textbook of Pediatric Dermatology, 2nd edn Oxford: Blackwell Science, 2006;997–1040.*

Disorders that commonly lead to epidermal PIH include acne, insect bites, pyodermas, atopic dermatitis, psoriasis and pityriasis rosea (Fig. 67.1). In contrast, dermal PIH is associated with dermatoses characterized by degeneration of the basal layer of the epidermis and inflammation at the dermal–epidermal junction, such as lichen planus, lichenoid drug reactions, lupus erythematosus and fixed drug eruptions. Upon treatment of the underlying disorder, epidermal PIH generally resolves over time, although fading may require months or years in darkly pigmented individuals. Dermal melanosis tends to persist longer and is sometimes permanent.

Pathology

As noted above, epidermal PIH is characterized by increased pigment in keratinocytes and dermal PIH by melanophages within the dermis.

Differential Diagnosis

As discussed previously, the size, shape and distribution of the hyperpigmented lesions can provide clues to the inflammatory disease or injury that preceded PIH (see Table 67.1), and a thorough skin examination may detect active primary lesions. A history of prior inflammatory lesions and medication use (including prescription, over-the-counter and alternative products) should be obtained. Disorders such as erythema dyschromicum perstans, melasma, pityriasis versicolor and atrophoderma of Pasini and Pierini should be considered in patients without evidence of preceding inflammation by history or on examination. Occasionally, a biopsy may assist in making the diagnosis.

Treatment

Provided that the underlying dermatosis is successfully treated, PIH eventually improves in most patients, especially those with epidermal hypermelanosis. Sun protection, including daily application of a broad-spectrum sunscreen, can help to prevent accentuation of the pigmentation by UV exposure. Topical hydroquinone (2–4%) may lead to lightening over 3–6 months if the increase in pigmentation is limited to the epidermis. As with melasma (see below), use of a topical retinoid and corticosteroid together with hydroquinone may be more effective than monotherapy. Topical azelaic acid and α-hydroxy acids are additional therapeutic options. Laser therapy has limited benefits, especially for individuals with darkly pigmented skin, and it may lead to hypopigmentation. Q-switched ruby, alexandrite and Nd:YAG lasers are variably successful in removing dermal pigment (see Ch. 137).

ERYTHEMA DYSCHROMICUM PERSTANS

Synonyms: ■ Ashy dermatosis ■ Dermatosis cenicienta (Cinderella dermatosis)

Key features

- Most common in individuals with skin phototypes III–IV
- Gray–brown to blue–gray macules and patches in a symmetric distribution
- Favors the neck, trunk and proximal extremities
- A consistently effective treatment is not currently available

Introduction

Ramirez first described erythema dyschromicum perstans (EDP) in 1957, referring to affected individuals as *los cenicientos* (ashen ones).

Fig. 67.1 Epidermal postinflammatory hyperpigmentation. The lesions were due to pemphigus foliaceus (**A**), contact dermatitis from a contraceptive patch (**B**), insect bites (**C**) and transient neonatal pustular melanosis (**D**). Note the residual inflammation and "breakfast–lunch–dinner" configuration in C. *A, C & D, Courtesy, Julie V Schaffer, MD. B, Courtesy, Andrew Alexis, MD MPH.*

This is an asymptomatic, slowly progressive eruption that is characterized by circumscribed areas of dermal pigmentation[2].

Epidemiology

Although there have been reports of this entity worldwide, the majority of patients with EDP are from Latin America. There is no gender preference. The disorder usually presents during the second to third decade, but it occasionally develops in younger children or older adults.

Pathogenesis

The etiology of EDP is not known. Although it has been postulated that a cell-mediated immune reaction to an ingestant, contactant or microorganism underlies the discrete areas of pigmentary incontinence, no causal agent has consistently identified[2]. In most patients, a trigger is never found. However, there have been reports of EDP developing in association with the ingestion of ammonium nitrate, oral X-ray contrast media, and medications (e.g. benzodiazepines, penicillin); exposure to various pesticides, fungicides or toxins; endocrinopathies such as thyroid disease; and whipworm and HIV infections. The presence of the HLA-DR4 allele may represent a risk factor for EDP in Mexican patients.

Clinical Features

Oval, circular or irregularly shaped macules and patches that are 0.5 to 3 cm in diameter and slate-gray to blue–brown in color develop gradually in a symmetric pattern (Fig. 67.2). The initial site of involvement is often the trunk, with subsequent spread to the neck, proximal upper extremities, and sometimes the face. The mucous membranes are spared, and the palms, soles and scalp are rarely affected. Occasionally, early stage lesions have a thin, raised, erythematous border, which tends to resolve over a few months, and the long axis of lesions may follow skin cleavage lines. Peripheral hypopigmentation may be seen in older lesions.

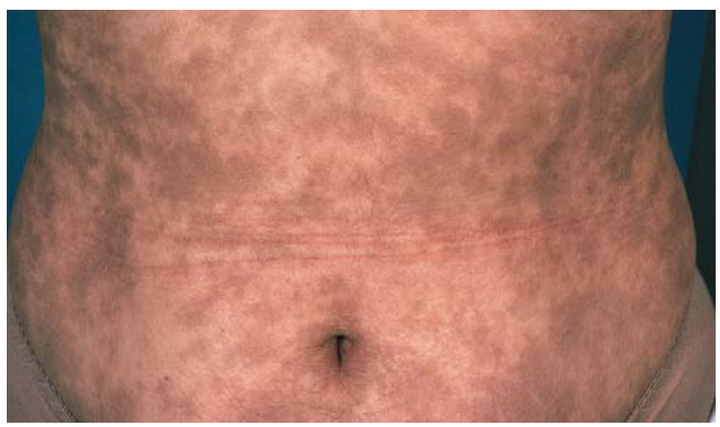


Fig. 67.2 Erythema dyschromicum perstans (ashy dermatosis). Multiple gray–brown macules and patches on the abdomen. The "ashy" color is characteristic.

EDP is usually asymptomatic but can be mildly pruritic. The disease progresses slowly and usually does not regress in adults. However, in one study of 33 prepubertal children, the majority of whom were

Caucasian, the disease spontaneously resolved in two-thirds of the patients, with no recurrences over the ensuing 2–3 years[3].

Pathology

In early ("active") lesions, vacuolar degeneration of the basal cell layer, a perivascular mononuclear cell infiltrate in the upper dermis, and increased epidermal melanin and dermal melanophages are seen. Colloid bodies and dermal hemosiderin may be present. Immunohistochemical findings include expression of cell adhesion and lymphocyte activation molecules (e.g. CD36, intercellular adhesion molecule-1 [ICAM-1], CD69, CD94) that are associated with inflammation and activation of cytotoxic T cells[4]. In later ("inactive") lesions, the number of dermal melanophages is increased but hydropic changes within the basal cell layer are absent and the dermal mononuclear cell infiltrate is minimal.

Differential Diagnosis

The differential diagnosis of EDP includes a lichenoid drug eruption (see Ch. 11), lichen planus (especially lichen planus pigmentosus), a generalized fixed drug eruption, other dermal forms of PIH, macular urticaria pigmentosa, and (less often) infectious diseases such as leprosy or pinta. Of note, the PIH that follows pityriasis rosea is usually epidermal.

Treatment

There is no consistently effective therapy for EDP. Topical corticosteroids and hydroquinone are generally of no benefit. Oral corticosteroids, antibiotics, antimalarials, isoniazid and griseofulvin, as well as UV light therapy, have produced variable results. Successful treatment with dapsone and clofazimine has been reported in small series.

LICHEN PLANUS PIGMENTOSUS

Key features

- Variant of lichen planus most commonly described in adults with skin phototypes III-V
- Gray–brown to dark brown macules and patches in either a photodistribution or an inverse (intertriginous) pattern

Lichen planus pigmentosus (LPP) is an uncommon variant of lichen planus that favors young to middle-aged adults with skin phototypes III–V, including those from India[5,6], Latin America and the Middle East. It presents as irregularly shaped or oval, brown to gray–brown macules and patches in either sun-exposed areas (especially the forehead, temples and neck) or intertriginous zones (Fig. 67.3). It is usually asymptomatic, but some patients describe mild pruritus or burning. In contrast to EDP, early lesions with an erythematous border are not a feature of LPP. While the distribution is symmetric in the vast majority of patients, a unilateral linear variant has also been described.

Fig. 67.3 Lichen planus pigmentosus. Multiple coalescing brown to gray–brown macules in the axilla of a middle-aged woman.

Occasionally, a reticulated or follicular pattern is observed. The palms, soles, nails and oral mucosa are usually not involved. In one series of 124 patients with LPP, 19 were noted to also have typical lesions of lichen planus[6]. LPP is a chronic disorder with exacerbations and remissions. Histologic findings include basal cell degeneration, a mild perivascular or band-like infiltrate in the upper dermis, and dermal melanophages.

The etiology of LPP is unknown. The photodistribution in some patients suggests that UV can play a pathogenic role, and topical application of mustard oil (which contains allyl isothiocyanate, a potential photosensitizer) and amla oil have been proposed as possible inciting agents[6]. The differential diagnosis includes the actinic and inverse variants of lichen planus (see Ch. 11), a lichenoid drug eruption, EDP, melasma, the entities listed in Table 67.2, PIH and cutaneous T-cell lymphoma. In one uncontrolled study, lightening of the pigmentation occurred in 54% (7/13) of patients treated with topical tacrolimus for 12–16 weeks[7].

MELASMA

Synonyms: ■ Chloasma ■ Mask of pregnancy

Key features

- At least 90% of patients are women
- Increased prevalence in individuals who are Hispanic, or of Asian or African descent
- Most common location is the face, followed by the forearms
- Symmetric patches of hyperpigmentation with irregular borders due to increased melanin within the epidermis and/or dermis

Introduction and Epidemiology

Melasma is a common acquired disorder characterized by symmetric, hyperpigmented patches with an irregular outline, occurring most commonly on the face. It is most prevalent among young to middle-aged women who are Hispanic or of Asian, African or Middle Eastern descent (i.e. those with more darkly pigmented skin). Exacerbating factors include pregnancy, use of oral contraceptives and sun exposure.

Pathogenesis

Although the exact pathogenesis of melasma is unknown, it is hypothesized that following exposure to UV irradiation (or another inducer), hyperfunctional melanocytes within involved skin produce increased amounts of melanin[8,9]. The key role of UV irradiation is supported by fading of lesions during winter months and a distribution pattern demonstrating involvement of sun-exposed regions and sparing of relatively sun-protected sites such as the philtrum. Additional important pathogenic factors include the skin phototype (favoring individuals with more darkly pigmented skin) and estrogens (predilection for women and association with pregnancy and oral contraceptive use). Other medications (e.g. phenytoin, phototoxic drugs) and disorders (e.g. autoimmune thyroid disease) also have the potential to aggravate melasma. Increased expression of KIT and stem cell factor within the lesional epidermis and dermis, respectively, may play a role in the hyperpigmentation of melasma.

Clinical Features

Light to dark brown or brown–gray patches with irregular borders appear primarily on the face (Fig. 67.4). The areas of hypermelanosis are distributed symmetrically in three classic patterns: (1) *centrofacial* (most common), involving the forehead, cheeks, nose, upper lip (sparing the philtrum) and chin; (2) *malar*, affecting the cheeks and nose; and (3) *mandibular*, along the jawline. Less common sites include the extensor aspect of the forearms and mid upper chest. Lesions often first appear or are accentuated following exposure to UV irradiation or during pregnancy. In lightly pigmented individuals, this "mask of pregnancy" frequently diminishes or disappears after parturition, but it tends to persist in women with more darkly pigmented skin.

DIFFERENTIAL DIAGNOSIS OF MELASMA	
Disorder	**Key differences from melasma/comments**
Drug-induced hyperpigmentation or discoloration	• History of medication use (e.g. doxycycline, amiodarone; see Table 67.3) • Hyperpigmentation less patterned and less irregular in outline • Discrete oval or round shape of fixed drug eruption rarely confused with melasma • May follow phototoxic drug reaction • Oral contraceptives and phenytoin may exacerbate melasma
Postinflammatory hyperpigmentation, e.g. due to cutaneous lupus erythematosus, photosensitivity reactions, contact dermatitis (e.g. irritant contact dermatitis to hydroquinone or tretinoin) or other forms of dermatitis	• History of inflammatory phase with erythema, scale and possible pruritus or burning • Primary lesions – may be admixed or elsewhere on body
Actinic lichen planus	• Fine scale overlying violaceous lesions if inflammatory phase still present • Histologic features: hydropic degeneration of basal layer, lichenoid infiltrate
Lichen planus pigmentosus	• Often begins on the temples/in the preauricular area and involves the neck ± intertriginous sites • Coexistent classic lichen planus (~20% of patients) • Histologic features: vacuolar degeneration of basal layer; variable lichenoid infiltrate and epidermal atrophy
Pigmented contact dermatitis (Riehl's melanosis)	• Favors sites of application of contactants, especially cosmetics • May be reticulated • Brown–grey color due to dermal melanin deposits • Histologic features: vacuolar degeneration of basal layer and lichenoid infiltrate in early lesions
Exogenous ochronosis	• History of hydroquinone application to areas of hyperpigmentation followed by progressive darkening • Superimposed small pigmented papules may also be seen • Histologic features: banana-shaped, yellow–brown deposits in the dermis
Acquired bilateral nevus of Ota-like macules (Hori's nevus)	• Asian women, usually during the fourth or fifth decade of life • Multiple brown–gray to brown–blue macules, primarily in the malar region • Less common sites: lateral forehead, temples, upper eyelids, nasal root or alae • Lack of ocular or mucosal involvement • Histologic features: pigment-producing dermal melanocytes
Erythema dyschromicum perstans	• Inflammatory phase with rim of erythema occasionally seen • Lesions slate-gray to blue–brown • Distribution includes sun-protected areas
Poikiloderma of Civatte	• Presence of atrophy and telangiectasias • Favors lateral and inferior aspects of anterior neck; sparing of perifollicular skin and submental region
Erythromelanosis follicularis faciei et colli	• Red–brown patches on lateral cheeks and neck • Superimposed tiny pale follicular papules
Cutaneous mercury deposits	• History of use of mercury-containing soaps or creams • Dermatitis often present • Histologic features: brown–black granules free in dermis, in association with elastic fibers and within macrophages

Table 67.2 Differential diagnosis of melasma.

Melasma has also been subdivided into four types based upon the primary location of the pigment: epidermal, dermal, mixed or indeterminate (e.g. in patients with very dark skin pigmentation). In theory, lesions with increased epidermal melanin are accentuated and those with increased dermal melanin become less obvious (i.e. blend with uninvolved skin) with Wood's lamp examination. However, clinicopathologic studies utilizing adjacent uninvolved skin as controls have shown that Wood's lamp examination does not correlate with histologic findings[9,10]. In addition, no completely dermal form of melasma was observed histologically when bilateral nevus of Ota-like macules (a form of dermal melanocytosis sometimes misdiagnosed as melasma; see Table 67.2) were excluded. Further studies are needed to determine the clinical utility and prognostic significance (considering that epidermal pigmentation is more likely to respond to topical therapies) of Wood's lamp examination.

Pathology

Compared to uninvolved adjacent skin, increased melanin deposition is observed in all layers of the epidermis. An increased number of melanophages may also be seen. Epidermal melanocytes are normal to increased in number, and they are enlarged with prominent dendrites[9,10].

Ultrastructurally, lesional melanocytes contain an increased number of melanosomes. In addition, the mitochondria, Golgi apparatus and rough endoplasmic reticulum are increased in number or amount. These findings support the theory of hyperfunctional melanocytes, presumably stimulated by UV irradiation or hormones (see Pathogenesis above).

Differential Diagnosis

The differential diagnosis of melasma is reviewed in Table 67.2. These disorders are distinguished from melasma based upon historical aspects (e.g. drug ingestion, previous inflammation), color, distribution pattern, histologic features and (if present) primary inflammatory lesions.

Treatment

Diligent sun protection – including hats, clothing (if extrafacial), broad-spectrum sunscreens and avoidance – and patient motivation are necessary for any treatment regimen for melasma to be successful. Wood's lamp examination helps to delineate the extent of involvement and may distinguish between increased melanin primarily within the epidermis versus within both the epidermis and dermis (see above). Whereas epidermal pigmentation is somewhat amenable to topical therapies and chemical peels, dermal pigmentation is notoriously difficult to treat. In darkly pigmented individuals (e.g. those with indeterminate melasma), a skin biopsy is occasionally performed before treatment is initiated.

Fig. 67.4 Various forms of melasma and melasma-like hyperpigmentation. A Malar variant. **B** Mild centrofacial type with sparing of the philtrum. **C** Extension of the hyperpigmentation onto the mandible. **D** Involvement of the extensor forearm; note the same irregular outline as is seen on the face. **E** Melasma-like appearance in a patient with previous acute cutaneous lupus erythematosus. *C–E, Courtesy, Jean L Bolognia, MD.*

The most common topical regimen is a combination of hydroquinone (2–4%), tretinoin (0.05–0.1%) and a corticosteroid (class V–VII)[11]. For epidermal melasma, 2 months of therapy are typically required to initiate lightening and 6 months of treatment are often needed to achieve satisfactory results.

The mechanisms of action of hydroquinone include: (1) competing with tyrosine as a substrate for tyrosinase, the initial enzyme in the melanin biosynthetic pathway that converts tyrosine to dopaquinone (see Ch. 65); and (2) selective damage to melanosomes and melanocytes[12]. Side effects include irritant and allergic contact dermatitis, postinflammatory hyperpigmentation, and exogenous ochronosis (see below). The latter side effect is uncommon and is usually caused by prolonged use of hydroquinone at a concentration >2%.

Topical tretinoin as a monotherapy can be helpful, but the required treatment period is often 24 weeks or longer. Other topical agents that have been reported to lighten melasma include glycolic acid, kojic acid and azelaic acid, with the latter two agents acting as tyrosinase inhibitors. Salicylic acid and glycolic acid peels can be used as adjunctive therapy (see Ch. 154). Deeper chemical peels, laser therapy (e.g. Q-switched ruby, 1550 nm fractional) and dermabrasion have variable results and can cause scarring and dyspigmentation. Cosmetic camouflage is helpful for patients with recalcitrant melasma.

ADDITIONAL FORMS OF CIRCUMSCRIBED HYPERPIGMENTATION

Segmental Pigmentation Disorder

This term was coined by Metzker et al. in 1983 and re-introduced by Hogeling and Frieden in 2010[13]. It is a form of "pigmentary mosaicism" (i.e. a postzygotic genetic alteration leading to a regional change in pigment production potential) characterized by a block-like or "checkerboard" pattern of hyper- or (less often) hypopigmentation that usually becomes apparent in infancy. The hyperpigmented patches favor the trunk, with midline demarcation more often evident ventrally than dorsally and less distinct lateral borders. There are usually no associated extracutaneous anomalies.

Familial Progressive Hyperpigmentation

Familial progressive hyperpigmentation is an autosomal dominant disorder characterized by hyperpigmented patches in a widespread distribution including the palms, soles, lips and conjunctiva. The lesions begin to develop in infancy and increase in size, number and confluence with age. This condition can be caused by heterozygous gain-of-function mutations in the KIT ligand gene (*KITLG*)[14].

Primary (Localized) Cutaneous Amyloidosis

Macular and lichenoid forms of primary (localized) cutaneous amyloidosis (see Ch. 47) are associated with hyperpigmentation. The most common locations are the upper back (macular amyloidosis) or the extensor surface of the lower extremities (lichen amyloidosis), and there is a characteristic rippled pattern with parallel bands or ridges of hyperpigmentation. Areas of involvement are often pruritic, and rubbing plays a key role in the production of lesions. Histologically, melanophages as well as amyloid deposits that stain positively with antikeratin antibodies are seen within the upper dermis.

Mastocytosis

Cutaneous mastocytosis consists of a spectrum of disorders characterized by the accumulation of normal mast cells within the skin, and sometimes in other organs (see Ch. 118). The form of mastocytosis classically associated with hyperpigmentation is urticaria pigmentosa, where patients develop a few to several hundred brown to red–brown papules. However, solitary mastocytomas can also have a light brown color. Lesions of cutaneous mastocytosis typically urticate after they are stroked (Darier's sign), and an increased number of mast cells is seen in biopsy specimens. The cause of the pigmentation in this disorder may involve stem cell factor or mast cell-derived pro-opiomelanocortin

(POMC) peptides, e.g. α-melanocyte-stimulating hormone[15]. Somatic activating mutations in the gene that encodes the KIT receptor often underlie urticaria pigmentosa in both children and adults. Whereas the prognosis for childhood-onset urticaria pigmentosa is excellent, with spontaneous resolution over months to years, adult-onset disease is frequently persistent (see Ch. 118).

Pityriasis (Tinea) Versicolor

Pityriasis versicolor is a superficial skin infection caused by the yeast *Malassezia furfur* (see Ch. 77). Hypo- or hyperpigmented macules or very thin papules and plaques covered with fine scale are usually found on the upper trunk and proximal upper extremities but may also appear in other sites such as the neck, face and groin. There is often coalescence of lesions centrally, especially on the trunk. In light and electron microscopy studies, a similar number of melanocytes was noted in uninvolved skin as in hypo- and hyperpigmented lesions; the latter had a thickened stratum corneum that contained more organisms. The clinical differential diagnosis for the hyperpigmented form of pityriasis versicolor may include PIH and confluent and reticulated papillomatosis, but a KOH preparation of the scale distinguishes pityriasis versicolor from these entities.

Atrophoderma of Pasini and Pierini

Atrophoderma of Pasini and Pierini (see Ch. 99) is usually seen in young adults and has been postulated to represent an atrophic form of morphea. Most often, several oval hyperpigmented patches measuring 4–10 cm in diameter appear on the posterior trunk. There is a subtle depression of the entire lesion, but no induration or secondary changes. The depression can be appreciated by palpation of the edge of the lesion, with a characteristic "cliff sign" at the peripheral margin.

PIGMENTED LESIONS

Lentigines

Lentigines are reviewed in Chapter 112.

Café-au-Lait Macules

Café-au-lait macules (CALMs) are hyperpigmented macules or patches two to three shades darker than uninvolved skin (see Ch. 112). They are found in at least 10% of the population. Although often evident at birth (~3% of all neonates, up to 30% of black neonates), CALMs may not become apparent until infancy or early childhood in lightly pigmented individuals. The presence of multiple CALMs raises the possibility of neurofibromatosis type 1 or another genetic syndrome (see Table 61.4); Figure 61.10 outlines an approach to a young child with multiple CALMs. A CALM is usually easily distinguished from a fully developed congenital melanocytic nevus, but in infants there may be overlap in the clinical appearance of these two entities. The differential diagnosis also includes the earliest stage of a nevus spilus (before the "speckles" appear), a Becker's nevus or smooth muscle hamartoma, and a mastocytoma; segmental CALMs and "pigmentary mosaicism" have significant overlap. Although laser treatment of CALMs has been reported (see Ch. 137), responses vary and recurrence of pigmentation is common.

DRUG-INDUCED HYPERPIGMENTATION OR DISCOLORATION

Key features

- Localized or generalized hypermelanosis or discoloration may be seen
- Although several classes of drugs are known to induce hyperpigmentation or discoloration, the most common are minocycline, antimalarials, chemotherapeutic agents and zidovudine
- Longitudinal, transverse or diffuse melanonychia may also be present

A wide range of medications (most commonly chemotherapeutic agents, antimalarials, minocycline and zidovudine) and chemicals can lead to cutaneous hypermelanosis or discoloration (Table 67.3, Figs 67.5–67.8). The underlying mechanisms vary from induction of melanin production to deposition of drug complexes or heavy metals within the dermis. The pigmentation can be circumscribed or generalized. Although it usually resolves with discontinuation of the offending drug, the course may be prolonged[16]. Melanonychia (longitudinal, transverse or diffuse) and oral mucosal pigmentation may also be observed.

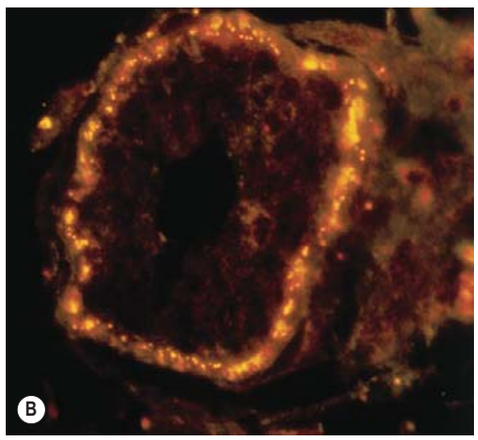


Fig. 67.5 Argyria. **A** Diffuse slate-gray discoloration of the palms. **B** Darkfield microscopy of an eccrine gland. Note the refractile nature of the granules and their location in the membrana propria. *A, Courtesy, Mary Beth Cole, MD, and Michael L Smith, MD.*

Fig. 67.6 Blue–violet discoloration of previous leprosy lesions in a patient treated with clofazimine. *Courtesy, Anne Burdick, MD.*

DRUGS AND CHEMICALS ASSOCIATED WITH HYPERPIGMENTATION OR DISCOLORATION		
Drug or chemical	**Clinical features**	**Histopathology/comment**
	CHEMOTHERAPEUTIC AGENTS	
BCNU (carmustine)	• Hyperpigmentation at sites of topical application (not with parenteral administration)	• Hyperplasia of basal melanocytes • Increased melanin within the epidermis
Bleomycin (intravenous or intralesional)	• Linear, flagellate bands that favor the trunk and may be associated with minor trauma (see text) • Transverse melanonychia • Hyperpigmentation overlying joints/pressure points or localized to striae and palmar creases • Sclerodermoid changes	• Increased epidermal melanin but no increase in the number of melanocytes • Usually relatively few dermal melanophages
Busulfan	• Generalized hyperpigmentation resembling Addison's disease; sometimes associated with drug-induced pulmonary fibrosis	• Increased melanin within basal keratinocytes and dermal macrophages
Cyclophosphamide	• Diffuse hyperpigmentation of the skin and mucous membranes • Pigment localized to the nails (transverse, longitudinal or diffuse melanonychia), palms and soles, or teeth	• Cutaneous hyperpigmentation usually regresses within 6 to 12 months after therapy is discontinued
Dactinomycin	• Generalized hyperpigmentation, most prominent on the face	• Pigmentation fades after treatment is discontinued
Daunorubicin	• Hyperpigmentation of sun-exposed areas • Transverse brown–black melanonychia	
Doxorubicin	• Hyperpigmentation overlying the small joints of the hands and involving the palms (especially the creases), soles and oral mucosa (buccal, tongue) • Transverse melanonychia	• Increased epidermal melanin • Increased number of melanocytes
5-Fluorouracil	• Hyperpigmentation in sun-exposed areas (~5% of patients treated systemically; often follows an erythematous photosensitivity reaction) • Increased pigmentation of skin overlying veins in which the drug was infused • Other sites include the dorsal aspects of the hands, palms/soles and radiation ports • Transverse or diffuse melanonychia; lunular pigmentation	• Postinflammatory hyperpigmentation
Hydroxyurea	• Reversible hyperpigmentation over pressure points and on the back • Longitudinal, transverse or diffuse melanonychia; lunular pigmentation	• Lichenoid eruption with postinflammatory hyperpigmentation can also occur
Mechlorethamine (nitrogen mustard)	• Topical use for cutaneous T-cell lymphoma may result in generalized hyperpigmentation • More intense in lesional skin	• Disaggregation of melanosomes within keratinocytes • Increased number of melanocytes
Methotrexate	• Uniform hyperpigmentation in sun-exposed areas (occasionally follows an erythematous photosensitivity reaction)	• Uncommon
	ANTIMALARIALS	
Chloroquine, hydroxychloroquine, quinacrine	• Gray to blue–black pigment, usually pretibial, with (hydroxy)chloroquine; face, hard palate, sclerae and subungual areas may be involved • Diffuse yellow to yellow–brown discoloration with quinacrine • Discoloration affects up to 25% of patients	• Dermal deposition of melanin-drug complexes; hemosiderin around capillaries • May fade after discontinuation of drug, but rarely resolves completely
	HEAVY METALS	
Arsenic	• Areas of bronze hyperpigmentation ± superimposed "raindrops" of lightly pigmented skin; favors axillae, groin, palms, soles, nipples and pressure points • Dyspigmentation appears 1–20 years after arsenic exposure, with a strong dose-response relationship • Palmoplantar keratoses and squamous cell carcinoma typically develop after dyspigmentation (see Chs 58 & 88)	• Dermal and epidermal deposition of arsenic • Increased epidermal melanin synthesis
Bismuth	• Generalized blue–gray discoloration of the face, neck and dorsal hands • Oral mucosa and gingivae may be involved	• Bismuth granules in the papillary and reticular dermis
Gold (chrysiasis)	• Permanent blue–gray discoloration in sun-exposed areas, mostly around the eyes	• Gold particles within lysosomes in dermal macrophages, especially in perivascular and perieccrine areas
Iron	• Permanent brown pigment at injection sites or in areas of application of ferric subsulfate (Monsel's) solution as a hemostatic agent • Dermal hemosiderin deposits (due to lysis of extravasated red blood cells and release of their iron stores) are commonly observed in the setting of venous hypertension, in pigmented purpuric dermatoses and as a side effect of sclerotherapy of superficial veins	• Pigment coats collagen fibers and is deposited in dermal macrophages
Lead	• "Lead line" in gingival margin • Nail discoloration	• Lead line is due to subepithelial deposition of lead granules
Mercury	• Slate-gray discoloration, particularly in skin folds	• Brown–black granules free in dermis, in association with elastic fibers and within macrophages
Silver (argyria)	• Diffuse slate-gray discoloration (Fig. 67.5A), increased in sun-exposed areas; occurs in settings of occupational exposure, alternative medications or systemic absorption from use of silver sulfadiazine on extensive burns/wounds • The nail unit (diffuse or localized to the lunulae) and sclerae may also be affected • Sites of topical application (e.g. of silver sulfadiazine to burns or ulcers)	• Silver granules in the basement membrane and the membrana propria of eccrine glands; highlighted by darkfield illumination (Fig. 67.5B)

Table 67.3 Drugs and chemicals associated with hyperpigmentation or discoloration. BCNU, 1,3-bis (2-chloroethyl)-1-nitrosourea. *Adapted from Kang S, Lerner EA, Sober AJ, Levine N. In: Levine N (ed.). Pigmentation and Pigmentary Disorders. Boca Raton: CRC Press. 1993;417–31.*

Continued

DRUGS AND CHEMICALS ASSOCIATED WITH HYPERPIGMENTATION OR DISCOLORATION		
Drug or chemical	**Clinical features**	**Histopathology/comment**
	HORMONES	
Oral contraceptives	• Melasma; increased pigmentation of nipples and nevi	• Increased melanocytes and increased melanin synthesis
ACTH/MSH (ACTH is rarely used; [Nle4-D-Phe7]-α-MSH currently not FDA-approved)	• Diffuse brown or bronze hyperpigmentation, accentuated in sun-exposed sites	• Increased melanin synthesis
	MISCELLANEOUS COMPOUNDS	
Amiodarone	• Slate-gray to violaceous discoloration of sun-exposed skin, especially the face (less common than erythema from photosensitivity) • Fair-skinned patients after long-term, continuous therapy	• Yellow–brown granules in dermal macrophages, mostly in a perivascular distribution • By EM, lysosomal inclusions composed of a lipid-like substance • Usually fades completely over months to years after discontinuation of drug, but sometimes persists
Azidothymidine (zidovudine, AZT)	• Longitudinal > transverse and diffuse melanonychia (up to 10% of patients); blue lunulae • Mucocutaneous hyperpigmentation (e.g. widespread diffuse, acral, oral macules); most common in patients with darkly pigmented skin, and may be accentuated in areas of friction or sun exposure	• Skin biopsy shows increased melanin in the epidermis and dermal melanophages • Fades gradually after drug is discontinued
Clofazimine	• Diffuse red to red–brown discoloration of skin, conjunctivae • Violet–brown to blue–gray (Fig. 67.6) discoloration, especially of lesional skin	• Red color secondary to drug in fat (highly lipophilic) • Blue–violet color secondary to brownish granular pigment within dermal macrophages • By EM, phagolysosomes contain amorphous granular material and lamellar structures characteristic of lipofuscin • Fades gradually after discontinuation of drug
Diltiazem	• Slate-gray to gray–brown discoloration of sun-exposed skin in patients with skin phototypes IV–VI; perifollicular accentuation and a reticular pattern may be observed	• Sparse lichenoid infiltrate and numerous dermal melanophages
Dioxins	• Hyperpigmentation may occur in sun-exposed areas • Chloracne is a more common skin finding	• Rare, except in accidental exposure
Hydroquinone	• Hyperpigmentation in areas of application due to irritant contact dermatitis (i.e. postinflammatory) or exogenous ochronosis; the latter may also result in small "caviar-like" papules	• In exogenous ochronosis, yellow–brown banana-shaped fibers in papillary dermis (Fig. 67.7)* • Presumed mechanism is metabolism by melanocytes of hydroquinone into ringed structures that serve as precursors of ochronotic fibers • May fade upon discontinuation of hydroquinone; variable improvement with pigment-directed Q-switched lasers
Imatinib	• Localized or diffuse hyperpigmentation (<5% of patients) • Diffuse melanonychia, repigmentation of gray hair, and pigmentation of the gingiva and teeth	• Localized or diffuse hypo- or depigmentation is more common (40–60% of darkly pigmented patients)
Minocycline	• *Type I*: blue–black discoloration in sites of inflammation and scars, including those due to acne (Fig. 67.8C) • *Type II*: blue–gray macules/patches (1 mm–10 cm in size) within previously normal skin, most often on the shins (Fig. 67.8A,B); sometimes misdiagnosed as ecchymoses • *Type III*: diffuse "muddy brown" pigmentation that is most prominent in sun-exposed areas • Blue-black discoloration may also involve nails, sclerae, oral mucosa, bones, thyroid and teeth	• Iron-containing (types I, II) or melanin-containing (type II) pigment granules within the dermis; the former can be intra- or extracellular and may represent hemosiderin and/or a minocycline derivative plus chelated iron • Increased melanin within the basal epidermis and/or dermal melanophages (type III) • Minocycline is a highly lipid-soluble, yellow, crystalline material that turns black with oxidation • Fades after discontinuation of medication, but may take months or even years; for types I and II, treatment with Q-switched pigment-directed lasers (similar to tattoo removal) may decrease the discoloration
Psoralens	• Diffuse hyperpigmentation after exposure to UVA light following oral administration (PUVA) • Circumscribed or linear streaks of hyperpigmentation can be seen with topical exposure (e.g. topical PUVA or phytophotodermatitis [exposure to psoralen-containing plants plus sunlight])	• Proliferation of follicular melanocytes, with increased synthesis and transfer of melanin • Singly dispersed melanosomes within keratinocytes • Psoralens are furocoumarin compounds originally derived from plants
Psychotropic drugs (chlorpromazine, thioridazine, imipramine, desipramine, amitriptyline)	• Slate-gray discoloration in sun-exposed areas	• Golden-brown granules in the upper dermis • Electron-dense inclusion bodies

*Similar histologic findings are seen in alkaptonuria (also referred to as ochronosis), an autosomal recessive disease caused by deficiency in homogentisic acid oxidase, which results in accumulation of homogentisic acid in the tissues; this insoluble pigment binds to collagen and leads to blue–black discoloration (e.g. of the helices and sclerae; see Ch. 63).

Table 67.3 Drugs and chemicals associated with hyperpigmentation or discoloration (cont'd). ACTH, adrenocorticotropic hormone; EM, electron microscopy; FDA, Food and Drug Administration; MSH, melanocyte-stimulating hormone. *Adapted from Kang S, Lerner EA, Sober AJ, Levine N. In: Levine N (ed.). Pigmentation and Pigmentary Disorders. Boca Raton: CRC Press. 1993;417–31.*

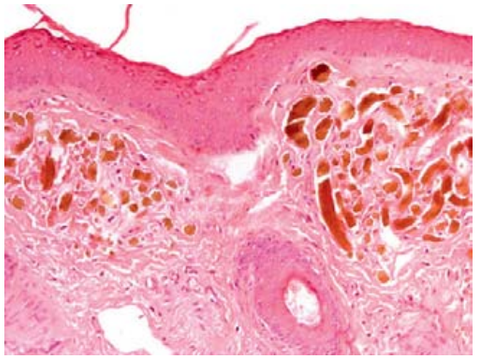


Fig. 67.7 Histopathologic features of exogenous ochronosis secondary to topical hydroquinone. Yellow–brown banana-shaped fibers are seen in the papillary dermis. *Courtesy, Lorenzo Cerroni, MD.*

Fig. 67.8 Minocycline-induced pigmentation. **A** The distribution on the shins and the gray–blue color can be similar to that seen with antimalarials. **B** Sometimes the discoloration is misdiagnosed as ecchymoses, but the subsequent color changes of green and yellow do not occur. **C** Blue–black pigmentation within acne scars and inflammatory papules. *C, Courtesy, Richard Antaya, MD.*

ADDITIONAL FORMS OF DIFFUSE HYPERPIGMENTATION

In addition to medications, diffuse hyperpigmentation can be caused by metabolic abnormalities, nutritional deficiencies, and several inherited and acquired syndromes. An approach to the patient with diffuse hyperpigmentation is provided in Figure 67.9.

LINEAR HYPERPIGMENTATION

Linear hyperpigmentation can have a variety of etiologies, including postinflammatory changes, drug reactions and mosaic genetic alterations that result in hypermelanosis along the lines of Blaschko (see Ch. 62). Pigmentary demarcation lines represent normal dorsal–ventral patterning of the skin. In the evaluation of a patient with linear hyperpigmentation, an initial step is to determine whether or not the hypermelanosis follows the lines of Blaschko.

PIGMENTARY DEMARCATION LINES

Synonyms: ■ Futcher's lines ■ Voight's lines ■ Ito's lines

Key features

- Lines of demarcation between dorsal surfaces (which are relatively hyperpigmented) and ventral surfaces
- Physiologic pattern of human pigmentation
- More often apparent in individuals with darkly pigmented skin
- Most commonly seen on the anterolateral upper arm and posteromedial thigh

Introduction

In all skin types, the dorsal skin surfaces are relatively hyperpigmented compared to the ventral surfaces. In individuals with darkly pigmented skin, visible lines of demarcation between dorsal and ventral surfaces are more conspicuous, especially on the anterolateral portion of the upper arm (Fig. 67.10A). These demarcation lines are bilateral, symmetric and present from infancy through adulthood. Additional lines occur on the posteromedial aspect of the thighs (Fig. 67.10B), upper chest (Fig. 67.10C) and paraspinal region of the back (Table 67.4; Fig. 67.11).

FIVE MAJOR FORMS OF PIGMENTARY DEMARCATION LINES

Type	Description
A	A vertical line along the anterolateral portion of the upper arm that may extend into the pectoral region (most commonly observed type)
B	A curved line on the posteromedial thigh that extends from the perineum to the popliteal fossa and occasionally to the ankle
C	A vertical or curved hypopigmented band on the mid chest that results from two parallel pigmentary demarcation lines
D	A vertical line in a pre- or paraspinal location
E	Bilateral chest markings (hypopigmented macules and patches) in a zone that runs from the mid third of the clavicle to the periareolar skin

Table 67.4 Five major forms of pigmentary demarcation lines.

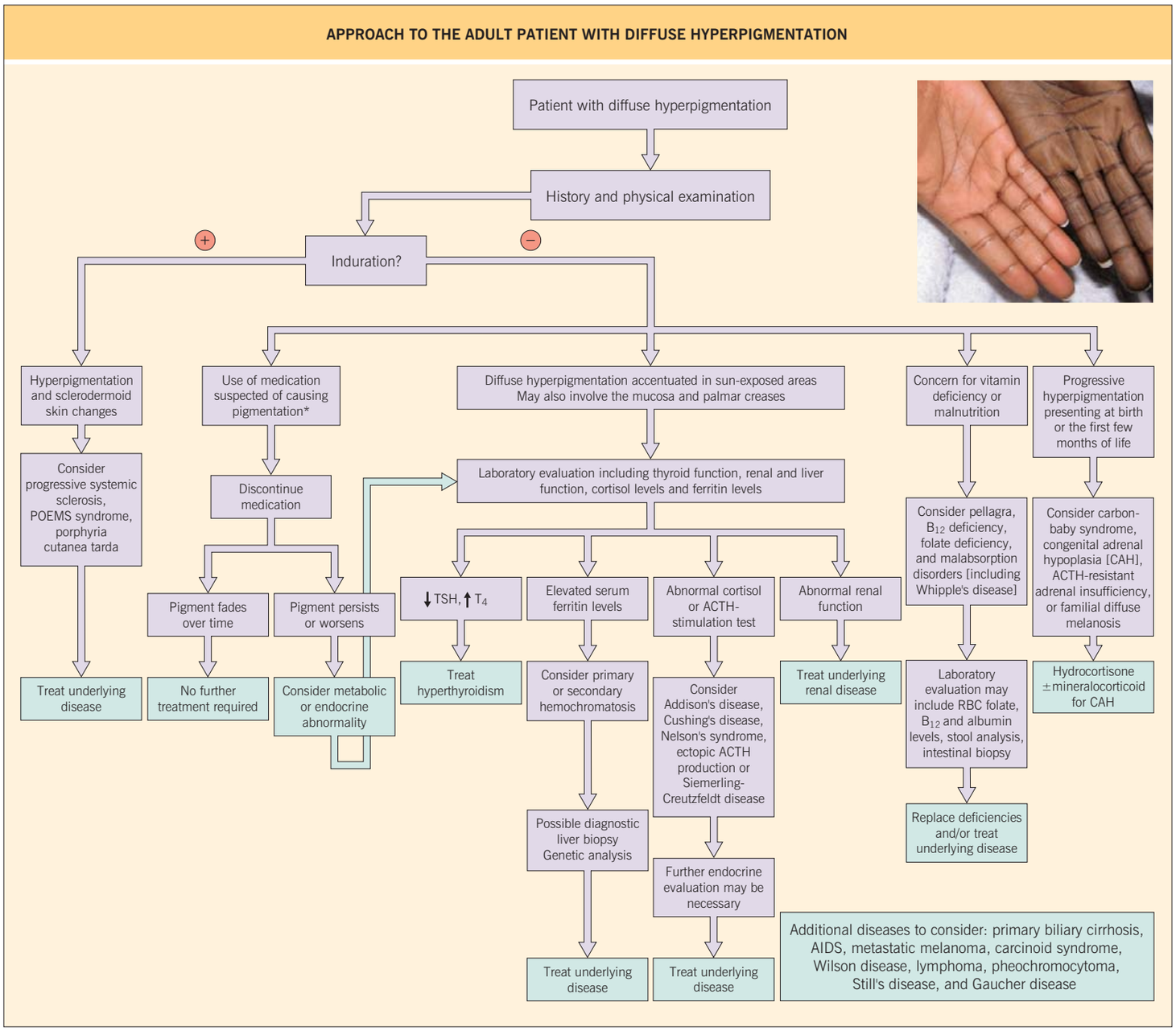


Fig. 67.9 Approach to the adult patient with diffuse hyperpigmentation. The palm on the right in the inset photograph shows diffuse hyperpigmentation in a patient with POEMS syndrome (*p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *m*onoclonal gammopathy and *s*kin lesions). ACTH, adrenocorticotropic hormone; T_4, thyroxine; TSH, thyroid-stimulating hormone. *See Table 67.3 for a list of drugs and chemicals associated with diffuse hyperpigmentation.

Differential Diagnosis

PIH may occasionally be confused with pigmentary demarcation lines types A, B and D. However, in the latter there is no preceding inflammation or injury and the lines are perfectly symmetric and stable over time. Types C and E pigmentary demarcation lines may be confused with linear nevoid hypopigmentation. Linea nigra, the linear hyperpigmentation that extends from the umbilicus to the pubis in pregnant women (see Fig. 27.10B), is easily distinguished from a pigmentary demarcation line.

Treatment

These are normal pigmentation patterns, and no treatment is indicated.

LINEAR POSTINFLAMMATORY HYPERPIGMENTATION

PIH is the most common cause of acquired hyperpigmentation, with the circumscribed variant (see above) seen more often than diffuse or linear forms. In general, PIH is more clinically apparent in individuals with darkly pigmented skin than in those with lightly pigmented skin.

Clinical Features

Linear PIH occurs when there has been a preceding contact dermatitis with a linear pattern (e.g. phytophotodermatitis [Fig. 67.12] or due to poison ivy; see Ch. 17), another linear inflammatory dermatosis (e.g. koebnerized psoriasis), linear trauma (e.g. burns, abrasions, dermatitis

Fig. 67.10 Pigmentary demarcation lines (PDLs). A The most common PDL (type A) is on the upper arm, with relative hypopigmentation on the ventral surface. **B** Type B PDLs on the posterior thighs, with relative hypopigmentation medially. **C** Type C PDL (composed of parallel lines) may be confused with linear nevoid hypopigmentation. *A, C, Courtesy, Jean L Bolognia, MD. B, Courtesy, Justin Finch, MD.*

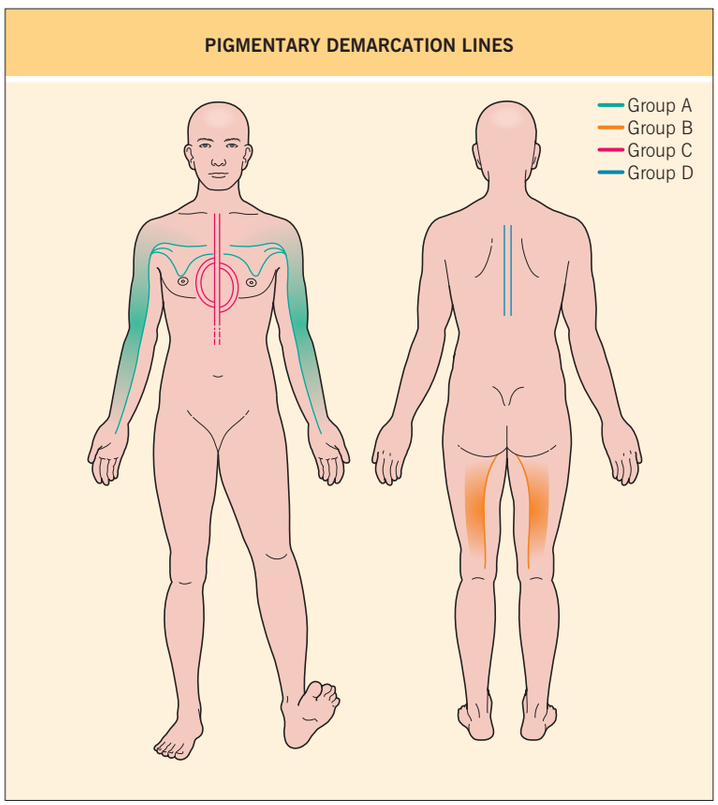


Fig. 67.11 Pigmentary demarcation lines.

Fig. 67.12 Linear epidermal hyperpigmentation due to phytophotodermatitis. *Courtesy, Julie V Schaffer, MD.*

artefacta; Fig. 67.13) or chemical phlebitis. Less often, PIH follows the lines of Blaschko because the antecedent inflammatory dermatosis did so, e.g. linear lichen planus. The color ranges from brown (epidermal) to brown–gray (dermal). PIH slowly fades over time, provided that further injury to the skin does not occur. However, resolution may not occur for months to years, especially in more darkly pigmented individuals and when the melanin is primarily dermal. The pathogenesis, histology and treatment of linear PIH are similar to those of the circumscribed form (see above).

Differential Diagnosis

Linear PIH is relatively easy to recognize when there is a history of preceding cutaneous injury or inflammation, but it is more difficult if the preceding event was transient or unnoticed. The differential diagnosis includes rare conditions such as flagellate pigmentation due to bleomycin or mushroom dermatitis (see below) as well as the common phenomenon of black dermographism. The latter occurs when metals, including those in jewelry (nickel, gold, silver), are abraded by harder substances such as powders that contain zinc oxide. The color varies from dark grey to black, and the deposits of metallic powder can be easily removed. Black lacquer deposits associated with poison ivy dermatitis can also result in linear pigmentation, but the color is jet black (see Ch. 17).

Fig. 67.13 Linear postinflammatory hyperpigmentation on the forehead. The lesions were due to neurotic excoriations.

Fig. 67.14 Flagellate pigmentation. This young man had received bleomycin as a treatment for his lymphoma. Note the linear excoriations. *Courtesy, David E Cohen, MD MPH.*

FLAGELLATE PIGMENTATION FROM BLEOMYCIN

Synonym: ■ Scratch dermatitis

Key features

- Occurs in 10–20% of patients treated with systemic bleomycin
- Linear hyperpigmented streaks are most often seen on the chest and back
- Reversible once the drug is discontinued
- Additional findings may include circumscribed hyperpigmentation of the skin overlying joints, transverse melanonychia and sclerodermoid changes

Introduction

Bleomycin is a cytotoxic antibiotic used to treat malignancies such as Hodgkin disease and testicular carcinoma. It is also occasionally used intralesionally for sclerotherapy of vascular malformations or treatment of warts. Flagellate or "streaked" hyperpigmentation due to bleomycin was first recognized in 1970[17].

Epidemiology

Flagellate hyperpigmentation is a fairly common side effect, occurring in 10–20% of patients treated with systemic bleomycin and occasionally in those who receive intralesional bleomycin.

Pathogenesis

The pigmentation appears to be dose-dependent, but the pathogenesis is poorly understood. The pigmentation may represent a form of PIH, and preceding flagellate erythema is observed in a subset of patients. The configuration of the lesions is suggestive of a relationship to scratching. However, attempts to reproduce the lesions by scratching the skin of patients receiving bleomycin have often been unsuccessful, and some patients deny pruritus or previous scratching[18]. Other hypotheses include a bleomycin-induced local increase in melanogenesis or alteration of "pigment maturation"[17].

Clinical Features

Bleomycin-associated pigmentation can be circumscribed, diffuse or flagellate. Circumscribed lesions are typically found over joints or in other pressure points, but hyperpigmentation can also be localized to the palmar creases, striae, or sites of adhesive electrode pads. Flagellate pigmentation usually occurs after cumulative doses of 100–300 mg; however, it has been reported after doses as low as 15 to 30 mg (including intralesional injections of warts or vascular malformations)[17,18]. Flagellate pigmentation appears from 1 day to 9 weeks after administration of the drug. Some patients have pruritus (ranging from mild to severe) or linear urticarial lesions preceding the pigmented streaks, but others have neither associated symptoms nor antecedent lesions. The linear bands or streaks are brown in color and are most commonly seen on the chest and back (Fig. 67.14).

Additional cutaneous side effects of bleomycin include painful nodules on the fingers, verrucous plaques on the knees and elbows, sclerodermoid changes, and digital gangrene due to Raynaud's phenomenon. Nail changes can include melanonychia (typically transverse) as well as Beau's lines, onychomadesis and onycholysis.

Pathology

Varying histologic findings have been reported in bleomycin-induced flagellate hyperpigmentation, from basal layer hypermelanosis to spongiosis confined to the basal layer in association with a perivascular lymphohistiocytic infiltrate and pigmentary incontinence. By electron microscopy, an increased number and size of melanosomes within the basal keratinocytes may be seen; the melanocytes sometimes contain enlarged mitochondria[19].

Differential Diagnosis

Linear forms of PIH should be considered in the differential diagnosis (see above). However, a history of systemic bleomycin administration coupled with the characteristic clinical picture usually points to the correct diagnosis. Shiitake mushroom dermatitis (see below) can also present as flagellate lesions, but a history of ingestion of or occupational exposure to raw shiitake mushrooms allows a distinction to be made, as does the presence of a prominent papular component. Flagellate erythema can occur in patients with dermatomyositis, and fixed reddish-brown plaques and hyperpigmented streaks in bizarre linear arrays have been observed in patients with adult-onset Still's disease; histologically, these eruptions are characterized by an interface dermatitis (in dermatomyositis) and necrotic keratinocytes in the upper epidermis plus a dermal neutrophilic infiltrate (in Still's disease).

Treatment

While there is no specific therapy, recognition that bleomycin is the culprit is important as these patients are usually receiving multiple medications. Pruritus can be treated with topical corticosteroids and oral antihistamines. The pigmentation usually fades over 3 to 4 months, once the course of chemotherapy is complete and the bleomycin is discontinued.

FLAGELLATE MUSHROOM DERMATITIS

Synonyms: ■ Shiitake mushroom dermatitis ■ Shiitake-induced toxicoderma ■ Mushroom worker's disease

Key features

- Occurs after eating large amounts of raw or partially cooked shiitake mushrooms
- A second form occurs in persons who cultivate shiitake mushrooms
- Flagellate streaks initially composed of papules or petechiae are seen on the face, scalp, trunk and proximal extremities

Introduction

Shiitake mushroom dermatitis occurs in individuals who have ingested significant amounts of raw shiitake mushrooms or in those who cultivate these mushrooms. It can result in linear streaks of papules or petechiae that may be confused with the flagellate pigmentation of bleomycin[20].

History

Toxicoderma caused by shiitake mushrooms was first described in the Japanese literature in 1977. Since then, over 100 cases of "shiitake dermatitis" have been reported from Japan and Europe.

Epidemiology

Shiitake dermatitis from the ingestion of raw or partially cooked mushrooms occurs most often in Japan. Mushroom worker's disease is seen most frequently in Japan, Finland and elsewhere in Europe, and less commonly in the US.

Pathogenesis

A thermolabile toxin in shiitake mushrooms is probably responsible for this dermatosis. Prick and patch tests using shiitake mushroom extract are negative in patients who have ingestion-related dermatitis and even oral rechallenge can be negative. A phototoxic mechanism has also been proposed[20]. In mushroom worker's disease, an allergic alveolitis has been described, but specific IgE antibodies are lacking. Skin testing is positive in some patients with the occupational form of the disease.

Clinical Features

In shiitake mushroom dermatitis, pruritic papules, vesicles and edema develop on the face, scalp, trunk and proximal extremities. Scratching leads to long, flagellate streaks composed of petechiae or papules on the trunk and extremities. This can be followed by a linear pattern of either discoloration due to hemosiderin or PIH. Erythematous photoinduced skin lesions have been observed in half of the Japanese cases of shiitake mushroom dermatitis, and fever and malaise are occasional associated findings[20].

In mushroom worker's disease, fever, chills and cough are associated symptoms.

Pathology

Spongiosis and necrotic keratinocytes are seen within the epidermis in addition to a lymphocytic dermal infiltrate[20].

Treatment

The acute dermatitis can be treated with topical corticosteroids and oral antihistamines. Resolution occurs within 1 to 8 weeks if the mushrooms are avoided. Thoroughly cooking shiitake mushrooms will prevent the disorder in those individuals who are unable to tolerate eating raw mushrooms. However, patients with respiratory or skin symptoms due to occupational exposure should completely avoid shiitake mushrooms[21].

HYPERPIGMENTATION ALONG THE LINES OF BLASCHKO

The lines of Blaschko are characterized by a V-shape on the posterior midline, an S-shape on the abdomen, and spirals on the posterior scalp[22,23] (see Ch. 62). Dermatoses that follow the lines of Blaschko result from mosaicism.

Linear and Whorled Nevoid Hypermelanosis

Synonyms: ■ Linear nevoid hyperpigmentation ■ Reticulate hyperpigmentation of Iijima, Naito and Uyeno ■ Zebra-like hyperpigmentation in whorls and streaks ■ Reticulate and zosteriform hyperpigmentation ■ Progressive cribriform and zosteriform hyperpigmentation

Key features

- Hyperpigmentation in whorls and streaks following the lines of Blaschko
- Usually becomes apparent within the first year of life
- Associated systemic findings occur in a minority of affected individuals
- Increased melanin within the epidermis and few melanophages

Introduction

Linear and whorled nevoid hypermelanosis (LWNH), first described in the 1970s, is characterized by swirls and streaks of macular hyperpigmentation along the lines of Blaschko[24]. Occasionally, there are associated systemic abnormalities.

Epidemiology

LWNH is a sporadic disorder with no gender preference. It is viewed as an uncommon disorder but is probably under-recognized.

Pathogenesis

LWNH is a genetically heterogeneous mosaic skin condition characterized by a clone of skin cells with increased pigment production[25]. A variety of underlying mosaic chromosomal anomalies have been reported.

Clinical features

Swirls and streaks of brown pigmentation usually appear early during the first year of life (Fig. 67.15). The full extent of skin involvement is

Fig. 67.15 Linear and whorled nevoid hypermelanosis on the trunk. This young African-American girl had developmental delay. Note the distribution along the lines of Blaschko. *Courtesy, Julie V Schaffer, MD.*

typically apparent by the time the child is 2–3 years of age[24]. The linear hyperpigmentation tends to persist indefinitely. Occasionally, patients with "pigmentary mosaicism" will develop both hypo- and hyperpigmented streaks, which may be referred to as "linear nevoid pigmentation".

Up to a quarter of patients with LWNH who present to a pediatric dermatologist have extracutaneous findings, which typically become apparent during infancy and may be neurologic, musculoskeletal or (less often) cardiac in nature[25]. However, the exact incidence of extracutaneous abnormalities in LWNH is unknown.

Pathology

LWNH is characterized by increased melanin within basal keratinocytes and, in some cases, a slight increase in the density of melanocytes. There are few dermal melanophages.

Differential diagnosis

The differential diagnosis includes other disorders characterized by hyperpigmentation along the lines of Blaschko (Table 67.5; Figs 67.16 & 67.17). The hyperpigmented stage (stage 3) of incontinentia pigmenti (IP) is distinguished by its grayish-brown color, a predominance of melanophages rather than epidermal pigment (Fig. 67.18), fading over time and (in most patients) a history of previous inflammatory vesicular and verrucous stages (1 and 2, respectively). Some epidermal nevi initially have minimal or no palpable component, but they eventually become elevated. Of note, a mother and child previously reported as an example of "familial LWNH" (with histologic findings of increased epidermal melanin but no pigment incontinence in affected skin) were subsequently found to have hypohidrotic ectodermal dysplasia with immunodeficiency due to a hypomorphic *NEMO* mutation[26].

Treatment

There is currently no effective treatment, although future developments in laser therapy may hold promise. Camouflage cosmetics may be helpful.

Incontinentia Pigmenti

A full discussion of IP can be found in Chapter 62. This X-linked dominant multisystem disorder is characterized by skin lesions distributed along the lines of Blaschko, including vesicles (stage 1), verrucous lesions (stage 2), hyperpigmentation (stage 3) and, eventually, hypopigmentation (stage 4). The third stage usually presents within the first year of life and is characterized by gray to gray–brown streaks and whorls along the lines of Blaschko (Fig. 67.19). The trunk is a common

DISORDERS WITH HYPERPIGMENTATION THAT CAN FOLLOW BLASCHKO'S LINES
INHERITED AND/OR EARLY ONSET
• Linear and whorled nevoid hypermelanosis (a form of "pigmentary mosaicism")
• Third stage of incontinentia pigmenti
• Chimerism
• Early epidermal nevus
• X-linked reticulate pigmentary disorder*
• Focal dermal hypoplasia (Goltz syndrome; usually hyperpigmented macules in a linear array)
• Conradi-Hünermann-Happle syndrome
• Café-au-lait macules of McCune–Albright syndrome†
• Seckel syndrome‡
ACQUIRED
• Hyperpigmentation secondary to linear lichen planus or lichen planus pigmentosus
• Linear fixed drug eruption
• Linear atrophoderma of Moulin (Fig. 67.17)
• Linear biphasic cutaneous amyloidosis‡
*Female patients.
†Most often in broad bands or with a block-like configuration.
‡Single case.

Table 67.5 Disorders with hyperpigmentation that can follow Blaschko's lines.

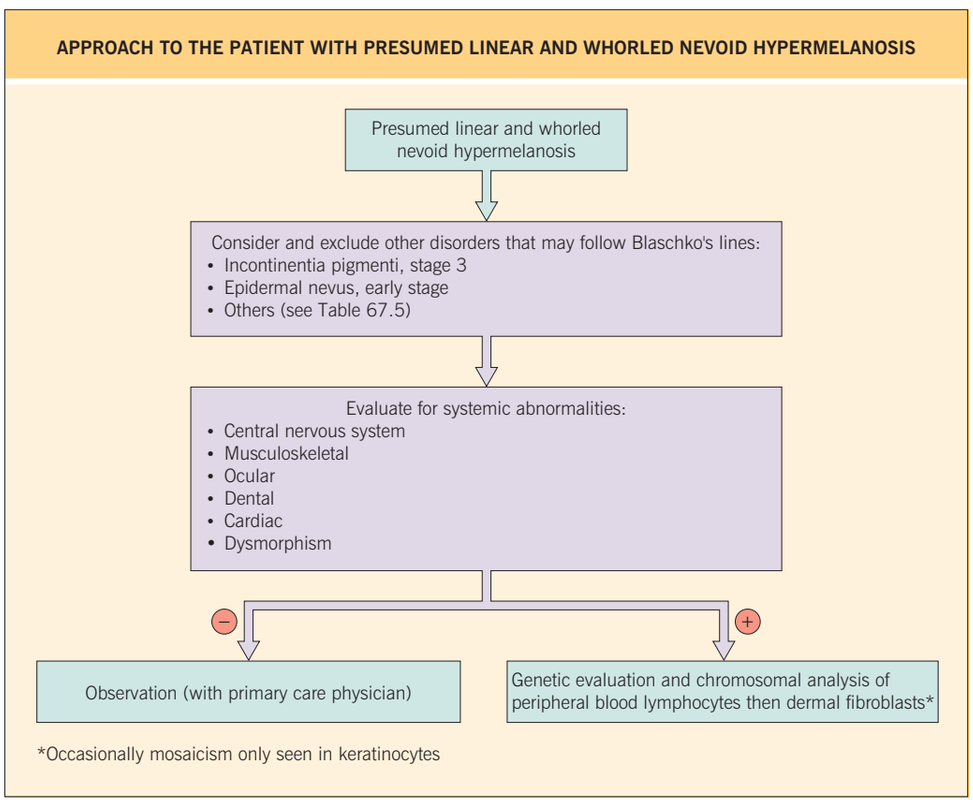


Fig. 67.16 Approach to the patient with presumed linear and whorled nevoid hypermelanosis. In general, the initial evaluation is clinical, with additional studies only as indicated based on abnormalities that are evident. Genetic abnormalities are currently detected primarily at the chromosomal (not gene) level; decisions regarding performance of conventional chromosomal analysis and/or array comparative genomic hybridization are made on a case-by-case basis.

Fig. 67.17 Linear hyperpigmentation due to atrophoderma of Moulin. Note the subtle depression of the lesions on the upper lateral thigh. *Courtesy, Jean L Bolognia, MD.*

Fig. 67.19 Stage 3 incontinentia pigmenti in a 2-year-old child. Note the characteristic gray–brown color, and the distribution along the lines of Blaschko.

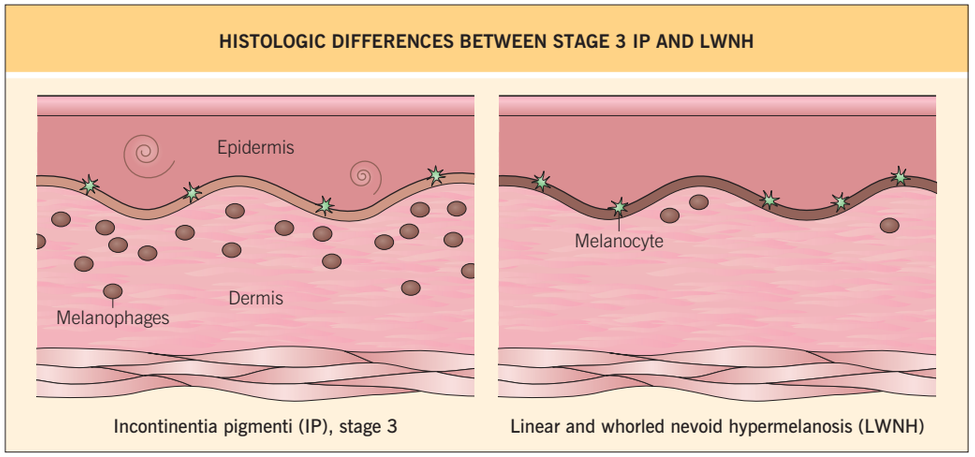


Fig. 67.18 Histologic differences between stage 3 incontinentia pigmenti (IP) and linear and whorled nevoid hypermelanosis (LWNH).

area of involvement. The pigmentation fades gradually during late childhood to adolescence. IP is due to mutations in the *NEMO* gene. The gradual fading of stage 3 lesions reflects increased apoptosis within the affected streaks, followed by replacement with normal skin.

RETICULATED HYPERPIGMENTATION

Disorders characterized by true reticulated macular hyperpigmentation are rare. Initial evaluation should exclude other more common entities such as confluent and reticulated papillomatosis of Gougerot and Carteaud (see Ch. 109), where the lesions are elevated and favor the neck and upper trunk (Fig. 67.20), and the hyperpigmentation of erythema ab igne, which has a widely spaced net-like pattern corresponding to the arrangement of the cutaneous venous plexus (see Ch. 88). A similar violaceous to brown-colored net-like pattern can also be seen on the lower extremities of patients with livedo reticularis. Reticulated hyperpigmentation is an occasional feature of other skin disorders, such as its occurrence on the anterolateral neck in patients with atopic dermatitis ("atopic dirty neck") and in association with epidermolysis bullosa herpetiformis.

When a true reticulated pigmentary disorder exists, the family history should be reviewed and the patient carefully examined for associated abnormalities. The following section discusses prurigo pigmentosa and six genodermatoses associated with reticulated hyperpigmentation. Additional entities that feature reticulated hyperpigmentation are listed in Table 67.6.

PRURIGO PIGMENTOSA

First described by Nagashima in 1971[27], this idiopathic disorder is characterized by a markedly pruritic eruption of erythematous papules and papulovesicles on the back, neck and chest. Crops of inflammatory lesions develop rapidly and then involute within a week, leaving macular reticulated hyperpigmention. Recurrences tend to occur at the same site, and lesions in multiple stages are often evident. The condition favors young adults, with a female : male ratio of ≥2 : 1; the majority of reported patients have been from Japan. Three histopathologic stages have been identified: (1) neutrophilic exocytosis, spongiosis, papillary dermal edema and a superficial perivascular infiltrate of neutrophils; (2) intra-/subepidermal vesiculation, necrotic keratinocytes and a patchy lichenoid infiltrate of predominantly lymphocytes; (3) parakeratosis and dermal melanophages[28]. Treatment with oral minocycline, doxycycline or dapsone is usually effective for the inflammatory component of prurigo pigmentosa. The condition does not respond to corticosteroids (topical or systemic) or antihistamines.

Fig. 67.20 Confluent and reticulated papillomatosis of Gougerot and Carteaud. **A** On the neck and back of a teenage girl. **B** On the chest of an older woman. *A, Courtesy, Seth Orlow, MD PhD.*

DISORDERS CHARACTERIZED BY RETICULATED PIGMENTATION	
Disorder	**Key features**
Confluent and reticulated papillomatosis of Gougerot and Carteaud	Elevated with rough texture; favors neck and upper trunk; responds well to minocycline
Erythema ab igne	Widely spaced net that corresponds to vascular pattern; due to heat injury (see Ch. 88)
Atopic dirty neck	Anterolateral neck
Dyskeratosis congenita*	X-linked recessive (XLR) form more common than autosomal dominant (AD) and autosomal recessive (AR) forms; pterygium, leukoplakia, pancytopenia, mucosal squamous cell carcinoma, leukemia (see Table 67.7); mutations in the genes that encode dyskerin (XLR), the TERC (AD) or TERT (AD, AR) subunit of telomerase, TINF2 (AD), NOP10 (AR), NHP2 (AR) or TCAB1 (AR)
Fanconi's anemia*	Autosomal recessive; more often diffuse hypermelanosis; radial ray bony defects, pancytopenia, leukemia (see Table 67.7)
X-linked reticulate pigmentary disorder	X-linked recessive (only males have generalized reticulated pigmentation); neonatal colitis, recurrent pneumonia, hypohidrosis, photophobia; amyloid deposits in adults
Dowling–Degos disease (DDD)	Autosomal dominant; reticulated hyperpigmentation of major flexures (may be composed of or admixed with discrete hyperpigmented macules and papules), comedones on the back and neck, pitted facial scars; due to loss-of-function mutations in keratin 5 gene
Galli–Galli disease	Acantholytic variant of DDD
Haber syndrome	Rosacea-like facial eruption plus the clinical features of DDD
Pigmentatio reticularis faciei et colli	Possible variant of DDD; hyperpigmentation of the face and neck plus multiple epidermoid cysts
Epidermolysis bullosa simplex (EBS) herpetiformis (Dowling–Meara) and EBS with mottled pigmentation*	"Mottled" appearance due to mutations in the genes that encode keratin 5 and 14 (with a specific P25L keratin 5 mutation usually underlying EBS with mottled pigmentation) (see Ch. 32)
Prurigo pigmentosa	Typically young Japanese women; favors the back, neck and chest; recurrent crops of pruritic papulovesicles that resolve with a reticulated pattern of hyperpigmentation
Mendes da Costa disease*	Traumatic bullae and hyperpigmentation, usually acral; dwarfism, atrichia
Dermatopathia pigmentosa reticularis	Autosomal dominant; persistent reticulated hyperpigmentation, alopecia, nail dystrophy; palmoplantar keratoderma and hypoplastic dermatoglyphics in some patients; mutation in the keratin 14 gene
Naegeli–Franceschetti–Jadassohn syndrome	Autosomal dominant; fading reticulated hyperpigmentation, dental anomalies, hypohidrosis, palmoplantar keratoderma, hypoplastic dermatoglyphics, nail dystrophy; mutations in the keratin 14 gene
Reticulate acropigmentation of Kitamura	Primarily autosomal dominant; atrophic acral lentigo-like lesions, palmoplantar and dorsal phalangeal pitting
Reticulate genital hyperpigmentation associated with localized vitiligo*	Affected individuals had congenital or acquired reticulate hyperpigmentation of the genitalia, which was followed by the development of vitiligo in the same region
Cantu syndrome	Reticulated pigmentation of face, forearms and feet; palmoplantar keratoderma
Mitochondrial disorders	Sun-exposed areas (e.g. cheeks, dorsal aspects of the forearms and hands); additional cutaneous findings include hypertrichosis, hair shaft abnormalities and acrocyanosis (see Ch. 63)
Postinflammatory	Lichenoid dermatoses (e.g. lichen planus pigmentosus); contact dermatitis (e.g. due to benzoyl peroxide)
Drug-induced	Diltiazem (sun-exposed areas); chemotherapeutic agents such as 5-fluorouracil and bleomycin (see Table 63.7)

*Also dyschromatosis.

Table 67.6 Disorders characterized by reticulated pigmentation. TERC, telomerase RNA component; TERT, telomerase reverse transcriptase; TCAB1, telomerase Cajal body protein-1; TINF2, telomere repeat binding factor 1-interacting nuclear factor 2.

DYSKERATOSIS CONGENITA

Synonym: ■ Zinsser–Engman–Cole syndrome

Key features

- 90% of patients are male, as the most common form is X-linked recessive
- Triad of reticulated hyperpigmentation, nail dystrophy (e.g. pterygium) and leukoplakia
- Continuous lacrimation (epiphora) due to lacrimal duct atresia
- Bone marrow dysfunction (thrombocytopenia, anemia, pancytopenia)
- Predisposition to malignancy, especially mucosal squamous cell carcinoma, leukemia and Hodgkin disease

Introduction

First described in 1906 by Zinsser, dyskeratosis congenita (DKC) is a genodermatosis characterized by progressive bone marrow failure and the mucocutaneous triad of reticulated hyperpigmentation, nail dystrophy and leukoplakia. In addition, affected individuals have an increased risk of developing squamous cell carcinoma (especially mucosal), acute myelogenous leukemia and Hodgkin disease[29].

Epidemiology

The most common form of DKC has an X-linked recessive pattern of inheritance. As a result, as many as 90% of patients are male. However, autosomal dominant and autosomal recessive forms of DKC also exist.

Pathogenesis

The X-linked recessive form of DKC is caused by mutations in the *DKC1* gene, which encodes the dyskerin protein that interacts with the telomerase enzyme[30] (Fig. 67.21). Telomerase is composed of two subunits, TERC (telomerase RNA component) and TERT (telomerase reverse transcriptase). Heterozygous mutations in the genes that encode these subunits or the telomere repeat binding factor 1-interacting nuclear factor 2 (TINF2), a component of the shelterin complex that plays an integral role in telomere structure and function, can lead to autosomal dominant forms of DKC[31,32]. In addition, biallelic mutations in the genes that encode TERT, telomerase Cajal body protein-1 (TCAB1; also known as WRAP53), or the NOP10 and NHP2 ribonucleoprotein analogs that associate with the telomerase complex have been found to underlie autosomal recessive forms of DKC[33,34]. Heterozygous mutations in the gene encoding TERT can also result in familial adult-onset pulmonary fibrosis without the skin findings or other manifestations of DKC[35].

Telomerase prevents the progressive shortening of chromosomes that would otherwise occur with DNA replication. Tissues with high replication rates (e.g. the bone marrow and skin) are particularly vulnerable when telomerase is not functioning properly. Telomerase dysfunction also leads to chromosome instability, which can result in tumorigenesis. DKC may also be considered as a premature aging syndrome, since short telomeres lead to early senescence in affected individuals.

Clinical Features

A lacy reticulated pattern of hyperpigmentation develops during the first decade of life. This occurs primarily on the neck (Fig. 67.22A&B), upper chest and upper arms and may be admixed with macules of hypopigmentation. In some areas, telangiectasias and epidermal atrophy are also seen, i.e. poikiloderma. Additional cutaneous features include wrinkled skin on the extremities, dorsal aspects of the hands,

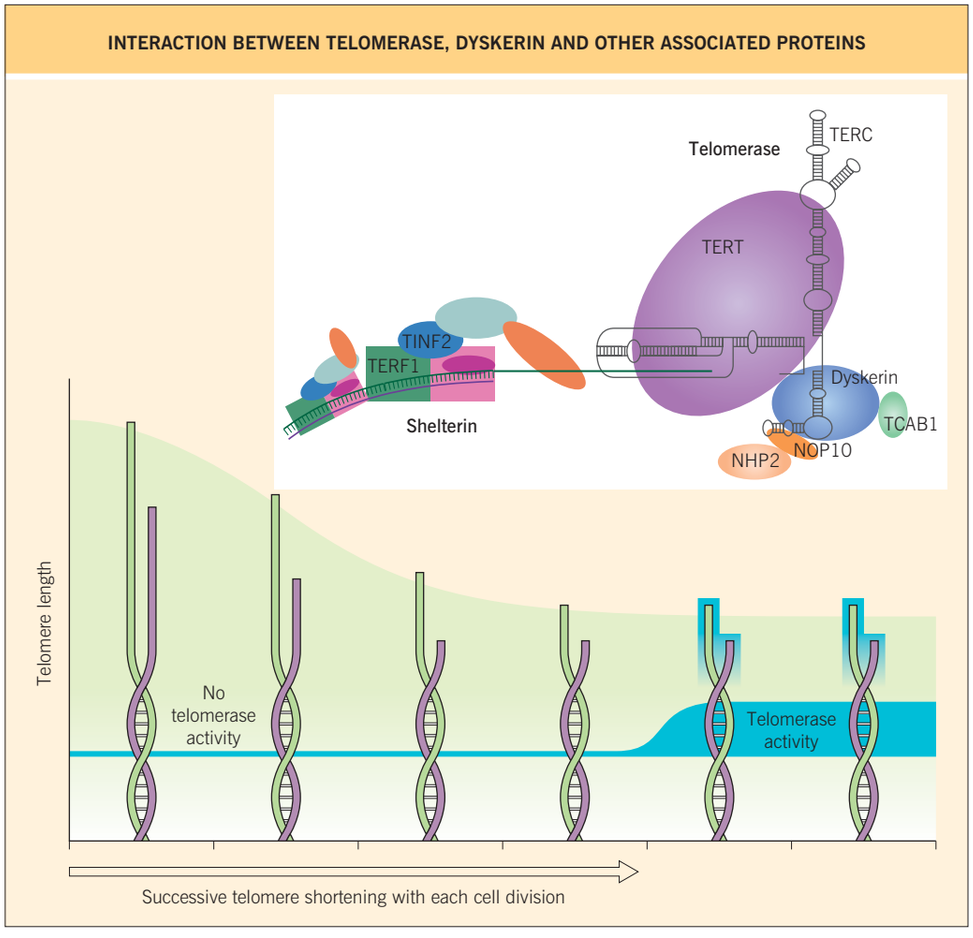


Fig. 67.21 Interaction between telomerase, dyskerin and other associated proteins. Telomerase, the enzyme that protects against progressive shortening of the chromosomes with each successive cell division, is composed of two subunits: an RNA component (TERC) and reverse transcriptase (TERT). Dyskerin, the protein that is dysfunctional in patients with X-linked recessive dyskeratosis congenita, interacts with telomerase and plays a role in its proper function. Autosomal dominant DKC can result from dysfunction of the TERC subunit, the TERT subunit or the telomere repeat binding factor 1 (TERF1)-interacting nuclear factor 2 (TINF2); the latter is a component of the shelterin complex that plays an essential role in telomere structure and function. Autosomal recessive DKC can be caused by mutations in the genes encoding the TERT subunit; telomerase Cajal body protein-1 (TCAB1), which associates with dyskerin; or the NOP10 and NHP2 ribonucleoprotein analogues that associate with the telomerase complex.

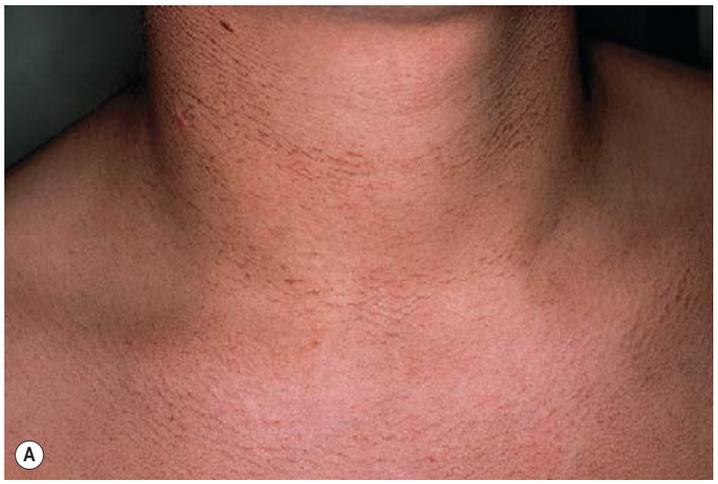


Fig. 67.22 Dyskeratosis congenita. A Reticulated hyperpigmentation on the chest and neck of a teenage boy. **B** More pronounced reticulated and confluent hyperpigmentation on the shoulder and axilla. **C** Longitudinal ridging, splitting and early pterygium formation in another teenage boy. *A, Courtesy, Seth Orlow, MD PhD. B, Courtesy, Eugene Mirrer, MD. C, Courtesy, Anthony Mancini, MD.*

and genitalia; palmoplantar hyperhidrosis and hyperkeratosis; frictional bullae; and acrocyanosis.

Nail involvement is present in the vast majority of patients, typically appearing during early childhood. Initial changes include longitudinal ridging and splitting, followed by pterygia formation (Fig. 67.22C) and occasionally complete nail loss. Premalignant leukoplakia occurs in most patients, usually manifesting during early adolescence. White plaques on the oral mucosa are observed most commonly, with a predilection for the lateral portions of the tongue. Involvement of the urethra, vagina and anus may also be seen. The teeth may be malformed, missing, or have aberrant spacing or extensive caries. Epiphora (continuous lacrimation) due to lacrimal duct atresia is common[29].

Bone marrow failure occurs in 50–90% of patients and is a major cause of mortality. It presents during the second or third decade with anemia, thrombocytopenia or pancytopenia. Malignancies tend to develop during the third or fourth decade, most notably squamous cell carcinomas of the mouth, anus, cervix, vagina, esophagus and skin. There is also an increased risk of myelodysplasia, acute myelogenous leukemia, Hodgkin disease and gastrointestinal carcinomas[29].

Other systemic manifestations that have been described include testicular atrophy, pulmonary fibrosis, liver cirrhosis, developmental delay, and immunologic dysfunction leading to opportunistic infections. Of note, increased severity in successive generations (anticipation) due to progressive telomere shortening characterizes autosomal dominant forms of DKC, and *TINF2* mutations tend to result in severe DKC with onset in early childhood. However, family members who are asymptomatic carriers of *TERT* mutations have also been described. *Hoyeraal–Hreidarsson syndrome* is an allelic condition characterized by bone marrow failure, immunodeficiency, microcephaly, cerebellar hypoplasia and growth retardation. Also caused by *DKC1* mutations, it typically leads to death in early childhood. *Revesz syndrome* is another related disorder that features progressive neurologic deterioration, intracranial calcifications and exudative retinopathy together with the manifestations of DKC; it is caused by heterozygous mutations in the *TINF2* gene.

Pathology

Histologically, the features of poikiloderma vasculare atrophicans are seen, with telangiectasias and epidermal thinning as well as foci of increased pigment within the basal layer. In the early stage, hydropic degeneration of basilar keratinocytes and a band-like inflammatory infiltrate in the upper dermis may be evident. In the late stage, the epidermis is markedly thinned and flattened and melanophages are present in the upper dermis.

Short telomere length can be detected in leukocytes from patients with DKC by flow fluorescence *in situ* hybridization[36].

Differential Diagnosis

Fanconi's anemia is also associated with pigmentary abnormalities, pancytopenia and an increased risk of neoplasia (e.g. leukemia); this disorder is compared to DKC in Table 67.7. Naegeli–Franceschetti–Jadassohn (NFJ) syndrome and dermatopathia pigmentosa reticularis (DPR) differ by their lack of leukoplakia and bone marrow involvement (see below). Patients with chronic GVHD may develop poikilodermatous skin changes and lacy white patches of the oral mucosa. However, GVHD is usually easily distinguished by the history of a hematopoietic stem cell transplant (or, rarely, a solid organ transplant). Additional entities associated with poikiloderma are discussed in Chapter 63.

Treatment

Management of DKC patients requires multidisciplinary care. Longitudinal surveillance of all mucosal surfaces is indicated to monitor for the development of squamous cell carcinoma within areas of

COMPARISON OF DYSKERATOSIS CONGENITA AND FANCONI'S ANEMIA		
	Dyskeratosis congenita	**Fanconi's anemia (FA)**
Pigmentation	Lacy reticulated hyperpigmentation favoring the neck and upper chest, with onset during the first decade of life Sometimes admixed with hypopigmented macules Poikiloderma may be present (telangiectasias and epidermal atrophy)	More generalized, diffuse hyperpigmentation; less often reticulated Sometimes admixed with hypopigmented macules Multiple café-au-lait macules may be present
Hematologic abnormalities	Anemia, leukopenia, thrombocytopenia, pancytopenia Onset typically in 2nd decade	Anemia, leukopenia, thrombocytopenia, pancytopenia Onset typically in 1st decade
Associated malignancies	Increased risk, in particular SCC (esp. mucosal), acute myelogenous leukemia, Hodgkin disease	Increased risk, in particular SCC (esp. of head & neck), acute myelogenous leukemia, hepatocellular cancer; increased risk of breast and pancreatic cancer with *heterozygous* mutations in some FA genes*
Additional clinical findings	Nail abnormalities (e.g. pterygium), leukoplakia, hyperhidrosis, palmoplantar hyperkeratosis, frictional bullae, acrocyanosis, epiphora (continuous lacrimation)	Radial ray bony defects involving the thumb, short stature, renal and cardiac malformations, hypogonadism and other endocrinopathies
Exposure of lymphocytes to mitomycin C or diepoxybutane	No chromosomal breakage	Enhanced chromosomal breakage and rearrangement
Inheritance	Most common form is X-linked recessive (~90% of patients are male); occasionally autosomal dominant or autosomal recessive	Autosomal recessive (at least 11 complementation groups); rarely X-linked recessive (1 complementation group; ~1% of patients)

*For example, *BRCA2* (*FAD1*).

Table 67.7 Comparison of dyskeratosis congenita and Fanconi's anemia. SCC, squamous cell carcinoma.

leukoplakia. Sun and cigarette avoidance are advisable. Bone marrow failure can be treated with supportive transfusions of blood products and the use of androgens (e.g. oxymetholone), erythropoietin and granulocyte colony-stimulating factor. Although hematopoietic stem cell transplantation can potentially cure bone marrow failure and leukemia in patients with DKC, it has historically been associated with a high rate of complications and poor long-term survival.

NAEGELI–FRANCESCHETTI–JADASSOHN SYNDROME

Key features

- Autosomal dominant disorder due to heterozygous mutations in the keratin 14 gene
- Reticulated hyperpigmentation beginning by 2 years of age and often fading during adolescence
- Hypohidrosis and heat intolerance
- Dental anomalies, including early loss of teeth
- Palmoplantar keratoderma, with absent or hypoplastic dermatoglyphics

Introduction

NFJ syndrome is a rare autosomal dominant genodermatosis that is characterized by reticulated hyperpigmentation as well as ectodermal dysplasia (primarily dental anomalies and hypohidrosis) and hypoplastic dermatoglyphics.

History

First described by Naegeli in 1927, NFJ was initially confused with incontinentia pigmenti. In 1954, Franceschetti and Jadassohn re-examined the original family and noted the autosomal dominant pattern of inheritance.

Epidemiology

Affected families have been of Swiss and British descent.

Pathogenesis

NFJ syndrome is caused by truncating mutations in the non-helical head domain of the keratin 14 gene (*KRT14*) (see Fig. 56.5) that result in haploinsufficiency[37]. This leads to increased susceptibility of keratinocytes to tumor necrosis factor-α (TNF-α)-induced apoptosis, which explains the hyperpigmentation secondary to pigment incontinence observed in affected individuals and points to a role of the N-terminal portion of keratin 14 in regulating apoptosis during morphogenesis of cutaneous appendages.

Clinical Features

Brown or gray–brown reticulated hyperpigmentation develops by the age of 2 years, without a preceding inflammatory stage. The pigmentary changes are most often observed on the abdomen and periocular and perioral regions, with variable involvement of the neck, trunk, proximal extremities, axillae and groin. The hyperpigmentation often fades after puberty and may eventually disappear. Some infants have bullae on their feet during the newborn period. Decreased sweat gland function with lifelong heat intolerance is a problem for many patients. Other cutaneous manifestations include absent or hypoplastic dermatoglyphics, palmoplantar keratoderma (diffuse or punctate), and onychodystrophy (onycholysis, subungual hyperkeratosis and congenital malalignment of the great toenails). Dental anomalies are common and include abnormally shaped teeth, supernumerary teeth, and yellow spotted tooth enamel. Early total loss of teeth may occur.

Pathology

Histologically, the hyperpigmented skin demonstrates pigment incontinence, i.e. melanophages.

Differential Diagnosis

The lack of leukoplakia, bone marrow failure or an increased risk of malignancies in patients with NFJ syndrome differentiates it from DKC. Although NFJ syndrome lacks the prominent alopecia and more persistent hyperpigmentation that characterize DPR, there is significant overlap between these allelic disorders. The hyperpigmentation of stage 3 IP follows Blaschko's lines and is usually preceded by an inflammatory stage (see above). X-linked reticulate pigmentary disorder often presents with hypohidrosis and dental anomalies as well as reticulate hyperpigmentation, but additional systemic manifestations as well as the inheritance pattern distinguish it from NFJ. Hypohidrosis, onychodystrophy, dental anomalies, and hypoplastic or absent dermatoglyphics can be seen in other forms of ectodermal dysplasia. Reticulated hyperpigmentation and palmoplantar keratoderma may

develop in patients with epidermolysis bullosa simplex due to mutations in keratin 5 or 14, but blistering is more prominent. In addition, patients with Kindler syndrome may have absent or hypoplastic dermatoglyphics, but they develop poikiloderma rather than reticulated hyperpigmentation (see Ch. 63).

Treatment

Treatment is supportive. Genetic counseling should be offered to affected individuals planning future children.

DERMATOPATHIA PIGMENTOSA RETICULARIS

Key features

- Autosomal dominant disorder due to mutations in the keratin 14 gene
- Persistent reticulated hyperpigmentation with truncal predominance
- Non-scarring alopecia of the scalp, eyebrows and axillae
- Onychodystrophy
- Absent dermatoglyphics and punctate keratoderma in some patients

Introduction and Pathogenesis

DPR is a rare genodermatosis that was recognized as a distinct entity in the 1970s. Like NFJ (see above), a heterozygous truncating mutation in the non-helical head domain of the keratin 14 gene has been shown to cause DPR[37].

Clinical Features

DPR presents by the second year of life with the triad of reticulated hyperpigmentation, non-scarring alopecia and onychodystrophy[38]. The reticulated hyperpigmentation has a predilection for the trunk but also occurs on the proximal extremities, and it persists during adulthood (Fig. 67.23). The nail involvement may result in pterygia formation. Variable features include absent dermatoglyphics, hypo- or hyperhidrosis, and a punctate palmoplantar keratoderma.

Pathology

Histologically, the hyperpigmented skin demonstrates pigment incontinence, i.e. melanophages.

Fig. 67.23 Dermatopathia pigmentosa reticularis. Persistent hyperpigmentation in a reticulated pattern extending from the lower abdomen to the thigh in a young man. *Courtesy, Julie V Schaffer, MD.*

Differential Diagnosis

There is clinical overlap with the NFJ syndrome (e.g. reticulated hyperpigmentation, nail dystrophy, punctate keratoderma, absent dermatoglyphics), but the latter lacks alopecia and has less persistent hyperpigmentation. Additional diagnostic considerations are as discussed above for NFJ.

X-LINKED RETICULATE PIGMENTARY DISORDER

Synonyms: ■ Partington syndrome type II ■ Familial cutaneous amyloidosis ■ X-linked reticulate pigmentary disorder with systemic manifestations

Key features

- Reticulated hyperpigmentation along the lines of Blaschko in women and in a generalized pattern in men
- Recurrent infections and multiple systemic manifestations in male patients
- Some adult patients have amyloid deposits within the dermis

Introduction

This rare genodermatosis is characterized by reticulated brown hyperpigmentation that is generalized in male patients and along the lines of Blaschko in female patients. Affected males have severe systemic complications that often lead to premature death. The disorder was first described by Partington et al. in 1981[39], and several additional families have subsequently been identified[40–42]. The pathogenesis is unknown, but the disorder has been mapped to Xp21.11–p21.3.

Epidemiology

Partington's original kindred had English and Scottish heritage[39]. Other reported families (all unrelated) had Maltese, Lebanese, Spanish and mixed Dutch, French and German ancestries[40–42].

Clinical Features

In *female* patients with this X-linked disorder, manifestations appear to be limited to the skin. At birth or within the first few weeks of life, female infants develop lacy or reticulated areas of hyperpigmentation in streaks that follow the lines of Blaschko. Although the lesions are reminiscent of stage 3 IP, there are no preceding vesicular or verrucous stages. The hypermelanosis may fade during adulthood.

In *male* patients, the reticulated hyperpigmentation is generalized (Fig. 67.24), initially developing on the inner thighs, buttocks or cheeks between 4 months and 5 years of age. Affected boys often have severe systemic manifestations, including a low birthweight, neonatal colitis, failure to thrive during infancy, seizures and hemiplegia, as well as gastroesophageal reflux, urethral strictures and inguinal hernias. Recurrent pneumonias and chronic obstructive pulmonary disease are nearly always present in male patients and can lead to premature death. Intelligence may be normal or development delayed. Additional features include dental anomalies, hypohidrosis, xerosis, photophobia, corneal clouding, and skeletal changes such as delayed bone age and shortened metacarpals. Blonde unruly hair with a frontal upsweep is a notable clinical finding; in fair-skinned patients, the hair may become silver-gray[39–41].

Pathology

Although the histologic features of the cutaneous hyperpigmentation are similar in male and female patients, they are fairly nonspecific. Findings include increased epidermal melanin, pigment incontinence with dermal melanophages, and dyskeratosis[39]. Amyloid deposits in the upper dermis (keratin-positive as in macular amyloidosis) were also noted in adults (but not children) from the original Canadian family and a recently reported kindred[39,42]. As with macular amyloidosis, deposits were not found in other tissues.

Fig. 67.24 X-linked reticulate pigmentary disorder. There is reticulated hyperpigmentation of the face and neck in this 11-year-old boy, as well as blond, coarse hair. *Courtesy, K Robin Carder, MD.*

Fig. 67.25 Dowling–Degos disease. Hyperpigmented macules forming a reticulated pattern in the axilla. *Courtesy, Thomas Schwarz, MD.*

Differential Diagnosis

In boys, other entities with reticulated hyperpigmentation should be considered (see Table 67.6), particularly DKC and NFJ syndrome, especially when there are recurrent infections (DKC), hypohidrosis (NFJ syndrome) or dental anomalies (both DKC and NFJ syndrome). In female carriers, the differential diagnosis includes the disorders listed in Table 67.5.

Treatment

Treatment is supportive. Genetic counseling is indicated for families planning future pregnancies.

DOWLING–DEGOS DISEASE

Synonyms:
- Reticular pigmented anomaly of the flexures
- Reticulated pigmented anomaly of the flexures

Key features

- Reticulated hyperpigmentation in flexural sites
- Comedone-like lesions on the back and neck
- Pitted facial scars
- Autosomal dominant with variable penetrance
- Caused by loss-of-function mutations in the gene that encodes keratin 5

Introduction

Dowling–Degos disease (DDD) is an uncommon autosomal dominant condition characterized by acquired reticular hyperpigmentation in intertriginous sites.

Epidemiology

There is no racial or sex predilection, and it has been reported worldwide.

Pathogenesis

DDD is caused by loss-of-function mutations in the non-helical head domain of the keratin 5 gene (*KRT5*) (see Fig. 56.5) that lead to haploinsufficiency[43]. Interestingly, a missense mutation in the same region of *KRT5* underlies epidermolysis bullosa simplex with mottled pigmentation (see Ch. 32). The head domain of keratin 5 has been found to interact with Hsc70, a chaperone involved in vesicle uncoating, and it has been postulated that keratin 5 has a role in melanosome trafficking.

Clinical Features

Onset is typically during the third to fourth decade of life. The reticulated hyperpigmentation is admixed with and sometimes composed of lentigo-like brown macules; small brown papules with variable hyperkeratosis may also develop. These findings progressively increase over time, initially appearing in the axillae (Fig. 67.25) and groin with later involvement of the intergluteal and inframammary folds, neck, trunk and inner aspects of the arms and thighs. Some patients report pruritus of the affected flexural areas. Comedone-like lesions on the back or neck, pitted perioral scars, epidermoid cysts and hidradenitis suppurativa represent additional features in some patients.

Pathology

Histologically, there is increased pigmentation of the basal layer and finger-like rete ridges with thinning of the suprapapillary epithelium. This results in an "antler-like" pattern arising from the under surface of the epidermis and hair follicles. Dermal melanophages and a mild perivascular lymphohistiocytic infiltrate are also observed[44]. *Galli–Galli disease* represents a variant of DDD (also caused by *KRT5* mutations) with prominent suprabasal non-dyskeratotic acantholysis in biopsy specimens of lesional skin in addition to the usual clinical and histologic features[45].

Differential Diagnosis

Acanthosis nigricans is distinguished clinically by velvety plaques and histologically by less pronounced elongation of the rete ridges. In addition, there is no follicular involvement. Patients with neurofibromatosis type 1 develop lentigines (oftentimes referred to as "freckles") in the axillae and groin, but this disorder is usually easy to distinguish from DDD.

The spectrum of DDD-like disorders that feature reticulate pigmentation include reticulate acropigmentation of Kitamura (see below) and Haber syndrome. Patients with *Haber syndrome* develop a photosensitive rosacea-like facial eruption during adolescence, which is followed by the appearance of keratotic papules, comedone-like lesions, pitted

scars and reticulate hyperpigmentation on the trunk and proximal extremities as well as in the axillae.

Treatment

Topical hydroquinone, tretinoin, adapalene and corticosteroids have been used with varying success. Improvement following treatment with the erbium:YAG laser has also been reported[46].

RETICULATE ACROPIGMENTATION OF KITAMURA

Synonym: ■ Kitamura reticulate acropigmentation

Key features

- Atrophic reticulated or lentigo-like hyperpigmentation that favors the dorsal aspects of the hands and feet and appears during childhood
- Pits on the palms, soles and dorsal phalanges
- Autosomal dominant inheritance pattern

Introduction

Reticulate acropigmentation of Kitamura is a rare genodermatosis characterized by atrophic hyperpigmented macules that appear during childhood and initially have an acral distribution. Two-thirds of reported patients have been Japanese, but the condition has been described in individuals with other ethnic backgrounds.

Clinical Features

During childhood, slightly depressed lentigo-like hyperpigmented macules develop on the dorsal aspects of the hands and feet and often assume a reticulated pattern. These macules slowly darken over time and subsequently may spread to other sites of the body during adulthood. Sunlight may aggravate the condition. Pits are found on the palms, soles and dorsal phalangeal surfaces, and breaks in the dermatoglyphics are also evident.

Pathology

Examination of the hyperpigmented macules shows epidermal atrophy and elongated rete ridges that contain an increased amount of melanin. An increased number of DOPA-positive melanocytes are seen in the basal layer of the epidermis.

Differential Diagnosis

In contrast to the more common solar lentigines, the hyperpigmented macules of acropigmentation of Kitamura are slightly atrophic and develop at an earlier age. Unlike dyschromatosis symmetrica hereditaria (see below), white macules are not admixed with the brown macules. Reticulate acropigmentation of Kitamura may represent a variant of Dowling–Degos disease (see above) with a different distribution pattern.

Treatment

Treatment options are similar to those listed above for Dowling–Degos disease.

DYSCHROMATOSES

Dyschromatoses are characterized by the presence of both hypo- and hyperpigmentation (Figs 67.26–28). Often, at least one component of the dyspigmentation is guttate. The two classic dyschromatoses, dyschromatosis symmetrica hereditaria and dyschromatosis universalis hereditaria, are discussed in this section. A more recently recognized entity, acquired brachial cutaneous dyschromatosis, is also described. Additional dyschromatoses are listed in Table 67.8.

Fig. 67.26 Dyschromic amyloidosis cutis. An admixture of reticulated hyperpigmentation and guttate hypopigmentation are evident. *Courtesy, Seth J Orlow, MD PhD.*

Fig. 67.27 Dyschromatosis symmetrica hereditaria. An admixing of multiple hypo- and hyperpigmented macules on the hands more so than on the forearms. *Courtesy, Peter Ehrnstrom, MD.*

Fig. 67.28 Dyschromatosis universalis hereditaria. Both hypo- and hyperpigmentation were present in a widespread distribution. *With permission from Urabe K, Hori Y. Dyschromatosis. Semin Cutan Med Surg. 1997;16:81–5.*

DYSCHROMATOSES	
Disorder	**Key features**
GENETIC DISORDERS	
Dyschromatosis symmetrica hereditaria	Symmetrical dyschromatosis of distal extremities, especially dorsal aspects of hands and feet; palms, soles and mucous membranes spared Usually presents by age 6 years Caused by heterozygous mutations in *ADAR* (*DSRAD*) gene (encodes double-stranded RNA-specific adenosine deaminase) Vast majority of patients are Japanese or Chinese (see text)
Dyschromatosis universalis hereditaria	Truncal or generalized hyper- and hypopigmented macules; can occur on palms and soles, but not mucous membranes Usually presents by age 6 years, often becoming apparent in the first year of life Majority of patients are Japanese (see text)
Xeroderma pigmentosum (XP)	Lentigines and hypopigmented macules on dorsal aspects of hands and feet, face and other chronically sun-exposed sites Actinic damage beginning in infancy and early childhood, with skin cancers often developing during the first decade of life Autosomal recessive disorder caused by defective nucleotide excision repair (complementation groups A–G) or error-free bypass (XP-variant) of UV-induced DNA damage
Dyskeratosis congenita	Reticulated hyperpigmentation can be admixed with macules of hypopigmentation; nail dystrophy and leukoplakia Predisposition to malignancies (see Table 67.7) Most common form is X-linked recessive
Epidermolysis bullosa simplex with mottled pigmentation	Acral blistering early in childhood, mottled pigmentation, punctate keratoses of the palms and soles, and dystrophic, thickened nails Typically due to a specific keratin 5 mutation (P25L; see Ch. 32)
Wende–Bauckus/Pegum syndrome	At 1 year of age, background hyperpigmentation (gray–brown) develops on the trunk > extremities Tiny white macules on the trunk with confluence in flexures
Ziprkowski–Margolis syndrome	Diffuse pigmentary dilution of the hair and skin, sparing the buttocks and genital region Later, multiple hyperpigmented macules appear, giving the skin a leopard-like appearance Congenital sensorineural deafness, heterochromia irides X-linked recessive inheritance
Chédiak-Higashi syndrome (CHS) and Griscelli syndrome (GS)	In addition to pigmentary dilution of the skin, patients may develop diffuse hyperpigmentation with superimposed guttate hypopigmentation in sun-exposed areas Silvery hair with clumps of melanin, bleeding diathesis (CHS), neurologic abnormalities (CHS, GS1), immunodeficiency (CHS, GS2) (see Ch. 66 and Table 60.4)
Syndromes with ectodermal dysplasia	
• Berlin syndrome	Generalized grayish-brown hyperpigmentation with superimposed guttate hypopigmented macules Sparse eyebrows with absent lateral aspect, delayed dentition/hypodontia, short stature, sexual underdevelopment in male patients, mental retardation Described in one family (Iranians living in Israel; four affected siblings; consanguineous parents)
• Lucky/Winter syndrome	Generalized hyperpigmentation with superimposed guttate hypopigmented macules (latter most prominent in flexural sites) Scant lightly pigmented hair, enamel hypoplasia (single central incisor in one patient), "digitalized" thumbs, short stature Likely autosomal dominant inheritance
• Acromelanosis albo-punctata	Diffuse hyperpigmentation with superimposed guttate hypopigmentation affecting acral and flexural areas, with atrophic skin on the dorsal aspects of the hands and feet Keratotic follicular papules on the legs, pili torti, platonychia
EXPOSURES	
Arsenic	From systemic ingestion of inorganic arsenic Background of bronze hyperpigmentation with superimposed "raindrop"-like guttate hypopigmented macules Palmoplantar keratoses, Bowen's disease, basal cell carcinoma and squamous cell carcinoma Increased risk of certain internal malignancies
Diphencyclopropenone (DPCP)	Used for topical immunotherapy for alopecia areata of the scalp Hyperpigmented patches with superimposed confetti-like hypopigmented macules occurring mainly on treated areas of the scalp, sometimes at remote untreated sites Described in four patients among 243 patients treated with DPCP
Monobenzyl ether of hydroquinone	Dyschromia with confetti-like hyper-, hypo- or depigmented macules occurring following topical application; typically used for depigmentation therapy in patients with severe vitiligo
Betel leaf (*Piper betle*)	Contact leukomelanosis on the face following application of betel leaves (used as a home remedy for hyperpigmentation) Initially described in Taiwanese patients
Photoleukomelanodermatitis of Kobori	Dyschromic drug eruption that occurs after ingestion of afloqualone, thiazides or tetracyclines, followed by exposure to sunlight
INFECTIONS	
Secondary syphilis (necklace of Venus)	Background hyperpigmentation with superimposed white macules on neck (see Ch. 82)
Pinta	During late phases, copper-colored and slate-blue macules become admixed with depigmented macules and patches (see Ch. 74)

Table 67.8 Dyschromatoses. See Table 67.7 for Fanconi's anemia.

Continued

DYSCHROMATOSES	
Disorder	**Key features**
OTHER	
Dyschromic amyloidosis cutis	Generalized guttate leukoderma plus reticulated macules of hyperpigmentation (see Fig. 67.26), primarily in sun-exposed skin Onset before puberty; may have autosomal dominant inheritance Small foci of amyloid deposits in the papillary dermis
Kwashiorkor	Protein malnutrition, usually in an infant or young child Small hypopigmented macules in diaper area and on thighs, lower abdomen and back in addition to hyperpigmented areas "Flaky paint" dermatosis

Table 67.8 Dyschromatoses (cont'd). See Table 67.7 for Fanconi's anemia.

DYSCHROMATOSIS SYMMETRICA HEREDITARIA

Synonyms: ■ Acropigmentation of Dohi ■ Symmetrical dyschromatosis of the extremities

Key features

- Small, irregular hypopigmented and hyperpigmented macules on the dorsal aspects of the distal extremities, especially the hands and feet
- Autosomal dominant disorder caused by mutations in the *ADAR* (*DSRAD*) gene, which encodes an RNA-specific adenosine deaminase

Introduction

Dyschromatosis symmetrica hereditaria (DSH) was first reported by Toyama in 1929. It is characterized by both hyper- and hypopigmented macules of varying size on the dorsal surfaces of the distal extremities. The vast majority of reports have come from Japan, China, and Korea, but DSH has also been described in European, Afro-Caribbean and Indian patients[47]. The prevalence in Japan is approximately 1.5 per 100 000[48].

Pathogenesis

DSH has an autosomal dominant inheritance pattern with high penetrance. It is caused by mutations in the *ADAR (DSRAD)* gene, which encodes the double-stranded RNA-specific adenosine deaminase[48–50].

Clinical Features

Hyper- and hypopigmented macules arise in infancy or early childhood. The macules often increase in size and number until adolescence, when they stabilize; darkening after sun exposure may be observed. This dyschromatosis favors the distal extremities (see Fig. 67.27) and is usually most marked on the dorsal aspects of the hands and feet; it spares the palms, soles and mucous membranes. Spontaneous clearing has not been described. A few patients with dystonia and neurologic deterioration associated with a particular *ADAR* mutation have been reported.

Pathology

In the hyperpigmented macules, there is increased melanin within basal keratinocytes, while the hypopigmented macules demonstrate a decrease in the density of DOPA-positive melanocytes.

Differential Diagnosis

Reticulate acropigmentation of Kitamura lacks hypopigmented macules, while vitiligo lacks hyperpigmented macules. Patients with xeroderma pigmentosum also develop hyper- and hypopigmented macules during childhood, but the lesions are in a photodistribution that includes the face and upper trunk. In dyschromatosis universalis hereditaria (see below), the dyschromic lesions have a similar clinical appearance, but they may be present at birth in some patients and, more importantly, the primary distribution is truncal (see Table 67.8).

Treatment

Current treatments are unsatisfactory. Strict sun avoidance may decrease the contrast between the hypo- and hyperpigmented macules[50].

DYSCHROMATOSIS UNIVERSALIS HEREDITARIA

Key features

- Hyperpigmented and hypopigmented macules in a generalized distribution, with onset in early childhood
- Most reported patients have been Japanese

Introduction and Pathogenesis

Dyschromatosis universalis hereditaria (DUH) is a rare disorder characterized by hypo- and hyperpigmented macules in a generalized distribution. Initially described in 1933, this condition is most common in Japan but has also been reported in patients from other parts of Asia and Europe. Its relationship to dyschromatosis symmetrica hereditaria is unclear. Autosomal dominant and recessive forms of DUH have been linked to 6q24.2–q25.2 and 12q21–q23, respectively. Interestingly, familial progressive hyper- and hypopigmentation, which is characterized by autosomal dominant inheritance with reduced penetrance and lesions ranging from small macules to large patches, was recently found to be caused by heterozygous activating mutations in the KIT ligand gene (*KITLG*) at 12q22[51]. Whether the form of DUH associated with this locus is due to *KITLG* mutations remains to be determined.

Clinical Features

Over 80% of DUH patients develop dyschromia by 6 years of age, and approximately 20% have dyspigmentation at birth. Numerous hyperpigmented and hypopigmented macules of various sizes develop on the head, neck, trunk (see Fig. 67.28) and extremities, including the dorsal aspects of the hands and feet. Hyperpigmented macules on the face can resemble ephelides or lentigines. The dyschromia may involve the palms and soles, but it spares the mucous membranes. There is no seasonal change or spontaneous regression with age[52]. Extracutaneous abnormalities reported in isolated cases of DUH include short stature and high-frequency deafness; abnormalities in erythrocytes, platelets and tryptophan metabolism; bilateral glaucoma and unilateral cataract; and seizures[53].

Pathology

A focal increase or decrease in the melanin content of the basal layer is seen in the hyperpigmented and hypopigmented areas, respectively[53].

Differential Diagnosis

Xeroderma pigmentosum may have similar dyspigmentation, but it is in a photodistribution and associated with premature actinic damage (see Ch. 86). Additional causes of dyschromatosis are outlined in Table 67.8.

Treatment

There is no satisfactory treatment.

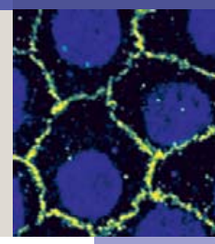
ACQUIRED BRACHIAL CUTANEOUS DYSCHROMATOSIS

This acquired dyschromatosis was described in 2000[54] and primarily affects Caucasian women in the fifth to seventh decades of life. It is characterized by chronic, asymptomatic gray–brown patches with geographic borders interspersed with hypopigmented macules on the dorsal aspect of the forearms[54]. Affected individuals often have evidence of chronic sun exposure clinically (e.g. poikiloderma of Civatte) or histologically (e.g. solar elastosis).

REFERENCES

1. Masu S, Seiji M. Pigmentary incontinence in fixed drug eruptions. Histologic and electron microscopic findings. J Am Acad Dermatol. 1983;8:525–532.
2. Shwartz RA. Erythema dyschromicum perstans: the continuing enigma of Cinderella or ashy dermatosis. Int J Dermatol. 2004;43:230–232.
3. Silverberg NB, Herz J, Wagner A, Paller AS. Erythema dyschromicum perstans in prepubertal children. Pediatr Dermatol. 2003;20:398–403.
4. Baranda L, Torres-Alvarez B, Cortes-Franco R, et al. Involvement of cell adhesion and activation molecules in the pathogenesis of erythema dyschromicum perstans (ashy dermatitis). The effect of clofazimine therapy. Arch Dermatol. 1997;133:325–329.
5. Bhutani LK, Bedi TR, Pandhi RK, Nayak NC. Lichen planus pigmentosus. Dermatologica. 1974;149:43–50.
6. Kanwar AJ, Dogra S, Parsad D, Radotra BD. A study of 124 Indian patients with lichen planus pigmentosus. Clin Exp Dermatol. 2003;28:481–485.
7. Al-Mutairi N, El-Khalawany M. Clinicopathological characteristics of lichen planus pigmentosus and its response to tacrolimus ointment: an open label, non-randomized, prospective study. J Eur Acad Dermatol Venereol. 2010;24:535–540.
8. Sanchez NP, Pathak MA, Sato S, et al. Melasma: a clinical, light microscopic, ultrastructural, and immunofluorescence study. J Am Acad Dermatol. 1981;4:698–710.
9. Grimes PE, Yamada N, Bhawan J. Light microscopic, immunohistochemical and ultrastructural alterations in patients with melasma. Am J Dermatopathol. 2005;27:96–101.
10. Kang WH, Yoon KH, Lee E-S, et al. Melasma: histopathological characteristics in 56 Korean patients. Br J Dermatol. 2005:146:228–237.
11. Guevara IL, Pandya AG. Melasma treated with hydroquinone, tretinoin, and a fluorinated steroid. Int J Dermatol. 2001;40:212–215.
12. Palumbo A, d'Ischia M, Misuraca G, Prota G. Mechanism of inhibition of melanogenesis by hydroquinone. Biochim Biophys Acta. 1991;1073:85–90.
13. Hogeling M, Frieden IJ. Segmental pigmentation disorder. Br J Dermatol. 2010;162:1337–1341.
14. Wang ZQ, Si L, Tang Q, et al. Gain-of-function mutation of KIT ligand on melanin synthesis causes familial progressive hyperpigmentation. Am J Hum Genet. 2009;84:672–677.
15. Artuc N, Bohm M, Grutzkau A, et al. Human mast cells in the neurohormonal network: expression of POMC, detection of precursor proteases, and evidence for IgE-dependent secretion of α-MSH. J Invest Dermatol. 2006;126:1976–1981.
16. Lerner EA, Sober AJ. Chemical and pharmacologic agents that cause hyperpigmentation or hypopigmentation of the skin. Dermatol Clin. 1988;6:327–337.
17. Cortina P, Garrido JA, Tomas JF, et al. "Flagellate" erythema from bleomycin. With histopathological findings suggestive of inflammatory oncotaxis [see comments]. Dermatologica. 1990;180:106–109.
18. Abess A, Keel DM, Graham BS. Flagellate hyperpigmentation following intralesional bleomycin treatment of verruca plantaris. Arch Dermatol. 2003;139:337–339.
19. Fernandez-Obregon AC, Hogan KP, Bibro MK. Flagellate pigmentation from intrapleural bleomycin. A light microscopy and electron microscopy study. J Am Acad Dermatol. 1985;13:464–468.
20. Hanada K, Hashimoto I. Flagellate mushroom (Shiitake) dermatitis and photosensitivity. Dermatology. 1998;197:255–257.
21. Tarvainen K, Salonen JP, Kanerva L, et al. Allergy and toxicodermia from shiitake mushrooms. J Am Acad Dermatol. 1991;24:64–66.
22. Bolognia JL, Orlow SJ, Glick SA. Lines of Blaschko. J Am Acad Dermatol. 1994;31:157–190; quiz 190–2.
23. Happle R, Assim A. The lines of Blaschko on the head and neck. J Am Acad Dermatol. 2001;44:612–615.
24. Kalter DC, Griffiths WA, Atherton DJ. Linear and whorled nevoid hypermelanosis. J Am Acad Dermatol. 1988;19:1037–1044.
25. Nehal KS, PeBenito R, Orlow SJ. Analysis of 54 cases of hypopigmentation and hyperpigmentation along the lines of Blaschko. Arch Dermatol. 1996;132:1167–1170.
26. Kosaki K, Shimasaki N, Fukushima H, et al. Female patient showing hypohidrotic ectodermal dysplasia and immunodeficiency (HED-ID). Am J Hum Genet. 2001;69:664–666.
27. Nagashima M. Prurigo pigmentosa – clinical observations of our 14 cases. J Dermatol. 1978;5:61–67.
28. Böer A, Misago N, Wolter M, et al. Prurigo pigmentosa: a distinctive inflammatory disease of the skin. Am J Dermatopathol. 2003;25:117–129.
29. Knight S, Vulliamy T, Copplestone A, et al. Dyskeratosis Congenita (DC) Registry: identification of new features of DC. Br J Haematol. 1998;103:990–996.
30. Knight SW, Heiss NS, Vulliamy TJ, et al. X-linked dyskeratosis congenita is predominantly caused by missense mutations in the *DKC1* gene. Am J Hum Genet. 1999;65:50–58.
31. Savage SA, Giri N, Baerlocher GM, et al. TINF2, a component of the shelterin telomere protection complex, is mutated in dyskeratosis congenita. Am J Hum Genet. 2008;82:501–509.
32. Walne AJ, Vulliamy T, Beswick R, et al. *TINF2* mutations result in very short telomeres: analysis of a large cohort of patients with dyskeratosis congenita and related bone marrow failure syndromes. Blood. 2008;112:3594–3600.
33. Vulliamy T, Beswick R, Kirwan M, et al. Mutations in the telomerase component NHP2 cause the premature ageing syndrome dyskeratosis congenita. Proc Natl Acad Sci U S A. 2008;105:8073–8078.
34. Zhong F, Savage SA, Shkreli M, et al. Disruption of telomerase trafficking by *TCAB1* mutation causes dyskeratosis congenita. Genes Dev. 2011;25:11–16.
35. Tsakiri KD, Cronkhite JT, Kuan PJ, et al. Adult-onset pulmonary fibrosis caused by mutations in telomerase. Proc Natl Acad Sci U S A. 2007;104:7552–7557.
36. Alter BP, Baerlocher GM, Savage SA, et al. Very short telomere length by flow fluorescence *in situ* hybridization identifies patients with dyskeratosis congenita. Blood. 2007;110:1439–1447.
37. Lugassy J, Itin P, Ishida-Yamamoto A, et al. Naegeli-Franceschetti-Jadassohn syndrome and dermatopathia pigmentosa reticularis: two allelic ectodermal dysplasias caused by dominant mutations in *KRT14*. Am J Hum Genet. 2006;79:724–730.
38. Heimer WL, Brauner G, James WD. Dermatopathia pigmentosa reticularis: a report of a family demonstrating autosomal dominant inheritance. J Am Acad Dermatol. 1992;26:298–301.
39. Partington MW, Marriott PJ, Prentice RS, et al. Familial cutaneous amyloidosis with systemic manifestations in males. Am J Med Genet. 1981;10:65–75.
40. Ades LC, Rogers M, Sillence DO. An X-linked reticulate pigmentary disorder with systemic manifestations: report of a second family. Pediatr Dermatol. 1993;10:344–351.
41. Anderson RC, Zinn AR, Kim J, Carder KR. X-linked reticulate pigmentary disorder with systemic manifestations: report of a third family and literature review. Pediatr Dermatol. 2005;2:122–126.
42. Fernandez-Guarino M, Torrelo A, Fernandez-Lorente M, et al. X-linked reticulate pigmentary disorder: report of a new family. Eur J Dermatol. 2008;18:102–103.
43. Betz RC, Planko L, Eigelshoven S, et al. Loss-of-function mutations in the keratin 5 gene lead to Dowling-Degos disease. Am J Hum Genet. 2006;78:510–519.
44. Kim YC, Davis MD, Schanbacher CF, Su WP. Dowling-Degos disease (reticulate pigmented anomaly of the flexures): a clinical and histopathologic study of 6 cases. J Am Acad Dermatol. 1999;40:462–467.
45. Hanneken S, Rütten A, Pasternack SM, et al. Systematic mutation screening of *KRT5* supports the hypothesis that Galli-Galli disease is a variant of Dowling-Degos disease. Br J Dermatol. 2010;163:197–200.
46. Wenzel G, Petrow W, Tappe K, et al. Treatment of Dowling-Degos disease with Er:YAG-laser: results after 2.5 years. Dermatol Surg. 2003;29:1161–1162.
47. Oyama M, Shimizu H, Ohata Y, et al. Dyschromatosis symmetrica hereditaria (reticulate acropigmentation of Dohi): report of a Japanese family with the condition and a literature review of 185 cases. Br J Dermatol. 1999;140:491–496.
48. Miyamura Y, Suzuki T, Kono M, et al. Mutations of the RNA-specific adenosine deaminase gene (*DSRAD*) are involved in dyschromatosis symmetrica hereditaria. Am J Hum Genet. 2003;73:693–699.
49. Gao M, Wang PG, Yang S, et al. Two frameshift mutations in the RNA-specific adenosine deaminase gene associated with dyschromatosis symmetrica hereditaria. Arch Dermatol. 2005;141:193–196.
50. Chao SC, Huang CY, Yang MH. A novel nonsense mutation of the *DSRAD* gene in a Taiwanese family with dyschromatosis symmetrica hereditaria. Eur J Dermatol. 2006;16:449–450.
51. Amyere M, Vogt T, Hoo J, et al. *KITLG* mutations cause familial progressive hyper- and hypopigmentation. J Invest Dermatol. 2011;131:1234–1239.
52. Urabe K, Hori Y. Dyschromatosis. Semin Cutan Med Surg. 1997;16:81–85.
53. Al Hawsawi K, Al Aboud K, Ramesh V, Al Aboud D. Dyschromatosis universalis hereditaria: report of a case and review of the literature. Pediatr Dermatol. 2002;19:523–526.
54. Rongioletti F, Rebora A. Acquired brachial cutaneous dyschromatosis: a common pigmentary disorder of the arm in middle-aged women. J Am Acad Dermatol. 2000;42:680–684.

Biology of Hair and Nails 68



David de Berker, Claire A Higgins, Colin Jahoda and Angela M Christiano

Key features

- The pilosebaceous unit and nail apparatus are epidermal derivatives that produce two of the hardest epithelial structures known in mammalian biology
- The hair follicle is the only continuously regenerating organ in the mammalian body
- Hair and nails serve multiple functions, including protection, sensation and social communication
- Hair shafts and nail plates largely consist of dead, terminally differentiated keratinocytes (trichocytes and onychocytes) whose durability is based on the presence of abundant keratin intermediate filaments
- While hairs grow in a cyclic fashion, nail production is continuous
- The hair cycle includes phases of growth (anagen), regression (catagen), resting (telogen) and hair shaft shedding (exogen)
- The hair follicle is a major reservoir for epithelial and melanocyte stem cells; it also represents a site of immune privilege
- The nail apparatus consists of the nail plate (a fully cornified structure) and other specialized epithelial tissues, including the nail matrix (which produces the nail plate), nail bed and nail folds (proximal and lateral)

PRINCIPLES OF APPENDAGE MORPHOGENESIS

In mammals, the development of skin appendages occurs through evolutionarily conserved mechanisms. In all cases, appendages form as a result of interactions between two adjacent tissue layers, the ectoderm (epidermis) and underlying mesoderm (dermis). Appendage morphogenesis is characterized by key inductive events that ultimately lead to formation of the final structure, whether it be a hair, nail, feather, mammary gland or (in oral mucosa) tooth (Fig. 68.1). For example, the hair follicle first arises as a small epithelial bud, subsequently progressing to a complex, multi-cylindrical structure with associated sebaceous and apocrine glands (Fig. 68.2).

The basic principles of appendage development were generated from a series of classic homo- and heterospecific tissue recombination experiments performed in the 1970s, which have served as the foundation for research in this field[1,2]. These experiments demonstrated that the initial "message" for the development of all types of skin appendages is from the dermal mesenchyme (stage 0), which does not itself change morphologically but rather signals the overlying epithelium to thicken and form a placode (stage 1) (Fig. 68.3). The type of appendage that develops is determined within the epidermis. Canonical (β-catenin-dependent) WNT (*w*ingless-type *int*egration site) signals are candidates for the dermal message, and it is thought that they precede other activators and regulators of appendage development[3].

BIOLOGY OF HAIR

Hair Follicle Morphogenesis

WNT signaling plays key roles in hair follicle development. In mice, lack of WNT signaling through overexpression of the WNT inhibitor Dickkopf homolog 1 (DKK1) prevents hair follicle formation[3], while overexpression of β-catenin (which acts downstream of WNT; see Fig. 55.8) in the epidermis converts interfollicular epidermis to a placode fate[4]. Loss-of-function mutations in the *WNT10A* gene, which encodes an activator of WNT signaling, cause autosomal recessive forms of ectodermal dysplasia in humans, including odonto-onycho-dermal dysplasia and Schöpf–Schulz–Passarge syndrome (see Ch. 63). The spectrum of cutaneous findings that can result from *WNT10A* mutations includes hypotrichosis, nail dystrophy, palmoplantar keratoderma with eccrine syringofibroadenomatosis, and apocrine hidrocystomas[5]. In addition, heterozygous missense mutations in the adenomatosis polyposis coli down-regulated 1 gene (*APCDD1*) can cause hereditary hypotrichosis simplex, which manifests with progressive, generalized hair loss and thinning of the hair shaft (miniaturization). The APCDD1 protein normally inhibits WNT/β-catenin signaling by binding to WNT and low-density lipoprotein receptor-related proteins (LRPs) upstream of β-catenin (see Fig. 55.8), and mutations in APCDD1 lead to dysregulation of this pathway[6].

In normal mouse hair follicle development, WNT and β-catenin expression is observed in the presumptive placode following the initial dermal signal. This directly increases transcription of the ectodysplasin A receptor gene (*Edar*), which leads to augmented nuclear factor-κB (NF-κB) signaling[7]. Expression of EDAR within the primary follicle placode also suppresses placode inhibitory signals from the surrounding epidermis, which refines WNT/β-catenin expression within the placode. A reaction-diffusion mechanism involving WNT and DKK signaling within the epidermis is believed to modulate hair follicle spacing, with competing gradients of placode-promoting (WNT) and placode-inhibiting (DKK) morphogens[8,9]. These gradients demarcate the placode border and establish regular intervals between follicles.

After the determination of placode fate, reciprocal signaling cascades between the mesenchyme and overlying epithelium continue to drive hair follicle morphogenesis. This communication results from a complex interplay among secreted signaling molecules, which include WNT and NF-κB pathway components and other proteins (see Fig.

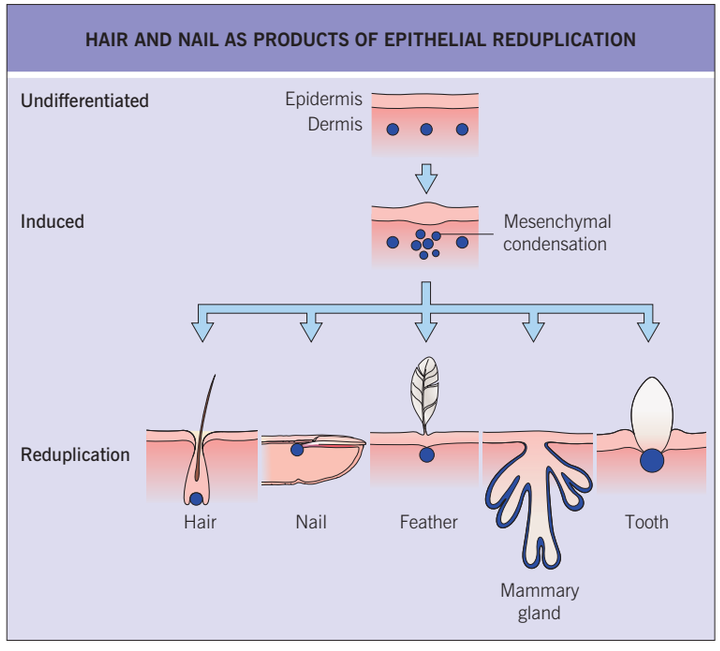


Fig. 68.1 Hair and nail as products of epithelial reduplication. *Reproduced with permission from: Chuong C-M. Morphogenesis of epithelial appendages: variations on top of a common theme and implications in regeneration. In: Chuong C-M, ed. Molecular Basis of Epithelial Appendage Morphogenesis. Austin: R.G. Landes Company, 1998:3–13.*

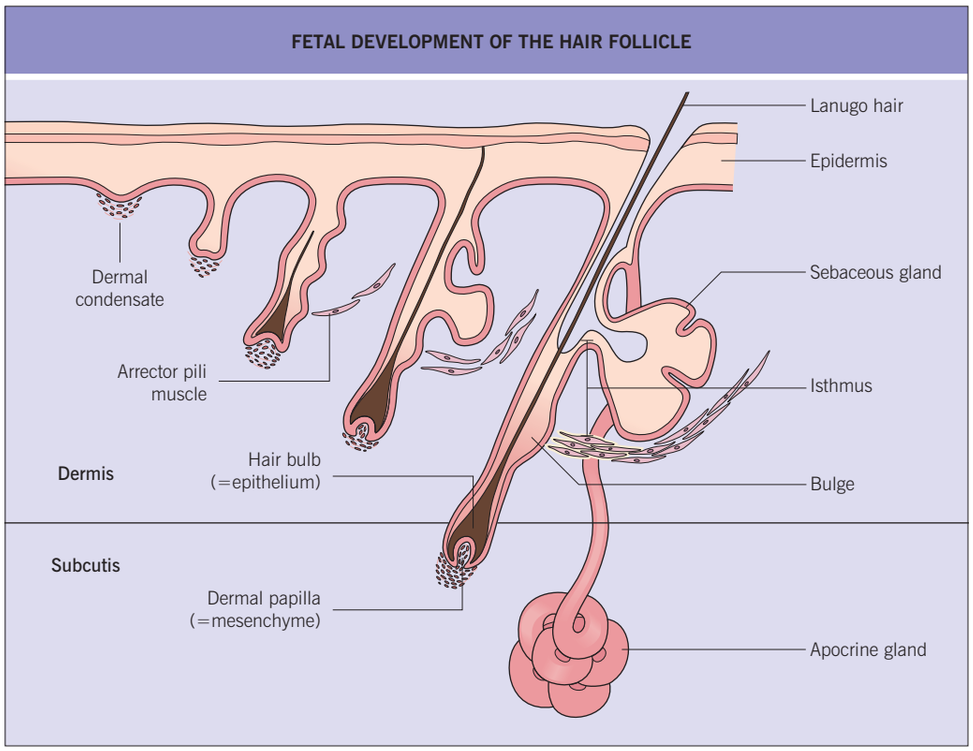


Fig. 68.2 Fetal development of the hair follicle.

68.3). After placode formation, an epithelial signal leads to clustering of the underlying mesenchyme and formation of a dermal condensate. A second dermal signal then leads to proliferation of the epidermis and epidermal invasion of the dermis by a column of epithelial cells that forms the hair germ (stage 2), followed by the hair peg (stage 3–4) and subsequently the bulbous peg (stage 5–8) (see Fig. 68.3)[10]. In the placode stage, activated WNT and EDAR control the localized accumulation of sonic hedgehog (SHH), which is essential for the downgrowth of the hair germ[11]. Primary cilia located on dermal cells within the condensate coordinate the signaling activities of SHH. In mice that lack SHH or have abnormal cilia assembly, the dermal condensate forms but subsequent proliferation and downgrowth of the epithelium are arrested[12,13]. Hemidesmosomal integrins also have a physical role in hair germ invagination, and mice with deficient β1 or β4 integrins have evaginated hair germs that cannot physically move downward into the dermis[14,15]. In addition, there is evidence that microRNAs have important roles in skin and hair follicle development. For example, mice with ablation of Dicer, a microRNA processing enzyme, display evagination of the hair germ but (since hemidesmosomes are intact) no physical severing of the papilla–hair germ interface[16].

During normal follicle invagination, the mesenchymal condensate is progressively engulfed by the epidermal cells, and it eventually becomes the enclosed dermal papilla of the follicle. Although epithelial growth is initially downward, it reverses in response to WNT and bone morphogenic protein (BMP) signaling from the newly formed dermal papilla. As a result, the overlying matrix in the hair bulb initiates a program of upward differentiation, giving rise to the layers of the hair shaft and inner root sheath. Epithelial cell fate depends upon the relative position of a matrix cell with respect to the dermal papilla, resulting in production of the concentric layers of the hair follicle[17]. An early effector of this signaling within the matrix is the distal-less homeobox 3 (DLX3) transcription factor, which directly regulates the expression of hair keratin genes in the hair shaft and inner root sheath[18]. A dominant frameshift mutation in the *DLX3* gene results in tricho-dento-osseous syndrome[19], a form of ectodermal dysplasia that features defects in hair, teeth and bone.

The generation of mouse models has increased our understanding of hair biology and facilitated the identification of genes that are expressed in the hair follicle[20]. Mutations in many of these genes have been found to underlie human diseases, including non-syndromic hair disorders and syndromes with manifestations that involve other skin appendages and/or extracutaneous tissues (see Table 69.7). Determining how these genetic defects lead to specific disease phenotypes has helped to elucidate the function of the encoded proteins in normal hair follicle morphogenesis and cycling.

Complex neural networks develop in conjunction with hair follicle morphogenesis. Nerve fibers arrive at the skin first and are located at presumptive follicular sites, running parallel to a dense network of blood vessels (Fig. 68.4). Developing follicles become innervated around stage 5, with nerve fibers encircling the isthmus and bulge regions[21]. Neurotrophins released from the follicular epithelium stimulate and determine the density of the innervation. Similarly, signaling proteins that promote angiogenesis, such as vascular endothelial growth factor (VEGF), are released from the epithelium and increase the vascular network surrounding follicles[22].

Hair follicle patterning

Although the basic architectural principles are similar in all hair follicles and shafts, different types of hairs can be produced in a single organism. In the dorsal skin of mice, hair follicle development occurs in three successive waves: (1) large, straight primary (guard or tylotrich) hairs, which comprise 1–3% of total hairs and have two sebaceous glands, on embryonic day 14.5; (2) secondary awl (straight, comprise ~30% of the coat) and auchene (one bend, only 0.1% of the coat) hairs on day 16.5; and (3) tertiary (zigzag) hairs, which account for ~70% of the coat and have several bends, on day 18.5. The mouse coat therefore contains four distinct hair types, in addition to specialized hairs such as the vibrissae (whiskers) and tail hairs[23]. EDAR is necessary for placode development in primary hair follicles[24] but not for induction of secondary hair follicles, which utilize signaling pathways that involve Noggin and (SRY-box 18) SOX18 expression within the dermal papillae[25,26]. In humans, hypohidrotic ectodermal dysplasia with abnormal morphogenesis of scalp hair, sweat glands and teeth results from mutations in the genes encoding components of the EDAR/NF-κB signaling pathway, including EDAR, its ligand ectodysplasin A and the downstream effector EDAR-associated death domain[27]. In addition, a non-synonymous single nucleotide polymorphism (SNP) within the *EDAR* gene is associated with increased hair thickness in Asian populations[28]. These clinical observations underscore the importance of the EDAR/NF-κB signaling pathway in human appendage development. However, whether EDAR affects the patterning of human hair follicles is not yet known. Interestingly, mutations in the human *SOX18* gene cause lymphedema and telangiectasias as well as hypotrichosis[29].

All of the hairs of the mouse dorsal coat have anterior–posterior polarity along the body axis, and they are formed parallel to one another to form a sleek coat. Several proteins, including SHH and neural cell

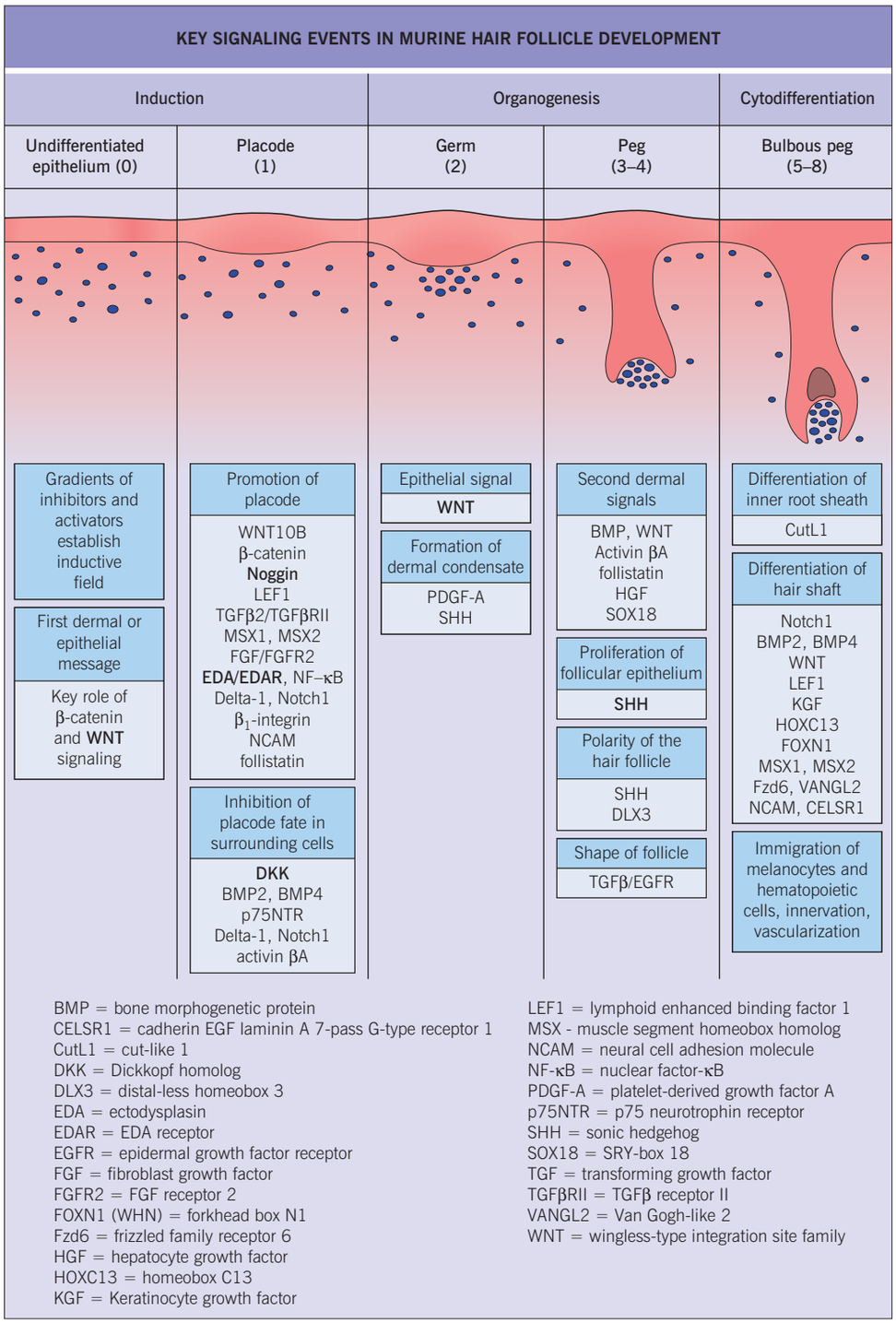


Fig. 68.3 Key signaling events in murine hair follicle development. *Adapted from Millar SE. Molecular mechanisms regulating hair follicle development. J Invest Dermatol. 2002;118:216–25.*

adhesion molecule (NCAM), have an asymmetric distribution within the follicle. This pattern is established by a conserved planar cell polarity (PCP) pathway during hair germ development[30]. PCP proteins Van Gogh-like 2 (VANGL2) and cadherin epidermal growth factor laminin A seven-pass G-type receptor 1 (CELSR1) respond to directional cues and are necessary for the correct polarization of follicles within the skin[30,31]. Mutations in *Vangl2* or the frizzled family receptor 6 (*Fzd6*) affect the early global alignment of hair follicles, resulting in hair germs that initially grow directly down. However, over time the follicles reorient themselves in competing patterns, with local alignment producing characteristic whorls on the back of the mouse[32,33]. Hair whorls are frequently observed in mammals, such as on the occipital scalp in humans, between the eyes in horses and cattle, and on the upper chest in dogs[32].

Under physiologic conditions, human hair follicle morphogenesis occurs only once. Lanugo, vellus and terminal hairs (Table 68.1) follow the same basic architectural principles. The first "coat" that is formed is fine, long, variably pigmented lanugo hair, which is shed in an anterior to posterior wave during the seventh and eighth months of gestation. A second coat of fine, shorter, unpigmented lanugo hair then grows in all areas except the scalp and is shed 3–4 months after birth, leading to almost complete alopecia on the body; pigmented hairs on the scalp (which have variable lengths and diameters) are also shed postnatally in an anterior to posterior wave. After these first two cycles, hair starts to grow in an asynchronous "mosaic" pattern rather than in waves. In prepubertal children, hair is typically terminal on the scalp, eyelashes and eyebrows, while it is vellus on the face, trunk and extremities. During puberty, vellus hairs in some sites come under the influence of androgens and start to enlarge, becoming terminal hairs. Conversely, terminal hairs on the scalp can revert to miniaturized vellus-like hairs in postpubertal individuals with androgenetic alopecia. Congenital generalized hypertrichosis (Ambras syndrome) is characterized by a disruption in the patterning of hairs, with terminal hairs growing at sites that normally have

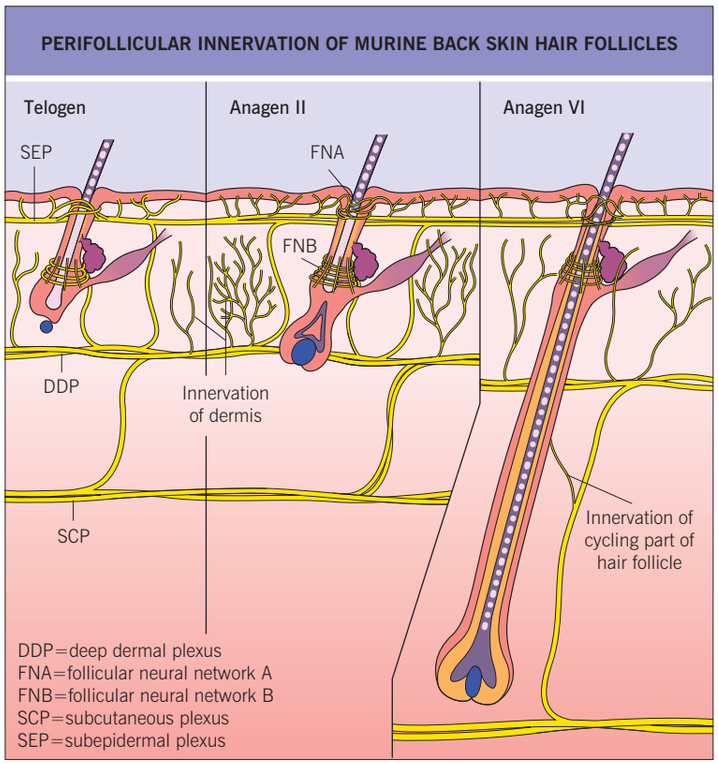


Fig. 68.4 Perifollicular innervation of murine back skin hair follicles. *Adapted from Paus R, Peters EM, Eichmüller S, Botchkarev VA. Neural mechanisms of hair growth control. J Invest Dermatol Symp Proc. 1997;2:61–8.*

vellus follicles[34]. Recently, a position effect that down-regulates the expression of the trichorhinophalangeal syndrome I gene (*TRPS1*) was found to underlie this hypertrichosis phenotype in both humans and mice[35]. A position effect caused by copy number variations affecting the transcription factor SOX9 has been linked to hypertrichosis with or without gingival hyperplasia[36].

In most mammals, there are differences in the hair pattern in different body sites, for example on dorsal skin, ventral skin and the face. While the ectoderm involved in skin and hair development is non-neural and relatively homogeneous, the mesenchyme has various origins that may explain the regionalization of different hair types. The dorsal dermis is derived from the somite dermomyotome, the ventral dermis has a somatopleural origin, and the craniofacial dermis arises from the neural crest[37–39]. The dermal progenitors at each of these sites are specified by different signaling pathways. Mice display regional differences in skin thickness as well as hair color and type. The postnatal identity of their skin is acquired by embryonic day 12.5, with the T-box 15 (TBX15) transcription factor appearing within dorsal skin to demarcate the dorsal ventral boundary[40].

In humans, androgen dependence is a feature that varies in the follicles at different body sites. Follicles in the frontal scalp are normally androgen-dependent, whereas occipital scalp follicles are hormonally insensitive and therefore less susceptible to androgenetic alopecia. When hair follicles from the occipital scalp are transplanted to the frontal scalp, they typically retain the pigmentary characteristics, androgen sensitivity and growth rate of the donor site[41]. However, in other instances, transplanted hairs take on characteristics of the recipient site, such as scalp hairs moved into the eyebrow region. It remains to be established exactly which characteristics are more influenced by the recipient site versus the donor site following transplantation.

Postnatal hair follicle development

Although hair follicle formation in general occurs prior to birth, adult mammalian skin retains the capacity for hair follicle morphogenesis. In adult mouse and rabbit skin, WNT-dependent *de novo* hair follicle formation occurs after wounding[42,43]. It is therefore reasonable to view therapeutic intervention to initiate *de novo* hair follicle formation on the human scalp as an achievable goal. Trans-species end-bulb formation and hair fiber growth has been demonstrated after the implantation of intact dermal papillae from human donors onto amputated vibrissa follicles[44]. In addition, allogeneic transplantation of hair follicle dermal sheath tissue can induce new follicle formation in the recipient, with protection from rejection due to its immune privileged status[45]. In addition to hair papillae transplants, cultured tooth mesenchymal papilla cells from humans and rats have been shown to induce hair fiber formation in an amputated follicle, highlighting the level of conservation among appendage papillae[46]. Papilla cells in rodents show much more inductive potency than those in humans. Rodent hair follicle papilla cells can reprogram differentiated glabrous epidermis to make a *de novo* hair follicle, and they are also capable of initiating trans-differentiation of amnion or even differentiated adult corneal epithelium into epidermis complete with hair follicles[47–49]. This represents a classic example of simple epithelial reprogramming, which was recently demonstrated in a broader context by the reprogramming of thymic epithelium into skin and hair follicles[50].

The Mature Hair Follicle: Cycling and Anatomy

Once the mature follicle is generated during embryogenesis and early postnatal life, it begins to cycle and continues to do so throughout its lifetime. The phases of the hair cycle include active growth (anagen), regression (catagen) and rest (telogen) (Fig. 68.5). As noted above, mouse follicles cycle in a wave along the anterior to posterior axis, while human follicles cycle in a mosaic pattern. Hair follicle cycling is an autonomous phenomenon that continues even when hair follicle units are isolated from the skin to grow in culture[51]. Distinct morphologic changes occur as the follicle transitions through the different stages of the hair cycle. The lower portion of the follicle undergoes growth and regression, while the upper region of the follicle (including the sebaceous gland, isthmus, infundibulum and hair canal) remains permanent.

The process of cycling makes the hair follicle a dynamic structure, enabling animals to change their coats depending on the season (e.g. for camouflage and insulation; Table 68.2) and for the lengths of hairs to vary depending on the site. Coat changes involve two processes: (1) shedding of the old coat, which (inclusive of signals and structural changes preceding fiber loss) has been referred to as a fourth stage of the hair cycle termed "exogen"; and (2) initiation of the new hair fiber growth[52]. Another term that has been introduced is "kenogen", which refers to a telogen follicle that has lost its club fiber but has not yet transitioned to anagen. Androgenetic alopecia is characterized by an increased proportion of follicles in kenogen[53].

Anagen

The duration of anagen, the period of active hair fiber production, depends on the species, body site and other factors (Table 68.3). Anagen is subdivided into six substages (anagen I–VI); in mice it has a duration of 1–3 weeks[54], compared to the human scalp where anagen can last several years[55]. The start of anagen (as observed in mouse skin) is associated with an increase in the dermal papilla cell number, due mainly to an influx of cells from the surrounding dermal sheath. The cells of the dermal sheath that surround the base of the follicle are also progenitors in dermal papilla regeneration after removal of the lower follicle[56,57]. The increase in cell number at the start of anagen is accompanied by an increase in extracellular matrix material. This doubles the size of the dermal papilla[58], the width of which is directly proportional to the thickness of the hair shaft produced by the follicle. The degree of axial symmetry within the hair bulb determines the curvature of the final hair structure[59].

The dermal papilla signals to the surrounding matrix cells, whose proximity to the dermal papilla specifies their fate[17]. As the matrix cells begin to differentiate, they form precursor cells of the different follicle lineages. Migrating upwards, these cells undergo specialized programs of differentiation, expressing defined sets of keratins to form seven concentric epithelial lineages of the follicle (Fig. 68.6). The outer root sheath is the outermost layer of the epidermal portion of the follicle. In contrast to the other epithelial components of the follicle, the outer root sheath does not originate from upward growth of matrix cells, but rather directly from the bulge, a stem cell niche in the permanent portion of the follicle (see below)[60].

Catagen

Following completion of hair fiber growth, the follicle enters catagen, which is divided into eight substages (catagen I–VIII) that take the

TRICHOLOGY TERMS	
Hair (follicle) cycle	Autonomous, rhythmic transformation of fully developed hair follicles through phases of growth, regression and resting; essentially controlled by the follicle itself (by an as yet enigmatic "hair cycle clock"), yet modulated by numerous systemic/extrafollicular factors
Anagen	Growth stage of the hair follicle cycle
Catagen	Involution of the lower two-thirds of the hair follicle by massive keratinocyte apoptosis
Telogen	Resting phase of the hair follicle cycle
Exogen	Phase of active hair shaft shedding (during anagen IV)
Kenogen	Telogen follicle with no club hair present
Hair bulb	Lowermost portion of the hair follicle
Hair matrix	Rapidly proliferating keratinocytes that terminally differentiate to produce the hair shaft
Club hair	Fully keratinized proximal tip of hair shaft, formed during late catagen and telogen; brush-like appearance; characteristic of telogen follicles
Vellus hair (follicle)	Very short, non-pigmented, and usually non-medullated; absence of arrector pili muscle; tiny vellus follicles can display extremely large sebaceous glands (face); undergo full hair cycle, yet much shorter than terminal hair
Terminal hair	Large, usually pigmented and medullated hair
Lanugo hair	Fine hair on the fetal body; shed *in utero* or during the first weeks of life
Vibrissae	Special sensory hair follicles with unique anatomy and biology, found on the upper lips/snout region of rodent skin, but not in humans; largest and most densely innervated hair follicles with special sinusoid blood supply; first hair follicles to develop
Tylotrich hair follicle	Large sensory hair follicles interspersed within truncal skin, most notably in rodents; extra large, long hair shaft, typically associated with double sebaceous gland and an innervated epidermal Merkel cell complex (Pinkus' Haarscheibe); second type of hair follicle to develop
Non-tylotrich pelage hair	Majority of all hair follicles, last to develop
Effluvium	Excessive shedding of hair shafts (=process)
Alopecia	Abnormal hair loss (=result)
Hirsutism	Excessive vellus-to-terminal hair conversion in androgen-dependent areas in women
Miniaturization	Terminal-to-vellus hair conversion (e.g. on the balding scalp during androgenetic alopecia); these miniaturized follicles still have an arrector pili muscle (unlike true vellus hairs)
Infundibulum of follicle	Region extending from the junction with the interfollicular epidermis to the opening of the sebaceous gland; displays cornification similar to that of the interfollicular epidermis
Isthmus of follicle	Region located between the opening of the sebaceous gland and the site of insertion of the arrector pili muscle; displays trichilemmal keratinization
Arrector pili muscle	Inserts at the level of the bulge; pulls up hair ("goose bumps")
Bulge	Segment of the outer root sheath located at the level of arrector pili muscle insertion; major seat of epithelial stem cells of the hair follicle
Secondary hair germ	Additional seat of epithelial and also of melanocyte stem cells; located between club hair and dermal papilla in telogen hair follicle
Connective tissue sheath (CTS)	Special mesenchymal follicular sheath that is tightly attached to the hair follicle basement membrane and is continuous with the follicular dermal papilla
Follicular dermal papilla (DP)	Onion-shaped, closely packed, specialized fibroblast population with inductive and morphogenic properties; hair cycle-dependent fibroblast trafficking occurs between CTS and DP; volume of DP determines size of hair bulb and, thus, hair shaft diameter
Inner root sheath (IRS)	Packages and guides the hair shaft; cornifies
Outer root sheath (ORS)	Merges distally into the epidermis and proximally into the hair bulb; provides slippage plane, nutrition, regulatory molecules, and stem cells
Follicle pigmentary unit	Melanin-producing hair follicle melanocytes located above and around the upper one-third of the DP; transfer eu- or pheomelanosomes to differentiating hair follicle keratinocytes in the precortical matrix; goes largely into apoptosis during each catagen phase, regenerated from melanocyte stem cells in hair germ (and from non-melanogenic ORS melanocytes?) during anagen

Table 68.1 Trichology terms. *Courtesy, John P Sundberg, DVM, PhD.*

follicle from late anagen to telogen[61]. Catagen lasts approximately 2 weeks in humans, regardless of the site and follicle type[62]. The initiation of catagen is characterized by a nearly 50% reduction in the volume of the dermal papilla, due to loss of extracellular matrix as well as migration of dermal papilla cells into the surrounding dermal sheath[58]. Melanocytes in the hair bulb also begin to down-regulate melanogenesis. Later, there is cessation of mitotic activity within the matrix cells of the bulb, and the remaining hair precursor cells differentiate to form the base of the hair shaft, now termed the "club fiber".

The club fiber migrates up the follicle, and a germ capsule termed the trichilemmal sac forms around the fiber's base. The club fiber itself is formed from cortical and cuticle cells only, and it is characterized by a lack of pigmentation. The electron-dense, non-nucleated layer of trichilemmal keratin around its proximal end has a characteristic "brush" structure that protrudes outwards and between the outer root sheath cells surrounding the club[63]. Abundant desmosomes between the trichilemmal keratin and surrounding tissue are thought to physically anchor the club fiber within its trichilemmal sac until it receives the correct signal for release[64].

As the club fiber moves up the follicle, the dermal papilla (which is initially still in the subcutaneous fat) becomes separated from the club by an epithelial strand that is surrounded by a thickened, convoluted basement membrane (the glassy membrane)[65]. Apoptosis in the epithelial strand creates an "apoptotic force" that draws the dermal papilla up to just beneath the club fiber in the dermis, leaving behind a trailing dermal sheath called the streamer or stele[52]. Loss-of-function mutations in the hairless gene (*HR*) can result in atrichia with papular lesions (APL)[66,67], a rare autosomal recessive disease characterized by complete hair loss early in life and later eruption of papular lesions. Hairless is required for apoptosis in the epithelial strand, which brings the dermal papilla up beneath the club fiber and secondary hair germ in a position to activate the start of the next anagen phase. This explains why individuals with APL are born with hair, which is then lost and never grows back. More recently, activating mutations in the

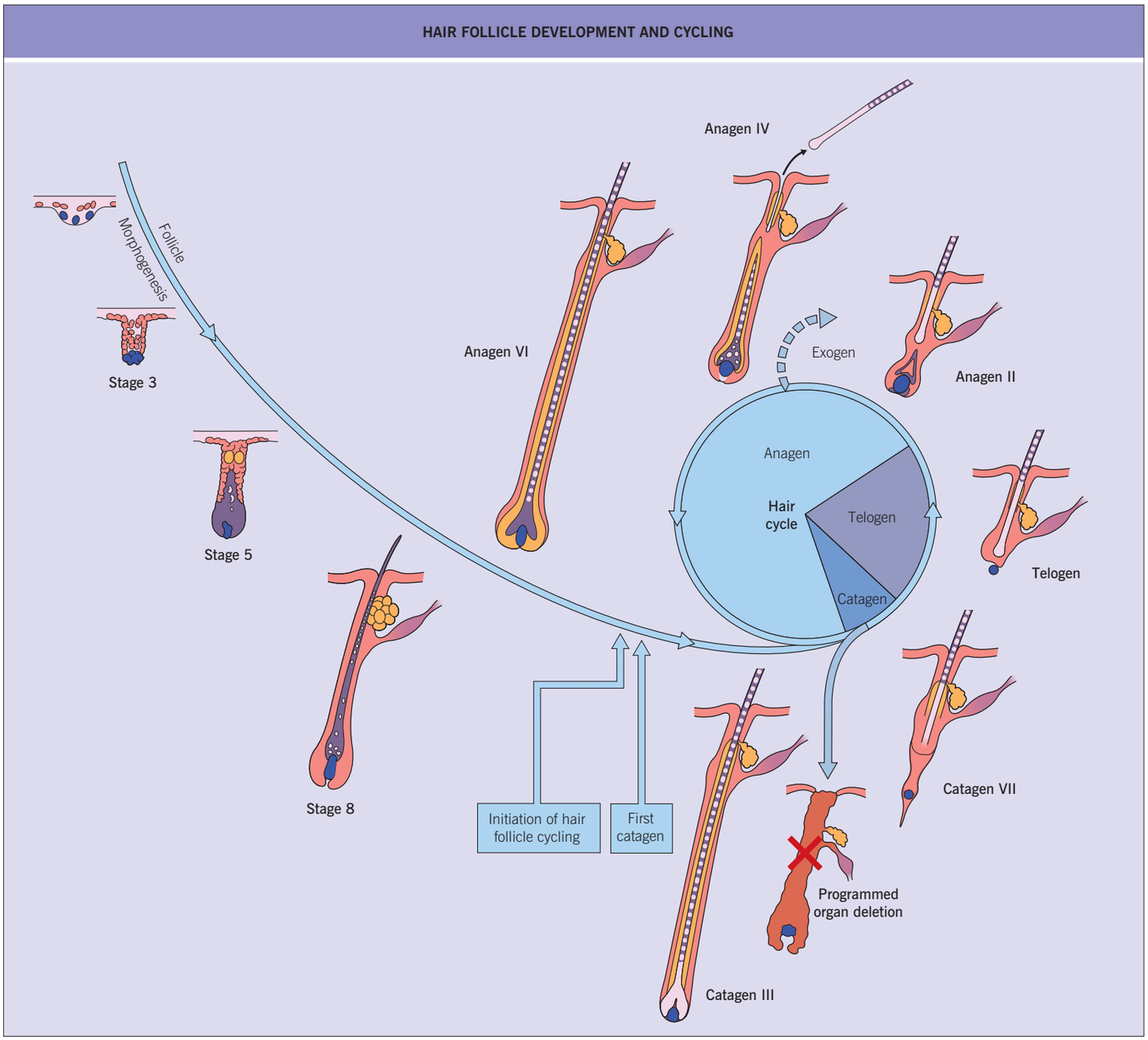


Fig. 68.5 **Hair follicle development and cycling.**

upstream open reading frame of *HR* were found to underlie a different form of sparse hair known as Marie Unna hypotrichosis[68].

Telogen

Once apoptosis in the epithelial strand draws the dermal papilla upward so it is adjacent to the club fiber and secondary hair germ, the follicle has entered telogen. The duration of telogen can be as short as 2 days in mice, compared to approximately 3 months for human scalp hairs. The hair germ is derived from the bulge during the catagen to telogen transition and lies adjacent to it, separating the bulge from the dermal papilla[69]. As in hair follicle morphogenesis, epithelial–mesenchymal cross-talk is required to activate the new anagen phase. Indeed, anagen progression recapitulates the middle and later stages of hair follicle development, and many factors that drive follicle morphogenesis (e.g. WNT, SHH, noggin) also play important roles in telogen to anagen transition (Fig. 68.7). The bulge is relatively quiescent during telogen, which is often referred to as the resting phase. However, the hair germ (which is biochemically distinct from the bulge) is responsive to anagen-initiating signals from the dermal papilla and starts to show enhanced proliferative and transcriptional activity in late telogen, leading to the initiation of anagen[69].

The macro-environment surrounding the hair follicle also takes part in regulating cycle transitions. BMPs in the subcutaneous fat are capable of maintaining follicles in a "refractory" telogen, and cessation of this inhibitory activity by BMPs enables the follicle to progress to a "competent" telogen with a hair germ that is responsive to anagen-initiation signals and capable of entering a new anagen phase[70]. Fluctuations of microRNA levels (e.g. microRNA-31) in the follicle and its macro-environment may also silence certain gene expression patterns, promoting a switch from telogen to anagen[71]. After secondary hair germ activation, the germ cells begin to contribute to the hair matrix and concentric layers of the follicle via an upward movement, while bulge cells generate the outer root sheath in a downward movement[72]. In follicles with a longer anagen duration, the proliferative capacity of the matrix is not enough to sustain growth. The "stem cell trafficking theory" proposes that a continuous migration of precursor cells from the bulge down the outer root sheath prevents exhaustion of the germinative matrix during anagen[73].

FUNCTIONS OF HAIR AND NAILS
FUNCTIONAL PROPERTIES OF HAIR SHAFTS
• Social and sexual communication • Camouflage • Protection against chemical and physical damage • Protection against insects • Provide sensory "antennae" • Insulation against heat loss, overheating and desiccation • Removal from the skin surface of parasites, dirt, debris and squames by the outward-moving hair shaft • Facilitation of sebum, apocrine sweat and pheromone secretion • Organ of scavenging and excretion via the melanized hair shaft, which serves to deposit and extradite unwanted molecules • Hair shaft medulla can serve as a fiber-optic device for conversion of UV light into heat (polar bear)
FUNCTIONAL PROPERTIES OF PILOSEBACEOUS UNITS
• Production, extrusion, containment and mooring of pigmented hair shafts • Crucial stem cell reservoir (e.g. for keratinocytes, melanocytes) • Reservoir for Langerhans cells • Highly sensitive tactile organs that sense hair shaft movements • Generate sebum, apocrine sweat and pheromones
FUNCTIONAL PROPERTIES OF NAILS
• Social and sexual communication (color, shape, length) and aesthetic appearance • Protection of the distal phalanges of the digits from mechanical, chemical and biological trauma • Contribute to the tactile discrimination and fine motor capacities of the fingertips • Provide the ability to scratch and groom • Rudimentary natural weapons • Contribute to pedal biomechanics essential for full motor functioning of the feet

Table 68.2 Functions of hair and nails. *Courtesy, John P Sundberg, DVM, PhD.*

Exogen

The stimulus for entry into catagen, and hence the formation of a club hair, typically occurs several months before the hair is shed in humans[74,75]. Shedding of overhair is loosely coupled with anagen in mouse pelage follicles[76], while club fiber release is a very predictable event in rat whisker follicles. In the latter instance, the club fiber is retained in its own silo through the following anagen and then cast off prior to the onset of catagen in a regulated manner[77]. In humans, the club fiber is not usually retained through subsequent anagens; instead, it is believed to be shed in the telogen to anagen transition. The term "exogen" was introduced into the literature in 1998 to represent the shedding of the club fiber from its silo as well as the preceding signals and structural changes in the follicle[52]. Exogen is considered to be an active event rather than a passive process where the club fiber is dislodged due to mechanical forces from the new growing fiber. A gradual decrease in the adhesion of the club fiber within its epithelial silo has been observed prior to its programmed release from the follicle[77].

Structure of the hair fiber

In response to signaling from the dermal papilla, the matrix cells at the base of the follicle proliferate and then differentiate during anagen, forming the different layers of the follicle. The three central lineages (medulla, cortex and hair cuticle) form the hair fiber, which fulfills the primary function of the anagen follicle – hair production. Surrounding the hair fiber are the three concentric layers that compose the inner root sheath (IRS): the IRS cuticle, Huxley's layer and Henle's layer. The IRS undergoes a complex program of differentiation in the anagen follicle, with Henle's layer terminally differentiating shortly after formation. The IRS cuticle differentiates further up the follicle, followed by Huxley's layer; all three layers undergo desmosomal remodeling during terminal differentiation[78]. The IRS forms a mechanically supportive tube around the hair fiber, but it is degraded by proteolytic enzymes within the follicle at the level of the isthmus[79], allowing the hair shaft to enter the hair canal and emerge from the skin surface without an associated IRS.

The seventh concentric layer that originates from the matrix in line with the hair fiber and IRS is the companion layer, which is a single cell thick. Regarded as the "slippage plane" between the inner root sheath and the surrounding outer root sheath during anagen, the companion layer enables directional hair growth. It is attached to the IRS through "Flugelzellen" structures that extend from Huxley's layer through Henle's layer and link to the companion layer via numerous desmosomes[80,81]. A "barrel" of transversely orientated intermediate filaments on the inner side of the companion layer are thought to provide support for the inner root sheath, protecting it from the compressive forces of the expanding outer root sheath.

Hair Keratins

The 54 functional keratin genes that have been identified to date (see Table 56.2) encode 28 type I and 26 type II keratins, which form heterodimeric pairs containing one keratin of each type. There are 11 type I hair keratins, designated K31–K40 (previously known as Ha1–Ha8, Ka35 and Ka36), and six type II hair keratins, designated K81–K86 (previously known as Hb1–Hb6) (see Ch. 56); the remainder are epithelial keratins[82–84]. Compared to epithelial keratins, hair keratins possess more sulfur in their head and tail domains, which allows them to form tight cross-links with associated proteins[85].

Different hair and epithelial keratins are expressed in the various concentric layers of the hair follicle, with hair keratins found primarily in the cortex and hair cuticle (see Fig. 56.6)[86]. Autosomal dominant monilethrix, which features fragile "beaded" hairs and follicular hyperkeratosis, is caused by mutations in the helix termination and initiation motifs of several type II hair keratins: K81, K86 and (less commonly) K83[87,88]. These keratins are highly expressed within the hair cortex and are critical to its development[87,88]. Mutations in the gene encoding K85, another type II hair keratin that is important for hair follicle development, underlie autosomal recessive pure hair and nail ectodermal dysplasia. K85 is primarily expressed in the matrix of the follicle, which may explain the relatively severe phenotype (total alopecia) observed in these patients[89,90].

Some epithelial keratins exhibit hair follicle specificity (Fig. 68.8). The type I keratins K25, K27 and K28 and the type II keratin K71 are expressed within the IRS (cuticle, Huxley's layer and Henle's layer). In addition, K74 is restricted to Huxley's layer, while K73 and K72 are found in the IRS cuticle[85,91]. Mutations in the gene encoding K71 (the only type II keratin expressed in Henle's layer) have been linked to hair disorders in mice and dogs but not yet in humans. However, mutations in the gene encoding K74 can cause autosomal dominant woolly hair, which is characterized by slowly growing, short hair that (unlike autosomal recessive forms of woolly hair) has a normal density[92]. To date, none of the type I hair or epithelial keratins have been linked to human disease.

The companion layer contains only one keratin, the type II epithelial K75. K75 is also expressed in the medulla of the hair shaft and in fungiform papillae of the tongue. Pseudofolliculitis barbae and loose anagen hair syndrome have been linked to defects in K75[82,85,93]. Although the outer root sheath expresses several keratins, including K5/K14, K6a/K16 and K6b/K17 (see Fig. 68.8), patients with pachyonychia congenita due to mutations in the latter keratin pairs only occasionally exhibit hair abnormalities such as pili torti (primarily with K17 defects)[94].

Desmosomes in the Hair Follicle

Desmosomes are specialized adhesive structures that couple neighboring cells together in a variety of tissues, with particular importance in epithelia and the myocardium[95,96]. Each desmosome is connected to the intermediate filament cytoskeletons of the interacting cells, which imparts resilience and resistance to mechanical stress (see Ch. 56). Desmogleins (Dsg1–4) and desmocollins (Dsc1–3) are desmosome-specific cadherin family members that interact in the intercellular space to couple the two halves of the desmosome; they are connected to intermediate filaments via the linker cytoplasmic plaque proteins plakoglobin, plakophilins (Pkp1–3) and desmoplakin (see Fig. 56.8)[97]. Mutations in genes encoding desmosomal components can result in diseases affecting the hair (woolly or fragile hair, hypotrichosis) as well as the skin (e.g. palmoplantar keratoderma, fragility/blistering) and heart (cardiomyopathy), producing multisystem disorders such as Naxos disease, Carvajal syndrome and ectodermal dysplasia/skin fragility syndrome (see Fig. 56.8 and Ch. 58).

BASIC INFORMATION ON HUMAN HAIR FOLLICLES	
Total number	~5 000 000 (mostly vellus)
Number of scalp hair follicles	~100 000 Blondes: + 20% Redheads: – 20%
Average density of hairs on the scalp	Terminal + vellus: 1135/cm^2 (newborn)* 615/cm^2 (20–30 years)* 485/cm^2 (30–50 years)* 435/cm^2 (70–80 years)* African-Americans, Asians: lower density Terminal only: ~250/cm^2 Bald scalp (45–70 years): 330/cm^2* Highest density: cheek + forehead*
Hair embryology	Development progresses at fixed intervals in cephalocaudal direction, becoming first visible in eyebrow, upper lip and chin regions (9th week) At 16 weeks, hair shafts are formed in these regions Hair follicles are formed in sequential waves of interspersed follicles
Hair cycle distribution for terminal scalp hair	Anagen: 85–90% Telogen: 10–15% Catagen: <1%
Duration of hair cycle phases	Anagen: 2–6 years Catagen: 2–3 weeks Telogen: 3 months } Terminal scalp hair There are substantial variations in anagen duration: Terminal mustache: 4–14 weeks Terminal on arms: 6–12 weeks Terminal on legs: 19–26 weeks Vellus: 6–12 weeks Premature anagen induction is induced by plucking of telogen hair shafts (depilation) Estrogens prolong anagen Thyroxine promotes growth, corticosteroids retard anagen onset
Number of lifetime cycles per scalp follicle	10–20
Physiologic hair shedding rate (scalp)	~100–200/day (substantial interindividual and seasonal variations)
Hair shaft production rate (scalp)	~0.35 mm/day, 1 cm/month Hair production is not influenced by cutting/shaving Estrogens reduce hair growth rate Androgens increase hair growth rate and hair diameter in androgen-dependent sites (e.g. beard)
Hair shaft diameter and length	Vellus: <0.03 mm; 1–2 mm Terminal: >0.06 mm; 1–50 cm Average diameter: Asian hair (circular): 120 µm Caucasian (elliptic): 50–90 µm
Hair shaft structures	Cuticle (outside), cortex, medulla (center) Cuticle maintains hair fiber integrity Cortex contains bulk of hair keratins and keratin-associated proteins Hair fiber strength is largely due to disulfide bonding Medulla consists of loosely connected trichocytes with large intercellular air spaces; provides insulation (animals)
Hair shaft pigmentation	Dark hair: predominance of eumelanin Blond/red hair: predominance of pheomelanin Melanosomes of hair cortex larger than those of epidermis
Hair graying (canities)	Generally commences in the third to fourth decade of life on the temples, spreading later to crown and occiput; by the age of 50 years, 50% of the population has at least 50% grey hair
Hair patterns	Pubic hair: horizontal (90% of women, 20% of men), acuminate (10% of women, 50% of men) Diffuse chest hair: normally grows only in men, after puberty (until 6th decade) Axillary: appears about 2 years after first pubic hairs, more sparse in Asians than Caucasians; frequently absent in older individuals Trichoglyphics: single, clockwise parietal whirl present in 95% of individuals

*Data from Giacometti L. The anatomy of the human scalp. In: Montagna W (ed). *Advances in Biology of Skin, Vol VI: Aging*. Oxford: Pergamon Press, 1965:97–120.

Table 68.3 Basic information on human hair follicles.

All four desmogleins are found in the hair follicle, with differentiation-specific expression patterns[98,99]. Dsg4 is the only desmosomal cadherin that is highly expressed in the hair shaft cortex, including the keratinizing zone in which hair keratins are abundant. Dsg4 is also present in the precortex, lower hair cuticle, upper IRS cuticle and interfollicular epidermis (granular and cornified layers)[98,100]. Several transcription factors (e.g. lymphoid enhancer-binding factor 1 [LEF1], homeobox C13 [HOXC13], forkhead box N1 [FOXN1]) regulate the expression of both Dsg4 and hair keratins in differentiating trichocytes[101]. Dsg4 is a key mediator of keratinocyte adhesion in the hair follicle, where it coordinates the transition from proliferation to differentiation[100]. Mutations in *DSG4* can cause localized autosomal recessive hypotrichosis and autosomal recessive monilethrix[100,102–104].

Although hair shedding and alopecia result when Dsg3 is disrupted in mice, showing its importance in the development and maintenance of the murine hair follicle[105,106], to date, similar hair phenotypes have

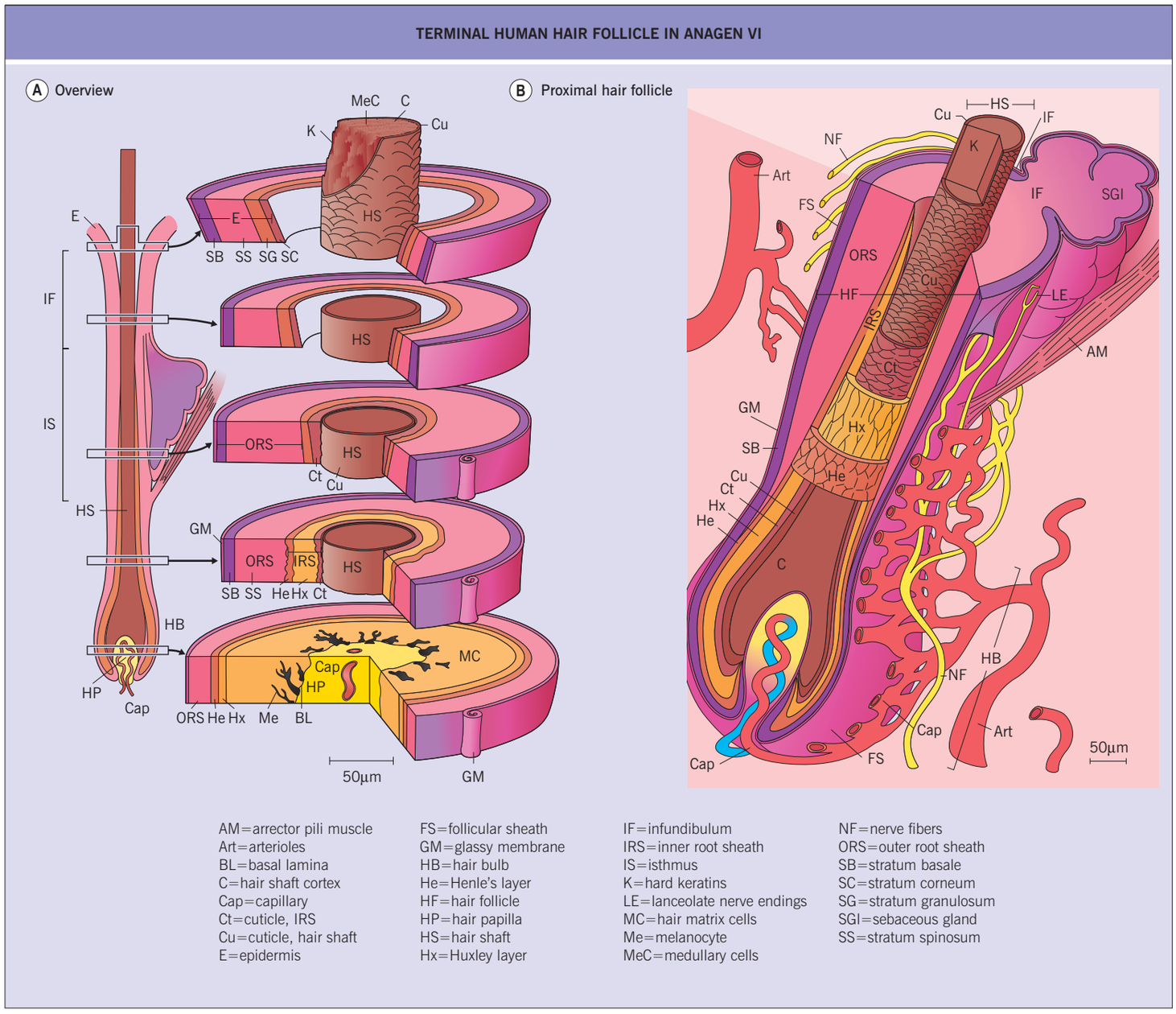


Fig. 68.6 Terminal human hair follicle in anagen VI. A Overview. **B** Proximal hair follicle.

not been identified in humans with Dsg3 defects. However, abnormal hair can represent the primary manifestation of mutations in the genes encoding Dsc3 (autosomal recessive hypotrichosis and recurrent skin "vesicles") and corneodesmosin (*CDSN*; autosomal dominant hypotrichosis simplex of the scalp)[107,108]. In addition, loss-of-function *CDSN* mutations underlie an autosomal recessive inflammatory peeling skin syndrome[109]. Corneodesmosin is a secreted glycoprotein that is present in later stages of differentiation of the IRS as well as within modified desmosomes in the stratum corneum (where its proteolysis has a role in desquamation)[110]. Similar to the observations in humans, *Cdsn*-knockout mice die soon after birth due to severe epidermal barrier defects[111], and grafting of corneodesmosin-deficient skin onto nude mice leads to the initial growth of thin, slightly curly hair with subsequent hair loss. These findings highlight the importance of corneodesmosin for hair growth and epidermal barrier function.

Hair Follicle Stem Cells

Adult stem cells have the ability to self-renew and to regenerate tissues, both in homeostasis and during wound repair. Given the dynamic remodeling seen with the cyclic regeneration of the hair follicle, it has long been postulated that it contains one or more stem cell niche(s) (see Ch. 2). Studies in the 1990s showed that slow-cycling, label-retaining cells (characteristics of stem cells) are localized in the bulge area of the follicle (named for the swelling evident at this site in rodents)[60].

Although the bulge architecture in mice is not pronounced until 3 weeks after birth, slow-cycling bulge cells can be identified during early stages of murine hair follicle morphogenesis by the marker SOX9[112]. During anagen in adult mouse skin, bulge stem cells express distinctive markers, including SOX9 as well as S100A4, CD34, transcription factor 3 (TCF3), LIM homeobox 2 (LHX2), nuclear factor of activated T cells calcineurin-dependent 1 (NFATc1), leucine-rich repeat-containing G-protein-coupled receptor 5 (LGR5), and keratin 15[113–117]. Bulge stem cells also share gene expression patterns with hematopoietic, neural and embryonic stem cells[117]. The molecular architecture of the bulge is not identical in mice and humans, and until relatively recently the location of the bulge in human follicles was unclear as it is not a morphologically distinct entity. However, laser capture microdissection and microarray-based analysis of human anagen hair follicles identified distinctive human bulge cells with clonogenic potential that express CD200 but (in contrast to bulge cells in mice) not CD34 (see Table 2.3)[118].

When follicles cycle through telogen in mice, a secondary hair germ is formed just above the dermal papilla but below the bulge. Bulge cell

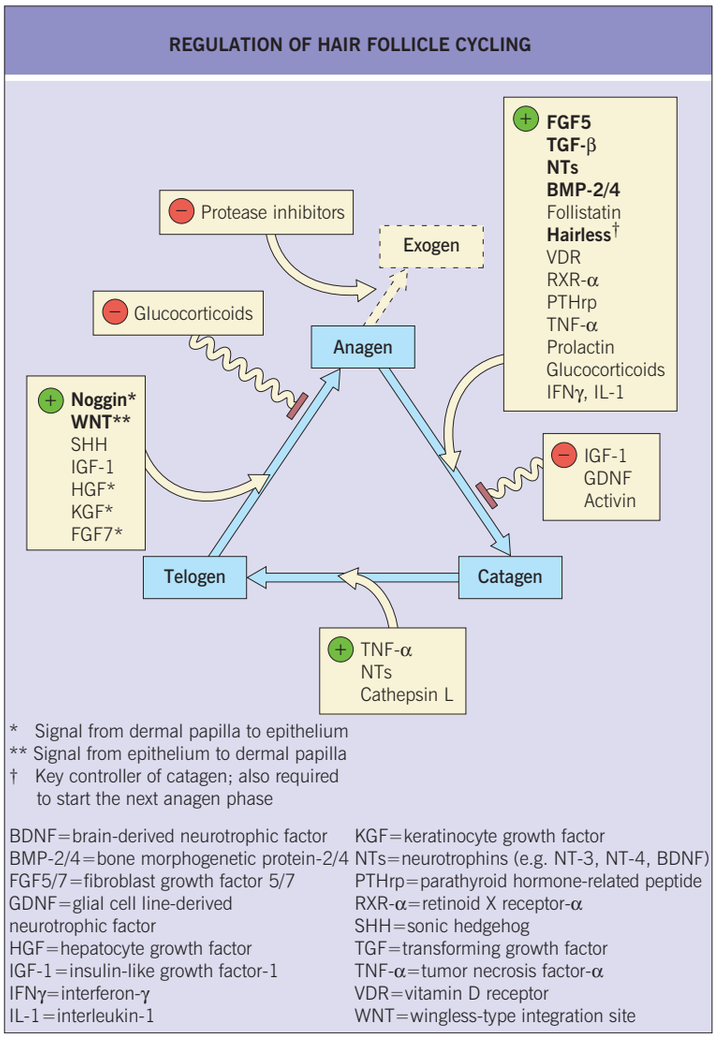


Fig. 68.7 Regulation of hair follicle cycling.

progeny that migrated out of the niche during the previous anagen (en route to becoming transit amplifying cells) are capable of migrating back again and regaining stem cell characteristics[119]. Some markers are expressed in both the secondary hair germ and the bulge, including keratin 15, LHX2, TCF3 and (at low levels) SOX9[69]; in addition, LGR5 is expressed in the germ but only the lower bulge cells[116]. Markers highly expressed in the secondary hair germ but not the bulge include P-cadherin and LEF1[69]. Following wounding, bulge and hair germ cells can both contribute to the interfollicular epidermis[120]; however, this does not occur under homeostatic conditions. There are other stem cell niches located in the follicle above the bulge that contribute to both the hair follicle and interfollicular epidermal lineages in mice. An LGR6-positive population is found in the central isthmus[121], while leucine-rich repeats and immunoglobulin-like domains 1 (LRIG1)- and Blimp1-positive populations are present in the upper isthmus[122,123], with these cells maintaining the sebaceous glands and interfollicular epidermis. There is also a stem cell antigen-1 (SCA1)-positive cell population in the infundibulum that is thought to contribute to skin homeostasis[124].

The dermal papilla and dermal sheath represent a mesenchymal stem cell niche within the follicle. Under homeostatic conditions, dermal papilla cells rarely divide after formation of the initial condensate during morphogenesis, yet their gene expression profile is dynamic throughout development and the hair cycle. If removed from their niche, dermal papilla cells have the ability to differentiate into osteogenic, myogenic and adipogenic lineages[125–127]. Dermal papilla cells can also show hematopoietic activity both *in vitro* and *in vivo*, where they are capable of reconstituting the entire hematopoietic system of an irradiated mouse[128]. In addition to their ability to transdifferentiate, a major function of dermal papilla cells is related to their inductive potential. Isolated and cultured dermal cells from adult follicles are capable of stimulating a range of committed epithelia to form follicles, inclusive of progenitor stem cells[47,49,129,130]. Understanding how dermal papilla cells are capable of inducing *de novo* follicle formation would provide answers to many intriguing questions related to adnexal development.

The Hair Follicle and the Immune System

The hair follicle represents an immune privileged site, which is defined as a location in the body where foreign tissue grafts can survive for

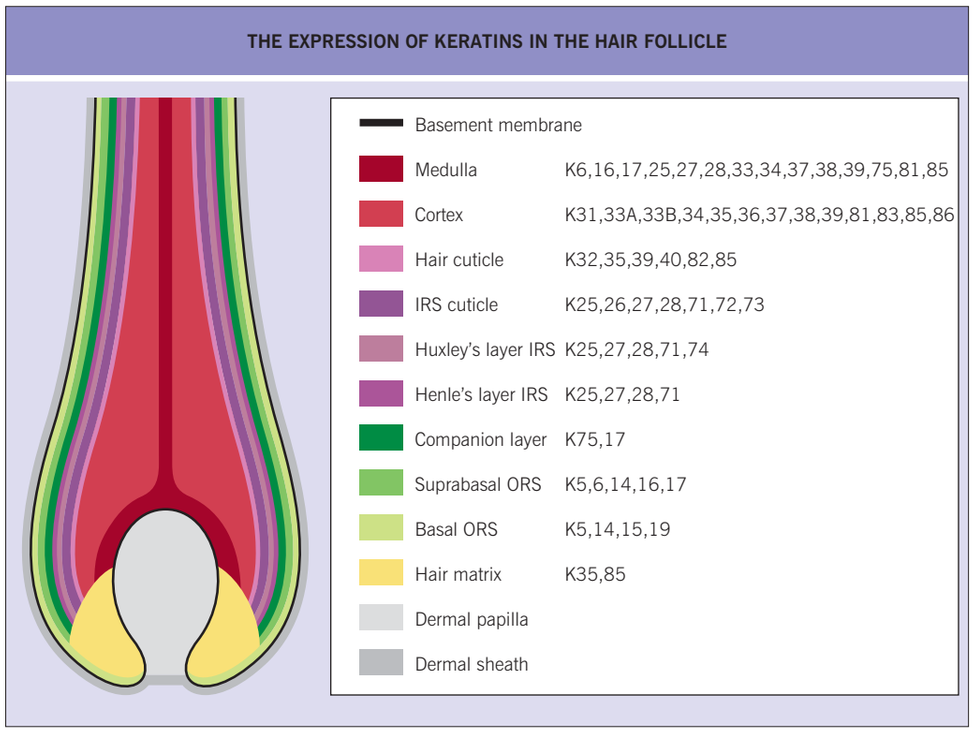


Fig. 68.8 The expression of keratins in the hair follicle.

extended periods of time without immune rejection[131]. Other immune privileged sites include the anterior chamber of the eye, testis, brain and placenta. The immune privileged status of the hair follicle underscores its evolutionary importance. Functions of the hair in different species include maintaining an adequate internal body temperature and providing protection against other environmental changes, toxins and infectious agents (see Table 68.2).

Initial evidence regarding the immune protection of the hair follicle came from the classic "Billingham experiment" in 1971[132], in which skin from black guinea pigs was transplanted onto an immunologically incompatible strain of white guinea pigs. The color of the grafted skin changed to white, reflecting the expected immune response against the foreign epidermal melanocytes. However, pigmented hairs grew within the grafts, showing that the foreign hair follicle melanocytes survived. Later experiments demonstrated that application of the contact allergen picryl chloride to mouse skin during the early anagen phase of the hair cycle led to a significant decrease in sensitization compared to application during the telogen phase[133], suggesting that the immune system around the hair follicles is suppressed specifically during the anagen phase. Features of the human anagen hair bulb that protect it from an immune response are summarized in Table 68.4.

Until recently, the immune privilege of the hair follicle was thought to be restricted to the matrix region during the anagen phase. However, evidence has accumulated that the immune privilege of the hair follicle extends to the bulge region and is present at this site during the entire hair cycle[142]. Because the bulge represents the hair follicle stem cell niche, sustained immune privilege in this region may be essential for the survival of the follicle.

Insights into the basis of hair follicle immune privilege (see Table 68.4) have begun to emerge in the past decade through the study of autoimmune hair disorders, but our understanding of this phenomenon is far from complete. Two mechanisms can underlie an immune reaction directed against the hair: (1) a primary attack of the immune system against the hair follicle; or (2) a breakdown in hair follicle immune privilege leading to a secondary attack by the immune system[131,134,135]. The latter hypothesis is favored, but definitive evidence for this process is still lacking. Because the hair matrix immune privilege is mainly restricted to the anagen phase[135], it has been postulated that an autoantigen from melanocytes, which are active during the anagen phase, could be responsible for initiating the immune response against the hair follicle that occurs in alopecia areata. Indeed, antibodies against melanocyte-associated antigens have been found in patients with this condition[143,144].

It is thought that collapse of hair follicle immune privilege begins with induction of major histocompatibility complex (MHC) class I molecule expression, which allows presentation of autoantigens to the immune system, on the follicular epithelium[145]. In hair follicles affected by alopecia areata, there is increased expression of MHC class I polypeptide-related sequence A (MICA). $CD8^+$ T cells and natural killer (NK) cells accumulate around affected hair follicles and exhibit increased expression of the NKG2D activating receptor, but decreased expression of inhibitory receptors such as killer cell immunoglobulin-like receptor three domains long cytoplasmic tail 1 (KIR3DL1) and heterodimeric CD94/NKG2A[131,135,136]. UL16 binding protein 3 (ULBP3), a NKG2D ligand, was recently shown to be upregulated in the dermal sheath and papilla of hair follicles affected by alopecia areata[136]. These observations indicate that hair follicles in patients with alopecia areata lose their immune privilege and express danger signals in their outermost layer, leading to self-destruction. There is also down-regulation of immunosuppressant molecules such as transforming growth factor (TGF)-β1, α-melanocyte stimulating hormone (MSH), indoleamine 2,3-dioxygenase (IDO)-1, and the IK cytokine (which inhibits the functions of interferon [IFN]-γ) in the setting of alopecia areata[131,134,135,142]. IFN-γ plays a pivotal role in the pathogenesis of alopecia areata by inducing the expression of MHC class II antigens (normally absent in the hair follicle matrix and dermal sheath), thereby propagating the immune response and contributing to destruction of the hair follicle[131,134].

A recent genome-wide association study (GWAS) in patients with alopecia areata implicated genes that are involved in immune regulation, in particular the function of regulatory T cells (e.g. cytotoxic T lymphocyte-associated protein 4 [CTLA4], interleukin [ILs]-2 and -21, the IL-2 receptor A [CD25], ULBPs, Eos [an Ikaros transcription factor]), as well as those expressed in the follicle (e.g. syntaxin 17, peroxiredoxin 5)[136]. Such studies may provide insights into potential therapeutic targets. For example, treatment with an CTLA4–Ig fusion protein that inhibits costimulation of T cells was shown to prevent disease onset in a mouse model of alopecia areata[146].

MECHANISMS CONTRIBUTING TO THE IMMUNE PRIVILEGE OF THE HAIR FOLLICLE

Mechanism of immune evasion	Function of the molecules affected
Down-regulated expression of MHC class I, MICA and β_2-microglobulin	Required for presentation of autoantigens to the immune system
Down-regulated expression of MHC class II	Required for functioning of antigen-presenting cells
Upregulated expression of IL-10, transforming growth factor-β1 (TGF-β1) and α-melanocyte stimulating hormone (α-MSH)	Immunosuppressive actions
Increased production of Fas-ligand (FasL)	Induces apoptosis of activated T cells; known to be crucial for maintenance of immune privilege in the eye, brain and fetus
Low expression of heterodimeric CD94/NKG2C and NKG2D receptors on NK cells and $CD8^+$ cytotoxic T cells as well as of the NKG2D ligand UL16 binding protein 3 (ULBP3)	These receptors activate NK cells and $CD8^+$ cytotoxic T cells upon ligand binding; NKG2D has been implicated in the immune attack on the hair follicle in alopecia areata
High expression of killer cell immunoglobulin-like receptors (KIRs) and heterodimeric CD94/NKG2A receptors on NK cells	These receptors inhibit NK cells
Increased production of indoleamine 2,3-dioxygenase (IDO)-1	Inhibits lymphocyte proliferation
Increased production of IK cytokine	Inhibits interferon-γ-induced expression of MHC class II antigens
Lack of lymphatic vessels around the hair follicle	Recruit immune cells

Table 68.4 Mechanisms contributing to the immune privilege of the hair follicle[134–141]. IL, interleukin; MHC, major histocompatibility complex; MICA, MHC class I polypeptide-related sequence A; NK, natural killer.

BIOLOGY OF NAILS

Like its phylogenetic ancestors (e.g. claws, hoofs), the nail protects the distal phalanges and contributes to a variety of motor and sensory functions (see Table 68.2). Two key aspects of nail biology are how nails grow and from what part of the nail apparatus they arise. The composition of nails and the characteristics of the surrounding soft tissues are other important considerations, including their natural constituents and features as well as potential exogenous or "biomarker" elements that may indicate an individual's environment or state of health[147,148]. An understanding of these aspects of the nail unit, in addition to its anatomy and development, can maximize the clinician's ability to accurately assess, correctly diagnose and effectively treat patients with nail disorders. However, our current knowledge of the regulation of nail development and growth on a molecular level is relatively poor, and acquisition of data has been hampered by the difficulty in obtaining nail-producing tissues and growing nails and/or nail matrix keratinocytes in culture. Tools such as mouse models (considering the substantial homology between murine claws and human nails), improved methods for organ-culturing microdissected components of the human nail apparatus, and the development of nail-equivalent *in vitro* systems will hopefully help to better elucidate the molecular mechanisms of nail biology in the future.

Nail Unit Anatomy

An understanding of nail biology and disease requires knowledge of the local anatomy (Fig. 68.9)[149,150]. The first distinction is between the nail

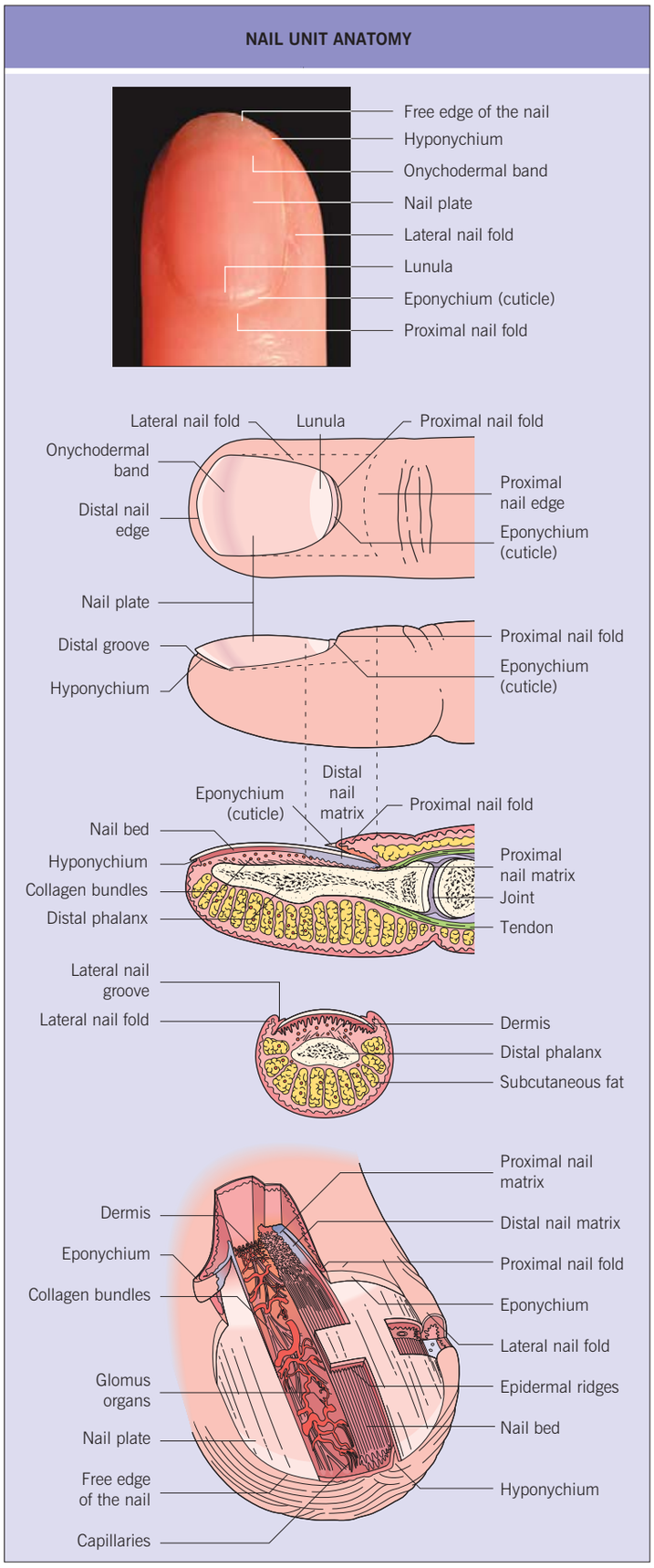


Fig. 68.9 Nail unit anatomy.

plate and the soft tissues supporting it. The nail plate is a hard, semitransparent, slightly convex sheet comprised of tightly packed corneocytes termed onychocytes. It contains abundant "hard" hair-type keratins, which are embedded in a matrix of sulfur-rich high-cysteine and high-glycine/tyrosine proteins (see below). The dermis of the nail apparatus (beneath its epithelial structures) is a fibrocollagenous network that is "sandwiched" between the hard tissues of the nail plate and the underlying bone, lacking associated subcutaneous soft tissues or pilosebaceous units. As a result, bacterial infections in this region have a higher risk of spread to the adjacent bone (i.e. osteomyelitis of the distal phalanx) than in most other sites of the body.

The nail plate is surrounded on three edges by nail folds (one proximal and two lateral). The proximal nail fold, a double layer of skin overlying the proximal part of the nail, protects this area from trauma, solvents and infectious agents that might otherwise alter nail shape and structure. The dorsal layer of the proximal nail fold is continuous with the skin of the digit, while the ventral layer is continuous with the nail matrix. The cuticle (eponychium) is a thin strip of cornified epithelium that adheres to the nail at the edge of the proximal nail fold and acts as a seal against ingress. Damage to the cuticle results in a predisposition to inflammation of the nail fold; conversely, inflammation of the nail folds disrupts normal maturation of the epithelium and cuticle formation. Nail fold inflammation can also disturb the underlying matrix and alter nail plate production, most often manifesting as transverse ridging. The proximal nail fold may also help to mold the emerging nail, forming a relatively thin structure that grows obliquely from its point of origin in the matrix.

The longitudinal axis of nail growth is also guided by the lateral nail folds, which compress the nail plate from each side and contribute to its transverse curvature. The lateral margins of the nail bed form deep sulci that follow the curve of the distal phalanx and then fold back on themselves to produce the lateral nail folds. These sulci help to attach the nail to the soft tissues and, similar to the proximal nail fold and cuticle, provide a seal at the nail margin.

The structures bounded by the nail folds are the nail matrix proximally and the nail bed distally and medially. The half-moon-shaped lunula, which is most prominent on the thumb, demarcates the junction between the matrix and the nail bed. The lunula is less apparent, due in part to concealment by the proximal nail fold, with progression from the second to fifth finger. The lunulae of the toes are hidden by their relatively prominent proximal nail folds (which may serve a protective function) and (especially for the great toes) thicker nail plates[149,150].

The nail plate is in continuity with the matrix from which it arises, while the nail bed represents its underlying support structure and extends from the distal margin of the lunula to the onychodermal band (a thin pinkish transverse strip proximal to the whitish onychocorneal band; see Fig. 68.9). A longitudinal pattern of rugose rete ridges in the nail bed increases the surface area of its attachment to the ventral aspect of the nail, which has corresponding ridges. This enhances adhesion between these surfaces and enables the free edge of the nail to be used as a levering tool without lifting the nail or causing pain. Histologically, both the nail bed and matrix normally lack a granular layer. The presence of a granular layer in these sites is a sign of pathology, such as the altered nail bed behavior associated with subungual hyperkeratosis.

The nail is in close proximity to the underlying distal phalanx, and bone morphogenic proteins (BMPs) are thought to have roles in the morphogenesis of both structures. When the distal phalanx and/or interphalangeal joint are affected by an inflammatory disease such as psoriasis, involvement of the nail matrix (and hence nail plate) often occurs. Congenital absence of part of the distal phalanx is typically accompanied by a small or otherwise altered nail (e.g. congenital onychodysplasia of the index fingers), further illustrating the relationship between these two structures[151]. In the neonatal period, digit tip regeneration can occur in humans after partial amputation. This appears to require the presence of a residual nail unit and to involve the expression of BMP-4 and the muscle segment homeobox 1 (MSX1) transcriptional repressor[152]. In later life, regeneration does not occur upon partial amputation of the fingertip due to trauma or osteolysis in the setting of scleroderma, and secondary nail changes typically ensue.

The vascular supply of the digit is through two dorsolateral and two ventrolateral arteries that lack an internal elastic lamina and have a tortuous morphology that helps them to withstand flexion and other movements. There is substantial communication between these vascular networks, particularly distally via plexuses in the proximal nail fold and digital pulp. This provides the digit with a blood supply of more than one origin and direction, which ensures continued flow in the event of trauma or a sustained grip that decreases supply from the ventral vessels. The pulp plexus is located within a recess produced by

the gap between the ventral prominence of the distal phalanx and the rim of the distal interphalangeal joint[153].

In a cold environment, which leads to constriction of arterioles, arteriovenous anastomoses (Sucquet–Hoyer canals) within glomus bodies maintain sufficient blood supply to the distal digits. Glomus bodies are encapsulated oval structures containing modified smooth muscle cells that dilate upon exposure to the cold. These structures are most prominent in the subungual tissue, which represents the most common site of the glomus tumor, a benign proliferation of glomus cells[154] (see Ch. 114).

In the proximal nail fold, the dermal capillaries normally form a regular pattern of "hairpin" loops with a thin efferent limb and a more tortuous, thicker afferent limb. The organization of nail bed vessels is similar, although the hairpin turn is less evident. Dermatoscopic examination (capillaroscopy) of nail fold vessels can help to assess a patient's acral microvascular status. The pattern and/or patency of the capillaries in the proximal nail fold and nail bed is often altered in patients with an autoimmune connective tissue diseases (AI-CTD) or embolic disorder. The nail folds of patients with lupus erythematosus typically show dilated, tortuous capillaries of normal density, whereas scleroderma and dermatomyositis feature hemorrhages and decreased capillary density characterized by avascular areas alternating with dilated capillary loops. Acral infarction due to embolization (e.g. in the setting of endocarditis) can result in leakage of blood into the nail bed, referred to as splinter hemorrhages. These lesions can also develop secondary to trauma, psoriasis (which is associated with an increased number of papillary dermal vessels, disrupted nail integrity, and shearing forces with the nail bed) and AI-CTD.

The nerve supply of the digit follows the pattern of the vascular supply, with two dorsal and two ventral branches that have some overlap distally in their sensory territories[150]. Because the fingertips have an important role in sensory perception, nerve endings that transmit pain (type I fibers), touch (Meissner and Pacinian bodies) and temperature are all abundant. The function of these nerve endings may be compromised by pressure due to relatively minor trauma and edema within the fascial envelope that encloses a finger or toe.

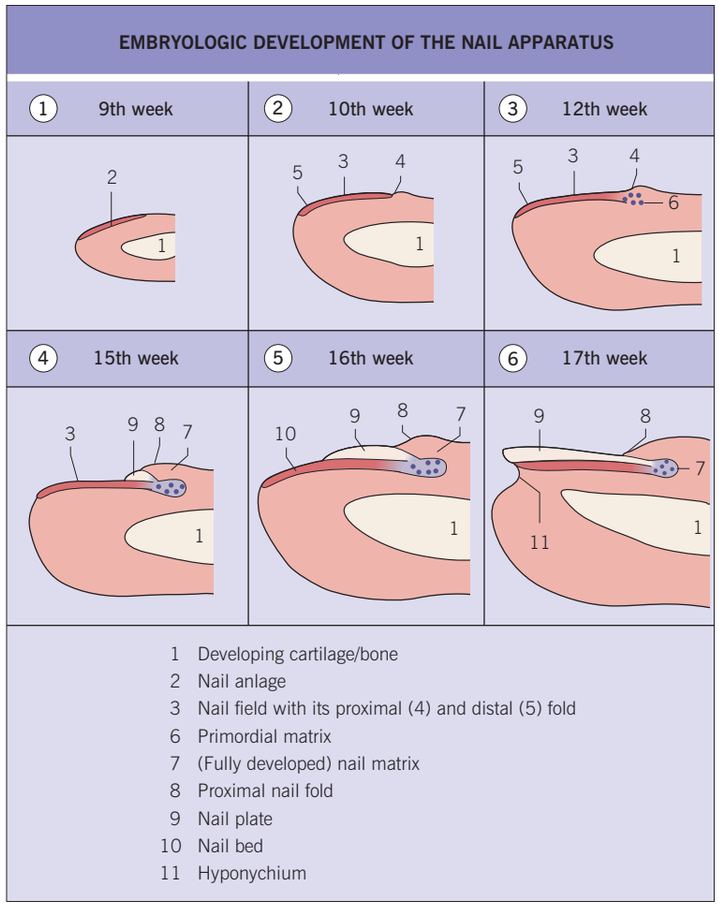


Fig. 68.10 Embryologic development of the nail apparatus.

Nail Embryology

The nail primordium becomes evident at 8 weeks' gestational age as a transverse ridge on the distal dorsal surface of the digit (Fig. 68.10) (see Ch. 2). Over the next 4 weeks, the ridge takes a more proximal position and eventually invaginates beneath the emerging proximal nail fold. The outline of the nail unit is established by 16 weeks' gestational age, and the nail plate completely covers the nail bed during the fifth month.

Study of inherited nail diseases has provided clues into some of the processes that regulate the formation of the nail unit. An autosomal recessive form of anonychia congenita is caused by loss-of-function mutations in the gene encoding R-spondin 4 (RSPO4) , which functions in the WNT signaling pathway[155]. Mouse studies have demonstrated expression of *Rspo4* in digit mesenchyme during embryogenesis, and it is thought to influence induction of the nail unit in the overlying epithelium.

Nail–patella syndrome is another genetic disorder that has contributed to our understanding of the organization of nail development. The nail changes in this autosomal dominant condition include triangular lunulae and absent or hypoplastic nails, with most prominent involvement of the thumbnail and other radial digits; however, an individual nail is usually more severely affected on its ulnar side. Extracutaneous manifestations include hypoplastic patellae, iliac horns, nephropathy and glaucoma. Nail–patella syndrome is caused by mutations in the gene encoding the LIM homeobox transcription factor 1β (LMX1B), which influences dorsoventral limb patterning[156,157]. In Clouston syndrome, a form of ectodermal dysplasia due to mutations in the gap junction β6 gene (*GJB6*) that encodes connexin 30, thickened nails with onycholysis occur in association with hypotrichosis and palmoplantar keratoderma (see Ch. 63)[158]. These genetic nail diseases illustrate the importance of communication between cells and tissues in the morphogenesis of the nails as well as other adnexal structures and organs. These messaging systems use the same "code" to initiate a variety of events in different tissues. Other genetic diseases affect the nails through alteration of their structural components, such as keratins or the constituents of the basement membrane.

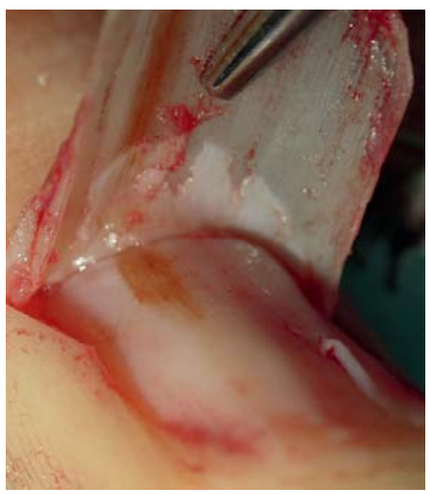


Fig. 68.11 Nail matrix biopsy to determine the etiology of longitudinal melanonychia. Note that the pigment in the nail extends to the proximal part of the matrix in the nail plate and (as seen when the nail is lifted) the matrix itself.

Nail Matrix

"Nail matrix" is a functional and anatomical term; although there is currently general consensus with regard to these definitions, disagreement about the precise functional role of the matrix (see below) can potentially lead to confusion about its exact anatomy.

Matrix anatomy

The anatomical boundaries of the "classical" matrix are most easily visible when the subungual tissues are seen during a surgical procedure in which the nail is avulsed and the proximal nail fold retracted (Fig. 68.11). This reveals two zones of tissues on which the nail rests, a proximal pale nail matrix and a distal pinker nail bed. Their arcuate junction is evident through the nail plate as the lunula (half moon).

The most lateral portion of the matrix may be "buried" in the sulcus of the lateral nail fold; because this can be difficult to access surgically, procedures designed to remove the lateral part of the nail matrix sometimes leave behind a small piece of matrix that produces a detached spicule of nail. Proximally, the matrix extends to the point of flexure of the proximal nail fold, where the latter structure turns back over and protects the proximal margin of the nail (see Fig. 68.9). Compared to epidermal keratinocytes, those in the nail matrix are larger and have a higher rate of proliferation.

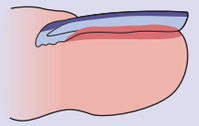
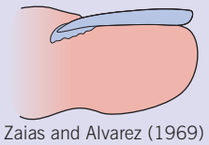
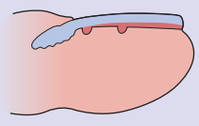
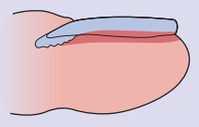
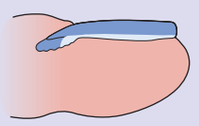
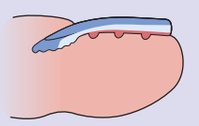
Matrix function

For more than 50 years, anatomists and clinical scientists have investigated the relationship between the matrix and production of the nail (Fig. 68.12). Early work by Lewis[159] used static histology of silver-stained longitudinal sections of the nail unit to delineate three layers that he postulated were derived from separate epithelial surfaces within the nail unit: (1) the ventral aspect of the proximal nail fold (upper nail plate); (2) the "classical" matrix as defined above (mid nail plate); and (3) the nail bed (lower nail plate). This led to the misconception that there are three areas of matrix, dorsal, ventral and intermediate. Subsequent studies in squirrel monkeys (which have digits similar to those in humans) using *in vivo* autoradiography provided evidence that most, if not all, of the nail plate is generated from the "classical" matrix[160]. In these experiments, systemic injection of tritiated thymidine was followed by amputations at different time points, demonstrating that the thymidine reached the nail plate via the matrix. Injection of radiolabeled glycine into the nail unit of human volunteers who then had nail biopsies also showed that the matrix is the main source of the nail plate[161].

In the early 1990s, Johnson and colleagues[162,163] found that between the distal margin of the lunula and the end of the nail bed, the nail plate of the great toe increases in thickness by ~20%. They inferred from this observation that the nail bed contributes this proportion of the nail plate. Histologic assessment of nail plates obtained in a similar manner (avulsion) from the great toe confirmed this increase in thickness but showed that the number of cells in the vertical axis of the nail plate does not increase from the proximal to distal nail bed. These results suggested that the nail plate thickens because of compaction (e.g. due to distal-to-proximal compression) rather than an active contribution from the underlying nail bed[164]. Walking while wearing footwear produces low-grade, repetitive trauma to the free edge of the great toenail, which would explain such an effect[164].

Immunohistochemical staining with proliferating cell nuclear antigen or Ki-67 demonstrates minimal proliferative activity in the nail bed but substantial activity in the matrix, further supporting that the matrix is the source of the nail plate[165]. The correlation between anatomy and function explains the different patterns of nail disease that result from pathology affecting the matrix versus the nail bed (see Table 71.1). It also accounts for the potential for permanent nail deformity following surgical intervention or biopsy of the matrix, but not for similar interventions involving the nail bed. Because the proximal half of the matrix produces approximately 80% of the nail plate, surgeries or biopsies in this area are more likely to produce nail dystrophy than those of the distal matrix. Onychocytes migrate upward and distally along an oblique axis during their maturation and differentiation; as a result, the proximal part of the matrix produces the dorsal portion of the nail plate, while the distal part of the matrix synthesizes the ventral portion of the nail plate. Abnormalities in the proximal matrix underlie clinical findings such as pitting and longitudinal ridging/splitting, whereas disruption of the distal matrix can cause true leukonychia.

THEORIES ON THE ORIGIN OF THE NAIL PLATE

Origin of the nail plate	Evidence	Schematic, reference
Three portions of the nail matrix form three corresponding parts of the nail plate, which is characterized by a three-layer structure: Dorsal part = Proximal nail fold → Upper nail plate Intermediate part = Classical nail matrix → Intermediate nail plate Ventral part = Nail bed → Lower nail plate	Light microscopy and silver staining of human nails	 Lewis (1954)
Cells of the classical matrix are the origin of the whole nail plate	*In vivo* auto–radiography (with tritiated thymidine) in squirrel monkeys	 Zaias and Alvarez (1969)
Cells of the classical matrix produce nearly the total nail plate. Only a few cells of the nail bed in poorly defined locations take part in forming the nail plate	*In vivo* auto–radiography (with radiolabeled glycine) in human volunteers	 Norton (1971)
The regrowth of nail plates following traumatic avulsion of great toenails was investigated: approximately 20% of the nail plate's thickness was added when the nail grew over the nail bed, suggesting a nail bed contribution to the nail plate's growth	Changes in nail plate's thickness during nail growth in human volunteers	 Johnson et al. (1991,1993)
Cells of the proximal half of the matrix produce approximately 80% of the nail plate, whereas 1% or less of the nail plate is contributed by the nail bed. In psoriatic nails, the nail bed contribution may increase to over 25%	Immunohisto-chemical labeling in healthy human nails with antibodies to proliferating cell nuclear antigens and antigen Ki-67	 Healthy nail  Psoriatic nail de Berker and Angus (1996); de Berker et al. (1996)

Sites of origin and their contributions to the nail plate:

- Proximal matrix within nail fold (dorsal matrix)
- Nail bed
- Nail matrix
- Proximal half of nail matrix
- Distal half of nail matrix

Fig. 68.12 Theories on the origin of the nail plate. *Adapted fom Dawber RP, de Berker DA, Baran R. Science of the nail apparatus. In: Baran R, Dawber RP, de Berker DA, et al (eds). Diseases of the Nails and their Management. Oxford: Blackwell Science, 2001;1–47.*

Nail Unit Melanocytes

Melanocytes are found in the nail matrix but not in the normal nail bed. In general, foci of pigment in the nail bed that are separated from the nail folds and matrix are not melanocytic in origin[166], with possible exceptions including a metastatic melanoma and a partially amelanotic melanoma that is continuous with the matrix or nail fold. Nail matrix melanocytes are most abundant in the distal matrix and are found in suprabasal layers as well as the basal layer, which may reflect a distinct expression pattern of adhesion molecules (e.g. of α_2, α_3 and β_1 integrins) that regulate interactions between melanocytes and keratinocytes[166a].

The main distribution pattern of melanin in the nail plate is pigmented bands, referred to as longitudinal melanonychia, which vary in number, intensity and width depending on their etiology (see Ch. 71). Multiple streaks of longitudinal melanonychia due to active nail matrix melanocytes are commonly found in individuals with darkly pigmented skin, sometimes as a result of trauma or inflammation affecting the matrix. In contrast, nail matrix melanocytes in individuals with lightly pigmented skin are normally quiescent, and longitudinal melanonychia (especially an isolated band in an adult) in such patients usually requires a nail matrix biopsy (see Ch. 149) to exclude the possibility of melanoma.

Inadequate biopsy specimens (e.g. too small, non-representative) can lead to a delay in diagnosis and less favorable prognosis[167].

The Nail Immune System

The nail unit (in particular the proximal matrix) represents a site of relative immune privilege, with reduced expression of MHC class I and II antigens and decreased numbers of antigen-presenting cells. Although these features may be of benefit in preventing over-reactivity to environmental antigens, they could also increase vulnerability to human papillomavirus infections and their potential oncogenic effects, which can result in periungual squamous cell carcinomas[168].

Nail Keratins

Multiple types of keratins are expressed in the nail apparatus (Fig. 68.13), and they account for 80% of the dry weight of the nail plate. The nail plate and matrix contain "hard" hair-type keratins with a large number of sulfur-containing amino acids that facilitate cross-linking between keratin molecules. This reduces the amount of water associated with these proteins and makes them more rugged and resistant to chemical destruction compared with "soft" epithelial keratins[169].

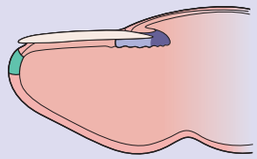
The pattern of keratin expression within the nail unit explains the involvement of this structure in several genodermatoses that are caused by keratin defects[170,171]. Pachyonychia congenita (PC) is an autosomal dominant disorder caused by mutations in the genes encoding keratins 6a or 16 (classically referred to as PC1) and 6b or 17 (classically referred to as PC2) (see Chs 58 & 71). These keratins are expressed in the nail bed, hair follicle and sebaceous gland as well as palmoplantar, injured (e.g. ulcer margins) and hyperproliferative epidermis. PC features thickening of the nail plate, much of which represents compaction of dense subungual hyperkeratosis, together with painful palmoplantar keratoderma, follicular keratoses and variable oral leukokeratosis and cysts (e.g. steatocystoma multiplex). Nail fragility as well as alopecia characterize the pure hair–nail ectodermal dysplasia that results from mutations in the gene for keratin 85. In these patients, keratin 85 lacks two cysteine residues, which may compromise nail integrity via diminished cross-linking of amino acids within keratins.

The nail bed does not express keratins 1 and 10, which characterize terminally differentiated stratified epithelia such as the epidermis. It has been postulated that the presence of the nail plate overlying the nail bed inhibits further differentiation of the latter structure. Indeed, if the nail plate is avulsed, the nail bed develops a cornified layer over the next 3 to 4 weeks.

Other Nail Plate Components

In addition to keratins, the nail plate contains structural proteins high in sulfur (with elevated cysteine content) or glycine and tyrosine (see Fig. 68.13). Other molecules and elements within the nail plate include water (normally ~10–15%, compared to ~15–25% for the epidermis), lipids (primarily cholesterol) and minerals (e.g. iron, zinc, calcium). The nail plate is relatively porous and ~1000-fold more permeable to water than is the epidermis; as a result, nails can be rapidly dehydrated and hydrated. Low water content in nails leads to brittleness, while nails composed of >30% water are soft and opaque. Although calcium is present in the nail plate, it does not influence the hardness of the nail.

DISTRIBUTION OF KERATINS AND NON-KERATIN PROTEINS IN THE NAIL APPARATUS



Anatomical region	Keratins (key examples)		Non-keratin proteins
	Soft keratins	Hard keratins	
Nail plate	K14, K16, K17, K5, K6	K31–K34 K81–K84	Ultra-high-sulfur proteins High-sulfur proteins High-glycine/tyrosine proteins Trichohyalin
Proximal nail matrix	K10, K14, K16, K17 K1, K5, K6		Actin, involucrin, filaggrin*, trichohyalin*, plasminogen activator inhibitor type II, laminin
Distal nail matrix	K10, K14, K20 K1, K5	K31	
Nail bed	K14, K16, K17, K5, K6, K7		Trichohyalin, plasminogen activator inhibitor type II, laminin
Hyponychium	K10, K14, K1, K5		Laminin
Tip	K16, K17 K6		
Embryonic nail unit	K19		*detected in monkey nails

Fig. 68.13 Distribution of keratins and non-keratin proteins in the nail apparatus. *Adapted fom Dawber RP, de Berker DA, Baran R. Science of the nail apparatus. In: Baran R, Dawber RP, de Berker DA, et al (eds). Diseases of the Nails and their Management. Oxford: Blackwell Science, 2001;1–47.*

THE NAIL APPARATUS: BASIC INFORMATION AND TERMINOLOGY	
Nail plate thickness	Toenails are usually thicker than fingernails Toenails: 1.4 mm in women, 1.65 mm in men Fingernails: 0.5 mm in women, 0.6 mm in men
Growth rate	Fingernails usually grow faster than toenails Fingernails: 2–3 mm/month Toenails: 1 mm/month Complete replacement of a nail requires 6 (fingernails) to 18 months (toenails)
Nail plate	Tightly packed cornified cells (onychocytes) arranged in a lamellar pattern (weakly eosin+, strongly acid-fast+); largest on the great toe (covers ~50% of the digit); fingernails have a longer longitudinal axis compared to the transverse axis, while toenails usually have a longer transverse axis
Nail matrix	Epithelium situated above the middle part of the distal phalanx of the digits; keratinizes without a granular layer and generates the nail plate; contains many melanocytes (up to 300/mm^2 in African-Americans), predominantly in suprabasal layers
Nail bed	Thin epithelium consisting of 2–5 cell layers with abrupt keratinization and no granular layer; typically no melanocytes
Proximal nail fold	Epithelium with a granular layer; its dorsal part corresponds to the skin of the dorsum of the digit and contains sweat glands but is devoid of pilosebaceous units; densely innervated; the ventral part is thinner and connects with the nail matrix epithelium
Hyponychium	An epithelium equivalent to the volar skin containing granular and thick cornified layers
Nail pigmentation	Banded pigmentation (longitudinal melanonychia) is common in Asians or African-Americans (seen in ~75% of African-Americans by 20 years of age and nearly 100% by 50 years of age); relatively uncommon in Caucasians

Table 68.5 The nail apparatus: basic information and terminology. *Courtesy, John P Sundberg, DVM, PhD.*

Likewise, the white "flecks" that are commonly seen in the nail plate (especially in children) have nothing to do with calcium but rather reflect small disturbances in the compaction of onychocytes, usually related to trauma.

The nail can also contain markers of various metabolic processes and exposures to exogenous substances (e.g. drugs, environmental pollutants). Biomarkers in the nail plate include glycosylated keratin in patients with diabetes mellitus[172], high sodium levels in those with cystic fibrosis[173], and increased amounts of lipids in hyperlipidemic individuals[174]. Exogenous substances that are found in the nail plate in settings of systemic exposure due to environmental contamination include arsenic, lead and other heavy metals[175,176]. Drugs taken for medical purposes or recreationally may also be present in the nail plate, depending on their binding properties and lipid solubility[177]. Analysis of nicotine in the toenails can be used to track exposure to cigarette smoke via inhalation[178], and a range of narcotics can be identified in nail clippings, either in deposits beneath the free edge of the nail plate due to recent direct contact or incorporated into the nail plate via systemic exposure over previous months[179]. For neonates, it is possible to measure *in utero* exposure to some drugs using nail analysis[180].

Nail Growth

Nail growth (Table 68.5) is typically measured in the longitudinal axis (e.g. using a vernier caliper) from a defined reference point to the free edge or by monitoring the movement over time of a transverse groove made at the peak of the lunula[181]; the mass of nail produced in clippings over a fixed period can also be determined. When a systemic event or local trauma disrupts nail growth for a brief period, a transverse groove (reflecting the contour of the proximal margin of the matrix) appears and grows outward with the affected nail, allowing the timing of the inciting phenomenon to be estimated. This clinical sign is known as Beau's lines, named after the Parisian cardiologist Justin Beau who described these bands in patients recovering from typhoid[182].

Multiple physiologic conditions, medical disorders and drug exposures can influence nail growth (Table 68.6). The appearance of decreased nail growth is occasionally explained by substantial thickening of the nail plate that deviates the axis of growth such that nail is accumulating upwards in the vertical axis as well as outward in the longitudinal axis. Examples include onychogryphosis and yellow nail syndrome[183] (see Ch. 71), which are both accompanied by retraction of the proximal nail fold that may normally have a role in molding and flattening the early nail. In these instances, measurement of nail bulk rather than length illustrates that the nails are actually growing, but in a different direction.

FACTORS THAT CAN INFLUENCE NAIL GROWTH

Factor/ condition	Reduction of growth	Acceleration of growth
Age	Elderly	Young
Time of day	Night	Day
Seasons	Winter	Summer
Anatomic location	Toes Thumb, little finger	Fingers Middle finger
Physiologic states		Pregnancy
Extracutaneous disorders	Fever Poor nutrition Denervation, immobilization Infections (e.g. mumps, tuberculosis)	Hyperthyroidism Arteriovenous shunting
Cutaneous disorders	Onychomycosis	Psoriasis, pityriasis rubra pilaris
Drugs	L-Dopa Calcium, vitamin D Methotrexate Azathioprine Etretinate/acitretin	Itraconazole Etretinate/acitretin (in psoriasis patients)

Table 68.6 Factors that can influence nail growth.

REFERENCES

1. Dhouailly D, Sengel P. [Morphogenesis of feather and hair, studied by means of heterospecific associations of dermis and epidermis between chicken and mice]. C R Acad Sci Hebd Seances Acad Sci D. 1972;275:479–82.
2. Kollar EJ. The induction of hair follicles by embryonic dermal papillae. J Invest Dermatol. 1970;55:374–8.
3. Andl T, Reddy ST, Gaddapara T, Millar SE. WNT signals are required for the initiation of hair follicle development. Dev Cell. 2002;2:643–53.
4. Zhang Y, Andl T, Yang SH, et al. Activation of beta-catenin signaling programs embryonic epidermis to hair follicle fate. Development. 2008;135:2161–72.
5. Adaimy L, Chouery E, Megarbane H, et al. Mutation in WNT10A is associated with an autosomal recessive ectodermal dysplasia: the odonto-onycho-dermal dysplasia. Am J Hum Genet. 2007;81:821–8.
6. Shimomura Y, Agalliu D, Vonica A, et al. APCDD1 is a novel Wnt inhibitor mutated in hereditary hypotrichosis simplex. Nature. 2010;464:1043–7.
7. Zhang Y, Tomann P, Andl T, et al. Reciprocal requirements for EDA/EDAR/NF-kappaB and Wnt/beta-catenin signaling pathways in hair follicle induction. Dev Cell. 2009;17:49–61.
8. Bazzi H, Fantauzzo KA, Richardson GD, et al. The Wnt inhibitor, Dickkopf 4, is induced by canonical Wnt signaling during ectodermal appendage morphogenesis. Dev Biol. 2007;305:498–507.
9. Sick S, Reinker S, Timmer J, Schlake T. WNT and DKK determine hair follicle spacing through a reaction-diffusion mechanism. Science. 2006;314:1447–50.
10. Hardy MH. The secret life of the hair follicle. Trends Genet. 1992;8:55–61.
11. Pummila M, Fliniaux I, Jaatinen R, et al. Ectodysplasin has a dual role in ectodermal organogenesis: inhibition of Bmp activity and induction of Shh expression. Development. 2007;134:117–25.
12. St-Jacques B, Dassule HR, Karavanova I, et al. Sonic hedgehog signaling is essential for hair development. Curr Biol. 1998;8:1058–68.
13. Lehman JM, Laag E, Michaud EJ, Yoder BK. An essential role for dermal primary cilia in hair follicle morphogenesis. J Invest Dermatol. 2009;129:438–48.
14. Dowling J, Yu QC, Fuchs E. Beta4 integrin is required for hemidesmosome formation, cell adhesion and cell survival. J Cell Biol. 1996;134:559–72.
15. Raghavan S, Bauer C, Mundschau G, et al. Conditional ablation of beta1 integrin in skin. Severe defects in epidermal proliferation, basement membrane formation, and hair follicle invagination. J Cell Biol. 2000;150:1149–60.
16. Yi R, O'Carroll D, Pasolli HA, et al. Morphogenesis in skin is governed by discrete sets of differentially expressed microRNAs. Nat Genet. 2006;38:356–62.
17. Legue E, Nicolas JF. Hair follicle renewal: organization of stem cells in the matrix and the role of stereotyped lineages and behaviors. Development. 2005;132:4143–54.
18. Hwang J, Mehrani T, Millar SE, Morasso MI. Dlx3 is a crucial regulator of hair follicle differentiation and cycling. Development. 2008;135:3149–59.
19. Price JA, Bowden DW, Wright JT, et al. Identification of a mutation in DLX3 associated with tricho-dento-osseous (TDO) syndrome. Hum Mol Genet. 1998;7:563–9.
20. Sundberg JP, Peters EM, Paus R. Analysis of hair follicles in mutant laboratory mice. J Investig Dermatol Symp Proc. 2005;10:264–70.
21. Peters EM, Botchkarev VA, Muller-Rover S, et al. Developmental timing of hair follicle and dorsal skin innervation in mice. J Comp Neurol. 2002;448:28–52.
22. Mattioli M, Barboni B, Turriani M, et al. Follicle activation involves vascular endothelial growth factor production and increased blood vessel extension. Biol Reprod. 2001;65:1014–19.
23. Duverger O, Morasso MI. Epidermal patterning and induction of different hair types during mouse embryonic development. Birth Defects Res C Embryo Today. 2009;87:263–72.
24. Laurikkala J, Pispa J, Jung HS, et al. Regulation of hair follicle development by the TNF signal ectodysplasin and its receptor Edar. Development. 2002;129:2541–53.
25. Pennisi D, Gardner J, Chambers D, et al. Mutations in Sox18 underlie cardiovascular and hair follicle defects in ragged mice. Nat Genet. 2000;24:434–7.
26. Botchkarev VA, Botchkareva NV, Sharov AA, et al. Modulation of BMP signaling by noggin is required for induction of the secondary (nontylotrich) hair follicles. J Invest Dermatol. 2002;118:3–10.
27. Shimomura Y, Wajid M, Weiser J, et al. Identification of mutations in the EDA and EDAR genes in Pakistani families with hypohidrotic ectodermal dysplasia. Clin Genet. 2009;75:582–4.
28. Fujimoto A, Kimura R, Ohashi J, et al. A scan for genetic determinants of human hair morphology: EDAR is associated with Asian hair thickness. Hum Mol Genet. 2008;17:835–43.
29. Irrthum A, Devriendt K, Chitayat D, et al. Mutations in the transcription factor gene SOX18 underlie recessive and dominant forms of hypotrichosis-lymphedema-telangiectasia. Am J Hum Genet. 2003;72:1470–8.
30. Devenport D, Fuchs E. Planar polarization in embryonic epidermis orchestrates global asymmetric morphogenesis of hair follicles. Nat Cell Biol. 2008;10:1257–68.
31. Ravni A, Qu Y, Goffinet AM, Tissir F. Planar cell polarity cadherin Celsr1 regulates skin hair patterning in the mouse. J Invest Dermatol. 2009;129:2507–9.
32. Guo N, Hawkins C, Nathans J. Frizzled6 controls hair patterning in mice. Proc Natl Acad Sci USA. 2004;101:9277–81.
33. Wang Y, Chang H, Nathans J. When whorls collide: the development of hair patterns in frizzled 6 mutant mice. Development, 2010;137:4091–9.
34. Baumeister FA, Egger J, Schildhauer MT, Stengel-Rutkowski S. Ambras syndrome: delineation of a unique hypertrichosis universalis congenita and association with a balanced pericentric inversion (8) (p11.2; q22). Clin Genet. 1993;44:121–8.
35. Fantauzzo KA, Tadin-Strapps M, You Y, et al. A position effect on TRPS1 is associated with Ambras syndrome in humans and the Koala phenotype in mice. Hum Mol Genet. 2008;17:3539–51.

36. Sun M, Li N, Dong W, et al. Copy-number mutations on chromosome 17q24.2-q24.3 in congenital generalized hypertrichosis terminalis with or without gingival hyperplasia. Am J Hum Genet. 2009;84:807–13.
37. Mauger A. [The role of somitic mesoderm in the development of dorsal plumage in chick embryos. I. Origin, regulative capacity and determination of the plumage-forming mesoderm]. J Embryol Exp Morphol. 1972;28:313–41.
38. Dhouailly D, Olivera-Martinez I, Fliniaux I, et al. Skin field formation: morphogenetic events. Int J Dev Biol. 2004;48:85–91.
39. Osumi-Yamashita N, Ninomiya Y, Doi H, Eto K. The contribution of both forebrain and midbrain crest cells to the mesenchyme in the frontonasal mass of mouse embryos. Dev Biol. 1994;164:409–19.
40. Candille SI, Van Raamsdonk CD, Chen C, et al. Dorsoventral patterning of the mouse coat by Tbx15. PLoS Biol. 2004;2:E3.
41. Dinh HV, Sinclair RD, Martinick J. Donor site dominance in action: transplanted hairs retain their original pigmentation long term. Dermatol Surg. 2008;34:1108–11.
42. Billingham RE, Russell PS. Incomplete wound contracture and the phenomenon of hair neogenesis in rabbits' skin. Nature. 1956;177:791–2.
43. Ito M, Yang Z, Andl T, et al. Wnt-dependent de novo hair follicle regeneration in adult mouse skin after wounding. Nature. 2007;447:316–20.
44. Jahoda CA, Oliver RF, Reynolds AJ, et al. Trans-species hair growth induction by human hair follicle dermal papillae. Exp Dermatol. 2001;10:229–37.
45. Reynolds AJ, Lawrence C, Cserhalmi-Friedman PB. Trans-gender induction of hair follicles. Nature. 1999;402:33–4.
46. Reynolds AJ, Jahoda CA. Cultured human and rat tooth papilla cells induce hair follicle regeneration and fiber growth. Differentiation. 2004;72:566–75.
47. Ferraris C, Chaloin-Dufau C, Dhouailly D. Transdifferentiation of embryonic and postnatal rabbit corneal epithelial cells. Differentiation. 1994;57:89–96.
48. Ferraris C, Chevalier G, Favier B, et al. Adult corneal epithelium basal cells possess the capacity to activate epidermal, pilosebaceous and sweat gland genetic programs in response to embryonic dermal stimuli. Development. 2000;127:5487–95.
49. Fliniaux I, Viallet JP, Dhouailly D, Jahoda CA. Transformation of amnion epithelium into skin and hair follicles. Differentiation. 2004;72:558–65.
50. Bonfanti P, Claudinot S, Amici AW, et al. Microenvironmental reprogramming of thymic epithelial cells to skin multipotent stem cells. Nature. 2010;466:978–82.
51. Philpott MP, Westgate GE, Kealey T. An in vitro model for the study of human hair growth. Ann N Y Acad Sci. 1991;642:148–64; discussion 164–6.
52. Stenn K, Parimoo S, Prouty S. Growth of the hair follicle: a cycling and regenerating biological system. In: Chuong CM (ed.). Molecular Basis of Epithelial Appendage Morphogenesis. Austin, TX: RG Landes, 1998:111–30.
53. Rebora A, Guarrera M. Kenogen. A new phase of the hair cycle? Dermatology. 2002;205:108–10.
54. Chase HB, Rauch R, Smith VW. Critical stages of hair development and pigmentation in the mouse. Physiol Zool. 1951;24:1–8.
55. Kligman AM. Pathologic dynamics of human hair loss. I. Telogen effluvium. Arch Dermatol. 1961;83:175–98.
56. Oliver RF. Histological studies of whisker regeneration in the hooded rat. J Embryol Exp Morphol. 1966;16:231–44.
57. Jahoda CA, Horne KA, Mauger A, et al. Cellular and extracellular involvement in the regeneration of the rat lower vibrissa follicle. Development. 1992;114:887–97.
58. Tobin DJ, Gunin A, Magerl M, et al. Plasticity and cytokinetic dynamics of the hair follicle mesenchyme: implications for hair growth control. J Invest Dermatol. 2003;120:895–904.
59. Thibaut S, Gaillard O, Bouhanna P, et al. Human hair shape is programmed from the bulb. Br J Dermatol. 2005;152:632–8.
60. Cotsarelis G, Sun TT, Lavker RM. Label-retaining cells reside in the bulge area of pilosebaceous unit: implications for follicular stem cells, hair cycle, and skin carcinogenesis. Cell. 1990;61:1329–37.
61. Muller-Rover S, Handjiski B, van der Veen C, et al. A comprehensive guide for the accurate classification of murine hair follicles in distinct hair cycle stages. J Invest Dermatol. 2001;117:3–15.
62. Kligman AM. The human hair cycle. J Invest Dermatol. 1959;33:307–16.
63. Pinkus H, Iwasaki T, Mishima Y. Outer root sheath keratinization in anagen and catagen of the mammalian hair follicle. A seventh distinct type of keratinization in the hair follicle: trichilemmal keratinization. J Anat. 1981;133(Pt 1):19–35.
64. Higgins CA, Westgate GE, Jahoda CA. From telogen to exogen: mechanisms underlying formation and subsequent loss of the hair club fiber. J Invest Dermatol. 2009;129:2100–8.
65. Parakkal PF. Morphogenesis of the hair follicle during catagen. Z Zellforsch Mikrosk Anat. 1970;107:174–86.
66. Ahmad W, Faiyaz ul Haque M, Brancolini V, et al. Alopecia universalis associated with a mutation in the human hairless gene. Science. 1998;279:720–4.
67. Cichon S, Anker M, Vogt IR, et al. Cloning, genomic organization, alternative transcripts and mutational analysis of the gene responsible for autosomal recessive universal congenital alopecia. Hum Mol Genet. 1998;7:1671–9.
68. Wen Y, Liu Y, Xu Y, et al. Loss-of-function mutations of an inhibitory upstream ORF in the human hairless transcript cause Marie Unna hereditary hypotrichosis. Nat Genet. 2009;41:228–33.
69. Greco V, Chen T, Rendl M, et al. A two-step mechanism for stem cell activation during hair regeneration. Cell Stem Cell. 2009;4:155–69.
70. Plikus MV, Mayer JA, de la Cruz D, et al. Cyclic dermal BMP signalling regulates stem cell activation during hair regeneration. Nature. 2008;451:340–4.
71. Mardaryev AN, Ahmed MI, Vlahov NV, et al. Micro-RNA-31 controls hair cycle-associated changes in gene expression programs of the skin and hair follicle. FASEB J. 2010;24:3869–81.
72. Panteleyev AA, Jahoda CA, Christiano AM. Hair follicle predetermination. J Cell Sci. 2001;114(Pt 19):3419–31.
73. Oshima H, Rochat A, Kedzia C, et al. Morphogenesis and renewal of hair follicles from adult multipotent stem cells. Cell. 2001;104:233–45.
74. Johnson E. Moulting cycles. Mammal Review. 1972;1:198–208.
75. Randall VA, Ebling FJ. Seasonal changes in human hair growth. Br J Dermatol. 1991;124:146–51.
76. Milner Y, Sudnik J, Filippi M, et al. Exogen, shedding phase of the hair growth cycle: characterization of a mouse model. J Invest Dermatol. 2002;119:639–44.
77. Higgins CA, Richardson GD, Westgate GE, Jahoda CA. Exogen involves gradual release of the hair club fibre in the vibrissa follicle model. Exp Dermatol. 2009;18:793–5.
78. Donetti, E, Boschini E, Cerini A, et al. Desmocollin 1 expression and desmosomal remodeling during terminal differentiation of human anagen hair follicle: an electron microscopic study. Exp Dermatol. 2004;13:289–97.
79. Blount M, Goff S, Slusarewicz P. In vitro degradation of the inner root sheath in human hair follicles lacking sebaceous glands. Br J Dermatol. 2008;158:22–30.
80. Clemmensen OJ, Hainau B, Hansted B. The ultrastructure of the transition zone between specialized cells ("Flugelzellen") of Huxley's layer of the inner root sheath and cells of the outer root sheath of the human hair follicle. Am J Dermatopathol. 1991;13:264–70.
81. Langbein L, Rogers MA, Praetzel S, et al. A novel epithelial keratin, hK6irs1, is expressed differentially in all layers of the inner root sheath, including specialized huxley cells (Flügelzellen) of the human hair follicle. J Invest Dermatol. 2002;118:789–99.
82. Schweizer J, Langbein L, Rogers MA, Winter H. Hair follicle-specific keratins and their diseases. Exp Cell Res. 2007;313:2010–20.
83. Schweizer J, Bowden PE, Coulombe PA, et al. New consensus nomenclature for mammalian keratins. J Cell Biol. 2006;174:169–74.
84. Langbein L, Rogers MA, Winter H, et al. The catalog of human hair keratins. I. Expression of the nine type I members in the hair follicle. J Biol Chem. 1999;274:19874–84.
85. Rogers MA, Langbein L, Praetzel-Wunder S, et al. Human hair keratin-associated proteins (KAPs). Int Rev Cytol. 2006;251:209–63.
86. Moll R, Divo M, Langbein L. The human keratins: biology and pathology. Histochem Cell Biol. 2008;129:705–33.
87. van Steensel MA, Steijlen PM, Bladergroen RS, et al. A missense mutation in the type II hair keratin hHb3 is associated with monilethrix. J Med Genet. 2005;42:e19.
88. Smith F. The molecular genetics of keratin disorders. Am J Clin Dermatol. 2003;4:347–64.
89. Shimomura Y, Wajid M, Kurban M, et al. Mutations in the keratin 85 (KRT85/hHb5) gene underlie pure hair and nail ectodermal dysplasia. J Invest Dermatol. 2010;130:892–5.
90. Naeem M, Wajid M, Lee K, et al. A mutation in the hair matrix and cuticle keratin KRTHB5 gene causes ectodermal dysplasia of hair and nail type. J Med Genet. 2006;43:274–9.
91. Langbein L, Rogers MA, Praetzel-Wunder S, et al. K25 (K25irs1), K26 (K25irs2), K27 (K25irs3), and K28 (K25irs4) represent the type I inner root sheath keratins of the human hair follicle. J Invest Dermatol. 2006;126:2377–86.
92. Shimomura Y, Wajid M, Petukhova L, et al. Autosomal-dominant woolly hair resulting from disruption of keratin 74 (KRT74), a potential determinant of human hair texture. Am J Hum Genet. 2010;86:632–8.
93. Winter H, Schissel D, Parry DA, et al. An unusual Ala12Thr polymorphism in the 1A alpha-helical segment of the companion layer-specific keratin K6hf: evidence for a risk factor in the etiology of the common hair disorder pseudofolliculitis barbae. J Invest Dermatol. 2004;122:652–7.
94. Langbein L, Schweizer J. Keratins of the human hair follicle. Int Rev Cytol. 2005;243:1–78.
95. Garrod D, Chidgey M. Desmosome structure, composition and function. Biochim Biophys Acta. 2008;1778:572–87.
96. Holthofer B, Windoffer R, Troyanovsky S, Leube RE. Structure and function of desmosomes. Int Rev Cytol. 2007;264:65–163.
97. Green KJ, Simpson CL. Desmosomes: new perspectives on a classic. J Invest Dermatol. 2007;127:2499–515.
98. Bazzi H, Getz A, Mahoney MG, et al. Desmoglein 4 is expressed in highly differentiated keratinocytes and trichocytes in human epidermis and hair follicle. Differentiation. 2006;74:129–40.
99. Wu H, Stanley JR, Cotsarelis G. Desmoglein isotype expression in the hair follicle and its cysts correlates with type of keratinization and degree of differentiation. J Invest Dermatol. 2003;120:1052–7.
100. Kljuic A, Bazzi H, Sundberg JP, et al. Desmoglein 4 in hair follicle differentiation and epidermal adhesion: evidence from inherited hypotrichosis and acquired pemphigus vulgaris. Cell. 2003;113:249–60.
101. Bazzi H, Demehri S, Potter CS, et al. Desmoglein 4 is regulated by transcription factors implicated in hair shaft differentiation. Differentiation. 2009;78:292–300.
102. Moss C, Martinez-Mir A, Lam H, et al. A recurrent intragenic deletion in the desmoglein 4 gene underlies localized autosomal recessive hypotrichosis. J Invest Dermatol. 2004;123:607–10.
103. Schaffer JV, Bazzi H, Vitebsky A, et al. Mutations in the desmoglein 4 gene underlie localized autosomal recessive hypotrichosis with monilethrix hairs and congenital scalp erosions. J Invest Dermatol. 2006;126:1286–91.
104. Zlotogorski A, Marek D, Horev L, et al. An autosomal recessive form of monilethrix is caused by mutations in DSG4: clinical overlap with localized autosomal recessive hypotrichosis. J Invest Dermatol. 2006;126:1292–6.
105. Koch PJ, Mahoney MG, Ishikawa H, et al. Targeted disruption of the pemphigus vulgaris antigen (desmoglein 3) gene in mice causes loss of keratinocyte cell adhesion with a phenotype similar to pemphigus vulgaris. J Cell Biol. 1997;137:1091–102.
106. Amagai M, Tsunoda K, Suzuki H, et al. Use of autoantigen-knockout mice in developing an active autoimmune disease model for pemphigus. J Clin Invest. 2000;105:625–31.
107. Ayub M, Basit S, Jelani M, et al. A homozygous nonsense mutation in the human desmocollin-3 (DSC3) gene underlies hereditary hypotrichosis and recurrent skin vesicles. Am J Hum Genet. 2009;85:515–20.
108. Levy-Nissenbaum E, Betz RC, Frydman M, et al. Hypotrichosis simplex of the scalp is associated with nonsense mutations in CDSN encoding corneodesmosin. Nat Genet. 2003;34:151–3.
109. Oji V, Eckl KM, Aufenvenne K, et al. Loss of corneodesmosin leads to severe skin barrier defect, pruritus, and atopy: unraveling the peeling skin disease. Am J Hum Genet. 2010;87:274–81.
110. Shimomura Y, Christiano AM. Biology and genetics of hair. Annu Rev Genomics Hum Genet. 2010;11:109–32.
111. Leclerc EA, Huchenq A, Mattiuzzo NR, et al. Corneodesmosin gene ablation induces lethal skin-barrier disruption and hair-follicle degeneration

related to desmosome dysfunction. J Cell Sci. 2009;122(Pt 15):2699–709.
112. Nowak JA, Polak L, Pasolli HA, Fuchs E. Hair follicle stem cells are specified and function in early skin morphogenesis. Cell Stem Cell. 2008;3:33–43.
113. Nguyen H, Rendl M, Fuchs E. Tcf3 governs stem cell features and represses cell fate determination in skin. Cell. 2006;127:171–83.
114. Rhee H, Polak L, Fuchs E. Lhx2 maintains stem cell character in hair follicles. Science. 2006;312:1946–9.
115. Horsley V, Aliprantis AO, Polak L, et al. NFATc1 balances quiescence and proliferation of skin stem cells. Cell. 2008;132:299–310.
116. Jaks V, Barker N, Kasper M, et al. Lgr5 marks cycling, yet long-lived, hair follicle stem cells. Nat Genet. 2008;40:1291–9.
117. Morris RJ, Liu Y, Marles L, et al. Capturing and profiling adult hair follicle stem cells. Nat Biotechnol. 2004;22:411–17.
118. Ohyama M, Terunuma A, Tock CL, et al. Characterization and isolation of stem cell-enriched human hair follicle bulge cells. J Clin Invest. 2006;116:249–60.
119. Hsu YC, Pasolli HA, Fuchs E. dynamics between stem cells, niche, and progeny in the hair follicle. Cell. 2011;144:92–105.
120. Ito M, Liu Y, Yang Z, et al. Stem cells in the hair follicle bulge contribute to wound repair but not to homeostasis of the epidermis. Nat Med. 2005;11:1351–4.
121. Snippert HJ, Haegebarth A, Kasper M, et al. Lgr6 marks stem cells in the hair follicle that generate all cell lineages of the skin. Science. 2010;327:1385–9.
122. Jensen KB, Collins CA, Nascimento E, et al. Lrig1 expression defines a distinct multipotent stem cell population in mammalian epidermis. Cell Stem Cell. 2009;4:427–39.
123. Horsley V, O'Carroll D, Tooze R, et al. Blimp1 defines a progenitor population that governs cellular input to the sebaceous gland. Cell. 2006;126:597–609.
124. Jensen UB, Yan X, Triel C, et al. A distinct population of clonogenic and multipotent murine follicular keratinocytes residing in the upper isthmus. J Cell Sci. 2008;121(Pt 5):609–17.
125. Rufaut NW, Goldthorpe NT, Wildermoth JE, Wallace OA. Myogenic differentiation of dermal papilla cells from bovine skin. J Cell Physiol. 2006;209:959–66.
126. Richardson GD, Arnott EC, Whitehouse CJ, et al. Cultured cells from the adult human hair follicle dermis can be directed toward adipogenic and osteogenic differentiation. J Invest Dermatol. 2005;124:1090–1.
127. Jahoda CA, Whitehouse J, Reynolds AJ, Hole N. Hair follicle dermal cells differentiate into adipogenic and osteogenic lineages. Exp Dermatol. 2003;12:849–59.
128. Lako M, Armstrong L, Cairns PM, et al. Hair follicle dermal cells repopulate the mouse haematopoietic system. J Cell Sci. 2002;115(Pt 20):3967–74.
129. Reynolds AJ, Jahoda CA. Cultured dermal papilla cells induce follicle formation and hair growth by transdifferentiation of an adult epidermis. Development. 1992;115:587–93.
130. Pearton DJ, Yang Y, Dhouailly D. Transdifferentiation of corneal epithelium into epidermis occurs by means of a multistep process triggered by dermal developmental signals. Proc Natl Acad Sci USA. 2005;102:3714–19.
131. Gilhar A. Collapse of immune privilege in alopecia areata: coincidental or substantial? J Invest Dermatol. 2010;130:2535–7.
132. Billingham RE. Transplantation immunity evoked by skin homografts and expressed in intact skin. Adv Biol Skin. 1971;11:183–98.
133. Hoffman U, Tokura Y, Nishijima T, Takigawa M, Paus R. Hair cycle-dependent changes in skin immune functions: anagen-associated depression of sensitization for contact hypersensitivity in mice. J Invest Dermatol. 1996;106:598–604.
134. Kang H, Wu WY, Lo BK, et al. Hair follicles from alopecia areata patients exhibit alterations in immune privilege-associated gene expression in advance of hair loss. J Invest Dermatol. 2010;130:2677–80.
135. Ito T. Hair follicle is a target of stress hormone and autoimmune reactions. J Dermatol Sci. 2010;60:67–73.
136. Petukhova L, Duvic M, Hordinsky M, et al. Genome-wide association study in alopecia areata implicates both innate and adaptive immunity. Nature. 2010;466:113–17.
137. Deng L, Mariuzza RA. Structural basis for recognition of MHC and MHC-like ligands by natural killer cell receptors. Semin Immunol. 2006;18:159–66.
138. Groh V, Steinle A, Bauer S, Spies T. Recognition of stress-induced MHC molecules by intestinal epithelial γδ T cells. Science. 1998;279:1737–40.
139. Gilhar A, Paus R, Kalish RS. Lymphocytes, neuropeptides, and genes involved in alopecia areata. J Clin Invest. 2007;117:2019–27.
140. Middleton D, Curran M, Maxwell L. Natural killer cells and their receptors. Transpl Immunol. 2002; 10:147–64.
141. Long EO. Regulation of immune responses through inhibitory receptors. Annu Rev Immunol. 1999;17: 875–904.
142. Meyer KC, Klatte JE, Dinh HV, et al. Evidence that the bulge region is a site of relative immune privilege in human hair follicles. Br J Dermatol. 2008;159:1077–85.
143. Gilhar A, Kalish RS. Alopecia areata: a tissue specific autoimmune disease of the hair follicle. Autoimmun Rev. 2006;5:64–9.
144. Gilhar A, Landau M, Assy B, et al. Melanocyte-associated T cell epitopes can function as autoantigens for transfer of alopecia areata to human scalp explants on Prkdc(scid) mice. J Invest Dermatol. 2001;117: 1357–62.
145. Paus R, Slominski A, Czarnetzki BM. Is alopecia areata an autoimmune-response against melanogenesis-related proteins, exposed by abnormal MHC class I expression in the anagen hair bulb? Yale J Biol Med. 1993;66:541–54.
146. Carroll JM, McElwee KJ, King EL, et al. Gene array profiling and immunomodulation studies define a cell-mediated immune response underlying the pathogenesis of alopecia areata in a mouse model and humans. J Invest Dermatol. 2002;119:392–402.
147. Baran R, Dawber RPR, de Berker DAR, et al. (eds). Baran and Dawber's Diseases of the Nails and Their Management, 3rd edn. Oxford: Blackwell Science, 2001.
148. Scher RK, Daniel CR. Nails: Diagnosis, Therapy, Surgery, 3rd edn. Philadelphia: WB Saunders, 2005.
149. Zook EG. Anatomy and physiology of the perionychium. Hand Clin. 2002;18:553–9.
150. Haneke E. Surgical anatomy of the nail apparatus. Dermatol Clin. 2006;24:291–6.
151. Miura T, Nakamura R. Congenital onychodysplasia of the index fingers. J Hand Surg. 1990;15A:793–7.
152. Allan CH, Fleckman P, Fernandes RJ, et al. Tissue response and Msx1 expression after human fetal digit tip amputation in vitro. Wound Repair Regen. 2006;14:398–404.
153. Hasegawa K, Pereira BP, Pho RW. The microvasculature of the nail bed, nail matrix, and nail fold of a normal human fingertip. J Hand Surg. 2001;26A:283–90.
154. Wolfram-Gabel R, Sick H. Vascular networks of the periphery of the fingernail. J Hand Surg. 1995;20B:488–92.
155. Blaydon DC, Ishii Y, O'Toole EA, et al. The gene encoding R-spondin 4 (RSPO4), a secreted protein implicated in Wnt signaling, is mutated in inherited anonychia. Nat Genet. 2006;38:1245–7.
156. Dunston JA, Hamlington JD, Zaveri J, et al. The human LMX1B gene: transcription unit, promoter, and pathogenic mutations. Genomics. 2004;84:565–76.
157. Sweeney E, Fryer A, Mountford R, et al. Nail patella syndrome: a review of the phenotype aided by developmental biology. J Med Genet. 2003;40:153–62.
158. Smith FJ, Morley SM, McLean WH. A novel connexin 30 mutation in Clouston syndrome. J Invest Dermatol. 2002;118:530–2.
159. Lewis BL. Microscopic studies of foetal and mature nail and surrounding soft tissue. Arch Dermatol. 1954;70:732–7.
160. Zaias N, Alvarez J. The formation of the primate nail plate. An autoradiographic study in squirrel monkeys. J Invest Dermatol. 1968;51:120–36.
161. Norton LA. Incorporation of thymidine 3H and glycine-2 3H in the nail matrix and bed of humans. J Invest Dermatol. 1971;56:61–8.
162. Johnson M, Comaish JS, Shuster S. Nail is produced by the normal bed: a controversy resolved. Br J Dermatol. 1991;125:27–9.
163. Johnson M, Shuster S. Continuous formation of nail along the bed. Br J Dermatol. 1993;128:277–80.
164. de Berker D, MaWhinney B, Sviland L. Quantification of regional matrix nail production. Br J Dermatol. 1996;134:1083–6.
165. de Berker D, Angus B. Markers of epidermal proliferation are limited to nail matrix in normal nail. Br J Dermatol. 1996;135:555–9.
166. de Berker D, Graham A, Dawber RPR, Thody A. Melanocytes are absent from the normal nail bed: the basis of a clinical dictum. Br J Dermatol. 1996;134:564.
166a. Tosti A, Cameli N, Piraccini BM, et al. Characterisation of nail matrix melanocytes with anti-PEP1, anti-PEP8, TMH-1 and HMB-45 antibodies. J Am Acad Dermatol. 1994;31:193–6.
167. Tan KB, Moncrieff M, Thompson JF, et al. Subungual melanoma: a study of 124 cases highlighting features of early lesions, potential pitfalls in diagnosis, and guidelines for histologic reporting. Am J Surg Pathol. 2007;31:1902–12.
168. Ito T, Ito N, Saathoff M, et al. Immunology of the human nail apparatus: the nail matrix is a site of relative immune privilege. J Invest Dermatol. 2005;125:1139–48.
169. Gniadecka M, Faurskov Nielsen O, Christensen DH, Wulf HC. Structure of water, proteins, and lipids in intact human skin, hair, and nail. J Invest Dermatol. 1998;110:393–8.
170. Perrin C, Langbein L, Schweizer J. Expression of hair keratins in the adult nail unit: an immunohistochemical analysis of the onychogenesis in the proximal nail fold, matrix and nail bed. Br J Dermatol. 2004;151:362–71.
171. de Berker D, Wojnarowska F, Sviland L, et al. Keratin expression in the normal nail unit: markers of regional differentiation. Br J Dermatol. 2000;142:89–96.
172. Sueki H, Nozaki S, Fujisawa R, et al. Glycosylated proteins of skin, nail and hair: application as an index for long-term control of diabetes mellitus. J Dermatol. 1989;16:103–10.
173. Roomans GM, Afzelius BA, Kollberg H, Forslind B. Electrolytes in nails analysed by X-ray microanalysis in electron microscopy. Considerations on a new method for the diagnosis of cystic fibrosis. Acta Paediatr Scand. 1978;67:89–94.
174. Salamon T, Lazović-Tepavac O, Nikulin A, et al. Sudan-IV-positive material of the nail plate related to plasma triglycerides. Dermatologica. 1988;176:52–4.
175. Hussein Were F, Njue W, Murungi J, Wanjau R. Use of human nails asbio-indicators of heavy metals environmental exposure among school age children in Kenya. Sci Total Environ. 2008;393:376–84.
176. Sengupta MK, Mukherjee A, Hossain MA, et al. Groundwater arsenic contamination in the Ganga-Padma-Meghna-Brahmaputra plain of India and Bangladesh. Arch Environ Health. 2003;58:701–2.
177. Dykes PJ, Thomas R, Finlay AY. Determination of terbinafine in nail samples during systemic treatment for onychomycoses. Br J Dermatol. 1990;123:481–6.
178. Al-Delaimy WK, Willett WC. Measurement of tobacco smoke exposure: comparison of toenail nicotine biomarkers and self-reports. Cancer Epidemiol Biomarkers Prev. 2008;17:1255–61.
179. Cingolani M, Scavella S, Mencarelli R, et al. Simultaneous detection and quantitation of morphine, 6-acetylmorphine, and cocaine in toenails: comparison with hair analysis. J Anal Toxicol. 2004;28:128–31.
180. Mari F, Politi L, Bertol E. Nails of newborns in monitoring drug exposure during pregnancy. Forensic Sci Int. 2008;179:176–80.
181. Bean WB. Nail growth: 30 years of observations. Arch Intern Med. 1974;134:497–502.
182. Weismann K. Beau and his description of transverse depressions on nails. Br J Dermatol. 1977;97:571–2.
183. Moffitt DL, de Berker DA. Yellow nail syndrome: the nail that grows half as fast grows twice as thick. Clin Exp Dermatol. 2000;25:21–3.

Alopecias 69

Leonard C Sperling, Rodney D Sinclair and Laila El Shabrawi-Caelen

Chapter Contents

Androgenetic alopecia *1093*
Telogen effluvium *1098*
Trichotillomania *1099*
Alopecia areata *1100*
Cicatricial (scarring) alopecias *1104*
Hair shaft abnormalities *1109*

Key features

- Genetically determined sensitivity of scalp hair follicles to adult levels of androgens
- Miniaturization of hairs in a symmetric "pattern" on the crown, vertex and frontal regions
- Antiandrogen medications can be used for successful treatment

INTRODUCTION

The pilosebaceous unit includes the hair follicle, the arrector pili muscle, the sebaceous gland and, where present, the apocrine gland (see Chs 35 & 68). The bulb is the lowest portion of the follicle and it contains the hair matrix epithelium and the mesenchymal dermal papilla. Whereas the bulb undergoes cyclical involution and regeneration, the infundibulum and isthmus represent the permanent part of the follicle.

Keratinocytes within the matrix rapidly proliferate and differentiate into six distinct cell lineages. Cells arising from the central matrix just above the dermal papilla give rise to the hair shaft, which consists of three components – the *medulla* (centrally), *cortex* and *hair shaft cuticle* (outermost). The outer aspects of the matrix give rise to the inner root sheath (IRS), a structure that is also composed of three layers: (1) the *IRS cuticle* (innermost), which interlocks with the hair shaft cuticle and anchors the shaft; (2) the *Huxley layer*; and (3) the *Henle layer* (outermost; see Ch. 68). Henle's layer then abuts the outer root sheath (ORS) epithelium.

The IRS is the first structure within the hair follicle to cornify, forming a hard cylindrical case around the emerging hair shaft; it also seals the lower portion of the pilosebaceous unit from the environment. Just below the entry of the sebaceous gland duct, the inner root sheath desquamates, creating a space between the shaft and the ORS, allowing for sebaceous gland excretory flow. Of note, the ORS is continuous with the overlying epidermis.

The arrector pili muscle attaches to the hair follicle at the *bulge*. Certain epithelial cells within the ORS bulge have stem cell-like properties and are involved in hair follicle regeneration and cycling[1] (see Chs 2 & 68). Theoretically, if this site is permanently injured, hair regrowth cannot occur.

In this chapter, the major non-cicatricial (non-permanent) alopecias will be reviewed first, followed by a discussion of cicatricial alopecias. This will be followed by a review of structural hair shaft abnormalities.

ANDROGENETIC ALOPECIA

Synonyms: ■ Male pattern and female pattern hair loss (MPHL and FPHL) ■ Common balding ■ Hereditary balding or thinning

Introduction

Androgenetic alopecia (AGA) is an androgen-dependent, hereditary physical trait resulting from the conversion of scalp terminal hairs into miniaturized vellus hairs in a characteristic pattern[1]. The frequency and severity increase with age, and at least 80% of Caucasian men and ~50% of women show evidence of AGA by age 70 years[2,3].

Pathogenesis

High concordance of MPHL amongst monozygotic twins indicates a strong genetic predisposition. The inheritance is polygenic and a

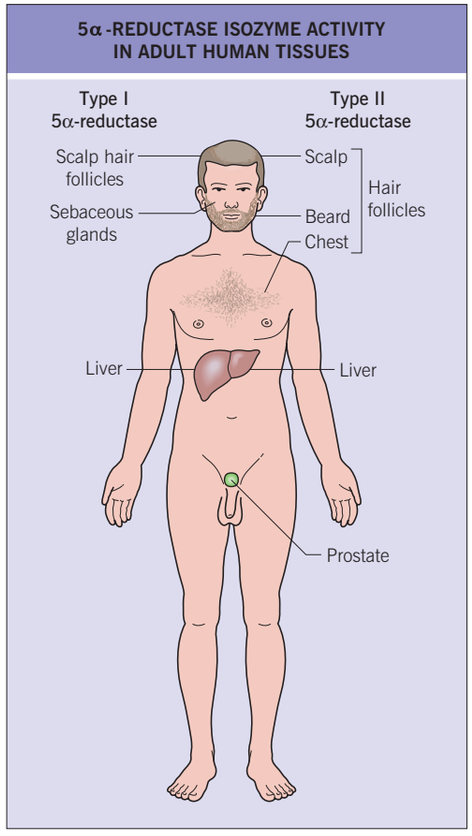


Fig. 69.1 5α-reductase isozyme activity in adult human tissues.

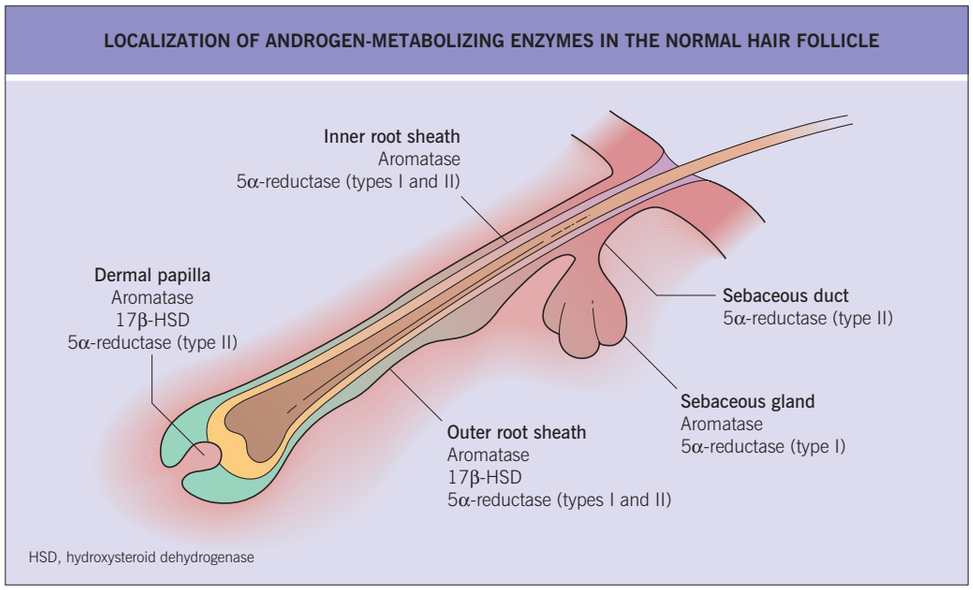


Fig. 69.2 Localization of androgen-metabolizing enzymes in the normal hair follicle. *Courtesy, Maria K Hordinsky, MD.*

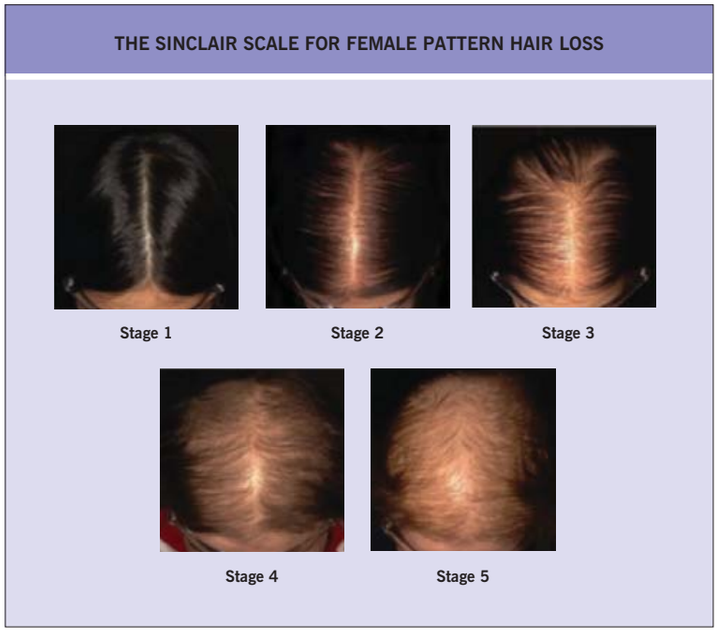


Fig. 69.3 The Sinclair scale for female pattern hair loss. Stage 1 – normal; Stage 2 – widening of the central part line; Stage 3 – widening of the part line with translucency of the hairs at its border; Stage 4 – development of a bald area anteriorly along the part line; and Stage 5 – advanced hair loss.

number of genetic loci have been implicated, including those that encode the androgen receptor (MPHL) and aromatase, which converts testosterone to estradiol (FPHL)[4,5]. Androgen hormones clearly initiate and promulgate MPHL in genetically susceptible individuals, and while inhibition of androgen biosynthesis or action will arrest the progression of MPHL, it will only partially reverse the miniaturization of hairs.

In men, the expression of AGA is related in particular to the androgen hormone dihydrotestosterone (DHT). Testosterone is converted to DHT by the enzyme 5α-reductase, of which there are two isoenzymes, type I and type II. Type I 5α-reductase is present predominantly in sebaceous glands and the liver, whereas type II 5α-reductase dominates in scalp, beard and chest hair follicles, as well as in the liver and the prostate gland (Fig. 69.1). The genetic absence of type II 5α-reductase prevents development of male AGA[1].

Investigators have localized androgen-metabolizing enzymes to various regions of the hair follicle (Fig. 69.2). In scalp biopsy specimens obtained from men with AGA, 5α-reductase activity and DHT levels are increased compared to non-balding scalp skin[6]. DHT is implicated in the appearance of miniaturized hair follicles and hair shafts, and decreased levels in both the skin and the blood have been associated with a reversal of miniaturization.

In women, a similar androgen-related pathophysiology is postulated[4]. Women who develop balding shortly after puberty often have a positive family history for pattern hair loss in both male and female family members. In women who develop pattern alopecia during the perimenopausal period and menopause, it may be due to a genetic predisposition as well as alterations in androgen metabolism at the level of the hair follicle and systemic hormonal changes[7].

Rarely, AGA develops in prepubertal children (ages 6–10 years)[8]. Affected boys and girls demonstrate a FPHL pattern without bitemporal recession, and they have a strong family history of AGA (present in at least one parent). No evidence has been found for abnormal circulating testosterone levels or precocious puberty.

Clinical features

MPHL is symmetric and progressive with some pattern variation. Hamilton[9] and then Norwood[10] first classified the patterns of male AGA based upon frontoparietal and frontal recession as well as vertex thinning (see Fig. 157.2). Occasionally, a "male type" pattern with frontotemporal and vertex thinning is seen in women, and then they too can be classified with the Hamilton or Norwood system.

However, the most common pattern of FPHL is diffuse central thinning of the crown with preservation of the frontal hairline. Often there is frontal accentuation of the hair loss, creating a "Christmas tree" pattern[11]. Examination of the central part width can be used to classify severity of FPHL via the Sinclair scale (Fig. 69.3)[12] and it can be compared to the occipital part width (Fig. 69.4)[1,13]. The findings by trichoscopy are shown in Figure 69.5.

Pathology

Scalp hairs exist as clusters (follicular units) composed of three to five shaft-producing follicles serviced by a single arrector pili muscle. One by one, as follicles miniaturize, the follicular units within thinning regions of the scalp begin to produce only one or two terminal hairs. Once all the follicles within a follicular unit miniaturize, baldness is observed[5]. Histopathologic findings of MPHL and FPHL are described in Table 69.1 and illustrated in Figure 69.10.

Fig. 69.4 Female androgenetic alopecia. Comparison of the part line on the crown (**A**) and the occiput (**B**).

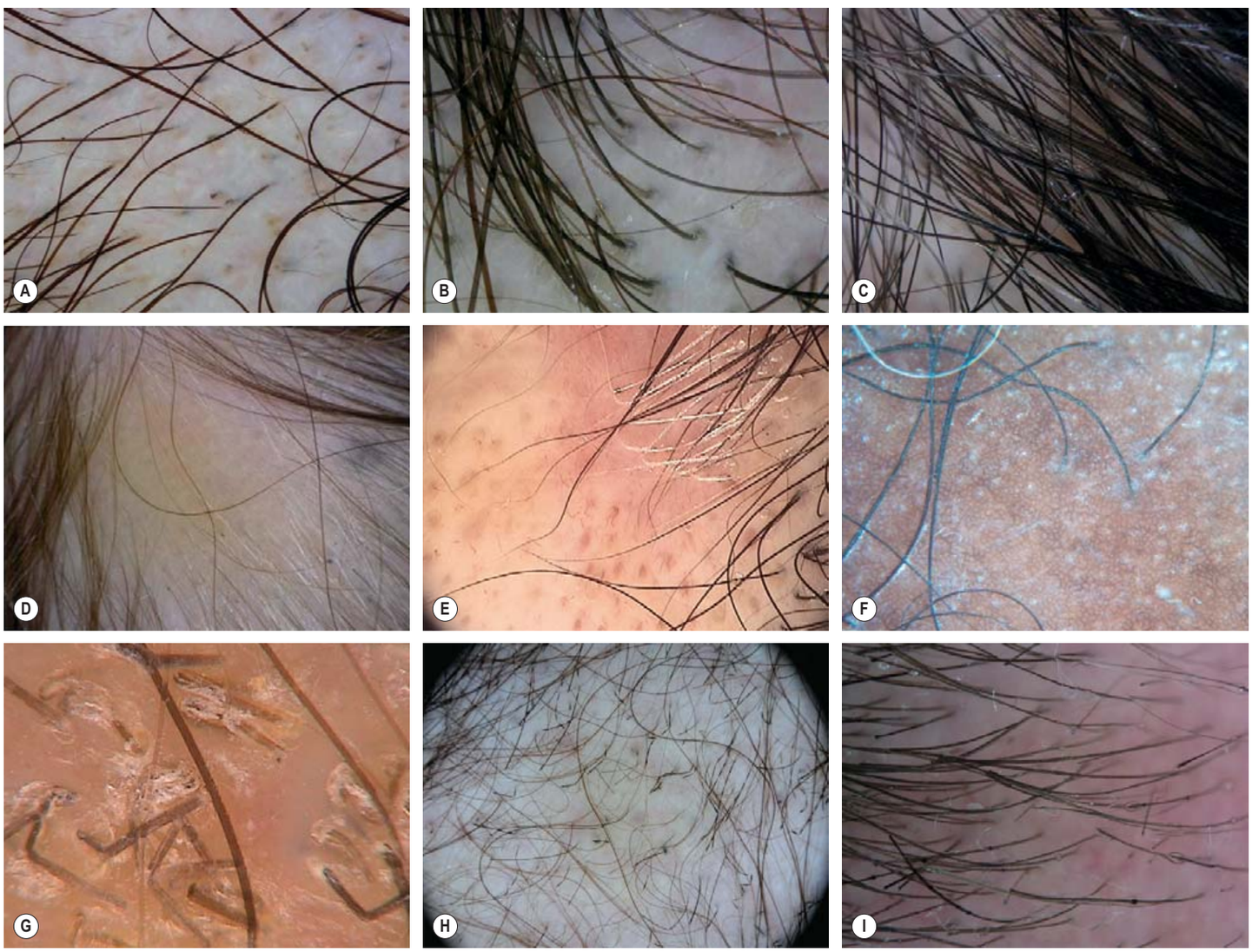


Fig. 69.5 Trichoscopy. A Alopecia areata (AA): yellow dots, exclamation point hairs and dystrophic hairs are characteristic features; the color of the yellow dots may vary from yellow to yellow–pink. Note some vellus-like hair shafts. **B** Androgenetic alopecia (AGA): a diversity of hair shaft diameters affects >20% of the hairs. Brown halos around hair shafts (peripilar sign) is a subtle clue. **C** Telogen effluvium: the hair shafts are of equal diameter (unlike AGA). **D** Temporal triangular alopecia: vellus-like, depigmented hair shafts, but no yellow dots or dystrophic hairs as are seen in AA. **E** Discoid lupus erythematosus (DLE): follicular red dots are a characteristic sign and they correspond histopathologically to dilated vessels, extravasated erythrocytes and keratin plugs. **F** Lichen planopilaris: discrete white dots due to loss of melanin over scarred fibrotic tracts and perifollicular fibrosis. The fibrosis in DLE is more diffuse. **G** Tinea capitis: comma hairs are a clue to the diagnosis. **H** Monilethrix: the presence of broken hair shafts plus hairs with a beaded appearance allows a bedside diagnosis. **I** Trichorrhexis invaginata (bamboo hairs) in a patient with Netherton syndrome: broken hair shafts and nodose swellings. *E–G, Courtesy, Antonella Tosti, MD.*

HISTOLOGIC FEATURES OF VARIOUS FORMS OF ALOPECIA
MALE AND FEMALE PATTERN HAIR LOSS (ANDROGENETIC ALOPECIA) (see Fig. 69.10)
• Normal *total* number of follicles and no significant inflammation • Increased number and percentage of vellus hairs • Numerous fibrous "streamers" • Slightly increased telogen count • Uninvolved scalp (e.g. occiput) appears normal
TELOGEN EFFLUVIUM
• Normal *total* number of hairs • Normal number of terminal (large) hairs • Increase in the telogen count to >20% (>15% is suggestive) • Absence of inflammation and scarring • Telogen count seldom exceeds 50%; >80% is inconsistent with telogen effluvium
TRICHOTILLOMANIA
• Follicles are normal size • Total number of hairs (both terminal and vellus) is normal • Incomplete, disrupted follicular anatomy • Increased number of terminal catagen and/or telogen hairs • Trichomalacia and pigment casts • No significant inflammation
ALOPECIA AREATA (see Fig. 69.10)
Early, progressive disease ("acute" and "subacute")[15]
• Normal *total* number of hairs • Peribulbar mononuclear cell infiltrate (with occasional eosinophils), predominantly affecting terminal anagen and catagen hair bulbs • Occasional exocytosis of inflammatory cells into bulbar epithelium • Degenerative changes of hair matrix • Increased number of terminal catagen and telogen hairs • Increased number of miniaturized hairs • Trichomalacia and marked narrowing of hair shafts
Longstanding and stable disease ("chronic")[15]
• Majority of hairs in catagen or telogen phases • Numerous miniaturized, "arrested", rapidly cycling hairs, referred to as *nanogen* hairs • Mild peribulbar mononuclear cell infiltrate around those nanogen hairs possessing anagen-like or catagen-like bulbs
POSTOPERATIVE (PRESSURE-INDUCED) ALOPECIA
• Early stage includes vascular thrombosis and inflammation within the dermis and superficial fat • Necrosis of the epidermis and eccrine coils when severe • In conjunction with alopecia, synchronized conversion of most or all of the terminal hair follicles to the catagen/telogen phase (*without* hair miniaturization) • Pigment casts, incontinent pigment within collapsed root sheaths, and trichomalacia (but not distorted follicular anatomy)
PSORIASIFORM ALOPECIA
• Psoriasiform epidermal changes may or may not be present • Marked increase in percentage of catagen/telogen hairs, associated with hair miniaturization • Occasional miniaturized follicle showing peribulbar chronic inflammation; plasma cells rare or absent • Marked diminution in number of sebaceous glands
TNF-α INHIBITOR-INDUCED PSORIASIFORM ALOPECIA
• Psoriasiform dermatitis often present • Increase in catagen/telogen hairs and miniaturization of hairs, similar to alopecia areata • Some peribulbar and superficial perivascular inflammation present, often with several eosinophils and plasma cells in the infiltrate
CENTRAL CENTRIFUGAL CICATRICIAL ALOPECIA
• Premature desquamation of the inner root sheath • Eccentric epithelial atrophy (thinning) with hair shafts in close proximity to the dermis • Concentric lamellar fibroplasia (onion skin-like fibrosis) of affected follicles • Variably dense lymphocytic perifollicular inflammation, primarily at the level of the upper isthmus and lower infundibulum • Occasional fusion of infundibula (polytrichia) • In advanced lesions, total destruction of the follicular epithelium with retained hair shaft fragments and granulomatous inflammation • In pustular lesions ("folliculitis decalvans"), intrafollicular and perifollicular infiltrates rich in neutrophils and lymphocytes
LICHEN PLANOPILARIS[15–24] (see Fig. 69.10)
• Band-like mononuclear cell infiltrate obscuring the interface between follicular epithelium and dermis; vacuolar alteration at the interface and hypergranulosis within affected infundibula is typical • Colloid or Civatte bodies are occasionally found as part of the interface alteration • Inflammation affects the *upper* portion of the follicle (infundibulum and isthmus) most severely • Occasionally, epidermal changes of lichen planus are found • Over time, perifollicular fibrosis becomes prominent and the lymphocytic infiltrate seems to "back away" from the follicle • An artifactual cleft between epithelium and stroma is often found, with epithelium "floating" within the cleft • Grouped globular immunofluorescence (usually IgM), adjacent to the follicular epithelium, is the characteristic pattern[25,26]

Table 69.1 Histologic features of various forms of alopecia.

Continued

HISTOLOGIC FEATURES OF VARIOUS FORMS OF ALOPECIA
DISCOID LESIONS OF LUPUS ERYTHEMATOSUS[15,18,23,24,27]
• Vacuolar interface alteration of the epidermis and follicular epithelium; epidermis may be spared • The interface change in follicles is usually vacuolar rather than lichenoid (less inflammation) • Chronic inflammation (often including plasma cells) of the eccrine sweat glands and arrector pili is sometimes present • Increased dermal mucin is often present • Granular deposits of IgG and C3 (less commonly IgM or IgA) at the dermal–epidermal junction and/or the junction of the follicular epithelium and dermis are typical
ACNE KELOIDALIS
• Perifollicular, chronic inflammation (lymphocytic and plasmacytic), most intense at the level of the isthmus and lower infundibulum • Lamellar fibroplasia, most marked at the level of the isthmus • Loss of sebaceous glands • Total follicular destruction in advanced disease
DISSECTING CELLULITIS OF THE SCALP
• Moderately dense, perifollicular lymphocytic inflammation affecting the lower half of the dermis and extending down into the subcutaneous fat • Numerous intact and seemingly undamaged follicles with intact sebaceous glands surrounded by an infiltrate of acute and chronic inflammation (early disease) • Increased percentage of catagen/telogen hairs • Initially, lymphocytes dominate the infiltrate, but eventually neutrophils become more numerous, especially in longstanding, fluctuant lesions • Vascular proliferation accompanies the infiltrate as the disease evolves, and the deep dermis and subcutaneous fat begin to exhibit the histologic findings of granulation tissue • Eventually, chronic abscesses become lined with squamous epithelium derived from the overlying epidermis, and true sinus tracts are formed • When inflammation subsides, there is dense fibrosis of the dermis and the superficial fat with loss of follicles
"END-STAGE" CICATRICIAL ALOPECIA[15]
• A decreased total number of hairs, especially terminal hairs • Loss of the sebaceous glands in zones of follicular loss • Residual, "naked" hair shafts surrounded by mild, granulomatous inflammation • Follicular streamers (stelae) without overlying follicles • Cylindrical columns of connective tissue representing the sites of former follicles
TRACTION ALOPECIA (END-STAGE)
• The total number of terminal hairs is markedly reduced • Distinct columns of connective tissue replace some follicles, leaving obvious "blank spaces" • The sebaceous glands associated with the remaining hair follicles are still intact and sebaceous glands often persist in follicular units that seem to have lost all of their hair-producing epithelium • No significant perifollicular inflammation • Rarely, retained "naked" hair shafts are seen in otherwise typical cases of end-stage traction alopecia; the significance of the finding is unclear

Table 69.1 Histologic features of various forms of alopecia (cont'd).

Differential diagnosis

The diagnosis of MPHL is straightforward unless it is coincidentally associated with other non-scarring hair diseases such as alopecia areata or telogen effluvium. Initial recognition of FPHL may coincide with a superimposed telogen effluvium. Early-onset or severe patterned hair loss in women should suggest the possibility of pathologic hyperandrogenism, and appropriate screening laboratory tests (total and free testosterone, dehydroepiandrosterone sulfate, and 17-hydroxy-progesterone) should be performed (see Ch. 70).

Treatment

A topical formulation, minoxidil (2% and 5%), and an oral drug, finasteride, have been approved by the US Food and Drug Administration (FDA) for the treatment of men with male AGA. Minoxidil is considered to be a biological response modifier and 1 ml is applied to the affected area twice a day. The most frequently reported adverse reactions are mild scalp dryness and irritation, and, rarely, allergic contact dermatitis. Minoxidil-induced hair growth is commonly associated with shedding of telogen hairs and a paradoxical worsening of hair loss approximately 4 to 6 weeks following initiation of treatment. This resolves with continued treatment.

Finasteride (1 mg daily; Fig. 69.6), a type II 5α-reductase inhibitor, has been found to be effective in the treatment of balding in men[28]. Patients should be informed that higher doses of finasteride (5 mg/day) have been associated with high-grade prostatic carcinomas in elderly men, although the overall incidence of prostatic carcinoma seems to be *reduced*[29]. With regard to the effects of finasteride (1 mg/day) on lowering serum concentrations of prostate-specific antigen (PSA), the recommendation is to adjust serum PSA concentrations by 40–50% when performing prostate cancer screening[30]. Finasteride therapy stops hair loss in 90% of men for at least 5 years, and hair can regrow in 65% of men. Continued use of the product is necessary to sustain regrowth, which is also true for topical minoxidil; halting the medication will be associated with resumption of hair loss. Surgical hair replacement, specifically hair transplantation and scalp reduction, are other alternatives for the treatment of male androgenetic alopecia (see Ch. 157). In the US, 2% and 5% topical minoxidil are approved for the management of FPHL. The latter may occur with hyperandrogenemia, and women may benefit from oral contraceptives (to suppress ovarian androgen production), spironolactone (Fig. 69.7), or, if appropriate, finasteride therapy[31–34]. If oral finasteride or spironolactone is used in women with childbearing potential, appropriate contraception should be utilized (given the risk of feminization of the male fetus), with oral contraceptives being the rational choice. While finasteride (1 mg per day) appears to be ineffective in postmenopausal women[35], when given at higher daily doses of 2.5 and 5 mg, it can improve FPHL[36,37].

Dutasteride is a combined type I and type II 5α-reductase inhibitor. A dose of 0.5 mg/day leads to a greater reduction in serum and scalp DHT levels than does finasteride at 5 mg/day. This suggests that dutasteride may be a more effective therapy. While there are emerging case reports of dutasteride leading to improvement of FPHL, the potential teratogenicity, prolonged biologic half-life preclude its use in women of childbearing age[38,39]. Hair transplantation can also be offered to women with severe FPHL.

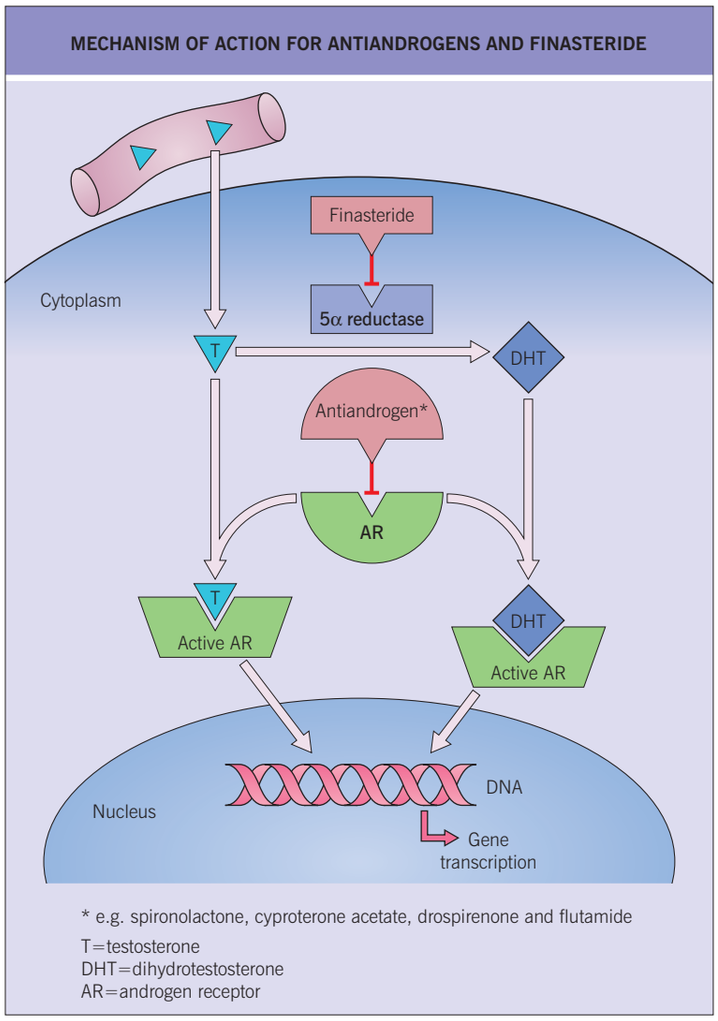


Fig. 69.6 Mechanism of action for antiandrogens and finasteride.

Fig 69.7 Female pattern hair loss in a 10-year-old girl. A Prior to treatment. **B** Obvious improvement following 5 years of therapy with oral spironolactone and topical minoxidil.

TELOGEN EFFLUVIUM

Key features

- Increased shedding of otherwise normal telogen hairs in response to a pathologic or normal physiologic change in health status
- A chronic form with no discernible precipitating factor is observed in some women
- Laboratory evaluation is directed by history, physical examination, and microscopic evaluation of shed or plucked hairs

CAUSES OF TELOGEN EFFLUVIUM

- Shedding of the newborn (physiologic)
- Postpartum (physiologic)
- Chronic telogen effluvium[42] (no attributable cause or illness)
- Postfebrile (extremely high fevers, e.g. malaria)
- Severe infection
- Severe chronic illness (e.g. HIV disease[43], systemic lupus erythematosus)
- Severe, prolonged psychological stress
- Postsurgical (implies major surgical procedure)
- Hypothyroidism and other endocrinopathies (e.g. hyperparathyroidism, hyperthyroidism)
- Crash or liquid protein diets; starvation/malnutrition
- Drugs:
  - discontinuation of oral contraceptives
  - retinoids (acitretin, isotretinoin) and vitamin A excess
  - anticoagulants (especially heparin)
  - antithyroid (propylthiouracil, methimazole)
  - anticonvulsants (e.g. phenytoin, valproic acid, carbamazepine)
  - interferon-α-2b
  - heavy metals
  - β-blockers (e.g. propranolol)

Table 69.2 Causes of telogen effluvium. For a complete list of associated drugs, see ref. 41.

Introduction

In the normal scalp, 90–95% of the follicles will be in the *anagen* phase and the remainder (5–10%) will be in the *telogen* phase (with about 50–100 hairs shed daily; see Fig. 68.5). Only a few follicles will be in the transitional or *catagen* phase. The biologic clock that determines the end of the anagen phase and the beginning of the catagen/telogen phase is a complex phenomenon whose molecular basis is beginning to be understood (see Ch. 68). The human hair can only grow for a few months to years before it becomes a telogen hair and is shed. Scalp hair grows longer than hair on other parts of the body because the length of its anagen phase is longer. Unlike mammals that molt, hair growth in humans is such that shedding of each follicle is independent of surrounding follicles. Consequently, a fairly uniform density of hair is maintained at all times. Various metabolic alterations such as pregnancy, malnutrition and other stresses are capable of adjusting the biologic clock within hair follicles, and it is possible for abnormally large numbers of hairs to enter the telogen phase simultaneously. When this happens, the hair loss is termed a *telogen effluvium*[40].

Pathogenesis

Depending on the cause of telogen effluvium, the period of excessive shedding can vary. Telogen effluvium is by far the most common form of hair loss seen as a side effect of medications or in association with systemic diseases or altered physiologic states. The causes of telogen effluvium are listed in Table 69.2. However, a fair number of women have been found to have a telogen effluvium without any discernible precipitating cause[42]. This chronic telogen effluvium primarily affects women between the ages of 30 and 60 years and is a diagnosis of exclusion.

If there is a definable precipitating event, hair loss begins approximately 3 months after this event. It takes that period of time for a hair follicle to progress through the telogen phase and to finally be shed. There is neither clinical nor histologic evidence of inflammation in a "pure" telogen effluvium.

Most drugs that have been associated with hair loss, with the exception of antineoplastic agents, cause hair loss via telogen effluvium. While numerous medications have been associated with hair loss, only a subset of these commonly causes telogen effluvium. The most prominent offenders are retinoids (acitretin and isotretinoin)[44], anticonvulsants, antithyroid medications, anticoagulants, lithium, interferons and β-adrenergic blocking agents. More complete lists of medications associated with alopecia are readily available[41].

Clinical features

Thinning of the hair involves the entire scalp and may also be noted on other hairy regions of the body (e.g. pubic and axillary hair). A gentle

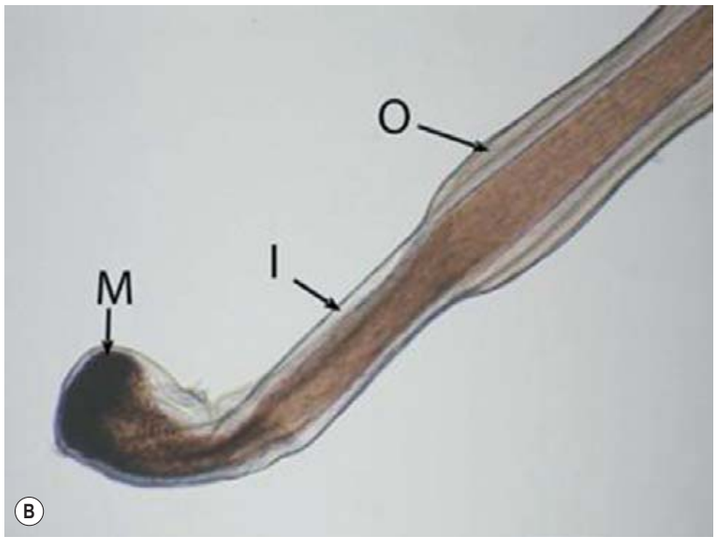


Fig. 69.8 Microscopic features of anagen and telogen hairs. A Telogen shaft showing a club-shaped bulb. **B** Anagen shaft with attached root sheaths, demonstrating a pigmented and distorted bulb; M, matrix; I, inner root sheath; O, outer root sheath. **C** Ruffled cuticle of loose anagen hair. *C, Courtesy, Julie V Schaffer, MD.*

hair pull may be positive for two or more normal telogen hairs (Fig. 69.8). A forcible hair pluck[45] (trichogram) will show a mixture of normal anagen and telogen hairs with the percentage of telogen in excess of 20%. While a telogen count of 15–20% is suggestive of abnormal shedding, >20% is diagnostic. In an active telogen effluvium, a 60-second timed hair count[45] will usually be in excess of 100 hairs (the mean normal value is 10 hairs)[46]. This method, which involves combing the hair forward for 60 seconds over cloth of a contrasting color before shampooing, can be used to follow the progression and eventual resolution of a telogen effluvium. The histopathologic findings in telogen effluvium are outlined in Table 69.1.

Eventually complete hair regrowth is expected. The prognosis for women with chronic telogen effluvium is relatively good, for although hair shedding can continue for many years, this does not appear to lead to baldness[47]. The prognosis for telogen effluvium associated with systemic disease is excellent if the precipitating cause is eliminated.

When the cause is unclear, the evaluation of a patient with telogen effluvium includes thyroid and chemistry panels, sedimentation rate, hematocrit and ferritin (as a reflection of total body iron storage). According to literature recommendations, ferritin levels should be at least 40 ng/dl, but the significance of abnormal values is uncertain[48]. In persistent cases of telogen effluvium, i.e. those lasting beyond 6 months, a scalp biopsy specimen submitted for horizontal sectioning can prove useful in excluding early AGA; the ratio of terminal to vellus hairs counted at the level of the isthmus allows distinction[49]. However, there is the possibility of the coexistence of the two disorders. Trichoscopy findings are shown in Figure 69.5.

TRICHOTILLOMANIA

Key features

- Self-induced plucking or breakage of hair
- Often associated with psychological stress or a personality disorder
- Incomplete and distorted follicular anatomy is a histologic hallmark

Introduction

The term "trichotillomania" is derived from the Greek *thrix*, hair; *tillein*, pulling out; and *mania*, madness. Trichotillomania is seen more commonly in females than in males, and in children more than adults. Onset of the disease is usually during early childhood to adolescence, and its prevalence is uncertain.

Pathogenesis

Trichotillomania is listed in the American Psychiatric Association's diagnostic classification system, DMS-4, and is grouped under the "impulse-control disorders not elsewhere classified causing clinically significant distress or impairment" (Table 69.3)[50]. However, many patients who chronically pull their hair do not meet all of the DSM-4 criteria for trichotillomania.

Individuals with trichotillomania may be a very heterogeneous group and include those with a mild habit as well as others who have an impulse-control disorder, personality disorder, body dysmorphic disorder, mental retardation or a psychosis[51]. Often the hair pulling that occurs during infancy and early childhood (boys>girls) resolves without treatment.

Clinical features

Individuals with trichotillomania usually pluck scalp hair, resulting in patchy or full alopecia of the scalp (see Ch. 7). Some patients may also pluck from other hair-bearing regions such as the eyebrows, eyelashes, face, extremities or pubic region. Patches of alopecia often have bizarre shapes, irregular borders, and contain hairs of varying lengths. Plucking may cause hair shaft fractures, and emerging shafts tend to feel "rough". In severe cases, hairs in the occiput tend to be spared. The clinical diagnosis can be supported by creating a "hair growth window" by repeatedly (weekly) shaving a small area of involved scalp to demonstrate normal, dense regrowth.

The histopathologic changes seen in trichotillomania are listed in Table 69.1. When incomplete or distorted follicular anatomy is found, suspected plucking is confirmed.

DSM-4 DIAGNOSTIC CRITERIA FOR TRICHOTILLOMANIA
1. Recurrent pulling out of one's hair resulting in noticeable hair loss
2. An increasing sense of tension immediately before pulling out the hair or when attempting to resist the behavior
3. Pleasure, gratification or relief when pulling out the hair
4. The disturbance is not better accounted for by another mental disorder and is not due to a general medical condition (e.g. a dermatologic condition)
5. The disturbance provokes clinically marked distress and/or impairment in occupational, social or other areas of functioning

Table 69.3 DSM-4 diagnostic criteria for trichotillomania.

The differential diagnosis includes tinea capitis, alopecia areata and monilethrix, which can be excluded by history, physical examination, trichoscopy, KOH examination, fungal culture and scalp biopsy. Trichoscopy findings are illustrated in Figure 69.5.

Treatment

No specific treatment approach has been established as effective in any large controlled study[52]. Hypnosis, behavioral modification therapy, insight-oriented psychotherapy and pharmacologic therapy have all been tried, but success rates are low. If a pharmacological therapy is considered, the recommended first-line medication is clomipramine. Selective serotonin reuptake inhibitors (SSRIs) have been tried without convincing success.

ALOPECIA AREATA

Key features

- Non-scarring patterned alopecia, most commonly presenting as circular areas of alopecia
- Organ-specific autoimmune disease involving T cells
- Can lead to total scalp hair loss (alopecia totalis) or complete scalp and body hair loss (alopecia universalis)

Introduction

Celsus is credited with describing patterns of hair loss using the Greek word *alopekia*, meaning fox mange, and Sauvages coined the term "alopecia areata". Alopecia areata is a non-cicatricial alopecia that is postulated to be a hair-specific autoimmune disease, with genetic factors involved in disease susceptibility and severity[53–55]. A concordance rate of 55% has been found in identical twin studies, implicating both genetic and environmental factors.

In the acute progressive stage of alopecia areata, lymphocytic infiltrates are seen around, and sometimes within, the hair bulb region of anagen follicles[31]. Despite the presence of this inflammatory infiltrate, the follicle retains its potential to produce hair, implying that the follicular stem cells remain viable.

The chronic relapsing nature of alopecia areata and its profound effect on physical appearance make the development of this condition a distressing and life-changing event for many affected individuals[56].

Epidemiology

The prevalence of alopecia areata in the US is approximately 0.1% to 0.2% of the population[57]. The average lifetime risk of developing alopecia areata is estimated to be 1.7%. Overall, one in five patients with alopecia areata reports that another family member has the disease.

Pathogenesis

T-lymphocyte interaction with follicular antigens (autoantigens) has been implicated in alopecia areata[53]. The importance of T cells in this disease has been demonstrated by several investigators. Sections of scalp skin from patients with alopecia areata will grow hair when engrafted onto congenitally athymic nude mice, and it is possible to transfer alopecia areata to human skin explants on SCID mice by the injection of scalp-infiltrating lymphocytes (both $CD4^+$ and $CD8^+$ T cells are required), but not with non-follicular scalp homogenates[58]. Melanocyte-associated antigens recognized by T cells might also function as possible autoantigens[59].

Normal anagen hair follicle keratinocytes typically lack expression of class I and class II major histocompatibility (MHC) antigens, suggesting immunologic privilege of the human hair follicle bulb[60]. In alopecia areata, human leukocyte antigens (HLA-A, -B, -C, -DR) become expressed by the hair follicle, allowing an interaction of cytotoxic T lymphocytes with hair matrix cells. In a recent genome-wide association study, single nucleotide polymorphisms were observed within the HLA region as well as in genes involved in the activation of regulatory T cells and natural killer cells (Table 69.4)[60a].

Clinical features

Alopecia areata commonly presents as round or oval patches of non-scarring hair loss (Fig. 69.9A). Short "exclamation point" hairs (i.e. distal end broader than the proximal end) can often be seen, particularly at the margins of areas of alopecia (Fig. 69.9B). Other presentations include alopecia totalis (loss of all scalp hair), alopecia universalis (loss of all scalp and body hair; Fig. 69.9C), and an ophiasis pattern (band-like pattern of hair loss along the periphery of the temporal and occipital scalp; Fig. 69.9D). The reticular variant is characterized by recurrent patchy disease, and patients experience hair loss in one area and, at the same time, spontaneous hair regrowth in another site. The rare diffuse variant of alopecia areata (see Fig. 69.9B) can manifest with widespread thinning or may primarily affect the top of the head. Non-pigmented hairs may initially be spared, and, as a result, some patients with diffuse involvement note rapid graying of the hair. With regrowth, the hairs may be initially gray or white, but usually repigmentation is observed within a few weeks or months[61].

In addition to the hair follicle, nails may be involved. The most common abnormality is nail pitting, but other changes described include trachyonychia (sandpaper-like roughness due to excessive longitudinal ridging; Fig. 69.9E), brittle nails, onycholysis, koilonychia and, rarely, onychomadesis[62] (see Ch. 71).

Disease associations are listed in Table 69.4. The histopathologic features of alopecia areata (Fig. 69.10) are described in Table 69.1, and trichoscopy findings are shown in Figure 69.5.

Differential diagnosis

Tinea capitis, trichotillomania, temporal triangular alopecia, traction alopecia, secondary syphilis and loose anagen syndrome need to be considered in the differential diagnosis of alopecia areata, in addition to pressure-related alopecia, aplasia cutis and "burnt-out" cicatricial alopecia. The diffuse variant may initially be confused with telogen effluvium and androgenetic alopecia. Usually, the history and clinical examination (including trichoscopy) is sufficient to distinguish between these conditions, but performing a scalp biopsy may prove useful.

Treatment

Treatment studies are difficult to perform because the disease has an unpredictable course and may improve on its own. To allow for the evaluation of treatments for alopecia areata, guidelines have been established to facilitate research[63].

Numerous therapies are available for the management of alopecia areata[53,64] (Table 69.5), and several can be utilized in combination. The treatment of patchy alopecia areata may include topical[65] or intralesional corticosteroids[66], topical minoxidil (2% or 5%), topical anthralin (0.5–1% cream applied daily; see Ch. 129), and combination therapy. The concentration of intralesional corticosteroid is usually 3–5 mg/ml of triamcinolone acetonide, and injections can be repeated every 4–8 weeks. This medication should be injected at the level of the mid dermis to target the diseased, miniaturized hair bulbs.

A dependable and safe treatment for extensive disease (totalis or universalis) has yet to be found, although spontaneous recovery is

Fig. 69.9 Alopecia areata. A Circular area of alopecia in a child. **B** Diffuse variant with multiple exclamation point hairs characterized by a distal end that is broader than the proximal end. **C** Total alopecia of the scalp, eyebrows and eyelashes in a patient with alopecia universalis. **D** Ophiasis with a band-like pattern of hair loss along the periphery of the temporal and occipital scalp. **E** Trachyonychia in a patient with alopecia areata. *B & E, Courtesy, Julie V Schaffer, MD.*

possible (albeit rarely), even in longstanding disease. Approximately 80% of patients will respond to high-dose systemic corticosteroids (e.g. 40 mg triamcinolone intramuscularly monthly, or daily oral prednisolone or dexamethasone tapered over 6–8 weeks); however ~50% will relapse with dose reduction or cessation of therapy[67]. Long-term maintenance therapy with oral corticosteroids is rarely justified and steroid-sparing agents such as azathioprine and methotrexate are unreliable.

Topical immunotherapy (with diphencyprone or squaric acid dibutyl ester) is the most promising treatment for extensive disease[62]. Clinicians interested in using topical immunotherapy should carefully review the published protocols[62] (Table 69.6). PUVA, potent topical corticosteroids under plastic occlusion, and systemic targeted immunomodulators ("biologics") have all been tried with less success. Of note, patients with the ophiasis pattern of hair loss are more resistant to therapy than are other patients with similar amounts of hair loss.

ALOPECIA AREATA: DISEASE AND GENETIC ASSOCIATIONS
• Associated diseases: – Atopy (allergic rhinitis, atopic dermatitis, asthma); >40% in some studies – Autoimmune thyroid disease (e.g. Hashimoto's thyroiditis), vitiligo, inflammatory bowel disease – Autoimmune polyendocrinopathy syndrome type 1 (autosomal recessive; due to mutations in the autoimmune regulator gene [*AIRE*]; up to 30% of patients have alopecia areata) – Type 1 diabetes increased in *relatives* of patients with alopecia areata • HLA associations: – HLA-DQB1*0301 (DQ7), HLA-DQB1*03 (DQ3), and HLA-DRB1*1104 (DR11); HLA-DQB1*03 appears to be a susceptibility HLA marker for all forms of alopecia areata, whereas the HLA alleles DRB1*0401 (DR4) and HLA-DQB1*0301 (DQ7) are considered markers for severe longstanding alopecia totalis/universalis[54,55] • Additional genome-wide associations[60a]: – Function of Treg cells: *CTLA4, IL-2/IL-21, IL2RA, Eos* – Expressed within the hair follicle: *PRDX5, STX17* – *ULBP* gene cluster - encodes activating ligands of NK cell receptor NKG2D

Table 69.4 Alopecia areata: disease and genetic associations. *PRDX5* encodes an anti-oxidant enzyme and *STX17* is associated with the gray hair phenotype in horses. CTLA4, cytotoxic T lymphocyte-associated antigen 4; IL, interleukin, IL-2RA, interleukin receptor A; ULBP, cytomegalovirus UL16-binding protein.

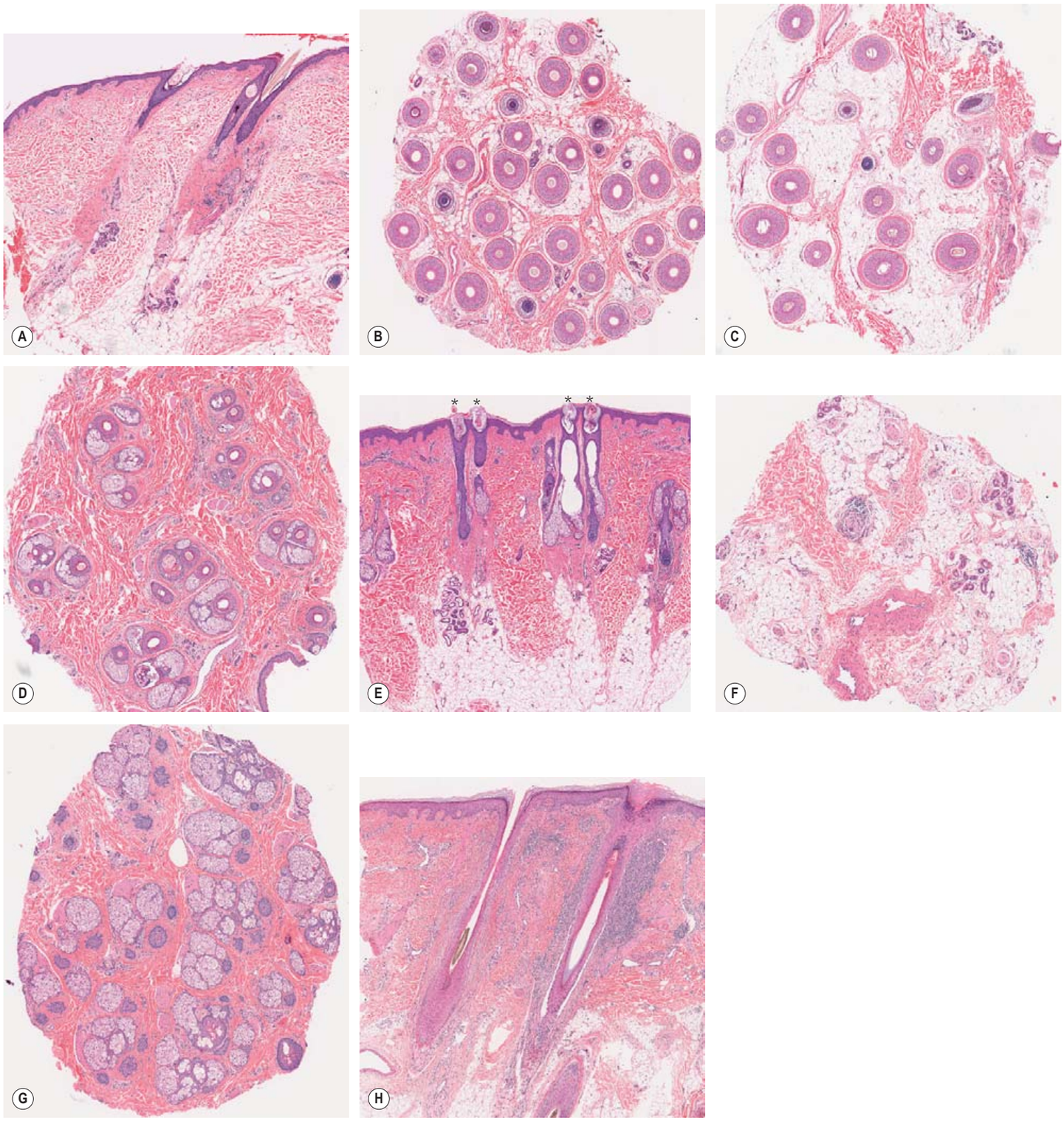


Fig. 69.10 Histologic features of androgenetic alopecia, alopecia areata and lichen planopilaris. A Androgenetic alopecia with the characteristic miniaturization of hair follicles (vertical section). **B** Normal scalp (horizontal section). **C** Androgenetic alopecia with variation in hair follicle size (horizontal section; compare to B). **D** Androgenetic alopecia at the level of the isthmus with miniaturized vellus-like hair follicles and no significant inflammation (horizontal section). **E** Alopecia areata with miniaturized, vellus-like hair follicles, one of which has a peribulbar lymphocytic infiltrate (vertical section). A clue to the diagnosis is the dilatation of the follicular infundibula which corresponds to the yellow dots by trichoscopy (asterisks)[14]. **F** Alopecia areata with the characteristic peribulbar lymphocytic infiltrates (horizontal section). **G** Alopecia areata at the level of the isthmus demonstrating exclusively telogen follicles (horizontal section). **H** Lichen planopilaris. Focal hypergranulosis at the acrotrichium and a dense perifollicular lymphocytic infiltrate. Note the Max-Joseph spaces between the hair follicle and the perifollicular sheath.

The treatment of eyebrows with intralesional corticosteroids is usually helpful, even in extensive cases. When eyelashes are absent, the wearing of eyeglasses can serve as a distracting cosmetic enhancement. All patients should be directed to the resources provided by the National Alopecia Areata Foundation (www.naaf.org) for a wealth of information about support groups, wigs, cosmetics and the latest research.

Lastly, two animal models, the *C3H/HeJ* mouse model and the Dundee rat model, are now available to investigators to help with the development, testing and analysis of new forms of therapy[68].

TREATMENT OPTIONS FOR THE MANAGEMENT OF ALOPECIA AREATA
Topical and intralesional corticosteroids (1) Topical irritants (e.g. anthralin, tazarotene, azelaic acid) (2) Topical minoxidil (2)
Topical immunotherapy (e.g. squaric acid dibutyl ester, diphencyprone) (1) Systemic corticosteroids, pulsed dosing* (especially if rapidly progressive) (2) Topical or oral photochemotherapy (PUVA) (2) Excimer laser (3) Photodynamic therapy (3)
Systemic corticosteroids, chronic (2) Systemic cyclosporine (3)
*e.g. oral prednisolone 300 mg (5 mg/kg for children) monthly for a minimum of three doses.

Table 69.5 Treatment options for the management of alopecia areata. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

TOPICAL IMMUNOTHERAPY FOR ALOPECIA AREATA
TREATMENT PROTOCOL FOR DIPHENCYPRONE (DPCP) OR SQUARIC ACID DIBUTYL ESTER (SADBE)*
• Sensitize with a 2% solution in acetone applied to a 4 × 4 cm area on one side of the scalp • After 1 week (2 weeks if the initial reaction is severe), a 0.001% solution is applied to all affected areas on the same side of the scalp • Each week, DPCP or SADBE is applied to the same side of the scalp – The *concentration* is titrated according to the severity of the reaction the previous week, with a goal of maintaining a low-grade, tolerable degree of erythema, scaling and pruritus for 24–36 hours after application – *Concentrations* are increased incrementally as follows: 0.001%, 0.01%, 0.025%, 0.05%, 0.1%, 0.25%, 0.5%, 1%, 2% • Once hair growth is established, the other side is also treated • Initial responses are usually seen after 12 weeks, and therapy is discontinued if there is no response by 24 weeks • Frequency of treatment can be decreased in the presence of full regrowth
ADDITIONAL INFORMATION
• Acetone solutions should be applied using a generous amount of cotton at the end of a wooden stick† • Following application: – The sensitizer is left on the scalp for 48 hours, then washed off – *Patients* should avoid touching the scalp for 6 hours – The *scalp* should be protected from light to avoid degradation of DPCP • SADBE must be refrigerated • Side effects include lymphadenopathy, severe or widespread eczematous reactions, and postinflammatory pigment alterations (particularly in patients with darkly pigmented skin)
CONTRAINDICATIONS
• Pregnancy (although teratogenicity has not been established) • Malignancies and blood dyscrasias
*Not FDA-approved. †Application by medical personnel is recommended.

Table 69.6 Topical immunotherapy for alopecia areata.

OTHER NON-CICATRICIAL (NON-SCARRING) ALOPECIAS

Postoperative (Pressure-Induced) Alopecia

This form of hair loss is seen most commonly in patients who have undergone lengthy surgical procedures under general anesthesia, and who had one portion of their scalp in prolonged contact with the operating table[69]. Less commonly, the condition is found in patients who sustain blunt trauma to the scalp[70,71].

Postoperative alopecia typically presents as a solitary, roughly oval patch at the site of greatest pressure, usually the upper occiput. Early on, erythema and induration are found in the central portion of the affected area. Nearly total hair loss with fairly sharp demarcation from the surrounding scalp occurs just a few weeks after the initial trauma. Usually, complete hair regrowth occurs, although several cases of permanent (i.e. cicatricial) hair loss have been reported.

The histologic findings in postoperative alopecia change as the lesion evolves (see Table 69.1)[15].

Temporal Triangular Alopecia

Also known as congenital triangular alopecia, temporal triangular alopecia may be present at birth or acquired during the first decade of life[72]. Rarely, lesions occur outside the temporal area or present during adulthood. The lancet-shaped lesions are a few centimeters in width, may be unilateral or bilateral, and are oriented so that that the tip of the "lancet" points superiorly and posteriorly (Fig. 69.11). Lesions appear hairless, but very fine vellus hairs can be seen with magnification and trichoscopy (see Fig. 69.5). Once present, the patches of alopecia persist for life.

Microscopically, there are *normal* numbers of follicles, but almost all are vellus hairs. All other features of the epidermis, dermis and other adnexa are entirely normal, and inflammation is absent.

Lipedematous Alopecia (Lipedematous Scalp)

This scalp disease does not fit well into any particular category. Coskey[73] first used the term "lipedematous alopecia" to describe a disorder of unknown cause characterized by a thick boggy scalp vertex and hair loss[73–75]. This disease has been described primarily in women with darkly pigmented skin and its coexistence in some patients with central vertex hair loss has raised the possibility of an association with central centrifugal cicatricial alopecia. The primary pathologic finding is an approximate doubling of scalp thickness as a result of edema and subsequent expansion of the subcutaneous fat layer. If there is prominent alopecia, histopathologic changes include not only a thickened adipose layer, but also replacement of hair follicles with fibrous tracts without discernible inflammation[76,77]. Surgery may be appropriate for small, well-circumscribed areas of alopecia[78].

In some instances, there is little or no alopecia[75], and so Lee and colleagues[79] have suggested that such cases be called lipedematous scalp, rather than lipedematous alopecia.

Fig. 69.11 Temporal triangular alopecia. The tip of the "lancet" points superiorly. *Courtesy, Jean L Bolognia, MD.*

Psoriasis of the Scalp and TNF-α Inhibitor-Induced Psoriasiform Alopecia

The occurrence of alopecia in the context of psoriasis is more common than expected. Usually, the alopecia is circumscribed (75%), rather than diffuse (25%)[80]. A specific finding is hair loss in tufts as thick psoriatic plaques are shed from the scalp. The latter can coincide with

antipsoriatic therapy[80]. Only rarely will psoriasis of the scalp lead to a scarring alopecia[81,82].

More recently, psoriasiform scalp alopecia has been observed in patients (with or without a history of psoriasis) receiving TNF-α inhibitors, in particular infliximab and adalimumab[83]. In protracted cases, scarring alopecia may ensue[83]. Histologically, the findings can vary (see Table 69.1).

Congenital Atrichia with Papules

This very rare condition is discussed because the genetic background of the disease has been well characterized[84]. Affected individuals fail to regrow nearly all their hair after shedding their initial growth of hair shortly after birth. Follicular cysts and milia-like lesions appear on the skin in later life[85]. This phenotype has been associated with mutations in two different genes: the *hairless* gene on chromosome 8p21 and the vitamin D receptor gene on chromosome 12q12–q14, explaining the associated vitamin D-dependent rickets. Additional inherited disorders with alopecia, in which the genetic bases are known, are outlined in Table 69.7.

CICATRICIAL (SCARRING) ALOPECIAS

Introduction

In this chapter, the terms *cicatricial alopecia* and *scarring alopecia* will be considered synonymous. "Cicatricial" or "scarring" implies that follicular epithelium has been replaced by connective tissue. The broadest definition of scarring alopecia might include all forms of alopecia

INHERITED DISORDERS WITH HYPOTRICHOSIS AND/OR HAIR SHAFT ABNORMALITIES			
Disorder	**Mode of inheritance**	**Gene or gene product**	**Gene symbol**
INHERITED DISORDERS WITH HYPOTRICHOSIS AND/OR HAIR SHAFT ABNORMALITIES			
Argininosuccinic aciduria*	AR	Argininosuccinate lyase	*ASL*
Atrichia with papular lesions	AR	Hairless (zinc finger transcription factor)	*HR*
Björnstad syndrome	AR	BCS1-like (mitochondrial membrane protein)	*BCS1L*
Cartilage–hair hypoplasia (Ch. 60)	AR	RNA component of mitochondrial RNA-processing endoribonuclease	*RMRP*
Giant axonal newuropathy with curly hair	AR	Gigaxonin	*GAN*
Hypohidrotic ectodermal dysplasia	X-linked AD	Ectodysplasin-A Ectodysplasin anhidrotic receptor gene or the EDAR-associated death domain gene	*EDA1* *EDAR or EDARADD*
Hypotrichosis, Mari type	AR	Lipase H	*LIPH*
Hypotrichosis, Marie Unna type	AD	5 prime upstream open reading frame of *HR* (hairless) gene	*HR*
Hypotrichosis simplex	AD	Adenomatosis polyposis down-regulated 1 gene	*APCDD1*
Hypotrichosis simplex of the scalp	AD	Corneodesmosin	*CDSN*
Hypotrichosis with juvenile macular dystrophy	AR	Cadherin 3 (P-cadherin)	*CDH3*
Keratosis follicularis spinulosa decalvans (KFSD)	XR	Membrane-bound transcription factor peptidase, site *2*	*MBTPS2*
Keratosis, ichthyosis and deafness	AD	Connexin-26	*GJB2*
Laron syndrome (pituitary dwarfism II)	AR	Growth hormone receptor	*GHR*
Localized autosomal recessive hypotrichosis	AR	Desmoglein 4	*DSG4*
Menkes disease†	XR	Cu^{2+}-transporting P-type ATPase 7A	*ATP7A*
Monilethrix	AD AD AD AR	Keratin 81 Keratin 83 Keratin 86 Desmoglein 4	*KRT81* *KRT83* *KRT86* *DSG4*
Netherton syndrome	AD	Serine protease inhibitor LEKTI	*SPINK5*
Pure hair nail ectodermal dysplasia	AD	Keratin 85, KRTHB5 gene	*KRT85*
T-cell immunodeficiency and congenital alopecia (Ch. 60)	AR	Forkhead box N1 (winged helix nude)	*FOXN1*
Trichothiodystrophy (TTD)	AR AR AR AR	XPB; TFIIH subunit, DNA helicase (functions in nucleotide excision repair and as a basal transcription factor) XPD; TFIIH subunit, DNA helicase (functions in nucleotide excision repair and as a basal transcription factor) General TFIIH, polypeptide 5 (TTDA; functions in nucleotide excision repair and as a basal transcription factor) Chromosome 7 open reading frame 11 (TTD-nonphotosensitive 1)	*ERCC3* *ERCC2* *GTF2H5* *C7orf11*
Vitamin D-dependent rickets with alopecia	AR	Vitamin D receptor	*VDR*

*Pili torti has also been observed in patients with other urea cycle defects such as citrullinemia.
†Allelic with occipital horn syndrome (see Table 55.5).

Table 69.7 Inherited disorders with hypotrichosis and/or hair shaft abnormalities. Hair and/or nail abnormalities can also be observed in patients with disorders of keratinization, epidermolysis bullosa and ectodermal dysplasias (see Tables 55.3, 32.1 & 55.5). AD, autosomal dominant; AR, autosomal recessive; ERCC, excision repair cross-complementing; mt, mitochondrial inheritance; TFIIH, transcription factor IIH; XP, xeroderma pigmentosum; XR, X-linked recessive. *Courtesy, Julie V Schaffer, MD.*

in which hair follicles are permanently lost. In most cases, it is assumed that *permanent injury of the follicular stem cell region has occurred*. In contrast, non-scarring alopecia is potentially reversible. A few hair diseases demonstrate a *biphasic* pattern, where non-scarring hair loss is seen *early* in the course of the disease, and permanent hair loss becomes apparent in the *later* stages of the disease[27]. Examples include androgenetic alopecia, alopecia areata and traction alopecia. These forms of alopecia are generally considered to be non-scarring. However, after many years or decades of continuous active disease, permanent dropout of follicles occurs.

In *primary* scarring alopecia, the target of inflammation appears to be the follicle. In *secondary* scarring alopecia, the follicle is merely an "innocent bystander" in the disease process. Examples of secondary scarring alopecia include deep burns, radiation dermatitis, cutaneous malignancies, cutaneous sarcoidosis, morphea, necrobiosis lipoidica, and certain chronic infections such as cutaneous tuberculosis. The various forms of secondary scarring alopecia should have distinctive clinical and histologic features typical of the underlying disease.

Performing a scalp biopsy may be helpful not only in establishing a diagnosis but also in assessing the degree of inflammation and injury to the stem cell region. Specimens should be at least 4 mm in diameter and extend into the fat. Ideally, two should be obtained – one for vertical sectioning, the other for horizontal sectioning. Recently, a HoVert technique was described in which a 4mm punch biopsy is transected ~1mm below the skin surface in order to create an epidermal disc (for vertical sections) and a lower portion (for horizontal sections)[85a].

The classification of primary cicatricial alopecia is both confusing and controversial[16,86]. Most of these diseases demonstrate some overlap in clinical and histologic features, blurring the distinction between disorders. In 2001, a North American Hair Research Society workshop developed a *provisional* classification (Table 69.8) to facilitate future discussion and research[86]. This scheme divides the entities into "lymphocytic", "neutrophilic", and "mixed lymphocytic and neutrophilic" forms[27,86–89].

Even advocates of this classification scheme, which is based on histologic findings, have found that it can fail to achieve reliable clinicopathologic correlation[88]. For the sake of simplicity, primary, inflammatory cicatricial alopecia can be divided into six diagnostic groups[15,16]. They are:

- central centrifugal cicatricial alopecia
- lichen planopilaris
- discoid lesions of lupus erythematosus
- acne keloidalis (folliculitis keloidalis, acne keloidalis nuchae)
- dissecting cellulitis (perifolliculitis abscedens et suffodiens)
- cicatricial alopecia, not otherwise classified.

Older terms such as pseudopelade, pseudopelade of Brocq, and folliculitis decalvans are poorly defined, and they are used in various ways by different authors and clinicians. Almost all of these older terms can be incorporated into one of the six categories already listed. However, some of the older terms (as well as some newer ones such as "tufted folliculitis") will be discussed in this section for the sake of clarity. End-stage traction alopecia will also be discussed in this section because it has many of the features of a cicatricial alopecia.

PROPOSED WORKING CLASSIFICATION OF PRIMARY CICATRICIAL ALOPECIA
GROUP 1: LYMPHOCYTIC
• Discoid lesions of lupus erythematosus (see Ch. 41) • Lichen planopilaris (LPP; see Ch. 11) – Classic LPP – Frontal fibrosing alopecia – Graham Little syndrome • Classic pseudopelade (*Brocq's alopecia* is the author's preferred term) • Central centrifugal cicatricial alopecia • Alopecia mucinosa (see Ch. 46) • Keratosis follicularis spinulosa decalvans (see Ch. 38) • Graft-versus-host disease
GROUP 2: NEUTROPHILIC
• Folliculitis decalvans • Dissecting cellulitis
GROUP 3: MIXED
• Acne keloidalis (see Ch. 38) • Acne necrotica • Erosive pustular dermatosis (see Ch. 87)
GROUP 4: NONSPECIFIC
• Cicatricial pemphigoid (see Ch. 30) • Busulfan-induced alopecia

Table 69.8 Proposed working classification of primary cicatricial alopecia. Adapted from ref. 86.

Central Centrifugal Cicatricial Alopecia

Synonyms: ■ Hot comb alopecia ■ Follicular degeneration syndrome ■ Pseudopelade of the central scalp ■ "Folliculitis decalvans" of the central scalp and vertex (for the highly inflammatory form)

Key features

- Slowly progressive, symmetric cicatricial alopecia centered on the crown or vertex
- Most often found in black women of African descent
- Early and mild disease can be effectively treated

Introduction

Over the years, central centrifugal cicatricial alopecia (CCCA) has been given several names because the condition is characterized by a spectrum in the degree and type of inflammation, resulting in some clinical variation[16,90–92]. All variants of CCCA have the following features in common:

- chronic and progressive disease, with eventual spontaneous "burn out" after years or decades
- disease predominantly centered on the crown or vertex
- disease that expands in a roughly symmetric fashion, with the greatest disease activity occurring in a peripheral zone of variable width, surrounding a central, alopecic zone
- clinical or histologic evidence of inflammation in the active, peripheral zone.

Epidemiology

CCCA is the most common form of scarring alopecia in any population that includes a significant number of black patients. Among African-Americans, CCCA is responsible for more cases of scarring alopecia than all other forms combined. The majority of black patients with CCCA are women, with a female: male ratio of about 3 : 1[91,92].

Pathogenesis

Caustic hair care products or the use of "hot combs" may aggravate the disease or hasten its progression, but cannot fully explain its pathogenesis. Virtually all African-American women with CCCA are using or have used chemical hair relaxers for styling purposes, but few men have used anything except pomades. Patients experience progression of the disease even after all chemical treatments (if any) are discontinued.

The current hypothesis is that patients are predisposed to follicular damage because of an anatomic abnormality, namely premature desquamation of the inner root sheath (IRS)[16,91,92]. Premature desquamation of the IRS can be observed in follicles that are otherwise normal, suggesting that it represents a very early phase of the disease. This change can occasionally be seen in other conditions in which follicles are subject to marked inflammation and degenerative changes. However, as a manifestation of *early* disease, premature IRS desquamation may be unique to CCCA and may predispose the affected follicles to injury or inflammation.

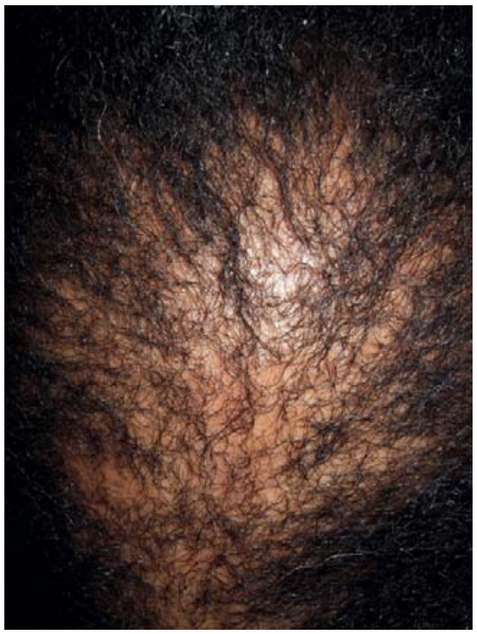


Fig. 69.12 Central centrifugal cicatricial alopecia in an African-American woman. Alopecia is most prominent on the crown and/or vertex.

Clinical features

The disease begins and remains most severe on the crown or vertex of the scalp, gradually expanding in a centrifugal fashion (Fig. 69.12). Symptoms may be mild or absent. Most patients note only mild, episodic pruritus or tenderness of involved areas. A few isolated hairs, some showing polytrichia (tufting as in "baby doll hair" or a hair brush), may be stranded in the otherwise denuded central zone. Longstanding or severe disease can result in hair loss covering the entire crown of the scalp.

Pustules and crusting may be found in the minority of patients who suffer from rapidly progressive disease or bacterial superinfection ("folliculitis decalvans")[93,94]. The pustules of CCCA are most likely a manifestation of bacterial superinfection and/or the immune response of the patient to degenerating follicular components[16]. However, some authors have argued that "folliculitis decalvans" is a primary staphylococcal infection[94]. In any case, a 2- to 3-week course of antibiotics or systemic corticosteroids can temporarily eliminate the purulent component of CCCA.

Pathology

The most productive area for biopsy is the peripheral, partially alopecic fringe, but even apparently "normal" scalp several centimeters from the clinically involved area may be diseased at the microscopic level. In most cases, transverse sections at several levels are required for a definitive diagnosis. Involved follicles will demonstrate some or all of the histopathologic features listed in Table 69.1.

Differential diagnosis

All conditions that can result in a progressive pattern of alopecia affecting the crown can mimic CCCA. These include male and female pattern alopecia, lichen planopilaris, and even unusual cases of chronic cutaneous lupus erythematosus. Other entities in the differential diagnosis are tinea capitis (kerion) and true bacterial infections of the scalp. Those who contend that "folliculitis decalvans" is a separate entity would add it to the list.

Treatment

For relatively non-inflammatory disease, a combination of a long-acting oral tetracycline (e.g. doxycycline or minocycline) plus a potent topical corticosteroid (e.g. clobetasol or fluocinonide) is usually sufficient to halt progression. Prolonged treatment for years is usually required for this chronic disease. For highly inflammatory cases ("folliculitis decalvans"), an initial 10-week regimen of oral rifampin and clindamycin (both at 300 mg twice daily) was very effective in a non-blinded, non-controlled study[94]. Maintenance therapy (such as oral doxycycline plus topical clobetasol) should follow.

Lichen Planopilaris

Key features

- Inflammatory, cicatricial alopecia with several different patterns of hair loss
- Most common cause of Brocq's alopecia (end-stage cicatricial alopecia)
- Frontal fibrosing alopecia is a distinctive clinical subset
- Can be very resistant to treatment

Introduction

Lichen planopilaris (LPP) affects women more often than men, and Caucasians are more often affected than dark-skinned individuals. Up to 50% of patients may develop lesions of the glabrous skin and mucous membranes or nail changes characteristic of lichen planus (see Ch. 11)[68]. Like lichen planus, the etiology of LPP is not known, but is presumably related to the cause(s) of lichen planus.

Clinical features

The clinical course of hair loss in LPP may be insidious or fulminant and the pattern highly variable. Patients with indolent scalp disease may be asymptomatic, but pruritus and tenderness are often present. Most commonly, there are several scattered foci of partial hair loss with associated perifollicular erythema, follicular spines and scarring (Fig. 69.13). A pattern of hair loss suggestive of central centrifugal cicatricial alopecia or Brocq's alopecia can also occur[17,95]. The diagnosis of LLP *cannot* be based on clinical features alone.

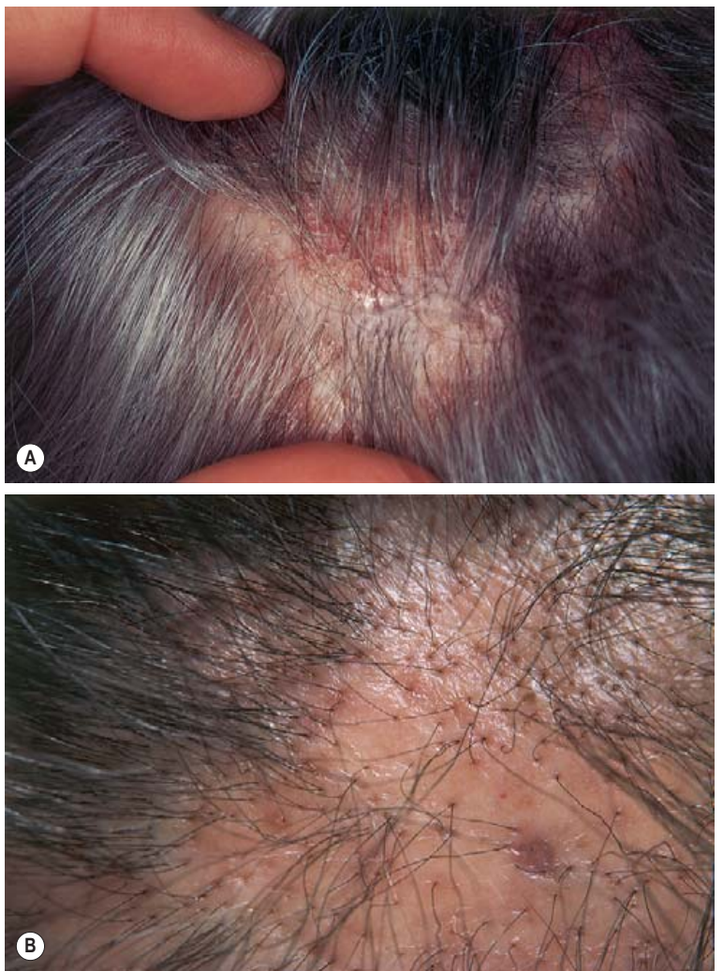


Fig. 69.13 Lichen planopilaris. A Perifollicular erythema in association with scale. **B** Later stage showing scarring with loss of follicular openings, but less erythema. *A, Courtesy, Jean L Bolognia, MD.*

Fig. 69.14 Frontal fibrosing alopecia. Progressive hair loss along the anterior hairline. *Courtesy, Kalman Watsky, MD.*

A condition termed "frontal fibrosing alopecia" was initially reported in several Australian, postmenopausal, Caucasian women[96,97]. Although most patients are elderly women (mean age in one series, 67 years), an identical pattern of hair loss has been observed in premenopausal women. There is progressive hair loss along the anterior hairline (Fig. 69.14) and the eyebrows. The histopathologic features are similar to those found in LPP. Frontal fibrosing alopecia appears to be just one of several clinical patterns of hair loss that can be seen in LPP. However, lesions of lichen planus are usually not found elsewhere in these patients and the lichenoid inflammation does not affect the interfollicular epidermis.

Possibly related to LPP is the Graham Little syndrome. This rare condition is characterized by patchy cicatricial alopecia of the scalp, non-scarring alopecia of the axillary and pubic areas, and grouped spinous follicular papules resembling lichen spinulosus or keratosis pilaris on the trunk and extremities (see Ch. 11)[89].

Pathology

The histopathologic features of LPP are listed in Table 69.1 and illustrated in Figure 69.10; the trichoscopy features are seen in Figure 69.5.

Treatment

LPP can be difficult to treat. Therapeutic recommendations include oral antimalarial drugs (e.g. hydroxychloroquine) and corticosteroids (topical, intralesional and oral)[89,97a,97b]. Recently, pioglitazone hydrochloride (a PPAR-γ agonist) was used with reported success[98]. Various other anecdotal or uncontrolled studies have reported that oral cyclosporine, oral mycophenolate mofetil, systemic retinoids or low-dose weekly oral methotrexate may be effective in some patients. These latter treatments should be used with caution, and they may themselves cause some degree of alopecia or potentially serious side effects. While some cases of LPP may burn out spontaneously, many others progress for years.

Discoid Lesions of Lupus Erythematosus

Synonym: ■ Scarring alopecia of lupus erythematosus

Key features

- Discoid lesions of lupus erythematosus occur most commonly on the face, ears and scalp
- Various clinical patterns of scalp involvement can be found
- Histopathologic findings can resemble those found in lichen planopilaris

Fig. 69.15 Late-stage chronic lupus erythematosus. Burnt-out discoid lesions of lupus erythematosus mimicking Brocq's alopecia.

Introduction

Discoid lesions are a form of cutaneous lupus erythematosus (LE) that can occur in patients with chronic cutaneous LE or systemic LE (see Table 41.2). Discoid lesions usually occur in adults, and are more common in women. Although discoid lesions are seen in patients with systemic LE, the majority of patients do not have systemic disease[99]. Among patients with skin disease only, about 50% will have scalp lesions, and very few of the patients with discoid lesions confined to the scalp will ever develop systemic LE[100].

Clinical features

The diagnosis of discoid lesions of LE requires histologic confirmation and cannot be based solely on the clinical appearance of scalp lesions. They may resemble classic discoid lesions elsewhere (see Ch. 41), with erythema, epidermal atrophy, and dilated, plugged follicular ostia in addition to alopecia. Central hypopigmentation and peripheral hyperpigmentation are commonly seen in dark-skinned individuals. However, the distribution and degree of clinical inflammation varies among patients, and the scalp lesions may resemble alopecia areata, lichen planopilaris, linear morphea, central centrifugal cicatricial alopecia or Brocq's alopecia (Fig. 69.15)[15]. Although pruritus or tenderness is common, the condition may be asymptomatic.

Pathology

The histopathologic findings are listed in Table 69.1 and trichoscopy findings in Figure 69.5.

Treatment

Discoid lesions usually respond to oral antimalarial drugs (e.g. hydroxychloroquine) and corticosteroids (topical, intralesional and oral) (see Ch. 41)[89]. If initiated early, a surprising amount of regrowth can occur. Various anecdotal or uncontrolled studies have reported that oral medications including cyclosporine, mycophenolate mofetil, retinoids, thalidomide and low-dose weekly methotrexate may be effective in some patients.

Acne Keloidalis

Synonyms: ■ Acne keloidalis nuchae ■ Folliculitis keloidalis

Key features

- Most common in black men, but can occur in women and Caucasians
- A primary form of cicatricial alopecia
- Often occurs in conjunction with central centrifugal cicatricial alopecia

Introduction

Acne keloidalis typically affects young black men and occasionally young black women[15,16,101,102]. It is at least 10 times more common in blacks than in whites and comprises nearly 0.5% of all dermatologic conditions in the black population[103]. However, this disorder can occur in white men and on rare occasion in white women.

Pathogenesis

The cause of acne keloidalis remains undetermined. The notion that lesions are caused by "ingrowing" hairs, analogous to the situation in pseudofolliculitis barbae, has been disproved[102]. Acne keloidalis is frequently found in association with central centrifugal cicatricial alopecia (CCCA), suggesting a common or related pathogenesis. Occasionally, the papular lesions and hair loss of acne keloidalis extend up onto the vertex of the scalp, producing a clinical "overlap" between this disorder and CCCA. In biopsy specimens, special stains for bacteria demonstrate relatively few organisms, suggesting that bacterial overgrowth is not of pathogenetic importance.

Clinical and histopathologic features

Acne keloidalis begins as small, smooth, firm papules admixed with occasional pustules on the occipital scalp and posterior neck (see Ch. 38). In a minority of patients, lesions are more numerous on the vertex and crown, and so it is best to use the term acne keloidalis without the modifier *nuchae*. With time, the papules resolve and leave small zones of alopecia within a field of papular lesions. In many patients, the papules coalesce and form firm, hairless, keloid-like protuberant plaques (hence the term *keloidalis*) that can be painful and cosmetically disfiguring. Abscesses and sinuses exuding pus may be present in advanced cases.

The histopathologic findings[102] are listed in Table 69.1.

Treatment

Treatment is easiest and most effective when instituted during the early (papular) phase. In the authors' experience, a regimen involving the chronic use of a potent topical corticosteroid such as clobetasol and a long-acting oral antibiotic such as doxycycline is effective in halting progression of the disease. Treatment of large keloidal lesions requires surgical excision below the level of the hair bulbs.

Dissecting Cellulitis of the Scalp

Synonym: ■ Perifolliculitis capitis abscedens et suffodiens

Key features

- A component of the "follicular occlusion tetrad"
- Early disease spares the hair follicles
- Inflammation is deep (subcutaneous fat and deep dermis)

Introduction

Dissecting cellulitis is an uncommon but distinctive and often debilitating disease. It is part of the "follicular occlusion triad" that includes hidradenitis suppurativa and acne conglobata (see Ch. 38) or tetrad that includes pilonidal sinus. However, isolated scalp disease is often seen. Dissecting cellulitis most commonly affects young adult men, especially black men, but can be seen (albeit rarely) in Caucasians and women[15,104–106]. Although follicular hyperkeratosis rather than infection is thought to play a primary role in pathogenesis, bacterial superinfection can occur.

Clinical and histopathologic features

Lesions begin as multiple, firm scalp nodules, most commonly on the mid and posterior vertex and upper occiput. The nodules rapidly develop into interconnecting, boggy, fluctuant, oval and linear ridges that eventually discharge purulent material (Fig. 69.16). There can be surprisingly little pain, and patients often seek help because of hair loss and a foul-smelling discharge.

Fig. 69.16 Dissecting cellulitis of the scalp and acne keloidalis in an African-American man.

The histopathologic findings are listed in Table 69.1.

Differential diagnosis

On rare occasions, tinea capitis can mimic dissecting cellulitis. Other highly inflammatory forms of cicatricial alopecia (particularly "folliculitis decalvans") can sometimes be confused with dissecting cellulitis.

Treatment

Various case reports indicate that isotretinoin (0.5–1.5 mg/kg daily until 4 months after achieving a clinical remission) may be an effective therapy for this condition[107], although relapses are common. Unfortunately, isotretinoin is not always effective. TNF-α inhibitors have been used with success[11,108] but to date have not been critically studied. Other treatment options include intralesional corticosteroids, oral antibiotics, and surgical approaches ranging from incision and drainage to excision with grafting.

Cicatricial Alopecia, Not Otherwise Classified

The diagnosis of "inflammatory cicatricial alopecia" or "burnt-out cicatricial alopecia" is preferable to coining a new or seemingly "specific" name for every puzzling clinical and histologic variation that is encountered.

"Burnt-out" or "end-stage" cicatricial alopecia

In patients with progressive hair loss, the diagnosis of "burnt-out cicatricial alopecia" invites additional biopsy specimens[15]. Although the patient's disease may truly be in remission, more often the histologic pattern of "end-stage" disease is due to sampling of an older, inactive portion of the lesion. The histologic findings are listed in Table 69.1.

Brocq's alopecia (Pseudopelade of Brocq)

In the authors' opinion, the term "pseudopelade of Brocq"[109,110] is a source of much confusion and should be abandoned. Brocq's alopecia is not a distinct disease but rather a clinical *pattern* of end-stage cicatricial alopecia. This pattern can be seen in lichen planopilaris, discoid lupus erythematosus and other forms of cicatricial alopecia[16,17,95]. If a definitive diagnosis of another form of cicatricial alopecia can be made, the term "Brocq's alopecia" cannot be used.

Brocq's alopecia is uncommon and usually affects Caucasian adults who discover discrete, asymptomatic areas of scalp hair loss. In some patients, the disease is slowly progressive, but in others it worsens in "spurts", with periods of activity followed by "dormant" periods. Brocq's alopecia results in irregularly shaped and often widely distributed and grouped bald patches on the scalp (Fig. 69.17)[111]. Patients with exclusive crown or vertex involvement may actually represent examples of "burnt-out" central centrifugal cicatricial alopecia (CCCA).

In most cases of Brocq's alopecia, the expected histologic findings are those of a "burnt-out" cicatricial alopecia.

Fig. 69.17 Brocq's alopecia. Irregularly shaped areas of scarring alopecia along the midline. *Courtesy, Kalman Watsky, MD.*

Fig. 69.18 "Tufted folliculitis". Note the multiple hairs arising from a single follicular orifice within the area of scarring alopecia. *Courtesy, Kalman Watsky, MD.*

"Folliculitis decalvans"

"Folliculitis decalvans" is used in different ways by different authors, and so must be redefined each time the term is used. Usually, it is applied to highly inflammatory forms of cicatricial alopecia, where inflammatory, perifollicular papules and pustules dominate the clinical picture. Often (but not always) *Staphylococcus aureus* can be grown from pustular or crusted lesions. Some authors believe that a primary staphylococcal infection of the scalp is the cause of folliculitis decalvans[94].

The majority of these patients, especially African-American patients, prove to have CCCA if appropriate "early" lesions are selected for histologic evaluation[16]. However, a "folliculitis decalvans" clinical pattern can be seen in patients who eventually prove to have tinea capitis or lichen planopilaris.

Histologically, folliculitis decalvans presents as dense, perifollicular inflammation of the upper portion of follicles, with partial or complete epithelial destruction. Usually, both acute and chronic inflammation is present, but lymphocytic, neutrophilic or granulomatous inflammation may dominate the picture. Plasma cells are often part of the mix, but this is a common, nonspecific finding seen in chronic, inflammatory conditions of the scalp.

Mild cases can be managed with topical clindamycin and antiseptic shampoos, but treatment of severe disease is more complicated and may involve maintenance therapy with oral tetracyclines. In one series of patients, long-term remissions were observed with a combination of oral rifampin and clindamycin[102].

"Tufted folliculitis"

The "tufting" seen in this *pattern* of hair disease[112] is common to several forms of scarring alopecia. It is not a specific disease, but an end stage of several different conditions (Fig. 69.18). In the opinion of the authors, this diagnostic nomenclature should be abandoned[16].

Tufting occurs when the infundibular epithelia of damaged follicles heal with the formation of a large, common infundibulum. A zone of fibrosis separates individual clusters of damaged follicles. Another name for this phenomenon is *polytrichia*. Although tufting is fairly common in cases of CCCA, it can occasionally be seen in a wide variety of other disorders, including acne keloidalis, dissecting cellulitis, pemphigus and inflammatory tinea capitis.

Traction Alopecia (End-Stage)

Traction alopecia is a *biphasic* form of hair loss. Initially, the hair loss is temporary, hair regrowth can occur, and the condition behaves like a non-cicatricial form of alopecia. However, if excessive traction is maintained for years, the hair loss may eventually become permanent (end-stage or "burnt-out"). There may be a lag period of a decade or more between the period of traction and the onset of permanent hair loss. Patients with traction alopecia are usually African-American women who present in their 30s and 40s with a several-year history of persistent, bitemporal or frontal hair loss (Fig. 69.19)[113]. Occasionally, there also may be folliculitis within the areas of alopecia. Patients may deny having worn tight braids since childhood, but often other forms of traumatic styling (e.g. "curlers") have been employed. More recently, whether or not traction is the only, or even the major, causative factor has been questioned[114].

Fig. 69.19 Traction alopecia. Favors the frontotemporal area in African-American women and is due to traumatic types of hair styling.

The histologic findings in acute, reversible traction alopecia and permanent, longstanding, "burnt-out" traction alopecia are entirely different. The acute form resembles a mild form of trichotillomania[15,115]. End-stage disease, which is most commonly found in young African-American women, has the features listed in Table 69.1.

HAIR SHAFT ABNORMALITIES

Introduction

The hair shaft consists of three major regions: the medulla, cortex and cuticle (see Ch. 68). Epithelial and trichocyte (hair) keratins have been mapped to two keratin gene clusters – the acidic keratin cluster (type

I) at 17q12–q21 and the basic keratin gene cluster (type II) at 12q11–q13 – and so genetic studies of inherited hair abnormalities have focused on these regions. A few of the disorders listed in Table 69.7 do have underlying mutations in keratin genes, e.g. monilethrix.

This chapter will divide structural hair abnormalities (Fig. 69.20) into two broad categories – those associated with increased hair fragility and those *not* associated with increased hair fragility. In the analysis of hair shaft abnormalities with routine light microscopy, the best examinations are done by analyzing the proximal 1 to 2 inches of cut hair shafts. Shafts may also be examined by transmission or scanning electron microscopy, and amino acid analysis can be performed to detect low sulfur levels.

Structural Hair Abnormalities Associated with Increased Hair Fragility

"Bubble hair"

This distinctive hair shaft abnormality is usually seen in young women with a localized area of uneven, fragile hairs. The involved hair is straighter and stiffer than normal. By light microcopy, the hair shafts contain large, irregularly spaced "bubbles" that expand and thin the hair cortex (see Fig. 69.20). Hair fractures occur at the site of larger bubbles.

The problem is caused by traumatic hair care techniques involving heat, as from a malfunctioning hair dryer[116]. Once the damaged hair is trimmed, the condition resolves completely with gentle hair styling.

Monilethrix

Synonym: ■ Beaded hair

Monilethrix is a term of Greek and Latin derivation meaning "necklace hair". This disorder is inherited in an autosomal dominant fashion with variable expression. Monilethrix has been mapped to the epithelial keratin gene cluster on 12q11–q13, and point mutations have been found in the hair cortex-specific keratin genes *KRT86* (most often; previously referred to as *hHb6*) and *KRT81* (previously referred to as

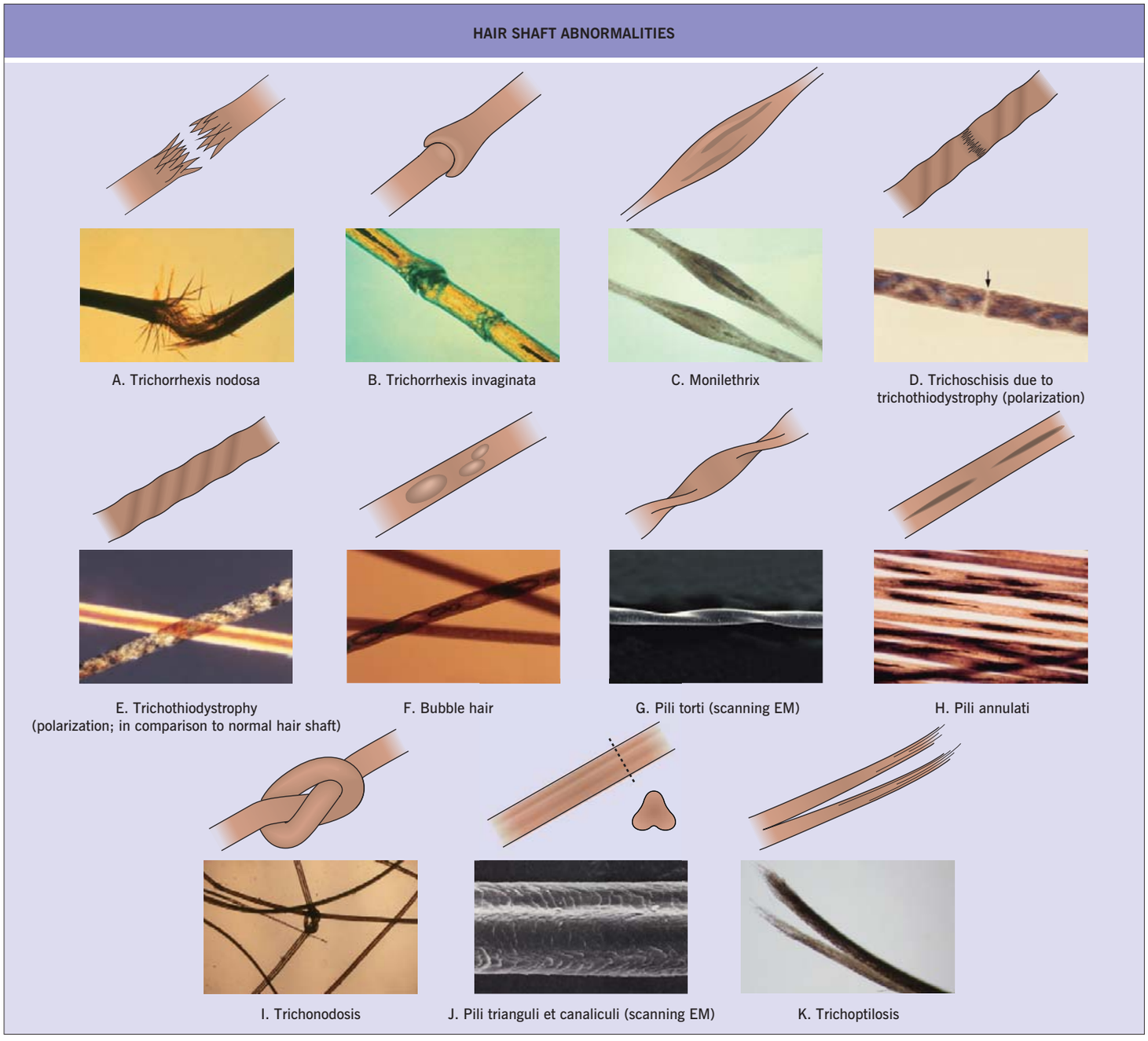


Fig. 69.20 Hair shaft abnormalities. EM, electron microscopy. *A & B, Courtesy, Maria K Hordinsky, MD; F, Courtesy, Jean L Bolognia, MD.*

Fig. 69.21 Monilethrix. Hypotrichosis due to breakage of fragile hairs. Note the small perifollicular papules with scale.

hHb1; see Ch. 56)[85]. In addition, mutations have been found in the genes that encode K83 and (in patients with an autosomal recessive form of monilethrix) desmoglein 4.

Affected individuals usually have normal-appearing hair at birth, but within the first few months of life these fibers are replaced by short, fragile, brittle hair (Fig. 69.21). Usually, the scalp is the only region involved, but in more extensive cases there may be eyebrow, eyelash and nail involvement (koilonychia most commonly). Perifollicular erythema and follicular hyperkeratosis are commonly observed. Hair fibers have uniform elliptical nodes of normal thickness and intermittent abnormal constrictions (see Fig. 69.20).

Pili torti

Pili torti is characterized by a flattened shaft and twisting of the hair fiber on its own axis (see Fig. 69.20). The twists are typically narrow and occur in groups of three to ten twists, giving the hair fiber a spangled appearance. Classic pili torti is part of a clinical syndrome associated with ectodermal abnormalities (keratosis pilaris, nail dystrophies, dental abnormalities). Hair may be sparse or abnormal from birth, or it may be normal at birth and then during infancy become replaced by brittle and fragile hair. Body hair also may be absent or sparse. Light microscopic examination reveals grouped twists of flattened hair.

In Björnstad syndrome, an autosomal recessive condition caused by mutations in the *BCS1L* gene, pili torti is associated with sensorineural hearing loss[117]; therefore, children with pili torti should have early testing for hearing loss. Other inherited diseases that can feature pili torti include Menkes disease (see below), Bazex–Dupré–Christol syndrome (see Ch. 99), hypotrichosis with juvenile macular dystrophy (due to P-cadherin mutations), Laron syndrome (primary growth hormone insensitivity), ectodermal dysplasias, mitochondrial disorders, and urea cycle defects (e.g. citrullinemia, argininosuccinic aciduria).

There is no treatment for pili torti, but it may improve at puberty. Although late-onset pili torti presents after puberty as patchy scalp alopecia, eyebrow and eyelash fibers may demonstrate fractures in childhood. Acquired pili torti-like hair shaft twisting has been reported in association with anorexia nervosa and oral retinoid therapy.

Menkes disease (trichopoliodystrophy or Menkes steely hair disease) is an X-linked recessive disorder of copper metabolism, with affected males having pili torti, severe psychomotor retardation, growth failure, seizures and other neurologic abnormalities[85]. Additional manifestations include a characteristic pudgy face with a "cupid's bow" upper lip, doughy skin and diffuse cutaneous hypopigmentation. Trichorrhexis nodosa can also affect the hair shafts in Menkes disease and is an additional source of hair fragility. The majority of patients die in early childhood. Features of the disease are the direct or indirect result of copper deficiency, and it is caused by mutations in *ATP7A*, a gene that encodes a copper-transporting ATPase. Clinically, hair is sparse in density, depigmented, lusterless, and looks and feels like steel wool. In suspected cases, the evaluation should include both the hair mount examination and serum copper and ceruloplasmin determinations. The presence of streaks of pili torti and/or hypopigmentation in mothers, sisters and maternal aunts of patients with Menkes disease may identify heterozygote female carriers.

Trichorrhexis invaginata

Trichorrhexis invaginata, also known as bamboo hair, is commonly seen in association with ichthyosis linearis circumflexa in patients with Netherton syndrome. The disorder results from pathogenic mutations in the *SPINK5* gene, which codes for a serine protease inhibitor termed LEKTI (see Ch. 57).

Atopy is commonly seen in affected individuals. The hair abnormality usually becomes evident in infancy with the development of short, sparse and very fragile hair. The breakage points consist of intussusceptions of the distal shaft ("ball") into the proximal shaft ("socket") due to defective cornification of the cortex (see Fig. 69.20). Fracture of the shaft may leave the proximal shaft with a golf tee-shaped end. In adults, the scalp hair tends to improve but bamboo defects in the eyebrow and body hair may persist.

Trichorrhexis nodosa

This is the most common of all the structural hair abnormalities and is characterized on light microscopic examination by a hair shaft fracture in which the individual cortical cells and their fragments splay out, appearing like the ends of two brushes pushed into one another (see Fig. 69.20). The abnormality is presumably caused by damage to the cuticular cells of the shaft and subsequently to the intercellular cement substance that normally binds cells together. Trichorrhexis nodosa may be a congenital or acquired abnormality. It may be seen in children with mental retardation and argininosuccinic aciduria or citrullinemia. Three variants of acquired trichorrhexis nodosa have been identified: (1) *proximal* trichorrhexis nodosa, which is commonly seen in patients after years of uncomplicated hair straightening; (2) *distal* trichorrhexis nodosa, which occurs as a result of acquired, cumulative, cuticular damage; and (3) *circumscribed* trichorrhexis nodosa, which may occur in the scalp, moustache or beard[118].

Trichothiodystrophy

Trichothiodystrophy is an autosomal recessive disorder characterized by sulfur-deficient hair. Vera Price and colleagues coined the term and recognized early on that trichothiodystrophy was a marker for a neuroectodermal symptom complex. Microscopic examination of hair fibers reveals transverse fractures (trichoschisis), alterations in the cuticle, and alternating light and dark bands under polarizing light[119] (see Fig. 69.20). Clinical features may vary greatly and range from an isolated hair abnormality to a constellation of findings (see Ch. 57). Several acronyms have been developed to describe the different clinical phenotypes seen. PIBIDS refers to a phenotype consisting of: P (photosensitivity), I (ichthyosis), B (brittle hair), I (intellectual impairment with low IQ), D (decreased fertility) and S (short stature). Some patients may also exhibit spasticity, tremors and ataxia, nail dystrophy, dental caries, cataracts, bony defects and immunodeficiency[85,120]. Approximately half of trichothiodystrophy patients are photosensitive (see Ch. 87).

Trichothiodystrophy is caused by several functionally related genetic defects involving the TFIIH/XPD-XPB complex (see Ch. 86). Current thinking is that transcription factor IIH has a dual function – transcription and DNA repair[85].

In order to diagnose trichothiodystrophy, it has been suggested that hairs demonstrate a low sulfur content *and* one of the following findings: trichoschisis, alternating light and dark bands by polarizing microscopy, or an absent or severely damaged hair cuticle by scanning electron microscopy[119,121].

Structural Hair Abnormalities *Not* Associated with Increased Hair Fragility

Acquired progressive kinking of the hair

The term encompasses several conditions characterized by acquired curling of the scalp hair. In the most common variant, young men develop curly, frizzy and lusterless hair in the frontotemporal region or vertex of the scalp, with subsequent progression to androgenetic

alopecia in the affected areas. Localized and diffuse forms of acquired hair kinking that are *not* associated with hair thinning have been described.

Loose anagen hair syndrome

The classic presentation of loose anagen hair syndrome is a young girl with fairly short blond hair that seldom needs cutting and who has diffuse or patchy alopecia without an increase in hair fragility. Boys and dark-haired children can also be affected. Anagen hair can be easily and painlessly pulled from the scalp, and microscopic examination reveals a ruffled proximal cuticle (see Fig. 69.8C), absence of the root sheath, and a bent matrix. Familial cases have been reported. The defect is thought to be a result of faulty cornification of the inner root sheath. This would then interfere with normal interdigitation of the inner root sheath cuticle with the hair cuticle, leading to poor anchoring. Improvement occurs with aging. The differential diagnosis includes telogen effluvium, alopecia areata and trichotillomania.

Pili annulati

Also known as ringed hair, this condition is characterized by hair shafts that have bright and dark bands when viewed by reflected light. The bright bands are related to light scattered from periodically occurring clusters of abnormal, air-filled cavities within the hair. The condition may be sporadic or seen as an autosomal dominant trait. On microscopic examination of a hair mount, the air-filled cavities are seen as dark regions (see Fig. 69.20).

Pili bifurcati

This hair fiber anomaly is characterized by bifurcation of the hair fiber at multiple irregular intervals along the shaft, forming separate rami, which then again fuse. Each ramus has its own cuticle.

Pili multigemini

The term pili multigemini is associated with multiple hair shafts arising from one papilla. Each hair fiber has its own inner root sheath but all the fibers are surrounded by a common outer root sheath. Multigeminate hairs are usually found in the beard region. The differential diagnosis includes trichostasis spinulosa and compound follicles.

Spun-glass hair (uncombable hair)

This entity is also known as pili trianguli et canaliculi and refers to a rare hair abnormality in which hair has a "spun glass" appearance due to the reflection of light from variably oriented, flattened hair surfaces. Hair is characteristically stiff and difficult to comb. Abnormal keratinization of the internal root sheath is postulated to cause the irregularly shaped hair shafts, which have a triangular shape on cross-section and a longitudinal groove that is best seen by scanning electron microscopy (see Fig. 69.20).

Woolly hair

Human hair may at times develop a woolly appearance. The presence of woolly hair may be congenital and can be inherited as either an autosomal dominant or recessive trait. Some patients present with a circumscribed patch of woolly hair (woolly hair nevus) (Fig. 69.22). Microscopic examination may reveal elliptical cross-sections, axial twisting and occasional trichorrhexis nodosa. Woolly hair is found in association with palmoplantar keratoderma (PPK) and cardiomyopathy in two autosomal recessive disorders – Naxos disease (diffuse non-epidermolytic PPK; due to plakoglobin mutations) and Carvajal syndrome (striate epidermolytic PPK; due to desmoplakin mutations). The triad of woolly hair, striate PPK and fatal cardiomyopathy has also been described in a family with a dominant-negative desmoplakin mutation. In addition, desmoplakin mutations underlie the autosomal recessive skin fragility/woolly hair syndrome. Woolly hair is occasionally observed in patients with Noonan syndrome and cardio-facio-cutaneous syndrome. Other conditions reported in association with woolly hair include ulerythema ophryogenes, keratosis pilaris, ichthyosis, osteoma cutis, abnormal teeth, nail dystrophy and intractable diarrhea during infancy. Kinky (but not truly woolly) hair is a feature of giant axonal neuropathy and tricho-dento-osseus syndrome.

Fig. 69.22 Woolly hair nevus. Circumscribed area where scalp hair is wavier and has a woolly appearance.

Alopecia of sites other than the scalp

While alopecia of the scalp is the primary focus of this chapter, alopecia can occur in any hair-bearing site. For example, in alopecia areata, there can be involvement of the eyebrows, eyelashes and even all the body hair. Occasionally, anagen effluvium will affect body hair as well as scalp hair. In addition, the presence of alopecia within an erythematous plaque may serve as a clue to the diagnosis of follicular (alopecia) mucinosis. There are also "patterned" alopecias of unknown etiology that can affect the anterolateral shin and thigh that are most obvious in men. Lastly, hypotrichosis of the lateral third of the eyebrows may serve as a clue to the presence of hypothyroidism.

REFERENCES

1. Simpson N, Barth J. Hair patterns: hirsuties and baldness. In: Rook A, Dawber R (eds). Diseases of the Hair and Scalp, 3rd edn. Oxford: Blackwell Scientific, 1997:67–122.
2. Severi G, Sinclair R, Hopper JL, et al. Androgenetic alopecia in men aged 40–69 years: prevalence and risk factors. Br J Dermatol. 2003;149:1207–13.
3. Gan DC, Sinclair RD. Prevalence of male and female pattern hair loss in Maryborough. J Investig Dermatol Symp Proc. 2005;10:184–9.
4. Yip L, Zaloumis S, Irwin D, et al. Gene-wide association study between the aromatase gene (CYP19A1) and female pattern hair loss. Br J Dermatol. 2009;161:289–94.
5. Yazdabadi A, Magee J, Harrison S, Sinclair R. The Ludwig pattern of androgenetic alopecia is due to a hierarchy of androgen sensitivity within follicular units that leads to selective miniaturization and a reduction in the number of terminal hairs per follicular unit. Br J Dermatol. 2008;159:1300–2.
6. Sawaya ME, Price VH. Different levels of 5alpha-reductase type I and II, aromatase, and androgen receptor in hair follicles of women and men with androgenetic alopecia. J Invest Dermatol. 1997;109:296–300.
7. Knochenhauer E, Azziz R. Ovarian hormones and adrenal androgens during a woman's life span. J Am Acad Dermatol. 2001;45(3 suppl.):S105–15.
8. Tosti A, Iorizzo M, Piraccini BM. Androgenetic alopecia in children: report of 20 cases. Br J Dermatol. 2005;152:556–9.
9. Hamilton J. Patterned loss of hair in man; types and incidence. Ann N Y Acad Sci. 1951;53:708–14.
10. Norwood OT. Male pattern baldness: classification and incidence. South Med J. 1975;68:1359–65.
11. Olsen EA, Messenger AG, Shapiro J, et al. Evaluation and treatment of male and female pattern hair loss. J Am Acad Dermatol. 2005;52:301–11.
12. Messenger AG, Sinclair R. Follicular miniaturization in female pattern hair loss: clinicopathological correlations. Br J Dermatol. 2006;155:926–30.

13. Ludwig E. Classification of the types of androgenic alopecia (common baldness) arising in the female sex. Br J Dermatol. 1977;97:249–56.
14. Müller CS, El Shabrawi-Caelen L. "Follicular swiss cheese pattern" — another clue to alopecia areata. J Cutan Pathol. 2011;38:185–9.
15. Sperling LC. An Atlas of Hair Pathology with Clinical Correlations. New York: Parthenon Publishing Group, 2003.
16. Sperling L, Solomon A, Whiting D. A new look at scarring alopecia. Arch Dermatol. 2000;136:235–42.
17. Amato L, Mei S, Massi D, et al. Cicatricial alopecia; a dermatopathologic and immunopathologic study of 33 patients (pseudopelade of Brocq is not a specific clinico-pathologic entity). Int J Dermatol. 2002;41:8–15.
18. Annessi G, Lombardo G, Gobello T, Puddu P. A clinicopathologic study of scarring alopecia due to lichen planus: comparison with scarring alopecia in discoid lupus erythematosus and pseudopelade. Am J Dermatopathol. 1999;21:324–31.
19. Elston D, Bergfeld W. Cicatricial alopecia (and other causes of permanent alopecia). In: Olsen E (ed.). Disorders of Hair Growth. New York: McGraw-Hill, 1994.
20. Matta M, Kibbi AG, Khattar J, Salman SM, Zaynoun ST. Lichen planopilaris: a clinicopathologic study. J Am Acad Dermatol. 1990;22:594–8.
21. Mehregan DA, Van Hale HM, Muller SA. Lichen planopilaris: clinical and pathologic study of forty-five patients. J Am Acad Dermatol. 1992;27:935–42.
22. Waldorf DS. Lichen planopilaris. Histopathologic study of disease. Progression to scarring alopecia. Arch Dermatol. 1966;93:684–91.
23. Whiting DA. Cicatricial alopecia: clinico-pathological findings and treatment. Clin Dermatol. 2001;19:211–25.
24. Headington JT. Cicatricial alopecia. Dermatol Clin. 1996;14:773–82.
25. Ioannides D, Bystryn JC. Immunofluorescence abnormalities in lichen planopilaris. Arch Dermatol. 1992;128:214–16.
26. Smith WB, Grabski WJ, McCollough ML, Davis TL. Immunofluorescence findings in lichen planopilaris: a contrasting experience. Arch Dermatol. 1992;128:1405–6.
27. Templeton S, Solomon A. Scarring alopecia: a classification based on microscopic criteria. J Cutan Pathol. 1994;21:97–109.
28. Whiting DA, Olsen EA, Savin R, et al. Efficacy and tolerability of finasteride 1 mg in men aged 41 to 60 years with male pattern hair loss. Eur J Dermatol. 2003;13:150–60.
29. Klein EA, Tangen CM, Goodman PJ, et al. Assessing benefit and risk in the prevention of prostate cancer: the prostate cancer prevention trial revisited. J Clin Oncol. 2005;23:7460–6.
30. D'Amico AV, Roehrborn CG. Effect of 1 mg/day finasteride on concentrations of serum prostate-specific antigen in men with androgenetic alopecia; a randomised controlled trial. Lancet Oncol. 2007;8:21–5.
31. Shum KW, Cullen DR, Messenger AG. Hair loss in women with hyperandrogenism: four cases responding to finasteride. J Am Acad Dermatol. 2002;47:733–9.
32. Trueb RM. Finasteride treatment of patterned hair loss in normoandrogenic postmenopausal women. Dermatology. 2004;209:202–7.
33. Sinclair R, Wewerinke M, Jolley D. Treatment of female pattern hair loss with oral antiandrogens. Br J Dermatol. 2005;152:466–73.
34. Iorizzo M, Vincenzi C, Voudouris S, et al. Finasteride treatment of female pattern hair loss. Arch Dermatol. 2006;142:298–302.
35. Price VH, Roberts JL, Hordinsky M, et al Lack of efficacy of finasteride in postmenopausal women with androgenetic alopecia. J Am Acad Dermatol. 2000;43:768–76.
36. Iorizzo M, Vincenzi C, Voudouris S, et al. Finasteride treatment of female pattern hair loss. Arch Dermatol. 2006;142:298–302.
37. Trüeb RM; Swiss Trichology Study Group. Finasteride treatment of patterned hair loss in normoandrogenic postmenopausal women. Dermatology. 2004;209:202–7.
38. Olszewska M, Rudnicka L. Effective treatment of female androgenic alopecia with dutasteride. J Drugs Dermatol. 2005;4:637–4.
39. Sinclair R, Wewerinke M, Jolley D. Treatment of female pattern hair loss with oral antiandrogens. Br J Dermatol. 2005;152:466–73.
40. Kligman A. Pathologic dynamics of human hair loss. I. Telogen effluvium. Arch Dermatol. 1961;83: 175–98.
41. Litt JZ. Litt's Drug Eruptions and Reactions Manual, 16th edn. New York: Informa Healthcare, 2010.
42. Whiting DA. Chronic telogen effluvium: increased scalp hair shedding in middle-aged women. J Am Acad Dermatol. 1996;35:899–906.
43. Smith K, Skelton H, DeRusso D, et al. Clinical and histopathologic features of hair loss in patients with HIV-1 infection. J Am Acad Dermatol. 1996;34: 63–8.
44. Berth-Jones J, Shuttleworth D, Hutchinson P. A study of etretinate alopecia. Br J Dermatol. 1990;122:751–5.
45. Sperling L. Evaluation of hair loss. Curr Probl Dermatol. 1996;8:97–136.
46. Wasko CA, Mackley CL, Sperling LC, et al. Standardizing the 60 second hair count. Arch Dermatol. 2008;144:759–62.
47. Sinclair R. Chronic telogen effluvium: a study of 5 patients over 7 years. J Am Acad Dermatol. 2005;52(2 Suppl 1):12–16.
48. Sinclair R. There is no clear association between low serum ferritin and chronic diffuse telogen hair loss. Br J Dermatol. 2002;147:982–4.
49. Tosti A, Piraccini BM. Diagnosis and Treatment of Hair Disorders. An Evidence Based Atlas. London: Taylor & Francis, 2007:59.
50. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th edn. text revision. Washington, DC: American Psychiatric Association, 2000.
51. Duke DC, Keely ML, Geffken GR, Storch EA. Trichotillomania: a current review. Clin Psychol Rev. 2010;30:181–93.
52. Ravindran AV, da Silva TL, Ravindran LN, et al. Obsessive-compulsive spectrum disorders: a review of the evidence-based treatments. Can J Psychiatry. 2009;54:331–43.
53. Norris D. Alopecia areata: current state of knowledge. J Am Acad Dermatol. 2004;51(1 suppl.):S16–17.
54. Martinez-Mir A, Zlotogorski A, Ott J, et al. Genetic linkage studies in alopecia areata. J Investig Dermatol Symp Proc. 2003; 8:199–203.
55. Martinez-Mir A, Zlotogorski A, Gordon D, et al. Genomewide scan for linkage reveals evidence of several susceptibility loci for alopecia areata. Am J Hum Genet. 2007;80:316–28.
56. Tosti A, Bellavista S, Iorizzo M. Alopecia areata: a long term follow-up study of 191 patients. J Am Acad Dermatol. 2006;55:438–41.
57. Safavi K. Prevalence of alopecia areata in the First National Health and Nutrition Examination Survey [Letter]. Arch Dermatol. 1992;128:702.
58. Gilhar A, Landau M, Assy B, et al. Mediation of alopecia areata by cooperation between CD4+ and CD8+ T lymphocytes: transfer to human scalp explants on P*rkdc(scid)* mice. Arch Dermatol. 2002;138:916–22.
59. Gilhar A, Landau M, Assy B, et al. Melanocyte-associated T cell epitopes can function as autoantigens for transfer of alopecia areata to human scalp explants on P*rkdc(scid)* mice. J Invest Dermatol. 2001;117:1357–62.
60. Gilhar A, Kam Y, Assy B, Kalish RS. Alopecia areata induced in *C3H/HeJ* mice by interferon-gamma: evidence for loss of immune privilege. J Invest Dermatol. 2005;124:288–9.
60a. Petukhova L, Duvic M, Hordinsky M, et al. Genome-wide association study in alopecia areata implicates both innate and adaptive immunity. Nature. 2010;466: 113-7.
61. Wade MS, Sinclair RD. Persistent depigmented regrowth after alopecia areata. J Am Acad Dermatol. 2002;46:619–20.
62. Madani S, Shapiro J. Alopecia areata update. J Am Acad Dermatol. 2000;42:549–66.
63. Olsen E, Hordinsky M, McDonald-Hull S, et al. Alopecia areata investigational assessment guidelines. National Alopecia Areata Foundation. J Am Acad Dermatol. 1999;40:242–6.
64. Ross EK, Shapiro J. Management of hair loss. Dermatol Clin. 2005;23:227–43.
65. Tosti A, Iorizzo M, Botta GL, Milani M. Efficacy and safety of a new clobetasol propionate 0.05% foam in alopecia areata: a randomized, double-blind placebo-controlled trial. J Eur Acad Dermatol Venereol. 2006;20:1243–7.
66. Chang KH, Rojhirunsakool S, Goldberg LJ. Treatment of severe alopecia areata with intralesional steroid injections. J Drugs Dermatol. 2009;8:909–12.
67. Kurosawa M, Nakagawa S, Mizuashi M, et al. A comparison of the efficacy, relapse rate and side effects among three modalities of systemic corticosteroid therapy for alopecia areata. Dermatology. 2006;212:361–5.
68. Tang L, Sundberg JP, Lui H, Shapiro J. Old wine in new bottles: reviving old therapies for alopecia areata using rodent models. J Investig Dermatol Symp Proc. 2003;8:212–16.
69. Boyer J, Vidmar D. Postoperative alopecia: a case report and literature review. Cutis. 1994;54:321–2.
70. Lee WS, Lee SW, Lee S, Lee JW. Postoperative alopecia in five patients after treatment of aneurysm rupture with a Guglielmi detachable coil: pressure alopecia, radiation induced, or both? J Dermatol. 2004;31:848–51.
71. Khalaf H, Negmi H, Hassan G, Al-Sebayel M. Postoperative alopecia areata: is pressure-induced ischemia the only cause to blame? Transplant Proc. 2004;36:2158–9.
72. Trakimas C, Sperling L, Skelton HI, et al. Clinical and histologic findings in temporal triangular alopecia. J Am Acad Dermatol. 1994;31:205–9.
73. Coskey RJ, Fosnaugh RP, Fine G. Lipedematous alopecia. Arch Dermatol. 1961;84:619–22.
74. Fair KP, Knoell KA, Patterson JW, et al. Lipedematous alopecia: a clinicopathologic, histologic and ultrastructural study. J Cutan Pathol. 2000;27:49–53.
75. Martin JM, Monteagudo C, Montesinos E, et al. Lipedematous scalp and lipedematous alopecia: a clinical and histologic analysis of 3 cases. J Am Acad Dermatol. 2005;52:152–6.
76. González-Guerra E, Haro R, Angulo J, et al. Lipedematous alopecia: an uncommon clinicopathologic variant of nonscarring but permanent alopecia. Int J Dermatol. 2008;47:605–9.
77. Piraccini BM, Voudouris S, Pazzaglia M, et al. Lipedematous alopecia of the scalp. Dermatol Online J. 2006;12:6.
78. Yip L, Mason G, Pohl M, Sinclair R. Successful surgical management of lipoedematous alopecia. Australas J Dermatol. 2008;49:52–4.
79. Lee JH, Sung YH, Yoon JS, Park JK. Lipedematous scalp. Arch Dermatol. 1994;130:802–3.
80. Runne U, Kroneisen-Wiersma P. Psoriatic alopecia: acute and chronic hair loss in 47 patients with scalp psoriasis. Dermatology. 1992;185:82–7.
81. van de Kerkhof PC, Chang A. Scarring alopecia and psoriasis. Br J Dermatol. 1992;126:524–5.
82. Wright AL, Messenger AG. Scarring alopecia in psoriasis. Acta Derm Venereol. 1990;70:156–9
83. El Shabrawi-Caelen L, La Placa M, Vincenzi C, et al. Adalimumab-induced psoriasis of the scalp with diffuse alopecia: a severe potentially irreversible cutaneous side effect of TNF-alpha blockers. Inflamm Bowel Dis. 2010;16:182–3.
84. Zlotogorski A, Hochberg Z, Mirmirani P, et al. Clinical and pathologic correlations in genetically distinct forms of atrichia. Arch Dermatol. 2003;139:1591–6.
85. Stratigos AJ, Baden HP. Unraveling the molecular mechanisms of hair and nail genodermatoses. Arch Dermatol. 2001;137:1465–71.
85a. Nguyen JV, Hudacek K, Whitten JA, et al. The HoVert technique: a novel method for the sectioning of alopecia biopsies. J Cutan Pathol. 2011;38:401–6.
86. Olsen EA, Bergfeld WF, Cotsarelis G, et al. Summary of North American Hair Research Society (NAHRS)-sponsored Workshop on Cicatricial Alopecia, Duke University Medical Center, February 10 and 11, 2001. J Am Acad Dermatol. 2003;48:103–10.
87. Solomon A. The transversely sectioned scalp biopsy specimen: the technique and an algorithm for its use in the diagnosis of alopecia. Adv Dermatol. 1994;9:127–57.
88. Mirmirani P, Willey A, Headington JT, et al. Primary cicatricial alopecia: histopathologic findings do not distinguish clinical variants. J Am Acad Dermatol. 2005;52:637–43.
89. Ross EK, Tan E, Shapiro J. Update on primary cicatricial alopecias. J Am Acad Dermatol. 2005;53:1–37.
90. LoPresti P, Papa C, Kligman A. Hot comb alopecia. Arch Dermatol. 1968;98:234–8.
91. Sperling L, Sau P. The follicular degeneration syndrome in black patients: "hot comb alopecia" revisited and revised. Arch Dermatol. 1992;128:68–74.
92. Sperling L, Skelton H, Smith K, et al. The follicular degeneration syndrome in men. Arch Dermatol. 1994;130:763–9.
93. Brooke RC, Griffiths CE. Folliculitis decalvans. Clin Exp Dermatol. 2001;26:120–2.
94. Powell J, Dawber R, Gatter K. Folliculitis decalvans including tufted folliculitis: clinical, histological and therapeutic findings. Br J Dermatol. 1999;140:328–33.

95. Silvers DN, Katz BE, Young AW. Pseudopelade of Brocq is lichen planopilaris: report of four cases that support this nosology. Cutis. 1993;51:99–105.
96. Faulkner CF, Wilson NJ, Jones SK. Frontal fibrosing alopecia associated with cutaneous lichen planus in a premenopausal woman. Australas J Dermatol. 2002;43:65–7.
97. Kossard S, Lee M-S, Wilkinson B. Postmenopausal frontal fibrosing alopecia: a frontal variant of lichen planopilaris. J Am Acad Dermatol. 1997;36:59–66.
97a. Chiang C, Sah D, Cho BK, et al. Hydroxychloroquine and lichen planopilaris: efficacy and introduction of Lichen Planopilaris Activity Index scoring system. J Am Acad Dermatol. 2010;62:387–92.
97b. Sperling LC, Nguyen J. Treatment of lichen planopilaris: some progress, but a long way to go. J Amer Acad Dermatol. 2010;62:398–401.
98. Mirmirani P, Karnik P. Lichen planopilaris treated with a peroxisome proliferator-activated receptor gamma agonist. Arch Dermatol. 2009;145:1363–6.
99. Yell JA, Mbuagbaw J, Burge SM. Cutaneous manifestations of systemic lupus erythematosus. Br J Dermatol. 1996;135:355–62.
100. Callen JP. Systemic lupus erythematosus in patients with chronic cutaneous (discoid) lupus erythematosus. Clinical and laboratory findings in seventeen patients. J Am Acad Dermatol. 1985;12:278–88.
101. Herzberg A, Dinehart S, Kerns B, Pollack S. Acne keloidalis. Transverse microscopy, immunohistochemistry and electron microscopy. Am J Dermatopathol. 1990;12:109–21.
102. Sperling L, Homoky C, Pratt L, Sau P. Acne keloidalis is a form of primary, scarring alopecia. Arch Dermatol. 2000;136:479–84.
103. Halder RM, Grimes PE, McLaurin CI, et al. Incidence of common dermatoses in a predominantly black dermatologic practice. Cutis. 1983;32:388, 390.
104. Halder RM. Hair and scalp disorders in blacks. Cutis. 1983;32:378–80.
105. Moyer DG, Williams RM. Perifolliculitis capitis abscedens et suffodiens. A report of six cases. Arch Dermatol. 1962;85:378–84.
106. Stites PC, Boyd AS. Dissecting cellulitis in a white male: a case report and review of the literature. Cutis. 2001;67:37–40.
107. Scerri L, Williams HC, Allen BR. Dissecting cellulitis of the scalp: response to isotretinoin. Br J Dermatol. 1996;134:1105–8.
108. Sukhatme SV, Lenzy YM, Gottlieb AB. Refractory dissecting cellulitis of the scalp treated with adalimumab. J Drugs Dermatol. 2008;7:981–3.
109. Brocq L, Lenglet E, Ayrignac J. Recherches sur l'alopecie atrophiante, variete pseudopelade. Ann Dermatol Syphilol. 1905;6:1–32, 97–127, 209–37.
110. Ronchese F. Pseudopelade. Arch Dermatol. 1960;82:336–43.
111. Dawber R. What is pseudopelade? Clin Exp Dermatol. 1992;17:305–6.
112. Isomura I, Morita A, Tamada Y. A case of tufted hair folliculitis. J Dermatol. 2002;29:427–30.
113. Scott DA. Disorders of the hair and scalp in blacks. Dermatol Clin. 1988;6:387–95.
114. Goldberg LJ. Cicatricial marginal alopecia: is it all traction? Br J Dermatol. 2009;160:62–8.
115. Sperling L, Lupton G. The histopathology of non-scarring alopecia. J Cutan Pathol. 1995;22:97–114.
116. Detwiler S, Carson J, Woosley J, et al. Bubble hair. J Am Acad Dermatol. 1994;30:54–60.
117. Richards KA, Mancini AJ. Three members of a family with pili torti and sensorineural hearing loss: the Bjornstad syndrome. J Am Acad Dermatol. 2002;46:301–3.
118. Whiting D. Structural abnormalities of the hair shaft. J Am Acad Dermatol. 1987;16:1–25.
119. Sperling LC, DiGiovanni JJ. "Curly" wood and tiger tails: an explanation for light and dark banding with polarization in trichothiodystrophy. Arch Dermatol. 2003;139:1189–92.
120. Faghri S, Tamura D, Kraemer KH, Digiovanni JJ. Trichothiodystrophy: a systematic review of 112 published cases characterizes a wide spectrum of clinical manifestations. J Med Genet. 2008;45:609–21.
121. Itin PH, Sarasin A, Pittelkow MR. Trichothiodystrophy: update on the sulfur-deficient brittle hair syndromes. J Am Acad Dermatol. 2001;44:891–920.

Hypertrichosis and Hirsutism 70

Francisco M Camacho-Martínez

Key features

- Hypertrichosis represents the growth of hair in an excessive amount, whereas hirsutism is excessive growth of terminal hairs in a "male pattern" in a female patient
- Hypertrichosis may be generalized or localized, with etiologies ranging from genodermatoses to underlying hamartomas to repeated trauma
- Hirsutism is related to hormonal factors, in particular an increase in circulating androgen levels and/or enhanced end-organ sensitivity to androgens
- In women, the major sources of androgens are the adrenal glands and the ovaries; dysfunction of these organs must be considered when a patient presents with hirsutism
- If minimal or no hormonal abnormalities are found, the patient may be diagnosed as having constitutional hirsutism or familial hirsutism
- Depending on the origin of the hirsutism, treatment is based on administration of antiandrogens, glucocorticosteroids and/or contraceptives, combined with topical medications and physical measures

HYPERTRICHOSIS

Introduction

Hypertrichosis describes the growth of an excessive amount of hair on any area of the body. The term is frequently confused with *hirsutism*, which should only be applied to women with excessive growth of terminal hairs in a "male pattern" due to androgen overproduction or increased end-organ sensitivity to androgens[1,2]. Hypertrichosis can be classified based on its distribution (generalized versus localized), the age of onset (congenital or programmed from birth versus acquired), and the type of hair (lanugo or vellus versus terminal).

Clinical Features

Generalized hypertrichosis

Generalized hypertrichosis is the presence of lanugo hair, excess vellus hair, or terminal hair on much of the cutaneous surface, including an acquired transformation of terminal hair into lanugo hair (Fig. 70.1). Lanugo is the non-pigmented, non-medullated, fine hair that covers the fetus and can grow to several centimeters in length; it is normally shed *in utero* or during the first few weeks of life and replaced by vellus hair on the body and terminal hair on the scalp.

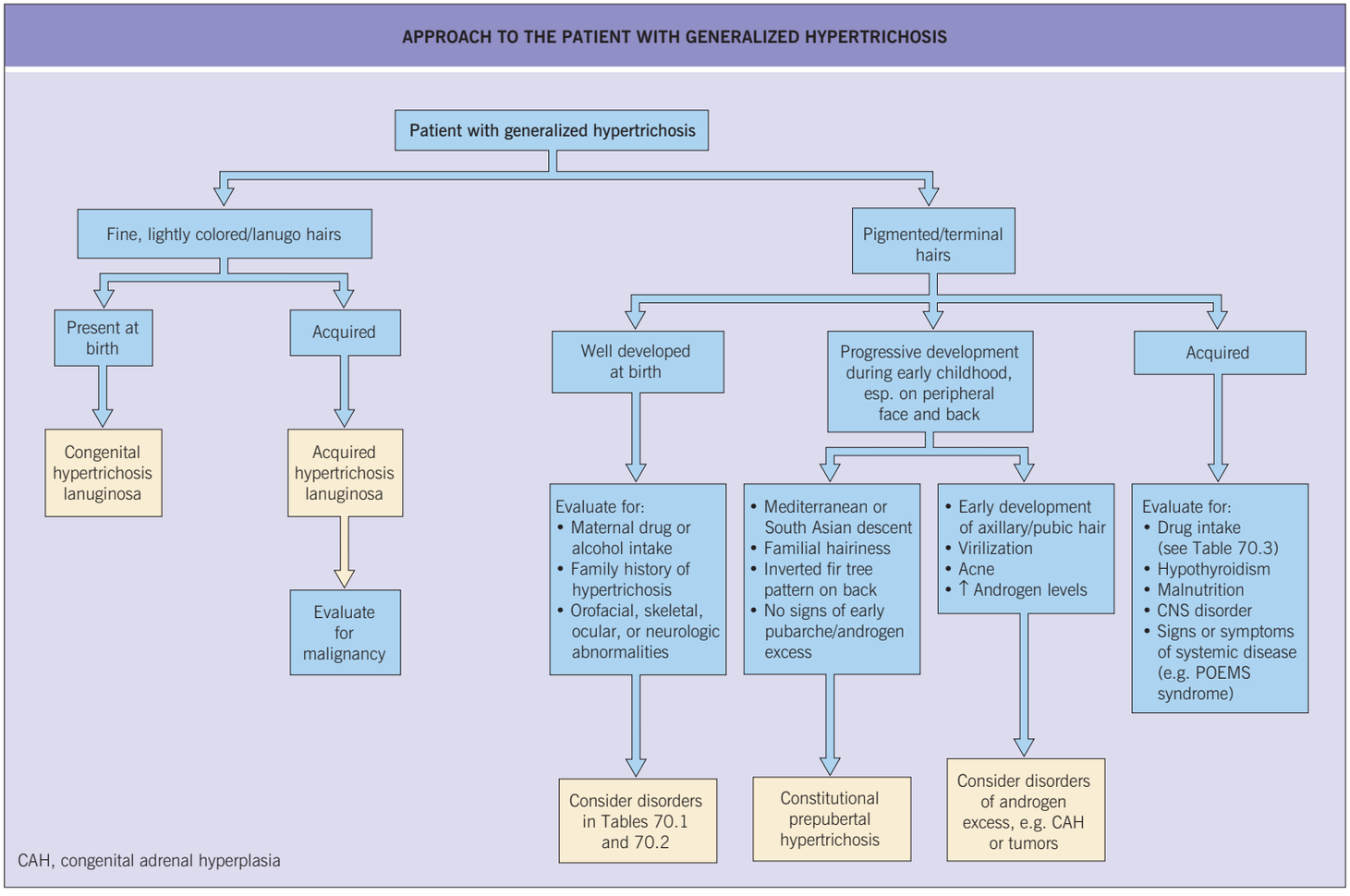


Fig. 70.1 Approach to the patient with generalized hypertrichosis. POEMS syndrome: *p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *m*onoclonal gammopathy, *s*kin lesions.

HEREDITARY DISORDERS CHARACTERIZED BY CONGENITAL GENERALIZED HYPERTRICHOSIS		
Disorder	**Inheritance (locus)**	**Other key features**
INCREASED HAIR IS THE MAJOR FEATURE		
Congenital hypertrichosis lanuginosa	AD	• Fine, downy, silvery-gray to blond lanugo hair • May be shed over the first year of life • Occasional dental anomalies; rarely other associations (see text)
Universal hypertrichosis	AD	• Thicker, longer hair most prominent on the frontal, temporal and preauricular areas of the face, the back and the proximal extremities* • Increases during infancy and tends to persist
Ambras syndrome	AD (8q22)	• Fine, silky, long hair (e.g. >10 cm) uniformly distributed on the face (including nose), ears and shoulders • Persists for life • Minor facial dysmorphism, dental anomalies, supernumerary nipples • Decreased expression of TRPS1*
X-linked hypertrichosis	XR† (Xq24–q27.1)	• Curly, shorter, dark hair most prominent on the face and upper body • Anteverted nostrils, prognathism; occasional dental anomalies, deafness
ASSOCIATED WITH GINGIVAL HYPERPLASIA, FACIAL DYSMORPHISM, SKELETAL DEFECTS, OCULAR ANOMALIES AND/OR MENTAL RETARDATION		
Gingival fibromatosis with hypertrichosis	AD (17q24.2–q24.3)	• Dark terminal hairs on the peripheral face, central back, and extremities • Gingival hyperplasia, coarse facies, MR, seizures
Cantú syndrome	AD	• Gingival hyperplasia, coarse facies, osteochondrodysplasia, macrosomia at birth, cardiomegaly
Zimmermann–Laband syndrome	AD (3p14.3)	• Gingival hyperplasia, coarse facies, hypoplastic nails and distal phalanges, joint hyperextensibility, macrosomia at birth, HSM, MR
Coffin–Siris syndrome	AR (7q32-q34)	• Sparse scalp hair, coarse facies, hypoplastic fifth fingernails and distal phalanges, GR, MR
Schinzel–Giedion syndrome	AR (18q12.3; *SETBP1*)	• Midfacial vascular stain, midfacial retraction, hyperconvex nails, hypoplastic distal phalanges and dermatoglyphs, GU anomalies, GR, MR
Gorlin–Chaudry–Moss syndrome	AR	• Craniofacial dysostosis with midfacial hypoplasia, hypoplastic distal phalanges, ocular and dental anomalies, genital hypoplasia, GR
Adducted thumbs syndrome	AR	• Arthrogryposis, craniosynostosis, myopathy
Barber–Say syndrome	AR	• Lax skin, ectropion, macrostomia, coarse facies, hypoplastic nipples, GR
Amaurosis congenita, cone–rod type, with hypertrichosis	AR	• Photophobia, visual impairment due to retinal dystrophy
CAHMR syndrome‡	AR	• *Ca*taracts, *h*ypertrichosis, *MR*
Acromegaly + hypertrichosis‡	AD	• Acromegaloid facies

*This pattern of distribution is also observed in prepubertal hypertrichosis (see text).
†Female carriers may manifest with nevoid hypertrichosis following Blaschko's lines.
‡Single family reported.

Table 70.1 Hereditary disorders characterized by congenital generalized hypertrichosis. AD, autosomal dominant; AR, autosomal recessive; GR, growth retardation; GU, genitourinary; HSM, hepatosplenomegaly; MR, mental retardation; TRPS1, tricho-rhino-phalangeal syndrome 1 protein; XR, X-linked recessive.

Congenital hypertrichosis lanuginosa

This is a rare autosomal dominant disease in which lanugo hair is not replaced by normal vellus hair. The fine, silvery-gray to blond hair continues to grow, reaching lengths of up to 10 cm and covering the entire body surface except for the palms, soles, dorsal surface of the distal phalanges, and prepuce. The hair growth is said to lead to a "dog" or "monkey" face. Associated dental abnormalities, malformations of the ear, glaucoma, pyloric stenosis, photophobia, and, rarely, physical and mental retardation have been reported.

Acquired hypertrichosis lanuginosa

This "paraneoplastic disease" is associated with a variety of internal malignancies, most often carcinoma of the lung, colon or breast. Acquired hypertrichosis lanuginosa can precede the diagnosis of the neoplasm, and it may also be associated with abnormalities of the tongue (e.g. burning pain) and other paraneoplastic dermatoses such as acanthosis nigricans, palmoplantar keratoderma, the sign of Leser–Trélat and acquired ichthyosis (see Ch. 53). The lanugo hair appears over the entire body within a short period of time, although in mild forms it may be localized to the face, leading to a "simian" appearance. Lanugo hair may even develop in areas of androgenetic alopecia.

Congenital generalized hypertrichosis

There are multiple rare inherited disorders that present with congenital generalized hypertrichosis, either as the sole manifestation or in association with gingival hyperplasia, facial dysmorphism, skeletal defects, mental retardation and other congenital anomalies (Table 70.1). A variety of additional hereditary diseases and syndromes can feature diffuse hypertrichosis (Table 70.2), which may be apparent at birth or develop early in life. Intrauterine exposure to medications such as minoxidil can also lead to congenital generalized hypertrichosis.

Prepubertal hypertrichosis

Prepubertal hypertrichosis is a relatively common finding in otherwise healthy infants and children, most often occurring in individuals of Mediterranean or South Asian descent. Pigmented hair is present in a widespread, diffuse distribution and becomes more obvious during childhood. There is involvement of the face (especially the forehead, temples and preauricular area), proximal extremities and back; hairs in the latter location assume an "inverted fir tree" pattern. Bushy eyebrows and a low anterior hairline represent additional features.

The facial distribution pattern of prepubertal hypertrichosis can overlap with that of familial hirsutism (see below), and there may be a family history of excessive hairiness. Mildly elevated serum levels of total and free testosterone have been observed in a subset of girls with prepubertal hypertrichosis, while others have a normal androgen profile[3]. These findings suggest multiple etiologies for this clinical pattern of hypertrichosis, including androgen excess as well as a greater constitutional propensity for hair growth.

HEREDITARY DISEASES AND CONGENITAL SYNDROMES ASSOCIATED WITH HYPERTRICHOSIS		
Disorder	**Sites of hypertrichosis**	**Other key features**
DYSMORPHIC SYNDROMES		
Cornelia de Lange syndrome	• Forehead, lateral face, shoulders, back • Low anterior hairline, synophrys, trichomegaly	• Distinctive facies, upper extremity anomalies, microcephaly, GR, MR, "growling cry" • AD; *NIPBL* mutations
Rubinstein–Taybi syndrome	• Lateral face, shoulders, back • Thick eyebrows, trichomegaly	• Midfacial vascular stains, keloids, pilomatricomas • Broad thumbs/halluces, beaked nose, high-arched palate, short stature, MR • AD; *CREBBP* mutations
DISORDERS WITH PRIMARY CUTANEOUS FEATURES		
Porphyrias	• Sun-exposed areas • Favors lateral face in PCT, HEP, VP • Face, trunk, extremities in CEP	• See Ch. 49
Lipodystrophy syndromes (e.g. Berardinelli–Seip syndrome, leprechaunism)	• Face, neck, extremities • Low hairline	• See Ch. 101
Erythrokeratodermia variabilis	• Trunk and extremities	• See Ch. 57
Dystrophic epidermolysis bullosa*	• Areas of previous blistering	• See Ch. 32
Ichthyosis bullosa of Siemens*	• Extremities	• See Ch. 57
METABOLIC DISORDERS		
Mucopolysaccharidoses†	• Trunk, extremities	• See Ch. 48
Congenital hypothyroidism	• Back, extremities	• See Ch. 46
MITOCHONDRIAL DISORDERS		
Leigh syndrome due to *SURF1* mutations	• Forehead, extremities	• Progressive neurodegeneration
MELAS syndrome	• Lower extremities	• *M*itochondrial *e*ncephalopathy, *l*actic *a*cidosis, and stroke-like episodes
INTRAUTERINE EXPOSURES‡		
Fetal hydantoin syndrome	• Face, back, extremities	• Gingival hyperplasia, coarse facies, hypoplastic nails and distal phalanges, GR
Fetal alcohol syndrome	• Face, back, extremities	• Midfacial hypoplasia, GR, CNS anomalies
MORPHEAFORM OR SCLERODERMOID DISORDERS		
Winchester syndrome	• Hypertrichosis and hyperpigmentation overlying areas of skin thickening	• Gingival hyperplasia, carpal/tarsal osteolysis, osteoporosis, coarse facies, GR • AR; matrix metalloproteinase-2 gene mutations
H syndrome§	• Lower trunk and lower extremities (in association with areas of *h*yperpigmentation & induration‖)	• Sensorineural *h*earing loss, short *h*eight, *h*eart anomalies, *h*epatosplenomegaly, scrotal masses, hypergonadotropic *h*ypogonadism, antibody-negative insulin-dependent diabetes mellitus, facial telangiectasias • AR; *SLC29A3* mutations (encodes nucleoside transporter hENT3)
Stiff skin syndrome	• Variable	• See Ch. 43
Linear melorheostosis¶	• Overlying affected skin and bone	• Hyperostosis ("candle wax" appearance) with overlying scleroderma • Due to *LEMD3* mutations

*Hypertrichosis is an uncommon feature.
†Hypertrichosis may also be observed in other lysosomal storage diseases, e.g. Krabbe disease and GM1-gangliosidosis, as well as sialuria.
‡Also minoxidil and diazoxide.
§Allelic with pigmented hypertrichotic dermatosis with insulin-dependent diabetes (PHID) syndrome.
‖Polyclonal perivascular lymphohistiocytic infiltration with numerous plasma cells in the dermis and subcutis.
¶Hypertrichosis has also been described overlying linear scleroderma in the absence of melorheostosis.

Table 70.2 Hereditary diseases and congenital syndromes associated with hypertrichosis. Varying degrees of hypertrichosis (predominantly facial or generalized) have also been observed in children with chromosomal anomalies, e.g. partial trisomy of 1q, 3q, 4p or 17q. AD, autosomal dominant; AR, autosomal recessive; CEP, congenital erythropoietic porphyria; GR, growth retardation; HEP, hepatoerythropoietic porphyria; MR, mental retardation; PCT, porphyria cutanea tarda; VP, variegate porphyria.

Acquired generalized hypertrichosis

Acquired generalized hypertrichosis is most often related to drug ingestion (Table 70.3). Drug-induced hypertrichosis is characterized by slow growth of terminal hair of medium thickness. The findings are most evident on the forehead, temples, flexor aspects of the extremities, and trunk. Drug-related hypertrichosis is usually reversible, and differs in distribution from drug-induced hirsutism.

Generalized hypertrichosis can represent a sign or consequence of a variety of systemic conditions, including disorders of the CNS (e.g. traumatic brain injuries), POEMS syndrome (*p*olyneuropathy *o*rganomegaly, *e*ndocrinopathy, *m*onoclonal gammopathy and *s*kin lesions), juvenile hypothyroidism, juvenile dermatomyositis, acrodynia, malnutrition (including anorexia nervosa) and advanced HIV infection.

Localized hypertrichosis

Most cases of localized hypertrichosis involve a switch from vellus to terminal hair in sites that do not usually bear terminal hair. Localized hypertrichosis can develop as a component of a hamartoma, as an isolated congenital lesion, as a manifestation of a systemic disease (inherited or acquired), and as a consequence of cutaneous trauma or inflammation.

Congenital localized hypertrichosis

Hamartomas, including those with delayed clinical presentation, and congenital abnormalities characterized by hypertrichosis of a specific anatomic site (Fig. 70.2, Tables 70.4 & 70.5) are included in this category.

HYPERTRICHOSIS DUE TO DRUGS	
ANTIBIOTICS	
• Streptomycin	
ANTI-INFLAMMATORY DRUGS	
• Benoxaprofen	• Glucocorticosteroids
VASODILATORS	
• Diazoxide • **Minoxidil**	• Prostaglandin E1
DIURETICS	
• Acetazolamide	
ANTICONVULSANTS	
• **Phenytoin**	
IMMUNOSUPPRESSIVES	
• **Cyclosporine**	• Mycophenolate mofetil
PSORALENS	
• Trimethylpsoralen	• Methoxypsoralen
ANTISEPTIC AGENTS	
• Hexachlorobenzene	
CHELATORS	
• Penicillamine	
OTHER	
• Interferon-α • Fenoterol	• EGFR inhibitors (e.g. cetuximab, panitumumab, erlotinib, gefitinib)

Table 70.3 Hypertrichosis due to drugs. Most common drugs are in bold. EGFR, epidermal growth factor receptor.

HEREDITARY HYPERTRICHOSIS AFFECTING SPECIFIC ANATOMIC SITES			
Condition	**Inheritance**	**Onset**	**Other features**
Hypertrichosis cubiti (hairy elbow syndrome)	AD	Birth to early childhood	• Short stature*
Hairy palms and soles	AD	Birth	
Hypertrichosis of the auricle	AD†	Childhood or adolescence	• Primarily affects males
Hypertrichosis of the eyebrows	?	Adolescence	
Trichomegaly of the eyelashes	AD vs AR	Childhood	
Hypertrichosis of the nasal tip	?	Adolescence	• Primarily affects males
Anterior cervical hypertrichosis	AD‡	Birth to early childhood	• Sensory and motor neuropathy* • Mental retardation* • Hallux valgus*
Posterior cervical hypertrichosis	AD	Birth	• Kyphoscoliosis
Polythelia, including the hairy variant§	AD¶	Adolescence	• Urinary tract anomalies*

*Occasional finding.
†Recently shown not to be Y-linked in a cohort of Indian men; congenital hypertrichosis of the pinna can be seen in the offspring of diabetic mothers and in individuals with XYY syndrome.
‡Possible AR inheritance in one consanguineous family.
§Tuft of hair along the "mammary line".
¶Approximately 10% of cases are familial.

Table 70.4 Hereditary hypertrichosis affecting specific anatomic sites. AD, autosomal dominant; AR, autosomal recessive.

HYPERTRICHOSIS OF THE EYEBROWS AND EYELASHES
SYNOPHRYS
• Isolated trait • Waardenburg syndrome (see Ch. 66) • Cornelia de Lange syndrome (see Table 70.2) • Zimmerman–Laband syndrome (see Table 70.1) • Amaurosis congenita, cone–rod type, with hypertrichosis (see Table 70.1) • Mucopolysaccharidoses (see Ch. 48)
INHERITED AND/OR CONGENITAL TRICHOMEGALY
• Isolated trait • Oliver–McFarlane syndrome* • Cornelia de Lange and Rubinstein–Taybi syndromes (see Table 70.2) • Congenital hypertrichosis lanuginosa and Ambras syndrome (see Table 70.1) • Cantú, Coffin–Siris and Barber–Say syndromes (see Table 70.1) • Amaurosis congenita, cone–rod type, with hypertrichosis (see Table 70.1) • Hermansky–Pudlak syndrome (see Ch. 66) • Kabuki and floating harbor syndromes† • Fetal alcohol syndrome (see Table 70.2)
ACQUIRED TRICHOMEGALY
• HIV infection • Medications (systemic): cyclosporine, EGFR inhibitors (e.g. cetuximab, gefitinib), topiramate, tacrolimus, interferon-α • Medications (ophthalmic): latanoprost, bimatoprost • Hypothyroidism • Porphyrias • Dermatomyositis, systemic lupus erythematosus • Malnutrition, anorexia nervosa • Kala-azar
DISTICHIASIS (DOUBLE ROW OF EYELASHES)
• Lymphedema–distichiasis syndrome‡ • Setleis syndrome (double upper and absent lower lashes; see Ch. 64)

*Autosomal recessive (AR) disorder also featuring sparse scalp hair, mental retardation (MR), short stature, and retinal pigmentary degeneration.
†Autosomal dominant (AD) disorders featuring distinctive facies, growth retardation, and, in the former, MR.
‡AD condition due to *FOXC2* mutations (see Ch. 104).

Table 70.5 Hypertrichosis of the eyebrows and eyelashes. EGFR, epidermal growth factor receptor.

Fig. 70.2 Hypertrichosis cubiti. Multiple terminal hairs on both elbows in a child.

Fig. 70.3 Hypertrichosis in association with a Becker's nevus. *Courtesy, Jean L Bolognia, MD.*

Fig. 70.4 Nevoid hypertrichosis of the scalp in a young boy. There was no underlying melanocytic nevus or hyperpigmentation. *Courtesy, Jean L Bolognia, MD.*

Congenital melanocytic nevus and plexiform neurofibroma
Congenital melanocytic nevi often have associated hypertrichosis. The increased hair growth may be noted at birth, but often becomes more prominent during infancy or early childhood. Hypertrichosis can be seen in small-, medium- and large-sized congenital melanocytic nevi (see Ch. 112). A particularly dense growth of terminal hairs may accompany scalp nevi. Plexiform neurofibromas can also have associated hyperpigmentation and hypertrichosis.

Becker's nevus (melanosis)
This is a hamartoma characterized by macular hyperpigmentation with irregular borders, usually located on the upper lateral trunk (anterior or posterior). Some patients have associated hypertrichosis while others do not. The pigmentation usually arises during the first decade of life, whereas the hypertrichosis typically appears in the second decade (Fig. 70.3). Becker's nevi most often occur in boys and men, and in rare instances are inherited in an autosomal dominant pattern.

Occasionally, asymmetry of the extremities and hyperplasia or hypoplasia of the affected areas (especially ipsilateral mammary hypoplasia in women or, less often, the Poland anomaly) may be present. Rarely, there may be an association with genitourinary tract abnormalities (SNUB syndrome: *s*upernumerary *n*ipples, *u*ropathies, *B*ecker's nevus)[4]. Because of their benign nature, surgical removal of Becker's nevi is not recommended. Epilation can be performed by various techniques, but attempts at decreasing pigmentation via laser therapy are often not successful.

A smooth muscle hamartoma (SMH; see Ch. 117), which exists on a spectrum with Becker's nevus, may present as a circumscribed hypertrichotic plaque with variable hyperpigmentation. Rarely, there is a generalized form of SMH that presents as extensive hypertrichosis and folding of the skin and has been reported under the term "Michelin tire baby". Lastly, the hypertrichosis observed in the setting of hemimaxillofacial dysplasia, which manifests with facial asymmetry due to unilateral maxillary enlargement, gingival hyperplasia and hypoplastic teeth, is often associated with a Becker's nevus or SMH.

Other hamartomas and infantile tumors
Hypertrichosis can also overlie the following skin lesions: plaque-type blue nevus, fibrous hamartoma of infancy, dermal dendrocyte hamartoma, eccrine angiomatous hamartoma, congenital plaque-like glomangioma, and tufted angioma.

Nevoid hypertrichosis
This is an uncommon congenital alteration characterized by the growth of terminal hairs in a circumscribed area. In general, there are no extracutaneous associations in *primary nevoid hypertrichosis*; the skin within the affected area is normally pigmented and there is no underlying hamartoma (Fig. 70.4). Nevoid hypertrichosis has been observed to follow Blaschko's lines, as reported in female "carriers" of X-linked hypertrichosis (see Table 70.1). *Secondary nevoid hypertrichosis* can be associated with lipodystrophy, hemihypertrophy, scoliosis and abnormalities of the underlying vasculature. Nevoid hypertrichosis can also occur together with epidermal nevi or nevoid hypopigmentation, likely reflecting the phenomenon of "twin spotting".

Spinal dysraphism and the hair collar sign
The term "dysraphism" is defined as an "alteration of the formation of a fold or elevation which is constituted in the midline of the human body as a consequence of the union of two lateral portions". In spinal dysraphism, abnormal closure of the neural tube leads to defects in the vertebral column and/or spinal cord (see Ch. 64). Skin lesions "marking" a hidden vertebral defect are usually located in the dorsal midline. The "faun tail" is most often a sign of spina bifida occulta or diastematomyelia (split spinal cord), and is typically located in the lumbosacral region. In addition, a ring of hypertrichosis ("hair collar sign") surrounding membranous aplasia cutis or ectopic neural tissue in the scalp reflects the origin of these midline lesions as "incomplete" neural tube defects.

Localized hypertrichosis in hereditary and acquired systemic diseases
There are multiple genodermatoses characterized by the presence of localized hypertrichosis as a major or secondary diagnostic feature (see Table 70.2)[5,6]. For example, hypertrichosis within sun-exposed areas is one of the signs of the porphyrias – in particular, porphyria cutanea tarda (Fig. 70.5) and congenital erythropoietic porphyria[7]. Likewise, the low frontal hairline and synophrys (confluent eyebrows) in the Cornelia de Lange syndrome are important diagnostic features of that entity[8]. Localized hypertrichosis may also be observed in acquired systemic diseases, such as infrapatellar hypertrichosis in juvenile dermatomyositis or hypertrichosis overlying pretibial myxedema, indurated plaques of Rosai–Dorfman disease, and areas affected by reflex sympathetic dystrophy.

Acquired localized hypertrichosis
After repeated trauma, friction, irritation or inflammation, the hair within affected areas of skin may become longer and thicker (e.g. hypertrichosis of the back in sack carriers, hypertrichosis of a fractured limb after the application of a plaster cast, hypertrichosis of the posterior neck in people who bear heavy weights) (Fig. 70.6)[9]. Sites of chronic rubbing and scratching due to pruritus may also develop hypertrichosis. Transient localized hypertrichosis has been observed within vaccination sites and varicella scars as well as sites of wart removal and laser epilation. In addition, hypertrichosis has been described overlying lipoatrophy following lupus panniculitis and within resolving lesions of psoriasis and morphea.

Localized hypertrichosis has been reported after PUVA therapy. Sites of application of potent topical corticosteroids, tacrolimus, and creams containing mercury or iodine can also develop localized hypertrichosis, as can sites of repeated irritation from anthralin. Prostaglandin F-2α

Fig. 70.5 Facial hypertrichosis in a woman due to porphyria cutanea tarda.

Fig. 70.6 Acquired localized hypertrichosis. Hypertrichosis, hyperpigmentation and epidermal hyperplasia at the site of friction.

analogues (e.g. latanoprost, bimatoprost), which are topical agents used for the treatment of glaucoma, were noted to induce trichomegaly of the eyelashes (Fig. 70.7) as well as brown iris pigmentation. Recently, bimatoprost was FDA-approved for the enhancement of eyelash growth[10,11]. Latanoprost has also been used to treat eyelash alopecia in alopecia areata universalis[11a].

Treatment

The therapies currently available to treat hypertrichosis are limited to "depilation" with creams, electrolysis, and hair removal with lasers. Various laser systems have been developed for epilation of unwanted hair, e.g. Nd:YAG, diode and alexandrite lasers; this is in addition to hair removal utilizing an intense pulsed non-coherent light source (see Ch. 137). Among the cream depilatories, those containing barium sulfate have been shown to be especially effective, although they cause irritation more frequently than the "calcium thioglycolate" depilatory creams. Shaving and other cosmetic maneuvers (e.g. plucking) may also be employed[1,12].

Fig. 70.7 Unilateral trichomegaly. Bimatoprost ophthalmic solution (0.03%) was applied to one eye to treat glaucoma. *Courtesy, Jean L Bolognia, MD.*

HIRSUTISM

Introduction

The term "*hirsutism*" is defined by the presence, in women, of terminal hairs in a male pattern, in contrast to *hypertrichosis*, which is simply an increase in the amount of hair (lanugo, vellus or terminal). Hirsutism reflects an increase in circulating androgens (whose source is primarily the ovary or adrenal gland) or an enhanced end-organ response to androgens[13–15]. At puberty, secondary sexual characteristics develop and, in men, this leads to the appearance of terminal hair on the face (mustache, beard), chest, shoulders, back, arms, thighs, pubic and lower abdominal areas, and buttocks. When this pattern of hair growth is seen in women, the diagnosis is hirsutism (see Fig. 70.14).

Epidemiology

Hirsutism, as defined by a score of ≥8 on the Ferriman and Gallwey scale (see below), affects approximately 5% of women of reproductive age in the general population. In a study of North American women, 35% had terminal hairs on the linea alba, 17% in the periareolar area, 16% in the lumbosacral area, and 10% in the upper pubic triangle[1,13].

Classification

For clinical and therapeutic purposes, hirsutism can be classified into several different types (Table 70.6)[13,16–18].

Clinical Features

Constitutional or dermatologic hirsutism

Hirsutism may be accompanied by seborrhea, acne and androgenetic alopecia, dermatologic manifestations that are the result of the actions of androgens on target tissues. In 1982, Orfanos[19] coined the term "SAHA syndrome" (*s*eborrhea, *a*cne, *h*irsutism and *a*lopecia) for this "dermatologic androgenization syndrome". Although the same constellation of clinical findings may occur in patients with polycystic ovary syndrome (PCOS) and other disorders of androgen excess, isolated SAHA can be distinguished by a lack of substantial hormonal abnormalities, anovulatory menstrual cycles, or ultrasonographic evidence of polycystic ovaries. The characteristics of the four types of dermatologic hirsutism are reviewed in Table 70.6 (Figs. 70.8 & 70.9)[16,17].

HAIR-AN syndrome

The "HAIR-AN syndrome" is a familial virilization syndrome characterized by *h*yper*a*ndrogenemia (HA) in association with *i*nsulin *r*esistance (IR) and *a*canthosis *n*igricans (AN)[20]. This is not part of the SAHA syndrome, but may overlap with PCOS. HAIR-AN is found in 2% to 5% of hirsute patients.

CLASSIFICATION OF TYPES OF HIRSUTISM		
Type	**Circulating hormone levels**	**Clinical findings**
CONSTITUTIONAL (DERMATOLOGIC) – NORMAL OR SLIGHTLY INCREASED CIRCULATING LEVELS OF TESTOSTERONE		
Familial	Normal values*	Generally facial with prolongation of preauricular hair implantation line (Fig. 70.9)
Adrenal (persistent adrenarche syndrome; adrenal SAHA syndrome)	Mild increase in DHEA-S	Thin young women who may feel "stressed"; predominantly central hirsutism (anterior neck → upper pubic area; Fig. 70.8); intense seborrhea, nodulocystic acne, FAGA I–II (occasionally male pattern); oligomenorrhea
Ovarian (excess ovarian androgen release syndrome; ovarian SAHA syndrome)	Mild increase in free testosterone (DHEA-S normal)	Young women; tend to be obese; mild lateral facial and mammary hirsutism; intense seborrhea, papulopustular acne, FAGA I; normal menses or polymenorrhea
Hyperprolactinemic (SAHA syndrome with hyperprolactinemia)	Slight increase prolactin	Central and lateral hirsutism; sometimes seborrhea, acne, FAGA I; oligomenorrhea; occasionally galactorrhea
ENDOCRINE ORGAN-BASED		
Adrenal hirsutism		See text
Congenital adrenal hyperplasia (e.g. 21-hydroxylase deficiency)	↑ 17-OH progesterone; ↑ DHEA-S; ↑↑ ACTH; normal–↑ free testosterone	
Hypercorticism (Cushing's syndrome) – primary nodular hyperplasia – adenoma – carcinoma	↑ cortisol; 17-OH progesterone normal / ↑; ↓ ACTH (adenoma or carcinoma); ↑–↑↑↑ DHEA-S (especially with adrenal tumors); ↑–↑↑ free testosterone	More rapid appearance with adrenal carcinoma
Ovarian hirsutism		See text
Polycystic ovary syndrome (PCOS)	↓ FSH; ↑ LH; LH/FSH > 3; normal DHEA-S; normal–↑ free testosterone; ↓ SHBG; ↑ estrone; insulin resistance; dyslipidemia	
Hyperthecosis	Normal LH, FSH; normal DHEA-S; ↑↑ estrone; higher testosterone than PCOS	
Ovarian tumors	Normal DHEA-S; ↑↑–↑↑↑ free testosterone	
Pituitary hirsutism		See text
Cushing's disease	↑ ACTH leading to ↑ DHEA-S and cortisol	
Prolactin-secreting pituitary adenoma	↑ Prolactin	
Psychogenic drugs†	↑ Prolactin	
ECTOPIC HORMONE PRODUCTION		
ACTH (e.g. small cell lung CA, carcinoids)	↑–↑↑ ACTH	More rapid appearance when due to malignancy
HCG (choriocarcinomas)	↑–↑↑ beta-HCG	
DRUGS (IATROGENIC)		
Anabolic steroids	Elevated parent drug or metabolite in blood, urine or hair	

*Hirsutism presumably due to increased end-organ sensitivity.
†Block dopamine-mediated inhibition of prolactin secretion.

Table 70.6 Classification of types of hirsutism. Patients with liver disease can have a decrease in sex hormone binding globulin (SHBG), and a subsequent increase in free testosterone, which may exacerbate other causes of hirsutism. There is also conversion of androgens (e.g. Δ-4-androstenedione > testosterone) into estrogens, both in the ovaries and in the periphery (adipose tissue, liver). In theory, a reduction in this conversion could lead to an increase in circulating androgens. ACTH, adrenocorticotropic hormone; DHEA-S, dehydroepiandrosterone sulfate; FAGA, *f*emale *a*ndrog*e*netic *a*lopecia (for Ludwig grading system, see Ch. 69); FSH, follicle-stimulating hormone; HCG, human chorionic gonadotropin; LH, luteinizing hormone; SAHA, *s*eborrhea, *a*cne, *h*irsutism, *a*lopecia; SHBG, sex hormone-binding globulin.

Adrenal hirsutism

Adrenal hirsutism should be considered in a patient of any age presenting with obvious central hirsutism (i.e. anterior neck to upper pubic area), together with *f*emale *a*ndrogenetic *a*lopecia (FAGA; Ludwig I–III) or male pattern androgenetic alopecia, signs of virilization, and a thin body habitus[13,14].

Non-tumoral adrenal hirsutism

Adrenal hyperplasias

Congenital adrenal hyperplasia (CAH) is due to a congenital deficiency of one of the enzymes involved in the synthesis of adrenal steroids (Fig. 70.10). This leads to an accumulation of the intermediate product normally metabolized by the deficient enzyme. As these intermediate products are not recognized by the pituitary, the negative feedback mechanism is not initiated, resulting in very high levels of ACTH.

21-Hydroxylase deficiency is responsible for 95% of all cases of CAH. The salt-wasting form of classic CAH presents during the first 2 weeks of life with dehydration and electrolyte abnormalities (due to cortisol deficiency); affected female neonates are typically noted to have ambiguous genitalia, while male neonates may manifest with only subtle hyperpigmentation of the genitals, flexural areas and palmoplantar creases. These patients, as well as individuals with less severe forms of classic CAH, show premature growth of axillary and pubic hair during early childhood (precocious pubarche), which is soon followed by hirsutism accompanied by acne and the onset of patterned alopecia. Virilization, which can be viewed as an advanced degree of defeminization, is often observed (Table 70.7). Lack of breast development in women and a large penis with small testicles and no spermatogenesis in men are associated findings.

Late-onset CAH (attenuated CAH) is due to partial enzyme deficiencies (e.g. of 21-hydroxylase), and it becomes clinically apparent when

Fig. 70.8 Central hirsutism (score 3 for the lower abdomen) in a woman with adrenal SAHA (*s*eborrhea, *a*cne, *h*irsutism and *a*lopecia) syndrome.

Fig. 70.9 Familial hirsutism. Prolongation of the preauricular hair implantation line with terminal hairs of the lateral lower face and neck.

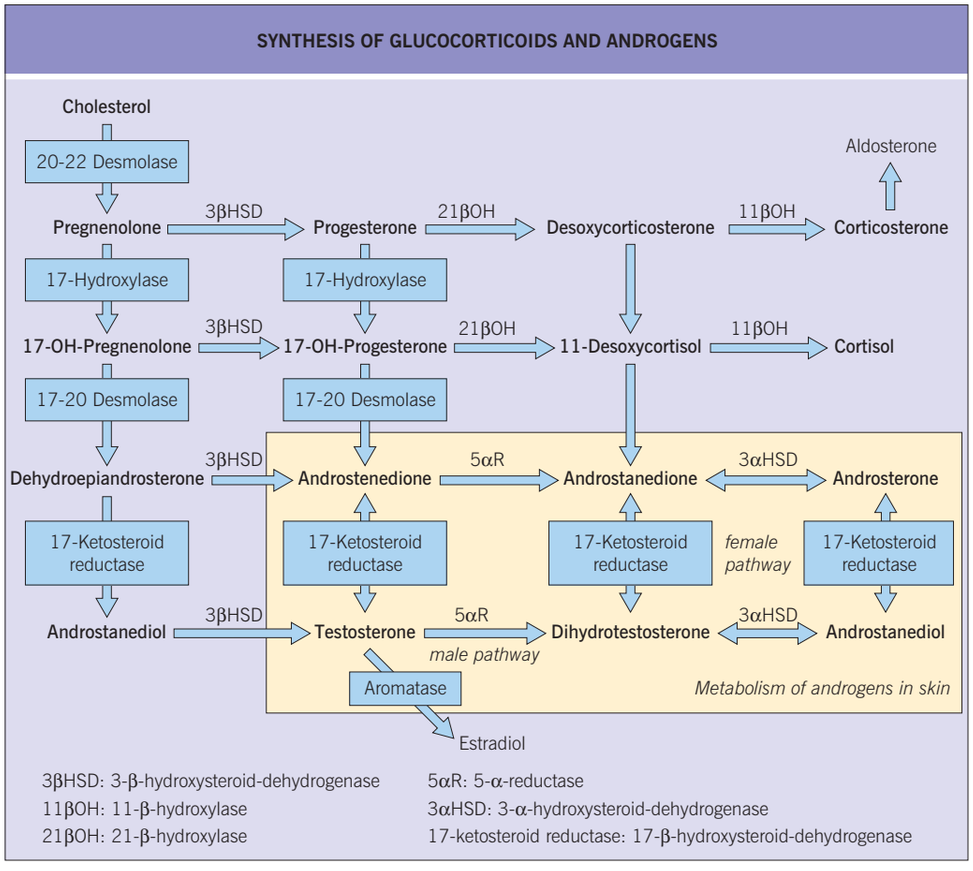


Fig. 70.10 Synthesis of glucocorticoids and androgens. The most common cause of congenital adrenal hyperplasia is 21-hydroxylase deficiency. This leads to an accumulation of 17-OH-progesterone.

DIFFERENCES BETWEEN DEFEMINIZATION AND VIRILIZATION

Defeminization	Virilization
Acne	Hirsutism
Female androgenetic alopecia (FAGA)	Female androgenetic alopecia of male pattern (FAGAM)
Menstrual alterations (e.g. oligomenorrhea)	Amenorrhea
Breast atrophy and loss of female body contours	Muscle mass increased
Decreased rugosity of the vaginal columns	Clitoromegaly
Infertility	Coarsening of the voice

Table 70.7 Differences between defeminization and virilization.

demand for steroids increases at puberty or thereafter. Virilization is again a clinical feature; however, 40% of patients only have hirsutism.

Cryptic CAH is a form of CAH described in family members of patients with CAH who have the same biochemical alterations as the affected individuals, but no clinical manifestations.

Hypercortisolism (Cushing's syndrome)

Cushing's syndrome may be associated with either high plasma ACTH levels (pituitary hyperproduction and "ectopic ACTH syndrome") or a nearly complete lack thereof (adrenal primary nodular hyperplasia, adrenal adenoma or carcinoma). All patients have an increase in plasma cortisol, which is the cause of the major clinical features, e.g. central obesity with "moon facies" and "buffalo hump", hypertension, glucose intolerance, purple striae, and ecchymoses. Patients with adrenal

hyperplasia (usually due to ACTH hyperstimulation by a pituitary adenoma) or adrenal adenomas typically have an insidious onset of symptoms, but with an adrenal carcinoma or ectopic ACTH production by a malignant tumor, manifestations appear more rapidly. If there is significant production of androgens, which is not the norm for adrenal adenomas, there will be a virilization syndrome with hirsutism in addition to the typical manifestations of Cushing's syndrome.

Tumoral adrenal hirsutism

A virilizing adrenal adenoma or carcinoma may be responsible for severe hirsutism. Acne, androgenetic alopecia, amenorrhea and seborrhea occur together with the other characteristic signs of Cushing's syndrome.

Ovarian hirsutism

If the patient presents with hirsutism greater than grade 2 that is predominantly lateral (i.e. on the neck and the breasts), FAGA I–II, acne, seborrhea, obesity and obvious menstrual disorders, the presumed diagnosis is hirsutism of ovarian origin. Like adrenal hirsutism, this may have a tumoral or non-tumoral etiology.

Non-tumoral ovarian hirsutism

Polycystic ovary syndrome

This syndrome was described by Stein and Leventhal in 1935, and is characterized by infertility, secondary amenorrhea or menstrual alterations, and, often, obesity, in association with large polycystic ovaries (Fig. 70.11)[21]. Biochemically, one can see a decrease in follicle-stimulating hormone (FSH) and an increase in luteinizing hormone (LH), as well as an increase in estrone and testosterone. Occasionally, the serum prolactin levels are also increased. PCOS is the most common cause of clinically evident androgen excess, affecting approximately 5% of women of reproductive age. It is a heterogeneous disorder that may be inherited in an autosomal dominant pattern or as a complex multigenic trait.

After a normal menarche, patients develop persistent oligo- or amenorrhea that is frequently accompanied by infertility. Acne is observed in 70% of patients and hirsutism in 90%. The associated hirsutism is usually lateral, i.e. on the breasts, lateral aspects of the face and neck, as well as on the abdomen (Fig. 70.12). At least 50% of patients are obese, and some develop acanthosis nigricans. There are no signs of genital virilization. These patients have large ovaries with a pearly gray surface, a thickened capsule and cysts with hyperplasia of the internal theca, but no signs of activity in the granulosa. Women with PCOS have a higher prevalence of insulin resistance[22], dyslipidemia and hypertension, as well as obesity, components of the "metabolic syndrome" that confer an increased risk of atherosclerotic cardiovascular disease. Patients should be screened for these conditions and followed accordingly (see Fig. 70.11).

Ovarian hyperthecosis

This is similar to PCOS, but with greater production of androgens, especially testosterone. The patients present with signs of virilization, hirsutism (Fig. 70.13), and even androgenic alopecia. Serum levels of LH and FSH are normal, but estrone levels are greatly elevated.

Tumoral ovarian hirsutism

If hirsutism is mild relative to the degree of virilization in an older (especially postmenopausal) woman, one should think about the possibility of an ovarian tumor. Arrhenoblastomas, hilus cell tumors, Brenner's tumors, and gonadoblastomas can all be causes of tumoral ovarian hirsutism.

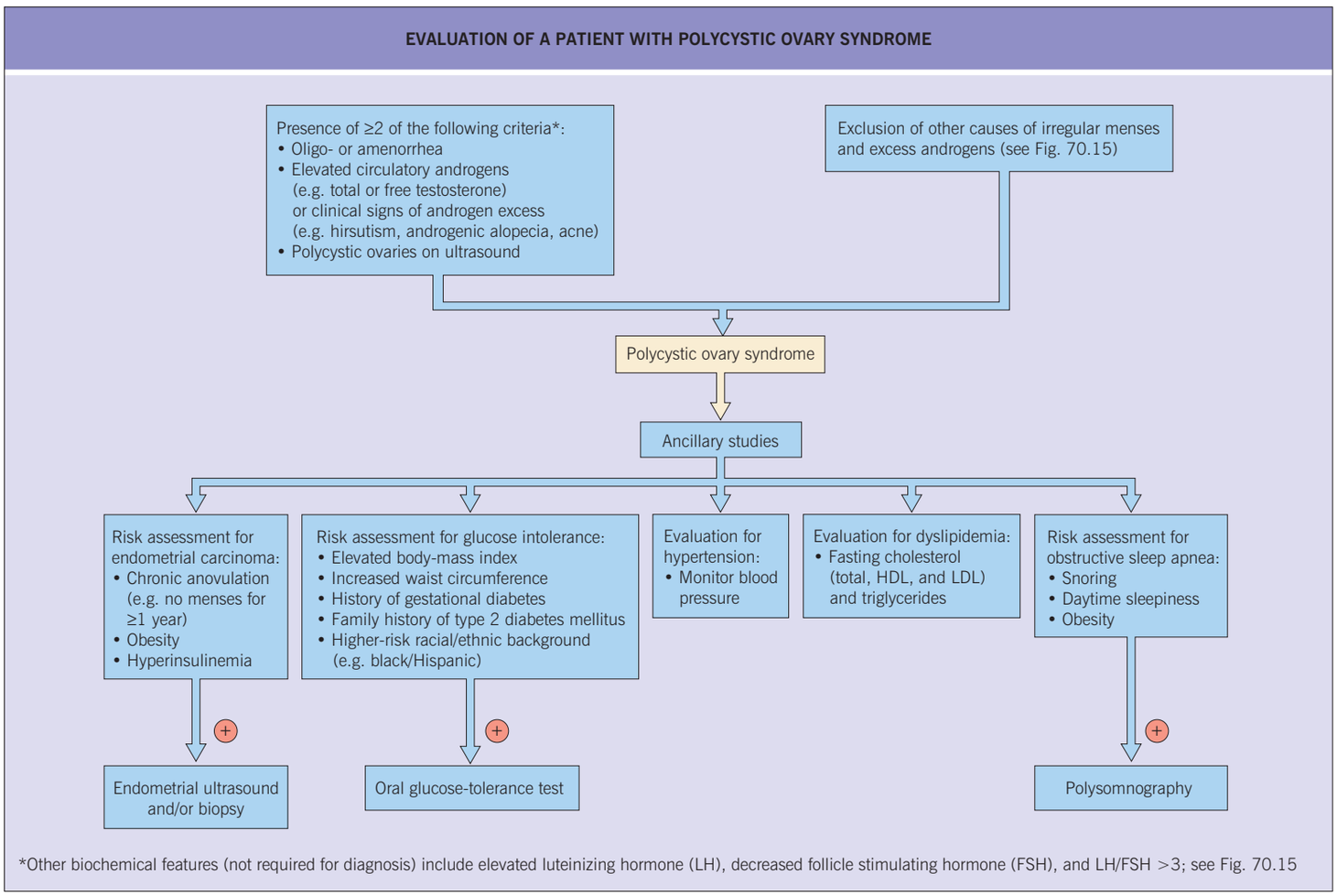


Fig 70.11 Evaluation of a patient with polycystic ovary syndrome (PCOS). Polycystic ovaries alone, without an ovulatory disorder or hyperandrogenism, constitute a risk factor for the development of PCOS[36,37]. *Adapted from Ehrman DA. Polycystic ovary syndrome. N Engl J Med. 2005;352:1223–36.*

Fig. 70.12 Hirsutism in a young woman with polycystic ovary syndrome.

Fig. 70.13 Facial hirsutism (score 4) due to ovarian hyperthecosis. *Courtesy, Robert Hartman, MD.*

Pituitary hirsutism

This type of hirsutism is due to the secretion of hormones from the anterior pituitary, particularly ACTH (see Cushing's syndrome above) and prolactin. There are a number of etiologies of hyperprolactinemia, although pituitary adenomas and drugs are the major causes. Clinical features are the "amenorrhea–galactorrhea syndrome" and infertility. Usually, women are younger than 50 years of age and present with FAGA, acne, seborrhea, and hirsutism; the latter is both central and lateral, with a slight predominance of central hirsutism. There are signs of virilization, and galactorrhea is present in 30–80% of the patients. Amenorrhea occurs in 70% of the cases and, conversely, 15–25% of amenorrheic (but not pregnant) women have hyperprolactinemia. Biochemical investigations will show, above all, an increase in prolactin.

Iatrogenic hirsutism

This type of hirsutism tends to be localized to the lateral aspects of the face and back. Anabolic steroids (e.g. danazol) and oral contraceptives of the nonsteroidal progestogen type have been reported to cause hirsutism. Once the anabolic steroids are discontinued, there are no associated laboratory abnormalities and the hirsutism improves or resolves.

Hirsutism due to ectopic hormones

Patients develop central or lateral hirsutism, depending on the hormone produced by the tumor.

Diagnosis

The first step in evaluating a woman with hirsutism is to determine the source of the responsible androgens, i.e. adrenal cortex or ovaries. The marker for adrenal gland androgens is DHEA-S, and the marker for androgens produced by the ovaries is Δ-4-androstenedione. Dihydrotestosterone (DHT), the androgen responsible for androgenetic alopecia and hirsutism, is produced from testosterone by 5-α-reductase type 2 in the hair follicles of the scalp, beard area and chest (see Ch. 69). In contrast, 5-α-reductase type 1 in sebaceous glands generates the DHT involved in the pathogenesis of acne[14].

It should be noted that, as a general rule, "whenever there is hirsutism which appears abruptly and which evolves quickly, one must first suspect that there is an ovarian, adrenal or pituitary tumor". When hirsutism is mainly localized on the areola and the lateral surfaces of the face and neck, the androgens usually have an ovarian origin, whereas if the location is central, with a distribution from the pubic triangle to the upper abdominal area and from the presternal region to the neck and the chin, the origin is usually adrenal. When there is only hair on the lateral aspect of the face and on the back, the hirsutism is usually iatrogenic. With time, however, the distribution can evolve to include both central and lateral involvement.

The Ferriman and Gallwey score reflects functional hirsutism when the score is 9–14, and organic hirsutism when the score is greater than 15 (Fig. 70.14). Abraham's classification of hirsutism is also used to assess degree of severity (Table 70.8)[13,23]. The different diagnostic possibilities in a patient presenting with hirsutism are outlined in Figure 70.15 and Table 70.6. After the patient has been examined for clinical signs that suggest a particular diagnosis (e.g. features of acromegaly or Cushing's syndrome, physical virilization or defeminization, hypertension and galactorrhea), a biochemical evaluation should be initiated. The author recommends measuring total and free testosterone, DHEA-S, prolactin, SHBG, Δ-4–androstenedione and 3-α-androstanediol glucuronide, a metabolite of DHT. Depending on the results of these tests, the laboratory evaluation can be expanded[13,18]. If substantial abnormalities are detected, referral to an endocrinologist or gynecologic endocrinologist is usually indicated.

Treatment

When SAHA syndrome is diagnosed in a patient with minimal clinical findings and no biochemical abnormalities (i.e. familial hirsutism), topical and "dermato-cosmetic" treatments are appropriate[13,24–26,26a] (see below).

Systemic treatment

Persistent adrenarche syndrome (adrenal SAHA syndrome)

Adrenal suppression is achieved with glucocorticosteroids. Dexamethasone at an initial dose of 0.5 mg every night for 3 months and then alternate nights for 3 months can be used versus a nightly dose of 0.25 mg. Prednisone at a nightly dose of 7.5 mg for 2 months, subsequently reduced to 5 mg nightly for 2 months and then 2.5 mg nightly until 6 months of treatment are completed, is an alternative regimen. Deflazacort at an initial dose of 30 mg daily for 1 month, with a maintenance dose of 6 mg daily for up to 2 years, can also be used.

Antiandrogen therapy includes cyproterone acetate, spironolactone, flutamide, finasteride and drospirenone (see Fig. 69.6). *Cyproterone acetate* (not currently available in the US) acts by interfering with the binding of DHT to the androgen receptor and by inhibiting the secretion of FSH and LH due to its progestogen action. The recommended dose is 50–100 mg/day from the 5th to the 15th days of the menstrual cycle, for a 6-month period. As cyproterone acetate can cause feminization of the male fetus as well as menstrual alterations, the addition of ethinyl estradiol is recommended. Side effects include loss of libido, mood swings, fatigue, mastodynia, hypertension, weight gain and venous thromboembolism. It is contraindicated in patients with

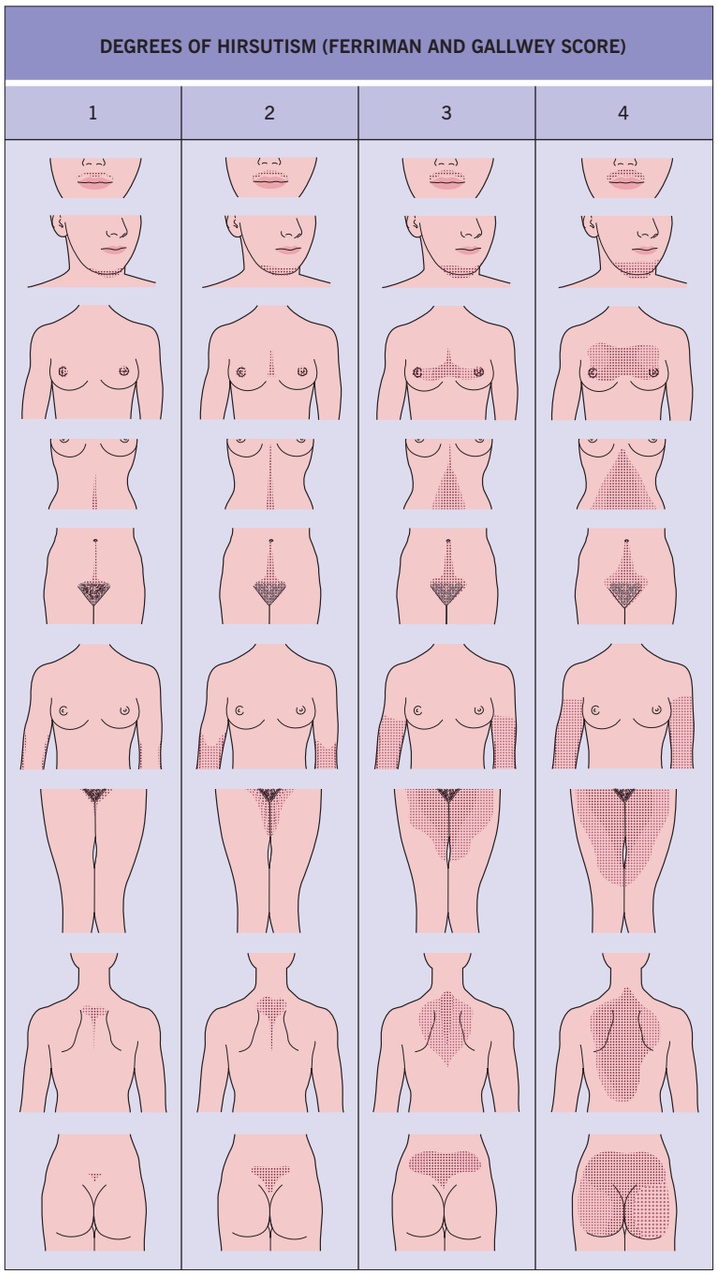


Fig. 70.14 Degrees of hirsutism. The Ferriman and Gallwey score is the sum of the values for each of the nine body areas illustrated. The score reflects functional hirsutism when it is 9–14 and organic hirsutism when it is >15.

ABRAHAM'S CLASSIFICATION OF HIRSUTISM	
Score	**Classification**
<8	Normal
8–16	Discrete
17–25	Moderate
>25	Important

Table 70.8 Abraham's classification of hirsutism. Based on the Ferriman & Gallwey score (see Fig. 70.14).

liver disease. Cyproterone acetate may be the most effective treatment for the alopecia of SAHA syndrome.

Spironolactone is an antagonist of aldosterone (pregnancy category C) that also has antiandrogen activity, decreasing the levels of total testosterone. It is used to treat SAHA with hirsutism and acne at a dose of 50–200 mg/day for at least 6 months. Potential side effects include menstrual irregularities, a decrease in libido, breast enlargement, hyperkalemia, headache, gastrointestinal complaints and fetal feminization[27]. This medication is also used in acne treatment, as discussed in Chapter 36.

Flutamide is a pure, nonsteroidal antiandrogen (pregnancy category D). It is used at a dose of 750 mg daily (in divided doses) for prostatic carcinoma. Side effects include xerosis and toxic hepatitis that may be severe; monitoring of liver function tests is recommended[28]. In the opinion of the author, this is the most effective antiandrogen currently available for the treatment of adrenal SAHA or hirsutism in women with normal ovaries. Low doses of 62.5–125 mg daily can be used[29,30]. As it may also cause feminization of the male fetus, contraception must be employed.

Finasteride is a potent nonsteroidal antiandrogen (pregnancy category X) that acts by inhibiting 5-α-reductase type 2, blocking the conversion of testosterone to DHT. When 72 patients with *persistent adrenarche syndrome* were treated with 2.5 mg daily for 2 years, a 93% reduction in facial hirsutism and a 73% reduction in corporal hirsutism was observed[23] (Fig. 70.16), with no prominent side effects. Other authors have demonstrated that hirsutism, as measured by the Ferriman and Gallwey score, was reduced by finasteride at a dose of 5 mg daily[31].

Drospirenone is a 17-α-spironolactone derivative with progestogenic, antiandrogenic and antialdosterone-like activities[32]. Doses of 3 mg/day during the 21-day cycle along with 30 mcg of ethinyl estradiol is currently considered as an option for the treatment of SAHA, especially because drospirenone does not cause weight gain.

Excess ovarian androgen release syndrome (ovarian SAHA syndrome)

Ovarian suppression includes the use of contraceptives containing an estrogen, ethinyl estradiol, and a progestogen with minimal androgenic activity (e.g. norgestimate). Ethinyl estradiol stimulates the production of SHBG (thereby reducing free testosterone) and it also decreases ovarian androgen production. Cyproterone acetate (see above) and ethinyl estradiol can be used in a sequential pattern for a period of up to 6 months.

Gonadotropin-releasing hormone (GRH) agonists such as leuprolide acetate at a dose of 3.75 mg IM every 28 days for 6 consecutive months suppress pituitary and gonadal function through a reduction in LH and FSH levels. Subsequently, levels of ovarian steroids, androstenedione, testosterone and free testosterone will also be reduced, especially in patients with PCOS. This treatment is expensive and is generally used in severe forms of ovarian hyperandrogenism or HAIR-AN syndrome[26]. More recently, triptorelin (another GRH agonist) was introduced as a therapy for ovarian SAHA, with excellent results. Its effect on hirsutism, as measured by the Ferriman and Gallwey score, was similar to that seen with cyproterone acetate and flutamide treatment. Triptorelin may result in increased levels of serum lipids[33].

Antiandrogens such as flutamide at a dose of 125 mg daily, always accompanied by oral contraceptives, can also be used to treat ovarian SAHA.

SAHA syndrome with hyperprolactinemia

These patients should be treated by a gynecologist with endocrinologic expertise or an endocrinologist. However, when the predominant clinical picture is dermatologic, 2.5 to 7.5 mg/day of *bromocriptine* can be prescribed. *Cabergoline*, another dopamine receptor agonist that suppresses pituitary prolactin production, may also be used in hyperprolactinemic hirsutism, with the advantage that it is only taken once weekly[34].

Iatrogenic hirsutism

The responsible drug must be eliminated. Dermato-cosmetic methods may also be required.

Topical therapy[35]

A topical formulation containing spironolactone and its metabolite, canrenone, at a concentration of 1–3% has been used, with acceptable results, in the treatment of hirsutism in SAHA. Topical eflornithine (15% cream), twice daily, represents another treatment for facial hirsutism. Its safety and effectiveness have been demonstrated in double-blind studies[25,32,35a].

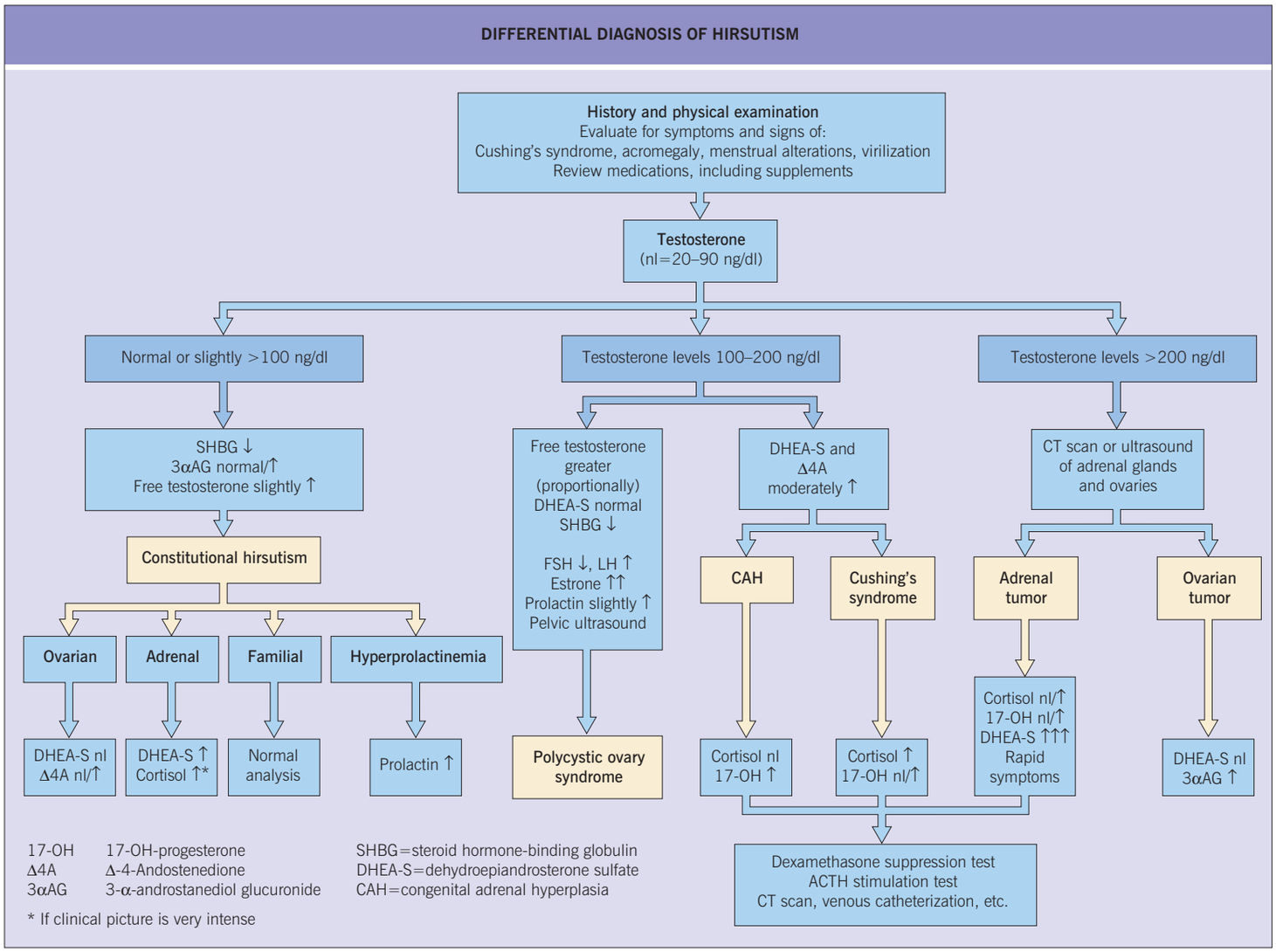


Fig. 70.15 Differential diagnosis of hirsutism. The optimum time to assess circulating follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels is 3–5 days after cessation of menses.

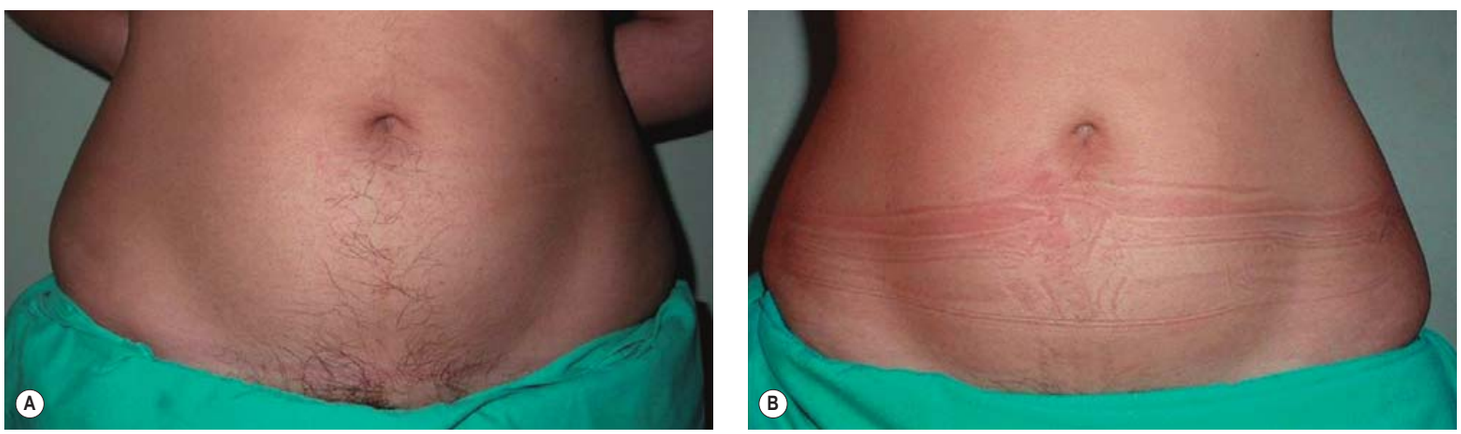


Fig. 70.16 Adrenal SAHA (*s*eborrhea, *a*cne, *h*irsutism and *a*lopecia) syndrome. Before (**A**) and after (**B**) finasteride treatment (2.5 mg daily) for 1 year.

Dermato-cosmetic therapy

There are many therapeutic options in this category, all of which have advantages and disadvantages[12,35]. Hair bleaching is a popular practice, and may be carried out with 6% hydrogen peroxide or a 20% ammonia solution. *Shaving* and *depilation with tweezers, wax or chemical substances* such as 2–4% calcium thioglycolate are also common maneuvers. Compliance often requires dissuasion of the belief that this will enhance thicker hair growth. Electrolysis (see Ch. 140) as well as laser and light-source epilation are, at least hypothetically, methods for "definite depilation". Alexandrite, Nd:YAG and diode are lasers used for this purpose (see Ch. 137). Lastly, *weight loss* improves hirsutism in some hyperandrogenic women.

Surgical therapy

In the case of ovarian and adrenal tumors, surgical intervention is usually required. Surgery is also an option for some pituitary tumors.

REFERENCES

1. Camacho F. Hypertrichosis. In: Camacho F, Montagna W (eds). Trichology. Diseases of the Pilosebaceous Follicle. Madrid: Aula Médica, 1997:243–63.
2. Olsen E. Hypertrichosis. In: Olsen E (ed.). Disorders of Hair Growth. Diagnosis and Treatment, 2nd edn. New York: McGraw-Hill, 2003:399–430.
3. Gryngarten M, Bedecarràs P, Ayuso S, et al. Clinical assessment and serum hormonal profile in prepubertal hypertrichosis. Horm Res. 2000;54:20–5.
4. García-Hernández MJ, Camacho F. Nevo de Becker. Diagnóstico diferencial y asociaciones. Piel. 1998;13: 513–17.
5. Molho-Pessach V, Agha Z, Aamar S, et al. The H syndrome: a genodermatosis characterized by indurated, hyperpigmented, and hypertrichotic skin with systemic manifestations. J Am Acad Dermatol. 2008;59:79–85.
6. Cliffe ST, Kramer JM, Hussain K, et al. SLC29A3 gene is mutated in pigmented hypertrichosis with insulin-dependent diabetes mellitus syndrome and interacts with the insulin signaling pathway. Hum Mol Genet. 2009;18:2257–65.
7. Herrera A, Moruno A. Congenital erythropoietic porphyria affecting two brothers. Br J Dermatol. 1999;141:547–50.
8. Wendelin DS, Pope DN, Mallory SB. Hypertrichosis. J Am Acad Dermatol. 2003;48:161–79.
9. Camacho F. Acquired circumscribed hypertrichosis in the 'costaleros' who bear the 'pasos' in the Holy Week of Sevilla. Arch Dermatol. 1995;131:361–3.
10. Chiba T, Kashiwagi K, Ishijima K, et al. A prospective study of iridal pigmentation and eyelash changes due to ophthalmic treatment with latanoprost. Jpn J Ophthalmol. 2004;48:141–7.
11. Tosti A, Pazzaglia M, Voudouris S, Tosti G. Hypertrichosis of the eyelashes caused by bimatoprost. J Am Acad Dermatol. 2004;51:S149–50.

11a. Coronel-Pérez IM, Rodríguez-Rey EM, Camacho-Martínez FM. Latanoprost in the treatment of eyelash alopecia in alopecia areata universalis. J Eur Acad Dermatol Venereol. 2010;24:481–5.

12. García C, Alamoudi H, Nakib M, Zimmo S. Alexandrite laser hair removal is safe for Fitzpatrick skin types IV-VI. Dermatol Surg. 2000;26:130–4.
13. Camacho F. Hirsutism. In: Camacho F, Montagna W (eds). Trichology. Diseases of the Pilosebaceous Follicle. Madrid: Aula Médica, 1997:265–98.
14. Randall VA. Androgens. The main regulator of human hair growth. In: Camacho F, Randall VA, Price VH (eds). Hair and its Disorders. Biology, Pathology and Management. London: Martin Dunitz, 2000:70–82.
15. Dawber R, Sinclair R. Hirsuties. Clin Dermatol. 2001;19: 189–99.
16. Camacho F. Constitutional hirsutism. The SAHA syndrome. In: Camacho F, Randall VA, Price VH (eds). Hair and its Disorders. Biology, Pathology and Management. London: Martin Dunitz, 2000: 359–67.
17. Camacho F. SAHA syndrome. In: Camacho F, Montagna W (eds). Trichology. Diseases of the Pilosebaceous Follicle. Madrid: Aula Médica, 1997:673–90.
18. Camacho F. Hirsutismo. Enfoque clinico-terapéutico I. Act Terap Dermatol (Arg). 2001;24:96–108.
19. Orfanos CE. Antiandrogenos en dermatologia. Arch Argent Dermatol. 1982;32:52–5.
20. Camacho F, Muñoz MA. HAIRAN syndrome. In: Van Neste D, Randall V (eds). Hair Research for the Next Millennium. Amsterdam: Elsevier, 1996:289–92.
21. Rosenfield RL. What every physician should know about polycystic ovary syndrome. Dermatol Ther. 2008; 21:354–61.
22. Landay M, Huang A, Azziz R. Degree of hyperinsulinemia, independent of androgen levels, is an important determinant of the severity of hirsutism in PCOS. Fertil Steril. 2009;92:643–7.
23. Ferriman D, Gallwey JD. Clinical assessment of body hair growth in women. J Clin Endocrinol Metab. 1961;21: 1440–7.
24. Camacho F. Drug treatment of hirsutism. In: Camacho F, Randall VA, Price VH (eds). Hair and its Disorders. Biology, Pathology and Management. London: Martin Dunitz, 2000:369–81.
25. Camacho F. Hirsutismo. Enfoque clínico-terapéutico II. Act Terap Dermatol (Arg). 2001;24:190–206.
26. Falsetti L, Gambera A, Platto C, Legrenzi L. Management of hirsutism. Am J Clin Dermatol. 2000;1:89–99.

26a. Blume-Peytavi U, Gieler U, Hoffmann R, et al. Unwanted facial hair: affects, effects and solutions. Dermatology. 2007;215:139–46.

27. Spritzer PM, Lisboa KO, Mattiello S, Lhullier F. Spironolactone as a single agent for long-term therapy of hirsute patients. Clin Endocrinol. 2000;52:587–94.
28. Castelo-Branco C, Moyano D, Gomez O, et al. Long-term safety and tolerability of flutamide for the treatment of hirsutism. Fertil Steril. 2009;91:1183–8.
29. Falsetti L, Gambera A, Legrenzi L. Comparison of finasteride versus flutamide in the treatment of hirsutism. Eur J Endocrinol. 1999;141: 1–7.
30. Muderris II, Bayram F, Guven M. Treatment of hirsutism with lowest-dose flutamide (62.5 mg/day). Gynecol Endocrinol. 2000;14:38–41.
31. Castello R, Tosti F, Perrone F. Outcome of long-term treatment with 5-alpha-reductase inhibitor finasteride in idiopathic hirsutism. Clinical and hormonal effects during 1 year course of therapy and 1 year follow up. Fertil Steril. 1996;66:734–40.
32. Shah D, Patel S. Treatment of hirsutism. Gynecol Endocrinol. 2009;25:205–7.
33. Pazos F, Escobar-Morreale HF, Balsa J, et al. Prospective randomized study comparing the long-acting gonadotropin-releasing hormone agonist triptorelin, flutamide, and cyproterone acetate, used in combination with an oral contraceptive, in the treatment of hirsutism. Fertil Steril. 2000;71:122–8.
34. Colao A, Lombardi G, Annunziato L. Cabergoline. Exp Opin Pharmacother. 2000;1:555–74.
35. Ramos-e-Silva M, Ribeiro MC, Carneiro LV. Hair removal. Clin Dermatol. 2001;19:437–44.

35a. Hamzavi I, Tan E, Shapiro J, Lui H. A randomized bilateral vehicle-controlled study of eflornithine cream combined with laser treatment versus laser treatment alone for facial hirsutism in women. J Am Acad Dermatol. 2007;57:54–9.

36. Camacho FM. Hirsutism. In: Blume-Peytavi U, Tosti A, Whiting DA, Trüeb R (eds). Hair Growth and Disorders. Berlin: Springer-Verlag, 2008;357–77.
37. Lowenstein EJ. Diagnosis and management of the dermatologic manifestations of the polycystic ovary syndrome. Dermatol Ther. 2006;19:210–23.

This page intentionally left blank

Nail Disorders 71

Antonella Tosti and *Bianca Maria Piraccini*

Chapter Contents

Anatomy 1129
Nail signs 1129
Congenital and hereditary nail diseases 1134
The nail in dermatologic diseases 1136
The nail in systemic diseases 1138
Infections 1141
Environmental nail disorders 1142
Traumatic nail abnormalities 1142
Nail tumors 1144

ANATOMY (Fig. 71.1)

Key features

- Nail matrix → nail plate production
  proximal matrix → dorsal nail plate
  distal matrix (lunula) → ventral nail plate
- Proximal nail fold → nail matrix protection
- Nail bed and hyponychium → nail plate adhesion and distal detachment
- Nail growth rate:
  fingernails: 3 mm/month
  toenails: 1 mm/month

The nail plate is a fully keratinized structure produced by the germinative epithelium of the nail matrix. As it grows, the nail plate emerges from the proximal nail fold and progresses distally, lying across and strictly adhering to the nail bed. As the nail plate approaches the tip of the digit, it detaches from the underlying tissues, forming the hyponychium. Proximally and laterally, the nail plate is surrounded by the nail folds. The proximal nail fold consists of two layers of epithelium – a dorsal layer, which is the distal continuation of the skin of the dorsum of the digit, and a ventral layer, which is continuous with the nail matrix.

The nail matrix is responsible for the production of the nail plate and consists of an epithelium that keratinizes without the formation of a granular layer. Nail matrix keratinization occurs along an oblique axis, reflecting the upward and distal movement of cells during the process of maturation and differentiation[1]. For this reason, the proximal portion of the nail matrix produces the dorsal portion of the nail plate, while the distal matrix is responsible for the production of the ventral nail plate. The distal portion of the nail matrix is visible through the transparent nail plate as a white, distally convex half moon known as the lunula. The matrix contains melanocytes that are normally quiescent; however, they may become activated and synthesize melanin, which is transferred to the surrounding keratinocytes. Distal migration of melanin-containing keratinocytes then gives rise to a pigmented nail plate[2].

Nail plate production occurs continuously, proceeding from the 15th week of embryonic life until death. Under normal conditions, the mean growth rate of a fingernail is 3 mm/month and that of a toenail is 1 mm/month. Nail growth rate can be influenced by several factors, including age, systemic diseases, and medications.

NAIL SIGNS

By clinical examination, it is possible to identify which site within the nail apparatus is affected by a particular disease process (Table 71.1 &

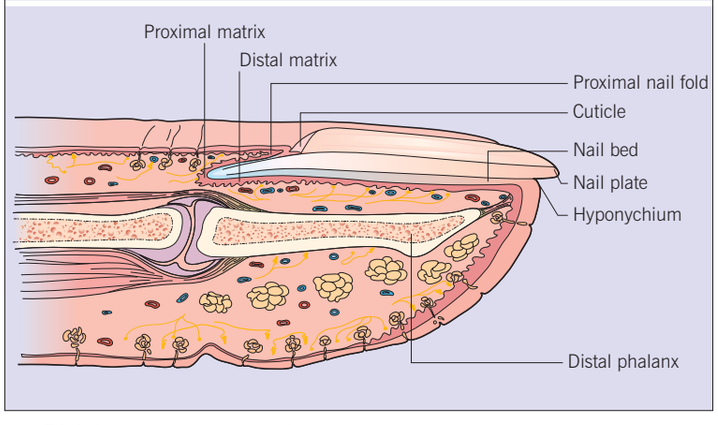


Fig. 71.1 Schematic drawing of the nail apparatus in longitudinal section.

CORRELATION OF NAIL FINDINGS WITH ANATOMIC SITE OF NAIL DAMAGE	
Affected site	**Clinical manifestation**
Proximal matrix	Beau's lines Pitting Longitudinal ridging Longitudinal fissuring Trachyonychia
Distal matrix	True leukonychia
Proximal + distal matrix	Onychomadesis Koilonychia Nail thinning
Nail bed	Onycholysis Subungual hyperkeratosis Apparent leukonychia Splinter hemorrhages

Table 71.1 Correlation of nail findings with anatomic site of nail damage.

Fig. 71.2). Recognizing specific nail signs is very important in understanding and diagnosing nail dystrophies[1,3,4]. Nail signs can be schematically divided into three major categories:

- signs due to abnormal nail matrix function
- signs due to nail bed disorders
- signs due to deposition of pigment within the nail plate.

Nail Signs due to Abnormal Nail Matrix Function

Beau's lines

Key features

- Transverse depressions
- More evident in the central portion of the nail plate
- Most often traumatic
- Involvement of multiple digits suggests a systemic cause

First described by Beau in 1846, these transverse depressions of the nail plate surface result from a temporary interruption of the mitotic activity of the proximal nail matrix. The depth of the depression indicates the extent of the damage within the matrix; the width of the depression (along the longitudinal axis) indicates the duration of the insult. Beau's lines grow distally with the nail plate, with multiple lines indicating repeated damage. Most commonly, Beau's lines are caused by mechanical trauma (e.g. manicures, onychotillomania) or dermatologic disease of the proximal nail fold (e.g. eczema, chronic paronychia). The presence of Beau's lines at the same level in all nails suggests a systemic cause (e.g. severe or febrile illness, erythroderma, drugs).

Onychomadesis (nail shedding)

Key features

- Proximal detachment of the nail
- Most often traumatic
- Involvement of multiple digits suggests a systemic cause

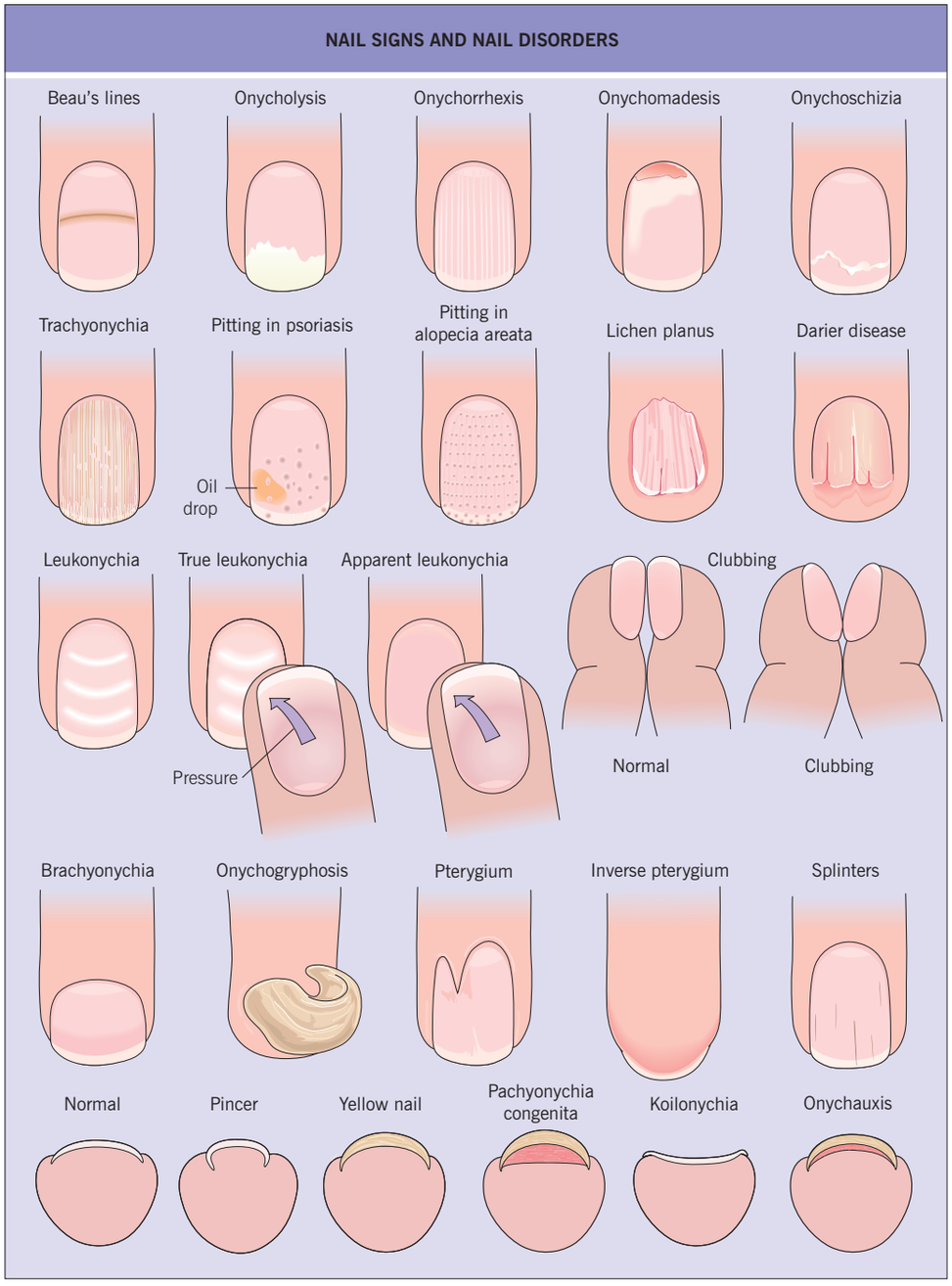


Fig. 71.2 Nail signs and nail disorders.

Fig. 71.3 Onychomadesis after an episode of acute paronychia.

The term "onychomadesis" describes the detachment of the nail plate from the proximal nail fold and is due to a severe insult that produces a complete arrest of nail matrix activity (Fig. 71.3). Onychomadesis appears as a sulcus that replaces the proximal nail plate. The causes of onychomadesis are the same as those for Beau's lines[4a].

Pitting

Key features

- Punctate depressions of the nail plate surface
- Migrate distally with nail growth
- Proximal nail matrix damage by psoriasis, alopecia areata, eczema

Pitting describes the presence of small depressions on the nail plate surface (Fig. 71.4). Pits are due to foci of abnormal keratinization of the proximal nail matrix that result in clusters of parakeratotic cells in the dorsal nail plate. These clusters are easily detached, leaving the pits. Diseases that produce nail pitting include psoriasis, alopecia areata and eczema.

Onychorrhexis

Key features

- Thinning
- Longitudinal ridging and fissuring
- Diffuse nail matrix damage by lichen planus is a possible cause
- Mild disease is a common manifestation of aging

Onychorrhexis produces longitudinal ridging and fissuring of the nail plate. Often associated with nail thinning, it indicates diffuse damage to the nail matrix. Diseases commonly responsible for onychorrhexis include lichen planus, impaired vascular supply, trauma, and tumors that compress the nail matrix. Mild longitudinal ridging of the nails is a common feature of aging.

Trachyonychia (twenty-nail dystrophy, sandpapered nails)

Key features

- Nail roughness
- Often associated with thinning
- Conditions that may cause trachyonychia include alopecia areata (common), lichen planus (rare), psoriasis (rare) and eczema (very rare)

Fig. 71.4 Nail pitting due to psoriasis. Pits are large, deep and irregularly scattered, in contrast with alopecia areata, where they are small, superficial and geometrically distributed.

Fig. 71.5 Trachyonychia (twenty-nail dystrophy). The nails seem sandpapered in a longitudinal direction.

Trachyonychia is a specific nail plate surface abnormality characterized by diffuse homogeneous roughness (Fig. 71.5). In most patients, the affected nails are opaque, lusterless and rough; the nail plate surface has longitudinal ridging due to fine superficial striations distributed in a regular, parallel pattern (sandpapered nails). A less common variant, referred as shiny trachyonychia, is characterized by multiple small punctate depressions distributed in a geometric pattern within parallel, longitudinal lines. Conditions that may cause trachyonychia include alopecia areata, lichen planus, psoriasis and eczema. Some authors use the term "twenty-nail dystrophy" for idiopathic cases of trachyonychia in children (see below), even though the disease does not necessarily involve all 20 nails.

True leukonychia

Key features

- White opaque discoloration
- Punctate, striate or diffuse
- Most often traumatic
- Distal nail matrix damage
- Needs to be distinguished from apparent leukonychia (nail bed discoloration)
- Needs to be distinguished from pseudoleukonychia (nail plate invasion by fungi), which is typical of superficial white onychomycosis. In this case the nail plate surface is friable due to the presence of keratin debris and fungal elements

The nail plate has a normal surface but loses its transparency and looks white because of the presence of parakeratotic cells within its ventral portion. True leukonychia is caused by diseases that disturb distal nail matrix keratinization and it presents with three morphologic variants:

- **Punctate leukonychia**. The nail plate shows small opaque white spots that move distally with nail growth and sometimes disappear before reaching the distal nail. It is caused by trauma and is most commonly observed in the fingernails of children.
- **Striate leukonychia**. The nail plate shows one or more transverse white opaque parallel lines. It is frequently observed in the fingernails of women, due to matrix trauma secondary to manicures. It may also occur in great toenails as a consequence of trauma from shoes. It is also typical of Mees' lines, the white transverse bands seen in arsenic and thallium poisoning[5].
- **Diffuse leukonychia**. The nail plate is completely or almost completely opaque and white. Total leukonychia is rare and sometimes hereditary. It may be associated with keratoderma and other congenital defects such as deafness.

Koilonychia (spoon nails)

Key features
- Thinned concave nails
- Physiologic in the toenails of children

The nail plate is thinned, flat and spoon-shaped due to upward eversion of its lateral edges. Although it is physiologic and resolves spontaneously in children's toenails, in adults it is most commonly occupational in origin or associated with severe iron deficiency.

Nail Signs due to Nail Bed Disorders

Onycholysis

Key features
- Distal nail plate detachment
- Detached nail looks yellow–white
- Commonly due to environmental trauma, psoriasis or onychomycosis

The nail plate is detached from the nail bed and appears white because of the presence of air in the subungual space. Pigmentation of the onycholytic area may occur as a consequence of microbial colonization or blood extravasation. In addition to environmental trauma, the nail bed disorders that most commonly produce onycholysis are psoriasis and onychomycosis (Fig. 71.6). Photo-onycholysis may be precipitated by UV light exposure, either alone or in combination with medications such as tetracycline.

Onychauxis

Key features
- Nail thickening
- Subungual hyperkeratosis
- Commonly due to psoriasis or onychomycosis

The nail plate appears thickened due to the presence of subungual scales. Causes of subungual hyperkeratosis include psoriasis, onychomycosis and eczema.

Apparent leukonychia

Key features
- White discoloration that fades with pressure
- Nail plate transparency maintained
- Often due to drugs (chemotherapeutic agents) or systemic diseases (e.g. hypoalbuminemia)

The nails are white because of abnormalities in the color of the nail bed and this is usually due to nail bed edema. Apparent leukonychia does not move distally with nail growth and the white discoloration fades with pressure (see below for different types).

Splinter hemorrhages

Key features
- Thin longitudinal dark-red subungual lines
- Most often traumatic
- Damage to longitudinally oriented nail bed capillaries

Splinter hemorrhages appear as dark-red, thin longitudinal lines, usually localized to the distal portion of the nail. The shape of the hemorrhages is due to the longitudinal orientation of nail bed capillaries.

The most common causes of splinter hemorrhages are trauma, psoriasis and onychomycosis. Proximal splinters are rare and possible indicators of systemic diseases, including endocarditis (infectious and marantic), vasculitis (including septic vasculitis), trichinosis and the antiphospholipid antibody syndrome.

A recently described vascular lesion of the nail bed is the "red comet", which occurs in ~30% of patients with tuberous sclerosis complex[5a]. Red comets appear as longitudinal short red streaks, partially blanchable with compression, with an enlarged distal end; they extend from the mid to the distal third of the nail and never reach the free edge of the nail. Red comets are thought to represent telangiectasias plus extravasated blood.

Nail Signs due to Deposition of Pigment

Key features
- Exogenous → convex proximal border
- Endogenous → concave proximal border (distally convex)
- Subungual deposition → often associated with onycholysis

Causes of nail pigmentation include staining from external pigment, presence of pigment under the nail plate, and deposition of pigment within the nail plate. Nail pigmentation from external staining typically follows the shape of the proximal nail fold. Common examples are yellow–brown nail discoloration due to nicotine in smokers or darkening of the nail plate due to hair dyes in hairdressers. Subungual deposition of pigment is often seen with *Pseudomonas* colonization, where the green discoloration of the nail results from the production of pyocyanin by the bacteria. Dermatophytes usually cause a yellow–white subungual pigmentation. The nail plate may be pigmented secondary to melanin deposition or deposition of other pigments such as iron or gold. A Fontana–Masson stain of a nail clipping is useful in differentiating melanin from other pigments.

Longitudinal melanonychia

Key features
- Longitudinal brown to black band
- Commonly seen in darkly pigmented individuals
- Single band may be a sign of nail melanoma
- Multiple bands often due to drugs or systemic disease

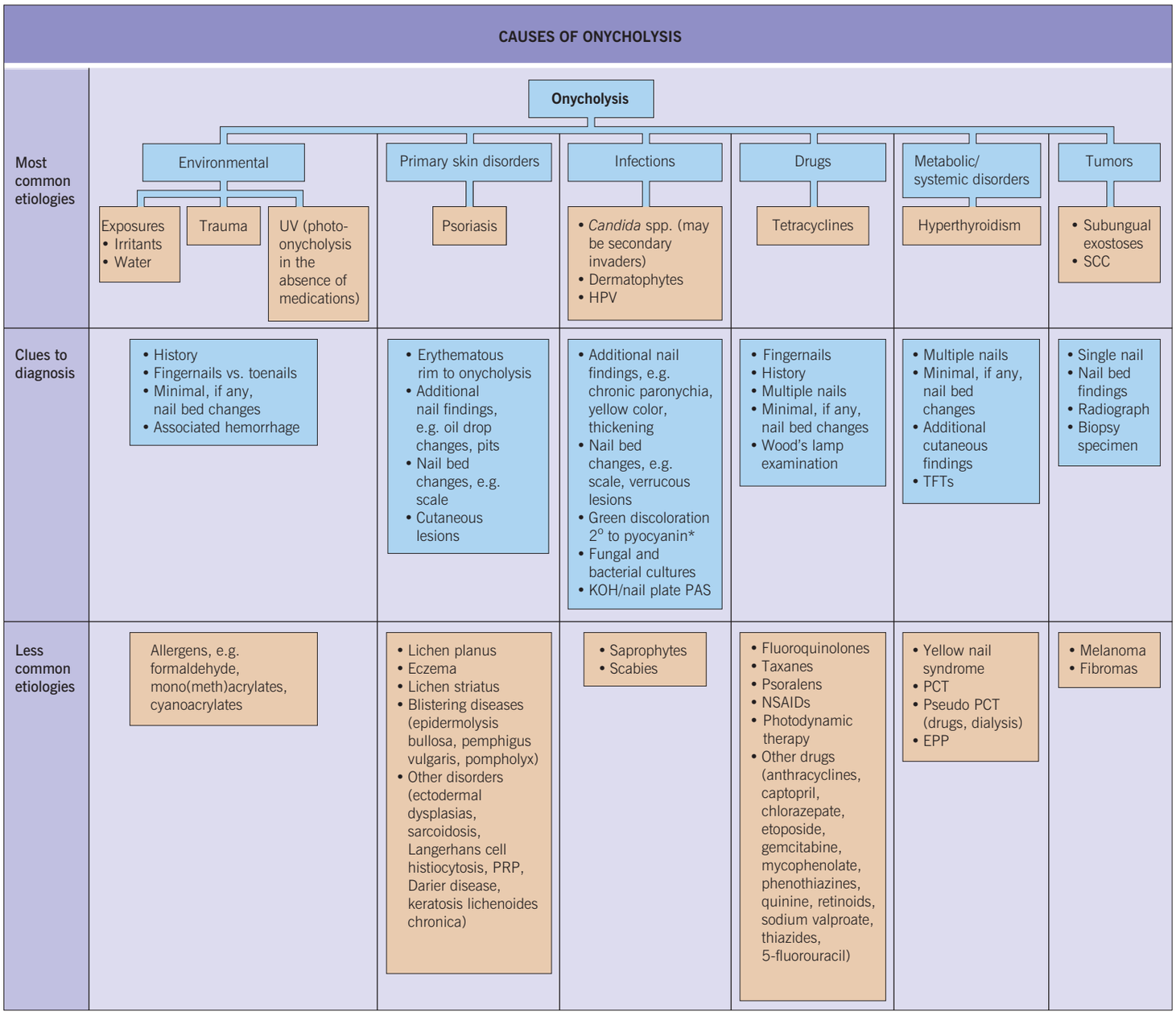


Fig. 71.6 Causes of onycholysis. *Due to secondary colonization with *Pseudomonas aeruginosa*. EPP, erythropoietic protoporphyria; HPV, human papillomavirus infection; NSAIDs, nonsteroidal anti-inflammatory drugs; PCT, porphyria cutanea tarda; PRP, pityriasis rubra pilaris; SCC, squamous cell carcinoma; TFTs, thyroid function tests.

Longitudinal melanonychia is very commonly observed in individuals with darkly pigmented skin, and up to 90% of adult African-Americans have one or more pigmented bands. It is seen much less frequently in Caucasians. Longitudinal melanonychia is due to the presence of melanin within the nail plate, and it may be caused by simple activation of nail matrix melanocytes or by melanocyte hyperplasia as in a lentigo, nevus or melanoma.

Clinically, melanonychia presents as one or more longitudinal pigmented bands extending from the proximal nail fold to the distal margin (Fig. 71.7)[6]. The band of melanonychia can vary in color from light brown to black and the pigmentation may be homogeneous or variable. The width ranges from a few millimeters to the whole nail width. Multiple bands are usually due to melanocyte activation (Table 71.2).

A range of dermoscopic patterns has been described for longitudinal melanonychia (e.g. regular, thin, parallel light brown lines reflecting melanocytic activation), but their accuracy with regard to the diagnosis of subungual melanoma has not been established (see below)[7,8]. Nonetheless, epiluminescence microscopy is increasingly being performed and further studies correlating dermoscopic patterns with histopathologic findings are anticipated. In addition, intraoperative dermoscopy is being employed to assist in determining margins for excision[8a].

A detailed description of biopsy procedures for longitudinal melanonychia is found in Chapter 149 (see Fig. 149.17).

Hutchinson's sign

Key features

- Brown–black periungual pigmentation
- Possible sign of nail melanoma
- Needs to be distinguished from pseudo-Hutchinson's sign (dark bands producing "illusory" pigmentation of the proximal nail fold due to cuticle transparency)

CAUSES OF LONGITUDINAL MELANONYCHIA	
Melanocyte activation	Racial Trauma • manicure • nail biting/onychotillomania • frictional, primarily in toenails Drugs • cancer chemotherapeutic agents, e.g. doxorubicin, 5-fluorouracil • zidovudine (AZT) • psoralens Radiation Pregnancy Laugier–Hunziker syndrome/Peutz–Jegher syndrome Addison's disease HIV infection Postinflammatory • lichen planus • pustular psoriasis • onychomycosis (*T. rubrum* and *Scytalidium* spp.)
Non-melanocytic tumors	Bowen's disease Verrucae Basal cell carcinoma Subungual keratosis Myxoid cyst
Melanocyte hyperplasia	
Nail matrix nevus	
Nail matrix melanoma	

Table 71.2 Causes of longitudinal melanonychia.

First described by Hutchinson in 1886, this eponymous sign represents pigmentation of the proximal nail fold or the hyponychium in association with longitudinal melanonychia. Hutchinson's sign, in the setting of nail melanoma, is due to horizontal growth of the tumor. Although pigmentation of the proximal and lateral nail fold or hyponychium is a feature of congenital melanocytic nevi[9], the development in adults of periungual pigmentation in conjunction with longitudinal melanonychia is very suggestive of melanoma.

Green nail syndrome

Key features

- Greenish-black or greenish-blue nail plate discoloration due to pyocyanin
- Predisposing factors include exposure to water, detergents and soaps
- Needs to be distinguished from a hematoma, melanocytic nevus, melanoma or an *Aspergillus* infection

In green nail syndrome, the nail has a greenish-black or greenish-blue color due to the deposition of pyocyanin, a blue–green pigment produced by *Pseudomonas aeruginosa*, underneath the onycholytic nail plate (see Ch. 74). It is often accompanied by paronychia. Predisposing factors include prolonged exposure to water, use of detergents and soaps, nail trauma and other causes of onycholysis. Not surprisingly, this disorder is seen in barbers, dishwashers, bakers and medical personnel. Green nail syndrome is important because affected hospital staff may spread *Pseudomonas aeruginosa* to debilitated patients. The diagnosis is usually clinical, and, if necessary, can be confirmed by Gram stain and culture of exudate and nail fragments. Treatment involves avoiding predisposing factors, wearing protective gloves, clipping back of the nail, and the use of topical solutions of 2% sodium hypochlorite or acetic acid for 1–4 months.

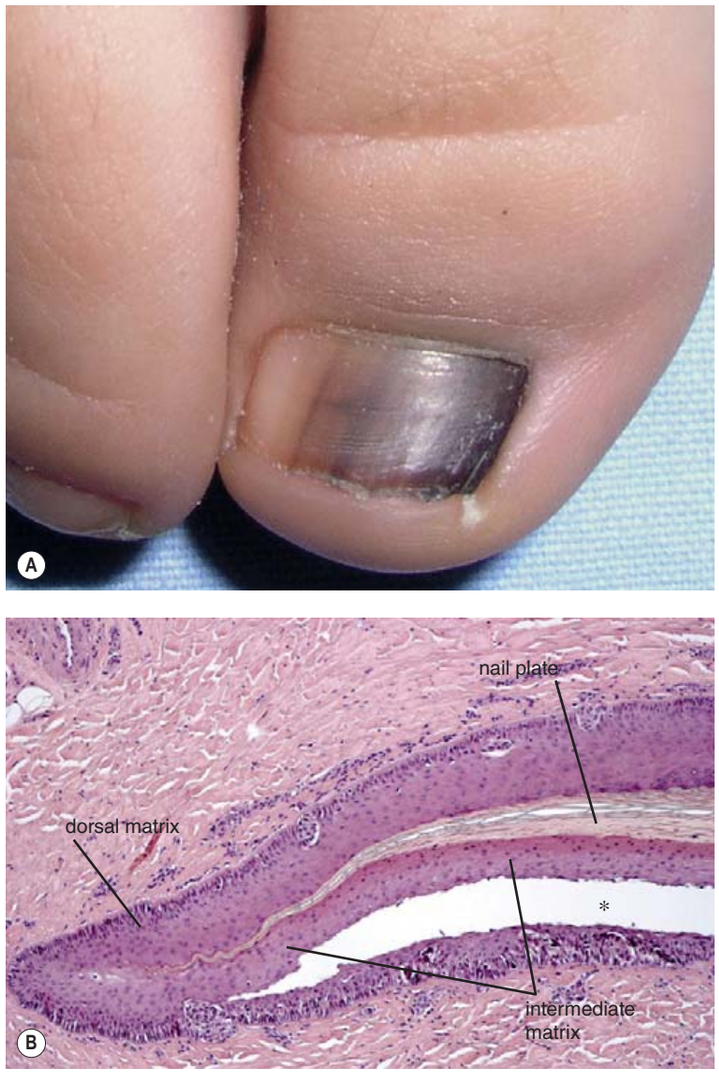


Fig. 71.7 Longitudinal melanonychia due to a congenital melanocytic nevus of the nail matrix. A The pigmentation involves approximately 75% of the nail plate and the color varies from light brown to black. **B** The biopsy specimen shows nests of melanocytes within the basal layer and lower portion of the nail matrix epithelium. The cleft (*) represents an artifact.

CONGENITAL AND HEREDITARY NAIL DISEASES

The congenital and hereditary nail diseases include a number of conditions in which nail abnormalities are present at birth or develop during infancy. In some cases, the nail abnormalities are key features for the diagnosis of syndromes or hereditary diseases.

Congenital Malalignment of the Great Toenails

Key features

- Lateral deviation of the nail plate
- Often bilateral
- Predisposing factor for ingrown toenails

Congenital malalignment of the great toenails was first described by Samman in 1978 and well characterized by Baran et al. in 1979. It is common, but no prevalence data are available. Congenital malalignment of the great toenails is possibly caused by an abnormality in the ligament that connects the matrix to the periosteum of the distal phalanx. The nail plate of the hallux is laterally deviated with respect to the longitudinal axis of the distal phalanx. This results in nail matrix damage with Beau's lines and onychomadesis (Fig. 71.8). The nail plate

Fig 71.8 Congenital malalignment of the great toenails. The longitudinal axis of the nail plate is deviated laterally. There is also onychomadesis of both great toenails and mild nail thickening with lateral ingrowing of the right great toenail.

is often thickened and transversely overcurved. Congenital malalignment of the great toenails is frequently bilateral and is the most common cause of ingrown toenails in children and adolescents. The condition often improves spontaneously[10].

Congenital Hypertrophy of the Lateral Fold of the Hallux

Key features

- Hypertrophic lateral nail fold
- Newborns and infants

Hypertrophic lateral nail folds in newborns were first described by Martinet et al. in 1984. The hypertrophy is usually present at birth; it is characterized by an overgrowth of the soft tissue of the internal portion of the lateral nail fold, resulting in a hypertrophic lip that partially covers the nail plate. This abnormal growth may deviate the nail laterally and/or cause nail embedding with an acute inflammatory reaction and pain. The abnormality is usually bilateral and may regress spontaneously after a few years[11].

Racquet Thumbs (Brachyonychia)

Key features

- Congenital
- Broad and short thumbnail

Racquet thumb is a common malformation due to shortening of the distal phalanx. It is usually inherited as an autosomal dominant trait. The nail is shortened and abnormally wide. Racquet nails are usually an isolated finding and radiologic examination demonstrates a short distal phalanx.

Nail–Patella Syndrome (Onycho-osteodysplasia; Fong Disease)

Key features

- Hypoplasia of the radial side of the thumbnails
- Triangular lunulae
- Presence of bone abnormalities

Nail–patella syndrome is an autosomal dominantly inherited condition first described by Chatelain in 1820. It has been associated with mutations in the *LMX1B* gene, which encodes a transcription factor that regulates collagen synthesis. The condition most frequently involves the thumb and may also involve the other fingers but to a lesser extent (Fig. 71.9). The nails are absent or hypoplastic, and the dystrophy is usually more marked on the radial side of the digit. A triangle-shaped lunula is commonly observed. The nail changes are typically associated with bony abnormalities, including absent or hypoplastic patellae, radial head dysplasia, and iliac crest exostoses ("horns"). In children, the diagnosis is best confirmed by the presence of iliac horns on pelvic X-ray.

Nephropathy develops in approximately 40% of patients. This leads to renal insufficiency in up to 8% of cases.

Fig. 71.9 Nail hypoplasia in nail–patella syndrome. There is hypoplasia of the nails of the first and second digits. This gradient of severity of nail involvement is characteristic.

Epidermolysis Bullosa

Key features

- Periungual/subungual blistering
- Periungual granulation tissue
- Onycholysis
- Nail thickening and shortening
- Pterygium and nail atrophy

Nail abnormalities are common in all forms of epidermolysis bullosa (EB). Repeated blistering produces onycholysis with shortening and thickening of the nail due to nail bed scarring. Involvement of the matrix can result in nail thinning and atrophy. Dystrophic or absent nails with periungual granulation tissue are characteristic of junctional EB, Herlitz type and laryngo-onycho-cutaneous syndrome. Nail abnormalities may precede the development of skin blistering, as in "late onset" junctional EB and pretibial dominant dystrophic EB, or the nail dystrophy may be an isolated finding, as in some families with dominant dystrophic EB.

Ectodermal Dysplasias

Key features

- Abnormal development of hair, teeth and/or eccrine glands
- Nail shortening and thickening
- Nail hypoplasia

Ectodermal dysplasias were first described by Weech in 1929 and classified by Freire-Maia in 1977. Nail abnormalities are an important sign in a large number of these syndromes, where they are associated with hair, teeth and/or eccrine gland abnormalities (see Ch. 63). Most frequently, the nails are short and thickened with onycholysis. All the fingernails and toenails are usually affected.

Pachyonychia Congenita

Key features

- Thickened and extremely hard nails
- Severe nail bed hyperkeratosis
- All digits eventually involved
- Palmoplantar keratoderma

Pachyonychia congenita was first described by Jadasson and Lewandowski in 1906. Pachyonychia congenita is due to mutations in keratin genes *KRT6a* and *KRT16* in type I and *KRT6b* and *KRT17* in type II.

Nail abnormalities are present in both of the two major forms of pachyonychia congenita. The nails are thickened with an increased transverse curvature due to severe nail bed hyperkeratosis. Nail trimming is extremely difficult. Associated findings include hyperhidrosis, oral leukokeratosis, follicular hyperkeratosis and palmoplantar keratoderma, with pain on ambulation. Premature dentition and pilosebaceous cysts are observed more frequently in type II (see Table. 58.4).

Darier Disease (Follicular Dyskeratosis)

Key features

- Red and white longitudinal streaks
- V-shaped indentation (notching) of the distal margin
- Multinucleated giant cells in the nail bed epithelium

Nail abnormalities of Darier disease are common and diagnostic, and were first described by Ronchese in 1965. The nail plate has multiple red and white longitudinal streaks (Fig. 71.10). Distally, wedge-shaped subungual hyperkeratosis and fissuring of the free margin of the nail plate are also seen. The latter occur in conjunction with the white and red bands. Histologically, there is hyperplasia of the nail bed epithelium with multinucleated epithelial giant cells, but not suprabasal clefts[12]. Nail changes do not improve with oral retinoid therapy. Similar nail abnormalities may be seen in patients with Hailey–Hailey disease. A single, red longitudinal band (longitudinal erythronychia) with distal subungual hyperkeratosis is not sufficient for diagnosing Darier disease of the nails, since single bands may be due to a subungual benign tumor (onychopapilloma) and, less often, Bowen's disease[13,13a].

THE NAIL IN DERMATOLOGIC DISEASES

Several dermatologic diseases often have associated nail abnormalities that may prove helpful in confirming the clinical diagnosis.

Fig. 71.10 Darier disease. Alternating longitudinal red and white streaks with wedge-shaped subungual hyperkeratosis, V-shaped notching of the distal margin, and fissuring.

Psoriasis

Key features

- Several nails affected
- Diagnostic signs (fingernails only): irregular pitting, salmon patches ("oil drop" sign), onycholysis with an erythematous border
- In toenails, psoriasis is usually clinically indistinguishable from onychomycosis
- Often associated with psoriatic arthropathy
- The Koebner phenomenon worsens nail symptoms

Nail abnormalities are present in up to 50% of patients with psoriasis and may be the only manifestation of the disease. Nail psoriasis is often associated with psoriatic arthritis and enthesitis[14]. Clinical findings that are diagnostic for nail psoriasis include irregular pitting, salmon patches of the nail bed, and onycholysis with an erythematous border. These signs are often seen together in the same patient and are localized to the fingernails. Psoriatic pits are large, deep, and irregularly scattered within the nail plate (see Fig. 71.4); they may be covered by whitish, easily detachable scales. The "oil drop" sign (salmon patches) appears as an irregular area of yellow–orange discoloration visible through the nail plate (Fig. 71.11). Onycholysis surrounded by an erythematous border is also typical in nail psoriasis. Patients with psoriasis often have other nail abnormalities that are not diagnostic, as they are commonly seen in other conditions. These include splinter hemorrhages, subungual hyperkeratosis, nail plate thickening and crumbling, and paronychia.

Diseases that should be differentiated from nail psoriasis are listed in Table 71.3.

Treatment

Nail psoriasis rarely responds to topical treatment and is often aggravated by sun exposure. Treatment measures are reviewed in the therapeutic ladder (Table 71.4).

Acrodermatitis Continua of Hallopeau (Hallopeau's Acrodermatitis, Dermatitis Repens)

Key features

- Recurrent, self-limited episodes of painful inflammation
- Pustules involving the nail bed and periungual skin
- Fingernails most commonly affected, often one digit

Fig. 71.11 Nail psoriasis. The nails show salmon patches ("oil drop" changes) and onycholysis with an erythematous border.

DIFFERENTIAL DIAGNOSIS OF NAIL PSORIASIS	
• **Onychomycosis** – psoriasis of the toenails may be difficult to distinguish from onychomycosis without mycologic or histologic examination of nail clippings	• **Alopecia areata** – pits are small and geometrically distributed
• **Idiopathic onycholysis and traumatic onycholysis** – the area of onycholysis is not surrounded by erythema and there is an absence of subungual hyperkeratosis	• **Acrokeratosis paraneoplastica (Bazex syndrome; paraneoplastic acrokeratosis)** – the psoriasiform eruption has a typical acral distribution with involvement of the nose and ears

Table 71.3 Differential diagnosis of nail psoriasis.

THERAPEUTIC LADDER FOR NAIL PSORIASIS
• Avoid trauma (3)
• Topical vitamin D_3 analogues: calcipotriene (calcipotriol) – nail bed psoriasis (2)
• Topical tazarotene 0.1% gel: nail bed psoriasis (2)
• Topical calcipotriene plus betamethasone dipropionate ointment – nail bed psoriasis (2)
• Intralesional corticosteroid (e.g. 2.5–5.0 mg/ml triamcinolone acetonide in saline) – nail matrix psoriasis (1)
• Acitretin (0.2–0.3 mg/kg/day) – nail matrix and nail bed psoriasis (1)
• Methotrexate – if indicated for additional manifestations (2)
• Cyclosporine – if indicated for additional manifestations (2)
• Targeted immunomodulators ("biologic therapies") – if indicated for additional manifestations (2)

Table 71.4 Therapeutic ladder for nail psoriasis. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

Fig. 71.12 Acrodermatitis continua of Hallopeau. Recurrent pustular eruption of the nail bed and distal finger.

Acrodermatitis continua was first described by Crocker in 1888 and better classified by Hallopeau in 1890. Nail involvement is a typical feature of Hallopeau's acrodermatitis, which is usually limited to one digit. It can also occur in patients with palmoplantar or generalized pustular psoriasis. Patients complain of relapsing episodes of acute painful inflammation with pustules around and under the nail plate (Fig. 71.12). Other symptoms include onycholysis, onychomadesis, and scaling of the nail bed and periungual skin. Acrodermatitis continua of the nail is, in most cases, not associated with cutaneous plaques of psoriasis vulgaris. Proximal spread of the disease is unusual[15].

The differential diagnosis of acrodermatitis continua is outlined in Table 71.5.

DIFFERENTIAL DIAGNOSIS OF ACRODERMATITIS CONTINUA OF HALLOPEAU	
• **Acute contact dermatitis and dyshidrotic hand eczema** – lesions are usually vesicular rather than pustular, with palmar and/or plantar involvement	• **Onychomycosis due to non-dermatophyte molds** – may be associated with periungual or subungual inflammation and a purulent discharge. Toenails are most commonly affected and the nail plate contains fungal organisms; fungal cultures are required
• **Bacterial or viral paronychia** – a relapsing course is not typical of bacterial infection; relapses are seen in HSV infection, but the nail heals completely between episodes	

Table 71.5 Differential diagnosis of acrodermatitis continua of Hallopeau. HSV, herpes simplex virus.

Treatment

- Topical vitamin D3 analogues (calcipotriene [calcipotriol], calcitriol) or the combination of calcipotriene plus betamethasone dipropionate. Distal nail bed disease is most easily treated with a solution or lotion as the vehicle.
- Acitretin (0.3 mg/kg/day for 4–6 months) in severe cases.

Parakeratosis Pustulosa

Key features

- Exclusively seen in children
- Psoriasiform lesions
- One fingernail usually affected

Parakeratosis pustulosa was first described by Sabouraud in 1931 and better characterized by Hjorth and Thomsen in 1967. It is seen exclusively in children, in whom it is usually limited to one digit, most often the thumb or the index finger. In most patients, nail changes are preceded by erythema, scaling and vesicles of the fingertip. The affected digit shows mild psoriasiform changes with onycholysis and subungual hyperkeratosis. The nail abnormalities are usually more marked on one side of the nail. The disease usually regresses spontaneously, but some children develop psoriasis.

Treatment

Treatment is with emollients, topical corticosteroids and/or calcipotriene.

Lichen Planus

Key features

- Longitudinal fissuring of the nail plate (onychorrhexis)
- Possible cicatricial outcome (dorsal pterygium)
- Several nails usually affected
- Histologic examination is required for diagnosis when nail involvement is isolated

Nail abnormalities are present in approximately 10% of patients with lichen planus (see Ch. 11). However, nail lichen planus is most frequently seen in the absence of skin, scalp or mucosal involvement. Clinical findings that are diagnostic include nail thinning, ridging and fissuring, and dorsal pterygium[16] (Fig. 71.13). These signs indicate matrix involvement and require prompt treatment to avoid scarring. Dorsal pterygium results from adhesion of the proximal nail fold to the nail bed due to matrix destruction and disappearance of the nail plate. Nail bed lichen planus produces nonspecific nail changes such as onycholysis, nail thickening and yellow discoloration.

Fig. 71.13 Nail lichen planus. Note the nail thinning with longitudinal ridging and fissuring.

DIFFERENTIAL DIAGNOSIS OF NAIL LICHEN PLANUS
• **Systemic amyloidosis** – thinning and fissuring are associated with splinter hemorrhages; histologic examination demonstrates amyloid deposits within the nail matrix and nail bed dermis • **Lichen striatus** – the lichenoid nail changes are restricted to one or two digits and limited to one side of the nail plate • **Dyskeratosis congenita** – lichenoid nail changes are associated with oral leukoplakia and reticulated hyperpigmentation • **Nail pterygium due to bullous diseases** – the history differs and there are often associated cutaneous and/or mucosal lesions • **Nail pterygium due to digital ischemia** – the digits are typically cold and there is a history of Raynaud's phenomenon • **Graft-versus-host disease** – similar lichenoid nail changes • **Additional entities** – psoriasis, onychomycosis and the yellow nail syndrome

Table 71.6 Differential diagnosis of nail lichen planus.

When isolated, this diagnosis may be difficult to establish and it requires histologic evaluation. The differential diagnosis of nail lichen planus is outlined in Table 71.6.

Treatment

Treatment with systemic therapies may be required to avoid pterygium formation (see Ch. 11). Intralesional injections of corticosteroid (2.5–5.0 mg/ml triamcinolone acetonide in saline) may be utilized when the disease involves a few nails[16a].

Trachyonychia (Twenty-Nail Dystrophy, Sandpapered Nails)

Key features

- Nail roughness due to excessive longitudinal ridging
- Several nails are usually affected
- More common in children
- Often associated with alopecia areata
- Benign outcome

Trachyonychia was first described by Alkiewicz in 1950. Identical nail abnormalities were given the name "twenty-nail dystrophy" by Hazelrigg et al. in 1977. Twenty-nail dystrophy or trachyonychia describes a spectrum of nail plate surface abnormalities that produce nail roughness. Since the nail changes do not always involve all 20 nails, the term "trachyonychia" (from the Greek word meaning rough) is preferred over twenty-nail dystrophy by most authors. It may occur in association with alopecia areata (12% of children and 3% of adults with severe alopecia areata) or it may be idiopathic. The latter is more common in children.

The nails are thin, opaque and lusterless and give the impression of having been sandpapered in a longitudinal direction (i.e. vertically striated sandpapered nails) (see Fig. 71.5). The cuticles are often hyperkeratotic. Trachyonychia is fairly asymptomatic and patients complain only of brittleness and the cosmetic appearance. In addition to alopecia areata, this finding is occasionally caused by several inflammatory diseases that mildly disturb nail matrix keratinization, including lichen planus, eczema and psoriasis. Determination of the underlying inflammatory disease responsible for the trachyonychia requires a nail biopsy. However, this is generally not recommended because of the benign nature of the disease and trachyonychia improves spontaneously in the majority of patients.

When used to treat hair and cutaneous manifestations, systemic corticosteroids and systemic retinoids can also improve trachyonychia in patients with alopecia areata and psoriasis, respectively.

Alopecia Areata

Key features

- Geometric pitting
- Children are most commonly affected

Nail abnormalities are present in approximately 20% of adults and 50% of children with alopecia areata. Signs that are characteristic of nail alopecia areata include geometric pitting and trachyonychia. The pits are small, superficial and regularly distributed in a geometric pattern (grid-like). Additional nail abnormalities observed in alopecia areata include punctate leukonychia, erythema of the lunula, and onychomadesis. Trachyonychia is more common in children and most frequently seen in male patients with alopecia totalis or universalis.

Eczema (Dermatitis)

Key features

- Irregular pitting and Beau's lines
- Subungual hyperkeratosis
- Chronic paronychia

Hand eczema is often associated with nail changes. In acute eczema, there are vesicles and erythema of the proximal nail fold and the hyponychium. Nail matrix damage produces irregular pitting and Beau's lines; onychomadesis can occur in severe cases. Chronic eczema frequently localizes to the hyponychium, resulting in subungual hyperkeratosis, onycholysis and fissuring of the hyponychium. Chronic eczema of the proximal nail fold can lead to chronic paronychia. In atopic dermatitis, the nail plate frequently shows mild superficial abnormalities such as irregular pits and Beau's lines. Controlling the skin disease results in gradual improvement of the nails.

THE NAIL IN SYSTEMIC DISEASES

Abnormalities of the nails have been anecdotally reported in a number of systemic diseases, but most of these abnormalities are nonspecific. In this chapter, we will discuss only those nail changes that are useful in the diagnosis of systemic disorders.

The Nail Plate in Forensic Medicine

Key features

- Drug exposure
- Poisoning
- Genetic analysis

The slow growth rate of nails makes it possible to utilize nail clippings to detect previous exposure to drugs or toxins (e.g. heroin). Compounds that can be measured in the nails include heavy metals and drugs[5].

Clubbing (Hippocratic Fingers, Watch-Glass Nails, Drumstick Fingers)

Key features

- Bulbous digits
- Watch-glass nails
- Greater than 180° angle between the proximal nail fold and nail plate (Lovibond's sign)

First described by Hippocrates in the first century BC, clubbing may be congenital or acquired. Acquired clubbing is uncommon and in 80% of cases is associated with pulmonary diseases[17].

Clubbing is caused by enlargement of the soft tissue of the distal digit. The nail plate is enlarged and excessively curved, with a greater than 180° widening of the angle between the proximal nail fold and the nail plate (see Fig. 71.2). In hypertrophic osteoarthropathy, clubbing is associated with hypertrophy of the extremities and painful pseudo-inflammatory joint disease. Systemic conditions associated with clubbing are outlined in Table 71.7.

SYSTEMIC CONDITIONS ASSOCIATED WITH CLUBBING	
CONGENITAL/GENETIC	
Cardiovascular disorders	Congenital heart disease (usually cyanotic) Pulmonary arteriovenous malformations (often in the setting of hereditary hemorrhagic telangiectasia)
Bronchopulmonary disease	Cystic fibrosis
Other	Pachydermoperiostosis (see Ch. 98)
ACQUIRED	
Bronchopulmonary diseases	Neoplasms (primary or metastatic cancers, pleural tumors) Chronic infections (abscesses of the lungs, tuberculosis) Bronchiectasis Pulmonary fibrosis, sarcoidosis
Cardiovascular diseases	Aneurysm or dialysis fistula (unilateral clubbing); congestive cardiac failure; bacterial endocarditis
Gastrointestinal diseases	Inflammatory bowel disease Carcinomas Infestations, e.g. amebiasis, ascariasis Liver disorders, e.g. chronic active hepatitis, cirrhosis
Infection	HIV infection Arterial graft sepsis (clubbing limited to perfused extremities)
Endocrine diseases	Thyroid disease (primarily hyperthyroidism)* Secondary hyperparathyroidism
Other	POEMS syndrome Laxative abuse Hemiplegia (unilateral) Trauma, median nerve injury (unidigital)

*Most often in the setting of thyroid acropachy (clubbing together with digital swelling and periosteal reaction) in patients with autoimmune thyroid disease.

Table 71.7 Systemic conditions associated with clubbing.

Yellow Nail Syndrome

Key features

- Arrest in nail growth
- Yellow–green nails
- Absence of the cuticle
- Overcurvature and thickening
- All or most nails are affected

The yellow nail syndrome was first described by Samman and White in 1964. It is not common and its pathogenesis is still unknown. Linear nail growth is arrested or greatly reduced. The nails are thickened and transversely and longitudinally overcurved with disappearance of the cuticle. The nail color varies from pale yellow to dark yellow–green (Fig. 71.14). Onycholysis is frequently seen, as is nail plate shedding. In most patients, all 20 nails are involved. Characteristically, the nail abnormalities are associated with lymphedema and respiratory tract involvement, including chronic bronchitis, bronchiectasis, sinusitis and pleural effusions. The diagnosis of yellow nail syndrome, however, requires only the presence of the typical nail changes.

Treatment

Treatment is not effective in all cases and must be prescribed for several months:

- vitamin E 1200 IU/day
- pulse itraconazole (400 mg daily for 1 week a month) or fluconazole (150 mg daily for 1 week a month); theoretically, the drugs act by accelerating nail growth.

Fig. 71.14 Yellow nail syndrome. Note the overcurvature of the nail and loss of the cuticle, in addition to the yellow discoloration.

Apparent Leukonychia

Key features

- White discoloration that fades with pressure
- Nail plate transparency is maintained

On the basis of the pattern of the nail discoloration, three different types of apparent leukonychia can be distinguished. Nail bed edema may be a common factor.

- Terry's nails were described by Terry in 1954 as a common sign of liver cirrhosis, occurring in up to 80% of patients. The leukonychia affects the whole nail except for a 1 to 2 mm distal band. Terry's nails are also frequently seen in normal individuals.
- Muehrcke's nails were described by Muehrcke in 1956 in patients with hypoalbuminemia (nephrotic syndrome). They are a very common finding in patients receiving combination chemotherapy. The nail has multiple transverse whitish bands, parallel to the lunula (Fig. 71.15).

Fig. 71.15 Muehrcke's nails. There are multiple parallel transverse white bands. The curvature matches that of the lunula.

- Half-and-half nails. First reported by Bean in 1963, half-and-half nails are detected in up to 25% of patients with chronic renal disease who are undergoing hemodialysis. The leukonychia affects the proximal half of the nail. Half-and-half nails may also be seen in normal individuals.

Pseudoinflammatory Nail Changes

Key features
- Cold painful whitlow: digital ischemia
- Painless whitlow and normal temperature: bone metastases

The distal portion of the digit is greatly enlarged and red, simulating an acute paronychia, but the skin temperature is cold or normal. This picture may be caused by digital ischemia or metastases to the distal phalanges. In digital ischemia, the digit is cold and painful. The most common causes include arterial obstruction and autonomic neuropathies causing ischemia (including diabetes). Digital metastases are usually painless; metastases in the fingers are most commonly associated with pulmonary neoplasms and those in the toes with genitourinary neoplasms. X-ray examination is required for the diagnosis[18].

Peripheral Neuropathies

Key features
- Nail abnormalities limited to the first three digits: carpal tunnel syndrome
- Onychomadesis with pseudopyogenic granuloma: mild peripheral nerve injury

Examination of the nail may suggest the diagnosis in carpal tunnel syndrome, since nail abnormalities are limited to the first three fingers and are associated with fingertip paresthesias. Depending on the severity of nerve damage, nail changes vary from Beau's lines to onychomadesis and necrosis. Neurologic examination and electromyography confirm the diagnosis.

Onychomadesis associated with pseudopyogenic granuloma of the proximal nail fold is a sign of mild and transitory peripheral nerve injury. It is typically seen in patients with phalanx, metacarpal or wrist bone fractures during or after cast immobilization. Patients often report a history of pain or paresthesias of the hand during the period of immobilization. The condition spontaneously resolves over a few weeks[19].

Autoimmune Connective Tissue Disorders

Key features
- Nail fold capillary abnormalities
- Cuticular hemorrhages
- Ventral pterygium
- Nail beaking

Abnormalities in the proximal nail fold capillaries are frequently seen in autoimmune connective tissue disorders, as they occur in most patients[20]. Roughness, hemorrhages and necrosis of the cuticles are common in dermatomyositis and scleroderma, where capillaroscopy shows reduced capillary density and avascular areas alternating with dilated capillary loops. In systemic lupus erythematosus, capillaroscopy shows a normal capillary density with dilated tortuous capillaries.

Ventral pterygium (pterygium inversus unguis) is characterized by the adhesion of the distal nail plate to the hyponychium, resulting in pain during nail trimming. Ventral pterygium is a distinctive sign of scleroderma related to impaired peripheral perfusion[21]. In scleroderma, ischemic changes and bone resorption may result in nail beaking with bending of the nail plate around the shortened fingertip (see Fig. 43.2).

HIV Infection

Key features
- Proximal subungual onychomycosis due to *Trichophyton rubrum*
- *Candida* onychomycosis
- Longitudinal melanonychia
- Squamous cell carcinoma

Onychomycoses are common in HIV-infected patients, occurring in up to 25% of affected individuals. Dermatophytes are most commonly responsible, but *Candida* spp. and molds are also often isolated[22]. Although a large number of nail abnormalities have been reported in association with AIDS[17], only a few clinical entities can be considered typical of this disease.

- Proximal subungual onychomycosis due to *T. rubrum*. This variety of onychomycosis is considered a marker for HIV infection and immunodeficiency. The proximal nail plate is opaque and white due to the presence of fungi in its ventral portion.
- *Candida* onychomycosis. *Candida* does not invade the nail plate of immunocompetent individuals, and the diagnosis of true *Candida* onychomycosis indicates immunosuppression – often, HIV infection.
- Longitudinal melanonychia. Usually, several nails are involved, and it is often associated with skin hyperpigmentation.
- HPV-induced squamous cell carcinoma. Longstanding periungual warts in HIV patients should always raise the suspicion of squamous cell carcinoma and be examined histologically. HPV types 16 and 35 have been detected in such lesions[23].

Drug-Induced Nail Abnormalities (Table 71.8)

Key features
- Involvement of most or all nails
- Beau's lines and onychomadesis
- Painful hemorrhagic onycholysis
- Multiple bands of melanonychia
- Paronychia with pyogenic granulomas

Drug-induced nail changes usually involve several or all nails. The pathogenesis is most often toxic in nature[24].

DRUG-INDUCED NAIL ABNORMALITIES	
Nail abnormality	**Responsible agents**
Beau's line and onychomadesis	Chemotherapeutic agents
True leukonychia	Chemotherapeutic agents
Nail thinning and brittleness	Chemotherapeutic agents Retinoids
Onycholysis/photo-onycholysis (see Fig. 71.6)	Chemotherapeutic agents, particularly taxanes Tetracyclines Psoralens NSAIDs
Apparent leukonychia (e.g. Muehrcke's nails)	Chemotherapeutic agents, particularly polychemotherapy including anthracyclines, vincristine
Melanonychia	Chemotherapeutic agents Psoralens Zidovudine (AZT)
Discoloration (non-melanin)	Minocycline Antimalarials Gold
Paronychia and periungual pyogenic granulomas	Retinoids Antiretroviral drugs (indinavir, efavirenz, lamivudine) Epidermal growth factor receptor (EGFR) inhibitors (cetuximab, gefitinib, erlotinib, panitumumab) Methotrexate Capecitabine (prodrug of 5-fluorouracil) Sirolimus
Ischemic changes	Beta-blockers Bleomycin

Table 71.8 Drug-induced nail abnormalities.

- Cancer chemotherapeutic agents, due to their cytotoxic properties, are the most frequent cause of nail changes. These include Beau's lines, onychomadesis, fragility, pigmentation, onycholysis, paronychia, and vascular problems, including subungual hemorrhages, hematomas and ischemia. Painful subungual hemorrhages and abscesses are typically seen with taxanes (paclitaxel and docetaxel).
- Paronychia associated with pyogenic granulomas has been reported with epidermal growth factor receptor (EGFR) inhibitors used as chemotherapeutic agents (see Ch. 21). Nail changes appear from 1 to 3 months after starting treatment and disappear after interruption of treatment.
- Oral retinoids are frequently responsible for nail abnormalities, especially nail fragility, paronychia and pyogenic granulomas.
- Antiretroviral drugs often cause nail pigmentation, paronychia and pyogenic granulomas (Fig. 71.16).
- Although uncommon, photo-onycholysis is a characteristic side effect of tetracyclines, taxanes, psoralens and photodynamic therapy (see Fig. 71.6).
- Certain drugs (e.g. anticoagulants and anticonvulsants) taken during pregnancy may impair the development of the digits, leading to congenital nail hypoplasia.

INFECTIONS

Acute Paronychia

Key features
- Painful whitlow
- Recurrent when due to herpes simplex virus (HSV)
- Viral and bacterial cultures are mandatory

Fig. 71.16 Multiple periungual pyogenic granulomas in a patient taking indinavir.

Fig. 71.17 Acute paronychia. In addition to the erythema and purulent discharge, there is significant tenderness.

The affected digit becomes swollen, red and painful (Fig. 71.17). Compression of the nail fold may produce purulent drainage. Acute paronychia is most commonly due to bacteria, in particular *Staphylococcus aureus* or *Streptococcus pyogenes*, and it follows minor trauma to the nail. Recurrent episodes of acute paronychia should raise the suspicion of an HSV infection. Viral cultures, direct fluorescent antibody assay, and/or PCR should be obtained to identify the responsible agent.

Treatment

- Drainage of the abscess.
- Systemic antibiotics according to culture results.
- Systemic antivirals when due to HSV.

Warts (see Ch. 79)

Key features
- Periungual keratotic papules
- Hyperkeratosis of the cuticle
- Onycholysis and subungual hyperkeratosis
- In recalcitrant lesions, consider the possibility of squamous cell carcinoma

Periungual warts are common in nail biters, in whom they are multiple and involve several nails. The warts appear as keratotic papules, and when localized to the proximal nail fold, they frequently produce periungual hyperkeratosis simulating a hyperkeratotic cuticle. Nail bed warts lead to uplifting of the nail plate with onycholysis. Squamous cell

THERAPEUTIC LADDER FOR PERIUNGUAL WARTS
• Keratolytics (2)
• Cryotherapy (2)
• Topical cantharidin (2)
• Topical imiquimod (2)
• Intralesional injection of *Candida, Trichophyton* or mumps skin test antigens (1)
• Topical immunotherapy[§] (2)
• Laser: CO_2, erbium:YAG, pulsed dye (2)
• Photodynamic therapy (2)
• Ablative CO_2 fractional laser followed by PDT* (2)
*With methyl 5-aminolevulinic acid and red light.
[§]For details, see Table. 129.13.

Table 71.9 Therapeutic ladder for periungual warts. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports. PDT, photodynamic therapy.

carcinoma can arise in or mimic a verruca; therefore, suspicious lesions must be further evaluated.

Treatment

See therapeutic ladder (Table 71.9).

Onychomycosis (Tinea Unguium)

See Chapter 77.

ENVIRONMENTAL NAIL DISORDERS

Brittle Nails (Fragility, Onychoschizia)

Key features

- Lamellar exfoliation (onychoschizia)
- Fingernails affected
- Nail dehydration due to environmental factors

Brittle nails are very common and usually affect women. Nail brittleness results from dehydration of the nail plate as a result of environmental factors such as frequent handwashing. In lamellar onychoschizia, the distal nail plate splits horizontally into multiple layers (see Fig. 71.2). Other signs of nail brittleness include splitting, softening and onychorrhexis.

Treatment

- Avoidance of water and chemical exposure.
- Biotin (2.5–5 mg/day).
- Topical moisturizers and humectants.

Chronic Paronychia

Key features

- Proximal nail fold inflammation
- Absence of the cuticle
- Fingernails affected
- Nail plate surface abnormalities

Chronic paronychia commonly involves the fingernails of adult women. Although the pathogenesis is still debated, there is accumulating evidence that the condition represents a contact reaction to irritants or allergens[25]. Occupational chronic paronychia is common in food handlers. Chronic paronychia is clinically characterized by inflammation of the proximal nail fold with erythema, edema and absence of the cuticle. One or several fingernails (especially the thumb and second or third fingers of the dominant hand) are affected. Damage to the nail matrix results in nail plate surface abnormalities such as Beau's lines[26]. Chronic paronychia usually assumes a prolonged course with superimposed, recurrent, self-limited episodes of acute exacerbation. Secondary infections with *Candida* spp. and *Pseudomonas aeruginosa* are common.

Treatment

- Avoidance of water and chemical exposure.
- Topical corticosteroids.
- Topical imidazoles.
- Topical antiseptics (e.g. 4% thymol in 95% ethanol).
- Systemic antifungals are not useful.

Idiopathic Onycholysis

Key features

- Limited to fingernails
- White or green discoloration
- Absence of subungual hyperkeratosis

Idiopathic onycholysis frequently involves the fingernails as a consequence of repetitive water immersion and exposure to irritants (see Fig. 71.6). The affected nail is detached from the nail bed and often shows an abnormal color due to secondary microbial contamination of the subungual space[26].

Treatment

- Avoidance of water and chemical exposure.
- Clipping of the detached nail plate.
- Topical antiseptics.

TRAUMATIC NAIL ABNORMALITIES (Table 71.10)

Onychotillomania

Key features

- Cuticle absent and proximal nail fold inflamed
- Nail plate surface abnormalities, e.g. longitudinal central depression
- Melanonychia
- Hemorrhages and crusts

Self-induced nail abnormalities are common, but often not recognized due to the wide variety of nail signs and the difficulty in obtaining a correct clinical history.

- Nail biting may affect the nail plate and/or the proximal nail fold; the trauma often produces nail matrix damage with secondary nail plate abnormalities, including surface irregularities and longitudinal melanonychia.
- Habit-tic deformity affects the thumb and is due to the nervous habit of rubbing and pushing back the mid-portion of the cuticle of the thumb with the index finger. The nail plate of the thumb shows multiple midline Beau's lines with a prominent longitudinal central depression. Median canaliform dystrophy of Heller, also known as dystrophia unguis mediana canaliformis, is characterized by an inverted fir tree-like split or canaliform defect in the nail plate (Fig. 71.18) and is possibly a variant of habit-tic deformity[27].
- Nail destruction associated with psychiatric disorders. The clinical picture is variable, with nail plate destruction, hemorrhages, and periungual crusts and erosions. Instruments (scissors, clippers, etc.) are often utilized to destroy the nails.

NAIL CHANGES ASSOCIATED WITH A MANICURE OR PEDICURE	
Nail abnormality	**Etiology**
Beau's lines	Matrix damage from cuticle removal
True leukonychia (transverse)	Matrix damage from cuticle removal
Nail brittleness (onychorrhexis, onychoschizia)	Nail varnish solvents; electric drills
Nail brittleness (superficial granulation)	Prolonged nail polish wearing
Distal onycholysis ("roller coaster")	Mechanical (nail tools utilized to clean the nail plate free edge)
Diffuse onycholysis	Mechanical (artificial nails acting as a lever)
Diffuse onycholysis	Chemical (acrylic nails)
Discoloration (yellow/orange)	Nail varnishes
Acute paronychia Chronic paronychia Periungual pyogenic granulomas Periungual warts	Periungual cuts from sharp instruments Contact allergy Constant cuticle removal Periungual wounds Mechanical trauma to the cuticle

Table 71.10 Nail changes associated with a manicure or pedicure.

Fig. 71.18 Median canaliform dystrophy (of Heller).

Treatment

- Topical preparations that taste unpleasant.
- Bandages.
- Serotonin reuptake inhibitors (fluoxetine, paroxetine, sertraline).

Subungual Hematoma

Key features

- History of acute trauma
- Purple–red to black in color
- Typical dermoscopic features
- Discoloration moves distally with nail growth

Acute hematomas occur after trauma severe enough to lead to accumulation of blood under the nail plate. Toenails are most commonly affected. Acute hematomas are typically associated with pain, and compression of the matrix may cause secondary nail plate dystrophy. An X-ray of the digit may be advisable to exclude a bone fracture.

Repeated microtrauma or hemorrhagic conditions produce asymptomatic small subungual hematomas of the nails that are incorporated within the ventral nail plate and migrate distally with nail growth. The color of subungual hematomas ranges from purple–red to black. Dermoscopy is useful for differentiating hematomas from melanin deposition[28].

Treatment

Acute hematomas require drainage of the blood by creating a hole through the nail plate.

Traumatic Toenail Abnormalities

Key features

- Onycholysis without subungual hyperkeratosis
- Leukonychia and melanonychia
- Often bilateral
- Podiatric abnormalities
- Retronychia characteristically affects the proximal nail fold

Traumatic toenail abnormalities are most commonly seen in women who wear high-heeled pointed shoes.

- Traumatic onycholysis of the hallux is the most common clinical presentation. The onycholysis may be distal, where the detachment is caused by compression of the distal pulp by poorly fitting shoes, or lateral, when there is overlapping of the second toe onto the first. Clipping of the detached nail plate reveals a normal nail bed. The differential diagnosis includes onychomycosis, but here the onycholysis is associated with subungual hyperkeratosis.
- Transverse leukonychia of the hallux results from repeated microtrauma by shoes to untrimmed, long, great toenails[29]. Multiple bands of true leukonychia move distally with nail growth.
- Frictional melanonychia affects the toenails of the fourth and/or fifth digits of women. It is due to activation of nail matrix melanocytes by friction from shoes or from the adjacent digit. The bands may be multiple and black in color.
- Retronychia is caused by embedding of the nail into the proximal nail fold following trauma and may present with inflammation of the proximal nail fold.

Onychogryphosis

Key features

- Ram's horn nails
- Thick, hard, yellow–brown nail plate
- Hallux most frequently affected
- Elderly patients

Onychogryphosis is common in elderly persons and almost exclusively affects the toenails, usually the hallux. The nail acquires a typical ram's horn shape due to asymmetric growth. The nail plate is thick, hard and yellow–brown. Multiple transverse striations are often present. Nail hardness and self-neglect may lead to monstrous deformities.

Pincer Nails (Trumpet Nails)

Key features

- Nail bed pinching by overcurved nail plate
- Toenails most frequently affected
- Severe pain
- Subungual exostosis should be excluded by X-ray examination

Pincer nails are usually seen on the toes and may be hereditary or acquired; the latter is most commonly due to ill-fitting shoes. The nail plate displays an excessive transverse overcurvature, especially in its distal portion (see Fig. 71.2). This results in compression of the distal nail bed with severe pain[30].

Treatment

Lateral matricectomy (see Ch. 149) is the treatment of choice. Surgery is necessary when a subungual exostosis is present.

Ingrown Toenails (Onychocryptosis)

Key features

- Teenagers and young adults
- Congenital malalignment often present
- Precipitated by improper nail cutting and hyperhidrosis
- Painful inflammation of the lateral fold
- Growth of granulation tissue

Lateral ingrowing usually affects the hallux of young adults with congenital malalignment of the great toenails. Precipitating factors include improper or aggressive nail cutting and trauma. Penetration of nail plate spicules into the lateral nail fold epithelium causes painful inflammation. Chronic onychocryptosis is characterized by the growth of granulation tissue that eventually undergoes epithelialization[1].

Distal embedding is a common complication of nail avulsion. The nail plate growth is blocked by the hyponychium, which forms a distal rim. Retronychia represents the ingrowth of the proximal nail plate into the proximal nail fold, with one to three nail plates misaligned beneath the uppermost nail plate[31]. There may be associated proximal periungual pyogenic granulomas.

Treatment

- Prevention through patient education.
- Removal of the embedded spicule.
- Uplifting of the lateral nail plate with cotton or dental floss.
- Granulation tissue may be prevented by topical antibiotics and topical corticosteroids or treated by cryotherapy, chemical cautery or electrodesiccation.
- Chemical (88% phenol), laser or excisional surgical removal of the lateral matrix is advisable in severe cases.
- In retronychia, surgical avulsion of the proximally embedded nail plate as well as the underlying plate(s) is necessary.

NAIL TUMORS

Nail surgery is discussed in Chapter 149.

Benign Tumors

Pyogenic granuloma (botryomycoma)

Key features

- Bleeding angiomatous papulonodule
- Periungual or subungual
- Often traumatic

Pyogenic granulomas commonly appear within the nail apparatus, where they may be periungual or subungual, and often follow penetrating trauma. Other common causes of pyogenic granuloma of the nail include ingrown toenails, systemic drugs (e.g. retinoids, EGFR inhibitors), peripheral nerve damage, and frictional onycholysis due to prolonged walking[32,32a]. The tumor appears as a bleeding, friable, soft red papulonodule (see Fig. 71.16). When subungual, it is associated with onycholysis. The differential diagnosis includes amelanotic melanoma. Treatment is surgical.

Fibromas/Fibrokeratomas

Key features

- Filiform growth
- Nail plate furrow
- Possible sign of tuberous sclerosis

Isolated periungual and subungual fibromas are not rare in the general population. Multiple lesions occur in 50% of patients with tuberous sclerosis (Koenen's tumors). Periungual fibromas appear as pink or skin-colored papules originating from the proximal nail fold. The fibroma may compress the nail matrix and produce a longitudinal groove in the nail plate. Subungual fibromas that grow underneath the nail plate produce longitudinal erythronychia or onycholysis. A fibrokeratoma is characterized by a hyperkeratotic tip and may be surrounded by a collarette of raised skin.

Subungual exostosis

Key features

- Subungual hard nodule
- Onycholysis
- Toenails (especially hallux)
- X-ray examination is diagnostic

Subungual exostoses, first described by Dupuytren in 1847, are the most common benign bony proliferations associated with nail abnormalities. Subungual exostoses are commonly precipitated by trauma and usually seen on the great toe of young patients (Fig. 71.19A). An exostosis produces a firm, tender subungual nodule that elevates the nail plate. The nodule may ulcerate or become hyperkeratotic. The diagnosis is confirmed by X-ray examination (Fig. 71.19B)[33].

Myxoid cysts (mucous cyst)

Key features

- Proximal nail fold swelling
- Nail plate depression and grooves
- Periodic fluid drainage

First described by Hide in 1883, myxoid cysts are the most common nail tumor, often occurring in middle-aged women. Typically located in the proximal nail fold of the fingernails, they appear as small soft nodules that often spontaneously drain a viscous jelly-like fluid. Compression of the matrix produces nail plate depression and grooves (Fig. 71.20). Occasionally, the cysts are subungual. These cysts are connected to the distal interphalangeal joint by a tract, and osteoarthritis of the distal joint is a frequent association[34].

Treatment

Possible treatments for myxoid cysts include sclerotherapy, cryosurgery, and intralesional corticosteroid injections. Caution must be taken because septic arthritis is a potential complication of surgical procedures that allow access of surface bacteria into the underlying synovial space. All of these procedures are associated with a high frequency of relapses. Definitive cure of myxoid cysts can be obtained with surgical procedures that include ligature of the pedicle that connects the cyst to the joint.

Fig. 71.19 Subungual exostosis. A Skin-colored subungual nodule elevating the nail plate. **B** Radiograph of the digit demonstrating the subungual bony proliferation.

Fig. 71.20 Myxoid cyst. The longitudinal nail groove is a result of the compression of the nail matrix by the cyst.

Fig. 71.21 Onychomatricoma. The nail is thickened and overcurved with longitudinal yellow streaks. The distal border shows several holes.

Glomus tumor

Key features
- Severe pain
- Temperature sensitivity
- Subjective symptoms contrast with minimal clinical signs

First described by Wood in 1812, a glomus tumor arises from the neuromyoarterial glomus cells of the nail bed dermis. It is associated with severe pain that radiates proximally and is often aggravated by physical or thermal stimuli (especially cold). Subjective symptoms typically exceed clinical signs. The tumor appears as a red–bluish nail bed macule visible through the transparent nail plate (see Ch. 149). MRI allows the diagnosis in doubtful cases (see Ch. 114).

Onychomatricoma

Key features
- Localized longitudinal thickening with transverse overcurvature
- Yellow–white discoloration
- Multiple, longitudinal, tumor-containing hollows
- Holes in the distal nail

First described by Baran and Kint in 1992, onychomatricoma is a rare neoplasm that produces localized or diffuse thickening of the nail plate with perforations consisting of multiple longitudinal hollows that contain the digitating tumor. Most commonly, onychomatricoma arises within the fingernails of middle-aged individuals[35] (Fig. 71.21). A frontal view of the nail typically reveals multiple holes in the thickened free margin. The affected nail is thickened and yellow–white in color, with multiple splinter hemorrhages.

Histologically, the tumor is characterized by multiple fibroepithelial projections that extend into the thickened nail plate. The tumor epithelium is identical to that of the normal nail matrix and keratinizes without a granular layer.

Melanocytic nevi of the nail matrix

Key features
- Longitudinal melanonychia
- Onset in childhood

Nail matrix nevi are an uncommon cause of longitudinal melanonychia, especially in comparison with melanocyte activation (see Table 71.2). They usually develop during childhood and often involve the fingers, especially the thumb[36,37]. The color, width and pigment

distribution may vary considerably and it is not unusual to observe fading or darkening of the pigmentation over time. Pigmentation of the periungual tissues is also possible.

Treatment

Optimal management of nail matrix nevi is still debated. The authors' approach is immediate excision of rapidly growing lesions and excision of all lesions after puberty (see Ch. 149).

Malignant Tumors

Malignant tumors of the nail are summarized below. For further details of the disorders and their treatment, see Chapters 108 and 113.

Bowen's disease (squamous cell carcinoma in situ)

Key features

- Verrucous lesion
- Onycholysis
- Melanonychia

Bowen's disease of the nail is uncommon and is seen most often in middle-aged men. Fingers of the left hand are most commonly involved[38]. Clinically, it may be difficult to differentiate Bowen's disease from warts. The affected digit shows periungual or subungual verrucous lesions with onycholysis and longitudinal melanonychia (Fig. 71.22). Predisposing factors include HPV infection and chronic X-ray exposure.

Fig. 71.22 Bowen's disease. The lateral portion of the nail plate is absent. The nail bed shows hyperkeratosis with scaling and fissuring of the epithelium.

Keratoacanthoma

Key features

- Painful subungual nodule
- Rapid growth
- Osteolysis on radiography

Keratoacanthoma is an extremely rare tumor that usually affects the thumb or the index or middle fingers. It appears as a painful subungual keratotic nodule that grows rapidly over a period of weeks. Deep invasion with bone destruction is frequent. A history of trauma is often reported. In contrast to cutaneous keratoacanthomas, keratoacanthomas of the nail do not regress spontaneously[39].

Squamous cell carcinoma

Key features

- Verrucous lesion
- Ulcerated nodule
- Onycholysis
- Nail plate destruction

Squamous cell carcinoma is the most frequent malignant tumor of the nail apparatus. It most commonly affects the fingernails of middle-aged men. A number of studies have confirmed a causative role for HPV, mostly HPV-16, in the development of this tumor. Clinically, there is a slowly growing periungual or subungual mass that may ulcerate and bleed. Periungual swelling and inflammation are often seen. Bony involvement may occur but metastases are extremely rare[40].

Verrucous carcinoma (carcinoma cuniculatum, epithelioma cuniculatum)

Key features

- Rapidly growing verrucous nodule
- Nail destruction

Fig. 71.23 Amelanotic melanoma. Note the diffuse nail destruction and ulceration.

Verrucous carcinoma is a rare, low-grade variant of squamous cell carcinoma characterized by locally aggressive clinical behavior but low potential for metastasis. It rarely involves the nail apparatus. Clinically, the tumor appears as a rapidly growing nodule that often destroys the nail. Bone resorption is common.

Melanoma

Key features

- Longitudinal melanonychia
- Thumb is the most frequent site
- Nail plate destruction
- Hutchinson's sign
- Amelanotic in 25% of cases

Nail melanoma is rare, accounting for 0.7–3.5% of all melanomas. It most frequently involves the thumb of middle-aged individuals, and patients often report a history of trauma. Diagnosis is often delayed, and in 25% of cases the tumor is amelanotic. The 5-year survival is only 15%[41]. From a clinical standpoint, nail melanoma may have the following features:

- Longitudinal melanonychia. The pigmented band is usually dark brown or black in color, with blurred margins. Nail plate abnormalities result from nail matrix damage. The dermoscopic

ABCDEF RULE FOR CLINICAL SUSPICION OF NAIL MELANOMA	
A	• age (peak incidence – 5th to 7th decades of life) • African-Americans, Asians and native Americans (1/3 of all nail melanoma cases)
B	• brown to black • breadth (3 mm or wider) • borders (variegated)
C	• change in the nail band (color/size) • lack of change in the nail morphology despite presumed adequate treatment
D	• digit most commonly involved (thumb and big toe)
E	• extension of the pigment into the proximal and/or lateral nailfold (Hutchinson's sign)
F	• family or personal history of dysplastic nevi or melanoma

Table 71.11 ABCDEF rule for clinical suspicion of nail melanoma. *Adapted from Levit EK, et al. The ABC rule for clinical detection of subungual melanoma. J Am Acad Dermatol. 2000;42:269–74.*

pattern that has been associated with melanoma is a brown background with longitudinal lines that are irregular in color, thickness and spacing. However, a recent study indicated that these dermoscopic patterns were not useful in the early detection of nail melanoma, as dermoscopy did not improve accuracy in the clinical diagnosis of melanoma[42].

- A subungual pigmented lesion that may have ulcerated and is associated with onycholysis and nail destruction.
- An amelanotic nodule that frequently ulcerates and bleeds, resembling a pyogenic granuloma (Fig. 71.23).

The presence of Hutchinson's sign (pigmentation of the periungual tissues due to superficial spreading of the tumor) should raise the suspicion of nail melanoma. An ABCDEF of nail melanoma has been proposed, to facilitate diagnosis (Table 71.11)[43].

REFERENCES

1. Zaias N. The Nail in Health and Diseases, 2nd edn. Connecticut: Appleton & Lange, 1990.
2. Tosti A, Cameli N, Piraccini BM, et al. Characterization of nail matrix melanocytes with anti-PEP1, anti-PEP8, TMH-1, and HMB-45 antibodies. J Am Acad Dermatol. 1994;31:193–6.
3. Baran R, Kechijian P. Understanding nail disorders. Eur J Dermatol. 2001;11:159–62.
4. Baran R, Dawber RPR, Tosti A, et al. A Text Atlas of Nail Disorders. Diagnosis and Treatment. London: Martin Dunitz, 1996.

4a. Davia JL, Bel PH, Ninet VZ, et al. Onychomadesis outbreak in Valencia, Spain associated with hand, foot, and mouth disease caused by enteroviruses. Pediatr Dermatol. 2011;28:1–5.

5. Daniel CR 3rd, Piraccini BM, Tosti A. The nail and hair in forensic science. J Am Acad Dermatol. 2004;50:258–61.

5a. Aldrich CS, Hong CH, Groves L, et al. Acral lesions in tuberous sclerosis complex: insights into pathogenesis. J Am Acad Dermatol. 2010;63:244–51.

6. Baran R, Kechijian P. Longitudinal melanonychia (melanonychia striata): diagnosis and management. J Am Acad Dermatol. 1989;21:1165–75.
7. Jellinek NJ. Dermoscopy between the lines. Arch Dermatol. 2010;146;431–3.
8. Tosti A, Piraccini BM, de Farias DC. Dealing with melanonychia. Semin Cutan Med Surg. 2009;28:49–54.

8a. Hirata SH, Yamada S, Enokihara MY, et al. Patterns of nail matrix and bed of longitudinal melanonychia by intraoperative dermatoscopy. J Am Acad Dermatol. 2011;65:297–303.

9. Kawabata J, Ohara K, Hino H, et al. Two kinds of Hutchinson's sign, benign and malignant. J Am Acad Dermatol. 2001;44:305–7.
10. Baran R. Significance and management of congenital malalignment of the big toenail. Cutis. 1996;58:181–4.
11. Piraccini BM, Parente GL, Varotti E, et al. Congenital hypertrophy of the lateral nail folds of the hallux: clinical features and follow-up of seven cases. Pediatr Dermatol. 2000;17:348–51.
12. Zaias N, Ackerman AB. The nail in Darier-White disease. Arch Dermatol. 1973;107:193–9.
13. de Berker DA, Perrin C, Baran R. Localized longitudinal erythronychia: diagnostic significance and physical explanation. Arch Dermatol. 2004;140:1253–7.

13a. Jellinek NJ. Longitudinal erythronychia: suggestions for evaluation and management. J Am Acad Dermatol. 2011;64:167. e1–11.

14. McGonagle D. Enthesitis: an autoinflammatory lesion linking nail and joint involvement in psoriatic disease. J Eur Acad Dermatol Venereol. 2009;23(Suppl 1):9–13.
15. Piraccini BM, Tosti A, Iorizzo M, et al. Pustular psoriasis of the nails: treatment and long term follow-up of 46 patients. Br J Dermatol. 2001;144:1000–5.
16. Tosti A, Peluso AM, Fanti PA, et al. Nail lichen planus: clinical and pathologic study of twenty-four patients. J Am Acad Dermatol. 1993;28:724–30.

16a. Piraccini BM, Saccani E, Starace M, et al. Nail lichen planus: response to treatment and long term follow-up. Eur J Dermatol. 2010;20:489–96.

17. Daniel CR III, Sams WM, Scher RK. Nails in systemic disease. In: Scher RK, Daniel CR III (eds). Nails: Therapy, Diagnosis, Surgery, 2nd edn. Philadelphia: WB Saunders, 1997:219–50.
18. Baran R, Tosti A. Metastatic carcinoma to the terminal phalanx of the big toe: report of two cases and review of the literature. J Am Acad Dermatol. 1994;31:259–63.
19. Tosti A, Piraccini BM, Camacho-Martinez F. Onychomadesis and pyogenic granuloma following cast immobilization. Arch Dermatol. 2001;137:231–2.
20. Cutolo M, Sulli A, Secchi ME, et al. The contribution of capillaroscopy to the differential diagnosis of connective autoimmune diseases. Best Pract Res Clin Rheumatol. 2007;21:1093–108.
21. Caputo R, Cappio F, Rigoni C, et al. Pterygium inversum unguis. Report of 19 cases and review of the literature. Arch Dermatol. 1993;129:1307–9.
22. Gupta AK, Taborda P, Taborda V, et al. Epidemiology and prevalence of onychomycosis in HIV-positive individuals. Int J Dermatol. 2000;39:746–53.
23. Turowski CB, Ross AS, Cusack CA. Human papillomavirus-associated squamous cell carcinoma of the nail bed in African-American patients. Int J Dermatol. 2009;482:117–20.
24. Piraccini BM, Iorizzo M, Antonucci A, Tosti A. Drug-induced nail abnormalities. Expert Opin Drug Safety. 2004;3: 57–65.
25. Tosti A, Piraccini BM. Paronychia. In: Amin S, Lahti A, Maibach HI (eds). Contact Urticaria Syndrome. Boca Raton: CRC Press, 1997:267–78.
26. Daniel CR III, Iorizzo M, Piraccini BM, et al. Grading simple chronic paronychia and onycholysis. Int J Dermatol. 2006;45:1447–8.
27. Griego RD, Orengo IF, Scher RK. Median nail dystrophy and habit tic deformity: are they different forms of the same disorder? Int J Dermatol. 1995;34:799–800.
28. Braun RP, Baran R, Le Gal FA, et al. Diagnosis and management of nail pigmentations. J Am Acad Dermatol. 2007;56:835–47.
29. Baran R, Perrin C. Transverse leukonychia of toenails due to repeated microtrauma. Br J Dermatol. 1995;133: 267–9.
30. Baran R, Haneke E, Richert B. Pincer nails: definition and surgical treatment. Dermatol Surg. 2001;27:261–6.
31. de Berker DA, Richert B, Duhard E, et al. Retronychia: proximal ingrowing of the nail plate. J Am Acad Dermatol. 2008;58:978–83.
32. Richert B. Frictional pyogenic granuloma of the nail bed. Dermatology. 2001;202:80–1.

32a. Piraccini BM, Bellavista S, Misciali C, et al. Periungual and subungual pyogenic granuloma. Br J Dermatol. 2010;163: 941–53.

33. Lemont H, Christman RA. Subungual exostosis and nail disease and radiologic aspects. In: Scher RK, Daniel CR III (eds). Nails: Therapy, Diagnosis, Surgery, 2nd edn. Philadelphia: WB Saunders, 1997:317–25.
34. de Berker D, Goettman S, Baran R. Subungual myxoid cysts: clinical manifestations and response to therapy. J Am Acad Dermatol. 2002;46:394–8.
35. Baran R, Kint A. Onychomatrixoma: filamentous tufted tumour in the matrix of a funnel-shaped nail. A new entity (report of 3 cases). Br J Dermatol. 1992;126: 510–15.
36. Tosti A, Baran R, Piraccini BM, et al. Nail matrix nevi: a clinical and histopathologic study of twenty-two patients. J Am Acad Dermatol. 1996;34:765–71.
37. Goettmann-Bonvallot S, Andre J, Belaich S. Longitudinal melanonychia in children: a clinical and histopathologic study of 40 cases. J Am Acad Dermatol. 1999;41:17–22.
38. Sau P, McMarlin SL, Sperling LC, et al. Bowen's disease of the nail bed and periungual area. A clinicopathological analysis of seven cases. Arch Dermatol. 1994;130:204–9.
39. Baran R, Goettmann S. Distal digital keratoacanthoma: a report of 12 cases and a review of the literature. Br J Dermatol. 1998;139:512–15.
40. Dalle S, Depape L, Phan A, et al. Squamous cell carcinoma of the nail apparatus: clinicopathological study of 35 cases. Br J Dermatol. 2007;156:871–4.
41. Banfield CC, Redburn JC, Dawber RPR. The incidence and prognosis of nail apparatus melanoma. A retrospective study of 105 patients in four English regions. Br J Dermatol. 1998;139:276–9.
42. Di Chiacchio N, Hirata SH, Enokihara MY, et al. Dermatologists' accuracy in early diagnosis of melanoma of the nail matrix. Arch Dermatol. 2010;146:382–7.
43. Levit EK, Kagen MH, Scher RK, et al. The ABC rule for clinical detection of subungual melanoma. J Am Acad Dermatol. 2000;42:269–74.

This page intentionally left blank

Oral Disease 72

Carl M Allen and Charles Camisa

Chapter Contents

Developmental conditions of the oral cavity *1149*
Syndromes of the head and neck *1151*
Periodontal and dental disease *1152*
Physical and chemical injuries *1154*
Allergic and immunologic diseases *1157*
Epithelial pathology *1160*
Salivary gland diseases *1163*
Oral manifestations of hematologic/oncologic disease *1166*
Oral manifestations of systemic disease *1167*
Oral manifestations of HIV infection *1168*

Introduction

From a histologic standpoint, the oral mucosa is an amazingly diverse anatomic region. This is not surprising when one considers the various tasks and environmental interactions that take place within the mouth. Sites that are associated with the friction of mastication, such as the hard palate and attached gingivae, show prominent rete ridge formation and a thick layer of orthokeratin. The dorsal tongue has a papillary architecture with prominent parakeratin production, while the posterior lateral tongue has a surface epithelium with embedded taste receptors. The soft palate and labial mucosa exhibit only a modest degree of parakeratosis and are associated with numerous salivary glands; the buccal mucosa is similar, but variable numbers of heterotopic sebaceous glands (Fordyce granules) may be seen in this area.

DEVELOPMENTAL CONDITIONS OF THE ORAL CAVITY

Fordyce Granules

Synonyms: ■ Ectopic sebaceous glands ■ Heterotopic or anomalous sebaceous glands ■ Fordyce spots

Key features

- Common variation of normal sebaceous glands
- Multiple yellowish papules of the buccal mucosa and vermilion zone of the upper lip

Introduction

Fordyce granules are sebaceous glands that are located in the vermilion zone of the lips and the oral mucosa. Historically, these sebaceous glands have been considered ectopic; however, because they are such a common clinical finding in the oral cavity, Fordyce granules should be regarded as a variation of normal anatomy. "Free" sebaceous glands (see below) can also be found on the eyelids (meibomian glands), areolae (Montgomery tubercles), labia minora and prepuce (Tyson glands).

Epidemiology

Fordyce granules are found in both sexes and are less common in children. The prevalence of Fordyce granules is as high as 70% to 85% in the adult population[1].

Clinical features

Fordyce granules characteristically present as asymptomatic, usually multiple, yellow to yellow–white papules. The papules are usually no more than 1–2 mm in size, and they often occur bilaterally. They are most commonly found on the buccal mucosa and the vermilion portion of the upper lip. Puberty appears to stimulate their development[2].

Pathology

Fordyce granules are similar to sebaceous glands found in the skin, but they are not associated with hair follicles, i.e. they are "free" sebaceous glands[1].

Treatment

Since Fordyce granules are considered a normal variation of anatomy, no treatment is indicated.

Geographic Tongue

Synonyms: ■ Benign migratory glossitis ■ Glossitis areata migrans ■ Stomatitis areata migrans ■ Benign migratory stomatitis

Key features

- Red, well-demarcated patches on the lateral and dorsal tongue with scalloped thin white borders
- Psoriasiform mucositis of unknown etiology
- No treatment is generally necessary

Introduction

Geographic tongue is a common, benign clinical condition of unknown etiology that primarily affects the tongue, although rarely it can occur in other sites within the mouth, such as the buccal mucosa, labial mucosa and soft palate. When it occurs in sites other than the tongue, the tongue is almost always involved as well.

Epidemiology

Geographic tongue is a condition that affects both sexes, with a prevalence of 1–3% in the general population[2].

Clinical features

Geographic tongue typically presents on the dorsum of the tongue as multiple well-delineated areas of erythema surrounded by a yellowish-white serpiginous border (Fig. 72.1). Within the areas of erythema, there is atrophy of the filiform papillae. The lesions may begin as small white patches. These then develop a central red atrophic zone, which slowly increases in size. Many patients are unaware they have a geographic tongue, and it is often found on routine oral examination[3]. Patients who are aware of their lesions frequently report that the lesions appear to migrate. Geographic tongue is usually asymptomatic, although some patients may experience a burning sensation or sensitivity to hot or spicy foods. Some investigators have suggested that geographic tongue occurs with increased frequency in patients with psoriasis (including pustular psoriasis), in atopic individuals, and in patients with fissured tongue (discussed below).

Pathology

Because the microscopic features of geographic tongue are similar to those of psoriasis, the former is often termed "psoriasiform mucositis".

Fig. 72.1 Geographic tongue. A florid example, demonstrating well-delineated areas of erythema partially surrounded by white serpiginous borders.

Fig. 72.2 Fissured tongue. Numerous asymptomatic furrows and grooves on the dorsal tongue.

At the edge of the lesion, there is a characteristic loss of the papillary surface morphology of the tongue, elongation of rete ridges, a varying degree of hyperparakeratosis and spongiosis, and the presence of numerous, typically confluent, superficial intraepithelial neutrophilic microabscesses[2].

Treatment

Geographic tongue generally requires no treatment other than assuring the patient that it represents a benign condition. If symptoms such as burning, sensitivity, pain or tenderness are present to a severe extent and interfere with the patient's lifestyle, application of a potent topical corticosteroid gel may provide some relief.

Fissured Tongue

Synonyms: ■ Scrotal tongue ■ Plicated tongue ■ Lingua plicata ■ Furrowed tongue

Introduction

Fissured tongue is a common, benign clinical condition of unknown etiology that affects the dorsum of the tongue. As the name implies, few to numerous furrows or grooves are seen on the dorsum of the tongue. Heredity appears to be a factor, with some evidence suggesting that the condition represents a polygenic trait, or an autosomal dominant trait with incomplete penetrance or expressivity. As mentioned previously, fissured tongue is often found in association with geographic tongue, with some researchers suggesting that the same gene or genes may be associated with both conditions. Fissured tongue may be a component of the Melkersson–Rosenthal syndrome (see below). It is a common finding in Down syndrome and is occasionally seen in association with Cowden syndrome, pachyonychia congenita, and acromegaly (in the setting of macroglossia).

Epidemiology

Fissured tongue affects both sexes, with the reported prevalence ranging from 2% to 30% of adults, depending on the population studied[3].

Clinical features

Fissured tongue typically presents as multiple asymptomatic grooves on the dorsum of the tongue (Fig. 72.2). The grooves are usually 2–3 mm in depth, and can occur in isolated areas of the tongue (especially centrally) or involve the entire dorsal surface.

Treatment

Fissured tongue is a benign condition requiring no treatment.

Hairy Tongue

Synonyms: ■ Black hairy tongue ■ Lingua villosa nigra

Key features

- Retention of keratin on the tips of filiform papillae
- Not due to yeast infection
- Best managed using a tongue scraper

Introduction

Hairy tongue is a common, benign clinical condition that basically represents accumulation of varying amounts of keratin on the dorsum of the tongue. Normally, the rate of keratin production on the dorsal tongue equals the rate at which keratin is naturally debrided during chewing and swallowing. If a patient has reduced food intake or a primarily soft or liquid diet, then the keratin simply accumulates. It is not a sign of any underlying systemic disease in an otherwise healthy and non-debilitated patient, as was historically believed. Factors that may be associated with increased production of keratin include smoking, poor oral hygiene, use of oxidizing mouthwashes, and hot beverages.

Epidemiology

Hairy tongue affects both sexes, with a prevalence reported as 0.5–5% of the population.

Clinical features

Hairy tongue presents as confluent hair-like projections on the dorsum of the tongue, especially its mid portion (Fig. 72.3). The elongated papillae are usually yellow to brown–black, although a wide range of colors may occur due to differential exogenous staining from food, tobacco or chromogenic bacteria. Overgrowth of the latter may occur in the setting of oral or systemic antibiotic therapy. Some patients complain of bad breath, bad taste, or a gagging sensation when the tongue contacts the palate. A distinctly different entity is pigmented papillae of the tongue, in which multiple, uniformly spaced, tiny brown papules (representing normal fungiform papillae) are seen on the tip and lateral aspects of the tongue in darkly pigmented individuals.

Pathology

Microscopic examination reveals pronounced accumulation of parakeratosis at the tips of otherwise normal filiform papillae. Often, bacteria can be seen colonizing the surface.

Treatment

Hairy tongue is a benign condition requiring no treatment. Some patients desire treatment due to the unaesthetic nature of the process,

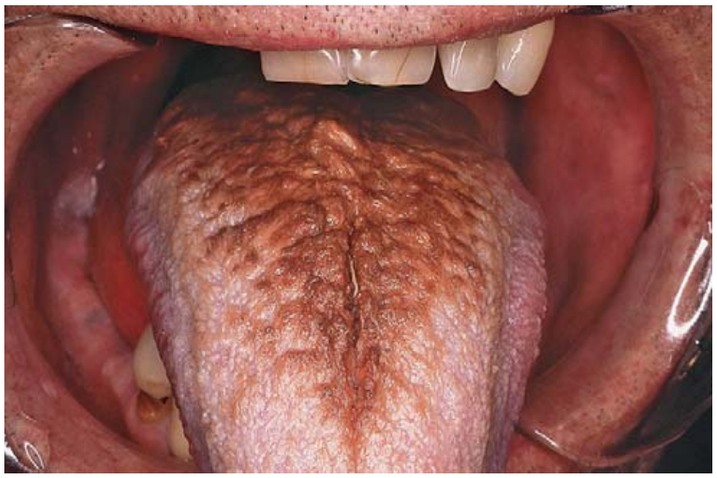


Fig. 72.3 Hairy tongue. The dorsum of the tongue exhibits marked accumulation of keratin and brown discoloration.

Fig. 72.4 Median rhomboid glossitis. On the dorsum of the tongue (anterior to the circumvallate papillae), there is a well-demarcated, smooth area with loss of the filiform papillae.

or because of the altered taste, bad breath, or gagging sensation. In such cases, patients should be encouraged to scrape the tongue with a tongue scraper or brush it while tooth brushing.

Median Rhomboid Glossitis

Synonym: ■ Central papillary atrophy

Key features

- Red, well-demarcated area in the midline of the posterior dorsal tongue
- Consistently associated with candidiasis
- Responds partially or completely to antifungal therapy

Introduction

Median rhomboid glossitis was formerly thought to be a developmental defect resulting from failure of the embryonic tuberculum impar to be covered by the lateral processes of the tongue. However, it is not usually seen in children but is found in up to 1% of adults, and it often resolves with anticandidal therapy.

Clinical features

Median rhomboid glossitis appears as a well-demarcated, diamond- or oval-shaped area of erythema and atrophy on the dorsum of the tongue (Fig. 72.4), anterior to the circumvallate papillae. The surface may be smooth or lobulated. It is usually asymptomatic but may also be associated with chronic multifocal candidiasis affecting the palate and angles of the mouth. Median rhomboid glossitis accompanied by palatal inflammation in the area of contact with the tongue lesion may represent a sign of HIV infection or other causes of immunosuppression.

Pathology

Histologically, there is loss of the filiform papillae and tubular hyphae of *Candida albicans* are embedded within the parakeratin layer. However, the diagnosis is usually made clinically and then confirmed by demonstration of pseudohyphae in a KOH preparation or a PAS-stained exfoliative cytologic preparation.

Treatment

The mucosal alteration resolves completely or partially after a course of appropriate anticandidal therapy such as clotrimazole troches or oral fluconazole.

SYNDROMES OF THE HEAD AND NECK

Nevoid Basal Cell Carcinoma Syndrome

Nevoid basal cell carcinoma syndrome (NBCCS) is an autosomal dominant disorder due to *PTCH* mutations (see Ch. 107), and up to 50% of cases may represent new mutations[4]. In addition to numerous cutaneous basal cell carcinomas (BCCs) and palmoplantar pits, patients develop skeletal anomalies and odontogenic keratocysts of the jaws (see Table 108.5). The latter are detected via a panoramic radiograph of the jaws (recommended annually). Odontogenic keratocysts should be removed completely as they can be very aggressive, leading to significant resorption of the jawbones and even pathologic fractures.

Gardner Syndrome

Synonym: ■ Familial colorectal polyposis

Introduction

Gardner syndrome is a rare autosomal dominant disorder characterized by multiple osteomas, premalignant colorectal polyps, epidermoid cysts, desmoid tumors and cutaneous fibromas (see Ch. 63). Because Gardner syndrome is due to mutations in the adenomatous polyposis coli (*APC*) gene, it is allelic with "familial adenomatous polyposis" (FAP). Without surgical intervention, development of colorectal carcinoma is inevitable.

Osteomas most commonly develop in the maxilla and mandible, and along with bilateral CHRPE (*c*ongenital *h*ypertrophy of the *r*etinal *p*igment *e*pithelium), represent the earlier manifestations of this syndrome. Screening and treatment recommendations are discussed in Chapter 63.

Multiple Endocrine Neoplasia Syndrome Type 2B

Synonyms: ■ Multiple endocrine neoplasia type 3 ■ Multiple mucosal neuroma syndrome

Key features

- Rare autosomal dominant syndrome, with high penetrance but variable expressivity
- Multiple mucosal neuromas involving the conjunctivae, lips and tongue
- Increased prevalence of pheochromocytoma
- Medullary thyroid carcinoma often develops as early as the first or second decade

Introduction

Multiple endocrine neoplasia syndrome type 2B (MEN 2B) is one of a group of inherited conditions characterized by hyperplasia or neoplasia of endocrine glands (e.g. thyroid, parathyroid, adrenal, pituitary; see Table 63.2). This syndrome is caused by missense mutations in the *RET* proto-oncogene (in particular, Met918Thr) which encodes a tyrosine kinase receptor[5].

Clinical features

The most distinctive feature of MEN 2B is the development of mucosal neuromas[6], which are present in almost all patients and are usually asymptomatic. Lesions often begin to appear during the first decade of life as soft, painless papules or nodules that favor the lips and tongue, but may also be found on the buccal mucosa, gingiva and palate. The most significant aspect of this condition is the development of medullary thyroid carcinoma in more than 90% of patients, usually during the first or second decade of life, with reports of occurrence as early as 7 months of age.

Pathology

The mucosal neuromas of MEN 2B are histopathologically distinct and are termed "plexiform neuromas". They consist of hyperplastic bundles of nerves that are surrounded by a thickened perineurium and are situated within otherwise normal-appearing submucosal connective tissue.

Treatment

Analysis of the *RET* gene should be performed in patients with clinical evidence of the disease as well as in asymptomatic individuals with an affected parent. Although detection of premalignant thyroid hyperplasia and medullary thyroid carcinoma is possible by measuring serum or urine calcitonin levels, especially after provocation with calcium and pentagastrin, this is less sensitive and specific than genetic analysis. Based upon the specific *RET* mutation detected, the recommended age for prophylactic thyroidectomy varies from age 1–6 months (level 3 risk group, e.g. codon 918 [>95% of patients]) to 10 years (level 1 risk group). Pheochromocytoma screening can be performed by measuring plasma free metanephrine or 24-hour urinary metanephrine and vanillylmandelic acid levels.

PERIODONTAL AND DENTAL DISEASE

Necrotizing Ulcerative Gingivitis

Synonyms: ■ Vincent infection ■ Trench mouth ■ Fusospirochetal gingivitis ■ Acute necrotizing ulcerative gingivitis ■ Necrotizing gingivostomatitis

Key features

- Painful, hemorrhagic, necrotic gingivae with classic "punched-out" interdental papillae
- Mixed bacterial infection in susceptible hosts with predisposing risk factors
- Predisposing risk factors include immunosuppression, malnutrition, stress, smoking, and poor oral hygiene

Introduction

Necrotizing ulcerative gingivitis is a condition of the gums characterized by pain, bleeding and necrosis of gingival interdental papillae. A mixed population of bacteria, including spirochetes, *Prevotella intermedia*, *Fusobacterium*, *Treponema* and *Selenomonas* spp., represents the primary etiology[7].

Epidemiology

Necrotizing ulcerative gingivitis affects both sexes and is seen primarily in young to middle-aged adults. Its prevalence in the normal population is less than 0.1%. This frequency increases in patients with predisposing factors such as underlying immunosuppression, malnutrition, poor oral hygiene, psychological and physical stress, and smoking.

Clinical features

It is characterized by ulcerated, "punched-out" lesions of the gingival interdental papillae. There is generalized edema, erythema, hemorrhage and necrosis of the gingivae. Other signs and symptoms include fever, malaise, lymphadenopathy, and often a foul odor from the mouth. Patients typically complain of "sore and bleeding gums".

Pathology

Because the primary etiologic agents are bacteria belonging to the normal oral flora, bacterial culture results are nonspecific, as are the histopathologic findings. The diagnosis is based chiefly on characteristic clinical findings.

Treatment

In general, the most appropriate therapy is provided by a dentist or a dental specialist, such as a periodontist. Debridement after topical or local anesthesia should be the first step; this is combined with broad-spectrum antibiotic therapy[8]. Chlorhexidine oral rinses (0.12%) may reduce the bacterial load, and warm salt water rinses may be recommended for comfort.

Desquamative Gingivitis

Key features

- A clinical descriptor for oral manifestations of an underlying immune-mediated vesiculoerosive disease
- Characterized by diffusely smooth, red, and sometimes painful gingivae
- Histopathology and immunofluorescence studies are required for appropriate diagnosis and subsequent treatment of the underlying condition

Introduction

The term "desquamative gingivitis" is used by clinicians to describe the gingival manifestations of several vesiculoerosive diseases. Clinically, the gingival epithelium is erythematous and it spontaneously sloughs or can be removed with manipulation. Desquamative gingivitis is not a diagnosis; rather, it is a characteristic clinical pattern that may be seen with a number of immune-mediated conditions[9]. Histologic and immunopathologic investigations are usually required to obtain a definitive diagnosis. This generally reveals a diagnosis of one of the following: lichen planus (Ch. 11), mucous membrane (cicatricial) pemphigoid (Ch. 30) or, less frequently, pemphigus vulgaris (Ch. 29), lichenoid mucositis (idiopathic, drug-induced or foreign body-related), linear IgA bullous dermatosis, lupus erythematosus, epidermolysis bullosa acquisita or chronic ulcerative stomatitis (Fig. 72.5).

Epidemiology

The majority of individuals affected with desquamative gingivitis are over 40 years of age, and most are women.

Clinical features

Patients with desquamative gingivitis usually present with the chief complaint of "sore gums". The most common clinical manifestations include diffuse gingival erythema with varying degrees of mucosal sloughing and erosion. Vesicle or blister formation involving the gingivae may also be seen.

Pathology

The histopathologic and immunopathologic features of desquamative gingivitis depend on which of the aforementioned vesiculoerosive diseases it represents. Patients should be evaluated by incisional biopsy and specimens should be processed for both routine histology and direct immunofluorescence microscopy[10]. In addition, serum can be sent for indirect immunofluorescence testing or ELISA to detect circulating

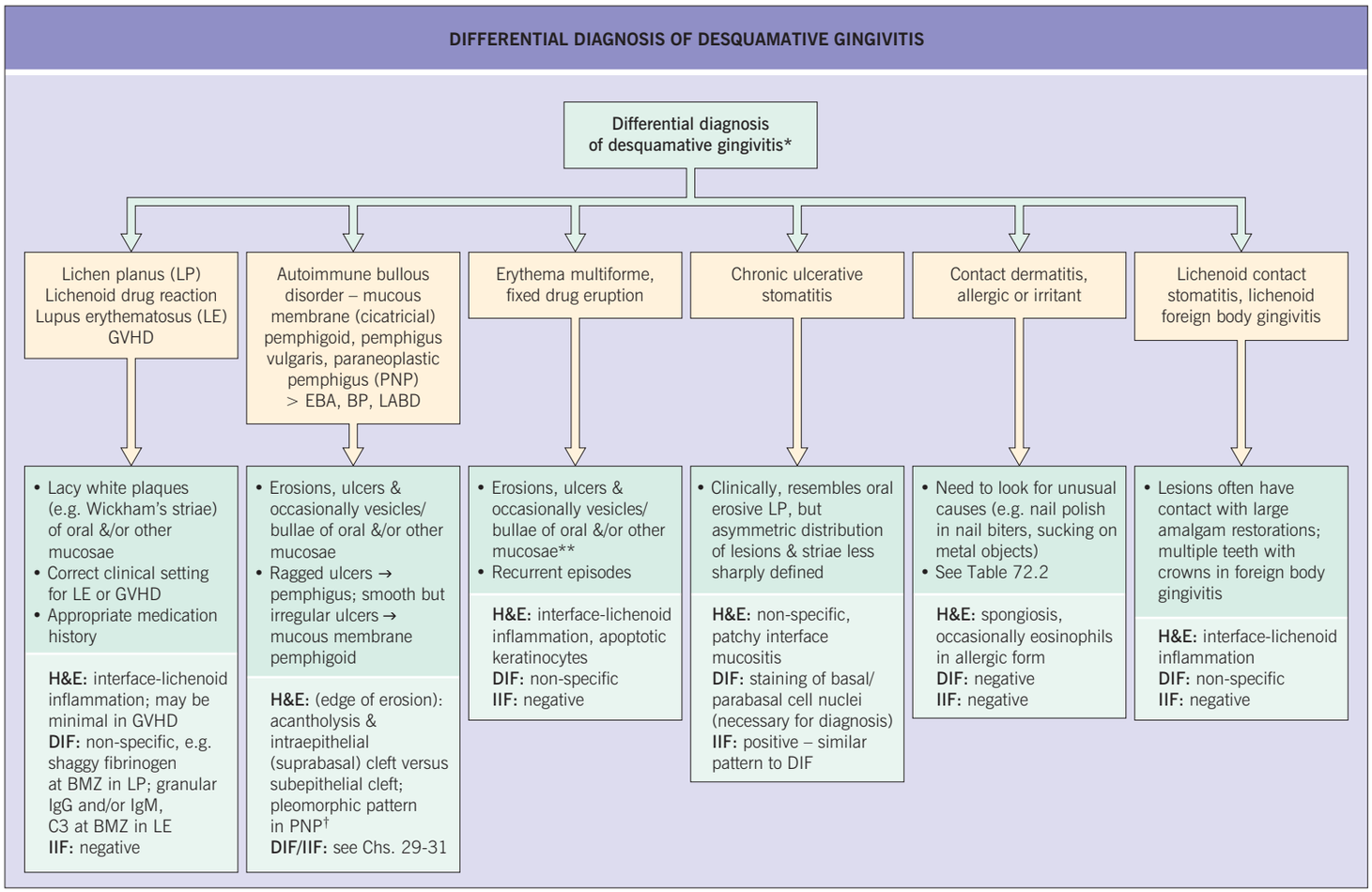


Fig. 72.5 Differential diagnosis of desquamative gingivitis. If the gingivae are painful, hemorrhagic and necrotic with punched-out interdental papillae, then necrotizing ulcerative gingivitis is the clinical diagnosis. For presumed chronic ulcerative stomatitis, the detection of circulating anti-p63 antibodies via ELISA may assist in diagnosis. *No cutaneous lesions present. **Other mucosae – more so for erythema multiforme. †The pleomorphic pattern in paraneoplastic pemphigus includes features of pemphigus and erythema multiforme as well as lichenoid inflammation. BP, bullous pemphigoid; BMZ, basement membrane zone; DIF, direct immunofluorescence (IF); EBA, epidermolysis bullosa acquisita; GVHD, graft-versus-host disease; IIF, indirect IF; LABD, linear IgA bullous dermatosis.

autoantibodies. Specific findings will depend upon the underlying disease.

Treatment

Once a diagnosis is established, appropriate treatment for the responsible condition can follow. Meticulous dental prophylaxis (cleaning), oral hygiene instructions, and longitudinal evaluation are recommended. Reducing bacterial plaque often decreases the severity of lesions and is an important adjunct to medical therapy[10].

Sequelae of Dental Caries

Key features

- Dental infections can spread beyond the periapical region of teeth
- Periapical abscess, osteomyelitis, cellulitis, intraoral dental sinus, and cutaneous sinus are potential sequelae
- Emergent cases require immediate treatment to avoid airway obstruction or possible sepsis

Introduction

Bacterial infections involving carious teeth can sometimes spread beyond the pulp of the tooth. When they do, they often invade the periapical area of the tooth within the bone. The accumulation of inflammatory cells and bacterial debris at the apex of a non-vital tooth is termed a "*periapical abscess*". Without resolution, there is the possibility that the abscess may extend further into medullary bone and cause *osteomyelitis*[11]. If the host immune defenses are compromised or if the invading bacteria are particularly virulent, this lesion may progress, perforating the cortical bone and extending into the overlying soft tissues and fascial spaces as *cellulitis*. This usually manifests as a painful, diffuse swelling of facial soft tissues. If the bacteria are only moderately virulent, the infection may be contained but will eventually erode through to either an oral mucosal surface (resulting in an *intraoral dental sinus tract*; "*parulis*") or facial skin, producing a *cutaneous sinus of dental origin* (Fig. 72.6). If a chronic path of drainage is achieved by an abscess, patients may be asymptomatic because of a lack of accumulation of purulent and inflammatory material. Without drainage, signs and symptoms of acute inflammation may become evident.

Clinical features

The clinical presentation of cellulitis includes diffuse, tender swelling of the facial soft tissues. The areas involved and the severity of the infection can vary tremendously. Dysphagia, headache, fever, lymphadenopathy and pain may be present. Sepsis is a less common complication. Two potential complications are mentioned because they represent a greater danger to patients and demand immediate attention. *Ludwig's angina* is the swelling of the submandibular, submental and sublingual spaces. This presentation of cellulitis is emergent because it can rapidly spread to the retropharyngeal space, obstructing breathing, and even spread to the mediastinum. *Cavernous sinus thrombosis* due to a dental abscess may initially present as swelling of the canine space. Infraorbital, ocular and eventually CNS involvement may develop.

An intraoral dental sinus tract is characterized by a soft, non-tender, erythematous papule that develops on the alveolar process, typically in

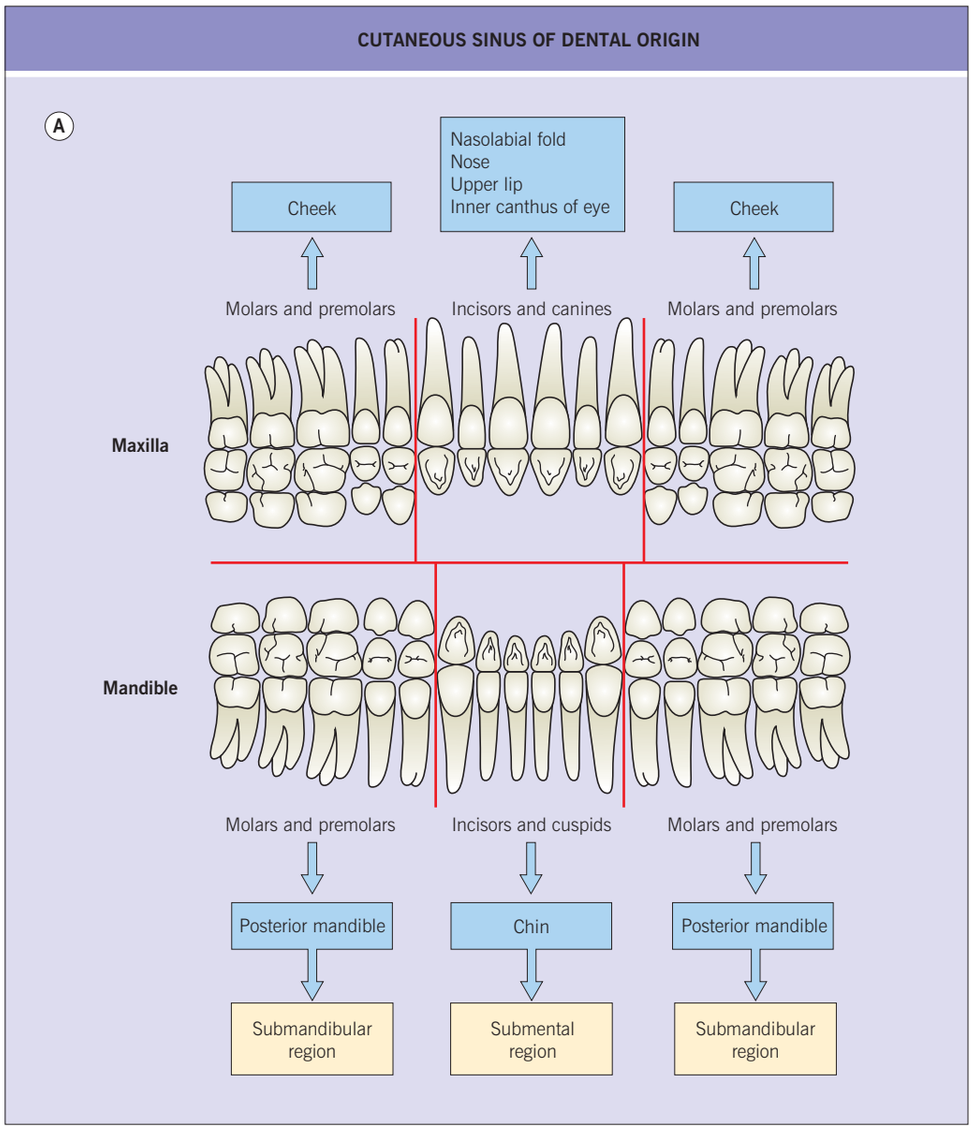


Fig. 72.6 Cutaneous sinus of dental origin. **A** Typical pathways and sites of extraoral drainage of dental sinuses. The majority of cutaneous sinus tracts are associated with mandibular teeth. Dental abscesses in the maxilla (**B**) and mandible (**C**) channelize and drain through the overlying skin. The lesion may be mistaken for a pyogenic granuloma or a neoplasm. *A, Adapted from Cioffi GA, Terezhalmy GT, Parlette HL. Cutaneous draining sinus tract: an odontogenic etiology. J Am Acad Dermatol. 1986;14:94–100, with permission. C, Courtesy, Judit Stenn, MD.*

the same region as the apex of the offending non-vital tooth. Such sinus tracts are frequently asymptomatic, but patients may describe periodic episodes of a salty or bitter taste that probably coincides with the discharge of purulent exudate. A cutaneous sinus of dental origin appears as an erythematous papule, often with an ulcerated or umbilicated center, or as a depression with associated fibrosis (see Fig. 72.6). Cervicofacial actinomycosis must be excluded (see Ch. 74).

Treatment

Treatment involves elimination of the focus of infection, which often requires extraction of the involved tooth, incision and drainage, appropriate antibiotic therapy, and airway management, if necessary.

PHYSICAL AND CHEMICAL INJURIES

Fibroma

Synonyms: ■ Irritation or traumatic fibroma ■ Fibrous hyperplasia or nodule

Key features

- Smooth, pink, soft nodule, typically on the buccal mucosa
- Asymptomatic unless persistently irritated or traumatized

Introduction

Fibroma is the most common "tumor" of the oral cavity, but it most likely represents reactive hyperplasia of fibrous connective tissue in response to local trauma.

Epidemiology

Irritation fibromas most commonly occur during the fourth to sixth decades. Women outnumber men 2:1, based on biopsy specimens submitted for examination.

Clinical features

The typical lesion is a sessile, soft, smooth-surfaced pink nodule similar in color to normal mucosa and located along the bite line of the buccal mucosa. They also occur on the labial mucosa, tongue and gingiva. Size varies, but fibromas are usually less than 1.5 cm in diameter.

Pathology

Microscopic examination shows an unencapsulated mass of hyperplastic fibrous connective tissue with minimal inflammation. The overlying epithelium may be atrophic or hyperkeratotic secondary to friction or biting; sometimes there is also ulceration.

Treatment

Irritation fibromas are cured by conservative surgical excision. It is important to submit the tissue for histopathologic examination

because other benign or malignant tumors may clinically resemble fibromas.

Chemical Burn

Synonyms: ■ Aspirin burn ■ Mucosal burn

Key features

- "Burns" can occur when caustic chemicals come into contact with the oral mucosa
- A superficial, white, sloughing membrane represents coagulative necrosis of the epithelium
- Treatment consists of removal of the offending agent and palliative care

Introduction

Numerous chemicals and drugs come into contact with the oral mucosa, and some of these are caustic enough to cause superficial burns[12]. A variety of agents have been reported as being responsible for these burns, including aspirin, vitamin C tablets, hydrogen peroxide, silver nitrate, phenol, eugenol, rubbing alcohol, battery acid, gasoline, various dental materials, and many over-the-counter toothache medicaments[2]. Aspirin (acetylsalicylic acid, pH 3.5) is one of the most commonly recognized medications responsible for mucosal damage[13]. Patients often place a tablet on the oral mucosa overlying a sore tooth in an attempt to alleviate dental pain, and the resultant continuous contact produces injury.

Clinical features

Most caustic agents cause characteristic damage to the mucosa. This may appear initially as just an erythematous zone. With greater concentration or longer duration of exposure to the chemical, a wrinkled white membrane that represents superficial necrosis becomes evident (Fig. 72.7)[14].

Pathology

Microscopic evaluation reveals coagulative necrosis of the epithelium. The necrosis begins on the surface and may extend partially into the epithelium, or it may involve its entire thickness.

Treatment

A chemical burn is a self-resolving condition requiring no treatment except for discontinuing or preventing exposure to the offending agent. Application of emollient pastes or topical anesthetics as a palliative measure may provide some temporary relief.

Morsicatio Buccarum

Synonyms: ■ Chronic cheek chewing ■ Chronic cheek biting

Key features

- Factitial habit
- Bilateral shaggy white lesions of the anterior buccal mucosa
- No treatment indicated

Introduction

Chronic irritation or injury to the buccal mucosa from repetitive chewing, biting or nibbling produces a characteristic appearance clinically[2]. Similar changes may also be observed on the labial mucosa.

Clinical features

Morsicatio buccarum typically presents as bilateral shaggy white lesions of the anterior buccal mucosa that approximate the area where the upper and lower teeth meet (occlusal plane). The white areas are ragged and shredded (Fig. 72.8). Foci of erythema, erosion or traumatic ulceration are rarely identified.

Pathology

Microscopic evaluation reveals marked hyperparakeratosis of the surface epithelium, which demonstrates a ragged morphology. Varying degrees of vacuolization and spongiosis are observed in the superficial portion of the epithelium. Surface colonization by bacteria is also a frequent feature. Although these findings are relatively nonspecific, in the appropriate clinical setting they are highly suggestive of this factitial habit.

Treatment

Morsicatio buccarum is a benign condition requiring no treatment.

Fig. 72.7 Aspirin burn. To relieve a toothache, this patient placed an aspirin in the mouth adjacent to the symptomatic tooth. Note the wrinkled white membrane that represents superficial epithelial necrosis.

Fig. 72.8 Cheek chewing (morsicatio buccarum). Repetitive nibbling of the superficial layers of the epithelium resulted in these changes. Note that the characteristic shaggy, white lesion approximates the area where the upper and lower teeth meet.

Traumatic Ulcer

Key features

- Acute or chronic injury to the oral mucosa may cause a traumatic ulcer
- Commonly occurs on the tongue, lips or buccal mucosa
- May mimic oral squamous cell carcinoma
- Self-limited process that heals within 3–6 days following removal of etiologic agent

Introduction

The etiology of a traumatic ulcer is related to acute or chronic injury to the oral mucosa. The injury is often mechanical in nature, such as biting the tongue or cheek accidentally, or lacerating the mucosa with sharp foods or objects (e.g. the sharp edge of a fractured tooth).

Clinical features

Traumatic ulcers are moderately painful lesions. They are characterized by mild erythema surrounding a central ulcer that is covered by a yellow fibrinopurulent membrane (Fig. 72.9). Sometimes there is a white border of hyperkeratosis surrounding the ulcer. Traumatic ulcers occur most commonly on the tongue, lips and buccal mucosa, although other sites may be involved. They are usually self-limiting, if the etiologic agent is removed, and generally heal within 3–6 days. Since traumatic ulcers can clinically mimic oral squamous cell carcinomas (SCCs), biopsy is indicated if the ulcer does not resolve within 2–3 weeks following elimination of potential causes.

Treatment

Remove any obvious causative agent. Application of a thin protective film of cellulose compound, with or without a topical anesthetic as a palliative measure, may provide some relief.

Drug-Related Gingival Enlargement (Hyperplasia)

Key features

- Enlargement of the gums noted during the first year of drug administration
- Typically associated with phenytoin, nifedipine or cyclosporine
- Severity correlated with patient susceptibility and level of oral hygiene

Fig. 72.9 Traumatic ulcer. This lesion of the lateral tongue demonstrates a yellow fibrinopurulent membrane with a white border of hyperkeratosis. Compare this to the exophytic, ulcerated mass depicted in Fig. 72.17, which represents oral squamous cell carcinoma.

Introduction

Many systemic medications have been reported to be associated with gingival enlargement (Table 72.1), but a high prevalence has been noted only with phenytoin (50%), nifedipine (25%) and cyclosporine (25%). Although it is still controversial whether the risk of developing this side effect is dose-related, there is a definite correlation with poor oral hygiene.

Clinical features

During the first year of drug administration, gingival enlargement commences in the interdental papillae of the anterior teeth on the labial side. The hyperplasia may extend over part or all of the involved teeth. Edentulous areas are usually spared, but significant hyperplasia under poorly maintained dentures has been reported. The enlarged gingiva is usually normal in color, firm, and nodular or lobulated. However, associated inflammation can lead to a red, edematous or friable appearance.

Pathology

Microscopically, redundant tissue of normal composition or an increased amount of collagen with a normal density of fibroblasts is seen. When the specimen is clinically inflamed, there is increased vascularity and a chronic inflammatory cell infiltrate.

Treatment

A rigorous regimen of oral hygiene consisting of frequent professional cleaning and home plaque control utilizing chlorhexidine rinses helps to prevent drug-associated gingival enlargement. Discontinuation of the suspected offending drug or even substitution with another drug of the same class may result in cessation or some regression of the gingival hyperplasia.

If all else fails, then extirpation of the excess gingival tissue, a procedure normally performed by a periodontist, remains the treatment of choice. Samples of excised tissue should be submitted for histopathologic evaluation as there are other causes of gingival enlargement (see Table 72.1).

CAUSES OF GINGIVAL ENLARGEMENT (HYPERPLASIA, HYPERTROPHY)	
SYSTEMIC MEDICATIONS	
Common	
Anticonvulsants (phenytoin, phenobarbital, lamotrigine, valproate, vigabatrin, ethosuximide, topiramate, primidone)	
Calcium channel blocking agents (**nifedipine**, amlodipine, diltiazem, felodipine, verapamil)	
Cyclosporine*	
Uncommon	
Antibiotics (erythromycin, cotrimoxazole)	Sertraline
Lithium	Oral contraceptives, estrogens
Amphetamines	
• Local inflammatory factors – poor oral hygiene, periodontal disease • Hormone-related – pregnancy, acromegaly • Granulomatous disorders – orofacial granulomatosis, Crohn's disease, sarcoidosis • Wegener's granulomatosis • Vitamin C deficiency (scurvy) • Gingival fibromatosis/multiple gingival fibromas – tuberous sclerosis, Cowden disease, hereditary gingival fibromatosis • Leukemia – acute monocytic leukemia, acute myelomonocytic leukemia > other types of myelogenous or lymphocytic leukemias • Other malignancies – Kaposi sarcoma • Deposits – primary systemic amyloidosis, infantile systemic hyalinosis, mucopolysaccharidoses, fucosidosis, Fabry disease	
*Consider substitution with oral tacrolimus	

Table 72.1 Causes of gingival enlargement (hyperplasia, hypertrophy).

Contact Stomatitis

Synonyms: ■ Oral mucosal cinnamon reaction ■ Lichenoid amalgam reaction ■ Contact lichenoid reaction

Key features

- Cinnamon flavoring and dental amalgam (silver-containing filling material) may cause lichenoid changes of the oral mucosa
- Red, white or mixed lesions are seen, with varying degrees of erosion, ulceration or striae formation
- Lesions may be located where the offending agent contacts the mucosa for a prolonged period of time
- Removal of the offending agent should be curative

Introduction

Numerous foods, artificial flavorings, food additives, and materials used in dentistry have been implicated as etiologic agents of allergic or irritant contact stomatitis (Table 72.2). Two of these, namely cinnamon flavoring (found in many foods, gums, candies and dentifrices) and dental amalgam ("silver" dental fillings), may lead to unique clinicopathologic features.

Epidemiology

The frequency of true allergic reactions due to contact with antigenic substances is probably not as high for the oral mucosa as for the skin. The reduced reactivity of the oral mucosa has been attributed to many factors, including the brief period of contact of agents with the mucosa, the more rapid dispersal and absorption of antigens, and the diluting and neutralizing properties of saliva.

Clinical features

The clinical features of contact stomatitis from *cinnamon flavoring* can vary; sometimes it produces localized lesions on the buccal mucosa or lateral borders of the tongue that appear as shaggy white keratotic areas[2] (Fig. 72.10). The buccal lesions may resemble oral lichen planus or morsicatio buccarum clinically, while the tongue lesions may resemble oral hairy leukoplakia or SCC. Erosion, ulceration and erythema can also be seen. Gingival involvement appears as swelling and erythema.

Contact stomatitis from *dental amalgam* occurs mainly at sites adjacent to amalgam restorations, such as the posterior buccal mucosa and ventrolateral surface of the tongue[15]. When the mucosa is relaxed, the lesion is characteristically seen to directly contact the amalgam restoration, which is often on the buccal (rather than occlusal) surface of the tooth (Fig. 72.11). The lesions may be white or erythematous, with or without peripheral striae, and they can resemble oral lichen planus. Ulceration or erosion may also be observed. With both amalgam and cinnamon reactions, pain is not a universal finding although it may be present.

POTENTIAL CAUSES OF CONTACT STOMATITIS OR CHEILITIS
ALLERGIC
• Flavorings: cinnamon, mint, menthol, vanillin • Dental metals: mercury, gold, nickel, palladium, copper, silver, cobalt, chromium, beryllium, tin, zinc • Dental adhesives: acrylate compounds, eugenol • Topical anesthetics: benzocaine • Essential oils: clove, lemon, orange
IRRITANT
• Aspirin • Dental chemicals: eugenol, peroxides, phenol, sodium hypochlorite • Chlorhexidine mouth rinse • Silver nitrate stick • Sodium lauryl sulfate (in toothpaste)

Table 72.2 Potential causes of contact stomatitis or cheilitis.

Pathology

Biopsy specimens of contact stomatitis from dental amalgam or cinnamon flavoring often demonstrate a lichenoid mucositis. The cinnamon reaction may have a psoriasiform pattern, whereas, in general, patients with contact stomatitis have spongiosis histologically. In lichenoid mucositis, the epithelium may have hyperkeratosis, basilar crowding and atypia, atrophy of the spinous layer, lymphocytic exocytosis, and, sometimes, ulceration. Immediately subjacent to the epithelium is a band of chronic inflammatory cells that, in some areas, effaces the rete ridge architecture. A perivascular infiltrate composed primarily of lymphocytes with occasional plasma cells frequently surrounds small blood vessels. Longstanding amalgam reactions are characterized by a much broader band of lichenoid inflammation compared to routine lichen planus, and it is not unusual to find well-defined germinal centers within the lymphocytic infiltrate.

Treatment

With contact stomatitis due to cinnamon flavoring, the lesions disappear within a week of discontinuing the offending product, but may

Fig. 72.10 Contact stomatitis from artificial cinnamon flavoring. Use of artificial cinnamon-flavored gum caused this shaggy, white keratotic lesion of the buccal mucosa.

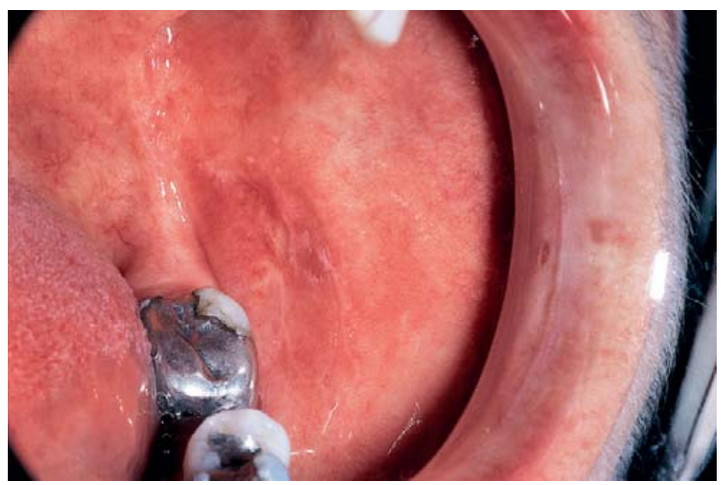


Fig. 72.11 Lichenoid stomatitis secondary to amalgam hypersensitivity. Superficial erosions with radiating white striae are localized to the buccal mucosa adjacent to a large amalgam restoration.

reappear quickly with reuse of the product or other cinnamon-containing agents, confirming the cause. When contact stomatitis secondary to amalgam is suspected, patch testing is recommended and should include organic and inorganic mercury as well as amalgam and the other dental metals. The offending restoration may be treated conservatively at first by polishing, smoothing and recontouring (in addition to cleaning the teeth to remove plaque), but if these measures fail, appropriate alternative dental materials, such as composite (a white plastic-like material), gold or porcelain fused to metal, can be used to replace the amalgam restoration[16].

Recurrent Aphthous Stomatitis

Synonyms: ■ Recurrent oral aphthae ■ Aphthous ulcers ■ Canker sores ■ Simple or complex aphthosis

Key features

- The three forms of simple recurrent aphthous stomatitis are minor, major and herpetiform
- Lesions are painful, typically less than 5 mm in diameter, round to oval, and appear creamy-white with an erythematous halo
- The pathomechanism is unknown, but immunologic factors may be involved
- Usually controlled through the use of topical corticosteroids

Introduction

Recurrent aphthous stomatitis is a relatively common ulcerative disorder of the oral cavity. While the etiology remains obscure, it is likely to be a multifactorial disorder influenced by a host of predisposing factors. Recurrent aphthous stomatitis is believed by some to be the result of a dysfunction of the immune system, resulting in immunologically mediated damage to epithelial cells[17,18]. This abnormal immune response may be triggered or influenced by trauma, hematinic (iron, folate or vitamin B_{12}) deficiencies, hormonal fluctuations, psychological stress, infectious agents, food hypersensitivities, genetic factors, and HIV infection. Complex aphthosis, the almost constant presence of more than three oral aphthae or oral and genital aphthae, requires the exclusion of Behçet's disease, inflammatory bowel disease, cyclic neutropenia, vitamin deficiencies (e.g. B_{12}, folate), HIV infection and other disorders listed in Table 72.3[18].

Epidemiology

Recurrent aphthous stomatitis is a common disorder that has been documented to affect 10–50% of certain professional student populations. A recent large retrospective series from a referral oral medicine center identified a male predilection, and the peak prevalence occurs during the second decade[18].

Clinical features

There are three categories of simple aphthae. *Minor aphthae*, the most common form, are characterized by round to ovoid, shallow, painful ulcers that are usually less than 5 mm in diameter. Individual lesions are covered by a creamy-white pseudomembrane and have a rather sharply defined border and an erythematous rim (Fig. 72.12). The ulcers are typically limited to the non-keratinized oral mucosa, with common sites of involvement including the labial and buccal mucosa, floor of the mouth, ventral surface of the tongue, soft palate and oropharyngeal mucosa. These lesions usually heal without scarring within 1–2 weeks. Most patients experience infrequent recurrences, although some may have almost continuous lesional activity.

Major aphthae are characterized by larger ulcerations, typically >1 cm and sometimes approaching 3 cm. Lesions are usually deeper, persist for up to 6 weeks, and may heal with scarring. Major aphthae are associated with considerable oral pain, and are sometimes accompanied by fever and malaise.

Herpetiform aphthae are very uncommon, consisting of multiple small, painful ulcerations that superficially resemble primary HSV infection. Up to 100 ulcers are possible at one time. Herpetiform aphthae are typically confined to non-keratinized mucosa and are recurrent, features that help distinguish the condition from primary HSV infection.

The aphthae in patients with complex aphthosis generally resemble minor aphthous ulcers except that there is a greater number of lesions, although major and/or herpetiform aphthae may occur[19,20].

RECURRENT APHTHAE – ETIOLOGIES AND DIFFERENTIAL DIAGNOSIS

ETIOLOGIES

- Idiopathic (immune-mediated)
- Related to an underlying systemic disorder: inflammatory bowel disease, systemic lupus erythematosus, HIV infection, Behçet's disease, reactive arthritis*, cyclic neutropenia, PFAPA (*p*eriodic *f*ever, *a*phthous stomatitis, *p*haryngitis and *a*denitis) syndrome, certain hereditary periodic fever syndromes (e.g. HIDS, NOMID)
- Possibly related to an underlying nutritional disorder (controversial): vitamin B_{12}, folate or iron deficiency

DIFFERENTIAL DIAGNOSIS

Recurrent erosions and ulcerations due to:

- An inflammatory disorder, e.g. erythema multiforme, fixed drug eruption, contact stomatitis – less pain at onset, less peripheral erythema
- Recurrent herpes simplex – only involves mucosa overlying bone (hard palate, attached gingiva) in immunocompetent hosts
- Trauma – less pain at onset, less peripheral erythema, more ragged edges

*Previously referred to as Reiter's disease.

Table 72.3 Recurrent aphthae – etiologies and differential diagnosis. HIDS, hyperimmunoglobulinemia D with periodic fever syndrome; HIV, human immunodeficiency virus; NOMID, neonatal-onset multisystem inflammatory disease.

Fig. 72.12 Recurrent aphthous stomatitis. Shallow, creamy-white ulceration surrounded by an intensely red halo and located on non-keratinized mucosa, representing a classic presentation.

Pathology

Histopathologic features are relatively nonspecific. Early lesions may show a neutrophilic vessel-based submucosal infiltrate. In most patients, however, the appearance and distribution of lesions allow for the diagnosis to be made clinically.

Treatment

The primary goals of therapy are promotion of healing, management of pain and nutrition, and prevention of recurrence[20]. Application several times daily of a thin film of a superpotent topical corticosteroid gel, as early as possible in the course of an outbreak, will typically reduce significantly the pain and time to healing. Topical analgesics may be included for transient relief of pain. While it is not possible to

THERAPEUTIC LADDER FOR COMPLEX APHTHOSIS
LOCAL THERAPY (AGENTS MAY BE USED IN COMBINATION)
Local anesthetics (2)
Superpotent topical corticosteroids (1*/2) or corticosteroid inhalers (2)
Intralesional corticosteroids (2)
Topical tacrolimus (3)
SYSTEMIC THERAPY
Colchicine (1†/2)
Dapsone (1†/2)
Combination of colchicine and dapsone (2)
Thalidomide (1)
*Clobetasol propionate in an adhesive denture paste.
†In patients with Behçet's disease.

Table 72.4 Therapeutic ladder for complex aphthosis. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports. *Adapted from Letsinger JA et al. J Am Acad Dermatol. 2005;52:500–8, with permission.*

prevent recurrences, the frequency of episodes is often reduced following topical corticosteroid therapy. Patients with complex aphthosis may require therapy with oral colchicine, dapsone or even thalidomide (Table 72.4).

Behçet's Disease

Synonym: ■ Behçet's syndrome

Key features

- Recurrent oral and genital aphthae
- Anterior or posterior uveitis and/or retinal vasculitis
- Erythema nodosum-like and papulopustular lesions

Behçet's disease is a rare chronic multisystem disorder that is more prevalent in countries located along the ancient Silk Road (see Ch. 26)[21,22]. Episodes of disease activity may be intermittent, with exacerbations and remissions of unpredictable duration and frequency. Oral aphthae are present in 99% of patients with Behçet's disease, and they frequently occur before any other signs of the disease develop. These aphthae are usually multiple, no larger than 6 mm in diameter, and last approximately 1–3 weeks, with uneventful healing and no scarring[22].

Systemic manifestations, clinical criteria for the diagnosis of Behçet's disease, and treatment options are outlined in Tables 26.11, 26.13 and 26.14, respectively.

Eosinophilic Ulcer of the Oral Mucosa

Synonyms: ■ Eosinophilic ulcer of the tongue ■ Traumatic eosinophilic granuloma ■ Riga–Fede disease (childhood variant)

Introduction

Eosinophilic ulcer of the oral mucosa represents an uncommon, self-limited ulcerative condition. Approximately half of the patients report antecedent trauma. A similar disorder, referred to as Riga–Fede disease[23], has been described on the ventral tongue of infants and toddlers with erupted mandibular incisor teeth who are nursing, as well as in children with congenital insensitivity to pain. The infiltrate is composed of numerous eosinophils admixed with large, atypical mononuclear cells that have been characterized in various studies as representing macrophages, myofibroblasts and, most recently, a clonal population of $CD30^+$ T lymphocytes. The latter observation has led some authors to speculate that a subset of eosinophilic ulcers may be an oral counterpart of cutaneous $CD30^+$ lymphoproliferative disorders (e.g. lymphomatoid papulosis)[24]. Of note, at least one recent report observed that ulcers with a clonal population of T cells did not behave any differently than polyclonal lesions[25].

Epidemiology

Eosinophilic ulcers can occur in any age group, from infants and young children to the elderly. There is no gender predominance.

Clinical features

Although the majority of eosinophilic ulcers are located on the tongue, they can also appear on the buccal, labial, alveolar or palatal mucosa. The initial lesion is a rapidly enlarging, firm nodule that develops a central ulceration with elevated borders and an indurated base; it is typically covered with a fibrinous exudate. The ulcers are usually 1–2 cm in diameter and may or may not be painful. Multiple lesions are sometimes observed.

Pathology

Histologically, eosinophilic ulcers are characterized by a dense, diffuse infiltrate of eosinophils and pleomorphic mononuclear cells that extends deeply into the submucosal tissue and underlying striated muscle. Large, atypical cells may represent $CD30^+$ T lymphocytes. The base of the ulcer is composed of poorly formed granulation tissue that may have an increased number of capillaries with prominent endothelial cells.

Treatment

Most eosinophilic ulcers resolve spontaneously within a few months, so treatment other than supportive care is not required. Because SCC can be in the differential diagnosis, a biopsy is often performed; the latter may trigger healing. Recurrences occasionally occur.

Orofacial Granulomatosis

Subtype/synonyms: ■ Granulomatous cheilitis: cheilitis granulomatosa, Miescher's cheilitis

Key features

- Persistent, non-tender swelling of the lip and/or face
- Non-caseating granulomatous inflammation

Introduction

Orofacial granulomatosis is a term introduced in 1985 by Wiesenfeld to describe non-infectious, non-necrotizing granulomatous disorders of the lips, face and oral cavity[26]. These include granulomatous cheilitis as well as orofacial manifestations of Crohn's disease and sarcoidosis[27]. The etiology of most forms of orofacial granulomatosis is unknown. Some investigators, however, have suggested that it may be an allergic response consisting of cell-mediated hypersensitivity to foods, food additives, or certain flavoring agents in common oral hygiene products[28].

Epidemiology

It occurs primarily in young adults and usually presents during the second or third decade. There is no notable sex predilection.

Clinical features

Orofacial granulomatosis is a chronic process that usually presents as diffuse enlargement of the lips or facial swelling. Oral ulceration, gingival overgrowth or mucosal tags are less commonly seen. Swelling may be intermittent initially, but eventually it persists[29]. Lip involvement is termed "granulomatous cheilitis" and usually only the upper or lower lip is affected (Fig. 72.13). Rarely, granulomatous cheilitis has been reported with facial nerve palsy and fissured tongue, resulting in the condition known as Melkersson–Rosenthal syndrome.

For most patients, the disorder is relatively asymptomatic. The differential diagnosis may include angioedema, although the swelling that

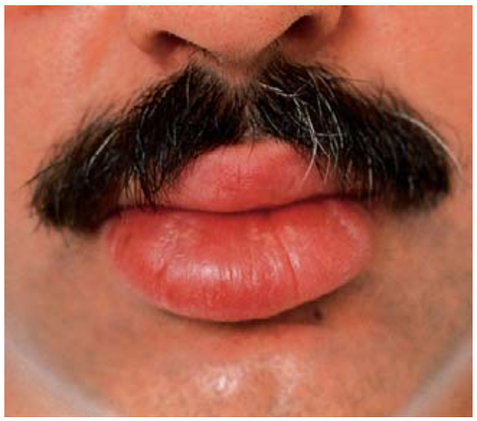


Fig. 72.13 Cheilitis granulomatosa. Slightly asymmetric swelling, predominantly of the lower lip. A biopsy specimen demonstrated non-caseating granulomas.

characterizes that condition typically resolves spontaneously within 24–48 hours.

Pathology

The most striking histopathologic feature of orofacial granulomatosis is non-necrotizing granulomatous inflammation, although in some cases the granulomas are rather sparse.

Treatment

Intralesional corticosteroids can be used to treat orofacial granulomatosis. Because of its tendency to relapse, repeated corticosteroid injections may be necessary. Systemic agents, such as dapsone, clofazimine, hydroxychloroquine, thalidomide, tumor necrosis factor (TNF)-α inhibitors (e.g. adalimumab, infliximab [approved for Crohn's disease]), or even systemic corticosteroids, have also been used. In addition, long-term courses of oral antibiotics (e.g. tetracyclines, erythromycin) have been tried.

Wegener's Granulomatosis

Key features

- Necrotizing granulomatous vasculitis of the upper and lower respiratory tract and necrotizing glomerulonephritis
- Destructive ulcerated lesions of the oral and nasal cavity
- Pathognomonic friable "strawberry gums" may be seen
- Up to 80% of patients have antineutrophil cytoplasmic antibodies (ANCA)

Introduction/clinical features

Wegener's granulomatosis (WG) is a necrotizing granulomatous disease of unknown etiology that, without treatment, is often fatal (see Ch. 24). The criteria for the diagnosis of both the classic and limited forms of WG are outlined in Figure 40.5.

While there is a superficial form of WG, characterized by involvement of the skin or oral mucosa without systemic manifestations, it is noteworthy that skin and/or mucosal involvement may represent the initial presentation of classic or limited WG.

Because WG commonly involves the nose, nasopharynx and paranasal sinuses, epistaxis, sinusitis and nasal obstruction are common complaints. Destruction of the nasal cartilage may result in perforation of the nasal septum and/or saddle nose deformity[30]. Oral manifestations can include rather destructive oropharyngeal, lingual or gingival ulcerations. The gingivae may exhibit petechial hemorrhage that is superimposed on a friable micropapular surface, an essentially pathognomonic appearance termed "strawberry gums" (Fig. 72.14)[31,32]. Gingival pain and bleeding are common.

Pathology

Biopsy specimens from pulmonary lesions of WG show vasculitis of small to medium-sized arteries with necrotizing granulomatous inflammation, while skin biopsies can demonstrate leukocytoclastic vasculitis and/or granulomatous inflammation[30]. However, such classic features are infrequently observed in oral biopsy specimens.

Fig. 72.14 Wegener's granulomatosis – strawberry gums. The affected areas of the gingiva are red–purple, micropapular and friable, with a resemblance to ripe strawberries.

Treatment

The treatment of classic WG consists of systemic corticosteroids and cyclophosphamide[33], and oral lesions typically respond to this regimen.

EPITHELIAL PATHOLOGY

Oral Leukoplakia/Erythroplakia

Key features

- Leukoplakia and erythroplakia are strictly clinical diagnoses
- Leukoplakia is the most common premalignant condition of the oral cavity
- Biopsy is mandatory in order to assess the degree of dysplasia and to exclude invasive SCC

Introduction

Oral leukoplakia is defined as a white patch or plaque that cannot be characterized clinically or pathologically as any other disease. The development of oral leukoplakia is strongly associated with the use of tobacco, primarily in the combustible form, and alcohol. It is regarded as a premalignant condition[34].

The term "erythroplakia" is used to describe an intraoral lesion that is similar in appearance to erythroplasia of Queyrat, a form of SCC *in situ* affecting the glans penis. Erythroplakia is defined as a red patch that does not represent any other recognizable condition, and biopsy specimens usually show more advanced dysplastic changes compared to leukoplakia.

Epidemiology

Oral leukoplakia is the most common premalignant oral mucosal lesion. Its prevalence in various adult populations has been reported to range from 1% to 5%, although a recent study from the US suggested a lower prevalence of approximately 0.5%. In general, there is a male predominance. Leukoplakia usually develops after the age of 30 years, with a peak incidence in those over 50 years of age. Erythroplakia is a far less common condition than oral leukoplakia. There is no apparent

Fig. 72.15 Leukoplakia. Sharply demarcated, white plaque involving the ventral surface of the tongue and floor of the mouth.

sex predilection and lesions tend to occur during the sixth or seventh decade[35].

Clinical features

Oral leukoplakia may appear as a homogeneous white or a non-homogeneous "speckled" (red and white) plaque that usually has sharply demarcated borders (Fig. 72.15). Leukoplakia should not be confused with leukoedema, which is a gray–white discoloration of the buccal mucosa and represents a normal variant; the latter becomes less apparent when stretched. Common sites of involvement include the floor of the mouth, the lateral and ventral surfaces of the tongue, and the soft palate. Non-homogeneous lesions and those of the tongue and floor of the mouth have been reported to have a higher risk for malignant transformation[34].

Erythroplakia is characterized as a flat or slightly elevated, velvety, rather sharply circumscribed plaque. The lesions are often asymptomatic. They may be clinically indistinguishable from inflammatory conditions. Sites of involvement are similar to those of oral leukoplakia.

Pathology

Lesions of leukoplakia usually demonstrate benign features, with simple hyperkeratosis seen most frequently. Epithelial dysplasia, if present, ranges from mild to severe, although carcinoma *in situ* or even invasive SCC may be encountered. Erythroplakia, on the other hand, generally shows more advanced dysplastic features, with 90% of lesions demonstrating severe epithelial dysplasia, carcinoma *in situ* or invasive carcinoma at the time of biopsy[35].

Treatment

Because both oral leukoplakia and erythroplakia are considered premalignant, biopsy is mandatory. If no dysplasia or mild dysplasia is evident, the decision to treat may depend upon the site of the lesion. Leukoplakia in low-risk sites (buccal mucosa, labial mucosa, hard palate) may warrant periodic clinical evaluation, with cessation of any potentially carcinogenic habits. Moderate or severely dysplastic lesions often require complete removal and continued monitoring.

Erythroplakic lesions typically require prompt surgical removal and careful follow-up. The methods of treatment for both leukoplakia and erythroplakia include surgical excision, cryosurgery and CO_2 laser ablation[36]. Recurrence rates of 30% or greater have been described, despite what appears clinically to be complete removal, although one report noted just a 10% recurrence rate after laser ablation and a mean follow-up period of 52 months[36]. The high recurrence rates have led to anecdotal use of adjunctive therapy with agents such as topical imiquimod. To date, there have been very few well-controlled, randomized, prospective studies concerning the management of leukoplakia and erythroplakia[37,38].

Proliferative Verrucous Leukoplakia

Key features

- Lack of association with traditional risk factors for oral cancer
- Multifocal red and white plaques, with a varying degree of verrucous change
- Lesions have often been present for decades and eventually transform into either verrucous carcinoma or SCC

Introduction

In 1985, a multifocal precancerous condition of the oral mucosa, proliferative verrucous leukoplakia (PVL), was first described[39]. Often the patients had had lesions for decades, and eventually transformation to either SCC or verrucous carcinoma was documented.

Epidemiology

In contrast to "routine" leukoplakia (see above), patients with PVL tend to be women and significantly fewer have traditional risk factors for oral cancer (e.g. smoking and/or alcohol abuse). Multiple studies have failed to link PVL to human papillomavirus (HPV) infection[40].

Clinical features

At the time of diagnosis, many of the patients with PVL have had the condition for years. Due to a prominent host response to the epithelial atypia, the early stages of PVL may resemble oral erosive lichen planus (which may account for many of the reports of so-called malignant transformation of lichen planus). Initially, there is usually a mixture of red and white patches in multiple sites. Often the lesions are discrete rather than confluent. Over time, the lesions acquire a fine papillary or verrucous surface, although this may require decades[41]. When ulceration, marked thickening or induration develops, this typically is a sign that malignant transformation to either verrucous carcinoma or SCC has occurred.

Pathology

The histopathologic features of PVL can vary tremendously, depending upon the stage at which it is biopsied and the site chosen for biopsy. In the earliest phases, the histology may appear very bland, with only hyperorthokeratosis and perhaps epithelial atrophy or basilar hyperplasia[41]. Over time, varying degrees of epithelial dysplasia develop, but these changes can be focal and may differ depending upon the site. Eventually, features of verrucous carcinoma and/or SCC can be seen.

Treatment

Treatment of PVL is problematic because surgical excision, the most commonly utilized treatment modality for routine oral leukoplakia, has not proven to be effective in controlling PVL. Prognosis is generally considered to be guarded to poor, and in one of the larger long-term studies, only 15% of the patients were alive and disease-free at a mean of 11.6 years[42].

Nicotine Stomatitis

Synonym: ■ Stomatitis nicotina

Key features

- Characterized by gray–white mucosa with umbilicated papules
- Associated with the application of heat to the palatal mucosa, usually from pipe smoking

Introduction

Nicotine stomatitis is most commonly seen in pipe smokers, and it is probably due to the heat that the pipe stem directs toward the palatal mucosa[43]. Of note, palatal lesions clinically identical to those seen in pipe smokers have also been observed in hot tea and coffee drinkers[44].

Fig. 72.16 Nicotine stomatitis. Gray–white palatal mucosa with numerous umbilicated papules representing inflamed palatal mucous glands.

Clinical features

Nicotine stomatitis presents as a gray or white discoloration of the palate due to increased keratinization (Fig. 72.16). Umbilicated papules with red central puncta, representing inflamed palatal salivary gland orifices, may be present[43]. These changes are more prominent toward the posterior hard palate and anterior soft palate.

Pathology

While the condition should not generally require biopsy, the histopathologic features include hyperkeratosis and parakeratosis, acanthosis, and mild chronic sialodochitis.

Treatment

Treatment is usually not necessary. Cessation of smoking will typically result in complete resolution within 1–2 weeks.

Actinic Cheilitis

Synonym: ■ Actinic cheilosis

Key features

- Primarily affects the vermilion zone of the lower lip in fair-skinned individuals
- Scaling, roughness and/or erosions
- Characterized by some degree of epithelial dysplasia histologically

Introduction

Actinic cheilitis is a common condition similar to actinic keratosis and is typically confined to the vermilion zone of the lower lip.

Epidemiology

Actinic cheilitis is seen most commonly in white, fair-skinned men over 40 years of age[45]. As with actinic keratoses, the condition is predominantly observed in people who have had significant amounts of exposure to ultraviolet irradiation[46].

Clinical features

Early features of actinic damage to the lower vermilion zone include loss of normal dermatoglyphics, atrophy, and blurring of the margin between the vermilion zone and the skin. Evolution to precancerous actinic cheilitis is heralded by the development of scaling and roughness. Initially this may be localized, but multifocal areas of involvement are not unusual. Fissuring and erosions are eventually seen as the condition progresses.

Pathology

The basic microscopic features of actinic cheilitis consist of thickening of the epithelium and hyperkeratosis. It is important to note that different areas within the same lesion may show different degrees of epithelial dysplasia. Examination of multiple sections is often indicated to identify areas of severe dysplasia, carcinoma *in situ*, or invasive SCC.

Treatment

Actinic cheilitis frequently represents a "field change", and while only focal areas may appear worrisome, the widespread nature must be considered in treating the patient[47]. In some patients, it can be difficult to distinguish epithelial dysplasia from *in situ* or even invasive SCC[46].

Treatment options for typical actinic cheilitis consist of cryosurgery, topical agents such as 5-fluorouracil or imiquimod, and photodynamic therapy. Treatment of severe actinic cheilitis consists of vermilionectomy with submission of the tissue for histopathologic examination. CO_2 laser ablation has also been used to treat this condition, usually after the presence of invasive SCC has been excluded.

Oral Squamous Cell Carcinoma

Key features

- The most common malignancy of the oral cavity
- Develops primarily in middle-aged or elderly men
- Significant association with the use of tobacco and alcohol
- Most common intraoral sites are the lateral and ventral surfaces of the tongue and floor of the mouth

Introduction

SCC is the most common malignancy of the oral cavity, and it is strongly associated with the use of tobacco and the consumption of alcohol[48]. Other etiological factors include betel nut chewing, primarily in the Indian subcontinent and Southeast Asia, and HPV infection, especially types 16 and 18[49]. Carcinomas of the vermilion zone of the lower lip are associated with actinic damage secondary to chronic sun exposure. Lastly, a recent study suggested that a slightly increased risk for oral SCC might be inherited[50].

Epidemiology

SCC accounts for more than 90% of all malignant neoplasms of the mouth and oropharynx. In the US, over 30 000 new cancers of the oral cavity are diagnosed annually. While typically a disease of middle-aged or elderly men, and accounting for 4% of all cancers within this group, there is some evidence that suggests an increasing incidence of oral SCC among women and younger patients. In fact, in some series, up to 16% of newly diagnosed cases were in individuals between the ages of 18 and 45 years[51]. Although very few SCCs in the oral cavity proper (anterior to the tonsillar pillars) are HPV-positive, in the oropharynx (behind the anterior tonsillar pillar), HPV status has been shown to influence prognosis, with HPV-positive tumors having a better prognosis[51a].

Clinical features

While any intraoral site may be affected, the most common sites are the lateral and ventral surfaces of the tongue and the floor of the mouth.

Clinically, oral SCC may present as an ulcer, an exophytic mass, or an endophytic process with varying degrees of induration (Fig. 72.17). The surface is typically irregular, rough or granular. These lesions are often painless early on in their disease course. Patients may present with dysphagia or dysphonia[52].

Pathology

Oral SCCs are histologically similar to those occurring elsewhere (see Ch. 108).

Treatment

Treatment of oral SCC consists of various combinations of surgery, radiotherapy and chemotherapy. Radiation therapy plus chemotherapy allows for organ preservation and decreases the risk of metastases. Ninety percent of recurrences occur within 2 years of initial treatment.

Fig. 72.17 Squamous cell carcinoma. Ulcerated, indurated, exophytic mass involving the right lateral border of the tongue, a typical presentation and site for this tumor.

In comparison to SCC of the skin, intraoral lesions are characterized by significantly more aggressive behavior. In addition, oral cancers are often diagnosed at a relatively advanced stage. Therefore, the prognosis is less favorable. Five-year survival rates for stage I or II disease approach 80%, while the 5-year survival rate for stages III and IV is 30% or less. In addition, oral cancer patients have a 2–3% annual risk of developing a second primary SCC of the upper aerodigestive tract after treatment of their original tumor.

Verrucous Carcinoma

Subtype/synonyms: ■ Oral verrucous carcinoma: oral florid papillomatosis, Ackerman tumor

Key features

- Uncommon, low-grade variant of SCC
- White and exophytic, with a papillary or warty (verrucous) topography
- Characterized by slow, persistent growth

Introduction

Verrucous carcinoma is often considered a low-grade variant of SCC. In addition to the oral mucosa, similar lesions occur in the anogenital region, plantar surface of the foot, and laryngeal mucosa.

Epidemiology

Verrucous carcinoma is a rare variant of SCC, with an incidence of 1–3 per 1 million population[53]. The disease usually affects men over 50 years of age. While HPV, particularly HPV-6 and HPV-11, may be detected in some of these tumors, its precise etiologic role is still unclear.

Clinical features

The most common site of involvement for verrucous carcinoma is the oral mucosa, particularly the palate, buccal mucosa and alveolar processes. Clinically, lesions present as slowly growing, white, exophytic, papillomatous or warty proliferations with well-demarcated borders. Ulceration is uncommon.

Pathology

Histopathologically, verrucous carcinoma is characterized by hyperkeratosis and an extremely acanthotic epithelium with a papillary or verrucous surface[54]. The epithelium is well differentiated, with minimal atypia and rare mitotic figures. A dense infiltrate of chronic inflammatory cells is frequently present in the superficial connective tissue. Excised lesions should be examined with multiple sections because as many as 25% of verrucous carcinomas show foci of typical SCC.

Treatment

The treatment of choice for verrucous carcinoma is wide surgical excision[55]. Adjunctive therapy with imiquimod and/or oral retinoids has been anecdotally reported to be useful. Traditionally, radiation therapy is not employed because of concern regarding anaplastic transformation; however, there are case reports of successfully combining chemotherapy plus radiation therapy.

SALIVARY GLAND DISEASES

Mucocele

Synonyms: ■ Mucous cyst of oral mucosa ■ Ranula (when located on the floor of the mouth)

Key features

- Common condition caused by disruption of a minor salivary gland duct with resultant spillage of mucus into the submucosal tissue
- Affects a wide age range
- Most commonly seen on the lower labial mucosa
- Often has to be surgically excised to provide complete resolution

Introduction

A mucocele is one of the more commonly encountered disorders of the oral mucosa. Mucoceles develop when a minor salivary duct is disrupted, resulting in the escape of mucus into the adjacent submucosal connective tissue (see Ch. 110).

Epidemiology

While the majority of mucoceles are detected in younger individuals (second through fourth decade), the lesion can be seen at any age.

Clinical features

The patient will typically report the sudden onset of a painless, soft submucosal swelling. Any color change is dependent on how deep the swelling is relative to the surface mucosa, with very superficial lesions often appearing vesicular, slightly deeper mucoceles having a bluish tinge (Fig. 72.18), and the deepest lesions having no discernible color change. Patients often describe the lesion as having multiple cycles of swelling, rupturing and refilling. While the lower labial mucosa is the most common site of involvement, any oral mucosal area that contains minor salivary glands can potentially develop a mucocele[56]. In particular, they sometimes develop on the ventral tongue, buccal mucosa and posterior hard palate, but the upper labial mucosa is a rare site. A lesion that appears to be a mucocele in the retromolar region (behind the last molar tooth in the mandible) should be examined histologically, as mucoepidermoid carcinoma is seen with some frequency in this location.

Pathology

Histopathologically, a collection of mucus is surrounded by chronic inflammatory cells (consisting primarily of macrophages) as well as granulation tissue. Lobules of inflamed minor salivary glands are often included in the tissue sample.

Treatment

While some very superficial mucoceles may undergo rupture followed by reconnection of the duct to the surface, most mucoceles require surgical excision of the mucus deposit plus the adjacent minor salivary glands in order to resolve the process. Occasionally, a mucocele will

Fig. 72.18 Mucocele. Soft nodule with bluish hue in a typical location: lower lateral labial mucosa.

Fig. 72.19 Cheilitis glandularis. Erythematous mucosal macules on the lower lip at sites of inflamed salivary gland ducts. There is also evidence of actinic cheilitis.

recur after surgery, but this is not common. Other therapeutic modalities are outlined in Chapter 110.

Cheilitis Glandularis

Key features

- Rare condition characterized by inflammatory hyperplasia of the lower labial salivary glands
- Primarily affects adult men
- Possibly associated with chronic sun exposure or irritation
- Dysplasia is often present in the overlying epithelium

Introduction

Cheilitis glandularis is a rare anomaly of the lips, consisting of an inflammatory hyperplasia of the lower labial salivary glands, which may result from chronic irritation[57].

Epidemiology

It is seen primarily in adult men. The lower lip is most commonly involved, and the condition has been associated with an increased risk for the development of SCC.

Clinical features

The clinical presentation of cheilitis glandularis may vary from slight hypertrophy of the lower lip to nodular enlargement that results in its eversion[58]. The secretory ducts become dilated and inflamed, appearing as pinpoint red mucosal macules (Fig. 72.19).

Pathology

Histopathologically, there are focal dense accumulations of inflammatory cells within and around the mucous glands. The vermilion zone often displays actinic cheilitis.

Treatment

The treatment of cheilitis glandularis consists of vermilionectomy of the lower lip, with or without cosmetic debulking.

Necrotizing Sialometaplasia

Key features

- Uncommon ulcerative process of the posterior hard palate thought to be due to ischemia
- Frequently misdiagnosed as a malignancy, both clinically and histologically

Introduction

Necrotizing sialometaplasia is an uncommon disorder that is most likely due to an interruption of the blood supply to salivary gland tissue, typically in the region of the posterior hard palate or anterior soft palate, leading to ischemic necrosis[59]. While such a disruption in blood supply can follow surgical procedures in the area, in most patients the cause of the ischemic injury is unknown. Very infrequently, a submucosal malignancy may occlude the palatal blood vessels[60,61].

Epidemiology

The condition is almost always seen in adult patients, with a slight male predominance in most series.

Clinical features

The patient will usually complain of the sudden onset of swelling of the palate, in addition to pain, paresthesia or anesthesia of the area. Within 1–2 weeks, the ischemic tissue sloughs, and the patient will often state that "part of the roof of my mouth fell out". This leads to a well-demarcated ulcer with a border that is minimally elevated or flush with the surrounding intact mucosa. By palpation, the ulcer has no underlying induration or mass.

Pathology

Because ulcerated oral malignancy is often the leading diagnosis clinically, this may influence the histopathologic interpretation, especially if the pathologist is not familiar with the disorder. A misdiagnosis of mucoepidermoid carcinoma or SCC is not unusual, as the benign squamous metaplasia of the ductal epithelium can mimic a malignancy. Confinement of the metaplastic and ischemic changes to the original boundaries of the salivary gland lobules is the key diagnostic feature[62].

Treatment

Once the diagnosis of necrotizing sialometaplasia is established, additional treatment is not required. Depending upon the size of the defect, it may take several weeks to heal.

Sjögren's Syndrome

Key features

- Autoimmune disorder characterized by keratoconjunctivitis sicca and xerostomia
- Primarily affects women

Introduction/clinical features

Sjögren's syndrome (SjS) is the second most common autoimmune connective tissue disease, exceeded only by rheumatoid arthritis (see

Ch. 45). While the etiology and pathogenesis remain unclear, patients are known to produce a number of autoantibodies, including IgG antibodies against SS-A (Ro) and SS-B (La) (see Ch. 40). Patients with SjS have a 40-fold increased risk of lymphoma, predominantly the non-Hodgkin B-cell type[63].

SjS is a systemic disorder that presents primarily as dry eyes (keratoconjunctivitis sicca)[64] and dry mouth (xerostomia). Primary SjS is characterized by these features alone (sicca syndrome), whereas secondary SjS consists of sicca syndrome in association with another autoimmune disorder, such as systemic lupus erythematosus or rheumatoid arthritis.

Symptoms of SjS are the result of decreased glandular function secondary to lymphocytic infiltration, primarily by $CD4^+$ T cells. Both the major and minor salivary glands may be affected, leading to reduced salivary production. Major gland involvement is clinically evident in fewer than half of affected patients, presenting as firm, diffuse, nontender or slightly tender enlargement that is usually bilateral.

Patients express variable degrees of ocular and oral dryness[65], with a gradual onset of symptoms in most cases. Oral pain may be present, along with dysphagia and difficulty wearing prostheses[66]. Xerostomia frequently leads to increased dental caries, in particular along the gum line. There is an increased susceptibility to oral candidiasis as well[65]. Systemic manifestations are discussed in Chapter 45.

Pathology

The diagnosis of SjS may be difficult to appreciate initially, due to the often insidious onset of the disease. Salivary gland biopsy is frequently used to support the diagnosis of SjS and there are two pathologic appearances. In the parotid gland, benign lymphoepithelial lesions consist of a proliferation and infiltration of lymphocytes in the glandular tissue in association with hyperplasia and metaplasia of salivary duct epithelium, forming the characteristic epimyoepithelial islands. Minor salivary gland involvement by SjS is characterized by focal aggregates of 50 or more lymphocytes (constituting one "focus") adjacent to normal-appearing acini[65]. A minimum of five glands must be harvested from the lower labial mucosa, and a focus score of one or greater in a 4 mm^2 area of glandular tissue is generally considered to be consistent with the disease[67]. However, given the lack of international consensus, criteria do vary slightly with some pathologists requiring two or more foci.

Although harvesting these minor salivary glands is a relatively simple surgical procedure[68], some clinicians reserve it for patients whose clinical and serologic findings are equivocal[69]. Review by an oral pathologist may improve detection of the diagnostic histologic features[67]

Treatment

The treatment for SjS consists of symptomatic care and management of the associated complications. Sugarless gum and candy may be used to stimulate salivary flow. Artificial salivary substitutes can also be beneficial. Pilocarpine or cevimeline may be prescribed to stimulate glandular function for those patients with functioning residual salivary tissue. Treatment of systemic features is discussed in Chapter 45.

THE DIFFERENTIAL DIAGNOSIS OF INTRAORAL TUMORS AND TUMOR-LIKE LESIONS
DEVELOPMENTAL LESIONS
• Congenital inclusion cysts – Bohn nodules (alveolar ridge) – Epstein pearls (palate) • Torus • Lingual thyroid • Dermoid cyst • Enteric duplication cyst • Nasoalveolar cyst • Lymphatic malformation
REACTIVE/INFLAMMATORY CONDITIONS
• Mucocele • Fibroma* • Melanoacanthoma • Eosinophilic ulcer • Pyogenic granuloma • Peripheral giant cell granuloma • Necrotizing sialometaplasia • Nodular fasciitis
BENIGN SALIVARY GLAND NEOPLASMS
• Pleomorphic adenoma • Monomorphic adenoma • Papillary cystadenoma
OTHER BENIGN NEOPLASMS
• Squamous papilloma • Infantile hemangioma • Angiomyoma • Myofibroma, hemangiopericytoma • Granular cell tumor† • Neurofibroma • Schwannoma • Palisaded encapsulated neuroma • Melanotic neuroectodermal tumor of infancy • Ameloblastoma • Lipoma
MALIGNANT SALIVARY GLAND NEOPLASMS
• Adenoid cystic carcinoma • Mucoepidermoid carcinoma • Adenocarcinoma
OTHER MALIGNANT NEOPLASMS
• Squamous cell carcinoma • Melanoma • Lymphoma • Kaposi sarcoma • Rhabdomyosarcoma • Osteosarcoma • Fibrosarcoma • Liposarcoma
*Ossification may occur. †A congenital epulis represents a granular cell tumor of the alveolar ridge.

Table 72.5 The differential diagnosis of intraoral tumors and tumor-like lesions.

Salivary Gland Tumors

Key features

- Usually seen on the palate
- In general, benign tumors are diagnosed more often than malignant tumors
- Slight female predominance

Introduction/epidemiology

Tumors of the minor salivary glands are uncommon, constituting approximately 15% of all salivary gland neoplasms. However, whenever an intraoral submucosal mass is detected, the diagnosis of a salivary gland neoplasm should be considered.

Clinical features/pathology

Most salivary gland tumors present as a painless, rubbery, firm swelling. Pain may be noted, however, in malignant tumors. Occasionally, ulceration is present, clinically mimicking SCC. The posterior hard palate/anterior soft palate is the most frequently affected site, followed by the upper lip and buccal mucosa. Pleomorphic adenoma and mucoepidermoid carcinoma represent the most common benign and malignant tumors, respectively (Table 72.5)[70,71].

Treatment

The treatment of benign salivary gland tumors consists of conservative surgical excision. Malignant tumors usually require more extensive removal. Radiotherapy is generally used as a postsurgical adjunct.

ORAL MANIFESTATIONS OF HEMATOLOGIC/ONCOLOGIC DISEASE

Chemotherapy- and Radiotherapy-Induced Oral Mucositis

Key features

- Chemotherapy-induced oral mucositis usually develops in patients who have been treated with cytotoxic drugs and subsequently develop neutropenia
- Radiotherapy-induced oral mucositis most commonly occurs in patients treated for head and neck malignancies
- Erosions, ulcerations and hemorrhagic crusting of the oral mucosa are seen
- Self-healing, but recurrent, in patients receiving multiple cycles of chemotherapy

Introduction

Drug-induced direct cytotoxic effects on oral epithelial cells, in combination with neutropenia (which also predisposes patients to superimposed infections), often leads to the development of ulcers of the oral mucosa. The ulcers usually develop 4–7 days after administration of the chemotherapeutic agent(s) and tend to be less severe in those who have received recombinant human granulocyte colony-stimulating factor (G-CSF). For those individuals undergoing hematopoietic stem cell transplantation who have received high-dose chemotherapy plus radiotherapy, treatment with recombinant human keratinocyte growth factor (palifermin) also reduces the severity of mucositis[72].

Radiotherapy for head and neck malignancies can cause direct cytotoxic damage to the oral epithelium as well, with painful mucositis usually appearing after the third week of treatment[73].

Clinical features

Characteristically, a single or multiple round, oval or irregularly shaped ulcers are seen, usually on the gingivae or other mucosal sites that are frequently traumatized (lateral tongue, buccal mucosa). Pain may or may not be present. Diagnosis is based upon clinical features as well as the temporal relationship to chemotherapy administration or initiation of radiotherapy.

The differential diagnosis includes infections (e.g. viral or candidal) and, for more longstanding lesions, oral SCC. Of note, the association of neutropenia and oral ulcers is also seen in patients with cyclic neutropenia, with crops of lesions coinciding with the nadir of the neutropenia.

Treatment

Resolution typically occurs within 2 to 3 weeks of completing the chemotherapy cycle or radiotherapy[74]. Although palifermin can reduce the severity of oral mucositis (see above), it also leads to a markedly thickened layer of keratin on the dorsum of the tongue and a resultant whitish discoloration. Maintenance of oral hygiene (e.g. use of soft toothbrushes and rinses), topical anesthetics, non-narcotic or narcotic analgesics[73], and antimicrobial agents can also be helpful.

Leukemia

Key features

- Associated intraoral findings include infections and gingival hemorrhage
- Gingival enlargement occurs most commonly with monocytic and myelomonocytic leukemias

Introduction

While oral infections related to neutropenia and immunosuppression from chemotherapy are common, direct involvement of the oral mucosa by leukemic cells is rather unusual.

Clinical features

There are numerous oral manifestations associated with leukemia and its treatment[75]. Most common is bruising or spontaneous and persistent hemorrhage due to thrombocytopenia. Leukopenia results in poor healing and an increased prevalence of viral, fungal and bacterial infections. The tissues may exhibit an overall pallor of anemia or ulcerative gingivitis. Diffuse, firm, non-tender gingival enlargement can result from infiltration of the gingival connective tissue by leukemic cells, primarily in patients with monocytic or myelomonocytic forms of leukemia[76].

Treatment

Multi-agent chemotherapy and allogeneic hematopoietic stem cell transplantation are most commonly used to treat acute leukemias. Management of oral complications requires establishment of a definitive diagnosis for the particular complaint and treating it accordingly.

Lymphoma

Key features

- Non-Hodgkin lymphomas typically account for over 80% of lymphomas
- Relatively uncommon within the oral cavity, where it presents as an extranodal proliferation

Introduction/epidemiology

Non-Hodgkin lymphoma comprises a heterogeneous group of lymphoid neoplasms whose biologic behavior ranges from relatively indolent to highly aggressive[77]. Unlike Hodgkin disease, up to 40% of non-Hodgkin lymphomas may arise in extranodal sites, including the oral cavity.

In general, non-Hodgkin lymphoma is a disease of older adults and increases in incidence with age. HIV-infected individuals appear to have a greater risk of developing *oral* non-Hodgkin lymphoma[78].

Clinical features

The head and neck region is the second most common extranodal site for non-Hodgkin lymphoma, after the gastrointestinal tract[79]. The most common intraoral locations are the palate and the buccal vestibule. Lymphoma in these areas presents as a soft to rubbery-firm, slowly growing, mucosa-colored to purplish swelling. Ulceration may be present, mimicking SCC. Overlying telangiectasias may also be evident. Pain is usually not a prominent feature.

Pathology

Non-Hodgkin lymphomas of the oral cavity are primarily of the B-cell type.

Treatment

Treatment for non-Hodgkin lymphoma consists of chemotherapy and/or monoclonal antibodies (e.g. rituximab). The survival rates for non-Hodgkin lymphomas are highly variable, depending upon tumor classification and stage.

Melanoma

Key features

- Oral mucosal melanomas are rare, constituting less than 1% of all melanomas
- Approximately one oral melanoma is detected annually per 10 million individuals in the US
- Predominantly affects men, with an average age of 55 years

Introduction/epidemiology

Oral melanomas account for far less than 1% of all oral malignancies, and occur in the US at an annual rate of 1.2 per 10 million population[80]. Men are affected more often than women, with most cases diagnosed between 40 and 70 years of age (mean age of 55 years)[81].

Fig. 72.20 Amalgam tattoo. Foreign body tattoos are the most common cause of acquired oral pigmentation, and most of them are due to iatrogenic implantation of dental amalgam. In this case, the amalgam was used to seal the apices of endodontically treated teeth, resulting in tattooing of the maxillary vestibule. Histologically, darkly staining deposits are seen within the dermis.

Clinical features

Clinically, oral melanomas exhibit virtually all of the features of their cutaneous counterparts. The preferred site for oral melanomas is the hard palate, followed by the maxillary attached gingiva[82]. The differential diagnosis includes foreign body tattoo (Fig. 72.20), blue nevus, oral melanotic macule, physiologic pigmentation, and melanoacanthoma. Melanomas are usually painless. Uncommonly, they may be amelanotic, resembling erythroplakia, a pyogenic granuloma, or an invasive SCC.

Pathology

Histopathologically, oral melanomas feature infiltration of the connective tissue by atypical melanocytes (as well as proliferation within the epithelium), with or without melanin production (see Ch. 113). For those lesions devoid of melanin, the diagnosis may be confirmed by immunohistochemistry using antibodies directed against S100 protein, HMB45, MART-1/Melan-A or MITF.

Unlike cutaneous melanomas, mucosal melanomas of the head and neck are usually in a vertical growth phase at the time of diagnosis. While the majority of these mucosal melanomas apparently have a minimal associated radial growth phase[83], it is possible that they are simply discovered at a more advanced stage due to their location[80].

Treatment

The treatment of choice for oral melanoma is wide surgical excision with adequate negative margins[84]. Sentinel lymph node biopsy also provides useful prognostic information[85]. While standard chemotherapy and radiotherapy appear to have little impact on the course of the disease, targeted therapies (e.g. tyrosine kinase inhibitors) may improve survival.

Whereas the overall 5-year survival rate for cutaneous melanoma is at least 90%, that of oral mucosal melanoma is only about 15%, with a median survival post-diagnosis of less than 2 years.

ORAL MANIFESTATIONS OF SYSTEMIC DISEASE

Amyloidosis

Key features

- Systemic or localized deposition of fibrillar proteins
- May be primary or secondary
- Most commonly affects the kidney and heart
- Amyloid deposits within the tongue can occur and may produce macroglossia

Introduction

Amyloidosis is a term for diseases sharing the common feature of extracellular deposition of pathologic insoluble fibrillar proteins within organs and tissues (see Ch. 47). Systemic amyloidosis occurs as a primary disease in association with plasma cell disorders such as multiple myeloma or secondary to chronic inflammatory diseases. It can also be inherited or occur as part of the aging process[86].

Clinical features

Macroglossia, a classic feature that occurs in about 20% of patients with primary systemic amyloidosis, is characterized by firm enlargement of the tongue[87,88]. Scalloping of its edge can develop and sometimes the macroglossia is accompanied by secondary ulceration. Hemorrhagic papules and plaques may also appear on the tongue or in other oral mucosal sites. Taste disturbances have been noted with or without macroglossia, and xerostomia can result from involvement of the salivary glands[86]. Cutaneous and systemic features are discussed in Chapter 47.

Pernicious Anemia

Key features

- Most common cause of vitamin B_{12} deficiency
- Affects up to 2% of the population over the age of 60 years
- Immunologically mediated condition with antibodies directed against intrinsic factor and parietal cells of the stomach
- Tongue may appear smooth and beefy red

Introduction

Pernicious anemia is an autoimmune disorder characterized by megaloblastic hematopoiesis and/or neuropathy due to vitamin B_{12} deficiency[89]. It is the most common underlying cause of this vitamin deficiency and is associated with chronic atrophic gastritis. Of note, B_{12} deficiency is also seen in vegetarians, post-gastrectomy and individuals with tapeworm infections.

Patients with pernicious anemia produce antibodies directed against intrinsic factor and parietal cells of the fundus and body of the stomach. The malabsorption of vitamin B_{12} is due to intrinsic factor deficiency.

Epidemiology

Pernicious anemia is a relatively common disorder, and is present in up to 2% of individuals over 60 years of age. There is a slight female predilection. In addition, there may be a genetic predisposition, as the disease occurs 20 times more frequently in close relatives[89].

Clinical features

Pernicious anemia typically has an insidious onset, with patients eventually presenting with symptoms of anemia. Peripheral neuropathies are frequently reported, along with CNS involvement that ranges from demyelination to axonal degeneration.

Oral manifestations consist primarily of glossitis and stomatitis[90,91]. These changes may occur in the absence of symptomatic anemia. Atrophic glossitis manifests as a smooth, "beefy-red" tongue, with patchy, ill-defined areas of erythema gradually evolving to more diffuse dorsal tongue involvement (Fig. 72.21). Some patients experience a generalized sore mouth or burning sensation. Taste disturbances have also been reported. The differential diagnosis of atrophic glossitis includes other nutritional deficiencies (e.g. folate, iron, niacin and riboflavin) and candidiasis.

Treatment

Injection of vitamin B_{12} often leads to rapid improvement of oral signs and symptoms.

Crohn's Disease

Synonym: ■ Regional enteritis

Fig. 72.21 Pernicious anemia/candidiasis. Erythematous, atrophic tongue as a manifestation of pernicious anemia with a superimposed candidal infection.

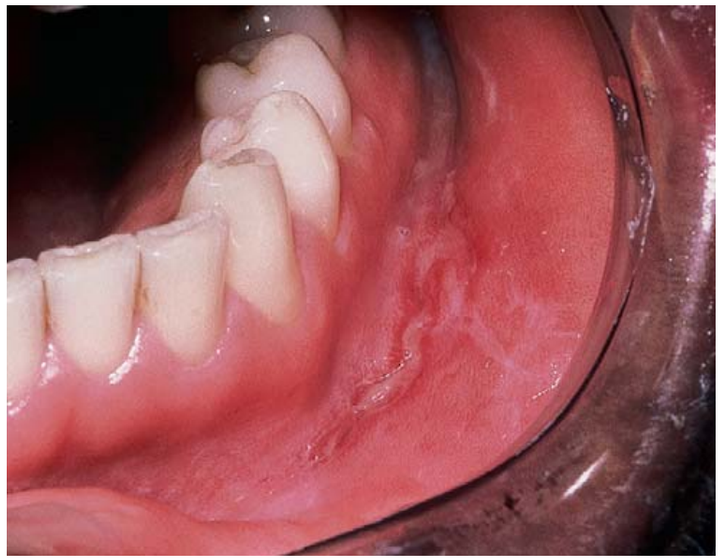


Fig. 72.22 Crohn's disease. Linear ulceration of the mandibular vestibule: the classic oral manifestation of this disease.

Key features

- Chronic granulomatous disorder affecting any segment of the gastrointestinal tract from the oral cavity to the anus
- Most commonly affects the distal ileum and/or proximal colon
- Oral involvement is uncommon and usually presents as linear ulceration of the buccal vestibule, although persistent swelling of the labial or buccal mucosa may be seen

Introduction/epidemiology

Crohn's disease represents an idiopathic chronic granulomatous disorder of the gastrointestinal tract. The condition has also been termed "regional enteritis", due to the alternating of affected areas with unaffected areas.

Crohn's disease is usually diagnosed before the age of 30 years, with peak prevalence in the second and third decades. The disease affects men and women approximately equally, but Caucasians are affected more frequently than other ethnic groups[92].

Clinical features

Oral signs and symptoms reportedly occur in 5–15% of patients with Crohn's disease. Linear fissures and/or ulcers of the vestibule are the most common clinical presentation (Fig. 72.22). Patients may also present with persistent, firm, painless swelling of the labial, buccal or facial tissues[92]. This may resemble granulomatous cheilitis both clinically and histologically[93] (see above). Cobblestone lesions of the buccal mucosa and vestibule may also be seen. Fibrosis and adhesions can occur as sequelae of these lesions. Additional manifestations include oral aphthae and pyostomatitis vegetans[94].

Pathology

Histopathologically, the oral lesions of Crohn's disease show non-necrotizing granulomatous inflammation. Sarcoidosis, a foreign body reaction, and infection should be excluded.

Treatment

Oral lesions typically respond to therapy for bowel lesions, but topical or intralesional corticosteroids are also effective[95]. Treatment of the gastrointestinal involvement may include systemic corticosteroids, often with sulfasalazine. Azathioprine, 6-mercaptopurine, methotrexate, TNF-α inhibitors (e.g. adalimumab, infliximab, certolizumab) and natalizumab (an integrin receptor antagonist) are also used to treat Crohn's disease[96].

Pyostomatitis Vegetans

Key features

- Typically associated with inflammatory bowel disease
- Multiple "snail-track" pustules superimposed upon diffuse mucosal erythema

Introduction

Pyostomatitis vegetans is a rare mucocutaneous disorder that is often associated with an underlying gastrointestinal disorder such as ulcerative colitis or, less commonly, Crohn's disease[97]. Pyostomatitis vegetans may represent an oral mucosal variant of pyoderma gangrenosum.

Epidemiology

Most cases of pyoderma vegetans are diagnosed in individuals 20 to 60 years of age. Men are affected more commonly than women.

Clinical features

Pyostomatitis vegetans is characterized by multiple tiny, creamy-yellow pustules set against a diffuse, intensely erythematous background. The pustules are often arranged in a linear serpentine fashion, and are often described as having a "snail-track" appearance. The pustules are easily ruptured, leading to shallow erosions and ulcerations. While any area of the oral cavity may be affected, the labial, gingival and buccal mucosa are most commonly involved. The dorsum of the tongue is usually spared[97]. The differential diagnosis includes herpetiform aphthae and oral pemphigus vulgaris.

Pathology

Intraepithelial and/or subepithelial microabscesses containing numerous eosinophils as well as neutrophils are seen.

Treatment

Treatment of pyostomatitis vegetans is focused on controlling the underlying gastrointestinal disease if it is identified. In patients without inflammatory bowel disease, therapy most often consists of moderate to high doses of systemic corticosteroids, sometimes in combination with azathioprine. Management of the associated gastrointestinal disease often results in improvement in the oral lesions.

ORAL MANIFESTIONS OF HIV INFECTION

This subject is reviewed in Chapter 78.

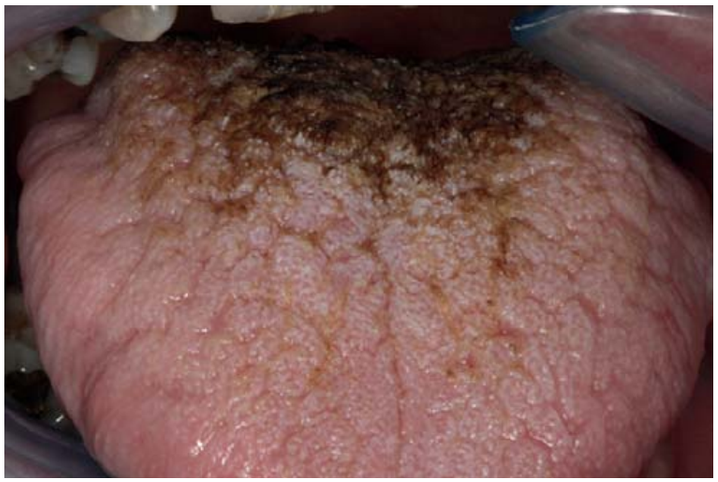
REFERENCES

1. Daley TD. Pathology of intraoral sebaceous glands: a review. J Oral Pathol Med. 1993;22:241–5.
2. Neville BW, Damm DD, Allen CM, et al. Oral and Maxillofacial Pathology, 3rd edn. Philadelphia: WB Saunders, 2009.
3. Yarom N, Cantony U, Gorsky M. Prevalence of fissured tongue, geographic tongue and median rhomboid glossitis among Israeli adults of different ethnic origins. Dermatology. 2004;209;88–94.
4. Gorlin RJ. Nevoid basal cell carcinoma (Gorlin) syndrome. Genet Med. 2004;6:530–9.
5. Hampel H, Allen CM, Chernausek SD, et al. De novo RET mutation positive multiple endocrine neoplasia 2B and hereditary nonpolyposis colorectal cancer syndrome occurring in the same family. J Endocr Genet. 2000;1: 143–7.
6. Accurso B, Mercado A, Allen CM. Multiple endocrine neoplasia 2B presenting with orthodontic relapse. Angle Orthod. 2010;80:585–90.
7. Wade DN, Kerns DG. Acute necrotizing ulcerative gingivitis-periodontitis: a literature review. Mil Med. 1998;163:337–42.
8. Corbet EF. Diagnosis of acute periodontal lesions. Periodontology 2000. 2004;34:204–16.
9. Leao JC, Ingafou M, Khan A, et al. Desquamative gingivitis: retrospective analysis of disease associations of a large cohort. Oral Dis. 2008;14:556–60.
10. Lo Russo L, Fedele S, Guiglia R, et al. Diagnostic pathways and clinical significance of desquamative gingivitis. J Periodontol. 2008;79:4–24.
11. Pynn BR, Sands T, Pharoah MJ. Odontogenic infections: anatomy and radiology (part I). Oral Health. 1995;85: 7–21.
12. Baruchin AM, Lustig JP, Nahlieli O, et al. Burns of the oral mucosa. J Craniofac Surg. 1991;19:94–6.
13. Rawal SY, Claman LJ, Kalmar JR, et al. Traumatic lesions of the gingival: a case series. J Periodontol. 2004;75: 762–9.
14. Regezi JA, Sciubba J, Jordan RCK. Oral Pathology: Clinical Pathologic Correlations, 5th edn. Philadelphia: WB Saunders, 2007.
15. Laeijendecker R, Dekker SK, Burger PM, et al. Oral lichen planus and allergy to dental amalgam restorations. Arch Dermatol. 2004;140:1434–8.
16. Pezelj-Ribarić S, Prpić J, Miletić I, et al. Association between oral lichenoid reactions and amalgam restorations. J Eur Acad Dermatol Venereol. 2008;22: 1163–7.
17. Muñoz-Corcuera M, Esparza-Gómez G, González-Moles MA, et al. Oral ulcers: clinical aspects. A tool for dermatologists. Part I. Acute ulcers. Clin Exp Dermatol. 2009;34:289–94.
18. McCullough MJ, Abdel-Hafeth S, Scully C. Recurrent aphthous stomatitis revisited; clinical features, associations, and new association with infant feeding practices? J Oral Pathol Med. 2007;36:615–20.
19. Rogers RS. Recurrent aphthous stomatitis: clinical characteristics and associated systemic disorders. Semin Cutan Med Surg. 1997;16:278–83.
20. Letsinger JA, McCarty MA, Jorizzo JL. Complex aphthosis: a large case series with evaluation algorithm and therapeutic ladder from topicals to thalidomide. J Am Acad Dermatol. 2005;52:500–8.
21. Keogan MT. Clinical Immunology Review Series: an approach to the patient with recurrent orogenital ulceration, including Behçet's syndrome. Clin Exp Immunol 2009;156:1–11.
22. Helm TN, Camisa C, Allen C, et al. Clinical features of Behçet's disease: report of four cases. Oral Surg Oral Med Oral Pathol. 1991;72:300–34.
23. Taghi A, Motamedi MH. Riga-Fede disease: a histological study and case report. Indian J Dent Res. 2009;20:227–9.
24. Alobeid B, Pan LX, Milligan L, et al. Eosinophil-rich CD30+ lymphoproliferative disorder of the oral mucosa. A form of "traumatic eosinophilic granuloma." Am J Clin Pathol. 2004;121:43–50.
25. Salisbury CL, Budnick SK, Li S. T-cell receptor gene rearrangement and CD30 immunoreactivity in traumatic ulcerative granuloma with stromal eosinophilia of the oral cavity. Am J Clin Pathol. 2009;132:722–7.
26. Allen CM, Camisa C, Hamzeh S, et al. Cheilitis granulomatosa: report of six cases and review of the literature. J Am Acad Dermatol. 1990;23:444–50.
27. Alawi F. Granulomatous diseases of the oral tissues: differential diagnosis and update. Dent Clin North Am. 2005;49:203–21.
28. Leão JC, Hodgson T, Scully C, et al. Review article: orofacial granulomatosis. Aliment Pharmacol Ther. 2004;20:1019–27.
29. Al Johani K, Moles DR, Hodgson T, et al. Onset and progression of clinical manifestations of orofacial granulomatosis. Oral Dis. 2009;15:214–19.
30. Weeda LW Jr, Coffey SA. Wegener's granulomatosis. Oral Maxillofac Surg Clin North Am. 2008;20:643–9.
31. Ruokonen H, Helve T, Arola J, et al. "Strawberry like" gingivitis being the first sign of Wegener's granulomatosis. Eur J Intern Med. 2009;20:651–3.
32. Manchanda Y, Tejasvi T, Handa R, et al. Strawberry gingiva: a distinctive sign in Wegener's granulomatosis. J Am Acad Dermatol. 2003;49:335–7.
33. Carruthers D, Sherlock J. Evidence-based management of ANCA vasculitis. Best Pract Res Clin Rheumatol. 2009; 23:367–78.
34. Warnakulasuriya S, Johnson NW, van der Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. J Oral Pathol Med. 2007;36: 575–80.
35. Shafer WG, Waldron CA. Erythroplakia of the oral cavity. Cancer. 1975;36:1021–8.
36. van der Hem PS, Nauta JM, van der Wal JE, et al. The results of CO2 laser surgery in patients with oral leukoplakia: a 25 year follow up. Oral Oncol. 2005;41: 31–7.
37. Mehanna HM, Rattay T, Smith J, et al. Treatment and follow-up of oral dysplasia – a systematic review and meta-analysis. Head Neck. 2009;31:1600–9.
38. Lodi G, Porter S. Management of potentially malignant disorders: evidence and critique. J Oral Pathol Med. 2008;37:63–9.
39. Cabay RJ, Morton TH Jr, Epstein JB. Proliferative verrucous leukoplakia and its progression to oral carcinoma: a review of the literature. J Oral Pathol Med. 2007;36:255–61.
40. Bagan JV, Jimenez Y, Murillo J, et al. Lack of association between proliferative verrucous leukoplakia and human papillomavirus infection. J Oral Maxillofac Surg. 2007;65:46–9.
41. van der Waal I, Reichart PA. Oral proliferative verrucous leukoplakia revisited. Oral Oncol. 2008;44:719–21.
42. Silverman S Jr, Gorsky M. Proliferative verrucous leukoplakia: a follow-up study of 54 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1997;84: 154–7.
43. Schwartz DL. Stomatitis nicotina of the palate: report of two cases. Oral Surg Oral Med Oral Pathol. 1965;20: 306–15.
44. dos Santos RB, Katz J. Nicotinic stomatitis: positive correlation with heat in mate tea drinks and smoking. Quintessence Int. 2009;40:537–40.
45. Cavalcante AS, Anbinder AL, Carvalho YR. Actinic cheilitis: clinical and histological features. J Oral Maxillofac Surg. 2008;66:498–503.
46. Kaugars GE, Pillion T, Svirsky JA, et al. Actinic cheilitis. A review of 152 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1999;88:181–6.
47. Markopoulos A, Albanidou-Farmaki E, Kayavis I. Actinic cheilitis: clinical and pathologic characteristics in 65 cases. Oral Dis. 2004;10:212–16.
48. Neville BW, Day TA. Oral cancer and precancerous lesions. CA Cancer J Clin. 2002;52:195–215.
49. Kademani D. Oral cancer. Mayo Clin Proc. 2007;82:878–87.
50. Garavello W, Foschi R, Talamini R, et al. Family history and the risk of oral and pharyngeal cancer. Int J Cancer. 2008;122:1827–31.
51. Hart AKE, Karakla DW, Pitman KT, et al. Oral and oropharyngeal squamous cell carcinoma in young adults: a report on 13 cases and a review of the literature. Otolaryngol Head Neck Surg. 1999;120: 828–33.

51a. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Eng J Med. 2010;363:24–35.

52. Prince S, Bailey BMW. Squamous carcinoma of the tongue: review. Br J Oral Maxillofac Surg. 1999;37: 164–74.
53. Bouquot JE. Oral verrucous carcinoma: incidence in two US populations. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1998;86:318–24.
54. Walvekar RR, Chaukar DA, Deshpande MS, et al. Verrucous carcinoma of the oral cavity: a clinical and pathological study of 101 cases. Oral Oncol. 2009;45: 47–51.
55. Ogawa A, Fukuta Y, Nakajima T, et al. Treatment results of oral verrucous carcinoma and its biological behavior. Oral Oncol. 2004;40:793–7.
56. Granholm C, Olsson Bergland K, Walhjalt H, et al. Oral mucoceles; extravasation cysts and retention cysts. A study of 298 cases. Swed Dent J. 2009;33:125–30.
57. Nico MM, de Melo N, Lourenço SV. Cheilitis glandularis: a clinicopathological study in 22 patients. J Am Acad Dermatol. 2010;62;233–8.
58. Cohen DM, Green JG, Diekmann SL. Concurrent anomalies: cheilitis glandularis and double lip: report of a case. Oral Surg Oral Med Oral Pathol. 1988;66:397–9.
59. Kominek P, Blasch P. Necrotizing sialometaplasia: a potential diagnostic pitfall. Ear Nose Throat J. 2006;85:604–5.
60. Lee DJ, Ahn HK, Koh ES, et al. Necrotizing sialometaplasia accompanied by adenoid cystic carcinoma on the soft palate. Clin Exp Otorhinolaryngol. 2009;2:48–51.
61. Dominguez-Malagon H, Mosqueda-Taylor A, Cano-Valdez AM. Necrotizing sialometaplasia of the palate associated with angiocentric T-cell lymphoma. Ann Diagn Pathol. 2009;13:60–4.
62. Carlson DL. Necrotizing sialometaplasia: a practical approach to the diagnosis. Arch Pathol Lab Med. 2009;133:692–8.
63. Jonsson R, Moen K, Vestrheim D, et al. Current issues in Sjögren's syndrome. Oral Dis. 2002;8:130–40.
64. Akpek EK, Klimava A, Thorne JE, et al. Evaluation of patients with dry eye for presence of underlying Sjögren syndrome. Cornea. 2009;28:493–7.
65. Daniels TE, Fox PC. Salivary and oral components of Sjögren's syndrome. Rheum Dis Clin North Am. 1992;18:571–88.
66. Fox PC, Bowman SJ, Segal B, et al. Oral involvement in primary Sjögren syndrome. J Am Dent Assoc. 2008;139:1592–601.
67. Stewart CM, Bhattacharyya I, Berg K, et al Labial salivary gland biopsies in Sjögren's syndrome: still the gold standard? Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;106:392–402.
68. Caporali R, Bonacci E, Epis O, et al. Safety and usefulness of minor salivary gland biopsy: retrospective analysis of 502 procedures performed at a single center. Arthritis Rheum. 2008;59:714–20.
69. Bamba R, Sweiss NJ, Langerman AJ, et al. The minor salivary gland biopsy as a diagnostic tool for Sjögren syndrome. Laryngoscope. 2009;119:1922–6.
70. Waldron CA, El-Mofty SK, Gnepp DR. Tumors of the intraoral minor salivary glands: a demographic and histologic study of 426 cases. Oral Surg Oral Med Oral Pathol. 1988;66:323–33.
71. Pires FR, Pringle GA, Paes de Almeida O, et al. Intra-oral minor salivary gland tumors: a clinicopathological study of 546 cases. Oral Oncol. 2007;43:463–70.
72. McDonnell AM, Lenz KL. Palifermin: role in the prevention of chemotherapy- and radiation-induced mucositis. Ann Pharmacother. 2006;40:86–94.
73. Mañas A, Palacios A, Contreras J, et al. Incidence of oral mucositis, its treatment and pain management in patients receiving cancer treatment at Radiation Oncology Departments in Spanish hospitals (MUCODOL Study). Clin Transl Oncol. 2009;11:669–76.
74. Bhatt V, Saleem A. Review: Drug-induced neutropenia – pathophysiology, clinical features, and management. Ann Clin Lab Sci. 2004;34:131–7.
75. Burke VP, Startzell JM. The leukemias. Oral Maxillofac Surg Clin North Am. 2008;20:597–608.
76. Wu J, Fantasia JE, Kaplan R. Oral manifestations of acute myelomonocytic leukemia: a case report and review of the classification of leukemias. J Periodontol. 2002;73:664–8.
77. Zapater E, Bagán JV, Carbonell F, et al. Malignant lymphoma of the head and neck. Oral Dis. 2010;16:119–28.
78. Cattaneo C, Facchetti F, Re A, et al. Oral cavity lymphomas in immunocompetent and human immunodeficiency virus infected patients. Leuk Lymphoma. 2005;46:77–81.
79. Jordan RC, Speight PM. Extranodal non-Hodgkin's lymphomas of the oral cavity. Curr Top Pathol. 1996;90:125–46.
80. Lourenço SV, Sangüeza AM, Sotto MN, et al. Primary oral mucosal melanoma: a series of 35 new cases from South America. Am J Dermatopathol. 2009;31:323–30.
81. Barker BF, Carpenter WM, Daniels TE, et al. Oral mucosal melanomas: the WESTOP Banff workshop proceedings.

Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1997;83:672–9.
82. Buchner A, Merrell PW, Carpenter WM. Relative frequency of solitary melanocytic lesions of the oral mucosa. J Oral Pathol Med. 2004;33:550–7.
83. Hicks MJ, Flaitz CM. Oral mucosal melanoma: epidemiology and pathobiology. Oral Oncol. 2000;36:152–69.
84. Mücke T, Hölzle F, Kesting MR, et al. Tumor size and depth in primary malignant melanoma in the oral cavity influences survival. J Oral Maxillofac Surg. 2009;67:1409–15.
85. Civantos FJ, Moffat FL, Goodwin WJ. Lymphatic mapping and sentinel lymphadenectomy for 106 head and neck lesions: contrasts between oral cavity and cutaneous malignancy. Laryngoscope. 2006;112(Suppl.109):1–15.
86. Falk RH, Comenzo RL, Skinner M. The systemic amyloidoses. N Engl J Med. 1997;337:898–909.
87. Viggor SF, Frezzini C, Farthing PM, et al. Amyloidosis: an unusual case of persistent oral ulceration. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009;108:e46–50.
88. van der Waal RI, van de Scheur MR, Huijgens PC, et al. Amyloidosis of the tongue as a paraneoplastic marker of plasma cell dyscrasia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2002;94:444–7.
89. Lu SY, Wu HC. Initial diagnosis of anemia from sore mouth and improved classification of anemia by MCV and RDW in 30 patients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2004;98:679–85.
90. Graells J, Ojeda RM, Muniesa C, et al. Glossitis with linear lesions: an early sign of vitamin B12 deficiency. J Am Acad Dermatol. 2009;60:498–500.
91. Rebelo-Pontes HA, Conte-Neto N, Bechara-Ferreira K, et al. Oral manifestations of B12 deficiency: a case report. J Can Dent Assoc. 2009;75:533–7.
92. Kalmar JR. Crohn's disease: orofacial considerations and disease pathogenesis. Periodontology 2000. 1994;6:101–15.
93. Bogenrieder T, Rogler G, Vogt T, et al. Orofacial granulomatosis as the initial presentation of Crohn's disease in an adolescent. Dermatology. 2003;206:273–8.
94. Fatahzadeh M. Inflammatory bowel disease. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009;108:e1–10.
95. Daley TD, Armstrong JE. Oral manifestations of gastrointestinal diseases. Can J Gastroenterol. 2007;21:241–4.
96. Sánchez AR, Rogers RS III, Sheridan PJ. Oral ulcerations are associated with the loss of response to infliximab in Crohn's disease. J Oral Pathol Med. 2005;34:53–5.
97. Hegarty AM, Barrett AW, Scully C. Pyostomatitis vegetans. Clin Exp Dermatol. 2004;29:1–7.



Hairy tongue. The dorsum of the tongue exhibits marked accumulation of keratin and brown discoloration.

Anogenital (Non-venereal) Disease 73

Susan M Cooper and Fenella Wojnarowska

Chapter Contents

Introduction ... 1171
Lichen sclerosus ... 1171
Lichen planus ... 1173
Zoon's balanitis/vulvitis ... 1175
Epithelial disorders of the anogenital region ... 1175
Premalignant and malignant lesions ... 1177
Dysesthetic genital pain syndromes ... 1180
Benign lesions ... 1183
The anogenital region and systemic disease ... 1183
Infections ... 1183
Erosive genital disease ... 1184

INTRODUCTION

The diagnosis and management of skin diseases in the anogenital region may be complex. The juxtaposition of urinary, genital and alimentary tracts (Fig. 73.1) gives rise to special considerations at this site, and disease of any of these major systems may present with cutaneous manifestations. Many systemic diseases preferentially affect the genital area. Local factors, including warmth, moisture, irritants, friction and the effects of body fluids, are important in this region, contributing to skin problems.

Skin conditions may be more difficult to diagnose in the anogenital region than at other cutaneous sites, as typical appearances may be lost and there may be hesitation to perform biopsies. Examination of the scalp, nails and oral cavity frequently assists in diagnosis. Special considerations apply to treatment, as the natural occlusion of this area may increase the percutaneous absorption of topical corticosteroids, with the potential for cutaneous atrophy and/or hypothalamic–pituitary–adrenal axis suppression. Warmth and moisture may also increase the risk of bacterial and yeast infections.

Only a limited number of symptoms in the anogenital area are possible, and pruritus and genital pain may be the presenting feature of a wide variety of diseases.

LICHEN SCLEROSUS

Synonyms: ■ Lichen sclerosus et atrophicus ■ Balanitis xerotica obliterans (men) ■ Kraurosis vulvae (women)

Key features

- Chronic inflammatory disease with a predilection for the anogenital region
- Pruritus is the most frequent symptom
- Major clinical signs are pallor, atrophy, fissures and foci of hyperkeratosis
- Scarring may cause loss of the normal architecture of the vulva in women and phimosis in men

Introduction

Lichen sclerosus is a chronic inflammatory disease that preferentially affects the anogenital region, although any cutaneous site may be affected; 15–20% of patients with genital lichen sclerosus will have extragenital disease[1]. Symptoms may be longstanding as there is frequently a delay in diagnosis. Patients require long-term evaluation due to the risk of scarring and the risk of developing squamous cell carcinoma.

History

The initial clinical description of lichen sclerosus was by Hallopeau in 1889 and the characteristic histologic features were described by Darier in 1892. Over the years there has been much confusion over nomenclature, with the use of terms such as leukoplakia, lichen albus, kraurosis vulvae, and lichen sclerosus et atrophicus. The International Society for the Study of Vulvovaginal Disease (ISSVD) favors "lichen sclerosus".

Epidemiology

Lichen sclerosus is 6–10 times more prevalent in women than in men. The disorder may occur at any age, but the two peaks of onset are during childhood and either after menopause or in the 4th or 5th decade (in men). Although most studies have centered on white European patients, there are reports of lichen sclerosus occurring in Africans and Asians. Powell et al.[2] calculated a prevalence of 1 in 660 women and an annual incidence of 51.9/100 000 in postmenopausal women. The incidence of lichen sclerosus in boys may be underestimated; when foreskins of circumcised boys were examined, 14% were found to have the characteristic features of lichen sclerosus[3].

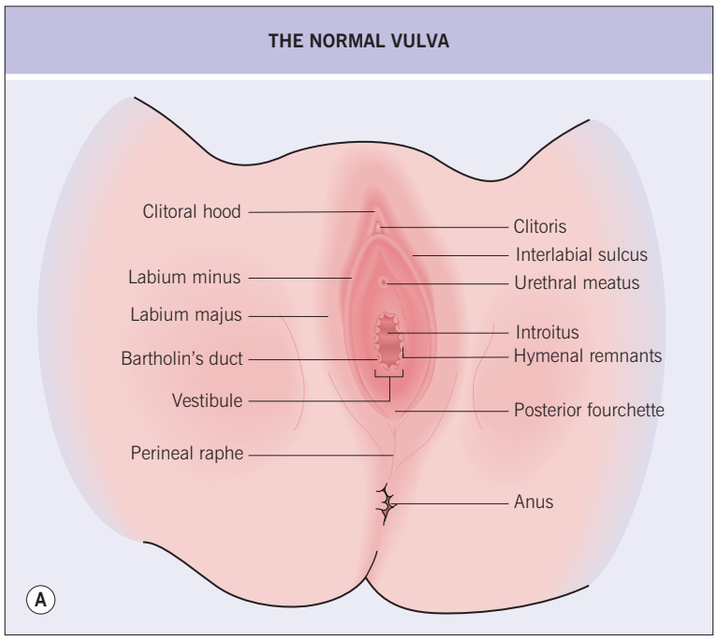
Etiology

The cause of lichen sclerosus remains unknown. An inherited tendency is suggested by the occurrence of familial cases, the association with HLA-DRB1*12 (and the related haplotype DRB1*12/DQB1*0301/04/09/010)[4] and the association with other autoimmune disorders such as thyroid disease, vitiligo and morphea[5]. An infectious etiology has been proposed, but *Borrelia* or other spirochetal infection has not been confirmed in large studies. Anti-extracellular matrix protein and anti-basement membrane zone antibodies have been reported in lichen sclerosus sera, but the pathogenicity of these antibodies remains to be determined[6,7]. Local friction or rubbing may induce lesions of lichen sclerosus via the Koebner phenomenon, and some cases of early-onset lichen sclerosus may be associated with the antiandrogenic oral contraceptive pill. In uncircumcised males, chronic exposure of susceptible epithelium to urine due to naviculomeatal dysfunction has been proposed as causative[7a].

Clinical features

Both male and female patients may present with pruritus or soreness, but rarely may be entirely asymptomatic[8]. Dyspareunia is frequently reported. Children with lichen sclerosus are more likely to present with urinary or bowel symptoms (e.g. constipation) or hemorrhagic bullae, which may lead to a misdiagnosis of child abuse[9].

In women, the characteristic clinical findings are vulvar hypopigmentation and thin, wrinkled, atrophic skin in a figure-of-eight distribution encircling the vulvar and perianal region (Fig. 73.2). Focal areas of hyperkeratosis, erosions and fissures are frequently seen. Additional cutaneous features that are helpful in identification are purpura (Fig. 73.3), telangiectasias, and rarely, hemorrhagic blisters. Lichen sclerosus is a scarring disease and therefore some architectural change



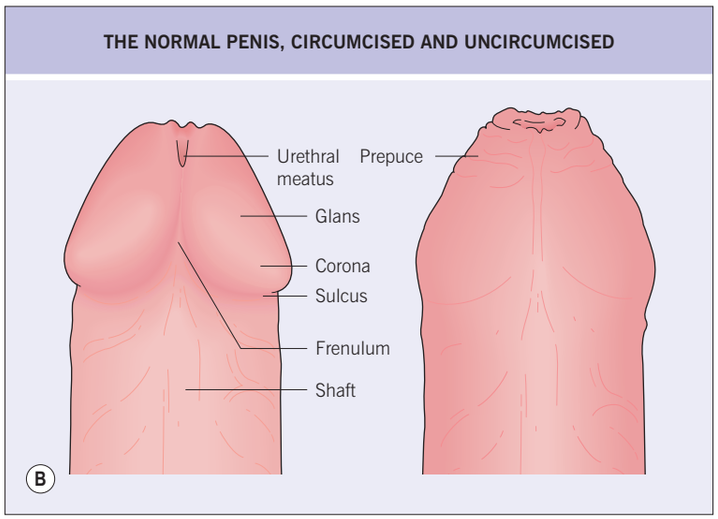


Fig. 73.1 Genital anatomy. A The normal vulva. **B** The normal penis, circumcised and uncircumcised.

Fig. 73.2 Lichen sclerosus of the perianal region.

Fig. 73.3 Lichen sclerosus of the vulva with characteristic purpura. *Courtesy, Kalman Watsky, MD.*

is common (Fig. 73.4). Burying of the clitoris secondary to midline fusion or fusion of the labia minora to the labia majora may occur. In untreated or severe disease, there may be total loss of the labia minora and narrowing of the introitus. Lichen sclerosus affects the glans penis and foreskin of men (Fig. 73.5) and, in contrast to in women, involvement of the perianal region is uncommon. The disease usually presents with pruritus, pain and dyspareunia. Affected boys may have recurrent balanitis and a poor urinary stream, and some may require circumcision.

Extragenital lichen sclerosus favors the submammary region, as well as the shoulders, neck and wrists, presenting as asymptomatic, hypopigmented, wrinkled patches with follicular plugging (see Ch. 44); occasionally, there are multiple guttate lesions. The diagnosis is established by a combination of the characteristic clinical and histologic findings.

Pathology

The principal histologic findings are compact orthokeratosis, follicular plugging (in non-mucosal sites), a thinned epidermis, vacuolization of the basal layer, and hyalinization of the papillary dermis. A deep band-like lymphocytic infiltrate is often observed. Squamous hyperplasia may be present and may be associated with an increased risk of squamous cell carcinoma. In bullous lichen sclerosus there is extensive vacuolar degeneration of the basal layer with clefting. Early on, the papillary dermis may be edematous and homogenous, but, with time, hyalinization and sclerosis are observed. Histologic examination of the skin is imperative as it can be difficult to distinguish lichen sclerosus from mucous membrane (cicatricial) pemphigoid or erosive lichen planus on the basis of clinical appearance alone. Occasionally, despite marked clinical changes, the disease cannot be confirmed histologically and repeat biopsies over time may be needed to establish the diagnosis. In lesions that have been treated with potent topical corticosteroids, ascertaining the diagnosis histologically may prove challenging.

Differential diagnosis

Very mild or early disease may be confused with dermatitis. The presence of vulvar scarring necessitates the exclusion of other scarring disorders such as erosive lichen planus and mucous membrane pemphigoid. The absence of oral or vaginal mucosal involvement helps to distinguish lichen sclerosus from erosive lichen planus. In children, sexual abuse must be considered; however, the diagnoses of lichen sclerosus and sexual abuse are not mutually exclusive.

The principal differential diagnoses are:

- erosive lichen planus
- mucous membrane pemphigoid
- lichen simplex chronicus
- morphea

Fig. 73.4 Lichen sclerosus of the vulva. There is marked architectural change with loss of the labia minora and marked midline fusion.

Fig. 73.5 Lichen sclerosus of the penis. Erythematous and white plaque on the glans. *Courtesy, Ronald P Rapini, MD.*

- vulvar eczema
- child sexual abuse.

Treatment

The main aim of therapy is to bring the disease under control as quickly as possible with the fewest side effects. For initial treatment (after the diagnosis is established), a potent topical corticosteroid such as clobetasol propionate 0.05% ointment is prescribed. One possible regimen is daily application of clobetasol propionate 0.05% ointment to the affected area for 3 months[8–10]. This alleviates symptoms in the majority of patients, often within weeks. Subsequently, the corticosteroid is tapered down over 2 weeks and the clinical remission maintained by occasional application of a corticosteroid, using less than 30 g in any 6-month period. In some patients there is complete resolution of signs as well as symptoms, with the exception of the scarring, which is irreversible[8].

There is no longer any role for vulvectomy in the management of lichen sclerosus unassociated with malignancy. Similarly, testosterone creams are less effective and have the potential to cause virilization. In longstanding disease where narrowing of the introitus has resulted in dyspareunia, surgical refashioning may be helpful. Dilators may also be needed, in addition to psychosexual counseling.

Longitudinal evaluation is essential for patients with lichen sclerosus because both men and women[8,11] are at increased risk of developing genital squamous cell carcinomas (estimates of the risk are approximately 2–5%). Women with lichen sclerosus may develop differentiated vulvar intraepithelial neoplasia (VIN) which has a high risk of becoming squamous cell carcinoma as compared to undifferentiated VIN (HPV-associated disease). Men are also at risk of penile intraepithelial neoplasia. Non-healing fissures, ulcers or nodules must be examined histologically. Written educational material and patient support groups are very helpful (e.g. www.lichensclerosus.org). It is essential that patients who notice any of the features of malignancy have ready access to medical care to allow prompt assessment.

The first- and second-line therapies for anogenital lichen sclerosus are outlined in Table 73.1. There have been several case series demonstrating success with topical calcineurin inhibitors; however, given the risk of malignant transformation in this condition, the authors caution against chronic maintenance therapy until long-term safety data are available.

THERAPIES FOR ANOGENITAL LICHEN SCLEROSUS
FIRST-LINE
Soap substitutes and emollients (3) Superpotent topical corticosteroids (3-month course) (2) Circumcision in men, if phimosis (2)
SECOND-LINE
In some patients, longer-term maintenance with potent topical corticosteroids (2) Surgery to correct narrowing of introitus and reverse clitoral burying (3) Topical calcineurin inhibitors (2) Circumcision in men, if unresponsive to medical treatment (3)

Table 73.1 Therapies for anogenital lichen sclerosus. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

LICHEN PLANUS

Synonyms: ■ Vulvovaginal gingival syndrome (erosive lichen planus in women) ■ Peno-gingival syndrome in men ■ Mucosal lichen planus

Key features

- Four distinct forms of genital lichen planus are observed: (1) papules or plaques in the setting of generalized cutaneous lichen planus; (2) erosive disease; (3) hypertrophic disease; and (4) lichen planopilaris
- Although cutaneous disease is often self-limiting, mucous membrane disease is more persistent
- The classic findings in cutaneous disease are violaceous, flat-topped papules and plaques; lacy white streaks typically occur on the genitalia as well as the oral mucosa
- Erosive lichen planus often involves multiple mucous membrane sites – in particular, the vulva, vagina and oral mucosa

Introduction

Approximately 50% of women and 25% of men with cutaneous lichen planus have genital involvement. The classic violaceous papules and plaques typically affect the labia minora and majora or the mons pubis in women and the glans or shaft of the penis in men. Erosive lichen planus is a distinct subtype of the disease, characterized by severe, scarring erosive disease of the vestibule, introitus, vagina and oral cavity[12,13]. Hypertrophic genital lichen planus and lichen planopilaris are the least frequent forms.

History

Erasmus Wilson reported a patient with vulvar lichen planus in 1867, but the first histologic description of lichen planus was by Darier in 1909. Isolated case reports of vaginal involvement with vaginal discharge and hyperemic vaginal mucosa appeared in the 1950s, and the term "desquamative inflammatory vaginitis" was introduced in 1968.

Fourteen years later, Pelisse recognized erosive lichen planus as a distinct subtype of lichen planus and gave it the name "vulvo-vaginal-gingival syndrome"[13].

Epidemiology

Lichen planus is more prevalent in women, generally presenting in the sixth decade. The exact prevalence is unknown, but, in the UK, lichen planus accounts for approximately 1% of referrals to dermatologists. In the vulvar clinic, genital lichen planus is less frequently encountered than lichen sclerosus, but it is likely that some cases of genital involvement in cutaneous lichen planus may be missed.

Etiology

Lichen planus probably represents T cell-mediated damage to epidermal cells that express altered self or foreign antigens on their surface, but the exact etiology is unknown (see Ch. 11). Some cases of lichen planus may be drug-induced, but whether this is true for genital disease is uncertain. Chronic liver disease, particularly that due to hepatitis C infection, may be associated with lichen planus in certain parts of the world such as the Mediterranean basin and Japan, but not in the UK[14]. There is an association of erosive lichen planus of the vulva with autoimmune disease[5].

Clinical features

There are four distinct presentations of genital lichen planus, as follows.

- In classic lichen planus, the genital lesions are similar to those in other cutaneous sites but lacy reticulation may be very prominent. Genital involvement is usually limited to the mons pubis and the labia majora and minora in women versus the glans penis and shaft in men (see Ch. 11). Penile plaques are frequently annular (Fig. 73.6A). Scarring is not a feature of classic lichen planus. Severe cutaneous pruritus is the usual presenting symptom, but sometimes genital lesions are asymptomatic. The lesions are usually self-limiting.
- Erosive lichen planus occurs much more frequently in women than in men. Pain and dyspareunia are the most common complaints. In female patients, extensive erosions occur around the vaginal orifice, edged by lacy white reticulations; similar lesions may also occur on the labia (Fig. 73.6B). Erosive lichen planus frequently leads to scarring, resulting in distortion of the vulvar architecture. In severe cases, there may be complete obliteration of the vaginal canal and urinary retention. Vaginal involvement can present as a discharge, erythema and contact bleeding of the vaginal mucosa, and scarring with adhesions. Oral involvement is frequently observed, usually in the form of a desquamative gingivitis, but lacy white reticulations and erosions may also occur. Erosions limited to the perianal area alone have been described.
- In the hypertrophic form of lichen planus, hyperkeratotic white plaques on the vulva or shaft of the penis may be seen.
- In lichen planopilaris, follicular keratotic papules are limited to the hair-bearing labia majora and the mons pubis, but may also occur on the scalp, trunk, axillae and extremities.

Pathology

The typical histologic findings are irregular epidermal acanthosis, accentuation of the granular layer, liquefactive degeneration of the basal layer, and a band-like dermal infiltrate of lymphocytes. It is more difficult to interpret biopsy specimens of mucous membranes, where these findings are more variable. In erosive disease, as there is loss of the epithelium, the specimen should include the edge of the erosion as well as the surrounding lacy reticulated pattern. Despite this, it is often impossible to unequivocally confirm the disease, but histologic evaluation can aid in excluding other disorders in the differential diagnosis.

Differential diagnosis

The main differential diagnoses are lichen sclerosus and mucous membrane pemphigoid. Direct immunofluorescence may be necessary to exclude pemphigoid. Orogenital ulceration raises the possibility of Behçet's disease (see Ch. 26); however, simple aphthous stomatitis and HSV infection are more likely causes of oral and genital ulcers, respectively. Lichenoid drug eruptions and graft-versus-host disease may give lichen planus-like changes. Early lichen planus may be confused with vulvar eczema, and in the setting of significant pruritus, there may be superimposed lichen simplex chronicus. For hypertrophic disease, vulvar intraepithelial neoplasia, squamous cell carcinoma and lichen simplex chronicus are the major differential diagnoses.

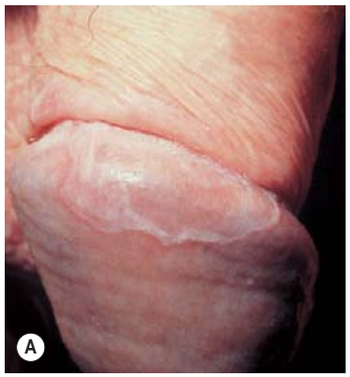


Fig. 73.6 Lichen planus. A An annular band is seen on the glans of the penis. This is a typical finding. **B** Erosive lichen planus of the vulva with fissures and an extensive white lacy pattern. *A, Courtesy, R Turner, MD.*

Treatment

The treatment of genital lichen planus is outlined in Table 73.2. Potent or moderately potent corticosteroid ointments will control most symptoms of classic genital lichen planus, as the disease is usually self-limiting. Hypertrophic disease may require intralesional corticosteroids.

The management of erosive lichen planus is more difficult, as the disease is often more persistent. The majority of patients will respond to a 3-month course of topical clobetasol propionate 0.05% (as described for lichen sclerosus) and thereafter can be maintained on moderately potent corticosteroids[15]. A combination of a moderately potent corticosteroid with a topical antifungal cream (e.g. econazole) may be as effective as more potent corticosteroids, particularly for maintenance therapy. For more resistant disease, there are anecdotal case reports of benefit from topical tacrolimus, systemic immunosuppressants (e.g. mycophenolate mofetil), and oral hydroxychloroquine. Low-dose weekly methotrexate, as for oral erosive lichen planus, may be helpful for severe disease[16]. Tricyclic antidepressants can be used to treat an associated vulvar pain syndrome. Erosive vaginal disease may require surgery to lyse adhesions, and the regular use of vaginal dilators with a corticosteroid ointment may help prevent recurrence.

Long-term evaluation of these patients is advised because of the risk of malignant transformation. In our study of a cohort of women with erosive lichen planus (and a mean follow-up period of 72 months), a 2.4% incidence of squamous cell carcinoma development was observed[15]. For further details on the treatment of lichen

THERAPIES FOR ANOGENITAL LICHEN PLANUS
FIRST-LINE
Soap substitutes and emollients (3) Superpotent topical corticosteroids (2) For vaginal disease, corticosteroid foams*, enemas*, suppositories* or ointments (± dilators) (2)
SECOND-LINE
Longer-term maintenance with superpotent topical corticosteroids or combined moderately potent corticosteroid/antifungal/antibacterial preparations (2) Surgery to correct narrowing of introitus and reverse clitoral burying in women or circumcision in men (3) Topical calcineurin inhibitors (3) Intralesional corticosteroid (hypertrophic disease) (3) Systemic immunosuppressants (3) Systemic antibiotics (minocycline ± nicotinamide) (3)
*Available for the treatment of inflammatory bowel disease.

Table 73.2 Therapies for anogenital lichen planus. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

planus, including systemic agents for severe, refractory disease, see Chapter 11.

ZOON'S BALANITIS/VULVITIS

Synonyms: ■ Plasma cell balanitis/vulvitis ■ Vulvitis/balanitis circumscripta plasmacellularis ■ Zoon's erythroplasia

Key features

- Male predominance
- Erythematous, moist, speckled, discrete plaques
- Involvement of adjacent surfaces produces "kissing" lesions in men
- In men, cured by circumcision

Introduction

There is no doubt that this condition occurs in men, but its existence as a separate entity in women has been questioned. Many of the clinical features in women are indistinguishable from those of erosive lichen planus, mucous membrane pemphigoid or lupus erythematosus, and the lichenoid features histologically overlap with erosive lichen planus. Moreover, in many of the reported cases in women, it is not possible to exclude these three diagnoses.

Epidemiology

Zoon's balanitis may occur at any age but is usually seen from the third decade onwards in uncircumcised men.

Etiology

The etiology is unknown, but poor penile hygiene or chronic irritation from warmth or rubbing has been suggested. The condition does not occur in circumcised men.

Clinical features

In men, the lesions on the glans penis may be asymptomatic or give rise to pruritus or dysuria. The lesions are erythematous, discrete, moist plaques with a "cayenne pepper" speckled appearance and an orange hue. "Kissing" lesions are typical with involvement of adjacent, touching areas, e.g. around the urethral meatus (Fig. 73.7). Shallow erosions may resolve slowly, leaving a rusty stain[17].

In women, erythematous plaques similar to those in men may be seen anywhere on the vulva. Lesions may be asymptomatic or cause dyspareunia, dysuria, pruritus or pain.

Fig. 73.7 Zoon's balanitis. There are moist "kissing" lesions on adjacent surfaces of the glans and prepuce.

Pathology

The typical histologic picture is a dense lichenoid infiltrate in the upper and mid dermis with an abundance of plasma cells. Additional features include "lozenge-shaped" keratinocytes, vascular proliferation, hemosiderin deposition and erythrocyte extravasation.

Differential diagnosis

In order to establish the diagnosis, a biopsy is usually performed. The major disorder in the differential diagnosis is erosive lichen planus, but when the plaques are well demarcated, the possibility of cutaneous malignancy (e.g. squamous cell carcinoma *in situ* and extramammary Paget's disease) must be considered.

Treatment

In men, a circumcision will almost always cure the disease. Potent topical corticosteroids may provide some symptomatic relief, but medical measures are generally ineffective.

EPITHELIAL DISORDERS OF THE ANOGENITAL REGION

Dermatitis

Key features

- Appearance ranges from mild erythema to gross lichenification
- Pruritus and soreness are the main complaints
- A mixed etiology is common
- Exogenous irritants and allergens must be sought

Introduction

Although anogenital dermatitis has traditionally been subdivided into endogenous dermatitis (e.g. seborrheic dermatitis and atopic dermatitis), lichen simplex chronicus, and exogenous dermatitis (e.g. allergic or irritant contact dermatitis), in practice it is often difficult to distinguish between these subtypes. A mixed picture, in which endogenous dermatitis is worsened by exogenous irritants or allergens, is commonly observed. Lichen simplex chronicus may develop secondarily to other anogenital diseases such as candidiasis, psoriasis and lichen sclerosus.

Pathogenesis

In an Oxford study, 97% of patients with vulvar dermatitis had an endogenous predisposition, having either an atopic background or

seborrheic dermatitis[18]. The anogenital area is susceptible to irritants, and allergic contact dermatitis is very prevalent in this site; the latter is usually due to topical medications. Psychological issues and local environmental problems such as heat, sweating and over-cleansing may be contributing factors.

Clinical features

The cutaneous features are varied, ranging from mild, usually poorly demarcated erythema to gross lichenification (Fig. 73.8). Symptoms include pruritus (Figs 73.9 & 73.10), soreness and superficial dyspareunia in women. In lichen simplex chronicus, there is unremitting itching plus scratching or rubbing. Fissuring is common, especially perianally. The typical anogenital sites affected are the labia majora and the mons pubis in women, the crura and scrotum in men, and the perianal area in both sexes. Lichenification is most often seen on the scrotum in men and the labia majora in women. Signs of seborrheic dermatitis, e.g. a scaly scalp and greasy scaling and erythema of nasolabial folds and eyebrows as well as erythema at other flexural sites (inframammary, intergluteal fold and axillae), should be sought. Atopic dermatitis at other sites will usually be obvious from the history or examination.

Differential diagnosis

The key to making the diagnosis is a thorough dermatologic examination. The diagnosis is usually made on the basis of clinical appearance, but a skin biopsy can be helpful in excluding other diagnoses. Plaques of psoriasis are often more well defined than those of dermatitis. Extramammary Paget's disease should also be considered, but these lesions are also sharply demarcated. It is important to identify irritants and possible allergens through a careful history and possibly patch testing. In addition, bacterial and *Candida* cultures should be performed to exclude superimposed infection, which is common in the anogenital region. Early lesions of lichen sclerosus may be indistinguishable from dermatitis.

Treatment

Treatment is directed at reducing pruritus and soreness. If the area is acutely inflamed, potent topical corticosteroids, often in combination with topical antifungal agents, topical antibacterial agents and/or topical immunomodulators, are helpful. Over a period of a few weeks, the topical corticosteroid can be tapered to one that is moderately potent.

Fig. 73.8 Vulvar dermatitis. Lichenification is prominent. The underlying diagnosis was atopic dermatitis.

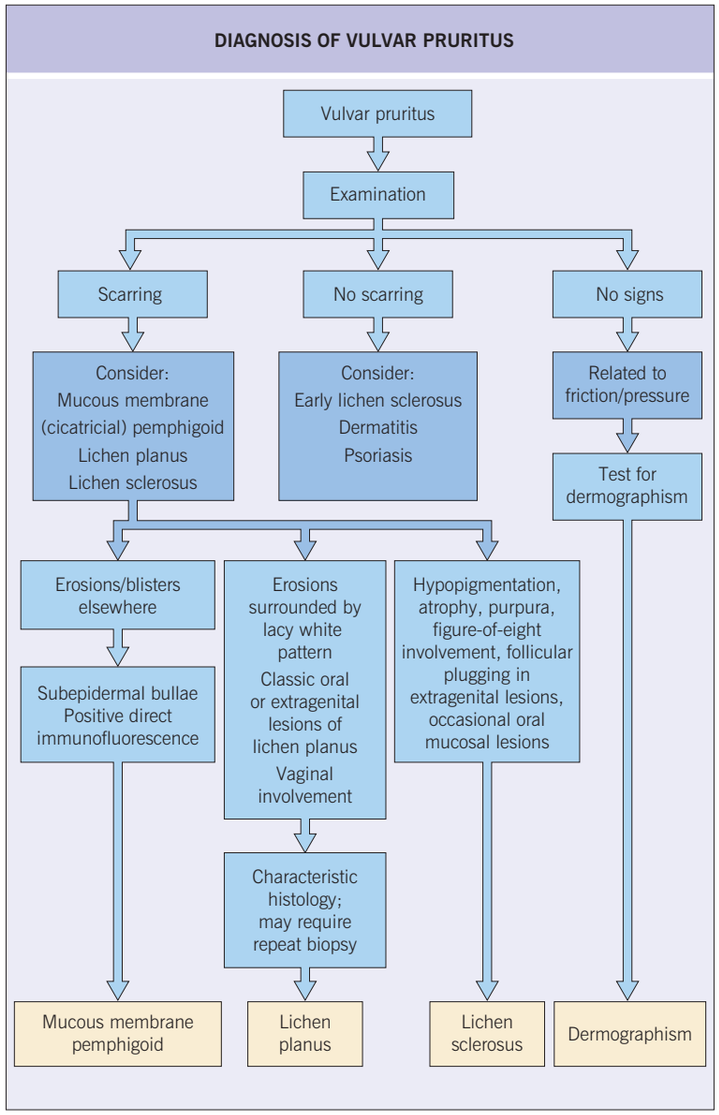


Fig. 73.9 Diagnosis of vulvar pruritus.

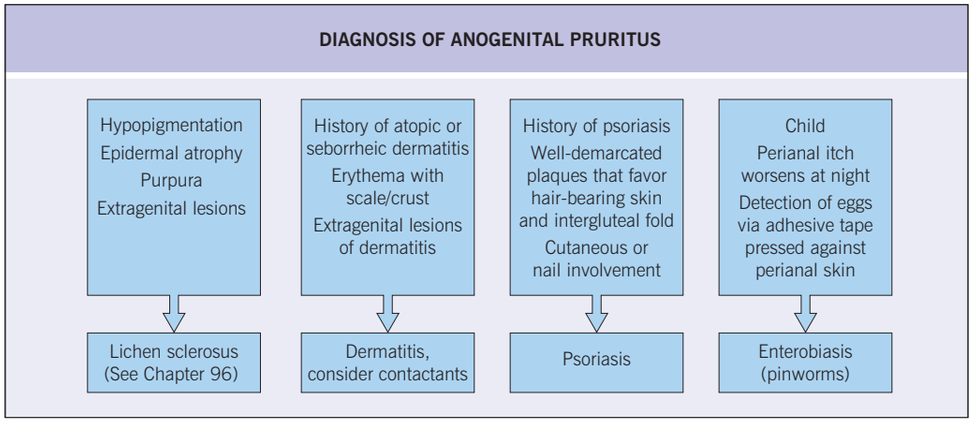


Fig. 73.10 Diagnosis of anogenital pruritus. Histologic evaluation may be required to confirm the clinical diagnosis (e.g. lichen sclerosus) or to exclude more unusual etiologies (e.g. extramammary Paget's disease). Systemic contact dermatitis reactions in this region may also be very pruritic.

The regular use of bland emollients and the substitution of an emollient for soap should be advised in all cases. Irritants, e.g. fragranced bath products, soap and medicated wipes, must be avoided. Exacerbating factors, including stress, heat, excessive washing and candidiasis, should be identified. When lichenification is present, it is especially important to break the itch–scratch cycle. Additional therapies include sedative antihistamines or tricyclic antidepressants, usually doxepin, at bedtime (see Ch. 6).

Contact Dermatitis

It is important to consider the possibility of contact dermatitis in any patient with dermatitis, a history of reactions to topical medications, or treatment-resistant disease. Contact dermatitis of the anogenital region may be irritant or allergic (see Chs 14 & 15)[19]. Irritant contact dermatitis is seen in infants as diaper dermatitis and in older patients as a consequence of overzealous cleanliness, urinary or fecal incontinence, chronic diarrhea, or bowel disease including tumors or inflammatory bowel disease.

Allergic contact dermatitis of the anogenital region occurs in men and women[20]. Relevant allergens include topical anesthetics, corticosteroids, fragrances, preservatives, rubber chemicals and spermicides. Type I immediate hypersensitivity reactions may occur to latex and seminal fluid, and there is the possibility of consort contact dermatitis. Allergic contact dermatitis must be considered in all patients with perianal dermatitis, because medications (topical, per anum) are frequently used by both sexes. Hemorrhoid creams and medicated toilet paper are common culprits.

Psoriasis

Key features

- Erythematous well-defined plaques
- Evidence of psoriasis elsewhere on total-body skin examination
- Intergluteal cleft frequently affected
- Poor response to treatment

Psoriasis of the anogenital region may look quite different from psoriasis at other sites (see Ch. 8). The typical silvery scale is lost, as in other flexural sites such as the axillae and submammary region.

Clinical features

In women, erythematous, smooth, clearly demarcated plaques typically affect the labia majora and the mons pubis. Psoriasis is usually confined to the hair-bearing areas, so the labia minora are unaffected. Men may have circumscribed plaques on the glans penis and shaft of the penis (Fig. 73.11). Persistent, painful fissuring of the perianal area and the intergluteal cleft can be a severe problem in both sexes.

Differential diagnosis

Often the diagnosis is very straightforward, established from a combination of the clinical appearance in the genital region plus typical lesions elsewhere on the body or classic nail changes. Seborrheic dermatitis may be difficult to distinguish from psoriasis, and, sometimes, clear features of both psoriasis and seborrheic dermatitis are seen in the same patient, when the term "sebopsoriasis" seems appropriate. The differential diagnosis includes tinea cruris (especially if there are pustules, an active border, extension of lesions onto the buttock or upper inner thigh, and/or concomitant tinea pedis or unguium) and erythrasma. On the glans penis, reactive arthritis (formerly Reiter's disease) may provoke lesions identical to those of psoriasis.

Treatment

Unfortunately, topical therapy for anogenital psoriasis is not entirely satisfactory. Many topical agents suitable for use on the body, such as coal tar, anthralin, vitamin D derivatives or retinoids, may be too irritating in flexural sites. Moderately potent topical corticosteroid–antibiotic combinations remain the most useful therapy; however, in intertriginous sites, corticosteroid-induced atrophy remains a concern. Topical tacrolimus or pimecrolimus may also be helpful in such occluded sites. Some patients will improve when a systemic agent is used (e.g. methotrexate, cyclosporine, TNF inhibitors), usually for widespread disease.

Fig. 73.11 Psoriasis of the penile shaft. Well-demarcated erythematous plaque with slight scale. Similar lesions can be seen in patients with reactive arthritis (formerly Reiter's disease). *Courtesy, Jean L Bolognia, MD.*

PREMALIGNANT AND MALIGNANT LESIONS

Intraepithelial Neoplasia (Vulvar, Penile, Anal)

Synonyms: ■ Bowen's disease ■ Bowenoid papulosis ■ Erythroplasia of Queyrat ■ Squamous cell carcinoma *in situ*

Key features

- Premalignant condition
- Human papillomaviruses are a common association

Introduction

The term "intraepithelial neoplasia" defines an intraepithelial change within anogenital epithelium that is premalignant. On the vulva it is termed VIN (vulvar or vulval intraepithelial neoplasia); on the penis, PIN (penile intraepithelial neoplasia); and on or around the anus, AIN (anal intraepithelial neoplasia). The terminology has been very confusing and it is now recommended that the terms Bowen's disease, erythroplasia of Queyrat, and bowenoid papulosis should not be used for lesions in the anogenital area. However, dermatologists still recognize a distinct clinical variant, bowenoid papulosis, characterized by discrete papules in a younger age group and a tendency for spontaneous regression. Additionally, some authorities believe that erythroplasia of Queyrat and Bowen's disease remain useful terms in men[21].

Epidemiology

It may occur at any age. The incidence in young women is rising.

Pathogenesis

Oncogenic human papillomaviruses are implicated in many cases of intraepithelial neoplasia (chiefly HPV types 16, 18, 31 and 33). There is an association with smoking and immunosuppression, including HIV infection. Lichen sclerosus and lichen planus are also predisposing factors.

Pathology

Intraepithelial neoplasia is characterized by nuclear hyperchromasia, disorderly maturation of keratinocytes, and coarse nuclear chromatin. Multiple mitotic figures are usually visible above the basal layer. VIN

Fig. 73.12 Penile intraepithelial neoplasia. Persistent erythema not responding to topical corticosteroids. *Courtesy, R Turner, MD*

Fig 73.13 Bowenoid papulosis variant of intraepithelial neoplasia. A Multiple red–brown to brown papules on the shaft of the penis. **B** Coalescence of red–brown to brown papules on the upper inner thigh. *B, Courtesy, Robert Hartman, MD.*

was originally graded 1–3 depending on the degree of abnormalities within the epidermis. More recently, VIN was reclassified into *usual type* VIN associated with HPV infection and a *differentiated type* that arises in the setting of lichen sclerosus or lichen planus[22].

Clinical features

The clinical presentation is varied. Erythematous well-demarcated plaques that look similar to plaques of Bowen's disease in extragenital sites may occur on the vulva, or the keratinized epithelium of the penis in men. Alternatively, warty white plaques, erosions or hyperpigmented patches may be seen. Shiny erythematous plaques may occur on the glans and prepuce of the uncircumcised male (erythroplasia of Queyrat; Fig. 73.12). In patients with bowenoid papulosis-type lesions, distinct red–brown papules are seen on the genitalia (Fig. 73.13A), which may extend to the inner thighs (Fig. 73.13B). Differentiated VIN usually presents as small ulcers or keratotic plaques.

Differential diagnosis

Intraepithelial neoplasia must be distinguished from inflammatory conditions such as lichen sclerosus, as well as condyloma acuminatum, Zoon's balanitis/vulvitis, and cutaneous malignancies, in particular, invasive squamous cell carcinoma.

Treatment

Treatment options depend on the site, the extent of disease, the age of the patient, and the type of intraepithelial neoplasia (see above). In localized disease, a biopsy to establish the diagnosis, followed by local excision, is preferred, so long as the surgery is not too mutilating. Recurrence is a problem with all treatment modalities. In men, circumcision is offered, as this may reduce the risk of progression to invasion[21]. Observation may be an option in selected cases if treatment is not feasible; however, if progression is observed, then surgical excision is necessary. Differentiated VIN associated with lichen sclerosus or lichen planus has a high risk of progression to invasive disease and must be excised. Cryosurgery is rarely indicated in the opinion of the authors, as recurrence rates are very high; laser therapy also has a high recurrence rate. Medical treatments such as topical fluorouracil or imiquimod may be helpful in some cases although local side effects may be severe. In some, but not all, patients, imiquimod can lead to histologic regression of disease and viral clearance[23]. In widespread disease, simple vulvectomy has been performed, but only after exhaustion of all other options.

Long-term evaluation is recommended and should include serial examinations and cervical and anal cytology, especially in the setting of HIV infection. Examination of sexual partners should be advised.

Invasive Squamous Cell Carcinomas

Key features

- Most common tumor in the anogenital region
- Etiology is different from squamous cell carcinomas arising in actinically damaged skin

Epidemiology

Squamous cell carcinomas (SCCs; see Ch. 108) most frequently occur in the elderly, although they may occur in younger adults. The incidence of genital SCC in women is rising.

Pathogenesis

HPV infection and lichen sclerosus account for the majority of SCCs of the anogenital region. HPV-associated tumors tend to arise in the younger adult, while lichen sclerosus-related tumors occur in postmenopausal women or older men[24,25]. Smoking and immunosuppression are also risk factors. SCC is very rare in circumcised men, and the presence of a foreskin, which can lead to trapping of smegma and low-grade inflammation, may predispose one to the development of carcinoma. SCC of the genital region is rarely due to cumulative UV light exposure[24], although there have been reports of SCC of the penis and scrotum developing in men who had received multiple PUVA treatments. Tar, chimney soot, asbestos and petroleum products are known carcinogens in the case of scrotal SCC.

Clinical features

In men, the majority of lesions present on the glans, the coronal sulcus or the prepuce as ulcers or plaques. The ulcers often have a heaped-up

edge (Fig. 73.14). In the uncircumcised man, delay in diagnosis may occur because of an associated phimosis masking the tumor. Although any area on the vulva may be involved, the labia are the most frequent sites. The clinical presentation varies from non-healing ulcers or fissures to nodules and plaques. Invasive anal carcinoma may arise from the anal margin or from within the lower anal canal.

Differential diagnosis

SCC must be distinguished from other tumors such as amelanotic melanomas or basal cell carcinomas. It is important to biopsy any suspicious lesion that develops in the anogenital area, particularly in the context of predisposing diseases such as lichen sclerosus, HPV infection and HIV infection.

Treatment

Treatment is usually surgical, with the extent of surgery dependent on both the size and depth of invasion. Consultation with a gynecologist or urologist with expertise in oncology is usually indicated. In addition to excision of the primary tumor, histologic examination of regional lymph nodes may be necessary, depending on the clinical stage. Microscopically controlled surgery can be utilized in an attempt to avoid mutilating surgery.

Anogenital Melanoma (see Ch. 113)

Key features

- Rare tumor not related to UV exposure
- Usually arises *de novo*, i.e. in the absence of a pre-existing benign melanocytic neoplasm
- Poor prognosis, due primarily to depth of invasion at time of diagnosis
- Mucosal lentiginous melanoma is the most common histologic type

Introduction

Although anogenital melanoma is a rare tumor, melanoma is the second most common primary tumor of the vulva in women.

Epidemiology

The incidence of vulvar melanoma has been estimated at 0.19 per 100 000 in a Swedish population[26], but similar figures are not available for men. Vulvar melanomas account for 0.3% of all melanomas in women. Compared with melanomas elsewhere, vulvar and penile melanomas occur in an older population, typically in the seventh decade, although they may appear at any age.

Pathogenesis

Melanoma is a multifactorial disease, but two of the major factors – sun exposure and melanocytic nevi – play a minimal (nevi) or no known (UV) role in anogenital melanoma. The latter may explain why the number of new cases of vulvar melanoma is falling while the incidence of cutaneous melanomas in the Western world is rising.

Fig. 73.14 Invasive squamous cell carcinoma of the foreskin. This patient with psoriasis had received PUVA therapy without genital protection.

Clinical features

In women, melanomas may present with bleeding, a "lump" or pruritus. Amelanotic melanomas account for approximately one-quarter of cases. Melanoma can arise throughout the genital tract, including the cervix and the vagina, as well as any site on the vulva. The labia majora and the clitoris are the most common tumor sites. In men, a crusted nodule is the most frequent presentation[27]. Most tumors arise on the glans penis, although they may occur at any site, including the scrotum.

The prognosis for anogenital melanoma is significantly worse than for the more common cutaneous melanomas. Reported 5-year survival rates vary from 35% to 60% for vulvar melanomas, less than 30% for penile melanomas, and less than 10% for anorectal melanomas. A key factor is the greater Breslow thickness due to delay in diagnosis, but it remains to be determined whether anogenital melanomas are fundamentally more aggressive.

Pathology

On genital skin, mucosal lentiginous melanoma is the most frequent histologic type of melanoma. Nodular and superficial spreading melanomas occur less frequently. Mucosal lentiginous melanomas show many histologic similarities to acral lentiginous melanomas. As with cutaneous melanoma, prognosis is determined by tumor thickness at presentation.

Differential diagnosis

For macular lesions, the major differential is a genital lentigo. Palpable pigmented melanomas must be distinguished from atypical-appearing seborrheic keratoses, melanocytic nevi and bowenoid papulosis. Melanocytic nevi that are superimposed on lichen sclerosus may have an atypical clinical appearance and the histologic features of a persistent nevus. Anal amelanotic melanoma may initially be misdiagnosed as hemorrhoids.

Treatment

Due to the rarity of the tumor, there have been no randomized therapeutic trials. Vulvar and penile melanomas are therefore treated similarly to cutaneous melanoma. Radical vulvectomy with bilateral lymph node dissection was the historical practice, but less aggressive treatment has gained favor over the past 25 years. Although the surgical margins for cutaneous melanoma have been reduced significantly, the exact surgical margins for anogenital melanomas are still debated. The role of prophylactic inguinal node dissection and sentinel lymph node biopsy is also controversial. Palliative radiotherapy has been tried for very extensive local disease. Immunotherapy (e.g. ipilimumab) may improve survival rates and depending upon the presence of specific mutations, targeted therapies such as tyrosine kinase inhibitors could be considered.

Basal Cell Carcinoma (see Ch. 108)

Basal cell carcinoma may occur in the anogenital area and is usually diagnosed as a squamous cell carcinoma prior to biopsy or excision. Rarely, it has been reported to metastasize.

Extramammary Paget's Disease

Key features

- Rare intraepithelial adenocarcinoma
- May be primary or secondary to an underlying malignancy
- Associated with an underlying visceral malignancy in 10–20% of patients

Introduction

Extramammary Paget's disease can be *primary*, arising as an intraepithelial adenocarcinoma, or *secondary*, due to pagetoid spread of an adjacent or contiguous *in situ* or invasive neoplasm. Extramammary Paget's disease may become invasive and metastasize via the lymphatic system.

Epidemiology

Elderly Caucasian women most commonly develop this malignancy, but in Japan there is a male predominance.

Etiology

The histogenesis of primary Paget's disease has been long debated but Toker cells have been proposed as the cell of origin[28]. Secondary Paget's disease represents a cutaneous extension of an underlying adnexal adenocarcinoma (see Ch. 111) or an underlying visceral malignancy (most commonly colorectal or urothelial, but it may also be cervical, prostatic, ovarian or endometrial).

Clinical features

The vulva in women and the perianal region in men are the most commonly affected sites[29,30]. There may be associated pruritus or burning or the lesions may be asymptomatic. A slowly expanding erythematous plaque is typical, with a sharp demarcation between normal and involved skin (Fig. 73.15A,B). Scattered areas of white scale and erosion can give rise to a "strawberries and cream" appearance.

Pathology

The diagnosis must be confirmed by histologic examination. Vacuolated Paget cells in the epidermis are distinctive (Fig. 73.15C), but immunohistochemical staining is necessary to exclude the important differential diagnoses of pagetoid melanoma and intraepithelial neoplasia (Fig. 73.16), as well as to help differentiate between primary and secondary disease[31]. An underlying adnexal tumor must be sought.

Differential diagnosis

Extramammary Paget's disease may be misdiagnosed as dermatitis or lichen simplex chronicus, leading to a delay in diagnosis. Psoriasis, erosive lichen planus and candidiasis are additional entities that might be confused with this neoplasm.

Treatment

A thorough search for internal malignancies associated with extramammary Paget's disease should be performed, especially when suggested by the immunocytochemical findings and location (e.g. an internal malignancy is approximately five times more likely when there is perianal as opposed to vulvar or penoscrotal involvement). The evaluation should include a full cutaneous and lymph node examination, colonoscopy, cystoscopy, and, in women, a complete pelvic and breast examination, plus imaging of the pelvis and a mammogram. In men, a prostate-specific antigen (PSA) level and prostate examination are also required.

In the anogenital region, treatment is by Mohs micrographic surgery or wide local excision; however, the multifocal nature of extramammary Paget's disease and the fact that clinically inapparent extensions of the disease may be present make recurrences very frequent. Other treatment options include topical imiquimod, radiotherapy, photodynamic therapy, CO_2 laser ablation, and topical 5-fluorouracil. Combination therapy is often employed.

Long-term follow-up is recommended for these patients.

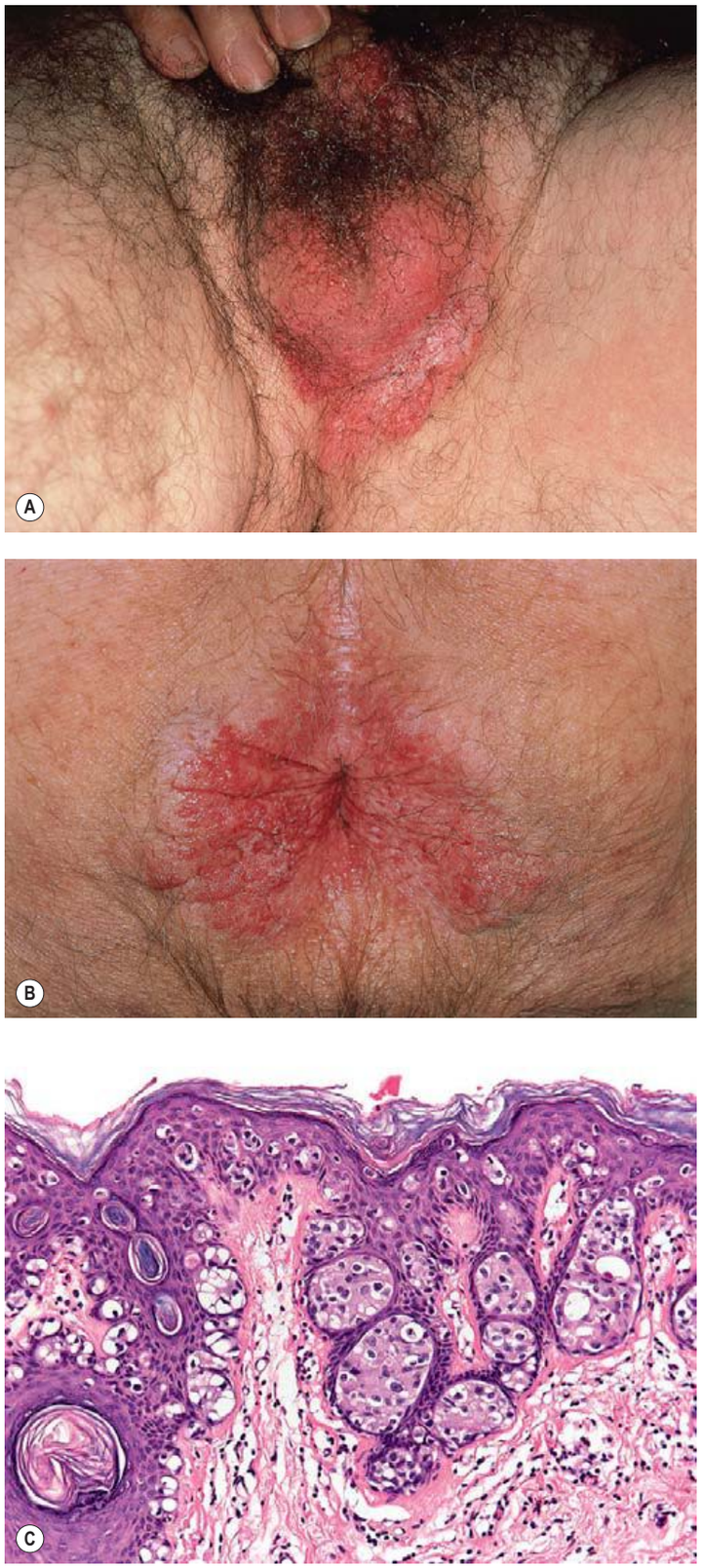


Fig. 73.15 Extramammary Paget's disease. A Erythematous plaque with hydrated scale at the base of the scrotum. **B** Well-demarcated perianal plaque with both erosions and scale, giving rise to a "strawberries and cream" appearance. **C** Photomicrograph demonstrating pagetoid cells within the epidermis, both as single cells and in nests. *B, Courtesy, Kalman Watsky, MD. C, Courtesy, Lorenzo Cerroni, MD.*

DYSESTHETIC GENITAL PAIN SYNDROMES

The term "dysesthetic genital pain syndrome" encompasses a number of disorders in which the clinical appearance is normal despite the patient's experience of severe disabling pain (notably in the absence of a clinically identifiable neurologic disorder; Fig. 73.17). Although still a matter of debate, these disorders are usually considered to be regional pain syndromes. Unmedullated C fibers transmit pain and touch, and it is now recognized that these nerve fibers can be remodeled after a stimulus has passed, explaining why perception of subsequent stimuli may be altered. Relatively minor inflammation or trauma, often unrecalled, may precipitate the onset of pain. Vulvar pain has been recently reclassified by the International Society for the Study of Vulvovaginal Disease (ISSVD; Table 73.3)[32].

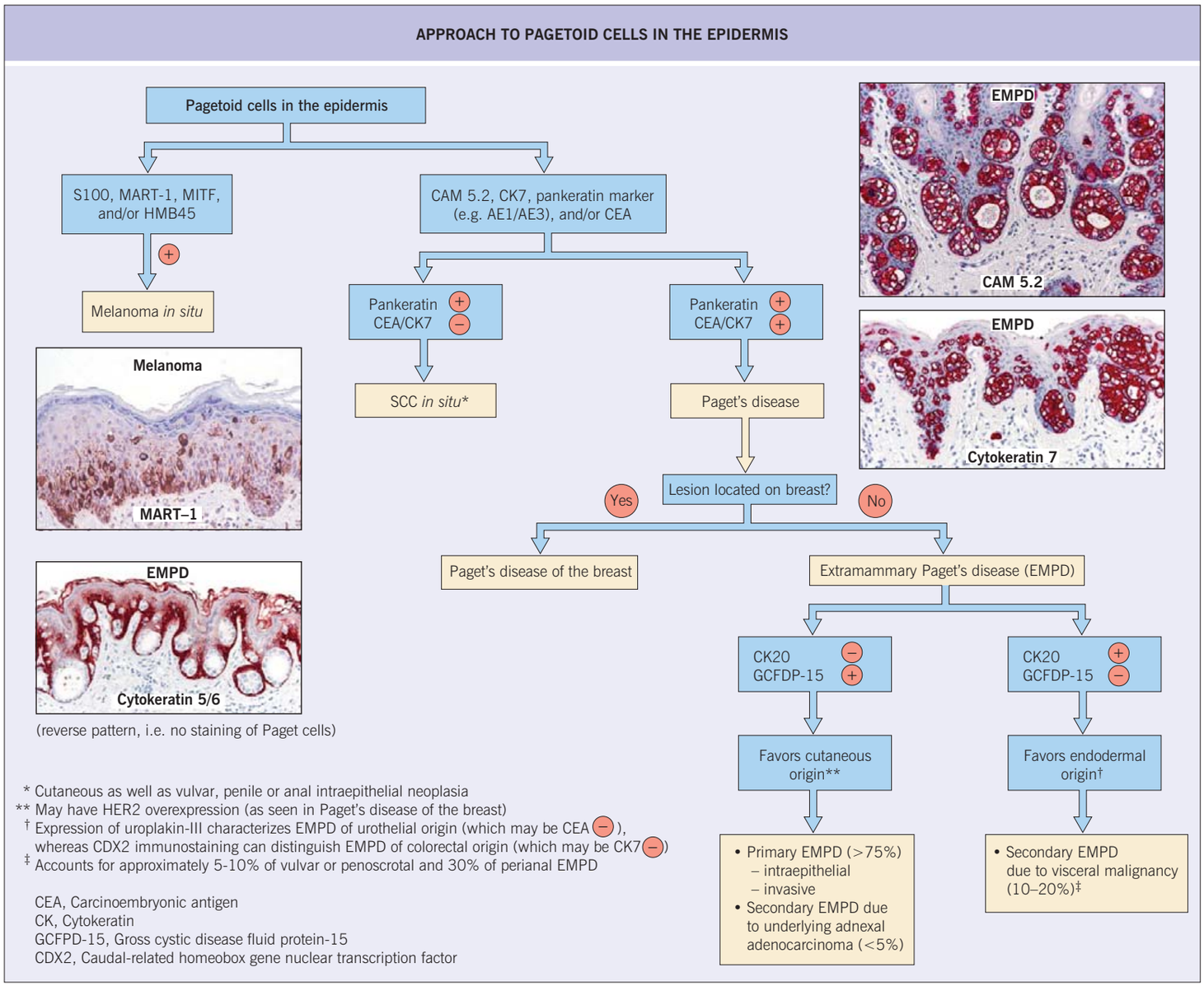


Fig. 73.16 Algorithm for the approach to Paget cells in the epidermis. The CAM 5.2 immunohistochemical stain is positive in >95% of Paget's disease (mammary and extramammary) and approximately one-third of Bowen's disease; it stains low-molecular-weight keratins. AE1 stains most subfamily A keratins (but not 12, 17 and 18) while AE3 stains subfamily B keratins.

Localized Vulvodynia (Vestibulodynia)

Key features

- Superficial dyspareunia
- Tenderness on localized pressure within the vulvar vestibule
- Occurs in young, sexually active women

Introduction

"Localized vulvodynia" is now the preferred term for this specific subtype of the vulvar pain syndrome, characterized by superficial dyspareunia and point tenderness within the vestibule, often at 5 and 7 o'clock[33].

Clinical features

This particular localized pain syndrome occurs in the young premenopausal sexually active woman whose main complaint is one of dyspareunia on penetration. Insertion of tampons may be impossible. The vulva looks entirely normal but there is pain when the vestibular area is pressed by a cotton-tipped applicator.

Differential diagnosis

Localized vulvodynia must be differentiated from other causes of vulvar pain (see Table 73.3). Hymenal and posterior vestibule fissures and herpes simplex must be excluded. A fungal culture should be obtained to exclude *Candida* infection.

Treatment

It is important to explain the diagnosis in detail to the patient, providing written information and patient support group information where possible. Regular application of bland emollients and avoidance of irritants such as detergents and fragranced products are helpful. Local desensitization by applying emollients with increasing pressure over weeks is helpful in our experience but there are very few treatments for this condition that have been supported by clinical trials. Topical local anesthetic agents (e.g. 5% lidocaine) applied before intercourse may be helpful. Tricyclic antidepressants, starting with small doses (e.g. 10 mg)

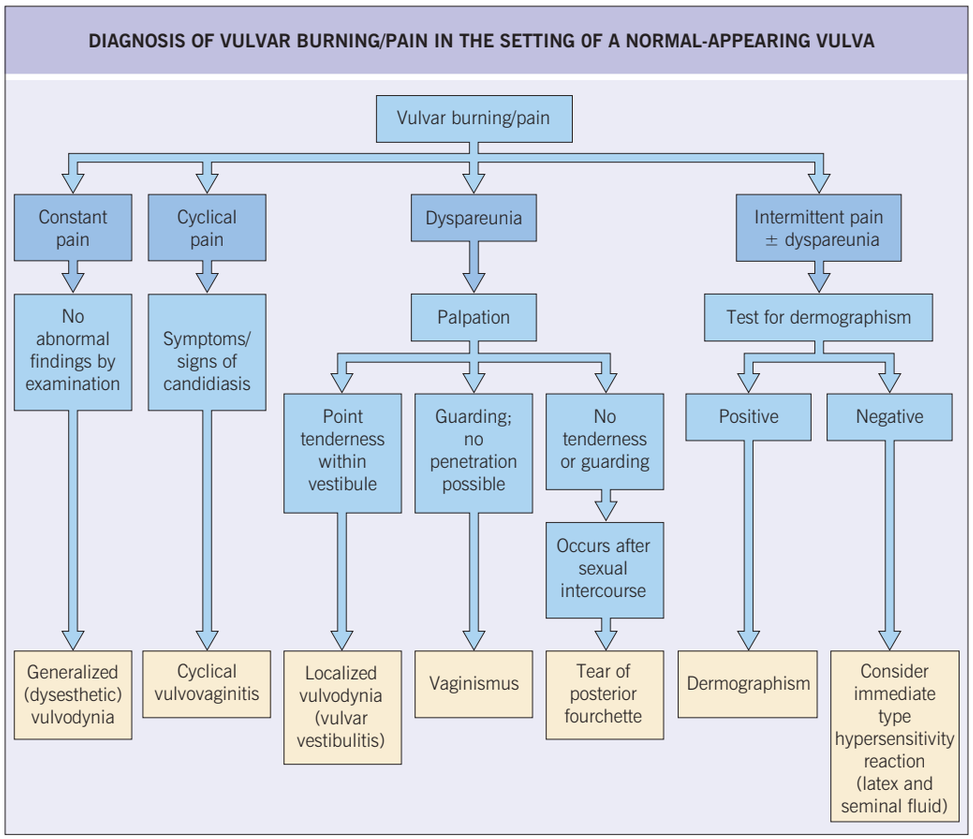


Fig. 73.17 Diagnosis of vulvar burning/pain in the setting of a normal-appearing vulva.

ISSVD TERMINOLOGY AND CLASSIFICATION OF VULVAR PAIN
VULVAR PAIN RELATED TO A SPECIFIC DISORDER
• Infectious (e.g. candidiasis, HSV infection, herpes zoster) • Inflammatory (e.g. lichen planus, immunobullous disorders) • Neoplastic (e.g. Paget's disease, squamous cell carcinoma) • Neurologic (e.g. herpes neuralgia, spinal nerve compression)
VULVODYNIA
Localized (vestibulodynia, clitorodynia, hemivulvodynia, etc.)
• Provoked (sexual, non-sexual, or both) • Unprovoked • Mixed (provoked and unprovoked)
Generalized (dysesthetic vulvodynia)
• Provoked (sexual, non-sexual, or both) • Unprovoked • Mixed (provoked and unprovoked)

Table 73.3 ISSVD terminology and classification of vulvar pain (2003).

of amitriptyline nightly and increasing slowly (over several weeks) to 100 mg nightly if necessary, are often used; nortriptyline is a less sedating alternative. Topical corticosteroid/antifungal ointments or oral gabapentin have been effective in some patients. There is increasing evidence for the role of surgery in selected cases[34]. Some evidence exists for the efficacy of pelvic floor electromyography and biofeedback, and there are anecdotal reports of the benefits of a low oxalate diet and oral calcium citrate.

Generalized Vulvodynia/Scrotodynia (Dysesthetic Vulvodynia/Scrotodynia)

Key features

- Burning and/or pain
- Clinical examination of vulva or scrotum is normal

Introduction

Persistent burning pain is characteristic and patients have often consulted many doctors before the correct diagnosis is made. Depression may be a feature of any chronic pain syndrome. There is an association with fibromyalgia and the irritable bowel syndrome.

Scrotodynia is probably analogous to vulvodynia; however, there is less published on the subject[35]. Precipitating events include sexual activity, exercise, friction and heat. Pain may also affect the penis.

Clinical features

Pain, often accompanied by a burning sensation, is felt over the entire vulva, scrotum or penis, and may extend down the thighs. The genital area may hurt even when nothing is touching it. Often, symptoms are worse on sitting or walking up stairs. Wearing of underwear may be impossible. On inspection, the scrotum or vulva looks entirely normal.

Differential diagnosis

Other causes of genital pain, e.g. infection (bacterial, viral or fungal), lichen sclerosus or lichen planus, must be excluded by examination before the diagnosis can be made. A potassium hydroxide (KOH) preparation and/or fungal culture to exclude candidiasis is essential. It is important to test for dermographism, as treatment with antihistamines may greatly benefit these patients.

Treatment

Treatment strategies are very similar to those for localized vulvodynia or scrotodynia (see above)[33]. In addition, acupuncture may be helpful. Referral to a pain clinic, with management by a special team of anesthesiologists and psychologists, is often useful. Some authors consider that early diagnosis and treatment may shorten the duration of symptoms. Despite a variety of treatments, there remains a group that fails to respond.

Cyclical Vulvovaginitis

Some women experience premenstrual exacerbation of their pain, and *Candida* infection has been implicated (see below). Fisher et al.[36] suggested that estrogen sensitivity may be an important factor.

BENIGN LESIONS OF THE GENITALIA
COMMON
• Epidermoid cysts • Pearly penile papules • Vestibular papillomatosis • Angiokeratomas • Urethral caruncle
LESS COMMON
• Fox–Fordyce disease • Syringomas • Idiopathic calcinosis of the scrotum • Hidradenoma papilliferum

Table 73.4 Benign lesions of the genitalia.

Anal Pain

Anal pain may occur in both men and women and it shares many features with vulvodynia and scrotodynia. Associated depression is frequent.

BENIGN LESIONS

A wide variety of benign lesions can be found in the anogenital area (Table 73.4). Some of the more important lesions are discussed below.

Epidermoid Cysts

Epidermoid cysts are frequently encountered on the glabrous labia majora and scrotum, and may be multiple. They are yellow, vary in size, and may become inflamed. Treatment is by excision, but this is only necessary if the cyst is symptomatic.

Vestibular Papillomatosis

Papillomas within the vestibule are found in approximately 45% of premenopausal women and 10% of postmenopausal women. They are pink, asymptomatic, fine projections. Women should be reassured that the finding is normal.

THE ANOGENITAL REGION AND SYSTEMIC DISEASE

Inflammatory Bowel Disease

Crohn's disease must be suspected in patients with recurrent abscesses, sinuses or fistulas in the perineal region. Often, multiple firm perianal skin tags are seen. Perianal disease may precede bowel symptoms by a number of years. Marked, firm, granulomatous labial swelling is rarely the initial presentation (see Ch. 93). A lesional biopsy will reveal non-caseating granulomas.

Zinc Deficiency

Zinc deficiency may be genetic, as in the autosomal recessively inherited condition acrodermatitis enteropathica, or acquired, as in premature babies or full-term infants who are breastfed. An extensive periorificial eruption is typical.

Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (see Ch. 91) may present with erythema, papulonodules or ulcers in the perineal area.

Behçet's Disease

Behçet's disease is a rare multisystem inflammatory disorder in which recurrent oral aphthae combine with some of the following clinical features: genital erosions or ulcers, arthritis, uveitis, neurologic disorders such as cranial nerve palsies and mono- and hemiparesis, arterial and venous thromboses, and pathergy (see Ch. 26). The disease is more prevalent in men and in those from the Mediterranean basin and Japan; it typically presents in young adults in their third or fourth decade of life. Recurrent flares and remissions are to be expected. Treatment is with a variety of immunosuppressive drugs or thalidomide.

INFECTIONS

Sexually transmitted infections (see Chs 78 & 81) and condylomata acuminata (see Ch. 79) are described elsewhere, but some miscellaneous infections that favor the anogenital region are discussed below.

Perianal Streptococcal Disease

The typical presentation is that of a 3- or 4-year-old boy with erythema and sometimes crusting of the perianal area[37] (see Ch. 74). Constipation is frequent because of the discomfort. The disease can be associated with guttate psoriasis and is frequently misdiagnosed as irritant dermatitis or candidiasis. Specimens for bacterial culture must be obtained. The group A β-hemolytic streptococcus is responsible. Treatment is with oral penicillin or erythromycin.

Recurrent Toxin-Mediated Perineal Erythema

Recurrent toxin-mediated perineal erythema is an unusual condition that presents 2–3 days after a throat infection as a fine diffuse macular erythema of the perineal region[38]. Marked local edema may be present and the hands may be similarly affected. Desquamation follows the erythema and the condition can be recurrent. Streptococcal or staphylococcal pharyngitis is the most common cause and the erythema is toxin-mediated. Long-term prophylactic penicillin may be beneficial in some patients.

Kawasaki Disease

Kawasaki disease is thought to be mediated by bacterial toxins, but the exact cause has not been elucidated. It is a disease of children. In up to two-thirds of cases, perineal erythema may be a presenting feature (see Ch. 81); additional findings include a strawberry tongue, fissured lips, fever and lymphadenopathy, followed by desquamation of the hands and feet. Coronary artery aneurysms may be life-threatening. Treatment is with aspirin and IVIg.

Fournier's Gangrene

Fournier's gangrene is a severe necrotizing infection of the external genitalia, perineum or perianal area that occurs in patients with an underlying predisposition such as diabetes or immunosuppression[39]. The infection is polymicrobial. Extensive surgical debridement with a prolonged course of systemic antibiotics is necessary.

Erythrasma

Pigmented patches or thin plaques with fine scale tend to occur in flexural areas, including the groin. Coral pink fluorescence under Wood's lamp examination is diagnostic. Distinction from dermatophytosis is usually possible clinically, as scaling is diffuse in erythrasma and there is no tendency toward central clearing.

Dermatophytosis

Chronic, slowly advancing, scaly erythematous lesions may be seen in the groin (tinea cruris) or the medial buttocks in addition to the upper thighs. Central clearing is often present and pustules may be seen; there is usually (if not always) concomitant tinea pedis and/or unguium. The diagnosis is made by microscopy and culture of skin scrapings.

Cutaneous Candidiasis

Key features

- *Candida* spp. are normal commensals of the gastrointestinal tract
- Precipitating factors must be sought, e.g. diabetes, systemic corticosteroids, systemic antibiotics

Introduction

Candidiasis is one of the most common infections of the genital and perianal skin. It is important to confirm the infection by microscopy (KOH preparation) and culture because many genital skin problems in men and women are erroneously attributed to candidiasis.

Epidemiology

Candida spp. are normal commensals in the gastrointestinal tract. In addition, approximately 15–30% of asymptomatic women are vaginal carriers of *Candida* spp.; during pregnancy, this rises to 40%[40].

Etiology

It seems likely that the development of candidiasis represents failure of a host response to the yeast[41]. Candidiasis is more commonly seen in uncontrolled diabetics, the immunosuppressed, and during treatment with broad-spectrum antibiotics, high-dose estrogen or topical corticosteroids. Copper-containing intrauterine devices may predispose to infection. Candidiasis can be sexually transmitted and this is probably most important in recurrent infections.

Clinical features

In men, balanitis, balanoposthitis, or a more widespread involvement of the perianal area, perineum and groin is seen. Balanitis is more common in the uncircumcised man. The skin is erythematous and glazed with yellow pustules and erosions. In severe infections, edema may prevent retraction of the foreskin.

Women complain of severe pruritus and vaginal discharge. Creamy white curds are visible on the vaginal walls, and there is vulvar erythema, but pustules are seen only rarely. In the postmenopausal woman, the atrophic mucosa may become dry, sore and erythematous as a result of a candidal infection.

In both men and women, candidiasis may affect the perianal area. In this site, sheet-like erythema is seen and fissuring is common. The inguinal-scrotal fold in men is a frequent site of involvement, and here, in addition to the erythema, the skin focally may appear white due to overhydration of the accompanying scale. Satellite lesions, including pustules, are frequently seen.

In babies, candidiasis is a common cause of diaper dermatitis. There may be rapid spread of erythema and pustules that typically affect the skin creases, unlike the more common irritant dermatitis. Rarely, a nodular ulcerated variant may occur.

Differential diagnosis

It is very important to establish the diagnosis because many inflammatory conditions of the genitalia such as lichen sclerosus and contact dermatitis are treated initially as a "yeast" infection. The presence of the pseudohyphae of *Candida* is not sufficient to make the diagnosis; the appropriate clinical signs must also be present. Subcorneal pustules and erosions are also seen in impetigo, but this is easily excluded by a bacterial culture. In women, other causes of a vaginal discharge include bacterial vaginosis and *Trichomonas*.

Treatment

It is essential to determine whether there are any underlying causes, for example, uncontrolled diabetes. Topical polyene or imidazole antifungals may suffice in localized balanitis or intertrigo. If there is severe pruritus, the addition of a mild topical corticosteroid may be helpful. In vaginal candidiasis, vaginal suppositories containing nystatin or an imidazole can be used. Single-dose oral treatment is an alternative, e.g. fluconazole 150 mg, for vaginal disease. In difficult infections, in the immunocompromised patient and in vulvar disease, more prolonged systemic treatment is necessary, e.g. fluconazole 50–100 mg daily for 14 days (level of evidence, 3). Antimicrobial therapies are discussed in more detail in Chapter 127.

Recurrent Candidiasis

Recurrent candidiasis can be defined as more than three episodes of candidiasis per year. Precipitating factors must be identified. Advice should be given on foreskin hygiene and keeping the perineal area cool with cotton underwear. Sexual transmission may be an important factor in recurrent candidiasis and, therefore, treatment of both partners may be justified. Three possible regimens are oral fluconazole 150 mg weekly for 6 months, clotrimazole 500 mg vaginal tablet weekly for 6 months, or itraconazole 200 mg BID orally once monthly for 6 months.

Cyclical Vulvovaginitis

Cyclical vulvovaginitis is recurrent vulvovaginitis with or without the typical candidal discharge. Pain is cyclical, corresponding to a particular phase of the menstrual cycle, and is associated with superficial dyspareunia. Although *Candida* cannot always be cultured, the vulvovaginitis is usually responsive to prolonged courses of oral antifungal medication.

EROSIVE GENITAL DISEASE

Erosions and ulcerations are seen in a wide variety of conditions (Table 73.5). Genital aphthae and HSV are common. Erosions may occur after scratching or rubbing or as a result of blister formation. To determine the cause of the erosions, it is essential to take a careful history and perform a full examination of the skin, including the mucosal surfaces. For example, a white lacy pattern on the buccal mucosa may suggest a diagnosis of lichen planus. Further investigations will be determined by the clinical appearance, but swabs for bacterial and fungal culture are often necessary. Biopsies of lesional skin for light microscopy and perilesional skin for direct immunofluorescence are indicated if an autoimmune blistering disorder is suspected.

Acquired Autoimmune Blistering Disorders

Introduction

Immunofluorescence (direct and indirect) is an essential investigation in suspected blistering conditions as it may be very difficult to

CAUSES OF GENITAL EROSIONS
Lichen sclerosus
Erosive lichen planus
Genital aphthae
Infection • Candidiasis • Impetigo (*Staphylococcus/Streptococcus*) • Herpes simplex viral infection or herpes zoster • Primary syphilis, chancroid • Cytomegalovirus, Epstein-Barr virus*, *Mycoplasma* • Tuberculosis
Squamous cell carcinoma and other malignancies
Intraepithelial neoplasia
Zoon's plasma cell balanitis/vulvitis
Acquired bullous diseases • Pemphigus vulgaris • Bullous pemphigoid • Mucous membrane (cicatricial) pemphigoid • Linear IgA bullous dermatosis • Epidermolysis bullosa acquisita • Erythema multiforme, Stevens–Johnson syndrome • Fixed drug eruption
Inherited bullous disease • Hailey–Hailey disease • Epidermolysis bullosa
Complex aphthosis – Behçet's disease, inflammatory bowel disease
Crohn's disease
Extramammary Paget's disease
Langerhans cell histiocytosis
Necrolytic migratory erythema, acrodermatitis enteropathica
Papular acantholytic dyskeratosis
Toxic erythema of chemotherapy
*Diagnosed via EBV IgM antibodies or PCR; favors female children and adolescents.

Table 73.5 Causes of genital erosions.

distinguish between the different blistering disorders on clinical grounds alone[42]. This is particularly true in the anogenital region.

Bullous pemphigoid (see Ch. 30)

Bullous pemphigoid is the most common blistering disorder of the elderly, although it may occur at any age: for example, localized vulvar pemphigoid has been described in children[43]. Bullous pemphigoid has a propensity to develop in flexural sites, therefore the genital region is frequently affected; scarring is not a feature of genital involvement. Tense blisters are seen arising from urticarial plaques or from normal skin. Mucosal involvement occurs in 50% of patients. A prodromal phase of pruritic urticarial plaques without blisters may be present for months or years.

Mucous membrane (cicatricial) pemphigoid (see Ch. 30)

Mucous membrane pemphigoid is a scarring blistering disorder. In the genital region, it is clinically indistinguishable from erosive lichen planus unless blisters are seen or described; thus, histology and immunofluorescence are essential (Fig. 73.18). Men report penile lesions, dysuria, difficulty in retracting the foreskin due to phimosis, and change in urinary stream due to meatal stenosis. Women report pain, pruritus and dysuria. The associated scarring frequently causes marked architectural change of the vulvar area, with labial fusion, introital narrowing and, less frequently, urethral stenosis.

Fig. 73.18 Mucous membrane pemphigoid of the vulva. Ulcerations and scarring of the perianal area and perineum (positive direct immunofluorescence distinguished this from erosive lichen planus).

Linear IgA bullous dermatosis (see Ch. 31)

Linear IgA bullous dermatosis is a rare disease that can affect both adults and children. Involvement of the genital and perioral regions is frequently seen, especially in children. Annular polycyclic lesions are characteristic, with multiple blisters at the peripheral margins.

Pemphigus vulgaris (see Ch. 29)

Pemphigus vulgaris has a predilection for mucosal sites. Fragile blisters may be seen elsewhere on the skin, but on the genitalia widespread erosions are observed. Vulvovaginal involvement may occur.

Principles of treatment for the bullous disorders

The extent and severity of the disease determine the specific treatment. The aim is to control symptoms with the fewest possible medication-associated side effects. Treatment usually consists of a mixture of topical and systemic anti-inflammatory and immunosuppressive agents. Great symptomatic relief can be gained from the use of potent topical corticosteroids, either as sole treatment in localized disease or as an adjunct to systemic treatment in widespread or more severe disease. Secondary infection, including candidiasis, is a particular problem in the genital region.

Acquired Reactive Bullous Disease

Erythema multiforme and Stevens–Johnson syndrome

Erythema multiforme (EM) and Stevens–Johnson syndrome (SJS) may present as a bullous eruption, particularly in the genital region. In recurrent EM, an associated HSV infection should be sought, remembering that there may be a delay of up to 2 weeks from infection to appearance of the lesions. In recurrent cases, a trial of prophylactic oral antiviral therapy may be indicated. Involvement of two or more mucosal sites points to SJS, in which drugs are the most common etiology (see Ch. 20).

Fixed drug eruption (see Ch. 21)

Recurrent erythematous, blistered or eroded plaques may occur on both skin and mucous membranes[44]. Often, cutaneous lesions are strikingly round, but this may not hold true in mucous membrane sites. The lesions reoccur in exactly the same site with each exposure to the drug. Genital lesions frequently appear as erosions rather than blisters. Many drugs are capable of causing a fixed drug eruption, but common culprits are acetaminophen (paracetamol), tetracyclines, trimethoprim–sulfamethoxazole, and nonsteroidal anti-inflammatory drugs.

Inherited Bullous Disease

Hailey–Hailey disease (see Ch. 59)

Patients with autosomal dominant Hailey–Hailey disease have recurrent involvement of flexural areas. Expanding erythematous plaques with superimposed erosions and sometimes vesicles and pustules are seen. In the inguinal creases, there is a particular tendency to form hypertrophic plaques. Secondary infection with bacteria, fungi and HSV is a frequent problem and must be excluded in any exacerbation. Topical corticosteroids in combination with antifungal/antibacterial agents can ease symptoms. CO_2 laser ablation can also prove helpful.

REFERENCES

1. Powell JJ, Wojnarowska F. Lichen sclerosus. Lancet. 1999;353:1777–83.
2. Powell JJ, Wojnarowska F, Hollowood K, et al. What is the incidence of lichen sclerosus? Br J Dermatol. 2000;143(suppl. 57):30.
3. Chalmers RJ, Burton PA, Bennett RF, et al. Lichen sclerosus et atrophicus: a common and distinctive cause of phimosis in boys. Arch Dermatol. 1984;120:1025–7.
4. Gao XH, Barnardo MC, Winsey S, et al. The association between HLA DR, DQ antigens, and vulval lichen sclerosus in the UK: HLA DRB112 and its associated DRB112/DQB10301/04/09/010 haplotype confers susceptibility to vulval lichen sclerosus, and HLA DRB10301/04 and its associated DRB10301/04/DQB10201/02/03 haplotype protects from vulval lichen sclerosus. J Invest Dermatol. 2005;125:895–9.
5. Cooper SM, Ali I, Baldo M, et al. The association of lichen sclerosus and erosive lichen planus of the vulva with autoimmune disease: a case-control study. Arch Dermatol. 2008;144:1520–1.
6. Oyama N, Chan I, Neill SM, et al. Autoantibodies to extracellular matrix protein 1 in lichen sclerosus. Lancet. 2003;362:118–23.
7. Howard A, Dean D, Cooper S, et al. Circulating basement membrane zone antibodies are found in lichen sclerosus of the vulva. Australas J Dermatol. 2004;45:12–5.

7a. Bunker CB. Comments on the British Association of Dermatologists guidelines for the management of lichen sclerosus. Br J Dermatol. 2011;164:894–5.

8. Cooper SM, Gao XH, Powell JJ, et al. Does treatment of vulvar lichen sclerosus influence its prognosis? Arch Dermatol. 2004;140:702–6.
9. Neill SM, Lewis FM, Tatnall FM, Cox NH. British Association of Dermatologists' guidelines for the management of lichen sclerosus. Br J Dermatol. 2010;163:672–82.
10. Smith YR, Haefner HK. Vulvar lichen sclerosus: pathophysiology and treatment. Am J Clin Dermatol. 2004;5:105–25.
11. Powell J, Robson A, Cranston D, et al. High incidence of lichen sclerosus in patients with squamous cell carcinoma of the penis. Br J Dermatol. 2001;145:85–9.
12. Lewis FM. Vulval lichen planus. Br J Dermatol. 1998;138:569–75.
13. Pelisse M, Leibowitch M, Sedel D, et al. Un nouveau syndrome vulvo-vaginal-gingival: lichen plan erosive plurimuqueux. Ann Dermatol Venereol. 1982;109:797.
14. Cooper SM, Kirtschig G, Jeffery KJ, et al. No association between hepatitis B or C viruses and vulval lichen planus in a UK population. BJOG. 2004;111:271–3.
15. Cooper SM, Wojnarowska F. Influence of treatment of erosive lichen planus of the vulva on its prognosis. Arch Dermatol. 2006:142;289–94.

16. Torti DC, Jorizzo JL, McCarthy MA. Oral lichen planus: a case series with emphasis on therapy. Arch Dermatol. 2007;143:511–15.
17. Yoganathan S, Bohl TG, Mason G. Plasma cell balanitis and vulvitis (of Zoon). A study of 10 cases. J Reprod Med. 1994;39:939–44.
18. Crone AM, Stewart EJC, Wojnarowska F, et al. Aetiological factors in vulvar dermatitis. J Eur Acad Dermatol Venereol. 2000;14:181–6.
19. Margesson LJ. Contact dermatitis of the vulva. Dermatol Ther. 2004;17:20–7.
20. Warshaw EM, Furda LM, Maibach HI, et al. Anogenital dermatitis in patients referred for patch testing. Arch Dermatol 2008;144;749–55.
21. Singh S, Bunker C. Male genital dermatoses in old age. Age Aging 2008;37:500–4.
22. Sideri M, Jones RW, Wilkinson EJ, et al. Squamous vulvar intraepithelial neoplasia: 2004 modified terminology, ISSVD Vulvar Oncology Subcommittee. J Reprod Med. 2005;50:807–10.
23. van Seters M, van Beurden M, ten Kate FJ, et al. Treatment of vulvar intraepithelial neoplasia with topical imiquimod. N Engl J Med. 2008;358:1465–73.
24. Crum CP. Carcinoma of the vulva: epidemiology and pathogenesis. Obstet Gynecol. 1992;79:448–54.
25. Shah KV. Human papillomaviruses and anogenital cancers. N Engl J Med. 1997;337:1386–8.
26. Ragnarsson-Olding BK, Kanter-Lewensohn LR, Lagerlof B, et al. Malignant melanoma of the vulva in a nationwide, 25-year study of 219 Swedish females: clinical observations and histopathologic features. Cancer. 1999;86:1273–84.
27. Oldbring J, Mikulowski P. Malignant melanoma of the penis and male urethra. Report of nine cases and review of the literature. Cancer. 1987;59:581–7.
28. Willman JH, Golitz LE, Fitzpatrick JE. Vulvar clear cells of Toker: precursors of extramammary Paget's disease. Am J Dermatopathol. 2005;27:185–8.
29. Kanitakis J. Mammary and extramammary Paget's disease. J Eur Acad Dermatol Venereol. 2007;21 :581–90.
30. Hatta N, Yamada M, Hirano T, et al. Extramammary Paget's disease: treatment, prognostic factors and outcome in 76 patients. Br J Dermatol 2008;158;414–18.
31. Brown HM, Wilkinson EJ. Uroplakin-III to distinguish vulvar Paget disease from Paget disease secondary to urothelial carcinoma. Hum Pathol. 2002;33:545–8.
32. Moyal-Barracco M, Lynch PJ. 2003 ISSVD terminology and classification of vulvodynia: a historical perspective. J Reprod Med. 2004;49:772–7.
33. Haefner HK, Collins ME, Davis GD, et al. The vulvodynia guideline. J Low Genit Tract Dis. 2005;9:40–51.
34. Goetsch MF. Patients' assessments of a superficial modified vestibulectomy for vestibulodynia. J Reprod Med. 2008;53:407-12.
35. Markos A. The male genital burning syndrome (dysaesthetic peno/scrotodynia). Int J STD AIDS. 2002 ;13:271–2.
36. Fisher G, Spurrett B, Fischer A. The chronically symptomatic vulva: aetiology and management. Br J Obstet Gynaecol. 1995;102:773–9.
37. Kokx NP, Comstock JA, Facklam RR. Streptococcal perianal disease in children. Pediatrics. 1987;80: 659–63.
38. Manders SM. Toxin-mediated streptococcal and staphylococcal disease. J Am Acad Dermatol. 1998;39:383–98.
39. Smith GL, Bunker CB, Dinneen MD. Fournier's gangrene. Br J Urol. 1998;81:347–55.
40. Spinillo A, Pizzoli G, Colonna L, et al. Epidemiologic characteristics of women with idiopathic recurrent vulvovaginal candidiasis. Obstet Gynecol. 1993;81:721–7.
41. Sobel JD. Pathogenesis and treatment of recurrent vulvovaginal candidiasis. Clin Infect Dis. 1992;14(suppl. 1):148–53.
42. Marren P, Wojnarowska F, Venning V, et al. Vulvar involvement in autoimmune bullous diseases. J Reprod Med. 1993;38:101–7.
43. Oranje AP, van Joost T. Pemphigoid in children. Pediatr Dermatol. 1989;6:267–74.
44. Marren P, Wojnarowska F. Erosive vulvovaginitis. In: Black MM, McKay M, Braude P (eds). Obstetric and Gynaecologic Dermatology. London: Mosby, 1995:125–34.

JEAN L. BOLOGNIA
JOSEPH L. JORIZZO
JULIE V. SCHAFFER

VOLUME TWO

Third Edition

Dermatology

SECTION EDITORS

Jeffrey P. Callen
Lorenzo Cerroni
Warren R. Heymann
George J. Hruza
Anthony J. Mancini
James W. Patterson
Martin Röcken
Thomas Schwarz

ELSEVIER
SAUNDERS

ExpertConsult.com Expert Consult Premium Edition

Third Edition

Dermatology

Edited by

Jean L Bolognia MD
Professor of Dermatology
Department of Dermatology
Yale Medical School
New Haven, CT, USA

Joseph L Jorizzo MD
Professor and Former
(Founding) Chair
Department of Dermatology
Wake Forest University School of Medicine
Winston-Salem, NC;
Adjunct Professor
Department of Dermatology
Weill Cornell Medical College
New York, NY, USA

Julie V Schaffer MD
Associate Professor of Dermatology and Pediatrics
Director of Pediatric Dermatology
Department of Dermatology
New York University School of Medicine
New York, NY, USA

Section Editors

Jeffrey P Callen MD FACP
Professor of Medicine (Dermatology)
Chief, Division of Dermatology
University of Louisville
Louisville, KY, USA

Lorenzo Cerroni MD
Associate Professor of Dermatology
Director, Research Unit Dermatopathology
Department of Dermatology
Medical University of Graz
Graz, Austria

Warren R Heymann MD
Professor of Medicine and Pediatrics
Head, Division of Dermatology
Cooper Medical School of Rowan University
Camden, NJ;
Clinical Professor of Dermatology
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, PA, USA

George J Hruza MD
Clinical Professor of Dermatology and Otolaryngology-Head and Neck Surgery
St. Louis University
St. Louis, MO;
Medical Director
Laser and Dermatologic Surgery Center
Chesterfield, MO, USA

Anthony J Mancini MD
Professor of Pediatrics and Dermatology
Northwestern University Feinberg School of Medicine;
Head, Division of Pediatric Dermatology
Children's Memorial Hospital
Chicago, IL, USA

James W Patterson MD
Professor of Pathology and Dermatology
Director of Dermatopathology
University of Virginia Health System
Charlottesville, VA, USA

Martin Röcken MD
Professor and Chairman
Department of Dermatology
Eberhard Karls University of Tübingen
Tübingen, Germany

Thomas Schwarz MD
Professor and Chairman
Department of Dermatology and Allergology
University Hospital Schleswig-Holstein
Kiel, Germany

ELSEVIER
SAUNDERS

For additional online content visit
www.expertconsult.com
Expert CONSULT

Bacterial Diseases 74

Christian R Millett, Analisa V Halpern, Annette C Reboli and Warren R Heymann

Chapter Contents

Normal skin flora 1187
Gram-positive bacteria 1187
Staphylococcal and streptococcal skin infections 1187
Clostridial skin infections 1200
Corynebacterial skin infections 1200
Other gram-positive skin infections 1203
Gram-negative bacteria 1204
Neisseria meningitidis 1204
Pseudomonas aeruginosa 1206
Bartonella 1207
Other Gram-negative skin infections 1210
Ehrlichiosis and anaplasmosis 1214
Spirochetes 1214
Borrelia burgdorferi 1214
Non-venereal (endemic) treponematoses 1216
Leptospirosis 1217
Bacteria previously classified as fungi 1217

Key features

- Roughly 20% of outpatient dermatology visits are for bacterial skin infections
- Staphylococci and streptococci cause the majority of bacterial skin conditions, which range from common infections (e.g. impetigo) to rare multisystem disorders (e.g. toxic shock syndrome)
- An increase in the prevalence of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) is a growing concern
- Various systemic diseases and immunodeficiency states predispose patients to bacterial skin infections that can be severe and refractory to treatment

NORMAL SKIN FLORA

The cutaneous flora (microbiome) is relatively simple compared to the diverse communities of microorganisms that inhabit the mouth, digestive tract, and vagina. Skin flora is composed of aerobic cocci, aerobic and anaerobic coryneform bacteria, Gram-negative bacteria, and yeast. These organisms help to prevent skin infections by providing ecological competition for pathogenic microorganisms and by hydrolyzing lipids of sebum to produce free fatty acids, which are toxic to many bacteria. The ecology of particular areas of the skin is determined by the availability of moisture, presence of sebaceous lipids, and gaseous environment. Table 74.1 lists the organisms that commonly inhabit normal skin[1].

NORMAL SKIN FLORA

Class	Organisms	Location on body
Aerobic cocci	*Staphylococcus aureus**, *S. saprophyticus, S. epidermidis*†, *Micrococcus luteus, M. roseus, M. varians*	All body sites, especially intertriginous areas
Aerobic coryneform bacteria	*Corynebacterium minutissimum, C. lipophilicus, C. xerosis, C. jeikeium, Brevibacterium epidermidis*	Intertriginous areas (e.g. axillae, groin, toe webs)
Anaerobic coryneform bacteria	*Propionibacterium acnes, P. granulosum, P. avidum*	Sebaceous glands and follicles
Gram-negative bacteria	*Acinetobacter* spp.	Axillae, perineum, antecubital fossae
Yeast	*Malassezia furfur*	Skin rich in sebaceous glands (e.g. scalp)

*Whether or not *S. aureus* is a true resident or contaminant of the skin is a matter of controversy. However, it is commonly found in the anterior nares (35% of population), perineum (20%), and axillae and toe webs (5–10%).
†*S. epidermidis* is the most common coccus on human skin.

Table 74.1 Normal skin flora. *Adapted from Leyden J. Pathophysiology of certain bacterial diseases. In: Soter N, Baden H (eds). Pathophysiology of Dermatologic Diseases. New York: McGraw-Hill, 1991:427–51.*

GRAM-POSITIVE BACTERIA

STAPHYLOCOCCAL AND STREPTOCOCCAL SKIN INFECTIONS

Impetigo

Synonyms: ■ Bullous impetigo: pemphigus neonatorum ■ Impetigo contagiosa ■ Non-bullous impetigo: crusted impetigo ■ Staphylococcal impetigo ■ Streptococcal impetigo

Key features

- *Staphylococcus aureus* and, to a lesser degree, group A β-hemolytic *Streptococcus* spp. are the major causes of impetigo
- Represents the most common bacterial skin infection in children
- Nasal carriers of *S. aureus* are at particular risk of developing impetigo
- Treatment decisions should consider resistance patterns of *S. aureus*

Introduction

Impetigo is a common, contagious, superficial skin infection that can present in non-bullous and bullous forms (Fig. 74.1; see Fig. 34.2A). The most common pathogen in both non-bullous and bullous impetigo is *Staphylococcus aureus*, and group A β-hemolytic *Streptococcus*

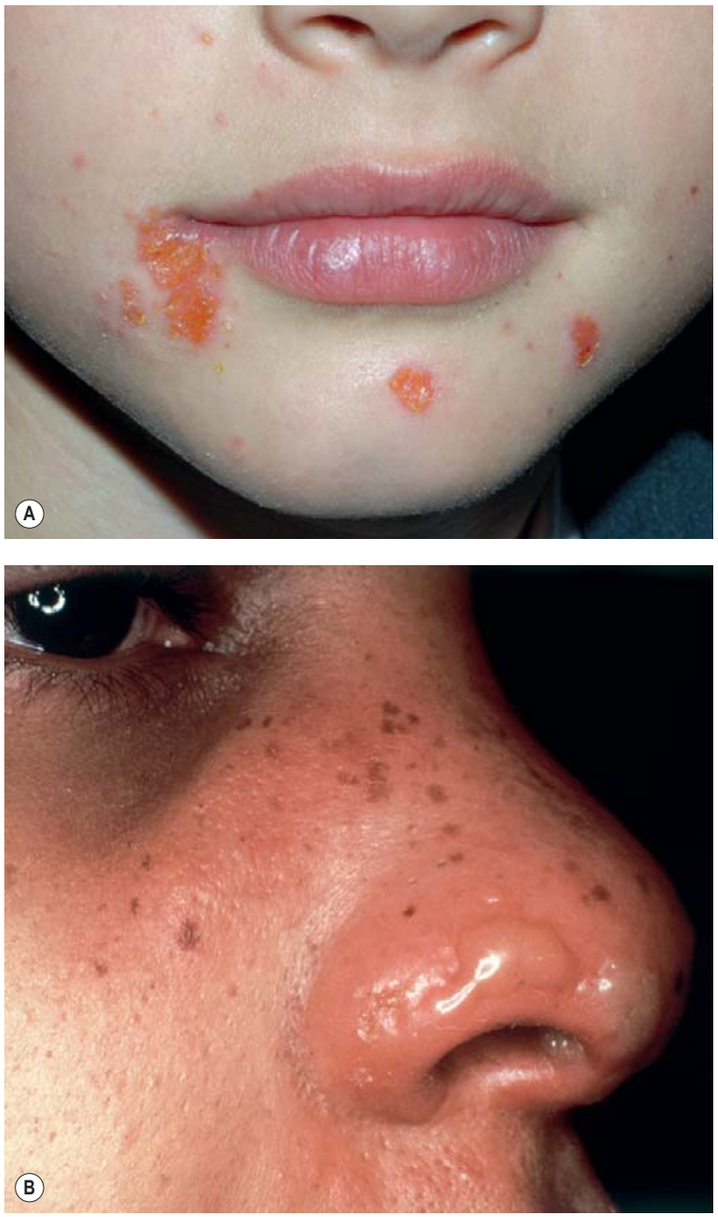


Fig. 74.1 Staphylococcal impetigo. A Honey-colored crusts on the chin of a child with non-bullous impetigo. **B** Superficial bullae and dry erosion on the nose due to bullous impetigo. *A, Courtesy, Julie V Schaffer, MD.*

(*Streptococcus pyogenes*) represents another important cause of non-bullous impetigo. Overall, non-bullous impetigo accounts for approximately 70% of cases. Table 74.2 compares the clinical characteristics and complications of bullous and non-bullous impetigo.

Epidemiology

Impetigo frequently occurs in children (especially those <6 years of age), and worldwide it represents the most common bacterial skin infection in this group. Adults most commonly acquire impetigo through contact with infected children. Impetigo is extremely contagious, spreading rapidly via direct person-to-person contact or through fomites. In temperate climates, peak incidence is in the summer months. Predisposing factors include a warm ambient temperature, high humidity, poor hygiene, an atopic diathesis, skin trauma, and participation in contact sports (e.g. wrestling, football). Nasal, pharyngeal, axillary and/or perineal colonization with *S. aureus* imparts an increased risk for developing impetigo and other staphylococcal infections.

Pathogenesis

Non-bullous impetigo is usually caused by *S. aureus* or (less often in temperate climates) *Str. pyogenes*. Infection typically occurs at sites of scratching (e.g. insect bites, atopic dermatitis), minor trauma (e.g. an abrasion, laceration or burn) or other skin infections (e.g. varicella). Disruption of the skin barrier allows the bacteria to adhere, invade and establish infection.

Bullous impetigo results from the local production of exfoliative toxins (ETA, ETB) by phage group II *S. aureus* at site(s) of cutaneous infection; systemic elaboration of the same toxins is the cause of staphylococcal scalded skin syndrome (SSSS; see below). In both diseases, blister formation is mediated by exfoliative toxin binding to the desmosomal protein desmoglein 1 and cleaving its extracellular domain, thus leading to acantholysis within the epidermal granular layer. *S. aureus* can be cultured from fluid within the blisters of bullous impetigo, but not those of SSSS. Bullous impetigo is more likely to develop on clinically intact skin (especially in intertriginous sites) than is non-bullous impetigo.

Clinical features

The clinical features of impetigo are outlined in Table 74.2[2,3].

Pathology

In *non-bullous impetigo*, small neutrophilic vesiculopustules are present within the epidermis. Spongiosis frequently underlies the pustule. The upper dermis contains an intense infiltrate of neutrophils and lymphocytes. Gram-positive cocci are present in the lesions.

In *bullous impetigo*, there is cleavage of the upper epidermis, typically within the granular layer. Acantholysis mimicking pemphigus foliaceus may be observed. Relatively few inflammatory cells are present within the blister cavity, and a neutrophilic infiltrate is often found in the upper dermis. Gram-positive cocci may be evident.

Diagnosis and differential diagnosis

The diagnosis of impetigo is usually made clinically; exudate from beneath the crust or fluid from intact bullae can be sent for culture to confirm the diagnosis and (especially for more extensive cases requiring systemic therapy) determine susceptibility to antibiotics. Leukocytosis is seen in approximately half of patients with impetigo. The differential diagnosis of non-bullous and bullous impetigo is presented in Table 74.3.

Treatment

For healthy patients with a few superficial lesions and no systemic symptoms, either mupirocin 2% ointment or retapamulin 1% ointment can be prescribed. These topical medications are often equally (if not more) effective than oral antibiotics for limited disease. Treatment should also include cleansing the affected area and removing crusts (which can be facilitated by wet dressings).

Table 74.4 outlines treatment options for impetigo. The extent of skin involvement, the presence of complications (e.g. cellulitis, lymphangitis), comorbid conditions (e.g. atopic dermatitis, varicella), the patient's immune status, and local drug-resistance patterns (e.g. the prevalence of community-associated methicillin-resistant *S. aureus* [CA-MRSA]) should be taken into account when deciding whether topical, oral or intravenous therapy is most appropriate[4,5]. The efficacy of antimicrobial treatment of streptococcal impetigo in preventing acute post-streptococcal glomerulonephritis is not known; in contrast to pharyngitis, a link between streptococcal pyoderma and acute rheumatic fever has not been established. Methods for "decolonizing" the nares and skin of patients with recurrent staphylococcal impetigo are discussed in the folliculitis section below.

Bacterial Folliculitis

Introduction

Bacterial folliculitis is a superficial or deep infection of the hair follicle. A furuncle develops when the entire follicle and surrounding tissue are involved (see below)[6].

Epidemiology and pathogenesis

S. aureus is the most common infectious cause of folliculitis (see Ch. 38). Gram-negative folliculitis occasionally develops in acne vulgaris patients treated with long courses of oral antibiotics. In addition, pseudomonal folliculitis can result from the use of improperly chlorinated

CHARACTERISTIC FEATURES OF BULLOUS AND NON-BULLOUS IMPETIGO		
	Non-bullous impetigo	**Bullous impetigo**
Epidemiology	• ~70% of all cases of impetigo • Children most often affected	• Less common • Often occurs in the neonatal period (see Ch. 34), but children also affected
Clinical lesions	• Early: single 2–4 mm erythematous macule that rapidly evolves into a short-lived vesicle or pustule • Late: superficial erosion with a typical "honey-colored" yellow crust and rapid direct extension of infection to surrounding skin	• Early: small vesicles enlarge into 1–2 cm superficial bullae • Late: flaccid, transparent bullae measuring up to 5 cm in diameter; after rupture there is a collarette of scale, but no thick crust; usually little surrounding erythema
Distribution	• Face (around the nose and mouth) and extremities	• Face, trunk, buttocks, perineum, axillae and extremities
Associated findings	• Mild lymphadenopathy may be present	• Usually no systemic symptoms but can be associated with weakness, fever and diarrhea
Clinical course	• Usually a benign, self-limited process • Usually resolves within 2 weeks without scarring if untreated	• Usually resolves in 3–6 weeks without scarring if not treated
Complications	• In 5% of cases, non-bullous impetigo caused by *S. pyogenes* (serotypes 1, 4, 12, 25 and 49) results in acute post-streptococcal glomerulonephritis (APSG)* • Risk of APSG is not altered by treatment with antibiotics • Impetigo has not been linked to a risk of rheumatic fever	• In infants/young children and adults with immunodeficiency or renal failure, exfoliative toxin may disseminate and cause staphylococcal scalded skin syndrome
*Associated with anti-DNase B and antistreptolysin O (ASO) antibodies.		

Table 74.2 Characteristic features of bullous and non-bullous impetigo[2,3].

DIFFERENTIAL DIAGNOSIS OF NON-BULLOUS AND BULLOUS IMPETIGO		
	Most common	**Less common**
Non-bullous impetigo	Insect bites Eczematous dermatoses Herpes simplex viral infection Candidiasis	Inflammatory tinea corporis/faciei Varicella Scabies Pediculosis Pemphigus foliaceus
Bullous impetigo	Bullous insect bite reactions Thermal burns Herpes simplex viral infection	Autoimmune bullous dermatoses (e.g. linear IgA bullous dermatosis, bullous pemphigoid) Bullous erythema multiforme Stevens–Johnson syndrome Bullous mastocytosis

Table 74.3 Differential diagnosis of non-bullous and bullous impetigo.

TREATMENT OPTIONS FOR IMPETIGO AND ECTHYMA*				
	Uncomplicated		**Complicated**	
	First-line	**Second-line**	**First-line**	**Second-line**
Impetigo	Mupirocin 2% ointment - or - retapamulin 1% ointment - or - fusidic acid 2% cream†	β-lactamase-resistant penicillin - or - first-generation cephalosporin - or - clindamycin - or - macrolide‡	IV ceftriaxone (daily dosing)	IV ampicillin/sulbactam - or - IV cefuroxime
Ecthyma	β-lactamase-resistant penicillin (e.g. dicloxacillin) - or - first-generation cephalosporin (e.g. cephalexin)			
*See Table 74.5 for treatment recommendations for community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA). †Not available in the US; increasing rates of *S. aureus* resistance have been reported. ‡In communities with low levels of resistance.				

Table 74.4 Treatment options for impetigo and ecthyma. See Chapter 127 for specific antibiotics within each class.

hot tubs and whirlpools. Predisposing factors for staphylococcal folliculitis include occlusion, maceration and hyperhydration of the skin; shaving, plucking or waxing hair; use of topical corticosteroids; hot and humid weather; atopic dermatitis; and diabetes mellitus.

Clinical features

Staphylococcal folliculitis most frequently involves the face (especially the beard area), scalp, chest, back, axillae and buttocks (see Ch. 38). The appearance depends on the depth of follicular involvement. Superficial folliculitis (Bockhart's impetigo) presents with small (1–4 mm) pustules or crusted papules on an erythematous base. The lesions are frequently clustered and heal without scarring. Sycosis barbae, a type of deep folliculitis, appears as large erythematous papules, often with a central pustule and sometimes coalescing to form plaques studded with pustules and crusts. Bacterial folliculitis may be pruritic or (especially with deeper involvement) tender[7].

Diagnosis and differential diagnosis

The diagnosis of bacterial folliculitis is usually made based on clinical inspection. Gram staining and bacterial cultures can help to identify the causative organisms, which is especially useful in severe, recurrent or treatment-resistant cases. The differential diagnosis includes other forms of folliculitis (see Ch. 38) as well as acne vulgaris, rosacea, chloracne, pseudofolliculitis barbae, and keratosis pilaris.

Treatment

Superficial staphylococcal folliculitis can be treated with antibacterial washes that contain chlorhexidine or triclosan. Topical antibiotics such as mupirocin or clindamycin may also be used for 7–10 days to treat localized lesions. When staphylococcal folliculitis is widespread or recurrent, oral β-lactam antibiotics (e.g. a β-lactamase-resistant penicillin or first-generation cephalosporin), tetracyclines or (depending on local resistance patterns) macrolides can be prescribed. Although pseudomonal folliculitis is often self-limited, ciprofloxacin is an option for more severe cases.

In patients with recurrent staphylococcal folliculitis and their close contacts, application of mupirocin 2% ointment twice daily to the nares for 5–10 days can be used to eradicate nasal carriage of *S. aureus*; methods to decolonize the skin (e.g. axillae, perineum/groin, submammary area) include topical mupirocin, washes containing chlorhexidine or triclosan, and dilute sodium hypochlorite baths (e.g. 0.5 cup household bleach [6% sodium hypochlorite] in a full standard bathtub). Elimination of bacterial contamination of potential fomites such as keyboards, toys and sports equipment (e.g. shoulder pads, wrestling mats) should also be considered (e.g. using ethanol- or sodium hypochlorite-based disinfectants).

Abscesses, Furuncles and Carbuncles

Introduction

Abscesses and furuncles (boils) are collections of pus that are "walled-off" from the surrounding tissues. Whereas an abscess can occur anywhere in or on the body, a furuncle, by definition, involves a hair follicle. A contiguous collection of furuncles is termed a carbuncle.

Epidemiology and pathogenesis

Furuncles most often occur in adolescents and young adults. *S. aureus* is usually the causative organism, although anaerobic bacteria are occasionally cultured from recurrent furuncles in the anogenital region. Predisposing factors include chronic *S. aureus* carriage, diabetes mellitus, obesity, poor hygiene, and immunodeficiency states (e.g. chronic granulomatous disease, hyperimmunoglobulin E syndrome)[8].

Clinical features

Abscesses are localized collections of pus that are usually inflamed. They can arise in any cutaneous site. Furuncles are acute, inflammatory abscesses of hair follicles and surrounding tissue, and, as such, occur only in hair-bearing skin. The most common locations are the face, neck, axillae, buttocks, thighs and perineum. Sites prone to friction or minor trauma, such as the area under a belt, are also susceptible. Furuncles usually begin as firm, tender, red nodules that progressively enlarge and become painful and fluctuant (Fig. 74.2); rupture results in decreased pain. Systemic symptoms are usually absent, although regional lymphadenopathy may develop. Furunculosis (multiple or recurrent furuncles) can be associated with chronic *S. aureus* carriage.

Carbuncles are collections of furuncles that extend deep into the subcutaneous tissue. The surface usually displays multiple draining sinus tracts and occasionally ulcerates. They usually occur in areas with thicker skin (e.g. nape of neck, back, thigh). Systemic symptoms are usually present. Carbuncles are slow to heal and lead to scarring.

Pathology

Biopsy specimens reveal a dense neutrophilic infiltrate in the subcutaneous tissue. Furuncles are characterized by an acute, suppurative reaction involving the follicle below the infundibulum, as well as perifollicular necrosis with fibrinoid debris.

Fig. 74.2 Furuncle secondary to methicillin-resistant *Staphylococcus aureus*. Fluctuant erythematous nodule with a central pustule. *Courtesy, Julie V Schaffer, MD.*

Diagnosis and differential diagnosis

Diagnosis is based primarily on clinical appearance. Gram stains and cultures from the lesion support the diagnosis. Extensive furuncles and carbuncles can be associated with leukocytosis. A ruptured epidermoid or pilar cyst, hidradenitis suppurativa ("acne inversa") and cystic acne should be considered in the differential diagnosis.

Treatment

For simple furuncles, warm compresses may promote maturation, drainage and resolution. Larger or deeper fluctuant lesions typically require incision and drainage. Systemic antibiotic therapy is recommended (in conjunction with incision and drainage if possible) in the following situations: (1) furuncles around the nose, in the external auditory canal or in other locations where drainage is difficult (e.g. elsewhere on the face, hands, genitalia); (2) severe or extensive disease (e.g. multiple sites); (3) lesions with surrounding cellulitis/phlebitis or associated with signs/symptoms of systemic illness; (4) lesions not responding to local care; and (5) patients with concerning comorbidities or immunosuppression[9,10]. Given the high proportion of furuncles that are caused by MRSA, empiric coverage with antibiotics such as doxycycline, trimethoprim–sulfamethoxazole (TMP-SMX) or (depending on local resistance patterns) clindamycin should be considered (see below). Patients with recurrent furunculosis may benefit from eradication of *S. aureus* from the nares, axilla and perineum (see Bacterial Folliculitis above).

Methicillin-Resistant *Staphylococcus aureus*

Introduction

Methicillin resistance was first noted in isolates of *S. aureus* in 1961. Although initially associated with nosocomial infection (healthcare-associated [HA]-MRSA), in recent years CA-MRSA has become a growing problem among young, otherwise healthy individuals[11]. Although there is considerable regional variation, overall, MRSA represents the most common cause of purulent skin and soft tissue infections presenting to emergency departments in the US[12,13].

Clinical features

Furunculosis is the most frequent manifestation of CA-MRSA infection (see Fig. 74.2). These lesions can evolve into large abscesses, cellulitis or necrotic plaques (which may be misdiagnosed as spider bites). Less often, impetigo (bullous or non-bullous), SSSS and folliculitis are seen, and life-threatening complications such as septic shock, toxic shock syndrome and necrotizing fasciitis occasionally develop.

Pathogenesis

The cause of methicillin resistance is the production of an altered penicillin-binding protein (PBP), called PBP2a, with decreased affinity

for β-lactam antibiotics (which interfere with bacterial cell wall synthesis by binding to PBPs). PBP2a is the protein product of the *mecA* gene, which is located within a specific mobile genetic element called the staphylococcal cassette chromosome *mec* (SCC*mec*). Acquisition of different SCC*mec* elements by *S. aureus* led to the emergence of HA-MRSA (usually SCC*mec* types I–III) and CA-MRSA (usually SCC*mec* types IV and V) strains; methicillin-resistant coagulase-negative staphylococci are thought to represent a reservoir of SCC*mec* for CA-MRSA. Many CA-MRSA strains also encode virulence factors such as Panton-Valentine leukocidin (PVL), a pore-forming cytotoxin that can cause destruction of leukocytes and tissue necrosis.

As a reflection of their distinct SCC*mec* elements, CA-MRSA and HA-MRSA have different patterns of antibiotic resistance. CA-MRSA is typically susceptible to multiple non-β-lactam antibiotics, whereas HA-MRSA is usually resistant to several antimicrobial classes, including aminoglycosides, macrolides and clindamycin. However, some isolates of the USA300 clone, which currently causes most CA-MRSA skin infections in the US[13], have developed resistance to macrolides, clindamycin, tetracycline (less often doxycycline), quinolones and mupirocin.

Resistance to macrolides (e.g. erythromycin) in staphylococci may result from: (1) active drug efflux via a pump encoded by the *msrA/msrB* gene (frequent in MRSA isolates); or (2) modification of the bacterial ribosome by the erythromycin ribosomal methylase encoded by *erm* genes, which produces cross-resistance to clindamycin[14]. Erythromycin stimulates expression of *erm*, which leads to clinically relevant resistance. If initial sensitivity testing shows resistance to erythromycin and susceptibility to clindamycin, resistance to clindamycin will still develop if *erm* is present, since bacterial variants with constitutive expression of this gene commonly arise and are selected for during clindamycin therapy. This "inducible resistance" can be assessed with the D-test (double-disk diffusion) (Fig. 74.3).

Diagnosis and treatment

When an *S. aureus* infection is suspected, culture and susceptibility testing should be performed, whenever feasible, to guide antibiotic selection. Prior to obtaining these results, empiric antibiotic therapy (Table 74.5) can be chosen based on the prevalence of MRSA and resistance patterns in a given community as well as the severity of the infection[10]. Vancomycin should be considered for patients with severe infections, especially in geographic regions where CA-MRSA is prevalent and in individuals with a history of MRSA colonization or intravenous drug use[15].

Blistering Distal Dactylitis

Blistering distal dactylitis is a localized infection of the volar fat pad of a finger or, less often, a toe, with occasional involvement of the nail fold or more proximal portion of the digit. Darkening of the skin is often observed for several days to a week before blister formation. The infection most commonly occurs in children aged 2–16 years.

Group A *Streptococcus* spp. or *S. aureus* are usually the causative organisms. Inoculation may follow local skin trauma or autoinoculation from nose picking[16]. The differential diagnosis includes herpetic whitlow, a thermal or chemical burn, acute paronychia, bullous impetigo and frictional bullae.

Drainage and a 10-day course of an oral antistaphylococcal antibiotic are recommended. Although topical therapy with mupirocin has been described, systemic therapy can prevent development of new sites of infection as well as local extension.

Ecthyma

Ecthyma is a deep form of non-bullous impetigo characterized by extension into the dermis to produce a shallow ulcer (Fig. 74.4). It can be caused by a primary infection with *Str. pyogenes* or streptococcal superinfection of a pre-existing ulceration or excoriated insect bite. Tables 74.4 and 74.6 summarize the clinical aspects and treatment of ecthyma[17].

Staphylococcal Scalded Skin Syndrome

Synonyms: ■ Ritter's disease ■ Pemphigus neonatorum

Introduction

Staphylococcal scalded skin syndrome (SSSS) is caused by hematogenous dissemination of the same exfoliative toxins that lead to bullous

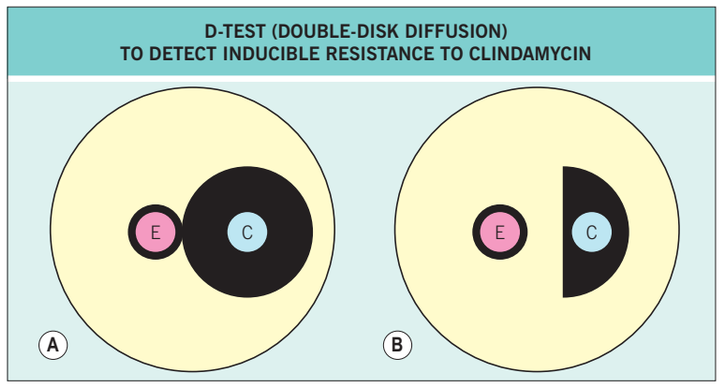


Fig. 74.3 D-test (double-disk diffusion) to detect inducible resistance to clindamycin. Erythromycin (E) and clindamycin (C) disks are placed 15–17 mm apart on an agar plate inoculated with the organism. Following incubation, the zones of inhibition around the disks are evaluated. If the zone around the clindamycin disk is circular in shape and of sufficient size (**A**), the organism is negative for inducible resistance. However, if the portion of the zone adjacent to the erythromycin disk is "flattened", producing a "D" shape (**B**), the organism is positive for inducible resistance to clindamycin.

EMPIRIC THERAPY FOR SKIN INFECTIONS SUSPECTED TO BE CAUSED BY COMMUNITY-ASSOCIATED METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* (CA-MRSA)

Minor infections*		Severe infections		
First-line	**Second-line**	**First-line**	**Second-line**	**Third-line**
Trimethoprim–sulfamethoxazole† Minocycline† Doxycycline† Clindamycin	Linezolid	Vancomycin	Linezolid Daptomycin Telavancin	Quinupristin-dalfopristin Tigecycline

*E.g. furuncles/abscesses (if antibiotic treatment is indicated; see text), purulent cellulitis, and infections that failed to respond clinically to treatment with an antistaphylococcal β-lactam; for non-purulent cellulitis or when oral therapy is needed for impetigo (see Table 74.4), first-line treatment is a β-lactamase-resistant penicillin (e.g. dicloxacillin) or a first-generation cephalosporin (e.g. cephalexin, cefadroxil).

†Do not provide coverage of group A streptococci; if coverage of the latter and CA-MRSA is desired, can be combined with a β-lactam.

Table 74.5 Empiric therapy for skin infections suspected to be caused by community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA). If present, wound exudate should be sent for culture/sensitivity prior to beginning therapy. Quinolones and macrolides are not optimal for treatment of CA-MRSA because resistance is common and may develop rapidly. *Based on Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children: executive summary. Clin Infect Dis. 2011;52:285–92.*

Fig. 74.4 Ecthyma. Ulceration with hemorrhagic crust on the wrist due to infection with group A streptococci. *Courtesy, Kalman Watsky, MD.*

CLINICAL FEATURES OF ECTHYMA	
Clinical findings	• Fewer than 10 lesions are typically seen, most commonly on the lower extremities • An initial vesiculopustule enlarges (0.5–3 cm in diameter) over the course of several days, and develops a hemorrhagic crust • The ulcer has a "punched-out" appearance and a purulent, necrotic base • Lesions are slow to heal and produce scarring
Risk factors	• Young age (children), lymphedematous limbs, poor hygiene, neglect (including the elderly), immunosuppression, scratching (e.g. of insect bites), trauma
Complications	• Lesions are often contaminated with staphylococci • Systemic symptoms and bacteremia are rarely seen • Cellulitis and osteomyelitis are extremely infrequent
Diagnosis	• Clinical appearance • Culture of moist, purulent base; skin biopsy with deep-tissue Gram stain and culture occasionally required
Differential diagnosis	• Ecthyma gangrenosum • Ulcers due to vasculitis, vasculopathies, other causes (see Ch. 105)

Table 74.6 Clinical features of ecthyma.

Fig. 74.5 Staphylococcal scalded skin syndrome. **A** Diffuse erythema with an early superficial erosion in the antecubital fossa. **B** More extensive involvement on the neck with a wrinkled appearance of the erythematous skin in addition to peeling and multiple erosions. *Courtesy, Julie V Schaffer, MD.*

impetigo when produced locally. Cleavage of the epidermis through the granular layer results in the formation of tender, flaccid bullae[18].

Epidemiology

SSSS is primarily a disease of infants and young children, who have decreased renal toxin clearance (especially neonates) and/or a lack of toxin-neutralizing antibodies. Occasionally, adults with chronic renal insufficiency or immune suppression are affected. Outbreaks occurring in neonatal nurseries are usually secondary to asymptomatic carriage of a toxigenic strain of *S. aureus* by healthcare workers or parents. A male predominance exists (2:1 male:female ratio in sporadic cases, 4:1 in epidemics)[19].

Pathogenesis

Most cases of SSSS are caused by phage group II strains (e.g. types 55, 71) of *S. aureus* (which can be methicillin-sensitive or resistant) that produce exfoliative (also know as epidermolytic) toxins (ETs). ETA (chromosomally encoded) and ETB (plasmid encoded) are serine proteases that bind and cleave desmoglein 1 (Dsg1). This causes splitting of the desmosomes, which leads to disruption of the epidermal granular layer and bulla formation. Desmoglein 1 is targeted by autoantibodies in pemphigus foliaceus, which has identical histological features to SSSS.

In contrast to bullous impetigo, where the effects of the ETs are limited to the site(s) of infection, in SSSS the toxin diffuses from a focus of infection and (in the absence of specific antitoxin antibody) spreads hematogenously to produce widespread effects. In children, the infectious focus is usually in the nasopharynx or conjunctivae, whereas staphylococcal pneumonia or bacteremia may be present in adults[20].

Clinical features

There is often a prodrome of malaise, fever, irritability and severe tenderness of the skin. The patient may have purulent rhinorrhea or conjunctivitis as a manifestation of the underlying staphylococcal infection. Erythema typically first appears on the head (accompanied by variable facial edema) and in intertriginous sites, often with generalization within 48 hours. The skin subsequently develops a wrinkled appearance owing to the formation of flaccid, sterile bullae within the superficial epidermis (Fig. 74.5). The Nikolsky sign is positive. Classically, the flexural areas are the first to exfoliate, leaving behind moist skin and thin, varnish-like crusting. Patients demonstrate characteristic periorificial (e.g. perioral, periocular) crusting and radial fissuring (see Figs 34.14 & 81.17). Intraoral lesions do not occur.

COMPARISON OF TOXIC EPIDERMAL NECROLYSIS AND STAPHYLOCOCCAL SCALDED SKIN SYNDROME		
	TEN	**SSSS**
Cause	Usually drug-induced	Infection with toxin-producing *S. aureus*
Age	Primarily adults	Primarily infants and young children
Histology	Dermal–epidermal separation with epidermal necrosis; dermis has a variable inflammatory infiltrate	Granular layer split in epidermis; dermis lacks inflammatory infiltrate
Distribution of rash	Areas of sparing often present	Generalized with flexural accentuation
Mucous membranes	Involved, erosions	Uninvolved
Nikolsky's sign	In some areas, difficult to elicit	Present in seemingly uninvolved skin
Face	Vermilion lip erosions and crusting	Perioral and periocular crusting and radial fissuring with mild facial swelling
Treatment	IVIg, corticosteroids (controversial) and supportive care (similar to a burn victim)	Antibiotics (β-lactamase-resistant) and supportive care

Table 74.7 Comparison of toxic epidermal necrolysis (TEN) and staphylococcal scalded skin syndrome (SSSS). Also see Fig. 81.17. *Adapted from Habif T. Clinical Dermatology: A Color Guide to Diagnosis and Therapy. New York: Mosby-Year Book, 1996:256–7, 570–4.*

Scaling and desquamation continue for the next 3–5 days, followed by re-epithelialization without scarring. With proper treatment, SSSS resolves in 1–2 weeks, usually without sequelae. The mortality rate is 3% for children but >50% in adults[21].

Pathology

Histologic examination shows a sharply demarcated zone of cleavage at or below the stratum granulosum. There are usually no inflammatory cells in the bullae. The upper dermis also lacks an inflammatory infiltrate, and no organisms are seen on Gram stain of biopsy specimens.

Diagnosis and differential diagnosis

SSSS is generally a clinical diagnosis. Although cultures taken from intact bullae are negative, *S. aureus* may be cultured from the conjunctiva, nasopharynx, feces or pyogenic foci on the skin. Blood cultures are almost always negative in children but may be positive in adults. The leukocyte count can be elevated or normal. Examination of frozen sections is occasionally helpful in confirming the level of the split in the bullae. Slide latex agglutination, double immunodiffusion or enzyme-linked immunosorbent assay (ELISA) tests can identify the toxins responsible for SSSS.

The differential diagnosis may include sunburn, a drug reaction, Kawasaki disease, extensive bullous impetigo, a viral exanthem, toxic shock syndrome, GVHD and pemphigus foliaceus. Differentiation from toxic epidermal necrolysis (TEN) is outlined in Table 74.7 and Fig. 81.17.

Treatment

Patients with severe, generalized forms of SSSS require hospitalization and parenteral antibiotics. Oral treatment with a β-lactamase-resistant antibiotic (e.g. dicloxacillin, cephalexin) for a minimum of 1 week is usually sufficient for milder disease. Identification and decolonization of *S. aureus* carriers (see Folliculitis section above) are important, especially in hospital-acquired cases[22].

Toxic Shock Syndrome

Introduction

Toxic shock syndrome (TSS) is an acute multisystem disease caused by a *S. aureus* exotoxin (Table 74.8).

CASE DEFINITIONS FOR THE TOXIC SHOCK SYNDROMES
TOXIC SHOCK SYNDROME
• Fever: temperature >102°F (or >38.9°C) • Rash: diffuse macular erythroderma • Desquamation: 1–2 weeks after the onset of illness (especially palms and soles) • Hypotension: systolic blood pressure <90 mmHg for adults (<5th percentile for children) • Involvement of three or more of the following organ systems: – Gastrointestinal – Muscular – Central nervous – Renal – Hepatic – Mucous membranes (erythema) – Hematologic (platelets <100 000/mm^3) • Negative results for the following tests (if done): – Blood and cerebrospinal fluid cultures (blood culture may be positive for *Staphylococcus aureus*) – Serologic tests for Rocky Mountain spotted fever, leptospirosis, measles
STREPTOCOCCAL TOXIC SHOCK SYNDROME
• Isolation of group A streptococci from a normally sterile site* (e.g. blood, cerebrospinal fluid, tissue biopsy, surgical wound) or • Isolation of group A streptococci from a non-sterile site† (e.g. throat, sputum, vagina, superficial skin lesion) and • Hypotension: systolic blood pressure <90 mmHg for adults (<5th percentile for children) and • Two or more of the following signs: – Renal impairment – Coagulopathy (platelets <100 000/mm^3 or disseminated intravascular coagulation) – Liver impairment – Acute respiratory distress syndrome – Generalized erythematous macular rash ± desquamation – Soft tissue necrosis (e.g. necrotizing fasciitis, myositis, gangrene)
*Defined as a definite case. †Defined as a probable case, excluding any other possible etiology.

Table 74.8 Case definitions for the toxic shock syndromes. See www.cdc.gov/osels/ph_surveillance/nndss/print/toxic_shock_syndrome_current.htm for details on the current case definitions.

Epidemiology and pathogenesis

In the early 1980s, there was an outbreak of TSS in young women using highly absorbent tampons ("menstrual" TSS). The incidence of menstrual TSS then declined substantially following changes in tampon manufacturing and use, and in a recent population-based study it accounted for approximately half of TSS cases[23a]. TSS can also occur in patients who have undergone surgical procedures. In addition, it may develop in association with cutaneous pyodermas, postpartum infections, abscesses, burns, and infections associated with nasal packing or insulin pump infusion sites. Non-menstrual TSS affects both sexes equally.

TSS is due to infection or colonization with strains of *S. aureus* that produce toxic shock syndrome toxin-1 (TSST-1). The absence of

THE TOXIC SHOCK SYNDROMES		
	Staphylococcal	**Streptococcal**
Typical patient	Young (15–35 years) and healthy	Young (20–50 years) and healthy
Diffuse macular erythroderma	Very common	Less common
Vesicles and bullae	Rare	Uncommon (5%)
Localized extremity pain	Rare	Common
Soft tissue infection	Rare	Common
Hypotension	100%	100%
Renal impairment	Common	Common
Predisposing factors	Surgical packing, surgical meshes, abscesses, contraceptive sponge, tampon	Lacerations, bites, bruises, varicella
Positive blood cultures	<15%	>50%
Mortality	<3%	30–60%

Table 74.9 The toxic shock syndromes (staphylococcal versus streptococcal).

antibodies against TSST-1 represents a risk factor for the development of TSS. This toxin is thought to act as a "superantigen" that binds to major histocompatibility complex (MHC) class II molecules of antigen-presenting cells (APCs) and the Vβ region of T-cell receptors in a non-antigen-specific manner, which leads to massive release of cytokines and chemokines as well as clonal T-cell expansion (see section on Streptococcal TSS)[23]. Of note, the *neonatal TSS-like exanthematous disease* (see Ch. 10) occurs during the first week of life due to colonization with TSST-1-producing *S. aureus* (usually methicillin-resistant) and has a relatively mild course due to the immature, relatively anergic state of T cells in newborns.

Clinical features

TSS is characterized by the sudden onset of high fever with myalgias, vomiting, diarrhea, headache and pharyngitis. Rapid progression to hypotensive shock can occur, but the clinical spectrum ranges from relatively mild to fulminant fatal disease. The dermatologic manifestations are more extensive and predictable in staphylococcal TSS than in streptococcal TSS (Table 74.9). Patients usually develop diffuse erythema or a scarlatiniform exanthem that starts on the trunk and spreads to the extremities (Fig. 74.6). Additional findings include erythema and edema of the palms, soles and oral mucosa as well as a strawberry tongue, hyperemia of the conjunctivae, and (with disease progression) generalized non-pitting edema. Desquamation of the hands and feet occurs 1–3 weeks after the onset of symptoms.

After recovery, Beau's lines and nail shedding can be seen. In severe cases, telogen effluvium may occur. With proper treatment, the majority of patients completely recover. However, complications include decreased renal function, prolonged weakness and fatigue, protracted myalgias, vocal cord paralysis, upper extremity paresthesias, carpal tunnel syndrome, arthralgias, amenorrhea and gangrene[24].

Pathology

Biopsy specimens of the eruption show an infiltrate of neutrophils and lymphocytes in the superficial dermis. Papillary dermal edema as well as epidermal spongiosis and exocytosis may be noted. Hair follicles and eccrine sweat glands display similar findings.

Diagnosis and differential diagnosis

A high index of suspicion is required in order to make a timely diagnosis. Table 74.8 outlines the case definition of TSS. The possibility of streptococcal TSS (see Table 74.9 and below) should also be considered. TSS can have clinical overlap with Kawasaki disease, scarlet fever, SSSS, early TEN, Rocky Mountain spotted fever and leptospirosis[25].

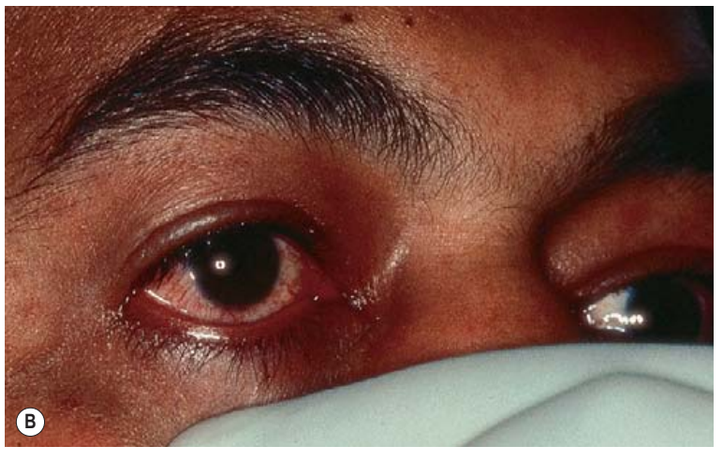


Fig. 74.6 Toxic shock syndrome due to *Staphylococcus aureus* infection. **A** Blotchy erythema is evident on the thigh. **B** Hyperemia of the conjunctiva is seen.

Treatment

Severe cases of TSS require intensive monitoring and supportive therapy. Hypotension can be treated with intravenous fluids and vasopressor agents. Foreign bodies (e.g. surgical mesh, nasal packing, tampons) should be removed and abscesses drained. Beta-lactamase-resistant antibiotics are used to eradicate the toxin-producing staphylococci; MRSA is responsible for only a small proportion of TSS cases[23a]. Some advocate using antibiotics that suppress protein (and thereby toxin) production, such as clindamycin, and administration of intravenous immunoglobulin (IVIg) may help to neutralize the toxin[26]. In severe cases of shock unresponsive to antibiotics, low-dose corticosteroids have been used[27].

Scarlet Fever

Synonym: ▪ Scarlatina

Introduction

Primarily a disease of children, scarlet fever was often fatal in the pre-antibiotic era. The erythematous exanthem and enanthem are due to toxins produced by group A β-hemolytic streptococci.

Epidemiology and pathogenesis

Scarlet fever is caused by streptococcal pyrogenic exotoxins (SPEs) types A, B and C (also referred to as erythrogenic toxins), which are produced by group A streptococci and lead to immune activation. The majority of cases occur between 1 and 10 years of age; by the age of 10 years, 80% of the population has developed anti-SPE antibodies that prevent development of the eruption. Scarlet fever usually follows tonsillitis or pharyngitis and is most common during the late fall, winter and spring in temperate climates. However, it occasionally develops as a complication of wound ("surgical scarlet fever"), post-burn, pelvic or puerperal infections[28].

Clinical features

Scarlet fever is typically preceded by the sudden onset of a sore throat, headache, malaise, chills, anorexia, nausea and high fevers. Patients, especially young children, may experience vomiting, abdominal pain and seizures. The eruption begins 12–48 hours later as blanchable erythema on the neck, chest and axillae. There is subsequent generalization (usually within 12 hours) and development of tiny superimposed papules with a sandpaper-like texture ("sunburn with goose pimples"). Pastia's lines (linear petechial streaks) are seen in the axillary, antecubital and inguinal areas. The cheeks are flushed with circumoral pallor. The throat is red and edematous, developing an exudate after 3–4 days; palatal petechiae and tender cervical adenopathy are often evident. The tongue is initially white with bright red papillae, but later becomes beefy red ("strawberry tongue"). Desquamation occurs after 7–10 days, most prominently on the hands and feet (see Fig. 74.8A&B), and can last for 2–6 weeks. Possible complications of scarlet fever and the underlying streptococcal infection include otitis, mastoiditis, sinusitis, pneumonia, myocarditis, meningitis, arthritis, hepatitis, acute glomerulonephritis and rheumatic fever[20].

Pathology

Biopsy specimens reveal engorged capillaries and dilated lymphatics, most prominent around hair follicles. Dermal edema, perivascular neutrophilic infiltrates and small areas of hemorrhage represent additional findings. Spongiosis and parakeratosis are seen during the desquamative stage.

Diagnosis and differential diagnosis

Clinical diagnosis is usually not difficult. There is almost always an elevated leukocyte count with a left shift. Eosinophilia of 10–20% is often seen after 2–3 weeks of convalescence. Hemolytic anemia can occur, and mild albuminuria and hematuria may be present early in the disease. Nasal and/or throat cultures grow group A streptococci. Detection of antistreptolysin O (ASO), antihyaluronidase, antifibrinolysin and anti-DNase B antibodies can also be useful in confirming the streptococcal infection.

The differential diagnosis of scarlet fever may include a drug eruption, a viral exanthem, toxic shock syndrome, early SSSS, Kawasaki disease and recurrent toxin-mediated perineal erythema. Infection with *Arcanobacterium haemolyticum*, a Gram-positive rod, can result in pharyngitis and a scarlatiniform exanthem in adolescents and young adults.

Treatment

As with other group A streptococcal infections, penicillin (or amoxicillin) is the drug of choice; a 10–14-day course is usually sufficient. A clinical response can be expected within 24–48 hours. Antibiotic treatment as long as 10 days after the onset of symptoms will prevent the development of rheumatic fever. In penicillin-allergic patients, a first-generation cephalosporin (if no history of an immediate-type reaction), clindamycin or a macrolide can be used (although some strains of group A streptococci are resistant to macrolides).

Streptococcal Toxic Shock Syndrome

Synonyms: ▪ Streptococcal toxic shock-like syndrome ▪ Toxic streptococcal syndrome

Introduction

Streptococcal TSS is a rapidly progressive, life-threatening illness caused by infection with toxin-producing group A streptococci.

Epidemiology and pathogenesis

Streptococcal TSS mainly affects healthy individuals between 20 and 50 years of age. A disruption of the cutaneous barrier usually serves as the portal of bacterial entry. In contrast to the occult infections that predominate in staphylococcal TSS, many cases are associated with invasive soft tissue infections (e.g. necrotizing fasciitis) with virulent (e.g. M types 1 and 3) strains of group A streptococci, and the majority of patients are bacteremic[29]. Toxins that have been implicated include SPEs A, B and C as well as the more potent streptococcal mitogenic exotoxin Z (SMEZ). Streptolysin O may also act synergistically with SPE-A.

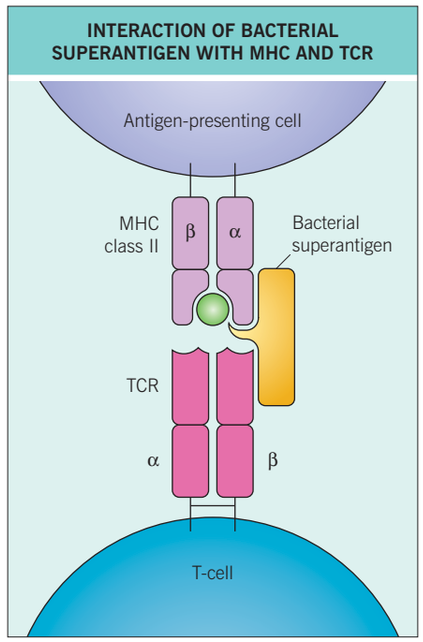


Fig. 74.7 Interaction of bacterial superantigen with the major histocompatibility complex (MHC) and the T-cell receptor (TCR). *Adapted from Janeway CA, Travers P, Walport M, Shlomchik M. Immunobiology: the Immune System in Health and Disease, 6th edn. New York: Garland Science, 2004.*

Similar to staphylococcal TSS, the clinical manifestations of streptococcal TSS result from massive cytokine release due to superantigen activity of bacterial exotoxins. Superantigens bind directly (without intracellular processing) to MHC class II molecules on APCs (outside the antigen-presenting groove) and the Vβ region of the T-cell receptor (Fig. 74.7), thereby stimulating T cells in a relatively nonspecific manner. A given superantigen–T-cell interaction may lead to the activation of 5–30% of the entire circulating T-cell population, compared to ~0.01% for conventional antigens. This leads to production of huge amounts of cytokines, especially tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1) and IL-6; there is also upregulation of Toll-like receptors (TLRs) 2 and 4, which augments deleterious effects of endotoxin from Gram-negative bacteria (e.g. those colonizing the gut) as well as streptococci, resulting in further elaboration of proinflammatory mediators. As a consequence, patients develop clinical manifestations such as fever, erythematous eruptions, vomiting, hypotension, and tissue injury in multiple organ systems[20]. The use of nonsteroidal anti-inflammatory drugs (NSAIDs), which lessen fever and other signs of infection, might delay the diagnosis and treatment of a streptococcal soft tissue infection, allowing TSS to occur[30].

Clinical features

Streptococcal TSS is defined as a group A streptococcal infection with an early onset of shock and organ failure (see Table 74.8). The most common initial symptom is severe local pain in an extremity. Although 50% of patients display signs of a soft tissue infection (e.g. swelling, tenderness, erythema), some present with only pain and no obvious physical findings. The development of a violaceous hue, bullae or necrosis points to a deeper infection, such as necrotizing fasciitis or myositis, and portends a worse outcome.

The disease may begin insidiously with nonspecific flu-like symptoms, such as fever, chills, myalgias and diarrhea. CNS symptoms (e.g. confusion, altered consciousness) are commonly seen. A generalized blanching macular erythema is observed much less often than in staphylococcal TSS, but blistering is more likely to occur. Desquamation on the hands and feet eventually appears in 20% of patients. Shock and multiorgan failure usually develop 48–72 hours after the onset of symptoms. Complications of streptococcal TSS can include renal failure, disseminated intravascular coagulation, and acute respiratory distress syndrome. The mortality rate for streptococcal TSS ranges from 30% to 60%.

Pathology

Biopsy specimens from skin lesions may show spongiosis, necrotic keratinocytes, subepidermal blister formation, and a neutrophilic and/or lymphocytic perivascular infiltrate in the dermis[31].

Diagnosis and differential diagnosis

Published criteria require isolation of group A streptococci from a sterile site for a "definite" diagnosis, combined with hypotension and clinical or laboratory abnormalities in two or more organ systems (see Table 74.8). Serum creatinine often rises early in the course, and creatine phosphokinase is elevated in the setting of necrotizing fasciitis or myonecrosis. The white blood cell count may be increased or normal with a substantial left shift[32]. Although staphylococcal and streptococcal TSSs share some common features, major differences exist (see Table 74.9).

Treatment

Most cases require intensive supportive therapy. Hypotension should be treated with aggressive intravenous fluid and vasopressors. Clindamycin inhibits the production of bacterial toxins and is a component of first-line antimicrobial treatment (together with penicillin); linezolid also blocks toxin production, and administration of IVIg to neutralize toxins may be of benefit. Early surgical intervention (e.g. drainage, debridement, fasciotomy, amputation) is crucial for necrotizing soft tissue infections and can be life-saving[33].

Erysipelas

Synonym: ■ St Anthony's fire

Introduction

Erysipelas is a superficial variant of cellulitis caused primarily by group A streptococci that affects the dermis with prominent lymphatic involvement; in contrast, classic cellulitis is centered in the deep dermis and subcutaneous tissues[34].

History

In the Middle Ages, erysipelas was thought to be caused by ingestion of the fungus *Claviceps purpurea*, which produces ergot alkaloids and is found in contaminated rye. The eponymous distinction refers to St Anthony, an Egyptian monk and healer who was believed to be the only person able to provide relief from erysipelas. An eleventh century hospital, the French House of St Anthony, had "fiery red" interior walls and was strictly devoted to the care of patients with erysipelas.

Epidemiology and pathogenesis

Erysipelas is a disease of the very young, the aged, the debilitated, and those with lymphedema or chronic cutaneous ulcers. Women outnumber men, but boys are more commonly affected than girls in the pediatric age group. There is an increased frequency during the summer months. The incidence of erysipelas has increased since the late 1980s.

Erysipelas is usually caused by group A streptococci; groups G, B, C and D streptococci are occasionally implicated. *S. aureus*, *Pneumococcus* spp., *Klebsiella pneumoniae*, *Yersinia enterocolitica* and *Haemophilus influenzae* type b can also cause an erysipelas-like infection.

Clinical features

Although erysipelas classically affects the face (Fig. 74.8C), the lower extremity is now the most common location. After an incubation period of 2 to 5 days, there is an abrupt onset of fever, chills, malaise and nausea. A few hours to a day later, a sharply marginated erythematous plaque with a ridge-like border develops and progressively enlarges. It is clearly demarcated from the surrounding skin (Fig. 74.8D), hot, tense and indurated with non-pitting edema. The affected area is painful to palpation and may burn. Regional lymphadenopathy is usually present, with or without lymphangitis. Pustules, vesicles, bullae and small areas of hemorrhagic necrosis may also form. Complications of erysipelas are uncommon and usually occur in patients with underlying disease. When the infection resolves, desquamation and postinflammatory pigmentary changes may ensue[35].

Pathology

Biopsy specimens reveal diffuse edema and a neutrophilic infiltrate in the dermis. Dilation of the lymphatics, foci of suppurative necrosis, and dermal–epidermal separation are often seen. There is no primary necrotizing vasculitis, thrombosis or leukocytoclasis.

Diagnosis and differential diagnosis

Diagnosis is based primarily on clinical findings. Laboratory evaluation shows an elevated leukocyte count with a left shift. Blood cultures are positive in only ~5% of cases. Although cultures from pustules or bullae may be helpful, the sensitivity of cultures of skin biopsy specimens is low, especially in immunocompetent hosts. Anti-DNase B and ASO titers are useful indicators of the streptococcal etiology. Direct immunofluorescence and latex agglutination tests can be used to detect streptococci within skin specimens.

The differential diagnosis of erysipelas includes other forms of cellulitis and soft tissue infections (e.g. erysipeloid, necrotizing fasciitis) as well as inflammatory causes of "pseudocellulitis" (Table 74.10).

Treatment

A 10- to 14-day course of penicillin is the treatment of choice for erysipelas caused by streptococci. Although macrolides such as erythromycin may be used in penicillin-allergic patients, some strains of *Str. pyogenes* are macrolide-resistant. Erysipelas may recur in patients with abnormal local circulation (e.g. lymphedema), and penicillin prophylaxis is occasionally required[36]. The future development of an effective vaccine against *Streptococcus* spp. could dramatically change the epidemiology of the infections caused by this microorganism[37].

Streptococcal Intertrigo

Intertrigo caused by group A streptococci is an under-recognized entity that usually affects young children. Infants are particularly vulnerable due to irritation and friction in moist, deep skin folds of the neck,

CAUSES OF "PSEUDOCELLULITIS"

Infections and bites
- Arthropod bite reactions (e.g. insect, spider)
- Erythema migrans
- Herpes zoster
- Toxin-mediated erythema (e.g. recurrent toxin-mediated perineal erythema)

Neutrophilic dermatoses
- Sweet's syndrome, neutrophilic panniculitis
- Familial Mediterranean fever, other periodic fever syndromes

Drug reactions
- Fixed drug eruptions (especially non-pigmenting)
- Vaccine/injection site reactions
- Toxic erythema of chemotherapy (e.g. due to gemcitabine)

Other inflammatory disorders
- Allergic contact dermatitis (including airborne and dermal)
- Phytophotodermatitis
- Well's syndrome
- Panniculitis, e.g. lipodermatosclerosis, erythema nodosum
- Thrombophlebitis
- Angioedema
- Interstitial granulomatous dermatitis, inflammatory granuloma annulare
- Inflammatory morphea

Metabolic disorders
- Gout

Malignancy
- Erysipeloid skin metastases (especially breast carcinoma)

Table 74.10 Causes of "pseudocellulitis".

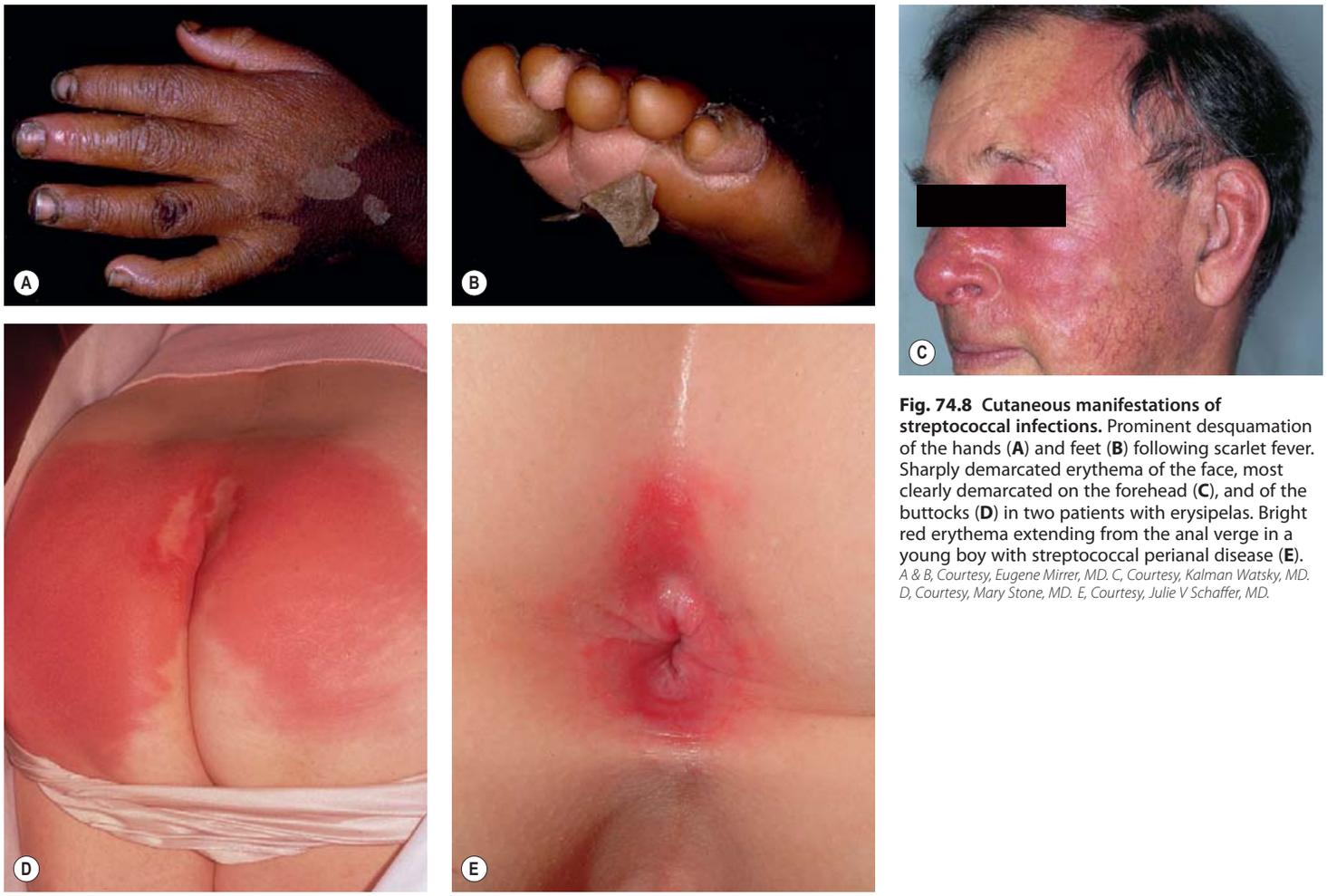


Fig. 74.8 Cutaneous manifestations of streptococcal infections. Prominent desquamation of the hands (**A**) and feet (**B**) following scarlet fever. Sharply demarcated erythema of the face, most clearly demarcated on the forehead (**C**), and of the buttocks (**D**) in two patients with erysipelas. Bright red erythema extending from the anal verge in a young boy with streptococcal perianal disease (**E**).
A & B, Courtesy, Eugene Mirrer, MD. C, Courtesy, Kalman Watsky, MD. D, Courtesy, Mary Stone, MD. E, Courtesy, Julie V Schaffer, MD.

axillae, antecubital and popliteal fossae, and inguinal region. Sharply demarcated, intensely erythematous patches or thin plaques are observed in an intertriginous site, often accompanied by a foul odor. In contrast to intertriginous candidiasis, satellite lesions are uncommon. Affected children occasionally exhibit irritability and low-grade fevers. Bacterial culture can confirm the diagnosis, which should be considered when simple intertrigo fails to respond to barrier creams and other measures to reduce friction and minimize moisture. A 10-day course of oral penicillin is usually effective[38].

Perianal Streptococcal Disease

Synonym: ▪ Perianal cellulitis ▪ Perianal streptococcal dermatitis

Perianal disease caused by infection with group A streptococci presents as sharply demarcated, bright red erythema extending 2–3 cm around the anal verge (Fig. 74.8E). Patients may complain of perianal pruritus or irritation, painful defecation, blood-streaked stools, or soiling of undergarments due to anal leakage. Systemic symptoms are absent. Children, especially boys under the age of 4 years, are most commonly affected. Perianal infection may be preceded by pharyngitis and should be considered in patients with an outbreak of guttate psoriasis.

Other causes of perianal erythema or pruritus include a *S. aureus* infection[38a], candidiasis, seborrheic dermatitis, pinworm infection, inflammatory bowel disease, child abuse, and the early phase of Kawasaki disease. Perianal streptococcal disease can be diagnosed with skin culture. In a recent randomized controlled study, a 7-day course of cefuroxime was found to be more effective than a 10-day course of penicillin in the treatment of perianal streptococcal disease[39].

Cellulitis

Introduction

Cellulitis is an infection of the deep dermis and subcutaneous tissue that manifests as areas of erythema, swelling, warmth and tenderness[40].

Epidemiology and pathogenesis

Cellulitis in immunocompetent adults is most often caused by group A streptococci or *S. aureus*, and the latter organism is the most frequent etiology in children. Although *H. influenzae* was once a common cause of cellulitis in pediatric patients, it is now rare due to routine vaccination against *H. influenzae* type b. A mixture of Gram-positive cocci and Gram-negative aerobes and anaerobes is often implicated in cellulitis surrounding diabetic and decubitus ulcers. Bacteria typically gain access to the dermis via a break in the skin barrier in immunocompetent individuals, but a bloodborne route is common in immunocompromised patients. Lymphedema, alcoholism, diabetes mellitus, intravenous drug abuse, and peripheral vascular disease are all risk factors for cellulitis. Recurrent bouts of cellulitis may result from damage to the lymphatic system (e.g. from a lymph node dissection, saphenous vein harvest or prior episode of cellulitis)[41,42].

Clinical features

Cellulitis is often preceded by systemic symptoms such as fever, chills and malaise. The affected area displays all four of the cardinal signs of inflammation: rubor (erythema), calor (warmth), dolor (pain), and tumor (swelling). The borders are usually ill-defined and non-palpable. In severe infections, vesicles, bullae (Fig. 74.9), pustules or necrotic tissue may be present. Ascending lymphangitis and regional lymph node involvement may occur. In children, cellulitis most often affects the head and neck, whereas in adults it tends to involve

Fig. 74.9 Bullous cellulitis. Extensive soft tissue infection of the lower extremity due to group A streptococcal infection.

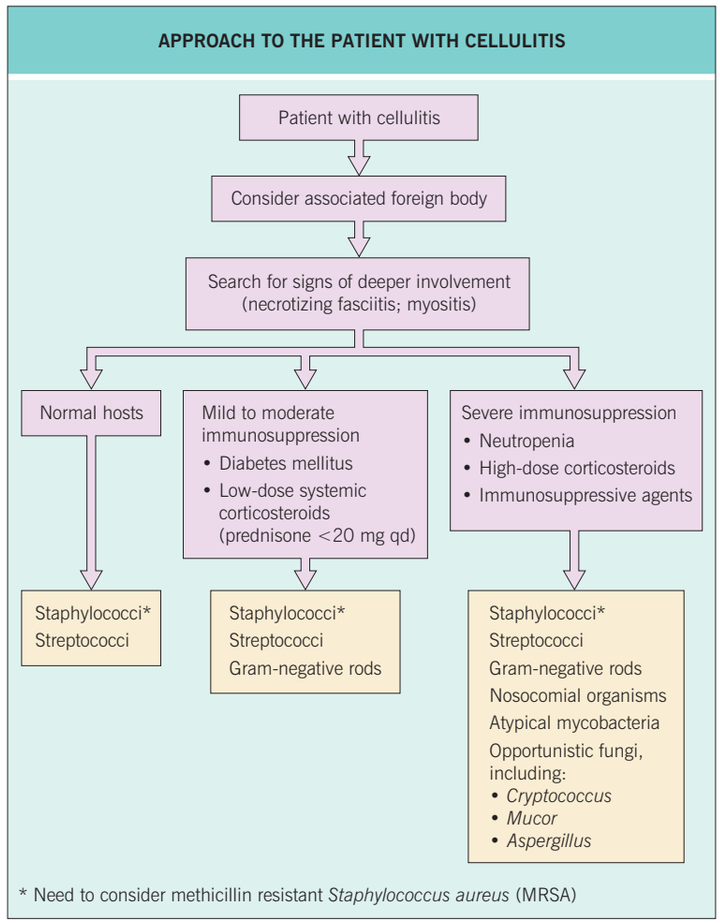


Fig. 74.10 Approach to the patient with cellulitis.

the extremities. Intravenous drug users typically develop cellulitis of the upper extremities (the usual sites of drug injection). Complications are uncommon, potentially including acute glomerulonephritis (if caused by a nephritogenic strain of streptococcus), lymphadenitis, subacute bacterial endocarditis, and recurrences related to abnormal lymphatic damage[42].

Pathology

A mild or moderate inflammatory infiltrate composed of lymphocytes and neutrophils can be seen throughout the dermis, often extending into the subcutaneous fat. Edema (occasionally leading to subepidermal bullae) and dilation of lymphatics and small blood vessels are also evident. With special stains, the causative organism may be identified.

Diagnosis and differential diagnosis

The diagnosis of cellulitis is usually clinical (Fig. 74.10). The leukocyte count is often normal or only slightly elevated. Blood cultures are almost always negative in immunocompetent hosts. An exception is *H. influenzae* cellulitis, where there is usually an increased leukocyte count with a left shift and positive blood cultures. Atypical organisms are more common in children and immunocompromised patients, and needle aspiration or skin biopsy may help to identify the infectious etiology. The differential diagnosis of lower extremity cellulitis includes deep vein thrombosis and inflammatory diseases such as stasis dermatitis, superficial thrombophlebitis and panniculitis (especially lipodermatosclerosis). While superficial thrombophlebitis often presents with redness and tenderness, the absence of a fever and the presence of a palpable cord aid in the diagnosis. Misdiagnosis of lipodermatosclerosis as cellulitis often leads to unnecessary hospitalizations. Additional causes of "pseudocellulitis" are listed in Table 74.10.

Treatment

Treatment of cellulitis is typically targeted against group A streptococci and *S. aureus*. For uncomplicated cases, a 10-day course of an oral antibiotic that covers these organisms (e.g. dicloxacillin, cephalexin or clindamycin) is appropriate. Hospitalization and parenteral antibiotics may be necessary for patients who are seriously ill, have facial involvement or fail to respond to oral therapy. If MRSA is suspected (e.g. cellulitis in association with an abscess), agents such as clindamycin, TMP-SMX or doxycycline should be used (see Table 74.5); if group A streptococcal infection is also a possibility, the latter agents should be combined with a β-lactam. Diabetic or decubitus ulcers complicated by cellulitis require broad-spectrum coverage (e.g. piperacillin/tazobactam or, in penicillin-allergic patients, metronidazole plus ciprofloxacin). Adjunctive measures include immobilization and elevation of an affected extremity and the application of wet dressings to areas with bullae or exudate. If signs and symptoms do not improve after 36–48 hours of treatment, cultures and susceptibilities should be obtained and antibiotics adjusted accordingly. NSAIDs may mask the signs and symptoms of deeper necrotizing infections and should be avoided when treating cellulitis. The clinical features and treatment of other types of cellulitis (e.g. *Erysipelothrix rhusiopathiae*, *Vibrio vulnificus*) are discussed below[43].

Pyomyositis

Pyomyositis is a primary bacterial infection of the skeletal muscles, most commonly caused by *S. aureus*[36]. Once referred to as tropical myositis, it is becoming more prevalent in temperate climates. Predisposing factors include trauma, diabetes mellitus, HIV infection, intravenous drug use and other forms of immunosuppression. Patients often present with a 1–2-week history of low-grade fevers, myalgias, and progressive firmness, pain and enlargement of a deep soft tissue mass. Palpation of the affected area reveals "woody" induration. Muscle abscess formation occurs during the second stage of disease, and septicemia may follow.

MRI is the diagnostic modality of choice for the first stage of the disease; ultrasound-guided aspiration may be helpful later in the course. Treatment includes incision and drainage as well as appropriate intravenous antibiotics until clinical improvement is noted, followed by oral antibiotics for a total of 3 weeks[36].

Botryomycosis

Synonyms: ■ Granular bacteriosis ■ Bacterial pseudomycosis

Introduction

Botryomycosis (named for its characteristic groups of granules that resemble grapes) is a rare, chronic, purulent and granulomatous bacterial infection that primarily affects the skin and is most often caused by *S. aureus*.

Epidemiology and pathogenesis

Botryomycosis is found worldwide, and over two-thirds of patients have only skin involvement. The disease affects all ages and has a slight male predominance (male : female ratio, 3 : 2). Although most cases are due to infection with *S. aureus*, it has also been caused by *Pseudomonas*, *Proteus*, *Moraxella*, *Serratia* and *Corynebacteria* spp. Defects of cellular immunity, particularly low T-lymphocyte counts, have been associated with the development of botryomycosis[44].

Clinical features

Botryomycosis presents as cutaneous and subcutaneous nodules, ulcers or verrucous plaques. Multiple sinuses and fistulas may discharge purulent fluid or yellow granules composed of bacterial masses. Most patients have localized disease on the extremities, and it may be preceded by trauma. The lesions may be pruritic, tender, or involve the underlying muscle or bone. Systemic symptoms are infrequent. Visceral botryomycosis most often affects the lungs and is extremely rare, occurring primarily in immunocompromised patients or following surgery[45].

Pathology

Biopsy specimens reveal a chronic inflammatory reaction with fibrosis and foreign body giant cells. The most distinctive feature is 1–3 mm granular bodies (grains) that represent bacteria, cells and debris. Grains have basophilic centers and a homogeneous, eosinophilic, hyaline periphery thought to be secondary to a host immunoglobulin response (Splendore–Hoeppli phenomenon). The granules stain with PAS, Gram and Giemsa.

Diagnosis and differential diagnosis

When botryomycosis is suspected, both bacterial and fungal cultures should be obtained and a skin biopsy performed for histopathologic examination (as well as culture). Microscopic examination (fresh mount or 20% KOH) shows coarsely lobulated granules with club-like projections. Gram staining of crushed granules usually displays masses of staphylococci. The differential diagnosis of cutaneous botryomycosis includes mycetoma, actinomycosis, a ruptured epidermoid cyst, a staphylococcal abscess, orf, tuberculosis, and dimorphic fungal or atypical mycobacterial infections.

Treatment

Botryomycosis is typically treated surgically with debridement or excision in conjunction with antibiotic therapy. The CO_2 laser has also been used successfully.

Necrotizing Fasciitis

Synonyms: ■ Type 1 – polymicrobial necrotizing fasciitis ■ Type 2 – group A streptococcal necrotizing fasciitis ■ "Flesh-eating bacteria" syndrome ■ Fournier's gangrene ■ Synergistic necrotizing cellulitis

Introduction

Necrotizing fasciitis is characterized by rapidly progressive necrosis of subcutaneous fat and fascia, which can be life-threatening without prompt recognition, aggressive surgical intervention and immediate antibiotic therapy.

Epidemiology and pathogenesis

Approximately 500–1500 cases of necrotizing fasciitis are reported each year in the US. Risk factors include diabetes mellitus, immunosuppression, cardiac or peripheral vascular disease, and renal failure, but it can also occur in young, previously healthy individuals. Necrotizing fasciitis may follow penetrating or blunt injury or develop in the absence of preceding trauma. Other predisposing factors include intravenous drug use, recent surgery, varicella, and decubitus or ischemic ulcers.

Mortality rates range from 20% to 40%. Higher mortality is associated with female sex, older age, greater extent of infection, delay to first debridement, an elevated serum creatinine or lactic acid level, disease due to group A streptococci, and a greater degree of organ dysfunction at the time of admission to hospital. Diabetes mellitus can also result in higher mortality, particularly if renal dysfunction or peripheral vascular disease is also present[46,47].

In children, necrotizing fasciitis is most commonly caused by group A streptococci. In adults, it frequently results from a polymicrobial infection (typically following trauma or surgery) with anaerobic and aerobic bacteria, including streptococci, *S. aureus*, *Escherichia coli*, *Bacteroides* and *Clostridium* spp. Uncommon pathogens include *V. vulnificus*, *Aeromonas hydrophila*, *Pseudomonas aeruginosa* and *H. influenzae* type b[48]. Opportunistic fungal infections, such as zygomycosis, can cause necrotizing fasciitis in immunocompromised patients[49].

Clinical features

Infection begins with an area of exquisite tenderness, erythema, warmth and swelling that does not respond to antibiotics. The skin appears shiny and tense. Initially, severe pain may be out of proportion to skin findings. The disease progresses at an alarming rate, with the skin changing from red and purple to a characteristic gray–blue color in ill-defined patches within 36 hours of onset. Violaceous and/or hemorrhagic bullae may develop. Necrosis of the superficial fascia and fat produces a thin, watery, malodorous fluid (Fig. 74.11). The area may later become anesthetic as cutaneous nerves are destroyed. The subcutaneous tissues may feel hard and "woody" on palpation. Patients can become extremely toxic, with fever, chills, malaise, leukocytosis, tachycardia and shock. The most common site of involvement is the extremities, although the trunk is often affected in children. When necrotizing fasciitis involves the perineum and genitalia, it is referred to as Fournier's gangrene[50].

Pathology

Gangrene of the subcutaneous tissues, with spread along fascial planes, is followed by involvement of the overlying skin. Fibrinoid necrosis is present in the media of vessels passing through the destroyed fascia, and fibrin thrombi are evident. The epidermis, dermis and skin appendages in the area of gangrene undergo coagulation necrosis. Infiltration with neutrophils and mononuclear cells as well as numerous bacteria occurs in upper layers of the dermis.

Diagnosis and differential diagnosis

Early in the disease course, it is often difficult to differentiate necrotizing fasciitis from cellulitis. The presence of severe pain or anesthesia suggests a deeper component, and an MRI can delineate the depth of tissue involvement. Other clues that suggest necrotizing fasciitis rather

Fig. 74.11 Necrotizing fasciitis. Necrosis of the subcutaneous fat and fascia of the inner aspect of the upper arm in an elderly patient with diabetes mellitus. Note the watery discharge. *Courtesy, Jean L Bolognia, MD.*

than cellulitis include rapidly spreading tense edema, hemorrhagic bulla formation, grayish discoloration, foul-smelling discharge and an elevated creatine phosphokinase level. Figure 74.12 outlines an algorithm for assessing and treating suspected necrotizing fasciitis. Conditions that can mimic necrotizing fasciitis include trauma with hematoma formation, clostridial myonecrosis, pyomyositis, phlebitis, bursitis and arthritis.

Treatment

Extensive surgical debridement (fasciotomy) is the mainstay of effective treatment. On occasion, amputation is necessary. Therapy (which can be directed by results of a Gram stain of exudate) should be initiated with a β-lactam/β-lactamase inhibitor with broad-spectrum coverage against streptococci, staphylococci, Gram-negative bacilli and anaerobes (e.g. ampicillin/sulbactam or piperacillin/tazobactam, often administered together with clindamycin and ciprofloxacin); an alternative is a carbapenem. In a patient with true penicillin allergy, empiric therapy with ciprofloxacin plus metronidazole or clindamycin can be used. Coverage of *Pseudomonas* spp. is particularly important for neutropenic patients. Hyperbaric oxygen therapy remains controversial, though it may be beneficial for a subset of patients with anaerobic Gram-negative necrotizing fasciitis; however, surgery and antimicrobial therapy should never be postponed. IVIg may be useful for patients with severe group A streptococcal infection. Nutritional support is crucial for enhancing postoperative wound healing, and, eventually, reconstructive surgery is often necessary[51].

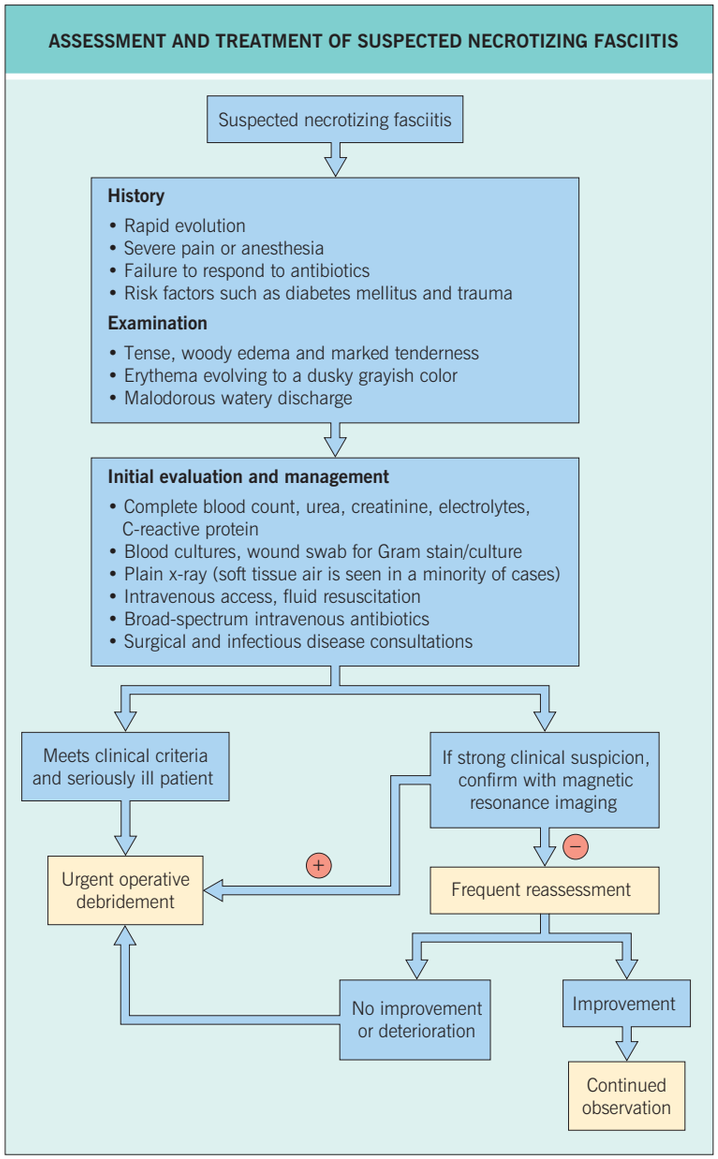


Fig. 74.12 Algorithm for assessment and treatment of suspected necrotizing fasciitis.

Bacteremia/Septicemia

Staphylococcal septicemia may occur in the absence of any cutaneous or internal focus of infection. Immunocompromised states, erythroderma (especially secondary to Sézary syndrome), central venous catheters, abnormal or prosthetic heart valves, and intravenous drug use are all risk factors for Gram-positive bacteremia. A large percentage of patients with late-stage cutaneous T-cell lymphoma eventually succumb to septicemia, especially staphylococcal. The skin lesions of *S. aureus* septicemia are classically pustular petechiae, purulent purpura, and subcutaneous abscesses that probably represent hematogenous spread of the infection to the skin. Biopsy specimens show nonspecific inflammation, often with a positive Gram stain, and cultures grow *S. aureus*. When *S. aureus* bacteremia leads to endocarditis, a number of other characteristic skin signs may appear, including petechiae, splinter hemorrhages, Osler's nodes (resulting from immune complex deposition and small vessel vasculitis) and Janeway lesions (septic emboli forming microabscesses). Clinically, Osler's nodes are tender, erythematous papules and nodules with white centers that favor the finger pads and thenar/hypothenar eminences, whereas Janeway lesions are painless, small hemorrhagic macules or papules on the palms and soles. Both staphylococcal bacteremia and endocarditis are treated with prolonged courses of intravenous antibiotics.

CLOSTRIDIAL SKIN INFECTIONS

Clostridia are spore-forming Gram-positive rods that are ubiquitous soil saprophytes and part of the normal intestinal flora. While *Clostridium perfringens* is an obligate anaerobe and thus proliferates in hypoxic or ischemic tissue, *C. septicum* is much more aerotolerant and requires a smaller infective dose.

C. perfringens produces two membrane-active toxins, α-toxin and perfringolysin, which have synergistic effects. Alpha-toxin possesses biologic activity akin to phospholipase C and sphingomyelinase, while perfringolysin disrupts endothelial cell integrity, impairs recruitment of phagocytes and induces intravascular platelet aggregation, leading to reduced arteriolar blood flow. Impaired oxygen delivery then results in tissue hypoxia and anaerobic glycolysis of muscle tissues. Production of hydrogen sulfide and CO_2 accounts for the characteristic "gas" gangrene visualized on radiographic imaging. Local progression results in myonecrosis, whereas shock and multiorgan failure can occur when the toxins enter the systemic circulation.

The majority of cases of anaerobic cellulitis (a necrotizing subcutaneous infection) and myonecrosis (gas gangrene) are caused by clostridia. These diseases are compared and their treatment outlined in Table 74.11. Soft tissue crepitus, evidence of gas on plain films, or a foul-smelling brownish discharge ("dirty dishwater") should prompt the clinician to suspect a clostridial infection, especially following trauma or surgery in patients with diabetes mellitus and peripheral vascular disease[52,53].

CORYNEBACTERIAL SKIN INFECTIONS

Corynebacteria are Gram-positive rods that account for nearly half of the cutaneous flora. A warm, moist local environment represents a risk factor for infection of the skin with non-diphtherial corynebacteria[54].

Erythrasma

Erythrasma is a superficial and often chronic skin infection caused by excessive proliferation of *Corynebacterium minutissimum* within the stratum corneum. The organism's growth is favored by moist, occluded intertriginous areas, including the groin, axillae, intergluteal fold, inframammary region, umbilicus, and web spaces between the toes. Other predisposing factors include a warm humid climate, poor hygiene, hyperhidrosis, obesity, diabetes mellitus, advanced age and immunosuppression[55]. Whether the associated scale precedes and promotes development of erythrasma or results from bacterial overgrowth is a matter of debate.

CLOSTRIDIAL ANAEROBIC CELLULITIS AND MYONECROSIS		
	Anaerobic cellulitis*	**Myonecrosis (gas gangrene)**
Risk factors (for both conditions)	Trauma (penetrating, "crush" injuries) or surgery, with improper/incomplete debridement or contamination of the wound Diabetes mellitus, peripheral vascular disease Injection drug use (e.g. black tar heroin) Colonic disease or malignancy (*C. septicum* myonecrosis)	
Organism†	*C. perfringens* > other anaerobic bacteria (e.g. *Bacteroides, Peptostreptococcus*, *Prevotella* spp.)	*C. perfringens* (~80%) > *C. novyi*, *C. septicum*
Incubation period	>3 days	12–24 hours
Course	Rapid	Very rapid
Exudate	Thin, dark gray–brown, foul-smelling ("dirty dishwater")	Thin, dark gray–brown, foul-smelling ("dirty dishwater")
Overlying skin changes	Minimal	Dark yellow to bronze discoloration, necrosis, bullae
Swelling	Minimal	Severe
Crepitus	Usually present (with abundant gas in subcutaneous tissues and along fascial planes)	Sometimes present
Pain	Absent or mild	Severe
Fever	Low-grade	Low-grade
Toxemia	Absent or mild	Present (e.g. tachycardia, hypotension, oliguria)
Bacteremia/laboratory findings	Typically absent/minimal	Bacteremia in ~15%; marked leukocytosis, hemolytic anemia
Treatment (for both conditions)	• Early, aggressive surgical debridement (repeated every 24–48 hours until clinical resolution) • The causative clostridial organisms are typically sensitive to penicillin; however, because the infections may be polymicrobial, broad-spectrum coverage (e.g. with clindamycin plus a third-generation cephalosporin) is indicated until culture results are available • Adjunctive hyperbaric oxygen therapy	

*Can progress to myonecrosis.
†Infections may be polymicrobial, which can lead to overlap with necrotizing fasciitis.

Table 74.11 Clostridial anaerobic cellulitis and myonecrosis.

Lesions are pink to red, well-defined patches that are covered with fine scales and have associated wrinkling. With time, the red color fades to brown (Fig. 74.13A,C). The condition is asymptomatic or mildly pruritic. A "disciform" variant can occur in a more widespread distribution outside the usual intertriginous locations (Fig. 74.13D); this is occasionally the presenting manifestation of type 2 diabetes mellitus. Interdigital erythrasma is the most common bacterial infection of the foot and the most frequent form of erythrasma. It presents as asymptomatic, chronic maceration with fissuring or scaling of interspaces[56]. Progression of erythrasma to cellulitis or bacteremia in immunocompromised patients has occasionally been reported.

When lesions are illuminated with a Wood's lamp, bright coral-red fluorescence appears as a result of porphyrin produced by the bacteria (Fig. 74.13B). Gram staining of the scale demonstrates Gram-positive filaments and rods, and corynebacteria can be cultured on Tissue Culture Medium 199. The differential diagnosis of intertriginous erythrasma includes tinea, seborrheic dermatitis and cutaneous candidiasis, while interdigital erythrasma needs to be distinguished from tinea and complex toe web infections[57].

Topical therapies include 20% aluminum chloride, clindamycin, erythromycin, azole antifungals, and Whitfield ointment (salicylic and benzoic acids). Oral erythromycin or tetracyclines can be used for widespread or recalcitrant cases. Use of antibacterial soaps may help to prevent recurrences.

Pitted Keratolysis

Synonyms: ▪ Keratolysis plantare sulcatum ▪ Ringed keratolysis

Introduction

Pitted keratolysis is a non-inflammatory bacterial infection of palmoplantar skin.

Epidemiology and pathogenesis

Pitted keratolysis occurs worldwide in temperate and tropical climates. Hyperhidrosis, prolonged occlusion, and increased skin surface pH are predisposing factors. Most infections are caused by *Kytococcus sedentarius* (formerly *Micrococcus sedentarius*), but other bacteria such as *Dermatophilus congolensis*, *Corynebacterium* and *Actinomyces* spp. have been implicated. *K. sedentarius* produces two serine proteases (K1 and K2) that degrade keratin in the stratum corneum[58]. Sulfur-containing compounds released by the bacteria lead to a characteristic associated malodor.

Clinical features

Small (1–7 mm), crater-like depressions are present within the stratum corneum on weight-bearing regions of the soles (Fig. 74.14) and (rarely) the palms. These pits may coalesce into large craters or rings of craters. There is usually no associated erythema, and the condition often goes unnoticed by the patient. Hyperhidrosis and malodor are common associated findings.

Pathology

Well-defined "pits" extend approximately two-thirds of the way into the stratum corneum. Gram, PAS and Gomori methenamine silver stains reveal bacteria in the walls and at the bottom of the craters. No inflammation is observed.

Diagnosis and differential diagnosis

The diagnosis of pitted keratolysis is usually clinical. There is no fluorescence on examination with a Wood's light. The differential diagnosis includes plantar warts, tinea pedis, palmoplantar punctate keratoderma, pits of nevoid basal cell carcinoma syndrome, Darier disease and circumscribed palmoplantar hypokeratosis.

Treatment

Topical erythromycin, clindamycin, mupirocin, tetracycline and azole antifungals have all been reported to lead to a rapid resolution of pitted keratolysis[54]. Oral erythromycin is occasionally indicated for extensive involvement. Aluminum chloride 20% solution or (in recalcitrant cases) botulinum toxin can be used to treat the associated hyperhidrosis.

Fig. 74.13 Erythrasma. A Pink to brown scaly patches on the upper inner thighs. **B** Coral-red fluorescence upon illumination with a Wood's lamp. **C** Hyperpigmented plaques in the inguinal and periumbilical areas. **D** Well-demarcated, scaly, hyperpigmented plaque of disciform erythrasma. *A, B, Courtesy, Louis A Fragola, Jr, MD.*

Fig. 74.14 Pitted keratolysis of the plantar surface of the foot. Multiple small craters with decreased stratum corneum that favor pressure points on the plantar surface. *Courtesy, Kalman Watsky, MD.*

Trichomycosis Axillaris

Trichomycosis axillaris is a superficial corynebacterial infection that results in concretions on the shafts of axillary and (less often) pubic hairs. The hair shafts develop adherent yellow, red or black nodules or cylindrical sheaths that can be seen with the naked eye (Fig. 74.15). There is a characteristic odor, and the sweat occasionally takes on a red color and stains clothing. However, like pitted keratolysis, the condition frequently goes unnoticed. Wood's lamp examination reveals a pale yellow fluorescence, and Gram staining of the concretions shows Gram-positive rods. The differential diagnosis includes white piedra, black piedra and hair casts (see Ch. 77). Shaving the affected hair provides an instant cure, and use of antimicrobial cleansers can prevent recurrences. Additional treatment options include topical erythromycin or clindamycin[54].

Cutaneous Diphtheria

Cutaneous infection with *Corynebacterium diphtheriae* is endemic in several tropical countries and some urban poor populations (e.g. recent reports of a nontoxigenic but invasive strain in Vancouver[58a]), where it is spread by person-to-person contact in a highly contagious manner. However, it is very rare in most parts of the world. For children living in endemic regions, cutaneous diphtheria represents a form of immunization, as toxin is absorbed slowly from skin lesions and induces high levels of antibodies. In addition to children, elderly and immunocompromised individuals are most commonly affected, with predisposing factors including poor hygiene, injection drug use and skin trauma. Vaccination against diphtheria does not necessarily prevent cutaneous disease.

Cutaneous diphtheria most commonly presents as an ulcer (ecthyma diphthericum) with a punched-out appearance and variable gray

Fig. 74.15 Trichomycosis axillaris. Cylindrical sheaths and beading of the axillary hairs. A yellow color is seen most commonly.

Fig. 74.16 Ecthyma diphthericum. Punched-out ulcer with a black eschar on the upper lip.

"pseudomembranous" eschar (Fig. 74.16). Acral sites are favored, and a pustule or crusted dermatitis may also be observed. Lesions are commonly co-infected with *S. aureus* or *Str. pyogenes*. Local lymphadenopathy and toxin-mediated complications, such as myocarditis and polyneuritis, are rare.

Gram stain and culture of the exudate can establish the diagnosis. Treatment includes a 10-day course of oral antibiotics (penicillin or erythromycin are first-line), thorough cleansing of the wound site, a topical antibiotic and (for toxigenic strains) intravenous diphtheria antitoxin[59].

OTHER GRAM-POSITIVE SKIN INFECTIONS

Cutaneous Anthrax

Key features

- *Bacillus anthracis* causes pulmonary, gastrointestinal and cutaneous disease
- Cutaneous anthrax has traditionally been considered an occupation-related condition
- In this century, *B. anthracis* re-emerged as a potential agent of biological warfare and terrorism

Introduction and epidemiology

The name *Bacillus anthracis* is derived from the Greek word for coal, *anthrakis*, reflecting the black, coal-like eschars. *B. anthracis* is an aerobic, sporulating, Gram-positive rod measuring 1–1.5 × 3–5 microns. The bacterium causes disease in humans via three routes: inhalation, ingestion and cutaneous inoculation; the last-mentioned produces the least severe form of anthrax and accounts for ~95% of infections. Anthrax is primarily a disease of animals (e.g. sheep, cows, horses, goats) that is endemic in parts of western Asia and Africa. Most human cases are due to occupational exposure to infected animals or their carcasses (including hides and wool; "woolsorter's disease")[60]. Two thousand cases are reported annually worldwide, with <10 per year in the US.

History

The fifth and sixth plagues of Egypt that are described in the book of Exodus are thought to have been anthrax. *B. anthracis* was the first bacterium proven to be the etiologic agent of a specific disease, independently demonstrated by Dr Robert Koch and Dr Louis Pasteur. Anthrax was first used as a biological weapon during World War I. Release of anthrax from a biological weapons complex in the Soviet Union in 1979 resulted in 66 fatalities. In 2001, anthrax spores were sent through the US mail as a terrorist weapon, resulting in 11 cases of inhalational anthrax and 5 fatalities[61].

Pathogenesis

Anthrax spores are environmentally hardy and can survive for decades in the soil. Full virulence requires the presence of both an antiphagocytic capsule and three toxin components (protective antigen, lethal factor and edema factor) that combine to form two toxins: lethal toxin and edema toxin. Edema toxin impairs neutrophil function and affects water homeostasis, leading to edema; lethal toxin causes release of TNF-α and IL-1β[62].

Clinical features

The clinical features of cutaneous anthrax are outlined in Table 74.12[63]. Additional key points include the following:

- The lack of pain despite a necrotic eschar helps to differentiate cutaneous anthrax from the bite of a brown recluse spider.
- A pustular primary lesion is unlikely to be cutaneous anthrax, although "cloudy" vesicles may be seen. The term "malignant pustule", which is often attributed to anthrax, is a misnomer.
- Vesicles may discharge serosanguineous fluid containing numerous organisms, which are evident on Gram stain.
- Lymphangitis and painful lymphadenopathy with systemic symptoms (fever, malaise, headache) occur rarely.
- Antibiotic therapy does not alter the progression from vesicle to ulcer to eschar, as the process is toxin-mediated.
- Multiple lesions, when present, tend to cluster in the same area of the body.

Pathology

Spongiosis, papillary dermal edema, and a superficial and deep inflammatory infiltrate with abundant neutrophils are observed. Substantial

CUTANEOUS ANTHRAX – CLINICAL CHARACTERISTICS
• Incubation period averages 7 days (range 1–12 days) • A purpuric macule or papule develops in an exposed area (e.g. forearm, neck, chest, finger); the papule may resemble an insect bite and can be pruritic • Within 48 hours of the lesion's appearance, a vesicle (1–3 mm) forms with surrounding non-pitting edema • The central vesicle ulcerates and small vesicles may form around the ulcer • The lesion becomes hemorrhagic and depressed, and a *painless,* black necrotic eschar forms centrally with an increase in the surrounding erythema and edema • The eschar dries, loosens and sloughs over the next 1–2 weeks, with no permanent scar

Table 74.12 Cutaneous anthrax – clinical characteristics. *Adapted from Carucci JA, McGovern TW, Norton SA, et al. Cutaneous anthrax management algorithm. J Am Acad Dermatol. 2002;47:766–9.*

hemorrhage is often evident, and the inflammatory infiltrate may involve nerves. Extensive ulceration and coagulative necrosis can be seen in older lesions. Elongated Gram-positive bacilli are present, often in small clusters. Spores grow readily on all routine culture media at 37°C, with a "jointed bamboo-rod" cellular appearance and a unique "curled-hair" colonial morphology.

Diagnosis and differential diagnosis

Gram staining of exudate or touch preparations can aid in rapid diagnosis. The organism grows in culture within 6–24 hours; however, antibiotic administration for more than 24 hours prevents the recovery of pathogens in culture.

Laboratory personnel must be alerted to the possibility of anthrax to ensure that the *Bacillus* isolate is not assumed to be *B. cereus* and that further speciation is performed. Definitive diagnosis requires specific testing such as phage gamma lysis and detection of capsule and wall antigens. Serologic assays can become positive as early as 10 days after onset of symptoms, with peak titers at 40 days.

The differential diagnosis includes cutaneous infection with *Bacillus megaterium*[63a], a brown recluse spider bite, the eschar of several rickettsial diseases, soft tissue infections (e.g. cellulitis), orf, milker's nodule, opportunistic bacterial and fungal infections, and entities in the ulceroglandular category (e.g. tularemia; see below).

Treatment

Without antibiotic treatment, mortality from cutaneous anthrax may be as high as 20% (usually from septicemia), but that number falls to almost zero with proper antimicrobial therapy. Although antibiotics do not alter the evolution of the cutaneous lesions (which are toxin-mediated), the likelihood of systemic illness is reduced. In the US, cutaneous anthrax is assumed to potentially be associated with a concomitant inhalational exposure; as a result, the Centers for Disease Control and Prevention (CDC) recommend antibiotic therapy for at least 60 days (rather than 7–10 days). Quinolones (e.g. ciprofloxacin 500 mg orally twice daily) are first-line agents, with doxycycline as an alternative therapy[64].

An anthrax vaccine, consisting of an inactivated cell-free filtrate of a non-encapsulated, attenuated strain of *B. anthracis*, is available. It is approved for use as postexposure prophylaxis and can be administered in conjunction with antimicrobials in cases of bioterrorism. Following the initial dose, the vaccine is administered at 4 weeks and 6, 12 and 18 months, followed by yearly boosters.

Bacillus cereus Infection

Bacillus cereus is a large Gram-positive rod best known for causing mild food poisoning. However, it can also produce primary cutaneous disease as well as life-threatening pneumonia, meningitis or necrotizing fasciitis in immunocompromised patients. Skin infection typically presents as a single necrotic bulla, and *B. cereus* infection should be considered in neutropenic patients with such a lesion. These individuals typically present with high fevers and negative blood cultures. Vancomycin is considered the drug of choice, but quinolones and imipenem may also be used[65].

Erysipeloid

Synonyms: ■ Diamond skin disease ■ Erysipeloid of Rosenbach (localized cutaneous form) ■ Pseudoerysipelas

Erysipeloid is an acute cutaneous infection caused by *Erysipelothrix rhusiopathiae*, a Gram-positive, non-motile, smooth or curved bacillus. It is caused by traumatic inoculation of the organism into the skin, which most often occurs in fishermen or persons who prepare meat, poultry or fish. There are two types of erysipeloid, localized and generalized, and they usually occur within 1 week of inoculation. The *localized form* is characterized by an erythematous to violaceous area of non-suppurative cellulitis (Fig. 74.17), which can be pruritic or painful. Hemorrhagic vesicles may develop. Although the classic finding is involvement of the finger webs with sparing of the terminal phalanges, other sites may be affected. Constitutional symptoms are unusual in localized erysipeloid, which is typically a self-limited condition. However, the *generalized form* presents with fever and arthralgias in addition to widespread cutaneous lesions. The latter range from perifollicular papules to erythematous plaques to macular purpura and necrosis. Complications can include endocarditis, septic arthritis, and cerebral and other visceral abscesses. The organism is often difficult to culture, and PCR-based assays can help to establish the diagnosis[66]. Erysipelas, cellulitis, spider bites and fixed drug eruptions may simulate localized erysipeloid (see Table 74.10). Most patients with untreated localized disease recover spontaneously. Penicillin is the drug of choice; erythromycin, cephalosporins and tetracyclines are alternatives. The best means of prevention is using gloves when preparing fish or meat[67].

Fig. 74.17 Erysipeloid. Erythema and edema with vesicle formation on the hand and fifth digit.

Listeriosis

Listeria monocytogenes is a motile Gram-positive bacillus that is ubiquitous in the environment (e.g. soil, water, vegetation) and represents a common veterinary pathogen (especially in sheep and cattle). In humans, infection is usually acquired by eating contaminated food and primarily affects the elderly, pregnant women and immunocompromised individuals (e.g. those with HIV infection or receiving immunosuppressive medications). These patients most often develop a gastrointestinal illness (accompanied by fever, myalgias and bacteremia) or meningitis. Neonatal septicemia and meningitis due to vertical transmission can also occur and may be associated with disseminated skin lesions ranging from pustules (or occasionally vesicles) to petechiae and purpura to granulomatous papules and nodules. In addition, veterinarians and farmers who assist animals in parturition may acquire primary cutaneous listeriosis, which typically presents with pustular or papular lesions on the arms and hands. The first-line treatment for listeriosis is ampicillin, and TMP-SMX represents an alternative; *L. monocytogenes* is resistant to cephalosporins.

GRAM-NEGATIVE BACTERIA

NEISSERIA MENINGITIDIS

Acute and Chronic Meningococcemia

Introduction

Meningococcemia is characterized by fever and a petechial eruption, and it has acute and chronic forms. The causative organism, *Neisseria meningitidis*, is an aerobic Gram-negative diplococcus.

Epidemiology and pathogenesis

Meningococcal infections occur worldwide and affect primarily infants (6 months to 1 year), adolescents and young adults. There is a male predominance, with a male:female ratio of 3–4 : 1. Most cases develop in the winter and spring. Individuals with asplenia or deficiency (congenital or acquired) in a terminal complement component (C5–C9),

properdin, factor D or immunoglobulins are at increased risk of infection (see Ch. 60). In addition, there is evidence that patients with low TNF-α production, high IL-10 production, or homozygosity of certain alleles at the IL-1 locus are at increased risk of a fatal outcome[68].

At least 13 strains of *N. meningitidis* are known, of which strains A, B, C, Y and W-135 are most often implicated in human disease. *N. meningitidis* owes its virulence to its polysaccharide capsule. Proliferation of *N. meningitidis* in contact with host cells increases the production of a bacterial transferase that adds phosphoglycerol onto its type IV pili; this modification results in bacterial detachment and migration across the epithelium, a prerequisite for dissemination and invasive disease[69]. The bacteria elaborate an endotoxin that triggers inflammatory processes leading to shock, multiorgan failure and purpura fulminans.

The only known reservoir is the human nasopharynx. Rates of carriage in the US range from 5% to 15%. Transmission is by the respiratory route, with an incubation period of 2–10 days. Active or passive exposure to tobacco smoke, as well as concurrent viral infection of the upper respiratory tract, disrupts the integrity of the respiratory mucosa and thereby increases the risk of invasive meningococcal disease.

Clinical features

Infection with *N. meningitidis* most often results in an asymptomatic carrier state, which leads to lifelong immunity against that subgroup. Upper respiratory symptoms as well as bacteremia without sepsis may also occur. When acute meningococcemia develops, one-third to one-half of patients present with a petechial eruption, typically in association with a fever, chills, myalgias and headache. Retiform purpura (Fig. 74.18) and ischemic necrosis may follow. Bullous hemorrhagic lesions occasionally arise, most commonly on the trunk and lower extremities. In a minority of patients, only a transient, blanchable morbilliform eruption is seen. Hypotension, meningitis, meningoencephalitis, pneumonia, arthritis, pericarditis, myocarditis and progression to disseminated intravascular coagulation (DIC) can occur in association with the petechial and purpuric eruption of acute meningococcemia.

Chronic meningococcemia is a rare disease that is characterized by recurrent episodes of fever, arthralgias, and the development of erythematous macules and papules 12–24 hours after the onset of fevers (Fig. 74.19). The skin lesions may develop into tender nodules with indistinct borders. Petechiae, retiform purpura, pustules and erythema multiforme-like lesions have also been described. The fever and rash of chronic meningococcemia tend to resolve concurrently and then recur within 2–10 days.

Pathology

Biopsy specimens from patients with acute meningococcemia show leukocytoclastic vasculitis and thrombosis; organisms can be visualized with Gram stain in 70% of cases. In chronic meningococcemia, a perivascular infiltrate composed of lymphocytes and a few neutrophils can be appreciated; leukocytoclastic vasculitis may be seen in petechial lesions.

Diagnosis and differential diagnosis

The initial diagnosis is often clinical. Time is of the essence in diagnosing patients with meningococcemia and initiating treatment, as rapid decompensation occurs in acute infections. Cultures for *N. meningitidis* from blood and skin as well as cerebrospinal, synovial and pericardial fluid may have a low sensitivity, especially after administration of antibiotics. Latex agglutination tests that detect group A, B, C, Y and W-135 antigens in the CSF and urine have good specificity but low sensitivity. PCR-based assays have better sensitivity (which may be higher in skin biopsy specimens than blood or CSF samples[70]) and specificity, and their use is increasing (where available). The diagnosis of chronic meningococcemia can be confirmed via blood cultures obtained during a febrile episode.

Acute meningococcemia must be differentiated from enteroviral infections (which can present with meningitis and a petechial exanthem), Rocky Mountain spotted fever, septic vasculitis due to acute bacteremia and endocarditis, TSS, purpura fulminans, leptospirosis and various non-infectious vasculitides. The differential diagnosis of chronic meningococcemia includes bacterial endocarditis, Sweet's syndrome, Henoch–Schönlein purpura, rat-bite fever, erythema multiforme and chronic gonococcemia. The arthralgias associated with chronic meningococcemia must not be confused with rheumatic disease, as administration of corticosteroids could provoke progression of the infection[71].

Treatment

The treatment of choice for acute meningococcemia is high-dose intravenous penicillin; chloramphenicol and quinolones are alternatives in patients with a history of immediate-type hypersensitivity to penicillins (although some strains are resistant to the latter agents). In areas of high penicillin resistance or when other forms of bacterial meningitis are considerations, a third-generation cephalosporin can be utilized. Chronic meningococcemia is treated with similar antibiotics. All close contacts should receive prophylactic treatment with ciprofloxacin, rifampin, azithromycin or ceftriaxone. Experimental therapies that have been tried in small numbers of patients include activated protein C, anti-endotoxin monoclonal antibodies, tissue plasminogen activator, antithrombin III infusion, topical nitroglycerin, plasmapheresis and extracorporeal membrane oxygenation[72]. To date, these interventions have not proven to be effective in decreasing mortality.

A quadrivalent vaccine that protects against serogroups A, C, Y and W-135 is available in the US and is routinely given to children at the age of 11–12 years (with a booster at age 16 years) and to other individuals

Fig. 74.18 Acute meningococcemia. Purpura with irregular outline and central gunmetal grey color. *Courtesy, Kalman Watsky, MD.*

Fig. 74.19 Chronic meningococcemia. Multiple erythematous crusted papules and nodules on the arm.

at high risk for infection, such as college students who live in dormitories and military recruits. The duration of immunity is 3–5 years, and the vaccine it not effective in children less than 2 years of age[73],

PSEUDOMONAS AERUGINOSA

Pseudomonas aeruginosa is a ubiquitous Gram-negative, strictly aerobic, motile bacillus. It is widely distributed in the soil and on plants, growing especially well in aqueous environments. This organism has relatively low virulence and usually requires a local anatomic or immunologic defect to cause disease. Primary cutaneous infection with *P. aeruginosa* can occur in otherwise healthy individuals in areas exposed to high levels of moisture in conjunction with skin barrier disruption; these infections have a very good prognosis. In contrast, cutaneous manifestations of *Pseudomonas* sepsis in immunocompromised individuals are associated with a grave prognosis[74].

Green Nail Syndrome

In green nail syndrome, the nail develops green–black to green–blue discoloration due to pyocyanin, a blue–green pigment produced by *P. aeruginosa* (Fig. 74.20). Predisposing factors include frequent or prolonged exposure to water, excessive use of detergents and soaps, nail trauma, and other causes of onycholysis. The diagnosis of green nail syndrome is usually clinical; if necessary, it can be confirmed by Gram stain and culture of exudate and nail fragments. The differential diagnosis includes a subungual hematoma, melanocytic nevus, melanoma and *Aspergillus* infection. Treatment involves avoidance of predisposing factors, clipping the nail, and topical application of a quinolone or aminoglycoside (e.g. tobramycin) solution for 1–4 months. In refractory cases, removal of the affected nail can be considered.

Pseudomonal Pyoderma and Blastomycosis-like Pyoderma

Pseudomonal pyoderma is a superficial infection of the skin with *P. aeruginosa*. Features include a blue–green purulence, a "grape juice-like" or "mousy" odor, and a moth-eaten appearance of the skin. The borders are often macerated and eroded (Fig. 74.21). Pseudomonal pyoderma can complicate burns, decubitus ulcers and other chronic cutaneous ulcers. Pseudomonal pyoderma often plays a role in Gram-negative toe web infections and in "infectious eczematoid dermatitis" on the hands and feet or in the anogenital region.

Blastomycosis-like pyoderma is a rare condition that presents as large verrucous plaques with multiple pustules and elevated borders. Histologic examination reveals pseudoepitheliomatous hyperplasia with intraepidermal abscesses; fungi are not seen, and fungal cultures are negative. This condition usually occurs in immunocompromised patients, and other bacteria (e.g. *S. aureus*) have also been implicated.

Treatment of these conditions includes systemic antipseudomonal antibiotics, topical antimicrobial and drying agents, and debridement (e.g. of the hyperkeratotic rim in web space infections). Additional treatment options for blastomycosis-like pyoderma include surgical excision, electrodesiccation and curettage, and ablative laser therapy.

Otitis Externa and Malignant Otitis Externa

P. aeruginosa colonizes 1–2% of normal ear canals. However, acute pseudomonal infection can result in otitis externa ("swimmer's ear"). In this condition, the external auditory canal is swollen and macerated with a green, purulent discharge. The tympanic membrane is uninvolved, and manipulation of the pinna results in extreme pain. An exudative dermatitis of the external ear and retroauricular area may also be present. Treatment includes removal of canal debris, antibiotic eardrops (preferably those that also cover *S. aureus*, since co-infection is common), and possibly the instillation of a cotton wick. Oral therapy is only occasionally required.

Malignant otitis externa is a severe variant that is seen most often in elderly diabetic patients and those with HIV infection or other immunodeficiencies. Manifestations include severe pain, persistent drainage, and the development of granulation tissue at the junction of the osseous and cartilaginous portions of the auditory canal. Local lymphadenopathy and parotid swelling may be present. Deeper invasion can result in osteomyelitis of the skull, nerve palsies, mastoiditis, sepsis and sigmoid sinus thrombosis. Treatment includes extended courses of intravenous antipseudomonal penicillins or cephalosporins as well as oral ciprofloxacin, and surgical intervention may be required[75].

Auricular chondritis secondary to *Pseudomonas* spp. has also been associated with piercing of the cartilaginous portion of the pinna[76].

Pseudomonal Folliculitis

Pseudomonal folliculitis ("hot tub folliculitis") is associated with the use of whirlpools, hot tubs and (less often) swimming pools with low chlorine levels[77]. Erythematous, edematous perifollicular papules and papulopustules arise 8–48 hours after exposure and resolve spontaneously in 7–14 days (see Ch. 38). The lesions frequently occur in sites covered by bathing suits, and the face and neck are usually spared. Associated symptoms (which do not reflect systemic spread of *P. aeruginosa*) may include pruritus, painful eyes, earaches, a sore throat, headache, fever, painful swollen breasts, malaise, rhinorrhea, nausea, vomiting and abdominal pain.

The diagnosis can be confirmed by isolation of *P. aeruginosa*, especially serotype O-11, from lesions. The differential diagnosis includes other forms of folliculitis (e.g. due to *S. aureus*) and papular urticaria.

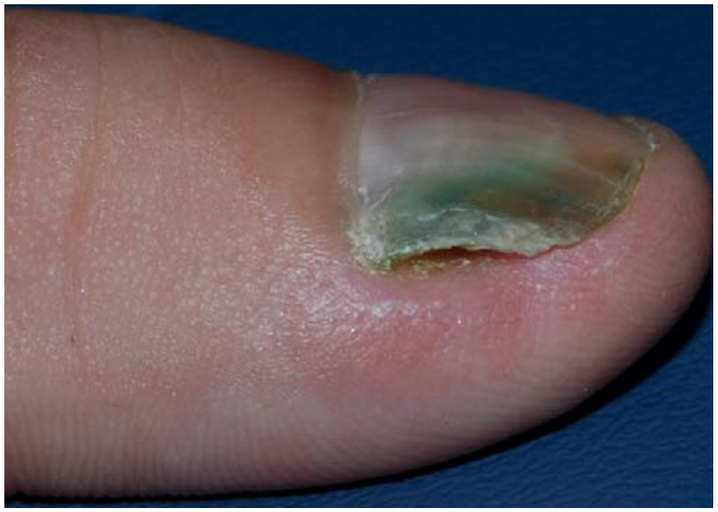


Fig. 74.20 Green nail syndrome. Blue–green discoloration of the nail due to pyocyanin produced by *Pseudomonas aeruginosa*. Note the associated onycholysis. *Courtesy, Julie V Schaffer, MD.*

Fig. 74.21 Superficial infection of the skin with *Pseudomonas*. Note the maceration, erosions and moth-eaten appearance of the skin. *Courtesy, Kalman Watsky, MD.*

Fig. 74.22 Pseudomonas hot-foot syndrome. Tender erythematous nodules on the heel. *Courtesy, Justin J Green, MD.*

Treatment is generally not indicated in immunocompetent hosts, as it is usually a self-limited process. In the case of widespread eruptions, recurrences, immunosuppression or associated systemic symptoms, an oral quinolone or topical gentamicin can be used.

Pseudomonas Hot-Foot Syndrome

Pseudomonas hot-foot syndrome occurs after swimming or wading in pool water that contains high concentrations of *P. aeruginosa*. The soles may be diffusely erythematous, and extremely painful, red-to-purple, 1–2 cm nodules develop on weight-bearing surfaces (Fig. 74.22); palmar involvement occasionally occurs. Systemic symptoms are uncommon. Histologic examination of the nodules shows perivascular and periecrine neutrophilic infiltrates with microabscess formation. The condition is self-limiting and requires only symptomatic treatment. Idiopathic palmoplantar hidradenitis (see Ch. 39) has identical clinical features and may be pathogenically related to pseudomonas hot-foot syndrome. Additional diagnostic considerations may include pernio, symmetric lividities and erythema nodosum[78].

Ecthyma Gangrenosum

P. aeruginosa septicemia occurs primarily in patients who are immunocompromised, with severe neutropenia representing a major predisposing factor. Fever, hypotension and alterations in consciousness often develop, and ecthyma gangrenosum is an occasional cutaneous manifestation. Lesions are usually few in number and begin as erythematous or purpuric macules, most commonly located in the anogenital area or on the extremities. They then evolve into hemorrhagic vesicles or bullae, which rupture and become necrotic ulcers with a central black eschar. The surrounding tissue is erythematous and tender (Fig. 74.23). Of note, a localized anogenital form of ecthyma gangrenosum can also occur in immunocompromised patients (including premature infants[79]) and may not be associated with identifiable bacteremia.

Histologic examination shows a necrotizing hemorrhagic vasculitis, and Gram-negative rods can be seen in the medial and adventitial walls of deeper vessels. The intima is characteristically spared. Multiple lesions, prolonged neutropenia, and a delay in antibiotic treatment portend a poor prognosis. Once the diagnosis is suspected, biopsy and tissue culture of a skin lesion (as well as blood and urine cultures) should be performed, followed by prompt initiation of intravenous therapy with an aminoglycoside and an antipseudomonal penicillin. Nowadays, *Pseudomonas* sepsis is seen less frequently in oncology patients due to shorter durations of neutropenia (secondary to the use of colony-stimulating factors and peripheral blood stem cell rather than bone marrow transplants) and administration of prophylactic antibiotics.

Clinically identical lesions can result from septic emboli due to other organisms, including *E. coli, Aeromonas hydrophila, Burkholderia cepacia, Candida, Fusarium, Aspergillus* and other saprophytic fungi[80].

Fig. 74.23 Ecthyma gangrenosum. Embolic lesion of *Pseudomonas aeruginosa* on the chest. Note the necrotic center and inflammatory border.

BARTONELLA

The genus *Bartonella* encompasses species formerly designated as *Rochalimaea* and *Grahamella*. *Bartonella* are small, pleomorphic, facultative intracellular Gram-negative bacilli closely related to *Brucella* species. Although there are 21 known species of *Bartonella*, only three are known to cause human disease, namely *B. henselae* (cat scratch disease), *B. quintana* (trench fever) and *B. bacilliformis* (Carrion's disease). Both *B. henselae* and *B. quintana* also cause bacillary angiomatosis and endocarditis. One study found that two-thirds of patients with Henoch–Schönlein purpura had antibodies to *B. henselae*[81]. Depending on factors such as the immune status of the infected individual, a particular *Bartonella* species can cause either acute or chronic infection and manifestations ranging from vascular proliferation to suppuration[82].

Bartonellosis

Synonyms: ■ Carrion's disease ■ Oroya fever ■ Verruga peruana

Introduction

Bartonellosis is a potentially life-threatening biphasic infection caused by *Bartonella bacilliformis*. Two clinical forms of bartonellosis are recognized: (1) Oroya fever, an acute febrile disease with associated hemolytic anemia; and (2) verruga peruana (Peruvian wart), a chronic disease characterized by cutaneous vascular lesions.

History

The biphasic nature of bartonellosis was first described in 1540 by Miguel de Steta. In 1885, a medical student, Daniel Carrion, died of complications of Oroya fever after inoculating himself with blood derived from a lesion of verruga peruana, proving a common causality for the two disease states.

Epidemiology and pathogenesis

The disease is transmitted by the bite of a Phlebotomine sand fly (*Lutzomyia verrucarum*). It occurs in mountain valleys of Peru, Ecuador and southwestern Colombia, where the vector resides. There is no racial, gender or age predilection, but the disease tends to be milder in children than in adults. The incubation period varies between 3 and 14 weeks.

Clinical features

The onset of *Oroya fever* is often sudden, with dyspnea, weakness, pallor, tachycardia, fever, thirst, anorexia, arthralgias and headache. A precipitous drop in the erythrocyte count may occur secondary to

massive hemolysis, and hyperbilirubinemia and hemoglobinuria can result. After the initial septicemia, a variable degree of immunodeficiency ensues. During this phase, a third of patients develop secondary bacterial infections; when death occurs, it is often secondary to an enteropathic bacterial infection, especially with *Salmonella enterica*. Lymphadenopathy, splenomegaly, and megaloblastic hyperplasia of the bone marrow are seen in severe cases. Patients with Oroya fever usually require 8–10 weeks for full recovery.

Most patients who recover from Oroya fever develop cutaneous nodules during or after their convalescent period, but *verruga peruana* can also appear in previously asymptomatic individuals. Bright red papules and nodules (2 mm to several centimeters in diameter) appear within small erythematous patches. Lesions may be sessile or pedunculated and are usually located on the head and extremities. Hemorrhage, ulceration and secondary bacterial infection can occur. In the absence of complications, lesions usually heal without scarring but may recur[83].

Pathology

The histologic features of verruga peruana vary and can resemble those of a pyogenic granuloma or Kaposi sarcoma. Masses of intracytoplasmic *Bartonella* organisms (Rocha–Lima inclusions) are present within swollen endothelial cells (as well as red blood cells); the bacilli are also found extracellularly. Thrombosis and occlusion of vessels occurs.

Diagnosis and differential diagnosis

The presence of organisms within red blood cells or within the cytoplasm of endothelial cells is diagnostic. *B. bacilliformis* can be isolated from blood cultures and an ELISA is available. The differential diagnosis of verruga peruana includes multiple pyogenic granulomas, bacillary angiomatosis, warts, molluscum contagiosum and yaws.

Treatment

Table 74.13 outlines the treatment recommendations for bartonellosis.

Cat Scratch Disease

Synonyms: ■ Cat scratch fever ■ Subacute regional lymphadenitis ■ Inoculation lymphoreticulosis ■ English–Wear infection

Introduction

Cat scratch disease (CSD) is caused by infection with *Bartonella henselae*. In immunocompetent hosts, it is a benign, self-limited illness characterized by tender regional lymphadenitis that lasts for weeks to months. Over 90% of patients report a recent scratch and/or bite from a cat[84].

Epidemiology and pathogenesis

Approximately 20 000 cases of CSD are diagnosed annually in the US. CSD occurs worldwide and has a predilection for younger persons (median age 15 years). Both sexes are equally affected. In the US, CSD is most common during the fall and winter. Transmission of infection among cats occurs via a flea vector (*Ctenocephalides felis*). Although flea-vectored transmission to humans has not been documented, it could explain some cases in which there is no history of exposure to cats.

Clinical features

CSD is the most common cause of persistent lymphadenopathy (longer than 3–4 weeks) in children and adolescents. Lymphadenopathy usually presents 2–4 weeks after a scratch and can last 2–6 months (or longer if fibrosis occurs). A single, large (1–10 cm), tender, mobile lymph node, with erythema and swelling of the overlying skin, is most often noted in the axilla. Suppuration occurs in only 10–25% of patients. A skin lesion (e.g. a red papule or crusted pustule) develops at the inoculation site in two-thirds of patients.

Although most patients are otherwise well, the lymphadenopathy can be accompanied by fevers, malaise, fatigue, weakness and headaches. Additional manifestations such as encephalopathy, hepatic granulomas, osteomyelitis and pulmonary involvement develop in up to 15% of patients. The oculoglandular syndrome of Parinaud (unilateral conjunctivitis and ipsilateral preauricular lymphadenopathy) occurs in ~5% of individuals with CSD. Immunosuppressed patients (e.g. those with HIV infection) are prone to a more severe and complicated disease course.

Pathology

Affected lymph nodes display central necrosis surrounded by histiocytic and epithelioid cells with an inner palisading layer. Giant cells with a peripheral zone of lymphoid cells are also evident. The primary skin lesion can show similar changes, albeit less well developed. The Warthin–Starry silver stain demonstrates bacilli within areas of necrosis. Electron microscopic examination shows the bacteria to be extracellular and in small groups.

Diagnosis and differential diagnosis

For patients who present with regional adenopathy and a history of a recent cat scratch, the diagnosis is usually made clinically. A sensitive and specific assay for *B. henselae* antibodies is available, and antibody titers are usually high during the first few weeks after the onset of lymphadenopathy; PCR-based testing can also be performed. Other causes of lymphadenopathy such as infections (bacterial, fungal or viral), reactive hyperplasia, drug reactions or malignancy can be excluded by fine-needle aspiration histology or biopsy and culture of lymph node tissue[85].

Treatment

Table 74.13 outlines current recommendations for the treatment of CSD.

Bacillary Angiomatosis

Synonyms: ■ Epithelioid angiomatosis ■ Disseminated cat scratch disease

Introduction

Bacillary angiomatosis is caused by infection with *B. henselae* or *B. quintana*. Vascular proliferation is the predominant feature of this condition, which most often affects HIV-infected individuals.

History

The disorder was first described in 1983 as subcutaneous vascular proliferations in individuals with AIDS. Electron microscopy and Warthin–Starry-stained sections of the lesions revealed small bacilli. In 1989, LeBoit and colleagues coined the name "bacillary angiomatosis" and proposed histologic criteria for the disorder. In the early 1990s, *R. quintana* and *R. henselae* (subsequently reclassified in the genus *Bartonella*) were recognized as the causes of bacillary angiomatosis (see Table 74.13).

Epidemiology and pathogenesis

Bacillary angiomatosis is an uncommon disease that is most often seen in HIV-infected patients when their $CD4^+$ count is <200 cells/mcl (see Ch. 78). Fortunately, with the advent of effective antiretroviral therapy (ART), the prevalence of bacillary angiomatosis has decreased substantially. The associated vascular proliferation may be due to an angiogenic factor produced by *B. henselae* and *B. quintana*. Only 20% of patients with bacillary angiomatosis due to *B. henselae* report a preceding cat scratch or bite, compared to 90% of those with CSD[86].

Clinical features

Cutaneous lesions of bacillary angiomatosis may present as superficial angiomatous papules and nodules, violaceous lichenoid plaques, or deep subcutaneous nodules. The papules and nodules resemble pyogenic granulomas (Fig. 74.24A) and may be smooth-surfaced, pedunculated, or surrounded by a collarette of scale. These lesions may display central umbilication, crusting or ulceration. Subcutaneous nodules are often several centimeters in diameter and skin-colored; overlying erosions or ulcerations may develop. Less commonly, bacillary angiomatosis presents as a cellulitic erythematous plaque that can involve the underlying bone. The host immune status largely

MAJOR HUMAN DISEASES CAUSED BY BARTONELLA SPECIES AND THEIR TREATMENT								
Species	**Disease**	**Vector**	**Reservoir/ host**	**Epidemiology**	**Recommended treatment**	**First-line**	**Second-line**	**Notes**
B. bacilliformis	Bartonellosis (Carrion's disease, Oroya fever, verruga peruana)	Phlebotomine sand fly (*Lutzomyia verrucarum*)	Human	• Andean mountain valley regions of Peru, Ecuador and southwestern Columbia (altitudes of 2500–8000 feet) • More common in immunologically naive tourists and transient workers • Milder in children	• Oroya fever	Chloramphenicol* plus β-lactam antibiotic Quinolone (norfloxacin, ciprofloxacin) [>6 years of age, non-pregnant]	Trimethoprim–sulfamethoxazole Macrolide Doxycycline	• Successful treatment does not eliminate risk for developing verruga peruana • Adjunctive treatment needed with chloramphenicol, as treatment failures have been seen with monotherapy • Death occurs in ~40% of untreated individuals
					• Verruga peruana	Rifampin Streptomycin [traditional]	Ciprofloxacin Azithromycin	• Only 5% of patients recall an acute febrile illness • Disappearance of skin lesions within 1 month with treatment
B. henselae	Cat scratch disease	Cat flea (*Ctenocephalides felis*)	Cat	• Primarily seen in young people (<18 years) in the fall and winter • Immunocompetent > immunocompromised	• Mild to moderate, uncomplicated	Supportive care (analgesics) only Needle aspiration of suppurative lymph nodes	Azithromycin Doxycycline *plus* rifampin	• Azithromycin shown to decrease lymph node volume but not effective in preventing dissemination or complications
					• Severe, complicated	Doxycycline *plus* rifampin		• Severe disease includes retinitis, encephalopathy, visceral spread
	Bacillary angiomatosis			• Immunocompromised (e.g. common in HIV)	• Mild, uncomplicated bacillary angiomatosis	Erythromycin	Doycycline Azithromycin Clarithromycin	• Jarish–Herxheimer-like reaction may occur • Treatment failures seen with quinolones, trimethoprim–sulfamethoxazole, narrow-spectrum cephalosporins • Use of iv antibiotics recommended for GI intolerance or poor absorption states • Doxycycline *plus* rifampin recommended for CNS disease because of better CNS penetration
	Bacillary peliosis hepatis			• Immunocompromised				
	Bacteremia (chronic afebrile)		*(Cat exposure not a risk factor in bacteremia)*	• Immunocompetent or immunocompromised				
	Endocarditis			• Late complication of chronic bacteremia	• Severe, complicated bacillary angiomatosis	Erythromycin Doxycycline *plus* rifampin Doxycycline *plus* aminoglycoside		
B. quintana	Trench fever "Five day fever" "Urban trench fever" "Quintan fever"	Human body louse (*Pediculosis humanus*)	Human	• First reported in World War I troops, now associated with homelessness and poor hygiene ("urban trench fever")				
	Bacillary angiomatosis			• Immunocompromised (e.g. common in HIV)				
	Bacteremia (chronic afebrile)			• Immunocompetent or immunocompromised				
	Endocarditis			• Late complication of chronic bacteremia				

*Gray baby syndrome can develop in premature neonates who receive chloramphenicol.

Table 74.13 Major human diseases caused by *Bartonella* species and their treatment[82]. Fever and splenomegaly due to bacteremia with *Bartonella rochalimae* (a recently recognized species) has also been described.

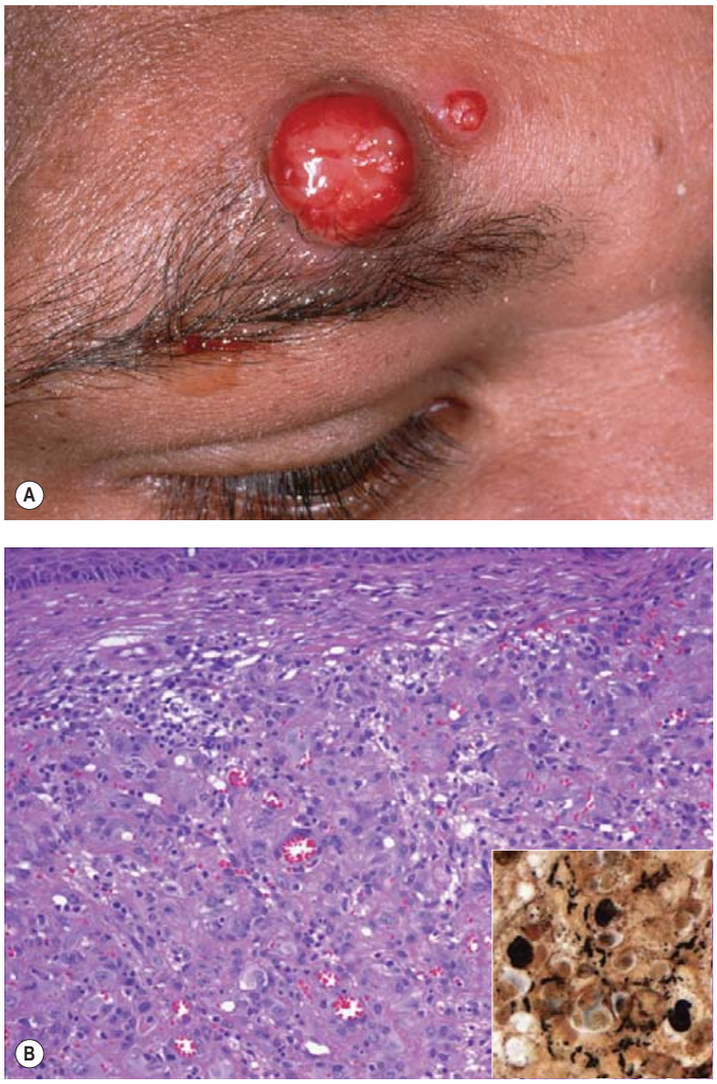


Fig. 74.24 Bacillary angiomatosis. A Bright red nodule and papule on the forehead. **B** Histologically, a dermal proliferation of vessels with plump endothelial cells is evident and scattered neutrophils are present in the accompanying infiltrate. Bacilli (in this case *Bartonella henselae*) are identified with the Warthin–Starry stain (insert). *B, Courtesy, James Patterson, MD.*

determines the number and distribution of the lesions. Immunocompetent patients may have a single lesion at the site of inoculation, whereas the entire cutaneous surface can be affected in those who are severely immunocompromised.

Extracutaneous bacillary angiomatosis may occur with or without cutaneous disease and can affect any organ. Bacillary peliosis hepatis caused by *B. henselae* (but not *B. quintana*) presents with nausea, vomiting, diarrhea, abdominal pain, hepatosplenomegaly and elevated liver enzymes. Bacillary peliosis splenis may lead to pancytopenia and require splenectomy. Patients can also present with malaise and night sweats[87].

Pathology

Biopsy specimens reveal lobular proliferations of capillaries and venules, plump and protuberant endothelial cells, and a marked neutrophilic infiltrate with evidence of leukocytoclasis throughout the interstitium (Fig. 74.24B). In H&E-stained sections, interstitial clumps of bacilli appear as purplish granular material. Bacteria can be readily identified with a Warthin–Starry stain (see Fig. 74.24B, insert).

Diagnosis and differential diagnosis

PCR-based assays are a rapid and sensitive method to identify *Bartonella* from tissue specimens. Culture of *B. henselae* or *B. quintana* on chocolate or supplemented agar may take 20 to 40 days. Testing to detect antibodies against *B. henselae* (but not *B. quintana*) is sensitive and specific.

The clinical differential diagnosis includes pyogenic granulomas, Kaposi sarcoma, cherry angiomas, angiokeratomas, verruga peruana and a disseminated atypical mycobacterial infection. Histologically, bacillary angiomatosis can be confused with verruga peruana, Kaposi sarcoma, pyogenic granuloma and angiosarcoma.

Treatment

Cutaneous lesions begin to improve within 1 week of appropriate antibiotic therapy and resolve completely within 4 weeks. At least 3 months of treatment is recommended, as therapeutic failures and relapses can occur with shorter courses. Immunosuppressed patients with disease relapses may require maintenance therapy. Surgical excision of solitary cutaneous lesions, although effective, is usually not necessary. Table 74.13 outlines treatment recommendations for bacillary angiomatosis.

OTHER GRAM-NEGATIVE SKIN INFECTIONS

Brucellosis

Synonyms: ■ Undulant fever ■ Malta fever ■ Bang's disease

Brucellosis is a chronic granulomatous disease caused by *Brucella*, a genus of Gram-negative coccobacilli[88]. Approximately 500 000 cases occur worldwide annually, the majority in the Middle East. Transmission occurs through the consumption of contaminated unpasteurized milk products (commonly raw goat's milk and cheese), direct contact with infected animal parts, or inhalation of aerosolized particles. Infection is rare in the US (100–200 cases per year) and is primarily an occupational disease of farmers, laboratory personnel, butchers and veterinarians. Children tend to have a more benign course, with fewer complications and better response to treatment.

Brucellosis demonstrates substantial clinical variability (Fig. 74.25). The acute form is characterized by nonspecific signs and symptoms (e.g. fever, malaise, headache, diaphoresis, arthralgias, myalgias, back pain, lymphadenopathy and hepatosplenomegaly). Patients with chronic brucellosis are afebrile but experience arthralgias, headaches, myalgias, diaphoresis, cyclic depression, sexual impotence, spondylitis, episcleritis and uveitis. Malodorous perspiration is highly characteristic. Skin lesions occur in <10% of patients, most often presenting as a disseminated eruption of violaceous papulonodules. Other cutaneous manifestations of brucellosis include erythema nodosum-like lesions, extensive purpura and a morbilliform eruption[89]. Endocarditis represents the major cause of death.

Acute brucellosis may mimic mononucleosis, influenza, malaria, typhoid fever, typhus, tularemia, tuberculosis or sarcoidosis. The chronic form can be confused with rheumatologic, neurologic or psychosomatic conditions. Multidrug regimens are recommended for brucellosis, with doxycycline (first-line) in various combinations with streptomycin, rifampin, quinolones, aminoglycosides and TMP-SMX. There is some concern regarding the use of rifampin in areas with a high prevalence of tuberculosis, as resistance may develop.

Glanders

Glanders is principally a disease of horses, mules and donkeys that is caused by *Burkholderia mallei* (formerly *Pseudomonas mallei*), a nonmotile, strictly aerobic, non-pigment-producing, Gram-negative bacillus. Glanders is endemic in Africa, Asia, the Middle East, and Central and South America. Human disease is rare, occurring chiefly in those with direct contact with infected animals, such as veterinarians, animal caretakers, abattoir workers and laboratory personnel. Tissue damage results from production of exotoxins, including pyocyanin (interferes with electron transfer), lecithinase (causes cell lysis), collagenase, lipase and hemolysin.

Glanders has four clinical forms (septicemic, localized, pulmonary and chronic). Acute *septicemic* glanders is characterized by malaise, anorexia, chills, fever, diarrhea, prostration and joint pains. Patients may have flushing, cyanosis, a disseminated pustular eruption, cellulitis, lymphangitis, erythroderma and/or jaundice. Multiorgan failure ensues, and the mortality rate is ~50% (>90% without treatment).

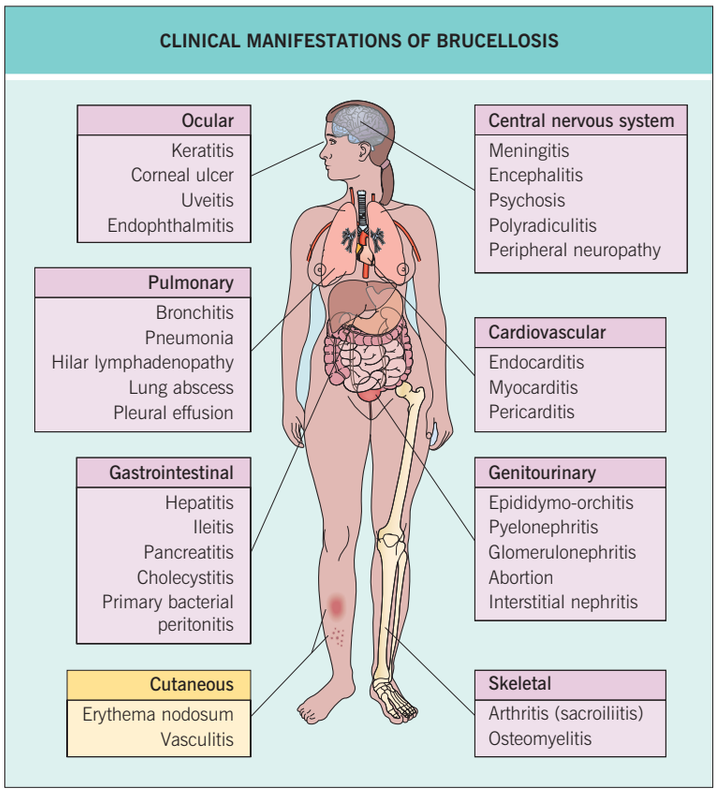


Fig. 74.25 Clinical manifestations of brucellosis. *With permission from Slack MPE. Gram-negative coccobacilli. In: Armstrong D, Powderly WG (eds). Infectious Diseases. Edinburgh: Mosby, 2004.*

In the *localized* form, a nodule, pustule or vesicle surrounded by hemorrhagic edema appears at the inoculation site after approximately 1 to 5 days. The superficial portion of the lesion sloughs, producing an ulcer with a gray–brown base. Glanders may also involve the nose and cause ulceration or perforation of the nasal septum or palate. *Chronic* glanders features malaise, myalgias and often fevers. Painful subcutaneous and intramuscular abscesses may appear at any site, and they may ulcerate, drain or extend into joints, periosteum and bone. Multiple subcutaneous and intramuscular nodules ("farcy buds") appear along the draining lymphatics, and the term "farcy pipes" refers to the firm cords that result from lymphatic involvement.

Glanders should be considered when localized cutaneous abscesses and secondary lesions appear in the path of lymphatic drainage (see Table 77.15). Accurate diagnosis can be made with serologic testing. For localized disease, a 60- to 150-day course of oral amoxicillin/clavulanate, doxycycline or TMP-SMX can be prescribed. Alternatives include ciprofloxacin, streptomycin, gentamicin, imipenem and ceftazidime[90].

Melioidosis

Synonym: ▪ Whitmore disease

Melioidosis is caused by *Burkholderia pseudomallei* (formerly *Pseudomonas pseudomallei*), a mobile, obligately aerobic, non-spore-forming bacillus found in soil and water. The name melioidosis is derived from the Greek words *melis*, meaning "donkey distemper", and *eidos*, meaning "resembles glanders". Melioidosis is endemic in Southeast Asia and northern Australia, but it also occurs in South Pacific islands, Africa, India, the Middle East, and Central and South America. Infection develops via direct contact of abraded or lacerated skin with contaminated soil or water as well as through ingestion, inhalation or sexual intercourse. It is more common in adults with underlying medical conditions (e.g. diabetes mellitus, renal insufficiency).

Acute melioidosis can produce localized cutaneous infections, pneumonia or septicemia. *Subacute* melioidosis, primarily a pulmonary disease, is frequently confused with tuberculosis. *Chronic* melioidosis is characterized by abscesses and granulomas in multiple sites. Cutaneous manifestations may include cellulitis, subcutaneous abscesses, granulomatous lesions, ecthyma gangrenosum, purpura, pustules and urticaria.

Both complement-fixing and agglutinating antibodies appear within 4 to 6 weeks after infection. PCR-based and other molecular diagnostic techniques are also available.

Treatment of melioidosis is difficult, and sensitivity studies should be performed. Current treatment guidelines favor imipenem, ceftazidime, piperacillin/tazobactam, tetracyclines or TMP-SMX; *B. pseudomallei* has shown resistance to quinolones, macrolides and aminoglycosides. Intensive supportive care lowers the mortality rate to about 20% (vs 40–50% in some areas). Melioidosis has a high relapse rate (approximately 10%), and long-term antibiotic therapy is needed, as *B. pseudomallei* can remain latent in the body for up to 25 years[91,92].

Because *B. mallei* and *B. pseudomallei* represent potential agents of bioterrorism, attempts are being made to develop vaccines for these infections[93].

Cutaneous Malacoplakia (Malakoplakia)

Cutaneous malacoplakia is a rare chronic infectious condition that is characterized by granulomatous inflamation with distinctive macrophages that are unable to phagocytose and kill bacteria effectively. It occurs primarily in immunocompromised hosts, particularly solid organ transplant recipients, and is most commonly due to *E. coli*, although *Pseudomonas, Proteus, Klebsiella, Staphylococcus* and *Mycobacterium* spp. have also been implicated.

Most cases of malacoplakia affect the genitourinary tract. Cutaneous lesions usually involve the perianal region and can present as ulcerations, abscesses with multiple draining sinuses, yellow-to-pink soft papules, and erythematous indurated nodules.

Histologic examination of involved tissue shows highly characteristic findings. *Michaelis–Gutmann bodies* are intracytoplasmic laminated concretions that represent accumulations of calcified, iron-containing phagolysosomes; they stain with PAS, von Kossa, Perls' and Giemsa stains. *von Hansemann cells* are large macrophages that contain Michaelis–Gutmann bodies and stain positively for CD68, lysozyme and α_1-antitrypsin. The histopathologic differential diagnosis may include sarcoidosis, infectious granulomas, Langerhans cell histiocytosis, granular cell tumor and fibrous histiocytoma.

The treatment of malacoplakia is difficult. Localized disease may be amenable to surgical excision. Prolonged courses of antibiotics, including quinolones, TMP-SMX and clofazimine, have been used successfully. Ascorbic acid and bethanechol chloride have been employed to increase intracellular cGMP and improve macrophage function. In severe cases, reducing the dosage of immunosuppressive therapy (if possible) may be of benefit[94,95].

Tularemia

Synonyms: ▪ Deer fly fever ▪ Rabbit fever ▪ Pahvant Valley plague

Tularemia is a bacterial infection caused by *Francisella tularensis*, a Gram-negative, non-motile coccobacillus. First described in 1911 as a plague-like illness, there are 150–200 cases per year in the US. Skin or mucous membranes are the portal of entry for infections associated with tick or deer fly bites and exposure to the organism via abrasions. Inhaled or ingested organisms rarely cause the disease. Rabbits, hares and ticks are the main reservoirs for *F. tularensis*. Although infected rabbits and their carcasses are classically described as the main sources of infection, deer flies and ticks are more significant vectors.

Tularemia occurs in six clinical forms according to the mode of transmission: ulceroglandular, glandular, oculoglandular, oropharyngeal/gastrointestinal, typhoidal/septicemic, and pneumonic (Fig. 74.26). Ulceroglandular tularemia is the most common form and is characterized by both lymphadenopathy and an erythematous, indurated, punched-out ulcer that may last for several weeks. The lymph nodes can become fluctuant and suppurate. Occasionally, ulceration or lymphadenopathy occur in isolation. Other rare cutaneous manifestations include buboes, a morbilliform eruption, erythema nodosum and erythema multiforme.

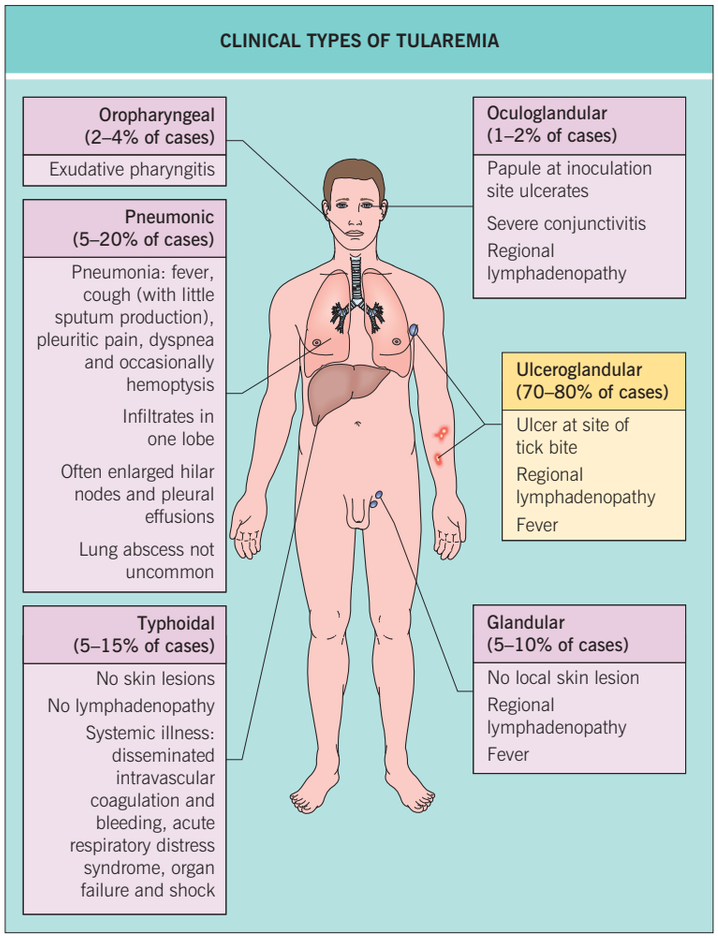


Fig. 74.26 Clinical types of tularemia. *Adapted with permission from Slack MPE. Gram-negative coccobacilli. In: Armstrong D, Powderly WG (eds). Infectious Diseases. Edinburgh: Mosby, 2004.*

Because of concern regarding the potential use of *F. tularensis* as a biologic weapon, tularemia is a reportable disease in the US[96]. Fluorescent antibody testing is rapid and reliable. Attempts to culture *F. tularensis* are usually not made due to its high infectivity, risk to laboratory workers, and inability to grow on most media. The differential diagnosis of ulceroglandular tularemia includes other ulceroglandular entities (e.g. bubonic plague, tuberculous chancre, rat-bite fever, glanders), anthrax, soft tissue infections (i.e. *Staphylococcus, Streptococcus*, *Pasteurella multocida*), and infectious causes of a sporotrichoid pattern (see Ch. 77).

Treatment options include a 10-day course of streptomycin (the classic first-line agent), gentamicin or a quinolone; alternatives include a 14–21-day course of doxycycline or chloramphenicol (longer due to a higher risk of relapse with these bacteriostatic medications)[97]. A Jarisch–Herxheimer-like reaction may occur following the initiation of therapy.

Haemophilus influenzae Cellulitis

Haemophilus influenzae is a Gram-negative coccobacillus that can cause facial cellulitis with a violaceous hue in infants and young children (usually 6–24 months of age) following an upper respiratory tract infection. It favors the buccal and periorbital areas and is often associated with high fevers, an increased leukocyte count with a left shift, and positive blood cultures. Routine vaccination of children against *H. influenzae* type b has greatly reduced the incidence of this form of cellulitis[98]. First-line therapy for severe *H. influenzae* infections is a third-generation cephalosporin; selection of empiric antibiotic therapy for cellulitis is discussed above.

Rhinoscleroma

Rhinoscleroma is a slowly progressive, chronic granulomatous infection involving the nose and upper respiratory tract. It is caused by *Klebsiella rhinoscleromatis*, a short, immotile Gram-negative bacillus that is a subspecies of *Klebsiella pneumoniae*. Endemic foci exist in Central Europe, Egypt, India, Indonesia, Mexico, Central America and tropical Africa. Deficiencies of cellular, but not humoral, immunity cause ineffective phagocytosis by macrophages, giving rise to large, vacuolated, non-lipidized histiocytes with intracellular bacteria (Mikulicz cells)[99]. Clinical features, diagnostic techniques, the differential diagnosis and treatment recommendations are outlined in Table 74.14. Histologic findings mimicking Rosai–Dorfman disease have been observed in the lymph nodes of a patient with rhinoscleroma[100].

RHINOSCLEROMA – CLINICAL FEATURES, DIFFERENTIAL DIAGNOSIS AND TREATMENT	
Risk factors	• Poor hygiene, poor nutrition and living in overcrowded conditions
Stage one: rhinitic/catarrhal/atrophic	• Nonspecific rhinitis • Purulent rhinorrhea and crusting • Nasal obstruction
Stage two: granulomatous/infiltrative/hypertrophic	• Granulomatous nodules form in the nose, pharynx and larynx • Dysphonia, anosmia and anesthesia of soft palate may occur • Epistaxis, deformity of the nose, destruction of the nasal cartilage (Hebra nose)
Stage three: sclerotic/cicatricial	• Nodules replaced by fibrous tissues with resultant extensive scarring and stenosis often requiring surgical intervention (e.g. tracheotomy, reconstruction of the airway)
Diagnosis	• Presence of Mikulicz cells and Russell bodies on routine histology – *Mikulicz cells*: large, vacuolated, non-lipidized histiocytes with intracellular bacteria – *Russell bodies*: plasma cells with aggregates of condensed immunoglobulins • PAS, Giemsa, silver and Gram stains are reliable • Immunoperoxidase studies are sensitive and specific • Cultures are positive in only ~50% of cases • "Crypt-like" irregularities of the trachea can be seen on computed tomography
Differential diagnosis (see Table 45.3)	• Mucocutaneous (New World) leishmaniasis, paracoccidioidomycosis (and other dimorphic fungal infections), rhinosporidiosis, leprosy, yaws, tertiary syphilis, nasal tuberculosis, sarcoidosis, Wegener's granulomatosis, nasal T-cell/natural killer cell lymphoma, basal cell and squamous cell carcinoma, extranodal Rosai–Dorfman disease
Treatment	• Antimicrobial therapy for 6 months or until nasal biopsy is negative; tetracycline is first-line therapy along with surgical correction of obstructed airway • Rifampin and ciprofloxacin are alternative antibiotics • Sclerotic lesions respond to ciprofloxacin • Bacterial superinfection is common, requiring treatment with clindamycin or a third-generation cephalosporin

Table 74.14 Rhinoscleroma – clinical features, differential diagnosis and treatment.

Salmonellosis

Salmonellosis refers to the spectrum of infections caused by Gram-negative aerobic bacilli in the genus *Salmonella*. Enteric fever due to *S. typhi* is known as typhoid fever[101], and a similar clinical syndrome of enteric fever produced by non-typhoidal strains such as *S. paratyphi* is referred to as paratyphoid fever. *S. typhi* is spread via direct contact with persons who have typhoid fever or are chronic carriers. In contrast, non-typhoidal *Salmonella* is most commonly acquired from inadequately cooked poultry and eggs, resulting in gastroenteritis.

Typhoid fever is characterized by fever, headache, malaise, myalgias, cough, sore throat, nausea, vomiting, diarrhea and constipation. The characteristic cutaneous sign, "rose spots", are pink, blanching, slightly elevated papules that measure 2–8 mm and are usually found on the anterior trunk in groups of 5–15 lesions. They occur in up to 50% of patients with typhoid fever and less often in non-typhoidal enteric fever. Rose spots often occur in crops during the second to fourth weeks of the illness, and *Salmonella* spp. can usually be cultured from these lesions. Other cutaneous manifestations of salmonellosis include erythema multiforme, Sweet's syndrome, hemorrhagic bullae, pustular dermatitis, and a generalized erythematous eruption known as erythema typhosum.

A history of travel to endemic areas (e.g. Southeast Asia, South America), persistence of fevers, and positive cultures aid in distinguishing salmonellosis from influenza and other viral infections. Since the late 1980s, *S. typhi* has developed resistance to all the drugs that were then used as first-line treatments (chloramphenicol, TMP-SMX and ampicillin). Currently, quinolones are first-line therapy, although resistance has begun to emerge (especially in Asia). Third-generation cephalosporins are the treatment of choice in children.

Rat-Bite Fever

Synonyms: ▪ Haverhill fever ▪ Erythema arthriticum epidemicum

Streptobacillus moniliformis infections result in an acute illness characterized by fever, arthritis and a rash. While the disorder is usually caused by a bite (rat-bite fever), it can also occur from close contact with rodents or ingestion of contaminated food, water or raw milk (Haverhill fever).

The incidence of rat-bite fever is highest in urban areas with poor sanitation where there is a large population of rats. Erythema, edema, abscess formation, ulceration and secondary infection may develop at the site of the bite. Regional lymphadenopathy is common. Paroxysms of fever interspersed with afebrile periods as well as headaches, nausea, vomiting and myalgias may occur. In infants and children, weight loss and diarrhea can be significant. One of the hallmarks of the disease is a migratory polyarthritis that occurs in 50% of cases and may mimic rheumatoid arthritis. At 2 to 4 days following the onset of fever and arthritis, most patients with rat-bite fever develop an acrally distributed eruption involving the palms and soles. Morbilliform macules and papules, petechiae, vesicles, pustules and crusts may be seen.

The triad of fever, arthritis/arthralgias and a rash can be caused by numerous infectious diseases, including viral infections (e.g. enteroviruses, EBV, parvovirus B19) Rocky Mountain spotted fever, acute or chronic meningococcemia, acute rheumatic fever and secondary syphilis. Non-infectious causes include Still's disease, systemic lupus erythematosus, serum sickness-like drug reactions, Sweet's syndrome, Schnitzler's syndrome and periodic fever syndromes.

Penicillin is the drug of choice for rat-bite fever and is usually administered for a week, although patients with septicemia may require up to 6 weeks of parenteral therapy. Tetracyclines and streptomycin are also effective. Erythromycin, clindamycin and cephalosporins have been used as well, but studies of their efficacy are lacking. Although most infections resolve spontaneously within 2 weeks, 10–15% of untreated cases are fatal[102].

Plague

Plague is an acute bacterial infection caused by *Yersinia pestis*, a Gram-negative, rounded, bipolar bacillus transmitted by fleas and rodents (Fig. 74.27). The highest incidence of *Y. pestis* infection is in Southeast Asia. In the US, most human infections occur in two regions: (1) northern New Mexico, northern Arizona and southern Colorado; and (2) California, southern Oregon and far western Nevada. Plague also occurs in Africa, South America and other regions of Asia.

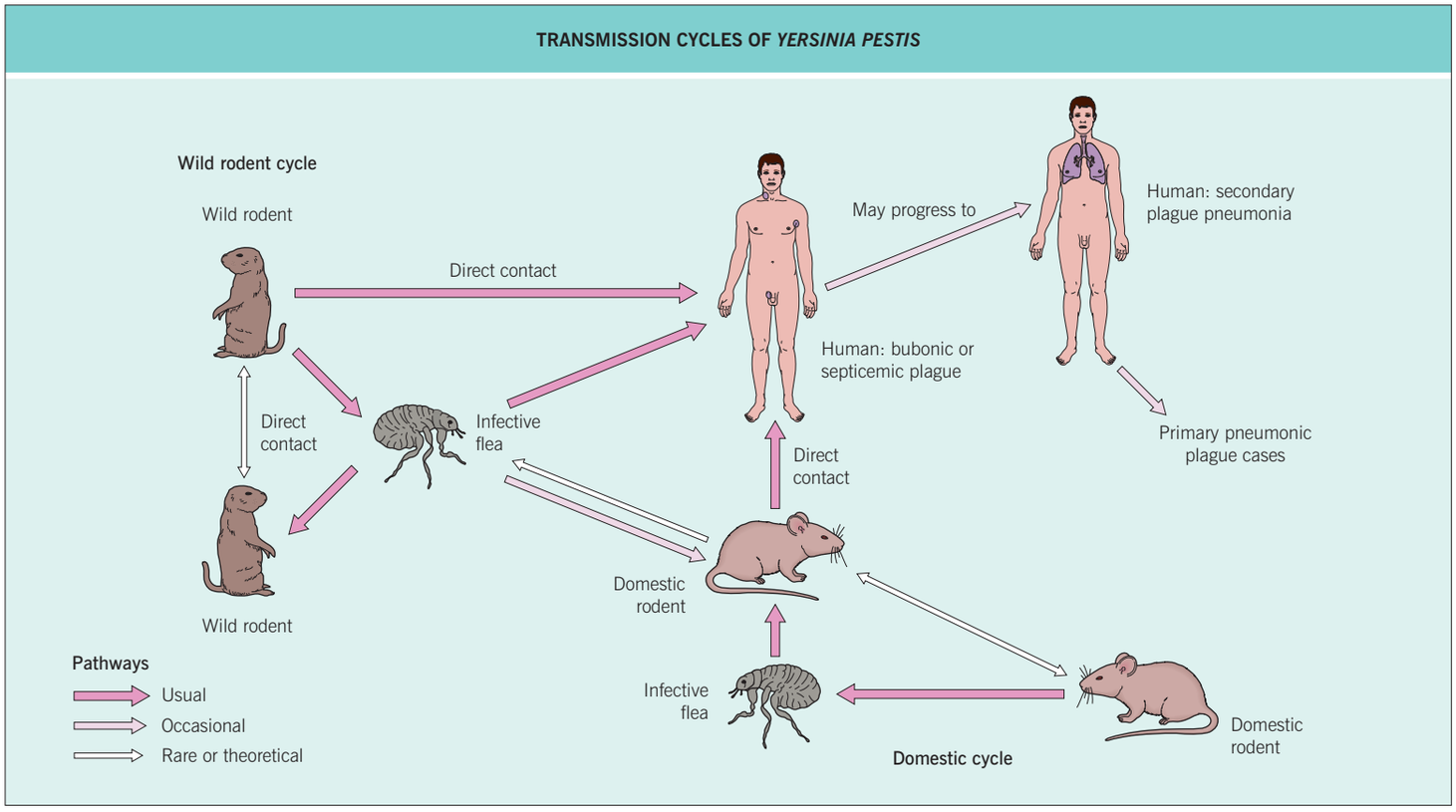


Fig. 74.27 Transmission cycles of *Yersinia pestis*. *With permission from Dennis DT, Gage KL. Plague. In: Armstrong D, Powderly WG (eds). Infectious Diseases. Edinburgh: Mosby, 2004.*

RISK FACTORS FOR *VIBRIO* INFECTION
ACQUISITION OF INFECTION
Cutaneous exposure to contaminated seawater and/or shellfish
• Exposure to warm coastal salt water (April–October in temperate climates) • Handling shellfish • New injury to the skin or a pre-existing wound predisposes to a primary cutaneous infection, which can lead to cellulitis, necrotizing fasciitis and/or septicemia in susceptible hosts (see below)
Consumption of contaminated raw/undercooked seafood
• Classically raw oysters, but also found in clams, crabs and other shellfish • Leads to an acute gastrointestinal illness in immunocompetent individuals and septicemia in susceptible hosts (see below)
UNDERLYING MEDICAL CONDITIONS THAT PREDISPOSE TO SEVERE INFECTIONS
Liver disease
• Hemochromatosis – *V. vulnificus* is ferrophilic and requires higher levels of iron than other pathogens – Patients have decreased hepcidin antibacterial activity • Alcoholic cirrhosis
Diabetes mellitus
• Peripheral neuropathy predisposes to cutaneous wounds that serve as a portal of entry
Gastrointestinal disease
• Peptic ulcer disease – Antacid use may lead to increased survival of *V. vulnificus* • Gastrointestinal surgery
Immunosuppression
• HIV infection and AIDS • Leukemia or lymphoma • Treatment with corticosteroids or chemotherapy
End-stage renal disease

Table 74.15 Risk factors for *Vibrio* infection.

Fig. 74.28 Hemorrhagic bullae of the leg secondary to *Vibrio vulnificus* infection.

Three clinical forms of plague are recognized: bubonic, septicemic and pneumonic. The symptoms of *bubonic* plague are variable. Constitutional symptoms may be lacking or severe. In approximately 10% of patients, the inoculation wound develops into a pustule or ulcer. This is followed by painful regional lymphadenopathy; suppuration and discharge from the lymph nodes may occur. In *septicemic* plague, vesicles, carbuncles, petechiae and purpura may be seen. Necrotic lesions and hemorrhage from the nasopharynx or gastrointestinal tract have also been described. In *pneumonic* plague, the patient develops acute pneumonitis. Apathy, delirium, coma and seizures occur in seriously ill patients. Bubonic plague may simulate tularemia, rat-bite fever, sporotrichosis, tuberculosis, streptococcal ecthyma, syphilis or lymphogranuloma venereum. Septicemic plague must be differentiated from typhus, typhoid fever, tularemia, malaria and other bacteremias.

Untreated bubonic plague has a 25–50% fatality rate, while untreated septicemic or pneumonic plague is nearly always fatal. Streptomycin and other aminoglycosides (e.g. gentamicin) are first-line treatments for plague. Doxycycline and quinolones may be used when oral therapy is acceptable. Chloramphenicol (which attains high concentrations in the cerebrospinal fluid) is the drug of choice for plague meningitis or endophthalmitis. Postexposure prophylaxis with doxycycline or ciprofloxacin, if taken within 7 days, is extremely effective in preventing disease[103]. The development of a vaccine against pneumonic and bubonic plague has been technically difficult to achieve.

Vibrio vulnificus Infection

The genus *Vibrio* constitutes a group of Gram-negative anaerobic bacteria, among which *V. vulnificus* is the most common cause of cutaneous disease. *V. vulnificus* infections occur most commonly in men over 40 years of age who have chronic liver disease or diabetes mellitus and a history of exposure to seawater or raw seafood[104]; additional risk factors are listed in Table 74.15. The clinical presentation of *V. vulnificus* septicemia includes fever, chills, nausea, vomiting, diarrhea, abdominal cramps and hypotension. Skin lesions develop in 75% of these patients, with progression from erythematous and purpuric macules to vesicles and hemorrhagic bullae (Fig. 74.28) to necrotic ulcers in a manner reminiscent of purpura fulminans. Wounds acquired in or contaminated by seawater can also lead to *Vibrio* cellulitis that is erythematous, edematous and painful, typically with rapid evolution to hemorrhagic bullae. Progression to necrotizing fasciitis or myositis occasionally occurs. First-line treatment is doxycycline (oral or intravenous) plus a third-generation cephalosporin (intravenous or intramuscular); alternative regimens include a quinolone or the combination of an aminoglycoside and TMP-SMX. Necrotic lesions may require surgical debridement[105].

EHRLICHIOSIS AND ANAPLASMOSIS

These infections are discussed in Chapter 76.

SPIROCHETES

BORRELIA BURGDORFERI

Lyme Disease

Synonym: ▪ Lyme borreliosis

Lyme disease is a multisystem disorder with prominent skin findings that is caused by *Borrelia* species of spirochetes. Although found worldwide, it has a particularly high incidence in North America and Europe, representing the most common tick-borne disease in the US. Lyme disease can occur year-round, but most cases present in the summer. If diagnosed in its early stages, it is a completely curable illness.

The species of *Ixodes* tick vector differs depending on the geographic region, e.g. *I. pacificus* in the western US, *I. scapularis* (also called *I. dammini*) in the eastern US and Great Lakes region, *I. ricinus* in Europe, and *I. peisulcatus* in Asia. *B. burgdorferi* is the predominant etiologic organism in the US, whereas *B. garinii* and *B. afzelii* are the predominant causes of Lyme disease in Europe[106]. This may explain the occurrence of borrelial lymphocytoma and acrodermatitis chronica atrophicans in Europe but not the US. Once the spirochete is in the midgut of the tick vector (after feeding on an infected host, e.g. white-tailed deer), it produces outer surface protein C (OspC), which enables it to traverse the midgut epithelium, enter the hemocoel, and make its way to the salivary glands. *B. burgdorferi* is ultimately transmitted to

humans via the tick's saliva. The rate of transmission is low in the first 24 hours of attachment and increases dramatically after 48 hours.

Chapter 19 describes the clinical features and treatment of Lyme disease, in particular erythema migrans (Fig. 74.29), and Table 74.16 outlines the extracutaneous manifestations of Lyme disease. The next sections discuss borrelial lymphocytoma and acrodermatitis chronica atrophicans.

Borrelial Lymphocytoma

Synonyms: ■ Lymphadenosis benigna cutis ■ Lymphocytoma cutis ■ Cutaneous lymphoid hyperplasia ■ Spiegler–Fendt lymphoid hyperplasia, pseudolymphoma of Spiegler and Fendt, sarcoidosis of Spiegler and Fendt ■ Cutaneous B- or T-cell pseudolymphoma

Lymphocytoma is a benign, reactive form of lymphoid hyperplasia that can be attributed to various stimuli, including *Borrelia* infection. Borrelial lymphocytoma usually appears during the early disseminated stage of Lyme disease (see Ch. 19). Because it is caused by *B. afzelii* and *B. garinii* (neither of which is present in North America), borrelial lymphocytoma is virtually never seen in those who have not traveled outside of the US, although it occurs in approximately 1% of patients with Lyme disease in Europe.

Fig. 74.29 Erythema migrans. Expanding erythematous plaque on the neck (**A**) and on the lateral trunk (**B**). *B, Courtesy, Dennis Cooper, MD.*

The formation of a lymphocytoma following a tick bite was first reported in 1950, but it was not until 1986 that *Borrelia* was cultured from such a lesion. A firm, bluish-red, occasionally tender nodule or plaque appears most commonly on the earlobes in children and the nipple/areola in adults, less often developing on the genitalia, trunk or extremities. It may be associated with regional lymphadenopathy.

Histologically, the epidermis is normal and separated from the dermal infiltrate by a Grenz zone. The dense dermal infiltrate of lymphocytes forms a pattern that closely resembles the architecture of a lymphoid follicle. The histologic differential diagnosis includes an arthropod bite reaction and cutaneous lymphoma, with the presence of Bcl-2 protein within follicular cells and monoclonality by PCR favoring the latter (see Ch. 119)[107]. Of note, *B. burgdorferi*-associated B-cell lymphomas have been described[108]. Borrelial lymphocytoma responds to the antibiotics used for Lyme disease (see Ch. 19) as well as to topical and intralesional corticosteroids[109].

Acrodermatitis Chronica Atrophicans

Synonym: ■ Herxheimer disease

Acrodermatitis chronica atrophicans (ACA) is a cutaneous manifestation of chronic Lyme disease. First described in Europe in 1883 by Buchwald as "idiopathic atrophy", it is most commonly due to an infection with *B. afzelii* (although it has also been associated with *B. burgdorferi* and *B. garinii*). As a result, it is extremely rare in the US but is seen in approximately 10% of patients with Lyme disease in Europe.

ACA occurs 6 months to 8 years after the initial infection, predominantly in women 40–70 years of age, and appears to be associated with long-term persistence of *Borrelia* organisms in the skin. It is a biphasic disorder consisting of an early, easily treatable, inflammatory stage and a late, treatment-resistant, atrophic stage. Initially, erythematous to violaceous plaques and nodules develop on the acral portion of the extremities, often insidiously. The skin is frequently doughy and swollen. This early stage follows a waxing and waning course for weeks to years. In the late stage, the skin has a glistening ("cigarette-paper") appearance with prominent blood vessels (Fig. 74.30). Fibrous nodules may form on extensor surfaces (ulnar or tibial bands). Hypopigmentation, hyperpigmentation, pain, pruritus, hyperesthesia, paresthesias and scaling may also be present. Rarely, the condition may be complicated by the development of basal cell or squamous cell carcinoma[110].

In biopsy specimens of early lesions, a dermal perivascular lymphocytic infiltrate with plasma cells, telangiectatic endothelial-lined spaces, and mild epidermal atrophy is seen. Histologic examination of late lesions shows an atrophic epidermis and an interstitial lymphocytic infiltrate with plasma cells and occasional histiocytes and mast cells. The dermis may be attenuated, with periadnexal fibrosis. The differential diagnosis may include eczematous dermatitis (including stasis), cold injury, atrophy secondary to chronic use of potent topical corticosteroids, severe photodamage, and, in the case of fibrotic lesions, scars, morphea and fibromatoses[111].

MAJOR EXTRACUTANEOUS FEATURES OF LYME DISEASE	
General	Fever, malaise, headache, regional lymphadenopathy, non-productive cough
Eyes	Conjunctivitis, keratitis, iritis, episcleritis, retrobulbar neuritis
Neurologic	Meningitis, encephalitis, Guillain–Barré syndrome, Bell's palsy, psychiatric syndromes, optic atrophy, ataxia
Cardiac	Heart block, arrhythmias, pericarditis, myocarditis, cardiomyopathy, congestive heart failure
Rheumatologic	Arthralgias, tendinitis, oligoarthritis, bone calcifications and cysts
Genitourinary	Orchitis, softening of the testes, proteinuria, microhematuria

Table 74.16 Major extracutaneous features of Lyme disease.

Fig. 74.30 Acrodermatitis chronica atrophicans. The acral skin is atrophic, shiny and wrinkled, with prominent superficial veins.

Fig. 74.31 Cutaneous yaws on the knee of an adolescent from Indonesia. *Courtesy, Peter Ehrnstrom, MD.*

NON-VENEREAL (ENDEMIC) TREPONEMATOSES

Yaws, pinta and endemic syphilis are caused by organisms that are morphologically and antigenically identical to the causative organism of venereal syphilis, *Treponema pallidum* (see Ch. 82). All three diseases have chronic relapsing courses with major dermatologic manifestations. The primary route of transmission is person-to-person via skin, mucous membrane or possibly fomite contact. With the exception of pinta, children are most often affected.

The diagnosis of yaws, pinta and endemic syphilis is based primarily upon clinical features. The same serologic assays used for venereal syphilis can be used to diagnose the endemic treponematoses, but a positive test does not differentiate among the four diseases. Treponemal tests (e.g. TPHA, FTA-ABS, MHA-TP) are specific for treponemal infections (see Ch. 82) and may remain positive for life, regardless of treatment. The non-treponemal tests (e.g. VDRL, RPR) may indicate a current or recent infection, or a biological false-positive result (in 1–3% of the population). The vast majority of false-positive sera have antibody titers of <1 : 4. The quantitative non-treponemal tests are particularly useful in the evaluation of patients following therapy; a fourfold decrease in antibody titers indicates successful treatment, while a fourfold rise indicates reinfection or relapse. Diagnosis can also be made through darkfield examination of exudates from lesions.

Treatment of the non-venereal treponematoses is similar to that for venereal syphilis. The World Health Organization (WHO) recommends that patients over 10 years of age with active disease be given 2 400 000 U of benzathine penicillin, while those under 10 years of age should receive 50 000 U/kg. Family members, close contacts and patients with latent disease are similarly treated. Patients allergic to penicillin can receive doxycycline as recommended for venereal syphilis[112].

Yaws

Synonyms: ■ Pian (French) ■ Frambösie (German) ■ Buba (Spanish) ■ Parangi (Malay)

Yaws is a three-stage infection caused by *T. pallidum* subspecies *pertenue*. It occurs in warm, humid, tropical climates, most often in Africa, Asia, South and Central America, and the Pacific islands. A recent resurgence of the disease has been reported[113]. Yaws most commonly involves the lower extremities of children under 15 years of age (Fig. 74.31). A "mother yaw", the main lesion of the *primary* stage, occurs at the site of inoculation within 10 days to 3 months. It begins as an erythematous, infiltrated, painless papule that over time enlarges peripherally to become 1–5 cm in diameter, then ulcerates and develops an amber-yellow crust. The lesion is rich in treponemes and eventually heals spontaneously over 3 to 6 months.

"Daughter yaws", the lesions of *secondary* yaws, are smaller and more widespread than the primary lesion. They usually occur adjacent to body orifices, such as the nose and mouth, and can expand or ulcerate. Both types of lesions are highly infectious. Only 10% of patients progress to the final stage, during which abscesses form, become necrotic and ulcerate. The ulcers may coalesce into serpiginous tracts, which heal with significant scarring and produce crippling deformities. Yaws can also cause various forms of periostitis, dactylitis and osteitis, with the latter potentially leading to curvature of the tibia ("saber shins").

Histologic examination of early yaws lesions demonstrates spongiosis, acanthosis and papillomatosis. Characteristic neutrophilic intraepidermal microabscesses and a moderate to dense dermal inflammatory infiltrate composed mostly of plasma cells and lymphocytes can be seen. Silver stains easily identify treponemes in specimens. The skin lesions of yaws can resemble venereal syphilis, eczema, psoriasis, verrucae, calluses, scabies, tungiasis, sarcoidosis and vitamin deficiencies[114].

Pinta

Pinta affects the skin exclusively and is caused by an infection with *T. carateum*. The disease is found only in the western hemisphere (Central and South America) in semiarid, warm climates. All ages are equally affected. The *primary* lesions occur 7 days to 2 months after inoculation, most often on the lower extremities. They begin as tiny macules or papules surrounded by an erythematous halo. Over a period of months, they develop into poorly defined, erythematous, infiltrated plaques that measure 10–12 cm in diameter. *Secondary* lesions ("pintids") start as small, scaly papules, subsequently enlarging and coalescing into psoriasiform plaques. They are initially red but later become slate-blue, brown, gray and black. The primary and secondary lesions are highly infectious. *Tertiary* pinta is characterized by symmetric depigmented, vitiligo-like lesions, which may be atrophic or hyperkeratotic and are not considered to be infectious.

Biopsy specimens of primary and secondary lesions reveal moderate acanthosis, slight spongiosis, and a superficial dermal inflammatory infiltrate around dilated blood vessels. Some lesions show lichenoid changes, with hyperkeratosis, hypergranulosis, and vacuolar degeneration of the basal layer. The depigmented lesions of late pinta have epidermal atrophy and a complete absence of melanin. Except for long-standing, late depigmented lesions, treponemes can be visualized in biopsy specimens with silver stains. Early pinta is difficult to differentiate from venereal syphilis, yaws and endemic syphilis. The early lesions can also be confused with eczema, psoriasis, leprosy, lichen planus, lupus erythematosus and tinea corporis. The lesions of late pinta are frequently mistaken for vitiligo[114].

Endemic Syphilis

Synonym: ■ Bejel

Endemic syphilis is caused by an infection with *T. pallidum* subspecies *endemicum*. Most cases are seen in the arid, warm climates of North Africa and the Arabian Peninsula as well as in Southeast Asia. Children under 15 years of age are most commonly affected. In contrast to yaws and pinta, a *primary* lesion is rarely noticed. It usually consists of an inconspicuous small papule or ulcer in the oropharynx or on the nipples of breastfeeding women. In *secondary* endemic syphilis, patches on mucous membranes, split papules, angular stomatitis, non-pruritic papular skin eruptions, and generalized lymphadenopathy are usually seen. Condylomata lata are also frequently present. During the secondary stage, some patients experience osteoperiostitis of the long bones, which can cause nocturnal leg pain.

Six months to several years after inoculation, some patients develop the *tertiary* stage of endemic syphilis. Gumma formation may lead to gross mutilation of the skin, mucous membranes, muscle, cartilage and bone. Without treatment, disfiguring lesions of the palate and nasal septum may occur, leading to difficulty in articulation and swallowing. The eyes and bones can also be severely affected in late-stage endemic syphilis.

The histologic picture closely resembles that of venereal syphilis. In the early stages, biopsy specimens demonstrate a perivascular dermal infiltrate of mostly plasma cells and lymphocytes. Oral lesions may resemble venereal syphilis, aphthosis, perlèche, vitamin deficiencies and primary herpes simplex viral infection. The mutilating nasopharyngeal lesions of endemic syphilis can be mistaken for tertiary venereal syphilis, leprosy, rhinoscleroma, mucocutaneous leishmaniasis, paracoccidioidomycosis and tuberculosis (see Tables 45.3 & 74.14)[114].

LEPTOSPIROSIS

Synonyms: ■ Fort Bragg fever ■ Pretibial fever ■ Weil's disease

Leptospirosis is a worldwide zoonosis caused by spirochetes in the genus *Leptospira*. It is transmitted via contact of non-intact skin or mucous membranes with urine (or other body fluids, with the exception of saliva) from infected mammals (e.g. rodents, dogs, livestock, wild animals), either directly or from drinking or swimming in contaminated water. Veterinarians, farmers, slaughterhouse or sewer workers, and recreational water sport participants are most often affected. Leptospirosis occurs in an anicteric form (~90% of cases) and a more severe icteric form (~10% of cases). After an incubation period of 7–12 days, an initial "septicemic" stage of fevers, chills and myalgias lasting 3–7 days is followed by an "immune" stage (during which serologic tests are positive) that can result in meningitis, uveitis, and renal, hepatic and/or pulmonary dysfunction. Cutaneous manifestations include erythematous macules, papules, patches and/or plaques in a widespread distribution or (especially with *L. interrogans* serovar Autumnalis) localized to the shins, as well as petechiae and purpura secondary to vascular involvement. Antibiotic treatment is most effective early in the disease course; options include oral doxycycline, amoxicillin or azithromycin and (for more severe disease) intravenous penicillin or third-generation cephalosporins.

BACTERIA PREVIOUSLY CLASSIFIED AS FUNGI

ACTINOMYCOSIS

Introduction

Actinomycosis is a subacute or chronic bacterial infection characterized by suppurating abscesses, granulomatous inflammation and sinus formation. *Actinomyces israelii*, an anaerobic or microaerophilic Gram-positive, non-acid-fast actinomycete, is the most common causative organism. Cervicofacial (accounting for two-thirds of infections), pulmonary/thoracic and gastrointestinal forms exist.

Fig. 74.32 Cervicofacial actinomycosis or "lumpy jaw". Soft tissue swelling and draining erythematous nodules are seen. The discharge contained sulfur granules.

Epidemiology and pathogenesis

Actinomycosis is seen worldwide, and men are affected three times more often than women. Humans are the only known reservoir for *Actinomyces* spp. *A. israelii* is part of the normal flora of the oral cavity and is also found in the gastrointestinal tract and female genital tract. The most important predisposing factor is trauma, especially dental procedures. *Actinomyces* spp. are not considered particularly pathogenic, and their virulence is enhanced by co-infection with other organisms. In actinomycotic mycetoma, species of *Actinomyces* other than *A. israelii* are usually responsible for the formation of sulfur granules (see Ch. 77).

Clinical features

In patients with *cervicofacial* actinomycosis ("lumpy jaw"), there is usually a history of poor dental hygiene, dental disease, or a previous orofacial injury or procedure. An initial bluish swelling in the mandibular area progresses to brawny erythematous nodules, which gradually increase in size and form fistulous abscesses (Fig. 74.32). These eventually drain purulent material with characteristic yellow "sulfur granules" that represent clumps of bacteria. Multiple sinus tracts, fever, pain and leukocytosis may develop. Lymphadenopathy is usually absent.

Pulmonary actinomycosis (15–20% of patients) occurs after bacteria gain access to the lung through the aspiration of infected oral material. Pulmonary cavities are usually seen at the bases of the lungs. Extension to the pleura and chest wall may occur, and pleurocutaneous fistulas can develop. *Gastrointestinal* actinomycosis is usually preceded by trauma or inflammatory disease but may occur spontaneously. Granulomatous lesions involving the bowel can eventually extend to the abdominal wall, producing a brawny, erythematous mass with draining sinus tracts. Actinomycosis may also involve the central nervous, musculoskeletal and other organ systems[115].

Pathology

An intense neutrophilic infiltrate is followed by the development of granulomatous inflammation with giant cells. Histiocytes, plasma cells and epithelioid cells can be seen at the periphery of the abscess, while characteristic granules representing microcolonies of *Actinomyces* are seen centrally. Histologically these "sulfur granules" have a basophilic center and acidophilic periphery; they measure up to 28 microns in diameter.

Diagnosis and differential diagnosis

Careful microscopic examination of purulent material should be performed to detect the sulfur granules that are characteristic of actinomycosis (or actinomycotic mycetoma). They are composed of

FOUR MAJOR CLINICAL FORMS OF CUTANEOUS NOCARDIOSIS	
PRIMARY	
Actinomycotic mycetoma	• Half of all cases of actinomycotic mycetoma are due to *Nocardia* species* • Traumatic inoculation causes a painless nodule that enlarges, suppurates and drains via sinus tracts • Purulent discharge contains sulfur granules • The foot is the usual site of involvement • May involve underlying muscle and bone
Lymphocutaneous	• Occurs days to weeks after trauma • Appears as a crusted pustule or abscess resistant to antibiotics • Ascending lymphatic streaks, a sporotrichoid pattern of papulonodules, and tender palpable lymph nodes may be seen
Superficial cutaneous	• Traumatic implantation of foreign objects (including soil and gravel) into the skin • The diagnosis is based on a high index of suspicion, lack of response to routine antibiotic treatment, and laboratory results
SECONDARY	
Pulmonary/systemic	• Subcutaneous abscesses of the chest wall • Pustules, nodules, cutaneous fistulae • Almost universally fatal if left untreated • Most commonly caused by *Nocardia asteroides*
*In Mexico and Central and South America, *N. brasiliensis* is the etiology of 90% of actinomycotic mycetomas, whereas in the US, most mycetomas are caused by true fungi.	

Table 74.17 Four major clinical forms of cutaneous nocardiosis.

Gram-positive, branching filaments that fragment into diphtheroid forms and coccobacilli; acid-fast staining is negative. Cervicofacial actinomycosis may resemble symbiotic anaerobic (e.g. *Eikenella corrodens*) and aerobic bacterial infections, tuberculosis (scrofuloderma), dimorphic fungal infections, dental sinus tracts and even neoplasms.

Treatment

The drug of choice for actinomycosis is penicillin G or ampicillin. Deep-seated, chronic infections should be treated with 2–6 weeks of intravenous therapy followed by 3–12 months of oral penicillin. For acute infections, 2–3 weeks of oral penicillin plus incision and drainage and surgical excision of sinus tracts is sufficient. Doxycycline, erythromycin and clindamycin are acceptable alternatives for penicillin-allergic patients. Imipenem has been shown to be effective in treatment-resistant cases. In order to avoid relapse, therapy should be extended beyond the resolution of symptoms.

NOCARDIOSIS

Introduction

Nocardiosis is caused by various species of *Nocardia*, a filamentous, Gram-positive, acid-fast organism. *Nocardia* is recognized as an opportunistic pathogen in immunocompromised individuals, causing disseminated or systemic disease; in contrast, cutaneous nocardiosis commonly occurs in immunocompetent hosts.

Epidemiology and pathogenesis

Nocardiosis has a worldwide distribution and affects all age groups. Men are affected three times more often than women, and children may be more prone to developing lymphocutaneous disease. *Nocardia* spp. are ubiquitous in the soil. Localized trauma (e.g. puncture wounds), occupational exposures (e.g. farmers, gardeners) and immunodeficiency are risk factors for contracting nocardiosis.

Clinical features

The three major forms of primary cutaneous nocardiosis are: (1) mycetoma (see Ch. 77); (2) lymphocutaneous nocardiosis; and (3) superficial cutaneous nocardiosis. In addition, approximately 10% of patients with pulmonary-systemic nocardiosis develop secondary skin lesions. In immunosuppressed patients, lesions may present as widely disseminated subcutaneous nodules[116]. Table 74.17 details the various clinical presentations of *Nocardia* infection[117].

Pathology

Histologically, an intense neutrophilic infiltrate with abscess formation is seen. Sulfur granules are observed in *Nocardia* mycetoma but are absent in other forms of cutaneous nocardiosis. Organisms are not visible in routinely stained sections but appear as branching filaments on Gram stain. *Nocardia* also stains with Grocott–Gomori methenamine silver and acid-fast stains.

Diagnosis and differential diagnosis

Nocardia grows easily on all common laboratory media. However, the laboratory should be notified if *Nocardia* is suspected, because its growth is slow and specimens must be held for up to 2 weeks. Nocardiosis should be suspected in patients with sporotrichoid lesions or trauma-associated superficial cutaneous infections that do not respond to routine treatment. It should also be considered in patients at risk for opportunistic infections.

Treatment

Sulfonamides are the drugs of choice for nocardiosis. Minocycline is an effective alternative for sulfonamide-allergic patients, and linezolid may be added in resistant cases. For subcutaneous abscesses, surgical treatment is often required. Local forms of nocardiosis should be treated for 6–12 weeks, whereas immunocompromised patients and those with disseminated disease require 3–12 months of antimicrobial therapy.

REFERENCES

1. Noble W. Skin bacteriology and the role of *Staphylococcus aureus* in infection. Br J Dermatol. 1998;139:9–12.
2. Darmstadt G, Lane A. Impetigo: an overview. Pediatr Dermatol. 1994;11:293–303.
3. Shriner D, Schwartz R, Janniger C. Impetigo. Cutis. 1994;45:30–2.
4. Koning S, Verhagen AP, van Suijlekom-Smit LW, et al. Interventions for impetigo. Cochrane Database Syst Rev. 2004;(2):CD003261.
5. Ladhani S, Garbash M. Staphylococcal skin infections in children: rational drug therapy recommendations. Paediatr Drugs. 2005;7:77–102.
6. Wickboldt L, Fenske N. Streptococcal and staphylococcal infections of the skin. Hosp Pract. 1986;3:41–7.
7. Plewig G, Jansen T. Acneiform dermatoses. Dermatology. 1998;196:102–7.
8. Brook I, Fiengold S. Aerobic and anaerobic bacteriology of cutaneous abscesses in children. Pediatrics. 1981;67:891–5.
9. Meislin H, Lerner S, Graves M. Cutaneous abscesses: anaerobic and aerobic bacteriology and outpatient management. Ann Intern Med. 1977; 87:145–9.
10. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. Clin Infect Dis. 2011;52:285–92.

11. Daum RS. Skin and soft-tissue infections caused by methicillin-resistant *Staphylococcus aureus*. N Engl J Med. 2007;357:380–90.
12. Gorwitz R. A review of community-associated methicillin resistant *Staphylococcus aureus* skin and soft tissue infections. Pediatric Infect Dis J. 2008;27:1–7.
13. Kil E, Heymann WR, Weinberg J. Methicillin-resistant *Staphylococcus aureus*: an update for the dermatologist. Cutis. 2008;81:227–32, 247–52.
14. Schmitz FJ, Sadurski R, Kray A, et al. Prevalence of macrolide-resistance genes in *Staphylococcus aureus* and *Enterococcus faecium* isolates from 24 European university hospitals. J Antimicrob Chemother. 2000; 45:891–4.
15. Zetola N, Francis JS, Nuermberger EL, Bishai WR. Community-acquired meticillin-resistant *Staphylococcus aureus*: an emerging threat. Lancet Infect Dis. 2005;5:275–86.
16. Lyon M, Doehring MC. Blistering distal dactylitis: a case series in children under nine months of age. J Emerg Med. 2004;26:421–3.
17. Carroll J. Common bacterial pyodermas. Postgrad Med. 1996;100:311–22.
18. Ladhani S, Evans R. Staphylococcal scalded skin syndrome. Arch Dis Child. 1996;78:85–8.
19. Cribier B, Piemont Y, Grosshans E. Staphylococcal scalded skin syndrome in adults: a clinical review illustrated with a new case. J Am Acad Dermatol. 1994;30:319–24.
20. Manders S. Toxin-mediated streptococcal and staphylococcal disease. J Am Acad Dermatol. 1998;39:383–98.
21. Gemmell C. Staphylococcal scalded skin syndrome. J Med Microbiol. 1994;43:318–27.
22. Resnick S. Staphylococcal toxin-mediated syndromes in children. Semin Dermatol. 1992;11:11–8.
23. Stevens D. The toxic shock syndromes. Infect Dis Clin North Am. 1996;10:727–46.
23a. DeVries AS, Lesher L, Schlievert PM, et al. Staphylococcal toxic shock syndrome 2000-2006: epidemiology, clinical features, and molecular characteristics. PLoS One. 2011;6:e22997.
24. Bach M. Dermatologic signs in toxic shock syndromes – clues to diagnosis. J Am Acad Dermatol. 1983;8:343–7.
25. Update on toxic shock syndrome FDA Drug Bull. 1980;10:17–9.
26. Lappin E, Ferguson AJ. Gram-positive toxic shock syndromes. Lancet Infect Dis. 2009;9:281–90.
27. Keh D, Sprung CL. Use of corticosteroid therapy in patients with sepsis and septic shock: an evidence-based review. Crit Care Med. 2004;32(suppl.):S527–33.
28. Bialecki C, Feder H, Grant-Kels J. The six classic childhood exanthems: a review and update. J Am Acad Dermatol. 1989;21:891–903.
29. Macias ES, Pereira FA, Rietkerk W, Safai B. Superantigens in dermatology. J Am Acad Dermatol. 2011;64:455–72.
30. Wolf J, Rabinowitz L. Streptococcal toxic shock-like syndrome. Arch Dermatol. 1995;131:73–7.
31. Vuzevski V, Van Joost T, Wagenvoort J. Cutaneous pathology in toxic shock syndromes. Int J Dermatol. 1989;28:94–7.
32. Agerson AN, Wilkins EG. Streptococcal toxic shock syndrome after breast reconstruction. Ann Plast Surg. 2005;54:553–6.
33. Feingold D. Group A streptococcal infections: an old adversary reemerging with new tricks? Arch Dermatol. 1996;132:67–70.
34. Chartier C, Grosshans E. Erysipelas. Int J Dermatol. 1990;29:459–67.
35. Bratton R, Nesse R.. St. Anthony's fire: diagnosis and management of erysipelas. Am Fam Phys. 1995;51:401–4.
36. Grosshans E. The red face: erysipelas. Clin Dermatol. 1993;11:307–13.
37. O'Loughlin RE, Roberson A, Cieslak PR, et al; Active Bacterial Core Surveillance Team. The epidemiology of invasive group A streptococcal infection and potential vaccine implications: United States, 2000–2004. Clin Infect Dis. 2007;45:853–62.
38. Honig P, Frieden IJ, Kim HJ, Yan AC. Streptococcal intertrigo: an underrecognized condition in children. Pediatrics. 2003;112:1427–9.
38a. Heath C, Desai N, Silverberg NB. Recent microbiological shifts in perianal bacterial dermatitis: *Staphylococcus aureus* predominance. Pediatr Dermatol. 2009;26:696–70.
39. Meury SN, Erb T, Schaad UB, Heininger U. Randomized, comparative efficacy trial of oral penicillin versus cefuroxime for perianal streptococcal dermatitis in children. J Pediatr. 2008;153:799–802.
40. Lewis R. Soft tissue infections. World J Surg. 1998;22:146–51.
41. Bernard P, Beden C, Mounier M, et al. Causes of erysipelas and cellulitis in adults. Arch Dermatol. 1989;125:779–804.
42. Sachs M. Cutaneous cellulitis. Arch Dermatol. 1991;124:493–500.
43. Davison A, Rotstein O. The diagnosis and management of common soft-tissue infections. Can J Surg. 1988;31:333–6.
44. Bonifaz A, Carrasco E. Botryomycosis. Int J Dermatol. 1996;35:381–8.
45. Ahdout D, Rickman L, Haghighi P, Heard W. Botryomycosis in the acquired immunodeficiency syndrome. Cutis. 1995;55:149–52.
46. Kramer LM, Doering LV. Necrotizing fasciitis: a case of clostridial myonecrosis. Am J Crit Care. 2001;10:181–7.
47. Hasham S, Matteucci P, Stanley PR, Hart NB. Necrotising fasciitis. BMJ. 2005;330:830–3.
48. Bingol-Kologlu M, Yildiz R, Alper B, et al. Necrotizing fasciitis in children: diagnostic and therapeutic aspects. J Pediatr Surg. 2007;42:1892–7.
49. Garg A, Sujatha S, Garg J, et al. Fulminant necrotizing fasciitis caused by zygomycetes. J Cutan Pathol. 2009;36:815–16.
50. Stone D, Gorbach S. Necrotizing fasciitis: the changing spectrum. Infect Dis Dermatol. 1997;15:213–20.
51. File T, Ran J. Group A streptococcus necrotizing fasciitis. Comp Ther. 2000;26:73–81.
52. Chapnick E, Abter E. Necrotizing soft-tissue infections. Infect Dis Clin North Am. 1996;10:835–55.
53. Present D, Meislin R, Schaffer B. Gas gangrene: a review. Orthop Rev. 1990;19:333–41.
54. Blaise G, Nikkels AF, Hermanns-Le T, et al. *Corynebacterium*-associated skin infections. Int J Dermatol. 2008;47:884–90.
55. Tschen J, Ransdell W. Disciform erythrasma. Cutis. 1983;31:541–7.
56. Shelley W, Shelley E. Coexistent erythrasma, trichomycosis axillaris, and pitted keratolysis: an overlooked corynebacterial triad? J Am Acad Dermatol. 1982;7:752–7.
57. Hodson S, Henslee T, Tachibana D, Harvey C. Interdigital erythrasma. Part I: A review of the literature. J Am Podiatr Med Assoc. 1988;78:551–8.
58. Longshaw CM, Wright JD, Farrell AM, Holland KT. Kytococcus sedentarius, the organism associated with pitted keratolysis, produces two keratin-degrading enzymes. J Appl Microbiol. 2002;93:810–16.
58a. Lowe CF, Bernard KA, Romney MG. Cutaneous diphtheria in the urban poor population of Vancouver, British Columbia, Canada: a 10-year review. J Clin Microbiol. 2011;49:2664–6.
59. Hofler W. Cutaneous diphtheria. Int J Dermatol. 1991;30:845–7.
60. Donegan S, Bellamy R, Gamble CL. Vaccines for preventing anthrax. Cochrane Database Syst Rev. 2009;(2):CD006403.
61. Waterer GW, Robertson H. Bioterrorism for the respiratory physician. Respirology. 2009;14:5–11.
62. Inglesby TV, O'Toole T, Henderson DA, et al; for the Working Group on Civilian Biodefense. Anthrax as a biological weapon, 2002: updated recommendations for management. JAMA. 2002;287:2236–52.
63. Bartlett JG, Inglesby TV Jr, Borio L. Management of anthrax. Clin Infect Dis. 2002;35:851–8.
63a. Duncan KO, Smith TL. Primary cutaneous infection with *Bacillus megaterium* mimicking cutaneous anthrax. J Am Acad Dermatol. 2011;65:e60–1.
64. Centers for Disease Control and Prevention. Update: Investigation of bioterrorism-related anthrax and interim guidelines for exposure management and antimicrobial therapy, October 2001. MMWR Morb Mortal Wkly Rep. 2001;50:909–19.
65. Khavari P, Bolognia J, Eisen R, et al. Periodic acid-Schiff-positive organisms in primary cutaneous *Bacillus cereus* infection. Arch Dermatol. 1991;127:543–6.
66. Veraldi S, Girgenti V, Dassoni F, Gianotti R. Erysipeloid: a review. Clin Exp Dermatol. 2009;34:859–62.
67. Barnett J, Estes S, Wirman J, Morris R, Staneck J. Erysipeloid. J Am Acad Dermatol. 1983;9:116–23.
68. Rosenstein NE, Perkins BA, Stephens DS, et al. Epidemiologic features of meningococcal disease. N Engl J Med. 2001;344:1378–88.
69. Chamot-Rooke J, Mikaty G, Malosse C, et al. Posttranslational modification of pili upon cell contact triggers *N. meningitidis* dissemination. Science. 2011;331:778–82.
70. Staquet P, Lemee L, Verdier E, et al. Detection of *Neisseria meningitidis* DNA from skin lesion biopsy using real-time PCR: usefulness in the aetiological diagnosis of purpura fulminans. Intensive Care Med. 2007;33:1168–72.
71. Singh J, Arrieta AC. Management of meningococcemia. Indian J Pediatr. 2004;71:909–13.
72. Leclerc F, Leteurtre S, Cremer R, et al. Do new strategies in meningococcemia produce better ourcomes? Crit Care Med. 2000;28:S60–3.
73. Drage C. Life-threatening rashes: dermatologic signs of four infectious diseases. Mayo Clin Proc. 1999;74:68–72.
74. Silvestre J, Bettloch M. Cutaneous manifestations due to Pseudomonas infection. Int J Dermatol. 1999;38:419–31.
75. Carfrae MJ, Kesser BW. Malignant otitis externa. Otolaryngol Clin North Am. 2008;41;537–49.
76. Keene WE, Markum AC, Mansour S. Outbreak of *Pseudomonas aeruginosa* infections caused by commercial piercing of upper ear cartilage. JAMA. 2004;291:981–5.
77. Green J. Localized whirlpool folliculitis in a football player. Cutis. 2000;65:359–62.
78. Fiorillo L, Zucker M, Sawyer D, Lin A. The pseudomonas hot-foot syndrome. N Engl J Med. 2001;345:335–8.
79. Boisseau AM, Sarlangue J, Perel Y, et al. Perineal ecthyma gangrenosum in infancy and early childhood: septicemic and nonsepticemic forms. J Am Acad Dermatol. 1992;27:415–18.
80. Gueluer H, Ergun T, Demircay Z. Ecthyma gangrenosum. Int J Dermatol. 1999;38:298–305.
81. Ayoub EM, McBride J, Schmiederer M, Anderson B. Role of *Bartonella henselae* in the etiology of Henoch-Schonlein purpura. Pediatr Infect Dis J. 2002;21:28–31.
82. Rolain JM, Brouqui P, Koehler JE, et al. Recommendations for treatment of human infections caused by *Bartonella* species. Antimicrob Agents Chemother. 2004:48:1921–33.
83. Nosal J. Bacillary angiomatosis, cat-scratch disease, and bartonellosis: what's the connection? Int J Dermatol. 1997;36:405–11.
84. Shinall E. Cat-scratch disease: a review of the literature. Pediatr Dermatol. 1990;7:11–8.
85. Smith D. Cat-scratch disease and related clinical syndromes. Am Fam Phys. 1997;55:1783–9.
86. Manders S. Bacillary angiomatosis. Clin Dermatol. 1996;14:295–9.
87. Spach D. Bacillary angiomatosis. Int J Dermatol. 1992;31:19–24.
88. Pappas G, Akritidis N, Bosilkovski M, Tsianos E. Brucellosis. N Engl J Med. 2005;352:2325–36.
89. Milionis H, Christou L, Elisaf M. Cutaneous manifestations in brucellosis: case report and review of the literature. Infection. 2000;28:124–6.
90. Bossi P, Tegnell A, Baka A, et al. Bichat guidelines for the clinical management of glanders and melioidosis and bioterrorism-related glanders and melioidosis. Euro Surveill. 2004;9:E3–4.
91. White NJ. Melioidosis. Lancet. 2003;361:1715–22.
92. Thibault FM, Hernandez E, Vidal DR, et al. Antibiotic susceptibility of 65 isolates of *Burkholderia pseudomallei* and *Burkholderia mallei* to 35 antimicrobial agents. J Antimicrob Chemother. 2004;54:1134–8.
93. Bondi SK, Goldberg JB. Strategies towards vaccines against *Burkholderia mallei* and *Burkholderia pseudomallei*. Expert Rev Vaccines. 2008;7:1357–65.
94. Remond B, Dompmartin A, Moreau A, et al. Cutaneous malacoplakia. Int J Dermatol. 1994;33:538–42.
95. Lowitt M, Kariniemi A, Niemi K, Kao G. Cutaneous malacoplakia: a report of two cases and review of the literature. J Am Acad Dermatol. 1996;34:325–31.
96. Centers for Disease Control and Prevention. Tularemia – United States, 1990–2000. MMWR Morb Mortal Wkly Rep. 2002;51:181–4.
97. Dennis DT, Ingelsby TV, Henderson DA. Tularemia as a biological weapon. JAMA. 2001;285:2763–74.
98. Rasmussen J. *Haemophilus influenzae* cellulitis. Br J Dermatol. 1973;88:547–50.
99. Fernandez-Vozmediano JM, Armario Hita JC, Gonzalez Cabrerizo A. Rhinoscleroma in three siblings. Pediatr Dermatol. 2004;21:134–8.
100. Kasper HU, Hegenbarth V, Buhtz P. Rhinoscleroma associated with Rosai-Dorfman reaction of regional lymph nodes. Pathol Int. 2004;54:101–4.
101. Parry CM, Hien TT, Dougan G, et al. Typhoid fever. N Engl J Med. 2002;347:1770–82.
102. Centers for Disease Control and Prevention (CDC). Rat-bite fever – New Mexico, 1996. MMWR Morb Mortal Wkly Rep. 1998;47:89–91.

103. Cobbs CG, Chansolme DH. Plague. Dermatol Clin. 2004;22:303–12.
104. Hlady WG, Klontz KC. The epidemiology of *Vibrio* infections in Florida, 1981–1993. J Infect Dis. 1996;173:1176–83.
105. Borenstein M, Kerdel F. Infections with *Vibrio vulnificus*. Dermatol Clin. 2003;21:245–8.
106. Hengge UR, Tannapfel A, Tyring SK, et al. Lyme borreliosis. Lancet Infect Dis. 2003;3:489–500.
107. Leinweber B, Colli C, Chott A, et al. Differential diagnosis of cutaneous infiltrates of B lymphocytes with follicular growth pattern. Am J Dermatopathol. 2004;26:4–13.
108. Grange F, Wechsler J, Guillaume JC, et al. *Borrelia burgdorferi*-associated lymphocytoma cutis simulating a primary cutaneous large B-cell lymphoma. J Am Acad Dermatol. 2002;47:530–4.
109. Malane M, Grant-Kels J, Feder H, Luger S. Diagnosis of Lyme disease based on dermatologic manifestations. Ann Intern Med. 1991;114:490–7.
110. Leverkus M, Finner AM, Pokrywka A, et al. Metastatic squamous cell carcinoma of the ankle in long-standing untreated acrodermatitis chronic atrophicans. Dermatology. 2008;217:215–18.
111. Leslie T, Levell N, Cutler S, et al. Acrodermatitis chronica atrophicans; a case report and review of the literature. Br J Dermatol. 1994;131:687–93.
112. Koff A, Rosen T. Nonvenereal treponematoses: yaws, endemic syphilis, and pinta. J Am Acad Dermatol. 1993;29:519–35.
113. Asiedu K: The return of yaws. Bull World Health Organ. 2008;86:507–8.
114. Antal GM, Lukehart SA, Meheus AZ. The endemic treponematoses. Microbes Infect. 2002;4:83–94.
115. Warren N. Actinomycosis, nocardiosis, and actinomycetoma. Dermatol Clin. 1996;14:85–95.
116. Jiminez-Galanes Marchan S, Meneu Diaz JC, Caso Maestro O, et al. Disseminated nocardiosis: a rare infectious complication following non-heart beating donor liver transplantation. Transplant Proc. 2009;41:2495–7.
117. Lederman ER, Crum NF. A case series and focused review of nocardiosis: clinical and microbiologic aspects. Medicine (Baltimore). 2004;83:300–13.

Mycobacterial Infections 75

Marcia Ramos-e-Silva and Maria Cristina Ribeiro de Castro

Chapter Contents

Leprosy 1221
Cutaneous tuberculosis 1228
Non-tuberculous mycobacterioses 1235

In 1896, the name "mycobacteria" was given to a large group of bacteria that produce filamentous pellicles similar to molds (when grown in liquid media). These organisms are thin, slightly curved to straight, non-motile and non-spore-forming, with a waxy coating that makes them resistant to most stains. Mycobacteria are also acid-fast, which means they are not readily decolorized by acid after staining[1–3]. The genus *Mycobacterium* contains more than 50 species, a number of which have been recognized during the past 30 years[1,3]. While some species may be saprophytic or pathogenic depending on the immunologic state of the host[2,4], *M. leprae* and *M. tuberculosis* are virulent and constitute an important world health problem. Research on leprosy has been greatly hampered by the inability to culture the organism (it has the longest doubling time of all known bacteria), but the discovery of the genomic sequence of *M. leprae* in 2001[5] was a significant advancement.

Although the classic mycobacterioses, leprosy and tuberculosis, have been known since antiquity, in the past few decades there has been a worldwide explosion in the incidence of mycobacterial infections. Several factors have played a role in this increase, including the emergence of resistant strains of *M. tuberculosis* and a rise in the number of immunocompromised hosts, including those with AIDS[3]. The different species of mycobacteria that are associated with cutaneous disease are outlined in Table 75.1 utilizing Runyon's classification[1,3,6].

This chapter will address the species of mycobacteria that are of greatest interest to dermatologists: *M. leprae, M. tuberculosis* and non-tuberculous mycobacteria that cause infections of the skin.

LEPROSY

Synonym: ■ Hansen's disease

Key features

- Chronic infectious disease caused by the bacillus *Mycobacterium leprae*, an intracytoplasmic parasite of macrophages and Schwann cells
- Slowly progressive disease characterized by granulomas and neurotropism, with a predilection for the skin as well as peripheral nerves
- The primary skin lesion is erythematous or hypopigmented, and it is often anesthetic
- Based upon the clinicopathologic findings (which reflect the degree/type of immunity), leprosy is divided into two major forms – lepromatous (a predominantly Th2 response) and tuberculoid (a predominantly Th1 response)
- In lepromatous leprosy, multiple organisms are present in the dermis (and in nasal secretions), whereas in tuberculoid leprosy, there are only a few organisms

MYCOBACTERIA THAT CAUSE CUTANEOUS DISEASE

Group and pigment	Rate of growth	Pathogens
Slow growers		
Photochromogens*	2–3 weeks	*M. kansasii, M. marinum, M. simiae*
Scotochromogens†	2–3 weeks	*M. scrofulaceum, M. szulgai, M. gordonae, M. xenopi*
Nonchromogens‡	2–3 weeks	*M. tuberculosis, M. avium, M. intracellulare, M. ulcerans, M. haemophilum, M. malmoense, M. terrae, M. genavense, M. bovis§, M. nonchromogenicum*
Rapid growers	3–5 days	*M. fortuitum, M. chelonae, M. smegmatis, M. abscessus, M. immunogenum, M. goodii, M. wolinskyi, M. cosmeticum, M. mucogenicum*
Non-cultured (to date)		*M. leprae*

*Capable of yellow pigment formation upon exposure to light.
†Capable of yellow pigment production without light exposure.
‡Incapable of pigment production.
§Including bacillus Calmette-Guérin.

Table 75.1 Mycobacteria that cause cutaneous disease. Modified classification of Runyon[1,3,6].

Introduction

Leprosy is a chronic infectious disease with prominent involvement of the skin and nerves that is caused by the bacillus *Mycobacterium leprae*. It is divided into two major forms that depend upon the degree and type of immunity – lepromatous (a predominantly Th2 response) and tuberculoid (a predominantly Th1 response). Leprosy is a serious health issue in a number of low-income countries. Although it seldom kills, leprosy represents a deforming, disabling and stigmatizing disease[7,8]. Once worldwide in distribution, leprosy is now seen primarily in tropical and subtropical regions of Asia, Africa, and Central and South America (Fig. 75.1). The geographic distribution is probably related more to a lower standard of living and poorer hygiene than to the warmer climate[10,11]. Early diagnosis and prompt therapy are key components in the strategy to control this chronic infectious disease[8].

History

The first written descriptions of leprosy may date back to as early as 600 BC in India, and to 200 BC in China and Japan. Many of the cases mentioned in the Bible may actually have been psoriasis, vitiligo or other skin disorders rather than leprosy. The earliest scientific evidence of leprosy has come from an Egyptian skeleton and two Coptic mummies from the second century BC and the fifth century AD, respectively.

One theory was that leprosy was brought from India to the Mediterranean basin by Alexander the Great's soldiers between 327 and 326 BC and then spread throughout the Greek and Roman Empires. Recent studies utilizing comparative genomics have shown that all extant cases of leprosy are attributable to a single clone, and the disease appears to have originated in the Near East or eastern Africa. During the Middle Ages, leprosy reached epidemic proportions in Europe and then spread to the New World via the wave of exploration in the late fifteenth and sixteenth centuries. Independent of geographic location, the afflicted have frequently been ostracized by their communities and families[9,10,12].

During the nineteenth century, Danielssen and Boeck provided the first modern description of leprosy, and in the 1870s, a third Norwegian, Gerhard Henrik Armauer Hansen, conducted landmark studies on the microbiology and epidemiology of *M. leprae*. Mitsuda created the skin test for leprosy in 1919[10,11,13], and the value of sulfones in the treatment of leprosy was reported by Faget and colleagues in 1942[14]. Rabello advanced the notion of polar forms of leprosy in 1938, with a formal presentation in 1953 at the International Congress of Leprosy. In 1966, Ridley and Jopling suggested a classification of leprosy based on the immunologic status of the patient[10,11,13] (see below).

Epidemiology

In the early 1980s, an estimated 11–15 million people worldwide were thought to have leprosy[11,15], compared to only 212 000 in 2010. The number of new cases per year has decreased from more than 500 000 in 2003 to fewer than 250 000 in 2010[9,16]. The substantial reduction in the number of affected individuals reflects the impact of multidrug therapy[17]. The goal of the World Health Organization (WHO) is a prevalence rate of less than 1 case per 10 000 persons, which has been achieved in all but a few countries[16].

In the Americas, the highest incidence is seen in Brazil, especially in western Amazonia[9,11–13] (see Fig. 75.1). Although men and women are equally affected, the lepromatous form of leprosy is seen twice as often in men as in women. Leprosy affects all races and ages; however, its peak incidence occurs in individuals between 10–15 and 30–60 years of age[7,11,18].

The three requirements for the spread of leprosy are: a contagious patient, a susceptible person, and close or intimate contact. In endemic countries, the vast majority of new cases are in children and young adults who have close relatives with contagious forms of the disease. Of note, the risk of acquiring the disease from household contacts is 25%, emphasizing the public health importance of domicile control[11]. The incubation period varies widely, from months to over 30 years, but it is usually 4–10 years[18]. The organism is spread predominantly via nasal and oral droplets from the bacilliferous patient and much less often from eroded skin. Even after 1 to 7 days, the bacillus is still viable in dried secretions. Inoculation is via the nasal mucosa or, less commonly, through breaks in the skin barrier. Transmission also depends on the infectivity of the contagious patient[12,13,19]. An unusual mode of transmission, reported from India, was via reused tattoo needles.

Although leprosy primarily affects humans, it can be found or reproduced in armadillos, monkeys and mice[8]. The same strain of *M. leprae* has been found to infect wild armadillos and humans in the southern US, suggesting that leprosy represents a zoonosis in this region[20].

Pathogenesis

The bacillus *M. leprae* is a very small, slightly curved rod that is characteristically acid-fast. It is an obligate intracellular microorganism that has a predilection for macrophages and Schwann cells. The major sites of involvement are the peripheral nerves, skin, mucous membranes, bones and viscera (e.g. testes, liver)[12]. The bacillus requires a temperature of ~35°C to grow, and thus has a preference for cooler regions of the body (e.g. the nose, testicles and ear lobes) as well as regions where the peripheral nerves are close to the skin[18,21].

The fact that the majority of exposed individuals do not develop disease implies that there is variability in susceptibility/resistance, depending upon genetic and environmental factors. For example, susceptibility and the type of immune response appear to correlate with

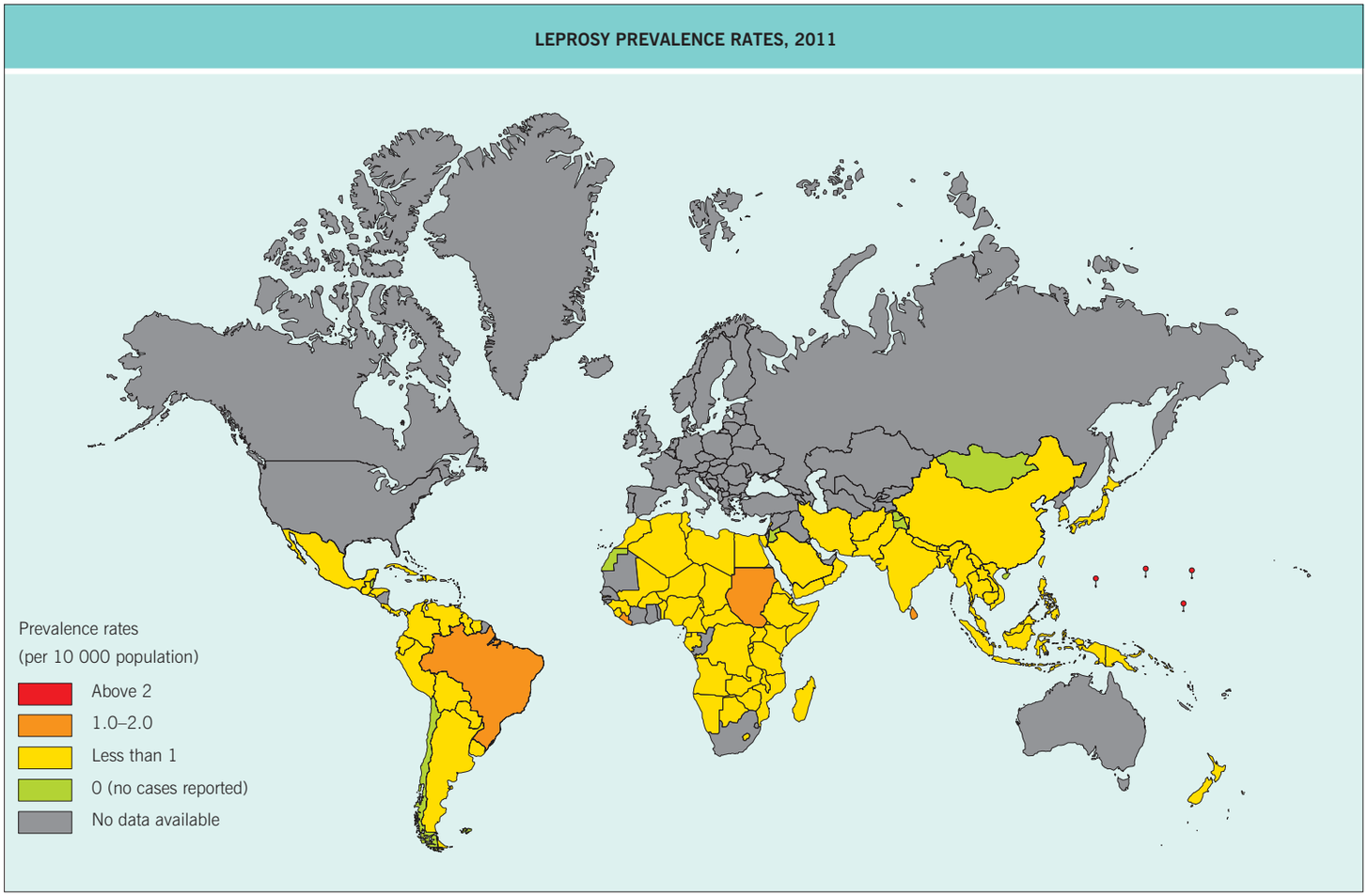


Fig. 75.1 Leprosy prevalence rates, 2011. The World Health Organization (WHO) has achieved its goal of a prevalence rate of less than 1 case per 10 000 persons in all but a few countries. *Reproduced from the World Health Organization, 2011*[9].

specific HLA types, such that individuals with HLA-DR2 and HLA-DR3 are more likely to develop the tuberculoid form and those with HLA-DQ1 the lepromatous form[11,18]. Polymorphisms in several genes, including those that encode tumor necrosis factor (TNF)-α, interleukin (IL)-10, lymphotoxin-α (a low-producing allele associated with early-onset leprosy), leukotriene A_4 hydrolase, the vitamin D receptor, and Toll-like receptor (TLR) 2, have also been shown to be related to either overall susceptibility or the particular form of leprosy that develops (although there is variability in different populations)[22–24]. In Vietnamese and Brazilian populations, a leprosy susceptibility locus on chromosome 6q25–q26 contains 17 markers in a block of approximately 80 kilobases that overlaps the 5′ regulatory region shared by the Parkinson's disease gene *PARK2* (encoding parkin, an E3 ubiquitin protein ligase) and the co-regulated gene *PACRG*[25]. In addition, genome-wide association studies in Chinese populations have linked variants in genes encoding proteins in the nucleotide-binding oligomerization domain containing-2 (NOD2) pathway (which regulates the innate immune response) with susceptibility to leprosy (especially the multibacillary form); of note, variants in some of the same genes have been associated with Crohn's disease[26].

Depending upon the level of specific cell-mediated immunity (as reflected in the lepromin test), the disease can progress without restraint, limit itself, or resolve spontaneously. Humoral immunity is increased in forms that are associated with minimal cell-mediated immunity (i.e. the lepromatous end of the spectrum; Fig. 75.2)[8,11]. For example, serum levels of antibodies against phenolic glycolipid-1 (PGL-1; an *M. leprae*-specific antigen) are highest in patients with lepromatous leprosy[27].

Macrophages play an important role in the body's attempt to eliminate *M. leprae*, producing cytokines such as IL-1, TNF-α and IL-12 when they encounter this organism. These cytokines then stimulate the number and activity of other macrophages. Studies in humans have shown that a predominantly Th1 $CD4^+$ T-cell response is seen in patients with tuberculoid leprosy. This response produces cytokines (IL-2, interferon [IFN]-γ and TNF-β) that maintain the inflammation. In patients with lepromatous leprosy, a predominantly Th2 response leads to the release of a different set of cytokines (IL-4, IL-5, IL-10 and IL-13), which suppress macrophage activity[21,28]. The cell wall of *M. leprae* contains lipid complexes, including phenolic glycolipid-1 (PGL-1), which may play a role in suppressing the T-cell response and IFN-γ production (as well as the organism's invasion of Schwann cells)[21,29,30].

More recent studies have provided additional insights into the pathogenesis of leprosy. Within lesions of tuberculoid leprosy, $CD4^+$ T cells that express the antimicrobial protein granulysin have been detected at a sixfold greater frequency when compared to lepromatous skin lesions[31]. Tuberculoid lesions also have stronger expression of TLR2 and TLR1, activation of which can induce differentiation of both macrophages and dendritic cells. $CD1b^+$ dendritic cells (which promote T-cell activation and secretion of proinflammatory cytokines) were not detected in lesions from patients with progressive lepromatous leprosy[32]; instead, these lesions had upregulation of genes belonging to the leukocyte immunoglobulin-like receptor (LIR) family. LIR-7 has been shown to suppress innate host defense by several mechanisms, including blocking antimicrobial activity triggered by TLRs[33].

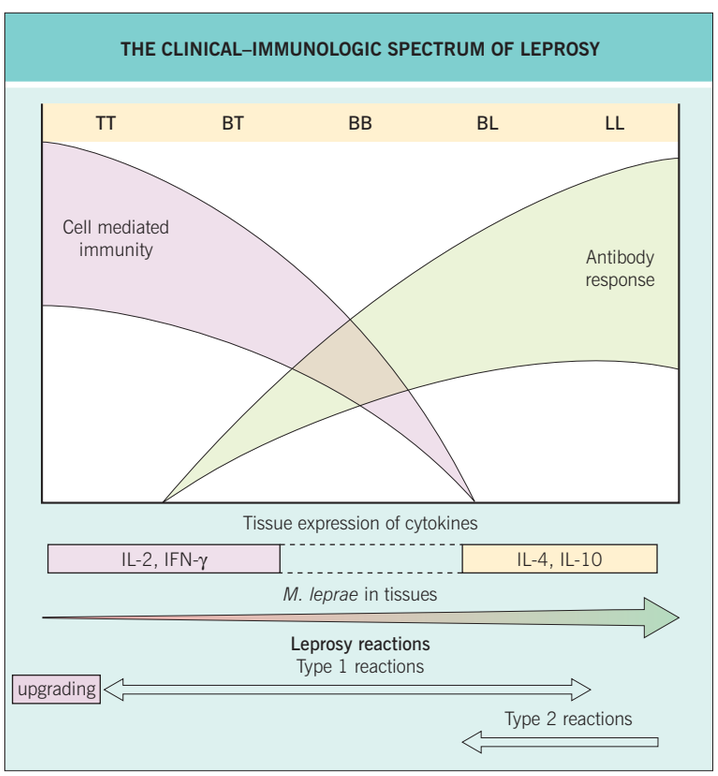


Fig. 75.2 The clinical-immunologic spectrum of leprosy. This reflects the underlying host immunity as measured by the T-lymphocyte and antibody responses to *Mycobacterium leprae*. Spontaneous and drug-induced fluctuations in the immune response are responsible for type 1 and type 2 reactions. TT, tuberculoid leprosy; BT, borderline tuberculoid leprosy; BB, mid-borderline leprosy; BL, borderline lepromatous leprosy; LL, lepromatous leprosy; IFN, interferon; IL, interleukin. *Adapted from Britton WJ. Leprosy. In Cohen J, Powderly WG (eds). Infectious Diseases. London: Mosby, 2003. With permission of Elsevier.*

Clinical Features

There is a wide spectrum of clinical findings in leprosy. After advancing the notion of polar forms of leprosy in 1938, Rabello, a Brazilian dermatologist, divided leprosy into four types: (1) lepromatous, which occurs in patients with depressed cell-mediated immunity; (2) tuberculoid, in patients with intact cell-mediated immunity; (3) dimorphous; and (4) indeterminate. The dimorphous form is "unstable" and capable of evolving into lepromatous or tuberculoid forms, depending upon whether there is improvement or worsening of cell-mediated immunity (see Fig. 75.2). In 1966, Ridley and Jopling created a classification, also based on polar forms, with lepromatous (LL) at one end, tuberculoid (TT) at the other end, and three types of borderline leprosy in between: borderline lepromatous (BL, immunodepressed end), borderline-borderline (BB, in the middle), and borderline tuberculoid (BT, immunocompetent end)[11,13,18,34].

In 1997, the WHO created an operational system in order to facilitate the classification and therapy of leprosy in endemic areas with no access to laboratory facilities. This scheme divides leprosy into three groups: (1) paucibacillary, single-lesion leprosy (one skin lesion); (2) paucibacillary leprosy (two to five skin lesions); and (3) multibacillary leprosy (more than five skin lesions). This simplified classification is based solely on the number of cutaneous lesions, independent of their size, location or histologic features. However, on a global basis, the classification scheme outlined in Table 75.2 is still the one most commonly employed[35,36].

The clinical manifestations of leprosy involve primarily the skin and the nervous system (see Table 75.2). In addition to anesthesia or hypesthesia of individual cutaneous lesions, peripheral nerves can become enlarged and palpable. Certain peripheral nerves are more commonly affected, based primarily upon their more superficial location. Palpation of these nerves is an integral component of the physical examination of a patient with leprosy (Fig. 75.3). The clinician should also determine via a neurologic examination whether there is a general decrease in sensation to pain, temperature and/or touch (e.g. on the distal extremities). This is in addition to inspection for neuropathic changes (e.g. muscle atrophy, flexion contractures of the fourth and fifth fingers), vasomotor alterations and secretory disturbances (e.g. dry eyes and nose)[13,18].

Lepromatous leprosy, the form with the least cellular immunity and greatest number of bacilli, is characterized initially by multiple, poorly defined, erythematous macules, papules, nodules and plaques. Lesions are widespread, and they are usually rather symmetric in distribution. The most common sites of involvement are the face, buttocks and lower extremities. Infiltration of the skin of the forehead can lead to a leonine facies (Fig. 75.4). Additional signs and late sequelae include madarosis, saddle nose (Fig. 75.5), infiltration of both earlobes, and acquired ichthyosis on the lower extremities (Fig. 75.6). Anesthesia in a stocking or glove distribution may develop, often together with enlarged peripheral nerves and neuropathic changes. Ocular

CLASSIFICATION OF LEPROSY						
Clinical findings	**LL**	**BL**	**BB**	**BT**	**TT**	**I**
Type of lesions	Macules, papules, nodules, diffuse infiltration	Macules, papules, plaques, infiltration	Plaques and dome-shaped, punched-out lesions	Infiltrated plaques	Infiltrated plaques, often hypopigmented	Macules, often hypopigmented
Number of lesions	Numerous	Many	Many	Single, usually with satellite lesions, to more than 5	One or few (up to 5)	One or few
Distribution	Symmetric	Tendency to symmetry	Evident asymmetry	Asymmetric	Localized, asymmetric	Variable
Definition	Vague, difficult to distinguish normal versus affected skin	Less well-defined borders	Less well-defined borders	Well-defined, sharp borders	Well-defined, sharp borders	Not always defined
Sensation	Not affected	Diminished	Diminished	Absent	Absent	Impaired
Bacilli in skin lesions	Many (globi)	Many	Many	Few (1+), if any, detected	None detected	Usually none detected

Table 75.2 Classification of leprosy. LL, lepromatous leprosy; BL, borderline LL; BB, mid-borderline leprosy; BT, borderline TT; TT, tuberculoid leprosy; I, indeterminate. *Adapted from A Guide to Leprosy Control, 2nd ed. Geneva: World Health Organization, 1988:27–28.*

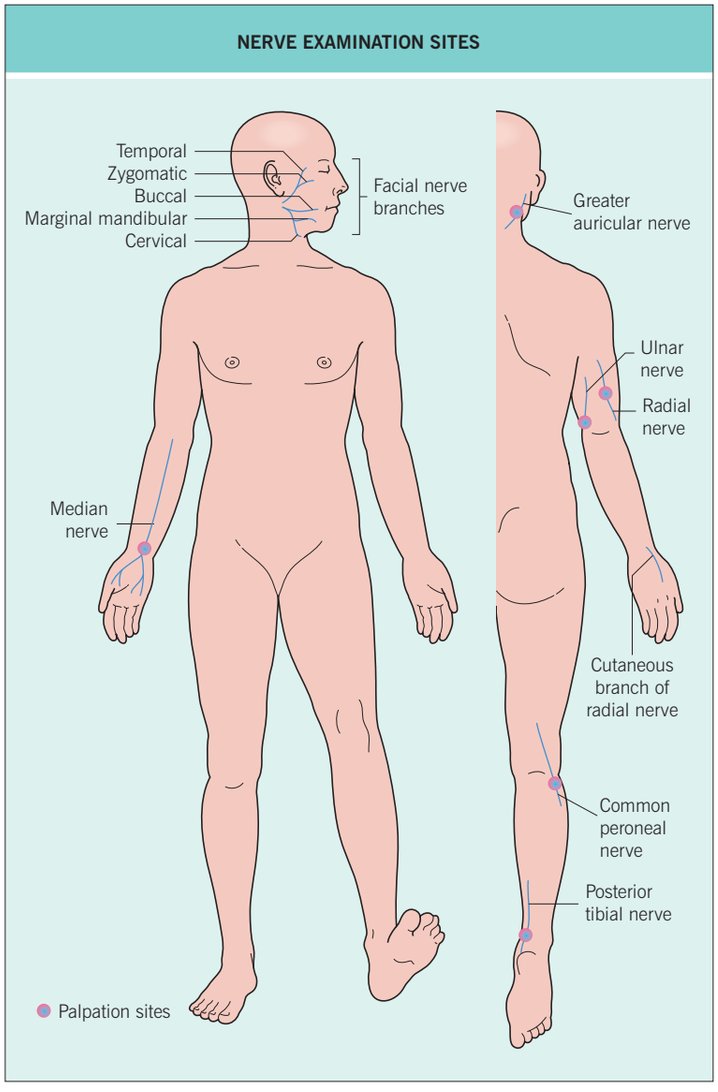


Fig. 75.3 Nerve examination sites.

Fig. 75.4 Lepromatous leprosy. A Note the diffuse infiltration with leonine facies and madarosis. **B** Numerous nodules on the forearms. *B, Courtesy, Louis A Fragola, Jr, MD.*

Fig. 75.5 Sequelae of leprosy. A The patient has madarosis, a saddle nose, and blindness in the left eye. **B** Ocular involvement and bluish discoloration of affected skin due to treatment with clofazimine.
A, Courtesy, Evangeline Handog, MD. B, Courtesy, Louis A Fragola, Jr, MD.

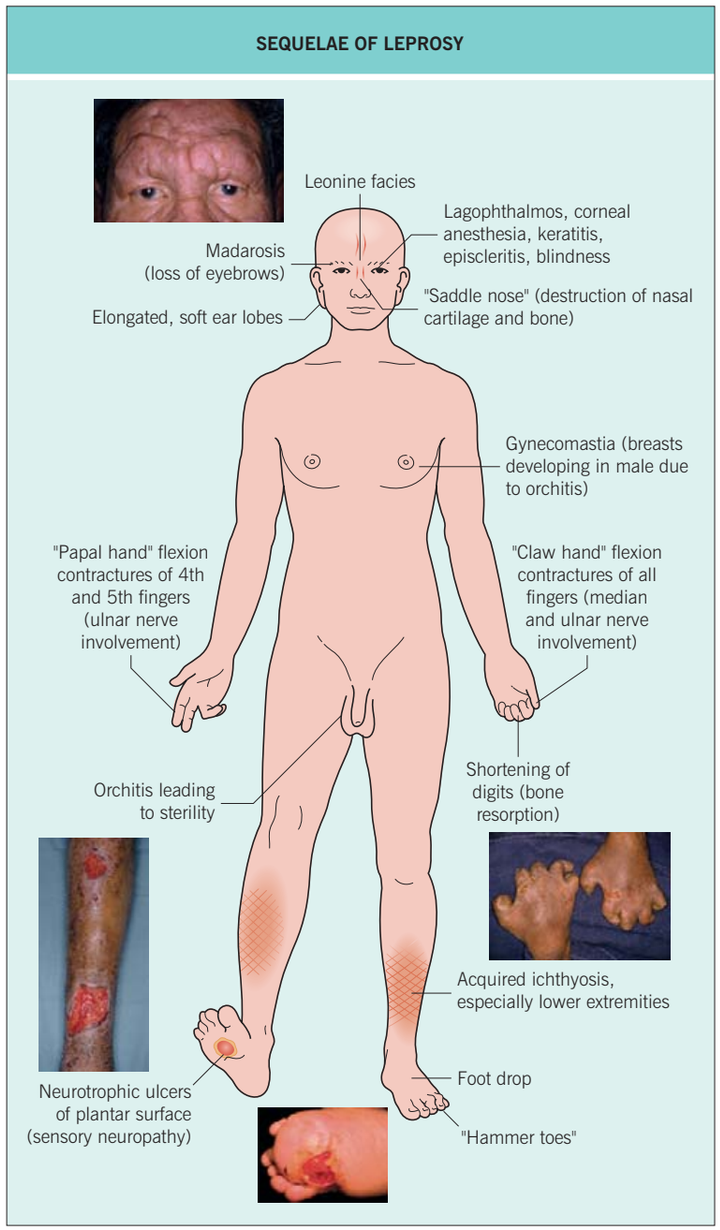


Fig. 75.6 Sequelae of leprosy. *Inserts, Courtesy, Louis A Fragola, Jr, MD, and Joyce Rico, MD.*

manifestations such as lagophthalmos (inability to completely close the eyes) and corneal and conjunctival anesthesia due to involvement of branches of the facial and trigeminal nerves, respectively, are sometimes present in severe cases[18]. *Histoid leprosy* is a clinically distinct variant of multibacillary disease that some authors classify as a variant of lepromatous leprosy. It is characterized by the development of dermatofibroma-like papules and nodules.

Borderline leprosy, as its name implies, has features that are intermediate between the two ends of the spectrum. Cutaneous lesions (Fig. 75.7) are usually asymmetric, e.g. there may be unilateral earlobe swelling. The severity of the cutaneous and peripheral nervous system abnormalities depends upon whether the patient is "leaning" towards the lepromatous pole (BL) or the tuberculoid pole (BT; see Table 75.2). Within the cutaneous plaques, hair is usually absent.

In *tuberculoid leprosy*, only a few well-demarcated plaques are seen and sometimes only neural involvement is present. The borders of the skin lesions are often slightly elevated, and this represents the preferred site for histologic examination. In some patients, the papules or plaques are erythematous, while in others, especially in darkly pigmented individuals, they are hypopigmented (Fig. 75.8). There is typically partial, but not complete, pigment loss. The plaques should be examined for alopecia as well as anesthesia or hypesthesia. Unilateral neuropathic changes, especially of the extremities (e.g. resorption of the digits), may be seen[11,15,34].

One of the major problems faced by clinicians and patients, especially during treatment, is the development of reactions (see Fig. 75.2). These are characterized by acute inflammation (Fig. 75.9) that appears suddenly. Type 1 reactions can affect patients with any form of leprosy (except for the early indeterminate form), with a predilection for those in borderline categories, while type 2 reactions most often occur in those with lepromatous or borderline lepromatous leprosy. In addition to the administration of antimicrobial drugs, the most frequent causes of reactions are pregnancy[37], other infections and even mental distress. The immunopathogenesis, clinical manifestations and treatment of the two major types of inflammatory reactions are outlined in Table 75.3[38]. *Type 1 (reversal) reactions* are due to a change in the immunologic state of the patient and are often associated with neuritis. When there is an increase in cell-mediated immunity, this is referred to as an "upgrading" reaction.

Type 2 reactions are due to the formation of immune complexes in association with an excessive humoral reaction. They typically occur when patients with lepromatous forms of leprosy undergo treatment. A type 2 reaction represents a small vessel vasculitis (cutaneous and systemic), and the most common clinical manifestation is *erythema nodosum leprosum* (see Fig. 75.9B)[13,18,21,39]. In addition, patients (usually from Central or South America) with the diffuse form of lepromatous leprosy may develop the *Lucio phenomenon*, a reactional state characterized by thrombotic phenomena as well as necrotizing cutaneous small vessel vasculitis. On a worldwide basis, leprosy is a common cause of cutaneous vasculitis, especially in low-income countries[7,40].

Pathology and Laboratory Evaluation

There are three basic histopathologic patterns observed in leprosy: lepromatous, tuberculoid and borderline. In the *lepromatous* pattern, an infiltrate is seen in the dermis, subcutis, lymph nodes, abdominal organs (e.g. kidney and liver), testicles and bone marrow. The infiltrate contains Virchow cells, which are macrophages with numerous bacilli as well as lipid droplets in their cytoplasm. In H&E-stained sections,

Fig. 75.7 Borderline lepromatous leprosy. Multiple erythematous plaques are seen, some with central clearing.

Fig. 75.8 Tuberculoid leprosy. Note the elevated border and central hypopigmentation. *Courtesy, Robert Hartman, MD.*

Fig. 75.9 Leprosy reactions. A Type 1 "upgrading" reaction in a patient with borderline lepromatous disease characterized by marked inflammation of a facial plaque. **B** Erythema nodosum leprosum (type 2 reaction) with the appearance of multiple red papulonodules as a result of immune complex-mediated small vessel vasculitis in a patient with lepromatous leprosy. *B, Courtesy, Louis A Fragola, Jr, MD.*

TWO MAJOR TYPES OF LEPROSY REACTIONAL STATES		
	Type 1 – Reversal reaction with "upgrading"	**Type 2 – Vasculitis (most commonly erythema nodosum leprosum)**
Immune mechanism	Enhancement of cell-mediated immunity with a Th1 cytokine pattern	Excessive humoral immunity with a Th 2 cytokine pattern and formation of immune complexes; may be accompanied by increased cell-mediated immunity
Pathogenic process	Delayed-type hypersensitivity reaction	Cutaneous and systemic small vessel vasculitis
Leprosy category	Borderline (BT, BB, BL) or tuberculoid with immunologic recovery during or after treatment	Lepromatous and BL > BB; especially patients with a high bacterial index who are undergoing treatment
Clinical characteristics	• Increased inflammation in established skin lesions • Emergence of "new" skin lesions • Acute nerve pain or tenderness (neuritis) and loss of function • Recent (<6 month history) or progressive neurologic impairment in the absence of painful nerves	• Nodular skin lesions • Fever, myalgias, malaise • Severe joint swelling and pain • Iridocyclitis • Lymphadenitis • Hepatosplenomegaly • Orchitis • Glomerulonephritis
Treatment	Prednisone	Thalidomide

Table 75.3 Two major types of leprosy reactional states[13,18,21,38,39]. Secondary amyloidosis may occur in patients with type 2 reactional states.

these cells have a foamy appearance. With Sudan III stain, the lipid inside the Virchow cells appears orange. The bacilli in leprosy can be detected by Gram, Ziehl-Neelsen, Fite (the most commonly used) or Wade stain, all of which stain the bacilli a bright red color. Sudan III and Sudan IV (also known as scarlet red) stain the bacilli black and red, respectively. Methenamine silver stains are also useful for detecting fragmented acid-fast bacilli. For lesions where bacilli are scanty, it is recommended that at least six sections be examined before declaring them negative[13,41].

A band of normal-appearing dermis (Unna band or Grenz zone) separates the epidermis from the infiltrate, which is composed of plasma cells and lymphocytes in addition to Virchow cells (Fig. 75.10). Both isolated bacilli and globi (clumps of bacilli) are seen in the dermis; when the patient is undergoing successful therapy, the organisms fragment and become granular. Cutaneous nerves demonstrate lamination of the perineurium, giving them an onion-skin appearance. In the histoid variant, a well-circumscribed proliferation of spindle cells (which contain numerous bacilli) is seen; the bacilli typically line up along the long axis of the cell.

In the *tuberculoid* pattern of leprosy (Fig. 75.11), a dermal granulomatous infiltrate is seen that may have a linear pattern as it follows the course of a nerve. Epithelioid cells and Langhans giant cells are surrounded by lymphocytes. The cutaneous nerves are edematous, and there is an absence of organisms, even with special stains. The inflammation and fragmentation of nerve fibers in tuberculous leprosy differentiate it from sarcoidosis and other granulomatous disorders.

The *borderline* pattern contains histologic features of both the lepromatous form (e.g. Virchow cells) and tuberculoid form (e.g. granulomas). Predominance of the former versus the latter is dependent upon whether the patient has the BL, BB or BT form of borderline leprosy. There are three different histologic "scenarios" in borderline leprosy:

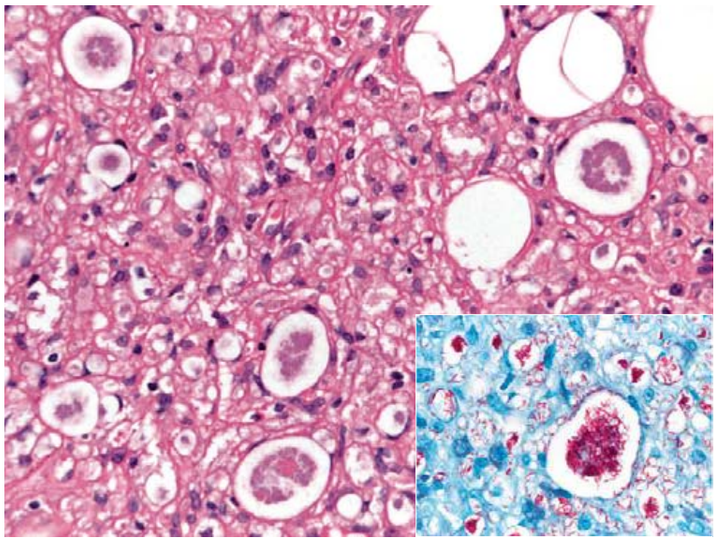
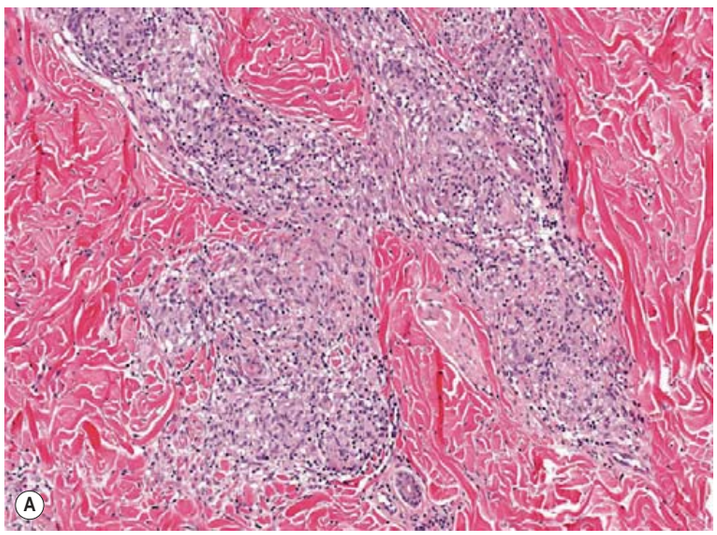


Fig. 75.10 Lepromatous leprosy. Diffuse dermal infiltrate of foamy histiocytes; note the globi which represent clumping of mycobacteria. Fite stain highlighting the numerous bacilli as well as globi (insert). *Courtesy, Lorenzo Cerroni, MD.*



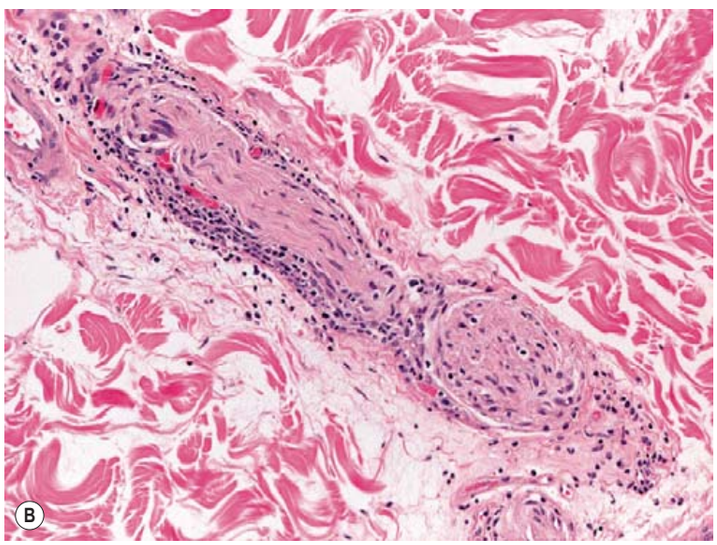


Fig. 75.11 Tuberculoid leprosy. A Granulomatous nodular infiltrate within the dermis. **B** Nerve involvement characterized by a sparse perineural infiltrate with lymphocytes, histiocytes and plasma cells. *Courtesy, Lorenzo Cerroni, MD.*

(1) the patient has some lesions with a lepromatous pattern and other lesions with a tuberculoid pattern; (2) Virchow and tuberculoid patterns are seen in the same lesion; and (3) lesions have a mixture of foamy and epithelioid cells.

Indeterminate leprosy is usually difficult to diagnose histologically. Only a patchy infiltrate of lymphocytes or histiocytes around blood vessels or appendages is seen[8,15]. There are no granulomas or Virchow cells[7,13], and organisms are usually absent.

When leprosy is suspected, the diagnosis of several forms (e.g. LL, BL) can be confirmed by finding bacilli in cutaneous scrapings, lymph nodes or nasal secretions. Samples for bacilloscopy may be obtained from the earlobes, forehead, chin, extensor forearms, and dorsal fingers, as well as the buttocks and trunk. To avoid bleeding, a fold of skin is firmly squeezed between the finger and thumb of the examiner or with forceps, and a small incision is made with a scalpel blade. The liquid obtained is smeared onto a slide and allowed to dry. The smear is usually stained by the Fite (or Ziehl-Neelsen) method and a search is made for red rods (against a blue background) at 100× with oil immersion[8]. Organisms are found in 100% of patients with lepromatous leprosy, in 75% of those with borderline leprosy, and in only 5% of those patients with tuberculoid leprosy. A biopsy specimen of the skin lesions should be obtained, especially in patients with suspected tuberculoid leprosy (see above).

The detection of *M. leprae* DNA in fresh skin samples and split skin smears by PCR has been described. In one study utilizing this technique, detection of *M. leprae*-specific repetitive sequence (RLEP) in biopsy specimens was shown to be more sensitive than detection of an 18 kDa protein gene (80% vs 57%)[42]. PCR analysis can also be performed on biopsies of nasal mucosa. In addition, immunohistochemical staining of biopsy specimens for the PGL-1 antigen may prove helpful in paucibacillary disease.

Serologic assays for anti-PGL antibodies are only sensitive for the diagnosis of leprosy in the setting of multibacillary disease. However, measurement of these antibodies can help to classify patients, monitor the response to treatment, and predict leprosy reactions[43]. Serum levels of anti-PGL-1 IgG and IgM antibodies are highest in those with lepromatous disease and lowest (or absent) in those with BT or tuberculous disease, therefore representing a marker of mycobacterial "load" in affected individuals. Elevation of anti-PGL IgM antibody levels is also associated with reactions and impairment of nerve function[27].

Three classic tests – the histamine, pilocarpine and Mitsuda tests – can be done to aid in diagnosis and determining prognosis. However, nowadays these tests are done less frequently. In the first, a drop of 0.001% histamine is placed on the suspect patch and another one on normal skin. Both areas are pricked with a needle (through the drop) and, after 10 minutes, the intensity and extent of the wheal and flare are recorded. This response is dependent upon the integrity of sympathetic nerves fibers, and, in hypopigmented lesions of leprosy (the type of lesion most commonly tested), it will be decreased, delayed or absent[8,10].

In the pilocarpine test, tincture of iodine is applied to the suspect lesion (and normal skin as a control) prior to the injection of pilocarpine into these sites. Afterwards, these areas are dusted with a starch powder that will turn blue if there is normal sweating. Because sweating depends on the integrity of parasympathetic nerve fibers, it is decreased in lesions of leprosy. Quinizarine, which turns from white to blue, can be used instead of iodine and starch[8].

The lepromin or Mitsuda test consists of an intradermal injection of 0.1 ml of a suspension of heat-killed *M. leprae*. The response is positive when a nodule forms at the site of injection 3 to 4 weeks later, indicating that the patient is able to mount a specific cell-mediated response to the bacilli. The test provides prognostic, but not diagnostic, information. It is positive in TT and BT leprosy[8].

Lastly, leprosy, especially LL and BL, is one of the causes of biologically false-positive Venereal Disease Research Laboratory (VDRL) and fluorescent treponemal antibody absorption (FTA-ABS) assays for syphilis (see Ch. 82).

Differential Diagnosis

A number of skin diseases may be confused with leprosy. Hypopigmented lesions can mimic pityriasis alba, pityriasis versicolor, mycosis fungoides or sarcoidosis. The circinate erythematous plaques may be misdiagnosed as tinea corporis, sarcoidosis, lichen planus, psoriasis or

mycosis fungoides. The differential diagnosis of the infiltrated plaques or nodules includes leishmaniasis, syphilis, sarcoidosis, lymphoma and cutaneous tuberculosis[12,15]. The neurologic findings may be confused with other types of peripheral neuropathy (e.g. due to diabetes mellitus, nutritional disorders, vasculitis, poliomyelitis or syringomyelia), while the deforming acral features may suggest Dupuytren's contractures, scleroderma, tabes dorsalis, or other diseases associated with neuropathic changes[11,12,15].

The differential diagnosis of a type 1 reaction includes acute lupus erythematosus, cellulitis and drug reactions, while in patients with type 2 reactions, the possibility of other vasculitides and panniculitides (including erythema nodosum; see Ch. 100) needs to be considered. The individual lesions of erythema nodosum leprosum appear in crops but resolve relatively rapidly and are widespread, whereas the lesions of erythema nodosum are longer-lived and favor the shins.

Treatment

The WHO recommends multidrug regimens that are safe, effective and easily administered (Table 75.4). If bacilloscopy is available, patients are considered to have paucibacillary leprosy if no bacilli are found; they are treated with rifampin monthly plus a sulfone (usually dapsone) daily for 6 months, and then observed for 2 years. For patients with paucibacillary disease and a single lesion, single-dose therapy ('ROM scheme': single dose of 600 mg *r*ifampin, 400 mg *o*floxacin and 100 mg *m*inocycline), has yielded good results. If at least one bacillus is detected via bacilloscopy, the patient should receive rifampin, clofazimine and dapsone for 1 to 2 years and then be observed for 5 years. A second option is to combine a sulfone with clofazimine[44–46]. Pediatric therapeutic schemes recommended by a WHO are also summarized in Table 75.4.

Multidrug therapy is extremely effective. Importantly, after the first dose, the patient is no longer infectious to others (i.e. transmission of leprosy is interrupted). All patients who complete the prescribed regimen are considered cured, as there are virtually no relapses. Bacilli may be found but they are non-viable. Drugs that may play a significant role in the treatment of leprosy in the future include other quinolones (e.g. moxifloxacin, sparfloxacin), clarithromycin and ansamycins[47–49]. Rifapentine (a rifampin derivative) has higher peak serum concentrations, a longer serum half-life and more bactericidal activity against *M. leprae* than does rifampin. In addition, moxifloxacin appears to be more bactericidal than ofloxacin. As a result, the combination of rifapentine, moxifloxacin and minocycline (PMM) may be superior to rifampin, ofloxacin and minocycline (ROM)[49].

For the two major inflammatory reactions, additional medications are often required. Oral prednisone (20–60 mg per day) is used for type 1 (reversal) reactions, while thalidomide (100–200 mg per day) is the principal therapy for type 2 reactions (erythema nodosum leprosum). Systemic corticosteroids are also recommended for the Lucio phenomenon. Although thalidomide remains the treatment of choice for type 2 reactions, its teratogenicity can be problematic and it is unavailable in many countries where leprosy is endemic. Lenalidomide and pomalidomide are thalidomide analogues with different side-effect profiles (e.g. less teratogenicity, more myelosuppression) that could have potential utility in the treatment of type 2 reactions. Additional drugs with possible benefit in type 2 reactions include clofazimine, cyclosporine (which has been used for corticosteroid-resistant type 1 reactions), chloroquine, pentoxifylline and phosphodiesterase type-4 inhibitors (e.g. roflumilast)[49–51].

Although leprosy is now considered a curable disease with a good prognosis and excellent survival rate, it can still be incapacitating and stigmatizing. It is very important to make the diagnosis as early as possible and to examine contacts, since treatment provided in the early stages of the disease prevents disability. Recognition of leprosy in its initial phases (in particular the cutaneous findings) by healthcare professionals as well as the general population in endemic countries is essential in order to reduce the impact of this disease[8].

CUTANEOUS TUBERCULOSIS

Key features

- Infection of the skin due to *Mycobacterium tuberculosis*, an acid- and alcohol-fast bacillus
- Increases in the incidence of tuberculosis (TB) in recent years are attributed to the HIV epidemic, emergence of resistant strains of *M. tuberculosis*, and a decline in TB control efforts
- Exogenous exposure produces primarily the tuberculous chancre and TB verrucosa cutis
- Endogenous infection can lead to scrofuloderma, miliary TB and lupus vulgaris
- Tuberculids include a papulonecrotic eruption, lichen scrofulosorum and erythema induratum

Introduction

Tuberculosis (TB) has affected humans since prehistoric times. There was, however, a worldwide explosion in its incidence in the late 1980s and early 1990s, and consequently a resurgence of cutaneous TB[2,52–54]. This phenomenon has been attributed to the HIV epidemic, the emergence of resistant strains of *Mycobacterium tuberculosis*, increased use of immunosuppressive therapies, more migration of people around the world, and a decline in TB control efforts[52,53], superimposed on the pre-existing factors of poverty and malnutrition.

MULTIDRUG THERAPY/WHO SCHEME FOR THE TREATMENT OF LEPROSY						
	Rifampin	**Clofazimine**	**Dapsone**	**Ofloxacin**	**Minocycline**	**Therapy duration**
MB (>5 lesions*)	600 mg once monthly	300 mg once monthly and 50 mg daily	100 mg daily	–	–	12 blister packs over 12 to 18 months
PB (2–5 lesions*)	600 mg once monthly	–	100 mg daily	–	–	6 blister packs over 6 to 9 months
PB (single lesion*)	600 mg × 1	–	–	400 mg × 1	100 mg × 1	Single dose
DOSE ADJUSTMENTS FOR CHILDREN						
10 to 14 years of age, MB†	450 mg once monthly	150 mg once monthly and 50 mg every other day	50 mg daily	–	–	12 blister packs over 12 to 18 months
<10 years of age, MB†	300 mg once monthly	100 mg once monthly and 50 mg twice weekly	25 mg daily	–	–	12 blister packs over 12 to 18 months
5 to 14 years of age, single lesion PB	300 mg × 1	–	–	200 mg × 1	50 mg × 1	Single dose

*WHO classification for endemic areas when no facilities for performing bacilloscopy are available.
†For PB disease (2–5 lesions), clofazimine is not required and the duration of therapy is 6 to 9 months.

Table 75.4 Multidrug therapy/WHO scheme for the treatment of leprosy. These recommendations are those currently standardized by the WHO[7,36,44–46]. MB, multibacillary; PB, paucibacillary.

History

There are paleopathologic findings suggesting *M. tuberculosis* infections as early as 3700 BC in Egypt, and 2500 to 1500 BC in Europe. Utilizing PCR, *M. tuberculosis* DNA has been demonstrated in mummified remains from ancient times. In 1826, Laennec first reported cutaneous TB in the form of a "prosector's wart". Rokitansky and Virchow subsequently described the histologic features of cutaneous TB in detail, comparing them to those of visceral TB. The discovery of *M. tuberculosis* by Koch in 1882 and the advances in descriptive pathology during the nineteenth century helped to establish cutaneous TB as part of the spectrum of this infectious disease[53,54].

Epidemiology

M. tuberculosis is not particularly virulent, as only 5% to 10% of infections lead to clinical disease. This bacterium has a worldwide distribution; it is more prevalent in regions with a cold and humid climate but can also occur in the tropics (Fig. 75.12)[55]. The incidence of cutaneous TB parallels that of pulmonary TB and is therefore seen more commonly in low-income countries and impoverished populations. HIV-infected individuals and those receiving immunosuppressive therapies (especially TNF-α inhibitors; see Ch. 128) are at particular risk for the development and reactivation of TB.

Pathogenesis

M. tuberculosis is the predominant etiologic agent in cutaneous TB. Occasionally, *M. bovis* and bacille Calmette-Guérin (BCG), an attenuated strain of *M. bovis*, may produce skin lesions[39,52].

M. tuberculosis is a slender, non-motile, aerobic, non-spore-forming, filamentous rod. It is an acid- and alcohol-fast bacillus that has a waxy coating with a high lipid content, which makes it resistant to degradation after phagocytosis[56].

M. tuberculosis disseminates primarily via inhalation of aerosolized droplets of saliva from individuals with active disease; transmission by ingestion or inoculation can also occur[56]. Intact skin provides an effective protective barrier against invasion of the organism, but a break in the mucocutaneous barrier can facilitate its entrance[57]. Untreated infected individuals who do not have underlying medical problems have a 5% to 10% lifetime risk of progression to active TB; this risk increases substantially with immunosuppression (e.g. HIV infection or treatment with medications such as TNF-α inhibitors).

Studies using a model of zebrafish infected with *Mycobacterium marinum* have demonstrated that granulomas, which are classically considered as host-protective structures formed to control infection, actually contribute to early bacterial growth and facilitate its spread[58] (Fig. 75.13). Mycobacteria induce granuloma formation by releasing the early secreted antigenic target 6 (ESAT-6) protein, which stimulates neighboring epithelial cells to produce matrix metalloproteinase-9 (MMP-9). MMP-9 enhances recruitment of macrophages that contribute to bacterial proliferation and spread as well as maturation of the nascent granuloma[59]. Increased production of other MMPs (e.g. MMP-1, MMP-3) has also been shown to drive tissue destruction in TB[60]. Eventually, development of adaptive immunity results in the curtailment (but not eradication) of bacterial growth by $CD4^+$ and $CD8^+$ effector T cells. The mature granuloma therefore represents an equilibrium between mycobacterial growth and the host immune response, and MMPs represent potential targets for antimycobacterial therapy.

The interaction of T cells and mycobacterial antigens, which are displayed on the surface of antigen-presenting cells, induces the liberation of interferons and other cytokines. These substances promote the activation and expression of MHC class II on antigen-presenting cells as well as the IL-2 receptor on T cells. During the initial sensitization, memory T cells are generated and will remain for decades in lymphoid organs and the circulation[52]. In mice, the intracellular pathogen resistance 1 gene (*Ipr1*) within the supersusceptibility to tuberculosis 1 (sst1)

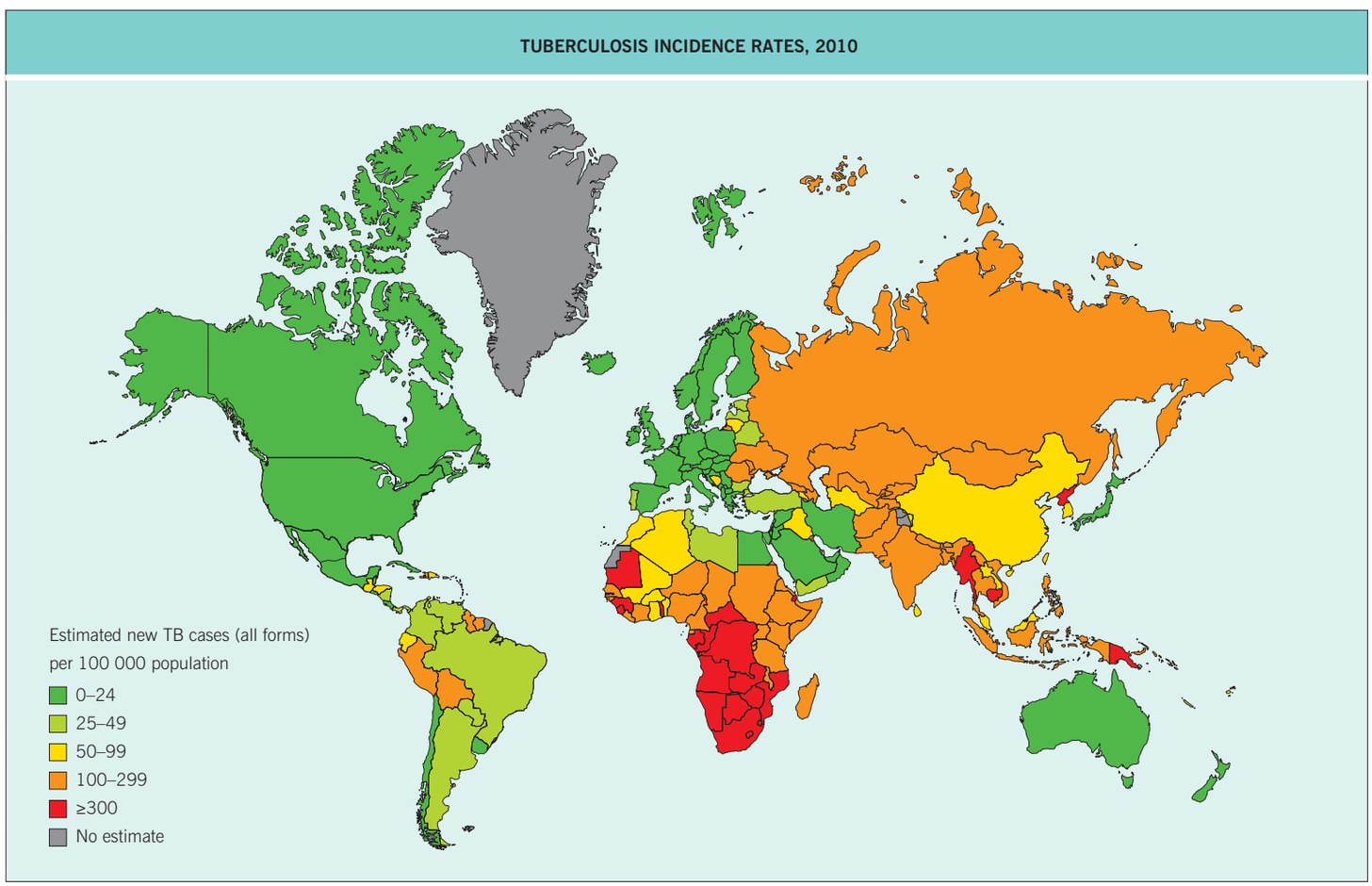


Fig. 75.12 Tuberculosis incidence rates, 2010. *Reproduced from the World Health Organization[55].*

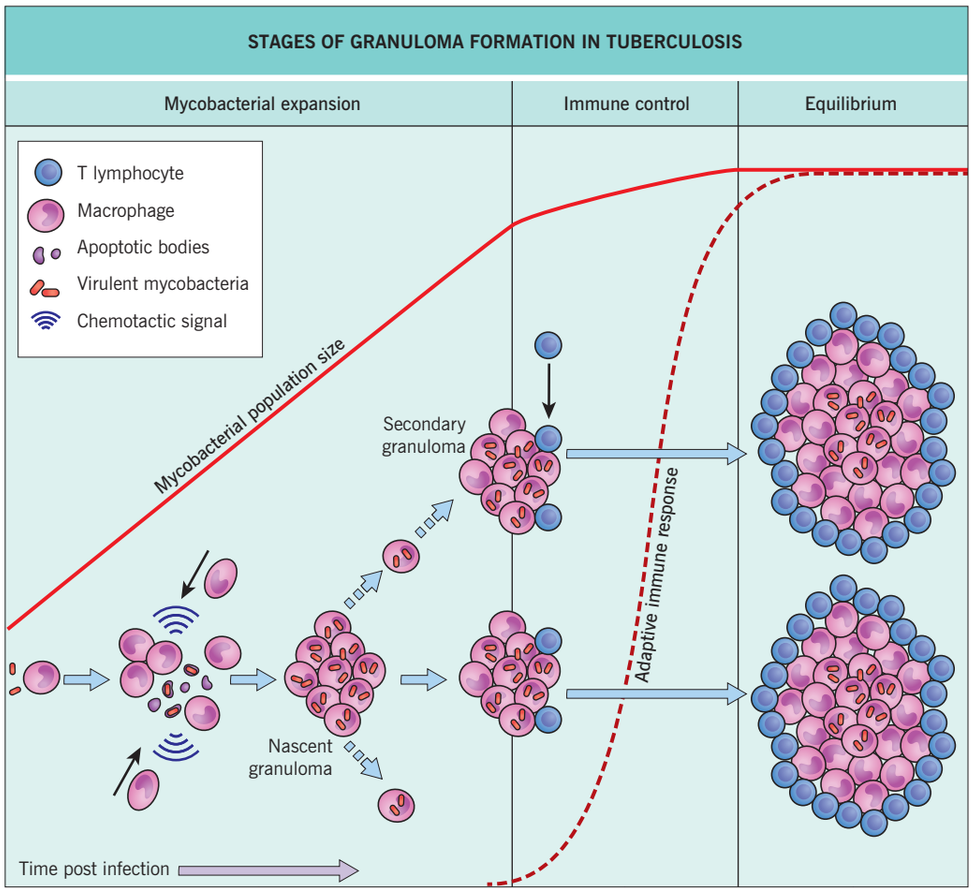


Fig. 75.13 Stages of granuloma formation in tuberculosis. The initial stage of tuberculosis is characterized by expansion of the mycobacterial population in the absence of adaptive immunity. Mycobacterial multiplication and spread are facilitated by the formation of the nascent granuloma. Infected macrophages undergo apoptosis and recruit additional macrophages, which phagocytose remnants of infected cells and their mycobacterial contents. Some of these newly infected macrophages then seed secondary granuloma formation. When adaptive immunity eventually occurs, $CD4^+$ and $CD8^+$ effector T cells curtail mycobacterial growth. Although this controls the infection, it is not eradicated. The mature granuloma therefore represents an equilibrium between mycobacterial proliferation and the host response. *Adapted with permission from Bold TB & Ernst JD. Who benefits from granulomas, mycobacteria or host? Cell. 2009;136:18–19.*

locus encodes a protein that mediates innate immunity to *M. tuberculosis* and other intracellular organisms. Ipr1 is expressed in macrophages and limits the multiplication of *M. tuberculosis* within these cells[61].

The sensitization status of the host to mycobacterial antigens (e.g. previously infected vs never exposed), the degree of cell-mediated immunity of the host, the route of infection, and the pathogenicity of the infective strain of mycobacteria determine the resulting infection (Table 75.5). In HIV-infected patients, cell-mediated immunity is impaired; as a consequence, there may be reactivation of quiescent disease[52,57].

Clinical Features

Cutaneous TB has a wide variety of clinical presentations[3,52,54,56,62]. Lesions can be due to direct inoculation of *M. tuberculosis* from an exogenous source, e.g. tuberculous chancre, TB verrucosa cutis and, occasionally, lupus vulgaris. Skin involvement due to endogenous infection may appear as scrofuloderma, acute miliary TB, a tuberculous gumma, orificial TB and lupus vulgaris (see Table 75.5). In addition, immune reaction to *M. tuberculosis* can have several cutaneous manifestations, which are called tuberculids.

Cutaneous tuberculosis

A *tuberculous chancre* develops 2 to 4 weeks after the inoculation of *M. tuberculosis* into the skin of an individual without a history of TB. It is a painless, firm, reddish-brown papulonodule that slowly enlarges, eventually eroding to form a sharply demarcated ulcer[3,52,56]. Frequently there is spread to draining lymphatics and regional lymph nodes[52]; the combination of the latter with a tuberculous chancre is analogous to the Ghon complex in the lung[52,56]. The skin lesion usually heals spontaneously within 3 to 12 months, leaving an atrophic scar and calcified regional lymph nodes. The tuberculous chancre may occasionally evolve into verrucous plaques, scrofuloderma-like lesions or lupus vulgaris[54,56].

Tuberculosis verrucosa cutis results from exogenous inoculation of *M. tuberculosis* at sites prone to trauma in previously infected individuals[3,56]. The lesion begins as a small, asymptomatic, indurated wart-like papule with a subtle inflammatory rim (Fig. 75.14). It gradually enlarges, often in a serpiginous manner, to form a firm reddish-brown verrucous plaque. The center of the lesion may become fluctuant, with pus and keratinaceous debris expressed by slight pressure[3,54,56]. After several years, the plaque can heal spontaneously[52].

Scrofuloderma begins as a firm, deep-seated, subcutaneous nodule that has accumulated inflammatory material and necrotic tissue, best characterized as a "cold abscess". The suppurative nodule later becomes fluctuant and drains, with ulceration and sinus tract formation (Fig. 75.15). Because of the drainage, the bacilli secondarily infect the overlying dermis. The borders of the ulcers are often blue, the margins are undermined, and the base is covered with soft granulation tissue. Multiple ulcers can appear. After healing, keloids and retracted tethered scars develop at the sites of infection. The original focus of TB is usually underlying lymph nodes or bones, but it may be joints or the epididymis[3,52,54,63].

Orificial tuberculosis usually results from autoinoculation of *M. tuberculosis*, although occasionally it has an exogenous origin. The affected patients typically have advanced internal TB in the setting of impaired cell-mediated immunity. The mucosal or cutaneous lesions occur within or adjacent to a natural orifice that is draining an active internal tuberculous infection, primarily pulmonary, intestinal or anogenital. The most common location is the mouth, especially the tongue. The initial lesion is an edematous red papule that ulcerates (Fig. 75.16) and develops undermined edges. The ulcers are painful, recalcitrant to treatment, and do not tend to heal spontaneously[3,56].

Lupus vulgaris (Fig. 75.17) is a form of cutaneous TB that occurs in previously sensitized individuals with a strongly positive delayed-type hypersensitivity (DTH) reaction to tuberculin (reflecting cell-mediated immunity). It can develop secondarily from TB verrucosa cutis or scrofuloderma as well as from other endogenous and exogenous sources; lupus vulgaris also occasionally arises following BCG inoculation. The typical lesion is a red–brown plaque composed of papulonodules with an "apple-jelly" color on diascopy. As the plaque expands, central scarring often develops. This can lead to substantial tissue destruction over a period of years. Lupus vulgaris has a number of clinical presentations

CLINICAL PRESENTATIONS OF CUTANEOUS TUBERCULOSIS							
	Tuberculous chancre	**Tuberculosis verrucosa cutis**	**Scrofuloderma**	**Orificial tuberculosis**	**Lupus vulgaris**	**Acute miliary tuberculosis**	**Tuberculous gumma**
Synonyms	Primary inoculation tuberculosis, cutaneous primary complex	Warty tuberculosis, prosector's wart, lupus verrucosus	Tuberculosis cutis colliquativa	Acute tuberculous ulcer, tuberculosis cutis orificialis	Tuberculosis luposa	Tuberculosis cutis disseminata, tuberculosis cutis acuta generalisata	Metastatic tuberculous ulcer, metastatic tuberculous abscess
Incidence	Rare except in Asia; 1–2% of cutaneous tuberculosis	Most common form of cutaneous tuberculosis (e.g. ~40% of cases in Hong Kong)	Common in immigrants from developing countries	Rare	Low: 10–15% of cutaneous tuberculosis; women affected 2–3 times more often than men	Rare; infants and young children, seldom adolescents or adults	Children with low socioeconomic status or immunocompromised hosts
Transmission	Inoculation into skin and/or mucosa of previously uninfected person, i.e. with no specific immunity	Inoculation into skin and/or mucosa of previously infected person with moderate or high immunity	Contiguous involvement of skin overlying a focus of tuberculosis, usually in lymph node or bone. Also reported after BCG vaccination	Autoinoculation of mucosa or skin adjacent to a natural orifice draining an active internal tuberculous infection	Direct extension; hematogenous or lymphatic spread from a tuberculous focus; reinfection; BCG vaccination	Hematogenous dissemination from primary lung focus in patient with low immunity; may follow viral infection	Acute hematogenous dissemination from a primary focus during periods of bacillemia and lowered resistance
Tuberculin skin test	Early: negative Later: positive	Positive	Usually positive	Variable, often negative	Usually positive	Usually negative	Usually negative
Histopathology	• Acute: nonspecific neutrophilic inflammation with necrosis; bacilli • Later: granulomatous inflammation with central caseation, epithelioid and Langhans giant cells; disappearance of bacilli	Acute inflammation in the epidermis, pseudoepitheliomatous hyperplasia, microabscesses in upper dermis, sparse granulomatous foci; occasionally bacilli present	Tuberculous granulation tissue and caseation necrosis in the deeper dermis; bacilli can be isolated from pus	Nonspecific inflammatory infiltrate and necrosis, some tubercles with caseation deep in dermis; bacilli easily found	Well-developed tubercles with scant caseation, nonspecific inflammatory infiltrate; no visible bacilli	Necrosis, nonspecific inflammatory infiltrate surrounded by macrophages, sometimes developing into small abscesses; abundant bacilli	Massive necrosis and abscess formation; large number of bacilli
Diagnosis	Histology and culture PCR IGRA*	Culture PCR IGRA	Culture PCR IGRA	Histology and culture PCR Presence of another focus of TB IGRA*	Histology and culture PCR IGRA	Smear, histology and culture; PCR Presence of another focus of TB IGRA*	Culture and histology PCR IGRA*
Differential diagnosis	Other pyogenic ulcers and chronic chancriform lesions, including the following: sporotrichosis, dimorphic or opportunistic fungal infections, *M. marinum* infection, nocardiosis, tularemia, syphilis, cat scratch disease	Warts, verrucous fungal infections (e.g. chromomycosis), tertiary syphilis, hypertrophic lichen planus	Dimorphic or opportunistic fungal infections, non-tuberculous mycobacterial infections, syphilitic gumma, actinomycosis, chronic bacterial osteomyelitis, adenitis with drainage, hidradenitis suppurativa, severe acne conglobata	Painful ulcerative diseases that affect orifices and periorificial skin: HSV, recurrent aphthous stomatitis, pemphigus, histoplasmosis	Sarcoidosis, discoid lupus erythematosus, dimorphic fungal infections, leishmaniasis, tertiary syphilis, squamous cell carcinoma	Varicella, enteroviral exanthems, rickettsialpox, PLEVA	Panniculitis, dimorphic or opportunistic fungal infection, syphilitic gumma, hidradenitis suppurativa
*May have an indeterminate result early in the disease course or in immunocompromised patients.							

Table 75.5 Clinical presentations of cutaneous tuberculosis. BCG, bacille Calmette-Guérin; IGRA, interferon-γ release assay (e.g. QuantiFERON® TB Gold [In-Tube], T-SPOT®.TB; see Table 75.6).

Fig. 75.14 Tuberculosis verrucosa cutis. A wart-like papule at the site of exogenous inoculation in a patient with immunity against *M. tuberculosis*.

Fig. 75.15 Scrofuloderma. Plaques and nodules with central ulceration as well as resultant scarring with retraction.

Fig. 75.16 Orificial tuberculosis. A non-healing ulcer of the nasal mucosa.
Courtesy, Louis A Fragola, Jr, MD.

including the following: (1) plaque-type; (2) ulcerative or mutilating; (3) vegetating; (4) tumor-like; and (5) papulonodular. The head and neck region is the most commonly affected site, in particular the nose, cheeks and ear lobes[3,54,56]. Mucosa, especially oral, can also be involved.

The initial lesions of *miliary tuberculosis* are pinhead-sized, bluish-red papules capped by minute vesicles. The vesicles develop a tiny central umbilication followed by the formation of crusts. When the papules heal, they leave a residual white scar with a brownish rim[3,52,56]. The cutaneous lesions are the result of a bacteremia, and the primary focus is often in the lungs.

A *tuberculous gumma* is also due to a bacteremia with cutaneous seeding. It can present as a firm subcutaneous nodule that slowly softens or as an ill-defined fluctuant swelling. The overlying skin gradually breaks down to form an undermined ulcer, often with sinus tract formation. The extremities are more often affected than the trunk[3].

Tuberculids

The tuberculids represent a group of disorders that classically were associated with a focus of internal TB. They are considered immune reactions within the skin due to hematogenous dissemination of *M. tuberculosis* or its antigens from a primary source, in an individual with strong antituberculous cell-mediated immunity. Often beginning as an immune complex-mediated reaction, they evolve into a granulomatous inflammatory response.

Because the supporting evidence is often circumstantial, there is an ongoing debate as to the pathogenesis of tuberculids and their association with *M. tuberculosis*[3,54,62]. Arguments in favor of an association with *M. tuberculosis* include a positive tuberculin skin reaction in affected patients; the presence of *M. tuberculosis* DNA (as detected by PCR) in lesions of erythema induratum, lichen scrofulosorum and papulonecrotic tuberculid; and a positive response to antituberculous chemotherapy. In addition, many of the lesions demonstrate granulomatous inflammation. However, those who argue against an association state that there are multiple causes of granulomatous inflammation and an active focus of TB is usually not found in patients with tuberculids. Also, a positive tuberculin test simply reflects a past exposure to TB. However, the argument that corticosteroids can improve these eruptions is not a particularly strong one against an association, since other infectious diseases, e.g. viral hepatitis, can improve with such therapy and one would expect an antigen-driven inflammatory process to respond to corticosteroids. Although the positive PCR findings are not absolute proof of pathogenesis, in the setting of appropriate controls, they do provide strong evidence in favor of an association.

Papulonecrotic tuberculid presents with dusky red papules or papulopustules that are widely distributed in a somewhat symmetric pattern (Fig. 75.18). Individual lesions may have central necrosis and are usually asymptomatic; occasionally there is associated pruritus. Papulonecrotic tuberculid is seen most often in children and young adults, and lesions favor the extensor surfaces of the arms and legs and the buttocks. Usually there is spontaneous healing of individual lesions, often with scar formation. Multiple cyclic eruptions are characteristic, even after antimycobacterial therapy. PCR for mycobacterial DNA and the tuberculin test are positive[3,54]. Histologically, there is evidence of leukocytoclastic vasculitis and wedge-shaped necrosis in the dermis; later on, a perivascular mononuclear cell infiltrate and granuloma formation can be seen. The history and clinical appearance aid in the diagnosis, which is bolstered by the histologic findings. The differential diagnosis may include pityriasis lichenoides et varioliformis acuta (PLEVA) and small vessel vasculitis.

The early lesions of *lichen scrofulosorum*, a rare disorder, are firm, typically perifollicular, pink or yellow–brown, tiny flat-topped papules with variable scale. These asymptomatic papules are grouped in clusters, predominantly on the trunk. Lesions may persist for months and then disappear without scarring. Although it is seen in all age groups, children with nodal or skeletal TB are most frequently affected. This type of tuberculid has also been reported after BCG vaccination and it can be triggered by tuberculin testing in highly reactive patients. Histologic examination demonstrates superficial granulomas around hair follicles and sweat ducts, with little or no caseation necrosis. No bacilli are found; however, PCR testing has demonstrated *M. tuberculosis* DNA within lesions. The differential diagnosis includes lichen nitidus, lichen planus and other lichenoid dermatoses (see Ch. 12) as well as "id" reactions, Blau syndrome, sarcoidosis and secondary syphilis[3,54,62].

Erythema induratum (*nodular vasculitis*) is a form of lobular panniculitis that is associated with *M. tuberculosis* infection in a subset of affected individuals (especially in countries with a high prevalence of TB) (see Ch. 100). The term *erythema induratum of Bazin* is reserved for cases related to *M. tuberculosis*. Immune complex deposition (which may play a role in the vasculitic component) and a delayed-type hypersensitivity reaction to mycobacterial antigens are thought to be involved in the pathogenesis of this condition[39,62]. Women are most commonly affected (approximately 80–90% of patients), with peaks in incidence during early adolescence and around menopause.

Fig. 75.17 Lupus vulgaris. A Annular granulomatous plaque with central scarring. **B** Coalescing pink-brown papules. **C** Red-brown plaque on the neck. *C, Courtesy, Eugene Mirrer, MD.*

Fig. 75.18 Papulonecrotic tuberculid. Erythematous papules and papulopustules on the heel.

Fig. 75.19 Site of a BCG vaccination. Enlarging granulomatous plaque (BCGitis).

Symptoms often begin after exposure to low temperatures. Typically, subcutaneous nodules appear on the calves of both legs; they may involute or break down, creating irregular deep ulcers with undermined bluish borders. Healing results in atrophic hyperpigmented scars. Histologically, a lobular (or lobular plus septal) panniculitis is seen. A neutrophilic vasculitis with mural thickening of subcutaneous arteries and veins and perivascular cuffing may also be evident. Fat necrosis and granulomas can sometimes be observed. Bacilli are absent and caseation is rare[3,54].

Other entities such as erythema nodosum, lupus miliaris disseminatus faciei, granulomatous rosacea and lichenoid tuberculid were formerly considered tuberculids, but they are no longer included in this category[62].

BCG inoculation

BCG vaccination is performed with attenuated *M. bovis*. By increasing the degree of protection against *M. tuberculosis* infection, this vaccine has reduced the worldwide incidence of TB considerably. It can, however, cause complications (Fig. 75.19), which include localized or generalized tuberculids, lupus vulgaris, scrofuloderma and other nonspecific reactions such as fever, local inflammation, subcutaneous abscesses with or without ulceration, severe regional lymphadenitis, osteitis, and tuberculous foci in distant organs. Rarely, it can lead to a fatal infection[62]. Injections of methanol extraction residue (MER) of BCG have been used as adjuvant immunotherapy in patients with melanoma and can also result in nodules and subcutaneous abscesses (Fig. 75.20).

Diagnosis

In addition to the use of tuberculin skin tests, *M. tuberculosis* infection can be diagnosed with IFN-γ release assays (e.g. QuantiFERON® TB Gold [In-Tube], T-SPOT®.TB). These assays determine whether exposure to recombinant peptides from *M. tuberculosis* (ESAT-6, culture filtrate protein [CFP]-10, ±TB7.7) stimulates IFN-γ production by T cells within patient blood samples. In general, IFN-γ release assays have greater specificity and similar sensitivity compared to tuberculin skin

Fig 75.20 Complication of injection of methanol extraction residue (MER) of BCG. Nodules, some of which have ulcerated, arranged in a linear "lymphatic" pattern in a patient with a high-risk extremity melanoma who had received an injection of MER of BCG as adjuvant immunotherapy.

ADVANTAGES AND DISADVANTAGES OF IFN-γ RELEASE ASSAYS AND TUBERCULIN SKIN TESTING

	Tuberculin skin test	IFN-γ release assays
Advantages	Does not require a laboratory Relatively low cost	Requires a single patient visit Results can be available within 24 hours Prior BCG vaccination does not cause a false-positive result Does not boost responses measured by subsequent tests
Disadvantages	Requires two patient visits Results are not available for 48 hours Prior BCG vaccination can cause a false-positive result May boost responses in subsequent tests Infections with non-tuberculous mycobacteria may lead to a false-positive result	Requires laboratory processing within 16 hours (for QuantiFERON® TB Gold In-Tube) or 8–30 hours (for T-SPOT®.TB; the latter if use T-cell Xtend®) Relatively high cost Infections with some non-tuberculous mycobacteria (e.g. *M. kansasii, M. szulgai* and *M. marinum*) may lead to a false-positive result
Situations where preferable	Children <5 years of age	Patient groups that historically have low rates of returning for a second visit (e.g. homeless persons, drug users) Individuals who have received BCG

Table 75.6 Advantages and disadvantages of interferon-γ (IFN-γ) release assays and tuberculin skin testing. Both types of tests may be negative in patients with early active tuberculosis. Indeterminate IFN-γ release assay results due to failure of the internal positive control (i.e. a "low mitogen" response) are more common in immunocompromised individuals and young children. Indeterminate results due to inappropriately high IFN-γ levels in the negative control ("high nil") can also occur. Testing with a second method after an initial negative test may be useful when the risk of infection/progression is high or when there is clinical suspicion of active tuberculosis. The QuantiFERON® TB Gold (In-Tube) test directly measures IFN-γ levels, whereas the T-SPOT®.TB test determines the number of IFN-γ-producing T cells; both use a peripheral blood sample. BCG, bacille Calmette-Guérin.

tests; when QuantiFERON® TB Gold and T-SPOT®.TB are compared, the former may have slightly higher specificity and the latter marginally higher sensitivity[64]. The US Centers for Disease Control and Prevention (CDC) guidelines state that an IFN-γ release assay may be used in place of a tuberculin skin test in all situations where the latter would be employed. Advantages and disadvantages of these methods of TB detection as well as special situations where one type of test would be preferred are listed in Table 75.6.

CLASSES, ACTIVITIES AND CROSS-RESISTANCES OF THE ANTITUBERCULOUS AGENTS

Agent	Class of compound	Spectrum of activity	Cross-resistance to other antituberculous agents
FIRST-LINE AGENTS			
Rifampin	Antibiotic	Broad	Other rifamycins
Isoniazid	Synthetic	Tubercle bacilli	None
Pyrazinamide	Synthetic	Tubercle bacilli	None
Ethambutol	Synthetic	Tubercle bacilli	None
Rifapentine	Antibiotic	Broad	Other rifamycins
Rifabutin	Antibiotic	Broad	Other rifamycins
SECOND-LINE AGENTS			
Kanamycin, amikacin, streptomycin	Aminoglycoside antibiotics	Broad	Other aminoglycosides, viomycin, capreomycin
Capreomycin, viomycin	Tuberactinomycin antibiotics	Tubercle bacilli	Aminoglycosides
Levofloxacin, ofloxacin, moxifloxacin, gatifloxacin	Quinolone antibiotics	Broad	None
Ethionamide, prothionamide	Thioamides	Tubercle bacilli	Thiacetazone
Cycloserine, terizidone	Synthetic	Broad	None
para-Aminosalicylic acid	Synthetic	Tubercle bacilli	None
THIRD-LINE AGENTS			
Clofazimine	Riminophenazine antileprotic	Mycobacteria	None
Amoxicillin/clavulonate	Antibiotic	Broad	None
Linezolid	Antibiotic	Broad	None
Imipenem	Antibiotic	Broad	None
Thiacetazone	Synthetic	Tubercle bacilli	Ethionamide, prothionamide
Clarithromycin	Antibiotic	Broad	None

Table 75.7 Classes, activities and cross-resistances of the antituberculous agents. Agents that are active against *M. tuberculosis* may also show activity against some other species of mycobacteria. Strains of *M. bovis* are naturally resistant to pyrazinamide. There are only limited data on other activities of capreomycin and viomycin. *Adapted from Grange JM, Zumla A. Antituberculosis agents. In Cohen J, Powderly WG (eds). Infectious Diseases. London: Mosby, 2003. With permission from Elsevier..*

Treatment

Treatment of the cutaneous forms of TB is the same as that for systemic TB (Table 75.7 & Fig. 75.21). Administration of appropriate therapy not only provides a direct benefit to individuals with active or latent infection (the latter via a 9-month course of isoniazid to prevent disease) but also prevents bacterial resistance and reduces transmission of *M. tuberculosis*[52,56]. In addition to the increase in *multidrug-resistant TB* that accompanied the resurgence of this disease in the late 1980s and early 1990s, *extensively drug-resistant TB* strains that are even more difficult to treat have also emerged in all regions of the world (Table 75.8). The current CDC-recommended regimens for tuberculosis therapy are outlined in Table 75.9[65]. In addition to "repurposing" existing antibiotics (e.g. quinolones, amoxicillin with clavulanate, linezolid, clarithromycin) for use in patients with extensively drug-resistant TB, novel drugs currently being investigated in clinical trials include nitroimidazole/nitroimidazopyran agents (OPC-67863 and PA-824; inhibit synthesis of proteins and cell wall lipids), a

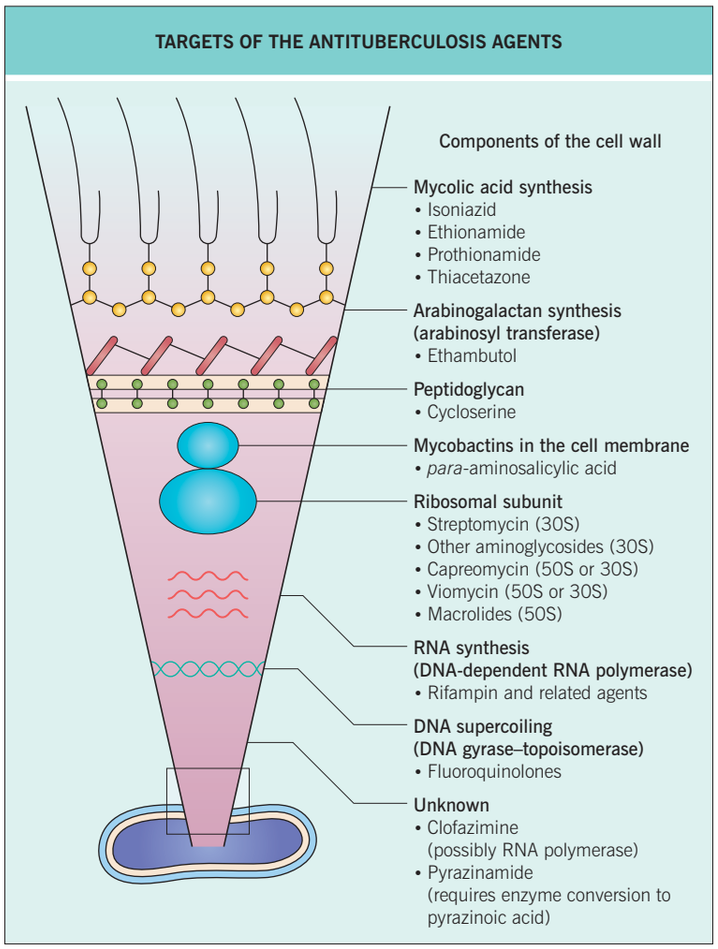


Fig. 75.21 Targets of the antituberculous agents. *Adapted from Grange JM, Zumla A. Antituberculous agents. In: Cohen J, Powderly WG (eds). Infectious Diseases. London: Mosby, 2003. With permission from Elsevier..*

MULTIDRUG-RESISTANT AND EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS
MULTIDRUG-RESISTANT TUBERCULOSIS (MDR-TB)
• Resistant to isoniazid and rifampin, the two most effective first-line drugs • Estimated to account for 4% of all new TB cases worldwide in 2009
EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS (XDR-TB)
• Resistant to isoniazid and rifampin • Resistant to quinolones, the most effective second-line drugs • Resistant to at least one of three injectable second-line drugs: amikacin, kanamycin or capreomycin • Estimated to account for 5% to 10% of cases of MDR-TB

Table 75.8 Multidrug-resistant and extensively drug-resistant tuberculosis.

diarylquinoline (TMC207; targets ATP synthase), an oxazolidinone (AZD5847; inhibits protein synthesis), and an ethambutol analogue (SQ109; thought to inhibit cell wall biosynthesis and have synergistic effects with other agents)[66–68]. With regard to vaccines, sequential administration of BCG and a recombinant modified vaccinia virus Ankara (MVA) expressing antigen 85A can induce robust antimycobacterial immunity[69].

Although the production of nitric oxide by macrophages is known to help control infection by *M. tuberculosis*, the organisms can persist within these cells. Proper function of the mycobacterial proteosome appears to play an important defensive role, and, in the future, inhibition of proteosome function could provide a novel therapeutic approach[70].

NON-TUBERCULOUS MYCOBACTERIOSES

Synonyms: ■ Atypical mycobacterioses ■ Mycobacteria other than tuberculosis (MOTT) ■ Environmental mycobacterioses ■ Anonymous mycobacterioses ■ Opportunistic mycobacterioses

Key features

- Over a dozen species of mycobacteria, found in the natural environment and transmitted via inoculation into the skin, can produce cutaneous disease
- Clinical presentations include pustules, keratotic plaques and nodules (with or without suppuration), a sporotrichoid (lymphocutaneous) pattern, and ulcers with draining sinuses
- Disseminated infections usually occur in immunocompromised hosts
- Although suggested by a history of exposure, the diagnosis rests on isolation or identification of the responsible organism

Introduction

Non-tuberculous ("atypical") mycobacteria were first isolated in 1931 by Pinners, who also discovered that these organisms were different from *M. tuberculosis* – they were not virulent in the guinea pig model, and they responded poorly to antituberculous therapy[71]. Their importance as human pathogens, however, was not appreciated until the 1950s[72].

These environmental mycobacteria are found in water, wet soil, house dust, dairy products, cold-blooded animals, vegetation and human feces. Non-tuberculous mycobacterioses are transmitted by inhalation, ingestion or percutaneous penetration, which can result in pulmonary, lymph node or skin disease[6,71]. The type of disease depends on the species of mycobacteria, the route and degree of exposure, and the immune status of the host[1].

Recognition of non-tuberculous mycobacterial infections is important given the increasing incidence in immunosuppressed as well as normal hosts[53,73–75]. For example, in high-income countries, disseminated non-tuberculous mycobacteriosis is one of the most common systemic bacterial opportunistic infections in AIDS patients[4,53]. Cutaneous (and systemic) non-tuberculous mycobacterial infections are frequently misdiagnosed because of their nonspecific or sometimes subtle clinical presentations, especially in patients who are immunosuppressed, combined with inadequate biopsy and culture techniques[71]. These infections should be suspected in patients with indolent ulcers, nodules or plaques, especially in the setting of immunosuppression. Therapy varies depending on the causative organism (Table 75.10)[71,76–83]; however, initial empiric treatment with clarithromycin can be considered while waiting for culture and sensitivity results in patients with clinical presentations suggestive of a cutaneous non-tuberculous mycobacterial infection[84].

In 1954, Runyon proposed the first classification system for non-tuberculous mycobacteria based upon rate of growth *in vitro* and pigment production following exposure to light (see Table 75.1). Given advances in identification (including genomic analysis), more than 100 species of mycobacteria are now recognized. Selected non-tuberculous mycobacteria of dermatologic interest will be discussed in this chapter.

Mycobacterium ulcerans

Synonyms: ■ Buruli ulcer ■ Bairnsdale ulcer ■ Searle's ulcer

Introduction and history

M. ulcerans is a slow-growing, acid-fast bacillus that characteristically infects the skin and subcutaneous tissues, producing indolent ulcers. Worldwide, after leprosy and tuberculosis, Buruli ulcer is the third most common mycobacteriosis in immunocompetent hosts[76]. The initial description of patients with huge cutaneous ulcers was made by Cook

DRUG REGIMENS FOR CULTURE-POSITIVE PULMONARY TUBERCULOSIS CAUSED BY DRUG-SUSCEPTIBLE ORGANISMS

Initial phase			Continuation phase			Range of total doses (minimal duration)	Rating‡ (evidence)§	
Regimen	Drugs	Interval and doses* (minimal duration)	Regimen	Drugs	Interval and doses*,† (minimal duration)		HIV⁻	HIV⁺
1	INH RIF	7 days per week for 56 doses (8 wk) or 5 days per week for 40 doses (8 wk)¶	1a	INH/RIF	7 days per week for 126 doses (18 wk) or 5 days per week for 90 doses (18 wk)¶	182–130 (26 wk)	A (I)	A (II)
	PZA		1b	INH/RIF	Twice weekly for 36 doses (18 wk)	92–76 (26 wk)	A (I)	A (II)**
	EMB		1c††	INH/RPT	Once weekly for 18 doses (18 wk)	74–58 (26 wk)	B (I)	E (I)
2	INH RIF PZA EMB	7 days per week for 14 doses (2 wk), then twice weekly for 12 doses (6 wk), or 5 days per week for 10 doses (2 wk)¶, then twice weekly for 12 doses (6 wk)	2a	INH/RIF	Twice weekly for 36 doses (18 wk)	62–58 (26 wk)	A (II)	B (II)**
			2b††	INH/RPT	Once weekly for 18 doses (18 wk)	44–40 (26 wk)	B (I)	E (I)
3	INH RIF PZA EMB	Three times weekly for 24 doses (8 wk)	3a	INH/RIF	Three times weekly for 54 doses (18 wk)	78 (26 wk)	B (I)	B (II)
4	INH RIF EMB	7 days per week for 56 doses (8 wk) or 5 days per week for 40 doses (8 wk)¶	4a	INH/RIF	7 days per week for 217 doses (31 wk) or 5 days per week for 155 doses (31 wk)¶	273–195 (39 wk)	C (I)	C (II)
			4b	INH/RIF	Twice weekly for 62 doses (31 wk)	118–102 (39 wk)	C (I)	C (II)

*When DOT is used, drugs may be given 5 days/week and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with seven daily doses, extensive experience indicates this would be an effective practice.

†Patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive an 8-month (31-week; either 217 doses [daily] or 62 doses [twice weekly]) continuation phase.

‡Definitions of evidence ratings: A = preferred; B = acceptable alternative; C = offer when A and B cannot be given; E = should never be given.

§Definitions of evidence ratings: I = randomized clinical trial; II = data from clinical trials that were not randomized or were conducted in other populations; III = expert opinion.

¶Five-day-a-week administration is always given by DOT. Rating for 5 day/week regimens is A(III).

**Not recommended for HIV-infected patients with $CD4^+$ cell counts <100 cells/mcl.

††Options 1c and 2b should be used only in HIV-negative patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitation on initial chest radiograph. For patients started on this regimen and found to have a positive culture from the 2-month specimen, treatment should be extended an extra 3 months.

Table 75.9 Drug regimens for culture-positive pulmonary tuberculosis caused by drug-susceptible organisms. Among patients with extrapulmonary tuberculosis, regimen 1 is recommended as initial therapy unless the organisms are known or strongly suspected of being resistant to the first-line drugs. If PZA cannot be used in the initial phase (i.e. regimen 4), the continuation phase must be increased to 7 months. Doses of medications (maximum dose) when given *daily*: INH, isoniazid 5 mg/kg (300 mg); RIF, rifampin 10 mg/kg (600 mg); PZA, pyrazinamide 25 mg/kg (2000 mg); EMB, ethambutol 18 mg/kg (1600 mg); RPT, rifapentine, which is given once weekly at 10 mg/kg. DOT, Directly Observed Therapy. From ref. 65.

in 1897 in Uganda (Buruli is a county in Uganda). It was not until the late 1940s, in Australia, that the agent was isolated and characterized by MacCallum and colleagues[1,76].

Epidemiology

M. ulcerans infections have been reported in more than 30 countries around the world. The primary endemic foci are wetlands in tropical or subtropical countries[76]; although the exact mode of transmission is not known, exposure to water from rivers or ponds (or even exposure to mud) is thought to play a role. The organism is harbored by snails, fish and water insects, and it can be isolated from aquatic plants. In Australia, koalas and opossums are naturally infected.

Agricultural activities and consequent deforestation have contributed to recent increases in the incidence of *M. ulcerans* infections, especially in West Africa. Focal outbreaks have followed floods and human migrations. The countries most affected are in Central Africa (e.g. Uganda, the Democratic Republic of Congo) and West Africa (e.g. the Ivory Coast, Ghana, Benin). Some Southeast Asian countries and Australia have major foci of infection, and there have been a few reports from South America and Mexico[72,76].

The disease is rarely transmitted from patient to patient, and the agent is typically introduced into the skin by minor trauma. Children under 15 years of age are more commonly affected, but the infection can occur in all age groups[72,76].

Pathogenesis

After inoculation into the skin, the *M. ulcerans* organisms proliferate and form abundant clumps of extracellular acid-fast bacilli. The organisms are found at the base of the ulcer and within adjacent necrotic subcutaneous tissue as well as in surrounding normal-appearing skin. The extracellular location of the mycobacteria (i.e. lack of phagocytosis) and the unique pathology (cell death) are thought to be a reflection of a plasmid-encoded immunomodulatory macrolide toxin, mycolactone[85]. Numerous disseminated lesions may cause systemic toxic effects[76]. HIV-infected individuals do not appear to be predisposed to this infection.

Clinical features

The initial lesion is usually a single, asymptomatic, firm, non-tender, mobile subcutaneous nodule that measures 1 to 2 cm in diameter. After 1 or 2 months, the nodule becomes fluctuant and ulcerates. The resultant painless ulcer has a deep necrotic base with undermined edges, and it often expands to 15 cm or more in diameter. The vast majority of lesions are on the extremities (lower > upper). There is little or no regional lymphadenopathy or systemic manifestations. Edema can develop in adjacent tissues. Without treatment, ulcers may remain small and heal as depressed scars, or they may spread rapidly over large areas of skin (even an entire limb), causing extensive scarring and

TREATMENT OF NON-TUBERCULOUS ("ATYPICAL") MYCOBACTERIAL INFECTIONS		
Agent	**Local**	**Systemic medications: alone or combined**
M. ulcerans	For ulcers, surgical excision; local heat (40°C); hyperbaric oxygen	For early lesions (nodules, plaques), rifampin plus streptomycin (or rifampin plus clarithromycin) for at least 4 weeks*; nitrogen oxide-releasing topical creams
M. marinum		Clarithromycin, minocycline > doxycycline†, rifampin, ethambutol, trimethoprim–sulfamethoxazole; two agents for serious infections (e.g. clarithromycin + rifampin or ethambutol)
M. kansasii		Isoniazid (or clarithromycin) + rifampin + ethambutol ± pyridoxine; other options (depending on susceptibilities) include azithromycin, moxifloxacin, streptomycin and sulfamethoxazole
M. fortuitum	Surgical excision	Ciprofloxacin, ofloxacin, clarithromycin‡, trimethoprim–sulfamethoxazole, minocycline, doxycycline; at least two agents for serious infections
M. chelonae	Surgical excision	Clarithromycin; for severe infections, combine clarithromycin with linezolid, imipenem, tobramycin, amikacin, doxycycline and/or ciprofloxacin (often resistant to latter two agents)
M. abscessus	Surgical excision	Clarithromycin or azithromycin + (for serious infections) amikacin, cefoxitin or imipenem
M. avium complex		Clarithromycin or azithromycin + ethambutol ± rifampin or rifabutin
M. haemophilum	Surgical excision	Clarithromycin + rifampin ± ciprofloxacin or amikacin
M. scrofulaceum	Surgical excision	Isoniazid + rifampin, clarithromycin

*WHO recommends 8 weeks[81].
†Resistance to tetracyclines has been reported.
‡Often have inducible resistance to macrolides.

Table 75.10 Treatment of non-tuberculous ("atypical") mycobacterial infections[71,72,76–83]. Therapy for 3 to 6 months or more is often required. If clinical suspicion is high for a non-tuberculous mycobacterial infection, empiric treatment with clarithromycin can be considered while waiting for culture and sensitivity results.

deformity. Structures such as the eye, breast or genitalia are sometimes lost or severely damaged. Underlying bone can become involved, and progressive osteomyelitis may require amputation[72,76].

Pathology

Histologically, granulomatous inflammation may be seen in association with substantial necrosis, predominantly in the subcutaneous fat[1,72]. There is also contiguous coagulation necrosis of the deep dermis and destruction of nerves, appendages and blood vessels. Interstitial edema is noted. In active lesions, inflammatory cells are few in number, presumably as a result of the immunosuppressive activity of the toxin. With healing, there is a granulomatous response. Many acid-fast bacilli can be seen in characteristic clumps, particularly in the center of the lesion[72,76].

Diagnosis and differential diagnosis

Clumps of acid-fast bacilli may be seen in Ziehl-Neelsen-stained smears from the necrotic base of an ulcer or a similarly stained biopsy specimen (e.g. of the necrotic tissue at the ulcer base or undermined edge and in the subcutis). *M. ulcerans* can be cultured, but visible growth often requires 6 to 8 weeks of incubation at 32°C. Molecular techniques such as PCR prove useful in establishing the diagnosis, especially when culture and histopathology are negative[72,76]. In one series of 70 patients with Buruli ulcers, a modified PCR assay had a sensitivity of 98%, while the sensitivities of direct smear, culture and histology were 42%, 49% and 82%, respectively[86].

The differential diagnosis depends upon the stage of disease. During the initial phase, when a subcutaneous nodule is present, *M. ulcerans* infection must be differentiated from other forms of panniculitis (infectious and non-infectious; see Ch. 100), cysts, nodular fasciitis, a foreign body granuloma and other granulomatous diseases. During the ulcerative phase, considerations may include fungal infections, pyoderma gangrenosum, suppurative panniculitis and other causes of ulcers (see Ch. 105)[1].

Treatment

Surgical excision is the treatment of choice for ulcers (see Table 75.10). This is obviously easier to accomplish when the ulcers are small, and large ulcers often require skin grafts[1,72]. Continuous local heating to 40°C by circulating water jackets promotes healing, even without excision[61]. Hyperbaric oxygen can also be useful[1,3], but drug therapy for ulcers is often disappointing[3]. Unfortunately, amputation of limbs is sometimes necessary[72].

A trial of oral rifampin (10 mg/kg) plus intramuscular streptomycin (15 mg/kg) daily for at least 4 weeks may convert early lesions (nodules, plaques) from culture-positive to culture-negative (see Table 75.10). Recent studies in a mouse model suggest that treatment with an oral regimen of clarithromycin plus rifampin or rifapentine has similar efficacy[87]. Physical therapy is important when the patient is at risk for contractures. There is no effective prophylaxis, but vaccination with BCG may lead to limited, relatively short-lived protection[76].

Mycobacterium marinum

Synonyms: ■ Fish tank granuloma ■ Swimming pool granuloma ■ Infection by *M. balnei*

Introduction and history

M. marinum is a free-living organism that causes disease in freshwater and saltwater fish and sporadically in humans. The latter results from exposure to contaminated water when there are breaks in the skin barrier[78]. *M. marinum* was first isolated from saltwater fish in the Philadelphia Aquarium in 1926 by Aronso[1,3]. The first report of human disease was in 1951, when the agent was found in granulomatous skin lesions of individuals who swam in a contaminated swimming pool[3].

Epidemiology and pathogenesis

M. marinum is found in aquatic environments, including fresh, salt and brackish water. When cleaning fish tanks at home or in the workplace (e.g. restaurants, fish markets), trauma to the hands may result in exposure to *M. marinum*. The infection can also affect swimming pool bathers, as this organism seems to be rather resistant to chlorine[1].

Cutaneous infection with *M. marinum* requires a portal of entry, e.g. abraded or traumatized skin[1]. The incubation period is typically 2 to 3 weeks, but it can range from 1 week to 2 months[1]. In several case series of skin infections with non-tuberculous mycobacteria, *M. marinum* was the most common species identified[83].

Clinical features

The initial lesion is a single bluish-red inflammatory nodule or pustule at the site of inoculation, which is often on an upper extremity (Fig. 75.22A). It then forms a crusted ulcer, suppurative abscess or verrucous nodule[1,3]. Multiple lesions can develop along the course of the draining lymphatics, i.e. sporotrichoid (lymphocutaneous) spread (Fig. 75.22B; see Table 77.15). Among the non-tuberculous mycobacterioses, *M. marinum* is the most common etiology of this pattern. Occasionally, deeper infections are complicated by tenosynovitis, septic arthritis or, rarely, osteomyelitis. As with other non-tuberculous mycobacterioses, disseminated lesions can occur in immunocompromised hosts (Fig. 75.22C).

Fig. 75.22 ***Mycobacterium marinum*** **infections.** A range of presentations, including an erythematous plaque with scale-crust at the inoculation site on the lateral hand (**A**), a sporotrichoid pattern with the inoculation site on the distal third finger (**B**), and disseminated necrotic lesions on the face of an immunocompromised patient (**C**).

Pathology

The histologic features, as in other mycobacterial infections, range from acute and chronic inflammation to well-formed tuberculoid granulomas. Fibrinoid changes and caseation necrosis can occur[3]. In immunocompetent individuals, organisms are often difficult to find.

Diagnosis and differential diagnosis

The clinical features combined with a history of trauma in a wet environment or exposure to fish tanks suggests the possibility of *M. marinum* infection. The diagnosis is confirmed by culture, which is positive in 70% to 80% of cases[78]. When this infection is suspected, the laboratory should be notified in advance and care must be taken to provide proper culture conditions. *M. marinum* grows best at 31°C, in contrast to the optimal incubation temperature of 37°C for many other mycobacteria[78]; growth becomes evident after a mean of approximately 3 weeks, and identification of the species and its antimicrobial susceptibility pattern often requires 2 months[83]. PCR for detection of a 65 kDa heat shock protein gene can also be performed.

Infection due to *M. marinum* should be differentiated from sporotrichosis and the entities outlined in Table 77.15 as well as tuberculosis verrucosa cutis. It is not associated with marked regional lymphadenitis.

Treatment

M. marinum is usually sensitive to the antimicrobial drugs listed in Table 75.10[71]; however, sensitivity testing should always be requested as part of the laboratory evaluation[78]. Based on usual *in vitro* susceptibility patterns and clinical responsiveness, initial empiric treatment with clarithromycin (pending culture and sensitivity results) has been recommended when there is suspicion of an *M. marinum* infection[83].

Mycobacterium kansasii

Introduction and history

M. kansasii is a mycobacterium that is closely related antigenically to *M. tuberculosis.* There is evidence that an infection with this organism provides increased immunity against tuberculosis[72].

M. kansasii was first reported in 1953 as the "yellow bacillus". This characteristic pigmentation is due to the deposition of β-carotene crystals after exposure to light[1].

Epidemiology and pathogenesis

This organism is found throughout the world, but it is more prevalent in temperate zones such as in the US, UK, northern France and Belgium. It has been isolated from cattle and swine, but the natural reservoir may be water. Middle-class, middle-aged, white men of urban origin are most commonly affected[3,72].

The lung is the major site of infection with *M. kansasii,* and the diagnosis of pulmonary disease rests on examination and culture of sputum[3]. Cutaneous infection is usually acquired via minor trauma such as puncture wounds[62].

Clinical features

Verrucous plaques, ulcers and nodules are observed, and the lesions may be arranged in a lymphocutaneous (sporotrichoid) pattern. The majority of patients with cutaneous involvement have some alteration in immune status[1,3,72]. Papulonecrotic lesions and cellulitis are less common presentations[3]. Iijima and Sasaky[88] divided cutaneous mycobacteriosis due to *M. kansasii* into three types: (1) chronic granulomatous; (2) primary cutaneous pyogenic; and (3) disseminated acute pyogenic, which occurs primarily in immunocompromised individuals.

Pathology

Histologic features are as variable as the clinical presentations. Typical tuberculoid granulomas may be seen, or a dense neutrophilic infiltrate may be evident, with or without abscess formation and epidermal necrosis[72]. In some patients, the findings are indistinguishable from those of *M. tuberculosis* infection[1].

Diagnosis and differential diagnosis

M. kansasii can be isolated from lesional skin biopsy specimens, and the laboratory should be advised to provide appropriate culture conditions to detect slow-growing mycobacteria[1,72]. The rarity of diagnosis of primary cutaneous *M. kansasii* infections may be a reflection of the failure to grow the organisms in culture as well as difficulties in phenotyping. PCR analysis may circumvent these potential problems[89].

Table 75.5 and the *M. ulcerans* section above outline the differential diagnosis of verrucous plaques and ulcers, respectively. Sporotrichosis and other non-tuberculous mycobacterial infections need to be considered when there is a sporotrichoid pattern (see Table 77.15). A combination of histologic examination, special stains, and culture for bacteria and fungi usually distinguishes these entities.

Treatment

A combination of antituberculous medications must be used, especially when the infection is disseminated[3,72]. Resistance may occur, and although different drug regimens have been recommended (see Table 75.10), sensitivity testing should be performed to optimize therapy[1,3,72].

Fig. 75.23 Suppurative lymphadenitis due to *Mycobacterium fortuitum* infection. The inoculation chancre was on the foot. From ref. 90. *Courtesy, Rubem Azulay, MD.*

Mycobacterium fortuitum, Mycobacterium chelonae and *Mycobacterium abscessus*

Synonyms: ▪ *M. chelonei* = *M. chelonae* ▪ Turtle tubercle bacillus

Introduction and history

These three organisms are often grouped together as the fortuitum complex[71]. Although they can be distinguished on the basis of DNA and serologic analyses, they result in infections with similar clinical features[3].

In 1903, Friedmann[57] isolated *M. chelonae*. Two subspecies (*chelonae* and *abscessus*) were initially identified, but *M. abscessus* was reclassified as a separate species in 1992[1]. *M. chelonae* was once used in an attempt to develop a vaccine as immunotherapy for *M. tuberculosis* infections[71]. In 1905, Küster described *M. fortuitum* as a frog pathogen, and for this reason it was originally named *M. ranae*. Costa-Cruz used the name *M. fortuitum* in 1938 for what he believed to be a new species isolated from a skin abscess that occurred after an injection[1,90].

Epidemiology and pathogenesis

The organisms exist as saprophytes, and they are found in water, soil, dust and animals. Cutaneous infections are uncommon, and immunocompromised patients are more susceptible to severe disease caused by these species of mycobacteria[71,91].

Infections typically occur following trauma, surgery or other procedures, including contact with contaminated medical instruments (e.g. liposuction, mesotherapy), placement of implants (e.g. prosthetic breast implants) and tattooing[74,75,92]. A post-injection abscess is another frequent presentation[3], e.g. after acupuncture or botulinum toxin injection. Furunculosis of the lower extremities has also been observed following footbaths in nail salon customers[73]. Less often, cutaneous infection is the result of dissemination from an endogenous source[71].

Clinical features

This group of mycobacteria can produce a variety of clinical diseases, including non-cavitary pneumonia, keratitis, endocarditis, lymphadenitis, osteomyelitis and skin infections (Fig. 75.23). The cutaneous manifestations range from cellulitis (Fig. 75.24), abscesses and papulopustules to sinuses and ulcers with extensive subcutaneous necrosis and serosanguineous or purulent discharge[71]. However, the most common presentation is multiple erythematous subcutaneous nodules, frequently occurring on the distal limbs or in a sporotrichoid pattern[3,90,91].

Pathology

The presence of both neutrophilic microabscesses and granuloma formation with foreign body-type giant cells is characteristic[1]. Necrosis may occur[3].

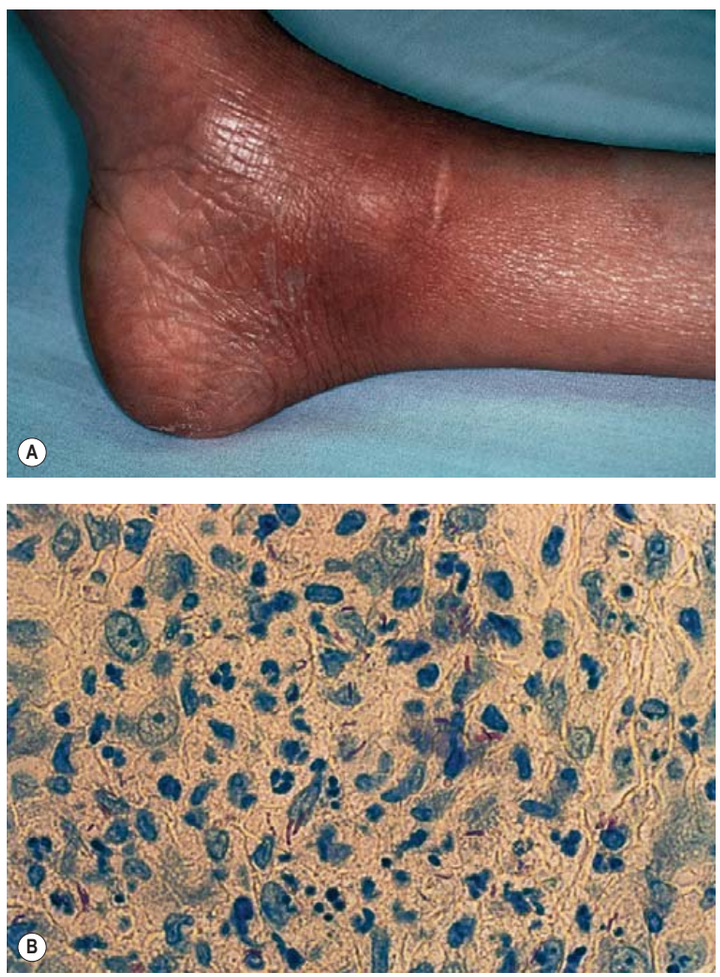


Fig. 75.24 *Mycobacterium chelonae* infection. This immunosuppressed patient presented with an area of warmth and mild erythema on the ankle (**A**). Acid-fast bacilli (stained red) in a biopsy specimen (**B**).

Diagnosis and differential diagnosis

Culture of biopsy material must be performed. When an abscess is present, a biopsy specimen that includes the wall is preferred, rather than aspiration of pus. The organisms grow on routine bacterial culture media, such as 5% sheep blood agar or chocolate agar, within 7 days. In addition, PCR detection of the 16S–23S rRNA gene internal transcribed spacer sequences can be performed.

The disease should be considered in patients with therapy-resistant or "cold" abscesses. It can also be confused with foreign body reactions, subcutaneous mycoses or osteomyelitis[3].

Treatment

Treatment is dependent on the type and extent of the lesions[1]. These organisms are resistant to antituberculous drugs, but, to date, nearly all *M. chelonae* and 80% of *M. fortuitum* isolates have been sensitive to clarithromycin. Excision and debridement may be required for abscesses and ulcers. Recommended antibiotics, prescribed either alone or in combination, are listed in Table 75.10[3,71,77]; prolonged courses may be required.

Mycobacterium avium complex

Synonyms: ■ *M. avium* ■ *M. avium intracellulare* (MAI) ■ *M. intracellulare*

Introduction

M. avium (the avian tubercle bacillus) and *M. intracellulare* are closely related and difficult to differentiate, so it is common to refer to them as *M. avium* complex (MAC) or *M. avium intracellulare* (MAI)[3,71].

MAC is a facultative mycobacterium that only occasionally produced human disease before the AIDS epidemic[1,3]. The incidence of infection then increased sharply, and MAC became one of the most common causes of opportunistic bacterial infections in patients with AIDS[3,71]. The infection often occurs during the terminal stage of AIDS and causes disseminated disease in 15–40% of such patients[71].

Epidemiology and pathogenesis

The organism is found in the environment, including fresh and salt water, soil, dairy products and domestic animals[3,71]. It may be transmitted via inhalation into the lungs, or via water and food into the gastrointestinal tract, without person-to-person transmission[1]. As many as 30% of samples of normal human feces yield isolates of MAC[1,3].

Chronic pulmonary infection is the most common clinical manifestation of MAC infection in those who are not co-infected with HIV, followed in frequency by cervical and inguinal lymphadenitis and osteomyelitis. Lymphadenitis is seen more often in children. Cutaneous lesions may be primary after a traumatic inoculation, which is rare, or secondary to a disseminated infection in an immunocompromised host[3,71].

Clinical features

In patients with AIDS, there is often disseminated disease. It is characterized by nonspecific symptoms such as fever, night sweats, weight loss, bone pain, hepatosplenomegaly and lymphadenopathy. Serum alkaline phosphatase levels may be elevated[1]. Skin involvement is unusual and most often presents with papulopustules and multiple purulent leg ulcers[1]. Nodules with abscess formation (Fig. 75.25), panniculitis, sinus tracts, folliculitis and granulomatous plaques may also be seen[3,71]. A papulonecrotic tuberculid-like eruption due to disseminated MAC has been reported in patients with AIDS[71].

Pathology

Macrophages contain large numbers of bacilli without necrosis, and spindle cell transformation of macrophages, forming a histoid-like lesion (as in leprosy) can occur[40]. The histologic features resemble those of lepromatous leprosy (see above).

Diagnosis and differential diagnosis

In disseminated disease, the diagnosis is often established by culture of the blood or specimens from bone marrow or liver biopsies[3]. Depending on the site(s) of involvement, cultures can also be performed on sputum or biopsies of skin and lymph nodes[78]; PCR analysis is also available.

The differential diagnosis includes pyoderma, folliculitis, other causes of panniculitis and ulcers, dimorphic fungal infections, lepromatous leprosy and cutaneous tuberculosis.

Fig. 75.25 ***Mycobacterium avium*** **complex cellulitis in an immunocompromised patient.** Note the sporotrichoid (lymphocutaneous) pattern of the coalescing nodules with abscess formation.

Treatment

Table 75.10 provides a list of the medications that have been used alone or in combination[1,3] to treat MAC infections. In immunocompromised patients with disseminated infection, antimicrobial therapy should be given for life[3].

Mycobacterium haemophilum

Introduction

M. haemophilum is a short, slightly curved rod that occurs singly or in a cord-like arrangement. It is a fastidious organism that requires ferric ions to grow, provided as hemin, hematin, hemoglobin or ferric ammonium citrate. In initial studies, growth was only observed with the addition of hemolyzed sheep erythrocytes; as a consequence, the organism was given the name *M. haemophilum*[72,79].

Epidemiology and pathogenesis

M. haemophilum infection occurs primarily in immunocompromised hosts. To date, more than half of the reported cases have occurred in patients with AIDS, but it can also be seen in other immunosuppressed patients, e.g. organ transplant recipients. However, this organism can also cause cervical lymphadenitis in healthy children. The majority of affected individuals are from cities located near the ocean, the Mediterranean Sea, or the Great Lakes of North America[72,79]. The natural habitat of *M. haemophilum* and the route of infection have not yet been identified[72,79].

Clinical features

This bacillus can produce several different types of cutaneous lesions[72]. Immunosuppressed adults most often present with a single bluish-red tender pustule, papulonodule or plaque, which evolves into an abscess and/or ulcer[72,79]. Lesions may also be multiple and are usually located on the extremities, often overlying joints. In addition, *M. haemophilum* can cause contiguous septic arthritis, osteomyelitis and pneumonia. Immunocompetent children infected by this organism frequently have isolated cervical, submandibular or perihilar lymphadenitis[79].

Pathology

Suppurative and granulomatous inflammation is seen, sometimes with well-formed tuberculoid granulomas, Langhans giant cells, necrosis (with or without caseation) and large numbers of acid-fast bacilli. The bacilli can be found aggregated in globi, resembling those seen in lepromatous leprosy[72,79].

Diagnosis and differential diagnosis

The diagnosis is established by culture of the bacillus from tissue or synovial fluid; in some patients, blood cultures are positive. However, this organism requires a special environment to grow, with a source of iron and a temperature between 30°C and 32°C[72,79]. Due to these stringent requirements, it may not be isolated using routine techniques[1]; PCR analysis is also available.

In immunocompetent children with cervical or submandibular lymphadenitis, the possibility of MAC infection should be considered[79], along with the more common causes of lymphadenitis (e.g. EBV, CMV). The differential diagnosis of the cutaneous lesions is similar to that for the other non-tuberculous mycobacterioses (see *M. avium* and *M. fortuitum)*.

Treatment

M. haemophilum is often resistant to antituberculous drugs, except for the rifamycins, such as rifampin and rifabutin. The combination of rifampin and clarithromycin (±amikacin) has been used successfully (see Table 75.10). The duration of therapy must be at least 6 to 9 months and even longer in immunosuppressed patients. Surgical excision is also an option when the disease is localized, e.g. adenitis in an immunocompetent child[72,79].

Mycobacterium scrofulaceum

Introduction

M. scrofulaceum was formerly grouped with MAC in a complex called MAIS (*M. avium-intracellulare-scrofulaceum*), but they were separated due to the different clinical manifestations. *M. scrofulaceum* produces self-limited disease, particularly lymphadenitis, while MAC typically causes chronic lung disease and, less often, osteomyelitis. *M. scrofulaceum* may also cause cervical lymphadenitis with sinus formation clinically indistinguishable from scrofuloderma[62].

Epidemiology and pathogenesis

This organism is most prevalent in the southeastern US. It is widely distributed and has been isolated from raw milk, other dairy products, pooled oysters, soil and water[79]. Bacilli can be found in environments with a warm temperature, low pH and dissolved oxygen, and high soluble zinc, humic acid and fulvic acid. It has also been found on the skin of healthy people and in cutaneous lesions of leprosy[80].

In general, infection by *M. scrofulaceum* affects children and seems to occur via inhalation or ingestion. Focal infection resulting from contamination during surgical procedures involving lymph nodes may also occur. Cutaneous disease in a campground worker with corticosteroid-treated systemic lupus erythematosus and no history of preceding trauma has been reported. It was suggested that the lesions resulted from a subclinical bacteremia[79,80].

Clinical features

M. scrofulaceum may cause pulmonary disease and local lymphadenitis, primarily in the submandibular and submaxillary regions. It is usually a benign self-limited disease with no systemic symptoms except for mild neck pain. The involved lymph nodes slowly enlarge over several weeks, and eventually ulceration and drainage occur with fistula formation. This organism can also produce skin lesions in a sporotrichoid pattern, but it rarely causes disseminated infection[79]. Primary cutaneous disease due to inoculation of *M. scrofulaceum* is unusual[79].

Pathology

In the lymph nodes, widespread abscess formation is the typical finding; histiocytes and granulomas may be inconspicuous. It may be difficult to differentiate *M. scrofulaceum* lymphadenitis from that due to *M. tuberculosis*[62] when there are tuberculoid granulomas with central necrosis and abscess formation. The bacilli are found within involved lymph nodes[79]. In the skin, abscess formation is typically seen.

Diagnosis and differential diagnosis

In addition to histologic examination, culture of sputum, skin or involved lymph nodes helps to confirm the diagnosis. The infection should be distinguished from other causes of cervical lymphadenopathy (see *M. haemophilum*), particularly infection with *M. tuberculosis*[79]. However, *M. tuberculosis* usually affects tonsillar and anterior cervical nodes, while *M. scrofulaceum* typically affects submandibular and submaxillary nodes. When lesions have a sporotrichoid pattern, *M. marinum* infections and other non-tuberculous mycobacterioses should be considered (see Table 77.15)[80].

Treatment

The treatment of choice is total excision of the involved lymph nodes[62,79] because, in general, antibiotic therapy is unsatisfactory. However, promising results have been reported with isoniazid plus rifampin[80]. Successful treatment with clarithromycin has also been described (see Table 75.10)[79].

REFERENCES

1. Hautmann G, Lotti T. Atypical mycobacterial infections of the skin. Dermatol Clin. 1994;12:657–68.
2. Eisenstadt J, Hall GS. Microbiology and classification of mycobacteria. Clin Dermatol. 1995;13:197–206.
3. Yates VM, Rook GAW. Mycobacterial infections. In: Burns T, Breathnach S, Cox N, Griffiths C (eds). Rook's Textbook of Dermatology, 7th edn. London: Blackwell Science. 2004;28.1–39.
4. Portaels F. Epidemiology of mycobacterial diseases. Clin Dermatol. 1995;13:207–22.
5. Cole ST, Eiglmeier K, Parkhill J, et al. Massive gene decay in the leprosy bacillus. Nature. 2001;409:1007–11.
6. Neves RG, Pradinaud R. Micobacterioses atípicas. In: Neves RG, Talhari S (eds). Dermatologia Tropical. Rio de Janeiro: Medsi, 1995:283–90.
7. Sugita Y. Leprosy. Clin Dermatol. 1995;13:235–43.
8. Ramos-e-Silva M, Rebello PFB. Leprosy. Recognition and treatment. Am J Clin Dermatol. 2001;2:203–11.
9. World Health Organization. Prevalence of leprosy. http://www.who.int/lep/situation/prevalence/en/index.html
10. Bryceson A, Pfaltzgraff RE. Leprosy, 3rd edn. Edinburgh: Churchill Livingstone, 1990.
11. Canizares O, Harman R, Adriaans B. Leprosy. In: Canizares O, Harman R (eds). Clinical Tropical Dermatology, 2nd edn. Boston: Blackwell Scientific, 1992:165–200.
12. Sehgal VN. Leprosy. Dermatol Clin. 1994;12:629–44.
13. Azulay RD, Azulay DR. Mycobacterioses. In: Azulay RD, Azulay DR (eds). Dermatologia, 4th edn. Rio de Janeiro: Guanabara Koogan, 2006:302–22.
14. Faget GH, Johansen FA, Ross H. Sulfanilamide in the treatment of leprosy. Public Health Rep. 1942;57:1892–9.
15. Schaller K. Color Atlas of Tropical Dermatology and Venereology. New York: Springer-Verlag, 1994.
16. World Health Organization. Leprosy today. http://www.who.int/lep/en/
17. World Health Organization. Elimination of leprosy as a public health problem (update). Wkly Epidemiol Rec. 1998;2:308–12.
18. Britton W. Leprosy. In: Cohen J, Powderly WG (eds). Infectious Diseases. London: Mosby, 2003:1507–13.
19. Bhatia A, Katoch K, Narayanan R, et al. Clinical and histopathological correlation in the classification of leprosy. Int J Lepr Other Mycobact Dis. 1993;61:433–8.
20. Truman RW, Singh P, Sharma R, et al. Probable zoonotic leprosy in the Southern United States. N Engl J Med. 2011;364:1626–33.
21. Foss NT. Hanseníase: aspectos clínicos, imunológicos e terapêuticos. An Bras Dermatol. 1999;74:113–19.
22. Fabozzi G, Modiano G, Poccia F, et al. Is there a genetic basis for human susceptibility to leprosy? IUBMB Life. 2005;57:119–21.
23. Misch EA, Berrington WR, Vary JC Jr, et al. Leprosy and the human genome. Microbiol Mol Biol Rev. 2010;74:589–620.
24. Alcaïs A, Alter A, Antoni G, et al. Stepwise replication identifies a low-producing lymphotoxin-alpha allele as a major risk factor for early-onset leprosy. Nat Genet. 2007;39:517–22.
25. Mira MT, Alcais A, Nguyen VT, et al. Susceptibility to leprosy is associated with PARK2 and PACRG. Nature. 2004;427:636–40.
26. Zhang FR, Huang W, Chen SM, et al. Genomewide association study of leprosy. N Engl J Med. 2009;361:2609–18.
27. Jadhav R, Suneetha L, Kamble R, et al. Analysis of antibody and cytokine markers for leprosy nerve damage and reactions in the INFIR cohort in India. PLoS Negl Trop Dis. 2011;5:e977.
28. Yamamura M, Uyemura K, Deans RJ, et al. Defining protective responses to pathogens: cytokine profiles in leprosy lesions. Science. 1991;254:277–9.
29. Brennan JP. *Mycobacterium leprae*: the significance of our knowledge of its composition and antigenicity. Hansen Int. 1998;(special):s103–10.
30. Sampaio EP, Moraes MO, Pessolani MCV, Sarno EM. Role of Th1 cytokines in host defenses against *Mycobacterium leprae*. In: Kotb M, Calandra T (eds). Cytokines and Chemokines in Infectious Diseases Handbook. Totowa: Humana Press, 2003:163–86.
31. Ochoa MT, Stenger S, Sieling PA, et al. T-cell release of granulysin contributes to host defense in leprosy. Nat Med. 2001;7:174–9.
32. Krutzik SR, Tan B, Li H, et al. TLR activation triggers the rapid differentiation of monocytes into macrophages and dendritic cells. Nat Med. 2005;11:653–60.
33. Bleharski JR, Li H, Meinken C, et al. Use of genetic profiling in leprosy to discriminate clinical forms of the disease. Science. 2003;301:1527–30.
34. Ridley DS, Jopling WH. Classification of leprosy according to immunity. Int J Lepr. 1966;34:255–73.
35. World Health Organization. A Guide to Leprosy Control, 2nd edn. Geneva: World Health Organization, 1988:27–8.
36. World Health Organization. Leprosy elimination – MDT overview and regimens. http://www.wpro.who.int/sites/leprosy/treatment/treatment_mdt.htm
37. Cestari TF. Hanseníase e gestação. In: Talhari S, Neves RG (eds). Hanseníase, 3rd edn. Manaus: Grafica e Editora Tropical, 1997:83–6.

38. Oliveira MLW. Infecções por micobactérias. In: Ramos-e-Silva M, Castro MCR (eds). Fundamentos de Dermatologia. Rio de Janeiro: Atheneu, 2010:913–42.
39. Ramos-e-Silva M, Fernandes NC. Parasitic diseases including tropical diseases. In: Parish LC, Brenner S, Ramos-e-Silva M (eds). Women's Dermatology. London: Parthenon, 2001:291–302.
40. Ramos-e-Silva M, Carneiro SCS. Cutaneous vasculitis in Latin America. Clin Dermatol. 1999;17:663–70.
41. Lucas S. Bacterial disease. In: Elder D, Elenitsas R, Johnson B Jr, Murphy GF (eds). Lever's Histopathology of the Skin, 9th edn. Philadelphia: Lippincott-Raven, 2004:551–90.
42. Kang TJ, Kim SK, Lee SB, et al. Comparison of two different PCR amplification products (the 18-kDa protein gene vs. RLEP repetitive sequence) in the diagnosis of *Mycobacterium leprae*. Clin Exp Dermatol. 2003;28:420–4.
43. Moura RS, Calado KL, Oliveira ML, Bührer-Sékula S. Leprosy serology using PGL-I: a systematic review. Rev Soc Bras Med Trop. 2008;41:11–8.
44. Jain S, Sehgal V. Multidrug therapeutical challenges in leprosy. Int J Dermatol. 1997;36:493–6.
45. WHO/LEP. Action programme for the elimination of leprosy. Status report (updated). Geneva: WHO, 1997:10–1.
46. WHO/APEL. Action programme for the elimination of leprosy. Efficacy of a single-dose multidrug therapy for the treatment of single lesion paucibacillary leprosy. Single-lesion Multicentre Trial Group. Indian J Lepr. 1997;69:121–9.
47. Franzblau SG, Hastings RC. In vitro and in vivo activities of macrolides against *Mycobacterium leprae*. Antimicrob Agents Chemother. 1988;32:1758–62.
48. Grosset JH, Ji BH, Guelpa-Lauras CC, et al. Clinical trial of pefloxacin and ofloxacin in the treatment of lepromatous leprosy. Int J Lepr Other Mycobact Dis. 1990;58:281–95.
49. Prasad PV, Kaviarasan PK. Leprosy therapy, past and present: can we hope to eliminate it? Indian J Dermatol. 2010;55:316–24.
50. Hernandez C, Cetner AS, Jordan JE, et al. Tuberculosis in the age of biologic therapy. J Am Acad Dermatol. 2008;59:363–80.
51. Kaplan G. Potential of thalidomide and thalidomide analogues as immunomodulatory drugs in leprosy and leprosy reactions. Lepr Rev. 2000;71:S117–20.
52. Sehgal VN, Bhattacharya SN, Jain S, Logani K. Cutaneous tuberculosis: the evolving scenario. Int J Dermatol. 1994;33:97–104.
53. Schuster M. Mycobacterial disease: a historical and epidemiologic perspective. Clin Dermatol. 1995;13:191.
54. MacGregor RR. Cutaneous tuberculosis. Clin Dermatol. 1995;13:245–55.
55. World Health Organization. Global tuberculosis control 2010. www.who.int/tb/publications/global_report/2010/en/index.html
56. Sehgal VN. Cutaneous tuberculosis. Dermatol Clin. 1994;12:645–53.
57. Sehgal VN, Sehgal R, Bajaj P, et al. Tuberculosis verrucosa cutis (TBVC). J Eur Acad Dermatol Venereol. 2000;14:319–21.
58. Davis JM, Ramakrishnan L. The role of the granuloma in expansion and dissemination of early tuberculous infection. Cell. 2009;136:37–49.
59. Volkman HE, Pozos TC, Zheng J, et al. Tuberculous granuloma induction via interaction of a bacterial secreted protein with host epithelium. Science. 2010;327:466–9.
60. Elkington P, Shiomi T, Breen R, et al. MMP-1 drives immunopathology in human tuberculosis and transgenic mice. J Clin Invest. 2011;121:1827–33.
61. Pan H, Yan BS, Rojas M, et al. *Ipr1* gene mediates innate immunity to tuberculosis. Nature. 2005;434:767–72.
62. Adrians B, Dominguez-Soto L, Canizares O, Harman R. Tuberculosis of the skin. In: Canizares O, Harman R (eds). Clinical Tropical Dermatology, 2nd edn. Boston: Blackwell Science, 1992:201–15.
63. Ramos-e-Silva M, Marques AS, Rocha GL. Tuberculose cutânea associada à tuberculose osteoarticular. An Bras Dermatol. 1986;61:245–50.
64. Mazurek GH, Jereb J, Vernon A, et al. Updated guidelines for using interferon gamma release assays to detect *Mycobacterium tuberculosis* infection - United States, 2010. MMWR Recomm Rep. 2010;59:1–25.
65. American Thoracic Society, CDC, Infectious Diseases Society of America. Treatment of tuberculosis. MMWR Recomm Rep. 2003;52:1–77.
66. Andries K, Verhasselt P, Guillemont J, et al. A diarylquinoline drug active on the ATP synthase of *Mycobacterium tuberculosis*. Science. 2005;307:223–7.
67. Caminero JA, Sotgiu G, Zumla A, et al. Best drug treatment for multidrug-resistant and extensively drug-resistant tuberculosis. Lancet Infect Dis. 2010;10:621–9.
68. Yew WW, Lang C, Leung CC. Treatment of tuberculosis: update 2010. Eur Resp J. 2011;37:441–62.
69. McShane H, Pathan AA, Sander CR, et al. Recombinant modified vaccinia virus Ankara expressing antigen 85A boosts BCG-primed and naturally acquired antimycobacterial immunity in humans. Nat Med. 2004;10:1240–4.
70. Darwin KH, Ehrt S, Gutierrez-Ramos JC, et al. The proteasome of *Mycobacterium tuberculosis* is required for resistance to nitric oxide. Science. 2003;302:1963–6.
71. Kullavanijaya P. Atypical mycobacterial cutaneous infection. Clin Dermatol. 1999;17:153–8.
72. Groves R. Unusual cutaneous mycobacterial diseases. Clin Dermatol. 1995;13:257–63.
73. Winthrop KL, Abrams M, Yakrus M, et al. An outbreak of mycobacterial furunculosis associated with footbaths at a nail salon. N Engl J Med. 2002;346:1366–71.
74. Haiavy J, Tobin H. *Mycobacterium fortuitum* infection in prosthetic breast implants. Plast Reconstr Surg. 2002;109:2124–8.
75. Brickman M, Parsa AA, Parsa FD. *Mycobacterium cheloneae* infection after breast augmentation. Aesthetic Plast Surg. 2005;29:116–18.
76. Meyers WM. Buruli ulcer (*Mycobacterium ulcerans* infection). Armed Forces Institute of Pathology. http://www.who.int/gtb-buruli/archives/yamoussoukro/abstracts/meyers.htm Washington: WHO, 2001.
77. Chan-Tompkins NH. Toxic effects and drugs interactions of antimycobacterial therapy. Clin Dermatol. 1995;13:223–33.
78. Gluckman S. Mycobacterium marinum. Clin Dermatol. 1995;13:273–6.
79. Weitzul S, Eichhorn PJ, Pandya AG. Nontuberculous mycobacterial infections of the skin. Dermatol Clin. 2000;18:359–77.
80. Hautmann G, Lotti T. Diseases caused by *Mycobacterium scrofulaceum*. Clin Dermatol. 1995;13:277–80.
81. Jogi R, Tyring SK. Therapy of nontuberculous mycobacterial infections. Dermatol Ther. 2004; 17:491–8.
82. Alcaide F, Calatayud L, Santin M, Martin R. Comparative in vitro activities of linezolid, telithromycin, clarithromycin, levofloxacin, moxifloxacin, and four conventional antimycobacterial drugs against *Mycobacterium kansasii*. Antimicrob Agents Chemother. 2004;48:4562–5.
83. Griffith DE, Aksamit T, Brown-Elliot BA, et al. An official ATS-IDSA statement: diagnosis, treatment and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007;175:367-416.
84. Dodiuk-Gad R, Dyachenko P, Ziv M, et al. Nontuberculous mycobacterial infections of the skin: a retrospective study of 25 cases. J Am Acad Dermatol. 2007;57:413–20.
85. Adusumilli S, Mve-Obiang A, Sparer T, et al. *Mycobacterium ulcerans* toxic macrolide, mycolactone modulates the host immune response and cellular location of *M. ulcerans in vitro* and *in vivo*. Cell Microbiol. 2005;7:1295–304.
86. Phillips R, Horsfield C, Kuijper S, et al. Sensitivity of PCR targeting the IS2404 insertion sequence of *Mycobacterium ulcerans* in an assay using punch biopsy specimens for diagnosis of Buruli ulcer. J Clin Microbiol. 2005;43:3650–6.
87. Almeida D, Converse PJ, Ahmad Z, et al. Activities of rifampin, rifapentine and clarithromycin alone and in combination against *Mycobacterium ulcerans* disease in mice. PLoS Negl Trop Dis. 2011;5:e933.
88. Iijima M, Sasaky S. Cutaneous atypical mycobacteriosis due to *Mycobacterium kansasii*: a case report and a review of the literature. Nippon Hifuka Gakkai Zasshi. 1990;100:711–20.
89. Tzen CY, Chen TL, Wu TY, et al. Disseminated cutaneous infection with *Mycobacterium kansasii*: genotyping versus phenotyping. J Am Acad Dermatol. 2001;45:620–4.
90. Azulay RD, Neves RG, Estrella RR, et al. Complexo primário cutáneo-ganglionar por *Mycobacterium fortuitum*. AMB Rev Assoc Med Bras. 1974;20:177–81.
91. Demitsu T, Nagato H, Inoue T, et al. Cutaneous *Mycobacterium chelonae* infection with bilateral sporotrichoid involvement. Int J Dermatol. 2001;40:597–9.
92. Goldman J, Caron F, de Quatrebarbes J, et al. Infections from tattooing. Outbreak of *Mycobacterium chelonae* in France. BMJ. 2010;341:c5483.

Rickettsial Diseases 76

David H Walker

Chapter Contents

Spotted fever and typhus group rickettsial infections *1243*
Scrub typhus *1248*
Human ehrlichioses *1249*
Human granulocytotropic anaplasmosis *1250*
Q fever *1250*

Key features

- Rickettsiae are small, obligately intracellular, Gram-negative bacteria
- Rickettsiae reside in an arthropod host (tick, flea, louse or mite) during part of their life cycle
- The arthropod vector transmits the rickettsiae in its saliva or feces during feeding
- The major vertebrate target cells of *Rickettsia* (endothelium), *Orientia* (endothelium), *Ehrlichia* (monocytes or neutrophils), *Anaplasma* (neutrophils) and *Coxiella* (macrophages) determine to a large degree the pathogenesis of the disease
- In most spotted fever rickettsioses and scrub typhus, an eschar at the site of the vector's inoculation of organisms is an important physical sign
- A rash is the diagnostically critical clinical manifestation of Rocky Mountain spotted fever, other spotted fevers, murine typhus and louse-borne typhus
- One of the most common rickettsial diseases in travelers is African tick bite fever, which is seen in those who have been on safari or bush walking in southern Africa

INTRODUCTION

Members of the order Rickettsiales are small, obligately intracellular, Gram-negative bacteria that reside in an arthropod host for at least part of their life cycle[1]. At least 19 bacterial species belonging to four genera (*Rickettsia, Orientia, Ehrlichia* and *Anaplasma*) in this order and the related *Coxiella* genus in the order Legionellales are known agents of human diseases (Table 76.1). Cutaneous manifestations vary from nearly always present in some spotted fevers and typhus to rare in others, such as human granulocytotropic anaplasmosis and Q fever (Table 76.2). Clinical recognition of a rash is frequently the event that leads to appropriate antimicrobial treatment for life-threatening Rocky Mountain spotted fever (RMSF) and other rickettsioses.

SPOTTED FEVER AND TYPHUS GROUP RICKETTSIAL INFECTIONS

History

Epidemic typhus was described by Fracastorius in Italy in 1546; RMSF, by Maxey in Idaho in 1899; and boutonneuse fever, by Conor in Tunisia in 1910. At least ten of the diseases in this group and/or their etiologic agents were described or discovered in the last two decades. A rickettsial agent was first identified in 1906 in the Bitterroot Valley of western Montana by Howard Ricketts, who also recognized its transmission by feeding ticks. In 1916, S. Burt Wolbach visualized this agent, subsequently named *Rickettsia rickettsii*, within endothelial cells. Charles Nicolle discovered in 1909 that lice transmitted epidemic typhus, and over the next few years this disease was found to be caused by another rickettsial organism, *Rickettsia prowazekii*. Epidemic louse-borne typhus influenced the outcome of most European wars after 1500, including Napoleon's failed Russian invasion in 1812 and World War I, during and after which typhus affected 25 million persons and caused 3 million deaths in Russia. In 1934, recrudescent typhus (Brill–Zinsser disease) was determined to be caused by reactivation of latent *R. prowazekii* infection. Endemic or murine typhus was shown during the 1930s to have a rat reservoir and flea vector.

Epidemiology

Spotted fever group rickettsiae are maintained in nature principally via transmission of the bacteria in infected ova from one generation of tick, mite or flea to the next (see Table 76.1). During feeding, infected ticks instill saliva containing rickettsiae into their host's skin. Thus, the seasonal and geographic distribution of particular diseases (Fig. 76.2) depends upon the range and the host-seeking activity of the particular vector tick, mite or flea. For example, RMSF usually occurs during tick season (from late spring until the end of summer).

Typhus group rickettsiae are deposited on the host's skin in the feces of feeding human body lice (*R. prowazekii*) or fleas (*R. typhi*). The organisms are subsequently scratched into the skin, rubbed into mucous membranes, or inhaled. Humans who recover from louse-borne typhus remain latently infected and years later may develop recrudescent illness (Brill–Zinsser disease) and associated rickettsemia. Such individuals can infect feeding lice, which may then spread the disease to another person and ignite an epidemic. In addition, a zoonotic cycle of *R. prowazekii* is maintained in flying squirrels and their fleas and lice[2]. *R. typhi* is maintained in natural cycles, classically in rats and oriental rat fleas as well as in opossums and cat fleas.

Pathogenesis

After entry into the dermis, rickettsiae spread throughout the body via the bloodstream. They attach to vascular endothelial cells by outer membrane protein B and, in the case of spotted fever group rickettsiae, outer membrane protein A as well[3]. The organisms enter the cells by induced phagocytosis and then escape from the phagosome into the cytosol, where they obtain amino acids, nucleotides and other building blocks for growth from the host cell and divide by binary fission[3]. Spotted fever group rickettsiae move intracellularly and from cell to cell by stimulating propulsion via the host cell's actin, resulting in a contiguous network of infected endothelial cells that represent the source of the vascular-based disease manifestations (including skin lesions). The spotted fever rickettsiae injure the host endothelium by stimulating these cells to produce toxic reactive oxygen species, and typhus group rickettsiae replicate within the infected endothelial cell until it bursts.

The major pathophysiologic effect of rickettsial infection is increased vascular permeability, which can result in edema, hypovolemia and hypotension[4]. Although endothelial cells of the microcirculation are infected in every organ, the critical target organs in life-threatening infections are the lung and brain. A fatal outcome can result if increased vascular permeability leads to non-cardiogenic pulmonary edema, acute respiratory distress syndrome and meningoencephalitis.

As the infection progresses, macrophages and lymphocytes infiltrate the walls of affected vessels and act as effector cells, secreting cytokines

EPIDEMIOLOGY OF RICKETTSIAL INFECTIONS			
Agent	**Disease**	**Transmission**	**Geographic distribution**
Rickettsia rickettsii	Rocky Mountain spotted fever	**Bite of tick:**	
		Dermacentor variabilis (Fig. 76.1)	Eastern two-thirds and Pacific Coast of US
		D. andersoni	Rocky Mountain states
		Rhipicephalus sanguineus	Southwestern US; northern Mexico
		Amblyomma cajennense, *A. aureolatum*	Central and South America
Rickettsia akari	Rickettsialpox	**Bite of mouse mite**:	
		Liponyssoides sanguineus	North America; Eurasia
Rickettsia conorii	Boutonneuse fever (Mediterranean spotted fever)	**Bite of tick**:	
		Rhipicephalus sanguineus	Southern Europe; Africa; western and southern Asia
		Rh. pumilio	Southern Russia
Rickettsia sibirica	North Asia tick typhus, lymphangitis-associated rickettsiosis	**Bite of tick**:	
		Dermacentor nuttallii, *D. silvarum*, *Haemaphysalis concinna*, *Hyalomma asiaticum*, other species	Eurasia and Africa
Rickettsia australis	Queensland tick typhus	**Bite of tick**:	
		Ixodes holocyclus	Eastern Australia
Rickettsia honei	Flinders Island spotted fever	**Bite of tick**:	
		Bothriocroton hydrosauri, other species	Australia and southeastern Asia (Flinders Island is located between Tasmania and Australia)
Rickettsia japonica	Japanese spotted fever	**Bite of tick**:	
		vector status not established for ticks that carry the agent (*Haemaphysalis flava*, *H. longicornis*, *Ixodes ovatus*, *Dermacentor taiwanensis*)	Japan, and eastern Asia
Rickettsia felis	Flea-borne spotted fever	**By flea:**	
		e.g. *Ctenocephalides felis*	Worldwide
Rickettsia africae	African tick bite fever	**Bite of tick:**	
		Amblyomma hebraeum	Southern Africa
		A. variegatum	Central, eastern, and western Africa; Caribbean islands
Rickettsia parkeri	Maculatum disease (American tick bite fever)	**Bite of tick:**	
		Amblyomma maculatum, A. americanum	North America
		A. triste	South America
Rickettsia aeschlimannii	Unnamed disease	**Bite of tick**:	
		Hyalomma marginatum	Africa
Rickettsia slovaca	Tick-borne lymphadenopathy*	**Bite of tick**:	
		Dermacentor marginatus, *D. reticularis*	Europe
Rickettsia prowazekii	Epidemic louse-borne typhus	**Feces of human body louse** (*Pediculus humanus* var. *corporis*)	South America; Africa; Eurasia
	Brill–Zinsser disease	**None (recrudescence of latent infection)**	
	Flying squirrel typhus	**Contact with flying squirrel** (*Glaucomys volans*) and its fleas and lice	North America
Rickettsia typhi	Murine (endemic) typhus	**Feces of fleas**:	
		Xenopsylla cheopis	Worldwide
		Ctenocephalides felis	North America
Orientia tsutsugamushi	Scrub typhus	**Bite of larval trombiculid mites**:	
		L. deliense, *L. fletcheri*, *L. scutellare*, *L. arenicola*	Southern and eastern Asia; islands of the southwestern Pacific and Indian Oceans; northern Australia
		e.g. *L. pallidum*	Japan; Korea; Russian Far East
		e.g. *L. scutellare*	China; Malaysia
		e.g. *L. deliense*, *L. fletcheri*, *L. arenicola*	Tropical regions
Ehrlichia chaffeensis	Human monocytotropic ehrlichiosis	**Bite of tick**:	
		Amblyomma americanum (Fig. 76.1), *Dermacentor variabilis*	Southeastern and South Central US
Ehrlichia ewingii	*Ehrlichia ewingii* infection	**Bite of tick:**	
		Amblyomma americanum	Southeastern and South Central US
Anaplasma phagocytophilum	Human granulocytotropic anaplasmosis	**Bite of tick:**	
		Ixodes scapularis (Fig. 76.1)	Northern US
		I. pacificus	Far western US
		I. ricinus, *I. persulcatus*	Eurasia
Coxiella burnetii	Q fever	**Aerosol** of infected products of parturition of ruminants and other animals**	Worldwide

*Also reported to be caused by *Rickettsia raoultii*.
**Less common means of transmission include ingestion of contaminated dairy products and tick bites (e.g. *Dermacentor* spp.)

Table 76.1 Epidemiology of rickettsial infections. Additional potentially emerging rickettsial infections for which a small number of cases have been described include: *Rickettsia massiliae* (*Rhipicephalus* spp.; Europe, South America); *Rickettsia* species 364D (*Dermacentor occidentalis*; California); and *Rickettsia heilongjiangensis* (*Haemaphysalis* spp.; Eastern Asia – "Far East spotted fever"). A new *Ehrlichia* species transmitted by *Ixodes scapularis* was recently found to cause a febrile illness in the upper midwestern US.

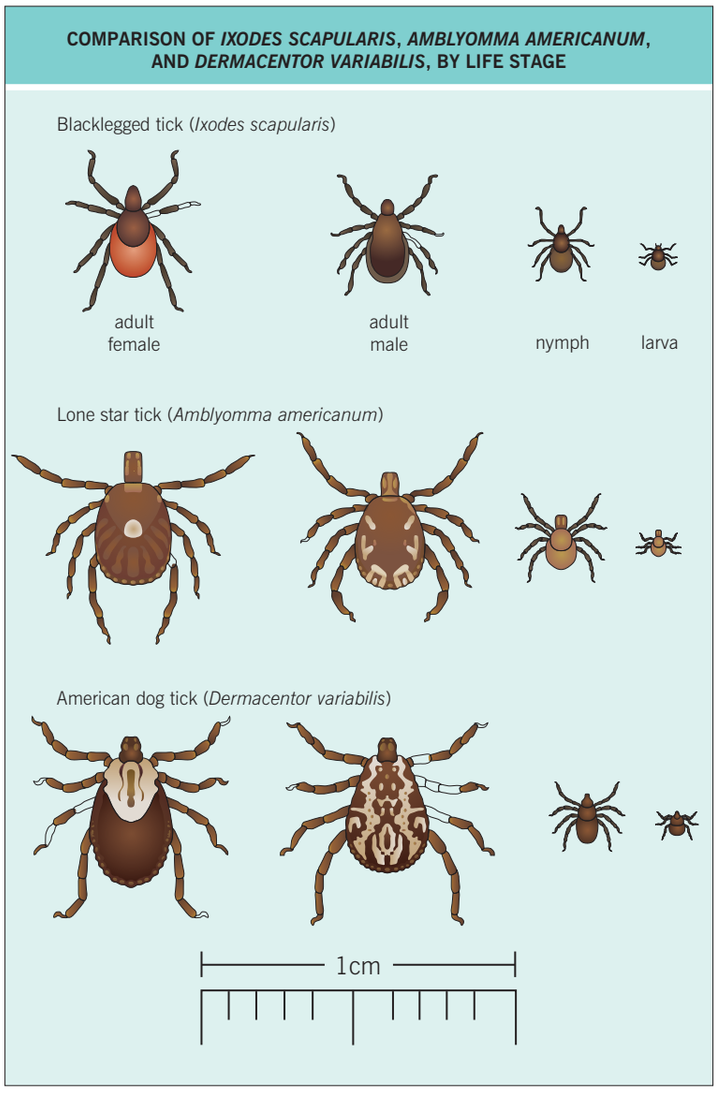


Fig. 76.1 Comparison of *Ixodes scapularis* (blacklegged tick), *Amblyomma americanum* (lone star tick) and *Dermacentor variabilis* (American dog tick), by life stage. *From Chapman AS, et al. MMWR Recomm Rep. 2006;55:1–27.*

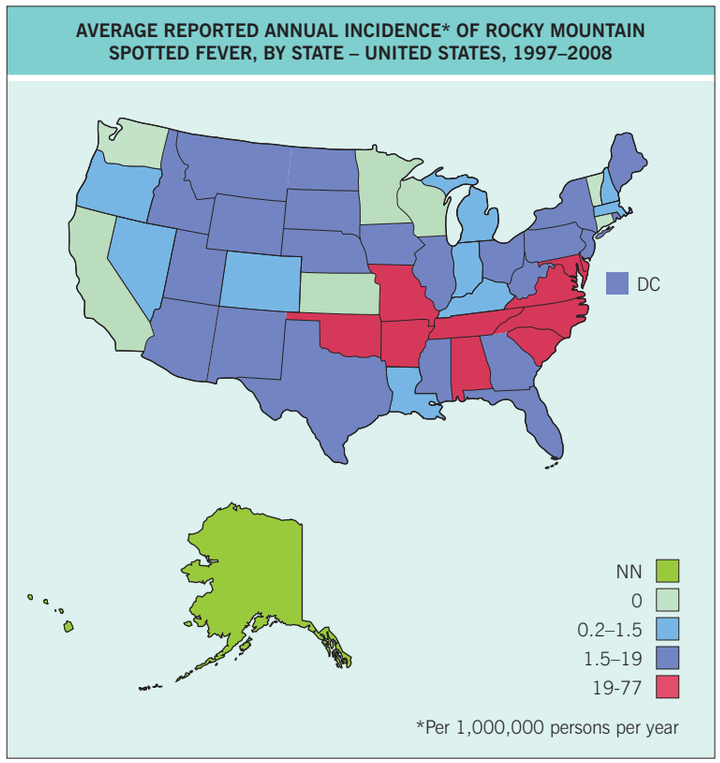


Fig. 76.2 Average reported annual incidence of Rocky Mountain spotted fever, by state – United States, 1997–2008. *From www.cdc.gov/rmsf/stats/#reportsurv.*

such as interferon-γ and tumor necrosis factor-α. Infected endothelial cells and macrophages themselves are activated by cytokines, resulting in killing of intracellular rickettsiae by mechanisms involving nitric oxide, reactive oxygen species, and tryptophan starvation (via enzymatic degradation of this amino acid). Recruited cytotoxic T cells are critical to the apoptotic elimination of infected endothelial cells, which occurs through perforin-dependent pathways. A combination of rickettsicidal mechanisms and killing of infected endothelial cells ultimately leads to clearance of the infection. Antibodies to rickettsiae play a role in the prevention of reinfection.

Clinical Features

Clinical course and systemic features

Rickettsial infections typically begin with fever (>102°F [38.9°C] in two-thirds of patients during the first 3 days of the illness and in 90% thereafter) accompanied by a severe headache and myalgias. Nausea, vomiting, abdominal pain and even abdominal tenderness are also frequent symptoms early in the disease course. When a rash develops, it usually appears on day 3 to 6 of the illness (see below and Table 76.2). Cough (related to pneumonitis and/or pulmonary edema) and confusion or lethargy (related to encephalitis) may represent additional symptoms[5]. Patients often have thrombocytopenia, although full-blown disseminated intravascular coagulation is rare[6], and hyponatremia frequently occurs secondary to increased antidiuretic hormone secretion in response to hypovolemia. Additional laboratory findings may include anemia and abnormal liver and renal function tests. As the clinical course progresses, hypotension, acute renal failure, respiratory failure and coma may develop[7].

Severe rickettsioses continue to have fatalities owing to misdiagnosis and/or initiation of *delayed* antirickettsial treatment, with mortality rates as follows: ~4% for RMSF and louse-borne typhus; ~3% for boutonneuse fever; and ~1% for murine typhus[8,9]. If *not treated* with an appropriate antimicrobial agent, approximately 25% and 15% of patients with RMSF and louse-borne typhus, respectively, will die[10]. The case fatality rate is higher with older age, male gender, and underlying diseases.

Shared cutaneous features

In many types of spotted fevers other than RMSF (see Table 76.2), an eschar consisting of a central area of dermal and epidermal necrosis (typically measuring 0.5–2 cm in diameter) surrounded by a zone of erythema appears during the incubation period (usually 4–10 days) (see Fig. 76.7A). This represents the site of inoculation of rickettsiae by the tick or mite[11,12]. The rash of rickettsial diseases typically begins as erythematous macules around the wrists and ankles (spotted fevers) (Fig. 76.3) or axillae (typhus fevers). The exanthem evolves during the course of the illness, with lesions eventually appearing on most of the body, often with relative sparing of the face. Macules and papules develop on the palms and soles (often relatively late in the disease course) in approximately half of the patients with spotted fevers (Fig. 76.4). Macules reflect vasodilation related to infection of endothelial cells in the dermal microcirculation. As perivascular edema develops secondary to leakage of fluid from damaged blood vessels, macules become papules. When endothelial cell destruction leads to more severe vascular injury, petechiae appear within the lesions (Fig. 76.5), which can coalesce and become purpuric (Fig. 76.6). Cutaneous necrosis, including gangrene of the digits, extremities, ears or prepuce, occurs in 4% of patients with RMSF and occasionally in epidemic typhus, owing to more severe infection of the microcirculation in acral sites with a cooler temperature that is more favorable for rickettsial growth.

Features of specific diseases

RMSF usually follows the classic clinical course described above. After an incubation period of 2–14 (mean, 7) days following the tick bite

DERMATOLOGIC MANIFESTATIONS OF RICKETTSIAL INFECTIONS				
Disease	**Rash incidence (%)**	**Appearance of rash after onset of illness**	**Characteristics**	**Eschar (%)**
Rocky Mountain spotted fever	90	3–5 days	Early macules, later papules; petechiae in 50% of cases	<1
Rickettsialpox	100	2–3 days	Early macules and papules; later papulovesicles and crusts	90
Boutonneuse fever	97	3–5 days	Early macules, later papules	50
North Asian tick typhus	100	4–5 days	Macules and papules	75
Queensland tick typhus	90	2–6 days	Macules, papules and vesicles	75
Flinders Island spotted fever	85	A few days	Early macules and papules, later (in some patients) petechiae	50
Japanese spotted fever	100	A few days	Early macules, later (in some patients) petechiae	90
Flea-borne spotted fever	83	A few days	Macules and papules; occasionally pustules	17
African tick bite fever	50	3–5 days	Generally relatively few lesions; macules, often vesicles	90, often multiple
Maculatum disease (American tick bite fever)	80	2–4 days	Macules, papules, often vesicles	100
R. aeschlimannii infection	50	Not known	Macules, papules	100
Tick-borne lymphadenopathy	5	Not reported	Macules, papules	100
Epidemic louse-borne typhus	50–100	4–5 days	Early macules, later papules; petechiae	None
Brill–Zinsser disease	50	4–6 days	Macules, papules	None
Flying squirrel typhus	66	2–8 days	Macules, papules	None
Murine (endemic) typhus	80	5 days	Early macules, later papules	None
Scrub typhus	50	4–6 days	Early macules, later papules	60–90
Human monocytotropic ehrlichiosis	40	Median, 5 days	Macules, papules, occasionally petechiae	None
Ehrlichiosis ewingii infection	None	NA	NA	None
Human granulocytotropic anaplasmosis	Rare	NA	NA	None
Q fever	Rare	Associated with chronic infection	Macules, papules, palpable purpura; rarely erythema nodosum	None

Table 76.2 Dermatologic manifestations of rickettsial infections. NA, not applicable.

Fig. 76.3 Rocky Mountain spotted fever. The cutaneous lesions often appear first on the wrists and ankles. *Courtesy, Philippe Berbis, MD.*

Fig. 76.4 Rocky Mountain spotted fever. Petechiae on the palms and soles often develop relatively late in the disease course. *Courtesy, Ronald P Rapini, MD.*

(which 40% of patients do not recall), affected individuals present with fever, myalgias, headache and, in >50% of patients, gastrointestinal symptoms. The rash typically appears 3–5 days after onset of the illness as subtle erythematous macules on the wrists and ankles, which is followed by centripetal spread to the trunk, formation of papular lesions, and eventual development of petechiae (~50% of patients). However, cutaneous findings are absent in 10–15% patients and may be difficult to recognize in darkly pigmented skin.

R. parkeri and *R. africae*, closely related strains of spotted fever group rickettsiae transmitted by *Amblyomma* ticks, cause two similar emerging infections, ***Maculatum disease*** (***American tick bite fever***) and ***African tick bite fever***, respectively. The former is endemic in the south central and southeastern US (the range of *A. maculatum*, the Gulf Coast tick; see Fig. 76.10) and in South America, while the latter is endemic in sub-Saharan Africa and represents the rickettsial disease with the highest incidence among travelers returning to the US[13,14].

Fig. 76.5 Rocky Mountain spotted fever. Petechiae are present within erythematous papules and plaques on the buttocks. Some of the lesions have a retiform pattern.

Fig. 76.6 Rocky Mountain spotted fever. Retiform purpura on the distal lower extremity in a patient with more severe disease.

Fig. 76.7 Rickettsialpox. **A** Eschar at the site of the mite bite. **B** Scattered papules with hemorrhagic crusts.

Patients with these conditions typically present with mild constitutional symptoms (e.g. fever, headache, myalgias), one or more eschars, and tender lymphadenopathy in the region draining the eschar(s). In 50–80% of affected individuals, usually 2–4 days after disease onset, a rash develops on the trunk and extremities (sometimes involving the palms and soles). The eruption may be relatively sparse and often features small central vesicles or pustules within erythematous macules and papules. No deaths have been reported for either type of infection. Despite the substantial difference in severity, it is likely that many *R. parkeri* infections are misdiagnosed as RMSF owing to serologic cross-reactivity with *R. rickettsii*[15].

Rickettsialpox occurs primarily in urban areas, especially cities in the northeastern US. A papulovesicle arises within 48 hours at the site of the bite of a mite that parasitizes house mice and eventuates in an eschar with surrounding erythema and induration (Fig. 76.7A). Constitutional symptoms (e.g. fever, headache, myalgias) begin 1 to 2 weeks later, followed in 2 to 3 days by a cutaneous eruption that often involves the face (Fig. 76.7B) as well as the trunk and extremities, in no particular sequence. Approximately 20 to 40 skin lesions typically develop, evolving from erythematous macules and papules to papulovesicles to hemorrhagic crusts. The palms and soles are occasionally affected, and an enanthem characterized by small erosions on the tongue, palate and pharynx may occur.

Pathology

Rickettsial infection is multifocal, which is reflected in the scattered distribution of cutaneous lesions. However, randomly obtained tissue samples are unlikely to contain the classic finding of a lymphohistiocytic vasculitis, which is present in the center of a petechial macule or papule. The early finding of perivascular edema is difficult to identify histopathologically because of formalin-associated tissue shrinkage. In more developed lesions, extravasated erythrocytes (corresponding to petechiae) are observed. Thrombosis occurs in a minuscule portion of infected blood vessels, and, when present, is usually a non-occlusive hemostatic plug in a focus of denuded endothelium. Later in the disease course, vasculitis can be detected histopathologically in the skin and other organs. The inflammatory infiltrate around and within vessel walls is composed of macrophages and lymphocytes (Fig. 76.8).

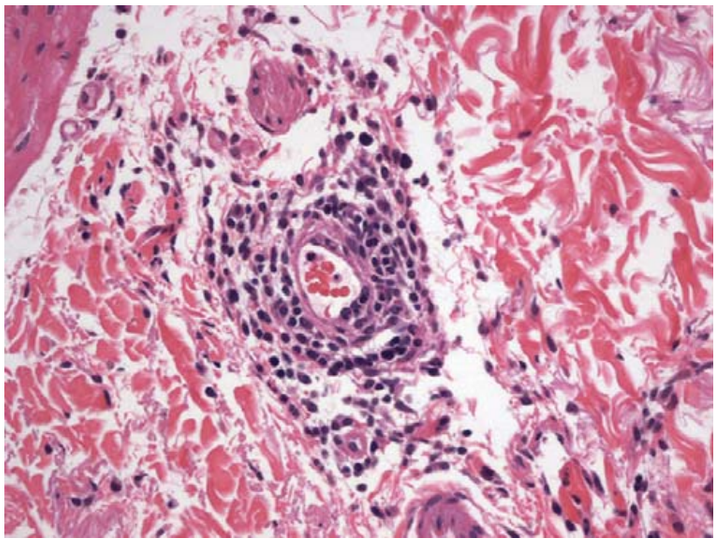


Fig. 76.8 Histologic findings in Rocky Mountain spotted fever. Typical lymphohistiocytic vasculitis involving a dermal blood vessel. *Courtesy, James W Patterson, MD.*

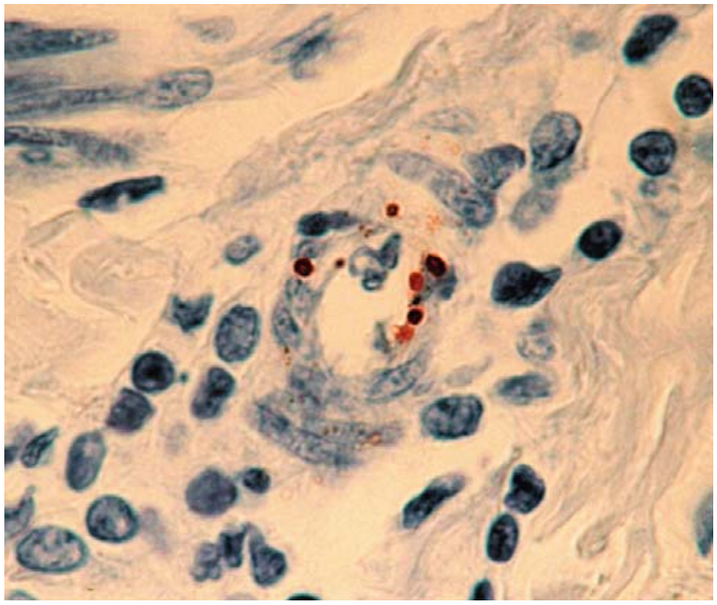


Fig. 76.9 Immunohistochemical detection of spotted fever rickettsiae. Organisms within the endothelium of a dermal blood vessel are highlighted by brown staining.

Diagnosis and Differential Diagnosis

The diagnosis of rickettsiosis is based on clinical and epidemiologic criteria such as the signs, symptoms and potential tick exposure[16]. It is essential to begin empiric treatment with effective antirickettsial agents based on clinical suspicion rather than awaiting laboratory confirmation. Indeed, serologic diagnosis is usually retrospective, because antibodies do not develop until day 7 of the illness or later[17]. Circulating rickettsiae are generally too few early in the illness to be detected by PCR-based assays, but rickettsiae can be identified by immunofluorescence or immunohistochemistry in a biopsy specimen of an eschar or a maculopapular lesion (Fig. 76.9), especially if the latter is petechial.

Prior to the onset of the rash, the differential diagnosis may include a wide variety of viral infections (which often present with similar symptoms), ehrlichiosis and typhoid fever. Patients with prominent nausea and vomiting are often suspected to have viral or bacterial enterocolitis. The abdominal pain and tenderness can suggest an acute surgical abdomen, and this has led to exploratory laparotomies. Cough and crackles on auscultation due to pulmonary edema may lead to suspicion of bacterial or viral pneumonia. Neurologic signs and cerebrospinal fluid pleocytosis can suggest viral or bacterial meningoencephalitis, while jaundice and elevated hepatic enzymes may prompt the consideration of viral hepatitis or leptospirosis.

When the cutaneous eruption initially develops, the differential diagnosis may include a viral exanthem, a drug eruption, ehrlichiosis, Kawasaki disease and early secondary syphilis. Exanthems due to enteroviruses, Epstein–Barr virus, parvovirus B19, adenovirus, dengue fever and measles can have a petechial component (see Fig. 81.2). When petechial and/or purpuric lesions become more prominent, meningococcemia, small vessel vasculitis, disseminated gonococcal infection, dengue hemorrhagic fever and other viral hemorrhagic fevers (see Table 81.7) may also be considered. In patients with thrombocytopenia, immune thrombocytopenic purpura or thrombotic thrombocytopenic purpura represent additional possibilities. The differential diagnosis for rickettsialpox and other rickettsial eruptions with a vesicular component may include vesicular viral exanthems (e.g. due to coxsackieviruses), varicella, disseminated HSV infection, pityriasis lichenoides et varioliformis acuta (PLEVA), drug eruptions, bullous insect bite reactions, and scabies. Cutaneous necrosis resembling an eschar can be seen in spider bites, ecthyma, ecthyma gangrenosum (typically in immunocompromised hosts), cutaneous anthrax, *Bacillus cereus* infection, cutaneous diptheria, tularemia, scrub typhus (see below), and primary syphilis.

Treatment

The drug of choice for rickettsial infections in nearly all patients, including young children, is doxycycline (Table 76.3)[9,16]. Chloramphenicol is a less effective alternative, having a higher rate of fatal outcomes. However, chloramphenicol is generally recommended for treatment of RMSF during pregnancy.

Mild cases of boutonneuse fever in children have been treated with azithromycin or clarithromycin with an outcome equivalent to treatment with chloramphenicol, and these macrolide antibiotics (as well as josamycin, a related agent not available in the US) may represent therapeutic options for mild rickettsioses during pregnancy. Fluoroquinolones have also been used successfully to treat patients with boutonneuse fever and murine typhus. Of note, treatment of severe rickettsial infection with macrolides or fluoroquinolones is not recommended.

SCRUB TYPHUS

Scrub typhus was described in association with red mites in China in 313 AD. *Orientia tsutsugamushi* was discovered in Japan by Nagayo and Ogata in the 1920s and early 1930s. This organism differs from *Rickettsia* spp. in its cell wall composition, having entirely unrelated proteins and a distinct ultrastructure as well as lacking lipopolysaccharide. *Orientia tsutsugamushi* is maintained in nature via transovarial transmission by its vector, trombiculid mites (see Table 76.1). Eggs laid by infected mites hatch with the emergence of infected larvae (chiggers) that feed on the rat population. Both humans and rats are dead-end hosts.

It is estimated that one million cases of scrub typhus occur annually, affecting rural populations in a large portion of Asia (from Afghanistan to Japan) and northern Australia. Infection of more than 3% of the population per month has been documented in endemic regions of southeast Asia. Immunity is strain-specific and transient, resulting in reinfections. The severity of the illness is age-dependent and varies geographically.

A cutaneous eschar forms at the site of chigger feeding in 60–90% of primary infections. This is followed by regional lymphadenopathy, fever and headache; generalized lymphadenopathy, conjunctival hyperemia and hearing loss may also develop[18]. A rash occurs in approximately half of patients, usually appearing as erythematous macules on the trunk 4 to 6 days after disease onset. Lesions then become papular, with subsequent centrifugal spread. Interstitial pneumonia frequently occurs, presenting with cough, tachypnea and radiographic infiltrates; meningoencephalitis is a less common manifestation[19]. In severe cases, acute respiratory distress syndrome, acute renal failure and hypotensive shock may develop.

TREATMENT OF RICKETTSIAL DISEASES				
	Medication	**Adult dose**	**Pediatric dose**	**Treatment duration**
• First choice for virtually all rickettsial infections in children and adults*	Doxycycline	100 mg po or iv twice daily	2.2 mg/kg (max. 100 mg) po or iv twice daily	Until ≥3 days after defervescence, for a minimum total course of 5–7 days†
• First choice for non-life-threatening RMSF in pregnant women	Chloramphenicol‡	500 mg iv every 6 hours	Not recommended	Until ≥3 days after defervescence, for a minimum total course of 5–7 days†
• First choice for non-life-threatening HME or HGA in pregnant women • Alternative for resistant scrub typhus	Rifampin	300 mg po twice daily	10 mg/kg (max. 300 mg) twice daily	Until ≥3 days after defervescence, for a minimum total course of 7–10 days
• First choice for scrub typhus in pregnant women and potentially in children • Alternative for mild rickettsioses (e.g. early boutonneuse fever) during pregnancy or in children	Azithromycin§	500 mg po daily	10 mg/kg po daily	3 days

*With the exception of infections in pregnant women, although doxycycline administration during pregnancy can be considered in life-threatening situations when the suspicion of RMSF or other severe rickettsioses is high; other tetracyclines are also effective for rickettsial infections.
†Recommended by the CDC; others recommend a 10-day course.
‡May be associated with gray baby syndrome when administered late in the third trimester of pregnancy.
§Clarithromycin may also be considered.

Table 76.3 Treatment of rickettsial diseases. Empiric treatment with an appropriate agent should be initiated immediately when a diagnosis of Rocky Mountain spotted fever (RMSF), human monocytotropic ehrlichiosis (HME), human granulocytotropic anaplasmosis (HGA) or another potentially severe rickettsiosis is suspected clinically.

Tetracyclines, particularly doxycycline, are generally the first-line treatment for scrub typhus. Chloramphenicol, another traditional therapy for this condition, is less effective than doxycycline, but azithromycin is equally effective as doxycycline and represents an option for pregnant women. Of note, resistance of *O. tsutsugamushi* to doxycycline and chloramphenicol has been documented in northern Thailand[20], and resistant infections have been treated successfully with azithromycin or rifampin.

HUMAN EHRLICHIOSES

Ehrlichial infections have been well known to veterinarians for >75 years, but human infection was not recognized until 1986, when *Ehrlichia chaffeensis* was implicated as the etiologic agent of human monocytotropic ehrlichiosis (HME)[21]. In 1999, *E. ewingii* was found to cause human infections (most often in immunosuppressed patients) with clinical manifestations similar to HME[22]. *Ehrlichia* spp. are obligately intracellular, Gram-negative bacteria that target monocytes/macrophages (*E. chaffeensis*) or neutrophils (*E. ewingii*), in which they reside as a cytoplasmic microcolony that is occasionally visible in a peripheral blood smear. Both agents are maintained in a zoonotic cycle involving persistently infected white-tailed deer as the major reservoir and lone star ticks (*Amblyomma americanum*), which are found primarily in the south central and southeastern US (with extension as far north as Illinois and Connecticut), as the primary vector (Fig. 76.10; see Table 76.1)[21]. In addition, a new *Ehrlichia* species transmitted by *Ixodes scapularis* was recently found to cause human infections clinically similar to HME in the upper midwestern US[22a].

HME is a serious infectious disease with a ~3% case fatality rate. Its incidence is likely underestimated due to the lack of specific clinical findings, and one study found that ehrlichial infection was twice as likely as RMSF among febrile patients living in North Carolina with a history of a recent tick bite[16]. Patients with HME and *Ehrlichia ewingii* infection typically present with fever, headache and myalgias; common laboratory abnormalities include thrombocytopenia, leukopenia and elevated transaminases. Progression to acute respiratory distress syndrome, meningoencephalitis and toxic shock syndrome-like manifestations can occur, even in immunocompetent individuals with HME. In addition, overwhelming ehrlichial infection may develop in immunocompromised hosts, such as those with HIV infection and organ transplant recipients[23,24].

Approximately 30–40% of patients with HME have cutaneous manifestations, which develop a median of 5 days after the onset of the illness and may be more common in children[25]. Macular, maculopapular and petechial eruptions involving the trunk and extremities are most often observed, but the morphology and distribution of skin lesions can vary considerably[25,26] (Table 76.4). *Ehrlichia ewingii* infection has not been reported to have cutaneous manifestations[22]. The differential diagnosis of ehrlichioses is similar to that of rickettsioses (see above).

PCR-based assays can identify *Ehrlichia* spp. and *Anaplasma phagocytophilum* (see below) in blood samples and assist in the rapid diagnosis of these infections; however, empiric treatment should be initiated based on clinical suspicion rather than awaiting laboratory confirmation. Doxycycline is the drug of choice for both HME and *Ehrlichia ewingii* infection. *In vitro* evidence suggests that chloramphenicol is not an effective therapy for these infections.

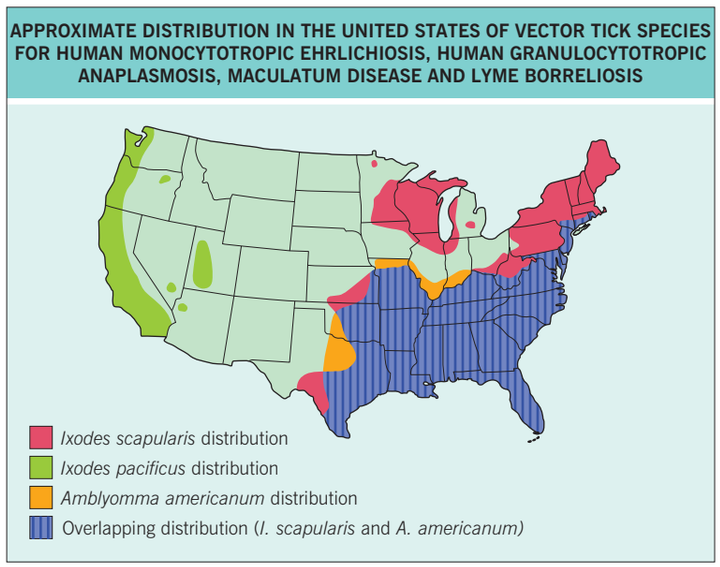


Fig. 76.10 Approximate distribution in the US of vector tick species for human monocytotropic ehrlichiosis, human granulocytotropic anaplasmosis, Maculatum disease and Lyme borreliosis. It has been postulated that *Amblyomma maculatum*, which is classically found primarily along the Atlantic and Gulf coasts, has a range as broad as that of *Amblyomma americanum*. *From Chapman AS, et al. MMWR Recomm Rep. 2006;55:1–27.*

CUTANEOUS MANIFESTATIONS OF HUMAN MONOCYTOTROPIC EHRLICHIOSIS
Macular or maculopapular exanthematous eruptions
Mottled or diffuse macular erythema (transient or persistent)
Petechiae (favor the palms, soles, trunk and palate)
Vesicles
Edema (especially of hands, feet and scrotum)
Purpuric papules (with histologic evidence of vasculitis)
Nodules secondary to polyarteritis nodosa
Ulceration (reported on the penis)

Table 76.4 Cutaneous manifestations of human monocytotropic ehrlichiosis. Several types of lesions may be present simultaneously or sequentially in an individual patient.

HUMAN GRANULOCYTOTROPIC ANAPLASMOSIS

Anaplasma phagocytophilum, previously referred to as the "human granulocytotropic ehrlichiosis (HGE) agent", is an obligately intracellular bacterium (closely related to *Ehrlichia* spp.) that causes human granulocytotropic anaplasmosis (HGA; formerly known as HGE). HGA occurs in the same geographic distribution as Lyme borreliosis (and babesiosis) owing to their transmission by the same *Ixodes* spp. tick vectors (see Table 76.1 and Fig. 76.10). The clinical features of HGA are similar to those of HME, but HGA has a lower case fatality rate (0.5–1%), often presents with peripheral neuropathy (but rarely leads to meningoencephalitis), and seldom has dermatologic manifestations (≤5% of cases)[27]. Interestingly, Sweet's syndrome has been described in association with HGA[28]. As for HME, the first-line treatment is doxycycline.

Q FEVER

Coxiella burnetii differs substantially from organisms in the order Rickettsiales, being more closely related to bacteria of the genus *Legionella*. Although *C. burnetii* are obligately intracellular bacteria found in many species of ticks, they are transmitted to humans primarily by inhalation of aerosols generated from the placenta and birth fluids of infected animals such as sheep, cattle and cats (see Table 76.1). The bacteria target macrophages, where they thrive in the acidic environment of phagolysosomes. The presence of a stable extracellular form accounts for their persistence in the environment.

The acute disease typically presents as a nonspecific febrile illness; atypical pneumonia or granulomatous hepatitis occasionally occur. Chronic Q fever most often manifests as "culture-negative" endocarditis affecting a previously damaged heart valve.

Cutaneous manifestations of Q fever are rare (see Table 76.2). A truncal maculopapular rash, an urticarial eruption, erythema nodosum, palpable purpura, palatal petechiae, and vasculitis (reported in association with mixed cryoglobulinemia) have all been described in patients with Q fever.

REFERENCES

1. Yu XJ, Walker DH. Family I. Rickettsiaceae. In: Brenner DJ, Kreig NR, Staley JT (eds). Bergey's Manual of Systematic Bacteriology: Proteobacteria v. 2, 2nd edn. New York: Springer-Verlag, 2005:96–116.
2. Chapman AS, Swerdlow DL, Dato VM, et al. Cluster of sylvatic epidemic typhus cases associated with flying squirrels, 2004–2006. Emerg Infect Dis. 2009;15:1005–11.
3. Valbuena G, Walker DH. Infection of the endothelium by members of the order Rickettsiales. Thromb Hemost. 2009;102:1071–9.
4. Walker DH. Rickettsiae and rickettsial infections: the current state of knowledge. Clin Infect Dis. 2007;45S:39–44..
5. Kaplowitz LG, Fischer JJ, Sparling PF. Rocky Mountain spotted fever: a clinical dilemma. Curr Clin Top Infect Dis. 1981;2:89–108.
6. Elghetany MT, Walker DH. Hemostatic changes in Rocky Mountain spotted fever and Mediterranean spotted fever. Am J Clin Pathol. 1999;112:159–68.
7. Helmick CG, Bernard KW, D'Angelo LJ. Rocky Mountain spotted fever: clinical, laboratory, and epidemiological features of 262 cases. J Infect Dis. 1984;150:480–8.
8. Dumler JS, Taylor JP, Walker DH. Clinical and laboratory features of murine typhus in south Texas, 1980 through 1987. JAMA. 1991;266:1365–70.
9. Holman RC, Paddock CD, Curns AT, et al. Analysis of risk factors for fatal Rocky Mountain spotted fever: evidence for superiority of tetracyclines for therapy. J Infect Dis. 2001;184:1437–44.
10. Raoult D, Ndihokubwayo JB, Tissot-Dupont H, et al. Outbreak of epidemic typhus associated with trench fever in Burundi. Lancet. 1998;353:353–8.
11. Jensenius M, Fournier PE, Vene S, et al. African tick bite fever in travelers to rural sub-equatorial Africa. Clin Infect Dis. 2003;36:1411–17.
12. Walker DH, Occhino C, Tringali GR, et al. Pathogenesis of rickettsial eschars: the tache noire of boutonneuse fever. Hum Pathol. 1988;19:1449–54.
13. Jensenius M, Davis X, von Sonnenburg F. Multicenter geosentinel analysis of rickettsial diseases in international travelers, 1996–2008. Emerg Infect Dis. 2009;15:1791–8.
14. Paddock CD, Finley RW, Wright CS, et al. *Rickettsia parkeri* rickettsiosis and its clinical distinction from Rocky Mountain spotted fever. Clin Infect Dis. 2008;47:1188–96.
15. Walker DH, Paddock CD, Dumler JS. Emerging and re-emerging tick-transmitted rickettsial and ehrlichial infections. Med Clin North Am. 2008;92:1345–61.
16. Chapman A, Bakken JS, Folk SM, et al. Tickborne Rickettsial Diseases Working Group. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever, ehrlichioses, and anaplasmosis – United States. MMWR Recomm Rep. 2006;55:1–27.
17. Walker DH, Bouyer DH. *Rickettsia* and *Orientia*. In: Murray PR (ed.). Manual of Clinical Microbiology v.1, 9th edn. Washington, DC: ASM Press, 2007:1036–45.
18. Watt G, Walker DH. Scrub typhus. In: Guerrant RL, Walker DH, Weller PF (eds). Tropical Infectious Diseases: Principles, Pathogens, & Practice, 2nd edn. Philadelphia: Elsevier, 2006:557–63.
19. Silpapojakul K, Ukkachoke C, Krisanapan S, Silpapojakul K. Rickettsial meningitis and encephalitis. Arch Intern Med. 1991;151:1753–7.
20. Watt G, Chouriyagune C, Ruangweerayud R, et al. Scrub typhus infections poorly responsive to antibiotics in northern Thailand. Lancet. 1996;348:86–9.
21. Paddock CD, Childs JE. *Ehrlichia chaffeensis*: a prototypical emerging pathogen. Clin Microbiol Rev. 2003;16:37–64.
22. Buller RS, Arens M, Hmiel SP, et al. *Ehrlichia ewingii*, a newly recognized agent of human ehrlichiosis. N Engl J Med. 1999;341:148–55.

22a. Pritt BS, Sloan LM, Johnson DK, et al. Emergence of a new pathogenic *Ehrlichia* species, Wisconsin and Minnesota, 2009. N Engl J Med. 2011;365:422–9.

23. Fishbein DB, Dawson JE, Robinson LE. Human ehrlichiosis in the United States, 1985 to 1990. Ann Intern Med. 1994;120:736–43.
24. Olano JP, Masters E, Hogrefe W, et al. Human monocytotropic ehrlichiosis, Missouri. Emerg Infect Dis. 2003;9:1579–86.
25. Schutze GE, Buckingham SC, Marshall GS, et al. Human monocytic ehrlichiosis in children. Pediatr Infect Dis J. 2007;26:475–9.
26. Pick N, Potasman I, Strenger C, et al. Ehrlichiosis associated vasculitis. J Intern Med. 2000;247:674–8.
27. Bakken JS, Dumler JS. Human granulocytic anaplasmosis. Infect Dis Clin North Am. 2008;22:443–8.
28. Halasz CL, Niedt GW, Kurtz CP, et al. A case of Sweet syndrome associated with human granulocytic anaplasmosis. Arch Dermatol. 2005;141:887–9.

Fungal Diseases 77

Boni E Elewski, Lauren C Hughey, Jenny O Sobera and Roderick Hay

Key features

- Cutaneous fungal infections are broadly divided into those that are limited to the stratum corneum, hair and nails, and those that involve the dermis and subcutaneous tissues
- Superficial fungal infections of the skin are most often due to dermatophytes and *Candida* spp.
- "Subcutaneous" mycoses are often the result of implantation, while systemic or "deep" mycoses of the skin usually represent hematogenous spread or extension from underlying structures
- In the immunocompromised host, opportunistic fungi, e.g. *Aspergillus* and *Mucor* spp., can lead to both cutaneous and systemic infections

This chapter reviews common cutaneous fungal infections, and they are subdivided into three major groups: (1) "superficial"; (2) "subcutaneous"; and (3) "deep" or systemic (Table 77.1).

SUPERFICIAL MYCOSES

Introduction

The superficial mycoses are due to fungi that only invade fully keratinized tissues, i.e. stratum corneum, hair and nails. They can be further subdivided into those that induce minimal, if any, inflammatory response, e.g. pityriasis (tinea) versicolor, and those that lead to more substantial cutaneous inflammation, e.g. dermatophytoses (Table 77.2).

Non-inflammatory superficial mycoses

Synonyms: ■ Tinea nigra: tinea nigra palmaris et plantaris, superficial phaeohyphomycosis ■ Piedra: molestia de Beigel, trichomycosis nodularis ■ Pityriasis versicolor: tinea versicolor, dermatomycosis furfuracea, tinea flava

History

In 1846, Eichstedt first noted the disease known today as pityriasis (tinea) versicolor. Over the ensuing 150 years, *Malassezia furfur* (previously known as *Pityrosporum ovale* and *P. orbiculare*) came to be recognized as the causative microbe. More recently, however, studies have pointed to *M. globosa* as a causative organism[1]. In 1865, Beigel first described piedra after isolating a fungus (which was likely actually a contaminant) from a wig. Tinea nigra was first described in the 1890s by Cerqueira, who named it "keratomycosis nigricans palmaris"[2].

Epidemiology

Tinea nigra and piedra typically occur in tropical climates such as Central and South America, Africa, Asia and, occasionally, in the southeastern US. While any race, age or gender may be infected, the typical patient is a young adult. *Trichosporon beigelii* (see Table 77.2 for the revised subdivision of the *Trichosporon* genus), the cause of white piedra, is also recognized as an opportunistic pathogen.

The geographic distribution of *Malassezia* spp. is worldwide (Table 77.3). In fact, they are part of the normal flora of human skin (predominantly *M. sympodialis*). Although pityriasis versicolor occurs most frequently in tropical climates with high ambient temperatures and high humidity, it is also a common disorder in temperate climates. No racial or gender differences have been observed. The typical patient is a young adult, but people of any age may develop the disease. Interestingly, *Malassezia* requires oil to grow, accounting for the increased incidence in adolescents and preference for sebum-rich areas of the skin. *Malassezia* has been implicated in several other skin diseases, including seborrheic dermatitis and atopic dermatitis, but the latter remains controversial. Neonatal cephalic pustulosis (neonatal acne) may also be associated with *Malassezia* spp., particularly *M. sympodialis*[3] (see Ch. 34).

Pathogenesis

Hortaea werneckii (formerly *Exophiala werneckii*) and *Piedraia hortae* are both environmental pathogens. *H. werneckii* (tinea nigra) can be found in soil, sewage, and even shower stalls under humid conditions. The source of exposure to *P. hortae* (black piedra) is thought to be the soil. There is no known transmission of these organisms from human to human. *T. beigelii* (white piedra) is also acquired from the environment; however, it may occasionally be part of the normal flora of the skin and mucous membranes[4], particularly inguinal and axillary skin.

M. furfur (and other species) normally live on human skin in amounts so minute as to be undetectable on potassium hydroxide (KOH) examination of stratum corneum[5]. Pityriasis versicolor occurs when the round yeast form transforms to the mycelial form. In tropical climates, this change is a result of high temperatures and high humidity. In temperate climates, various factors have been implicated, including oily skin, excessive sweating, immunodeficiency, poor nutrition, pregnancy and corticosteroid use. Because this yeast is lipophilic, use of bath oils

ORGANIZATION OF CUTANEOUS MYCOSES	
Superficial	Involve stratum corneum, hair and nails
Subcutaneous	Involve dermis or subcutaneous tissue Often due to implantation
Systemic ("deep") "True" pathogens Opportunistic	Involve dermis or subcutaneous tissue Skin involvement usually reflects hematogenous spread or extension from underlying structures Primary or secondary skin lesions in immunocompromised hosts

Table 77.1 Organization of cutaneous mycoses.

SUPERFICIAL MYCOSES OF THE SKIN		
	Cutaneous disorder	**Pathogen(s)**
Minimal, if any, inflammation	Pityriasis (tinea) versicolor Tinea nigra Black piedra White piedra	*Malassezia furfur, M. globosa* *Hortaea werneckii* *Piedraia hortae* *Trichosporon beigelii**
Inflammatory response common	Tinea capitis, barbae, faciei, corporis, cruris, manuum, pedis Cutaneous candidiasis	*Trichophyton, Microsporum, Epidermophyton* spp. *Candida albicans*, other *Candida* spp.

**Trichosporon beigelii* has been reclassified into at least six pathogenic species: *T. asahii* (most often associated with disseminated trichosporonosis), *T. asteroides*, *T. cutaneum*, *T. inkin* (most often associated with white piedra of pubic hair), *T. mucoides* and *T. ovoides*.

Table 77.2 Superficial mycoses of the skin.

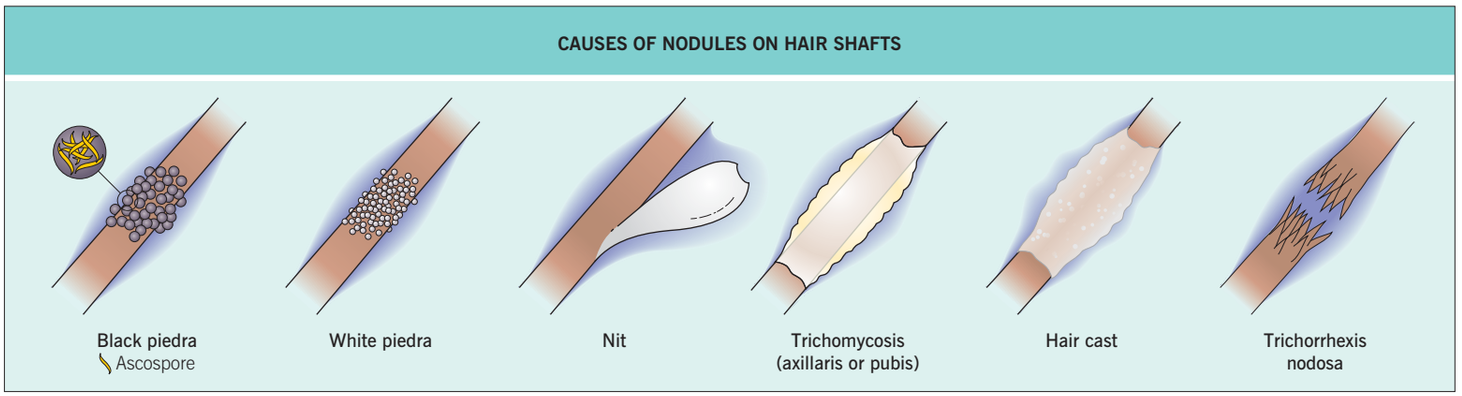


Fig. 77.1 Causes of nodules on hair shafts.

DIFFERENT SPECIES OF *MALASSEZIA* AND COMMON CLINICAL PRESENTATIONS	
Species of *Malassezia*	**Common clinical presentations**
M. furfur	Pityriasis versicolor, seborrheic dermatitis, folliculitis, neonatal cephalic pustulosis, blepharitis, and systemic infections in neonates receiving intravenous fat emulsions
M. globosa	Seborrheic dermatitis, pityriasis versicolor, folliculitis, neonatal cephalic pustulosis
M. sympodialis	Pityriasis versicolor, neonatal cephalic pustulosis*
M. pachydermatitis	Often isolated from domestic and wild animals; has occasionally been implicated in cases of systemic infection in humans; may play a role in chronic dermatitis and otitis externa
M. restricta	Seborrheic dermatitis, pityriasis versicolor
M. sloofiae	Uncommon isolate
M. obtusa	Uncommon isolate

*Most commonly isolated species in this disorder.

Table 77.3 Different species *of Malassezia* and common clinical presentations.

COMPARISON OF BLACK AND WHITE PIEDRA		
	White piedra	**Black piedra**
Nodule color	White (occasionally red, green or light brown)	Brown to black
Nodule firmness	Soft	Hard
Nodule adherence to the hair shaft	Loose	Firm
Typical anatomic location	Face, axillae and pubic region (occasionally scalp)	Scalp and face (occasionally pubic region)
Favored climate	Tropical	Tropical
Causative organism	*Trichosporon beigelii**	*Piedraia hortae*
KOH examination of "crush prep" of cut hair shafts	Non-dematiaceous hyphae with blastoconidia and arthroconidia	Dematiaceous hyphae with asci and ascospores†
Culture on Sabouraud's agar	Moist, cream-colored, yeast-like colonies‡	Slow-growing, dark green to dark brown–black colonies
Treatment	Clip affected hairs, wash affected hairs with antifungal shampoo	Clip affected hairs, wash affected hairs with antifungal shampoo

*See Table 77.2 for the revised subdivision of the *Trichosporon* genus.
†Sexual reproduction
‡Growth inhibited by cycloheximide.

Table 77.4 Comparison of black and white piedra[6].

Fig. 77.2 Tinea nigra. Single, sharply demarcated brown macule on the finger. *Courtesy, Frank Samarin, MD.*

and skin lubricants may increase the risk of disease. Risk factors for *Pityrosporum* folliculitis include chronic antibiotic use, immunosuppression and local occlusion.

Clinical features

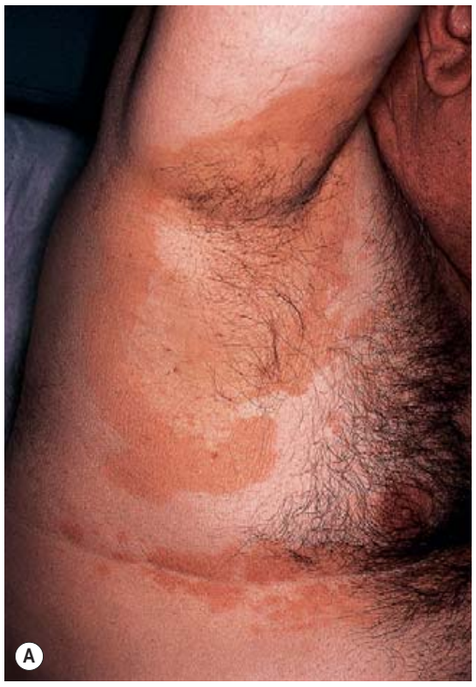
Piedra

Piedra is a superficial infection of the hair shaft. "Piedra" means "stone", reflecting the fungal elements' adherence to one another to form nodules along the hair shaft. There are two major forms – black piedra and white piedra – which are distinguished by their clinical appearance and findings on microscopic examination (Table 77.4). Patients with black piedra typically present with asymptomatic brown to black nodules along the hair shaft. Infection usually commences under the cuticle of the hair shaft and extends outward. Hair breakage may occur as a result of shaft rupture at the site of the nodules. As the nodules enlarge, they can even envelope the hair shaft (Fig. 77.1).

In white piedra, the infection also begins beneath the cuticle and grows through the hair shaft, causing weakening and breakage of the hair. The soft, less adherent nodules of white piedra are generally white but may also be red, green or light brown in color. The incidence of white piedra in the pubic region has increased since the start of the HIV pandemic. In immunosuppressed patients, *T. beigelii* can cause trichosporonosis, a serious systemic infection with fungemia, fever, pulmonary infiltrates, skin lesions (papulovesicular and purpuric, often with central necrosis) and renal disease[4].

Tinea nigra

After a 10- to 15-day incubation period, tinea nigra most commonly presents as a single, sharply marginated, brown (Fig. 77.2) to gray–green macule or patch that can be velvety or have mild scale. There are usually no associated symptoms (i.e. pruritus), and no predispositions have been identified. Although most frequently seen on the palms, tinea nigra can also appear on the soles, neck and trunk. Although palmoplantar lesions are said to resemble acquired acral melanocytic



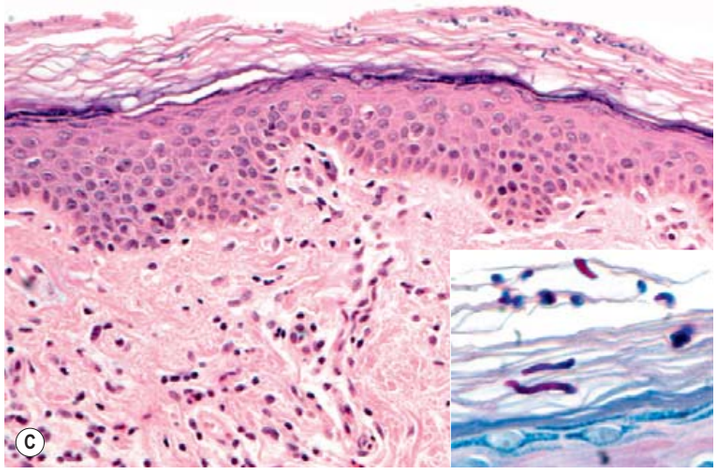


Fig. 77.3 Pityriasis (tinea) versicolor. **A** Hyperpigmented variant. **B** Hypopigmented variant on the face. **C** Yeast and short hyphae in the stratum corneum highlighted by a PAS stain (insert). *A, B, Courtesy, Kalman Watsky, MD. C, Courtesy, Lorenzo Cerroni, MD.*

nevi, the former are usually larger, lighter in color, and lack the linear striations of acral nevi. Tinea nigra can also have darker pigmentation of the advancing border as compared to the center. While the disease tends to be chronic, recurrence after effective treatment is infrequent except in the case of re-exposure.

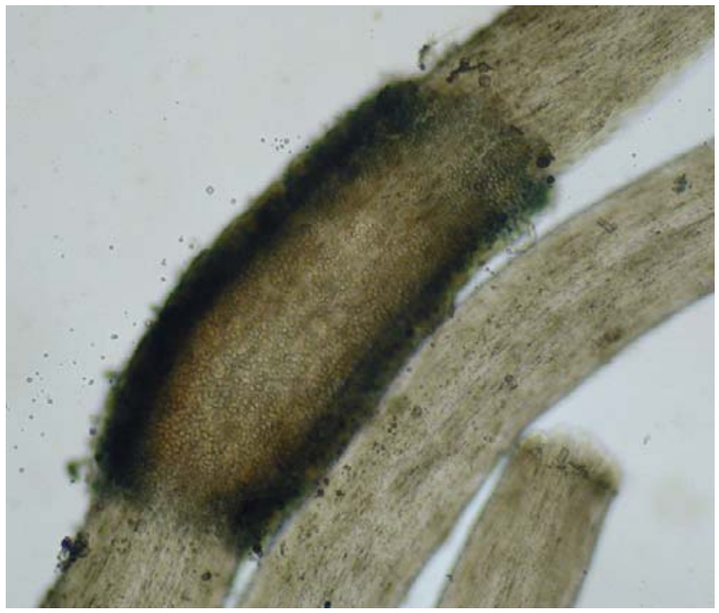


Fig. 77.4 White piedra. Potassium hydroxide preparation of a nodule on the hair shaft showing arthroconidia and blastoconidia.

Pityriasis (tinea) versicolor

Patients usually present with multiple oval to round patches or thin plaques with mild, fine scale. Demonstration of this associated scale may require scratching or stretching the skin surface. The lesions are often confluent centrally within areas of involvement, which may be extensive. Seborrheic regions, in particular the upper trunk and shoulders, are the favored sites of involvement. Less frequently, lesions are seen on the face (especially in children), scalp, antecubital fossae, submammary region and groin. Involvement of flexural areas is sometimes referred to as "inverse" pityriasis versicolor.

The most common colors are brown (hyperpigmented; Fig. 77.3A) and whitish-tan (hypopigmented; Fig. 77.3B); occasionally there is mild inflammation leading to a pink color. Decreased pigmentation may be secondary to the inhibitory effects of dicarboxylic acids on melanocytes (these acids result from metabolism of surface lipids by the yeast) or decreased tanning, due to the ability of the fungus to filter sunlight. In general, pityriasis versicolor is asymptomatic and the major concern is its appearance.

Pityrosporum folliculitis

This condition is most commonly seen in young women and is characterized by pruritic, monomorphic follicular papules and pustules on the upper trunk, arms, neck and, occasionally, the face. It is due to excessive growth of *M. furfur* and *M. globosa* within the hair follicle, with resulting inflammation (from yeast products and free fatty acids produced from fungal lipase). Only yeast forms are observed, i.e. no hyphal forms as in pityriasis versicolor.

Pathology and fungal culture

For black and white piedra, cut hair shafts are placed in KOH and a "crush preparation" is examined microscopically. In a black piedra nodule, dematiaceous hyphae are seen around an organized cluster of asci, each of which contains eight ascospores. The ascospores represent the sexual phase of *P. hortae*. *P. hortae* grows very slowly when cultured and yields a green to black colony with a velvety texture (asexual phase)[7].

KOH preparation of a crushed white piedra nodule reveals non-dematiaceous hyphae, blastoconidia and arthroconidia (Fig. 77.4), representing the asexual state. When cultured, *T. beigelii* grows rapidly, forming moist, cream-colored, yeast-like colonies that resemble "butter cream frosting". On Mycosel® agar, the organism is inhibited by the presence of cycloheximide. *T. beigelii* is often isolated from skin and nail specimens, and the significance of this must be correlated with clinical findings.

Biopsies of pityriasis versicolor and tinea nigra are usually not performed, as KOH examination of associated scale is typically

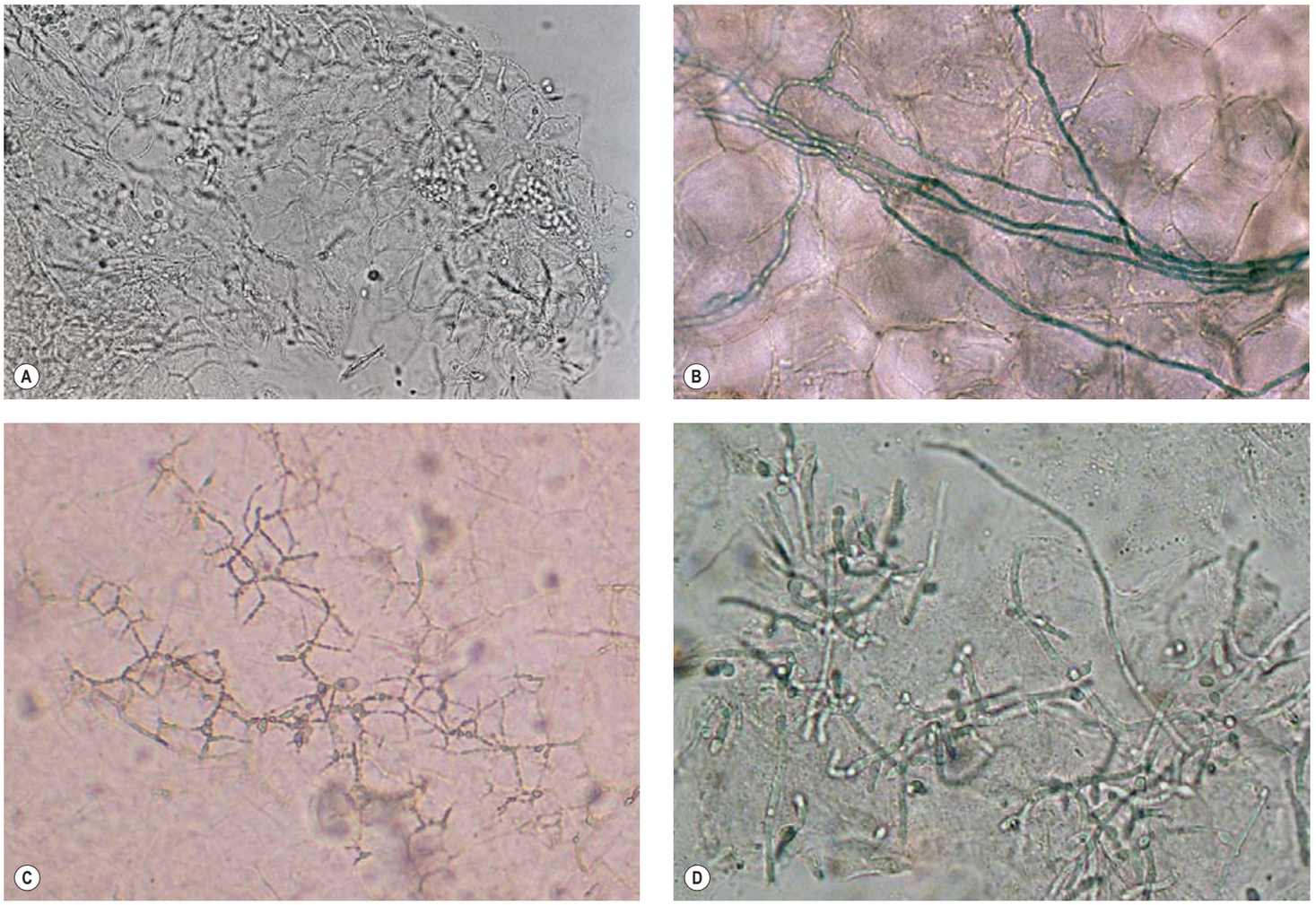


Fig. 77.5 Potassium hydroxide preparations. A Superficial skin scrapings from pityriasis (tinea) versicolor demonstrating yeast and short mycelial forms. **B** A dermatophyte, in this case *Trichophyton tonsurans*, demonstrating branching hyphae; chlorazol black stain **C** "Mosaic" pattern of cell walls that should not be misinterpreted as hyphae. **D** Yeast and pseudohyphae of candidiasis. *A, Courtesy, Ronald P Rapini, MD. C, Courtesy, Louis A Fragola, Jr, MD. D, Courtesy, Frank Samarin, MD.*

diagnostic. In pityriasis versicolor, both hyphal and yeast forms are seen; although likened to "spaghetti and meatballs", the findings more closely resemble "ziti and meatballs" (Fig. 77.5A). In tinea nigra, KOH examination reveals septate pigmented hyphae. When biopsy specimens are obtained, similar findings are observed within the stratum corneum. In KOH examination of expressed follicular contents or biopsy specimens of *Pityrosporum* folliculitis, only yeast forms are seen. Cultures of *H. werneckii* first appear as pasty, green-black colonies with a yeast-like appearance, and then change after approximately 2 weeks to a fuzzy, dematiaceous (dark in color) mold. Culture of *Malassezia* is generally not required; if necessary, the plate must be overlaid with sterile oil because of the organism's lipophilic nature.

Differential diagnosis

Piedra is generally diagnosed by clinical and microscopic inspection of a hair shaft and must be distinguished from pediculosis (nits), hair casts, trichorrhexis nodosa, trichomycosis axillaris (see Ch. 74 and Fig. 77.1), and the scales of psoriasis and eczema. Unlike eczema and psoriasis, the scalp will typically appear normal in piedra.

In most patients, the diagnosis of tinea nigra is made clinically and confirmed via KOH examination and/or fungal culture. Its distinction from acral melanocytic nevi has been discussed previously (see above); occasionally, tinea nigra could be confused with a fixed drug eruption, postinflammatory hyperpigmentation, or staining from chemicals, pigments and dyes. Cutaneous melanoma has even been clinically misdiagnosed as tinea nigra.

Clinical examination is often sufficient to recognize pityriasis versicolor. However, pityriasis alba and other forms of postinflammatory hypopigmentation (see Ch. 66), vitiligo, seborrheic dermatitis, pityriasis rosea, tinea corporis and secondary syphilis may be diagnostic considerations. Progressive macular hypomelanosis, which presents as non-scaly hypopigmented macules on the trunk of young adults and may be caused by *Propionibacterium acnes,* is often misdiagnosed as residual hypopigmentation related to pityriasis versicolor. Wood's light examination (revealing bright yellow fluorescence) and then direct microscopy of scales can confirm the diagnosis of pityriasis versicolor. *Pityrosporum* folliculitis must be differentiated from other causes of folliculitis (see Table 38.1), in particular itching folliculitis, as well as acne vulgaris.

Treatment

Clipping hairs with adherent nodules as well as shampooing the affected hairs with 2% ketoconazole shampoo is usually an effective treatment for piedra (see Table 77.4). Oral terbinafine may also be of therapeutic benefit. For treatment of tinea nigra, topical keratolytic agents such as Whitfield's ointment (typically 6% benzoic acid plus 3% salicylic acid[8]) are effective, as are topical azole or allylamine antifungal medications. Several weeks of therapy may be required to prevent recurrence of disease. Systemic therapy is generally not indicated, and griseofulvin is not effective.

Patients with pityriasis versicolor usually respond to topical antimycotic treatments. Treatment of all the skin from the neck down to the knees, even if only a small area is clinically involved, may lead to higher success rates. Ketoconazole (1% or 2%) or 2.5% selenium sulfide shampoo is quite effective. Treatment can be administered twice weekly for 2 to 4 weeks; the preparation is left on the skin for 10–15 minutes before rinsing. Other topical alternatives include azole/allylamine creams and lotions, 50% propylene glycol in water, nystatin, salicylic

acid and a variety of over-the-counter dandruff shampoos. Residual pigmentary changes often require weeks to months to resolve.

Systemic therapy with ketoconazole, fluconazole or itraconazole (see Ch. 127) can also be utilized for pityriasis versicolor. In randomized controlled trials of oral ketoconazole, cure rates varied from 84% (200 mg × 5 days) to 100% (200 mg × 5 weeks), while a cure rate of 100% was observed in several randomized controlled trials following a 5-day course of oral itraconazole (200 mg daily)[9]. One open-label trial of oral fluconazole (300 mg once weekly for 2 weeks) reported a 98% cure rate; there are few comparative studies of oral antifungal medications[9]. The rate of recurrence of pityriasis versicolor is very high, especially in hot humid climates. Patients at high risk for recurrence may be helped by using ketoconazole shampoo once weekly as a body cleanser. Another preventative measure is once-monthly dosing of oral ketoconazole (400 mg), fluconazole (300 mg) or itraconazole (400 mg). The treatment of *Pityrosporum* folliculitis is reviewed in Chapter 38.

Dermatophytoses

Synonyms: ■ Tinea corporis: ringworm, tinea circinata, tinea glabrosa ■ Tinea cruris: ringworm of the groin, eczema marginatum, jock itch, gym itch ■ Tinea barbae: tinea sycosis, barber's itch, ringworm of the beard ■ Tinea capitis: ringworm of the scalp/hair, tinea tonsurans, herpes tonsurans ■ Tinea pedis: ringworm of the foot, athlete's foot ■ Tinea unguium: ringworm of the nail, dermatophytic onychomycosis

Introduction

Dermatophytoses are fungal infections caused by three genera of fungi that have the unique ability to invade and multiply within keratinized tissue (hair, skin and nails). These fungi, collectively called "dermatophytes", are alike in their physiology, morphology and pathogenicity. The three genera are *Microsporum*, *Trichophyton* and *Epidermophyton*; species within these genera that do not invade keratinized tissue in animals or humans are not considered as dermatophytes. In naming clinical infections due to dermatophytes, "tinea" precedes the Latin name for the involved body site, e.g. "tinea pedis" refers to a dermatophyte infection of the foot. Ten species of dermatophytes are commonly isolated (Table 77.5), and an additional 20 are cultured occasionally. The most common dermatophytes causing disease in humans worldwide[11] are listed in Table 77.5.

History

Dermatophyte infections have been described since ancient times. In 1910, Sabouraud published the current categorization in which dermatophytes are classified by genera.

Epidemiology

Some dermatophytes are restricted geographically, while others are found worldwide. *Trichophyton rubrum*, for example, is the most common dermatophyte and has a global distribution, while *T. concentricum* is endemic to certain parts of the South Pacific and South America. Human travel and migration, coupled with advances in antifungal therapy, have brought about changes in the geographic distribution of dermatophytes. Other important epidemiologic factors include socioeconomic status, occupation, air conditioning and the use of footwear.

Overall, dermatophytoses occur most frequently in postpubertal hosts. One major exception is tinea capitis (dermatophytosis of the scalp), which occurs primarily in children. Risk factors for the development of a dermatophyte infection during childhood include household exposure to tinea capitis or tinea pedis; environmental factors such as contaminated hats, brushes and barber instruments; and (especially for tinea unguium) Down syndrome. Individuals with chronic mucocutaneous candidiasis or common variable immunodeficiency have a propensity to develop severe, chronic or recurrent dermatophytoses (see Ch. 60). Dermatophyte infections tend to be more severe and recurrent in HIV-infected patients. Men more frequently have tinea pedis, tinea cruris and tinea unguium than women.

Pathogenesis

Transmission of dermatophytes to humans occurs via three sources, each resulting in infections with characteristic features (Table 77.6).

DERMATOPHYTES ISOLATED AROUND THE WORLD		
		Thallus (macroscopic) appearance* and/or microscopic findings
MOST COMMON		
Trichophyton	*mentagrophytes* var. *mentagrophytes*	Granular front, buff reverse; pencil-shaped macroconidia, clusters of round microconidia, spiral hyphae
	mentagrophytes var. *interdigitale*	Downy front, buff reverse; see above
	rubrum	White wooly front, venous blood reverse; pencil-shaped macroconidia, teardrop-shaped microconidia
	tonsurans	Granular front, mahogany reverse; pencil-shaped macroconidia, microconidia of varying sizes
	verrucosum	Convoluted, cream to gray, compact; chains of chlamydospores at 37°C
	violaceum	Creamy, waxy, becomes violet
Microsporum	*canis*	White wooly front, orange reverse; multi-celled, spindle-shaped macroconidia with thick walls and rough surface
	ferrugineum	Folded red–orange (rust-colored) front
	gypseum	Cinnamon–tan granular front; multi-celled, cucumber-shaped macroconidia with thin walls
Epidermophyton	*floccosum*	Khaki green, suede to granular; beaver tail-shaped macroconidia; no microconidia
LESS COMMON		
Trichophyton	*ajelloi*	Powdery surface, resembles *Microsporum* spp.
	concentricum	Glabrous colonies; antler-like hyphae
	equinum	Club-shaped macroconidia
	gourvilii	Waxy, pink to red front
	megninii	Pink, felt-like front with red reverse
	schoenleinii	Glabrous; antler- and nailhead-like hyphae; rat-tail-like macroconidia (media often fissured)
	simii	Club-shaped macroconidia in clusters
	soudanense	Yellow to apricot front with fringed border
	terrestre	Cream to yellow granular surface
	yaoundei	Glabrous, chocolate-brown front
Microsporum	*amazonicum*	Multi-celled, spindle-shaped, macroconidia with large inclusions
	audouinii	Flat, tan front with salmon reverse; pectinate (comb-like) hyphae
	cookei	Oval, thick-walled macroconidia
	equinum	One- to four-celled macroconidia resembling *M. canis*
	fulvum	Bullet-shaped macroconidia with spiral hyphae
	gallinae	Diffusable pink–red pigment
	nanum	Two-celled macroconidia
	persicolor	Pink to red front and reverse, resembles *T. mentagrophytes*
	praecox	Powdery front with yellow–orange reverse
	racemosum	Cream-colored powdery front
	vanbreuseghemii	Largest macroconidia

*On Sabouraud's agar.

Table 77.5 Dermatophytes isolated around the world[10].

While dermatophytes are not especially virulent and typically invade only the outer, cornified layers of the skin, they can be responsible for considerable morbidity. The first stage of infection involves contact with and adherence of the infectious elements of the fungus (arthroconidia) to the skin. The ability of certain fungi to adhere to a particular host arises from a variety of microbial mechanisms and host factors[2].

Dermatophytes, unlike most other fungi, produce keratinases (enzymes that break down keratin), which allow invasion of the fungi

TYPES OF DERMATOPHYTES BASED ON MODE OF TRANSMISSION		
Category	**Mode of transmission**	**Typical clinical features**
Anthropophilic	Human to human	Mild to non-inflammatory, chronic
Zoophilic	Animal to human	Intense inflammation (pustules and vesicles possible), acute
Geophilic	Soil to human or animal	Moderate inflammation

Table 77.6 Types of dermatophytes based on mode of transmission.

COMMON DERMATOPHYTES THAT CAUSE TINEA CORPORIS	
Dermatophyte	**Clinical features**
ANTHROPOPHILIC	
Trichophyton rubrum	Commonly harbored by hair follicles; may produce concentric rings; can recur; causative organism in Majocchi's granuloma (nodular folliculitis) and most common cause of tinea corporis
T. tonsurans	Commonly seen in adults who care for children with tinea capitis caused by this organism
Epidermophyton floccosum	Generally restricted to groin, feet; responsible for eczema marginatum
T. concentricum	Responsible for tinea imbricata; infections typically chronic
T. mentagrophytes var. *interdigitale*	Causes interdigital tinea pedis, tinea cruris and onychomycosis
ZOOPHILIC	
T. mentagrophytes var. *mentagrophytes*	May be associated with dermatophytid reaction; causes inflammatory tinea pedis and tinea barbae; associated with exposure to small mammals
Microsporum canis	Associated with pet exposure (cat or dog)
T. verrucosum	May mimic bacterial furunculosis; associated with exposure to cattle
GEOPHILIC	
M. gypseum	Frequently associated with outdoor/occupational exposure; lesions may be inflammatory or bullous

Table 77.7 Common dermatophytes that cause tinea corporis.

into the stratum corneum. Mannans in the cell walls of dermatophytes have immuno-inhibitory effects. In *T. rubrum*, the mannans may also decrease epidermal proliferation, thereby decreasing the likelihood of the fungus being sloughed off prior to invasion. This mechanism is thought to contribute to the chronicity of infections caused by *T. rubrum*[12]. However, host factors such as protease inhibitors may limit the extent of invasion. If invasion is successful, disease occurs.

The severity of clinical disease is also affected by several host factors. Sebum has an inhibitory effect on dermatophytes, and the degree of disease activity may be related to the number and activity of sebaceous glands in a particular body region. Breaks in the skin barrier or macerated skin encourage dermatophyte invasion, and increased susceptibility may be inherited or related to the competency of the immune system. Once dermatophytes have invaded and begun to proliferate in the skin, several mechanisms aid in limiting the infection to keratinized tissue. These include the preference of dermatophytes for the cooler temperature at the skin's surface, serum factors that inhibit dermatophyte growth (e.g. β-globulins, ferritin and other metal chelators)[2] and the host immune system. Further invasion or dissemination is extremely unusual (see below). Other conditions influencing dermatophyte infections include skin disorders such as Darier disease, Hailey–Hailey disease and ichthyoses that affect cutaneous barrier function.

Clinical features

Tinea corporis

Tinea corporis is a dermatophyte infection of the skin of the trunk and extremities, excluding the hair, nails, palms, soles and groin. The infection is generally restricted to the stratum corneum and most commonly affects exposed skin. While tinea corporis occurs worldwide, it is most common in tropical regions. Any dermatophyte can potentially cause tinea corporis, but *T. rubrum* is the most common pathogen worldwide, followed by *T. mentagrophytes* (Table 77.7).

Tinea corporis can result from human-to-human (including autoinoculation, e.g. from tinea capitis or pedis), animal-to-human (often transmitted by domestic animals) or soil-to-human spread (see Table 77.6). Other factors that can predispose an individual to tinea corporis include occupational or recreational exposure (e.g. military housing, gymnasiums, locker rooms, outdoor occupations, wrestling), contact with contaminated clothing and furniture, and immunosuppression[13].

There are multiple clinical presentations of tinea corporis, and they can mimic other dermatologic conditions (Table 77.8). As with most dermatophyte infections, the extent of inflammation depends on the causative pathogen and the immune response of the host. Also, because hair follicles serve as reservoirs for infection, areas of the body with more hair follicles may be more resistant to treatment.

The typical incubation period is 1 to 3 weeks. Infection spreads centrifugally from the point of skin invasion, with central clearing of the fungus, typically resulting in annular lesions of varying sizes

DIFFERENTIAL DIAGNOSES OF DERMATOPHYTE INFECTIONS				
Tinea corporis	**Tinea cruris**	**Tinea faciei**	**Tinea capitis**	**Tinea pedis**
Dermatitis – Nummular eczema – Atopic – Stasis – Contact – Seborrheic (petaloid) Pityriasis versicolor Pityriasis rosea Parapsoriasis Erythema annulare centrifugum Annular psoriasis Subacute lupus erythematosus Granuloma annulare Impetigo	Cutaneous candidiasis Intertrigo – Seborrheic dermatitis – Psoriasis Erythrasma Contact dermatitis Lichen simplex chronicus Parapsoriasis/mycosis fungoides Hailey–Hailey disease Langerhans cell histiocytosis	Dermatitis – Seborrheic – Perioral – Contact Rosacea Lupus erythematosus Acne vulgaris Annular psoriasis (children)	Seborrheic dermatitis Alopecia areata Trichotillomania Psoriasis If pustules: – Pyoderma – Folliculitis If scarring: – Lichen planus – Discoid lupus erthematosus – Folliculitis decalvans – Central centrifugal cicatricial alopecia	Dermatitis – Dyshidrotic – Contact Psoriasis – Vulgaris – Pustular Juvenile plantar dermatosis Secondary syphilis If interdigital: – Erythrasma – Bacterial infection, e.g. GNR

Table 77.8 Differential diagnoses of dermatophyte infections. GNR, Gram-negative rods.

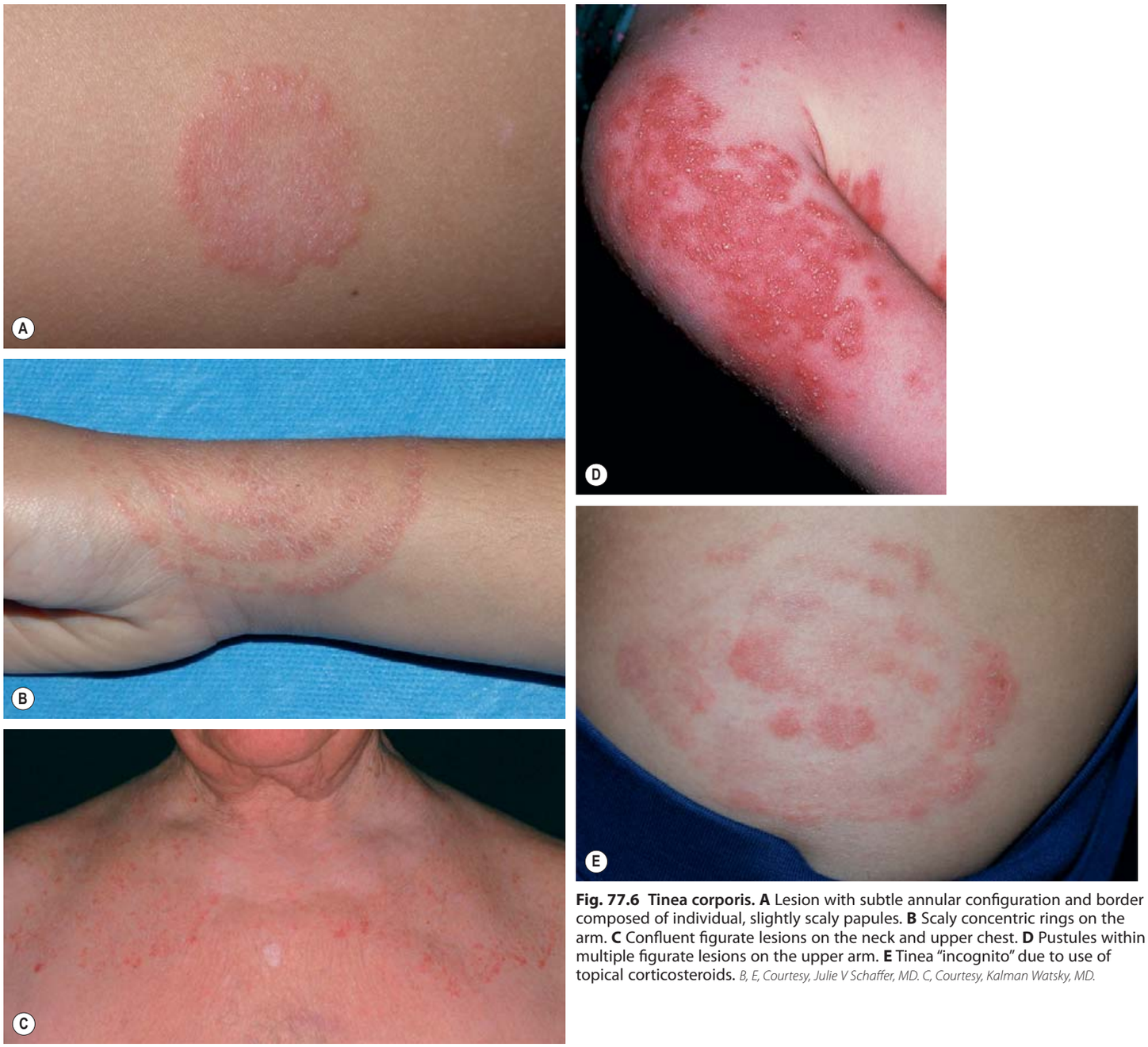


Fig. 77.6 Tinea corporis. A Lesion with subtle annular configuration and border composed of individual, slightly scaly papules. **B** Scaly concentric rings on the arm. **C** Confluent figurate lesions on the neck and upper chest. **D** Pustules within multiple figurate lesions on the upper arm. **E** Tinea "incognito" due to use of topical corticosteroids. *B, E, Courtesy, Julie V Schaffer, MD. C, Courtesy, Kalman Watsky, MD.*

(Fig. 77.6A). However, lesions may assume other shapes (e.g. arcuate, circinate, oval) (Fig. 77.6B–D). Most are scaly, although scale may be lessened or absent if topical corticosteroids have been used (tinea "incognito") (Fig. 77.6E). Pustules within the active border are suggestive of tinea (see Fig. 77.6D). Lesions can also be vesicular, granulomatous or verrucous in appearance. Associated symptoms include pruritus and burning.

Clinical variants of tinea corporis include tinea profunda, Majocchi's granuloma and tinea imbricata. Tinea profunda results from an excessive inflammatory response to a dermatophyte (analogous to a kerion on the scalp). It may have a granulomatous or verrucous appearance and be mistaken for cutaneous tuberculosis, a dimorphic fungal infection or squamous cell carcinoma. Majocchi's granuloma, usually caused by *T. rubrum*, is characterized by perifollicular papulopustules or granulomatous nodules (Fig. 77.7). This variant, commonly seen in women who have tinea pedis or onychomycosis and shave their legs, represents a deep dermatophyte folliculitis in which the wall of the follicle is disrupted. The lesions may be extensive or even vegetating and can also occur in the setting of immunosuppression.

Tinea imbricata is a dermatophytosis caused by the anthropophilic dermatophyte *T. concentricum*. It causes chronic infections in an equatorial band encompassing the South Pacific, Asia, and Central and South America. The clinical presentation consists of concentric annular rings resembling erythema gyratum repens.

Tinea cruris

Tinea cruris is a dermatophyte infection of the inguinal region, in particular the inner aspects of the upper thighs (Fig. 77.8) and crural folds, with occasional extension onto the abdomen and buttocks. While tinea cruris occurs worldwide, like most other dermatophyte infections, it is more common in tropical environments. The three most common causative agents are *Epidermophyton floccosum*, *T. rubrum* and *T. mentagrophytes* (Table 77.9).

This disease is more often seen in men than in women, since the scrotum provides a warm and moist environment that encourages fungal growth and men are more likely to have tinea pedis and onychomycosis as a source of dermatophytes. Other predisposing factors include obesity and excessive perspiration. Tinea cruris is frequently

Fig. 77.7 Majocchi's granuloma. Perifollicular inflammation and pustules on the buttocks due to *Trichophyton rubrum*.

Fig. 77.8 Tinea cruris. Note the arciform erythematous border on the upper inner thigh.

TINEA CRURIS: COMMON CAUSATIVE PATHOGENS	
Dermatophyte	**Clinical features**
Trichophyton rubrum	• Most common cause of tinea cruris • Infection tends to be chronic • Fungus not viable in scale (e.g. on furniture, rugs, linens) for long periods of time • Frequent extension to buttocks, waist and thighs
Epidermophyton floccosum	• Commonly associated with "epidemics" of tinea cruris in locker rooms or dormitories • Infection is acute (rarely chronic) • Arthroconidia are viable in scale (e.g. on furniture, rugs, linens) for long periods of time • Infection rarely extends beyond groin region • Causative agent of "eczema marginatum" (well-demarcated borders with multiple small vesicles or, sometimes, vesiculopustules)
T. mentagrophytes, in particular var. *mentagrophytes*	• Infection tends to be more severe and acute, with intense inflammation and pustule formation • May rapidly spread to the trunk and lower extremities, causing a severe inflammatory condition • Often acquired from animal dander

Table 77.9 Tinea cruris: common causative pathogens.

Fig. 77.9 Tinea manuum. Diffuse scaling of the palm of one hand, with accentuation in the creases.

associated with tinea pedis because clothing that is brought over the feet is contaminated and then comes in contact with skin in the groin region.

The initial sign of infection is usually an area of erythema and pruritus in the fold between the scrotum and the inner thigh. Characteristic lesions are sharply demarcated with a raised, erythematous, scaly advancing border that may contain pustules or vesicles. The lesion may initially be circinate and then become serpiginous. The disease can remain unilateral or become bilateral.

The duration of infection depends on the causative pathogen. Infections with *T. rubrum* and many other anthropophilic species tend to be chronic (sometimes even leathery and lichenified), while the zoophilic form of *T. mentagrophytes* (var. *mentagrophytes*) and other animal-acquired strains often cause acute infections with a prominent inflammatory component (with or without pustules; see Table 77.9). The scrotum itself is generally spared in tinea cruris. If the scrotum is involved or there are erosions or satellite pustules, cutaneous candidiasis should be considered. Measures to prevent recurrences of tinea cruris include wearing loose clothing, drying thoroughly after bathing, using topical powders, weight reduction (if obese), laundering contaminated clothing and linens, and treating concomitant tinea pedis.

Tinea manuum

Dermatophyte infections on the dorsal aspect of the hand have a clinical presentation similar to tinea corporis. However, dermatophyte infection of the palm and interdigital spaces has distinct characteristics and is referred to as tinea manuum. The reason for the two different clinical pictures is thought to be related to the lack of sebaceous glands on the palms. The typical causative organisms are the same as those for tinea pedis and tinea cruris: *T. rubrum*, *T. mentagrophytes* and *E. floccosum*. Two non-dermatophyte fungi that cause "tinea manuum" are *Scytalidium dimidiatum* and *S. hyalinum*.

Moccasin-type tinea pedis is often present in patients with tinea manuum, and the two share clinical features such as chronicity and hyperkeratosis. Tinea manuum is usually non-inflammatory and often unilateral ("two feet and one hand syndrome") (Fig. 77.9); there is diffuse hyperkeratosis of the palms and digits that fails to respond to emollients[14]. An important clinical clue is tinea unguium of the involved

hand, but infection of all the fingernails is uncommon. Other presentations include exfoliative, vesicular and papular variants. The differential diagnosis may include psoriasis, irritant or allergic contact dermatitis, dyshidrosis and a "dermatophytid" reaction.

Tinea barbae

Tinea barbae is a dermatophytosis that involves the bearded areas of the face and neck in men. The causative organisms are typically zoophilic dermatophytes, namely *T. mentagrophytes* var. *mentagrophytes* and *T. verrucosum*. Infection with *Microsporum canis* or *T. rubrum* is uncommon. In certain geographic regions, other anthropophilic dermatophytes (*T. schoenleinii, T. violaceum* and *T. megninii*) are endemic and cause tinea barbae. Disease is often acquired from animals. In the past, a common cause of infection was contaminated razors in barbershops. With the increased use of disposable razors and disinfectants, however, the incidence of tinea due to this source has been dramatically reduced.

Because zoophilic organisms are the most common culprit and due to the large number of terminal hair follicles in the affected areas, the clinical presentation tends to be severe, with intense inflammation and multiple follicular pustules. Abscesses, sinus tracts, bacterial superinfection and even kerion-like boggy plaques can develop. Patients may have constitutional symptoms such as malaise as well as lymphadenopathy and even scarring alopecia. A second type of tinea barbae is superficial, less inflammatory, and similar to tinea corporis; *T. rubrum* is usually the causative agent in this variant (Fig. 77.10). Alopecia may be present in the center of the lesion, but it is reversible. Other conditions that can mimic tinea barbae include bacterial folliculitis, viral infections (herpes simplex or zoster), acne vulgaris, cervicofacial actinomycosis and a dental sinus tract. Spontaneous resolution may occur if all of the infected hairs fall out.

Fig. 77.10 Tinea barbae. More superficial form due to *Trichophyton rubrum*. Several follicular pustules are seen. *Courtesy, Jean L Bolognia, MD.*

Tinea faciei

While some dermatophyte infections of the face have classic features, e.g. scale, annular configuration, pustules in the border (Fig. 77.11), others can be more difficult to diagnose clinically ("tinea incognito"; see Table 77.8) and require a high index of suspicion.

Tinea capitis

Tinea capitis (Fig. 77.12) is a common dermatophyte infection of the scalp in children, whereas adult infection occurs infrequently. The causative pathogens are members of only two genera: *Trichophyton* and *Microsporum*. *T. tonsurans* is currently the most common cause of tinea capitis in the US (accounting for ≥90% of cases), with a predilection for individuals of African descent[15], and *M. canis* is the second most frequent etiology. The incidence of tinea capitis due to *T. violaceum* (which is endemic in Africa) has recently increased in some areas of the US, likely reflecting immigration patterns. Worldwide, there is a great deal of variation in the epidemiology of tinea capitis, but *T. tonsurans* (as well as *M. canis*) has become a major cause of tinea capitis in Europe and elsewhere. The anthropophilic dermatophyte *M. audouinii*, which was once common and then subsequently diminished secondary to social and therapeutic advances, has recently reappeared in Europe and may potentially re-emerge in the US as well.

Different clinical presentations arise from the various causative organisms. For example, *T. tonsurans* causes an endothrix infection (see below), which classically results in "black dot" tinea capitis due to hair breakage near the scalp. In contrast, *M. audouinii* is an ectothrix form of tinea capitis that typically presents with dry, scaly patches of alopecia ("gray patch" tinea capitis). The pathogenicity of the culprit organism is not the only factor in determining the severity of disease; the host immune response to the organism plays an important role as well. Tinea capitis can range from a non-inflammatory scaling that resembles seborrheic dermatitis (especially *T. tonsurans*; Fig. 77.12A) to a severe pustular eruption with alopecia, known as a kerion. Alopecia with or without scale is the most common presentation of tinea capitis (Fig. 77.12B–D). The alopecia may occur in discrete patches or involve the entire scalp. Use of dermoscopy can highlight "comma", "corkscrew" and dystrophic broken hairs that represent clues to the diagnosis of tinea capitis (see Ch. 69)[16]. Many patients have posterior cervical and posterior auricular lymphadenopathy, which is helpful in differentiating tinea capitis from less inflammatory scalp disorders that cause alopecia, such as alopecia areata.

A kerion results from advanced disease coupled with an exaggerated host response that leads to boggy, purulent plaques with abscess formation and associated alopecia (Fig. 77.12E). Some patients may even

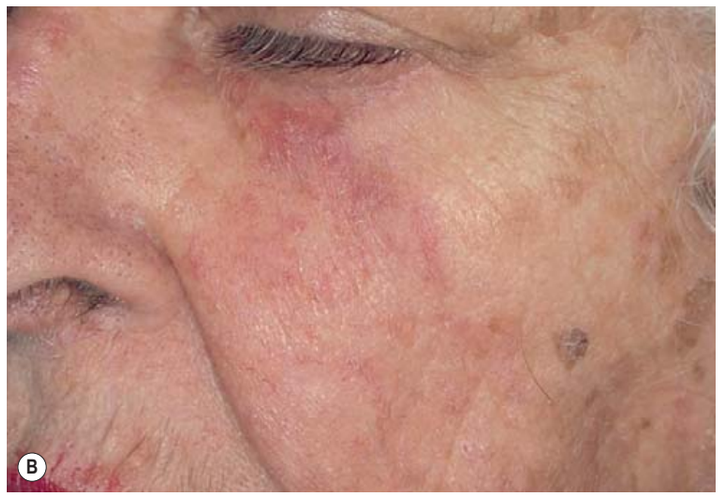


Fig. 77.11 Tinea faciei. A Area of erythema and scale on the nose and philtrum of a young child. **B** Serpiginous lesion with minimal scale on the upper cheek of an older woman. *A, Courtesy, Julie V Schaffer, MD. B, Courtesy, Jean L Bolognia, MD.*

become systemically ill with extensive lymphadenopathy. The hair in the affected area usually returns, but the longer the infection persists, the more likely the alopecia will be permanent. If a kerion is misdiagnosed as a bacterial abscess or other condition and treated (after incision and drainage or partial excision) with antibiotics, the infection will likely worsen, thereby increasing the likelihood of scarring alopecia.

The "carrier state" of *T. tonsurans* tinea capitis refers to a clinical situation in which there are no obvious signs or symptoms of a scalp infection, yet a positive fungal culture is obtained. Although also seen in children, this typically occurs in adults who have been exposed to infected children. The carriers shed the fungus and are considered contagious[17]. Consequently, some experts advocate treating all carriers with oral or topical antimycotics.

For those dermatophytes that invade hair, three patterns of invasion exist: endothrix, ectothrix and favus (Fig. 77.13):

- The *endothrix pattern* results from infection with anthropophilic fungi in the genus *Trichophyton* and is characterized by non-fluorescent arthroconidia within the hair shaft (see Fig. 77.12F). The clinical presentation varies from scaling to "black dots" with patchy alopecia to kerion formation. *T. tonsurans* and *T. violaceum* are important causes of endothrix infection.
- The *ectothrix pattern* occurs when arthroconidia are formed from fragmented hyphae outside the hair shaft (see Fig. 77.13). Cuticle destruction ensues. Ectothrix infection can be fluorescent (*Microsporum*) or non-fluorescent (*Microsporum* and *Trichophyton*), as determined by Wood's lamp examination. Clinical features vary from patchy, scaly alopecia with little inflammation (that may mimic alopecia areata) to kerion formation.
- *Favus* is the most severe form of dermatophyte hair infection and is most frequently caused by *T. schoenleinii*. Hyphae and air spaces are observed within the hair shaft, and a bluish-white fluorescence by Wood's light examination is typically seen. Favus presents as thick, yellow crusts composed of hyphae and skin debris ("scutula"). Scarring alopecia may develop in chronic infections (Fig. 77.14).

There are many scalp and hair disorders that lead to scaling or alopecia (scarring and non-scarring) that are not due to fungal infections (see Table 77.8). However, one should always consider and exclude a fungal infection (especially in children), because the treatment is typically quite simple and effective, and chronic untreated tinea capitis can lead to

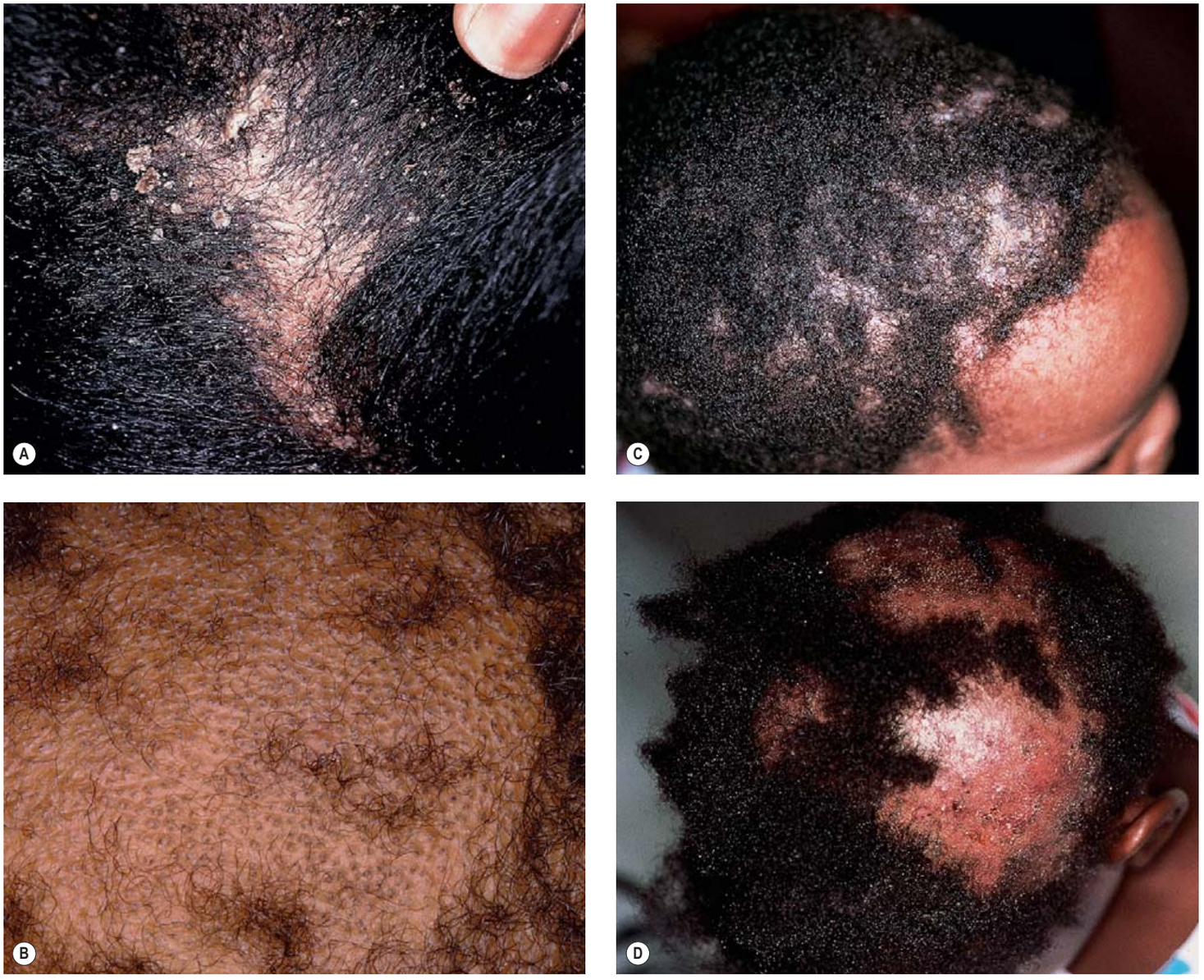


Fig. 77.12 Tinea capitis. The range of clinical presentations of tinea capitis due to *Trichophyton tonsurans*, from mild scalp scaling (**A**) to patchy alopecia with black dots (**B**) or scale (**C**) to large areas of alopecia with pustules and scale-crust (**D**). *B, Courtesy, Louis A Fragola, Jr, MD.*

Continued

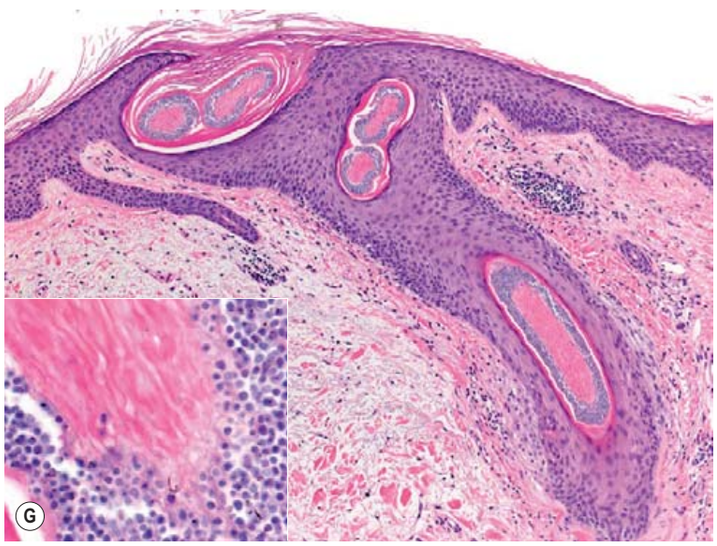


Fig. 77.12 Tinea capitis (cont'd). E Kerion formation due to *T. tonsurans.* Microscopic examination of involved hairs demonstrates an endothrix pattern (KOH–chlorazol black stain; **F**). Histologic examination shows arthroconidia and hyphae within hair shafts to the level of Adamson's fringe (limit of the zone of keratinization; insert) (**G**). *G, Courtesy, Lorenzo Cerroni, MD.*

scarring alopecia. Oral therapy is required, as the drug must penetrate the hair follicle to be effective. Also important in the management of tinea capitis are preventive measures. Because the disease is contagious, all individuals residing with the infected patient should be examined for signs of tinea capitis and appropriately treated. Chronicity may develop if a child is continually re-exposed from untreated family members. Appropriate adjunctive treatment for household contacts (as well as the patient) includes regular (e.g. every other day) use of an antifungal shampoo, such as 2% ketoconazole or 2.5% selenium sulfide, until the patient is free of disease. Although routine screening in schools is difficult, screening children who have two or more infected classmates may be beneficial[18]. Also, combs, brushes and headwear used by the patient should be disinfected or (preferably) discarded.

Tinea pedis

Tinea pedis is a dermatophyte infection of the soles and interdigital web spaces of the feet. Infection of the dorsal aspect of the foot is considered tinea corporis. The feet are the most common location for dermatophyte infections, and the majority of the US adult population has experienced tinea pedis. This condition is more common in adults than children and is found around the world, affecting both sexes. The lack of sebaceous glands and the moist environment created by occlusive shoes are important factors in the development of tinea pedis[19]. In fact, tinea pedis is uncommon in populations that do not wear shoes. However, the fungus may be acquired from going barefoot (locker rooms, gyms, public facilities). Host factors that contribute to the pathogenesis of tinea pedis have yet to be identified.

The dermatophytes that are typically responsible for tinea pedis are *T. rubrum*, *T. mentagrophytes*, *E. floccosum* and *T. tonsurans* (in children). Non-dermatophyte pathogens that produce clinical findings identical with tinea pedis include *S. dimidiatum* and *S. hyalinum* (moccasin and interdigital types) and, occasionally, *Candida* spp. (interdigital type). There are four major clinical types of tinea pedis, as outlined in Table 77.10: moccasin (Fig. 77.15A), interdigital (Fig. 77.15B), inflammatory (Fig. 77.15C) and ulcerative. Each type has different associated morbidities and complications that can affect diagnostic considerations and therapeutic options. These include bacterial superinfection (the "dermatophytosis complex"), dermatophytid reactions, cellulitis (especially in patients who have venous hypertension, harvested saphenous veins and chronic edema), and even osteomyelitis leading to amputation in diabetics. Other conditions that can mimic tinea pedis are listed in Table 77.8. KOH examination and culture easily differentiate the moccasin and inflammatory forms of tinea pedis from these entities[20]. Erythrasma can be diagnosed with Wood's light examination because of its "coral red" fluorescence. The use of oral antifungals should be considered in diabetics, immunocompromised patients, and those with moccasin-type tinea pedis. Finally, other dermatophyte infections often occur together with tinea pedis – in particular, tinea cruris, onychomycosis and tinea manuum – and these sites should be examined.

Tinea unguium (dermatophytic onychomycosis)

Onychomycosis is a term used to encompass all fungal infections of the nail and includes those due to dermatophytes as well as non-dermatophytes. It is divided into three patterns based upon the point of fungal entry into the nail unit:

- *distal/lateral subungual,* with invasion via the hyponychium (most common; Fig. 77.16A–C)
- *superficial white,* with direct penetration into (and usually confinement to) the dorsal surface of the nail plate (often due to *T. mentagrophytes* [var. *interdigitale*]; see Fig. 77.16D,E)
- *proximal subungual,* with invasion under the proximal nail fold (frequently in immunocompromised hosts).

Onychomycosis can be challenging to manage due to difficulties in diagnosis, the requirement for long treatment periods, potential side effects of systemic medications, and frequent recurrences. Although many consider onychomycosis solely as an annoyance, patients with the condition often complain of discomfort and pain associated with trimming the nails, running, and other activities such as dancing. In addition, serious complications such as cellulitis can result from onychomycosis, especially in patients who are diabetic or

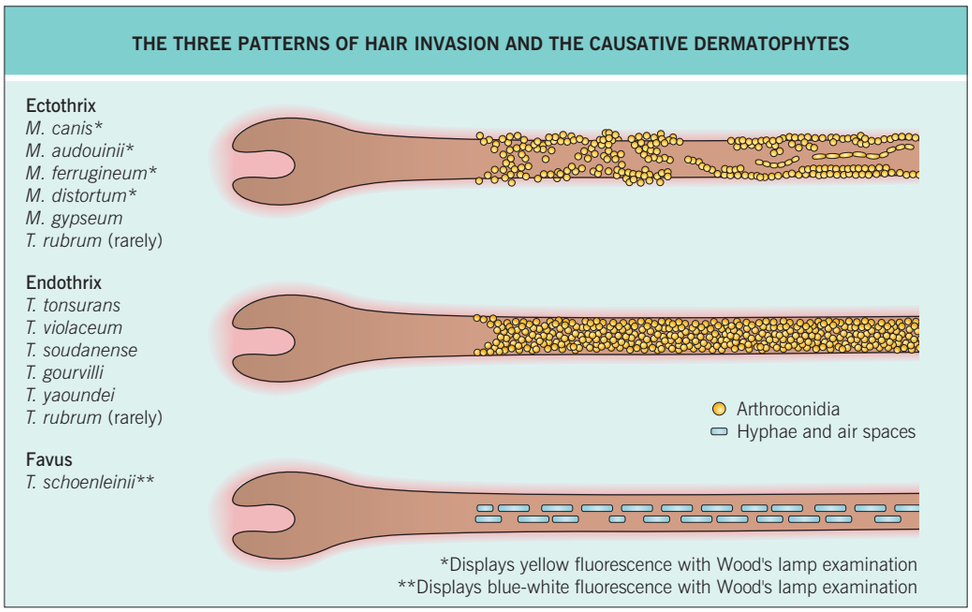


Fig. 77.13 The three patterns of hair invasion and the causative dermatophytes.

Fig. 77.14 Favus due to *Trichophyton schoenleinii*. Scarring alopecia with erosions and several scutula on the occipital scalp. The latter represent masses of keratin plus fungi.
Courtesy, Israel Dvoretzky, MD.

immunocompromised. Infections with non-dermatophytes such as *Fusarium* spp. (see below) are of particular concern in the latter group.

Tinea unguium refers specifically to dermatophyte infection of the nail unit. It occurs worldwide, affects men more often than women, and is frequently associated with chronic tinea pedis. Trauma and other nail disorders represent predisposing factors. All dermatophytes can cause tinea unguium, but the most common causative pathogens are *T. rubrum*, *T. mentagrophytes* and *E. floccosum* (and, rarely, *Microsporum* spp.).

Toenail infections are considerably more common than fingernail infections, and only rarely does fingernail onychomycosis occur without concurrent toenail infection. A single nail may be involved, but more commonly, multiple nails on one or both hands or feet are affected. In the distal/lateral subungual type, invasion of the hyponychial region leads to hyperkeratosis of the nail bed. With further progression of infection, there is yellowing and thickening of the distal nail plate as well as onycholysis (Fig. 77.16A,B), which provides an ideal environment for further proximal invasion and growth of the dermatophyte. Eventually, the entire nail bed and plate may become involved (total dystrophic pattern).

The clinical appearance of the superficial white type of onychomycosis can vary based on host factors (e.g. immunosuppression) and the causative organism. Discrete white patches (Fig. 77.16D) are seen in the classic form due to *T. mentagrophytes* (var. *interdigitale*). However, transverse striate bands (Fig. 77.16E), origination from the proximal nail fold (which may overlap with the proximal subungual type if there is also invasion under the nail fold), and deeper invasion of the nail plate can also occur. These variants are more likely be caused by *T. rubrum* (with more invasive forms observed in healthy children as well as individuals with HIV infection) or (with deep invasion of the nail plate) non-dermatophyte molds such as *Fusarium* spp.[21]

Although nail dystrophy can be the result of a number of insults and conditions (e.g. trauma, psoriasis and inherited disorders; see Ch. 71; Fig. 77.17), an estimated 50% or more of cases are due to fungal infection (onychomycosis). Dermatophytes account for ~90% of cases of onychomycosis, and the remainder are due to yeasts or non-dermatophyte molds (Table 77.11). *Candida* spp. are often found in association with chronic paronychia (see Ch. 71), and infection of the nail may occur in this setting. The fingernails are usually affected, with ridging, yellow discoloration and onycholysis. *Candida* spp. are a relatively common cause of onychomycosis in children less than 3 years of age, and nail involvement also represents a manifestation of chronic mucocutaneous candidiasis (see Ch. 60).

Pathology

Tinea pedis, manuum, faciei, cruris and corporis are usually diagnosed via KOH examination (see Fig. 77.5B,C) and occasionally with fungal cultures. The chlorazol black E stain can help to highlight fungal elements in KOH preparations. Use of calcofluor, a fluorescent stain specific for the chitin in the fungal cell wall, and examination with a fluorescent microscope can also demonstrate fungi (apple-green fluorescence).

If biopsies are performed of cutaneous dermatophyte infections, hyphae are seen within the stratum corneum; the fungi are made more apparent by PAS or silver stains. In dermatophytoses affecting glabrous skin, spongiosis, parakeratosis and pustules are often seen. In onychomycosis, hyphae and arthroconidia may be visible in the nail plate and nail bed with PAS staining, and little to no inflammation is generally present[2]. Histologic examination of formalin-fixed, PAS-stained nail plates is a quick and reliable method for diagnosing onychomycosis (see Fig. 77.16F), with a sensitivity of 80% to >95% (compared to 35–60% for culture alone)[22]. Biopsy specimens of tinea capitis, Majocchi's granuloma and tinea barbae can demonstrate hyphae or arthroconidia within hair shafts and are usually done if the diagnosis is suspected but KOH examination and culture are negative. However, false-negative results are a potential problem and tissue should also be sent for culture.

Table 77.10 The four major types of "tinea pedis" caused by dermatophytes and non-dermatophytes. CMI, cell-mediated immunity.

THE FOUR MAJOR TYPES OF "TINEA PEDIS" CAUSED BY DERMATOPHYTES AND NON-DERMATOPHYTES			
Type	**Causative organism**	**Clinical features**	**Treatment considerations**
Moccasin	*Trichophyton rubrum* *Epidermophyton floccosum*	Diffuse hyperkeratosis, erythema, scaling and fissures on one or both plantar surfaces; frequently chronic and difficult to cure*; may be associated with fungal CMI deficiency	Topical antifungal plus product with urea or lactic acid; may require oral antifungal therapy
	Scytalidium hyalinum *S. dimidiatum*		
Interdigital	*T. mentagrophytes* (var. *interdigitale*) *T. rubrum* *E. floccosum*	Most common type; erythema, scaling, fissures and maceration in the web spaces; the two lateral web spaces are most commonly affected; "dermatophytosis complex" (fungal infection followed by bacterial invasion†) can develop; pruritus common; may extend to dorsum and sole of foot	Topical antifungal; may require topical or oral antibiotic if superimposed bacterial infection
	S. hyalinum *S. dimidiatum* *Candida* spp. *Fusarium* spp.		
Inflammatory (vesicular)	*T. mentagrophytes* (var. *mentagrophytes*)	Vesicles and bullae on the medial foot; often associated with the dermatophytid reaction‡	Topical antifungal usually sufficient
Ulcerative	*T. rubrum* *T. mentagrophytes* *E. floccosum*	Typically an exacerbation of interdigital tinea pedis; ulcers and erosions in the web spaces; commonly secondarily infected with bacteria; seen in immunocompromised and diabetic patients	Topical antifungal; may require topical or oral antibiotics if secondary bacterial infection (common)

Dermatophytes Non-dermatophytes

*Because of the thickness of stratum corneum on plantar surfaces and the inability of *T. rubrum* to elicit an immune response sufficient to eliminate the fungus[20].

†Often *Pseudomonas, Proteus* spp.or *Staphylococcus aureus.*

‡Reaction to fungal elements presenting as a dyshidrotic-like eruption on the ÿngers and palms (culture negative for fungus).

Fig. 77.15 Tinea pedis. Diffuse scaling in the moccasin type (**A**), maceration between the third and fourth toes in the interdigital form (**B**), and erythema, scale-crust and bullae in the inflammatory form (**C**). The patient in A also has involvement of the right hand, i.e. one hand–two feet tinea. *B, Courtesy, Jean L Bolognia, MD.*

Differential diagnosis

Careful clinical examination is the first and most important step in diagnosing dermatophyte infections. Because many other conditions can mimic dermatophytoses (see Table 77.8 and Fig. 77.17), KOH examination and/or culture are often necessary to confirm the diagnosis. Guidelines for proper specimen collection are outlined in Figure 77.18. Because all dermatophytes have hyaline hyphae, they essentially look the same in KOH preparations (see Fig. 77.5B). When identification of the particular species will provide helpful information or culture is needed to confirm the diagnosis, the specimen is cultured at 25–30°C (and in some instances also at 37°C) for 2 to 4 weeks.

Colonial morphology, microscopic examination of conidia (the asexual propagules formed *de novo* by the fungus), noting the growth rate/requirements, and biochemical tests allow precise identification of the dermatophyte. The presence or absence of microconidia (usually small and unicellular) and macroconidia (usually larger and multicellular) and the typical features of each (such as shape and cell wall texture) remain fairly consistent among genera (Fig. 77.19). Other distinguishing microscopic features include the identification of arthroconidia (infective fungal elements) and chlamydoconidia. Sometimes, conidia may not be present in culture ("sterile" organism), and the hyphal patterns (spiral, pectinate, antler, racquet, and nodular bodies)

Fig. 77.16 Tinea unguium. Onycholysis, yellowing, crumbling and thickening of the fingernails (**A**), thumb nails (**B**) and toenails (**C**) in the distal/lateral subungual variant. Diffuse (**D**) and striate (**E**) white discoloration of the toenail in the superficial white variant. Hyphae within a formalin-fixed, PAS-stained nail plate (**F**). *A, C, D, Courtesy, Jean L Bolognia, MD. B, Courtesy, Louis A Fragola, Jr, MD. F, Courtesy, Mary Stone, MD.*

may be important in identification of the organism. The color, texture and topography of the colony are features that are typical of, or even unique to, a particular species (see Table 77.5).

Dermatophytes are able to grow on media containing cycloheximide (e.g. Mycosel®, DTM [dermatophyte test medium]). However, some clinically relevant non-dermatophyte fungi do not (e.g. *Scopulariopsis brevicaulis*, *Aspergillus* spp., *Cryptococcus neoformans*, *Candida tropicalis*, *Pseudallescheria boydii*, *Trichosporon beigelii*). These can potentially be missed if specimens, in particular from nails, are grown only on cycloheximide-containing media[23].

Treatment

Topical antifungals (see Ch. 127) are the first-line treatment for many patients with uncomplicated, localized cutaneous dermatophyte infections such as tinea corporis, tinea cruris and tinea pedis. The major potential adverse reaction is irritant (or, occasionally, allergic) contact dermatitis, usually from the alcohols or other components in the vehicle[24]. Systemic antifungal therapy, although associated with a higher incidence of side effects (including potentially severe adverse reactions; see Ch. 127), is required to cure certain infections, including tinea manuum, capitis and unguium. Suggested regimens are presented

in Table 77.12. In general, oral treatment is also needed for infections involving extensive areas of skin, in hairy sites other than the scalp (e.g. tinea barbae), or associated with excessive inflammatory reactions. The adjunctive use of topical products containing glycolic acid, lactic acid or urea may help to reduce the amount of hyperkeratosis in infections such as tinea manuum and tinea pedis.

Treatment of tinea unguium deserves special consideration. Oral antifungal therapy is generally required (see Table 77.12), with the occasional exception of classic superficial white onychomycosis, and removal of dermatophytomas (subungual pockets of densely packed hyphae) is recommended. Although "cure" rates of up to 80% (or higher with prolonged therapy) have been reported[7] with newer antifungal drugs (itraconazole, fluconazole and terbinafine), recurrent disease, especially in toenails, is common. Preventive measures include breathable footwear and cotton socks, antifungal or absorbent powders, frequent nail clipping and avoiding re-exposure (e.g. not going barefoot in locker rooms). Old shoes often harbor large numbers of infectious organisms and should be discarded or treated with disinfectants or antifungal powders.

Combination therapy consisting of a topical corticosteroid plus a topical antifungal has been advocated by some clinicians for the treatment of dermatophyte infections. While a reduction in inflammation can be seen, the negative effects of high-potency corticosteroids on immune defenses coupled with restrictions on treatment duration to avoid side effects such as striae lead to an unacceptable failure rate[25]. Low-potency corticosteroids are a safer option when anti-inflammatory activity is needed.

Invasive dermatophytosis

Rarely, dermatophytes proliferate within the dermis. Invasion or dissemination of dermatophytes is most often seen in the setting of a chronic dermatophyte infection (most commonly *T. rubrum*) in an

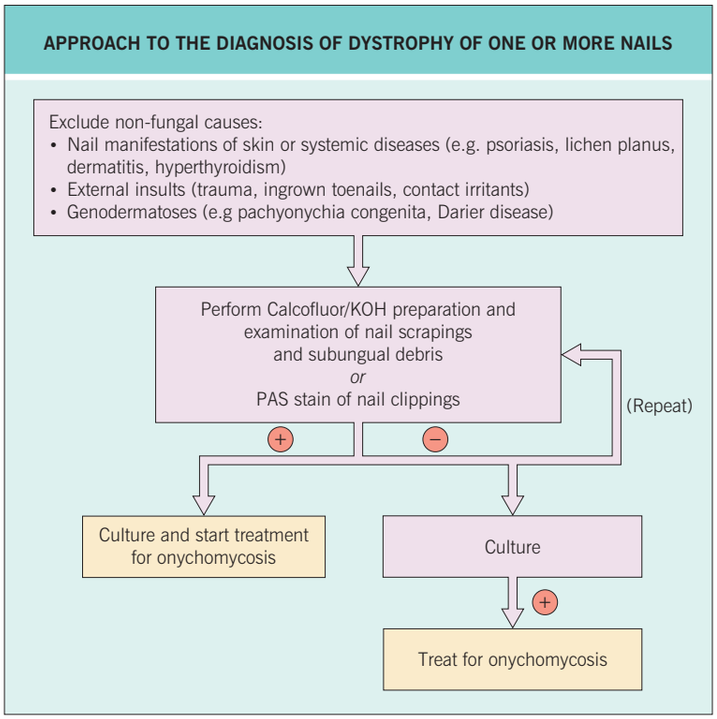


Fig. 77.17 Approach to the diagnosis of dystrophy of one or more nails. An organized approach is essential in correctly and efficiently diagnosing onychomycosis.

NON-DERMATOPHYTE MOLDS THAT CAN CAUSE ONYCHOMYCOSIS

Fungus	Key features
Fusarium spp.	Superficial white pattern*
Aspergillus spp.	Superficial white pattern*
Acremonium	Superficial white pattern*
Scopulariopsis brevicaulis	Lateral yellow–brown discoloration KOH of nail reveals lemon-shaped conidia and atypical hyphae
Scytalidium hyalinum	Whitish discoloration of the nail†
Scytalidium dimidiatum	Black discoloration of the nail†

*Deeper invasion of the nail plate can also occur.
†May also be associated with paronychia or tinea pedis.

Table 77.11 Non-dermatophyte molds that can cause onychomycosis.

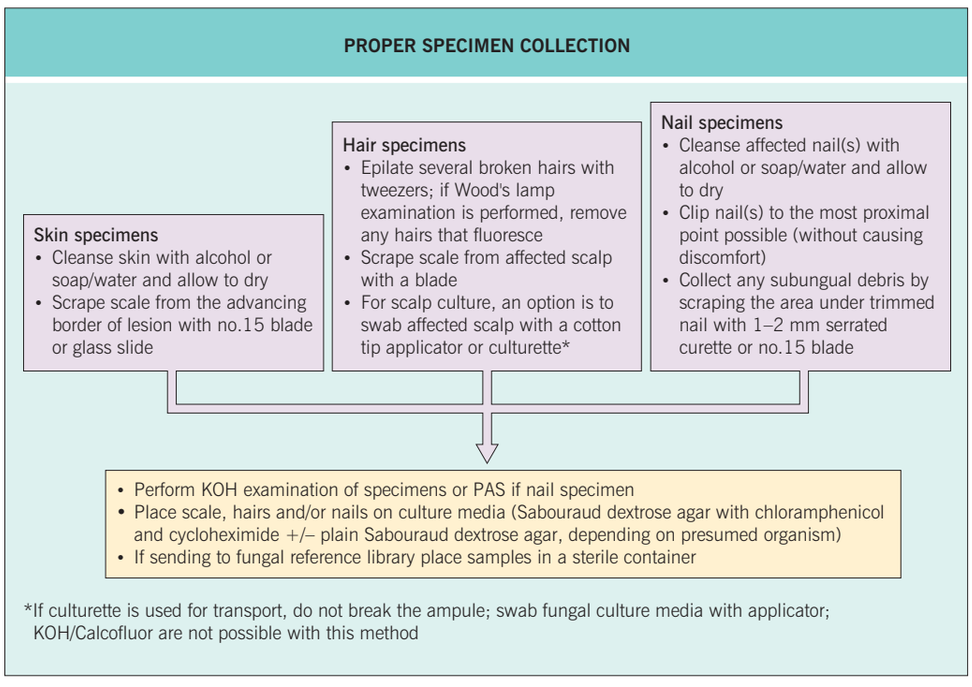


Fig. 77.18 Proper specimen collection. Proper collection of skin, hair and nails is important. Following these simple guidelines will help the clinician to achieve the most accurate diagnosis. *Courtesy, Judy Warner.*

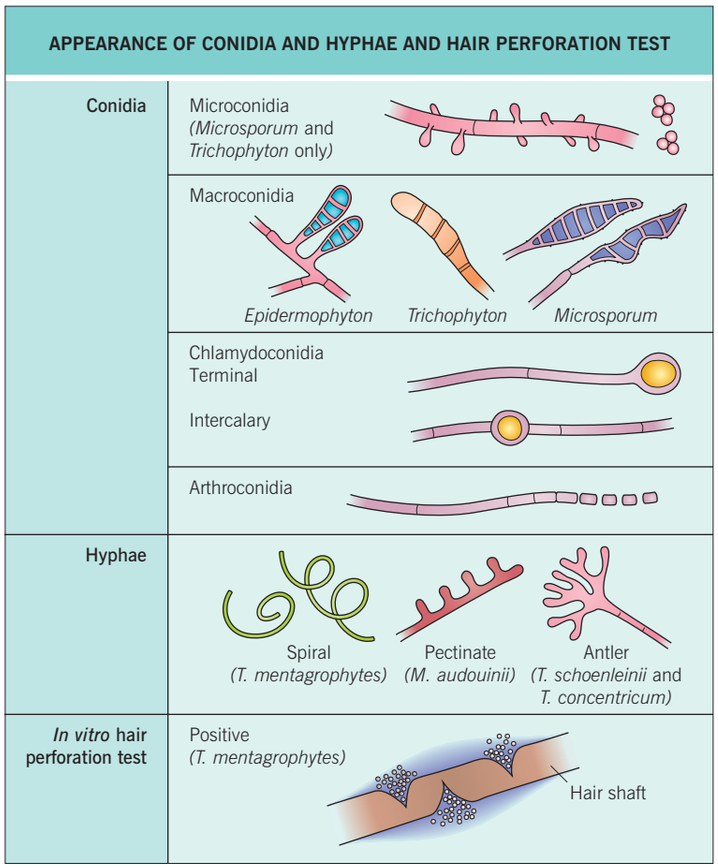


Fig. 77.19 Microscopic appearance of various forms of conidia and hyphae and the *in vitro* hair perforation test.

immunosuppressed individual. Hematogenous spread can lead to an acute onset of ulcerating or draining dermal and subcutaneous nodules. A more indolent process can also occur and most often presents as tender nodules on the extremities. Currently, the recommended treatment is surgical excision (if localized) and systemic itraconazole or terbinafine[26,27], but amphotericin B, griseofulvin and ketoconazole have also been used successfully.

Mucocutaneous Candida *infections*

Mucocutaneous candidiasis has a wide spectrum of clinical presentations. Early descriptions of oral candidiasis (thrush) were made by Hippocrates. In the 1940s, the association between oral antibiotics and candidal infections was recognized. Oral infection often presents as thrush (white exudate resembling cottage cheese; pseudomembranous form) (Fig. 77.20A,B) or as a patch of erythema (chronic atrophic form); it can also produce adherent white plaques (chronic hyperplastic form) as well as glossitis (painful atrophy of the dorsal tongue). Other presentations include denture stomatitis, angular cheilitis (perlèche) (Fig. 77.20C), vulvovaginitis and balanitis (see Ch. 73). Predisposing factors for mucocutaneous candidiasis include diabetes mellitus, xerostomia, occlusion, hyperhidrosis, the use of corticosteroids and broad-spectrum antibiotics, and immunosuppression, including HIV infection[28]. In the case of angular cheilitis, overlap of the skin at the angles of the mouth, which is common in edentulous and elderly patients, is a key contributing factor, along with use of orthodontic appliances, drooling, atopic dermatitis, and (occasionally) iron or vitamin deficiencies (e.g. B_2).

Cutaneous *Candida* infections present with markedly erythematous, sometimes erosive, patches that are often accompanied by satellite papules and pustules (Fig. 77.20D–F). The most common sites of involvement are intertriginous zones (e.g. submammary, beneath pannus, inguinal creases, intergluteal fold) and the scrotum, as well as the diaper area in infants. Candidiasis is sometimes superimposed on intertriginous seborrheic dermatitis or psoriasis. *Candida* can also infect the periungual areas (e.g. in the setting of chronic paronychia), nails (see Onychomycosis above) and web space between the third and fourth fingers (erosio interdigitalis blastomycetica; Fig. 77.20G), especially in individuals whose hands are frequently exposed to water.

Mucocutaneous candidiasis is most commonly due to *C. albicans*, followed by *C. tropicalis*. The diagnosis is established by the presence of budding yeast and pseudohyphae on KOH examination (see Fig. 77.5D) and by a positive fungal culture. *C. albicans* and *C. stellatoidea* can be distinguished by their ability to form chlamydocondidia on cornmeal-Tween 80 agar. Identifying and removing predisposing factors is very important in the management of mucocutaneous candidiasis. Topical nystatin and azole antifungals are generally effective therapy[29,30]. When oral therapy is required, options include fluconazole and itraconazole (see Ch. 127). Treatment options for various forms of mucocutaneous candidiasis are outlined in Table 77.13.

Chronic mucocutaneous candidiasis

This is discussed in detail in Chapter 60. Chronic mucocutaneous candidiasis is not a single entity but rather a clinical manifestation of a number of disorders, including primary immunodeficiencies. Patients have defects in cellular immunity that prevent effective handling of *Candida* organisms, leading to chronic, sometimes therapy-resistant, infections of the skin (including granulomatous lesions), nails and mucosae. Some patients have associated autoimmune endocrinopathies as well as alopecia areata and vitiligo. Therapy involves oral fluconazole and itraconazole (see Table 77.13).

Granuloma gluteale infantum/adultorum and perianal pseudoverrucous papules/nodules

Granuloma gluteale infantum/adultorum is a reactive condition that occurs in the setting of chronic, severe irritant contact dermatitis in the anogenital region of either infants with chronic diarrhea or children and adults with encopresis or urinary incontinence[31]. It exists on a spectrum with perianal pseudoverrucous papules/nodules, and the term *Jacquet's erosive dermatitis* has been used for a variant with prominent punched-out erosions[32]. Erythematous to violaceous nodules and plaques, often ovoid in shape and sometimes eroded, develop on the vulva (Fig. 77.21), lower buttocks, perianal region and occasionally the scrotum. Similar to *Candida* infections, satellite pustules may also be seen. In addition to chronic irritation (e.g. from frequent loose stools), predisposing factors may include occlusion, topical corticosteroid use and candidal infection. Histologically, epidermal hyperplasia, a variably dense mixed inflammatory infiltrate in the dermis and vascular proliferation are typically observed. Although barrier creams and topical antifungal agents may have some benefit, the condition tends to persist until the irritant trigger is eliminated.

SUBCUTANEOUS MYCOSES

The "subcutaneous" mycoses are due to a large and diverse group of organisms that cause disease when implanted or otherwise introduced into the dermis or subcutis. Chromoblastomycosis, mycetoma, sporotrichosis and lobomycosis are discussed in detail in this section.

Another chronic subcutaneous fungal infection is basidiobolomycosis, which is caused by *Basidiobolus ranarum*. Although this organism is an environmental saprophyte that is found worldwide, the associated infection occurs most commonly in children living in tropical and subtropical climates. The most common portal of entry is the skin, typically after arthropod bites or minor trauma. Clinically, the disease manifests as a solitary, painless, indurated subcutaneous nodule or swelling of the thigh or buttock. The classic treatment is saturated solution of potassium iodide (SSKI; see Ch. 100), although successful results have been reported with ketoconazole and trimethoprim–sulfamethoxazole. Surgical excision is not recommended. A related organism, *Conidiobolus coronatus*, causes an infection that has similar clinical features but typically affects the face (especially the nasal region).

Although not a true fungal disease, protothecosis is treated with antifungal agents and is due to implantation. *Prototheca* (usually *P. wickerhamii*) is a genus of achlorophyllic algae that can be introduced

SUGGESTED SYSTEMIC REGIMENS FOR DERMATOPHYTOSES				
	Fluconazole	**Griseofulvin**	**Itraconazole***	**Terbinafine**
Tinea pedis (moccasin type)/ tinea manuum (adults)	150–200 mg/week × 4–6 weeks	750–1000 mg/day (microsize) or 500–750 mg/day (ultramicrosize) × 4 weeks	200–400 mg/day × 1 week	250 mg/day × 2 weeks
Tinea pedis (moccasin type)/ tinea manuum (children)	6 mg/kg/week × 4–6 weeks	15–20 mg/kg/day (microsize suspension) × 4 weeks	3–5 mg/kg/day (maximum 400 mg) × 1 week	Daily dosing as for tinea capitis (see below) × 2 weeks
Tinea unguium (adults)	Toenail ± fingernail involvement: 150–200 mg/week × 9 months	1–2 g/day (microsize) or 750 mg/day (ultramicrosize) until nails are normal†	200 mg/day × 12 weeks or 200 mg bid × 1 week/month for 3–4 consecutive months	250 mg/day × 12 weeks
	Fingernail involvement only: 150–200 mg/week × 6 months	1–2 g/day (microsize) or 750 mg/day (ultramicrosize) until nails are normal†	200 mg/day × 6 weeks or 200 mg bid × 1 week/month for 2 consecutive months	250 mg/day × 6 weeks
Tinea unguium (children)	6 mg/kg/week × 3–4 months (fingernails) or 5–7 months (toenails)	20 mg/kg/day (microsize suspension) until nails are normal†	5 mg/kg/day (<20 kg), 100 mg/day (20–40 kg), 200 mg/day (40–50 kg), or 200 mg bid (>50 kg) × 1 week/ month for 2 (fingernails) or 3 (toenails) consecutive months	62.5 mg/day (<20 kg), 125 mg/day (20–40 kg) or 250 mg/day (>40 kg) × 6 weeks (fingernails) or 12 weeks (toenails)
Tinea corporis (extensive, adults)	150–200 mg/week × 2–4 weeks	500–1000 mg/day (microsize) or 375–500 mg/day (ultramicrosize) × 2–4 weeks	200 mg/day × 1 week	250 mg/day × 1 week
Tinea corporis (extensive, children)	6 mg/kg/week × 2–4 weeks	15–20 mg/kg/day (microsize suspension) × 2–4 weeks	3–5 mg/kg/day (maximum 200 mg) × 1 week	Daily dosing as for tinea capitis (see below) × 1 week
Tinea capitis (adults)‡	6 mg/kg/day × 3–6 weeks	10–15 mg/kg/day (ultramicrosize; usually maximum 750 mg/day) × 6–8 weeks	5 mg/kg/day (maximum 400 mg) × 4–8 weeks	250 mg/day × 3–4 weeks§
Tinea capitis (children)‡	6 mg/kg/day × 3–6 weeks	20–25 mg/kg/day (microsize suspension) × 6–8 weeks	5 mg/kg/day (maximum 500 mg) × 4–8 weeks	Granules: 125 mg (<25 kg), 187.5 mg (25–35 kg) or 250 mg (>35 kg) × 3–4 weeks§

*Not approved in US for use in children.
†No longer commonly used for this indication.
‡Combined with 2.5% selenium sulfide shampoo or ketoconazole 2% shampoo; "id" reaction should not be confused with a medication allergy.
§Not recommended for *Microsporum canis*, unless given at double-dose.

Table 77.12 Suggested systemic regimens for dermatophytoses. bid, twice daily.

into the skin via trauma, often in the setting of exposure to contaminated water. Common clinical presentations include solitary cutaneous plaques (sometimes eczematous), nodules or ulcers, as well as olecranon bursitis. The extremities are the most frequent sites of involvement. Although immunocompetent patients typically have chronic, stable disease, patients who are immunocompromised can have widespread disease, including algemia. Protothecosis is difficult to treat; surgical excision and systemic antifungals (e.g. amphotericin B) are more effective in immunocompetent hosts.

Chromoblastomycosis

Synonyms: ■ Chromomycosis ■ Cladosporiosis ■ Verrucous dermatitis ■ Phaeosporotrichosis ■ Pedroso's disease ■ Fonseca's disease

Introduction

Chromoblastomycosis presents as a "verrucous dermatosis" and is caused by several genera of dematiaceous (pigmented) fungi. Typically chronic in nature, an expanding verrucous plaque on the lower, or occasionally upper, extremity is the classic presentation. There are six fungi that are responsible for the vast majority of cases: *Fonsecaea pedrosoi*, *Fonsecaea compacta*, *Fonsecaea monophora*, *Phialophora verrucosa*, *Cladophialophora carrionii (formerly Cladosporium carrionii)* and *Rhinocladiella aquaspera*. The clinical presentation and colonial morphologies of each of these fungi are very similar, and differentiation is based on microscopic and conidial characteristics.

History

Pedroso first recognized chromoblastomycosis in 1911. Four years later, Medlar and Lane reported the first case in the US (in Boston)[33]. There has been some confusion over the proper naming of this condition. At one point, chromoblastomycosis was thought to be closely related to blastomycosis; however, cellular division does not occur via budding ("blasto-") but rather via internal septation, hence the preference for the term "chromomycosis". Nonetheless, some authors have argued that the latter is also confusing, because it has the same meaning as phaeohyphomycosis (see below), and so they prefer the term "chromoblastomycosis".

Epidemiology and pathogenesis

Chromoblastomycosis is most commonly found in tropical and subtropical climates and occasionally in temperate zones such as the US, Europe and Canada. Farmers, miners and others working in rural areas are at higher risk than the general population. Men 20 to 60 years of age are more often affected, probably due to increased occupational exposure, which accounts for up to 90% of cases[34].

The fungi responsible for causing chromoblastomycosis are found in the soil and in decaying plants and wood. The disease is typically

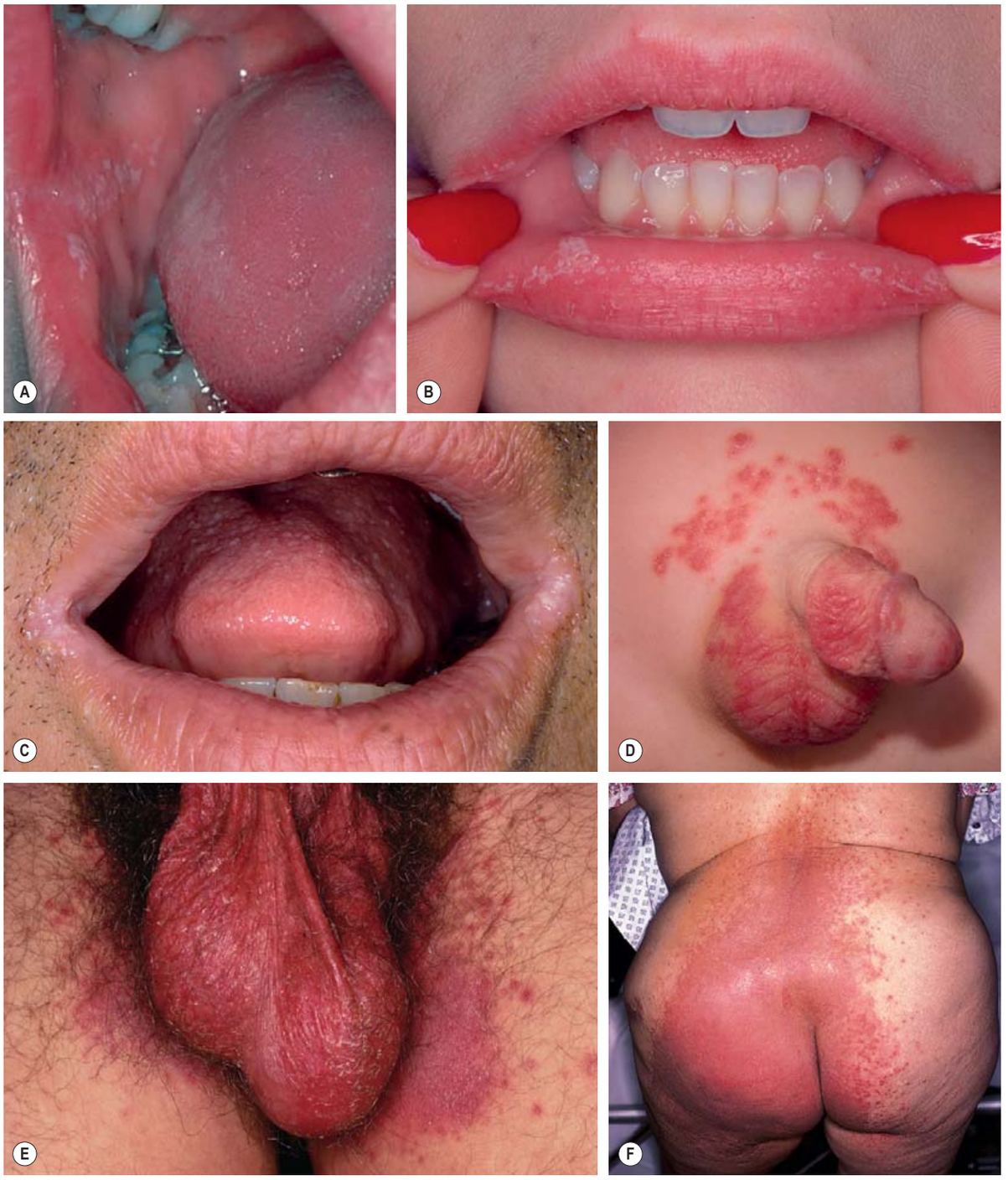


Fig. 77.20 Mucocutaneous candidiasis. A, B Thrush with "cottage cheese"-like exudate on the buccal mucosa (**A**) and labial mucosa at the vermilion border (**B**). **C** Angular cheilitis (perlèche). **D** Candidiasis of the suprapubic area and penis in a young boy. Note the collarettes of scale on the coalescing, brightly erythematous papules. **E** Candidiasis of the scrotum and medial thighs with beefy red erythema, scale and satellite papules. **F** This infection occurred in a hospitalized patient with diabetes mellitus who was receiving broad-spectrum antibiotics. Note the multiple satellite lesions. **G** Erosio interdigitalis blastomycetica in the classic location between the third and fourth fingers. *A, Courtesy, Judit Stenn, MD. B, D, Courtesy, Louis A Fragola, Jr, MD. C, Courtesy, Kalman Watsky, MD. E, G, Courtesy, Eugene Mirrer, MD.*

TREATMENT OF MUCOCUTANEOUS *CANDIDA* INFECTIONS	
Type of infection	**Treatment regimen (adult doses unless otherwise indicated)**
Oropharyngeal candidiasis	**Nystatin*** 100 000 units/ml suspension: • Children and adults – 4–6 ml swish and swallow qid • Infants – 2 ml (1 ml inside each cheek) qid **Clotrimazole*** 10 mg troche five times daily **Fluconazole**† 200 mg po on day 1, then 100–200 mg po daily *Continue treatment for 7–14 days after clinical resolution*
Esophageal candidiasis	**Fluconazole*** 200–400 mg po on day 1, then 100–400 mg daily **Itraconazole** 200 mg po daily **Voriconazole** 200 mg po or iv bid **Posaconazole** 400 mg po bid **Caspofungin** 50 mg po iv daily *Continue treatment for 7–14 days following resolution of symptoms, for a minimum of 21 days total*
Candidal vulvovaginitis‖	**Fluconazole*** 150 mg po single dose or (for severe disease or an immunosuppressed patient) three doses at 3-day intervals **Butoconazole** 2% vaginal cream, 5 g daily for 1–3 days **Clotrimazole***,‡ • 1% vaginal cream (or other topical formulation), 5 g daily for 7–14 days • Vaginal suppositories: 100 mg daily for 7 days or 200 mg daily for 3 days **Miconazole***,‡ • 2% cream, 5 g daily for 7 days • Vaginal suppositories: 100 mg daily for 7 days, 200 mg daily for 3 days, or 1200 mg single dose **Tioconazole*** 6.5% cream, 5 g single dose **Terconazole*** • 0.4% or 0.8% cream, 5 g daily for 7 or 3 days, respectively • 80 mg vaginal suppository daily for 3 days **Nystatin** 100 000 units vaginal suppository daily for 14 days *For suppression in patients with recurrent infections:* **Fluconazole** 150 mg weekly for 6 months **Clotrimazole** vaginal suppository, 200 mg twice weekly or 500 mg weekly for 6 months
Chronic mucocutaneous candidiasis	**Fluconazole** • *Eradication:* 400–800 mg po daily for 4–6 months • *Suppressive therapy*§: 200 mg po daily
Candidal intertrigo or balanitis‖	Topical **imidazole** (see Table 127.15) or **ciclopirox** cream or lotion twice daily for 1–2 weeks or until resolved¶ *Systemic agents for recalcitrant or severe cases*§*:* **Fluconazole** • 50 to 100 mg po daily for 14 days • 150 mg po weekly for 2–4 weeks **Itraconazole** 200 mg po twice daily for 14 days

*Recommended as first-line treatment for immunocompetent individuals.
†Recommended as first-line treatment for HIV-infected patients (or other immunosuppressed individuals) with moderate to severe disease, recurrent infection or a CD4 count of <200 cells/mcl.
‡Preferred treatments (with 7-day regimens) for pregnant patients.
§Outside the setting of chronic mucocutaneous candidiasis, chronic systemic suppressive therapy in immunosuppressed individuals is discouraged due to the risk of colonization with resistant organisms.
‖In cases of recurrent vulvovaginitis, treatment of the patient's sexual partner is controversial; in contrast, for recurrent balanitis, eradication of *Candida* from the sexual partner's genital tract is generally recommended.
¶After clinical resolution, topical treatments may be continued twice weekly to prevent recurrence.

Table 77.13 Treatment of mucocutaneous *Candida* infections. Candidal onychomycosis can be treated with the oral fluconazole or itraconazole regimens described for tinea unguium in Table 77.12. See Table 127.20 for pediatric dosing of fluconazole. bid, twice daily; iv, intravenously; po, orally; qid, four times daily.

contracted from trauma to the lower extremities, particularly as a result of not wearing shoes. The organism is introduced into the dermis or subcutis via implantation.

Clinical features

The disease usually presents as a papule or nodule on the leg, which progresses to form a verrucous (Fig. 77.22A) or granulomatous (Fig. 77.22B) plaque. The lesion may appear annular as the central portion resolves with scarring. Several lesions may coalesce to form a multi-nodular mass, or multiple lesions may exist as discrete islands scattered within unaffected skin. It is thought that autoinoculation from scratching may be responsible for the spread of infection. Typically, only one extremity is affected. Sometimes, a subcutaneous nodule or mass is the presenting lesion. There are usually no constitutional symptoms.

Pathology

Pseudoepitheliomatous hyperplasia, intraepidermal abscesses, and suppurative and granulomatous inflammation within the dermis are the typical histologic findings. Round, pigmented bodies, which are said to resemble "copper pennies" (6 to 12 microns; Fig. 77.22C), are present in the dermis, both extracellularly and within giant cells. These are unique to chromoblastomycosis and are also known as "Medlar bodies" or sclerotic bodies[2]. Detection of organisms via PCR of tissue samples has been reported for the more common species.

Differential diagnosis

After a thorough clinical examination, a biopsy is indicated to exclude other infectious diseases characterized by granulomatous lesions associated with scarring, such as cutaneous tuberculosis, tertiary syphilis, blastomycosis and leishmaniasis. Mycetoma is another implantation mycosis that commonly affects the lower extremity, but edema, draining sinuses and grains point to this diagnosis. If a biopsy is not feasible, a KOH examination of scrapings from a pigmented portion of the lesion can be performed. The presence of Medlar bodies is diagnostic (excluding other entities such as blastomycosis), but hyphae may also be seen. Culture growth (at 25–30°C) is slow and the different genera produce similar colonial morphologies. The major differences between genera

Fig. 77.21 Granuloma gluteale infantum. **A** Multiple dark red papules and nodules in the anogenital region of an infant. **B** Coalescing moist, pink papules on the vulva and suprapubic area of another infant. *A, Courtesy, Robert Hartman, MD. B, Courtesy, Julie V Schaffer, MD.*

are the microscopic features, in particular the type of conidia produced in culture. The three major types are:

- Cladophialophora-like (long branching side chains with shield cells at branch points)
- Phialophora-like (conidia resemble overflowing buds in a vase)
- Rhinocladiella-like (overall configuration similar to a mascara brush).

Treatment

Therapeutic options are limited. Some authors have advocated heat therapy based on evidence that the causative organisms will not grow at high temperatures. For small lesions, surgical excision can be attempted together with systemic antifungal treatment. 5-Flucytosine combined with either oral thiabendazole, intravenous amphotericin B or an oral triazole has been reported to be efficacious. Itraconazole alone (200–400 mg/day) administered for at least 6 months may have cure rates of up to 80–90%[35]. Successful treatment with voriconazole or posaconazole has also been described. In a small series, oral terbinafine (500 mg/day) given for at least 7 months was described as effective[36]. Other treatment considerations include cryosurgery and the addition of antibiotics if the lesion is secondarily infected.

Mycetoma

Synonyms: ■ Madura foot ■ Maduromycosis

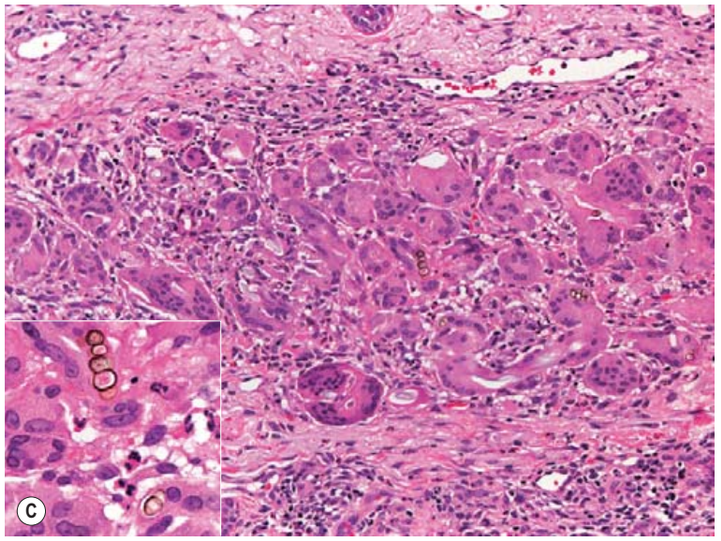


Fig. 77.22 Chromoblastomycosis. Annular and figurate plaques due to central clearing and scarring with a verrucous surface on the arm (**A**) and a more granulomatous appearance on the leg (**B**). **C** Brown-colored sclerotic body (see insert) within a mixed granulomatous and neutrophilic dermal infiltrate. *C, Courtesy, C Massone, MD.*

Introduction

Mycetoma (often referred to as "Madura foot") is a Greek term for "fungal tumor". It is a granulomatous infection of dermal and subcutaneous tissue that may extend to muscle or even bone and is due to implantation. Mycetoma is differentiated from other mycoses by its characteristic draining sinuses containing grains (sclerotia, sulfur granules) and local edema. Three different subtypes exist: actinomycotic mycetoma (caused by filamentous aerobic and anaerobic organisms, e.g. *Nocardia brasiliensis* [see Ch. 74], *Actinomadura madurae*),

eumycotic mycetoma (caused by true fungi) and botryomycosis (caused by true bacteria, e.g. *Staphylococcus aureus, Pseudomonas* spp.; see Ch. 74).

History and epidemiology

Dr John Gill provided the first formal description of mycetoma in 1842, in Madura (India), hence the name "Madura foot"[37]. Mycetoma is endemic to tropical and subtropical climates. Actinomycotic mycetoma is more prevalent in Central and South America, while eumycotic mycetoma is more common in Africa. The typical patient is a man between 20 and 50 years of age.

Pathogenesis

In most cases, causative organisms are acquired from the soil via direct inoculation into the skin, leading to a dermal and subcutaneous fungal infection. Deeper invasion can subsequently occur, i.e. to muscle and bone. This process may occur rapidly or over many years. Sometimes, multiple sites of involvement appear in the vicinity of the original lesion, likely due to multiple injuries rather than contiguous spread of disease. Lack of protective footwear, malnutrition, and exposed cuts and abrasions are risk factors for infection.

Clinical features

The foot is the most common site of infection, followed by the hand, trunk and scalp. Involvement is typically unilateral and begins as a painless papule. Once the subcutaneous tissues are infected, the surrounding soft tissue swells and eventually forms purulent draining sinuses (Fig. 77.23A). The drainage contains the characteristic grains (sclerotia), which represent compact masses of fungal colonies and vary in size from minute to almost a centimeter in diameter. Invasion of deeper tissues then ensues, and sometimes cavities are formed within involved bone. Surprisingly, this disease is generally asymptomatic. All three subtypes can have a similar clinical presentation.

Pathology

Pseudoepitheliomatous hyperplasia is a common histologic finding that accompanies suppurative and granulomatous inflammation of the dermis and subcutis as well as fibrosis. The characteristic grains represent tightly packed colonies of organisms (Fig. 77.23B). Estimation of the diameter of the filaments comprising the grain (as compared to the size of the nuclei of surrounding inflammatory cells) allows a distinction between eumycotic (thicker filaments) and actinomycotic (thin, fine filaments) mycetomas. Special stains, e.g. silver (Grocott) and Brown–Brenn can aid in distinguishing the subtype (see Ch. 0).

Differential diagnosis

To establish the diagnosis of mycetoma, both the history and clinical appearance are important considerations. However, differentiating mycetoma from conditions with similar presentations (e.g. actinomycosis, coccidioidomycosis) requires laboratory evaluation. In addition to noting the color of the grains (Table 77.14), KOH examination, Gram stain and culture (bacterial and fungal) of exudate from a sinus tract and/or tissue should be performed.

Fig. 77.23 Madura foot. A Note the soft tissue swelling of the foot as well as multiple nodules with pustular discharge. **B** Histology of a grain, which represents tightly packed colonies of fungal organisms. *B, Courtesy, Lorenzo Cerroni, MD.*

COLORS OF GRAINS AND GEOGRAPHIC DISTRIBUTION OF EUMYCOTIC AND ACTINOMYCOTIC MYCETOMAS

Pathogen		Grain color	Geographic distribution
Eumycotic	*Madurella mycetomatis*	Black	North, Central and South America; Caribbean, Africa, Europe, Middle East, Asia
	Madurella grisea	Black	North, Central and South America; Africa, Asia
	Leptosphaeria senegalensis	Black	Africa, Asia
	*Pseudallescheria boydii**	White	North, Central and South America; Africa, Oceania, Asia, Europe
	Acremonium spp.	White	North, Central and South America; Asia, Europe, Oceania
Actinomycotic	*Nocardia brasiliensis*†	White	Worldwide (all *Nocardia* spp.)
	Nocardia asteroides‡	White	
	Nocardia caviae	Yellow–white	
	Actinomyces israelii§	Yellow–white	Worldwide
	Actinomadura madurae	Pink or white	Worldwide
	Actinomadura pelletieri	Red	North and South America, Africa, India
	Streptomyces somaliensis	Brown or yellow	Africa (arid regions)

*Most common cause in the US.
†Most common cause in Mexico.
‡Rare.
§Very rare cause of mycetoma; usually causes actinomycosis (e.g. cervicofacial, thoracic and abdominal), which also has draining sinuses and grains.

Table 77.14 Colors of grains and geographic distribution of eumycotic and actinomycotic mycetomas.

Treatment

For the best outcome, eumycotic mycetoma must be diagnosed early and surgically excised (including a large margin of normal surrounding tissue) before the underlying bone becomes involved. Once the lesion has been excised, systemic antifungal therapy is administered. Amphotericin B is not very effective. Depending upon the particular fungus, ketoconazole, itraconazole, fluconazole, voriconazole, posaconazole and terbinafine have been used to treat eumycotic mycetomas[38]. The medical treatment of actinomycotic mycetoma consists primarily of streptomycin or amikacin plus either trimethoprim–sulfamethoxazole or dapsone; therapy is continued for months to years.

Sporotrichosis

Synonym: ▪ Rose gardener's disease

Introduction

Sporotrichosis is a subcutaneous mycosis that is caused by the dimorphic organism *Sporothrix schenckii*. A gardener being pricked by a contaminated rose thorn is a classic vignette for the acquisition of sporotrichosis. Although various clinical presentations are possible, the most common one is a lymphocutaneous or "sporotrichoid" pattern, which refers to the primary inoculation site plus spread of the infection along the lymphatics in a nodular pattern.

Epidemiology

S. schenckii is present in the soil throughout the world. However, sporotrichosis is endemic to Mexico, Central America and South America as well as other areas such as South Africa. In these locations, exposure to the organism typically occurs in individuals who work outdoors. In temperate climates, such as in the US and Canada, the disease most often develops in gardeners, especially those growing orchids and roses. Sphagnum moss is often implicated as the source of *S. schenckii*. All age groups are affected, but it is more common in adults. In the past decade, the incidence of sporotrichosis in the Rio de Janeiro region of Brazil has increased >100-fold due to transmission by infected cats, which (in contrast to humans) harbor large numbers of organisms in cutaneous ulcers[39].

Pathogenesis

Sporotrichosis is most commonly acquired from cutaneous inoculation, especially by vegetation such as thorns and wood. With the exception of cats in Brazil, animal-to-human transmission is rare. Multiple inoculations may occur simultaneously, not to be confused with spread of a single primary lesion. The presentation and course of sporotrichosis depends on the host immune response as well as the size and virulence of the inoculum. In naive hosts, involvement of regional lymphatics ensues. In those with a prior history of exposure to *S. schenckii*, no lymphatic spread occurs, and a "fixed" ulcer[40] or granulomatous plaque develops at the site of inoculation; the latter is often seen on the face (especially in children living in endemic areas).

Extensive cutaneous disease with or without systemic involvement is also possible, especially in an immunocompromised host. Cases of inhaled sporotrichosis have been reported with systemic and cutaneous dissemination, similar to disseminated histoplasmosis and other dimorphic fungal infections.

Clinical features

The initial presentation of sporotrichosis is a single papule at a site of injury, most commonly on the hand, appearing several weeks after inoculation. The lesion then becomes eroded or ulcerated with purulent drainage, but it is generally not painful. Additional lesions appear weeks later, typically developing as dermal and subcutaneous nodules and ulcers along the path of lymphatic drainage (often up the arm; Fig. 77.24A). This is the well-known "sporotrichoid" pattern. The involved lymphatic vessels may become fibrosed[41]. Lesions of "fixed cutaneous sporotrichosis" can have a granulomatous appearance, often with ulceration, and disseminated lesions typically present as subcutaneous nodules.

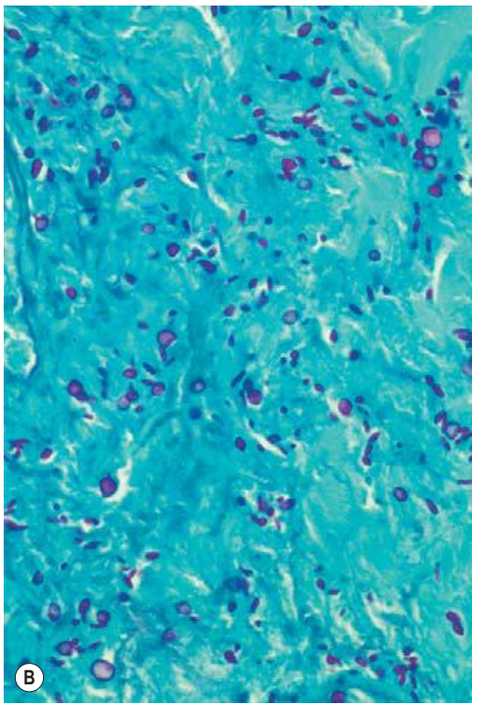


Fig. 77.24 Lymphocutaneous (sporotrichoid) pattern. **A** An eroded nodule on the thumb representing the primary lesion with a secondary lesion along the lymphatics due to sporotrichosis. **B** Multiple yeast forms of *Sporothrix schenckii* in the dermis; note that many of the organisms have the characteristic cigar shape. **C** Ulcerated nodule on the extensor forearm with multiple more proximal nodules due to nocardiosis in a patient with lymphoma who was receiving systemic corticosteroids. *B, Courtesy, Ronald P Rapini, MD. C, Courtesy, Jean L Bolognia, MD.*

Pathology

Histologically, suppurative and granulomatous inflammation is found in the dermis and subcutis. The causative organisms are rarely evident; staining with fluorescent-labeled antibodies may aid in recognition of the cigar-shaped yeast forms, which are difficult to identify. Asteroid bodies are often seen. When numerous fungi are present (e.g. in an

INFECTIOUS CAUSES OF A LYMPHOCUTANEOUS ("SPOROTRICHOID") PATTERN
MOST COMMON
Atypical mycobacteria, especially *M. marinum*, but also other species (e.g. *M. chelonae*, *M. kansasii*)
Sporotrichosis
UNUSUAL
Nocardiosis (Fig. 77.24C)
Pyogenic bacteria (e.g. *Staphylococcus aureus, Streptococcus pyogenes*)
Pseudallescheria boydii
RARE (IN HIGH-INCOME COUNTRIES)
Leishmaniasis
Tularemia*
Tuberculosis*
Dimorphic fungi (other than *Sporothrix schenckii*)
Opportunistic fungi in immunocompromised hosts (e.g. *Fusarium*, *Alternaria* spp.)
Glanders (*Burkholderia mallei)**
Cat scratch disease*
Anthrax
Cowpox
Acanthamoeba spp.
*Often ulceroglandular.

Table 77.15 Infectious causes of a lymphocutaneous ("sporotrichoid") pattern. There are also non-infectious causes such as lymphoma, Langerhans cell histiocytosis and in-transit metastases. In addition, perineural spread of leprosy can mimic a lymphocutaneous pattern.

immunocompromised host), budding yeast and cigar-shaped organisms can often be visualized with PAS (Fig. 77.24B) or silver stains.

Differential diagnosis

When there is a sporotrichoid pattern, the major entity to be excluded is an atypical mycobacterial infection, in particular with *M. marinum*; less common causes are outlined in Table 77.15. As organisms are not typically seen by KOH or histopathologic examination, culture (of pus or tissue) is often required to definitively diagnose sporotrichosis; a nested PCR assay can also be used to detect organisms in clinical samples[42]. *S. schenckii* is a member of the dimorphic family of fungi (see below), and whether a hyphal or yeast form develops depends on the temperature. Growth is rapid at 25°C, revealing a glabrous white to brown mold that becomes firm, wrinkled and more darkly pigmented over time. Microscopically, delicate conidia are clustered at the ends of conidiophores (specialized hyphae); single, thick-walled pigmented conidia can also arise from hyphae. At 37°C, on enriched glucose-containing media, there are slow-growing, whitish, pasty, yeast-like colonies. On microscopic examination of the latter, cigar-shaped budding yeasts are seen. The differential diagnosis of fixed plaque sporotrichosis and disseminated lesions is broad and includes other granulomatous disorders, both infectious and inflammatory.

Treatment

Topical therapy is not effective. Oral saturated solution of potassium iodide (SSKI) has been used with success. Although neither fungistatic nor fungicidal, SSKI is thought to affect the host's immune reaction to the organism. Its cost is low, but it has a bitter taste as well as potential side effects (e.g. iododerma, gastrointestinal upset and thyroid suppression; see Ch. 100). Based upon multicenter, non-randomized trials and case series, the Mycoses Study Group of the Infectious Disease Society of America has recommended itraconazole (100–200 mg/day) for 3–6 months as the treatment of choice for lymphocutaneous or fixed cutaneous sporotrichosis[43]. The drug is generally safe and well tolerated, and the relapse rate is low. Amphotericin B may be indicated in severe or disseminated disease.

Lobomycosis

Synonyms: ■ Keloidal blastomycosis ■ Lacaziosis ■ Lobo's disease

Lobomycosis is a chronic fungal infection characterized by cutaneous nodules that resemble keloids. The causative organism, *Lacazia loboi* (previously known as *Loboa loboi*), is closely related to *Paracoccidioides brasiliensis* and has never been cultured *in vitro*[44]. Lobomycosis occurs in Central and South America and has been linked to contact with dolphins and the marine environment as well as soil and vegetation in rural areas. Infection typically occurs after minor trauma and most often affects men[45].

Lobomycosis presents as asymptomatic, firm, keloid-like nodules that favor the distal extremities, ears (especially the helices) and face but can also affect the trunk (Fig. 77.25A,B). The lesions enlarge slowly over years, forming broad, multinodular plaques that may have a smooth surface or (occasionally) a verrucous appearance and ulceration. Histologic evaluation shows highly characteristic chains of thick-walled, yeast-like cells (known as "brass knuckles") with intercellular bridges (Fig. 77.25C); PAS or silver stains highlight these organisms, which can also be identified in scrapings from the surface of skin lesions[46]. Additional findings include a dermal granulomatous infiltrate and either atrophy or pseudoepitheliomatous hyperplasia of the epidermis. Treatment with surgical excision or cryosurgery is employed if feasible, since antifungal medications are typically ineffective. However, clofazamine and itraconzole may be of some benefit for patients with widespread disease[47].

SYSTEMIC MYCOSES

This section reviews systemic infections caused by opportunistic as well as true fungal pathogens. The true pathogens are generally dimorphic and cause infection in hosts with normal immune status, while opportunistic pathogens, which are generally less virulent, take advantage of the immunocompromised state.

True Pathogens

Introduction

The systemic mycoses due to true pathogens include histoplasmosis, blastomycosis, coccidioidomycosis and paracoccidioidomycosis. They are caused by dimorphic fungi, meaning the organisms can exist in two forms – as molds (with septate hyphae and conidia) in nature and as other forms (usually yeasts) in living tissue and (with the exception of *Coccidioides immitis*) at 37°C. Each pathogen has certain geographic preferences (Fig. 77.26; see below). Acquisition of disease is typically through inhalation of the causative fungi, leading to pulmonary symptoms and pneumonitis. The vast majority of infections resolve spontaneously, and patients are left with strong, specific immunity. Disseminated histoplasmosis and coccidioidomycosis may occur in HIV-infected persons, as can disseminated infections with *S. schenckii* (dimorphic) and *Penicillium marneffei* (dimorphic and opportunistic).

Histoplasmosis

Synonyms: ■ Darling's disease ■ Cave disease ■ Ohio valley disease ■ Reticuloendotheliosis

Introduction

Histoplasmosis is caused by the dimorphic fungus *Histoplasma capsulatum* var. *capsulatum*[48].

Epidemiology

H. capsulatum is found in the soil in warm, moist climates, particularly the Mississippi, Ohio, and St. Lawrence river valleys in the US and Canada. Between 80% and 90% of persons from endemic areas may exhibit positive histoplasmin skin testing[49]. Birds, fowl and even bats are significant reservoirs for histoplasmosis. Because the feces of these animals contain the organisms, the areas in which they live can harbor infectious fungal spores. Caves, schoolyards, construction sites, unoccupied buildings, and chicken coops tend to be high-risk areas.

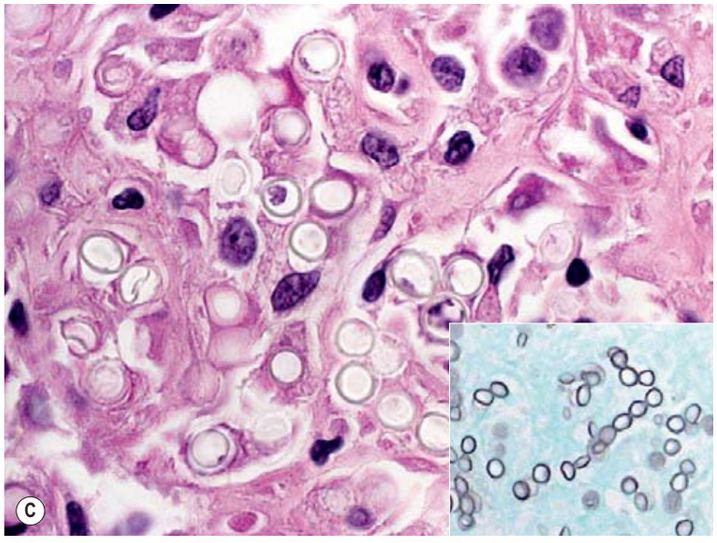


Fig. 77.25 Lobomycosis. A, B Multinodular pinkish-brown plaques with a keloid-like appearance on the helix and back. **C** Spherical organisms with doubly refractile walls are seen within the dermis. Chain formation is commonly observed (insert; Grocott methenamine silver stain). *A, B Courtesy, Regina Carneiro, MD, and Caroline Brandao, MD. C, Courtesy, C Massone, MD.*

Pathogenesis
Histoplasmosis is caused either by inhalation of *H. capsulatum* or, rarely, by direct cutaneous inoculation of the fungus. Immunocompetent hosts can acquire the disease, but immunocompromised hosts have a higher risk of dissemination. Clinical presentations include acute and chronic pulmonary histoplasmosis, disseminated histoplasmosis, and primary cutaneous histoplasmosis. In disseminated histoplasmosis, the most common sites of involvement (after the lung) are the spleen, lymph nodes, bone marrow and liver; calcifications within the lymph nodes, lungs and spleen can serve as evidence of prior infection. Cutaneous manifestations most commonly result from disseminated disease.

Clinical features
The skin lesions of histoplasmosis are nonspecific, making the diagnosis virtually impossible with physical examination alone. When chronic disseminated histoplasmosis occurs in immunocompetent hosts, oral ulcers are the most common mucocutaneous finding; nodules and vegetative plaques are occasionally seen in these individuals. Disseminated histoplasmosis in immunocompromised hosts (including those with HIV infection) can present with mucocutaneous erosions or ulcers as well as multiple erythematous papules or nodules with scale or crust (Fig. 77.27A,B). In African histoplasmosis, a variant caused by *H. capsulatum* var. *duboisii*, most patients present with mucocutaneous, subcutaneous and bone lesions.

Pathology
Microscopic examination of biopsy specimens demonstrates characteristic intracellular yeast forms surrounded by a rim of clearing (Fig. 77.27C). Histiocytes and giant cells are the host cells in histoplasmosis, which is in the differential diagnosis of "parasitized macrophages" (Table 77.16). For easier identification of the fungi, tissue may be stained with PAS or Gomori methenamine silver.

Differential diagnosis
Because cutaneous histoplasmosis has a wide spectrum of clinical presentations, the diagnosis usually rests on histologic examination and culture of involved skin tissue. To evaluate for disseminated disease, bone marrow (sensitivity 70–90%) and blood should be cultured at 25°C and 37°C, with plates held for up to a month. At 25°C, characteristic tuberculate macroconidia develop. Additional diagnostic tests include cultures of sputum and body fluids, polysaccharide antigen testing of blood and urine (useful in detecting disseminated disease), histoplasmin skin testing (indicated only in non-endemic areas), and serologic assays to measure antibody responses (complement fixation, immunodiffusion). Highly sensitive and specific PCR-based assays can be used to identify histoplasmosis in blood and tissue[50,51]. Diseases in the differential diagnosis include other dimorphic fungal infections (e.g. paracoccidioidomycosis), mucocutaneous tuberculosis, major aphthae, and oral squamous cell carcinoma. For primary cutaneous histoplasmosis, entities in Table 77.15 should be considered.

Treatment
In primary, self-limited, asymptomatic histoplasmosis, treatment may not be necessary. However, in symptomatic or disseminated disease, systemic antifungal therapy is required. Amphotericin B, given intravenously and titrated up to 1 mg/kg/day, is currently the most effective therapy and should be used initially for severe disease, followed by itraconazole. In immunocompetent hosts with mild to moderate, stable disease, itraconazole (200–400 mg/day) is the treatment of choice[52]; ketoconazole can also be used. HIV-infected patients with disseminated histoplasmosis require lifelong maintenance therapy with itraconazole after initial treatment with amphotericin B (if required for severe disease). Successful treatment with voriconazole and posaconazole have also been described[53].

Blastomycosis

Synonyms: ▪ North American blastomycosis ▪ Gilchrist's disease

Introduction
Blastomyces dermatitidis is a dimorphic fungus and the causative agent of blastomycosis.

Epidemiology
This disease is endemic to North America, particularly the Mississippi and Ohio river valleys, Great Lakes region and the southeastern states. While all ages and genders can be affected, adult men are most likely to develop systemic infection, and children are more likely to develop acute pulmonary blastomycosis rather than chronic or cutaneous

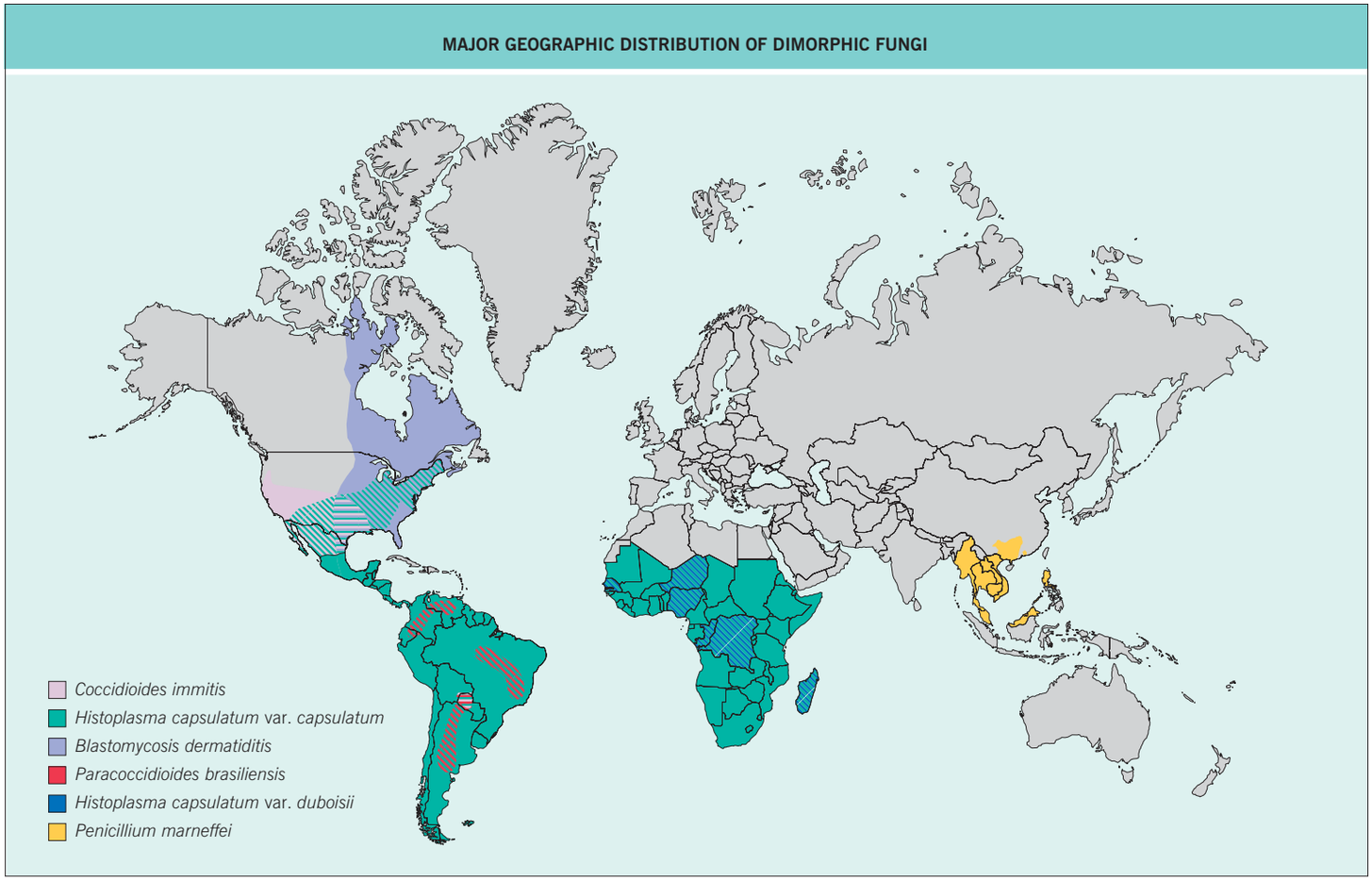


Fig. 77.26 Major geographic distribution of dimorphic fungi. *Courtesy, Braden A Perry, MD.*

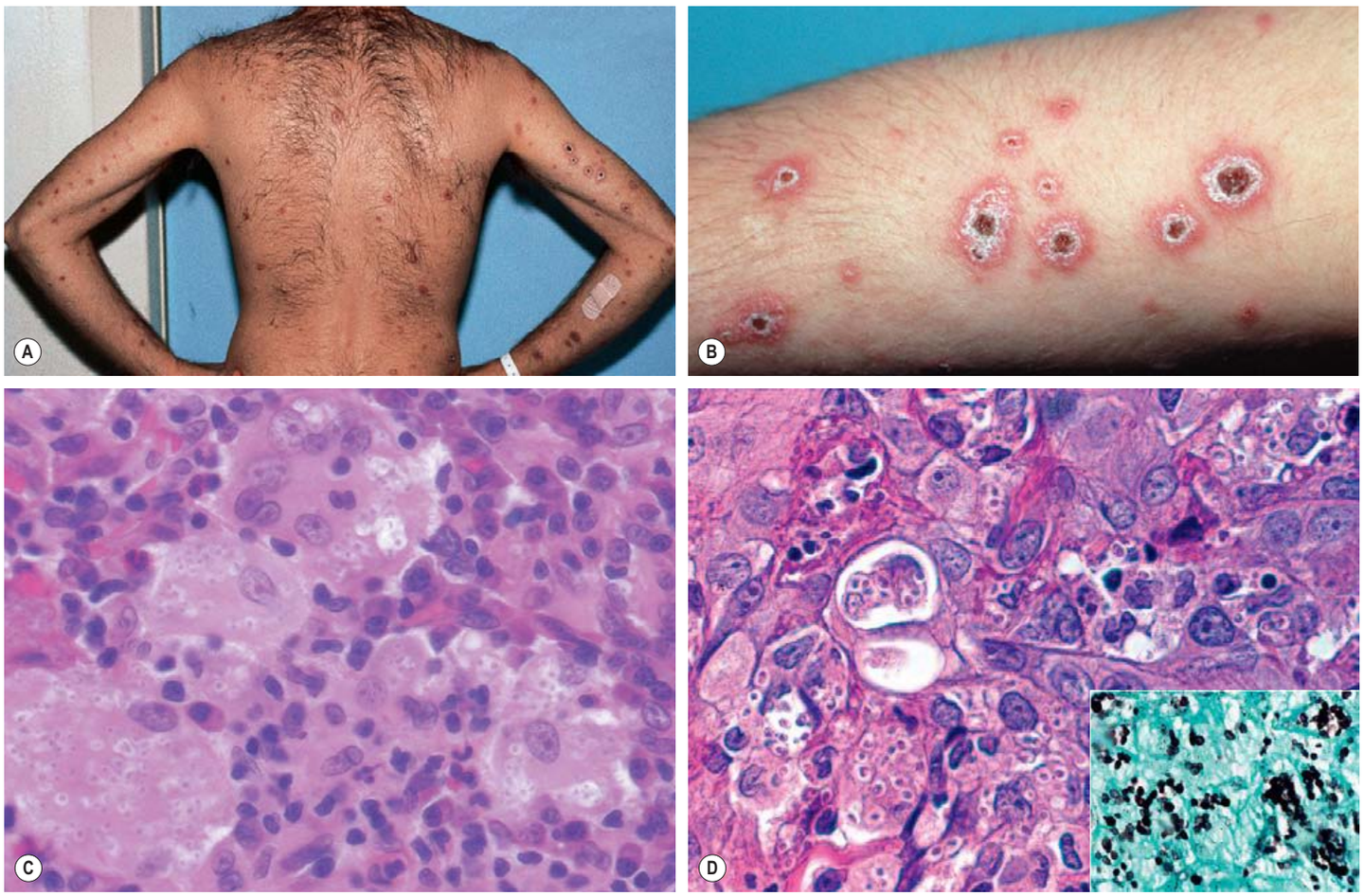


Fig. 77.27 Histoplasmosis. A, B Disseminated papules and nodules with scale-crust in a patient with AIDS. **C** Numerous yeasts within giant cells as well as dermal macrophages. **D** The organisms are highlighted with a Grocott methenamine silver stain (insert). *C, Courtesy, Jennifer McNiff, MD. D, Courtesy, C Massone, MD.*

DIFFERENTIAL DIAGNOSIS OF PARASITIZED MACROPHAGES		
Disease	**Organism**	**Key features**
Rhinoscleroma	*Klebsiella rhinoscleromatis*	Russell bodies (dilated endoplasmic reticulum cisternae containing aggregated immunoglobulins; form within plasma cells); Mikulicz cell (large histiocyte containing organisms)
Granuloma inguinale	*Calymmatobacterium granulomatis*	"Donovanosis"; Donovan bodies (vacuoles containing bacilli within macrophages)
Histoplasmosis	*Histoplasma capsulatum*	Yeast within cytoplasm of macrophages; surrounded by clear halo
Leishmaniasis	*Leishmania* spp.	Non-encapsulated organism; contains nucleus and paranucleus (kinetoplast)
Penicilliosis	*Penicillium marneffei*	Small yeast within macrophages; resembles histoplasmosis

Table 77.16 Differential diagnosis of parasitized macrophages[2].

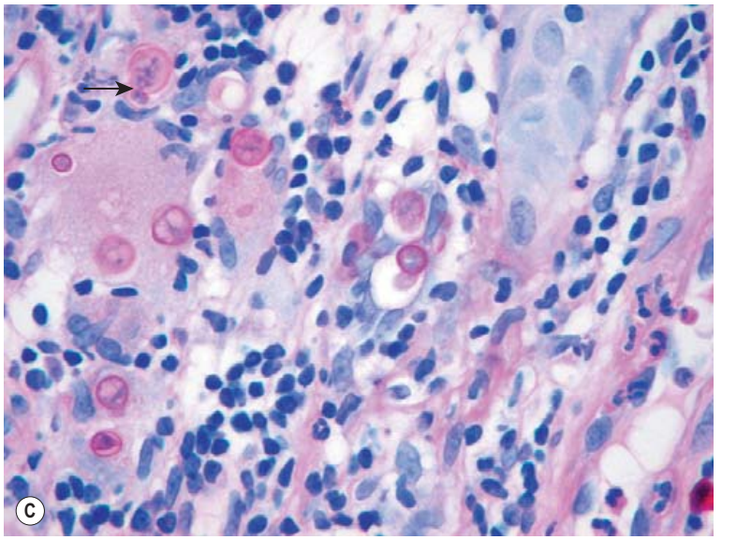


Fig. 77.28 Blastomycosis. A Facial plaque with scale-crust and a border with a granulomatous appearance. **B** Well-demarcated plaques with erosions, central scarring and black crusting. **C** Budding yeast forms in the dermis, several of which are within a giant cell (PAS stain). Note the single, broad-based budding (arrow).
A, Courtesy, Louis A Fragola, Jr, MD. B, Courtesy, Paul Lucky, MD. C, Courtesy, Mary Stone, MD.

disease. The soil is probably the most important source of infection, making those who have occupations with frequent outdoor exposure at higher risk than the remainder of the population. Blastomycosis has also been observed in other countries, including Africa and India.

Pathogenesis
The lungs are typically the first site of infection, via inhalation of organisms. In contrast to infections with other dimorphic fungi, secondary cutaneous dissemination is a common occurrence and may even be the first sign of disease. Cutaneous manifestations are sometimes seen in the absence of overt pulmonary disease. Primary cutaneous blastomycosis is uncommon and results from direct inoculation of the skin from trauma, such as in the laboratory.

Clinical features
The most common cutaneous findings are papulopustules and well-demarcated verrucous plaques with scale-crust (Fig. 77.28A,B) and pustules within their borders. Central ulceration can occur, and more advanced disease may have an appearance similar to pyoderma gangrenosum. The number of lesions can vary from one to several, and they tend to occur on exposed skin. Healing begins centrally and is followed by cribriform scarring. Mucous membrane involvement is occasionally observed.

Pulmonary infection is subclinical in up to 50% of patients with inhalation blastomycosis. Bone involvement may occur and presents as osteomyelitis with rare extension to muscle; genitourinary disease is uncommon.

Pathology
Histologic examination of skin lesions demonstrates pseudoepitheliomatous hyperplasia, suppurative and granulomatous inflammation, and round yeast forms with characteristic broad-based budding and thick, double-contoured walls. This budding pattern helps to differentiate blastomycosis from other fungal infections. Methenamine silver and PAS staining (Fig. 77.28C) allow better visualization of the fungi within giant cells and neutrophilic abscesses. Similar budding yeast forms can be seen in sputum samples.

Differential diagnosis
Cutaneous blastomycosis must be differentiated from other cutaneous infections (e.g. verrucae, folliculitis, nocardiosis, tuberculosis and chromoblastomycosis as well as those due to other dimorphic fungi), inflammatory dermatoses (e.g. pyoderma gangrenosum, halogenoderma, sarcoidosis) and neoplasms (e.g. squamous cell carcinoma). Lesions of blastomycosis-like pyoderma, an exaggerated vegetative response to a prolonged primary or secondary bacterial infection, can also resemble cutaneous blastomycosis. Current or past residence in an area in which blastomycosis is endemic is a helpful clue.

Identification of characteristic broad-based budding yeast forms in pus by KOH or calcofluor examination is diagnostic of blastomycosis. Either skin tissue or pus should be cultured at both 37°C and 25°C. The former temperature allows identification of the budding yeast form, while the characteristic colonial morphology with white spikes (coremia) is observed at 25°C. Other tests such as blastomycin skin testing and complement fixation testing are not usually helpful. PCR-based assays are also available[54].

Treatment

Blastomycosis, like histoplasmosis, requires systemic treatment with amphotericin B (given at the same doses) when severe or progressive. In mild to moderate non-CNS disease, itraconazole (200–400 mg/day) is the treatment of choice[55]. Ketoconazole (400–800 mg/day) and fluconazole (400–800 mg/day) are alternative medications. Voriconazole has shown promising activity against *Blastomyces* both *in vitro* and in animal models[53,56]. In case reports and small series, it has been used successfully to treat blastomycosis, either alone or in combination with liposomal amphotericin B[57]. Occasionally, surgical treatment is indicated.

Coccidioidomycosis

Synonyms: ■ Valley fever ■ Desert rheumatism ■ San Joaquin valley fever ■ California disease

Introduction

Coccidioidomycosis is caused by the dimorphic, highly virulent pathogen *Coccidioides immitis*.

Epidemiology

Coccidioidomycosis occurs predominantly in the summer and fall in the southwestern US, northern Mexico, and Central and South America. The arthroconidia of *C. immitis* are inhaled via dust particles. Primary infection of the respiratory tract shows no gender or age preference, but disseminated disease is more common in Mexicans (5×), African-Americans (25×) and Filipinos (175×). Immunosuppressed states (e.g. HIV infection) and pregnancy also predispose to dissemination; Caucasian women are most likely to have more limited disease.

Pathogenesis

C. immitis is thought to be the most virulent of all fungi. Infectious arthroconidia are inhaled and cause pulmonary infection in the vast majority of people living in endemic areas. The infection is asymptomatic in approximately 60% of affected individuals, while the remainder develop flu-like symptoms several weeks after exposure[58]. Dissemination to the skin and other organs can occur and depends on host factors (see above). Rarely, primary cutaneous coccidioidomycosis results from direct inoculation of the organism into the skin.

Clinical features

Symptomatic primary inhalation coccidioidomycosis typically presents as a flu-like syndrome with fatigue, anorexia, fever, cough and pleuritic chest pain. The cutaneous manifestations can occur alone or in combination with the above symptoms and are grouped into four patterns:

- papules, pustules, plaques, abscesses and sinus tracts, with the face being the most common site of involvement (Fig. 77.29A,B)
- ulcerations
- toxic erythema in the form of a diffuse macular eruption seen early in the disease and sometimes mimicking contact dermatitis
- hypersensitivity reactions such as erythema multiforme and erythema nodosum.

In HIV-infected patients, the papules may resemble molluscum contagiosum. Bone and meningeal involvement can also occur, presenting as osteomyelitis and meningitis, respectively.

Pathology

Biopsy specimens of specific lesions (types 1 and 2 above) reveal characteristic endospore-containing spherules that measure 30–60 microns when mature (Fig. 77.29C). PAS and silver methenamine stains are helpful in identifying immature spherules. A suppurative granulomatous reaction with histiocytes, lymphocytes and giant cells typically surrounds the spherules and released endospores.

Differential diagnosis

Coccidioidomycosis can be diagnosed via direct examination (with KOH or calcofluor) and culture of infected tissue, pus or body fluids. Histologically, sporangia (up to 300 microns in diameter) containing numerous endospores can also be seen in mucosal polyps due to *Rhinosporidium seeberi*. When cultured at 25°C or 37°C, *C. immitis* proliferates quickly (within days) and yields a white to tan to brown colony with varying morphology. Microscopically, septate hyphae that form thick-walled, barrel-shaped arthroconidia are seen at both temperatures. These arthroconidia alternate with thin-walled, vacant cells, which rupture and release the infectious arthroconidia when mature (Fig. 77.30). The infectious hyphal forms produced in culture should be examined with extreme caution, as the examiner is at risk for contracting the disease.

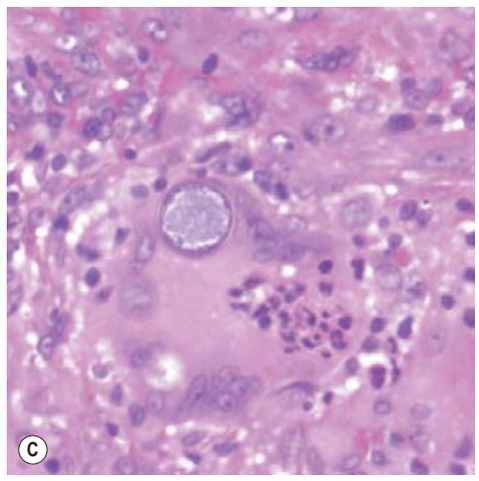


Fig. 77.29 Coccidioidomycosis. Moist erythematous plaque on the face (**A**) and multiple papules and suppurative nodules on the arm (**B**) in two patients living in the southwestern US. **C** An endospore-containing spherule within a giant cell. *C, Courtesy, Jennifer McNiff, MD.*

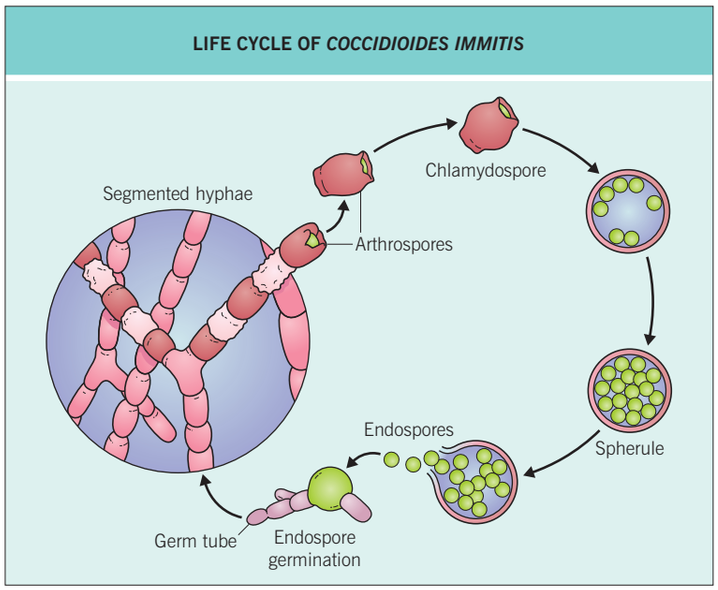


Fig. 77.30 Life cycle of *Coccidioides immitis*.

Serologic testing and exoantigen testing are useful in making the diagnosis of coccidioidomycosis. PCR-based assays are also available, and *in situ* hybridization has been described[54,59].

Treatment

As in the other dimorphic fungal infections, systemic antifungal therapy is required for severe or disseminated disease. Amphotericin B is the most effective medication, and the intravenous dose for severe disease is 1.0–1.5 mg/kg/day (higher dose for patients with AIDS). The chronic nature of disseminated disease requires prolonged therapy with ketoconazole (at least 400 mg/day)[60] or itraconazole (400 mg/day), and, in the case of meningitis, fluconazole. Voriconazole and posaconazole, which have *in vitro* activity against coccidioidomycosis equal or superior to that of itraconazole[53], have been used successfully (alone or in combination with liposomal amphotericin B) to treat disseminated disease.

Paracoccidioidomycosis

Synonyms: ■ South American blastomycosis ■ Brazilian blastomycosis

Introduction and epidemiology

Paracoccidioidomycosis is caused by the dimorphic fungus *Paracoccidioides brasiliensis*. It is endemic to the Central and South American countries of Brazil, Argentina, Venezuela, Ecuador and Colombia.

Pathogenesis

P. brasiliensis is a dimorphic saprophyte that is found in the soil. In most cases, infection occurs via inhalation of the conidia from the environment. Pulmonary disease ensues and can be followed by dissemination to the skin, mucous membranes, gastrointestinal tract, spleen, adrenal glands and lymph nodes.

Clinical features

Paracoccidioidomycosis has several different clinical presentations with varying prognoses. In many patients, the primary pulmonary disease is subclinical to mild. When progressive disseminated disease occurs, mucocutaneous involvement is commonly seen. Lesions are often painful and ulcerative or verrucous; they are typically found on the face and in the nasal and oral mucosae (Fig. 77.31A,B). The ulcerations are referred to as "moriform stomatitis". Lymphangitic spread may occur, resulting in cervical lymphadenopathy.

Another clinical presentation is that of primary mucocutaneous paracoccidioidomycosis. This frequently has an intraoral and perioral distribution due to trauma from chewing contaminated sticks and leaves.

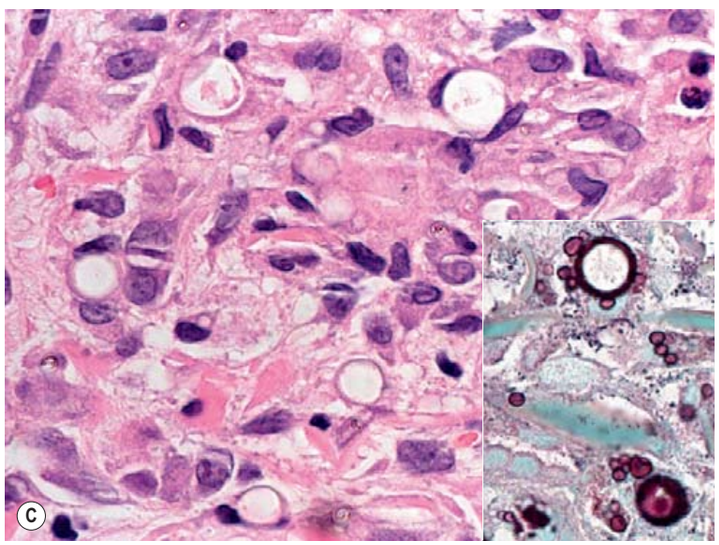


Fig. 77.31 Paracoccidioidomycosis. Ulcerated plaques on the palate (**A**) and verrucous granulomatous red–brown plaques with crusting involving the perioral region and upper lip (**B**). **C** Dermal histiocytic infiltrate and yeast forms with multiple small, narrow-based buds. The organisms are highlighted with a Grocott methenamine silver stain (insert). *A, B, Courtesy, Marcia Ramos-e-Silva, MD PhD. C, Courtesy, C Massone, MD.*

Granulomatous lesions are typically seen. Primary cutaneous paracoccidioidomycosis can also occur via direct inoculation of the skin, resulting in the development of a verrucous papule or plaque or cutaneous ulceration.

Pathology

The histologic features of paracoccidioidomycosis resemble those of blastomycosis (see above). Pseudoepitheliomatous hyperplasia is accompanied by suppurative and granulomatous inflammation. Yeast forms are found within and outside of giant cells. Large, thick-walled organisms with multiple narrow-based buds may be seen, leading to an outline that resembles a "mariner's wheel" (Fig. 77.31C).

Differential diagnosis

The differential diagnosis includes mucocutaneous leishmaniasis, Wegener's granulomatosis, NK-cell lymphoma, and syphilis (endemic and epidemic) (see Table 45.3). Microscopic examination and culture

of the organism are essential for diagnosing paracoccidioidomycosis. KOH or calcofluor examination of an appropriate specimen (sputum, dermal scraping, or pus) may reveal round to ovoid cells with narrow-based buds, which are also seen when the organism is cultured at 37°C.

Treatment

There are several effective treatment options for paracoccidioidomycosis, including amphotericin B, systemic azoles and sulfonamides. Prolonged therapy is generally required. In disseminated disease, systemic therapy with amphotericin B or an azole antifungal is indicated. Itraconazole is a preferred treatment because it provides reasonable efficacy and side-effect profile, as well as low potential for recurrent disease. Treatment with voriconazole can also be effective. Attempts to modulate the immune system via peptides derived from the *P. brasiliensis* 43 kDa glycoprotein have been described[61].

Opportunistic Pathogens

Introduction

Opportunistic mycotic infections may occur in individuals with primary or secondary immunodeficiencies. Worldwide, disseminated candidiasis and aspergillosis are the two most common systemic mycoses in neutropenic patients. Less commonly, zygomycosis, phaeohyphomycosis (due to pigmented fungi; see below) and hyalohyphomycosis (due to non-pigmented [hyaline] fungi; most often fusariosis) are seen (Fig. 77.32). Disseminated histoplasmosis, coccidioidomycosis, penicilliosis and cryptococcosis are the systemic mycoses seen most commonly in the setting of HIV infection. Opportunistic pathogens are less virulent (compared to true pathogens) and impart no specific protective immunity to those infected.

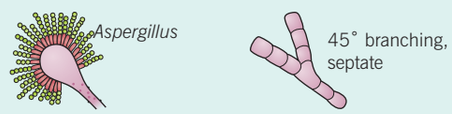
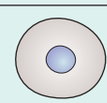
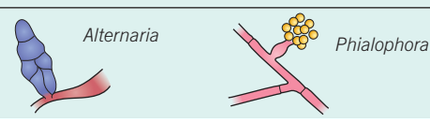
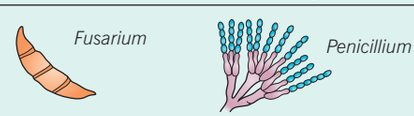
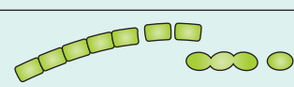
History

Aspergillosis was among the first mycoses recognized, with the initial report of a human case by Sluyter in 1847. In 1855, Kurchenmeister isolated *Mucor* from the lung and described zygomycosis. Benham distinguished cryptococcosis from blastomycosis in the 1930s. *Fusarium* emerged as an opportunistic pathogen in neutropenic oncology patients in the 1990s.

Epidemiology

With the exception of several dimorphic fungi, opportunistic fungal infections occur worldwide and have no geographic predilection. The causative pathogens are commonly found in the environment. For example, *Aspergillus* spp., Zygomycetes and *Fusarium* spp. are soil saprophytes found in decaying vegetation. *Cryptococcus neoformans* can be isolated from avian (especially pigeon) droppings. *Penicillium marneffei* is endemic to Southeast Asia and China, where the reservoir is thought to be in bamboo rats, but infection has been reported in the US. Lastly, *Candida* spp. commonly colonize the skin and gastrointestinal tract[1].

CUTANEOUS FEATURES OF COMMON OPPORTUNISTIC MYCOSES

Mycosis	Common cutaneous presentations	Microscopic appearance
Systemic candidiasis† • *Candida albicans* • *C. tropicalis* (frequent skin lesions) • *C. glabrata, C. krusei* (intrinsic fluconazole resistance)	Firm erythematous papules and nodules, often with a pale center (but possibly hemorrhagic); ecthyma gangrenosum-like lesions	
Aspergillosis† • *Aspergillus flavus* and *fumigatus*	Necrotic papulonodules, subcutaneous nodules (secondary cutaneous); may be associated with an intravenous catheter site (primary cutaneous); disseminated disease usually results from primary pulmonary involvement; galactomannan (more specific, lower sensitivity) and 1,3β-D-glucan (less specific for aspergillosis) serum assays can be used to screen high-risk patients	
Zygomycosis† • *Mucor* • *Rhizopus* • *Absidia*	Ecthyma gangrenosum-like lesions, cellulitis, facial edema (commonly unilateral due to contiguous spread of sino-orbital disease), necrotic papulonodules, plaques, large hemorrhagic crusts on the face; may be associated with an intravenous catheter site (primary cutaneous)	
Cryptococcosis** • *Cryptococcus*	Ulceration, cellulitis, molluscum contagiosum-like lesions; assays to detect cryptococcal antigens in blood or CSF are available	
Phaeohyphomycosis* • *Alternaria* • *Exophiala* • *Phialophora*	Subcutaneous cysts, ulcerated plaques, hemorrhagic pustules, necrotic papulonodules	
Hyalohyphomycosis*† • *Fusarium* • *Penicillium* • *Paecilomyces*	Umbilicated or necrotic papules, pustules, abscesses, cellulitis, subcutaneous nodules; *Fusarium* infection is often associated with a periungual focus	
Trichosporonosis • *Trichosporon* spp.	Papulovesicles, purpuric papules, necrotic papulonodules	

* Less common
**Especially in the setting of AIDS
†With use of prophylactic fluconazole and (more recently) voriconazole in high-risk oncology patients, incidences of systemic candidiasis and (with voriconazole use) aspergillosis have decreased, but incidences of zygomycosis and (with fluconazole use) fusariosis and other hyalohyphomycoses have increased

Fig. 77.32 Cutaneous features of common opportunistic mycoses. While the lesions of opportunistic fungal infections seem nonspecific, certain presentations may be more likely associated with a particular species.

Overall, the incidence of opportunistic mycoses has increased in conjunction with the HIV pandemic and greater use of immunosuppressive therapy. In fact, some opportunistic mycoses are considered to be AIDS-defining diseases (see Ch. 78). In contrast, the incidence of disseminated candidiasis has fallen with the use of prophylactic fluconazole in high-risk oncology patients (e.g. neutropenic patients with hematologic malignancies, hematopoietic stem cell transplant recipients). In the future, the same may happen with aspergillosis and fusariosis with the use of voriconazole. However, these agents lack activity against the organisms that cause zygomycosis, which may continue to increase in incidence unless the use of prophylactic antifungals that cover Zygomycetes (e.g. posaconazole) becomes routine.

Pathogenesis

Aspergillosis is an opportunistic mycosis that is caused by fungi in the genus *Aspergillus*, most often *A. fumigatus* and *A. flavus*. Burns, sites of trauma, surgical wounds, intravenous catheters (Fig. 77.33A) and macerated skin underlying occlusive dressings typically serve as portals of entry in primary cutaneous aspergillosis[62]. The risk of dissemination is significant in immunocompromised individuals. In *secondary* cutaneous aspergillosis (a more common form), the conidia are inhaled, producing a primary lung infection that is followed by dissemination to the skin. Immunosuppression – particularly neutropenia plus chronic use of corticosteroids and sometimes late-stage AIDS – is a major risk factor for the development of invasive or disseminated aspergillosis.

Fungi in the class Zygomycetes and order Mucorales cause zygomycosis, which is also called mucormycosis. The genera most commonly responsible are *Rhizopus, Mucor* and *Absidia*. Risk factors include poorly controlled diabetes mellitus as well as other forms of immunosuppression, especially when associated with neutropenia. *Primary* infections can be rhino-orbito-cerebral, pulmonary, gastrointestinal or cutaneous (via direct inoculation of the skin in settings similar to those of primary cutaneous aspergillosis), and hematogenous dissemination may occur in immunocompromised hosts. Skin lesions that arise from contiguous spread (e.g. from the sinuses) or dissemination are referred to as *secondary* cutaneous zygomycosis. Aspergillosis and zygomycosis are both characterized by necrotic skin lesions due to the angioinvasive nature of these organisms.

Cryptococcus neoformans is the causative pathogen in cryptococcosis. This organism (which can be acquired from pigeons) is inhaled, resulting in a primary pulmonary infection with subsequent dissemination to the CNS, bone and skin. The latter is referred to as *secondary* cutaneous cryptococcosis. *Primary* cutaneous cryptococcosis can also occur, but the diagnosis is made after a systemic evaluation has been performed. Immunocompetent hosts may acquire this infection, but they have a low risk for dissemination, while immunocompromised hosts, particularly those with AIDS, often develop disseminated disease. The use of antiretroviral therapy (ART; formerly referred to as highly active antiretroviral therapy [HAART]) in HIV-infected individuals has led to a dramatic decrease in the incidence of cryptococcosis.

Yeasts belonging to the genus *Candida* are responsible for candidiasis, which can present as a mucocutaneous condition (see above) or (in immunocompromised hosts) a disseminated infection that often originates from the gastrointestinal tract. The ability of *Candida* to exist in the form of pseudohyphae in tissue and blastoconidia in the bloodstream allows for adaptation and evasion of host defenses[63]. *C. albicans* is the most common species, but *C. tropicalis* is often implicated as the causative agent of fungemia in patients with leukemia. Neutropenia, especially in patients who have received prolonged courses of corticosteroids, sets the stage for disseminated candidiasis; patients are usually also receiving broad-spectrum antibiotics.

Hyalohyphomycosis includes infections with *Penicillium, Paecilomyces* and *Fusarium* spp. (see Fig. 77.32). These molds are found in the soil and throughout the environment and can cause disseminated infections in immunocompromised hosts. Disseminated infections with *Fusarium*, an angioinvasive organism, most often affect neutropenic oncology patients and may originate from a periungual focus (e.g. paronychia, onychomycosis). *Penicillium marneffei* is a dimorphic fungus, and HIV patients are particularly at risk.

Clinical features

All of the opportunistic mycoses can present with several different types of cutaneous lesions (see Fig. 77.32). Skin findings range from firm papules (Fig. 77.33B) and necrotic papulonodules (Fig. 77.33C) to hemorrhagic bullae (Fig. 77.33D) and ulcers. Subcutaneous nodules and cellulitis (Fig. 77.33E,F) can also be seen.

In disseminated aspergillosis, the CNS, kidneys and heart (in addition to the lungs) are often involved in severe widespread disease. The prognosis is poor but improves when the patient is no longer neutropenic or corticosteroids are discontinued. Secondary cutaneous zygomycosis due to an underlying sinus infection may initially present with subtle unilateral facial swelling and mild erythema, while advanced disease is characterized by large areas of necrosis covered by a thick hemorrhagic crust.

Secondary cutaneous cryptococcosis is associated with a poor overall prognosis, with a mortality rate of up to 80% if left untreated[64]. Findings range from papulonodules to ulcers and abscesses, and they may resemble lesions of herpes viral infections or molluscum contagiosum (Fig. 77.33G). Approximately 15% of patients with systemic cryptococcosis have skin lesions, and no predictable body distribution has been identified[65].

Cutaneous lesions of disseminated candidiasis frequently present as firm pink papules or nodules (see Fig. 77.33B) on the trunk and extremities. The lesions often have a pale center but may be purpuric in patients with thrombocytopenia. Other presentations include ecthyma gangrenosum-like lesions (hemorrhagic bulla followed by necrotic eschar), pustules, abscesses and purpura (in thrombocytopenic patients). While *C. albicans* is the most commonly associated species, *C. tropicalis* is more likely to produce cutaneous lesions[56]. Systemic sites of involvement include the liver, spleen, muscle, kidney, retina and heart valves. A sepsis-like syndrome may occur, with tachycardia, hypotension, dyspnea and high fevers.

Like histoplasmosis, *P. marneffei* typically infects the liver, spleen and lymph nodes. The skin may be involved with umbilicated papules that resemble molluscum contagiosum, necrotic nodules and acneiform lesions. The most common sites are the face (particularly the forehead), arms and trunk. When mucosal surfaces are involved, ulcers and papules are seen; prominent lymphadenopathy is often present.

Skin lesions develop in approximately 75% of patients with disseminated fusariosis, typically presenting as targetoid erythematous, ecthyma gangrenosum-like or purpuric nodular lesions in a widespread, scattered distribution. Affected individuals often have high fevers and severe myalgias.

Pathology

Histologic examination of lesions of cutaneous aspergillosis demonstrates 45° dichotomous branching of hyaline, septate hyphae (Fig. 77.34A) that are best demonstrated with silver or PAS staining. Suppurative and granulomatous inflammation and/or necrosis may be observed.

In zygomycosis, there are highly characteristic broad, non-septate hyphae that have 90° branching and have been likened to ribbons (Fig. 77.34B). PAS staining may be helpful. Suppuration and necrosis, as well as blood vessel invasion by the fungi, are often seen.

Histologic findings in cryptococcosis are described as either gelatinous (numerous organisms with little inflammation) or granulomatous (fewer organisms with more inflammation and little necrosis). While a PAS stain highlights the central yeast forms (Fig. 77.34C), mucicarmine or Alcian blue is used to visualize the characteristic capsule. India ink preparations, e.g. of CSF or dermal scrapings, also demonstrate the presence of the capsule. The wider the capsule and the more severe the immunocompromise, the less the inflammation.

In disseminated candidiasis, budding yeast and pseudohyphae are seen in the dermis, rather than in the stratum corneum as in mucocutaneous candidiasis.

P. marneffei has microscopic characteristics similar to histoplasmosis. The small organisms are numerous and found within macrophages and giant cells (see Table 77.16). The histologic findings of fusariosis are similar to those of aspergillosis, with acute-branching, septate hyphae, angioinvasion, necrosis and a variable granulomatous infiltrate.

Fig. 77.33 Clinical findings of opportunistic fungal infections in immunocompromised hosts. Primary cutaneous aspergillosis characterized by hyperpigmented plaques with brown–black scale-crusts at the site of intravenous catheters on the arm (**A**); firm pink papulonodule due to disseminated candidiasis (**B**); erythematous papulonodule with central necrosis due to embolus of *Mucor circinelloides* (**C**); necrotic hemorrhagic bulla due to embolus of *Aspergillus flavus* (**D**); cellulitis with area(s) of necrosis due to *Rhizopus* (**E**) and *Cryptococcus neoformans* (**F**); and crusted molluscum contagiosum-like lesions due to disseminated cryptococcosis (**G**). *C, Courtesy, Julie V Schaffer, MD. F, Courtesy, Kalman Watsky, MD. G, Courtesy, Athanasia Syrengelas, MD PhD.*

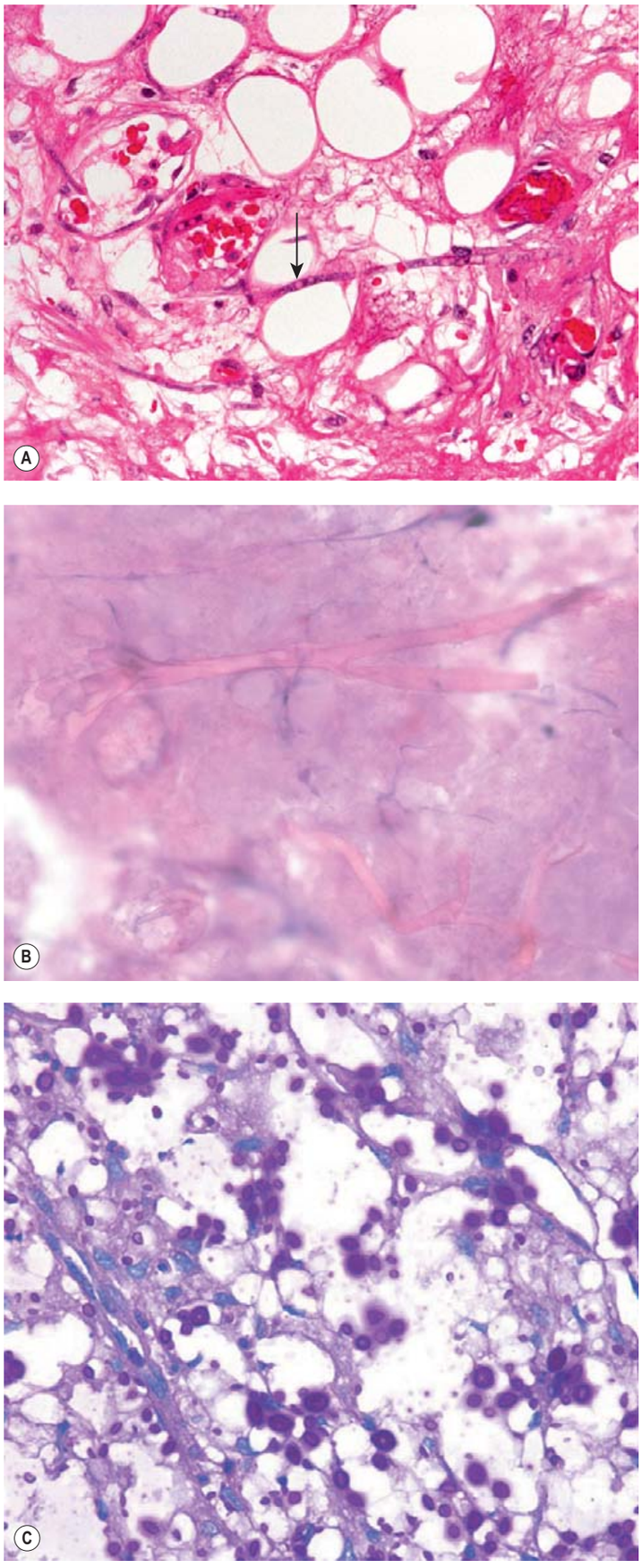


Fig. 77.34 Histologic findings of opportunistic fungal infections in immunocompromised hosts. A Septate hyphae (arrow) with 45° branching in necrotic skin from a patient with disseminated aspergillosis. **B** Ribbon-like, non-septate *Rhizopus* hyphae in a "touch" preparation of dermal scrapings from the base of a necrotic bulla. **C** Numerous dermal yeast forms with gelatinous capsules in secondary cutaneous cryptococcosis. *A, Courtesy, Lorenzo Cerroni, MD. B, Courtesy, Jean L Bolognia, MD. C, Courtesy, Athanasia Syrengelas, MD PhD.*

Differential diagnosis

Microscopic examination of dermal scrapings (using KOH or calcofluor), histologic analysis, and culture of skin tissue are used to diagnose opportunistic fungal infections. The former studies are important considering that many of these organisms can also represent culture contaminants[66]. The clinical differential diagnosis ranges from folliculitis and molluscum contagiosum to cellulitis and ecthyma gangrenosum due to a disseminated bacterial infection. When there are necrotic eschars, the possibility of herpes zoster or vasculitis may be raised (see Fig. 77.32).

Macroscopically, cultures of *Aspergillus flavus* and *A. fumigatus* have been likened to "south sea islands" because the central portion is khaki green (*flavus*) or blue–green (*fumigatus*) with a rim of white to yellow color. Microscopically, spherical "heads" with conidia forming on the exterior are seen. In zygomycoses, culture reveals fast-growing "woolly" colonies in most instances. Microscopically, rhizoids, round sporangia and sporangiospores (asexual spores formed within sporangia) are seen (see Fig. 77.32)[67]. Culture of *Cryptococcus neoformans* yields a cream-colored colony that is similar in appearance to *Candida* colonies. On birdseed agar, the *C. neoformans* colony becomes brown. Because *P. marneffei* is a dimorphic fungus, at 25°C the mold form is seen with a diffusible red pigment, and at 37°C the colony appears as a yeast.

Antibodies against the capsule can be detected in cryptococcosis, and high titers herald a poor prognosis. Serum assays for components of the fungal cell wall, such as 1,3 β-D-glucan (detects a variety of fungi, including *Aspergillus* and *Fusarium*) and galactomannan (relatively specific for *Aspergillus* but somewhat less sensitive), have been used to screen high-risk patients for early evidence of an invasive fungal infection. PCR-based assays have also become available for detection of many opportunistic fungi (especially *Aspergillus*)[68,69].

Treatment

Prevention of opportunistic mycoses in high-risk patients can be aided by reduced exposure to environments such as construction sites and the use of ventilation systems. Prophylaxis with systemic antifungals (e.g. fluconazole, posaconazole, voriconazole) is commonly administered to patients receiving myelosuppressive chemotherapy and hematopoietic stem cell transplant recipients, both before and during periods of neutropenia. Even in the absence of neutropenia, individuals on chronic high-dose systemic corticosteroids (e.g. with chronic GVHD) are at significant risk for opportunistic fungal infections and represent another group now receiving prophylaxis. In the past, a febrile neutropenic patient unresponsive to systemic broad-spectrum antibiotics was empirically begun on amphotericin B. Nowadays, that patient might receive voriconazole, posaconazole or one of the echinocandins (e.g. caspofungin; Table 77.17; see Ch. 127). Of note, voriconazole is a triazole that has activity against *Aspergillus* and *Fusarium* as well as *Candida* (but not Zygomycetes); it causes photosensitivity (and increased risk of squamous cell carcinoma and melanoma) and, like itraconazole, drug–drug interactions due to inhibition of cytochrome P450. Posaconazole, another triazole with a similar range of activity (but also covering Zygomycetes), is used for both treatment and prophylaxis of opportunistic fungal infections.

Once an opportunistic mycosis is diagnosed, prompt treatment is essential. Primary cutaneous infections with opportunistic molds, if localized, can be surgically excised, followed by administration of oral antifungals. Disseminated infections carry a poor prognosis and are frequently fatal, particularly when treatment is delayed or ineffective. Amphotericin B (including lipid formulations) has been the standard treatment for several decades. However, voriconazole has proven superior for invasive fungal infections due to *Aspergillus*, and, in the case of disseminated candidiasis, caspofungin is now administered[70] (see Ch. 127). For systemic infections due to other opportunistic fungi, amphotericin B is still employed, but voriconazole does have activity against *Fusarium* and posaconazole has activity against both *Fusarium* and Zygomycetes.

In addition to amphotericin B and several triazoles, terbinafine may have activity against *P. marneffei*, which has a high mortality rate if inadequately treated. Unfortunately, recurrence is likely unless treatment is continued indefinitely[71].

TREATMENT OF OPPORTUNISTIC MYCOSES							
	Aspergillosis	Zygomycosis	Cryptococcosis	Candidiasis	Penicilliosis	Fusariosis	Forms of administration
Amphotericin B	+	+	+	+	+	+	iv
Itraconazole (200–400 mg/day)	+	–	+	+	+	–	po, iv
Fluconazole	–	–	+	+	–	–	po, iv
Voriconazole	+	–	+	+	+	+	po, iv
Posaconazole	+	+	+	+	+	+	po
Caspofungin	+	–	–	+	–	–	iv
Micafungin	+	–	–	+	–	–	iv
Anidulafungin	+	–	–	+	–	–	iv

Table 77.17 Treatment of opportunistic mycoses. Appropriate selection of therapy for opportunistic infections is essential, given the likelihood of rapid, widespread dissemination and high mortality rates[51]. iv, intravenously; po, orally.

Phaeohyphomycosis

Introduction and history

Phaeohyphomycosis refers to infections with a group of dematiaceous fungi (i.e. pigmented due to melanin in the cell wall) that produce distinct brown to black hyphae in tissue rather than Medlar bodies or grains (see chromoblastomycosis and eumycotic mycetoma above). Although systemic disease can occur, particularly spread to the CNS from a primary lung source, this section will focus on the other three forms of phaeohyphomycosis – superficial, cutaneous and subcutaneous.

Ajello and colleagues coined the term "phaeohyphomycosis" in 1974. Initially, the list of causative pathogens was limited, but presently it is extensive and continues to lengthen[72].

Epidemiology

Because phaeohyphomycosis encompasses infections caused by many fungi, the epidemiology is complex. All age groups and both genders may be affected. There may be a slightly higher incidence in men due to increased environmental and occupational exposure. The culprit fungi in phaeohyphomycosis are found in plants and soil, making individuals with certain occupations, activities and cultural habits (such as not wearing protective footwear) at higher risk of developing the infection.

Pathogenesis

Superficial phaeohyphomycosis includes tinea nigra and black piedra (see above), while cutaneous phaeohyphomycosis includes infections of the hands, feet and nails that mimic tinea infections in the same locations (e.g. *S. hyalinum*, *S. dimidiatum*; see Table 77.10). Trauma is typically the cause of subcutaneous phaeohyphomycosis. Both immunocompetent and immunocompromised hosts may acquire this disease. The immune status of the patient has a significant effect on the severity and the likelihood for disseminated disease; *Cladosporium trichoides (Cladophialophora bantiana)* is most commonly associated with CNS disease[64]. Secondary cutaneous phaeohyphomycosis occurs when dematiaceous fungi spread from other sites to the skin.

Clinical features

The clinical presentation of cutaneous phaeohyphomycosis is similar to that of dermatophyte infections of the hands, feet or nails. Subcutaneous phaeohyphomycosis most commonly presents as a nodule or plaque in regions of the body that are prone to trauma. The course is usually chronic, with slowly progressive disease. Clinical manifestations of disseminated disease include nonspecific skin lesions (papules, plaques, nodules) and signs of cerebral involvement.

Pathology

Histologic examination of cutaneous and subcutaneous phaeohyphomycosis reveals pigmented hyphae in the stratum corneum and dermis/subcutis, respectively (Fig. 77.35). In the latter, cyst-like abscesses (possibly surrounded by a fibrous capsule) can be seen, hence the term phaeomycotic cysts. Occasionally, implanted material (e.g. a splinter) may also be observed.

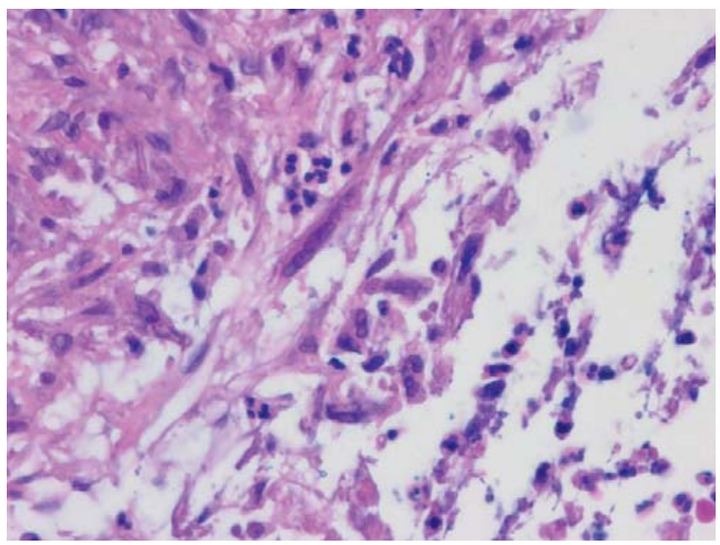


Fig. 77.35 Hyphae within a phaeohyphomycotic cyst.

Differential diagnosis

For the subcutaneous and systemic forms, the differential diagnosis may include a foreign body granuloma, cutaneous leishmaniasis, chromoblastomycosis and dimorphic fungal infections. KOH examination (superficial and cutaneous types), culture (all types) and histopathology (usually just subcutaneous and systemic types) allow the diagnosis to be made. Determination of genera and species requires fungal culture, but histopathology is useful in determining the extent of invasion and in differentiating causative pathogens from contaminants in culture specimens. *Exophiala jeanselmei* and *E. dermatitidis* are the organisms most commonly isolated from subcutaneous phaeohyphomycosis.

Treatment

Subcutaneous disease is surgically excised[73], if possible; complete surgical excision is usually curative. Systemic disease due to dematiaceous fungi continues to be a therapeutic dilemma, as it is difficult to eliminate with oral antifungals alone. Nevertheless, itraconazole, given at a dose of 200 mg twice daily for a prolonged course (>12 months), has some efficacy for the non-surgical treatment of phaeohyphomycosis. Close follow-up is required and includes repeat cultures and histologic analyses of affected sites. Additional treatments for systemic disease include voriconazole, posaconazole, amphotericin B and flucytosine.

Pneumocystis

In the past, *Pneumocystis jiroveci* (formerly referred to as *Pneumocystis carinii*) was classified as a protozoan. Currently, it is considered to be a fungus, based on genetic and biochemical analyses. This opportunistic infection occurs in individuals who are immunocompromised, including those with AIDS. The lungs are the most common site of infection (pneumonia), but, on occasion (<3% of patients), there is dissemination to other sites such as the liver, spleen and lymph nodes.

Cutaneous involvement is rare and is characterized by erythematous or skin-colored, non-tender papules or nodules[74]; there may be associated ulceration. The external ear (including the auditory canal) represents the most commonly reported site of involvement. Histologically, a diffuse infiltrate of foamy cells is seen within the dermis. Special stains (e.g. Grocott methenamine silver, Giemsa, Steiner) can be used to highlight the organisms, as can monoclonal antibodies; detection of *P. jiroveci* is also possible via PCR.

The most common treatment for pneumocystosis is trimethoprim–sulfamethoxazole (TMP-SMZ). Additional therapies include parenteral pentamidine and oral atovaquone. Prophylaxis in the setting of immunosuppression usually consists of oral TMP-SMZ or, less often, aerosolized pentamidine, oral dapsone or oral atovaquone. Prophylaxis is important for dermatologic patients receiving systemic corticosteroids combined with immunosuppressive agents such as azathioprine and cyclophosphamide.

REFERENCES

1. Crespo EV, Delgado FV. *Malassezia* species in skin diseases. Curr Opin Infect Dis. 2002;15:133–42.
2. Rippon JW. Medical Mycology: The Pathogenic Fungi and the Pathogenic Actinomycetes, 3rd edn. Philadelphia: WB Saunders, 1988.
3. Bernier V, Weill FX, Hirigoyen V, et al. Skin colonization by *Malassezia* species in neonates: a prospective study and relationship with neonatal cephalic pustulosis. Arch Dermatol. 2002;138:215–18.
4. Assaf RR, Weil ML. The superficial mycoses. Dermatol Clin. 1996;14:57–67.
5. Brodell RT, Elewski B. Superficial fungal infections. Errors to avoid in diagnosis and treatment. Postgrad Med. 1997;101:279–87.
6. Elewski BE. The superficial mycoses, the dermatophytoses, and select dermatomycosis. In: Elewski BE (ed). Cutaneous Fungal Infections, 2nd edn. Massachusetts: Blackwell Science, 1998:13–72.
7. Elewski BE, Hazen PG. The superficial mycoses and the dermatophytes. J Am Acad Dermatol. 1989;21:655–73.
8. Lesher JL Jr, Smith JG Jr. Antifungal agents in dermatology. J Am Acad Dermatol. 1987;17:383–94.
9. Gupta AK, Bluhm R, Summerbell R. Pityriasis versicolor. J Eur Acad Dermatol Venereol. 2002;16:19–33.
10. Rebell G, Taplin D. Dermatophytes: Their Recognition and Identification, 2nd printing. Coral Gables, FL: University of Miami Press, 1974.
11. Rinaldi MG. Dermatophytosis: epidemiological and microbiological update. J Am Acad Dermatol. 2000;43:S120–4.
12. Dahl MV. Dermatophytosis and the immune response. J Am Acad Dermatol. 1994;31:S34–41.
13. Elewski BE. Tinea corporis. In: Demis DJ (ed). Clinical Dermatology, 20th revision. Philadelphia: JB Lippincott, 1993;Vol. 3, Unit 17–6:1–9.
14. Elewski BE, Nagashima-Whalen L. Superficial fungal infections of the skin. In: Hoeprich PD, Jordan MC, Ronald AR (eds). Infectious Diseases, 5th edn. Philadelphia: JB Lippincott, 1994:1029–49.
15. Abdel-Rahman SM, Farrand N, Schuenemann E, et al. The prevalence of infections with *Trichophyton tonsurans* in schoolchildren: the CAPITIS study. Pediatrics. 2010;125:966–73.
16. Hughes R, Chiaverini C, Bahadoran P, et al. Corkscrew hair: a new dermoscopic sign for diagnosis of tinea capitis in black children. Arch Dermatol. 2011;147:355–6.
17. Elewski B. Tinea capitis. Dermatol Clin. 1996;14:23–31.
18. Hajjeh R. Tinea capitis: a public health perspective. Contemp Pediatr. 2001; Update on Tinea Capitis:12.
19. Leyden JJ, Aly R. Tinea pedis. Semin Dermatol. 1993;12:280–4.
20. Masri-Fridling GD. Dermatophytosis of the feet. Dermatol Clin. 1996;14:33–40.
21. Baran R, Faergemann J, Hay RJ. Superficial white onychomycosis: a syndrome with different fungal causes and paths of infection. J Am Acad Dermatol. 2007;57:879–82.
22. Lawry MA, Haneke E, Strobeck K, et al. Methods for diagnosing onychomycosis: a comparative study and review of the literature. Arch Dermatol. 2000;136:1162–4.
23. Weitzman I, Padhye AA. Dermatophytes: gross and microscopic. Dermatol Clin. 1996;14:9–22.
24. Smith EB. The treatment of dermatophytosis: safety considerations. J Am Acad Dermatol. 2000;43:S113–19.
25. Zuber TJ, Baddam K. Superficial fungal infection of the skin. Where and how it appears help determine therapy. Postgrad Med. 2001;109:117–20, 123–6, 131–2.
26. Nir-Paz R, Elinav H, Pierard GE, et al. Deep infection by *Trichophyton rubrum* in an immunocompromised patient. J Clin Microbiol. 2003;41:5298–301.
27. Chastain MA, Reed RJ, Pankey GA. Deep dermatophytosis: report of 2 cases and review of the literature. Cutis. 2001:67:457–62.
28. Pappas AA, Ray TL. Cutaneous and disseminated skin manifestations of candidiasis. In: Elewski BE (ed). Cutaneous Fungal Infections, 2nd edn. Massachusetts: Blackwell Science, 1998:91–117.
29. Goldstein SM. Advances in the treatment of superficial *Candida* infections. Semin Dermatol. 1993;12:315–30.
30. Hay RJ. Yeast infections. Dermatol Clin. 1996;14: 113–24.
31. Bluestein J, Furner BB, Phillips D. Granuloma gluteale infantum: case report and review of the literature. Pediatr Dermatol. 1990;7:196–8.
32. Goldberg NS, Esterly NB, Rothman KF, et al. Perianal pseudoverrucous papules and nodules in children. Arch Dermatol. 1992;128:240–2.
33. Elgart GW. Chromoblastomycosis. Dermatol Clin. 1996;14:77–83.
34. Tomecki KJ, Steck WD, Hall GS, Dijkstra JW. Subcutaneous mycoses. J Am Acad Dermatol. 1989;21:785–90.
35. Tuffanelli L, Milburn PB. Treatment of chromoblastomycosis. J Am Acad Dermatol. 1990;23:728–32.
36. Bonifaz A, Saul A, Paredes-Solis V, et al. Treatment of chromoblastomycosis with terbinafine: experience with four cases. J Dermatolog Treat. 2005;16:47–51.
37. Welsh O. Mycetoma. Semin Dermatol. 1993;12:290–5.
38. McGinnis MR. Mycetoma. Dermatol Clin. 1996;14:97–104.
39. Galhartdo MC, De Oliveira RM, Valle AC, et al. Molecular epidemiology and antifungal susceptibility patterns of *Sporothrix schenckii* isolates from a cat-transmitted epidemic of sporotrichosis in Rio de Janeiro, Brazil. Med Mycol. 2008;46:141–51.
40. Elgart ML. Subcutaneous and miscellaneous mycoses. In: Elewski BE (ed). Cutaneous Fungal Infections, 2nd edn. Massachusetts: Blackwell Science, 1998:155–97.
41. Hoeprich PD. Sporotrichosis. In: Hoeprich PD, Jordan MC, Ronald AR (eds). Infectious Diseases, 5th edn. Philadelphia: JB Lippincott, 1994:1050–4.
42. Hu S, Chung WH, Hung SI, et al. Detection of *Sporothrix schenckii* in clinical samples by a nested PCR assay. J Clin Microbiol. 2003;41:1414–18.
43. Kauffman CA, Hajjeh R, Chapman SW. Practice guidelines for the management of patients with sporotrichosis. For the Mycoses Study Group, Infectious Diseases Society of America. Clin Infect Dis. 2000;30:684–7.
44. Vilela R, Mendoza L, Rosa PS. Molecular model for studying the uncultivated fungal pathogen *Lacazia loboi*. J Clin Microbiol. 2005;43:3657–61.
45. Paniz-Mondolfi AE, Jaimes OR, Jones LD. Lobomycosis in Venezuela. Int J Dermatol. 2007;46:180–5.
46. Talhari C, Chrusciak-Talhari A, de Souza JVB, et al. Exfoliative cytology as a rapid diagnostic tool for lobomycosis. Mycoses. 2008;52:187–9.
47. Carneiro FP, Maia LB, Moraes MA, et al. Lobomycosis: diagnosis and management of relapsed and multifocal lesions. Diagn Microbiol Infect Dis. 2009;65:62–4.
48. Body BA. Cutaneous manifestations of systemic mycoses. Dermatol Clin. 1996;14:125–35.
49. Hay RJ. Histoplasmosis. Semin Dermatol. 1993;12:310–14.
50. Bracea A, Tosello ME, Girardini JE. Molecular detection of *Histoplasma capsulatum* var. *capsulatum* in human clinical samples. J Clin Microbiol. 2003;41:1753–5.
51. Reiss E, Obayashi T, Orle K, et al. Non-culture based diagnostic tests for mycotic infections. Med Mycol. 2000;38(suppl. 1):147–59.
52. Wheat J, Sarosi G, McKinsey D, et al. Practice guidelines for the management of patients with histoplasmosis. Infectious Diseases Society of America. Clin Infect Dis. 2000;30:688–95.
53. Ghannoum MA, Kuhn DM. Voriconazole – better chances for patients with invasive mycoses. Eur J Med Res. 2002;7:242–56.
54. Bialek R, Gonzalez GM, Begerow D, Zelck UE. Coccidioidomycosis and blastomycosis: advances in molecular diagnosis. FEMS Immunol Med Microbiol. 2005;45:355–60.
55. Chapman SW, Bradsher RW Jr, Campbell GD Jr, et al. Practice guidelines for the management of patients with blastomycosis. Infectious Diseases Society of America. Clin Infect Dis. 2000;30:679–83.
56. Sugar AM, Liu XP. Efficacy of voriconazole in treatment of murine pulmonary blastomycosis. Antimicrob Agents Chemother. 2001;45:601–4.
57. Panicker J, Walsh T, Kamani N. Recurrent central nervous system blastomycosis in an immunocompetent child treated successfully with sequential liposomal amphotericin B and voriconazole. Pediatr Infect Dis J. 2006;25:377–9.
58. Pappagianis D. Coccidioidomycosis. Semin Dermatol. 1993;12:301–9.
59. Stevens DA. Diagnosis of fungal infections: current status. J Antimicrob Chemother. 2002;49(suppl. 1):11–19.
60. Lesher JL. Therapeutic agents for dermatologic fungal diseases. In: Elewski BE (ed.). Cutaneous Fungal Infections, 2nd edn. Massachusetts: Blackwell Science, 1998:321–46.
61. Yasuda MA. Pharmacological management of paracoccidioidomycosis. Expert Opin Pharmacother. 2005;6:385–97.
62. van Burik JA, Colven R, Spach DH. Cutaneous aspergillosis. J Clin Microbiol. 1998;36:3115–21.
63. Ray TL. Systemic candidiasis. Dermatol Clin. 1989;7:259–68.
64. Durden FM. Elewski B. Cutaneous involvement with *Cryptococcus neoformans* in AIDS. J Am Acad Dermatol. 1994;30:844–8.
65. Barfield L, Iacobelli D, Hashimoto K. Secondary cutaneous cryptococcosis: case report and review of 22 cases. J Cutan Pathol. 1988;15:385–92.
66. Bohler K, Metze D, Poitschek C, Jurecka W. Cutaneous aspergillosis. Clin Exp Dermatol. 1990;15:446–50.
67. Elgart ML. Zygomycosis. Dermatol Clin. 1996;14:141–6.
68. Playford EG, Kong F, Sun Y, et al. Simultaneous detection and identification of *Candida, Aspergillus*, and *Cryptococcus* species by reverse line blot hybridization. J Clin Microbiol. 2006;44:876–80.
69. McMullan R, Metwally L, Coyle PV, et al. A prospective clinical trial of a real-time polymerase chain reaction assay for the diagnosis of candidemia in nonneutropenic, critically ill adults. Clin Infect Dis. 2008;46:890–6.
70. Stone EA, Fung HB, Kirschenbaum HL. Caspofungin: an echinocandin antifungal agent. Clin Ther. 2002; 4:351–77.
71. Conant MA. Fungal infections in immunocompromised individuals. Dermatol Clin. 1996;14:155–62.
72. Rinaldi MG. Phaeohyphomycosis. Dermatol Clin. 1996;14:147–53.
73. McGinnis MR, Winn EW. Phaeohyphomycosis. In: Hoeprich PD, Jordan MC, Ronald AR (eds). Infectious Diseases, 5th edn. Philadelphia: JB Lippincott, 1994:1054–9.
74. Bundow DL, Aboulafia DM. Skin involvement with *Pneumocystis* despite dapsone prophylaxis: a rare cause of skin nodules in a patient with AIDS. Am J Med Sci. 1997;313:182–6.

Cutaneous Manifestations of HIV Infection

78

Armin Rieger, T Minsue Chen and Clay J Cockerell

Key features

- Cutaneous disorders in the setting of HIV infection represent a vast spectrum of diseases. As immunity deteriorates, variable presentations, opportunistic infections, mixed infections and adverse drug reactions are increasingly likely
- Because the cutaneous findings often correlate with immune status, a more focused differential diagnosis may be generated if the viral load and $CD4^+$ cell count are known. For example, seborrheic dermatitis and oral hairy leukoplakia first appear in patients with $CD4^+$counts >500 cells/mm^3, whereas giant mollusca and large non-healing perirectal ulcers due to herpes simplex virus are typically seen in patients with counts of less than 50 cells/mm^3
- With the advent of antiretroviral therapy (ART; formerly referred to as highly active antiretroviral therapy [HAART]), skin disorders such as herpes zoster and *Mycobacterium avium* complex infection may become clinically apparent or worsen when the immune status improves, a phenomenon known as the immune reconstitution inflammatory syndrome (IRIS)
- Unusual skin eruptions, skin diseases with exaggerated presentations (e.g. seborrheic dermatitis, molluscum contagiosum), sudden acute exacerbations (e.g. psoriasis), and treatment failures (e.g. refractory dermatophyte infection) should alert the clinician to the possibility of underlying HIV infection
- Several of the medications employed in ART lead to frequent drug reactions and significant drug–drug interactions

INTRODUCTION

Since the onset of the human immunodeficiency virus (HIV) pandemic in the 1980s, cutaneous disorders have been recognized as important clues to both the diagnosis of HIV infection and the existence of an associated systemic disease (including other infections).

The epidemiology of HIV infection and its complications has changed in many regions of the world with the advent of antiretroviral therapy (ART; formerly referred to as highly active antiretroviral therapy [HAART]). Although eradication of HIV infection is not possible with current medications, HIV infection/AIDS in the ART era has become a chronic, manageable disorder. As a consequence, many of the skin disorders associated with HIV disease (e.g. Kaposi sarcoma) as well as serious opportunistic infections are observed less frequently than in the past. However, with longer survival, medical problems that previously were less common have emerged (e.g. anal intraepithelial neoplasia), and ART itself has created new dermatologic challenges, including drug reactions, lipodystrophy and immune reconstitution inflammatory syndrome (IRIS). While the incidence of opportunistic infections has fallen in high-income countries, resurgence of risky behavior along with the mistaken belief that ART can "rescue and cure" infected patients may lead to a future increase in HIV infection. Unfortunately, in low-income countries where ART is not readily available, opportunistic infections are still common and are often the source of morbidity and mortality.

HISTORY

June 2011 marked the thirtieth anniversary of the identification of the acquired immunodeficiency syndrome (AIDS). The first description was officially made by Dr Michael S Gottlieb, who reported five cases of *Pneumocystis jiroveci (carinii)* pneumonia in healthy young men from Los Angeles, California[1–3]. Subsequently, the major causative agent was identified and named human immunodeficiency virus type 1 (HIV-1; hereafter referred to has HIV), and homology to an African zoonosis was demonstrated. Both blood-related and sexual transmission were identified, and recognition of mother-to-child transmission led to specific measures for delivery and breastfeeding. Universal precautions have been adopted for the handling of blood and body fluids, and ART was introduced in 1996.

EPIDEMIOLOGY

HIV infection/AIDS is a pandemic that still poses one of the greatest challenges in global public health. It has disproportionately affected resource-poor countries and disadvantaged persons, such as commercial sex workers, intravenous drug users and those living in poverty, as well as men who have sex with men.

Approximately 34 million people in the world are currently living with HIV infection (~22 million of whom reside in sub-Saharan Africa) and nearly 32 million have died since 1981[4]. It is estimated that there are currently over 2.5 million children living with HIV infection and 18 million children who have been orphaned because of AIDS. In 2009, there were approximately 2.7 million new HIV infections (including 390 000 children) and 1.8 million AIDS-related deaths worldwide. HIV has had an especially disastrous effect in sub-Saharan Africa (Fig. 78.1). However, in this region as well as several other areas with a high prevalence of HIV infection (e.g. India, Thailand and Caribbean countries), the HIV incidence rate has decreased or stabilized over the past 5–10 years[4]. In contrast, the HIV infection rates in Central Asia and Eastern Europe (particularly in the Russian Federation and Ukraine) have risen substantially during the past decade, especially in high-risk groups (i.e. intravenous drug users and sex workers); as a result, the prevalence of HIV infection has more than doubled in this region.

Currently, AIDS is the leading cause of death in Africa and the fourth leading cause of death in low-income countries worldwide[5]. On a global basis, access to antiretroviral drugs is still limited, although in the last few years it has improved in low- and middle-income countries. Prevention and treatment efforts require political leadership, national programs and adequate funding, as well as societal awareness and response[6,7].

PATHOGENESIS

HIV (including HIV-2, which is discussed separately below, as well as HIV-1) is an enveloped, single-stranded RNA virus belonging to the genus *Lentivirus* within the family Retroviridae. HIV has substantial genetic variability due to the high error rate and recombinogenicity of its reverse transcriptase as well as the very rapid turnover of the virus in infected individuals. The incubation period ranges from 3 to 6 weeks, but it may be shorter when it is transmitted hematogenously and/or when the viral inoculum is large. Upon initial infection, the virion binds to $CD4^+$ T lymphocytes, monocyte-macrophages and dendritic cells. Changes in conformation induce fusion of the viral envelope with the plasma membrane. Next, its outer coat is removed and the virus particle is internalized (Fig. 78.2). The RNA genome is released into the cytoplasm and transcribed by a reverse transcriptase enzyme that produces a DNA copy of the HIV RNA. The DNA copy is then integrated into the host DNA and can be expressed as a cellular gene. As

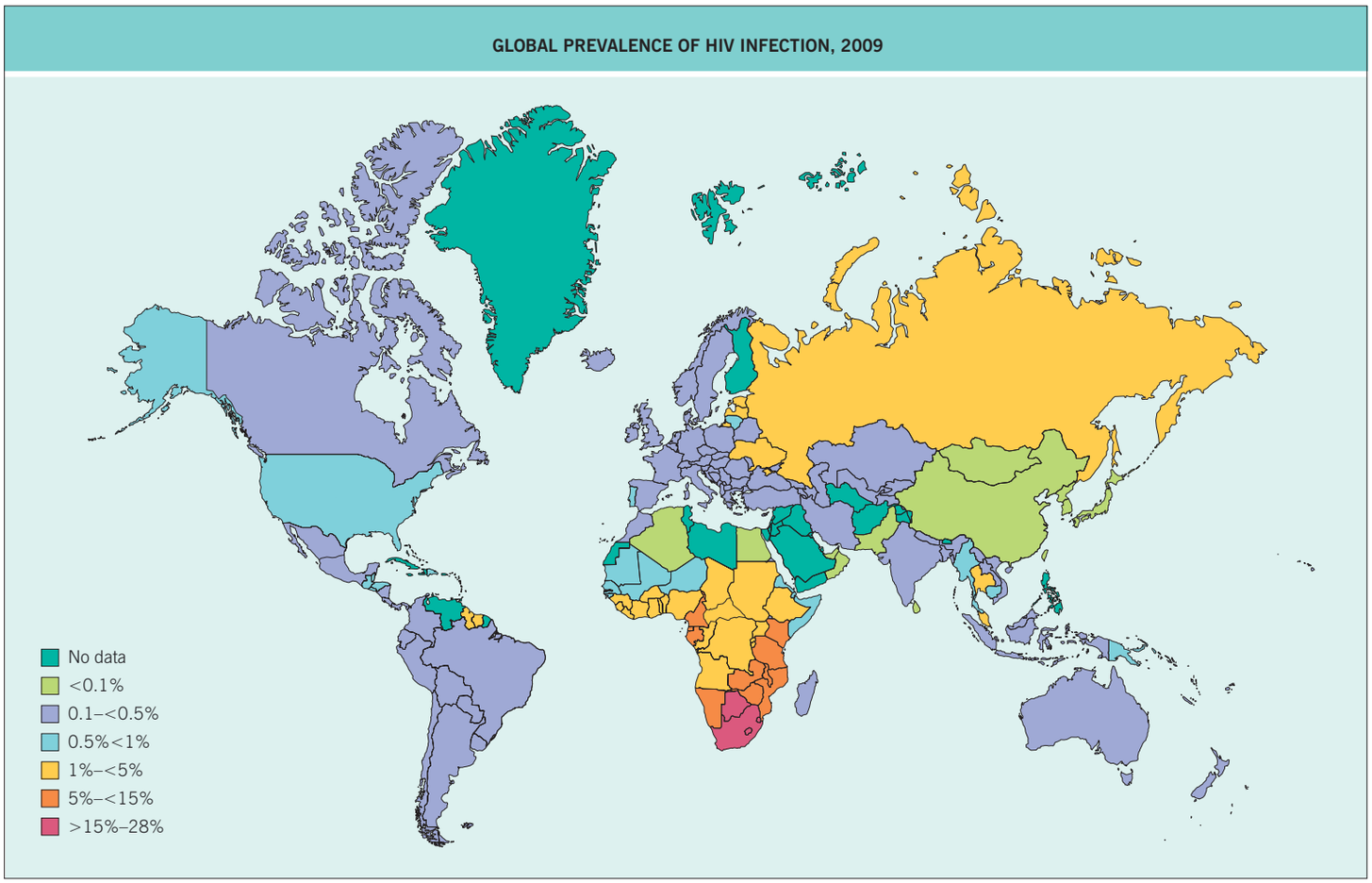


Fig. 78.1 Global prevalence of HIV infection, 2009. The estimated percentage of the adult population living with HIV infection in each country is indicated. The worldwide estimate of the number of persons living with HIV is 34 million. *From the Joint United Nations Programmes on HIV/AIDS.*

a result, there is transcription of viral DNA into RNA, which either becomes the genome of new viral particles or is translated into viral proteins. Cleavage of the latter into structural components of the virus is accomplished by proteases. Intact viruses are then produced and host cells are destroyed. $CD4^+$ cells are affected primarily, significantly impairing the host's immune system, especially the cellular component. On average, over one billion HIV particles are produced daily, leading to a decline in the infected individual's $CD4^+$ cell count[8].

In the humoral response to HIV, antibodies (IgG, IgM, IgA) directed against viral proteins are typically detectable within 12 weeks of infection. In the cellular response, $CD8^+$ cytotoxic T lymphocytes (CTLs) directed against HIV begin to function within 10 days of exposure to viral antigens and are therefore present before seroconversion or development of peak levels of viral RNA. The development of a CTL response correlates with the reduction in viremia during the acute retroviral syndrome and is an important factor in controlling HIV infection throughout the disease course. In addition to their effects on viral replication, CTL activity (including cytokine production) has implications for the infectious, inflammatory and neoplastic complications of HIV infection. Although $CD4^+$ helper T lymphocytes have a role in the initial response to HIV infection, they become dysfunctional early in the disease course (even before their numbers decline). The decreased ability of infected helper T lymphocytes to proliferate and produce IL-2 is central to the pathogenesis of HIV infection. Of note, infection of Langerhans cells by HIV can also affect the immune response. Despite vigorous anti-HIV immune responses, HIV-infected individuals are not capable of clearing the infection. However, occasional patients (known as "long-term non-progressors") tolerate the virus without developing significant clinical disease[8,9].

The earliest cutaneous manifestation of HIV infection is an acute morbilliform exanthem that is often accompanied by fever and lymphadenopathy (see below). During this phase, the virus disseminates widely, seeding lymphoid organs and other internal sites such as the CNS. Over time, an immunodeficient state referred to as AIDS ensues, complicated by opportunistic infections and neoplasms, many of which have mucocutaneous manifestations[10]. In a person infected with HIV, AIDS is defined by a $CD4^+$ cell count of <200 cells/mm^3 (or $CD4^+$ T-cell percentage of <14) and/or the presence of an AIDS-defining condition (Table 78.1).

The natural history of HIV infection varies considerably. There is evidence that additional acute infections (viral or non-viral) increase HIV viral load, but the significance of this phenomenon to the patient's overall course has not been established[11]. Some patients develop AIDS within 2–3 years, ("rapid progressors"), whereas others remain free from AIDS for more than 10–15 years ("long-term non-progressors" or "long-term survivors"). For untreated disease, the median time of progression to AIDS is approximately 10 years. However, institution of ART has an immense impact on the disease course. ART's profound effect on HIV replication enables reconstitution of $CD4^+$ T cells. This immune reactivation can result in a variety of inflammatory sequelae, referred to as the immune reconstitution inflammatory syndrome (IRIS), ranging from unmasking or paradoxically "worsening" infections or neoplasms to exacerbations of inflammatory disorders (see below).

HIV-2 is another human retrovirus that causes immune deficiency due to depletion of $CD4^+$ cells. The viral structure, modes of transmission, and immune deficiency syndrome it produces are virtually identical to those of HIV-1, and patients are commonly co-infected with HIV-1[12]. Compared to HIV-1, HIV-2 has several distinct features, including genetic differences, five- to eightfold less transmissibility, rare vertical transmission, a longer period of latency, and a slower rate of $CD4^+$ cell count decline and clinical progression. The outcome among HIV-2-infected patients may be slightly better, as the degree of immunodeficiency may be less. Most infections are diagnosed in endemic

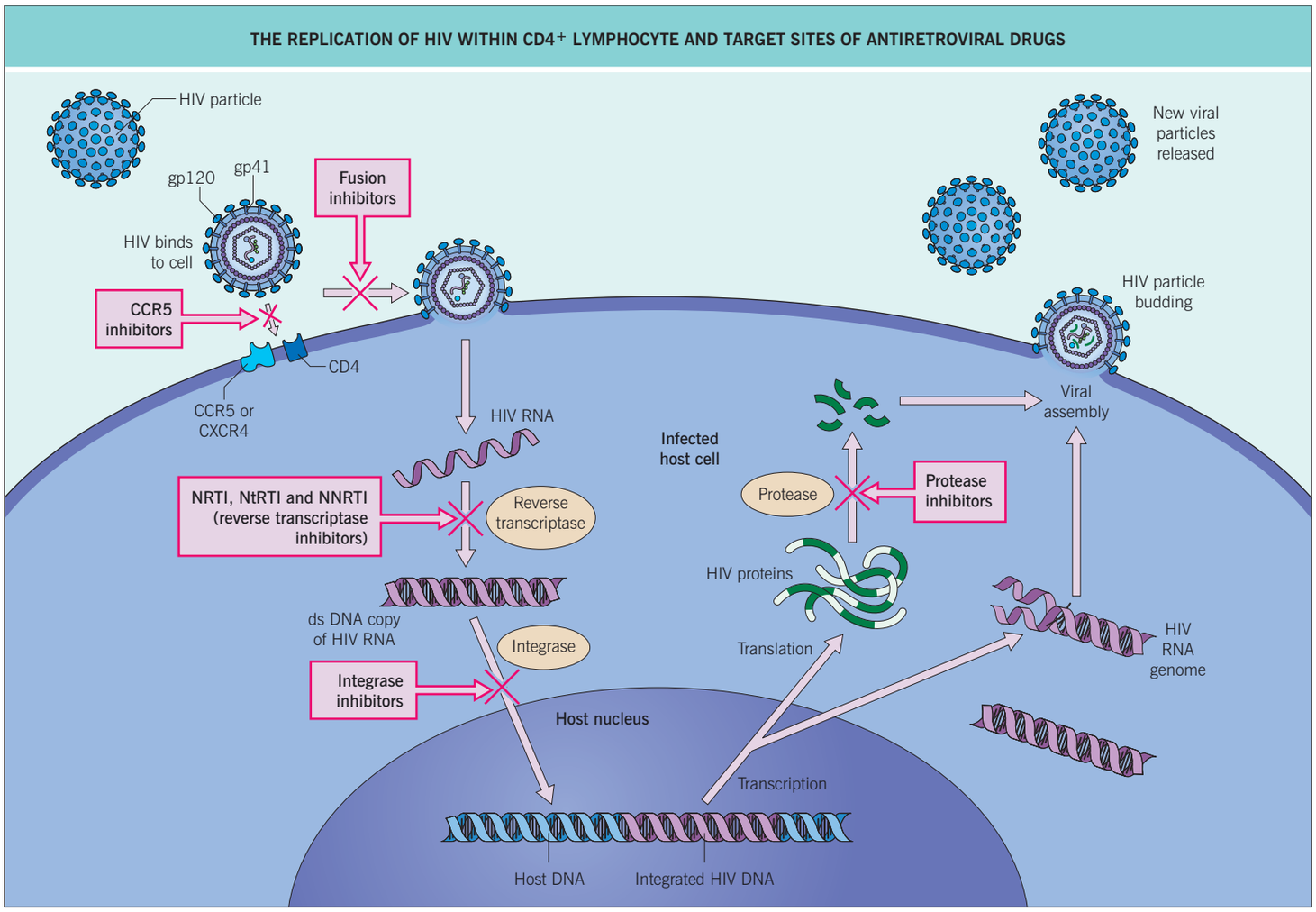


Fig. 78.2 Replication of HIV within CD4+ lymphocyte and target sites of antiretroviral drugs. CCR5, CC-chemokine receptor 5; NRTI, nucleoside reverse transcriptase inhibitor; NtRTI, nucleotide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor.

areas (primarily West Africa); however, HIV-2 serology should not only be tested in individuals who are native to an endemic area, but also in those who have had sex with or shared a needle with an individual from an endemic area.

INFECTIOUS HIV-RELATED CUTANEOUS DISORDERS

Cutaneous infections associated with HIV seropositivity can be divided into five major categories: viral, bacterial, fungal, parasitic and ectoparasitic (the latter representing infestations rather than true infections). Patients with HIV acquired via sexual contact are at increased risk of (and should be tested for) other sexually transmitted diseases, which are discussed in Chapter 82; the converse is also true. In addition, the presence of erosions and ulcerations in the anogenital region due to diseases such as syphilis and herpes simplex infections can increase the risk of HIV transmission.

Viral Infections

Exanthem of primary HIV infection (acute retroviral syndrome)

The earliest cutaneous manifestation of HIV infection may be an exanthem occurring as a manifestation of the primary infection (Table 78.2). The latter is defined as the presence of HIV-1 in the plasma (based on detection of viral RNA or DNA by PCR and/or p24 antigen) *prior* to the development of HIV-1 antibodies (as determined by ELISA or Western blot). Primary HIV infection can be asymptomatic, but up to 80% of newly infected individuals report a history of a "viral illness" (Fig. 78.3). Also referred to as "acute retroviral syndrome", this usually occurs 2–4 weeks after HIV exposure and lasts from a few days to over 10 weeks. Reminiscent of acute mononucleosis, the most common signs and symptoms include fever, lymphadenopathy, pharyngitis and a morbilliform exanthem. The cutaneous eruption lasts 4–5 days and is typically generalized, with most pronounced involvement on the face and trunk (and often sparing the distal extremities). Additional manifestations, which can include oral or anogenital ulcers, are outlined in Figure 78.3. Due to an initial burst of HIV replication, a decline in $CD4^+$ T cells can be observed (see Fig. 78.3), only occasionally to levels that allow the development of opportunistic infections[13,14]. There is some evidence that a more severe acute retroviral syndrome portends a more aggressive disease course. The acute retroviral syndrome may be confused with a drug reaction or other infections (e.g. EBV, hepatitis B virus, enteroviruses, cytomegalovirus, secondary syphilis). The diagnosis therefore requires a high degree of clinical suspicion (not just in high-risk groups) and is confirmed by specific laboratory tests for HIV RNA/DNA and/or p24 antigen.

Herpes simplex virus (HSV)

Oral, labial and genital HSV infections in relatively immunocompetent HIV-infected individuals are typical in appearance and severity, with recurrence rates similar to those observed in the general population[15]. However, once significant immune suppression develops, lesions may progress to chronic, non-healing, deep ulcerations that favor the

AIDS-DEFINING CONDITIONS IN PATIENTS INFECTED WITH HIV		
CD4⁺ count <200 cell/mm³ and/or	**Adult or adolescent**	**Children***
Serious bacterial infections, multiple or recurrent (at least two culture-confirmed infections within a 2-year period)†	–	+
Lymphoid interstitial pneumonitis	–	+
Candidiasis of the esophagus, bronchi, trachea or lungs	+	+
Cervical cancer, invasive	+	+
Coccidioidomycosis, disseminated or extrapulmonary	+	+
Cryptococcosis, extrapulmonary	+	+
Cryptosporidiosis, chronic intestinal (>1 month duration)	+	+
Cytomegalovirus disease (other than liver, spleen or lymph nodes), including retinitis with loss of vision	+	+
Encephalopathy, HIV-related	+	+
Herpes simplex viral infection: mucocutaneous (>1 month duration), esophagitis, pneumonitis or bronchitis	+	+
Histoplasmosis, disseminated or extrapulmonary	+	+
Isosporiasis, chronic intestinal (>1 month duration)	+	+
Kaposi sarcoma	+	+
Lymphoma, Burkitt's or immunoblastic	+	+
Lymphoma, primary, of brain	+	+
Mycobacterium avium complex or *M. kansasii*, disseminated or extrapulmonary	+	+
Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)	+	+
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary	+	+
Pneumocystis jiroveci pneumonia	+	+
Pneumonia, recurrent bacterial (two or more episodes within a 1-year period)	+	+
Progressive multifocal leukoencephalopathy	+	+
Salmonella septicemia, recurrent, non-typhoid	+	+
Toxoplasmosis of the brain	+	+
Wasting syndrome due to HIV	+	+

*CDC criteria define children as less than 13 years of age.
†Serious bacterial infections include: septicemia, pneumonia, meningitis, bone or joint infection, and an abscess of an internal organ or body cavity (excluding otitis media, superficial skin infections, mucosal abscesses, and indwelling catheter-related infections).

Table 78.1 AIDS-defining conditions in patients infected with HIV. *Data from: 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep. 1992;41(RR-17).*

perianal region (Fig. 78.4), genitalia and tongue. More frequent recurrences are also observed when the CD4⁺ count falls to <100 cells per cubic millimeter[16,17].

Orofacial lesions associated with nasogastric tube use[18] and herpes simplex folliculitis have been described[19]. Untreated ulcerative lesions usually slowly enlarge and occasionally become verrucous. In suspected cases, scrapings of the ulcer edge for Tzanck smear (low sensitivity in this setting), direct fluorescent antibody (DFA) assay, HSV PCR and viral culture should be performed and, if negative, a skin biopsy performed[20–22]. In the setting of treatment failure, viral isolates should be tested for resistance against acyclovir and related antivirals. In most instances of resistance, reduced thymidine kinase activity is detected[23], and alternative drugs (e.g. foscarnet, cidofovir) that do not require thymidine kinase activity have to be prescribed.

Varicella zoster virus (VZV)

In HIV-infected individuals, the spectrum of primary varicella ranges from a typical course to fatal pulmonary involvement. HIV-infected patients have a 7–15 times greater relative risk of developing herpes zoster, with reactivation of latent virus occurring as cell-mediated immunity declines. The development of zoster in an HIV-infected individual is predictive of progression to more severe immune suppression, especially if associated with fever[20,24,25]. Although the classic dermatomal eruption may be seen, HIV-associated zoster can also be multidermatomal, ulcerative, chronic, verrucous and/or widely disseminated with systemic involvement (see Ch. 80). Bacterial superinfection, acyclovir resistance, therapeutic failure, and multiple recurrences are not uncommon[25]. Vasculitis with bone necrosis and exfoliation of teeth may develop if the blood supply to the mandible and maxilla are compromised[26].

Development of herpes zoster with an unusual presentation (e.g. multidermatomal, verrucous, disseminated) should prompt HIV testing. HIV-infected patients at risk for varicella who are exposed to individuals who either have varicella or are recent vaccinees may require prophylaxis with varicella zoster immune globulin (VZIG) or acyclovir[25]. Of note, herpes zoster is one of the conditions that may occur in the immune recovery syndrome, i.e. a paradoxical worsening of clinical status due to an increased ability to mount an inflammatory response (see Table 78.5), and it often appears when CD4⁺ cell counts rise to a level of approximately 250 per cubic millimeter[27]. Treatment options are outlined in Chapter 80, but in HIV-infected patients, antiviral therapy should be extended until there is clinical resolution.

Poxvirus

Molluscum contagiosum commonly affects patients with HIV infection who have significantly reduced CD4⁺ cell counts[28]. They may develop classic dome-shaped umbilicated papules as well as larger (>1 cm), coalescent and disfiguring lesions that are often resistant to treatment (Fig. 78.5). Although any part of the body can be affected, the lesions favor the face, neck and intertriginous areas.

The clinical differential diagnosis includes basal cell carcinoma and cutaneous involvement of infections with *Cryptococcus* spp., *Histoplasma capsulatum* and other dimorphic fungi. Shaving in affected areas should be avoided to prevent spread via autoinoculation. Although spontaneous regression may occur with antiretroviral therapy[20,24,29], the overall incidence of molluscum contagiosum infections remains high[30]. In addition to destructive modalities (e.g. curettage), imiquimod and topical cidofovir[31] have been used successfully to treat molluscum contagiosum in HIV-infected patients.

Vaccinia is an extremely uncommon skin disorder. Because the vaccinia virus vaccine is live and not attenuated, persons with impaired cell-mediated immunity may develop progressive vaccinia by vaccination or by inoculation from skin lesions in a vaccinee. Currently, virtually all individuals who receive the vaccinia vaccine are military recruits. Generalized vaccinia with fever and toxic symptoms typically develops 6–9 days after vaccination or other exposure to the virus. Skin lesions appear as loculated umbilicated vesicles that progress to pustules and heal with a pitted scar[29].

Human papillomavirus (HPV)

HPV is transmitted by direct person-to-person contact (which can be sexual in nature) or via fomites[32]. HPV-induced lesions are common in the general population but even more prevalent in HIV-infected individuals, and it has been demonstrated that HIV Tat protein upregulates the expression of HPV[20]. Lesions may be extensive, with multiple verrucae on the face, limbs and genitalia that coalesce into large plaques; bowenoid papulosis can also develop (see Ch. 79). In addition, "acquired epidermodysplasia verruciformis" (AEDV) presenting with widespread flat warts and pityriasis versicolor-like macules due to infection with HPV types in the genus beta can occur (see Ch. 80). HIV-infected individuals may develop squamous cell carcinomas (SCCs) in association with AEDV and other cutaneous (e.g. digital related to high-risk HPV types) as well as anogenital warts[32,33]. Institution of ART does not appear to result in clearance of warts and may be associated with the eruptive appearance of new lesions, sometimes in association with a

CORRELATION OF $CD4^+$ CELL COUNT WITH SPECIFIC HIV-ASSOCIATED DISORDERS				
System*	**>500 $CD4^+$ cells/mm^3**	**<500 $CD4^+$ cells/mm^3**	**<250 $CD4^+$ cells/mm^3**	**<50 $CD4^+$ cells/mm^3**
Dermatologic	Acute retroviral syndrome Oral hairy leukoplakia Vaginal candidiasis Seborrheic dermatitis	Oropharyngeal candidiasis (thrush) Herpes zoster Psoriasis, severe or refractory Eruptive atypical melanocytic nevi and melanoma Kaposi sarcoma	Eosinophilic folliculitis Seborrheic dermatitis, refractory Mollusca, extensive Bacillary angiomatosis Miliary/extrapulmonary tuberculosis Herpes simplex viral infection, disseminated Cryptococcosis, disseminated Histoplasmosis, disseminated Coccidioidomycosis, disseminated Botryomycosis Non-Hodgkin lymphoma	Large, non-healing mucocutaneous herpes simplex viral infections (e.g. perianal) Papular pruritic eruption Giant mollusca Perianal ulcers due to cytomegalovirus Aspergillosis Acquired ichthyosis *Mycobacterium avium* complex infections Major aphthae
Respiratory	Bacterial pneumonia and sinusitis	Pneumococcal pneumonia Pulmonary tuberculosis Lymphocytic interstitial pneumonia (pediatric)	*Pneumocystis jiroveci* pneumonia (PCP)	*Pseudomonas* spp. pneumonia
Nervous	Aseptic meningitis Guillain–Barré syndrome	Mononeuritis multiplex	HIV-associated dementia Cerebral toxoplasmosis Peripheral neuropathy Progressive multifocal leukoencephalopathy	Primary CNS lymphoma
Hematologic	Persistent generalized lymphadenopathy	Anemia Idiopathic thrombocytopenic purpura	Non-Hodgkin lymphoma	
Other	Myopathy	Cryptosporidiosis Cervical/anal intraepithelial neoplasia Cervical cancer Anal cancer	Esophageal candidiasis Wasting Microsporidiosis Vacuolar myelopathy Cardiomyopathy	Cryptosporidiosis, refractory Cytomegalovirus retinitis, extraocular systemic cytomegalovirus infection
*Diseases occur with increasing frequency and severity at lower $CD4^+$ cell counts.				

Table 78.2 Correlation of $CD4^+$ cell count with specific HIV-associated disorders.

clinically evident inflammatory response (i.e. a form of IRIS; see below)[34,35].

Furthermore, HIV-infected patients have a higher risk of developing cervical intraepithelial neoplasia (CIN) and anal intraepithelial neoplasia (AIN), with the latter affecting approximately three-quarters of HIV-infected men who have sex with men (MSM)[36]. Immunosuppression, as evidenced by depressed $CD4^+$ cell counts, is associated with more rapid progression from low-grade to high-grade premalignant lesions. ART-induced immune reconstitution does not appear to prevent high-grade CIN or AIN from progressing to cancer, and longer survival due to ART has been associated with an increase in the incidence of anal cancer in HIV-infected individuals[37,38]. Anal cancer developed in 3% of HIV-infected MSM over a 5-year period in one prospective study[36], and the overall rate is >50-fold higher than in the general population[39]; a ~5-fold increased risk of penile cancer has also been documented. Monitoring should include serial physical examinations of the anogenital area, colposcopy/proctoscopy, cervical and anal HPV determination and cytology (utilizing the Papanicolaou [Pap] smear), followed by histologic confirmation when indicated; sensitivity can be increased by repetitive examinations[40]. Of note, recurrence rates of cervical cancer following standard therapy are significantly higher in HIV-infected women than in HIV-negative women.

Treatment decisions for cutaneous and anogenital warts in the setting of HIV infection depend upon the size and location of the lesions as well as the presence or absence of histologic atypia; the threshold for biopsy should be low, and several sites may need to be sampled to exclude SCC. Therapeutic options for warts include standard cytotoxic/destructive and immunomodulatory (e.g. topical imiquimod) approaches as well as alternative modalities such as topical or intralesional cidofovir. However, treatment is often challenging and relapse rates are high. Of note, the quadrivalent HPV vaccine (Gardasil™) was recently found to be safe and immunogenic in HIV-infected children; hopefully, use of HPV vaccines in young HIV-infected individuals will help to prevent (and even stimulate immune responses against existing) genital warts, dysplasias and cancer.

Epstein–Barr virus (EBV)

Oral hairy leukoplakia is an EBV-associated mucosal condition that represents an early sign of HIV infection. It develops in up to 25% of HIV-infected individuals[24] but can also occur in patients with other forms of immunosuppression (e.g. in organ transplant recipients). Development of oral hairy leukoplakia predicts disease progression if ART is not administered[41]. Lesions are usually asymptomatic and appear as corrugated white plaques with hair-like projections along the lateral aspect of the tongue (Fig. 78.6). There is no association with malignant degeneration. Although treatment is usually not necessary, topical or oral antiviral agents, podophyllin resin or gentian violet can be of benefit. Antiretroviral therapy may also lead to regression of the plaques[41].

Cytomegalovirus (CMV)

Despite ART, CMV remains an important cause of serious opportunistic infections in patients with advanced AIDS. Common clinical manifestations include retinitis, esophagitis and colitis. Despite the high frequency of CMV viremia, cutaneous disease is relatively uncommon; presentations include ulcers (especially in the anogenital area), verrucous or hyperpigmented plaques, purpuric papules, vesicles and morbilliform eruptions[20,42]. Ulcers may develop on any mucosal surface and are usually a sign of disseminated disease. Demonstration of intranuclear CMV inclusions within dermal endothelial cells usually proves to be a more sensitive assay than viral cultures (see Fig. 80.23). Of note, because many of the ulcerative lesions are co-infected with HSV or VZV, and CMV can also be detected in non-lesional skin, a primary role for CMV in the pathogenesis of these lesions has been questioned[43].

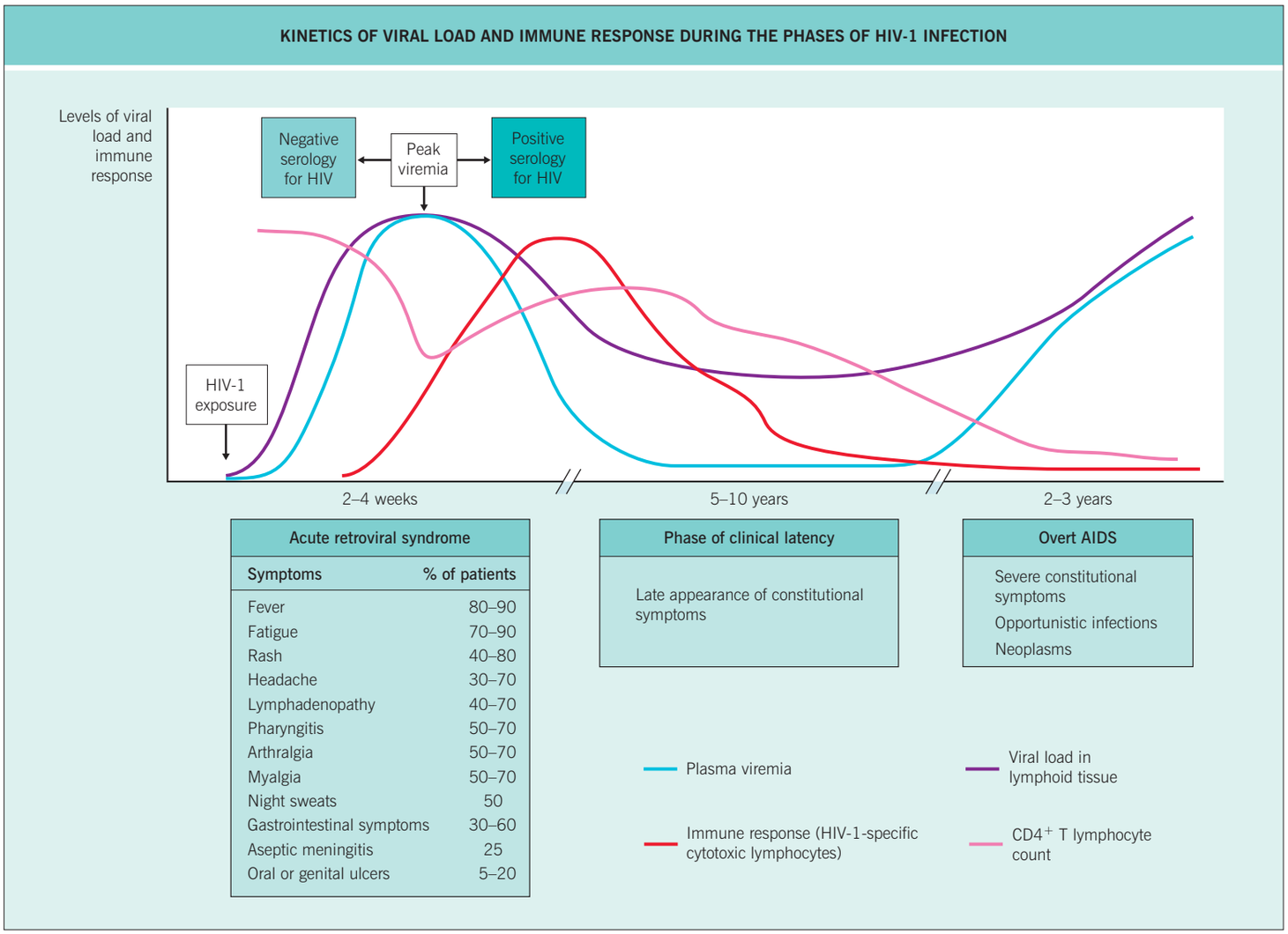


Fig. 78.3 Kinetics of viral load and immune response during the phases of HIV-1 infection. After HIV-1 exposure, initial virus replication and spread occur in the lymphoid organs, and systemic dissemination of HIV-1 is reflected by the peak of plasma viremia. A clinical syndrome of varying severity is associated with this phase of primary HIV-1 infection in up to 80% of HIV-1-infected persons. Down-regulation of viremia during the transition from the primary to the early chronic phase coincides with the appearance of HIV-1-specific cytotoxic T lymphocytes and with the progressive resolution of the clinical syndrome. The long phase of clinical latency is associated with active virus replication, particularly in the lymphoid tissue. During the clinically latent period, $CD4^+$ T-lymphocyte counts slowly decrease, as does the HIV-1-specific immune response. When $CD4^+$ T-lymphocyte counts decrease below 200 cells/ml (i.e. when overt AIDS occurs), the clinical picture is characterized by severe constitutional symptoms and by the possible development of opportunistic infections and/or neoplasms. *Adapted with permission of Elsevier from Bart PA, Pantaleo G. The immunopathogenesis of HIV-1 infection. In: Cohen J, Powderly WG (eds). Infectious Diseases. Edinburgh: Mosby, 2004.*

Fig. 78.4 Chronic ulcerative herpes simplex viral infection in an HIV-infected patient. Slowly enlarging ulcers of the buttocks and perianal area. Note the scalloping of the border.

Fig. 78.5 Molluscum contagiosum. Large lesions with coalescence in an HIV-infected patient.

Fig. 78.6 Oral hairy leukoplakia. Shaggy white keratotic plaques along the lateral aspect of the tongue. A corrugated pattern is often seen. *Courtesy, Charles Camisa, MD.*

Bacterial Infections

The immunosuppression of HIV infection predisposes affected individuals to recurrent and potentially severe cutaneous bacterial infections, which can be localized or widespread and sometimes have unusual clinical appearances. Indwelling venous catheters, excoriations and ulcers with non-bacterial etiologies in HIV-infected individuals impair cutaneous barrier function and further increase the risk of bacterial infections. In addition to the entities discussed below, cutaneous bacterial infections that can occur in association with HIV infection include necrotizing fasciitis, nocardiosis, malacoplakia and pseudomonal "hot tub" folliculitis, "malignant" otitis externa and ecthyma gangrenosum.

Staphylococcus aureus

Staphylococcus aureus is the most common bacterial pathogen in patients infected with HIV, with common presentations including impetigo, folliculitis, furunculosis and cellulitis. The incidence of soft tissue infections with methicillin-resistant *S. aureus* (MRSA) is over sixfold higher in HIV-infected individuals that in those without HIV-infection. Pyogenic bacterial infections generally respond to treatment with antibiotics to which they are susceptible and/or (for furunculosis) incision and drainage, but unusual presentations (e.g. botryomycosis) may be refractory to therapy. Use of intranasal mupirocin and skin cleansers containing chlorhexidine gluconate can temporarily eradicate bacterial colonization (which is especially common among HIV-infected individuals), but it usually recurs.

Bacillary angiomatosis

Bacillary angiomatosis is a bacterial infection that can affect virtually any body site, but it favors the skin and subcutaneous tissue. Lesions of variable size and shape may be seen, including red to purple "vascular-appearing" papules or nodules and ulcers (see Ch. 74). The number of lesions ranges from one to more than hundreds. It has been postulated that a vasoproliferative factor may lead to their formation.

Gram-negative bacilli in the genus *Bartonella* are responsible for this disease, specifically *B. henselae* (associated with cat scratches/bites and exposure to cat fleas) and *B. quintana* (associated with poverty and poor hygiene)[44]. *B. quintana* may be transmitted from human to human by the body louse, *Pediculus humanus* var. *corporis*, although other as yet unidentified vectors may be also involved. Cutaneous lesions induced by *B. henselae* and *B. quintana* are indistinguishable, but the extracutaneous manifestations differ. Subcutaneous and osseous involvement is associated with *B. quintana* infections, whereas visceral disease is seen more often with *B. henselae* infections. Diagnosis is usually based on histologic features, i.e. characteristic vascular proliferation and numerous bacilli visualized by Warthin–Starry staining. Culture of *Bartonella* spp. and detection via PCR of the blood and/or tissue may also be helpful[45].

Resolution usually occurs with institution of appropriate antibiotic therapy (e.g. macrolides or tetracyclines)[20,46]. Optimal duration of antimicrobial treatment has yet to be defined, but a minimum of 2 months is recommended. If left untreated, death may ensue from pulmonary or hepatic failure[42].

Mycobacteria

Cutaneous tuberculosis can develop during advanced stages of HIV infection. Other mycobacteria such as *Mycobacterium avium* complex, *M. kansasii, M. haemophilum* and *M. fortuitum* may also produce skin lesions. Erythematous papules and nodules, ulcers, verrucous plaques and deep nodules can all be observed. Pruritus is generally absent and patients may be febrile. The common practice of prophylaxis with antimycobacterial medications as well as the use of ART has led to a decrease in the frequency of this complication[20].

Syphilis

Syphilis is caused by *Treponema pallidum* (see Ch. 82). Although classic papulosquamous secondary lesions are often seen, unusual presentations may be observed in hosts with HIV infection, including a noduloulcerative form, papular eruptions that mimic molluscum contagiosum, syphilitic palmoplantar keratoderma and lues maligna[42]. Lues maligna is an aggressive, widespread variant of secondary syphilis with a prodrome of fever, headaches and myalgia followed by an eruption of papulopustular or necrotic lesions[47]. CNS involvement occurs more frequently and with greater severity in individuals with HIV infection, and neurosyphilis should be considered in HIV-infected patients with neurologic symptoms. All patients with HIV infection should be tested for syphilis, and vice versa.

Fungal Infections

Cutaneous presentations of fungal infections in HIV-infected individuals range from localized superficial skin lesions to a manifestation of disseminated multiple-organ disease, and clinical morphologies may be atypical. Implementation of ART has significantly decreased the incidence of cutaneous fungal infections in this patient population[48].

Candidiasis

Candidiasis is the fungal infection most frequently encountered in association with HIV infection, and its incidence correlates with lower $CD4^+$ cell counts[49]. Ninety percent of patients with AIDS develop candidiasis of the oropharynx[41]. Perlèche with painful fissures at the oral commissures and persistent candidal infections of intertriginous zones are also commonly seen in HIV-infected individuals[42]. Other signs suggesting immune suppression include chronic paronychia, onychodystrophy and refractory vaginal candidiasis. Disseminated candidiasis has been reported and may be fatal in those with HIV infection[20].

Antiretroviral therapy has a beneficial effect on candidiasis, decreasing the prevalence of oral lesions and reducing the oral candidal load[50]. Conventional therapy (e.g. oral fluconazole) is indicated when the patient is symptomatic[42]; however, persons with $CD4^+$ counts <50 cells/mm^3 should be advised that excessive antifungal use can promote resistance.

Dermatophytoses

The severity of dermatophyte infections is increased in immunosuppressed hosts (see Ch. 77). In such patients, even minor infections can serve as a source of morbidity by providing portals of entry for serious bacterial pathogens. Cutaneous involvement can be atypical in appearance, and lesions may be more widespread and resistant to therapy. Spread of interdigital tinea pedis onto the dorsal foot, Majocchi's granuloma (a deep folliculitis with rupture of the follicle wall) and proximal white onychomycosis have all been associated with HIV infection[21,24]. The goals are to eradicate the infection as well as to prevent recurrence. The latter includes local measures such as absorbent powders[24].

Systemic fungal infections

Cryptococcosis and any of the dimorphic fungal infections (including histoplasmosis, coccidioidomycosis, blastomycosis, paracoccidioidomycosis, sporotrichosis and penicilliosis) can lead to disseminated disease in HIV-infected patients. Disseminated cryptococcosis (Fig. 78.7) and histoplasmosis are seen most commonly, followed by coccidioidomycosis and sporotrichosis[51]. In affected individuals, the $CD4^+$

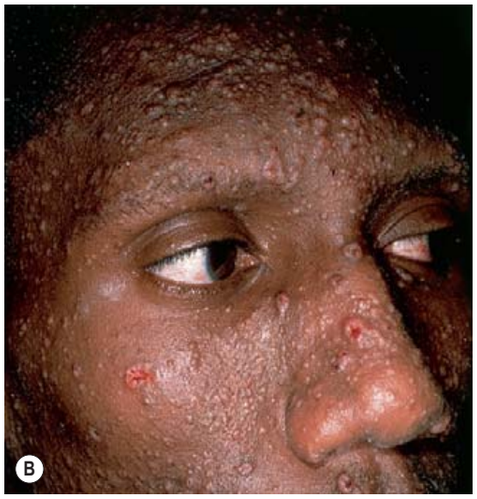


Fig. 78.7 Disseminated cryptococcosis in the setting of AIDS. **A** Several ulcers with rolled borders. **B** Numerous molluscum contagiosum-like lesions. Microscopic examination and culture of either dermal scrapings or a biopsy specimen confirm the diagnosis.

DIFFERENTIAL DIAGNOSIS OF ORAL EROSIONS AND ULCERS IN HIV-INFECTED PATIENTS
INFLAMMATORY
Aphthae, major and minor (Fig. 78.8)
Stevens–Johnson syndrome, toxic epidermal necrolysis
INFECTIOUS
Herpes simplex and herpes zoster viral infections, acute and chronic
Cytomegalovirus (often component of co-infection with above)
Dimorphic or opportunistic fungal infections, e.g. histoplasmosis, cryptococcosis
Extragenital chancre
Mucous patches of secondary syphilis
Mycobacterial infections (tuberculosis and mycobacteria other than tuberculosis)
Necrotizing ulcerative gingivitis/periodontitis
NEOPLASTIC
Squamous cell carcinoma
Kaposi sarcoma
Lymphoma

Table 78.3 Differential diagnosis of oral erosions and ulcers in HIV-infected patients.

Fig 78.8 Major aphthae in a patient with AIDS. Resolution of these lesions may require thalidomide.

counts are usually <250 cells/mm^3 (see Table 78.2). These infections present with a wide range of morphologies, including pustules, crusted papules, papulonodules, verrucous plaques and mucocutaneous ulcerations[51].

In addition to signs of CNS involvement (e.g. meningitis), disseminated cryptococcosis may be associated with translucent dome-shaped papules with central umbilication (often on the face) that resemble mollusca contagiosa (see Fig. 78.7B)[52]. Cutaneous lesions of histoplasmosis and coccidioidomycosis can also appear on the face, and oral ulcerations are commonly seen in disseminated histoplasmosis (Table 78.3)[24]. Widely distributed crusted cutaneous ulcers have been reported in sporotrichosis[42]. Skin biopsy and culture of dermal tissue should be performed for any new, unexplained or unusual lesion where the differential diagnosis includes a disseminated bacterial, mycobacterial or fungal infection. Detection of cryptococcal antigen in the serum or cerebrospinal fluid (CSF) may be helpful in the diagnosis of systemic disease. Although intravenous amphotericin B remains a primary form of therapy, other antifungal agents (e.g. itraconazole, fluconazole, voriconazole, posaconazole, caspofungin) may prove useful (see Ch. 76). Unfortunately, these fungal infections are difficult to eradicate and relapses are common.

Pneumocystis jiroveci

P. jiroveci (formerly *P. carinii*) is now categorized as fungal organism rather than a protozoan (see Ch. 77). *Pneumocystis* pneumonia (referred to as PCP) is by far the most frequent form of infection. Disseminated cutaneous *P. jiroveci* infection is extremely rare and may appear as molluscum contagiosum-like papules, bluish cellulitic plaques, and/or deeply seated abscesses in the external auditory canal or nares[53]. It is theorized that aerosolized pentamidine administered for pulmonary infection may produce an unfavorable environment in the lung, leading to retrograde spread of the organism through the eustachian tubes. Standard therapy such as intravenous trimethoprim–sulfamethoxazole (TMP-SMX) or pentamidine is given for disseminated *Pneumocystis* infection in the setting of HIV infection[20,42]. Pulmonary prophylaxis with oral TMP-SMX or aerosolized pentamidine is recommended when the CD4$^+$ count is <200 cells/mm^3. Prophylactic treatment can be discontinued when, in the course of ART, CD4$^+$ counts have risen to >200 cells/mm^3 for >3 months[54].

Other fungal infections

In addition to those described above, a number of other fungal infections have occasionally been reported in patients with HIV disease. These include disseminated infections with *Scedosporium/Pseudallescheria* spp. and primary cutaneous (e.g. associated with an intravenous catheter site) as well as disseminated zygomycosis or aspergillosis[20]. *Prototheca* are achlorophyllic algae that occasionally cause cutaneous lesions (e.g. plaques, nodules, ulcers) in individuals with HIV, usually following skin trauma and/or exposure to contaminated water.

Parasitic Infections

Leishmaniasis

Leishmaniasis is a protozoal infection transmitted primarily by sand flies and is due to organisms of the genus *Leishmania* (see Ch. 83). HIV-associated leishmaniasis may occur in both endemic and non-endemic regions of the world. Endemic areas include the Mediterranean basin, India, east Africa, Sudan and Brazil. Individuals who were born in or once traveled to endemic areas may also develop disease, pointing

to recrudescence of a previously controlled latent infection. A decrease in the incidence of visceral leishmaniasis after the introduction of ART has been observed in several Mediterranean countries.

Multiple organs may be parasitized, and, when the skin is involved, the lesions typically present as ulcerated nodules or plaques (up to 2 cm in diameter) that favor the extremities. Atypical presentations in HIV-infected patients include disseminated lesions, diffuse erythema and induration, and large necrotic ulcerations[55]. Erosions and ulcerations of the lips, palate and nasal mucosa can be seen in mucocutaneous forms. If left untreated, destruction of cartilaginous structures may result in disfigurement. Fever, hepatosplenomegaly and varying degrees of pancytopenia may also be present.

The diagnosis of cutaneous leishmaniasis is established via microscopy, *in vitro* culture or PCR of lesional tissue. In HIV-infected patients, amphotericin B (which acts by T-cell-independent mechanisms) typically has better efficacy than pentavalent antimonials[42,56]. In a randomized open-label study, oral miltefosine (phosphocholine hexyl ester) and amphotericin B had similar cure rates[57].

Strongyloidiasis

Strongyloides stercoralis is an intestinal helminth endemic to tropical and subtropical regions. In the US, it is endemic in the rural Southeast and Appalachia. HIV-associated cutaneous strongyloidiasis may be caused by larval penetration of the skin and superficial veins giving rise to the migrating serpiginous urticarial eruption known as larva currens. Dissemination (i.e. hyperinfection) may occur in immunosuppressed individuals[58], and, when the skin is affected, lesions can mimic a number of other conditions such as urticaria and livedo reticularis; on the lower trunk, they may resemble purpuric "thumbprints" (see Ch. 83). Eosinophil counts are commonly elevated. Identification of larvae in biopsy specimens as well as sputum, duodenal or gastric contents, or CSF confirms the diagnosis, as does identification of eggs in stool specimens. *S. stercoralis* hyperinfection is almost universally fatal, with poor response to treatment with ivermectin or thiabendazole[20,59].

Acanthamebiasis

In acanthamebiasis, dissemination to the skin and CNS can occur in profoundly immunocompromised patients[60]; the usual cause is *Acanthamoeba castellani*, a microorganism that is part of the normal oral flora. Necrotic nodules and painful ulcerations on the trunk and extremities develop in these patients. Careful inspection on tissue sections will reveal amebic cysts, trophozoites and histiocyte-like cells with erythrophagocytosis. The infection is reported to respond to metronidazole[20].

Ectoparasitic Infestations

Scabies

Scabies, an infestation with the mite *Sarcoptes scabiei* var. *hominis*, is the most common ectoparasitic skin infestation in HIV-infected patients (see Ch. 84). Severe infestation may develop as a consequence of diminished cell-mediated immunity. Cutaneous lesions vary from the "classic" crusted papules to pruritic dermatitis to keratotic and crusted plaques[61] (Fig. 78.9); the latter may or may not be pruritic. Burrows, commonly found on the hands, wrists, ankles and interdigital areas, are less apparent in HIV-infected patients[62]. Also, the ears, face and scalp (sites not usually affected in immunocompetent adults) are commonly involved in immunosuppressed patients. In crusted (Norwegian) scabies, hyperkeratotic lesions may be generalized with subungual debris and marked nail thickening due to an extraordinary mite load; thousands to millions may be present on a single patient. Secondary infection with bacteremia and fatal septicemia has been reported in HIV-infected patients with scabies[62].

Crusted scabies, in particular, is extremely contagious. In any itchy HIV-infected patient, there should be a high index of suspicion for scabies. Persistent scaly or crusted eruptions should be scraped and examined for mites, and dermoscopic evaluation may also be useful in identifying mites. The hyponychium is a protected area, and, if scraped, can be a high-yield site for mites[62].

Therapy for scabies is aimed at eliminating the causative ectoparasite and providing symptomatic relief with topical and systemic antipruritics[21]. HIV-infected individuals with scabies are usually treated initially with standard therapies (e.g. topical permethrin; see Ch. 84), but they may require multiple courses. Treatment with oral ivermectin is also highly effective and is generally used in those who do not respond to standard regimens. Mites under the nails, failure to treat contacts and failure to dry laundered bed linens and clothing at high temperatures are common causes of reinfestation. Scale-crusts often serve as reservoirs for mites, and keratolytic agents such as 6% salicylic acid ointment can facilitate exfoliation as well as penetration of topical medications.

Fig. 78.9 Crusted (Norwegian) scabies in the setting of HIV infection. Crusted and keratotic plaque on the elbow that is teeming with mites.

Demodicosis

Demodicosis is caused by the mites *Demodex folliculorum* and *D. brevis* and has been reported in association with HIV infection. Rosacea-like demodicosis may be more frequent in HIV-positive patients. These eruptions, usually affecting the head and neck region, are similar in morphology to, and must be differentiated from, other pruritic papular eruptions (see below)[63]. Microscopic examination of skin scrapings placed in mineral oil demonstrates multiple mites. *Demodex* infection usually responds to treatment with topical permethrin, gamma benzene hexachloride or metronidazole, or with oral metronidazole[20,24,42]; refractory cases may require ivermectin.

Insect bite reactions

Insect bite reactions can be severe in HIV-infected patients and should be differentiated from other causes of pruritus, including non-infectious papular pruritic disorders associated with HIV infection.

NON-INFECTIOUS HIV-RELATED CUTANEOUS DISORDERS

A number of non-infectious dermatoses have been described in association with HIV infection. The development of inflammatory disorders that are characteristic of HIV infection or unusual presentations (e.g. increased severity, eruptive onset or atypical morphology) of other inflammatory conditions should alert the clinician to consider HIV infection as a possible underlying factor.

Papulosquamous Disorders

Seborrheic dermatitis

Seborrheic dermatitis is the most common skin disorder to affect HIV-infected individuals (up to 85%) and is seen in all stages of the disease (see Table 78.2)[20]. Clinical findings may be similar to those seen in the general population, i.e. erythema and yellowish, greasy scale on the scalp and face as well as involvement of other locations such as the central chest and inguinal creases. However, exaggerated presentations with exuberant facial plaques can also occur and should raise

the possibility of HIV infection, as should a sudden onset or acute worsening of seborrheic dermatitis. The disease may be more difficult to control with conventional therapy, including that aimed against *Malassezia* spp. (see Ch. 13).

Psoriasis

The overall incidence of psoriasis is probably not increased in the setting of HIV infection, although its clinical presentation tends to be more severe. It may develop at any stage of HIV infection[64]; as with seborrheic dermatitis, a rapid onset of "eruptive" psoriasis can serve as a clue to an underlying HIV infection, and psoriasis tends to worsen with declining immune status. Two clinical subgroups have been described: (1) patients with a personal and/or family history of psoriasis, in whom chronic plaque psoriasis is the most common clinical presentation; and (2) those who develop psoriasis after becoming infected with HIV and more commonly have palmoplantar involvement and psoriatic arthritis. An "inverse" distribution involving inguinal creases and genitalia may also occur[22]. The psoriasis is often extensive (Fig. 78.10) or erythrodermic, and exudative crusting or exacerbation with staphylococcal or streptococcal infections may be observed[65]. It can be associated with significant nail dystrophy, arthritis and reactive arthritis (formerly Reiter's disease)[65].

For HIV-associated psoriasis that is refractory to topical therapies, phototherapy and systemic retinoids represent first- and second-line treatments, respectively[65–67]. Immunosuppressive agents such as methotrexate, cyclosporine and tumor necrosis factor-α (TNF-α) inhibitors should be used with caution in HIV-infected patients. A beneficial effect of zidovudine on HIV-associated psoriasis (independent of $CD4^+$ cell counts) has been described[65]. However, worsening of psoriasis following ART-associated elevation in $CD4^+$ counts has been reported.

Reactive arthritis (formerly Reiter's disease)

All patients with newly diagnosed reactive arthritis should undergo HIV testing, as the association between the two conditions is strong[21]. In HIV-infected patients with HLA-B27, reactive arthritis commonly occurs after genitourinary or gastrointestinal infections. Treatment of cutaneous lesions is similar to that for psoriasis[24].

Other papulosquamous dermatoses

Generalized xerosis can be seen in HIV-infected patients and may be associated with refractory pruritus. When the $CD4^+$ count drops below 50 cells/mm^3, acquired ichthyosis with large plate-like scales may develop, beginning on the legs and often becoming widespread. Atopic dermatitis is a frequent problem in children with AIDS and is often difficult to control with conventional therapy[24,68] (see Ch. 12). Pityriasis rubra pilaris (PRP) can develop in conjunction with HIV infection (referred to as type VI PRP; see Ch. 9). In this setting, PRP is typically generalized and may occur together with follicular spines, acne conglobata and hidradenitis suppurativa (HIV-associated follicular syndrome).

Fig. 78.10 Severe psoriasis in a patient with AIDS. Both sudden acute exacerbations and treatment resistance can be observed.

Non-infectious papular pruritic disorders

Papular pruritic disorders are common in HIV infection, and the extreme itch can be debilitating. The pathogenesis of these pruritic dermatoses is not entirely clear[20]. Hypersensitivity reactions to drugs or parasites, peripheral eosinophilia with increased levels of IgE, "hyperreactive" basophils and mast cells, and circulating pruritogens associated with systemic disorders (e.g. hepatobiliary disease, renal disease, lymphoma) can contribute to the development of these conditions. Neural irritation related to HIV infection as well as autonomic dysfunction with diminished sweating and sebaceous gland secretion may also contribute to the pruritus.

The differential diagnosis of itchy papules is extensive. Underlying infections/infestations and systemic etiologies must be excluded, particularly scabies and adverse drug reactions. In some instances, primary lesions are absent, and prurigo nodularis or lichen simplex chronicus may be the only finding. Knowledge of the patient's medications, exposures, travel history and prior treatments can aid in diagnosis, and histologic evaluation may also be helpful.

Papular pruritic eruption of AIDS

Papular pruritic eruption (PPE) of AIDS is characterized by marked pruritus and greater involvement of the extremities than the trunk or face. It is more prevalent in Africa than in North America or Europe. Some authors believe that PPE represents a spectrum of pruritic disorders, including eosinophilic folliculitis[64], while others have suggested that it is an exaggerated response to arthropod antigens[69]. Clinically, the lesions are symmetrically distributed, non-follicular papules, often with secondary changes (e.g. excoriations, formation of prurigo nodularis).

Eosinophilic folliculitis

Eosinophilic folliculitis (see Ch. 38) is one of the most characteristic and common pruritic dermatoses associated with HIV disease, usually occurring in patients with $CD4^+$ counts <200 cells/mm^3. One theory is that it results from an exaggerated reaction to *Malassezia* yeast or other organisms normally present within the follicular infundibula and is a reflection of immune dysregulation leading to a Th2-predominant immune response. Excoriated follicular papules and rare intact pustules are found primarily on the face and upper trunk[64] (Fig. 78.11). Cultures are negative and peripheral eosinophilia may be present[24].

Eosinophilic folliculitis associated with HIV infection differs from Ofuji's disease in its intense pruritus but lack of circinate or palmoplantar lesions. In addition to infectious causes of folliculitis (e.g.

Fig. 78.11 Eosinophilic folliculitis. Due to associated pruritus, follicular papules are often excoriated; lesions favor the head and upper torso.

Pityrosporum, *Demodex*) , acne vulgaris, rosacea and drug reactions should be excluded[70]. Although topical corticosteroids, topical tacrolimus, topical permethrin, UVB phototherapy, systemic antibiotics, itraconazole, dapsone and oral retinoids (e.g. isotretinoin) have each shown some efficacy[24,71], HIV-associated eosinophilic folliculitis may prove recalcitrant to therapy. The impact of ART varies, with anecdotal reports of beneficial effects[72] as well as flares shortly after its institution[73,74].

Hair and Nail Disorders

A variety of disorders of the hair and nails have been recognized in HIV-infected individuals. Alopecia can occur due to infectious etiologies such as severe tinea capitis or secondary syphilis, and serious systemic infections can trigger telogen effluvium. Although alopecia in association with nucleoside analogue treatment has been reported (see Table 78.4), hair regrowth has also been observed after initiating zidovudine therapy[75].

The hair of HIV-infected patients may spontaneously straighten and become softer and more silky, or it can become lusterless and dull[75]. Sudden graying of the hair has been observed with HIV infection, and it may develop via mechanisms similar to those of alopecia areata or AIDS-related vitiligo[75]. Trichomegaly of the eyelashes, a sign of prolonged anagen phase, has also been noted in AIDS patients, including those receiving interferon-α and zidovudine[20,76]. The causes of these phenomena remain unknown and may be related to HIV infection of the hair follicle or concomitant nutritional deficiencies.

Nail disorders also commonly develop in HIV-positive patients. Proximal subungual onychomycosis, the least common of the three forms of onychomycosis, is often a reflection of immunosuppression, including HIV infection (see Ch. 77). Chronic candidiasis with paronychia and nail ridging can be seen, as can nail infections with *Scopulariopsis brevicaulis* and *Alternaria* spp. Patients receiving zidovudine may develop hyperpigmentation of the nail plates as a reflection of increased melanin within melanocytes and dermal melanophages (Fig. 78.12). Protease inhibitors, especially indinavir, have been associated with paronychia and ingrown toenails[77]. Beau's lines (transverse ridging 2–3 months after serious physiologic stress), psoriatic nail pitting and onycholysis may also be seen[75].

Vasculitis

Systemic vasculitis should be considered if an HIV-infected patient has fever of unknown origin or unexplained multisystem disease. Causes of vasculitis in the setting of HIV infection range from systemic infections to drug reactions to inflammatory disease. Arteries and veins of all sizes can be involved and any organ, including the brain, skin and neuromuscular tissues, may be affected. The pathogenesis includes immune complex-mediated disease as well as direct vessel wall damage by infectious agents. Treatable infectious causes should always be sought, e.g. hepatitis C and hepatitis B viruses, HSV, CMV, *Toxoplasma*, *Pneumocystis*, *Salmonella*, *M. tuberculosis* and *Mycobacterium leprae*.

Polyarteritis nodosa-like vasculitis with peripheral neuropathy or digital ischemia occasionally occurs in HIV-infected individuals. Unlike classic polyarteritis nodosa, multisystem involvement is often absent. Usually there is no evidence of hepatitis B viral infection. As expected, cutaneous small vessel vasculitis usually presents as palpable purpura[78,79]. Erythema elevatum diutinum, a chronic form of cutaneous leukocytoclastic vasculitis, has also been reported when $CD4^+$ counts are <200 cells per cubic millimeter[80]. Clinically, the skin lesions are similar to those seen in non-HIV-infected individuals and appear as persistent erythematous papules and nodules that favor extensor surfaces; failure to respond to dapsone has been reported in some patients.

Fig. 78.12 Zidovudine-associated melanonychia. Patients receiving zidovudine may develop longitudinal streaks, horizontal bands and diffuse hyperpigmentation.

Photosensitivity Reactions

UV light hypersensitivity

UV light "hypersensitivity" may be a presentation of HIV disease or related to photosensitizing medications such as sulfonamides. Cutaneous lesions are characteristically pruritic, lichenoid, violaceous plaques in sun-exposed areas[24], i.e. a photolichenoid reaction.

Porphyria cutanea tarda

The acquired form of porphyria cutanea tarda (see Ch. 49) is not uncommonly observed in the setting of HIV infection. When phlebotomy proves difficult because of coexistent anemia, low-dose antimalarial therapy (e.g. hydroxychloroquine three times weekly) should be considered. Avoidance of triggering factors such as alcohol and sunlight can be helpful, and serum ferritin levels and hepatitis C serologies should be obtained[81,82].

Chronic actinic dermatitis

Chronic actinic dermatitis (see Ch. 87) may also be associated with HIV infection, presenting as chronic, scaly, erythematous plaques[24]. There is usually evidence of photosensitivity, which often extends into the visible light range. Sometimes it may represent evolution of a persistent photodrug eruption.

Metabolic Changes

HIV/ART-associated lipodystrophy

Changes in body fat distribution are commonly observed in HIV-infected patients receiving ART, and this is referred to as HIV/ART-associated lipodystrophy or fat redistribution syndrome[83]. Patients may present with various constellations of findings, including lipoatrophy of the face, limbs and buttocks (see Ch. 101); central obesity ("protease pouch", "crix belly"); dorsocervical lipomatosis ("buffalo hump"); and breast hypertrophy. Hypertriglyceridemia and insulin resistance are also commonly observed. On the face, the lipoatrophy occurs predominantly on the cheek, temples and periorbitally. The resultant clinical appearance is highly characteristic and stigmatizing, potentially causing not only psychosocial stress but also decreased adherence to the antiretroviral medication regimen.

Proposed mechanisms for the lipoatrophy component include the following effects of antiretroviral drugs: (1) impaired differentiation and increased apoptosis of adipocytes; (2) increased lipolysis and decreased lipogenesis; and (3) mitochondrial toxicity[84,85]. While lipoatrophy and visceral obesity do share several risk factors (e.g. age, viral load, duration of therapy, $CD4^+$ count), lipoatrophy is associated with being Caucasian and exposure to and duration of treatment with nucleoside reverse transcriptase inhibitors (especially stavudine)[86], whereas visceral obesity/abnormal fat accumulation is associated with female sex and protease inhibitor use. Thus, the possibility has been raised that these two findings reflect separate pathophysiologic processes.

Although substituting non-nucleoside reverse transcriptase inhibitors for the protease inhibitor in a given regimen does not change the likelihood of lipodystrophy, substitution of non-thymidine analogues for stavudine (a thymidine analogue) can lead to a gradual improvement of peripheral lipoatrophy as well as dyslipidemia[87]. Other pharmacological interventions, such as administration of pravastatin, pioglitazone

and uridine, can result in fat gain in areas of peripheral lipoatrophy[88]. In contrast to the small and gradual benefits of pharmacologic treatments for lipoatrophy, surgical interventions are often successful and can provide almost immediate improvement in appearance. Surgical approaches for lipoatrophy include autologous fat transplants[89] and injection of degradable or non-degradable synthetic fillers, such as poly-L-lactic acid[90] or silicone.

Tesamorelin, an injectable growth hormone-releasing factor analogue, was recently approved by the US Food and Drug Administration (FDA) as a treatment to reduce excess visceral abdominal fat in patients with HIV/ART-associated lipodystrophy[91]. Lifestyle modification and other pharmacologic interventions, such as the use of metformin[92], may also help to decrease truncal and visceral fat. Cosmetic surgery (e.g. liposuction) is an option for the management of large dorsocervical lipomatosis, although the risk of recurrence exists.

Malnutrition

Decreased appetite and reduced intake of food along with nausea and malabsorption are common in HIV-infected patients, and they often suffer from gastrointestinal side effects of medications and infectious diarrhea. Cutaneous manifestations of malnutrition may be encountered, including those associated with kwashiorkor and deficiencies of vitamins B_{12} and A[93,94] (see Ch. 51). Nutritional replacement should be initiated once the deficiency is recognized, as severe malnutrition can be life-threatening[93,95].

Miscellaneous Conditions

Primary cutaneous mucinoses have been linked to HIV infection (see Ch. 46). Most commonly, localized lichen myxedematosus or acral persistent papular mucinosis occurs in an individual with a relatively advanced stage of HIV infection. *Granuloma annulare* is also occasionally observed in HIV-infected patients, and the lesions may be widely disseminated or have an atypical distribution pattern. *Major aphthae* (especially oral lesions; see Ch. 72) can represent a therapeutic challenge in HIV-infected individuals. After excluding infectious etiologies (see Table 78.3), systemic therapy (e.g. thalidomide) is often required. Additional findings that are occasionally observed in individuals with HIV infection include *hyperpigmentation* (in addition to that related to photosensitivity, systemic drugs or adrenal insufficiency), especially of the face, and *linear telangiectasias* on the chest.

NEOPLASTIC HIV-RELATED CUTANEOUS DISORDERS

A number of different cutaneous neoplasms may develop in patients with HIV infection. Diagnosis is established primarily by clinical assessment and histologic examination. Aggressive treatment and heightened awareness are imperative for improving prognosis.

Squamous and Basal Cell Carcinomas

As in immunocompetent individuals, fair skin and sun exposure (cumulative and intense intermittent) are risk factors for the development of basal cell carcinoma (BCC) and SCC[96]. Compared with the general population, HIV-infected individuals have a three- to fivefold higher risk of developing these non-melanoma skin cancers, which tend to appear at a younger age and are more often multifocal and located on the trunk and extremities[20,96–98]. Cutaneous SCCs in HIV-infected individuals have a high risk of recurrence and metastasis. Although BCC metastases have been reported, overall, BCCs do not behave more aggressively in patients with HIV infection[20]. As discussed above, HPV infection (in particular, high-risk genital and genus beta types) increases the risk of anogenital, oral, digital and EDV-associated cutaneous SCCs in HIV-infected individuals[37–39], and aggressive treatment is often required to prevent recurrences and metastases[20]. Monitoring strategies for HPV-associated AIN, CIN and SCC are outlined in the section on HPV (see above).

Lymphomas

Cutaneous lymphomas of B- or T-cell lineage may develop in HIV-infected adults and children[98,99], often in the setting of significant immune suppression with $CD4^+$ counts <200 cells/mm^3. Clinically, pink to violaceous papules and nodules are usually seen; the lesions often ulcerate and sometimes simulate panniculitis[20]. HIV infection-associated lymphomas are most often non-Hodgkin B-cell type and high or intermediate grade. Additional differences from lymphomas in the general population include a younger age of onset, more advanced stages and extranodal involvement (especially of the CNS, intestine and skin) at presentation[24]. Approximately one-half of non-Hodgkin lymphomas in HIV-infected patients are associated with EBV infection.

A decrease in the incidence of all types of lymphoma in HIV-infected individuals has been noted since the introduction of ART. Antiretroviral therapy also significantly improves the clinical outcome and overall survival of patients with AIDS-related lymphoma. A prior diagnosis of AIDS (see Table 78.1) and bone marrow involvement are associated with an unfavorable prognosis[100].

Cutaneous T-cell lymphoma, in particular the mycosis fungoides variant, and T-cell lymphoproliferative disorders (which can mimic mycosis fungoides clinically) can occur in patients with HIV infection[20,24,42,98], albeit much less frequently than B-cell lymphomas. The possibility of adult T-cell leukemia and lymphoma caused by human T-cell leukemia/lymphotropic virus type I (HTLV-1) needs to be considered and excluded.

Kaposi Sarcoma

The neoplasm most closely associated with HIV infection is Kaposi sarcoma (KS)[101]. With the widespread use of ART, the incidence of HIV-related KS has declined significantly in high-income countries. However, elsewhere it remains a significant source of morbidity, especially in sub-Saharan Africa. The etiologic agent, human herpesvirus type 8 (HHV-8), can be transmitted via exposure to the semen or saliva of infected individuals[24,99] (see Ch. 80). It is estimated that KS comprises 20% of childhood malignancies in African countries.

Clinically, skin lesions vary from small violaceous papules to large plaques to ulcerated nodules[42] (Fig. 78.13). The upper body is typically involved, often along skin lines in a pityriasis rosea-like pattern and at sites of local trauma[20,24]. Lesions also develop on the face, in particular the nose, and on oral mucosal surfaces, including the gingiva and hard palate[20]. Internal involvement is common in HIV-related KS, most often affecting the lymph nodes (potentially leading to lymphedema), gastrointestinal tract and lungs.

Several treatment options exist and should be selected according to the stage of HIV disease, the extent of KS involvement, comorbidities, and the likelihood of receiving effective ART. Regression may be observed with reversal of immune suppression by ART, and for patients with less extensive disease, it may be reasonable to start ART alone and monitor the response. However, flares of KS can also occur as a manifestation of immune reconstitution following initiation of ART.

HIV-associated KS responds fairly well to local destruction, e.g. cryotherapy, topical alitretinoin (9-*cis*-retinoic acid) gel, superficial radiotherapy, intralesional vinblastine or interferon, and intravenous liposomally encapsulated doxorubicin, daunorubicin or paclitaxel[24,102,103]. Radiotherapy is contraindicated for oral lesions, as AIDS patients are more likely to develop severe radiation-associated mucosal ulcers and stomatitis.

Other Cutaneous Neoplasms

Eruptive atypical nevi have been described in HIV-positive patients[42]. Melanoma has been reported in association with HIV infection, but the prognosis (based on AJCC staging) is similar to that seen in immunocompetent hosts[21]. Cutaneous smooth muscle tumors, including leiomyomas and leiomyosarcoma, occur more frequently in HIV-infected pediatric patients and may be associated with EBV infection[24,104].

DIFFERENTIAL DIAGNOSIS AND DIAGNOSIS

Differential Diagnosis of HIV-associated Skin Conditions

As noted above, HIV-infected individuals can develop a wide variety of infectious, inflammatory and neoplastic disorders of the skin, many of which have overlapping clinical features. Cutaneous eruptions range

Fig. 78.13 Kaposi sarcoma in the setting of HIV infection. Violaceous papules and plaques on the face (**A**), palate (**B**), trunk (**C**) and extremity (**D**). Oral candidiasis is also seen (**B**). Some of the lesions on the back follow cleavage lines (**C**). *D, Courtesy, Thomas Horn, MD.*

from "textbook" classic forms to bizarre variants that present a diagnostic challenge. Serious and potentially fatal diseases must be considered and distinguished first and foremost. In particular, disseminated fungal infections and adverse drug reactions (see below) may be life-threatening and require early intervention with systemic antifungal agents or withdrawal of the offending medication, respectively.

The spectrum of cutaneous diseases tends to correlate with the immune status of the HIV-infected patient. Although HIV-1 RNA (copies/ml plasma) is a marker for disease progression, levels vary during acute infection and no defined relationship between viral load and opportunistic infections exists. However, an association between HIV-related disease incidence and the $CD4^+$ cell count has been established[105] (see Table 78.2), and this allows for a more focused differential diagnosis. In general, disseminated and extensive disease presentations occur with increasing frequency at lower $CD4^+$ cell counts.

Although it does not induce an immunodeficiency syndrome, HTLV-1 primarily infects $CD4^+$ lymphocytes in a mechanism similar to that of HIV-1 and HIV-2. HTLV-1 is endemic primarily in the Caribbean basin, southern Japan, northern Iran, Papua New Guinea and some parts of Africa and also exhibits vertical (mother-to-child) transmission. Co-infections with HIV and HTLV-1 have generated substantial interest. The incidence ranges from 3% to 25% of HIV-infected individuals. It has been postulated that an HTLV-1 protein acts indirectly on the long terminal repeat (LTR) region of both HTLV-1 and HIV-1, inducing interleukin-2 (IL-2) and IL-2 receptors that accelerate HIV-1 proliferation and subsequent T-cell death. Interestingly, co-infection is associated with higher $CD4^+$ cell counts (by 75–80%). However, the lymphocyte proliferation is nonspecific and does not appear to provide immunologic benefit. Thus, in patients co-infected with HIV-1 and HTLV-1, the absolute $CD4^+$ cell count may not be as reliable as in others with regard to immune status[11]. The HTVL-1-related diseases infective dermatitis and adult T-cell leukemia/lymphoma are discussed in Chapters 13 and 120, respectively.

Diagnosis of HIV-associated Skin Conditions and HIV Infection

In HIV-infected patients, the diagnosis of cutaneous disorders is established based on the clinical appearance coupled with confirmatory studies such as scrapings, cultures, biopsies and serologic assays. Given their immunocompromised state, patients often have mixed infections (Fig. 78.14) or combination infectious–neoplastic or inflammatory–neoplastic lesions. Other factors such as age, sex and anatomic distribution assist in narrowing the differential diagnosis.

Virtually any cutaneous lesion in an HIV-infected patient may be caused by a potentially treatable infectious agent. Histologic examination and culture of biopsy specimens may be required for diagnosis. Additional evaluation with special stains and serologic or molecular tests may be necessary. Special growth requirements for fastidious opportunistic organisms need to be anticipated. It should be remembered that mixed infections may also be present[12].

HIV serologic testing should be performed in any patient who requests it. Testing is recommended for individuals in high-risk groups (e.g. men who have sex with men, intravenous drug users, commercial sex workers) and those who have sexually transmitted infections, active tuberculosis or are pregnant. Atypical herpes zoster (especially in a young person), chronic HSV infection, refractory mucocutaneous candidiasis, generalized lymphadenopathy, extranodal lymphoma or the

Fig. 78.14 Oral herpes simplex viral infection and oral candidiasis. This combined infection was in an otherwise healthy young man who proved to be HIV-positive.

Fig. 78.15 Exacerbation of leprosy due to immune reconstitution inflammatory syndrome following institution of ART therapy. *Courtesy, Beatriz Trope, MD PhD.*

occurrence of generalized pruritus, dementia, aseptic meningitis, peripheral neuropathy, fever, diarrhea or weight loss with unknown etiology should prompt testing for HIV.

HIV seroconversion usually occurs 6 weeks after initial infection. Criteria for HIV seropositivity include positive ELISA results confirmed by a positive Western blot study (usually requiring reactivity against at least two of the viral protein markers p24, gp41 or gp120/160). Non-reactive results are obtained during a seronegative "window" that can last up to 3 months after the initial infection. Thus, if HIV infection is strongly suspected, methods for detection of viral antigens or nucleic acid rather than anti-HIV antibodies need to be employed. Fourth-generation HIV screening assays have been developed that attempt to shorten the seronegative window by simultaneous detection of anti-HIV antibodies and p24 antigen.

Early (i.e. in the process of seroconversion) or advanced HIV disease, HIV-2 infection, the presence of alloantibodies (seen with pregnancy, blood transfusions or organ transplantation) or autoantibodies (seen in autoimmune connective tissue diseases, other autoimmune diseases or malignancy) may lead to an indeterminate test result in which both the ELISA and Western blot studies are positive but with reactivity against only one protein marker present. Repeat tests should be performed in 2–6 months for confirmation. Individuals with an indeterminate test result who are in the process of seroconverting will usually become seropositive within 1 month.

If necessary, HIV RNA or DNA PCR and/or isolation of the virus by culture can be used to confirm the diagnosis in questionable cases. However, the specificity of a single plasma viral load test is only about 97% and false-positive results, particularly in the range of <5000 copies/ml, have been described[106]. Importantly, HIV postexposure prophylaxis may hamper detection of the virus by culture or PCR and delay seroconversion.

TREATMENT

Antiretroviral Therapy (ART)

Fifteen years ago, the treatment of HIV infection was revolutionized by the development of combination ART regimens (previously known as HAART). The different classes of antiretroviral agents target various aspects of the HIV life cycle (see Fig. 78.2): (1) *nucleoside* (including zidovudine [AZT], the first agent developed [in 1987]), *nucleotide* and *non-nucleoside reverse transcriptase inhibitors* (*NRTIs, NtRTIs and NNRTIs,* respectively) terminate viral DNA chain synthesis; (2) the *integrase inhibitor* prevents integration of viral DNA into the host genome; (3) *protease inhibitors* abrogate viral processing and assembly; (4) the *CC-chemokine receptor 5 (CCR5) inhibitor* blocks binding of viral particles to the CCR5 co-receptor on host cells (with a host rather than viral target); and (5) the *fusion inhibitor* disrupts fusion of the viral envelope with the cell membrane (Table 78.4). ART can profoundly suppress viral propagation, leading to the reconstitution of $CD4^+$ lymphocyte counts and a dramatic decrease in disease-related morbidity and mortality. As a consequence, the annual mortality from AIDS has declined by >75% since 1995 in high-income countries.

Currently, first-line initial ART includes two N(t)RTIs (typically tenofovir and emtricitabine) and one NNRTI (usually efavirenz). The International AIDS Society–USA 2010 guidelines for adults with HIV infection recommend introduction of ART for symptomatic patients and asymptomatic patients with a $CD4^+$ cell count ≤500 cells/mm^3 or certain conditions/comorbidities (e.g. HIV RNA >100 000 copies/ml, decline in the $CD4^+$ cell count of >100 cells/mm^3/year, pregnancy, active hepatitis B or C viral infection, cardiovascular disease, a serodiscordant partner)[107]. Important factors to consider include viral resistance, patient adherence, potential adverse effects and drug interactions.

Response to therapy is monitored by quantitative HIV RNA PCR (as plasma viremia is a strong prognostic indicator of HIV disease progression)[108]. Suppression of HIV replication to below the limit of quantification for as long as possible is therefore a critical goal of ART. When HIV replication is adequately suppressed (i.e. below 50 copies/ml plasma), evolution of viral resistance to antiretroviral drugs is minimal. However, continuous replication in the presence of antiretroviral drugs, whether due to patient non-adherence, pre-existent drug resistance and/or low drug levels, can rapidly exhaust currently available treatment options.

In addition to increasing life expectancy in those with HIV infection, ART has resulted in a significant decrease in the incidence of several of its cutaneous manifestations, including candidiasis, KS, eosinophilic folliculitis, opportunistic mycoses/mycobacterioses, and oral hairy leukoplakia. However, the prevalence of HPV and poxvirus infections and incidence of anal cancer have actually increased[30]. It is possible that other cutaneous neoplasms will be seen with greater frequency as patients survive longer. While in developed countries the spectrum of concerns related to HIV has shifted from opportunistic infections to long-term complications (e.g. cancer, co-infection with other viruses such as hepatitis C, and the metabolic effects of ART), patients in developing countries continue to be ravaged by HIV infection, with high treatment costs and underdeveloped infrastructure continuing to be major obstacles.

Immune Reconstitution Inflammatory Syndrome (IRIS)

Paradoxically, exacerbations of the clinical manifestations of infectious and neoplastic (due to inflammatory immune reactions) as well as inflammatory diseases have been observed following institution of ART, especially when $CD4^+$ cell counts rise at least twofold from depressed levels (usually <50 cells/mm^3). Examples include herpes zoster, leprosy (Fig. 78.15), and disseminated *Mycobacterium avium* complex and CMV infections. This phenomenon has been referred to by various names, including IRIS, immune reconstitution-associated disease (IRAD) and immune reconstitution/recovery/restoration disease/syndrome. Distinguishing IRIS-associated flares of inflammation from active opportunistic infections or drug reactions may be difficult[27,109]. The majority of patients with IRIS have cutaneous

ADVERSE REACTIONS TO DRUGS USED TO TREAT HIV INFECTION		
Drug (abbreviation, trade name)	**Important adverse reactions/interactions**	
	Mucocutaneous	**Other**
NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS		
Abacavir (ABC, Ziagen®)	• Hypersensitivity syndrome*, Sweet's syndrome (rare)	• Hypersensitivity syndrome*,†
Didanosine (ddI, Videx®)	• Xerostomia, alopecia • Lipodystrophy • Small vessel vasculitis (rare)	• Pancreatitis, optic neuritis, peripheral neuropathy, lactic acidosis, hepatic steatosis
Emtricitabine (FTC, Emtriva®)	• Xerosis, "rash" (morbilliform, pustular, urticaria), palmoplantar hyperpigmentation	†
Lamivudine (3TC, Epivir®)	• Paronychia, alopecia, "rash", pruritus	• Pancreatitis (pediatric patients)†
Stavudine (d4T, Zerit®)	• Lipodystrophy • Peripheral edema	• Peripheral neuropathy, pancreatitis, muscle weakness, lactic acidosis, hepatic steatosis
Tenofovir (TDF, Viread®)	• Morbilliform, vesicular and urticarial eruptions	• Renal impairment, hypophosphatemia
Zalcitabine (ddC, Hivid®)‡	• Macular eruption, urticaria, oral/esophageal ulcers	• Pancreatitis, peripheral neuropathy†
Zidovudine (AZT, Retrovir®)	• Blue–brown pigmentation of nails and mucosae, cutaneous hyperpigmentation • Urticaria, morbilliform eruption, small vessel vasculitis, anaphylaxis • Lipodystrophy • Acral/periarticular reticulate erythema	• Bone marrow suppression, increased MCV, thrombocytopenia, nausea, dilated cardiomyopathy, myopathy, lactic acidosis, hepatic steatosis
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS		
Delavirdine (DLV, Rescriptor®) Efavirenz (EFV, Sustiva®) Etravirine (ETR, Intelence®) Nevirapine (NVP, Viramune®) Rilpivirine (RPV, Edurant®)	• Morbilliform eruption (usually within first 3–6 weeks), SJS, TEN, DRESS • In the case of nevirapine, higher incidence (especially in women), which may be reduced by dose escalation; also oral ulcers	• Hepatotoxicity • CNS symptoms • Delaviridine inhibits CYP450 3A4, nevirapine induces CYP450 3A4
INTEGRASE INHIBITOR		
Raltegravir (RAL, Isentress®)	• "Rash", SJS, TEN, DRESS	• Myopathy, rhabdomyolysis
PROTEASE INHIBITORS		
Amprenavir (APV, Agenerase®)‡ Atazanavir (ATV, Reyataz®) Darunavir (Prezista®) Fosamprenavir (FPV, Lexiva®) Indinavir (IDV, Crixivan®) Lopinavir/Ritonavir (Kaletra®) Nelfinavir (NFV, Viracept®) Ritonavir (RTV, Norvir®) Saquinavir (SQV, Invirase®) Tipranavir (TPV, Aptivus®)	• Morbilliform eruption, generalized erythema, SJS • Lipodystrophy syndrome, striae formation • Paronychia, ingrown toenails • Pruritus, xerosis • Desquamative cheilitis, oral numbness • Icterus, esp. atazanavir	• Hyperlipidemia, insulin resistance • Increased risk of cardiovascular disease with long-term exposure • Spontaneous bleeding in hemophiliacs • Avascular necrosis of the hip • Hepatotoxicity • Metallic taste, esp. indinavir • Inhibit CYP450 3A4, esp. ritonavir
CC-CHEMOKINE RECEPTOR 5 (CCR5) INHIBITOR		
Maraviroc (MVC, Selzentry®)§	• "Rash"	• Hepatotoxicity with allergic features • May increase risk of myocardial ischemia • Postural hypotension
FUSION INHIBITOR		
Enfuvirtide (T-20, Fuzeon®)	• Injection site reactions (granulomatous inflammation) • Morbilliform eruption	• Frequency of painful injection site reactions and high cost limit use
COMBINATIONS		
Abacavir/Lamivudine (ABC/3TC, Epzicom®) Efavirenz/Emtricitabine/Tenofovir (EFV/FTC/TDF, Atripla®) Emtricitabine/Tenofovir (FTC/TDF, Truvada®) Emtricitabine/rilpivirine/tenofovir DF (FTC/RPV/TDF, Complera®) Lamivudine/Zidovudine (3TC/AZT, Combivir®) Abacavir/Lamivudine/Zidovudine (ABC/3TC/AZT, Trizivir®)	See above	See above

*Includes fever, malaise, gastrointestinal symptoms and sometimes a cutaneous eruption; occurs in 5–8% of patients within the first 8 weeks of receiving abacavir and is an absolute contraindication for repeat administration; associated with HLA-B*5701 allele, screening for which is commercially available and recommended prior to initiating/reinitiating therapy.
†Uncommonly lactic acidosis and hepatic steatosis.
‡No longer available in the US.
§Requires an assay to screen for co-receptor tropism, since this drug is only active in patients who do not have virions that use CXCR4 for cell entry; has an immunomodulatory effect that is independent of its effect on HIV replication.

Table 78.4 Adverse reactions to drugs used to treat HIV infection. CY, cytochrome; DRESS, drug rash with eosinophilia and systemic symptoms; MCV, mean corpuscular volume; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

CUTANEOUS DISEASES THAT CAN "FLARE" DUE TO THE IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME
INFECTIONS
Mycobacterium tuberculosis
Mycobacterium leprae
Mycobacterium avium complex and other species
Herpes simplex virus 1 and 2
Varicella–zoster virus
EBV (e.g. oral hairy leukoplakia)
Cytomegalovirus
Human papillomavirus
Molluscum contagiosum virus
Candida spp.
Dermatophytes
Cryptococcus spp.
Histoplasma capsulatum, *Penicillium marneffei*
Demodex, *Malassezia* spp. (e.g. folliculitis)
Leishmania spp.
INFLAMMATORY DISORDERS
Psoriasis, seborrheic dermatitis
Sarcoidosis
Foreign body reactions (granulomatous)
Eosinophilic folliculitis
Acne vulgaris, rosacea
Papular pruritic eruption
Lupus erythematosus (systemic, discoid, tumid), relapsing polychondritis
Alopecia areata
Dyshidrotic eczema
NEOPLASMS
Kaposi sarcoma
Non-Hodgkin lymphoma
Multiple eruptive dermatofibromas

Table 78.5 Cutaneous diseases that can "flare" due to the immune reconstitution inflammatory syndrome (IRIS).

manifestations, and skin diseases that can be exacerbated by IRIS are listed in Table 78.5[110].

Drug–Drug Interactions

Knowledge of potential drug interactions is necessary to prevent adverse reactions and therapeutic failures. The human cytochrome P450 system metabolizes a number of drugs used to treat HIV infection and associated complications. Cytochrome P450 3A4 inhibitors, which include most of the protease inhibitors and delavirdine, impair drug metabolism, leading to accumulation of drugs that share the same metabolic pathway (see Ch. 131). Cytochrome P450 3A4 mixed inducers/inhibitors and inducers (e.g. efavirenz and nevirapine, respectively) may accelerate clearance of other medications and may necessitate dose adjustments. Cytochrome P450-independent interactions include: (1) an increase in intracellular drug levels and toxicity of didanosine when used in combination with ribavirin and/or tenofovir[111]; and (2) a decrease in atazanavir concentration when coadministered with tenofovir[112].

Drug Eruptions

Adverse cutaneous reactions to drugs can range from extremely mild to life-threatening, and they may be caused by either a single drug or drug combinations[110,113,114]. Unfortunately, drug eruptions are common in HIV-infected individuals, likely reflecting underlying immune dysregulation, and represent a frequent source of morbidity. Because these patients typically take multiple medications, identification of the causal agent or combination of agents is often a complex and frustrating process (see Ch. 21).

Morbilliform drug eruptions are the most common presentation of drug hypersensitivity, and the incidence is significantly higher in HIV-infected patients than in the general population. Patients may also present with urticaria, pruritus, vasculitis, exfoliative erythroderma, photodermatitis, Stevens–Johnson syndrome and toxic epidermal necrolysis. An adverse drug reaction should be high on the differential diagnosis list when a patient taking several medications develops a cutaneous eruption.

Protease inhibitors may cause retinoid-like effects, including paronychia, ingrown toenails, desquamative cheilitis and xerosis[77]. Lipodystrophy syndrome, as described previously, may also develop. Oral numbness has been observed, especially with therapeutic doses of ritonavir[115]. The major cutaneous and extracutaneous side effects of the other classes of antiretroviral drugs are outlined in Table 78.4.

Trimethoprim–sulfamethoxazole (TMP-SMX) is the most common drug to cause a cutaneous reaction in HIV-infected patients[20]. Often taken for prophylaxis or treatment of *Pneumocystis jiroveci* pneumonia or toxoplasmosis, TMP-SMX leads to an exanthematous eruption and fever in 50–60% of HIV-infected patients treated intravenously with this agent (typically 8–12 days after initiating therapy). This occurrence is 10 times more frequent than in the general population[66]. Stevens–Johnson syndrome and toxic epidermal necrolysis can also occur secondary to TMP-SMX.

Although close observation and documentation is often adequate as most cutaneous drug eruptions regress (especially the morbilliform type), if systemic signs such as fever develop or epidermal detachment is observed, the suspected offending agent(s) should be withdrawn immediately as this may herald a more serious, possibly life-threatening, complication. With some drugs such as zidovudine, sulfonamides and dapsone, patients may be successfully desensitized after an adverse drug reaction[66]. Drug rechallenge should be done under controlled circumstances. Rechallenge is contraindicated for abacavir and is not recommended for NNRTIs.

CONCLUSIONS

The number and variety of cutaneous manifestations of HIV infection are greater than those in any other organ. These complications are a source of significant morbidity and, in some cases, mortality. Although ART has decreased the incidence of many opportunistic infections, other adverse sequelae such as IRIS, drug reactions, metabolic disturbances, HPV infections and SCCs remain common and may even be increasing in incidence due to longer survival of HIV-infected individuals. By recognizing the spectrum of skin conditions associated with HIV infection and performing appropriate diagnostic tests, treatment can be administered in a timely fashion and outcomes optimized.

REFERENCES

1. Gottlieb MS, Schroff R, Schanker HM, et al. *Pneumocystis carinii* pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. N Engl J Med. 1981;105:1425–31.
2. Anonymous. First report of AIDS. MMWR Morb Mortal Wkly Rep. 2001;50:429.
3. Gottlieb MS. AIDS – past and future. N Engl J Med. 2001;344:1788–91.
4. Joint United Nations Programme on HIV/AIDS. UNAIDS Report on the Global AIDS epidermic 2010: www.unaids.org/globalreport/Global_report.htm.
5. The World Health Organization Fact Sheets: www.who.int/mediacentre/factsheets/fs310/en/index.html.
6. Anonymous. The global HIV and AIDS epidemic, 2001. MMWR Morb Mortal Wkly Rep. 2001;50:434–9.
7. Piot P, Bartos M, Ghys PD, et al. The global impact of HIV/AIDS. Nature. 2001:410:968–73.
8. O'Connell KA, Bailey JR, Blankson JN. Elucidating the elite: mechanisms of control in HIV-1 infection. Trends Pharmacol Sci. 2009;30:631–7.
9. McMichael AJ, Borrow P, Tomaras GD, et al. The immune response during acute HIV-1 infection: clues for vaccine development. Nat Rev Immunol. 2010;10:11–23.
10. Weiss RA. Gulliver's travels in HIVland. Nature. 2001;410:963–7.
11. Harrison LH, Schechter M. Coinfection with HTLV-1 and HIV: increase in HTLV-1-related outcomes but not accelerated HIV disease progression? AIDS Patient Care STDs. 1998;12:619–23.
12. Bartlett JG, Gallant JE. 2000–2001 Medical Management of HIV Infection. Baltimore: Johns Hopkins University Press, 2000 (see *http://www.hopkins-aids.edu*).
13. Gupta KK. Acute immunosuppression with HIV seroconversion. N Engl J Med. 1993;41:88–90.
14. Vento S, Di Perri G, Garofano T, et al. *Pneumocystis carinii* pneumonia during primary HIV-1 infection. Lancet. 1993;342:24–5.
15. Safrin S, Ashley R, Houlihan C, et al. Clinical and serologic features of herpes simplex virus infection in patients with AIDS. AIDS. 1991;5:1107–10.

16. Schacker T, Zeh J, Hu HL, et al. Frequency of symptomatic and asymptomatic herpes simplex virus type 2 reactivations among human immunodeficiency virus-infected men. J Infect Dis. 1998;78:1616–22.
17. Bagdades EK, Pillay D, Squire SB, et al. Relationship between herpes simplex virus ulceration and CD4+ cell counts in patients with HIV infection. AIDS. 1992; 6:1317–20.
18. Salvini F, Carminati G, Pinzani R, et al. Chronic ulcerative herpes simplex virus infection in HIV-infected children. AIDS Patient Care STDs. 1997;11:421–8.
19. Weinberg JM, Turiansky GW, James WD. Viral folliculitis. AIDS Patient Care STDs. 1999;13:513–16.
20. Porras B, Costner M, Friedman-Kien AE, Cockerell CJ. Update on cutaneous manifestations of HIV infection. Med Clin North Am. 1998;82:1033–80.
21. Wong D, Shumack S. Managing HIV. Part 5: Treating secondary outcomes. 5.1 HIV and skin disease. Med J Aust. 1996;164:352–6.
22. Helton JL. Genital dermatology in the HIV-infected patient. AIDS Patient Care STDs. 1997;11:237–43.
23. Erlich KS, Mills J, Chatis P, et al. Acyclovir-resistant herpes simplex virus infections in patients with the acquired immunodeficiency syndrome. N Engl J Med. 1989;320:293–6.
24. Myskowski PL, Ahkami R. Dermatologic complications of HIV infection. Med Clin North Am. 1996;80: 1415–35.
25. Vafai A, Berger M. Zoster in patients infected with HIV: a review. Am J Med Sci. 2001;321:372–80.
26. Foltyn P, Marriott D, Managing HIV. Part 5: Treating secondary outcomes. 5.2 HIV and oral disease. Med J Aust. 1996;164:357–9.
27. Masur H, Kaplan J. Current status of opportunistic infection in patients with HIV infection in the era of highly active antiretroviral therapy. Curr Clin Top Infect Dis. 2001;21:64–82.
28. Husak R, Garbe C, Orfanos CE. Mollusca contagiosa in HIV infection. Clinical manifestation, relation to immune status and prognostic value in 39 patients. Hautarzt. 1997;48:103–9.
29. Diven DG. An overview of poxviruses. J Am Acad Dermatol. 2001;44:1–16.
30. Hengge UR, Franz B, Goos M. Decline of infectious skin manifestations in the era of highly active antiretroviral therapy. AIDS. 2000;14:1069–70.
31. Toro JR, Wood LV, Patel NK, Turner ML. Topical cidofovir: a novel treatment for recalcitrant molluscum contagiosum in children infected with human immunodeficiency virus 1. Arch Dermatol. 2000; 136:983–5.
32. Rozenberg F, Deleuze J, Morini JP, et al. Epidermodysplasia verruciformis in human immunodeficiency virus-infected patients: a marker of human papillomavirus-related disorders not affected by antiretroviral therapy. Arch Dermatol. 2011;147:590–6.
33. Gormley RH, Groft CM, Miller CJ, et al. Digital squamous cell carcinoma and association with diverse high-risk human papillomavirus types. J Am Acad Dermatol. 2011;64:981–5.
34. Meys R, Gotch FM, Bunker CB. Human papillomavirus in the HAART era of HIV: an immune reconstitution associated disease (IRAD)? Br J Dermatol. 2010;162:6–11.
35. Meys R, Macedo C, Jones R, et al. Cutaneous human papillomavirus-related immune reconstitution-associated disease in human immunodeficiency virus: an under-recognized phenomenon. Br J Dermatol. 2011;164:458–9.
36. Kreuter A, Potthoff A, Brockmeyer NH, et al. German Competence Network HIV/AIDS. Anal carcinoma in human immunodeficiency virus-positive men: results of a prospective study from Germany. Br J Dermatol. 2010;162:1269–77.
37. Seaberg EC, Wiley D, Martínez-Maza O. Cancer incidence in the multicenter AIDS Cohort Study before and during the HAART era: 1984 to 2007. Cancer. 2010;116:5507–16.
38. Simard EP, Pfeiffer RM, Engels EA. Cumulative incidence of cancer among individuals with acquired immunodeficiency syndrome in the United States. Cancer. 2011;117:1089–96.
39. Chaturvedi AK, Madeleine MM, Biggar RJ, Engels EA. Risk of human papillomavirus-associated cancers among persons with AIDS. J Natl Cancer Inst. 2009;101:1120–30.
40. Palefsky JM, Holly EA, Hogeboom CJ, et al. Anal cytology as a screening tool for anal squamous intraepithelial lesions. J Acquir Immune Defic Syndr Hum Retrovirol. 1997;14:415–22.
41. Lecours AD. Understanding common oral lesions associated with HIV. Clin Rev. 2001;11:96–106.
42. Ray MC, Gately LE III. Dermatologic manifestations of HIV infection and AIDS. Infect Dis Clin North Am. 1994; 8:583–605.
43. Dauden E, Fernandez-Buezo G, Fraga J, et al. Mucocutaneous presence of cytomegalovirus associated with human immunodeficiency virus infection: discussion regarding its pathogenetic role. Arch Dermatol. 2001;137:443–8.
44. Gasquet S, Maurin M, Brouqui P, et al. Bacillary angiomatosis in immunocompromised patients. AIDS. 1998;12:1793–803.
45. Koehler JE, Quinn FD, Berger TD, et al. Isolation of *Rochalimaea* species from cutaneous and osseous lesions of bacillary angiomatosis. N Engl J Med. 1992;327:1625–31.
46. Koehler JE, Tappero JW. Bacillary angiomatosis and bacillary peliosis in patients infected with human immunodeficiency virus. Clin Infect Dis. 1993;17:612–24.
47. Kumar B, Muralidhar S. Malignant syphilis: a review. AIDS Patient Care STDs. 1998;12:921–5.
48. Hengge UR, Franz B, Goos M. Decline of infectious skin manifestations in the era of highly active antiretroviral therapy. AIDS. 2000;14:1069–70.
49. Fidel PL Jr. Vaginal candidiasis: review and role of local mucosal immunity. AIDS Patient Care STDs. 1998;12: 359–66.
50. Arribas JR, Hernandez-Albujar S, Gonzalez-Garcia JJ, et al. Impact of protease inhibitor therapy on HIV-related oropharyngeal candidiasis. AIDS. 2000;14:979–85.
51. Cohen PR, Grossman ME. Recognizing skin lesions of systemic fungal infections in patients with AIDS. Am Fam Physician. 1994;49:1627–34.
52. Durden FM, Elewski B. Cutaneous involvement with *Cryptococcus neoformans* in AIDS. J Am Acad Dermatol. 1994;30:844–8.
53. Sandler B, Potter TS, Hashimoto K. Cutaneous *Pneumocystis carinii* and *Cryptococcus neoformans* in AIDS. Br J Dermatol. 1996;134:159–63.
54. Ledergerber B, Mocroft A, Reiss P. Discontinuation of secondary prophylaxis against *Pneumocystis carinii* pneumonia in patients with HIV infection, who have responded to antiretroviral therapy. N Engl J Med. 2001;344:168–74.
55. Lindoso JA, Barbosa RN, Posada-Vergara MP, et al. Unusual manifestations of tegumentary leishmaniasis in AIDS patients from the New World. Br J Dermatol. 2009;160:311–18.
56. Murray HW. Kala-azar as an AIDS-related opportunistic infection. AIDS Patient Care STDs. 1999;13:459–65.
57. Sundar S, Jha TK, Thakur CP, et al. Oral miltefosine for Indian visceral leishmaniasis. N Engl J Med. 2002; 347:1739–46.
58. Gompels MM, Todd J, Peters BS, et al. Disseminated strongyloidiasis in AIDS: uncommon but important. AIDS. 1991;5:329–32.
59. Sarangarajan R, Ranganathan A, Belmonte AH, Tchertkoff V. *Strongyloides stercoralis* infection in AIDS. AIDS Patient Care STDs. 1997;11:407–14.
60. Sison JP, Kemper CA, Loveless M, et al. Disseminated acanthamoeba infection in patients with AIDS: case reports and review. Clin Infect Dis. 1995;20:1207–16.
61. Schlesinger I, Oelrich M, Tyring SK. Crusted (Norwegian) scabies in patients with AIDS: the range of clinical presentations. South Med J. 1994;87:352–6.
62. Orkin M. Scabies in AIDS. Semin Dermatol. 1993;12:9–14.
63. Barrio J, Lecona M, Hernanz JM, et al. Rosacea-like demodicosis in an HIV-positive child. Dermatology. 1996;192:143–5.
64. Hamann ID, Barnetson RS. Non-infective mucocutaneous presentations of human immunodeficiency virus infection. Australas J Dermatol. 1997;38:105–12.
65. Morar N, Willis-Owen SA, Maurer T, Bunker CB. HIV-associated psoriasis: pathogenesis, clinical features, and management. Lancet Infect Dis. 2010;10:470–8.
66. Finkelstein M, Berman B. HIV and AIDS in inpatient dermatology. Dermatol Clin. 2000;18:509–20.
67. Memon K, Van Voorhees AS, Bebo BF, et al. Psoriasis in patients with HIV infection: from the Medical Board of the National Psoriasis Foundation. J Am Acad Dermatol. 2010;62:291–9.
68. Froschl M, Land HG, Landthaler M. Seborrheic dermatitis and atopic eczema in human immunodeficiency virus infection. Semin Dermatol. 1990;9:230–2.
69. Resneck JS Jr, Van Beek M, Furmanski L, et al. Etiology of pruritic papular eruption with HIV infection in Uganda. JAMA. 2004;292:2614–21.
70. Fearfield LA, Rowe A, Francis N, et al. Itchy folliculitis and human immunodeficiency virus infection: clinicopathological and immunological features, pathogenesis and treatment. Br J Dermatol. 1999; 141:3–11.
71. Berger TG, Heon V, King C, et al. Itraconazole therapy for human immunodeficiency virus-associated eosinophilic folliculitis. Arch Dermatol. 1995;131:358–60.
72. Hayes BB, Hille RC, Goldberg LJ. Eosinophilic folliculitis in two HIV-positive women. Arch Dermatol. 2004; 140:463–5.
73. Moyle M, Woolley IJ, Thevarajan I, Korman TM. Eosinophilic folliculitis: an example of "immune reconstitution folliculitis"? AIDS. 2004;18:2350–2.
74. Simpson-Dent S, Fearfield LA, Staughton RC. HIV associated eosinophilic folliculitis – differential diagnosis and management. Sex Transm Infect. 1999;75:291–3.
75. Prose NS, Abson KG, Scher RK. Disorders of the nails and hair associated with human immunodeficiency virus infection. Int J Dermatol. 1992;31:453–7.
76. Grossman MC, Cohen PR, Grossman ME. Acquired eyelash trichomegaly and alopecia areata in a human immunodeficiency virus-infected patient. Dermatology. 1996;193:52–3.
77. Garcia-Silva J, Almagro M, Juega J, et al. Protease inhibitor-related paronychia, ingrown toenails, desquamative cheilitis and cutaneous xerosis. AIDS. 2000;14:1289–91.
78. Cebrian M, Miro O, Font C, et al. HIV-related vasculitis. AIDS Patient Care STDs. 1997;11:245–58.
79. Chetty R. Vasculitides associated with HIV infection. J Clin Pathol. 2001;54:275–8.
80. Dronda F, Gonzalez-Lopez A, Lecona M, Barros C. Erythema elevatum diutinum in human immunodeficiency virus-infected patients – report of a case and review of the literature. Clin Exp Dermatol. 1996;21:222–5.
81. Blauvelt A, Harris HR, Hogan DJ, et al. Porphyria cutanea tarda and human immunodeficiency virus infection. Int J Dermatol. 1992;31:474–9.
82. O'Connor WJ. Porphyria cutanea tarda and HIV: two cases associated with hepatitis C. AIDS Patient Care STDs. 1998;12:341–6.
83. Liss M, Boyle BA. HAART-associated body habitus and metabolic changes, part 2. AIDS Read. 2000;10:688–91.
84. Liss M, Boyle BA. HAART-associated body habitus and metabolic changes, part 1. AIDS Read. 2000;10:622, 629–31.
85. Villarroya F, Domingo P, Giralt M. Lipodystrophy in HIV-1 infected patients: lessons for obesity research. Int J Obes (Lond). 2007;31:1763–76.
86. Shlay JC, Visnegarwala F, Bartsch G, et al. Body composition and metabolic changes in antiretroviral-naive patients randomized to didanosine and stavudine vs. abacavir and lamivudine. J Acquir Immune Defic Syndr. 2005;38:147–55.
87. McComsey G, Ward D, Hessenthaler S, et al. Improvement in lipoatrophy associated with highly active antiretroviral therapy in human immunodeficiency virus-infected patients switched from stavudine to abacavir or zidovudine: The results of the TARHEEL study. Clin Infect Dis. 2004;38:263–70.
88. del Mar Gutierrez M, Mateo G, Domingo P. Strategies in the treatment of HIV-1-associated adipose redistribution syndromes. Expert Opin Pharmacother. 2007;8:1871–84.
89. Negredo E, Higueras C, Adell X, et al. Reconstructive treatment for antiretroviral-associated facial lipoatrophy: a prospective study comparing autologous fat and synthetic substances. AIDS Patient Care STDS. 2006;20:829–37.
90. Burgess CM, Quiroga RM. Assessment of the safety and efficacy of poly-L-lactic acid for the treatment of HIV-associated facial lipoatrophy. J Am Acad Dermatol. 2005;52:233–9.
91. Falutz J, Mamputu JC, Potvin D, et al. Effects of tesamorelin (TH9507), a growth hormone-releasing factor analog, in human immunodeficiency virus-infected patients with excess abdominal fat: a pooled analysis of two multicenter, double-blind placebo-controlled phase 3 trials with safety extension data. J Clin Endocrinol Metab. 2010;95:4291–304.

92. van Wijk JP, de Koning EJ, Cabezas MC, et al. Comparison of rosiglitazone and metformin for treating HIV lipodystrophy: a randomized trial. Ann Intern Med. 2005;143:337–46.
93. Tang AM, Smit E. Selected vitamins in HIV infection: a review. AIDS Patient Care STDs. 1998;12:263–73.
94. Alam M, Grossman ME, Longley BJ, Schneiderman PI. Kwashiorkor in patients with AIDS. Cutis. 2001;67:321–4, 327.
95. Kennedy CM, Kuhn L, Stein Z. Vitamin A and HIV infection: disease progression, mortality and transmission. Nutr Rev. 2000;58:291–303.
96. Volm MD, Von Roenn JH. Non-AIDS-defining malignancies in patients with HIV infection. Curr Opin Oncol. 1996;8:386–91.
97. Mueller N. Overview of the epidemiology of malignancy in immune deficiency. J Acquir Immune Defic Syndr. 1999;21(suppl. 1):S5–10.
98. Wilkins K, Turner R, Dolev JC, et al. Cutaneous malignancy and human immunodeficiency virus disease. J Am Acad Dermatol. 2006;54:189–206.
99. Levine AM, Scadden DT, Zaia JA, Krishnan A. Hematologic aspects of HIV/AIDS. Hematology Am Soc Hematol Educ Program. 2001;463–78.
100. Lascaux AS, Hemery F, Goujard C, et al. Beneficial effect of highly active antiretroviral therapy on the prognosis of AIDS-related systemic non-Hodgkin lymphomas. AIDS Res Hum Retroviruses. 2005;21:214–20.
101. Duvic M. Human immunodeficiency virus and the skin: selected controversies. J Invest Dermatol. 1995;105(suppl.):117S–21S.
102. Wernz JC. Liposomal drug targeting in the treatment of Kaposi's sarcoma. AIDS Patient Care STDs. 1996;10:362–7.
103. Gill P, Tulpule A, Espina BM, et al. Paclitaxel is safe and effective in the treatment of advanced AIDS-related Kaposi's sarcoma. J Clin Oncol. 1999;17:1876–83.
104. Mueller BU. HIV-associated malignancies in children. AIDS Patient Care STDs. 1999;13:527–33.
105. Jung AC, Paauw DS. Diagnosing HIV-related disease: using the CD4 count as a guide. J Gen Intern Med. 1998;13:131–6.
106. Rich JD, Merriman NA, Mylonakis E, et al. Misdiagnosis of HIV infection by HIV-1 plasma viral load testing: a case series. Ann Intern Med. 1999;130:37–9.
107. Thompson MA, Aberg JA, Cahn P, et al. Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society-USA panel. JAMA. 2010;304:321–33.
108. Mellors JW, Rinaldo CR Jr, Gupta P, et al. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. Science. 1996;272:1167–70.
109. Hengge UR, Franz B, Goos M. Decline of infectious skin manifestations in the era of highly active antiretroviral therapy. AIDS. 2000;14:1069–70.
110. Introcaso CE, Hines JM, Kovarik CL. Cutaneous toxicities of antiretroviral therapy for HIV: part II. Nonnucleoside reverse transcriptase inhibitors, entry and fusion inhibitors, integrase inhibitors, and immune reconstitution syndrome. J Am Acad Dermatol. 2010;63:563–9.
111. Fleischer R, Boxwell D, Sherman K. Nucleoside analogues and mitochondrial toxicity. Clin Infect Dis. 2004;38:e79–80.
112. Taburet AM, Piketty C, Chazallon C, et al. Interactions between atazanavir-ritonavir and tenofovir in heavily pretreated human immunodeficiency virus-infected patients. Antimicrob Agents Chemother. 2004;48:2091–6.
113. Introcaso CE, Hines JM, Kovarik CL. Cutaneous toxicities of antiretroviral therapy for HIV: part I. Lipodystrophy syndrome, nucleoside reverse transcriptase inhibitors, and protease inhibitors. J Am Acad Dermatol. 2010;63:549–61.
114. Borras-Blasco J, Navarro-Ruiz A, Borras C, Castera E. Adverse cutaneous reactions associated with the newest antiretroviral drugs in patients with human immunodeficiency virus infection. J Antimicrob Chemother. 2008;62:879–88
115. Notermans DW, Jurriaans S, de Wolf F, et al. Decrease of HIV-1 RNA levels in lymphoid tissue and peripheral blood during treatment with ritonavir, lamivudine and zidovudine. Ritonavir/3TC/ZDV Study Group. AIDS. 1998;12:167–73.

79 Human Papillomaviruses

Reinhard Kirnbauer and Petra Lenz

Synonyms: ■ Verrucae vulgares (singular: verruca vulgaris) – common warts ■ Verrucae palmares et plantares – hand and foot warts ■ Verrucae planae – flat warts, plane warts ■ Condylomata acuminata (singular: condyloma acuminatum) – genital warts ■ Condylomata plana – flat cervical condylomas, plane condylomas ■ Squamous intraepithelial lesion (SIL) – cervical intraepithelial neoplasia (CIN); vulvar (VIN); vaginal (VaIN); penile (PIN); anal (AIN) ■ Buschke–Löwenstein tumor – giant condylomata acuminata, condylomata acuminata gigantea ■ Florid oral papillomatosis – Ackerman tumor ■ Papillomatosis cutis carcinoides – Gottron tumor ■ Focal epithelial hyperplasia – Heck's disease

Key features

- Human papillomaviruses (HPVs) comprise a large group of approximately 120 genotypes that infect the epithelia of skin or mucosa and most commonly cause benign papillomas or warts
- Epidermodysplasia verruciformis (EV) is an inherited disease characterized by generalized flat warts or pityriasis versicolor-like macules, caused by chronic infection with HPV types in the genus β
- EV-associated HPV types are also detected in skin cancers and normal skin. These viruses are activated by UV exposure, immunosuppression, and specific host genetic background (EV)
- Anogenital HPV is a highly prevalent, sexually transmitted infection (STI) seen predominantly in young adults. Condylomata acuminata or benign anogenital warts are typically caused by HPV-6 or -11, which are considered to be low-risk types
- Persistent infection with high-risk HPV types, predominantly HPV-16 and -18, is the major cause of cervical cancers and a subset of vaginal, vulvar, penile, anal, oropharyngeal, and digital neoplasias
- Patients with cellular immunodeficiencies are at higher risk for persistent HPV infection and progressive disease
- No effective antiviral treatment for warts exists, and most therapies focus on destruction of visible lesions or induction of a cellular immune response
- Highly effective prophylactic HPV vaccines based on virus-like particles (VLPs) have been licensed for the prevention of genital warts and/or associated vulvar, vaginal and cervical cancer

INTRODUCTION

Papillomaviruses are a large group of DNA viruses that are widely distributed in animals and humans, most commonly inducing benign papillomas or warts[1]. Recurrent skin and anogenital warts may be disfiguring, impose a considerable psychological burden, and are a frequent cause of medical office visits. A subset of human papillomaviruses (HPVs) designated as high-risk types, most often HPV-16 and -18, is now recognized as the primary etiologic agent for: cervical cancer and its precursor lesions; a subset of the malignancies at other anogenital sites and in the upper aerodigestive tract; and, rarely, squamous cell cancer of the digits. In contrast, infection with the common cutaneous HPV types 1, 2, 4, 27, etc. is not thought to have any oncogenic potential[1]. In immunocompromised patients, HPV infections tend to persist and result in an increased risk of developing anogenital neoplasias. The high prevalence of genital HPV infection in sexually active young adults is a major concern, as effective antiviral treatments do not exist. More than a decade ago, prophylactic vaccines based on virus-like particles (VLPs) that prevent transmission in animal models of papillomavirus infection were developed[2]. Human vaccine studies subsequently demonstrated safety and nearly complete (>90%) efficacy for the prevention of type-specific genital HPV infection and the development of associated dysplasias[3–5].

History

The infectious etiology of human warts had long been suspected[1], and experimental transmission of common warts with a cell-free extract was demonstrated over 100 years ago[6]. The descriptions of cottontail rabbit papillomavirus (CRPV) in 1933 and of the rare genodermatosis *epidermodysplasia verruciformis* (EV) demonstrated the oncogenic potential of papillomaviruses. Following the cloning of the first papillomavirus genome in the late 1970s, the plurality of human and animal papillomaviruses became evident[7]. Based on genome sequencing, HPV types can be grouped into phylogenetic trees with a remarkable relationship to biologic data, e.g. mucosal and cutaneous types, high-risk and low-risk genital HPV, EV-associated HPV[7]. Today, the genomes of 120 HPV types have been fully characterized and additional partial DNA sequences have been obtained, indicating the existence of at least 200 HPV genotypes[8]. In 1976, zur Hausen proposed an association between papillomaviruses and cervical cancer[9], and subsequent molecular studies led to the recognition of a subset of HPV types in a high proportion of cervical carcinomas. The identification of biologic differences between "high-risk" and "low-risk" mucosal HPV confirmed infection with oncogenic HPV as the main cause of cervical cancer and its precursor lesions[10].

EPIDEMIOLOGY

Genital infection with HPV occurs most commonly by intimate contact, while infection of non-genital skin may occur via direct skin-to-skin contact or indirectly through contaminated surfaces and objects (e.g. swimming pool, gymnasium). Basal keratinocytes, which serve as the primary targets for HPV infection, are exposed to the virus through minor abrasions, and infection is promoted by maceration. Autoinoculation of virus from the lesion to adjacent skin is observed frequently, especially for digital or flat warts. Using sensitive polymerase chain reaction (PCR)-based detection, normal-appearing skin surrounding HPV-associated lesions and even skin of healthy volunteers may contain HPV DNA. These observations help to explain the high recurrence rate of warts (e.g. 20–50% for genital condylomata) and the observation that treatment may not prevent further transmission of the virus. Papillomaviruses are resistant to heat and desiccation due to the absence of a viral envelope, and even laser fumes may contain infectious virions[11].

Cutaneous warts are caused by a small group of specific HPV types, with an overall prevalence of 20% in schoolchildren and a decline thereafter with increasing age[12,13]. Patients living in larger households often report an infected cohabitant, supporting the concept of person-to-person transmission. The majority of warts will regress spontaneously within 1–2 years. Reinfection with the same HPV type appears uncommon after clearance, suggesting that protective type-specific immunity may develop[14].

Genital warts in prepubertal children are uncommon and produce special concern in healthcare providers. Although viral transmission

may occur during delivery, from close family contacts, or by autoinoculation from skin warts, the possibility that these lesions may have been caused by sexual abuse should always be carefully considered[15].

Infection of the lower anogenital tract with HPV is one of the most common sexually transmitted infections (STIs). The prevalence of cervical HPV infection varies greatly in different countries and by age; it is particularly high in young women, ranging from 20% to 45%. In a study of 608 sexually active female college students, 26% were diagnosed with genital HPV infection at study entry and another 43% acquired HPV infections of the cervix over the next 3 years[16]. A 60% incidence of new genital HPV infections over a 2-year period in sexually active male college students has also been reported[17]. In the US, an estimated 20 million people have genital HPV infections at any one time. Behavioral risk factors include sexual intercourse at an early age and the number of lifetime sexual partners[7]. Circumcised men are less likely to carry and transmit HPV infection. In men who have sex with men (MSM), anal HPV infection is very prevalent (up to 75%).

The public health impact of genital HPV infection is evident by the high number of initial visits to physicians' offices for treatment of genital warts (e.g. 360 000 in 2008 in the US) and the frequency of consequences such as abnormal Pap smears and cervical neoplasia (Fig. 79.1). The annual cost burden of genital HPV infection is estimated to be $6 billion in the US, making it the second most costly STI after HIV infection[18].

Most genital papillomavirus infections resolve spontaneously, whereupon HPV DNA becomes undetectable by PCR. The median duration of high-risk HPV infections in women is 8 months and persistence is found in 30% after 1 year and in 9% after 2 years[7]. Persistent cervical infection with high-risk HPV types represents the most important risk factor for the development of cervical pathology, including carcinoma. HPV-16 is detected in approximately 50% of cervical cancers and high-grade dysplasias. Together, HPV-16, -18, -31 and -45 are found in approximately 80% of cervical cancers[7].

Worldwide, an estimated 525 000 cases of cervical cancer are diagnosed annually, resulting in approximately 275 000 deaths[19]. The disease occurs predominantly in low-income countries that lack effective cervical screening programs. In the US, prevention and early detection programs have reduced the incidence rate of cervical cancer by approximately 75%, to 8 per 100 000 women per year. In 2010, 12 200 new cases of cervical cancer were diagnosed in the US, resulting in 4200 deaths. High-risk oncogenic HPV types account for most of the observed risk for developing cervical cancer, although smoking, cervical inflammation, parity and oral contraceptive use have been proposed as cofactors[7]. Although there is little evidence for hematogenous spread of HPV, approximately 60% of patients with anogenital infections develop low-titer, type-specific antibodies during the course of infection[20]. Titers tend to decrease slowly and may persist for years after viral clearance.

Immune suppression in HIV-infected patients and organ transplant recipients results in HPV infections that are more frequent, persistent, and likely to progress to intraepithelial neoplasias, with $CD4^+$ T-cell depletion and HIV viral load being important risk factors. In studies analyzing anal swabs, up to 93% of HIV-seropositive MSM were positive for HPV DNA, compared to 60% of HIV-negative MSM[21]. HPV-associated anal intraepithelial neoplasia (AIN), a likely anal cancer precursor, is found in up to 36% of HIV-infected MSM, compared to 20% of HIV-negative MSM. Antiretroviral therapy has shown no or only a modest beneficial effect on the incidence and progression of AIN or cervical intraepithelial neoplasia (CIN). Similarly, organ transplant recipients are at an increased risk for developing warts and genital neoplasias[22]. They also have a higher incidence of premalignant and malignant skin neoplasias, e.g. actinic keratoses, Bowen's disease or squamous cell carcinomas (SCCs), especially in sun-exposed areas.

Not only cutaneous tumors from organ transplant recipients, but also tumors, "healthy skin" and plucked hairs from immunocompetent patients often contain DNA of β HPV types (see below)[7,22]. These forms of HPV only result in highly active viral replication leading to cytopathic effects and clinical lesions in patients with EV or other forms of immunosuppression[22]. In skin swab samples, children from 1 month to 4 years of age have a high prevalence (from 50% to 70%) of HPV DNA[23], indicating that normal-appearing human skin is colonized with a multiplicity of HPV types very early in life, most likely through close skin-to-skin contact. HPV DNA has also been detected in psoriatic lesions[24] and skin cancers from PUVA-treated patients; however, highly sensitive PCR-based methods were required to amplify the HPV DNA and viral gene transcription has not been reported.

Recurrent respiratory papillomatosis (RRP) is characterized by exophytic lesions of the airways. It occurs in juvenile- and adult-onset forms and is caused by HPV-6 and -11. Despite its low incidence of 0.4–1.2 per 100 000[16], RRP is the most common benign tumor of the larynx. It is believed that in childhood-onset RRP, vertical HPV transmission from mother to child occurs by aspiration during delivery through an infected birth canal[25]. Although treatment should be considered in pregnant women with condylomata in order to reduce viral load, there is insufficient evidence to support cesarean section to prevent development of RRP in the offspring. Adult-onset RRP more likely results from genital-to-oral transmission.

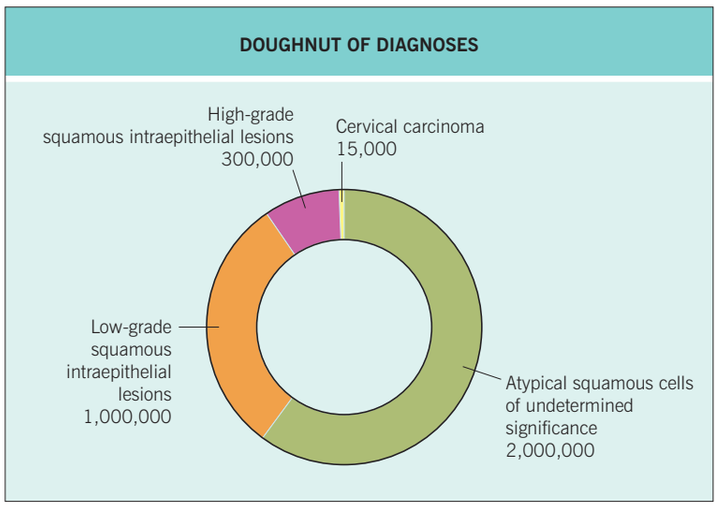


Fig. 79.1 Doughnut of diagnoses. The annual incidence of HPV-associated cervical pathologies in the US is given. The number of patients diagnosed with entities in this spectrum declines dramatically from atypical squamous cells of undetermined significance (ASCUS) to low-grade squamous intraepithelial lesions (LSIL) to high-grade squamous intraepithelial lesions (HSIL) to cervical carcinoma. *Adapted from Division of STD Prevention; Prevention of Gential HPV Infection and Sequelae: Report of an External Consultants' Meeting. Atlanta, GA: Centers for Disease Control and Prevention, 1999.*

PATHOGENESIS

Papillomavirus Evolution

Historically, the papillomaviruses have been grouped together with the polyomaviruses, but their fundamentally different biology and genetic organization resulted in their reclassification as individual families in 2000[8]. The National Center for Biotechnology Information (NCBI) nucleotide sequence database (www.ncbi.nlm.nih.gov) currently lists 120 different HPV types as well as numerous incompletely characterized putative new HPV types. By definition, a novel type has more than 10% dissimilarity from any previously characterized type in the DNA sequences of three HPV genes (E6, E7 and L1). A dissimilaritity of 2–10% is defined as a subtype, and <2% as a variant[8].

By comparing DNA sequences in conserved portions of the papillomavirus genomes across different types, a phylogenetic tree establishing the degree of relatedness among these types has been generated[8]. Two genera, the α- and β-papillomaviruses, encompass almost all known HPV types, with the genus α-papillomavirus containing mucosal and cutaneous HPV types that are pathogenic in normal hosts and the genus β containing the types associated with EV; γ, μ and ν genera contain additional cutaneous types. Within each genus, HPV types are grouped according to sequence homology into species, which often share similar biologic and pathologic properties (e.g. HPV-16 and -31). Present models postulate that HPVs co-evolved with our human ancestors and novel HPV types or variants were generated through either genetic drift or natural selection via adoption of specialized ecologic niches. Genetic recombination between HPV types does not occur.

Virology

Papillomaviruses are non-enveloped, double-stranded DNA viruses approximately 55 nm in diameter[7]. The spherical capsid is composed of two virally encoded proteins: (1) L1, the major structural protein; and (2) L2, a minor structural protein. During virion assembly within cells, L1 proteins form pentamers called capsomeres, and 72 capsomeres multimerize to form the viral capsid with an icosahedral symmetry arranged on a $T = 7$ surface lattice. The capsid surrounds the viral DNA, thereby protecting it from degradation, and it also enables the virus to bind efficiently to target cells. Packaged viral DNA is associated with cellular histones, forming a mini chromosome. In contrast, the early (E) viral proteins are not incorporated into infectious virions.

When expressed in cell culture, the L1 major capsid proteins of papillomaviruses self-assemble into virus-like particles (VLPs) that are morphologically similar to native virions (Fig. 79.2)[26]. Papillomavirus VLPs display type-specific and neutralization epitopes that are used to detect serum antibodies and as the basis for prophylactic vaccines (see below)[27,28].

The HPV genome, approximately 8 kilobases (kb) in length, is composed of three domains: the upstream regulatory region (URR), the early region, and the late region (Fig. 79.3). The URR, approximately 1 kb in length, lacks open reading frames (ORFs) and contains the origin of replication and many of the control elements for transcription and replication. The early region, approximately 4 kb in length, contains the ORFs for genes expressed early in the papillomavirus life cycle. The late region, approximately 3 kb in length, encodes the capsid proteins (see above)[7].

Papillomavirus Life Cycle

The papillomaviruses are highly species-specific, and productive infection has never been observed outside natural host tissue. The papillomavirus life cycle is completed only in fully differentiated squamous epithelia. This has impeded its study in monolayer tissue culture cells, where late gene expression and virion production do not occur. Only a small number of HPV types have been successfully propagated in mouse xenograft or raft culture systems, and limited amounts of infectious virions have been generated[7].

Productive infection and induction of hyperproliferation are initiated when the virus enters proliferating basal epithelial cells (Fig. 79.4). This layer of cells is not normally accessible to the virus because of the mechanical barrier provided by the overlying differentiated cell layers. Therefore, it is likely that infection requires an abrasion or other trauma to the epithelium to expose the basal cells to the virus. Our knowledge about early steps of infection such as viral entry and uncoating is limited. The receptor(s) that mediate virus binding to epithelial cells have not been definitively identified, but binding appears to depend on the L1 major capsid protein, and cell surface and/or basement membrane heparan sulfate is necessary for efficient infection *in vitro*[29,30]. The amino terminus of the L2 minor capsid protein is then cleaved by furin (a proprotein convertase), which exposes both a cross-neutralization epitope on L2 and a binding site (thought to be on L1) that facilitates viral entry via a putative secondary receptor on keratinocytes[30,31]. Upon infection, the covalently closed circular DNA genome becomes established as a low-copy autonomous replicon in the nuclei of basal cells, thereby creating a long-term reservoir of viral DNA.

The program of viral gene expression is intimately linked to the differentiation state of the infected cells. The E genes are transcribed at low levels in the basal cell layer and stratum malpighii. The first genes to be expressed following infection are the E1 and E2 genes, which are responsible for controlling the transcription of other viral genes and replication of the viral genome. HPVs do not encode the enzymes required for transcription or replication of viral DNA. Consequently, HPV is entirely dependent on the co-opting of cellular machinery for these functions. One major effect of HPV proteins E5, E6 and E7 is that the epidermal cell cycle, which is normally blocked for cells that are suprabasal, continues so that HPV genome copy number can be amplified to high levels during vegetative viral replication for assembly into virions (see Fig. 79.4). The E6 and E7 proteins of the high-risk mucosal HPV types act as viral oncoproteins, but no such functions are associated with the corresponding proteins of the low-risk mucosal and EV types[7]. There is limited understanding of possible differences between oncogenic (e.g. HPV-5, -8) and the non-oncogenic β HPV types.

In combination with other cellular proteins, E6 from high-risk mucosal HPV causes the ubiquitin-mediated degradation of the cellular protein p53. Elevated levels of p53 arrest cells in the G1 phase of the cell cycle or induce apoptotic cell death, so that E6-facilitated destruction of p53 removes a brake on suprabasal cell cycling. One of the principal effects of high-risk mucosal HPV E7 is to bind to the underphosphorylated form of RB (the retinoblastoma tumor suppressor protein). A physiologic role of underphosphorylated RB is to bind to and inhibit the function of the E2F transcription factor (see Ch. 107). When HPV E7 binds RB, E2F is liberated from this inhibition and is thereby able to induce the expression of genes required for DNA replication. Both E6 and E7 are multifunctional proteins, and while their effects on p53 and RB are critical ones, they do have additional targets

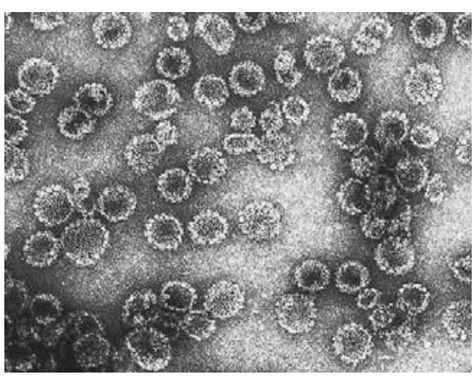


Fig. 79.2 Transmission electron photomicrograph of purified HPV-16 virus-like particles (VLPs). A prophylactic vaccine that contains HPV-6, -11, -16, -18 VLPs has been approved for the prevention of anogenital warts and cancers. Following expression in cell culture, the L1 capsid protein self-assembles into VLPs (empty capsids approximately 50 nm in diameter devoid of HPV DNA) that display type-specific and neutralization surface epitopes similar to native virions. *Courtesy, Saeed Shafti-Keramat, MD.*

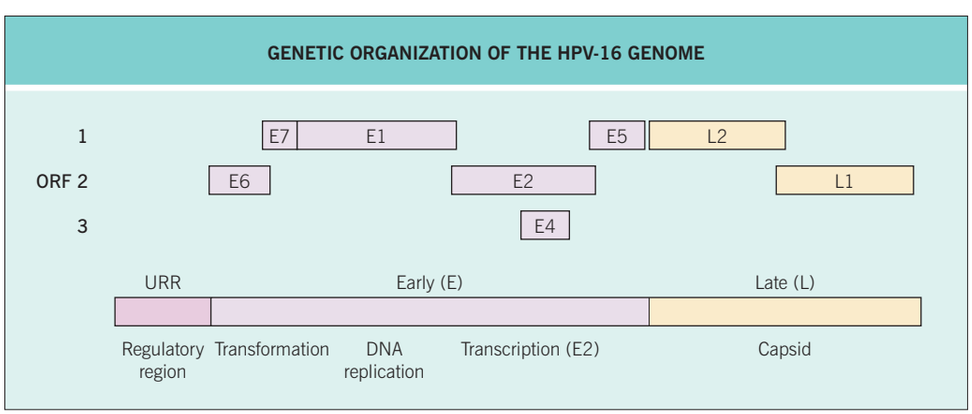


Fig. 79.3 Genetic organization of the HPV-16 genome. This is a linearized map of the 7.9 kb circular double-stranded genome. All open reading frames (ORFs) reside on one strand. Early (E) and late (L) regions are indicated. The upstream regulatory region (URR) contains the origin of replication and control elements for transcription and replication.

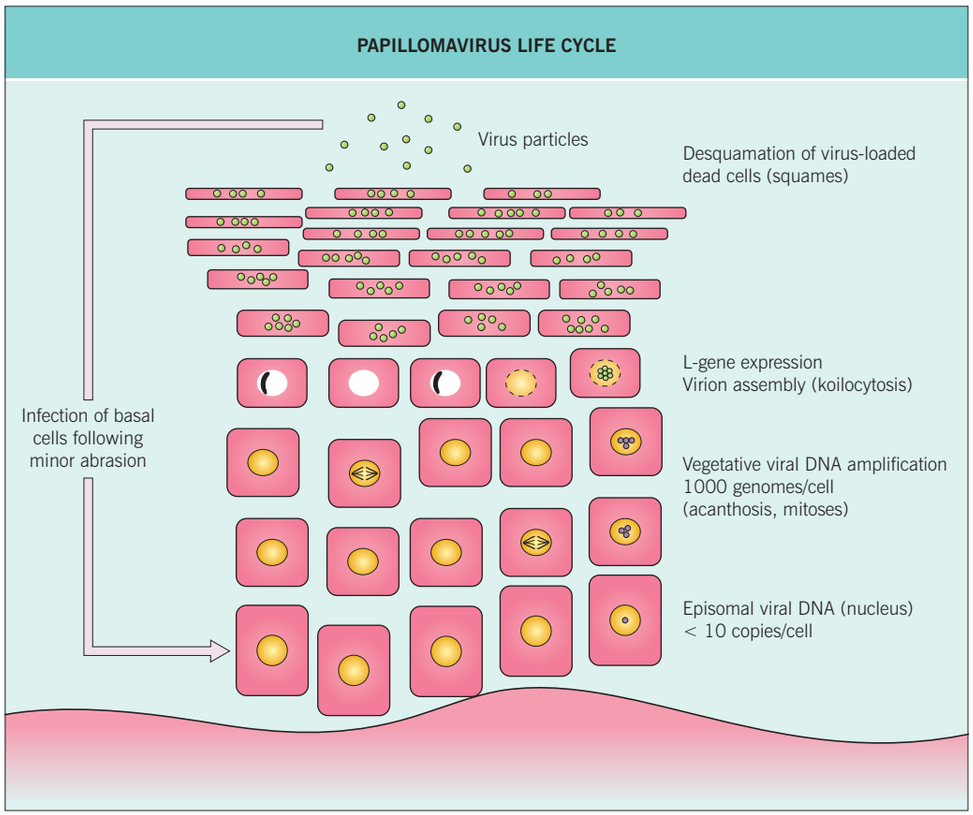


Fig. 79.4 The papillomavirus life cycle. The figure depicts a productive (virion-producing) benign wart. *Adapted from Orth G. Epidermodysplasia verruciformis. In: Salzman NP, Howley PM (eds). The Papovaviridae: Volume 2 The Papillomaviruses. New York: Plenum Press; 1987:199–243.*

important to the oncogenic potential of the virus. These include activation of telomerase by E6, binding of histone deacetylases by E7, and synergistic effects of both proteins that lead to centrosome abnormalities and chromosomal instability[7].

The genes for the virion structural proteins, i.e. the late (or L) genes, are expressed in the terminally differentiated superficial layers of the epithelium. The more superficial epithelial layers also have higher levels of expression of E1 and E2 and amplification of viral DNA. The amplified genomes are encapsulated by the L1 and L2 capsid proteins to generate infectious virions, and virus particles are observed in the granular layer of the epithelium and above. Virus assembly is not believed to lyse the cells; instead, the virus is shed with the cornified layer as cells slough from the epithelial surface (see Fig. 79.4). E4 proteins are hypothesized to disrupt the intracellular filamentous network of keratinocytes, which may facilitate virus release from the corneocytes[7].

Host Immune Response

Persistent papillomavirus infections are common, indicating that HPVs have evolved mechanisms to evade immune surveillance. There is no viremic phase during the life cycle, so a systemic immune response is avoided. In addition, low levels of viral proteins are expressed in the basal cell layer and stratum malpighii of the epidermis, where they would be most likely to be recognized by Langerhans cells and infiltrating lymphocytes. Only in the more immunologically privileged terminally differentiated layers is there extensive production of virion proteins, with shedding of infectious virus exclusively from the external epithelial surface[7]. Despite the relative success of papillomaviruses in evading immune responses, up to two-thirds of cutaneous warts spontaneously regress within 2 years, and lesions of multifocal infections often regress concomitantly. There is also an increased prevalence of warts in patients with suppressed cell-mediated immunity. In contrast, patients with underlying defects in humoral immunity do not seem to be predisposed to HPV infections, suggesting a primary role of cell-mediated responses.

Although low amounts of virion capsid proteins are produced in the lower epidermal cell layers, serum antibodies specific to conformational virion epitopes of high-risk HPV-16 can be detected in more than half of women with low-grade or asymptomatic genital HPV-16 infections[32]. It is unknown if these antibodies play a role in limiting reinfection with the same type from autoinoculation or from an infected sexual partner.

Latent HPV infections are defined as persistence of HPV DNA in clinically and cytologically normal epithelium. It is difficult to distinguish true viral latency from persistent infection with a low level of DNA replication. The mechanisms by which HPV enters into and is activated out of latency are unknown[7].

Oncogenic Potential of HPV

Different HPV types have markedly different oncogenic potentials. The vast majority of cervical cancers, for example, contain the sequences of one of five HPV types: 16, 18, 31, 33 or 45[33]. In contrast, infection with HPV-6 or -11 occurs commonly in benign or low-grade intraepithelial lesions but is very rarely associated with the development of anogenital malignancies. HPV-5 and -8 DNA sequences are frequently detected in SCCs associated with EV.

Progression of HPV-associated cervical lesions to invasive cancer typically requires several decades. Both persistent HPV infection and the accumulation of additional genetic mutations are required in the current model of multistage carcinogenesis[7]. Integration of the viral genome randomly into the host DNA is a common event, invariably leading to loss of E1 and E2 expression. In HPV-16 and -18, E2 functions to repress the transcription of E6 and E7 genes. Therefore, integration is thought to increase expression of E6 and E7, which are selectively retained and expressed at elevated levels in carcinomas, suggesting a critical role for oncogenic progression (see above)[7].

Differences in the activities of E6 and E7 genes between oncogenic and non-oncogenic HPV types principally account for the different risk of progression. E6 and E7 proteins derived from high-risk HPV types (e.g. 16 and 18) degrade p53 and interact with RB (respectively) with greater efficiency than do E6 and E7 proteins from low-risk types (e.g. 6 and 11)[7]. Degradation of p53 by E6, which eliminates from infected cells the principal "guardian of the genome" (the protein responsible for cell cycle arrest in the presence of damage to cellular DNA), can lead to the accumulation of genetic mutations in infected cells. Thus, carcinogenic progression appears to be promoted or facilitated by increased E6 and E7 expression as well as the activity of external carcinogens, resulting in genomic instability[7].

CLINICAL FEATURES

Cutaneous and mucosal HPV types form two distinct groups that infect either skin or mucosa. However, viral tropism is not absolute, as DNA of skin types may be found in genital or oral warts, and, in rare cases, mucosal types may be associated with skin lesions. Clinical manifestations depend on the HPV type involved, the anatomic location, and the immune status of the host (Table 79.1).

Cutaneous Infections

Cutaneous HPV types comprise a small group of viruses that infect the skin and induce common warts (Latin *verrucae vulgares*; singular *verruca vulgaris*), palmar and plantar warts (*verrucae palmares et plantares*), mosaic warts, flat warts (*verrucae planae*) and butcher's warts (see Table 79.1). In general, classification of warts is based on morphology, histology and anatomic location.

Common warts are hyperkeratotic, exophytic, dome-shaped papules or plaques that are typically associated with HPV-1, -2, -4, -27 or -57. These warts are most frequently located on the fingers and dorsal surfaces of the hands (Figs 79.5 & 79.6) or in other sites prone to trauma such as the knees or elbows, but they may occur anywhere on the skin surface. Involvement of the proximal nail fold and/or ablative therapy at that location may destroy the matrix, resulting in onychodystrophy (see Fig. 79.6). Characteristic features of common warts are punctate black dots representing thrombosed capillaries and bleeding after shaving of the hyperkeratotic surface (Fig. 79.7). Autoinoculation by scratching may cause a linear arrangement of warts. Slender, exophytic filiform warts can also develop, especially in periorificial locations on the face.

Palmar and plantar warts appear as thick, endophytic papules on the palms, soles, and lateral aspects of the hands and feet, with gently sloping sides and a central depression resembling an anthill (hence the term *myrmecia*, meaning anthill). On the soles, these are often painful

CLINICAL MANIFESTATIONS AND ASSOCIATED HUMAN PAPILLOMAVIRUS (HPV) TYPES

	Frequently detected	Less frequently detected
SKIN LESIONS		
• Common, palmar, plantar, myrmecial and mosaic warts	1, 2, 27, 57	4, 29, 41, 60, 63, 65
• Flat warts	3, 10	28, 29
• Butcher's warts	7	1, 2, 3, 4, 10, 28
• Digital squamous cell carcinoma and Bowen's disease	16	26, 31, 33, 34, 35, 51, 52, 56, 73
• Epidermodysplasia verruciformis (EV)	3, **5**, **8**	**9**, **12**, **14**, **15**, **17**, **19–25**, **36–38**, **47**, **49**, 50, etc.
• EV – squamous cell carcinoma	**5**, **8**	**14**, **17**, **20**, **47**
MUCOSAL LESIONS		
• Condylomata acuminata	6, 11	40, 42–44, 54, 61, 70, 72, 81
• High-grade intraepithelial neoplasias (including cervical condylomata plana, bowenoid papulosis, erythroplasia of Queyrat) and invasive cancer	16	18, 26*, 31, 33, 35, 39, 45, 51, 52, 53*, 56, 58, 59, 62, 66*, 68, 73, 82
• Buschke–Löwenstein tumor	6, 11	
• Recurrent respiratory papillomatosis, conjunctival papillomas	6, 11	
• Heck's disease (focal epithelial hyperplasia)	13, 32	

*Probably carcinogenic[33].

Table 79.1 Clinical manifestations and associated human papillomavirus (HPV) types. HPV types in the genus β are in bold.

Fig. 79.5 Verrucae vulgares (common warts). *Courtesy, A Geusau, MD.*

Fig. 79.6 Periungual common warts. Destruction of the nail matrix and bed can lead to partial (**A**) or complete (**B**) absence of the nail plate. Bowen's disease may be considered in the differential diagnosis, especially for a single, recalcitrant digital wart.

Fig. 79.7 Verrucae plantares (plantar warts). The photo was taken after shaving of the hyperkeratotic surface; the black dots represent thrombosed capillaries.

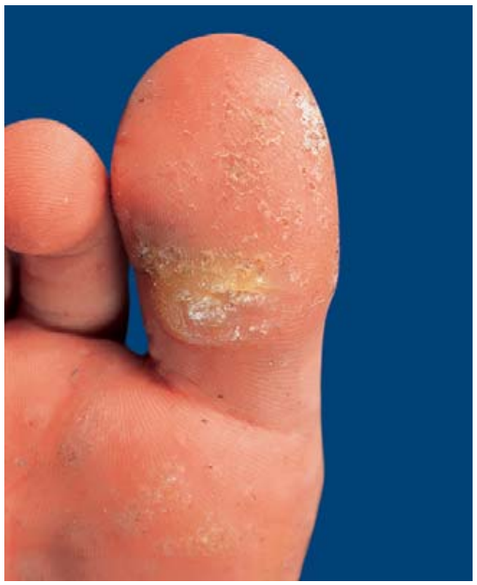


Fig. 79.8 Myrmecial wart. The wart at the base of the distal phalanx of the hallux is painful due to deep endophytic growth; in addition, there are confluent plaques of superficial warts (mosaic warts).

Fig. 79.9 Extensive and chronic verrucosis of the sole causing pain when walking. HPV-2a was isolated from the lesions of this otherwise immunocompetent and healthy patient.

Fig. 79.10 Verrucae planae (flat warts). Multiple skin-colored or pink (**A**) to brown (**B**) smooth-surfaced, flat-topped papules. These lesions are typically caused by HPV-3 or -10. *B, Courtesy, Julie V Schaffer, MD.*

from pressure when walking, due to their deep inward growth (Fig. 79.8). Plantar warts that coalesce into large plaques are referred to as *mosaic warts* (see Fig. 79.8). Extensive chronic verrucosis that is notoriously resistant to therapy has been observed in immunocompromised individuals and, at times, in patients with no apparent immune dysfunction (Fig. 79.9). Inclusion warts of the sole are plantar cysts from which HPV types 4, 60, 63 and 65 have been isolated[34]. In studies from Europe, the closely related HPV types 1, 2, 27 and 57 caused the majority of palmoplantar warts, and they occurred most commonly in patients 6–10 years of age[35,36]. Although a higher incidence of HPV-2-related warts was reported in atopic children, other investigators have failed to find such an association.

Flat warts are skin-colored or pinkish to brown, relatively smooth-surfaced, slightly elevated, flat-topped papules that are most commonly located on the dorsal hands, arms or face, often in a linear array (Fig. 79.10). They are usually caused by HPV types 3 or 10, and less often by 28 and 29.

Butcher's warts, which earn their name from their occurrence in meat- (or fish-) processing professionals, appear as extensive verrucous papules or cauliflower-like lesions on the dorsal, palmar or periungual aspects of the hands and fingers. These warts are associated with HPV-7, not animal papillomavirus types.

Epidermodysplasia verruciformis (EV), first described in 1922 by Lewandowski and Lutz, is a rare genetic disease. It is characterized by a particular susceptibility to cutaneous infections with HPV types in the genus β (see above), which do not produce clinical lesions in immunocompetent individuals[37]. The disease usually manifests in childhood with highly polymorphic, widespread lesions. About two-dozen specific HPV types have been described in EV patients, a subset of which (mainly types 5 and 8) is also detected in EV-associated skin cancers. EV typically has an autosomal recessive pattern of inheritance and is caused by truncating mutations in two genes, *TMC6 (EVER1)* and *TMC8 (EVER2)*, that encode transmembrane proteins localized to the endoplasmic reticulum[38]. These proteins form a complex that interacts with the zinc transporter 1 (ZnT1) and affects intracellular zinc distribution, downregulating zinc-associated transcription factors[39]. Inhibition of ZnT1-TMC6/8 function by the HPV E5 protein is thought to facilitate viral infection; β HPV types lack E5, but they become pathogenic in EV patients with TMC6/8 defects[39].

Patients with EV present with widespread, discrete or confluent papules that resemble flat warts (Fig. 79.11); scaly, pinkish (Fig. 79.12) or hypopigmented guttate macules and thin plaques that resemble pityriasis versicolor represent another characteristic finding. In an individual patient, warts that appear clinically distinct often contain different HPV types, and each skin lesion usually contains several HPV types. Actinic keratoses usually arise after the age of 30 years and slowly transform into invasive SCCs in approximately half of EV patients. These tumors have low metastatic potential and develop primarily in sun-exposed areas such as the forehead, ears and hands, implicating UV irradiation as an important co-carcinogen. Patients with EV should be educated about the importance of minimizing sun exposure, and family members should be screened for the presence of similar lesions.

Fig. 79.11 Epidermodysplasia verruciformis. Confluent scaly papules and plaques resembling flat warts.

Fig. 79.12 Epidermodysplasia verruciformis. Generalized erythematous macules and plaques are seen in the same patient as shown in Fig. 79.11. Lesions tested positive for HPV-8 and -36.

It may be difficult to differentiate flat warts from EV-associated lesions based on histology alone (see below), and the presence of lesional β HPV DNA (e.g. HPV-5, -8, etc.) can establish the diagnosis in an otherwise healthy individual. Beta HPV types can also induce a sporadic EV-like eruption in immunosuppressed patients, including transplant recipients and those with AIDS or a lymphoma. In addition, β HPV sequences have been isolated from the normal skin of healthy individuals by highly sensitive DNA detection methods, indicating that the general population acts as the reservoir for these HPV types.

WHIM syndrome is a rare, autosomal dominant primary immunodeficiency disorder characterized by HPV-induced *w*arts (cutaneous and genital), *h*ypogammaglobulinemia, recurrent bacterial *i*nfections and neutropenia due to *m*yelokathexis (retention of mature neutrophils in the bone marrow) (see Ch. 60). It is caused by mutations in the gene encoding the chemokine CXC receptor 4 (CXCR4), which result in impaired leukocyte trafficking and homing[40].

Fig. 79.13 Penile condylomata acuminata (genital warts). Both sessile and exophytic warts are present.

WILD syndrome is a recently characterized disorder that features *w*arts, cellular *i*mmunodeficiency, primary *l*ymphedema and multifocal anogenital *d*ysplasia. The patient reported had extensive warts, including condylomata acuminata and lesions that clinically (but not histologically) resembled those in EV. A variety of α HPV types were detected in the cutaneous and genital lesions[41].

Mucosal Infections

More than 40 HPV types preferentially infect the mucosa of the anogenital and upper aerodigestive tracts. Subclinical infections are much more common than visible warts. Application of 5% acetic acid (aceto-whitening) may aid in the identification of subclinical lesions as white areas.

Condylomata acuminata (singular: *condyloma acuminatum*), or anogenital warts, are found on the external genitalia and the perineum, perianally, or in adjacent areas such as the inguinal fold and mons pubis. Lesions may extend into the vagina, urethra, or anal canal (but rarely beyond the dentate line). Condylomata are typically discrete, sessile, smooth-surfaced exophytic papillomas or acuminate warts and may be skin-colored, brown or whitish (especially when macerated in moist areas) (Fig. 79.13). They lack the thick cuirass of horny scale present on cutaneous warts and frequently measure one to several millimeters in diameter. Condylomata may also present as pedunculated or broad-based papillomas up to several centimeters in diameter or as large confluent plaques (Fig. 79.14). *Condylomata plana*, or flat cervical warts, may be difficult to recognize without aceto-whitening and the use of a (magnifying) colposcope. High-grade intraepithelial neoplasias are usually caused by high-risk types, mainly HPV-16, -18 and -31, whereas low-grade lesions may contain low-risk as well as high-risk HPV types.

Bowenoid papulosis manifests as multiple red–brown papules or confluent plaques on the external genitalia, on the perineum, or perianally (Figs 79.15 & 79.16; see Fig. 73.13). These lesions primarily affect young adults and may clinically resemble genital warts, but histologically represent a high-grade squamous intraepithelial lesion (HSIL) or SCC *in situ*[42]. *Erythroplasia of Queyrat* is a distinct entity, presenting clinically as a well-demarcated, velvety erythematous plaque on the glabrous skin of the penis or vulva that histologically is an HSIL (Fig. 79.17). A biopsy is warranted for pigmented, erosive, bleeding and/or therapy-resistant genital lesions to exclude malignancy. Bowenoid papulosis and erythroplasia contain high-risk HPV types, predominantly HPV-16, and thus may represent a precursor lesion of vulvar, penile or perianal cancer.

Fig. 79.14 Condylomata acuminata. A Perianal papillomas that are macerated due to moisture from occlusion. **B** Confluent lesions forming hyperpigmented plaques in the perineal region and along the inguinal fold. A depigmented scar is seen at the site of treatment with liquid nitrogen.

Fig. 79.15 Bowenoid papulosis of the vulva (histologically vulvar intraepithelial neoplasia, VIN). Extensive red–brown or whitish papules and plaques containing high-risk mucosal HPV in an HIV-positive patient. Analogous high-grade squamous intraepithelial lesions (HSIL) were present perianally (AIN) and on the cervix (CIN).

Fig. 79.16 Bowenoid papulosis of the anus positive for high-risk mucosal HPV in a homosexual man. Histology revealed high-grade anal intraepithelial neoplasia (AIN).

Buschke–Löwenstein tumor (giant condylomata acuminata), *oral florid papillomatosis*, *epithelioma cuniculatum* of the sole, and *papillomatosis cutis carcinoides* of the skin comprise a group of "semi-malignant" verrucous carcinomas that are locally invasive and destructive but rarely metastasize[43] (see Ch. 108). Buschke–Löwenstein is a rare tumor of the anorectal area and external genitalia associated with the low-risk HPV types 6 or 11 that usually cause condylomata acuminata. The basis for the difference in biologic behavior between these two entities has not been established. In rare cases, pre-existing anogenital condylomata may progress into large exophytic cauliflower-like tumor masses that infiltrate deeply into underlying tissues and form fistulas and abscesses (Fig. 79.18). The histology of the Buschke–Löwenstein tumor may appear remarkably benign and resemble that of condylomata acuminata (Fig. 79.19), although focal frank malignant transformation can occur spontaneously or following X-irradiation. High-resolution imaging and a large biopsy are essential for identifying the extent of the infiltration and foci of SCC. Radical surgery may cure the disease, but recurrences are frequent, resulting in a high morbidity rate.

Oral warts appear as small, soft, pink or white, slightly elevated papules and plaques on the buccal, gingival or labial mucosa (Fig. 79.20), the tongue or the hard palate. Oral condylomata are associated with HPV types 6 and 11 and may result from digital or oral-genital sexual transmissions. In HIV-positive patients, oral papillomas are frequently detected and may contain unusual HPV types such as 7, 71, 72 and 73. In *focal epithelial hyperplasia*, or Heck's disease, multiple circumscribed papules resembling flat warts or condylomata are found on the gingival, buccal or labial mucosa. This disorder is rare in Caucasians but relatively common in children who are native South Americans, native Greenlanders, or from South African communities. It is associated exclusively with HPV-13 or -32.

HPV (especially type 16) is a causative agent in about 25% of oropharyngeal cancers, particularly those affecting the lingual and palatine tonsils. HPV-associated oropharyngeal cancers are relatively frequent in non-smokers and have a predilection for younger patients

Fig. 79.17 Erythroplasia of Queyrat. A well-demarcated velvety plaque of the prepuce positive for high-risk HPV; histology detected a high-grade penile intraepithelial neoplasia (PIN).

Fig. 79.18 Giant condylomata acuminata (Buschke–Löwenstein tumor). Cauliflower-like, deeply infiltrating giant condylomata acuminata in an older woman.

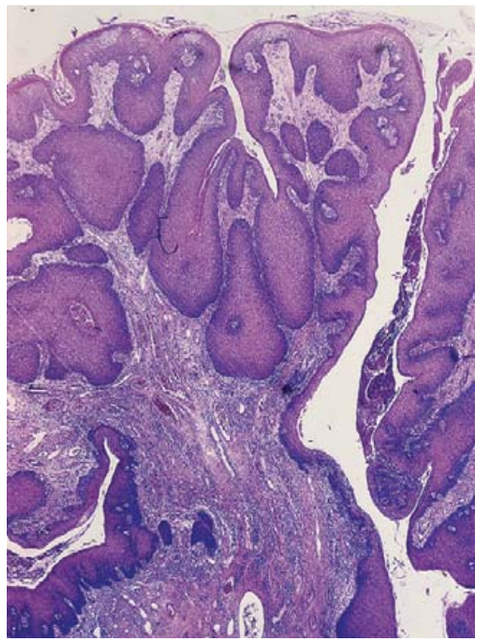


Fig. 79.19 Histology of a Buschke–Löwenstein tumor. There is downward extension of bulbous rete ridges without penetration of the basement membrane plus a lack of cellular atypia.

Fig. 79.20 Oral warts. Papillomas of the labial mucosa in a 6-year-old child.

with high-risk sexual behavior[44]. Although poorly differentiated histopathologically, they appear to have a better prognosis than HPV-negative oropharyngeal cancers[45].

In *oral florid papillomatosis*, multiple, confluent warty lesions associated with HPV-6 or -11 are found in the oral cavity or the nasal sinuses. The development of these lesions is believed to be promoted by smoking, X-irradiation and chronic inflammation. Patients with oral papillomas need frequent examinations and repeated biopsies for early diagnosis of progression to verrucous carcinoma.

Recurrent respiratory papillomatosis (RRP) features benign exophytic laryngeal papillomas caused by HPV-6 and -11[25]. Patients classically present with a triad of hoarseness, stridor and respiratory distress. Papillomas arise most often at the transition zones between the squamous and cilia-bearing epithelia of the larynx and subglottis, but they may rarely extend to the distal trachea, the bronchi or even the bronchoalveoli. Malignant transformation of laryngeal papillomas into SCCs in patients with long-lasting disease has been reported, and exogenous factors such as X-irradiation, smoking, chemical toxins or chemotherapy have been implicated as co-carcinogens.

PATHOLOGY

The histopathologic changes induced by HPV infection are variable, reflecting the myriad of clinical presentations and different anatomic sites. In productive HPV infections, a common motif in epithelial cells is the presence of cytoplasmic vacuoles isolating the nucleus from the cytoplasmic membrane. Cells with this distinctive vacuolization are referred to as koilocytotic (hollow) cells, and the presence of koilocytosis is a useful feature distinguishing verrucae from other types of papillomas[46].

Common and Deep Palmoplantar Warts

Common warts are well circumscribed from the surrounding skin and characteristically have steeply sloping "church spire" papillomatosis heaped with ortho- and parakeratosis (Fig. 79.21). Parakeratosis is most commonly observed directly overlying the summits of the papillomatosis; there is marked acanthosis and the rete ridges are elongated. In palmoplantar warts, the lateral edges of the wart bow inward to create a cup-shaped invagination below the papillomatosis. Higher-power

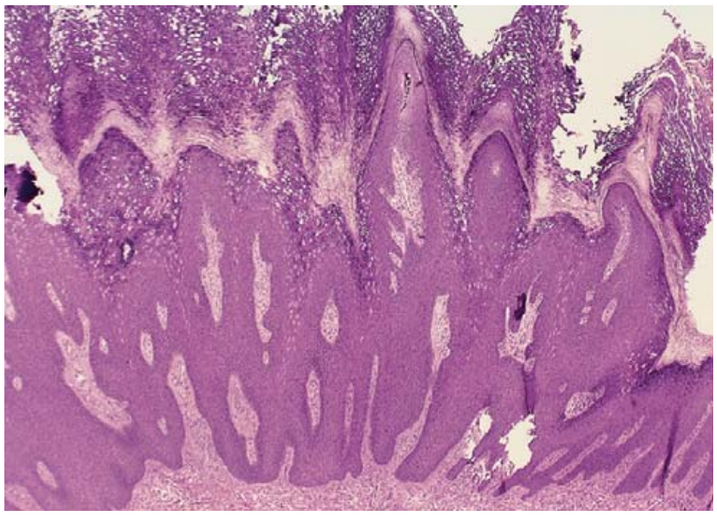


Fig. 79.21 Histology of verruca vulgaris. Note the characteristic features of "church spire" papillomatosis heaped with ortho- and parakeratosis, acanthosis, hypergranulosis and koilocytosis. *Courtesy, R Tyler, MD.*

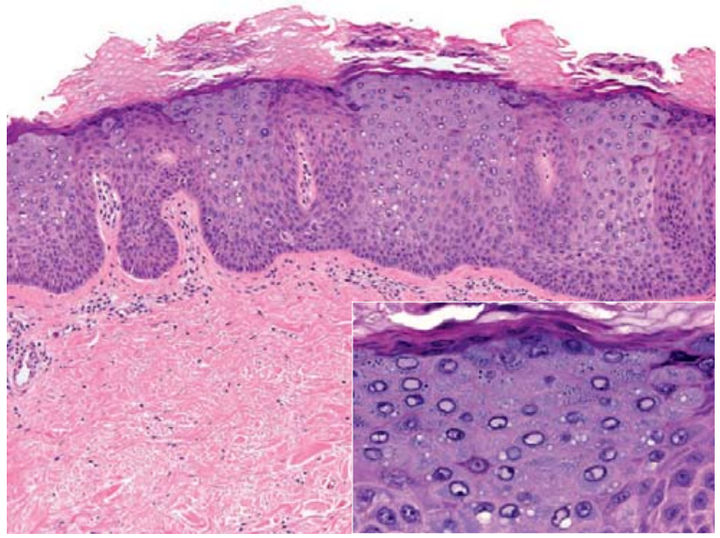


Fig. 79.22 Histology of epidermodysplasia verruciformis. Note the cells with perinuclear halos and blue–gray, granular cytoplasm in the mid to upper epidermis (insert). *Courtesy, Lorenzo Cerroni, MD.*

examination reveals hypergranulosis and condensed coarse cytoplasmic keratohyalin-like granules of variable size and shape within the granular layer, along with vacuolization of cells on top of, or sometimes between, the papillae. Koilocytosis is typically observed in or immediately below the granular layer. The papillary dermis underlying the elongated rete ridges shows increased vascularity, with some vessels being thrombosed. These thromboses correspond to the "black dots" that can be detected on clinical examination, especially of pared warts.

Flat Warts

The characteristic features of flat warts include orthokeratosis alternating with parakeratosis, acanthosis, no or minimal papillomatosis, a uniformly thickened granular layer, and vacuolization of cells in the granular and upper malpighian layers (termed "bird's eyes")[46].

Some patients with flat warts develop clinically evident inflammation around these warts, which may precede their spontaneous involution. Characteristic histologic features of regressing flat warts include parakeratosis, spongiosis, exocytosis of mononuclear cells into the lower epidermis, and (occasionally) satellite cell necrosis. By immunohistochemistry, helper T cells predominate and HLA-DR antigen, a marker of immune activation, is detected on the surface of the infiltrating lymphocytes and on some keratinocytes. Many of these changes can also be observed in regressing condylomata, suggesting that wart regression is mediated, at least in part, by a delayed-type hypersensitivity-like cellular immune response directed against keratinocytes expressing wart antigens[47].

Epidermodysplasia Verruciformis

In patients with EV, the flat warts and pityriasis versicolor-like lesions exhibit orthokeratosis with a basket-weave appearance, parakeratosis and acanthosis. Under higher power, some cells within the hyperplastic stratum malpighii have characteristic cytopathic changes. These cells are large with perinuclear halos and a cytoplasm that has a blue–gray pallor and contains keratohyaline granules of various sizes and shapes (Fig. 79.22). Keratinocytic dysplasia and actinic keratoses may be evident, especially in biopsies of lesions in sun-exposed areas[46]. Because the histologic picture is nonspecific, it may be difficult to differentiate typical flat warts from EV-associated lesions based on histology alone.

Anogenital Warts

The most consistent histologic features seen in condylomata include epidermal hyperplasia, parakeratosis, koilocytosis and papillomatosis. The papillomatosis is more gently rounded than is seen in common warts. The upper portions of the epithelia of mucosal surfaces normally have some degree of cytoplasmic vacuolization, so its detection is specific for condylomata acuminata only if present within the deeper portions of the stratum malpighii[46]. Mitotic figures may be evident, and prior treatment with podophyllotoxin (which interferes with microtubule formation in cells undergoing mitosis) can induce the appearance of aberrant mitoses that could potentially lead to misdiagnosis as SCC.

Giant Condylomata of Buschke–Löwenstein

The histology of the Buschke–Löwenstein tumor shares many features with condylomata acuminata, but there is marked downward extension of characteristically bulbous rete ridges and less vacuolization of epidermal cells (see Fig. 79.19). Mitotic figures are rarely detectable, and, when present, are normal. While customarily associated only with extension into and destruction of local tissue, metastases to local lymph nodes from foci of SCC arising in these tumors have been reported[43].

Squamous Intraepithelial Neoplasias

Persistent infection with high-risk HPV types can lead to intraepithelial neoplasia that may progress to invasive carcinoma. The precancerous lesions represent a continuum of morphologic changes with indistinct boundaries. In CIN grade I, nuclear enlargement and hyperchromasia is observed in the lower epithelial layers; these changes may be accompanied by cytoplasmic halos (koilocytotic atypia). The next stage (CIN II) shows progressive atypia in all layers of the epithelium, with abnormal differentiation of the keratinizing cell layers. The atypical cells have an increased nuclear–cytoplasmic ratio, variability of nuclear size, and an increased number of mitotic figures, including abnormal mitoses and hyperchromasia. In CIN III, the epithelium is totally replaced by immature, atypical cells with a lack of surface differentiation. The analogous lesions of the vulva, vagina, penis and anus are termed VIN (vulvar intraepithelial neoplasia; Fig. 79.23), VaIN (vaginal intraepithelial neoplasia), PIN (penile intraepithelial neoplasia) and AIN (anal intraepithelial neoplasia), respectively. Clinically, these may appear as erythematous or whitish plaques (erythroplasia, leukoplakia) or red–brown papules (bowenoid papulosis) (see Figs 73.12, 73.13, 79.15, 79.16 & 79.17).

DIFFERENTIAL DIAGNOSIS

The diagnosis of cutaneous and genital warts is straightforward if typical clinical features are present. Occasionally, various other diagnoses have to be considered and a biopsy may be required for confirmation and to identify dysplastic lesions. Immunohistochemistry with antibodies directed against cross-reacting epitopes of papillomavirus capsid proteins allows the detection of virions in palmoplantar warts, which are highly productive infections, but has limited sensitivity in genital warts and dysplasias. There is no routine infectivity assay

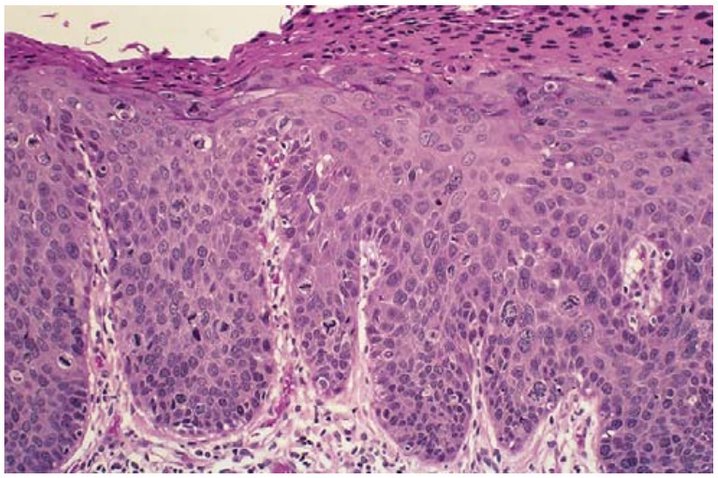


Fig. 79.23 Histology of vulvar intraepithelial neoplasia (VIN). Note the characteristic features of abnormal keratinocyte maturation, nuclear pleomorphism, and dyskeratosis. *Courtesy, R Tyler, MD.*

Fig. 79.24 Extensive and treatment-resistant penile warts in a renal transplant recipient.

available to detect virions in clinical samples, and diagnostic tests are therefore based on the molecular detection of papillomavirus DNA. Commercially available tests that utilize *in situ* hybridization (e.g. Hybrid Capture® II, Digene [available in the US]; Amplicor HPV® and Linear Array HPV Genotyping®, Roche [not available in the US]) can identify low-risk versus high-risk mucosal HPV types in clinical samples with high sensitivity and specificity. PCR-based techniques can also detect a broad range of genital and skin HPV types[48,49]. Development of circulating antibodies against the L1 major capsid protein is common following infection with genital HPV types, and ELISAs using L1 VLPs as the antigen have been useful in epidemiologic studies[32]. However, due to low antibody titers and variable intervals between infection and seroconversion, this assay is not used for diagnosis in individual patients.

Common Warts

Seborrheic keratoses (SKs), actinic keratoses (AKs), cutaneous horns (which can arise from warts as well as AKs, SCCs, SKs and other neoplasms; see Ch. 109), keratoacanthomas, other SCCs, trichilemmomas, Spitz nevi, and amelanotic melanomas may resemble common warts, and even tuberculosis verrucosa cutis or a plaque of psoriasis or hypertrophic lichen planus can have a warty clinical appearance. A wart-like periungual plaque on the finger may occasionally represent Bowen's disease and harbor high-risk HPV types 16 or 18. Similarly, amelanotic melanoma can masquerade as a persistent periungual wart and should be clinically suspected if erosion or subtle pigmentation is present. The differential diagnosis of flat warts may include acrokeratosis verruciformis, Gottron's papules of dermatomyositis (distinguished by their localization over the knuckles), lichen nitidus and lichen planus. Although both lesions of lichen planus and flat warts can develop in a linear array, the presence of Wickham's striae points to the former diagnosis. Plantar clavi (corns) are often misdiagnosed as warts, although verruca typically can be differentiated by the presence of punctate black dots representing thrombosed capillaries; in addition, shaving of the keratotic wart surface leads to capillary bleeding from the superficially located dermal papillae. Punctate palmoplantar keratoderma, punctate porokeratosis, arsenical keratoses and poromas can mimic plantar warts.

In patients with cellular immunodeficiencies, including organ transplant recipients and those with AIDS or hematologic malignancies, the number as well as incidence of cutaneous and genital warts is increased (Fig. 79.24). Warts that appear at less common sites such as the face and the neck need to be differentiated from mollusca contagiosa. In immunosuppressed patients, macular and flat warts may resemble EV, but the clinical setting and absence of a family history can aid in establishing the correct diagnosis. Other heritable immunodeficiencies that predispose affected individuals to the development of warts include WHIM syndrome (see above), idiopathic $CD4^+$ lymphopenia, DOCK8 deficiency, and severe combined immunodeficiencies (see Ch. 60).

Anogenital Lesions

Condylomata acuminata are rarely confused with condylomata lata of secondary syphilis, but serologic testing for syphilis (and, as indicated, other sexually transmitted diseases) is recommended in patients with genital warts, and dark-field examination for spirochetes may be required. Mollusca contagiosa preferentially involve the mons pubis and can be distinguished by their umbilication, with dermoscopy revealing a multilobular, yellow–white central structure surrounded by a "crown" of vessels. In men, pearly penile papules are normal anatomic structures consisting of several rows of discrete, monomorphic, dome-shaped, 1 to 2 mm papules circumferentially around the corona and/or sulcus of the glans penis (see Ch. 116). An analogous picture exists in women, called vestibular papillomatosis, with tiny, uniformly shaped, finger-like projections at the introitus and on the labia minora. Sebaceous glands of the prepuce and labia majora appear as white–gray to yellow, small papules with a regular array. Epidermoid cysts, steatocystomas or angiokeratomas of the scrotum seldom pose diagnostic problems.

Detection of subclinical genital HPV infection requires soaking with 5% acetic acid for 3 to 5 minutes; this leads to whitening ("aceto-whitening") of lesions, and the use of a colposcope for magnification will further increase diagnostic accuracy. However, aceto-whitening is not specific for HPV-induced lesions and is also observed in infectious or inflammatory conditions such as *Candida* vulvitis or balanoposthitis, psoriasis, lichen planus or eczematous dermatitis.

Bowenoid papulosis consists of red–brown papules or confluent, sometimes leukoplakia-like plaques that may be difficult to distinguish from condylomata (see Figs 79.15 & 79.16). Erythroplasia of Queyrat is a well-defined, velvety erythematous plaque of the glans or vulva that must be differentiated from erosive lichen planus and Zoon's balanitis (see Fig. 79.17 and Ch. 73). Bowen's disease can present as a solitary patch or plaque, sometimes scaly, of the vulva or penis, most often in older individuals. Extramammary Paget's disease appears as a well-defined red plaque in the groin or pubic region or on the vulva, penile root or perianal skin, with distinctive histopathologic features (see Ch. 73).

Vulvar carcinomas are etiologically heterogeneous. Carcinomas with basaloid or warty histology are related to HPV infection, whereas keratinizing squamous carcinomas are not[50]. Basaloid and warty vulvar carcinomas typically arise in younger women, are found adjacent to vulvar intraepithelial neoplasia (VIN), and are associated with risk factors related to sexual practices. Close to 90% of high-grade VIN (see Fig. 79.15) and basaloid and warty vulvar carcinomas contain high-risk HPV DNA (most often HPV-16, -31 and -33), suggesting a common etiology. In contrast, the more common keratinizing vulvar carcinoma in older women, which typically arises adjacent to lichen sclerosus and

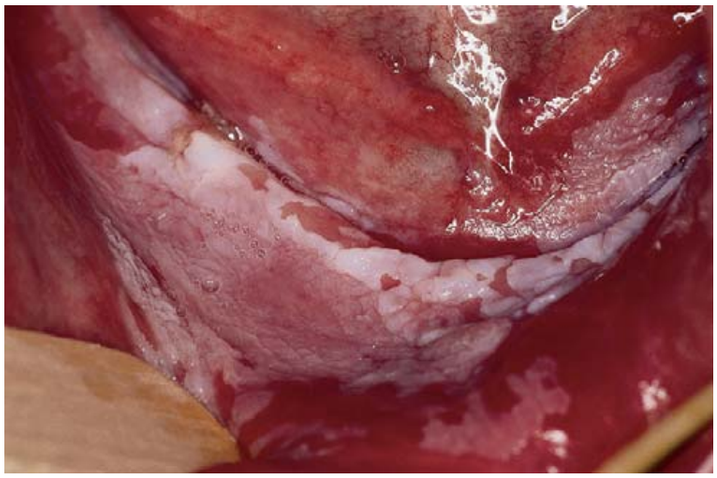


Fig. 79.25 Verrucous proliferative leukoplakia of the oral cavity. The lesions have focally progressed to invasive squamous cell carcinoma; HPV DNA was not detectable by PCR.

epidermal hyperplasia, infrequently contains HPV DNA and thus is regarded as a distinct entity[51].

Heterogeneity in etiology has also been described for anal SCC[51,52]. In both genders, the majority of anal cancers are attributable to HPV infection. Cancers of the anal canal that are positive for high-risk HPV (16, 18, 31, 33) tend to occur in younger men and women with high-risk sexual behaviors (especially MSM), have basaloid histology, and arise adjacent to AIN. In contrast, HPV-negative anal cancers usually affect older men, are well keratinized, and arise from perianal skin without AIN. Heterogeneous etiology has also been described for penile cancer, analogous to that observed for vulvar and anal squamous cell cancers[51]. Immunosuppression and a history of HPV-associated malignancy are notable risk factors for the development of a (second) anogenital cancer attributable to HPV.

Anogenital warts in children may give rise to suspicion of sexual abuse (see Ch. 90). In the majority of cases, however, the presence of several criteria will argue for a non-abusive transmission of HPV. These include an age less than 3 years, wart location somewhat distant from the anus or vulva, detection of HPV-2 or other skin-specific HPV types, genital condylomata in the mother, and an absence of signs of physical abuse or of other sexually transmitted diseases[15].

Giant condyloma acuminatum, or Buschke–Löwenstein tumor, is clinically suspected by its size and the presence of fistulas or abscesses (see Fig. 79.18). Histologic findings may be remarkably banal, and distinction from large benign genital warts can therefore be difficult at an early stage (see Fig. 79.19)[43,53]. However, high-resolution imaging reveals the extent of infiltration, and a large biopsy with serial sectioning may detect locally destructive growth and, rarely, transformed foci of SCC.

Oral Warts

Oral warts (see Fig. 79.20) or condylomata may resemble the papules of focal epithelial hyperplasia (Heck's disease); the latter is very rare in Caucasians. A distinct oral condition with the descriptive name "verrucous proliferative leukoplakia" is clinically similar to oral florid papillomatosis but does not contain HPV DNA and has a high risk of progression to metastatic squamous cell cancer (Fig. 79.25)[54]. Additional diagnostic considerations may include leukoedema (grayish-white translucent plaques, sometimes with a "moth-eaten" appearance, that favor the buccal mucosa and may become less evident upon stretching), a white sponge nevus and hereditary benign epithelial dyskeratosis.

THERAPY

General Considerations

There is currently no specific antiviral therapy available to cure HPV infection. Existing modalities focus primarily on the destruction or removal of visible lesions or induction of cytotoxicity against infected cells (Table 79.2). Because of the benign and self-limited nature of warts, treatments that cause scarring should be avoided. There is no evidence that aggressive treatment results in a better long-term outcome, and temporary interruption of therapy is an option. Common warts often regress spontaneously in children and therefore may not require treatment. A simplified algorithm for the approach to treatment of common warts is presented in Figure 79.26.

Genital warts may be disfiguring and pose a significant psychological burden. HPV infection is typically widespread and multifocal throughout the anogenital tract, and subclinical lesions are often present. Thus, regardless of the applied therapeutic modality, reported recurrence rates are high (25–65%) and it is unproven whether treatment reduces transmission rates to new sexual partners. Limiting the number of partners remains the mainstay of decreasing transmission. Condom use may also be helpful, and it has promoted regression of flat penile lesions and CIN as well as clearance of HPV in couples infected with the same HPV type[55]. Treatment is time-consuming, uncomfortable and limited to visible warts and intraepithelial neoplasias with a high risk of progression. A simplified treatment algorithm is shown in Figure 79.27. Current therapies for genital warts are summarized in Table 79.2 and include destructive, antiproliferative and immunomodulatory modalities[56].

MANAGEMENT OF ANOGENITAL WARTS WITH GRADING OF RECOMMENDATIONS
CYTOTOXIC OR ANTIVIRAL AGENT
• Podophyllotoxin 0.5% solution, 0.15% cream (1) • Cidofovir 1% gel (1), intralesional injection (3)
PHYSICAL DESTRUCTION
• Cryotherapy (liquid nitrogen, cryoprobe) (1) • Trichloroacetic acid (TCA) 70–90% solution (1) • Potassium hydroxide 5% solution (2) • Electrosurgery (1) • Scissors excision (1) • Laser vaporization (2) • Photodynamic therapy with topical aminolevulinic acid (1)
IMMUNOMODULATORY
• Imiquimod 5% cream (1) • Sinecatechins (green tea catechins) 15% ointment (1) • Topical immunotherapy with squaric acid dibutyl ester (3) • Intralesional immunotherapy with skin test antigens (2) • Intralesional interferons (1, but inconsistent results)
OTHER
• Oral isotretinoin (1)

Table 79.2 Management of anogenital warts with grading of recommendations. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports[56].

Local Destructive Therapy

Destructive or ablative therapies for *genital warts* include cryotherapy, trichloroacetic acid (TCA), electrosurgery, curettage, scalpel or scissors excision, laser vaporization and photodynamic therapy with topical aminolevulinic acid. When anesthesia is required, topical application or injection of a local agent (see Ch. 143) is usually sufficient, although general anesthesia may be indicated for surgical debulking of large lesions and occasionally in children. Ablative laser therapy is also useful for vaginal, vulvar or anal intraepithelial neoplasias. Precautions should be taken to avoid inhalation of virus particles in the aerosol plume when laser or electrosurgical procedures are performed. Application of TCA 70–90% solution is a commonly utilized office-applied therapy that results in local tissue destruction. Although scarring may occur following dermal injury, TCA has the advantage of a complete lack of systemic toxicity and it can be used during pregnancy. Cryotherapy is inexpensive, effective and does not require anesthesia; as a result, it is often used as a first-line therapy followed by patient-applied podophyllotoxin. Liquid nitrogen is applied with a cotton swab, spray gun or

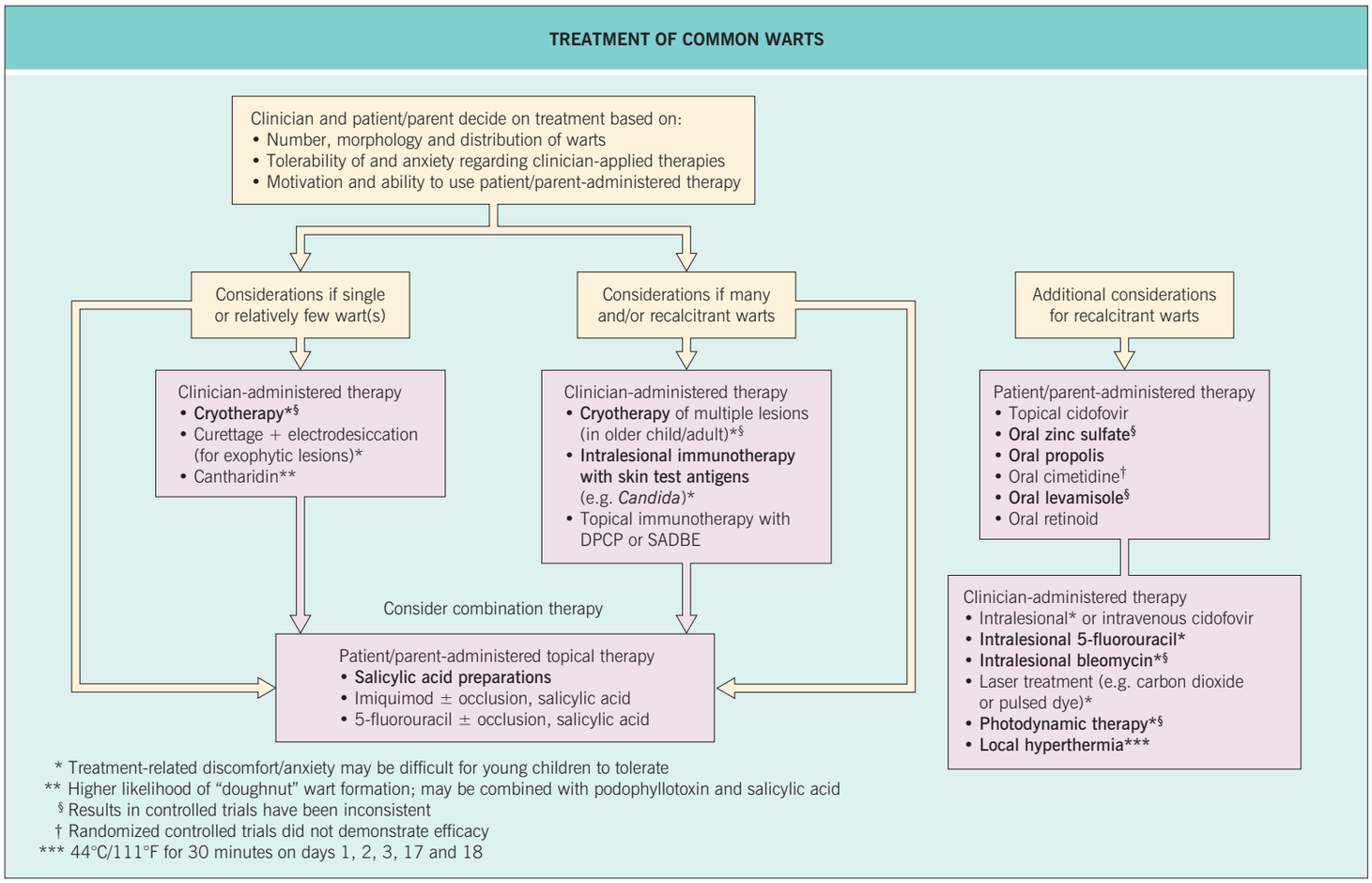


Fig. 79.26 Treatment of common warts. Therapies found to be effective in controlled trials are in bold. DPCP, diphenylcyclopropenone; SADBE, squaric acid dibutyl ester.

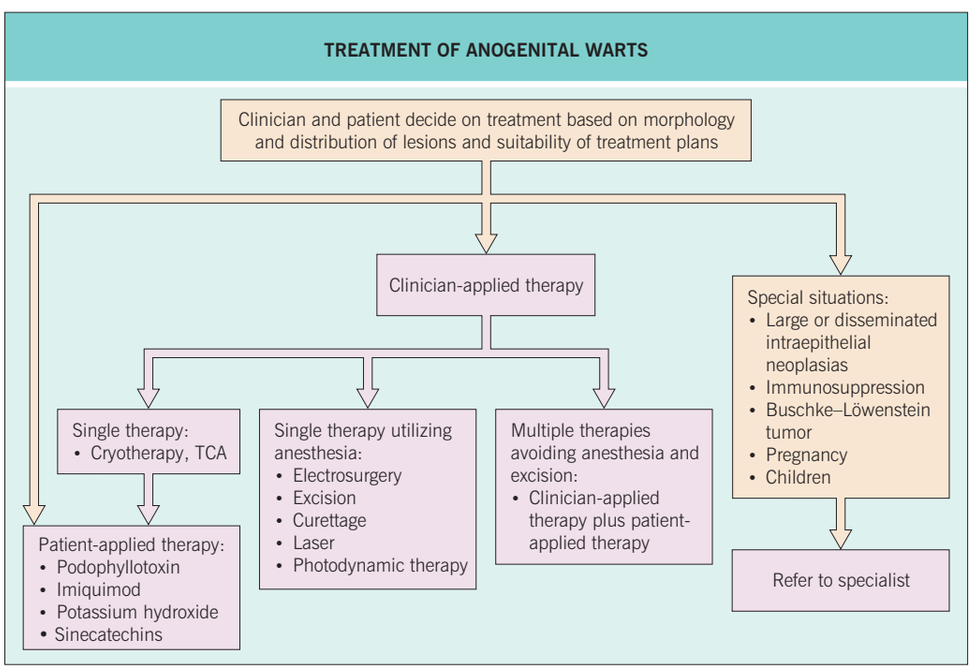


Fig. 79.27 Treatment of anogenital warts. TCA, trichloroacetic acid.

closed system cryoprobe (see Ch. 138). Two freeze–thaw cycles, the extent of which is visually controlled, lead to wart necrosis, and multiple treatments result in remission rates of 78% to 88%, with recurrences in 20–40% of patients[57]. At-home application of potassium hydroxide (KOH) 5% solution has induced regression of genital warts in men[58].

Cutaneous warts may be treated by daily application of salicylic acid/lactic acid/collodion (1:1:4) or other salicylic acid preparations for up to 12 weeks, which results in regression in two-thirds of patients. Application of petrolatum to the surrounding normal skin protects against the corrosive effect of the concentrated acid. Weight pressure causes deep inward growth of plantar warts (myrmecia), and the

resulting pain can be reduced by repeated shaving of the hyperkeratotic surface to a level at which capillary bleeding occurs. Cryotherapy with liquid nitrogen (see above) may be utilized for persistent or recurrent verrucae, including periungual lesions, with cure rates similar to or better than salicylic acid preparations in randomized controlled studies[58a–c]. Other in-office or at-home freezing products (e.g. those containing dimethyl ether and propane) are less effective. Cryotherapy that does not include a rim of surrounding skin or topical application of the blistering agent cantharidin (see Ch. 85) may produce a "doughnut wart" due to clearance in the center but not at the periphery of the lesion. Additional destructive modalities include curettage or scissor excision (especially for filiform warts and other exophytic lesions), electrosurgery (see Ch. 140), laser treatment (e.g. with CO_2 or pulsed dye lasers) and photodynamic therapy. Combination therapy with the application of topical agents following destruction may reduce the rate of recurrence.

Topical and Intralesional Cytotoxic Therapy

Podophyllin is a crude resin extract from the roots of the May apple *Podophyllum peltatum* (North America) or *Podophyllum emodi* (Far East) that has been used since 1942 for the treatment of genital warts. Systemic toxicity can occur when applied in large volumes, and death, intrauterine demise and teratogenicity have been reported. Because of low efficacy and potential toxicity, podophyllin use is no longer recommended[55]. Podophyllotoxin has been identified as the most active constituent of podophyllin. A regimen of patient self-applied podophyllotoxin 0.5% solution twice a day for 3 days repeated in weekly cycles was shown to be effective and without evidence of systemic absorption and toxicity. In a controlled randomized trial, podophyllotoxin 0.5% solution or 0.15% cream was superior to podophyllin 25% solution for the treatment of genital warts[57]. Erythema and erosions are the most common side effects. Both podophyllin and podophyllotoxin are contraindicated during pregnancy.

Warts of the urethral meatus and urethra are difficult to manage, and stenosis and stricture due to therapy are potentially serious complications. 5-Fluorouracil (5-FU) 5% cream can be applied twice a week to treat intraurethral condylomata or, as an alternative to destructive treatments, intraepithelial neoplasias of the external genitalia. However, its use in the genital area is limited by inflammatory side effects. Successful treatment of cutaneous warts with 5-FU 5% cream applied daily under occlusion or together with salicylic acid has also been described in children and adults[59], and effective therapy with intralesional 5-FU has been reported.

Intralesional bleomycin is occasionally used to treat recalcitrant cutaneous warts, but injections are painful and may result in excessive cutaneous necrosis.

Topical Immunomodifiers

Imiquimod is an imidazoquinoline compound with immunomodulatory activities that has been approved by the US Food and Drug Administration (FDA) for the topical treatment of condylomata acuminata. Imiquimod has been shown to interact with Toll-like receptors 7 and (to a lesser degree) 8, resulting in activation of cytokine secretion from monocytes/macrophages (including interferon-α, interleukin-12 and tumor necrosis factor-α) as well as stimulation of antigen-presenting dendritic cells (see Ch. 128).

In an initial randomized, double-blind, placebo-controlled clinical trial, complete clearance of genital warts occurred in 50% of patients treated with imiquimod 5% cream compared to 11% of those treated with vehicle control; recurrence rates were low (<15%) in both groups[60]. Response rates were higher for warts on mucosal sites (i.e. female and uncircumcised male patients) than for lesions on the penile shaft or suprapubic area, suggesting the importance of crossing the stratum corneum barrier for effective treatment. Later studies confirmed the therapeutic effect of imiquimod for anogenital warts and documented that this treatment resulted in a reduction of viral load, presumably due to activation of cellular immune responses. A direct comparison of imiquimod and cryotherapy for genital warts found an earlier response with imiquimod, slightly higher efficacy with cryotherapy, and similar recurrence rates[61]. In clinical practice, destruction of genital warts by the physician followed by patient-applied imiquimod (often requiring several cycles) is favorable over either modality alone[62]. Imiquimod has also been applied via suppositories (anal tampons) to prevent recurrence of anal condylomata following surgical ablation, or as primary treatment for anal condylomata and AIN in order to avoid the risk of scarring and stenosis of the anal canal associated with surgical procedures[63].

Therapeutic efficacy of imiquimod 5% cream has also been described for persistent cutaneous warts. In a controlled study (right versus left comparison) involving 14 immunosuppressed patients with recalcitrant warts on their hands and/or feet, a 36% response rate was observed for warts treated with imiquimod (three times weekly for 8 weeks, daily for 8 weeks, then daily with occlusion for 8 weeks) compared to 7% for untreated warts[64]. Improvement of common and flat warts with imiquimod therapy (daily application; ± occlusion for common warts) has also been reported in uncontrolled studies in immunocompetent patients[65]. Occlusion and/or concurrent use of salicylic acid or cryotherapy may increase imiquimod's penetration through the stratum corneum, which is especially important in acral sites.

Side effects of imiquimod include application site reactions (inflammation, erosion) that may require treatment-free periods. Imiquimod therapy is often more costly than other treatment options.

Sinecatechins 15% ointment, which contains green tea leaf-derived catechins thought to have immunostimulatory and antiproliferative properties, is FDA-approved as a topical treatment for anogenital warts. In randomized double-blind clinical studies, application of this product three times daily for up to 16 weeks led to complete clearance of anogenital warts in approximately 55% of patients (with frequent local irritation), compared to 35% of those treated with a vehicle control[65a].

Systemic Immunomodifiers

Interferons have been used topically, intralesionally and systemically for genital warts in controlled trials and have failed to demonstrate consistent efficacy. Systemic therapy, which is expensive and causes dose-related toxic side effects, is thus not recommended for routine clinical use. However, interferons may be helpful as an adjunct or salvage therapy in selected patients[53,57].

Anecdotal reports have described the successful treatment of recalcitrant common or flat warts as well as EV lesions with oral cimetidine (30–40 mg/kg daily divided into two to three doses; maximum of 2400 mg daily), which may stimulate production of interferon-γ and interleukin-2. However, three double-blind, placebo-controlled studies failed to confirm efficacy of cimetidine therapy for recalcitrant common warts. Two recent randomized controlled trials of oral zinc sulfate therapy (10 mg/kg to a maximum dose of 600 mg daily for 2 months) for treatment-resistant cutaneous warts had disparate results, with complete clearance rates in zinc-treated patients of 78% (27/32) in one study and 16% (4/25) in the other, compared with 12–13% in both placebo groups[66,67].

Immunotherapy

Increasing evidence that cellular immune responses play a critical role in wart clearance has inspired the development of topical and intralesional immunotherapy regimens for patients with multiple and/or recalcitrant warts. In a large uncontrolled study[68], 154 children and adults with recalcitrant palmoplantar warts underwent successful topical sensitization with 2% diphenylcyclopropenone (DPCP) followed by at least six applications of 0.5–4% DPCP to their warts at 3-week intervals. An 88% complete clearance rate was observed after an average of 6 months, with only local side effects (pruritus, blistering, eczematous reactions). Similar clearance rates have been reported for other contact sensitizers such as squaric acid dibutyl ester (SADBE), with application frequencies ranging from daily to monthly (often twice weekly), and regression of distant untreated warts has also been described.

Intralesional injection of *Candida*, *Trichophyton* and/or mumps skin test antigens represents another approach to immunotherapy for warts in immunocompetent adults and children. In a randomized controlled clinical trial, a significantly higher clearance rate for treated as well as distant untreated common warts was observed in patients receiving intralesional antigen as compared to placebo at 3-week intervals for a total of up to five treatments (60% versus 22%, and 41% versus 19%,

respectively)[69]. Effective treatment of flat warts and anogenital warts with topical and intralesional immunotherapy has also been described.

Antiviral Agents

Cidofovir is an acyclic nucleoside phosphonate with broad-spectrum activity against DNA viruses, including HSV and molluscum contagiosum, and it is approved for the systemic treatment of cytomegalovirus retinitis in AIDS patients. Although limited by the potential for renal toxicity, systemic treatment with cidofovir has shown efficacy in patients with HPV-associated lesions, including extensive cutaneous warts and severe RRP with pulmonary involvement. Intralesional injection of cidofovir and topical application of 1–3% cidofovir incorporated into an ointment, cream or gel base have been successfully used in a limited number of immunocompetent or immunosuppressed (e.g. HIV-infected) patients with cutaneous warts, condylomata acuminata, intraepithelial neoplasias or RRP[70,71].

Retinoids

The effects of retinoids on keratinocyte differentiation and proliferation may lead to inhibition of HPV replication and assembly. Eradication of extensive cutaneous or genital warts with oral retinoid therapy (e.g. acitretin or isotretinoin) has been reported in immunocompetent and immunosuppressed patients[72,73]. Successful treatment of flat warts with topical tretinoin or tazarotene has also been described.

Special Considerations

Early diagnosis of Buschke–Löwenstein tumor and other verrucous carcinomas is important to allow wide excision with clear resection margins. Surgery is the only established treatment that may cure the disease, although recurrence rates are high and the tumor can ultimately result in death. Cytotoxic chemotherapy and injections of interferon-α have led to remissions or cure in individual patients[43,53].

In transplant recipients and HIV-infected patients, skin and genital warts tend to resist standard treatment modalities. A surgical approach followed by non-invasive treatment of recurrent warts may be appropriate. In placebo-controlled studies, local application of imiquimod reduced genital wart area by more than 50% in 38% of HIV-infected patients. Imiquimod cream has also been used in individual cases of AIN and VIN[57], supporting a role for cellular immune enhancement for treatment of HPV-induced neoplasia.

During pregnancy, genital warts can increase in size and destructive procedures including surgery, cryotherapy, TCA application and laser treatments are appropriate to remove lesions, which may theoretically reduce the risk for the newborn to acquire RRP[25]. However, this assumption is not proven and the presence of condylomata is not an indication for delivery by cesarean section. Podophyllin and podophyllotoxin are teratogenic and thus must not be used in pregnant women.

The treatment of intraepithelial neoplasias (bowenoid papulosis, erythroplasia of Queyrat, Bowen's disease) is generally more aggressive than that of benign condylomata[56]. Prior to therapy, an aiming biopsy (e.g. colposcopically directed) is always required to exclude (micro) invasion histologically. For patients with bowenoid papulosis and erythroplasia who are younger than 45 years of age, superficial destruction (e.g. with cryotherapy or laser vaporization) of lesions may be appropriate to avoid mutilation[74]. In immunocompetent patients less than 35 years of age, bowenoid papulosis is regarded as a benign and self-limited disease[75]. Nevertheless, prolonged observation appears mandatory to detect recurrences.

HPV Vaccines

More than a decade ago, recombinant DNA technology was used to generate a prophylactic vaccine that consists of the L1 major capsid protein, which self-assembles into empty capsids designated virus-like particles (VLPs) (see Fig. 79.3)[26]. VLPs resemble native virions morphologically and immunologically, and they carry neutralization epitopes on their surface. However, as a safety advantage, they do not contain the potentially oncogenic viral DNA. Systemic immunizations with VLPs induce high-titer, long-lasting and type-specific neutralizing antibodies[27,76].

Prophylactic vaccinations in several animal models of papillomavirus infection were spectacularly successful in preventing natural or experimental infection of skin and mucosa[2,77]. In phase I/II human trials, systemic immunizations with VLP-based vaccines were nontoxic and highly immunogenic, inducing robust neutralizing antibody responses[76]. Based on these promising results, large-scale prophylactic vaccination trials were conducted to evaluate the safety and efficacy of two agents in preventing genital HPV infection and associated lesions in young women: (1) a quadrivalent vaccine of HPV-6, -11, -16, -18 VLPs (Gardasil™; Merck); and (2) a bivalent vaccine of HPV-16, -18 VLPs (Cervarix™; GlaxoSmithKline). Study endpoints were detection of HPV DNA and the development of dysplasias (squamous intraepithelial lesions) or (for the quadrivalent vaccine) anogenital warts. These studies showed near-complete protection (>90% vaccine efficacy) against vaccine-type HPV infection as well as 100% protection in the prevention of genital warts, low-grade dysplasias and high-grade dysplasias associated with the vaccine HPV types (for at least 5 years)[3–5,78,79]. The quadrivalent vaccine was also found to be nearly 90% effective in preventing genital warts caused by HPV types 6 and 11 in young men. While post-marketing evaluation of the duration of efficacy of the vaccines is ongoing, trial results have demonstrated stabilized antibody titers 5 years after vaccination, suggesting induction of a strong B-cell memory response. Also, in studies where girls and boys between the ages of 10 and 15 years were vaccinated, more than 99% have seroconverted, and they developed antibody titers that were even higher than those in women 16 to 23 years of age[80].

Two HPV vaccines are now commercially available (see above), with a primary goal of universally vaccinating children and adolescents prior to the onset of sexual activity (ideally before 12 years of age). Gardasil™ is FDA-approved for use in individuals (female and male) 9 to 26 years of age to prevent anogenital warts, dysplasias and cancer. Cervarix™ is FDA-approved for use in girls and women ages 9 to 25 years to prevent cervical dysplasia and cancer. Information gained from ongoing studies will aid in answering additional questions, including: cross-protection against related HPV types; benefits of including additional HPV types; the effects of vaccination on the incidences of cervical, vulvar, vaginal and anal cancers and genital warts in the general population; whether vaccination will reduce the carriage rate of oropharyngeal HPV-16 and the incidence of HPV-16-associated head and neck squamous cell cancer; duration of protection (when to boost); utility of surrogate assays for neutralizing antibodies; and correlates of protection.

At present, high-risk HPV types 16, 18, 31 and/or 45 are detected in about 80% of cervical cancers worldwide. A second-generation nonavalent VLP vaccine that targets seven oncogenic and two low-risk HPV types is currently being evaluated in clinical trials. As high-risk HPV-associated penile and anal cancer are relatively rare in men, vaccines that include low-risk HPV-6 and -11 VLPs to prevent genital warts might encourage male vaccination, which is likely to increase vaccine efficiency in the population as a whole due to herd immunity[27,76]. As an alternative approach to generate a broader-spectrum vaccine, genetic engineering has been employed to develop L1 VLPs that also express type-common epitopes of the minor capsid protein L2, which can induce cross-protective immunity to a variety of mucosal and even cutaneous HPV types[81–83]. Oral vaccination with attenuated *Salmonella typhimurium* expressing L1 may become a cost-effective alternative strategy for implementing HPV vaccination in developing countries. Such countries cannot afford HPV VLP vaccination programs or cytology (Pap) screening, yet they carry >80% of the worldwide burden of cervical cancer[19,84].

Successful experiments in animals have encouraged efforts to develop therapeutic vaccines against HPV infections. Most papillomavirus infections are self-limited, and it is generally agreed that a cellular immune response (albeit poorly understood) is required for clearance of infection. Cell-mediated immunity to L1 or L2 is unlikely to exhibit therapeutic efficacy, as capsid proteins are expressed neither in basal cells that harbor HPV DNA nor in progressed lesions that do not produce virions. Candidate rejection antigens are the E6 and E7 oncoproteins, which are selectively retained and expressed in cervical dysplasia and cancer, and E1 or E2 proteins, which are required to maintain the viral genome as an episome. Multiple strategies have been employed, including vaccinations with papillomavirus proteins fused to or combined with immunostimulants or dendritic cells in addition to attenuated viral or DNA expression vectors (for review, see ref. 85).

Chimeric VLPs have been engineered to incorporate an early protein such as E7 into an L1 or L1/L2 capsid. The induction of cytotoxic T-lymphocyte responses to the E7 oncoprotein, in addition to antibodies directed against the L1 capsid protein, provides both therapeutic and prophylactic benefit in mouse tumor models[86]. These strategies may prove effective in low-grade dysplasia or condylomata that have a high likelihood of spontaneous regression. However, mechanisms of immune evasion such as downregulation of MHC type I expression may diminish the success of therapeutic vaccines and, thus, favor their application as an adjunct to established ablative therapies. Also, safety issues associated with live attenuated or DNA vectors and with vaccines containing E6 or E7 oncoproteins are complex[76,87].

DISCLAIMER

This project has been funded in whole or in part with federal funds from the National Cancer Institute, National Institutes of Health, under Contract No. HHSN261200800001E. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

REFERENCES

1. zur Hausen H. Papillomavirus infection – a major cause of human cancers. Biochim Biophys Acta. 1996;1288:F55–78.
2. Kirnbauer R, Chandrachud L, O'Neil B, et al. Virus-like particles of bovine papillomavirus type-4 in prophylactic and therapeutic immunization. Virology. 1996;219:37–44.
3. Paavonen J, Naud P, Salmerón J, et al. HPV PATRICIA Study Group. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. Lancet. 2009;374:301–14.
4. Koutsky LA, Ault KA, Wheeler CM, et al. A controlled trial of a human papillomavirus type 16 vaccine. N Engl J Med. 2002;347:1645–51.
5. Ault KA, Future II Study Group. Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. Lancet. 2007;369:1861–8.
6. Ciuffo G. Infesto positivo con filtrato di verruca volgare. Giorn Ital Mal Venereol. 1907;48:12–17.
7. Howley PM, Lowy DR. Papillomaviruses. In: Knipe DM, Howley PM (eds). Fields Virology, 5th edn. Philadelphia: Lippincott Williams & Wilkins, 2001:2299–354.
8. Bernard HU, Burk RD, Chen Z, et al. Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. Virology. 2010;401:70–9.
9. zur Hausen H. Condylomata acuminata and human genital cancer. Cancer Res. 1976;36:794.
10. zur Hausen H. Papillomaviruses causing cancer: evasion from host-cell control in early events in carcinogenesis. J Natl Cancer Inst. 2000;92:690–8.
11. Roden RB, Lowy DR, Schiller JT. Papillomavirus is resistant to desiccation. J Infect Dis. 1997;176:1076–9.
12. Kilkenny M, Merlin K, Young R, Marks R. The prevalence of common skin conditions in Australian school students: 1. Common, plane and plantar viral warts. Br J Dermatol. 1998;138:840–5.
13. Plunkett A, Merlin K, Gill D, et al. The frequency of common nonmalignant skin conditions in adults in central Victoria, Australia. Int J Dermatol. 1999;38:901–8.
14. de Koning MN, ter Schegget J, Eekhof JA, et al. Evaluation of a novel broad-spectrum PCR-multiplex genotyping assay for identification of cutaneous wart-associated human papillomavirus types. J Clin Microbiol. 2010;48:1706–11.
15. Cohen BA, Honig P, Androphy E. Anogenital warts in children. Clinical and virologic evaluation for sexual abuse. Arch Dermatol. 1990;126:1575–80.
16. Ho GY, Bierman R, Beardsley L, et al. Natural history of cervicovaginal papillomavirus infection in young women. N Engl J Med. 1998;338:423–8.
17. Partridge JM, Hughes JP, Feng Q, et al. Genital human papillomavirus infection in men: incidence and risk factors in a cohort of university students. J Infect Dis. 2007:196;1128–36.
18. Division of STD Prevention. Prevention of Genital HPV Infection and Sequelae: Report of an External Consultants' Meeting. Atlanta, GA: Centers for Disease Control and Prevention, 1999.
19. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin. 2011;61:69–90.
20. Nonnenmacher B, Hubbert NL, Kirnbauer R, et al. Serologic response to human papillomavirus type 16 (HPV-16) virus-like particles in HPV-16 DNA-positive invasive cervical cancer and cervical intraepithelial neoplasia grade III patients and controls from Colombia and Spain. J Infect Dis. 1995;172:19–24.
21. Chin-Hong PV, Palefsky JM. Human papillomavirus anogenital disease in HIV-infected individuals. Dermatol Ther. 2005;18:67–76.
22. Pfister H. Chapter 8: Human papillomavirus and skin cancer. J Natl Cancer Inst Monogr. 2003;(31):52–6.
23. Antonsson A, Karanfilovska S, Lindqvist PG, Hansson BG. General acquisition of human papillomavirus infections of skin occurs in early infancy. J Clin Microbiol. 2003;41:2509–14.
24. Favre M, Orth G, Majewski S, et al. Psoriasis: a possible reservoir for human papillomavirus type 5, the virus associated with skin carcinomas of epidermodysplasia verruciformis. J Invest Dermatol. 1998;110:311–17.
25. Silverberg MJ, Thorsen P, Lindeberg H, et al. Condyloma in pregnancy is strongly predictive of juvenile-onset recurrent respiratory papillomatosis. Obstet Gynecol. 2003;101:645–52.
26. Kirnbauer R, Booy F, Cheng N, et al. Papillomavirus L1 major capsid protein self-assembles into virus-like particles that are highly immunogenic. Proc Natl Acad Sci U S A. 1992;89:12180–4.
27. Kirnbauer R. Papillomavirus-like particles for serology and vaccine development. Intervirology. 1996;39: 54–61.
28. Lowy DR, Frazer IH. Chapter 16: Prophylactic human papillomavirus vaccines. J Natl Cancer Inst Monogr. 2003;31:111–16.
29. Shafti-Keramat S, Handisurya A, Kriehuber E, et al. Different heparan sulfate proteoglycans serve as cellular receptors for human papillomaviruses. J Virol. 2003;77:13125–35.
30. Kines RC, Thompson CD, Lowy DR, et al. The initial steps leading to papillomavirus infection occur on the basement membrane prior to cell surface binding. Proc Natl Acad Sci U S A. 2009;106:20458–63.
31. Richards RM, Lowy DR, Schiller JT, et al. Cleavage of the papillomavirus minor capsid protein, L2, at a furin consensus site is necessary for infection. Proc Natl Acad Sci U S A 2006;103:1522–7.
32. Kirnbauer R, Hubbert NL, Wheeler CM, et al. A virus-like particle enzyme-linked immunosorbent assay detects serum antibodies in a majority of women infected with human papillomavirus type 16. J Natl Cancer Inst. 1994;86:494–9.
33. Munoz N, Bosch FX, de Sanjose S, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med. 2003;348:518–27.
34. Egawa K. New types of human papillomaviruses and intracytoplasmic inclusion bodies: a classification of inclusion warts according to clinical features, histology and associated HPV types. Br J Dermatol. 1994;130:158–66.
35. Rubben A, Kalka K, Spelten B, Grussendorf-Conen EI. Clinical features and age distribution of patients with HPV 2/27/57-induced common warts. Arch Dermatol Res. 1997;289:337–40.
36. de Koning MN, ter Schegget J, Eekhof JA, et al. Evaluation of a novel broad-spectrum PCR-multiplex genotyping assay for identification of cutaneous wart-associated human papillomavirus types. J Clin Microbiol. 2010:48;1706–11.
37. Majewski S, Jablonska S. Epidermodysplasia verruciformis as a model of human papillomavirus-induced genetic cancer of the skin. Arch Dermatol. 1995;131:1312–18.
38. Ramoz N, Rueda LA, Bouadjar B, et al. Mutations in two adjacent novel genes are associated with epidermodysplasia verruciformis. Nat Genet. 2002;32:579–81.
39. Lazarczyk M, Pons C, Mendoza JA, et al. Regulation of cellular zinc balance as a potential mechanism of EVER-mediated protection against pathogenesis by cutaneous oncogenic human papillomaviruses. J Exp Med. 2008;205:35–42.
40. Hernandez PA, Gorlin RJ, Lukens JN, et al. Mutations in the chemokine receptor gene CXCR4 are associated with WHIM syndrome, a combined immunodeficiency disease. Nat Genet. 2003;34:70–4.
41. Kreuter A, Hochdorfer B, Brockmeyer NH, et al. A human papillomavirus-associated disease with disseminated warts, depressed cell-mediated immunity, primary lymphedema, and anogenital dysplasia: WILD syndrome. Arch Dermatol. 2008;144:366–72.
42. Schwartz RA, Janniger CK. Bowenoid papulosis. J Am Acad Dermatol. 1991;24:261–4.
43. Handisurya A, Rieger A, Horvath Z, et al. Rapid progression of an anal Buschke-Löwenstein tumor into a metastasizing squamous cell carcinoma in an HIV-infected patient. Sex Transm Infect. 2009;85:261–3.
44. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. N Engl J Med. 2007;356:1944–56.
45. Gillison ML, Lowy DR. A causal role for human papillomavirus in head and neck cancer. Lancet. 2004;363:1488–9.
46. Lever WF, Elder DE. Lever's Histopathology of the Skin, 8th edn. Philadelphia: Lippincott-Raven, 1997.
47. Coleman N, Birley HD, Renton AM, et al. Immunological events in regressing genital warts. Am J Clin Pathol. 1994;102:768–74.
48. Boxman IL, Berkhout RJM, Mulder LH, et al. Detection of human papillomavirus DNA in plucked hairs from renal transplant recipients and healthy volunteers. J Invest Dermatol. 1997;108:712–15.
49. Iftner A, Klug SJ, Garbe C, et al. The prevalence of human papillomavirus genotypes in nonmelanoma skin cancers of nonimmunosuppressed individuals identifies high-risk genital types as possible risk factors. Cancer Res. 2003;63:7515–19.
50. Trimble CL, Hildesheim A, Brinton LA, et al. Heterogeneous etiology of squamous carcinoma of the vulva. Obstet Gynecol. 1996;87:59–64.
51. Gillison ML, Shah KV. Chapter 9: Role of mucosal human papillomavirus in nongenital cancers. J Natl Cancer Inst Monogr. 2003;(31):57–65.
52. Frisch M, Fenger C, van den Brule AJ, et al. Variants of squamous cell carcinoma of the anal canal and perianal skin and their relation to human papillomaviruses. Cancer Res. 1999;59:753–7.
53. Geusau A, Heinz-Peer G, Volc-Platzer B, et al. Regression of deeply infiltrating giant condyloma (Buschke-Löwenstein tumor) following long-term intralesional interferon alfa therapy. Arch Dermatol. 2000;136:707–10.
54. Hansen LS, Olson JA, Silverman S Jr. Proliferative verrucous leukoplakia. A long-term study of thirty patients. Oral Surg Oral Med Oral Pathol. 1985;60:285–98.
55. Hogewoning CJ, Bleeker MC, van den Brule AJ, et al. Condom use promotes regression of cervical intraepithelial neoplasia and clearance of human papillomavirus: a randomized clinical trial. Int J Cancer. 2003;107:811–16.
56. von Krogh G, Lacey CJN, Gross G, et al. European course on HPV associated pathology: guidelines for primary care physicians for the diagnosis and management of anogenital warts. Sex Transm Infect. 2000;76:162–8.

57. Sonnex C, Lacey CJ. The treatment of human papillomavirus lesions of the lower genital tract. Best Pract Res Clin Obstet Gynaecol. 2001;15:801–16.
58. Loureiro WR, Cação FM, Belda W Jr, et al. Treatment of genital warts in men with potassium hydroxide. Br J Dermatol. 2008;158:180–1.
58a. Kwok CS, Holland R, Gibbs S. Efficacy of topical treatments for cutaneous warts: a meta-analysis and pooled analysis of randomized controlled trials. Br J Dermatol. 2011;165:233–46.
58b. Cockayne S, Hewitt C, Hicks K, et al. Cryotherapy versus salicylic acid for the treatment of plantar warts (verrucae): a randomised controlled trial. BMJ. 2011;342:d3271.
58c. Bruggink SC, Gussekloo J, Berger MY, et al. Cryotherapy with liquid nitrogen versus topical salicylic acid application for cutaneous warts in primary care: randomized controlled trial. CMAJ. 2010;182:1624–30.
59. Gladsjo JA, Alió Sáenz AB, Bergman J, et al. 5% 5-Fluorouracil cream for treatment of verruca vulgaris in children. Pediatr Dermatol. 2009;26:279–85.
60. Edwards L, Ferenczy A, Eron L, et al. HPV Study Group. Self-administered topical 5% imiquimod cream for external anogenital warts. Arch Dermatol. 1998;134:25–30.
61. Stefanaki C, Katzouranis I, Lagogianni E, et al. Comparison of cryotherapy to imiquimod 5% in the treatment of anogenital warts. Int J STD AIDS. 2008;19:441–4.
62. Schöfer H. Evaluation of imiquimod for the therapy of external genital and anal warts in comparison with destructive therapies. Br J Dermatol. 2007;157:52–5.
63. Kaspari M, Gutzmer R, Kaspari T, et al. Application of imiquimod by suppositories (anal tampons) efficiently prevents recurrences after ablation of anal canal condyloma. Br J Dermatol. 2002;147:757–9.
64. Harwood CA, Perrett CM, Brown VL, et al. Imiquimod cream 5% for recalcitrant warts in immunosuppressed individuals. Br J Dermatol. 2005;152:122–9.
65. Kim MB, Ko HC, Jang HS, et al. Treatment of flat warts with 5% imiquimod cream. J Eur Acad Dermatol Venereol. 2006;20:1349–50.
65a. Tatti S, Stockfleth E, Beutner KR, et al. Polyphenon E: a new treatment for external anogenital warts. Br J Dermatol 2010;162:176–84.
66. Yaghoobi R, Sadighha A, Baktash D. Evaluation of oral zinc sulfate effect on recalcitrant multiple viral warts: a randomized placebo-controlled clinical trial. J Am Acad Dermatol. 2009;60:706–8.
67. López-García DR, Gómez-Flores M, Arce-Mendoza AY, et al. Oral zinc sulfate for unresponsive cutaneous viral warts: too good to be true? A double-blind, randomized, placebo-controlled trial. Clin Exp Dermatol. 2009;34:e984–5.
68. Upitis JA, Krol A. The use of diphenylcyclopropenone in the treatment of recalcitrant warts. J Cutan Med Surg. 2002;6:214–17.
69. Horn TD, Johnson SM, Helm RM, Roberson PK. Intralesional immunotherapy of warts with mumps, *Candida*, and *Trichophyton* skin test antigens: a single-blinded, randomized, and controlled trial. Arch Dermatol. 2005;141:589–94.
70. Snoeck R, Bossens M, Parent D, et al. Phase II double-blind, placebo-controlled study of the safety and efficacy of cidofovir topical gel for the treatment of patients with human papillomavirus infection. Clin Infect Dis. 2001;33:597–602.
71. Field S, Irvine AD, Kirby B. The treatment of viral warts with topical cidofovir 1%: our experience of seven paediatric patients. Br J Dermatol. 2009; 160:223–4.
72. Choi YL, Lee KJ, Kim WS, et al. Treatment of extensive and recalcitrant viral warts with acitretin. Int J Dermatol. 2006;45:480–2.
73. Georgala S, Katoulis AC, Georgala C, et al. Oral isotretinoin in the treatment of recalcitrant condylomata acuminata of the cervix: a randomised placebo controlled trial. Sex Transm Infect. 2004;80:216–18.
74. Gross G. Klinik und Therapie anogenitaler Warzen und papillomvirusassoziierter Krankheitsbilder. Hautarzt. 2001;52:6–17.
75. von Krogh G. Management of anogenital warts (condylomata acuminata). Eur J Dermatol. 2001;11: 598–603.
76. Schiller JT, Lowy DR. Papillomavirus-like particle based vaccines: cervical cancer and beyond. Expert Opin Biol Ther. 2001;1:571–81.
77. Breitburd F, Kirnbauer R, Hubbert NL, et al. Immunization with viruslike particles from cottontail rabbit papillomavirus (CRPV) can protect against experimental CRPV infection. J Virol. 1995;69: 3959–63.
78. Harper DM, Franco EL, Wheeler CM, et al; HPV Vaccine Study group. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. Lancet. 2006;367:1247–55.
79. Villa LL, Costa RL, Petta CA, et al. High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus-like particle vaccine through 5 years of follow-up. Br J Cancer. 2006;95:1459–66.
80. Block SL, Nolan T, Sattler C, et al. Comparison of the immunogenicity and reactogenicity of a prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in male and female adolescents and young adult women. Pediatrics 2006;118:2135–45.
81. Pastrana DV, Gambhira R, Buck CB, et al. Cross-neutralization of cutaneous and mucosal papillomavirus types with anti-sera to the amino terminus of L2. Virology. 2005;337:365–72.
82. Slupetzky K, Gambhira R, Culp TD, et al. A papillomavirus-like particle (VLP) vaccine displaying HPV16 L2 epitopes induces cross-neutralizing antibodies to HPV11. Vaccine. 2007;25:2001–10.
83. Schellenbacher C, Roden R, Kirnbauer R. Chimeric L1-L2 virus-like particles as potential broad-spectrum human papillomavirus vaccines. J Virol. 2009;83:10085–95.
84. Baud D, Ponci F, Bobst M, et al. Improved efficiency of a Salmonella-based vaccine against human papillomavirus type 16 virus-like particles achieved by using a codon-optimized version of L1. J Virol. 2004;78: 12901–9.
85. Christensen ND. Emerging human papillomavirus vaccines. Expert Opin Emerg Drugs. 2005;10:5–19.
86. Greenstone HL, Nieland JD, deVisser KE, et al. Chimeric papillomavirus virus-like particles elicit antitumor immunity against the E7 oncoprotein in an HPV16 tumor model. Proc Natl Acad Sci U S A. 1998; 95:1800–5.
87. Stanley MA. Immunobiology of papillomavirus infection. J Reproduct Immunol. 2001;52:45–59.

This page intentionally left blank

Human Herpesviruses 80

Natalia Mendoza, Vandana Madkan, Karan Sra, Beau Willison, L Katie Morrison and Stephen K Tyring

Chapter Contents

Herpes simplex viruses (HSV-1 and HSV-2) 1321
Varicella–zoster virus (HHV-3) 1328
Epstein–Barr virus (HHV-4) 1334
Cytomegalovirus (HHV-5) 1336
Human herpesvirus type 6 (HHV-6) 1338
Human herpesvirus type 7 (HHV-7) 1339
Human herpesvirus type 8 (HHV-8) 1340

The human herpesviruses (HHVs) are categorized into three groups: alpha, beta and gamma herpesvirinae (Table 80.1). Each virus contains a core of linear double-stranded DNA, an icosahedral capsid 100–110 nm in diameter, and an envelope with glycoprotein spikes on its surface. The pathogenesis of herpesvirus infections follows the sequence of primary infection, latency and reactivation. The eight human herpesviruses are discussed at length in this chapter and include the following: herpes simplex virus types 1 and 2 (HSV-1, HSV-2), varicella–zoster virus (VZV), Epstein–Barr virus (EBV), cytomegalovirus (CMV), human herpesvirus type 6 (HHV-6), human herpesvirus type 7 (HHV-7) and human herpesvirus type 8 (HHV-8).

HERPES SIMPLEX VIRUSES (HSV-1 AND HSV-2)

Synonyms/clinical variants: ■ Herpes – herpes simplex ■ Cold sore – fever blister, herpes febrilis, herpes labialis ■ Herpes gladiatorum – scrum pox ■ Herpetic whitlow ■ Genital herpes – herpes progenitalis

Key features

- Herpes simplex viruses produce primary and recurrent vesicular eruptions that favor the orolabial and genital regions
- The use of sensitive and specific serologic markers has provided insights into the epidemiology of HSV infections
- Antiviral therapy has significantly influenced the course and spectrum of HSV disease

Introduction

HSV-1 and HSV-2 are ubiquitous pathogens that produce primarily orolabial and genital herpes infections. Genital herpes is one of the most common sexually transmitted infections worldwide. Enhanced knowledge of the clinical manifestations, pathogenesis and histopathology of HSV infections has been paralleled by advances in the development of diagnostic markers that differentiate between the two HSV types and treatments for HSV infections. The use of sensitive and specific serologic markers has enabled the epidemiology of HSV infections to be deciphered, while antiviral therapy has allowed clinicians to control the course and extent of HSV disease. Prevention of HSV infections via molecularly derived vaccines remains an important goal.

History

Herpetic lesions have been described since antiquity, including by the noted physicians Hippocrates and Galen. The word "herpes" was first defined by Greek scholars as "to creep or crawl" in reference to the spreading nature of the skin lesions. The association between orolabial herpetic lesions and genital infection was first recognized during the late eighteenth century. However, better understanding of the pathogenesis of herpes infections did not occur until the twentieth century. Lipschitz was the first to suggest antigenic differences between the two HSV types, but it was not until 1968 that Nahmias and Dowdle demonstrated that HSV-1 was more frequently associated with orolabial and HSV-2 with genital infections[1]. In the past several decades, there have been critical insights into the pathogenesis of HSV infections as well as advances in their diagnosis, treatment and prevention.

Epidemiology

Herpes simplex viruses have a worldwide distribution. Their interaction with human hosts has the following components: (1) *primary infection* (first HSV infection, without pre-existing antibodies to HSV-1 or HSV-2) and *non-primary initial infection* (infection with one HSV type in an individual with pre-existing antibodies to the other HSV type), both of which may be symptomatic or asymptomatic; (2) *latency* in sensory ganglia; and (3) *reactivation* resulting in *recurrent infection* with asymptomatic viral shedding or clinical manifestations (recrudescence). It is estimated that approximately one-third of the world's population has experienced a symptomatic HSV infection.

In children less than 10 years of age, most herpetic infections are caused by HSV-1 (>80–90%). Analyses performed on a global basis have demonstrated HSV-1 antibodies in 50–90% of individuals 20 to 40 years old, with lower seroprevalences in higher-income countries (e.g. ~60% in the US)[2]. Although HSV-2 remains the cause of most genital herpes infections (70–90% overall)[3], recent studies have shown an increasing proportion due to HSV-1 in the US, Canada and the UK. In these countries, HSV-1 now accounts for the majority of genital herpes infections in young adults (especially college students)[4,5].

In the Centers for Disease Control and Prevention's (CDC's) 2005–2008 National Health and Nutrition Examination Survey (NHANES)[6], the seroprevalence of HSV-2 among individuals 14–49 years of age in the US was 16% overall, with higher rates in women (21%, versus 11.5% in men) and blacks (39%). Of note, 80% of those with positive serology had never had clinical symptoms or a previous diagnosis of genital HSV infection. Other factors associated with acquisition of genital herpes include an age of 15–30 years (period of greatest sexual activity), an increased number of sexual partners, lower levels of income and education, homosexuality and HIV-positivity; conversely, genital HSV-2 infection also increases the risk of acquiring and transmitting HIV infection[4].

Pathogenesis

Transmission of HSV can occur even during asymptomatic periods of viral shedding. HSV-1 is spread primarily through direct contact with contaminated saliva or other infected secretions, while HSV-2 is spread primarily by sexual contact. Virus replicates at the mucocutaneous site of infection and then travels by retrograde axonal flow to the dorsal root ganglia, where it establishes latency until reactivation. Latency enables the virus to exist in a relatively non-infectious state for varying periods of time in its host. HSV-1 can induce intracellular accumulation of CD1d molecules in antigen-presenting cells, providing a possible explanation for how this virus evades detection and establishes latency. Normally, CD1d molecules are transported to the cell surface, where

THE EIGHT HUMAN HERPESVIRUSES, THEIR CLASSIFICATION AND DIFFERENTIAL DIAGNOSES				
Human herpesvirus	**Classification**	**Predominant cell type infected**		**Differential diagnosis**
		Lytic infection	**Latent infection**	
Herpes simplex virus type 1 (HSV-1) (HHV-1)	Alphaherpesvirinae	Epithelial cells	Neurons	Orolabial herpes: aphthous stomatitis, erythema multiforme major, Stevens–Johnson syndrome, herpangina, pharyngitis (e.g. due to EBV), oral candidiasis, mucositis secondary to chemotherapy
Herpes simplex virus type 2 (HSV-2) (HHV-2)	Alphaherpesvirinae	Epithelial cells	Neurons	Genital herpes: trauma, chancre (primary syphilis), aphthae, EBV-related ulcers, CMV-related ulcers (AIDS), chancroid, granuloma inguinale, lymphogranuloma venereum
Varicella–zoster virus (VZV) (HHV-3)	Alphaherpesvirinae	Epithelial cells	Neurons	Varicella: vesicular viral exanthem (e.g. coxsackieviruses), PLEVA, rickettsialpox, disseminated HSV, insect bites, drug eruption, scabies, smallpox
				Herpes zoster: zosteriform HSV, contact dermatitis, phytophotodermatitis, bullous impetigo, cellulitis
Epstein–Barr virus (EBV) (HHV-4)	Gammaherpesvirinae	B cells, epithelial cells	B cells	Group A streptococcal infection, acute viral hepatitis, drug reaction with eosinophilia and systemic symptoms (DRESS)*, toxoplasmosis, lymphoma, and primary CMV, HHV-6 and HIV infections
				For genital ulcers: see genital herpes
Cytomegalovirus (CMV) (HHV-5)	Betaherpesvirinae	Lymphocytes, macrophages, endothelial cells	Lymphocytes, macrophages	EBV-induced infectious mononucleosis, toxoplasmosis, viral hepatitis, lymphoma
				For genital ulcers: see genital herpes
Human herpesvirus 6 (HHV-6)	Betaherpesvirinae	$CD4^+$ T cells	Lymphocytes, monocytes	Viral exanthems (e.g. measles, rubella and enterovirus, adenovirus, EBV and parvovirus infections), scarlet fever, Rocky Mountain spotted fever, Kawasaki disease
Human herpesvirus 7 (HHV-7)	Betaherpesvirinae	T cells	T cells	Similar to HHV-6
Human herpesvirus 8 (HHV-8)	Gammaherpesvirinae	Lymphocytes	Lymphocytes, endothelial cells	Acroangiodermatitis (pseudo-KS), bacillary angiomatosis, ecchymosis, hemangioma, angiosarcoma, pyogenic granuloma, pseudolymphoma/lymphoma

*Also referred to as drug-induced hypersensitivity syndrome (DIHS).

Table 80.1 The eight human herpesviruses, their classification and differential diagnoses. KS, Kaposi sarcoma; PLEVA, pityriasis lichenoides et varioliformis acuta.

they present lipids and stimulate natural killer T cells, thus promoting an immune response[7]. HSV's mechanisms to evade the immune system also include down-regulation of various immunologic cells and cytokines (Table 80.2).

The goals of the early host immune response against HSV are to limit viral replication and recruit other inflammatory cells. Toll-like receptors are critical to the first line of innate immune defense against HSV, and their functions include priming $CD8^+$ T cells. HSV-specific memory $CD8^+$ T cells, which are selectively activated and retained in latently infected sensory ganglia, have important roles in controlling the infection and preventing symptomatic recurrences (see Table 80.2).

HSV can be reactivated either spontaneously or by a trigger such as emotional stress, ultraviolet light, fever, local tissue damage, or immunosuppression. Typically, reactivation will produce vesicular lesions localized to the skin. However, viremia followed by widespread internal organ involvement can occur in immunocompromised hosts.

Clinical Features

HSV infections have a wide range of clinical presentations, and asymptomatic infection is very common. In primary infections, symptoms typically occur within 3 to 7 days after exposure. A prodrome of tender lymphadenopathy, malaise, anorexia and fever often occurs before the onset of mucocutaneous lesions, which may be preceded by localized pain, tenderness, burning or tingling. Painful, grouped vesicles appear on an erythematous base and may become umbilicated, followed by progression to pustules, erosions and/or ulcerations with a characteristic scalloped border. Crusting of lesions and resolution of symptoms typically occurs within 2 to 6 weeks. A similar prodrome can precede recurrent lesions, but these are often fewer in number, with decreased severity and duration compared to those of a primary infection.

The majority of primary orolabial infections are asymptomatic. Symptomatic infections often present as gingivostomatitis in children or as pharyngitis and a mononucleosis-like syndrome in young adults. The mouth and lips are the most common sites of involvement (Fig. 80.1), with lesions typically appearing on the buccal mucosa and gingivae. Edema and painful oropharyngeal ulcerations can lead to dysphagia and drooling. Recurrent lesions appear most often on the vermilion border of the lip. Less common sites are the perioral skin, nasal mucosa, oral mucosa overlying bone (e.g. hard palate) and the cheek (Fig. 80.2). In immunocompromised hosts, recurrent herpes infections can involve intraoral "soft" mucosa (i.e. mucosa that does not overlie bone).

Primary and non-primary initial genital herpes infections are frequently asymptomatic but (especially with the former) can also present as an excruciatingly painful, erosive balanitis, vulvitis or vaginitis. In women, lesions often also involve the cervix, buttocks and perineum and are associated with inguinal adenopathy and dysuria (Fig. 80.3). Genital lesions in men typically occur on the glans or shaft of the penis, and the buttocks are occasionally affected. Systemic complaints and complications are more common in women. Extragenital lesions, urinary retention and aseptic meningitis occur in 20%, 10–15% and 10% of affected women, respectively[8]. In contrast, aseptic meningitis is a rare complication of primary genital herpes infection in men. The presence of more extensive local involvement, regional lymphadenopathy and fever generally distinguishes primary herpes infection from recurrent disease.

Genital HSV infections can result in subclinical viral shedding or clinically evident recurrences (more frequent with HSV-2 than HSV-1), which are often relatively mild. Usually, a limited number of vesicles reappears on the genitalia or buttocks (especially in women) (Fig. 80.4),

INTERACTION OF HERPES SIMPLEX VIRUSES WITH THE IMMUNE SYSTEM: HOST RESPONSES AND VIRAL EVASION MECHANISMS

HOST IMMUNE RESPONSES TO HSV INFECTION

Innate immunity

- HSV is detected by Toll-like receptors (TLRs; see Ch. 4) on epithelial cells, antigen-presenting cells (APCs), plasmacytoid dendritic cells (DCs) and NK cells
  - TLR2 on the cell surface interacts with a viral surface glycoprotein* and leads to proinflammatory cytokine production (via NF-κB activation), including IL-1β, IL-6, IL-8, IL-12, TNF-α and MCP-1
  - TLR3 on endosomes interacts with double-stranded RNA (which accumulates in HSV-infected cells) and leads to IFN-β and -λ production**
  - TLR9 on endosomes interacts with viral genomic DNA (unmethylated CpG sequences) and leads to IFN-α production (via NF-κB activation)
- HSV is also recognized by intracellular nucleic acid sensors (e.g. IFN-γ-inducible protein 16) that detect HSV DNA and stimulate type I IFN (IFN-α and -β) production
- Type I IFNs increase expression of IFN-stimulated genes; their effects include inhibiting translation/promoting degradation of viral mRNA, inducing DC maturation, and (in part through stimulation of IL-15 production) promoting NK cell survival and proliferation
- NK cells release IFN-γ and destroy virus-infected cells (e.g. via release of perforin and granzyme B)
- $CD8^+$ T cells are primed in a process that requires TLR3 signaling by $CD8\alpha^+$ DCs
- Collectively, these responses limit HSV replication, promote host cell apoptosis, and recruit and activate DCs, other APCs, neutrophils, and other leukocytes of both innate and adaptive lineages
- Evidence is emerging that innate immune defenses also have roles in the control of latent HSV infections

Adaptive immunity

- $CD4^+$ T cells are recruited to the site of infection and activated by DCs
- $CD4^+$ T cells release IFN-γ, which induces secretion of chemokines (e.g. CXCL9 and CXCL10 by epithelial cells) that recruit cytotoxic $CD8^+$ T cells
- $CD8^+$ T cells (which also release IFN-γ) kill infected cells through perforin and Fas-mediated pathways, clearing the active infection
- Following the priming and contraction phases of the T-cell response, virus-specific $CD8^+$ T cells accumulate (referred to as memory inflation) and provide immunosurveillance; viral latency and periodic restimulation by subclinical HSV reactivation maintain this pool of cells
- B cells are recruited to the site of infection and activated by $CD4^+$ T cells to produce antibodies
- Regulatory T cells are present, but their exact role (e.g. preventing excessive immune responses versus diminishing the efficiency of viral clearance) has not been determined

HSV'S MECHANISMS OF IMMUNE EVASION

- HSV inhibits signaling through TLRs, e.g. the HSV-1 ICP0 protein reduces TLR2 signaling
- The HSV virion host shut-off (VHS) protein degrades mRNA; it prevents DC activation by a TLR-independent pathway
- HSV decreases cell surface expression of CD1d by APCs; this prevents presentation of lipid antigens that stimulate NK cells
- HSV decreases langerin expression by and increases apoptosis of Langerhans cells
- The HSV ICP47 protein binds to TAP and blocks loading of peptides onto MHC class I molecules, and "empty" MHC class I molecules are degraded by the proteasome
- The HSV-1 glycoprotein B manipulates the MHC class II processing pathway by hijacking HLA-DR from its normal transport route to the cell surface
- The HSV-1 glycoprotein C blocks complement activation, and glycoprotein E functions as an IgG Fc receptor that can block host responses such as antibody-dependent cellular cytotoxicity
- The HSV protein tristetraprolin destabilizes mRNA and can target proinflammatory cytokines such as TNF-α
- HSV can block cytokine effects by other mechanisms, e.g. inducing expression of suppressor of cytokine signaling-1 (SOCS-1) in keratinocytes and thereby abrogating the effects of IFN-γ
- HSV can induce expression of Fas ligand on the surface of monocytes/macrophages, causing apoptosis of interacting T cells and NK cells

*Not yet identified; viral envelope fusion with the host cell membrane during entry leaves viral proteins on the cell surface.
**Mutations in the genes encoding TLR3 or proteins required for TLR3 signaling (e.g. UNC-93B, TRAF3) lead to particular susceptibility to HSV encephalitis.

Table 80.2 Interaction of herpes simplex viruses (HSV) with the immune system: host responses and viral evasion mechanisms. HLA, human leukocyte antigen; ICP, infected cell polypeptide; IFN, interferon; IL, interleukin; MCP-1, monocyte chemotactic peptide 1; MHC, major histocompatibility complex; NK, natural killer; TAP, transporter associated with antigen processing; TRAF3, tumor necrosis factor (TNF) receptor-associated factor 3.

Fig. 80.1 Initial orolabial herpes simplex virus (HSV) infections. **A** Primary herpes gingivostomatitis due to HSV-1 in a child. Note the coalescing lesions with scalloped borders. **B** HSV-2 infection in a teenager (primary versus non-primary initial infection). Note the scalloped borders.
A, Courtesy, Julie V Schaffer, MD. B, Courtesy, Jean L Bolognia, MD.

with resolution within 1 week. Complications are uncommon. The frequency of recurrences correlates directly with the severity of the primary infection and tends to decrease over the next several years. The time interval between recurrences varies greatly, with individuals having an average of four to seven outbreaks annually. Surprisingly, although the majority of individuals with HSV-2 seropositivity report no history of genital herpes infection, symptomatic infection is eventually diagnosed in 50% of this group of patients.

Other Clinical Presentations of HSV Infection

HSV infection can occur anywhere on the skin or mucous membranes. The clinical settings and manifestations of other cutaneous and extracutaneous presentations of HSV infection, including those in immunocompromised individuals and neonates[9–13], are summarized in Table 80.3 (Figs 80.5 to 80.9).

Diagnosis and Pathology

Multiple laboratory tests are available to diagnose HSV infection, including viral culture, direct fluorescent antibody assays (DFA; Fig. 80.10), molecular techniques and serology. In addition to a Tzanck smear (see below), DFA is frequently performed as an initial diagnostic

Fig. 80.2 Recurrent herpes simplex virus type 1 infection on the cheek. Occasionally, such lesions are misdiagnosed as cellulitis or bullous impetigo. *Courtesy, Kalman Watsky, MD.*

Fig. 80.3 Primary genital herpes. In addition to 1–2 mm hemorrhagic crusts, there are perifollicular vesiculopustules.

Fig. 80.4 Recurrent genital herpes. A Intact grouped vesicles on the penis. Note the genital wart at the base of the penis. **B** Grouped vesiculopustules on the buttock, a common location in women. **C** Healing ulcerations with scalloped borders on the penis. *A & B, Courtesy, Louis A Fragola, Jr, MD. C, Courtesy, Joseph L Jorizzo, MD.*

test due to its greater sensitivity, ability to distinguish between HSV and VZV, and rapid turnaround time. Identification of HSV by viral culture usually requires 2–5 days. In addition to being the preferred method for identifying HSV in the cerebrospinal fluid, polymerase chain reaction (PCR) is increasingly being used as a rapid, sensitive and specific method to detect HSV DNA in specimens from the skin and other organs.

For prevalence or incidence studies and to establish serostatus, the Western blot represents the gold standard for serologic assays; it is 99% sensitive and specific for HSV antibodies. In addition, several commercially available serologic tests can reliably identify patients who have been infected with HSV and can distinguish between HSV-1 and HSV-2 antibodies based on type-specific glycoproteins G-1 from HSV-1 and G-2 from HSV-2. The sensitivity and specificity of each of these assays varies depending on the test and the setting; of note, the mean time to seroconversion following initial infection is 3–4 weeks[14].

A Tzanck smear of scrapings from early lesions (e.g. the base/edges of a freshly unroofed vesicle) reveals multinucleated epithelial giant cells in the majority of HSV outbreaks (~60–75%; Fig. 80.11). In routinely stained biopsy specimens as well as Tzanck smears, HSV-1 cannot be differentiated from HSV-2. Enlarged, slate-gray keratinocyte nuclei with margination of chromatin represent an early histologic finding, which is followed by intraepidermal vesiculation associated with ballooning degeneration of keratinocytes (most prominent at the base of the vesicle) (Fig. 80.12). These swollen, pale keratinocytes often fuse to form multinucleated giant cells and may contain eosinophilic intranuclear inclusion bodies surrounded by an artifactual cleft (Cowdry type A inclusions). Ballooning degeneration can affect adnexal structures as well as the interfollicular epidermis. A variably dense dermal

OTHER CLINICAL PRESENTATIONS OF HERPES SIMPLEX VIRUS INFECTIONS		
Form of infection	**Clinical settings and HSV type(s)**	**Cutaneous and/or extracutaneous findings**
	PREDOMINANTLY MUCOCUTANEOUS	
Eczema herpeticum (Kaposi's varicelliform eruption)	• Most often in infants/children > adults with atopic dermatitis (Fig. 80.5); risk is associated with mutations in the gene encoding filaggrin • Can also occur in patients with an impaired skin barrier due to other conditions such as burns, pemphigus (foliaceus, vulgaris), Darier disease, Hailey–Hailey disease, mycosis fungoides, Sézary syndrome and ichthyoses • Usually due to HSV-1	• Rapid, widespread cutaneous dissemination of HSV infection in areas of dermatitis/skin barrier disruption • Monomorphic, discrete, 2–3 mm punched-out erosions with hemorrhagic crusts (see Fig. 80.5) are evident more often than intact vesicles • May have fevers, malaise and lymphadenopathy • Occasionally complicated by bacterial superinfections (e.g. with *Staphylococcus aureus* and/or group A streptococci) or systemic dissemination of HSV infection
Herpetic whitlow	• Often in young children (usually due to HSV-1; Fig. 80.6A) • Increasing frequency in adolescents/adults (Fig. 80.6B, C) secondary to digital–genital contact (usually due to HSV-2) • Historically in dental and medical personnel who did not use gloves	• HSV infection of the digits presenting with pain, swelling and vesicular lesions (see Fig. 80.6); appearance of vesicles may be delayed • Recurrences in the same location can be a clue to the diagnosis • Often misdiagnosed as blistering dactylitis or paronychia
Herpes gladiatorum	• Participation in contact sports such as wrestling (Fig. 80.7) • Usually due to HSV-1	• Distribution of cutaneous HSV infection (sometimes widespread), reflecting sites of contact with another athlete's skin lesions
Herpes simplex folliculitis	• Shaving with a blade razor (e.g. *herpetic sycosis* in a man's beard area) • Usually due to HSV-1 • HIV-positive or otherwise immunocompromised individuals	• Rapid development of follicular vesicles and pustules • See Table 38.1
Severe/chronic HSV infections	• Immunocompromised patients, e.g. hematopoietic stem cell or solid organ transplant recipients and individuals with HIV infection or leukemia/lymphoma	• Most common presentation is chronic, enlarging ulcerations (Fig. 80.8A,B) • Cutaneous lesions may affect multiple sites or be disseminated • Skin findings are often atypical, e.g. verrucous, exophytic and pustular lesions • Recurrences can involve oral mucosa, including the tongue (Fig. 80.8C) and areas that do not overlie bone • Involvement of the respiratory tract, esophagus and remainder of the gastrointestinal tract may also occur
	PREDOMINANTLY EXTRACUTANEOUS	
Ocular HSV infection	• Newborns (often due to HSV-2; see below) • Usually due to HSV-1 in children and adults	• Primary infection: unilateral or bilateral keratoconjunctivitis with eyelid edema, tearing, photophobia, chemosis and preauricular lymphadenopathy • Branching dendritic lesions of the cornea represent a pathognomonic finding • Recurrent episodes (typically unilateral) are common • Complications include corneal ulceration and scarring, globe rupture and blindness
Herpes encephalitis	• Most common cause of fatal sporadic viral encephalitis in the US • Associated with mutations in the genes encoding Toll-like receptor 3 or UNC-93B, which impair interferon-based cellular antiviral responses (see Table 80.2) • Usually due to HSV-1	• Manifestations can include fever, altered mental status, bizarre behavior and localized neurologic findings • The temporal lobe is often involved • Mortality ≥70% without treatment; residual neurologic defects in most survivors • Herpes labialis is a coincidental finding
	CUTANEOUS AND EXTRACUTANEOUS	
Neonatal HSV infection[9]	• Occurs in approximately 1:10 000 newborns in the US[9,10], usually resulting from exposure to HSV during a vaginal delivery • Risk of transmission is highest (30–50%) for women who acquire a genital HSV infection (which is often asymptomatic) near the time of delivery • Risk of transmission is low (<1–3%) for women with recurrent genital herpes • Due to HSV-2 or HSV-1 (latter accounts for 30–50% of cases)	• Onset from birth to 2 weeks of age, but usually ≥5 days of age • Localized (favoring the scalp and trunk) (Fig. 80.9) or disseminated cutaneous lesions; involvement of the oral mucosa, eye, CNS and multiple internal organs can occur • Vesicles may progress to bullae and erosions (see Ch. 34) • Encephalitis can present with lethargy, irritability, poor feeding, temperature instability, seizures and a bulging fontanelle • For CNS or disseminated disease, mortality is >50% without treatment and ~15% with treatment; many survivors have neurologic deficits

Table 80.3 Other clinical presentations of herpes simplex virus (HSV) infections.

infiltrate of lymphocytes, neutrophils and eosinophils is observed, with a tendency to be milder in recurrent disease. Vascular changes may include areas of hemorrhagic necrosis and perivascular cuffing. Epidermal necrosis is sometimes extensive, especially in the setting of disseminated skin lesions.

Differential Diagnosis

Orolabial herpes can sometimes be confused with aphthous stomatitis, erythema multiforme major or Stevens–Johnson syndrome, herpangina, pharyngitis (e.g. due to EBV), oral candidiasis, and chemotherapy-induced mucositis (see Table 80.1). Oral aphthae typically present as a single or few lesion(s) on the buccal mucosa without associated vesicles. Erythema multiforme major (which is most often triggered by HSV) and Stevens–Johnson syndrome can usually be distinguished from HSV by the presence of characteristic cutaneous as well as mucosal lesions. In herpangina, the posterior pharynx is more commonly involved, unlike in HSV infection, which favors the anterior portion of the mouth. Exudative tonsillitis, diffuse hyperemia of the oropharynx, and petechiae on the hard and soft palate are common manifestations of EBV-induced mononucleosis. Although a white, curd-like coating of the tongue, buccal mucosa and pharynx is the most common presentation of oral candidiasis, there is also an erythematous form of the disease. Of note, in immunocompromised hosts, the possibility of coexisting infections must be considered.

Fig. 80.5 Eczema herpeticum. Monomorphic, punched-out erosions with a scalloped border in this infant with a history of facial atopic dermatitis. *Courtesy, Julie V Schaffer, MD.*

Fig. 80.7 Herpes gladiatorum. Grouped vesicles and erosions on the neck of a high-school wrestler. *Courtesy, Louis A Fragola, Jr, MD.*

Fig. 80.6 Herpetic whitlow. On the finger of a child (**A**) and on the finger (**B**) and toe (**C**) in adults. Herpetic whitlow is sometimes misdiagnosed as cellulitis or blistering distal dactylitis, or, depending on the distribution, paronychia. *B, Courtesy, Eugene Mirrer, MD. C, Courtesy, Louis A Fragola, Jr, MD.*

Trauma, syphilitic chancres, chancroid and lymphogranuloma venereum are included in the differential diagnosis of genital herpes (see Ch. 82). The syphilitic chancre is usually a single lesion that is neither painful nor recurrent. Chancroid often manifests as several tender ulcers with a yellowish-gray exudate overlying a base of granulation tissue, while lymphogranuloma venereum presents with a transient papule, herpetiform vesicle, erosion or ulcer; both conditions typically result in tender inguinal lymphadenopathy. Genital aphthae and EBV-related genital ulcers can be difficult to distinguish from herpetic lesions without viral culture, DFA or PCR. Additional entities in the differential diagnosis of genital erosions are listed in Table 73.5.

Treatment and Prevention

FDA-approved antiviral agents for treatment of recurrent episodes of orolabial herpes in immunocompetent persons include oral valacyclovir (2 g twice daily for 1 day), oral famciclovir (single dose of 1.5 g) and topical 1% penciclovir (Table 80.4), which result in a decreased duration of mucocutaneous lesions, viral shedding and pain (especially if started at the first symptom or sign of a recurrence). Topical acyclovir 5% ointment is approved for limited mucocutaneous HSV infections in immunocompromised individuals. Both valacyclovir and famciclovir have been shown to reduce the frequency of orofacial herpes outbreaks after laser resurfacing[15].

For the treatment of primary and recurrent genital herpes, oral antivirals are the agents of choice (see Table 80.4). With early initiation (e.g. within 24–48 hours of onset), acyclovir, famciclovir and valacyclovir reduce the duration of viral shedding, pain and time to healing for first-episode and recurrent genital herpes. Intravenous acyclovir is indicated for neonatal HSV infection, severe infections in immunocompromised hosts, severe eczema herpeticum and patients with systemic complications. In immunocompromised patients, it is important to treat with oral or intravenous antivirals until the cutaneous lesions are completely healed.

Chronic suppressive therapy with the above oral antiviral agents (see Table 80.4) is usually reserved for patients with six or more outbreaks per year, although clinicians often exercise more lenient criteria for initiation of therapy for individuals with physically or emotionally severe outbreaks, an insufficient prodrome to benefit from episodic therapy, or immunosuppression. In addition to decreasing the frequency of (or even eliminating) symptomatic outbreaks, suppressive therapy reduces asymptomatic viral shedding by 95% and can prevent transmission of genital herpes to a susceptible partner[16]. Daily suppressive therapy (together with consistent condom use and avoidance of sexual activity during recurrences) is therefore also recommended for individuals with genital herpes who have a seronegative partner. Resiquimod 0.01% gel, a topically active immune response modifier, has been investigated for the treatment of recurrent genital herpes and was found to delay the time to the first recurrence, decrease the total number of recurrences, and reduce asymptomatic viral shedding[17].

The emergence of acyclovir-resistant HSV is an increasing concern for immunocompromised individuals. Foscarnet is the only antiviral drug approved by the FDA for treatment of acyclovir-resistant HSV. Cidofovir is another antiviral agent that has shown efficacy in the

Fig. 80.8 Herpes simplex virus infections in immunocompromised hosts. Enlarging ulcerations in a child with acute lymphocytic leukemia who was presumed to have a *Rhizopus* infection (**A**) and in a young man with AIDS (**B**). Coalescence of eroded, yellow–white papules and plaques on the tongue (**C**).

Fig. 80.9 Neonatal herpes. Grouped papulovesicles with an erythematous base on the chest. Note the scalloped borders in areas of coalescence. *Courtesy, Frank Samarin, MD.*

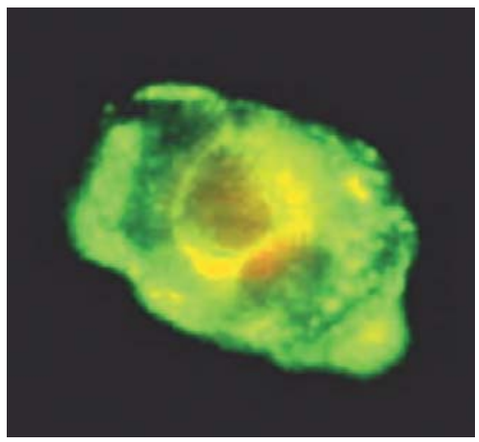


Fig. 80.10 Direct fluorescent antibody assay. A keratinocyte that is infected with herpes simplex virus fluoresces green. This assay can also detect the presence of varicella–zoster virus and has a rapid turnaround time. *Courtesy, Marie L Landry, MD.*

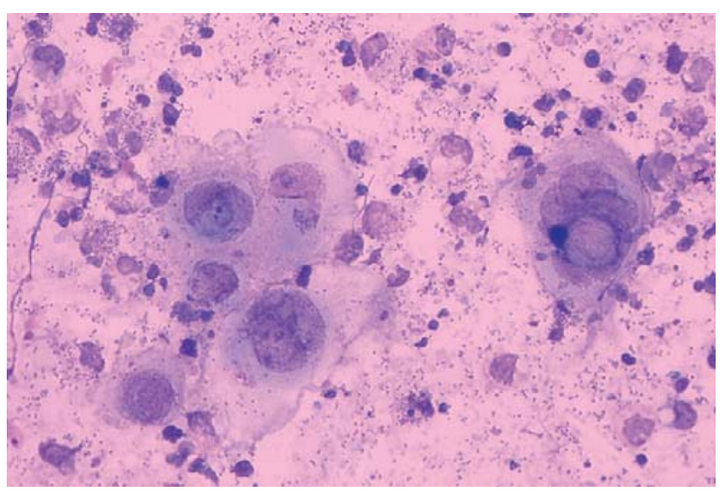


Fig. 80.11 Tzanck smear. Note the multinucleated epithelial giant cells from a patient with herpes simplex viral infection. *Courtesy, Louis A Fragola, Jr, MD.*

treatment of acyclovir-resistant HSV. The use of foscarnet or *systemic* cidofovir is limited by potentially severe side effects (particularly renal toxicity) and the requirement for intravenous administration. Although not FDA-approved, *topical* cidofovir has been advocated by the CDC as a "user-friendly", albeit expensive, alternative treatment[18].

Individuals co-infected with HIV and HSV have more severe outbreaks and more frequent viral shedding than those without HIV infection. When added to the medical regimen of HIV-infected patients, antiherpetic suppressive therapy appears to allow the co-infected person to respond better to antiretroviral therapy and to reduce genital and plasma HIV-1 RNA levels, but it does not seem to decrease the risk of HIV-1 transmission[19,20]. Oral acyclovir, famciclovir and valacyclovir can be used for genital and orolabial HSV in the setting of HIV infection as long as there is no evidence of acyclovir resistance.

There is significant interest in prevention of HSV disease. Between 70% and 80% of HSV is transmitted during periods of asymptomatic viral shedding. Sexual abstinence is the only method for absolute prevention of genital herpes, which can be transmitted even with the use of condoms[21]. In addition to antiviral therapy, patient education regarding prevention of genital herpes transmission is essential. There is

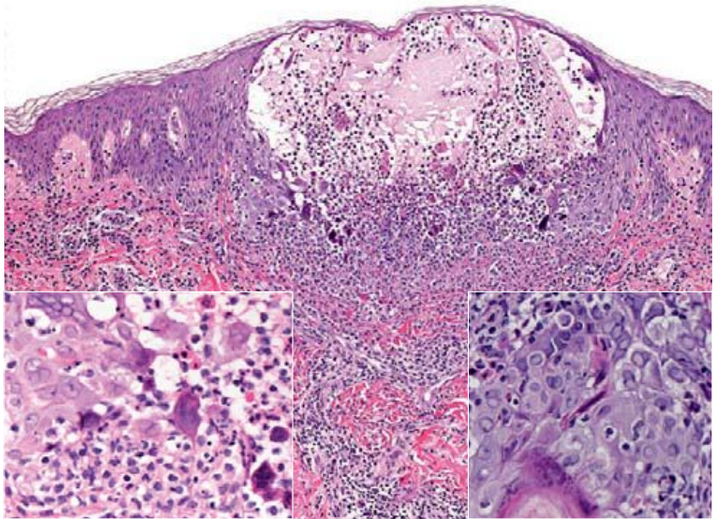


Fig. 80.12 Histology of herpes simplex viral infection. Intraepidermal vesicle with ballooning degeneration of keratinocytes and multinucleated giant cells; the latter arise from the fusion of infected keratinocytes. Note the steel-gray nuclei with margination of chromatin and inclusions (inserts). *Courtesy, Lorenzo Cerroni, MD.*

currently no licensed vaccine available for HSV, although several vaccines are under development and evaluation for prevention of HSV infection and recurrences.

VARICELLA–ZOSTER VIRUS (HHV-3)

Synonyms/clinical forms: ■ Varicella – chickenpox ■ Herpes zoster – shingles

Key features

- VZV is the etiologic agent of varicella (chickenpox) and herpes zoster (shingles)
- VZV has a high morbidity and mortality rate in immunocompromised hosts
- Antiviral treatment as well as vaccination can reduce or eliminate serious disease-associated sequelae and decrease the incidence of VZV infection

Introduction

VZV is the etiology of varicella (chickenpox) and herpes zoster (shingles). Varicella is usually symptomatic, and before the advent of the varicella vaccine, it occurred in 90% of children in the US by the time they reached 10 years of age. Herpes zoster represents reactivation of latent VZV infection and develops in approximately 20% of healthy adults and 50% of immunocompromised persons. VZV infection in immunocompromised hosts has substantial morbidity and mortality, which must be considered in the clinical management of these patients. Early initiation of antiviral treatment can reduce or eliminate serious sequelae of VZV infections.

History

Heberden first distinguished chickenpox from smallpox in 1767[22]. The term "chickenpox" is thought to come from either the French word "chiche-pois" for chickpea (referring to the size of the vesicles) or the Old English word "gigan" meaning "to itch". The relationship between varicella and herpes zoster was first recognized in 1888, when von Bokay described the development of varicella in children following exposure to those with herpes zoster infection. Kundratiz (1922) and Bruusgarrd (1932) more convincingly demonstrated the association between the two diseases by the development of varicella in susceptible children who had been inoculated with vesicle fluid from patients with herpes zoster. This was followed by the identification of the same virus in both diseases, confirming that their etiologies were identical.

Epidemiology

VZV has a worldwide distribution and 98% of the adult population is seropositive. In the pre-vaccine era, varicella affected 90% of children <10 years of age and approximately 4 million cases occurred annually in the US[23], with large outbreaks during the winter and spring. Since the introduction of the varicella vaccine in 1995, the overall incidence of varicella has decreased by ~85%, with evidence of herd immunity. The age of peak incidence also shifted from 5–9 years to 10–14 years, and a higher rate of breakthrough varicella among immunized children in the latter age group led to the addition of a second varicella vaccine dose to the routine childhood immunization schedule in 2006[24].

Although the incidence and severity of herpes zoster increase substantially in middle to late adulthood, it can occur at any age and is more common in younger persons who had a varicella infection within the first year of life. Overall, individuals with a history of varicella have a 20% lifetime chance of developing zoster. The annual incidence of herpes zoster in the US and Europe is classically 2.5/1000 persons between ages 20 and 50 years, 5/1000 between ages 51 and 79 years, and 10/1000 in those older than 80 years of age[25]. However, there is evidence that exposure to varicella can protect seropositive adults from the development of zoster, and it has been postulated that widespread vaccination against varicella could reduce this immune boosting effect and increase the incidence of zoster. Whether this hypothetical increase will be counterbalanced by the zoster vaccine remains to be determined. Other risk factors for herpes zoster include mental and physical stress, immunocompromise (especially that due to HIV infection, allogeneic hematopoietic stem cell transplantation, and bortezomib therapy for multiple myeloma[26]), and a family history of zoster[27].

Pathogenesis

Airborne droplets are the usual route of transmission of varicella, although direct contact with vesicular fluid is another mode of spread. The incubation period ranges from 11 to 20 days. Varicella is extremely contagious, and 80–90% of susceptible household contacts develop a clinically evident infection[23]. The affected individual is infectious from 1 to 2 days before skin lesions appear until all of the vesicles have crusted.

During varicella infection, primary viremia occurs after an initial 2 to 4 days of viral replication within regional lymph nodes. A cycle of viral replication in the liver, spleen and other organs is then followed by secondary viremia, which seeds the entire body 14 to 16 days post-exposure. During this period, the virus travels to the epidermis by invading capillary endothelial cells. VZV subsequently travels from mucocutaneous lesions to dorsal root ganglion cells, where it remains latent until reactivation at a later date.

Herpes zoster appears upon reactivation of VZV, which may occur spontaneously or be induced by stress, fever, radiation therapy, local trauma or immunosuppression. During a herpes zoster outbreak, the virus continues to replicate in the affected dorsal root ganglion and produces a painful ganglionitis. Neuronal inflammation and necrosis can result in a severe neuralgia that intensifies as the virus spreads down the sensory nerve. Fluid from herpes zoster vesicles can transmit VZV to seronegative individuals, leading to varicella (not herpes zoster, which reflects reactivation of latent VZV from a prior infection). The transmission rate to susceptible household contacts is ~15% for zoster, compared to >70% for varicella.

Clinical Features

Varicella

Varicella may begin (in adults > children) as a prodrome of mild fever, malaise and myalgia. This is followed by an eruption of pruritic, erythematous macules and papules, starting on the scalp and face, then spreading to the trunk and extremities (Fig. 80.13). Lesions rapidly evolve over 12 to 14 hours into 1–3 mm clear vesicles surrounded by narrow red halos ("dew drops on a rose petal"). The number of vesicles varies from only a few to several hundred, and there is often

ANTIVIRAL THERAPY FOR HERPES SIMPLEX VIRUS AND VARICELLA–ZOSTER VIRUS	
Disease context	**Drug and dosage**
HERPES SIMPLEX INFECTIONS	
Orolabial herpes* (recurrence)	Penciclovir: 1% cream applied q2 h × 4 days Acyclovir + hydrocortisone: 5%/1% cream applied 5×/d × 5 days Famciclovir: 1.5 g po × 1 dose Valacyclovir: 2 g po bid × 1 day
Genital herpes (first episode)	Acyclovir: 200 mg po 5×/d × 10 days or 400 mg po tid × 10 days Famciclovir: 250 mg po tid × 10 days Valacyclovir: 1 g po bid × 10 days
Genital herpes (recurrence)	Acyclovir: 400 mg po tid × 5 days or 800 mg po bid × 5 days or 800 mg po tid × 2 days Famciclovir: 1 g po bid × 1 day or 500 mg po × 1 dose then 250 mg po bid × 2 days or 125 mg po bid × 5 days Valacyclovir: 500 mg po bid × 3 days or 1 g po qd x 5 days
Chronic suppression	Acyclovir: 400 mg po bid Famciclovir: 250 mg po bid Valacyclovir: 500 mg po qd for <10 outbreaks/year or 1 g po qd for ≥10 outbreaks/year
Neonatal	Acyclovir: 20 mg/kg iv q8 h × 14–21 days
Immunocompromised	*Recommend use until all mucocutaneous lesions are healed* Acyclovir: 400 mg po 5×/d or 5 mg/kg (if age ≥12 y) to 10 mg/kg (if age <12 y) iv q8 h Famciclovir: 500 mg po bid Valacyclovir: 1 g po bid
Eczema herpeticum/Kaposi's varicelliform eruption	*Recommend use for 10–14 days or (especially if immunocompromised) until all mucocutaneous lesions are healed* Acyclovir: 15 mg/kg (400 mg max) po 3–5×/d or, if severe, 5 mg/kg (if age ≥12 y) to 10 mg/kg (if age <12 y) iv q8 h Famciclovir: 500 mg po bid Valacyclovir: 1 g po bid
Genital herpes, recurrent in the setting of HIV infection	*Recommend use until all mucocutaneous lesions are healed* Acyclovir: 400 mg po tid Famciclovir: 500 mg po bid Valacyclovir: 1 g po bid
Chronic suppression in the setting of HIV infection	Acyclovir: 400–800 mg po bid–tid Famciclovir: 500 mg po bid Valacyclovir: 500 mg po bid
Acyclovir-resistant HSV in immunocompromised patients	Foscarnet: 40 mg/kg iv q8–12 h × 2–3 weeks (or until all lesions are healed) Cidofovir: 1% cream or gel qd × 2–3 weeks or (for severe disease) 5 mg/kg iv weekly × 2 weeks then every other week (together with probenecid)
VARICELLA–ZOSTER VIRUS INFECTIONS	
Varicella	Acyclovir: 20 mg/kg (800 mg max) po qid × 5 days Valacyclovir†: 20 mg/kg (1 g max) po tid × 5 days
Zoster	Acyclovir: 800 mg po 5×/d × 7–10 days Famciclovir: 500 mg po tid × 7 days Valacyclovir: 1 g po tid × 7 days
Immunocompromised	Acyclovir: 10 mg/kg (500 mg/m^2) iv q8 h × 7–10 days *or until cropping has ceased* (depending on the setting, consider continuing until lesions are healed)

*Indications for and efficacy of antiviral treatment for initial episodes of orolabial herpes in immunocompetent adults have not been defined, but the regimens used for initial genital episodes can be considered in individuals with severe disease; acyclovir 15 mg/kg (200 mg max) po 5×/d × 7 days (initiated within 3 days of disease onset) has been shown to be beneficial in young children with primary herpes gingivostomatitis.

†FDA-approved for ages 2–17 years; pharmacies can compound valacyclovir tablets into an oral suspension (25 or 50 mg/ml).

Table 80.4 Antiviral therapy for herpes simplex virus and varicella–zoster virus. bid, twice daily; iv, intravenously; po, orally; q2 h, every 2 hours; qd, once a day; qid, four times a day; tid, three times a day.

involvement of the oral mucosa (see Fig. 80.13D). Sparing of the distal and lower extremities is common. Older lesions evolve to form pustules and crusts and heal within 7 to 10 days. The presence of lesions in all stages of development is a hallmark of varicella.

The disease course is usually self-limited and benign in healthy children. However, prior to introduction of the varicella vaccine, complications resulted in 11 000 hospitalizations annually in the US. Secondary bacterial infection of the skin with subsequent scarring is the most common complication. CNS sequelae are uncommon (<1 : 1000 cases) and may include encephalitis and acute cerebellar ataxia[28]; Reye's syndrome (encephalitis plus fatty liver) is now rare due to avoidance of acetylsalicylic acid in children with varicella. Varicella in adolescents and adults is often more severe than that in children, with an increased number of skin lesions (see Fig. 80.13A) and more frequent development of pneumonia, which has a 10–30% mortality rate if untreated[29]. Occasional complications include thrombocytopenia, hepatitis, glomerulonephritis, optic neuritis, keratitis, arthritis, myocarditis, pancreatitis, orchitis and vasculitis.

Maternal varicella during the first 20 weeks of pregnancy is associated with a ~2% risk of congenital varicella syndrome (varicella embryopathy). Possible congenital defects include a low birthweight, cutaneous scarring, ocular abnormalities, cortical atrophy, psychomotor retardation and hypoplastic limbs. Children whose mothers had varicella during pregnancy may also develop zoster early in life without ever having extrauterine varicella. Lastly, severe neonatal varicella (without amelioration by maternal antibodies) can occur when maternal varicella develops between 5 days before and 2 days after delivery.

In immunocompromised individuals, varicella can lead to significant morbidity and mortality. These patients frequently have a more extensive and atypical cutaneous eruption, often with hemorrhagic or purpuric lesions[11]. Involvement of the lungs, liver and CNS is common.

Herpes zoster

Reactivation of VZV may occur at any time after the development of varicella. Herpes zoster begins with a prodrome of pruritus, tingling,

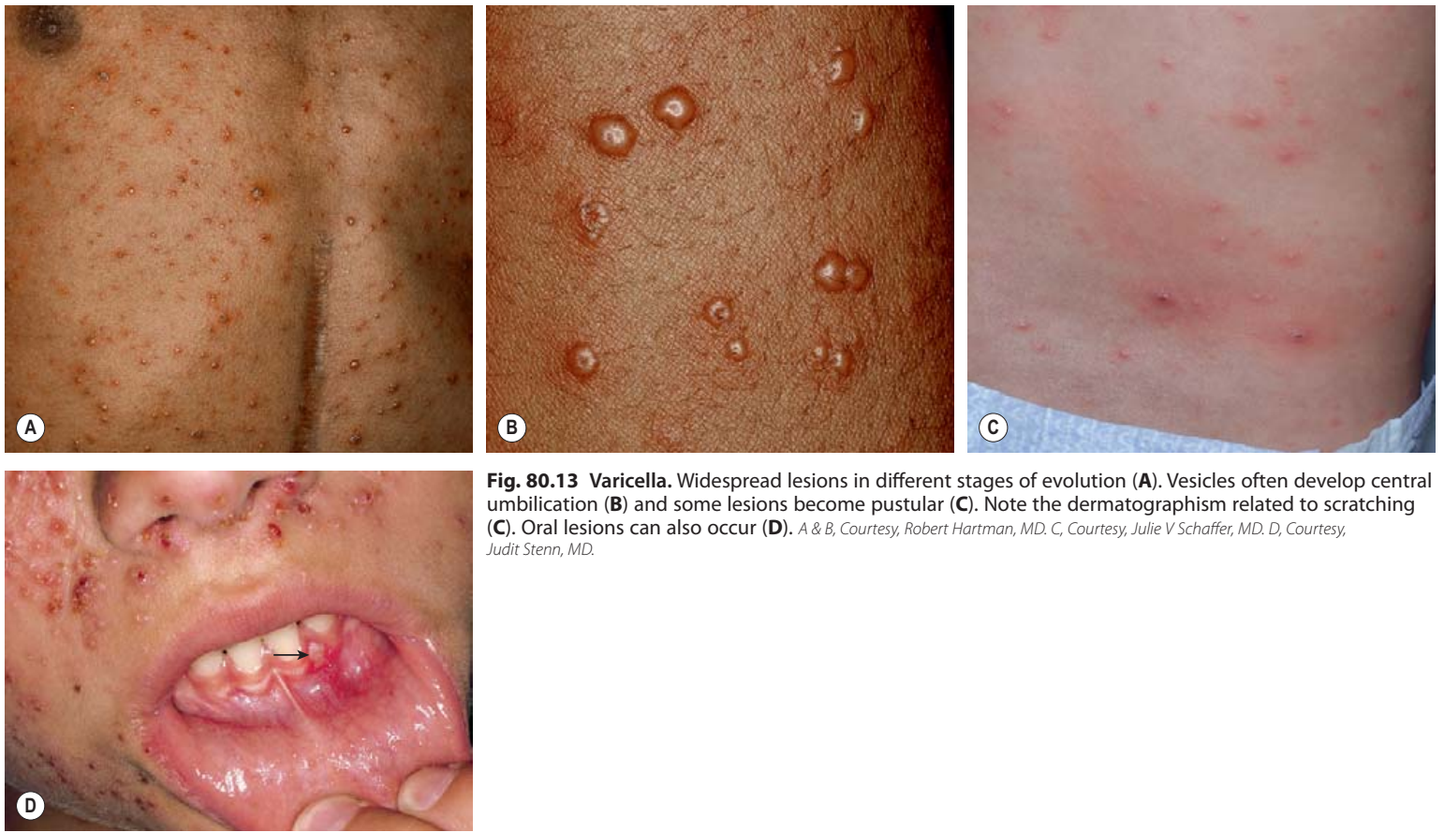


Fig. 80.13 Varicella. Widespread lesions in different stages of evolution (**A**). Vesicles often develop central umbilication (**B**) and some lesions become pustular (**C**). Note the dermatographism related to scratching (**C**). Oral lesions can also occur (**D**). *A & B, Courtesy, Robert Hartman, MD. C, Courtesy, Julie V Schaffer, MD. D, Courtesy, Judit Stenn, MD.*

tenderness, hyperesthesia and/or intense pain (which can mimic a myocardial infarction, surgical abdomen or toothache) in >90% of patients. These symptoms occasionally occur without subsequent skin lesions, a phenomenon referred to as "zoster sine herpete". However, most patients develop a painful eruption of grouped vesicles on an erythematous base in a dermatomal distribution (Figs 80.14 & 80.15); the lesions can involve more that one contiguous dermatome and occasionally cross the midline. Edematous papules and plaques may precede the appearance of vesicles, and progression to pustules or bullae can occur (see Fig. 80.15). Any cutaneous site may be affected, with the trunk representing the most common location, followed by the face. VZV DNA can often be detected in the peripheral blood and saliva of patients with herpes zoster, even after initiation of antiviral treatment[30,31].

Herpes zoster usually resolves without sequelae in children and young adults with intact immune systems. However, the pain, cutaneous lesions and complications of herpes zoster become more severe with increasing age and immune compromise. The most common complication is postherpetic neuralgia, which is characterized by dysesthetic pain (e.g. a burning or stabbing sensation, allodynia) that persists after the skin lesions have healed. This affects 10–20% of all herpes zoster patients and increases in both incidence and severity with age[32,33]. Complications of herpes zoster related to the dermatome that is affected are presented in Table 80.5. Other complications can include secondary bacterial infection, scarring, meningoencephalitis, pneumonitis and hepatitis. Cutaneous disorders that can develop within sites of previous herpes zoster, including granulomatous (Fig. 80.16) and pseudolymphomatous lesions, are listed in Table 80.6.

In immunocompromised hosts, herpes zoster may be more severe and can have unusual clinical presentations, e.g. persistent crusted, verrucous lesions in HIV-infected patients (Fig. 80.17) or postherpetic hyperhidrosis[11,34]. Disseminated cutaneous disease (defined as more than 20 vesicles outside the area of primary or adjacent dermatomes) and/or visceral involvement occurs in approximately 10% of immunocompromised persons with zoster (Fig. 80.18)[35].

Diagnosis and Pathology

A clinical diagnosis can usually be made based upon the history (including previous varicella or vaccine administration) and physical examination. A Tzanck smear and/or DFA (see above and Figs 80.10 & 80.11) can help to rapidly confirm the diagnosis. The latter (but not the former) can differentiate between HSV and VZV. Varicella and herpes zoster have the same histologic findings as HSV infections (see above and Fig. 80.12), but immunohistochemical staining can distinguish between the two viruses.

Additional laboratory tests include viral culture, serology and PCR. Viral culture is a very specific test; however, it is not very sensitive and results may not be available for >1 week. Serologic assays are diagnostic of VZV if the convalescent serum has at least a fourfold increase in the VZV titer relative to the acute serum. As a result, serology is only useful in retrospect. PCR is a highly sensitive and rapid technique, and its use for the detection of VZV is increasing.

Differential Diagnosis

The differential diagnosis of varicella may include vesicular viral exanthems (e.g. due to coxsackieviruses), disseminated HSV infection, pityriasis lichenoides et varioliformis acuta (PLEVA), rickettsialpox, drug eruptions, bullous insect bite reactions and even scabies. Although no longer naturally occurring, smallpox also manifests with a widespread vesicular eruption; its distinct clinical features are reviewed in Chapter 81. For herpes zoster, diagnostic considerations may include zosteriform HSV infections (which often recur in the same site), bacterial skin infections (e.g. cellulitis, bullous impetigo), localized contact dermatitis and phytophotodermatitis. The entities listed above can usually be differentiated from VZV infections based on the history and clinical presentation, but laboratory studies and histologic evaluation are sometimes needed.

Treatment and Prevention

Varicella

Varicella in immunocompetent children can be treated symptomatically with antipyretics (e.g. acetaminophen), antihistamines, calamine lotion and tepid baths. If started within 24 to 72 hours after the onset of the cutaneous eruption, acyclovir has been shown to decrease the duration and severity of varicella[36]. Oral acyclovir and valacyclovir are FDA-approved for the treatment of varicella in children (2–17 years of age) while acyclovir is approved for adults (see Table 80.4).

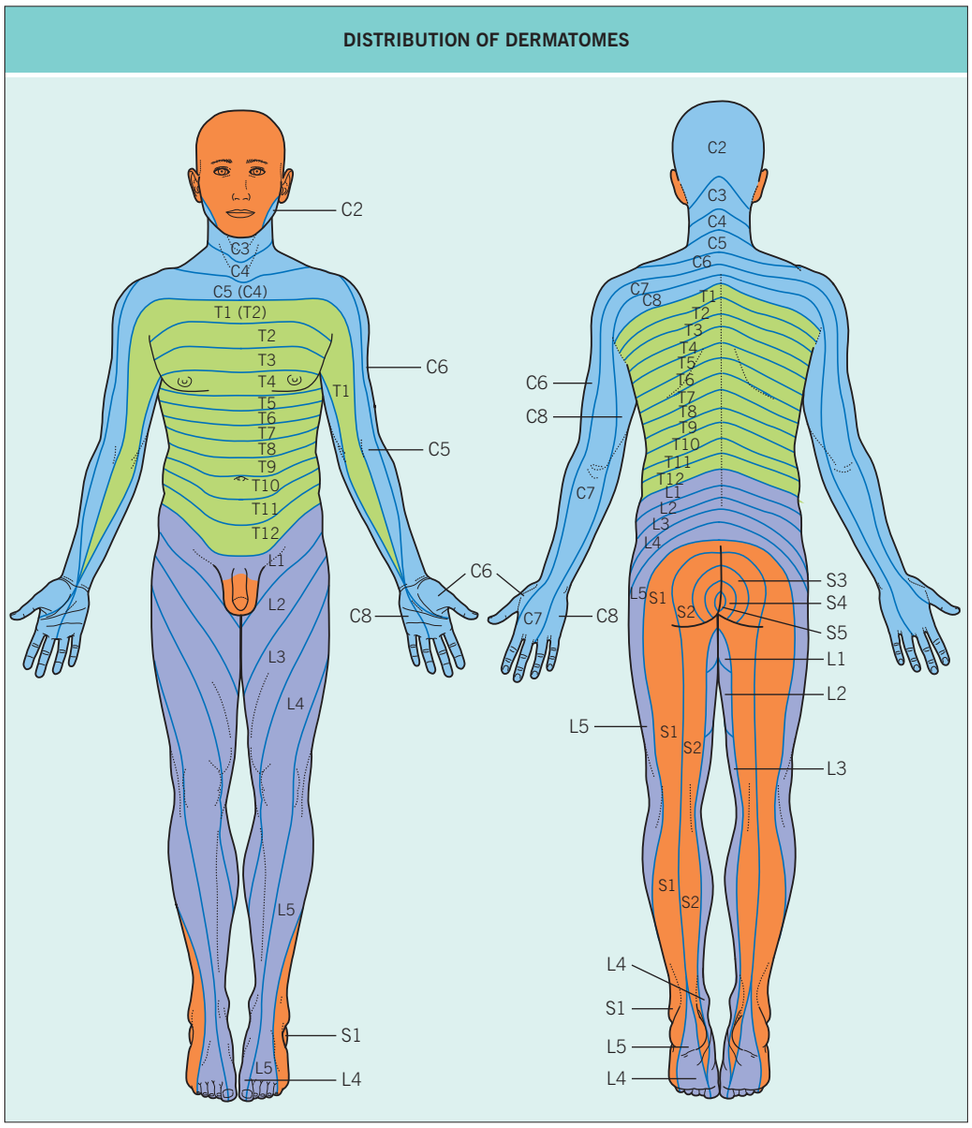


Fig. 80.14 Distribution of dermatomes.

CLINICAL FINDINGS RELATED TO THE DERMATOME INVOLVED IN HERPES ZOSTER		
Dermatome/nerve involved	**Cutaneous findings**	**Extracutaneous findings**
Ophthalmic division of the trigeminal nerve (V1; ~10–15% of zoster patients)	• *Hutchinson's sign* refers to increased risk of ocular involvement if skin lesions are in the distribution of the nasociliary branch, which supplies the nasal tip, dorsum and root of the nose and the medial canthus as well as the cornea	• ~50% of patients have ocular involvement, which can include conjunctivitis, (epi)scleritis, keratitis, uveitis, acute retinal necrosis and optic neuritis • May lead to ocular scarring and visual loss
Geniculate ganglion of the facial nerve – *Ramsay Hunt syndrome*	• Lesions affecting the external auditory canal, tympanic membrane, anterior two-thirds of the tongue and/or hard palate	• Ear pain • Facial nerve paralysis (peripheral) • Loss of taste in anterior two-thirds of the tongue • Dry mouth and eyes • If the vestibulocochlear nerve is also affected: tinnitus, hearing loss and/or vertigo
Cervical dermatome	• Lesions in a cervical dermatome	• Peripheral motor neuropathy of the arm, which may result in muscle atrophy with gradual recovery of strength • Diaphragmatic weakness (C3–5)
Thoracic dermatome	• Lesions in thoracic dermatome	• Abdominal muscle weakness • Abdominal wall pseudohernia
Lumbar dermatome	• Lesions in lumbar dermatome	• Peripheral motor neuropathy of the leg, which may result in muscle atrophy with gradual recovery of strength

Table 80.5 Clinical findings related to the dermatome involved in herpes zoster.

Fig. 80.15 Herpes zoster. A–C Erythematous, edematous plaques with early vesicle formation. Note the perifollicular accentuation (**B**). **D & E** Later stages of evolution with prominent pustule formation (**D**) and a dusky purple color associated with older vesicles (**E**). **F** Ophthalmic zoster (V1) with sharp midline demarcation of erythema and crusts on the forehead as well as contralateral periorbital edema. **G** Bullous variant on the flexor arm. *B, Courtesy, Jean L Bolognia, MD. C, Courtesy, Louis A Fragola, Jr, MD.*

Fig. 80.16 Granulomatous dermatitis in the site of previous herpes zoster. Pink papules and plaques developed several weeks after an episode of herpes zoster in the same dermatomes. A sharp midline demarcation was observed on the back. Histologically, a granulomatous dermatitis was present within the dermis and focally a perineural distribution pattern was seen. *Courtesy, Rebecca Vaughn, MD.*

Fig. 80.17 Chronic verrucous zoster in an HIV-infected patient.

Fig. 80.18 Disseminated cutaneous zoster with multiple violet–black papules on the feet. Patients with disseminated cutaneous skin lesions should be evaluated for possible visceral involvement, e.g. hepatic, pulmonary, CNS, especially if they are immunocompromised.

CUTANEOUS DISORDERS THAT CAN DEVELOP WITHIN SITES OF HERPES ZOSTER

Acneiform – comedones, furunculosis, "acneiform eruption", rosacea (trigeminal distribution)
Dermatitis and urticaria – contact dermatitis (allergic and irritant), chronic localized urticaria
Granulomatous – granuloma annulare (including perforating variant), granulomatous dermatitis (sarcoidal, tuberculoid, unclassified, periadnexal, perineural; see Fig. 80.16), granulomatous vasculitis, lichenoid and granulomatous dermatitis*
Infiltrative – pseudolymphoma†, xanthomatous, Rosai-Dorfman disease
Malignancies, hematologic – leukemia (especially CLL), lymphoma cutis
Malignancies, other – Kaposi sarcoma (HIV-associated form), angiosarcoma, solid-organ metastases
Papulosquamous – psoriasis, lichen planus, lichenoid GVHD*
Sclerosing – lichen sclerosus, morphea, hypertrophic scars/keloids
Ulcerative – trophic syndrome (trigeminal, cervical)
Miscellaneous – acquired perforating disorder (acquired perforating collagenosis), nodular solar degeneration, tinea

*"Giant cell lichenoid dermatitis" has also been described within herpes zoster scars in an allogeneic bone marrow transplant recipient.
†In patients with chronic lymphocytic leukemia, may actually represent leukemia cutis.

Table 80.6 Cutaneous disorders that can develop within sites of herpes zoster. List does not include routine scarring and acute complications such as bacterial infections. Additional possible associations include basal cell carcinoma and squamous cell carcinoma. CLL, chronic lymphocytic leukemia.

These antiviral agents are recommended for varicella in healthy adolescents and adults as well as in children with chronic or pulmonary disorders. Intravenous acyclovir is indicated for varicella in immunocompromised patients, including those receiving chronic systemic corticosteroid therapy, due to their increased risk of more severe disease and complications[36].

Administration of varicella zoster immune globulin (125 U/10 kg, 625 U maximum) within 96 hours of varicella exposure is recommended to provide passive prophylaxis to non-immune immunocompromised individuals and pregnant women as well as high-risk neonates (see above)[37]. Protection lasts for ~3 weeks. In the US, this product is currently only available under an FDA-approved investigational new drug expanded access protocol (24-hour telephone number: 800-843-7477). Another option for postexposure varicella prophylaxis in these patient groups is administration of intravenous immunoglobulin (IVIg; ≥400 mg/kg), which contains high levels of varicella-specific IgG[38]. Prophylactic oral acyclovir administration with usual varicella dosing (see Table 80.4) for 1 week, starting 7–10 days after exposure, can also be considered. Lastly, postexposure varicella vaccination (within 72–120 hours) may prevent or modify disease in non-immune individuals who are ≥12 months of age, immunocompetent and eligible to receive this live attenuated vaccine (see below).

Approved by the FDA in 1995, the live attenuated VZV vaccine (Oka strain; Varivax®) is highly efficacious, with seroprotection rates of ~85% after one dose and ≥99% after two doses in healthy children. Two doses of the vaccine, routinely given at ages 12–15 months and 4–6 years, are now recommended in order to improve protection and counteract waning vaccine-induced immunity (see below). Studies indicate that one dose of the vaccine is 70–90% effective in preventing infection and 95–100% effective in preventing severe disease, and recipients of two doses are more than threefold less likely to develop breakthrough varicella than those who received one dose. The incidence and severity of both varicella (usually due to wild-type VZV) and zoster (most often due to the attenuated Oka strain) (Fig. 80.19) are decreased in vaccine recipients compared to unimmunized children. However, in a report based on surveillance of 350 000 subjects who received one vaccine dose, loss of vaccine-induced immunity over time was observed, e.g. within 1 year of vaccination, there were 1.6 cases of varicella per 1000 person-years versus 58.2 per 1000 person-years at 9 years post-vaccination[39]. Of note, because this is a live viral vaccine, administration is contraindicated during pregnancy and in individuals with immunosuppression due to hematologic malignancies, HIV infection (if $CD4^+$ T-cell percentage is <15% or count <200 cells/μl), other T-cell immunodeficiencies, or systemic immunosuppressive therapy (e.g. prednisone ≥2 mg/kg daily or, if weight >10 kg, ≥20 mg daily for ≥2 weeks).

Fig. 80.19 Herpes zoster following varicella vaccination. This healthy 3-year-old boy developed an eruption of erythematous papulovesicles in the C5 and C6 dermatomes of the right arm. He had received the varicella vaccine in the right shoulder at age 12 months, and several erythematous, edematous papulonodules had appeared in the region of the injection 2 weeks later.
Courtesy, Julie V Schaffer, MD.

Herpes zoster

For herpes zoster, beginning antiviral treatment within 72 hours of the development of skin lesions is optimal, but initiation up to 7 days after onset also appears to be beneficial. Acyclovir, famciclovir and valacyclovir are all FDA-approved for the treatment of herpes zoster in immunocompetent individuals and result in decreased severity and duration of both skin lesions and pain (see Table 80.4). In controlled studies of immunocompetent individuals >50 years of age with acute herpes zoster, famciclovir and valacyclovir were equally effective (and similar or superior to acyclovir) at reducing the frequency and duration of postherpetic neuralgia[40]. Intravenous acyclovir is indicated for the treatment of zoster in immunocompromised patients as well as those with serious complications[23].

Multiple treatments are available for patients who develop postherpetic neuralgia. Low-dose tricyclic antidepressants have demonstrated considerable efficacy and appear to act by a mechanism independent from their antidepressant effects. In a randomized, controlled, multicenter trial, gabapentin (in doses up to 3600 mg/day) was found to be effective in the treatment of pain and sleep interference associated with postherpetic neuralgia[41]. Combined treatment with nortriptyline and gabapentin reduced pain more than either agent alone in another randomized controlled trial[42]. In one open study, the use of gabapentin together with valacyclovir during acute herpes zoster was more effective in preventing postherpetic neuralgia than treatment with valacyclovir alone in historical controls[43]. Although treatment with prednisone in addition to acyclovir can reduce acute pain in patients with herpes zoster, several controlled trials have failed to demonstrate a difference in the incidence or severity of postherpetic neuralgia with this combination compared to acyclovir monotherapy[44]. An 8% capsaicin patch, recently approved by the FDA for treatment of postherpetic neuralgia, was found to reduce pain for up to 12 weeks after a 1-hour application[45]. Other treatments used for postherpetic neuralgia include analgesics, EMLA cream, lidocaine patches, narcotic analgesics, pregabalin, nerve blocks and biofeedback.

Because reactivation of VZV is linked with states of decreased cell-mediated immunity, the varicella vaccine was studied as a method of prophylaxis for herpes zoster. Two initial investigations showed that vaccination increased immunity against VZV in elderly patients, while a third study demonstrated enhanced immunity for only 1 year after vaccine administration, with 10–15% of vaccine recipients failing to develop any enhanced immunity[8]. However, a subsequent large trial utilizing a 14-fold more concentrated version of the varicella vaccine in almost 40 000 adults (age ≥60 years) showed a 51% reduction in the development of herpes zoster and 67% decrease in the incidence of postherpetic neuralgia in vaccine recipients[46]. These results led to FDA approval of this live attenuated vaccine (Zostavax®) in 2006. The Advisory Committee on Immunization Practices (ACIP) recommends a single dose for all immunocompetent individuals ≥60 years of age, whether or not they have a history of varicella or herpes zoster[47]. It is not indicated as a treatment for active herpes zoster or postherpetic neuralgia.

EPSTEIN–BARR VIRUS (HHV-4)

Synonym: ■ Infectious mononucleosis – glandular fever

Key features

- EBV is responsible for a variety of clinical diseases, most notably infectious mononucleosis; it is also associated with lymphoproliferative disorders and lymphomas
- Knowledge of EBV-specific serologies and other laboratory tests for EBV is essential for the clinician

Introduction and History

EBV is a ubiquitous human herpesvirus (HHV-4) that is responsible for a broad spectrum of clinical diseases, including infectious mononucleosis, oral hairy leukoplakia (see Ch. 78), hydroa vacciniforme (see Ch. 87), and a variety of lymphoproliferative disorders, lymphomas (B- and T-cell) and other malignancies (Table 80.7). It replicates well in B lymphocytes and can lead to their immortalization. EBV was named after its two discoverers, who found this herpesvirus in an African Burkitt lymphoma in 1964. In 1968, a link between infectious mononucleosis and EBV was established[48]. Since then, various clinical disorders have been associated with EBV and are classified based on the type of cell infected and state of viral infection.

Epidemiology

In high-income countries, the prevalence of EBV infection in the general population approaches 95% by early adulthood. Peaks of incidence occur in individuals 1 to 6 and 14 to 20 years of age. Approximately 60–80% of young children in low-income countries are seropositive for EBV, compared to ≤50% in the US. Most children with primary EBV infection have either no symptoms or a mild, nonspecific febrile illness. In contrast, approximately 50% of adolescents and young adults with primary EBV infection develop infectious mononucleosis. In the US, EBV is commonly associated with B-cell lymphomas (~20%) and lymphoproliferative disorders (both polyclonal and monoclonal) in immunocompromised patients. Worldwide, EBV is also implicated in Burkitt lymphoma (particularly the African-endemic form) and nasopharyngeal carcinoma (primarily in Asia) (see Table 80.7).

Pathogenesis

EBV is transmitted primarily through infectious saliva and occasionally via blood transfusion, although its presence in genital secretions and breast milk has been reported[49,50]. The virus preferentially infects human mucosal epithelial cells and B lymphocytes, with primary infection originating within the oropharyngeal epithelium. Infectious mononucleosis results from active viral replication, which is subsequently terminated by the host immune response.

After infectious mononucleosis resolves, circulating B lymphocytes can become latently infected with EBV as the virus enters cells by specifically binding to cell surface complement receptors CR2 or CD21. As the B lymphocyte divides, expression of the EBV nuclear antigen-1

EBV-ASSOCIATED DISORDERS
Infectious mononucleosis
Gianotti–Crosti syndrome
Genital ulcers
Oral hairy leukoplakia
Hydroa vacciniforme and related conditions
• Typical hydroa vacciniforme
• Severe hydroa vacciniforme-like eruptions*
Severe hypersensitivity to mosquito bites*
Lymphadenitis, including Kikuchi's disease
Lymphoproliferative disorders and lymphomas
• Post-transplant lymphoproliferative disorder/lymphoma
• Childhood T- or NK-cell lymphoproliferative disorder/lymphoma
• X-linked lymphoproliferative syndrome
• Hemophagocytic lymphohistiocytosis
• Endemic Burkitt lymphoma
• Extranodal NK/T-cell lymphoma (nasal type)
• EBV-positive diffuse large B-cell lymphoma of the elderly
• Other non-Hodgkin lymphomas (including T-cell)
• Hodgkin disease
Other malignancies
• Nasopharyngeal carcinoma
• Gastric carcinoma
Smooth muscle tumors
*Present with bullous, necrotic and ulcerative skin lesions together with fever, lymphadenopathy, hepatosplenomegaly and natural killer (NK)-cell lymphocytosis; can progress to a T- or NK-cell lymphoma or hemophagocytic lymphohistiocytosis.

Table 80.7 EBV-associated disorders. Other skin conditions that are only occasionally associated with EBV include erythema nodosum, urticaria, erythema multiforme and pityriasis lichenoides (see text).

Fig. 80.20 Genital ulcers associated with primary EBV infection. Extreme pain with urination required placement of a Foley catheter in this 13-year-old girl. EBV-related genital ulcers are often misdiagnosed as a genital herpes simplex virus infection.

Fig. 80.21 Ampicillin-induced eruption in a patient with infectious mononucleosis due to EBV infection. Erythematous macules and papules have become confluent on the upper trunk.

gene (*EBNA-1*) is essential for replication of EBV DNA. Furthermore, the EBNA-1 protein and the virally encoded latent membrane protein-2 (LMP-2) are important in establishment of EBV latency within B lymphocytes and evasion from the cellular immune system[51]. In the presence of a normally functioning immune system, cell-mediated immune responses toward EBV antigens generally prevent the transformation and immortalization of B lymphocytes. However, in patients with deficient cell-mediated immunity, B lymphocytes can become immortalized and give rise to EBV-induced lymphoproliferative disorders.

Cell-mediated immunity to EBV infection is persistent and protects against developing infectious mononucleosis upon re-exposure to an EBV (including different types and strains) later in life. The humoral immune response, although it generates antibodies to a variety of EBV antigens, does not appear to be protective. Latent virus in EBV-infected B lymphocytes can subsequently reinfect the oropharyngeal epithelium, resulting in periodic EBV reactivation and viral shedding for the lifetime of the host.

Clinical Features

EBV-induced infectious mononucleosis most commonly occurs in adolescents and young adults between the ages of 15 and 25 years. After an incubation period of 30 to 50 days, a clinical triad of pharyngitis, fever and lymphadenopathy (especially cervical) occurs in >80% of patients. An initial prodrome of headache, malaise and fatigue may precede onset of the triad. Fever can last up to 10 days. Splenomegaly is found in >50% of patients and can be accompanied by hepatomegaly. Other clinical findings may include exudative pharyngitis (often gray–white), anorexia, nausea, vomiting, cough and arthralgias.

EBV infection can have a variety of dermatologic manifestations. A faint, nonspecific erythematous exanthem has been reported in up to 70% of hospitalized patients and ~10% of all patients with infectious mononucleosis[52]. The exanthem typically develops on day 4 to 6 of the illness and may last up to 1 week. It can be morbilliform, urticarial, scarlatiniform, vesicular, erythema multiforme-like, purpuric or petechial in nature, usually beginning on the trunk and proximal upper extremities with later extension to the face and forearms. Eyelid petechiae, periorbital edema, and petechiae at the junction of the hard and soft palate may also be observed. Resolution of the illness usually occurs after 2 to 3 weeks, although symptoms of fatigue and malaise may last longer. Painful genital ulcers, typically measuring >1 cm with ragged purple–red margins, occasionally develop in patients (especially adolescent girls) with primary EBV infection (Fig. 80.20); PCR or *in situ* hybridization has confirmed the presence of lesional EBV in some cases[53]. Cutaneous conditions that are occasionally associated with primary EBV infection include Gianotti–Crosti syndrome (see Ch. 81), erythema nodosum, urticaria, acrocyanosis, erythema multiforme, erythema annulare centrifugum, pityriasis lichenoides, and linear IgA bullous dermatosis.

Administration of ampicillin or amoxicillin, and less commonly penicillin or cephalosporins, to patients with infectious mononucleosis frequently (up to 90% with the former agents) leads to the development of a "hypersensitivity" skin reaction. This usually develops 7 to 10 days following institution of the antibiotic. Typically, a pruritic, pink to copper-colored, scarlatiniform or morbilliform eruption develops on extensor surfaces and pressure points and then becomes confluent as it spreads onto the trunk and extremities (Fig. 80.21). Desquamation occurs 1 week later. The mechanism of this enhanced immune response to aminopenicillins in the setting of EBV infection is not well understood. In general, such reactions (in the absence of a pre-existing allergy) do not preclude the use of this class of antibiotics after the infectious mononucleosis resolves.

EBV-induced infectious mononucleosis can have serious complications. Splenic rupture (usually after trauma) occurs in 0.2% of affected

adults. Significant enlargement of oropharyngeal lymphoid tissue can lead to airway compromise. Other potential complications include hepatitis, thrombocytopenia, hemolytic anemia, glomerulonephritis and CNS disturbances.

Diagnosis and Pathology

Laboratory findings in patients with infectious mononucleosis include mild to moderately elevated hepatic transaminase levels, mild thrombocytopenia, and an absolute and relative lymphocytosis (up to 50 000 cells/dl) with 20% to 40% atypical lymphocytes. Atypical lymphocytosis is not pathognomonic for EBV infection, as a variety of infectious agents and drugs can also cause this phenomenon. Diagnosis is usually made by a positive monospot test (a simple slide test that detects IgM heterophile antibodies) or increased titers of heterophile antibodies; the latter reach a titer of >1 : 40 in approximately 90% of young adults infected with EBV. Heterophile antibodies are capable of agglutinating sheep, horse or bovine erythrocytes, and they typically become detectable 1 week to 1 month after the onset of symptoms and persist for 3 to 18 months.

Because heterophile antibody titers are positive (≥1 : 40 titer) in only a minority of young children with a primary EBV infection, EBV-specific serologies are often necessary to establish the diagnosis in this age group. Titers of at least three different antibodies should be assessed to determine the stage of EBV infection, allowing differentiation between an acute primary, past/latent and reactivated infection (Table 80.8)[52].

PCR-based assays to detect EBV DNA in peripheral blood or tissue samples are also available. Markedly elevated peripheral blood levels are found in patients with infectious mononucleosis and in immunodeficient individuals with EBV-associated lymphoproliferative disorders (who do not mount an effective immune response). Of note, lower levels of EBV DNA can also be detected in the peripheral blood of healthy individuals with a latent EBV infection. *In situ* hybridization for EBV-encoded small RNA (EBER) represents a widely available, sensitive method to detect EBV-infected cells in the skin and other tissues. This assay can be performed on paraffin-embedded specimens, and EBER-positive cells are prominent in EBV-related dermatoses (e.g. T cells in hydroa vacciniforme) and malignancies, but absent in inflammatory dermatoses and lymphomas that are not related to EBV infection.

Primary EBV infection is not associated with any pathognomonic histologic findings. Features are similar to those observed with other viral exanthems, i.e. slight spongiosis, parakeratosis and a perivascular lymphocytic infiltrate. Additional findings may include focal keratinocyte necrosis, mild ballooning degeneration, and, rarely, multinucleated keratinocytes, but less prominent than with HSV and VZV. Aminopenicillin-induced eruptions in the setting of infectious mononucleosis often demonstrate vacuolar interface changes and spongiosis in association with a denser dermal inflammatory infiltrate. Biopsies of involved lymph nodes typically show reactive lymphoid hyperplasia.

Differential Diagnosis

The differential diagnosis of EBV-induced infectious mononucleosis includes drug reaction with eosinophilia and systemic symptoms (DRESS, see Ch. 21 and HHV-6 section below), which can be distinguished by exposure to an implicated drug and features such as eosinophilia and marked facial edema, as well as group A streptococcal infection, acute viral hepatitis, toxoplasmosis, lymphoma, and primary CMV, HHV-6 and HIV infections. A combination of history, physical examination, and laboratory studies can differentiate among these diseases.

Treatment

In most cases of infectious mononucleosis, the disease is self-limited and treatment is supportive. Although acyclovir does inhibit EBV replication, in controlled studies where primary EBV infection was treated with acyclovir or acyclovir combined with systemic corticosteroids, there was no effect on clinical outcome[54]. In one study of healthy individuals with a past/latent EBV infection, the administration of valacyclovir for 1 year reduced the number of EBV-infected B cells in the peripheral blood compared to an untreated control group[55]. Due to their multiple side effects, corticosteroids are reserved for only complicated cases of infectious mononucleosis associated with hemolytic anemia, severe thrombocytopenia or lymphadenopathy resulting in airway compromise[56]. In patients with EBV-associated lymphoproliferative disorders, reduction of immunosuppression can lead to spontaneous resolution, especially when the disorder is polyclonal.

CYTOMEGALOVIRUS (HHV-5)

Key features

- CMV is the leading infectious cause of congenital deafness and mental retardation (TORCH syndrome) as well as the leading cause of blindness (due to retinitis) in AIDS patients
- Neonates and immunocompromised hosts are at risk for severe clinical infections

Introduction

CMV is endemic in all parts of the world, and it is the most common cause of intrauterine infection in humans. In immunocompetent hosts, 95% of infections are asymptomatic or subclinical. Neonates and immunocompromised individuals, especially those with AIDS, allogeneic hematopoietic stem cell transplant recipients and patients receiving alemtuzumab, are at risk for severe clinical manifestations of CMV infection.

EBV SEROLOGIES					
Antibody	**Timing of appearance**	**Timing of disappearance**	**Acute primary infection**	**Past/latent infection**	**Reactivated (RA)/chronic active (CA)* infection**
VCA IgM	Prior to onset of symptoms	Usually within 3 months	Positive	Negative	Negative in RA/variable in CA
VCA IgG	With onset of symptoms	Persists for life	Positive	Positive	Positive
EA IgG†	With onset of symptoms	Usually within 3–6 months; positive if active infection‡	Positive	Negative	Positive
EBNA IgG	1–6 months after onset of symptoms, upon establishment of latency	Persists for life	Negative	Positive	Positive in RA/variable in CA

*Associated with hemophagocytic lymphohistiocytosis, lymphoproliferative disorders and lymphomas.
†Not usually included in routine serologic testing.
‡Also persists in ~20% of healthy individuals.

Table 80.8 EBV serologies. EA, early antigen; EBNA, EBV nuclear antigen; VCA, viral capsid antigen.

History

In 1881, Ribbert first observed "protozoan-like cells" in the organs of a stillborn baby with presumed congenital syphilis. Before the discovery of a viral etiology, the disease was initially called "cytomegalic inclusion disease" based on the characteristic enlarged cells (cytomegalia) and intranuclear inclusions. In 1956, human CMV was independently isolated *in vitro* by three groups of investigators led by Weller, Rowe and Smith. Originally known as the "salivary gland virus" or "salivary inclusion disease virus", cytomegalovirus was given its current name by Weller and his colleagues in 1960[57].

Epidemiology

The prevalence of CMV infection is inversely proportional to socioeconomic status. For example, 80–100% of the African population is CMV-seropositive compared with 60–70% of the US and Western European populations. The increased seroprevalence in low-income countries is thought to be due to crowded living conditions, poor hygiene and greater numbers of individuals caring for an infant. Age-related prevalence studies in the US have shown highest risks of CMV acquisition during early childhood, adolescence and the reproductive years.

Among toddlers in day-care centers, CMV seropositivity is especially high. In adults, CMV infections are often contracted through sexual contact. Blood transfusions carry a 3–4% risk of CMV infection per transfusion unit[58]. To decrease this risk, leukocyte-depleted blood can be used in immunosuppressed patients.

Due to an increasing number of HIV-seropositive individuals worldwide, higher rates of solid organ and hematopoietic stem cell transplantation, and more frequent use of immunosuppressive agents, the incidence of disseminated CMV infection has increased. CMV is considered to be one of the most important viral infections in patients with AIDS due to its significant morbidity (e.g. blindness, gastroenteritis) and mortality in this population. Of note, in the US, congenital CMV infection occurs in approximately 0.5–1.5% of all newborn infants[59].

Pathogenesis

Transmission of CMV is via body fluids, including saliva, blood, urine, semen, breast milk and cervical and vaginal secretions, as well as in transplanted organs and hematopoietic stem cells. CMV can also be spread indirectly by contaminated fomites, such as toys. Transplacental transmission of CMV to the fetus is more likely in the setting of a primary infection in the mother, with 40% of fetuses becoming infected, compared to <1% in recurrent cases.

CMV has an estimated incubation period of 4 to 8 weeks. It is a cytotoxic virus that causes cell enlargement (cytomegaly) and nuclear condensation (inclusion). Using blood leukocytes as a transport medium, the virus disseminates throughout the body, infecting various organs during the viremia. CMV infection may be either primary or recurrent, and the latter can result from either viral reactivation or reinfection with a different antigenic type.

Following primary infection, CMV persists in a latent state for the life of the host and rarely causes disease. In immunocompromised individuals, however, reactivation of latent virus can lead to recurrent infection characterized by persistent viral replication, viremia and dissemination to distant organs. Cell injury and tissue destruction contribute to organ damage by directly altering cellular function and producing an inflammatory response.

The organ infected depends on the age of the host. Infection in healthy children and adults often involves the lymphoid tissues, while fetal and neonatal infection commonly affects the salivary glands and neurons. Infection in immunocompromised individuals frequently involves the retina and lungs as well as the liver and gastrointestinal tract[60].

Clinical Features

Although most cases of CMV infection are subclinical (>90%), a "mononucleosis-like syndrome" similar to that seen with EBV is the most common clinical presentation in immunocompetent persons (Table 80.9). This syndrome has been described in both immunocompetent and immunocompromised individuals after a blood transfusion. Infected patients develop a sore throat without an exudate in addition to fever, malaise, myalgias, lymphadenopathy and hepatosplenomegaly.

CUTANEOUS MANIFESTATIONS OF CMV INFECTIONS
IMMUNOCOMPETENT HOST
Mononucleosis-like syndrome
• Maculopapular/morbilliform eruption
• Petechiae and purpura
• Ampicillin-induced eruption
• Urticaria
• Erythema nodosum
Congenital infections
• "Blueberry muffin" lesions (extramedullary erythropoiesis; see Ch. 121)
• Petechiae and purpura
• Vesicles
IMMUNOCOMPROMISED HOST
Cutaneous vasculitis
Maculopapular/morbilliform eruption
Petechiae and purpura
Ulcers
Vesicles
Verrucous plaques
Nodules and hyperpigmented plaques

Table 80.9 Cutaneous manifestations of CMV infections.

Fig. 80.22 TORCH syndrome due to cytomegalovirus. Multiple purpuric papules of dermal erythropoiesis. *Courtesy, Mary S Stone, MD.*

Atypical lymphocytosis and elevated liver enzymes may also occur. An exanthem, which can be morbilliform, urticarial, petechial or purpuric, develops in a small percentage of patients. As with infectious mononucleosis, the administration of ampicillin or related drugs during this symptomatic period leads to a cutaneous eruption in 80–100% of individuals. Although the clinical course of CMV-induced mononucleosis is self-limited, rare complications include hemolytic anemia, thrombocytopenia, granulomatous hepatitis, Guillain–Barré syndrome, meningoencephalitis, myocarditis, interstitial pneumonia, arthritis, and gastrointestinal and genitourinary manifestations.

Congenital CMV infection is the leading infectious cause of deafness and mental retardation in the US. Approximately 5–10% of infected neonates have symptoms at birth, presenting with jaundice, hepatosplenomegaly, intrauterine growth retardation, thrombocytopenia, chorioretinitis, seizures and/or intracranial calcifications. Cutaneous manifestations include purpuric papules and nodules of dermal hematopoiesis (Fig. 80.22) which are sometimes referred to as "blueberry muffin" lesions (see Ch. 121), as well as petechiae, purpura and vesicles. Another 10–15% of children are born with asymptomatic CMV infection and later develop sequelae, most often sensorineural hearing loss. Perinatal CMV infection is often asymptomatic; however, a limited number of infected infants develop pneumonitis, lymphadenopathy or hepatosplenomegaly[59].

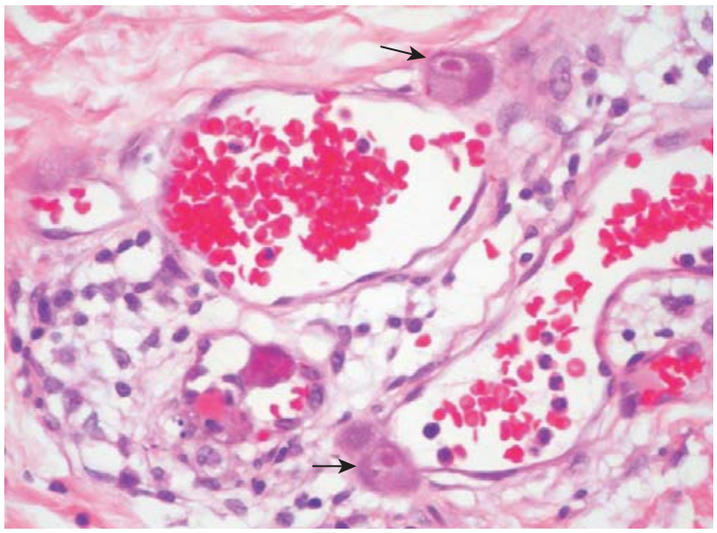


Fig. 80.23 Histology of cytomegalovirus (CMV) infection. Enlarged endothelial cells with a prominent intranuclear inclusion (arrows) are typical of CMV infection.

In AIDS patients, CMV may cause chronic ulcers of the perineum or leg, chorioretinitis, esophagitis, colitis and pneumonitis, as well as endocrine, bone marrow, CNS and renal abnormalities. Cutaneous manifestations are often atypical and range from vesicles to nodules to verrucous plaques. In recipients of solid organ and hematopoietic stem cell transplants, gastrointestinal involvement and interstitial pneumonia are the most serious manifestations of CMV infection, respectively[60].

Diagnosis and Pathology

The diagnosis of CMV infection is established by a variety of methods. Culture of CMV in human fibroblasts is the traditional diagnostic "gold standard", but this takes several days to weeks. Detection of CMV in tissue cultures within 24–48 hours is possible with the shell vial assay, in which monoclonal antibodies specific for early CMV antigens are employed. In addition to CMV-specific serologies, assays that detect CMV antigenemia (via recognition of the pp65 antigen within leukocytes) or CMV DNA (via PCR; necessary in neutropenic patients) are commonly employed to identify and monitor viremia and systemic infection[61]. CMV retinitis in patients with AIDS is diagnosed by ophthalmologic examination.

Like other viral exanthems, the histologic features of the acute exanthem of CMV infection include mild spongiosis and a sparse perivascular lymphocytic infiltrate in the upper dermis. Epidermal changes are minimal since CMV does not infect keratinocytes. However, it does infect endothelial cells, which can have an "owl's eye" appearance that is pathognomonic for CMV infection. The cells are enlarged two- to threefold and contain purplish, crystalline intranuclear inclusion bodies surrounded by a clear halo (Fig. 80.23). These cytomegalic cells are most likely to be evident in ulcers, and vascular dilatation is another common finding. CMV vasculitis, a manifestation of disseminated disease, is characterized by marked endothelial swelling and inflammation.

Differential Diagnosis

The clinical differential diagnosis of the mononucleosis-like syndrome of CMV infection includes EBV-induced infectious mononucleosis (which is generally more severe and often associated with exudative pharyngitis), toxoplasmosis, viral hepatitis, DRESS and lymphoma. A high index of suspicion is necessary to diagnose CMV-induced ulcers and atypical cutaneous manifestations in immunocompromised patients.

Treatment and Prevention

Management is targeted at prevention plus prophylactic antiviral treatment in susceptible immunocompromised individuals as well as antiviral treatment in those who are symptomatic. Treatment of CMV-induced mononucleosis in immunocompetent individuals, however, is only supportive. As a preventive measure, tissues (particularly hematopoietic stem cells) from CMV-seronegative donors are used preferentially for seronegative recipients and vice versa (i.e. seropositive recipients are matched with seropositive donors). While some clinicians utilize pre- and post-transplant CMV prophylaxis (especially when the donor and/or recipient are seropositive), others employ pre-emptive management by following blood CMV antigen or DNA levels and initiating therapy if they increase.

The first-line agents for treatment (as well as prophylaxis) of CMV infections in immunocompromised patients are ganciclovir (intravenous; intravitreal injections/implants for localized retinitis) and valganciclovir (oral). When patients fail to respond to these medications or develop significant side effects, foscarnet and then cidofovir are additional options[62] (Table 80.10). High-titer anti-CMV immunoglobulins are also occasionally used[62]. Relapse is common after discontinuation of any of these antiviral agents.

A live attenuated CMV vaccine has been found to induce a humoral immune response in healthy individuals and transplant recipients, with neutralizing antibodies that persist for over 4 years. It also decreases symptoms in transplant patients who received CMV-infected organs. Further studies are currently being conducted on alternative vaccines, including subunit and recombinant formulations.

TREATMENT FOR CMV INFECTIONS IN IMMUNOCOMPROMISED PATIENTS

Medication	Route	Major side effects
Ganciclovir	iv, intravitreal implant or injection	Bone marrow suppression, GI symptoms > renal insufficiency, neuropathy
Valganciclovir	po	
Cidofovir	iv*, intravitreal injection	Renal toxicity
Foscarnet	iv, intravitreal injection	Renal toxicity
Fomivirsen	Intravitreal injection	

*Initially given weekly for 2 weeks for AIDS-related CMV retinitis.

Table 80.10 Treatment options for CMV infections in immunocompromised patients. iv, intravenous; po, orally.

HUMAN HERPESVIRUS TYPE 6 (HHV-6)

Synonyms: ■ Roseola infantum – exanthem subitum, sixth disease

Key features

- HHV-6 is the cause of exanthem subitum, a common febrile disease of early childhood
- Although it is usually a benign condition without long-term consequences, HHV-6 can be life-threatening if reactivated in the setting of immunosuppression

Introduction

HHV-6 is the etiologic agent of exanthem subitum (roseola infantum), one of the most common viral exanthems in infants and young children. Although HHV-6 infection usually is a benign disease without long-term sequelae, the virus remains latent and can be life-threatening if reactivated in the setting of immunosuppression.

History

Zahorsky distinguished exanthem subitum from other exanthems in 1910 and is credited for its first description. In 1988, Yamanishi and colleagues used serologic methods to confirm that HHV-6 caused exanthem subitum[63]. A subsequent study discovered two distinct variants of the virus: HHV-6A and HHV-6B, each with different biologic, immunologic and genetic characteristics. Variant B is primarily the cause of

exanthem subitum, while the pathogenic role of variant A is unclear, except that it is identified more frequently in patients with AIDS.

Epidemiology

HHV-6 is found worldwide. Infection is most common in young children, occurring between the ages of 6 months and 3 years in 95% of cases, with a peak incidence between 6 and 12 months of age. Boys and girls are equally affected. Seroprevalence studies have shown that maternal IgG against HHV-6 is transferred to 70–97% of fetuses. The level of these maternal antibodies in infants wanes by 6 months of age, but subsequent primary infections result in a peak HHV-6 seroprevalence of 90–100% at 3 to 4 years of age. Antibody levels then decline again, with a prevalence of 66% to 94% in adults[64]. Despite the high seroprevalence, only 30% of children develop clinical manifestations of exanthem subitum. Infections occur throughout the year but are most common in the spring.

Pathogenesis

HHV-6 has a tropism for $CD4^+$ T lymphocytes, but it can infect a variety of other cells, including neurons. Transmission is through infected saliva, although HHV-6 DNA has been isolated from the cervix and may cause perinatal infection. After primary HHV-6 infection, the virus establishes lifelong latency in $CD4^+$ T lymphocytes, with the potential for reactivation. Immunosuppressed patients are at particular risk for HHV-6 reactivation, sometimes with severe consequences[65]. Serologic studies suggest that HHV-6 can also be transmitted via transplanted tissues.

The effects of HHV-6 in HIV-infected patients are unclear. Some studies have shown an increase in the seroprevalence of HHV-6 in these patients, while others found a decrease or little difference from the overall population. *In vitro* studies have described both increased and decreased replication of HIV-1 in cells co-infected with HHV-6 and HIV-1. In AIDS patients, co-infection may cause further immunosuppression, but more research is needed to confirm or disprove this hypothesis[63].

Patients with lymphoproliferative malignancies such as Hodgkin disease, follicular large cell lymphoma, acute myelogenous leukemia, Burkitt's lymphoma and angioimmunoblastic T-cell lymphoma have higher HHV-6 antibody titers than healthy individuals, as do patients with systemic lupus erythematosus, multiple sclerosis and chronic fatigue syndrome. Of note, HHV-6 DNA has been demonstrated in lesions of Rosai–Dorfman disease[66], and HHV-6 has been postulated to have a role in the pathogenesis of pityriasis rosea (together with HHV-7; see below). The causal relationship of HHV-6 to these diseases is unproven. HHV-6 and other herpesviruses (e.g. EBV, CMV and HHV-7) have been implicated in the pathogenesis of DRESS syndrome (see Ch. 21). It has been postulated that drug-related immunosuppression or induction of viral replication by the drug leads to viral reactivation, which stimulates a cellular immune response directed against herpesviruses and likely cross-reacting with the drug.

Clinical Features

The classic clinical manifestations of exanthem subitum occur in about 30% of those with primary HHV-6 infections. Typically, an otherwise well-appearing infant presents with a high fever (102–105°F; 38.9–40.6°C) that lasts for 3–5 days, followed by a cutaneous eruption as the fever begins to subside. The incubation period ranges from 5 to 15 days, but it is most often 9 to 10 days. The fever may be intermittent and tends to peak in the early evening. The cutaneous eruption usually lasts for 24–48 hours and may develop before the temperature returns to normal or up to 2 days afterwards. The lesions are discrete, circular or elliptical, "rose-red" macules and papules that are 2–5 mm in diameter and occasionally surrounded by a white halo. The cutaneous eruption commonly affects the trunk (Fig. 80.24), proximal extremities, neck and less often the face; its appearance can be very similar to rubella or rubeola. An enanthem of red papules on the soft palate (Nagayama's spots) may also be seen, and ulcers on the uvula and at the palatoglossal junction represent a characteristic finding. Eyelid edema, mild upper respiratory symptoms, injection of the tympanic membranes, cervical or occipital lymphadenopathy and a bulging anterior fontanelle may also be evident.

Fig. 80.24 Exanthem subitum (roseola infantum). Small pink–red macules and papules developed on the trunk and neck of this 9-month-old boy during defervescence of a high fever that had lasted for 5 days. *Courtesy, Julie V Schaffer, MD.*

The most common complication of exanthem subitum is febrile seizures, which occur in 10–15% of affected infants and children[67]. Infection with or reactivation of HHV-6 in immunocompromised patients can lead to fever and a cutaneous eruption as well as more serious consequences such as hepatitis, pneumonitis, bone marrow suppression, encephalitis and transplanted tissue rejection[63].

Diagnosis and Pathology

In healthy individuals, HHV-6 infection is typically diagnosed clinically. Serology may be helpful in ambiguous situations. The presence of IgM antibodies indicates primary infection, but this assay is not reliable for the detection of reactivation. A fourfold increase in IgG in paired samples from the acute and convalescent phases of the disease can give retrospective confirmation of HHV-6 reactivation.

Other diagnostic tools include PCR-based assays and viral culture. PCR detection of cell-free HHV-6 DNA in serum or plasma has diagnostic utility. However, qualitative PCR using cellular specimens (e.g. peripheral blood mononuclear cells) cannot reliably distinguish between latent and active infection.

The histopathologic features of exanthem subitum are similar to those of other viral exanthems. A sparse perivascular lymphocytic infiltrate within the dermis is observed without other specific changes.

Differential Diagnosis

The differential diagnosis of exanthem subitum is primarily other viral exanthems (e.g. rubeola, rubella, and enterovirus, adenovirus, EBV and parvovirus infections); other considerations may include scarlet fever, Rocky Mountain spotted fever and Kawasaki disease (see Ch. 81).

Treatment

Although HHV-6 infection is usually self-limited, serious complications can occur in immunocompromised patients. Evidence-based recommendations regarding specific antiviral agents and dosages are not yet available to guide treatment in immunocompromised hosts. Some studies have shown that phosphonoacetic acid, foscarnet and ganciclovir may inhibit HHV-6, and a few case studies have reported successful treatment of serious infections with foscarnet and ganciclovir.

HUMAN HERPESVIRUS TYPE 7 (HHV-7)

Key feature

- HHV-7 is a lymphotropic virus that has been linked to reactivation of HHV-6 in some patients with exanthem subitum

HHV-7 is a ubiquitous lymphotropic herpesvirus that was first isolated by Frenkel et al.[68] in 1990. Its epidemiology appears to be similar to that of HHV-6, with a seroprevalence of over 85% in the US. Infections with HHV-7 mainly occur during the first 5 years of life (with a peak at 1–2 years of age) and then typically remain latent. Transmission via saliva is most likely, since HHV-7 is only known to replicate in human salivary glands; however, HHV-7 has also been found in cervical secretions.

Little is understood about the pathogenesis of HHV-7, except that it utilizes the CD4 molecule as its receptor. HHV-7 down-regulates the expression of CD4 molecules on lymphocytes and may down-regulate the infectivity of HIV, since both viruses compete for the same receptor. A T-lymphocytic viral vector utilizing HHV-7 has been developed for potential use in gene therapy for diseases affecting $CD4^+$ T lymphocytes, such as AIDS, autoimmune diseases and T-cell lymphomas[65].

The virus grows best in cord blood lymphocytes and has a limited range of host tissues compared to that of HHV-6, although HHV-7 antigen has been found in human lungs, mammary glands and skin[69]. Compared to HHV-6, HHV-7 is less cytopathic, associates more with cells and grows more slowly in culture. Significant homology exists between the two viruses and limited antigenic cross-reactivity has been demonstrated between HHV-7 and HHV-6A (but not HHV-6B)[65]. However, HHV-7 is serologically distinct from HHV-6, and immunity to HHV-7 is not conferred with HHV-6 antibodies (or vice versa).

HHV-7 has not been clearly established as a causative factor for clinical disease, although it has been linked to several conditions. A subset of cases of exanthem subitum have been associated with reactivation of HHV-6 (particularly variant B) in conjunction with primary infection with HHV-7. The cutaneous eruption associated with HHV-7-induced exanthem subitum is lighter in color and presents later in the disease course than that of primary HHV-6 infection[70]. Neurologic complications, such as febrile seizures and acute hemiplegia, have also been reported with HHV-7-induced exanthem subitum.

HHV-7 and pityriasis rosea (PR) were first associated when HHV-7 DNA was detected via PCR in blood monocytes, plasma and lesional skin from 12 patients with PR, but not in the plasma or skin of controls[71]. Although some subsequent studies were unable to isolate HHV-7 DNA from PR lesions, others supported a role for HHV-7, and possibly HHV-6, in PR[72].

Methods to detect HHV-7 infection include serologic tests, PCR, viral culture and immunohistochemical staining. The differential diagnosis is similar to that of exanthem subitum. There is no available treatment for HHV-7 infection, although several antiviral agents are under investigation.

HUMAN HERPESVIRUS TYPE 8 (HHV-8)

Synonym: ■ Kaposi sarcoma-associated herpesvirus (KSHV)

Key features

- HHV-8 is a latent virus found in virtually all lesions of all types of Kaposi sarcoma (KS) worldwide
- The seroprevalence of HHV-8 corresponds to the incidence rates of KS and varies by geographic location
- The features of primary infection with HHV-8 have not yet been identified, and its associated diseases are postulated to be a result of viral reactivation

Introduction

HHV-8, previously called Kaposi sarcoma-associated herpesvirus (KSHV), is a latent virus found in all types of Kaposi sarcoma (KS) worldwide.

History

In 1872, Moriz Kaposi described a rare cutaneous neoplasm, predominantly affecting elderly men of Ashkenazi Jewish and/or Mediterranean descent, that subsequently came to be known as Kaposi sarcoma (KS). There was little medical interest in this disease until its incidence suddenly increased in young homosexual men at the onset of the AIDS epidemic. In 1994, the association of KS and HHV-8 was recognized when herpes-like DNA sequences were identified in KS lesions from an AIDS patient. Associations of HHV-8 with other cancers in AIDS patients, such as Castleman's disease and body cavity-based lymphomas, were noted in 1995 and 1996.

Epidemiology

HHV-8 is found in KS lesions worldwide. The incidence of the classic form of KS peaks after the sixth decade of life, and it typically occurs in men of Mediterranean and Ashkenazi Jewish descent. In the era prior to antiretroviral therapy (ART; formerly referred to as highly active antiretroviral therapy [HAART]), HIV-positive men having sex with men developed KS at a rate 20 000 times greater than that of the general population[73]. In southern equatorial Africa, the African-endemic form of KS accounts for approximately 10% of all malignancies. This type of KS affects two distinct age groups: young adults (mean age, 35 years; men > women) and young children (mean age, 3 years).

Seroprevalence of HHV-8 varies geographically, ranging from less than 5% in North America, Britain and Northern Europe to about 10% in Southern Europe and 30% to 80% in African countries. In North America and Europe, HHV-8 antibodies are present in approximately 30% of HIV-1-infected men who have sex with men[74].

Pathogenesis

The mechanisms of HHV-8 transmission are not fully understood. Receptive anal intercourse appears to be a factor for transmission, as the seroprevalence of HHV-8 is higher in men who have sex with men than in HIV-infected women. The number of same-sex male partners and the presence of HIV infection may be other risk factors[65]. There is increasing evidence that exposure to saliva (e.g. via close non-sexual contact among family members or sexual practices involving saliva) represents an important route of HHV-8 transmission. In areas in Africa where HHV-8 is endemic, seroprevalence is high in young children, and some but not all studies have found that this is associated with mother-to-child horizontal transmission; vertical transmission is uncommon[75,76]. HIV-infected infants have a significantly increased risk of HHV-8 infection[76]. HHV-8 transmission by blood transfusion has also been demonstrated[77].

KS is an endothelial malignancy and the neoplastic cells are closely related to lymphatic endothelial cells. Although HHV-8 is found in the vast majority of cases in all types of KS, there is no agreement on the exact mechanism by which HHV-8 results in the development of KS. However, studies have shown that HHV-8 can infect both lymphatic and blood vascular endothelial cells and induce transcriptional reprogramming, leading to expression of lymphangiogenic molecules. Unlike co-infections with HHV-8 and HIV-1, co-infections with HHV-8 and HIV-2 do not often result in KS. While immunosuppression of the host is commonly thought to promote replication of the HHV-8 virus, it is noteworthy that KS is much more strongly associated with HIV-1 infection than with immunosuppression in transplant recipients, suggesting a more complex process.

Primary effusion lymphoma and multicentric Castleman's disease have also been associated with HHV-8. Exactly how these distinct diseases are related to this virus is still unknown.

Clinical Features

The four KS types (classic, HIV/AIDS-related, immunosuppression-associated, and African-endemic; see Ch. 114) have somewhat different presentations and clinical courses, although all typically feature red, brown or violaceous papules, plaques and nodules. Edema is often present in all types.

The lesions of *classic KS* tend to have a spongy feel during the early stage of the disease and become more firm with time. They initially develop as purplish-red plaques (Fig. 80.25), primarily on the lower legs of elderly men of Mediterranean descent, and can later become brown, hyperkeratotic and/or eczematous. The oral mucosa and gastrointestinal tract are rarely involved, and the disease typically has a slow progression.

Fig. 80.25 Classic Kaposi sarcoma. Multiple red–violet nodules with hemorrhagic crusting and plaques on the ankle and foot. *Courtesy, Joyce Rico, MD.*

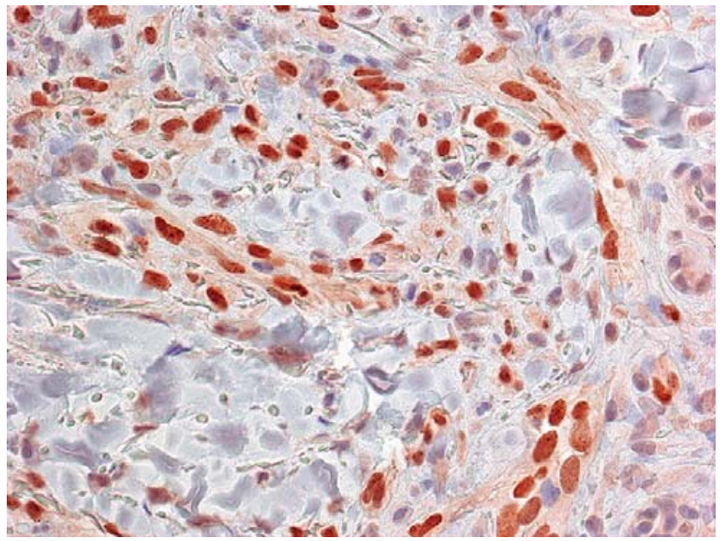


Fig. 80.26 Kaposi sarcoma. Immunohistochemical staining utilizing antibodies against a latent nuclear antigen (LNA-1) demonstrates the presence of HHV-8. *Courtesy, Shawn Cowper, MD.*

AIDS-related KS (see Ch. 78) typically presents as more widely distributed macules, patches or plaques, which occasionally become exophytic or ulcerative. Involvement of the oral cavity and face occurs more often than in classic KS and may be one of the first indications of HIV infection. Involvement of the genital mucosa, lungs and gastrointestinal tract (particularly the stomach and duodenum) is common. Approximately 80% of AIDS patients with KS develop gastrointestinal involvement. Oral lesions can cause significant discomfort as well as difficulties with speech and eating; gastrointestinal involvement may lead to nausea, vomiting, bleeding, perforation and/or ileus; and pulmonary involvement can result in persistent cough, bronchospasm or dyspnea. AIDS-related KS has a variable clinical course, and, in general, prognosis is related to the degree of immune impairment and overall health of the patient. However, flares of KS can occur as a manifestation of immune reconstitution following initiation of ART.

Immunosuppression-associated KS can have a clinical course similar to that of AIDS-related KS, with rapid progression and dissemination unless immunosuppressive medications are discontinued or their doses markedly decreased. Changing from a calcineurin inhibitor to sirolimus (rapamycin), which inhibits the HHV-8 lytic replication cycle and has antineoplastic and antiangiogenic as well as immunosuppressive effects, can result in improvement or disappearance of KS lesions (and avoid organ rejection in transplant recipients).

There are four subtypes of *African-endemic KS*: nodular, lymphadenopathic, florid and infiltrative. The nodular subtype is characterized by a small number of well-circumscribed cutaneous nodules and typically has an indolent course in young adults. The fulminant lymphadenopathic subtype predominantly affects the lymph nodes of children and is often fatal. The florid and infiltrative forms frequently have a large number of cutaneous lesions on one or more extremities. These latter two types are aggressive and may spread deeply into the subcutaneous tissue, muscle and bone.

Diagnosis and Pathology

The diagnosis of KS is confirmed by a skin biopsy of a suspected lesion. Serology for HHV-8 is not required. Immunohistochemical staining utilizing antibodies against latent nuclear antigen 1 can demonstrate the presence of HHV-8 within biopsy specimens of KS (Fig. 80.26)

The histologic features of each variant of KS are typically the same (see Ch. 114): vascular channels lined by atypical endothelial cells and surrounded by a proliferation of spindle-shaped cells. Characteristic histologic changes are associated with each stage of KS. During the patch stage, there is a proliferation of small, jagged, endothelial-lined spaces in the superficial dermis. These vessels may lead to separation of collagen bundles. A perivascular lymphocytic infiltrate (± plasma cells) is variably observed.

During the plaque stage, spindle cells that express endothelial markers infiltrate the dermal collagen bundles of the deeper dermis. Irregular, cleft-like vascular channels are seen along with hemosiderin deposits and hyaline globules. A perivascular lymphocytic infiltrate is prominent in this stage and remains throughout the disease course.

During the nodular stage, well-circumscribed sheets and fascicles of spindle cells within a network of slit-like vascular spaces infiltrate the dermis and subcutaneous tissue. Cytologic atypia, mitotic figures and single erythrocytes trapped within the network are seen.

Differential Diagnosis

The differential diagnosis of KS lesions may include the following: acroangiodermatitis (pseudo-KS), bacillary angiomatosis, ecchymosis, hemangiomas (e.g. microvenular, hobnail or spindle cell), angiosarcoma, pseudolymphoma/lymphoma and cutaneous metastases.

Treatment

The goals for treatment of KS are to reduce symptoms and slow progression. Options include cryotherapy, radiotherapy, topical alitretinoin, intralesional interferon-α, systemic chemotherapy, and, for AIDS-related KS, ART. The latter has markedly reduced the incidence of AIDS-related KS although, as noted above, flares of KS can occur with immune reconstitution. Surgery is usually not effective.

Unless they bleed, are cosmetically bothersome, or cause functional impairment, monitoring may be preferred for small, slowly growing, early-stage cutaneous lesions. When treatment is indicated, classic KS and AIDS-associated KS lesions often respond well to radiotherapy[78] (see Ch. 139). However, recurrences at the peripheral margin of the radiation ports are not uncommon. Topical alitretinoin gel is considered moderately effective[79].

Intralesional interferon-α has been reported to produce complete responses. Side effects include pain, local inflammation and flu-like systemic symptoms. For early lesions, intralesional vinblastine may result in improvement (at least for a period of several months) in a significant percentage of cases. Systemic chemotherapeutic agents, such as vinblastine and anthracyclines (e.g. doxorubicin, daunorubicin), have traditionally been used for extensive classic and endemic KS[80]. More recently, however, these have been replaced by liposomal-encapsulated anthracyclines (first-line therapy) and paclitaxel (partial or complete response in >50% of HIV-infected patients). Treatments that are being investigated include antiangiogenic agents (e.g. bevacizumab, lenalidomide), sirolimus, tyrosine kinase inhibitors (e.g. imatinib), matrix metalloproteinase inhibitors, and valganciclovir (which can inhibit HHV-8 replication)[81].

CONCLUSION

The eight human herpesviruses are associated with a wide spectrum of clinical features. During the past two decades, a marked expansion in the number of immunocompromised patients has led to significant increases in the diversity and severity of clinical presentations of human herpesvirus infections. Thus, it is imperative to be aware of the various manifestations of these viral infections and to initiate appropriate diagnostic tests. There are a number of antiviral drugs available for HSV, VZV and CMV infections, and the clinician must be aware of the indications, contraindications, dosages and limitations of these agents. Unfortunately, only two licensed vaccines exist for human herpesvirus, the varicella and varicella zoster vaccines. Therefore, public health measures remain critical for controlling the spread of these viruses. It is anticipated that better diagnostic tests, antiviral drugs and vaccines for human herpesviruses will become available in the near future.

REFERENCES

1. Wildy P. Herpes: history and classification. In: Kaplan AS (ed). The Herpesviruses. New York: Academic Press, 1973.
2. Xu F, Sternberg MR, Kottiri BJ, et al. Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. JAMA. 2006;296:964–73.
3. Nahmias AJ, Lee FK, Bechman-Nahmias S. Sero-epidemiological and sociological patterns of herpes simplex virus infection in the world. Scand J Infect Dis. 1990;69;19–36.
4. Gupta R, Warren T, Wald A. Genital herpes. Lancet. 2007;370:2127–37.
5. Peña KC, Adelson ME, Mordechai E, et al. Genital herpes simplex virus type 1 in women: detection in cervicovaginal specimens from gynecological practices in the United States. J Clin Microbiol. 2010;48:150–3.
6. Centers for Disease Control and Prevention (CDC). Seroprevalence of herpes simplex virus type 2 among persons aged 14-49 years – United States, 2005-2008. MMWR Morb Mortal Wkly Rep. 2010;59:456–9.
7. Yuan W, Dasgupta A, Cresswell P. Herpes simplex virus evades natural killer T cell recognition by suppressing CD1d recycling. Nat Immunol. 2006;7:835–42.
8. Corey L, Adams H, Brown A, Holmes KK. Genital herpes simplex virus infections: clinical manifestations, course, and complications. Ann Intern Med. 1983;98:958–72.
9. Corey L, Wald A. Maternal and neonatal herpes simplex virus infections. N Engl J Med. 2009;361:1376–85.
10. Flagg EW, Weinstock H. Incidence of neonatal herpes simplex virus infections in the United States, 2006. Pediatrics. 2011;127:e1–8.
11. Wauters O, Lebas E, Nikkels AF. Chronic mucocutaneous herpes simplex virus and varicella zoster virus infections. J Am Acad Dermatol. 2011 Epub ahead of print.
12. Barnes DW, Whitley RJ. CNS diseases associated with varicella zoster virus and herpes simplex virus infections: pathogenesis and current therapy. Neurol Clin. 1986;4:265–83.
13. Whitley RJ. Herpes simplex virus infections. In: Remington JS, Klein JO (eds). Infectious Diseases of the Fetus and Newborn Infant. Philadelphia: WB Saunders, 1990:282–305.
14. Ashley RL, Militoni J, Lee F, et al. Comparison of Western blot (immunoblot) and glycoprotein G-specific immunodot enzyme assay for detecting antibodies to herpes simplex virus types 1 and 2 in human sera. J Clin Microbiol. 1988;26:662–7.
15. Wall SH, Ramey SJ, Wall F. Famciclovir as antiviral prophylaxis in laser resurfacing procedures. Plast Reconstr Surg. 1999;104:1103–8.
16. Corey L, Wald A, Patel R, et al. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. N Engl J Med. 2004;350:11–20.
17. Spruance SL, Tyring SK, Smith M, Meng TC. Application of a topical immune response modifier, resiquimod gel, to modify the recurrence rate of recurrent genital herpes: a pilot study. J Infect Dis. 2001;184:196–200.
18. Martinez CM, Luks-Golger DB. Cidofovir in acyclovir-resistant herpes infections. Ann Pharmacother. 1997;31:1519–21.
19. Nagot N, Ouédrago A, Foulongne V, et al. Reduction of HIV-1 RNA levels with therapy to suppress herpes simplex virus. N Engl J Med. 2007;356:790–9.
20. Celum C, Wald A, Lingappa JR, et al. Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2. N Engl J Med. 2010;362:427–39.
21. Wald A, Langenberg AG, Link K, et al. Effect of condoms on reducing the transmission of herpes simplex virus type 2 from men to women. JAMA. 2001;285:3100–6.
22. Scott-Wilson JH. Why 'chicken' pox? Lancet. 1978;1: 1152.
23. McCrary ML, Severson J, Tyring SK. Varicella zoster virus. J Am Acad Dermatol. 1999;41:1–14.
24. Marin M, Meissner HC, Seward JF. Varicella prevention in the United States: a review of successes and challenges. Pediatrics. 2008;122:e744–51.
25. Hope-Simpson RE. The nature of herpes zoster: a long-term study and a new hypothesis. Proc R Soc Lond B. 1965;58:9–20.
26. Chanan-Khan A, Sonneveld P, Schuster MW, et al. Analysis of herpes zoster events among bortezomib-treated patients in the phase III APEX study. J Clin Oncol. 2008;26:4784–90.
27. Hicks LD, Cook-Norris RH, Mendoza N, et al. Family history as a risk factor for herpes zoster: a case-controlled study. Arch Dermatol. 2008;144:603–8.
28. McKendall RR, Klawans HL. Nervous system complications of varicella-zoster virus. In: Vinken PJ, Bruyn GW (eds). Handbook of Clinical Neurology, Vol. 34. Amsterdam: Elsevier, 1978:161.
29. Weber DM, Pellecchia JA. Varicella pneumonia: study of prevalence in adult men. JAMA. 1965;257:843–8.
30. Satyaprakash AK, Tremaine AM, Stelter AA, et al. Viremia in acute herpes zoster. J Infect Dis. 2009;200:26–32.
31. Mehta SK, Tyring SK, Gilden DH, et al. Varicella-zoster virus in the saliva of patients with herpes zoster. J Infect Dis. 2008;197:654–7.
32. Hope-Simpson RE. Postherpetic neuralgia. J R Coll Gen Pract. 1975;25:571–5.
33. Ragozzino MW, Melton LJ III, Kurland LT, et al. Population-based study of herpes zoster and its sequelae. Medicine (Baltimore). 1982;61:310–16.
34. Chopra KF, Evans T, Severson J, Tyring SK. Acute varicella zoster with postherpetic hyperhidrosis as the initial presentation of HIV infection. J Am Acad Dermatol. 1999;41:119–21.
35. Glesby MJ, Moore RD, Chaisson RE. Clinical spectrum of herpes zoster in adults infected with human immunodeficiency virus. Clin Infect Dis. 1995;21:370–5.
36. Dunkel LM, Arvin AM, Whitley RJ, et al. A controlled trial of acyclovir for chickenpox in normal children. N Engl J Med. 1991;325:1539–44.
37. Ross AH, Lencher E, Reitman G. Modification of chickenpox in family contacts by administration of gamma globulin. N Engl J Med. 1962;267:369–76.
38. Maranich AM, Rajnik M. Varicella specific immunoglobulin G titers in commercial intravenous immunoglobulin preparations. Pediatrics. 2009; 124:e484–8.
39. Chaves SS, Gargiullo P, Zhang JX, et al. Loss of vaccine-induced immunity over time. N Engl J Med. 2007;356:1121–9.
40. Tyring SK, Beutner KR, Tucker BA, et al. Antiviral therapy for herpes zoster: randomized, controlled clinical trial of valacyclovir and famciclovir therapy in immunocompetent patients 50 years and older. Arch Fam Med. 2000;9:863–9.
41. Rowbotham M, Harden N, Stacey B, et al. Gabapentin for the treatment of postherpetic neuralgia. JAMA. 1998; 280:1837–42.
42. Gilron I, Bailey JM, Tu D, et al. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial. Lancet. 2009;374:1252–61.
43. Lapolla W, Digiorgio C, Haitz K, et al. Incidence of postherpetic neuralgia after combination treatment with gabapentin and valacyclovir in patients with acute herpes zoster: open-label study. Arch Dermatol. 2011; 147:901–7.
44. Whitley RJ, Weiss H, Gnann JW Jr. Acyclovir with and without prednisone for the treatment of herpes zoster. A randomized, placebo-controlled trial. The National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Ann Intern Med. 1996;125:376–83.
45. Backonja M, Wallace MS, Blonsky ER, et al. NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia: a randomised, double-blind study. Lancet Neurol. 2008;7:1106–12.
46. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med. 2005;352:2271–84.
47. Harpaz R, Ortega-Sanchez IR, Seward JF. Prevention of herpes zoster: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2008;57:1–30.
48. Henle G, Henle W, Diehl V. Relation of Burkitt's tumor-associated herpes-type virus to infectious mononucleosis. Proc Natl Acad Sci USA. 1968;59: 94–101.
49. Junker AK, Thomas EE, Radcliffe A, et al. Epstein-Barr virus shedding in breast milk. Am J Med Sci. 1991;302:220–3.
50. Israele V, Shirley P, Sixbey JW. Excretion of the Epstein-Barr virus from the genital tract of men. J Infect Dis. 1991;163:1341–3.
51. Miller CL, Burkhardt AL, Lee JH, et al. Integral membrane protein 2 of Epstein-Barr virus regulates reactivation from latency through dominant negative effects on protein-tyrosine kinases. Immunity. 1995;2:155–66.
52. Mendoza N, Diamantis M, Arora A, et al. Mucocutaneous manifestations of Epstein-Barr virus infection. Am J Clin Dermatol. 2008;9:295–305.
53. Halvorsen JA, Brevig T, Aas T, et al. Genital ulcers as initial manifestation of Epstein-Barr virus infection: two new cases and a review of the literature. Acta Derm Venereol. 2006;86:439–42.
54. Tynell E, Aurelius E, Brandell A, et al. Acyclovir and prednisolone treatment of acute infectious mononucleosis: a multicenter, double-blind, placebo-controlled study. J Infect Dis. 1996;174:324–31.
55. Hoshino Y, Katano H, Zou P, et al. Long-term administration of valacyclovir reduces the number of Epstein-Barr virus-infected B cells but not the number of EBV DNA copies per B cell in healthy volunteers. J Virol. 2009;83:11857–61.
56. Schooley RT. Epstein-Barr virus (infectious mononucleosis). In: Mandell GL, Bennett JE, Dolin R (eds). Principles and Practice of Infectious Diseases, 4th edn. New York: Churchill Livingstone, 1995:1364–77.
57. Riley HD Jr. History of the cytomegalovirus. South Med J. 1997;90:184–90.
58. Bowden RA. Transfusion-transmitted cytomegalovirus infection. Hematol Oncol Clin North Am. 1995;9: 155–66.
59. Whitley RJ, Cloud G, Gruber W, et al. Ganciclovir treatment of symptomatic congenital cytomegalovirus infection: results of a phase II study. National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. J Infect Dis. 1997;175:1080–6.
60. Drago G, Aragone MG, Lugani C, Rebora A. Cytomegalovirus infection in normal and immunocompromised humans: a review. Dermatology. 2000;200:189–95.
61. Hudnall SD, Chen T, Tyring SK. Species identification of all eight human herpesviruses with a single nested PCR assay. J Virol Methods. 2004;116:19–26.
62. Meyers JD. Prevention and treatment of cytomegalovirus infection. Ann Rev Med. 1991;42:179–87.
63. Drago F, Rebora A. The new herpesviruses: emerging pathogens of dermatological interest. Arch Dermatol. 1999;135:71–5.
64. Leach CT, Sumaya CV, Brown NA. Human herpesvirus 6: clinical implications of a recently discovered, ubiquitous agent. J Pediatr. 1992;121:173–81.
65. Levy .JA. Three new human herpesviruses (HHV6, 7, and 8). Lancet. 1997;349:558–63.
66. Scheel MM, Rady PL, Tyring SK, Pandya AG. Sinus histiocytosis with massive lymphadenopathy: presentation as giant granuloma annulare and detection of human herpesvirus 6. J Am Acad Dermatol. 1997;37:63–6.
67. Mancini AJ. Exanthems in childhood: an update. Pediatr Ann. 1998;27:163–70.
68. Frenkel N, Schirmer E, Wyatt L, et al. Isolation of a new herpesvirus from CD4+ T cells. Proc Natl Acad Sci USA. 1990;87:748–52.

69. Kempf W, Adams V, Mirandola P, et al. Persistence of human herpesvirus 7 in normal tissues detected by expression of a structural antigen. J Infect Dis. 1998;178:841–5.
70. Tanaka K, Kondo T, Torigoe S, et al. Human herpesvirus 7: another causal agent for roseola (exanthem subitum). J Pediatr. 1994;125:1–5.
71. Drago F, Ranieri E, Malaguti F, et al. Human herpesvirus 7 in patients with pityriasis rosea. Dermatology. 1997;195:374–8.
72. Broccolo F, Drago F, Careddu AM, et al. Additional evidence that pityriasis rosea is associated with reactivation of human herpesvirus-6 and -7. J Invest Dermatol. 2005;124:1234–40.
73. Beral V. Epidemiology of Kaposi's sarcoma. Cancer Surv. 1991;10:5–22.
74. Gao SJ, Kingsley L, Li M, et al. KSHV antibodies among Americans, Italians, and Ugandans with and without Kaposi's sarcoma. Nat Med. 1996;2:925–8.
75. Bourboulia D, Whitby D, Boshoff C, et al. Serologic evidence for mother-to-child transmission of Kaposi sarcoma-associated herpesvirus infection. JAMA. 1998;280:31–2.
76. Minhas V, Crabtree K, Chao A, et al. Early childhood infection by human herpesvirus 8 in Zambia and the role of human immunodeficiency virus type 1 coinfection in a highly endemic area. Am J Epidemiol. 2008;168:311–20.
77. Hladik W, Dollard SC, Mermin J, et al. Transmission of human herpesvirus 8 by blood transfusion. N Engl J Med. 2006;355:1331–8.
78. Piedbois P, Frikha H, Martin L, et al. Radiotherapy in the management of epidemic Kaposi's sarcoma. Int J Radiat Oncol Biol Phys. 1994;30:1207–11.
79. Duvic M, Friedman-Kien AE, Looney DJ, et al. Topical treatment of cutaneous lesions of acquired immunodeficiency syndrome-related Kaposi sarcoma using alitretinoin gel: results of phase 1 and 2 trials. Arch Dermatol. 2000;136:1461–9.
80. Lee FC, Mitsuyasu RT. Chemotherapy of AIDS-related Kaposi's sarcoma. Hematol Oncol Clin North Am. 1996;10:1051–68.
81. Casper C, Krantz EM, Corey L, et al. Valganciclovir for suppression of human herpesvirus-8 replication: a randomized, double-blind, placebo-controlled, crossover trial. J Infect Dis. 2008;198:23–30.

RECOMMENDATIONS OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES FOR ADMINISTRATION OF THE VARICELLA VACCINE

Category	Varicella vaccine administration
Routine childhood vaccination	• 2 doses – First at age 12–15 months – Second at age 4–6 years*
Individuals ≥13 years of age without evidence of varicella immunity, especially: – Students, teachers, residents/staff in institutional settings – Healthcare providers – If household contacts are immunocompromised or children – Postpartum/non-pregnant women of childbearing age – International travelers	• 2 doses, 4–8 weeks apart
Second dose catch-up vaccination for individuals >6 years of age who received 1 dose previously	• 1 additional dose – ≥3 months after previous dose if <13 years old – ≥4 weeks after previous dose if ≥13 years old
HIV-infected individuals: – 1–8 years of age with $CD4^+$ T-cell percentage ≥15% – >8 years of age with $CD4^+$ T-cell count ≥200 cells/mcl	• 2 doses, 3 months apart
Postexposure vaccination in individuals who received 1 dose previously	• 1 additional dose, ideally within 3–5 days, if: – ≥3 months after previous dose for those <13 years old – ≥4 weeks after previous dose for those ≥13 years old
Postexposure vaccination in individuals ≥1 year of age without evidence of varicella immunity	• Administer first dose within 3–5 days
Contraindications • Allergy to vaccine components • Immunocompromised states including: hematologic malignancies, HIV infection with $CD4^+$ T-cell percentage <15% or count <200 cells/mcl, other T-cell immunodeficiencies, systemic immunosuppressive therapy (e.g. prednisone ≥2 mg/kg/day or, if weight >10 kg, ≥20 mg/day for ≥2 weeks) • Pregnancy	
*May be given earlier provided that the interval between the two doses is ≥3 months.	

Recommendations of the Advisory Committee on Immunization Practices for administration of the varicella vaccine. Varicella vaccination is generally required for entry to child care centers, schools, colleges and other educational institutions. Skin lesions directly related to the attenuated virus (usually ≤5 papules or papulovesicles; localized to the area of injection in half of cases) develop in 5–10% of vaccinated individuals, usually 5–25 days after immunization.

This page intentionally left blank

Other Viral Diseases 81

Anthony J Mancini and Ayelet Shani-Adir

Chapter Contents

Enterovirus infections *1346*
Measles *1348*
Rubella *1349*
Erythema infectiosum *1349*
Roseola infantum (primarily covered in Ch. 80) *1352*
Unilateral laterothoracic exanthem *1352*
Gianotti–Crosti syndrome *1353*
Poxvirus infections *1354*
Viral hemorrhagic fevers, including dengue *1357*
West Nile virus infection *1358*
Chikungunya fever *1359*
Barmah Forest and Ross River virus infections *1359*
Rabies *1361*
Cutaneous manifestations of hepatitis A, B and C infection *1361*
Viral-associated trichodysplasia of immunosuppression *1361*
Kawasaki disease *1362*

INTRODUCTION

Viral infections are frequently associated with cutaneous manifestations, especially in children, in whom they are the most common cause of exanthems. An exanthem is defined as a skin eruption occurring as a sign of a general disease. Viral exanthems may present with distinctive cutaneous features or in an entirely nonspecific fashion, and at times they may pose a significant diagnostic challenge, even to the most astute clinician. While dermatologists are most likely to be consulted for atypical or less widely recognized exanthems, a solid working knowledge of the classic disorders, whether common (e.g. fifth disease) or rare in high-income countries (e.g. measles), is essential.

This chapter describes classic childhood exanthems, less common exanthems, eruptions associated with poxvirus infections, and the cutaneous manifestations of hepatitis A, B and C virus infections. Kawasaki disease, which features a polymorphic exanthem together with other mucocutaneous findings and systemic manifestations that can mimic a viral syndrome, is also discussed. In contrast to the symptomatic management of most viral exanthems, prompt recognition and initiation of therapy for Kawasaki disease is necessary to prevent potentially life-threatening complications. Herpesvirus infections, including infectious mononucleosis, are covered in Chapter 80. Structural features and sizes of major types of viruses that infect humans are shown in Figure 81.1.

Nonspecific viral exanthems are the most common type of exanthem seen in children. These eruptions lack distinctive features such as specific lesional morphologies, distribution patterns, natural histories, or enanthems (eruption on the mucous membranes). They most often present with blanchable erythematous papules and macules in a widespread distribution on the trunk and extremities, and less often the face. Associated symptoms such as a low-grade fever, myalgias, headache, rhinorrhea or gastrointestinal complaints may be present. Although multiple infectious agents can cause such exanthems, the most common etiologies in children are the non-polio enteroviruses (see below) in the summer/fall and respiratory viruses (including adenovirus, parainfluenza virus, respiratory syncytial virus and influenza virus) in the winter. Nonspecific exanthems tend to be self-limited, with spontaneous resolution within 1 week, and supportive therapy is usually sufficient. While identification of the exact etiologic agent

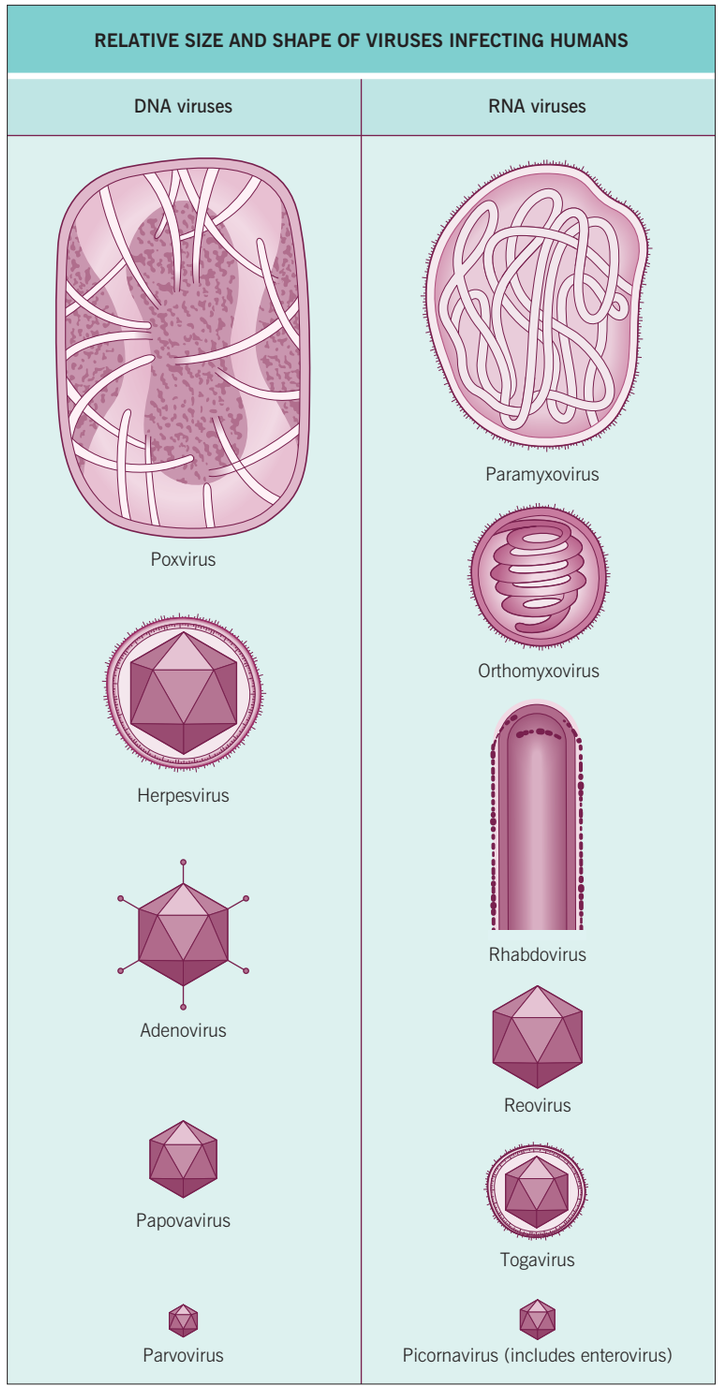


Fig. 81.1 Relative size and shape of viruses infecting humans. *Adapted from Hsiung's Diagnostic Virology Yale University Press, 1994.*

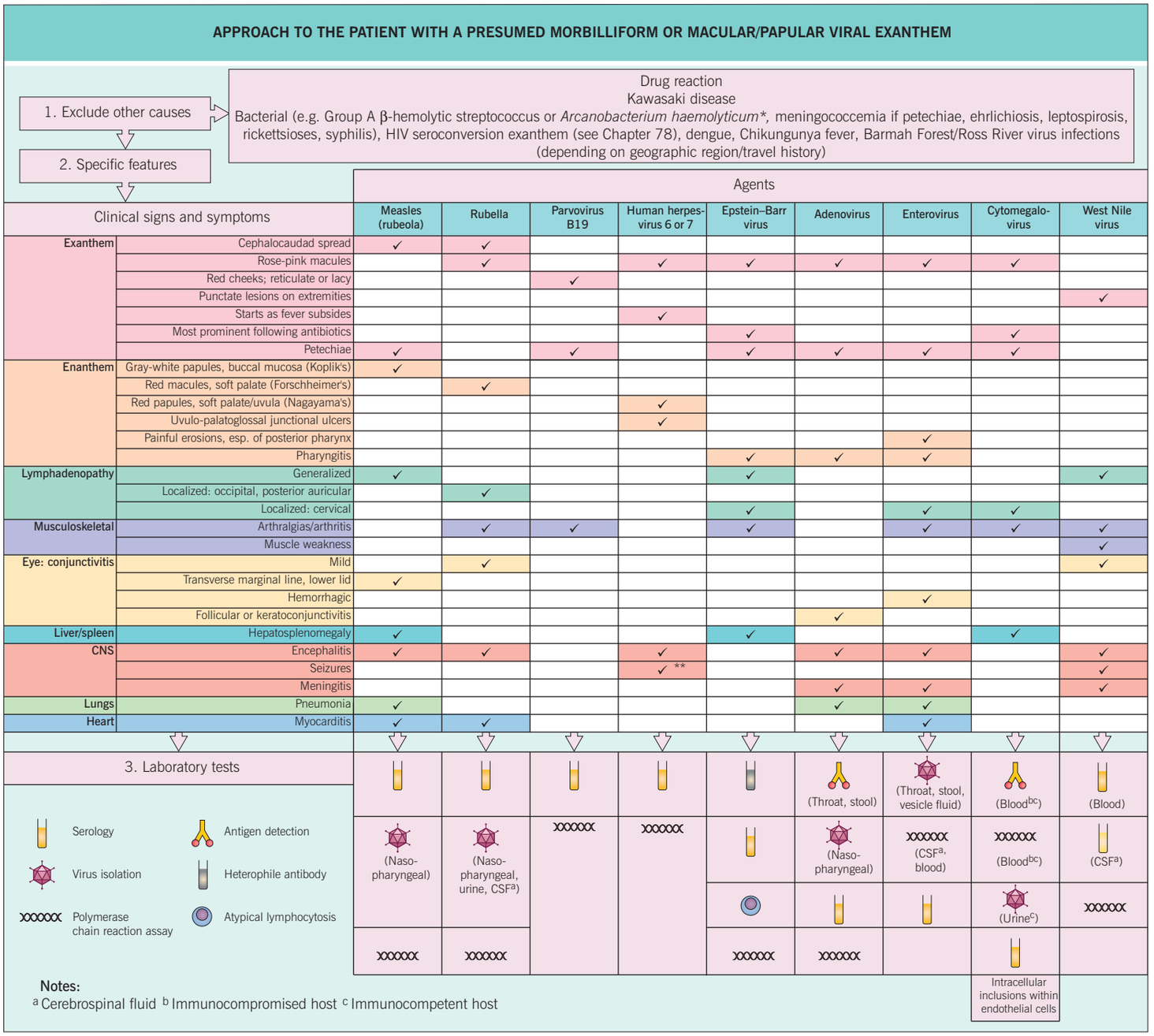


Fig. 81.2 Approach to the patient with a presumed morbilliform or macular/papular viral exanthem. *Gram-positive rod; may result in severe pharyngitis and scarlatiniform exanthem in adolescents and young adults. **Usually febrile seizures.

would be desirable, in many instances it is not necessary or clinically feasible. Figure 81.2 outlines the clinical features to be considered when evaluating the patient with a morbilliform ("maculopapular") viral exanthem, highlighting similar and different aspects of various etiologies. Diagnostic considerations in patients presenting with fever and a "rash" are listed in Figure 0.10.

ENTEROVIRUS INFECTIONS

Key features

- Most common in summer and fall
- Exanthems include erythematous, vesicular and petechial types
- Meningitis and encephalitis possible

Introduction

The enteroviruses, a subgroup of the picornavirus family, cause a wide array of illnesses associated with exanthems. The non-polio enteroviruses include echoviruses and coxsackievirus types A and B, with a total of 64 serotypes. These viruses consist of a single-stranded RNA genome with an unenveloped capsid.

Epidemiology

Enteroviral infections, a worldwide phenomenon, are usually transmitted human-to-human via fecal–oral or respiratory routes, and they can also be spread from mother to infant in the peripartum period. Exposure to virus in fecally contaminated water in swimming pools or via ingestion of oysters may be responsible for some infections. Clinical attack rates are highest in young children, and infections occur more frequently in lower socioeconomic groups. In temperate climates, infections are most common in the summer and fall. The usual incubation period is 3–6 days.

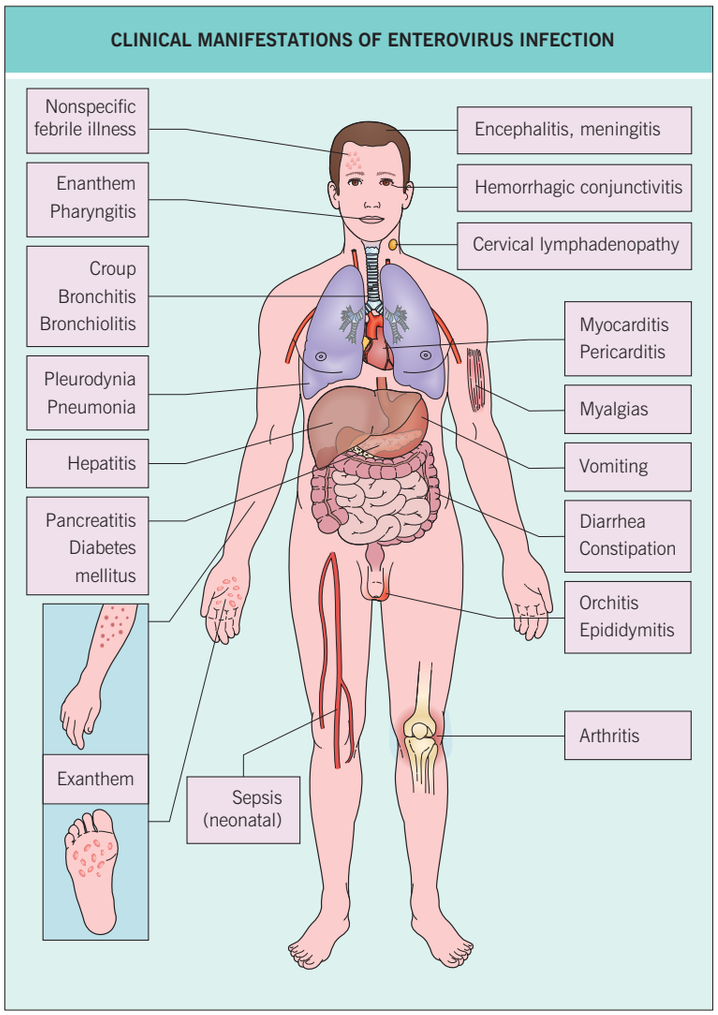


Fig. 81.3 Clinical manifestations of enterovirus infection.

Fig. 81.4 Hand-foot-and-mouth disease. Note the oval vesicle and erythematous macules on the plantar surface. *Courtesy, Julie V Schaffer, MD.*

Pathogenesis

Enteroviruses infect epithelial surfaces of the pharynx and lower alimentary tract. They then replicate in lymphoid tissues and disseminate via an initial minor viremia. Subsequently, replication may occur at multiple anatomic sites, including the CNS, heart, liver, adrenals, respiratory tract, skin and mucous membranes[1]. This replication correlates with the appearance of clinical symptoms. A major viremia occurs during the period of viral multiplication in the secondary infection sites.

Clinical Features and Differential Diagnosis

Figure 81.3 depicts the potential clinical manifestations of an enteroviral infection.

The most common and well-recognized exanthematous illness due to enteroviruses is *hand-foot-and-mouth disease* (HFMD). This disorder is characterized by a vesicular eruption on the palms and soles (Fig. 81.4) in conjunction with an erosive stomatitis. The dorsal aspect of the hands and feet may be involved as well as the buttocks and perineum; oral lesions are most common on the tongue, buccal mucosa, palate, uvula and anterior tonsillar pillars. Onychomadesis occasionally occurs following HFMD as a consequence of temporary nail matrix arrest related to the viral infection[2].

Patients with HFMD often present with fever and malaise, and they may have a mild prodrome prior to the onset of the exanthem. Numerous coxsackievirus serotypes have been implicated, most commonly type A16. Although HFMD generally runs a benign and self-limited course, since 1998 there have been multiple outbreaks of severe enterovirus 71 infection in the Asia-Pacific region, which have resulted in cardiopulmonary and neurologic complications and even deaths in affected individuals (primarily young children)[3].

Herpangina is a febrile illness, primarily of children 3–10 years of age, characterized by painful vesicles and erosions on the soft palate, uvula, tonsils, pharynx and buccal mucosa. An exanthem is usually absent. Coxsackievirus groups A and B, as well as echoviruses, are the usual pathogens.

In addition to the highly characteristic presentations of HFMD and herpangina, enteroviruses cause a diverse spectrum of exanthems that may be morbilliform, rubelliform, roseola-like, urticarial, scarlatiniform, vesicular, pustular and petechial. The majority of enteroviral exanthems feature erythematous macules and papules in a widespread distribution. Petechiae are fairly common, especially with echovirus 9 infection, and may lead to consideration of a more serious infection such as meningococcemia. Non-polio enteroviruses often infect newborns, producing a nonspecific erythematous exanthem and additional features such as fever, gastroenteritis, hepatitis, pneumonia and meningoencephalitis[4,5].

In 1969, Cherry et al.[6] reported four children with fever and transient, spontaneously resolving vascular papules (with dilated blood vessels but no proliferative component histologically) in association with echovirus 25 or 32 infection. Subsequently, three more children with similar lesions were described; although etiologic confirmation was not pursued, the nomenclature *eruptive pseudoangiomatosis* was proposed[7]. Since that time, more than 50 additional cases have been reported (including adults as well as children), with documentation of the viral agent (enteroviruses > cytomegalovirus [CMV] or EBV) in a small subset.

While HFMD and herpangina are fairly straightforward clinical diagnoses, other less specific exanthematous illnesses due to enteroviruses may have a broad differential diagnosis. Important factors that may point to the etiology include the season, exposure history, geographic location, and clinical signs and symptoms.

Specific confirmation of enteroviral infection may be accomplished via the use of viral culture or polymerase chain reaction (PCR)-based assays. The viruses can be recovered from throat and stool swabs or from fluid from cutaneous vesicles. Enterovirus polymerase chain reaction (PCR) is most widely employed for cerebrospinal fluid samples. Serologic diagnosis is difficult due to the large number of different serotypes and the time delay, which make it clinically less useful. Table 81.1 lists types of serologic assays of antibody responses.

Pathology

Skin biopsy is generally not a useful diagnostic procedure in enteroviral infections. Histopathologic features of the vesicular lesions of HFMD include epidermal necrosis with intraepidermal vesicles, a lack of inclusion bodies or multinucleation, and a nonspecific dermal inflammatory infiltrate.

Treatment

For the majority of enteroviral exanthems, the course is self-limited, the prognosis is excellent, and supportive care suffices. However, in

SEROLOGIC ASSAYS OF ANTIBODY RESPONSES	
Assay	**Principle**
Neutralization	Visual read of infected cell monolayers incubated with test sera, looking for CPE inhibition
Radioimmunoassay (RIA)	Ab and Ag bind, then radiolabeled antiglobulin added, *or* radiolabeled Ag added and it binds Ab; radioactivity measured
Enzyme-linked immunosorbent assay (ELISA)	Microplates coated with Ag, serum and enzyme-labeled antiglobulin added, then enzyme substrate added and color change measured
Western blot	Ag mixture separated by electrophoresis, transferred to membrane, serum added and then labeled antiglobulin; seen as colored bands
Latex agglutination	Ag-coated latex particles incubated with serum, Ab agglutinates particles
Hemagglutination inhibition (HI)	Serially diluted test sera mixed with viral Ag, then animal erythrocytes added; inhibition of agglutination measured
Complement fixation	Ag added to serially diluted test sera; Ag–Ab complex binds complement, so the latter is unavailable for lysis of sheep erythrocytes in the presence of Ab to erythrocytes
Immunodiffusion	Ab and soluble Ags combine to produce visible lines of precipitate in a gel
Immunofluorescence	Test sera added to infected cell monolayer, then fluorescein-labeled anti-IgG Ab added; examined with fluorescence microscope

Table 81.1 Serologic assays of antibody responses. Ab, antibody; Ag, antigen; CPE, cytopathic effect.

certain patient populations (e.g. immunosuppressed individuals or neonates), an enteroviral infection may be associated with potentially life-threatening complications. Pleconaril, a drug that interferes with enterovirus attachment and uncoating by binding to the protein capsid, has been demonstrated to be effective both *in vitro* and in clinical studies, and it holds promise as a specific antiviral therapy for serious enteroviral infections[8].

MEASLES

Synonym: ■ Rubeola

Key features

- Incidence greatly decreased with vaccination
- Prodrome of cough, coryza, conjunctivitis and Koplik spots
- Cephalocaudad spread of exanthem

Introduction and History

The incidence of measles has markedly decreased since the introduction of the live vaccine in 1963. Despite high vaccination coverage, measles outbreaks continue to occur in both high-income and low-income countries, and the disease is still regarded as a major health burden. Use of the vaccine is estimated to have reduced global measles morbidity and mortality by 74% and 85%, respectively, compared with the prevaccine era[9].

Epidemiology

The incubation period of measles, which is highly contagious and spread via respiratory droplets, is 10–14 days. In the prevaccine era, measles was endemic throughout the year in heavily populated areas, without regard to age or gender. During the 1989–1990 epidemic, reported measles cases in the US increased six- to ninefold (over the mean of 3000 cases diagnosed annually between 1985 and 1988). Target populations during that epidemic were unvaccinated children younger than 5 years of age from low-income families and vaccinated school-aged children who failed to develop immunity against the virus. Sixty percent of the reported deaths during this epidemic were among children younger than 5 years of age. These statistics highlighted the need for more than one dose of vaccine; as a result, a two-dose measles vaccine schedule was recommended in 1989, which greatly influenced the incidence of measles in the US[10]. Although the median number of cases of measles diagnosed annually in the US is now ~50, outbreaks still occur; for example, there were 118 cases reported to the Centers for Disease Control and Prevention (CDC) from January to May of 2011, most in unvaccinated children and adults exposed to infection "imported" from Europe (which had a concurrent outbreak) and Southeast Asia[11]. Such observations underscore the importance of sustained efforts at universal vaccination against measles.

Fig. 81.5 Measles. Pink macules and minimally elevated papules. *Courtesy, Louis A Fragola, Jr, MD.*

Pathogenesis

Measles is caused by an RNA virus in the Paramyxoviridae family, and humans are the natural host and reservoir of infection. The disease starts with replication of the virus within the epithelial cells of the respiratory tract, with subsequent spread to the lymphoid tissue and blood, resulting in viremia. The virus can then disseminate to internal organs, including the lungs, liver and gastrointestinal tract.

Clinical Features and Differential Diagnosis

Measles classically presents with a prodrome of fever, cough, nasal congestion and rhinoconjunctivitis. A pathognomonic enanthem, Koplik spots, appears during the prodrome and is composed of gray–white papules on the buccal mucosa. The exanthem develops over 2–4 days and consists of erythematous macules and papules that begin on the forehead, hairline and behind the ears and then spread in a cephalocaudad direction (Fig. 81.5). On the fifth day, the exanthem starts to fade in the same order as it appeared.

The differential diagnosis of measles includes other viral infections (e.g. with enteroviruses or EBV), a drug eruption and Kawasaki disease (see Fig. 81.2). In a series of measles–mumps–rubella (MMR)-vaccinated children with measles- and rubella-like illnesses, the etiologies included enteroviruses, parvovirus B19 and human herpesvirus-6 (HHV-6)[12].

Atypical measles (due to exposure to wild-type virus in the setting of partial immunity) has been reported in several groups, including recipients of killed measles vaccine (used from 1963 to 1968), those who failed vaccination, and immunocompromised individuals. It is characterized by high fevers, cough and pulmonary infiltrates that reflect immune complex deposition (related to non-protective, complement-fixing antibodies). Coryza and conjunctivitis are generally absent, and the exanthem is variable, potentially including vesicles, petechiae, purpura and acral edema.

Complications of measles include otitis, pneumonia, encephalitis and myocarditis. Subacute sclerosing panencephalitis is a delayed neurodegenerative disorder that can occur as a complication of measles many years after the acute disease. It is characterized by seizures, personality changes, coma and death. Laboratory diagnosis of measles can be accomplished by virus isolation or detection via reverse PCR (RT-PCR) in nasopharyngeal secretions (or urine) as well as serologic assays for measles-specific antibodies (IgM or IgG).

Pathology

The histopathologic findings include a superficial perivascular lymphocytic infiltrate together with variable spongiosis and dyskeratosis.

Treatment

There is no specific antiviral therapy for measles. Because low serum vitamin A levels are associated with increased measles-related morbidity and mortality, the World Health Organization (WHO) recommends vitamin A administration for all children with acute measles (daily for 2 days; 200 000 IU if ≥12 months, 100 000 IU if 6–11 months, 50 000 IU if <6 months).

Prevention of measles by vaccination is the most effective way to reduce measles morbidity and mortality. The current recommended measles immunization strategy is for an initial dose of vaccine at 12–15 months of age and a second dose at 4–6 years of age[13]. For unvaccinated individuals exposed to measles, administration of the vaccine within 3 days or intramuscular or intravenous immunoglobulin (IM/IVIg) within 6 days of the exposure may provide some protection.

RUBELLA

Synonym: ■ German measles

Key features

- Exanthem of rose-pink macules with cephalocaudad spread
- Tender lymphadenopathy (especially occipital, posterior auricular)
- Joint involvement common
- Fetal infection associated with multiple congenital anomalies

Introduction and History

Rubella is caused by an RNA virus in the Togaviridae family. Although usually a mild, self-limited disease in children and adults, it can cause major complications when transmitted to a fetus *in utero*, including miscarriage, stillbirth and severe congenital malformations.

Epidemiology

The disease is spread via respiratory droplets, with an incubation period of 16–18 days. The incidence of rubella has markedly declined since the licensure of the MMR vaccine in 1969. For example, in the US, the incidence of rubella has declined more than 98% (<15 cases reported to the CDC annually in the past decade). Rubella has a worldwide distribution and occurs most often in the spring.

Pathogenesis

The primary site of infection is the nasopharynx, followed by spread to regional lymph nodes and a subsequent viremia.

Clinical Features and Differential Diagnosis

Rubella typically presents with a mild prodrome that includes fever, headache and upper respiratory symptoms. In children, many cases are subclinical. One to 5 days following the prodrome, an eruption of erythematous macules and papules appears on the face, spreading in a cephalocaudad direction. Erythematous petechial macules may also be present on the soft palate (Forchheimer's spots). The eruption is often accompanied by tender lymphadenopathy, especially of the occipital, posterior auricular and cervical regions. The cutaneous eruption tends to fade in 2–3 days in the same order as it appeared.

Complications of rubella include arthralgias and arthritis (especially in postpubertal girls and women) and, less frequently, hepatitis, myocarditis, pericarditis, hemolytic anemia and thrombocytopenia. Encephalitis occurs in approximately 1 in 6000 cases[14].

Rubella can be diagnosed by detection of anti-rubella IgM antibodies or a fourfold increase in specific IgG antibodies; virus isolation or detection via RT-PCR (e.g. from a nasal wash, throat swab or urine) is also possible. The exanthem of rubella is fairly nonspecific and the differential diagnosis includes other viral exanthems (e.g. adenovirus, enterovirus, measles, EBV) and toxin-mediated eruptions such as scarlet fever. The occipital lymphadenopathy and the typical progression of the eruption can be helpful in diagnosing the disease.

Congenital rubella occurs when a nonimmune pregnant woman transfers the virus to the fetus. Birth defects occur most commonly following infection during the first 16 weeks of pregnancy. Congenital rubella syndrome is characterized by cataracts, deafness, congenital heart defects (patent ductus arteriosus, ventricular septal defects) and CNS abnormalities (microcephaly, developmental delay). A "blueberry muffin baby" presentation due to dermal hematopoiesis is occasionally observed (see Ch. 121).

Pathology

Reported histopathologic findings include a superficial perivascular infiltrate with mild spongiosis. Atypical lymphocytes may be evident in the cutaneous infiltrate as well as in peripheral blood.

Treatment

Treatment of rubella is supportive. The current recommended immunization schedule for rubella vaccine (given in conjunction with the measles and mumps vaccines) is for an initial dose at 12–15 months and a second dose at 4–6 years[13]. In a pregnant woman who has been exposed to rubella, serologic testing (IgG and IgM) should be performed. Prophylaxis via administration of IM/IVIg to rubella-susceptible women exposed to confirmed rubella early in pregnancy may be considered, but it does not reliably prevent fetal infection. If rubella-specific IgM antibodies or a diagnostic rise in IgG anti-rubella antibodies (the latter not useful following IM/IVIg administration) are detected, the patient should be offered prenatal counseling.

ERYTHEMA INFECTIOSUM

Synonyms: ■ Fifth disease ■ "Slapped cheek" disease ■ Parvovirus B19 infection

Key features

- "Slapped cheeks" followed by lacy extremity-predominant eruption
- Marked affinity of parvovirus B19 for erythrocyte precursors
- Fetal infection may result in anemia, fetal hydrops or death

Introduction and History

Human parvovirus B19 (B19), the only parvovirus known to infect humans, was accidentally discovered in 1975 by Yvonne Cossart and colleagues, who were screening blood samples for hepatitis B virus. The small, single-stranded DNA virus, which was named after the panel of sera in which it was found (number 19, row B), was identified as the etiology of erythema infectiosum in 1983. Subsequent elucidation of the pathogenesis of human B19 infections has led to its association (both definitive and proposed) with a wide variety of clinical findings (Table 81.2).

PARVOVIRUS B19 CLINICAL ASSOCIATIONS
ESTABLISHED ASSOCIATIONS
Asymptomatic infection
Erythema infectiosum
Arthropathy
Hydrops fetalis
Papular-purpuric gloves and socks syndrome
Petechial eruptions in generalized, bathing trunk and acral + perioral distributions
Degos-like lesions
Transient aplastic crises in at-risk individuals*
Chronic anemia
Thrombocytopenic purpura
Hepatitis
POSSIBLE ASSOCIATIONS
Vasculitides: • Small vessel vasculitis • Henoch–Schönlein purpura • Polyarteritis nodosa • Wegener's granulomatosis
Neurologic disease
Chronic fatigue syndrome
Systemic lupus erythematosus-like illness
Unilateral laterothoracic exanthem
Hemophagocytic lymphohistiocytosis
*Patients suffering from decreased red cell production (e.g. iron deficiency, thalassemias) or increased red cell destruction (e.g. sickle cell anemia, hereditary spherocytosis, pyruvate kinase deficiency, glucose-6-phosphate dehydrogenase deficiency), as well as patients with HIV infection and recipients of allogeneic hematopoietic stem cell or solid organ transplants.

Table 81.2 Parvovirus B19 clinical associations.

Epidemiology

Infection with B19 occurs in a seasonal pattern, with a peak incidence of erythema infectiosum during the winter and spring. Transmission is via respiratory secretions, blood products, and vertically from a mother to her fetus, and the incubation period is between 4 and 14 days. B19 infection occurs worldwide and is most common in school-aged children. A cyclical pattern of epidemics of B19 infection seems to exist, with peaks about every 6 years[15] and individual community epidemics lasting 3–6 months. The seroprevalence of B19 antibodies increases in direct proportion with age, such that 2–15% of children 1–5 years of age are immune, 15–60% of those between 5 and 19 years, and 30–80% of adults.

Pathogenesis

B19 has a strong tropism for erythroid progenitor cells, and the erythrocyte "P antigen" (globoside) is the cellular receptor to which the virus binds. In fact, individuals who lack the P antigen (blood group P_1^k or p phenotypes) seem to be naturally resistant to B19 infection[16].

After initial infection of the respiratory tract, a B19 viremia occurs, ending at the time of the appearance of anti-B19 IgM antibody (around 8–10 days post inoculation; Fig. 81.6). During the period of viremia, a reticulocytopenia occurs, lasting 7–10 days[15]. One week after the appearance of IgM antibody, anti-B19 IgG appears and coincides with the appearance of the rash and arthralgia. An immune-mediated process is suggested by the temporal disconnect between the viremia and the clinical symptoms.

The anemia and reticulocytopenia tend to be inconsequential in the normal host but may result in transient aplastic crises or pancytopenia in at-risk individuals, such as those with disorders resulting in enhanced red blood cell destruction or decreased production (see Table 81.2). Fetal infection from intrauterine virus transmission causes fetal anemia of varying severity (see below).

Clinical Features and Differential Diagnosis

The most common illness caused by B19 infection is erythema infectiosum, which is most common in children between 4 and 10 years of age. Mild prodromal symptoms (e.g. low-grade fever, myalgias, headache) may occur 7–10 days before the characteristic exanthem appears. The initial stage of the exanthem consists of bright red macular erythema of the cheeks, with sparing of the nasal bridge and circumoral regions (Fig. 81.7A). One to 4 days later, the second stage appears in the form of erythematous macules and papules on the extremities and (to a lesser extent) the trunk, progressing to a lacy, reticulated pattern (Fig. 81.7B,C). This exanthem typically lasts from 1 to 3 weeks (occasionally longer) but fluctuates in intensity during this time, often with exacerbations upon exposure to sunlight or overheating. The differential diagnosis of erythema infectiosum may include scarlet fever, enteroviral infection and rubella, but the diagnosis is usually straightforward when the characteristic eruption is present. Although the evanescent exanthem of systemic-onset juvenile idiopathic arthritis (Still's disease) is also accentuated by heat, it is accompanied by episodic high fevers, has a more chronic course and often exhibits the Koebner phenomenon.

Arthralgia or arthritis occurs in up to 10% of patients with erythema infectiosum and is usually self-limited (typically resolving in 1–3 weeks but sometimes lasting for months). It tends to affect the small joints of the hands as well as the wrists, knees and ankles. Joint involvement related to B19 infection is more common in adults, especially women, occurring in up to 30–60% of those with acute infection[17]. Arthropathy may be seen without an accompanying exanthem.

The manifestations of fetal B19 infection range from self-limited anemia to hydrops, spontaneous miscarriage or stillbirth. The greatest susceptibility is associated with infections acquired before 20 weeks' gestation, and most fetal losses occur between 20 and 28 weeks' gestation. Third-trimester fetal demise may also occur, but it is less often associated with fetal hydrops[18]. The overall risk of fetal loss in the setting of acute B19 infection during pregnancy is 2–6%[19–21]. However, the majority of infants born to B19-infected mothers are delivered asymptomatic at term. There is no evidence for long-term neurodevelopmental sequelae for surviving infected infants, and congenital malformations have not been conclusively demonstrated.

A distinctive syndrome of painful erythema, petechiae and purpura involving the palms and soles was first described in 1990 by Harms et al[22]. Papular-purpuric gloves and socks syndrome (PPGSS) was subsequently demonstrated to be associated with acute B19 infection, although other infectious etiologies have also been reported (e.g. coxsackievirus B6, HHV-6). This syndrome is most often observed in the spring and may occur at any age (including children), but it has a predilection for young adults. The hallmark findings are edema and erythema of the palms and soles in association with petechiae and purpura (Fig. 81.8), with occasional extension onto the dorsal surfaces. Patients may complain of burning and pruritus. Additional manifestations can include an enanthem of erosions and petechiae involving the palate, pharynx and tongue, as well as fever and mild prodromal symptoms. Therapy is symptomatic, and spontaneous resolution occurs over 1–2 weeks. Although few studies have addressed the immune response in PPGSS, based on limited data it appears that patients develop the mucocutaneous lesions while still viremic, which implies contagiousness and therefore has different epidemiologic implications than the classic eruption of erythema infectiosum.

When diagnostic confirmation of B19 infection is indicated, detection of serum anti-B19 IgM antibody is the preferred method, and its presence indicates infection within the previous 2–4 months. PCR-based assays are especially useful for diagnosing infection in the immunocompromised host.

Pathology

Skin biopsy is generally not useful in the diagnosis of B19 infections. In patients with PPGSS, histologic evaluation has revealed a lymphocytic dermal infiltrate and positive staining of dermal blood vessel endothelial cells and epidermal keratinocytes with anti-B19 antibodies.

Treatment

No specific antiviral therapy is available for B19 infections. Children with erythema infectiosum usually feel quite well and often require no treatment. Nonsteroidal anti-inflammatory drugs are useful if symptomatic arthropathy is present. Predisposed patients with aplastic crisis

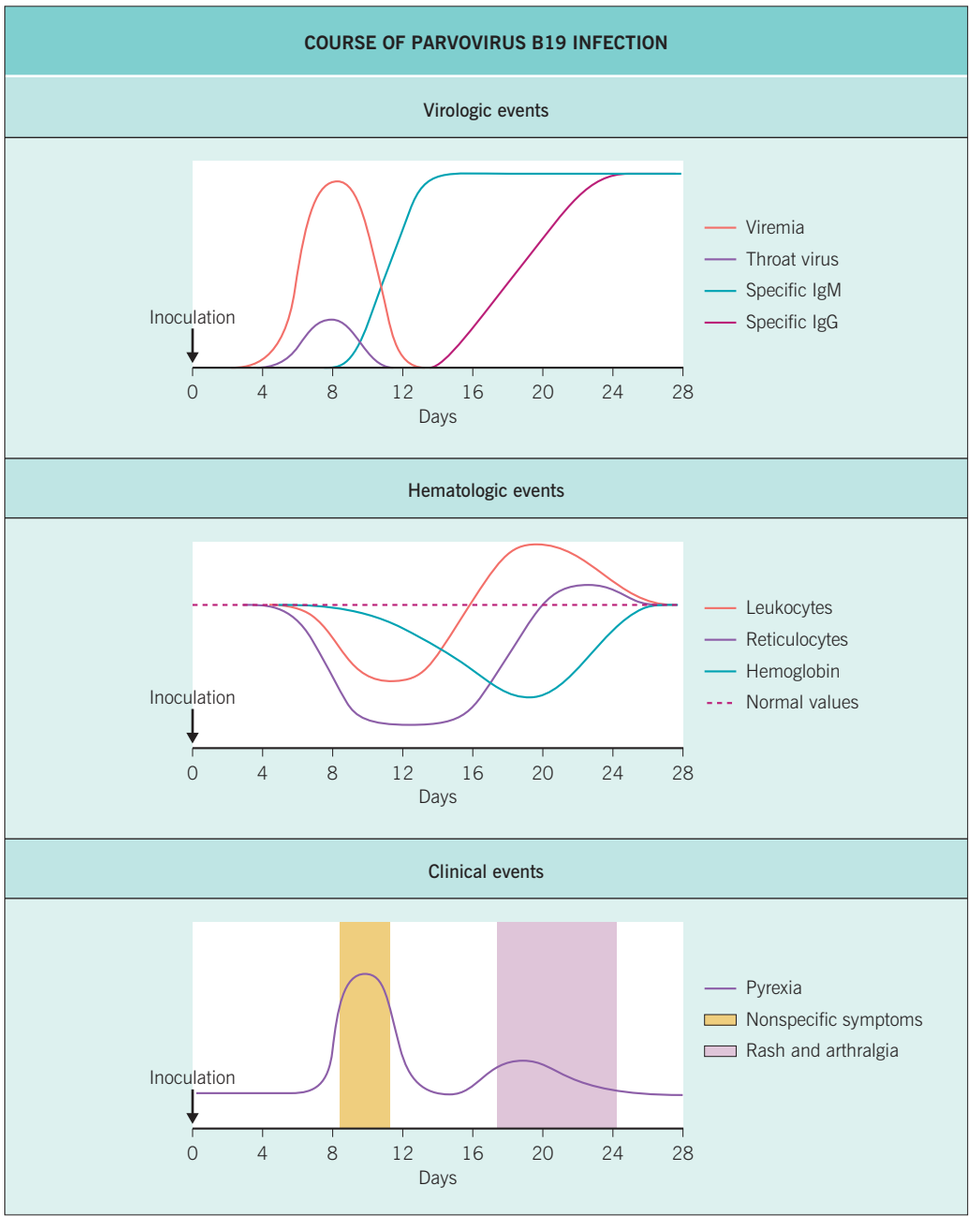


Fig. 81.6 Course of parvovirus B19 infection. Volunteers were infected with parvovirus B19 and the virologic, hematologic and clinical events that followed were recorded. *Reprinted from Cohen J, Powderly WG. Infectious Diseases, 2nd edn, 2004, Mosby, St Louis, with permission from Elsevier.*

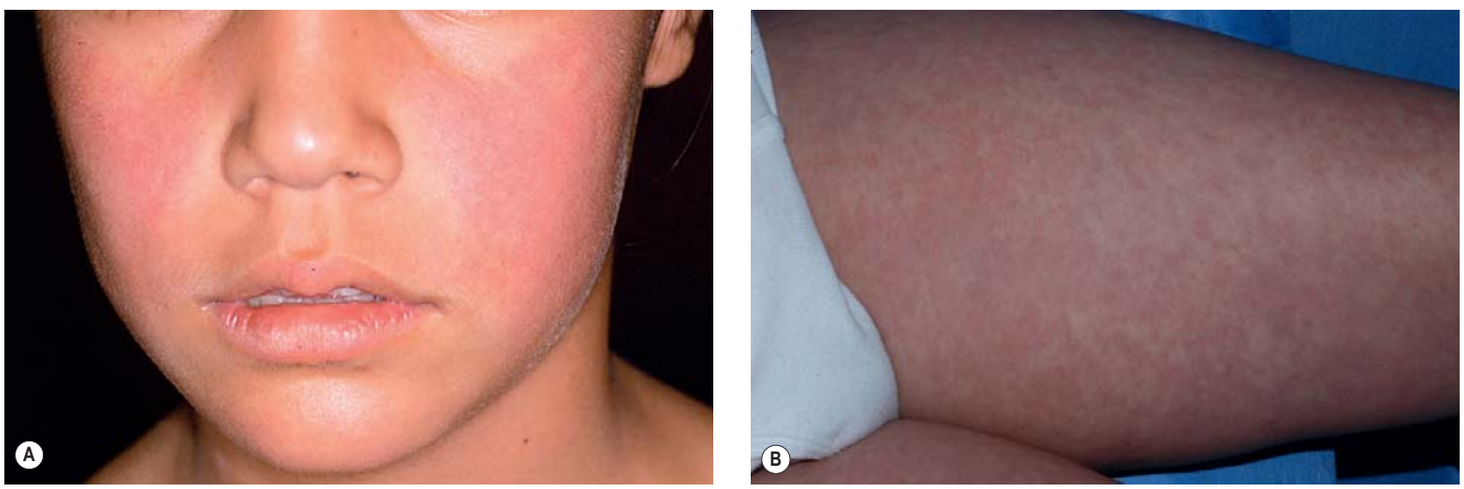


Fig. 81.7 Erythema infectiosum. Bright red macular erythema on the cheeks (**A**). Lacy, reticulated erythematous eruption on the thigh (**B**) during the second stage of the exanthem. *A, Courtesy, Louis A Fragola, Jr, MD. B, Courtesy, Kalman Watsky, MD.*

Continued

Fig. 81.7 Erythema infectiosum (cont'd). **C** Lacy, reticulated erythematous eruption on the arms during the second stage of the exanthem. *Courtesy, Julie V Schaffer, MD.*

Fig. 81.8 Papular-purpuric gloves and socks syndrome. Erythematous patches with petechiae on the plantar surface.

may require red blood cell transfusions. Pregnant women with confirmed primary B19 infection during the first two trimesters should undergo serial fetal ultrasonography, and management of severely affected fetuses is possible with *in utero* transfusions and other interventions such as digoxin therapy.

ROSEOLA INFANTUM

Synonyms: ■ Exanthem subitum ■ Sixth disease

Key features

- High fever followed by an exanthem at defervescence
- Affects primarily infants and toddlers
- Febrile seizures possible

Roseola infantum is a common febrile illness of infancy that is primarily caused by human herpesvirus-6 (HHV-6) infection (and occasionally associated with human herpesvirus-7 infection [HHV-7]) (see Ch. 80). The majority of cases occur between 6 months (when levels of protective maternal antibodies wane) and 3 years of age, with a peak incidence at age 6–12 months. Between 40% and 80% of children are seropositive for HHV-6 by 13 months of life[23,24], and the vast majority of the remainder by 3 years; however, less than a third of infections result in the classic clinical manifestations of roseola infantum. Roseola infantum may occur at any time during the year but is most common in the spring. The incubation period of HHV-6 is usually 9–10 days.

This common disorder is characterized by a high fever (to 40–40.5°C; 104–105°F) for 3–5 days in an infant who otherwise appears well. Seizures occur during the febrile period in up to 10% of patients. Defervescence is then accompanied by the appearance of rose-pink macules and papules on the trunk, neck, proximal extremities and occasionally the face. Mild upper respiratory symptoms, injection of the tympanic membranes, cervical or occipital lymphadenopathy, edematous eyelids and a bulging anterior fontanelle may also be present. An enanthem of red papules on the soft palate and uvula (Nagayama spots) can develop, and uvular and palatoglossal junctional ulcers represent a characteristic finding[25]. The skin eruption fades over a few days, and, in the majority of cases, patients do well with no sequelae. A substantial proportion of nonspecific fevers or fever with otitis media in infants may also be due to HHV-6 infection.

Additional pathogenic features and clinical manifestations of HHV-6 infection, including reactivation in the settings of immunosuppression and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, are discussed in Chapter 80.

UNILATERAL LATEROTHORACIC EXANTHEM

Synonym: ■ Asymmetric periflexural exanthem of childhood

Key features

- Initial unilateral distribution, most often affecting the axilla and lateral trunk
- Subsequent generalization, but maintains unilateral predominance
- Spontaneous resolution over 3–6 weeks
- Presumed to be viral in etiology, although exact cause unknown

Introduction and History

Unilateral laterothoracic exanthem (ULTE) was first described in 1962[26]. This papular exanthem of childhood is initially characterized by a unilateral periflexural (often axillary) location, with lesions spreading in a centrifugal pattern to the contralateral side as the disease progresses. The term "unilateral laterothoracic exanthem" was first introduced in 1992 based upon observations in a series of 18 children[27].

Epidemiology

ULTE occurs most commonly in toddlers and preschool-aged children, with an age range of 6 months to 10 years. The male to female ratio is 1:2, and most of the reported patients have been Caucasian. The disease is widespread in Europe and North America, and the majority of cases occur in the spring.

Pathogenesis

The etiology of ULTE remains unknown despite multiple attempts to identify a causative infectious agent. The seasonal pattern, associated prodrome, reports of familial cases and lack of response to systemic antibiotics suggest a viral etiology. In some published studies in which screening for multiple viruses (e.g. EBV, CMV, HHV-6, HHV-7 and others) was performed, no etiologic agent has been consistently demonstrated. A relationship to infection with *Spiroplasma*, parvovirus B19 and EBV has been suggested in individual cases[28,29].

Clinical Features and Differential Diagnosis

The eruption typically begins with a unilateral distribution (Fig. 81.9), most commonly in the axillary region, followed in frequency by the

Fig. 81.9 Unilateral laterothoracic exanthem. Erythematous macules and papules involving the left axilla and upper flank (**A**) and a slightly more extensive distribution on the left lateral trunk (**B**).

trunk, arm and thigh. It is usually morbilliform or eczematous in nature and tends to spread to contralateral areas but maintains a unilateral predominance.

The exanthem may be preceded by an upper respiratory or gastrointestinal prodrome. Mild fever, diarrhea, and/or rhinitis are noted in up to 60% of patients, and pruritus is reported in up to two-thirds of cases. Lymphadenopathy may also be present. The disease lasts 3–6 weeks and then resolves spontaneously, usually without recurrence.

The differential diagnosis includes contact dermatitis (the most common initial misdiagnosis), a nonspecific viral exanthem, a drug eruption, atypical pityriasis rosea, scabies, miliaria, tinea corporis and (if there is prominent involvement of the extremities) Gianotti–Crosti syndrome. An eczematous eruption with a distribution pattern similar to ULTE can occur in association with molluscum contagiosum in the same sites. Laboratory evaluation is generally unnecessary.

Pathology

Histologic features are nonspecific and include a superficial perivascular infiltrate that is predominantly lymphocytic, mild spongiosis, and exocytosis of lymphocytes into the epidermis. The dermal infiltrate may be accentuated around eccrine ducts.

Treatment

Supportive treatment is indicated in symptomatic patients, although topical corticosteroids tend to be of minimal help. Parents should be reassured that the exanthem will resolve spontaneously in about 3–6 weeks.

GIANOTTI–CROSTI SYNDROME

Synonyms: ■ Papular acrodermatitis of childhood ■ Papulovesicular acrolocated syndrome

Key features

- Symmetric papular eruption on the extremities, face and buttocks
- EBV represents the most common etiology
- Association with hepatitis B virus in some patients

Introduction and History

Gianotti–Crosti syndrome was first described by Gianotti in 1955 and by Gianotti and Crosti in 1956. This condition is characterized by the acute onset of a symmetric papular eruption localized to the face, extremities and buttocks, and it occurs primarily in children. In 1964, Gianotti and Crosti reported the coexistence of anicteric hepatitis and Gianotti–Crosti syndrome, and in the 1970s an association with hepatitis B virus was described by several groups. However, subsequent reports demonstrated that Gianotti–Crosti syndrome can be associated with a variety of viral triggers (Table 81.3).

"Papulovesicular acrolocated syndrome" was the term used by Gianotti in 1985 to distinguish a more vesicular variant that is characterized by a lack of hepatitis, greater degree of pruritus and more prolonged course[30]. Subsequent reports have suggested that differences in clinical manifestations are more likely related to host characteristics than to the etiologic agent[31], and "Gianotti–Crosti syndrome" is currently the most widely accepted nomenclature.

Epidemiology

Gianotti–Crosti syndrome has a worldwide distribution and occurs most often in young children. In one large series of patients, the age range was between 6 months and 14 years, with a mean age of 2 years[31]. It most commonly occurs in spring and early summer.

Pathogenesis

Gianotti–Crosti syndrome is regarded as a self-limited cutaneous response to various infections. Hepatitis B virus and EBV are the most frequently reported etiologic agents, with EBV being by far the most common cause in the US. Other potential etiologic associations are summarized in Table 81.3. Although the pathogenic mechanisms at play in Gianotti–Crosti syndrome are not clear, there is some suggestion that immunizations or immune imbalance may enhance the risk of developing the exanthem following certain infections.

Clinical Features and Differential Diagnosis

Gianotti–Crosti syndrome is often preceded by an upper respiratory syndrome with mild constitutional symptoms. The exanthem begins abruptly, with monomorphic, skin-colored to pink–red, edematous papules that are symmetrically distributed on the face, buttocks and extensor surfaces of the extremities (Fig. 81.10). In some patients, lesions may be limited to the face[32]. The trunk is usually spared, although some extension onto the trunk does not exclude the diagnosis[33]. Lesions tend to be asymptomatic and may occasionally be

POTENTIAL ETIOLOGIES REPORTED IN ASSOCIATION WITH GIANOTTI–CROSTI SYNDROME
VIRAL
• **Hepatitis B virus***
• **Epstein–Barr virus†**
• Hepatitis A and C viruses
• Cytomegalovirus
• Coxsackievirus
• Respiratory syncytial virus
• Adenovirus
• Parainfluenza virus
• Rotavirus
• Parvovirus B19
• Mumps virus
• Human herpesvirus-6
• Herpes simplex virus 1
• Influenza virus
• Human immunodeficiency virus
NON-VIRAL
• Group A β-hemolytic streptococci
• *Mycoplasma pneumoniae*
• *Bartonella henselae*
• *Neisseria meningitidis*
VACCINES
• Polio
• Diphtheria–pertussis–tetanus (DPT)
• Measles–mumps–rubella (MMR)
• Hepatitis B > A
• Influenza
*Reported most commonly in Europe. †Most common cause in US.

Table 81.3 Potential etiologies reported in association with Gianotti–Crosti syndrome. A pruritic Gianotti–Crosti syndrome-like eruption can also occur in patients with molluscum contagiosum.

Fig. 81.10 Gianotti–Crosti syndrome. **A** Monomorphic erythematous papules on the thigh. **B** A more exuberant eruption of coalescing edematous, erythematous papules on the thighs and knees.

vesicular or purpuric. Systemic manifestations include a low-grade fever and lymphadenopathy (mainly inguinal and axillary) that can persist for a few months; hepatomegaly and splenomegaly occur less often.

The differential diagnosis of Gianotti–Crosti syndrome may include a drug eruption, papular urticaria, other viral exanthems, erythema multiforme and molluscum contagiosum. An inflammatory response to molluscum contagiosum (often heralding clearance of the lesions) can present with an eruption of monomorphic erythematous papules that favor the elbows and knees; this "id" reaction-like phenomenon can resemble Gianotti–Crosti syndrome but tends to be extremely pruritic and to respond to treatment with topical corticosteroids.

Pathology

The histopathologic findings are nonspecific and include acanthosis, hyperkeratosis and a lymphohistiocytic perivascular infiltrate in the dermis with dilation of dermal capillaries. A lichenoid pattern has also been reported[34], as have marked papillary edema and increased numbers of cytotoxic T lymphocytes in the dermal infiltrate[35]. It has been suggested that the variety of histologic findings reflects the diversity of agents that may cause the condition.

Treatment

The treatment for Gianotti–Crosti syndrome is supportive, although topical corticosteroids are often of little benefit. A thorough history and physical examination should be performed, and laboratory tests for hepatitis or specific viral agents (e.g. hepatitis B virus, EBV) should only be obtained if clinically indicated. Spontaneous resolution usually occurs within 3–4 weeks, although the eruption may occasionally persist for up to 8 weeks.

POXVIRUS INFECTIONS

Key features

- The world was declared free from smallpox in 1980
- Molluscum contagiosum represents the most common poxvirus infection in humans

The family Poxviridae are large, brick- or ovoid-shaped, double-stranded DNA viruses that are characterized by cytoplasmic replication. Diseases caused by poxviruses include smallpox, vaccinia, cowpox, monkeypox, tanapox, orf, milker's nodules and molluscum contagiosum (Table 81.4). The most historically significant of these was smallpox, which at one time was endemic throughout the world and responsible for millions of human deaths. The last epidemic of smallpox in the US was in 1949, and in 1980, the World Health Assembly declared the world free from smallpox. However, two reference collections remain (one in the US, one in Russia), and fears have been expressed that smallpox could be exploited for bioterrorism. The infection that has clinical features most similar to smallpox is varicella; a comparison of these two conditions is provided in Table 81.5.

Because of concerns about smallpox being used as a bioterrorism agent[42,43], extensive recommendations have been adopted for handling of a suspected outbreak (*www.bt.cdc.gov/agent/smallpox/*). The current strategy is known as ring vaccination, and it involves isolation of patients with suspected infection and immunization of all identified contacts (as well as their contacts). If given within 3 to 4 days following exposure, smallpox vaccination may prevent or minimize the severity of disease. All first responders and healthcare workers who come into contact with a suspected patient should be prior vaccinees[44].

SELECTED POXVIRUS INFECTIONS

Disease	Virus/genus	Host	Clinical findings	Treatment	Comment
Smallpox	Variola/ Orthopoxvirus	Humans	*Major criteria** • Febrile prodrome (>101°F[†], 1–4 days prior to rash onset with headache, backache or abdominal pain) • Firm, deep-seated, well-circumscribed vesicles/pustules • Lesions in the same stage of development in any one area of the body *Minor criteria* • Centrifugal distribution[‡] • First lesions in the pharynx, oral mucosa • Patient appears "toxic" • Slow evolution of rash (i.e. 1–2 days for each stage: macule, papule, vesicle) • Lesions on the palms and soles See Table 81.5 for additional findings	Supportive; prophylaxis with vaccination	• Enters via respiratory tract • Incubation period – 7 to 17 days • Variola major = severe form with high mortality rate; variola minor (alastrim) = mild form • Complications: panophthalmitis, blindness, arthritis, encephalitis • Usual causes of death: toxemia, immune complex deposition, hypotension • High risk of smallpox – 3 major criteria; moderate risk – febrile prodrome + *either* 1 other major criterion *or* ≥4 minor criteria; low risk – no febrile prodrome or febrile prodrome + <4 minor criteria • Laboratory diagnosis: variola real-time PCR (+), orthopox real-time PCR (+), non-variola orthopoxvirus real-time PCR (–), EM (if available), viral culture (acceptable specimens: vesicular "touch prep", vesicle roof, vesicular swab, biopsy tissue) • Theoretically eradicated; potential use as bioterrorism agent
Vaccinia	Vaccinia/ Orthopoxvirus	Humans	• Papule at the vaccination site (usually deltoid or thigh) develops into vesiculopustules, then crust (Fig. 81.11A) • Occasionally, satellite lesions • Lymphadenopathy, fever, malaise common	Supportive; heals with pitted scar	• Used for smallpox vaccination (historically, general population; nowadays, military and first responders, including healthcare workers) • New live vaccine (ACAM2000™) from a single purified isolate of the previous vaccine (Dryvax®; last manufactured in 1978) that is aseptically propagated in cell culture began to be utilized in 2008 (with >200 million doses in the US Strategic National Stockpile) • Possible adverse events[§]: – superinfection of the vaccination site or regional lymph nodes – inadvertent autoinoculation (non-ocular) – contact transmission (non-ocular) – ocular vaccinia – generalized vaccinia (more severe in immunocompromised hosts) – eczema vaccinatum (atopic dermatitis, Darier disease) (Fig. 81.11B) – postvaccination non-viral pustulosis – progressive vaccinia (immunocompromised hosts) – erythema multiforme (Fig. 81.11C), Stevens–Johnson syndrome – fetal vaccinia – postvaccinial CNS disease – myo/pericarditis – dilated cardiomyopathy (controversial) • Additional cutaneous findings that can develop 1–3 weeks post vaccination include urticarial and exanthematous eruptions lasting 4–15 and 7–20 days, respectively • Laboratory diagnosis: variola real-time PCR (–), orthopox real-time PCR (+), non-variola orthopoxvirus real-time PCR (+), viral culture (acceptable specimens: same as for smallpox)
Monkeypox	Monkeypox/ Orthopoxvirus	Monkeys (especially captive), rodents, humans	• Malaise, fever and flu-like symptoms precede eruption • Number of lesions varies from a few to >100 • Papules progress to vesiculopustules then crust • Various stages may be present simultaneously • Usually has a centrifugal distribution[‡]; often involving the palms and soles • Lymphadenopathy and respiratory symptoms common	Supportive; post-exposure smallpox vaccination; cidofovir for severe cases; usually | self-limited course; lesions heal with scarring	• Primarily in Africa • Acquired via cutaneous inoculation or inhalation (human-to-human may be possible)[36,37] • Incubation period – approx. 10–12 days • Outbreak in US in 2003 due to human contact with infected prairie dogs exposed to an infected Gambian giant rat from Ghana[38] • Laboratory diagnosis: variola real-time PCR (–), orthopox real-time PCR (+), viral culture (acceptable specimens: same as for smallpox) • Smallpox vaccination protective

*Per the CDC (www.bt.cdc.gov/agent/smallpox/).
[†]38.3°C
[‡]Concentrated on the face and extremities.
[§]Case definitions are in ref. 41.

Table 81.4 Selected poxvirus infections. CNS, central nervous system; EM, electron microscopy.

SELECTED POXVIRUS INFECTIONS					
Disease	**Virus/genus**	**Host**	**Clinical findings**	**Treatment**	**Comment**
Cowpox	Cowpox/ Orthopoxvirus	Cattle (now a rare host), cats, rodents, humans	• Painful papule at site of contact with lesions on infected animals (usually cats) • Hands and face most common sites of involvement • Erythematous, edematous papule rapidly becomes vesicular, pustular, then hemorrhagic • Progresses to ulcer with crust and eschar • Lymphadenopathy, fever and flu-like symptoms	Supportive; heals over 4 weeks with scarring; scars often large and depressed	• Primarily in Europe and Central Asia • Less common than orf or milker's nodule • May be transmitted by cats with subclinical infections • Incubation period – 7 days • Occasionally severe disease, including generalized eruptions in patients with atopic dermatitis
Orf (ecthyma contagiosum, sore mouth disease, scabby mouth disease, contagious pustular dermatosis, infectious pustular dermatitis)	Orf/ Parapoxvirus	Sheep, goats, reindeer, humans	• Papules (1 to few) on hands (Fig. 81.12A) at sites of contact with infected animals (lesions favor perioral area and udders of ewes), carcasses or fomites (e.g. fences, barn doors) • Progression through several stages: – maculopapular – targetoid – weeping nodule – regenerative dry stage with black dots – papillomatosis – regression with a dry crust • May be accompanied by lymphangitis, lymphadenopathy, malaise, fever	Supportive; topical imiquimod may stimulate early regression; usually heals without scarring	• Endemic in sheep and goats • At-risk occupations: shepherds, butchers, veterinary surgeons, sheepshearers • Histologic findings depend on stage of the lesion and include epidermal necrosis, vacuolated keratinocytes, a dense mixed dermal infiltrate, and delicate finger-like projections of the epidermis into the dermis; eosinophilic inclusion bodies (intracytoplasmic > intranuclear) (Fig. 81.12B) • Laboratory diagnosis: histologic examination of skin lesion ± EM; parapox real-time PCR (+), orf real-time PCR (+) • Erythema multiforme occasionally occurs 10 to 14 days later
Milker's nodules (bovine papular stomatitis, pseudocowpox)	Paravaccinia/ Parapoxvirus	Cattle, humans	• Papule develops at site of contact with lesions on infected animals (e.g. muzzles of calves, teats of cows) • Often single lesions; favor hands and forearms • Cutaneous lesions virtually identical to orf	Supportive	• Endemic in cattle • At-risk occupations: dairy farmers, ranchers, butchers, veterinary surgeons • Laboratory diagnosis: histologic findings ± EM (see orf); parapox real-time PCR (+), paravaccinia real-time PCR (+)
Deer-associated parapoxvirus infection	Parapoxvirus	Deer, humans	• Friable violaceous nodule at site of non-healing cut obtained while field dressing a deer carcass • Single lesion on a finger • Fever following biopsy in one patient	Supportive	• Reported in deer hunters in the Eastern US[39] • Histologic findings include epidermal hyperplasia ± necrosis, intracytoplasmic eosinophilic inclusion bodies in keratinocytes, dilated vascular spaces with swollen endothelial cells, and variable lymphohistiocytic and neutrophilic infiltrates • Parapox real-time PCR (+)
Tanapox	Tanapox/ Yatapoxvirus	Non-human primates, humans	• Isolated skin lesion, usually on the leg • Macular, papular, pustular, ulcerative and crusted stages • Local swelling and lymphadenopathy common • Associated fever and flu-like symptoms	Supportive; heals over 6–8 weeks with scarring	• Endemic in equatorial Africa • Transmission to humans probably occurs via an arthropod vector, although direct transmission also possible[40]

Table 81.4 Selected poxvirus infections (cont'd). EM, electron microscopy.

With the eradication of smallpox, molluscum contagiosum (MC) became the only remaining poxvirus infection to specifically afflict humans. This disorder is caused by the MC virus (MCV), a member of the *Molluscipox* genus of Poxviridae. Two molecular subtypes of the virus, MCV I and MCV II, result in indistinguishable skin lesions[45]. MC is a common, self-limited condition in children. It also occurs in adults, usually as a sexually transmitted disease, and has been observed with increasing frequency in immunocompromised hosts, most notably HIV-infected individuals. Transmission is via skin-to-skin contact and, less commonly, fomites.

MC lesions are firm, umbilicated, pearly papules with a waxy surface. They can occur anywhere on the skin surface but are most common in skin folds (e.g. axillae, neck); on the lateral trunk, thighs and buttocks; and in the genital region (Fig. 81.13A); facial lesions can also occur and are often especially distressing to the patient (Fig. 81.13B). Widespread, large and occasionally deforming lesions may be seen in the setting of immunosuppression, particularly AIDS (see Ch. 78). An associated molluscum dermatitis is common (Fig. 81.13C), especially in children with atopic dermatitis. Inflammation of MC lesions can occur and signals the development of a host immune response (Fig. 81.13B–D). As noted above, an id reaction-like eruption of pruritic erythematous papules that favor the elbows and knees occasionally develops in conjunction with an inflammatory response to MC.

The differential diagnosis of MC may include appendageal tumors, verrucae, condylomata acuminata, basal cell carcinoma, juvenile xanthogranuloma, melanocytic nevi (especially Spitz nevi), papular granuloma

Fig. 81.11 Smallpox vaccine. A Crusted papule at the site of vaccination, 14 days following administration. **B** Eczema vaccinatum in a patient with atopic dermatitis. Spread from the vaccination site (arrow) to areas of eczema occurred due to the impaired skin barrier. **C** Erythema multiforme-like reaction associated with marked erythema and edema at the vaccination site. *B, C, Courtesy, Louis A Fragola, Jr, MD.*

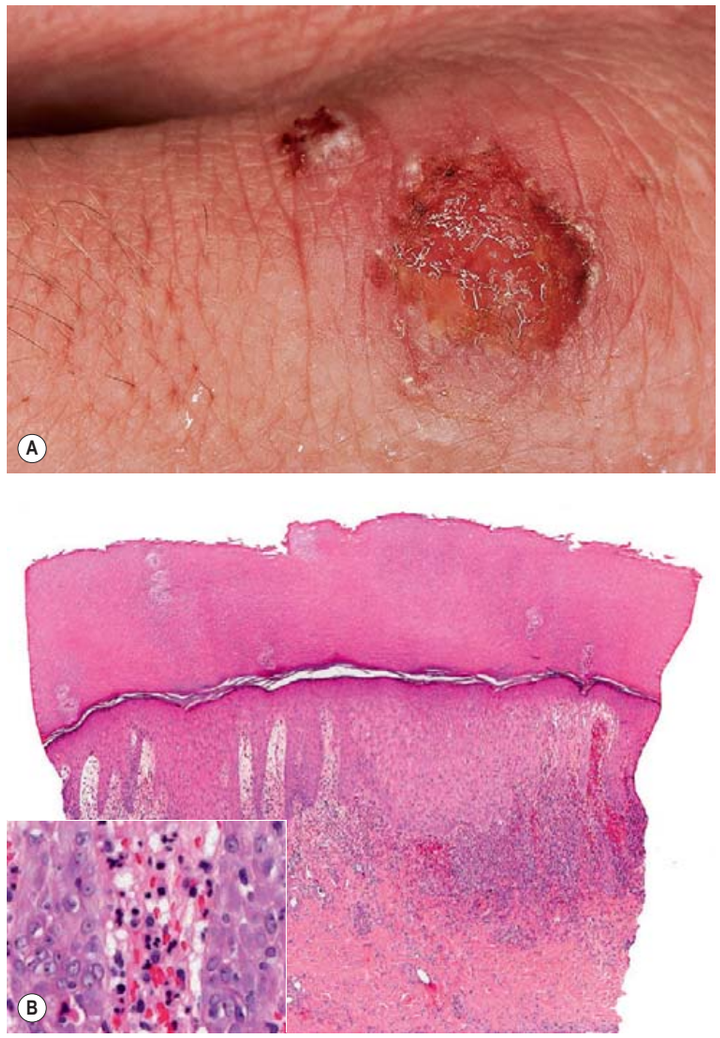


Fig. 81.12 Orf. A Vesiculopustule and ulceration on the finger. **B** Histology showing epidermal necrosis, vacuolated keratinocytes and intracytoplasmic inclusion bodies (insert). *B, Courtesy, Lorenzo Cerroni, MD.*

annulare and pyogenic granuloma. In immunocompromised hosts, infectious processes such as cryptococcosis or histoplasmosis can mimic MC. Inflammatory reactions to molluscum may resemble nummular dermatitis, staphylococcal furunculosis, Gianotti–Crosti syndrome or ULTE. Histologic evaluation of an MC lesion reveals large, intracytoplasmic inclusion bodies (molluscum bodies or Henderson–Patterson bodies, Fig. 81.13E) within epidermal keratinocytes, which increase in size as they move toward the skin surface.

MC resolves spontaneously in immunocompetent children, with the time interval between onset and clearance of the lesions ranging from several months to several years. However, treatment may be requested when there are numerous or cosmetically significant lesions. Therapeutic options include curettage, manual expression, cryotherapy, chemovesicants, and topical agents such as keratolytics, imiquimod and cidofovir (Table 81.6). In children, application of cantharidin (see Ch. 129) is a safe and reasonably effective treatment that has the benefit of non-traumatic in-office application. However, it may require more visits than curettage[46]. Treatment of molluscum dermatitis with a topical corticosteroid may help to reduce associated pruritus and prevent autoinoculation from scratching.

VIRAL HEMORRHAGIC FEVERS, INCLUDING DENGUE

The hemorrhagic fevers are a group of zoonotic viral infections that range in severity from a mild, self-limited febrile illness to a severe, life-threatening disease. Cutaneous manifestations of the hemorrhagic fevers are nonspecific and include petechiae, purpura and mucosal hemorrhage. Patients with serious infections suffer from shock, bleeding and multiorgan failure, with a high mortality rate. Viral hemorrhagic fevers are most common in South America and Africa, although a worldwide distribution is seen with some of the agents. In the US, hantavirus can cause an illness marked by respiratory failure and

COMPARISON OF VARICELLA/DISSEMINATED ZOSTER TO SMALLPOX		
	Varicella/disseminated zoster	**Smallpox**
Prodrome	None or mild fever and malaise	Fever ≥101°F* for 1 to 4 days prior to onset of eruption, plus prostration, headache, chills, backache and/or gastroinestinal symptoms
Distribution of lesions	Face/scalp initially; trunk affected more than distal extremities May have an enanthem	Lesions concentrated on face and limbs; can progress to involve entire body surface Enanthem often precedes cutaneous eruption
Stage of lesions	Different stages (papules, vesicles, pustules) are seen simultaneously in any one area of the skin	Adjacent lesions are all at same stage of development (synchronous)
Type of lesions	Relatively superficial, with evolution from macules/papules to vesicles to pustules	Begin as papulovesicles and then become firm, deep-seated pustules with a tendency to confluence
Course	Lesions tend to appear in crops over a 3-day period	Lesions spread over 1–2 weeks, and crusting develops over 1 week
Scarring	Rare in uncomplicated cases	Common and marked

*38.3°C.

Table 81.5 Comparison of varicella/disseminated zoster to smallpox.

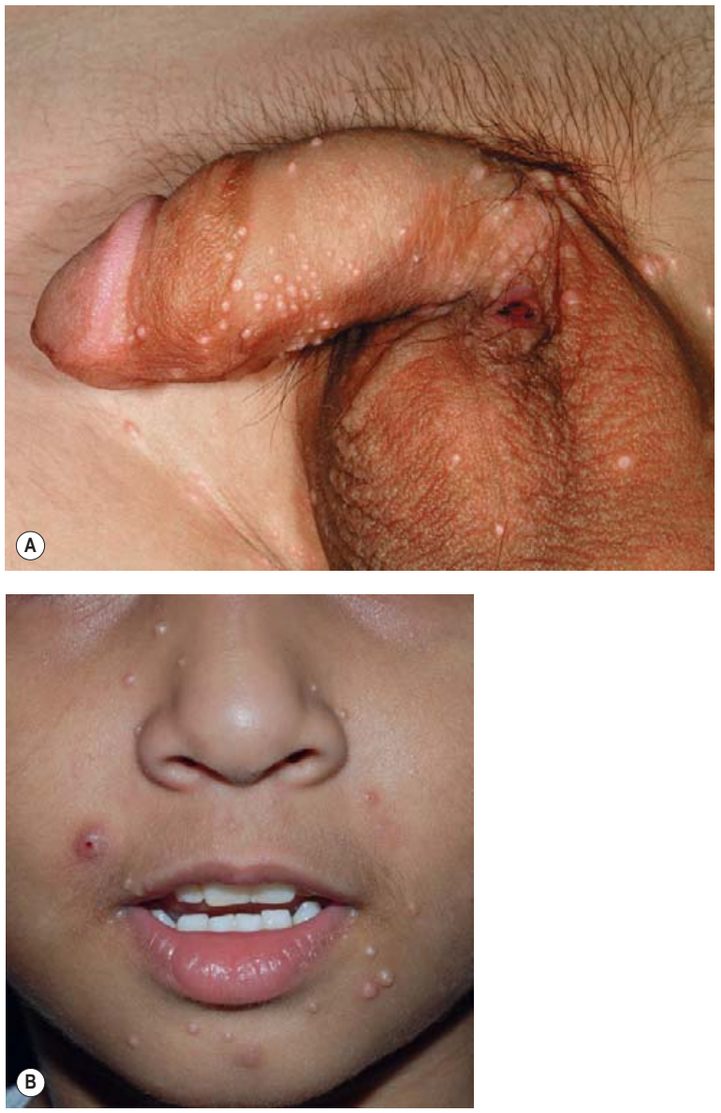


Fig. 81.13 Molluscum contagiosum. Multiple pearly, umbilicated papules in the genital area (**A**) and on the face (**B**); note the inflamed lesion on the right cheek. Inflammatory reactions are a sign of the host immune response to the virus. *B, Courtesy, Julie V Schaffer, MD.*

Continued

cardiovascular collapse, but thrombocytopenia is not as prominent a feature as in Old World hantavirus infections. Table 81.7 lists the epidemiologic characteristics of several of these disorders, while dengue is discussed separately below.

Dengue, including dengue hemorrhagic fever (DHF), is a febrile illness caused by the dengue virus, of which there are four distinct serotypes: DENV-1, -2, -3 and -4. These viruses are members of the Flaviviridae family, and infection is transmitted to humans by mosquitoes. In endemic areas (Fig. 81.14), the virus can be transmitted vertically (i.e. from mother to fetus)[47]. Epidemics may occur when the virus is introduced into a new geographic area by travelers.

Each of the four dengue viruses has a spectrum of manifestations ranging from asymptomatic infection to potentially lethal disease[48]. After an incubation period of 3–8 days, affected individuals develop a biphasic fever, headaches, myalgias, nausea, vomiting and retro-orbital pain. A cutaneous eruption is present in up to 50% of patients; it may be morbilliform or scarlatiniform, with some areas of sparing ("white islands in a sea of red"). Minor hemorrhagic manifestations can occur, including petechiae, epistaxis and gingival bleeding; severe hemorrhage is rare[49]. DHF, the more serious variant of this viral infection, may be more common following reinfection with a second serotype of the virus. Dengue shock syndrome (DSS) with cardiovascular collapse rarely occurs. The diagnosis of DHF or DSS can be confirmed by recovery of the virus in culture, serologic assays or PCR analysis. No specific therapy exists for dengue, but with intensive supportive care the mortality rate can be decreased to 1%[49].

WEST NILE VIRUS INFECTION

West Nile virus (WNV), a single-stranded RNA virus in the Flaviviridae family, is an enzoonotic agent most commonly found in Africa, Europe and Asia. It is transmitted among wild birds (especially crows, ravens and jays) by *Culex* mosquitos. In the past decade, outbreaks of human disease have occurred, and since 1999 there has been geographic expansion of the virus within the US; human cases have been reported in all of the contiguous states, with >1000 deaths to date[50–52]. Although transmitted primarily by mosquito bites, transmission can also occur via blood transfusions, solid organ transplantation, and possibly breastfeeding[53,54].

West Nile virus infection most commonly occurs between late spring and early fall, during periods of active mosquito feeding. Approximately 80% of infections are clinically asymptomatic. In symptomatic patients, manifestations include fever, headache, malaise, anorexia, nausea, vomiting, eye pain, lymphadenopathy, encephalitis, myalgias and muscle weakness; the latter can sometimes be quite severe. Older patients have a higher risk of developing more severe neurologic disease.

An exanthem occurs in up to 25% of patients with West Nile virus infection. It has been described as a nonspecific macular, papular and erythematous eruption[53]. Both predominance on the extremities and small punctate lesions have been described. The diagnosis is confirmed by serum or cerebrospinal fluid IgM ELISA. Treatment is supportive; preventive measures include reducing the number of vector mosquitoes and avoidance of mosquito bites.

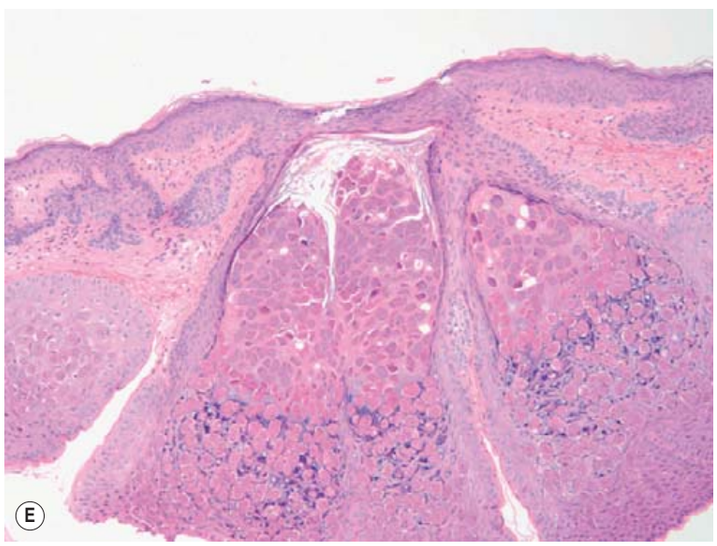


Fig. 81.13 Molluscum contagiosum (cont'd). C Inflamed lesions surrounded by "molluscum dermatitis". **D** Furuncle-like presentation of an inflamed molluscum. A culture revealed only normal skin flora. **E** Histologic evaluation shows numerous molluscum bodies. Demonstrating these bodies in a saline preparation of expressed lesional contents serves as a technique for bedside diagnosis. *D, Courtesy, Julie V Schaffer, MD. E, Courtesy Marjan Mirzabeigi, MD.*

TREATMENT OF MOLLUSCUM CONTAGIOSUM
NO THERAPY
Eventual spontaneous involution in immunocompetent patients Risks of spread (especially in atopic patients), associated dermatitis and pruritus
PHYSICAL MODALITIES
Cryotherapy (liquid nitrogen) (2) Curettage (1) Electrodesiccation (3) Manual extraction (3)
TOPICAL AND INTRALESIONAL THERAPY
Cantharidin (2) Cidofovir (2) Imiquimod (1) Podophyllotoxin (1) Potassium hydroxide 10% solution (2) Salicylic and lactic acids (2) Retinoids (3) Silver nitrate paste (2) Trichloroacetic acid (1) Candida antigen, intralesional (2) Interferon-α, intralesional (3)
LASER THERAPY
CO_2 (3) Pulsed dye (2)
SYSTEMIC THERAPY
Cidofovir (in HIV-infected patients) (3) Cimetidine (2) Griseofulvin (3) Antiretroviral therapy (in HIV-infected patients) (3) Interferon-α, subcutaneous (3)

Table 81.6 Treatment of molluscum contagiosum. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

CHIKUNGUNYA FEVER

Chikungunya fever is due to the chikungunya virus, a member of the Togaviridae family that has three genotypes (Asian, East African and West African). It is transmitted primarily by infected *Aedes aegypti* and *A. albopictus* mosquitoes. Of concern is the rising incidence and spread of this infection, especially in India, the islands of the Indian Ocean and Southeast Asia; outbreaks have also occurred in Italy and Africa. Like dengue fever, patients develop fever, headache, myalgias, nausea, vomiting and a rash, but there is no associated hemorrhagic component or shock syndrome. Cutaneous manifestations include morbilliform eruptions; acral or facial (sometimes localized to the nose) erythema and edema; genital, intertriginous and oral ulcers; and prominent postinflammatory hyperpigmentation on the face and extremities (including freckle-like macules, flagellate streaks and diffuse areas of involvement)[55]. Widespread vesiculobullous eruptions are common in infants and occasionally occur in older children and adults[56]. Severe low back pain and debilitating arthralgia are characteristic, and the latter may last for weeks to months. No specific treatment is available.

BARMAH FOREST AND ROSS RIVER VIRUS INFECTIONS

Like the chikungunya virus, Barmah Forest and Ross River viruses are members of the Togaviridae family that are transmitted to humans by *Aedes* mosquitoes[57,58]. Both Barmah Forest and Ross River virus infections are endemic in Australia. Patients present with fever, lethargy, myalgias and arthralgias. Arthritis represents a common feature of Ross River virus infection, whereas an exanthem is a more frequent manifestation of Barmah Forest virus infection (occurring in up to 90% of patients). The rash often begins with facial erythema and edema (especially of the nose and ears), which is followed by a macular,

EPIDEMIOLOGIC CHARACTERISTICS OF THE MOST IMPORTANT VIRAL HEMORRHAGIC FEVERS								
	Arenaviruses*		**Filoviruses**		**Bunyaviruses**			**Flaviviruses**
	Lassa virus	**Junin, Machupo, Guanarito, Sabia viruses**	**Ebola virus†**	**Marburg virus†**	**Hantavirus**	**Crimean-Congo fever virus†**	**Rift Valley fever virus**	**Yellow fever virus**
Geography	West Africa	South America, North America	Central and West Africa	East and Central Africa	Worldwide	Europe, Asia, Africa	Africa	South America and Africa
Primary source of infection	Rodent (*Mastomys natalensis*)	Rodent (*Calomys* and *Zygodontomys* spp.)	Unknown, possibly bats		Rodents; species depends upon location	Tick-bome (>27 species)	Mosquito	Mosquito-borne (*Aedes* and *Haemagogus* spp.)
Transmission	Nosocomial; rodent to human; person-to-person	Rodent to human	Nosocomial; possibly reservoir to human; person-to-person; also infected chimps and possibly monkeys can transmit to humans		Rodent to human	Nosocomial; tick to human; possibly animal to human; person-to-person	Mosquito to human; possibly animal to human via blood	Mosquito to human (human reservoir in outbreaks)
Risk factors	Close contact with *Mastomys* in rural West Africa; close contact with infected persons	Contact with rodents in certain agricultural areas of South America, possibly North America	Close contact with infected blood or secretions from infected persons; environmental risk unknown (possibly caves for Marburg)		Contact with rodent or rodent urine in dust; laboratory work with rodents	Tick bites; contact with infected livestock; contact with blood or secretions from infected people	Mosquito bites in rural Africa	Mosquito bites in rural West Africa and South American rainforests
Treatment	Responds to ribavirin when treated early	Junin responds to immune plasma given early; all may respond to ribavirin	No treatment; does not respond to ribavirin		Ribavirin may be beneficial early – trial and current use in China; open-label trial in US for acute pulmonary disease was inconclusive	Sensitive to ribavirin; several published reports of successful case treatment	Sensitive to ribavirin; limited data in monkeys; no human data	No therapy; does not respond to ribavirin
Vaccine	Vaccinia vectored glycoprotein vaccine protects primates; human vaccine under development	Attenuated vaccine to Junin virus has greatly reduced cases in Argentina; no vaccine available for others	Vaccine protective in primate studies	Vaccine protective in primate studies	M gene DNA vaccine expressing glycoproteins 1 and 2 protects small animals from challenge and elicits neutralizing antibodies in monkeys; also formalin-inactivated vaccine; studies in humans in Asia	Killed vaccine available in Eastern Europe and China, with no published trials but epidemiologic evidence of efficacy	Attenuated vaccine for animals; human vaccine under development	Live attenuated vaccine since 1940s; one of the most effective vaccines ever
Prevention	Avoid rodents	Avoid rodents	Unknown		Avoid rodents	Avoid ticks	Prevent mosquito bites	Prevent mosquito bites

*Arenaviruses have been isolated from wood rats in the southwestern USA – their capacity to cause human disease is uncertain.
†Ecchymoses most prominent in these infections.

Table 81.7 Epidemiologic characteristics of the most important viral hemorrhagic fevers. See text for discussion of dengue. *Adapted with permission from Cohen J, Powderly WG. Infectious Diseases, 2nd edn, 2004, Mosby, St Louis, with permission from Elsevier.*

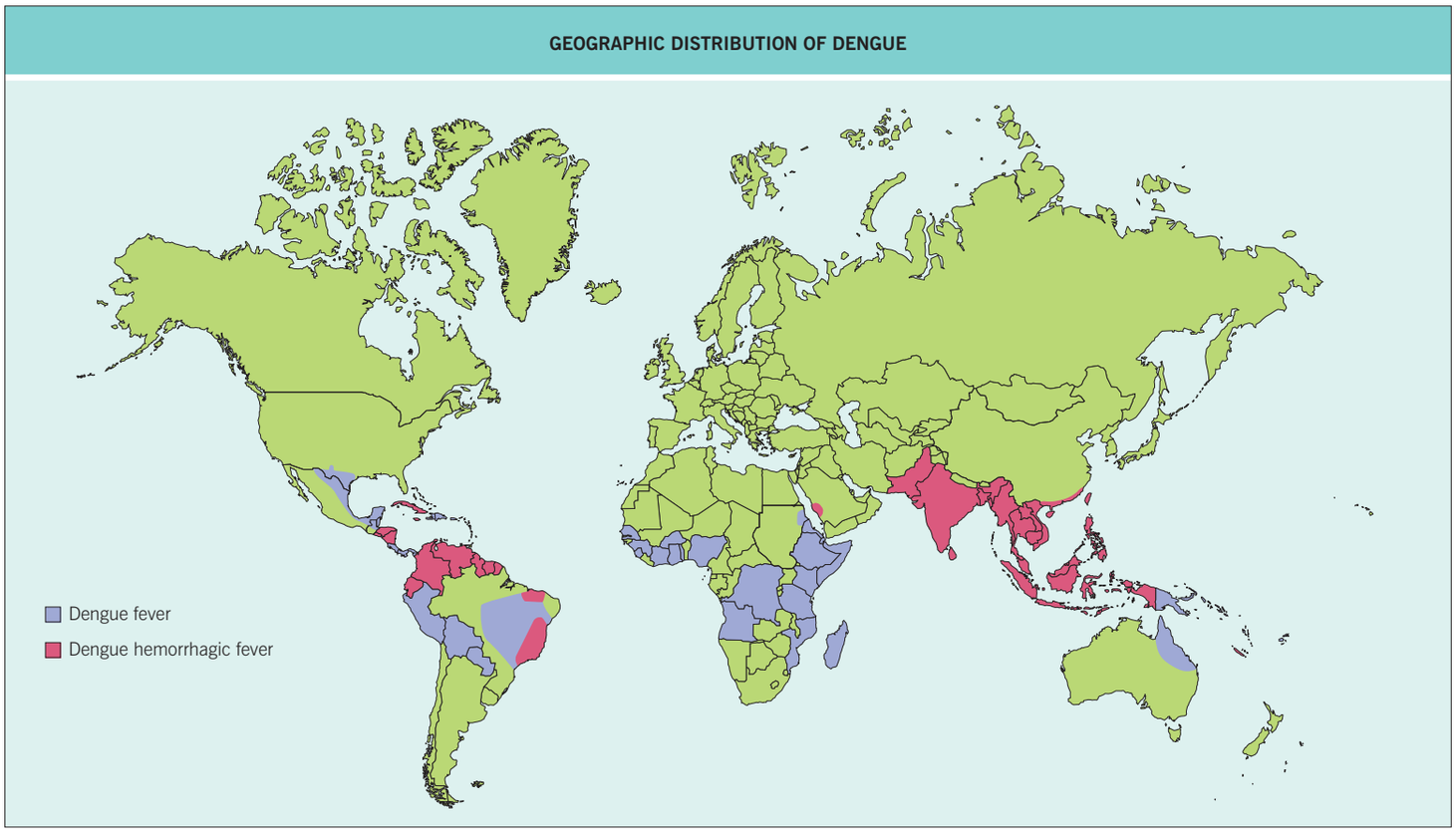


Fig. 81.14 Geographic distribution of dengue. Climate change has been postulated as a factor in expansion of the geographic distribution of dengue in the Americas. *Reprinted from Cohen J, Powderly WG. Infectious Diseases, 2nd edn, 2004, Mosby, St Louis, with permission from Elsevier.*

maculopapular, vesicular or purpuric eruption in a widespread distribution on the trunk and extremities. The diagnosis of either condition can be made by detection of specific antibodies via ELISA.

RABIES

Rabies is an acute viral disease that involves the CNS, can affect all mammals, and is transmitted by infected secretions. Most human exposures to rabies are via the bite of an infected animal, usually dogs in low-income countries and insect-eating bats in the US[59]. The etiologic agent is a neurotropic RNA virus belonging to the genus *Lyssavirus*. Following a bite, virus is inoculated into muscle and subcutaneous tissues, where it replicates locally. It then invades peripheral nerves, where it travels to the CNS (Fig. 81.15); the mean incubation period is 30–90 days, but it varies considerably and is shorter for a large inoculum via bites/lacerations in the head/neck region. Clinical features include prodromal flu-like symptoms followed by acute neurologic findings, either encephalitic (including hypersalivation and hydrophobia) or paralytic[60]. Rabies is nearly uniformly fatal, with death occurring within a few days of symptom onset. The diagnosis is confirmed by detection of rabies virus antigen in corneal smears or nuchal skin or brain biopsy specimens; PCR studies of saliva, skin and cerebrospinal fluid can also be performed to detect rabies virus RNA[59]. Post-exposure prophylaxis (consisting of wound cleansing, vaccination and administration of rabies immune globulin) is recommended for individuals exposed to the virus, and pre-exposure vaccination is recommended for those at high risk of rabies exposure[61].

CUTANEOUS MANIFESTATIONS OF HEPATITIS A, B AND C INFECTION

Infections with hepatitis A, B and C viruses (especially the latter two) are associated with a variety of cutaneous manifestations. Infections with hepatitis A, an RNA enterovirus, occasionally lead to cutaneous findings such as panniculitis, urticaria and a scarlet fever-like exanthem[62], whereas infections with hepatitis B and C viruses have been linked to the entities listed in Table 81.8.

CUTANEOUS MANIFESTATIONS OF HEPATITIS B AND/OR C INFECTION	
Small vessel vasculitis (B, C)	Necrolytic acral erythema (C)
Cryoglobulinemic vasculitis (C>B)	Porphyria cutanea tarda (B, C)
Urticarial vasculitis (B, C)	Pruritus (B, C)
Polyarteritis nodosa (B [classic]>C)	Lichen planus – particularly erosive oral disease (C)
Livedo reticularis (C)	Sarcoidosis (with interferon and/or ribavirin therapy; C>B)
Serum sickness-like reaction (B, C)	Erythema multiforme (B, C)
Urticaria (B, C)	Erythema nodosum (B>C)
Gianotti–Crosti syndrome (B>C)	

Table 81.8 Cutaneous manifestations of hepatitis B and/or C infection.

VIRAL-ASSOCIATED TRICHODYSPLASIA OF IMMUNOSUPPRESSION

Synonyms: ■ "Cyclosporine-induced" folliculodystrophy ■ Follicular dystrophy of immunosuppression ■ Pilomatrix dysplasia ■ Trichodysplasia of immunosuppression ■ (Viral-associated) trichodysplasia spinulosa ■ Viral-associated trichodysplasia

Viral-associated trichodysplasia is an increasingly recognized entity that was first described in 1999[63] and subsequently found to be associated with a novel polyomavirus[64]. More than 20 cases have been reported to date, all occurring in solid organ transplant recipients receiving immunosuppressive medications or in patients undergoing chemotherapy for a leukemia or lymphoma. Affected individuals present with numerous erythematous to skin-colored papules with a central spiny

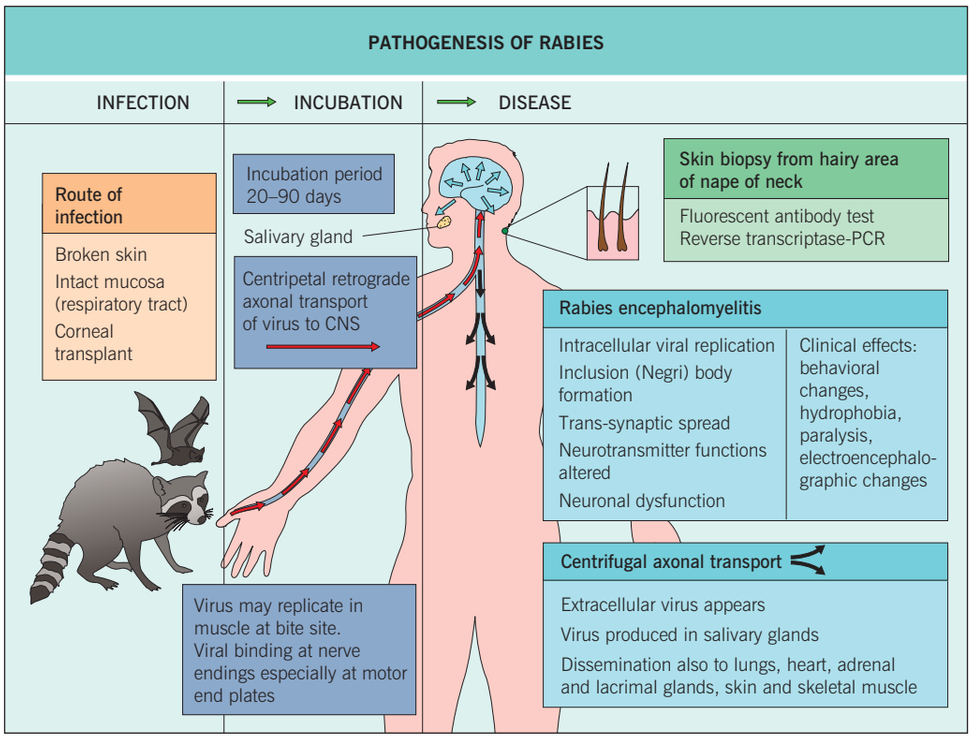


Fig. 81.15 Pathogenesis of rabies. *Reprinted from Cohen J, Powderly WG.Infectious Diseases, 2nd edn, 2004, Mosby, St Louis, with permission from Elsevier.*

projection on the face (especially the mid portion), ears, and (less often) extremities and trunk. Associated alopecia (of the eyebrows and eyelashes > other facial and body hair) and thickening of the skin resulting in a leonine appearance may also develop. Histologic evaluation shows distended follicles with abnormal maturation and a proliferation of nucleated eosinophilic cells with numerous large trichohyalin granules and abrupt inner root sheath-type cornification[65]. Electron microscopy demonstrates intranuclear icosahedral viral particles. The condition may improve following reduction or discontinuation of immunosuppressive medications, and successful treatment with topical cidofovir and oral valganciclovir has been described.

KAWASAKI DISEASE

Synonym: ■ Mucocutaneous lymph node syndrome

Key features

- Fever, conjunctival injection, oral mucosal changes, acral swelling and cervical lymphadenopathy
- Polymorphous exanthem, often with early perineal involvement
- Represents the most common cause of acquired heart disease in children in the US

Introduction and History

Kawasaki disease (KD) is an acute febrile multisystem disease that primarily affects children under 5 years of age. Initially described by Kawasaki in Japanese children[66], KD has subsequently been reported worldwide, and in the US it represents the leading cause of acquired heart disease in the pediatric population. Coronary artery aneurysms or ectasias develop in 15–25% of untreated KD patients, resulting in substantial morbidity and mortality. The clinical manifestations of KD can mimic a variety of other diseases, in particular viral exanthems, and the need to promptly treat KD in order to prevent potentially life-threatening complications makes differentiation among these entities essential.

Epidemiology

The peak incidence of KD is in children 2 years of age and younger, and 85% of patients with KD are <5 years of age; however, adults with KD have also been reported. The condition is 1.5 times more common in boys than in girls[67]. A peak incidence in late winter to early spring has been observed in North America. Epidemics have occurred in both Japan and the US and are characterized by a wave-like spread over a 2- to 4-year period[68]. KD is more common in children of Asian descent. Male gender and an age of <1 year or >6 years appear to be risk factors for the development of cardiovascular sequelae, which may be related to delayed diagnosis in the latter group[69].

Pathogenesis

The etiology of KD remains unknown, but several observations suggest an infectious cause, including the clinical features, seasonal variation in incidence, community outbreaks, rarity in infants under 6 months of age (who have potentially protective maternal antibodies), and infrequent recurrences[67]. However, conventional microbial cultures and serologic studies have failed to identify a causative agent. A pathogenic role for a bacterial toxin that acts as a superantigen has been hypothesized; although this remains unproven, it is supported by the increased prevalence of superantigen-encoded genes in the stool of KD patients compared to other febrile or healthy children[70].

In fatal cases of KD, IgA-producing plasma cells have been found in the coronary arteries, pancreas, kidney and upper respiratory tract; the latter finding is similar to that seen in children with fatal respiratory viral infections[71]. Oligoclonal KD antibodies synthesized *in vitro* have been shown to bind to cytoplasmic antigen in the proximal bronchial epithelium, coronary arteries and (in some tissues) macrophages of KD patients. Furthermore, electron microscopic studies have provided evidence of virus-like particles within intracellular inclusion bodies in the ciliated bronchial epithelium of patients with KD[72]. These findings are suggestive of a respiratory infectious agent with tropism for vascular tissue.

KD is characterized by marked activation of the immune system, with increased numbers of activated lymphocytes (both T and B) and mononuclear cells as well as increased levels of proinflammatory cytokines. A functional polymorphism in the inositol 1,4,5-trisphosphate 3-kinase C gene (*ITPKC*) has been shown to be significantly associated

with KD susceptibility and an increased risk of coronary artery lesions in children from the US and Japan. ITPKC acts as a negative regulator of T-cell activation through the nuclear factor of activated T cells (NFAT) signaling pathway, and the polymorphism (which reduces the efficiency of ITPKC splicing) may contribute to immune hyperreactivity in Kawasaki disease[73].

Clinical Features and Differential Diagnosis

The diagnostic criteria for KD include fever lasting at least 5 days plus the presence of four of the five following criteria:

- bilateral non-purulent conjunctival injection
- oropharyngeal changes including diffuse hyperemia, strawberry tongue and lip fissures
- cervical lymphadenopathy (usually unilateral)
- peripheral extremity changes including erythema, edema and (eventually) desquamation of the hands and feet
- a polymorphous exanthem.

The diagnosis of KD should be strongly considered in any child presenting with prolonged, unexplained fever in association with skin findings. The fever in KD is usually high-spiking (>39°C; 102°F), and it may not respond to antipyretics[67].

A cutaneous eruption is seen in >80% of patients with KD. It is usually composed of macular and papular erythematous lesions, often in a morbilliform pattern, but may also be erythema multiforme-like (Fig. 81.16A), urticarial, scarlatiniform or pustular. Vesiculobullous lesions, crusting and petechiae are all unusual in the exanthem of KD. In some patients, ulceration at the site of a bacillus Calmette-Guérin (BCG) vaccination has been observed during the course of the disease. A characteristic early cutaneous finding is erythema of the perineum, which often desquamates within 48 hours (Fig. 81.16A–C). Edema and brawny induration of the hands and feet are common early in the course of the disease (Fig. 81.6D), with eventual desquamation that is prominent in the periungual regions. Gangrene of the peripheral extremities occasionally occurs.

The conjunctival injection of KD is typically bulbar with sparing of the limbus (an avascular zone around the iris); it is not associated with increased tearing or an exudate. Keratitis and photophobia are uncommon and should suggest an alternative diagnosis. Oropharyngeal changes consist of dry, fissured lips, a "strawberry tongue" (Fig. 81.17) and (in some patients) diffuse hyperemia of the oral mucous membranes.

Cardiac involvement can include myocarditis, pericardial effusions, congestive heart failure and coronary aneurysms; the latter represent the source of greatest morbidity in KD. Valvular disease (usually mitral or aortic) may also occur. Tachycardia, murmurs, gallops or distant heart sounds may be noted on cardiac examination. Other possible sites of involvement include the CNS (extreme irritability, aseptic meningitis, cranial nerve palsies, sensorineural hearing loss), gastrointestinal tract (abdominal pain, diarrhea, hepatic dysfunction, obstructive jaundice, gallbladder hydrops), musculoskeletal system (arthralgias, arthritis) and the genitourinary tract (urethritis, meatitis, sterile pyuria).

"Incomplete" (sometimes called "atypical") KD may be diagnosed in patients with prolonged fever plus coronary artery disease (detected by echocardiography or coronary angiography) but fewer than four additional criteria (see above)[68,74]. This presentation tends to be more

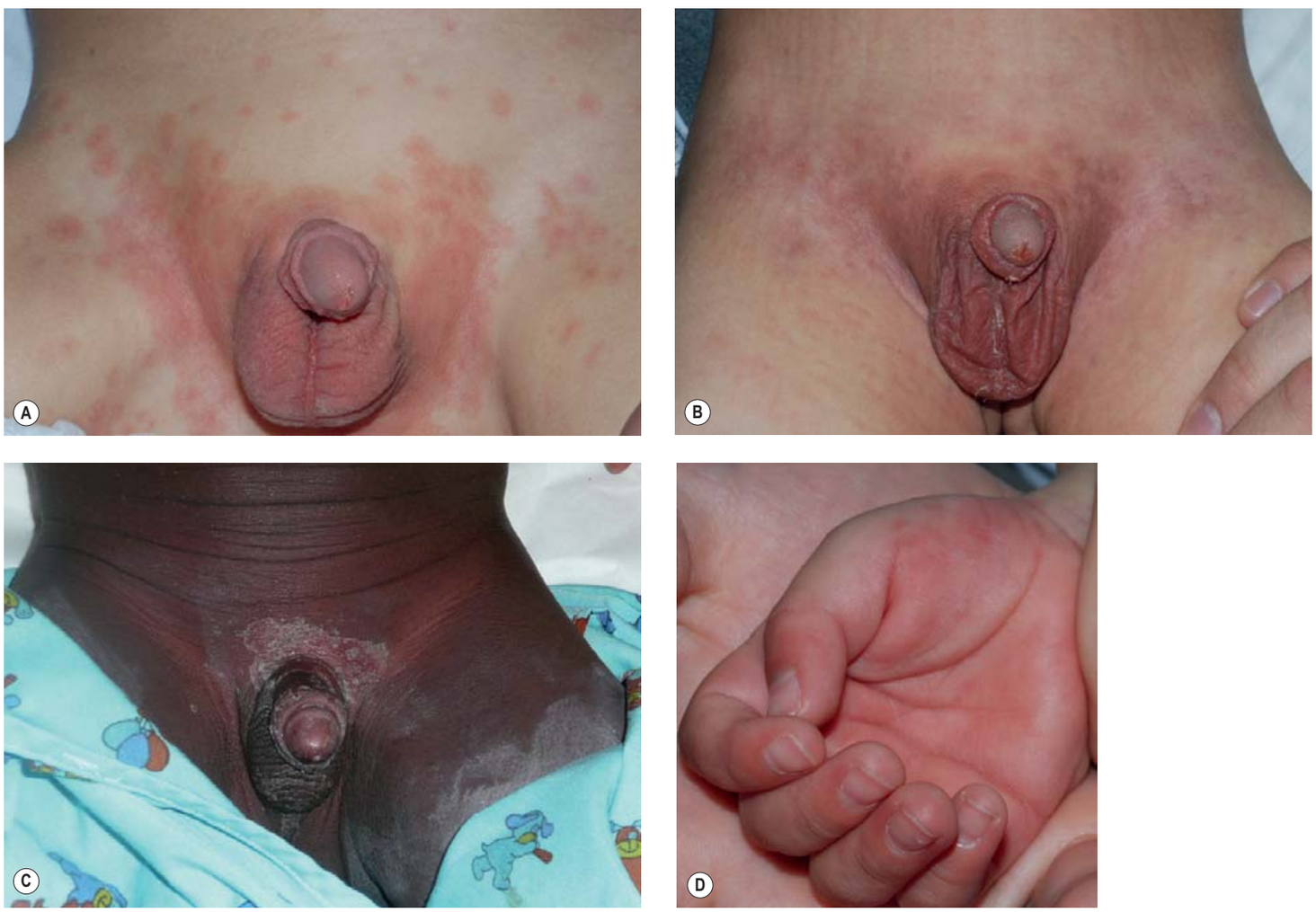


Fig. 81.16 Kawasaki disease. Erythema multiforme-like lesions becoming confluent in the perineal region on the second day of fever (**A**), followed by desquamation 2 days later (**B**). **C** Erythema (less evident due to the patient's darkly pigmented skin) and desquamation in the genital area. Involvement of the skin in this location is a characteristic early finding in Kawasaki disease. **D** Erythema and edema of the palm early in the disease course. *Courtesy, Julie V Schaffer, MD.*

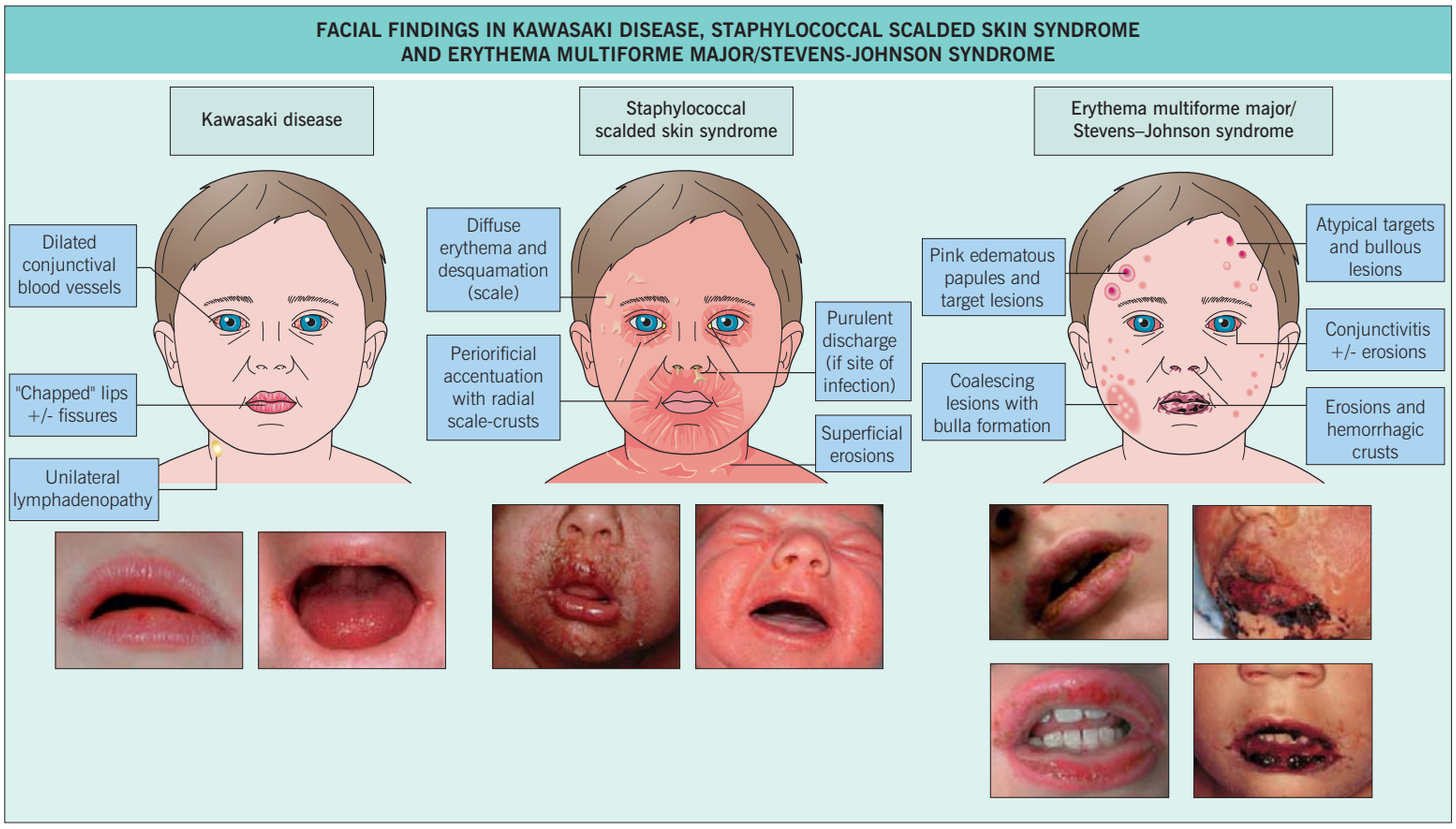


Fig. 81.17 Facial findings in Kawasaki disease, staphylococcal scalded skin syndrome and erythema multiforme major/Stevens–Johnson syndrome. Hemorrhagic crusting and erosions of the vermilion portion of the lips can also be seen in primary gingivostomatitis due to herpes simplex virus, pemphigus vulgaris and paraneoplastic pemphigus.

common in infants, and the diagnosis may be quite difficult to establish. In the child with prolonged fever, some diagnostic features of KD and laboratory evidence of an inflammatory process, KD should be strongly considered. An algorithm for evaluation of suspected incomplete KD has been proposed[74].

Laboratory findings in patients with KD include elevation of the white blood cell count (with neutrophil predominance), acute inflammatory markers (CRP, ESR) and hepatic transaminases, as well as hypoalbuminemia, sterile pyuria, anemia and (less often) thrombocytopenia. By the second to third week of illness, thrombocytosis is often present. Electrocardiographic findings include decreased R-wave voltage, ST-segment depression, and T-wave flattening or inversion.

The differential diagnosis of KD includes viral exanthems (e.g. measles, adenovirus), scarlet fever, toxic shock syndrome, staphylococcal scalded skin syndrome, erythema multiforme, a drug eruption, serum sickness-like reaction, systemic-onset juvenile inflammatory arthritis, infantile polyarthritis nodosa and periodic fever syndromes. Figure 81.17 shows the facial findings that differentiate KD from staphylococcal scalded skin syndrome and erythema multiforme major.

Pathology

Histologic findings are nonspecific and include dermal edema and a perivascular mononuclear infiltrate[68].

Treatment

During its acute phase, the treatment for KD is aimed at decreasing inflammation, and the current first-line therapy is IVIg administered in a single infusion of 2 g/kg over 10–12 hours. This regimen was demonstrated to be more efficacious in preventing coronary aneurysms than the prior recommendation of multiple daily infusions[75]. However, the mechanism of action of IVIg in the treatment of KD is unknown. With the utilization of IVIg, the incidence of coronary aneurysms decreases from 25% to ≤5–10%, and mortality from 2% to 0.3%. Aspirin is also recommended for the treatment of KD during its acute phase, with initial administration of 80–100 mg/kg daily divided into four doses (for 14 days or until afebrile for 48–72 hours), followed by a maintenance dosage of 3–5 mg/kg daily (usually for 6 to 8 weeks)[74].

Approximately 10–20% of children with KD have persistent or recrudescent fevers after receiving a single dose of IVIg. A second dose of IVIg may be given to patients who fail to become afebrile within 24–48 hours after completion of the first dose. Management options for refractory KD also include corticosteroids and infliximab[76–78]. One large randomized, double-blind trial found that initial treatment with pulsed corticosteroids plus conventional therapy (IVIg and aspirin) showed no benefit over conventional therapy alone in terms of hospital days, days of fever, rates of retreatment with IVIg or adverse events[79]. However, a recent randomized controlled study found that the addition of pulsed corticosteroids to initial IVIg therapy in patients at high risk of having refractory KD was associated with fewer days of fever and a lower likelihood of coronary artery dilation[79a]. Recent studies have shown that infliximab is well tolerated and effective (equally or more so than a second dose of IVIg) in the treatment of pediatric patients with IVIg-resistant Kawasaki disease[78,80].

Long-term cardiac follow-up of KD patients is recommended, as adults with a history of KD may have vascular endothelial dysfunction and an increased risk for early-onset atherosclerosis.

REFERENCES

1. Cherry JD. Enteroviruses: polioviruses (poliomyelitis), coxsackieviruses, echoviruses and enteroviruses. In: Feigin RD, Cherry JD (eds). Textbook of Pediatric Infectious Diseases. Philadelphia: WB Saunders, 1998:1787–838.
2. Davia JL, Bel PH, Ninet VZ, et al. Onychomadesis outbreak in Valencia, Spain associated with hand, foot, and mouth disease caused by enteroviruses. Pediatr Dermatol. 2011;28:1–5.
3. Solomon T, Lewthwaite P, Perera D, et al. Virology, epidemiology, pathogenesis, and control of enterovirus 71. Lancet Infect Dis. 2010;10:778–90.
4. Syriopoulou VP, Hadjichristodoulou CH, Daikos GL, et al. Clinical and epidemiological aspects of an enterovirus outbreak in a neonatal unit. J Hosp Infect. 2002;51:275–80.
5. Abzug MJ. Presentation, diagnosis, and management of enterovirus infections in neonates. Pediatr Drugs. 2004;6:1–10.
6. Cherry JD, Bobinski JE, Horvath FL, Comerci GD. Acute hemangioma-like lesions associated with ECHO viral infections. Pediatrics. 1969;44:498–502.
7. Prose NS, Tope W, Miller SE, Kamino H. Eruptive pseudoangiomatosis: a unique childhood exanthem? J Am Acad Dermatol. 1993;29:857–9.
8. Rotbart HA, Webster AD. Treatment of potentially lifethreatening enterovirus infections with pleconaril. Clin Infect Dis. 2001;32:228–35.
9. Cutts FT, Henao-Restrepo A, Olive JM. Measles elimination: progress and challenges. Vaccine. 1999;17(suppl. 3):S47–52.
10. Centers for Disease Control and Prevention. Epidemiology of measles – United States, 2001–2003. MMWR Morb Mortal Wkly Rep. 2004;53:713–16.
11. CDC. Measles – United States, January-May 20 2011. MMWR Morb Mortal Wkly Rep. 2011;60:666–8.
12. Davidkin I, Valle M, Peltola H, et al. Etiology of measles-and rubella-like illnesses in measles, mumps, and rubella-vaccinated children. J Infect Dis. 1998;178:1567–70.
13. American Academy of Pediatrics Committee on Infectious Diseases. Recommended childhood and adolescent immunization schedule: United States, 2005. Pediatrics. 2005;115:182.
14. Rosa C. Rubella and rubeola. Semin Perinatol. 1998;22:318–22.
15. Cherry JD. Parvovirus infections in children and adults. Adv Pediatr. 1999;46:245–69.
16. Brown KE, Hibbs JR, Gallinella G, et al. Resistance to parvovirus B19 infection due to lack of virus receptor (erythrocyte P antigen). N Engl J Med. 1994;330: 1192–6.
17. Balkhy HH, Sabella C, Goldfarb J. Parvovirus: a review. Bull Rheum Dis. 1998;47:4–9.
18. Norbeck O, Papadogiannakis N, Petersson K, et al. Revised clinical presentation of parvovirus B19-associated intrauterine fetal death. Clin Infect Dis. 2002;35:1032–8.
19. Gratacos E, Torres PJ, Vidal J, et al. The incidence of human parvovirus B19 infection during pregnancy and its impact on perinatal outcome. J Infect Dis. 1995;171:1360–3.
20. Miller E, Fairley CK, Cohen BJ, Seng C. Immediate and long term outcome of human parvovirus B19 infection in pregnancy. Br J Obstet Gynaecol. 1998;105:174–8.
21. Young NS, Brown KE. Parvovirus B19. N Engl J Med. 2004;350:586–97.
22. Harms M, Feldmann R, Saurat JH. Papular-purpuric "gloves and socks" syndrome. J Am Acad Dermatol. 1990;23:850–4.
23. Zerr DM, Meier AS, Selke SS, et al. A population-based study of primary human herpesvirus 6 infection. N Engl J Med. 2005;352:768–76.
24. Braun DK, Dominguez G, Pellett PE. Human herpesvirus 6. Clin Microbiol Rev. 1997;10:521–67.
25. Chua KB, Lam SK, AbuBakar S, et al. The predictive value of uvulo-palatoglossal junctional ulcers as an early clinical sign of exanthem subitum due to human herpesvirus 6. J Clin Virol. 2000;17:83–90.
26. Brunner MJ, Rubin L, Dunlap F. A new papular erythema of childhood. Arch Dermatol. 1962;85:539–40.
27. Bodemer C, de Prost Y. Unilateral laterothoracic exanthem in children: a new disease? J Am Acad Dermatol. 1992;27:693–6.
28. Taieb A, Megraud F, Legrain V, et al. Asymmetric periflexural exanthem of childhood. J Am Acad Dermatol. 1993;29:391–3.
29. Duarte AF, Cruz MJ, Baudrier T, et al. Unilateral laterothoracic exanthem and primary Epstein-Barr virus infection: case report. Pediatr Infect Dis J. 2009;28:549–50.
30. Gianotti F, Gianni E. The infantile acrodermatitis syndrome and Epstein-Barr virus infection. Hautarzt. 1985;60:1789–90.
31. Caputo R, Gelmetti C, Ermacora E, et al. Gianotti-Crosti syndrome: a retrospective analysis of 308 cases. J Am Acad Dermatol. 1992;26:207–10.
32. Yoshida M, Tsuda N, Morihata T, et al. Five patients with localized facial eruptions associated with Gianotti-Crosti syndrome caused by primary Epstein-Barr virus infection. J Pediatr. 2004;145:843–4.
33. Chuh AA. Truncal lesions do not exclude a diagnosis of Gianotti-Crosti syndrome. Australas J Dermatol. 2003;44:215–16.
34. Stefanato CM, Goldberg LJ, Andersen WK, Bhawan J. Gianotti-Crosti syndrome presenting as lichenoid dermatitis. Am J Dermatopathol. 2000;22:162–5.
35. Smith KJ, Skelton H. Histopathologic features seen in Gianotti-Crosti syndrome secondary to Epstein-Barr virus. J Am Acad Dermatol. 2000;43:1076–9.
36. Lewis-Jones S. Zoonotic poxvirus infections in humans. Curr Opin Infect Dis. 2004;17: 81–9.
37. Ligon BL. Monkeypox: a review of the history and emergence in the Western hemisphere. Semin Pediatr Infect Dis. 2004;15:280–7.
38. Reed KD, Melski JW, Graham MB, et al. The detection of monkeypox in humans in the Western Hemisphere. N Engl J Med. 2004;350:342–50.
39. Roess AA, Galan A, Kitces E, et al. Novel deer-associated parapoxvirus infection in deer hunters. N Engl J Med. 2010;363:2621–7.
40. Dhar AD, Werchniak AE, Li Y, et al. Tanapox infection in a college student. N Engl J Med. 2004;350:361–6.
41. Casey C, Vellozzi C, Mootrey GT, et al. Surveillance guidelines for smallpox vaccine (vaccinia) adverse reactions. MMWR Recomm Rep. 2006;55:1–16.
42. Gooze LL, Hughes EC. Smallpox. Semin Respir Infect. 2003;18:196–205.
43. Breman JG, Henderson DA. Diagnosis and management of smallpox. N Engl J Med. 2002;346:1300–8.
44. American Academy of Pediatrics Committee on Infectious Diseases. Smallpox vaccine. Pediatrics. 2002;110:841–5.
45. Gottlieb SL, Myskowski PL. Molluscum contagiosum. Int J Dermatol. 1994;33:453–61.
46. Hanna D, Hatami A, Powell J, et al. A prospective randomized trial comparing the efficacy and adverse effects of four recognized treatments of molluscum contagiosum in children. Pediatr Dermatol. 2006;23:574–9.
47. Sirinavin S, Nuntnarumit P, Supapannachart S, et al. Vertical dengue infection: case reports and review. Pediatr Infect Dis J. 2004;23:1042–7.
48. Mairuhu AT, Wagenaar J, Brandjes DP, van Gorp EC. Dengue: an arthropod-borne disease of global importance. Eur J Clin Microbiol Infect Dis. 2004;23:425–33.
49. Ligon BL. Dengue fever and dengue hemorrhagic fever: a review of the history, transmission, treatment, and prevention. Semin Pediatr Infect Dis. 2005;16:60–5.
50. Nash D, Mostashari F, Fine A, et al. The outbreak of West Nile virus infection in the New York City area in 1999. N Engl J Med. 2001;344:1807–14.
51. Petersen LR, Marfin AA. West Nile virus: a primer for the clinician. Ann Intern Med. 2002;137:173–9.
52. Rossi SL, Ross TM, Evans JD. West Nile virus. Clin Lab Med. 2010;30:47–65.
53. Anderson RC, Horn KB, Hoang MP, et al. Punctate exanthem of West Nile Virus infection: report of 3 cases. J Am Acad Dermatol. 2004;51:820–3.
54. Pealer LN, Marfin AA, Petersen LR, et al. Transmission of West Nile virus through blood transfusion in the United States in 2002. N Engl J Med. 2003;349:1236–45.
55. Bandyopadhyay D, Ghosh SK. Mucocutaneous features of Chikungunya fever: a study from an outbreak in West Bengal, India. Int J Dermatol. 2008;47:1148–52.
56. Robin S, Ramful D, Zettor J, et al. Severe bullous skin lesions associated with Chikungunya virus infection in small infants. Eur J Pediatr. 2010;169:67–72.
57. Gould EA, Coutard B, Malet H, et al. Understanding the alphaviruses: recent research on important emerging pathogens and progress towards their control. Antiviral Res. 2010;87:111–24.
58. Russell RC, Dwyer DE. Arboviruses associated with human disease in Australia. Microbes Infect. 2000;2:1693–704.
59. Jackson AC. Update on rabies. Curr Opin Neurol. 2002;15:327–31.
60. Woldehiwet Z. Clinical laboratory advances in the detection of rabies virus. Clin Chim Acta. 2005;351:49–63.
61. Leung AK, Davies HD, Hon KL. Rabies: epidemiology, pathogenesis, and prophylaxis. Adv Ther. 2007;24:1340–7.
62. Parsons ME, Russo GG, Millikan LE. Dermatologic disorders associated with viral hepatitis infections. Int J Dermatol. 1996;35:77–81.
63. Haycox CL, Kim S, Fleckman P, et al. Trichodysplasia spinulosa – a newly described folliculocentric viral infection in an immunocompromised host. J Invest Dermatol Symp Proc. 1999;4:268–71.
64. van der Meijden E, Janssens RW, Lauber C, et al. Discovery of a new human polyomavirus associated with trichodysplasia spinulosa in an immunocompromized patient. PLoS Pathog. 2010;6:e1001024.
65. Sperling LC, Tomaszewski MM, Thomas DA. Viral-associated trichodysplasia in patients who are immunocompromised. J Am Acad Dermatol. 2004;50:318–22.
66. Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes. Arerugi. 1967;16:178–222.
67. Burns JC. Kawasaki disease. Adv Pediatr. 2001;48:157–77.
68. Barron KS. Kawasaki disease in children. Curr Opin Rheumatol. 1998;10:29–37.
69. Muta H, Ishii M, Sakaue T, et al. Older age is a risk factor for the development of cardiovascular sequelae in Kawasaki disease. Pediatrics. 2004;114:751–4.
70. Suenaga T, Suzuki H, Shibuta S, et al. Detection of multiple superantigen genes in stools of patients with Kawasaki disease. J Pediatr. 2009;155:266–70.
71. Rowley AH, Shulman ST, Mask CA, et al. IgA plasma cell infiltration of proximal respiratory tract, pancreas, kidney, and coronary artery in acute Kawasaki disease. J Infect Dis. 2000;182: 1183–91.
72. Rowley AH, Baker SC, Shulman ST, et al. Ultrastructural, immunofluorescence, and RNA evidence support the hypothesis of a "new" virus associated with Kawasaki disease. J Infect Dis. 2011;203:1021–30.
73. Onouchi Y, Gunji T, Burns JC, et al. ITPKC functional polymorphism associated with Kawasaki disease susceptibility and formation of coronary artery aneurysms. Nat Genet. 2008;40:35–42.
74. Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Pediatrics. 2004;114:1708–33.
75. Newburger JW, Takahashi M, Beiser AS, et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. N Engl J Med. 1991;324:1633–9.
76. Shulman ST, Rowley AH. Advances in Kawasaki disease. Eur J Pediatr. 2004;163:285–91.
77. Burns JC, Mason WH, Hauger SB, et al. Infliximab treatment for refractory Kawasaki syndrome. J Pediatr. 2005;146:662–7.
78. Burns JC, Best BM, Mejias A, et al. Infliximab treatment of intravenous immunoglobulin-resistant Kawasaki disease. J Pediatr. 2008;153:833–8.
79. Newburger JW, Sleeper LA, McCrindle BW, et al. Randomized trial of pulsed corticosteroid therapy for primary treatment of Kawasaki disease. N Engl J Med. 2007;356:663–75.

79a. Ogata S, Ogihara Y, Honda T, et al. Corticosteroid pulse combination therapy for refractory Kawasaki disease: a randomized trial. Pediatrics. 2012;129:e17–23.

80. Son MB, Gauvreau K, Burns JC, et al. Infliximab for intravenous immunoglobulin resistance in Kawasaki disease: a retrospective study. J Pediatr. 2011;158:644–9.

This page intentionally left blank

Sexually Transmitted Infections 82

Angelika Stary and Georg Stary

Chapter Contents

Syphilis 1367
Gonorrhea 1379
Chancroid 1383
Lymphogranuloma venereum 1386
Donovanosis (granuloma inguinale) 1387

INTRODUCTION

The term "venereal diseases" was historically used to refer to infections that are sexually transmitted, i.e. syphilis, gonorrhea, chancroid, lymphogranuloma venereum, and granuloma inguinale. These disorders are now referred to as "sexually transmitted diseases" (STDs) or "sexually transmitted infections" (STIs), names that directly reflect recognition that they are caused predominantly by sexual contact with an infected person. For infections caused by pathogens for which non-sexual routes of transmission predominate, e.g. yeasts or cytomegalovirus, the term "sexually transmissible infections" is used. Table 82.1 lists the names of commonly encountered sexually transmitted or transmissible pathogens.

SEXUALLY TRANSMITTED AND TRANSMISSIBLE PATHOGENS	
Bacteria	*Neisseria gonorrhoeae* *Treponema pallidum* *Haemophilus ducreyi* *Chlamydia trachomatis* *Mycoplasma hominis, M. genitalium* *Ureaplasma urealyticum* *Gardnerella vaginalis* *Atopobium vaginae* *Mobiluncus curtisii, M. mulieris* *Klebsiella (Calymmatobacterium) granulomatis* *Shigella* spp. *Campylobacter* spp. *Helicobacter cinaedi, H. fennelliae*
Viruses	Human immunodeficiency virus, types 1 and 2 Herpes simplex virus, types 2 > 1 Human papillomavirus Hepatitis viruses, B > C and (via fecal-oral contact) A Cytomegalovirus Molluscum contagiosum virus Human T-cell leukemia/lymphotrophic virus, types I and II Human herpesvirus, type 8
Protozoa	*Trichomonas vaginalis* *Entamoeba histolytica* *Giardia lamblia*
Fungi	*Candida albicans*
Ectoparasites	*Phthirus pubis* *Sarcoptes scabiei*

Table 82.1 Sexually trans.mitted and transmissible pathogens.

SYPHILIS

Synonym: ■ Lues

Key features

- Syphilis is a sexually acquired, chronic infection caused by *Treponema pallidum* and is characterized by a variety of clinical manifestations
- Syphilis can also be transmitted before birth (congenital)
- It is an intermittently active disease with primary, secondary and tertiary stages as well as a latent period of variable length that occurs before the onset of tertiary syphilis
- Mucocutaneous manifestations vary from genital ulcers to widespread papulosquamous eruptions to granulomatous nodules
- Syphilis facilitates the transmission of HIV, especially in countries with a high rate of both infections

History

Syphilis has been of great historical importance and has played a major role in medicine for over a century. The disease was named after an afflicted shepherd named Syphilus in 1530. Theories on the origin of the disease in the late fifteenth century are controversial. One theory proposes that Christopher Columbus and his crew acquired the disease from Native Americans living in the Caribbean islands and brought it back to a nonimmune population in Europe in 1493, as signs of syphilis have been found in skeletons of pre-Columbian Native Americans[1]. Another theory is that venereal syphilis may have already been endemic but became more widespread and severe as a consequence of the wars at that time in Europe. Lastly, the environmental theory claims that venereal syphilis is a variant of other diseases caused by *Treponema* spp. and became modified by environmental factors, especially temperature[2,3].

Information on the natural course of untreated syphilis (Fig. 82.1) has come primarily from two large studies. The Oslo Study[4] was a prospective investigation of infected, but untreated, individuals conducted between 1890 and 1910, with a follow-up period of 50 years. Approximately one-quarter of infected persons had at least one additional relapse of secondary syphilis, often occurring during the first year (90%). Approximately 15% of infected persons developed benign late syphilis with gummas of the skin (70%), bones (10%) and mucous membranes (10%). Cardiovascular syphilis was reported in approximately 14% of men and 8% of women, while neurosyphilis was observed in 10% of men and 5% of women. Altogether, the study concluded that 17% of men and 8% of women died as a result of untreated syphilis.

The Tuskegee Study was undertaken in 1932 in infected black men, with regular examinations for short- and long-term consequences of untreated infection. This represented a highly unethical investigation, as penicillin treatment was withheld without written consent. The principal finding was an increased mortality rate in the syphilitic group compared to the controls, with an approximately 20% loss-of-life expectancy at an interval of 12 years. Specific lesions of late syphilis were found in about 14% of infected men at the 20-year evaluation, and 12% after 30 years, with cardiovascular syphilis and neurosyphilis representing the primary causes of death[5–7].

Epidemiology

Syphilis is distributed worldwide and is particularly problematic in low-income countries, where it is a leading cause of genital ulcer disease. Worldwide, the rates of primary and secondary syphilis decreased dramatically with the introduction of penicillin treatment after the Second World War. In contrast to Western European countries, an increase in the infection rate was observed during the late 1980s in rural southern and urban regions of the US. Although the number of syphilis cases per year in the US subsequently declined and in 2000 fell to its lowest point since reporting began in 1941, in the past decade the number of primary and secondary syphilis cases diagnosed per year in men has more than doubled (Fig. 82.2). In 2010, the incidence rate of primary and secondary syphilis in the US was 7.9 cases per 100 000 population in men and 1.1 cases per 100 000 population in women. In the US, the incidence in black and Hispanic individuals, as well as in men who have sex with men (MSM), is 5- to 25-fold higher than in other population groups. In a Centers for Disease Control and Prevention (CDC) study of MSM receiving care at STD clinics in eight US cities, rates of syphilis seroreactivity increased from 4% in 1999 to 11% in 2008.

With the resurgence of syphilis in Eastern Europe in the 1990s and migration of sex workers from this region to Western Europe, syphilis has been observed more frequently in Western European countries over the past decade.

Biology of *T. pallidum*

T. pallidum is a member of the genus *Treponema* of the order Spirochaetales, and it was identified in 1905 by Schaudinn and Hoffmann (Table 82.2)[8]. The characteristics of this microorganism are outlined in Table 82.3. Figure 82.3 represents a darkfield photomicrograph of *T. pallidum*.

Pathogenesis of Untreated Syphilis

Syphilis is a chronic systemic infection that progresses through active and latent stages (Fig. 82.4). Inoculation and penetration occurs via mucosal surfaces and abraded skin, followed by attachment to host cells and multiplication of the microorganism. Within a few hours, treponemes disseminate to the regional lymph nodes and internal organs[9].

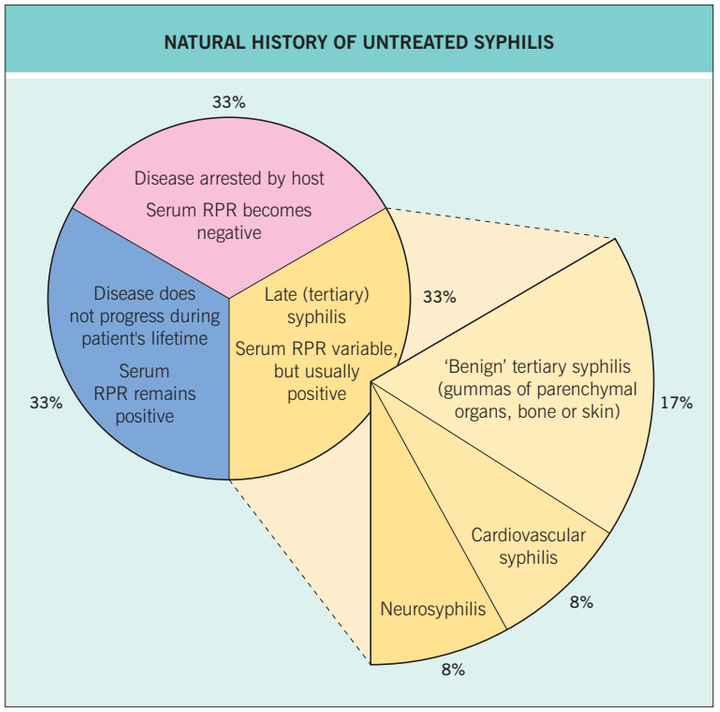


Fig. 82.1 Natural history of untreated syphilis. The data represent a composite of several studies. The specific antibody assays (e.g. MHA-TP) usually remain positive. RPR, rapid plasma reagin.

CLASSIFICATION OF THE SPECIES OF *TREPONEMA*

Order Spirochaetales
Genus *Leptospira*
Genus *Borrelia*
Genus *Treponema*

	Disease	Distribution	Transmission
T. pallidum subsp. *pallidum*	Venereal syphilis	Worldwide	Sexual, congenital (adults, newborns)
T. pallidum subsp. *pertenue*	Yaws	Tropics	Non-venereal (all ages)
T. pallidum subsp. *endemicum*	Endemic syphilis (Bejel)	Desert	Non-venereal (all ages)
T. carateum	Pinta	Tropics	Non-venereal (all ages)
T. denticola, *T. socranskii*	Periodontal disease	Worldwide	Non-venereal

Identical characteristics of organisms within the genus *Treponema*: morphology, antigenic properties, many DNA sequences, serologic detection, biochemical properties.

Different characteristics of organisms within the genus *Treponema*: transmission mode, geography, age of patients, appearance of clinical lesions.

Table 82.2 Classification of the species of *Treponema*.

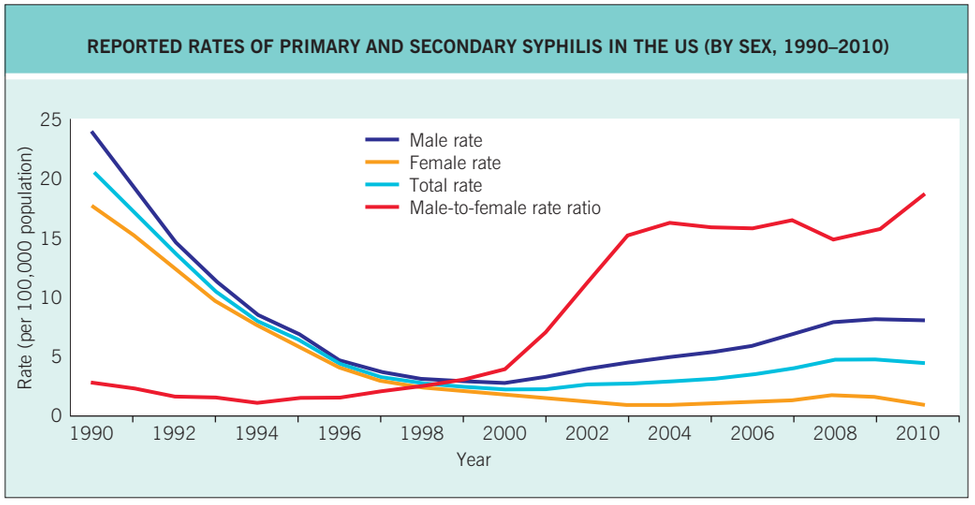


Fig. 82.2 Reported rates of primary and secondary syphilis in the US (by sex, 1990–2010). Note the elevated male : female ratio since 2000.

CHARACTERISTICS OF *TREPONEMA PALLIDUM*
• 6–20 microns in length, 0.1–0.18 microns in diameter
• Regular tight spirals
• Inability to survive outside an animal host
• Cannot be cultured *in vitro* for extended time period
• Limited capacity for DNA repair
• Outer membrane:
– lipid-rich
– contains uniform-sized *t*ransmembrane *r*are *o*uter *m*embrane *p*roteins (TROMP)
– lacks lipopolysaccharide
• Periplasmic flagella

Table 82.3 Characteristics of *Treponema pallidum*.

Fig. 82.3 Positive darkfield examination. Treponemes are recognized by their characteristic corkscrew shape, and deliberate forward and backward movement with rotation about the longitudinal axis. *From Morse et al. Atlas of Sexually Transmitted Diseases and AIDS, 3rd edn. London: Mosby; 2003.*

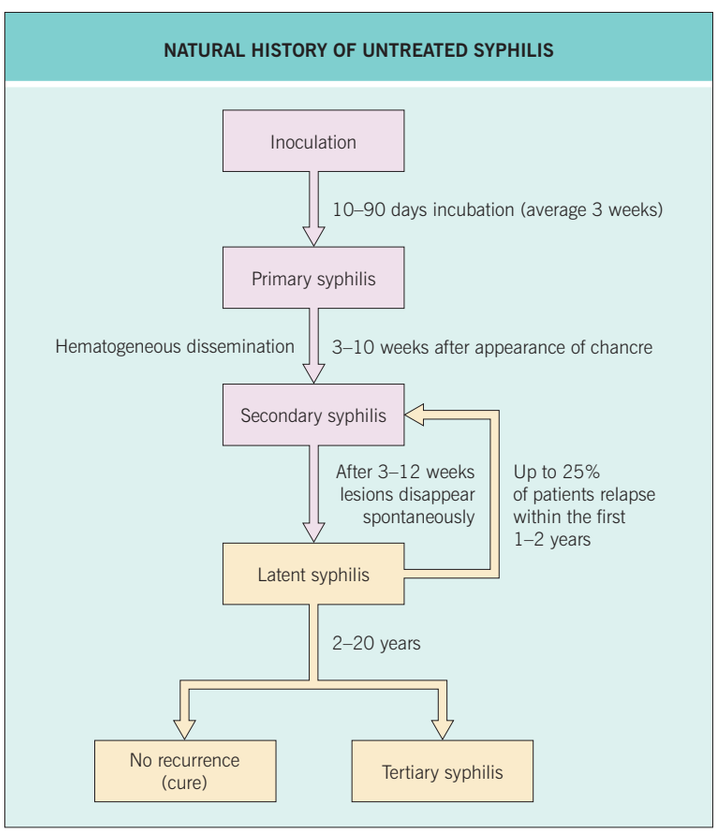


Fig. 82.4 Natural history of untreated syphilis. *Adapted from Rein MF, Musher DM. Late syphilis. In: Rein MF (ed.). Atlas of Infectious Diseases, Vol V: Sexually Transmitted Diseases. New York: Current Medicine, 1995:10.1–10.13.*

Primary stage

The primary lesion develops 10–90 days after infection (median of 3 weeks) as an indolent papule, followed by surface necrosis and the typical well-circumscribed ulceration that is firm to palpation (chancre), as well as enlarged regional lymph nodes. Histopathologically, the microorganism is observed among cells typical of a Th1-predominant cellular response; the latter leads to macrophage activation and destruction of a large number of treponemes. Several pathogenic mechanisms have been proposed, including an antigenically inert treponemal cell surface, resistance to phagocytosis, and premature down-regulation of the local host immune response.

Secondary stage

The secondary stage is characterized by dissemination and multiplication of the microorganism in different tissues, either simultaneously with or up to 6 months after healing of the primary local lesion. This stage follows primary syphilis in almost every patient in the absence of appropriate treatment. Circulating immune complexes (which contain treponemal outer membrane proteins), human fibronectin, antibodies and complement are present during this stage of the disease and play a role in the pathogenesis of the different types of lesions[10].

Secondary syphilis is characterized by a broad spectrum of clinical manifestations involving the skin as well as systemic signs such as malaise, fever and generalized enlargement of the lymph nodes. It lasts several weeks or months, with relapses in approximately 25% of patients. Pregnant women can infect a fetus via transplacental passage of the microorganism.

Latency

Latency is the period between healing of the clinical lesions and appearance of late manifestations, and it can last for many years. About 70% of untreated individuals will remain in this stage for the rest of their lives and are immune to new primary infection. Latent syphilis is divided into early (1 year or less) and late (more than 1 year) subsets, and it is characterized by positive serologic tests for specific antibodies (see below) without clinical signs or symptoms. Infectivity may occur intermittently due to the presence of treponemes in the bloodstream, and pregnant women with latent syphilis may infect the fetus *in utero*.

Tertiary stage

The tertiary stage is also called late syphilis and is characterized by the presence of a small number of organisms and a high cellular immune reactivity against the organism. Signs of late syphilis can be recognized in approximately one-third of untreated individuals several months to years after being infected with treponemes. The microorganisms may invade the central nervous and cardiovascular systems as well as the skin (and other organs), leading to damage related to host delayed-type hypersensitivity responses, which produce local inflammation and gummas in affected tissues.

Syphilis and HIV

Syphilis and other STIs that produce genital ulcers further increase the risk of acquiring HIV. Reasons for the increased risk of HIV transmission include:

- lack of an epithelial barrier due to ulceration of the skin or mucous membranes
- large numbers of macrophages and T cells with receptors for HIV
- production of cytokines by macrophages stimulated by treponemal lipoproteins.

In addition, syphilitic manifestations are altered in HIV-positive patients[11], with a higher likelihood of neurologic findings and (in those with secondary syphilis) ulcerative lesions.

Clinical Features

Syphilis is usually sexually acquired, but maternal–fetal transmission also occurs and can result in congenital syphilis. Syphilis is an intermittent disease with primary, secondary and tertiary stages as well as a latent period of variable length (divided into early and late subsets) that

precedes the onset of tertiary syphilis (see Fig. 82.4)[12]. The definitions of early and late syphilis by the CDC and World Health Organization (WHO) differ slightly. *Early syphilis* includes the primary and secondary stages as well as early latency (CDC: acquired <1 year previously; WHO: acquired <2 years previously). *Late syphilis* extends from late latency (CDC: acquired >1 year previously; WHO: acquired >2 years previously) through the tertiary stage.

Primary syphilis

The chancre usually presents as a single, indolent, round or oval, indurated ulcer (Fig. 82.5) that is associated with regional adenopathy. Some patients report a preceding painless papule that enlarged and ulcerated a few days later. The time of onset ranges from 10 to 90 days (average 3 weeks) after *T. pallidum* exposure. Untreated, chancres heal within a few weeks (Fig. 82.6).

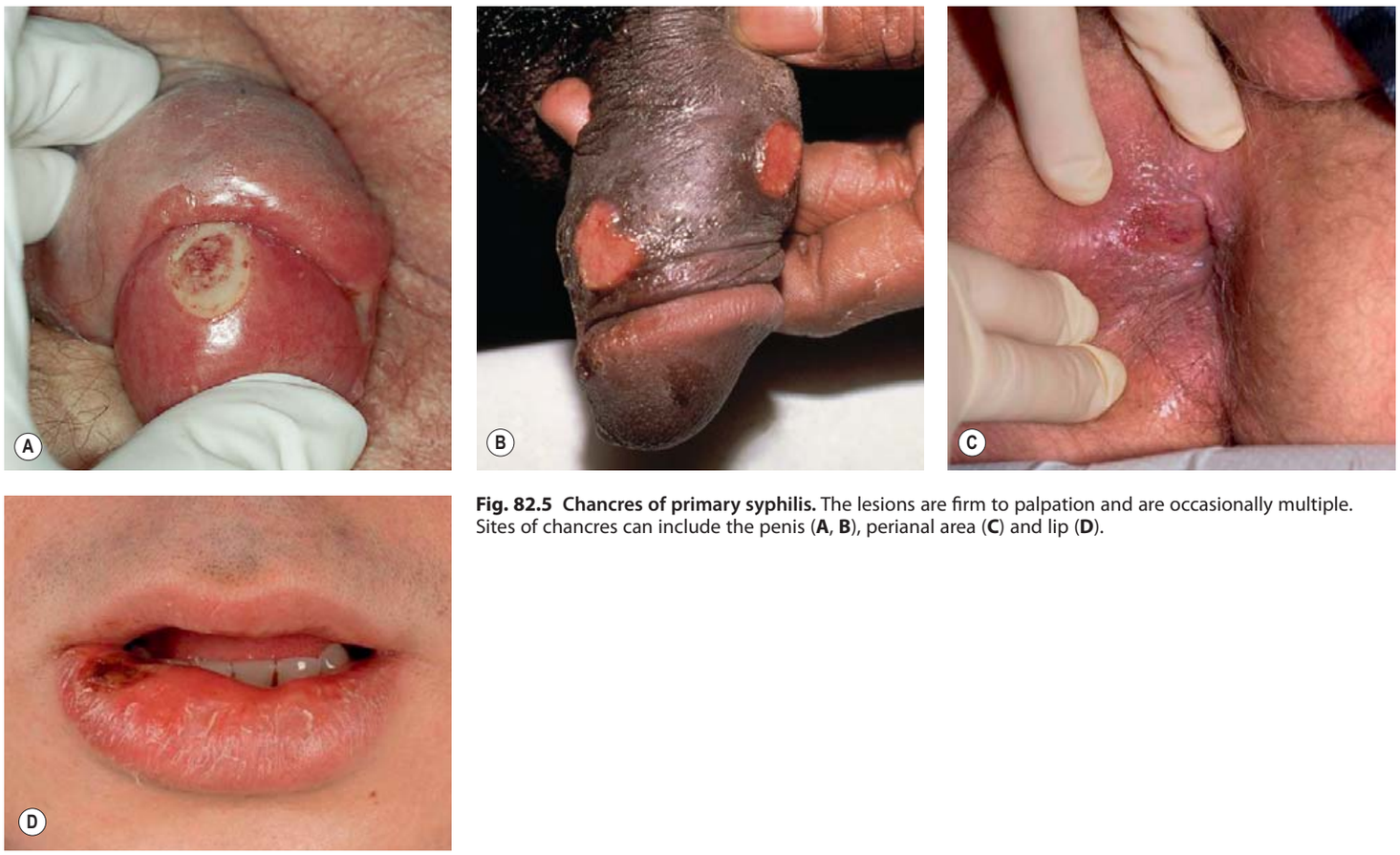


Fig. 82.5 Chancres of primary syphilis. The lesions are firm to palpation and are occasionally multiple. Sites of chancres can include the penis (**A**, **B**), perianal area (**C**) and lip (**D**).

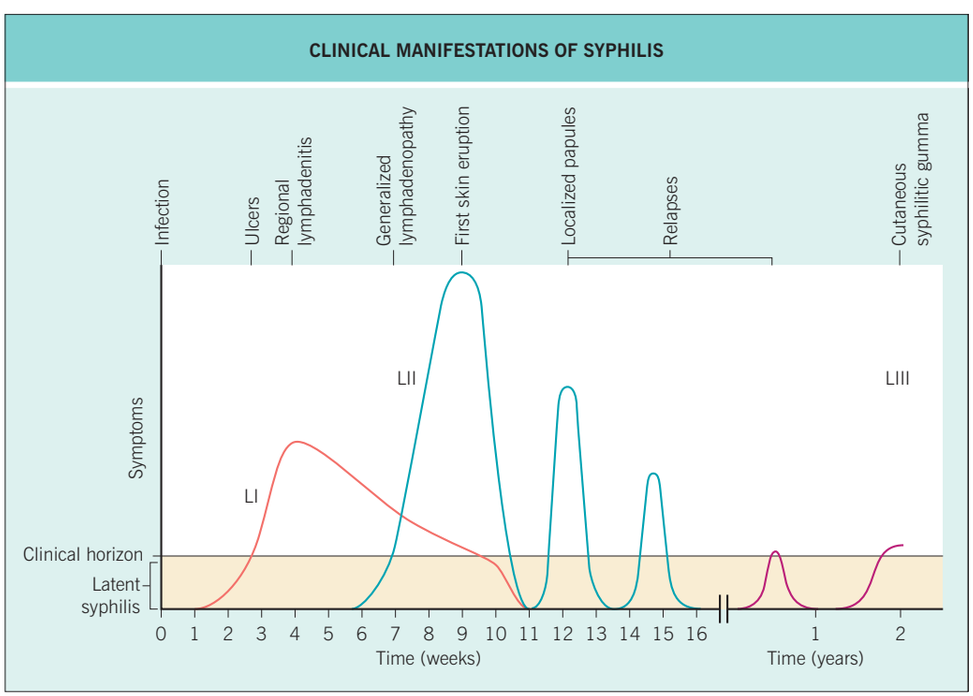


Fig. 82.6 Clinical manifestations of syphilis. LI, primary syphilis; LII, secondary syphilis; LIII, tertiary syphilis. *Adapted from Fritsch P, Zangerle R, Stary A. Venerologie. In: Fritsch P (ed.). Dermatologie und Venerologie. Berlin: Springer, 2004:865–886.*

Asymptomatic infections are common due to unrecognized chancres, especially when located in the cervical region in women; in these cases, syphilis is more frequently diagnosed during the secondary stage. The same applies to chancres located in the anal, perianal or rectal areas (see Fig. 82.5C), seen more commonly in men who have sex with men. The mechanism of spontaneous healing without treatment is not well understood and seems to depend on local immunity.

Laboratory diagnosis of primary syphilis includes the following:

- The presence of treponemes by darkfield microscopic examination of fluid from the surface of the chancre is the most sensitive and specific method for the diagnosis of primary syphilis (see Fig. 82.3).
- Antibodies to cardiolipin are present in about 80% of individuals at the onset of clinical symptoms. Cardiolipin, a component of mammalian cells, seems to be modified by treponemes such that antibodies are produced by the infected person and can be measured by the rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL) assay.
- Antibodies to surface proteins of *T. pallidum* as detected by hemagglutination assays (*T. pallidum* *h*em*a*gglutination test [TPHA], *m*icro*h*em*a*gglutination assay for antibodies to *T. pallidum* [MHA-TP]) or *f*luorescent *t*reponemal *a*ntibody *abs*orption (FTA-ABS) assay are present in 90% of patients with clinical symptoms of primary syphilis. Since antibodies usually remain positive for life, a differentiation between primary syphilis and an earlier infection may not be possible and darkfield examination should be undertaken.

Secondary syphilis

The secondary stage of the disease results from the hematogenous and lymphatic dissemination of treponemes after a few weeks or months (3–10 weeks). It is characterized by recurrent activity of the disease, with mucocutaneous as well as systemic manifestations. Prodromal symptoms include low-grade fever, malaise, sore throat, adenopathy, weight loss, muscle aches and sometimes a headache from meningeal irritation (Table 82.4).

During the second stage of syphilis, the most commonly observed clinical presentation (80%) is a generalized, non-pruritic papulosquamous eruption (Fig. 82.7). Lesions can range from 1–2 mm to 15–20 mm in diameter, and they vary in color from pink to violaceous to red–brown. Mucosal lesions range from small, superficial ulcers that resemble painless aphthae to large gray plaques (Fig. 82.8A,B). Condylomata lata are often observed in the moist regions of the anogenital area (Fig. 82.8C,D) due to local spreading of the microorganisms. Lymph node enlargement is present in the majority of patients. Focal neurologic findings occasionally occur.

Additional clinical presentations of secondary syphilis include annular or figurate plaques with central hyperpigmentation on the face (Fig. 82.9A), non-scarring "moth-eaten" alopecia, split papules at the oral commissures (Fig. 82.9B), granulomatous nodules and plaques (Fig. 82.9C) and crusted necrotic lesions (Fig. 82.9D). Malignant syphilis (lues maligna) is extremely rare; the disseminated lesions resemble primary chancres (Fig. 82.9E).

Without treatment, the lesions resolve over several weeks to months. Relapse occurs in approximately 20% of patients within 1 year, often with mucosal or mucocutaneous manifestations in the anogenital area.

Laboratory diagnosis of secondary syphilis includes the following:

- Presence of treponemes by darkfield examination of serous exudates from localized lesions of the skin and mucous membranes (the exception being the oral cavity; see below).
- Serologic tests are more useful in secondary (as compared to primary) syphilis. Cardiolipin antibodies (e.g. RPR or VDRL tests) as well as specific antibodies are always positive in patients with secondary (as well as tertiary or latent) syphilis; a mistakenly or temporarily negative non-treponemal test rarely occurs due to the prozone phenomenon or HIV infection, respectively (see Table 82.8).
- Occasionally, spirochetes are detected in biopsy specimens (see below)

Management considerations for patients diagnosed with secondary syphilis include the following:

CLINICAL FEATURES OF SECONDARY SYPHILIS

- **Prodromal symptoms and signs:**
  Weight loss
  Low-grade fever
  Malaise
  Headache (meningeal irritation)
  Sore throat
  Conjunctivitis (iridocyclitis)
  Arthralgia (periostitis)
  Myalgias
  Hepatosplenomegaly (mild hepatitis)
- **Generalized lymphadenopathy with indolent enlargement of lymph nodes (50–85%)**
- **Skin manifestations:**
  Early (10%): generalized eruption; non-pruritic, roseola-like, discrete macules, initially distributed on the flanks and shoulders
  Late (70%): generalized maculopapular and papulosquamous eruptions; more infiltrated lesions, often copper-colored; annular plaques on the face; corymbose arrangement (satellite papules around a larger central lesion); occurs in successive waves and is polymorphic
  Localized syphilids (specific infiltrations of treponemes; positive darkfield examination):
  – palms and soles: symmetric papules and plaques with a collarette of scale (collarette of Biett)
  – anogenital area: condylomata lata
  – seborrheic area: "corona veneris" along the hairline
  Hypopigmented macules, mainly on the neck (postinflammatory; "necklace of Venus")
- **Manifestations involving mucous membranes (30%):**
  Syphilitic perlèche, split papules
  Mucous patches: "plaques muqueuses" in the oropharynx (equivalent to condylomata lata in the genital area)
  Syphilitic sore throat: inflammation of the whole pharynx
- **Patchy alopecia (7%):** "moth-eaten" localized areas of hair loss; toxic telogen effluvium

Table 82.4 Clinical features of secondary syphilis.

- All patients should be tested for HIV infection, and testing should be repeated in those who fail to respond to treatment.
- Patients with ocular symptoms (e.g. photophobia, visual changes) should undergo ophthalmologic evaluation to assess for uveitis and neuroretinitis, including slit-lamp examination.
- A lumbar puncture and cerebrospinal fluid (CSF) analysis should be performed in patients with ocular or neurologic (e.g. headache, hearing loss, cranial neuropathies) signs/symptoms and when treatment failure is suspected (e.g. persistent/recurrent signs/symptoms or failure of non-treponemal test titers to decline fourfold within 6–12 months). Patients with HIV are at increased risk for neurosyphilis, especially if they have a CD4 count <350 cells/ml and/or a RPR titer of ≥1 : 32; however, unless neurologic symptoms are present, CSF examination in HIV patients has not been associated with improved clinical outcomes.

Latent syphilis

After a period of 3–12 weeks, untreated secondary syphilis typically resolves spontaneously, leaving the patient in an asymptomatic state. Diagnosis is based on a positive syphilis serology test result in the setting of no clinical evidence of treponemal infection. The two stages are:

- Early latent stage: within 1 year of the onset of latency (CDC definition), with the possibility of recurrence of the disease. About 90% of secondary relapses occur within the first year.
- Late latent stage: after 1 year from the onset of the disease (CDC definition); relapses after 1 year are very infrequent. This disease state may last for many months or years.

Experience regarding the outcome of late latent syphilis in the absence of treatment is based upon several studies. About one-third of infected individuals have a non-reactive RPR test, no sign of reactivation during the remainder of their lives, and only the specific antibody assays (e.g. MHA-TP, FTA-ABS) remain positive (see Fig. 82.1). Another

Fig. 82.7 Secondary syphilis. Widespread exanthem of pink papules (**A**), pityriasis rosea-like lesions localized to the arms in an HIV-positive man (**B**) and generalized papulosquamous lesions (**C**). Lesions on the palms (**D**) and soles (**E, F**) can have a collarette of scale. *B, Courtesy, Kalman Watsky, MD.*

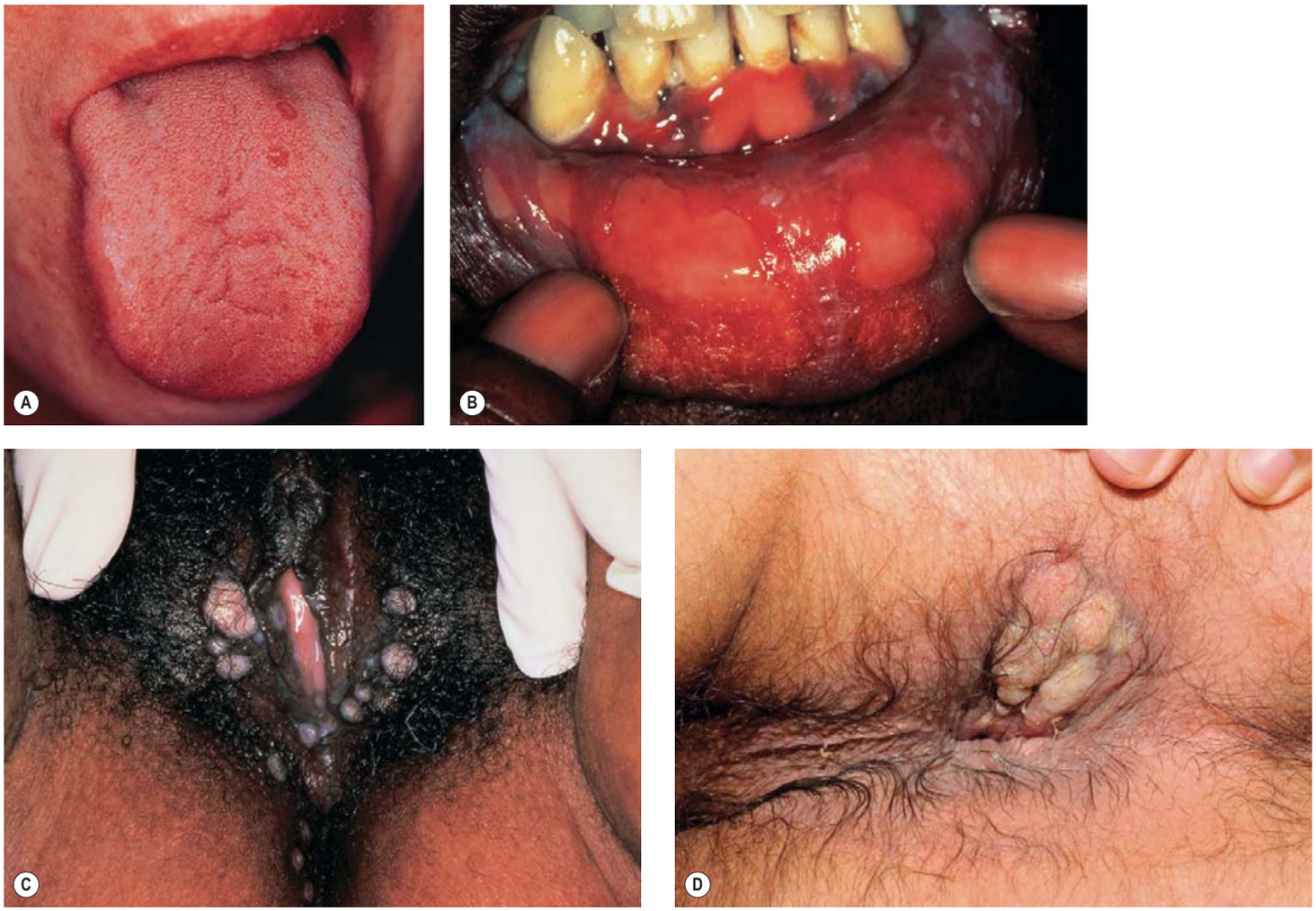


Fig. 82.8 Orogenital lesions of secondary syphilis. Oral lesions can vary from small superficial ulcers (**A**) to mucous patches (**B**). Condylomata lata in the vulvar (**C**) and anal (**D**) areas may be misdiagnosed as HPV infection (i.e. condylomata acuminata).

one-third of patients remain clinically asymptomatic for the rest of their lives, but antibodies against cardiolipin (e.g. RPR, VDRL) persist together with a positive MHA-TP or FTA-ABS assay. In the remaining one-third, clinical symptoms of tertiary syphilis occur.

Diagnosis of latent syphilis is established by reactivity in an RPR or VDRL assay, a positive MHA-TP or FTA-ABS test, and the absence of any clinical signs of the disease. The diagnosis is easy to establish if there is a history of a chancre or skin manifestations that fit the clinical picture of syphilis. In many cases, the medical history provides no useful information regarding the presence of clinical symptoms in the previous weeks to months or whether the patient was previously treated. In such instances, differentiation between early and late latency is not possible and patients are regarded as having late latent syphilis from a management standpoint (see below). Response of latent syphilis to treatment is indicated by a decline in the RPR or VDRL titer. Persistently high (e.g. lack of a fourfold decline within 12–24 months) or rising titers are a sign of treatment failure, and examination of the CSF should be performed.

Tertiary (late) syphilis

Classic tertiary syphilis, as a consequence of untreated syphilis, is nowadays rare. It has a variable range of manifestations that appear months to years after initial infection (Fig. 82.10). In particular, these include involvement of the skin, bones, CNS, heart and great vessels. Approximately one-half of patients with tertiary syphilis have "benign" late syphilis with the development of gummas (see Fig. 82.1), about one-quarter develop cardiovascular manifestations, and one-quarter develop neurologic symptoms (with additional overlap of different manifestations).

In tertiary syphilis, non-treponemal serologic tests are usually positive with high titers. Patients with tertiary syphilis (or any symptoms related to late syphilis) should undergo lumbar puncture and CSF examination to determine if neurosyphilis is present before therapy is initiated.

"Benign" late syphilis

The most common feature of late syphilis is gummas, which are locally destructive lesions in the skin, bones, liver and other organs. The gummas in the skin are nodular or noduloulcerative lesions, often with an arciform pattern (Fig. 82.11). They remain for weeks to months and then involute with scarring, but eventually new nodules reappear. With treatment, resolution of the lesions is prompt and complete. A solitary gumma that is located subcutaneously may become necrotic, similar to a "cold" abscess, resulting in ulceration of the skin or mucous membranes as well as destruction of underlying bones.

Bones are affected as frequently as the skin. The gumma is a destructive bony lesion that is typically accompanied by periostitis and osteitis. Clinical manifestations include pain, swelling and limited range of motion. Other sites that can be affected by gummas include the tongue and oral cavity, upper respiratory tract, myocardium, and digestive as well as nervous systems.

Cardiovascular syphilis

Cardiovascular syphilis has a late onset, with a latent period of 15–30 years, and it occurs in about 8–10% of individuals with untreated infection. During the early stage of the disease, *T. pallidum* demonstrates a predilection for the vasa vasorum of the proximal aorta and produces transmural inflammatory lesions, which lead to endarteritis of the

Fig. 82.9 Less common manifestations of secondary syphilis. A Annular plaques with central hyperpigmentation on the forehead. **B** Split papule at the oral commissure. **C** Granulomatous nodules and plaques. **D** Necrotic lesion with scale-crust in a patient with AIDS. **E** "Malignant" syphilis with multiple necrotic, ulcerated and crusted lesions associated with severe constitutional symptoms. *D, Courtesy, Judit Stenn, MD.*

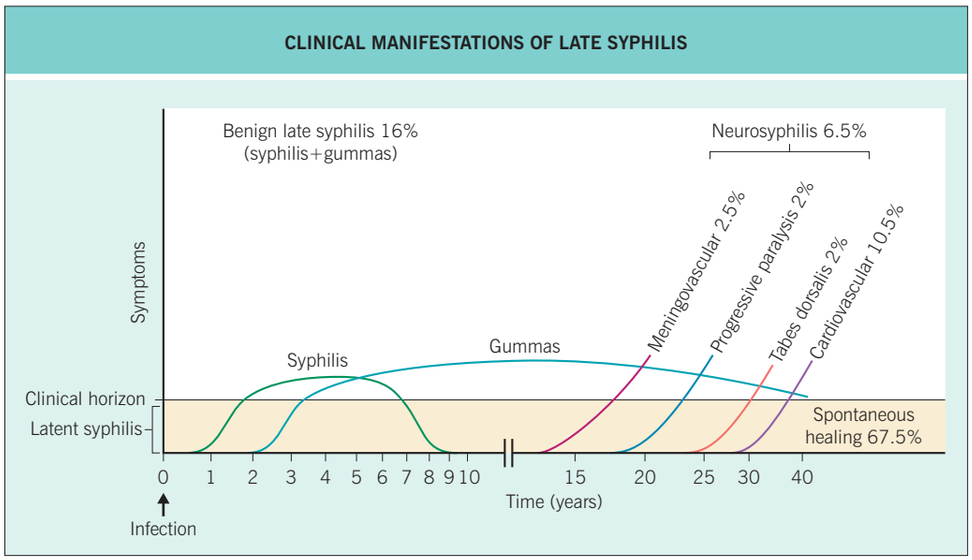


Fig. 82.10 Clinical manifestations of late syphilis. *Adapted from Fritsch P, Zangerle R, Stary A. Venerologie. In: Fritsch P (ed.). Dermatologie und Venerologie. Berlin: Springer, 2004:865–886.*

CLASSIFICATION OF NEUROSYPHILIS
• **Asymptomatic**
• Early
• Late
• **Meningeal**
• Acute syphilitic meningitis
• Meningovascular
• Cerebrovascular
• Spinal form
• **Parenchymatous**
• General paresis (dementia paralytica)
• Tabes dorsalis
• Taboparesis (mixed)
• Optic atrophy
• **Gummatous**
• Cerebral form
• Spinal form
• Both spinal and cerebral

Table 82.5 Classification of neurosyphilis. *Adapted from Merritt HH, Adams RD, Solomon HC. Neurosyphilis. New York: Oxford University Press, 1946.*

Fig. 82.11 Cutaneous gummas of tertiary syphilis. Arciform, erythematous eroded plaques with central scarring.

vessels. The organisms then remain there in a latent state for many years.

Neurosyphilis

Although classically a manifestation of tertiary syphilis, neurosyphilis can occur at any stage of the disease. Neurosyphilis is the reflection of a chronic (or sometimes acute) form of meningitis, with vascular and parenchymatous sequelae in the cerebrum and spinal cord (Table 82.5). Asymptomatic neurosyphilis is defined by the presence of abnormalities in the CSF (see below) but the absence of any neurologic symptoms or clinical findings. While in some individuals the CSF abnormalities may resolve spontaneously or persist into advanced age, asymptomatic neurosyphilis can progress to late symptomatic neurosyphilis.

The basic pathomechanism for cerebrovascular syphilis is an infarction secondary to syphilitic endarteritis; this can result in hemiparesis or hemiplegia. Parenchymatous neurosyphilis (general paresis, dementia paralytica, paretic neurosyphilis) is due to direct invasion of the cerebrum by treponemes. It is a rare and late form of neurosyphilis, with dementia and neurologic symptoms (e.g. paralysis) that (untreated) progress until death occurs.

Tabes dorsalis, which affects up to a third of patients with neurosyphilis after a long latent period, has a number of typical clinical signs and symptoms, including diplopia, lightning pains (painful paresthesias, especially of the extremities), loss of vibratory and position sense, reduced reflexes in the legs, ataxia, sphincter dysfunction, visceral crisis (abdominal, rectal and laryngeal pain), and Argyll Robertson pupils (abnormal pupillary light reflexes: loss of direct and consensual; retention of accommodation). Tabes dorsalis may burn out even without treatment.

Neurosyphilis in HIV-infected individuals

In the mid 1970s, the first cases of a so-called "atypical neurosyphilis" were described. With the subsequent recognition of co-infections with syphilis and HIV, it became apparent that neurosyphilis is common in HIV-infected individuals, and patients present with manifestations of early-onset neurosyphilis.

Laboratory diagnosis of neurosyphilis

In addition to the clinical findings, the diagnosis of neurosyphilis (including acute syphilitic meningitis, meningovascular syphilis and parenchymatous neurosyphilis) is based upon reactive blood and CSF serologies, which are almost always positive. CSF abnormalities include

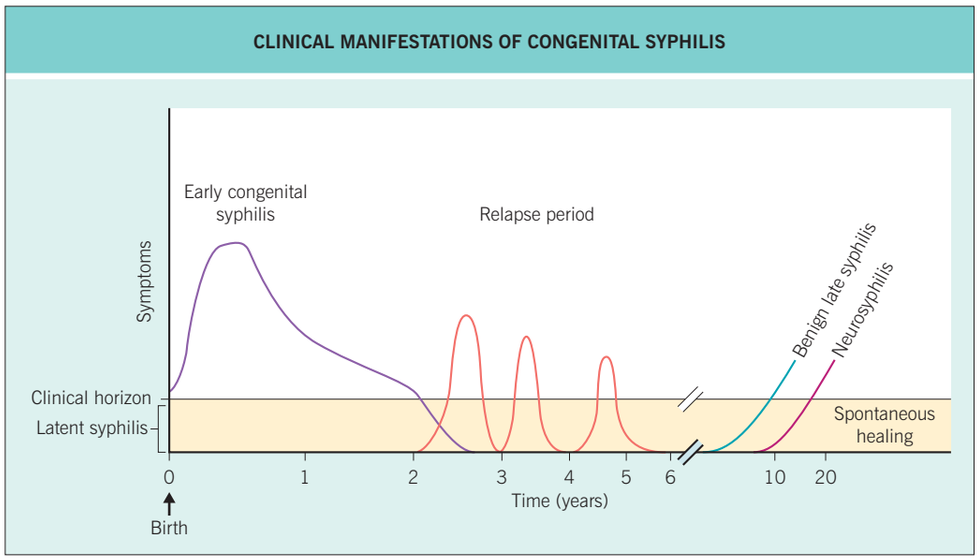


Fig. 82.12 Clinical manifestations of congenital syphilis. *Adapted from Fritsch P, Zangerle R, Stary A. Venerologie. In: Fritsch P (ed.). Dermatologie und Venerologie. Berlin: Springer, 2004:865–886.*

MOTHER-TO-CHILD TRANSMISSION OF UNTREATED SYPHILIS AND ITS CONSEQUENCES
RISK
• Infection of the mother from conception to 7th month of pregnancy: transmission in nearly 100% (often fetal demise or severe congenital syphilis)
• Infection at least 2 years before pregnancy: reduced risk of transmission to 50%
• Infection during 7th, 8th, or early 9th month: reduced risk of transmission
• Infection 3–6 weeks before labor: no placental transmission; risk of perinatal transmission
CONSEQUENCES OF INFECTION
• Spontaneous abortion (second or third trimester) (10%)
• Stillbirth (10%)
• Infant death (20%)
• Congenital syphilis (20%)
• Healthy child (40%)

Table 82.6 Mother-to-child transmission of untreated syphilis and its consequences.

Fig. 82.13 Congenital syphilis. Red–brown plaques on the plantar surface.

elevation of pressure, protein concentration and immunoglobulin level as well as a mononuclear pleocytosis. The presence of specific antitreponemal antibodies in the CSF is mandatory, but it is not proof of the diagnosis of neurosyphilis, since IgG antibodies can diffuse into the CSF or result from contamination of the CSF by blood. Establishment of local antibody synthesis is possible by using the CSF-IgG index, obtained by dividing the CSF to serum IgG ratio by the CSF to serum albumin ratio. A result >0.7 is indicative of IgG synthesis in the brain due to local inflammation. The intrathecal *T. pallidum* antibody index is calculated by dividing the TPHA titer in the CSF by the CSF to serum albumin ratio multiplied by a factor of 10^3, and an index >100 is indicative of the synthesis of treponemal-specific antibodies within the CNS. The presence of nonspecific antibodies, e.g. a positive VDRL test or RPR assay in CSF, is observed in most, but not all, cases, and a negative test does not exclude the presence of neurosyphilis.

Congenital syphilis

Congenital syphilis was initially described in 1497 and is therefore the oldest recognized congenital infection. In 1906, it was demonstrated via the Wassermann test that transmission of syphilis to the fetus required an infection in the pregnant woman.

There was an upsurge in congenital syphilis in Eastern Europe in the late 1990s, which paralleled the increased incidence of syphilis in adults and adolescents in this region. In the early 1990s, an increased frequency of congenital syphilis was also observed in some inner-city minority populations in the US[14]. In the US, there are currently approximately 10 cases of congenital syphilis per 100 000 live births. The risk of mother-to-child transmission of untreated syphilis and its potential consequences are listed in Table 82.6.

Early congenital syphilis

Infants generally present with symptoms during the neonatal period or within the first 3 months of life (Fig. 82.12). At the latest, they develop symptoms within the first 2 years of life. Typical manifestations are marasmic syphilis (i.e. cachexia) and skin lesions similar to those of acquired secondary syphilis (Fig. 82.13), except that they may be bullous (pemphigus syphiliticus) and tend to be more erosive. Additional clinical findings are "snuffles" (bloody or purulent mucinous nasal discharge), perioral and perianal fissures, lymphadenopathy and hepatosplenomegaly. Skeletal involvement (i.e. osteochondritis) may result in pseudoparalysis of Parrot because of reduced movement of the extremities due to pain; other manifestations include anemia, thrombocytopenia, syphilitic pneumonitis (pneumonia alba), hepatitis, nephropathy and congenital neurosyphilis.

Late congenital syphilis and stigmata

Late congenital syphilis in a child or adolescent corresponds to tertiary syphilis in an adult and is not infectious. The stigmata represent the

STIGMATA OF CONGENITAL SYPHILIS
CUTANEOUS
• Rhagades (radial periorificial [mouth, nose, eyes, anus] scars at sites of previous fissures)
DENTAL
• Hutchinson's teeth (peg-shaped, notched permanent incisors)* • Mulberry molars (multiple rounded rudimentary cusps on the permanent first molars) • Caries due to defective enamel
SKELETAL
• Saddle nose (depression of the nasal root due to destruction of cartilage/bone) • Frontal bossing of Parrot ("Olympian brow") • Hypoplastic maxilla, relatively prominent mandible • High palatal arch ± perforation • Higouménakis' sign (thickening of the medial clavicle) • Scaphoid scapulae • Saber shins (anterior tibial bowing) • Clutton's joints (painless synovitis and effusions of the knees)
OTHER
• Eighth nerve deafness* • Interstitial keratitis (leading to corneal ulcers and opacities)*
*Components of Hutchinson's triad.

Table 82.7 Stigmata of congenital syphilis.

LIMITATIONS OF NON-TREPONEMAL AND TREPONEMAL TESTS
NON-TREPONEMAL TESTS

• Lack of reactivity in early darkfield-positive primary syphilis
• Usually become negative with effective therapy (~15% of patients with early syphilis do not achieve a fourfold decline in titers 1 year after appropriate treatment, which is considered to represent a therapeutic failure)
• False-negative results
  • Prozone phenomenon: inhibition of flocculation in the setting of high titers of antibodies; requires serum dilution
  • Temporary negative result: secondary syphilis in the setting of HIV infection; reactive on subsequent testing
• Biologic false-positive results due to tissue damage
  • Pregnancy
  • Autoimmune diseases (e.g. lupus erythematosus)
  • Drug abuse
  • Lymphomas
  • Infectious diseases (e.g. malaria)
  • Vaccinations
  • Hepatic cirrhosis
  • Antiphospholipid syndrome
  • Idiopathic, familial
• False-positive: endemic treponematoses and borreliosis

TREPONEMAL TESTS
• Lack of reactivity in early darkfield-positive primary syphilis • Remain positive indefinitely, so not useful for monitoring response to treatment • Biologic false-positive: autoimmune diseases, HIV infection, hypergammaglobulinemia • False-positive: endemic treponematoses and borreliosis

Table 82.8 Limitations of non-treponemal and treponemal tests.

delayed consequences of localized inflammation at the sites of treponemal infection (Table 82.7). In about one-third of children, an interstitial keratitis is seen; this finding together with typical dental abnormalities (Hutchinson's teeth) and neural deafness forms the Hutchinson triad.

Laboratory diagnosis of congenital syphilis

A confirmed diagnosis of congenital syphilis requires laboratory demonstration of treponemes or child-specific antibodies. Serodiagnosis of congenital syphilis poses a difficult problem because IgG antibodies that are present may have been acquired transplacentally from the mother. A serum titer for a non-treponemal test that is fourfold higher than the mother's titer is suggestive of infection, but infected neonates may have lower titers. The detection of chromatographically separated 19S-antibodies in the FTA-ABS-19S-IgM test has a sensitivity of about 90%, similar to the IgM-capture ELISA. More recently, it has been shown that the detection of spirochetemia by PCR can improve the sensitivity of the diagnosis of congenital syphilis in neonates.

In late congenital syphilis, diagnosis is based on clinical findings in association with reactive serologic tests.

Laboratory Diagnosis of Syphilis

The diagnosis of syphilis is based on the direct detection of treponemes or treponemal DNA by microscopy or molecular biologic techniques as well as various serologic tests that assess antibody responses to either cardiolipin (non-treponemal tests) or treponemal antigens (treponemal tests). Diagnosis of the different stages of syphilis depends on the interpretation of laboratory test results, the presence of clinical signs and symptoms, and their history. All patients who have syphilis should also be tested for HIV infection.

Identification of T. pallidum

The detection of the microorganism depends on microscopic examination and molecular assays, since *T. pallidum* cannot be routinely cultured *in vitro*. For propagation and experimental studies, growth in rabbit testicles is possible.

Microscopic examination

Darkfield microscopy permits the definite diagnosis of syphilis by visual detection of motile spirochetes from lesions of the skin (see Fig. 82.3). It requires careful specimen collection, ideally consisting of serous fluid free of red blood cells. Identification is easy for an experienced microbiologist because of the typical episodic movements of the microorganism. Due to the presence of saprophytic spirochetes in the oral cavity, there is limited utility for darkfield examination of serous exudate from lesions in this site. Immunologic detection of the microorganism by the indirect fluorescent antibody test, which utilizes fluorescein-labeled anti-*T. pallidum* antibodies, is especially useful for oral lesions.

In the case of a negative result from microscopic examination, repeat testing is recommended. Serologic tests are also indicated.

Polymerase chain reaction-based assays

PCR-based assays for detection of *T. pallidum* DNA are commercially available and may be useful in special circumstances, e.g. neurosyphilis and congenital syphilis.

Serologic tests for syphilis

Non-treponemal tests

The VDRL and RPR tests and related assays such as the unheated serum reagin (USR), reagin screen test (RST) and toluidine red unheated serum test (TRUST) detect antibodies to cardiolipin. The latter is a component of mammalian cells that is incorporated and modified by treponemes, which results in the development of host antibodies against it (comparable with autoantibodies directed against phospholipids; see Ch. 23). All these tests measure IgG and IgM antibodies against this lipoprotein-like material released from damaged host cells and from treponemes.

Titers of these antibodies correlate with disease activity and are useful in screening and monitoring treatment (Fig. 82.14). *Qualitative* non-treponemal tests are suitable for screening purposes, and reactive results have to be confirmed by antibody titer. The performance of a *quantitative* non-treponemal test is generally requested even with a positive darkfield examination, in order to provide a baseline for longitudinal evaluation after antibiotic therapy. A fourfold decrease in the antibody titer indicates successful treatment, while a fourfold increase indicates relapse or reinfection. In the case of early and efficacious treatment, non-treponemal assays usually become negative. Limitations of the tests are listed in Table 82.8.

Treponemal tests

The major indication for treponemal tests for syphilis is confirmation of reactive non-treponemal tests. IgM and IgG antibodies are usually

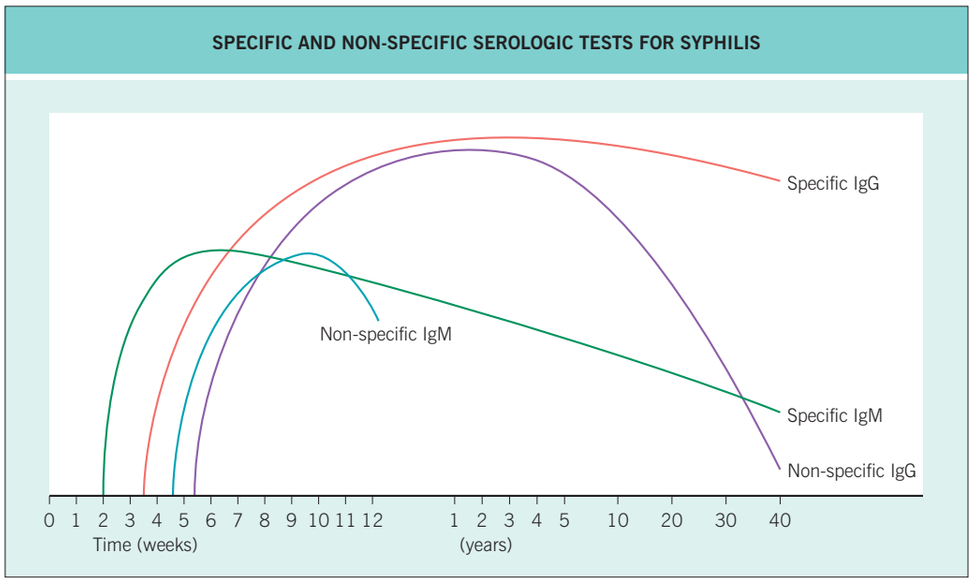


Fig. 82.14 Specific and nonspecific serologic tests for syphilis. These curves represent untreated patients. *Adapted from Fritsch P, Zangerle R, Stary A. Venerologie. In: Fritsch P (ed.). Dermatologie und Venerologie. Berlin: Springer, 2004:865–886.*

detected in these assays by the end of the fourth week after infection. Accurate quantitative evaluation is not useful. The specific treponemal tests generally remain positive indefinitely, and only in the case of treatment of very early syphilis do they revert to negative. The specificity is very high and false-positive reactions seldom occur. The sensitivity varies with the stage of syphilis: between 70% and 100% in primary syphilis, 100% in secondary and latent syphilis, and about 95% in late syphilis[15]. There is no differentiation between antibodies to *T. pallidum* and other treponemes and spirochetes.

Specific assays include the following:

- TPHA, MHA-TP, *T. pallidum p*article *a*gglutination test (TPPA): these assays measure antibodies directed against surface proteins of *T. pallidum* (sonicated fragments of treponemes) attached to rabbit erythrocytes as antigen carriers. Automatization is useful for large-scale testing and screening purposes. A positive result means that the patient had or still has active syphilis, but no assessment about the activity of the disease can be concluded from the qualitative result. Ninety percent of patients are positive at the time they seek medical care for a chancre.
- FTA-ABS assay: the serum reacts with the whole treponeme and forms antigen–antibody complexes visualized by fluorescein-isothiocyanate. To avoid nonspecific reactions with antibodies directed against saprophytic treponemes, a further step with Reiter treponemes is included to absorb nonspecific antibodies. The differentiation into IgM and IgG is possible by including selective anti-Ig antibodies.
- FTA-ABS-19S-IgM test: the isolated IgM antibody fraction is separately tested and provides a higher specificity than other tests. It is restricted to special situations, e.g. congenital syphilis or the differentiation of relapsing syphilis from reinfection.
- *S*olid *p*hase *hem*a*d*sorption test (SPHA) or IgM ELISA: the SPHA test is used for the detection of specific IgM antibodies that attach to the solid phase of microtiter plates by reacting with the treponemal antigen on rabbit erythrocytes as antigen carriers. IgM antibodies can also be measured by the ELISA technology. These tests are useful for the diagnosis of congenital syphilis, neurosyphilis (positive, but low-titer) and reinfection.

Pathology

In *primary syphilis*, there is ulceration and a diffuse dermal infiltrate of plasma cells, lymphocytes and histiocytes. Endothelial swelling is also present. Spirochetes may be detected with Warthin–Starry or immunohistochemical staining (see Fig. 0.32).

In *secondary syphilis*, the epidermis may be normal, psoriasiform, necrotic or ulcerated. Pustules may be found in the epidermis. Dermal infiltrates of plasma cells, lymphocytes and histiocytes can be perivascular, lichenoid, nodular or diffuse (Fig. 82.15). Older lesions of

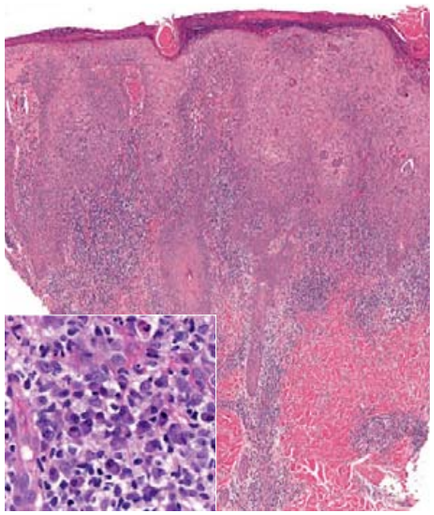


Fig. 82.15 Histology of secondary syphilis. Psoriasiform epidermal hyperplasia and a dense dermal infiltrate of plasma cells (see insert), lymphocytes and histiocytes are observed. *Courtesy, Lorenzo Cerroni, MD.*

secondary syphilis may be granulomatous and can resemble sarcoidosis except for the presence of plasma cells. Endothelial swelling and vascular proliferation can also be found in secondary syphilis. Spirochetes are identified in up to one-third of cases. Lues maligna is characterized by vasculitis.

In *tertiary syphilis*, tuberculoid granulomas (with or without caseation) are present together with plasma cells. Endothelial swelling is evident, but organisms are usually no longer seen.

Differential Diagnosis

The differential diagnoses for the different stages of syphilis are listed in Table 82.9.

Treatment

Penicillin G is still the treatment of choice for all stages of syphilis, and recommended regimens are listed in Table 82.10. A treponemicidal level of the antimicrobial should be achieved in the serum and (for patients with neurosyphilis) in the CSF. A penicillin level of >0.018 mg/l is considered treponemicidal, but the maximally effective *in vitro* concentration is considerably higher (0.36 mg/l)[16,17]. No tendency toward penicillin resistance has been detected in *T. pallidum*. Tetracyclines are used as second-line therapy if penicillin cannot be given; although a single 2 g dose of azithromycin can be effective[18], treatment failures due to macrolide-resistant *T. pallidum* have been reported.

DIFFERENTIAL DIAGNOSES FOR SYPHILIS
PRIMARY SYPHILIS
Other causes of genital ulcers should be considered: • Genital herpes • Genital trauma • Fixed drug eruption • Ulcerative genital carcinoma (e.g. squamous cell carcinoma) • Chancroid: jagged border, yellow exudate, painful • Lymphogranuloma venereum: transient, indurated, painless • Primary EBV infection • Behçet's disease
SECONDARY SYPHILIS
• Cutaneous: pityriasis rosea, guttate psoriasis, viral exanthems, lichen planus, pityriasis lichenoides chronica, primary HIV infection, drug eruption, nummular eczema, folliculitis • Mucous membranes: lichen planus; chronic aphthae; hand, foot and mouth disease; herpangina; perlèche • Condylomata lata: warts due to HPV, bowenoid papulosis, squamous cell carcinoma
TERTIARY SYPHILIS
• Cutaneous: lupus vulgaris, chromoblastomycosis, dimorphic fungal infections, leishmaniasis, lupus erythematosus, mycosis fungoides, sarcoidosis, tumors, venous ulcer

Table 82.9 Differential diagnoses for syphilis.

TREATMENT RECOMMENDATIONS FOR SYPHILIS IN SPECIAL SITUATIONS
PREGNANCY
Recommended: • Benzathine penicillin, 2.4 million units im weekly for two (early syphilis) or three (late syphilis) doses *or* • Procaine penicillin, regimen appropriate for the stage of syphilis (see Table 82.10)

In the case of penicillin allergy:
• Desensitization to penicillin *or*
• Alternative regimens*:
  • Azithromycin, 500 mg qd for 10 days *or*
  • Ceftriaxone, 1 g im or iv qd for 10–14 days

CONGENITAL
Neonate with proven or highly probable disease or born to mother with untreated early syphilis†: • Aqueous penicillin G, 50 000 U/kg iv q12h for the first 7 days of life, then q8h for 3 days (100 000–150 000 U/kg/day for a total of 10 days) *or* • Procaine penicillin, 50 000 U/kg im qd for 10–14 days
Neonate with no signs of disease born to mother with treated syphilis‡: • Benzathine penicillin, 50 000 U/kg im in a single dose
*Limited data; not recommended by the Centers for Disease Control (CDC) but included in the World Health Organization (WHO) and European Branch of the International Union against Sexually Transmitted Infections (IUSTI) guidelines. †CSF analysis should be performed prior to therapy. ‡Neonate with a normal physical examination and serum non-treponemal antibody titer less than fourfold the maternal titer; treatment is optional if the mother was fully treated before pregnancy.

Table 82.11 Treatment recommendations for syphilis in special situations. h, hours; im, intramuscularly; iv, intravenously; q, every; qd, daily.

TREATMENT RECOMMENDATIONS FOR SYPHILIS
EARLY SYPHILIS (PRIMARY, SECONDARY, AND EARLY LATENT [ACQUIRED <1 YEAR PREVIOUSLY])
Recommended: • Benzathine penicillin, 2.4 million units* im as a single dose *or* • Procaine penicillin, 1.2 million units im qd for 10 days†
Alternative regimens for penicillin-allergic patients‡: • Doxycycline, 200 mg qd (100 mg po bid preferred over a single 200 mg dose) for 14 days *or* • Tetracycline, 500 mg po qid for 14 days *or* • Ceftriaxone, 1 g im or iv qd for 8–10 days *or* • Azithromycin, 2 g po as a single dose§
LATE LATENT (ACQUIRED >1 YEAR PREVIOUSLY OR OF UNKNOWN DURATION), CARDIOVASCULAR AND GUMMATOUS SYPHILIS; RETREATMENT OF PRIMARY, SECONDARY OR LATENT SYPHILIS AFTER FAILED INITIAL TREATMENT¶
Recommended: • Benzathine penicillin, 2.4 million units* im weekly for three doses *or* • Procaine penicillin, 1.2 million units im qd for 20 days†
Alternative regimens for penicillin-allergic patients‡: • Doxycycline, 200 mg qd (100 mg po bid preferred over a single 200 mg dose) for 28 days *or* • Tetracycline, 500 mg po qid for 28 days
NEUROSYPHILIS AND OCULAR SYPHILIS
Recommended: • Aqueous penicillin G, 3–4 million units iv q4h (18–24 million units daily) for 10–14 days *or* • Procaine penicillin, 2.4 million units im qd plus probenecid, 500 mg po qid, both for 10–14 days
Alternative regimens for penicillin-allergic patients: • Ceftriaxone, 2 g im or iv qd for 10–14 days *or* • Consider desensitization
*In children, 50 000 U/kg up to the adult dose. †Alternative treatment regimen in the World Health Organization (WHO) guidelines (http://whqlibdoc.who.int/publications/2003/9241546263.pdf). ‡Limited data. §Resistance reported. ¶E.g. if RPR/VDRL titers fail to decrease fourfold or symptoms persist/progress; must first examine the CSF to exclude neurosyphilis.

Table 82.10 Treatment recommendations for syphilis. bid, twice daily; h, hours; im, intramuscularly; iv, intravenously; po, orally; q, every; qd, daily; qid, four times daily. Also see the Centers for Disease Control and Prevention (CDC) guidelines (www.cdc.gov/std/treatment/2010/STD-Treatment-2010-RR5912.pdf).

Recommended treatment regimens in the settings of pregnancy and congenital syphilis are summarized in Table 82.11. Although HIV-infected patients are at increased risk for neurologic complications and may have higher rates of treatment failure, prevention of these outcomes by altered therapeutic regimens has not been demonstrated. The CDC and International Union Against Sexually Transmitted Infections (IUSTI) currently recommend that HIV-infected individuals receive the same syphilis regimens as HIV-negative patients. Treatment guidelines and additional information are provided by the CDC (www.cdc.gov/mmwr) and IUSTI (www.iusti.org)[19]. Of note, a Jarisch–Herxheimer reaction characterized by the acute onset of fever, headache and myalgias can occur upon treatment of early syphilis.

The IUSTI recommends that non-treponemal tests (e.g. VDRL or RPR) be performed 1, 2, 3 and 6 months following antibiotic treatment of early syphilis, then every 6 months for up to 2 years post treatment[19]; the CDC suggests clinical and serologic evaluation at 6 and 12 months for uncomplicated cases, with more frequent and extended evaluation (e.g. at 3, 6, 9, 12 and 24 months) for HIV-infected patients. Evaluation of late syphilis at 6-month intervals for up to 3 years is recommended. In the setting of abnormal CSF findings, a CSF examination is recommended at 6-month intervals until cell counts are normal and the CSF-VDRL is negative. Evaluation of sexual partners and reporting are mandatory in many countries.

GONORRHEA

Synonyms: ■ Gonorrhea: "clap" ■ Disseminated gonococcal infection: arthritis-dermatosis syndrome

Key features

- Gonorrhea is the most common reportable STI in high-income countries
- It is caused by *Neisseria gonorrhoeae*, which infects the mucosal surfaces of the human genital tract (as well as the anus, rectum and mouth) after direct – usually sexual – contact with an infected person
- Cutaneous pustules as well as systemic symptoms such as arthritis and fever can result from hematogenous dissemination, which occurs in only a small percentage of infected individuals
- Overall, the incidence of gonorrhea has declined during the past several decades, although there has been a recent increase in Eastern Europe
- Over the past few decades, resistance of *N. gonorrhoeae* to various antimicrobials has increased in frequency

History

Gonorrhea was mentioned in ancient literature from China, Egypt, the Roman Empire and Greece, as well as in the Old Testament[20]. Over the centuries, several names have been used to denote infection with *N. gonorrhoeae*, including: "strangury", as used by Hippocrates; "clap", derived from the district of prostitution called "Les Clapier" in Paris; "gonorrhea", chosen by Galen (130 AD) to describe the urethral exudate as a "flow of seed"; and "M. Neisser", recognizing Albert Neisser, who discovered the microorganism in 1879 in stained smears from vaginal, urethral and conjunctival exudates.

Culture of *N. gonorrhoeae* was first described by Leistikow and Lüffler in 1882, and it was improved in 1964 by Thayer and Martin, who devised selective growth conditions on special agar plates[21]. Understanding the differences in the virulence of gonococci and studies of its molecular biology have led to greater insight into the pathology of the organism[22]. Treatment of gonococcal infections was problematic until sulfonamides were introduced in 1936 and penicillin in 1943. During the past 25 years, an increase in antimicrobial resistance to penicillin and other antibiotics, such as tetracyclines and quinolones, has been observed and has become problematic.

Epidemiology

During the past century, the incidence of gonorrhea was influenced by politics, with peaks at the ends of the First and Second World Wars. A sudden decrease in reported cases occurred after the introduction of penicillin and other effective antimicrobials. Subsequently, the sexual freedom of the 1970s led again to an increase in the incidence of gonorrhea. However, with the advent of the AIDS epidemic, sexual practices again changed due to concerns regarding transmission of HIV, and this had a remarkable impact on the incidence of gonorrhea. Gonorrhea rates in the US peaked in the mid 1970s and have remained relatively low and stable over the past 15 years.

Political changes in Eastern Europe led to an increased rate of gonorrhea (as well as syphilis) in the 1990s, especially in prostitutes and those with sexual exposure to prostitutes. Migration of sex workers with a high infection rate also increased the number of reported cases of gonorrhea in other regions of Europe, especially in urban areas and high-risk groups (e.g. men who have sex with men). This probably reflects an increase in unsafe sexual behavior, particularly among young people and in high-risk populations.

Similar to other venereal diseases, the incidence of gonorrhea varies with age and is highest in the 15- to 24-year-old age group, in which there is a higher rate in women than in men. In the US, African Americans have a 20-fold higher rate of gonococcal infections than Caucasian Americans. This may reflect different sexual behavior patterns and exposures as well as a better reporting system in public health institutions, which are more often utilized by African Americans.

Transmission

N. gonorrhoeae is a pathogen restricted to humans as its only host and transmitted primarily by sexual contact. The most efficient transmission occurs by vaginal or anal intercourse where there is physical contact with the mucosal surface of a sexual partner with an asymptomatic or mildly symptomatic infection. An exception is indirect contact among prepubescent girls sharing contaminated objects. There is no evidence that gonococci can be spread by air droplet transmission as occurs with meningococci. Vertical transmission can occur from an infected mother to the newborn during parturition, and this may lead to gonococcal conjunctivitis, pneumonia or even vulvovaginal infection.

Biology of *N. gonorrhoeae*

Gonococci are Gram-negative diplococci that typically grow in pairs. They exhibit multiple colony types when grown on hemoglobin-containing media in a 3% CO_2 atmosphere. The outer membrane structure of *N. gonorrhoeae* is typical for Gram-negative bacteria but, in contrast to *N. meningitidis*, it lacks the polysaccharide capsule that is responsible for the virulence of meningococci. Surface molecules on the outer membrane are involved in attachment, invasion and host injury, and they also represent important antigenic structures, especially the fibrillar pili (composed of 18 kDa pilin subunits)[23].

Gonococci require iron to grow, with sources including transferrin, lactoferrin and hemoglobin; acquisition of iron is mediated by binding to host proteins with a specific receptor. The microorganism cannot tolerate drying or low temperatures, and its growth is optimal at 35–37°C in a 5% CO_2 atmosphere on a complex growth medium containing inorganic iron, glucose, vitamins and cofactors as well as antibiotics.

Pathogenesis

Although there is increasing knowledge about the pathogenicity of this microorganism, the exact molecular mechanisms of invasion of gonococci into the host cell are still unknown. Several virulence factors are involved in the processes of adherence, inflammation and mucosal invasion[24]. Because pili increase adhesion to the host cell, they also play an important role in pathogenesis; this may explain why non-piliated gonococci have a reduced ability to cause infections in humans. The adherence of gonococci to the human epithelial host cell and to neutrophils is dependent not just on the pili but also on Opa ligands. Anti-pilus antibodies have been shown to block epithelial adherence and increase phagocytic killing. Expression of the transferrin receptor and full-length lipo-oligosaccharide (LOS) appear to increase infectivity. Gonococci are able to multiply and divide intracellularly, where they are immune to host defense mechanisms. Intracellular invasion is favored by expression of certain Opa proteins and non-sialylated LOS.

Gonococci have the ability to cause tissue destruction by production of a variety of peptides and lipids such as phospholipase, peptidases, lipid A and peptidoglycans. This plays a role in their damage of fallopian tubes and the development of postinflammatory arthritis.

Clinical Features

Gonorrhea has a broad spectrum of clinical manifestations in both men and women, including asymptomatic infections, local symptomatic mucosal infections (with or without local complications), and systemic dissemination (Table 82.12). Symptoms vary according to the site of infection and strain of organism.

The incubation period for gonorrhea is relatively short; it only takes 2–5 days until signs and symptoms of an infection with *N. gonorrhoeae* appear. Up to 10% of infected men and 50% of infected women lack clinical symptoms, which is especially common in rectal and pharyngeal infections[25].

Gonococcal infection in men

The most common clinical presentation of gonococcal infection in men is an acute anterior urethritis with dysuria and a urethral discharge that is typically purulent and profuse. In about one-quarter of infected men, the urethral symptoms are less pronounced, similar to those of non-gonococcal urethritis, and appear only after urethral manipulation ("stripping"). Without treatment, clinical symptoms disappear in most patients after about 6 months. Local complications can include inflammation of the Cowper's and Tyson's glands and gonococcal pyoderma; ascension of the infection may lead to epididymitis, prostatitis and vesiculitis. Patients with gonococcal epididymitis present with unilateral testicular pain and swelling accompanied by urethritis.

CLINICAL MANIFESTATIONS OF GONORRHEA
DISSEMINATED INFECTION
• Arthritis • Fever • Tenosynovitis • Acral cutaneous pustules • Scalp abscesses (in neonates at sites of fetal scalp monitor electrodes) • Endocarditis • Meningitis
DIRECT MUCOSAL INFECTION
• Urethritis • Cervicitis • Proctitis • Pharyngitis • Vulvovaginitis (children) • Ophthalmia neonatorum
LOCAL EXTENSION
• Prostatitis • Vesiculitis • Epididymitis • Salpingitis • Oophoritis • Pelvic inflammatory disease

Table 82.12 Clinical manifestations of gonorrhea.

Gonococcal infection in women

In about 50% of infected women, gonococcal infection is asymptomatic and therefore remains unnoticed. The primary site of gonococcal infection in women is the endocervical canal, with associated clinical symptoms consisting of increased vaginal discharge, dysuria, intermenstrual bleeding, and menorrhagia. Clinical inspection shows purulent cervical discharge with erythema and edema; swabbing of the endocervical canal results in a highly characteristic yellow color. Urethral colonization is present in 70–90% of infected women and is the usual site of infection in women who have had a hysterectomy. Occasionally, inflammation of Bartholin's glands is observed, with acute swelling of the labial folds and appearance of purulent discharge when pressure is applied to the gland.

The most common local complication in women is acute salpingitis or pelvic inflammatory disease (PID) due to ascension of the microorganisms. It occurs in approximately 10–20% of infected women (often developing immediately after a menstrual period) and may result in the long-term consequences of infertility, chronic pelvic pain and ectopic pregnancy. The clinical manifestations of PID vary and include lower abdominal pain, adnexal tenderness, elevation of the ESR, leukocytosis and fever. Gonorrheic perihepatitis (Fitz–Hugh–Curtis syndrome), with inflammation of the adjacent peritoneal area, is an infrequent complication in which symptoms of PID are accompanied by pain in the right upper quadrant that mimics acute cholecystitis.

Extragenital gonorrhea

Pharyngeal gonorrhea

This can occur in both men and women after oral sexual exposure. Because it is usually asymptomatic, the infection typically goes undetected and spontaneously resolves within a few weeks[26]. Pharyngeal gonorrhea may be an important source of urethral gonorrhea in men who have sex with men.

Rectal gonorrhea

Rectal gonorrhea is mainly seen in men who have sex with men and in heterosexual women who practice receptive anal intercourse. Rectal gonorrhea is asymptomatic in at least 50% of patients, but it may result in gonococcal proctitis that is accompanied by inflammation, rectal discharge, anal pruritus, bleeding, tenesmus and constipation.

Gonococcal infection in newborns is caused by inoculation with *N. gonorrhoeae* during delivery through an infected birth canal, and most often it presents with purulent conjunctivitis (ophthalmia neonatorum). Due to preventive application of antimicrobial ointment (usually erythromycin) immediately after birth, the rate of this gonococcal infection is currently low.

Fig. 82.16 Gonococcemia (arthritis–dermatosis syndrome). Pustule with surrounding erythema on the toe.

Gonococcal ophthalmia (including ophthalmia neonatorum)

Gonococcal ophthalmia is uncommon in adults but still represents a major cause of blindness in some low-income countries. Primarily due to self-inoculation and unusual sexual practices, it initially presents as purulent conjunctivitis and (if left untreated) can rapidly progress to severe keratitis followed by corneal opacification.

Gonococcal infection in newborns is caused by inoculation with *N. gonorrhoeae* during delivery through an infected birth canal, and most often it presents with purulent conjunctivitis (ophthalmia neonatorum). Due to preventive application of antimicrobial ointment (usually erythromycin) immediately after birth, the rate of this gonococcal infection is currently low.

Disseminated gonococcal infection

Arthritis–dermatosis syndrome (gonococcemia)

The most common clinical manifestation of gonococcal bacteremia is an acute arthritis–dermatosis syndrome, which occurs in approximately 0.5–1% of patients with mucosal gonorrhea[27]. Risk factors for disseminated gonococcal infection include menstruation (with the majority of cases in women developing during or immediately following menses) and deficiencies in the late complement components (C5–C9; see Ch. 60). The classic syndrome consists of fever, joint pain and a paucilesional eruption of hemorrhagic pustules. Gonococcal tenosynovitis affects primarily larger joints (e.g. knees, elbows, wrists, ankles) and is sometimes visible as erythema overlying the tendons.

The cutaneous lesions consist of scattered necrotic pustules due to an embolic septic vasculitis. They occur primarily on the distal portions of the extremities (Fig. 82.16) and contain gonococci. With a longer duration of symptoms, positive blood cultures become less common.

Laboratory Diagnosis

Laboratory diagnosis is based on the identification of *N. gonorrhoeae* in secretions from infected mucous membranes by using stained smears, cultures and/or molecular biologic techniques (Fig. 82.17). Samples are typically obtained from the endocervical canal in women (after wiping off exudate), the urethra in men (and occasionally in women who have had a hysterectomy), and (when indicated) the posterior pharynx. For diagnosis by nucleic acid amplification methods (see below), a vaginal swab or urine sample can also be used. Anorectal specimens should be obtained via direct visualization using anoscopy if possible.

Staining methods

Direct detection of Gram-negative diplococci within neutrophils in Gram-stained smears (Fig. 82.18) (or using a methylene blue stain) provides an immediate diagnosis, which is especially helpful in symptomatic individuals. Gram-stained urethral exudate detects between 95% and 98% of symptomatic infections in men, whereas Gram-stained cervical smears have a sensitivity of about 50%. The specificity of Gram-stained exudates depends primarily on the experience of the microscopist and on proper collection, and it may approach 100% in an optimal setting. However, when screening asymptomatic

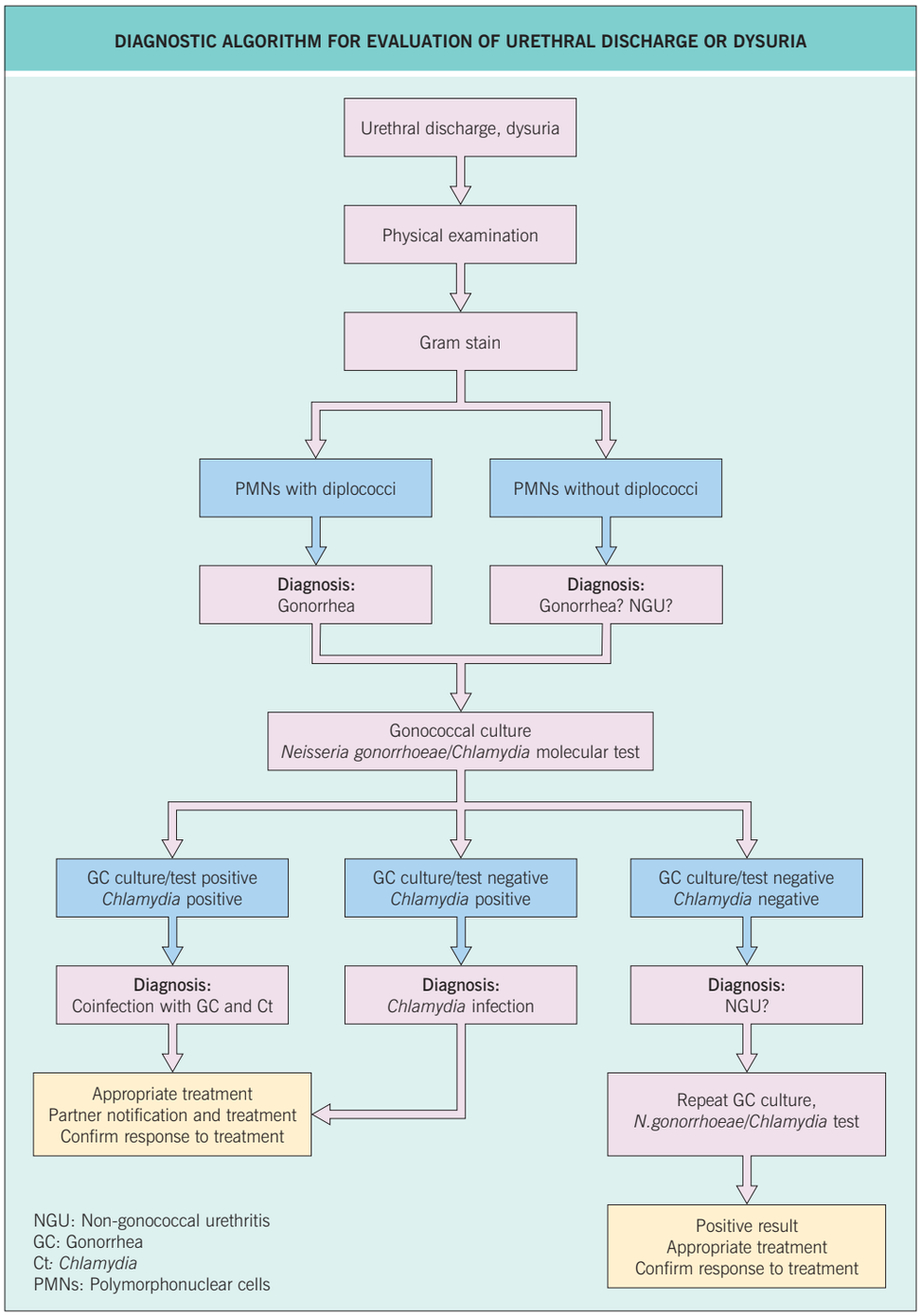


Fig. 82.17 Diagnostic algorithm for evaluation of urethral discharge or dysuria.

individuals, smears have lower sensitivity and are not cost-effective. Smears are not helpful for detection of rectal and pharyngeal gonorrhea due to the presence of a large number of other bacteria. Of note, Gram-negative diplococci may occasionally be seen in smears of the contents of pustules in disseminated gonococcal infections.

Culture techniques

Isolation of *N. gonorrhoeae* by culture is still considered to be the gold standard for the diagnosis of gonococcal infections, and positive results obtained by stained smears should be confirmed by culture. Culture is currently the only acceptable method for cases of rape or other medico-legal situations, and it allows sensitivity testing. Pustular lesions due to gonococcemia should be punctured for culture.

Currently available antibiotic-containing selective media (Thayer–Martin) or selective New York media have a sensitivity of 80–95% (depending on the symptomatic status of the infected person) for genital samples directly plated at the time of collection. Sensitivity is much lower for extragenital specimens such as those from the rectal area (<50%). The specificity of the culture is reported to be approximately 95% in the case of isolation from the genital region. Confirmation of a positive culture by *N. gonorrhoeae*-specific tests is recommended and is mandatory in cases of extragenital infection.

Non-culture techniques for gonococcal diagnosis

Diagnosis of gonococcal infections by molecular techniques is widely utilized and has advantages over culture when specimen transport and storage are potential problems. These tests also enable the diagnosis of chlamydial infection to be made from the same specimen collection tube and are more sensitive than culture for extragenital specimens. The disadvantage of non-culture techniques is the lack of antibiotic sensitivity testing. Therefore, if non-culture techniques are routinely used for gonococcal diagnosis, culture-based regional monitoring of gonococcal antimicrobial susceptibility is needed to determine the appropriate therapy.

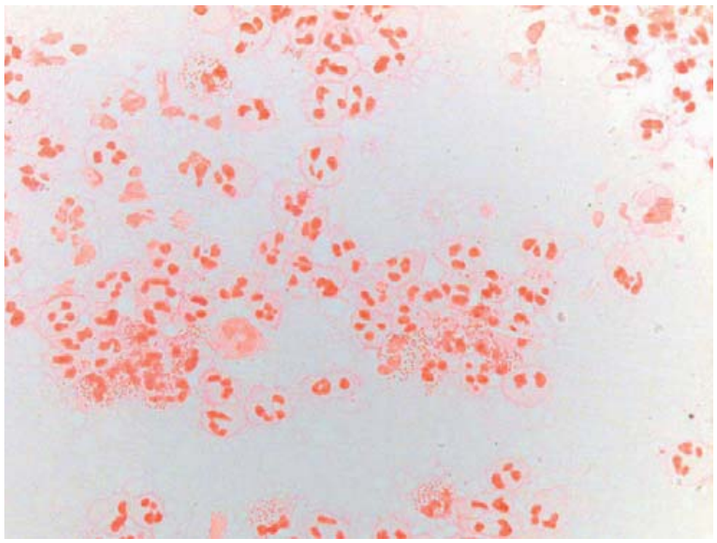


Fig. 82.18 Gonococci in a Gram-stained smear of urethral discharge. Neutrophils containing numerous Gram-negative diplococci, consistent with *Neisseria gonorrhoeae,* are evident.

Non-amplified DNA hybridization

The non-amplified DNA probe test (Gen-Probe PACE 2®) is still used in some parts of the world and is based on the hybridization of gonococcal RNA. It has a sensitivity and specificity comparable with that of culture.

Nucleic acid amplification techniques

Nucleic acid amplification tests (NAATs) that use PCR (e.g. COBAS Amplicor™, VERSANT® CT/GC DNA 1.0 Assay), transcription mediated amplification (APTIMA Combo 2®, APTIMA GC®) and the strand displacement amplification assay (ProbeTec™) detect gonococcal DNA or RNA (alone or in addition to chlamydial DNA). Advantages of these tests include use of "non-invasive" sample types (e.g. urine and vaginal or introital swabs)[28] and avoidance of problems with storage and transport (e.g. in field settings where culture facilities are not available). In asymptomatic patients and in samples from extragenital sites, amplification methods surpass the sensitivity of culture[29].

Pathology

Biopsies of skin lesions due to gonococcemia show epidermal necrosis with epidermal or dermal pustules. There is a septic neutrophilic vasculitis with extravasated erythrocytes and thrombi. Organisms are seldom demonstrated.

Differential Diagnosis

Other causes of urethral and cervical discharge in men and women must be considered, including infections with *Chlamydia trachomatis*, *Trichomonas vaginalis*, yeasts and anaerobic bacteria. The skin lesions of disseminated gonococcemia may need to be distinguished from folliculitis (e.g. bacterial), another disseminated infection, a neutrophilic dermatosis, cutaneous vasculitis or a pustular drug eruption.

Treatment

Although many antibiotics can be used for the treatment of gonorrhea, selection of therapy depends on the susceptibility of the organism that is isolated (or regional patterns), the anatomic site(s) of the infection, clinical symptoms, and the cost (especially in resource-poor settings) as well as potential side effects of the drug. Over the past few decades, strains of gonorrhea resistant to a number of antibiotics (including sulfonamides, penicillin, tetracyclines, erythromycin, spectinomycin and, more recently, quinolones) have emerged. The development of different types of resistance has led to regular revisions of gonococcal treatment recommendations. For example, in 2007, the CDC recommended that fluoroquinolones no longer be prescribed for the treatment of gonococcal infections in the US. Currently, third-generation cephalosporins are the antibiotics of choice for gonococcal infections (Table 82.13)[30]; however, treatment failures (especially with oral cephalosporins in Asian countries) and decreased *in vitro* sensitivity have been described. Single-dose therapy, preferably with intramuscular ceftriaxone, is recommended in order to maximize effectiveness and avoid patient non-compliance.

In the US, the empiric treatment of chlamydial infections concurrently with gonococcal treatment is recommended, because these two infections often occur together. However, if diagnostic testing for *Chlamydia* is negative, treatment of *C. trachomatis* is not necessary. Lastly, confirmation of cure, compliance with therapy, and partner notification are legal recommendations for gonococcal treatment and prevention in some countries.

TREATMENT RECOMMENDATIONS FOR GONOCOCCAL INFECTIONS
UNCOMPLICATED GONOCOCCAL INFECTIONS OF THE URETHRA, CERVIX OR RECTUM
Recommended regimens: • Ceftriaxone, 250 mg im as single dose (preferred) *or* • Cefixime, 400 mg po as single dose *or* • Other single-dose injectable cephalosporin regimens (e.g. ceftizoxime 500 mg im; cefoxitin 2 g im plus probenecid 1 g po; cefotaxime 500 mg im)
Alternative regimen: • Spectinomycin, 2 g im as single dose
UNCOMPLICATED GONOCOCCAL INFECTIONS OF THE PHARYNX
• Ceftriaxone, 250 mg im as single dose
GONOCOCCAL CONJUNCTIVITIS
• Ceftriaxone, 1 g im as single dose
DISSEMINATED GONOCOCCAL INFECTION
Recommended regimen: • Ceftriaxone, 1 g im or iv q24h until 24–48 hours after improvement begins, *then* cefixime, 400 mg po bid to complete at least 1 week of therapy
Alternative regimens: • Cefotaxime or ceftizoxime, 1 g iv q24h until 24-48 hours after improvement begins, then cefixime as above
Additional treatment for *C. trachomatis* (azithromycin 1 g as single dose or doxycycline 100 mg bid for 7 days) is recommended for all patients being treated for gonococcal infections, unless *Chlamydia* testing excludes co-infection
NEONATAL INFECTIONS
Disseminated gonococcal infection and gonococcal scalp abscesses in newborns • Ceftriaxone, 25–50 mg/kg iv or im qd for 7 days (10–14 if meningitis) *or* • Cefotaxime, 25 mg/kg iv or im q12h for 7 days (10–14 if meningitis)
Ophthalmia neonatorum or asymptomatic neonate born to mother with untreated gonorrhea • Ceftriaxone, 25–50 mg/kg iv or im as single dose, not to exceed 125 mg

Table 82.13 Treatment recommendations for gonococcal infections. bid, twice daily; h, hours; im, intramuscularly; iv, intravenously; po, orally; q, every; qd, daily.

CHANCROID

Synonyms: ■ Soft chancre ■ Ulcus molle

Key features

- Chancroid is characterized by acute genital ulcers and inguinal adenitis
- It is caused by the sexually transmitted Gram-negative and facultatively anaerobic bacterium *Haemophilus ducreyi*
- It is a rare disease in high-income countries, and its occurrence is closely linked with prostitution

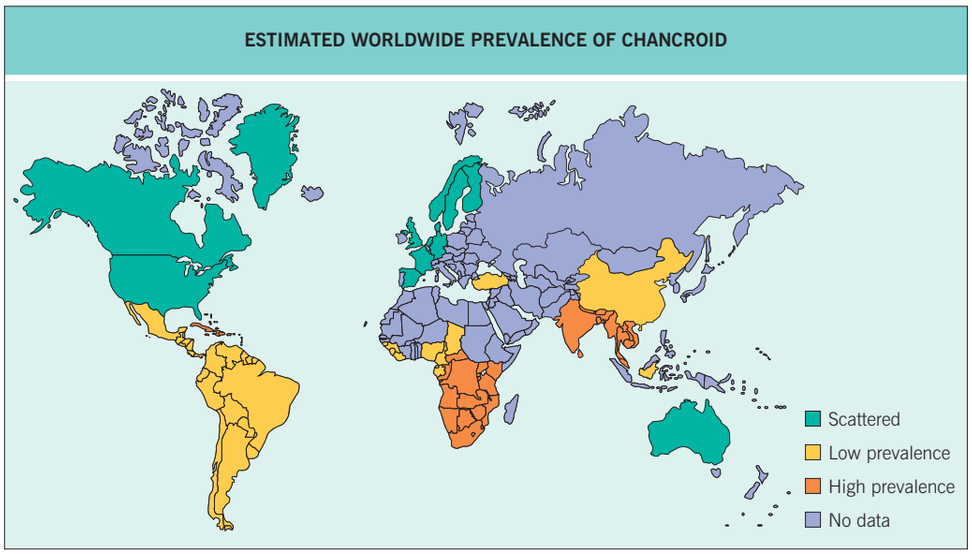


Fig. 82.19 Estimated worldwide prevalence of chancroid[32].

INFECTIOUS CAUSES OF GENITAL ULCER DISEASE				
Disease	**Incubation time**	**Clinical lesion**	**Diagnosis**	**Organism**
Genital herpes	3–7 days	Vesicles, erosions, ulcers; history of herpes infection; painful	DFA, Tzanck (if vesicles), culture, PCR	HSV 2 > 1
Primary syphilis	10–90 days, average 3 weeks	Non-purulent; usually single ulcer; indurated; relatively painless	Darkfield microscopy, serology	*Treponema pallidum*
Chancroid	3–10 days	Purulent; often multiple ulcers; soft, undermined edges; painful	Culture	*Haemophilus ducreyi*
LGV	3–12 days	Transient ulcer; indurated; painless	Serology, culture, PCR	*Chlamydia trachomatis* serovars L1–3
Donovanosis	2–12 weeks	Chronic ulcer; indurated, beefy red, friable	Smears, histology	*Klebsiella (Calymmatobacterium) granulomatis*

Table 82.14 Infectious causes of genital ulcer disease. DFA, direct fluorescent antibody assay; LGV, lymphogranuloma venereum.

History

In 1850, chancroid was first differentiated from syphilis. In 1889, Ducrey described the responsible organism as a streptobacillary rod, which he was able to subcultivate by serial autoinoculations into the forearm of a patient[31].

Epidemiology

The disease is common in parts of Africa, the Caribbean and Southeast Asia and endemic in many low-income countries (Fig. 82.19), with a worldwide annual incidence of about 7 million[33]. Outbreaks are occasionally reported in cities in high-income countries, predominantly within the US. In the US, the number of chancroid cases peaked in the early 1990s and has been very low for the past decade. In most of the disease settings, prostitutes are the reservoir for the microorganism, and men are much more frequently affected than women (ratio 10:1). In many low-income countries, chancroid is the most common cause of infectious genital ulcer disease (Table 82.14), with frequencies even higher than those of genital herpes.

Transmission

The source of infection is almost always sexual contact with infected women who have genital ulcers. The probability of transmitting chancroid after a single sexual contact is 0.35, and untreated infected women are estimated to be infectious for up to 45 days (while the clinical lesions are present)[34]. Asymptomatic carriers seem to be rare and there is no evidence that women harbor the organism for a significantly long period of time without clinical findings.

Chancroid and HIV

Chancroid and other diseases that produce genital ulcers are important risk factors for transmission of HIV. Men infected with HIV more often have had a history of genital ulcers compared with HIV-negative men[35]. The risk of acquiring HIV after having sexual contact with HIV-positive women was highest for uncircumcised men with genital ulcer disease compared with circumcised men with and without genital ulcer disease (29% versus 6% versus 2%). In women, the risk of becoming infected with HIV also increases with the number of episodes of genital ulcer disease.

The presence of increased numbers of $CD4^+$ lymphocytes and macrophages in ulcers due to infection with *H. ducreyi* provides an ideal opportunity for a latent HIV infection to become productive, with excretion of the virus into ulcer secretions. Genital lesions therefore become both a portal of viral entry for non-infected individuals and exit for HIV-infected persons[36].

Biology of the Organism

H. ducreyi is a Gram-negative, facultatively anaerobic bacillus of small size that shows a typical chaining pattern on Gram stain (Fig. 82.20). It does not share many similarities with other members of the genus *Haemophilus*.

Pathogenesis

The penetration of the microorganism occurs via microscopic barrier defects in the epidermis. Signs of inflammation develop due to infiltration of lymphocytes, macrophages and granulocytes in a primarily Th1

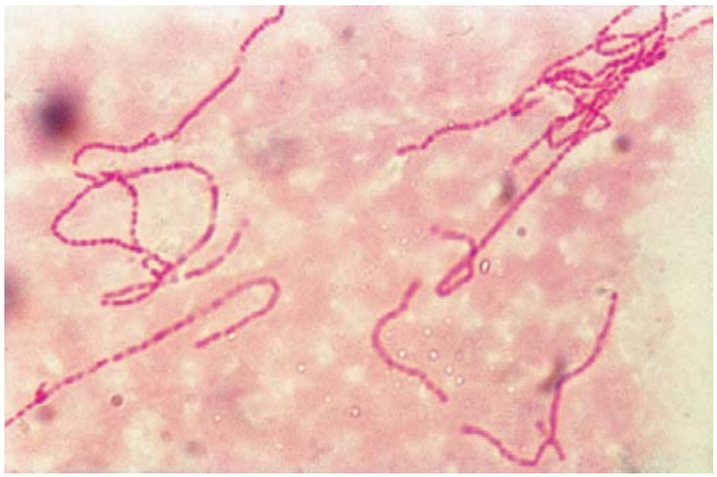


Fig. 82.20 Gram-stained smear in chancroid. This smear of exudate from a genital ulcer shows the characteristic chaining pattern of *H. ducreyi*.

cell-mediated immune response combined with pyogenic inflammation. Chancroid is associated with regional lymphadenitis due to the spread of the infection and resultant pyogenic inflammation.

Clinical Features

The incubation period is 3–10 days; usually, the onset of clinical symptoms occurs between days 4 and 7. In men, the lesion starts with a papule surrounded by erythema and soon progresses to a pustule and then a painful ulcer. The latter typically has a purulent base and soft, undermined edges and is sharply demarcated (Fig. 82.21A,B). In about one-half of infected men, several ulcers develop due to apposition with the initial lesion, and they can coalesce to form giant ulcers. Most lesions are located on the internal or external surface of the prepuce, in the coronal sulcus (particularly in uncircumcised men) or around the frenulum. They are often accompanied by edema of the prepuce.

Occasionally, a so-called "septic sore" can be observed on the shaft of the penis or prepuce, with pus trapped within the skin in the absence of an obvious ulcer. In this case, the pus that can be expressed is full of microorganisms[32]. In contrast to chlamydial infections, chancroid is symptomatic in almost all infected individuals.

Co-infections with syphilis or herpes simplex virus (HSV) are possible. In Kenya, approximately 4% of men with genital ulcer disease have a co-infection with both *T. pallidum* and *H. ducreyi* (ulcus mixtum) and about the same percentage have HSV plus *H. ducreyi*, which makes etiologic diagnosis based on clinical findings impossible.

In women, the majority of lesions are within the introital area; they may also occur on the cervix or vaginal wall, or in the perianal area, but rarely occur in an extragenital location. Lesions in women are sometimes only mildly symptomatic and are more often multiple.

In both men and women, painful inguinal lymphadenitis may accompany the genital lesions. It is more often observed in men (about 40% of patients) and is usually unilateral (see Fig. 82.21B). Inguinal buboes may rupture and lead to inguinal ulceration.

Pathology

Biopsies of chancroid classically have three zones of inflammation beneath the ulcers. The first zone has necrotic debris, fibrin and neutrophils. The middle zone is an area of granulation tissue, and the deepest zone contains lymphocytes and plasma cells. Gram-negative coccobacilli are only rarely found with tissue Gram or Giemsa stains and are best seen with smears.

Diagnosis

Material is usually obtained with a cotton swab, on which the organism can only survive for a few hours without being refrigerated at 4°C. Gram stain of *H. ducreyi* in a smear of the exudate shows a "school-of-fish" or "railroad track" pattern of small Gram-negative bacilli (see Fig. 82.20). The finding is not specific because other bacteria may have a similar arrangement, and it is insensitive because the responsible bacteria are only seen in about a third to a half of infected persons.

The accurate diagnosis of chancroid requires isolation of *H. ducreyi* on special culture media; small, non-mucoid semiopaque or translucent colonies appear after 24–72 hours if grown at 33–35°C in a 5–10% CO_2

Fig. 82.21 Chancroid. A Well-demarcated painful ulcers on the penis. **B** Multiple purulent ulcers with undermined borders. **C** Unilateral lymphadenitis with overlying erythema. *B, Courtesy, Joyce Rico, MD.*

atmosphere. Further identification methods are needed, such as the porphyrin test, to prove the requirement of hemin (factor X) for growth. There are variations in media (which are not widely available from commercial sources) and the sensitivity of culture is between 60% and 80%, depending on the quality and handling of the specimen, culture conditions and laboratory experience.

If culture is not possible or is inconclusive, diagnosis is based on the clinical picture and the exclusion of other microorganisms that cause genital ulcer disease, such as syphilis or genital herpes, as well as on the epidemiologic data and response to therapy.

Other diagnostic procedures, such as antigen detection methods, molecular biologic techniques or serologic tests, are under development and cannot yet be recommended for routine diagnosis. A PCR test may soon be on the market, allowing the diagnosis of a whole range of microorganisms causing genital ulcer disease, such as *T. pallidum*, *H. ducreyi* and HSV[37].

Differential Diagnosis

Other infections that cause genital ulcers have to be considered (see Table 82.14), as well as trauma, a fixed drug eruption, and, occasionally, carcinoma.

Treatment

Successful treatment can be achieved using several antimicrobial drugs (Table 82.15); ulcers improve within 3 days and typically heal in 14 days or less, depending on the initial lesions. The different treatment regimens cure about 95% of infected individuals, with azithromycin and ceftriaxone requiring only a single dose. Ciprofloxacin is contraindicated in pregnant and lactating women. In patients with HIV infection, the treatment recommendations are the same, but with a longer treatment course; close monitoring may be necessary because of delayed healing and possible treatment failures.

Sexual partners from the 10 days preceding the onset of symptoms should be examined and treatment offered regardless of whether the microorganism can be cultured or clinical symptoms are present.

LYMPHOGRANULOMA VENEREUM

Synonyms: ■ Durand–Nicolas–Favre disease ■ Climatic bubo ■ Strumous bubo ■ Poradenitis inguinale ■ Lymphogranuloma inguinale

Key features

- Lymphogranuloma venereum (LGV) is a rare STI caused by *Chlamydia trachomatis* serovars L1–3
- LGV is endemic in some areas of Africa, Asia and South America and is observed sporadically in other parts of the world
- The disease progresses through three stages: (1) initial infection of the genital mucosa; (2) inguinal lymphadenopathy that is usually unilateral; and (3) a firm mass and bubo with spontaneous drainage and involution, often accompanied by proctocolitis and involvement of perirectal or perianal lymphatic tissue

TREATMENT REGIMENS FOR CHANCROID
• Azithromycin, 1 g po, single dose
• Ceftriaxone, 250 mg im, single dose
• Ciprofloxacin, 500 mg po bid for 3 days*,†
• Erythromycin base, 500 mg po qid for 7 days†
*Contraindicated for pregnant or lactating women.
†Worldwide, isolates with intermediate resistance.

Table 82.15 Treatment regimens for chancroid. bid, twice daily; im, intramuscularly; po, orally; qid, four times daily.

History

Lymphogranuloma venereum (LGV) has been confused with other diseases that cause lymphadenopathy, especially syphilis, genital herpes and chancroid. A major diagnostic advantage arose with the introduction of the Frei test, a specific skin test established in 1925[38]. The first isolation of *Chlamydia* was reported in 1930, enabled by intracerebral inoculation of monkeys, followed in 1935 by cultivation in fertilized eggs[39].

Epidemiology

LGV is endemic in East and West Africa, Southeast Asia, India, South America and the Caribbean basin; it occurs sporadically throughout the rest of the world. In some countries, it is a reportable disease. LGV classically affects sailors, soldiers and travelers who acquire the disease in endemic regions. Data on the prevalence of LGV have often been based on the results of serologic tests and the Frei skin test, both of which are nonspecific and have cross-reactivity with other genito-ocular chlamydial infections.

LGV is reported more often in men than in women and the peak age correlates with the period of maximum sexual activity. However, the frequency of infection following sexual intercourse has not been well investigated. Since 2003, a series of outbreaks of LGV have been reported in Western Europe and the US[40]. The affected individuals were primarily men who lived in large cities and had sex with other men[41], many of whom had concurrent HIV infection and ulcerative proctitis.

Pathogenesis

Caused by specific *Chlamydia trachomatis* serovars (L1–3), LGV affects mainly the lymphatic tissue in the genitorectal area. The organisms enter the body via microscopic defects in the mucosa or the skin. The microorganisms then enter the lymphatics, leading to lymphangitis, perilymphangitis and infection of lymph nodes. Over a period of many weeks to months, the inflammatory process expands and results in periadenitis, involvement of a few neighboring lymph nodes, the development of abscesses (which can rupture), and the formation of fistulas and strictures. In the rectum, destruction and ulceration of the mucosa may occur. Local progression and systemic dissemination are both influenced by host immunity. Latent persistence of the microorganism within involved tissues may last for many years.

Clinical Features

The clinical manifestations of LGV can be separated into primary lesions, inguinal and ano-genito-rectal syndromes, and other manifestations (Table 82.16).

The initial clinical presentations vary, appearing after an incubation period of 3–12 days (see Table 82.16). In up to half of infected individuals, a herpetiform lesion develops at the site of exposure and heals rapidly without a scar. This transient lesion is most often located on the coronal sulcus in men and on the posterior vaginal wall in women, and it is usually accompanied by local lymphangitis. Cervicitis and urethritis are mild and often remain unrecognized. Rectal exposure might result in proctocolitis associated with rectal discharge, anal pain and tenesmus. Co-infection with other pathogens can sometimes be observed.

The secondary stage is characterized by the inguinal syndrome, in which unilateral lymphadenopathy (depending on the site of the primary infection) is accompanied by overlying erythema. The bubo is initially firm and then undergoes rapid enlargement, becoming more painful. Eventually the overlying skin develops a bluish discoloration and the bubo finally ruptures through the skin; pus may drain through numerous sinus tracts (Fig. 82.22), followed by healing. If untreated, relapses occur in about 20% of patients. Constitutional symptoms such as meningeal irritation, hepatitis and arthritis are rare and may occur due to systemic spread of the organism. Inguinal adenopathy is only observed in about one-third of infected women; proctitis and pain in the lower abdomen may be the only symptoms.

The manifestations of the ano-genito-rectal syndrome include proctocolitis and hyperplasia of the intestinal and perirectal lymphatic tissue, which lead to late manifestations dominated by local abscesses with anal fistulas as well as rectal strictures and stenoses[42].

CLINICAL MANIFESTATIONS OF LYMPHOGRANULOMA VENEREUM
INITIAL MANIFESTATIONS: 3–12 DAYS
• Papule • Erosion or ulcer • Herpetiform vesicle • Nonspecific urethritis or cervicitis
INGUINAL SYNDROME: 10–30 DAYS UP TO 6 MONTHS
• Regional lymphadenopathy (mostly inguinal and femoral; also perirectal, deep iliac) • Overlying erythema • Constitutional symptoms • Eruption of buboes • Pelvic inflammatory disease (PID), back pain
ANO-GENITO-RECTAL SYNDROME: MONTHS TO YEARS
• Proctocolitis • Hyperplasia of intestinal and perirectal lymphatic tissue • Perirectal abscesses • Ischiorectal and rectovaginal fistulas • Anal fistulas • Rectal strictures and stenoses
OTHER MANIFESTATIONS
• Urethro-genito-perineal syndrome • Peno-scrotal elephantiasis • Erythema nodosum • Submaxillary or cervical lymphadenopathy associated with oropharyngeal lesions

Table 82.16 Clinical manifestations of lymphogranuloma venereum.

Fig. 82.22 Lymphogranuloma venereum. Inguinal bubo that has ruptured and drained.

Additional manifestations include urinary incontinence because of papillary growth of the mucosa of the urethral meatus in women. Extragenital lesions in the oropharynx, due to infection from oral sexual contact, are difficult to diagnose.

Pathology

Histologically, the skin may be ulcerated. A diffuse mixed infiltrate of neutrophils, histiocytes, plasma cells and, sometimes, multinucleated giant cells is seen in the dermis. Although abscesses may occur in the skin, characteristic stellate abscesses are usually only observed in the lymph nodes. Organisms are rarely demonstrated within histiocytes (Gamma-Favre bodies) by Giemsa stain.

TREATMENT REGIMENS FOR LYMPHOGRANULOMA VENEREUM
• Recommended: doxycycline, 100 mg po bid • Alternative and in case of pregnancy: erythromycin base, 500 mg po qid
Duration for both regimens: at least 3 weeks

Table 82.17 Treatment regimens for lymphogranuloma venereum. bid, twice daily; po, orally; qid, four times daily.

Diagnosis

The diagnosis of LGV is based primarily on the detection of *Chlamydia*-specific DNA in lesional tissue by PCR or other nucleic acid amplification assays. This method is diagnostically more sensitive than is isolation of the organism via tissue culture. Typically, rectal specimens are tested for the presence of *C. trachomatis* and, if positive, are then genotyped in order to diagnose LGV. Serology testing is only recommended if it is performed in conjunction with DNA detection. In serologic assays, such as the complement fixation test or other assays that detect specific antibodies to the serovars L1–3 of *C. trachomatis*, the titer of antibodies is high. A differentiation of antibodies to L1–3 from those to other serovars is difficult but possible in the micro-immunofluorescence test. A disadvantage of this diagnostic procedure is the lack of commercial availability.

Differential Diagnosis

Other causes of lymphadenopathy in the genital region (e.g. chancroid, lymphoma, cat scratch disease) or of genital ulcers or erosions should be excluded by additional diagnostic procedures (see Table 82.14). Pyogenic and mycobacterial infections also need to be considered, as well as Crohn's disease, especially in the case of the ano-genital-rectal syndrome. Routine syphilis and HIV serologies are recommended and should be repeated after 3–6 months.

Treatment

Doxycycline is the treatment of choice, followed by macrolides (Table 82.17). Antibiotic treatment can cure the infection, but surgical intervention may be required in the case of large buboes.

Examination and treatment of sexual partners is required if contact occurred during the 30 days preceding the onset of symptoms. HIV-positive individuals may need prolonged treatment due to delayed resolution of symptoms.

DONOVANOSIS (GRANULOMA INGUINALE)

Synonyms: ■ Granuloma venereum ■ Granuloma inguinale tropicum ■ Granuloma venereum genitoinguinale ■ Granuloma genitoinguinale ■ Ulcerating sclerosing granuloma ■ Ulcerating granuloma of the pudendum ■ Serpiginous ulceration of the groin ■ Lupoid form of groin ulceration

Key features

- Donovanosis is a rare, chronic, progressive ulcerative bacterial infection with *Klebsiella granulomatis* (previously known as *Calymmatobacterium granulomatis*), a Gram-negative bacillus
- Ulcers occur primarily in the genital region
- The responsible microorganisms are found within macrophages in smears or biopsy specimens (Donovan bodies)

History

The disease was initially described in India as ulcerations followed by elephantiasis of the genitalia. The microorganism was first identified in 1905 by Donovan, who noted the characteristic Donovan bodies in macrophages and epithelial cells of the stratum malpighii[43]. In 1950,

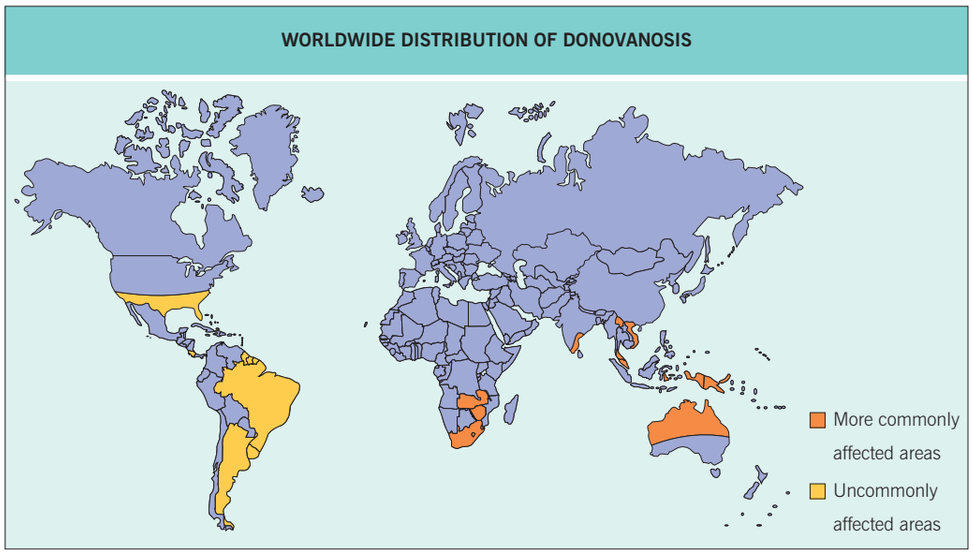


Fig. 82.23 Worldwide distribution of donovanosis.

Marmell and Santora proposed the name "donovanosis"[44]. Limited success in culturing the organism until the 1990s explains the slow progress in donovanosis research[45].

Epidemiology

In the pre-antibiotic era, donovanosis was distributed in both hemispheres, but now it is restricted to only a few low-income countries. A large number of cases, the majority in the 20- to 40-year-old age group, are reported from South Africa, India, Papua New Guinea and some parts of Australia (Fig. 82.23).

Although donovanosis is listed among the group of STIs, the disease can also occur in individuals who are not sexually active, and a wide variation in the prevalence of the infection (from 0.4% to 52%) is reported in sexual partners[46]. This is probably due to different diagnostic procedures and a long incubation period of up to 1 year. It is also not clear whether fecal contamination represents a route of non-sexual transmission.

Pathogenesis

Donovanosis is causes by *Klebsiella granulomatis* (previously known as *Calymmatobacterium granulomatis*), an intracellular Gram-negative bacillus. The primary lesion is a small cutaneous papule or nodule that contains mononuclear cells with cytoplasmic vacuoles that are filled with microorganisms. The cytoplasmic vacuoles can rupture and release bipolar Donovan bodies[47] of coccoid, coccobacillary and bacillary morphology.

Clinical Features

The average incubation period is thought to be approximately 17 days, but a range from 1 day to 1 year has been reported. A small papule or nodule initially appears and eventually ulcerates. The lesions of donovanosis are usually painless or mildly painful and slowly expand over a period of weeks to months. They are often highly vascular, with a beefy red appearance and a tendency to bleed (Fig. 82.24). Extensive tissue destruction may result, and a foul-smelling exudate is characteristic of necrotic donovanosis. Inguinal lesions occur in up to 20% of patients and are often combined with genital involvement. The most frequent sites of lesions in men are the prepuce, glans penis, frenulum and coronal sulcus. In women, the most common location is the vulvar area, where large ulcers as well as granulomatous or verrucous papules may be observed.

Extragenital lesions due to autoinoculation or secondary to dissemination have been observed in the skin, bones, abdominal cavity and oral cavity; they can involve any organ, with the bones most commonly affected. In some patients, primary extragenital lesions are seen.

Fig. 82.24 Donovanosis (granuloma inguinale). Large ulcers with a characteristic "beefy" appearance. *Courtesy, Joyce Rico, MD.*

Pathology

Histologically, ulceration with exuberant granulation tissue is evident. Pseudoepitheliomatous hyperplasia may be present at the ulcer edge. A diffuse infiltrate of histiocytes, plasma cells and a few lymphocytes is present in the dermis, sometimes with small neutrophilic abscesses. The organisms are easier to find in smears than in histologic sections. They are 1–2 microns in diameter and are within histiocytes, as is also characteristic of leishmaniasis, rhinoscleroma and histoplasmosis (see Table 77.16). Bipolar staining is found at two ends of the organisms (Donovan bodies), giving them a "safety pin" appearance.

Diagnosis

The diagnosis of donovanosis is usually based on the demonstration of Donovan bodies in smears from active lesions by Giemsa, Wright or Leishman stains. The smears are prepared from tissue scrapings or touch preparations of biopsies taken from the dermis or subcutis of lesions.

There are no serologic tests available for the diagnosis of donovanosis. Nucleic acid amplification assays such as PCR are under investigation, but they are not yet commercially available. Although successful culture of *K. granulomatis* has been reported in human peripheral blood

mononuclear cells and Hep2 cells, attempts to grow this organism in fertilized eggs or on routinely available artificial media have been unsuccessful.

Differential Diagnosis

Donovanosis is frequently confused with other diseases of the anogenital region. Other infectious causes of genital ulcer disease have to be considered (see Table 82.14); early lesions of secondary syphilis, especially condylomata lata, often have a clinical appearance similar to donovanosis. Carcinoma, amebiasis, tuberculosis, dimorphic fungal infections, pyoderma vegetans, Crohn's disease and pyoderma gangrenosum may represent additional diagnostic possibilities.

Treatment

The recommended treatment is doxycycline, but treatment regimens in different geographic areas reflect the availability of antibiotics; for example, in Papua New Guinea, chloramphenicol is used. Trimethoprim–sulfamethoxazole, quinolones and erythromycin (recommended during pregnancy) have also been shown to be effective in the treatment of donovanosis (Table 82.18). The recommended length of treatment is at least 3 weeks and until all lesions are healed. For azithromycin, successful treatment with a daily dose of 500 mg for 1 week has been reported[48]. However, the CDC 2010 guidelines recommend 1 g weekly for at least 3 weeks.

Examination of sexual partners is recommended if there has been sexual contact during the previous 60 days or if the partner is symptomatic. Relapses can occur 6–18 months later, despite effective initial treatment.

TREATMENT REGIMENS FOR DONOVANOSIS
RECOMMENDED:
• Doxycycline, 100 mg po bid
ALTERNATIVE:
• Trimethoprim–sulfamethoxazole, 1 double-strength (160 mg/800 mg) tablet po bid *or* • Ciprofloxacin, 750 mg po bid *or* • Erythromycin base, 500 mg po qid *or* • Azithromycin 1 g po once weekly
Duration for all regimens: until all lesions completely healed (at least 3 weeks)

Table 82.18 Treatment regimens for donovanosis. For any of the regimens, the addition of an aminoglycoside (e.g. gentamicin 1 mg/kg iv q8h) should be considered if lesions do not respond within the first few days of therapy.

REFERENCES

1. Rosahn PD. Autopsy studies in syphilis. J Vener Dis. 1947;649 Information supplement # 21, US Public Health Service, Venereal Disease Division, Washington DC, pp. 1–67.
2. Hollander DH. Treponematosis from pinta to venereal syphilis revisited: hypothesis from temperature determination of disease patterns. Sex Transm Dis. 1981;8:34–7.
3. Fieldsteel AH. Genetics of treponema. In: Schell RF, Musher DM (eds). Pathogenesis and Immunology of Treponemal Infection. New York: Marcel Dekker, 1983:39–55.
4. Gjestland T. The Oslo study of untreated syphilis: an epidemiologic investigation of the natural course of syphilis infection based on a restudy of the Boeck-Bruusgaard material. Acta Derm Venereol Suppl (Stockh). 1955;35(suppl. 34):3–368; Annex I-LVI.
5. Olansky S, Schuman SH, Peters JJ, et al. Untreated syphilis in the male Negro: X. Twenty years of clinical observation of untreated syphilitic and presumably non-syphilitic groups. J Chronic Dis. 1956;4:177–85.
6. Heller JR Jr, Bruyere PT. Untreated syphilis in the male Negro: II. Mortality during 12 years of observation. J Vener Dis Inf. 1946;27:34–8.
7. Rockwell DH, Yobs AR, Moore MB Jr. The Tuskegee study of untreated syphilis. Arch Intern Med. 1964;114:792–8.
8. Smibert RM. Genus III: Treponema Schaudinn 1905, 1728. In: Krieg NR, Holt JG (eds). Bergey's Manual of Systematic Bacteriology, Vol. 1. Baltimore: Williams, 1984:49–57.
9. Lukehart SA. Biology of *Treponemes*. In: Holmes KK, Sparling PF, Stamm WE, et al (eds). Sexually Transmitted Diseases. New York: McGraw-Hill, 2008:647–59.
10. Baughn RE, McNeely MC, Jorizzo JL, Musher DM. Characterization of the antigenic determinants and host components in immune complexes from patients with secondary syphilis. J Immunol. 1986;136:1406–14.
11. Marra CM. Syphilis and human immunodeficiency virus infection. Semin Neurol. 1992;12:43–50.
12. Sparling PF. Clinical manifestations of syphilis. In: Holmes KK, Sparling PF, Stamm WE, et al (eds). Sexually Transmitted Diseases. New York: McGraw-Hill, 2008:661–84.
13. Merritt HH, Adams RD, Solomon HC. Neurosyphilis. New York: Oxford University Press, 1946.
14. Shafii T, Radolf JD, Sanchez PJ, et al. Congenital syphilis. In: Holmes KK, Sparling PF, Stamm WE, et al (eds). Sexually Transmitted Diseases. New York: McGraw-Hill, 2008:1577–612.
15. Larsen SA, Steiner BM, Rudolph AH. Laboratory diagnosis and interpretation of tests for syphilis. Clin Microbiol Rev. 1995;8:1–21.
16. Rolfs RT. Treatment of syphilis 1993. Clin Infect Dis. 1995;29(suppl.):S23–38.
17. van Voorst Vader PC. Syphilis management and treatment. Dermatol Clin. 1998;16:699–711.
18. Riedner G, Rusizoka MJ, Todd J, et al. Single-dose azithromycin versus penicillin G benzathine for the treatment of early syphilis. N Engl J Med. 2005;353:1236–44.
19. French P, Gomberg M, Janier M, et al. 2008 European guidelines on the management of syphilis. Int J STD AIDS. 2009;20:300–9.
20. Morton RS. Gonorrhea. In: Rook A (ed.). Major Problems in Dermatology, Vol. 9. London: WB Saunders, 1977.
21. Thayer JD, Martin JE. Selective medium for the cultivation of *N. gonorrhoeae* and *N. meningitidis*. Public Health Rep. 1964;79:49–57.
22. Kellogg DS Jr, Peacock WL Jr, Deacon WE, et al. *Neisseria gonorrhoeae*: 1. Virulence genetically linked to clonal variation. J Bacteriol. 1963;85:1274–9.
23. Parge HE, Forest KT, Hickey MJ, et al. Structure of the fibre-forming protein pilin at 2.6A resolution. Nature. 1995;378:32–8.
24. Sparling PF. Biology of *Neisseria gonorrhoeae*. In: Holmes KK, Sparling PF, Stamm WE, et al (eds). Sexually Transmitted Diseases. New York: McGraw-Hill, 2008:607–26.
25. Handsfield HH, Lipman TO, Harnisch JP, et al. Asymptomatic gonorrhea in men: diagnosis, natural course, prevalence, and significance. N Engl J Med. 1974;290:117–23.
26. Wiesner PJ, Tronca E, Bonin P, et al. Clinical spectrum of pharyngeal gonococcal infections. N Engl J Med. 1973;288:181–5.
27. Hook EW III, Handsfield HH. Gonococcal infections in the adult. In: Holmes KK, Sparling PF, Stamm WE, et al (eds). Sexually Transmitted Diseases. New York: McGraw-Hill, 2008:627–45.
28. Smith KR, Ching S, Lee H, et al. Evaluation of ligase chain reaction for use with urine for identification of *Neisseria gonorrhoeae* in females attending a sexually transmitted disease clinic. J Clin Microbiol. 1995;33:455–7.
29. Stary A, Ching SF, Teodorowicz L, Lee H. Comparison of ligase chain reaction and culture for detection of *Neisseria gonorrhoeae* in genital and extragenital specimens. J Clin Microbiol. 1997;35:239–42.
30. Centers for Disease Control (CDC). Update to CDC's Sexually Transmitted Diseases Treatment Guidelines, 2006: fluoroquinolones no longer recommended for treatment of gonococcal infections. MMWR Morb Mortal Wkly Rep. 2007;56:332–6.
31. Ducrey A. Experimentelle Untersuchungen über den Ansteckungsstoff des weichen Schankers und über die Bubonen. Monatshr Prakt Dermatol. 1889;9: 387–405.
32. Ronald A. Chancroid. In: Mandell GL (ed.-in-chief), Rein MF (ed.). Atlas of Infectious Diseases. Vol. 5. Sexually Transmitted Diseases. New York: Current Medicine, 1995:16.1–10.
33. World Health Organization Press Release: WHO/64. Sexually transmitted diseases. Three hundred and thirty three million new, curable cases in 1995. Geneva: World Health Organization, 1995.
34. Brunham RC, Ronald AR. Epidemiology of sexually transmitted diseases in developing countries. In: Wasserheit J, Aral S, Holmes KK (eds). Research Issues in Human Behavior and Sexually Transmitted Diseases in the AIDS Era. Washington, DC: American Society for Microbiology, 1991:61–80.
35. Simonsen JN, Cameron DW, Gakinya MN, et al. Human immunodeficiency virus infection among men with sexually transmitted diseases. Experience from a center in Africa. N Engl J Med. 1988;319:274–8.
36. Spinola SM. Chancroid and *Haemophilus ducreyi*. In: Holmes KK, Sparling PF, Stamm WE, et al (eds). Sexually Transmitted Diseases. New York: McGraw-Hill, 2008:689–99.
37. Orle KA, Gates CA, Martin DH, et al. Simultaneous PCR detection of *Haemophilus ducreyi, Treponema pallidum*, and herpes simplex virus types 1 and 2 from genital ulcers. J Clin Microbiol. 1996;34:49–54.
38. Frei W. Eine neue Hautreaktion bei Lymphogranuloma inguinale. Klin Wochenschr. 1925;4:2148–9.
39. Favre M, Hellerstrom S. The epidemiology, aetiology and prophylaxis of lymphogranuloma inguinale. Acta Derm Venereol Suppl (Stockh). 1954;34:1–68.
40. French P, Ison CA, Macdonald N. Lymphogranuloma venereum in the United Kingdom. Sex Transm Infect. 2005;81:97–8.
41. Stark D, van Hal S, Hillman R, et al. Lymphogranuloma venereum in Australia: anorectal *Chlamydia trachomatis* serovar L2b in men who have sex with men. J Clin Microbiol. 2007;45:1029–31.
42. Stamm WE. Lymphogranuloma venereum. In: Holmes KK, Sparling PF, Stamm WE, et al. (eds). Sexually Transmitted Diseases. New York: McGraw-Hill, 2008:595–606.
43. Donovan C. Medical cases from Madras General Hospital. Ind Med Gaz. 1905;40:411–14.
44. Marmell M, Santora E. Donovanosis: granuloma inguinale. Am J Syph. 1950;34:83–90.
45. Kharsany AB, Hoosen AA, Kiepiela P, et al. Culture of *Calymmatobacterium granulomatis*. Clin Infect Dis. 1996;22:391.
46. Hart G. Donovanosis (granuloma inguinale). In: Mandell GL (ed.-in-chief), Rein MF (ed.). Atlas of Infectious Diseases. Vol. 5. Sexually Transmitted Diseases. 1999:1–10.
47. O'Farell N. Donovanosis. In: Holmes KK, Sparling PF, Stamm WE, et al. (eds). Sexually Transmitted Diseases. New York: McGraw-Hill, 2008;701–8.
48. Bowden FJ, Mein J, Plunkett C, Bastian I. Pilot study of azithromycin in the treatment of genital donovanosis. Genitourin Med. 1996;72;17–9.

This page intentionally left blank

Protozoa and Worms 83

Steven A Nelson and Karen E Warschaw

Chapter Contents

Protozoa 1391
Leishmaniasis 1391
Cutaneous diseases caused by ameboid protozoa 1397
Trypanosomiasis 1399
Toxoplasmosis 1404
Worms (helminths) 1406
Cutaneous larva migrans 1406
Onchocerciasis 1409
Filariasis 1416
Schistosomiasis and swimmer's itch 1417
Cysticercosis and echinococcosis 1419

Key features

- Protozoa are responsible for many tropical diseases that not only affect large regions of the world but also can have different clinical presentations in the Old versus the New World (e.g. leishmaniasis)
- Protozoal infections (e.g. toxoplasmosis) can lead to significant morbidity in immunocompromised hosts
- Worms (helminths) are common parasites with a worldwide distribution; cutaneous manifestations vary considerably, from pruritus ani to elephantiasis
- Even helminthic diseases with a restricted geographic distribution, such as onchocerciasis and echinococcosis, may be observed in individuals from non-endemic areas as a result of tourism, disaster relief efforts or military service

PROTOZOA

LEISHMANIASIS

Synonyms: ■ Old World cutaneous leishmaniasis: oriental sore, Delhi boil, Baghdad boil ■ New World cutaneous and mucocutaneous leishmaniasis: chiclero ulcer (Mexico), uta and espundia (Peru), ulcera de Bauru (Brazil), bush or forest yaws, pian boi (Guyanas) ■ Diffuse cutaneous leishmaniasis: anergic, disseminated, lepromatous or pseudolepromatous leishmaniasis ■ Visceral leishmaniasis: kala-azar, Dumdum fever

Key features

- Chronic parasitic (protozoan) disease in which organisms are found within phagolysosomes of mononuclear phagocytes
- The clinical manifestations of leishmaniasis depend on the host's cell-mediated immune response and the species of *Leishmania* involved; clinical subtypes include cutaneous, mucocutaneous, diffuse cutaneous, and visceral leishmaniasis
- The most common cutaneous finding is a papule that develops at the site of inoculation and then enlarges and ulcerates
- The vector is a sandfly infected with promastigotes
- Has a worldwide distribution but is endemic in Latin America, the Mediterranean basin, and parts of Asia and Africa

Introduction

Leishmaniasis encompasses a spectrum of chronic infections in humans and several animal species. It is caused by over 20 species of *Leishmania* (Table 83.1), flagellated protozoans belonging to the order Kinetoplastidae. Transmission is via the bite of infected female sandflies from the genera *Phlebotomus* and *Lutzomyia*.

The disease has a worldwide distribution, affecting millions of people in South America, the Mediterranean basin, and parts of Asia and Africa[1] (Figs 83.1 & 83.2). There are four major clinical patterns: (1) cutaneous, which is restricted to the skin and is seen more often in the Old World; (2) mucocutaneous, which affects both the skin and mucosal surfaces and occurs almost exclusively in the New World; (3) diffuse cutaneous, which occurs mainly in the New World; and (4) visceral, which affects the organs of the mononuclear phagocyte system, e.g. liver, spleen[2,3].

Epidemiology

Worldwide, there are approximately 2 million new cases of leishmaniasis annually, with cutaneous or mucocutaneous disease in >75% of affected individuals, and it is estimated that 12 million people are currently infected[3a]. Over 90% of cutaneous infections with *Leishmania* occur in the Middle East (Afghanistan, Algeria, Iran, Iraq, Saudi Arabia, Syria), Brazil and Peru, but the disease is also seen in the Mediterranean basin, sub-Saharan Africa, Central Asia, and India (see Fig. 83.1). South-central Texas is the only endemic area for cutaneous leishmaniasis in the US; most infections diagnosed in the US are acquired outside of the country[4]. Mucocutaneous leishmaniasis is endemic in Central America and the northern regions of South America. Although the visceral form of leishmaniasis has a worldwide distribution, it is seen most frequently in Africa and Asia[1,2,5].

Old World cutaneous leishmaniasis is usually due to *L. major* or *L. tropica*, and less often to *L. infantum* (Europe) or *L. aethiopica* (Ethiopia and Kenya) (see Table 83.1). In the New World, cutaneous leishmaniasis is caused primarily by subspecies of *L. mexicana* and mucocutaneous disease is associated with *L. braziliensis*. Diffuse cutaneous leishmaniasis is most commonly associated with *L. amazonensis*[3]. Infections with *L. donovani* (e.g. India, Bangladesh and the Sudan), *L. infantum* (e.g. Europe, especially in the setting of HIV infection) and *L. chagasi* (e.g. Central and South America) are the major causes of visceral leishmaniasis (Table 83.2). The species of *Leishmania* can also vary within a particular geographic region. For example, in the Middle East, *L. major* is found in rural areas where the primary animal reservoirs are desert rodents, whereas *L. tropica* is endemic in urban areas[5].

Canine and rodent species act as reservoirs for *Leishmania* (see Table 83.1). Transmission between these species (as well as to humans) is via sandflies, primarily of the genera *Phlebotomus* (Old World) and *Lutzomyia* (New World). Human-to-human spread of *L. tropica* can also occur. In general, humans contract leishmaniasis as accidental hosts when they intrude into the sandfly's habitat. Overall, the disease is seen most commonly in men between 20 and 40 years of age, but Old World cutaneous leishmaniasis occurs more often in children[2].

Pathogenesis

Leishmania spp. are obligate intracellular parasites that exist in two forms: the promastigote and the amastigote. In the gut of the sandfly,

EPIDEMIOLOGIC AND CLINICAL PATTERNS OF INFECTIONS WITH *LEISHMANIA* SPECIES

Complex	Major species	Major reservoirs	Major geographic distribution	Clinical patterns (in addition to cutaneous)	Clinical forms of the cutaneous pattern
Leishmania donovani	*L. donovani*	Humans	Sudan, Kenya, Tanzania, India, Bangladesh	**Visceral, PKD**, mucosal (rare)	(Uncommon)
	L. infantum	Dogs, foxes	Mediterranean region	**Visceral (favors children)**, PKD*, mucosal† (rare)	Favors children (uncommon)
	*L. chagasi***	Dogs, foxes, opossums	Central and South America		
Leishmania tropica	*L. major*	Rodents	Arid areas of Africa (north and south of the Sahara), Middle East and Central Asia	Mucosal (rare)	**Old World zoonotic/rural** (moist, early ulcerative with rapid course), recidivans (rare), lupoid (rare)
	L. tropica	Humans, dogs	Eastern Mediterranean region, Middle East, Central Asia	Visceral (rare), mucosal (rare)	**Old World anthroponotic/urban** (dry, late ulcerative with chronic course), recidivans, lupoid
	L. aethiopica	Hyraxes	Ethiopia, Kenya, Yemen	Diffuse cutaneous	
Leishmania mexicana	*L. mexicana*	Forest rodents	Mexico, Central America	Diffuse cutaneous (rare)	**New World** Variants include ulcerative, pustular, impetigo-like, erysipeloid, sarcoidosis-like, papulotuberous, verrucous, sporotrichoid, eczematous
	L. amazonensis	Forest rodents	South America	**Diffuse cutaneous**, mucocutaneous, visceral (rare), PKD (rare)	
	L. venezuelensis, pifanoi, garnhami	Unknown	Venezuela	Diffuse cutaneous (rare)	
Leishmania (Viannia) braziliensis	*L. braziliensis*	Forest rodents	Central and South America	**Mucocutaneous**, visceral†	
	L. guyanensis	Sloths, anteaters	Guyana, Brazil	Mucocutaneous	
	L. panamensis	Sloths	Panama, Costa Rica, Colombia	Mucocutaneous	
	L. peruviana	Dogs	Peru, Argentina		

*Rare/controversial; reported in children and in HIV-infected adults following antiretroviral therapy.
**Term used for *L. infantum* when found in the New World.
†Especially in immunocompromised hosts.

Table 83.1 Epidemiologic and clinical patterns of infections with *Leishmania* species. Common clinical patterns for particular species are in bold. Additional minor species include *L. garnhami*, *naiffi*, *lainsoni*, *colombiensis*, *shawi* and *archibaldi*. *Viannia* is a subgenus of *Leishmania*. Mucosal leishmaniasis refers to oronasal lesions not preceded or accompanied by cutaneous involvement. PKD, post-kala-azar dermal leishmaniasis. *Modified from Lupi O, Barlett BL, Haugen RN, et al. Tropical dermatology: tropical diseases caused by protozoa, J Am Acad Dermatol 2009;60:897–925 and Davidson RN, Leishmaniasis. In Cohen J, Powderly WG, eds, Infectious Diseases. Edinburgh: Mosby, 2004.*

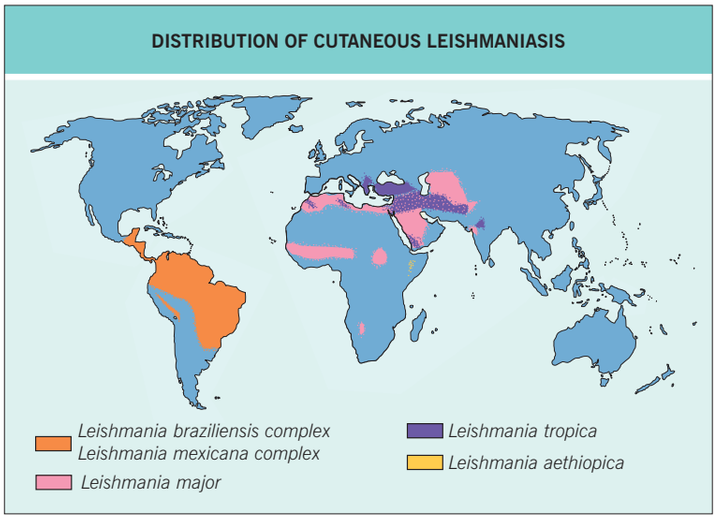


Fig. 83.1 Distribution of cutaneous leishmaniasis. Additional etiologies are in Figure 83.2. *Adapted with permission from Davidson RN, Leishmaniasis. In Cohen J, Powderly WG, eds, Infectious Diseases. Edinburgh: Mosby, 2004.*

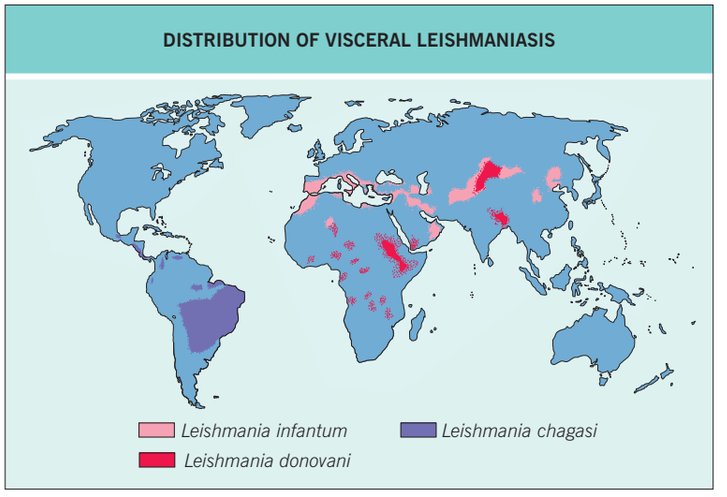


Fig. 83.2 Distribution of visceral leishmaniasis. These organisms, in particular *L. infantum* and *L. donovani*, can also cause cutaneous disease. *Adapted with permission from Davidson RN, Leishmaniasis. In Cohen J, Powderly WG, eds, Infectious Diseases. Edinburgh: Mosby, 2004.*

EPIDEMIOLOGY AND CLINICAL PATTERNS OF VISCERAL LEISHMANIASIS		
Type of disease	**Major species**	**Major geographic distribution**
Kala-azar (60% 10–20 years of age)	*Leishmania donovani*	India, China (north of Yangtze River), Kenya, Sudan
Infantile kala-azar (90% <10 years of age)	*L. infantum*	Central Asia, China, Iraq, France, Italy, Egypt, elsewhere in the Mediterranean basin, Saudi Arabia
	L. chagasi	Brazil, Colombia, Venezuela, Central America, Mexico
Oronasal kala-azar	*L. infantum**	France
Post-kala-azar dermal leishmaniasis	*L. donovani* *L. infantum*† *L. amazonensis*	India, China, Kenya Mediterranean basin South America
Atypical kala-azar complex (typically in adults)	*L. tropica* *L. amazonensis* *L. brazilensis**	Northeast Saudi Arabia South America South and Central America

*Especially in immunocompromised hosts.
†Controversial (see Table 83.1).

Table 83.2 Epidemiology and clinical patterns of visceral leishmaniasis.

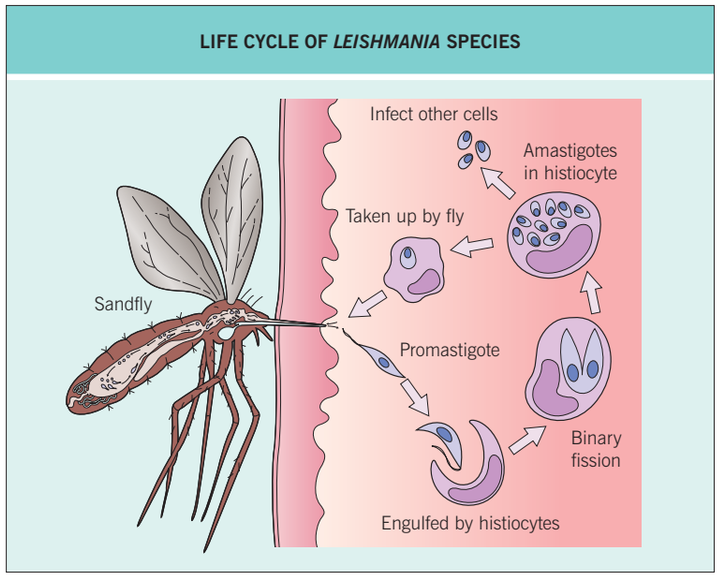


Fig. 83.3 Life cycle of *Leishmania* species. Promastigotes develop within the gut of the sandfly and then migrate to the proboscis.

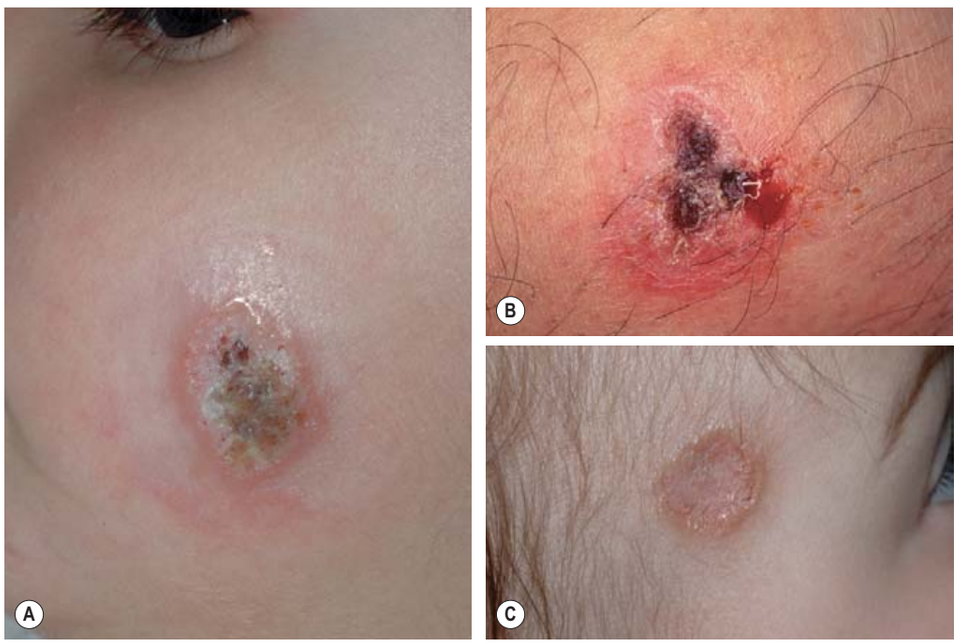


Fig. 83.4 Variable presentations of cutaneous leishmaniasis. Ulcerated plaques with rolled border (**A**) and central crusting (**A, B**). Plaque with translucent borders containing telangiectasias and central scarring (**C**). Cutaneous leishmaniasis is sometimes mistaken for a basal cell carcinoma. *A, C, Courtesy, Julie V Schaffer, MD.*

the organisms multiply as extracellular flagellated promastigotes. Following migration to the proboscis, the parasites are inoculated (in the promastigote form) via the sandfly bite. Once inoculated into the skin, the parasites are rapidly engulfed by the host's mononuclear phagocytes, where they transform into amastigotes and multiply via binary fission (Fig. 83.3). The incubation time from infection until the first clinical manifestation can vary from ≤2 weeks (cutaneous lesions; typically several weeks to 2 months) to more than 2 years (mucocutaneous lesions or visceral involvement; typically 3 to 9 months)[6].

The clinical manifestations of leishmaniasis primarily depend on the host's cell-mediated response and on the species of *Leishmania* involved (see Table 83.1). A robust Th1 response (i.e. production of interleukin-2 [IL-2] and interferon-γ [IFN-γ]) is associated with quicker resolution, whereas a lack of a Th1 response or the development of a Th2-type response (i.e. production of IL-4 and IL-10) is associated with progression of the disease[7–9]. Other factors that play a role in the parasite–human interaction include the amount of exposure to and the virulence of the parasite (e.g. macrophage-resistant strains of *Leishmania*). Mucocutaneous disease is associated with infection of the *Leishmania* organisms with *Leishmania* RNA virus-1 (LRV1); this virus is recognized by human Toll-like receptor 3, leading to a proinflammatory cascade that subverts the immune response to *Leishmania*, leading to persistence of the parasite and disease progression[9a].

IFN-γ is the most potent cytokine involved in the induction of cidal activity against the organisms residing within macrophage phagolysosomes. It leads to the production of oxygen species and activates naive $CD4^+$ cells to become Th1 cells (see Ch. 4). The latter differentiation process is aided by IL-12, which stimulates natural killer (NK) cells to produce IFN-γ[7,9,10]. Tumor necrosis factor-α (TNF-α) is also important for the control of *Leishmania* infections[8]. Produced by macrophages and NK cells, it amplifies the macrophage activation triggered by IFN-γ. Use of TNF-α inhibitors increases the risk of developing leishmaniasis, especially the visceral form[11].

Animals that have recovered from *L. tropica* or *L. donovani* infections acquire immunity against reinfection from the same species of *Leishmania*, but not against other species. Similarly, humans with the New World form of cutaneous leishmaniasis have been inoculated successfully with *L. tropica*. However, it has been reported that surviving an episode of visceral leishmaniasis confers lifelong immunity against all types of leishmaniasis.

Clinical Features

Cutaneous leishmaniasis

Cutaneous leishmaniasis is divided into two subsets based on the geographic region where the infection is acquired: Old World and New World. These two groups differ with regard to the causative organisms, vectors, reservoirs, clinical presentation, and prognosis[3]. Both Old World and New World cutaneous leishmaniasis usually begin as a small, well-circumscribed papule at the inoculation site. This lesion may slowly enlarge over several weeks into a nodule or plaque (Fig. 83.4) and then become ulcerated or verrucous. Exposed sites such as the face, neck, arms, and legs are most commonly involved (Fig. 83.5) For example, the chiclero ulcer results from infection on the ear in forest workers who collect gum from the chicle tree in Mexico and Central America. The lesions of leishmaniasis are often solitary but may be multiple, with the formation of satellites or lymphatic spread (sporotrichoid pattern; Fig. 83.6). The majority of acute cutaneous infections resolve spontaneously within several months with scarring[12] (cicatricial stage; Fig. 83.7), but a minority become chronic or disseminated.

Several clinical forms of Old World cutaneous leishmaniasis have been described, including zoonotic, anthroponotic, recidivans, and lupoid leishmaniasis. Zoonotic cutaneous leishmaniasis (rural, moist, or early ulcerative form) usually has a mild, rapid course and is caused by *L. major*. Anthroponotic cutaneous leishmaniasis (urban, dry, or late ulcerative), has a more chronic course and is caused by *L. tropica*[3]. Leishmaniasis recidivans is a chronic, destructive form that is characterized by recurrence at the site of an original ulcer, generally within 2 years and often at the edge of the scar[12]. Anthroponotic or, less frequently, zoonotic cutaneous leishmaniasis occasionally develops into chronic lupoid leishmaniasis, which clinically and histologically (epithelioid granulomas surrounded by lymphocytes) resembles the lupus vulgaris form of cutaneous tuberculosis. The amastigotes are few in number and difficult to find in lupoid leishmaniasis, making establishment of the diagnosis more challenging.

New World cutaneous leishmaniasis has a wide clinical spectrum, including patterns such as sporotrichoid, pustular, impetigo-like, eczematoid, sarcoidosis-like, erysipeloid, papulotuberous, and verrucous[12].

Diffuse (disseminated) cutaneous leishmaniasis

Diffuse cutaneous leishmaniasis usually develops in the setting of reduced cell-mediated immunity. *L. aethiopica* (in Africa) and *L. amazonensis* (in the Americas) are the most common causes (see Table 83.1). Multiple keloid-like lesions on the face and limbs are usually observed[3]. Nasal infiltration and ulceration may be present, but without destruction of the nasal septum. There may also be laryngeal and pharyngeal involvement[12].

Mucocutaneous leishmaniasis

After a time period ranging from a few months to more than 20 years, some patients infected with *Leishmania* spp. in the *Viannia* subgenus

Fig. 83.5 Ulcerative form of cutaneous leishmaniasis. A Multiple lower extremity ulcers in a rural worker. **B** Expanding ulcer on the leg as well as a positive Montenegro test. This type of lesion could be misdiagnosed as pyoderma gangrenosum. *A, Courtesy, Omar P Sangüeza, MD.*

Fig. 83.6 Sporotrichoid form of cutaneous leishmaniasis.

Fig. 83.7 Scars secondary to previous cutaneous leishmaniasis. Circular scars at previous sites of cutaneous leishmaniasis are often the only sign of a prior infection. *Courtesy, Omar P Sangüeza, MD.*

Fig. 83.8 Mucocutaneous leishmaniasis. There is edema and infiltration of the nose as well as focal deep ulceration of the vestibule and upper lip. *Courtesy, Omar P Sangüeza, MD.*

Fig. 83.9 Mucocutaneous leishmaniasis (espundia). Ulceration and induration of the nasal vestibule extending on to the cutaneous lip due to *Leishmania braziliensis*. *Courtesy, Kalman Watsky, MD.*

SYSTEMIC FEATURES OF VISCERAL LEISHMANIASIS (*L. DONOVANI*)	
Clinical features	**Proportion affected (%)**
Age <9 years	20 (*L. infantum* and *L. chagasi* more commonly affect children and infants)
Age <15 years	45
Fever	85–100
Wasting	70–100
Loss of appetite	60–75
Cough	70–85
Epistaxis	45–55
Diarrhea	25–55
Vomiting	2–35
Splenomegaly	90 (adults); >95 (children)
Hepatomegaly	55–65
Lymphadenopathy	55–85 (uncommon outside of Africa)
Jaundice	2–7
Edema	2–7
Laboratory findings	
Globulin >30 g/l	95
Albumin <30 g/l	90
Anemia	60–90
Leukopenia	85
Thrombocytopenia	75
Elevated bilirubin	15
Elevated liver transaminases	20
Elevated alkaline phosphatase	40
Positive *Leishmania* serology	95
Parasitologically proven	95

Table 83.3 Systemic features of visceral leishmaniasis *(L. donovani)*. The duration of symptoms is usually 2 to 4 months, but it is typically shorter in children. *With permission from Davidson RN, Leishmaniasis. In Cohen J, Powderly WG, eds, Infectious Diseases. Edinburgh: Mosby, 2004.*

(most commonly *L. braziliensis*; rarely *L. panamensis*, *L. guyanensis* or hybrid genotypes) develop mucocutaneous disease[13]. Mucosal lesions range from edema of the lips and nose to perforation of the nasal and laryngeal cartilage as well as the palate. Infiltration and/or ulceration of the nose, lips and oropharynx is characteristic (Fig. 83.8). Only rarely are the ocular or genital mucosae involved. In some patients, there is extensive loss of tissue in both the mouth and nose, causing a characteristic "tapir face" known as espundia (Fig. 83.9). Alterations in phonation because of destruction of the vocal cords may also occur[12–14].

Visceral leishmaniasis (kala-azar)

Visceral leishmaniasis, or kala-azar, occurs when the parasite spreads to the bone marrow, spleen, and liver[3]. It is most commonly caused by infection with *L. donovani* in adults and *L. infantum* or *L. chagasi* in children. The incubation period ranges from 1 to 36 months. Fever, wasting, cough, lymphadenopathy and hepatosplenomegaly are the most common systemic findings (Table 83.3). There may be an abrupt onset or slow progression, and the fever may be continuous or intermittent. Additional complications include enteritis, oronasal or gastrointestinal hemorrhage, pneumonia and nephritis, which may lead to death[12]. Cutaneous findings may be disease-specific (e.g. papules, nodules or ulcers at infected sites) or nonspecific (e.g. purpura, hyperpigmentation, xerosis and kwashiorkor-like hair discoloration).

Post-kala-azar dermal leishmaniasis develops as a sequela of untreated or treated visceral leishmaniasis[3] (Fig. 83.10). This form of cutaneous leishmaniasis is most commonly seen in Sudan and India, where it occurs in 50% and 10% of patients cured of visceral leishmaniasis, respectively[15]. The onset can be during or up to 20 years after treatment[15]. Skin findings can include hypopigmented macules, malar erythema, skin-colored nodules and verrucous papules[16].

Leishmaniasis and HIV

Co-infection of HIV and leishmaniasis can alter the progression and presentation of leishmaniasis, especially the visceral form[17] (see Ch.

Fig. 83.10 Post-kala-azar dermal leishmaniasis. Nodules of various sizes, some pedunculated, are seen in this patient who had been treated for kala-azar over a period of 6 months, 20 years previously. *With permission from Peters W, Pasvol G, Tropical Medicine and Parasitology, 6th edition. London: Mosby, 2007.*

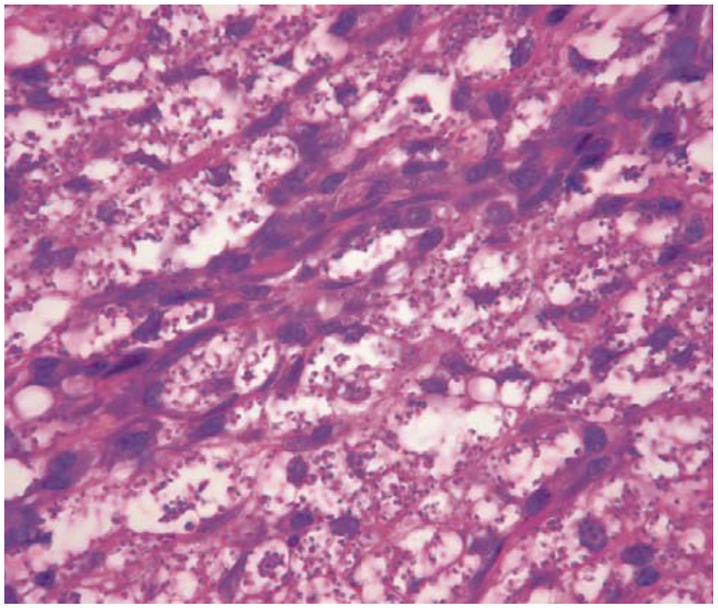


Fig. 83.11 Histopathology of leishmaniasis. Parasitized macrophages that contain amastigotes are seen in the dermis. *Courtesy, Jennifer McNiff, MD.*

78). HIV infection increases the risk of developing visceral leishmaniasis 100- to over 2000-fold. Co-infection often results in an atypical clinical presentation, reduced therapeutic response, and increased mortality. Chronic immune activation from the *Leishmania* infection may lead to increased HIV load and accelerated progression of AIDS, while the immunosuppressed state from HIV creates an ideal environment for parasitic growth[16]. Co-infection with HIV is thought to be present in 2% to >10% of patients with visceral leishmaniasis who live in *Leishmania*-endemic areas[17].

Pathology

Histologically, cutaneous lesions show areas of ulceration, pseudoepitheliomatous hyperplasia and a mixed inflammatory infiltrate composed of histiocytes, lymphocytes, plasma cells and neutrophils. Amastigotes are present within dermal macrophages (Fig. 83.11). Over time, lesions develop an increasing number of giant cells and a declining number of parasites; in chronic cutaneous leishmaniasis, caseation necrosis may be observed[14]. In the cicatricial stage, the epidermis becomes flattened and hyperpigmented in areas with dermal fibrosis. Identical changes are seen in mucosal lesions. The parasite can also be detected in the lymph nodes, bone marrow and spleen in patients with visceral leishmaniasis.

Diagnosis

The diagnosis of cutaneous leishmaniasis can be confirmed by demonstrating the presence of amastigotes in dermal macrophages within skin biopsy specimens, tissue impression smears (touch preparations), and smears of dermal scrapings[2,12,17a]. Giemsa, Wright or Feulgen stains are used to identify the organisms in smears and tissue: the cytoplasm appears blue, the nucleus pink and the kinetoplast a deep red[12]. The edge of a relatively new ulcer is the location of choice for obtaining dermal scrapings, a biopsy specimen or a needle aspirate; the latter two types of samples may be used for culture and polymerase chain reaction (PCR)-based assays (see below)[3,17a].

In longer-standing lesions of leishmaniasis, parasites may be scarce. In this context, the delayed skin reaction test (Montenegro skin test or Leishman reaction), which uses leishmanial antigens to induce a cell-mediated response, has traditionally been an important diagnostic tool. A phenolated suspension of killed promastigotes is injected intradermally, usually on the volar aspect of the forearm. The test is considered positive if a papule >5 mm in diameter forms at the site of inoculation after 48–72 hours (see Fig. 83.5B)[12]. It is positive in up to 90% of patients with cutaneous and mucocutaneous leishmaniasis of over 3 months' duration[3] and is invariably negative in patients with diffuse cutaneous (anergic) leishmaniasis[12]. However, the test (which is not approved by the US Food and Drug Administration [FDA]) cannot distinguish between past and present infections; positivity appears while the skin lesions are still active, and the test remains positive long after spontaneous cure. The test is usually negative during the febrile phase of visceral leishmaniasis, but it often becomes positive after cure.

For culturing *Leishmania*, specialized media are required, e.g. Nicolle–Novy–MacNeal (NNM) media or chick embryo media. Cultures are positive in approximately 40% of cases. Serologic and immunologic tests are also available, e.g. indirect immunofluorescence, ELISA, immunoprecipitation and isoenzyme electrophoresis. Serologic testing is most useful for visceral (and occasionally mucocutaneous) disease, although it is not specific due to cross-reactivity (e.g. with Chagas disease antibodies)[18]. PCR-based methods represent the most sensitive and specific diagnostic tests, and their availability is increasing[2,12]. The US FDA recently approved a real-time PCR assay for the diagnosis of leishmaniasis, and it is available through the Centers for Disease Control and Prevention (CDC)[17a].

Differential Diagnosis

The differential diagnosis of *cutaneous* leishmaniasis includes persistent arthropod bite reactions, basal cell carcinomas, non-tuberculous mycobacterioses and subcutaneous mycoses; other infectious causes of lesions in a lymphocutaneous pattern are listed in Table 77.15. *Mucocutaneous* leishmaniasis can resemble other infections such as paracoccidioidomycosis and tertiary syphilis. In addition, Wegener's granulomatosis and angiocentric NK/T-cell lymphoma should be considered when ulcerative mucocutaneous lesions affect the central part of the face (see Table 45.3). Histologic examination allows distinction between these diseases[13]. The histologic differential diagnosis includes other infections characterized by parasitized macrophages (see Table 77.16) and even neoplasms such as squamous cell carcinoma when pseudoepitheliomatous hyperplasia is present. The morphology and distribution of diffuse cutaneous leishmaniasis can mimic lepromatous leprosy; however, in the former the eyebrows are spared and the lesions are usually less infiltrative[12].

TREATMENT RECOMMENDATIONS FOR LEISHMANIASIS		
CUTANEOUS LEISHMANIASIS		
Drugs of choice	Sodium stibogluconate*	20 mg/kg/day IV or IM × 20 days
	Meglumine antimonate*	20 mg/kg/day IV or IM × 20 days
	Miltefosine	2.5 mg/kg/day PO (max 150 mg) × 28 days
Alternatives	Paromomycin	Topically BID × 10–20 days
	Pentamidine	2–3 mg/kg IV or IM daily or every other day × 4–7 doses
	Fluconazole†	200 mg/day or 6–8 mg/kg/day PO × 6 weeks
	Liposomal amphotericin B†	3 mg/kg on days 1-5, 14 and 21
MUCOCUTANEOUS LEISHMANIASIS		
Drugs of choice	Sodium stibogluconate*	20 mg/kg/day IV or IM × 28 days
	Meglumine antimonate*	20 mg/kg/day IV or IM × 28 days
	Liposomal amphotericin B	0.5–1.0 mg/kg IV daily or every other day × 4–8 weeks
	Miltefosine	2.5 mg/kg/day PO (max 150 mg) × 28 days

*Doses refer to mg of pentavalent antimony – 100 mg/ml for sodium stibogluconate (Pentostam®), 85 mg/ml for meglumine antimonate (Glucantime®).
†Limited evidence of efficacy; other azole antifungals that have been utilized (with variable results) include ketoconzaole (600 mg/day or 10 mg/kg/day PO × 4 weeks) and itraconzaole (7 mg/kg/day PO × 3 weeks).

Table 83.4 Treatment recommendations for leishmaniasis. The treatment regimen (drug, dose, duration) that is chosen depends upon the geographic region, species of *Leishmania*, location and severity (e.g. number and size of lesions) of disease, and host factors. The Centers for Disease Control (CDC) and World Health Organization (WHO) represent resources for up-to-date information. Sodium stibogluconate is not approved by the US Food and Drug Administration (FDA), but it is available from the CDC; meglumine antimonate, miltefosine and paromomycin are not readily available in the US. BID, twice daily; IM, intramuscular; IV, intravenous; PO, orally.

ADVERSE SIDE EFFECTS OF THE MOST COMMONLY USED DRUGS FOR LEISHMANIASIS		
Drug	**Side effect**	**Incidence**
Intralesional pentavalent antimony	Localized pain, erythema, edema	25–50%
Parenteral pentavalent antimony	Raised amylase/lipase and/or LFTs	>50%
	Myalgia, arthralgia	25–50%
	Abdominal pain/nausea	25–50%
	Thrombocytopenia/ leukopenia	<25%
	ECG changes or cardiotoxicity	<25%
Miltefosine	Motion sickness	>50%
	Nausea, vomiting and diarrhea	25–50%
	Elevated serum creatinine	25–50%
	Mildly elevated LFTs	<25%
	Teratogenicity*	>50%
Pentamidine	Nausea, vomiting and diarrhea	>50%
	Hyperglycemia	<25%
	Cardiotoxicity	<25%

*Contraindicated during pregnancy. Contraception is required during administration and for 2 months after the drug is discontinued.

Table 83.5 Adverse side effects of the most commonly used drugs for leishmaniasis. ECG, electrocardiogram; LFTs, liver function tests.

Treatment

Factors to consider when planning the treatment of leishmaniasis include the region of the world in which the infection was acquired, the species of *Leishmania*, the site(s) and severity of the infection, and host factors such as immune status and age. The risks and benefits of therapy need to be balanced, with goals of maximizing effectiveness while minimizing drug toxicity. Without treatment, Old World cutaneous leishmaniasis typically resolves within 2–4 months (*L. major*) or 6–15 months (*L. tropica*). New World cutaneous leishmaniasis caused by *L. mexicana* resolves within 3 months in >75% of cases. In contrast, cutaneous disease caused by *L. braziliensis* and *L. panamensis* spontaneously heals in less than 10% and 35% of cases, respectively. Cutaneous disease is treated to accelerate healing, to decrease scarring (especially important for lesions in cosmetically sensitive sites), and to prevent dissemination or relapse. Indications for treatment of cutaneous leishmaniasis include persistence for >6 months, location over a joint, and presence of multiple (≥5–10) or large (≥4–5 cm) lesions[19,20].

Parenteral pentavalent antimonials are the treatment of choice for cutaneous and mucocutaneous leishmaniasis, whereas liposomal amphotericin B is preferred for visceral leishmaniasis[19]. Table 83.4 summarizes first-line and alternative treatments for cutaneous and mucocutaneous leishmaniasis[20–25]. Table 83.5 lists frequent adverse reactions to the drugs most commonly used for the treatment of leishmaniasis. Additional interventions that have shown some efficacy for cutaneous and (in combination with other agents) mucocutaneous leishmaniasis include heat therapy[27], cryotherapy, photodynamic therapy and oral allopurinol.

Drugs or vaccines that completely prevent leishmaniasis have not yet been developed. The best form of protection is to avoid the bite of the sandfly and eliminate animal reservoirs. Personal protection includes applying DEET-based repellants, bed netting, barriers in the form of permethrin-treated clothing, and sleeping in minimal-risk areas. People are at increased risk of bites in the early morning and late evenings[21].

CUTANEOUS DISEASES CAUSED BY AMEBOID PROTOZOA

Ameboid protozoa (often referred to as amebas) are single-celled eukaryotes characterized by movement via pseudopodia (temporary cytoplasmic extensions). Organisms in this group that can produce cutaneous disease include *Entamoeba histolytica*, *Acanthamoeba* and *Balamuthia mandrillaris*. *E. histolytica* is a parasitic ameba with a worldwide distribution and may infect the skin via extension or inoculation from the gastrointestinal tract. *B. mandrillaris* and *Acanthamoeba* spp. are free-living amebas that can cause skin infections and granulomatous encephalitis in immunocompromised and (for *B. mandrillaris*) immunocompetent patients. Acanthamebiasis may present with papulonodules and ulcers on the trunk and extremities in patients with advanced HIV infection (see Ch. 78).

Amebiasis

Key features

- Amebiasis usually affects the gastrointestinal tract and rarely spreads to the skin
- The skin can become involved by extension of rectal amebiasis to the anus, perianal skin or vulva, as well as by a fistula from a liver abscess to the skin of the abdominal wall
- The cutaneous lesions are usually ulcers or verrucous plaques

Introduction

Amebiasis in humans is primarily a gastrointestinal infection caused by *Entamoeba histolytica*. However, there can be extraintestinal manifestations, including cutaneous involvement[28].

Epidemiology

E. histolytica infection results in approximately 50 million cases of invasive disease worldwide each year, causing 100 000 deaths annually[3]. A high prevalence of this infection is associated with poor sanitation, crowded living facilities and lower socio-economic status. In high-income countries, risk factors include a history of travel to or residence in high-prevalence areas, institutionalization immunosuppression, and promiscuous sexual behavior (especially involving men having sex with men). Humans are the reservoir for the disease, and an asymptomatic carrier may excrete up to 45 million cysts a day in the stool. Transmission of amebiasis is fecal–oral via contaminated hands, water or food and oral–anal sex.

Pathogenesis

Once the cyst is ingested, it makes its way to the colon, where it becomes a trophozoite. Although trophozoites can be excreted, cysts represent the primary excreted form[28,29]. The main mechanism by which *E. histolytica* produces disease is through tissue lysis[29]. The trophozoites kill target cells upon direct contact, due in part to the release of proteolytic enzymes, e.g. cathepsin B and collagenase. The trophozoites also have the capacity to destroy neutrophils, resulting in release of their intracellular contents, which further contribute to the destruction of host tissues. The mechanisms of defense against *E. histolytica* include mucosal immune responses (e.g. antiamebic IgA antibodies), cell-mediated immune defense (e.g. activated cytotoxic T lymphocytes and the production of lymphokines such as IFN-γ, which activate macrophages to kill the trophozoites), and non-immune host defenses (e.g. the production of mucus by colonic mucosa, inhibiting amebic adherence to and lysis of the mucosa).

Clinical features

Patients with symptomatic amebiasis due to *E. histolytica* typically present with colitis, i.e. abdominal pain, tenesmus, bloody diarrhea and mucosal ulcerations[28]. Extraintestinal complications, which can occur from hematogenous spread via invasion through the gastrointestinal epithelium, include hepatic abscesses, empyema and pericardial effusions[28,30]. The skin is affected in less than 1% of patients with amebiasis. Skin involvement occurs as a result of extension of rectal amebiasis to the anus, perianal skin or vulva; extension of a liver abscess to the skin of the abdominal wall; or inoculation of the penis during anal intercourse. Primary cutaneous amebiasis via external inoculation is exceedingly rare but has been reported on the face[31,32].

Fig. 83.12 Cutaneous amebiasis. Multiple large ulcers on the leg of a patient with amebiasis. Note the extensive tissue destruction and resemblance to pyoderma gangrenosum. *Courtesy, Omar P Sangüeza, MD.*

Cutaneous lesions can present either as ulcers (Fig. 83.12) or verrucous plaques. Ulcerative lesions are usually tender and somewhat oval in shape, with irregular borders and a gray–white necrotic base. One characteristic of these ulcers is extensive tissue destruction.

Pathology and diagnosis

Histologically, ulcerated lesions of cutaneous amebiasis have central necrosis with adjacent pseudoepitheliomatous hyperplasia. Mixed inflammatory infiltrates are present in the dermis and can extend into the subcutaneous tissue. Within the ulcerated and necrotic areas, it is possible to identify the trophozoites of *E. histolyticum*. They have ample, finely granular eosinophilic cytoplasm, eccentric nuclei and prominent nucleoli, and some may contain phagocytized red cells. Chronic lesions show prominent irregular epidermal hyperplasia and inflammatory infiltrates, with few organisms present. Touch and wet drop preparations from the pus may also be utilized to identify the trophozoites[3]. Examination of fresh stool has a low yield of demonstrating the trophozoite, and multiple stool samples must be obtained[28]. Where available, PCR may be used for detection of responsible organisms. If the diagnosis is made, consider evaluation of other body sites for involvement.

Differential diagnosis

In high-income countries, a patient with colitis and necrotic cutaneous ulcers would more likely have inflammatory bowel disease-associated pyoderma gangrenosum. Other infectious causes of skin ulcers, e.g. streptococci, dimorphic or opportunistic fungi, and mixed bacterial flora (phagedenic or tropical ulcer), should be excluded. Verrucous lesions in the anogenital region may be confused with condyloma acuminata and squamous cell carcinoma.

Treatment

For both adults and children, oral metronidazole is the drug of choice for amebiasis due to *E. histolytica*: for adults, 500–750 mg three times daily for 7–10 days, and for children, 35–50 mg/kg/day divided into three doses for 10 days. Other medications that have been used include diloxanide, tinidazole, pentamidine and iodoquinol[20].

Balamuthia mandrillaris Infection

Key features

- *B. mandrillaris* is a free-living ameba that causes a rare, usually fatal encephalitis in immunocompetent individuals
- Skin infection presents weeks to months prior to hematogenous spread to the central nervous system (CNS)
- Cutaneous lesions are slowly growing, indurated plaques on the central face

Introduction

B. mandrillaris is a free-living ameba that can infect the skin and subsequently lead to fatal encephalitis.

Epidemiology

At least three genera of free-living amebas cause disease in humans, including *Naegleria*, *Acanthamoeba* and *Balamuthia*[33]. These amebae are found worldwide in the soil and (especially for the former two organisms) fresh water. Cutaneous infection with *B. mandrillaris* or *Acanthamoeba* spp. may precede development of granulomatous encephalitis. Such infections may be acquired from exposure of microabrasions or open wounds in the skin to soil and water sources; encephalitis can also result from infection of the nasal/respiratory mucosa (e.g. via inhalation). *Naegleria fowleri* can cause an acute, fatal encephalitis but is not known to infect the skin.

B. mandrillaris is an uncommon but increasingly recognized cause of encephalitis, with approximately 200 cases reported worldwide to date, including more than 70 in the US[34]. Most of the affected individuals resided in warmer regions, including Latin America and the southern US[35]. Unlike *Acanthamoeba* infections, which only affect

Fig. 83.13 ***Balamuthia mandrillaris*** **infection. A** Indurated plaque on the nose. **B** Infiltration that has progressed to involve a large portion of the face. *With permission from Tyring S, Lupi O, Hengge U (eds), Tropical Dermatology. Churchill Livingstone, 2005.*

immunocompromised patients, most *B. mandrillaris* infections occur in immunocompetent individuals, favoring children as well as the elderly[3,5]. Boys and men are two to three times more likely to acquire the infection than girls and women[36]. In addition, nearly 50% of the *B. mandrillaris* infections identified in the US have been in individuals of Hispanic ethnicity[37,38]. Transmission of *B. mandrillaris* via solid organ transplantation has also been described.

Pathogenesis

B. mandrillaris is a free-living ameba that can exist both as a dormant cyst and as an infectious trophozoite. Because *B. mandrillaris* can cause disease in immunocompetent hosts, it is thought to be more virulent than *Acanthamoeba*. However, clinically unaffected individuals have been shown to have antibodies against *B. mandrillaris*[39]. The presence of predisposing factors (e.g. local disruption of the skin or mucosal barrier) are likely needed to acquire the infection. The trophozoites feed on human cells and spread to the CNS hematogenously[40].

Clinical features

B. mandrillaris causes a subacute to chronic granulomatous encephalitis that has a mortality rate of >80%[36,41]. In a subset of patients, CNS involvement is preceded by the development of a slowly expanding, indurated, asymptomatic plaque on the central face (Fig. 83.13) or (less often) other sites such as an extremity, the gluteal area or the oral mucosa[33]. A skin lesion may be present for weeks to months (average of 5–8 months) before the organism disseminates to the CNS[3]. As the plaque enlarges, it may become infiltrative (see Fig. 83.13B) and occasionally ulcerates. Although there is usually a single skin lesion, local "satellite" lesions or involvement of multiple sites can occur. Neurologic symptoms are similar to those in other forms of meningoencephalitis (e.g. headache, altered mental status, cranial nerve dysfunction), but may be more insidious and chronic.

Pathology and diagnosis

The diagnosis of *B. mandrillaris* infection is often made at autopsy or by skin biopsy[3]. In the dermis of affected skin, there is a mixed granulomatous infiltrate, which may obscure the cysts or trophozoites[3]. Immunohistochemical staining or PCR based analysis of skin specimens can provide definitive diagnosis[42]. Culture and isolation of *B. mandrillaris* requires a complex medium containing fetal bovine serum or a specialized cell type (e.g. monkey kidney cells, human lung fibroblasts)[42]. Examination of the cerebrospinal fluid (CSF) may show motile amebic trophozoites with pseudopod formation[33]. If the encephalitis is advanced, imaging studies will reveal calcified, mass-like brain lesions[43].

Treatment

Although various combinations of drugs (including pentamidine, sulfadiazine, azole antifungals, clarithromycin, flucytosine and miltefosine) have been tried for *B. mandrillaris* infection, none has been shown to be consistently effective.

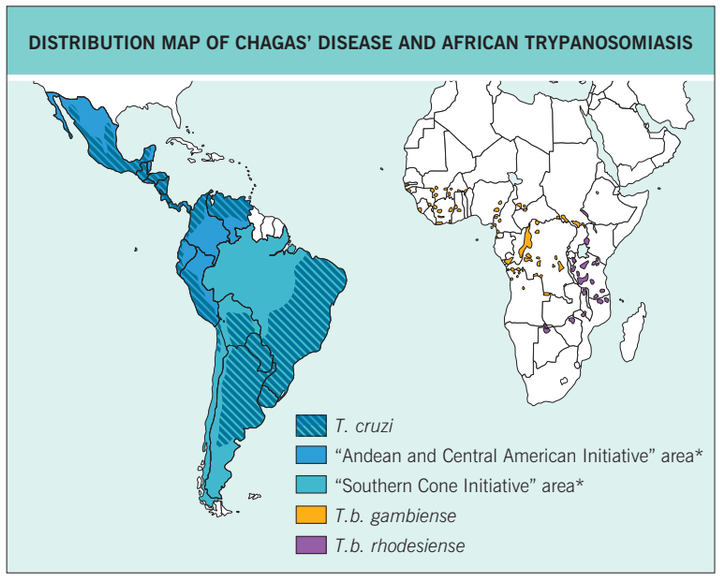


Fig. 83.14 Distribution map of Chagas disease and African trypanosomiasis. *Major programs begun in the 1990s to eliminate domestic vectors. *Adapted with permission from Peters W, Pasvol G, Tropical Medicine and Parasitology, 6th edition. London: Mosby, 2007.*

Synonyms: ■ American trypanosomiasis: Chagas disease, Chagas–Mazza disease ■ African trypanosomiasis: African sleeping sickness

TRYPANOSOMIASIS

Although the genus *Trypanosoma* consists of at least 20 species of protozoa, only two are known to cause human disease. American trypanosomiasis is caused by *T. cruzi* infection and is transmitted by reduviid bugs. African trypanosomiasis is caused by *T. brucei* infection and is transmitted by tsetse flies.

Key features

- An endemic disease in many areas of Central and South America
- Transmission of *T. cruzi* is via infected reduviid bugs and occasionally by contaminated blood
- A serious systemic disease with three phases (acute, indeterminate, and chronic). The chronic phase primarily affects the heart and gastrointestinal tract
- Following inoculation of the parasite into the skin, localized erythema and edema can develop in conjunction with regional lymphadenopathy (chagomas)
- When the conjunctiva is the portal of entry, edema of the palpebral and periocular tissue is seen (Romaña sign)

American Trypanosomiasis

Epidemiology

T. cruzi and its arthropod vectors (reduviid or kissing bugs) are found in the Americas, from the southern US to southern Argentina[44] (Fig. 83.14). Reduviid bugs feed mainly on human, animal or avian blood, but sometimes they engage in cannibalism or coprophagia, which may result in vector-to-vector transmission of *T. cruzi*. A favorite habitat for these bugs is cracks in the walls of mud huts in poor rural areas, and they are known as kissing bugs because of their habit of biting the face of humans. Direct transmission of *T. cruzi* via transfusion of contaminated blood can occur; since 2007, blood donated in the US has been screened for this organism[45]. In addition, transplacental transmission can result in congenital infection.

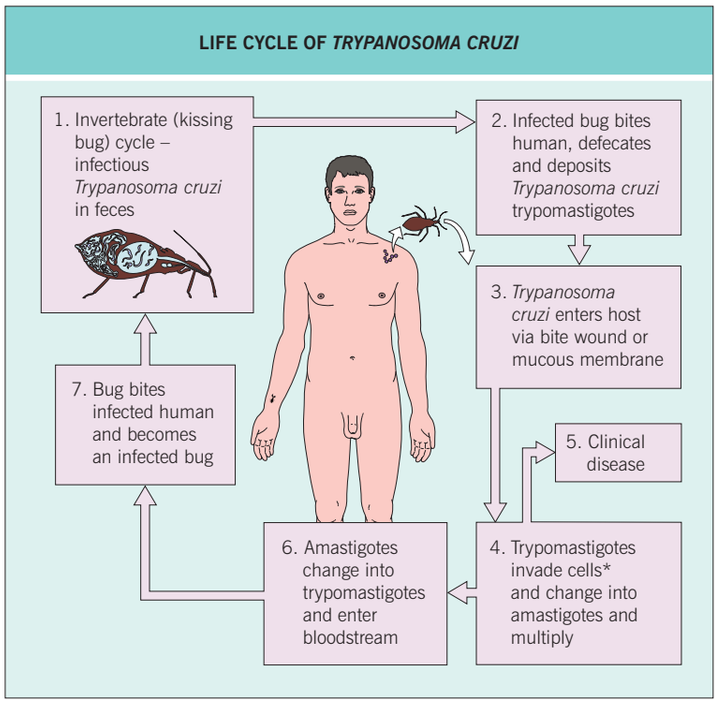


Fig. 83.15 Life cycle of *Trypanosoma cruzi*. *Smooth muscle of heart and skeletal muscle. *Adapted with permission from Keusch GT, Host response to infection. In: Cohen J, Powderly W, eds, Infectious Diseases, 2nd edition. London: Mosby, 2004.*

Fig. 83.16 Chagas disease. Young child with unilateral periorbital edema characteristic of this disease (Romaña sign) when the conjunctiva is the portal of entry. *Courtesy, Omar P Sangüeza, MD.*

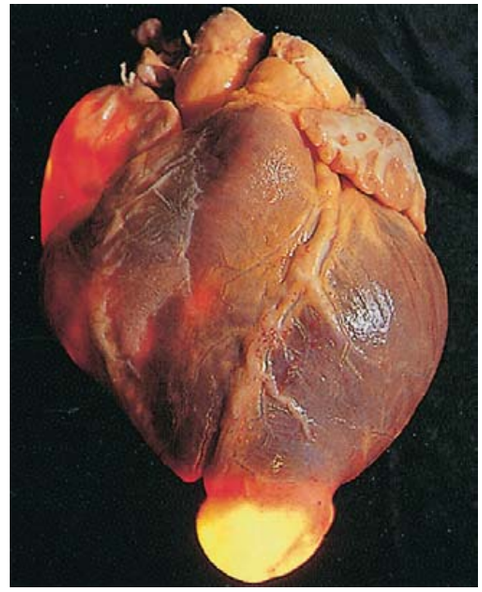


Fig. 83.17 Chagas disease: apical aneurysm of the heart. Mural thrombi may be present at the apex of the left ventricle, with marked thinning of the ventricular wall (illuminated). *With permission from Peters W, Pasvol G, Tropical Medicine and Parasitology, 6th edition. London: Mosby, 2007.*

It is estimated that 10 million people are infected with *T. cruzi*, and Chagas disease kills approximately 10 000 people per year[46], mostly in rural areas of Latin America. Chagas disease is the leading cause of parasitic death in Latin America and the third leading cause in the world. The acute form of the disease (see below) is seen more commonly in children, and, in some areas, 85% of children under the age of 10 years are infected. The incidence is much lower in the US, with most reported cases occurring in immigrants from Central America.

Pathogenesis

Blood-sucking reduviid bugs ingest trypomastigotes from the peripheral blood of vertebrate hosts (Fig. 83.15). Once the bug has become infected, it remains so for the rest of its life. The parasites transform into epimastigotes and multiply in the bug's midgut, later becoming metacyclic trypomastigotes in its hindgut. When the infected bug takes a subsequent blood meal, it usually defecates during or after feeding, depositing infective metacyclic trypomastigotes on the skin. The parasites penetrate the skin (generally via the bite wound) or mucosa (usually the conjunctiva). Following invasion of the host's cells, amastigotes multiply within the cytoplasm and then develop into trypomastigotes. The latter are released when the cells rupture and can either infect other cells or enter the bloodstream, where they may be ingested by new vectors.

The underlying pathogenesis of this disease is poorly understood, but the autonomic nervous system that innervates the heart and gastrointestinal tract appears to be a primary target. The visceral involvement seen in the chronic stage (see below) is thought to be a reflection of neuronal damage that occurs during the acute phase. An alternative hypothesis suggests that an autoimmune process is responsible for the systemic abnormalities seen during the chronic phase of the disease. In addition, trypomastigotes have the ability to penetrate the smooth muscle of the heart and the wall of the gastrointestinal tract[47].

Clinical features

Chagas disease has acute and chronic phases, and each has different clinical manifestations. Although the acute phase can affect individuals of any age, it is usually observed in children. At the cutaneous site of parasitic entry (see Fig. 83.15), some patients develop a chagoma, which is a localized area of erythema and swelling that is often accompanied by regional lymphadenopathy. When the conjunctiva is the portal of entry, the painless edema of the palpebral and periocular tissues that appears is referred to as the Romaña sign or ophthalmoganglionar complex[3] (Fig. 83.16). The Romaña sign occurs in approximately 80% of individuals infected by this route. In some patients, the swelling is accompanied by preauricular lymphadenopathy (Parinaud sign)[44].

These initial clinical findings can be accompanied by fever, malaise, anorexia and edema of the face and lower extremities. Some patients develop an eruption of erythematous macules, hepatosplenomegaly, thrombocytosis, leukocytosis and/or eosinophilia. The acute phase may last for up to 2 months, but it usually resolves spontaneously. In addition, inflammation at the sites of parasite entry can persist for several weeks[44]. Occasionally, patients develop myocarditis or meningoencephalitis that can be life-threatening[47].

After resolution of the acute phase, patients enter the indeterminate phase of Chagas disease. This stage is characterized by asymptomatic parasitemia and positive serology. Then, many years or even decades after the initial infection, an estimated 30% of patients will develop

Fig. 83.18 Chagas disease: radiograph of megaesophagus. Muscular degeneration and denervation of segments of the alimentary tract through destruction of the cells of Auerbach's plexus cause megaesophagus, megastomach and megacolon, which can be detected radiologically. *With permission from Peters W, Pasvol G, Tropical Medicine and Parasitology, 6th edition. London: Mosby, 2007.*

symptoms of the chronic phase of Chagas disease[48]. The heart is the organ most commonly affected (Fig. 83.17) and the clinical manifestations include congestive heart failure, arrhythmias and heart block[47]. The gastrointestinal tract is also frequently involved, leading to megacolon and megaesophagus (Fig. 83.18).

If patients who chronically harbor *T. cruzi* become immunosuppressed, reactivation of the disease can occur. When this happens, the disease is often more severe than in typical cases of Chagas disease and patients may develop ulcerative lesions[44].

Pathology

Histologically, at the site of parasite entry (chagoma), there is interstitial edema and a mononuclear cell infiltrate. Within cells in the subcutaneous tissue and muscle, aggregates of amastigotes may be seen. Enlarged lymph nodes are hyperplastic and intracellular amastigotes can be observed. In the chronic stage, trypanosomes are hard to find in affected organs.

Diagnosis and differential diagnosis

The diagnosis of acute Chagas disease is based upon the microscopic identification of either trypomastigotes in the blood (or CSF) or amastigotes within tissue. Because the concentration of parasites is low (even in the acute stage), hemoconcentration techniques are used to enhance the yield. If the parasites cannot be demonstrated microscopically, cultures of blood, CSF or tissue should be performed, as the latter is a more sensitive detection method. Xenodiagnosis represents a specific and relatively sensitive method for the diagnosis of Chagas disease; however, this technique is expensive and is only available in large laboratories in endemic areas. Specifically, trypanosome-free reduviid bugs are fed on patients and the feces or hindgut contents of the bugs are examined for epimastigotes 10 to 30 days later. This method can be used to confirm a serologic diagnosis in patients with chronic disease[44].

Serologic tests and PCR are useful for establishing the diagnosis of chronic Chagas disease. The most commonly employed serologic assays are indirect immunofluorescence, complement fixation, indirect hemagglutination and ELISA.

The nonspecific symptoms that may occur during the acute phase of Chagas disease (macular eruption and influenza-like symptoms) make the differential diagnosis broad. When the site of inoculation is the eye, other entities to consider include a reaction to a bite from another type of insect, angioedema and bacterial cellulitis.

Treatment

Treatment options for Chagas disease are limited and most effective during early disease[48]. The drug most commonly used is nifurtimox. It reduces the severity and duration of symptoms associated with the acute phase. However, parasitologic cure occurs in only 50% of treated patients and the efficacy of nifurtimox during the intermediate and chronic stages has not been proven. Another drug that is effective in the acute phase of the disease but less effective during the chronic stage is benznidazole (not available in the US)[49]. The side effects of these two medications are reviewed in Table 83.6.

Allopurinol and itraconazole have also been evaluated for the treatment of chronic Chagas disease[50]. However, to date, there is no evidence that pathologic changes of the chronic phase of this disease can be reversed by any therapy. Thus, chronic disease is managed primarily by supportive care (e.g. antiarrhythmics)[47].

Prevention of the infection involves education about sanitation and the use of residual insecticides in domestic areas. Vaccines are still being investigated but are not yet available.

Key features

- In West Africa, the disorder is due to *Trypanosoma brucei gambiense* infection, and in East Africa it is caused by *Trypanosoma brucei rhodesiense* infection
- The vectors are several species of tsetse flies
- Cutaneous manifestations include a localized bite reaction ("trypanosomal chancre") and an annular erythematous eruption that coincides with fever spikes

African Trypanosomiasis

Epidemiology

African trypanosomiasis affects approximately 30 000 individuals annually and results in over 3000 deaths per year[51]. The disease is almost invariably fatal if left untreated. There are two forms of African trypanosomiasis, which are named based on their non-overlapping geographic distributions in Africa (Table 83.7; see Fig. 83.14). The West African form, due to *Trypanosoma brucei gambiense*, is a chronic, anthroponotic disease with primarily neurologic features. The East African form, caused by *Trypanosoma brucei rhodesiense*, is an acute, zoonotic disease (with antelopes as a reservoir) that is often fatal. Fortunately, *T. b. rhodesiense* only occasionally infects humans, mainly farmers, hunters and tourists[52,53]. Both types of *T. brucei* are transmitted to humans by blood-sucking tsetse flies (genus *Glossina*), which are found in Africa. The flies become infected by ingesting blood from infected mammalian hosts (Fig. 83.19). Transmission transplacentally or via blood products may also potentially occur.

Pathogenesis

After inoculation, trypanosomes may produce a local chancre before spreading via the lymphatics to regional (and then distant) lymph nodes. The organisms disseminate to the bloodstream and eventually to the CNS, and they multiply by binary fission[54]. They escape significant immunologic response by continuously changing their surface glycoproteins[52,53].

Clinical features

Patients can develop an indurated, painful reaction at the portal of entry of the organisms, referred to as a "trypanosomal chancre" (Fig. 83.20). This is seen more commonly (70–80% of cases) in the East African form due to *T. b. rhodesiense*[44]. The lesion appears 1–2 weeks after the tsetse fly bite and heals spontaneously over several weeks.

The hemolymphatic stage occurs when the trypanosomes enter the lymphatic system and bloodstream 1–3 weeks after infection. Patients develop spiking fevers, malaise, and symmetrical lymphadenopathy. Enlargement of the lymph nodes of the posterior cervical triangle, referred to as Winterbottom's sign, is a classic finding in the West African form due to *T. b. gambiense*. Patients may have peripheral or facial edema, hepatosplenomegaly, and ascites[3]. A transient eruption (referred to as "trypanids") of annular and targetoid erythematous patches or urticarial plaques may occur in concert with fever spikes 6–8 weeks after onset of the illness. The eruption favors the trunk and is evident in 50% of fair-skinned patients[3,55].

ANTIHELMINTHIC DRUGS: THERAPEUTIC USES, SIDE EFFECTS AND CONTRAINDICATIONS				
Drug	**Therapeutic use**	**Toxicity and side effects**		**Precautions and contraindications**
		Systemic and cutaneous	**"Allergic"reactions**	
Thiabendazole	Strongyloidiasis, cutaneous larva migrans (second-line therapy), dracunculiasis	– GI: nausea, vomiting, anorexia > diarrhea, abdominal pain > elevated transaminases, cholestasis – Neurologic: dizziness, drowsiness > headache, paresthesias, weakness > tinnitus, seizures, hallucinations – Ocular: irritation, blurred vision, xerophthalmia – Other: crystalluria without hematuria, transient leukopenia, xerostomia	– Cutaneous: urticaria (3%), exanthem (<5%) > fixed drug eruption, pruritus, perianal "rash", flushing > angioedema, contact dermatitis, Jarisch–Herxheimer reaction, Stevens–Johnson syndrome – Fever, anaphylaxis	– FDA pregnancy category C – Discontinue during lactation – Use with caution if hepatic disease
Mebendazole	GI nematode infections (e.g. enterobiasis, ascariasis, ancylostomiasis), toxocariasis, trichinosis, sparganosis	– GI: nausea, vomiting, diarrhea, abdominal pain > elevated transaminases – Neurologic: dizziness, drowsiness > tinnitus, seizures – Hematologic: anemia, thrombocytopenia, leukopenia > agranulocytosis – Other: alopecia, oligospermia	– Cutaneous: exanthem, urticaria, angioedema, pruritus, flushing	– FDA pregnancy category C – Use with caution in children < 2 years of age
Albendazole	Cutaneous larva migrans, GI nematode infections (as above), echinococcosis, neurocysticercosis, toxocariasis	– GI: nausea, vomiting, diarrhea, abdominal pain, elevated transaminases > cholestasis – Neurologic: headache, dizziness > increased intracranial pressure (with treatment of neurocysticercosis), seizures – Hematologic: leukopenia > thrombocytopenia, agranulocytosis, pancytopenia – Other: alopecia	– Cutaneous: exanthem, urticaria > angioedema, Stevens–Johnson syndrome – Fever, anaphylaxis	– FDA pregnancy category C – Avoid during lactation – Use with caution if hepatic disease
Diethylcarbamazine	Filariasis, dirofilariasis, loiasis, toxocariasis (second-line therapy)	– GI: nausea, vomiting, anorexia – Neurologic: headache	– Mazzotti reaction: pruritus, lymphadenopathy > papular exanthem, fever, tachycardia, arthralgias, headache – Nodular swellings along the lymphatics – Leukocytosis, eosinophilia – Ocular: limbitis, punctate keratitis > uveitis, atrophy of the retinal pigment epithelium > retinal hemorrhage (*L. loa*) – Encephalitis (*L. loa*) – Proteinuria	– Appears to be safe for use during pregnancy (controlled studies show no fetal risk) – Avoid population-based administration in regions where onchocerciasis or loiasis is endemic
Ivermectin	Onchocerciasis, filariasis (second-line therapy), cutaneous larva migrans, ascariasis, strongyloidiasis	– GI: nausea, vomiting, diarrhea, elevated transaminases > cholestasis – Neurologic: dizziness > drowsiness, headache, tremor – Other: leukopenia	– Mazzotti-like reaction and ocular side effects (*O. volvulus*; see above) – Pruritus, urticaria, peripheral edema – Orthostatic hypotension	– FDA pregnancy category C – Considered safe during lactation
Praziquantel	Schistosomiasis; liver fluke and tapeworm infections (e.g. cysticercosis, sparganosis)	– GI: nausea, vomiting, abdominal discomfort > bloody diarrhea, elevated transaminases – Neurologic: headache, dizziness > drowsiness – Other: arrhythmias	– Cutaneous: pruritus > urticaria, exanthem – Arthralgias, myalgias – Fever – Meningismus, CSF pleocytosis, seizures (in neuro-cysticercosis)	– FDA pregnancy category B – Avoid during lactation – Contraindicated for ocular cysticercosis

Table 83.6 Antihelminthic drugs: therapeutic uses, side effects and contraindications. CSF, cerebrospinal fluid; GI, gastrointestinal.

Continued

The final stage (meningoencephalitic stage) of the disease is characterized by neurologic manifestations, including irritability, changes in personality, inability to concentrate, and daytime somnolence alternating with nighttime restlessness and insomnia, hence the term sleeping sickness[56]. Deep delayed hyperesthesia after a brisk tap or pinch (Kerandel's sign) reflects CNS involvement[55]. CSF examination demonstrates lymphocytic pleocytosis and increased protein content; in some patients, trypanosomes are evident when the fluid is centrifuged.

East African trypanosomiasis tends to follow a more acute course with earlier onset of CNS symptoms (which are often delayed months to years in the West African variant), and the stages are not as well

ANTIHELMINTHIC DRUGS: THERAPEUTIC USES, SIDE EFFECTS AND CONTRAINDICATIONS				
Drug	**Therapeutic use**	**Toxicity and side effects**		**Precautions and contraindications**
		Systemic and cutaneous	**"Allergic"reactions**	
Levamisole	GI nematode infections (e.g. ascariasis, ancylostomiasis; second-line therapy)	– GI: nausea, vomiting, diarrhea, abdominal discomfort – Neurologic: headache > dizziness, insomnia, paresthesias > multifocal leukoencephalopathy – Hematologic: leukopenia, anemia, thrombocytopenia > agranulocytosis – Other: dysgeusia, xerosis, alopecia, arthralgias	– Cutaneous: exanthem (5–10%) > pruritus, urticaria, angioedema, fixed drug eruption, lichenoid eruption, vasculitis/ vasculopathy (favors the ears), Stevens–Johnson syndrome – Stomatitis (5%) – Fever, anaphylaxis	– FDA pregnancy category C – Considered safe during lactation
Nifurtimox	Chagas disease	– GI: nausea, vomiting, anorexia > abdominal pain, diarrhea – Neurologic: paresthesias, weakness, headache, insomnia > psychiatric disturbances, seizures – Other: myalgias > leukopenia, oligospermia	– Cutaneous: exanthem, urticaria, angioedema – Fever, anaphylaxis	– FDA pregnancy category C
Benznidazole	Chagas disease	– GI: nausea, vomiting, anorexia – Neurologic: paresthesias, weakness – Hematologic: leukopenia > thrombocytopenia, agranulocytosis – Other: myalgias	– Cutaneous (more common than with nifurtimox): exanthem, urticaria, angioedema, generalized peripheral edema – Fever, lymphadenopathy, anaphylaxis	– FDA pregnancy category C
Suramin	African trypanosomiasis	– GI: nausea, vomiting > diarrhea, abdominal pain, elevated transaminases, cholestasis – Neurologic: palmoplantar hyperesthesia/paresthesias, weakness, headache > seizures – Ocular: blepharitis, conjunctivitis, photophobia, excessive lacrimation – Hematologic: leukopenia > agranulocytosis, hemolytic anemia, thrombocytopenia – Other: malaise, dysgeusia, proteinuria > renal or adrenal insufficiency	– Cutaneous: exanthem, urticaria > exfoliative dermatitis, generalized peripheral edema – Stomatitis – Fever, anaphylaxis (1 : 2000)	– FDA pregnancy category C – Use with caution if renal disease
Eflornithine	African trypanosomiasis (*T. brucei gambiense*)	– GI: diarrhea (40%) > nausea, vomiting, abdominal pain – Neurologic: dizziness, headache, seizures (~5%) – Hematologic: anemia (50%) > leukopenia (25%) > thrombocytopenia – Other: alopecia > hearing loss	– Cutaneous: exanthem – Fever	– FDA pregnancy category C

Table 83.6 Antihelminthic drugs: therapeutic uses, side effects and contraindications (cont'd). CSF, cerebrospinal fluid; GI, gastrointestinal.

COMPARISON BETWEEN WEST AFRICAN AND EAST AFRICAN TRYPANOSOMIASIS		
	West African trypanosomiasis	**East African trypanosomiasis**
Causative agent	*T. brucei gambiense*	*T. brucei rhodesiense*
Vector	Tsetse fly	Tsetse fly
Main host	Humans	Wild game > humans
Reservoir	Humans	Antelope, cattle
Location	West/central regions of sub-Saharan Africa	Ethiopia, Uganda, Zambia, Botswana, Tanzania, Mozambique
Clinical presentation	• Chancre uncommon • Chronic neurologic symptoms • Posterior cervical (Winterbottom sign) and supraclavicular lymphadenopathy • Trypanids (10–50% of patients, especially if lightly pigmented skin)	• Chancre common (75% of patients) • Acute neurologic symptoms • Axillary and epitrochlear lymphadenopathy • Trypanids common (especially if lightly pigmented skin) • Myocarditis/heart failure
Treatment		
Hemolymphatic stage	• Pentamidine	• Suramin
CNS involvement	• Melarsoprol or eflornithine	• Melarsoprol

Table 83.7 Comparison between West African and East African trypanosomiasis.

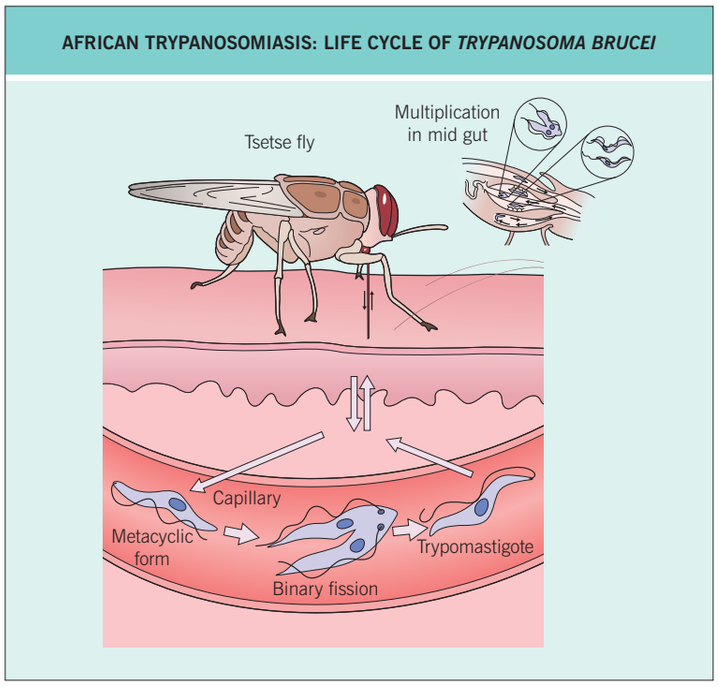


Fig. 83.19 African trypanosomiasis: life cycle of *Trypanosoma brucei*.

Fig. 83.20 Trypanosomal chancre. The bite reaction, the earliest clinical lesion, is known as a "trypanosomal chancre". It resembles a boil but is usually painless. Fluid aspirated from the nodule contains actively dividing trypanosomes. This reaction is seen more commonly in *T. b. rhodesiense* than in *T. b. gambiense* infection. *With permission from Peters W, Pasvol G, Tropical Medicine and Parasitology, 6th edition. London: Mosby, 2007.*

defined (see Table 83.7). In addition, East African trypanosomiasis may result in heart failure due to damage to myocardium, even before the onset of symptoms from CNS involvement[55,57].

Pathology and diagnosis

Definitive diagnosis requires identification of the parasites in the skin, blood (especially the buffy coat), lymph node or CSF. Routine histologic sections from skin lesions demonstrate a superficial perivascular lymphocytic infiltrate and mild spongiosis; trypanosomes are usually not seen. Serologic tests become positive about 2 weeks after the onset of infection[3]. PCR is the most sensitive test[58].

Differential diagnosis

The differential diagnosis of the chancre includes infectious disorders such as extragenital primary syphilis and primary inoculation tuberculosis, and entities that lead to an annular erythema are discussed in Chapter 19.

Treatment

The first-line treatments for the early/hemolymphatic stage of East and West African trypanosomiasis are suramin and pentamidine, respectively. For the meningoencephalitic stage, melarsoprol is the first-line treatment and eflornithine is an alternative for the West African form[3] (see Table 83.7).

Key features

- A common, worldwide disease caused by the protozoan *Toxoplasma gondii*
- Cutaneous involvement is unusual but occasionally occurs in immunocompromised individuals, pregnant women and neonates
- In congenital infections, the skin lesions are usually necrotic or hemorrhagic papules

TOXOPLASMOSIS

Introduction

Toxoplasma gondii is an intestinal coccidian parasite of domestic cats and other mammals. *Toxoplasma* infections in humans can be acquired or congenital. In immunocompetent hosts, the majority of infections are asymptomatic or produce only flu-like symptoms, with occasional development of lymphadenopathy or retinitis. In immunosuppressed patients, more severe disease can occur[59]. Cutaneous manifestations are rare and may be seen in both congenital and acquired forms of the disease[60].

Epidemiology

Worldwide, toxoplasmosis is a common infection in humans. The prevalence varies, depending upon geographic location and age. In the US, 50% of the population has antibodies against *T. gondii*, with higher rates in older individuals[61]. The main end host of *T. gondii* is the cat.

Pathogenesis

The life cycle of *T. gondii* is such that there are two major routes of infection (Fig. 83.21). The more direct route is ingestion of oocysts, which are excreted in the feces of host animals (usually the cat) and are highly resistant to environmental damage. Human infections are more commonly acquired by consumption of bradyzoite-containing cysts within meat. These cysts are found in all tissues of infected hosts but are most common in muscle and neural tissue (including the brain and eye) and therefore can be ingested in raw or undercooked contaminated meat. Milk is another source of bradyzoite-containing cysts. A particular concern for *T. gondii* infections acquired during early pregnancy is that tachyzoites can pass through the placental barrier to the fetus, leading to a serious infection and associated congenital abnormalities or miscarriage[62]. Infection can also be acquired through contaminated blood or through organ transplants from seropositive donors[62].

Clinical Features

Toxoplasmosis can be acquired or congenital, and the acquired form can be acute or chronic. In most instances (~90%), acute infection is asymptomatic. The most common clinical manifestations are lymphadenopathy (especially posterior cervical) and flu-like symptoms (e.g. fever, malaise, myalgia). In immunocompromised patients, symptoms are more severe and findings may include encephalitis, meningoencephalitis, pneumonitis, myocarditis, pericarditis, myositis and hepatitis[62].

Chronic acquired toxoplasmosis is usually asymptomatic, but some patients develop chorioretinitis. In this form, it is possible to identify

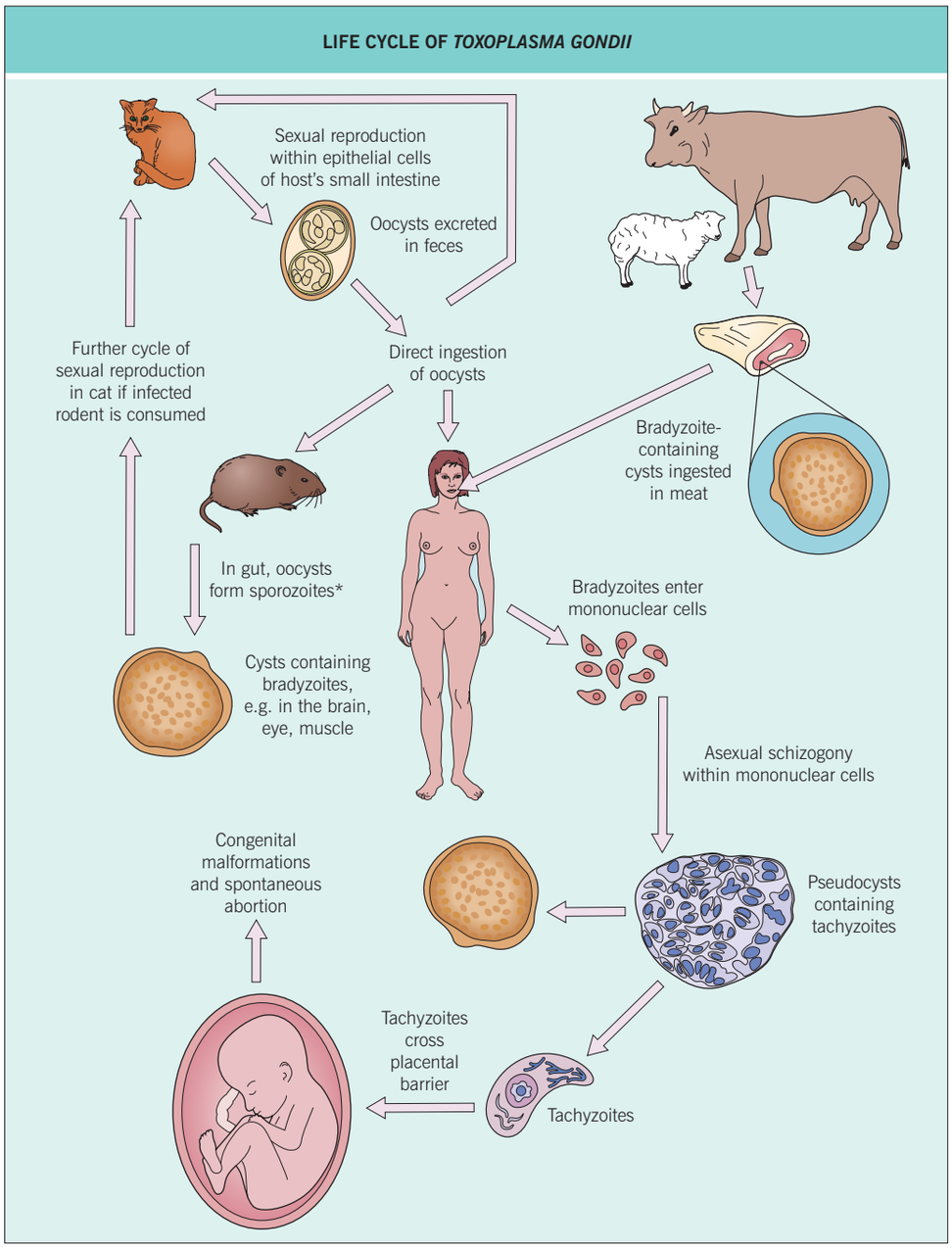


Fig. 83.21 Life cycle of *Toxoplasma gondii*. There is a wide range of mammalian hosts, the most important being the domestic cat. *Similar cycle of development in humans and other mammals. *Adapted from Peters W, Pasvol G, Tropical Medicine and Parasitology, 6th edition. London: Mosby, 2007.*

cysts within multiple organs, in particular the brain, heart and skeletal muscles.

The incidence of congenital toxoplasmosis is estimated to be 1 per 1000 to 1 per 10 000 live births in the US. Transmission of the disease is more likely if it is acquired by the mother during late pregnancy (10–25% in the first trimester versus 60–90% in the third trimester); however, the infection is more severe if transmission occurs early in gestation[63]. Most infected neonates are asymptomatic at birth (70–90%); however, in 10–30% chorioretinitis leads to visual loss, and >20% develop significant neurologic manifestations. The latter include deafness, microcephaly, hydrocephalus, developmental delay and seizures. Other potential findings in patients with congenital toxoplasmosis include hepatosplenomegaly, myositis, fever and thrombocytopenia.

Congenital toxoplasmosis can present with hemorrhagic or necrotic papules that favor the trunk. In acute acquired toxoplasmosis, cutaneous findings vary and may resemble roseola, erythema multiforme or papular urticaria; telangiectatic macules and vesicles are occasionaly observed[60]. Rarely, patients present with erythroderma, sclerodermatous manifestations or a dermatomyositis-like syndrome[64–66].

Pathology

Skin biopsy specimens can be helpful in establishing a specific diagnosis. In both congenital and acquired forms of toxoplasmosis, there is a superficial and deep perivascular infiltrate within the dermis, composed of lymphocytes, macrophages, plasma cells and eosinophils. In addition, dilated capillaries, foci of dermal hemorrhage and, occasionally, small vessel (leukocytoclastic) vasculitis can be seen. Although the cutaneous lesions are believed to reflect the immune response to the organism, tissue forms of *T. gondii* are found in approximately 50% of biopsy specimens of lesional skin. Trophozoites are seen within the cytoplasm of macrophages, both singly and inside small pseudocysts. Immunoperoxidase stains are very specific, and they are especially useful when there is only a small tissue sample[62]. Specific IgM and IgG antibodies against *Toxoplasma* can be detected in acute and convalescent serum samples from patients.

Differential Diagnosis

For neonates with congenital toxoplasmosis, other entities in the TORCH differential need to be considered (see Chs 80 & 121). For acquired toxoplasmosis, the differential diagnosis is extensive and

includes infectious diseases such as viral exanthems, meningococcemia and syphilis, as well as inflammatory diseases such as urticarial vasculitis, herpes simplex virus-associated erythema multiforme and autoimmune connective tissue diseases.

Treatment

Indications for treatment are severe acute infection, active chronic disease (e.g. in the skin or eye), congenital infection and an immunocompromised patient[59]. The most effective treatment is sulfadiazine (0.5–1.5 g four times daily in adults and 25–50 mg/kg four times daily in children) in combination with pyrimethamine (50–75 mg daily in adults and 1 mg/kg/day in children) and folinic acid. For patients allergic to sulfonamides, clindamycin can be used with pyrimethamine.

WORMS (HELMINTHS)

Medically important worms, or helminths, belong to two different phyla: Nematoda (roundworms) and Platyhelminthes (flatworms). The roundworms include free-living species as well as parasitic ones; they are unsegmented, and each species has two different sexes, a body cavity and a digestive tract. The flatworms are primarily parasitic worms that do not have a body cavity; they can be segmented or unsegmented, and most species are hermaphroditic. Flatworms can be further subdivided into two different classes: trematodes or flukes (the cause of schistosomiasis) and cestodes or tapeworms (the cause of cysticercosis and echinococcosis). Several helminthic infections have been chosen for more detailed discussion in the remainder of the chapter, and additional disorders are outlined in Table 83.8.

Of note, an alternative way of classifying worms is by their life cycle[67]. This schema divides associated infections into four classes: (1) soil-transmitted infections, including those due to hookworms (e.g. ancylostomiasis, cutaneous larva migrans; Fig. 83.22) and other nematodes (e.g. strongyloidiasis; Fig. 83.23) (Fig. 83.24); (2) infections transmitted mainly by insects, including onchocerciasis, filariasis and loiasis (Fig. 83.25); (3) infections due to trematodes (flukes) whose life cycle involves snails, such as fascioliasis and schistosomiasis (Fig. 83.26); and (4) infections acquired via ingestion, such as cysticercosis and echinococcosis (Fig. 83.27), enterobiasis (see Fig. 83.24), trichinosis (Fig. 83.28) and toxocariasis (Fig. 83.29).

Synonym: ■ Creeping eruption

Key features

- Due to larvae of animal hookworms (intestinal nematodes)
- Skin lesions are serpiginous and pruritic, representing the paths of migration of organisms within the epidermis
- The rate of migration is 1–2 cm per day
- Self-limited disease

CUTANEOUS LARVA MIGRANS

Cutaneous larva migrans is a serpiginous cutaneous eruption caused by the accidental penetration and migration of animal hookworm larvae through the epidermis. The infection has a worldwide distribution and occurs most frequently in warmer climates. The skin lesions are usually self-limited[67].

Epidemiology and Pathogenesis

Cutaneous larva migrans is caused by the larvae of hookworms that infect domestic dogs and cats (*Ancylostoma caninum*, *A. braziliense* and *Uncinaria stenocephala*). Although cutaneous larva migrans has a worldwide distribution[68], it is most commonly seen in warm climates, such as the southeastern US, Central and South America, Africa, and other tropical areas[67]. The infection is usually acquired by walking barefoot on ground contaminated with animal feces, but other body sites can become infected via contact with contaminated soil or sand. The larvae enter the skin and begin a prolonged process of migration within the epidermis. With rare exceptions, the parasite remains confined to the epidermis, producing visible tracts and intense pruritus. The parasite lacks collagenase, which is necessary to disrupt the basement membrane.

Clinical Features

Patients have intense localized pruritus that begins shortly after the hookworm penetrates the skin. Several days later, the pruritus is associated with small vesicles and/or one or more edematous, serpiginous "tracts" (see Fig. 83.22). Each larva produces one tract and migrates at a rate of 1 to 2 cm per day. The most frequent location is the distal lower extremities or buttocks. Additional sites of involvement may include the hands, thighs and, rarely, perianal area[68,69]. In severe infections, hundreds of such lesions may be found on a single patient. If untreated, a single larval tract may progress, then disappear for a few days, reappear, advance some more, and so on, for weeks or months, after which time it will spontaneously resolve. Unlike human hookworm disease and strongyloidiasis, the larvae rarely progress beyond the skin, and systemic manifestations such as migratory pulmonary infiltrates and peripheral eosinophilia (Loeffler's syndrome) are rarely seen. The only common systemic finding is a moderate peripheral blood eosinophilia. Due to intense pruritus and scratching, superimposed bacterial infections may complicate the clinical picture. Vesicles and bullae may develop in previously sensitized patients[67,70].

Pathology

Although the diagnosis is usually made clinically, based on the characteristic lesions and history of recent exposure (e.g. walking barefoot), biopsies are sometimes performed. It is unusual to see the parasite in biopsy specimens, but occasionally the larva can be identified within the epidermis. More commonly, cavities left by the parasite are located within the stratum corneum and are associated with spongiosis. In the dermis, there is a mixed inflammatory infiltrate composed of lymphocytes, histiocytes and numerous eosinophils. Occasionally, collections of eosinophils may be present in the epidermis and within hair follicles[67].

Differential Diagnosis

The clinical features of the cutaneous eruption are characteristic and the diagnosis is usually straightforward. The human species of intestinal hookworms (*A. duodenale* and *Necator americanus*) penetrate the skin prior to possible migration into venules (see Fig. 83.24), causing a pruritic nonspecific localized rash lasting 1–2 weeks that is referred to as "ground itch"[67,71]. Unlike cutaneous larva migrans, *A. duodenale* and *N. americanus* infections can progress to systemic hookworm disease, which manifests with anemia, malnutrition, and pulmonary and gastrointestinal symptoms (see Table 83.8). With these human species, autoinfection from larvae in the feces can occur, sometimes years after the initial infection.

The differential diagnosis may include allergic contact dermatitis, impetigo, inflammatory tinea, scabies, myiasis, and other nematode infections (e.g. strongyloidiasis). Larva currens is a localized (or occasionally more widespread) urticarial eruption that is caused by autoinfection with *Strongyloides stercoralis* in immunocompetent individuals (see Table 83.8); it typically begins perianally and then rapidly extends, as quickly as 5–10 cm per day, onto the buttocks, thighs and abdomen[72]. The lesions are relatively short-lived, lasting hours to days, but they often recur[73].

Treatment

Although cutaneous larva migrans is self-limited, its potential complications (e.g. impetigo and allergic reactions), together with the intense pruritus and the significant duration of the disease (sometimes several months), usually necessitate treatment. Freezing the leading edge of the skin track (cryotherapy) has been suggested, but this modality is rarely sufficient. Administration of a single 400 mg oral dose of

MAJOR PARASITIC WORMS THAT CAUSE DISEASES AND CUTANEOUS MANIFESTATIONS IN HUMANS								
Disease	**Organism**	**Distribution**	**Mode of spread**	**Skin findings**	**Systemic findings**	**Diagnosis**	**Therapy***	**Figure**
Ascariasis (roundworms), intestinal nematode	*Ascaris lumbricoides*	Widespread and high prevalence, esp. in tropical countries	Ingestion of eggs	None	Abdominal pain, diarrhea, intestinal obstruction, nutritional deficiencies, Loeffler's syndrome	Detection of eggs in the stools	Mebendazole Albendazole Pyrantel pamoate Ivermectin	83.24
Enterobiasis (pinworms), intestinal nematode	*Enterobius vermicularis*	Widespread and high prevalence, esp. in countries within temperate zones	Ingestion of eggs	Perianal and perineal pruritus	Restlessness Asymptomatic in most patients	Detection of eggs via adhesive cellophane tape pressed against perianal skin	Mebendazole Albendazole Pyrantel pamoate	83.24
Ancylostomiasis (hookworms), intestinal nematode	*Ancylostoma duodenale, Necator americanus*	Tropical and subtropical distribution	Percutaneous via contact with infective larvae in soil	Dermatitis ("ground itch") at the site of larval entry	Iron deficiency anemia, GI symptoms, Loeffler's syndrome, eosinophilia	Direct fecal smear examination for eggs	Mebendazole Albendazole Pyrantel pamoate	83.24
Strongyloidiasis, intestinal nematode	*Strongyloides stercoralis*	Occurs worldwide, esp. in tropical areas; in cooler climates found in warm humid mines	Percutaneous via contact with infective larvae; occasionally ingestion of larvae Autoinfection via penetration of perianal skin Hyperinfection in immunocompromised patients, due to penetration of intestinal mucosa	Generalized or localized urticarial eruption beginning perianally and extending to the buttocks, thighs, and abdomen (larva currens) "Thumbprint" purpura in hyperinfection (see Fig. 83.23)	Diarrhea, duodenitis, eosinophilia, pulmonary symptoms Symptoms more severe in immunocompromised patients	Examination of stool for larvae; rarely, diagnosis is made by lung biopsy or pulmonary cytology	Thiabendazole Ivermectin	83.24
Loiasis, tissue nematode	*Loa loa*	West and Central Africa	Transmitted by bite of tabanid flies of the genus *Chrysops* (mango flies) carrying infective larvae Mature in connective tissue	Transient localized subcutaneous edema (Calabar swellings), often of the hands, wrists and forearms; represent tracts of migrating adult worms; associated with pruritus and pain	Conjunctivitis (due to movement of adult worms under conjunctiva), eosinophilia, renal disease	Detection of microfilariae in blood during the daytime Occasionally, adult worms can be extracted from the eye	Diethylcarbamazine	83.25
Dirofilariasis, tissue nematodes of animals	*Dirofilaria immitis* (dog heartworms); *D. tunuis* (filaria of raccoons); *D. repens* (filaria of dogs and cats); *D. ursi* (filaria of bears)	*D. immitis* occurs worldwide; *D. tunuis* in Southeast US; *D. repens* in Europe and Asia; *D. ursi* in North America and Japan	Transmitted by mosquitoes carrying infective larvae Do not mature in humans	*D. tunuis, D. repens* and *D. ursi* cause small painful subcutaneous nodules with or without inflammation	*D. immitis* causes nodules in the lung	Detection of larvae by biopsy	Surgical excision Diethylcarbamazine Ivermectin	

*Details regarding the majority of these medications are provided in Table 83.6.

Table 83.8 Major parasitic worms that cause diseases and cutaneous manifestations in humans. Cutaneous larva migrans, onchocerciasis, filariasis, schistosomiasis, cysticercosis and echinococcosis are covered in the text.

Continued

MAJOR PARASITIC WORMS THAT CAUSE DISEASES AND CUTANEOUS MANIFESTATIONS IN HUMANS								
Disease	**Organism**	**Distribution**	**Mode of spread**	**Skin findings**	**Systemic findings**	**Diagnosis**	**Therapy***	**Figure**
Dracunculiasis (guinea worm), tissue nematode	*Dracunculus medinensis*	Africa, particularly Ghana and Sudan	Ingestion of infected water fleas of the genus *Cyclops* in drinking water migrate from intestine to subcutaneous tissue, usually of the legs	Papulonodule then blister and/or ulceration, usually of the lower extremity; calcified nodules	Anaphylactic shock, rheumatic symptoms	Confirmation of worms in the subcutaneous tissue Immunodiagnosis, e.g. ELISA Sequence analysis of 18S RNA	Gradual extraction of the worm (e.g. on a stick) ± metronidazole or thiabendazole	83.25
Trichinosis, tissue nematode	*Trichinella spiralis*	Widespread in temperate zones	Ingestion of encysted larvae from raw/undercooked animal meat, usually pork	Periorbital edema in severe infection, splinter hemorrhages	Most infections are subclinical Heavy infection also leads to fever, enteritis, myositis and eosinophilia; occasionally myocarditis and encephalitis	Confirmation of encysted larvae in the skeletal muscle; fluorescent antibody testing; ELISA	No satisfactory treatment Corticosteroids for severe symptoms plus mebendazole	83.28
Toxocariasis (visceral larva migrans), larval stage of dog roundworm, larval nematode	*Toxocara canis*	Worldwide distribution	Ingestion of eggs excreted by dogs Larvae migrate through the viscera as they are unable to mature into adults	Urticaria, cutaneous nodules	Cough, fever, hepatomegaly, eosinophilia; ocular and hepatic granulomas	Diagnosis is usually suggested clinically Confirmation by histologic examination is uncommon Serologic assay (Western blot)	Mebendazole Albendazole Diethylcarbamazine (second-line)	83.29
Sparganosis, larval stage of tapeworms of dogs and cats, cestode	*Spirometra*	Sporadic in most countries, seen most frequently in the Far East	Ingestion of larvae in intermediate hosts (e.g. snakes, frogs, fish) Occasionally application of frogs to eyes as poultice	Painless small subcutaneous nodules at sites of larval proliferation Edema if periorbital involvement	Rarely pulmonary or CNS involvement	Biopsy to identify larvae	Surgical excision Mebendazole Praziquantel	83.27
Fascioliasis (liver fluke), trematode	*Fasciola hepatica*	South America, Europe, Africa, China, Australia	Ingestion of metacercariae on aquatic plants, e.g. wild watercress	Ectopic fascioliasis is occasionally reported; cutaneous cysts	Fever, hepatomegaly, obstruction of bile duct (rare), eosinophilia	Detection of ova in feces or bile Abdominal CT	Bithionol Triclabendazole	83.26
Paragonimiasis (lung flukes), trematode	*Paragonimus westermani*	*Paragonimus westermani* in Far East; other species in West Africa, Central and South America	Consumption of flesh of freshwater crustaceans containing living metacercariae	Cutaneous paragonimiasis rare, but has been reported	Productive cough, hemoptysis, bronchitis, lung abscess, pleural effusion Symptoms related to ectopic worms in abdomen, brain, etc.	Examination of sputum or feces for eggs ELISA	Praziquantel Bithionol	83.26

*Details regarding the majority of these medications are provided in Table 83.6.

Table 83.8 Major parasitic worms that cause diseases and cutaneous manifestations in humans (cont'd). Cutaneous larva migrans, onchocerciasis, filariasis, schistosomiasis, cysticercosis and echinococcosis arecovered in the text.

Fig. 83.22 Cutaneous larva migrans. Note the characteristic serpiginous erythematous tracks on the lateral foot (**A**), both feet (**B**) and the shoulder (**C**). Vesiculation and crusting, **B** are sometimes seen. *B, Courtesy, Peter Klein, MD. C, Courtesy, Julie V Schaffer, MD.*

Fig. 83.23 Strongyloidiasis hyperinfection. Multiple purpuric lesions (sometimes referred to as "thumbprint" purpura) on the abdomen of an immunocompromised patient. *Courtesy, Jean L Bolognia, MD.*

albendazole to adults and children >2 years of age produces cure rates of 45–100%, but a dose of 400–800 mg/day (in children, 10–15 mg/kg/

Synonyms: ■ River blindness ■ Enfermedad de Robles ■ Erysipelas (erisipela) de la costa ■ Craw-craw

Key features

- *Onchocerca volvulus* is a tissue-dwelling nematode that is mainly found in Africa and transmitted by black flies
- Most clinical manifestations are caused by microfilariae in the skin and eyes
- Cutaneous manifestations include subcutaneous nodules that contain adult worms, a pruritic papular dermatitis, lichenification and leukoderma
- The diagnosis can be established by identification of microfilariae via microscopic examination of a skin sample (skin snip) or slit-lamp examination of the eyes

day with a maximum of 800 mg/day) for 3–5 days results in more consistent efficacy (cure rates of 80–100%)[70]. A single ivermectin dose of 12 mg in adults or 150 mcg/kg in children leads to cure rates of 80–100%. Topical application of 10–15% thiabendazole solution or ointment to affected areas can be performed for localized disease, but this has limited value for multiple lesions and requires application three times daily for at least 15 days. Oral thiabendazole is also effective but is less well tolerated than either albendazole or ivermectin[70].

ONCHOCERCIASIS

Introduction

Onchocerciasis, or river blindness, predominantly affects cutaneous and ocular tissue and is caused by *Onchocerca volvulus*, a filarial nematode[74]. Onchocerciasis most commonly occurs in inhabitants of tropical Africa and occasionally develops in residents of tropical areas in Central and South America and the Middle East. In the earlier stages of the disease, cutaneous manifestations include subcutaneous nodules

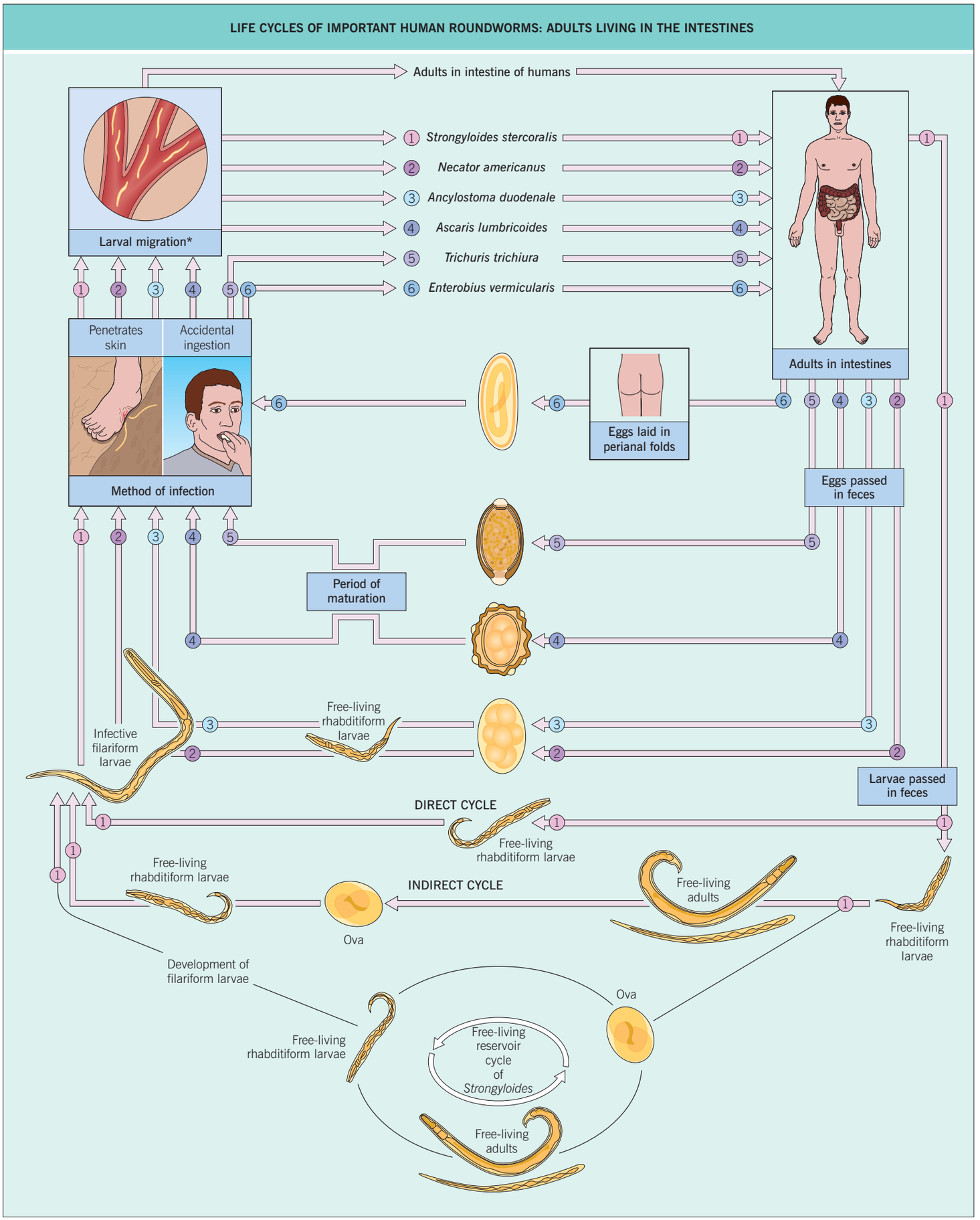


Fig. 83.24 Life cycles of important human roundworms: adults living in the intestines. *Larvae can migrate from venules into the right heart and lungs, then via alveoli into the trachea; eventually they are swallowed. *With permission from Cross JH, Helminths. In Cohen J, Powderly W, eds, Infectious Diseases, 2nd edition. London: Mosby, 2004.*

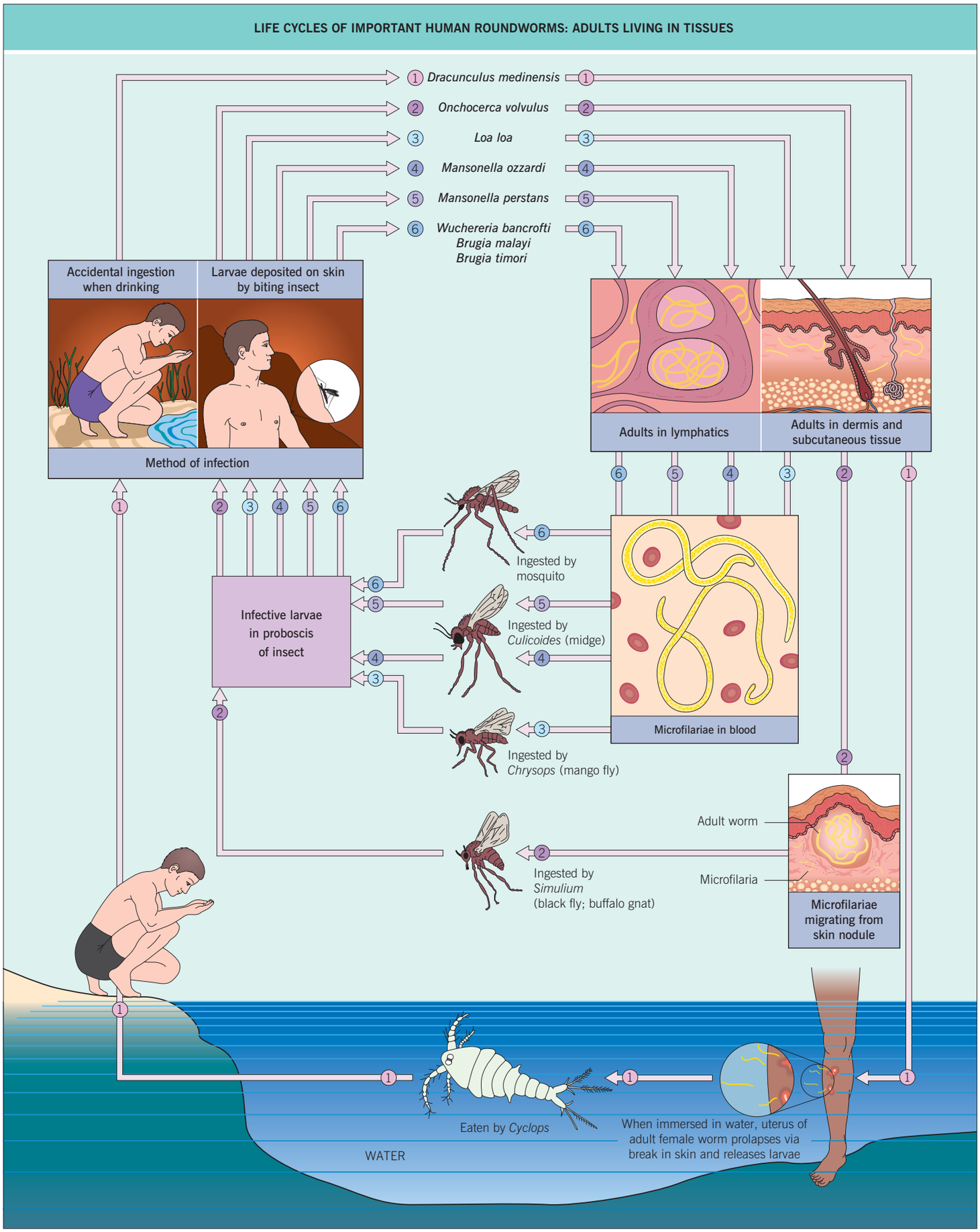


Fig. 83.25 Life cycles of important human roundworms: adults living in tissues. *With permission from Cross JH, Helminths. In Cohen J, Powderly W, eds, Infectious Diseases, 2nd edition. London: Mosby, 2004.*

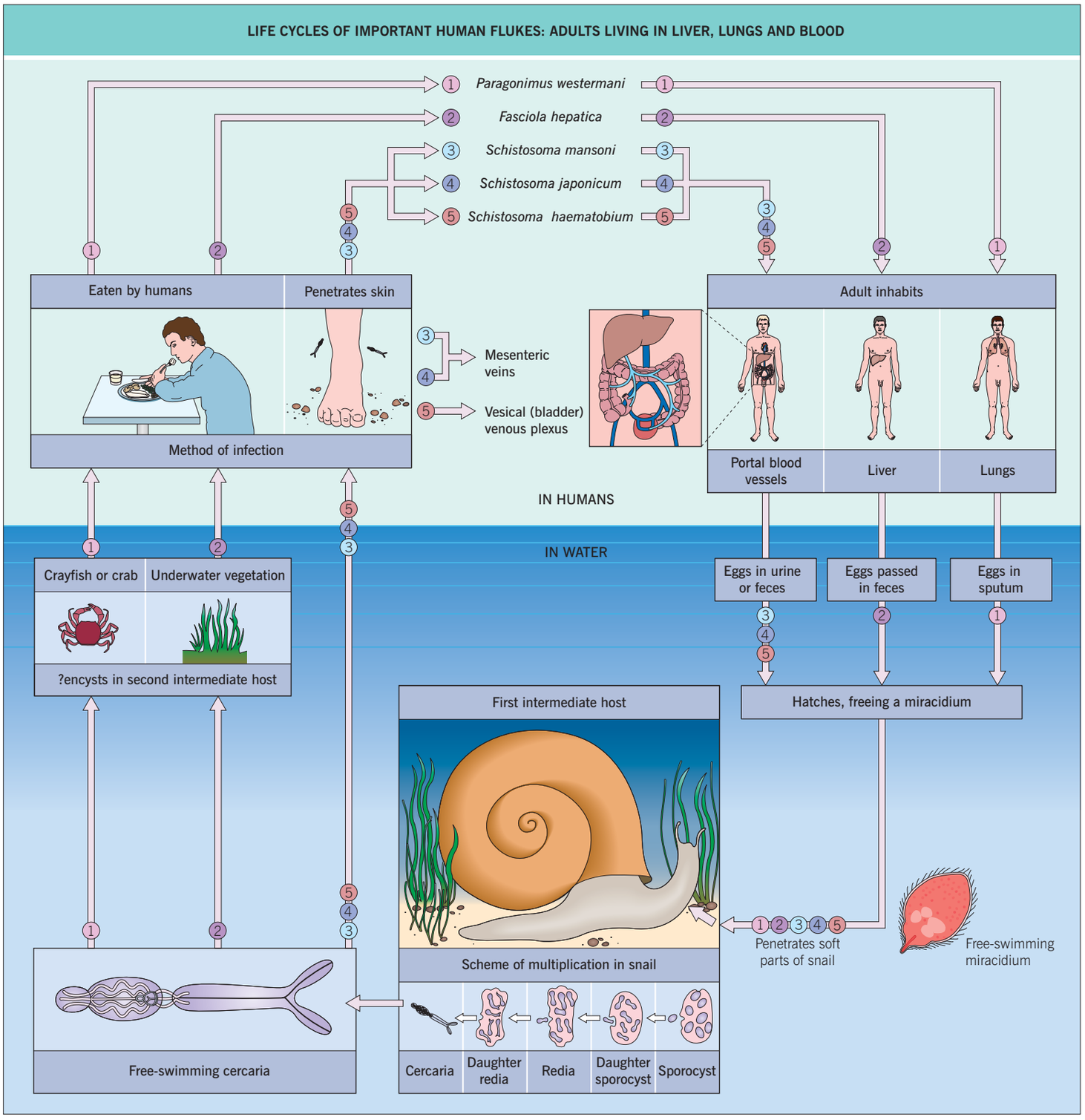


Fig. 83.26 Life cycles of important human flukes: adults living in the liver, lungs, intestines and blood. *Adapted with permission from Cross JH, Helminths. In Cohen J, Powderly, W, eds, Infectious Diseases, 2nd edition. London: Mosby, 2004.*

and pruritic papular dermatitis, while skin thickening and leukoderma are later findings. Progressive sclerosing keratitis can lead to blindness.

Epidemiology

Although onchocerciasis is not a fatal disease, it is severely debilitating and is estimated to affect 37 million people worldwide, in particular those living for prolonged periods of time near fast-flowing rivers in endemic areas[75]. Well-oxygenated water plays a significant role in this disease, because the larvae of *O. volvulus* have an obligatory aquatic stage during which they require high oxygen tension[74,76]. Severe disease requires repeated exposures over many years. Approximately 99% of all cases are acquired in equatorial Africa, but there are some endemic foci in the Middle East and in Central and South America (Fig. 83.30), where infected slaves introduced the disease.

Pathogenesis

Onchocerciasis is transmitted by the bite of an infected black fly (*Simulium* spp.). Because these flies often assume a "hump-backed" stance, they are sometimes referred to as "buffalo gnats". Black flies feed by "rasping" (abrading) the surface of the skin until a pool of blood forms, which they lap up. Microfilariae previously residing in the

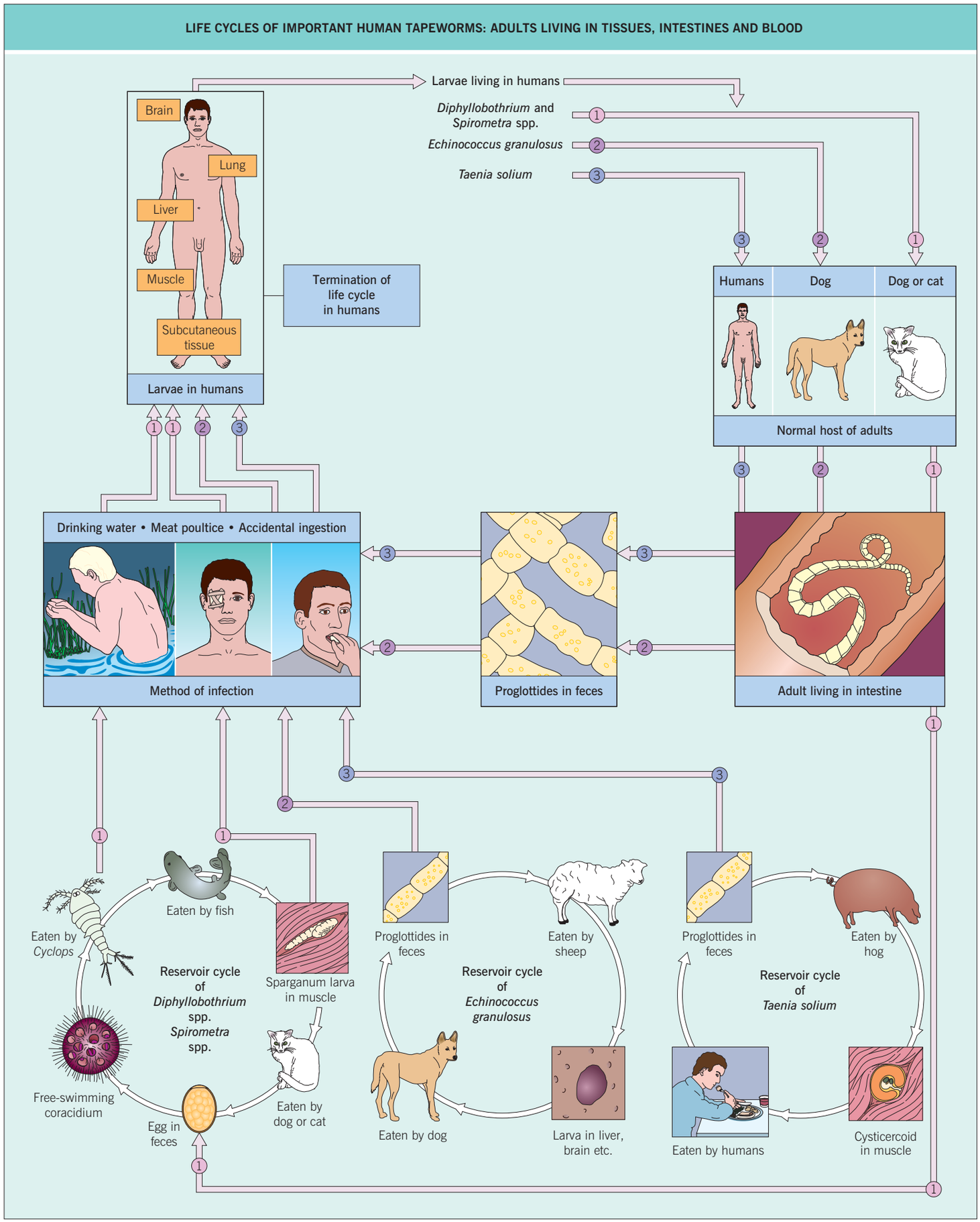


Fig. 83.27 Life cycles of important human tapeworms: adults living in tissues, intestines and blood. *Adapted with permission from Cross JH, Helminths. In Cohen J, Powderly W, eds, Infectious Diseases, 2nd edition. London: Mosby, 2004.*

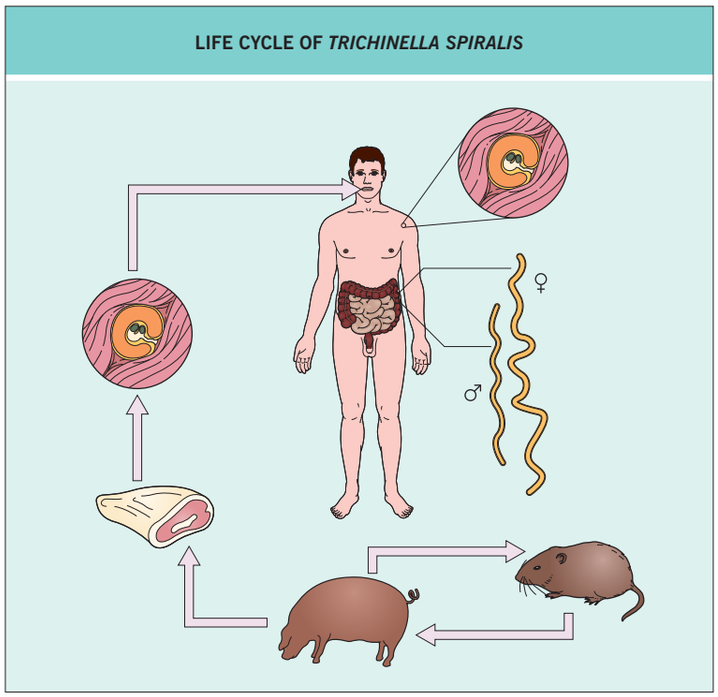


Fig. 83.28 Life cycle of *Trichinella spiralis*. This nematode is a zoonotic infection that circulates between rats and various carnivores. Trichinosis in humans commonly results from eating raw or inadequately cooked pork products such as sausages. Infection is acquired by eating muscle containing encysted larvae which excyst in the small intestine and develop into adults. Mature females deposit larvae which migrate from the gastrointestinal tract through tissues to reach skeletal muscles in which they then encyst. *With permission from Peters W, Pasvol G, Tropical Medicine and Parasitology, 6th edition. London: Mosby, 2007.*

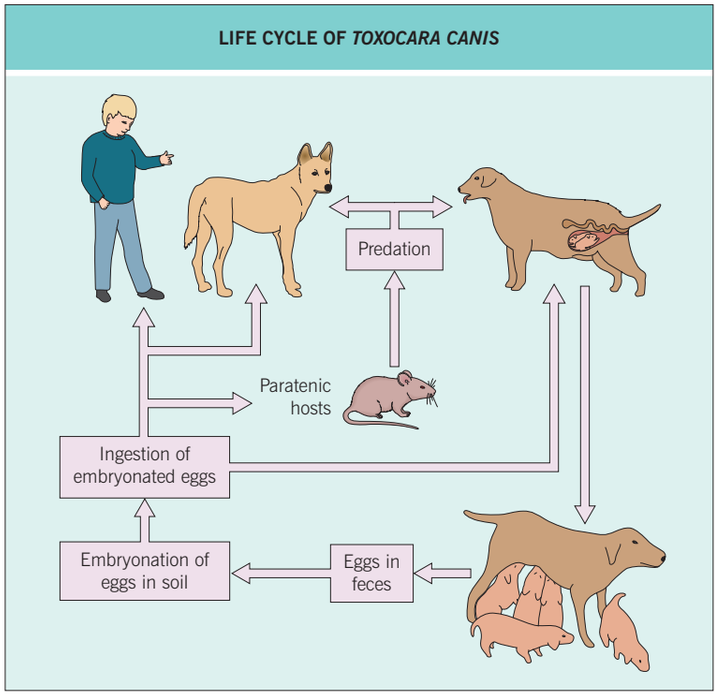


Fig. 83.29 Life cycle of *Toxocara canis*. This demonstrates the importance of transplacental transmission in maintaining canine infection, and the role of young dogs in transmitting infection to humans. *With permission from Gillespie S, Migrating worms. In Cohen J, Powderly W, eds, Infectious Diseases, 2nd edition. London: Mosby, 2004.*

dermis are present in this blood, and they penetrate the gut wall of the insect and migrate to its thoracic muscles, where they develop into larvae. The larvae then migrate to the proboscis, from which they will be transmitted to another human host during a blood meal[76] (see Fig. 83.25). *Wolbachia* bacterial endosymbionts are required for normal development of *O. volvulus* larvae and embryos, are thought to support

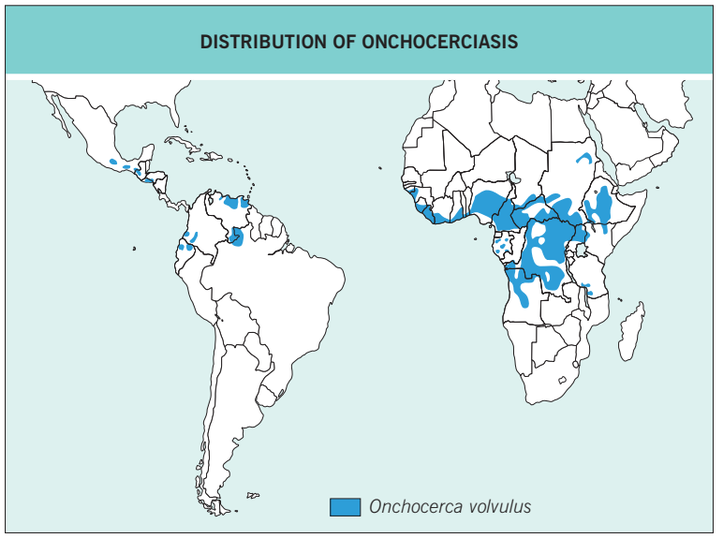


Fig. 83.30 Distribution of onchocerciasis. The disease is found primarily in Africa and Central and South America.

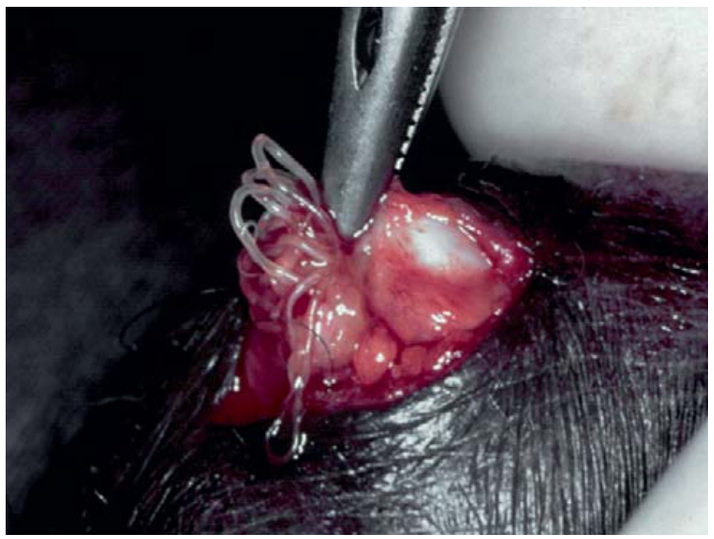


Fig. 83.31 Onchocerciasis. Extraction of adult worms from an onchocercal nodule on the buttocks.

the survival of adult worms, and drive immune responses that contribute to disease pathogenesis[76a].

Once in their human host, larvae take almost a year to reach maturity. The adult worms are large, measuring up to 50 cm in length. They are encapsulated within fibrous tissue and reside in nodules close to the surface of the skin or near joints. These nodules are known as "onchocercomas" (Fig. 83.31). Each female worm produces hundreds of microfilariae, which live for 1–2 years and migrate into the skin, connective tissue, eyes and lymph nodes. It is the microfilariae that cause most of the serious clinical features of onchocerciasis[77]. There is little inflammation until the microfilariae degenerate, which triggers a hypersensitivity reaction. In the skin, this results in intense pruritus and dermatitis.

Clinical Features

The primary manifestations of onchocerciasis involve the eye and the skin. Cutaneous findings are classified into the following groups: acute papular onchodermatitis, chronic papular onchodermatitis, lichenified onchodermatitis, onchocercal atrophy and depigmentation[78] (Fig. 83.32). Patients first present with subcutaneous nodules that are usually located over bony prominences; they favor the upper part of the body in patients living in Central and South America and the lower part of the body in those from Africa. The subcutaneous nodules represent fibrous tissue surrounding adult worms. An intermittent,

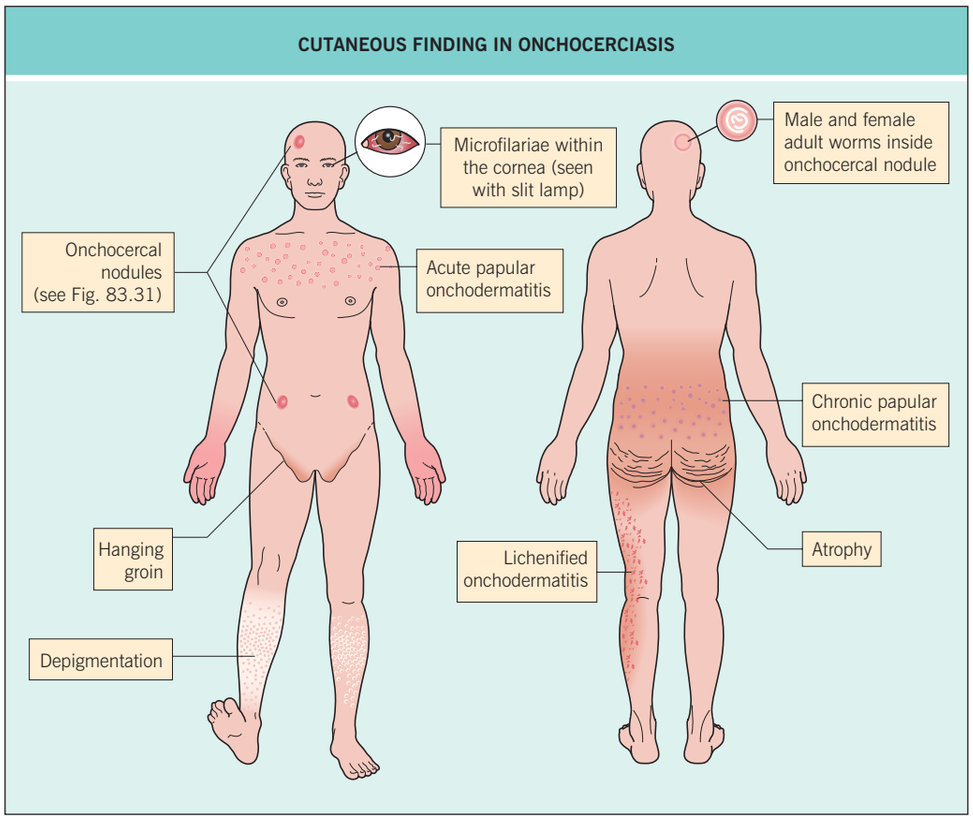


Fig. 83.32 Cutaneous findings in onchocerciasis.

Fig. 83.33 Onchocerciasis. Diffuse lichenification and hyperpigmentation in a patient with intense pruritus. Focal areas of leukoderma are also present.
Courtesy, Omar P Sangüeza, MD.

intensely pruritic acute papular onchodermatitis follows, in which small papules form around the microfilariae (called "craw-craw" in Africa).

In chronic onchocerciasis, the skin becomes thickened and wrinkled; this is accompanied by lichenification and hyperpigmentation (Fig. 83.33) and is sometimes referred to as "lizard" or "elephant" skin. The back, thighs and lower trunk are frequently affected, and sometimes hyperpigmentation is seen on one lower extremity in association with inguinal lymphadenopathy. Atrophy and a loss of pigment with sparing of perifollicular skin are also seen in late stage onchocerciasis. The latter changes, sometimes referred to as "leopard" skin, are most often evident on the shins[79] (see Ch. 66). Chronic lymphatic obstruction and involvement of the inguinal lymph nodes can lead to hanging groin or elephantiasis of the genitalia.

In Central America, young patients who are heavily infested may develop erythema on the face or upper trunk (erisipela de la costa). Older patients may have violaceous papules or plaques (mal morado), which can lead to leonine facies.

In addition to skin lesions, microfilariae can also be found in the conjunctivae; from there they can move through the cornea into the anterior and posterior chambers of the eye, leading to conjunctivitis, sclerosing keratitis, uveitis, chorioretinal lesions, optic atrophy and glaucoma[74]. Blindness occurs in the most severe cases. Dead microfilariae in the cornea can induce a tissue reaction that produces characteristic "snowflake" opacities.

Pathology

In onchodermatitis, microfilariae are present in all levels of the skin but are most concentrated in the dermal papillae, where they can infect black flies during feeding. Microfilariae are ~250 microns long with two or three pairs of anterior nuclei. Initially, they are surrounded by an infiltrate with numerous eosinophils. Lymphocytes, macrophages, plasma cells and mast cells may become more prominent at later stages, and epidermal hyperplasia (secondary to rubbing) may develop. The final outcome is fibrosis surrounding the microfilariae with minimal inflammation[80].

The adult female worms are found in a subcutaneous nodule. They are initially surrounded by an infiltrate containing many eosinophils, with progressive development of fibrosis.

Diagnosis

The clinical diagnosis of onchocerciasis is usually not difficult in endemic areas. It is confirmed by microscopic visualization of microfilariae as they emerge from multiple skin snips placed in saline (Fig. 83.34); these small, thin discs (including superficial dermis) are taken from skin near a nodule and over the shins, iliac crests or scapulae[81]. Onchocerciasis can also be diagnosed by the identification of the adult worm in an excised nodule. In heavily infected individuals, microfilariae can be found in the blood, sputum and urine. By slit-lamp examination, microfilariae (when present) are easily visualized within the anterior chamber of the eye. When skin snips are negative, the "Mazzotti test" may be helpful in diagnosing onchocerciasis: 50 mg of diethylcarbamazine (DEC) is administered orally, and a pruritic eruption develops within 15 minutes (as the microfilariae die) if the patient

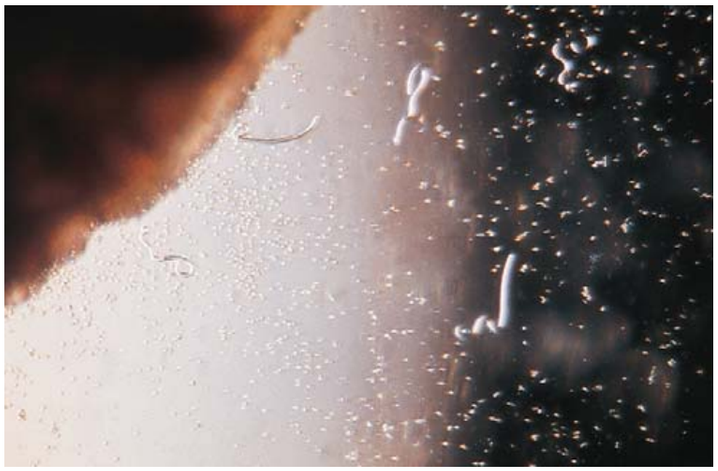


Fig. 83.34 Living microfilariae of *Onchocerca volvulus*. After some time, actively moving microfilariae emerge from the skin snip into the surrounding saline, where they can be counted. *With permission from Peters W, Pasvol G, Tropical Medicine and Parasitology, 6th edition. London: Mosby, 2007.*

is infected. In the "Mazzotti patch test", DEC is applied topically (e.g. in a 10% lotion under occlusion) to a small area of skin, which is examined 24 hours later for the development of papules and edema; this diagnostic method is not as sensitive as oral administration of DEC but less likely to produce a systemic reaction. A recently developed dipstick test to detect *Onchocerca volvulus* antigen in the urine or tears has a sensitivity of >90% and a specificity of 100%[82]. Tests based on antibody detection cannot distinguish between active and past infections.

Differential Diagnosis

Early lesions of onchocercal dermatitis must be distinguished from insect bites, scabies and atopic or allergic contact dermatitis. The chronic skin lesions may be mistaken for chronic eczema with postinflammatory pigmentary changes, leprosy or the leukoderma of scleroderma. The differential diagnosis of elephantiasis includes other types of filarial infestation (see Fig. 83.25), and a false-positive skin snip can occur if the tissue is contaminated with blood filariae, especially *Mansonella perstans* or *Loa loa*.

Treatment

Therapy for onchocerciasis has drastically improved as a result of the widespread use of oral ivermectin since 1987[83]. As the drug of choice, it is effective in rapidly killing microfilariae and in preventing their escape from gravid females. Ivermectin causes few or no adverse reactions and no Mazzotti reaction, whereas older drugs, e.g. diethylcarbamazine and suramin, are associated with severe hypersensitivity or dangerous toxic reactions. Ivermectin is administered as a single dose of 150 mcg/kg every 3 to 12 months. After treatment, microfilariae usually disappear from the skin within 1 week and from the eye within 3 months. Although multiple doses of oral ivermectin can kill adult worms, treatment is typically continued for the worm's lifetime (10–15 years). Administration of doxycycline (100–200 mg/day for 6 weeks) to target *Wolbachia* endosymbionts represents a promising therapeutic approach that can markedly reduce or eliminate microfilariae for >18 months[83a,83b]. Nodulectomy (see Fig. 83.31) is a popular method of treatment in countries where nodules on the head are common; their removal reduces the chance of ocular disease.

Preventive measures consist of spraying black fly breeding sites with larvicides and mass treatment of the population in endemic areas. In Africa, the use of a bacterium called *Bacillus thuringiensis israelensis* HI4 (BTI) to destroy the aquatic stages of *Simulium* black flies has reduced transmission.

Synonym: ■ Lymphatic filariasis, elephantiasis ■ Elephantiasis

Key features

- Filariasis is an infection of the lymphatic system by tissue nematodes (roundworms) acquired via mosquito vectors
- There are acute, chronic and asymptomatic forms of filariasis
- Manifestations of the acute phase include lymphangitis and orchitis
- Chronic disease is characterized by the sequelae of lymphatic obstruction, e.g. lymphedema, elephantiasis, hydroceles and chyluria; associated skin findings include hyperkeratosis, verrucous changes, soft tissue hypertrophy and fibrosis

FILARIASIS

Introduction

Lymphatic filariasis is an infection of the lymphatic system by two genera of filarial nematodes (roundworms). Several species of mosquitoes act as vectors (see Fig. 83.25). Cutaneous findings during the acute and chronic stages include lymphangitis and lymphedema accompanied by changes of elephantiasis.

Epidemiology

There are two major forms of filariasis, Bancroftian (due to *Wuchereria bancrofti*), causing 90% of infections, and Malayan (due to *Brugia malayi* and *B. timori*). The disease affects over 120 million people living in more than 80 countries located primarily within the tropical and subtropical regions of South America, Africa, Asia and the Pacific Islands. *W. bancrofti* is found worldwide, whereas *B. malayi* is restricted to South and East Asia. The distribution of *B. timori* is limited to islands in the Indonesian archipelago[84].

A number of mosquito species act as vectors for these filarial nematodes. The most important ones for *W. bancrofti* are *Culex quinquefasciatus*, *Anopheles gambiae*, *Anopheles funestus*, *Aedes polynesiensis*, *Aedes scapularis* and *Aedes pseudoscutellaris*. Both *B. malayi* and *B. timori* are transmitted by *Anopheles barbriostris*. *B. malayi* can also be transmitted by several species of *Aedes* and *Mansonia* mosquitoes[84,85].

Pathogenesis

Multiple bites from infected mosquitoes seem to be required to produce symptomatic infections, and the incubation period varies from 2 to 18 months. Larvae enter lymphatic vessels and then, once mature, the adult worms mate within the lymphatics or lymph nodes and release sheathed microfilariae into the bloodstream[84]. The mosquito then acquires microfilariae during a blood meal. Over several days, the microfilariae develop into larvae within the mosquito, which can then transmit infection to other humans during subsequent blood meals (see Fig. 83.25).

The clinical manifestations of lymphatic filariasis reflect a complex interplay of the pathogenic potential of the parasite, the immune response of the host, and secondary bacterial and fungal infections. Maturing adult worms provoke an eosinophilic and chronic inflammatory cell infiltrate around lymphatic vessels, leading to dilation and valvular damage with eventual scarring and obstruction of lymphatic flow. The death of worms within lymphatic vessels and lymph nodes results in an intense inflammatory reaction with granulomatous changes and necrosis[84]. *Wolbachia* bacterial endosymbionts are required for the worms' development, embryogenesis and survival; *Wolbachia* also stimulates an innate and adaptive immune response that leads to expression of vascular endothelial growth factors (VEGFs) that promote lymphangiogenesis, lymphatic endothelial proliferation and dilation of lymphatic vessels[83a].

Clinical Features

There are acute, chronic and asymptomatic forms of filariasis. Acute episodes of lymphangitis and fever typically last approximately one week and are usually recurrent, with 6 to 10 episodes per year. Early on, the affected body part appears clinically normal in between these episodes. Other common findings include orchitis and epididymitis.

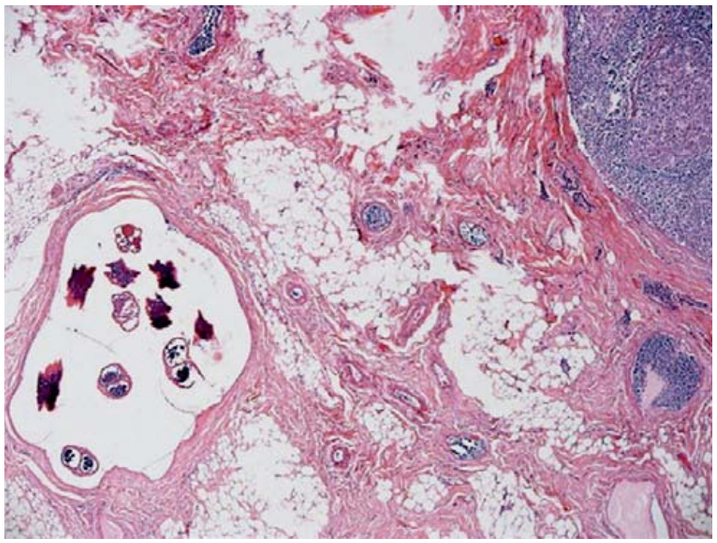


Fig. 83.35 Histopathology of filariasis. Dilated lymphatic with a mature adult worm and surrounding enlarged inguinal lymph nodes.

After 10 to 15 years of infection, the clinical features of chronic disease, i.e. the sequelae of lymphatic obstruction, are noted. These include lymphedema, elephantiasis, hydroceles and chyluria. Of note, in some communities in endemic regions, 40–60% of all the adult men have hydroceles. In sites of lymphedema and elephantiasis, the skin can be hyperkeratotic, verrucous and fibrotic with soft tissue hypertrophy and redundant folds. Fissures, ulceration and gangrene may also occur. Secondary bacterial and fungal infections are very common.

The two most commonly affected sites are the lower extremities and the genitalia. There are two major reasons for this particular distribution: (1) the female mosquito flies near the ground, thus it is more likely to bite the lower limbs, which is followed by retrograde involvement of the inguinal region; and (2) due to gravitational forces, the legs are at greater risk for venous hypertension and valvular incompetency and therefore more susceptible to the development of chronic lymphedema[84].

Tropical pulmonary eosinophilia occurs in some patients with filarial infections. Clinical findings include cough, wheezing, dyspnea, chest pain and fever accompanied by marked eosinophilia and pulmonary infiltrates. This may progress to restrictive pulmonary disease[86].

Travelers to endemic areas who became infected do not manifest the classic findings of filariasis. Instead, they have a hyperresponsive clinical presentation, known as "expatriate syndrome", with more intense inflammatory reactions to the filarial parasites. Clinical findings include lymphangitis, lymphadenitis and genital pain from the associated lymphatic inflammation, as well as urticaria, nonspecific cutaneous eruptions and peripheral eosinophilia[84].

Diagnosis

Detection of circulating filarial antigen is now the preferred method for diagnosis of Bancroftian filariasis, but similar tests are not currently available for Malayan filariasis. Alternatively, the diagnosis can be established by the demonstration of microfilariae in the blood, urine or other body fluids and tissues or by the identification of adult worms[87,88] (Fig. 83.35). Visualization of motile adult worms may be possible using ultrasound to evaluate infected lymphatics. As the parasite exhibits a nocturnal periodicity in humans, 10 p.m. to 2 a.m. is the optimal time period for collection and then direct smear of blood or other fluids. More recently, the use of filters with a pore size of 3 microns has improved the rate of detection of microfilariae in the blood and urine. However, parasite detection is not a particularly reliable method because many symptomatic patients are amicrofilaremic. Peripheral eosinophilia and elevated serum IgE are very common laboratory findings. In addition, more than 50% of microfilaremic patients with *W. bancrofti* infections have hematuria and/or proteinuria[88].

Differential Diagnosis

The differential diagnosis depends upon the stage of the infection. Acute infection may be misdiagnosed as a bacterial lymphangitis. Lymphedema and elephantiasis have multiple possible etiologies, including recurrent bacterial lymphangitis, severe venous hypertension, lymph node dissections, Milroy disease and Klippel–Trenaunay syndrome[89].

Treatment

The drug of choice is diethylcarbamazine, which is active against microfilariae but has a limited effect on adult worms. The usual course is 6 mg/kg/day for 12 days. Mass drug administration programs give at-risk individuals single yearly doses of two medications for at least 5 years: albendazole plus either diethylcarbamazine or (in regions where onchocerciasis is co-endemic) ivermectin[90]. Doxycycline (200 mg/day for 4–8 weeks) targeting the *Wolbachia* endosymbiont can also eliminate microfilariae, kill adult worms and improve lymphatic drainage. During the treatment period, antihistamines and glucocorticoids may be useful in decreasing the allergic reaction that may result from massive disintegration of microfilariae. Because severe reactions may follow the administration of diethylcarbamazine in patients who have loiasis or onchocerciasis, it is important to exclude other helminthic diseases before instituting therapy[89]. Other management strategies include elevation of the affected body part, compression stockings, anti-inflammatory drugs, treatment of secondary infections, and protection of the affected area from trauma[89].

Synonyms: ■ Schistosomiasis: bilharziasis ■ Swimmer's itch: clam digger's itch

Key features

- Schistosomiasis is a trematode (fluke) infection caused by five species of anthropophilic schistosomes, each with a specific geographic distribution and distinct intermediate host (snails)
- The disease is most commonly seen in Africa, the Far and Middle East, and South America
- Clinical stages include of cercarial dermatitis, Katayama fever, and chronic fibro-occlusive disease involving the liver, intestine and urinary tract
- The cercariae of more than 20 species of animal schistosomes may penetrate human skin and cause a transient dermatitis called swimmer's itch

SCHISTOSOMIASIS AND SWIMMER'S ITCH

Introduction

Schistosomiasis is a trematode (fluke) infection endemic to the tropics and subtropics caused by members of the superfamily Schistosomatoidea[91]. The disease has a worldwide distribution, affecting more than 200 million people in over 75 countries. Human disease can be caused by five schistosome species, most often *Schistosoma haematobium*, which infects the urinary system, and *S. japonicum* and *S. mansoni*, which infect the gastrointestinal tract[91]. In addition, when the cercariae of a number of other species that usually infect birds and mammals penetrate human skin, they can evoke "swimmer's itch", a local inflammatory response associated with marked pruritus.

Epidemiology

Schistosomes have a two-host life cycle (see Fig. 83.26). Snails serve as the intermediate host, while the definitive host is species-dependent. Humans are the major definitive host for five schistosome species[91], each of which has a specific geographic distribution (Fig. 83.36): *S. mansoni* occurs in Africa, South America and the Caribbean; *S. japonicum* in Japan, China and the Philippines; *S. haematobium* in Africa

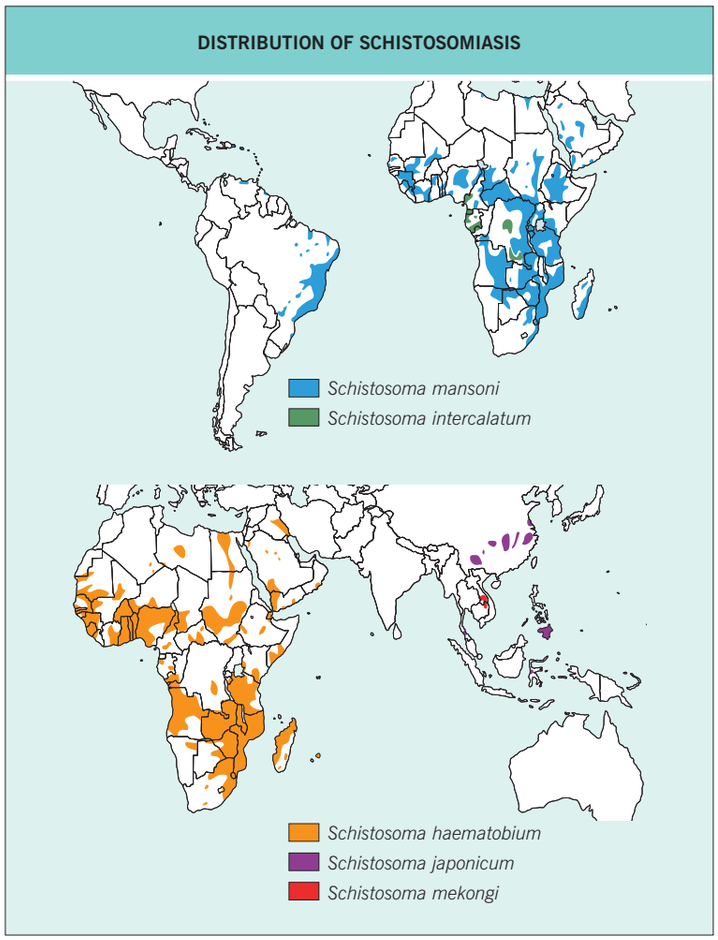


Fig. 83.36 Distribution of schistosomiasis. *Adapted from Peters W, Pasvol G, Tropical Medicine and Parasitology, 6th edition. London: Mosby, 2007.*

and the Middle East; *S. mekongi* in Southeast Asia; and *S. intercalatum* in West and Central Africa.

The geographic distribution of schistosomiasis has changed significantly in recent decades. It has almost been eradicated from Japan and the Caribbean islands, and the transmission cycle has been interrupted in North Africa, the Philippines, Saudi Arabia and Venezuela. However, environmental changes related to water resource development and population movements have led to spread of the disease to previously non-endemic areas such as sub-Saharan Africa. Schistosomiasis is now present in and around several major cities in northeastern Brazil and is a major public health problem in certain regions of China.

Swimmer's itch (cercarial dermatitis) is due to over 20 species of schistosomes that usually infect birds and mammals (e.g. *Trichobilharzia*, *Gigantobilharzia*, *Ornithobilharzia* spp.). It is a cutaneous disease with a worldwide distribution, having been documented in every continent except Antarctica. In the US, it has been observed most often in the north central states. Outbreaks of swimmer's itch are episodic.

Pathogenesis

Adult worms live in the venous system of the liver, rectum or urinary bladder of their definitive host. The eggs penetrate the rectum or bladder, to be passed into the feces or urine (see Fig. 83.26). In fresh water environments, the eggs hatch and release miracidia that penetrate the body of a snail, which acts as an intermediate host. For each schistosome species, a specific snail species acts as an intermediate host. In the snail, the miracidia develop into cercariae, the infective forms that can penetrate human skin on contact[92].

The species that are responsible for swimmer's itch complete their life cycle in birds and animals, including ducks, cows, sheep and rodents. In contrast to human schistosomes, which cause systemic disease, the cercariae of animal schistosomes die after penetration into human skin, inducing only a local inflammatory reaction. Because humans cannot support the development of these schistosomes, we represent incidental, "dead-end" hosts[91,93].

Fig. 83.37 Swimmer's itch. Numerous edematous dark red papules on the feet and ankles. *Courtesy, Kalman Watsky, MD.*

Clinical Features

The cutaneous manifestations produced by the anthropophilic species of schistosomes can be classified into five categories: cercarial dermatitis, Katayama fever, late nonspecific allergic dermatitis, perigenital infiltrative granulomas and extragenital infiltrative lesions[94–96]. Cercarial dermatitis is associated with cutaneous penetration by the cercariae. Though fairly common, patients rarely present with this transient, erythematous, pruritic papular or urticarial eruption at the site of inoculation. The reaction is relatively nonspecific and is more severe with *S. japonicum* and *S. mansoni* infections. Within hours of contact, macules develop and then either disappear or, more commonly, are replaced by small pruritic papules that may persist for a few days[92].

In some patients, a systemic allergic reaction (Katayama fever) occurs during the acute phase of a moderate or heavy infection. Affected individuals have an acute onset of fever, chills, sweats and headaches, in association with peripheral blood eosinophilia and urticaria. Katayama fever is seen most commonly with *S. japonicum* infections and is due to circulating immune complexes. Approximately 4 to 6 weeks later, some patients may experience another transient cutaneous reaction with nonspecific findings ranging from urticarial or purpuric lesions to periorbital edema[93,94,96].

Bilharziasis cutanea tarda is characterized by papular, granulomatous or verrucous lesions of the genital and perineal skin secondary to the deposition of ova within dermal vessels in this area[93,96]. Occasionally, "ectopic" cutaneous lesions have been observed due to inflammatory reactions to deposited ova. They have been described as hyperpigmented lichenoid papules in several patients[94] and may have a zosteriform distribution on the trunk.

Systemically, chronic infections with *S. mansoni* and *S. japonicum* are associated with hepatic fibrosis and cirrhosis (as a reaction to the ova), portal hypertension (including ascites and esophageal varices) and splenomegaly. Additional findings may include colonic polyps (which contain ova) and granulomas around ova in the liver, lung and colon (Hoeppli reaction). Urogenital infections with *S. haematobium* can lead to polypoid lesions composed of numerous ova, fibrosis and calcification. Calcified ova may be seen through the atrophic epithelium, leading to "sandy patches" that are pathognomic

of schistosomiasis on cystoscopy[97]. Additionally, the presence of numerous ova can lead to obstruction of the urinary tract and the development of hydronephrosis. Carcinoma of the bladder is a life-threatening complication.

Lesions of swimmer's itch have an appearance similar to that of cercarial dermatitis, i.e. pruritic papules at sites of inoculation (Fig. 83.37). As a result, areas of skin covered by clothing are spared[98]. The eruption may last for days but is self-limited.

Pathology

Histologically, cercarial dermatitis is characterized by spongiosis and a mixed inflammatory infiltrate composed of histiocytes, lymphocytes, neutrophils and eosinophils. Edema is present in the dermis. Genital and perineal lesions of bilharziasis cutanea tarda show hyperkeratosis and acanthosis and occasionally prominent pseudoepitheliomatous hyperplasia. The dermis may contain numerous ova, which can be associated with a granulomatous reaction. "Ectopic" extragenital lesions contain ova in the superficial dermis associated with granuloma formation.

Diagnosis

The diagnosis is usually established by microscopic detection of eggs in the urine or feces. In the case of *S. japonicum* and *S. mansoni* infections, microscopic evaluation of mucosal biopsy specimens may point to the diagnosis. An ELISA to detect antischistosomal IgG, IgM and IgE is available and is used to distinguish acute from chronic infection[5].

In addition, monoclonal antibodies that detect circulating antigens are quite sensitive and specific for establishing the diagnosis as well as assessing response to therapy (including cure)[99].

Differential Diagnosis

The diagnosis of cercarial dermatitis or swimmer's itch requires a history of exposure to contaminated water. The lesions may be confused with arthropod bites, but the distribution is clearly distinct from that of seabather's eruption, which affects areas under the swimsuit. The differential diagnosis of anogenital and ectopic cutaneous ova deposition includes secondary syphilis (in particular the granulomatous form), condyloma acuminatum, cutaneous Crohn's disease, granuloma inguinale and lichen planus.

Synonyms: ■ Echinococcosis: hydatidosis, hydatid disease

Key features

- Cestodes (tapeworms) that commonly affect animals (e.g. *Taenia solium*, *Echinococcus granulosus*) can also infect humans
- Cutaneous cysticercosis is characterized by small papulonodules that are usually multiple and asymptomatic; the brain (neurocysticercosis), eye, heart, other muscles and peritoneal cavity may also be affected
- In echinococcosis, the liver and lungs are the major sites of involvement, with development of one or more hydatid cysts. Allergic symptoms, such as urticaria, asthma and anaphylaxis, are uncommon

Treatment

Praziquantel is an antihelminthic agent that is safe and effective against all five human schistosomal species[100]. It is administered as two to three oral doses of 20 mg/kg over a single day. Side effects are mild and include abdominal discomfort, fever and headache.

Although topical remedies (e.g. phenolized calamine) and antihistamines have been recommended for swimmer's itch, no controlled studies have defined the most effective therapy[98,101]. If left untreated, the acute episode resolves spontaneously within 7–10 days.

The most effective way to prevent swimmer's itch is to avoid lakes and bodies of fresh water known to be infested, at least during those periods of the year when cercariae are most plentiful, i.e. during the early and mid summer in temperate regions. One method of environmental control is to treat feed corn so that ducks are cured of their worms. This minimizes the environmental impact because it obviates the need to add poisonous substances to lakes and ponds to kill the snails.

CYSTICERCOSIS AND ECHINOCOCCOSIS

Introduction

In the two stages of their life cycle (adult and larval), cestodes (tapeworms) can cause disease in humans. The adult worms reside in the *definitive* host's intestines (including humans) and are associated with mild or no clinical manifestations (see Fig. 83.27). In *intermediate* hosts, the larval stage can lead to clinical disease, e.g. cysticercosis or echinococcosis in humans[102].

Epidemiology

The four most common human cestodes (tapeworms) are *Taenia solium* (pork tapeworm), *Taenia saginata* (beef tapeworm), *Diphyllobothrium latum* and *Hymenolepis nana*. In humans, they cause primarily gastrointestinal symptoms, but the larval stage of *T. solium* also causes cysticercosis. Cysticercosis in pigs and cattle can be caused by larvae of *T. solium* and *T. saginata*, respectively. Cysticercosis has a worldwide distribution, affecting more than 50 million people, and it is more common in rural areas. Endemic regions include Central and South America, sub-Saharan Africa, India and East Asia[103].

Echinococcosis is a zoonosis caused by *Echinococcus* species, the definitive hosts of which are dogs and other members of the family Canidae. Humans are only infected by the larval stage, i.e. they are intermediate hosts and develop cysts within viscera. Most human disease is due to larval stages of *E. granulosus* and *E. multilocularis*. Echinococcosis occurs in tropical and subtropical countries worldwide, primarily in sheep- and cattle-raising areas. Endemic regions include the southern province of Brazil, the Middle East, parts of Asia, and Northern and East Africa. It is particularly common in Lebanon and Greece[102,103].

Pathogenesis

The adult tapeworm can reach a length of up to 30 feet in the intestinal tract of its definitive host. Its body has two main parts: a single head (scolex) for attachment to the host and many proglottids, each of which has male and female reproductive organs. Fertilized eggs accumulate in large numbers inside the uterine horns of the proglottids; the eggs can be released directly into the host's intestine or the entire gravid terminal proglottid can be excreted by the host[102]. Both eggs and proglottids are found in the host's stool (see Fig. 83.27).

When eggs or proglottids are ingested by a susceptible *intermediate* host, they develop into larvae called oncospheres. In humans, oncospheres can develop into encysted forms (cysticerci in cysticercosis) or generate germinal tissue with a cyst (hydatid in echinococcosis). Subsequent ingestion of cyst-containing tissues by a susceptible definitive host allows the development of the larvae into adults and completion of the life cycle[104].

Humans are the only definitive host for *T. saginata* (beef tapeworm) and *T. solium* (pork tapeworm), becoming infected with the adult form after eating poorly cooked muscle of a diseased animal (see Fig. 83.27). Humans are also intermediate hosts of *T. solium*, developing cysticercosis as a result of ingestion of food or water contaminated with infected human feces or via autoinfection from anus to mouth. In contrast, humans are only intermediate hosts of *E. granulosus* (as are sheep and cattle) as a result of ingesting contaminated dog feces. Dogs are the definitive host of *E. granulosus*, becoming infected with adult tapeworms after eating infected beef or lamb.

When humans are infected by the adult stage of *T. solium* (i.e. are the definitive host), the tapeworms within the intestine usually cause no morphologically identifiable change in the mucosa or submucosa. Some patients may develop moderate peripheral eosinophilia. Immunity plays only a limited role during infections with the adult stage and has little effect on the duration of infection or on the susceptibility to reinfection. However, immunity plays an important role when humans

are the intermediate host, i.e. develop cysticercosis. After penetrating the host's intestinal wall and disseminating, the oncosphere matures rapidly and by 10 weeks is fully developed. The cyst that forms is usually 0.5–1.0 cm in diameter and remains viable for 3 to 5 years before degenerating. At this time, the inflammatory response is markedly intensified, and calcification also often takes place[103,105,106]. The signs and symptoms triggered by these reactions depend on the location of the cysts. For example, if there are cysts at the base of the brain, a cysticercic meningitis may ensue. In brain tissue itself, cysts that calcify may cause seizures.

When humans ingest the eggs of *E. granulosus*, oncospheres penetrate the mesenteric vessels. While the majority are trapped by the liver sinusoids, some bypass the liver and are carried in the bloodstream to other organs and tissues. Within hours, an inflammatory response may be seen. If the larvae survive, they develop into hydatid cysts within 5 days. Cell-mediated immunity controls dissemination during the early phase of infection.

Clinical Features

In cysticercosis, cysts can develop in almost any organ or tissue in the body. Within the skin, small papulonodules are more often palpable than visible[105]. They are usually multiple and asymptomatic. The brain, eye, heart, other muscles and peritoneal cavity may also be affected. In a Brazilian study of 30 patients with cysticercosis, 90% had cysts in the subcutaneous tissue, skeletal muscle or mucous membranes, while the CNS was affected in <10%[103].

In echinococcosis, the cysts may be single or multiple and they affect primarily the liver (50–75%) and lungs (20%). The skin is involved in fewer than 2% of the patients. Cysts increase in size at the rate of approximately 1 cm/year. The clinical features are highly variable and reflect the location and size of the cysts. Most symptoms are due to mechanical pressure by the cyst mass or an allergic reaction (urticaria, wheezing, anaphylaxis) to foreign antigens in leaking cyst fluid[103].

Soft tissue cysts may present as firm subcutaneous nodules or as masses that are fluctuant and non-tender. *E. multilocularis* has been noted to cause multiple supraumbilical dermal and subcutaneous nodules with associated ulceration, local inflammation and painless cutaneous fistulas[103].

Diagnosis

The diagnosis of cysticercosis is often made by X-ray examination of the head or extremities, which reveals the calcified cysts. CT or MRI can also demonstrate lesions. ELISA and hemagglutination tests utilizing cyst vesicular fluid as antigen are 80–95% sensitive and specific. An enzyme-linked immunoblot assay is the serologic test of choice, as its specificity and sensitivity approach 100% and 94%, respectively[103].

The diagnosis of echinococcosis is based on detection of cysts via ultrasound, CT or MRI. Examination of the contents of the cyst and identification of the parasite provides confirmation. Peripheral

REFERENCES

1. DeNigris EJ, Garvin DF, Grogl M, et al. Leishmaniasis. In: Connor DH, Chandler FW, Schwartz DA (eds). Pathology of Infectious Diseases, Vol. II. Stamford: Appleton & Lange, 1997;1205–21.
2. Samady JA, Schwartz RA. Old World cutaneous leishmaniasis. Int J Dermatol. 1997;36:161–6.
3. Lupi O, Barlett BL, Haugen RN, et al. Tropical dermatology: tropical diseases caused by protozoa. J Am Acad Dermatol. 2009;60:897–925.

3a. den Boer M, Argaw D, Jannin J, Alvar J. Leishmaniasis impact and treatment access. Clin Microbiol Infect. 2011;17:1471–7.

4. Wright NA, Davis LE, Aftergut KS, et al. Cutaneous leishmaniasis in Texas: a northern spread of endemic areas. J Am Acad Dermatol. 2008;58:650–2.
5. Peters W, Pasvol G. Tropical Medicine and Parasitology, 5th edn. London: Mosby, 2001.
6. Wirth DF, Rogers WO, Barker R Jr, et al. Leishmaniasis and malaria: new tools for epidemiologic analysis. Science. 1986;234:975–9.
7. Pirmez C, Yamamura M, Uyemura K, et al. Cytokine patterns in the pathogenesis of human leishmaniasis. J Clin Invest. 1993;91:1390–5.
8. Da Cruz AM, de Oliveira MP, de Luca PM, et al. Tumor necrosis factor-alpha in human American tegumentary leishmaniasis. Mem Inst Oswaldo Cruz. 1996;91:225–9.
9. Carvalho EM, Correia-Filho D, Bacellar O, et al. Characterization of the immune response in subjects with self-healing cutaneous leishmaniasis. Am J Trop Med Hyg. 1995;53:273–7.

9a. Ives A, Ronet C, Prevel F, et al. Leishmania RNA virus controls the severity of mucocutaneous leishmaniasis. Science. 2011;331:775–8.

10. Bacellar O, Lessa H, Schriefer A, et al. Up-regulation of Th1-type responses in mucosal leishmaniasis patients. Infect Immun. 2002;70:6734–40.
11. Xynos ID, Tektonidou MG, Pikazis D, et al. Leishmaniasis, autoimmune rheumatic disease, and anti-tumor necrosis factor therapy, Europe. Emerg Infect Dis. 2009;15:956–9.
12. Machado-Pinto J, Azulay RD. Leishmaniasis. In: Tyring S, Lupi O, Hengge U (eds). Tropical Dermatology. London: Elsevier, 2006:41–8.
13. Sangueza OP, Sangueza JM, Stiller MJ, et al. Mucocutaneous leishmaniasis: a clinicopathologic classification. J Am Acad Dematol. 1993;28:927–32.
14. Peltier E, Wolkenstein P, Deniau M, et al. Caseous necrosis in cutaneous leishmaniasis. J Clin Pathol. 1996;49:517–19.
15. Salotra P, Sreenivas G, Beena KR, et al. Parasite detection in patients with post kala-azar dermal leishmaniasis in India: a comparison between molecular and immunological methods. J Clin Pathol. 2003;56:840–3.
16. Berman JD. Human leishmaniasis: clinical, diagnostic, and chemotherapeutic developments in the last 10 years. Clin Infect Dis. 1997;24:684–703.
17. Alvar J, Aparicio P, Aseffa A, et al. The relationship between leishmaniasis and AIDS: the second 10 years. Clin Microbiol Rev. 2008;21:334–59.

17a. CDC Parasitic Diseases Branch. Practical guide for laboratory diagnosis of leishmaniasis: www.cdc.gov/parasites/leishmaniasis/resources/pdf/cdc_diagnosis_guide_leishmaniasis.pdf

18. Vexenat A de C, Santana JM, Texeira AR. Cross-reactivity of antibodies in human infections by the kinetoplastid protozoa *Trypanosoma cruzi, Leishmania chagasi* and *Leishmania (vanni) braziliensis*. Rev Inst Med São Paulo. 1996;38:177–85.
19. Murray HW, Berman JD, Davies CR, et al. Advances in leishmaniasis. Lancet. 2005;366:1561–77.
20. Anonymous. Drugs for parasitic infections. Med Lett Drug Ther. 2007;5(suppl):e1–15.
21. Magill AJ. Cutaneous leishmaniasis in the returning traveler. Infect Dis Clin North Am. 2005;19:241–66.
22. Arevalo J, Ramierz L, Adaui V, et al. Influence of *Leishmania* (*Viannia*) species on the response to antimonial treatment in patients with American tegumentary leishmaniasis. J Infect Dis. 2007;195:1846–51.
23. Soto J, Arana BA, Toledo J, et al. Miltefosine for New World cutaneous leishmaniasis. Clin Infect Dis. 2004;38:1266–72.
24. Arana B, Mendoza C, Rizzo N, et al. Randomized, controlled, double-blind trial of topical treatment of cutaneous leishmaniasis with paromomycin plus methylbenzethonium chloride ointment in Guatemala. Am J Trop Med Hyg. 2001;65:466–70.
25. Sundar S, Jha TK, Thakeu CP, et al. Injectable paromomycin for visceral leishmaniasis in India. N Engl J Med. 2007;356:2571–81.
26. Alrajhi A, Ibrahim E, De Vol E, et al. Fluconazole for the treatment of cutaneous leishmaniasis caused by *Leishmania major*. N Engl J Med. 2002:346:891–5.
27. Reithinger R, Mohsen M, Wahid M, et al. Efficacy of thermotherapy to treat cutaneous leishmaniasis caused by *Leishmania tropica* in Kabul, Afghanistan: a randomized, controlled trial. Clin Infect Dis. 2005;40:1148–55.
28. Lack EE, Picken CP, Connor DH. Amebiasis – infection with *Entamoeba histolytica*. In: Connor DH, Chandler FW, Schwartz DA (eds). Pathology of Infectious Diseases, Vol. II. Stamford: Appleton & Lange, 1997:1123–33.
29. Ravdin J. Pathogenesis of disease caused by *Entamoeba histolytica*: studies of adherence, secreted toxin and contact-dependent cytolysis. Rev Infect Dis. 1986;8:247–60.
30. Bravo FG, Cabrera J, Gotuzzo E, Vivesvara GS. Cutaneous manifestations of infection by free-living amebas. In: Tyring S, Lupi O, Hengge U (eds). Tropical Dermatology. London: Elsevier, 2006:49–55.
31. Parshad S, Grover PS, Sharma A, et al. Primary cutaneous amoebiasis: case report with review of the literature. Int J Dermatol. 2002;41:676–80.
32. Al-Daraji WI, Husain EA, Robson A. Primary cutaneous amebiasis with a fatal outcome. Am J Dermatopathol. 2008;30:398–400.
33. Pritzker AS, Kim BK, Agrawal D, et al. Fatal granulomatous amebic encephalitis caused by *Balamuthia mandrillaris* presenting as skin lesion. J Am Acad Dermatol. 2004;50:S38–41.
34. Schuster FL, Visvesvara GS. Amebic encephalitides and amebic keratitis caused by pathogenic and opportunistic free-living amebas. Curr Treat Options Infect Dis. 2003;5:273–82.
35. Matin A, Ruqaiyyah S, Jayasekera S. Increasing importance of *Balamuthia mandrillaris*. Clin Microbiol Rev. 2008;21:435–48.
36. Siddiqui R, Khan NA. Balamuthia amoebic encephalitis: an emerging disease with fatal consequences. Microb Pathog. 2008;44:89–97.
37. Bakardjiev A, Azimi PH, Ashouri N, et al. Amebic encephalitis caused by *Balamuthia mandrillaris*: report of four cases. Pediatr Infect Dis J. 2003;22:447–53.
38. Schuster FL, Visvesvara GS. Free-living amebae opportunistic and non-opportunistic pathogens of humans and animals. Int J Parasitol. 2004;34:1001–27.
39. Huang ZH, Ferrante A, Carter RF. Serum antibodies to *Balamuthia mandrillaris*, a free-living amoeba recently demonstrated to cause granulomatous amoebic encephalitis. J Infect Dis. 1999;179:1305–8.
40. Siddiqui R, Orteg-Rivas A, Khan NA. *Balamuthia mandrillaris* resistance to hostile conditions. J Med Microbiol. 2008;57:428–31.
41. Bravo FG, Alvarez PJ, Gotuzzo E. *Balamuthia mandrillaris* infection of the skin and central nervous system: an emerging disease of concern to many specialties in medicine. Curr Opin Infect Dis. 2011;24:112–17.
42. Martinez AJ, Visvesvara GS. *Balamuthia mandrillaris* infection. J Med Microbiol. 2001;50:205–7.
43. Healy JF. Balamuthia amebic encephalitis: radiographic and pathologic findings. Am J Neuroradiol. 2002;23:486–9.
44. Semenovitch I, Lupi O. Trypanosomiasis. In: Tyring S, Lupi O, Hengge U (eds). Tropical Dermatology. London: Elsevier, 2006:29–39.
45. Leiby DA, Herron RM, Read EJ, et al. *Trypanosoma cruzi* in Los Angeles and Miami blood donors: impact of evolving donor demographics on seroprevalence and implications for transfusion transmission. Transfusion. 2002;42:549–55.
46. Barrett DP, Burchmore RJS, Stitch A, et al. The trypanosomiases. Lancet. 2003;362:1469–80.
47. Hagar JM, Rahimtoola SH. Chagas' heart disease. Curr Probl Cardiol. 1995;20:825–924.

48. Bern C. Antitrypanosomal therapy for chronic Chagas' disease. N Engl J Med. 2011;364:2527–34.
49. Boiani M, Boiani L, Denicola A, et al. 2H-benzimidazole 1,3-dioxide derivatives: a new family of water-soluble anti-trypanosomatid agents. J Med Chem. 2006;49:3215–24.
50. Apt W, Arribada A, Zulantay I, et al. Itraconazole or allopurinol in the treatment of chronic American trypanosomiasis: the regression and prevention of electrocardiographic abnormalities during 9 years of follow-up. Ann Trop Med Parasitol. 2003; 97:23–9.
51. Sternberg JM. Human African trypanosomiasis: clinical presentation and immune response. Parasite Immunol. 2004;26:469–76.
52. Quinn TC. African trypanosomiasis. In: Cecil RL, Goldman L, Bennett JC (eds). Cecil Textbook of Medicine, Vol. 2. Philadelphia: WB Saunders, 1996:1896–9.
53. Bryceson ADM, Hay RJ. Parasitic worms and protozoa. In: Rook A, Wilkinson DS, Ebling FJG, Champion RH (eds). Rook/Wilkinson/Ebling Textbook of Dermatology, Vol. 5. 6th edn. Oxford: Blackwell Science, 1998:1407–8.
54. Stich A, Barrett MP, Krishna S. Waking up to sleeping sickness. Trends Parasitol. 2003;19:195–7.
55. McGovern TW, Williams W, Fitzpatrick JE, et al. Cutaneous manifestations of African trypanosomiasis. Arch Dermatol. 1995;131:1178–82.
56. Welburn SC, Odiit M. Recent developments in human African trypanosomiasis. Curr Opin Infect Dis. 2002;15:477–84.
57. Rocha LAC, Ferreira FSC. Tripanossomiase humana Africana. In: Veronesi R, Ricardo V (eds). Tratado de Infectologia, Vol. 2. Sao Paulo, Brazil: Atheneu, 1996:1306–15.
58. Matete GO, Kajejo OA. Human African trypanosomiasis and human immunodeficiency virus co-infection in Western Kenya. East Afr Med J. 2005;82:20–3.
59. Dannemann BR, McCutchan JA, Israelski D, et al. Treatment of toxoplasmic encephalitis in patients with AIDS. A randomized trial comparing pyrimethamine plus clindamycin to pyrimethamine plus sulfadiazine. Ann Intern Med. 1992;116:33–43.
60. Mawhorter SD, Effron D, Blinkhorn R, Spagnuolo PJ. Cutaneous manifestation of toxoplasmosis. Clin Infect Dis. 1992;14:1084–8.
61. Jones JL, Kruszon-Moran D, Wilson M, et al. *Toxoplasma gondii* infection in the United States: seroprevalence and risk factors. Am J Epidemiol. 2001;154:357–65.
62. Frenkel JK, Fishback JL. Toxoplasmosis. In: Strickland GT (ed.). Hunter's Tropical Medicine and Emerging Infectious Diseases, 8th edn. Philadelphia: WB Saunders, 2000.
63. Many A, Koren G. Toxoplasmosis during pregnancy. Can Fam Physician. 2006;52:29–30.
64. Solovastru L, Amalinei C. Morphea associated with toxoplasmosis. Rev Med Chir Soc Med Nat Iasi. 2003;107:646–9.
65. Saberin A, Lutgen C, Humbel RL, et al. Dermatomyositis-like syndrome following acute toxoplasmosis. Bull Soc Sci Med Gran Duche Luxemb. 2004;2:109–19.
66. Kawakami Y, Hayashi J, Fujisaki T, et al. A case of toxoplasmosis with dermatomyositis. Kansenshogaku Zasshi. 1995;69:1312–15.
67. Assimwe FT, Hengge U. Other helminths: dracunculiosis, cutaneous larva migrans and trichinellosis. In: Tyring S, Lupi O, Hengge U (eds). Tropical Dermatology. London: Elsevier, 2006:71–80.
68. Roest MA, Ratnavel R. Cutaneous larva migrans contracted in England: a reminder. Clin Exp Dermatol. 2001;26:389–90.
69. Grassi A, Angelo C, Grosso MG, Paradisi M. Perianal cutaneous larva migrans in a child. Pediatr Dermatol. 1998;15:367–9.
70. Caumes E. Treatment of cutaneous larva migrans. Clin Infect Dis. 2000;30:811–14.
71. American Academy of Pediatrics. Hookworm infections. In: Pickering LK, Baker CJ, Long SS, McMillan JA (eds). Red Book: 2006 Report of the Committee on Infectious Diseases, 27th edn. Elk Grove Village, IL: America Academy of Pediatrics, 2006:374–5.
72. Smith JD, Goette DK, Odom RB. Larva currens. Cutaneous strongyloidiasis. Arch Dermatol. 1976;112:1161–3.
73. Bravo F, Sanchez MR. New and re-emerging cutaneous infectious diseases in Latin America and other geographic areas. Dermatol Clin. 2003;21:655–68.
74. Rehmus W, Nguyen J. Nematodal helminths: onchocerciasis. In: Tyring S, Lupi O, Hengge U (eds). Tropical Dermatology. London: Elsevier, 2006:62–7.
75. Stingl P. Onchocerciasis: developments in diagnosis, treatment and control. Int J Dermatol. 2009;48:393–6.
76. Hamada N, Fouque F. Black flies (Diptera: *Simuliidae*) of French Guyana: cytotaxonomy and a preliminary list of species. Mem Inst Oswaldo Cruz. 2001;96:955–9.
76a. Tamarozzi F, Halliday A, Gentil K, et al. Onchocerciasis: the role of *Wolbachia* bacterial endosymbionts in parasite biology, disease pathogenesis, and treatment. Clin Microbiol Rev. 2011;24:459–68.
77. Stingl P. Onchocerciasis: clinical presentation and host parasite interactions in patients of southern Sudan. Int J Dermatol. 1997;36:23–8.
78. Murdoch ME, Hay RJ, Mackenzie CD, et al. A clinical classification and grading system of the cutaneous changes in onchocerciasis. Br J Dermatol. 1993;129:260–9.
79. Vernick W, Turner SE, Burov E, Telang GH. Onchocerciasis presenting with lower extremity hypopigmented macules. Cutis. 2000;65:293–7.
80. Studeman K, Fishback JL, Connor DH. Onchocerciasis. In: Connor DH, Chandler FW, Schwartz DA (eds). Pathology of Infectious Diseases, Vol. II. Stamford: Appleton & Lange, 1997:1505–26.
81. Rosenblatt JE. Laboratory diagnosis of infections due to blood and tissue parasites. Clin Infect Dis. 2009;49:1103–8.
82. Ayong LS, Tume CB, Wembe FE, et al. Development and evaluation of an antigen detection dipstick assay for the diagnosis of human onchocerciasis. Trop Med Int Health. 2005;10:228–33.
83. Burnham G. Ivermectin treatment of onchocercal skin lesions: observations from a placebo-controlled, double-blind trial in Malawi. Am J Trop Med Hyg. 1995;52:270–5.
83a. Taylor MJ, Hoerauf A, Bockarie M. Lymphatic filariasis and onchocerciasis. Lancet. 2010;376:1175–85.
83b. Turner JD, Tendongfor N, Esum M, et al. Macrofilaricidal activity after doxycycline only treatment of *Onchocerca volvulus* in an area of Loa loa co-endemicity: a randomized controlled trial. PLoS Negl Trop Dis. 2010;4:e660.
84. Kalungi S, Tumwine LK. Nematodal helminths: filariasis. In: Tyring S, Lupi O, Hengge U (eds). Tropical Dermatology. London: Elsevier, 2006:57–61.
85. Ivoke N. Rural bancroftian filariasis in northwestern Cameroon: parasitological and clinical studies. J Commun Dis. 2000;32:254–63.
86. Boggild AK, Keystone JS, Kain K. Tropical pulmonary eosinophilia: a case series in a setting of nonendemicity. Clin Infect Dis. 2004;39:1128–8.
87. Dey P, Walker R. Microfilariae in a fine needle aspirate from a skin nodule. Acta Cytol. 1994;38:114–15.
88. Denham DA. The diagnosis of filariasis. Ann Soc Belg Med Trop. 1975;55:517–24.
89. Ottesen EA. Filariasis now. Am J Trop Med Hyg. 1989;41:9–17.
90. Solomon AW, Nayagam S, Pasvol G. Recent advances in tropical medicine. Trans R Soc Trop Med Hyg. 2009;103:647–52.
91. Leutscher P, Magnussen P. Trematodes. In: Tyring S, Lupi O, Hengge U (eds). Tropical Dermatology. London: Elsevier, 2006:85–91.
92. Stirewald MA, Hackey JR. Penetration of host skin by cercariae of *Schistosoma mansoni*. I. Observed entry into skin of mouse, hamster, rat, monkey and man. J Parasitol. 1956;42:565–80.
93. Gonzales E. Schistosomiasis, cercarial dermatitis, and marine dermatitis. Dermatol Clin. 1989;7:291–300.
94. Amer M. Cutaneous schistosomiasis. Dermatol Clin. 1994;12:713–17.
95. Farrell AM. Ectopic cutaneous schistosomiasis: extragenital involvement with progressive upward spread. Br J Dermatol. 1996;135:110–12.
96. Davis-Reed L, Theis JH. Cutaneous schistosomiasis: report of a case and review of the literature. J Am Acad Dermatol. 2000;42:678–80.
97. Torres VM. Dermatologic manifestations of *Schistosoma mansoni*. Arch Dermatol. 1976;11:539–42.
98. Mulvihill CA, Burnett JW. Swimmer's itch: a cercarial dermatitis. Cutis. 1990;46:211–13.
99. Elliott DE. Schistosomiasis: pathophysiology, diagnosis and treatment. Gastroenterol Clin North Am. 1996;25:599–602.
100. King CH, Mahmoud AF. Drugs five years later: praziquantel. Ann Intern Med. 1989;110:290–6.
101. Hoeffler DF. Cercarial dermatitis. Arch Environ Health. 1974;29:225–9.
102. Cook GC. Gastrointestinal helminth infections. Trans R Soc Trop Med Hyg. 1986;80:675–8.
103. Machado-Pinto J. Cestodes. In: Tyring S, Lupi O, Hengge U (eds). Tropical Dermatology. London: Elsevier, 2006:81–3.
104. Smyth JD, Heath DD. Pathogenesis of larval cestodes in mammals. Helm Abstr. 1970;39:1–23.
105. Falanga V, Kapoor W. Cerebral cysticercosis: diagnostic value of subcutaneous nodules. J Am Acad Dermatol. 1985;12:304–7.
106. Vianna LG, Macedo V, Costa JM. Musculocutaneous and visceral cysticercosis: a rare disease? Rev Inst Med Trop Sao Paulo. 1991;33:129–36.
107. Okelo GBA. Hydatid disease: research and control in Turkana. III. Albendazole in the treatment of inoperable hydatid disease in Kenya – a report of 12 cases. Trans R Soc Trop Med Hyg. 1986;80:193–5.

This page intentionally left blank

Infestations 84

Craig N Burkhart, Craig G Burkhart and Dean Scott Morrell

Chapter Contents

Scabies 1423
Head lice 1426
Crab lice 1429
Body lice 1430
Tungiasis 1431
Cutaneous myiasis 1432

SCABIES

Synonyms: ■ Itch mite infestation ■ "Seven-year itch"

Key features

- Human scabies is a pruritic condition caused by infestation with the host-specific mite *Sarcoptes scabiei* var. *hominis*, which lives its entire life within the epidermis
- Although the scabies mite is not a known vector for any systemic disease, secondary bacterial infections with *Streptococcus pyogenes* or *Staphylococcus aureus* may develop
- Transmission typically occurs via direct close contact with an infested person; fomite transmission is also possible and is much more common in severe and/or crusted cases
- Tolerance to standard topical scabicides is beginning to develop

Introduction

The scabies mite continues to plague all countries of the world. An estimated 300 million individuals are affected. Pruritus associated with this infestation is usually severe, especially at night, and treatment requires prescription scabicidal therapy.

History

Scabies has been a common companion of the human species for over 2500 years[1].

Epidemiology

Scabies is a worldwide problem and all ages, races and socioeconomic groups are susceptible. Environmental factors hastening spread include overcrowding, delayed treatment of primary cases, and lack of public awareness of the condition. There is considerable variation in prevalence, with rates in low income countries ranging from 4% to 100%[1,2]. Higher incidences occur with overcrowding related to natural disasters, wars, economic depression and refugee camps[1,2]. Scabies can be transmitted directly by close personal contact, sexual or otherwise, or indirectly via fomites. Prevalence is higher in children and people who are sexually active. Spread of the infestation among family members and other close contacts is common[2], but scabies is not a known vector for systemic disease.

Crusted scabies (formerly called Norwegian scabies) is found in individuals with compromised immune systems (e.g. the elderly, people infected with HIV, and solid organ transplant recipients) as well as those with decreased sensory functions and/or ability to scratch (e.g. patients with leprosy, HTLV-1 infection or paraplegia). Such individuals may experience minimal pruritus despite their infestation with a large number of mites and are highly contagious[3].

Pathogenesis

The highly host-specific, eight-legged mite *Sarcoptes scabiei* var. *hominis* causes human scabies (Fig. 84.1). Mites from animals are not a source of human infestation, but they can produce bite reactions (see Ch. 85). The scabies mite is 0.35 × 0.3 mm in size and too small to be seen by the naked eye. The entire 30-day life cycle of mites is completed within the epidermis (Fig. 84.2). Each day a female mite lays 3 eggs, which require approximately 10 days to mature. The number of mites living on an infested host can vary greatly, although there are usually fewer than a hundred and often no more than 10–15. However, patients with crusted scabies may have thousands of mites on their skin surface. In the environment of individuals suffering from this severe condition, live mites can be recovered in debris from sheets, the floor, screening curtains and chairs[4]. Scabies mites usually live 3 days or fewer off a human host, but those from patients with crusted scabies may live up to 7 days by feeding on sloughed skin.

The incubation period before symptoms develop can range from days to months. In first-time infestations, it usually takes 2–6 weeks before the host's immune system becomes sensitized to the mite or its by-products, resulting in pruritus and cutaneous lesions. A subsequent infestation is usually recognized within 24–48 hours. Asymptomatic scabies-infested individuals are not uncommon, and they can be considered "carriers"[4].

Clinical features

The epidemiologic history (e.g. pruritus in household members or close personal contacts), the distribution and types of lesions, and pruritus form the basis of the clinical diagnosis. The intense pruritus is classically accentuated at night and by a hot bath or shower. Pruritus may be present before any overt physical signs appear. Cutaneous lesions are symmetrical, typically involving the interdigital webbing of the hands, flexural aspect of the wrists, axillae, posterior auricular area, waist (including the umbilicus), ankles, feet and buttocks. In men, penile and scrotal lesions are common, while in women, the areolae, nipples and vulvar area are often affected. In infants, the elderly and immunocompromised hosts, all skin surfaces are susceptible, including the scalp and face[1,4].

Typically, small erythematous papules are present in association with a variable degree of excoriation (Fig. 84.3). Vesicles, indurated nodules, eczematous dermatitis and secondary bacterial infection are also common. The pathognomonic sign is the burrow, representing the tunnel that a female mite excavates while laying eggs. Clinically, the burrow is wavy, thread-like, grayish-white and 1–10 mm in length. Many patients, however, do not have any obvious burrows on inspection, especially in warm climates.

Acral vesiculopustules can represent a clue to the diagnosis of scabies in infants. Crusted scabies often manifests with marked hyperkeratosis that favors acral sites (including subungual areas; Fig. 84.4) but may be widespread. Areas of affected skin have sometimes been referred to as pachyderma. Secondary bacterial infections with *Staphylococcus aureus* or *Streptococcus pyogenes* sometimes develop. Peripheral eosinophilia can be the primary sign of scabies in patients with disorders of keratinization.

Confirmation of the diagnosis can be achieved by light microscopic examination of mineral oil preparations of skin scrapings (from infested

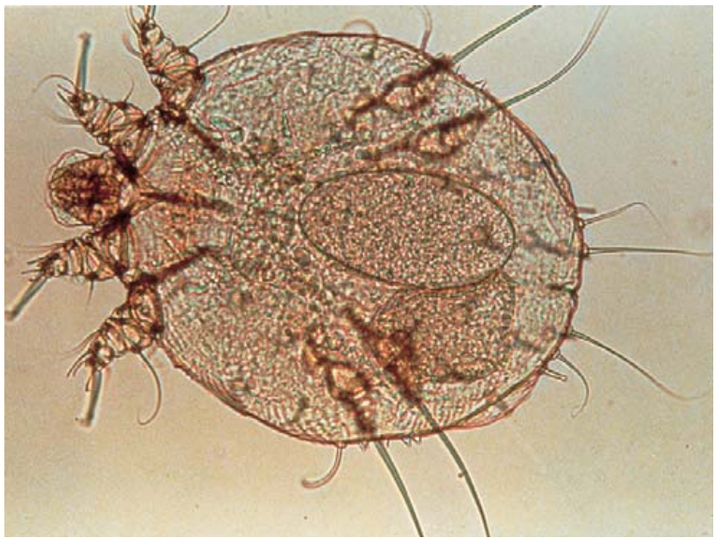


Fig. 84.1 Female scabies mite with egg. The female scabies mite in a potassium hydroxide wet mount obtained from skin scrapings, revealing a flattened, oval body with wrinkle-like corrugations, eight short legs, and an egg ready for deposition (40×). *With permission from Taplin D, Meinking TL. Infestations. In: Schachner LA, Hansen RC (eds). Pediatric Dermatology. 4th edn. Edinburgh: Mosby, 2011:1141–80.*

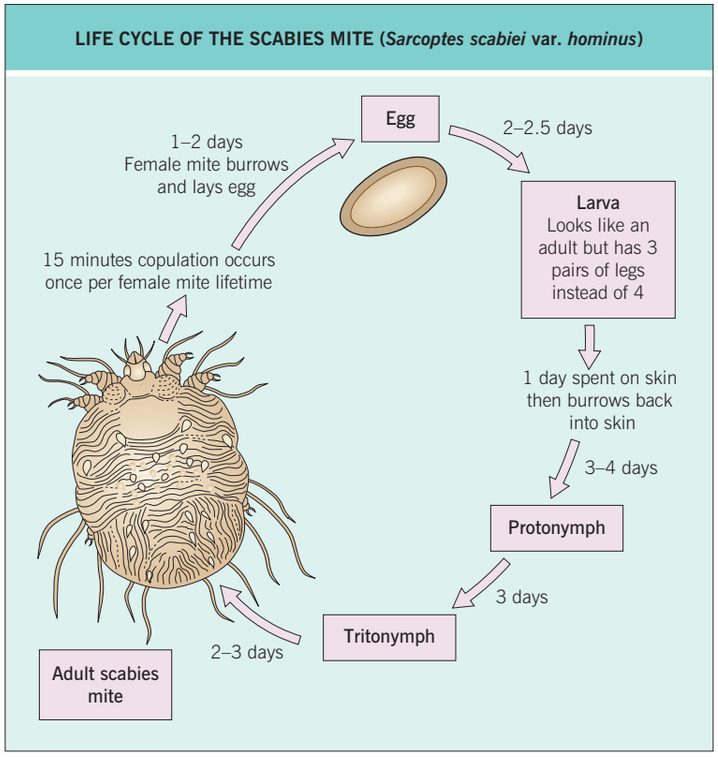


Fig. 84.2 Life cycle of the scabies mite (*Sarcoptes scabiei* var. *hominus*).

areas) for adult mites, eggs and/or fecal pellets (scybala; Fig. 84.5). A scalpel or curette may be used to obtain the skin sample. Microscopic examination of transparent adhesive tape following its application to infested areas of skin represents another diagnostic technique[4a]. Dermoscopy and confocal microscopy can prove useful for direct *in vivo* visualization of mites and eggs. A skin biopsy may confirm the clinical diagnosis, but only if the specimen obtained happens to contain the mite or its eggs. Often, however, the diagnosis simply rests on the clinical impression and response to treatment.

Pathology

A patchy to diffuse infiltrate with prominent eosinophils as well as lymphocytes and histiocytes is noted in the reticular dermis. On transection, a scabies mite may occasionally be seen within the epidermis (Fig. 84.6). Pink "pigtail"-like structures attached to the stratum corneum (which represent fragments of the adult mite exoskeleton) can serve as a clue to the diagnosis of scabies when mites, scybala and eggs are not identified[5].

Differential diagnosis

Unless burrows or (via dermoscopy) mites and eggs are noted clinically, a wide variety of pruritic skin diseases have to be considered in the differential diagnosis. These include atopic, allergic contact, autosensitization ("id" reaction) and nummular dermatitis as well as arthropod bites, pyoderma, dermatitis herpetiformis and bullous pemphigoid. Occasionally, scabies can mimic Langerhans cell histiocytosis clinically and histologically, as a dense infiltrate of Langerhans cells may be present. The clinical and histologic features of infantile scabies may also resemble those of the inflammatory stage of incontinentia pigmenti.

Treatment

Two topical treatments (1 week apart) with a prescription antiscabietic medication should be recommended (Table 84.1). The topical preparation is applied overnight to the entire body surface, from head to toe, in infants and the elderly. In other age groups, the face and scalp can be excluded from treatment. Special attention should be paid to the interdigital spaces, intergluteal cleft, umbilicus and subungual areas. To reduce the potential of reinfestation by fomite transmission, at the time of each treatment, clothing, linens and towels used within the previous week can be either washed in hot water and dried on high heat or stored in a bag for 10 days. The relatively common occurrence of asymptomatic mite carriers in households necessitates that all family members and close contacts be treated simultaneously, even if they have not developed any pruritus or clinical signs. Pets cannot harbor human mites and do not have to be treated.

Pruritus and lesions can persist for 2–4 weeks (or occasionally longer, especially for acral vesiculopustules in infants or nodular lesions) after successful treatment. This is referred to as "postscabietic" pruritus or dermatitis. Patients should be informed that such reactions do not imply treatment failure, but rather represent the body's response to dead mites that are eventually sloughed off (within 2 weeks) along with natural epidermal exfoliation. Many patients, however, experience relief from pruritus within 3 days. The second application of topical medication is performed in order to reduce the potential for reinfestation from fomites as well as to ensure killing of any nymphs that may have survived within the semi-protective environment of the egg and subsequently hatched (see Fig. 84.2).

Permethrin

Permethrin is a synthetic pyrethroid formulated in a 5% cream that is currently the standard topical scabicide. Like other pyrethroids, it inhibits sodium transport in arthropod neurons, thereby causing paralysis. Adverse reactions are rare and are usually related to brief stinging on application. Signs of tolerance to permethrin have been noted, but resistance has not been documented.

Lindane

Lindane (gamma-hexachlorocyclohexane), an organochlorine agent, is marketed worldwide in a 1% lotion or cream. CNS side effects may occur from increased percutaneous absorption through damaged skin, misuse, overuse or accidental ingestion. Because of the potential for CNS toxicity, lindane is contraindicated in premature infants, individuals with crusted scabies and other skin conditions (e.g. extensive atopic dermatitis) that may increase its systemic absorption, and patients with an uncontrolled seizure disorder. Worldwide, the development of lindane-resistant scabies is increasing[1]. Potential toxicity, relatively poor efficacy, widespread resistance, and issues related to environmental contamination make lindane an inferior treatment choice compared to permethrin or ivermectin. In 2003, the US Food and Drug Administration (FDA) issued a "black box" warning for lindane products, stating that they should be used with caution in infants, children, other individuals who weigh <110 pounds (50 kg) and the elderly due to an increased risk of neurotoxicity[6].

Crotamiton

An alternative scabicide is crotamiton, which is formulated in a 10% lotion and cream. Although it has an antipruritic effect, crotamiton can

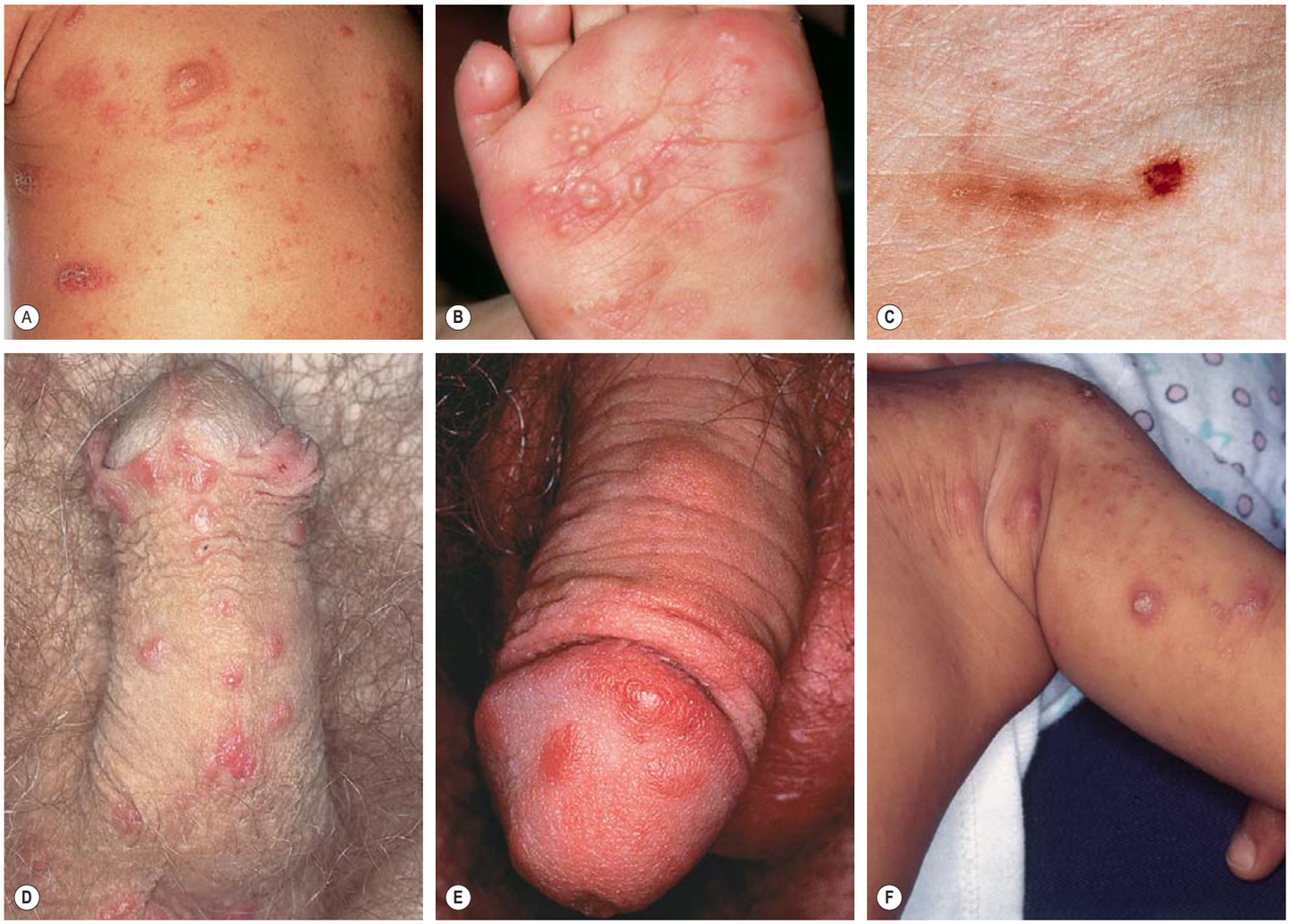


Fig. 84.3 Scabies. A, B Erythematous papules, linear burrows, areas of crusting and acral vesiculopustules in two infants with scabies. **C** Close-up of a linear burrow. **D, E** Penile involvement with erythematous papules and nodules. **F** Nodular scabies in an infant. *E, Courtesy, Robert Hartman, MD. F, Courtesy, Kalman Watsky, MD.*

Fig. 84.4 Crusted scabies. Scabies incognito in which a patient with impaired sensory function had an asymptomatic hyperkeratotic hand "rash". *Courtesy, Joyce Rico, MD.*

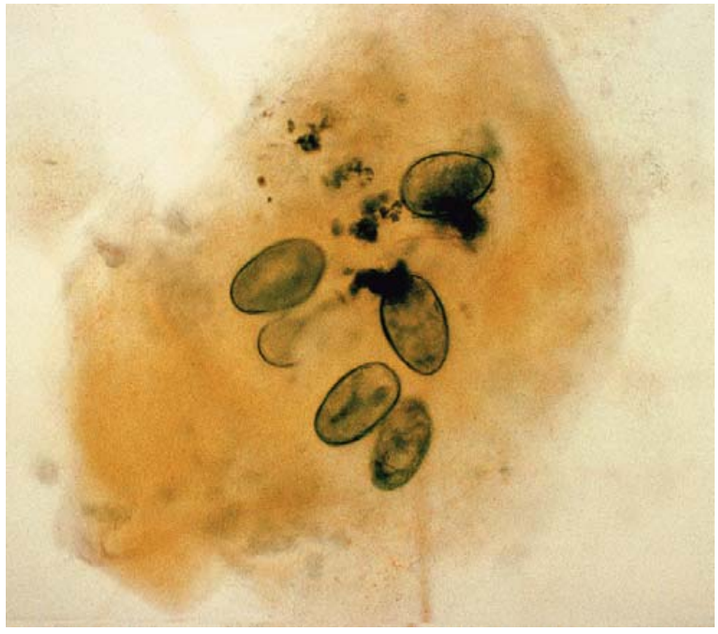


Fig. 84.5 Direct microscopy of a scraping from a patient with scabies. Note the eggs and scybala.

TOPICAL AND ORAL TREATMENTS FOR SCABIES					
Therapy	**Administration**	**Concerns**	**Efficacy & resistance**	**Use in infants**	**FDA pregnancy category**
Permethrin cream (5%)	Topically overnight on days 1 and 8	Allergic contact dermatitis in individuals with sensitivity to formaldehyde	Good, but some signs of tolerance developing	FDA approved for infants ≥2 months of age	B
Lindane lotion or cream (1%)	Topically overnight on days 1 and 8	Potential CNS toxicity, especially in individuals weighing <110 pounds (50 kg), the elderly and those with crusted scabies, other skin conditions or a history of seizures	Poor, resistance very common	Not recommended for infants, children or breastfeeding mothers; contraindicated in premature infants	C (but not recommended)
Sulfur ointment (5–10%)	Topically overnight for 3 successive days	Toxicity studies not performed	Not evaluated	Not established, but considered safe	Not rated, but considered safe
Crotamiton lotion or cream (10%)	Topically overnight for 3–5 days	Irritant contact dermatitis, especially in areas of denuded skin	Very poor; has antipruritic properties and may be used for postscabetic pruritus	Not established, but considered safe	C
Ivermectin (available as 3 mg tablets)	Oral dose of 200–400 mcg/kg on day 1 and repeat on day 8 or 14*	Potential CNS toxicity in infants and young children	Excellent	Safety not established for children weighing <33 pounds (15 kg) or breastfeeding mothers	C (but generally not recommended for scabies in pregnant women)

*Administration of second dose at 2 weeks recommended by CDC (www.cdc.gov).

Table 84.1 Topical and oral treatments for scabies.

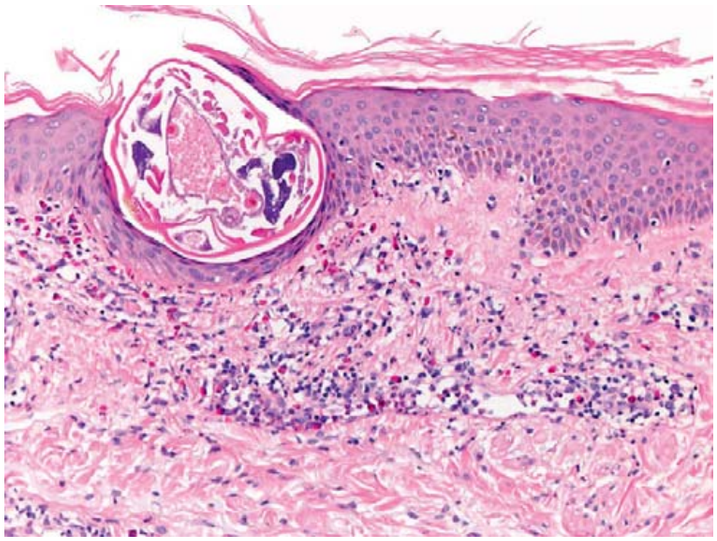


Fig. 84.6 Scabies – histologic features. A mite is evident in the stratum corneum and an eosinophil-rich dermal infiltrate is present. *Courtesy, Lorenzo Cerroni, MD.*

cause irritation of denuded skin. Of note, this topical medication is less effective than all of the other prescription options[7].

Sulfur ointment

Another alternative therapy for scabies is three consecutive overnight applications of 5–10% sulfur in a petrolatum base. A pharmacist must compound the medication, and toxicity studies have not been performed. Sulfur is messy, malodorous and irritating to the skin and can stain clothing. However, its efficacy has been reported to be as high as 92%[8].

Ivermectin

Ivermectin, although not FDA-approved for this indication, has been found to be effective for treating ectoparasites[1,9]. By blocking transmission across nerve synapses that utilize glutamate or γ-aminobutyric acid (GABA), it causes paralysis of peripheral motor function in insects[1,9]. In humans, GABA and glutamate are neurotransmitters within the cerebral cortex, and from early infancy on, the blood–brain barrier protects against potential ivermectin toxicity. In general, alternative therapies are recommended for children who weigh <33 pounds (15 kg), pregnant women and breastfeeding mothers because of the lack of safety data in these groups[1].

In clinical studies, ivermectin has proven to be extremely safe. Over 18 million people over 5 years of age are treated annually with ivermectin in the World Health Organization (WHO) Onchocerciasis Eradication Program. A single, questionable report of an increased death rate in patients receiving ivermectin[10] has been discounted as unrelated by the WHO, medical examiners and the scientific community.

Oral ivermectin can cure scabies. A dose of 200–400 mcg/kg is usually administered twice, 1–2 weeks apart[1,9]. Although there is only one report of mite resistance to this agent to date[11], increasing tolerance has been described in communities with a high prevalence of scabies[12]. Topical ivermectin in a 1% concentration appears to be effective, but further testing is warranted before recommending its widespread use[13]. In patients with subungual disease, addition of a topical scabicide is recommended because the oral medication will not penetrate into thickened keratotic debris.

HEAD LICE

Synonyms: ■ Pediculosis capitis ■ "Cooties"

Key features

- This worldwide infestation is caused by bloodsucking, wingless, six-legged insects that live only on the hairs of the scalp
- Diagnosis is usually confirmed by the presence of 0.8 mm eggs ("nits") firmly attached to scalp hairs
- Head lice are spread by head-to-head contact as well as by fomite transmission
- Resistance to traditional over-the-counter preparations (pyrethrins, permethrin) is growing; topical malathion and oral ivermectin can be used in resistant cases

Introduction

Lice are bloodsucking, wingless insects belonging to the suborder Anoplura. With 12 million cases per year in the US alone, a head lice

Fig. 84.7 Head louse family. From left to right: female, male and nymph.
With permission from Taplin D, Meinking TL. Infestations. In: Schachner LA, Hansen RC (eds). Pediatric Dermatology. 4th edn. Edinburgh: Mosby, 2011:1141–80.

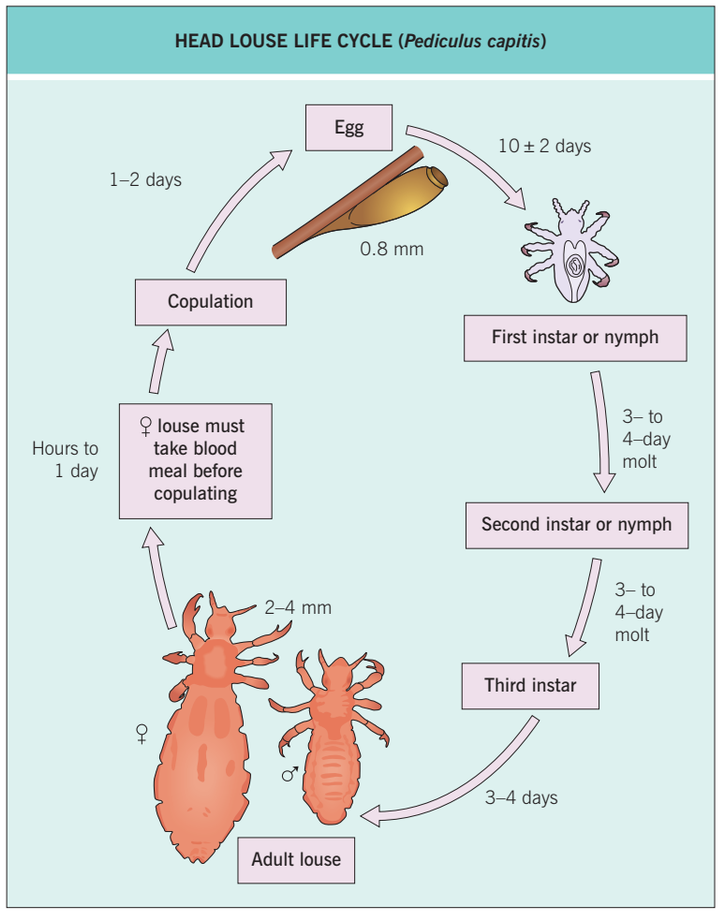


Fig. 84.8 Head louse life cycle (*Pediculus capitis*).

epidemic persists and resistance to standard treatments is rising. Treatment of resistent cases with prescription products (e.g. topical malathion or oral ivermectin) is becoming essential, requiring more physician involvement.

History

Head lice have infested mankind for thousands of years. Nits have been found on the hair of Egyptian and Peruvian mummies[1].

Epidemiology

Head lice are found worldwide with no strict limitations based upon age, sex, race or socioeconomic class. Children 3–11 years of age have the highest incidence, varying from 10% in Malaysia to 40% in Taiwan[1]. Infestation with head lice is more frequently observed in girls, probably due to their tendency to have longer hair as well as the common exchange of brushes, barrettes and other hair accessories. Head lice are distinctly uncommon in African-Americans, as lice in the US are unable to properly position themselves to lay eggs on coarse curly hair[14].

Pathogenesis

The head louse, *Pediculus capitis*, is a highly host-specific insect approximately the size of a sesame seed (2–3 mm; Fig. 84.7). These obligate human parasites feed exclusively on the blood of the host approximately every 4–6 hours. The female louse lives for 30 days, during which time she lays between 5 and 10 eggs a day on hair shafts (Fig. 84.8). The oval egg capsules (nits) measure 0.8 mm in length and are usually laid close to the scalp for warmth; in general, eggs located within 1 cm of the scalp are unhatched. In warm climates, however, viable nits may be found 15 cm or more from the scalp, especially in the area above the nape of the neck. The nits are cemented to individual hairs by means of a proteinaceous matrix that closely resembles the amino acid constituents of the human hair shaft itself[14,15]. Head lice rarely live for more than 36 hours away from the host without a blood meal; however, given an appropriate temperature (82–90°F/28–32°C) and humidity (70–90%), nits can survive and hatch after 10 days away from the host. Transmission occurs via direct head-to-head contact or by fomites such as combs, brushes, blow-dryers, hair accessories, bedding, helmets and other headgear[16].

Clinical features

Skin findings of head lice infestations are limited to the scalp, behind the ears and the nape of the neck. The classic symptom of intense pruritus can vary among patients. In the first infestation, it may take 2–6 weeks before pruritus is evident, reflecting the development of an immunologic response to the irritant components of the lice saliva or excreta. In repeat infestations, pruritus develops within the first 24–48 hours. However, a number of individuals are asymptomatic and can be considered "carriers". Although excoriations, erythema, pyoderma, and scaliness of the scalp and posterior neck are common findings, the diagnosis is made by the identification of nits and/or adult lice on the scalp hair. Viable eggs are usually tan to brown in color, whereas hatched eggs are clear to white (Fig. 84.9).

An occasional patient will present with a low-grade fever, irritability, lymphadenopathy and a secondary bacterial infection. Head lice can carry *S. aureus* and *Str. pyogenes* on their surfaces and are a common cause of pyoderma of the scalp[1].

Pathology

The epidermis and dermis may reveal signs of inflammation, but these alterations are neither specific nor diagnostic.

Differential diagnosis

Although several dermatoses, such as seborrheic dermatitis and psoriasis, can cause pruritus of the scalp, the finding of nits or adult lice is diagnostic. Nits are more firmly adherent to the hair shaft than dandruff, dried hair products (e.g. sprays, gels) or hair casts, and they must be differentiated from other causes of hair shaft nodules such as piedra (white or black) and trichorrhexis nodosa (see Fig. 77.1).

Treatment

The choice of treatment is based on the efficacy and potential toxicity of different agents, louse resistance patterns to insecticides in a particular geographic area, and ease of access to prescription remedies. Pediculicides remain the mainstay of therapy (Table 84.2). With all topical preparations (regardless of package instructions), two applications, 1 week apart, are advisable in order to: (1) kill any nits that survived treatment; (2) better defend against the seemingly growing resistance

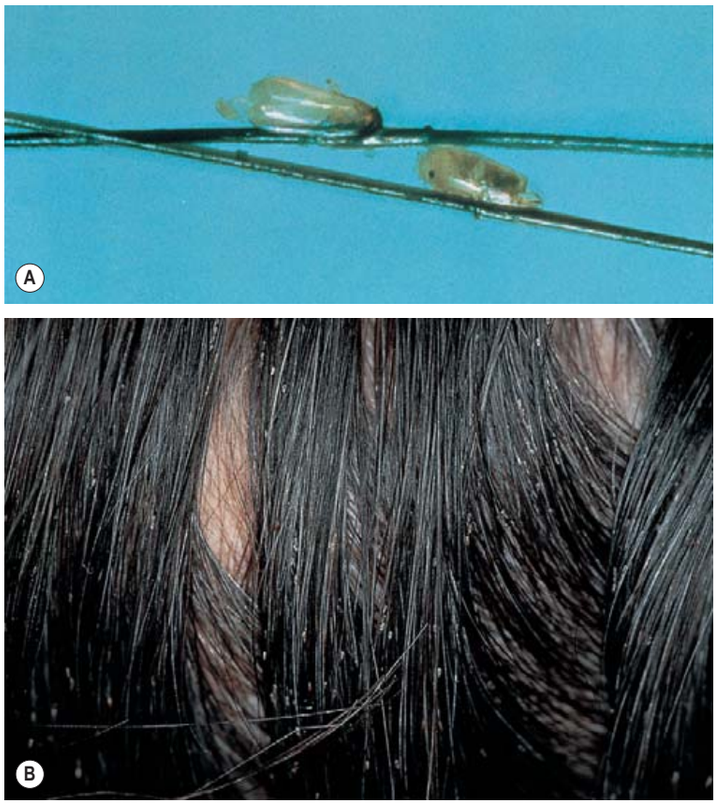


Fig. 84.9 Head lice. A The head louse egg or nit is 0.8 mm in length. **B** Head lice nits on hair. *With permission from Taplin D, Meinking TL. Infestations. In: Schachner LA, Hansen RC (eds). Pediatric Dermatology. 4th edn. Edinburgh: Mosby, 2011:1141–80.*

to most pediculicides; and (3) reduce the risk of reinfestation by means of fomites.

Unsubstantiated claims of successful treatment with alternative, non-pesticidal products, including petroleum jelly, hair pomade, olive oil, mayonnaise, vegetable oil and mineral oil, persist. Such products may slow the movements of adult lice and allow them to be more easily combed out of the scalp, but these substances are not lethal to lice. Some essential oils have been reported to be effective as lice therapy, and they are incorporated into various products that are usually found in health food stores. However, appropriate clinical studies are still necessary to confirm their safety and efficacy. Oral trimethoprim–sulfamethoxazole improves efficacy of topical agents but is not curative by itself[17].

Many school authorities enforce a "no-nit" policy and do not allow children to return to school if they have nits, regardless of whether they are viable or not. As a result, the tedious task of physically removing all nits via combs with closely spaced metal teeth is required. Currently there are no products that easily aid in nit removal[18]. Flexibility and understanding by school boards are more important than a straight adherence to a "no-nit" policy.

Pyrethrins

Pyrethrin insecticides are derived from a natural extract of flower heads of *Chrysanthemum cinerariaefolium*. Patients allergic to chrysanthemums, ragweed or related plants have experienced wheezing and dyspnea with use of the crude extract. In the US, pyrethrins and permethrin (see below) are the two FDA-approved, over-the-counter (OTC) pediculicides. Pyrethrins are presently formulated into lotions, shampoos, foam mousse, and cream rinses. The addition of piperonyl butoxide slows the biotransformation of pyrethrins by partially inhibiting the insects' cytochrome P450 enzymes, thereby initially improving effectiveness. Pyrethrin products are applied to the head for 10 minutes

TREATMENTS FOR HEAD LICE

Treatment	Group	Administration on days 1 and 8	Concerns	Efficacy & resistance
Permethrin cream rinse or lotion (1%)*	Synthetic pyrethroid	Topical application for 10 minutes to clean, dry hair	None	Poor–fair; resistance common
Permethrin cream (5%)†	Synthetic pyrethroid	Topical overnight application to clean, dry hair	Allergic contact dermatitis in individuals with sensitivity to formaldehyde	Poor–fair; resistance common
Pyrethrins (0.33%) synergized with piperonyl butoxide (4%), various formulations*	Natural botanicals	Topical application for 10 minutes to dry hair	Allergic reactions in individuals with sensitivity to chrysanthemums, ragweed and related plants	Poor–fair; resistance common
Malathion lotion or gel (0.5%)‡	Organophosphate cholinesterase inhibitor	Topical application for 8–12 hours to dry hair (Ovide® and gel products with isopropyl alcohol base are effective at 20 minutes)	Flammable isopropyl alcohol base; burning or stinging at sites of eroded skin	Excellent (in US); resistance noted in UK and France, but to date not in US
Carbaryl shampoo (0.5%)	Carbamate cholinesterase inhibitor	Topical application for 8–12 hours	Possible carcinogen	Poor–fair; resistance common (not approved in the US)
Lindane shampoo (1%)	Organochlorine	Topical application for 4 minutes to clean, dry hair, then add water to lather and rinse	Potential CNS toxicity; not recommended for infants, children, breastfeeding mothers or pregnant women (category C)	Poor; resistance common
Benzyl alcohol lotion (5%)§	Alcohol	Topical application for 10 minutes to dry hair	Potential skin irritation	Fair–good; no resistance noted to date
Spinosad cream rinse (0.9%)¶	Bacterial fermentation product	Topical application for 10 minutes to dry hair	None	Good; no resistance noted to date
Ivermectin (available as 3 mg tablets)	Avermectin	Oral dose of 200–400 mcg/kg	Potential CNS toxicity; not recommended for children weighing <33 pounds (15 kg), breastfeeding mothers or pregnant women (category C)	Excellent; no resistance noted to date

*Over-the-counter products.
†Approved for individuals ≥2 months of age; pregnancy category B.
‡Approved for individuals ≥6 years of age; pregnancy category B.
§Approved for individuals ≥6 months of age; pregnancy category B.
¶Approved for individuals ≥4 years of age; pregnancy category B.

Table 84.2 Treatments for head lice. All treatments should be given on two separate occasions, 1 week apart.

and then rinsed off. Treatment failures are now commonplace due to resistance[1,19].

Permethrin
Permethrin is the only synthetic pyrethroid that is used worldwide for head lice. The OTC 1% permethrin cream rinses and lotions are applied for 10 minutes; however, an 8–12-hour application of the 5% cream for scabies is an alternative therapy. Unfortunately, resistance to even the higher-concentration products has developed in head lice and other insects. Point mutations in the gene encoding the α-subunit of the insects' voltage-sensitive sodium channels commonly lead to a reduction in the binding affinity of permethrin and other pyrethroids. However, a recent German study found a >90% success rate for treatment with permethrin in children whose lice had these mutations (representing >90% of the entire head lice patient population), suggesting that other factors have a role in pyrethroid resistance[19a].

Lindane
Lindane, a chlorinated hydrocarbon, is available as a 1% prescription shampoo that is applied for 4 minutes. Because of possible CNS side effects, especially after prolonged applications beyond recommended time intervals, lindane is reserved for patients who fail to respond to other approved lice therapies. However, resistance is commonly observed. The FDA has issued a "black box" warning for lindane products (see above)[6].

Malathion
The prescription organophosphate malathion is a cholinesterase inhibitor. The current recommendation is to apply topical malathion for 8 to 12 hours, but a 20-minute application time appears to be sufficient[19]. The existing US product (Ovide® lotion) contains 78% isopropyl alcohol, which enhances its effectiveness but raises the issue of flammability. Although resistance to malathion products has appeared in the UK, in the US, resistance has not been observed to date with the currently available product (see Table 84.2)[20].

Carbaryl
Like malathion, carbaryl is a cholinesterase inhibitor. It is available in a 0.5% lotion and shampoo in the UK and other countries. This product is not presently available in the US. In comparison to malathion, carbaryl is potentially more toxic to patients, while being less lethal to lice.

Ivermectin
Oral administration of the antiparasitic agent ivermectin has had encouraging results for head lice[1]. In a recent European double-blind clinical trial, 95% of patients with resistant head lice (previously failed topical therapy with a pyrethrin or malathion) who received 400 mcg/kg of ivermectin on days 1 and 8 were lice-free on day 15, compared to 85% of those treated with topical malathion[21]. Ivermectin is an option for patients whose disease is resistant to topical therapies. As discussed above for scabies, children who weigh less than 33 pounds (15 kg) and pregnant or breastfeeding women should probably not receive oral ivermectin since safety data on these populations are not available.

Benzyl alcohol
In 2009, the FDA approved 5% benzyl alcohol lotion as a prescription treatment for head lice in children ≥6 months of age. Benzyl alcohol is thought to act via asphyxiation by preventing lice from closing their respiratory spiracles, which become blocked by the lotion; it is not ovicidal. In two randomized, double-blind, controlled clinical studies (total n = 250), 75% of patients were lice-free 14 days after the last of two 10-minute applications of benzyl alcohol (administered 1 week apart), compared to 5–25% of those treated with a vehicle control.

Spinosad
In 2011, spinosad was approved by the FDA as a new therapy for head lice in children ≥4 years of age. It is a fermentation product of the bacterium *Saccharopolyspora spinosa* that induces muscle spasms and paralysis in lice when applied topically. A clinical trial showed that 0.9% spinosad cream rinse left on for 10 minutes without nit combing had superior efficacy to 1% permethrin cream with nit combing, and spinosad had no significant clinical or laboratory side effects[22].

CRAB LICE

Synonyms: ■ *Pthirus pubis* or *Phthirus pubis* ■ Pubic lice ■ Pediculosis pubis ■ "Crabs"

Key features
- More properly designated "crab lice" (rather than "pubic lice") because infestations may involve other hair-bearing sites such as the beard, eyelashes, axillae and perianal region
- Transmitted by sexual or close contact and to a lesser extent via contaminated clothing, towels and bedding

Introduction
Infestation with *Pthirus pubis*, the crab louse, causes discomfort, pruritus and embarrassment and may coexist with other sexually transmitted infections.

History
The parasitic relationship between humans and crab lice dates back to prehistoric times.

Epidemiology
The incidence rate seems to be slightly higher in men, probably due to their increased amount of coarse body hair. Infestations with crab lice can be found in all socioeconomic and ethnic groups, although those of Asian descent or with minimal pubic hair are rarely infested. The highest prevalence is in men who have sex with men. Infestation is most frequently observed in those 15 to 40 years of age, correlating with increased levels of promiscuous sexual activity. Although infestation is often considered a sexually transmitted disease, individuals who have had no sexual exposures are occasionally infested via fomite transmission from contaminated clothing, towels or bedding[1].

Pathogenesis
Crab lice, *Pthirus pubis*, are approximately 1 mm in length with a wider, shorter body than head lice, and they resemble tiny crabs (Fig. 84.10). Their eggs, which are found attached to human hairs, are viable for up to 10 days; the adult crab louse can live for at least 36 hours away from the host. Crab lice have serrated edges on their first claw that enable them to ambulate on the entire body surface. Thus, infestation occurs not only in pubic hair, but also in hair of the scalp, eyebrows, eyelashes, moustache, beard, axillae and perianal area. Indeed, 60% of patients with pubic lice are infested in at least two

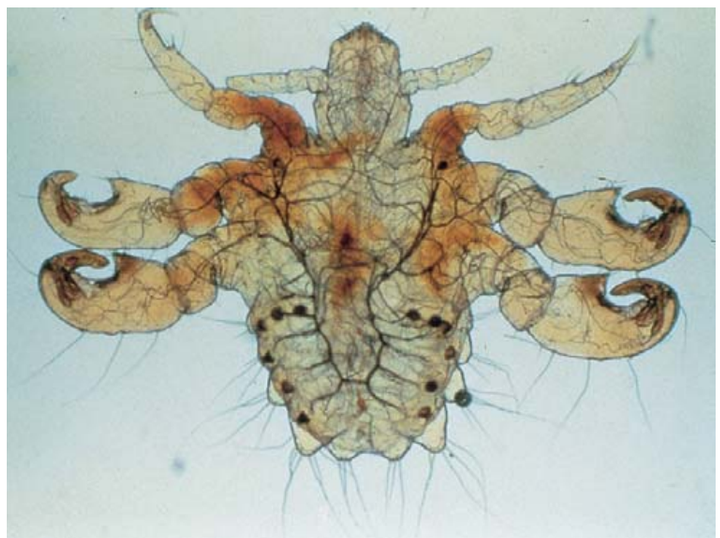


Fig. 84.10 Adult crab louse. Respiratory spiracles and circulatory system are easily seen (45×). *Courtesy, Tony Burns, MD.*

different hair-bearing sites. When the pubic area is shaved or treated, surviving crab lice can travel to other hairy areas of the body, including the scalp.

Clinical features

Crab lice infestations typically present with pruritus in the pubic region. Crab lice cling to the base of hairs (Fig. 84.11A), and they can be skin-colored or mimic hemorrhagic crusts. Other findings may include nits at the base of hair shafts, erythema around the hair follicles, excoriations, evidence of a secondary bacterial infection and lymphadenopathy. When the eyelashes are affected (Fig. 84.11B), feces that accumulate can resemble flecks of mascara. Macula caerulea are asymptomatic cutaneous lesions on the trunk and thighs that may be seen in individuals with chronic crab lice infestations. They are slate-gray to bluish, irregularly shaped macules measuring 0.5–1 cm in diameter. The breakdown of bilirubin to biliverdin by enzymes in louse saliva has been postulated to cause these lesions.

The possibility of additional sexually transmitted infections should be considered and the original source of the infestation sought in order to reduce the risk of recurrence.

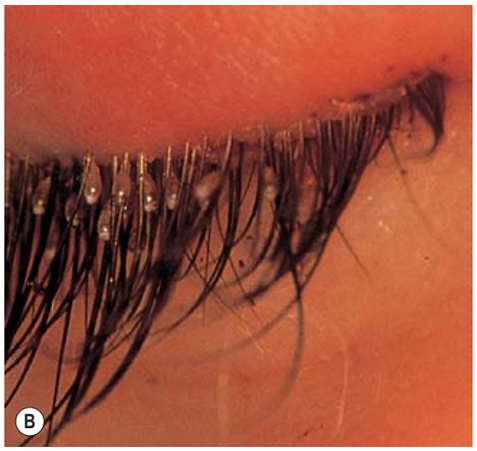


Fig. 84.11 Crab lice. **A** Both adult crab lice and nits are evident on pubic hairs. **B** Crab lice nits and feces on the eyelashes. *A, Courtesy, Louis A Fragola, Jr, MD. B, With permission from Taplin D, Meinking TL. Infestations. In: Schachner LA, Hansen RC (eds). Pediatric Dermatology. 4th edn. Edinburgh: Mosby, 2011:1141–80.*

Pathology

Crab lice cause nonspecific inflammatory changes in the epidermis and dermis. Because lice live on the surface of the skin, they would not be evident histologically.

Differential diagnosis

The identification of crab lice and/or their nits is diagnostic (see Fig. 84.10). Skin diseases associated with pruritus have to be considered in the differential diagnosis, including other infestations (e.g. scabies) and arthropod bites. Nits on pubic or axillary hairs must be distinguished from white piedra and trichomycosis pubis or axillaris.

Treatment

Topical insecticides are the standard therapy for crab lice. Sexual partners should be treated simultaneously. Most commonly, permethrin (1% or 5%) and synergized pyrethrin products are utilized (Table 84.3). As with head lice, all topical insecticides should be applied on two occasions, 1 week apart, to ensure a proper therapeutic approach to hatched eggs. Moreover, all hairy areas of the body must be inspected for the existence of lice and then treated if there is any possibility of their presence. A single application of these topical products to only pubic hair may limit success rates to as low as 55%[23].

Currently, the safest and most effective topical treatment is 5% permethrin cream applied generously overnight to all possibly infested hairy areas, and then repeated 1 week later[23]. Lindane has poor efficacy and higher toxicity, and the shampoo is not approved for extensive body application. Oral ivermectin on days 1 and 8 can be used for patients with perianal or eyelash involvement or when topical therapy is unsuccessful (see Table 84.3)[24].

BODY LICE

Synonyms: ■ Pediculosis corporis ■ Clothing lice

Key features

- An infestation of humans and their clothing, body lice infestation is most commonly found in the homeless, refugees, and victims of war and natural disasters
- Body lice do not live or lay eggs on people but in their clothing
- Infections transmitted by body lice include epidemic typhus, trench fever and relapsing fever

TREATMENTS FOR CRAB LICE

Treatment	Administration on days 1 and 8	Concerns	Efficacy
Permethrin (1%) cream rinse or synergized pyrethrin shampoo*	Topical application for 10 minutes to clean, dry hair	None	Fair
Permethrin cream (5%)	Topical application for 8–12 hours	Allergic contact dermatitis in individuals with sensitivity to formaldehyde	Good
Lindane shampoo (1%)	Topical application for 4 minutes to dry hair, then add water to lather and rinse	Potential CNS toxicity; not recommended for infants, children, breastfeeding mothers or pregnant women (category C)	Poor
Ivermectin (available as 3 mg tablets)	Oral dose of 250 mcg/kg	Potential CNS toxicity; not recommended for children <33 pounds (15 kg), breastfeeding mothers or pregnant women (category C)	Excellent

*Over-the-counter products.

Table 84.3 Treatments for crab lice. All crab lice treatments should be given on two separate occasions, 1 week apart, i.e. days 1 and 8.

Introduction

Body lice infestations are associated with overcrowding, poor hygiene, poverty, wars and natural disasters. These insects are the primary vectors for diseases caused by *Rickettsia*, *Borrelia* and *Bartonella* spp. (see Chs 74 & 76). Body lice look very similar to head lice but are larger in size.

Epidemiology

Body lice are found worldwide. Increased prevalence rates of body lice are tied to poor hygiene, poverty and homelessness. There are no racial, age or sex restrictions.

Pathogenesis

Pediculosis corporis is caused by an infestation of humans and their clothing by *Pediculus humanus* var. *corporis*. Besides exposure to conditions conducive to obtaining body lice, infestation requires an inability to wash and change clothes.

Several important human diseases are transmitted by the body louse. These include epidemic typhus (*Rickettsia prowazekii*) and relapsing fever (*Borrelia recurrentis*) as well as several diseases caused by *Bartonella quintana* – trench fever, bacillary angiomatosis and endocarditis[1]. Transmission of microorganisms from body lice to humans occurs not from the louse bites, but rather by contaminated fecal pellets being scratched into the bite site or excoriated skin or by inhalation of dry, powdery louse feces from infected bedding or clothing.

Clinical features

P. humanus var. *corporis* measures between 2.5 and 4.0 mm in length. Unlike head and crab lice, the nits and lice are rarely found on the patients' skin, save for feeding, as they reside primarily on the clothing of their hosts. This infestation leads to severe pruritus. The back, neck, shoulders and waist areas are commonly involved. Clinical findings include pinpoint red macules, small erythematous papules, crusts and excoriations, occasionally complicated by impetigo and lymphadenopathy. Blood and fecal pellets often stain clothing and bedding. On inspection, nits and adult lice are found along clothing seams that are in contact with the neck, axillae and waistline (Fig. 84.12).

Pathology

The epidermis has minimal spongiosis with nonspecific infiltrates of eosinophils and neutrophils in the dermis.

Differential diagnosis

Other causes of widespread pruritus and excoriations that may be considered in the differential diagnosis of body lice include systemic diseases (e.g. hepatic or renal impairment), drug reactions, atopic dermatitis, contact dermatitis (irritant or allergic), and other infestations (e.g. scabies).

Treatment

Preferably, the clothing and bedding of infested individuals are discarded in tightly sealed, plastic biohazard bags and incinerated. Only if the latter is not possible should disinfection be attempted. This involves fumigating the clothing or laundering it using hot water (temperature of ≥130°F/55°C) then machine drying it with high heat. Hot ironing of the seams of upholstered furniture can also be performed, and exposure to untreated infested items should be strictly avoided for 2 weeks. Topical insecticides are often applied to the body with regimens similar to those used for scabies, and this can eradicate concurrent infestations with scabies or crab lice as well as kill any body lice adherent to hairs.

Mass delousing in crowded, large populations due to natural disaster, war or famine is accomplished by dusting powders. These powders may contain DDT, malathion, dieldrin, lindane or permethrin.

Fig. 84.12 Body lice eggs in the seams of clothing.

TUNGIASIS

Synonyms: ■ *Tunga penetrans*: chigoe flea, jigger flea, burrowing flea, sand flea ■ Pique ■ Nigua ■ Pio and bicho de pie

Key features

- This infestation is caused by the burrowing flea, *Tunga penetrans*
- It is endemic in the Caribbean islands and parts of Central and South America, Africa, Pakistan and India
- The female flea burrows into the skin, then enlarges to create a 1 cm nodule with a central punctum through which eggs are ejected

Introduction

The burrowing flea, *Tunga penetrans*, is the causative agent of tungiasis. A female flea burrows into the upper dermis and enlarges to approximately 1 cm in diameter, creating a nodule with a central punctum through which eggs (fertilized or unfertilized) are eventually discharged.

History

Tungiasis was first reported in crew members on Christopher Columbus' original trip to the New World in 1492.

Epidemiology

Tungiasis can occur in anyone exposed to the flea, regardless of sex, race or age. It is indigenous to the Caribbean islands, with a prevalence ranging from 15% to 50%. Other areas of high incidence include parts of Central and South America, Africa, India and Pakistan.

Pathogenesis

Tunga penetrans is a wingless flea, 1 mm in size, that usually lives in warm, dry soil. Both sexes of this flea require an occasional blood meal from a warm-blooded animal for maturation[25]. Due to the fleas' limited jumping ability, the most common location for bites is the feet. Female fleas, rather than simply obtaining a blood meal, burrow headfirst into mammalian skin. They subsequently undergo marked abdominal hypertrophy, growing to 1 cm in diameter. The flea protrudes its rear cone through a central punctum that is always maintained; whether or not fertilization occurs via mating of the embedded female flea with a free-roaming male flea, over a hundred eggs are discharged within 3 weeks[26]. After expelling the eggs, the female dies and its remains are eventually sloughed from the skin.

Clinical features

Bites of immature fleas cause no symptoms; however, burrowing of the female flea into the skin can cause significant clinical morbidity. The burrowing is initially asymptomatic, but varying degrees of pain or pruritus usually develop. The first sign of disease is a small black dot, which evolves into a pearl-like whitish papule and then a larger nodule that is said to resemble a watch glass, with a clearly demarcated white halo surrounding the black central punctum. A peripheral zone of erythema is frequently evident. When the flea dies, a black crust covers the involuting lesion. The most common site of disease is the periungual area of the toes, followed by the soles and toe webs (Fig. 84.13). Ulceration, secondary infection and lymphangitis can accompany the infestation, and less common complications include tetanus, gangrene and amputation of a digit[25]. Over half of periungual infections lead to deformation or loss of the nail[27].

Fig. 84.13 Tungiasis in a child.

Pathology

A nonspecific inflammatory infiltrate surrounds the flea within the dermis.

Differential diagnosis

The differential diagnosis may include myiasis, tick bite reactions, cercarial dermatitis, pyoderma, plantar warts, verruga peruana and squamous cell carcinoma.

Treatment

Spontaneous recovery does occur; however, most clinicians and patients prefer to cure the infestation by removal of the female flea. In an early infestation, a sterile needle can be used to pry the insect from the skin. If treatment is delayed, curettage, electrodesiccation or surgical excision may be required. Careful cleaning of the cystic cavity speeds clinical resolution. Tetanus prophylaxis should be strongly considered. Substantial clinical benefit from topical and oral therapies for tungiasis has not been demonstrated. Topical application of ivermectin, metrifonate or thiabendazole may lead to more rapid demise of embedded fleas[28]. In a randomized controlled study, oral ivermectin was not found to have significant efficacy compared to placebo. Preventative measures include the use of insect repellents, wearing closed shoes or boots, and avoiding ground contact (e.g. sitting on sandy beaches) in endemic areas.

CUTANEOUS MYIASIS

Synonyms: ■ Names for the various flies associated with this entity include human botflies, screwworms, blowflies, fleshflies and tumbu flies

Key features

- Infestation of the skin by fly larvae (maggots)
- The larvae inhabit cutaneous wounds (wound myiasis) or burrow into the dermis causing boil-like lesions (furuncular myiasis)
- Although they usually cause minimal morbidity, larvae can cause problems when they involve the nasal cavity and sinuses

Introduction

Cutaneous myiasis is an infestation of the skin by developing larvae (maggots) of a variety of fly species within the arthropod order Diptera. The two main clinical types are wound and furuncular myiasis.

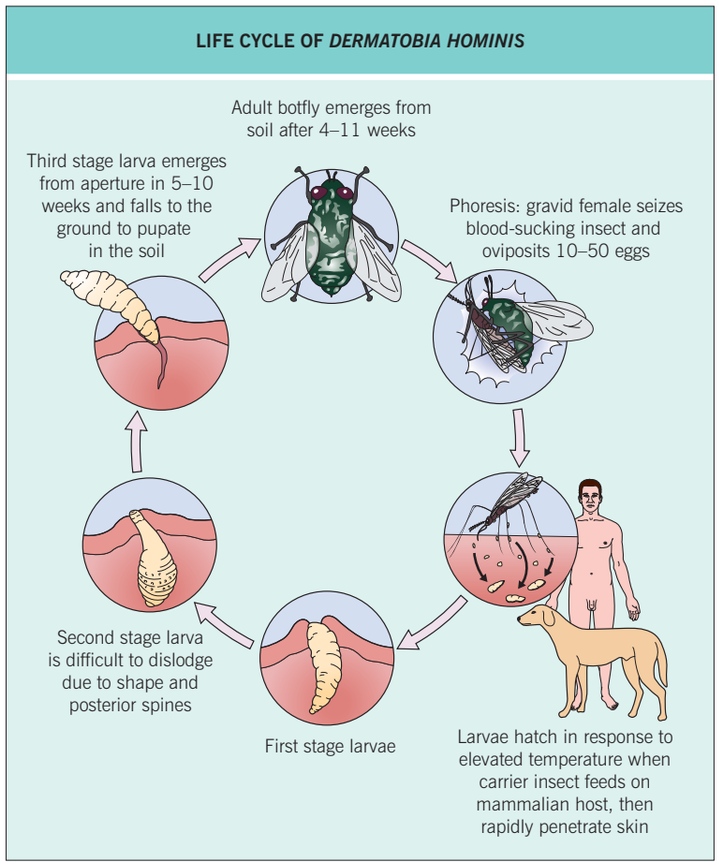


Fig. 84.14 Life cycle of *Dermatobia hominis* in cutaneous myiasis.

History

Maggots were central to Francisco Redi's experiment rejecting the theory of spontaneous generation. Wound debridement by maggots has been used for centuries, including during the American Civil War and by Napoleon's troops.

Epidemiology

Myiasis is a worldwide infestation with seasonal variation whose prevalence is related to latitude and the life cycle of the various species of flies. Its incidence is higher in the tropics and subtropics of Africa and the Americas. The flies responsible prefer a warm and humid environment, thus they are restricted to the summer months in temperate zones, while living year-round in the tropics.

Pathogenesis

Myiasis is the infestation of living humans (or other vertebrates) with dipterous larvae that feed on the host's tissues, liquid body substances or ingested food. Myiasis can be caused by several species of arthropods within the order Diptera, the two-winged true fly. The causative flies can be classified by: (1) taxonomic family; and (2) differences in pathogenic behavior of the fly species.

Worldwide, the most common flies that cause human infestation are *Dermatobia hominis* (human botfly) and *Cordylobia anthropophaga* (tumbu fly). The routes of transmission of fly larvae to human hosts differ among the fly species. For example, *D. hominis* lays its eggs on mosquitoes, which in turn deposit them on a warm-blooded mammal (Fig. 84.14). *C. anthropophaga* deposits its eggs on moist clothing and soiled blankets and in sand. The larva can live 15 days without feeding, but once it makes contact with a host, it penetrates the skin, which initiates further maturation. In endemic areas, people often iron their clothes after hanging them out to dry to kill the fly eggs. In wound myiasis, an open wound or orifice attracts flies to deposit their eggs. Any body area can be infested, and the most serious sequelae occur when the nasal cavity, sinuses or scalp are involved. The incubation

Fig. 84.15 Cutaneous myiasis. A Furuncular myiasis presenting as a papulonodule with a central punctum on the leg. **B** Wound myiasis in an amputation stump. **C** Botfly larva. *B, Courtesy, Louis A Fragola, Jr, MD.*

period for larvae to mature into adulthood depends on the fly and can range from 1 to 12 weeks.

Clinical features

Furuncular cutaneous myiasis, which is caused by the human botfly and tumbu fly, causes boil-like lesions. Whereas myiasis from the tumbu fly typically occurs on the trunk, thighs and buttocks, botfly lesions are usually on exposed areas of the body, including the scalp, face, forearms and legs. A pruritic papule develops within 24 hours of penetration, enlarging to 1–3 cm in diameter and up to 1 cm in height (Fig. 84.15A). These lesions can be painful or tender and may become crusted and purulent; there may be a sensation of movement.

In *wound* myiasis, the larvae are deposited in a suppurating wound or on decomposing flesh. *Cochliomyia hominivorax*, a screwworm, is the most common cause of this form of myiasis in the Americas, while *Chrysomya bezziana* is typically seen in Africa, Australia and Asia. The diagnosis is obvious when larvae are visible on the surface of the wound (Fig. 84.15B) and more difficult when they have burrowed beneath the surface.

Creeping (or migratory) cutaneous myiasis may be caused by *Hypoderma bovis* if there is exposure to infested cattle, or by *Gasterophilus intestinalis* in those who work with horses. This form of myiasis resembles cutaneous larva migrans, but the fly larvae migrate more slowly, persist for longer (often months), and are larger than helminth larvae[29].

Myiasis is a self-limiting infestation with minimal morbidity in the vast majority of cases. The major reasons for treatment are reduction of pain, cosmesis, and psychological relief. However, larvae such as *C. hominivorax* can infest around orifices of the head and may burrow into brain tissue. Ultrasound can assist in establishing the diagnosis, determining the size of the larvae, and evaluating the course of treatment[30].

Pathology

Histologically, an inflammatory response occurs in stages in which lymphocytes, giant cells, neutrophils, eosinophils, mast cells and plasma cells participate. The larvae can be seen in cross-section.

Differential diagnosis

Furuncular cutaneous myiasis should be differentiated from a ruptured epidermoid cyst, an abscess, furunculosis, a foreign body reaction, onchocerciasis, tungiasis, an exaggerated arthropod bite reaction, and lymphadenopathy.

Treatment

The larva in furuncular cutaneous myiasis should not be forcibly removed through the central punctum because its tapered shape with rows of spines and hooks prevents simple extrusion (Fig. 84.15C). Surgical debridement under local anesthesia is curative, although a foreign body reaction can occur if parts of the larva remain. Occlusion/suffocation approaches involve placement of petroleum jelly, liquid paraffin, beeswax, nail polish, heavy oil, lard or strips of bacon over the central punctum. Such blockage forces the aerobic larva to surface for air over the course of several hours – at which time, forceps aid in their capture. Alternatively, ethyl chloride sprays, liquid nitrogen, chloroform in vegetable oil or insecticides have been used alone or in combination. In addition, lidocaine can be injected into the base of the tissue cavity which the larva inhabits, thereby forcing the larva to the surface[29]. After removal of larvae, antiseptic dressings are indicated, as are antibiotics if secondary infection is present.

Wound myiasis requires debridement with irrigation to eliminate the larvae from the wound, or surgical removal. If burrowing has occurred, the method of extraction is identical to that for furuncular cutaneous myiasis.

An alternative treatment for all types of myiasis is oral ivermectin, which has proven especially helpful with oral and orbital involvement[29]. Surgical removal is not required unless requested by the patient, as the larvae are naturally sloughed within 2 weeks.

Myiasis can be a portal of entry for *Clostridium tetani*, and vaccination of affected individuals should be considered.

Preventative measures

In endemic areas, it is important to avoid activities that increase the risk of myiasis, such as wearing damp clothing or resting in sandy areas. The use of insect repellents (including on the scalp) can be useful in preventing mosquitoes that are harboring the larvae of the human botfly from depositing their living cargo.

REFERENCES

1. Meinking TL, Burkhart CG, Burkhart CN. Ectoparasitic diseases in dermatology: reassessment of scabies and pediculosis. In: James W (ed.). Advances in Dermatology, Vol. 15. St Louis: Mosby, 1999:67–108.
2. Burkhart CG. Scabies: an epidemiologic reassessment. Ann Intern Med. 1983;98:498–503.
3. Hengge U, Currie B, Lupi O, Schwartz R. Scabies: a ubiquitous neglected skin disease. Lancet Infect Dis. 2006;6:769–79.
4. Hicks M, Elston D. Scabies. Dermatol Ther. 2009;22: 279–92.
4a. Walter B, Heukelbach J, Fengler G, et al. Comparison of dermoscopy, skin scraping, and the adhesive tape test for the diagnosis of scabies in a resource-poor setting. Arch Dermatol. 2011;147:468–73.
5. Kristjansson AK, Smith MK, Gould JW, Gilliam AC. Pink pigtails are a clue for the diagnosis of scabies. J Am Acad Dermatol. 2007;57:174–5.
6. Anonymous. Labeling changes for lindane. FDA Consumer. 2003;37:6.
7. Taplin D, Meinking TL, Chen JA, et al. Comparison of crotamiton 10% cream (Eurax) and permethrin 5% cream (Elimite) for the treatment of scabies in children. Pediatr Dermatol. 1990;7:67–73.
8. Diaz M, Cazorla D, Acosta M. Efficacy, safety, and acceptability of precipitated sulphur petrolatum for topical treatment of scabies at the city of Coro, Falcon State, Venezuela. Revista Invest Clinica. 2004;56:615–22.
9. Meinking TL, Taplin D, Hermida JL, et al. The treatment of scabies with ivermectin. N Engl J Med. 1995;333:26–30.
10. Barkwell R, Shields S. Deaths associated with ivermectin treatment of scabies. Lancet. 1997;349:1144–5.
11. Currie BJ, Harumal P, McKinnon M, et al. First documentation of *in vivo* and *in vitro* ivermectin resistance in *Sarcoptes scabiei*. Clin Infect Dis. 2004;39: e8–12.
12. Mounsey KE, Holt DC, McCarthy JS, et al. Longitudinal evidence of increasing *in vitro* tolerance of scabies mites to ivermectin in scabies-endemic communities. Arch Dermatol. 2009;145:840–1.
13. Victoria J, Trujillo R. Topical ivermectin: a new successful treatment for scabies. Pediatr Dermatol. 2001;18: 63–5.
14. Burkhart CN, Burkhart CG. Head lice: scientific assessment of the nit sheath with clinical ramifications

and therapeutic options. J Am Acad Dermatol. 2005;53:129–33.
15. Burkhart CN, Stankiewicz BA, Pchalek I, et al. Molecular composition of the louse sheath. J Parasitol. 1999;85:559–61.
16. Takano-Lee M, Edman JD, Mullens BA, Clark JM. Transmission potential of the human head louse, *Pediculus capitis* (Anoplura: Pediculidae). Int J Dermatol. 2005:44:811–16.
17. Hipolito RB, Mallorca FG, Zuniga-Macaraig ZO, et al. Head lice infestation: single drug versus combination therapy with one percent permethrin and trimethoprim/sulfamethoxazole. Pediatrics. 2001;107:e30.
18. Burkhart CN, Burkhart CG, Pchalak I, et al. The adherent cylindrical nit structure and its chemical denaturation *in vitro*: an assessment with therapeutic implication for head lice. Arch Pediatr Adolesc Med. 1998;1152:711–12.
19. Meinking TL, Vicaria M, Eyerdam DH, et al. Efficacy of a reduced application time of Ovide lotion (0.5% malathion) compared to Nix crème rinse (1% permethrin) for the treatment of head lice. Pediatr Dermatol. 2004;21:670–4.
19a. Bialek R, Zelck UE, Fölster-Holst R. Permethrin treatment of head lice with knockdown resistance–like gene. N Engl J Med 2011;364:386–7.
20. Burkhart CN, Burkhart CG. Head lice revisited: *in vitro* standardized tests and differences in malathion formulations. Arch Dermatol. 2004;140:488–9.
21. Chosidow O, Giraudeau B, Cottrell, et al. Oral ivermectin versus malathion lotion for difficult-to-treat head lice. N Engl J Med. 2010;362:896–905.
22. Stough D, Shellabarger S, Quiring J, et al. Efficacy and safety of spinosad and permethrin creme rinses for pediculosis capitis (head lice). Pediatrics. 2009;124:e389–95.
23. Kalter DC, Sperber J, Rosen T, et al. Treatment of pediculosis pubis: clinical comparison of efficacy and tolerance of 1% lindane shampoo vs. 1% permethrin crème rinse. Arch Dermatol. 1987;123:1315–19.
24. Burkhart CG, Burkhart CN. Oral ivermectin for *Phthirus pubis*. J Am Acad Dermatol. 2004;51:1037–8.
25. Eisele M, Heukelback J, Van Marck E. Investigations on the biology, epidemiology, pathology and control of *Tunga penetrans* in Brazil: I. Natural history of tungiasis in man. Parasitol Res. 2003;90:87–99.
26. Nagy N, Abari E, D'Haese J, et al. Investigations on the life cycle and morphology of *Tunga penetrans* in Brazil. Parasitol Res. 2007;101:S233–42.
27. Feldmeier H, Eisele M, Van Marck E, et al. Investigations on the biology, epidemiology, pathology and control of *Tunga penetrans* in Brazil: IV. Clinical and histopathology. Parasitol Res. 2004;94:275–82.
28. Heukelbach J, Eisele M, Jackson A, et al. Topical treatment of tungiasis: a randomized, controlled trial. Ann Trop Med Parasitol. 2003;97:743–9.
29. McGraw TA, Turiansky GW. Cutaneous myiasis. J Am Acad Dermatol. 2008;58:907–26.
30. Bowry R, Cottingham R. Use of ultrasound to aid management of late presentation of *Dermatobia hominis* larva infestation. Emerg Med J. 1997;14:177–8.

Bites and Stings 85

Dirk M Elston

Chapter Contents

Insects 1435
Arachnids 1440
Centipedes and millipedes 1449
Snake bites 1449
Dog and cat bites 1450
Leeches 1450
Marine injuries 1451

INSECTS

Insect Bites And Stings (Class Insecta)

Key features

- Excoriated pruritic papules sometimes progress to persistent prurigo nodularis-like lesions
- Papular urticaria may be localized to sites of bites or generalized
- Vesicles and bullae can mimic bullous pemphigoid
- Pseudolymphomatous nodules occasionally develop
- Anaphylaxis is mainly related to hymenopterid stings
- Secondary infection is most often staphylococcal

Introduction

Insect bites and stings are prevalent throughout the world. In temperate climates they are primarily a seasonal phenomenon, although indoor infestations can persist year-round. Insects are important disease vectors worldwide, and personal protection against bites plays a major part in the prevention of disease[1]. Arthropods produce a wide spectrum of clinical lesions. Bullous arthropod reactions may suggest a diagnosis of immunobullous disease, and positive direct immunofluorescence has been reported, especially in the setting of scabies infestation. Pseudolymphomatous arthropod reactions can also create diagnostic confusion (see Ch. 121).

Pathogenesis

Insect venoms and saliva are complex. Immediate reactions are commonly related to histamine, serotonin, formic acid or kinins. Delayed reactions are typically manifestations of the host's immune response to proteinaceous allergens. Secondary infection is common. Although staphylococcal infections are seen most frequently, streptococcal infections also occur and inoculation of organisms via insect bites and stings is occasionally implicated in other infectious diseases such as nocardiosis and sporotrichosis. The list of vector-borne diseases is staggering, and many new and emerging infectious diseases are linked to arthropod vectors. For example, tick-borne encephalitis has rapidly become an important disease in Europe.

While some diseases have a single arthropod vector, others have multiple vectors and/or other means of transmission. For example, bites from ticks and handling of infected animals are the most common modes of tularemia transmission in the US, but the disease can also be acquired through bites by deerflies and other horseflies. The vector has an important influence on the patient population affected by a particular disease. For example, cat ownership is a risk factor for cat scratch disease, which is associated with *Bartonella henselae* transmission by fleas, while homelessness is a risk factor for trench fever, which is caused by *Bartonella quintana* transmission by lice; however, either organism–vector pair can cause *Bartonella* endocarditis and bacillary angiomatosis, explaining why these diseases affect both patient populations. Vector-borne diseases often become epidemic during war or following natural disasters, and poverty and homelessness contribute to the spread of vector-borne disease.

Roughly a quarter of reported cases of anaphylaxis are related to stings from insects in the order Hymenoptera (meaning membranous wings), which includes bees, wasps, hornets and ants. These insects can possess specialized stingers and produce complex venoms that contain substances such as formic acid, kinins and proteinaceous allergens. Insect sting hypersensitivity is more common in those with an atopic diathesis, and severe immediate reactions may also be an indication of underlying mastocytosis.

Clinical features

Characteristic insect bite reactions are grouped or disseminated, 2 to 8 mm, erythematous urticarial papules that are markedly pruritic and often excoriated (Fig. 85.1); they typically resolve over 5–10 days. Occasionally, bite reactions present as evanescent wheals or longer-lasting "papular urticaria" lesions that persist for weeks or even months, sometimes reactivating when new bites occur in different locations. In addition to lesions restricted to the sites of bites, papular urticaria may develop as a generalized phenomenon following insect bites. Edematous plaques, nodules and vesiculobullous reactions also occur frequently (Fig. 85.2). Chronic and resolving lesions are often hyperpigmented and can resemble prurigo nodularis. Insect bite reactions are most frequent in children 2–10 years of age and tend to involve exposed areas of the head, neck and extremities. Commonly, only one member of a family is affected, as most clinical manifestations relate to the individual's immune response rather than the bite itself.

Papulovesicular and nodular lesions resembling bites have been described in patients with chronic lymphocytic leukemia (see Ch. 33) and (less frequently) other hematologic malignancies. Although the lesions frequently appear months after the diagnosis of leukemia and are unrelated to its course or therapy, they can also herald development or recurrence of leukemia or lymphoma[2]. The clinical appearance, distribution and histologic features (including the presence of degranulating eosinophils) of the lesions suggest that they represent exaggerated bite reactions; although patients often do not recall having been bitten, reactivity to intradermal injection of mosquito antigen has been documented. Hypersensitivity to mosquito bites with development of bullous or necrotic skin lesions has also been described in individuals (typically Asian or Hispanic children and adolescents) with chronic EBV infection and proliferation of EBV-carrying natural killer (NK) cells (see Ch. 80)[3]. Screening for hematologic malignancies, latent EBV infection (including *in situ* hybridization to detect EBV RNA in biopsy specimens of lesional skin if positive serology) and NK-cell lymphocytosis should be considered in patients with unusual arthropod bite reactions.

Bee and wasp stings typically produce immediate burning pain, which is followed by the development of local erythema and swelling that usually subsides within a few hours to days but can be more severe and persistent in sensitized individuals. Atrial arrhythmias have been reported after bee stings, in the absence of anaphylaxis. Killer bee and wasp attacks may be associated with myoglobinuria or hemoglobinuria and acute tubular necrosis[4]. Although some patients with inflammatory arthritis have looked to bee stings as an alternative therapy, beekeepers may develop a chronic arthropathy related to stings.

Fig. 85.1 Insect bite reactions. In this patient, there are papulovesicles as well as excoriated papules with hemorrhagic crusting. In more darkly pigmented individuals, residual hyperpigmentation is common and can persist for months. *Courtesy, Julie V Schaffer, MD.*

Pathology

Histologic features suggestive of a bite or sting include the presence of a wedge-shaped perivascular lymphocytic infiltrate with eosinophils, endothelial prominence and overlying spongiosis or focal epidermal necrosis. Spongiosis may result in blister formation.

Differential diagnosis

Arthropod reactions account for many "cryptic" chronic skin eruptions. Features that should suggest an arthropod reaction include grouping of papules, patterns of eruption that correlate with exposure, and the histologic features noted above. When the physician suspects an arthropod reaction, a detailed history of outdoor exposure, pets, work and hobbies may be helpful.

Treatment

Camphor and menthol lotion and gel formulations may be useful in the control of pruritus. Topical anesthetic preparations can also be helpful, and those containing pramoxine are readily available and present a low risk of contact dermatitis. For more persistent bite reactions, topical corticosteroids are often required. In young children, mid-strength corticosteroid preparations may suffice, while in older children and adults, I generally recommend class 1 or 2 corticosteroids. These agents can be applied under occlusion to enhance efficacy, but this should be limited to a few applications to avoid potential side effects of cutaneous atrophy and striae.

When topical agents fail, intralesional injection of a corticosteroid (e.g. triamcinolone 10 mg/ml) or excision of the pruritic nodule may be necessary. Occasionally, pseudolymphomatous nodules may require triamcinolone concentrations as high as 40 mg/ml. Cutaneous atrophy can occur, especially if a higher concentration of corticosteroid is injected superficially. Atrophy may also be noted in a distribution corresponding to lymphatic drainage.

Prevention of bites is best accomplished through the use of protective clothing and repellents. Commonly used repellents are listed in Table 85.1. Factors that can influence the choice of a repellent include its efficacy, cost, convenience, odor and potential for irritation, as well as common arthropod pests in the area and the time of day, duration and environment of the exposure. DEET (N,N-diethyl-3-methylbenzamide, previously called N,N-diethyl-m-toluamide) remains the most widely used repellent for the prevention of bites from mosquitoes and most other insects. DEET is applied to exposed skin and can also be applied to clothing. While mosquitoes that carry dengue virus tend to bite during the day, the anopheline mosquitoes that carry malaria tend to bite at night, and pyrethroid-impregnated mosquito netting and chemoprophylaxis are additional preventative measures.

The duration of efficacy of DEET depends primarily upon the dose applied. It is also affected by the sex of the individual, with women receiving less protection than men (an observation that appears to be independent of serum estradiol levels). Efficacy may be reduced by the presence of skin abrasions. Rare toxic reactions include anaphylaxis and encephalopathy, and high concentrations of DEET can occasionally produce dramatic bullous eruptions.

Because of the potential for toxicity, the lowest effective DEET dose should be selected, especially in children. Many products with 10% or lower concentrations are available, although the American Academy of Pediatrics has stated that concentrations as high as 30% can be used safely in children 2 months of age or older (see Table 85.1). Although sunscreens have been shown to enhance DEET absorption in studies using artificial membranes and animal models, this is not thought to be clinically significant with normal use.

Fig. 85.2 Insect bite reactions. Sometimes patients develop large, erythematous, edematous plaques (**A**) or frank bullae (**B**). *Courtesy, Julie V Schaffer, MD.*

COMMONLY USED INSECT REPELLENTS	
CONVENTIONAL REPELLENTS IN EPA CLASSIFICATION	
DEET (N,N-diethyl-3-methylbenzamide)*	Effective against a wide range of arthropods
	Long history of use
Picaridin	Good evidence for mosquitoes
	Fewer studies support repellent effect against ticks
BIOPESTICIDE REPELLENTS IN EPA CLASSIFICATION	
IR3535 (3-[N-butyl-N-acetyl]-aminopropionic acid, ethyl ester)	Good evidence for mosquitoes in some, but not all, studies
	Fewer studies support repellent effect against ticks
p-Menthane-3,8-diol†	Good evidence for mosquitoes
	Fewer studies support repellent effect against ticks
Botanicals (e.g. soybean oil, citronella, neem oil, fennel oil, geraniol)	Have consumer appeal as "natural" repellents
	Best published evidence is for neem oil
	Lack of evidence does not necessarily equate to lack of efficacy, but available evidence to date suggests they are inferior to the synthetic repellents listed above

*There is a plateau of efficacy at 30% with long-acting products, and higher concentrations should generally be avoided. Because sunscreens require frequent reapplication and DEET does not, combination products with these ingredients are not recommended.
†The active ingredient of oil of lemon eucalyptus; use on children less than 3 years of age is not recommended.

Table 85.1 Commonly used insect repellents. Agents are listed in order of decreasing evidence of efficacy. EPA, Environmental Protection Agency.

Other effective repellents are available, and improved extended-release formulations are being developed[5–9]. Picaridin, IR3535 and p-menthane-3,8-diol perform reasonably well against a variety of mosquitoes and generally outperform soybean oil, citronella, neem oil, fennel oil and geraniol (see Table 85.1)[10]. For protection against the common mosquitoes *Aedes aegypti* and *Culex quinquefasciatus*, IR3535 may be comparable to DEET. The Mediterranean monk's pepper plant (*Vitex agnus-castus*) has demonstrated efficacy against *Ixodes ricinus* and *Rhipicephalus sanguineus* ticks as well as some mosquitoes, biting flies and fleas.

Because insect stings are often unexpected, allergic individuals should carry an epinephrine (adrenaline) autoinjector with them at all times. The EpiPen® autoinjector contains 0.3 ml of epinephrine 1:1000 (for individuals weighing >66 pounds [>30 kg]), while the EpiPen® Jr. contains 0.3 ml of epinephrine 1:2000 (for children weighing 33–66 pounds [15–30 kg]). Patients must receive instructions regarding the use of the autoinjector, which needs to be protected from heat and light as well as inspected periodically for brown discoloration of the contents. Bee stingers should be removed as rapidly as possible, with less concern for the exact method of removal.

Venom immunotherapy has been shown to improve quality of life for patients allergic to stings[11], reducing anxiety as well as the incidence and severity of local and systemic reactions. Desensitization protocols vary and should be discussed with an allergist. Rush (accelerated) immunotherapy can be performed for those with severe reactions, and it has a reasonable safety profile. In the setting of mastocytosis, immunotherapy may need to be continued indefinitely, frequently induces immediate hypersensitivity reactions, and is only partially effective. Omalizumab has been used in conjunction with immunotherapy for patients refractory to standard regimens, and this may help to prevent immunotherapy-related anaphylaxis[12].

Fire Ants

Key features

- Imported fire ants are red–brown in color and 1–2 mm in length
- When their mounds are disturbed, the ants swarm and sting in great numbers
- Immediate burning pain is followed by intensely pruritic grouped vesicles and pustules
- Fire ant allergy is an important cause of anaphylaxis in endemic areas

Introduction

The range of *Solenopsis invicta*, the red imported fire ant (originally from South America), has spread to encompass much of the southern and southwestern US, and its territory continues to expand. The size of fire ant mounds varies in proportion to the amount of rainfall. The mounds may be inconspicuous during periods of drought, but they can reach more than a foot (30 cm) in height after heavy rains. When the mound is disturbed, the ants swarm. Because of their small size, they are not felt until they all begin to sting simultaneously in response to a chemical signal. Fire ants are attracted to electrical boxes and therefore present a hazard to electricians. Indoor attacks by swarms of fire ants can be particularly dangerous to infants and elderly individuals with impaired mobility[13].

Pathogenesis

Fire ant venom is complex, and it acts by increasing membrane permeability and allowing release of histamine from mast cells. Allergic responses are directed at proteins within the venom. The venom is less concentrated in winter months, so winter sting reactions may be milder.

Clinical features

Fire ant stings begin as extremely painful wheals, then evolve into intensely pruritic vesicles and sterile pustules (Fig. 85.3). The fire ant

Fig. 85.3 Fire ant bites presenting as clusters of sterile pustules on the foot.

first grasps the skin with its mandibles; it then pivots and delivers a series of stings in a circular fashion, which may produce a rosette pattern. Scattered individual lesions are also common, especially when the victim is able to remove the ants before they have a chance to sting again. Secondary staphylococcal infections can occur after fire ant stings. The absence of persistent tenderness can help differentiate sterile pustular reactions from secondary infections. Life-threatening anaphylactic reactions to fire ant stings have become an important problem in the southern US[14].

Treatment

Patients with a life-threatening fire ant allergy should carry an epinephrine autoinjector with them at all times. Immunotherapy improves quality of life for those with severe fire ant allergies, and rush immunization protocols can be successful for those at high risk of stings[15,16]. Unfortunately, it is often impossible to avoid stings in endemic areas[17]. Local reactions may be treated with potent topical or intralesional corticosteroids. A variety of methods of fire ant control are available, including bait insecticides that have a low environmental impact and are reasonably effective as well as insecticide treatments for individual mounds.

Bedbugs

Key features

- Flattened oval body that is red–brown in color and 5–7 mm long in adults
- Segmented abdomen and vestigial wings
- Blood-sucking insects that feed at night and produce rows of pruritic, edematous papules

Introduction

In the past decade, there has been a worldwide resurgence of bedbugs, which are now frequently recognized in homes, hotels and dormitories[18–20]. Increases in international travel, expanded immigration, changes in pest control practices, and development of insecticide resistance have likely contributed to this trend.

Bedbugs belong to the family Cimicidae (order Hemiptera) and are blood-sucking mammalian and avian ectoparasites. They have a flattened oval body, a segmented abdomen, a retroverted labium (sucking mouthpiece), a semicircular to triangular scutellum (dorsal sclerotic plate), and antennae with four segments (Fig. 85.4). *Cimex lectularius* (the common bedbug) and *C. hemipterus* (found in warmer climates) affect humans most frequently; *C. lectularius* also parasitizes bats, chickens and other domestic animals. *C. lectularius* ranges in size from 5 to 7 mm, with females slightly longer than males. *C. hemipterus* is roughly 25% longer than *C. lectularius*. Interspecies mating occurs in nature.

Fig. 85.4 Bedbugs. Red–brown in color with a segmented abdomen and vestigial wings.

Bedbugs are nocturnal; they hide in cracks and crevices or behind peeling paint during the day and feed at night. There is a particularly high prevalence of bedbugs in homeless shelters and refugee camps.

Pathogenesis

Bedbug bite reactions result from an immune response to salivary proteins (e.g. nitrophorin) injected by the insect while feeding. Bedbugs digest their blood meal very slowly. The blood in the bug's gut remains relatively unclotted and is not membrane-bound. These factors may affect this arthropod's potential competence as a disease vector.

Clinical features

Bedbug bites typically present as pruritic, erythematous, edematous papules, sometimes with a visible central hemorrhagic punctum. As with other insect bites (see above), the clinical appearance and duration of lesions vary depending on the patient's degree of sensitization. Some individuals have little or no reaction to bedbug bites, and it is common for only one or a few family members (even among those sleeping in the same bed) to report lesions. Bites are often noted in linear groups of three (referred to as breakfast, lunch and dinner) but can also be otherwise clustered or scattered, favoring areas of the body that are exposed during sleep (e.g. the head, neck, shoulders, arms, legs and waist). Although affected individuals classically awake with new lesions, bite reactions can take several days to appear, and the latency tends to decrease with exposure to additional bites[18,20].

Bedbugs may be vectors for hepatitis B virus, although this is highly controversial. They have also been suspected to be vectors of American trypanosomiasis (Chagas disease). Fortunately, it appears unlikely that bedbugs present a significant risk for transmission of HIV. Bedbug dung may play a role in asthma.

Treatment

Bedbug bites can be treated as described above for other insect bites (e.g. with topical corticosteroids). Eradication of bedbugs from infested homes is difficult and often requires the assistance of professional exterminators. Elimination of cracks and crevices and removal of roosting bats or birds are essential. Various insecticides have activities against bedbugs, dichlorvos being among the best. Although insect repellents demonstrate some degree of efficacy against bedbugs, those bedbugs that still bite take progressively smaller meals in the face of increasing concentrations of repellent. Paradoxically, this may increase the chance of bedbugs spreading disease as they go from one individual to another. Insecticide-treated bed nets used to protect sleepers from mosquitoes in areas with endemic malaria have also been shown to reduce bedbug infestation, but this practice may contribute to pyrethroid resistance among bedbugs.

Triatome Reduviids

Synonyms: ■ Reduviid bugs ■ Kissing bugs ■ Assassin bugs

Key features

- Half-membranous wings (hard proximally and membranous distally) whose tips overlap
- Tan and dark "tiger stripes" on the abdomen
- Vector for American trypanosomiasis
- Bites can produce large, persistent edematous plaques

Introduction

Like bedbugs, triatome reduviids are true bugs of the order Hemiptera. They have half-membranous wings that overlap. Characteristically, the wings fail to cover the lateral portions of their "tiger-striped" abdomen (Fig. 85.5). The antennae are long, thin and composed of four segments; the position of the antennae is used to classify the bugs. The labium

Fig. 85.5 Triatome bug. Note that the wings fail to cover the lateral portions of the abdomen and the tan and dark "tiger stripes" on the abdomen.

(sucking mouthpiece) is straight and composed of three segments. Behind the head is a triangular pronotum (first segment of the thorax) with a broad posterior base.

Triatome reduviids are vectors for American trypanosomiasis (Chagas disease; see Ch. 83). The bugs have a pronounced gastrocolic reflex, defecating as they eat. Infectious feces are then inoculated into the bite site or conjunctiva by scratching or rubbing.

Triatome reduviids are often found in peri-domestic sites in Central and South America and the southern US, especially cracked stone walls and piles of tiles or bricks. They commonly feed on domestic animals, and trypanosome transmission may cross over between domestic and sylvatic life cycles. Control of this vector has been difficult, and insecticide spraying in affected communities is often followed by reinfestation originating from nearby livestock enclosures or wild populations of triatome reduviids.

Clinical features

Triatome reduviid bites are typically painless, and the first sign is delayed erythema, swelling and pruritus at the site. Exaggerated responses in the form of large urticarial plaques or vesiculobullous lesions are occasionally observed. Triatome reduviids are known as "kissing bugs" because of their tendency to bite the face, especially around the lips. Unilateral eyelid and periorbital swelling 1–2 weeks after conjunctival exposure to infected triatome feces is referred to as Romaña sign and represents a chagoma. Trypanosomes subsequently infect the autonomic nervous system, resulting in chronic complications that include cardiomegaly and megacolon (see Ch. 83). Triatome reduviids and cockroaches share antigens that are strongly immunogenic in atopic patients.

Blister Beetles

Synonyms: ■ Spanish fly ■ Rove beetle

Key features

- Oblong bodies and antennae composed of multiple short segments
- Wide variety of colors and patterns
- Contact with beetles results in vesicles and bullae due to their production of cantharidin

Introduction

Blister beetles (order Coleoptera) include members of the families Meloidae and Staphylinidae. The Meloidae are the best known, with species worldwide that result in blistering. Members of the family Oedemeridae are classified as "false" blister beetles but can also produce blistering. The blistering agent cantharidin is derived from blister beetles, where it appears to serve a protective function.

Much of what is known about blister beetles is extrapolated from studies of a few species. In *Epicauta funebris*, cantharidin has been identified in all ten life stages of the beetle, and it accumulates during the first five larval stages. When threatened, larvae protect themselves by exuding cantharidin in a milky oral fluid, rather than in the hemolymph that adult beetles discharge from leg joints. Adult male beetles contain up to 10% cantharidin by weight. If kept in isolation, females lose their larval reserves and must mate to preserve their stores of cantharidin. During mating, the female acquires cantharidin from her mate as a copulatory gift. She then transfers the cantharidin to her eggs, rendering them resistant to predation.

Clinical features

Contact with blister beetles typically results in vesicles and bullae. Epidemics of bullous skin lesions in hospital wards with open windows have been related to the light-seeking behavior of some species. "Nairobi eye", or rove beetle blistering, is caused by *Paederus eximius*, a blister beetle found in Northern Kenya. Eruption of pustules on an erythematous base due to contact with rove beetles in Pakistan has also been described.

Pathology

Histologic sections of the blisters demonstrate acantholysis in suprabasal keratinocytes. Disruption of cell outlines and cellular necrosis may be noted. The profile of adhesion molecule loss in cantharidin blisters is similar to that seen in Darier disease.

Treatment

Avoidance is the best measure, but immediate washing with soap and water may be of some benefit.

Fleas

Key features

- Laterally compressed bodies and large hind legs
- The most common flea on dogs is *Ctenocephalides felis*, the cat flea
- Produce intensely pruritic papules, vesicles and bullae, often grouped on the lower extremities
- Serve as vectors for endemic (murine) typhus, flea-borne spotted fever and plague

Introduction

Fleas (order Siphonaptera) are ubiquitous pests and show little host specificity. The most common flea on dogs is *Ctenocephalides felis*, the cat flea. *Pulex irritans*, the human flea (Fig. 85.6), is a common dog flea in some locations. It is also found on wild animals with no human contact. *Ctenocephalides* fleas have two ctenidia (combs) that resemble a mane of hair (pronotal comb) and mustache (genal comb) (Table 85.2).

Clinical features

Flea bites present as intensely pruritic papulovesicles, usually located on the lower legs. Other parts of the body may also be affected, especially when an infested pet has been groomed or held. Flea allergy is common, and allergic patients tend to react to a wide range of fleas. Flea pupae can lie dormant for many months then hatch rapidly in response to vibration. Individuals who enter a vacant house can find that fleas rapidly besiege them.

Fleas serve as vectors for endemic (murine) typhus, flea-borne spotted fever, plague and (primarily among cats) *Bartonella henselae* infections (see Chs 74 & 76). Endemic typhus is common in southern Texas and California, where the cat flea and *Xenopsylla cheopsis* (the oriental rat flea) are the primary vectors, respectively. The disease has also emerged with a worldwide distribution. Feeding alone can transmit endemic typhus, although fleas also defecate infectious bloody feces when feeding.

Tungiasis (caused by the jigger or sand flea, *Tunga penetrans*) usually presents with papular necrotic lesions on the feet, often located adjacent to the great toenail (see Ch. 84). The incidence peaks during dry weather. A gravid female flea is typically found within the upper dermis

Fig. 85.6 ***Pulex irritans*****, the human flea.** The body is laterally compressed and no combs are present.

Fig. 85.7 Characteristic train-track hemorrhage associated with exposure to ***Megalopyge opercularis*** **(puss caterpillar).**

CHARACTERISTIC ANATOMIC FEATURES OF SEVERAL COMMON TYPES OF FLEAS	
Flea	**Characteristics**
Pulex	Round frons (forehead); single pair of hairs behind antennae
Xenopsylla	Round frons; several pairs of hairs behind the antennae; pleural rod (vertical thickening in mesothorax)
Ctenocephalides felis	Two ctenidia (combs) on the head*; sloped frons; six hair-bearing notches on dorsal hind tibia
Ctenocephalides canis	Two ctenidia (combs) on the head*; round frons; eight hair-bearing notches on dorsal hind tibia
Sticktight flea	Flat frons; broad lacinia (serrated piercing lance-like mouthpart)
*Resemble a mane of hair and a mustache.	

Table 85.2 Characteristic anatomic features of several common types of fleas.

of the lesions. Infestation most often occurs in beach areas and urban slums, and the flea is common on dogs, cats and rats.

Treatment

Lufenuron, an agent that prevents fleas from reproducing, is effective for animals in oral and injectable formulations. Fipronil is effective as a topical agent for the prevention of flea infestation. Boric acid, growth regulators such as pyriproxyfen, and insecticides may be helpful adjunctive treatments for the infested environment. The best source of information is a knowledgeable veterinarian.

Tungiasis is usually treated surgically. A double-blinded randomized controlled trial of oral ivermectin (300 mcg/kg on two consecutive days) showed it to be ineffective in treating patients with multiple lesions.

Lepidopterism

Key features

- Caterpillar dermatitis is caused by the larval form of a butterfly or moth
- Dermatitis may also result from the hairs or scales of adult lepidopterids
- Severe systemic reactions may occur with some species
- Important cause of ophthalmia nodosa

Introduction

Lepidopterism refers to the broad spectrum of adverse reactions to caterpillars, cocoons, butterflies and moths. Some authors use the term erucism for solely cutaneous reactions to these organisms or specifically for reactions to caterpillars[21,22]. A wide variety of species has been implicated[21].

Pathogenesis

Much of the irritation due to contact with the hairs of lepidopterids is purely mechanical in nature. Toxin-mediated reactions may be related to histamine, kinins, plasminogen activators and other proteinaceous toxins associated with hairs (setae), spines or hemolymph. Allergy usually does not play a significant role in the reactions.

Clinical features

Cutaneous manifestations include pain, pruritus, erythema, swelling, hemorrhage (Fig. 85.7), papules and urticaria. Cutaneous reactions may be accompanied by systemic reactions (e.g. respiratory distress or a bleeding diathesis with intracranial hemorrhage) (Table 85.3). Contact with Australia's white-stemmed gum moth (*Chelepteryx collesi*) produces yellow discoloration of the skin.

Dermatitis due to gypsy moth caterpillars may result from direct contact with the caterpillar or from hairs on clothesline-dried clothing. Erythematous urticarial papules and macular erythema with pruritus are commonly localized to the flanks, feet, inner aspects of the arms and legs, and collar region.

Ocular lesions caused by caterpillar hairs (ophthalmia nodosa) are similar to those caused by tarantula hairs. Ocular reactions to hairs include acute "toxic" conjunctivitis, chronic mechanical keratoconjunctivitis, subconjunctival granulomatous nodules, iritis and vitreoretinal involvement. The hairs tend to migrate inward in the direction of the sharp tip.

Children who ingest caterpillars tend to develop focal or diffuse erythema and edema of the lips, tongue and buccal mucosa. Esophageal and tracheobronchial involvement can also occur. Removal of hairs and spines may require endoscopy.

ARACHNIDS

Tick Bites (Class Arachnida: Subclass Acarina)

Key features

- Hard ticks are important disease vectors (e.g. Lyme borreliosis, RMSF)

CUTANEOUS AND SYSTEMIC REACTIONS ASSOCIATED WITH LEPIDOPTERISM			
Moth/caterpillar common name	**Scientific name**	**Locale**	**Clinical findings**
Gypsy moth caterpillar	*Lymantria dispar*	Northeastern US	"Dermatitis" from direct contact or from hairs on clothesline-dried clothing
Io moth caterpillar	*Automeris io*	US	Immediate stinging sensation, "dermatitis" (often transient urticarial papules)
Saddleback caterpillar	*Acharia stimulea* (formerly *Sibine stimulea*)	US	Immediate stinging sensation, "dermatitis" (often transient urticarial papules)
Buck moth caterpillar	*Hemileuca maia*	Eastern US	Immediate stinging sensation, "dermatitis"
Puss caterpillar	*Lagoa crispata* (also known as *Megalopyge crispata*)	Oklahoma and eastern US	Immediate burning sensation, "dermatitis"; in Oklahoma, spines contain high concentrations of tannins (ingested from oak trees)
Southern flannel caterpillar, puss caterpillar, wooly asp	*Megalopyge opercularis*	Southern US, Mexico and Central America	Immediate intense radiating pain; characteristic "railroad track" pattern of hemorrhage (Fig. 85.7); edema, hives and systemic symptoms may occur
Saturniid moth caterpillar, giant silkworm moth	*Lonomia achelous, L. oblique*	Latin America	Local and severe systemic reactions, especially a bleeding diathesis (with complications such as renal failure)
Processionary caterpillars: pine, Cyprus and oak (characteristically travel single-file)	*Thaumetopoea pityocampa*, *T. wilkinsoni*, *T. processionea*	Mediterranean region, central Europe, Britain	Urticaria (often immunologic), angioedema, anaphylaxis, conjunctivitis, respiratory distress, abdominal pain, hypertension, lytic bone lesions in the digits; airborne urticating hairs are spread by the wind
Pine moth caterpillar and cocoon	*Dendrolimus punctatus*	China, imported elsewhere	"Dermatitis", arthritis (usually monoarticular), chondritis, ophthalmia nodosa
Tussock moth caterpillar	*Orgyia pseudotsugata*	Western US, especially Pacific Northwest	"Dermatitis", pruritus of the skin and eyes as well as respiratory symptoms (irritant and allergic mechanisms); forestry workers
Yellowtail moth (adult female)	*Hylesia metabus*, *H. alinda*	Mexico and South America (including *H. metabus* in the Venezuelan port of Caripito)	Papular urticaria ("Caripito itch"); ship crew members are classically affected

Table 85.3 Cutaneous and systemic reactions associated with lepidopterism. "Dermatitis" can include pruritic urticarial papules as well as eczematous reactions. Tape stripping of skin has been used to identify caterpillar hairs (setae). Caterpillars can have short spines projecting from a long slender shaft or short tapered shafts with ball-in-socket structures resembling trichorrhexis invaginata.

- *Ornithodoros* soft ticks transmit borrelial relapsing fever
- *Dermacentor* ticks hidden in the scalp represent an unusual cause of paralysis
- Correctly identifying the tick allows patients to be counseled appropriately
- Tick control measures are important in preventing disease

Introduction

Patients with tick bites often present with the tick still attached[23]. They are usually aware of the diagnosis, although some individuals may misinterpret the tick as a "new mole". Scalp attachments are particularly common for *Dermacentor* ticks, and the patient may be completely unaware of a tick that is hidden by hair. This is of concern considering that *Dermacentor* ticks produce a neurotoxin that can cause paralysis when these ticks are attached for ≥4 days[24,25]. Symptoms resolve rapidly when the tick is removed, but rare fatalities from tick paralysis have been reported. Any child presenting with rapidly progressive ascending flaccid paralysis should be examined for ticks. In Australia, *Ixodes* ticks can cause paralysis, but this occurs primarily in dogs.

Correct identification of an attached tick provides the physician with an opportunity to discuss tick control measures and symptoms of tick-borne disease[26,27]. Most hard ticks have a three-host life cycle. Larval (seed) ticks have six legs and feed on small animals in nature (see Fig. 76.1). The nymphs and adults feed on larger animals. Nymphs resemble small adult ticks, with eight legs, but are sexually immature. Because they attach for one long blood meal during each phase of the life cycle and search for a new host for each blood meal, ticks are efficient disease vectors. Hard ticks have a hard dorsal plate (scutum) and account for most medically important ticks, transmitting human diseases including Lyme borreliosis, ehrlichiosis, granulocytotropic anaplasmosis and a variety of rickettsial infections (including Rocky Mountain spotted fever; RMSF) (see Table 76.1). Soft ticks such as *Ornithodoros* (the vector of borrelial relapsing fever) lack a scutum and have retroverted mouthparts. These ticks tend to live in close association with a single host.

Clinical features

Once the tick has been removed, hypersensitivity reactions at the site are common. Papular, nodular and vesiculobullous lesions can occur and are typically pruritic. Hypersensitivity reactions presenting as erythematous plaques are commonly misinterpreted as erythema migrans. Nodules with pseudolymphomatous histology can also develop.

Treatment

Milder tick bite reactions may respond to application of a potent (class 1 or 2) topical corticosteroid; lesions may fail to improve unless the agent is occluded. More intense reactions often require intralesional corticosteroid injection, and some only respond to surgical excision. Often, the pruritus is so severe that patients express little concern about the discomfort and scar associated with the surgical procedure.

Most tick-borne diseases respond readily to tetracyclines. Empiric treatment of suspected RMSF is always appropriate, and therapy should never be delayed until confirmatory tests are available. The consequences of delayed diagnosis and treatment of RMSF are evidenced by reports of deaths in children[28]. Doxycycline is the drug of choice for children as well as adults with RMSF. Staining of teeth is unlikely with a short course of doxycycline, and chloramphenicol is less effective for RMSF.

Environmental measures

Exclusion of animal hosts from communities and recreational areas can be helpful in control of tick-borne illness (Table 85.4), although this may be difficult to achieve for small animal hosts (e.g. mice, rabbits). There is evidence that communities located close to wildlife reserves have higher rates of tick-borne illnesses. Oral agents, such as the

TICK CONTROL MEASURES	
Personal	**Environmental**
Protective clothing tightly laced, snapped or tied	Removal of leaf debris
Clothing treated with permethrin	Area acaricide application
Clothing treated with repellents such as DEET	Exclusion of animal hosts
Regular tick inspections	Acaricide-treated feed corn

Table 85.4 Tick control measures.

avermectins, can be placed in corn eaten by deer to kill ticks that feed on the deer. Injectable ivermectin is helpful in reducing tick infestation of livestock. Removal of leaf debris is a critical part of tick control efforts because it: (1) enables acaricides to reach the ticks; and (2) leads to a reduction in tick numbers via dehydration of adults (which require leaf debris to maintain hydration) and eggs (which require sufficient humidity to hatch).

Repellents

Permethrin, a pyrethroid insecticide with little mammalian toxicity, has been marketed as a tick repellent. The spray formulation is the most widely available form. Once applied to clothing, it is stable through several wash cycles. It is also suitable for treating sleeping bags, tents, and fabric used for insect screening. A liquid concentrate has been used to impregnate fabric for as long as the life of the garment. Permethrin is particularly helpful in the prevention of tick and chigger bites. These crawling arthropods must travel across the treated fabric, whereas flying insects tend to be attracted directly to exposed skin. The combination of a DEET-containing repellent and permethrin-treated clothing is generally highly effective against a wide range of biting arthropods.

Some North African camel ticks have demonstrated high-level resistance to permethrin. Instead of killing the tick, permethrin may produce a pheromone-like attachment response. This attachment phenomenon has not yet been described in North American ticks, but permethrin resistance does occur. High-level permethrin resistance in cattle ticks has been linked to outbreaks of bovine babesiosis and anaplasmosis in Mexico[29].

Methods to eliminate and prevent tick infestations in dogs include monthly topical application of products containing fipronil or permethrin, as well as collars impregnated with amitraz and pyriproxyfen[30].

Tick removal

Several plastic tick removal devices are marketed. I have had particular success with the "Tick Nipper™", an inexpensive plastic device that grasps the tick just behind the mouthparts without severing them. Similar devices have been made out of plastic spoons and credit cards with the aid of a sharp pair of scissors or hot blade. Petroleum jelly, fingernail polish, isopropyl alcohol and hot matches are generally ineffective.

Ticks should be removed as completely as possible, and care should be taken not to squeeze the abdomen. Gentle traction is generally preferred, but a twisting motion can also be used. Although the latter technique may leave a small mouth part, this is of little clinical consequence. Hands should be washed if they were in contact with the tick.

Antibiotic prophylaxis after tick bites

Antibiotic prophylaxis after tick bites remains controversial, and most authorities do not recommend its routine use. Certainly, it would be difficult to justify the cost and risks of widespread use of prophylactic antibiotics for every tick bite. On the other hand, if the ticks are correctly identified as endemic disease vectors and are heavily engorged, the risk–benefit ratio may weigh in favor of prophylactic treatment.

If the dose is sufficient and the antibiotic is given at the appropriate time, prophylaxis is capable of preventing tick-borne disease. However, because incubation periods vary, timing of a *single* dose of an antibiotic can be difficult. In the case of RMSF, a single dose can prevent disease if given shortly before the expected onset of illness, but a single dose may only delay the onset of clinical symptoms if administered too early in the course of incubation.

Therefore, because of this difficulty with correct timing, if the decision is made to administer a prophylactic antibiotic, I recommend a full 10-day course of therapy rather than single-dose prophylaxis. This recommendation also applies to *Ixodes* tick bites and Lyme disease; however, some authors do recommend single-dose prophylaxis for Lyme disease on a case-by-case basis (see Ch. 19). A controlled trial compared 10 days of oral doxycycline (with or without a single intravenous dose of ceftriaxone) versus 20 days of oral doxycycline for the treatment of early Lyme disease. During a 30-month follow-up, the response rate was similar for all three treatment groups in both on-study and intention-to-treat analyses.

Special consideration must be given to the prophylactic treatment of pregnant women. In such cases, the risks of prophylactic therapy for both the mother and the unborn child must be weighed against the risks and responsiveness to treatment of disease in both individuals.

Amblyomma Ticks

Synonym: ■ Lone star tick

Key features

- Ornate scutum (hard dorsal plate)
- Single white dorsal spot on female *Amblyomma americanum*
- Papular, nodular and bullous lesions at attachment sites
- *Amblyomma* ticks are vectors of ehrlichiosis, several rickettsial infections, southern tick-associated rash illness (STARI), and tularemia

Introduction

Amblyomma ticks are particularly common in the southern US. This, plus the characteristic white dorsal spot of the female *A. americanum* (Fig. 85.8), has given rise to the common name "lone star tick". Males have ornate markings that often form pale "inverted horseshoes" on the posterior portion of their dark scutum. *Amblyomma* ticks have prominent eyes, festoons (grooves in the posterior edge of the scutum) and long anterior mouthparts.

A. americanum has a wide distribution, from Texas to Iowa and Connecticut (see Fig. 76.10). The range of this tick is expanding, partly because of the explosion in the white-tailed deer population[31]. Other species of *Amblyomma* ticks are common in Africa, the Caribbean, and Central and South America. Some *Amblyomma* ticks attach to birds, and migration of avian hosts has been implicated in dissemination of tick-borne diseases.

Clinical features

Amblyomma tick attachments favor the legs, buttocks and groin and often affect people who work outdoors or take part in outdoor recreation (e.g. construction workers, fishermen, hunters, hikers), especially when new development displaces the tick's usual hosts. Patients usually become aware of *Amblyomma* tick bites while the tick is still attached. This is partly because the ticks often attach in large numbers. Once the tick has been removed, delayed-type hypersensitivity to tick antigens can lead to a reaction at the attachment site. Papular, nodular and bullous lesions are common.

A. americanum is the major vector of *Ehrlichia chaffeensis*, the agent of human monocytotropic ehrlichiosis[32]. This disease has been documented in more than 30 states, with systemic symptoms similar to those of RMSF (e.g. fever and headache) and variable cutaneous manifestations (see Ch. 76). *A. americanum* is also the primary vector for *Ehrlichia ewingii* infection.

Southern tick-associated rash illness (STARI; "Missouri Lyme disease") was originally described in Missouri but can also occur in other southern states[33]. It presents with an expanding erythematous annular plaque 3–14 days after *A. americanum* attachment, often in association with fever, headache, myalgias and arthralgias. Although the symptoms resemble those of Lyme disease, *Borrelia burgdorferi* does not appear to be involved, other infectious agents (e.g. *Borrelia*

Fig. 85.8 ***Amblyomma americanum*** **(lone star tick).** Note the characteristic white dorsal spot on the female ticks. The female's scutum often covers only a portion of the body to allow room for engorgement.

lonestari) have not been consistently identified, and the cause remains unknown.

Amblyomma ticks have been implicated in the transmission of RMSF (*Rickettsia ricketsii*; primarily in Central and South America, where it may be referred to as Brazilian spotted fever), American tick bite fever (*Rickettsia parkeri*), African tick bite fever (*Rickettsia africae*) and tularemia (see Chs 74 & 76).

Dermacentor Ticks

Synonyms: ■ *D. andersoni:* Rocky Mountain wood tick ■ *D. variabilis*: American dog tick

Key features

- Large ticks
- Ornate scutum (hard dorsal plate) with deep punctuations
- The adult tick prefers to attach to the head, neck and shoulder
- *D. variabilis* is the major vector for RMSF in the United States, while *D. andersoni* can transmit Colorado tick fever as well as RMSF

Introduction

Dermacentor ticks are commonly found in open areas with low bushy vegetation, but they are scarce in heavily wooded areas. Peak abundance of the tick is in April and May, declining by July. *Dermacentor* ticks have an ornate scutum, prominent eyes and festoons (grooves in the posterior scutum), small anterior mouthparts, and a rectangular basis capituli. Both *D. variabilis* (Fig. 85.9) and *D. andersoni* have brown legs, and coxa 1 (the attachment base for the first pair of legs) is bifid. Coxa 4 is greatly enlarged in the male, and males have no ventral plates. As in most hard ticks, the scutum in the female is smaller, leaving a portion of the abdomen exposed.

D. variabilis is found throughout the US, except for the Rocky Mountain states. In parts of Canada, its range overlaps with that of *D. andersoni*, which is generally confined to the Rocky Mountains. In Georgia and South Carolina, *D. variabilis* is the second most common tick found on humans (*A. americanum* being the most common).

Pathogenesis

During the course of engorgement, *D. andersoni* saliva downregulates cell-mediated immunity. This phenomenon may explain the delayed onset of many nodular tick bite reactions. It might represent an adaptive mechanism, allowing the tick to feed unnoticed.

Clinical features

Dermacentor ticks preferentially attach to the head and neck region; in contrast, *Amblyomma americanum* prefers the lower legs, buttocks and groin, and *Ixodes scapularis* shows less site preference but most often attaches to the trunk. Prolonged attachment of a *Dermacentor* tick is the most frequent cause of tick paralysis in the US (see above).

Fig. 85.9 ***Dermacentor variabilis*** **tick (engorged female) with an ornate scutum.** This species is the major vector for Rocky Mountain spotted fever in the US.

D. variabilis is the major vector for RMSF in the US. The highest incidence of RMSF is in the eastern states where this tick resides, especially in North Carolina (see Fig. 76.2). RMSF typically presents with fever and headache. An acral eruption of erythematous macules and/or petechiae may be evident but is commonly absent, especially early in the disease process. As many as 40% of patients with RMSF are not aware of a recent tick bite. As the mortality rate in RMSF is heavily dependent on the time between onset of symptoms and initiation of antibiotic therapy, the disease should be considered in every patient with fever and a headache in endemic areas.

D. andersoni is the major vector for RMSF in the Rocky Mountain states, and it is also the vector for the viral illness Colorado tick fever. Because the symptoms of Colorado tick fever overlap with those of RMSF, specific diagnostic tests such as paired serologic studies (acute and convalescent) and immunohistochemical staining, direct immunofluorescence or PCR-based analysis of lesional skin biopsy specimens can help to confirm the diagnosis of RMSF (although empiric treatment should not be delayed until the results are available). Additional diseases that can be transmitted by *Dermacentor* ticks include tularemia, rickettsial infections in Europe and Asia, and (occasionally) monocytotropic ehrlichiosis and Q fever (*Coxiella burnetii*).

Rhipicephalus Ticks

Synonym: ■ Brown dog tick

Key features

- Common dog ticks
- Most are brown with brown legs, a teardrop shape and inornate scutum (hard dorsal plate)
- Vectors for Boutonneuse fever and (occasionally) RMSF in the southwestern US

Introduction

Rhipicephalus ticks (Fig. 85.10) are common dog ticks that are typically brown in color with an inornate scutum. They have prominent eyes and festoons (grooves in the posterior scutum), but small mouthparts attached at a hexagonal basis capituli.

Fig. 85.10 ***Rhipicephalus*** **ticks.** Common brown dog ticks; the lower tick is engorged with blood.

Fig. 85.11 ***Ixodes scapularis*** **tick.** The inornate brown scutum is overshadowed by the large, cream-colored, engorged abdomen.

Clinical features

Rhipicephalus ticks carry RMSF (primarily in the southwestern US and Mexico) and Boutonneuse fever (see Ch. 76). They may also be vectors for Congo-Crimean hemorrhagic fever virus, although *Hyalomma* ticks usually transmit this condition.

Ixodes Ticks

Synonyms: ■ Black-legged tick ■ Deer tick

Key features

- Teardrop shape, often with dark legs
- Inornate brown scutum (dorsal hard plate) that is small relative to the large abdomen in females
- Vectors for Lyme disease, human granulocytotropic anaplasmosis, and babesiosis

Introduction

Ixodes scapularis (formerly also known as *I. dammini*), the eastern black-legged tick, is the best known of the *Ixodes* ticks. Adult females are typically found attached to the host in late fall and spring. Their small, inornate brown scutum is often overshadowed by a large, soft, cream-colored engorged abdomen (Fig. 85.11). These ticks have short anterior mouthparts, prominent broad "antennae" and an upside-down U-shaped ventral groove with its apex anterior to the anus.

Clinical features

Ixodes ticks are vectors for Lyme disease, babesiosis and human granulocytotropic anaplasmosis[34,35]. Babesiosis is a malaria-like illness, whereas anaplasmosis is an acute febrile illness characterized by leukopenia, thrombocytopenia and increased serum hepatic transaminases. In the western US, *I. pacificus* (the western black-legged tick) is the major vector for Lyme disease (see Fig. 76.10). In the Great Lakes region and eastern US, *I. scapularis* is the major vector. *I. ricinus* and *I. persulcatus* are important vectors for Lyme disease in Europe and Eurasia, respectively. Because the larval and nymph stages of the tick often attach to birds in the spring and summer, avian migration (particularly of robins) may be responsible for the broad geographic distribution of the tick and of Lyme disease.

A single *Ixodes* tick may transmit more than one disease. In one study of a rural New Jersey county, 55% of adult *I. scapularis* ticks carried at least one disease (Lyme disease, 43%; babesiosis, 5%; anaplasmosis, 17%) and 10% carried more than one of the three diseases. Co-infection with more than one of these three diseases is also common in Wisconsin and Minnesota, and *I. scapularis* has been reported to carry both Lyme disease and anaplasmosis in New York City parks. *Ixodes* ticks carry viral encephalitis in Europe and transmit rickettsial infections in Europe and Australia (see Table 76.1).

Mites (Class Arachnida: Subclass Acarina)

Key features

- Mites are identified by their mouthparts and legs; the shape of their body, dorsal plates, and shields (sternal, anal and genitoventral); and the setae (bristles or hairs) on the latter structures
- Trombiculid mites are typically larval (chiggers; six-legged) when attached to a host; they are vectors for scrub typhus
- *Cheyletiella* mites are commonly found on pets and may produce papular or vesiculobullous lesions in the owner
- Species that parasitize birds, mammals and grains can produce dermatoses; the house mouse mite is a vector for rickettsialpox

Introduction

Mites are small arachnids that range from 0.1 to 2 mm in length. Tens of thousands of species exist worldwide (Table 85.5). The majority are free-living, but thousands of species parasitize animals or plants. Like fleas, most mites lack host specificity. Mites of medical importance may cause skin lesions, incite allergic reactions (especially in atopic individuals), or spread disease (Table 85.6). Like ticks, mites mature through larval, nymph and adult stages. Typically, there is a single larval stage (referred to as chiggers in trombiculid mites) and several nymphal stages. Most mites lay eggs, but some, such as the spiny rat mite (*Laelaps echidninus*), are viviparous, producing non-motile larvae. The

MITE FAMILIES	
Acaridae	Food mites
Demodicidae	Follicle mites
Dermanyssidae	Bird, rodent mites
Glycyphagidae	Food mites
Haemoganasidae	Straw mites
Psoroptidae	Mange, scab mites
Pyemotidae	Grain mites, straw mites
Sarcoptidae	Scabies mites
Trombiculidae	Chigger, harvest mites

Table 85.5 Mite families.

MITES OF MEDICAL IMPORTANCE	
Acarus siro	Grain mite: hay, grain, house dust
	Baker's itch
Cheyletiella spp.	**Walking dandruff on pets**
Cheyletus malaccensis	Wheat mite
	Wheat warehouse itch (Japan)
Demodex spp.	**Folliculitis; possibly rosacea, blepharitis; demodectic mange in dogs and cats**
Dermanyssus gallinae, *D. avium*	Fowl mite: chickens, wild birds, rodents, rabbits
Dermatophagoides farinae, *D. pteronyssinus*	Dust mite (**allergy**): dust, blankets, mattresses, pillows, pets, stored foods and grains
Euroglyphus maynei	Dust mite (**allergy, cross-reactions with other dust mites**)
Glycyphagus domesticus	Cheese mite, barn mite, grocer's mite: cheese, grains, hay, mattresses
	Grocer's itch
Laelaps spp., *Androlaelaps* spp., *Eulaelaps* spp.	Rodent mites
Lepidoglyphus destructor	Dust mite, hay mite
Liponyssoides (Allodermanyssus) sanguineus	House mouse mite
	Rickettsialpox
Neotrombicula autumnalis	Harvest mite (Northern Europe)
Ophionyssus natricus	Snake mite
Ornithonyssus sylviarum, *O. bacoti*, *O. bursa*	Tropical rat mite, fowl mite, tropical fowl mite, northern fowl mite: rodents, chickens, wild birds, carnivores
Pyemotes ventricosus, *P. tritici*	Straw itch mite, grain mite: parasites of insects in grains and straw
Trombicula (Eutrombicula) alfreddugesi	Chigger mite, red bug
Trombicula (Leptotrombidium) akamushi, *L. deliense*, *L fletcheri*, *L arenicola*, *L. pallidum*, *L. pavlovskyi*, *L scutellare*	Scrub mite
	Scrub typhus
Tyrophagus putrescentiae	Mold mite, grain storage mite
	Copra itch

Table 85.6 Mites of medical importance. Scientific names, common names and associated diseases (in bold) are listed.

straw itch mite (*Pyemotes tritici*) retains its young until they emerge as sexually mature mites. Sarcoptic mites are relatively species-specific and complete their entire life cycle on the host (see Ch. 84).

Clinical features

Cutaneous reactions to mites are common and include papular, papulovesicular, bullous, urticarial and morbilliform eruptions (Fig. 85.12).

Fig. 85.12 Avian mite bites. Multiple erythematous pruritic papules, several of which have hemorrhagic crusts. The exposure was birds nesting on the patient's house. *Courtesy, Jean L Bolognia, MD.*

PREPARATION OF COLLECTED MITES FOR MICROSCOPIC EXAMINATION
PREFERRED METHOD
• Clear with either lactic acid or lactophenol (may take hours to days) • Wash with water • Mount in Hoyer's medium*
RAPID METHOD
• Mount live or alcohol-fixed mites directly in Hoyer's medium* • Mount live mites in Permount™ (details of mites less obvious)
*Prepared by adding 30 g of gum Arabic to 50 ml distilled water, then adding 200 g chloral hydrate followed by 20 g glycerin; filter through cheesecloth.

Table 85.7 Preparation of collected mites for microscopic examination. If mites are collected onto filters inside a vacuum cleaner, the filter samples are treated with KOH, then floated in a concentrated sugar solution to collect the mites.

Chigger bites most often affect the lower legs, skin at the edges of underwear, and the genital region. Larvae of trombiculid mites in Asia are vectors for scrub typhus, while house mouse mites transmit rickettsialpox (see Ch. 76). Eschars at the site of the bite are a clue to rickettsial disease, and serologic testing can be helpful. As with tick-borne rickettsial diseases, biopsy of the eschar can be sent for immunohistochemical staining to distinguish typhus group organisms from the spotted fever group.

Differential diagnosis

Mite-induced dermatoses are often misdiagnosed. Bullous lesions are especially common, and false-positive direct immunofluorescence has been described. Histologic features resembling those of an insect bite may suggest the correct diagnosis, as may a clinical pattern of skin lesions corresponding to areas of contact. However, eosinophil-filled subepidermal bullae occur in both mite infestation and pemphigoid, so a careful history is essential.

Mite-induced dermatitis can be associated with pets, rodents, straw bedding, bird nests, grains and even onion bulbs (see Table 85.6). Avian mite dermatitis may also be associated with pet rodents, such as gerbils. Pets should be examined by a knowledgeable veterinarian, and skin scraping, adhesive tape stripping or biopsy may reveal the mite(s) on the animal. Vacuum cleaners can also be fitted with filters to collect mites (Table 85.7). Another helpful technique is to spray areas of dandruff or crust on a pet with an acaricidal agent recommended by a veterinarian. A fine-toothed comb or toothbrush is then used to remove the scale-crust, which is placed in a sealed bag. When alcohol is added to the bag, scale-crust and hair will sink, whereas mites will float.

Treatment

Some types of mites inflict a "bite and run" injury, while others remain attached for a prolonged meal. Scraping, tape stripping or vigorous washing with soap and water are all effective in removing or killing many of the attached mites. Scrapings, tape strippings and biopsy specimens may be helpful diagnostically as well as therapeutically.

Definitive treatment requires avoidance or treatment of the infested source. Mite identification can be helpful in establishing the likely source. Management of free-living, zoonotic and grocery mites will differ. An acarologist can be of immeasurable value in this setting. Gary Mullen and Lance Durden have written a superb text that I strongly recommend entitled "Medical and Veterinary Entomology". As noted above, animals should be examined and treated by a veterinarian. In public parks and training areas, animal exclusion and acaricides may be helpful measures. Personal protection with permethrin-treated clothing is also of value.

Skin lesions in humans may be treated with topical antipruritics such as camphor and menthol, or with topical anesthetics such as pramoxine. Potent topical corticosteroid preparations can be helpful, especially when occluded. Intralesional corticosteroid injections and excision of pruritic nodules may be necessary. Bullous and excoriated lesions can develop secondary infections, and wound care is important. Popular home remedies typically center around efforts to remove or kill attached mites, and counterirritants (e.g. propylene glycol in deodorant sticks) are often applied in an effort to reduce itching. Patients may present with irritant and allergic contact dermatitis to antiseptics, nail polish or even battery acid.

Chiggers

Introduction

Trombiculid mites are oviparous, depositing their eggs on the ground, leaves or blades of grass. After several days, the egg cracks, but the mite remains in a quiescent prelarval stage. After the prelarval stage, the six-legged larvae (chiggers) actively search for a suitable host. It is the larval mite that is found attached to the host. After a prolonged meal, the larvae drop off and mature through the eight-legged free-living nymph and adult stages.

Clinical features

Chigger bites are intensely pruritic, especially in highly sensitized individuals. Grouped papules, vesicles or bullae are typically found on the lower extremities, or where elastic meets the skin. Seasonal penile swelling associated with pruritus and dysuria in children is referred to as the "summer penile syndrome", and it appears to represent a hypersensitivity response to chigger bites.

Treatment

The topical antipruritics and anesthetics discussed above may be helpful. Most patients presenting to a dermatologist require potent topical or intralesional corticosteroid therapy. Vigorous washing with soap and water immediately after the exposure is helpful. Treatment of clothing with permethrin is a useful strategy for prevention.

Cheyletiella

Introduction

Cheyletiella are non-burrowing mites that are commonly found on cats (*C. blakei*), rabbits (*C. parasitovorax*) and dogs (*C. yasguri*). In humans, they are a frequent cause of cryptic mite-induced dermatitis. Infestations in animals are variably pruritic and produce a subtle dermatitis that presents with dry white scales, which is sometimes termed "walking dandruff". The animal should be evaluated by a veterinarian, and it is important to note that a single negative scraping does not exclude cheyletiellosis. In a study of dogs with *Cheyletiella*, samples collected by using a vacuum cleaner on the dog were shown to be significantly more sensitive than tape stripping, hair plucking, or skin scraping.

Clinical features

The typical patient with *Cheyletiella* dermatitis is a young or middle-aged woman who presents with grouped pruritic papules (Fig. 85.13).

Fig. 85.13 ***Cheyletiella*** **bites.** These mites are non-burrowing and are found on cats, rabbits and dogs.

It is uncommon to find the mite on the patient. Bullous eruptions caused by *Cheyletiella* mites may also mimic immunobullous disease (see above section).

Treatment

Skin reactions in humans should be treated as described above. Ectoparasitic dips or shampoos are often used by veterinarians to treat the infested animal. Fipronil (in a pump spray formulation applied to the animal) can be used in conjunction with permethrin spray (applied to the environment) to treat canine cheyletiellosis. Topical amitraz (used to treat canine scabies) may also be effective for *Cheyletiella*.

Spider Bites (Class Arachnida: Order Araneae)

Introduction

Spiders are arachnids, related to scorpions, ticks and mites. Many species of toxic spiders are found worldwide. The bite of *Phoneutria* wandering spiders in Brazil can be fatal in children, but most spider bites result only in a local cutaneous reaction. Toxic spiders are often regional in distribution, and many are poorly characterized. The most clinically significant spiders are discussed below. It is noteworthy that many important species in the US were not native to North America, but were imported in recent years as a result of worldwide travel and commerce. Examples are the hobo spider and *Loxosceles laeta* spider.

Widow Spiders (*Latrodectus*)

Key features

- Black widows are large, shiny black spiders with a round abdomen
- A variety of black, brown and red widow spiders exist worldwide
- In *Latrodectus mactans*, a red hourglass shape is seen on the ventral abdomen
- Acute pain and edema occurs at the bite site
- Systemic symptoms mimic acute abdomen and may include rhabdomyolysis

Introduction

Widow spiders (*Latrodectus* spp.) are found worldwide, with five species (including black, brown and red variants) in North America alone. *Latrodectus mactans* is the most common black widow spider in North America, with a range that extends to the Caribbean islands. *L.*

tredecimguttatus, *L. curacaviensis* and *L. indistinctus* are black widow spiders found in Europe, South America, and Africa (where referred to as a button spider), respectively. Female black widow spiders from North American species have a red hourglass-shaped mark on the ventral abdomen, while other species from various areas of the world have different red patterns. Brown (*L. geometricus*) widow spiders (characterized by an orange ventral hourglass shape) have a widespread distribution that includes the US, South America, and Africa. Australia has the red-back spider (*L. hasselti*) and New Zealand the red katipo spider (*L. katipo*).

Widow spiders are typically found in woodpiles, in shoes and under outhouse seats. Human envenomation usually occurs when the spider's environment is disturbed, and the spider is inadvertently trapped or pressed against the skin. Widow spiders are more aggressive when protecting an egg sack.

Pathogenesis

Black widow venom contains latrotoxins that act by depolarizing neurons, increasing intracellular calcium and stimulating uncontrolled exocytosis of neurotransmitters. Divalent cation-dependent tetramers related to α-latrotoxin can insert into lipid bilayers, forming membrane pores. Calcium-independent receptors for latrotoxin have also been identified.

Clinical features

The degree of morbidity caused by widow spider bites varies depending upon the species, age and sex of the spider (with only adult females capable of envenomation), amount of venom injected and site of the bite. Local skin reactions are usually limited to transient erythema, edema, sweating and piloerection. Extracutaneous manifestations are often prominent and can include painful muscle spasms (initially around the bite site, then more widespread), symptoms suggestive of an acute surgical abdomen, headache and nausea; generalized diaphoresis may also occur. The symptoms of brown widow bites tend to be milder and restricted to the tissues near the bite.

Treatment

Benzodiazepines and intravenous calcium gluconate can be helpful for associated tetany. In one study, calcium gluconate was shown to be superior to methocarbamol (Robaxin®). Antivenin can produce rapid relief of tetany and complications such as priapism that are unresponsive to other agents.

Loxosceles Spiders

Key features

- Brown recluse spider (*Loxosceles reclusa*) has a small body and long legs
- Dark brown fiddle pattern present on cephalothorax
- Dermonecrotic reactions
- Systemic reactions include shock, hemolysis, renal insufficiency and disseminated intravascular coagulation
- Other *Loxosceles* spiders can produce similar reactions

Introduction

Loxosceles spiders are found throughout the world and classically have a dark brown violin-shaped marking on the dorsal cephalothorax (Fig. 85.14). In the US, bites from *L. reclusa* (the brown recluse spider), *L. laeta*, *L. rufescens*, *L. deserta* and *L. arizonica* can cause skin necrosis, although reactions to the last three species are generally mild. Many other spiders are capable of producing dermonecrotic or systemic reactions, and bites of other spiders are often erroneously attributed to the brown recluse spider. Brown recluse spiders are most common in the south central US, from Tennessee and Missouri to Oklahoma and Texas (Fig. 85.15). They are often found in woodpiles, in attics and under radiators.

Most bites occur when the spider has been disturbed. *Loxosceles* spiders are non-aggressive, and there are reports of families living in houses infested by thousands of brown recluse spiders without a single bite. This suggests that brown recluse bites are over-diagnosed, especially in regions where the spider is rare. The diagnosis can be confirmed either by an enzyme immunoassay to detect *Loxosceles* venom in a skin biopsy or plucked hairs (obtained up to 4 days after the bite) or by a passive hemagglutination inhibition test (as long as 3 days after the bite).

Fig. 85.14 Brown recluse spider (*Loxosceles reclusa*). This spider has a small body, long legs, three pairs of eyes, and a dorsal violin pattern on the cephalothorax.

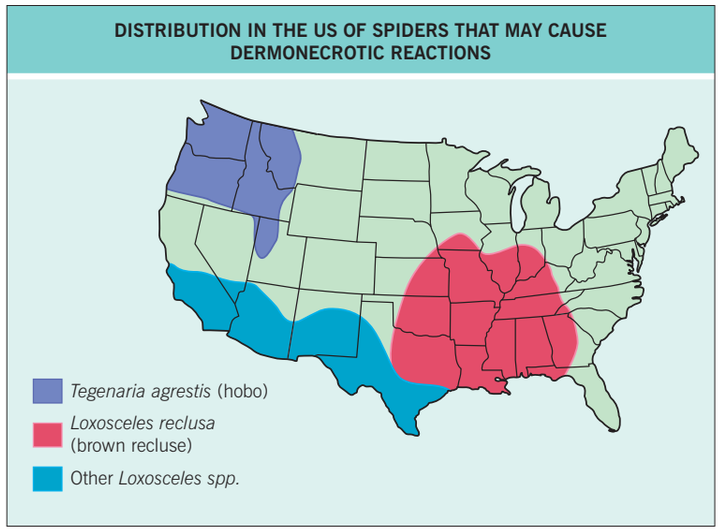


Fig. 85.15 Distribution in the US of spiders that may cause dermonecrotic reactions. *Adapted from: Sams HH, Dunnick CA, Smith ML, et al. Necrotic arachnidism. J Am Acad Dermatol. 2001;44:561–73.*

Pathogenesis

Sphingomyelinase D is the major toxin in brown recluse venom, and it interacts with serum amyloid protein. Hyaluronidase allows eschars to spread in a gravity-dependent fashion. Neutrophils are not directly activated by the venom, and neutrophil activation may be dependent upon the interaction between the venom and endothelial cells. The venoms of geographically diverse spiders such as *L. reclusa*, *L. laeta*, *L. deserta*, *L. gaucho* and *L. intermedia* have similar sphingomyelinase activity and electrophoretic profiles, with a major protein band at 32–35 kDa. All contain hyaluronidase as well as metalloproteinases with fibrinogenolytic activity. The similarity of these venom components and documented cross-reactivity suggests the potential for a single global *Loxosceles* antivenin[36].

Clinical features

Even in the case of brown recluse spiders, the majority of bites do not cause serious reactions. Local pain is frequently delayed until several hours after the bite, which most often occurs on an extremity. Cutaneous reactions typically begin with erythema and then develop central vesiculation or duskiness with a blanched halo, which may evolve into hemorrhagic bullae and necrosis (Fig. 85.16)[37]. Dermonecrotic reactions can eventuate in dry, necrotic eschars or ulceration. Upper airway obstruction caused by envenomation of the neck by brown recluse spiders has been reported. Systemic reactions include disseminated intravascular coagulation (DIC) and Coombs'-positive hemolytic anemia[38,39]. *L. arizonica*, a spider found in the southwestern US, causes less severe necrosis but has been implicated as a cause of shock.

Pathology

Histologic findings have been best described in laboratory models of brown recluse spider envenomation in rabbits[40]. The findings are time-dependent, with early biopsy specimens demonstrating a neutrophilic infiltrate. Later changes include "mummified" coagulative necrosis of the epidermis, adnexal epithelium and superficial dermis. A neutrophilic band-like infiltrate may still mark the border between viable skin and eschar. Small vessel vasculitis and thrombosis are often evident adjacent to the neutrophilic band, and larger vessel vasculitis resembling polyarteritis nodosa may account for the extent of tissue necrosis seen after some bites. Arterial thrombosis leading to gangrene of the foot has been reported[41].

Treatment

Optimal treatment to prevent dermonecrotic reactions remains elusive. Most bites can be treated with rest, ice and elevation. Intradermal injection of polyclonal anti-*Loxosceles* Fab antibody fragments can attenuate necrosis in an animal model up to 4 hours after envenomation, and antivenin may reduce the ultimate size of the necrotic area even when administered up to 48 hours after envenomation[42]. Hyperbaric oxygen therapy may decrease the final size of ulceration, although results have varied. Studies with more widely available agents such as dapsone, colchicine, triamcinolone and prednisone have been inconsistent and often disappointing. Dapsone therapy is complicated by the potential for hemolysis, especially in individuals who have an inherited glucose-6-phosphatase dehydrogenase (G6PD) deficiency. Given the potential for harm and the lack of consistent data showing any benefit, I do not recommend therapy with any systemic agent except antivenin (if available) and prednisone (in the case of systemic reactions). On the basis of anecdotal human data and limited animal data showing some suggestion of efficacy, intralesional triamcinolone can be tried[43].

Funnel Web Spiders

Key features

- Large, hairy, aggressive spiders found in dark, moist areas such as basements
- Funnel-shaped webs
- *Tegenaria agrestis* (hobo spider, aggressive house spider), found in the northwestern US, Canada and Europe, is 4–5 cm in diameter and may cause necrotic arachnidism
- Other funnel web spiders can produce local and systemic reactions

Introduction

When *Tegenaria agrestis* (hobo spider) was imported to North America from Europe, this funnel web spider found few major competitors and became common in human dwellings in the northwestern US (see Fig. 85.15), usually in basement webs at soil level in contact with concrete or stone. In Europe, the hobo spider has a largely rural habitat while the less aggressive *T. gigantea* (also known as *T. duellica*; giant house spider) and *T. domestica* (domestic house spider) are more likely to be found in human dwellings. The sternum of the hobo spider has a lightly colored center, with dark vertical bands on the sides. Medically important funnel web spiders are also found in Australia.

Fig 85.16 Brown recluse spider bite with central dusky necrosis.

Pathogenesis

Hobo spider toxins may cause local necrosis and directly affect the CNS. Australian funnel web spider robustoxin binds to autonomic and motor neurons. Agatoxins from *Agelenopsis apena*, the native American funnel web spider, target ion channels.

Clinical features

T. agrestis bites may produce necrosis, although there are few dermonecrotic reactions to bites from this spider documented in the literature. Bites are uncommon in Europe, because the spider is rarely found in European homes. Systemic symptoms can include headache, nausea and weakness; hemolysis and thrombocytopenia may also occur. Bites of Australian mygalomorph spiders, including the funnel web spiders of the genera *Hadronyche* and *Atrax* and mouse spiders of the genus *Missulena*, are often associated with severe pain, puncture marks, local redness and bleeding. Severe systemic symptoms (including myocardial injury) are more likely with funnel web spiders than with mouse or trapdoor mygalomorph spiders.

Tarantulas (Family Theraphosidae)

Key features

- Typically large hairy spiders, up to 15 cm in diameter
- Normally non-aggressive
- Urticating hairs are thrown at skin and eyes
- Important cause of ophthalmia nodosa

Introduction

Tarantulas are large hairy spiders common in the southwestern US. Many related species occur throughout the world. They are often sold in pet stores. Most tarantula bites do not produce severe systemic toxicity.

Many species of tarantulas possess urticating hairs in a characteristic patch on the dorsal abdomen. These hairs are used in a defensive fashion to drive predators from the spider's burrow. Vibrations of the hind legs are used to flick hairs at the perceived attacker. Urticating hairs are absent on most African and Asian species.

Clinical features

Itching at the site of urticating hair penetration may persist for several weeks after exposure. Hairs that penetrate the cornea can result in ophthalmia nodosa, a chronic granulomatous reaction that can lead to loss of vision.

Pathology

Urticating tarantula hairs penetrate the stratum corneum and epidermis and may extend as deep as the reticular dermis.

Scorpions (Class Arachnida: Order Scorpiones)

Key features

- Large anterior claws
- When threatened, the long tail is curved upward to sting
- Blunt thorn on the tail of *Centruroides* spp.

Introduction

Many toxic scorpions exist worldwide. Scorpions are typically found under tabletops, in woodpiles and in shoes. They sting when disturbed and accidentally trapped by a hand or foot. Several clinically relevant species are listed in Table 85.8.

Clinical features

Local and systemic symptoms (e.g. pain, paresthesia) are typically out of proportion to cutaneous signs such as erythema and edema, which are not usually prominent at the site of the sting.

Treatment

Antivenin is available in endemic areas and, along with supportive care, has been shown to reduce morbidity and mortality from severe scorpion envenomation[44,45]. However, application of ice is sufficient for most minor scorpion envenomations[46].

DIFFERENT SPECIES OF CLINICALLY IMPORTANT SCORPIONS

Locale	Species	Comments
Africa	*Parabuthus granulatus, P. capensis, P. transvaalicus, Uroplectes lineatus* and *Leiurus quinquestriatus*	Fat tails; highly toxic
Asia and North Africa	*Androctonus australis* and *Buthus occitanus tunetanus*	
Asia	*Androctonus crassicauda*	
Brazil	*Tityus serrulatus*	Yellow in color; implicated as a cause of death in children
Southwestern US, especially Arizona	*Centruroides exilicauda*	Rarely associated with deaths; public health risk has been overestimated
Central US, especially Texas	*Centruroides vittatus*	Painful sting
US, Mexico and Central America	*Centruroides noxious, C. limpidus* and C. *suffusus*	Toxic; some deaths attributed to *Centruroides exilicauda* may be due to these species

Table 85.8 Different species of clinically important scorpions.

CENTIPEDES (CLASS CHILOPODA) AND MILLIPEDES (CLASS DIPLOPODA)

Key features

Centipedes

- Long, worm-like bodies that are flattened dorsoventrally
- 17 or more segments; up to 20 cm in length
- Each segment, except the last one, has one pair of legs
- Pain, edema and erythema at bite sites

Millipedes

- Long, cylindrical, worm-like bodies with many segments
- Each segment has two pairs of legs and two pairs of respiratory spiracles
- Do not bite (biting jaws are absent), but can cause chemical irritant contact dermatitis

Introduction

Centipedes are fierce hunters. They inject a neurotoxic venom through venom ducts in their jaws. Millipedes do not bite but can cause burn-like reactions.

Clinical features

Centipede bites may produce pain, erythema and edema. They can bleed profusely and are frequently associated with paresthesia. Centipede ingestion by children can result in systemic toxicity. Rarely, bites lead to severe systemic symptoms such as coronary ischemia, rhabdomyolysis, proteinuria and renal failure. The Vietnamese centipede, *Scolopendra subspinipes*, is a large, aggressive tropical centipede that has recently become popular as a pet, and local bite reactions can be severe.

Millipedes do not bite, but they can secrete noxious substances that result in a chemical irritant contact dermatitis. Millipede burns frequently involve the eyes, and millipedes in line-dried clothing can produce widespread dermatitis. Of note, millipede burns and associated brownish skin discoloration (which can persist for months) may be misdiagnosed as child abuse.

Treatment

Centipede bites seldom require more than symptomatic treatment, although systemic symptoms may be very frightening to the patient. Children bitten by a centipede often report they have been bitten by a snake. The minor degree of edema compared to that associated with snake bites as well as the characteristic chevron shape of the centipede bite can be helpful distinguishing features. Ice packs, analgesics and hot water immersion provide similar improvements in pain after centipede envenomation[47], and ice is the most easily administered of these treatments.

SNAKE BITES

Key features

- Rapid onset of pain and swelling
- Symptoms depend on species and amount of venom injected
- Antivenin may be life-saving, but it does not prevent all complications and may cause anaphylaxis

Introduction

Snake bites occur primarily in individuals who engage in outdoor activities, especially camping and hiking. Occupational bite injuries may also affect those who raise snakes and are particularly common in those who extract venom. Death from a snake bite is rare in the US, but more common in Africa and Asia[48]. Although the overall incidence of severe rattlesnake bites in the US has decreased over time, the incidence of fatal rattlesnake bites has remained relatively stable[49].

Clinical features

Snake bites are typically associated with marked edema within an hour of the envenomation. Hemorrhage and necrosis are common. The presence of paired bite marks is often noted.

Treatment

Antivenin therapy is an important part of management and may be of benefit even after significant delays in administration. Adverse reactions to antivenin usually take the form of serum sickness or anaphylaxis. Preparations to treat anaphylaxis should be made before initiating antivenin therapy. Hypersensitivity to antivenin is a particular problem

for those who have been previously treated. The evaluation of antivenin reactions is complicated because serum sickness and snake bites share some signs and symptoms, and repeated snake bites can be independently associated with IgE-mediated anaphylaxis. Even in individuals who have never received previous treatment, snake antivenin can result in anaphylactoid reactions.

Thrombocytopenia induced by rattlesnake venom is only partially reversed by Antivenin (Crotalidae) Polyvalent administration, and DIC caused by North American crotalid snakebites can occur even after antivenin treatment. DIC also occurs with envenomation by some exotic vipers. In India, where the cost of antivenin therapy is a critical factor, low-dose regimens have been shown to be an effective alternative. However, data on Australian brown snake envenomation suggest that many patients are underdosed with antivenin.

Tourniquets have been associated with tissue ischemia if improperly applied. Studies have not been performed for all snakes, but for at least some, tourniquet application appears to be of little benefit.

DOG AND CAT BITES

Key features

- Bites may be unprovoked, especially with dogs
- Infection is common and pathogens include *Pasteurella* spp. and *Capnocytophaga canimorsus*
- Antibiotic treatment is generally considered mandatory

Introduction

Cat bites are commonly provoked, whereas the majority of dog bites are unprovoked[50]. Dog bites are particularly common in children, and the dog is usually a family pet or a neighbor's dog.

Rabies still occurs almost everywhere in the world, with exceptions including New Zealand, parts of Europe, parts of South America, and isolated Pacific islands. Rabies associated with dog bites remains a problem in low-income countries. Fortunately, because of vaccination programs, rabies related to dog bites is rare in high-income countries, where most human rabies is associated with bat exposure. In the US, rabies is carried primarily by bats, raccoons and skunks. Although unvaccinated dogs occasionally acquire rabies from wild animals, the canine rabies virus variant that is responsible for dog-to-dog transmission has not been identified in the US since 2004. Oral rabies vaccination programs using bait to target gray foxes and coyotes in Texas and raccoons in the eastern US have helped to decrease the spread of rabies.

Local health authorities should be contacted to report a dog or cat bite and (if necessary) to arrange for quarantine. Latex agglutination testing of dog saliva for rabies antigen is 95% sensitive compared to fluorescent antibody testing on brain smears.

Clinical features

Common pathogens associated with bite wounds include streptococci, staphylococci, *Pasteurella* spp., *Capnocytophaga canimorsus* and anaerobes. Breast implant infection and lung abscesses due to *Pasteurella multocida* have both been linked to cats, and staphylococcal endocarditis has been reported after a cat bite (without a preceding local infection); brain abscess formation has been observed following a dog bite. In immunocompromised patients, there is a significant risk of *Pasteurella* or *Capnocytophaga* sepsis. *Capnocytophaga canimorsus* sepsis has a high mortality rate and has been associated with purpura fulminans. Human bites have a higher likelihood of infections with *Staphylococcus aureus* and *Eikenella corrodens*. The most common pathogens associated with bite wound infections are listed in Table 85.9[51–54].

Treatment

A combination of a β-lactam antibiotic and a β-lactamase inhibitor (e.g. amoxicillin/clavulanic acid) provides good coverage for most organisms associated with dog and cat bites[51–54]. Alternatives include: (1) second-generation cephalosporins with anaerobic activity; (2) penicillin plus a first-generation cephalosporin; or (3) clindamycin plus a fluoroquinolone. Hospitalization of patients due to *Pasteurella*-infected animal bite wounds is strongly associated with initial use of suboptimal antibiotic therapy. With appropriate antibiotic therapy, primary repair is appropriate for dog bites to the face.

PATHOGENS ASSOCIATED WITH HUMAN AND ANIMAL BITE WOUND INFECTIONS

Bite	Pathogens
Human bites	*Staphylococcus aureus* *Streptococcus pyogenes* *Eikenella corrodens* Various anaerobes†
Cat bites	*Pasteurella multocida* (75%)* *Moraxella* spp. *Neisseria weaveri* *Bergeyella zoohelcum* Various anaerobes†
Dog bites	*Pasteurella* spp. (*canis* > *multocida*) (50%)* *S. aureus* (20%) *S. pyogenes* *N. weaveri* *Capnocytophaga canimorsus* *B. zoohelcum* Various anaerobes†
Horse and sheep bites	*Actinobacillus* spp. *Pasteurella* spp. Various anaerobes†
Marine animal bites	*Vibrio* spp. *Aeromonas hydrophila* *Pseudomonas* spp. *Plesiomonas shigelloides*

*Relatively short incubation period of 12–24 hours.
†May include *Fusobacterium, Bacteroides, Porphyromonas* and *Prevotella* spp.

Table 85.9 Pathogens associated with human and animal bite wound infections. Most infections are polymicrobial and include aerobic and anaerobic bacteria (median of 4–5 isolates), which can originate from the skin of the patient as well as the oral flora of the biting animal or human.

LEECHES

Key features

- Associated with fresh water
- Purpura and bleeding

Introduction

Leech attachments occur after contact with bodies of fresh water such as ponds or rivers.

Pathogenesis

Leeches prevent blood coagulation, partly through interference with platelet aggregation. Medical leeches have been associated with *Aeromonas hydrophila* wound infection.

Clinical features

Leech attachment sites often become purpuric and may bleed freely when the leech is removed. Leeches can attach to the tonsils (resulting in hemoptysis) or inside the nose (causing epistaxis). Disordered coagulation associated with massive bleeding and anemia has been reported after a leech bite[55].

Treatment

Leech removal is often complicated by bleeding or infection. Saturated salt solutions have been used to facilitate leech removal.

Leech therapy

Medical leeches and hyperbaric oxygen have been used together to enhance the survival of skin flaps subjected to venous occlusion. Sated leeches can be induced to continue feeding from the flap by posterior crop (stomach) incision and immersion in a serotonin solution.

MARINE INJURIES

Key features

- Marine organisms contain some of the most potent toxins known
- Drowning can occur after loss of consciousness following envenomation
- Penetrating injuries are prone to secondary infection
- Marine *Vibrio* infections are more common in patients with liver disease
- First aid for most marine venoms includes immersion in hot, but not scalding, water

Introduction

Penetrating marine injuries may be complicated by secondary bacterial infection. *S. aureus* is the most common organism, but *Vibrio* infections also occur. *Vibrio vulnificus* sepsis is strongly associated with liver disease, especially cirrhosis (see Ch. 74). Although most infections are related to ingestion of oysters or injuries in brackish water, the organism can survive on the skin for more than 24 hours, and infection has been reported after a penetrating injury on dry land. Seal finger, resulting from seal bites to the hand, is caused by *Mycoplasma* infection. Cutaneous infections with *Erysipelothrix rhusiopathiae* (see Ch. 74), *Aeromonas hydrophila* and *Mycobacterium marinum* (see Ch. 75) can also be acquired from trauma in an aquatic environment[56].

Pathogenesis

Cnidarians (including jellyfish, corals and sea anemones) are aquatic animals that produce specialized epidermal cells called cnidocytes with organelles referred to as nematocysts or stinging capsules. A physical (e.g. contact with a foreign body) or osmotic trigger causes a coiled, inverted, hollow filament within the nematocyst to be ejected externally and discharge its toxic contents.

Clinical features

Sea urchins are echinoderms with fragile spines that break easily in the skin. Pigment from the spine often diffuses into the wound, making it difficult to find and remove the spine. Only about 80 of the roughly 600 species of sea urchin have been described as being hazardous to humans. Long-spined urchins such as the black sea urchin (*Diadema setosum*) are often a problem and spines embedded near joints have been associated with synovitis and arthritis. Sea cucumbers, another type of echinoderm, can eject an irritating visceral liquid.

Seabather's eruption (sea lice) is characterized by pruritic papules located under the bathing suit (Fig. 85.17) and in intertriginous areas. It may be caused by a variety of stinging larvae, including the larvae of the thimble jellyfish (*Linuche unguiculata*), common in southern waters. Off the coast of Long Island, New York, it is caused by larvae of a sea anemone (*Edwardsiella lineata*). Swimmer's itch, in contrast, affects exposed areas, is more common in fresh water, and is related to cercariae (free-swimming larvae) of avian schistosomes (see Ch. 83).

Jellyfish stings result in immediate pain as well as delayed and (occasionally) recurrent cutaneous reactions. Erythematous, urticarial or hemorrhagic streaks may be observed (Fig. 85.18), and they tend to be longer and fewer in number following contact with larger jellyfish. A lichen planus-like eruption has been reported to follow jellyfish envenomation[57]. Inflammation distant from the site of envenomation has also been reported[58]. *Chironex fleckeri*, the Pacific box jellyfish or sea wasp, is generally considered the most dangerous of the jellies, and stings commonly result in shock. Confirmation of envenomation can be obtained by tape stripping of nematocysts from skin. *Physalia physalis*, the Portuguese man of war, is common in southern waters of the Atlantic. *Physalia utriculus*, the blue bottle jellyfish, is seen in the Pacific. *Cyanea* and *Chrysaora* sea nettles are common causes of jellyfish dermatitis. Storms often drive the jellies into shallow water in great numbers.

Haloclava producta, the "ghost anemone", is a burrowing sea anemone found off the east coast of the US and in the Gulf of Mexico. It is responsible for summer outbreaks of dermatitis off the coast of Long Island, New York. Corals are another group of stinging cnidarians in the same class (Anthozoa) as sea anemones. Coral cuts can be slow to heal and should be washed vigorously. Fire corals are false corals that produce intense stinging and a papular eruption that can last for several days. Cnidarian nematocysts found in seaweed and in the dorsal papillae of nudibranch sea slugs can also cause dermatitis. In addition, seaweed dermatitis may be caused by algae.

Fig 85.17 Seabather's eruption. Edematous pink papules in the same distribution as the bathing trunks. *Courtesy, Kalman Watsky, MD.*

Fig. 85.18 Blue bottle jellyfish sting. Painful grouped papules and papulovesicles in a linear arrangement on the right shoulder of a young man. *Courtesy, John Auld, MD.*

Red sponges and fire sponges (members of the phylum Porifera) both cause dermatitis. Sponge dermatitis is related to spicules embedded in the skin, but sponge diver's disease is caused by the stings of sea anemones attached to the base of sponges. Local itching and burning progress to erythema and vesiculation. Systemic symptoms such as nausea, vomiting and headache are common.

Two classes of the phylum Mollusca, cephalopods and gastropods, have been linked to human envenomation. The blue-ringed octopus contains a potent venom. This small cephalopod is often only 10 cm long and is found in waters off the coast of Australia. Envenomation from cone shells (marine gastropods) may be associated with a 20% mortality rate. The shells are about 10 cm in length and tend to be found in shallow water, mainly in tropical and subtropical climates.

Encounters with stingrays can result in soft tissue injury and embedded spines. Death has been reported after a penetrating chest injury from a stingray barb resulting in venom-induced myocardial necrosis. Injuries inflicted by stingrays occur in both fresh and salt water, and pain is the major manifestation. Venom injuries respond to hot water immersion.

Lionfish are common in subtropical and tropical waters. Since August 2000, lionfish have been reported along the eastern coast of the US, from Florida to New York. Lionfish belong to the family of scorpionfish (Scorpaenidae). The family includes the genera *Pterois* (lionfish), *Scorpaena* ("true scorpionfish", bullrout and sculpin) and *Synanceia* (stonefish). Stonefish are the most toxic members of the family, although all produce local pain as well as systemic symptoms. Catfish spine injuries occur in both salt and fresh water. They may be associated with local pain, bleeding and systemic symptoms.

Pathology

Marine *Vibrio* infections cause intense cellulitis affecting the subcutis and dermis. The superficial dermis is devitalized and lacks an inflammatory infiltrate. Bullae are subepidermal in location and non-inflammatory. Many organisms are present, especially around vessels.

Sea urchin spines examined by polarized light microscopy exhibit an ornate symmetric structure produced by calcite crystals. Cutaneous granulomatous reactions may occur.

Histologic sections from sites of jellyfish stings may demonstrate nematocysts penetrating the epidermis and papillary dermis.

Treatment

Avoidance is the best means of preventing injury, which can result from specimens in salt water fish tanks as well as in the ocean. When envenomation occurs in a swimmer, the individual should immediately be removed from the water to prevent drowning. Initial treatment for all marine envenomations includes soaking the site in hot, but not scalding, water to denature some of the venom proteins.

Antivenin is available for some of the more toxic species such as *C. fleckeri*, and it can neutralize cardiovascular effects of *C. fleckeri* envenomation in an animal model. In contrast, verapamil does not improve cardiovascular status and increases mortality in the same animal model. In an animal model of envenomation by *Chiropsalmus* species of box jellyfish, pretreatment with *C. fleckeri* antivenin or $MgSO_4$ did not have any effect on the venom-induced hypertensive response or the subsequent cardiovascular collapse. This highlights the importance of species identification following box jellyfish envenomation.

In a study of acute *Carybdea alata* box jellyfish stings, hot water immersion (40–41°C) was more effective than papain meat tenderizer or vinegar. Topical jellyfish sting inhibitors, including lotions in which they are combined with sunscreens, are available. Sea water can be used to remove jellyfish tentacles. Inactivation with acidic or alkaline solutions can be risky, as unexpected discharge of nematocysts may occur. Treatment with topical corticosteroids and calcineurin inhibitors may be helpful for delayed reactions[59].

Most fish envenomations should be treated with hot water immersion. In a study of fresh water ray envenomation, hot water immersion controlled acute pain, but it did not prevent skin necrosis.

REFERENCES

1. Elston DM. Life-threatening stings, bites, infestations, and parasitic diseases. Clin Dermatol. 2005;23:164–70.
2. Benmously R, Hammami H, Rouatbi M, et al. Insect bite-like reaction associated with the relapse of non-Hodgkin B cell-lymphoma. Eur J Dermatol. 2009;19:406–7.
3. Asada H. Hypersensitivity to mosquito bites: a unique pathogenic mechanism linking Epstein-Barr virus infection, allergy and oncogenesis. J Dermatol Sci. 2007;45:153–60.
4. Vachvanichsanong P, Dissaneewate P. Acute renal failure following wasp sting in children. Eur J Pediatr. 2009;168:991–4.
5. Katz TM, Miller JH, Hebert AA. Insect repellents: historical perspectives and new developments. J Am Acad Dermatol. 2008;58:865–71.
6. Naucke TJ, Kröpke R, Benner G, et al. Field evaluation of the efficacy of proprietary repellent formulations with IR3535 and picaridin against *Aedes aegypti*. Parasitol Res. 2007;101:169–77.
7. Pretorius AM, Jensenius M, Clarke F, et al. Repellent efficacy of DEET and KBR 3023 against *Amblyomma hebraeum* (Acari: Ixodidae). J Med Entomol. 2003;40:245–8.
8. Uzzan B, Konate L, Diop A, et al. Efficacy of four insect repellents against mosquito bites: a double-blind randomized placebo-controlled field study in Senegal. Fundam Clin Pharmacol. 2009;23:589–94.
9. Carroll JF, Benante JP, Klun JA, et al. Twelve-hour duration testing of cream formulations of three repellents against *Amblyomma americanum*. Med Vet Entomol. 2008;22:144–51.
10. Costantini C, Badolo A, Ilboudo-Sanogo E. Field evaluation of the efficacy and persistence of insect repellents DEET, IR3535, and KBR 3023 against *Anopheles gambiae* complex and other Afrotropical vector mosquitoes. Trans R Soc Trop Med Hyg. 2004;98:644–52.
11. Simons FE. Anaphylaxis: recent advances in assessment and treatment. J Allergy Clin Immunol. 2009;124:625–36.
12. Galera C, Soohun N, Zankar N, et al. Severe anaphylaxis to bee venom immunotherapy: efficacy of pretreatment and concurrent treatment with omalizumab. J Investig Allergol Clin Immunol. 2009;19:225–9.
13. Rupp MR, deShazo RD. Indoor fire ant sting attacks: a risk for frail elders. Am J Med Sci. 2006;331:134–8.
14. Partridge ME, Blackwood W, Hamilton RG, et al. Prevalence of allergic sensitization to imported fire ants in children living in an endemic region of the southeastern United States. Ann Allergy Asthma Immunol. 2008;100:54–8.
15. Haymore BR, McCoy RL, Nelson MR. Imported fire ant immunotherapy prescribing patterns in a large health care system during a 17-year period. Ann Allergy Asthma Immunol. 2009;102:422–5.
16. Judd CA, Parker AL, Meier EA, Tankersley MS. Successful administration of a 1-day imported fire ant rush immunotherapy protocol. Ann Allergy Asthma Immunol. 2008;101:311–15.
17. Letz AG, Quinn JM. Frequency of imported fire ant stings in patients receiving immunotherapy. Ann Allergy Asthma Immunol. 2009;102:303–7.
18. Reinhardt K, Kempke D, Naylor RA, Siva-Jothy MT. Sensitivity to bites by the bedbug, *Cimex lectularius*. Med Vet Entomol. 2009;23:163–6.
19. Kolb A, Needham GR, Neyman KM, et al. Bedbugs. Dermatol Ther. 2009;22:347–52.
20. Goddard J, deShazo R. Bed bugs (*Cimex lectularius*) and clinical consequences of their bites. JAMA. 2009;301:1358–66.
21. Hossler EW. Caterpillars and moths. Dermatol Ther. 2009;22:353–66.
22. Hossler EW. Caterpillars and moths: Dermatologic manifestations of encounters with Lepidoptera, Parts I and II. J Am Acad Dermatol. 2010;62:1–10, 13–28.
23. Aberer E. What should one do in case of a tick bite? Curr Probl Dermatol. 2009;37:155–66.
24. Krishnan AV, Lin CS, Reddel SW, et al. Conduction block and impaired axonal function in tick paralysis. Muscle Nerve. 2009;40:358–62.
25. Purwar S. Tick paralysis: an uncommon dimension of tick-borne diseases. South Med J. 2009;102:131.
26. Dana AN. Diagnosis and treatment of tick infestation and tick-borne diseases with cutaneous manifestations. Dermatol Ther. 2009;22:293–326.
27. Fritz CL. Emerging tick-borne diseases. Vet Clin North Am Small Anim Pract. 2009;39:265–78.
28. Centers for Disease Control and Prevention (CDC). Consequences of delayed diagnosis of Rocky Mountain spotted fever in children – West Virginia, Michigan, Tennessee, and Oklahoma, May–July 2000. MMWR Morb Mortal Wkly Rep. 2000;49:885–8.
29. Foil LD, Coleman P, Eisler M, et al. Factors that influence the prevalence of acaricide resistance and tick-borne diseases. Vet Parasitol. 2004;125:163–81.
30. Estrada-Pena A, Reme C. Efficacy of a collar impregnated with amitraz and pyriproxyfen for prevention of experimental tick infestations by *Rhipicephalus sanguineus, Ixodes ricinus*, and *Ixodes scapularis* in dogs. J Am Vet Med Assoc. 2005;226:221–4.
31. Paddock CD, Yabsley MJ. Ecological havoc, the rise of white-tailed deer, and the emergence of *Amblyomma americanum*-associated zoonoses in the United States. Curr Top Microbiol Immunol. 2007;315:289–324
32. Schutze GE, Buckingham SC, Marshall GS, et al. Tick-borne Infections in Children Study (TICS) Group. Human monocytic ehrlichiosis in children. Pediatr Infect Dis J. 2007;26:475–9.
33. Masters EJ, Grigery CN, Masters RW. STARI, or Masters disease: lone star tick-vectored Lyme-like illness. Infect Dis Clin North Am. 2008;22:361–76.
34. Bacon RM, Kugeler KJ, Mead PS; Centers for Disease Control and Prevention (CDC). Surveillance for Lyme disease – United States, 1992–2006. MMWR Surveill Summ. 2008;57:1–9.

35. Corapi KM, White MI, Phillips CB, et al. Strategies for primary and secondary prevention of Lyme disease. Nat Clin Pract Rheumatol. 2007;3:20–5.
36. Barbaro KC, Knysak I, Martins R, et al. Enzymatic characterization, antigenic cross-reactivity and neutralization of dermonecrotic activity of five Loxosceles spider venoms of medical importance in the Americas. Toxicon. 2005;45:489–99.
37. Sams HH, Dunnick CA, Smith ML, et al. Necrotic arachnidism. J Am Acad Dermatol. 2001;44:561–73.
38. McDade J, Aygun B, Ware RE. Brown recluse spider (*Loxosceles reclusa*) envenomation leading to acute hemolytic anemia in six adolescents. J Pediatr. 2010;156:155–7.
39. Parekh KP, Seger D. Systemic loxoscelism. Clin Toxicol (Phila). 2009;47:430–1.
40. Elston DM, Eggers JS, Schmidt WE, et al. Histological findings after brown recluse spider envenomation. Am J Dermatopathol. 2000;22:242–6.
41. Eckermann JM, Teruya TH, Bianchi C, et al. Arterial thrombosis and gangrene secondary to arachnidism. Vascular. 2009;17:239–42.
42. Pauli I, Minozzo JC, da Silva PH, et al. Analysis of therapeutic benefits of antivenin at different time intervals after experimental envenomation in rabbits by venom of the brown spider (*Loxosceles intermedia*). Toxicon. 2009;53:660–71.
43. Elston DM, Miller SD, Young RJ, et al. Comparison of colchicine, dapsone, triamcinolone, and diphenhydramine therapy for the treatment of brown recluse spider envenomation. A double blind, controlled study in a rabbit model. Arch Dermatol. 2005;141:595–7.
44. Sofer S, Bawaskar HS, Gueron M. Antivenom for children with neurotoxicity from scorpion stings. N Engl J Med. 2009;361:631–2.
45. Deshpande SB, Pandey R, Tiwari AK. Pathophysiological approach to the management of scorpion envenomation. Indian J Physiol Pharmacol. 2008;52:311–14.
46. Holve S. Venomous spiders, snakes, and scorpions in the United States. Pediatr Ann. 2009;38:210–7.
47. Chaou CH, Chen CK, Chen JC, et al. Comparisons of ice packs, hot water immersion, and analgesia injection for the treatment of centipede envenomations in Taiwan. Clin Toxicol (Phila). 2009;47:659–62.
48. Norris RL, Pfalzgraf RR, Laing G. Death following coral snake bite in the United States – first documented case (with ELISA confirmation of envenomation) in over 40 years. Toxicon. 2009;53:693–7.
49. Walter FG, Stolz U, Shirazi F, et al. Epidemiology of severe and fatal rattlesnake bites published in the American Association of Poison Control Centers' Annual Reports. Clin Toxicol (Phila). 2009;47:663–9.
50. Kaye AE, Belz JM, Kirschner RE. Pediatric dog bite injuries: a 5-year review of the experience at the Children's Hospital of Philadelphia. Plast Reconstr Surg. 2009;124:551–8.
51. Brook I. Management of human and animal bite wound infection: an overview. Curr Infect Dis Rep. 2009;11:389–95.
52. Patronek GJ, Slavinski SA. Animal bites. J Am Vet Med Assoc. 2009;234:336–45.
53. Dendle C, Looke D. Review article: Animal bites: an update for management with a focus on infections. Emerg Med Australas. 2008;20: 458–67.
54. Oehler RL, Velez AP, Mizrachi M, et al. Bite-related and septic syndromes caused by cats and dogs. Lancet Infect Dis. 2009;9:439–47.
55. Kose A, Zengin S, Kose B, et al. Leech bites: massive bleeding, coagulation profile disorders, and severe anemia. Am J Emerg Med. 2008;26:1067.e3–6.
56. Haddad V Jr, Lupi O, Lonaz JP, et al. Tropical dermatology: marine and aquatic dermatology. J Am Acad Dermatol. 2009;61:733–50.
57. Ghosh SK, Bandyopadhyay D, Haldar S. Lichen planus-like eruption resulting from a jellyfish sting: a case report. J Med Case Reports. 2009;3:7421.
58. Kapamajian MA, Ahmad A, Burnett JW, et al. Unilateral orbital inflammation in a child after a jellyfish sting to the lower extremities. Ophthal Plast Reconstr Surg. 2009;25:239–41.
59. Rallis E, Limas C. Recurrent dermatitis after solitary envenomation by jellyfish partially responded to tacrolimus ointment 0.1%. J Eur Acad Dermatol Venereol. 2007;21:1287–8.

This page intentionally left blank

Ultraviolet Light 86

Thomas M Rünger

Key features

- Exposure of the skin to UV light has acute, short-term effects and chronic, long-term effects, both of which are wavelength-dependent. Profound effects also occur with non-erythemogenic doses of UV light
- UV light affects the skin's immune system, exerting both pro- and anti-inflammatory responses
- UV light induces several different types of DNA damage in a wavelength-dependent manner, such as pyrimidine dimers and oxidative guanine base modifications
- Several DNA repair pathways are involved in the processing of UV light-induced DNA damage, including nucleotide excision repair, base excision repair, translesional DNA synthesis, and recombination repair
- UV light-induced mutations, which play a pivotal role in photocarcinogenesis, are different from those induced by other mutagens. Some base substitution mutations (e.g. C→T, CC→TT) are so typical for UV light that they have been termed "signature mutations", and they are commonly found in UV-induced skin cancers
- Disorders with an increased frequency of UV-induced skin cancers are characterized by an impaired cellular or host response to the effects of UV light

INTRODUCTION

Dermatologists are confronted daily with the effects of UV light on the skin, and often deal with them in a seemingly contradictory way. On the one hand, they have the responsibility of warning their patients against the deleterious effects of sunlight, such as sunburn, photoaging and sun-induced skin cancers, and on the other hand, they use UV radiation to treat skin disease. As with all medical interventions, dermatologists are weighing the risks versus the benefits when they use UV light for therapeutic purposes. In the phototherapy of inflammatory skin diseases, dermatologists also try to avoid the proinflammatory properties of UV radiation (e.g. the capability to induce sunburn) by choosing sub-erythemogenic doses. This clearly indicates that doses of UV light that do not induce sunburn still have profound effects on the skin. This applies not only to its short-term effects, but also to its long-term effects. A third and important aspect of photodermatology is the diagnosis and treatment of photosensitive or photoaggravated skin disorders (see Ch. 87).

Spectrum of UV Light

The sun emits UV radiation as part of an electromagnetic spectrum (see Fig. 134.1). It is usually subdivided, rather arbitrarily, into UVA (400–315 nm), UVB (315–290 nm), and UVC (290–200 nm). UVA has been further subdivided into UVA1 (400–340 nm) and UVA2 (340–315 nm). Of note, some authors use 320 nm as the demarcation between UVA and UVB. More than 95% of the sun's UV radiation that reaches the earth's surface is UVA. Practically all of the UVC, and much of the UVB, are absorbed by the oxygen and ozone in the earth's atmosphere, so that UV radiation below 290 nm is virtually undetectable at ground level. Nevertheless, the remaining UV radiation can still be absorbed by biologic molecules (DNA, protein, lipids), and it can damage and kill unprotected cells.

To survive in our environment, all living organisms had to develop protective mechanisms in order to prevent UV-induced killing and to maintain the stability of their genome. Such defenses include the development of UV-absorbing surface layers, enzymatic and non-enzymatic antioxidative defenses, repair processes, and removal of damaged cells. Through evolution, humans have lost most of the UV-protective fur, which remains an effective UV-protector only on the scalp (of most individuals). Nevertheless, the human skin is quite effective in protecting the rest of the organism from the harmful effects of solar UV irradiation, since UV radiation does not penetrate any deeper than the skin. Within the skin, the depth of penetration of UV light is wavelength-dependent[1,2] – i.e. the longer the wavelength, the deeper the penetration (Fig. 86.1). While UVA readily reaches the dermis, including its deeper portions, most of the UVB is absorbed in the epidermis, and only a small proportion reaches the upper dermis. UVC, if it reached the earth's surface, would be absorbed or reflected predominantly in the stratum corneum and in upper layers of the epidermis.

Some of the UV light reaching the skin is absorbed by biomolecules, thus eliciting photochemical and photobiological responses. A light-absorbing molecule is called a chromophore. Upon absorption of the radiation's energy, this chromophore is elevated to an excited state. Ensuing photochemical reactions may either change the chromophore directly, or, through energy transfer in a so-called photosensitized reaction, indirectly change a molecule other than the chromophore. Affected cells react, which in turn may lead to visible changes in exposed skin. When thinking about the biologic effects of different wavelengths in the different layers of the skin, it is necessary to consider that a particular wavelength can even have a biologic effect in a layer that it does not reach; for example, via secretion of a proinflammatory mediator in a higher layer[3].

Both short-term and long-term effects of exposure to UV light are wavelength-dependent. However, when comparing the photobiologic properties of UVB with those of UVA, it is important to remember that they are not two different entities, but rather a continuum of wavelengths, with gradually changing properties, and that the division between UVA and UVB is rather arbitrary. As noted previously, some authors use 320 nm, rather than 315 nm, as the demarcation between UVA and UVB.

Sunburn and Tanning

Visible, short-term, cutaneous effects of UV radiation include sunburn (solar erythema, possibly blister formation, desquamation) and tanning. Microscopically, short-term effects include epidermal edema with spongiosis, formation of sunburn cells (apoptotic keratinocytes), acanthosis, hyperkeratosis, depletion of Langerhans cells and an increase in basal layer and suprabasal melanin content, in addition to inflammatory infiltrates of lymphocytes and neutrophils and vasodilation. On a cellular and molecular level, UV exposure induces a multitude of damage responses, including the induction of stress proteins, repair processes and cytokine production. In a dose-dependent manner, exposed cells can either undergo apoptosis (visible histologically as sunburn cells) or cease proliferating (cell cycle arrest) in order to undergo repair (see Ch. 107). Hyperproliferation may follow the initial growth arrest, visible histologically as epidermal thickening.

The ability to induce sunburn (Fig. 86.2) rapidly declines with increasing wavelength. For example, UV light with a wavelength of 360 nm is approximately 1000-fold less erythemogenic than light with a wavelength of 300 nm. A UVB-induced sunburn reaches its peak between 6 and 24 hours after exposure. An immediate erythema reaction is rarely observed. In contrast, after exposure to a very high dose of UVA, an immediate erythema reaction can occur, followed by a distinct delayed erythema reaction after 6 to 24 hours. However, unless patients have increased UV sensitivity (e.g. decreased minimal

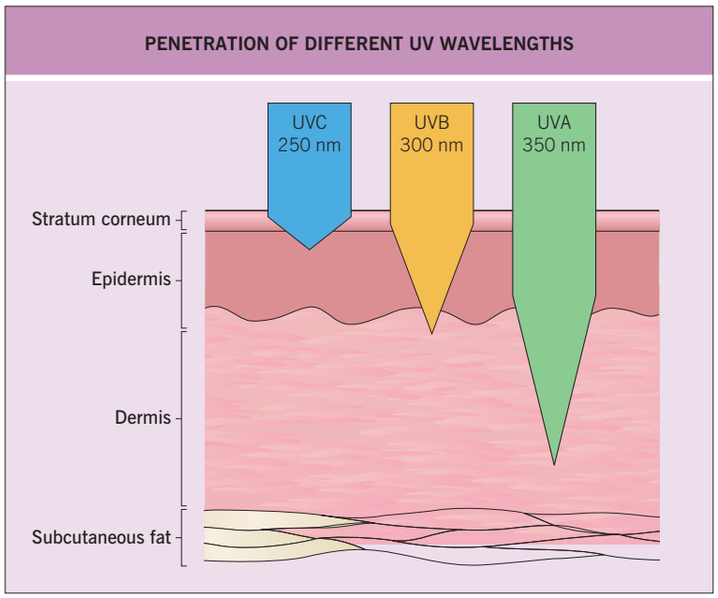


Fig. 86.1 Depth of penetration of different wavelengths of UV light into human skin. Depth of penetration varies greatly with the thickness of the different skin layers and their composition (e.g. melanin content). The beginning of the wedge-shaped portion of the penetration symbol represents a decrease to approximately one-third of the incident energy density, and the tip of the symbol represents a decrease to approximately 1%. Figure not drawn to scale.

Fig. 86.2 Sunburn. Twenty-four hours after an accidental 10-fold overdose of UVB prescribed as phototherapy. *With permission, Department of Dermatology, University of Würzburg, Germany.*

Fig. 86.3 Sequelae of exposure to UV light. **A** UVA-induced tan with reduced pigmentation within an area of relative ischemia (due to pressure while lying on a tanning bed); this leads to reduced UVA-induced, oxygen-dependent melanin oxidation within this area. **B** Sharp demarcation of solar lentigines and the dyspigmentation of photodamaged skin in a "sun worshipper". *Courtesy, Jean L Bolognia, MD.*

erythema dose [MED] to UVA; see Ch. 134), the doses of UVA present in natural sunlight are not sufficient to induce a sunburn. DNA is thought to be the chromophore for the delayed erythema reaction associated with UVB[4].

The tanning response of human skin to sun exposure is biphasic and also wavelength-dependent. Immediate pigment darkening occurs during and immediately after exposure, and is due to alteration (e.g. oxidation) and redistribution of existing melanin. It is most prominent with UVA. Delayed tanning is usually the result of an exposure to UVB, and it peaks approximately 3 days after sun exposure. Fair skin (skin type II) usually tans only with UVB doses above the erythema threshold (i.e. only with prior sunburn). Darker skin (skin types III and higher) also has a significant tanning response to sub-erythemogenic doses (without prior sunburn). A UVB-induced tan is based on an increased number of melanocytes, increased melanin synthesis, increased arborization of melanocytes, and increased transfer of melanosomes to keratinocytes (see Ch. 65). Again, it is necessary to emphasize that differences between UVA and UVB are gradual; for example, the shorter wavelengths of UVA (UVA2) exhibit tanning properties similar to those of UVB. However, a UVA-induced tan, such as from the use of a tanning bed (Fig. 86.3A), provides 5–10 times *less* protection against a sunburn from subsequent UV exposure than does a UVB-induced tan, probably due to the less pronounced epidermal thickening and hyperkeratosis that accompanies an UVA-induced tan.

EFFECTS OF ULTRAVIOLET LIGHT ON THE IMMUNE SYSTEM
CLINICAL OBSERVATIONS
Suggestive of proinflammatory/immune-stimulating effects
• Sunburn • Dermatoheliosis • Photodermatoses (phototoxic and photoallergic) • Photoaggravation of inflammatory skin diseases (e.g. psoriasis, atopic dermatitis, pityriasis rubra pilaris) • Induction of autoimmune connective tissue diseases (e.g. cutaneous lupus erythematosus (LE), flares of systemic LE) • Efficacy of UV phototherapy for the treatment of skin infections (e.g. lupus vulgaris)
Suggestive of anti-inflammatory/immunosuppressive effects
• Activation of recurrent orolabial herpes simplex • Increased risk of photocarcinogenesis in the setting of immunosuppression (e.g. solid organ transplant recipients) • Efficacy of UV phototherapy for the treatment of inflammatory skin diseases
CELLULAR AND MOLECULAR EVENTS IN UV-IRRADIATED SKIN
Mediating proinflammatory/immune-stimulating effects
• Release of proinflammatory mediators by resident and non-resident skin cells (e.g. serotonin, prostaglandins, IL-1, IL-6, IL-8, TNF-α) • Induction of antimicrobial peptides (hypothesized to explain why UV-irradiated skin is not prone to bacterial infections)
Mediating anti-inflammatory/immunosuppressive effects
• Depletion of Langerhans cells or modulation of their antigen-presenting function • Release of anti-inflammatory mediators by resident and non-resident skin cells (e.g. IL-10, α-MSH) • Induction of regulatory T cells (antigen-specific)

Table 86.1 Effects of ultraviolet light on the immune system. IL, interleukin; MSH, melanocyte-stimulating hormone; TNF, tumor necrosis factor.

An individual's tendency to develop sunburn and tanning after sun exposure has been used to categorize skin phototypes (see Table 134.3). These categories of an individual's susceptibility to short-term effects also correlate with the individual's susceptibility to long-term effects following sunlight exposure. In general, those individuals with higher acute sun sensitivity are also at greater risk for developing skin cancer after chronic UV exposure.

Effects on the Cutaneous Immune System

A sunburn exemplifies the profound effect that UV light has on the skin's immune function, in this case a proinflammatory effect. This, plus the clinical observations outlined in Table 86.1, provide evidence for the pro-inflammatory/immune-stimulating effects of UV light on the skin. On the other hand, UV light clearly has anti-inflammatory/immunosuppressive properties as well, exemplified by the efficacy of UV phototherapy in the treatment of inflammatory skin disorders. However, it is unlikely that there is a simple threshold between the UV doses that have proinflammatory and those that have anti-inflammatory effects. Proinflammatory, anti-inflammatory and immunomodulatory changes occur side-by-side within different arms of cellular and humoral immune reaction cascades, with varying dose–responses as well as modulation by wavelengths and many individual factors far beyond just the degree of skin pigmentation (skin types). An example of individual factors would be the observation that the majority of patients with psoriasis improve with UV phototherapy, but a small minority flares.

UV light-induced effects on the immune system involve not only the areas of skin directly exposed to UV light, but also non-irradiated sites[5–7]. An example of systemic immunosuppression is the development in non-exposed skin of antigen-specific immune tolerance to antigens that were initially applied to UV-exposed skin. This effect is known to be mediated by the release of immunosuppressive cytokines such as interleukin (IL)-10 and then ultimately by UV-induced regulatory T cells. Whereas in mice this UV-induced tolerance is highly reproducible, in humans it is highly variable – yet another example of the influence of individual factors. An example of systemic immune-stimulating effects is the UV-induced exacerbation of systemic disease in patients with systemic lupus erythematosus. Recently, it has been suggested that the immunosuppressive effects of UV light affect primarily the adaptive, antigen-specific immune system, while immunostimulatory effects target the innate immune system[8].

Cellular photoreceptors that mediate the signaling that leads to UV-induced immune responses are: DNA (via formation of DNA damage [DNA photoproducts]), urocanic acid in the stratum corneum (via UV-induced isomerization from the *trans*- to the *cis*-isoform), and membrane lipids (via UV-induced alteration of the membrane redox potential). While the immunosuppressive effects of UVB are well established, the relative contribution of UVA to the immunomodulatory properties of solar UV radiation is still a matter of debate, but evidence is accumulating that UVA also has prominent effects. Even less is known about the relationship of wavelength to the immunostimulatory effects of UV light.

Photoaging and Photocarcinogenesis

Long-term effects of chronic sun exposure include photoaging and photocarcinogenesis. In the case of photocarcinogenesis, UV exposure provides a one-two punch – not only does it generate DNA damage that leads to mutation formation and malignant transformation, but its immunosuppressive properties, including the induction of specific tolerance to antigens from UV-induced skin tumors, reduce the ability of the host immune-defense system to recognize and remove malignant cells. UV irradiation also impairs immune surveillance against cells infected with oncogenic viruses (e.g. certain HPV types) and may thereby further promote skin cancer formation. This may explain why cutaneous squamous cell carcinomas (SCCs) develop more frequently than basal cell carcinomas (BCCs) in immunosuppressed patients (e.g. solid organ transplant recipients), in contrast to immunocompetent individuals, in whom BCCs occur more commonly than SCCs.

The advantage of reduced immune reactivity following exposure to UV light is the prevention of illicit (auto)-immune reactions to transiently UV-altered cells. Any shift in the balance between pro- and anti-inflammatory responses toward a more immunosuppressed state increases the risk of UV-induced tumor formation, as occurs in chronically immunosuppressed patients. However, tilting this balance toward proinflammatory responses and autoimmunity increases the risk of developing photodermatoses or photoaggravated skin diseases such as lupus erythematosus. The critical nature of this balance is also exemplified by the observation that effective photoprotection commonly leads to spontaneous resolution of actinic keratoses, even though these precursor lesions have identifiable genetic changes that provide growth advantage over non-mutated cells (see Ch. 107).

In contrast to photocarcinogenesis, where the anti-inflammatory effects of UV light play a pivotal role, photoaging is characterized by a chronic inflammatory response to UV light. One of the most prominent features of cutaneous photoaging is wrinkling, which is due primarily to a loss of collagen fibers and deposits of abnormal degenerative elastotic material within the dermis (actinic elastosis). These changes are thought to be mediated by inflammation, with subsequent upregulation of extracellular matrix-degrading proteases and down-regulation of collagen synthesis. However, if the latter were due solely to UV-induced inflammation, wrinkling should be reversible with complete photoprotection, but of course this does not occur. Explanations for this lack of reversibility include UV-induced mitochondrial mutations[5] which lead to loss of cellular functions. In addition to changes within the dermal connective tissue, photoaging affects other components of the skin, including the epidermis, pigmentary system and vasculature.

As photocarcinogenesis commonly occurs in photoaged skin, this further demonstrates the simultaneous occurrence of pro- and anti-inflammatory responses to UV light. Both processes, photoaging and photocarcinogenesis, usually require several years of sun exposure before clinical manifestations are apparent (Fig. 86.3B). However, initial pigmentary changes of photoaging can sometimes be seen just weeks or months after a sunburn (e.g. the large-sized lentigines of the upper back that follow a blistering sunburn, also referred to as "sunburn freckles").

Due to its ability to penetrate deeper into the dermis, UVA in particular is thought to play an important role in the dermal changes of photoaging. Figure 86.4 depicts unilateral facial photoaging in an office

Fig. 86.4 Unilateral photoaging following 15 years of unilateral sun exposure through window glass. This individual had been working in the same office for 15 years, close to a window, with the left cheek always facing the window. Biopsy confirmed the diagnosis of nodular cutaneous elastosis with cysts and comedones (Favre–Racouchot disease). Since UVB does not penetrate window glass, this observation identifies UVA as an effective agent in photoaging. *Reproduced with permission from Moulin G, Thomas L, Vigneau M, Fiere A. Un cas unilateral d'élastose avec kystes et comédons de Favre et Racouchot. Ann Dermatol Venereol. 1994;121:721–3.*

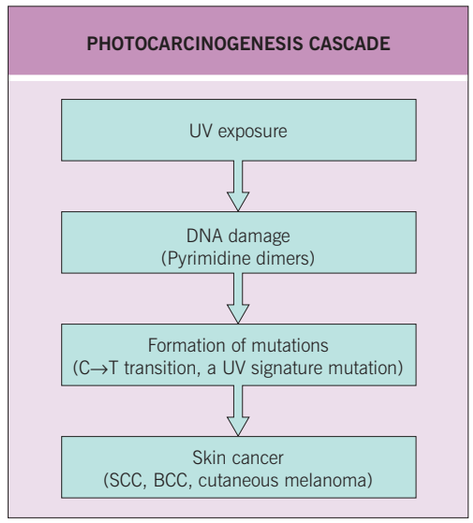


Fig. 86.5 Photocarcinogenesis cascade. UV-induced DNA damage generates mutations, which, after accumulation of a sufficient number of mutations in critical genes, may finally result in malignant transformation of single keratinocytes or melanocytes and with that formation of skin cancer.

worker whose face had been consistently side-on to the window during office hours for 15 years[6]. This case strikingly demonstrates the ability of UVA to induce photoaging, since only UVA, and not UVB, penetrates through window glass. The deeper penetration of UVA into the skin is significant for the process of photoaging, but it is not thought to be as important in photocarcinogenesis, since all UV-induced skin cancers (SCCs, BCCs and melanomas) arise from cells that reside within the epidermis, not from dermal cells. It is somewhat difficult to imagine that this difference (between epidermal and dermal cells) in their susceptibility to UV-induced carcinogenesis is due only to the more protected location of fibroblasts within the skin, given that fibroblasts are located just underneath the basal layer of epidermal cells. However, in mice, fibrosarcomas are readily induced by UVB, suggesting that the fibroblast is also susceptible to UV irradiation; therefore, it may just be that the thickness of the human epidermis prevents the malignant transformation of the fibroblast.

PHOTOCARCINOGENESIS

UV-Induced Tumor Formation

It is well established that exposure of the skin to UV light is a major risk factor for the development of cutaneous melanoma and non-melanoma skin cancer[7]. It is a process that, like cancer in general, involves a stepwise accumulation of specific genetic changes in a single cell, with subsequent clonal expansion. Usually, it takes decades until a tumor arises. It is commonly accepted that UV-induced skin cancers (BCC, SCC and melanoma) develop along the photocarcinogenesis chain of events outlined in Figure 86.5. The three major steps are:

- DNA damage formation after UV exposure
- mutation formation following DNA damage formation
- malignant transformation following mutation formation (see below).

There is limited information regarding which wavelengths of the UV spectrum are responsible for these effects. While the carcinogenic properties of short-wavelength UV light, in particular UVB, have been well established for some time, UVA has long been thought to be harmless due to its relative inability to induce sunburn. In recent years, however, it has been shown that UVA is capable of inducing cutaneous SCC in mice and is now recognized as an independent class I carcinogen[7]. Although a published photocarcinogenesis action spectrum for cutaneous SCC in mice showed a steep decline in tumor rate with increasing wavelength[9], it does not completely exclude a role for UVA. This is because natural sunlight contains much more UVA than UVB (depending on the time of day and weather: 20- to 100-fold more), which offsets at least some of the weaker effects of UVA. Additionally, UVA is less filtered by window glass or clothing, and it penetrates more effectively to the basal layer of the epidermis; these two factors may serve to increase its relative contribution to the long-term effects of sunlight exposure.

Even less is known about the action spectrum for the induction of melanoma, the deadliest form of skin cancer. However, there are some indications that UVA may play a particular role[10]. These suggestions come from the following:

- Experiments in melanoma-susceptible fish, in which UVA was much more effective in inducing melanoma.
- Another animal model, the opossum *Monodelphis domestica*, in which not only UVB but also UVA induced melanoma precursor lesions.
- Meta-analyses of multiple retrospective studies and one large prospective study indicate that the use of tanning beds (which contain mostly high-dose UVA emitters) increases the risk for melanoma[11,12]; a recent case control study found adjusted overall melanoma risks of 2.86 and 4.44 for users of UVB-enhanced and primarily UVA-emitting devices, respectively[12a].
- Reports that the use of sunscreens (which for decades contained no effective UVA filters and even today usually do not protect as efficiently against UVA as against UVB) increased melanoma risk[13], possibly due to an increased exposure to unfiltered UVA.

However, a role for UVA in the pathogenesis of melanoma has been questioned, as only UVB, not UVA, induced melanoma in a transgenic mouse model[14].

Cutaneous SCC and lentigo maligna melanoma are associated with a significantly high cumulative exposure to UV radiation, and they occur most commonly in chronically sun-exposed areas, such as the face, dorsal aspect of the hands, and extensor forearms. In contrast, the most common types of cutaneous melanoma (e.g. superficial spreading) usually arise in sites with intermittent sun exposure (e.g. the back in men and the lower legs in women), rather than in chronically sun-exposed areas, and they are associated with a history of sunburns. Several explanations for these phenomena have been proposed. One hypothesis suggests that melanocytes might be more prone to UV-induced mutagenesis following a single high dose of UV light, because of their relative inability to undergo apoptosis[15]. Possibly due to high levels of anti-apoptotic proteins such as Bcl-2, sunburn-induced apoptosis has not been described in melanocytes. Therefore, melanocytes with a high amount of DNA damage are more likely to survive than keratinocytes, which readily undergo apoptosis. Adaptive responses following repeated low-dose UV radiation, such as increased pigmentation or upregulation of DNA repair (see below for "intrinsic protective mechanisms"), protect both melanocytes and keratinocytes against the mutagenic assault from further low-dose UV exposures. However, in this situation, keratinocytes would be more prone to UV-induced mutagenesis, since they are proliferating more rapidly and are, therefore, more likely to replicate unrepaired DNA, thus leading to an increased

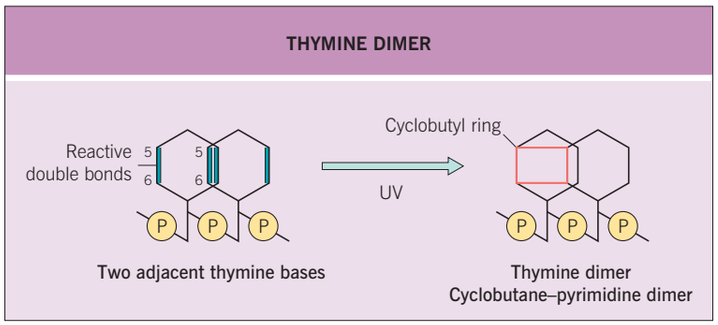


Fig. 86.6 Thymine dimer. Following excitation of the bases by UV light, a cyclobutane–pyrimidine dimer is formed by covalent linkage between two adjacent pyrimidines (here two thymine bases) and formation of a cyclobutyl ring.

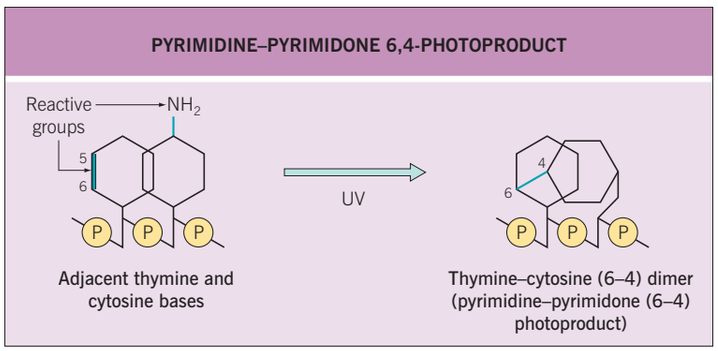


Fig. 86.7 Pyrimidine–pyrimidone 6,4-photoproduct. A pyrimidine–pyrimidone (6–4) photoproduct is formed by covalent linkage between C-6 and C-4 of two adjacent pyrimidines (here a thymine and a cytosine base), following excitation of the bases by UV light.

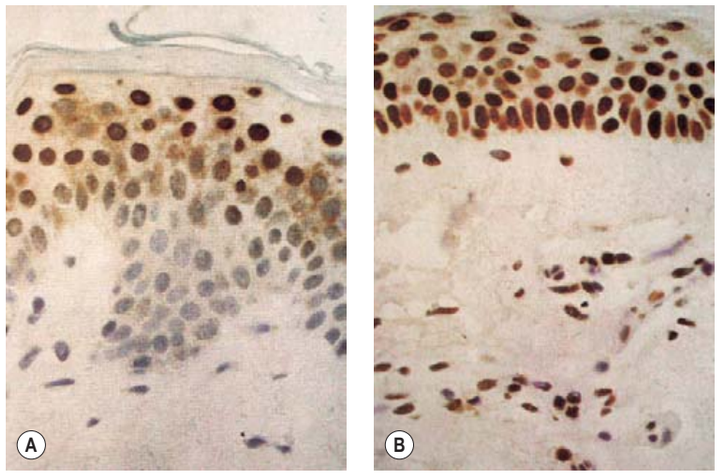


Fig. 86.8 A wavelength of 300 nm is more effective than one of 290 nm in inducing thymine dimers in the basal layer of the human epidermis. A After irradiation of human skin with monochromatic 290 nm UVB (2 MED) and staining with anti-thymine dimer antibodies, most cells in the basal layer show only blue counterstaining, while suprabasal layers demonstrate pronounced reactivity. **B** In contrast, with 2 MED of monochromatic 300 nm UVB, a pronounced immunostaining is also evident in the basal layer of the epidermis (as well as in cells within the dermis). *Reproduced with permission from Young AR, Chadwick CA, Harrison GI, et al. The similarity of action spectra for thymine dimers in human epidermis and erythema suggests that DNA is the chromophore for erythema. J Invest Dermatol. 1998;111:982–8.*

frequency of mutations. This could explain why keratinocytes are more vulnerable to the repeated low-dose UV irradiations of chronic sun exposure than are melanocytes.

UV Induction of DNA Damage

Different wavelengths of UV light induce different types of DNA damage. UVC and UVB, but much less so UVA, are capable of exciting the DNA molecule directly and subsequently generate DNA photoproducts[16]. Indeed, DNA is regarded as the chromophore for most of the biologic effects of UVB and UVC, including erythema, tanning, immunosuppression, mutagenesis and carcinogenesis[4]. DNA photoproducts are dimers, formed by covalently binding two adjacent pyrimidines in the same polynucleotide chain. The two major types of pyrimidine dimers are cyclobutane dimers (Fig. 86.6) and 6,4-photoproducts (Fig. 86.7).

Following acute cellular injury, including DNA damage, cells initiate damage response pathways, which may result in cell cycle arrest, apoptosis, induction of DNA excision repair pathways, changes in the expression of cell surface proteins, secretion of cytokines, etc. This explains how UV-induced DNA damage can result in acute effects, such as erythema or immune reactions (see Table 86.1). An upregulation of the transcription factor p53 plays a pivotal role in many of these cellular damage response pathways. However, the initial cellular sensor for the induction of damage response pathways has not been clearly identified. For DNA damage, the unwinding and bending of the DNA double helix by, for example, DNA photoproducts is important for at least DNA damage recognition and initiation of DNA repair.

Cyclobutane–pyrimidine dimers (CPDs) are the most common DNA photoproduct formed by UV irradiation of the skin. They are generated upon saturation of the 5,6 double bonds and formation of a four-membered cyclobutyl ring (see Fig. 86.6). CPDs are observed at all possible dipyrimidine sites, with the thymine–thymine dimer (T-T) being the most common, followed by C-T and T-C dimers. C-C dimers are the least common. The formation of CPDs is not a random phenomenon: it is influenced by the sequence and conformational context of the affected DNA sequence.

The 6,4-photoproduct is a non-cyclobutane dipyrimidine photoproduct, which is formed upon covalent linkage between the C-6 position of one pyrimidine and the C-4 position of the 3′ adjacent pyrimidine (see Fig. 86.7). The T-C (6–4) dimer is the most common dimer of this type, but C-C and T-T dimers are also observed after UV irradiation. Upon further irradiation with UV wavelengths between 280 and 360 nm, the normal isomers of 6,4-photoproducts can be converted to their Dewar valence isomers, which are less mutagenic than the normal isomers but may still contribute to solar mutagenesis[17]. A few other rare DNA photoproducts have been described, such as complex purine lesions and pyrimidine hydrates, but their physiologic significance in cutaneous photobiology is unknown.

The absorption maximum of DNA is at 260 nm. This makes UVC the most effective wavelength for the induction of DNA photoproducts in naked DNA. However, *in vivo*, due to the absorption of shorter wavelengths in upper layers of the epidermis, 300 nm (UVB) is the most effective wavelength for inducing DNA photoproducts in the basal layer of the epidermis (which harbors the most relevant cells for skin carcinogenesis). Figure 86.8 demonstrates how 300 nm is much more effective than 290 nm in inducing cyclobutane T-T dimers in the basal layer of human epidermis[4]. It has recently been shown that UVA can also generate pyrimidine dimers, albeit at a lower frequency than UVB (when solar-available doses are compared).

While formation of UVB-induced pyrimidine dimers results from the direct absorption of photons by bases of DNA, UV radiation can also damage DNA indirectly[18]. After absorption of photons by chromophores other than DNA, energy can be transferred either to DNA (type I photosensitized reaction) or to molecular oxygen, with reactive oxygen species in turn being able to damage DNA (type II photosensitized reaction). Of note, many of the biologic properties of UVA, including its toxicity to cells, are strictly dependent upon the presence of molecular oxygen[19], which points to a prominent role for reactive oxygen species. Although these reactive oxygen species are also formed by UVB, UVA has been shown to be responsible for almost all oxidative DNA damage after exposure of cells to natural sunlight[20]. Formation of pyrimidine dimers by UVA may involve a type I photosensitized reaction[21], unlike their direct formation by UVB.

UV-induced reactive oxygen species include singlet oxygen and probably other non-radical and radical reactive oxygen species, such as hydrogen peroxide and the superoxide radical[22]. Even the highly reactive hydroxyl radical may be formed by a reaction of hydrogen peroxide with

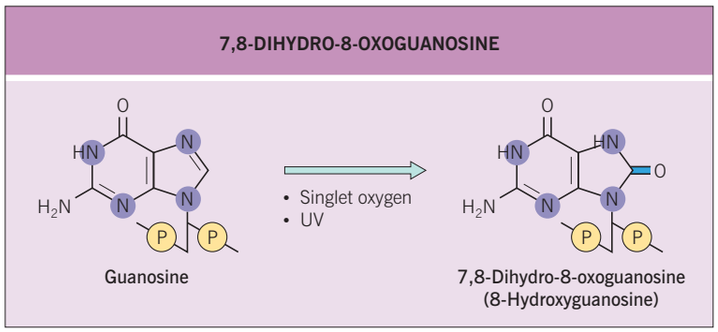


Fig. 86.9 7,8-Dihydro-8-oxoguanosine. 7,8-Dihydro-8-oxoguanosine (tautomer: 8-hydroxyguanosine) is an oxidation product of guanosine. It is formed by singlet oxygen, which is generated through a photosensitized reaction after excitation of a cellular chromophore by UV.

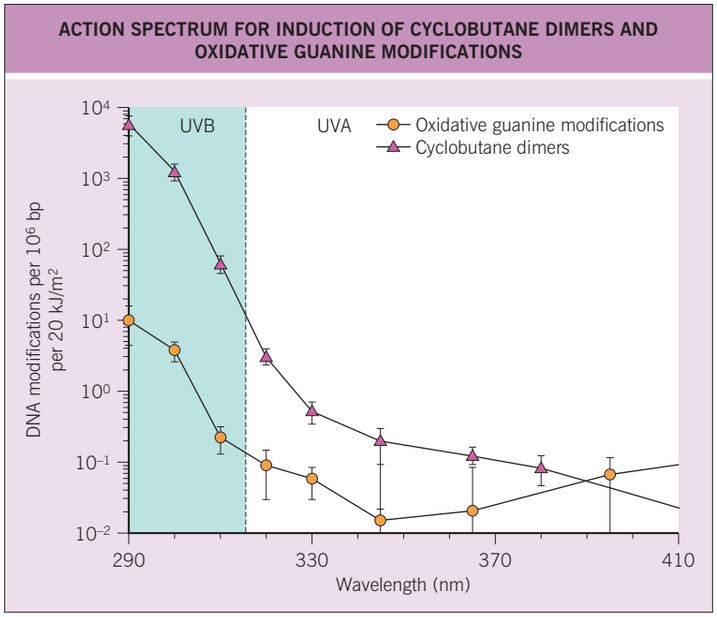


Fig. 86.10 Action spectrum for the induction of cyclobutane dimers and oxidative guanine modifications in Chinese hamster ovary cells. The number of DNA lesions was assessed by the ability of repair enzymes to incise DNA from cells irradiated with different wavelengths from a monochromator. The ability of UV light to induce cyclobutane dimers and oxidative DNA damage rapidly declines with increasing wavelengths, e.g. 320 nm UV light is approximately 1000-fold less capable of inducing cyclobutane dimers than is 290 nm UV light. This decline parallels well with the decline of skin cancer formation in mice from 300 to 340 nm (Utrecht–Philadelphia skin cancer action spectrum[9]). This decline does not mean that longer wavelengths do not contribute to photocarcinogenesis, because longer-wavelength UVA is much more abundant in natural sunlight than is UVB, which offsets at least some of the weaker effects of UVA. The second peak of oxidative base damage formation in the UVA range parallels with a second peak of skin cancer formation at 380 nm. Since there is no second peak of cyclobutane dimer formation with UVA, this has been interpreted as evidence that oxidative base damage contributes to mutagenesis and skin cancer formation. However, more recent data indicate that pyrimidine dimers are the most important pre-mutagenic DNA lesion not only for UVB, but also for UVA.

nuclear metals through a Fenton reaction. This oxidative stress affects not only DNA, but also membranes and proteins. The relative contribution of each (oxidative membrane damage, oxidative protein damage, oxidative DNA damage) to the different biologic effects of UV irradiation has not been well established. Singlet oxygen and the other reactive oxygen species react predominantly with guanine and generate several DNA changes, including the mutagenic and well-studied 7,8-dihydro-8-oxoguanosine (8-oxoG; Fig. 86.9).

Kielbassa et al.[23] published a UV action spectrum for the formation of dimers and oxidative guanine base modifications in mammalian cells (Fig. 86.10). Differences between the DNA-damaging properties of

Fig. 86.11 Xeroderma pigmentosum. Multiple skin cancers and lentigines on the face of a 12-year-old Hispanic boy. *Courtesy, Stanley Miller, MD.*

UVA, UVB and UVC are gradual, and, as noted previously, only a few pyrimidine dimers are generated by UVA. That said, there is mounting evidence that pyrimidine dimers are the most important pre-mutagenic DNA lesions not only in UVB-induced, but also in UVA-induced, mutation formation (see below), with oxidative DNA damage playing a minor role in mutagenesis[24,25]. Lastly, DNA double-strand breaks are probably not formed by either UVB[26] or UVA[26a].

Repair of UV-Induced DNA Damage

To counteract potentially mutagenic and cytotoxic effects, UV-induced DNA damage requires excision and replacement of damaged nucleotides by DNA repair pathways. No correction procedure is absolutely exact and error-free. If it were, UV-induced skin cancers would not occur in DNA repair-proficient individuals.

The bulky DNA photoproducts (pyrimidine dimers) are mutagenic, but they can be repaired by the nucleotide excision repair (NER) pathway. As exemplified by the hereditary disorder xeroderma pigmentosum (XP), a defect in this repair pathway increases UV sensitivity and UV mutagenesis in cells and results in non-melanoma and melanoma skin cancers in patients[27,28] (Fig. 86.11). The NER pathway is now well understood, in part through the identification and characterization of the different XP genes. XP includes seven genetic complementation groups (XPA through XPG), which represent different proteins in the NER pathway (Table 86.2), in addition to a separate form, XP variant. Although cells of some XP complementation groups usually exhibit a more impaired DNA repair than others (XPA, XPB, XPC and XPD), it is not possible to determine the affected DNA repair gene (XP complementation group) by the clinical phenotype alone. In addition, different mutations in the same gene can impair NER and/or the clinical phenotype to a varying degree.

NER involves recognition of DNA damage, incision of the DNA strand containing a lesion, and DNA synthesis and ligation to replace an excised oligonucleotide (24 to 32 residues). This is shown schematically in Figure 86.12. In active genes, the transcribed strand is corrected up to 10 times faster than the non-transcribed strand. Here, recognition of DNA damage is mediated via the RNA polymerase stalled at the site of a pyrimidine dimer plus recruitment of CSA and CSB (protein products of Cockayne syndrome complementation group A and group B genes); this initiates *transcription-coupled repair*. In non-transcribed genes and non-coding regions, the XPC and XPE proteins bind to UV-damaged DNA, marking it for further processing; this initiates *global genome repair*. After either form of DNA damage recognition, all subsequent steps of NER are identical. A key intermediate is an open, unwound structure formed around a DNA lesion in a reaction that uses the helicase activities of XPB and XPD. This creates sites for

DEFICIENT DNA REPAIR GENES		
Complementation group or inherited disorder	**Function of affected gene product in DNA repair**	**Also associated with:**
	NUCLEOTIDE EXCISION REPAIR	
XPA	High affinity for injured DNA (single strands) Has many interactions with other NER proteins Might have a role in assembling the DNA repair machinery around the DNA lesion	–
XPB	Subunit of the transcription factor TFIIH Unwinds the DNA helix around the DNA lesion with its 3′→5′ helicase function	XP/CS*, TTD
XPC	DNA damage recognition Only required for global genome repair, not for transcription-coupled repair	–
XPD	Subunit of the transcription factor TFIIH like XPB Unwinds the DNA helix around the DNA lesion with its 5′→3′ helicase function	XP/CS*, TTD
XPE	Affinity for UV-damaged DNA Might have an auxiliary role in DNA damage recognition	–
XPF	5′-repair endonuclease The ERCC1/XPF complex cuts at the single-strand to double-strand transition 5′ of the DNA lesion	–
XPG	3′-repair endonuclease Cuts at the single-strand to double-strand transition 3′ of the DNA lesion Stablilizes TFIIH	XP/CS*
TTDA	Subunit of TFIIH (TFB5) See XPB and XPD	
CSA	Only required for transcription-coupled repair Regulates recruitment of repair factors and chromatin remodelers upon stalling of RNA polymerase at the DNA lesion	–
CSB	Only required for transcription-coupled repair Regulates recruitment of repair factors and chromatin remodelers upon stalling of RNA polymerase at the DNA lesion	–
	TRANSLESIONAL DNA SYNTHESIS	
XP variant	DNA polymerase-η Bypasses T–T dimers with correct insertion of two A residues	–

*Xeroderma pigmentosum/Cockayne syndrome overlap syndrome.

Table 86.2 Deficient DNA repair genes. Deficient DNA repair genes underlie xeroderma pigmentosum (XP) complementation groups XPA to XPG, trichothiodystrophy (TTD), Cockayne syndrome (CS), and XP variant. In addition, mutations in TTDN1, a protein that may have a role in maintaining cell cycle integrity, can lead to a non-photosensitive form of TTD. ERCC1, excision repair cross complementing gene 1; NER, nucleotide excision repair; TFIIH, transcription factor IIH.

cutting by the endonucleases XPG on the 3′ side of the lesion and the XPF–ERCC1 complex on the 5′ side. A 24- to 32-residue oligonucleotide is released, and the gap is filled by DNA polymerase δ or ε and then sealed by DNA ligase 1.

Defects in NER are found not only in XP, but also in two other photosensitive disorders, Cockayne syndrome and the photosensitive form of the brittle hair syndrome trichothiodystrophy[28,29]. These disorders are not cancer-prone, but sometimes have features that overlap with those of XP. It is remarkable how different mutations in the XPB, XPD and XPG genes are associated with specific clinical phenotypes, i.e. only XP or XP/Cockayne syndrome overlap or trichothiodystrophy (see Table 86.2). There is no clear correlation between disease phenotype and specific mutations or between the severity of the DNA repair defect and the clinical phenotype. The transcription/repair syndrome hypothesis has been put forward in an attempt to explain these various discrepancies. According to this hypothesis, mutations in XPD or XPB could affect the repair function of transcription factor IIH (TFIIH; see Fig. 86.12), resulting in photosensitivity and cancer development, and/or affect the transcription function of TFIIH, accounting for the typical phenotypes of trichothiodystrophy and Cockayne syndrome.

Individual cancer and skin cancer risks are determined not just by a pronounced NER deficiency, as in XP, but also by more subtle variations in DNA repair efficiency, e.g. as a consequence of polymorphisms in DNA repair genes[30,31]. Likewise, a decline in DNA repair efficiency with age has been linked to the increasing risk of skin cancer with advancing age[32].

Cells from patients with XP variant have an intact NER (Table 86.3), yet a phenotype that is indistinguishable from the other XP complementation groups. Cells from these patients do not have a deficit in repairing DNA photoproducts, but a deficiency in what they do with unrepaired DNA photoproducts during replication (in the S phase of the cell cycle)[33]. Replicative DNA polymerases usually stall at unrepaired DNA lesions and detach from the DNA strand. For this situation, cells have a number of specialized DNA polymerases that are able to bypass different kinds of DNA damage and extend replication forks through damaged sites. Different polymerases perform this "translesional DNA synthesis" with variable fidelity.

Due to a mutation in the pol-η gene, cells from patients with XP variant lack the particular ability of DNA polymerase-η to bypass T-T dimers with correct insertion of two A residues[34]. This indicates that NER does not always repair all DNA lesions and that the function of a high-fidelity translesional DNA polymerase is crucial for maintaining genomic stability (if cells enter S phase with unrepaired DNA damage). In cells from patients with XP variant, NER can remove most of the T-T dimers, but because polymerase-η is deficient, any remaining dimers are more likely to be bypassed by polymerases that insert incorrect residues. This causes a UV-mutator phenotype. If DNA polymerase-η (or any other specialized translesional DNA polymerase) fails to bypass DNA damage during S phase, the cell is faced with a stalled replication fork. In these instances, DNA recombination repair, which utilizes strand invasion from the sister chromatid, can resolve the stalled replication fork. More recently, DNA recombination repair was also observed to occur after exposure to UV irradiation[26].

In contrast to the bulky pyrimidine dimers, which can only be repaired by NER, the non-bulky oxidative DNA base modifications can be processed by base excision repair[27,35]. As the name implies, the initial

step in base excision repair is the removal of a base rather than a nucleotide. This step is carried out by a DNA glycosylase, which removes the damaged DNA base by cleaving hydrolytically the base–deoxyribose glycosyl bond, leaving an apyrimidinic/apurinic (AP) site for further processing. This DNA glycosylase has substrate specificity for a particular kind of DNA base damage. The human DNA glycosylase, 8-oxoG DNA glycosylase 1, has specificity for oxidized guanine bases such as 8-oxoG (see above and Fig. 86.9), and it initiates processing of these lesions via base excision repair. Loss of this enzyme generates a cellular hypersensitivity to UVA, but does not increase UVA-associated mutation formation, further casting doubt regarding an important role for 8-oxoG in UVA-induced mutagenesis[36].

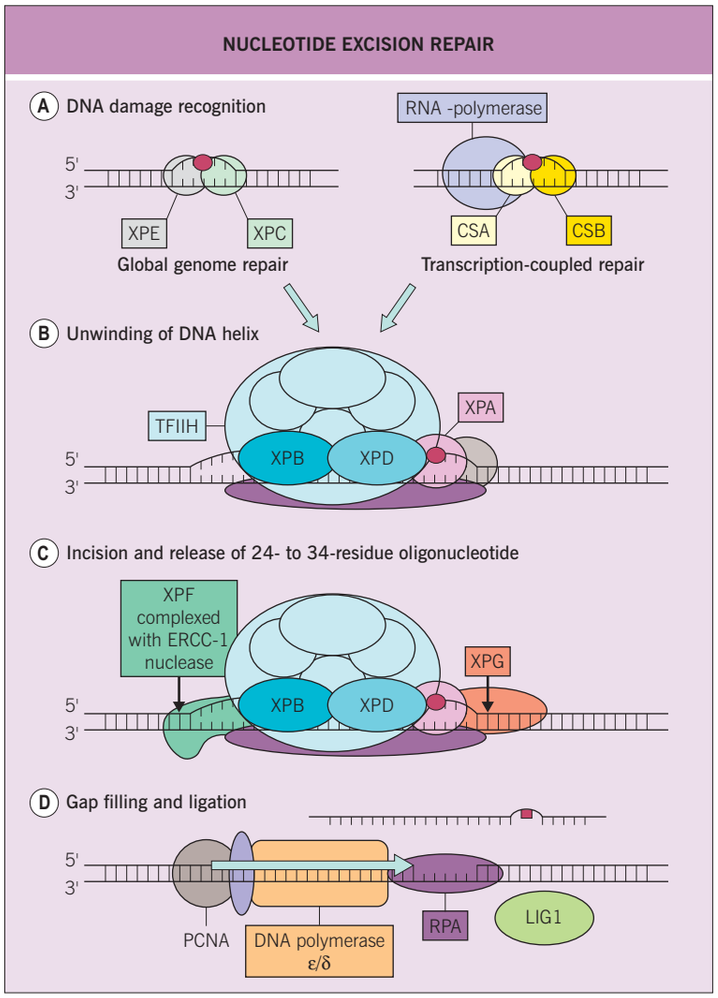


Fig. 86.12 Nucleotide excision repair. This pathway repairs "bulky" DNA lesions, including pyrimidine dimers (red dot). **A** DNA damage recognition in global genome repair is mediated by XPC and XPE. In transcription-coupled repair, DNA damage recognition is mediated by a stalled RNA polymerase plus recruitment of CSA and CSB. These two types of DNA damage recognition are then followed by identical steps in DNA repair. **B** Formation of an open bubble around the lesion by the helicase activity of XPB and XPD. **C** Incision 5′ and 3′ of the lesion by the endonucleases XPF and XPG. **D** Repair synthesis and gap closing after release of a 24- to 34-residue oligonucleotide. CSA/CSB, proteins that are dysfunctional in Cockayne syndrome; LIG1, DNA ligase 1; PCNA, proliferating cell nuclear antigen; RPA, replication protein A; TFIIH, transcription factor IIH; XP, xeroderma pigmentosum. *Adapted with permission from Lindahl T, Wood RD. Quality control by DNA repair. Science. 1999;286:1897–905.*

Mutation Formation

Many of the previously discussed forms of UV-induced DNA damage can result in mutation formation. Because mutations in several specific genes are usually required for a normal cell to undergo malignant transformation and these mutations are quite unlikely to occur in a single cell, genetic instability (a mutator phenotype) is thought to be required for the development of cancer, including skin cancer[37]. XP serves as an example of inherited genetic instability. While the amount of DNA damage formed in the skin following UV exposure is the same as in normal individuals, deficient repair of this damage introduces many more mutations at sites of DNA damage (compared to repair-intact individuals).

A somatic mutation in the p53 tumor suppressor gene is an example of an acquired UV-mutator phenotype. This gene encodes a 53 kDa transcription factor that has a critical role in cell cycle regulation and induction of apoptosis after DNA damage. Loss of p53 function can result in impaired cell cycle arrest following UV exposure. This then increases the likelihood that DNA will be replicated before removal of UV-induced DNA damage. This increases the frequency of mutation formation because replication of damaged DNA with misincorporation of bases across DNA damage is the most important mechanism for the formation of base substitution mutations.

Mutations in *p53* can be found in most cutaneous SCCs and actinic keratoses (see Ch. 107). In addition, chronically sun-exposed skin harbors many clonal proliferations of keratinocytes with *p53* mutations, which are undetectable by light microscopy. This indicates that *p53* mutations are an early event in the pathogenesis of UV-induced cutaneous SCC. Most of these clones, and some of the actinic keratoses, regress after cessation of sun exposure. This indicates that loss of p53 function through a *p53* mutation is not sufficient for malignant transformation, but that other mutations (probably many) need to accumulate in one cell, before this cell can undergo complete malignant transformation and develop into a tumor.

Most of the *p53* mutations in cutaneous SCCs and their precursors are C→T single base transition mutations at dipyrimidine sites[38]. Tandem CC→TT transition mutations are found in 10% of cutaneous SCCs. This spectrum of *p53* mutations is very different from *p53* mutations found in malignancies of internal organs; the latter do not have the preponderance of C→T mutations and have no CC→TT mutations. This, together with the fact that pyrimidine dimers most commonly cause C→T and some CC→TT mutations, provides convincing evidence for a crucial role of pyrimidine dimers in cutaneous photocarcinogenesis. Therefore, C→T, and especially CC→TT (Fig. 86.13), mutations have been termed "signature mutations" for UV mutagenesis. The latter can arise from either UVB or UVA[25] and represent the most common types of mutation produced by these wavelengths[24,39].

A possible explanation for why UVA causes more mutations per pyrimidine dimer than does UVB is that UVB induces a more protective, antimutagenic cellular response which leads to a reduction in the frequency of mutation formation at pyrimidine dimer sites[24,40]. Thus, exposure to a pure UVA source, as in phototherapy (high-dose UVA1) or tanning parlors, might be more carcinogenic than exposure to a UVA source that also contains UVB light.

The identification of UV signature mutations in the *p53* gene of cutaneous SCCs and actinic keratoses provides clear molecular

INHERITED DISORDERS WITH ABNORMAL DNA REPAIR – TYPES OF IMPAIRED FUNCTION

	Global genome NER	Transcription-coupled NER	Translesional DNA synthesis	Mismatch DNA repair
Xeroderma pigmentosum (XP)	+	+	+ (XP variant)	
Cockayne syndrome (CS)		+		
XP–CS overlap	+	+		
Trichothiodystrophy		+		
Muir–Torre syndrome				+

Table 86.3 Inherited disorders with abnormal DNA repair – types of impaired function. NER, nucleotide excision repair.

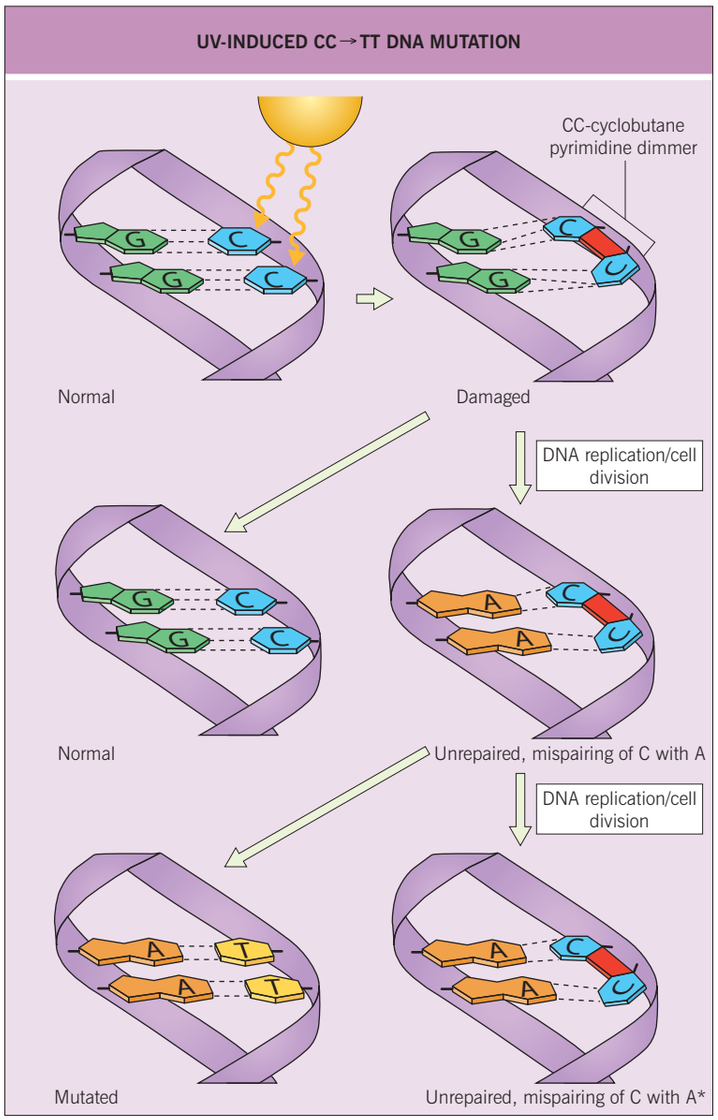


Fig. 86.13 UV-induced CC→TT DNA mutation. Following formation of a pyrimidine dimer between two adjacent cytosines and subsequent cell division, a CC→TT mutation results. This represents a UV signature mutation. *May give rise to more C→T mutations.

evidence that these lesions are induced by exposure to UV light. As noted previously, these *p53* mutations are found in very early precursor lesions and they result in a UV-mutator phenotype, clearly implicating UV exposure in the earliest stages of skin carcinogenesis (tumor initiation). The picture is different in BCCs and cutaneous melanomas, where *p53* mutations are later events in tumor progression. However, when they do occur in these two tumor types, the *p53* mutations are often C→T transitions as well. These findings point to UV exposure as not only an initiator of skin cancers, but also a contributor to its progression.

Most BCCs are characterized by an aberrant activation of the hedgehog signaling pathway, with mutations in *PTCH* and *SMO* (see Ch. 107). Many of the mutations in these genes are UV signature mutations, clearly implicating UV exposure in the pathogenesis of BCC. In cutaneous melanoma, several crucial genes have also been shown to carry C→T transitions, including *PTEN* and *CDKN2A* (see below)[41,42]. Recently, the entire genome of a melanoma metastasis cell line was sequenced and then compared to the sequence of a lymphoblastoid cell line from the same person[43]. A total of 33 345 somatic single and tandem base substitution mutations were detected in the melanoma cells, of which the majority (~70%) were UV signature mutations (C→T transitions). While the etiology of melanoma is clearly complex, these findings provide molecular evidence for UV exposure playing a significant role. Both melanomas and melanocytic nevi have a high frequency of T:A→A:T mutations in *BRAF* at one particular site (amino acid substitution V600E). Because these *BRAF* mutations have been found predominantly in melanomas from intermittently sun-exposed areas (and much less frequently in melanomas from unexposed areas or chronically UV-exposed areas), it has been suggested that this type of mutation is UV-induced[44]. However, such a mutation is not generated by any of the common types of UV-induced DNA lesions, and the pre-mutagenic lesion (i.e. the type of DNA damage that causes this type of mutation) remains elusive. Perhaps it is an unidentified, UV-induced thymine or adenine adduct.

Protection Against Photocarcinogenesis

To ensure that most of the damage inflicted by sun exposure will not lead to the formation of skin cancer, UV-exposed cells have several lines of defense against the photocarcinogenesis cascade (Fig. 86.14).

- In order to prevent DNA damage as a consequence of UV exposure, the epidermis has constitutive as well as inducible melanin. It can increase its thickness (which reduces UV exposure in the basal layer), and there are antioxidative enzymes within the epidermis which quench reactive oxygen species and reduce the formation of oxidative DNA damage[45]. Cellular melanin is a mixture of different polymerized pigments that absorb UV radiation (see Ch. 65). Illumination of the brown to black eumelanin generates the superoxide radical within the molecule, which is very rapidly scavenged. The red or yellow pheomelanin is a less effective radical scavenger; upon UV exposure, pheomelanin is degraded, with a net formation of superoxide. Therefore, pheomelanin is regarded as a photosensitizer, rather than a photoprotector like eumelanin.
- In order to prevent mutation formation after DNA damage has been introduced, cells have several different DNA repair systems (see above) as well as the ability to bypass DNA damage without inducing mutations. Cells also have the ability to halt proliferation (cell cycle arrest) in order to allow more time for repair, reducing the chance of replicating a damaged template, or they can die via apoptosis when they accrue overwhelming DNA damage.
- Even after mutations have fixed the inflicted damage for the lifetime of the affected cells, the organism still removes most of these cells, e.g. via immune surveillance.

Some of these protective mechanisms can be upregulated, facilitating an adaptive response to repeated UV "attacks". These include pigmentation, skin thickening, and antioxidant enzymes. DNA excision repair can also be upregulated in an SOS-like response[46]. In contrast, immune surveillance is down-regulated following UV exposures, likely contributing significantly to photocarcinogenesis (see above).

Exposure to UVA cannot be regarded as harmless, and dermatologists must warn not only against UVB but also UVA exposure. There are at least three areas where increased exposure to UVA might pose a public health risk.

- The use of high-dose UVA emitters for cosmetic purposes in tanning parlors is currently growing exponentially, and many researchers fear a second "melanoma epidemic" for that reason. It is estimated that approximately 35 million Americans use tanning beds or sunlamps every year[46a], especially teenagers and young adults.
- An increase in UVA exposure can also result from the use of sunscreens. According to Autier et al.[47], sunscreens are often used for their ability to prolong sun exposure. Since broad-spectrum sunscreens still do not filter UVA as efficiently as UVB, an increase in UVA exposure as a consequence of sunscreen use remains a problem.
- High-dose UVA1 phototherapy has been shown to be an effective treatment for atopic dermatitis, scleroderma, cutaneous T-cell lymphoma, and other dermatoses. However, the long-term risks of this treatment have not been established. Considering the possible role of UVA in the development of cutaneous melanoma, one must weigh the risks and benefits of the use of high-dose UVA1, especially in children.

In addition to the intrinsic protective mechanisms that counteract the chain of events leading to the formation of skin cancer, there are

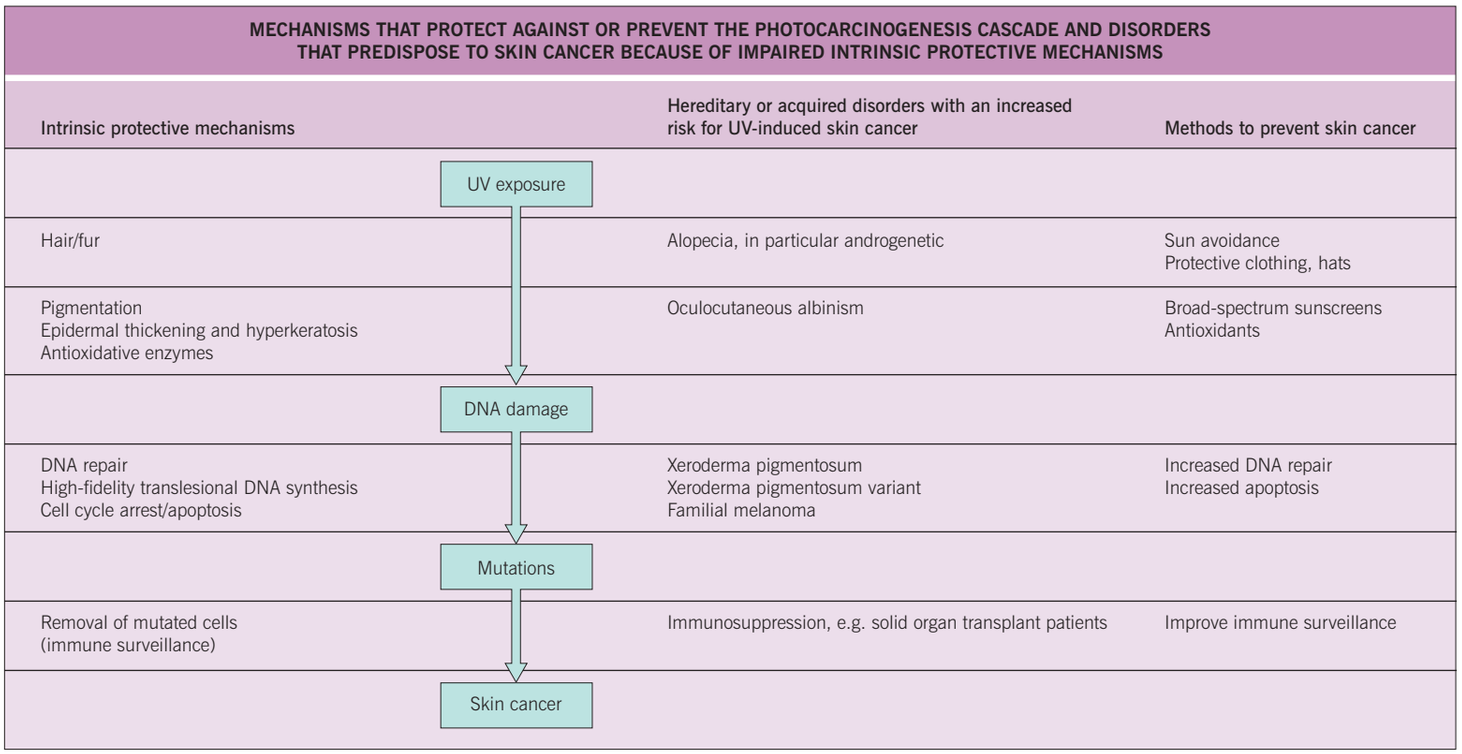


Fig. 86.14 Mechanisms that protect against or prevent the photocarcinogenesis cascade and disorders that predispose to skin cancer because of impaired intrinsic protective mechanisms. Several intrinsic mechanisms protect against the formation of skin cancer following UV exposure at different points of the photocarcinogenesis cascade of events. These mechanisms are impaired in disorders with increased risk for UV-induced skin cancer. Each step of the photocarcinogenesis cascade can be targeted for therapeutic modification and reduction of skin cancer risk.

extrinsic protective agents and protective behaviors that can help individuals reduce their skin cancer risk (see Fig. 86.14).

In order to prevent or reduce UV irradiation of the skin, one can avoid the sun, especially around midday, stay in the shade, wear protective clothing and/or wear sunscreens. Sunscreens are topical preparations that attenuate UV radiation before it enters the skin, by reflection, absorption or both (see Ch. 132). Reflectant products reflect UV from a film of inert metal particles, usually zinc oxide or titanium dioxide in a suitable vehicle. Absorbent sunscreens absorb UVB, UVA or both into specific chemicals (UV filters) and re-emit the energy as insignificant quantities of heat.

Sunscreens protect not only against the acute skin injury of sunburn, but also against UV-induced immune suppression, photoaging and skin cancer. The sun protection factor (SPF) of sunscreens, which indicates by what factor sunburn is prevented by sunscreen use (see Ch. 132), does not correlate well with protection factors for other non-erythema endpoints. Therefore, the SPF cannot be regarded as a reliable guide to non-erythema and chronic endpoints[48].

A good sunscreen should provide broad-spectrum protection against UVB and UVA, ideally in a balanced way with equal protection against both UVA and UVB. Additionally, it should have a comfortable vehicle to ensure its regular use and be photostable. Filters that degrade with UV exposure lose their effectiveness and need reapplication. In addition, degradation products may induce further reactions. This is why unstable sunscreen filters are more likely to cause photoallergic reactions.

In order to prevent oxidative damage – in particular, oxidative DNA damage – the addition of antioxidants to sunscreens has been advocated. However, their protective effects against any of the above-mentioned endpoints have not been well established, or are marginal at best. In addition, the finding that oxidative DNA damage might not contribute significantly to UVA-induced mutagenesis (as was previously thought) brings into question whether antioxidants provide any protection against skin cancer.

In order to be effective, sunscreens need to be applied in sufficient thickness and to all UV-exposed areas. Also, sunscreens should not be used to prolong sun exposure, because this would offset any protective effect and might even increase exposure to unfiltered or less-well-filtered wavelengths, such as UVA. As noted previously, this is one of the explanations for the seemingly contradictory finding (in some studies) that the use of sunscreens might increase, rather than decrease, the incidence of skin cancer, especially melanoma[49].

Topical application of DNA repair enzymes has been shown to increase DNA repair in skin cells and to accelerate removal of DNA photoproducts. In patients with XP, such applications have been reported to reduce the occurrence of actinic keratoses[50]. This indicates that it may be possible to prevent the formation of mutations after the introduction of DNA photoproducts with the use of such "enzymatic sunscreens". Similarly, it may be possible in the future to accelerate or improve the removal of damaged or mutated cells (e.g. by increasing apoptosis of damaged cells) or to improve immune surveillance (e.g. by vaccination).

RELATED DISEASES

Many disorders with an increased risk of UV-induced skin cancer are characterized by a deficiency in the intrinsic protective mechanisms discussed above (see Fig. 86.14). For example, men with androgenetic alopecia have a much higher risk of developing skin cancers on the scalp than do men who have retained their UV-protective hair cover. Diminution or lack of protective melanin, as in oculocutaneous albinism, increases the amount of DNA damage in the basal layer of the epidermis after UV irradiation and, subsequently, the risk of skin cancer, especially SCC. The different DNA repair defects of XP and the DNA damage-processing defect of XP variant (see Table 86.3) generate a UV-mutator phenotype, with an increased chance that DNA damage will result in the formation of a mutation.

Some cases of familial melanoma are caused by a germline mutation in the *CDKN2A (INK4A)* locus, which encodes two protein products, p16 and $p14^{ARF}$ (see Ch. 107). Intact p16 induces a G1 cell cycle arrest by inhibiting cyclin-dependent kinases 4 and 6, which in turn inhibits the phosphorylation of the retinoblastoma protein. Loss of p16 function, therefore, entails a loss of the G1 checkpoint, leading to abnormal

proliferation, unrestricted progression into S phase, and, importantly, no cell cycle arrest after UV irradiation. The second protein product, $p14^{ARF}$, is an upstream regulator of p53, which is also an important factor in mediating UV-induced growth arrest.

It is not easy to explain why disruption of cell cycle control due to silencing of or loss-of-function mutations in *CDKN2A* predisposes a person to primarily melanoma and much less so to internal neoplasms. Of note, loss of p16 or $p19^{ARF}$ (murine equivalent of $p14^{ARF}$) function not only impairs cell cycle control, but also impairs the ability of affected cells to repair DNA photoproducts (leading to a UV-mutator phenotype), perhaps providing an answer as to why silencing or mutations of *CDKN2A* predispose an individual to primarily UV-induced tumors[51]. The fact that germline *CDKN2A* mutations predispose to melanoma, but not to SCC or BCC, might be explained by the previously mentioned resistance of melanocytes to undergo apoptosis, while keratinocytes require another mutation (mostly in *p53*) to fail to undergo apoptosis despite increased UV-induced DNA damage[52].

In addition to inducing apoptosis in cells with overwhelming UV-induced DNA damage, p53 protects against UV mutagenesis by inducing cell cycle arrest after UV-induced damage and by stimulating DNA repair by directly binding to DNA repair enzymes. Consequently, loss of p53 function has been shown to result in a UV-mutator phenotype and reduced repair of UV-induced DNA damage. Li–Fraumeni syndrome is characterized by a germline mutation in the *p53* gene, and patients are predisposed to developing malignancies of various internal organs and possibly cutaneous melanoma[53].

REFERENCES

1. Anderson RR, Parrish JA. The optics of human skin. J Invest Dermatol. 1981;77:13–19.
2. Bruls WAG, Slaper H, van der Leun JC, Berrens L. Transmission of human epidermis and stratum corneum as a function of thickness in the ultraviolet and visible wavelengths. Photochem Photobiol. 1984;40:485–95.
3. Yarosh D, Dong K, Smiles K. UV-induced degradation of collagen I is mediated by soluble factors released from keratinocytes. Photochem Photobiol. 2008;84:67–8.
4. Young AR, Chadwick CA, Harrison GI, et al. The similarity of action spectra for thymine dimers in human epidermis and erythema suggests that DNA is the chromophore for erythema. J Invest Dermatol. 1998;111:982–8.
5. Krutmann J, Schroeder P. Role of mitochondria in photoaging of human skin: the defective powerhouse model. J Investig Dermatol Symp Proc. 2009;14:44–9.
6. Moulin G, Thomas L, Vigneau M, Fiere A. [A case of unilateral elastosis with cysts and comedones. Favre-Racouchot syndrome]. Ann Dermatol Venereol. 1994;121:721–3.
7. El Ghissassi E, Baan R, Straif K, et al. A review of human carcinogens - part D: radiation. Lancet Oncol. 2009;10:751–2.
8. Schwarz T. The dark and the sunny sides of UVR-induced immunosuppression: photoimmunology revisited. J Invest Dermatol. 2010;130:49–54.
9. de Gruijl FR, Sterenborg HJ, Forbes PD, et al. Wavelength dependence of skin cancer induction by ultraviolet irradiation of albino hairless mice. Cancer Res. 1993;53:53–60.
10. Rünger TM. The role of UVA in the pathogenesis of melanoma and non-melanoma skin cancer. Photodermatol Photoimmunol Photomed. 1999;15:212–16.
11. Gallagher RP, Spinelli JJ, Lee TK, et al. Tanning beds, sunlamps, and risk of cutaneous malignant melanoma. Cancer Epidemiol Biomarkers Prev. 2005;14:562–6.
12. Veierod MB, Weiderpass E, Thorn M, et al. A prospective study of pigmentation, sun exposure, and risk of cutaneous malignant melanoma in women. J Natl Cancer Inst. 2003;95:1530–8.

12a. Lazovich D, Vogel RI, Berwick M, et al. Indoor tanning and risk of melanoma: A case-control study in a highly exposed population. Cancer Epidemiol Biomarkers Prev. 2010;19;1557–68.

13. Autier P, Doré JF, Schifflers E. Melanoma and use of sunscreens: an EORTC case-control study in Germany, Belgium, and France. The EORTC melanoma cooperative group. Int J Cancer. 1995;61:749–55.
14. De Fabo EC, Noonan FP, Fears T, Merlino G. Ultraviolet B but not ultraviolet A radiation initiates melanoma. Cancer Res. 2004;64:6372–6.
15. Gilchrest BA, Eller MS, Geller AC, Yaar M. The pathogenesis of melanoma induced by ultraviolet radiation. N Engl J Med. 1999;340:1341–8.
16. Cadet J, Sage E, Douki T. Ultraviolet radiation-mediated damage to cellular DNA. Mutat Res. 2005;571:3–17.
17. Perdiz D, Grof P, Mezzina M, et al. Distribution and repair of bipyrimidine photoproducts in solar UV-irradiated mammalian cells. J Biol Chem. 2000;275:26732–42.
18. Piette J, Merville-Louis MP, Decuyper J. Damages induced in nucleic acids by photosensitization. Photochem Photobiol. 1986;44:793–802.
19. Danpure HJ, Tyrrell RM. Oxygen-dependence of near UV (365 nm) lethality and the interaction of near UV and x-rays in two mammalian cell lines. Photochem Photobiol. 1976;23:171–7.
20. Kvam E, Tyrell RM. Induction of oxidative DNA base damage in human skin cells by UV and near visible radiation. Carcinogenesis. 1997;18:2379–84.
21. Douki T, Reynaud-Angelin A, Cadet J, Sage E. Bipyrimidine photoproducts rather than oxidative lesions are the main type of DNA damage involved in the genotoxic effect of solar UVA radiation. Biochemistry. 2003;42:9221–6.
22. Darr D, Fridovich I. Free radicals in cutaneous biology. J Invest Dermatol. 1994;102:671–5.
23. Kielbassa C, Roza L, Epe B. Wavelength dependence of oxidative DNA damage induced by UV and visible light. Carcinogenesis. 1997;18:811–16.
24. Rünger TM, Kappes UP. Mechanisms of mutation formation with long-wave ultraviolet light (UVA). Photodermatol Photoimmunol Photomed. 2008;24:2–10.
25. Rünger TM. C to T transition mutations are not solely UVB-signature mutations, because they are also generated by UVA. J Invest Dermatol. 2008;128:2138–40.
26. Dunn J, Potter M, Rees A, Rünger TM. Activation of the Fanconi anemia/BRCA pathway and recombination repair in the cellular response to solar UV. Cancer Res. 2006;66:11140–7.

26a. Rizzo J, Dunn J, Rees A, Rünger TM. No formation of DNA double strand breaks and no activation of recombination repair with UVA. J Invest Dermatol. 2011;131:1139–48.

27. Lindahl T, Wood RD. Quality control by DNA repair. Science. 1999;286:1897–905.
28. de Boer J, Hoeijmakers JHJ. Nucleotide excision repair and human syndromes. Carcinogenesis. 2000;21:453–60.
29. Bootsma D. Nucleotide excision repair syndromes: xeroderma pigmentosum, Cockayne syndrome, and trichothiodystrophy. In: Vogelstein B, Kinzler KW (eds). The Genetic Basis of Human Cancer. New York: McGraw-Hill, 2002:211.
30. Wei Q, Lee JE, Gershenwald JE, et al. Repair of UV light-induced DNA damage and risk of cutaneous malignant melanoma. J Natl Cancer Inst. 2003;95:308–15.
31. Blankenburg S, Konig IR, Moessner R, et al. Assessment of 3 xeroderma pigmentosum group C gene polymorphisms and risk of cutaneous melanoma: a case-control study. Carcinogenesis. 2005;26:1085–90.
32. Wei Q. Effect of aging on DNA repair and skin carcinogenesis: a minireview of population-based studies. J Investig Dermatol Symp Proc. 1998;3:19–22.
33. Woodgate R. A plethora of lesion-replicating DNA polymerases. Genes Develop. 1999;13:2191–5.
34. Johnson RE, Kondratick S, Prakash S, Prakash L. hRAD30 mutations in the variant form of xeroderma pigmentosum. Science. 1999;285:263–5.
35. David SS, O'Shea VL, Kundu S. Base-excision repair of oxidative DNA damage. Nature. 2007;447:941–50.
36. Kappes UP, Rünger TM. No major role for 7,8-dihydro-8-oxoguanine in ultraviolet light-induced mutagenesis. Radiat Res. 2005;164:440–5.
37. Loeb LA. Cancer cells exhibit a mutator phenotype. Adv Cancer Res. 1998;72:25–56.
38. Wikondahl NM, Brash DE. Ultraviolet radiation induced signature mutations in photocarcinogenesis. J Investig Dermatol Symp Proc. 1999;4:6–10.
39. Ikehata H, Kawai K, Komura J, et al. UVA1 genotoxicity is meditated not by oxidative damage but by cyclobutane pyrimidine dimers in normal mouse skin. J Invest Dermatol. 2008;128:2289–96.
40. Rünger TM. How different wavelengths of the ultraviolet spectrum contribute to skin carcinogenesis: The role of cellular DNA damage responses. J Invest Dermatol. 2007;127:2103–5.
41. Hocker T, Tsao H. Ultraviolet radiation and melanoma: a systematic review and analysis of reported sequence variants. Hum Mutat. 2007;28:578–88.
42. Wang Y, DiGiovanna JJ, Stern JB, et al. Evidence of ultraviolet type mutations in xeroderma pigmentosum melanomas. Proc Natl Acad Sci U S A 2009;106:6279–84.
43. Pleasance ED, Cheetham RK, Stephens PJ, et al. A comprehensive catalogue of somatic mutations from a human cancer genome. Nature. 2010;463:191–6.
44. Maldonado JL, Fridlyand J, Patel H, et al. Determinants of BRAF mutations in primary melanomas. J Natl Cancer Inst. 2003;95:1878–90.
45. Halliwell B, Gutteridge JMC. Antioxidant defenses. In: Halliwell B, Gutteridge JMC (eds). Free Radicals in Biology and Medicine. New York: Oxford University Press, 1999:105.
46. Smith ML, Seo YR. p53 regulation of DNA excision repair pathways. Mutagenesis. 2002;17:149–56.

46a. Choi K, Lazovich D, Southwell B, et al. Prevalence and characteristics of indoor tanning use among men and women in the United States. Arch Dermatol. 2010;146:1356–61.

47. Autier P, Doré JF, Négrier S, et al. Sunscreen use and duration of sun exposure: a double-blind, randomized trial. J Natl Cancer Inst. 1999;91:1304–9.
48. Young AR, Walker SL. Sunscreens: photoprotection of non-erythema endpoints relevant to skin cancer. Photodermatol Photoimmunol Photomed. 1999;15:221–5.
49. Weinstock MA. Do sunscreens increase or decrease melanoma risk: an epidemiologic evaluation. J Investig Dermatol Symp Proc. 1999;4:97–100.
50. Yarosh D, Klein J, O'Conner A, et al. Effect of topically applied T4 endonuclease V in liposomes on skin cancer in xeroderma pigmentosum: a randomized study. Lancet. 2001;357:926–9.
51. Sarkar-Agrawal P, Vergilis I, Sharpless NE, et al. Impaired processing of DNA photoproducts and ultraviolet hypermutability with loss of p16INK4a or p19ARF. J Natl Cancer Inst. 2005;96:1790–3.
52. Rünger TM, Vergilis I, Sarkar-Agrawal P, et al. How disruption of cell cycle regulating genes might predispose to sun-induced skin cancer. Cell Cycle. 2005;4:643–5.
53. Malkin D, Li FP, Strong LC, et al. Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science. 1990;250:1233–8.

This page intentionally left blank

Photodermatologic Disorders 87

Henry W Lim and John LM Hawk

All skin is photosensitive as a result of containing molecules of appropriate shape (chromophores) that absorb ultraviolet radiation (UVR) energy during exposure. The latter is then either re-emitted harmlessly as less active radiation or diverted to power thermochemical reactions, leading to molecular, cellular, tissue and clinical changes, some repaired, some permanent. DNA is the most ubiquitous absorber, initiating UVR-induced changes including sunburning, tanning, hyperplasia, aging and carcinogenesis. Only certain individuals develop abnormal reactions, otherwise known as the photodermatoses, as a result either of *abnormal* tissue responses following normal absorption by endogenous molecules, or of largely *expected* responses following absorption by porphyrins or exogenously ingested or applied photosensitizing drugs or chemicals (Table 87.1). An algorithmic guide to the diagnosis of cutaneous photosensitivity is provided in Figure 87.1.

CLASSIFICATION OF PHOTODERMATOSES
• Immunologically mediated disorders (see Table 87.2) • Defective DNA repair disorders • Photoaggravated dermatoses • Chemical- and drug-induced photosensitivity – Exogenous: ingested or externally applied drugs or chemicals – Endogenous: cutaneous porphyrias; perhaps the Smith–Lemli–Opitz syndrome

Table 87.1 Classification of photodermatoses.

CLASSIFICATION OF IMMUNOLOGICALLY MEDIATED PHOTODERMATOSES
• Polymorphic light eruption • Actinic prurigo • Hydroa vacciniforme • Chronic actinic dermatitis • Solar urticaria

Table 87.2 Classification of immunologically mediated photodermatoses.

ABNORMAL CUTANEOUS EFFECTS OF UVR EXPOSURE

Polymorphic light eruption is consistently the most common photodermatosis, based upon relative frequency analyses from photodermatology centers worldwide; it is followed (in decreasing order of frequency) by photoaggravated dermatoses, drug-induced photosensitivity, chronic actinic dermatitis and solar urticaria[1]. It has been well documented that photodermatoses have a significant negative effect on patients' quality of life[2,3].

Immunologically-Mediated Photodermatoses

This group of disorders is outlined in Table 87.2.

Polymorphic light eruption

Synonyms: ■ Polymorphous light eruption ■ Benign summer light eruption (one clinical variant) ■ Juvenile spring eruption (one clinical variant)

Key features

- The most common photodermatosis
- Presents with papules, vesicles or plaques within hours of sun exposure; lasts for a few days
- Action spectra: UVB, UVA, and, rarely, visible light
- Management: photoprotection, narrowband (NB)-UVB, PUVA; occasionally, brief courses of oral corticosteroids for acute attacks

Introduction

Polymorphic light eruption (PMLE) is a common, sunlight-induced eruption affecting individuals of all races and skin colors[4]. Attacks are intermittent and follow minutes to hours (rarely days) of exposure of the skin to sunlight or artificial UVR. Non-scarring, pruritic, erythematous papules, papulovesicles, vesicles or plaques then develop minutes to hours later. The eruption is generally most severe in the spring and early summer, usually disappearing completely in the winter.

History

PMLE was first described by Carl Rasch in 1900 and mentioned again by Haxthausen in 1918.

Epidemiology

PMLE affects men and women of every race and skin type. The prevalence in the general population is inversely related to latitude, being highest in Scandinavia (22%), high in the UK and northern US (10–15%), and low in Australia (5%) and equatorial Singapore (around 1%)[4]. This is probably due to the development of UVR-induced immunologic tolerance, sometimes referred to as "hardening", secondary to constant solar exposure in sunny climates. Women are affected slightly more often than men, with the second and third decades being the most common times of onset.

Pathogenesis

Attacks of PMLE are produced by exposure to UVR (and perhaps, on occasion, visible light) from sunlight or other sources such as tanning beds. Spring and summer sunlight in temperate regions is most likely to induce outbreaks, however, generally at lower than the *m*inimal *e*rythema *d*ose (MED). Action spectra range from broadband UVB (BB-UVB) to UVA and rarely to visible radiation. Photoprovocation studies have shown a positive response in 50% of patients to narrowband UVB (NB-UVB), 50% to BB-UVA, and 80% to both UVB and UVA[5].

PMLE appears to be a delayed-type hypersensitivity (DTH) response to as yet undefined, endogenous cutaneous photoinduced antigens[3], although a form of heat shock protein has been suggested as one possible antigen[6]. Timed biopsy specimens, following solar-simulated irradiation (~0.6 MED), have shown perivascular infiltrates of lymphocytes, primarily $CD4^+$ (within hours) and $CD8^+$ (within days), in association with an increased number of dermal and epidermal antigen-presenting cells. Overall, these findings are suggestive of a DTH response. In addition, E-selectin, vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) are expressed in the same pattern as in other DTH responses.

Susceptibility to PMLE appears to be genetic, with up to 70% of the population having a propensity for developing this condition, but not all expressing it, because of variations in disease penetrance[7]. The inherited abnormality appears to be a *resistance* to the normal

UVR-induced suppression of the induction[8], but not the elicitation[9], of cutaneous DTH responses. As a result, in PMLE, a lesser degree of cutaneous immunosuppression following UVR exposure (compared to normal individuals) likely results in a persistent ability to mount a DTH response against UVR-altered endogenous cutaneous molecules, leading to the development of clinical lesions. Possible underlying mechanisms include: (1) an under-expression of apoptotic-cell clearance genes in keratinocytes, thus prolonging antigen presence; and/or (2) inefficient free radical removal, thereby increasing photo-antigen production. In evolutionary terms, UVR-induced cutaneous immunosuppression may protect against developing disruptive PMLE, but it can increase the risk of skin cancer; of note, PMLE patients appear to have a reduced tendency to develop such cancers[10].

Clinical features

PMLE occurs most commonly during the spring and early summer, following minutes to hours (occasionally days) of sun exposure. Outbreaks may also occur after exposure to snow-reflected sunlight or tanning bed use. The eruption develops minutes to hours after UVR exposure, then fades over one to several days or occasionally weeks, particularly with continuing exposure. However, the likelihood of occurrence often diminishes or ceases as summer or a sunny vacation proceeds, probably from the development of immunologic tolerance[9], sometimes called 'hardening'.

Typically, some, but virtually never all, of the exposed skin is affected. Lesions are basically symmetrically distributed, but frequently in a patchy fashion. Areas that are normally exposed to sunlight (e.g. face,

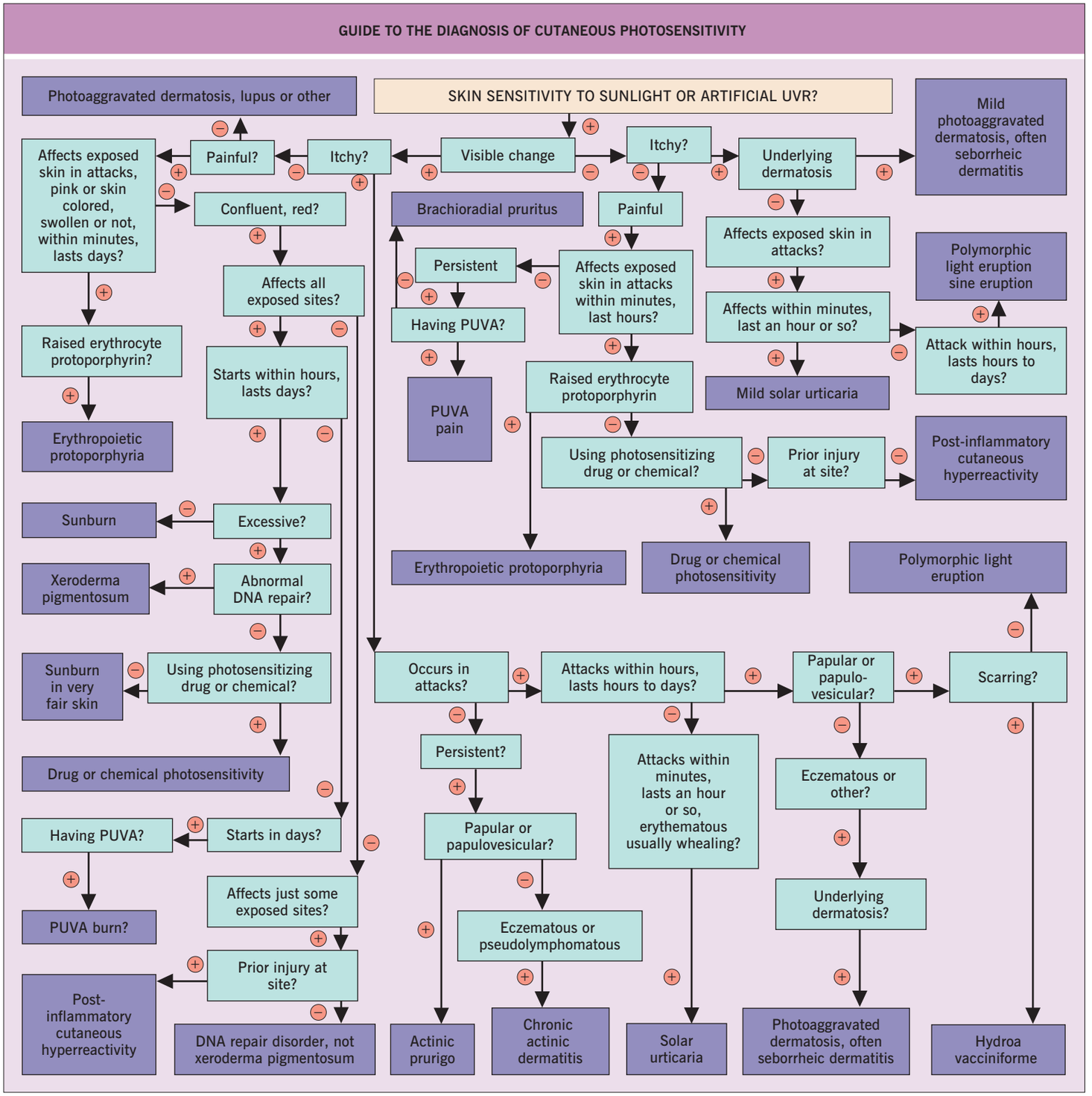


Fig. 87.1 Guide to the diagnosis of cutaneous photosensitivity. The diagnosis can generally be made from patient history and clinical findings, provided the titers of antinuclear antibodies and other LE-associated antibodies are normal.

Fig. 87.2 Polymorphic light eruption. Edematous erythematous plaques on the cheeks in a young child.

Fig. 87.3 Polymorphic light eruption of the upper extremity. Small papules (**A**), papulovesicles (**B**), and larger edematous papules and plaques (**C**).

dorsal hands) are often spared. The distribution pattern and type of lesions in a given patient are usually consistent. Areas commonly affected are the face, neck, outer aspects of the arms, and dorsal surfaces of the hands (Figs 87.2 & 87.3), but there may be more widespread involvement of sun-exposed sites (Fig. 87.4).

Lesions vary widely amongst patients, but are generally mildly to markedly pruritic, grouped, erythematous or skin-colored papules of varying sizes, not infrequently coalescing into large, smooth or unevenly surfaced plaques. In darkly pigmented individuals, the most common morphology is grouped, pinhead-sized papules in sun-exposed areas (see Fig. 87.3A). Vesicles, bullae, papulovesicles and confluent edematous swelling (particularly of the face) are also observed; rarely, only pruritus occurs. Occasionally, the helices of the ears (particularly in boys) may be principally affected, often with vesicles, in a form of PMLE referred to as juvenile spring eruption. General malaise, headache, fever, nausea and other symptoms rarely occur. PMLE may be lifelong; however, in a 32-year follow-up of 94 patients, the disease improved or resolved in 58% over a period of 16 years, and in 75% over a period of 32 years.

Pathology

There is variable epidermal spongiosis and a superficial and deep, perivascular and periappendageal, lymphohistiocytic dermal infiltrate, often with scattered eosinophils and neutrophils. Significant papillary dermal edema occurs commonly (Fig. 87.5). Rarely, difficulty in distinction from cutaneous lupus may occur if interface changes are significant, or from lymphoma if the dermal inflammatory cell infiltrate is marked.

Differential diagnosis

PMLE is distinguished from lupus erythematosus (LE), photoaggravated dermatoses (e.g. atopic dermatitis, seborrheic dermatitis), solar urticaria, and, rarely, erythropoietic protoporphyria (EPP) by history, clinicopathologic correlation and laboratory evaluation (Table 87.3; see Fig. 87.1). For photoaggravated dermatoses, the characteristic clinical features of the primary disorder and negative phototesting usually allow distinction.

Treatment

PMLE in its milder forms may respond to photoprotection. In patients with more severe disease, prophylactic, two-to-three times weekly sessions of NB-UVB phototherapy or psoralen photochemotherapy (PUVA), usually for 15 sessions in the spring, will be effective for several months[11]. For NB-UVB, an initial starting dose of 50–70% of the MED for NB-UVB is recommended, with the dose then increased by 10–15% per treatment. For PUVA, 0.5–0.6 mg/kg of 8-methoxypsoralen is given one hour before UVA exposure; the starting UVA dose ranges from 0.5 to 3 J/cm^2, depending upon skin phototype. Oral prednisone (0.5–1 mg/kg) may be used during the initial seven to ten days of phototherapy to minimize photoexacerbation. Once hardening is achieved, patients are asked to expose themselves weekly to noonday sunlight for 15–20 minutes (without sunscreen) for the remainder of the sunny season as maintenance.

Other treatment modalities include oral prednisone (<0.5 mg/kg, usually given for 5–7 days during vacations)[12] and, in very severe cases, azathioprine or cyclosporine. The efficacy of antimalarials, although popular, has been inconsistent in controlled trials[13,14].

Fig. 87.4 Polymorphic light eruption of the thigh. Edematous papules becoming confluent into plaques. *Courtesy, Jean L Bolognia, MD.*

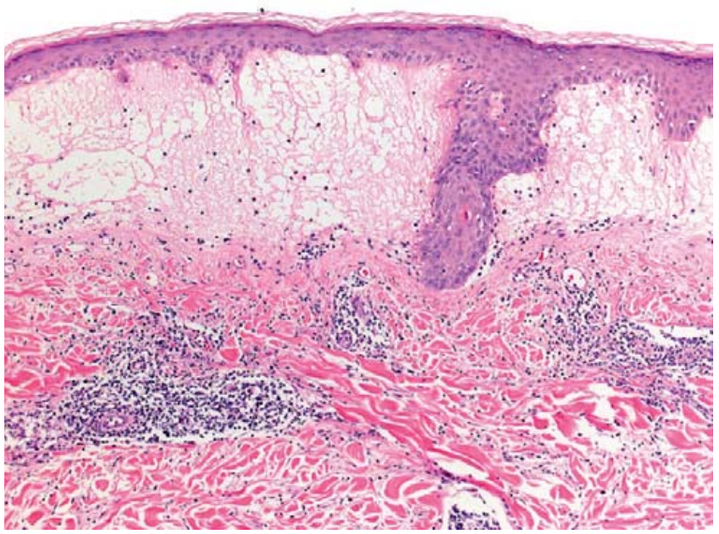


Fig. 87.5 Histopathology of polymorphic light eruption. Within the dermis, there is a perivascular mononuclear cell infiltrate as well as marked papillary edema. *Courtesy, Lorenzo Cerroni, MD.*

LABORATORY EVALUATION OF PHOTOSENSITIVITY
Routine histology
Antinuclear antibodies
Anti-Ro/SSA, -La/SSB antibodies
Plasma porphyrins, followed by complete porphyrin profile if positive (see Ch. 49)
Phototesting to UVA, UVB and visible light
Photopatch testing (see Fig. 87.12)
In infants and children, urinary amino acids

Table 87.3 Laboratory evaluation of photosensitivity.

Actinic prurigo

Synonyms: ■ Hutchinson's summer prurigo ■ Familial (or hereditary) polymorphous light eruption of American Indians ■ Hydroa aestivale

Key features

- Severe form common in Native Americans (especially Mestizos), often with cheilitis and conjunctivitis
- Can occur in all races, including Caucasians
- Childhood onset; often resolution by adolescence, but can persist indefinitely
- Intensely pruritic, crusted papules or nodules in sun-exposed sites
- Strong association with HLA-DR4 (DRB1*0401) and subtype DRB1*0407
- Management: photoprotection, NB-UVB, PUVA, thalidomide, topical calcineurin inhibitors

Introduction

Actinic prurigo is a not uncommon, sunlight-induced, pruritic and crusted, papular or nodular eruption involving uncovered and, to a lesser extent, covered skin[4,15]. A similar condition, first described in the 1960s and 1970s, affects North, Central and South Americans of native or mixed race. Actinic prurigo may be a persistent variant of PMLE.

History

Hutchinson first described this disorder in 1879, followed in 1918 by Haxthausen, who described it as a PMLE variant. In 1968, Londoño coined the term "actinic prurigo".

Epidemiology

Actinic prurigo is particularly common in Native Americans, especially Mestizos (mixed American Indian and European ancestry) and those living at high altitudes. It also occurs, but much less commonly, in Europe and the Far East. A familial form is relatively common.

Pathogenesis

UVR exposure is the provocative factor in actinic prurigo, in that the condition flares during the spring and summer and phototesting results are abnormal in approximately two-thirds of patients. Lesions can be provoked by UVB or UVA, with the remainder of patients (~1/3) having normal results.

The immunologic nature of actinic prurigo is supported by a study of Mexican Mestizo patients, where the remarkable therapeutic efficacy of thalidomide has been shown to be associated with an inhibition of TNF-α synthesis and the modulation of interferon-γ-producing $CD3^+$ cells[16]. The presence of a dense lymphocytic infiltrate and lymphoid follicles in lesional biopsy specimens from the lips provides further support for this concept[15].

Actinic prurigo may represent a persistent variant of PMLE, as clinical conversion between actinic prurigo and PMLE has been observed and in family studies, the two disorders are closely linked[17]. A strong association with HLA-DR4 (DRB1*0401) and subtype DRB1*0407 has been observed in both UK[17] and Mestizo patients[4], and this could well be the genetic factor that transforms PMLE into actinic prurigo. Indeed, the presence of this subtype is strongly suggestive of the diagnosis.

Clinical features

In general, actinic prurigo appears during childhood and is more frequently seen in girls. It often resolves by adolescence, but may persist indefinitely[4,15]. The eruption is usually worse during the summer in temperate climates, but is often not clearly related to sun exposure. In tropical regions of Latin America, it can persist year-round.

Erythematous papules or nodules, sometimes with hemorrhagic crusts due to excoriation, are present in sun-exposed sites, especially the face (including the nose) and the distal limbs (Fig. 87.6). Lesions may be scattered or densely distributed, and there are sometimes eczematous features or lichenification. Fine linear or pitted scars may appear as facial papules heal. In patients from the UK, involvement of covered sites, particularly the buttocks, has been well described

Fig. 87.6 Actinic prurigo. A The clinical features, including a photodistribution and worsening in the summer, are somewhat suggestive of polymorphous light eruption, but the lesions were persistent and the HLA type was that seen in association with actinic prurigo. Note the involvement of the ears. **B** The crusted papules are more dense on the distal arms.

Fig. 87.7 Actinic prurigo. This patient with severe actinic prurigo has involvement of the buttocks.

Fig. 87.8 Actinic prurigo. Significant cheilitis that is more severe on the lower lip in a Peruvian man with Native American (as well as European) ancestry.
Courtesy, Jean L Bolognia, MD.

(Fig. 87.7). Cheilitis and conjunctivitis are common in Native Americans, with cheilitis being the only clinical manifestation in up to 30% of Mestizo patients (Fig. 87.8)[4].

Pathology

In early lesions, there is epidermal spongiosis, acanthosis and a dermal perivascular mononuclear cell infiltrate with occasional eosinophils, but, unlike in PMLE, papillary edema is usually absent[15]. Later, crusts, more pronounced acanthosis, variable lichenification, excoriations, focal dermal papillary fibrosis and a heavier mononuclear cell infiltrate can be seen. These latter features may resemble those of chronic dermatitis, prurigo nodularis, or, very rarely, cutaneous B-cell lymphoma. Dermal lymphoid follicles have been observed in biopsy specimens taken from the lips[15]. Direct immunofluorescence microscopy is negative.

Differential diagnosis

Clinicopathologic correlation and laboratory evaluation (see Table 87.3) aid in excluding LE and childhood porphyrias. Insect bites are generally less persistent over time, while scabies is much more generalized and diagnosed by skin scrapings. Prurigo nodularis is not accentuated in sun-exposed skin.

Treatment

Constant photoprotection is helpful. For milder disease, topical corticosteroids and topical tacrolimus may be used. NB-UVB or PUVA should be considered next, with protocols similar to those for PMLE (see above). Resistant disease is best treated with oral thalidomide (50–100 mg nightly)[8,15], administered for several weeks until remission is achieved and then tapered to as low a maintenance dose as possible (e.g. 50 mg every second or third night). However, the risks of teratogenicity and peripheral neuropathy require very careful patient selection and supervision (see Ch. 130). Other possible systemic therapies include corticosteroids, azathioprine and cyclosporine.

Hydroa vacciniforme

Synonym: ■ Bazin's hydroa vacciniforme

Key features

- Very rare, childhood-onset photodermatosis
- Papules and plaques develop umbilicated vesiculation, followed by hemorrhagic crusting (often severe) and varioliform scarring
- Epstein-Barr viral infection has been detected in a number of patients
- Management requires very careful photoprotection, including against UVA, and perhaps low-dose phototherapy to avoid provocation

Introduction
Hydroa vacciniforme (HV) is a rare, sunlight-induced, childhood-onset, intermittent but permanently scarring disorder.

History
The condition was first reported by Bazin in 1862.

Epidemiology
HV is well recognized globally, including in the US, UK, continental Europe, Korea and Japan; it has a predilection for lightly pigmented individuals. Its rarity and lack of specific diagnostic tests (apart from its characteristic early histology) have made precise assessment of its distribution difficult. The condition typically has its onset during childhood, affecting boys slightly more often than girls and with more severe disease in boys. The disorder usually resolves during adolescence or early adulthood; rare familial cases have been noted[4,18].

Pathogenesis
Summer sunlight is generally required to provoke the eruption, although abnormal erythematous, or rarely vesicular, phototest responses to repeated monochromatic or broad-spectrum UVR exposure can be seen. While the exact nature of the reaction is unknown, its distribution, early time course and early clinical features are similar to those of PMLE, suggesting it may be a scarring variant of that condition. There have also been multiple reports from Asia and Latin America as well as Europe and the US of the presence of Epstein-Barr virus (EBV) within cutaneous lesions of apparent HV[19,20]. In these patients with chronic EBV infection, the clinical presentations can range from 'typical' HV to so-called severe HV-like eruptions. While no hematologic abnormalities were detected in the former group, those in the latter group had NK-cell lymphocytosis, exaggerated reactions to mosquito bites, and hemophagocytic syndrome. Several of the patients with severe HV-like eruptions have died of EBV-associated NK- or T-cell lymphoma or the hemophagocytic syndrome[19].

In a recent Japanese series, T cells positive for EBV RNA were detected in lesional skin infiltrates from 94% of children with clinically typical HV (17/18) and 11/11 patients with severe HV-like eruptions associated with systemic symptoms, but 0/32 skin biopsy samples from patients with various other dermatoses, including photodermatoses[19]. While the relationship between EBV infection and true photosensitive HV has yet to be firmly established, it is likely that HV and severe HV-like eruptions represent a clinical spectrum[20].

Clinical features
Symmetrical, clustered, pruritic or stinging erythematous macules develop in a photodistribution, especially on the face and dorsal aspects of the hands, within hours of summer sun exposure. Over the next several hours, the macules become tender papules or plaques surmounted by vesicles (Fig. 87.9) or bullae (often hemorrhagic), before umbilicating and condensing into hemorrhagic crusts over several days (Fig. 87.10). Healing then occurs over a period of weeks, leaving individual or confluent, sometimes telangiectatic, varioliform scars (see Fig. 87.10). Generalized malaise with fever or headache rarely accompanies the attacks. Of note, the quality of life in affected children was shown to be negatively impacted by their inability to play outdoors[18].

Fig. 87.9 Hydroa vacciniforme – early phase. There is a polymorphic light eruption-like appearance, but with vesicles around the mouth and umbilicated lesions on the nose.

Fig. 87.10 Hydroa vacciniforme. Hemorrhagic crusts are admixed with varioliform scars; the latter are the sequelae of repeated acute attacks. **A** Note the telangiectasias on the nasal tip. **B** More severe crusting and scarring.
A, Courtesy, Jean L Bolognia, MD.

Pathology
Progressive epidermal spongiosis precedes almost pathognomonic findings: prominent, reticular keratinocyte degeneration; the formation of intraepidermal vesicles containing fibrin and acute inflammatory cells; and confluent epidermal and occasionally focal upper dermal necrosis (Fig. 87.11)[4]. Early on, a perivascular lymphohistiocytic infiltrate is also seen, followed by neutrophilic invasion. Direct immunofluorescence microscopy findings are nonspecific.

Differential diagnosis
While LE and childhood porphyrias can be excluded by clinicopathologic correlation and laboratory evaluation (see Table 87.3), herpes simplex is excluded by a negative DFA assay or viral culture. In patients with severe HV-like eruptions associated with systemic EBV-related disease, the skin lesions typically become more severe and more widespread to include sun-protected sites; additional features include facial swelling (Fig. 87.12), ulcerated nodular skin lesions, exaggerated reactions to mosquito bites, high-grade fevers and hepatosplenomegaly, as

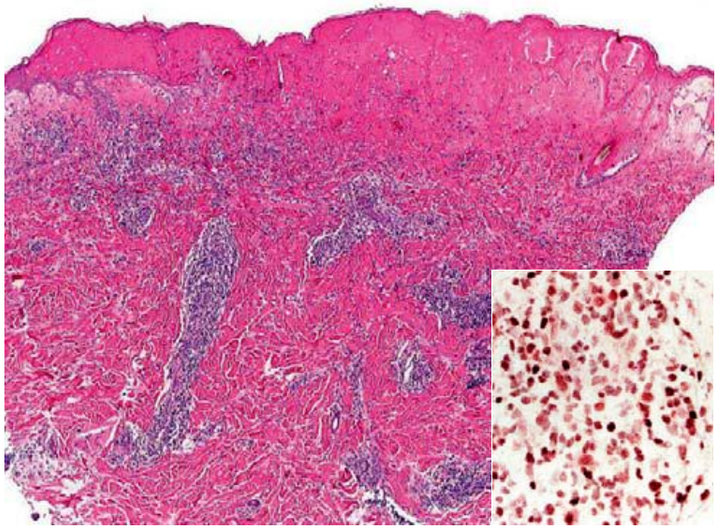


Fig. 87.11 Hydroa vacciniformis. Necrosis of the epidermis with dense, mainly perivascular, infiltrates of lymphocytes within the entire dermis. Note positivity of lymphocytes for Epstein-Barr virus as detected by *in situ* hybridization for EBER-1 (insert). *Courtesy, Lorenzo Cerroni, MD.*

Fig. 87.12 EBV-associated hydroa vacciniforme-like eruption. This Hispanic child had >50 000 copies of EBV DNA/100 000 WBCs as well as EBV DNA within skin lesions by *in situ* hybridization; he subsequently died of lymphoma. Note the facial edema, erythema, papulovesicles, hemorrhagic crusts and varioliform scars. *Courtesy, Richard Antaya, MD.*

well as leukopenia, thrombocytopenia, elevated hepatic transaminases and increased NK lymphocytes. A high circulating EBV DNA load is generally detected by PCR.

Treatment

HV is almost always refractory to treatment[4,18]. Photoprotection, including the use of tinted windows, can be useful in mild to moderate disease. Anecdotally, the following have been claimed as helpful: BB-UVB, NB-UVB, PUVA, β-carotene, antimalarials, azathioprine, thalidomide, cyclosporine and dietary fish oil.

Chronic actinic dermatitis

Synonyms: ■ Photosensitivity dermatitis and actinic reticuloid (PD/AR) syndrome ■ Persistent light reaction ■ Actinic reticuloid (severe clinical variant) ■ Photosensitivity dermatitis (milder UVB- and UVA-sensitive variant) ■ Photosensitive eczema (milder UVB only-sensitive variant)

Key features

- In sun-exposed areas, chronic eczematous eruption (acute, subacute or chronic lichenified) or pseudolymphomatous lesions
- Most common in men over 50 years of age
- Phototests positive to UVB; UVB and UVA; UVB, UVA and visible light; or just UVA
- Positive patch or photopatch tests common
- Management by photoprotection, avoidance of (photo)contact sensitizers, intermittent oral and topical corticosteroids, topical tacrolimus, low-dose PUVA, cyclosporine, azathioprine or mycophenolate mofetil
- Probability of spontaneous resolution is 10% over 5 years, 20% over 10 years

Introduction

Chronic actinic dermatitis (CAD)[21] is a rare, persistent, often disabling dermatosis of uncovered (and to a lesser extent, covered) skin, generally affecting older men, particularly in the summer. It is evoked by UVR and occasionally also visible light exposure, and probably represents a contact allergy-like DTH response against photoinduced endogenous antigen(s).

History

Reference to a condition suggestive of CAD was first made in 1933 by Haxthausen, then in the 1960s by Wilkinson in the UK and Jillson and Baughman in the US, with the latter authors terming it "persistent light reaction". In 1969, its severe form, actinic reticuloid, was described, followed shortly after by reports of two milder variants, photosensitive eczema and photosensitivity dermatitis. In 1979, the current global term, CAD, was introduced by Hawk and Magnus[22].

Epidemiology

CAD has been regularly observed in the US, continental Europe, UK, Far East, India and the African continent.

Pathogenesis

The action spectra for CAD include: UVB; UVB and UVA; UVB, UVA and visible light; and, rarely, just UVA, with UVB plus UVA representing the most common action spectrum. The eczematous clinical and histologic appearances of CAD, its dermal infiltrate of primarily $CD8^+$ T lymphocytes, and its pattern of adhesion molecule activation all closely mimic those of the DTH response of allergic contact dermatitis, strongly suggesting that CAD is a similar response, presumably against endogenous, photoinduced, cutaneous antigen(s).

CAD most commonly affects older outdoor workers and enthusiasts, often with a pre-existing allergic or photoallergic contact dermatitis to exogenous sensitizers such as *Compositae* or sunscreens, respectively[21,23]. It is therefore possible that chronic photodamage may partially ablate normal cutaneous immunosuppression in such individuals, with any exogenous contact dermatitis present simultaneously further enhancing cutaneous immune responsiveness against a presumptively weak endogenous photoantigen. It should be noted that positive patch testing to *Compositae*, commonly observed in the UK, has not been confirmed in the US and Japan[23].

It is likely that DNA, RNA or associated molecules may be involved in the pathogenesis of CAD, in that the shape of the CAD induction spectrum resembles that of sunburn inflammation, for which UVR absorption by DNA is now known to be responsible[21].

Clinical features

CAD occurs primarily in temperate zones, most commonly affecting older men of any race[21]; familial incidence has not been noted. The disorder may develop in previously normal skin, in patients with a prior history of dermatitis (in particular, photoallergic or allergic contact dermatitis), or perhaps rarely following longstanding oral drug photosensitivity or PMLE. Coexistent allergic contact sensitivity to plant antigens, fragrances or topical medications is also common. The CAD eruption is pruritic, patchy or confluent, and the eczematous lesions can be acute, subacute or chronic in nature; the latter is frequently associated with lichenification (Fig. 87.13). Scattered or widespread,

Fig. 87.13 Chronic actinic dermatitis. Chronic eczematous changes of the posterior neck with lichenification and a sharp cut-off at the collar in a patient with phototype V skin.

Fig. 87.14 Chronic actinic dermatitis. Lichenification and hyperpigmentation in sun-exposed sites with areas of depigmentation. Note the sparing of sun-protected areas (nasolabial fold and shoulder).

Fig. 87.15 Chronic actinic dermatitis. Chronic eczematous changes of the dorsal hand and wrist with associated hyperpigmentation and scaling. Note the sharp cut-off at the distal forearm.

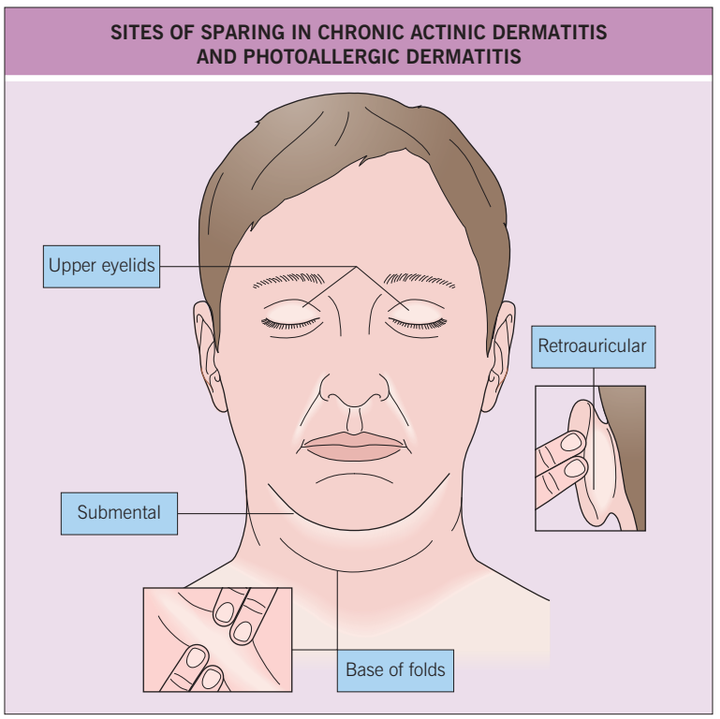


Fig. 87.16 Sites of sparing in chronic actinic dermatitis and photoallergic dermatitis. Relatively sun-protected sites include the upper eyelids, the nasolabial folds, the retroauricular areas, the submental region and the deepest portion of skin furrows. In airborne contact dermatitis these areas may be involved.

erythematous, shiny, infiltrated, pseudolymphomatous papules or plaques may be present in severely affected individuals.

Lesions develop primarily within sun-exposed sites (Figs 87.14 & 87.15), frequently with a sharp cut-off at the lines of clothing, and often with sparing in the depths of skin furrows, upper eyelids, finger webs, nasolabial folds or postauricular areas (Fig. 87.16). Occasionally, palmoplantar eczematous changes may also be present, while eyebrow or scalp hairs may be stubbly or lost from rubbing or scratching. Erythroderma rarely develops in severely affected patients. The probability of resolution has been estimated to be 10% over 5 years, 20% over 10 years, and 50% over 15 years[24].

Pathology

There is epidermal spongiosis and acanthosis, lymphocytic exocytosis, and a superficial and deep, often dense, perivascular lymphohistiocytic dermal cellular infiltrate, often containing eosinophils and plasma cells[21]. In more severely affected skin, erosions, focal epidermal necrosis, Pautrier microabscess-like epidermal cellular collections, dermal–epidermal junction fibrin deposition, dermal neutrophils with nuclear dust, vertically streaked papillary dermal collagen, and/or small, multinucleated dermal giant cells are often seen; in addition, the dense infiltrate, epidermal lymphocyte exocytosis and frequent nuclear polymorphism may on occasion suggest the erroneous diagnosis of cutaneous T-cell lymphoma (CTCL).

Differential diagnosis

Photoaggravated dermatoses are differentiated by the characteristic clinical features of the primary disorder and normal cutaneous irradiation responses. In drug- and chemical-induced photosensitivity, evidence is usually present of exposure to an inducing substance (see below).

In rare instances, patients with CTCL (see Ch. 120) may demonstrate a CAD-like photosensitivity, but phototesting abnormalities, if present, are usually mild and in the UVA range. In addition, CAD infiltrates are predominantly $CD8^+$ cells[21] and T-cell receptor gene rearrangement studies are negative. Very rarely, primary CTCL may present with severe CAD features; this should be considered if apparent CAD is totally refractory to treatment[25]. Erythrodermic CAD must be differentiated from other causes of erythroderma, if necessary by phototesting after the erythroderma has been controlled following days in the dark.

Treatment
Strict photoprotection and the avoidance of relevant contact allergens are of primary importance. Of note, computer and television screens are safe. Museum film or other filters can be placed on home and car windows. Topical or intermittent oral corticosteroid therapy along with emollient use is generally needed, while topical tacrolimus may also be helpful[21]. Therapy for refractory disease includes very-low-dose PUVA with initial high-dose oral and topical corticosteroid coverage over months, cyclosporine (3.5–5 mg/kg/day), azathioprine (1.0–2.5 mg/kg/day), and mycophenolate mofetil (1–2 g/day).

Solar urticaria

Key features
- A physical urticaria induced by sun exposure; lesions appear within 5 to 10 minutes and resolve over 1 to 2 hours
- The action spectrum generally includes both UVA and visible light, but rarely UVB
- There is a slight female predominance, with onset at any age
- Estimated probability of resolution is 15% at 5 years, 25% at 10 years
- Management: photoprotection; high-dose, non-sedating antihistamines; low-dose UVA; PUVA; plasmapheresis; and IVIg

Introduction
In solar urticaria, transient wheals appear within 5 to 10 minutes of exposure to UV or visible radiation. Lesions then resolve over 1 to 2 hours.

History
In 1905, solar urticaria was reported in a 47-year-old woman.

Epidemiology
Solar urticaria is a relatively uncommon disorder, with a prevalence in Tayside, Scotland, of ~3.1 per 100 000[26]. There is a slight female predominance, and the onset is most frequently during the fourth or fifth decade of life. Solar urticaria may occasionally coexist with PMLE, CAD and, very rarely, EPP[26].

Pathogenesis
As in other forms of urticaria (see Ch. 18), mast cells play a major role. Although factors triggering their degranulation have not been fully elucidated, an IgE-mediated response against photoinduced, endogenous cutaneous antigen(s) is a likely mechanism. This is supported by observations that whealing may be induced by previously *in vitro*-irradiated injections of autologous serum, and then blocked by anti-IgE antibody-containing serum. Also, in some patients, plasmapheresis is an effective treatment.

Clinical features
Patients present with whealing limited to sun-exposed areas, in particular the upper chest and outer aspects of the arms, within 5 to 10 minutes of sun exposure (Fig. 87.17). Occasionally, erythema without urtication may occur. The lesions then resolve over 1 to 2 hours. Patients almost invariably note an accompanying pruritus, burning sensation, or rarely pain, while severe attacks are rarely associated with malaise, light-headedness, nausea, bronchospasm and/or syncope.

Solar urticaria is best classified by its action spectrum, which may, however, gradually change over the ensuing years[27]. Most commonly, visible light is responsible, but usually with extension into the UVA waveband; UVB sensitivity is much less common. On occasion, continued regular skin exposure to UVR may decrease the likelihood of developing solar urticaria, a phenomenon referred to as hardening. The probability of spontaneous resolution has been estimated as being 15% at 5 years and 25% at 10 years after onset[26].

There are several uncommon manifestations of this disorder. *Fixed* solar urticaria is limited to specific areas, presumably due to mast cell alterations just at those sites[28]. In *delayed* solar urticaria, lesions last longer than 24 hours; however, this disorder probably represents a form of PMLE. *"Drug-induced"* solar urticaria has been reported following exposure to chlorpromazine, tetracycline, or tar.

Fig. 87.17 Solar urticaria. Wheal and flare responses within minutes of exposure to UVB irradiation in a patient undergoing phototesting.

Pathology
The histologic findings are similar to those of other urticarias, namely, mild dermal edema with a perivascular mixed neutrophilic and eosinophilic infiltrate; infiltration by mononuclear cells may also be seen. In addition, eosinophil major basic protein has been demonstrated within the dermis by immunofluorescence.

Differential diagnosis
The differential diagnosis includes other forms of urticaria, particularly heat urticaria, PMLE and, very rarely, EPP. A detailed history should differentiate solar urticaria from idiopathic urticaria and other physical urticarias. Phototesting of affected patients generally results in typical whealing within minutes (see Fig. 87.17), while the use of a water filter in front of the light source eliminates heat to exclude heat urticaria. The rare association of solar urticaria with EPP can be excluded by determination of RBC protoporphyrins (see Ch. 49). The time course of PMLE is distinct from that of solar urticaria, and LE can be excluded via laboratory evaluation (see Table 87.3).

Treatment
Oral non-sedating antihistamines, often in high doses and taken regularly or about an hour or so before expected sun exposure, are effective in ~50% of patients. Those with very mild disease may occasionally require only photoprotective measures; however, sunscreens do not generally protect well enough against UVA and visible light to be effective[29]. Graduated exposures to UVA or PUVA are occasionally helpful[30]. If these measures fail, more aggressive therapies such as plasmapheresis[31], omalizumab (anti-IgE antibody) or IVIg[32] can be tried. Graduated UV exposure has provided some patients a benefit for years.

Inherited Disorders Characterized by Defective DNA Repair

The major disorders characterized by both defective DNA repair and photosensitivity are discussed below and outlined in Table 87.4. The underlying pathogenesis is reviewed in greater detail in Chapter 86. Four of the disorders are associated with defects in one of the nucleotide excision repair (NER) proteins: xeroderma pigmentosum, Cockayne syndrome, UV-sensitive syndrome, and the photosensitive form of trichothiodystrophy[33–35]. A fifth disorder with an NER defect, cerebro-oculo-facio-skeletal (COFS) syndrome, has no associated photosensitivity, so it will not be discussed.

Xeroderma pigmentosum

Introduction
Xeroderma pigmentosum (XP) is an autosomal recessive condition associated with a marked increase in the development of malignancies, especially cutaneous. Seven genetically different complementation groups and an XP variant have been delineated.

History
XP was first described by Hebra and Kaposi in 1874.

INHERITED PHOTOSENSITIVITY DISORDERS ASSOCIATED WITH DEFECTIVE DNA NUCLEOTIDE EXCISION REPAIR OR CHROMOSOME INSTABILITY					
Disorder	**Clinical features**	**Inheritance**	**Photosensitivity**	**Action spectrum**	**Laboratory findings**
Xeroderma pigmentosum (XP)	• 1 per million in Western countries; 1 per 40 000 to 100 000 newborns in Japan • Photosensitivity, early-onset lentigines (typically by 2 years of age) • Basal cell carcinomas, squamous cell carcinomas and melanomas in sun-exposed areas • Median age for development of first non-melanoma skin cancers: 8 years • Photophobia, keratitis, corneal opacification and vascularization • Neurologic abnormalities: hyporeflexia, deafness, seizures (most common in groups A and D; do not usually occur in XP variant) • XP variant patients usually have no neurologic problems • Support group: www.xps.org	AR	Yes	290–340 nm	• Complementation groups A to G: defective global genomic nucleotide excision repair (GG-NER) of UVR-induced DNA damage (e.g. pyrimidine dimers) from any part of the genome • XP variant: defective DNA polymerase-η, resulting in insertion of incorrect residue during replication of DNA with UVR-induced damage • Defective genes for all the XP groups have been identified • Cells are hypersensitive to killing by UVR
Cockayne syndrome (CS)	• Over 180 patients reported to date • Photosensitivity without pigmentary changes. Loss of adipose tissue, prominent ears, dental caries, thinning of skin and hair • Hypogonadism, stooped posture, joint contractures, short stature with extremely thin body habitus ("cachectic dwarfism"), microcephaly, mental retardation, deafness • Calcification of basal ganglia, demyelination, pigmentary retinal degeneration, osteoporosis • No increase in malignancies in "pure" CS • CS type I: 80% of patients; onset at 2 years of age, progressive; life expectancy: second to third decades • CS type II: symptoms at birth, life span = 6–7 years • CS type III: late onset, normal growth and development • No correlation between genotype and phenotype • Combined XP/CS: solar lentigines, skin cancers, pigmentary retinal degeneration, basal ganglion calcification • Support group: www.cockayne-syndrome.org	AR	Yes	Unclear	• Defective transcription-coupled nucleotide excision repair (TC-NER), which targets transcriptionally active regions of the genome • CS cells are defective in the repair of pyrimidine dimer photoproducts and oxidative DNA base modifications typically induced by UVB and UVA, respectively • Two complementation groups: CS-A (mutations in *ERCC8*) and CS-B (mutations in *ERCC6*); identical phenotypes • Mutations in *XPB, XPD* and *XPG* genes have been associated with combined XP/CS phenotypes
UV-sensitive syndrome (UV^{S}S)	• Fewer than 10 patients reported to date • Considered to be a mild variant of CS • Photosensitivity, solar lentigines; otherwise normal	AR	Yes	Unclear	• Similar to CS: defective TC-NER, normal GG-NER; however, unlike CS, patients with UV^{S}S only defective in repair of UVB-induced photoproducts (not in repair of oxidative damage) • Mutations in *CSB, CSA*, and an undefined gene
Trichothiodystrophy (TTD)	• Over 100 patients reported to date • PIBI(D)S: *p*hotosensitivity, *i*chthyosis, *b*rittle hair, *i*ntellectual impairment, *d*ecreased fertility, short stature • Other features: microcephaly, receding chin, protruding ears • No increase in malignancies	AR	Yes (in 50% of patients)	Unclear	• Hair shaft: alternating light and dark bands ("tiger tail banding"), trichoschisis, trichorrhexis nodosa-like changes, "ribboning" • Reduction of cysteine-rich matrix proteins and low sulfur content in hair shafts • Mutations in *XPD, XPB*, general transcription factor IIH polypeptide 5 (*GTF2H5* or *TFB5*), and *C7orf11*
Bloom syndrome	• Over 250 patients reported to date; Ashkenazi Jews account for ~25% of families • Malar erythema and telangiectasias, café-au-lait macules and areas of hypopigmentation, elongated face with malar hypoplasia and prominent nose, short stature, diabetes mellitus, recurrent respiratory and GI infections • Increased frequency of leukemia, lymphoma, GI adenocarcinoma • Normal intelligence • Men: sterile due to defective sperm; women: reduced fertility • Patient registry: Bloom Syndrome Registry (www.med.cornell.edu/bsr)	AR	Yes	Unclear	• Decreased IgA, IgM, sometimes IgG • Mutations in *BLM (RECQL3)*, resulting in chromosomal instability (increased sister chromatid exchanges, chromosomal breakage and rearrangement) • Quadriradial configurations in lymphocytes and fibroblasts are diagnostic

Table 87.4 Inherited photosensitivity disorders associated with defective DNA nucleotide excision repair or chromosome instability.

Continued

INHERITED PHOTOSENSITIVITY DISORDERS ASSOCIATED WITH DEFECTIVE DNA NUCLEOTIDE EXCISION REPAIR OR CHROMOSOME INSTABILITY					
Disorder	**Clinical features**	**Inheritance**	**Photosensitivity**	**Action spectrum**	**Laboratory findings**
Rothmund–Thomson syndrome	• Over 300 patients reported to date • Erythema, edema and vesicles on the cheeks and face during the first few months of life, followed by poikiloderma that also typically affects the dorsal aspect of the hands/forearms and the buttocks • Sparse hair (scalp, eyebrows, eyelashes), hypoplastic nails, acral keratoses (in adolescents and adults), short stature, skeletal (e.g. radial ray defects, osteoporosis) and dental abnormalities, juvenile cataracts, chronic diarrhea/vomiting during infancy, pituitary hypogonadism (may be associated with midface hypoplasia/"saddle nose") • Osteosarcoma (10–30%), squamous cell carcinoma (<5%; often acral) • Normal immune function, intelligence and lifespan (in the absence of malignancy)	AR	Transient (early childhood)	UVA	• Mutations in *RECQL4*; protein product is a DNA helicase • Genomic instability may account for propensity for malignancies

Table 87.4 Inherited photosensitivity disorders associated with defective DNA nucleotide excision repair or chromosome instability (cont'd). AR, autosomal recessive.

Epidemiology

XP has an estimated incidence of one per million in newborns in Western countries, and 1 per 100 000 newborns in Japan[36].

Pathogenesis

In XP, there are seven genetically different complementation groups (A to G), each associated with a different site of impairment in global genomic nucleotide excision repair (GG-NER), i.e. impairment in the removal of DNA damage from any part of the genome[33]; the damaged DNA then accumulates, leading to mutations and cancer. XP-A through -G represent different proteins in the NER pathway (see Fig. 86.12). It should be noted that different mutations in the *XPB*, *XPD* and *XPG* genes can be associated with different phenotypes – either XP or XP/Cockayne syndrome – and mutations in the *XPB* and *XPD* genes can also be associated with trichothiodystrophy (see below). XP variant, which has normal NER, is due to mutations in the gene that encodes DNA polymerase-η (also known as Pol η, Pol H or hRad30A). This enzyme is responsible for bypassing the unrepaired DNA photoproduct during DNA replication; mutations thus result in the insertion of erroneous residues during replication.

Phototesting in XP patients has shown the action spectrum for inflammatory erythema of the skin to be in the 290 to 340 nm range. The MEDs corresponding to those wavelengths are generally quite reduced, with the peak responses often vesicular and delayed by a day or two.

Fig. 87.18 Xeroderma pigmentosum. A 17-year-old with skin phototype V who has hyper- and hypopigmentation admixed with scarring, lentigines and seborrheic keratoses. Note the squamous cell carcinoma *in situ* of the lower lip in association with severe actinic cheilitis. *Courtesy, Julie V Schaffer, MD.*

Clinical features

Patients usually have marked photosensitivity as well as the early onset of all major types of skin cancer (see Table 87.4). Starting from an early age, many also easily develop sunburns with erythema, edema and vesicles following minimal sun exposure. By the age of 2 years, practically all patients have developed solar lentigines. With continuing exposure, however, the skin gradually becomes xerotic, leading to the term 'xeroderma pigmentosum', or dry pigmented skin (Fig. 87.18).

Actinic keratoses, basal cell carcinomas (BCCs), squamous cell carcinomas (SCCs) and, less frequently, melanomas then develop in sun-exposed sites, also prematurely. In one study, the median age for initial non-melanoma skin cancer development was 8 years[37]. SCC of the tip of the tongue has also been reported, presumably secondary to UVR exposure.

Ocular abnormalities are observed in ~40% of patients. Severe photophobia, keratitis, corneal opacification and vascularization are common manifestations, while loss of eyelashes, ectropion, and SCC and melanoma of the UVR-exposed parts of the eyes are also frequently reported[37].

Approximately 20–30% of XP patients develop neurologic abnormalities, the most severe presentation being the DeSanctis–Cacchione syndrome, in which microcephaly, progressive mental retardation, retarded growth and sexual development, deafness, choreoathetosis, ataxia and quadriparesis may all occur. However, some XP patients develop a limited number of clinical manifestations, such as isolated hyporeflexia and progressive deafness. XP variant patients usually have no neurologic problems. Deep tendon reflex testing and routine audiometry are good screening tests for the presence of neurologic involvement. It has been postulated that these neurologic abnormalities are due to defective DNA repair in nerve cells, resulting in neuronal death. Patients with XP also have an approximately 10- to 20-fold increase in the incidence of internal malignancies, including tumors of the brain, lung, oral cavity, gastrointestinal tract, kidney and hematopoietic system.

Treatment

Management consists of extremely rigorous photoprotection. Oral calcium and vitamin D supplementation should also be recommended for these patients. Cryotherapy, electrodesiccation and curettage, and surgical excision are used to manage the premalignant and malignant skin tumors. Oral retinoids can be administered as chemopreventive agents, and, anecdotally, topical imiquimod has been reported to be useful. Topical application of the bacterial DNA repair enzyme T4 endonuclease V (T4N5) formulated in a liposomal delivery vehicle has been successful in decreasing the development of actinic keratoses and BCCs[38], although this product is currently not commercially available.

Cockayne syndrome

Introduction
Cockayne syndrome is a rare photosensitivity disorder transmitted in an autosomal recessive fashion (see Table 87.4); to date, over 180 patients have been reported[33].

History
This entity was first described by Cockayne in 1936.

Epidemiology
Cockayne syndrome has been reported from the US, Europe and Japan.

Pathogenesis
Cells from affected patients are hypersensitive to killing by UVR[33]. However, the fundamental defect in NER in Cockayne syndrome is different from that of XP. In the former, there is defective transcription-coupled NER (TC-NER), which requires a subset of NER proteins plus additional factors and targets the transcriptionally active regions of the genome. The dysfunction results in the inability to recover RNA synthesis after exposure to UVR. In contrast, XP cells have defective global genomic NER (GG-NER; see above).

In contrast to XP, to date there has never been a report of cancer in a patient with Cockayne syndrome, whose average lifespan is only 12 years (although there is considerable variation)[39,40]. One explanation is that cells with low-level damage due to defective TC-NER are eliminated in patients with Cockayne syndrome, protecting the body from carcinogenesis at the expense of accelerated aging.

There are two complementation groups with identical phenotypes: CS-A due to mutations in *ERCC8* (also known as *CSA*) and CS-B due to mutations in *ERCC6* (also known as *CSB*); 80% of patients have been assigned to the CS-B complementation group[36]. Several patients with an XP–Cockayne syndrome complex have also been reported (with mutations in *XPB, XPD* or *XPG*), typically demonstrating the solar lentigines and cutaneous neoplasms of XP, along with the pigmentary retinal degeneration and basal ganglia calcification of Cockayne syndrome[40].

Clinical features
Patients with Cockayne syndrome have been classified into three types based upon severity of symptoms and age of onset (see Table 87.4)[39]. Unlike individuals with XP, these patients have photosensitivity without significant pigmentary changes, but the action spectrum of the photosensitivity has not been determined. Progressive signs of premature aging occur, as does growth failure affecting the weight more than the length (i.e. cachectic dwarfism).

Treatment
This consists of symptomatic treatment only.

UV-sensitive syndrome

UV-sensitive syndrome (UV^sS) is a rare, photosensitive, autosomal recessive disease; to date, fewer than 10 patients have been reported, mostly from Japan[41,42]. It is considered to be a mild variant of Cockayne syndrome. Clinically, patients present with lentigines, but no neurologic abnormalities, nor an increased frequency of skin or internal cancers. All patients have photosensitivity, although the action spectrum has not been studied. The molecular defects are summarized in Table 87.4.

Trichothiodystrophy

Introduction
Trichothiodystrophy (TTD) is an autosomal recessive disorder with over 110 patients reported to date (see Table 87.4)[43].

History
The term 'trichothiodystrophy' was coined by Price in the late 1970s.

Epidemiology
The disorder appears to occur worldwide and affects men and women.

Pathogenesis
TTD with severe photosensitivity is associated with mutations in *ERCC2/XPD* (95% of patients), and rarely in *ERCC3/XPB*[35]. Mutations in chromosome 7 open reading frame 11 (*C7orf11*) underlie a non-photosensitive form of TTD, while mutations in a fourth gene that encodes the tenth subunit of transcription factor II H (TFIIH; see Ch. 86) also lead to TTD.

Clinical features
TTD has heterogeneous clinical manifestations, and several previously described syndromes (e.g. Amish brittle hair, Marinesco–Sjögren, Sabinas, Pollitt, Tay and IBIDS) are probably part of its spectrum. Unlike XP, TTD is not associated with skin cancers, and pigmentary alterations are uncommon.

The clinical features of TTD are frequently described by the acronym PIBI(D)S[43]:

Photosensitivity: Photosensitivity has been reported in up to 50% of affected patients, but the action spectrum is not known. Most patients with photosensitivity can be assigned to the XP-D complementation group. It should be noted that *XPD* mutations associated with XP result in impaired NER function, while *XPD* mutations that underlie TTD lead to an *in vitro* basal transcription defect[44]; this may explain the lack of an association of skin cancer with TTD.

Ichthyosis: A non-bullous congenital ichthyosiform erythroderma phenotype is commonly observed during infancy, and patients occasionally present with a collodion membrane. The erythema tends to fade over time, eventuating in ichthyosis of variable severity (see Ch. 57).

Brittle hair: This is the hallmark of TTD and is present in most, but not all, patients[43,45]. By polarizing microscopy, hair shafts demonstrate alternating bright and dark bands ('tiger tail banding') (see Fig. 69.20) Light microscopic findings include an irregular contour, trichoschisis (transverse fractures through the shafts) and, sometimes, trichorrhexis nodosa-like features. Hair shafts are flattened and may fold like a ribbon. There is also a reduction in cysteine-rich matrix proteins, resulting in defective cross-linking of the intermediate keratin filaments and a low sulfur content within the hair shaft. This defect may also account for the brittle nails and the ichthyosis seen in TTD.

Intellectual impairment: This ranges from mild to severe retardation.

Decreased fertility: This has been reported in patients of both sexes, but is not a prominent feature.

Short stature: Growth retardation is present to a varying degree.

Other manifestations include a characteristic facies with a receding chin and protruding ears, sideroblastic anemia, eosinophilia, and hepatic angioendotheliomas.

Treatment
No specific treatment is available.

Inherited Disorders Characterized by Chromosomal Instability

Bloom syndrome

Synonym: ▪ Congenital telangiectatic erythema

Introduction
Bloom syndrome is transmitted in an autosomal recessive fashion (see Table 87.4); as of the end of 2009, 265 patients were listed in the Bloom Syndrome Registry (www.med.cornell.edu/bsr)[46].

History
The condition was first reported by David Bloom, a New York City dermatologist, in 1954.

Epidemiology
Bloom syndrome was initially described as occurring most frequently amongst Ashkenazi Jews; however, of the 222 families in the Bloom Syndrome Registry, 75% were non-Jewish[39].

Pathogenesis
The gene (*BLM*), on chromosome 15q26.1, is a member of the RECQ helicase family. The functions of its protein product include unwinding

DNA and maintaining genomic stability. Mutations in *BLM* result in a tenfold increased rate of spontaneous sister chromatid exchanges, chromosomal breakage and rearrangements[47], while quadriradial configurations of chromosomes in lymphocytes and fibroblasts are a diagnostic feature.

Clinical features
Beginning within the first few weeks of life, patients typically develop erythema and telangiectasias of the malar areas and occasionally the dorsal aspects of the hands and forearms. Café-au-lait macules with adjacent areas of hypopigmentation are also common. While photoexacerbations of the erythema have been reported, the action spectrum remains unclear. Growth delay and short stature with a disproportionately small head are usually the most common reasons for parents to seek medical care[39].

Among the 265 patients in the Registry, the average age at death was 26 years[46]. In addition to recurrent infections due to an associated immunodeficiency, the chromosomal instability leads to a 150- to 300-fold increase in the frequency of malignancies, including lymphomas and leukemias (see Table 87.4).

Treatment
Symptomatic management and photoprotection are the only treatment strategies.

Rothmund–Thomson syndrome

Synonym: ■ Poikiloderma congenitale

Introduction
Rothmund–Thomson syndrome is a rare entity with autosomal recessive inheritance; to date, over 300 cases have been reported in the English literature[48] (see Table 87.4).

History
The disorder was first recognized by Auguste Rothmund, a German ophthalmologist, in 1868, before Sydney Thomson, a British dermatologist, described a similar entity in 1923. In 1957, William Taylor proposed the eponym Rothmund–Thomson syndrome.

Epidemiology
Patients have been reported from the US, Canada, Central and South America, Europe, Australia, Japan and Israel.

Pathogenesis
The majority of patients with Rothmund–Thomson syndrome have mutations in the *RECQL4* gene[49]. The protein product is a DNA helicase, which unwinds DNA and stabilizes the genome. *RECQL4* is in the same gene family as *BLM* (Bloom syndrome), and dysfunction of the helicase is thought to account for the increased susceptibility to cancers.

Clinical features
Patients typically present in the first few months of life with photodistributed erythema, edema and vesicles of the cheeks and face, which may extend to involve the buttocks and extremities. Over months to years, poikiloderma develops. In one patient, the action spectrum of the photosensitivity was in the UVA range. Up to one-third of patients develop osteosarcoma[48]. Other features are summarized in Table 87.4.

Differential diagnosis
In addition to the entities listed in Table 87.4, the differential diagnosis includes poikiloderma with neutropenia, an autosomal recessive disorder due to mutations in *C7orf57* that was first described in Navajo Native Americans[49a].

Treatment
Treatment is symptomatic and preventative only.

Kindler Syndrome
Kindler syndrome (see Ch. 63) is an autosomal recessive disorder with transient early-onset photosensitivity and blistering, followed by persistent poikiloderma; it is due to loss-of-function mutations in *KIND1* (*FERMT1*)[50–52]. This gene encodes the focal adhesion protein, fermitin family homolog-1, which is implicated in integrin activation. A decreased MED to UVB, and in some patients to UVA, has been reported.

PHOTOAGGRAVATED DERMATOSES
• Acne vulgaris
• Atopic dermatitis
• Bullous pemphigoid
• Carcinoid syndrome
• Cutaneous T-cell lymphoma (Sézary Syndrome)
• Dermatomyositis
• Disseminated superficial actinic porokeratosis
• Erythema multiforme
• Familial benign chronic pemphigus (Hailey–Hailey disease)
• Hartnup syndrome
• Keratosis follicularis (Darier disease)
• Lichen planus
• Lupus erythematosus
• Pellagra
• Pemphigus, including pemphigus foliaceus (erythematosus)
• Pityriasis rubra pilaris
• Psoriasis
• Reticular erythematous mucinosis (REM)
• Rosacea
• Seborrheic dermatitis
• Transient acantholytic dermatosis (Grover's disease)
• Viral infections, including herpes simplex, exanthems

Table 87.5 Photoaggravated dermatoses.

Photoaggravated Dermatoses

Key features
- The underlying disease is not caused, but rather exacerbated, by sun exposure, sometimes severely
- The most common of these conditions is photoaggravated seborrheic dermatitis, followed by rosacea, LE, Grover's disease, and psoriasis
- Monochromatic phototesting is usually normal (LE being the exception)
- Therapy focuses on treatment of the underlying disease

Introduction
A number of skin diseases that are not directly caused by UVR exposure may, in some patients, be worsened by it (Table 87.5). The reasons for such aggravation, however, have been poorly studied, with the exception of LE (see Ch. 41)[53].

History
By the 1930s, the photoaggravation of dermatoses was formally recognized, especially in psoriasis. Studies on UV exacerbation of viral exanthems were performed in the 1950s, followed by examination of the photosensitivity in LE during the 1960s.

Epidemiology
These dermatoses occur worldwide[53]. In photodermatology referral centers, as a group, the prevalence ranges from 15% to 25%[1].

Clinical features
The basic dermatosis may be mildly or severely exacerbated by UVR exposure (Fig. 87.19), usually within minutes to hours, but sometimes a day or more later. The UVR-exacerbated eruption is usually limited to sites characteristically involved by the underlying condition; less often the flare involves all sun-exposed sites. However, it is important to remember that the majority of patients with disorders such as psoriasis will improve following sun exposure or phototherapy.

Fig. 87.19 Photoaggravated atopic dermatitis induced by the solar simulator. This was the appearance 24 hours after irradiation.

Pathology
The histology is that of the underlying dermatosis.

Differential diagnosis
In general, photoaggravated dermatoses are recognized by the presence of the underlying skin disease (see Table 87.5). The differential diagnosis often includes PMLE, although PMLE is typically papular and pruritic, has negative lupus serology, and can be induced by photoprovocation tests (~80% of patients). It is important to note, however, that PMLE may sometimes coexist with photoaggravated dermatoses, in particular photosensitive psoriasis and LE. Photoaggravated atopic dermatitis, if widespread, may be confused with CAD; however, phototest results are positive in CAD. Lastly, UVR-induced exacerbations need to be distinguished from flares due to heat exposure.

Treatment
Treatment should focus on the underlying disorder and photoprotection. Topical corticosteroids, low-dose NB-UVB or PUVA may sometimes lead to improvement; rarely, short courses of oral corticosteroids are required.

Chemical- and Drug-Induced Photosensitivity

Key features
- Phototoxicity is characterized by an exaggerated sunburn-like reaction, usually caused by systemic agents
- Photoallergy presents with eczematous lesions, most commonly related to topical photoallergens
- The cutaneous porphyrias are an example of phototoxicity induced by endogenous agents
- Management: identification and avoidance of the offending agent; if avoidance is not possible, careful photoprotection; occasionally, evening dosing of medications such that their peak systemic levels occur during the night

Exogenous
Introduction
Photosensitivity induced by exogenous agents can be divided into phototoxicity and photoallergy (Table 87.6). Phototoxicity is the result of direct tissue and cellular injury following UVR-induced activation of a phototoxic agent; theoretically, phototoxicity can be induced in every individual. In contrast, photoallergy is a delayed-type hypersensitivity response consisting of a sensitization phase, an incubation period of 7 to 10 days (following the first exposure), and a clinical reaction after any subsequent challenge; only sensitized individuals can develop photoallergy.

COMMON PHOTOTOXIC AND PHOTOALLERGIC AGENTS

Common phototoxic agents	Common photoallergic agents
• Antiarrhythmics – Amiodarone – Quinidine • Triazole antifungals – Voriconazole • Diuretics – Furosemide – Thiazides • Nonsteroidal anti-inflammatory drugs – Nabumetone – Naproxen – Piroxicam • Phenothiazines – Chlorpromazine – Prochlorperazine • Psoralens – 5-Methoxypsoralen – 8-Methoxypsoralen – 4,5′,8-Trimethylpsoralen • Quinolones – Ciprofloxacin – Lomefloxacin – Nalidixic acid – Sparfloxacin • St. John's wort – Hypericin • Sulfonamides • Sulfonylureas • Tar (topical) • Tetracyclines – Doxycycline – Demeclocycline	Topical agents: • Sunscreens (e.g. oxybenzone [benzophenone-3]) • Fragrances – 6-Methylcoumarin – Musk ambrette – Sandalwood oil • Antimicrobial agents – Bithionol – Chlorhexidine – Fenticlor – Hexachlorophene • Nonsteroidal anti-inflammatory drugs – Diclofenac – Ketoprofen • Phenothiazines – Chlorpromazine – Promethazine Systemic agents: • Antiarrhythmics – Quinidine • Antimalarials – Quinine • Antifungals – Griseofulvin • Antimicrobials – Quinolones (e.g. enoxacin, lomefloxacin) – Sulfonamides • Nonsteroidal anti-inflammatory drugs – Ketoprofen – Piroxicam*

*Often have positive patch test to thimerosol.

Table 87.6 Common phototoxic and photoallergic agents.

History
Phototoxic agents have been used as medications from as early as 4000 BC, with the inhabitants of Mesopotamia (and later the Indians and Egyptians) employing plant-derived psoralens for the treatment of leukoderma. In 1913, Meyer-Betz demonstrated hematoporphyrin-induced phototoxicity on himself, while the current method of PUVA therapy was introduced in the 1970s. For almost a century, medications have been known to cause unwanted phototoxic reactions. Photoallergy was first recognized in 1939 based on a classic study by Epstein on sulfanilamide.

Epidemiology
While the exact prevalences of phototoxicity and photoallergy in the general population are unknown, their frequency in photodermatology referral centers has ranged from 5% to 15% for phototoxicity and from 4% to 8% for photoallergy[1,54,55].

Pathogenesis
The pathogenesis of phototoxicity involves the generation of oxygen free radicals, superoxide anions, hydroxyl radicals and singlet oxygen, which leads to a host of cytotoxic tissue effects. Other mechanisms of damage include the generation of stable photoproducts (reported with chlorpromazine and tetracyclines), the formation of photoadducts (reported with psoralens), and the generation of inflammatory mediators (reported with porphyrins and demeclocycline)[56].

The pathogenesis of photoallergy is identical to that of allergic contact dermatitis, with the exception of the requirement for the presence of UVR to induce photoallergen formation.

Fig. 87.20 Exogenous drug-induced photosensitivity and hyperpigmentation. Gray–brown patches involving the sun-exposed skin of a patient receiving diltiazem.

COMMONLY EMPLOYED PHOTOPATCH TEST AGENTS

Substance	Concentration (%)
Sunscreen agents	
Octyl methoxycinnamate (octinoxate)	10
Benzophenone-3 (oxybenzone)	10
Octyl dimethyl PABA (padimate 0)	10
Butyl methoxydibenzoylmethane (avobenzone)	10
4-Methylbenzylidene camphor (enzacamene)*	10
Benzophenone-4 (sulisobenzone)	10
Isoamyl methoxycinnamate*	10
Phenylbenzimidazole sulfonic acid (ensulizole)	10
Musk ambrette	1
Tribromosalicylanilide	1
Sesquiterpene lactone mix	0.1
Nonsteroidal anti-inflammatory agents†	
Naproxen	5
Ibuprofen	5
Diclofenac	1
Ketoprofen	2.5

*Not approved in the US.
†Observed as topical sensitizers primarily in Europe.

Table 87.7 Commonly employed photopatch test agents. Modified from ref. 62.

Clinical features

Phototoxicity

Following cutaneous or systemic exposure to a phototoxic agent *and* appropriate UVR, phototoxicity develops within hours; for the vast majority of such agents, the action spectrum is in the UVA range. Erythema and edema as well as burning and stinging sensations characterize the initial presentation, with vesicles and bullae seen in severely affected patients. Phototoxic reactions due to oral medications resemble an exaggerated sunburn. These reactions then resolve spontaneously with desquamation and hyperpigmentation once the photosensitizer or UVR is avoided.

Other less common manifestations of phototoxicity include pseudoporphyria (frequently caused by nonsteroidal anti-inflammatory drugs [NSAIDs], especially naproxen), photo-onycholysis (reported with tetracyclines and psoralens), slate-gray hyperpigmentation (reported with amiodarone, tricyclic antidepressants and diltiazem) (Fig. 87.20)[57], lichenoid eruptions (seen with quinine and quinidine), and a burning or painful sensation (amiodarone). Evolution of phototoxicity reactions into CAD (see above) has rarely been reported following exposure to thiazides, quinidine, quinine or simvastatin. The medications most commonly associated with phototoxicity are listed in Table 87.6.

5-Fluorouracil (5-FU), methotrexate and retinoids, three commonly used medications in dermatology, have also been associated with photosensitivity reactions; however, none is associated with UVR-induced activation of the drug. Exacerbation of 5-FU-induced inflammation by UVR usually occurs in sites with actinic keratoses. The administration of methotrexate occasionally causes a recurrence ('recall') of previous UVR-induced erythema. However, phototesting in patients taking methotrexate has been normal[58], and the mechanism for this 'recall' reaction remains unclear. Phototesting in patients taking isotretinoin or etretinate, or applying topical tretinoin, is also usually normal[59], and the propensity for these patients to develop UVR-induced erythema is most likely due to retinoid-induced thinning of the stratum corneum.

Phytophotodermatitis is another phototoxic reaction, with linear streaks of erythema occurring a day or so after skin contact with plants containing furocoumarins plus exposure to sunlight. Linear postinflammatory hyperpigmentation is a classic finding. Plants capable of inducing phytophotodermatitis include yarrow, parsley, celery, lime and fig (see Ch. 17). Therefore, this condition most commonly occurs in individuals whose outdoor activities expose them to such plants, such as vegetable harvesters and bartenders who mix drinks outdoors. Roofers and road workers occasionally develop phototoxicity secondary to exposure to tar and concomitant UVA from sunlight.

St John's wort (*Hypericum perforatum*), used to treat a variety of ailments including depression, contains hypericin, another known phototoxic agent. Increasingly, voriconazole is being prescribed for immunocompromised hosts, often for months or years in patients with allogeneic hematopoietic stem cell transplants and chronic GVHD. This can lead to phototoxic reactions as well as an increased risk for developing large hypertrophic actinic keratoses, aggressive cutaneous squamous cell carcinomas and perhaps cutaneous melanoma.

Photoallergy

In previously sensitized individuals, exposure to photoallergens and sunlight results in the development of a pruritic eczematous eruption. In more severely affected patients, vesicles and bullae may develop, though less commonly than in phototoxic reactions. In general, phototoxic and photoallergic reactions can be distinguished, as phototoxic reactions resemble a sunburn whereas the lesions of photoallergic reactions often resemble allergic contact dermatitis. That said, a detailed history and clinical examination of sites of involvement always provide insight.

In a study involving 2715 patients in the UK, sunscreen agents (especially benzophenone-3 [oxybenzone]) were the most common causes of photoallergy[60]; this finding has since been confirmed in a second study of 1155 patients[61]. However, the actual prevalence of photoallergy amongst sunscreen users is very low. Other common photoallergens include medications such as promethazine and NSAIDs, as well as fragrances and antibacterial products (see Table 87.6). Photoallergy can generally be confirmed by photopatch testing, where duplicate sets of photoallergens are placed on the patient's back and only one set is irradiated with UVA (Table 87.7). The interpretation of results from such testing is shown in Figure 87.21.

Pathology

Phototoxicity is characterized by scattered necrotic keratinocytes ('sunburn cells') and a dermal infiltrate of primarily lymphocytes and neutrophils. In contrast, photoallergy is characterized by epidermal spongiosis plus a dermal lymphohistiocytic infiltrate, indistinguishable from other causes of spongiotic dermatitis.

Differential diagnosis

Inflammatory phototoxic reactions should be distinguished from ordinary sunburn, which requires more UVR exposure, and LE (see Table

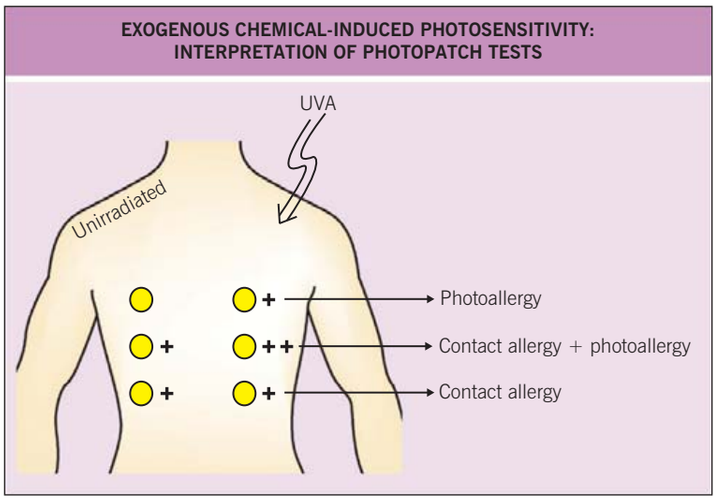


Fig. 87.21 Exogenous chemical-induced photosensitivity: interpretation of photopatch tests. This schematic demonstrates the interpretation of photopatch tests. The UVA dose is usually the lower of 5 J/cm^2, or 50% of the MED to UVA.

87.3). The differential diagnosis of photoallergic reactions includes all other forms of dermatitis that can involve sun-exposed areas, particularly airborne contact dermatitis and seborrheic and atopic dermatitis. In airborne contact dermatitis, all exposed sites can be involved, including the upper eyelids, submental region and postauricular areas; these sites are frequently spared in photoallergic contact dermatitis (see Fig. 87.16).

Treatment

The identification and avoidance of the offending agent are of prime importance. Sometimes this is not possible and strict photoprotection (UVB and UVA) is required. For phototoxic reactions, analgesia may be helpful. Topical corticosteroids, and, for severe flares, short courses of systemic corticosteroids, can be used for photoallergic dermatitis. Occasionally, evening dosing of a phototoxic drug can be done so that peak systemic levels occur during the night.

Endogenous

The cutaneous porphyrias, discussed in Chapter 49, represent the most obvious examples of photosensitivity induced by endogenous agents. The mechanism of porphyrin-induced phototoxicity involves reactive oxygen species, the complement system, mast cells and neutrophils (Fig. 87.22).

Smith–Lemli–Opitz syndrome, an autosomal recessive disorder with early onset of photosensitivity to UVA in 55% to 75% of patients, is probably another example[63,64]. Its frequency has been estimated to be 1 in 20 000 to 1 in 40 000 births in populations with northern and central European ancestry. Mutations in *DHCR7*, which encodes 7-dehydrocholesterol reductase, result in an accumulation of 7-dehydrocholesterol. The mechanism of the photosensitivity is unknown.

NORMAL CUTANEOUS EFFECTS OF UVR EXPOSURE

Key features

- Acute and subacute effects of UVR exposure include acute inflammatory erythema (sunburn), pigment darkening, delayed pigmentation, epidermal hyperplasia, immunologic changes and vitamin D_3 synthesis
- Chronic effects include photoaging and photocarcinogenesis
- UVR has been implicated in the development of actinic keratoses, squamous cell carcinoma, basal cell carcinoma and melanoma
- UVR effects are attenuated in individuals with pigmented skin

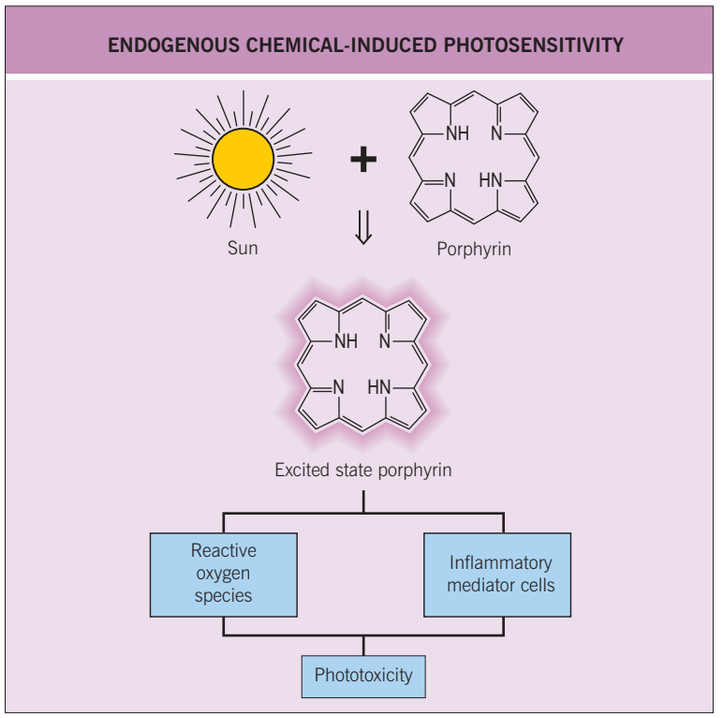


Fig. 87.22 Endogenous chemical-induced photosensitivity. The pathophysiology of phototoxicity as seen in the cutaneous porphyrias is shown.

This discussion is limited to the clinical aspects of UVR, as the underlying mechanisms are reviewed in Chapter 86.

Acute and Subacute Effects

These effects are primarily the result of UVR absorption by DNA, the exception being vitamin D synthesis.

Acute inflammatory erythema (sunburn)

Excessive UVR exposure leads to the acute inflammatory reaction of sunburn. Wavelengths around 300 nm are the most erythemogenic, with those between 260 and 280 nm a little less so. The lowest dose capable of inducing erythema, the so-called minimal erythema dose (MED), in individuals with Fitzpatrick skin type I is about 100 J/m^2 (10 mJ/cm^2) for UVC (100–280 nm), 300 J/m^2 (30 mJ/cm^2) for broadband UVB (280–315 nm), and 300 kJ/m^2 (30 J/cm^2) for broadband UVA (315–400 nm).

In a few individuals, brief immediate erythema occurs within seconds of UVR exposure and lasts for minutes[65]. Otherwise, the typical delayed bright red appearance of a sunburn develops confluently on all sufficiently exposed skin, beginning within 30 minutes to 8 hours, peaking at 12 to 24 hours and diminishing over hours to days in the case of UVB exposure. With UVC, the response is pinker in color and shorter in duration, starting within hours, peaking at 5 to 8 hours and fading over hours to a day or so; in the case of UVA, however, the reaction is deeper red in color, is usually more persistent, and often begins during irradiation, before fading over hours to days. After excessive exposure, edema and blistering may occur, which, if widespread, may lead to associated systemic symptoms such as chills and malaise. Such reactions are generally followed by pruritus and desquamation over a period of days to weeks.

Photoprotection is the best prevention[29]. However, once excessive UVR exposure has occurred, only symptomatic treatment can be offered (e.g. increased fluid intake, emollient creams or lotions); topical or oral nonsteroidal or steroidal anti-inflammatory agents must be administered as soon as possible after irradiation, or they will not help. If the sunburn is severe or life-threatening, hospitalization and treatment as for thermal burns are necessary.

Pigment darkening and delayed tanning

Immediate, often grayish, tanning of irradiated skin that lasts for 10–20 minutes may occur within seconds of ~20–120 kJ/m^2 of UVA

CUTANEOUS SIGNS OF SIGNIFICANT PHOTODAMAGE
Solar elastosis (Fig. 87.23A,B)
Nodular elastosis
Weathering nodules
Cutis rhomboidalis nuchae (Fig. 87.23C)
Colloid milium
Wrinkling (coarse > fine)
Favre-Racouchot syndrome (Fig. 87.23E)
Actinic comedonal plaque
Poikiloderma of Civatte (Fig. 87.23D)
Solar purpura and hemosiderin deposition (Fig. 87.23F)
Fragility (Fig. 87.23G)
Pseudoscars
Erosive pustular dermatosis (Fig. 87.23H)
Grover's disease (Fig. 87.25A,B)
Dyschromia
Solar lentigines, ephelides
Actinic keratoses
Squamous cell carcinoma
Basal cell carcinoma
Cutaneous melanoma, especially lentigo maligna
Acquired elastotic hemangioma

Table 87.8 Cutaneous signs of significant photodamage. Chronic use of voriconazole can lead to premature photodamage.

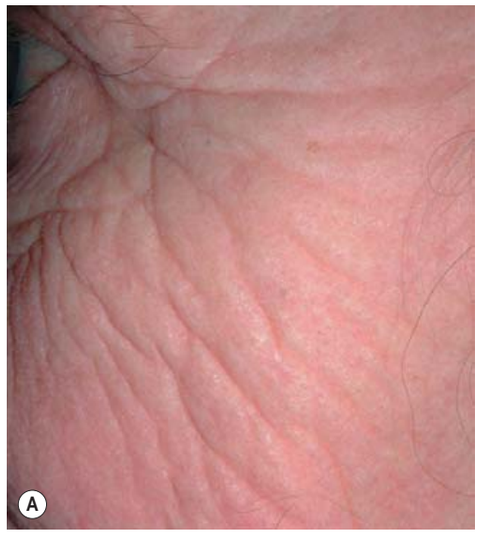


Fig. 87.23 Cutaneous signs of significant photoaging. A, B Solar elastosis of the cheek and arm with the characteristic yellow discoloration and thickening of the skin. **C** Cutis rhomboidalis nuchae with deep furrowing of the posterior neck.
B, Courtesy, Jean L Bolognia, MD.
Continued

irradiation, and perhaps also short-wavelength visible light, particularly in more darkly pigmented individuals[65]. This phenomenon, known as *immediate pigment darkening*, results from photo-oxidative darkening and the cellular redistribution of melanin within epidermal melanocytes. Pigmentation that persists for more than 2 hours after irradiation is referred to as *persistent pigment darkening*; it is brownish in color, lasts for up to 24 hours, and is also due to oxidation of pre-existing melanin. Persistent pigment darkening then blends with *delayed pigmentation,* or *tanning*, which develops in genetically competent individuals over hours to days and persists for weeks to months following approximately: 400 J/m^2 of broadband UVB (a little higher than the MED, particularly in fair-skinned persons); 150–200 kJ/m^2 of broadband UVA (a little less than the MED); or 100 J/m^2 of UVC (about equal to the MED). As a result of delayed tanning, later sunburning sensitivity is mildly decreased by a factor of two to four.

Epidermal hyperplasia

Hyperplasia lasting a month or so occurs over a period of hours to days following UVB or UVC, but generally not UVA, exposure. This results from a markedly increased cellular mitotic rate and DNA, RNA and protein synthesis, following several initial hours of inactivity[65]. Hyperplasia of the viable epidermis and thickening of the stratum corneum result in several-fold protection against later sunburning; this adds to, and may exceed, that simultaneously provided by delayed tanning, particularly in fair-skinned individuals.

Immunologic changes

Cutaneous UVB, UVC, and, to some extent, UVA irradiation alters epidermal Langerhans cell function, generates suppressor T lymphocytes, and changes the cutaneous cytokine profile[66]. This topic is discussed in greater detail in Chapter 86.

Vitamin D_3 synthesis

UVB (maximum: 300 ± 5 nm) irradiation quickly converts epidermal 7-dehydrocholesterol into previtamin D_3 (see Fig. 51.6)[67]; the latter then isomerizes to vitamin D_3 (cholecalciferol), which is then converted in the liver to 25-hydroxyvitamin D and subsequently in the kidneys to 1,25-dihydroxyvitamin D, its active form. UVR-induced vitamin D_3 synthesis is maximal at suberythemogenic doses.

Other changes

On occasion, otherwise healthy individuals develop *photo-onycholysis* and increased skin fragility with blistering (*pseudoporphyria*) following intense exposure to sunlight or tanning beds. This may be due to photosensitization by normal levels of endogenous substances such as porphyrins. *Mid-dermal elastolysis* is characterized by patches of finely wrinkled skin and the loss of elastic fibers in the mid-reticular dermis (see Ch. 99); its onset is frequently associated with intense UVR exposure. *Brachioradial pruritus*, characterized by primary pruritus of the outer arm, is associated with cervical radiculopathy; however, in many patients, UVR may act as a trigger of the symptoms (see Ch. 6).

Chronic Effects

Photoaging in fair-skinned patients

Photoaging refers to cutaneous changes secondary to long-term exposure to sunlight (Table 87.8). Characteristic clinical manifestations are outlined below.

Solar elastosis refers to thickening as well as yellow discoloration of the skin in chronically sun-exposed areas, often in association with marked wrinkling and most commonly seen on the face (Fig. 87.23A,B). Histologically, there is a marked increase in dermal

Fig. 87.23 Cutaneous signs of significant photoaging (cont'd) **D** Poikiloderma of Civatte with sparing of the anterior neck. **E** Multiple open comedones of the periorbital region in Favre–Racouchot syndrome. **F** Brown discoloration of the dorsal hand due to hemosiderin deposits from recurrent solar purpura. **G** Fragility of atrophic photodamaged skin of the shin. **H** Erosive pustular dermatosis of the bald scalp.
F, G, Courtesy, Jean L Bolognia, MD.

elastosis. Similar changes occur on the posterior neck and are sometimes referred to as *cutis rhomboidalis nuchae* (Fig. 87.23C), characterized by deep skin wrinkling and furrowing associated with a leathery texture.

A *solar lentigo* is a light brown to dark brown, even-colored or reticulated macule that occurs in sun-exposed areas, and although sometimes solitary, such lesions are more often multiple. The dorsal aspects of the hands, extensor forearms, upper trunk and face are the most commonly affected sites (see Ch. 112).

An *ephelide*, also known as a freckle, presents as a light brown to medium brown macule, usually less than 6 mm in diameter. Such lesions occur primarily on exposed areas of the face, but also on the shoulders and outer aspects of the arms. Numerous lesions are usually present.

Histologically, a solar lentigo is associated with elongation of the rete ridges and a mild increase in the number of melanocytes, while hyperpigmentation of the basal layer without elongation of the rete ridges is observed in an ephelide.

Poikiloderma of Civatte refers to reticulated red to red–brown patches with telangiectasias that spare perifollicular skin. It is most commonly observed on the lateral aspects of the neck in fair-skinned individuals with significant cumulative sun exposure (Fig. 87.23D). Characteristically, there is sparing of the central submental region. Mild atrophy and hyperpigmentation are sometimes present. Histologically, telangiectasias, dermal atrophy and irregular hyperpigmentation of the basal layer are observed.

In *Favre–Racouchot syndrome*, multiple large open comedones develop on the lateral and inferior aspects of the periorbital area (Fig. 87.23E), in association with marked solar elastosis of the surrounding skin. Histologically, there are dilated pilosebaceous openings and cyst-like spaces filled with horny material.

Colloid milium is characterized by translucent yellow papules that measure 1–3 mm in diameter. There are usually numerous, closely spaced lesions in chronically sun-exposed sites, especially the neck, face and dorsal hands. Histologically, homogeneous masses of colloid are present in the papillary dermis, which are PAS-positive and diastase-resistant.

Erosive pustular dermatosis classically presents as sterile pustules, crusts, erosions and mild inflammation arising within the photodamaged skin of a bald scalp (Fig. 87.23H). However, similar clinical findings can occur on the lower extremities of patients with venous hypertension and atrophic skin[68] and following perinatal scalp injuries. One theory is that the disorder is related to cutaneous atrophy. Erosive pustular dermatosis may be misdiagnosed as folliculitis, pyoderma or hypertrophic actinic keratoses, while the possibility of the Brunsting–Perry variant of mucous membrane (cicatricial) pemphigoid also needs to be considered. Although therapeutic responses vary, successful treatment with topical agents, in particular potent corticosteroids, tacrolimus and calcipotriene (calcipotriol), as well as oral isotretinoin, zinc sulfate and nimesulide (an NSAID that inhibits the respiratory burst of granulocytes) has been reported.

Photoaging in patients with skin of color

Photoaging is much less pronounced and has a delayed onset in individuals with more darkly pigmented skin[69] (Fig. 87.24). Small seborrheic keratoses, melasma and mottled hyperpigmentation are common signs of photoaging in East Asians, such as Chinese, Japanese and Koreans; in addition, any wrinkles are fine and do not appear before 50

Fig. 87.24 Photoaging in an African-American. Given her age, this 93-year-old woman has relatively fine wrinkling of her face, in addition to scattered seborrheic keratoses.

Fig. 87.25 Grover's disease. Crusted papules of the trunk **(A)** and obvious sparing of the sun-protected skin of the buttocks **(B)** in this patient with significant photodamage. *A, B, Courtesy, Jean L Bolognia, MD.*

years of age. South Asians, such as Indians, Pakistanis, Sri Lankans and Bangladeshis, often have darker skin; dyspigmentation and fine wrinkles are their main signs of photoaging. Lightly pigmented Latinos have changes similar to those seen in whites, while those with brown skin photoage in a manner similar to that seen in South Asians. Black-skinned individuals, including African-Americans, Afro-Caribbeans and people from Africa, have a wide range of Fitzpatrick skin types, from III to VI. Dyspigmentation is common in them, before fine wrinkles appear late in life.

Photocarcinogenesis

Chronic sun exposure has been associated with the development of actinic keratoses (AKs), SCC, BCC and melanoma, in particular lentigo maligna. Epidemiologic studies have shown that SCCs tend to develop within chronically sun-exposed areas in fair-skinned individuals; e.g. people who migrate to Australia early in life have a higher risk of developing SCC than immigrants who arrive when older. Furthermore, the incidence of BCC is higher in native-born Australians than immigrants, and a statistically significant association between *intermittent* sun exposure and the risk of BCC has also been reported. These findings are supported by the observation that the use of sunscreens led to a decrease in the development of AKs, SCCs, and, to a lesser extent, BCCs.[70] Exposure to tanning beds seems to be associated with an increased risk for developing these tumors as well as cutaneous melanoma[71]. Lastly, nevus density, considered a likely surrogate for melanoma development, has correlated with the degree of individual sun exposure[72,73].

Melanoma development in populations with more darkly pigmented skin has also been studied. An analysis of patients with cutaneous melanoma in the SEER database (1992–2001) concluded that a higher melanoma incidence was associated with an increased UV index and lower latitude only in non-Hispanic whites, but not in black or Hispanic populations[74]. This is also consistent with the observation that the proportion of acrolentiginous melanoma among all melanoma subtypes is greatest in people of color, especially in black-skinned individuals[75].

Grover's disease

Grover's disease, also known as transient (and later persistent) acantholytic dermatosis, most commonly occurs in Caucasian men over 40 years of age with significant photodamage. It peaks during the winter months, with a second peak at the end of summer. Pruritic, often crusted, skin-colored to pink papules and papulovesicles appear on the trunk, primarily in sun-exposed sites (Fig. 87.25). In addition to UV exposure, exacerbating factors include sweating, heat, friction, xerosis and, occasionally, ionizing radiation. While lesions may resolve over weeks to months, they commonly recur. Histologically, four patterns are seen (sometimes in combination): Darier disease-like; Hailey–Hailey disease-like; pemphigus vulgaris- or foliaceus-like; and spongiotic with acantholysis. The differential diagnosis of Grover's disease includes folliculitis, miliaria rubra, arthropod bites, multiple lichen planus-like keratoses, early pemphigus foliaceus and, when chronic, Darier disease. Except for the latter two entities, histologic examination allows distinction; the focal nature of the histologic findings, negative immunofluorescent microscopy and lack of additional clinical features (e.g. palmar keratoses, erythronychia with notching) points to the diagnosis of Grover's disease. Therapy can be frustrating, but includes primarily topical agents (e.g. corticosteroids, pramoxine, calcineurin inhibitors, vitamin D analogues) and oral antihistamines, in addition to avoidance of exacerbating factors. Occasionally, oral retinoids, PUVA and UVA1 have been tried.

REFERENCES

1. Kerr, HA, Lim, HW. A comparison of photosensitivity disorders in African Americans and Caucasians. J Am Acad Dermatol. 2007;57:638–43.
2. Jong CT, Finlay AY, Pearse AD, et al. The quality of life of 790 patients with photodermatoses. Br J Dermatol. 2008;159:192–7.
3. Richards HL, Ling TC, Evangelou G et al. Evidence of high levels of anxiety and depression in polymorphic light eruption and their association with clinical and demographic variables. Br J Dermatol. 2008;159:439–44.
4. Hönigsmann H, Hojyo-Tomoka MT. Polymorphous light eruption, hydroa vacciniforme, and actinic prurigo. In: Lim HW, Hönigsmann H, Hawk J (eds). Photodermatology. New York: Informa Healthcare, 2007:149–68.
5. Das S, Lloyd JJ, Walshaw D, Farr PM. Provocation testing in polymorphic light eruption using fluorescent ultraviolet (UV) A and UVB lamps. Br J Dermatol. 2004; 151:1066–70.
6. McFadden JP, Norris PG, Cerio R, et al. Heat shock protein 65 immunoreactivity in experimentally induced polymorphic light eruption. Acta Derm Venereol. 1994; 74:283–5.
7. McGregor JM, Grabczynska S, Vaughan RW, et al. Genetic modeling of abnormal photosensitivity in families with polymorphic light eruption and actinic prurigo. J Invest Dermatol. 2000;115:471–6.
8. van de Pas CB, Kelly DA, Seed PT, et al. Ultraviolet-radiation-induced erythema and suppression of contact hypersensitivity responses in patients with polymorphic light eruption. J Invest Dermatol. 2004;122:295–9.
9. Palmer RA, Hawk JLM, Young AR, Walker SL. The effect of solar-simulated radiation on the elicitation phase of contact hypersensitivity does not differ between controls and patients with polymorphic light eruption. J Invest Dermatol. 2005;124: 1308–12.
10. Lembo S, Fallon J, O'Kelly P, Murphy GM. Polymorphic light eruption and skin cancer prevalence: is one protective against the other? Br J Dermatol. 2008;159: 1342–7.
11. Man I, Dawe RS, Ferguson, J. Artificial hardening for polymorphic light eruption: practical points from ten years' experience. Photodermatol Photoimmunol Photomed. 1999;15:96–9.
12. Patel DC, Bellaney GJ, Seed PT, et al. Efficacy of short-course oral prednisolone in polymorphic light eruption: a randomized controlled trial. Br J Dermatol. 2000:143:828–31.

13. Corbett MF, Hawk JLM, Herxheimer A, Magnus IA. Controlled therapeutic trials in polymorphic light eruption. Br J Dermatol. 1982;107:571–81.
14. Murphy GM, Hawk JLM, Magnus IA. Hydroxychloroquine in polymorphic light eruption: a controlled trial with drug and visual sensitivity monitoring. Br J Dermatol. 1987;116:379–86.
15. Hojyo-Tomoka MT, Vega-Memije ME, Cortes-Franco R, Dominguez-Soto L. Diagnosis and treatment of actinic prurigo. Dermatol Ther. 2003;16:40–4.
16. Estrada-GI, Garibay-Escobar A, Nunez-Vazquez A, et al. Evidence that thalidomide modifies the immune response of patients suffering from actinic prurigo. Int J Dermatol. 2004;43:893–7.
17. Grabczynska SA, McGregor JM, Kondeatis E, et al. Actinic prurigo and polymorphic light eruption: common pathogenesis and the importance of HLA-DR4/DRB1* 0407. Br J Dermatol. 1999;140:232–6.
18. Huggins RH, Leithauser LA, Eide MJ, et al. Life quality assessment and disease experience of patient members of a Web-based hydroa vacciniforme support group. Photodermatol Photoimmunol Photomed. 2009;25: 209–15.
19. Iwatsuki K, Satoh M, Yamamoto T, et al. Pathogenic link between hydroa vacciniforme and Epstein-Barr virus-associated hematologic disorders. Arch Dermatol. 2006;142:587–95.
20. Cohen JI, Kimura H, Nakamura S, et al. Epstein-Barr virus-associated lymphoproliferative disease in non-immunocompromised hosts: a status report and summary of an international meeting, 8–9 September 2008. Ann Oncol. 2009;20:1472–82.
21. Hawk J, Lim HW. Chronic actinic dermatitis. In: Lim HW, Hönigsmann H, Hawk J (eds). Photodermatology. New York: Informa Healthcare, 2007:169–84.
22. Hawk JLM, Magnus IA. Chronic actinic dermatitis – an idiopathic photosensitivity syndrome including actinic reticuloid and photosensitive eczema [proceedings]. Br J Dermatol. 1979;101(suppl. 17):24.
23. Lim HW, Cohen D, Soter NA. Chronic actinic dermatitis: results of patch and photopatch tests with Compositae, fragrances and pesticides. J Am Acad Dermatol. 1998 ;38:108–11.
24. Dawe RS, Crombie IK, Ferguson J. The natural history of chronic actinic dermatitis. Arch Dermatol. 2000;136: 1215–20.
25. Agar N, Morris S, Russell-Jones R, et al. Case report of four patients with erythrodermic cutaneous T-cell lymphoma and severe photosensitivity mimicking chronic actinic dermatitis. Br J Dermatol. 2009;160:698–703.
26. Beattie PE, Dawe RS, Ibbotson SH, Ferguson J. Characteristics and prognosis of idiopathic solar urticaria: a cohort of 87 cases. Arch Dermatol. 2003;139:1149–54.
27. Ng JC, Foley PA, Crouch RB, Baker CS. Changes of photosensitivity and action spectrum with time in solar urticaria. Photodermatol Photoimmunol Photomed. 2002;18:191–5.
28. Tuchinda C, Leenutaphong V, Sudtim S, Lim HW. Fixed solar urticaria induced by UVA and visible light: a report of a case. Photodermatol Photoimmunol Photomed. 2005;21:97–9.
29. Kullavanijaya P, Lim HW. Photoprotection. J Am Acad Dermatol. 2005;52:937–58.
30. Beissert S, Stander H, Schwarz T. UVA rush hardening for the treatment of solar urticaria. J Am Acad Dermatol. 2000;42:1030–2.
31. Duschet P, Leyen P, Schwarz T, et al. Solar urticaria – effective treatment by plasmapheresis. Clin Exp Dermatol. 1987;12:185–8.
32. Maksimovic L, Fremont G, Jeanmougin M, et al. Solar urticaria successfully treated with intravenous immunoglobulins. Dermatology. 2009;218:252–4.
33. Cleaver JE, Lam ET, Revet I. Disorder of nucleotide excision repair: the genetic and molecular basis of heterogeneity. Nat Rev Genet. 2009;10:756–68.
34. Lehmann AR. DNA repair-deficient diseases, xeroderma pigmentosum, Cockayne syndrome and trichothiodystrophy. Biochimie. 2003;85:1101–11.
35. Hoeijmakers, JHJ. DNA damage, aging, and cancer. N Engl J Med. 2009;361:1475–85.
36. Capell BC, Tlougan BE, Orlow SJ. From the rarest to the most common: insights from progeroid syndromes into skin cancer and aging. J Invest Dermatol. 2009; 129:2340–50.
37. Kraemer KH, Lee MM, Scotto J. Xeroderma pigmentosum: cutaneous, ocular, and neurologic abnormalities in 830 published cases. Arch Dermatol. 1987;123:241–50.
38. Yarosh D, Klein J, O'Connor A, et al. Effects of topically applied T4 endonuclease V in liposomes on skin cancer in xeroderma pigmentosum: a randomized study. Xeroderma Pigmentosum Study Group. Lancet. 2001;357:926–9.
39. Spivak G. The many faces of Cockayne syndrome. Proc Natl Acad Sci U S A. 2004;101:15273–4.
40. Nance MA, Berry SA. Cockayne syndrome: review of 140 cases. Am J Med Genet. 1992;42:68–84.
41. Nardo T, Oneda R, Spivak G, et al. A UV-sensitive syndrome patient with a specific CSA mutation reveals separable roles for CSA in response to UV and oxidative DNA damage. Proc Natl Acad Sci U S A. 2009;106:6209 –14.
42. Cleaver JE, Lam ET, Revet I. Disorders of nucleotide excision repair: the genetic and molecular basis of heterogeneity. Nat Rev Genet. 2009;10756–68.
43. Faghri S, Tamura D, Kraemer KH, et al. Trichothiodystrophy: a systematic review of 112 published cases characterises a wide spectrum of clinical manifestations. J Med Genet. 2008;45:609–21.
44. Dubaele S, Proietti De Santis L, Bienstock RJ, et al. Basal transcription defect discriminates between xeroderma pigmentosum and trichothiodystrophy in XPD patients. Mol Cell. 2003;11:1635–46.
45. Liang C, Kraemer K, Morris A, et al. Characterization of tiger tail banding and hair shaft abnormalities in trichothiodystrophy. J Am Acad Dermatol. 2005;52: 224–32.
46. Bloom's Syndrome Registry. http://www.med.cornel.edu/bsr/. Accessed Nov. 26, 2009.
47. Killen MW, Stults DM, Adachi N, et al. Loss of Bloom syndrome protein destabilizes human gene cluster architecture. Hum Mol Genet. 2009;18:3417–28.
48. Wang LL, Levy LL, Lewis RA. Clinical manifestations in a cohort of 41 Rothmund-Thomson syndrome patients. Am J Med Genet. 2001;102:11–17.
49. Lindor NM, Furuichi Y, Kitao S, et al. Rothmund-Thomson syndrome due to *RECQ4* helicase mutations: report and clinical and molecular comparisons with Bloom syndrome and Werner syndrome. Am J Med Genet. 2000;90:223–8.
49a. Arnold AW, Itin PH, Pigors M, et al. Poikiloderma with neutropenia: a novel C16orf57 mutation and clinical diagnostic criteria. Br J Dermatol. 2010;163:866–9.
50. Penagos H, Jaen M, Sancho MT, et al. Kindler syndrome in Native Americans from Panama: report of 26 cases. Arch Dermatol. 2004;140:939–44.
51. Lai-Cheong JE, Parsons M, McGrath JA. The role of kindlins in cell biology and relevance to human disease. Int J Biochem Cell Biol. 2010;42:595–603.
52. Lai-Cheong JE, Parsons M, Tanaka A, et al. Loss-of-function *FERMT1* mutations in Kindler syndrome implicate a role for fermitin family homolog-1 in integrin activation. Am J Pathol. 2009;175:1431–41.
53. Werth VP, Hönigsmann H. Photoaggrevated dermatoses. In: Lim HW, Hönigsmann H, Hawk J (eds). Photodermatology. New York: Informa Healthcare, 2007:251–66.
54. Wong SN, Khoo LS. Analysis of photodermatoses seen in a predominantly Asian population at a photodermatology clinic in Singapore. Photodermatol Photoimmunol Photomed. 2005;21:40–4.
55. Crouch RB, Foley PA, Baker CS. Analysis of patients with suspected photosensitivity referred for investigation to an Australian photodermatology clinic. J Am Acad Dermatol. 2003;48:714–20.
56. Ferguson J, DeLeo VA. Drug and chemical photosensitivity: exogenous. In: Lim HW, Hönigsmann H, Hawk, J (eds). Photodermatology. New York: Informa Healthcare, 2007:199–217.
57. D'Agostino ML, Risser J, Robinson-Bostom L. Imipramine-induced hyperpigmentation: a case report and review of the literature. J Cutan Pathol. 2009; 36:799–803.
58. Guzzo C, Kaidby K. Recurrent recall of sunburn by methotrexate. Photodermatol Photoimmunol Photomed. 1995;11:55–6.
59. Slade HB, Shroot B, Feldman SR, et al. Reappraising the phototoxicity of tretinoin: a report of four controlled clinical trials. Photodermatol Photoimmunol Photomed. 2009;25:146–52.
60. Darvay A, White IR, Rycroft RJG, et al. Photoallergic contact dermatitis is uncommon. Br J Dermatol. 2001; 145:597–601.
61. Bryden AM, Moseley H, Ibbotson SH, et al. Photopatch testing of 1155 patients: results of the U.K. multicentre photopatch study group. Br J Dermatol. 2006;155: 737–47.
62. Bruynzeel DP, Ferguson J, Andersen K, et al. European Taskforce for Photopatch Testing. Photopatch testing: a consensus methodology for Europe. J Eur Acad Dermatol Venereol. 2004;18:679–82.
63. Anstey AV, Taylor CR. Photosensitivity in the Smith-Lemli-Opitz syndrome: the US experience of a new congenital photosensitivity syndrome. J Am Acad Dermatol. 1999;41:121–3.
64. Merkens LS, Wassif C, Healy K, et al. Smith-Lemli-Opitz syndrome and inborn errors of cholesterol synthesis: summary of the 2007 SLO/RSH Foundation scientific conference sponsored by the National Institutes of Health. Genet Med. 2009;11:359–64.
65. Hönigsmann H. Erythema and pigmentation. Photodermatol Photoimmunol Photomed. 2002;18: 75–81.
66. Gibbs NK, Tye J, Norval M. Recent advances in urocanic acid photochemistry, photobiology and photoimmunology. Photochem Photobiol Sci. 2008;7: 655–67.
67. Lehmann B, Meurer M. Vitamin D metabolism. Dermatol Ther. 2010;23:2–12.
68. Patton D, Lynch PJ, Fung MA, et al. Chronic atrophic erosive dermatosis of the scalp and extremities: a recharacterization of erosive pustular dermatosis. J Am Acad Dermatol. 2007; 57:421–7.
69. Halder RM, Richards GM. Photoaging in patients of skin of color. In: Rigel DS, Weiss RA, Lim HW, Dover JS (eds). Photoaging. New York: Marcel Dekker, 2004: 55–63.
70. Green AC, Williams GM, Logan V, Strutton GM. Reduced melanoma after regular sunscreen use: randomized trial follow-up. J Clin Oncol. 2011;29:257–63.
71. Lazovich D, Vogel RI, Berwick M, et al. Indoor tanning and risk of melanoma: a case-control study in a highly exposed population. Cancer Epidemiol Biomarkers Prev. 2010;19:1557–68.
72. Wachsmuth RC, Turner F, Barrett JH, et al. The effect of sun exposure in determining nevus density in UK adolescent twins. J Invest Dermatol. 2005;124:56–62.
73. Dodd AT, Morelli J, Mokrohisky ST, et al. Melanocytic nevi and sun exposure in a cohort of Colorado children: anatomic distribution and site-specific sunburn. Cancer Epidemiol Biomarkers Prev. 2007;16:2136–43.
74. Eide MJ, Weinstock MA. Association of UV index, latitude, and melanoma incidence in nonwhite populations – US Surveillance, Epidemiology, and End Results (SEER) program, 1992–2001. Arch Dermatol. 2005;141:447–81.
75. Bradford PT, Goldstein AM, McMaster ML, et al. Acral lentiginous melanoma: incidence and survival patterns in the United States, 1986–2005. Arch Dermatol. 2009;145:427–34.

Environmental and Sports-Related Skin Diseases

88

Mary Beth Cole and Michael L Smith

Chapter Contents

Injury due to heat exposure 1487
Injury due to cold exposure 1492
Injury due to water exposure 1494
Injury due to electricity 1496
Injury due to chemical exposure 1497
Frictional and traumatic injury to the skin 1501
Sports-related dermatoses 1505
Amputee-related dermatoses 1508
Musical instrument-related dermatoses 1508

The skin is the primary interface with the environment. Humans are unique among the Earth's creatures in their ability to manipulate the environment by manufacturing clothing, shelter, and heating and cooling devices to allow them to live in a variety of environmental extremes. Despite technologic advances that have allowed humans to live, work and play in most of the environments on the planet, deliberate or inadvertent exposure to those environments may subject individuals to injury. The following discussion will focus upon temperature-related skin diseases, water immersion injury, electrical burns, chemical injury, heavy metals in cutaneous disease, frictional and traumatic skin injury, sports-related dermatoses, and skin problems of instrumental musicians.

INJURY DUE TO HEAT EXPOSURE

Heat-Related Illnesses and Thermal Burns

Synonyms/variants: ■ Heat-related illnesses: heat cramps, heat syncope, heat edema, heat exhaustion, heat stroke ■ Thermal burns: burns

Key features

- Heat-related illnesses occur when the body's thermoregulatory mechanisms fail; correction of fluid and electrolyte balance is critical in their management
- For thermal burns, need to assess depth of burn (i.e. first, second or third degree) and surface area involved
- Burn treatment includes prevention of infection, serial excisions and skin substitutes

Introduction

Humans, like all other mammals and all birds, are homeothermic organisms, maintaining their core body temperature within a narrow range by varying cutaneous and visceral blood flow. Normal core body temperatures vary between 36°C and 37.5°C (96.8°F and 99.5°F). At normal core temperature, cutaneous blood flow is about 4% of cardiac output or 250 ml/min. Alteration of the cutaneous blood flow is performed by the hypothalamus in a delicate balancing act between heat retention and loss. Cutaneous, muscle and spinal cord temperature sensors send signals to the preoptic area of the anterior hypothalamus. Communication with the posterior hypothalamus sets up thermoregulatory mechanisms of vasomotor control, sweating and shivering.

When prolonged exposure to a hot environment leads to an increase in core temperature, the subsequent decrease in sympathetic output results in peripheral vasodilation, allowing an increase in cutaneous blood flow of up to 6–8 l/min. Cholinergic output stimulates sweating. These changes allow radiant, conductive, convective and evaporative heat loss. In contrast, cold temperature exposure leads to increased sympathetic output with peripheral vasoconstriction. Countercurrent heat exchange between parallel arteries and veins further reduces heat loss to the skin, helping to conserve core heat. The behavioral response of shivering generates heat through muscular activity[1].

When the normal hypothalamic regulatory setpoint is overcome by extremes of temperature, pathologic conditions result (Table 88.1). The following discussion will explore heat-related illnesses and thermal burns. Heat-induced urticaria is covered in Chapter 18.

History

It is speculated that King Edward and his armored crusaders lost the final battle of the Holy Land because the Arab horsemen were adapted and dressed appropriately for the severe heat.

Epidemiology

The frequency of heat-related illnesses is unknown, since milder forms resolve with simple measures. Heat-related illness accounted for more than 8000 deaths in the US between 1979 and 1999, and is responsible for 7% of wilderness deaths[1,2]. Risk factors are listed in Table 88.2.

Burn injuries are far more commonly reported, occurring in 2 million people per year in the US alone, and resulting in 60 000 hospitalizations and 6000 deaths, half of which occur in children[3,4]. The male:female ratio is 2:1. The main sources of burns in children are scald, flame and electrical. Abuse or neglect may account for up to 20% of pediatric burns. Mortality rates have declined in recent years due to improved resuscitative and surgical management. In the 1940s, burns in children involving 50% body surface area (BSA) had a 50% survival rate, whereas today, 50% of children with 90% BSA burns survive[3,4].

A unique form of burn injury is that due to fireworks, particularly sparklers[5]. In the US, fireworks account for over 12 000 emergency department visits annually. Blast injuries of the hand and eyes are seen in addition to burns.

Pathogenesis

Athletic activity can generate 800 to 1000 kcal/h of heat for prolonged periods. This results in a 1°C rise in core body temperature every 5 to 8 minutes. The normal thermoregulatory mechanisms dissipate this heat as it is generated. When the regulatory mechanisms fail, heat injury occurs. Heat illnesses are not defined by a specific temperature, but by the abnormal response to heat. Table 88.1 outlines the pathogenesis of heat-related disorders.

Thermal burns occur when skin is exposed to infrared radiation (800 to 170 000 nm) from an external heat source with a temperature exceeding 44°C (111°F). Time and temperature curves have been developed to determine maximum thermal exposure times. Necrosis of the epidermis occurs in about 45 minutes at 47°C (117°F) but in only 1 second at 70°C (158°F). Denaturation and coagulation of cellular proteins occur in thermal injury. Interstitial edema develops from altered osmotic pressure and capillary permeability. Several chemical mediators with vasoactive and tissue-destructive properties are released,

HEAT-RELATED ILLNESSES				
Condition	**Core temperature**	**Clinical features**	**Treatment**	**Pathogenesis**
Heat cramps	Normal	Painful spasm in large muscle groups, weakness, fatigue, N/V, **marked sweating**, tachycardia, ↑BP	Fluid and salt replacement	Dilutional hyponatremia due to free water, but not electrolytes, being replaced
Heat syncope	Normal	Nausea, sighing, yawning, restlessness, fainting (brief)	Avoid standing still in heat, flex legs, lie down if prodrome, cool off, replace fluid	Decreased cerebral blood flow due to volume depletion, peripheral vasodilation and decreased vasomotor tone in poorly acclimatized or elderly individuals
Heat edema	Normal	**Dependent edema** from vasodilatory pooling	None needed (self-limited)	Vasodilatory pooling
Heat exhaustion	Normal to 39°C (102.2°F)	Weakness, dizziness, headache, N/V, irritability, dyspnea/hyperventilation, malaise, myalgias/muscle cramps, tachycardia, orthostatic hypotension, **profuse sweating, piloerection**, impaired judgment, syncope Hypernatremic form: thirst, rare cramps Hyponatremic form: fatigue, cramps, history of excessive free water intake, altered mental status	Intravenous fluids and electrolytes, sprinkle water and fan or use ice packs, rest, cool environment	Volume and/or salt depletion
Heat stroke	>40°C (104°F)	**Anhidrosis to profuse sweating**, ↓BP, N/V, diarrhea, altered mental status (profound), seizures, coma, cardiac arrhythmias, ↑ transaminases, rhabdomyolysis, acute renal failure, DIC, respiratory alkalosis Poor prognostic indicators: T >42.2°C (108°F); coma >2 h; AST >1000 (day 1)	Rapid lowering of core temperature to 38°C (100.4°F), intravenous hydration, intensive care unit	End result of thermoregulatory failure; volume depletion leads to peripheral vasoconstriction and reduced transfer of heat peripherally; resultant core heating leads to organ failure

Table 88.1 Heat-related illnesses[1,2]. Cutaneous features are indicated in bold. AST, aspartate transaminase; BP, blood pressure; DIC, disseminated intravascular coagulation; N/V, nausea and vomiting; T, temperature.

RISK FACTORS FOR HEAT-RELATED ILLNESS	
• Occupational exposure	• Age (elderly, young child)
• Poverty	• Insufficient acclimatization
• Alcoholism, mental illness, dementia	• Obesity
• Medications (anticholinergics, phenothiazines, diuretics; see Table 39.9)	
Medical conditions • Excessive fluid loss (e.g. diarrhea, diabetes mellitus) • Suboptimal sweating (e.g. ectodermal dysplasias; see Tables 39.8 & 39.10) • Excessive sweating (see Tables 39.2 and 39.3) • Inadequate fluid intake (see above) • Decreased thirst (cystic fibrosis; see Table 39.12) • Abnormal thermoregulation (prior heat illness, malnutrition)	

Table 88.2 Risk factors for heat-related illness[1,2].

Fig. 88.1 Thermal burn. This superficial second-degree burn is characterized by bullae that contain serous fluid. *Courtesy, Kalman Watsky, MD.*

including prostaglandins, bradykinin, serotonin, histamine, lipid peroxides and oxygen radicals[4].

Clinical features

Although heat-related illnesses are not primary skin diseases, they can present with cutaneous findings. Their clinical features are summarized in Table 88.1.

Thermal burns of the skin differ in their clinical presentation, depending upon the depth of injury (Table 88.3)[4,6,7]. Conventional nomenclature categorizes cutaneous burn wounds as *first degree* (superficial; limited to epidermis), *second degree* (partial-thickness) and *third degree* (full-thickness). Second-degree burns are further subdivided into superficial (Fig. 88.1) and deep variants. Burns involving deeper structures such as muscle are sometimes referred to as fourth-degree burns. However, a definitive diagnosis of wound depth may not be possible for the first 24 to 72 hours because of vascular occlusive changes.

At sites where the dermis is thinner (ears, volar forearms, medial thighs, perineum), burns may be deeper than the initial presentation might suggest; this is also the case in the comparatively thinner skin of children and the elderly. Wounds that appear dull red from entrapment of clot (denatured hemoglobin) imply full-thickness injury[6].

The severity of burn injuries is based upon depth and BSA involvement. BSA is estimated in adults by the "rule of nines" (Fig. 88.2). This formula cannot be applied to children, since the head accounts for approximately 19% BSA in a 2-year-old, 15% in a 7-year-old, and 13% in a 12-year-old. Lund & Browder charts are useful for more accurate assessment of BSA involvement[4,6]. Initial evaluation should address airway and circulatory status; associated inhalation injury is seen in up to 25% of burn patients. Cardiovascular evaluation must address the issue of hypovolemic shock, regardless of burn severity. Urine output must be monitored because of the significant fluid loss and rhabdomyolysis that may compromise renal function[3,4,6].

Pathology

Pathologic features of thermal burns are summarized in Table 88.3.

Differential diagnosis

The differential diagnosis of heat injury is listed in Table 88.1. Although there is considerable overlap in clinical features, an important distinction is the degree of neurologic compromise. The most important

CLINICAL AND PATHOLOGIC FEATURES OF THERMAL BURNS			
Type	**Depth**	**Clinical features**	**Pathology**
First degree	Epidermis only	Pain, tenderness, erythema No blistering Heals without scar	Upper epidermal necrosis
Second degree – superficial	Epidermis and superficial dermis	Severe pain, tenderness, serous or hemorrhagic bullae, deep rubor, erosion and exudation Heals in 10–21 days with mild but variable scarring	More extensive epidermal necrosis with vertical elongation of keratinocytes Necrotic areas may have serous crust with neutrophils, fibrin and cellular debris Subepidermal bullae possible
Second degree – deep	Epidermis and most of dermis destroyed, including deep follicular structures	Intense pain but reduced sensation, deep red to pale and speckled in color Serosanguineous bullae and erosions May appear devitalized initially Prolonged healing time Hypertrophic scars and marked wound contracture	Destruction of entire epidermis, dermal collagen and most of adnexal structures Collagen bundles may be fused, with eosinophilic appearance Thrombosis of deep vessels common Granulation tissue present at junction of normal and injured tissue
Third degree	Full-thickness epidermal and dermal destruction	Dry, hard, charred, non-blanching, insensitive areas of coagulation necrosis Small lesions heal with significant scarring Most require surgical correction	Necrosis of entire epidermis and dermis, with extension into subcutis Inflammatory infiltrate at interface between burned and normal skin If scar forms, it exhibits hyalinized collagen, decreased elastic tissue, loss of arrector pili muscles

Table 88.3 Clinical and pathologic features of thermal burns[4,6,7].

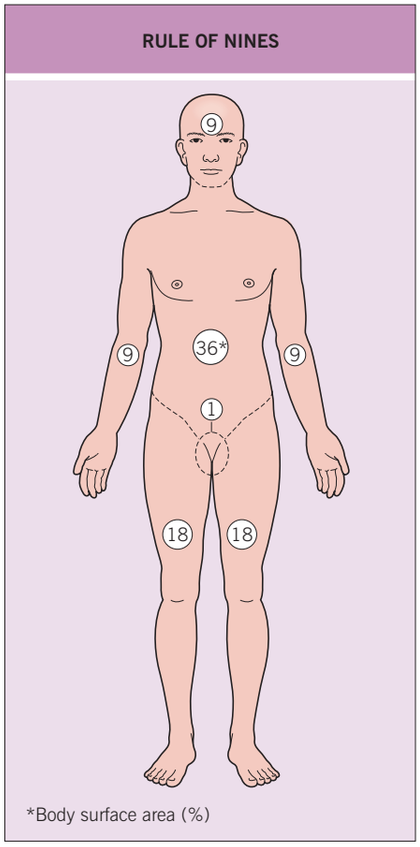


Fig. 88.2 Rule of nines. In adults, an estimate of burn extent is often based upon this surface area distribution chart. Infants and children have a relatively increased head : trunk surface area ratio. These estimates are also used for primary cutaneous disorders.

diagnostic issue with thermal burns is the depth of the injury (see Table 88.3).

Treatment

Management of heat-related injuries involves removal from the hot environment, rest, rehydration, restoration of electrolyte balance, and evaluation of involved systems (Table. 88.1; see Lugo-Amador et al.[1] for more details).

Initial management of burn victims includes assessment of cardiopulmonary status as well as the extent and depth of the burn. Information regarding resuscitation of burn victims is beyond the scope of this text, but can be found in references 3, 4 and 6. Management of the burn wound should start with cool compresses to ease pain and reduce heat. Then, the wound should be cleaned gently to remove any foreign material. The next step is prevention of infection, followed by creation of a proper healing environment (see Ch. 141). Topical antimicrobial agents shown to be effective in burn wound care include silver sulfadiazine, mafenide acetate and silver nitrate. Silver sulfadiazine has gained wide acceptance for both pediatric and adult burn treatment. However, percutaneous absorption can lead to leukopenia. Also, silver sulfadiazine produces a pseudoeschar that may interfere with burn depth assessment and prolonged application may lead to localized argyria. Superficial wounds may require little additional therapy[3,4,6].

Deeper burn wounds need more aggressive therapy, the most popular approach being serial excision. Third-degree burns are excised early, with indeterminate and deep second-degree wounds delayed until maximum depth and extent are known. Biologic dressings (e.g. pig skin, human allograft) were popular for several years, but have been largely displaced due to higher infection risk and poor healing. Newer skin substitutes such as acellular dermal matrix (AlloDerm®), bilaminar collagen-chondroitin sulfate and silicone (Integra®) and cultured epithelial autografts are gaining popularity[6] (see Ch. 145).

Erythema Ab Igne

Synonyms: ■ Toasted skin syndrome ■ Fire stains

Key features

- Localized areas of reticulated erythema and hyperpigmentation
- Chronic exposure to heat below the threshold for a thermal burn
- Commonly in lumbosacral region (heat applied to relieve pain) and shins (in regions without central heating in homes)
- Squamous atypia histologically
- Risk of cutaneous malignancy, particularly squamous cell carcinoma

Introduction

Chronic exposure to low levels of infrared heat can lead to the characteristic reticulated cutaneous pattern of erythema ab igne (EAI), with subsequent risk of malignant degeneration.

History

EAI, once a very common entity, was first described in the UK as a result of standing near stoves fired with peat. In the southern US, the custom of sitting around pot-bellied stoves to keep warm while

HEAT SOURCES REPORTED TO CAUSE ERYTHEMA AB IGNE	
• Heating pads	• Steam radiators
• Hot water bottles	• Heated car seats
• Electric stove/heater	• Heated reclining chairs
• Open fires	• Heating blanket
• Coal stoves	• Hot bricks
• Peat fires	• Infrared lamps
• Wood stoves	• Microwave popcorn
• Sauna belt	• Laptop computer*

*Anterior thighs » abdomen.

Table 88.4 Heat sources reported to cause erythema ab igne[8–10].

socializing also led to its development. Although the advent of central heating in much of the industrialized world has led to a dramatic decline in incidence, creative cultural and therapeutic applications of various heating devices continue to induce EAI[8–10].

Epidemiology

In the past, EAI was seen up to 10 times more frequently in women than in men. The vast majority of those affected were middle-aged or older. Risk factors include lack of central heating, occupations with close heat exposure, and medical conditions with symptoms relieved by heating or associated with decreased sensation. Recent reports of EAI due to laptop computers have appeared, including in teens engaged in prolonged gaming[11].

Pathogenesis

Long-term exposure to heat below the threshold for thermal burn is the primary etiologic factor in EAI. The precise pathophysiology is unknown, but the pattern corresponds with the dermal venous plexus. Repeated exposure to heat below 45°C (113°F) produces reticulated erythema followed by hyperpigmentation in the same pattern[9]. Heat sources reported to cause EAI are found in Table 88.4[8–10].

Clinical features

The initial presentation is a transient macular erythema in a broad reticulated pattern that easily blanches. The entire size and shape often approximates that of the heat source. As the heat exposure continues over time, the erythema evolves into a dusky hyperpigmentation, with lesions fixed and no longer blanchable (Fig. 88.3). Epidermal atrophy may overlie the reticulated pigmentation. Later-stage lesions may become somewhat keratotic and bullae may appear. Lesions are characteristically asymptomatic, although a slight burning sensation is sometimes noted[8].

Once the heat source is identified, it is important to determine if it is being used to relieve pain and, if so, the cause of the pain. A lumbosacral location usually points to musculoskeletal disease or, less often, bony metastases. EAI of the abdomen, flank or mid-back may reflect an attempt to relieve pain from inflammation (e.g. pancreatitis, peptic ulcer disease) or malignancy (e.g. pancreatic, gastric). Symptoms of pain should prompt a thorough review of systems and consideration of a search for occult disease. An inquiry into occupation and hobbies is also important, as EAI can develop in exposed areas, e.g. the forearms of bakers, the face or arms of glass blowers and foundry workers, and the anterior thighs in those with prolonged use of laptop computers[8,9,11].

The possible development of cutaneous squamous cell carcinoma (SCC) or Merkel cell carcinoma represents the major long-term risk. The latent period may be 30 years or more. Apparently, the risk of developing SCC is highest with hydrocarbon-fueled heat exposures, e.g. "peat fire cancers" on the shins of women, Japanese "Kairo cancers" and Tibetan "Kangri ulcers" due to coal-fired clothing warmers, and Chinese "Kang cancers" from sleeping on coal fire-heated bricks[8,9].

Pathology

The earliest histopathologic changes include epidermal atrophy, vasodilation and dermal pigmentation (both melanin and hemosiderin) (Fig. 88.4). As lesions progress, the epidermal atrophy becomes more pronounced, with flattening of the rete ridges. Focal hyperkeratosis and dyskeratosis are noted along with squamous atypia. Basal cell vacuolization has been reported and the dermal–epidermal junction may exhibit an interface dermatitis. The dermis appears thinned and sometimes

Fig. 88.3 Erythema ab igne – clinical features. **A** Earlier phase with pink reticulated patches predominating over reticulated hyperpigmentation. **B** Later phase with large area of reticulated hyperpigmentation and superimposed pink keratotic plaques centrally. *A, Courtesy, Jeffrey Callen, MD. B, Courtesy, Peter Klein, MD.*

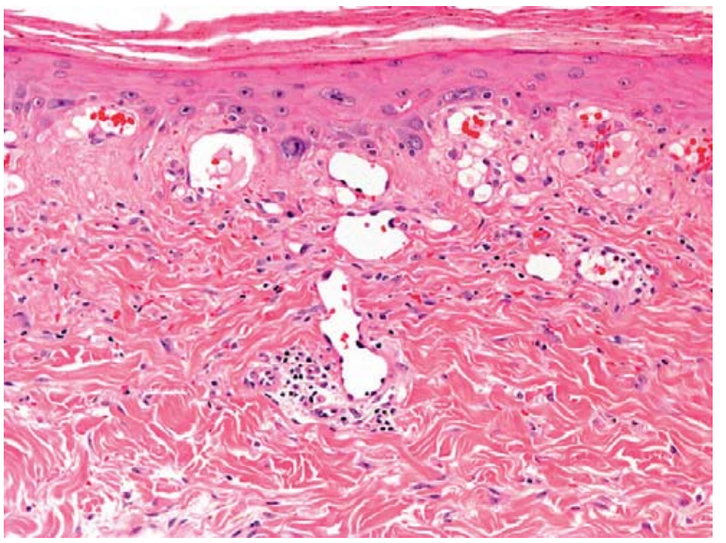


Fig. 88.4 Erythema ab igne – histologic features. The blood vessels within the superficial dermis are markedly dilated. There is hyperkeratosis and a mild perivascular infiltrate. Note also thinning of the epidermis with some apoptotic keratinocytes and atypical cells. *Courtesy, Lorenzo Cerroni, MD.*

edematous, with accumulation of abnormal elastic tissue and pigment as well as ectatic capillaries. Dermal capillaries may exhibit enlarged endothelial cells with hyperchromatic nuclei. Later lesions may also show basophilic degeneration of connective tissue. Hemosiderin deposition and prominent telangiectasias are seen most often in leg lesions. Ultrastructural evaluation also shows increased melanocyte dendritic processes, suggesting melanocyte activation[8,9,12].

Differential diagnosis

EAI needs to be distinguished from livedo reticularis, which is a temperature-sensitive vasculopathy (see Ch. 106) that favors the extremities but only occasionally develops associated hyperpigmentation. Cutis marmorata (see Ch. 106) and cutis marmorata telangiectatica congenita are less commonly considered in the differential diagnosis of EAI. The presence of telangiectasias along with atrophy and hyperpigmentation raises the possibility of poikiloderma and its various causes, e.g. cutaneous T-cell lymphoma (see Ch. 120), dermatomyositis (see Ch. 42) and several genodermatoses (see Ch. 63).

Treatment

Management consists primarily of removal of the offending heat source. The epidermal atypia is comparable to that of actinic keratoses, and anecdotally it has been treated successfully with topical 5-fluorouracil. As mentioned above, the use of heat to treat symptoms of pain should prompt a determination of the cause of this pain[8,9].

Burns Associated with Fluoroscopy and Magnetic Resonance Imaging (MRI)

Key features

- MRI may produce first-, second- or third-degree burns due to metal or wire contact with skin, creating a closed-loop conduction system
- Fluoroscopy, particularly when repeatedly performed in patients with cardiovascular disease, may result in radiation-induced injury

Introduction

The radiologic literature is replete with reports of superficial to full-thickness thermal or electrical burns occurring during MRI. Risk factors for MRI burns are listed in Table 88.5[13–15]. In addition, there are reports in the radiologic and dermatologic literature of ulcerations on the back following repeated fluoroscopy[16,17].

Pathogenesis

Although the precise cause of MRI burns is unknown, the presence of both pulsed radiofrequency and pulsed magnetic gradient fields is thought to play a role. If an electrically conductive loop is formed between the patient and an electrode, patient and wiring, or even small areas of skin–skin contact, current can be produced by the changing magnetic flux, causing a thermal or electrical burn. Resistance at the skin surface may create a thermal injury, while contact with wiring in a capacitative coupling may create electrical injury. Alternatively, the burn may result from formation of a resonant conducting loop with an extended wire creating a resonant antenna, heating maximally at the antenna tip[13–15,18].

The mechanism behind fluoroscopy-induced radiodermatitis is related to the dose of radiation that is delivered. Repeated procedures are notorious for increasing the risk[17]. Patients with diabetes mellitus, obesity, autoimmune connective tissue diseases (e.g. systemic sclerosis) or genetic defects involving repair of radiation-induced injury, as well as individuals receiving chemotherapy, appear to be more prone to developing this complication at lower doses of radiation[16].

Clinical features

Thermal burns appear soon after MRI, and may be partial- to full-thickness (see Table 88.3). The shape and size of the burns are determined by the conductor causing the injury (e.g. circular burns under ECG electrodes; figurate burns conforming to the shape of metallic wires or tattoo pigment deposition)[13,18].

RISK FACTORS FOR BURNS DURING MAGNETIC RESONANCE IMAGING	
ECG leads	Metallic body piercing jewelry
Monitoring cables	Tattoos
Pulse oximeter	Extremity skin-to-skin contact
Pins in halo fixation device	Clothing with metal threads
Transdermal patches	

Table 88.5 Risk factors for burns during magnetic resonance imaging[13–15]. ECG, electrocardiogram.

Fig. 88.5 Fluoroscopy-induced radiation dermatitis. The left upper back is a characteristic location for patients who have undergone attempts at coronary artery revascularization (e.g. angioplasty, stent placement). *Courtesy, Jeffrey Callen, MD.*

Fluoroscopy-induced radiation dermatitis may be acute, but, as time passes and the acute injury resolves, the patient may continue to develop further changes, including epilation of hair, desquamation, permanent erythema and eventual ulceration (Fig. 88.5)[16]. The left upper back is a characteristic location for patients with cardiovascular disease who have had cardiac catheterizations with attempts at revascularization (e.g. angioplasty, stent placement)[17].

Differential diagnosis

Because of the proximity of the MRI event to the detection of a burn injury, the diagnosis is generally straightforward. However, in the case of a tattoo burn, allergic contact dermatitis or foreign body granuloma formation within the tattoo may be considered. Timing of the event plus the sensation of a burn rather than pruritus should allow a distinction.

The differential diagnosis of fluoroscopy-induced disease includes fixed drug eruptions, contact dermatitis, herpes virus infection, impetigo and spider bites.

Treatment

Prevention of this injury by avoiding risk factors is ideal. However, when burns occur, they should be managed as any other thermal burn, or, in the case of fluoroscopy-induced injury, by limiting the dose delivered.

Airbag Burns

Key features

- Deployment of airbags causes numerous cutaneous injuries, including frictional and blunt trauma, thermal burns and, possibly, chemical burns
- Friction due to contact with the bag, thermal burning from the bag and its released gases, and exposure to corrosive aerosol produce the injuries

Introduction

Automobile airbags provide additional crash protection, with a resulting reduction in driver and passenger fatalities by up to 30%. Although patented in 1953, US manufacturers only began installation of airbags in the mid-1970s. European airbag installation began in 1981. Since 1997, new cars in the US have been required to have airbags. By 1999, 45% of cars and 41% of trucks in the US were thought to be compliant. Despite the beneficial effect, numerous injuries have resulted from airbag deployment, including burns, abrasions and lacerations[19,20].

Pathogenesis

Airbag activation consists of detection, inflation and deflation phases. The sudden deceleration caused by impact triggers sensors in the front bumper to fire a sodium azide canister inside the nylon rubber bag. The sodium azide ignites with an explosive release of hot nitrogen gas which inflates the bag in about 10 milliseconds at speeds exceeding 160 km/h. The hot nitrogen gas and other by-products are then vented out the upper sides of the bag away from the occupant, thus deflating the bag. Vented aerosol contains nitrogen, carbon mono- and dioxides, sodium hydroxide, ammonia, nitric oxide, metallic oxides and other trace gases, creating a corrosive environment. Friction and pressure from the bag, heat from the bag and gases, and contact with the corrosive aerosol may produce injury[19–21].

Clinical features

The cutaneous injuries produced by airbag deployment are summarized in Table 88.6. Chemical burns occur rarely, but appear to be a result of skin exposure to small amounts of the corrosive alkaline aerosol. The aerosolized particles need to dissolve in a water layer such as tears or sweat before creating a corrosive injury. Of note, alkali burns of the skin may continue to deepen and extend over time, unless all the corrosive chemical is washed away[19–21].

Differential diagnosis

The pattern of injury and history of airbag deployment makes the diagnosis obvious. However, it is important to determine whether a burn injury is purely thermal or if it has a chemical component. Assessment of tissue pH and monitoring for continued extension of the burn help determine whether an alkali injury exists.

AIRBAG INJURIES TO SKIN		
Type	**Frequency**	**Clinical features**
Abrasions/friction burns	64%	Patches of erythema or ecchymosis, typically with superficial erosion
Contusion	38%	Ecchymosis
Lacerations	18%	Variable severity
Thermal burns	8%	First and second degree most common (see Table 88.3)
		Localized full-thickness burn may result from metallic accessories or melted clothing
		Face and forearms, followed by hands, chest
Chemical burns	?	Painful, superficial, violaceous erythema and edema
		Partial- to full-thickness, often in splash pattern
Irritant dermatitis	?	Erythema and edema of upper chest, arms, face
		Burning or stinging sensation
		Desquamation and postinflammatory hyperpigmentation common

Table 88.6 Airbag injuries to skin[19–21].

Treatment

Prevention is, of course, the most valuable therapy. Newer airbag design modifications include repositioning of the exhaust vents to direct the escape of hot gases away from possible areas of skin contact. Seats should be positioned as far back from the airbag module as possible. Children too small to benefit from the adult three-point restraint should not be in the front passenger area. Children in any type of car seat or booster should never be put in the front seat. When a thermal or frictional injury occurs, local wound care and protection from secondary infection usually suffice.

Alkali burns require copious irrigation to dilute the corrosive substance. Acidic neutralization is contraindicated because of possible extension of injury by the resulting exothermic reaction. When the tissue pH is normal, local wound care is adequate.

INJURY DUE TO COLD EXPOSURE

Frostbite

Synonym: ■ First-degree frostbite – frost-nip

Key features

- Frostbite can occur when the skin temperature drops below about –2°C (28°F)
- Erythema, edema and numbness are replaced by marked hyperemia and pain
- Tissue freezing, vasoconstriction and inflammatory mediator release are central to the pathophysiology of frostbite
- Rapid rewarming in a warm water bath is the cornerstone of therapy

Introduction

Exposure to cold environments, whether during occupational or recreational activities, poses a risk of cold-related injury. Prolonged exposure may lead to hypothermia, frost-nip or frostbite. Hypothermia (i.e. a decline in core temperature below 35°C [95°F]) is a systemic process with minor cutaneous features and therefore will not be discussed in detail.

History

Cold injury predates recorded history – the quest for clothing, shelter and fire as protection from the elements must have preoccupied prehistoric humans. Mass casualties from cold injury have historically been seen most often in military conflicts. However, as interest in outdoor activities and the number of homeless individuals have risen, there has been increased exposure to cold among the general population[22,23].

Epidemiology

A 10-year retrospective assessment (1986 to 1995) of cold injury in members of the British Antarctic Survey found an incidence of 65.6 per 1000 per year seeking medical attention. Ninety-five percent had frostbite, 3% hypothermia and 2% cold water immersion foot. Superficial frostbite was the most common injury (74% of cases), and the face (nose and ears) was the most frequent site of involvement. Seventy-eight percent of the victims were injured during recreational activities. Although temperature and wind chill had no influence on severity of injury, the prevalence of cold injury increased with falling temperature, with a maximum prevalence at –25°C to –30°C (–13°F to –22°F). A major risk factor was prior cold injury[24].

In addition to homelessness, risk factors for frostbite include altered mental status, vehicular trauma, circulatory impairment, smoking and high altitude.

Pathogenesis

The underlying pathophysiology of frostbite is a combination of freezing, vascular insufficiency (constriction and occlusion) and damage due to inflammatory mediators. As extremities cool, the "hunting response of Lewis" (alternating vasoconstriction and vasodilation) occurs, ending with vasoconstriction. This tends to conserve the core temperature at the expense of the extremity, which tends toward ambient temperature. The head does not exhibit a vasoconstrictor response, except for the nose and ears. The trunk surface may cool slightly, but the core temperature is maintained. Frostbite is therefore unusual on the trunk or head (except the nose and ears), unless there is direct contact with ice or a refrigerant. The pathophysiologic stages of frostbite are summarized in Table 88.7, along with key clinical features[22,23].

FOUR STAGES OF FROSTBITE

Phase	Physiologic events	Clinical findings
I (cooling)	Cyclic vasoconstriction and vasodilation Extracellular ice formation (–2°C, 28°F) Intracellular ice crystal formation (if rapid freeze of >10°C or 18°F/min) Intravascular ice formation leads to erythrocyte sludging, vessel occlusion	Cool extremity Blanched appearance Numbness Hard, woody texture
II (thawing and rewarming)	Ice melts Dehydrated cells start to swell Loss of integrity of vessel walls, creating edema Vascular tone is compromised, leading to vasodilation Inflammatory mediator release leads to aggregation of platelets and leukocytes, causing thrombosis	Erythematous to violaceous color Intense pain Blisters form
III (extension of injury)	Thromboxane A2 levels increase Platelet and leukocyte aggregation extends into bordering tissue, creating vascular compromise	Blisters rupture
IV (resolution)	Tissue either re-epithelializes or desiccates and mummifies Vasomotor instability may persist indefinitely	Healing or amputation

Table 88.7 Four stages of frostbite[23].

Fig. 88.6 Frostbite. **A** Erythema, edema and hemorrhage are seen on the fingertips in a first-degree frostbite. **B** Bullae filled with clear fluid on the distal plantar surfaces in a second-degree frostbite. *B, Courtesy, Timothy Givens, MD.*

Clinical features

Frostbite has been divided into four categories of severity, analogous to burn injuries. These are only recognizable upon rewarming. *Frost-nip* (first-degree frostbite) presents with erythema, edema, cutaneous anesthesia and transient pain (Fig. 88.6A). Full recovery is expected, with only mild desquamation. *Second-degree frostbite* is characterized by marked hyperemia, edema and blistering, with clear fluid in the bullae (Fig. 88.6B). Healing occurs, but many patients have long-term sensory neuropathy, often with significant cold sensitivity.

Third-degree frostbite consists of full-thickness dermal loss, with hemorrhagic bulla formation or development of waxy, dry, mummified skin. The latter features are poor prognostic indicators for tissue loss. *Fourth-degree frostbite* is a full-thickness loss of the entire part, with skin, muscle, tendon and bone damage. Injuries of this severity lead to amputation[22–24]. Some authors advocate simple designation as superficial or deep injury, citing better prognostic accuracy.

Pathology

Superficial dermal edema and subepidermal bulla formation are typical findings in frostbite. Vascular permeability leads to hemorrhage, most pronounced in deep injury. The epidermis and involved dermis become necrotic, with an inflammatory infiltrate and granulation tissue at the junction with normal tissue[7].

Differential diagnosis

Frostbite injuries should be readily recognizable, given exposure history and typical presentation. A greater diagnostic challenge is determination of the depth of the injury (see above). One possible diagnosis in the differential is cold water immersion foot (see Table 88.9).

Treatment

Fundamental therapeutic goals in frostbite are rapid rewarming, prevention of further cold exposure, and restoration of circulation. Once the patient is in a setting in which re-freezing cannot occur, rapid water bath rewarming is indicated. The water bath temperature should be about 37–39°C (99–102°F). Rubbing the frozen extremity with ice, using dry heat, and slow rewarming are all contraindicated. In the hypothermic patient with frostbite injury, it is important to complete fluid resuscitation and core rewarming before limb rewarming, to prevent sudden hypotension and shock. Routine wound care, protection of the frostbitten part, and tetanus prophylaxis should then follow. Radiologic evaluation (MRI, bone scan, plain films) may help determine extent of injury and prognosis. Nowadays, triple-phase bone scans are considered the standard of care for assessing tissue viability during the initial days following injury[22].

Additional therapeutic suggestions have been based on animal studies, case reports or small series. Because of increased blood viscosity and sludging, thrombolytic therapy (e.g. heparin, streptokinase, iloprost, limaprost) has been suggested. Superficial white (nonhemorrhagic) bullae may be debrided to avoid prolonged exposure to prostaglandins and thromboxanes in blister fluid. Aloe vera, a thromboxane inhibitor, has been shown to be useful as a topical agent in superficial frostbite. The problem of vasoconstriction has been addressed by sympathectomy, with the most impressive effect being prevention of re-injury with repeat exposure to cold conditions. Pentoxifylline has been found to be useful, as have anti-inflammatory agents such as methylprednisolone, methimazole and aspirin[22,23,25].

Pernio

Synonyms: ■ Chilblains ■ Perniosis ■ Kibes

Key features

- Cold-sensitive inflammatory disorder in which erythrocyanotic discoloration of acral skin is accompanied by a sensation of itching or burning
- Common trigger is exposure to cold, wet, non-freezing conditions
- Must be distinguished from chilblain lupus erythematosus and cold-sensitive blood dyscrasias
- Nifedipine can be used to treat moderate to severe pernio

Introduction

Pernio is an abnormal inflammatory response to cold, damp, non-freezing conditions[26]. It is most common in areas without central heating.

History

Over a hundred years ago, pernio/chilblains was apparently common enough in Europe and the UK that the condition was well recognized. In 1881, Piffard[27] described it quite well:

"This affection, so common in cold climates, affects, by preference, the face, hands, nose, and ears. It is characterized by redness, usually with a purplish tinge, together with more or less pain of a burning character giving little or no trouble during the summer, but causing inconvenience and suffering as cold weather sets in."

Epidemiology

Exposure to cold, wet conditions is the major risk factor for pernio. This condition is common in the UK and northwestern Europe, particularly in those whose homes lack central heating. Women, children and the elderly are most commonly affected. Elderly patients may have a prolonged course, while younger patients improve spontaneously[28–30].

Pathogenesis

The precise pathogenesis of pernio is unknown, but the condition is thought to have a vascular origin. In children, it may be associated with cryoglobulins or cold agglutinins[30].

Clinical features

Pernio presents with single or multiple erythematous to blue–violet macules, papules or nodules (Fig. 88.7A). In severe cases, blistering and ulceration may be seen. Lesions are often symmetrically distributed on the distal toes and fingers, and less often on the heels, nose and ears. Deep pernio may be seen on the thighs, calves and buttocks as blue-erythrocyanotic plaques. Patients describe itching, burning or pain. Lesions often resolve in 1 to 3 weeks, except among elderly patients with venous insufficiency, in whom lesions can become chronic[29–32].

Pathology

Pernio has a nonspecific histology consisting of dermal edema plus a superficial and deep lymphohistiocytic infiltrate with peri-eccrine accentuation (Fig. 88.7B). The infiltrate is composed predominantly of T lymphocytes. Necrotic keratinocytes and lymphocytic vasculitis have been noted[29].

Differential diagnosis

Idiopathic pernio needs to be distinguished from several other cold-induced syndromes (Table 88.8)[28–33]. The latter can be assessed by laboratory evaluation including: (1) complete blood count to exclude hemolytic anemia and myelomonocytic leukemia; (2) cryoglobulin, cold agglutinin and cryofibrinogen levels to eliminate cold-sensitive dysproteinemia; and (3) serum protein electrophoresis and immunofixation electrophoresis to exclude a monoclonal gammopathy. Chilblain lupus erythematosus (Hutchinson), whose clinical features are similar to pernio, typically exhibits histologic features compatible with discoid lesions of lupus erythematosus and occurs in a patient with serologic evidence of autoimmunity (e.g. positive antinuclear antibody screen). Diagnosis of the lupus pernio form of sarcoidosis, which favors the nose, is confirmed by the presence of the histologic features of sarcoidosis[28,33].

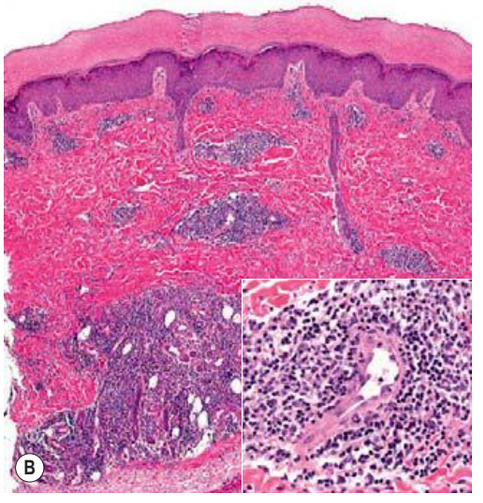


Fig. 88.7 Pernio – clinical and histologic features. A Violaceous macules and patches, primarily on the toes, but also on the plantar surface of the foot; note the associated scaling. **B** A dense perivascular and peri-eccrine lymphocytic infiltrate. Detail of predominantly lymphocytic perivascular infiltrate without atypical features (insert). Note the thickened stratum corneum characteristic of an acral site. *A, Courtesy, Jean L Bolognia, MD. B, Courtesy, Lorenzo Cerroni, MD.*

Treatment

Adequate clothing and avoidance of cold, damp conditions are important preventive measures, as are keeping feet dry and avoidance of smoking. In a double-blind, placebo-controlled trial, nifedipine (20 to 60 mg daily) was found to be efficacious for the treatment of pernio. None of the nifedipine-treated patients relapsed, while all of the placebo-treated patients developed new lesions[34]. It is effective in about 70% of patients with pernio. Other anecdotal remedies include topical corticosteroids, oral nicotinamide, phenoxybenzamine, sympathectomy and erythemogenic UVB phototherapy[28].

INJURY DUE TO WATER EXPOSURE

Immersion Foot

Synonyms: ■ Trench foot ■ Tropical jungle foot ■ Shelter foot ■ Paddy-field foot ■ Swamp foot ■ Jungle rot ■ Foxhole foot ■ Peripheral vasoneuropathy

Key features

- Injury occurs after continuous exposure of feet to moist, occluded conditions
- Cold water, warm water and tropical variants exist
- The underlying pathologic process is overhydration of the stratum corneum
- Neuropathy may persist indefinitely
- Feet exposed to immersion injury are more sensitive to re-injury

DIFFERENTIAL DIAGNOSIS OF SKIN LESIONS INDUCED BY NON-FREEZING COLD EXPOSURE			
Disorder	**Features**	**Possible associated conditions**	**Chapter reference**
Acrocyanosis	Red to purple discoloration Hands and feet Painless	Erythromelalgia Cryoproteins Anorexia nervosa	106 23 51
Pernio	Erythrocyanotic Symmetric distribution Painful		88
Raynaud's phenomenon	Clearly demarcated pallor, followed by blue then red discoloration Idiopathic form usually does not ulcerate	AI-CTD Blood dyscrasias Drugs Trauma	43
Livedo reticularis	Bluish, broad reticulated patches May be idiopathic	AI-CTD Hematologic disorders Vascular occlusive diseases Infections Medications	106
Cold panniculitis	Erythematous indurated plaques, most often on cheeks Children Clears in 2 weeks		100
Cold urticaria	Cold-induced wheals May be idiopathic	Cryoproteins Infections Malignancies Familial cold autoinflammatory syndrome	18
Chilblain lupus	Cold-induced acral lesions Histologic features of lupus erythematosus Coexistent lupus erythematosus		41
"Pulling boat hands"	Rowing in cold, wet conditions Papules to vesicles Itching, burning, tenderness		
Retiform purpura due to cryoproteins*	Favors acral sites		23
Cryoglobulins	Cold serum protein precipitate	Plasma cell dyscrasias Lymphoproliferative disorders	
Cryofibrinogen†	Cold plasma protein precipitate	Infections Malignancies	
Cold agglutinins†	RBCs agglutinate in cold Occasional RBC lysis in cold	Infections (e.g. with *Mycoplasma*, EBV, CMV) Lymphoproliferative disorders	
Cold hemolysins†	RBC lysis in cold Paroxysmal hemoglobinuria	Infections (e.g. viral, syphilis)	

*Acrocyanosis, Raynaud's phenomenon, livedo reticularis and cold urticaria can also be observed in association with cryoproteins.
†Rarely cause cold-related occlusion syndromes.

Table 88.8 Differential diagnosis of skin lesions induced by non-freezing cold exposure[28–33]. AI-CTD, autoimmune connective tissue disease; CMV, cytomegalovirus; EBV, Epstein–Barr virus; RBC, red blood cell.

Introduction

Immersion injury occurs in either cold or warm environments when the feet are exposed to continuous moisture with no opportunity for intermittent drying. Severe injury may produce permanent peripheral neuropathy and long-term morbidity.

History

Soldiers on the Western Front in World War I spent extended periods of time in the cold, wet, muddy conditions of trench warfare. The Second World War produced another variant, with shipwrecked troops spending days in partially submerged lifeboats. The Korean conflict and the Vietnam War led to more variations and tremendous numbers of casualties. The most recent military experience with immersion foot occurred during the Falklands War. Civilian immersion foot also occurs singly or in small groups, particularly among the homeless[35–38].

Epidemiology

Susceptibility to immersion foot is widely variable. Use of sandals or open shoes, constant activity, thinner plantar stratum corneum, and intermittent air drying seem somewhat protective. Risk factors for immersion foot include: prolonged occupational or recreational exposure to wet conditions, immobility, constrictive clothing, dehydration, poor nutritional status, smoking, altered mental status, peripheral vascular disease, uncontrolled diabetes, trauma, prolonged dependency of feet, and homelessness[35,37].

Pathogenesis

The underlying pathophysiology of all forms of immersion foot is overhydration of the stratum corneum. The permeability coefficient of plantar skin is approximately 10 times that of the dorsal foot skin, leading to increased water absorption. The plantar stratum corneum can absorb approximately 200% of its dry weight in water, with a proportionately higher absorption of fresh water than saline.

Warm water immersion foot (WWIF) results from severe hyperhydration of the stratum corneum, with subsequent maceration. Plantar skin temperature reaches body core temperature after about an hour in an impervious boot with 19°C (66°F) water. As the injury continues, inflammatory changes develop and may progress to a lymphocytic vasculitis with vascular compromise and erythrocyte extravasation (*tropical immersion foot* [TIF]). Eventual involvement of the dorsal foot skin develops with striking inflammation. Secondary infection may develop in the compromised tissue after 3–4 days, further complicating management and worsening morbidity[23,35,36,39].

Cold water immersion foot (CWIF) is more severe due to the addition of cold-induced vasospasm. Because water conducts heat 23 times

IMMERSION FOOT: WARM WATER, TROPICAL AND COLD WATER VARIANTS					
Variant	**Exposure temperature**	**Exposure time**	**Clinical features**	**Complications**	**Duration**
Warm water	15.5–32°C (60–90°F)	1–3 days	Thickening, softening and exaggerated wrinkling of soles (thicker soles worse) Ambulation painful ("walking on rope")		3 days
Tropical	21–32°C (70–90°F)	3–7 days	Prolonged warm water exposure In addition to plantar hyperhydration, dorsal foot becomes inflamed and edematous Pruritus, erythema and scattered vesicles Later purpura, brawny edema, maceration and scaling Fever, lymphadenopathy		>5 days
Cold water	15.5–21°C (60–70°F)	>7 days	Feet cold, heavy, stiff and numb May appear swollen Waxy white to mildly cyanotic	Infection Muscle atrophy Chronic venous stasis Joint contractures	
			Three phases after rewarming: 1. pre-hyperemic – feet cold, edematous and numb, with stocking anesthesia; purpura, blisters and necrosis possible; pulses not palpable	Trophic ulcers Myonecrosis Permanent axonal damage Bony changes such as hammer toe	Hours to days
			2. hyperemic – return of vascular and nerve function; tingling, pain and throbbing; increasing erythema and edema; skin anhidrotic, hot and painful to touch; ambulation difficult; vasomotor instability; dependent rubor, pallor upon elevation; bullae, intermittent cyanosis; infection risk high		Up to 10 weeks
			3. post-hyperemic – cold sensitivity with digital blanching, intermittent edema, hyperhidrosis, persistent peripheral neuropathy		Years

Table 88.9 Immersion foot: warm water, tropical and cold water variants[23,35,36].

faster than air, the cold water immersion invokes "thermo-protective" peripheral vasoconstriction. This creates hypoxic injury to nerves (initially large myelinated axons, but eventually all types) and muscle, with later injury to subcutaneous fat and blood vessels.

Clinical features

The clinical syndromes of immersion foot (Table 88.9)[23,35,36] are divided into the three variants previously discussed: WWIF, TIF, and CWIF. Although TIF is sometimes viewed simply as a prolonged and more severe variant of WWIF, it is discussed separately because prolonged warm water exposure does produce different clinical features.

Pathology

All forms of immersion foot demonstrate edema, thickening and fragmentation of the stratum corneum. Variable superficial dermal edema is noted. In more severe forms (TIF, CWIF), superficial dermal capillaries are narrowed due to edema or even frank lymphocytic vasculitis. CWIF produces much deeper damage in blood vessels (narrowing and fibrosis), muscle, nerves and bone.

Differential diagnosis

The differential diagnosis of immersion foot includes dermatophyte infection, cellulitis, pitted keratolysis, erythrasma, Gram-negative or complex toe web infections, and (occasionally in diabetics) candidiasis. The latter three conditions are usually confined to toe web spaces, and dermatophytosis is usually more patchy, with fine scale and no significant maceration outside the web spaces. Pitted keratolysis can be distinguished by history and by the presence of punched-out tiny pits in the plantar surface of the forefoot and heel. Cellulitis is not limited at the immersion water mark, and it can progress proximally.

Treatment

Prevention is the best treatment. Jungle boots have been shown to decrease the risk of WWIF when compared with thicker hiking boots. Once the condition develops, thorough and rapid drying is essential to restore function. CWIF patients must remain some distance from a heat source because the neuropathic insensitivity poses further risk of inadvertent thermal injury. WWIF can be prevented by frequent drying breaks and the use of silicone grease. The silicone has minimal value in TIF and is of no use in CWIF[36,38,39].

INJURY DUE TO ELECTRICITY

Electrical Burns

Key features

- The extent of an electrical burn injury may be much worse than the cutaneous contact burns suggest
- Contact point burns may be partial- to full-thickness
- Neurovascular, muscular and skeletal tissue may be damaged
- Lightning strikes can result in an erythematous, transient fern-like pattern on the skin

Introduction

Although electricity and lightning claim hundreds of lives each year, many more non-fatal injuries occur. The majority of electrical burns are work-related, particularly among electricians, linesmen and construction workers. Children are also a major risk group, with low-voltage (<1000 V) injury more common under 6 years of age and high-voltage injury in older children and adolescents. A survey of 700 electrical injury admissions to Parkland Memorial Hospital over a 20-year period showed electric arc (flash burn, no current) injury to be the most common (40%), followed by high voltage (38%), low voltage (20%), and lightning strikes (2%). Mortality was highest with lightning strikes[40].

Lightning is the second leading cause of weather-induced death in most of the world, with the incidence peaking during the summer months. Most lightning strike victims are men (usually between 15 and 45 years of age) involved in outdoor activities. In the US, lightning-associated injuries occur most commonly along the Gulf Coast and in the Rocky Mountains[40,41].

Pathogenesis

The severity of an electrical injury depends upon the strength and frequency of the electrical field, the duration of exposure, path of current, and relative resistance of the tissue. Acute tissue damage by strong (high-voltage) low-frequency fields is due to holes punched in cell membranes (electroporation), Joule heating of the extracellular fluid, and cell membrane protein denaturation through electroconformational coupling. The thermal effects (i.e. Joule and dielectric) depend upon tissue resistance to the flow of current. For example, bone has the most resistance of any body tissue, therefore generating the most heat. Resistance then decreases through fat, tendon, skin, muscle, blood vessels, and, finally, nerves (least resistance). An additional indirect effect is a field-generated formation of free radicals with subsequent lipid peroxidation and membrane disruption[42,43].

Lightning injury follows similar electrothermal principles, but with three important differences: (1) current and voltage are massive, e.g. 30 000 to 50 000 amperes (A), and a difference between clouds and object of 2 million V/m; (2) the superheating of air through which the current passes to 30 000°K, creating a high-pressure thermoacoustic shock wave (thunder) that may generate 100 atm of air pressure locally; and (3) the creation of internal conduction loops as the large magnetic field passes through the body. Injury can occur from a radial spread of current after lightning strikes the ground, from a direct hit, from flashover (current around body), or from blast effect[41].

Clinical features

Electrical burns usually range from partial- to full-thickness, and high-tension burns often involve deep tissue, with the current damaging muscle, nerves and vessels. Erythema, edema and blisters (partial-thickness damage) may result from a current of 20 to 35 mA/mm^2 with an exposure time of 20 seconds (heats skin to 50°C). At a higher current of 75 mA/mm^2 with the same exposure time, the temperature could rise to 90°C, causing skin perforation and charring.

Identification of so-called "entrance" and "exit" wounds is of no value, since 60 Hz alternating current (AC) has current changing directions 120 times per second. More important is determination of the extent of skin and internal injury. In some cases, current may arc between body parts, creating "kissing" wounds. High-voltage injuries may result in electroplating of skin with black metallic debris that leaves charred craters when removed. Additional thermal injury may occur when clothing or nearby items are ignited by an electrical arc[41,42].

Deep tissue injury can be considerably more severe than the cutaneous wounds might suggest. Muscle injury may be deceptively deep, since bone (with higher electrical resistance) retains heat more readily than other tissues. Edema in deep burns may result in compartment syndromes. High-tension AC and direct current (DC) can cause ventricular asystole, whereas low-tension AC, such as household current, is more likely to produce ventricular fibrillation, plus some patients develop chronic and recurrent arrhythmias. Considerable nerve, blood vessel and musculoskeletal injury may also be seen[41–43].

Lightning burns generally are more superficial due to the very brief contact. A unique pattern of skin lesions after a lightning strike is the "lightning print", "feathering" or Lichtenberg figures. These markings are erythematous, transient linear fern-like patterns that resolve in hours to days. While not a true burn, they are pathognomonic of lightning strike injury. Other cutaneous changes may include patchy mottling, erythema, blistering, full-thickness punctate skin loss, flash burns, thermal burns from ignited clothing, and contact burns from grounding. Although internal burn injuries are uncommon in lightning strikes because of the very brief duration, the internal electrical currents that are created are strong enough to cause cardiac arrest or seizures. Additional sequelae include profound neuromuscular shutdown (kerauno-paralysis), confusion, temporary amnesia, deafness and blindness, and prolonged or permanent neurologic disturbances, e.g. peripheral sensory neuropathy[41,42].

Pathology

Electrical burns are characterized by epidermal necrosis, with cytoplasmic strands extending into the cavity between damaged and normal skin. Keratinocytes may be elongated vertically, and collagen appears homogenized. Severe electrical burns destroy the entire skin, including the subcutis, often with accompanying necrosis of deeper blood vessel walls. The Lichtenberg figures after lightning injury display subcutaneous hemorrhage[7].

Treatment

Electrical injuries are very complex, often involving multiple organ systems, since any organ in the path of current can be damaged, and initial assessment may underestimate the extent of injury. Although full management of electrical burns should be carried out in level one trauma centers, initial management includes isolation of the patient from the power source, assessment of vital signs, cervical spine immobilization, determination of contact points on the skin, and, if possible, venous access. For more details, see the section above on thermal burns.

One special circumstance should be noted. Toddlers who sustain oral commissure burns from biting into electrical cords are at risk for delayed bleeding. About 10–14 days after the burn, the eschar comes off, often exposing a damaged labial artery. Direct pressure will control the bleeding, pending definitive care[41–43].

Chemical Burns and Exposures

These entities are discussed in several chapters, including those on irritant contact dermatitis (Ch. 15), occupational dermatoses (Ch. 16), plant dermatoses (Ch. 17) and child abuse (Ch. 90).

INJURY DUE TO CHEMICAL EXPOSURE

Chemical Hair Discoloration

Synonym: ■ Green hair – chlorotrichosis

Key features

- Hair discoloration may be a voluntary cosmetic change or the result of a chemical or metal exposure
- Green hair may result from exposure to copper or selenium
- Most hair discoloration normalizes over time

Introduction

Decorative hair coloring has risen to new heights with the flamboyant artistry of the past three decades. Brilliant pink, green, purple, blue and orange, and myriad styles, from a buzz cut to dramatic multicolored spikes, adorn many of today's youths. Much of this is deliberate decoration, but hair discoloration at any age may be an inadvertent, and sometimes unwanted, occurrence as well.

History

Green hair among copper workers was noted as early as 1654. More recently, such discoloration has been attributed to swimming pools[44].

Epidemiology

Most patients with unwanted hair discoloration have blond or white hair, although black hair may become discolored as well. Risk factors include exposure to the substances in Table 88.10[44–48], in addition to frequent contact with chlorinated water (especially swimmers), use of an alkaline shampoo, coloring or peroxide bleaching of hair, and mechanical or sun-induced hair damage[44,45].

Pathogenesis

Green hair discoloration due to copper occurs when metallic copper is released from pipes under acidic conditions into domestic or swimming pool water, or when copper algicides or chlorination are used to sanitize swimming pools. Damage to the hair cuticle by permanent wave treatments, frequent water exposure and sunlight allow the copper to penetrate the hair more readily. The copper content of discolored green hair (or golden hair in Asian patients) is considerably higher than in non-discolored hair in the same individual. Increased systemic copper may lead to elevated levels in hair, but does not cause a greenish

CAUSES OF UNINTENTIONAL HAIR DISCOLORATION		
Green	**Yellow to orange to golden**	**Purple**
• Copper	• Tar shampoo	• Alkalinized anthralin
• Selenium sulfide	• Anthralin	
• Tar shampoo	• Minoxidil	
• Cobalt	• Copper	
• Chromium		
• Nickel		
• Yellow mercuric oxide		
• Hypothyroidism*		
• Phenylketonuria*		
*Speculative.		

Table 88.10 Causes of unintentional hair discoloration[44–48]. See Table 66.11 and Fig. 66.11 for causes of diffuse hypomelanosis of scalp hair.

color change. The mechanism of selenium-induced green hair is unknown[44–46].

Yellowish hair discoloration appears to result from staining of lighter-colored hair, but the mechanisms are not known[47,48]. Nanko et al.[45] speculated that the golden color of Japanese swimmers' hair is due to water friction injury of the cuticle, allowing hypochlorous acid from the chlorination process to invade the cortex and degrade melanosomes. Copper seems to play a role as well, but the mechanism is uncertain.

Clinical features

The presenting concern is a progressive yellow to green discoloration of the hair. Scalp hair is the only hair involved, and the surface hair is more noticeably discolored than underlying hair.

Pathology

By electron microscopy, loss of the hair cuticle and wearing of the cortex layers were seen in discolored, golden hairs in Japanese swimmers[45]. In addition, there was a reduced number and density of melanosomes in the discolored hair relative to controls. X-ray spectrography demonstrated an increased chlorine content in both the discolored and normal hair of swimmers relative to controls, and a reduced sulfur content in only the discolored hairs.

Differential diagnosis

Hair discoloration is readily visible. The specific etiology and subsequent therapy needed may be determined by ascertaining the type of exposure (see Table 88.10) that led to the color change. For example, copper from cosmetic plant extracts and metallic eyeglass frames can produce green hair.

Treatment

Discontinuation of the offending exposure would seem the most prudent remedy. Numerous anecdotal remedies have been described, including hot oil, hydrogen peroxide, alkaline shampoos, penicillamine- or EDTA-based shampoos, commercial hair decolorizers, and hydroxyethyl diphosphonic acid[44].

Arsenical and Heavy Metal Dermatoses

Key features

- Chronic arsenic exposure may occur via drinking water contamination or occupational exposure
- Chronic arsenicism is characterized by mottled hyperpigmentation with areas of hypopigmentation, keratoses on the palms and soles (and other sites), and multiple non-melanoma skin cancers, particularly Bowen's disease
- Histologically, arsenical neoplasia is almost identical to actinic neoplasia

CLINICAL FEATURES OF ACUTE AND CHRONIC ARSENIC POISONING
ACUTE
Skin
• Flushing, erythema, facial edema, acrodynia, urticaria
• Loss of hair and nails
• Remaining nails show Mees' lines after 8 weeks
Gastrointestinal
• Nausea, vomiting, severe abdominal pain, profuse watery diarrhea, malabsorption
Neurologic
• Acute peripheral neuropathy
• May progress to Guillain–Barré-like ascending paralysis
Other
• Pancytopenia, metallic breath odor, cardiac arrhythmias, renal failure, respiratory failure
CHRONIC
Skin
• Hyperpigmentation of axillae, groin, nipples, palms, soles and pressure points, with superimposed guttate hypopigmentation ("raindrops on a dusty road")
• Alopecia
• Arsenical keratoses – precancerous papules on palms and soles (Fig. 88.8)
– Symmetric, yellow, punctuate, corn-like papules measuring 2–10 mm
– Favor thenar and hypothenar eminences, distal palms, lateral fingers, dorsal aspect of IP joints, weight-bearing plantar surfaces
– Rarely on trunk, proximal extremities, eyelids, genitalia
– May coalesce to plaques
• Blackfoot disease (vascular occlusive disease with blackening of skin)
Other
• Nasal septum perforation
• Peripheral neuropathy
• Bone marrow hypoplasia
• Diarrhea
• Hepatomegaly, hepatic fibrosis
• Obstructive or restrictive lung disease
• Diabetes mellitus
Malignancies
• Bowen's disease
– Any skin surface
– If no HPV, occurrence on sun-protected skin might suggest arsenic exposure
– Skin-colored to red papules and plaques that become keratotic
– Scale-crust removal leaves red, moist, papillomatous base
– Multiple lesions common
– Invasive squamous cell carcinoma develops in 5–20%
• Squamous cell carcinoma
– Arising in arsenical keratosis or Bowen's disease, has more aggressive behavior
– Metastasis in one-third
• Basal cell carcinoma
– Multiple, superficial, may resemble Bowen's disease
• Extracutaneous malignancies
– Genitourinary, especially bladder
– Lung
– Liver

Table 88.11 Clinical features of acute and chronic arsenic poisoning[49–53]. HPV, human papillomavirus; IP, interphalangeal.

Introduction

Arsenic is a ubiquitous metal, ranking 20th in abundance among all the elements. Exposure occurs via drinking water, agricultural uses, ore mining, and medicinal applications. Chronic exposure poses significant health risks, including development of benign and malignant tumors (Table 88.11)[49–53]. The other toxic and heavy metals and their cutaneous impact are outlined in Table 88.12[49–61]. Allergic contact dermatitis due to metals is covered in Chapter 14.

History

Medicinal effects of arsenic have been known since the days of Hippocrates and Galen. Early applications of arsenic included the treatment

TOXIC AND HEAVY METALS AND THEIR CUTANEOUS IMPACT					
Metal	**Form**	**Cutaneous health hazards**	**Treatment and protection**	**IDLH***	**Cancer risk**
Aluminum	Alum, sulfates	Irritant contact dermatitis	Wash off	–	–
Antimony	Metal	Irritant contact dermatitis	Soap wash immediately	50 mg/m^3	–
Arsenic	Inorganic	(see Table 88.11)	Avoidance, chelation	–	Lung, bladder and skin cancer
Barium	Chloride, nitrate	Irritant contact dermatitis, burns	Water flush immediately	50 mg/m^3	–
Beryllium	Metal	Dermatitis, granulomas	–	–	Lung cancer
Bismuth	Telluride	Irritant contact dermatitis	Soap wash immediately	–	–
Boron	Borates, oxide	Erythema, irritant contact dermatitis	Soap wash, water flush	–	–
Cesium	Hydrate, hydroxide	Irritant contact dermatitis, burns	Water flush immediately	–	–
Chromium	Hexavalent	Allergic and irritant contact dermatitis, skin ulceration, burns; systemic absorption can lead to renal failure, hepatic failure, anemia, coagulopathy	Water flush promptly	–	Lung cancer
Cobalt	Metal dust	Dermatitis, diffuse nodular fibrosis	Soap wash	20 mg/m^3	–
Copper	Metal dust	Dermatitis	Soap wash promptly	100 mg/m^3	–
Gold	Elemental salts	Most common: lichen planus, lichenoid drug eruption, allergic contact dermatitis, eczematous dermatitis, PR-like eruption, pruritus, flushing, erosive stomatitis Less common: chrysiasis, erythema nodosum, erythema multiforme, toxic epidermal necrolysis, exfoliative dermatitis	Avoid gold-laden liquor	–	–
Indium	Metal	Irritant contact dermatitis	Soap wash	–	–
Iron	Salts	Irritant contact dermatitis, mucosal irritation	Soap wash	–	–
Lead	Metal	Irritant contact dermatitis, gingival lead line	Soap wash promptly	100 mg/m^3	–
Lithium	Hydride	Irritant contact dermatitis, burns	Brush off gently, DO NOT WASH	0.5 mg/m^3	–
Magnesium	Carbonate	Irritant contact dermatitis	–	–	–
Manganese	Cyclopentadienyl tricarbonyl	Irritant contact dermatitis	Soap wash	–	–
Mercury	Elemental, inorganic, organic	Acrodynia, tattoo reaction (cinnabar), granulomas, exanthem, cutaneous hyperpigmentation, allergic and irritant contact dermatitis, baboon syndrome	Soap wash promptly	10 mg/m^3 (elemental) 2 mg/m^3 (organic)	–
Nickel	Elemental	Allergic contact dermatitis	Water wash immediately	10 mg/m^3	Lung and nasal cancer
Osmium	Tetroxide	Irritant contact dermatitis	Soap wash immediately	1 mg/m^3	–
Platinum	Metal	Irritant contact dermatitis	Soap wash	–	–
Polonium	^{210}Po radionuclide	Erythema, alopecia; ulceration in higher doses	Avoid ingestion; wash off	0.1–0.3 GBq (fatal in 3–4 weeks)	
Selenium	Elemental, alloy	Irritant contact dermatitis, skin burns	Soap wash immediately	1 mg/m^3	–
Silver	Metal	Argyria, irritant contact dermatitis, skin ulceration	Water flush	10 mg/m^3	–
Tellurium		Dermatitis, garlic smell of sweat	Soap wash promptly	25 mg/m^3	–
Thallium	Soluble	Alopecia, acneiform papules, keratotic plaques on hands and feet, Mees' lines	Water wash promptly	15 mg/m^3	–
Tin	Metal, organic	Irritant contact dermatitis, skin burns, pruritus	Water flush immediately	100 mg/m^3 (metal) 25 mg/m^3 (organic)	–
Tungsten		Irritant contact dermatitis	Soap/water wash immediately	–	–
Uranium		Irritant contact dermatitis, skin burns	Soap/water wash immediately	10 mg/m^3	Lung cancer
Vanadium	Dust, fume	Irritant contact dermatitis, green tongue	Soap wash promptly	–	–
Zinc	Chloride	Irritant contact dermatitis, skin burns (fixes tissue *in situ*), mucocutaneous hyperpigmentation	–	–	–

*Concentration posing immediate danger to life and health (IDLH). Since 1979, the National Institute for Occupational Safety and Health (NIOSH) has not allowed detectable levels of known carcinogens. Therefore there are no values in the IDLH column for carcinogens.

Table 88.12 Toxic and heavy metals and their cutaneous impact[49–61]. GBq, gigabecquerel; PR, pityriasis rosea.

of psoriasis, eczema, pemphigus, urticaria, furuncles, warts, lupus, epitheliomas, syphilis, leprosy, molluscum contagiosum, and lichen rubor[27]. Even in the late 1800s, cutaneous side effects of arsenic exposure were noted, including pruritus, papulosquamous eruptions, and palmoplantar keratoses.

Chemical forms of therapeutic arsenic include Fowler's solution (liquor potassii arsenitis), arsenici bromidum, arsenici iodidum, Pearson's solution (liquor sodii arseniatis), arsenicum hydrogenisatum, Donovan's solution (liquor arseni et hydrargyri iodidi), and Asiatic pills (arsenic with opium or pepper)[27,51]. Apparently, Fowler's solution and Asiatic pills are the most widely used, with the latter still available in India and the Far East. Traditional Chinese medicine may continue to use inorganic arsenic. Most of the Western World has abandoned arsenicals, although treatment of asthma with Fowler's solution continued until the 1960s in parts of the US. Arsenic trioxide is now used therapeutically for acute promyelocytic leukemia[49,50].

Metallic arsenic has been consumed in large quantities by the arsenic eaters of the Swiss and Austrian Alps, believing that such consumption improved physical strength. Inorganic arsenic (the toxic form) is believed to have caused Napoleon's death during his second exile at St Helena[49].

Epidemiology

Accidental exposure to arsenic still occurs via contaminated drinking water in more than 30 countries, including India, China, Taiwan, Chile, Argentina, Mexico, the Philippines, Bangladesh, Thailand and the US. Careless contamination of drinking water has resulted from mining of ores containing silver, gold, tin, copper, lead, tungsten, zinc and cobalt. The current World Health Organization provisional guideline value and the US Environmental Protection Agency limit of arsenic concentration in drinking water is 0.01 mg/l. This was recently decreased from the previous limit of 0.05 mg/l, since cutaneous and internal cancers may develop with the latter level of exposure. However, no chronic skin changes have been noted with arsenic concentrations <0.017 mg/l in drinking water. It is estimated that globally more than 100 million people are exposed to higher arsenic levels in drinking water than the 0.01 mg/l[49–53].

An estimated cumulative dose of arsenic capable of producing arsenical keratoses or skin cancer is about 0.5 to 1 g. Adverse effects have been noted when arsenic is in drinking water at a concentration as low as 0.05 mg/l, although many authors suggest that higher concentrations of 0.4 to 0.6 mg/l are required[51,52].

Chronic exposure to inorganic arsenic poses an increased risk for developing cancer (see Table 88.11). Trivalent inorganic arsenic is the most toxic form, with a latent period for chronic manifestations of 30 to 50 years[49]. Occupational exposure to arsenic may occur during the use of pesticides, herbicides or treated wood, and during electroplating, mining, smelting, wine making, carpentry, and manufacture of gallium arsenide computer microchips[49,53].

Pathogenesis

Many of the toxic effects of arsenic are through interference with cellular respiration and uncoupling of oxidative phosphorylation. Arsenic can cause chromosomal alterations and gene amplification, induce sister chromatid exchanges, inhibit DNA repair, and transform mammalian cells *in vitro*. The precise mechanism of tumor promotion is unknown, but arsenic has been shown to modulate expression of several key transcription factors, including tumor suppressor p53, nuclear factor-κB, and activating protein-1[49–53].

Clinical features

Arsenic exposure can be divided into acute and chronic forms. Acute exposure (medicinal, homicidal, suicidal) produces myriad cutaneous and systemic features. Chronic arsenic exposure (drinking water, occupational) produces altered pigmentation, keratoses and substantial malignancy risk (Fig. 88.8). See Table 88.11 for a summary of clinical features of acute and chronic arsenic poisoning.

Pathology

Arsenical keratoses exhibit marked hyperkeratosis with scattered parakeratosis and mild to moderate keratinocyte atypia. Vacuolation of keratinocytes may be noted and adnexal structures are spared. Basophilic degeneration of dermal connective tissue is highly variable. There are no features that clearly distinguish arsenical keratoses from actinic keratoses.

Arsenical Bowen's disease exhibits the same epidermal histologic features as common Bowen's disease (see Ch. 108). Although the superficial type is most commonly observed, the basal cell carcinomas associated with arsenic can be any of the clinicopathologic subtypes (see Ch. 108)[49,51].

Fig. 88.8 Cutaneous manifestations of exposure to arsenic. **A** Guttate hypopigmentation superimposed on hyperpigmentation resembles "raindrops on a dusty road". **B, C** Arsenical keratoses on the plantar and palmar surface. *A, Courtesy, John Steinbaugh, MD. C, Courtesy, Jeffrey Callen, MD.*

Differential diagnosis

Arsenical keratoses may resemble punctate palmoplantar keratoderma (including the porokeratotic variant) and verrucae vulgaris. Small pits are often noted when central keratotic plugs are removed from the papules in the inherited keratodermas, but not with arsenical keratoses. Family history and early onset are helpful in distinguishing palmoplantar keratodermas. In the nevoid basal cell carcinoma syndrome, there are persistent pits due to the localized absence of stratum corneum; additional clues are the characteristic facial features (see Ch. 108), odontogenic jaw cysts, and typical basaloid proliferative histology in the palmar pits.

Treatment

Chelation therapy is the mainstay of treatment for acute arsenicism. Dimercaprol (British anti-lewisite; BAL) is the most widely used agent. Other chelating agents reported as efficacious include dimercaptosuccinic acid and dimercaptopanesulfonic acid. For chronic arsenicism, chelation is controversial, but may reduce arsenic stores. Oral retinoids have been reported to reduce arsenical keratoses and decrease formation of arsenical basal cell carcinomas. Surgical extirpation, curettage, cryosurgery, topical chemotherapy, topical keratolytics and photodynamic therapy have been reported with some success. These treatments are all anecdotal or based upon small series[49,51].

FRICTIONAL AND TRAUMATIC INJURY TO THE SKIN

Corns and Calluses

Synonyms: ■ Corn – clavus, heloma ■ Hard corn – heloma durum ■ Soft corn – heloma molle ■ Callus – callosity, tyloma, intractable plantar keratosis

Key features

- Corns and calluses are keratotic lesions resulting from repeated trauma
- Ill-fitting footwear, bony protuberances and specific activities are contributing factors
- Hard corns are found on the dorsal aspects of the toes, while soft corns are in the interdigital web spaces
- Proper footwear and medical management usually suffice

Introduction

Repeated mechanical trauma to the feet, whether from poorly fitting footwear, anatomic differences, or work or leisure activities, produces hyperkeratosis. This otherwise natural protective response to injury may result in the formation of uncomfortable thickened areas of skin known as corns or calluses. Corns are more narrowly based and sharply defined, whereas calluses are broad based. Calluses also form on the hands from repeated trauma, but are usually asymptomatic[62].

Epidemiology

Risk factors for the development of corns and calluses on the feet include bony protuberances, abnormal biomechanical foot function, poorly fitted shoes, and repetitive trauma due to athletic activity[62].

Pathogenesis

Bony protuberances such as the condyles of metatarsal and phalangeal bones create outward pressure on the skin. Footwear and activities (walking, running) create counterpressure at these sites. The repeated friction and pressure leads to hyperkeratosis. The latter further compromises the site by increasing pressure. The cycle of friction, pressure and thickening continues until a corn or callus develops (Fig. 88.9)[62].

Fig. 88.9 Callus plus hard corns. Calluses are broad based and have increased skin markings while corns are round, more sharply defined papules with a central translucency and an interruption in dermatoglyphics. The skin overlying the second and third metatarsal heads is a common location for such lesions.
Courtesy, Jean L Bolognia, MD.

Clinical features

Hard corns (heloma durum) are firm, small, dome-shaped papules with translucent central cores, most commonly found on the dorsolateral fifth toes and dorsal aspects of other toes. Soft corns (heloma molle) are painful keratoses in the interdigital web spaces; they often become macerated. Opposing toes may exhibit "kissing lesions". Broad keratotic plaques, often under the metatarsal heads, are calluses.

A unique callus is seen on the tip of the second (and sometimes third) toe, with associated transverse ridging, thickening and splinter hemorrhages in the nail. This is known as tennis toe (see Fig. 88.14) or center's callus. Also seen in gymnasts, soccer players, runners, football players and dancers, it results from sudden stops with repeated collision between toe tip and shoe. In many cases, the second toe is found to project further forward than the hallux[62,63].

Differential diagnosis

These common lesions rarely elude diagnosis, but must be distinguished from verruca vulgaris. Warts and corns interrupt dermatoglyphics, while calluses often demonstrate accentuated lines. Paring of a corn reveals a central translucent whitish yellow core, as opposed to the thrombosed capillaries and multiple bleeding points seen in a wart. Paring of a callus reveals layers of yellowish keratin, without the multiple punctate thrombosed capillaries of a mosaic plantar wart.

Treatment

Treatment should be directed toward both symptomatic relief and correction of the biomechanical conflict. Paring of the callosity, with removal of the corn's central core, provides prompt relief. Filing after warm water soaking can be performed periodically. Topical agents such as salicylic acid or urea help soften the callosity. Soft cushions (silicone sheet, sheepskin) reduce friction and improve comfort. Properly fitted footwear and the use of appropriate orthotics lead to long-term solutions. If all of these maneuvers fail, a plain film to look for exostoses and referral to orthopedic surgery may be indicated[62,63].

Black Heel and Palm

Synonyms: ■ Talon noir ■ Tache noir ■ Calcaneal petechiae ■ Post-traumatic punctate intraepidermal hemorrhage ■ Post-traumatic cutaneous intracorneal blood

Key features

- Black macules on the palms or soles due to hemoglobin within the thickened stratum corneum
- Lesions are secondary to impact trauma and resolve with paring or time

Introduction

Black heel (or palm) is a post-traumatic intraepidermal hemorrhage seen most often in athletes. This harmless and self-healing process is a potential source of concern because of its dark black color.

History

Black heel was first described in 1961 by Crissey and Peachey[64] as calcaneal petechiae. A variety of subsequent reports under different monikers (see above) has led to confusion and debate over the proper nomenclature. The association with sports has been recognized since the beginning, with basketball the prototypical sport.

Epidemiology

Adolescents and young adults comprise the majority of patients with this entity. Sports participation is of paramount importance, particularly basketball, lacrosse, tennis, football, gymnastics and marching. Elderly patients with unusual palm and sole trauma may also be predisposed. Self-inflicted hammer injury can produce a similar clinical finding[64–66].

Pathogenesis

Black heel is a traumatic phenomenon thought to be due to shearing forces, often produced by sudden stopping or landing on the floor or ground. These shearing forces rupture papillary dermal blood vessels, with subsequent leakage of blood into the epidermis[66]. Hemoglobin resides in the stratum corneum for a longer transit time, and the position of the blood is out of reach of the phagocytic cells, maintaining the intact molecular structure of the hemoglobin[65,66].

Clinical features

The black or violet–black macules are asymptomatic and may be isolated or in clusters. They can form linear or horizontal arrays on the posterior or posterolateral aspect of the heel (Fig. 88.10A). Lesions are usually unilateral and favor the edge of the thick plantar keratin. Forefoot, toe and palmar lesions have also been observed (Fig. 88.10B,C); in patients with thickened stratum corneum due to disorders of cornification, extra-palmoplantar lesions can be seen. Paring of the stratum corneum reveals red–brown to red–violet specks of dried blood, and dermoscopy can also prove useful.

Pathology

Hyperkeratosis with "lakes of pigment"[66] within the stratum corneum form the characteristic histopathology. Iron stains may be negative (especially Prussian blue). Both the benzidine and Patent Blue V stains for hemoglobin are positive, perhaps because the intracorneal location has no phagocytic or proteolytic activity to allow formation of hemosiderin[65,66].

Differential diagnosis

The major entities in the differential diagnosis are cutaneous melanoma and verruca vulgaris. The ability to remove the lesion with gentle paring allows one to exclude a melanocytic lesion; positive staining for hemoglobin provides additional evidence. One author found the standard hemoccult test useful for confirming the presence of hemoglobin in parings[66].

Treatment

Once the diagnosis is ascertained, treatment is unnecessary.

Chondrodermatitis Nodularis Helicis

Synonyms:
- Chondrodermatitis nodularis chronica helicis
- Chondrodermatitis nodularis chronica helicis et antihelicis
- Ear corn

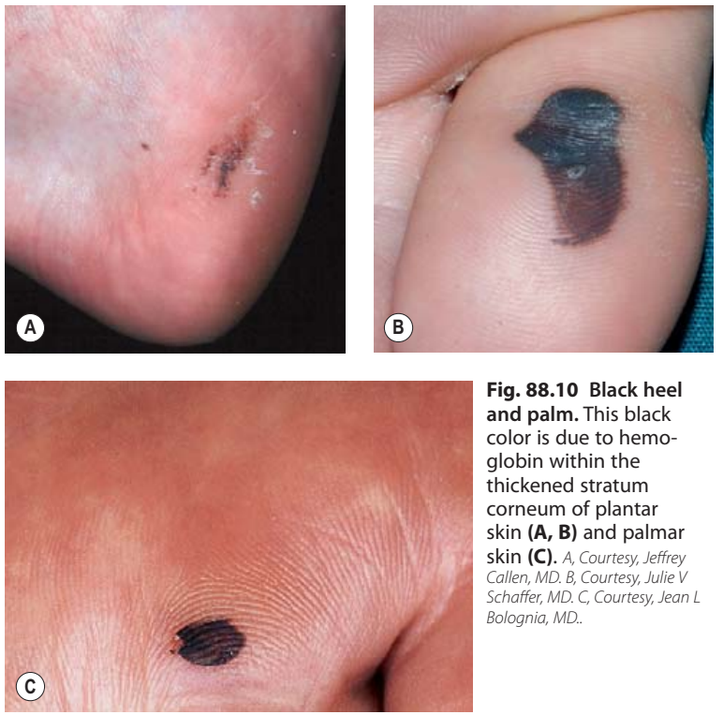


Fig. 88.10 Black heel and palm. This black color is due to hemoglobin within the thickened stratum corneum of plantar skin **(A, B)** and palmar skin **(C).** *A, Courtesy, Jeffrey Callen, MD. B, Courtesy, Julie V Schaffer, MD. C, Courtesy, Jean L Bolognia, MD..*

Key features

- Exquisitely tender nodules appear on the pinnae
- Most patients have unilateral lesions and are over 50 years of age

Introduction

Chondrodermatitis nodularis helicis (CNH) is a tender inflammatory process of the ear that was first described in 1915. Lesions are most common after age 40 years, with ~95% of cases occurring in those between 50 and 80 years of age. Both men and women are affected, with men having more lesions on the helix, and women, the antihelix. Bilateral lesions are seen in 6–10% of patients. Several cases of childhood CNH have been reported[67,68].

Pathogenesis

The precise etiology of CNH is unknown. Predisposing factors include actinic damage, cold exposure, trauma, local ischemia, and, occasionally, radiotherapy. A suggested pathogenesis is that helical lesions begin with perichondritis or folliculitis, extending secondarily to the skin. On the contrary, antihelical lesions may begin with pressure-induced ischemia, involving the cartilage secondarily. These concepts remain speculative[68].

Clinical features

CNH presents as skin-colored to erythematous, dome-shaped papulonodules with central crusts or keratin-filled craters (Fig. 88.11A). Surrounding inflammation may be noted. The majority of lesions occur on the upper helical rim or the middle to lower antihelical rim; these sites often correspond to the outermost portions of the pinna. The lesions of CNH are often exquisitely tender to palpation, and sleeping on the side of the affected ear may be impossible[68,69].

Pathology

The epidermis exhibits a well-circumscribed area of acanthosis, parakeratosis and hypergranulosis. A central crater with epidermal disruption may be filled with a keratotic plug or dermal debris. The underlying dermis shows degenerative changes with acellular collagen,

Fig. 88.11 Chondrodermatitis nodularis helicis. **A** Tender, erythematous papulonodule with central scale-crust on the mid antihelix of an older woman. This represented the site most susceptible to pressure-induced ischemia. **B** Central scale-crust, epithelial hyperplasia, fibrosis, granulation tissue and degenerated cartilage are seen on histologic examination. *A, Courtesy, Kalman Watsky, MD. B, Courtesy, Ronald P Rapini, MD.*

fibrosis (Fig. 88.11B), and variable lymphohistiocytic inflammation that is often granulomatous. Epithelioid cells may be present. The infiltrate extends into a thickened perichondrium[67–69].

Differential diagnosis

Lesions that are most commonly confused with CNH are squamous cell carcinomas, basal cell carcinomas, actinic keratoses, cutaneous horns, and weathering nodules. Additional entities to consider include verrucae, keratoacanthomas, calcinosis cutis, gouty tophi, and reactive perforating collagenosis. Although the marked tenderness and characteristic locations point to the diagnosis of CNH, histologic evaluation may be necessary to confirm the diagnosis[68].

Treatment

A variety of treatment modalities have been suggested for CNH, although few controlled studies have been performed. Small series of patients treated with topical corticosteroids or topical antibiotics showed variable success. The use of specially designed pillows to relieve pressure is operator-dependent. Intralesional corticosteroid injections have been successful in some small series.

Numerous surgical approaches have been suggested, including cryosurgery, electrodesiccation and curettage, full-thickness excision, carbon dioxide laser ablation, and excision of skin with partial cartilage excision. Surgical excision seems to be the favored modality, although a paucity of data exists. A retrospective cohort study of 41 patients treated surgically and 15 patients treated conservatively (circular foam pad with headband) showed that 66% of the surgical and 87% of the non-surgical patients were healed at follow-up. Selection bias, small sample size and variable follow-up times were problematic. Additional controlled studies will be necessary before conclusions can be drawn regarding optimal therapy[68,69].

Acanthoma Fissuratum

Synonyms: ■ Granuloma fissuratum (of the ears) ■ Spectacle frame acanthoma ■ Eyeglass frame acanthoma

Key features

- Retroauricular nodules with a central vertical groove or fissure occur at the site of eyeglass frame contact
- Refitting of the spectacle frame leads to resolution

Introduction

Ill-fitting eyeglass frames create a frictional injury in the postauricular sulcus or upper lateral nose leading to development of acanthoma fissuratum. The entity "granuloma fissuratum" was first described by Epstein[70] in 1965 and the term was derived from an earlier report of a buccal mucosal lesion of that name. The term "spectacle frame acanthoma" and the currently accepted designation "acanthoma fissuratum" were added to the literature in the 1970s[71,72].

Pathogenesis

Acanthoma fissuratum is thought to be due to pressure and friction created by eyeglass frames in the retroauricular sulcus or the upper lateral nose. Chronic irritation leads to collagen deposition. The collagen then appears to deteriorate, leading to local inflammation as a means of eliminating the abnormal collagen[73]. Additional factors that may contribute to the pathogenesis are composition and weight of the eyeglasses, roughness of the eyeglass frame, perspiration or local areas of dermatitis[72].

Clinical features

The classic lesion is a firm, skin-colored to erythematous nodule or plaque in the upper portion of the postauricular sulcus or upper lateral nose. The center of the lesion is characterized by the presence of a vertical groove or fissure (Fig. 88.12). There may be occasional tenderness, serous discharge or slight hyperkeratosis. A surrounding inflammatory halo may be noted[71–73].

Pathology

The epidermis exhibits irregular acanthosis, most marked at the lesion's periphery. In some instances, the appearance may be that of pseudoepitheliomatous hyperplasia. The central depression may show epidermal thinning or variable epidermal separation. Compact orthohyperkeratosis is noted over most of the lesion, with patchy areas of parakeratosis near the central groove. Dermal papillae exhibit dilated vessels and a moderately dense perivascular inflammatory infiltrate comprised of lymphocytes, histiocytes and plasma cells, with occasional neutrophils. Slight fibrosis may be noted in the superficial and mid dermis. Elastic tissue stains show no significant elastin within the nodule[71–73].

Differential diagnosis

These lesions are most commonly mistaken for cutaneous malignancies (e.g. basal cell carcinoma, Bowen's disease) or lichen simplex chronicus superimposed on seborrheic or allergic contact dermatitis and, less often, keloids. Although histologic examination can readily exclude the cutaneous carcinomas, the presence of pseudoepitheliomatous hyperplasia may create some confusion. However, the cellular atypia of squamous cell carcinoma should be absent in acanthoma fissuratum.

Fig. 88.12 Acanthoma fissuratum. Thin pink plaque with scale of the postauricular sulcus (arrow). Note the linear fissure.

Fig. 88.13 Weathering nodules. Multiple asymptomatic, small, whitish papules along the helix of an older man with photodamage. *Courtesy, Jean L Bolognia, MD.*

Treatment

Lesions should clear within a few months of discontinuation, replacement or proper adjustment of the offending spectacles. Excision should be considered for persistent lesions. Anecdotal success of intralesional corticosteroids has been reported[71,72].

Weathering Nodules of the Ear

Key features

- Asymptomatic whitish papules (2 to 3 mm) along the helices of middle-aged or elderly Caucasian men
- Histologically, a fibrous tissue spur with cartilage metaplasia
- No treatment needed

Introduction

Asymptomatic papules, known as weathering nodules, are seen on the helices of Caucasian men who have a history of significant cumulative sun exposure. The largest series published to date is that of Kavanagh et al.[74]; all of their patients were Caucasian men who had significant outdoor sun exposure either at work or with hobbies. The median age was 79 years (range 44–91). A survey of 100 geriatric male inpatients in the same geographic area revealed that four had similar lesions.

Pathogenesis

Although the precise pathogenesis is unknown, the consistent history of sun exposure and the presence of actinic damage suggest a role for UV light.

Clinical features

Weathering nodules are white or skin-colored, and are present along the free margin of the helix (Fig. 88.13). They are bilateral and multiple in most patients. Multiple lesions create a scalloped appearance to the helical rim. Individual lesions are 2 to 3 mm in diameter and slightly elevated. Patients generally have significant actinic damage elsewhere[74].

Pathology

Epidermal atrophy, solar elastosis and telangiectasias occur over the nodule. The nodule itself is a fibrous tissue spur with cartilage metaplasia extending upward from disrupted perichondrium. The spur is connected to the underlying cartilage. No inflammation or epidermal disruption are noted[74].

Differential diagnosis

Alternative diagnostic considerations include CNH, elastotic nodules, amyloidosis, gouty tophi, calcinosis cutis, granuloma annulare and rheumatoid nodules. Chondrodermatitis occurs in a similar clinical setting, but can be distinguished by the presence of ulceration and tenderness clinically, and marked inflammatory changes histologically. Elastotic nodules of the ear occur more often on the anterior ear or antihelix. They are waxy, firm, mildly tender nodules. Microscopically, these lesions exhibit thick coalescing elastic fibers and amorphous basophilic masses. No cartilaginous changes are seen. The deposits of amyloid, uric acid and calcium have distinctive appearances and staining characteristics[74,75]. Granuloma annulare and rheumatoid nodules consist of necrobiotic granulomas.

Treatment

Treatment is unnecessary, but Kavanagh et al.[74] note that two of their patients had received cryosurgery, with no local recurrence of the nodules.

Traumatic Auricular Hematoma

Synonyms: ■ Cauliflower ear ■ Wrestler's ear

Key features

- Trauma to the pinna avulses the anterior perichondrium from the underlying cartilage, then a subperichondrial hematoma can develop
- Drainage and replacement of the perichondrium can prevent development of fibroneocartilage

Introduction

Blunt trauma to the auricle can create a subperichondrial hematoma. If not corrected quickly, the hematoma will organize into a permanent disfiguring nodularity known as cauliflower ear. Therefore, early surgical correction is crucial.

History

Ancient Greek wrestlers were recognized by the stigma of a misshapen, thickened ear, the wrestler's "ear-mark". Similar ear injuries also are seen in boxers, rugby players, and piano movers. Early twentieth century Hong Kong opium dens produced a similar finding as opium abusers slept for long periods on the wooden pillows. Although past generations of wrestlers lined up after competition to have their ears "needled", soft plastic protective headgear has been available for several decades[76].

Epidemiology

Traumatic auricular hematoma is seen almost exclusively in male athletes who participate in wrestling, boxing or rugby. Piano movers are at risk as well, due to pressure on the ear while lifting.

Pathogenesis

A glancing blow or twisting movement against the anterolateral pinna avulses the anterior perichondrium from the underlying cartilage. Adhesion between skin structures and perichondrium is apparently stronger than between perichondrium and cartilage. These shearing forces rupture vessels that then bleed into the subperichondrial or intracartilaginous space, creating the auricular hematoma[76]. Regardless of the location of the hematoma, there is agreement that, if left untreated, the hematoma will organize into a solid mass with subsequent production of fibroneocartilage. Fibroneocartilage formation begins 7–10 days after injury. Calcification may also ensue. Repeated injury produces the multinodular deformity known as cauliflower ear[77].

Clinical features

A painless to slightly tender swelling appears on the upper anterior aspect of the pinna in the scaphoid or triangular fossa. If left untreated, the swelling persists and becomes firmer with time. The color varies from skin-colored to slightly bluish. No epidermal change is noted. Older lesions may feel soft and cystic or very firm[76,77].

Pathology

Histopathologic examination reveals a hematoma with fibrosis and foci of new cartilage formation. Older lesions may exhibit calcification and even ossification within the hematoma[76].

Differential diagnosis

The history of trauma and characteristic presentation readily aid in establishing the diagnosis. Other considerations include relapsing polychondritis, auricular pseudocyst and epidermoid cyst. Polychondritis should produce painful inflammatory episodes unrelated to trauma. Histologic features would confirm the inflammatory nature, even in the quiescent phase with thickening of the perichondrium. Auricular pseudocysts and epidermoid cysts are discussed in Chapter 110.

Treatment

Goals of treatment for auricular hematomas are evacuation of the hematoma, prevention of fluid reaccumulation, and maintenance of function and cosmesis. There is general consensus that treatment needs to proceed within 7 days (preferably the first 72 hours). Treatment modalities include aspiration, incision and drainage (with or without cartilage removal), and splinting to prevent recurrence[77]. Cochrane database investigators were unable to find controlled randomized or cohort studies to determine the best modality. Their conclusion was that there are no good data defining a best treatment, or even whether post-drainage treatment is needed[78].

SPORTS-RELATED DERMATOSES

Variants: ■ Tennis toe ■ Jogger's toe ■ Turf toe ■ Surfer's nodules ■ Surfer's knots ■ Jogger's nipple

Key features

- Cutaneous trauma produces abrasions, blistering, ecchymoses, callosities and unique sport-specific stigmata
- Allergic contact dermatitis in athletes is often due to rubber antioxidants and adhesives
- Cutaneous bacterial, viral and fungal infections occur more often in those engaged in sports with close physical contact
- Existing dermatoses may be exacerbated by sports participation

Introduction

Participation in sports may be associated with many types of cutaneous injuries or infections. Most of these problems are minor inconveniences. The following discussion will be organized into: mechanical trauma (acute, chronic); exposure-related dermatoses; infections; and exacerbation of existing conditions.

History

Cutaneous injury has been an accepted consequence of athletic activity at least since Ancient Greece. Stigmata such as the wrestler's "earmark" have been viewed as marks of athletic prowess.

Epidemiology

Sports participation has shown a steady increase over the past 30 years. Along with the gain in popularity of athletic activity has come an increase in sports-related dermatoses and infections. For example, herpes simplex viral infections were seen in 2.6% of high school and 7.6% of collegiate wrestlers in the 1984 season, and a third of wrestlers in a wrestling camp in 1989[79,80]; wrestlers are also at risk of developing tinea corporis gladiatorum[81]. More recently, cutaneous infections with community acquired MRSA have been observed among athletes, in particular football players and wrestlers[82,83]. Risk factors include frictional injuries, weight, poor hygiene, and sharing clothing and towels with team members.

Pathogenesis

The types of frictional and mechanical trauma that can lead to dermatoses in athletes are summarized in Table 88.13. For example, acne mechanica is thought to occur when the local microenvironment of the skin is altered by a combination of pressure, heat, moisture (perspiration), friction and occlusion[84].

Exposure to heat and cold are discussed in other sections of this chapter. The pathogenetic mechanisms underlying pre-existing dermatoses that may be aggravated by athletic activity are discussed in the respective sections.

Clinical features

Acute or chronic mechanical trauma during sports activity creates unique cutaneous lesions summarized in Table 88.13.

In some patients, chronic friction on extensor extremities during the summer is thought to produce frictional lichenoid dermatitis (summertime pityriasis). This malady affects prepubertal children (mostly boys) and is characterized by irregular clusters of pale to skin-colored, flat-topped, lichenoid papules on the elbows, knees, dorsal metacarpophalangeal and interphalangeal joints, and extensor shins and forearms. Mild pruritus may develop, although most children are asymptomatic[87].

Another common finding in athletes is the presence of striae distensae, or stretch marks. These are most common in sports that emphasize strength training by weightlifting, such as body builders, football players, wrestlers and gymnasts. Striae are also seen in non-athletic settings such as Cushing's syndrome, obesity, pregnancy and overuse of corticosteroids. In addition, striae are thought to occur in 70% of adolescent girls and 40% of adolescent boys[84].

Environmental exposure creates additional challenges for the sports enthusiast, especially with activity during temperature extremes. Summer heat poses risks such as heat exhaustion and heat stroke (see above). Mountain climbers, skiers (downhill and Nordic), biathletes, winter hikers and others are at risk for cold injury (see above). Water exposure in swimming, diving, snorkeling and scuba diving has intrinsic risks as well. Overhydration of the stratum corneum increases susceptibility to blisters, skin breakdown and cutaneous infection.

Allergic contact dermatitis is likely to be as common among athletes as the general population, but specific situations may make contact dermatitis more apparent due to the use of specialized equipment. Erythema in the distribution of a swimmer's goggles or scuba mask ("mask burn") may be seen, and individuals with more severe reactions can also develop vesiculation, weeping, crusting, pruritus and pain. Rubber antioxidant allergy is known to occur in this setting, with mercaptobenzothiazole, tetramethylthiuram and paraphenylenediamine derivatives being the major allergens. Rubber compounds in athletic

FRICTIONAL AND MECHANICAL DERMATOSES IN ATHLETES				
Condition	**Clinical features**	**Sports**	**Etiology/pathogenesis**	**Prevention/treatment**
Friction blisters* (see Ch. 33)	Bullae and superficial erosions	Any	Friction or tangential impact to foot while in warm moist shoes	Frequent drying of feet, lubrication, proper shoe fit, drain blisters/leave roof
Contusion*	Ecchymosis	Any	Perpendicular mechanical trauma producing vascular damage	Padding
Subungual hematoma*		Running, tennis, basketball	Sudden impact of toe tip with end of shoe	Enlarged shoe toe box with proper arch and metatarsal support, drainage of hematoma may be needed
Black heel*	See text			
Turf toe*	Painful, erythematous, edematous hallux	Football, soccer	Acute dorsal and plantar tendonitis	Rest
Jogger's nipple*	Pain, erythema, fissuring, occasional bleeding	Running	Repeated friction of rough shirt fabric	Woman: jogging bra Man: taping, lubrication, semisynthetic or silk shirt
Callosities	See text	Many		
Tennis toe	Toe tip callus, nail thickening, subungual hyperkeratosis (Fig. 88.14)	Tennis, running	Repeated trauma of longest toe against inside of toe box	Proper shoe fit, enlarged toe box, improved arch support
Nail dystrophy	Onycholysis, hematoma, subungual hyperkeratosis, paronychia	Many	Repeated trauma to nails	Keeping nails trimmed
Fibrotic nodules (e.g. surfer's knots)	Thick fibrotic nodules on knees, knuckles, dorsal feet	Surfing, boxing, football, marbles	Chronic pressure over bony prominences	Padding, position change, prone rather than kneeling on surfboard
Piezogenic papules	Multiple asymptomatic to tender yellowish outpouchings on the medial and lateral aspects of the heels when standing (Fig. 88.15)	Distance running, high-impact sports	Herniation of subcutaneous fat through small tears in plantar fascia	None known
Runner's rump	Small ecchymoses in upper gluteal cleft	Running	Constant friction with each stride	Lubrication
Alopecia and hypertrichosis	Transient alopecia on forearms followed by hypertrichosis	Gymnastics	Frictional alopecia, compensatory regrowth	
Swimmer's shoulder	Erythematous plaque on shoulder	Swimming	Friction of unshaven beard against the shoulder during the swim stroke	More frequent shaving

*Acute injury.

Table 88.13 Frictional and mechanical dermatoses in athletes[84–86].

Fig. 88.14 Chronic "tennis toe". Chronic and repeated trauma of the longer second toe against the end of the tennis shoe toe box during sudden stops creates the distal callus formation and nail plate thickening known as tennis toe.

Fig. 88.15 Piezogenic papules. Yellowish outpouchings on the heel represent herniation of subcutaneous fat through the plantar fascia in this sometimes painful condition.

shoes pose risks to individuals with contact sensitivity, particularly with thiourea, mercaptobenzothiazole and thiuram antioxidants. The resulting erythema, desquamation, vesiculation, fissuring, pain and pruritus of the feet can prove quite disabling for the athlete, particularly when alternative footwear without rubber (e.g. soccer cleats, baseball cleats) is not readily available. However, the development of polyurethane shoes by a few manufacturers offers an alternative for runners allergic to rubber components. Adhesives in tape, benzoin, topical antiseptics and antibiotics, dyes and leather tanning agents also may be problematic in several groups of athletes[84,86].

Acne mechanica occurs commonly in athletes in whom occlusive uniforms or protective gear create the right microenvironment. Football players flare during the August pre-season practice with follicular

papules, pustules and nodules on the forehead, preauricular areas, chin and shoulders, corresponding to forehead and ear pads of the helmet, chin strap and shoulder pads, respectively. Acne keloidalis of the lower occiput may be aggravated by the helmet as well. Other sports in which protective headgear may create acne mechanica include hockey, lacrosse and wrestling. Occlusive synthetic clothing of dancers and gymnasts, plastic benches of weight lifters, the golf bag shoulder strap, and the cradling of the shot against the neck in shot putters may also produce acne mechanica[84].

Heat, moisture, friction, and contact with other athletes or various surfaces increase the risk of some infectious conditions (Table 88.14). Several common monikers attest to the frequent association, such as "jock itch", "herpes gladiatorum", "athlete's foot" and "swimmer's ear". A report that evaluated the risk of staphylococcal infections in football players within a professional team noted that weight and turf injuries were risk factors and, therefore, linemen were more prone to developing this infection. However, practices of the trainers and the use of whirlpool equipment also pointed to risks associated with poor hygienic practices[82].

The final issue of sports-related skin disease is aggravation of pre-existing conditions. Psoriasis, vitiligo and lichen planus may exhibit a Koebner phenomenon, flaring in areas of skin injury such as abrasions. Epidermolysis bullosa simplex of the Weber–Cockayne type is worsened by friction on the feet and hands, particularly in warm summer months (see Ch. 32). Photosensitive dermatoses may be exacerbated by outdoor sun exposure (see Ch. 87). Both cholinergic and exercise-induced urticaria may worsen with heavy physical exertion[88] (see Ch. 18). Vibratory angioedema has also been reported with bicycling, walking, and jogging[90]. The reader is referred to The American Academy of Pediatrics guide for further information on medical conditions affecting sports participation[91].

Pathology

Many of the friction-induced conditions discussed here have histologic features similar to callosities (see above). Surfer's nodules show hyperkeratosis and mild acanthosis of the epidermis with increased numbers of normal-appearing collagen bundles. The overall histologic appearance is similar to that of a collagenoma[92]. The infectious processes are covered in detail in their respective chapters, as are the existing dermatoses aggravated by sports participation.

Treatment

Therapy for the non-infectious conditions discussed in this section is based primarily upon anecdotal reports and small series, and is

CUTANEOUS INFECTIONS IN ATHLETES

Condition	Common name	Clinical features	Organisms	Typical sport
Impetigo		Small vesicles to large bullae on glistening erythematous bases; honey-colored crusts	*Staphylococcus aureus*, β-hemolytic streptococci	Wrestling, European football (soccer), American football, swimming, gymnastics
Folliculitis		Erythematous follicular papules and pustules	*S. aureus*	Most sports
Hot tub folliculitis		Markedly erythematous, edematous follicular papulopustules, few in number, often involving axillae, breasts, pubic area and buttocks	*Pseudomonas aeruginosa*	Swimming; use of whirlpool, hot tub or Jacuzzi
Pseudomonas hot-foot syndrome		Tender nodules on soles	*P. aeruginosa*	Use of wading pool
Furuncles	Boils	Tender warm red nodules or abscesses on trunk or extremities	*S. aureus* (including MRSA)	Football, wrestling, basketball, swimming
Erythrasma		Reddish-brown dry patches in axillae, groin or toe webs	*Corynebacterium minutissimum*	Most sports, especially with occlusive clothing
Pitted keratolysis	Toxic sock syndrome	Malodorous feet with plantar 1–3 mm punched-out erosions extending only through the stratum corneum of overhydrated skin	*Corynebacterium* spp., *Micrococcus (Kytococcus) sedentarius*	Running, tennis, basketball
Otitis externa	Swimmer's ear	Pruritus may be followed by pain, discharge, tenderness of the pinna, sensation of fullness and reduced hearing	*P. aeruginosa* most common; also streptococci, diphtheroids and staphylococci	Swimming, diving (atopics at risk)
Swimming pool granuloma		Firm acral red papules	*Mycobacterium marinum*	Swimming
Verruca vulgaris	Warts	Verrucous, keratotic papules and plaques	Human papillomavirus	Any that use locker-room showers or public pools
Herpes simplex viral infection	Herpes gladiatorum	Clustered vesicles on erythematous bases at point of skin-to-skin contact	Herpes simplex virus	Wrestling
Molluscum contagiosum		Shiny, umbilicated 2–3 mm papules at the skin contact site	Parapoxvirus	Wrestling, swimming
Tinea pedis	Athlete's foot	Maceration, scaling, pruritus in toe webs; or diffuse plantar erythema and scale	*Trichophyton rubrum, T. mentagrophytes, Epidermophyton floccosum*	Any sport
Tinea cruris	Jock itch	Annular to polycyclic erythema with scaly, active borders, perifollicular papules or pustules; favors upper inner thighs	Same as tinea pedis	Any sport
Tinea corporis	Tinea gladiatorum	Except for location, the same as tinea cruris	*Trichophyton* spp.	Wrestling
Seabather's eruption	Sea lice	Pruritic papules on areas covered by bathing suit	*Edwardsiella lineata, Linuche unguiculata*	Salt water swimming
Swimmer's itch	Cercarial dermatitis	Pruritic erythematous papules on exposed skin	Duck schistosome cercaria	Fresh water pond and lake swimming and wading

Table 88.14 Cutaneous infections in athletes[79,80,82,84,88,89].

DERMATOLOGIC CONDITIONS IN LIMB AMPUTEES			
Physical/mechanical effects	**Allergic contact dermatitis (most common allergens)**	**Infections**	**Exacerbation of pre-existing condition**
• Callus • Verrucous hyperplasia • Hypertrichosis • Erythema • Blisters • Ulceration • Folliculitis (normal flora) • Inclusion cyst	• Para-phenylenediamine (PPD) • Formaldehyde • Epoxy resin • Mercapto mix • Fragrance mix	• Group A β-hemolytic *Streptococcus* – impetigo, cellulitis • *Staphylococcus aureus* – impetigo, cellulitis, folliculitis • *S. epidermidis* • Dermatophytes • *Candida* spp.	• Psoriasis • Eczema • Pyoderma gangrenosum

Table 88.15 Dermatologic conditions in limb amputees[93]. Localized pemphigoid of the stump has also been reported.

summarized in Table 88.13. Frictional lichenoid dermatitis responds to friction avoidance, the use of clothing to protect extensor surfaces, and moderate-potency topical corticosteroids[84,86–88]. Education and changes in practice behavior might aid in the prevention of infections in athletes.

AMPUTEE-RELATED DERMATOSES

Whether amputation is due to traumatic injuries (vehicular accidents, war-related, sports-related), environmental exposure, or a chronic medical condition (e.g. diabetes mellitus), skin disorders are a frequent complication, with reported incidences ranging from 35% to 75%. Table 88.15 lists dermatologic conditions observed in amputees. Implicated factors include higher level of amputation, higher activity level, and soft socket (as opposed to silicone) prostheses[93].

MUSICAL INSTRUMENT-RELATED DERMATOSES

Variants: ■ Cellist's chest or knee ■ Clarinetist's cheilitis ■ Drummer's digit ■ Fiddler's neck ■ Flautist's chin ■ Garrod's pads ■ Guitar nipple ■ Harpist's fingers

Key features

- Cutaneous disorders in musicians include frictional injury, irritant and allergic contact dermatitis, hyperhidrosis, acne mechanica and vascular compromise
- Dermatoses tend to be recurrent unless the posture, use or contact can be avoided
- Identification of the mechanism of injury is critical for successful therapy

Introduction

Musicians have unique cutaneous reactions related to countless hours of practice and performance required to master their art. Skin and associated soft tissue and musculoskeletal changes are therefore not uncommon. The major categories of injury in musicians are contact dermatitis, repetitive motion injury and dysautonomia.

History

One of the first reports of an occupational dermatosis is reputed to be the recognition of fiddler's neck in 1713. About the same time, Italian physician Bernadino Ramazzizi noted the peculiar distension and soft tissue laxity of the cheeks in horn players, and summarized the occupational problems of musicians[94].

Epidemiology

The injuries discussed below all require considerable devotion of time to practice and performance of the chosen instruments. Some of these conditions are considered marks of virtuosity, such as cellist's thumb. The impact of these conditions is greatest on professional musicians, although amateurs, and even beginners, may be afflicted[95].

Pathogenesis and clinical features

The clinical features and pathogenesis of dermatoses caused by musical instruments are summarized in Table 88.16.

Another common dermatosis that may occur in musicians is "lip licker's" dermatitis, characterized by erythema, fissuring and scaling in wind instrument players. Intraoral hyperkeratosis of the lip or shallow erosions may develop in patients with dental irregularities or orthodontic appliances. Salivary abnormalities may interfere with performance with wind instruments. Xerostomia is devastating to the wind player (especially brass), while increased salivation is problematic for the recorder player. Sialolithiasis has been seen in association with fiddler's neck.

Sharing of mouthpieces may increase the risk of transmission of infections such as herpes simplex virus, EBV, cytomegalovirus, and hepatitis A and B. Latent herpes simplex may be reactivated by the frictional trauma of wind instruments, with brass players tending to have upper lip lesions and woodwind players having lower lip lesions[96].

Hyperhidrosis of the palms may lead to corrosion of metal instruments or the inability to maintain proper contact with instrument keys or strings[97].

Allergic contact dermatitis associated with musical instruments is summarized in Table 88.17.

Pathology

Diagnosis of most of these conditions does not require histologic evaluation. However, fiddler's neck has been shown to exhibit epidermal hyperplasia with elongation of the rete ridges, follicular plugging, folliculitis and perifolliculitis, and epidermoid cyst formation[96].

Differential diagnosis

Fiddler's neck needs to be distinguished from localized cervical lymphadenitis, an inflamed epidermoid cyst, draining dental abscess, and acne mechanica from other causes (e.g. telephone, headset). Clinical history should suffice, along with the characteristic location and clinical features. For example, a dental abscess, scrofuloderma or cervical actinomycosis with fistula formation often leaves the area indented and bound to underlying structures.

Treatment

Discontinuation of the instrument is curative in almost all cases, but usually quite impractical. Professional musicians, in particular, need other options. Frictional injuries may be addressed with padding, or change in position of the instrument. Fiddler's neck, for example, seems less common if the dropping neck position is avoided. Anecdotal

DERMATOSES CAUSED BY MUSICAL INSTRUMENTS			
Condition (synonym)	**Clinical features**	**Pathogenesis**	**Associated instruments**
Acne mechanica (fiddler's neck, clarinetist's cheilitis, flautist's chin)	Follicular papules and pustules, lichenification, hyperpigmentation	Repetitive friction and pressure, coupled with occlusion and moisture (sweat, saliva)	Violin, viola, clarinet, saxophone, flute
Cellist's chest	Sternal skin tenderness, erythema, edema, hyperpigmentation	Pressure and friction	Cello
Cellist's knee	Erythema, scale, callus and hyperpigmentation of left medial knee	Friction callus	Cello
Finger calluses	Hyperkeratotic callosities on fingertip pads	Repetitive friction	All strings
Drummer's digit	Vesicle or erosion on the radial aspect of the left ring finger distal and middle phalanx, followed by callus formation	Friction from holding left drumstick in classical position	Drums
Garrod's pads (violinist's pads)	Calluses on dorsal aspect of proximal interphalangeal joints of left index and middle fingers	Repeated extension and flexion of extensor tendon over tightly flexed joint	Violin, viola
Guitar nipple	Unilateral mastitis with erythema, edema, pain	Pressure and friction of guitar sound box pressed against chest	Guitar
Paronychia, onycholysis, subungual hemorrhage		Repeated trauma to nail apparatus	Piano, strings (especially playing pizzicato), harp, guitar

Table 88.16 Dermatoses caused by musical instruments[94–96].

ALLERGIC CONTACT DERMATITIS ASSOCIATED WITH MUSICAL INSTRUMENTS		
Sensitizer/contactant	**Skin distribution**	**Instrument**
Rosin/colophony (abietic acid)	Hands, face, neck	Violin, viola, cello, double bass
Rosewood	Lips, chin, cheek	Strings, reeds
Makassar ebony	Chin	Violin
Cocobolo wood	Lips	Recorder
African blackwood	Lips	Recorder, oboe
Nickel	Chin	Violin
	Fingers, hands	Cello, sitar
	Lips, chin	Flute, brass
Reed (perhaps only irritant)	Lips	Saxophone, clarinet
Propolis (bee glue)	Hands	Violin
Chromium	Hands	Harp, violin
Paraphenylenediamine	Chin	Violin, viola

Table 88.17 Allergic contact dermatitis associated with musical instruments[94–98].

remedies for the treatment of fiddler's neck include astringents, benzoyl peroxide, keratolytics, tretinoin, topical erythromycin and application of French brandy.

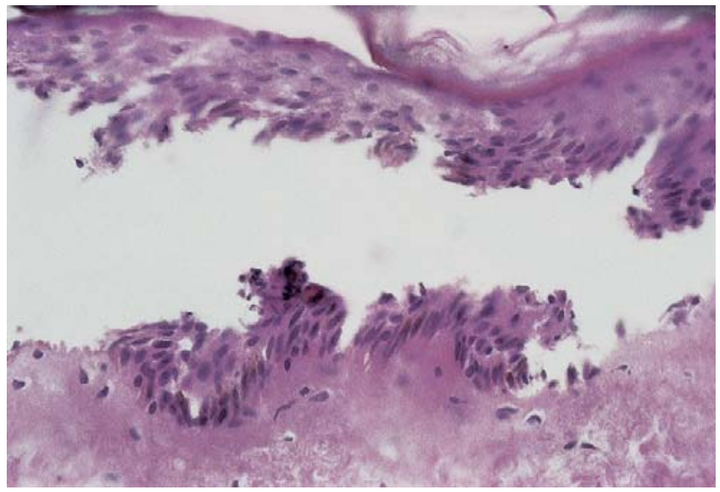
Treatment of excess salivation with a transdermal scopolamine patch has been reported. Remedies for hyperhidrosis include topical aluminum-based drying agents, iontophoresis, β-adrenergic blocking agents (especially if the hyperhidrosis is due to "stage fright"), calcium channel blockers, botulinum toxin A and ganglionectomy (see Ch. 39). Anticholinergic therapy is not useful for many musicians because of the frequent side effects of dry mouth and blurred vision[94–96]. If allergic contact dermatitis is suspected, patch testing can be performed (see Ch. 14).

REFERENCES

1. Lugo-Amador NM, Rothenhaus T, Moyer P. Heat-related illness. Emerg Med Clin North Am. 2004;22:315–27.
2. AAP Committee on Sports and Fitness. Climatic heat stress and the exercising child and adolescent. Pediatrics. 2000;106:158–9.
3. Ramzy PI, Barret JP, Herndon DN. Thermal injury. Crit Care Clin. 1999;15:333–52.
4. Passaretti D, Billmire DA. Management of pediatric burns. J Craniofac Surg. 2003;14:713–18.
5. Fogarty BJ, Gordon DJ. Firework related injury and legislation: the epidemiology of firework injuries and the effect of legislation in Northern Ireland. Burns. 1999;25:53–6.
6. Enoch S, Roshan A, Shah M. Emergency and early management of burns and scalds. BMJ. 2009;338:b1037.
7. Weedon D. Skin Pathology. Edinburgh: Churchill Livingstone, 1997:504–6.
8. Tan S, Bertucci V. Erythema ab igne: an old condition new again. CMAJ. 2000;162:77–8.
9. Radmanesh M. Erythema ab igne following sauna belt use for abdominal obesity and cellulite. Int J Dermatol. 2009;48:94–5.
10. Donohue KG, Nahm WK, Badiavas E, et al. Hot pop brown spot: erythema ab igne induced by heated popcorn. J Dermatol. 2002;29:172–3.
11. Arnold AW, Itin PH. Laptop computer-induced erythema ab igne in a child and review of the literature. Pediatrics. 2010;126:e1227–30.
12. Cavallari V, Cicciarello R, Torre V, et al. Chronic heat-induced skin lesions (erythema ab igne): ultrastructural studies. Ultrastruct Pathol. 2001;25:93–7.
13. Karoo ROS, Whitaker IS, Garrido A, Sharpe DT. Full-thickness burns following magnetic resonance imaging: a discussion of the dangers and safety suggestions. Plast Reconstr Surg. 2004;114:1344–5.
14. Muensterer OJ. Temporary removal of navel piercing jewelry for surgery and imaging studies. Pediatrics. 2004;114:e384–6.
15. Karch AM. Don't get burnt by the MRI: transdermal patches can be a hazard to patients. Am J Nurs. 2004;104:31.
16. Vlietstra RE, Wagner LK. X-ray burns: painful, protracted, and preventable. Clin Cardiol. 2008;31:145–7.
17. Frazier TH, Richardson JB, Fabre VC, Callen JP. Fluoroscopy-induced chronic radiation skin injury: a disease perhaps often overlooked. Arch Dermatol. 2007;143:637–40.
18. Dempsey MF, Condon B. Thermal injuries associated with MRI. Clin Radiol. 2001;56:457–65.
19. Corazza M, Trincone S, Virgili A. Effects of airbag deployment: lesions, epidemiology and management. Am J Clin Dermatol. 2004;5:295–300.
20. Ulrich D, Noah E-M, Fuchs P, Pallua N. Burn injuries caused by air bag deployment. Burns. 2001;27:196–9.
21. Masaki F. A new category of contact burn resulting from air bag infusion. Burns. 2005;31:118–19.
22. Imray C, Grieve A, Dhillon S. Cold damage to the extremities: frostbite and non-freezing cold injuries. Postgrad Med J. 2009;85:481–8.
23. Meffert JJ. Environmental skin diseases and the impact of common dermatoses on medical readiness. Dermatol Clin. 1999;17:1–17.
24. Cattermole TJ. The epidemiology of cold injury in Antarctica. Aviat Space Environ Med. 1999;70:135–40.

25. Long WB, Edlich RF, Winters KL, Britt LD. Cold injuries. J Long Term Eff Med Implants. 2005;15:67–78.
26. Simon TD, Soep JB, Hollister JR. Pernio in pediatrics. Pediatrics. 2005;116:e472–5.
27. Piffard HG. A Treatise on the Materia Medica and Therapeutics of the Skin. New York: William Wood and Co., 1881:236.
28. Parlette EC, Parlette HL. Erythrocyanotic discoloration of the toes. Cutis. 2000;65:223–6.
29. Cribier B, Djeridi N, Peltre B, Grosshans E. A histiologic and immunohistochemical study of chilblains. J Am Acad Dermatol. 2001;45:924–9.
30. Weston WL, Morelli JG. Childhood pernio and cryoproteins. Pediatr Dermatol. 2000;17:97–9.
31. Wanderer AA, Grandel KE, Wasserman SI, Farr RS. Clinical characteristics of cold-induced systemic reactions in acquired cold urticaria syndromes: recommendations for prevention of this complication and a proposal for a diagnostic classification of cold urticaria. J Allergy Clin Immunol. 1986;78:417–23.
32. Wigley FM, Flavahan NA. Raynaud's phenomenon. Rheum Dis Clin North Am. 1996;22:765–81.
33. Yazawa H, Saga K, Omori F, et al. The chilblain-like eruption as a diagnostic clue to the blast crisis of chronic myelocytic leukemia. J Am Acad Dermatol. 2004;50(suppl. 1):42–4.
34. Rustin MH, Newton JA, Smith NP, Dowd PM. The treatment of chilblains with nifedipine: the results of a pilot study, a double-blind placebo-controlled randomized study and a long-term open trial. Br J Dermatol. 1989;120:267–75.
35. Wrenn K. Immersion foot. A problem of the homeless in the 1990s. Arch Intern Med. 1991;151:785–8.
36. Zafren K. Clinical images: immersion injury. Wilderness Environ Med. 2000;11:269–71.
37. Oumeish OY, Parish LC. Marching in the army: common cutaneous disorders of the feet. Clin Dermatol. 2002; 20:445–51.
38. Moore JK. Do jungle boots stop jungle rot? Wilderness Environ Med. 2004;15:230–3.
39. Humphrey W, Ellyson R. Warm water immersion foot: still a threat to the soldier. Mil Med. 1997;162:610–11.
40. Arnoldo BD, Purdue GF, Kowalske K, et al. Electrical injuries: a 20–year review. J Burn Care Rehabil. 2004; 25:479–84.
41. Ritenhour AE, Morton MJ, McManus JG, et al. Lightning injury: a review. Burns 2008;34:585–94.
42. Lee RC. Injury by electrical forces: pathophysiology, manifestations, and therapy. Curr Probl Surg. 1997;34: 684–764.
43. Koumbourlis AC. Electrical injuries. Crit Care Med. 2002;30:S424–30.
44. Sticherling M, Christophers E. Why hair turns green. Acta Derm Venereol (Stockh). 1993;73:321–2.
45. Nanko H, Mutoh Y, Atsumi R, et al. Hair-discoloration of Japanese elite swimmers. J Dermatol. 2000;27:625–34.
46. Fitzgerald EA, Purcell SM, Goldman HM. Green hair discoloration due to selenium sulfide. Int J Dermatol. 1997;36:238–9.
47. Rebora A, Guarrera M. Hair discoloration caused by minoxidil lotion. J Am Acad Dermatol. 1989;21:1314.
48. Rogers MJ, Whitefield M, Marks VJ. Yellow hair discoloration due to anthralin. J Am Acad Dermatol. 1988;19:370–1.
49. Schwartz RA. Arsenic and the skin. Int J Dermatol. 1997;36:241–50.
50. Ratnaike RN. Acute and chronic arsenic toxicity. Postgrad Med J. 2003;79:391–6.
51. Mazumder DNG. Chronic arsenic toxicity and human health. Indian J Med Res. 2008;128:436–47.
52. Rahman MM, Ng JC, Naidu R. Chronic exposure of arsenic via drinking water and its adverse health impacts on humans. Environ Geochem Health. 2009; 31:189–200.
53. Vahter M, Akesson A, Liden C, et al. Gender differences in the disposition and toxicity of metals. Environ Res. 2007;104:85–95.
54. NIOSH Pocket Guide to Chemical Hazards. U.S. Department of Health and Human Services. Cincinnati: NIOSH Publications, 1997.
55. Russell MA, Langley M, Truett AP, et al. Lichenoid dermatitis after consumption of gold-containing liquor. J Am Acad Dermatol. 1997;36:841–4.
56. Boyd AS, Seger D, Vannucci S, et al. Mercury exposure and cutaneous disease. J Am Acad Dermatol. 2000; 43:81–90.
57. Järup L. Hazards of heavy metal contamination. Br Med Bull. 2003;68:167–82.
58. Moreno-Ramirez D, Garcia-Bravo B, Pichardo AR, et al. Baboon syndrome in childhood: easy to avoid, easy to diagnose, but the problem continues. Pediatr Dermatol. 2004;21:250–3.
59. Misra UK, Kalita J, Yadav RK, Ranjan P. Thallium poisoning: emphasis on early diagnosis and response to hemodialysis. Postgrad Med J. 2003;79:103–5.
60. Greenberg JE, Lynn M, Kirsner RS, et al. Mucocutaneous pigmented macule as a result of zinc deposition. J Cutan Pathol. 2002;29:613–15.
61. Harrison J, Leggett R, Lloyd D, et al. Polonium-210 as a poison. J Radiol Prot. 2007;27:17–40.
62. Freeman DB. Corns and calluses resulting from mechanical hyperkeratosis. Am Fam Physician. 2002; 65:2277–80.
63. Adams B, Lucky A. A center's callosities. Cutis. 2001; 67:141–2.
64. Crissey JT, Peachey JC. Calcaneal petechiae. Arch Dermatol. 1961;83:501.
65. Urbina F, Leon L, Sudy E. Black heel, talon noir or calcaneal petechiae? Australas J Dermatol. 2008;49: 148–51.
66. Wilkinson DS. Black heel. A minor hazard of sport. Cutis. 1997;20:393–6.
67. Rogers NE, Farris PK, Wang AR. Juvenile chondrodermatitis nodularis helices: a case report and literature review. Pediatr Dermatol. 2003;20: 488–90.
68. Oelzner S, Elsner P. Bilateral chondrodermatitis nodularis chronica helicis on the free border of the helix in a woman. J Am Acad Dermatol. 2003;49:720–2.
69. Moncrieff M, Sassoon EM. Effective treatment of chondrodermatitis nodularis chronica helicis using a conservative approach. Br J Dermatol. 2004;150: 892–4.
70. Epstein E. Granuloma fissuratum of the ears. Arch Dermatol. 1965;91:621–2.
71. Benedetto AV, Bergfeld WF. Acanthoma fissuratum: histopathology and review of the literature. Cutis. 1979;24:225–9.
72. Cerroni L, Soyer HP, Chimenti S. Acanthoma fissuratum. J Dermatol Surg Oncol. 1988;14:1003–5.
73. Thomas MR, Sadiq HA, Raweily EAA. Acanthoma fissuratum. J Laryngol Otol. 1991;105:301–3.
74. Kavanagh GM, Bradfield JWB, Collins CMP, Kennedy CTC. Weathering nodules of the ear: a clinicopathological study. Br J Dermatol. 1996;135:550–4.
75. Requena L, Aguilar A, Sanchez Yus E. Elastic nodules of the ears. Cutis. 1989;44:452–4.
76. Giffin CS. Wrestler's ear: pathophysiology and treatment. Ann Plast Surg. 1992;28:131–9.
77. Henderson JM, Salama AR, Blanchaert RH. Management of auricular hematoma using a thermoplastic splint. Arch Otolaryngol Head Neck Surg. 2000;126:888–90.
78. Jones SE, Mahendran S. Interventions for acute auricular hematoma. Cochrane Database Syst Rev. 2004;(2): CD004166.
79. Becker TM. Herpes gladiatorum: a growing problem in sports medicine. Cutis. 1992;50:150–2.
80. Sevier TL. Infectious disease in athletes. Med Clin North Am. 1994;78:389–412.
81. Adams BB. Tinea corporis gladiatorum. J Am Acad Dermatol. 2002;47:286–90.
82. Cohen PR. The skin in the gym: a comprehensive review of the cutaneous manifestations of community-acquired methicillin-resistant *Staphylococcus aureus* infection in athletes. Clin Dermatol. 2008;26:16–26.
83. Creech CB, Saye E, McKenna BD, et al. One-year surveillance of methicillin-resistant *Staphylococcus aureus* nasal colonization and skin and soft tissue infections in collegiate athletes. Arch Pediatr Adolesc Med. 2010;164:615–20.
84. Metelitsa A, Barankin B, Lin AN. Diagnosis of sports-related dermatoses. Int J Dermatol. 2004;43:113–19.
85. Biolcati G, Berlutti G, Bagarone A, Caselli G. Dermatological marks in athletes of artistic and rhythmic gymnastics. Int J Sports Med. 2004;25:638–40.
86. Kockentiet B, Adams B. Contact dermatitis in athletes. J Am Acad Dermatol. 2007;56:1048–55.
87. Fisher AA. Sports-related cutaneous reactions: part I. Dermatoses due to physical agents. Cutis. 1999;63: 134–6.
88. Conklin RJ. Common cutaneous disorders in athletes. Sports Med. 1990;9:100–19.
89. Nichols AW. Nonorthopaedic problems in the aquatic athlete. Clin Sport Med. 1999;18:395–411.
90. Schubert B, Seitz CS, Weigel C, et al. Angio-oedema induced by bicycling. Br J Dermatol. 2007;156:1056–8.
91. American Academy of Pediatrics, Committee on Sports Medicine and Fitness. Medical conditions affecting sports participation. Pediatrics. 2001;107:1205–9.
92. Cohen PR, Eliezri YD, Silvers DN. Athlete's nodules: sports-related connective tissue nevi of the collagen type (collagenomas). Cutis. 1992;50:131–5.
93. Koc E, Tunca M, Akar A, et al. Skin problems in amputees: a descriptive study. Int J Dermatol. 2008;47: 463–6.
94. Liu L, Hayden GF. Maladies in musicians. South Med J. 2002;95:727–34.
95. Fisher AA. Dermatitis in a musician. Part I: allergic contact dermatitis. Cutis. 1998;62:167–8.
96. Gambichler T, Uzun A, Boms S, et al. Skin conditions in instrumental musicians: a self-reported survey. Contact Dermatitis. 2008;58:217–22.
97. Hoppman RA, Burke WA, Patrone NA. Hyperhidrosis in the performing artist. Med Probl Perform Art. 1988;3: 60–2.
98. Lombardi C, Bottello M, Caruso A, et al. Allergy and skin diseases in musicians. Allerg Immunol (Paris). 2003;35: 52–5.

Electrical burn. It is characterized by erythema, edema, bulla formation and sloughing of the necrotic epidermis. *Courtesy of Timothy Givens MD.*



Pathology of an electrical burn. Blistering seen in a biopsy from a patient who died of an electrical burn. Notice the elongated keratinocyte nuclei. *Courtesy of Ronald P Rapini MD.*

89 Signs of Drug Abuse

Josep L Genebriera de Lamo, Mark R Pittelkow and Miguel Sanchez

INTRODUCTION

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-4), drug abuse is a non-conforming pattern of drug practice in a manner that deviates from medically recommended or socially accepted standards. Repeated drug abuse can progress to drug addiction, the result of drug-induced central nervous system (CNS) changes that lead to maladaptive alterations in spontaneous behavior and in the behavioral response to subsequent exposures to the drug. Physical dependence is associated with drug addiction, which denotes a constellation of cognitive, behavioral and physiologic symptoms manifested by compulsive drug use, tolerance, and withdrawal symptoms upon discontinuation of a drug (Table 89.1).

Drug abuse is a global problem and is directly responsible for minor to life-threatening and fatal illnesses and injuries, as well as adverse sociologic consequences (loss of occupational productivity and higher rates of poverty, crime, prison occupancy, domestic violence, child abuse or neglect) which increase the risk of infirmity and disability. According to the Office of National Drug Control Policy, the overall economic cost of drug abuse to American society during 2007 was estimated to be $193 billion.

Illicit drug use may be suspected or diagnosed on the basis of cutaneous findings. In fact, the skin is the tissue most evidently affected by intravenous drug addiction[1]. The wide spectrum of complications result from local or systemic effects (including toxic or allergic) of the drug itself, adulterants or infectious agents. Polydrug use, especially involving the consumption of alcohol and drugs, is common among drug addicts[1].

Amphetamines

Amphetamines were initially sold as a non-prescription appetite suppressant and rapidly became a favorite street drug ("pep pills", "Bennies"). Crystallized methamphetamine ("ice", "crystal", "glass", "tina"), an addictive stimulant with a high potential for abuse and dependence, produces an even stronger "rush" or "flash" when injected intravenously or inhaled. Oral ingestion of tablets ("speed", "meth", "chalk") or snorting powder merely produces a profound sense of euphoria. Smoking the base form ("snot") extends the duration of the "high" for up to 24 hours. Amphetamines can lead to reduced appetite, restlessness, insomnia and increased or distorted sensations; on physical examination, there may tachypnea, tachycardia and hypertension as well as flushing, sweating and even uncontrollable movements or shaking. Speed freaks (high-intensity abusers) progressively use the drug to remain euphoric, and with high doses or chronic use, xerostomia, xerosis, pruritus, acne excoriée and formication can occur, along with dental caries and loss of teeth ("meth mouth"). "Tweaking", continuous drug use without sleep for 3 to 15 days, is often associated with irritability, paranoia, violence and frustration due to inability to recreate the euphoric high.

Methylenedioxymethamphetamine (MDMA), also known as "ecstasy", "Adam", "XTC", "hug", "beans", or "love drug", is a synthetic stimulant and hallucinogen with a chemical structure similar to methamphetamine. MDMA causes a reduction in the concentration of serotonin transporters (SERTs) within the brain[2], and brain damage caused by heavy, prolonged use of MDMA may be long-lasting[3]. High doses can cause malignant hyperthermia, leading to rhabdomyolysis, renal failure and cardiovascular collapse. A staple at raves and PNP ("party and play") parties because of the associated increase in energy and reduction of sexual inhibition, crystallized methamphetamine and MDMA have been associated with unprotected, promiscuous sexual activity and especially high risk of contracting sexually transmitted diseases. More recently, "bath salts" (e.g. "Ivory Wave", "Cloud 9", "Vanilla Sky") that contain mephedrone, methylenedioxypyrovalerone (MDPV), or other cathinone or ampthetamine type stimulants have become popular and they can be injected, snorted, smoked or ingested orally.

FEATURES OF DRUG DEPENDENCE
• Recurrent and excessive drug use which may result in tolerance and withdrawal
• Recurrent social, occupational, psychological or physical problems as a result of excessive drug use
• Failed attempts to control substance use

Table 89.1 Features of drug dependence.

Benzodiazepines

Benzodiazepines are among the most frequently prescribed medications in the US, as they are in the UK, where surveys indicate that approximately 10% of the population take benzodiazepine sedatives regularly. Although they are only mild euphoriants, benzodiazepines are commonly misused by polydrug addicts (especially temazepam and flunitrazepam [Rohypnol®; "roofies"]), alcoholics and recreational drug users. Benzodiazepines are ingested (often with alcohol), snorted or, occasionally, injected. The most common side effects of benzodiazepines are related to their sedating and muscle-relaxing properties, e.g. decreased alertness and concentration and lack of coordination, respectively. Other side effects include depression, disinhibition, blurred vision and confusion, and with intravenous use, hypotension and hypoventilation.

Cannabis

Cannabis ("marijuana", "pot", "herb", "weed", "ganja", "Mary Jane") is the most frequently self-administered illicit drug. It is a mixture of dried shredded leaves and flowers of the *Cannabis sativa* plant, which contains the chemical delta-9-tetrahydrocannabinol (THC), and is usually smoked as a cigarette or through a pipe or bong. Marijuana cigarettes may be laced with other drugs, such as crack or heroin. The minimal amount of THC required to produce a perceptible psychoactive effect is ~10 mcg/kg body weight. A subjective change in perception may be accompanied by an impairment of concentration, psychomotor coordination and/or short-term memory. Arteritis has also been reported[4], and it may represent a particular form of Buerger's disease, with cannabis acting as a co-factor in young smokers. In a number of countries, there has been an increase in the use of synthetic cannabinoids ("Spice").

Cocaine

Cocaine ("coke", "blow", "toot", "flake", "snow") is an alkaloid stimulant and topical anesthetic which is extracted from the leaves of the *Erythroxylon coca* shrub. Crack ("base", "rock", "hubba", "gravel"), a freebase form of cocaine, is more addictive than heroin. It is produced by dissolving cocaine in water and baking soda and then heating the mixture until it crystallizes. Cocaine is injected or snorted, while crack is smoked.

In addition to Raynaud's phenomenon, cocaine use has been associated with small vessel vasculitis (leukocytoclastic vasculitis), necrotizing granulomatous vasculitis, acute generalized exanthematous pustulosis, and Stevens-Johnson syndrome[5,5a]. Its use can also lead to a number of cardiovascular side effects – Buerger's disease, hypertensive crisis, myocardial or cerebral infarction, and ventricular arrhythmias.

More recently, cocaine adulterated with levamisole has been associated with the development of neutropenia and ischemic vasculopathy with necrotizing purpura and ulceration (see below).

Gamma-Hydroxybutyrate

Gamma-hydroxybutyrate (GHB; "liquid ecstasy", "liquid X", "liquid G", "fantasy"), a "party drug", is a rapid-acting CNS depressant popular among revelers for its relaxant, euphoric and purported aphrodisiac properties. GHB can mentally and physically paralyze a person as well as induce memory loss, and it is used more often than flunitrazepam as a "rape drug". Because it reportedly promotes muscle mass and has been shown to elevate human growth hormone *in vivo*, GHB is commonly misused by bodybuilders.

Lysergic Acid Diethylamide

Lysergic acid diethylamide ("LSD", "acid"), an hallucinogen, is manufactured from the lysergic acid found in ergot, a fungus that grows on rye and other grains. It is often sold in single-dose (20 to 80 mcg) squares of blotter paper. LSD causes an altered experience of time, senses and memories, usually within 30–90 minutes after ingestion. Changes in auditory and visual perception (e.g. moving geometric patterns) are typical. In addition to pupil dilation and tachycardia, patients may develop sweating, sialorrhea, piloerection and a strong metallic taste.

Opiates

Also known as diacetylmorphine, heroin ("junk", "smack", "horse", "scag"), the fastest acting of all opiates, is three times more potent than morphine and still accounts for much of the illicit opiate abuse in the US. Because of its increased lipid solubility, it crosses the blood–brain barrier more rapidly, prompting a "rush" within 7 to 8 seconds after intravenous injection or 10–15 minutes after being snorted or smoked. There has been a growing tendency to sniff, snort ("shabbang") or smoke ("chase the dragon") heroin rather than inject it intravenously ("shoot up") or subcutaneously ("skin pop"). Opiate addicts may alternate injections of heroin and cocaine (crisscrossing) or inject highly addictive "speedballs" of the two drugs together. Methadone, an oral synthetic opioid with a half-life between 24 and 48 hours, is widely used as a substitute for heroin in narcotic treatment programs and for chronic pain.

Opiates remain the leading cause of fatal overdoses, with methadone, which is increasingly being obtained via the Internet, becoming a significant problem. Fentanyl, a narcotic analgesic that is 50 to 100 times more potent than morphine, is particularly prone to overdosing. Buprenorphine, a more potent and longer-lasting analgesic than morphine, appears to act as a partial agonist of μ and κ opioid receptors, but tolerance with chronic use may not develop, presumably due to the lack of δ-agonist activity.

Pentazocine is an oral benzomorphan opiate antagonist with a lower risk of drug dependence than opiates, but ingestion of pentazocine may precipitate withdrawal symptoms in persons physically dependent on opiates. However, when tablets are crushed, diluted and then injected in combination with the antihistamine tripelennamine (Pyribenzamine®), the euphoric effects are similar to those produced by heroin. The side effects are similar to those of morphine, but pentazocine may be associated with a greater risk of hallucinations. Severe necrosis and secondary infection of the skin and subcutaneous tissue, including underlying muscle, may develop at repeated injection sites of pentazocine.

Anabolic Steroids

Anabolic steroids promote the growth of skeletal muscle and the development of male sexual characteristics. They are ingested (oxandrolone, oxymetholone, stanozolol) or injected (nandrolone, testosterone, boldenone) intramuscularly by bodybuilders to increase muscle mass and by athletes to boost physical performance. Physical and psychological dependence can develop after habitual use. Higher risks for cardiovascular disease, hepatic disorders (e.g. peliosis hepatis, hepatic adenomas), infectious diseases (due to needle sharing) and perhaps mood disorders are among the long-term complications of anabolic steroid misuse. The cutaneous side effects are outlined in Table 89.3.

PATHOPHYSIOLOGY OF ADDICTION

Administration of addictive drugs, directly or indirectly, leads to an increase in dopamine activity within the mesolimbic system (reward circuit) as well as the frontal cortex, anterior cingulate and hippocampus. This is thought to play a role in incentive salience and craving. In addition, MRI studies have documented progressive loss of frontal lobe volume in both cocaine- and heroin-dependent addicts and this may lead to unrestricted behaviors.

EPIDEMIOLOGY

Approximately 5% of the world's population (i.e. 200 million people) uses illicit drugs and approximately 14 million of them inject drugs[6]. Drug abuse is a problem is both high- and low-income countries (Table 89.2; Fig. 89.1), and in 2009–2010, the United Nations Office of Drugs and Crime estimated that 2.8–4.5% of the global population (ages 15–64 years) misused cannabis, followed by amphetamines (0.3–1.3%)

SELF-REPORTED ALCOHOL AND ILLICIT DRUG USE AMONG HIGH SCHOOL SENIORS IN THE US (2008)

Drug	Use within the past year (%)
Alcohol	65
Marijuana	32
Opiates (other than heroin)	9
Stimulants	7
Tranquilizers	6
Hallucinogens	6
Sedatives	6
Cocaine	4
Inhalants	4
Anabolic steroids	1.5
Heroin	0.7

Table 89.2 Self-reported alcohol and illicit drug use among high school seniors in the US (2008). *From the US Department of Justice, Bureau of Justice Statistics (http://bjs.ojp.usdoj.gov/content/dcf/du.cfm).*

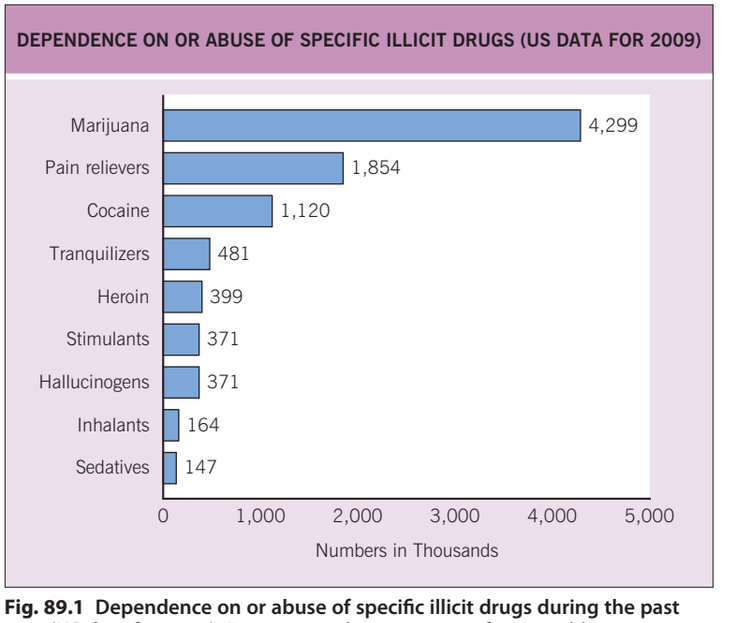


Fig. 89.1 Dependence on or abuse of specific illicit drugs during the past year (US data for 2009). Estimates in those 12 years of age or older. Hallucinogens include ectasy, lysergic acid (LSD) and phencyclidine (PCP). *Results from the 2009 National Survey on Drug Use and Health: Volume I. Summary of National Findings, U.S. Department of Health and Human Services Substance Abuse and Mental Health Services Administration Office of Applied Studies. www.oas.samhsa.gov/NSDUH/2k9NSDUH/2k9results.htm.*

Fig. 89.2 Injection sites ("skin tracks") in an intravenous drug user. There is overlying hyperpigmentation and scarring of veins due to inflammation from repeated non-sterile injections as well as injections of irritating drugs and adulterants.

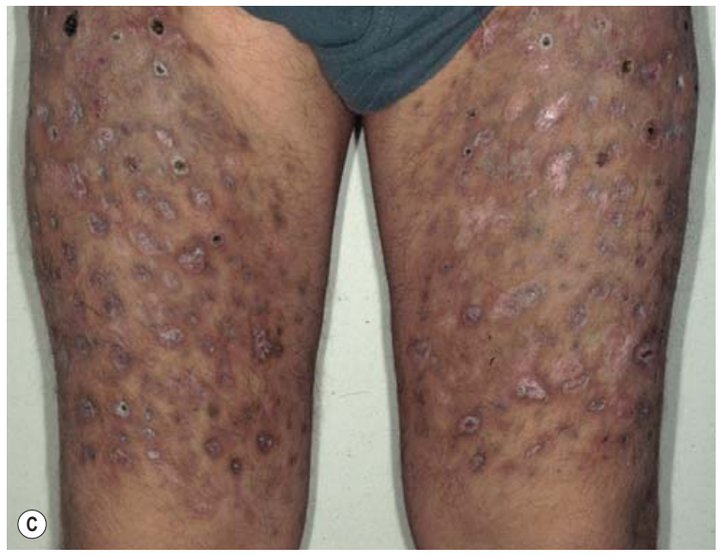


Fig. 89.3 "Skin popping" scars. A–C Multiple circular depressed scars, some with rims of postinflammatory hyperpigmentation, admixed with circular hemorrhagic crusts overlying ulcerations. Cocaine was injected into the thighs.

and opioids (0.5–0.8%)[3]. According to the National Survey on Drug Use and Health, in 2009, an estimated 21.8 million Americans 12 years of age or older were current (during the past month) illicit drug users.

CLINICAL FEATURES

Scars

Intravenous drug users have a number of recognizable stigmata, which identify their habit to anyone with experience in illicit drug use[7]. The most prominent of these are "skin tracks", which represent overlying hyperpigmentation and scarring of veins due to inflammation from repeated non-sterile injections as well as injections of irritating drugs and adulterants (Fig. 89.2). Early lesions in intravenous drug users consist of trails of punctures, crusted lesions and ecchymoses along the veins of an extremity[5]. Usually, the veins of the arms are initially used for injection, and when these become scarred, drug is injected into the vessels of the hand, digits, wrist, lower extremities, neck, axillae and eventually into any visible vein or palpable artery[7]. Increasingly, parenteral drug users are injecting themselves in the legs, feet and groin in order to avoid the presence of scars on exposed parts of the body which can persist for years.

Tissue injury also occurs from intradermal or subcutaneous injections and from accidental extravasation after intended injection into veins[5]. Drugs are injected subcutaneously and intradermally when patent vessels cannot be found. The resulting "skin popping" scars are depressed, irregular, circular and often dyschromic (Fig. 89.3). In some users, indurated, hypertrophic or keloidal scars form at these sites[7]. Drug users who cannot find intact veins may also rub powdered drugs into lacerations created with razor blades or knives.

Adulterants such as lactose, mannitol, dextrose, baking soda and flour are used to dilute ("cut") heroin and other powder drugs[7]. Many adulterants, especially quinine and dextrose, are highly sclerosing and more damaging to tissue than pure heroin[1]. Quinine is a popular adulterant because it has a bitter taste similar to heroin and it accentuates the narcotic euphoria. It is destructive to lymphatics and repeated injections can lead to chronic, non-pitting hand edema. More recently, levamisole-adulterated cocaine has been associated with the development of retiform purpura and cutaneous necrosis (see below).

The risk of thrombophlebitis and skin necrosis from injections of propoxyphene is so high that even the most determined addict ceases use of the drug after only a few weeks (Table 89.3)[5]. Highly vasoconstrictive, cocaine produces tissue ischemia, especially when extravasated. In fact, skin and muscle infarction have developed after inhalation of freebase cocaine. Due to their alkalinity, barbiturates, when injected into the skin, cause tender, erythematous, indurated plaques, which break down into deep ulcers and frequently become infected. Injection of the antihistamine tripelennamine, usually injected in combination with pentazocine or another opioid, also induces tissue necrosis and ulceration. Pentazocine injection may cause brawny, sclerodermatous skin thickening and large, irregularly shaped, deeply penetrating ulcers that may extend to muscle and then heal with significant atrophy (Fig. 89.4)[8]. Pentazocine-related cutaneous sclerosis develops more commonly in addicts with diabetes mellitus[8].

CUTANEOUS SIGNS OF DRUG ABUSE		
Lesion type	**Route(s)/associated drug(s)**	**Other associated signs**
Skin tracks	IV	Lymphedema
Skin popping scars	sc or dermal	Lymphedema
Ulcerations	IV/propoxyphene IV/cocaine sc/barbiturates sc, IM/pentazocine (± tripelennamine)	Circumferential pigmented bands (IV administration)
Retiform purpura with ulceration	Snorting, IV/cocaine adulterated with levamisole Smoking/crack cocaine adulterated with levamisole	Neutropenia
Sclerosis	sc, IM/pentazocine sc/barbiturates sc/cocaine	
Palmar and digital hyperkeratosis	Smoking/crack cocaine	Madarosis Linear and circular black plaques on the fingers and palms Cuts and blisters on the lips
Nasal verrucae	Snorting/cocaine or heroin	Nasal irritation Septal perforation
Pseudoaneurysm	Arterial injection	Petechiae/purpura Reduced peripheral pulses
Cellulitis	IV, sc, intradermal	Osteomyelitis and pyogenic arthritis
Cutaneous *Pseudomonas* infection	IV, sc, intradermal/heroin sc/pentazocine ± tripelennamine	Folliculitis
Wound botulism (*Clostridium botulinum*, especially type A)	IM, sc/black tar heroin or quinine-adulterated heroin	Lymphedema Skin popping scars
Excoriations & self-induced ulcers	Methamphetamine	Dry leathery skin Red dry nose Dental caries/loss of teeth Weight loss Paranoia
Formication or delusions of parasitosis	Cocaine Methamphetamine	
Pruritus	Heroin Cocaine (chronic) Methamphetamine	With heroin: Flushing Pseudoacanthosis nigricans
Papulopustular acneiform eruption	MDMA (ecstasy)	
Acne vulgaris	Anabolic steroids Methamphetamine Marijuana	Coarse skin Hirsutism Male and female pattern alopecia Increased hair growth in women Gynecomastia (in men) Testicular atrophy Clitoral enlargement Excoriations
Perinasal and perioral irritant dermatitis	Sniffing of volatile solvents and inhalants	

Table 89.3 Cutaneous signs of drug abuse. IM, intramuscular; IV, intravenous; MDMA, methylenedioxymethamphetamine; sc, subcutaneous.

Fibrous myopathy, joint restriction, muscle contractures, brachial plexus neuropathy, inflexible ankylosis and suppurative tenosynovitis are musculoskeletal and neurologic complications from intracutaneous and intravenous injections[1].

Bacterial Infections

Unless they participate in needle exchange programs, hardcore parenteral drug users rarely use sterile techniques and they may share needles, which predisposes them to frequent infections (Table 89.4). Skin and soft tissue infections are the most common diseases for which drug addicts seek healthcare or are hospitalized[9–11]. Among 127 intravenous drug users, 41% developed cellulitis, 32% an abscess with cellulitis, 16% an abscess alone, 10% infected skin ulcers, 7% necrotizing fasciitis and 5.5% septic phlebitis with cellulitis[11]. The most common presentation of cellulitis is an erythematous, tender, warm, edematous, indurated plaque (Fig. 89.5); however, only tenderness and edema may be apparent initially, and in more darkly pigmented skin, erythema may be difficult to appreciate. In contrast to the general population, cellulitis more frequently involves the upper extremity.

Lymphangitis associated with skin infection is common. In addition, underlying osteomyelitis and septic arthritis should be considered in cutaneous infections associated with injections. In some reports, up to one-third of hospitalized addicts with skin and soft tissue infections have an associated culture-proven bacteremia[7,11]. In a smaller subset, bacterial endocarditis develops, which is the most common systemic bacterial infection in intravenous drug users and accounts for 5% to 8% of hospitalizations[12] (see the discussion below).

The flora spectrum of street heroin does not correlate with the spectrum of bacteria causing infections in intravenous drug users[13]. Cellulitis is most frequently caused by *Staphylococcus aureus* and less often by streptococci (commensal flora)[11,12]. However, bacterial cultures and sensitivity testing are indicated in order to identify those cutaneous infections due to methicillin-resistant *Staphylococcus aureus* (MRSA), Gram-negative bacteria, anaerobes or unusual organisms and to determine the most effective antibiotic regimen[13]. The combination of

Fig. 89.4 Atrophic depressions of the thighs and extensive calcification from multiple pentazocine injections.

Fig. 89.5 Cellulitis of the lower extremity in an intravenous drug user.

INFECTIOUS COMPLICATIONS OF DRUG ABUSE	
Type of infection	**Organisms and/or associated features**
	BACTERIAL
Abscesses and cellulitis	• *Staphylococcus aureus* > *Streptococcus* spp. > Gram-negative bacilli, anaerobes • Often polymicrobial • Lymphangitis is common • *Clostridium* infection (e.g. *C. botulinum* type A) with adulterated heroin (e.g. black tar skin popping) • *Pseudomonas aeruginosa* with pentazocine ± tripelennamine or heroin injections • *Eikenella corrodens* with methylphenidate injections (esp. into the femoral triangle)
Necrotizing fasciitis	• Polymicrobial in 60–85% of cases • Includes anaerobes in ~10%
Pyomyositis	
Septic thrombophlebitis	• Associated with endocarditis or pulmonary emboli
Septic arthritis	• Increased likelihood of Gram-negative bacilli (esp. *Pseudomonas* spp.)
Osteomyelitis	• In *Pott's puffy tumor*, frontal sinusitis leads to frontal bone osteomyelitis and a subgaleal abscess; may be complicated by an epidural abscess
Endocarditis	• *S. aureus* > *Streptococcus viridans* > Gram-negative (esp. *Pseudomonas* spp.), polymicrobial • Often right-sided (e.g. tricuspid valve)
	FUNGAL
Candidiasis	• Disseminated candidiasis with pustular folliculitis; associated with injections of brown heroin • Septic arthritis, osteomyelitis, endocarditis (*C. parapsilosis, C. tropicalis*), septicemia ("fungemia syndrome")
Aspergillosis	• Pulmonary infections from contaminated marijuana • Dissemination and endocarditis may occur
Zygomycosis	• Cellulitic plaques or necrotic abscesses
	VIRAL
Hepatitis	• Hepatitis B viral infection may be associated with immune complex disease (e.g. arthritis, urticarial vasculitis) during the period of antigenemia • Syringe/needle sharing accounts for more than half of new cases of hepatitis C in the US
HIV	

Table 89.4 Infectious complications of drug abuse.

tripelennamine and pentazocine may promote the selective survival of *Pseudomonas aeruginosa*, and the use of quinine to adulterate heroin appears to predispose to *Clostridium* infection.

Wound botulism due to *Clostridium botulinum* type A occurs almost exclusively in drug addicts[14]. This particular infection is associated with parenteral injection, especially skin popping of black tar heroin, a form that derives its color from impurities during its manufacture and from adulterants. Black tar heroin is very hygroscopic and has a high water content, which supports the growth of organisms[15]. *C. sordelli* infection can present as toxic shock syndrome and *C. novyi* type A was responsible for an outbreak of severe infection with a high mortality rate in drug users who injected heroin extravascularly[16,17].

The spores of *C. botulinum* are not destroyed by heating the contaminated heroin and are inoculated into the subcutaneous tissue, where they germinate and produce toxin[15]. In the early stages, there is usually pain, tenderness and swelling, but a cellulitis or abscess may not be apparent. In cocaine snorters, the intranasal septum or paranasal sinuses may become infected. Botulism causes acute, usually descending and symmetric, flaccid paralysis with ophthalmoplegia, ptosis or other cranial nerve dysfunction. The diagnosis is supported by conventional electromyography. Treatment consists of high-dose penicillin, antitoxin and respiratory support.

In addition to injecting frequently and using non-sterile techniques (e.g. dirty needles), there are additional risk factors for the development of abscesses, including "skin popping", injecting speedballs (a mixture of cocaine and heroin that can induce ischemia within soft tissues)[18], HIV infection and "booting" (repeatedly flushing and pulling back during injection)[18a,18b]. Abscesses from subcutaneous drug injection are often multilobulated, deep and have extensive necrosis, requiring exploration and debridement. Superficial abscesses often rupture spontaneously, leaving punched-out ulcers. A single pathogen is cultured in over 50% of cases, and more than one organism is present in 33% to 45%[11]. Fever and leukocytosis are not particularly reliable measures of severity, as they are absent in 50% and 57% of cases, respectively[11]. Any type of bacteria may be cultured from these abscesses, but the more common are *Staphylococcus aureus* (20–60%), *Streptococcus* spp. (25%) and Gram-negative bacilli (up to 25%). Anaerobic bacteria are common as well, especially in polymicrobial infections. In one study, anaerobic bacteria were recovered from two-thirds of abscesses, and in one-third of these, they were the only cultured organism[19]. *Eikenella corrodens*,

an oral flora bacterium, has been cultured from some abscesses caused by injections of methylphenidate. Curiously, some abscesses develop months after a patient has ceased use of drugs.

Abscesses may be contiguous with underlying bone in the setting of associated osteomyelitis. In intravenous drug users, acute or chronic osteomyelitis develops from contiguous infection in surrounding soft tissue, hematogenous seeding of bacteria, or direct penetrating trauma from needles. The presence of osteomyelitis should be considered in anyone with continued pain after treatment of a soft tissue infection or with soft tissue infections that recur or respond slowly to appropriate treatment with antibiotics. Occasionally, septic arthritis can develop via these same mechanisms and may involve more unusual sites, e.g. the sternoclavicular joint in those who "shoot the pocket" (jugular vein)[20,20a].

Cervical abscesses usually occur in the anterior cervical triangle, and may cause life-threatening complications such as mediastinitis, pneumomediastinum, airway obstruction, internal jugular vein thrombosis, and extension into the carotid sheath. Abscesses in the groin may present with only tenderness and edema. These abscesses can be deep and extensive, especially if they originate in the femoral triangle. In general, the degree of pain usually exceeds that anticipated from the clinical findings.

MRI is superior to CT imaging in detecting the presence of fluid and purulent collections in skin, joints or tendon sheaths, but both are valuable in confirming the presence of deep and groin abscesses[21]. Sinography can be employed to delineate the extent of an abscess cavity or fistula. It is crucial to be aware that necrotizing fasciitis with or without myositis can present as erythema (77%), fluctuance (20%), edema (20%) or induration (43%), clinically resembling a non-fluctuant abscess yet requiring extensive subfascial debridement[22]. Fever and leukocytosis are often present. In some cases, only swelling or subtle cellulitis is apparent. However, severe pain, disproportionate to the physical findings, is present in 94% of cases[23]. If this complaint is disregarded or misinterpreted as a request for narcotics, the outcome can be devastating.

Notably, the classic cutaneous findings of necrotizing fasciitis, such as bullae (noted in 3% of patients), tissue crepitance (3%) and skin necrosis (10%), are usually absent, and only present in a small minority of patients[22]. For this reason, surgical exploration is mandatory in any parenteral drug user with cellulitis and unexplained severe pain[24]. Any necrotic tissue should be debrided surgically (Fig. 89.6), as the infection will progress in 75% of patients treated with only parenteral antibiotics[24]. Multiple organisms are cultured in 60% to 85% of cases, including anaerobes in 12% of patients. The presence of gas is not pathognomonic for *Clostridium* infection, as gas gangrene can also (but infrequently) be caused by other bacteria (e.g. usually mixed infections with *Enterococcus faecalis*, *Escherichia coli*, group G *Streptococcus*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Citrobacter diversus*, *Bacteroides bivius*, *Peptostreptococcus asaccharolyticus* or *Morganella morganii*).

Fig. 89.6 Necrotizing fasciitis of the upper extremity with extensive tissue necrosis in an intravenous drug user. Surgical debridement has been performed.

Fungal Infections

Dermatophytosis is very common in addicts. Disseminated candidiasis associated with injections of brown heroin was reported in the 1980s and found to be caused by an overgrowth of yeast in the lemon juice used to dissolve the heroin[25]. Initially, patients developed high fevers, rigors, headaches, myalgias and occasionally jaundice, but, at this stage, blood and urine cultures rarely demonstrated organisms. Usually after a week or so, up to 90% of the patients developed pustular folliculitis and painful nodules in hair-bearing areas (scalp, moustache and beard)[25]. The lesions resembled bacterial folliculitis but potassium hydroxide examination and lesional biopsy specimens demonstrated the presence of yeast. Other complications included ocular disease (chorioretinitis, uveitis, endophthalmitis, episcleritis), monoarthritis, painful costal osteochondritis and pleuritis[25].

Intravenous drug use is also a predisposing factor for zygomycosis. The characteristic cutaneous lesion is a cellulitic plaque or abscess with extensive necrotic tissue.

Granulomas

Injection of hydrous magnesium silicate (talc) or starch can produce granulomatous responses (Fig. 89.7) in the walls of veins as well as in the deep dermis and subcutaneous tissue, resulting in the formation of

Fig. 89.7 Foreign body granuloma formation leading to papules at the sites of injection of adulterated heroin.

firm, movable cutaneous nodules[26] (see Ch. 94). Talc is the main ingredient in some of the narcotic tablets that are crushed, diluted in liquid, and then injected. Talc granulomas may also develop in the lungs, liver, lymph nodes, spleen and bone marrow. Granulomas may not appear for up to 50 years after subcutaneous injection, because it is the conversion of silica to its colloidal form that stimulates the formation of granulomas[26]. When the inflammatory nodules ulcerate, they can heal with epidermal pigmentary changes, woody induration of the dermis and subcutaneous tissue, and retracted cicatrices.

Mucous Membrane Lesions

Snorting cocaine causes erythema of the nasal mucosa, nasal irritation, anosmia and rhinitis, and may lead to epistaxis, perforation of the nasal

Fig. 89.8 Tooth decay is a common physical finding in hardcore drug addicts (arrow). The term "meth mouth" is applied to those who abuse methamphetamines.

Fig. 89.9 Multiple excoriations in a cocaine addict. The patient felt "crawling" of his skin.

septum and osteolytic sinusitis. Nasal verrucae (snorters' warts) can also erupt in cocaine users. Less often, sniffing heroin causes these findings. A complex consisting of nasal collapse, septal perforation, palatal retraction and pharyngeal wall ulceration has been described in cocaine snorters. Cuts and blisters on the lips from glass or metal smoking pipes have been noted in addicts who smoke crack cocaine, while ageusia, halitosis and repeated lip smacking are additional signs of cocaine abuse. The labial mucosa may become dry in heroin or amphetamine users[7] and amphetamine use may also cause dysgeusia and xerostomia. There are reports of men applying cocaine powder on their glans penis to postpone ejaculation and of women rubbing cocaine on their genitals to enhance pleasure. These practices can lead to priapism, irritant dermatitis and even ulcerations. Penile ulcers have also developed after injections of heroin into the shaft veins.

Hardcore drug users frequently have marked dental and gingival disease due to poor hygiene (Fig. 89.8). Betel palm seeds (betel nuts) contain a narcotic stimulant and habitual chewing of these nuts, a practice in some areas of Southeast Asia, stains the teeth and is associated with the development of oral leukoplakia and submucosal fibrosis. The addictive habit of chewing *Catha edulis* tree leaves, which contain the narcotic Qat, is popular in several African and Middle Eastern countries and produces oral keratotic white plaques in approximately 20% of users.

Red or "bloodshot" eyes due to conjunctival vascular injection occurs with marijuana and sometimes with cocaine or phencyclidine (PCP) use. Repeated sniffing of volatile solvents and inhalants, such as butane gas, paint thinner, aerosol sprays, cleaning fluids and glues, can cause nasal, labial, perioral and perinasal irritant dermatitis (sniffer's rash). The skin lesions may be discrete papules or erosions that are often confused with acne.

Burns

Burns are common in addicts with an altered state of mind, including burns from lit matches, cigarettes, paraphernalia, and contact with fire during cooking. Cigarette burns typically occur on the digits and sternum as the cigarette was being held or smoked prior to loss of consciousness[7]. The necklace sign is produced by cigarette ashes, which fall on the neck when the smoking addict falls asleep. Singeing of the eyelashes and eyebrows, resulting in madarosis, may be caused by rising hot vapors during the smoking of crack cocaine. Crack addicts may also have linear or circular black plaques on the fingers and palms.

Ulcers

As has been previously described, ulcers can be caused by direct drug-related cutaneous, deep tissue or vascular injury, by accidental or incidental trauma, or by infection. When other venous accesses have been exhausted, drug users may attempt to inexorably maintain the granulation tissue of the ulcer (with its rich vascular network of capillaries) for injection of heroin or other drugs, resulting in chronic non-healing ulcers called "shooter's patches"[27].

Formication

Prolonged use of cocaine may lead to the development of formication, tactile hallucinations during which the patients sense that insects are crawling on or under their skin ("coke bugs")[5]. Repetitive, stereotypical skin picking leading to excoriations and disfiguring skin ulcers on the face and extremities is a common finding in methamphetamine abusers. Not uncommonly, these individuals also feel that bugs are crawling under their skin, and cocaine or crystal methamphetamine use should be considered in anyone who presents with delusions of parasitosis as well as neurotic excoriations (Fig. 89.9). Other signs of methamphetamine abuse are dry skin, pruritus with lichenification, unpleasant body odor, a red dry nose, sweating, premature aging, rotting teeth, aggressive behavior and paranoia. Acne, especially the excoriée type, has been described.

Additional Cutaneous Findings

Circumferential, pigmented bands due to pressure from tourniquets are common in intravenous drug users with darkly pigmented skin. "Soot tattoos" are produced by injections of residual carbon on the needle after flaming[5]. Self-induced tattoos have been considered a sign of drug abuse; however, the current popularity of tattoos and their pervasive presence in persons with present or past connections to street gangs have diminished the reliability of this sign[5]. Hyperkeratosis of the fingers and palms is common in heavy users of crack cocaine. Traumatic bullae at the site of injection are occasionally observed. Pressure erythema, bullae and ulcers develop in comatose patients after an overdose with barbiturates or other sedative drugs (Fig. 89.10) (see Ch. 35).

The combination of chronic cocaine use coupled with marijuana inhalation often leads to very pruritic skin. Also, the feeling of euphoria induced by heroin is frequently accompanied by skin flushing and itching, as well as a dry mouth, watery eyes and rhinorrhea. Generalized or focal, especially genital, itching during the euphoric stage following heroin administration has been named "high pruritus".

Fig. 89.10 Coma bulla. Large bulla with subsequent erosion on the medial ankle due to prolonged coma from barbiturate overdose.

Hyperhidrosis is a common adverse effect of amphetamines or LSD. Within 30 to 90 minutes of LSD ingestion, the user feels a wide range of emotions, accompanied by sweating, increased body temperature, dry mouth, tremors and dilated pupils. Piloerection, paresthesias and flushing are manifestations of the somatic phase of LSD intoxication, while pseudohallucinations and synesthesias occur during the perceptual phase. Delusions and visual hallucinations occur at higher doses. Hypoesthesia is a common manifestation of low-dose exposure to PCP.

There have been scattered reports in habitual MDMA (ecstasy) users of a papulopustular (acneiform) facial eruption, which may indicate a higher risk of severe adverse effects, such as hepatic damage. In some cases, the eruption responded to topical metronidazole[28]. Acne and other skin eruptions are anecdotally worsened by cannabis. Acne ranging from mild to cystic, especially on the trunk, is common among users of anabolic steroids. Other cutaneous effects of anabolic steroid abuse include oily hair and skin, male and female pattern alopecia, hirsutism in women and coarse skin (see Table 89.3). Most are reversible if the abuser stops taking the drugs, but some are permanent.

Drug-Induced Reactions

As expected, hypersensitivity reactions to drugs, especially morbilliform eruptions, urticaria (opiates, barbiturates, amphetamines, marijuana), bullous eruptions, fixed drug reactions, small vessel vasculitis, Stevens–Johnson syndrome and toxic epidermal necrolysis occur more frequently in illicit drug users than in the general population (Table 89.5). In one study, dermatographism was found in a quarter of patients comatose from a drug overdose. Angioedema due to barbiturates and heroin can cause eyelid as well as labial edema. Pigmented circular patches on the skin and mucous membranes may be extensive in addicts with fixed drug eruptions.

Vascular Lesions

The most common vascular lesions are ecchymoses and even hematomas over injected vessels. Petechiae may form distal to the placement of a tourniquet. *Vascular compromise* of the hands is common and is characterized by discoloration, edema and a cold temperature. Intense burning pain is often experienced after self-administered intra-arterial injection of drugs. This is followed within hours by edema of the affected limb. Although the peripheral pulses usually remain strong, cyanosis and patches of livedo reticularis can develop followed by distal ischemia and even necrosis. Ischemia and ulceration can appear after intra-arterial injection of a number of drugs, including temazepam (as high as 100% when injected into the radial artery), barbiturates, cocaine, heroin, pentazocine, diazepam, amphetamine and sodium thiopental[13]. Other manifestations reported after accidental or intentional drug

DRUG-INDUCED CUTANEOUS REACTIONS					
	Opiates	**Barbiturates**	**Amphetamines**	**Cocaine**	**Marijuana**
Morbilliform eruption	✓	✓	✓		✓
Bullous eruption	✓	✓		✓	
Fixed drug eruption	✓	✓	✓		
Small vessel vasculitis	✓	✓	✓	✓	
Stevens–Johnson syndrome	✓	✓		✓	
Toxic epidermal necrolysis	✓	✓			
Urticaria	✓	✓	✓	✓	✓
Acute generalized exanthematous pustulosis	✓*			✓*	✓*
Vasculopathy with retiform purpura				✓†	

*Isolated case reports.
†Levamisole-adulterated.

Table 89.5 Drug-induced cutaneous reactions.

injections into the radial artery include purpuric and pustular nodules, presumably as a result of embolization, as well as palmar cyanosis and edema with or without ulceration.

Septic thrombophlebitis results in tender, swollen extremities with or without erythema. A tender cord may be present when the affected vein is superficial, but deep vein thrombophlebitis is easily misdiagnosed as cellulitis or an abscess, either of which may be an associated complication. Deep vein thromboses are diagnosed via Doppler ultrasonography.

Pseudoaneurysms result from infected injuries to arteries (arterial wall or perivascular tissue) during intra-arterial injection of drugs ("hitting the pinkie"). They are most commonly seen in the groin, followed by the extremities, with the close proximity of the femoral artery to the femoral vein one possible explanation for those arterial injections that are inadvertent[29]. The typical lesion is a tender, diffusely indurated, pulsatile mass with an associated bruit (50–60% of cases) and decreased peripheral pulses (25%). Local suppuration and petechiae and purpura are often present. Half will resolve with antibiotics alone, but expanding lesions require proximal ligation of the vessel, resection of the pseudoaneurysm, and appropriate drainage. Otherwise, there is a risk of rupture due to necrosis. Mycotic aneurysms also occur in 15–25% of patients with infective endocarditis, most frequently in the femoral artery.

Infective endocarditis should be excluded in all injection-drug users with bacteremia. It is most commonly due to *S. aureus* and the tricuspid valve is involved in 70% of patients. Symptoms may include cough, dyspnea, fever and pleuritic chest pain. The mortality rate is <5%, but can be higher in HIV-infected individuals[30,31]. When left-sided, complications include brain and splenic abscesses due to septic emboli. Infective endocarditis associated with injection-drug use is also one of the rare settings in which polymicrobial endocarditis is encountered[20,30,31].

In addition to arterial disease (see above), cocaine can produce *superficial or deep venous thromboses*. Treatment consists of parenterally administered antibiotics, bed rest, elevation of any involved extremity, and anticoagulation; however, care must be taken to exclude a mycotic aneurysm, which can bleed, especially in the setting of anticoagulation. Distal thrombosis with extensive infarctive thigh lesions and associated hepatitis and glomerulonephritis has been reported with cocaine use, as has aortic thrombosis or dissection, acute arterial insufficiency and intestinal ischemia[29]. Most recently, levamisole-adulterated cocaine has been associated with the development of neutropenia and retiform purpura that can become necrotic (Fig. 89.11)[32–34]. Histologic examination demonstrates microvascular thromboses within the dermis, sometimes accompanied by leukocytoclastic vasculitis. Patients may also have antineutrophil cytoplasmic antibodies, decreased levels of protein C and S, or anti-phospholipid antibodies. Of note, levamisole can be detected in the serum, urine or crack pipes.

Arteriovenous fistula-associated angiomatoid nodules (pseudo-Kaposi sarcoma) in a patient with hepatitis B viral infection was reported as a possible complication of heroin use[35]. In addition, palpable purpura and tender nodules may appear as cutaneous manifestations of small and medium-sized vessel vasculitis due to hepatitis B or C viral infections or specific drugs. Repeated vascular injury and infection of the digits can cause irreversible contractures (camptodactyly) that resemble Dupuytren's disease.

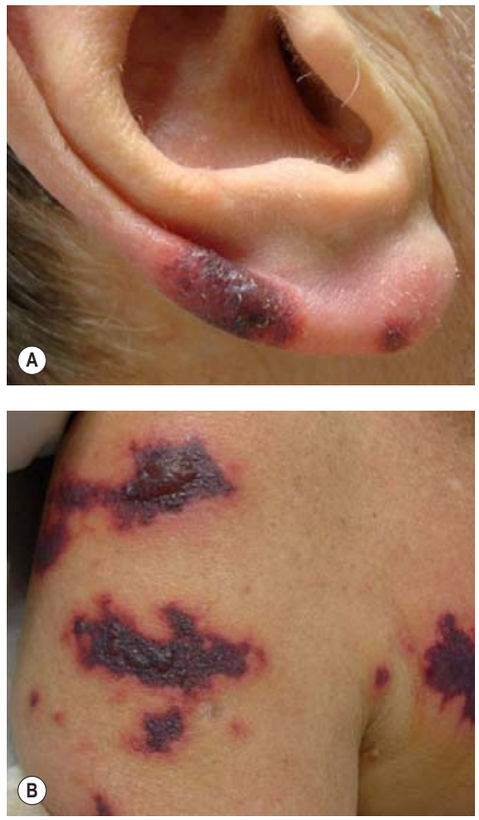


Fig. 89.11 Retiform purpura due to levamisole-adulterated cocaine. A, B The earlobe is a common site of involvement and purpuric lesions of the earlobe had been described previously as a side effect of levamisole. Up to 70% of the cocaine in the US at the time of writing contained levamisole but <3% of the heroin supply. *Courtesy, Jeffrey Callen, MD.*

Systemic Complications

Drug abuse may indirectly contribute to congenital cutaneous malformations and domestic violence (see Ch. 90). The estimated incidence of infective endocarditis (see above), a major cause of mortality in this population, is 1.5 to 3.3 cases per 1000 injection-drug users per year[20]. Several cutaneous signs (arterial emboli, conjunctival hemorrhages, splinter hemorrhages, Janeway lesions and Osler nodes) may be present. The prevalence of HIV infection among intravenous drug users with infectious endocarditis is very high, ranging from 45% to 90%. The US Centers for Disease Control and Prevention estimates that 55–60% of AIDS cases among women and one-third of overall AIDS cases in the US are linked to injection-drug use or sex with partners who inject drugs.

Parenteral drug users are also at high risk for contracting other bloodborne viruses such as hepatitis B and C and human T-lymphotrophic virus types 1 and 2 (HTLV-1, HTLV-2). Approximately 60% of all new cases of hepatitis C infections in the US are attributed to syringe and needle sharing with an infected individual. In some user populations, transmission of hepatitis C occurs so rapidly that within 6 months of beginning drug use, one-third of users are infected, and within 2 years, up to 90% have contracted the infection[36].

Drug addicts have high prevalences of all sexually transmitted diseases, due to multiple partners, prostitution and failure to use condoms. However, narcotic abuse is a common cause of false-positive non-treponemal syphilis screening tests (e.g. VDRL, RPR). In these cases, treponemal tests (e.g. MHA-TP, FTA-ABS) will be non-reactive. In addicts who have had syphilis, both types of tests will be positive, but the titers of the non-treponemal test may not decrease rapidly after treatment.

Cocaine may initiate scleroderma in susceptible individuals or unmask it at an earlier age in those with subclinical disease. However, the localized cutaneous induration induced by cocaine injections is reversible. Cases of Henoch–Schönlein purpura, polyarteritis nodosa and necrotizing angiitis with renal and pulmonary disease have been associated with the use of heroin. Nephrotic syndrome from amyloidosis has been reported in heroin skin poppers and intravenous drug users with chronically draining skin lesions[37].

TREATMENT

A detailed discussion of the management of drug addiction is beyond the scope of this chapter. Approaches are summarized in Table 89.6 and discussed elsewhere in the literature[38]. When providing care to persons suspected of drug addiction, it should be remembered that even admission of illicit drug use is difficult, as patients risk disapproval and overt or concealed rejection even from medical professionals.

The selection of antibiotics to treat skin infections should be guided by antibiotic sensitivities of the cultured organisms. With the emergence of community acquired MRSA, appropriate cultures of lesions and wounds have become more imperative than ever. Broad-spectrum antibiotic regimens that cover *S. aureus* should be prescribed until antibiotic sensitivity results are available. Treatment of cellulitis consists of splinting, limb elevation and intravenous antibiotics. Inclusion of vancomycin or linezolid (for MRSA) and clindamycin (for anaerobes) in the antibiotic regimen has been recommended for hand

TREATMENT OF DRUG ADDICTION	
Drug	**Treatments**
Opiates	• Drug detoxification – Office-based – Inpatient – Ultra-rapid under general anesthesia using naltrexone (plus clonidine, benzodiazepines and antiemetics) • Maintenance therapy – Agonist (methadone, levomethadyl*) – Partial agonist (long-acting buprenorphine) – Antagonist (naltrexone) • Pharmacologic therapy for withdrawal (e.g. clonidine, lofexidine, guanfacine) • Additional measures (counseling, psychotherapy, acupuncture)
Cocaine	• Drug rehabilitation • Anticonvulsants (e.g. topiramate, tiagabine), dopamine agonists/reuptake inhibitors† (e.g. amantadine, bromocriptine, pergolide, vanoxerine), antidepressants (e.g. bupropion), CNS stimulants (e.g. modafinil), $GABA_B$ receptor agonists (e.g. baclofen), N-acetylcysteine
Amphetamines	• Drug rehabilitation • Antidepressants (e.g. fluoxetine, imipramine, desipramine, mirtazapine), modafinil, antipsychotics (e.g. chlorpromazine, haloperidol, thioridazine)
*Withdrawn from the US market due to risk of cardiac arrhythmias. †To date, no statistical evidence of benefit for dopamine agonists.	

Table 89.6 Treatment of drug addiction. GABA, gamma-aminobutyric acid.

infections and should also be considered in infections that may result in loss of limb or life[13]. Hand infections must be aggressively treated, recognizing that amputation of the digits or the hand occurs in 10% of patients[13].

Even with surgical plus aggressive medical treatment, the mortality rate of necrotizing fasciitis in drug addicts is approximately 20% and limb amputation is necessary in another 18%[22]. A decrease in mortality from 27% to 7% was reported with a protocol consisting of aggressive diagnosis, intense intravenous broad-spectrum antimicrobial therapy, supportive care, early subfascial debridement, and follow-up debridement of the wound in 8 to 12 hours until no further necrotic tissue had formed. Between two and four debridements were required[23].

Skin grafting of large ulcers may be necessary when healing does not occur with compression and appropriate dressings. Some substance abusers may deliberately sabotage the skin graft by injecting through it or into the vacuum (VAC) dressing tubing[39]. Recovered parenteral drug users often wear long-sleeved shirts and other garments to hide the stigmata of their past addiction and may seek help in diminishing the appearance of these signs. Hypertrophic scars improve with intralesional injections of corticosteroids and pulsed dye laser treatments (see Ch. 98). Hyperpigmented scars require the use of pigment-specific lasers and bleaching agents, including hydroquinone. Tissue augmentation with hyaluronic acid or fat can improve the appearance of depressed scars. Such scars may also respond to low-fluency treatments with visible light lasers, which stimulate fibroblast proliferation.

REFERENCES

1. Del Giudice P. Cutaneous complications of intravenous drug abuse. Br J Dermatol. 2004;150:1–10.
2. Fischer C, Hatzidimitriou G, Wlos J, et al. Reorganization of ascending 5-HT axon projections in animals previously exposed to the recreational drug (+/–)3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). J Neurosci. 1995;15:5476–85.
3. Wareing M, Fisk JE, Murphy PN. Working memory deficits in current and previous users of MDMA ('ecstasy'). Br J Psychol. 2000;91:181–8.
4. Ducasse E, Chevalier J, Dasnoy D, et al. Popliteal artery entrapment associated with cannabis arteritis. Eur J Vasc Endovasc Surg. 2004;27:327–32.
5. Sim MG, Hulse G, Khong E. Injecting drug use and skin lesions. Aust Fam Phys. 2004;33:519–522.

5a. Brewer JD, Meves A, Bostwick JM, et al. Cocaine abuse: dermatologic manifestations and therapeutic approaches. J Am Acad Dermatol. 2008;59:483–7.

6. World Drug Report 2011. United Nations Office on Drugs and Crime. www.unodc.org/unodc/en/data-and-analysis/WDR-2011.html.
7. Burnett JW. Drug abuse. Cutis. 1992;49:307–308.
8. Furner BB. Parenteral pentazocine: cutaneous complications revisited. J Am Acad Dermatol. 1990;22:694–695.
9. Orangio GR, Pitlick SD, Della Latta P, et al. Soft tissue infections in parenteral drug abusers. Ann Surg. 1984;199:97–100.
10. White AG. Medical disorders in drug addicts: 200 consecutive admissions. J Am Med Assoc. 1973;223:1469–1471.
11. Hasan SB, Albu E, Gerst PH. Infectious complications in IV drug abusers. Infect Surg. 1988;7:218–232.
12. Tuazon CU, Sheagren JN. Staphylococcal endocarditis in parenteral drug abusers: source of the organism. Ann Intern Med. 1975;82:788–790.
13. Smith DJ Jr, Busuito MJ, Velanovich V, et al. Drug injection injuries of the upper extremity. Ann Plast Surg. 1989;22:19–24.
14. MacDonald KL, Cohen ML, Blake PA. The changing epidemiology of adult botulism in the United States. Am J Epidemiol. 1986;124:794–799.
15. Centers for Disease Control and Prevention (CDC). Wound botulism – California, 1995. MMWR Morb Mortal Wkly Rep. 1995;44:889–892.
16. Kimura AC, Higa JI, Levin RM, et al. Outbreak of necrotizing fasciitis due to *Clostridium sordelli* among black-tar heroin users. Clin Infect Dis. 2004;38:e87–91.
17. Update: *Clostridium novyi* and unexplained illness and death among injecting-drug users – Scotland, Ireland, and England. MMWR Morb Mortal Wkly Rep. 2000;49:543–5.
18. Murphy EL, DeVita D, Liu H, et al. Risk factors for skin and soft-tissue abscesses among injection drug users: a case-control study. Clin Infect Dis. 2001;33:35–40.

18a. Spijkerman IJ, van Ameijden EJ, Mientjes GH, et al. Human immunodeficiency virus infection and other risk factors for skin abscesses and endocarditis among injection drug users. J Clin Epidemiol. 1996;49:1149–54.

18b. Murphy EL, DeVita D, Liu H, et al. Risk factors for skin and soft-tissue abscesses among injection drug users: a case-control study. Clin Infect Dis. 2001;33:35–40.

19. Webb D, Thadepalli H. Skin and soft tissue polymicrobial infections from intravenous abuse of drugs. Western J Med. 1979;130:200–204.
20. Gordon RJ, Lowy FD. Bacterial infections in drug users. N Engl J Med. 2005;253:1945–1954.

20a. Stein MD. Medical complications of intravenous drug use. J Gen Intern Med. 1990;5:249–57.

21. Johnston C, Leogan MT. Imaging features of soft-tissue infections and other complications in drug users after direct subcutaneous infection ("skin popping"). AJR Am J Roentgenol. 2005;182:1195–1202.
22. Callahan TE, Schecter WP, Horn JK. Necrotizing soft tissue infection masquerading as cutaneous abscess following illicit drug injection. Arch Surg. 1998;133:812–818.
23. Sudarsky LA, Laschinger JC, Coppa GF, Spencer FC. Improved results from a standardized approach in treating patients with necrotizing fasciitis. Ann Surg. 1987;206:661–665.
24. Clark DD. Surgical management of infections and other complications resulting from drug abuse. Arch Surg. 1970;101:619–623.
25. Dupont B, Drouhet E. Cutaneous, ocular, and osteoarticular candidiasis in heroin addicts: new clinical and therapeutic aspects in 38 patients. J Infect Dis. 1985;152:577–591.
26. Posner DI, Guill MA III. Cutaneous foreign body granulomas associated with intravenous drug abuse. J Am Acad Dermatol. 1985;13:869–872.
27. Tice AD. An unusual, non-healing ulcer on the forearm. N Engl J Med. 2002;347:1725–1726.
28. Wollina U, Kammler HJ, Hasselbarth N, et al. Ecstasy pimples – a new facial dermatosis. Dermatology. 1998;197:171–173.
29. Coughlin PA, Mavor AL. Arterial consequences of recreational drug use. Eur J Vasc Endovasc Surg. 2006;32:389–96.
30. Hecht SR, Berger M. Right-sided endocarditis in intravenous drug users: prognostic features in 102 episodes. Ann Intern Med. 1992;117:560–6.
31. Levine DP, Crane LR, Zervos MJ. Bacteremia in narcotic addicts at the Detroit Medical Center. II. Infectious endocarditis: a prospective comparative study. Rev Infect Dis. 1986;8:374–96.
32. Waller JM, Feramisco JD, Alberta-Wszolek L, et al. Cocaine-associated retiform purpura and neutropenia: is levamisole the culprit? J Am Acad Dermatol. 2010;63:530–535.
33. Bradford M, Rosenberg B, Moreno J, Dumyati G. Bilateral necrosis of earlobes and cheeks: another complication of cocaine contaminated with levamisole. Ann Intern Med. 2010;152:758–759.
34. Walsh NM, Green PJ, Burlingame RW, et al. Cocaine-related retiform purpura: evidence to incriminate the adulterant, levamisole. J Cutan Pathol. 2010;37:1212–1219.
35. Fimiani M, Miracco C, Bianciardi S, Andreassi L. Pseudo-Kaposi's sarcoma in a drug addict. Int J Dermatol. 1986;25:651–652.
36. Garfein RS, Vlahov D, Galai N, et al. Viral infections in short-term injection drug users: the prevalence of the hepatitis C, hepatitis B, human immunodeficiency, and human T-lymphotropic viruses. Am J Public Health. 1996;86:655–661.
37. Neugarten J, Gallo GR, Buxbaum J, et al. Amyloidosis in subcutaneous heroin abusers ("skin poppers' amyloidosis"). Am J Med. 1986;81:635–640.
38. National Institute on Drug Abuse. Principles of Drug Addiction Treatment: A Research Based Guide. National Institutes of Health, Publication no. 00–4180, July 2000.
39. Williams AM, Southern SJ. Conflicts in the treatment of chronic ulcers in drug addict – case series and discussion. Br J Plast Surg. 2005;58:997–999.

Skin Signs of Abuse 90

Sharon S Raimer, Lauren Raimer-Goodman and Ben G Raimer

Chapter Contents

Child abuse 1521
Elder abuse 1525

Physical and psychological abuse are problems that may occur in any cultural environment. Although abuse is not limited to particular age groups, this chapter will focus on abuse inflicted upon children and elders – individuals who are often least able to defend themselves or escape their situation without recognition of the abuse by others.

CHILD ABUSE

Synonym: ■ Battered child syndrome

Key features

- Signs of physical abuse include: unexplained bruises; injuries of the thorax, abdomen, buttocks, genitals, chin, ears or neck; curvilinear marks; and cigarette burns or other well-demarcated burns
- Signs of sexual abuse include attenuation, fresh tears or scars of the hymen and/or the anal margin extending out onto perianal skin

Introduction

Child abuse is a term used to encompass the broad spectrum of non-accidental maltreatment of children, including physical, emotional and sexual abuse as well as neglect. Physical abuse is defined as a non-accidental injury of a child; the injury may be the result of a single abusive episode or occur over a longer period of time. Two out of every 100 infants under 1 year of age are victims of abuse or neglect[1]. In 2010, 11% of childhood injuries reported to the National Trauma Data Bank were due to intentional assault, and 6% of assault-related injuries resulted in death of the child[2]. Abused children are generally younger and more likely to sustain serious intracranial, thoracic and abdominal injuries than children who are injured accidentally[3]. Younger children are at greater risk because they are demanding, non-verbal and defenseless.

Parents may describe abused children as "difficult", which in fact may be true; however, the parents' attempts to intervene in an excessive and inappropriate manner constitute abuse. Premature infants, disabled children, and children with behavioral problems appear to be at increased risk of abuse. Parents who abuse their children were often themselves abused as children. They are frequently immature, dependent individuals who are socially isolated. Often, they do not handle stress well, and a personal or family crisis may trigger an abusive episode. It is important that all physicians recognize signs of physical abuse in children, as it tends to be repeated, and an intentionally injured child should be considered at high risk for the future occurrence of a severe physical injury.

Physical neglect is a failure to provide the necessities of life for a child, including nutrition, clothing, housing, medical care and a safe, supervised environment. Emotional abuse or neglect results when parents fail to provide a nurturing environment that permits the child to grow and reach his or her full potential.

Sexual abuse can be defined as engaging a child in a sexual activity that the child cannot comprehend, for which the child is developmentally unprepared and cannot give informed consent, and/or that violates the social and legal taboos of society[4]. The child's involvement may be coerced with physical threats, rewarded through bribes, or induced via misrepresentation of moral values. Sexual abuse can be assaultive or non-assaultive. Non-assaultive sexual abuse probably occurs frequently and often goes unreported since there is usually little or no physical injury to the child. Assaultive sexual abuse, on the other hand, is characterized by physical injury and violence. Both types of sexual abuse may result in severe emotional trauma to the child.

History

Maltreatment of children has always existed, but in 1946, Dr John Caffey, a pediatric radiologist, initiated medical concern about child abuse by reporting six children who presented with skeletal fractures and associated subdural hematomas that were clearly related to trauma[5]. The immense importance of this problem was not generally recognized until 1962, when Kempe et al.[6] coined the term *battered child syndrome*, the findings of which include inadequately explained signs of trauma, multiple fractures at different stages of healing, and/or failure to thrive that responds to either nutritional therapy or placing the child in an emotionally supportive environment.

Epidemiology

Child abuse is a worldwide problem that occurs among all ethnic and racial groups and in families of all socioeconomic and educational levels. In the US, single-parent families with incomes below 200% of the poverty threshold have much higher probabilities of violence[7]. Child abuse occurs more frequently when other problems such as unemployment, substance abuse, unplanned pregnancies or discord between parents increase the stress on individuals within the family. Boys are at greater risk for serious injury than are girls, and infant boys have the highest fatality rate[1].

The perpetrator of sexual abuse is often a person well known to the child, in most cases the natural father, followed in frequency by a stepfather or another close relative. Although reports of abuse are about three times more likely in girls than in boys[8], sexual abuse in boys may be more likely to go undetected and/or unreported. Epidemiologic studies have shown that the risk for sexual abuse rises during preadolescence[8]. Features related to family structure that have been associated with a small, but statistically significant, increase of sexual abuse are the presence of a stepfather in the household, children living without one or both of their natural parents, and children whose mothers are disabled, ill or extensively out of the home[8].

Clinical Features

Physical abuse

Physical abuse is frequently identified by *bruises* (ecchymoses) (Fig. 90.1) that may be located in areas not normally prone to accidental injury, most commonly the head and neck (particularly the face) followed by the buttocks, trunk and arms[9]. They often are large, multiple and occur in clusters. The shape of the bruises may help to identify the object with which the child was struck. Linear bruising is produced when an object such as a rod, stick or strap is used to strike a child. Hematomas and traumatic fractures of underlying bone may be present.

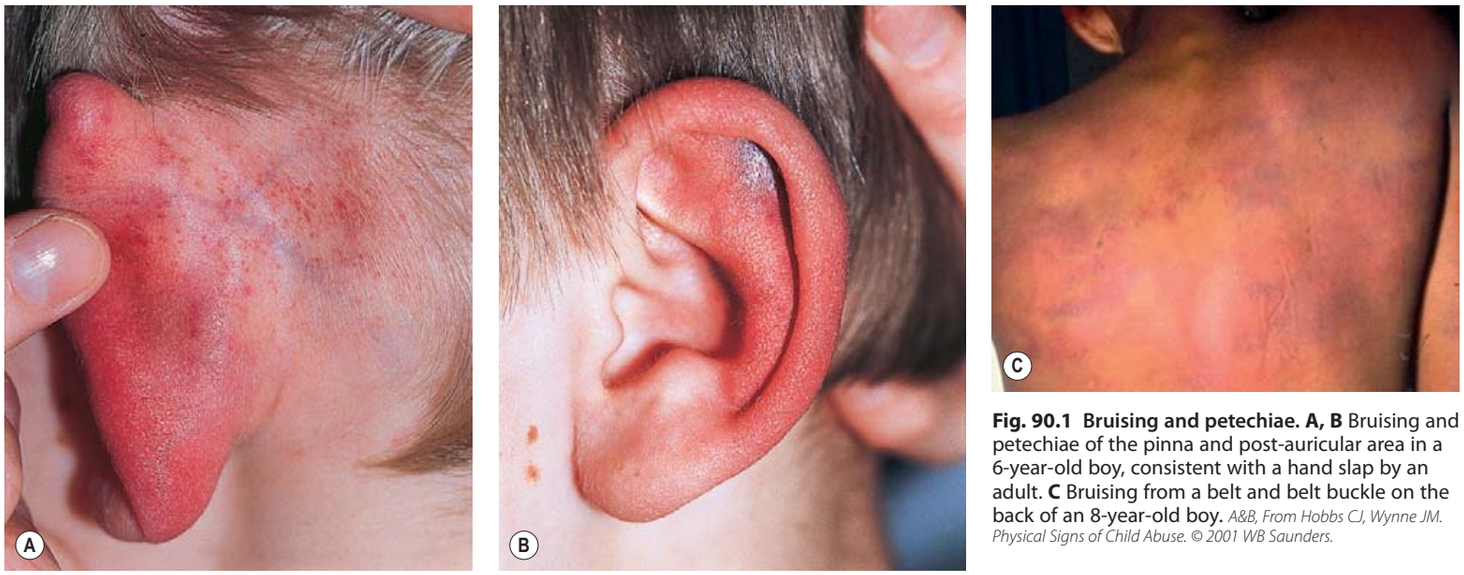


Fig. 90.1 Bruising and petechiae. A, B Bruising and petechiae of the pinna and post-auricular area in a 6-year-old boy, consistent with a hand slap by an adult. **C** Bruising from a belt and belt buckle on the back of an 8-year-old boy. *A&B, From Hobbs CJ, Wynne JM. Physical Signs of Child Abuse. © 2001 WB Saunders.*

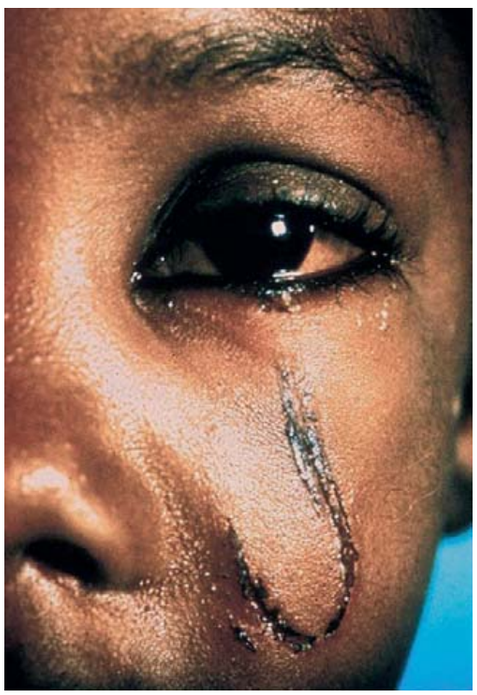


Fig. 90.2 Curvilinear mark on the cheek of a child from assault with an electric cord. A corneal abrasion was also present.

Fig. 90.3 Healing injury due to binding around the ankles.

Loop marks are perhaps the single most characteristic finding in child abuse (Fig. 90.2). Such curvilinear marks are produced by small ropes, cords, electrical cords or belts and appear randomly over the body as a result of striking a struggling child[10].

Buckle imprints from belts can often be matched to the particular belt buckle used to strike the child. Buckles produce deep ecchymoses (see Fig. 90.1C) and can result in injury to underlying organs and bones.

Pinch marks, particularly on the ears or in the genital region of boys, should alert the examining physician to the possibility of abuse. Male toddlers rarely sustain bruises on the genitalia secondary to a fall.

Blunt trauma can be a very severe form of abuse that may or may not result in cutaneous lesions. Blunt trauma to the abdomen can lead to severe injury or even death of a child. Soft intra-abdominal organs are injured when they are slammed against the vertebral column by a kick or severe blow delivered to the abdomen. Blunt trauma in the form of slapping injury causes capillaries to break between the digits, producing linear bruises that outline the fingers. This often leaves the imprint of a hand on the child's skin, which can frequently be matched to the perpetrator.

Binding injuries are more likely to occur when the perpetrator is emotionally disturbed or psychotic. Acute binding injuries cause edema of the soft tissue around the wrists and ankles that may resemble rope burns with redness and warmth or abrasions (Fig. 90.3). Chronic binding injuries may result in bands of postinflammatory hyperpigmentation.

Traumatic alopecia results from forcefully pulling out the scalp hair. The occipital region is the most common location. When a large tuft of hair is abruptly pulled out, the underlying scalp may hemorrhage with subsequent hematoma formation.

Human bite marks leave the indelible mark of the perpetrator and may serve to identify the abuser. Adult human bite marks, which can be identified by the width of the dental arch (>4 cm), must be distinguished from those of a child, since toddlers may be bitten by their peers. Human bites produce a crushing type of injury, whereas animal bites typically result in puncture wounds.

Thermal burns constitute an especially traumatic form of injury to the young child, and the abuser in such cases is likely to be suffering from a psychiatric disturbance. Cigarette burns represent a frequent form of thermal injury and tend to be randomly distributed (Fig. 90.4). Branding injuries take the shape of the heated object (Figs 90.5 & 90.6). Dunking scald injuries occur most often in infants and toddlers, and scalds on the buttocks may be associated with attempts to toilet train an infant. "Donut-type sparing" on the child's buttocks may be apparent when the buttocks are held against the cooler tub or basin while the surrounding hot water scalds the remaining immersed skin. Dunking scalds of the extremities leave a characteristic "stocking and

Fig. 90.4 Injury produced by a cigarette burn.

Fig. 90.5 Branding injury on the thigh from a fork.

Fig. 90.6 Burn injury from an iron.

Fig. 90.7 Burn injury due to dunking in hot water. Note the sharp line of demarcation of the burn on the arm (arrow).

glove" distribution with a very sharp demarcation of the burn (Fig. 90.7). In non-accidental burns, the adults responsible for the child (and possibly the burn) frequently claim not to have witnessed the burning incident, and other relatives commonly bring the child to the hospital[11]. A delay between the injury and seeking medical care often occurs with inflicted burns.

A child may present with skin signs of multiple types of physical abuse. Such a child may be severely injured at the time of presentation or, if not, should be considered at high risk for the future occurrence of a severe injury. Both acute and healing injuries are frequently present in chronically abused children.

Physical neglect

Physical neglect usually results in a constellation of relatively obvious findings, including signs of poor nutrition, hygiene and, at times, general health. Children may have old untreated injuries, dermatitis, and infestations of the skin and hair, and they typically have not received required childhood immunizations.

Emotional deprivation

Emotional neglect or deprivation accounts for at least one-half of the children in high-income countries placed under the pediatric diagnostic term *failure to thrive*. These children fail to grow and develop in their home environment despite adequate caloric intake, while they thrive with food and stimulation in a hospital setting or foster home. There are no characteristic physical findings or diagnostic laboratory tests for these children. The diagnosis can be rendered only after other potential causes of failure to thrive have been excluded, and it is usually confirmed when the child demonstrates "catch-up" growth and development outside the disturbed home environment.

PHYSICAL SIGNS OF CHILDHOOD SEXUAL ABUSE
DIAGNOSTIC
• Attenuation of the hymen with loss of tissue • Fresh tears or scars of the hymen • Anal margin extending out onto perianal skin
SUGGESTIVE
• Gaping hymenal opening • Notch or concavity in posterior half of hymen • Notch in anterior half of hymen (if asymmetric and associated with other abnormalities) • Anal fissures • Gaping of anal sphincter with mucosal prolapse • Laxity of anal sphincter with edema ("tire sign") • Dilated perianal veins • Reflex anal dilatation

Table 90.1 Physical signs of childhood sexual abuse.

Sexual abuse

The diagnosis of child sexual abuse is based on a combination of findings in the patient's history, physical examination and, when indicated, laboratory evaluation. Children rarely fabricate reports of sexual abuse, and any such description by a child should be thoroughly investigated. Unfortunately, false accusations by parents involved in custody disputes do occasionally occur and are a burden to the medical and legal systems.

Physical signs that are diagnostic or suggestive of childhood sexual abuse are described in Table 90.1. However, physical findings may be

absent following sexual abuse. Many types of sexual molestation, such as fondling and oral sodomy, do not usually leave physical signs. Even when mild or moderate injuries occur (e.g. petechiae, ecchymoses, abrasions, superficial lacerations), healing in the anogenital area often takes place within days, resulting in very subtle or undetectable physical findings[12,13]. Acute findings that should alert the physician to the possibility of abuse include fresh genital (Fig. 90.8) or anal injuries without an adequate explanation. In the absence of a history of trauma or severe constipation, anal fissures or scarring may be suggestive of abuse. Pierce[14] reported that among 50 children with a strong history of anal abuse, 41 (82%) had anal fissures or scars. In contrast, only 2 of 81 children with no history of sexual abuse had fissures and none had scars.

It is important to be aware of normal physical findings in the genital area of female children. Studies of newborn girls have noted that a hymen is invariably present and anterior hymenal clefts are common, but posterior clefts are not normally seen[12]. Anatomic features that are suggestive of penetration include narrowing of the posterior hymenal rim to less than 1 mm and complete hymenal clefts located between 4 and 8 o'clock[13]. The presence of semen (detected via testing for prostatic acid phosphatase) or sperm is indicative of abuse, and non-perinatally acquired syphilis, gonorrhea[12] or (if other modes of acquisition are also excluded) HIV infection confirms mucosal contact (most likely sexual) with infective bodily secretions. Perinatally acquired infections with *Chlamydia trachomatis* have been documented to persist as long as 28 months; therefore, infections with this organism in children younger than 3 years of age are not as suggestive of abuse.

Anogenital warts in children (see Ch. 79) may be perinatally acquired, transmitted during the routine care of children, autoinoculated from other sites of infection, or acquired as a result of sexual abuse. In most studies, proven abuse is uncommon in children with anogenital warts who are younger than 3 years of age[15].

Differential Diagnosis

Although it may be difficult to differentiate abuse from accidental injury in a child, the distribution of injuries is often helpful. Abused children have significantly more soft tissue injuries on the cheeks, trunk, genitalia and upper legs than accidentally injured children[9]. Labbe and Caouette[16] performed over 2000 skin examinations in 1467 normal children to determine the type and location of recent skin injuries. The majority of children over 9 months of age had at least one injury, usually a bruise, but 15 or more injuries was rare. The lower limbs were the most commonly involved sites. Less than 2% of the children had injuries to the thorax, abdomen, pelvis or buttocks, and less than 1% to the chin, ears or neck. Bruises were rare in infants who were not yet independently mobile. Therefore, injury in infants or in the locations mentioned above should arouse suspicion of the possibility of abuse.

There are several cutaneous disorders that can mimic child abuse (Table 90.2; Fig. 90.9). In addition, normal anatomic variants are sometimes mistaken for signs of childhood sexual abuse. For example, 25% of newborn girls have a white line (linea vestibularis) in the posterior vestibule that could be confused with scar tissue produced by sexual abuse. Other conditions that are occasionally misdiagnosed as sexual abuse are listed in Table 90.3.

Evaluation and Management

When any lesion suspicious for abuse is present, the entire cutaneous surface of the child as well as the oral, anal and genital mucosae should be examined. Child abuse should be suspected if parents lack an explanation for a child's injuries, relate circumstances not compatible with the physical findings, describe activities for which a child is developmentally incapable, give differing accounts or change their stories. A summary of recommended steps in the evaluation and management of suspected child abuse is provided in Table 90.4. Most countries (including the US) require physicians to report suspected physical abuse, neglect and sexual abuse of children. Legal protection is generally given to healthcare providers who make such reports in good faith.

When a child gives a history of sexual abuse or has physical findings highly suggestive of abuse, an immediate referral should be made to a child protective services agency. If the history and physical findings are less certain, it may be most appropriate for experienced medical personnel to make the decision of whether sexual abuse is likely and referral to child protective services is warranted, since the potential negative impact of misdiagnosis on the family structure is substantial[17]. Whenever feasible, any child suspected of being sexually abused should be examined by a pediatrician or gynecologist experienced in evaluating children for signs of abuse. Anogenital examination by multiple

Fig. 90.8 Multiple erosions and ulcerations in a child who was sexually abused. *Courtesy, Ronald P Rapini, MD.*

CONDITIONS THAT CAN MIMIC CHILD ABUSE

Condition	Comments
Bleeding into the skin (ecchymoses, purpura)	
• Multiple bruises due to platelet or clotting disorders	• Areas most commonly traumatized by children (e.g. shins, knees)
• Ehlers–Danlos syndrome, especially the vascular type (type IV)	• Common sites of trauma, especially shins
• Bruising due to "cupping" or cao gio (coin rubbing)	• Primarily children from SE Asia (see Ch. 133)
• Vasculitis, particularly Henoch–Schönlein purpura (HSP) and acute hemorrhagic edema of infancy	• Favors lower extremities as well as the buttocks in HSP and the face in acute hemorrhagic edema; associated edema and arthritis
Blue discoloration of skin mistaken as bruising	
• Dermal melanocytosis	• Lack of progression of color to green or yellow; favors presacrum and back
• Infantile hemangioma (deep) or vascular malformation	
Linear hyperpigmentation	
• Phytophotodermatitis	
• Sock-line or mitten-line hyperpigmentation	
Vesicles, bullae or erosions mistaken as non-accidental burns or other intentional injuries	
• Impetigo, ecthyma, blistering distal dactylitis	
• Erythema multiforme, fixed drug eruption	
• Bullous mastocytosis	
• Irritant contact dermatitis	• e.g. laxative-induced irritant contact dermatitis mimicking an immersion burn
• Arthropod bite reaction	
• Moxibustion	• Primarily children from SE Asia (see Ch. 133)
• Burn from a hot car seat or seat-belt buckle	
• Genetic disorders of skin fragility, e.g. forms of epidermolysis bullosa (see Ch. 32) or porphyria (see Ch. 49)	
Other	
• Osteogenesis imperfecta	• Multiple fractures, blue sclerae
• Hair tourniquet	
• Self-inflicted injury	

Table 90.2 Conditions that can mimic child abuse.

Fig. 90.9 Cutaneous disorders that may be misdiagnosed as physical or sexual abuse. A Linear hyperpigmented streaks on the back of a 2-year-old girl due to phytophotodermatitis; the parent had lime juice on her hand and touched the child. **B** Genital lichen sclerosus may have associated purpura or hemorrhagic bullae. **C** A perianal pyramidal protrusion in the typical location, just anterior to the anus in the midline. This finding is most common in infant girls. *A, Courtesy, Anthony J Mancini, MD. C, Courtesy, Julie V Schaffer, MD.*

physicians should be avoided if possible, given the potential trauma this may impose on the child. Lastly, because physical signs of sexual abuse may resolve within a few days, children should be evaluated by an experienced provider as soon as possible[13].

When the history and/or physical findings suggest the possibility of oral, genital or rectal contact, cultures and serologic tests to evaluate for sexually transmitted diseases are indicated. If the abuse occurred within 24 hours of the examination, samples should also be collected for forensic evidence[13].

Victims of all types of abuse may suffer long-term psychologic consequences. Some children withdraw and develop feelings of worthlessness, helplessness, hopelessness and depression. Others exhibit aggressive and impulsive behavior and are at risk for delinquency, substance abuse, absenteeism from school or work, adolescent pregnancy, sexual promiscuity and prostitution. Abused children are more likely as adults to be abusive to their own children and spouses. Thus, long-term psychologic support for abused children is desirable.

In summary, the dermatologist may be the first physician to encounter the abused child, so it is important to be alert for possible abuse, perform the appropriate documentation and testing, and report it to the proper authorities. It is often necessary to enlist the help of a primary care physician or gynecologist experienced in the evaluation of abuse. An atlas by Hobbs and Wynne[18] provides additional information and many color illustrations.

CONDITIONS OCCASIONALLY MISDIAGNOSED AS CHILDHOOD SEXUAL ABUSE

• Congenital anomalies
• Accidental injury
• Perianal streptococcal infection
• Lichen sclerosus (may be associated with purpura or hemorrhagic bullae)
• Genital vitiligo
• Localized vulvar bullous pemphigoid or other bullous diseases
• Crohn's disease
• Entities misdiagnosed as genital or perianal warts
  • Perianal pyramidal protrusion
  • Molluscum contagiosum
  • Pseudoverrucous papules and nodules due to fecal or urinary incontinence
  • Perianal papillomatous lesions of Goltz syndrome

Table 90.3 Conditions occasionally misdiagnosed as childhood sexual abuse.

EVALUATION AND MANAGEMENT OF SUSPECTED CHILD ABUSE
• Examine the entire cutaneous surface as well as oral, anal and genital mucosae; estimate the ages of individual traumatic lesions and identify any associated injuries • Detail all traumatic lesions in the medical record • Photograph injuries whenever possible • Funduscopic examination to assess for retinal hemorrhages* • Otoscopic examination to exclude hemotympanum • Skeletal survey to assess for unsuspected fractures, especially in children under 6 years of age • Treat acute injuries or infections • Report suspected abuse, initially by telephone and subsequently in writing, to the local child protective services agency • Protect the child from further injury while suspected abuse is being investigated • Long-term counseling for proven abuse
*Can occur secondary to head trauma or severe shaking; the presence of extensive, bilateral retinal hemorrhages in a child <3 years of age is strongly suggestive of abuse.

Table 90.4 Evaluation and management of suspected child abuse.

ELDER ABUSE

Key features

- Elder abuse may involve intentional actions that cause harm or create a serious risk of harm
- Failure by a caretaker to satisfy the basic needs of an elder or to protect the elder from harm also constitutes elder abuse

TYPES AND PREVALENCES OF ELDER ABUSE	
Type of elder abuse	**One-year prevalence rate (%)***
Physical abuse	1.6
Psychological abuse	4.6
Sexual assault	0.6
Material exploitation	5.2
Neglect	5.1

*Among 5777 adults aged 60 years or older in the US who were randomly selected to participate in a telephone interview-based study[21].

Table 90.5 Types and prevalences of elder abuse.

Introduction

The establishment in 1997 of the International Network for the Prevention of Elder Abuse, with representatives from countries throughout the world, demonstrated that there is international concern about elder abuse[19]. Key features (noted above) of elder abuse have been defined by a panel convened by the US National Academy of Sciences[20]. In most countries, both the healthcare system and legal statutes recognize the types of elder abuse listed in Table 90.5. Approximately one in four elders is at risk of abuse, and 6% have experienced significant abuse in the past month[21,22].

Risk Factors for Elder Abuse

Because of increased opportunities for contact and thus for conflict and tension, a shared living arrangement is a major risk factor for elder abuse[23]. Abuse also occurs in residential and nursing care facilities, and nearly one-third of such facilities have been cited for an abuse violation that caused or had the potential to cause harm to a resident[24]. Elderly individuals living alone are more likely to be victims of financial abuse, but they are at lower risk for other forms of abuse[25]. Physical abuse is reported to occur more frequently in elders with dementia, especially those with a history of aggressive behavior[26]. Social isolation has also been identified as a risk factor, with victims more likely to be isolated from friends and family (other than the person with whom they are living) than are non-victims[19]. Pathologic characteristics of perpetrators of elder abuse include mental illness, particularly depression and alcohol abuse[27]. Additionally, people who abuse elders may actually be dependent (e.g. financially) on the person they are abusing. In some cases, abuse stems from attempts by relatives (particularly adult offspring) to obtain the victim's resources[28].

Clinical Features and Assessment

In recent years, more data have become available on the clinical features of elder abuse. Lachs and Pillemer[19] proposed guidelines for medical assessment when elder abuse is suspected (Table 90.6), and Reis and Nahmiash[29] developed and validated the Indicators of Abuse screening tool for practitioners. Unfortunately, abused elders may not always have findings clearly attributable to abuse. Conversely, older individuals may have findings that mimic abuse but which are actually a result of accidental injuries or chronic disease[19].

If elder abuse is suspected, a comprehensive assessment should be done by a provider who has substantial experience with the clinical and psychosocial aspects of elder abuse. The patient should not be examined in the presence of the suspected abuser. The presence of other healthcare staff should also be minimized, since many patients are ashamed to admit that they are victims of elder abuse[19]. Although direct questions about abuse are appropriate, the interviewer may prefer to begin with general questions about safety issues and the home environment. Attempts to elicit details about the nature, frequency and provoking factors of abuse are recommended[19].

The physician must use considerable caution in interacting with a suspected abuser. One of the risks of confronting an alleged abuser is that access to the elderly person may be lost. If the physician deems it necessary to interview a suspected abuser, an empathetic nonjudgmental approach may be helpful[19].

POTENTIAL FINDINGS IN ELDER ABUSE	
Behavior observations	• Withdrawal • Absence of eye contact with interviewer • Infantilizing of patient by caregiver • Functionally impaired patient who presents without designated caregiver
General appearance	• Hygiene, cleanliness and appropriateness of dress
Skin and mucous membranes	• Skin turgor, other signs of dehydration • Multiple abrasions in various stages of evolution • Wrist or ankle lesions suggestive of restraint use • Bruises (shape may suggest implement used) • Decubitus ulcers • Lack of care provided for established skin lesions • Infestations • Immersion burn (stocking/glove distribution)
Head and neck	• Traumatic alopecia (distinguishable from androgenetic alopecia on basis of distribution) • Scalp hematomas, lacerations, abrasions
Genitourinary	• Rectal or vaginal bleeding could indicate sexual abuse
Musculoskeletal	• Examination for occult fracture, pain • Observe gait • Fractures that are not explained by mechanisms of reported injury

Table 90.6 Potential findings in elder abuse. *Adapted from Lachs MS, Pillemen K. Elder abuse. Lancet 2004;364:1263–72.*

INTERVENTIONS FOR ELDER ABUSE	
Context of elder abuse	**Potential interventions**
Abuse potentially related to stress from caring for impaired family member	Respite services Adult daycare Caregiver education programs (e.g. on what constitutes abuse) Recruitment of other family, informal, or paid caregivers to share burden of care Psychotherapy for caregiver Treatment for depression Social integration of caregiver to reduce isolation
Violence related to substance or alcohol misuse	Referral to alcohol or drug misuse rehabilitation programs as appropriate
Violence related to behavioral problems associated with mental health	Treatment referral
Spousal violence (often longstanding)	Marital counseling Support groups Shelter Orders of protection Victim advocacy
Abuse by aggressive dementia patient	Geriatric medical assessment of causes of underlying behavior
Financial exploitation by family members	Guardianship proceeding, power of attorney (transfer of legal authority) Protective services
Financial exploitation by paid caregiver	Referral to legal services Involvement of law enforcement Protective services

Table 90.7 Interventions for elder abuse. *From Lachs MS, Pilleman K. Elder abuse. Lancet 2004;364:1263–72.*

Management

Because elder abuse is multifactorial, Lachs and Pillemer[19] suggested potential interventions based on the context of abuse (Table 90.7). A multidisciplinary team involving physicians, nurses, social workers, elder care attorneys, and, when appropriate, adult protection agencies

and law enforcement officials is helpful when dealing with elder abuse. If the abused person is competent to make medical decisions and willing to accept intervention, education regarding elder abuse can be provided, a safety plan implemented (e.g. placement in a safe home, giving emergency phone numbers), and the patient as well as family members referred to appropriate services. If the patient's competency is in question and/or intervention is refused, the physician must determine if the individual has the mental capacity to make medical decisions. If not, conservatorship and an order of protection may be required.

In summary, dermatologists should remain vigilant in looking for physical signs of abuse in elderly patients, especially those who are dependent on caregivers. Patients suspected of being abused should be evaluated, wherever possible, by physicians with expertise in elder abuse. However, dermatologists who encounter or recognize the signs of elder abuse are responsible for initiating the evaluation process that protects these fragile members of society.

REFERENCES

1. U.S. Department of Health and Human Services, Administration for Children and Families, Administration on Children, Youth and Families, Children's Bureau. Child Maltreatment 2009. Washington, DC: U.S. Department of Health and Human Services, 2010:xii–xiii. Available from http://www.acf.hhs.gov/programs/cb/stats_research/index.htm#can.
2. Nathens AB (ed). National Trauma Data Bank Pediatric Report 2010. Chicago, IL. American College of Surgeons, 2010. Available from http://www.facs.org/trauma/ntdb/pdf/ntdbpediatricreport2010.pdf.
3. DiScala C, Sege R, Li G, Reece RM. Child abuse and unintentional injuries: a 10-year retrospective. Arch Pediatr Adolesc Med. 2000;154:16–22.
4. American Academy of Pediatrics Committee on Child Abuse and Neglect. Guidelines for the evaluation of sexual abuse of children. Pediatrics. 1991;87:254–60.
5. Caffey J. Multiple fractures in the long bones of infants suffering from chronic subdural hematoma. Am J Roentgenol Radium Ther. 1946;56:163–73.
6. Kempe CH, Silverman FN, Steele BF, et al. The battered child syndrome. JAMA. 1962;181:17–24.
7. Berger LM. Income, family characteristics, and physical violence toward children. Child Abuse Negl. 2005;29:107–33.
8. Finkelhor D. Epidemiological factors in the clinical identification of child sexual abuse. Child Abuse Negl. 1993;17:67–70.
9. Maguire S, Mann MK, Sibert J, Kemp A. Are there patterns of bruising in childhood which are diagnostic or suggestive of abuse? A systematic review. Arch Dis Child. 2005;90:182–6.
10. Raimer BG, Raimer SS, Hebeler JR. Cutaneous signs of child abuse. J Am Acad Dermatol. 1981;5:203–12.
11. Greenbaum AR, Donne J, Wilson D, Dunn KW. Intentional burn injury: an evidence-based, clinical and forensic review. Burns. 2004;30:628–42.
12. Bays J, Chadwick D. Medical diagnosis of the sexually abused child. Child Abuse Negl. 1993;17:91–110.
13. Adams JA. Guidelines for medical care of children evaluated for suspected sexual abuse: an update for 2008. Curr Opin Obstet Gynecol. 2008;20:435–41.
14. Pierce AM. Anal fissures and anal scars in anal abuse – are they significant? Pediatr Surg Int. 2004;20:334–8.
15. Cohen BA, Honig P, Androphy E. Anogenital warts in children. Clinical and virologic evaluation for sexual abuse. Arch Dermatol. 1990;126:1575–80.
16. Labbe J, Caouette G. Recent skin injuries in normal children. Pediatrics. 2001;108:271–6.
17. Vorenberg E. Diagnosing child abuse. The cost of getting it wrong. Arch Dermatol. 1992;128:844–5.
18. Hobbs CJ, Wynne JM. Physical Signs of Child Abuse: A Colour Atlas, 2nd edn. London: WB Saunders, 2001.
19. Lachs MS, Pillemer K. Elder abuse. Lancet. 2004;364:1263–72.
20. Bonnie RJ, Wallace RB (eds). Elder Mistreatment: Abuse, Neglect, and Exploitation in an Aging America. Washington, DC: National Academies Press, 2002.
21. Acierno R, Hernandez MA, Amstadter AB, et al. Prevalence and correlates of emotional, physical, sexual and financial abuse and potential neglect in the United States: the National Elder Mistreatment Study. Am J Public Health. 2010;100:292–7.
22. Cooper C, Selwood A, Livingston G. The prevalence of elder abuse and neglect: a systematic review. Age Ageing. 2008;37:151–60.
23. Lachs MS, Williams C, O'Brien S, et al. Risk factors for reported elder abuse and neglect: a nine-year observational cohort study. Gerontologist. 1997;37:469–74.
24. Lindbloom EJ, Brandt J, Hough LD, Meadows SE. Elder mistreatment in the nursing home: a systematic review. J Am Med Dir Assoc. 2007;8:610–16.
25. Choi NG, Kulick DB, Mayer J. Financial exploitation of elders: analysis of risk factors based on county adult protective services data. J Elder Abuse Negl. 1999;10:39–62.
26. Paveza GJ, Cohen D, Eisdorfer C, et al. Severe family violence and Alzheimer's disease: prevalence and risk factors. Gerontologist. 1992;32:493–7.
27. Reay AM, Browne KD. Risk factor characteristics in carers who physically abuse or neglect their elderly dependants. Aging Ment Health. 2001;5:56–62.
28. Greenberg JR, McKibben M, Raymond JA. Dependent adult children and elder abuse. J Elder Abuse Negl. 1990;2:73–86.
29. Reis M, Nahmiash D. Validation of the indicators of abuse (IOA) screen. Gerontologist. 1998;38:471–80.

Burn injury due to dunking in hot water by the father. *Courtesy of Leo Litter MD.*

This page intentionally left blank

Histiocytoses 91

Warren T Goodman and Terry L Barrett

Chapter Contents

Langerhans cell histiocytosis *1529*
Non-Langerhans cell histiocytoses..... *1535*
Malignant histiocytic disorders *1545*

Key features

- LCH is a clonal proliferative disorder
- LCH cells are S100-, CD1a-, and Langerin (CD207)-positive
- Ultrastructurally, intracytoplasmic Birbeck granules are seen
- Osteolytic bone lesions are common
- Diabetes insipidus is common

OVERVIEW

The histiocytoses represent a group of proliferative disorders with a common CD34-positive progenitor cell in the bone marrow. Three "histiocytes" of cutaneous importance are: (1) the Langerhans cell, which migrates to and from the epidermis and functions as a potent antigen-presenting cell (APC); (2) the mononuclear cell/macrophage (sometimes called the "true" histiocyte), which migrates to and from the dermis and has both phagocytic and APC properties; and (3) the dermal dendrocyte/dendritic cell, of which there are two subtypes. Type 1 dermal dendrocytes are factor XIIIa-positive and generally reside within the papillary dermis, whereas type 2 dermal dendrocytes are CD34-positive and are generally found within the reticular dermis. Type 1 dermal dendrocytes may be involved in phagocytosis, antigen presentation, inflammation, collagen production and wound healing, while the function of type 2 dermal dendrocytes is less certain.

Dysfunction of these various histiocytes has led to a group of well-known but poorly understood disorders. For years, many of the histiocytoses were known by numerous names, reflecting the lack of understanding and agreement regarding their origin. Electron microscopy and the development of immunohistochemical stains have provided insight into these conditions. It is now clear that the histiocytoses are closely related entities, with Langerhans cell histiocytosis (LCH) representing one group of disorders and non-Langerhans cell histiocytosis (non-LCH) representing another. Of note, each group represents a spectrum of disease, with overlap between entities.

This chapter covers the most common and several of the rarer histiocytic disorders in detail. In addition, the key features of the hemophagocytic syndromes (Table 91.1), the rare malignant histiocytic disorders (class III histiocytosis; see Table 91.3), and the even rarer dendritic cell hamartomas (see Table 91.4) are presented.

LANGERHANS CELL HISTIOCYTOSIS

Synonyms:

- Langerhans cell histiocytosis (LCH; class I histiocytosis, histiocytosis X), comprising:
  - Letterer–Siwe disease
  - Hand–Schüller–Christian disease
  - Eosinophilic granuloma
  - Congenital self-healing reticulohistiocytosis (Hashimoto–Pritzker disease)

Introduction

Langerhans cell histiocytosis (LCH) is a clonal proliferative disease of Langerhans cells that express an immunophenotype positive for S100, CD1a and Langerin (CD207), and which contain cytoplasmic Birbeck granules. LCH represents a disease spectrum with four prominent but overlapping syndromes:

- Letterer–Siwe disease
- Hand–Schüller–Christian disease
- eosinophilic granuloma
- congenital self-healing reticulohistiocytosis (Hashimoto-Pritzker disease).

Disease expression ranges from mild, sometimes asymptomatic, single-organ involvement to severe, progressive multisystem disease.

History

Letterer–Siwe disease, Hand–Schüller–Christian disease and eosinophilic granuloma were described in the early twentieth century. In 1953, Lichtenstein[2] grouped the three disorders into a single entity which he called *histiocytosis X*. In 1973, Hashimoto and Pritzker[3] described the entity congenital self-healing reticulohistiocytosis. Immunologic and ultrastructural studies confirmed the relationship of the pathologic cells in histiocytosis X and congenital self-healing reticulohistiocytosis to Langerhans cells, providing a basis for the Writing Group of the Histiocyte Society[4], in 1987, to reclassify them as "Langerhans cell histiocytoses".

Epidemiology

LCH occurs worldwide and most commonly develops in children ages 1–3 years, though disease can develop at any age. The reported incidence of LCH varies widely. However, an annual incidence of at least five per million children is often quoted, with the adult incidence suspected to be less than one-third that of children. LCH is more common in boys, with a male : female ratio of nearly 2 : 1. In adults, there may be a slight female predominance.

Some cases of LCH appear to be familial. One study described simultaneous development of LCH in four of five monozygotic twin pairs and in one of three dizygotic pairs[5]. Additionally, in two families with affected non-twin siblings, parental consanguinity was known in one and possible in the other.

Pathogenesis

Until recently, the pathogenesis of LCH was unknown. Viral and immunologic etiologies had long been considered, although to date no studies have demonstrated a primary immune abnormality in patients with LCH and there has been no consistent detection of viral genomes in LCH tissue[6]. In 2010, a significant percentage (57%) of LCH specimens were shown to harbor the *BRAF* V600E mutation[6a], as has been described in cutaneous melanomas. This finding strongly suggested that LCH is neoplastic and raised the possibility of the therapeutic use of *BRAF* inhibitors in the future.

CLINICAL FEATURES OF THE HISTIOCYTOSES			
Histiocytosis	**Usual age**	**Most common mucocutaneous sites**	**Other findings**
LANGERHANS CELL HISTIOCYTOSES			
Letterer–Siwe disease	0–2 years	Scalp, flexural areas, trunk	Visceral and bone lesions
Hand–Schüller–Christian disease	2–6 years	Scalp, flexural areas, trunk, gingival	Diabetes insipidus, bone lesions, exophthalmos
Eosinophilic granuloma	7–12 years	Skin lesions rare	Bone lesions primarily
Congenital self-healing reticulohistiocytosis (Hashimoto–Pritzker disease)	Congenital	Widespread, localized, or single lesion	Spontaneous resolution, but children should be followed longitudinally
NON-LANGERHANS CELL HISTIOCYTOSES			
Primarily cutaneous, usually self-resolving			
Juvenile xanthogranuloma	0–2 years	One to a few lesions >> numerous & widespread Head and neck > upper trunk > extremities	Rare eye and visceral lesions; spontaneous resolution; association with CALM, NF-1, and/or juvenile myelomonocytic leukemia
Benign cephalic histiocytosis	0–3 years	Face and neck > trunk and extremities	Usually none (diabetes insipidus rare); spontaneous resolution
Giant cell reticulohistiocytoma	Adults	Head (solitary lesion)	None; spontaneous resolution
Generalized eruptive histiocytoma	<4 and 20–50 years	Widespread (axial)	Recurrent crops; spontaneous resolution
Indeterminate cell histiocytosis	Any	Solitary or generalized Trunk & extremities > head & neck, genitalia	Uncommon visceral and bone lesions; possible association with B-cell lymphoma and leukemia
Primarily cutaneous, often persistent/progressive			
*Papular xanthoma	Any	Generalized (discrete yellow papules and papulonodules with relative sparing of flexural sites)	Mucous membrane involvement can occur occasionally
*Progressive nodular histiocytoma	Any	Generalized (discrete yellow papules and nodules, sometimes with prominent facial involvement)	May represent same entity as the progressive form of papular xanthoma[1]; mucous membrane involvement can occur
*Hereditary progressive mucinous histiocytosis	Childhood/ Adolescence	Generalized (skin-colored to erythematous papules and nodules)	Usually occurs in female patients; histologically, abundant dermal mucin in addition to histiocytes
Cutaneous, with frequent systemic involvement			
Necrobiotic xanthogranuloma	17–60 years	Periorbital > other face, trunk, extremities	Paraproteinemia due to plasma cell dyscrasia or lymphoproliferative disorder, hepatosplenomegaly
Multicentric reticulohistiocytosis	30–50 years	Head; hands, elbows (over joints); mucosa (oral, nasopharyngeal)	Arthritis (often destructive); up to 30% with internal malignancy
Rosai–Dorfman disease	10–30 years	Eyelids and malar area	Massive lymphadenopathy in a subset of patients, fever, hypergammaglobulinemia; skin-limited form increasingly recognized
Xanthoma disseminatum	Any	Flexural areas to widespread > mucosa (oral, nasopharyngeal)	Diabetes insipidus
Systemic, with skin involvement rare to unusual			
Erdheim–Chester disease*	Any	Skin involvement ~25% of patients: eyelids, scalp, neck, trunk, axillae (red–brown to yellow nodules and indurated plaques)	Fever, bone lesions, exophthalmos, diabetes insipidus; involvement of the lungs, kidneys, adrenals, heart, CNS, retroperitoneum and testes; high mortality rate
Sea-blue histiocyte syndrome (sea-blue histiocytosis)* • Inherited • Acquired	Usually adolescence/ young adulthood (inherited form)	Skin involvement rare (inherited form): facial (macular hyperpigmentation and nodules)	Histiocytes contain cytoplasmic granules that stain azure blue with May–Gruenwald stain; multiple organs involved; can be fatal

*Not covered in the body of the text.

Table 91.1 Clinical features of the histiocytoses. CALM, café-au-lait macule; NF, neurofibromatosis.

Continued

As mentioned previously, at least a small subset of LCH appears to be hereditary[5]. In addition, several studies by different investigators have demonstrated clonal $CD1a^+$ histiocytes in all LCH tissue tested[7,8]. Based upon these results, as well as the presence of oncogenic *BRAF* mutations, LCH is now best regarded as a clonal neoplastic disorder.

While several studies have demonstrated elevated levels of cytokines in lesions of patients with LCH, including TNF-α, interferon-γ, granulocyte–monocyte colony-stimulating factor (GM-CSF) and interleukin (IL)-1, IL-2, IL-4 and IL-10, these cytokines and interleukins are thought to promote various disease-related symptoms and morbidity, rather than being responsible for the development of disease.

Clinical features

The four well-described variants of LCH have significant clinical overlap. As a result, many clinicians no longer attempt to differentiate

CLINICAL FEATURES OF THE HISTIOCYTOSES			
Histiocytosis	**Usual age**	**Most common mucocutaneous sites**	**Other findings**
Hemophagocytic lymphohistiocytosis (HLH; hemophagocytic syndrome)* • Primary (genetic; see Table 60.5) – Familial HLH‡, Chédiak–Higashi syndrome, Griscelli syndrome type 2, and X-linked lymphoproliferative syndrome • Secondary (acquired) – Infection-associated (e.g. EBV, CMV)§ – Malignancy-associated (e.g. NK/T-cell lymphoma) – Macrophage activation syndrome associated with autoimmune connective tissue disease (e.g. Still's disease, systemic lupus erythematosus)	Primary: 0–2 years Secondary: any	Generalized (purpuric macules and papules, morbilliform eruptions, erythroderma, keratotic nodules) or acral (erythematous macules)†; malignancy-associated forms may present with lesions of cutaneous or subcutaneous T-cell lymphoma	Fever, hepatosplenomegaly, cytopenias, hypertriglyceridemia, hypofibrinogenemia, histologic evidence of hemophagocytosis (e.g. in the bone marrow, lymph nodes or spleen), low natural killer cell activity, hyperferritinemia, elevated soluble CD25 (plus evidence of infectious agent, malignancy or autoimmune connective tissue disease in secondary forms)

*Not covered in the body of the text.
†Skin biopsy specimens rarely demonstrate hemophagocytosis.
‡In the US, most commonly due to mutations in the gene that encodes perforin
§A list of infectious agents associated with HLH is available at www.cdc.gov/ncidod/eid/vol6no6/fisman_refs.htm.

Table 91.1 Clinical features of the histiocytoses (cont'd). EBV, Epstein-Barr virus; CMV, cytomegalovirus.

between the various syndromes that comprise LCH, recognizing that LCH is one disease with a wide clinical spectrum and a highly varied course. For historical context, the three classically described variants and the more recently recognized congenital self-healing reticulohistiocytosis are discussed here.

Letterer–Siwe disease is the acute diffuse form of LCH. It is a multisystem disease that nearly always develops prior to age 2 years, and commonly presents in children less than 1 year of age. Cutaneous involvement occurs in most patients as 1–2 mm pink to skin-colored papules, pustules and/or vesicles in the scalp, flexural areas of the neck, axilla and perineum, and on the trunk (Fig. 91.1A–C). Scale and crust with secondary impetiginization are common changes, as is the development of petechiae and purpura (Fig. 91.1D). The lesions tend to coalesce and become tender, especially when fissures develop in intertriginous zones (Fig. 91.1E). Palmoplantar and nail involvement can occur, as can soft tissue nodules (Fig. 91.1F). In patients with darkly pigmented skin, the lesions may appear relatively hypopigmented (Fig. 91.1G). The eruption is most often confused with seborrheic dermatitis, various forms of diaper dermatitis (see Ch. 13) or intertrigo, arthropod bites (including scabies), and varicella.

During the course of the disease, many organs can become infiltrated by clonal LCH cells. However, only if the key functions of the organ are affected is such involvement of prognostic significance. Lung, liver, lymph node and bone involvement commonly occur at some point during the illness. Osteolytic bone lesions are painful, usually multiple, and most frequently affect the cranium. Occasionally, the hematopoietic system can be involved, with thrombocytopenia and anemia portending a poor prognosis.

Classically, Hand–Schüller–Christian disease represents the triad of diabetes insipidus, bone lesions and exophthalmos. These patients tend to have a chronic progressive course. For most, Hand–Schüller–Christian disease begins between the ages of 2 and 6 years. Patients with the complete triad are rare, as exophthalmos is uncommon and often a late finding. Approximately 30% of patients develop skin or mucous membrane lesions. While early cutaneous lesions are similar to those seen in Letterer–Siwe disease, older lesions can become xanthomatous. Ulcerative nodules may develop in the oral and genital areas, with premature loss of teeth possible secondary to gingival lesions.

At least 80% of patients with Hand–Schüller–Christian disease develop bone lesions, the cranium being preferentially involved. Chronic otitis media occurs commonly in these patients and in patients with all forms of LCH. Diabetes insipidus, secondary to infiltration of the posterior pituitary by LCH cells, develops in approximately 30% of patients and is more common in those patients with cranial bone involvement. The chances of reversing the diabetes insipidus with radiation or chemotherapy are remote once symptoms develop. However, symptomatic treatment with vasopressin is effective.

Eosinophilic granuloma is a localized variant of LCH that generally affects older children, boys more than girls. Skin and mucous membrane lesions are rare, with a single asymptomatic granulomatous lesion of the bone the most common manifestation. The cranium is most frequently affected, though lesions can also develop within the ribs, vertebrae, pelvis, scapulae and long bones. A spontaneous fracture or otitis media may be the first sign of disease.

Congenital self-healing reticulohistiocytosis (Hashimoto–Pritzker disease) is a variant of LCH which is generally limited to the skin and rapidly self-healing. It presents at birth or in the first few days of life with a characteristic eruption of widespread red to purplish-brown papulonodules. After several weeks, the lesions crust and involute. Solitary papules or nodules (often eroded or ulcerated) and disseminated vesicular eruptions have also been observed (Fig. 91.2; see Ch. 34). Mucous membrane lesions are rare, although systemic involvement has been reported. While congenital self-healing reticulohistiocytosis is considered a benign, self-resolving disorder, its relationship to other LCH variants suggests a cautious approach with respect to prognosis.

Adults rarely develop LCH, but, when they do, the most commonly involved sites are the skin, lung and bone (see Fig. 91.1E). Diabetes insipidus can also develop and, as in children, is more likely when bony involvement of the skull is present. Severe multisystem disease, classically referred to as Letterer–Siwe disease, is rare in adults. However, LCH can be a progressive disease in adults, especially when both bone and extraskeletal sites are involved.

Two patterns of associations between LCH and malignancy have been noted[9]. First, an increased incidence of solid tumors and leukemia has been noted in patients previously treated for LCH. In 20 of 21 reported cases of acute lymphoblastic leukemia (ALL) or acute myelogenous leukemia occurring following treatment for LCH, the therapeutic regimens had included chemotherapy, radiotherapy, or both. It was suspected that the increased incidence of leukemias in this group was treatment-related. In addition, a few patients developed skin or solid tumors (e.g. basal cell carcinoma, osteosarcoma) within the fields of radiotherapy for their LCH.

Second, there may be an increased incidence of LCH developing in patients with ALL or solid tumors[9]. In 7 of 12 reported patients with both LCH and ALL, the leukemia preceded the LCH. There may also be an association between retinoblastoma and LCH. Of nine reported cases of solid tumors preceding LCH or developing concurrently with LCH, four were retinoblastomas[9].

The prognosis of patients with LCH varies dramatically. A high mortality rate is associated with multisystem disease, especially in children less than 2 years of age, and in any patient with multiorgan disease if the hematopoietic system, liver, lungs or spleen is involved. Even with

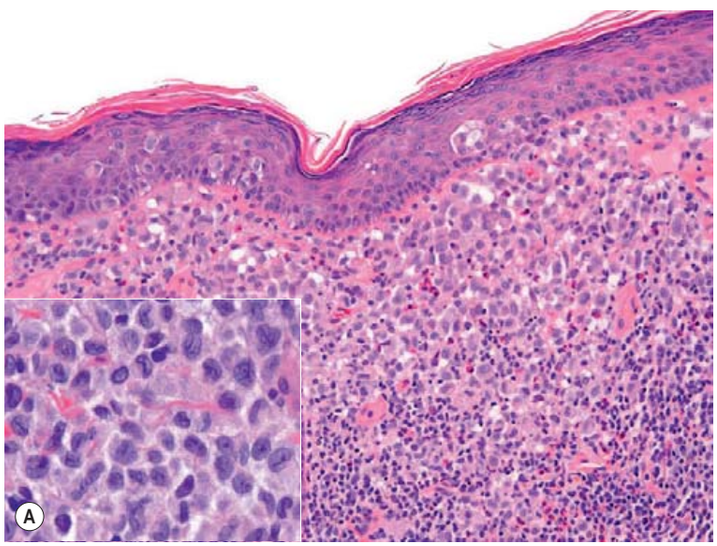
Fig. 91.1 Langerhans cell histiocytosis – clinical spectrum. A Scalp involvement may initially be diagnosed as seborrheic dermatitis; however, there are usually more discrete papules and crusting. **B** Pink, thin plaques with fissuring along the inguinal crease can also resemble seborrheic dermatitis. **C** Advanced disease with coalescence of papules into large plaques and prominent inguinal lymphadenopathy. **D** The presence of petechiae and purpuric papules is a clue to the diagnosis. **E** In an adult, the clinical presentation of inguinal involvement is similar to that of infants. **F** This subcutaneous nodule on the scalp involved the skull and represented the initial manifestation of multisystem Langerhans cell histiocytosis in an infant. **G** In patients with darkly pigmented skin, the papules can be hypopigmented. *B, Courtesy, Richard Antaya, MD. D, F, G, Courtesy, Julie V Schaffer, MD.*

aggressive treatment, mortality in this group of patients ranges from 35% to 55%[10]. Patients not falling into this category tend to do better. Nevertheless, progression or persistence of disease is common.

Pathology

Just as the clinical appearance of LCH is variable, so is the histologic appearance. In a typical papule, a proliferation of LCH cells is present in the papillary dermis (Fig. 91.3). These cells are large, 10–15 μm in diameter, with a reniform (kidney-shaped) nucleus. Usually, some epidermal infiltration by Langerhans cells is present, as well as interface changes. The dermal LCH cells are often admixed with eosinophils, neutrophils, lymphocytes and plasma cells. Mast cells may be present in large numbers. Secondary features such as crusting, pustule formation, hemorrhage or necrosis may obscure the characteristic LCH cell infiltrate. Older lesions that are no longer proliferative may appear granulomatous, xanthomatous or fibrous.

Fig. 91.2 Congenital self-healing reticulohistiocytosis (Hashimoto–Pritzker disease). Solitary eroded nodule on the plantar surface of a neonate. *Courtesy, Richard Antaya, MD.*



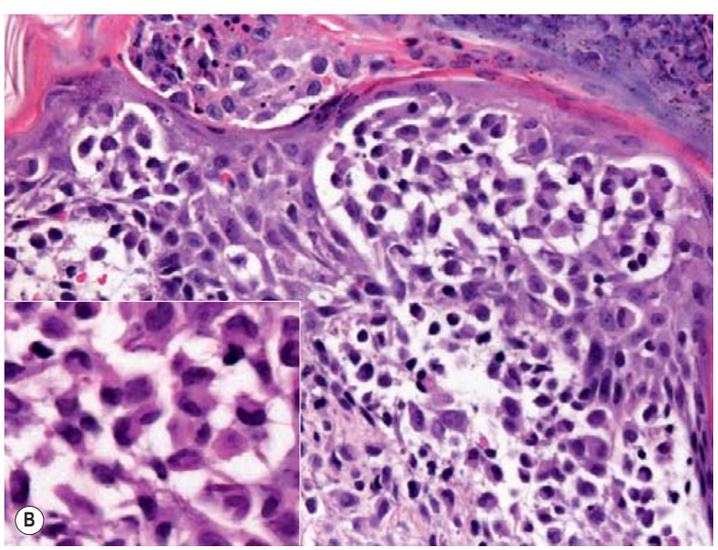


Fig. 91.3 Langerhans cell histiocytosis – histologic features. A A somewhat lichenoid infiltrate of large LCH cells with some involvement of the epidermis; the infiltrate also contains lymphocytes and numerous eosinophils. Insert, note the reniform-shaped nuclei. **B** Another example with larger collections of Langerhans cells within the epidermis. *B, Courtesy, Lorenzo Cerroni, MD.*

ANTIGENIC MARKERS OF THE HISTIOCYTOSES

Histiocytic disorder	S100	CD1a	Langerin (CD207)	CD68* (KP1/KiMP)	Factor XIIIa†
Langerhans cell histiocytoses	+	+	+	–	–
Juvenile xanthogranuloma	–	–	–	+	+
Benign cephalic histiocytosis	– (+)	–	–	+	+
Giant cell reticulohistiocytoma	–	–	–	+	+
Generalized eruptive histiocytoma	–	–	–	+	+
Indeterminate cell histiocytosis	+	+	–	+	+/–
Papular xanthoma‡	–	–	–	+	+
Progressive nodular histiocytosis‡	–	–	–	+	+
Hereditary‡ progressive mucinous histiocytosis	–	–	–	+	+
Necrobiotic xanthogranuloma	–	–	–	+	–
Multicentric reticulohistiocytosis	–	–	–	+	– (+)
Rosai–Dorfman disease	+	–	–	+	– (+)
Xanthoma disseminatum	–	–	–	+	+

*Classic macrophage/monocyte markers.
†Classic dermal dendrocyte marker.
‡Not covered in the body of the text.

Table 91.2 Antigenic markers of the histiocytoses. Classic results are provided and results may vary in specific cases. Staining for other classic macrophage/monocyte markers (e.g. HAM56) is variable.

In nodular lesions of congenital self-healing reticulohistiocytosis, the histology may be identical to other variants of LCH. However, lesions with sheets of histiocytes with abundant eosinophilic cytoplasm, so-called "reticulohistiocytes", intermixed with LCH cells and giant cells, have also been described. The cytoplasm of the reticulohistiocytes and the giant cells may have a "ground glass" appearance, as in multicentric reticulohistiocytosis.

In soft tissue nodules or bone lesions, LCH cells are readily identifiable, especially during the proliferative phase of the process, as the aggregates tend to be larger. In these lesions, sheets of LCH cells may be found, and a few mitoses may be seen. Older bone lesions, on the other hand, may show only xanthomatous or fibrous changes. Early lesions should be biopsied when possible.

Langerhans cells are of bone marrow origin (see Ch. 4). Clonal LCH cells have a similar though not identical immunophenotype to Langerhans cells. Like Langerhans cells, LCH cells show positive immunostaining for CD1a, Langerin (CD207) and S100 (Table 91.2), and do not characteristically express factor XIIIa (a marker for type 1 dermal dendrocytes) or classic macrophage/monocyte markers such as CD68 or HAM56 (Fig. 91.4). ATPase, peanut lectin and α-D-mannosidase are positive in LCH cells, but staining for these is less often performed, as CD1a staining is more specific. Langerin, a transmembrane C-type lectin that serves as an endocytic receptor, is a highly specific Langerhans cell marker. Because Langerin is the major protein of Birbeck granules, Langerin immunostaining can be used as a substitute for demonstration of Birbeck granules by electron microscopy. Both Langerin and CD1a have important roles in the uptake, processing and presentation of non-peptide (e.g. lipid) antigens by Langerhans cells.

Electron microscopy demonstrates Birbeck granules, which are rod- or racquet-shaped cytoplasmic structures pathognomonic for Langerhans cells and LCH cells (Fig. 91.5). On average, approximately 50%

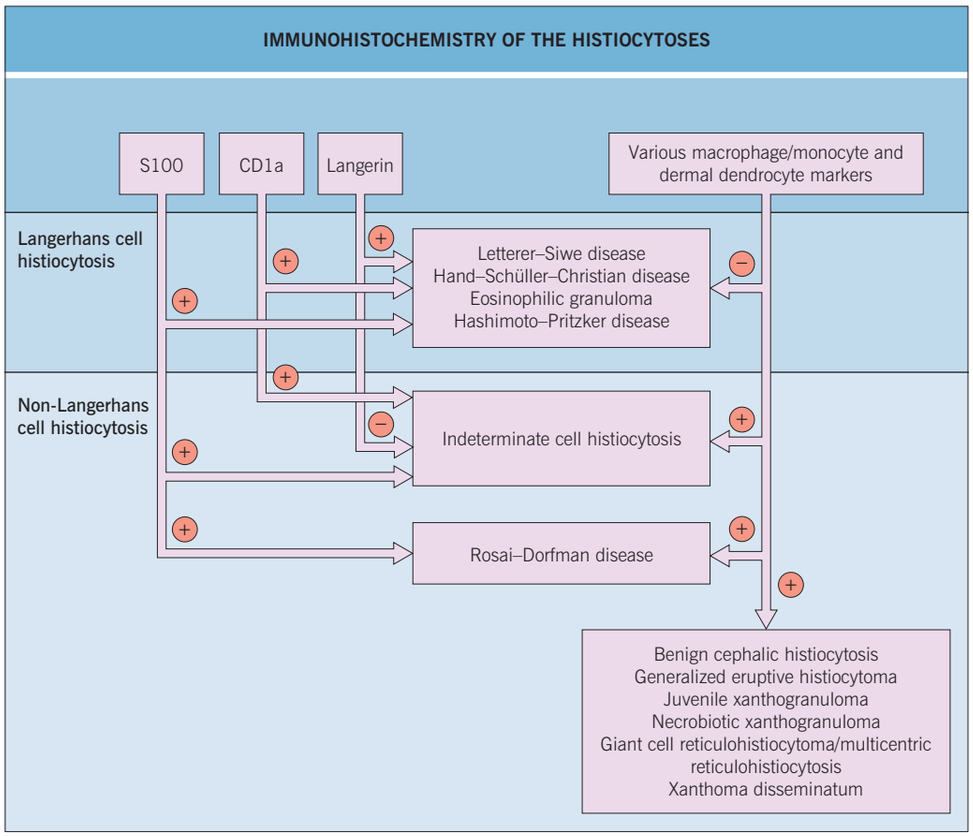


Fig. 91.4 Immunohistochemistry of the histiocytoses. Examples of classic macrophage/monocyte markers are CD68 and HAM56; an example of a classic dermal dendrocyte marker is factor XIIIa.

Fig. 91.5 Langerhans cell histiocytosis (Birbeck granules). Electron micrograph demonstrates classic racquet-shaped Birbeck granules in the cytoplasm of an LCH cell.

of cells will demonstrate Birbeck granules. With the availability of CD1a and Langerin staining, electron microscopy is performed less frequently today than in the past.

Differential diagnosis

The clinical differential diagnosis is vast and includes seborrheic dermatitis, various forms of diaper dermatitis (see Ch 13), and arthropod bites (including scabies), as well as leukemia, B- and T-cell lymphomas, multiple myeloma (bony lesions), urticaria pigmentosa and the non-Langerhans cell histiocytoses (see Table 91.1). However, the characteristic histologic features of LCH will lead one to suspect the diagnosis, which is confirmed with the combination of positive immunostaining for CD1a, S100 and Langerin (CD207; Fig. 91.6) or demonstration of Birbeck granules on electron microscopy.

Treatment

All patients diagnosed with LCH should undergo evaluation of the hematologic, pulmonary, hepatosplenic, renal and skeletal systems to determine the extent of disease. Further evaluation of the CNS and the bone marrow may be required. Treatment of LCH is dependent on the number of body systems involved and the severity of involvement.

For mild single-system skin disease (if treatment is required), topical corticosteroids, topical antimicrobials, narrowband UVB, PUVA, and topical nitrogen mustard (mechlorethamine) have been reported to be effective in case series, although potential side effects must be considered. For more extensive disease, thalidomide may be effective.

Localized bone lesions can be treated effectively with curettage. Symptomatic recurrent or new lesions, or those with a significant risk of fracture, cosmetic defect or functional abnormality, may require treatment with radiation. Treatment options for less problematic bone tumors include oral nonsteroidal anti-inflammatory drugs (NSAIDs) and intralesional corticosteroid injections.

Multisystem disease has traditionally been treated with systemic therapy. The LCH-1 clinical trial compared the effectiveness of vinblastine versus etoposide (in combination with a single dose of methylprednisolone)[10]. The vinblastine- and etoposide-based regimens were found to be equivalent with regard to disease response (58% vs. 65%, respectively), reactivation (61% vs. 55%), toxicity (47% vs. 58%) and survival (76% vs. 83%), as well as in prevention of disease-related permanent consequences such as diabetes insipidus, endocrinopathies (e.g. growth hormone deficiencies), orthopedic problems, hearing impairment, liver and lung failure, and CNS disease.

While it was also noted that a failure to respond to treatment at 6 weeks was a predictor of poor outcome, those patients who had multisystem disease but were over 2 years of age at diagnosis *and* had no involvement of the hematopoietic system, liver, lungs or spleen, had a 100% probability of survival. Perhaps the most significant shortcoming of treatment with either the vinblastine- or etoposide-based regimen, as shown in LCH-1, was the high rate of reactivation of disease (58% ± 6%). For these patients, multidrug chemotherapy is an option.

Information on current trials for multisystem disease as well as for adults with single-system disease are available at the website for the Histiocyte Society (www.histiocytesociety.org). Anecdotally, small

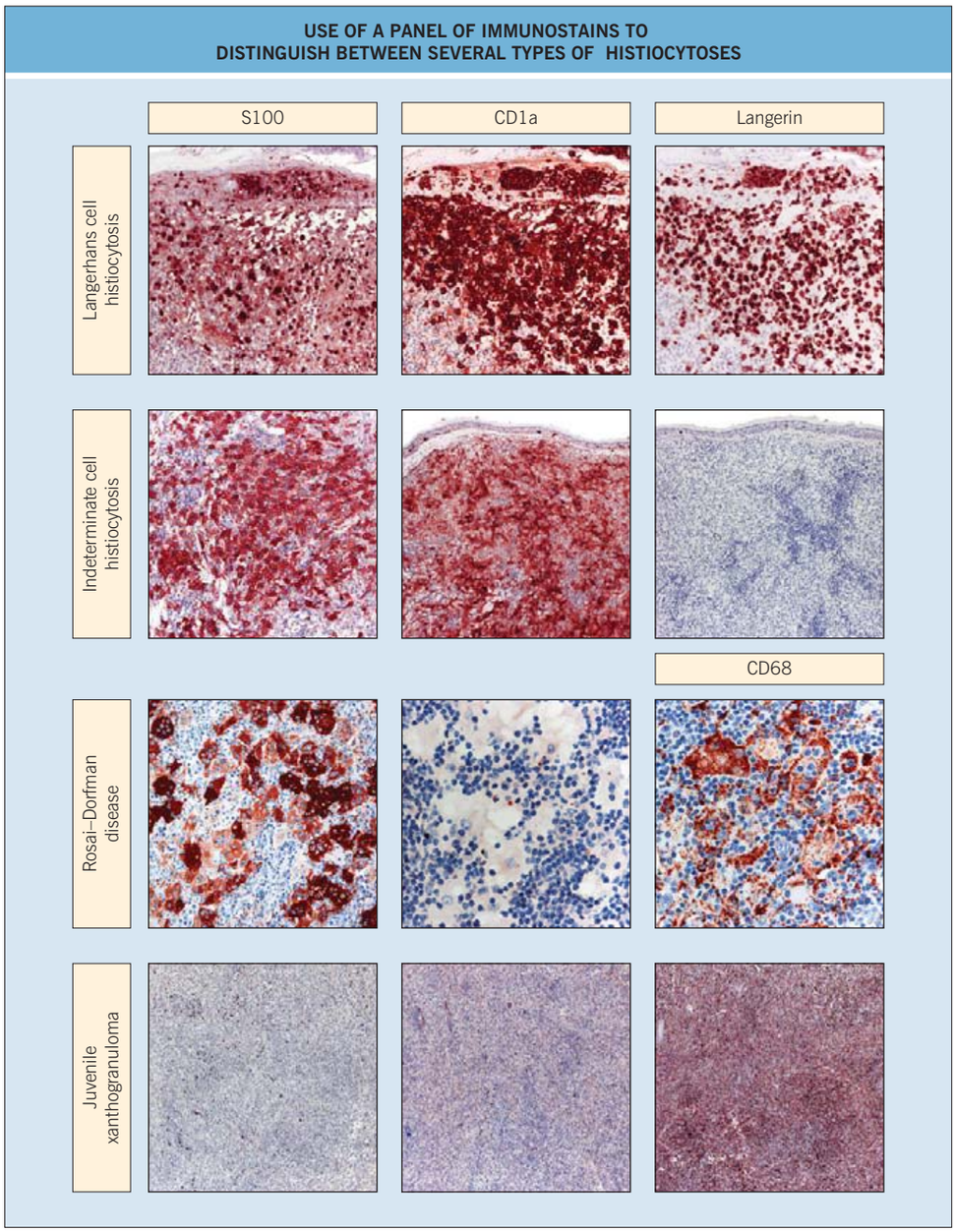


Fig. 91.6 Use of a panel of immunostains to distinguish between Langerhans cell histiocytosis and several types of non-Langerhans cell histiocytosis. See Table 91.2 for staining patterns. *Courtesy, Lorenzo Cerroni, MD.*

numbers of patients with reactivation of LCH have benefited from etanercept, cyclosporine or 2-chlorodeoxyadenosine (2-CdA), and there is currently an ongoing trial of 2-CdA plus cytosine arabinoside (ara-C). Imatinib mesylate was also reportedly beneficial in a case of multisystem LCH involving the brain which was unresponsive to radiation. For those with the most severe disease, hematopoietic stem cell, liver or lung transplantation may be required.

NON-LANGERHANS CELL HISTIOCYTOSES

Synonyms: ■ Class II histiocytosis ■ Non-X histiocytosis ■ Histiocytoses of mononuclear phagocytes other than Langerhans cells

Benign Cephalic Histiocytosis

Synonym: ■ Histiocytosis with intracytoplasmic worm-like bodies

Key features

- Infants <1 year of age most commonly affected
- Red to brown macules and papules of the face and neck
- Self-limiting disease, so no treatment required
- Ultrastructural finding: worm-like bodies

Introduction

Benign cephalic histiocytosis is a rare, self-limited histiocytic proliferative disorder of young children, primarily affecting the face.

History

Gianotti et al.[11], in 1971, described the condition as "infantile histiocytosis with intracytoplasmic worm-like bodies", based upon findings of comma-shaped structures by ultrastructural studies. The disorder was renamed "benign cephalic histiocytosis", based upon typical clinical findings, when it became clear that many histiocytic disorders had similar ultrastructural findings.

Epidemiology

Benign cephalic histiocytosis is rare, with approximately 40 cases having been described to date. The disorder typically begins by the age of 1 year and always within the first 3 years of life. There appears to be no gender predilection[12]. One adult patient with T-cell lymphoma was noted to have developed lesions similar to benign cephalic histiocytosis.

Pathogenesis

The pathogenesis of benign cephalic histiocytosis is not known. However, given a similar histopathology, ultrastructural appearance and immunohistochemical profile to juvenile xanthogranuloma and generalized eruptive histiocytoma, several investigators have suggested that benign cephalic histiocytosis may represent a variant of juvenile xanthogranuloma or generalized eruptive histiocytoma. Gianotti et al.[13], on the basis of a blinded histopathologic comparison that found great similarity between 14 benign cephalic histiocytosis, 25 juvenile xanthogranuloma, and 4 generalized eruptive histiocytoma specimens, believe that these three non-LCH self-healing histiocytoses should be viewed as a single disease with a spectrum of clinical features.

Clinical features

The eruption of benign cephalic histiocytosis is characterized by the evolution of 2–5 mm, red to red–brown macules and papules, first on the face (Fig. 91.7), with subsequent appearance on the ears and neck. Occasionally, lesions may develop on the trunk and arms, with infrequent involvement of the buttocks and thighs. The lesions spontaneously resolve after months or years. The papules flatten, become briefly hyperpigmented, and often disappear completely. Most children are otherwise healthy without involvement of the mucous membranes or internal organs. However, diabetes insipidus has been reported in a young girl with benign cephalic histiocytosis[14]. The course can be marked by exacerbations.

Pathology

Gianotti et al.[13] described three histologic patterns in benign cephalic histiocytosis: a papillary dermal pattern, a diffuse pattern, and a lichenoid pattern. In the papillary dermal pattern, the most common form, the infiltrate is well defined and closely approaches the epidermis. The histiocytes are pleomorphic and have abundant eosinophilic cytoplasm, with hyperchromatic, sometimes indented nuclei and large nucleoli. There are scattered lymphocytes and a few eosinophils. In the diffuse pattern, pleomorphic histiocytes are rare, with most histiocytes being round and regular with minimal cytoplasm. The infiltrate is dispersed throughout the dermis. In the lichenoid pattern, small regular histiocytes and occasional lymphocytes are seen perivascularly and in the superficial dermis. In all forms, Touton cells are absent and foamy cells are rare or absent.

The histiocytes in benign cephalic histiocytosis express CD11b, CD14b, CD68, HAM56 and factor XIIIa (see Fig. 91.4, Table 91.2)[15,16]. Typically, however, only immunostains for CD68 and occasionally factor XIIIa are performed. Ultrastructural studies have demonstrated cytoplasmic comma-shaped bodies, worm-like particles, and desmosome-like junctions between histiocytes. The comma-shaped bodies and worm-like particles are also found in LCH, juvenile xanthogranuloma, generalized eruptive histiocytoma and Rosai–Dorfman disease, so they are not as helpful diagnostically as originally thought.

Differential diagnosis

The differential diagnosis includes LCH and the non-LCH disorders, in particular juvenile xanthogranuloma and generalized eruptive histiocytoma (see Table 91.1). However, benign cephalic histiocytosis has characteristic clinical features, and the dome-shaped papulonodules of juvenile xanthogranuloma are usually few in number or occasionally numerous and widespread. Additionally, juvenile xanthogranuloma is often easily differentiated from benign cephalic histiocytosis by histopathology. Even in early juvenile xanthogranuloma, where foamy cells are few to none, Touton cells can be found on step sections[13]. Touton cells are reportedly not seen in benign cephalic histiocytosis.

Treatment

Benign cephalic histiocytosis is generally a self-limiting disorder and no treatment is usually needed. However, careful regular examinations of all patients with benign cephalic histiocytosis is recommended, as both exacerbations of the disease and diabetes insipidus can occur.

Generalized Eruptive Histiocytoma

Synonyms: ■ Eruptive histiocytoma ■ Generalized eruptive histiocytosis

Key features

- Adults affected more commonly than children
- Recurrent crops of numerous, small, red to brown papules
- Widespread axial distribution
- Self-limiting disease, so no treatment required

Introduction

Generalized eruptive histiocytoma is a very rare disorder, characterized by recurrent crops of small papules, axially distributed, which heal with hyperpigmented macules.

History

In the initial description of generalized eruptive histiocytoma in 1963, three adult patients were described by Winkelmann and Muller[17]. The disorder has also been described in children.

Epidemiology

Generalized eruptive histiocytoma is a very rare disease. Approximately 42 cases have been reported to date, with about one-quarter being children. There may be a male predilection. Onset in adults is from the third to sixth decade. In children, onset is usually before age 4 years.

Pathogenesis

The cause of generalized eruptive histiocytoma is unknown. As discussed in the section on benign cephalic histiocytosis, several authors have suggested that generalized eruptive histiocytoma, benign cephalic histiocytosis, and juvenile xanthogranuloma may represent different expressions of the same disorder. Generalized eruptive histiocytoma-like presentations have been seen early in the course of other non-LCH

Fig. 91.7 Benign cephalic histiocytosis. Multiple brown papules on the face of a young child.

Fig. 91.8 Generalized eruptive histiocytoma. Multiple firm red papules on the trunk.

disorders, leading some investigators to suggest that generalized eruptive histiocytoma may be an early, indeterminate stage of non-LCH[18].

Clinical features

The eruption is characterized by recurrent crops of red to brown papules. At each occurrence, hundreds of papules, less than 1 cm, are distributed on the trunk, proximal extremities, and occasionally the face (Fig. 91.8). The papules are usually arranged symmetrically, and mucosal surfaces are occasionally involved. Within several months, the lesions resolve completely or leave behind hyperpigmented macules or small scars. In some children, there may be a less symmetric distribution pattern and papules can become xanthomatous. Internal involvement has not been observed and the affected individuals are otherwise healthy.

Pathology

The superficial and mid dermis typically contain a nearly uniform infiltrate of histiocytes with a few lymphocytes. Rarely, a lichenoid pattern has been observed[13]. Xanthomatous cells are rare, but spindled cells can be seen; to date, giant cells have been reported in one case[19]. The histiocytes stain for lysozyme, α_1-antitrypsin, CD11b, CD14b, CD68 and factor XIIIa (see Fig. 91.4, Table 91.2)[20,21]. In practice, however, immunostains for only CD68 and occasionally factor XIIIa are performed. Ultrastructural studies demonstrate prominent cytoplasmic dense bodies, occasional worm-like bodies, and concentric laminated bodies.

Differential diagnosis

The differential diagnosis includes LCH, urticaria pigmentosa, eruptive syringomas, widespread papular granuloma annulare, and other non-LCH disorders. Of the latter, juvenile xanthogranuloma, xanthoma disseminatum, benign cephalic histiocytosis, indeterminate cell histiocytosis and papular xanthoma (see Table 91.1) can be the most difficult to differentiate from generalized eruptive histiocytoma. However, benign cephalic histiocytosis occurs in children and is most often localized to the head and neck, while the generalized lesions of papular xanthoma are yellow because of lipid accumulation and patients with xanthoma disseminatum have the tendency for plaque formation, a flexural distribution pattern, and the development of diabetes insipidus in addition to laryngeal, oral and eye lesions. By routine histology and immunostaining, generalized eruptive histiocytoma can be distinguished from indeterminate cell histiocytosis ($S100^+$, $CD1a^+$) and juvenile xanthogranuloma (Touton giant cells).

Treatment

No treatment is usually required as the disorder is self-limited and without systemic symptoms. There are, however, scattered reports of the use of isotretinoin, cryotherapy and PUVA. Careful follow-up of all patients with generalized eruptive histiocytoma is recommended, as more serious forms of non-LCH, including xanthoma disseminatum, have been reported to develop in patients with generalized eruptive histiocytoma.

Indeterminate Cell Histiocytosis

Key features

- Adults and children affected
- Both generalized and solitary variants exist
- Immunophenotypic profile – antigenic markers of both LCH ($S100^+$, $CD1a^+$) and non-LCH ($CD68^+$, etc.), but not Langerin (CD207)
- Primarily a cutaneous disorder, but visceral involvement and development of leukemia has occurred in a few patients

Introduction

Indeterminate cell histiocytosis is a very rare and somewhat controversial proliferative disorder of histiocytes which displays both LCH and non-LCH immunophenotypic features. There are two clinical variants – solitary and generalized.

History

Indeterminate cells were described in 1963, and a patient with features first recognized as indeterminate cell histiocytosis was reported by Wood et al.[22] in 1985. Fewer than 50 cases have been reported to date in the literature. Originally, indeterminate cell histiocytosis was thought to be closely related to LCH as the lesional cells were positive for S100 and CD1a, but they did lack Birbeck granules. However, it was later shown that the lesional cells also expressed macrophage/monocyte markers, leading to the proposal that indeterminate cell histiocytosis represented a disorder with overlap between LCH and non-LCH. Most recently, it has been noted that indeterminate cell histiocytosis primarily displays features of non-LCH (with the exception of the routine expression of S100 protein), and the suggestion has been made that most patients diagnosed with indeterminate cell histiocytosis actually have some variation of another non-LCH disorder[23].

Epidemiology

Indeterminate cell histiocytosis is extremely rare and has no apparent sexual predilection. The disorder occurs in adults, adolescents and infants, and a congenital form has also been reported.

Pathogenesis

The pathogenesis of indeterminate cell histiocytosis is unknown. As noted above, the question has been raised as to whether this disorder is actually a separate entity or represents a variation of one of the other non-LCH disorders[23].

Clinical features

While the majority of patients with indeterminate cell histiocytosis have involvement of the trunk and extremities, lesions have also been observed on the genitalia and in the head and neck region, including the eyelids and ears. Both a generalized form and a solitary form have been documented. In the generalized form, cutaneous lesions usually begin as firm red to brown papules, each less than 1 cm. In the solitary form, there is a single soft erythematous lesion, approximately 1 cm in diameter. Ulceration can occur. As lesions age, they become brown to yellow. The clinical course is variable and may wax and wane. Many patients may experience a partial or complete regression of lesions, while some have a progressive course.

Although mucous membrane involvement is rare, both corneal and conjunctival lesions have been reported. Patients are usually healthy, but visceral involvement and death have been reported in three instances. One infant developed an aggressive form of indeterminate

cell histiocytosis with a fatal course; the disease initially presented in the bone and then eventually spread to visceral organs and the skin[24]. To date, two cases have been associated with leukemia, one with mast cell leukemia and the other with acute myelogenous leukemia. The latter patient also had non-Hodgkin lymphoma prior to developing indeterminate cell histiocytosis.

Pathology

Histology often reveals a predominantly monomorphous infiltrate of histiocytes, either well circumscribed or more diffusely distributed within the dermis. Epidermotropism is less common than in LCH. Histiocytes often have an oncocytic appearance, with occasional spindled, scalloped or vacuolated cell variants. Touton giant cells can be present. Lymphocytes are commonly present and eosinophils are occasionally observed.

The immunophenotype of indeterminate cell histiocytosis demonstrates characteristics of *both* LCH and non-LCH. Lesional cells show expression of S100, CD1a, HAM56, CD68, lysozyme, α_1-antitrypsin, HLA-DR, CD11c, CD14b and factor XIIIa (see Fig. 91.4, Table 91.2)[19,24,25]. However, Langerin (CD207) is not expressed (see Fig. 91.6). The ultrastructural features of the histiocytes in indeterminate cell histiocytosis are similar to those seen in Langerhans cells except that no Birbeck granules are found.

Differential diagnosis

The clinical appearance of the cutaneous lesions of indeterminate cell histiocytosis is not unique. Similar-appearing papules in the same distribution can be found in generalized eruptive histiocytoma, juvenile xanthogranuloma and congenital self-healing reticulohistiocytosis (see Table 91.1). When lesions of indeterminate cell histiocytosis are limited to the head and neck, benign cephalic histiocytosis also must be considered. The diagnosis of indeterminate cell histiocytosis can be suspected based upon histopathology. However, confirmation requires the histiocytic infiltrate to demonstrate immunophenotypic features of both LCH (but without Langerin expression) and non-LCH disorders, and to lack Birbeck granules ultrastructurally.

Treatment

Treatment of cutaneous lesions is not usually required as the condition is often either self-limited or non-progressive, and the lesions are asymptomatic. A single lesion can be removed surgically. Several patients have been described with extensive disfiguring cutaneous disease who were treated with systemic chemotherapy (e.g. vinblastine, 2-chlorodeoxyadenosine, cyclophosphamide, and/or etoposide). The use of PUVA has also been reported. Because visceral involvement and leukemia can occur, careful follow-up of all patients with indeterminate cell histiocytosis is recommended.

Juvenile Xanthogranuloma

Key features

- Most common histiocytosis
- Usually infants and young children with involvement of the head and neck region and upper body
- Small and large nodular forms which acquire a yellow color as they mature
- Ocular lesions can cause blindness
- Rare association with both neurofibromatosis type 1 and juvenile myelomonocytic leukemia
- Touton giant cell characteristic histologic finding

Introduction

Juvenile xanthogranuloma is a fairly common non-LCH, most often affecting infants and young children. Cutaneous lesions usually resolve and most patients have an otherwise unremarkable course. Ocular juvenile xanthogranuloma can lead to blindness and there is an association of juvenile xanthogranuloma with neurofibromatosis type 1 (NF1) and juvenile myelomonocytic leukemia.

History

The term "juvenile xanthogranuloma" was suggested by Helwig and Hackney[26] in 1954 based upon histologic findings of xanthomatous histiocytes and giant cells. However, multiple cases of juvenile xanthogranuloma, under different names, had been reported during the first half of the twentieth century. The first case of juvenile xanthogranuloma was reported in 1905 by Adamson[27], who named the disorder "congenital xanthoma multiplex".

Epidemiology

Juvenile xanthogranuloma is a fairly common disorder and the most common histiocytic disease of childhood[28]. However, the true incidence may be underestimated, as many lesions, especially those which are solitary and small, may go unrecognized. In children, there is a male predominance of approximately 1.5:1; no sex predilection is noted in adults. A significant majority of reported patients are Caucasian. Almost 75% of cases appear during the first year of life, with over 15% being noted at birth. Juvenile xanthogranuloma is rare in adults, in whom its peak incidence is in the late twenties to early thirties, though lesions have been reported in the elderly. Most adult patients have solitary lesions.

Pathogenesis

The cause of juvenile xanthogranuloma is not known; however, it is often suggested that the condition is reactive with histiocytes possibly responding to a traumatic or infectious stimulus. The reason for the progressive lipidation of histiocytes in the absence of hyperlipidemia is not clear. However, it has been shown that in adult patients with xanthogranuloma, the uptake of low-density lipoprotein and the synthesis of cholesterol within macrophages is increased[29]. As discussed in the section on benign cephalic histiocytosis, several authors have suggested that generalized eruptive histiocytoma, benign cephalic histiocytosis, and juvenile xanthogranuloma may represent different expressions of the same disorder.

Clinical features

Gianotti and Caputo[30] described two common clinical variants of juvenile xanthogranuloma: a small nodular form and a large nodular form. Patients with the small nodular form, also known as the micronodular form, can present with many pink to red–brown, dome-shaped papules, 2–5 mm in diameter. The lesions are widely scattered on the upper part of the body and rapidly become yellow. In contrast, the more common large nodular form is characterized by one or a few nodules 1–2 cm in diameter. Both forms may coexist.

The most common location for juvenile xanthogranuloma is the head and neck (Fig. 91.9), followed by the upper torso, the upper extremities and the lower extremities. Oral juvenile xanthogranuloma is rare and usually presents as a solitary yellow nodule on the lateral aspect of the tongue or the midline of the hard palate. Unusual morphologic presentations include keratotic, pedunculated, subcutaneous, clustered, plaque-like and giant lesions.

Extracutaneous lesions have been reported in many organs, the eye being most commonly affected. Visceral, bone and CNS involvement (e.g. diabetes insipidus) is rare, although to date three deaths have been attributed to the disease[31]. The lung is the second most frequent extracutaneous site of disease. Ocular juvenile xanthogranuloma is almost always unilateral and develops in less than 0.5% of patients with cutaneous lesions. However, approximately 40% of patients with ocular juvenile xanthogranuloma have cutaneous lesions, always multiple, at the time of diagnosis[32]. Ocular involvement usually occurs before 2 years of age and often affects the iris. Hyphema (hemorrhage into the anterior chamber) and glaucoma are serious complications which can result in blindness. Early referral to an ophthalmologist for evaluation and possible treatment is important.

A well-recognized association exists between juvenile xanthogranuloma and café-au-lait macules. Some of these patients have a family history of NF1, while others fulfill the clinical criteria for NF1. Another well-known association is that of juvenile xanthogranuloma and juvenile myelomonocytic leukemia. Patients with NF1 also have an increased risk of developing juvenile myelomonocytic leukemia. A so-called "triple association" consisting of juvenile xanthogranuloma, NF1 and juvenile myelomonocytic leukemia has been observed in

Fig. 91.9 Juvenile xanthogranuloma. **A** Pink nodule with a few telangiectasias representing an early lesion. **B** Well-developed yellow–brown papulonodule on the chin, with the color reflecting the accumulation of lipid within histiocytes. *Courtesy, Julie V Schaffer, MD.*

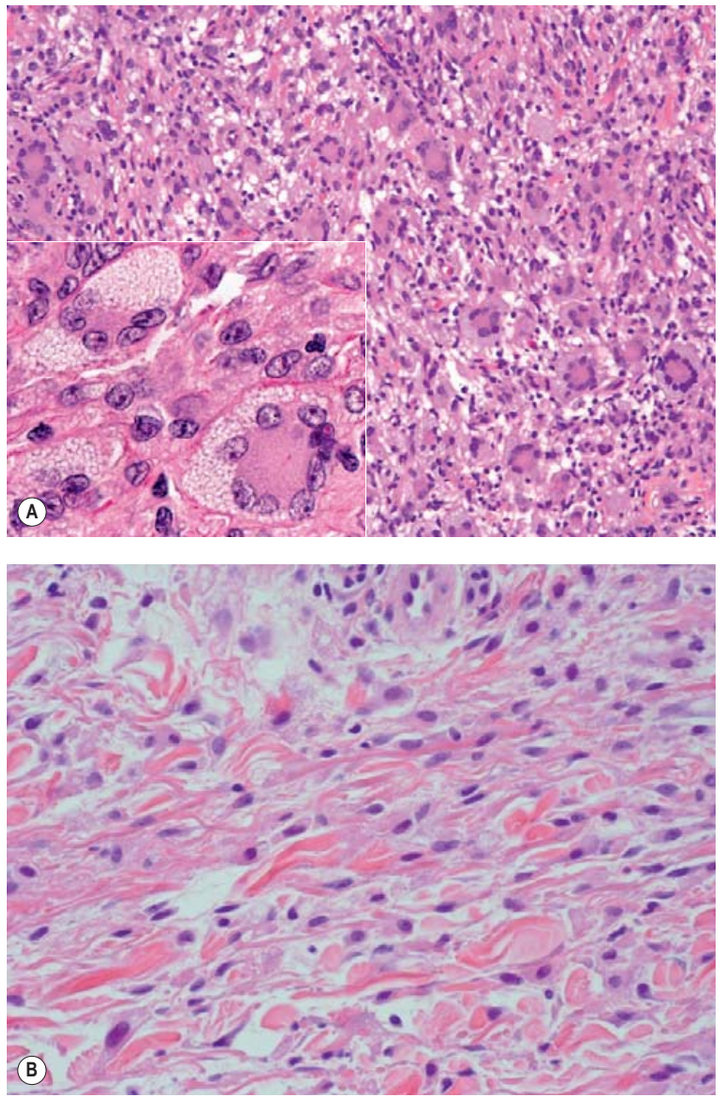


Fig. 91.10 Juvenile xanthogranuloma. **A** Dermal histiocytic infiltrate mixed with lymphocytes and scattered Touton giant cells. Insert, Touton giant cells have a "wreath-like" arrangement of nuclei within the cell. **B** In some cases, the histiocytes can be spindled.

several patients, and patients with juvenile xanthogranuloma and NF1 have at least a 20-times increased risk of developing juvenile myelomonocytic leukemia[33]. Other forms of leukemia have also been reported in association with juvenile xanthogranuloma, e.g. chronic lymphocytic leukemia in adults with multiple lesions.

In the majority of patients with disease limited to the skin, the course is self-limited and benign. These patients are otherwise in good health and lesions usually regress within 3–6 years. Hyperpigmentation, mild atrophy or anetoderma may remain.

Pathology

Typically, nodules demonstrate a well-demarcated dense infiltrate of histiocytes in the superficial dermis in small lesions, extending into the subcutis in larger lesions. There is often loss of the rete ridges, and ulceration occurs in some cases. Early lesions usually demonstrate monomorphous histiocytes with abundant eosinophilic cytoplasm. In mature lesions, the histiocytes develop lipid in their cytoplasm, creating a foamy "xanthomatous" appearance. Touton giant cells are a characteristic finding (Fig. 91.10). Lymphocytes, eosinophils and plasma cells are also scattered throughout the infiltrate. Variants without Touton giant cells or with many spindle cells have been reported, but serial sections typically reveal rare giant cells[13]. A rare lichenoid pattern has also been reported[13].

Juvenile xanthogranuloma histiocytes stain positively for HAM56, CD68 and factor XIIIa (see Fig. 91.6, Table 91.2)[34]. Some cases have shown expression of S100; CD1a is usually negative and Langerin (CD207) is always negative. By electron microscopy, comma-shaped bodies, lipid vacuoles, cholesterol clefts and myeloid bodies have been observed in the histiocytes.

Differential diagnosis

The major diagnostic dilemmas occur with the other non-LCH disorders and LCH, although the initial clinical differential diagnosis of a single lesion can be broad (e.g. molluscum contagiosum, Spitz nevus). Some examples of adult xanthogranuloma have been reported to have a similar clinical presentation, histology and immunophenotype as giant cell reticulohistiocytoma[35]. In general, the constellation of clinical and histopathologic features allows a distinction between juvenile xanthogranuloma and benign cephalic histiocytosis or generalized eruptive histiocytoma, the two most closely related non-Langerhans cell disorders. LCH can always be differentiated from juvenile xanthogranuloma by the use of immunostains.

Treatment

Due to the self-limiting nature of the eruption, no treatment is required. Occasionally, lesions are removed for cosmetic concerns, despite the anticipated spontaneous resolution. While ocular lesions often require intervention (e.g. topical corticosteroids for iris lesions, excision for limbal lesions), sites of systemic involvement can be followed without treatment unless their location interferes with normal function. For patients in the latter group, various chemotherapeutic regimens, radiotherapy, high-dose systemic corticosteroids, and cyclosporine have been tried in isolated case reports[36]. Given the possibility of spontaneous involution, however, it is difficult to gauge response to treatment.

Necrobiotic Xanthogranuloma

Synonym: ▪ Necrobiotic xanthogranuloma with paraproteinemia

Key features

- Average age of onset is the sixth decade
- Firm nodules and plaques with a yellow hue; may develop ulceration
- Most common site of involvement is the periorbital region
- Multisystem disease that includes hepatosplenomegaly and ocular involvement
- An IgG monoclonal gammopathy is seen in at least 80% of patients
- Paraproteinemia is due to plasma cell dyscrasias or lymphoproliferative disorders

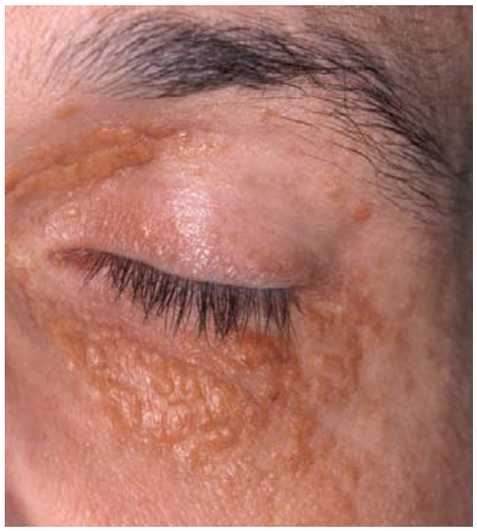


Fig. 91.11 Necrobiotic xanthogranuloma. Yellow–brown papules and plaques in a periorbital distribution in a patient with chronic lymphocytic leukemia. Such lesions may initially be mistaken for xanthelasma. *Courtesy, Kalman Watsky, MD.*

Introduction

Necrobiotic xanthogranuloma is a rare, progressive multisystem histiocytic disease characterized by destructive cutaneous and subcutaneous lesions. The vast majority of patients have a monoclonal gammopathy due to either a plasma cell dyscrasia or a lymphoproliferative disorder (see Ch. 119).

History

Necrobiotic xanthogranuloma was characterized in 1980 by Kossard and Winkelmann[37]. Their original eight patients demonstrated yellowish plaques, subcutaneous nodules, and an associated dysproteinemia. These authors also noted several reports published prior to 1980 representing unrecognized cases of necrobiotic xanthogranuloma.

Epidemiology

Necrobiotic xanthogranuloma is a rare disorder. In 1992, Mehregan and Winkelmann[38] reported their 32 patients with necrobiotic xanthogranuloma and reviewed the 16 reported cases from the world literature. Men and women are affected approximately equally. The average age of onset is the sixth decade.

Pathogenesis

While the pathogenesis of necrobiotic xanthogranuloma is as yet unknown, its strong association with monoclonal gammopathies has led to several hypotheses. The paraprotein may act either as a primary inciting agent or as a cofactor in eliciting a giant cell granulomatous reaction. In a recent study, there was no evidence of a monoclonal proliferation of plasma cells within the inflammatory infiltrate of skin lesions[39].

Clinical features

Cutaneous lesions, typically multiple, have appeared in all cases. The classic skin lesion is an asymptomatic indurated papule, nodule or plaque with a yellow "xanthomatous" hue (Fig. 91.11). Other reported features include telangiectasias, atrophy, ulceration of lesions and scarring, with scars being common sites for the development of new lesions.

The periorbital region is the most common site of involvement. The trunk, remainder of the face, and proximal extremities are also frequently involved. Approximately 50% of patients have ophthalmic manifestations, which include orbital masses, ectropion, ptosis, conjunctival lesions, keratitis and scleritis, episcleritis, anterior uveitis, and proptosis[40].

A hallmark feature of necrobiotic xanthogranuloma is the associated paraproteinemia, an IgG monoclonal gammopathy, which is found in at least 80% of cases. The paraproteinemia can be detected by serum protein electrophoresis and/or the more sensitive immunofixation electrophoresis. Other common findings include hepatomegaly, splenomegaly, an increased ESR, leukopenia, hypocomplementemia, and an underlying plasma cell dyscrasia (including myeloma). Less commonly, cryoglobulinemia and/or an underlying lymphoproliferative disorder are observed. Of the 48 patients described by Mehregan and Winkelmann[38], a plasma cell dyscrasia was found in 17 patients (with eight fulfilling the criteria for multiple myeloma) and lymphoproliferative disorders in two patients. Postmortem examination has demonstrated involvement of multiple organ systems, with endocardial necrobiotic xanthogranuloma found in most cases.

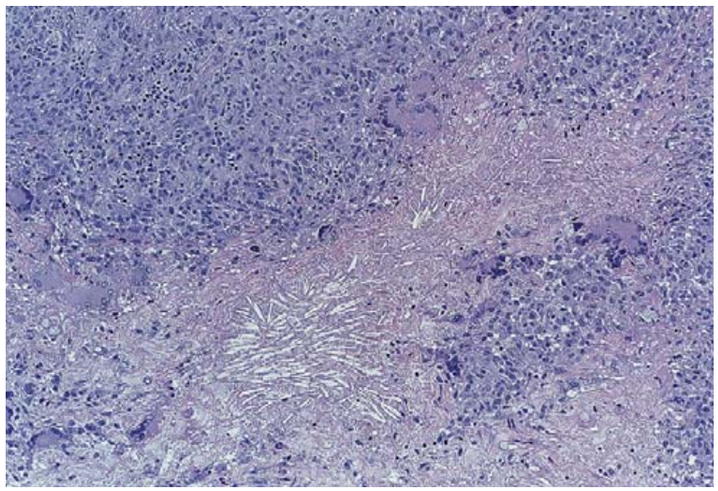


Fig. 91.12 Necrobiotic xanthogranuloma. A necrobiotic area contains cholesterol clefts. Surrounding this area are many bizarre multinucleated giant cells.

Ugurlu et al.[41] examined the outcomes in 26 patients with ocular and systemic manifestations of necrobiotic xanthogranuloma. Ten of their patients developed a plasma cell dyscrasia (including myeloma) or a lymphoproliferative disorder. The associated malignancy often developed after the onset of cutaneous manifestations and did not tend to be aggressive. Overall survival was 100% at 10 years and 90% at 15 years. A poorer survival rate was noted in a study of 22 patients by Finan and Winkelmann[42]. Two patients died of multiple myeloma within 10 years, and three others died of various solid tumor malignancies.

Pathology

Classic, non-ulcerated lesions have a normal epidermis and superficial dermis. A palisading xanthogranuloma is found in the middle dermis extending through the panniculus (Fig. 91.12). The granulomas consist of histiocytes, foam cells, lymphoid follicles, plasma cells and giant cells with zones of necrobiosis. Cholesterol clefts are found in areas of "necrobiosis" (altered collagen, in which there appears to be necrosis, loss of collagen bundle integrity, and nuclear debris). A prominent feature is the presence of both Touton giant cells and large, bizarre foreign body giant cells. These cells are found scattered within the granuloma and often at the margins of areas of necrobiosis. Histiocytic

cells stain positively for lysozyme, CD68 and CD11b (see Fig. 91.4, Table 91.2)[38,41,43].

Differential diagnosis

The clinical differential diagnosis includes necrobiosis lipoidica, normolipemic plane xanthomas, xanthelasma, non-LCH disorders (xanthoma disseminatum, multicentric reticulohistiocytosis, juvenile xanthogranuloma, Erdheim–Chester disease), foreign body granulomas, and sarcoidosis. Subcutaneous nodules also need to be distinguished from the nodules of rheumatoid arthritis and subcutaneous granuloma annulare. However, most of these disorders can be excluded on the basis of morphology, distribution pattern, histologic features and associated systemic manifestations (if any).

Treatment

No controlled clinical studies are available regarding the treatment of necrobiotic xanthogranuloma. Resolution or improvement of skin lesions has been seen in some patients treated with low-dose chlorambucil, melphalan or cyclophosphamide (± systemic corticosteroids), radiation therapy, CO_2 laser, and plasmapheresis. With rare exceptions, topical and locally injected corticosteroids have been tried with minimal or no benefit; in case series, systemic corticosteroids (including pulsed high-dose dexamethasone) have resulted in improvement in some patients. Ugurlu et al.[41] noted a 42% recurrence rate following surgical excision of lesions, and recommended against this intervention, if possible.

Reticulohistiocytosis

Synonyms for giant cell reticulohistiocytoma: ■ Solitary reticulohistiocytosis ■ Solitary reticulohistiocytoma

Key features

- Clinical spectrum ranges from a single lesion to multicentric reticulohistiocytosis with systemic involvement
- All forms are seen primarily in adults
- Papules and nodules favor the head, hands and elbows; periungual papules have been likened to "coral beads"
- 50% of patients develop mucous membrane lesions (oral and nasopharyngeal)
- Multicentric reticulohistiocytosis is associated with a destructive arthritis and, in some patients, solid organ malignancies
- Histiocytes have a characteristic "ground glass" appearance

Introduction

The reticulohistiocytoses are a rare group of closely related non-Langerhans cell histiocytoses which most commonly affect adults. The spectrum of disease ranges from a solitary cutaneous form to multicentric reticulohistiocytosis, a disease with both cutaneous and systemic features. Well-developed lesions demonstrate a classic histopathology consisting of mononucleated and multinucleated giant cells with a "ground glass" appearance.

History

Giant cell reticulohistiocytoma, an isolated cutaneous tumor sometimes referred to as a solitary reticulohistiocytoma, was first reported in 1950 by Zac[44]. The term multicentric reticulohistiocytosis was introduced by Goltz and Laymon[45] in 1954 to define those cases with both cutaneous and systemic manifestations. Familial histiocytic dermatoarthritis, described in 1973, is a very rare variant of multicentric reticulohistiocytosis, characterized by a familial occurrence and associated glaucoma, uveitis and cataracts[46].

Epidemiology

All forms of reticulohistiocytoses occur predominantly in Caucasian adults, with pediatric cases being exceptionally rare. Multicentric reticulohistiocytosis is uncommon, occurring most frequently in women during the fourth decade. Giant cell reticulohistiocytoma occurs in young adults and has no sexual predilection.

Pathogenesis

The pathogenesis of the reticulohistiocytoses is unknown. However, it has been speculated that it represents an abnormal histiocytic response to various stimuli. Mycobacteria have been suggested as a possible trigger for multicentric reticulohistiocytosis. In one old study, 56% of multicentric reticulohistiocytosis patients had a positive tuberculin skin test[47]. Multicentric reticulohistiocytosis has also been reported to respond to antituberculosis treatment. However, confirmation of mycobacteria within skin nodules is lacking. Others have suggested that the histiocytic response in multicentric reticulohistiocytosis is an immunologic process related to an underlying autoimmune or neoplastic disorder or even that the multicentric reticulohistiocytosis represents a systemic osteoclastic disease.

The cause of giant cell reticulohistiocytoma is even less clear. Some lesions are believed to occur after trauma. Cerio et al.[35] referred to giant cell reticulohistiocytoma synonymously with the solitary or eruptive adult form of xanthogranuloma.

Clinical features

Giant cell reticulohistiocytoma presents as a single, asymptomatic, yellow to red nodule. It can develop at any cutaneous site but is thought to favor the head. The patients are otherwise healthy and lesions tend to spontaneously resolve. Rarely, multiple cutaneous lesions develop without any evidence of systemic disease. Nodules are generally less than 1 cm in diameter.

Multicentric reticulohistiocytosis is a disease characterized by cutaneous and mucous membrane reticulohistiocytomas and severe arthropathy. There is an association with hyperlipidemia, a positive tuberculin skin test, systemic vasculitis, and autoimmune disease. Up to 28% of multicentric reticulohistiocytosis patients have reportedly had an associated malignancy, with bronchial, breast, stomach and cervical carcinomas being most common. An elevated ESR and anemia have been noted in approximately half of patients, and one-third demonstrate hypercholesterolemia. Rarely, monoclonal hypergammaglobulinemia and cryoglobulinemia have been observed. Fever and weight loss can occur.

Cutaneous lesions range from a few millimeters to 2 cm and are skin-colored to pink, red–brown or yellow. Lesions tend to be acrally distributed. Favored sites include the head, hands, fingers, ears, and articular regions of the limbs (Fig. 91.13). Small papules aligned along the periungual regions result in a characteristic "coral bead" appearance. Approximately one-half of patients develop papules and nodules of the oral, pharyngeal and nasal mucosa. Less common findings include a "leonine facies" secondary to severe facial involvement, periarticular rheumatoid-like nodules, an initial photodistribution, and secondary nail changes.

A 6–8-year course of symmetric, erosive arthritis of multiple joints is common and there is progression to arthritis mutilans in 45% of cases. The joints of the fingers and hands, as well as the knees and wrists, are most commonly involved, although any joint may be affected. Cartilaginous destruction of the nose and ears can lead to facial disfigurement. Rarely, there is histiocytic involvement of the heart, eye, lungs, thyroid, liver, kidney, muscle, salivary gland and/or bone marrow. For most, the disease spontaneously remits within 5–10 years, though patients are often left with significant disability. Fatal disease has been rarely reported in patients with widespread systemic involvement.

Pathology

Many believe that the histopathology of giant cell reticulohistiocytoma and multicentric reticulohistiocytosis is identical. Well-developed lesions demonstrate a dermal infiltrate of lymphocytes and histiocytes, with occasional plasma cells and eosinophils. The histiocytes have a characteristic appearance. They are both mononuclear and multinuclear, with abundant eosinophilic, homogenous and finely granular cytoplasm, creating a "ground glass" effect (Fig. 91.14). Multinucleated cells demonstrate nuclei arranged haphazardly, aligned at the periphery, or clustered in the center.

Giant cell reticulohistiocytoma and multicentric reticulohistiocytosis histiocytes stain positively for lysozyme and α_1-antitrypsin and also

Fig. 91.13 Multicentric reticulohistiocytosis. A Grouped firm red–brown papules on the dorsal surface of the fingers, hand and wrist in this 73-year-old African-American woman. **B** Grouped pink papulonodules on the elbow in a second patient. **C** A more subtle presentation in a third patient, with small pink papules and thin plaques that favor the skin overlying the small joints of the hands; this is the form that can initially be confused with dermatomyositis. *A, Courtesy, Susan D Laman, MD; B, Courtesy, Jean L Bolognia, MD; C, Courtesy, Kalman Watsky, MD.*

express CD68, CD11b, CD14 and HAM56 (see Fig. 91.4, Table 91.2)[35,48]. S100 is most often negative. Several case reports have shown positive staining for factor XIIIa, though Zelger et al.[49] found that factor XIIIa was positive in cases of giant cell reticulohistiocytoma and negative in multicentric reticulohistiocytosis lesions.

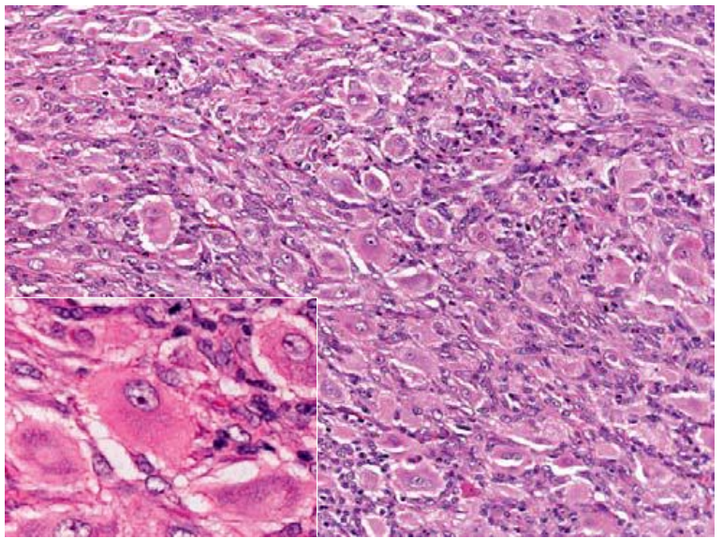


Fig. 91.14 Reticulohistiocytosis. Numerous mononucleated and multinucleated histiocytes extending throughout the dermis. These histiocytes have abundant eosinophilic, finely granular cytoplasm, creating a "ground glass" appearance (insert). *Courtesy, Lorenzo Cerroni, MD.*

Differential diagnosis

The nodule of giant cell reticulohistiocytoma is not distinctive, and the clinical differential diagnosis is broad (e.g. adnexal tumor, foreign body granuloma). Some examples of adult xanthogranuloma have been reported to have a similar clinical presentation, histology and immunophenotype to giant cell reticulohistiocytoma[35].

Multicentric reticulohistiocytosis must be differentiated from rheumatoid arthritis, dermatomyositis (especially when lesions are photodistributed), and the other histiocytoses, with juvenile xanthogranulomas, generalized eruptive histiocytosis, and cutaneous Rosai–Dorfman disease presenting the greatest challenge. While the constellation of clinical and histopathologic findings will eventually lead to the correct diagnosis, several biopsies over time may be required in some patients.

Treatment

Surgical excision of giant cell reticulohistiocytoma is curative. Most systemic therapy for multicentric reticulohistiocytosis has not been effective. Although not in controlled clinical trials, NSAIDs, oral corticosteroids, azathioprine, cyclophosphamide and chlorambucil have been tried, but with limited or no benefit. However, there are multiple case reports of substantial benefit with methotrexate, either alone or in combination with cyclophosphamide and corticosteroids[50]. Alendronate and inhibitors of TNF-α have recently been shown to be of value in isolated cases.

Rosai–Dorfman Disease

Synonyms: ■ Sinus histiocytosis with massive lymphadenopathy ■ Destombes–Rosai–Dorfman syndrome

Key features

- Children and young adults are most commonly affected
- Although massive, painless bilateral cervical lymphadenopathy is characteristic, extranodal sites, including the skin, can be the sole manifestation of the disease
- Skin-limited form is increasingly being recognized
- In the systemic form, cutaneous lesions occur in a minority of cases (~10%), are usually multiple, and are clinically nonspecific
- Fever and polyclonal hypergammaglobulinemia are often seen
- In the lymph nodes and the skin, emperipolesis is a common histologic feature

Introduction

Rosai–Dorfman disease is an uncommon, often protracted, histiocytic proliferative disorder. It is characterized by massive but painless bilateral cervical lymphadenopathy, fever, anemia, elevated ESR, neutrophilia and a polyclonal hypergammaglobulinemia. Cutaneous lesions occur in a minority of patients with systemic disease, are usually multiple, and are clinically nonspecific.

History

Sinus histiocytosis with massive lymphadenopathy was described as a distinct entity by Rosai and Dorfman[51] in 1969. However, the eponymous designation "Rosai–Dorfman disease" is more appropriate as some patients have extranodal lesions as the sole manifestation of the condition[52].

Epidemiology

For a time, there was a repository for cases of Rosai–Dorfman disease, rather than a registry in the true sense. In 1990, the repository contained 423 patients, and by 1995, almost 600 cases had been reported[53,54]. Rosai–Dorfman disease has a widespread geographic distribution, although there is a higher incidence in the West Indies. The systemic form occurs most commonly in children and young adults and is more frequently seen in male patients. In 1990, an equal percentage of white and black patients, 44% of each, were in the repository[53]. On the other hand, the skin-limited form occurs primarily in adults and favors women.

Pathogenesis

The etiology of Rosai–Dorfman disease has not been identified, though a viral pathogenesis has been postulated. HHV-6 sequences have been detected in involved lymph nodes[55], but this finding is nonspecific given the presence of HHV-6 in many reactive and infectious disorders of lymphoid tissue[56]. More recently, it has been suggested that Rosai–Dorfman disease may be closely related to autoimmune lymphoproliferative syndrome, an inherited disorder associated with defects in Fas-mediated apoptosis (see Table 60.5)[57].

Clinical features

While Rosai–Dorfman disease is often an indolent, self-limited disease, a protracted course marked by remissions and exacerbations occurs in many patients. The characteristic clinical feature is massive, painless, bilateral cervical lymphadenopathy. However, any nodal site may be involved, unilateral involvement may occur, and an absence of lymph node involvement has been reported in multiple patients. Fever is a frequent occurrence and most cases demonstrate an elevated ESR and polyclonal hypergammaglobulinemia. A common finding is mild anemia, though severe anemia has occurred. Neutrophilia is occasionally seen. There are multiple reports of non-Hodgkin lymphoma occurring in association with Rosai–Dorfman disease.

Immune disorders occur in approximately 15% of patients with Rosai–Dorfman disease. Anti-red blood cell autoantibodies and joint disease are the most common findings. Patients with immunologic abnormalities have an unfavorable prognosis. In one analysis, 10 of 14 fatal cases were noted to have some form of immune dysfunction[58]. Other unfavorable prognostic signs include disseminated nodal disease or involvement of the liver, kidney or lower respiratory tract.

Over 40% of patients with Rosai–Dorfman disease have at least one extranodal site of involvement. The most common extranodal sites are the skin and soft tissue, the eyelid and orbit, the upper respiratory tract, major salivary glands, CNS and bone. However, virtually any organ can be involved.

Cutaneous involvement occurs in approximately 10% of patients with the systemic form. The skin may be the only organ involved, with skin-limited disease increasingly being recognized. Cutaneous lesions are often multiple and appear as nonspecific red to red–brown or xanthomatous macules, papules, nodules or plaques (Fig. 91.15); in the skin-limited form, there may be a single lesion. Panniculitis has also been reported. The eyelids and malar regions are frequent sites of involvement.

Pathology

Rosai–Dorfman disease, or sinus histiocytosis with massive lymphadenopathy, is a disease which had been characterized by specific findings in the affected lymph nodes. However, consistent and unique histopathologic and immunohistochemical findings in the skin make diagnosis possible even in cases without lymph node involvement.

Affected lymph nodes demonstrate dilated sinuses containing neutrophils, lymphocytes, plasma cells, and histiocytes with large vesicular nuclei and abundant cytoplasm. A characteristic though not unique feature is emperipolesis, or the taking up of intact lymphocytes and plasma cells by the histiocytes. Neutrophils and red cells can also be internalized in a similar fashion.

Cutaneous lesions demonstrate a dense dermal infiltrate of histiocytes with scattered lymphocytes, plasma cells and neutrophils. The histiocytes have large vesicular nuclei, small nucleoli, and abundant foamy, eosinophilic cytoplasm with feathery borders (Fig. 91.16). Emperipolesis is a constant finding. Occasional findings include foamy histiocytes within dilated lymphatics, thick-walled venules with surrounding plasma cells, lymphoid aggregates, fibrosis and multinucleate histiocytes.

In Rosai–Dorfman disease, the histiocytes stain positively for S100, CD11c, CD14, CD68, laminin 5 and lysozyme (see Fig. 91.6, Table 91.2)[59]. Examples of positive staining for factor XIIIa have been reported. With the exception of one study from 1994[60], CD1a expression in Rosai–Dorfman disease has been shown to be negative.

Fig. 91.15 Cutaneous Rosai–Dorfman disease. Discrete, dome-shaped, brown papules.

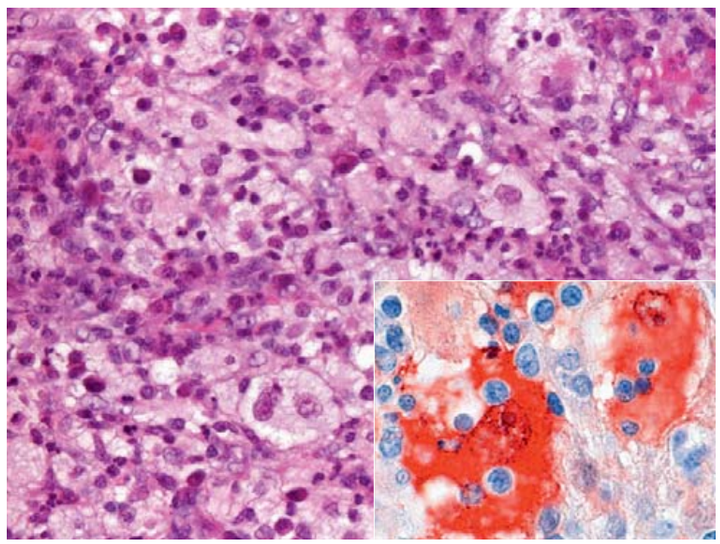


Fig. 91.16 Rosai–Dorfman disease. Large histiocytes with clear cytoplasm admixed with small lymphocytes and plasma cells. The large cells stain positively for S100 (insert), and the immunostain highlights lymphoid cells within the cytoplasm of large histiocytes (emperipolesis). *Courtesy, Lorenzo Cerroni, MD.*

Differential diagnosis

Given the clinically nonspecific cutaneous lesions found in Rosai–Dorfman disease, the differential diagnosis includes the other histiocytoses, sarcoidosis, infectious processes, and other infiltrative disorders. The diagnosis of cutaneous Rosai–Dorfman disease is based upon the combination of characteristic histologic and immunohistochemical findings. The differential diagnosis of massive lymphadenopathy includes Hodgkin lymphoma, non-Hodgkin lymphoma, chronic lymphocytic leukemia, metastases, infectious lymphadenopathies, and Kikuchi's disease (a histiocytic necrotizing lymphadenitis that often affects young Asian women). Rosai–Dorfman disease is differentiated by a typical combination of clinical and laboratory findings plus confirmatory histology and immunohistochemistry.

Treatment

Many lesions are asymptomatic and heal spontaneously, thus not requiring treatment. When treatment is indicated due to destructive lesions, disseminated disease or lesions causing physical compromise, radiotherapy, surgical excision, systemic corticosteroids and alkylating agents have been used with some success[61]. There are also a few isolated reports of improvement with thalidomide. However, due to the rarity of the disorder, there have been no controlled trials.

Fig. 91.17 Xanthoma disseminatum. Symmetric involvement of the major flexures is a characteristic finding. Note the yellow discoloration of some of the coalescing papulonodules. *Courtesy, David Wetter, MD.*

Xanthoma Disseminatum

Synonym: ■ Disseminated xanthosiderohistiocytosis

Key features

- Classic triad of cutaneous xanthomas, mucous membrane xanthomas, and diabetes insipidus
- Symmetric distribution
- Flexural and intertriginous involvement
- Upper airway lesions

Fig. 91.18 Xanthoma disseminatum. Sclerotic form of xanthoma disseminatum in a patient who developed multiple myeloma.

Introduction

Xanthoma disseminatum is a rare, normolipemic, histiocytic proliferative disorder affecting the skin, mucous membranes and, frequently, the hypothalamus and pituitary, leading to transient diabetes insipidus.

History

Four cases of "xanthomatosis disseminata" were described by Montgomery and Osterberg[62] in 1938. A review and characterization of the disorder was provided by Altman and Winkelmann[63] in 1962.

Epidemiology

Xanthoma disseminatum is a rare condition, with approximately 100 cases reported by 1995[64]. Men are more commonly affected than women. Age of onset ranges from 8 months to 85 years, though more than 60% of patients develop the disease before age 25 years.

Pathogenesis

The etiology of xanthoma disseminatum is unknown. As most patients have normal lipid levels, it has been suggested that xanthoma disseminatum represents a reactive proliferative disorder of histiocytes with secondary accumulation of lipid.

Clinical features

Patients with xanthoma disseminatum may demonstrate the triad of cutaneous xanthomas, xanthomas of mucous membranes, and diabetes insipidus. The primary xanthomatous lesion is a yellow, red or brown papule. The onset of disease is marked by the eruption of hundreds of papules, symmetrically arranged, on the face and in the flexural and intertriginous areas of the trunk and proximal extremities (Fig. 91.17). The lesions tend to cluster into well-formed, potentially disfiguring plaques (Fig. 91.18). Older lesions may become atrophic.

Mucous membrane lesions are found in 40–60% of patients with xanthoma disseminatum, the upper airway and oral mucosa being commonly involved. Corneal and conjunctival lesions can threaten vision. CNS involvement of the hypothalamus and pituitary stalk results in diabetes insipidus in 40% of patients. This is usually mild, transient and sensitive to vasopressin. Rare associations with xanthoma disseminatum have included monoclonal gammopathies due to plasma cell dyscrasias and thyroid disorders.

Caputo et al.[64] have suggested that patients follow one of three clinical courses: (1) a rare, self-healing form with spontaneous resolution of lesions; (2) the common persistent form in which lesions may never resolve; and (3) the very rare progressive form with organ dysfunction and CNS involvement. Disease-related mortality has been reported in a few cases, including one with associated CNS involvement outside the pituitary and hypothalamus[65].

Pathology

In the early stages, there is a dense dermal infiltrate of histiocytes with few foamy cells or other inflammatory cells. Fully developed lesions, however, demonstrate many foam cells with histiocytes, and scattered

CLINICAL AND IMMUNOPHENOTYPIC FEATURES OF THE MALIGNANT HISTIOCYTIC DISORDERS (HISTOCYTOSIS III)				
Disorder	**Epidemiology**	**Most common initial site**	**Immunophenotype**	**Prognosis**
Langerhans cell sarcoma	Adults > children; F > M	Skin	+ S100, CD1a, Langerin	Aggressive; > 50% mortality
Histiocytic sarcoma	Adults > children	GI, skin, soft tissue	+ CD68, CD163, lysozyme	Aggressive; 60–80% mortality
Interdigitating dendritic cell sarcoma	Adults > children	Solitary lymph node > skin	+ S100, vimentin, fascin; weakly + CD68, lysozyme, CD45	Aggressive; ~ 50% mortality
Follicular dendritic cell sarcoma	Adults > children	Cervical lymph node	+ CD21, CD35, CD23, clusterin; +/– S100, CD68	Indolent; 10–20% mortality

Table 91.3 Clinical and immunophenotypic features of the malignant histiocytic disorders (histiocytosis III). F, female; M, male.

THE DERMAL DENDROCYTE HAMARTOMAS					
	Epidemiology*	**Most common site**	**Clinical presentation**	**Pathology**	**Immunophenotype**
Medallion-like dermal dendrocyte hamartoma†	Congenital > acquired 13 pts, mostly female	Chest	Single, 2–16 cm erythematous, atrophic (wrinkled) patch or plaque	Dermal spindle cell proliferation	Majority + for both CD34 & factor XIIIa
Fat-storing hamartoma of dermal dendrocytes	Congenital 1 pt (male)	Lumbar‡	Single, reddish-brown plaque with nodularity	Lipidized histiocytes between collagen bundles within reticular dermis	+ Factor XIIIa (CD34 was not performed)
Dermal dendrocyte hamartoma with stubby white hair	Congenital 1 pt (female)	Back‡	Single, soft, red nodule with short white hairs	Spindle cells	+ CD34; – factor XIIIa
Congenital CD34+ granular cell dendrocytosis	Congenital 1 pt (male)	Face and extremities‡	Numerous skin-colored papules and plaques	"Granular cells" interstitially arranged, primarily within superficial dermis	+ CD34; – factor XIIIa

*To date.
†May require analysis for the *COL1A1-PDGFB* fusion gene (e.g. via fluorescence in situ hybridization [FISH]) to exclude an atrophic dermatofibrosarcoma protuberans, which can have similar clinicopathologic features (see Ch. 116)
‡Based on only one reported patient.

Table 91.4 The dermal dendrocyte hamartomas.

lymphocytes, plasma cells and Touton cells. Xanthoma disseminatum histiocytes stain for lysozyme and α_1-antitrypsin and also express CD68, CD11b, CD14, CD11c and factor XIIIa (see Fig. 91.4, Table 91.2)[64,66]. Typically, only CD68 and occasionally factor XIIIa immunostains are performed.

Differential diagnosis

The disorders most likely to be confused with xanthoma disseminatum include juvenile xanthogranuloma, eruptive xanthoma (see Ch. 92), generalized eruptive histiocytoma, papular xanthoma, and multicentric reticulohistiocytosis. Most often, these can be fairly easily differentiated based on clinical and histopathologic bases.

Treatment

As xanthoma disseminatum is a rare disease, there are no controlled trials for systemic therapy. Radiotherapy has been used to control airway obstructive disease. For cutaneous and mucosal lesions, oral corticosteroids have not been of value, while the effectiveness of clofibrate has been mixed. Cyclophosphamide has been effective in the control of mucosal lesions[65]. Cutaneous lesions have been treated by CO_2 laser, dermabrasion, radiotherapy, electrocoagulation, intralesional corticosteroids, cryotherapy and surgical excision.

MALIGNANT HISTIOCYTIC DISORDERS

Synonym: ■ Class III histiocytosis

The malignant histiocytic disorders are all very rare tumors (Table 91.3). Because most cases previously diagnosed as being of histiocytic origin have subsequently been shown to be either high-grade B-cell or T-cell lymphoid malignancies, their true incidence is uncertain. Nonetheless, the most recent WHO classification of tumors of hematopoietic and lymphoid tissues includes several true malignant histiocytic tumors[67].

DERMAL DENDROCYTE HAMARTOMAS

Synonyms: ■ $CD34^+$ dermal dendrocytomas ■ Plaque-like $CD34^+$ dermal fibroma

The dermal dendrocyte hamartomas are exceptionally rare and most cases are of recent description (Table 91.4)[68–71]. As the name implies, they are thought to be derived from dermal dendrocytes/dendritic cells, in particular $CD34^+$ dermal dendrocytes. The most common of these entities is the medallion-like dermal dendrocyte hamartoma[68].

REFERENCES

1. Caputo R, Passoni E, Cavicchini S. Papular xanthoma associated with angiokeratoma of Fordyce: considerations on the nosography of this rare non-Langerhans cell histiocytoxanthomatosis. Dermatology 2003;206:165–8.
2. Lichtenstein L, Histiocytosis X. integration of eosinophilic granuloma of bone, "Letterer-Siwe disease" and "Hand-Schüller-Christian" disease as related manifestations of a single nosologic entity. Arch Pathol. 1953;56:84–102.
3. Hashimoto K, Pritzker MS. Electron microscopic study of reticulohistiocytoma. An unusual case of congenital self-healing reticulohistiocytosis. Arch Dermatol. 1973;107:263–70.
4. Chu A, D'Angio GJ, Favara BE, et al. Histiocytosis syndromes in children. Lancet. 1987;2:41–2.
5. Arico M, Nichols K, Whitlock JA, et al. Familial clustering of Langerhans cell histiocytosis. Br J Haematol. 1999;107:883–8.
6. McClain K, Jin H, Gresik V, et al. Langerhans cell histiocytosis: lack of a viral etiology. Am J Hematol. 1994;47:16–20.
6a. Badalian-Very G, Vergilio J, Degar BA, et al. Recurrent *BRAF* mutations in Langerhans cell histiocytosis. Blood. 2010;116:1919-23.

7. Willman CL, Busque L, Griffith BB, et al. Langerhans'-cell histiocytosis (histiocytosis X) – a clonal proliferative disease. N Engl J Med. 1994;331:154–60.
8. Yu RC, Chu C, Buluwela L, et al. Clonal proliferation of Langerhans cells in Langerhans cell histiocytosis. Lancet. 1994;343:767–8.
9. Egeler RM, Neglia JP, Arico M, et al. The relation of Langerhans cell histiocytosis to acute leukemia, lymphomas, and other solid tumors. Hematol Oncol Clin North Am. 1998;12:369–78.
10. Gadner G, Grois N, Arico M, et al. A randomized trial of treatment for multisystem Langerhans' cell histiocytosis. J Pediatr. 2001;138:728–34.
11. Gianotti F, Caputo R, Ermacora E. Singuliére histiocytose Infantile à cellules avec particules vermiformes intracytoplasmiques. Bull Soc Fr Dermatol Syphiliogr. 1971;78:232–3.
12. Jih DM, Salcedo SL, Jaworsky C. Benign cephalic histiocytosis: a case report and review. J Am Acad Dermatol. 2002;47:908–13.
13. Gianotti R, Alessi E, Caputo R. Benign cephalic histiocytosis: a distinct entity or a part of a wide spectrum of histiocytic proliferative disorders of children? Am J Dermatopathol. 1993;15:315–19.
14. Weston WL, Travers SH, Mierau GW, et al. Benign cephalic histiocytosis with diabetes insipidus. Pediatr Dermatol. 2000;17:296–8.
15. Gianotti F, Caputo R, Ermacora E, et al. Benign cephalic histiocytosis. Arch Dermatol. 1986;122: 1038–43.
16. Zelger BG, Zelger B, Steiner H, et al. Solitary giant xanthogranuloma and benign cephalic histiocytosis –variants of juvenile xanthogranuloma. Br J Dermatol. 1995;133:598–604.
17. Winkelmann RK, Muller SA. Generalized eruptive histiocytoma: a benign papular histiocytic reticulosis. Arch Dermatol. 1963;88:586–96.
18. Sidoroff A, Zelger B, Steiner H, et al. Indeterminate cell histiocytosis – a clinicopathological entity with features of both X- and non-X histiocytosis. Br J Dermatol. 1996;134:525–32.
19. Seward JL, Malone JC, Callen JP. Generalized eruptive histiocytosis. J Am Acad Dermatol. 2004;50:116–20.
20. Caputo R, Ermacora E, Gelmetti C, et al. Generalized eruptive histiocytoma in children. J Am Acad Dermatol. 1987;17:449–54.
21. Repiso T, Roca-Miralles M, Kanitakis J, et al. Generalized eruptive histiocytoma evolving into xanthoma disseminatum in a 4-year-old boy. Br J Dermatol. 1995;132:978–82.
22. Wood GS, Hu CH, Beckstead JH, et al. The indeterminate cell proliferative disorder: report of a case manifesting as an unusual cutaneous histiocytosis. Dermatol Surg Oncol. 1985;11:1111–19.
23. Ratzinger G, Burgdorf WH, Metze D, et al. Indeterminate cell histiocytosis: fact or fiction? J Cutan Pathol. 2005;32:552–60.
24. Flores-Stadler EM, Gonzalez-Crussi F, Greene M, et al. Indeterminate-cell histiocytosis: immunophenotypic and cytogenetic findings in an infant. Med Pediatr Oncol. 1999;32:250–4.
25. Manente L, Cotellessa C, Schmitt I, et al. Indeterminate cell histiocytosis: a rare histiocytic disorder. Am J Dermatopathol. 1997;19:276–83.
26. Helwig EB, Hackney VC. Juvenile xanthogranuloma (nevoxantho-endothelioma). Am J Pathol. 1954;30:625–6.
27. Adamson NF. Congenital xanthoma multiplex in a child. Br J Dermatol. 1905;17:222.
28. Caputo R. Juvenile xanthogranuloma. In: Text Atlas of Histiocytic Syndromes: A Dermatological Perspective. London: Martin Dunitz, 1998:39–58.
29. Bergman R, Aviram M, Shemer A, et al. Enhanced low-density lipoprotein degradation and cholesterol synthesis in monocyte-derived macrophages of patients with adult xanthogranulomatosis. J Invest Dermatol. 1993;101:880–2.
30. Gianotti F, Caputo R. Histiocytic syndromes: a review. J Am Acad Dermatol. 1985;13:383–404.
31. Newman B, Weimin H, Nigro K et al. Aggressive histiocytic disorders that can involve the skin. J Am Acad Dermatol. 2007;56:302–16.
32. Chang MW, Frieden IJ, Good W. The risk of intraocular juvenile xanthogranuloma: survey of current practices and assessment of risk. J Am Acad Dermatol. 1996;34:445–9.
33. Zvulunov A, Barak Y, Metzker A. Juvenile xanthogranuloma, neurofibromatosis, and juvenile chronic myelogenous leukemia. World statistical analysis. Arch Dermatol. 1995;131:904–8.
34. Marrogi AJ, Dehner LP, Coffin CM, et al. Benign cutaneous histiocytic tumors in childhood and adolescence, excluding Langerhans' cells proliferations. A clinicopathologic and immunohistochemical analysis. Am J Dermatopathol. 1992;14:8–18.
35. Cerio R, Spaull J, Oliver GF, et al. A study of factor XIIIa and Mac 387 immunolabeling in normal and pathological skin. Am J Dermatopathol. 1990;12: 221–33.
36. Hernandez-Martin A, Baselga E, Drolet BA, et al. Juvenile xanthogranuloma. J Am Acad Dermatol. 1997;36:355–67.
37. Kossard S, Winkelmann RK. Necrobiotic xanthogranuloma. Australas J Dermatol. 1980;21:85–8.
38. Mehregan DA, Winkelmann RK. Necrobiotic xanthogranuloma. Arch Dermatol. 1992;128:94–100.
39. Wood AJ, Wagner VU, Abbott JJ, et al. Necrobiotic xanthogranuloma. A review of 17 cases with emphasis on clinical and pathologic correlation. Arch Dermatol. 2009;145:279–84.
40. Robertson DM, Winkelmann RK. Ophthalmic features of necrobiotic xanthogranuloma with paraproteinemia. Am J Ophthalmol. 1984;97:173–83.
41. Ugurlu S, Bartley GB, Gibson LE. Necrobiotic xanthogranuloma: long-term outcome of ocular and systemic involvement. Am J Ophthalmol. 2000;129:651–7.
42. Finan MC, Winkelmann RK. Necrobiotic xanthogranuloma with paraproteinemia. A review of 22 cases. Medicine. 1986;65:376–88.
43. Stork J, Kodetova D, Vosmik F, et al. Necrobiotic xanthogranuloma presenting as a solitary tumor. Am J Dermatopathol. 2000;22:453–6.
44. Zac FG. Reticulohistiocytoma ("ganglioneuroma") of the skin. Br J Dermatol Syphilol. 1950;62:351–5.
45. Goltz RW, Laymon CW. Multicentric reticulohistiocytosis of the skin and synovia. Arch Dermatol Syphilol. 1954;69:717–30.
46. Zayid I, Farraj S. Familial histiocytic dermatoarthritis: a new syndrome. Am J Med. 1973;54:793–800.
47. Barrow MV, Holubar K. Multicentric reticulohistiocytosis. A review of 33 patients. Medicine. 1969;48:287–305.
48. Gorman JD, Danning C, Schumacher HR, et al. Multicentric reticulohistiocytosis: case report with immunohistochemical analysis and literature review. Arthritis Rheum. 2000;43:930–8.
49. Zelger B, Cerio R, Soyer HP, et al. Reticulohistiocytoma and multicentric reticulohistiocytosis. Histopathologic and immunophenotypic distinct entities. Am J Dermatopathol. 1994;16:577–84.
50. Rentsch JL, Martin EM, Harrison LC, et al. Prolonged response of multicentric reticulohistiocytosis to low dose methotrexate. J Rheumatol. 1998;25:1012–15.
51. Rosai J, Dorfman RF. Sinus histiocytosis with massive lymphadenopathy. A newly recognized benign clinicopathological entity. Arch Pathol. 1969;87:63–70.
52. Weedon D. Rosai-Dorfman disease. In: Skin Pathology. New York: Churchill Livingstone, 1997:865–96.
53. Foucar E, Rosai J, Dorfman R. Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease): review of the entity. Semin Diagn Pathol. 1990; 7: 19–73.
54. Rosai J. Lymph nodes. In: Ackerman's Surgical Pathology, 8th edn. St. Louis: Mosby, 1996:1694–5.
55. Levine PH, Jahan N, Murari P, et al. Detection of human herpesvirus 6 in tissues involved by sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease). J Infect Dis. 1992;166:291–5.
56. Sumiyoshi Y, Kikuchi M, Ohshima K, et al. Human herpesvirus-6 genomes in histiocytic necrotizing lymphadenitis (Kikuchi's disease) and other forms of lymphadenitis. Am J Clin Pathol. 1993;99:609–14.
57. Marie I, Pittaluga S, Dale JK, et al. Histologic features of sinus histiocytosis with massive lymphadenopathy in patients with autoimmune lymphoproliferative syndrome. Am J Surg Pathol. 2005;29:903–11.
58. Foucar E, Rosai J, Dorfman RF. Sinus histiocytosis with massive lymphadenopathy. An analysis of 14 deaths occurring in a patient registry. Cancer. 1984;54: 1834–40.
59. Paulli M, Rosso R, Kindl S, et al. Immunophenotypic characterization of the cell infiltrate in five cases of sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease). Hum Pathol. 1992; 23:647–54.
60. Paulli M, Feller AC, Boveri E, et al. Cathepsin D and E co-expression in sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) and Langerhans' cell histiocytosis: further evidences of a phenotypic overlap between these histiocytic disorders. Virchows Arch. 1994;424:601–6.
61. Olsen EA, Crawford JR, Vollmer RT. Sinus histiocytosis with massive lymphadenopathy. Case report and review of a multisystemic disease with cutaneous infiltrates. J Am Acad Dermatol. 1988;18:1322–32.
62. Montgomery H, Osterberg AE. Xanthomatosis. Correlation of clinical, histopathologic and chemical studies of cutaneous xanthoma. Arch Derm Syphilol. 1938;37:373–402.
63. Altman J, Winkelmann RK. Xanthoma disseminatum. Arch Dermatol. 1962;86:582–96.
64. Caputo R, Veraldi S, Grimalt R, et al. The various clinical patterns of xanthoma disseminatum. Considerations on seven cases and review of the literature. Dermatology. 1995;190:19–24.
65. Hammond RR, Mackenzie IRA. Xanthoma disseminatum with massive intracranial involvement. Clin Neuropathol. 1995;14:314–21.
66. Zelger B, Cerio R, Orchard G, et al. Histologic and immunohistochemical study comparing xanthoma disseminatum and histiocytosis X. Arch Dermatol. 1992;128:1207–12.
67. Histiocytic and dendritic cell neoplasms, In: Swerdlow SH, Campo E, Harris HL, et al (eds). WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th ed. Lyon: International Agency for Research on Cancer (IARC), 2008:353–64.
68. Rodriguez-Jurado R, Palacios C, Duran-McKinster C, et al. Medallion-like dermal dendrocyte hamartoma: a new clinically and histopathologically distinct lesion. J Am Acad Dermatol. 2004;51:359–63.
69. Bork K, Gabbert H, Knopp J. Fat-storing hamartoma of dermal dendrocytes. Clinical, histologic, and ultrastructural study. Arch Dermatol. 1990; 126:794–96.
70. Koizumi H, Kumakiri M, Yamanaka K, et al. Dermal dendrocyte hamartoma with stubby white hair: a novel connective tissue hamartoma of infancy. J Am Acad Dermatol. 1995;32:318–21.
71. Chang SE, Choi JH, Sung KJ, et al. Congenital CD34-positive granular cell dendrocytosis. J Cutan Pathol. 1999;26:253–8.

Xanthomas 92

W Trent Massengale, Kafele T Hodari, Erin E Boh and Lee T Nesbitt Jr

Key features

- Cutaneous xanthomas can signal the presence of an underlying hyperlipidemia or monoclonal gammopathy
- An understanding of basic lipid metabolism provides insight into the underlying hyperlipoproteinemias as well as the formation of xanthomas
- The major forms of xanthomas associated with hyperlipidemia are: eruptive, tuberous, tendinous and plane (including xanthelasma)
- Normolipemic plane xanthomas occur in association with monoclonal gammopathies
- Histologically, lipid-laden macrophages (foam cells) are seen in the dermis
- Prompt recognition and proper treatment can lead to xanthoma resolution as well as prevention of potentially life-threatening complications

INTRODUCTION

Cutaneous xanthomas develop as a result of intracellular and dermal deposition of lipid. One of the major distinguishing clinical features of xanthomatous tissue is a characteristic yellow to orange hue. Xanthomas may present with a variety of morphologies, from macules and papules to plaques and nodules. As discussed below, the morphology and anatomic location of the lesions can suggest the type of underlying lipid disorder or the presence of a paraproteinemia.

Xanthomas can develop in the setting of primary or secondary disorders of lipid metabolism. Early recognition of these lesions can make a significant impact on the diagnosis, management and prognosis of patients who suffer from an underlying disease. It is therefore important for dermatologists to become familiar with the basic concepts of lipid metabolism and the associated disease states, as well as be able to recognize the often pathognomonic cutaneous findings.

EPIDEMIOLOGY

Hyperlipidemia is quite common in the general population. In North America alone, it is estimated that over 100 million people currently have an elevated serum cholesterol level >200 mg/dl. Despite the large number of people who suffer from hyperlipidemia, only a minority will develop cutaneous xanthomas. It is not always possible to predict who will develop xanthomas, because the exact mechanism by which they form is not yet fully understood. It is believed they result from the permeation of circulating plasma lipoproteins through dermal capillary blood vessels followed by phagocytosis of the lipoproteins by macrophages, forming lipid-laden cells known as foam cells[1]. However, the precise steps and their regulation are still an area of investigation.

PATHOGENESIS

There is strong evidence to support the theory that the lipids found in the various xanthomas are the same as those in the circulation[2]. The majority of plasma lipids are transported in complex structures known as lipoproteins. The basic structure of the lipoprotein allows the delivery of triglycerides and cholesterol to peripheral cells for their metabolic needs. This structure consists of a hydrophilic outer shell and a hydrophobic core. The outer shell consists of phospholipids, free cholesterol, and non-covalently linked specialized proteins known as apolipoproteins or apoproteins (apo). The inner core contains triglycerides and cholesterol esters.

Lipoproteins differ in their core lipid content. Triglycerides are the major core lipids in chylomicrons and very-low-density lipoproteins (VLDLs), while cholesterol esters dominate the core of low-density lipoproteins (LDLs), high-density lipoproteins (HDLs), and remnants of chylomicrons and VLDLs. The apoproteins found in the outer shell can also differ amongst the various lipoproteins (Table 92.1). These proteins serve several important functions, such as mediating the binding of lipoproteins to their respective receptors in target organs and activating enzymes involved in their metabolism.

There are two major pathways of lipoprotein synthesis (Fig. 92.1A). The exogenous pathway begins with dietary fat intake. Through the action of pancreatic lipase and bile acids, dietary triglycerides are degraded to fatty acids and monoglycerides. After absorption by the intestinal epithelium, the triglycerides are reformed and packaged with a small amount of cholesterol esters into the central core of a chylomicron. The outer shell of the chylomicron consists of phospholipids, free cholesterol, and several apoproteins, including B-48, E, A-I, A-II and C-II.

Chylomicrons then enter the lymphatics and eventually the systemic circulation via the thoracic duct. Once in the circulation, hydrolysis of the core triglycerides occurs, releasing free fatty acids to the peripheral tissues. This is mediated through the action of the enzyme lipoprotein lipase that is bound to capillary endothelium. The activation of the lipoprotein lipase system is complex and involves not only hormones such as insulin, but also apoproteins such as C-II, located on the lipoprotein outer surface.

After hydrolysis of approximately 70% of the original triglyceride content, a chylomicron "remnant" exists. The central core now contains predominantly cholesterol ester that has been acquired from circulating HDL molecules. The chylomicron remnant is taken up in the liver by specialized high-affinity apo B-100/E receptors that recognize the apoproteins E_3 or E_4 on its outer shell. Once in the liver, the remaining lipids enter hepatic storage and apoproteins such as B-48 are degraded.

IMPORTANT APOPROTEINS

Apoprotein	Lipoprotein association	Function and comments
A-I	Chylomicrons, HDLs	Major protein of HDL; activates *l*ecithin:cholesterol *a*cyltransferase (LCAT)
B-48	Chylomicrons, chylomicron remnants	Unique marker for chylomicrons
B-100	VLDLs, IDLs and LDLs	Major protein of LDL; binds to LDL receptor
C-II	Chylomicrons, VLDLs, IDLs and HDLs	Activates lipoprotein lipase
E (at least 3 alleles [E_2, E_3, E_4])	Chylomicrons, chylomicron remnants, VLDLs, IDLs and HDLs	Binds to LDL receptor

Table 92.1 Important apoproteins. HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

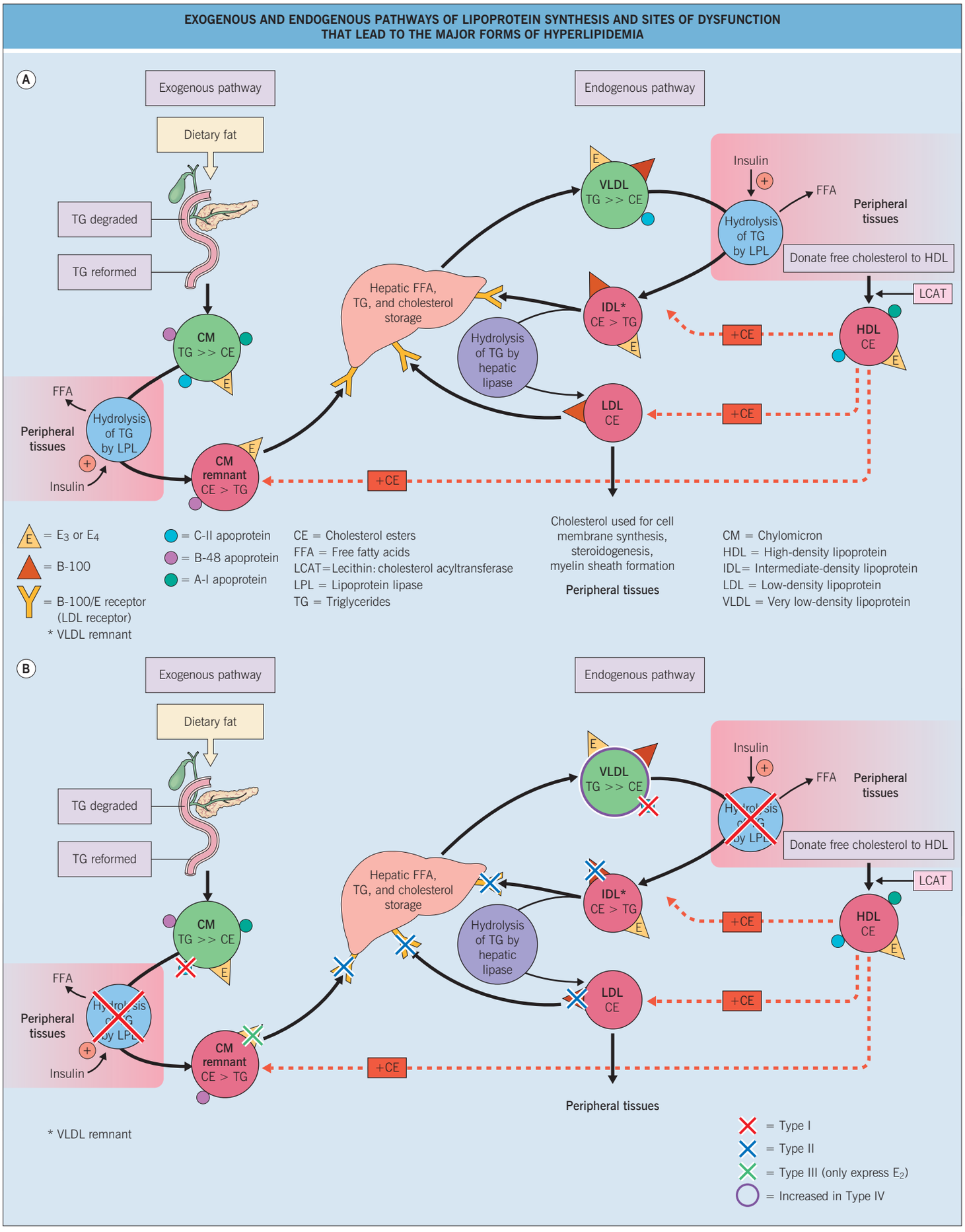


Fig. 92.1 Exogenous and endogenous pathways of lipoprotein synthesis (A) and sites of dysfunction that lead to the major forms of hyperlipidemia (B). Lipoprotein lipase (LPL) is activated by the C-II apoprotein.

IMPORTANT HYPERLIPOPROTEINEMIAS				
Type	**Pathogenesis**	**Laboratory findings**	**Clinical findings**	
			Skin (types of xanthoma)	**Systemic**
Type I (familial LPL deficiency, familial hyperchylomicronemia)	(a) Deficient or abnormal LPL (b) Apo C-II deficiency (c) Deficient glycosyl-phosphatidylinositol-anchored HDL-binding protein	Slow chylomicron clearance Reduced LDL and HDL levels Hypertriglyceridemia	Eruptive	No increased risk of coronary artery disease
Type II (familial hypercholesterolemia or familial defective apo B-100)	(a) LDL receptor defect (b) Reduced affinity of LDL for LDL receptor due to dysfunction of apo B-100 (ligand) (c) Accelerated degradation of LDL receptor due to missense *PCSK9* mutations* (d) Defective LDL receptor adaptor protein 1 (required for receptor internalization)	Reduced LDL clearance Hypercholesterolemia	Tendinous, tuberoeruptive, tuberous, plane (xanthelasma, intertriginous areas, interdigital web spaces†)	Atherosclerosis of peripheral and coronary arteries
Type III (familial dysbetalipoproteinemia, remnant removal disease, broad beta disease, apo E deficiency)	Hepatic remnant clearance impaired due to apo E abnormality; patients only express the apo E_2 isoform that interacts poorly with the apo E receptor	Elevated levels of chylomicron remnants and IDLs Hypercholesterolemia Hypertriglyceridemia	Tuberoeruptive, tuberous, plane (palmar creases) – most characteristic Tendinous	Atherosclerosis of peripheral and coronary arteries
Type IV (endogenous familial hypertriglyceridemia)	Elevated production of VLDL associated with glucose intolerance and hyperinsulinemia	Increased VLDLs Hypertriglyceridemia	Eruptive	Frequently associated with type 2 non-insulin-dependent diabetes mellitus, obesity, alcoholism (see Fig. 92.4)
Type V	Elevated chylomicrons and VLDLs; subset related to apo A-V defect	Decreased LDLs and HDLs Hypertriglyceridemia	Eruptive	Diabetes mellitus

*Gain-of-function mutations cause autosomal dominant hypercholesterolemia[4], whereas loss-of-function mutations (most prevalent in African-Americans) result in low LDL levels[5].
† Said to be pathognomonic for homozygous state.

Table 92.2 Important hyperlipoproteinemias. Apo, apolipoprotein; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LPL, lipoprotein lipase; PCSK9, proprotein convertase subtilisin/kexin type 9; VLDL, very-low-density lipoprotein.

The endogenous pathway begins with the hepatic formation of VLDL particles. The central core of the VLDL consists primarily of triglycerides. The triglycerides are derived from circulating free fatty acids and hepatic triglyceride stores. Important apoproteins found on the outer shell include B-100, E and C-II. In a fashion similar to the chylomicron, lipoprotein lipase mediates hydrolysis of the VLDL molecule, removing the majority of its triglyceride content, and cholesterol esters are acquired from HDL molecules. Lipoprotein lipase activation requires the presence of apo C-II on the VLDL outer shell. After removal of the majority of the triglyceride content, the VLDL "remnant", also known as an intermediate-density lipoprotein (IDL), can then be taken up in the liver by apo B-100/E receptors and degraded. IDLs that escape uptake by the hepatocyte are stripped of their remaining core triglycerides by extracellular hepatic lipases and enter the circulation as LDLs.

The LDL contains predominantly cholesterol ester in its central core and expresses B-100 on its surface. LDL delivers the cholesterol ester to peripheral tissues, where it can be converted to free cholesterol. Cholesterol has several important functions in the body, such as being an essential component of cell membrane bilayers. It is also important in the production of the myelin sheath of nerves, adrenal and gonadal steroidogenesis, and the production of bile acids. Hepatocytes play the major role in the catabolism of LDLs. Their uptake is mediated through the high-affinity apo B-100/E receptor found on the cell surface of the hepatocytes. Free cholesterol in excess of metabolic needs is re-esterified for storage.

HDLs serve several important functions in cholesterol metabolism. One of the primary functions of HDLs is the removal of cholesterol from the peripheral tissues. During this process, free cholesterol and phospholipids are transferred from the cell membranes of peripheral cells to the HDL molecules. The free cholesterol is then esterified by the enzyme *l*ecithin:*c*holesterol *a*cyl*t*ransferase, or LCAT. This enzyme requires the presence of the HDL apoprotein A-I. HDL molecules then transfer the cholesterol esters to other lipoproteins such as LDLs and remnants of chylomicrons or VLDLs for transportation back to the liver.

The liver plays the central role in the overall cholesterol economy. Hepatic intracellular cholesterol levels have a direct impact on the activity of HMG-CoA reductase, the rate-limiting enzyme of cholesterol synthesis, and on the expression of the high-affinity apo B-100/E receptor. When intracellular cholesterol levels are low, HMG-CoA reductase becomes activated and high-affinity apo B-100/E receptor expression increases. The increase in high-affinity receptors leads to increased uptake of cholesterol-containing lipoproteins such as chylomicron remnants, IDLs and LDLs. This is followed by the lowering of plasma cholesterol levels. As discussed later, this mechanism will be the basis for many of the pharmacologic interventions aimed at lowering cholesterol levels.

CLINICAL FEATURES

Due to the complexity of cholesterol homeostasis, there are several possible ways in which hyperlipidemia may occur. Genetic mutations can affect important enzymes, receptors or receptor ligands, with such defects leading to the overproduction of lipoproteins or the inhibition of their clearance (Fig. 92.1B). Each possible defect would lead to a different abnormal lipid profile.

In 1965, Lees and Frederickson[3] published a system for classifying various disorders of lipid metabolism based upon the electrophoretic migration of the serum lipoproteins present. This system for phenotyping hyperlipoproteinemias is used today in a modified form (Table 92.2). In the next section, descriptions of underlying lipid disorders will reference not only the Frederickson classification system, but also the specific molecular defects when possible.

With the exception of the homozygous form of familial hypercholesterolemia (type II), most cutaneous xanthomas do not appear until adulthood. Once the diagnosis is established, treatment of associated disorders (e.g. metabolic syndrome [see Table 53.5]) should reduce the incidence of potential systemic sequelae such as myocardial infarctions, cerebrovascular accidents and hepatitic steatosis.

Fig. 92.2 Eruptive xanthomas due to hypertriglyceridemia. The lesions favored the extensor surface of the lower extremities, in particular the knees.

Fig. 92.3 Eruptive xanthomas. Note the yellowish hue and the clustering of some of the lesions.

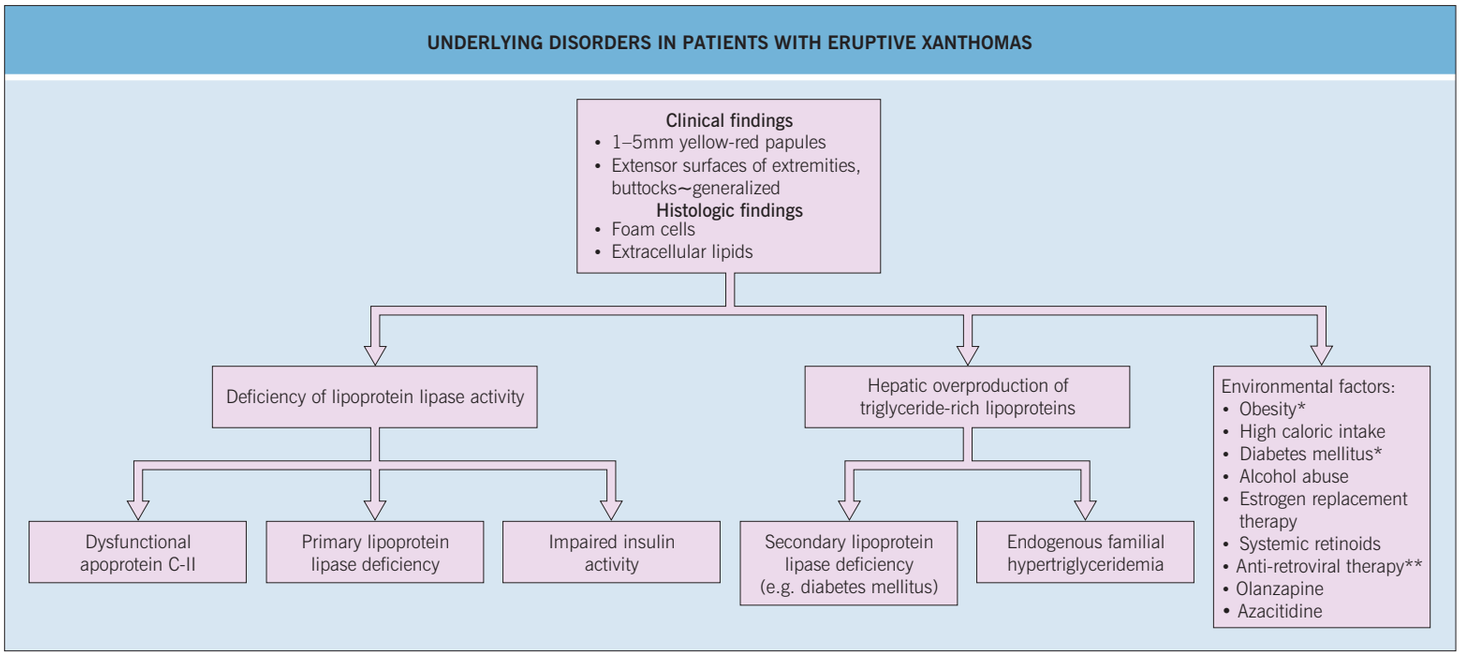


Fig. 92.4 Underlying disorders in patients with eruptive xanthomas. *Components of the metabolic syndrome[9] (see Table 53.5). **Examples include ritonavir, indinavir and stavudine.

Eruptive xanthomas

Eruptive xanthomas appear as erythematous to yellow papules, approximately 1 to 5 mm in diameter (Figs 92.2 & 92.3). They are usually distributed on the extensor surfaces of the extremities, buttocks and hands. Early in their development, lesions may have an inflammatory halo (likely due to their triglyceride component), which may be accompanied by tenderness and pruritus. The Koebner phenomenon has been reported to occur with eruptive xanthomas[6].

Eruptive xanthomas can be seen in the setting of primary or secondary hypertriglyceridemia. Triglyceride levels in patients with eruptive xanthomas often exceed 3000 to 4000 mg/dl. In the Frederickson classification of hyperlipidemias, hypertriglyceridemia can be seen in type I (elevated chylomicrons), type IV (elevated VLDLs) and type V (elevated chylomicrons and VLDLs).

One reason for elevated triglyceride levels is failure to remove such lipids from the circulation. Deficient activity of lipoprotein lipase will lead to accumulation of triglyceride-rich chylomicrons and VLDLs (see Fig. 92.1B). This can be related to abnormalities in the enzyme itself, as in *lipoprotein lipase deficiency* (*chylomicronemia syndrome*), or in other controlling factors such as *dysfunctional apoprotein C-II* or *impaired insulin activity* (Fig. 92.4)[7,8].

Another reason for increased triglyceride levels is hepatic overproduction of triglyceride-rich lipoproteins via the endogenous pathway. In *endogenous familial hypertriglyceridemia*, a genetic defect exists that causes the liver to respond abnormally to dietary carbohydrates and insulin, with overproduction of hepatic VLDLs. The result is a Frederickson type IV pattern of hypertriglyceridemia. Secondary acquired defects in lipoprotein lipase activity, such as those due to diabetes mellitus, are not uncommon in these patients. With this second insult, the lipoprotein lipase system can become saturated and, as a result, no longer handles dietary lipids, leading to chylomicron elevations as well. This pattern is classified as a Frederickson type V phenotype.

Environmental factors and underlying diseases commonly exacerbate genetic defects of triglyceride metabolism, leading to worsening of the hypertriglyceridemia with eruptive xanthoma formation. Such factors include obesity, high caloric intake, diabetes mellitus, alcohol abuse, oral estrogen replacement, and systemic medications that can lead to

Fig. 92.5 Tuberoeruptive xanthomas on the elbow of a child with homozygous familial hypercholesterolemia. Note the yellowish hue. *Courtesy, Julie V Schaffer, MD.*

Fig. 92.6 Nodular tuberous xanthoma of the elbow. *Courtesy, Lorenzo Cerroni, MD.*

hypertriglyceridemia (e.g. retinoids, protease inhibitors, olanzapine). The resultant pattern usually leads to a Frederickson type IV phenotype. Oral retinoid therapy (especially bexarotene) can elevate triglyceride levels through the elevation of hepatic VLDL secretion. With isotretinoin, this finding seems to be more prevalent in genetically predisposed individuals and may signal an increased risk for future metabolic syndrome[10]. Two of the five criteria for the clinical diagnosis of metabolic syndrome are lipid abnormalities – elevated triglycerides and reduced HDLs (see Table 53.5).

The treatment of eruptive xanthomas involves the identification and treatment of the underlying causes of the hypertriglyceridemia (see Fig. 92.4). Failure to recognize and treat the patient with hypertriglyceridemia could lead to complications such as acute pancreatitis. Pharmacologic and dietary lowering of the circulating triglycerides to reasonable levels will result in the prompt resolution of the eruptive lesions.

Tuberous/tuberoeruptive xanthomas

Tuberoeruptive and tuberous xanthomas are clinically and pathologically related and often described as being on a continuum. Tuberoeruptive xanthomas present as pink–yellow papules or nodules on extensor surfaces, especially the elbows and knees (Fig. 92.5). Tuberous lesions are noted to be larger than tuberoeruptive lesions and may exceed 3 cm in diameter (Fig. 92.6). Together, these lesions can be seen in hypercholesterolemic states such as *dysbetalipoproteinemia* (Frederickson type III) and *familial hypercholesterolemia* (Frederickson type II; see below). In contrast to eruptive xanthomas, tuberous xanthomas are usually slow to regress following institution of appropriate therapy.

Dysbetalipoproteinemia, or broad beta disease, is a genetic disorder of lipid metabolism that is inherited in an autosomal dominant fashion. It is caused by the presence of an isoform of apo E, mainly apo E_2, that is a poor ligand for the high-affinity apo B-100/E receptor (see Fig. 92.1B). This results in the poor hepatic uptake of chylomicron and VLDL remnants. As a result, the serum levels of both cholesterol and triglycerides are elevated. The cutaneous lesions that are most characteristic of this disease are tuberous or tuberoeruptive xanthomas (present in 80% of patients) and plane xanthomas of the palmar creases (*xanthoma striatum palmare*), which are present in two-thirds of patients[11].

Tendinous xanthomas

Tendinous xanthomas are firm, smooth, nodular lipid deposits that can affect the Achilles tendons (Fig. 92.7) or the extensor tendons of the hands (Fig. 92.8), knees or elbows. The overlying skin is normal in appearance. Ultrasound can aid in the diagnosis of subtle lesions of the Achilles tendon by demonstrating hypoechoic nodules or an increase in the anteroposterior diameter of the tendon[12]. The presence of tendinous xanthomas is almost always a clue to an underlying disorder of lipid metabolism. Lipid disorders that have been associated with this type of xanthoma include familial hypercholesterolemia, dysbetalipoproteinemia, and hypothyroidism (Table 92.3).

Fig. 92.7 Tendinous xanthoma. Linear swelling of the Achilles area, representing a tendinous xanthoma in a patient with dysbetalipoproteinemia.

Tendinous xanthomas are most frequently seen in the setting of *familial hypercholesterolemia*. This disorder results from a deficiency of normal LDL receptors on cell membranes, which leads to the poor hepatic clearance of circulating LDLs and, therefore, elevated LDL cholesterol levels (Frederickson type II). This condition is inherited in an autosomal dominant fashion with a high degree of penetrance. Homozygotes can have LDL cholesterol levels of 800 to 1000 mg/dl with widespread atherosclerosis and the appearance of xanthomas during the first decade of life. Heterozygosity for the disorder is more common and is estimated to occur in 1 in 500 individuals in the US. The types of xanthomas seen in this disorder include tendinous, tuberous, tuberoeruptive, and plane (including xanthelasma). Because of its relatively common occurrence, patients with tendinous xanthomas are more likely to have the heterozygous form of the disease than the rare homozygous state. Plane xanthomas of the intertriginous web spaces

Fig. 92.8 Tendinous xanthomas of the fingers in a patient with homozygous familial hypercholesterolemia. Note intertriginous plane xanthomas of the web spaces.

Fig. 92.9 Plane xanthomas of the antecubital fossae. This young patient had dysbetalipoproteinemia.

SECONDARY HYPERLIPIDEMIA – UNDERLYING DISORDERS
• Diabetes mellitus*
• Cholestasis
– Primary biliary cirrhosis (often plane xanthomas, including palmar)
– Alagille syndrome (elbows/knees, flexures, fingers, palms, helices)*,†
• Biliary atresia*
• Hypothyroidism*
• Nephrotic syndrome*
• Type I glycogen storage disease (von Gierke)*
*Xanthomas can develop during childhood.
†Autosomal dominant disorder due to *JAG1* or (in a small subset of patients) *NOTCH2* mutations, with cholestasis (due to paucity of intrahepatic bile ducts), elevated LDL (cholesterol) levels, cardiac defects, peculiar facies, growth retardation and posterior embryotoxon; xanthomas within body folds may become very firm[13–15].

Table 92.3 Secondary hyperlipidemia – underlying disorders.

Fig. 92.10 Plane xanthomas of the palmar creases (arrows) in a patient with dysbetalipoproteinemia. They are seen in approximately two-thirds of patients with this disorder. Plane xanthomas are also seen in the setting of cholestasis, e.g. biliary atresia or primary biliary cirrhosis.

of the fingers are thought to be pathognomonic for the homozygous condition (see Fig. 92.8)[16]. A closely related disorder, known as *familial defective apolipoprotein B-100*, has been described. In this dominantly inherited genetic disorder, the LDL receptor is normal. However, there is decreased affinity of LDL for the LDL receptor because the mutation affects its ligand, apo B-100. Patients may present with identical clinical findings as in familial hypercholesterolemia, although usually not as severe[17]. From a therapeutic standpoint, distinguishing this disorder from dysfunction or accelerated degradation of the LDL receptor (see Table 92.2) would become more important in the future should treatments aimed at correcting LDL receptor function become available.

Rarely, tendinous xanthomas can develop in the absence of a lipoprotein disorder. Two examples are *cerebrotendinous xanthomatosis* and *β-sitosterolemia*. In cerebrotendinous xanthomatosis, an enzymatic defect exists in the bile acid synthetic pathway, leading to the abnormal accumulation of an intermediate known as cholestanol. This intermediate is deposited in most tissues, including the brain, and can also form tendinous xanthomas[18]. In β-sitosterolemia, an abnormal accumulation of plant sterols occurs, leading to tendinous xanthoma formation.

Plane xanthomas and xanthelasma

Plane xanthomas are seen as yellow to orange, non-inflammatory macules, papules, patches and plaques. They can be circumscribed or diffuse. Their location can vary and the site often serves as a clue to the particular underlying disease state. For example, intertriginous plane xanthomas may occur in the antecubital fossae (Fig. 92.9) or the web spaces of the fingers (see Fig. 92.8), where they are almost pathognomonic for homozygous familial hypercholesterolemia[16]. Plane xanthomas of the palmar creases, or *xanthoma striatum palmare* (Fig. 92.10), are almost diagnostic for dysbetalipoproteinemia, especially when accompanied by tuberous xanthomas[19].

Xanthelasma, or *xanthelasma palpebrarum*, are commonly observed plane xanthomas of the eyelids (Fig. 92.11). Although the presence of xanthelasma warrants investigation for hyperlipidemia, the latter is present in only about one-half of the patients with these lesions. Younger patients with xanthelasma, or those with a strong family history of hyperlipidemia and xanthelasma, are more likely to have an underlying lipid disorder and should be appropriately screened.

Plane xanthomas of cholestasis may occur as a complication of diseases such as biliary atresia or primary biliary cirrhosis. In these conditions, unesterified cholesterol begins to accumulate in the blood, leading to plane xanthoma formation. The lesions often begin as localized plaques of the hands and feet, but can become generalized.

Plane xanthomas can also occur in a normolipemic patient, where they may signal the presence of an underlying monoclonal gammopathy (Fig. 92.12), usually due to a plasma cell dyscrasia, but occasionally secondary to a lymphoproliferative disorder such as B-cell lymphoma or Castleman's disease (see Ch. 119). This type of xanthoma can also be seen in patients with chronic myelomonocytic leukemia. In gammopathy-associated plane xanthomas, monoclonal IgG is thought to bind to circulating LDL, rendering the antibody–LDL complex more

Fig. 92.11 Xanthelasma palpebrarum with typical yellowish hue.

Fig. 92.12 Plane xanthoma. The large thin plaques have a yellow–orange color. On longitudinal evaluation, the patient was found to have a monoclonal gammopathy. *Courtesy, Whitney High, MD, JD.*

Fig. 92.13 Verruciform xanthoma of the oral mucosa. *Courtesy, Kishore Shetty, DDS.*

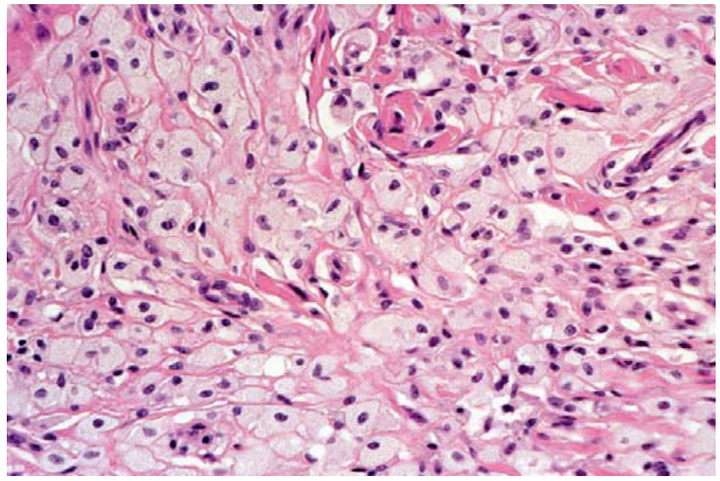


Fig. 92.14 Histology of a tuberous xanthoma. Foamy macrophages fill the dermis. *Courtesy, Lorenzo Cerroni, MD.*

susceptible to phagocytosis by macrophages[20]. Favored locations include the neck, upper trunk, flexural folds and periorbital region.

Verruciform xanthomas

Verruciform xanthomas are asymptomatic, planar or verrucous solitary plaques averaging 1 to 2 cm in diameter. They occur primarily in the mouth (Fig. 92.13), but sometimes in anogenital (including the scrotum) or periorificial sites. There is usually no associated hyperlipidemia and the lesions persist for years. Histologically, there is usually hyperkeratosis, acanthosis, papillomatosis and foamy macrophages limited to the submucosa or dermal papillae.

These lesions are also seen in the setting of lymphedema, epidermolysis bullosa, pemphigus, discoid lupus erythematosus and GVHD, as well as within cutaneous lesions of the X-linked dominant disorder *c*ongenital *h*emidysplasia with *i*chthyosiform erythroderma and *l*imb *d*efects (CHILD) syndrome. The latter is due to mutations in the *NSDHL* gene, which encodes 3β-hydroxysteroid dehydrogenase, an enzyme involved in cholesterol biosynthesis (see Ch. 57). In a recent molecular study of sporadic verrucous xanthomas, two of nine lesions were found to have a missense somatic mutation in exon 6 of the *NSDHL* gene (only exons 4 and 6 were examined) which differed from the mutations seen in CHILD syndrome[21]. The possibility was raised that enzymatic dysfunction leads to an excess formation and accumulation of lipid storage droplets, followed by formation of lipid-laden dermal macrophages.

Another hypothesis suggests that the foam cells could be due to damage to the epithelium much in the same way as the amyloid deposits within the dermal papillae in lichen amyloidosis. The few foam cells beneath the epithelium may be subtle and easy to miss, in which case verruciform xanthomas may be confused histologically with warts and other papillomatous conditions. Surgery is generally curative.

PATHOLOGY

The characteristic histologic finding in xanthomas is the foam cell. Foam cells consist of macrophages that contain imbibed lipid within their cytoplasm (Fig. 92.14). All xanthomas contain dermal infiltrates of lipid, but they may vary in the degree of lipid content, the inflammatory infiltrate, the amount and location of the infiltrate, and the presence of extracellular lipid. The histologic appearance of xanthomas is somewhat altered by routine processing, as formalin fixation can remove deposits of lipid and leave artifactual clefting. Polarized microscopy can be used to detect lipid material in the dermal infiltrates, as cholesterol esters are doubly refractile.

Eruptive xanthomas contain lipid deposits in the reticular dermis. Of note, early in lesion development, foam cells are relatively small in number and size. The initial inflammatory infiltrate is mixed, containing both neutrophils and lymphocytes. As increased lipidization occurs, the appearance of the lesion becomes more typical of a xanthoma, but foam cells remain fewer in number compared with other types of xanthomas. Extracellular lipids are present in the dermis, which are seen as artifactual clefts filled with a wispy faint blue–gray material.

Tuberous xanthomas demonstrate large aggregates of foam cells in the dermis, often accompanied by fibrosis but without a large number of inflammatory cells. Tendinous xanthomas have a similar histology but the foam cells are even larger in size. Cholesterol esters are present in these lesions and can be seen with polarized microscopy.

Plane xanthomas such as xanthelasma can have a unique histologic appearance. The foam cells in this type of xanthoma are more superficial than in other types of xanthomas. Small aggregates of foam cells are often present in the superficial dermis. The lesions are non-inflammatory and have minimal fibrosis. With xanthelasma, there are often clues as to the location of the lesion, such as a thin epidermis, fine vellus hair follicles, and striated muscle fibers that are characteristic of the eyelid.

DIFFERENTIAL DIAGNOSIS

A selection of the diseases included in the differential diagnosis of xanthomas is listed in Table 92.4.

TREATMENT

The treatment of xanthomas associated with hyperlipidemia requires the identification of the underlying lipoprotein disorder and other possible exacerbating factors. In addition to dietary measures, there are several lipid-lowering pharmacologic agents available to help lower lipid levels in patients with primary and secondary hyperlipidemia. Table 92.5 outlines their mechanisms of action, clinical effects and side effects. Correction of the underlying lipid disorder leads to the eventual resolution of the xanthomas in many patients. Xanthomas that have grown slowly over years, such as tendinous and tuberous xanthomas, are often slow to regress, whereas eruptive xanthomas may disappear within weeks of aggressive therapy.

Dietary measures are important components of successful lipid-lowering therapy, in addition to oral medications (see Table 92.5). Decreasing total caloric intake and the achievement of ideal body weight alone can make a significant impact on lipid levels in some patients. Dietary fat restriction to less than 30% of total caloric intake should be attempted. Mono-unsaturated fats such as olive oil should comprise the majority of the fat intake. Alcohol avoidance is essential, especially in patients with hypertriglyceridemia.

Xanthomas, particularly xanthelasma, can be treated surgically by excision or destructive methods. When xanthelasma excision is performed, it may be followed by suture or second intention healing[28]. Reported destructive methods for xanthelasma include laser surgery (CO_2, pulsed-dye or erbium:YAG lasers), chemical agents such as trichloroacetic acid, and cryosurgery[29–32]. Despite the initial success of the chosen method, the lesions often recur. Surgical excision has also been employed in the management of tendinous xanthomas. This can be technically difficult however, as the lipid deposits may be intertwined with the involved tendon[33].

DIFFERENTIAL DIAGNOSIS OF XANTHOMAS
• Eruptive xanthomas
– Non-Langerhans cell histiocytoses
Xanthoma disseminatum
Papular xanthoma
Generalized eruptive histiocytomas
Indeterminate cell histiocytosis
Rosai–Dorfman disease
Juvenile xanthogranuloma (micronodular form)
– Xanthomatous lesions of Langerhans cell histiocytosis
– Disseminated granuloma annulare
• Tuberous xanthomas
– Erythema elevatum diutinum
– Multicentric reticulohistiocytosis
• Tendinous xanthomas
– Giant cell tumor of the tendon sheath
– Rheumatoid nodule
– Subcutaneous granuloma annulare
• Xanthelasma
– Syringomas
– Necrobiotic xanthogranuloma
– *A*dult-onset *a*sthma and *p*erio*c*ular *x*anthogranuloma (AAPOX)
– Sebaceous hyperplasia
– Palpebral sarcoidosis

Table 92.4 Differential diagnosis of xanthomas.

LIPID-LOWERING MEDICATIONS				
Class of drug	**Mechanism of action**	**Clinical effects**	**Side effects/Interactions**	**Comments**
HMG-CoA reductase inhibitors ("statins")	• Competitive inhibition of the rate-limiting enzyme of hepatic cholesterol synthesis, with depletion of hepatocellular stores of cholesterol • Upregulation of hepatic LDL receptors (bind LDL & IDL; see Fig. 92.1) • Decreased endogenous VLDL production	• 25–45% decrease in LDL levels • 25% decrease in VLDL levels • 10% increase in HDL levels	• Elevations in hepatic transaminases • Myopathy (risk may be increased with co-administration of other medications, e.g. cyclosporine, nicotinic acid, fibrates) • Drug-induced dermatomyositis • May increase warfarin levels	• Useful for many lipid disorders, including *heterozygous* familial hypercholesterolemia, hypercholesterolemia due to diabetes • Not effective in *homozygous* familial hypercholesterolemia (LDL receptor function is lacking)
Bile acid-binding resins	• Bind to bile acids in the small intestine, preventing their reabsorption in the terminal ileum • Because of enhanced bile acid secretion, the liver must increase its synthesis of bile acids from cholesterol • Decrease in hepatic cholesterol stores leads to upregulation of hepatic LDL receptors (also increased HMG-CoA reductase activity)	• 10–35% decrease in LDL levels (even with increase in hepatic cholesterol synthesis)	• Elevation of triglyceride levels, especially if dysbetalipoproteinemia or pre-existing hypertriglyceridemia • GI upset & gritty texture of resin • Affect absorption of medications such as digitalis, thyroxine, warfarin	• Lowering of LDL levels can be further enhanced by the addition of an HMG-CoA reductase inhibitor or nicotinic acid • Effective in *heterozygous* familial hypercholesterolemia • Not effective in *homozygous* familial hypercholesterolemia

Table 92.5 Lipid-lowering medications. GI, gastrointestinal; HDL, high-density lipoprotein; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein. Based on refs 22–27.

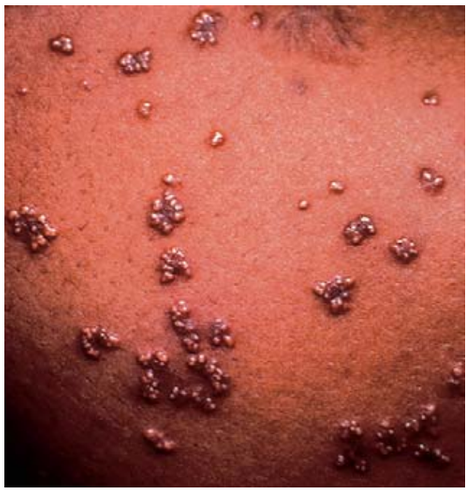
Continued

LIPID-LOWERING MEDICATIONS				
Class of drug	**Mechanism of action**	**Clinical effects**	**Side effects/Interactions**	**Comments**
Nicotinic acid (niacin)	• Lowers VLDL synthesis (and subsequently lowers LDL levels) • Enhances lipoprotein lipase activity (and subsequently lowers triglyceride levels)	• 20–80% decrease in triglyceride levels (rapid) • 10–15% decrease in LDL levels (slower) • 20–30 mg/dl increase in HDL	• Intense flushing and pruritus are common • Hepatic dysfunction • Worsening of glucose intolerance • Acanthosis nigricans, hyperpigmentation, xerosis • Increased risk of myopathy & rhabdomyolysis when administered with HMG-CoA reductase inhibitors	• Can be used in combination with HMG-CoA reductase inhibitors or bile acid-binding resins • Combination therapy for familial hypercholesterolemia • Treatment of severe hypertriglyceridemia refractory to fibric acid derivatives (to prevent pancreatitis)
Probucol	• Antioxidant • Presumably, lipid-lowering mechanism is independent of LDL receptors	• Lowers LDL levels • *Lowers* HDL levels • Dramatic resolution of tendon & plane xanthomas	• Lowers HDL levels	• No effect on triglyceride levels • Only agent (on market) that can lower cholesterol levels in *homozygous* familial hypercholesterolemia
Fibric acid derivatives (e.g. gemfibrozil, fenofibrate, clofibrate)	• Activation of lipoprotein lipase in peripheral tissues (e.g. muscle) • Decreases VLDL synthesis by suppression of the endogenous lipid pathway	• Dramatic improvement in lipid levels, with resolution of tuberous & palmar xanthomas (patients with dysbetalipoproteinemia) • Lowers triglyceride levels; prevents pancreatitis & eruptive xanthoma formation (patients with severe hypertriglyceridemia & chylomicronemia syndrome)	• Because of inhibition of the cytochrome P450 3A4 system, possibility of dermatologic drug interactions (e.g. increased plasma levels of bexarotene or cyclosporine) • Increased risk of myopathy when administered with HMG-CoA reductase inhibitors	• Treatment of hypertriglyceridemia
CETP inhibitors (e.g. anacetrapib)	• Inhibition of cholesteryl ester transfer protein (CETP) • CETP transfers cholesterol from HDLs to VLDLs or LDLs	• 40% decrease in LDL-C levels • Marked increase in HDL levels	• Increase in aldosterone and systolic blood pressure (torcetrapib) • Increase in transaminases and CPK	• Not FDA-approved • Another CTEP inhibitor (torcetrapib) was withdrawn from the market because of an increase in mortality

Table 92.5 Lipid-lowering medications (cont'd). CPK, creatine phosphokinase; HDL, high-density lipoprotein; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein. Based on refs 22–27.

REFERENCES

1. Parker F. Normocholesterolemic xanthomatosis. Arch Dermatol. 1986;122:1253–7.
2. Cruz PD Jr, East C, Bergstresser PR. Dermal, subcutaneous, and tendon xanthomas: diagnostic markers for specific lipoprotein disorders. J Am Acad Dermatol. 1988;19:95–111.
3. Lees RS, Frederickson DS. The differentiation of exogenous and endogenous hyperlipemia by paper electrophoresis. J Clin Invest. 1965;44: 1968–77.
4. Abifadel M, Varret M, Rabés J-P, et al. Mutations in *PCSK9* cause autosomal dominant hypercholesterolemia. Nat Genet. 2003;34:154–6.
5. Cohen J, Pertsemlidis A, Kotowski IK, et al. Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in *PCSK9*. Nat Genet. 2005;37:161–5.
6. Goldstein GD. The Koebner response with eruptive xanthomas. J Am Acad Dermatol. 1984;10:1064–5.
7. Santamarina-Fojo S. The familial chylomicronemia syndrome. Endocrinol Metab Clin North Am. 1998; 27:551–67.
8. Breckenridge WC, Alaupovic P, Cox DW, Little JA. Apolipoprotein and lipoprotein concentrations in familial apolipoprotein C-II deficiency. Atherosclerosis. 1982;44:223–35.
9. Azfar RS, Gelfand JM. Psoriasis and metabolic disease: epidemiology and pathophysiology. Curr Opin Rheumatol. 2008;20:416–22.
10. Rodondi N, Darioli R, Ramelet AA, et al. High risk for hyperlipidemia and the metabolic syndrome after an episode of hypertriglyceridemia during 13-cis retinoic acid therapy for acne: a pharmacogenetic study. Ann Intern Med. 2002;136:582–9.
11. Parker F. Xanthomas and hyperlipidemias. J Am Acad Dermatol. 1985;13:1–30.
12. Bude RO, Adler RS, Bassett DR. Diagnosis of Achilles tendon xanthoma in patients with heterozygous familial hypercholesterolemia: MR vs sonography. AJR Am J Roentgenol. 1994;162:913–17.
13. Schwartz R, Rehder K, Parsons DJ, Morrell DS. Intense pruritus and failure to thrive in Alagille syndrome. J Am Acad Dermatol. 2008;58(2 Suppl):S9–S11.
14. Alagille D, Odievre M, Gautier M, et al. Hepatic ductular hypoplasia associated with characteristic facies, vertebral malformations, retarded physical, mental and sexual development and cardiac murmur. J Pediatr. 1975;86:63–71.
15. Garcia MA, Ramonet M, Ciocca M, et al. Alagille syndrome: cutaneous manifestations in 38 children. Pediatr Dermatol. 2005;22:11–14.
16. Sethuraman G, Thappa DM, Karthikeyan K. Intertriginous xanthomas – a marker of homozygous familial hypercholesterolemia. Indian Pediatr. 2000;37:338.
17. Rauh G, Keller C, Kormann B, et al. Familial defective apolipoprotein B100: clinical characteristics of 54 cases. Atherosclerosis. 1992;92:233–41.
18. Bel S, Garcia-Patos V, Rodriguez L, et al. Cerebrotendinous xanthomatosis. J Am Acad Dermatol. 2001;45:292–5.
19. Alam M, Garzon MC, Salen G, Starc TJ. Tuberous xanthomas in sitosterolemia. Pediatr Dermatol. 2000;17:447–9.
20. Daoud MS, Lust JA, Kyle RA, Pittelkow MR. Monoclonal gammopathies and associated skin disorders. J Am Acad Dermatol. 1999;40:507–35.
21. Mehra S, Li L, Fan CY, et al. A novel somatic mutation of the 3β-hydroxysteroid dehydrogenase gene in sporadic cutaneous verruciform xanthoma. Arch Dermatol. 2005; 141:1263–7.
22. Dourmishev AL, Dourmishev LA. Dermatomyositis and drugs. Adv Exp Med Biol. 1999;455:187–91.
23. Stals H, Vercammen C, Peeters C, Morren MA. Acanthosis nigricans caused by nicotinic acid: case report and review of the literature. Dermatology. 1994;189: 203–6.
24. Yamamoto A, Matsuzawa Y, Yokoyama S, et al. Effects of probucol on xanthomata regression in familial hypercholesterolemia. Am J Cardiol. 1986;57:29H–35H.
25. Fujita M, Shirai K. A comparative study of the therapeutic effect of probucol and pravastatin on xanthelasma. J Dermatol. 1996;23:598–602.
26. Kajinami K, Nishitsuji M, Takeda Y, et al. Long-term probucol treatment results in regression of xanthomas, but in progression of coronary atherosclerosis in a heterozygous patient with familial hypercholesterolemia. Atherosclerosis. 1996;120:181–7.
27. Kuo PT, Wilson AC, Kostis JB, et al. Treatment of type III hyperlipoproteinemia with gemfibrozil to retard progression of coronary artery disease. Am Heart J. 1988;116:85–90.
28. Eedy DJ. Treatment of xanthelasma by excision with secondary intention healing. Clin Exp Dermatol. 1996;21:273–5.
29. Ullmann Y, Har-Shai Y, Peled IJ. The use of CO_2 laser for the treatment of xanthelasma palpebrarum. Ann Plast Surg. 1993;31:504–7.
30. Schonermark MP, Raulin C. Treatment of xanthelasma palpebrarum with the pulsed dye laser. Lasers Surg Med. 1996;19:336–9.
31. Mannino G, Papale A, De Bella F, et al. Use of Erbium: YAG laser in the treatment of palpebral xanthelasmas. Ophthalmic Surg Lasers. 2001;32:129–33.
32. Hawk JL. Cryotherapy may be effective for eyelid xanthelasma. Clin Exp Dermatol. 2000;25:351.
33. Bozentka DJ, Katzman BM. Two cases of surgically treated hand tendon xanthomas. Am J Orthop. 2001;30:337–9.



Eruptive xanthomas. Note the yellowish hue and 'mulberry' pattern in a patient with Frederickson type IV disease.

Nodular tuberous xanthomas of the elbows. This form occurred in a young patient with familial hypercholesterolemia.

Tuberoeruptive xanthomas of the elbow. Note the yellowish hue.

Plane xanthoma in a patient with a monoclonal IgG gammopathy. These lesions can be subtle clinically; arrows point to the edge of the xanthoma.

This page intentionally left blank

Non-infectious Granulomas 93

Amy Reisenauer, Kevin P White, Veselina Korcheva and Clifton R White Jr

Chapter Contents

Sarcoidosis 1557
Granuloma annulare 1563
Necrobiosis lipoidica 1566
Annular elastolytic giant cell granuloma 1568
Cutaneous Crohn's disease 1570

INTRODUCTION

The diseases discussed in this chapter are unified by similar histologic findings despite having disparate, often unknown, causes. Granulomatous dermatitis may be defined as having an inflammatory cutaneous infiltrate in which histiocytes are the preponderant inflammatory cells. While numerous non-infectious cutaneous disorders fall within this broad definition, cutaneous sarcoidosis is the prototype of granulomatous dermatitis. Many conditions mimic the appearance of sarcoidosis, including cutaneous Crohn's disease as well as certain foreign body reactions (see Ch. 94). Granuloma annulare, the closely related annular elastolytic giant cell granuloma (actinic granuloma), and necrobiosis lipoidica are the best-known examples of palisaded granulomatous dermatitis. Each of these entities will be reviewed in this chapter (Fig. 93.1 & Table 93.1). Additional non-infectious granulomatous disorders are covered in other chapters, including granulomatous cheilitis in Chapter 72, rheumatoid nodules and interstitial granulomatous dermatitis in Chapter 45, and primary immunodeficiency-associated sterile granulomatous dermatitis in Chapter 60.

SARCOIDOSIS

Synonyms/subsets: ■ Löfgren's syndrome – erythema nodosum, hilar adenopathy, fever, arthritis ■ Heerfordt's syndrome – parotid gland enlargement, uveitis, fever, cranial nerve palsy ■ Darier–Roussy disease – subcutaneous sarcoidosis

Key features

- A systemic granulomatous disorder of unknown origin that most commonly involves the lungs
- Cutaneous manifestations of sarcoidosis are seen in up to one-third of patients, and they may be the first clinical sign of the disease
- Red–brown to violaceous papules and plaques appear most often on the face, lips, neck, upper back and extremities
- Variants of sarcoidosis include lupus pernio, subcutaneous, ichthyosiform, angiolupoid and ulcerative
- Erythema nodosum is a nonspecific inflammatory skin finding associated with subacute, transient sarcoidosis
- Histologically, sarcoidosis is characterized by non-caseating epithelioid granulomas, usually without surrounding lymphocytic inflammation (i.e. "naked" granulomas)

History

Sarcoidosis was described initially by Sir Jonathan Hutchinson in 1875 and cutaneous sarcoidosis (lupus pernio) by Besnier in 1889. Caesar Boeck first coined the term "multiple benign sarkoid" in 1899.

Epidemiology

Sarcoidosis, which occurs in patients of all races and ages as well as both sexes, is characterized by a bimodal age distribution, with peaks between 25 and 35 years and then again between 45 and 65 years in women. In the US, there is an increased incidence of sarcoidosis in African-Americans, ranging from 35 to 64 per 100 000. Sarcoidosis in African-Americans tends to be more acute and severe than in other populations. African-American women in the fourth decade of life have the highest incidence, occurring with a rate of 107 per 100 000. In comparison, the incidence in Caucasians in the US ranges from 10 to 14 per 100 000. Worldwide, the incidence of sarcoidosis is highest in Sweden (64 per 100 000) and the UK (20 per 100 000) and lowest in Spain and Japan (both 1.4 per 100 000). A greater number of patients with new-onset sarcoidosis are reported in the winter and spring[1].

Pathogenesis

Sarcoidosis is a multisystem granulomatous disease characterized by hyperactivity of the cell-mediated immune system. Specifically, upregulation of $CD4^+$ T-helper cells of the Th1 subtype occurs following antigen presentation by monocytes bearing MHC class II molecules, which initiates formation of epithelioid granulomas in a variety of tissue types[2]. In the lung, an oligoclonal α/β T-cell population has been described, suggesting that antigenic triggers of sarcoidosis favor a progressive accumulation and activation of specific T-cell clones[3].

Increased production of Th1 cytokines, including interleukin (IL)-2 and interferon (IFN)-γ, as well as release of tumor necrosis factor (TNF)-α by macrophages, leads to B-cell stimulation and hypergammaglobulinemia. IL-12 is also thought to play a role in sarcoidosis as are $CD4^+$ T cells of the Th17 subtype[3a].

Monocyte chemotactic factor (MCF), produced by activated T-helper cells, attracts monocytes from the circulation into peripheral tissues. Compartmentalization of granuloma-forming T lymphocytes and monocytes within peripheral tissues leads to lymphopenia and decreased delayed-type hypersensitivity to common antigens (anergy), most pronounced during the initial stages of sarcoidosis. In addition, T regulatory cells may play a role in the anergic state. Perhaps the observation that IFN-α, especially when administered for hepatitis C viral infections, can induce cutaneous sarcoidosis will provide further insights into the immunopathogenesis.

The identity of the antigen responsible for the cascade of events leading to granuloma formation in patients with sarcoidosis remains uncertain. Some investigators have proposed an autoimmune etiology, while others have searched for an infectious cause. The latter is suggested by the observation that sarcoidal granulomas have developed in patients receiving organ transplants from donors with sarcoidosis. Mycobacterial DNA sequences have been identified in lung tissue, peripheral blood, skin, and cerebrospinal fluid in some studies of patients with sarcoidosis but not in others[4]. Sarcoidosis patients do not develop fulminant infectious symptoms when placed on immunosuppressive agents, which argues against a purely infectious etiology. In addition, mycobacteria have not been cultured from sarcoidal tissues. Possible viral causes of sarcoidosis, including human herpesvirus-8, have been postulated but not proven[5]. Sarcoidal lesions have been reported in HIV-infected patients upon immune restoration when given antiretroviral therapy. However, no evidence of infection with

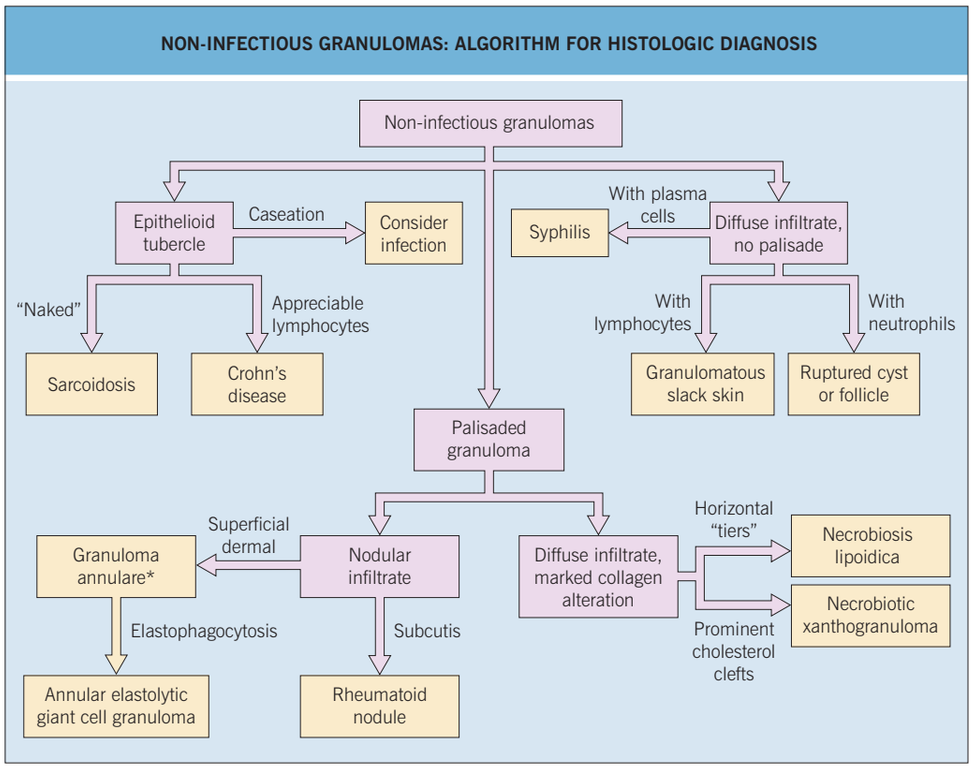


Fig. 93.1 Non-infectious granulomas: algorithm for histologic diagnosis. Interstitial granulomatous dermatitis and palisaded neutrophilic and granulomatous dermatitis may represent an additional diagnostic consideration (see Table 93.2). *May also have a patchy dermal interstitial pattern without palisades, or subcutaneous palisades with more mucin than rheumatoid nodules.

CLINICAL FEATURES OF THE MAJOR GRANULOMATOUS DERMATITIDES

	Sarcoidosis*	Classic granuloma annulare†	Necrobiosis lipoidica	AEGCG	Cutaneous Crohn's disease	Rheumatoid nodule
Average age (years)	25–35, 45–65	<30	30	50–70	35	40–50
Sex predilection	Female	Female	Female	None	Female	Male‡
Racial/ethnic predilection in US	African-American	None	None	Caucasian	Ashkenazi Jews	None
Sites	Symmetric on face, neck, upper trunk, extremities	Hands, feet, extensor aspects of extremities	Anterior and lateral aspects of distal lower extremities	Face, neck, forearms (sites of chronic sun exposure)	Genital areas, lower > upper extremities	Juxta-articular areas, especially elbows, hands, ankles, feet
Appearance	Red to red–brown papules and plaques; occasionally violaceous or annular	Papules coalescing into annular plaques	Plaques with elevated borders, telangiectasias centrally	Annular plaques	Dusky erythema and swelling, ulceration	Skin-colored, firm, mobile subcutaneous nodules
Size of lesions	0.2 to >5 cm	1–3 mm papules, annular plaques usually <6 cm	3 to >10 cm	1–6 cm	Variable	1–3 cm
No. of lesions	Variable	1–10	1–10	1–10	1–5	1–10
Associations	Systemic manifestations of sarcoidosis; interferon-α therapy for hepatitis C viral infection >> melanoma	Rare diabetes mellitus, HIV infection, malignancy	Diabetes mellitus	Actinic damage	Intestinal Crohn's disease	Rheumatoid arthritis
Special clinical characteristics	Occasional central atrophy and hypopigmentation; development within scars	Central hyperpigmentation	Yellow–brown atrophic centers, ulceration	Central atrophy and hypopigmentation	Draining sinuses and fistulas	Occasional ulceration, especially at sites of trauma

*Clinical variants include lupus pernio and subcutaneous (Darier–Roussy), psoriasiform, ichthyosiform, angiolupoid and ulcerative sarcoidosis.
†Clinical variants include generalized, micropapular, nodular, perforating, subcutaneous and patch granuloma annulare.
‡Although rheumatoid arthritis has a female:male ratio of 2–3:1.

Table 93.1 Clinical features of the major granulomatous dermatitides. AEGCG, annular elastolytic giant cell granuloma; HIV, human immunodeficiency virus.

Mycobacterium tuberculosis could be identified in these sarcoidosis-like lesions[6].

Genetic susceptibility to sarcoidosis has been associated with HLA-1, HLA-B8 and HLA-DR3 alleles[7], and, more recently, HLA-DRB1 and DQB1[8]. Polymorphisms in the gene encoding angiotensin-converting enzyme (ACE) have also been identified in patients with sarcoidosis. An environmental trigger for the disease is suggested by seasonal clustering of sarcoidosis with erythema nodosum in the spring. Occupational associations have been recorded in healthcare workers, firemen, and navy personnel on aircraft carriers[4].

While the etiologic agent clearly remains elusive, investigation of the immunopathogenesis of the disease (see above) has been aided by examining the cutaneous reaction produced by injection of a tissue suspension prepared from sarcoidal spleen. The suspension (Kveim-Siltzbach antigen) causes characteristic non-caseating granuloma formation in the skin of patients with sarcoidosis, and although this skin test is rarely performed nowadays, it was used in the past to help confirm the diagnosis. Immunohistochemical studies of the Kveim skin test have demonstrated a predominance of $CD4^+$ helper T cells and a paucity of $CD8^+$ suppressor T cells, B cells, and immunoglobulin deposition in the cutaneous granulomas. Peripheral blood monocytes are present in the skin for the first several days, but then transform into epithelioid histiocytes and multinucleated giant cells[2].

Clinical Features

Up to a third of patients with systemic sarcoidosis develop skin lesions, which may be the first or only clinical manifestation of the disease. Cutaneous sarcoidosis most commonly manifests as papules and plaques, often red–brown in color (Fig. 93.2A). Papules may be flat-topped in appearance. Sarcoidal lesions favor the face, lips, neck, upper trunk and extremities (Figs 93.2B–D), and are fairly symmetric in distribution. Classically, the cutaneous lesions lack secondary changes, but occasionally scale or ulcerations can develop. Less common presentations include hypopigmentation (Fig. 93.3A), subcutaneous nodules, acquired ichthyosis (Fig. 93.3B), alopecia and discrete micropapular lesions; erythroderma, erythema multiforme and verrucous plaques are rare manifestations. A classic finding is the development of cutaneous sarcoidosis within pre-existing scars or at sites of prior trauma (Fig. 93.2E).

Although many lesions are red–brown in color, they can vary from yellow–brown to erythematous (especially in lightly pigmented skin) to

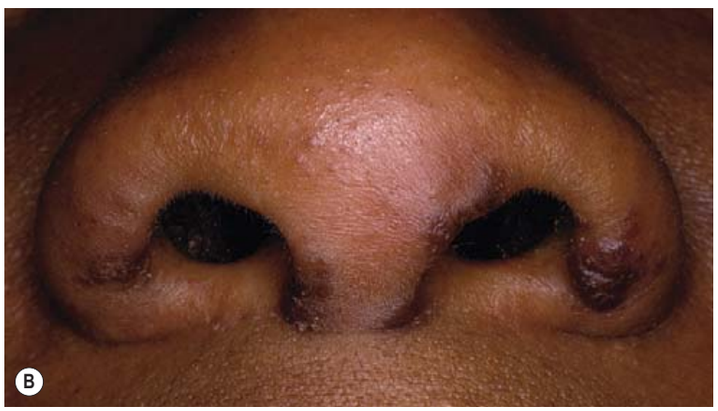


Fig. 93.2 Sarcoidosis. **A** Cutaneous sarcoidosis usually consists of papules and plaques with a typical reddish-brown color. **B, C** Lesions often favor the nose, lips and perioral region. **D** Hyperpigmented plaques, some of which have scale. **E** Papules of cutaneous sarcoidosis arising within a tattoo; the differential diagnosis includes foreign body reaction. *B, Courtesy, Louis A Fragola, Jr, MD.*

Fig. 93.3 Sarcoidosis – clinical variants. A The hypopigmented variant is more noticeable in individuals with darkly pigmented skin. **B** Ichthyosiform presentation with obvious scale. **C** Coalescing violaceous papules on the nose in lupus pernio; note the notching of the nasal rim. *A, Courtesy, Louis A Fragola, Jr, MD. B, Courtesy, Jean L Bolognia, MD.*

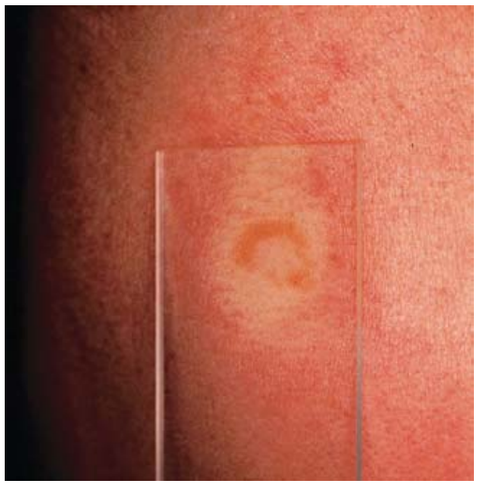


Fig. 93.4 Sarcoidosis. With diascopy, a yellow–brown, "apple jelly" color is seen.

Fig. 93.5 Erythema nodosum in a patient with sarcoidosis. These patients often have hilar lymphadenopathy. *Courtesy, Louis A Fragola, Jr, MD.*

violaceous; the latter color is often associated with lupus pernio. Upon diascopy, in which pressure induces blanching, the lesions are said to have the color of "apple jelly" (Fig. 93.4); this finding is usually easier to appreciate in lightly pigmented skin. Individual plaques can develop central clearing leading to an annular configuration or they can contain prominent telangiectasias (angiolupoid sarcoidosis). By dermoscopy, translucent yellow to orange globular-like or structureless areas associated with linear vessels may be seen in lesions of sarcoidosis.

Variants of sarcoidosis include Darier–Roussy disease and lupus pernio. Patients with Darier–Roussy sarcoidosis present with painless, firm, mobile nodules without epidermal changes. This variant represents sarcoidosis limited to the subcutaneous tissue. Lupus pernio is characterized by papulonodules and plaques, primarily involving areas most affected by cold (i.e. pernio), including the nose, ears and cheeks; there is often a beaded appearance along the nasal rim (Fig. 93.3C). Recognition of lupus pernio is important because of its association with chronic sarcoidosis of the lungs (approximately 75% of patients) and of the upper respiratory tract (approximately 50% of patients). In addition, cystic lesions within the bones of the distal phalanges are seen more frequently. Although most skin lesions of sarcoidosis are asymptomatic and, with treatment, resolve without scarring, lupus pernio is often the exception[9].

The most important nonspecific cutaneous manifestation of sarcoidosis is erythema nodosum (Fig. 93.5). Erythema nodosum is associated with subacute, transient sarcoidosis that usually resolves spontaneously and typically does not require systemic corticosteroid therapy. In general, there are no additional cutaneous manifestations. Biopsy specimens from erythema nodosum lesions show a granulomatous septal panniculitis (see Ch. 100). Sarcoidosis manifesting as erythema nodosum with hilar adenopathy, fever, migrating polyarthritis, and acute iritis is termed Löfgren's syndrome.

Nail changes can be seen in sarcoidosis, including clubbing, subungual hyperkeratosis, and onycholysis. Oral sarcoidosis may affect the soft mucosa, gingival tissue, tongue, hard palate, and major salivary glands. Heerfordt's syndrome (uveoparotid fever) includes parotid gland enlargement, uveitis, fever, and cranial nerve palsies, usually of the facial nerve.

Systemic manifestations of sarcoidosis are protean. Lung disease occurs in approximately 90% of patients, ranging from alveolitis to granulomatous infiltration of the alveoli, blood vessels, bronchioles,

pleura and fibrous septa[10]. The end stage of pulmonary sarcoidosis is fibrosis with bronchiolectasis and "honeycombing" of the lung parenchyma. Hilar and/or paratracheal lymphadenopathy, which is usually asymptomatic, occurs in 90% of patients.

Granulomatous inflammation also occurs in the liver, spleen and bone, as well as the kidney, gastrointestinal tract (upper and lower) and peripheral lymph nodes. Additional sites include the central and peripheral nervous systems, muscle, heart, endocrine glands (e.g. pituitary, thyroid) and bone marrow. Occasionally, there is involvement of the ear, breast, and male and female reproductive systems. Ocular sarcoidosis may present with granulomatous inflammation of the uveal tract (iris, ciliary body, choroid), retina, optic nerve, conjunctivae or lacrimal glands.

Childhood sarcoidosis is rare, and it usually presents with a triad of arthritis, uveitis and cutaneous lesions along with constitutional symptoms. Peripheral lymphadenopathy is frequently present, but pulmonary involvement is less common than in adults. Sarcoidosis should be considered in the differential diagnosis of any childhood illness with arthritis, especially if ocular symptoms are present.

Hypercalcemia is present in up to 10% of patients, and it is believed to be due to increased calcitriol synthesis by sarcoidal histiocytes. Subsequent hypercalciuria and nephrocalcinosis may lead to renal failure. Lymphopenia, leukopenia and an elevated ESR can be seen in up to 40% of patients.

Pathology

The histopathologic hallmark of sarcoidosis is the presence of superficial and deep dermal epithelioid cell granulomas devoid of prominent infiltrates of lymphocytes or plasma cells ("naked tubercles") (Fig. 93.6). Central caseation is usually absent, although fibrinoid deposition may be observed in up to 10% of cases. Multinucleated histiocytes ("giant cells") are usually of the Langhans type, with nuclei arranged in a peripheral arc or circular fashion. The giant cells may contain eosinophilic stellate inclusions known as asteroid bodies (Fig. 93.7) or rounded laminated basophilic inclusions known as Schaumann bodies. Asteroid bodies represent engulfed collagen, whereas Schaumann bodies likely represent degenerating lysosomes. Neither finding is specific for sarcoidosis.

A range exists within the histologic spectrum of sarcoidosis, from the characteristic tubercles with minimal or no surrounding lymphocytic inflammation to unusual cases with dense lymphocytic and plasmocytic infiltrates around and within the nodular histiocytic aggregates. Occasionally, these aggregates may extend into the subcutaneous fat, producing the clinical features of Darier–Roussy sarcoidosis and fibrosing panniculitis[11].

Diagnosis and Differential Diagnosis

Sarcoidosis is a diagnosis of exclusion, both clinically and histologically. In order to establish the diagnosis, a supportive clinical history must be accompanied by the histologic presence of non-caseating granulomas in at least one organ system. Radiologic findings include hilar and/or paratracheal lymph node enlargement with or without pulmonary infiltrates on chest radiography. High-resolution CT scans of the chest are more sensitive than radiographs in detecting parenchymal and nodal disease and may be used to delineate active inflammation from fibrosis. Pulmonary function tests reveal restrictive lung disease, with decreased vital capacity, residual volume, total lung capacity and diffusing capacity. Musculoskeletal radiographs may show joint effusions and cystic lesions in the small bones of the hands and feet. Histologically, the granulomatous lesions of the gastrointestinal tract can be indistinguishable from Crohn's disease or Whipple's disease.

Serologically, elevated antinuclear antibody titers occur in ~30% of patients. The serum angiotensin-converting enzyme (ACE) level is elevated in ~60% of patients; it has a false-positive incidence of 10%, making it a more useful test for monitoring disease progression than for establishing the diagnosis. Most patients exhibit lymphopenia, with a decreased $CD4^+$:$CD8^+$ ratio of circulating lymphocytes. Five percent of patients have non-hemolytic anemia, and one-quarter have eosinophilia. Both an elevated ESR and hypercalcemia may be present (see above).

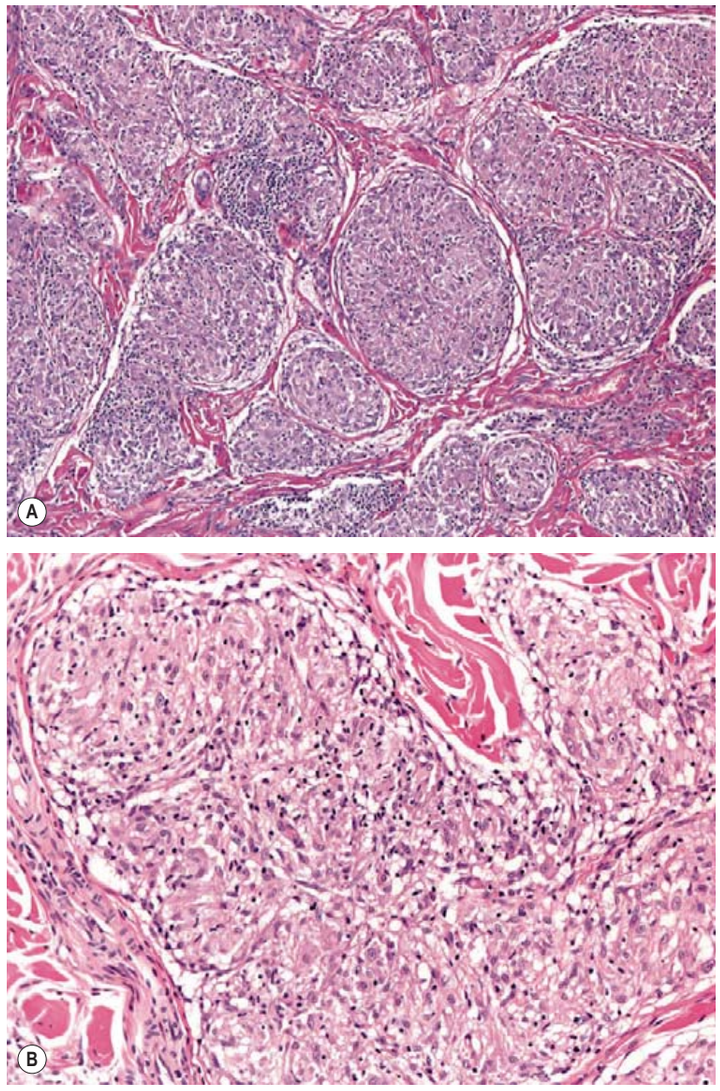


Fig. 93.6 Cutaneous sarcoidosis – histologic features. A Nodular aggregates of epithelioid histiocytes forming tubercles filling the dermis. **B** A sarcoidal tubercle with a sparse admixture of lymphocytes ("naked tubercle"). *Courtesy, Lorenzo Cerroni, MD.*

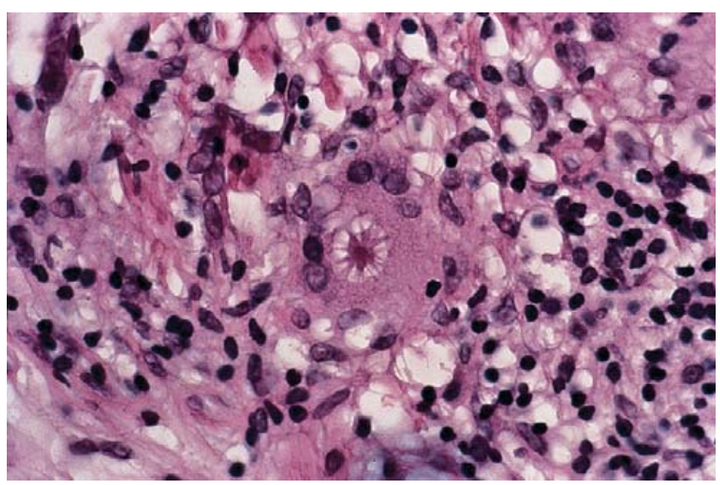


Fig. 93.7 Cutaneous sarcoidosis. An asteroid body within the cytoplasm of a multinucleated epithelioid histiocyte ("giant cell").

Like syphilis, sarcoidosis is a great mimic and the clinical differential diagnosis depends upon the type of presenting clinical lesions. For example, a list of other disorders, in addition to sarcoidosis, that can present with annular lesions is provided in Table 19.1. Papules, nodules and plaques may be nonspecific in clinical appearance, dictating biopsy,

and then the differential diagnosis rests upon the histopathologic findings. It is important to exclude the possibility of drug-induced cutaneous sarcoidosis (e.g. IFN-α for hepatitis C viral infection, TNF-α inhibitors).

The histologic differential diagnosis is broad, and includes multiple infections that lead to granulomatous inflammation. Special stains for acid-fast and fungal organisms should be obtained. When clinically appropriate, tissue culture should be performed. In tuberculoid leprosy, clues to the diagnosis include inflammation within and around peripheral nerves (where acid-fast *Mycobacterium leprae* occasionally may be demonstrated with a Fite stain), elongated tubercles (reflecting nerve involvement), and denser collections of lymphocytes and plasma cells around the tubercles. Lupus vulgaris is the form of cutaneous tuberculosis that is most difficult to distinguish from sarcoidosis histologically, due to the difficulty in demonstrating organisms in this variant. Histologic features of lupus vulgaris include caseation necrosis within the central portion of tubercles, denser collections of peripheral lymphocytes, and epidermal changes such as ulceration or pseudoepitheliomatous hyperplasia; this constellation usually allows its distinction from sarcoidosis. A QuantiFERON®-TB Gold test may provide additional information. It is especially important to exclude infectious etiologies before initiating immunosuppressive agents (e.g. TNF-α inhibitors).

Other histologic mimics include foreign body reactions to zirconium, beryllium, silica, tattoo ink or soft tissue fillers. Special laboratory techniques, including histochemical, microincineration or spectrophotometric examinations, may be required to identify the causative agents in zirconium and beryllium granulomas (see Table 94.3). Specimens should be polarized to exclude birefringent foreign material as a causative agent, although up to 20% of known sarcoidal granulomas will have foreign material present within them. This observation is particularly common in lesions from the elbows and knees. Therefore, the dermatologic diagnoses of foreign body granuloma and sarcoidosis are not mutually exclusive[12].

In addition, granulomatous mycosis fungoides, Hodgkin disease, granulomatous rosacea, cutaneous Crohn's disease, Blau syndrome (see Ch. 55), cheilitis granulomatosa, and the sarcoidal reaction to an underlying lymphoma can have histologic appearances similar to sarcoidosis. The histologic differences between sarcoidosis, granuloma annulare, necrobiosis lipoidica, annular elastolytic giant cell granuloma, rheumatoid nodule and interstitial granulomatous dermatitis are outlined in Table 93.2.

Treatment

Corticosteroids, in either topical, intralesional or systemic form, are the mainstay of therapy for systemic sarcoidosis (Table 93.3). Therapy is guided by disease severity and progression. The typical oral prednisone dose for systemic disease is 1 mg/kg/day for 4–6 weeks, followed by a slow taper over months to years as dictated by the pulmonary disease, sarcoidosis of the upper respiratory tract, ocular disease or other internal manifestations. Cutaneous sarcoidosis that is major in terms of disfigurement may respond to lower doses of prednisone, including every-other-day regimens. Hydroxychloroquine (200–400 mg/day) or chloroquine (250–500 mg/day) can be effective in controlling skin manifestations of sarcoidosis, particularly chronic disease. Other reported therapeutic agents for cutaneous disease include minocycline (200 mg/day), methotrexate (10–25 mg weekly), thalidomide (50–300 mg/day), isotretinoin (1 mg/kg/day for 3–8 months), and allopurinol (100–300 mg/day)[13–17]. Improvement of systemic and cutaneous sarcoidosis has been observed with TNF-α inhibitors, including infliximab, adalimumab and etanercept, but these agents may also trigger sarcoidosis[18,19]. One phase II trial of etanercept was terminated early due to adverse events (e.g. lymphoproliferative disorders). Benefit from leflunomide has also been reported[20].

Other treatments for cutaneous disease include superpotent topical corticosteroids with or without occlusion, intralesional triamcinolone (3–10 mg/ml every month), and PUVA[21,22]. Pulsed dye and CO_2 laser treatments and photodynamic therapy may be effective for lupus pernio, but there is also a report of laser therapy worsening the disease[23,24]. Surgical excisions with grafting have been performed for ulcerative sarcoidosis[25]. A treatment algorithm, based upon evidence-based methodology, has been proposed[26].

HISTOLOGIC FEATURES OF THE MAJOR GRANULOMATOUS DERMATITIDES

	Sarcoidosis	Granuloma annulare	Necrobiosis lipoidica	AEGCG	Cutaneous Crohn's disease	Rheumatoid nodule*	Interstitial granulomatous dermatitis*	Palisading neutrophilic and granulomatous dermatitis*
Typical location	Superficial and deep dermis†	Superficial and mid dermis†	Entire dermis, subcutis	Superficial and mid dermis	Superficial and deep dermis	Deep dermis, subcutis	Mid and deep dermis	Entire dermis
Granuloma pattern	Tubercle with few peripheral lymphocytes ("naked")	Palisading or interstitial	Diffuse palisading and interstitial; horizontal "tiers"	Palisading, irregular	Tubercle with surrounding lymphocytes	Palisading	Palisading in small "rosettes"	Palisading; prominent neutrophils and leukocytoclasia
Necrobiosis (altered collagen)	No	Yes ("blue")	Yes ("red")	No	No	Yes ("red")	Yes ("blue")	Yes ("blue")
Giant cells	Yes	Variable	Yes	Yes	Yes	Yes	Variable	Variable
Elastolysis	No	Variable	Variable	Yes	No	No	Variable	Variable
Elastophagocytosis	No	No	No	Yes	No	No	No	No
Asteroid bodies	Yes	Variable	Variable	Yes	No	No	Variable	Variable
Mucin	No	Yes	Minimal	No	No	Variable	Minimal	Variable
Extracellular lipid	No	Variable	Yes	No	No	Variable	No	No
Vascular changes	No	Variable	Yes	No	No	Yes	No	Yes

*See Chapter 45.
†Subcutaneous variant can also occur

Table 93.2 Histologic features of the major granulomatous dermatitides. Interstitial granulomatous dermatitis and palisading neutrophilic and granulomatous dermatitis are often considered two ends of a spectrum. Tan-shaded area is not covered in this chapter. AEGCG, annular elastolytic giant cell granuloma.

TREATMENT OF CUTANEOUS SARCOIDOSIS
Topical, intralesional or systemic corticosteroids (2)
Topical calcineurin inhibitors (3)
Minocycline (2)
Systemic hydroxychloroquine or chloroquine (2)
Intralesional chloroquine (3)
Allopurinol (3)
Isotretinoin (3)
Methotrexate (2)
PUVA (psoralen plus UVA) (3)
Thalidomide (2)
TNF-α inhibitors (adalimumab, infliximab, etanercept)* (3)
Leflunomide (2)
Mycophenolate mofetil (3)
Surgical excision (3)
Pulsed dye or CO_2 laser (3)
Photodynamic therapy (3)
*Can trigger sarcoidosis.

Table 93.3 Treatment of cutaneous sarcoidosis. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports. TNF, tumor necrosis factor.

can degrade connective tissue[31]. One ultrastructural study found that the main alteration in GA is elastic fiber degeneration and suggested that this disease is primarily a disorder of elastic tissue injury[32]. Familial cases of GA have been reported, including cases in identical twins, and an association may exist between generalized GA and HLA-Bw35[33]. Vessel-based mixed inflammatory cell infiltrates with endothelial swelling are sometimes detected in routine histopathologic specimens, and direct immunofluorescence studies of GA may show vessel-based deposits of immunoreactants, but a role for these findings in the pathogenesis of this disease has not been established.

Clinical Features

GA is a benign, usually self-limited, cutaneous disease that classically presents as arciform to annular plaques located on the extremities of young people (Fig. 93.8A)[28]. In general, the distribution of GA is: 60% isolated to the hands and arms, 20% on the legs and feet, 7% on both upper and lower extremities, 5% on the trunk, and 5% on the trunk plus other areas[34]. Facial lesions are rare. The plaques may be skin-colored, pink or violaceous in color, and, upon close inspection, are found to be composed of individual small papules measuring a few millimeters in diameter (Fig. 93.8B). These lesions are usually asymptomatic. Solitary umbilicated papules or nodules may also occur, especially on the fingers.

Generalized (disseminated) GA, which occurs in a minority of patients, is characterized by myriad, small, skin-colored to pink–violet

GRANULOMA ANNULARE

Synonyms: ■ Pseudorheumatoid nodule – subcutaneous granuloma annulare variant ■ Generalized granuloma annulare – disseminated granuloma annulare

Key features

- Small grouped papules assuming an annular configuration, often in a symmetrical and acral distribution
- Seen primarily in children and young adults
- Clinical variants include localized, generalized, micropapular, nodular, perforating, patch and subcutaneous forms
- A possible association with diabetes mellitus is controversial
- Histopathologically, there is an infiltrative or palisading granulomatous dermatitis with focal degeneration of collagen and elastin and deposition of mucin

History

Calcott Fox first described "ringed eruption of the fingers" in 1895. Radcliffe-Crocker called this entity granuloma annulare in 1902.

Epidemiology

Two-thirds of patients with granuloma annulare (GA) are less than 30 years of age. The female-to-male ratio is approximately 2:1 in this common disease.

Pathogenesis

The etiology of GA is unknown. Trauma, insect bite reactions, tuberculin skin testing, sun exposure, PUVA therapy, and viral infections have all been proposed as inciting factors[27,28]. Based on the T-cell subpopulations identified in GA lesions, a delayed-type hypersensitivity reaction to an unknown antigen has been postulated as the precipitating event[29]. Morphologic similarities to tuberculosis suggest that GA is caused by a Th1 inflammatory reaction, with IFN-γ-producing lymphocytes eliciting matrix degradation[30]. These lymphocytes release cytokines, including macrophage inhibitory factor, that cause monocytes to accumulate in the dermis and release lysosomal enzymes that

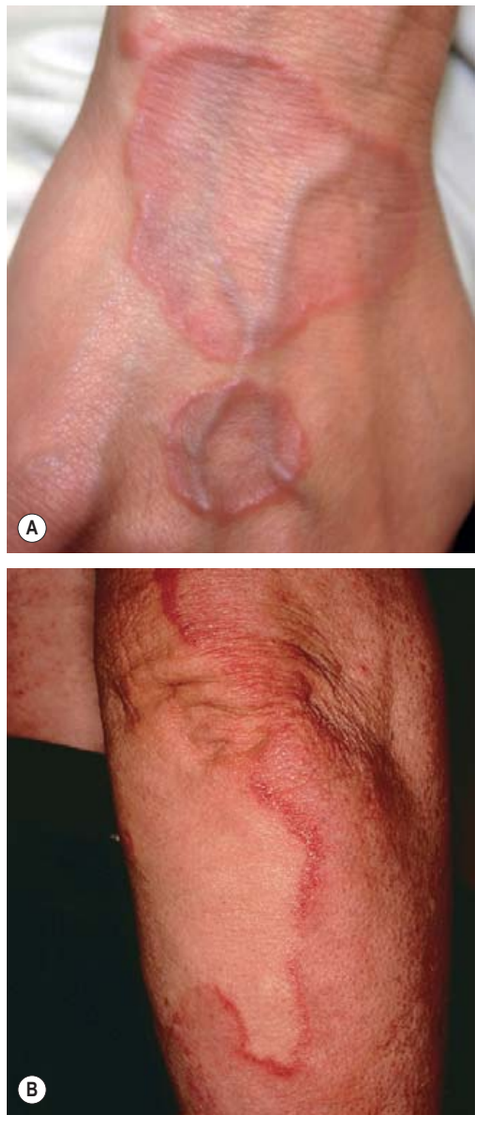


Fig. 93.8 Granuloma annulare. A Annular plaques on the dorsal aspect of the hand, a common location. **B** Larger lesion on the arm with a figurate border composed of coalescing papules. Note the red–brown color of previously involved skin.

Fig. 93.9 Disseminated granuloma annulare. Numerous papules and small annular plaques.

Fig. 93.10 Perforating granuloma annulare. Papules can have a central keratotic plug or umbilication. *Courtesy, Ronald P Rapini, MD.*

papules in a symmetric distribution on the trunk and extremities. Some of these papules may coalesce to form small annular plaques (Fig. 93.9). Generalized GA has a later age of onset, poorer response to therapy, and an increased prevalence of the HLA-Bw35 allele. In one study of 100 patients with generalized GA, 45% had lipid abnormalities, including hypercholesterolemia, hypertriglyceridemia or both[35].

Perforating GA presents clinically as small papules with central umbilication, scale-crust or focal ulceration, primarily on the dorsal hands and fingers (Fig. 93.10). This variant occurs up to 5% of patients with GA, and it exhibits transepidermal elimination of degenerating collagen histologically[36].

Deep dermal or *subcutaneous* GA manifests as large, painless, skin-colored nodules which may be mistaken for rheumatoid nodules, leading to the term pseudorheumatoid nodule. It has a predilection for children less than 6 years of age. Typical locations include the palms, hands, anterior tibial surfaces and feet, as well as the buttocks, scalp and, rarely, the eyelids[28]. As many as 50% of individuals with deep GA lesions also have associated classic lesions.

Patch GA is a distinct variant that is characterized by patches of erythema on the extremities and trunk. Symmetrical lesions on the dorsum of the feet often present as macular (i.e. "patch") disease. Although an annular configuration may be absent, presence of the classic histopathologic findings of interstitial GA (see below) allow for the diagnosis to be made microscopically.

GA has been described as a paraneoplastic granulomatous reaction to solid organ tumors, Hodgkin disease, non-Hodgkin lymphoma and granulomatous mycosis fungoides[37–40]. In these patients, the clinical pattern is frequently atypical, with painful lesions in unusual locations, including the palms and soles.

Many reports either supporting or refuting the association of GA with diabetes mellitus have been published. In a retrospective study of 84 patients, 12% were found to have diabetes mellitus, and these patients were more likely to suffer from chronic relapsing GA than were non-diabetic patients[41]. In a larger retrospective study of 1383 patients, diabetes mellitus was diagnosed in 21% of patients with generalized GA, compared with ~10% of patients with localized GA[35].

Classic GA and perforating GA may occur in herpes zoster scars (see Table 80.6)[42]. Atypical variants of GA, including photodistributed, have been associated with HIV infection[43].

Pathology

GA is a granulomatous dermatitis characterized by focal degeneration of collagen and elastic fibers, mucin deposition, and a perivascular and interstitial lymphohistiocytic infiltrate in the upper and mid dermis. The key to the histopathologic diagnosis of GA is the identification of histiocytes in one of three patterns. The most common (accounting for ~70% of cases) is the interstitial or infiltrative pattern (Fig. 93.11), in which scattered histiocytes are distributed between collagen fibers. Degeneration of collagen fibers is minimal, but granular, basophilic mucin deposition between collagen bundles can be highlighted with Alcian blue and colloidal iron stains[31]. The second pattern (25% of cases) is more obvious and is easier to diagnose. It consists of one to several palisading granulomas with central connective tissue degeneration surrounded by histiocytes and lymphocytes (Fig. 93.12). Mucin is abundant in the center of the palisaded granuloma, and fibrin, neutrophils and nuclear dust may also be present. The final pattern is rare, and it consists of epithelioid histiocytic nodules that can resemble cutaneous sarcoidosis.

Increased mucin can be detected in approximately 70% of biopsy specimens from GA lesions. The sensitivity of detection is increased by using at least two different mucin stains, such as colloidal iron and Alcian blue. Elastic tissue is reduced or absent within the histiocytic aggregates in approximately 20% of generalized GA and 35% of localized GA cases[44].

Ultrastructurally, degeneration of elastic and collagen fibers is seen; the latter consists of collagen fiber swelling, loss of periodic banding, fragmentation, and dissolution of fiber structure with replacement by a granular and finely fibrillar material. Collagen degeneration is more common in localized GA than in generalized GA[44]. Elastophagocytosis is occasionally noted, but is not a prominent histopathologic feature.

As noted previously, vascular changes in GA are variable, but include fibrin, C3 and IgM deposition in vessel walls (detected by direct immunofluorescence) and occlusion of vascular lumina[45]. One study found that the presence of leukocytoclastic or granulomatous vasculitis or a thrombotic vasculopathy within the lesions of GA was predictive of associated systemic disease[46], and the possibility of palisading neutrophilic and granulomatous dermatitis as a reflection of disorders such as rheumatoid arthritis needs to be considered (see Ch. 45).

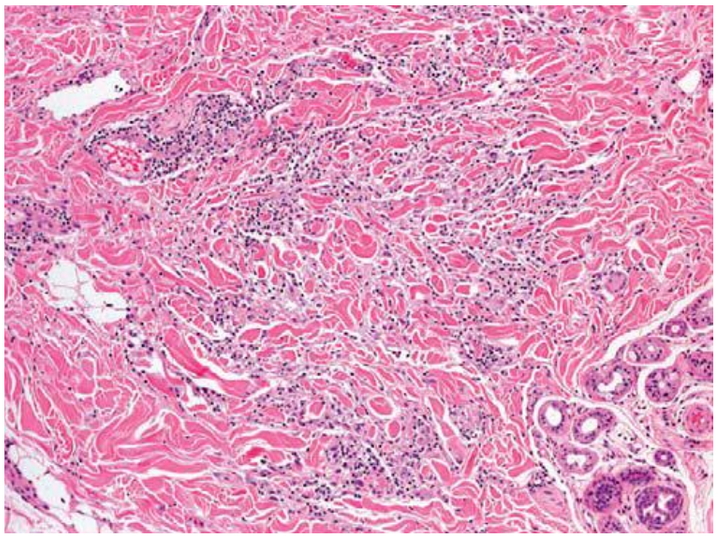
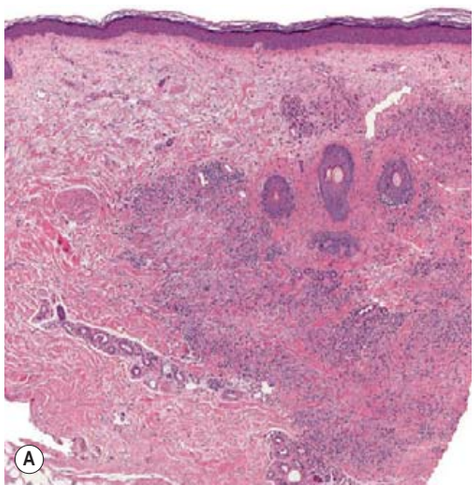


Fig. 93.11 Granuloma annulare, interstitial pattern. Infiltration of histiocytes between the dermal collagen fibers, with scant mucin. *Courtesy, Lorenzo Cerroni, MD.*

Fig. 93.13 Papular granuloma annulare of the dorsal hand. Several of the lesions have a central dell. *Courtesy, Joyce Rico, MD.*



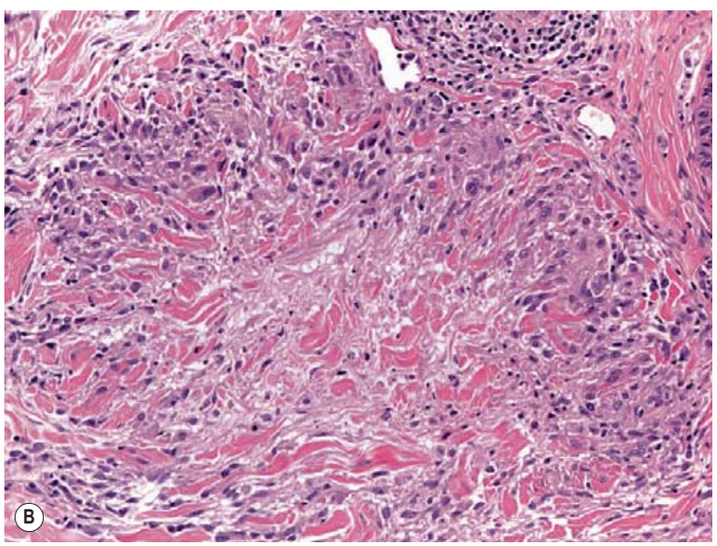


Fig. 93.12 Granuloma annulare, palisaded pattern. A Multiple palisaded granulomas within the dermis. Degenerative collagen and mucin deposition are present in the central portion of the granulomas. **B** A palisaded granuloma with epithelioid histiocytes surrounding an anuclear dermis characterized by altered collagen and pallor due to deposition of acid mucopolysaccharides/glycosaminoglycans (mucin). *Courtesy, Lorenzo Cerroni, MD.*

In deep GA, the histologic findings are usually of the palisaded granulomatous type and extend into the deep dermis or subcutaneous fat. In perforating GA, there is a superficial histiocytic infiltrate with transfollicular and/or transepidermal elimination of granulomatous inflammation.

Differential Diagnosis

GA is diagnosed based on its clinical and histopathologic features – there are no laboratory tests which aid in confirming the diagnosis. When the diagnosis of deep GA versus rheumatoid nodule is in question, a rheumatoid factor level identifies patients at risk for the latter. Rheumatoid nodules also demonstrate fibrin rather than mucin histologically.

The clinical differential diagnosis for conventional GA includes the annular entities listed in Table 19.1, including annular sarcoidosis and annular elastolytic giant cell granuloma. A clue to the latter is central hypopigmentation and/or atrophy. Arcuate and annular plaques of mycosis fungoides or borderline leprosy may also simulate GA, requiring biopsy for definitive diagnosis.

Papular GA (Fig. 93.13) can simulate flat warts, secondary syphilis, early eruptive xanthomas, and the non-X-histiocytoses (see Ch. 91). *Subcutaneous* GA can be clinically similar to rheumatoid nodules, the nodules of rheumatic fever, tendinous xanthomas, epithelioid sarcoma, subcutaneous sarcoidosis, and deep granulomatous infections. *Perforating* GA must be differentiated from primary perforating disorders (see Ch. 96) and, occasionally, perforating calcinosis cutis, perforating gout or molluscum contagiosum, based on histopathologic findings[28].

The clinical and histologic differences between GA, sarcoidosis, necrobiosis lipoidica, annular elastolytic giant cell granuloma, rheumatoid nodule and interstitial granulomatous dermatitis are outlined in Tables 93.1 and 93.2. The histopathologic differential diagnosis of GA also includes morphea, cutaneous T-cell lymphoma, xanthomas, epithelioid sarcoma and, rarely, scleromyxedema.

Treatment

Given the self-limited and benign nature of GA, reassurance and clinical observation may be the treatment of choice for localized, asymptomatic disease. High-potency topical corticosteroids with or without occlusion and intralesional corticosteroid injections are the usual first-line local therapies. Other treatment options include cryosurgery, PUVA or UVA1 therapy, and CO_2 laser treatment (Table 93.4)[47–49]. In a small series, multiple intralesional injections of recombinant human IFN-γ led to improvement[50]; however, side effects and cost may make this treatment difficult to justify.

Systemic agents are reserved for severe cases, and include oral niacinamide (nicotinamide; 500 mg three times daily)[51], isotretinoin (0.5–0.75 mg/kg/day)[52], antimalarials (chloroquine 3 mg/kg/day or hydroxychloroquine 6 mg/kg/day)[35,53], dapsone (100 mg/day)[54] and pentoxifylline[55]. In one series of six patients, a combination of three antibiotics (rifampin, ofloxacin and minocycline) administered monthly for 3 months led to improvement (see Table 93.4)[56].

TREATMENT OF GRANULOMA ANNULARE
Topical corticosteroids (3)
Intralesional corticosteroids (2)
Topical calcineurin inhibitors (3)
Topical imiquimod (3)
Cryosurgery (2)
Hydroxychloroquine or chloroquine (2)
Niacinamide (nicotinamide) (3)
Minocycline + ofloxacin + rifampin* (3)
Pentoxifylline (3)
Intralesional interferon (3)
5-lipoxygenase inhibitor (zileuton) plus vitamin E† (3)
Dapsone (3)
Isotretinoin (3)
PUVA (psoralen plus UVA) or UVA1 (2)
Cyclosporine (3)
TNF-α inhibitors (adalimumab, infliximab) (3)
Methotrexate (3)
Fumaric acid esters (3)
Chlorambucil (3)
Photodynamic therapy with topical 5-aminolevulinic acid (3)
CO_2 laser (3)
Surgical excision (3)

*Administered monthly: minocycline (100 mg), ofloxacin (400 mg) and rifampin (600 mg) × 3 months
†Doses of 2400 mg po daily (zileuton) and 400 IU po daily (vitamin E).

Table 93.4 Treatment of granuloma annulare. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

Use of more toxic and/or expensive therapies are controversial, but reports exist for cyclosporine (3–4 mg/kg/day for 3 months)[57], chlorambucil[58], etretinate[59] and photodynamic therapy[60] being beneficial in individual or small groups of patients. With regard to TNF-α inhibitors, there are multiple case reports of adalimumab and infliximab being effective for generalized GA[61,62], with variable results for etanercept[63]. However, no large, randomized, double-blind, placebo-controlled studies have been performed to support the use of these systemic medications.

Spontaneous resolution of GA occurs within 2 years in 50% of patients, but there is a 40% recurrence rate. The recurrent lesions tend to occur at the original sites, but clear more rapidly (80% within 2 years). The duration of untreated lesions has been reported to range from a few weeks to several decades[64].

NECROBIOSIS LIPOIDICA

Synonym: ■ Necrobiosis lipoidica diabeticorum

Key features

- Plaques with violaceous to red–brown, palpable peripheral rims and yellow–brown atrophic centers with telangiectasias
- The most common site is the shins
- Ulceration can occur following trauma
- The proportion of patients with diabetes mellitus varies from 15% to 65%
- Pathogenesis is unknown
- Pathology shows palisading granulomatous dermatitis with a "layered" appearance, often with perivascular plasma cells

History

First called "dermatitis atrophicans diabetica" by Oppenheim in 1929, the condition was renamed necrobiosis lipoidica diabeticorum (NLD) by Urbach in 1932. The first non-diabetic patient with NLD was described in 1935 by Goldsmith, generating the more general term necrobiosis lipoidica, which is currently preferred. Nonetheless, the abbreviation NLD is ingrained in our lexicon.

Epidemiology

In a study of 171 patients, Muller and Winkelmann found that diabetes mellitus, usually type 1, was present in approximately 65% of patients with NLD[65]. An additional 12–15% of patients with NLD demonstrated abnormal glucose tolerance tests. Also, over half of the patients with no evidence of diabetes and a normal glucose tolerance test reported a positive family history of glucose intolerance[65,66]. However, a more recent retrospective study of 65 patients with NLD seen in a dermatology outpatient clinic found that only 11% had diabetes mellitus at the time of presentation. An additional 11% were later diagnosed with impaired glucose tolerance or diabetes[67].

There is no proven connection between a patient's level of glycemic control and the likelihood of developing NLD lesions, but diabetic patients with NLD do appear to have a higher rate of diabetes-related complications such as peripheral neuropathy, retinopathy and limited joint mobility[68]. Only 0.03% of patients with diabetes have NLD. The female-to-male ratio is approximately 3:1.

Pathogenesis

The cause of NLD remains unknown. There is no HLA linkage. Immunologically mediated vascular disease has been suggested as the primary cause of the altered collagen seen in NLD, and this hypothesis is supported by the presence of immunoreactants deposited in vessel walls of lesional as well as uninvolved skin in patients with NLD[69]. Previous immunofluoresence studies had also found evidence for immune complex vasculitis in NLD[70]. It is has also been postulated that the microangiopathic vessel changes seen in diabetic patients could contribute to the development of collagen degeneration and subsequent dermal inflammation. Elevated plasma levels of fibronectin, factor VIII-related antigen, and α_2-macroglobulin have been detected in patients with NLD, but the significance of these findings has not been determined[71]. Theories regarding abnormally elevated platelet adhesion, increased thromboxane A_2 production, and increased blood viscosity within NLD lesions remain speculative.

Some investigators consider NLD to be primarily a disease of collagen, with inflammation occurring as a secondary event. Anticollagen antibodies have been detected in patients with both NLD and GA, but no significant increase in antibody levels as compared with control patients has been demonstrated[72]. The concentration of collagen is decreased in NLD lesions, and electron microscopy reveals a loss of the cross-striations of collagen fibrils and significant variation in the diameter of individual fibrils. Fibroblasts cultured from NLD lesions synthesize less collagen than their counterparts from unaffected skin[73]. Overhydration of collagen due to hyperglycemia can lead to increased collagen cross-linking and stiffness, but it is unclear if this phenomenon occurs in NLD.

From central Europe, there was a report of the detection of *Borrelia* spp. via focal floating microscopy in NLD[74], but these findings need to be confirmed.

Clinical Features

Clinically, NLD is characterized by yellow–brown, atrophic, telangiectatic plaques with an elevated violaceous rim, typically present in the pretibial region (Fig. 93.14). The plaques are usually multiple and bilateral. Lesions start as small, firm, red–brown papules that gradually enlarge and then develop central epidermal atrophy. Ulceration occurs in approximately a third of lesions (see Fig. 53.21), usually following minor trauma. Less typical anatomic locations for NLD include the upper extremities, face and scalp, where the lesions may be more annular or serpiginous in configuration and are less atrophic. As a result, there is significant overlap with annular elastolytic giant cell granuloma.

Decreased sensation to pinprick and fine touch, hypohidrosis and partial alopecia can be found within NLD plaques. Decreased S100 staining within the cutaneous nerves of inflammatory plaques has been

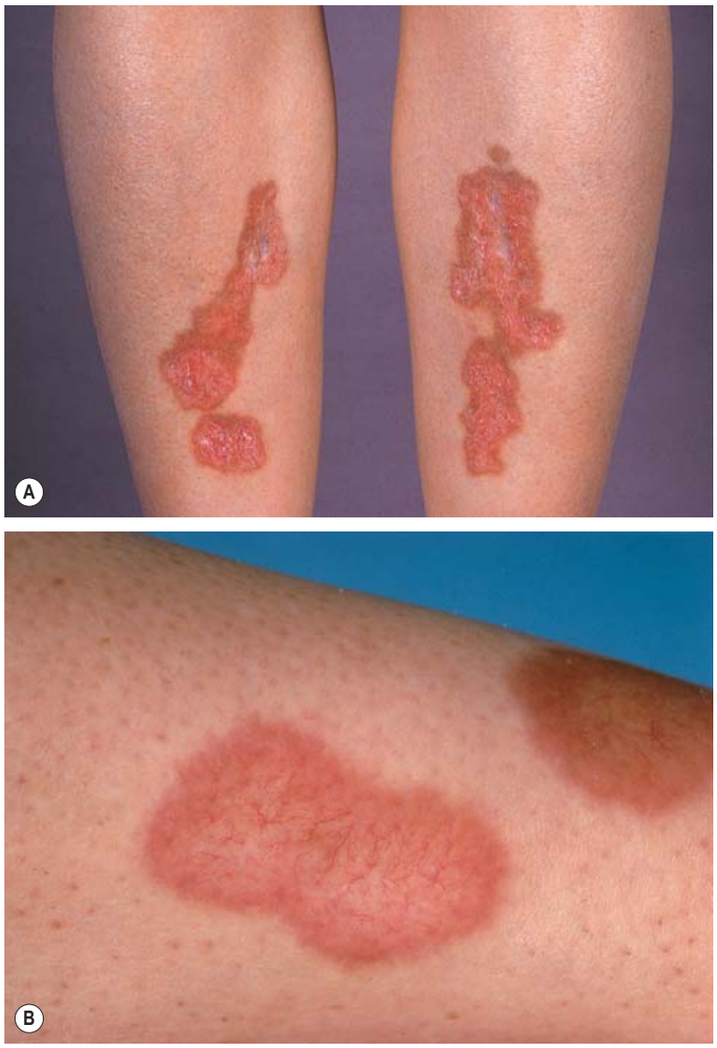
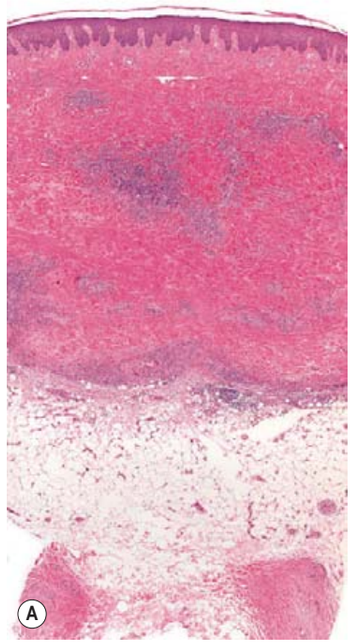


Fig. 93.14 Necrobiosis lipoidica. A Pink–brown atrophic plaques on the shins. **B** Annular plaques with central telangiectasias.



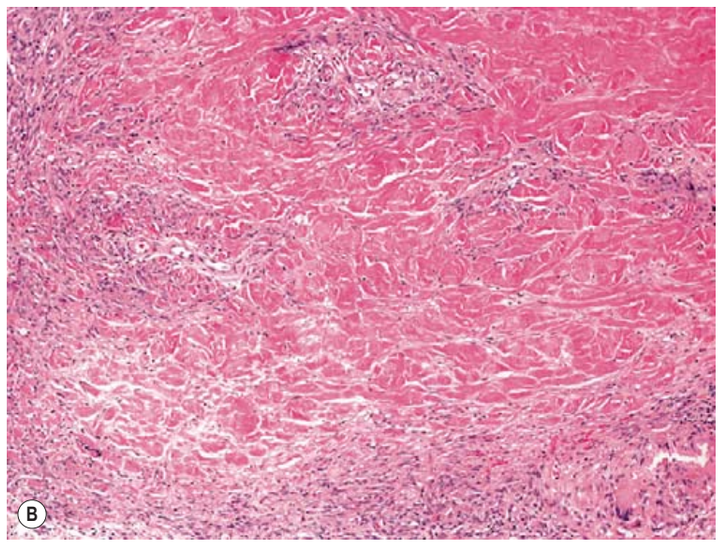


Fig. 93.15 Necrobiosis lipoidica – histologic features. A Multiple granulomas within the entire dermis extending into the subcutaneous fat. Note the layered tiers of granulomatous inflammation aligned parallel to the skin surface. **B** Palisaded granuloma composed of epithelioid histiocytes with altered collagen centrally. *Courtesy, Lorenzo Cerroni, MD.*

observed, with degenerative neural changes possibly accounting for the loss of sensation[68]. Of note, the cutaneous nerves in GA demonstrate normal S100 staining patterns. Although the lesions of NLD are typically asymptomatic, some patients report pruritus, dysesthesia or pain. Lesions that ulcerate after trauma or from transepidermal elimination of altered collagen and elastic fibers can be very painful. Rarely, squamous cell carcinoma has been reported to develop within lesions of NLD[75].

Pathology

Biopsy specimens, particularly from the palpable inflammatory border, reveal a diffuse palisaded and interstitial granulomatous dermatitis (Fig. 93.15), with "layered" tiers of granulomatous inflammation aligned parallel to the skin surface involving the entire dermis and extending into the subcutaneous fat septae. The epidermis is normal or atrophic. There is a superficial and deep perivascular infiltrate that is predominantly lymphocytic but also contains plasma cells and occasionally eosinophils. The granulomatous inflammation includes multinucleated histiocytes but no asteroid bodies.

Focal loss of elastic tissue can be demonstrated in areas of connective tissue sclerosis. Between the layers of inflammatory cells, there are horizontal tiers of degenerated collagen, with fibers of irregular size and shape. Extracellular lipid deposition in these foci can be identified only via staining frozen tissue sections with an oil red O stain. However, this is seldom done from a practical standpoint. In contrast to GA, there is no significant mucin deposition in the center of the palisading granulomas.

Early lesions of both NLD and GA may have foci of leukocytoclasia, but NLD shows more prominent endothelial cell swelling, fibrosis and hyalinization; the latter can lead to blood vessel wall thickening or even endarteritis obliterans. The vessel walls often contain a PAS-positive, diastase-resistant material suggesting neutral glycosaminoglycans[71].

NLD occasionally presents with less sclerotic collagen and more typical epithelioid cell granulomas rather than the horizontally tiered pattern of altered collagen and palisaded granulomatous inflammation described above. Vascular changes are rare, and this form of NLD is felt to have a weaker association with diabetes mellitus than the classic lesions[71].

Immunofluorescent studies of NLD lesions have yielded conflicting results, and are not performed routinely. Deposits of C3, IgM and IgA have been noted around dermal blood vessels (lesional skin)[70] as has vascular deposition of C3, fibrin and IgM (both lesional and non-lesional skin)[69]. However, in another study, positive immunofluorescence was detected in only 4 of 14 lesional skin biopsies[76]. Fibrin is consistently found deposited in areas of altered collagen[77].

Differential Diagnosis

Clinically, the differential diagnosis of NLD includes primarily GA, necrobiotic xanthogranuloma, sarcoidosis, diabetic dermopathy and lipodermatosclerosis. Other entities in the differential diagnosis include additional forms of panniculitis (see Ch. 100), granulomatous infections (e.g. leprosy, tertiary syphilis, dimorphic fungal infections), morphea, lichen sclerosus and sclerosing lipogranuloma.

Lesions of GA and sarcoidosis generally do not exhibit the same degree of atrophy, telangiectasias or yellow–brown color as NLD lesions, although prominent telangiectasias can be present in angiolupoid sarcoidosis and can occur following injections of triamcinolone. However, there are reports of NLD and sarcoidosis coexisting in the same patient[78]. Necrobiotic xanthogranuloma is characterized by yellow, indurated, often periorbital (among other sites) plaques, and it is associated with a paraproteinemia. The lesions of diabetic dermopathy are located on the shins, but they are macular and hyperpigmented. Injection of substances such as paraffin, cottonseed oil, sesame oil or beeswax may cause plaque-like indurations with ulcerations mimicking NLD, but the ensuing lesions of sclerosing lipogranuloma are rarely located on the legs.

The major entity in the histopathologic differential diagnosis for NLD is GA. Whereas the inflammation in NLD is diffuse and involves the entire dermis extending into subcutaneous fat septae, GA is patchy with discrete foci of granulomatous inflammation amid areas of uninvolved dermis. There is usually deposition of mucin within areas of granulomatous inflammation in GA but not in NLD. In general, NLD has more giant cells, plasma cells, vascular changes, collagen degeneration, and extracellular lipid deposition than GA.

Necrobiotic xanthogranuloma can be differentiated from NLD histologically by the presence of abundant cholesterol clefts in necrobiotic xanthogranuloma. One case report did describe NLD with prominent cholesterol clefts and transepithelial elimination of cholesterol crystals via hair follicles[79]. Transepidermal elimination of elastic fibers has also been observed and should not be misconstrued with entities such as elastosis perforans serpiginosa[80].

Treatment

No treatment for NLD has proven to be effective in large, double-blind, placebo-controlled studies. In patients with diabetes mellitus, control of blood glucose levels usually does not have a significant effect on the course of NLD. Spontaneous remission after an average of 8 to 12 years was observed in only 17% of 171 patients with NLD in one study[65].

First-line therapy includes potent topical corticosteroids for early lesions and intralesional corticosteroids injected into the active borders of established lesions. Because the histologic changes can extend well into normal-appearing skin in clinically active NLD lesions[68], some authors advocate the injection of intradermal corticosteroids into a rim of clinically normal skin around expanding plaques in an effort to halt disease progression. In addition, 5-week courses of systemic corticosteroids were found to be effective in a series of six patients with an average follow-up period of 7 months, but this can elevate serum glucose levels[81].

Other therapies are directed at increasing fibrinolysis or decreasing platelet aggregation and thromboxane A_2 synthesis in order to decrease the microangiopathy and vascular thrombosis seen in lesions of NLD. Stanozolol, inositol niacinate (inositol nicotinate), nicofuranose, ticlopidine hydrochloride and pentoxifylline are all agents that have been used towards this end in anecdotal reports or uncontrolled case series. The use of stanozolol is limited by its potential hepatotoxicity and ticlopidine can cause agranulocytosis. A 16-patient controlled trial of aspirin (40 mg/day) versus placebo showed no significant difference between the groups[82]. A 12-patient controlled trial of aspirin (300 mg three times daily) plus dipyridamole (75 mg three times daily) versus placebo also showed no significant effects of treatment[83]. Perilesional heparin injection has been reported in the Russian literature[84].

Niacinamide (500 mg three times daily) has been used with some success in both NLD and GA, and it is postulated to inhibit the release of lymphokines and decrease macrophage migration[71]. Small series of patients have also been treated successfully with antimalarials[85], with the proposed mechanism of action being inhibition of antigen presentation and decreased production of several cytokines (e.g. TNF-α, IL-6, IFN-γ). There are reports of TNF-α inhibitors (etanercept, infliximab) leading to improvement of NLD, including recalcitrant ulcerated lesions[86]. In a limited number of patients, systemic cyclosporine also improved severe, ulcerating NLD on the lower legs[87,88].

Other reported topical therapies include granulocyte–macrophage colony-stimulating factor or bovine collagen[89] for ulcerations and tretinoin gel (0.025% twice daily) to decrease lesional atrophy[90]. In addition, improvement with topical PUVA[91,92], UVA1 phototherapy[93], mycophenolate mofetil (500 mg twice daily)[94] and thalidomide[95] has been described.

If surgical therapy becomes necessary for severe ulcerations that are refractory to medical treatment, excision to deep fascia or periosteum must be performed to minimize the chance of recurrence. Split-thickness skin grafting is performed following excision.

ANNULAR ELASTOLYTIC GIANT CELL GRANULOMA

Synonyms: ■ Actinic granuloma ■ Giant cell elastophagocytosis ■ Miescher's granuloma of the face ■ Atypical (annular) necrobiosis lipoidica of the face and scalp

Key features

- Asymptomatic annular plaques, predominantly on the head and neck and other chronically sun-exposed sites
- The border of each plaque is elevated and erythematous, while the center is slightly atrophic and hypopigmented
- Histopathologically, non-palisading granulomas with histiocytes, foreign body type multinucleated giant cells and lymphocytes
- Elastic fibers are absent within the central portion of the lesion, and some elastic fibers are found within giant cells (elastophagocytosis)
- No collagen alteration, mucin or lipid deposition, or vascular changes are seen histopathologically

History

O'Brien[96] described the entity known as actinic granuloma in 1975 but attributed the first description of this disease to Georgouras in 1964. O'Brien used "actinic" in the name of this disorder because he believed that its etiology was linked to ultraviolet and infrared radiation. This nosologic theory was rejected by Hanke et al.[97] whose patients did not all demonstrate significant solar elastosis histologically but otherwise fit O'Brien's clinical and histopathologic descriptions. These authors coined the descriptive term "annular elastolytic giant cell granuloma" in 1979. Upon review of the literature, both O'Brien and Hanke realized that the diseases they were describing had previously been reported under other names, including atypical necrobiosis lipoidica of the face and scalp[98], Miescher's granuloma of the face[99], and possibly granuloma multiforme[100].

Epidemiology

Annular elastolytic giant cell granuloma (AEGCG) is an uncommon disease that occurs predominantly in middle-aged women, at least 30 years of age but usually over 40. Patients have been reported from several regions of the world, including Australia, the UK, the US, the Caribbean basin and Africa.

Pathogenesis

Debate exists as to whether annular elastolytic giant cell granuloma is a distinct clinical entity or a variant of GA[101,102]. Its pathogenesis is not understood, but it may be related to inflammation precipitated by

Fig. 93.16 Annular elastolytic giant cell granuloma. The border resembles granuloma annulare but the central portion is hypopigmented and/or atrophic (**A, B**). A biopsy specimen that includes the area outlined in **A** would contain the three characteristic histologic zones: absence of elastic fibers, granulomatous inflammation, and normal skin. Longitudinal sectioning of the surgical specimen is preferred. *B, Courtesy, Kalman Watsky, MD.*

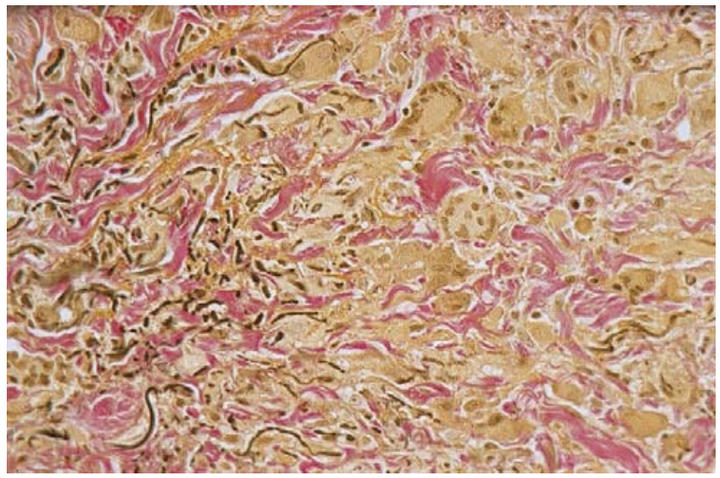


Fig. 93.17 Annular elastolytic giant cell granuloma – histologic features. Loss of elastic fibers (black) is seen amid the granulomatous infiltrate (yellow). The remaining collagen is stained red (Verhoeff–van Gieson stain). *Courtesy, Ronald P Rapini, MD.*

actinic damage. Specifically, O'Brien postulated that "a state of autoaggression develops in relation to the damaged [elastic] fibers", in an attempt to repair or remodel damaged skin[96]. T lymphocytes involved in AEGCG are predominantly of the helper-inducer subset, suggesting that the pathogenesis may involve a cell-mediated immunologic response to a weakly antigenic determinant on altered elastotic fibers[102]. However, destruction of elastic tissue has also been observed in classic GA and NLD, leading to the argument that this finding may be a secondary event caused by the granulomatous inflammation rather than a precipitating one[97]. A few patients with AEGCG as well as diabetes mellitus, NLD and/or sarcoidosis have been reported, as have rare patients with lymphoma or leukemia[103,104].

Clinical Features

Patients with AEGCG have large annular plaques with a raised erythematous border (3–5 mm) and a slightly atrophic, hypopigmented center, distributed mainly in chronically sun-exposed areas (Fig. 93.16). The sites of predilection include the neck, face, upper trunk and arms. Early on, skin-colored or pink papules may appear, singly or in small groups, before they coalesce into annular plaques. Scale is rarely observed. In contract to NLD, there is no yellow color, telangiectasias or associated alopecia. Individual lesions measure 1–10 cm in diameter, and the total number of lesions is generally fewer than 10. Patients are usually asymptomatic, although pruritus has been reported. A single plaque lasts for months to years, after which spontaneous remission may occur, leaving mottled dyspigmentation or normal-appearing skin[96].

Pathology

Sections through the raised border of an AEGCG lesion show a nonpalisading granulomatous infiltrate of histiocytes, foreign body type multinucleated giant cells (with haphazardly arranged nuclei), and lymphocytes within the mid to upper dermis; there is an absence of altered collagen or mucin or lipid deposition[105]. Elastic fibers are identified adjacent to and within the giant cells, giving rise to the term elastophagocytosis. Asteroid bodies that stain with acid orcein (like elastic fibers) are observed within the multinucleated giant cells. These findings are not specific for AEGCG, but they are seen less frequently in other granulomatous disorders such as GA and NLD. Elastic tissue stains, such as the Verhoeff–van Gieson stain, show a characteristic complete absence of elastic fibers in the areas affected (or previously affected) by granulomatous inflammation (Fig. 93.17). Normal quantities of elastin are seen in the deeper dermis. Sections from previously involved skin show normal elastic and elastotic fibers surrounding a well-demarcated zone of dermis that remains free of elastic tissue staining.

There are no vascular changes other than a sparse perivascular lymphocytic infiltrate. Basophilic solar elastosis may be present, and was observed in all of O'Brien's patients with actinic granuloma. The epidermis may be normal or slightly thinned. Direct immunofluorescence studies for fibrin, C3, IgG, IgM and IgA are negative.

Occasionally, histiocytes and epithelioid cells form tubercles that are indistinguishable from sarcoidal granulomas.

Differential Diagnosis

The diagnosis of AEGCG is based on the characteristic clinical appearance and histopathologic findings outlined above. There are no helpful laboratory tests. The clinical differential diagnosis includes the annular variants of the diseases outlined in Table 93.1, as well as erythema annulare centrifugum (different distribution), annular lichen planus and secondary syphilis (central hyperpigmentation), tinea corporis and granulomatous infections. Granuloma multiforme (Mkar disease) clinically resembles AEGCG, but it occurs in Africa and histologically has prominent collagen alteration surrounded by palisading granulomas. Therefore, it may be a variant of GA rather than AEGCG.

Other entities in the histologic differential diagnosis include granulomatous slack skin, mid-dermal elastolysis, anetoderma and acquired cutis laxa. Special stains for acid-fast bacilli and fungal organisms should be performed to exclude an infectious granulomatous process such as tuberculosis, leprosy or deep fungal infections. Culture and/or PCR of tissue can be performed, depending upon the clinical situation.

Treatment

AEGCG is a persistent condition that responds poorly or inconsistently to topical or intralesional corticosteroids, PUVA therapy and antimalarial drugs[106]. There are case reports of improvement following 8 weeks of cyclosporine (5 mg/kg/day) or 16 weeks of chloroquine therapy (200–400 mg/day)[107,108]. Excision of lesions followed by partial-thickness

skin grafting has been performed with no recurrence at 15 months of follow-up[109], but this would rarely be required. In individual patients, cryotherapy, cauterization and methotrexate were reported to be ineffective.

CUTANEOUS CROHN'S DISEASE

Synonym: ■ Metastatic Crohn's disease

Key features

- Erythematous plaques, often on the buttocks and genital skin
- Cutaneous non-caseating granulomatous lesions that are not contiguous with intestinal Crohn's disease have been referred to as "metastatic"
- Approximately 20% of patients with cutaneous lesions have no preceding diagnosis of gastrointestinal Crohn's disease

History

Crohn's disease, first described in 1932, is characterized by segmental granulomatous inflammation of the intestinal tract and frequently involves cutaneous tissues as well.

Epidemiology

Crohn's disease usually begins between the second and fourth decades of life. Mucosal and skin findings occur in 20–45% of patients[110], and include distant cutaneous (metastatic) Crohn's disease, contiguous perianal Crohn's disease, oral Crohn's disease, reactive dermatologic disorders (e.g. erythema nodosum, pyoderma gangrenosum) and nutritional skin changes[111].

Cutaneous Crohn's disease is relatively rare, with fewer than 100 cases reported in the literature. Two-thirds of the patients are women, and the mean age of onset is 35 years. Fewer than 20 cases have been reported in children. Approximately 20% of the reported cases had skin disease that preceded the diagnosis of intestinal Crohn's disease by 3 months to 8 years.

Pathogenesis

Cutaneous Crohn's disease occurs in association with or precedes intestinal Crohn's disease. A number of genetic abnormalities which can lead to an exaggerated T-cell response to certain commensal enteric bacteria and defective microbial clearance, including after breaks in the mucosal barrier or an alteration in the balance in gut flora (dysbiosis), have been linked to Crohn's disease. The protein products of these genes have several functions, including regulation of NF-κB function (e.g. *NOD2* [*CARD15*]) and autophagy (*ATG16L1*). Like psoriasis, Crohn's disease is a predominantly Th1- and Th17-mediated disease, and elevated levels of IL-23 and IL-17 are present within involved tissues[112].

Clinical Features

Cutaneous Crohn's disease may be either genital or extragenital, with genital involvement found in approximately two-thirds of children and one-half of adults. Labial or scrotal erythema and swelling are the usual presenting signs[113] (Fig. 93.18). Non-genital disease presents with dusky erythematous plaques, often followed by the development of ulceration with undermined edges, draining sinuses and fistulas, and scarring. These lesions have been observed on the lower extremities and soles (38%), abdomen and trunk (24%), upper extremities and palms (15%), face and lips (11%), flexural areas (8%), and in a generalized distribution (4%)[111,114].

Perianal lesions, which may extend to the adjacent perineum, buttocks or abdomen, consist of ulcers, fissures, sinus tracts or vegetating plaques[115]. These are seen in approximately one-third of patients with intestinal Crohn's disease. Abdominal surgical sites, such as laparotomy scars, colostomies and ileostomies, may also be sites of granulomatous inflammation. For semantic purposes, these lesions are considered to be "contiguous" Crohn's disease rather than "metastatic" Crohn's disease, but show the same histopathologic features.

Fig. 93.18 Cutaneous Crohn's disease. Note the swelling and violaceous discoloration of the labia majora in this prepubescent girl. *Courtesy, Joseph L Jorizzo, MD.*

Oral lesions occur in 5–20% of patients with Crohn's disease, and these may consist of cobblestoning of the buccal mucosa, tiny gingival nodules, small aphthae-like ulcers, linear ulcerations, angular cheilitis and ulceration, pyostomatitis vegetans, gingival hyperplasia, cheilitis granulomatosa, diffuse oral swelling, or indurated fissuring of the lower lip. Histologically, 90% of oral lesions associated with Crohn's disease contain granulomas[115]. Other reactive cutaneous manifestations of Crohn's disease include cutaneous polyarteritis nodosa, erythema nodosum, erythema multiforme, finger clubbing, leukocytoclastic vasculitis, epidermolysis bullosa acquisita, palmar erythema, a pustular response to trauma (pathergy), and pyoderma gangrenosum. Zinc deficiency may cause an acrodermatitis enteropathica-like syndrome in patients with severe Crohn's disease[111].

There is no consistent correlation between the appearance of skin lesions and intestinal Crohn's disease activity. Cutaneous Crohn's disease is more commonly associated with colorectal rather than small intestinal disease.

Pathology

In both cutaneous and oral lesions of Crohn's disease, nodular, non-caseating epithelioid tubercles with surrounding lymphocytes are found in the superficial and deep dermis, sometimes extending into the subcutaneous fat. There are a few scattered multinucleated Langhans-type giant cells and a sparse perivascular lymphohistiocytic infiltrate. The histopathologic changes are the same as those seen in intestinal lesions.

Differential Diagnosis

Clinically, the differential diagnosis of cutaneous Crohn's disease includes other granulomatous disorders such as cutaneous sarcoidosis, mycobacterial infections, deep fungal infections and foreign body reactions. Other infections, such as actinomycosis or cellulitis, may mimic cutaneous Crohn's disease. Ulcerated lesions may be misdiagnosed as pyoderma gangrenosum. In the case of genital swelling and ulcerations, one must consider granuloma inguinale, schistosomiasis, hidradenitis suppurativa, and chronic lymphedema due to obstruction[114].

The histologic picture of cutaneous Crohn's disease is, at times, indistinguishable from other granulomatous diseases with tuberculoid features, including lupus vulgaris. In the latter, central necrosis within tubercles is a helpful distinguishing clue. Differentiating cutaneous Crohn's disease from sarcoidosis can also be challenging, although Crohn's disease usually has denser collections of lymphocytes. Zirconium and beryllium granulomas, other foreign body granulomas, and infectious granulomas must all be considered in the histologic differential diagnosis. Special stains for acid-fast bacilli and fungal organisms

should be obtained, and all skin biopsies should be polarized to look for foreign bodies.

Treatment

Cutaneous Crohn's disease tends to be chronic, and its severity is not related to the activity of the patient's intestinal disease. Oral metronidazole is an effective treatment (250 mg three times daily), and is frequently paired with topical or intralesional corticosteroids. Systemic agents reported for the treatment of cutaneous Crohn's disease include oral corticosteroids, sulfasalazine, azathioprine, 6-mercaptopurine, and TNF-α inhibitors (e.g. infliximab, adalimumab)[116]. Surgical excision of lesions is often complicated by wound dehiscence and disease recurrence.

FOREIGN BODY GRANULOMAS (see Ch 94)

Key features

- The most common cause of a foreign body granuloma is rupture of a follicle or cyst
- Inflammation may be either a suppurative and diffuse granulomatous dermatitis or a nodular mononuclear granulomatous dermatitis
- Clues to the inciting foreign body should be sought by polarizing the specimen and searching for cornified cells, tattoo pigment, suture remnants, splinter material, etc.

REFERENCES

1. Demirkok SS, Basaranoglu M, Akbilgic O. Seasonal variation of the onset of presentations in stage 1 sarcoidosis. Int J Clin Pract. 2006;60:1443–50.
2. Kataria YP, Holter JF. Immunology of sarcoidosis. Clin Chest Med. 1997;18:719–39.
3. Silver RF, Crystal RG, Moller DR. Limited heterogeneity of biased T-cell receptor V beta gene usage in lung but not blood T cells in active pulmonary sarcoidosis. Immunology. 1996;88:516–23.

3a. Facco M, Cabrelle A, Teramo A, et al. Sarcoidosis is a Th1/Th17 multisystem disorder. Thorax. 2011;66:144–50.

4. English JC, Patel PJ, Greer KE Sarcoidosis. J Am Acad Dermatol. 2001;44:725–43.
5. DiAlberti L, Piattelli A, Artese L, et al. Human herpesvirus 8 in sarcoid tissues. Lancet. 1997;350:1655–61.
6. Lassalle S, Selva E, Hofman V, et al. Sarcoid-like lesions associated with the immune restoration inflammatory syndrome in AIDS: absence of polymerase chain reaction detection of *Mycobacterium tuberculosis* in granulomas isolated by laser capture microdissection. Virchows Arch. 2006;449:689–96.
7. Martinetti M, Tinelli C, Kolek V, et al. The sarcoidosis map: a joint survey of clinical and immunogenetic findings in two European countries. Am J Respir Crit Care Med. 1995;152:557–64.
8. Iannuzzi MC, Rybicki BA, Teirstein AS Sarcoidosis. N Engl J Med. 2007;357:2153–65.
9. Yanardag H, Pamuk ON, Pamuk GE. Lupus pernio in sarcoidosis: clinical features and treatment outcomes of 14 patients. J Clin Rhematol. 2003;9:72–6.
10. Sheffield EA. Pathology of sarcoidosis. Clin Chest Med. 1997;18:741–54.
11. Resnik KS. Subcutaneous sarcoidosis histopathologically manifested as fibrosing granulomatous panniculitis. J Am Acad Dermatol. 2006;55:918–19.
12. Marcoval J, Mana J, Moreno A, et al. Foreign bodies in granulomatous cutaneous lesions of patients with systemic sarcoidosis. Arch Dermatol. 2001;137:427–30.
13. Baughman RP, Lower EE. Steroid-sparing alternative treatments for sarcoidosis. Clin Chest Med. 1997;18:853–64.
14. Voelter-Mahlknecht S, Benex A, Metzger S, Fierlbeck G. Treatment of subcutaneous sarcoidosis with allopurinol. Arch Dermatol. 1999;135:1560–1.
15. Lee JB, Koblenzer PS. Disfiguring cutaneous manifestation of sarcoidosis treated with thalidomide: a case report. J Am Acad Dermatol. 1998;39:835–8.
16. Georgiou S, Monastirli A, Pasmatzi E, Tsambaos D. Cutaneous sarcoidosis: complete remission after oral isotretinoin therapy. Acta Derm Venereol. 1998;78:457–9.
17. Bachelez H, Senet P, Cadranel J, et al. The use of tetracyclines for the treatment of sarcoidosis. Arch Dermatol. 2001;137:69–73.
18. Clementine RR, Lyman J, Zakem J, et al. Tumor necrosis factor-alpha antagonist-induced sarcoidosis. J Clin Rheumatol. 2010;16:274–9.
19. Dhaille F, Viseux V, Caudron A, et al. Cutaneous sarcoidosis occurring during anti-TNF-alpha treatment: Report of two cases. Dermatology. 2010;220:234–7.
20. Pinto P, Dougados M. Leflunomide in clinical practice. Acta Reumatol Port. 2006;31:215–24.
21. Liedtka JE. Intralesional chloroquine for the treatment of cutaneous sarcoidosis. Int J Dermatol. 1996;35:682–3.
22. Patterson JW, Fitzwater JE. Treatment of hypopigmented sarcoidosis with 8-methoxypsoralen and long wave ultraviolet light. Int J Dermatol. 1982;21:476–80.
23. Goodman MM, Alpern K. Treatment of lupus pernio with the flashlamp pulsed dye laser. Lasers Surg Med. 1992;12:549–51.
24. Green JJ, Lawrence N, Heymann WR. Generalized ulcerative sarcoidosis induced by therapy with the flashlamp-pumped pulsed dye laser. Arch Dermatol. 2001;137:507–8.
25. Collison DW, Novice F, Banse L, et al. Split-thickness skin grafting in extensive ulcerative sarcoidosis. J Dermatol Surg Oncol. 1989;15:679–83.
26. Badgwell C, Rosen T. Cutaneous sarcoidosis therapy updated. J Am Acad Dermatol. 2007;56:69–83.
27. Mills A, Chetty R. Auricular granuloma annulare. A consequence of trauma? Am J Dermatopathol. 1992;14:431–3.
28. Muhlbauer JE Granuloma annulare. J Am Acad Dermatol. 1980;3:217–30.
29. Buechner SA, Winkelmann RK, Banks PM. Identification of T-cell subpopulations in granuloma annulare. Arch Dermatol. 1983;119:125–8.
30. Fayyazi A, Schweyer S, Eichmeyer B, et al. Expression of IFN-gamma, coexpression of TNF-alpha and matrix metalloproteinases and apoptosis of T lymphocytes and macrophages in granuloma annulare. Arch Dermatol Res. 2000;292:384–90.
31. Umbert P, Winkelmann RK. Histologic, ultrastructural, and histochemical studies of granuloma annulare. Arch Dermatol. 1977;113:1681–6.
32. Hanna WM, Moreno-Merlo F, Andrighetti L. Granuloma annulare: an elastic tissue disease? Case report and literature review. Ultrastruct Pathol. 1999;23:33–8.
33. Friedman-Birnbaum R, Haim S, Gideone O, Barzilai A. Histocompatibility antigens in granuloma annulare. Br J Dermatol. 1978;98:425–8.
34. Cronquist SD, Stashower ME, Benson PM. Deep dermal granuloma annulare presenting as an eyelid tumor in a child, with review of pediatric eyelid lesions. Pediatr Dermatol. 1999;16:377–80.
35. Dabski K, Winkelmann RK. Generalized granuloma annulare: clinical and laboratory findings in 100 patients. J Am Acad Dermatol. 1989;20:39–47.
36. Penas PF, Jones-Caballero M, Fraga J, et al. Perforating granuloma annulare. Int J Dermatol. 1997;36:340–8.
37. Barksdale SK Perniciaro C, Hailing KC, Strickler JG. Granuloma annulare in patients with malignant lymphoma: clinicopathologic study of thirteen new cases. J Am Acad Dermatol. 1994;31:42–8.
38. Ono H, Yokozeki H, Katayama I, Nishioka K. Granuloma annulare in a patient with malignant lymphoma. Dermatology. 1997;195:46–7.
39. Cohen PR. Granuloma annulare associated with malignancy. Southern Med J. 1997;90:1056–9.
40. Wong WR, Yang U, Kuo TT, Chan HL. Generalized granuloma annulare associated with granulomatous mycosis fungoides. Dermatology. 2000;200:54–6.
41. Studer EM, Calza AM, Saurat JH. Precipitating factors and associated diseases in 84 patients with granuloma annulare: a retrospective study. Dermatology. 1996;193:364–8.
42. Ohata C, Shirabe H, Takagi K, Kawatsu T. Granuloma annulare in herpes zoster scars. J Dermatol. 2000;27:166–9.
43. O'Moore EJ, Nandawni R, Uthayakumar S, et al. HIV-associated granuloma annulare (HAGA): a report of six cases. Br J Dermatol. 2000;142:1054–6.
44. Dabski K, Winkelmann RK. Generalized granuloma annulare: histopathology and immunopathology. J Am Acad Dermatol. 1989;20:28–39.
45. Dahl MV, Ullman S, Goltz RW. Vasculitis in granuloma annulare: histopathology and direct immunofluorescence. Arch Dermatol. 1977;133:463–7.
46. Magro CM, Crowson AN, Regauer S. Granuloma annulare and necrobiosis lipoidica tissue reactions as a manifestation of systemic disease. Hum Pathol. 1996;27:50–6.
47. Blume-Peytavi U, Zouboulis CC, Jacobi H, et al. Successful outcome of cryosurgery in patients with granuloma annulare. Br J Dermatol. 1994;130:494–7.
48. Muchenberger S, Schopf E, Simon JC Phototherapy with UV-A-1 for generalized granuloma annulare [letter]. Arch Dermatol. 1997;133:1605.
49. Setterfield J, Huilgol SC, Black MM. Generalised granuloma annulare successfully treated with PUVA. Clin Exp Dermatol. 1999;24:458–60.
50. Weiss JM, Muchenberger S, Schopf E, Simon JC. Treatment of granuloma annulare by local injections with low-dose recombinant human interferon gamma. J Am Acad Dermatol. 1998;39:117–19.
51. Ma A, Medenica M. Response of generalized granuloma annulare to high-dose niacinamide. Arch Dermatol. 1983;119:836–9.
52. Ratnavel RC, Norris PG. Perforating granuloma annulare: response to treatment with isotretinoin. J Am Acad Dermatol. 1995;32:126–7.
53. Simon M Jr, von den Driesch P. Antimalarials for control of disseminated granuloma annulare in children. J Am Acad Dermatol. 1994;31:1064–5.
54. Steiner A, Pehamberger H, Wolff K. Sulfone treatment of granuloma annulare. J Am Acad Dermatol. 1985;13:1004–8.
55. Rubel DM, Wood G, Rosen R, Jopp-McKay A. Generalised granuloma annulare successfully treated with pentoxifylline. Australas J Dermatol. 1993;34:103–8.
56. Marcus DV, Mahmoud BH, Hamzavi IH. Granuloma annulare treated with rifampin, ofloxacin, and minocycline combination therapy. Arch Dermatol. 2009;145:787–9.
57. Filotico R, Vena GA, Coviello C, Angelini G. Cyclosporin in the treatment of generalized granuloma annulare. J Am Acad Dermatol. 1994;30:487–8.
58. Kossard S, Winkelmann RK. Low-dose chlorambucil in the treatment of generalized granuloma annulare. Dermatologica. 1979;158:443–50.
59. Asano Y, Saito A, Idezuki T, Igarashi A. Generalized granuloma annulare treated with short-term administration of etretinate. J Am Acad Dermatol. 2006;54:s245–7.
60. Kim YJ, Kang HY, Lee ES, Kim YC. Successful treatment of granuloma annulare with topical 5-aminolaevulinic acid photodynamic therapy. J Dermatol. 2006;33:642–3.

61. Murdaca G. Anti-tumor necrosis factor-alpha treatment with infliximab for disseminated granuloma annulare. Am J Clin Dermatol. 2010;11:437–9.
62. Knoell KA. Efficacy of adalimumab in the treatment of generalized granuloma annulare in monozygotic twins carrying the 8.1 ancestral haplotype. Arch Dermatol. 2009;145:610–11.
63. Kreuter A, Altmeyer P, Gambichler T. Failure of etanercept therapy in disseminated granuloma annulare. Arch Dermatol. 2006;142:1236–7.
64. Wells RS, Smith MA. The natural history of granuloma annulare. Br J Dermatol. 1963;75:199–205.
65. Muller SA, Winkelmann RK. Necrobiosis lipoidica diabeticorum. A clinical and pathological investigation of 171 cases. Arch Dermatol. 1966;93:272–81.
66. Muller SA, Winkelmann RK. Necrobiosis lipoidica diabeticorum. Results of glucose-tolerance tests in nondiabetic patients. J Am Med Assoc. 1966;195:433–6.
67. O'Toole EA, Kennedy U, Nolan JJ, et al. Necrobiosis lipoidica: only a minority of patients have diabetes mellitus. Br J Dermatol. 1999;140:283–6.
68. Boulton AJM, Cutfield RG, Abouganem D, et al. Necrobiosis lipoidica diabeticorum: a clinicopathologic study. J Am Acad Dermatol. 1988;18:530–7.
69. Quimby SR, Muller SA, Schroeter AL. The cutaneous immunopathology of necrobiosis lipoidica diabeticorum. Arch Dermatol. 1988;124:1364–71.
70. Ullman S, Dahl MV Necrobiosis lipoidica. An immunofluorescence study. Arch Dermatol. 1977;113:1671–3.
71. Lowitt MH, Dover JS Necrobiosis lipoidica. J Am Acad Dermatol. 1991;25:735–48.
72. Evans CD, Pereira RS, Yuen CT, Holden CA. Anti-collagen antibodies in granuloma annulare and necrobiosis lipoidica. Clin Exp Dermatol. 1988;13:252–4.
73. Oikarinen A, Mortenhumer M, Kallioinen M, Savolainen ER. Necrobiosis lipoidica: ultrastructural and biochemical demonstration of a collagen defect. J Invest Dermatol. 1987;88:227–32.
74. Eisendle K, Baltaci M, Kutzner H, Zelger B. Detection of spirochaetal microorganisms by focus floating microscopy in necrobiosis lipoidica in patients from central Europe. Histopathology. 2008;52:877–84.
75. Lim C, Tschuchnigg M, Lim J. Squamous cell carcinoma arising in an area of long-standing necrobiosis lipoidica. J Cutan Pathol. 2006;33:581–3.
76. Laukkanen A, Fraki JE, Vaatainen N, et al. Necrobiosis lipoidica: clinical and immunofluorescent study. Dermatologica. 1986;172:89–92.
77. Nieboer C, Kalsbeek GL. Direct immunofluorescence studies in granuloma annulare, necrobiosis lipoidica and granulomatosis disciformis Miescher. Dermatologica. 1979;158:427–32.
78. Graham-Brown RA, Shuttleworth D, Sarkany I. Coexistence of sarcoidosis and necrobiosis lipoidica of the legs – a report of two cases. Clin Exp Dermatol. 1985;10:274–8.
79. De la Torre C, Losada A, Cruces MJ. Necrobiosis lipoidica: a case with prominent cholesterol clefting and transepithelial elimination. Am J Dermatopathol. 1999;21:575–7.
80. McDonald L, Zanolli MD, Boyd AS. Perforating elastosis in necrobiosis lipoidica diabeticorum. Cutis. 1996;57:336–8.
81. Tappeiner G. Necrobiosis lipoidica: treatment with systemic corticosteroids. Br J Dermatol. 1992;126:542–5.
82. Beck H, Bjerring P, Rasmussen I, et al. Treatment of necrobiosis lipoidica with low-dose acetylsalicylic acid. Acta Derm Venereol. 1985;65:230–4.
83. Statham B, Finlay AY, Marks R. A randomized double blind comparison of an aspirin dipyridamole combination versus a placebo in the treatment of necrobiosis lipoidica. Acta Derm Venereol. 1981;61:270–1.
84. Wilkin JK. Perilesional heparin injections for necrobiosis lipoidica. J Am Acad Dermatol. 1983;8:904.
85. Durupt F, Dalle S, Debarbieux S, et al. Successful treatment of necrobiosis lipoidica with antimalarial agents. Arch Dermatol. 2008;144:118–19.
86. Suárez-Amor O, Pérez-Bustillo A, Ruiz-González I, Rodriguez-Prieto MA. Necrobiosis lipoidica therapy with biologicals: an ulcerated case responding to etanercept and a review of the literature. Dermatology. 2010;221:117–21.
87. Smith K. Ulcerating necrobiosis lipoidica resolving in response to cyclosporine-A. Dermatol Online J. 1997;3:2.
88. Darvay A, Acland KM, Russell-Jones R. Persistent ulcerated necrobiosis lipoidica responding to treatment with cyclosporin. Br J Dermatol. 1999;141:725–7.
89. Spenceri EA, Nahass GT. Topically applied bovine collagen in the treatment of ulcerative necrobiosis lipoidica diabeticorum. Arch Dermatol. 1997;133:817–18.
90. Heymann WR. Necrobiosis lipoidica treated with topical tretinoin. Cutis. 1996;58:53–4.
91. Patel GK, Harding KG, Mills CM. Severe disabling Köebnerizing ulcerated necrobiosis lipoidica successfully managed with topical PUVA. Br J Dermatol. 2000;143:668–9.
92. McKenna DB, Cooper EJ, Tidman MJ. Topical psoralen plus ultraviolet A treatment for necrobiosis lipoidica. Br J Dermatol. 2000;143:1333–5.
93. Beattie PE, Dawe RS, Ibbotson SH, Ferguson J. UVA1 phototherapy for treatment of necrobiosis lipoidica. Clin Exp Dermatol. 2006;31:235–8.
94. Reinhard G, Lohmann F, Uerlich M, et al. Successful treatment of ulcerated necrobiosis lipoidica with mycophenolate mofetil. Acta Derm Venereol. 2000;80:312–13.
95. Kukreia T, Petersen J. Thalidomide for the treatment of refractory necrobiosis lipoidica. Arch Dermatol. 2006;142:20–2.
96. O'Brien JP. Actinic granuloma: an annular connective tissue disorder affecting sun- and heat-damaged (elastotic) skin. Arch Dermatol. 1975;111:460–6.
97. Hanke CW, Bailin PL, Roenigk HM. Annular elastolytic giant cell granuloma. J Am Acad Dermatol. 1979;1:413–21.
98. Dowling GB, Wilson-Jones E. Atypical (annular) necrobiosis lipoidica of the face and scalp. Dermatologica. 1967;135:11–26.
99. Mehregan AH, Altman J. Miescher's granuloma of the face. Arch Dermatol. 1973;107:62–4.
100. Leiker DL, Kok SH, Spaas JAJ Granuloma multiforme. Int J Lepr. 1964;32:368–76.
101. MacGrae JD Actinic granuloma. A clinical, histopathological and immunocytochemical study. Arch Dermatol. 1986;122:43–7.
102. Regaz A, Ackerman AB. Is actinic granuloma a specific condition? Am J Dermatopathol. 1979;1:43–53.
103. Garg A, Kundu R, Plotkin O, Aronson IK. Annular elastolytic giant cell granuloma heralding onset and recurrence of acute myelogenous leukemia. Arch Dermatol. 2006;142:532–3.
104. Boussault P, Tucker ML, Weschler J, et al. Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma associated with an annular elastolytic giant cell granuloma. Br J Dermatol. 2009;160:1126–8.
105. Tock CL, Cohen PR. Annular elastolytic giant cell granuloma. Cutis. 1998;62:181–7.
106. Lim KB, Phay KL. Annular elastolytic giant-cell granuloma. Int J Dermatol. 1987;26:463–4.
107. Tsutsui K, Hirone T, Kubo K, Matsui Y. Annular elastolytic giant cell granuloma: response to cyclosporin A. J Dermatol. 1994;21:426–9.
108. Ozkaya-Bayazit E, Buyukbabani N, Baykal C, et al. Annular elastolytic giant cell granuloma: sparing of a burn scar and successful treatment with chloroquine. Br J Dermatol. 1999;140:525–30.
109. Schwarz T, Lindlbauer R, Gschnait F. Annular elastolytic giant cell granuloma. J Cutan Pathol. 1983;10:321–6.
110. Repiso A, Alcantara M, Munoz-Rosas C, et al. Extraintestinal manifestations of Crohn's disease: prevalence and related factors. Rev Esp Enferm Dig. 2006;98:510–17.
111. Burgdorf W. Cutaneous manifestations of Crohn's disease. J Am Acad Dermatol. 1981;5:689–95.
112. Balfour Sartor R. Mechanisms of disease: pathogenesis of Crohn's disease and ulcerative colitis. Nat Clin Pract Gastroenterol Hepatol. 2006;3:390–407.
113. Gonzalez-Guerra E, Angulo J, Vargas-Machuca I, et al. Cutaneous Crohn's disease causing deformity of the penis and scrotum. Acta Derm Venereol. 2006;86:179–80.
114. Ploysangam T, Heubi JE, Eisen D, et al. Cutaneous Crohn's disease in children. J Am Acad Dermatol. 1997;36:697–704.
115. McCallum DI, Kinmont PDC Dermatologic manifestations of Crohn's disease. Br J Dermatol. 1968;80:1–8.
116. Rispo A, Scarpa R, DiGirolamo E, et al. Infliximab in the treatment of extra-intestinal manifestations of Crohn's disease. Scand J Rheumatol. 2005;34:387–91.

94 Foreign Body Reactions

MA Abdallah, MMA Abdallah and Marwa A-R Abdallah

Chapter Contents

Foreign body reactions to inorganic and metallic compounds.. *1575*
Reactions to organic and biologic products..... *1579*
Injectable soft tissue fillers *1580*

Key features

- Foreign body reactions represent inflammatory responses to inorganic and high-molecular-weight organic materials that have been introduced into the skin and are variably resistant to degradation
- Routes of introduction can vary from accidental or self-inflicted to surgical procedures and topical application of medications
- The most common clinical presentation is red to red–brown papules, nodules or plaques (with or without ulceration) that are due to granulomatous inflammation
- Less common presentations of foreign body reactions include lichenoid or pseudolymphomatous, or a fistula or draining wound
- Histologic findings vary from granulomas (foreign body, sarcoidal, palisading) to lichenoid, eczematous or pseudolymphomatous patterns
- Diagnosis of foreign body reactions requires a high index of suspicion, thorough history, recognition of distinctive distribution patterns, and histologic examination (including polarized microscopy)

GENERAL CONSIDERATIONS

Definition

Literally, any material – living or non-living – introduced into the body is a "foreign body" and is treated by our immune system as "non-self" in order to elicit an appropriate response. Such a broad definition also includes infectious agents, but they are covered elsewhere (see Chs 74–85). This chapter will focus on non-living materials that have been introduced into the dermis or subcutis[1–3]. They represent inorganic compounds or organic material of high molecular weight that resist degradation by the body's inflammatory cells or their products. Foreign bodies reported to elicit skin reactions are listed in Table 94.1.

Routes of Entry

Accidental

Inoculation with foreign bodies may occur unintentionally during various activities such as gardening (wood splinters, cactus spines) and swimming and diving (coelenterate envenomation, sea urchin spines), or it may result accidentally, such as in a blast injury (silica particles) or motor vehicle accident.

Surgical procedures

Contamination of wounds by talc or starch powders used for lubrication of surgical gloves may incite a foreign body reaction. Surgical sutures can also cause a foreign body response. Histologically, suture granulomas are commonly seen in excisional specimens of previously sampled cutaneous tumors. More recently, foreign body reactions have been observed in association with 2-octyl cyanoacrylate, a tissue adhesive used for small superficial wounds and lacerations, as well as a copolymer-containing lubricating agent used for liposuction[3a,3b].

Iatrogenic

Foreign material implanted into the skin for the purpose of tissue augmentation, e.g. injectable soft tissue fillers, can induce reactions in some individuals (Fig. 94.1). Paraffin is still being used illegally for tissue augmentation, and a paraffin foreign body reaction can also occur after the application of paraffin-containing materials such as nasal packs[4].

Tattooing

Tattooing is the introduction of an exogenous pigment into the dermis, either deliberately or accidentally, resulting in permanent discoloration of the skin.

Topical application

Deodorants and antipruritic preparations containing zirconium oxide applied to the skin surface may cause foreign body reactions. Of note, zirconium lactate was generally banned in 1978.

Self-inflicted

Self-administered intravenous injections, a common practice among drug addicts, may lead to the introduction of foreign material into the skin.

Pathogenesis

The initial tissue response to most foreign substances involves an accumulation of neutrophils which usually fail to properly deal with the foreign body. Its persistence attracts monocytes and local tissue macrophages that engulf the foreign material and become activated. Engulfed material may resist degradation and remain sequestered within the macrophages. Activated macrophages secrete a variety of specific biologically active substances, e.g. cytokines, that attract additional macrophages and blood monocytes. The formation of a chronic granuloma represents an attempt by the body to sequester a persistent indigestible material. Individual macrophages may become larger (epithelioid histiocytes) or fuse to form multinucleated foreign body giant cells. The infiltrate also contains T lymphocytes and fibroblasts. The pathogenesis of other patterns of reactions, e.g. lichenoid, pyogenic granuloma-like, pseudolymphomatous, remains speculative.

Clinical Features

The host response and, consequently, the clinical presentations of foreign body implantation are variable (Tables 94.2 & 94.3). An acute inflammatory response occurs shortly after the entry of the foreign material. This may resolve, to be followed weeks, months or even years later by a chronic inflammatory response. Although the latter may have a variety of clinical presentations, red to red–brown papules, nodules and plaques (with or without ulceration) are most commonly observed.

CLASSIFICATION OF FOREIGN BODIES ACCORDING TO THEIR ORIGINS AND ROUTES OF ENTRY		
Origin		**Route of entry**
	NON-BIOLOGIC (INORGANIC/METALLIC COMPOUNDS)	
	Tattoo inks	Decoration Cosmetic Accidental Iatrogenic
	Paraffin	Tissue augmentation Topical paraffin-containing preparations
	Silicone (polydimethyl siloxane) liquid or gel	Tissue augmentation
	Silica	Wound contamination Blast injuries
	Talc	Surgical procedures Wound contamination Umbilical stump contamination Intravenous injection of self-prepared drugs
	Zirconium	Topical application: deodorants, antipruritic medications
	Beryllium	Laceration by broken fluorescent lamps (historical) Inhalation
	Aluminum	Subcutaneous injection of aluminum-containing vaccines
	Zinc	Subcutaneous injection of insulin–zinc preparations
	Other synthetic fillers, e.g. poly-L-lactic acid, calcium hydroxylapatite, polymethylmethacrylate	Tissue augmentation
	BIOLOGIC	
Produced in the skin but normally isolated from body's defense mechanisms	Hair keratin (see Ch. 38)	Ruptured follicle or cyst* Ingrown hair Barber's sinus
	Nail keratin	Ingrown nail Accidental
Produced by other living organisms	Starch	Surgical procedures
	Cactus spines	Accidental Occupational
	Jellyfish and corals	Accidental Swimming or diving
	Sea urchin spines (see Ch. 85)	Accidental Swimming or diving
	Silk sutures	Surgical procedures
	Hyaluronic acid	Tissue augmentation
	Bovine collagen	Tissue augmentation
Miscellaneous	Corticosteroids	Intralesional injection
	Sutures, primarily absorbable (rarely nylon or polypropylene)	Surgical procedures
	Polyamide synthetic "hair" fibers	Scalp "hair" restoration
	2-octyl cyanoacrylate	Tissue adhesive for small, superficial wounds and lacerations

*Most common cause of a foreign body reaction in the skin.

Table 94.1 Classification of foreign bodies according to their origins and routes of entry.

Over time, the lesions may become firmer due to fibrosis. The pattern and arrangement of the cutaneous lesions will correspond to the route of inoculation, and observation of this patterning, in association with relevant patient history, is crucial.

In addition to nodules and plaques, other forms of foreign body reaction include pyogenic granuloma-like lesions[5], lichenoid lesions[6,7], and a chronic draining fistula or wound[8].

Pathology

Apart from the acute reaction to the trauma that accompanies the introduction of the foreign body, a chronic reaction is the usual response. Although different patterns of chronic local tissue reactions have been described, including lichenoid[6], chronic inflammatory and pseudolymphomatous[9], the most common is the granulomatous type of reaction[10,11] (see Table 94.3). Granulomas that develop as a reaction to foreign bodies are of two major types:

- allergic (immunologic)
- non-allergic ("foreign body").

The allergic type is characterized by the presence of collections of individual epithelioid histiocytes associated with variable numbers of lymphocytes and fewer multinucleated Langhans-type giant cells[11]. In the non-immunologic type, the foreign body giant cell (Fig. 94.2) is the most conspicuous component of the infiltrate, which also contains histiocytes, lymphocytes and other inflammatory cells.

A histologic decision as to whether a granuloma is of the foreign body type or of the allergic type is not always possible and different patterns may be seen in the same section. It is noteworthy that foreign body reactions in HIV-infected patients are different, with abundant

CLINICAL PRESENTATIONS OF FOREIGN BODY REACTIONS	
Clinical presentation	**Foreign substance**
Erythema, induration, papules, nodules (with or without ulceration)	Tattoo inks, paraffin, silicone*, silica, beryllium (local), starch, soft tissue fillers (e.g. hyaluronic acid)
Sarcoidosis-like granulomatous papules	Tattoo inks, talc, zirconium, beryllium (systemic), soft tissue fillers (e.g. bovine collagen, hyaluronic acid)
Pyogenic granuloma-like lesions	Talc, keratin (ingrown nail)
Pseudofolliculitis barbae, "ingrown" hairs of the pubic region and upper thighs	Keratin
Pruritic lichenoid papules and plaques (often in an irregular linear pattern)	Tattoo inks, jellyfish and coral stings
Abscess	Keratin (e.g. pilonidal disease), zinc, paraffin, soft tissue fillers
Sinus tract/fistula	Suture, keratin (pilonidal disease, barber's sinus)
Persistent subcutaneous nodules at injection site	Aluminum, soft tissue fillers containing synthetic particles (see Table 94.4)
Photoallergic eczematous reaction	Tattoo ink containing cadmium sulfide (yellow), cadmium selenide (red) or azo dyes (yellow, red)
*Often a delayed onset (years).	

Table 94.2 Clinical presentations of foreign body reactions.

Fig. 94.1 Granulomatous reaction to bovine collagen injection.

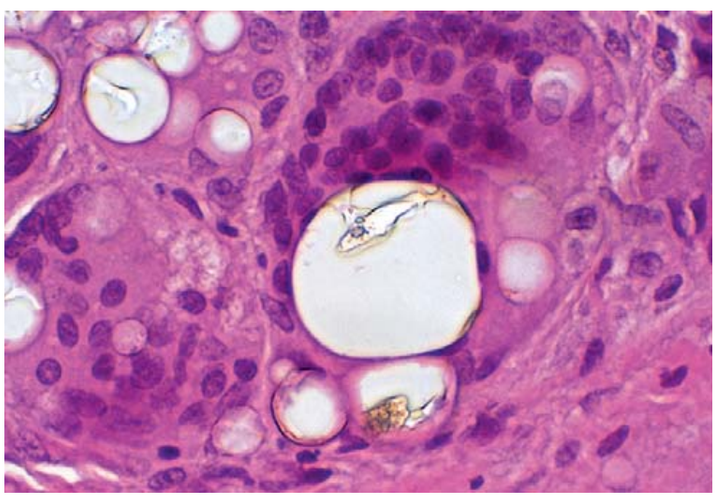


Fig. 94.2 Birefringent foreign body is engulfed by a foreign body-type giant cell with the typical haphazard array of nuclei. *Courtesy, Thomas D Horn, MD.*

individual macrophages, but no giant cells, suggesting an immunologic dysfunction[12]. The foreign material inciting a reaction may be detected in conventional H&E-stained sections or may require special procedures for its identification (see Table 94.3).

Diagnosis

Foreign body reactions should be considered in the differential diagnosis of localized inflammatory nodules and plaques, especially when there is a persistent draining wound or sinus. Occasionally, they appear as pyogenic granulomas or localized lichenoid papules. Clinical morphology is usually not distinctive, but there may be a suggestive distribution pattern, and a thorough history is indispensable for arriving at the correct diagnosis.

Histologic examination confirms the granulomatous nature of the lesion and occasionally foreign bodies may show distinctive microscopic features in H&E-stained sections (Fig. 94.3). However, special procedures are usually required for an accurate diagnosis, particularly microscopic examination with polarized light (Fig. 94.4). Imaging techniques such as plain radiography, ultrasonography, CT scanning and MRI are of little practical value in visualizing small cutaneous foreign bodies, even if the foreign body is radio-opaque.

Identification of the chemical nature of the foreign body requires sophisticated physicochemical procedures that necessitate special processing of the tissue sample and are available in only a few research centers. Energy dispersive X-ray analysis (EDXA), electron energy loss spectroscopy (EELS), laser microprobe mass analysis, and infrared spectrophotometry are examples (see Table 94.3).

To summarize, accurate identification of a foreign body reaction depends on a high index of suspicion, thorough history-taking, and histologic examination, including polarized microscopy.

FOREIGN BODY REACTIONS TO INORGANIC AND METALLIC COMPOUNDS

Tattoo

A tattoo may occur accidentally or deliberately for cosmetic and decorative purposes. Accidental tattooing results from unintentional deposition of exogenous pigmented substances such as asphalt, graphite or carbon within injured skin (Fig. 94.5). Automobile, bicycle and skating accidents as well as puncture wounds are the most common causes of traumatic tattoos. In decorative tattooing, the pigment is introduced into the dermis via needles or a tattoo gun to create various designs, group-identity symbols, or writings. Cosmetic tattoos are also done to define lip contours, replace eyeliner, or hide an abnormality in skin color. An iatrogenic tattoo may remain after the use of ferrous subsulfate (Monsel's solution) for hemostasis.

CLINICAL AND HISTOPATHOLOGIC FEATURES OF FOREIGN BODY REACTIONS					
Foreign body	**Clinical presentations**	**Histologic reaction patterns**	**Other distinctive features**	**Birefringent**	**Other detection methods**
Tattoo inks	Erythema, induration, papules, nodules Lichenoid papules and plaques Eczematous dermatitis (including photoallergic reactions)	Foreign body or (with certain dyes) sarcoidal granulomas Lichenoid dermatitis Spongiotic dermatitis Pseudolymphoma	Pigment granules scattered throughout the infiltrate, extra- and intracellular (macrophages)		EDXA
Silica	Nodules, indurated plaques within scar Disseminated papules (blast injuries) Prolonged incubation period	Granulomas (sarcoidal > foreign body)	Colorless crystals, extra- and intracellular	√	IRS or EDXA
Talc	Sarcoid-like papules Thickening and erythema of an old scar Involvement of intertriginous zones, iv injection sites Umbilical stumps Pyogenic granuloma-like	Sarcoidal or foreign body granulomas Pyogenic granuloma-like	Needle-shaped or round talc crystals: clear, blue–green or yellow–brown	√	EDXA
Zirconium	Persistent, soft, brownish papules Involvement of axillary skin	Sarcoidal granulomas			EDXA
Beryllium, local skin reaction	Nodule, ulcer	Caseating granulomas			EELS
Beryllium, systemic	Widely scattered papules (<1% of cases)	Sarcoidal granulomas			Bronchoalveolar lavage
Aluminum	Persistent subcutaneous nodules at injection site	Granulomas with peripheral lymphocytes and eosinophils Pseudolymphoma			EDXA
Zinc	Furuncles at injection sites	Early: dense neutrophilic infiltrate Late: granulomas and fibrosis	Rhomboidal crystals	√	EDXA
Starch	Papules, nodules	Foreign body granulomas	Ovoid basophilic starch granules PAS-positive	√	
Cactus	Dome-shaped, skin-colored papules with a central black dot	Early: neutrophils Late: sarcoidal or foreign body granulomas	Spines, extra- and intracellular (giant cells) PAS-positive	√	
Jellyfish, corals, sea urchin spines	Pruritic lichenoid papules and plaques (onset 2–3 weeks after exposure) Linear, zig-zag and whip-like (flagellate) patterns of erythema/edema (early), hyperpigmentation or lichenoid papules (late)	Lichenoid dermatitis	Calcite crystals (sea urchin spines)	√ (sea urchin spines)	
Keratin	Pseudofolliculitis/acne keloidalis Pyogenic granuloma-like lesions, ingrown nails Pilonidal disease	Foreign body granulomas	Other inflammatory cells	√	
Intralesional corticosteroids	Skin-colored to yellow–white papules or nodules develop at the site of a previous intralesional injection of corticosteroid The incubation period varies between weeks to months	Foreign body granulomas	Pale bluish material on H&E		
Suture	Wound appears inflamed, red, edematous (or develops papules or nodules) and opens to form a fistula	Foreign body granulomas		√	

Table 94.3 Clinical and histopathologic features of foreign body reactions. The order of the entities in this table corresponds to that in the text. Injectable soft tissue fillers are reviewed in Table 94.4. EDXA, energy dispersive X-ray analysis; EELS, electron energy loss spectroscopy; IRS, infrared spectrophotometry; iv, intravenous.

Decorative tattoos often contain a number of pigments that are combined to create different hues. These may be inorganic salts of metals, such as mercury in cinnabar (red, becoming historical), cobalt (blue), chromium (green), cadmium (yellow, red), ferric hydrate (sienna) and manganese (purple), or organic preparations, such as sandalwood, brazilwood and carmine[10]. The red color is most commonly associated with nodular reactions (Fig. 94.6).

Clinical features

Delayed reactions may occur within a few weeks of the tattoo placement, but have been reported over 15 years later[13]. Most commonly, erythematous nodules or plaques are seen, but there may be lichenoid or eczematous lesions. The reactions are usually confined to the site of the tattoo (see Fig. 94.6). Tenderness and erythema vary according to the degree of inflammation and may be absent. Rarely, a photoallergic reaction, presenting as pruritic inflamed nodules, occurs in red or yellow tattoos containing cadmium sulfide following exposure to UV light[13].

Tattoo pigments may migrate to the regional lymph nodes and at the time of lymph node sampling may clinically mimic metastatic melanoma.

Pathology

Different patterns of an inflammatory response can be elicited, including sarcoidal, foreign body granulomatous, lichenoid and pseudolymphomatous[9]. In non-inflamed tattoos, the dermis shows granules of different sizes, shapes and colors, located both within macrophages and extracellularly in the absence of an inflammatory infiltrate[14]. Most tattoo pigments appear black with H&E staining, regardless of the clinical color, but sometimes red or yellow colors are apparent histologically.

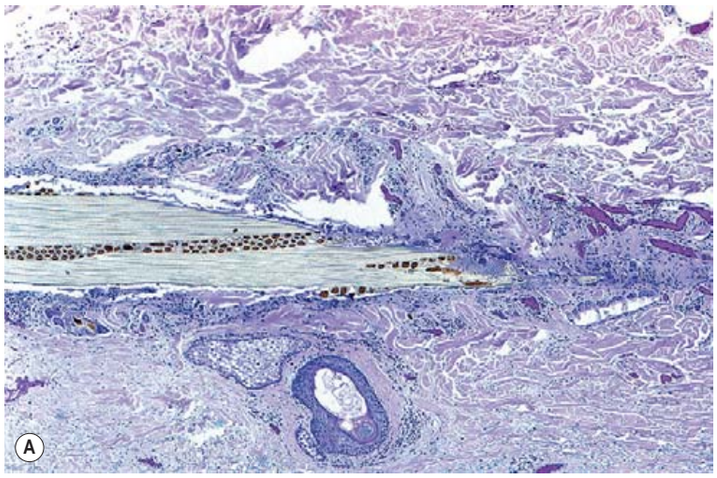


Fig. 94.3 Granulomatous foreign body reactions to implanted organic material. Wood splinter (**A**) versus bee stinger (**B**). *A, Courtesy, Ronald P Rapini, MD.*

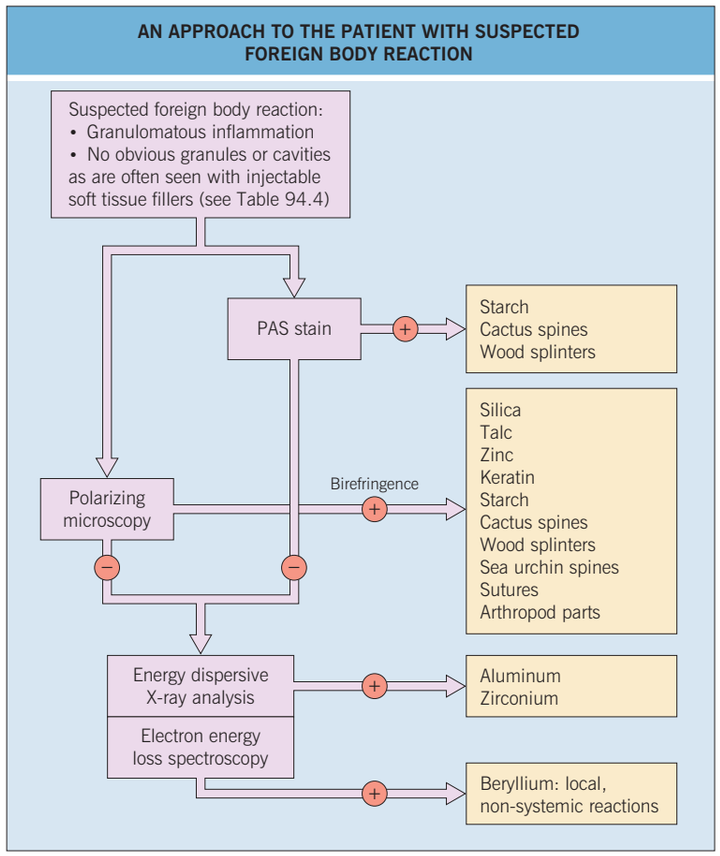


Fig. 94.4 An approach to the patient with suspected foreign body reaction.

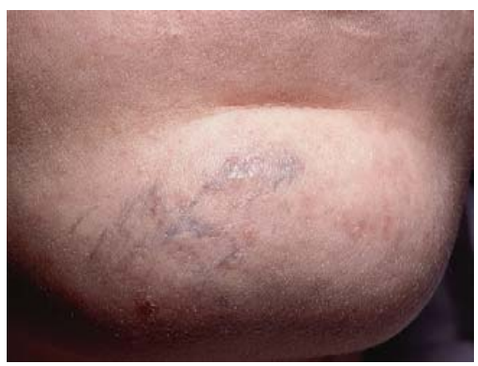


Fig. 94.5 Traumatic tattoo of the chin. Bluish discoloration and slight erythema, predominantly due to silica. *Courtesy, Ronald P Rapini, MD.*

Diagnosis and differential diagnosis

The presence of inflammatory lesions confined to the site of a tattoo suggests the diagnosis. The differential diagnosis includes other inflammatory disorders that may arise in tattoos, e.g. sarcoidosis. Inoculation of certain infectious agents (e.g. atypical mycobacteria) may mimic pigment-induced inflammation within a tattoo. Identification of the causative pigment is generally unnecessary unless further tattooing is anticipated. Other causes of dermal pigmentation include melanin, hemosiderin, lipofuscin, silver, gold, minocycline, amiodarone and chlorpromazine. Special stains to identify melanin and iron (hemosiderin) may be useful (see Ch. 0).

Treatment

Although many therapeutic modalities for tattoo removal have been used, some of them can result in significant scarring. Nowadays, lasers (e.g. Q-switched ruby, alexandrite, Nd:YAG) represent the primary treatment modality, allowing for selective destruction of chromophores while leaving adjacent collagen intact. The specific type of laser chosen depends on the tattoo ink colors and the wavelengths to which they best respond[15] (see Ch. 137). Several wavelengths are required to treat multicolored tattoos optimally.

Surgical excision can be considered for the treatment of inflamed tattoos. Topical corticosteroids are often ineffective, but intralesional

Fig. 94.6 Granulomatous reaction to the red (cinnabar) portions of a tattoo. Over the past several years, cinnabar (mercuric sulfide) has been gradually replaced by cadmium selenide (cadmium red), ferric hydrate (sienna) and organic compounds. *Courtesy, Ronald P Rapini, MD.*

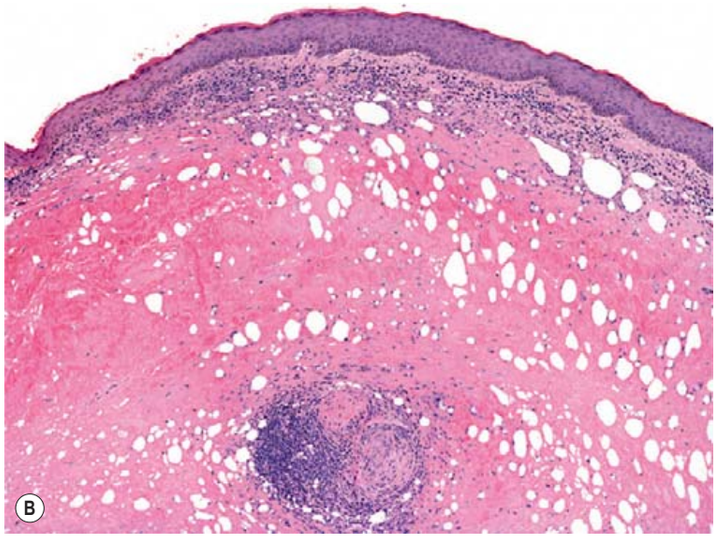


Fig. 94.7 Sclerosing lipogranuloma of the penis. A The penis was injected in order to relieve urinary retention following a motorbike accident, and an ulcerated, indurated yellow plaque with telangiectasias developed at the site. **B** Histologic examination showed sclerosis as well as multiple circular and oval empty spaces within the dermis. *Courtesy, Glen Foxton, MD, and Clare Tait, MD.*

corticosteroids may lead to improvement; laser therapy is not advised because of the risk of inducing a systemic reaction, following release of pigment from macrophages, in an already sensitized patient[15].

Paraffin (Sclerosing Lipogranuloma)

Paraffin, being a mineral oil, is not hydrolyzed by tissue lipases and is treated by the body as a foreign substance. Augmentation of body contour by local injection of paraffin, although banned in most countries, is still performed in some regions of the world and is mostly done by non-medical personnel. Accidental paraffinoma of the orbit and palpebra has been reported following intraoperative placement of paraffin-impregnated gauze packs within the nasal cavity.

Clinical features

In those cases due to injected paraffin, the genitalia and breast are the most common sites of involvement (Fig. 94.7A). Clinically, non-tender firm nodules and indurated plaques are seen, sometimes with ulceration or abscess formation and involvement of subcutaneous tissue (see Ch. 100). The interval between the time of injection and the development of lesions may span many years.

Pathology

The dermis shows a characteristic "Swiss cheese" appearance due to the presence of numerous ovoid or round cavities where the paraffin resided prior to processing (Fig. 94.7B). Between the cavities, there is fibrotic connective tissue and a cellular infiltrate composed of macrophages, variable numbers of multinucleated foreign body giant cells, and lymphocytes. Some of the macrophages have foamy cytoplasm. In specially processed tissue, the foreign material stains with fat stains[16], although less intensely than neutral fats, helping to differentiate paraffinoma from reactions to silicone, which also have numerous cavities but negative fat stains.

Treatment

Excision with appropriate tissue reconstruction is the only means of therapy.

Silicone

Silicone (polydimethyl siloxane), either in its liquid form or as silicone gel-filled implants, is used for tissue augmentation, and, in some patients, its use has been followed by foreign body reactions.

Clinical features

Silicone gel-filled implants are widely used for breast augmentation and reconstruction after mastectomy and may be followed, usually after months or years, by the formation of cutaneous nodules and plaques at the site. Silicone is also employed to correct HIV-related lipoatrophy. Silicone reaches the dermis if the implant capsule ruptures as a result of trauma or there is leakage from the capsule[17]. Nodular foreign body granulomatous reactions evolve some years after rupture or leakage[17], and can slowly progress, resulting in sclerosis and ulceration of involved skin. Spread of the leaked gel from the implant down into the arm or abdominal wall has been reported and leads to the development of nodules distant from the site of the implant.

Similar nodules and indurated plaques, sometimes with ulceration, have been seen following injections of liquid silicone into the subcutaneous tissue[18].

In the literature, there are anecdotal reports of patients in whom autoimmune connective tissue diseases such as scleroderma and systemic lupus erythematosus developed after breast augmentation with silicone-filled prostheses. However, carefully controlled epidemiologic studies have not supported a causal link.

Pathology

A biopsy specimen is critical to establishing the diagnosis. Histologic sections have a "Swiss cheese" appearance due to the presence of silicone-filled cavities surrounded by histiocytes, lymphocytes and eosinophils. The histiocytes may be foamy or multinucleated. Fibrous tissue within the areas separating the cavities is also seen. In contrast to paraffinomas, the cavity contents do not stain with lipid stains.

Treatment

Excision of persistent symptomatic lesions is recommended.

Silica

Wounds or penetrating injuries accidentally contaminated with silica (silicon dioxide) contained in sand, soil, rocks and glass may be followed some years later by the formation of a foreign body reaction. The period between inoculation and development of a reaction may be as long as 25 years. This extended "incubation" period is due to the very slow release of colloidal silica (the only form capable of inciting a reaction) from the large particles of silica introduced into the body[19]. Reactions to silica are thought to be due to a delayed-type hypersensitivity response.

Clinical features

At first, the wound heals, but then papules, nodules or indurated plaques develop within the scar years later. Multiple disseminated lesions may follow trauma produced by the explosion of land mines and bombs[19]. Macrocheilitis was described following a road accident that occurred 25 years prior to the development of the foreign body reaction[20].

Pathology

The dermis contains multiple nodular aggregates of granulomas, usually sarcoidal and less often foreign body, separated by strands of

connective tissue. Langhans- and foreign body-type giant cells are usually numerous in both types of granuloma. Colorless crystals may be observed within the cytoplasm of the giant cells or lying free in the interstitium. These bodies are birefringent when examined with polarized microscopy.

Differential diagnosis

Granulomatous lesions occurring at the site of an old scar may mimic systemic sarcoidosis clinically and histologically[21]. The presence of foreign material within a sarcoidal granuloma does not exclude sarcoidosis, since some granulomas of sarcoidosis appear to be attracted to old scars. Examination under polarized light will identify silica crystals, but by-products of histiocyte metabolism are known to crystallize rarely.

Treatment

Excision of persistent symptomatic lesions is recommended. Spontaneous resolution of silica granuloma, although reported, is exceptional.

Talc

Talc (hydrous magnesium silicate) that contaminates wounds, erosions, umbilical stumps or intravenous puncture sites is another important cause of foreign body reactions. Because of its widespread use, it is a common cause of foreign body granulomas. Talc is a component of many dusting powders and antibiotic powders and is still preferred by some surgeons as a lubricant for surgical gloves.

Despite repeated warnings in the medical literature, dusting of raw umbilical stumps with antibiotic powders containing talc was reported to be the most frequent cause of umbilical granulomas[5]. Talc may also enter the skin through abrasions and fissures, particularly in intertriginous areas in obese persons who apply talc powder liberally[22]. Tablet forms of medications contain, in addition to the pharmacologically active material, talc as a filler to hold the tablet together. Tablets are frequently crushed and then suspended in solutions by drug addicts prior to intravenous injection[23], and foreign body reactions may develop at intravenous injection sites. Talc may also reach the lungs via inhalation (usually occupational) or through injections of self-prepared drugs.

Clinical features

As with reactions to other forms of silica, the lesions usually take a long time to appear. The clinical appearance is varied: it may take the form of erythematous papules or nodules suggestive of sarcoidosis, or appear as thickening and erythema of an old scar. Despite the long latency period, the diagnosis should be considered, especially when lesions appear in certain sites, e.g. the umbilicus in infants, inguinal area in patients with a history of intertrigo, injection sites in intravenous drug addicts.

Pathology

The histologic features may be similar to those of sarcoidosis or noncaseating tuberculosis. Alternatively, there may be granulomatous inflammation consisting of histiocytes and foreign body giant cells. A few of these cells may contain clear, blue–green or yellow–brown, needle-shaped or round crystals. Under polarized light, talc crystals appear as white birefringent particles[5]. A picture simulating a pyogenic granuloma plus giant cells has also been described[5].

Treatment

Excision of persistent symptomatic lesions is recommended.

Zirconium

Some zirconium salts are components of antiperspirant preparations as well as over-the-counter preparations used in the treatment of allergic contact dermatitis. Sodium zirconium lactate was the first salt incriminated as a cause of foreign body reactions and was banned in the late 1970s. Subsequently, zirconium oxide and aluminum–zirconium complex have also been shown to be capable of producing the same reaction. Development of the granulomas represents a delayed-type hypersensitivity reaction to zirconium[24].

In sensitized individuals, persistent, soft, red–brown papules appear in areas to which zirconium-containing preparations were applied. The axillary skin is the most frequently affected site.

Histologically, non-caseating granulomas resembling a sarcoidal reaction are seen[24]. The small size of the zirconium particles does not allow their detection with polarized light microscopy; however, energy dispersive X-ray analysis can prove their presence (see Table 94.3).

Beryllium

In the past, beryllium-containing compounds were widely used in the manufacture of fluorescent light tubes, and industrial exposure resulted in serious systemic and local complications. As a result, their use was discontinued.

Occupational inhalation of beryllium particles results in systemic berylliosis, in which the primary pathology is in the lung and skin involvement is rare (<1%). The cutaneous granulomas of systemic berylliosis consist of widely scattered papules with no secondary changes. Laceration or puncture of the skin by broken fluorescent tubes used to result in local cutaneous berylliosis. Wounds heal slowly and are followed by persistent erythema, swelling, induration and possible ulceration.

Histologically, cutaneous lesions of systemic berylliosis are indistinguishable from sarcoidosis. Local berylliosis, on the other hand, has a caseating tuberculoid pattern[11]. In systemic berylliosis, bronchioalveolar lavage is recommended for diagnosis.

Aluminum

Rare hypersensitivity reactions to the aluminum adjuvant in vaccines and hyposensitization immunotherapy do occur. Persistent subcutaneous granulomatous nodules appear at the site of injection several months after vaccination[25]. Histologically, granuloma formation with central granular debris surrounded by a histiocytic mantle is seen. A dense lymphoid infiltrate with eosinophils is present at the periphery[25]. Of note, *topical* application of aluminum chloride for hemostasis produces a stippled appearance within macrophages in the healing wound.

Zinc

A zinc-induced granuloma at the site of an injection is a rare complication of zinc-containing insulin[26]. Sterile furuncles develop at the injection sites and eventually heal with atrophic scars. Histologically, an initial stage characterized by a dense neutrophilic infiltrate is followed by granuloma formation that ends in fibrosis. By polarizing microscopy, birefringent rhomboid crystals are seen.

Zirconium, beryllium, aluminum and zinc granulomas may be surgically excised if they are symptomatic.

REACTIONS TO ORGANIC AND BIOLOGIC PRODUCTS

Starch

Granulomas may result from the contamination of wounds with starch used as a lubricant for surgical gloves.

Pathology

Foreign body granulomas with multinucleated giant cells are seen. Starch granules appear as ovoid basophilic structures. They react with PAS and are birefringent in polarized light[27].

Cactus spines

Accidental implantation of cactus spines into the skin results from contact with cacti in gardens and fields. Occupational exposure occurs in persons peeling and selling prickly pear fruit, especially in the Middle East and Latin America. Most of the reported cases are due to contact with the genus *Opuntia*[28].

At the time of injury, acute inflammation occurs and then in some patients, eventually evolves into a typical foreign body reaction. The lesions occur primarily on the hands and fingers as clusters of dome-shaped, skin-colored papules with a central black dot, sometimes called sabra dermatitis. This often resembles scabies or fiberglass dermatitis.

Pathology

Two types of granulomatous reaction have been described: an allergic reaction consisting of epithelioid cells and Langhans- and foreign

body-type giant cells[28], as well as foreign body-type granulomas[11]. The granulomas occupy the entire dermis, surrounding spine fragments which stain intensely red with PAS stain. Wood splinters and thorns of other plant origin have a similar suppurative or granulomatous reaction. However, most splinters appear brown with a rectangular pattern of cell walls (see Fig. 94.3A). Fungal hyphae may be present within the plant material, but they seldom invade the surrounding dermis in the healthy host.

Cnidaria (Coelenterata) – Jellyfish, Corals

Members of the phylum Cnidaria (Coelenterata) include jellyfish, corals and sea anemones (see Ch. 85). Almost all cnidarians possess nematocysts, or stinging capsules. Each nematocyst contains toxins and a coiled thread-like apparatus with a barbed end that functions as a flexible syringe. When the nematocyst comes into contact with the victim, the barbed end of the thread-like organ is discharged and the toxin is injected into the skin.

Clinical features

Jellyfish and coral stings elicit similar cutaneous reactions: an early primary irritant toxic reaction in all exposed persons, and a delayed-type hypersensitivity reaction in a small percentage. A sharp burning pain is felt and, within minutes, the affected area becomes erythematous and edematous and may form blisters. The acute response may be accompanied by an immediate-type hypersensitivity reaction including urticaria, angioedema and even anaphylaxis. The lesions resolve, leaving postinflammatory hyperpigmentation in a streaky flagellate fashion corresponding to where the coral or jellyfish brushed the skin. In some individuals, new lesions appear a few weeks later at previously involved sites (average 3 weeks)[7]. The latter are severely pruritic, shiny, lichenoid papules and plaques and are arranged in a number of patterns, including linear, zig-zag and whip-like (Fig. 94.8).

Pathology

The lesions that comprise the delayed response have a lichenoid tissue reaction.

Treatment

First aid includes soaking the site in hot, but not scalding, water (denatures proteins). Subsequent use of topical potent corticosteroids, antihistamines and systemic corticosteroids is controversial. Treatment of acute reactions is reviewed in Chapter 85. Intralesional corticosteroids are the most effective therapy for delayed-type hypersensitivity reactions.

Fig. 94.8 Coral envenomation. Delayed lichenoid reaction on the calf. The patient accidentally came into contact with a coral reef and developed acute dermatitis that resolved, to be followed 3 weeks later by this severely itchy eruption that responded favorably to intralesional triamcinolone injection.

Keratin

In addition to ruptured epidermoid cysts, dermatologic foreign body reactions to keratin are involved in three common, distressing conditions that occur in otherwise healthy young persons: pseudofolliculitis, ingrown nails, and sacrococcygeal pilonidal sinus disease.

Keratin, normally sequestered from the body's immune surveillance by the surrounding epithelium, is treated as foreign if it directly contacts the dermis. This may occur as a result of ruptured hair follicles, epidermoid cysts or acne lesions, or because of external keratin sources (e.g. ingrown hairs or nails), or through accidental entry of hairs into the interdigital skin, especially of barbers and dog groomers.

Pseudofolliculitis barbae and acne keloidalis nuchae

In pseudofolliculitis barbae, there is a foreign body inflammatory reaction surrounding a hair that has been previously shaved or plucked (see Ch. 38). This condition affects mainly those with curly hair, with an incidence of more than 50% amongst blacks. Certain inherent properties of the hairs in affected individuals, in particular a curled flattened elliptical shape, play an important pathogenetic role. Because the shaft is curved, it grows back toward the skin surface. The flattened elliptical hair shaft when shaved develops a pointed tip, which facilitates re-entry of the hair into the skin. A foreign body reaction to keratin results in the development of inflammatory papules and pustules that result in hyperpigmentation or small keloidal scars[8].

Pseudofolliculitis also affects women who regularly remove hair from the pubic region, axillae and legs by plucking or shaving. Papules containing embedded hairs, pustules and cysts develop in affected areas, often resolving with significant postinflammatory hyperpigmentation.

Treatment

Apart from cessation of shaving or laser epilation of the affected areas, nearly all therapeutic modalities are unrewarding. For further details, see Chapters 38 and 137.

Pilonidal sinus

Most cases of pilonidal sinus occur in the sacrococcygeal region (see Fig. 38.15). Much less often, it is seen in the umbilical region[8], and, rarely, interdigitally in barbers[29].

Sacrococcygeal pilonidal sinuses may be asymptomatic (debris-filled pit) or present as a draining sinus or an acute abscess. The condition is more common in young men. There is often an underlying cyst with associated granulation tissue, fibrosis and frequently tufts of hairs. Excisional specimens reveal a sinus tract extending into the subcutaneous tissue and dermis, surrounded by chronic inflammation. Hairs are found in the sinuses in three-quarters of the cases[30].

Small, asymptomatic or slightly tender, openings in the interdigital web spaces of the hands have been observed in barbers. The lesions are caused by the penetration of short hairs into the interdigital spaces, inciting an inflammatory foreign body granuloma. The clinical course is usually self-limited but can be complicated by repeated infections, which may require surgical excision of the involved area[29]. Histologically, a sinus tract lined by epidermis and containing one or several hairs is seen. Hairs extending deeper than the sinus tract incite a foreign body reaction.

INJECTABLE SOFT TISSUE FILLERS

With the exception of autologous fat, all injectable soft tissue fillers, resorbable or non-resorbable, represent foreign bodies and therefore have the potential to cause foreign body reactions (Fig. 94.9). Depending upon the particular filler, these reactions can range from relatively common (e.g. paraffin) to rare (e.g. hyaluronic acid)[31]. Paraffin and silicone are discussed above and the histopathologic features of inflammatory reactions to various fillers are outlined in Table 94.4[32].

Hyaluronic Acid

Currently, hyaluronic acid is the most commonly utilized injectable soft tissue filler, in part because the incidence of foreign body reactions is much lower (0.42%) than that reported for bovine collagen (3–4%)[31]. When a reaction does occur, the injected site becomes firm, tender, edematous and erythematous, and abscess formation may occur. The foreign body reaction begins approximately 6 to 8 weeks after hyaluronic

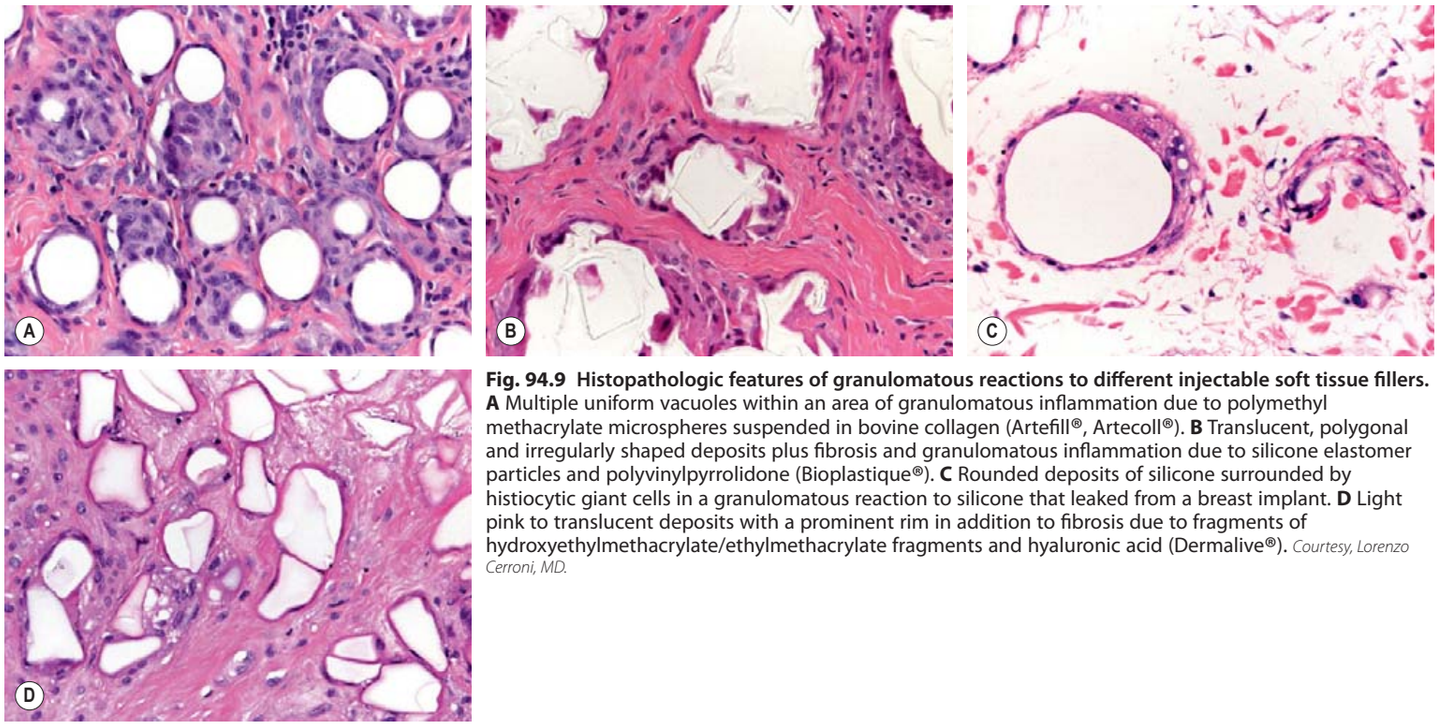


Fig. 94.9 Histopathologic features of granulomatous reactions to different injectable soft tissue fillers. **A** Multiple uniform vacuoles within an area of granulomatous inflammation due to polymethyl methacrylate microspheres suspended in bovine collagen (Artefill®, Artecoll®). **B** Translucent, polygonal and irregularly shaped deposits plus fibrosis and granulomatous inflammation due to silicone elastomer particles and polyvinylpyrrolidone (Bioplastique®). **C** Rounded deposits of silicone surrounded by histiocytic giant cells in a granulomatous reaction to silicone that leaked from a breast implant. **D** Light pink to translucent deposits with a prominent rim in addition to fibrosis due to fragments of hydroxyethylmethacrylate/ethylmethacrylate fragments and hyaluronic acid (Dermalive®). *Courtesy, Lorenzo Cerroni, MD.*

HISTOPATHOLOGIC FEATURES OF INJECTABLE SOFT TISSUE FILLERS

Category	Chemical composition	Trade names®,™	Histopathologic features
Resorbable within months	Bovine collagen	Zyderm, Zyplast	Palisading granulomas with foreign body giant cells; eosinophilic bovine collagen at the center of the granulomas; immunoperoxidase staining with anti-bovine collagen type I antibodies
	Human collagen – Bioengineered – Cadaveric – Autologous	Cosmoderm, Cosmoplast Cymetra	Granulomatous reaction
	Hyaluronic acid	Hylaform, Restylane, Juvéderm, Perlane, Captique, Prevelle Silk, Elevess, Bolotero, Macrolane	Irregular clusters of basophilic material surrounded by histiocytes and giant cells; positive Alcian blue stain
Resorbable within years	Hyaluronic acid plus dextranomer microparticles	Matridex, Reviderm intra	Suppurative granuloma surrounding bluish-grey filamentous material and round, bluish, spherical particles
	Poly-L-lactic acid microspheres plus sodium carboxymethyl-cellulose	Sculptra, New-Fill	Foreign body granuloma around fusiform or oval, translucent particles, birefringent under polarized light
	Calcium hydroxylapatite plus carboxymethylcellulose	Radiance, Radiesse	Foreign body granuloma surrounding bluish, rounded particles
Permanent	Paraffin*		Foreign body granuloma with "Swiss cheese" appearance (Fig. 94.7B); positive fat stains (e.g. oil red O); detected by IRS
	Silicone oil or silicone gel	Silikon 1000†, SilSkin, MDX 4-4011, Adatosil 5000	Foreign body granuloma with "Swiss cheese" appearance (Fig. 94.9C); histiocytes may be foamy; negative fat stains; detected by EDXA; radio-opaque on X-ray
	Silicone particles (100-600 microns) suspended in polyvinylpyrrolidone	Bioplastique	Foreign body reaction with translucent, irregular, non-birefringent particles dispersed in a sclerotic stroma (Fig. 94.9B)
	Polymethylmethacrylate microspheres plus bovine collagen	Artefill, Artecoll, Arteplast	Granulomatous infiltrates around vacuolar structures of homogenous shape and size (Fig. 94.9A)
	Hydroxyethylmethacrylate/ethylmethacrylate fragments in hyaluronic acid	Dermalive, Dermadeep	Foreign body granuloma around polygonal, irregular, translucent pink structures (Fig. 94.9D)
	Polyacrylamide hydrogel	Aquamid, Interfall, Formacryl, Amazingel, Argiform, Bio-Formacryl, OutLine, Royamid, Kosmogel	Foreign body granuloma surrounding a basophilic, multi-vacuolated material
	Polyalkylimide gel	Bio-Alcamid	Basophilic, amorphous, granular material surrounded by inflammatory infiltrates
	Polyvinylhydroxide microspheres suspended in polyacrylamide gel	Evolution	No reports of side effects to date; limited local reactions at test sites in volunteers

*Banned in most countries; also seen after application of paraffin-impregnated gauze packs.
†FDA-approved for intraocular use.

Table 94.4 Histopathologic features of injectable soft-tissue fillers. EDXA, energy dispersive X-ray analysis; IRS, infrared spectrophotometry (non-processed tissue). Adapted from ref. 32.

acid injection, and spontaneous resolution occurs over 6 to 24 weeks. This reaction responds to intralesional injections of corticosteroid or hyaluronidase (see Ch. 158)[33].

Bovine Collagen

As the first FDA-approved injectable soft tissue filler for facial rhytides, bovine collagen implants have been widely used. However, bovine collagen has been largely replaced by less antigenic fillers, in particular hyaluronic acid (see above).

Despite negative skin testing (which is required prior to treatment), a small proportion of treated patients still develop a local reaction after injection. Two types of reactions have been reported: non-immunogenic and immunogenic. The former is characterized by localized tissue necrosis, which occurs shortly after implantation, and such reactions are probably the result of local vascular interruption; two-thirds of local necrotic events have occurred in the glabellar area[34]. The most common hypersensitivity reaction is the development of induration and erythema at the treatment site. It usually resolves spontaneously in less than a year. Rarely, abscesses ensue as a manifestation of hypersensitivity to bovine collagen (4 in 10 000 cases) and they may persist for several weeks. Periods of remission and exacerbation may occur, ranging from 1 to more than 24 months[34].

Intralesional corticosteroids are recommended for inflammatory reactions. Abscesses may be drained prior to injection.

Fig 94.10 Foreign body reactions to polyamide synthetic "hair" implantation. In addition to multiple perifollicular granulomas, there is evidence of chronic folliculitis. *Courtesy, Marwa Abdallah, MD.*

MISCELLANEOUS

Intralesional Corticosteroids

Foreign body reactions to intralesional corticosteroids are quite rare despite the widespread use of this treatment modality. Reactions result from failure of the injected material to disperse in the usual manner or from incomplete absorption, leaving a small residuum that evokes a foreign body reaction[35].

Histologically, pools of granular, lightly stained material surrounded by a histiocytic and foreign body granulomatous infiltrate are seen in the dermis. Cellular reactions are absent around sites of recent injections[35].

Sutures

Nylon and polypropylene sutures used in contemporary surgery are relatively inert (see Ch. 144), but most other materials regularly produce chronic inflammation and granuloma formation. The incubation period varies from weeks[36] to years[37].

The incision site may appear inflamed, red and edematous. A fistula may develop, through which the suture material is extruded. Inflammation persists until the suture material is totally removed.

Histologically, granulomatous inflammation of various types is seen surrounding suture material: foreign body, histiocytic, palisading, or a combination thereof[36,37]. Transepidermal elimination of the suture material occurs[36].

Polyamide "Hair" Implants

In patients with androgenetic alopecia in whom autologous hair transplantation is not feasible (e.g. inadequate donor sites), polyamide "hair" fibers have been used for synthetic scalp hair restoration. Although some authors have reported complications in only ~1% of patients, foreign body reactions are a real risk (Fig. 94.10)[38]. Polyamide fiber hair restoration is not approved in the US.

Mesotherapy

Although this technique usually involves the subcutaneous injection of phosphatidylcholine plus a detergent solvent (e.g. deoxycholic acid) and leads to the dissolution of fat cells, there is no standardization of injected materials. Therefore, in addition to irritant cutaneous necrosis and atypical mycobacterial infections, granulomatous reactions have been observed[39].

REFERENCES

1. Del Rosario RN, Barr RJ, Graham BS, Kaneshiro S. Exogenous and endogenous cutaneous anomalies and curiosities. Am J Dermatopathol. 2005;27:259–67.
2. Jaworsky C. Analysis of cutaneous foreign bodies. Clin Dermatol. 1991;9:157–78.
3. Lammers RL, Magill T. Detection and management of foreign bodies in soft tissue. Emerg Med Clin North Am. 1992;10:767–81.
3a. Dragu A, Unglaub F, Schwarz S, et al. Foreign body reaction after usage of tissue adhesives for skin closure: a case report and review of the literature. Arch Orthopaed Trauma Surg. 2009;129:167–9.
3b. Shanesmith RP, Vogiatzis PI, Binder SW, Cassarino DS. Unusual palisading and necrotizing granulomas associated with a lubricating agent used in lipoplasty. Am J Dermatopathol. 2010;32:448-52.
4. Feldmann R, Harms M, Chavaz P, et al. Orbital and palpebral paraffinoma. J Am Acad Dermatol. 1992;26:833–5.
5. McCallum DI, Hall GF. Umbilical granulomata – with particular reference to talc granuloma. Br J Dermatol. 1970;83:151–6.
6. Hindson C, Foulds I, Cotterill J. Laser therapy of lichenoid red tattoo reaction. Br J Dermatol. 1995;133:665–6.
7. Addy JH. Red sea coral contact dermatitis. Int J Dermatol. 1991;30:271–3.
8. Halder RM. Pseudofolliculitis barbae and related disorders. Dermatol Clin. 1988;6:407–12.
9. Ploysangam T, Breneman DL, Mutasim DF. Cutaneous pseudolymphomas. J Am Acad Dermatol. 1998;38:877–95.
10. Sowden JM, Byrne JP, Smith AG, et al. Red tattoo reactions: X-ray microanalysis and patch-test studies. Br J Dermatol. 1991;124:576–80.
11. Hirsh BC, Johnson WC. Pathology of granulomatous diseases. Foreign body granulomas. Int J Dermatol. 1984;23:531–8.
12. Smith KJ, Skelton HG III, Yeager J, et al. Histologic features of foreign body reactions in patients infected with human immunodeficiency virus type 1. The Military Medical Consortium for Applied Retroviral Research. J Am Acad Dermatol. 1993;28:470–6.
13. Goldstein M. Mercury-cadmium sensitivity in tattoos. A photoallergic reaction in red pigment. Ann Intern Med. 1967;67:984–9.
14. Abel EA, Silberberg I, Queen D. Studies of chronic inflammation in a red tattoo by electron microscopy and histochemistry. Acta Derm Venereol. 1972;52:453–61.
15. Kilmer SL. Laser treatment of tattoos. Dermatol Clin. 1997;15:409–17.
16. Urbach F, Wine SS, Johnson WC, et al. Generalized paraffinoma (sclerosing lipogranuloma). Arch Dermatol. 1971;103:277–85.
17. Raso DS, Greene WB, Harley RA, Maize JC. Silicone deposition in reconstruction scars of women with silicone breast implants. J Am Acad Dermatol. 1996;35:32–6.
18. Mastruserio DN, Pesqueira MJ, Cobb MW. Severe granulomatous reaction and facial ulceration occurring after subcutaneous silicone injection. J Am Acad Dermatol. 1996;34:849–52.
19. Mesquita-Guimaraes J, Azevedo F, Aguiar S. Silica granulomas secondary to the explosion of a land mine. Cutis. 1987;40:41–3.

20. Harms M, Masouye I, Saurat JH. Silica granuloma mimicking granulomatous cheilitis. Dermatologica. 1990;181:246–7.
21. Marcoval J, Moreno A, Mana J. Foreign bodies in cutaneous sarcoidosis. J Cutan Pathol. 2004;31:516.
22. Pucevich MV, Rosenberg EW, Bale GF, et al. Widespread foreign-body granulomas and elevated serum angiotensin-converting enzyme. Arch Dermatol. 1983;119:229–34.
23. Posner DI, Guill MA III. Cutaneous foreign body granulomas associated with intravenous drug abuse. J Am Acad Dermatol. 1985;13:869–72.
24. Skelton HG III, Smith KJ, Johnson FB, et al. Zirconium granuloma resulting from an aluminum zirconium complex: a previously unrecognized agent in the development of hypersensitivity granulomas. J Am Acad Dermatol. 1993;28:874–6.
25. Cominos D, Strutton G, Busmanis I. Granulomas associated with tetanus toxoid immunization. Am J Dermatopathol. 1993;15:114–17.
26. Jordaan HF, Sandler M. Zinc-induced granuloma – a unique complication of insulin therapy. Clin Exp Dermatol. 1989;14:227–9.
27. Leonard DD. Starch granulomas. Arch Dermatol. 1973;107:101–3.
28. Suzuki H, Baba S. Cactus granuloma of the skin. J Dermatol. 1993;20:424–7.
29. Zerboni R, Moroni P, Cannavo SP, et al. Interdigital pilonidal sinus in barbers. Med Lav. 1990;81: 138–41.
30. Sondenaa K, Pollard ML. Histology of chronic pilonidal sinus. APMIS. 1995;103:267–72.
31. Lowe NJ, Maxwell CA. Hyaluronic acid skin fillers: adverse reactions and skin testing. J Am Acad Dermatol. 2001;45:930–3.
32. Requena L, Requena C, Christensen L, et al. Adverse reactions to injectable soft tissue fillers. J Am Acad Dermatol. 2011;64:1–34.
33. Born T. Hyaluronic acids. Clin Plast Surg. 2006;33: 525–38.
34. Hanke CW, Higley HR, Jolivette DM, et al. Abscess formation and local necrosis after treatment with Zyderm or Zyplast collagen implant. J Am Acad Dermatol. 1991;25:319–26.
35. Bhawan J. Steroid-induced 'granulomas' in hypertrophic scar. Acta Derm Venereol. 1983;63:560–3.
36. Goette DK. Transepithelial elimination of suture material. Arch Dermatol. 1984;120:1137–8.
37. Marcus VA, Roy I, Sullivan JD, et al. Necrobiotic palisading suture granulomas involving bone and joint: report of two cases. Am J Surg Pathol. 1997;21:563–5.
38. Palmieri B, Griselli G, D'Ugo A, et al. Evaluation of polyamide synthetic hair. A long-term clinical study. Panminerva Med. 2000;42:49–53.
39. Gokdemir G, Küçükünal A, Sakiz D. Cutaneous granulomatous reaction from mesotherapy. Dermatol Surg. 2009;35:291–3.

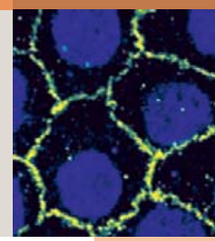
Silica granulomas. *Courtesy of Kenneth Greer MD.*

This page intentionally left blank

Biology of the Extracellular Matrix

95

Leena Bruckner-Tuderman



Key features

- Extracellular matrices (ECMs) represent specifically organized networks of collagens, elastin, glycoproteins and proteoglycans that have distinct structural roles and specific functional properties in all tissues
- ECMs are biologically active, interact with cells, and regulate cellular functions during development, regeneration and normal tissue turnover
- Mutations in genes encoding ECM proteins cause a broad spectrum of human diseases, from Ehlers–Danlos syndrome to epidermolysis bullosa, and components of the ECM are targeted in autoimmune diseases such as bullous pemphigoid, epidermolysis bullosa acquisita and lichen sclerosus
- The collagen family contains 28 different subtypes. All collagens consist of three polypeptide α-chains, which are folded into a triple helix. In each chain, every third amino acid is glycine (Gly), and thus a sequence of an α-chain can be expressed as $(Gly\text{-}X\text{-}Y)_n$. A hallmark of collagens is the presence of hydroxyproline (Hyp) in the Y position of this repeat sequence. Collagens are expressed in all tissues of the human body, and distinct sets of collagens co-polymerize into highly organized suprastructures, e.g. fibrils and filaments, in a tissue-specific manner
- Elastin provides tissues with their elasticity. Elastin monomers contain repetitive hydrophobic sequences and are highly cross-linked. The cross-links between several individual molecules provide for both elasticity and insolubility of the elastic fibers, which can be stretched by 100% or more and still return to their original form. In addition to elastin, elastic fibers in the dermis also contain a microfibrillar component that attaches the fibers to the surrounding structures

INTRODUCTION

The different types of extracellular matrix (ECM) represent specifically organized assemblies of the macromolecules listed in Table 95.1. The macromolecules have characteristic patterns of aggregation into insoluble suprastructures with a high degree of order at successive hierarchic levels[1]. Each of these structures is tissue-specific and adapted to the particular needs of a given tissue. At first glance, the major constituents are often similar in functionally diverse ECMs. However, different types of quantitatively minor molecular components associate with major elements in tissue-specific suprastructural arrays determined by their relative compositions. The matrix suprastructures may be likened to alloys, each having metallurgic properties that differ from each other and those of the pure metals (Fig. 95.1).

Individual ECM macromolecules are usually oligomers composed of one or several polypeptides. Intimate contacts between the subunits are formed by coiled-coil structures, such as the collagen triple helix or supercoiled α-helices comprised of three or more polypeptides. In addition, large matrix macromolecules can be regarded as linear sequences of structural modules that are similar in a large variety of proteins[1]. The modules can be recognized by several cellular receptors, but receptor clustering is determined in a tissue-specific manner and the response may be different in different tissues.

Our knowledge of ECM macromolecules has expanded dramatically in recent years due to the great power of both molecular genetics and proteomics. A multitude of molecules have been characterized and their expression, regulation, tissue specificity and functions discerned[2]. The assembled ECM structures are generally adhesive, enabling the attachment of tissue-specific cells, leukocytes, tumor cells, and even microorganisms. Through integrin-mediated interactions with cells, matrix molecules control cell proliferation, differentiation and migration, especially during development and regenerative processes. Without contact with the ECM, many cells undergo apoptosis. Furthermore, the ECM can function as a reservoir of information; certain proteoglycans and proteins bind growth factors (e.g. transforming growth factor [TGF]-β) and release and activate them as needed to control cellular functions[2]. To date, mutations in approximately 50 different genes encoding ECM molecules have been found to underlie heritable disorders in humans and mice.

STRUCTURE AND FUNCTION OF THE EXTRACELLULAR MATRIX

Collagens

The collagen family of proteins plays an important role in maintaining the integrity of most tissues. The family currently includes 28 proteins formally defined as collagens[3] (Table 95.2). These proteins contain at least 43 distinct polypeptide chains, each encoded by a different gene, and more than 15 other proteins have a collagen-like domain (e.g. macrophage scavenger receptor 1 and 2, ectodysplasin, pulmonary surfactant proteins).

Collagen triple helix

All collagens consist of three polypeptide chains, known as α-chains, which are folded into a triple helix. In some collagens, the α-chains are identical (homotrimers), while others contain two or three different α-chains (heterotrimers). In each polypeptide chain, every third amino acid is glycine (Gly), and the sequence of an α-chain can be expressed as $(Gly\text{-}X\text{-}Y)_n$, where X and Y represent other amino acids and n varies according to the length of the α-chain. A high number of proline (Pro) and hydroxyproline (Hyp) residues are in the X and Y positions, respectively, and hydrogen bonds between the hydroxyl groups of Hyp contribute to the stability of the helix. The prototype collagen (type I) has an uninterrupted Gly-X-Y repeat sequence that is almost 1000 amino acid residues in length. This forms a rigid, rod-like structure with a diameter of 1.5 nm and length of 300 nm. In some collagens, the $(Gly\text{-}X\text{-}Y)_n$ repeats are interrupted by one or more amino acids. The interruptions may be numerous and longer than the $(Gly\text{-}X\text{-}Y)_n$ repeats, and they provide the molecule with flexibility, which is important for the specific functions of a given collagen type[3].

Biosynthesis of collagens

Collagen biosynthesis involves a number of post-translational modifications (Fig. 95.2). Some collagens are first synthesized as procollagens that have propeptide extensions at their N-terminus, their C-terminus, or both termini. The main intracellular steps in collagen biosynthesis include the following:

- cleavage of signal peptides
- hydroxylation of certain Pro and lysine (Lys) residues to 4-Hyp, 3-Hyp, and hydroxylysine (Hyl)

COMPONENTS OF THE EXTRACELLULAR MATRIX	
Collagens (28 types)	Laminins (18)**
Elastin	Proteoglycans (Table 95.3)
Fibrillins (3 types)	Glycoproteins (Table 95.4)
LTBPs (4 types)	Integrins
Fibulins* (7 types)	Modifying enzymes

*Fibulins are believed to function as intra-molecular bridges that stabilize ECM structural networks (e.g. elastic fibers, microfibrils or basement membrane structures).
**15 of which are well characterized.

Table 95.1 Components of the extracellular matrix (ECM). These belong to several protein superfamilies. The molecules assemble into mixed fibrils and networks in a tissue-specific manner. Several enzymes are involved in the biosynthesis and modification of ECM assemblies. Integrins are the main cellular receptors for the ECM. LTBP, latent TGF-β binding protein.

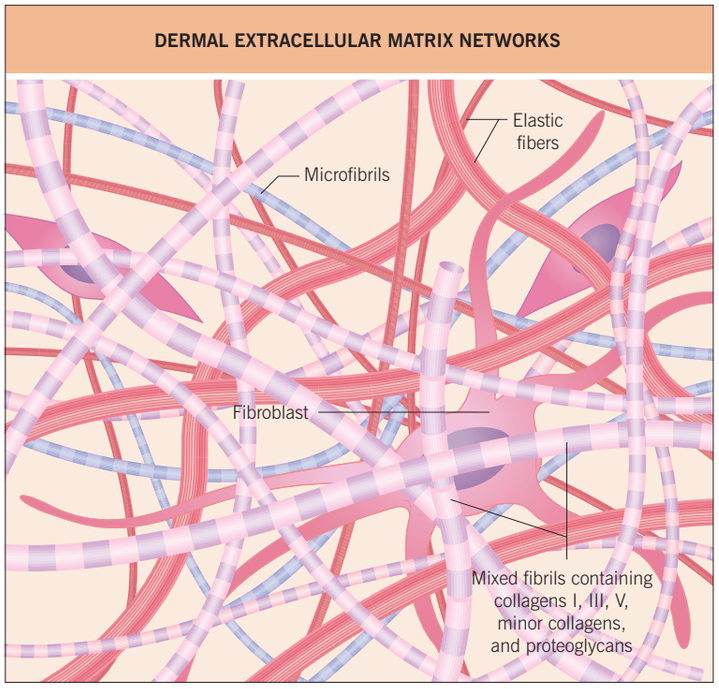


Fig. 95.1 Dermal extracellular matrix networks. Different molecules polymerize into distinct fibril networks and, within the mesh of the networks, cells are embedded in the amorphous extrafibrillar matrix. The fibril networks interact with each other, with the extrafibrillar matrix and with the cells. These networks have a dual function: support of the tissue and regulation of cellular functions.

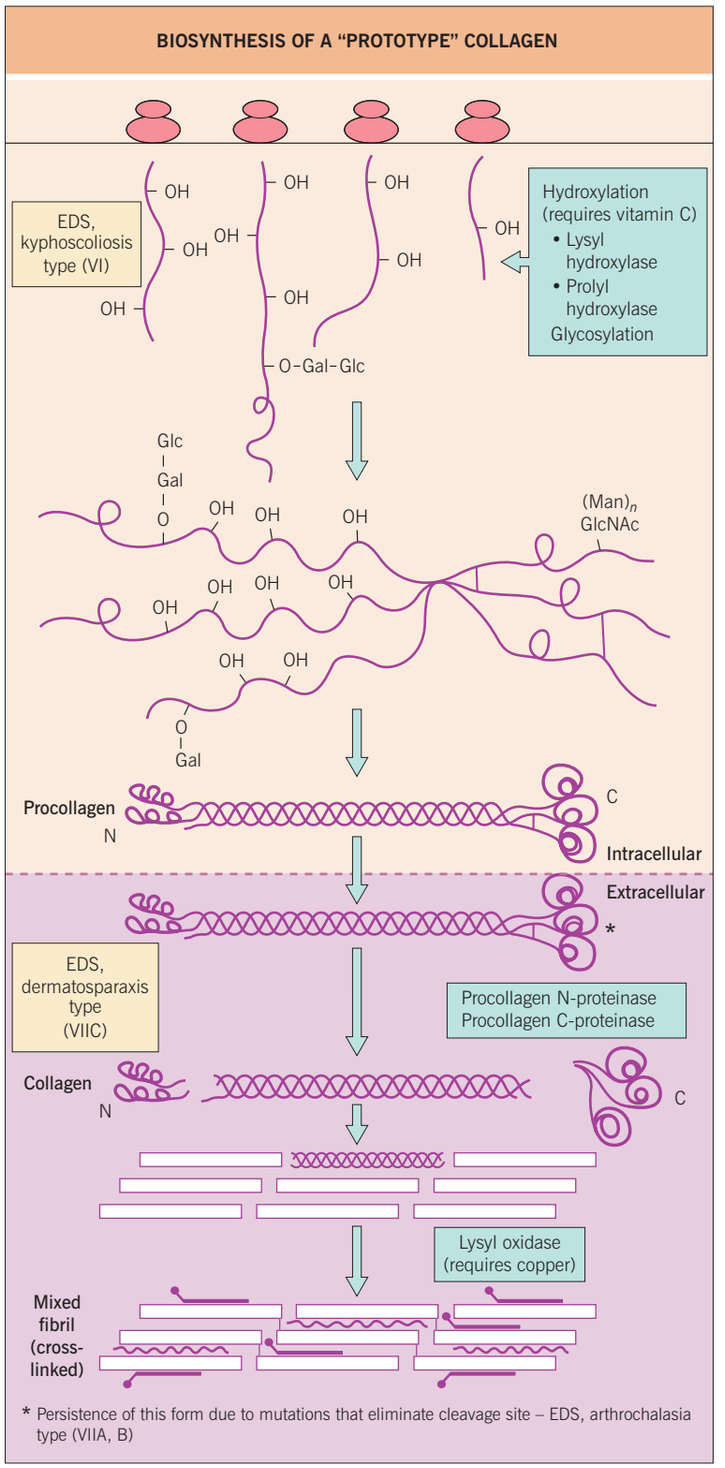


Fig. 95.2 Biosynthesis of a "prototype" collagen. The procollagen α-chains are synthesized in the rough endoplasmic reticulum. During its synthesis, certain prolyl and lysyl residues on the nascent polypeptide are hydroxylated and modified by glycosylation. Three α-chains associate to form a trimer and fold into a triple helix. The newly formed triple helical procollagen is secreted into the extracellular space, where the N- and C-terminal propeptides are cleaved by specific proteases. The mature collagen molecules assemble to form mixed fibrils with other collagens and non-collagenous molecules. The suprastructures are stabilized by covalent cross-links. EDS, Ehlers–Danlos syndrome. *Adapted from Myllyharju J, Kivirikko KI. Collagens, modifying enzymes and their mutations in humans, flies and worms. Trends Genet. 2004;20:33–43.*

- glycosylation of some of the Hyl residues to galactosyl-Hyl and glucosylgalactosyl-Hyl
- glycosylation of certain asparagine residues
- association of the α-chains in a specific manner
- formation of intra- and interchain disulfide bonds
- folding of the triple helix.

After the chains have become associated and sufficient Hyp residues have been formed in each chain, a nucleus of the triple helix forms (usually in the C-terminal region) and propagates towards the other end of the molecule in a zipper-like fashion[4]. The procollagen molecules are then transported from the endoplasmic reticulum across the Golgi apparatus without leaving the lumen of the Golgi cisternae. During this transport, the molecules begin to aggregate laterally and form early fibrils ready for secretion[5]. The *extracellular* steps in biosynthesis typically include cleavage of the N- and/or C-terminal propeptides, assembly into suprastructures with other collagens and non-collagenous components, and formation of covalent cross-links.

The specific enzymes involved in the biosynthesis of collagens include prolyl-4-hydroxylase and prolyl-3-hydroxylase, which hydroxylate Pro residues to Hyp, and lysyl hydroxylases, which hydroxylate Lys residues to Hyl. These enzymes require O_2, Fe^{2+}, α-ketoglutarate and ascorbate (vitamin C) as cofactors for the reactions. In the rough endoplasmic reticulum, glycosyltransferases add glucosylgalactosyl disaccharides onto the α-chains. The same intracellular enzymes modify all collagen

Table 95.2 The collagen family of proteins. The names of types found in the skin are in bold italics. Multiplexins are collagens with multiple triple helix domains and interruptions. ECM, extracellular matrix; FACITs, fibril-associated collagens with interrupted triple helices.

THE COLLAGEN FAMILY OF PROTEINS			
Type	**Chains**	**Gene**	**Tissue distribution**
FIBRIL-FORMING COLLAGENS			
Collagen I	α_1(I), α_2(I)	*COL1A1*, *COL1A2*	Skin, most ECM
Collagen II	α_1(II)	*COL2A1*	Cartilage, vitreous humor
Collagen III	α_1(III)	*COL3A1*	Skin (including fetal skin), lung, vasculature
Collagen V	α_1(V), α_2(V), α_3(V)	*COL5A1*, *COL5A2*, *COL5A3*	Skin, with collagen I heterotypic fibrils
Collagen XI	α_1(XI), α_2(XI), α_3(XI)	*COL11A1*, *COL11A2*, *COL11A3*	With collagen II heterotypic fibrils
Collagen XXIV*	α_1(XXIV)	*COL24A1*	Developing bone and cornea
Collagen XXVII*	α_1(XXVII)	*COL27A1*	Cartilage, eye, ear, lung
FACITS			
Collagen IX	α_1(IX), α_2(IX), α_3(IX)	*COL9A1*, *COL9A2*, *COL9A3*	With collagen II heterotypic fibrils
Collagen XII	α_1(XII)	*COL12A1*	Skin, tissues containing collagen I
Collagen XIV	α_1(XIV)	*COL14A1*	Skin, tissues containing collagen I
Collagen XVI	α_1(XVI)	*COL16A1*	Skin, many tissues
Collagen XIX	α_1(XIX)	*COL19A1*	Basement membranes, fetal muscle
Collagen XX	α_1(XX)	*COL20A1*	Skin, cornea, cartilage, tendon
Collagen XXI	α_1(XXI)	*COL21A1*	Many tissues, including skin
Collagen XXII*	α_1(XXII)	*COL22A1*	Tissue junctions (including between the anagen hair follicle and dermis)
Collagen XXVI*	α_1(XXVI)	*COL26A1*	Testis, ovary
BASEMENT MEMBRANE COLLAGENS			
Collagen IV	α_1(IV), α_2(IV), α_3(IV), α_4(IV), α_5(IV), α_6(IV)	*COL4A1*, *COL4A2*, *COL4A3*, *COL4A4*, *COL4A5*, *COL4A6*	All basement membranes, isoforms vary Skin: α_1(IV), α_2(IV), α_5(IV) and α_6(IV)
MICROFIBRILLAR COLLAGENS			
Collagen VI	α_1(VI), α_2(VI), α_3(VI)	*COL6A1*, *COL6A2*, *COL6A3*	Skin, other microfibril-containing tissues
NETWORK-FORMING COLLAGENS			
Collagen VIII	α_1(VIII), α_2(VIII)	*COL8A1*, *COL8A2*	Skin, subendothelial matrices
Collagen X	α_1(X)	*COL10A1*	Hypertrophic cartilage
ANCHORING FIBRIL COLLAGEN			
Collagen VII	α_1(VII)	*COL7A1*	Skin, mucous membranes, cornea
TRANSMEMBRANE COLLAGENS			
Collagen XIII	α_1(XIII)	*COL13A1*	Skin, many tissues
Collagen XVII	α_1(XVII)	*COL17A1*	Skin, mucous membranes, cornea
Collagen XXIII*	α_1(XXIII)	*COL23A1*	Lung, cornea, brain, skin, tendon, kidney
Collagen XXV*	α_1(XXV)	*COL25A1*	Brain, neurons
MULTIPLEXINS			
Collagen XV	α_1(XV)	*COL15A1*	Many tissues; parent molecule of restin†
Collagen XVIII	α_1(XVIII)	*COL18A1*	Many tissues, including skin, subendothelial matrices; parent molecule of endostatin†
NOVEL COLLAGENS			
Collagen XXVIII	α_1(XXVIII)	*COL28A1*	Schwann cells; fetal skin and calvaria

*Classification based upon cDNA sequence.
†Inhibitors of angiogenesis.

chains[4]. The *extracellular* processing enzymes have a higher substrate specificity. Procollagen I N-proteinase cleaves the N-propeptide of procollagens I and II. This enzyme is a member of the disintegrin and metalloproteinase (ADAM) proteinase family and is also designated as ADAM with thrombospondin type 1 motif (ADAMTS)-2. Procollagen C-proteinase cleaves the C-propeptide of collagens I, II, III, V and VII. It is a member of the tolloid proteinase family and is also called bone morphogenetic protein (BMP)-1, since it was initially co-purified with other BMPs from bone extracts. Cross-linking between collagen molecules involves the ε-amino groups of Lys and Hyl and is catalyzed by lysyl oxidase, a copper-requiring enzyme[4]. Another enzyme that catalyzes cross-linking of at least some collagens is tissue transglutaminase. Collagen VII-containing anchoring fibrils in the upper dermis appear to be transaminated, and collagen VII serves as a substrate for tissue transglutaminase-2 *in vitro*[6].

The collagen family of proteins

The length and continuity of the triple helical domains vary among the collagen types. For practical purposes, the collagens have been divided into groups according to their ability to form supramolecular aggregates, which are depicted in Figure 95.3. The types and tissue distributions of the collagens in each group are listed in Table 95.2, and those found in the skin are discussed below. More detailed information on all the collagen types is available in recent reviews[1,3–5].

Collagens of the skin

Collagens account for 75% of the dry weight and 20–30% of the volume of the dermis. Different collagens polymerize into distinct suprastructures and have specific functions in the dermis as well as in epidermal and vascular basement membranes. "Pure" collagen fibrils do not exist; these fibrils are always mixtures of several collagens and other molecules, e.g. proteoglycans[1]. Classic, ultrastructurally recognizable, cross-banded fibrils in the dermis contain collagens I, III, V, XII and XIV. The characteristic cross-banding (Fig. 95.4) with periodicity of 64 nm results from precise lateral packing of the different collagens within the fibrils (see Fig. 95.3). Collagen I is the major component of the fibrils, and the amount of other collagens varies. For example, during embryonic development and wound repair, the content of collagen III is higher than in the steady-state situation. Of note, collagen III is also an important component of the vasculature, in particular arterial walls. Collagen VI, a highly glycosylated and disulfide-bonded collagen, is a component of almost all tissues, including the skin. *In vitro*, it polymerizes to form beaded filaments (see Fig. 95.3), but *in vivo* in the dermis, the ultrastructure of the collagen VI fibrils is reminiscent of microfibrils.

The collagen IV molecules in different basement membranes are composed of six genetically distinct but structurally homologous α-chains, which form three major networks: (1) α_1/α_2-containing; (2) $\alpha_3/\alpha_4/\alpha_5$-containing; and (3) $\alpha_1/\alpha_2/\alpha_5/\alpha_6$-containing[3]. In the skin, the α_1/α_2-containing collagen IV network dominates within the dermal–epidermal junction (see Ch. 28), but the $\alpha_1/\alpha_2/\alpha_5/\alpha_6$-containing network is also thought to be present[3]. The chain composition is determined by the carboxy-terminal non-collagenous (NC1) domains; covalent interactions between these domains link α-chains to each other and have a role in the formation of collagen IV dimers (composed of two triple-helical protomers). In addition, connections between amino-terminal 7S domains lead to formation of collagen IV tetramers (composed of four triple helical protomers; see Figs 28.5 and 95.3).

Two collagens are essential for the cohesion of the epidermis and dermis (see Ch. 28). Collagen VII is the major, if not sole, component of the anchoring fibrils that attach the basement membrane to the dermal ECM. Collagen XVII (also known as bullous pemphigoid antigen 2) is a component of the anchoring filaments that bind the basal keratinocytes to the lamina densa (basement membrane proper). It is a transmembrane collagen in type II orientation with a long extracellular C-terminal region containing a multiply-interrupted triple helix referred to as collagenous domains 1–15 (see Fig. 31.9). The ectodomains can be shed from the cell surface by transmembrane proteases[7], a process important for regulation of cell adhesion and migration. Basal

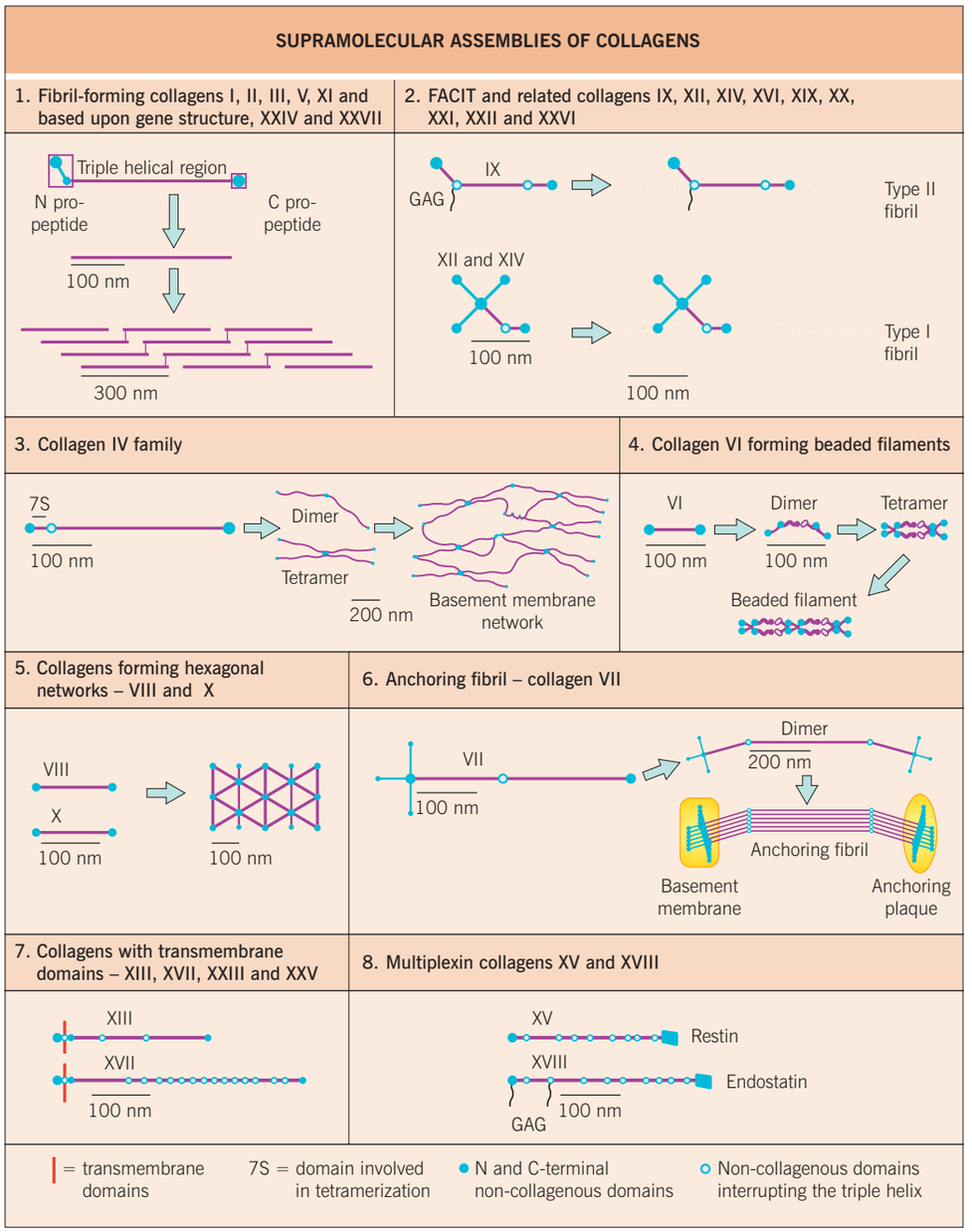


Fig. 95.3 Supramolecular assemblies of collagens. The suprastructures formed by different collagens are shown. Non-collagenous components also interact with the fibrils and networks. The suprastructural organization of the transmembrane collagens XIII and XVII and the multiplexin collagens XV and XVIII is not known yet (panels 7 and 8). These collagens are in close vicinity to basement membranes and are likely to participate and/or interact with the different basement membrane networks. FACIT, fibril-associated collagens with interrupted triple helices; GAG, glycosaminoglycans. *Adapted from Myllyharju J, Kivirikko KI. Collagens, modifying enzymes and their mutations in humans, flies and worms. Trends Genet. 2004;20:33–43.*

keratinocytes also express a second transmembrane collagen, type XIII, which is a component of focal contacts.

The vascular basement membranes in the skin contain yet other collagens – namely, collagens VIII and XVIII. Collagen VIII builds hexagonal networks below the endothelial basement membranes (see Fig. 95.3) and, thus, structurally strengthens the vascular wall. Collagen XVIII is localized at the dermal side of vascular basement membranes. Its C-terminal fragment, endostatin (see Fig. 95.3), is proteolytically released from the collagen molecule and has independent biological functions that include inhibition of angiogenesis[3].

Most collagens in the skin are products of dermal fibroblasts. Exceptions include: (1) collagen XVII, a surface component of epidermal keratinocytes; (2) collagen VII, which can be synthesized by both keratinocytes and fibroblasts; and (3) collagens VIII and XVIII, which are produced by endothelial cells. Several genetic and acquired diseases are associated with abnormalities of skin collagens or the enzymes that process them (see Tables 95.5 & 95.6, and discussion below).

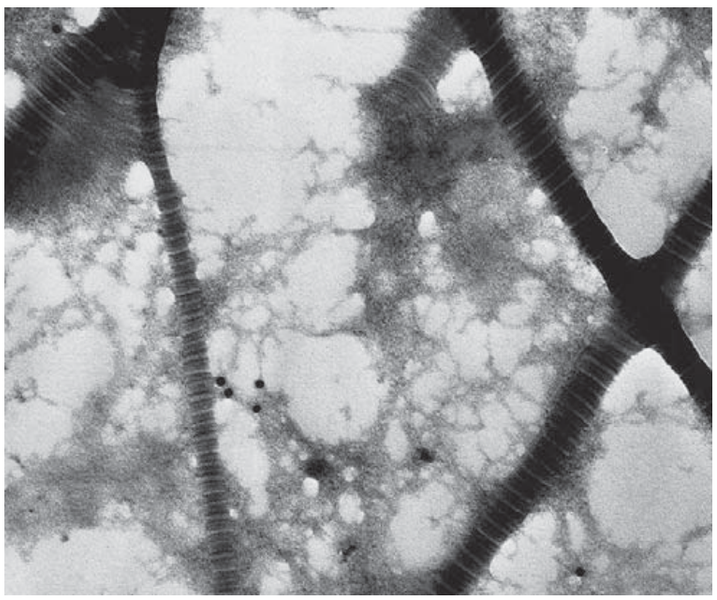


Fig. 95.4 Fibrillar and filamentous networks extracted from human skin. The large cross-banded fibrils represent dermal mixed fibrils containing collagens I, III and V; other minor collagens; and decorin (a proteoglycan). The cross-banding has a characteristic periodicity of 64 nm. The filamentous network in the background contains microfibrillar and basement membrane components. In this immunoelectron photomicrograph, the black dots are colloidal gold particles coupled to anti-collagen IV antibodies, indicating that basement membrane networks are strongly associated with the dermal fibrillar networks. *Courtesy, Uwe Hansen, MD.*

Elastic Fibers

The elasticity of many tissues, including the skin, depends upon the structure of elastic fibers, which can have variable compositions. A characteristic property of these fibers is that they can be stretched by 100% or more and still return to their original form. The main components of elastic fibers are elastin and microfibrils.

Elastin

Elastin is a highly cross-linked protein[8]. Its monomer, tropoelastin, contains repetitive modules of hydrophobic amino acids (Val-Gly-Val-Pro-Gly)$_n$ and exists in several tissue-specific splice variants. Ala- and Lys-rich repeats form critical cross-linking domains and may interrupt the basic repetitive structure. Lysyl oxidase, the same copper-dependent enzyme that catalyzes collagen cross-linking (see above), catalyzes the formation of desmosine cross-links between elastin molecules, which account for both the elasticity and insolubility of elastic fibers. Although elastin makes up the bulk of mature elastic fibers, the precise interactions between microfibrils and elastin that occur during elastic fiber assembly are not currently known. A current model based on coordinated, spatially and temporally regulated assembly is presented in Figure 95.5.

Microfibrils

Microfibrils (10 to 12 nm in diameter) insert into the basement membrane in a perpendicular orientation (classically referred to as "oxytalan fibers") and extend into the papillary dermis (Fig. 95.6), where they gradually merge with elastic fibers that contain a relatively small amount of elastin and form a plexus parallel to the dermal–epidermal junction (classically referred to as "elaunin fibers"). Such fibers appear to be continuous with the elastic fibers within the reticular dermis, which contain more abundant elastin. Microfibrils consist mainly of fibrillins[9], but they also contain and associate with other proteins, such as microfibril-associated glycoproteins (MAGPs), latent TGF-β binding proteins (LTBPs), fibulins, elastin microfibril interfacer (EMILIN)-1 and, in the papillary dermis, collagen XVI[8,9]. Fibrillins 1–3 are large glycoproteins that contain both epidermal growth factor (EGF) and cysteine (Cys) repeats. The EGF repeats bind calcium, which is required for stabilization of the protein. Fibrillin-1 interacts with perlecan in the epidermal basement membrane to attach the microfibrils to the dermal–epidermal junction.

A new paradigm has emerged from recent investigations demonstrating that, in addition to guiding elastic fiber assembly and providing structural support, fibrillins function together with LTBPs to regulate cell signaling[10]. The four members of the LTBP family are high-molecular-weight glycoproteins characterized by EGF-like and 8-Cys repeats, and they all associate with the small latent complex of TGF-β

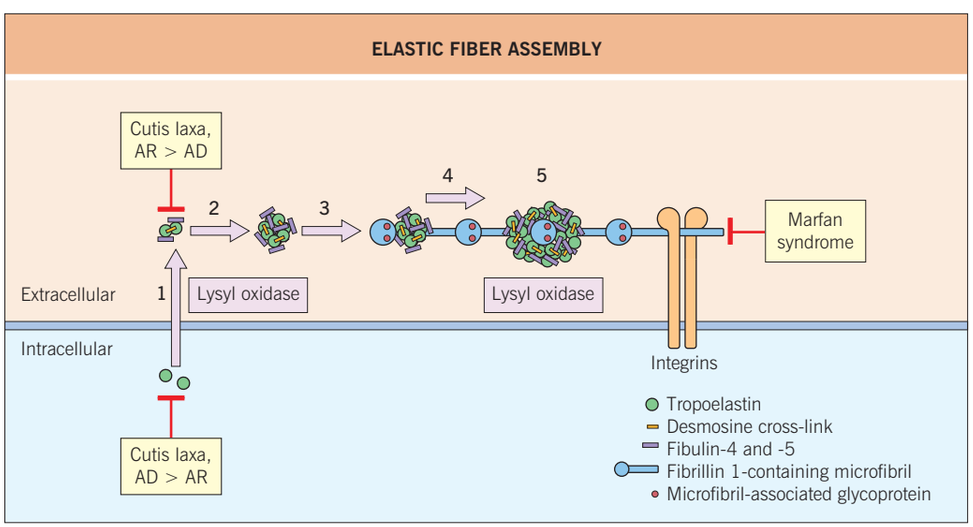


Fig. 95.5 Elastic fiber assembly. This model is based on current knowledge of interactions between elastin, microfibrillar proteins and cells in generating a functional elastic fiber. Tropoelastin is secreted and cross-linked by lysyl oxidase on the cell surface (**1**). Additional elastin is added to the aggregates (**2**), which are then transferred onto pre-existing fibrillin-1-containing microfibrils (**3**) that bind to the cell surface via integrins. Fibulin-4 and -5 interact with the elastin aggregates, enhance cross-linking and bind to fibrillin-1, thus augmenting the transfer of elastin aggregates to the microfibrils. The elastin aggregates and the microfibrils develop into larger structures (**4**) and are further cross-linked by lysyl oxidase (**5**) to form a functional elastic fiber. *Adapted from Wagenseil JE, Mecham RP. New insights into elastic fiber assembly. Birth Defects Res C Embryo Today. 2007;81:229–40.*

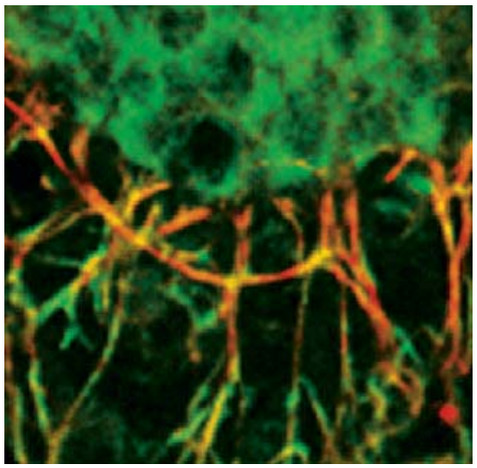


Fig. 95.6 Microfibrils in the papillary dermis. Confocal scanning microscopy of microfibrils, which emerge from the epidermal basement membrane and traverse the papillary dermis perpendicularly. The immunostaining is with antibodies to fibrillin-1 (red) and latent TGF-β complex (green). The orange–yellow color demonstrates co-localization of both proteins on the microfibrils.

Courtesy, Michael Raghunath, MD. See also Raghunath M, Unsöld C, Kubitscheck U, et al. The cutaneous microfibrillar apparatus contains latent transforming growth factor-beta binding protein-1 (LTBP-1) and is a repository for latent TGF-beta1. J Invest Dermatol. 1998;111:559–64.

(see below; Fig. 95.7). The LTBP-1/latent TGF-β complex (referred to as the large latent complex) binds to fibrillin-containing microfibrils. Together, they control bioavailability of TGF-β in the skin and other tissues. LTBPs contain multiple proteinase-sensitive sites, providing the means to solubilize the large latent complex from ECM structures, and both soluble and ECM-associated forms are known to exist. Another group of signaling molecules that can bind to fibrillins are the bone morphogenetic proteins (BMPs)[10]. These are secreted as cross-linked dimeric complexes that are associated through their prodomains, which interact directly with the amino-terminus of fibrillin. Fibrillins and LTBPs therefore have important roles in targeting latent, activatable TGF-β and BMPs into different ECMs. Thus, microfibrils serve not only as a force-bearing element and scaffolding for elastin deposition in the dermis, but also as an important repository for signaling molecules in the skin[2,9,10].

The Extrafibrillar Matrix

The dermal fibril networks and cells are embedded in an amorphous extrafibrillar material that binds water and provides the hydrated consistency of the skin. Previously, this amorphous material was presumed to be biologically unstructured and inert and was called the "ground substance". This prediction turned out to be incorrect – the extrafibrillar matrix is molecularly and structurally diverse, highly organized, and biologically active. It contains a number of proteoglycans and glycoproteins as well as hyaluronic acid and water. The functions of the extrafibrillar matrix are adapted to the biologic needs of each tissue. For example, during embryonic development, water-binding proteoglycans and glycosaminoglycans (GAGs) form a hydrated milieu for cell migration and proliferation. During development and tissue remodeling, glycoproteins of the extrafibrillar matrix are essential for formation of the correct tissue architecture.

GAGs are polysaccharides composed of sulfated and acetylated sugars with negative charges that can bind large amounts of ions and water. The most prominent and ubiquitous *protein-free* GAG is hyaluronic acid, a giant polysaccharide composed of thousands of N-acetylglucosamine/glucuronic acid disaccharides. Other GAGs, however, bind to proteins with a serine hydroxyl group, forming a proteoglycan (Fig. 95.8)[11]. Proteoglycans differ remarkably in their protein content and the number, type and length of their GAG side chains (Table 95.3). Four different *proteoglycan-bound* GAGs are known: chondroitin sulfate, dermatan sulfate, keratan sulfate and heparan sulfate[11]. Versican is the most important proteoglycan in the dermis (see Fig. 95.8). It is associated with the elastic fiber system and forms huge complexes with hyaluronic acid, which provide the skin with its tautness. Versican can be synthesized by fibroblasts, smooth muscle cells and epithelial cells.

Perlecan is a major heparan sulfate proteoglycan found in all basement membranes, including the epidermal basement membrane[12]. Small leucine-rich proteoglycans (SLRPs) are characterized by a protein core of Leu-rich repeats and Cys-bonded loops, with only one or two GAG chains. SLRPs that are found in the skin include decorin, biglycan, fibromodulin, lumican and keratocan[11]. Decorin has multiple functions; for example, it binds to collagen fibrils and TGF-β. Biglycan is a cell surface proteoglycan that also binds to TGF-β, and fibromodulin regulates formation of collagen-containing fibrils. Syndecans are transmembrane heparan sulfate proteoglycans that regulate cell adhesion to the ECM and subsequent cytoskeletal organization. Syndecans 1, 2 and 4 are expressed in the skin and can be found in keratinocytes, dendritic cells and fibroblasts, where they are thought to mediate "outside-in" cell signaling[11].

Laminins and Other Glycoproteins

Laminins, a family of basement membrane glycoproteins with 18 members (three of which are not yet well characterized), are expressed in all tissues. Each laminin isoform is a trimer consisting of an α-, β- and γ-chain[13,14]. The current laminin nomenclature (revised in 2005) is based on the chain composition, e.g. the laminin isoform that is composed of α_3-, β_3- and γ_2-chains is referred to as laminin 332 (formerly known as laminin 5)[15]. In the skin, the epidermal basement membrane contains laminins 332, 311 (formerly known as laminin 6) and 511 (formerly known as laminin 10), and the vascular basement membrane contains laminins 411 (formerly laminin 8) and 511. The structure, biologic functions and sequelae of genetic defects of laminins expressed in the skin are discussed in more detail in Chapters 28 and 32.

Other glycoproteins with important functions in the skin are listed in Table 95.4.

Functions of the Extracellular Matrix

Structural role of the extracellular matrix

In the past, the ECM was regarded as a structural scaffold that gave organs their shape and consistency. Over the past decade, considerable progress has been made in our understanding of the broad spectrum of distinct ECM suprastructures and their specific functions[1,2]. For example, corneal stroma contains stacked sheets of parallel fibrils with a uniform and small diameter. In each consecutive layer, the fibrils are oriented almost perpendicularly to the adjacent layers, rendering the tissue resistant to high tensile forces in two dimensions and, at the same time, allowing undisturbed penetration of visible light. Basement membranes are sheets with limited tensile strength but important tissue-specific properties that allow for particular cell attachments and regulate morphogenesis, differentiation and barrier functions. In the dermis, various ECM networks are embedded in the water-binding extrafibrillar matrix, maintaining the elasticity, resilience and tautness of the skin. At the dermal–epidermal junction, specific basement membrane-associated aggregates ensure strong adhesion of the epidermis and the dermis and, as a result, provide resistance against external shearing forces (see Ch. 28).

Regulation of cellular functions

In addition to their structural roles, ECMs are biologically active. *In vitro* studies and transgenic and knockout mouse models (see Ch. 3) have demonstrated the importance of ECMs as potent regulators of cellular functions during development, regeneration, wound healing, inflammation and tumorigenesis. ECM macromolecules can influence a multitude of cellular processes and events, such as adhesion, migration, cytoskeletal organization, determination of cell shape and polarization, division, differentiation and apoptosis.

Cells use a variety of receptors, such as integrins and cell surface proteoglycans, to recognize signals from the ECM[2]. The family of β_1 integrins represents the most common class of matrix receptors. The α-subunit of the integrin determines the specificity for individual matrix protein ligands, but the affinity and degree of specificity vary. Some integrins recognize only one ligand, while others can bind to several matrix proteins.

Signals from the ECM can have different effects on the cell[16]. For example, they can induce clustering of integrins on the cell surface and lead to formation of protein complexes between the cytoplasmic domains of the integrins and the cytoskeleton, thereby influencing cell shape. Alternatively, activation of integrins by the ECM can stimulate signal transduction pathways involving focal adhesion kinase (protein tyrosine kinase 2), paxillin and tensin. ECM–integrin interaction may also induce mitogen-activated protein kinase-mediated regulation of transcription,

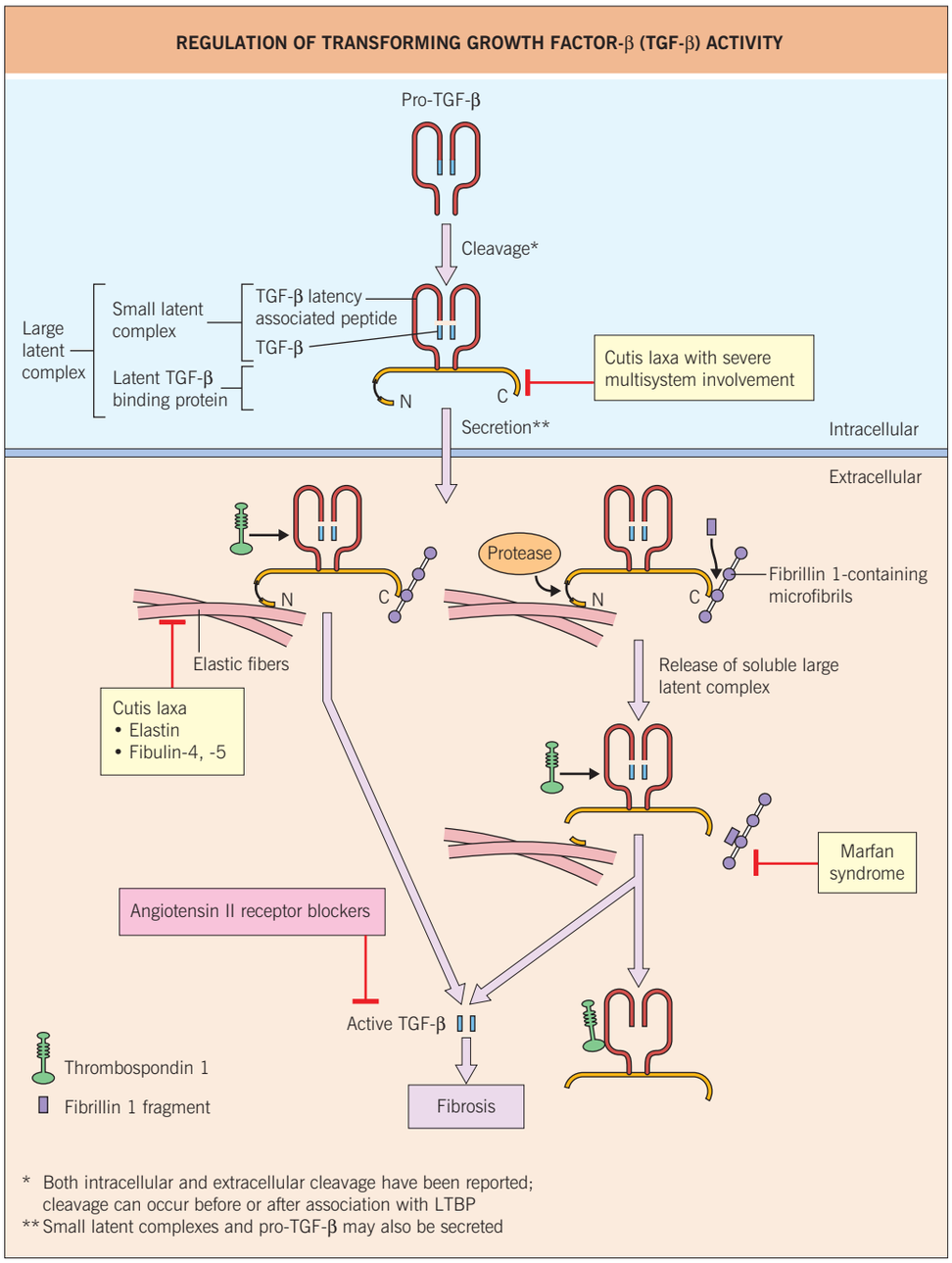


Fig. 95.7 Regulation of transforming growth factor-β (TGF-β) activity. TGF-β is synthesized as an inactive homodimeric propeptide, pro-TGF-β. After cleavage, mature TGF-β is sequestered in an inactive form via its continued association (now non-covalent) with the latency-associated peptide (LAP; forming the small latent complex) and covalent linkage of the LAP to the latent TGF-β binding protein (LTBP; forming the large latent complex). In addition, the large latent complex becomes attached to the extracellular matrix (ECM) via covalent linkage of the LTBP N-terminus with ECM proteins and non-covalent association of the LTBP C-terminus with fibrillin-1 (a member of the LTBP/fibrillin superfamily). Solubilization of the large latent complex from the ECM can occur via proteolytic cleavage of susceptible hinge regions within the LTBP and disruption of the fibrillin-1–LTBP interaction by fibrillin-1 fragments. Binding of ECM glycoproteins such as thrombospondin 1 to the LAP results in the release of active TGF-β that can bind to its receptors and promote fibrosis. *Adapted from August P, Suthanthiran M. Transforming growth factor beta signaling, vascular remodeling, and hypertension. N Engl J Med. 2006;354:2721–3.*

cell proliferation and differentiation. A further level of regulation of integrin-mediated ECM signaling results from the regulation of integrin activation through divalent cations, phospholipids and other agents[17].

Growth factors of the TGF-β family are potent regulators of ECM formation, in addition to their immunomodulatory functions and regulatory roles in cell growth[2]. They are secreted from cells as latent complexes containing TGF-β and its propeptide latency-associated peptide (LAP). In most cells, LAP is covalevntly linked to LTBP, forming the large latent complex (see above and Fig. 95.7). The secreted large latent complexes associate covalently with the ECM proteins via the N-termini of the LTBPs. TGF-β can be released from the complexes by various matrix-degrading proteinases originating from fibroblasts or inflammatory cells. In addition to the LTBPs, several other ECM molecules can bind to TGF-β and modulate its activity, such as thrombospondin and the core proteins of the proteoglycans decorin, biglycan and fibromodulin[2].

DISEASES RELATED TO ECM DEFECTS

Molecular studies of the genes and proteins involved in diseases of the ECM have produced a wealth of information regarding the normal biology of the ECM[18–21]. Putative functions for many matrix macromolecules were found for the first time, or confirmed, when mutations in their genes were shown to cause diseases. For example, functions of the minor fibrillar collagens V, IX and XI in controlling the collagen fibril diameter have been ultimately proven via studies of animal or human genetic disorders[3]. The fundamental roles of collagens VII and XVII in dermal–epidermal adhesion became clear when mutations in the corresponding genes were discovered in patients with hereditary epidermolysis bullosa (EB)[18]. Genetic ECM diseases with cutaneous manifestations are listed in Table 95.5, and the molecular mechanisms and pathophysiology of selected conditions are delineated below. Ehlers–Danlos syndrome (EDS), cutis laxa and pseudoxanthoma elasticum (PXE) are covered in more depth in Chapter 97, and EB is discussed in Chapter 32.

Ehlers–Danlos syndrome

The quantitatively major components of the collagen fibrils found in the ECMs of many tissues (e.g. skin, tendon, bone, cartilage) are collagens I, II (absent from the skin) and III. Smaller amounts of other "minor" collagens (e.g. types V, IX, XI, XII, XIV) are expressed in a tissue-specific manner[3]. Mutations in the genes encoding major or minor collagens can result in distinct constellations of

PROTEOGLYCANS OF THE SKIN			
Proteoglycan	**Gene**	**Size of the core protein (kDa)**	**Glycosaminoglycan (GAG) side chains (number)**
Versican	*CSPG2*	265–370, splice variants	Chondroitin/dermatan sulfate (10–30)
Perlecan	*HSPG2*	400–467	Heparan/chondroitin sulfate (3)
Decorin*	*DCN*	40	Chondroitin/dermatan sulfate (1)
Fibromodulin*	*RMOD*	42	Keratan sulfate (2–3)
Lumican*	*LUM*	38	Keratan sulfate (3–4)
Keratocan*	*KERA*	38	Keratan sulfate (3–5)
Biglycan*	*BGN*	40	Chondroitin/dermatan sulfate (2)
Syndecans 1, 2, 4	*SDC1* *SDC2* *SDC4*	35–120	Heparan/chondroitin sulfate (3–5)

*Small leucine-rich proteoglycan.

Table 95.3 Proteoglycans of the skin.

GLYCOPROTEINS OF THE SKIN	
Glycoproteins	**Key functions**
Fibronectin	Cell adhesion and migration
Vitronectin	Cell adhesion and migration
Thrombospondins (4 types)	Cell-to-cell and cell-to-matrix communication
Matrilins (4 types)	Matrix assembly, cell adhesion
Tenascins (4 types)	Regulation of cellular function

Table 95.4 Glycoproteins of the skin.

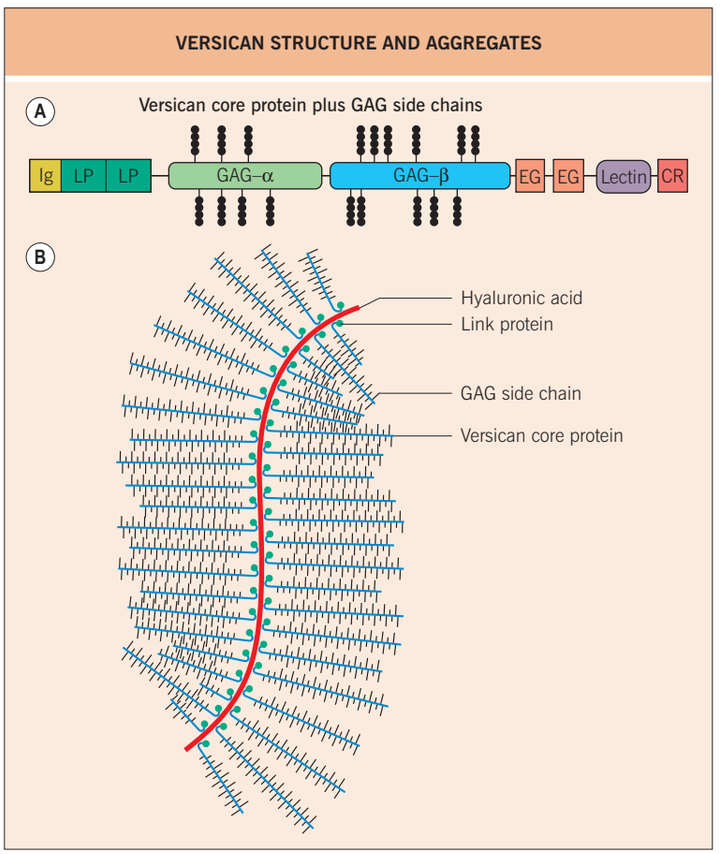


Fig. 95.8 Versican structure and aggregates. A The core protein contains several structural motifs important for glycosaminoglycan (GAG) and ligand binding. The N-terminal immunoglobulin-type repeat (Ig) is followed by two consecutive link-protein type modules (LP), which are involved in mediating the binding of the core protein to hyaluronic acid. The GAG binding domain, which comes in tissue-specific alternative splice variants, GAG-α and/or GAG-β, carries the GAG side chains. It is followed by structural motifs, including two epidermal growth factor-like repeats (EG), a C-type lectin domain (Lectin), and a complement regulatory protein-like module (CR). **B** In the dermis, versican can form huge aggregates with hyaluronic acid (red). The core protein (blue), which carries a number of GAG side chains (black), is bound to hyaluronic acid via its link-protein domain (green; LP module in the scheme in panel A). The aggregates can bind large amounts of water, and thus provide for the tautness of the skin. *Adapted from Iozzo RV. Matrix proteoglycans: from molecular design to cellular function. Ann Rev Biochem. 1998;67:609–52.*

abnormalities in different organs, including several types of EDS (see Ch. 97)[19]. For example, defects in the *COL3A1* gene encoding collagen III are responsible for the vascular type of EDS (type IV), an autosomal dominant condition that presents with thin translucent skin, excessive bruising, and life-threatening arterial, gastrointestinal and uterine ruptures. Mutations in the *COL3A1* gene have also been found in a subset of patients with arterial aneurysms as the primary clinical manifestation.

Alterations in several genes encoding minor fibrillar collagens can also cause severe connective tissue diseases, suggesting pivotal functions for these quantitatively minor components. The α_1- and the α_2-chains of collagen V co-polymerize with collagens I and III and have a role in the control of fibrillogenesis. They limit the solubility of macromolecules in the fibrils and regulate the geometry of lateral aggregation as well as the overall shapes and sizes of the collagen aggregates. Consistent with this concept, the classic type of EDS (types I & II) rarely results from mutations in the *COL1A1* gene encoding the α_1-chains of collagen I, whereas mutations in the *COL5A1* and *COL5A2* genes encoding the α_1- and α_2-chains of collagen V account for approximately 50% of patients[21]. Patients with this form of EDS exhibit variable degrees of skin hyperelasticity and fragility, atrophic scarring and joint hypermobility (Fig. 95.9A). Since collagen V is a heterotrimeric molecule consisting of α_1(V) and α_2(V) with or without α_3(V) chains, *COL5A3* is another candidate gene for EDS (although mutations in this gene have not been identified to date). Mutations in the gene encoding tenascin-X, a glycoprotein in the extrafibrillar matrix, can cause a recessive form of EDS with similar clinical findings of hyperextensible skin and joint hypermobility[21].

Mutations in genes that encode proteins involved in the post-translational modification of collagen (see above and Fig. 95.2) have been found to underlie other forms of EDS. For example, loss-of-function mutations in the lysyl hydroxylase 1 gene lead to abnormal lysyl hydroxylation and glycosylation of collagens in patients with the kyphoscoliosis type of EDS (type VIA), a recessive disease characterized by hyperextensible and fragile skin as well as hypermobile joints, scoliosis and ocular fragility. Recently, mutations in the gene encoding dermatan-4-sulfotransferase 1 (required for biosynthesis of dermatan sulfate) have been identified in patients with musculocontractural EDS (type VIB), which presents with craniofacial abnormalities, joint contractures and wrinkled palms together with the findings of the kyphoscoliosis type.

GENETIC EXTRACELLULAR MATRIX DISEASES OF THE SKIN				
Protein	**Gene**	**Inheritance**	**Disease**	**Phenotypic features in the skin* and other organs**
Collagen I (α1- and α2-chains)	*COL1A1*	AD	EDS, arthrochalasia (type VIIA)	***Skin hyperextensibility and fragility,*** joint hypermobility, congenital hip dislocation†
		AD	EDS, classic (type I; rare cause of this EDS type)	See below
	COL1A2	AD	EDS, arthrochalasia (type VIIB)	See above
		AR	EDS, cardiac valvular	Cardiac valve defects, otherwise similar to classic EDS (see below)
Collagen III	*COL3A1*	AD	EDS, vascular (type IV)	***Translucent, fragile skin with extensive bruising;*** arterial fragility, intestinal and uterine rupture‡
Collagen V (α1- and α2-chains)	*COL5A1* *COL5A2*	AD	EDS, classic (type I – severe; type II – milder)	***Skin hyperextensibility and fragility,*** joint hypermobility
Collagen VI	*COL6A1* *COL6A2* *COL6A3*	AD, AR	Ullrich disease	***Puffy skin,*** distal joint hypermobility, muscular dystrophy
Collagen VII	*COL7A1*	AD, AR	Dystrophic epidermolysis bullosa	***Skin fragility and blistering***
Collagen XVII	*COL17A1*	AR	Junctional epidermolysis bullosa	***Skin fragility and blistering***
Fibrillin-1	*FBN1*	AR	Marfan syndrome	***Striae,*** characteristic body habitus, aortic dilation/dissection‡
		AD	Congenital stiff skin syndrome	***Diffusely thick and hard skin, nodules on fingers,*** joint contractures, short stature, entrapment neuropathy
Elastin	*ELN*	AD > AR	Cutis laxa, AD > AR	***Lax, redundant skin***
Fibulin-4	*FBLN4*	AR	Cutis laxa, AR type I	***Lax, redundant skin;*** emphysema and arterial anomalies
Fibulin-5	*FBLN5*	AR > AD	Cutis laxa, AR type I > AD	***Lax, redundant skin;*** emphysema and arterial anomalies (AR form)
Latent TGF-β binding protein-4	*LTBP4*	AR	Cutis laxa with severe pulmonary, gastrointestinal and urinary abnormalities	***Lax, redundant skin;*** features in name of disorder, dysmorphic facies, joint hyperextensibility, hypotonia
TGF-β receptors 1 & 2	*TGFRB1* *TGFRB2*	AD	Loeys–Dietz syndrome (types I and II)‡	Aortic aneurysms, arterial tortuosity, skeletal anomalies, joint hypermobility; primarily in type II: ***translucent skin, easy bruising, atrophic scarring;*** primarily in type I: craniofacial anomalies
Tenascin-X	*TNXB*	AR	EDS, AR due to tenascin-X deficiency	***Skin hyperextensibility,*** joint hypermobility
		AD	EDS, hypermobility (type III)	***Variable skin hyperextensibility,*** joint hypermobility with recurrent dislocations
Extracellular matrix protein-1	*ECM1*	AR	Lipoid proteinosis	Hyalin deposition in the dermis and submucosal tissues, hoarse voice, intracranial calcifications
ABCC6 transporter	*ABCC6*	AR	Pseudoxanthoma elasticum (PXE)	***Yellowish papules, lax skin,*** retinal angioid streaks, cardiovascular disease
ATPase, $Cu2^{+}$-transporting, α-polypeptide	*ATP7A*	X-R	Occipital horn syndrome	***Lax skin,*** tortuous arteries, joint hypermobility, occipital calcifications
Solute carrier family 2, member 10 (a glucose transporter)	*SLC2A10*	AR	Arterial tortuosity syndrome	***Lax skin, ± telangiectasias on the cheeks,*** tortuous arteries, joint hypermobility
Solute carrier family 39, member 13 (a zinc transporter)	*SLC39A13*	AR	EDS-like spondylocheirodysplasia	***Skin hyperextensibility and fragility, atrophic scarring, wrinkled palms,*** joint hypermobility, growth retardation
Lysyl hydroxylase 1	*PLOD1*	AR	EDS, kyphoscoliosis (type VIA)	***Skin hyperextensibility and fragility,*** ocular fragility, joint hypermobility, scoliosis
Lysyl hydroxylase 3	*PLOD3*	AR	Bone fragility with contractures, arterial rupture and deafness	Features in name of disorder, acral ***blistering, easy bruising,*** dysmorphic facies, hypoplastic nails, osteopenia, cataracts, delayed growth and development
		AD	Epidermolysis bullosa simplex-like phenotype	***Skin fragility and blistering***
ADAMTS-2 (procollagen N-proteinase)	*ADAMTS2*	AR	EDS, dermatosparaxis (type VIIC)	***Sagging, doughy, fragile skin;*** characteristic facies

*Elastosis perforans serpiginosa can also develop in patients with EDS and pseudoxanthoma elasticum.
† A phenotype with features of both EDS and osteogenesis imperfecta has also been reported.
‡ The phenotype of Loeys–Dietz syndrome can mimic Marfan syndrome (type I) or vascular EDS (type II).

Table 95.5 Genetic extracellular matrix diseases of the skin. Diseases and phenotypic features are colored based on the primary cutaneous manifestation (when applicable) as follows: ***orange***, hyperextensible skin (as in classic EDS); ***pink***, extensively bruised skin (as in vascular EDS); ***peach–tan***, skin fragility with blistering (as in epidermolysis bullosa); ***light blue***, lax skin (as in cutis laxa); ***dark blue***, yellowish papules ± lax skin (as in pseudoxanthoma elasticum). ABCC6, ATP-binding cassette subfamily C member 6; AD, autosomal dominant; ADAM, a disintegrin and metalloproteinase; AR, autosomal recessive; EDS, Ehlers–Danlos syndrome; TGF, transforming growth factor; X-R, X-linked recessive.

Continued

GENETIC EXTRACELLULAR MATRIX DISEASES OF THE SKIN				
Protein	**Gene**	**Inheritance**	**Disease**	**Phenotypic features in the skin* and other organs**
Dermatan-4-sulfotransferase 1	*CHST14*	AR	EDS, musculocontractural[§]	***Skin hyperextensibility and fragility, wrinkled palms,*** ocular fragility, joint contractures and hypermobility, scoliosis, craniofacial abnormalities
Galactosyltransferase-I	*B4GALT7*	AR	EDS, progeroid	***Skin hyperextensibility,*** joint hypermobility, progeroid facies, osteopenia, mental and growth retardation
Vacuolar H^+-A2 subunit	*ATP6V0A2*	AR	Cutis laxa, AR type IIA Wrinkly skin syndrome	***Lax skin,*** facial dysmorphism, large fontanelles, microcephaly, delayed development ± growth, strabismus, joint hypermobility
Pyrroline-5-carboxylate reductase 1	*PYCR1*	AR	Cutis laxa, AR type IIB De Barsy syndrome (DBS)	***Lax skin,*** facial dysmorphism, large fontanelles, microcephaly, delayed development and growth, joint hypermobility; corneal opacities, cataracts & athetosis in DBS
Pyrroline-5-carboxylate synthetase	*ALDH18A1*	AR	Mental retardation, joint hypermobility and ***skin laxity***	Features in name of disorder, with or without hyperammonemia
γ-glutamyl carboxylase	*GGCX*	AR	PXE-like disorder with multiple coagulation factor deficiency	***Yellowish papules, lax skin,*** retinal angioid streaks, cardiovascular disease, bleeding diathesis
Golgin, RAB6-interacting	*GORAB*	AR	Gerodermia osteodysplastica	***Lax skin (primarily on dorsal hands and feet),*** progeroid facies with prognathism, short stature, osteoporosis
Ras and Rab interactor 2	*RIN2*	AR	Macrocephaly, ***alopecia, cutis laxa*** and scoliosis (MACS)	Features in name of disorder, facial dysmorphism, gingival hypertrophy, joint hyperextensibility
Filamin A (actin-binding protein 280)	*FLNA*	X-D	EDS, periventricular nodular heterotopia variant	***Variable skin hyperextensibility,*** aortic dilation, periventricular nodular heterotopia, joint hypermobility

*Elastosis perforans serpiginosa can also develop in patients with EDS and pseudoxanthoma elasticum.
[§]Exists on a spectrum with adducted thumb-clubfoot syndrome, which is caused by mutations in the same gene.

Table 95.5 Genetic extracellular matrix diseases of the skin (cont'd). Diseases and phenotypic features are colored based on the primary cutaneous manifestation (when applicable) as follows: ***orange***, hyperextensible skin (as in classic EDS); ***light blue***, lax skin (as in cutis laxa); ***dark blue***, yellowish papules ± lax skin (as in pseudoxanthoma elasticum). *ALDH18A1*, aldehyde dehydrogenase 18 family, member A1; AR, autosomal recessive; *CHST14*, carbohydrate sulfotransferase 14; EDS, Ehlers–Danlos syndrome; X-D, X-linked dominant.

Failure to cleave the N-propeptide from procollagen I causes the arthrochalasia type of EDS (types VIIA & VIIB), a dominant disorder that features severe joint hypermobility, including dislocations. The persistence of this propeptide on collagen I molecules drastically alters fibrillogenesis, and the fibrils that form are thin and highly irregular in diameter. Affected individuals typically have a splice-site mutation in the *COL1A1* or *COL1A2* gene that causes exon skipping and elimination of the cleavage site for ADAMTS-2 (procollagen I N-proteinase) in the proα_1(I) or proα_2(I) chain[21]. Loss-of-function mutations in the *ADAMTS2* gene itself cause another form of EDS, the dermatosparaxis type (type VIIC; Fig. 95.9B), in which (similar to collagen I in the arthrochalasia type), procollagen N-propeptides persist and sterically disturb polymerization of the collagen fibrils in the skin and other tissues[21]. This recessive condition has a distinct, severe phenotype that includes characteristic facies and sagging, fragile skin with a doughy consistency.

Cutis laxa

Cutis laxa is an uncommon ECM disease characterized by genetic heterogeneity and clinical variability (see Ch. 97); acquired variants also exist[19]. In all cases, the primary diagnostic feature is loose, hyperextensible skin with decreased resilience and elasticity, leading to an appearance of "too large skin" and premature aging (Fig. 95.9C). The skin changes are often accompanied by extracutaneous manifestations, including pulmonary emphysema, bladder diverticula and pulmonary artery stenosis. Histologically, there is marked fragmentation or diminution of elastic fibers.

Multiple genes are involved in the pathogenesis of recessive and dominant forms of cutis laxa (see Table 95.5), including those that encode the elastic fiber components elastin, fibulin-4 and fibulin-5[19,22,23]. A severe developmental syndrome featuring cutis laxa and extensive pulmonary, gastrointestinal and urinary abnormalities is caused by mutations in the latent TGF-β binding protein-4 gene (*LTBP4*), demonstrating that the role of TGF-β signaling in ECM assembly is essential for proper development[24].

Other inherited disorders are characterized by secondary effects on elastic fiber deposition or degradation[19]. For example, elastic fibers are calcified and fragmented secondary to decreased activity of anti-mineralization proteins in PXE (see below and Ch. 97), and elastic fibers are prematurely degraded due to unregulated elastase activity in patients with α_1-antitrypsin deficiency and some forms of acquired atrophoderma. Decreased or aberrant deposition of elastic fibers in certain tissues is also characteristic of Marfan syndrome.

Marfan syndrome

Fibrillin-1 is the major component of microfibrils and has an important structural role in elastic fibers. The highly homologous fibrillin-2 exhibits different spatial and temporal expression during development, and the functional relationship between the two molecules is not fully understood. Fibrillin-1 mutations underlie Marfan syndrome, an autosomal dominant disorder with variable connective tissue weakness of the skin as well as skeletal, ocular and cardiovascular systems[10,19,21]. The cutaneous manifestations can include striae and elastosis perforans serpiginosa. In addition to structural disturbances in elastic fibers and microfibrils due to mutant fibrillin, emerging data suggest that fibrillin mutations preclude or decrease the sequestration of latent TGF-β complexes (see above), thus rendering them more prone to activation. This leads to unproductive tissue remodeling, abnormal cell behavior and loss of ECM integrity[10]. Mutations in the gene encoding fibrillin-2 lead to a Marfan syndrome-like condition called congenital contractural arachnodactyly, which is characterized by skeletal abnormalities in the absence of ocular and cardiovascular features[21].

Heterozygous mutations in the genes encoding the TGF-β receptors 1 and 2 underlie Loeys–Dietz syndrome. Type I Loeys–Dietz syndrome is characterized by aortic aneurysms, generalized arterial tortuosity, craniofacial malformations (e.g. bifid uvula, cleft palate, hypertelorism), skeletal anomalies and joint laxity. Type II Loeys–Dietz syndrome has less craniofacial involvement and also features cutaneous manifestations similar to those of the vascular type of EDS, including translucent

Fig. 95.9 Phenotypic manifestations of genetic extracellular matrix defects. A Classic Ehlers–Danlos syndrome (type II) with slightly overstretchable skin results from mutations in the collagen V genes. **B** Dermatosparaxis showing fragile skin with purpura and a "doughy" texture due to mutations in the gene for ADAMTS-2. **C** Cutis laxa can be caused by mutations in several different genes, including those encoding the elastic fiber components elastin, fibulin-4 and fibulin-5. **D** Junctional epidermolysis bullosa with skin blisters after minimal friction can be caused by mutations in the collagen XVII gene. *B, Courtesy, Julie V Schaffer, MD. C, Courtesy, Thomas Schwarz, MD.*

skin, easy bruising and atrophic scarring[20,21]. The phenotypic overlap with Marfan syndrome and vascular EDS is not surprising considering the association between fibrillin and latent TGF-β and the role of TGF-β in regulating collagen expression.

Pseudoxanthoma elasticum

PXE (see Ch. 97) is a heritable disorder characterized by cutaneous, vascular and ocular (classically angioid streaks) involvement that results from the accumulation of fragmented and calcified elastic fibers in the dermis, arterial walls and Bruch's membrane, respectively. The skin findings – laxity and yellowish papules and plaques – are the most common and often the earliest manifestations of PXE.

Although PXE has traditionally been considered as a prototypic heritable ECM disorder, it is caused by mutations in the gene that encodes the ATP-binding cassette (ABC) subfamily C member 6 (ABCC6) transmembrane transporter, which is primarily expressed in the liver[25]. Mutations in the γ-glutamyl carboxylase gene (*GGCX*) can also lead to a PXE-like phenotype together with deficiency in vitamin K-dependent coagulation factors. GGCX catalyzes the vitamin K-dependent γ-glutamyl carboxylation that activates the matrix gla protein (MGP), which functions as an inhibitor of pathologic mineralization, as well as coagulation factors. Although the substrates of ABCC6 remain to be determined, it is speculated that this transporter may export a GGCX cofactor (e.g. a vitamin K–glutathione conjugate) from the liver into the circulation, with loss of ABCC6 function resulting in reduced activation of MGP and, as a consequence, connective tissue calcification[25].

Epidermolysis bullosa

EB represents a diverse group of hereditary diseases characterized by mechanical fragility of the skin that results in cutaneous blister formation (see Ch. 32)[18,26]. Mutations in the collagen VII gene (*COL7A1*) cause both dominant and recessive forms of dystrophic EB[27]. Because collagen VII is a component of the anchoring fibrils, cleavage occurs at the level of these fibrils in the uppermost dermis (just below the lamina densa). Patients with severe forms of recessive dystrophic EB are nullizygotes harboring mutations that lead to premature termination codons[27]. As a consequence, anchoring fibrils and collagen VII are absent from the skin. Milder forms of dystrophic EB are associated with missense mutations in one or both copies of the *COL7A1* gene. When heterozygous, such mutations often exert dominant-negative effects, since structurally aberrant collagen VII molecules are assembled and incorporated into the anchoring fibrils, rendering them functionally inadequate.

Mutations in the *COL17A1* gene encoding the α_1(XVII) chain of collagen XVII, a homotrimeric transmembrane collagen localized to the hemidesmosome-anchoring filament complex of basal keratinocytes[7], can cause junctional EB. This recessive EB subtype is characterized by

cleavage within the lamina lucida of the epidermal basement membrane. Patients with two null alleles of *COL17A1* tend to have widespread blistering (generalized non-Herlitz junctional EB; Fig. 95.9D), whereas those with two missense mutations and some preservation of collagen XVII function exhibit milder clinical phenotypes (localized non-Herlitz junctional EB)[28].

Laminin 332 (formerly known as laminin 5) is a major structural component of the lamina densa, where it secures epidermal adhesion by linking $\alpha_6\beta_4$ integrin on the cell surface to collagen VII of the anchoring fibrils. Like defects in collagen XVII, mutations in the genes encoding the three polypeptide chains of laminin 332 cause junctional EB. The most severe form, Herlitz junctional EB, is often fatal during infancy; it results from null mutations and a complete lack of laminin 332 in the skin. Missense mutations are associated with milder forms of the disease (e.g. generalized non-Herlitz junctional EB)[28].

Other hereditary matrix diseases with skin symptoms

Muscular dystrophies (Ullrich disease [more severe], Bethlem myopathy [milder]) can be caused by mutations in the *COL6A1, COL6A2* and *COL6A3* genes encoding the α_1(VI), α_2(VI) and α_3(VI) chains of collagen VI[19]. This collagen forms beaded filaments/microfibrils in several tissues, including the muscle and skin. Extramuscular manifestations – a puffy consistency of the skin and joint hyperlaxity – likely reflect abnormalities of the microfibrillar networks in the dermis and synovia.

Mutations in the extracellular matrix protein-1 gene (*ECM1*) cause lipoid proteinosis, a recessive multi-organ disease characterized by the accumulation of hyalinized material in many tissues, including the dermis (see Ch. 48)[29]. ECM-1 is a 85 kD glycoprotein that binds to fibulins, perlecan and laminin 332[30].

Loss-of-function mutations in both copies of the *PLOD3* gene encoding lysyl hydroxylase 3, an enzyme with important roles (including glucosyltransferase and galactosyltransferase activities) in the post-translational modification of collagens[31], have been found to underlie a severe, multi-organ connective tissue disease which features fragile skin that is prone to blistering as well as bruising (see Table 95.5). *PLOD3* haploinsufficiency has also been documented in a family with a phenotype limited to skin blistering. *In vitro* studies have demonstrated that even a moderate decrease in lysyl hydroxylase 3 activity has deleterious consequences for the deposition and organization of the ECM[32].

Extracellular matrix components as autoantigens

Several ECM components are targeted in autoimmune diseases affecting the kidney, cartilage and skin (Table 95.6). Autoantigens in these conditions include the α_3- and α_5-chains of collagen IV in Goodpasture disease[33], collagen II in relapsing polychondritis, and collagens VII and XVII in the autoimmune blistering diseases EB acquisita and bullous pemphigoid, respectively[34]. The autoantigen in p200 pemphigoid, a novel autoimmune subepidermal blistering disease, was recently identified as the γ1-chain of laminin located at the dermal–epidermal junction[35].

Antibodies to fibrillin-1 have been described in patients with systemic sclerosis (especially individuals of Choctaw Native American or Japanese descent) and morphea (especially those with linear and generalized subtypes). The mutated protein in lipoid proteinosis, ECM-1, is the target of autoantibodies in patients with lichen sclerosus, which also features dermal hyalinization[29].

The immunodominant epitopes in autoimmune disorders are often localized to one or several distinct structural domains and, therefore, recombinant domains can be employed for precise diagnostic testing. It is thought that binding of autoantibodies to ECM components disturbs their supramolecular aggregation or ligand binding, which in turn leads to functional deficiency and corresponding clinical symptoms.

EXTRACELLULAR MATRIX COMPONENTS AS TARGETS IN AUTOIMMUNE DISEASES

Disease(s)	Autoantigen(s)	Biologic and clinical features
Goodpasture disease	Collagen IV, α_3- and α_5-chains	Glomerulonephritis, pneumonitis with hemoptysis
Relapsing polychondritis, arthritis	Collagen II; collagen IX	Chondritis of ear, larynx and trachea; arthritis
Pemphigoid (various subtypes)	Collagen XVII (BP, PG, MMP)*; laminin 332 (MMP); laminin-γ1 chain (p200 pemphigoid)	Skin blistering
Epidermolysis bullosa acquisita	Collagen VII	Skin blistering, fragility
Bullous eruption of systemic lupus erythematosus (SLE)	Collagen VII	Skin blistering with underlying SLE
Scleroderma†	Fibrillin-1; PDGF receptor	Skin fibrosis
Lichen sclerosus	Extracellular matrix (ECM) protein-1	Inflammation, epidermal atrophy, hyalinization of the dermis

*Also the autoantigen in linear IgA bullous dermatosis.
†Not confirmed in large patient cohorts.

Table 95.6 Extracellular matrix components as targets in autoimmune diseases. BP, bullous pemphigoid; PDGF, platelet-derived growth factor; MMP, mucous membrane (cicatricial) pemphigoid; PG, pemphigoid gestationis.

Skin aging and other acquired ECM abnormalities

Changes in the dermal ECM contribute to both chronologic and photoinduced skin aging. Morphologic hallmarks of aged skin include reduced microfibrils in the papillary dermis, disorganized elastic fibers, and reduction and weakening of other ECM fibril networks. Although the molecular details of these ECM changes are not fully understood, it is generally accepted that the structurally perturbed dermal networks cannot bind adequate amounts of hyaluronic acid and, consequently, water, which leads to lax and wrinkled skin. The biosynthetic activity of all cells diminishes during aging, but reduced synthesis of dermal collagens by fibroblasts is a particularly prominent feature. This has been shown to be mediated by decreased TGF-β and connective tissue growth factor (CTGF) signaling[36]. Increased degradation of ECM components also occurs and destabilizes network structures. The deleterious effects of UV irradiation include release of cytokines from the epidermis and generation of reactive oxygen species. These mediators induce inflammatory processes and stimulate expression and activation of a spectrum of matrix metalloproteinases and serine proteinases such as elastase, which can degrade ECM networks[37].

Weakened ECMs lead to disturbed wound healing and a bruising tendency in scurvy, a disease resulting from an insufficient supply of ascorbic acid (vitamin C). This vitamin is an essential cofactor for prolyl and lysyl hydroxylases, which modify collagens during their biosynthesis and are required for cross-linking[4].

In fibrotic disorders such as scleroderma (systemic sclerosis) and keloids, thickened skin reflects excessive ECM in the dermis. The reasons for the accumulation are not fully understood; inflammation-mediated upregulation of ECM synthesis (e.g. collagen, fibrillins, proteoglycans) via TGF-β and CTGF are believed be causative mechanisms in scleroderma (see Ch. 43). A keloid is an overgrowth of dense fibrous tissue in the skin as a result of trauma. The cellularity of keloids is increased, and the ECM shows abnormal thin fibrils that are haphazardly organized in dense nodules. Various abnormalities of ECM biosynthesis have been measured in keloid fibroblasts *in vitro*, and matrix assembly is perturbed[38]. Gene profiling studies indicated a role for multiple fibrosis-related pathways in the pathogenesis of keloids[39], but the regulatory mechanisms leading to excessive ECM accumulation still remain unclear. A genetic predisposition for keloid formation seems to exist. Among Caucasians, 5–10% of individuals with keloids have a positive family history; among Africans, the prevalence is much higher.

Animal Models

Mouse models for ECM diseases have produced new insights into pathomechanisms, allowed further assessment of abnormalities observed in human diseases, and enabled testing of novel therapeutic approaches[40]. For example, mice with a targeted mutation in one

collagen V gene were noted to have thin, fragile skin with disorganized and loosely packed fibrils, which pointed to collagen V genes as candidates for EDS prior to the detection of human mutations. Likewise, a tenascin-X-deficient mouse reproduced the symptoms of human recessive EDS, i.e. greatly disturbed biomechanical properties of the skin but milder joint abnormalities.

For fibrillin-1, transgenic mouse models have been used to discern genotype–phenotype correlations. Analyses of different models revealed an association between fibrillin-1, microfibril assembly and TGF-β signaling, showing that a defect in the latter is central to Marfan syndrome pathogenesis and phenotypic variability[9,10].

Targeted ablation of the elastin gene in mice leads to fatal obstructive arterial disease characterized by subendothelial cell proliferation and reorganization of smooth muscle, suggesting that elastin has a role in regulating cellular proliferation[8]. The phenotype of heterozygous mice suggested that human supravalvular aortic stenosis may be caused by functional hemizygosity of the elastin gene, which was confirmed by mutational analysis in humans. Of note, while loss-of-function elastin mutations that lead to haploinsufficiency are associated with supravalvular aortic stenosis, cutis laxa can result from dominant-negative missense mutations in the elastin gene.

Collagen VII-deficient mice recapitulate the clinical, genetic, immunohistochemical and ultrastructural characteristics of recessive dystrophic EB in humans[19]. Collagen VII knockout mice die during the first 2 weeks of life, while mice with hypomorphic mutations have a severe phenotype but live into adulthood[41]. These mice have provided significant information regarding the molecular pathogenesis of recessive dystrophic EB, and they have become useful for testing cellular and molecular approaches to therapy[42]. Mice lacking collagen XVII exhibit a moderately severe form of junctional EB[43] and are also being used to study novel therapeutic approaches.

Mice harboring disrupted proteoglycan genes have demonstrated the importance of these molecules for cutaneous tautness and integrity[11]. The decorin knockout mouse has fragile skin with markedly reduced tensile strength, associated with coarser, irregular ECM fibers in the skin and tendons; these findings established the fundamental role for decorin in regulating collagen fibrillogenesis *in vivo*. Mice with a disrupted syndecan 4 gene have a significant wound-healing defect and impaired angiogenesis within granulation tissue, suggesting that this cell surface proteoglycan has an important role in wound healing and angiogenesis.

Abnormalities in collagen-processing enzymes also occur spontaneously in animals. Bovine dermatosparaxis is a recessively inherited connective tissue disorder that, like the human form of this disease, features extreme fragility and droopiness of the skin as well as joint laxity. Both human and bovine dermatosparaxis result from mutations in the gene encoding ADAMTS-2, which excises the N-propeptide of procollagens I and II[19].

Potential for Biologically Valid Molecular Therapies

Clarification of the molecular mechanisms underlying ECM disorders forms a basis for novel therapeutic approaches. Diseases well suited for such therapies include recessive forms of EB caused by a lack of collagen VII, collagen XVII or laminin 332. Currently, preclinical and clinical pilot trials on gene-, cell- and protein-based therapies are ongoing for recessive dystrophic and junctional EB (reviewed in refs 44 & 45).

Gene therapy with delivery of gene-corrected stem cells or vectors directing the expression of the missing protein has the advantage of continuous protein biosynthesis in the skin but may carry a risk of oncogenesis. Retroviruses, lentiviruses and non-viral transposon-mediated gene transfer have been successfully used to restore collagen VII or laminin 332 synthesis in keratinocytes *in vitro*. In the first human pilot study on EB, laminin-β3-deficient skin of an adult patient was corrected by transplantation of stem cell-enriched epidermal grafts transduced *ex vivo* with a retroviral vector expressing normal *LAMB3* cDNA. The treatment resulted in sustained synthesis and proper assembly of functional laminin 332 and, clinically, an absence of blistering in the corrected epidermis.

For recessive dystrophic EB, cell- and protein-based therapies have also shown promise. Murine and human studies have demonstrated that intradermal injection of allogeneic fibroblasts leads to increased deposition of collagen VII at the dermal–epidermal junction and clinical improvement for several months. Intriguingly, a systemic approach using bone marrow transplantation after total or partial myeloablation has resulted in substantial proportions of donor cells in the skin, increased collagen VII deposition at the dermal–epidermal junction and variably decreased blistering in children with recessive dystrophic EB. Protein therapy with intradermal injection of recombinant human collagen VII (which has a long half-life) has been shown to result in correct protein deposition within anchoring fibrils and reduced blistering in mouse models of dystrophic EB.

For the treatment of dominant disorders, strategies to silence expression of the mutated allele (preventing dominant-negative effects) or to supplement with normal protein (correcting haploinsufficiency) hold promise[46].

Better understanding of molecular and cellular disease mechanisms disclosed an unexpected pharmacologic approach to the treatment of Marfan syndrome[47]. Since excessive TGF-β signaling contributes to the development of aortic aneurysms in individuals with this condition, it was hypothesized that TGF-β antagonists might prevent or partially reverse this disease manifestation. Indeed, angiotensin II receptor blockers are now successfully employed to prevent aortic root dilation in patients with Marfan syndrome[48].

Future development of successful therapies for connective tissue disorders will also depend on the progress in our understanding of "alloy" formation by matrix macromolecules. This endeavor will be facilitated not only by the analysis of aggregate formation by matrix macromolecules or their mixtures *in vitro*, but also by the elucidation of further genetic defects and their consequences in animal or human diseases, as well as the generation of transgenic animals as models for human disorders. This combined information will help us to understand and treat not only inherited ECM diseases but also many common disorders currently considered as acquired.

REFERENCES

1. Bruckner P. Suprastructures of extracellular matrices: paradigms of functions controlled by aggregates rather than molecules. Cell Tissue Res. 2010;339:7–18.
2. Hynes RO. The extracellular matrix: not just pretty fibrils. Science. 2009;326:1216–19.
3. Gordon MK, Hahn RA. Collagens. Cell Tissue Res. 2010;339:247–57.
4. Myllyharju J, Kivirikko KI. Collagens, modifying enzymes and their mutations in humans, flies and worms. Trends Genet. 2004;20:33–43.
5. Canty EG, Kadler KE. Procollagen trafficking, processing and fibrillogenesis. J Cell Sci. 2005;118:1341–53.
6. Raghunath M, Hopfner B, Aeschlimann D, et al. Cross-linking of the dermo-epidermal junction of skin regenerating from keratinocyte autografts. Anchoring fibrils are a target for tissue transglutaminase. J Clin Invest. 1996;98:1174–84.
7. Has C, Kern JS. Collagen XVII. Dermatol Clin. 2010;28:61–6.
8. Wagenseil JE, Mecham RP. New insights into elastic fiber assembly. Birth Defects Res C Embryo Today. 2007;81:229–40.
9. Ramirez F, Sakai LY. Biogenesis and function of fibrillin assemblies. Cell Tissue Res. 2010;339:71–82.
10. Ramirez F, Dietz HC. Extracellular microfibrils in vertebrate development and disease processes. J Biol Chem. 2009;284:14677–81.
11. Schaefer L, Schaefer RM. Proteoglycans: from structural compounds to signaling molecules. Cell Tissue Res. 2010;339:237–46.
12. Iozzo RV. Basement membrane proteoglycans: from cellar to ceiling. Nat Rev Mol Cell Biol. 2005;6:646–56.
13. Miner JH. Laminins and their roles in mammals. Microsc Res Tech. 2008;71:349–56.
14. Durbeej M. Laminins. Cell Tissue Res. 2010;339:259–68.
15. Aumailley M, Bruckner-Tuderman L, Carter WG, et al. A simplified laminin nomenclature. Matrix Biol. 2005;24:326–32.
16. Humphries JD, Byron A, Humphries MJ. Integrin ligands at a glance. J Cell Sci. 2006;119:3901–3.
17. Legate KR, Wickström SA, Fässler R. Genetic and cell biological analysis of integrin outside-in signaling. Genes Dev. 2009;23:397–418.
18. Aumailley M, Has C, Tunggal L, Bruckner-Tuderman L. Molecular basis of inherited skin-blistering disorders, and therapeutic implications. Expert Rev Mol Med. 2006;8:1–21.

19. Royce P, Steinmann B (eds). Connective Tissue and its Heritable Disorders. Molecular, Genetic and Medical Aspects, 2nd edn. New York: Wiley-Liss Inc, 2002.
20. Malfait F, De Paepe A. Bleeding in the heritable connective tissue disorders: mechanisms, diagnosis and treatment. Blood Rev. 2009;23:191–7.
21. Callewaert B, Malfait F, Loeys B, et al. Ehlers-Danlos syndromes and Marfan syndrome. Best Pract Res Clin Rheumatol. 2008;22:165–89.
22. Morava E, Guillard M, Lefeber DJ, et al. Autosomal recessive cutis laxa syndrome revisited. Eur J Hum Genet. 2009;17:1099–110.
23. Mégarbané H, Florence J, Oliver Sass J, et al. An autosomal-recessive form of cutis laxa is due to homozygous elastin mutations, and the phenotype may be modified by a heterozygous fibulin 5 polymorphism. J Invest Dermatol. 2009;129:1650–5.
24. Urban Z, Hucthagowder V, Schürmann N, et al. Mutations in *LTBP4* cause a syndrome of impaired pulmonary, gastrointestinal, genitourinary, musculoskeletal, and dermal development. Am J Hum Genet. 2009;85:593–605.
25. Uitto J, Li Q, Jiang Q. Pseudoxanthoma elasticum: molecular genetics and putative pathomechanisms. J Invest Dermatol. 2010;130:661–70.
26. Fine JD, Eady RA, Bauer EA, et al. The classification of inherited epidermolysis bullosa (EB): report of the Third International Consensus Meeting on Diagnosis and Classification of EB. J Am Acad Dermatol. 2008;58:931–50.
27. Bruckner-Tuderman L. Dystrophic epidermolysis bullosa: pathogenesis and clinical features. Dermatol Clin. 2010;28:107–14.
28. Chaudhari P, Marinkovich MP. What's new in blistering disorders? Curr Allergy Asthma Rep. 2007;7:255–63.
29. Chan I, Liu L, Hamada T, et al. The molecular basis of lipoid proteinosis: mutations in extracellular matrix protein 1. Exp Dermatol. 2007;16:881–90.
30. Sercu S, Zhang L, Merregaert J. The extracellular matrix protein 1: its molecular interaction and implication in tumor progression. Cancer Invest. 2008;26:375–84.
31. Salo AM, Cox H, Farndon P, et al. A connective tissue disorder caused by mutations of the lysyl hydroxylase 3 gene. Am J Hum Genet. 2008;83:495–503.
32. Risteli M, Ruotsalainen H, Salo AM, et al. Reduction of lysyl hydroxylase 3 causes deleterious changes in the deposition and organization of extracellular matrix. J Biol Chem. 2009;284:28204–11.
33. Pedchenko V, Bondar O, Fogo AB, et al. Molecular architecture of the Goodpasture autoantigen in anti-GBM nephritis. N Engl J Med. 2010;363:343–54.
34. Hertl M, Eming R, Veldman C. T cell control in autoimmune bullous skin disorders. J Clin Invest. 2006;116:1159–66.
35. Dainichi T, Kurono S, Ohyama B, et al. Anti-laminin gamma-1 pemphigoid. Proc Natl Acad Sci U S A. 2009;106:2800–5.
36. Quan T, Shao Y, He T, et al. Reduced expression of connective tissue growth factor (CTGF/CCN2) mediates collagen loss in chronologically aged human skin. J Invest Dermatol. 2010;130:415–24.
37. Quan T, Qin Z, Xia W, et al. Matrix-degrading metalloproteinases in photoaging. J Invest Dermatol Symp Proc. 2009;14:20–4.
38. Ikeda M, Naitoh M, Kubota H, et al. Elastic fiber assembly is disrupted by excessive accumulation of chondroitin sulfate in the human dermal fibrotic disease, keloid. Biochem Biophys Res Commun. 2009;390:1221–8.
39. Smith JC, Boone BE, Opalenik SR, et al. Gene profiling of keloid fibroblasts shows altered expression in multiple fibrosis-associated pathways. J Invest Dermatol. 2008;128:1298–310.
40. Aszódi A, Legate KR, Nakchbandi I, et al. What mouse mutants teach us about extracellular matrix function. Annu Rev Cell Dev Biol. 2006;22:591–621.
41. Fritsch A, Loeckermann S, Kern JS, et al. A hypomorphic mouse model of dystrophic epidermolysis bullosa reveals mechanisms of disease and response to fibroblast therapy. J Clin Invest. 2008;118:1669–79.
42. Kern JS, Loeckermann S, Fritsch A, et al. Mechanisms of fibroblast cell therapy for dystrophic epidermolysis bullosa: high stability of collagen VII favors long-term skin integrity. Mol Ther. 2009;17:1605–15.
43. Nishie W, Sawamura D, Goto M, et al. Humanization of autoantigen. Nat Med. 2007;13:378–83.
44. Uitto J, McGrath JA, Rodek U, et al. Progress in epidermolysis bullosa research: toward treatment and cure. J Invest Dermatol. 2010;130:1778–84.
45. De Luca M, Pellegrini G, Mavilio F. Gene therapy of inherited skin adhesion disorders: a critical overview. Br J Dermatol. 2009;161:19–24.
46. Fritsch A, Spassov S, Elfert S, et al. Dominant-negative effects of *COL7A1* mutations can be rescued by controlled overexpression of normal collagen VII. J Biol Chem. 2009;284:30248–56.
47. Habashi JP, Judge DP, Holm TM, et al. Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. Science. 2006;312:117–21.
48. Brooke BS, Habashi JP, Judge DP, et al. Angiotensin II blockade and aortic-root dilation in Marfan's syndrome. N Engl J Med. 2008;358:2787–95.

96 Perforating Diseases

Ronald P Rapini

Synonyms: ■ Hyperkeratosis follicularis et parafollicularis in cutem penetrans: Kyrle disease ■ Acquired perforating dermatosis: acquired reactive perforating collagenosis, acquired reactive perforating dermatosis, perforating disorder of uremia

Key features

- Group of disorders with transepidermal elimination of collagen, elastic tissue or necrotic connective tissue
- Papules or nodules with keratotic plugs
- Elastosis perforans serpiginosa is associated with genetic diseases or penicillamine administration and involves elastic tissue; lesions are typically annular and most commonly occur on the neck
- Reactive perforating collagenosis occurs after minor trauma, involves collagen, and often involves the upper extremities
- Acquired perforating dermatosis is almost always associated with diabetes mellitus or the pruritus of renal failure; it favors the lower extremities of adults
- Broadband or narrowband UVB phototherapy appears to be the most effective treatment for acquired perforating dermatosis

INTRODUCTION

The perforating diseases (Table 96.1) are a group of papulonodular skin disorders characterized by keratotic plugs or crusts in which dermal connective tissue "perforates" or is eliminated through the epidermis. There are two prototypic perforating diseases, both of which can be inherited. They are reactive perforating collagenosis (RPC), in which primarily collagen fibers perforate the epidermis[1], and elastosis perforans serpiginosa (EPS), in which primarily elastic fibers perforate. The third major perforating disease is acquired perforating dermatosis, which usually develops during adulthood in association with diabetes mellitus and/or the pruritus of renal failure[2]. Many textbooks traditionally list "perforating folliculitis" as the fourth perforating disease[3], but, in the opinion of the author, this seems unjustified. It does not appear to be a specific entity, since perforation or rupture of follicles occurs in a wide variety of diseases classified as folliculitis, regardless of whether the pathogenesis involves bacteria, fungi, *Demodex* mites, physical trauma or other mechanisms.

Some authorities have expanded the concept of the preceding so-called "primary" perforating diseases to include a variety of unrelated "secondary" perforating disorders in which transepidermal elimination of a substance occurs as a secondary component of a primary dermatosis (Table 96.2). As in most of the preceding perforating disorders, the epidermis often becomes hyperplastic, eventually surrounds the material to be extruded, and subsequently causes the material's elimination via normal keratinocyte maturation. Some of these disorders are discussed elsewhere in this text and involve perforation of endogenous substances, exogenous foreign material, infectious organisms, granulomas, and even neoplastic cells[4].

HISTORY

In 1916, Kyrle reported a diabetic woman with generalized hyperkeratotic nodules, which he called "hyperkeratosis follicularis et parafollicularis in cutem penetrans". Lutz first described EPS as "keratosis follicularis serpiginosa" in 1953, and, in 1955, Miescher described the histologic findings, naming it "elastoma intrapapillare perforans verruciforme". Mehregan, Schwartz and Livingood reported the first child with RPC in 1967. Mehregan and Coskey expanded the concept of perforating disease to include perforating folliculitis in their article in 1968.

EPIDEMIOLOGY

The perforating diseases are found worldwide, without any clear racial predilection. The very rare childhood-onset form of RPC is commonly familial, and childhood-onset EPS is occasionally familial. Although the exact inheritance pattern for both is still uncertain, isolated inherited EPS may have an autosomal dominant pattern. EPS affects nearly four times more men than women, but the sex distribution is about equal in RPC and acquired perforating dermatosis. Perforating folliculitis is said to be more common in women. In patients receiving maintenance hemodialysis, acquired perforating dermatosis is observed in an estimated 4.5% to 11%[5].

PATHOGENESIS

The precise pathogenesis for the perforating disorders is unknown. As it is unlikely that dermal connective tissue or hair shafts actively perforate into the epithelium, some have argued that "transepidermal elimination" is a more accurate term. The term "perforating" is embedded in the dermatologic lexicon, however, and is easier to say. Epithelium becomes hyperplastic and eventually surrounds the abnormal connective tissue, just as it appears to do with wood splinters or other foreign bodies. In acquired perforating dermatosis, pruritus probably leads to chronic scratching, which results in epithelial hyperplasia, as in prurigo nodularis. Indeed, many of the patients have common prurigo nodules in addition to classic perforating lesions. The possibility has been raised that enlargement of a hyperkeratotic plug could lead to penetration through the base of the hyperplastic epidermis, i.e. the perforation is caused by the plug above rather than being due to the abnormal connective tissue below.

Primary perforating diseases may be due to either genetic or acquired abnormalities of collagen or elastic fibers. In EPS, as well as some cases of acquired perforating dermatosis in which elastic fibers were perforating, enhanced expression of elastin receptors was detected in the epidermis surrounding the elastic material[6]. Recently, it was proposed that scratching exposes keratinocytes to *a*dvanced *g*lycation *e*nd product (AGE)-modified extracellular matrix proteins, in particular collagen types I and III. This would then lead to terminal differentiation of keratinocytes via the AGE receptor (CD36), followed by upward movement of keratinocytes along with glycated collagen[7].

Fibronectin levels have been shown to be increased in the serum of patients with diabetes mellitus and uremia, and fibronectin has also been found to be increased within the skin at sites of transepidermal elimination[8]. This may be significant, since fibronectin plays a role in epithelial cell signaling, locomotion and differentiation. It binds to type IV collagen (the type found in basement membranes) and to keratinocytes, and may incite epithelial proliferation and perforation. In one study of RPC, the investigators demonstrated that it was type IV collagen that was being transepidermally eliminated[9]. Increased expression of transforming growth factor-β_3 (TGF-β_3), matrix metalloproteinase-1 (MMP-1), and tissue inhibitor of metalloproteinase-1 (TIMP-1) has been observed in lesional skin of acquired RPC[10], but this enhanced expression may be a reflection of concurrent wound healing.

MAJOR PERFORATING DISEASES					
Disease	**Incidence**	**Time of onset**	**Most common location**	**Perforating substance**	**Associations**
Familial reactive perforating collagenosis (RPC)	Very rare	Childhood	Arms, hands, sites of trauma	Collagen	None
Elastosis perforans serpiginosa (EPS)	Rare, M > F	Childhood, early adulthood; variable with penicillamine-induced EPS	Neck, face, arms, other flexural areas	Elastic tissue	Genetic diseases (see Fig. 96.13), penicillamine
Perforating folliculitis	Common	Early adulthood	Trunk, extremities	Necrotic material	May simply be ordinary folliculitis with follicular rupture, i.e. not a specific entity
Acquired perforating dermatosis, includes acquired RPC, Kyrle disease* and, rarely, acquired EPS	Common (10% of dialysis patients)	Adulthood	Legs or generalized	Necrotic material, collagen or, uncommonly, elastic tissue	Diabetes, renal disease, pruritus, rarely liver disease; may be end stage of perforating folliculitis
Perforating calcific elastosis	Very rare, more common in black women	Adulthood	Abdomen, periumbilical	Calcified elastic tissue	Multiparity, obesity, hypertension

*In the opinion of some authors.

Table 96.1 Major perforating diseases. F, female; M, male.

SECONDARY PERFORATING DISEASES
ENDOGENOUS SUBSTANCES
Chondrodermatitis nodularis helicis Hematomas Perforating pseudoxanthoma elasticum Perforating calcinosis Gout (urate crystals) Papular mucinosis (mucin)
GRANULOMAS
Perforating granuloma annulare (Fig. 93.10) Necrobiosis lipoidica Sarcoidosis Rheumatoid nodule
EXOGENOUS FOREIGN MATERIAL
Silica Wood splinters
INFECTIOUS DISEASES
Chromomycosis Leprosy Schistosomiasis
TUMOR CELLS
Melanoma Paget's disease Mycosis fungoides Pilomatricoma Nevus sebaceus

Table 96.2 Secondary perforating diseases. For a more extensive list, see ref. 4.

Fig. 96.1 Reactive perforating collagenosis. This keratotic papule on the upper extremity followed minor trauma in a healthy man who had developed similar papules since childhood.

Other proposed pathomechanisms include abnormal vitamin A or D metabolism, enzyme release from neutrophils[11], and microangiopathy related to diabetes. Deposition of substances such as uric acid, hydroxyapatite or silicon[12] has also been implicated in the pathogenesis of perforating disorders.

CLINICAL FEATURES

Reactive Perforating Collagenosis

Familial RPC is a rare disorder that begins during childhood[1,13]. After superficial trauma, patients develop keratotic papules that reach a size of 5–8 mm over the following 3–4 weeks (Fig. 96.1). The Koebner phenomenon may occur, in which injury to the skin results in the formation of new lesions, often in a linear distribution. Koebnerization is more commonly observed with RPC than with the other perforating disorders, but it has been reported with all of them. Arms and hands are the most common sites of involvement in RPC. The papules tend to spontaneously resolve over 6–10 weeks. Verrucous perforating collagenoma (*collagenome perforant verruciformé*) is a very rare nonfamilial variant of RPC in which severe trauma to the skin results in verrucous papules with transepidermal elimination of collagen[14]. Acquired RPC that begins during adulthood usually occurs in association with diabetes mellitus or renal insufficiency, and these cases are best classified as acquired perforating dermatosis, even though the histopathology can be identical to the inherited form of RPC.

Elastosis Perforans Serpiginosa

EPS is a rare disorder beginning during childhood or early adulthood. About 40% of cases occur in association with other genetic disorders, including Down syndrome, Ehlers–Danlos syndrome, osteogenesis imperfecta, Marfan syndrome (Fig. 96.2), pseudoxanthoma elasticum (PXE), Rothmund–Thomson syndrome, and acrogeria. In a survey of pediatric dermatologists, the majority performed a detailed history and careful physical examination, but did not embark upon an extensive search for these genetic disorders in an otherwise healthy child or adolescent with EPS[15].

Fig. 96.2 Elastosis perforans serpiginosa in the setting of Marfan syndrome. Annular papules and plaques developed on the ear.

Fig. 96.3 Elastosis perforans serpiginosa. Papules arranged in an annular configuration on the neck.

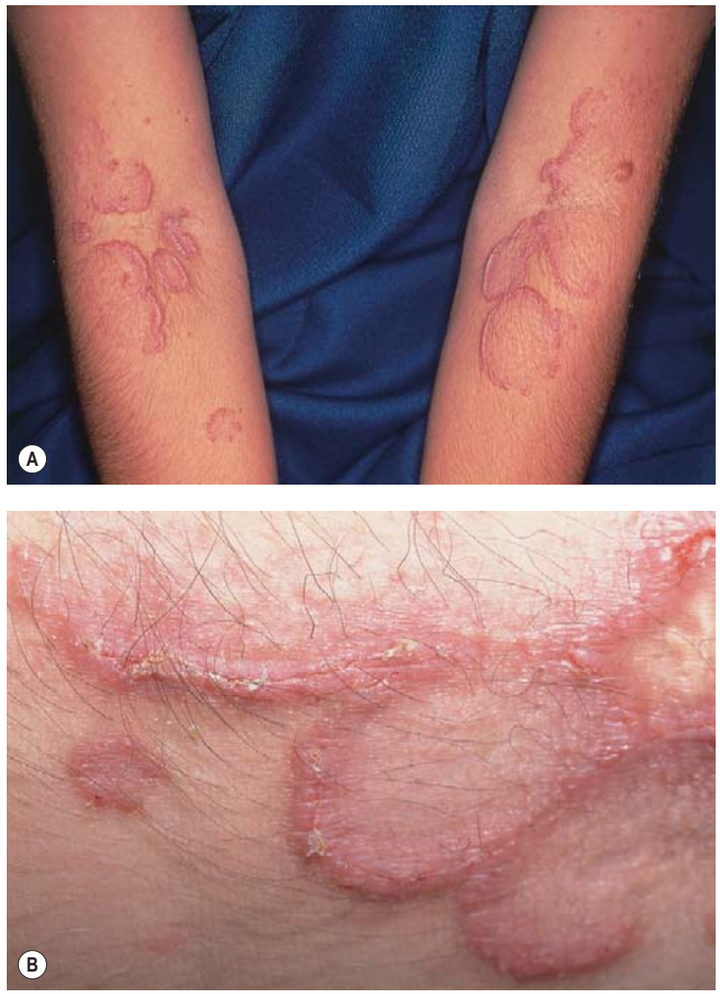


Fig. 96.4 Penicillamine-induced elastosis perforans serpiginosa. A Multiple annular plaques favoring the antecubital fossae. **B** Closer view with foci of hyperkeratosis at sites of transepidermal elimination.

Very rare cases of EPS associated with renal failure (clearly more rarely encountered than the acquired form of RPC) are best classified as acquired perforating dermatosis. EPS has also been reported to be induced by the drug penicillamine, which disrupts desmosine cross-links within elastin (see Ch. 97)[16]. Because penicillamine is used to treat Wilson disease, the possibility of copper metabolism playing a role in the pathogenesis of EPS has been raised, but EPS is also seen in patients with cystinuria or rheumatoid arthritis who have received penicillamine.

Lesions of EPS are keratotic, 2–5 mm papules that tend to be arranged in a serpiginous or annular pattern, most commonly on the lateral neck (Fig. 96.3), but also on the face, arms (Fig. 96.4) or other flexural areas. The rings of papules may reach several centimeters in diameter. Most patients experience no symptoms or only mild pruritus. Like RPC, the lesions may spontaneously resolve, but they tend to persist longer, often for several years.

Acquired Perforating Dermatosis and Kyrle Disease

Acquired perforating dermatosis has been used as a catch-all term for those examples of perforating disease arising in adults, usually in association with diabetes mellitus and/or the pruritus of renal failure[2]. The majority of the patients with chronic renal failure are receiving dialysis, and most of those with diabetes have associated nephropathy[17]. This disorder can also occur in conjunction with other causes of pruritus, from insect bites and scabies to lymphoma and hepatobiliary diseases, including primary biliary cirrhosis and malignancies. In addition, acquired perforating dermatosis may arise in sites of trauma (e.g. healing herpes zoster) or following exposure to several classes of drugs (e.g. TNF-α inhibitors, bevacizumab, sirolimus, indinavir). While an association with hypothyroidism and hyperparathyroidism has been reported, most of these patients also had established risk factors (e.g. diabetes, nephropathy). In a series of 22 patients with acquired perforating dermatosis, three were healthy and had no known associated illnesses and two were renal transplant recipients[17].

Acquired perforating dermatosis occurs most commonly on the legs (Fig. 96.5), but generalized or widely scattered papules or nodules can be seen (Figs 96.6 & 96.7). Extensor surfaces are favored over flexures and the mucous membranes are spared. A clue to the diagnosis is the presence of a central keratotic core, which is sometimes physically removed by the patient. Occasionally, a giant variant is observed, where lesions are up to 2 cm in diameter[18]. Rarely, secondary infections due to bacteria (e.g. *Staphylococcus aureus*), atypical mycobacteria (e.g. *Mycobacterium abscessus*) or fungi (e.g. *Mucor* spp.) have been reported.

Largely on the basis of their histologic findings, patients with acquired perforating dermatosis have been variably designated in the literature as having RPC, EPS[2], perforating folliculitis[13] or perforating PXE. Since the pathologic findings vary from lesion to lesion in the same patient, it seems unwise to subclassify patients in this way. Since some, but not necessarily all, of these lesions appear to be follicular, and since manipulation of the lesions by patients frequently alters the histologic changes, the term "acquired perforating dermatosis" was proposed to

Fig. 96.5 Acquired perforating dermatosis. Numerous papules and nodules on the legs in a patient with both renal failure and diabetes mellitus.

Fig. 96.7 Acquired perforating dermatosis. Note the linear arrangement of the keratotic papules (Koebner phenomenon).

Fig 96.6 Acquired perforating dermatosis. Keratotic papules on the arm of a diabetic woman on hemodialysis. Note the central keratotic core which is sometimes dislodged by the patient.

Fig. 96.8 Perforating calcific elastosis. When a biopsy was performed from the elevated edge of this supraumbilical plaque in a multiparous African-American woman, resistance was felt, as well as a grinding sound.

encompass all of these cases. Furthermore, since Kyrle had used the phrase "follicularis et parafollicularis" to emphasize that not all lesions were proved to be centered on follicles, the eponym Kyrle disease has been used synonymously with acquired perforating dermatosis by some authorities[2]. However, others do not consider Kyrle disease to be an entity, or prefer to define it as merely representing the presence of end-stage excoriated hyperplastic nodules of folliculitis[2].

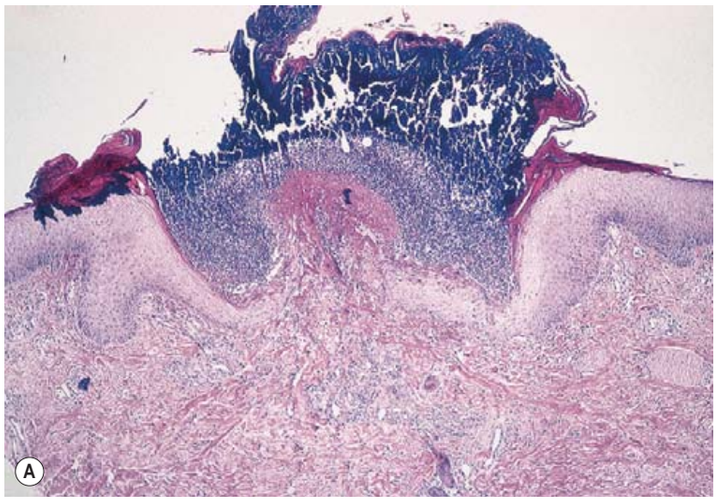
Perforating Calcific Elastosis

This disorder is characterized by plaques that favor the abdomen, especially the periumbilical region of middle-aged, obese, hypertensive, multiparous black women (Fig. 96.8)[19]. Involvement of the breast in patients with renal disease has also been observed. The plaques may be verrucous or have keratotic papules at their periphery. In histologic sections stained with H&E or von Kossa or Verhoeff-van Gieson stains, calcified elastic fibers (identical to those in PXE) are seen undergoing transepidermal elimination. However, affected patients do not have the other clinical findings of PXE. Similar transepidermal elimination has been observed in patients who treated their dermatitis with a commercially available calcium salt water normally used for making bean curd[20] or had their dermatitis exposed to calcium chloride contained in ice-melting salt.

PATHOLOGY

In all the perforating diseases, there is a plug of crusting or hyperkeratosis, with variable parakeratosis, depending upon the stage of the lesion (Fig. 96.9A). As the plug enlarges, epithelial hyperplasia develops, sometimes with dyskeratosis of keratinocytes. At the site of perforation, the epithelial hyperplasia often resembles an elephant snout or crab claw. However, sections from multiple levels through the tissue may need to be examined to find the site of perforation. Some lesions may have aggregates of neutrophils in the dermis, while older lesions, particularly those of EPS, tend to have lymphocytes, macrophages or multinucleated giant cells in the dermis at the site of perforation.

In RPC, collagen fibers are seen within the plug or within the epidermis (Figs 96.9B & 96.10), whereas in EPS, elastic fibers are seen



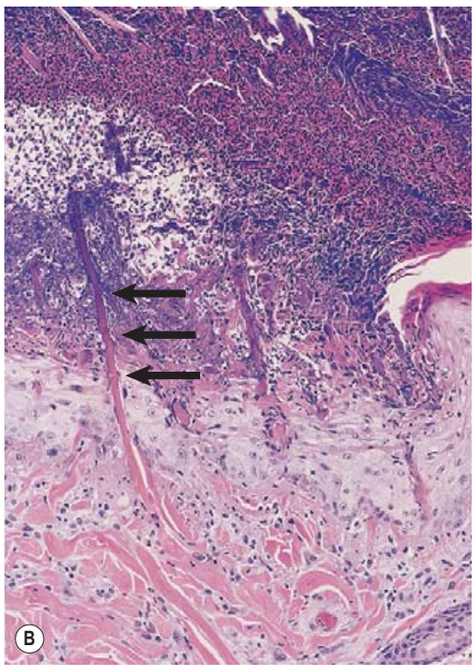


Fig 96.9 Acquired perforating dermatosis (acquired reactive perforating collagenosis).
A Scanning view of a crusted keratotic plug in a patient whose biopsy showed perforating collagen fibers.
B Higher magnification demonstrating collagen fibers extending through the epidermis (arrows) into the crusted plug.

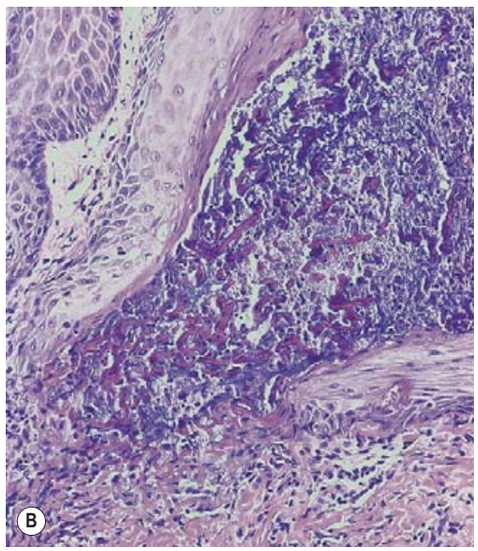


Fig. 96.11 Elastosis perforans serpiginosa.
A Hyperplastic epidermis clutches the increased dermal elastic fibers like a claw. **B** Transepidermal elimination of neutrophils and elastic fibers from the dermis through a channel in the epidermis.

Fig. 96.10 Reactive perforating collagenosis. Transepidermal elimination of red collagen fibers through the spinous layer and into the stratum corneum (Verhoeff–van Gieson stain).

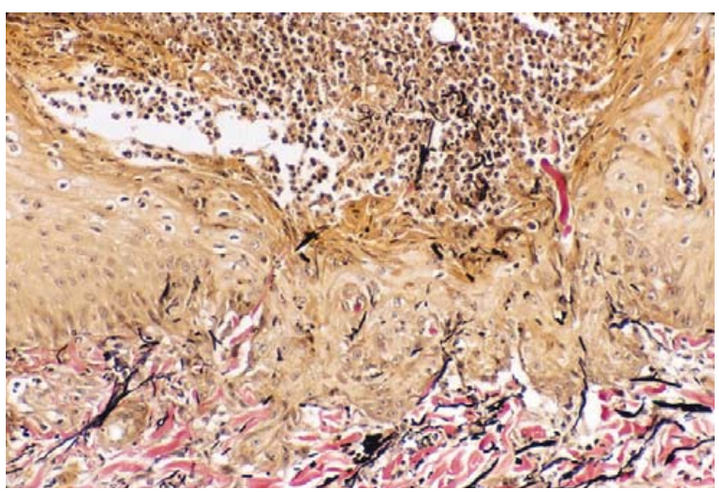


Fig 96.12 Acquired perforating dermatosis. Transepidermal elimination of both collagen (red) and elastic fibers (black) into a crust with many neutrophils is seen (Verhoeff–van Gieson stain).

DIFFERENTIAL DIAGNOSIS OF PERFORATING DISEASES
REACTIVE PERFORATING COLLAGENOSIS AND ACQUIRED PERFORATING DERMATOSIS
Excoriations from a variety of causes (prurigo simplex)
Prurigo nodularis
Folliculitis
Arthropod bites
Perforation of exogenous foreign material
Perforation of endogenous substances
Multiple keratoacanthomas
Dermatofibromas
If Koebner phenomenon: psoriasis, lichen planus, verrucae
ELASTOSIS PERFORANS SERPIGINOSA (RESEMBLES OTHER ANNULAR DISEASES; SEE CH. 19)
Granuloma annulare, Tinea — Common annular diseases
Sarcoidosis
Actinic granuloma (annular elastolytic giant cell granuloma)
Perforating pseudoxanthoma elasticum
Porokeratosis
Discoid lupus erythematosus

Table 96.3 Differential diagnosis of perforating diseases.

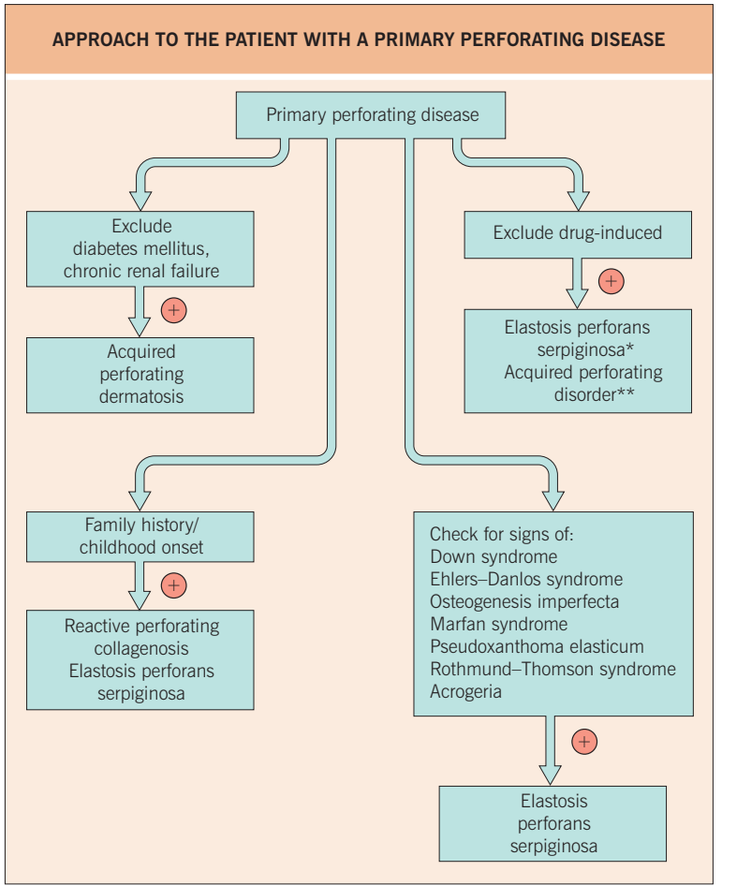


Fig. 96.13 Approach to the patient with a primary perforating disease. *Penicillamine. **Tumor necrosis factor-alpha inhibitors, bevacizumab, sirolimus, indinavir.

instead (in the same location; Fig. 96.11). In RPC, the dermal connective tissue adjacent to the plug appears unremarkable, while in EPS, an increased amount of brightly eosinophilic elastic tissue is often present in the superficial dermis. The Verhoeff–van Gieson stain is most helpful, because collagen fibers appear red and elastic fibers appear black (Fig. 96.12). However, in EPS, the elastic fibers higher up in the epidermis may lose their ability to stain black. In penicillamine-induced EPS, characteristic "lumpy-bumpy" elastic fibers with lateral buds resembling a "bramble bush" are seen in both lesional and non-lesional skin.

Biopsy findings in acquired perforating dermatosis vary according to the stage of evolution of the lesion. The histology may be identical to childhood RPC or EPS, or perforating folliculitis. In other cases, it may be less specific, with amorphous degenerated material within the perforations. This material often cannot be clearly identified as collagen or elastic fibers, but sometimes both are present (see Fig. 96.12)[2].

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes other disorders characterized by papules or nodules with central keratotic plugs or crusts (Table 96.3). When the Koebner phenomenon occurs, other disorders that can also arise in a linear pattern should be considered, e.g. psoriasis, lichen planus and verrucae. EPS may be confused with other disorders that are annular or serpiginous (see Ch. 19), but usually the individual keratotic plugs within the ring make it distinctive. Histologically, elastic fibers are commonly observed within the epidermis at the base of keratoacanthomas or any condition that leads to pseudoepitheliomatous hyperplasia, especially healing wounds.

Since many patients with acquired perforating dermatosis have coexisting folliculitis and prurigo nodularis, it is important to realize that these patients may have multiple different types of lesions at different stages of development and that a biopsy of just one lesion may not be representative of the entire process. Figure 96.13 provides an algorithm for the approach to the patient with a primary perforating disorder.

TREATMENT

Table 96.4 summarizes the various treatments that have been reported, most of which are anecdotal or based upon small case series. There

TREATMENT OF PERFORATING DISEASES
TOPICAL
Retinoids (e.g. tretinoin, tazarotene)[21] (3)
Corticosteroids (3)
Menthol (3)
Salicylic acid (3)
Sulfur (3)
Benzoyl peroxide (3)
Emollients (3)
Imiquimod (3)
SYSTEMIC
Antihistamines (e.g. doxepin) (3)
Corticosteroids (intralesional, intramuscular, oral) (2)
Retinoids (vitamin A, acitretin, isotretinoin)[16] (2)
Antibiotics (e.g. doxycycline, clindamycin, erythromycin, tetracycline, rifampin)[22,23] (3)
Methotrexate (3)
Charcoal (3)
Allopurinol[18] (3)
OTHER
Avoid trauma and scratching (wearing gloves, trimming of fingernails, behavior modification, transcutaneous nerve stimulator[24]) (3)
Cellophane-tape stripping (for EPS) (3)
Phototherapy (broadband or narrowband UVB; PUVA)[25] (2)
Cryotherapy (3)
Electrosurgical destruction (3)
Laser ablation (e.g. CO_2, Er:YAG, pulsed dye)[26] (3)
Excision of larger bothersome lesions (3)
Renal transplantation, if kidney failure[12] (3)

Table 96.4 Treatment of perforating diseases. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports. EPS, elastosis perforans serpiginosa.

have been no well-designed, placebo-controlled studies of therapeutic interventions. The inherited forms of RPC and EPS generally remain mild and localized and are therefore not so problematic. Local measures may be successful, but some authors have declared treatment to be largely ineffective. The patient with mild RPC may be satisfied simply to avoid trauma and wait for lesions to resolve spontaneously.

EPS may be treated with local cryotherapy, tangential excision, electrosurgical destruction, lasers (e.g. pulsed dye, Er:YAG) or cellophane tape stripping. However, aggressive treatment is more likely to result in scarring. As with RPC, spontaneous resolution of lesions makes it difficult to evaluate therapies.

Treatment of generalized acquired perforating dermatosis or extensive perforating folliculitis is often difficult. Sedating antihistamines and other typical "anti-itch" treaments (see Ch. 6) are often prescribed in an attempt to reduce the associated pruritus. Phototherapy (broadband or narrowband UVB or PUVA) is a particularly good choice for patients with renal disease, since it often relieves their coexisting pruritus. Other therapies that are sometimes helpful include intralesional corticosteroids and oral[14] or topical retinoids. Anecdotally, some patients have attributed rapid improvement to a change in the type of dialysis tubing or equipment employed, or even an alteration in the methods used during the actual dialysis procedure (personal observation). Occasional dialysis patients with acquired perforating dermatosis have been cured after renal transplantation[12].

REFERENCES

1. Flannigan SA, Tucker SB, Rapini RP. Recurrent hyperkeratotic papules from superficial trauma: reactive perforating collagenosis (RPC). Arch Dermatol. 1985;121:1554–5, 1557–8.
2. Rapini RP, Hebert AA, Drucker CR, et al. Acquired perforating dermatosis. Evidence of combined transepidermal elimination of both collagen and elastic fibers. Arch Dermatol. 1989;125:1074–8.
3. Rubio FA, Herranz P, Robayna G, et al. Perforating folliculitis: report of a case in an HIV-infected man. J Am Acad Dermatol. 1999;40:300–2.
4. Karpouzis A, Giatromanolaki A, Sivridis E, Kouskoukis C. Acquired reactive perforating collagenosis: current status. J Dermatol. 2010;37:585–92.
5. Cordova KB, Oberg TJ, Malik M, Robinson-Bostom L. Dermatologic conditions seen in end-stage renal disease. Semin Dial. 2009;22:45–55.
6. Fujimoto N, Akagi A, Tajima S, et al. Expression of the 67-kDa elastin receptor in perforating skin disorders. Br J Dermatol. 2002;146:74–9.
7. Fujimoto E, Kobayashi T, Fujimoto N, et al. AGE-modified collagens I and III induce keratinocyte terminal differentiation through AGE receptor CD36: epidermal-dermal interaction in acquired perforating dermatoses. J Invest Dermatol. 2010;130:405–14.
8. Bilezikci B, Seckin D, Demirhan B. Acquired perforating dermatosis in patients with chronic renal failure: a possible role for fibronectin. J Eur Acad Dermatol Venereol. 2003;17:230–2.
9. Herzinger T, Schirren CG, Sander CA, et al. Reactive perforating collagenosis – transepidermal elimination of type IV collagen. Clin Exp Dermatol. 1996;21:279–82.
10. Gambichler T, Birkner L, Stucker M, et al. Up-regulation of transforming growth factor-beta3 and extracellular matrix proteins in acquired reactive perforating collagenosis. J Am Acad Dermatol. 2009;60:463–9.
11. Zelger B, Hintner H, Aubock J, et al. Acquired perforating dermatosis. Transepidermal elimination of DNA material and possible role of leukocytes in pathogenesis. Arch Dermatol. 1991;127:695–700.
12. Saldanha LF, Gonick HC, Rodriguez HJ, et al. Silicon-related syndrome in dialysis patients. Nephron. 1997;77:48–56.
13. Ramesh V, Sood N, Kubba A, et al. Familial reactive perforating collagenosis: a clinical, histopathological study of 10 cases. J Eur Acad Dermatol Venereol. 2007; 21:766–70.
14. Delacretaz J, Gattlen JM. Transepidermal elimination of traumatically altered collagen. Report of three cases and consideration on the relationship between 'collagenome perforant verruciformé' and reactive perforating collagenosis. Dermatologica. 1976;152:65–6.
15. Vearrier D, Buka RL, Roberts B, et al. What is the standard of care in the evaluation of elastosis perforans serpiginosa? A survey of pediatric dermatologists. Pediatr Dermatol. 2006;23:219–24.
16. Ratnavel RC, Norris PG. Penicillamine-induced elastosis perforans serpiginosa treated successfully with isotretinoin. Dermatology. 1994;189:81–3.
17. Saray Y, Seckin D, Bilezikci B. Acquired perforating dermatoses: clinicopathological features in twenty-two cases. J Eur Acad Dermatol Venereol. 2006;20:679–88.
18. Hoque SR, Ameen M, Holden CA. Acquired reactive perforating collagenosis: four patients with a giant variant treated with allopurinol. Br J Dermatol. 2006;154:759–62.
19. Lopes LC, Lobo L, Bajanca R. Perforating calcific elastosis. J Eur Acad Dermatol Venereol. 2003; 17:206–7.
20. Lee SJ, Jang JW, Lee WC, et al. Perforating disorder caused by salt-water application and its experimental induction. Int J Dermatol. 2005;44:210–14.
21. Outland JD, Brown TS, Callen JP. Tazarotene is an effective therapy for elastosis perforans serpiginosa. Arch Dermatol. 2002;138:169–71.
22. Gonul M, Cakmak SK, Gul U, et al. Two cases of acquired perforating dermatosis treated with doxycycline therapy. Int J Dermatol. 2006;45:1461–3.
23. Kasiakou SK, Peppas G, Kapaskelis AM, Falagas ME. Regression of skin lesions of Kyrle's disease with clindamycin: implications for an infectious component in the etiology of the disease. J Infect. 2005;50: 412–16.
24. Chan LY, Tang WY, Lo KK. Treatment of pruritus of reactive perforating collagenosis using transcutaneous electrical nerve stimulation. Eur J Dermatol. 2000;10:59–61.
25. Mii S, Yotsu R, Hayashi R, et al. Acquired perforating collagenosis successfully treated with narrow-band ultraviolet B. Acta Derm Venereol. 2009; 89:530–1.
26. Saxena M, Tope WD. Response of elastosis perforans serpiginosa to pulsed CO2, Er:YAG, and dye lasers. Dermatol Surg. 2003;29:677–8.

This page intentionally left blank

Heritable Disorders of Connective Tissue 97

Franziska Ringpfeil and Jouni Uitto

Chapter Contents

Ehlers–Danlos syndrome *1607*
Pseudoxanthoma elasticum *1612*
Cutis laxa *1615*

Key features

- Heritable connective tissue disorders with skin involvement comprise a phenotypically diverse group of conditions
- Recognition of characteristic skin findings is often critical to establishing the diagnosis and identifying associated internal involvement, which may include life-threatening cardiovascular disease (e.g. in the vascular type of Ehlers–Danlos syndrome and pseudoxanthoma elasticum)
- Heritable connective tissue disorders can be caused by mutations in genes encoding structural extracellular matrix (ECM) proteins (e.g. collagens, components of elastic fibers), enzymes that modify these structural proteins, and other proteins with effects on the ECM (e.g. via transport or regulatory functions)

Introduction

Heritable connective tissue diseases manifest with a broad range of phenotypic abnormalities, and the relative degrees of cutaneous and extracutaneous involvement vary considerably. At one end of the spectrum, the clinical findings are mild and limited to a single organ such as the skin, while at the other end of the spectrum, the cutaneous manifestations may be part of multi-organ pathology causing considerable morbidity and even mortality[1,2]. Tremendous progress has been made toward understanding the molecular bases of heritable disorders of connective tissue. This has led to improved classification and prognostication, with better recognition of phenotypic spectrums and relationships among disorders.

The connective tissue meshwork is critical for organogenesis during embryonic development and homeostatic maintenance of tissues, with complex protein assembly and cell-matrix interactions. The principal fibrillar components of the extracellular matrix (ECM) of the skin are networks consisting of collagen and elastic fibers (see Ch. 95). Recognition of the complex interactions among the various types of collagen, elastic fibers (which consist of elastin and a number of associated microfibrillar proteins) and other ECM components has allowed the identification of critical metabolic as well as structural features that are a prerequisite for normal physiologic functions. The study of heritable disorders of connective tissue has demonstrated the considerable impact of disruption of various individual components of the ECM and related proteins.

Classic, "primary" heritable disorders of connective tissue caused by mutations in the genes encoding collagen and structural components of elastic fibers include several forms of Ehlers–Danlos syndrome (EDS) and cutis laxa (CL), respectively. In addition to primary defects in the genes for structural components themselves or enzymes modifying these proteins, the ECM can be perturbed by seemingly unrelated pathologic processes. Examples of the latter, which can be considered as "secondary" connective tissue disorders, include pseudoxanthoma elasticum (PXE) and homocystinuria.

This chapter provides detailed discussions of EDS, PXE and CL. In addition, Marfan syndrome, homocystinuria, osteogenesis imperfecta and Buschke–Ollendorff syndrome are presented in Table 97.1. These and other genetic diseases that affect the ECM of the skin are also summarized in Table 95.5.

EHLERS–DANLOS SYNDROME

Synonym: ■ Cutis hyperelastica

Key features

- Clinically and genetically heterogeneous group of connective tissue disorders caused by defective function of various collagens, collagen-processing enzymes and tenascin-X (a collagen-associated protein)
- Autosomal dominant and autosomal recessive inheritance patterns
- Cutaneous features include hyperextensible and fragile skin, easy bruising and poor wound healing
- Extracutaneous features include joint hypermobility, scoliosis and, particularly in the vascular type, a significant risk of spontaneous arterial, intestinal or uterine rupture

History

A survey of the literature reveals descriptions of patients with features of Ehlers–Danlos syndrome (EDS) as early as the mid-1600s. The first comprehensive report of the systemic nature of this condition was published in 1892 by Tschernogobow[3]. Drs Ehlers and Danlos, Danish and French dermatologists, respectively, contributed to a comprehensive clinical description in the early 1900s, and this constellation of findings became known as the Ehlers–Danlos syndrome in 1936. The genetic nature of EDS was noted in 1949, and soon thereafter it was suggested that the phenotype resulted from defects in the collagen meshwork. The genetic heterogeneity of EDS became evident in the 1960s, and molecular defects in collagen synthesis were first described in 1972.

In the past, EDS was divided into as many as 11 subtypes (numbered I–XI) based primarily upon clinical features. In 1997, a consensus conference was held and a revised nosology was proposed[4] (Table 97.2). Currently, the molecular basis of most major forms of EDS is known[5,6].

Epidemiology

Features suggestive of EDS (e.g. loose-jointedness) are present in a relatively large number of individuals in the general population especially in certain African groups. However, more stringent diagnostic criteria that include findings in the skin and joints, at a minimum, limit the incidence of EDS to approximately 1 in 5000. Although all forms of EDS can cause considerable morbidity, only one variant, the vascular type (previously type IV), typically causes premature demise of affected individuals[7].

Pathogenesis

EDS is a clinically and genetically heterogeneous group of connective tissue disorders caused by defective function of the collagen meshwork (Fig. 97.1). The collagen family is now known to consist of 28 distinct proteins that differ in their tissue distributions and functions[8] (see Ch. 95). Each collagen consists of three α-chain polypeptides, which

ADDITIONAL HERITABLE DISORDERS OF CONNECTIVE TISSUE WITH CUTANEOUS FINDINGS

Disease	Cutaneous findings	Extracutaneous manifestations	Inheritance	Associated gene/protein product
Marfan syndrome	Striae, elastosis perforans serpiginosa, decreased subcutaneous fat on extremities	Skeletal abnormalities (e.g. disproportionately long limbs, arachnodactyly, scoliosis), lens subluxations (upward), cardiovascular abnormalities (e.g. dilation/dissection of ascending aorta*)	AD	*FBN1*/fibrillin-1 defects (the major component of microfibrils)†
Homocystinuria	Malar flush, livedo reticularis, diffuse pigmentary dilution, tissue paper-like scars	Marfanoid habitus, lens subluxations (downward), venous and arterial thrombosis‡, mental retardation	AR	*CBS*/cystathionine synthase enzyme deficiency (resulting in increased plasma homocysteine§); rarely, methylenetetrahydrofolate reductase, 5-methyltetrahydrofolate-homocysteine methyltransferase, or 5-methyltetrahydrofolate-homocysteine methyltransferase reductase deficiency (enzymes that convert homocysteine back to methionine)
Osteogenesis imperfecta	Thin skin	Bone fragility, blue sclerae, dentinogenesis imperfecta (in a subset of patients)	AD	*COL1A1*, *COL1A2*/type I collagen defects
Buschke–Ollendorff syndrome	Connective tissue nevi (dermatofibrosis lenticularis disseminata); occasionally cutaneous sclerosis associated with melorheostosis	Osteopoikilosis ("spotted" bones); occasionally melorheostosis (sclerotic bone resembling "dripping candle wax" on radiographs; reflects a postzygotic "second hit" in the *LEMD3* gene); rarely otosclerosis	AD	*LEMD3*/LEM domain-containing 3, an antagonist of bone morphogenic protein (BMP) and TGF-β signaling

*In addition to traditional treatment with β-blockers, angiotensin II receptor blockers (e.g. losartan), which antagonize pathogenic transforming growth factor (TGF)-β signaling, can prevent aortic root dilation in patients with Marfan syndrome; administration of doxycycline, which inhibits metalloproteinases-2 and -9, may also be of benefit.
†Mutations in the genes encoding TGF-β receptors 1 and 2 can lead to a phenotype that mimics Marfan syndrome.
‡Methionine-restricted, cysteine-supplemented diet plus pyridoxine recommended.
§Elevated plasma homocystine and homocysteine can be detected in patients with homocystinuria (but only homocysteine in hyperhomocysteinemia).

Table 97.1 Additional heritable disorders of connective tissue with cutaneous findings. Other rare genetic diseases of the extracellular matrix are listed in Table 95.5. AD, autosomal dominant; AR, autosomal recessive.

are synthesized as precursor molecules, pro-α-chains; a trimeric collagen molecule may be either a homotrimer or heterotrimer (i.e. consisting of the same versus two or three genetically different kinds of polypeptides, respectively). There are 43 different pro-α-chains, each encoded by a distinct gene[8].

The pathogenesis of EDS can involve mutations in genes for collagen-processing enzymes as well as those encoding collagen α-chains. The latter result in either dominant-negative effects (e.g. disruption of trimers and fibrils due to incorporation of mutant collagen α-chains) or haploinsufficiency. The precise phenotype depends upon the nature of the mutation(s) and the type of collagen or other protein that is affected.

Lysyl hydroxylase deficiency, caused by mutations in the corresponding gene, *PLOD*, results in reduced hydroxylysine content of collagen polypeptides and an altered cross-linking profile of collagen fibrils. This leads to the recessively inherited kyphoscoliosis type of EDS (previously known as type VIA). Mutations affecting another collagen-processing enzyme, the procollagen I N-peptidase (encoded by the *ADAMTS2* gene) that is responsible for the cleavage of amino-terminal propeptides from triple-helical type I procollagen, result in the formation of irregular and thin collagen fibrils with reduced mechanical properties. The collagen fibrils appear "hieroglyphic" in cross-section and contain type I collagen with an intact N-propeptide, termed pN-collagen. Procollagen I N-peptidase deficiency leads to the recessively inherited dermatosparaxis type of EDS (previously known as type VIIC).

Dominant-negative effects leading to EDS are caused by mutations in different collagen genes, including those encoding α-chains of type I (*COL1A1, COL1A2*), type III (*COL3A1*) and type V (*COL5A1, COL5A2*) collagens. Characteristically, these types of genetic lesions are splice site mutations resulting in an in-frame deletion of a single exon, or missense mutations resulting in a glycine substitution in the collagenous domain. Since the expression levels of these "mutated" polypeptides is the same as for the normal chains and they are incorporated into the polymeric collagen molecules, they affect the triple helix formation and/or thermal stability of the collagen triple helices by a dominant-negative mechanism. The presence of the mutant chains typically results in defective secretion of collagen molecules, and, as a consequence, the collagen fibrils are often reduced in amount as well as structurally abnormal.

Haploinsufficiency is caused by a heterozygous loss-of-function mutation, usually associated with a premature termination codon. These types of mutations often result in unstable mRNA that undergoes accelerated decay, leading to an absence of the corresponding polypeptide. Haploinsufficiency can also be caused by a missense mutation encoding a polypeptide that cannot be incorporated into collagen triple helices. Haploinsufficiency occurs when the synthesis of only 50% of the normal amount of the collagen is not enough to form fully functional fibrils, thus resulting in a disease phenotype.

Both dominant-negative mutations in *COL3A1* and haploinsufficiency of type III collagen can cause the vascular type of EDS (previously known as type IV). Collagen III is an important component of arterial and intestinal walls and a less abundant component of dermal connective tissue. However, a reduced amount of type III collagen leads to small or variably sized dermal collagen fibrils and thinning of the dermis, emphasizing the pivotal role of type III collagen in fibrillogenesis. A decreased amount of collagen III in the dermis has also been detected in some patients with the periodontitis (previously known as type VIII) and kyphoscoliosis types of EDS (which, unlike vascular EDS, are not caused by *COL3A1* mutations).

The classic type of EDS (previously known as types I and II) can be caused by dominant-negative mutations in *COL5A1* and *COL5A2* or (in 30–50% of cases) haploinsufficiency of type V collagen (*COL5A1*). The role of type V collagen in collagen fibrillogenesis is to limit fibril diameter, explaining the approximately 25% increase in fibril diameter that is observed by electron microscopy in affected individuals. Mutations in the genes encoding the pro-α-chains of type I collagen (*COL1A1*, *COL1A2*) that correspond to the cleavage site of procollagen N-peptidase result in the dominantly inherited arthrochalasia type of EDS (previously known as types VIIA and VIIB), while procollagen I N-peptidase deficiency leads to dermatosparaxis, a recessively inherited condition.

Complete tenascin-X deficiency (i.e. via biallelic null mutations) leads to an autosomal recessive form of EDS with features similar to those of classic EDS[9]. Tenascin-X is an ECM protein that is thought to have a role in reinforcing associations among collagen fibrils. The

CLASSIFICATION OF EHLERS–DANLOS SYNDROME				
EDS type*	**Traditional classification†**	**Clinical features**	**Inheritance**	**Mutated gene/protein**
Classic	I, II	Hyperextensible skin, joint hypermobility, atrophic scars, easy bruising, absence of the inferior labial and lingual frenula	AD, AR‡	*COL5A1*, *COL5A2*/α_1- and α_2- chains of type V collagen; *TNXB*/tenascin-X Rarely, *COL1A1*/α_1-chain of type I collagen
Hypermobility	III	Joint hypermobility, pain and dislocations; absence of inferior labial and lingual frenula	AD	*TNXB*/tenascin-X (~10% of affected individuals, predominantly female)
Vascular	IV	Thin, translucent skin; arterial, gastrointestinal and uterine rupture; excessive bruising, small joint hypermobility, characteristic facies	AD	*COL3A1*/α_1-chain of type III collagen
Kyphoscoliosis	VIA	Hyperextensible and fragile skin, neonatal hypotonia, joint hypermobility, congenital scoliosis, ocular fragility	AR	*PLOD1*/lysyl hydroxylase§
Musculocontractural	VIB	Hyperextensible and fragile skin, wrinkled palms, joint contractures and hypermobility, scoliosis, ocular fragility, craniofacial abnormalities	AR	*CHST14*/dermatan-4-sulfotransferase 1 (allelic with adducted thumb–clubfoot syndrome)
Arthrochalasia	VIIA, VIIB	Hyperextensible and fragile skin, severe joint hypermobility with congenital bilateral hip dislocation, scoliosis	AD	*COL1A1*, *COL1A2*/α_1- and α_2-chains of type I collagen
Dermatosparaxis	VIIC	Severe skin fragility, sagging and redundant skin that is soft and doughy, easy bruising, hernias, distinctive facies	AR	*ADAMTS2*/procollagen I N-peptidase
EDS, cardiac valvular		Cardiac valve defects, otherwise similar to classic EDS (see above)	AR	α_2-chain of type I collagen
EDS, progeroid		Skin hyperextensibility, joint hypermobility, progeroid facies, osteopenia, mental and growth retardation	AR	*B4GALT7*/galactosyl transferase-1
EDS, periventricular nodular heterotopia variant		Variable skin hyperextensibility, aortic dilation, periventricular nodular heterotopia, joint hypermobility	X-D	*FLNA*/filamin A (actin-binding protein 280)
EDS-like spondylocheirodysplasia		Skin hyperextensibility and fragility, atrophic scarring, wrinkled palms, joint hypermobility, growth retardation	AR	*SLC39A13*/solute carrier family 39, member 13 (a zinc transporter)

*According to the 1997 Villefranche Consensus Meeting[4].
†Replaced by the Consensus classification[4].
‡The classic forms due to type V collagen mutations are inherited in an autosomal dominant (AD) fashion, while those caused by tenascin-X deficiency are autosomal recessive (AR).
§Analysis of the urine for an increased deoxypyridinoline:pyridinoline ratio can be used as a screening test for kyphoscoliosis-type EDS.

Table 97.2 Classification of Ehlers–Danlos syndrome (EDS). The traditional EDS types V (X-linked), VII (periodontitis) and X (fibronectin) have unknown molecular bases and are not included in the current nosology. Previous EDS types IX and XI have been reclassified as occipital horn syndrome (see Table 97.6) and familial joint hypermobility syndrome, respectively. AD, autosomal dominant; ADAMTS2, *a d*isintegrin-like *a*nd *m*etalloprotease domain with *t*hrombospondin type 1 motifs 2; AR, autosomal recessive; COL, collagen; PLOD1, *p*rocollagen-*l*ysine 1, 2-*o*xoglutarate 5-*d*ioxygenase 1; X-D, X-linked dominant.

pathogenic consequences of tenascin-X deficiency have been substantiated by the observation of hyperextensible skin with reduced tensile strength in *Tnx*-null mice[10] ("knockout mice"; see Ch. 3).

Clinical Features

The general features of EDS include hyperextensible, fragile skin and joint hypermobility[4] (Fig. 97.2A,B). However, different subtypes of EDS have additional manifestations, both clinical and molecular, which allow their classification into six major categories (defined by the 1997 consensus conference[4]) (Fig. 97.3); several other novel variants of EDS have also been recognized (see Table 97.2). Typical skin findings are present, to a varying degree, in all subtypes of EDS[11]. The skin tends to be fragile, splitting readily as a result of trauma, particularly on the knees, elbows, shins and forehead. The wounds present with a gaping, "fish-mouth" appearance, and the resulting scars are typically atrophic and widen over time (Fig. 97.2C). Wound healing may be delayed and dehiscence is common. Sites of repeated trauma develop a variety of secondary lesions such as molluscoid pseudotumors, which are fleshy nodules of redundant skin and fibrous tissue that favor the knees and elbows. Another frequent finding is subcutaneous spheroids (Fig. 97.2D), which appear over bony prominences as multiple small, hard, mobile nodules that are thought to represent calcified fat globules. Easy bruising is commonly observed, reflecting the fragility of small blood vessels. Dermatologic disorders that are occasionally associated with (but not specific to) EDS include elastosis perforans serpiginosa and piezogenic papules.

The *classic type of EDS* (previously types I and II) represents the most common variant and is usually inherited in an autosomal dominant fashion. Rarely, this phenotype has an autosomal recessive pattern of inheritance, sometimes in association with congenital adrenal hyperplasia due to deletion of the contiguous genes encoding tenascin-X and 21-hydroxylase. The major clinical features of classic EDS include hypermobile joints and hyperextensible skin that heals with widened, atrophic scars, which often have a "cigarette paper" appearance. The skin also tends to be soft, velvety and prone to bruising. At least half of affected individuals can touch the tip of their nose with their tongue (Gorlin's sign), compared to 10% of the general population (Fig. 97.2E). Although classic EDS may be associated with mild aortic root dilation and mitral valve prolapse (each in ~5% of patients), these findings are rarely of clinical significance[12]. Other frequent musculoskeletal manifestations include pes planus, hypotonia and temporomandibular joint dysfunction.

The *hypermobility type of EDS* (previously type III) has an autosomal dominant inheritance pattern. The primary clinical features are generalized joint hypermobility and hyperextensible, smooth and velvety skin. Other manifestations include recurrent joint dislocations, which can cause chronic joint and limb pain as well as eventual osteoarthritic changes.

The *vascular type of EDS* (previously type IV) is inherited in an autosomal dominant fashion. These patients have thin, translucent skin with extensive bruising and are at high risk for arterial, intestinal and uterine ruptures[13]. Spontaneous arterial rupture has the highest incidence in the third and fourth decades of life but may occur earlier.

COLLAGEN BIOSYNTHESIS, SECRETION AND FIBRIL ASSEMBLY – RELATIONSHIP OF PATHOLOGY TO THE MAJOR SUBTYPE OF EHLERS-DANLOS SYNDROME

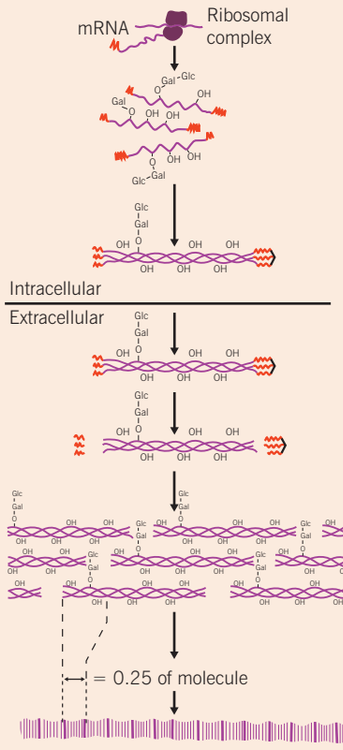
Physiology	Pathology	EDS subtype (mode of inheritance)
 Synthesis, hydroxylation and glycosylation of pro-α polypeptides of type I, III and V collagens	**Lysyl hydroxylase** deficiency results in reduced hydroxylysine content and altered cross-linking profile	Kyphoscoliosis (AR)
Formation of interchain S-S bonds at the carboxyl ends followed by triple helix formation	Dominant-negative mutations or haploinsufficiency in ***COL3A1*** affect triple helix formation, thermal stability, and secretion of type III collagen molecules	Vascular type (AD)
Secretion of procollagen	Dominant-negative mutations in the recognition sites for procollagen N-peptidase in ***COL1A1*** and ***COL1A2*** prevent cleavage of amino-terminal propeptides	Arthrochalasia (AD)
Removal of propeptides by specific proteases	Loss-of-function mutations in **procollagen-N-peptidase** result in the formation of only thin collagen fibrils	Dermatosparaxis (AR)
Fibril assembly	Dominant-negative mutations in ***COL5A1*** and ***COL5A2*** or haploinsufficiency in ***COL5A1*** result in abnormal or reduced amount of collagen fibrils	Classical type (AD)
Stabilization of fibrils by intermolecular cross-linking	Absence of **tenascin-X** leads to reduced collagen fibril density	Classical type (AR)

Fig. 97.1 Collagen biosynthesis, secretion and fibril assembly – relationship of pathology to the major subtype of Ehlers–Danlos syndrome. AD, autosomal dominant; AR, autosomal recessive; Glc-Gal, glucosyl-galactosyl residue attached to the hydroxyl group (OH) of lysine residues; S-S bonds, disulfide bonds.

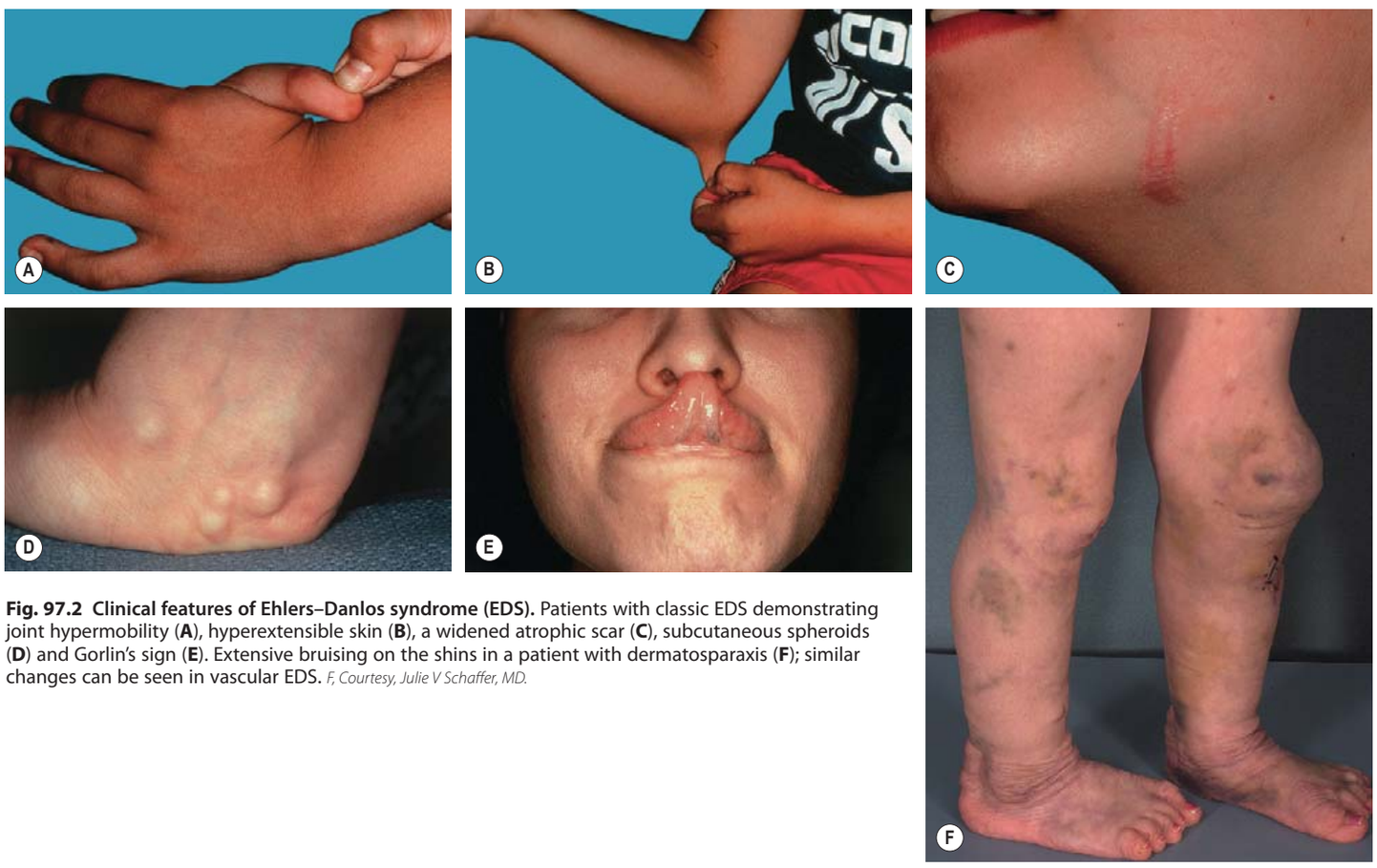


Fig. 97.2 Clinical features of Ehlers–Danlos syndrome (EDS). Patients with classic EDS demonstrating joint hypermobility (**A**), hyperextensible skin (**B**), a widened atrophic scar (**C**), subcutaneous spheroids (**D**) and Gorlin's sign (**E**). Extensive bruising on the shins in a patient with dermatosparaxis (**F**); similar changes can be seen in vascular EDS. *F, Courtesy, Julie V Schaffer, MD.*

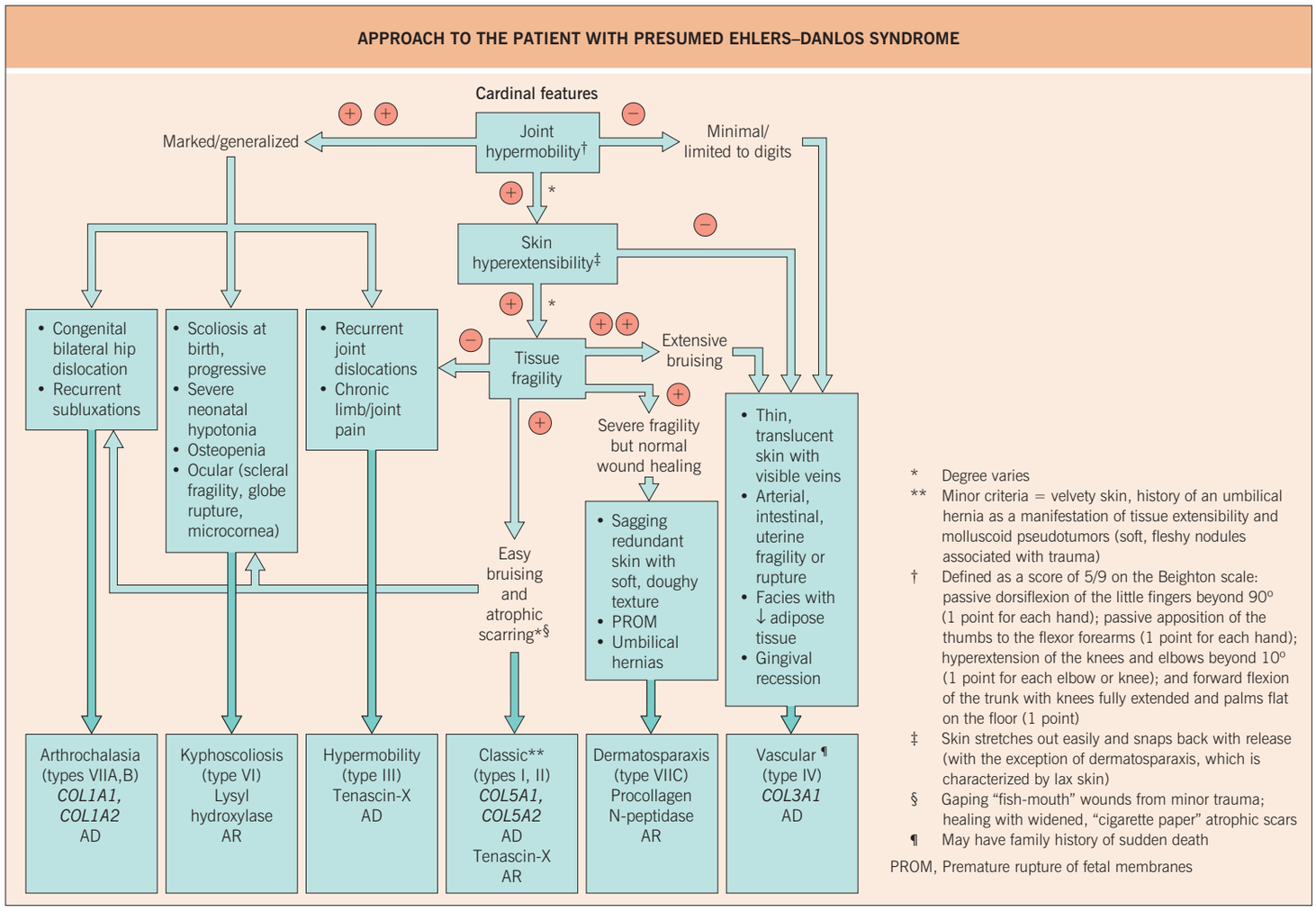


Fig. 97.3 Approach to the patient with presumed Ehlers–Danlos syndrome. AD, autosomal dominant; AR, autosomal recessive.

Affected individuals often have a characteristic facial appearance, with a "pinched" nose, thin lips, hollow cheeks and prominent "staring" eyes due to decreased periorbital adipose tissue.

The *kyphoscoliosis type of EDS* (previously type VIA) is inherited in an autosomal recessive fashion. Major features are skin hyperextensibility, generalized joint hypermobility, severe hypotonia at birth (leading to delayed gross motor development), progressive congenital scoliosis, and scleral fragility that can lead to rupture of the ocular globe. Additional findings may include atrophic scars, easy bruising, fragility of other tissues (rarely arterial rupture), a marfanoid habitus, microcornea and osteopenia.

The *arthrochalasia type of EDS* (previously types VIIA and VIIB) is inherited in an autosomal dominant fashion. The major clinical features include severe generalized joint hypermobility with recurrent subluxations and congenital bilateral hip dislocation. Patients may also present with hyperextensible skin, atrophic scars, easy bruising, hypotonia, scoliosis and mild osteopenia.

The *dermatosparaxis type of EDS* (previously type VIIC) is an autosomal recessive disorder that, unlike other forms of EDS, presents with skin that is sagging and redundant as well as extremely fragile. The skin has a highly characteristic soft, doughy consistency, and it tears and bruises easily (Fig. 97.2F). Additional findings include premature rupture of fetal membranes, large umbilical or inguinal hernias, delayed closure of the fontanelles, distinctive facies with puffy eyelids and micrognathia, blue sclerae, gingival hyperplasia, abnormal dentition and short limbs.

Pathology

Histopathologic examination of the skin may suggest or support the presence of a connective tissue disorder when a thin reticular dermis with reduced and/or disorganized collagen fibrils is seen. However, in general, the histopathologic findings are not diagnostic. Nonspecific increases in elastic fibers have been reported, particularly in areas of repeated trauma or molluscoid pseudotumors.

Electron microscopy often shows the presence of collagen fibrils with variable diameters and occasional large "cauliflower" fibrils with an irregular contour. Characteristic hieroglyphic fibrils can be encountered in the dermatosparaxis type of EDS. Immunohistochemical demonstration of intracellular accumulation of type III collagen may be helpful in pointing to the vascular type of EDS.

In general, the diagnosis of EDS is clinical. Protein electrophoresis of collagens extracted from cultured dermal fibroblasts can be helpful in demonstrating specific collagen defects (see Fig. 97.1), particularly in the vascular, arthrochalasia and dermatosparaxis types of EDS[13]. Analysis of the urine for an increased deoxypyridinoline : pyridinoline ratio may be used as a screening test for kyphoscoliosis-type EDS, and tenascin-X deficiency can be demonstrated by an ELISA of a serum sample[9]. Genetic testing is available for all of the major forms of EDS except the hypermobility type.

Differential Diagnosis

Several previously described rare subtypes of EDS, including type V (X-linked variant), type VIII (periodontitis type) and type X (fibronectin type), have been excluded (at least for the present) from the EDS nosology due to a lack of clear descriptions of their clinical features and unknown molecular bases. The previous EDS type IX, an X-linked recessive condition known as occipital horn syndrome, is now considered to represent a form of cutis laxa (see Table 97.6) rather than EDS. In contrast to cutis laxa, which is characterized by loose and sagging skin with decreased resilience, the skin of patients with EDS (with the exception of the dermatosparaxis type) retains its elasticity and recoil. Although some patients with EDS (in particular the kyphoscoliosis

COMPARISON OF SELECTED CLINICAL FEATURES IN EHLERS–DANLOS SYNDROME AND MARFAN SYNDROME		
	Ehlers–Danlos syndrome	**Marfan syndrome**
Molluscoid pseudotumors	++	–
Skin	Hyperextensibility, "fish–mouth" atrophic scars	Striae
Joint hypermobility	++ (often severe)	+ (mild–moderate)
Easy bruising	++	–
Pectus excavatum	–	++
Scoliosis	+	++
High-arched palate	–	++
Ectopia lentis	+	++
Myopia	+	++
Mitral valve abnormalities	+	++
Stature	Variable	Tall

Table 97.3 Comparison of selected clinical features in Ehlers–Danlos syndrome and Marfan syndrome. ++, common feature; +, occasional feature; –, not a feature.

type) have a marfanoid body habitus, they do not typically exhibit other findings of Marfan syndrome (Table 97.3), a distinct heritable connective tissue disorder due to mutations in the fibrillin-1 gene (*FBN1*) (see Table 97.1).

The phenotype of Loeys–Dietz syndrome type II can mimic that of vascular EDS, with overlapping features including translucent skin, easy bruising, atrophic scarring, joint hypermobility and arterial rupture (see Table 95.5). Patients with vascular EDS and other types that result in extensive bruising are often suspected to have a bleeding disorder, and they may present to a dermatologist after a hematologic evaluation fails to reveal any abnormalities. In addition to the major forms of EDS discussed above, other uncommon variants should also be considered (see Table 97.2).

Treatment

Currently, no specific treatment is available for any of the subtypes of EDS. The most important intervention is prevention of trauma to the skin, such as the use of shin guards and avoidance of contact sports. Use of sutures with prolonged tensile strength may improve healing and the appearance of surgical scars. In the vascular type of EDS, affected individuals are at high risk of arterial and bowel ruptures, and pregnancies may be complicated by uterine rupture. Early diagnosis of this type of EDS is critical to enable prompt recognition and optimal management of complications as well as to provide reproductive counseling and close monitoring during pregnancies[13].

PSEUDOXANTHOMA ELASTICUM

Synonym: ■ Grönblad–Strandberg syndrome

Key features

- An autosomal recessive disorder characterized by clumped and distorted elastic fibers with deposits of calcium
- Cutaneous features include yellowish papules, "cobblestoning" and redundant folds in flexural areas
- Calcification of elastic fibers in the walls of medium-sized arteries can lead to luminal narrowing and clinical sequelae such as claudication, renovascular hypertension, angina and myocardial infarctions
- Angioid streaks reflect breaks in the calcified elastic lamina of Bruch's membrane; choroidal neovascularization and hemorrhage can result in loss of visual acuity
- Gastrointestinal hemorrhage represents another possible complication

History

The French dermatologist Balzer first described the skin manifestations of PXE and associated elastic degeneration in the skin and heart in 1884[14], which was followed 5 years later by a similar case report by Chauffard[15]. Based on these two cases, Darier coined the name "pseudo-xanthome élastique" in 1896 to differentiate this condition from xanthomas (hence pseudoxanthoma)[16]. In the late 1920s, Grönblad[17] and Strandberg[18] recognized the association of the characteristic skin manifestations with angioid streaks, and the cardiovascular manifestations were better defined two decades later. More recently, the molecular defects that underlie PXE were identified, clarifying the mode of inheritance (which had previously been the subject of much debate)[19,20].

Epidemiology

PXE is an autosomal recessive disease, with estimates of prevalence ranging from 1 in 25 000 to 1 in 100 000. It occurs in all races without geographic predilection and appears to have a slight female preponderance[21]. Skin changes of PXE usually appear during childhood, but the diagnosis is frequently not made until serious systemic or ocular complications develop in the third or fourth decade of life. Mild cutaneous and ocular findings have also been observed in heterozygous carriers[22].

Pathogenesis

Loss-of-function mutations in both copies of the *ABCC6* gene can be identified in most patients with PXE. *ABCC6* encodes an ABC-cassette transporter with a high degree of homology to the multidrug resistance-associated proteins. ABCC6 is predominantly expressed in the basolateral membrane of hepatocytes, where it serves as an efflux pump. Unlike other members of this protein family, ABCC6 does not seem to confer any significant chemotherapy resistance; however, there may be some functional overlap considering that ABCC6 is believed to play a role in cellular detoxification.

Mutations in both copies of the γ-glutamyl carboxylase gene (*GGCX*) have recently been found to cause PXE-like skin changes plus deficiency in vitamin K-dependent coagulation factors[23]. A combination of heterozygous mutations in *GGCX* and *ABCC6* has also been identified in patients with cutaneous findings of PXE[24]. The GGCX enzyme catalyzes the vitamin K-dependent γ-glutamyl carboxylation that is necessary for activation of both coagulation factors in the liver and the matrix gla protein in peripheral connective tissues. When carboxylated (activated), matrix gla protein prevents ectopic mineralization.

Although the physiologic and pathologic substrates of ABCC6 are still unknown, it has been speculated that it exports a GGCX cofactor (e.g. a vitamin K–glutathione conjugate) from the liver into the circulation. In addition, serum levels of fetuin A, a major anti-mineralization protein that is secreted from the liver into the blood, are significantly reduced in PXE[25]. An ABCC6 defect could therefore result in decreased plasma anti-mineralization capacity due to reduced matrix gla protein and/or fetuin-A activity, allowing progressive mineralization of elastic fibers in target organs[26] (Fig. 97.4). Calcification of elastic fibers in the mid and deep dermis, the media and intima of mid-sized arteries, and Bruch's membrane of the eye produces the characteristic clinical and histopathologic changes of PXE.

Clinical Features

PXE primarily affects the elastic fiber networks of the skin, eyes and cardiovascular system. There is tremendous variability in severity even among siblings, and sometimes only one or two of these organ systems show signs of the disease.

PXE owes its name to the characteristic cutaneous findings, which bear some resemblance to xanthomas and represent the most frequent manifestation of the condition. Thin, yellowish papules typically appear in flexural areas during the first or second decade of life. The lateral neck is usually affected first (Fig. 97.5A,B). Over time, the papules coalesce to form cobblestone-like plaques, giving rise to a "plucked chicken skin" appearance (Fig. 97.5C). Other flexural sites that may be affected include the antecubital and popliteal fossae, wrists, axillae, groin and periumbilical area in multiparous women (not to be confused with *perforating periumbilical calcifying elastosis*, a localized, acquired,

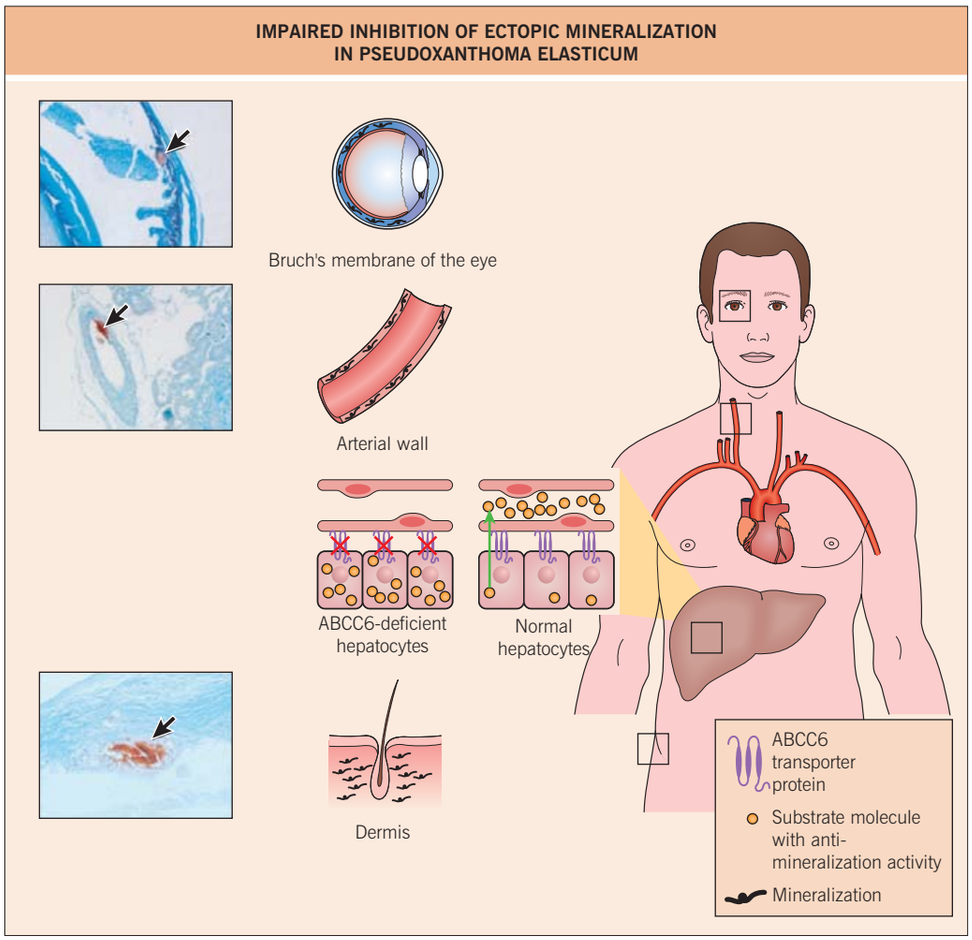


Fig. 97.4 Impaired inhibition of ectopic mineralization in pseudoxanthoma elasticum. The normal liver expresses high levels of the ABC-binding cassette subfamily C member 6 (ABCC6) protein, which serves as an efflux pump on the basolateral surface of hepatocytes, transporting molecules from inside these cells to the circulation. In patients with pseudoxanthoma elasticum (PXE), an absence of ABCC6 transporter activity in the liver results in reduced circulating concentrations of molecules that serve as physiologic anti-mineralization factors. This leads to calcification of connective tissues in the eye, arterial walls (media and intima) and dermis. The presence of calcium is evident on histopathological examination of these tissues (Alizarin red staining; see arrows in left panels) in ABCC6-/- mice, which recapitulate the features of human PXE. *Redrawn from Uitto J, Li Q, Jiang Q. Pseudoxanthoma elasticum: molecular genetics and putative pathomechanisms. J Invest Dermatol. 2010;130:661–70.*

Fig. 97.5 Clinical features of pseudoxanthoma elasticum. Yellowish papules and "cobblestoned" plaques on the neck (**A, B**) and in the antecubital fossa (**C**). Thickened, yellowish sagging skin in the axilla (**D**). *C, D, Courtesy, Julie V Schaffer, MD.*

purely cutaneous PXE-like condition [Table 97.4; see Ch. 96]). Involvement of non-flexural sites may occur in patients with more extensive disease.

With advanced disease, firm papules or plaques may develop as a result of increased dermal calcium deposition, and extrusion of this yellowish material through the epidermis as "perforating PXE" occasionally occurs. Loss of recoil due to impaired function of the elastic fiber network often leads to sagging of the skin, which is most notable in the axillae (Fig. 97.5D) and groin. Mucosal involvement presents as yellow papules, which are most often apparent on the lower lip (Fig. 97.6). Prominent creases develop on the chin in two-thirds of affected individuals <30 years of age and the vast majority of older patients.

DIFFERENTIAL DIAGNOSIS OF PSEUDOXANTHOMA ELASTICUM			
Disorder	**Patient characteristics**	**Clinical features**	**Histologic features**
Actinic elastosis	History of chronic sun exposure; lightly pigmented skin; middle-aged and older adults	Yellow to gray, thickened, lax, finely to coarsely wrinkled skin; photodistribution on the lateral forehead, neck, dorsal aspect of the forearms	Masses of basophilic, amorphous, degenerated elastic fibers in the papillary and upper reticular dermis
Late-onset focal dermal elastosis	7th–9th decades	Multiple 1–3 mm yellow papules; may coalesce; neck, axillae, groin, antecubital and popliteal fossae	*Increased* normal-appearing elastic fibers in the mid and deep reticular dermis
Elastoderma	3rd–4th decades	Localized areas of lax, pendulous skin; neck, trunk, arm	*Increased* normal- and abnormal-appearing elastic fibers throughout the dermis, extending into the subcutis
Perforating periumbilical calcific elastosis*	Multiparous black women; 5th–8th decades†	Plaque composed of coalescing keratotic papules (most apparent at the periphery); periumbilical area‡	Transepidermal elimination of calcified, distorted elastic fibers
PXE-like papillary dermal elastolysis§	6th–9th decades; primarily women	Multiple 2–3 mm yellow or skin-colored papules coalescing to form plaques with a cobblestone appearance; neck, flexor forearms, axillae, lower abdomen, inframammary folds	*Decreased* elastic tissue in a band-like distribution in the papillary dermis, with fragmentation and clumping of elastic fibers
White fibrous papulosis of the neck§	5th–9th decades; Japanese men, Caucasian women	Multiple 2–3 mm whitish papules; neck > upper trunk	*Decreased* elastic fibers in the papillary and mid reticular dermis; thickened collagen bundles

*Also referred to as periumbilical perforating PXE.
†Occasionally associated with an increased calcium–phosphate product in the setting of chronic renal failure.
‡Similar lesions have been reported on the breasts.
§Within the spectrum of fibroelastolytic diseases of the skin.

Table 97.4 Differential diagnosis of pseudoxanthoma elasticum (PXE). The differential diagnosis also includes PXE-like skin lesions in patients receiving D-penicillamine, after local exposure to saltpeter, and in longstanding end-stage renal disease. In addition, the possibility of underlying β-thalassemia or sickle cell anemia needs to be considered.

Fig. 97.6 Mucosal lesions in pseudoxanthoma elasticum. Yellow papules on the inner aspect of the lower lip.

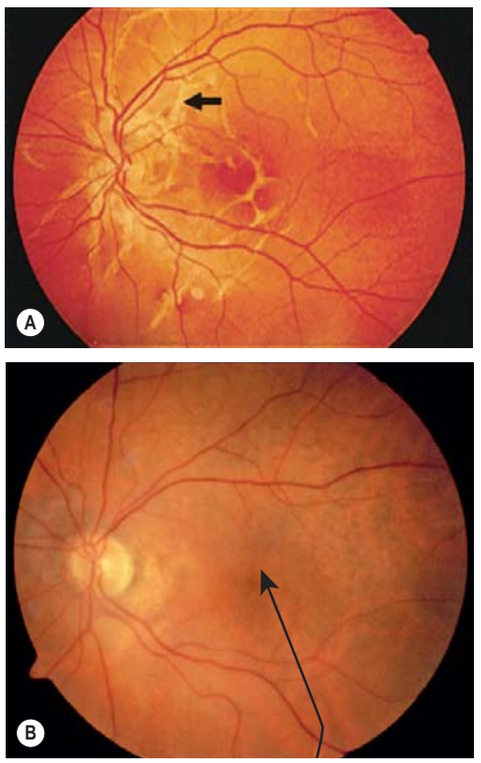


Fig. 97.7 Funduscopic findings in pseudoxanthoma elasticum (PXE). **A** Broad, lightly colored streaks (arrow) represent angioid streaks. **B** Mottling with "peau d'orange" color changes (arrow) over the entire retinal pigment epithelium, which may precede the onset of angioid streaks and represents the most common ophthalmologic finding in PXE.

The classic ocular finding in PXE is angioid streaks (Fig. 97.7A), which may be evident as early as the first decade of life and can be found in virtually all PXE patients by 30 years of age[21]. Angioid streaks are usually asymptomatic and reflect breaks in the calcified elastic lamina of Bruch's membrane, which is derived from the retina and choroid plexus. These fractures can lead to choroidal neovascularization, and the newly formed vessels are prone to hemorrhage with subsequent scarring. This process ultimately results in progressive loss of vision (especially in central fields), which usually becomes apparent after 40 years of age and occasionally leads to legal blindness.

Angioid streaks are highly characteristic but not pathognomonic of PXE. They can be encountered in a variety of metabolic and heritable disorders, including Paget's disease of the bone, sickle cell anemia, thalassemia, EDS and lead poisoning, as well as in the setting of age-related degeneration of Bruch's membrane. Mottling of the retinal pigment epithelium (referred to as "peau d'orange" changes) (Fig. 97.7B) is actually the most prevalent ophthalmologic finding in PXE and may precede the development of angioid streaks. Less commonly, macular degeneration, optic drusen and "owl's eyes" (paired hyperpigmented spots) may be detected.

Cardiovascular manifestations of PXE often cause significant morbidity and may even result in early death. PXE affects primarily mid-sized arteries, especially of the extremities, and progressive calcification of the elastic media and intima leads to the formation of atheromatous plaques. Sequelae may include intermittent claudication, loss of peripheral pulses, renovascular hypertension, angina pectoris, myocardial infarction and stroke, which typically occur at a much younger age than in the general population. Calcified blood vessels of the gastric and intestinal mucosa have an increased propensity for hemorrhage, and patients frequently present with gastrointestinal bleeding, particularly from the stomach[21]. Patients with PXE also have an increased prevalence of mitral valve prolapse.

Individuals with *GGCX* mutations have cutaneous, ocular and cardiovascular findings similar to those of classic PXE. The skin manifestations tend to be more extensive (affecting non-flexural areas of the trunk and extremities) and severe, with redundant folds of skin that resemble cutis laxa. Loss of visual acuity secondary to ocular

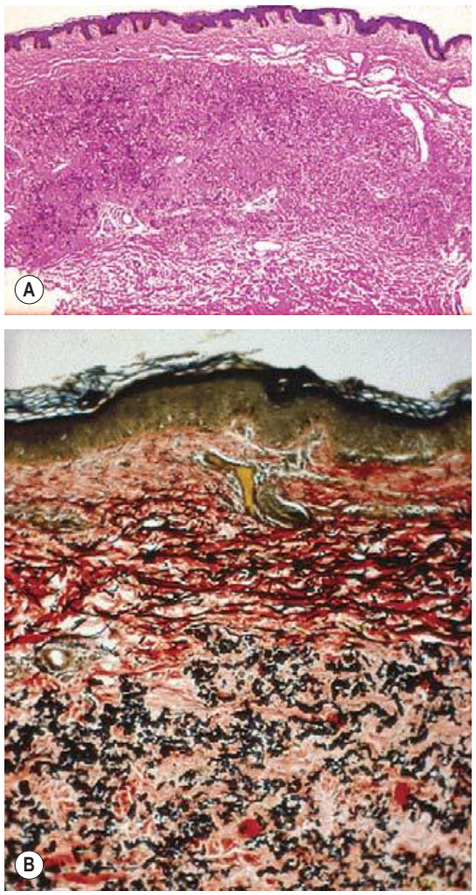


Fig. 97.8 Histopathology of pseudoxanthoma elasticum (PXE). **A** Purple clumps in the mid and deep reticular dermis in H&E-stained sections represent calcium deposits on elastic fibers in advanced PXE. **B** Verhoeff–van Gieson elastic stain can reveal black-staining, irregularly clumped elastic fibers in earlier disease.

involvement has not been described. Additional hemorrhagic complications may occur secondary to the associated coagulation factor deficiency, including epistaxis, gingival bleeding, menorrhagia and intracranial hemorrhage.

A MULTIDISCIPLINARY APPROACH TO MANAGEMENT OF PSEUDOXANTHOMA ELASTICUM

SKIN
No specific treatment is available Surgical intervention for excessive skin folds[39]
EYES
Prevention and early detection • Biannual funduscopic examination • Regular use of an Amsler grid to assess for central visual field defects • Use of sunglasses • Diet/vitamins rich in antioxidants • Avoidance of head trauma, heavy straining and smoking
Treatment • Laser photocoagulation or photodynamic therapy with verteporfin for choroidal neovascularization related to angioid streaks in patients with visual symptoms (recurrence rate 65% for laser therapy)[40] • Intravitreal injections of VEGF antagonists (e.g. bevacizumab)[41] • Macular translocation (only for extensive neovascularization)[42]
CARDIOVASCULAR SYSTEM
Prevention and early detection • Baseline electrocardiogram and echocardiogram • Annual cardiac examination • Healthy lifestyle with balanced diet, regular exercise, weight control, and avoidance of smoking and excessive alcohol intake • Magnesium supplementation* (e.g. magnesium carbonate-containing phosphate binders)[43] • Moderate calcium intake (as appropriate for age) • Low-dose therapy with acetylsalicylic acid if not contraindicated
Treatment • Correction of hyperlipidemia and hypertension • Low-dose acetylsalicylic acid, pentoxyfylline, cilostazol or clopidogrel for intermittent claudication
*A diet high in magnesium was shown to reduce connective tissue mineralization in a mouse model of PXE[43].

Table 97.5 A multidisciplinary approach to management of pseudoxanthoma elasticum. VEGF, vascular endothelial growth factor.

Pathology

Characteristic light microscopic changes in the skin consist of distorted, fragmented elastic fibers in the mid and deep reticular dermis. In advanced cases, calcium deposits on these altered elastic fibers are visible in routinely stained sections as purple clumps (Fig. 97.8A). Similar changes are observed in the media of mid-sized arteries. In early disease, stains for elastin (Verhoeff–van Gieson; Fig. 97.8B) and calcium (von Kossa) are sometimes necessary to visualize the characteristic alterations in the elastic fibers. In some patients without skin manifestations who are suspected to have PXE because of other findings, such as angioid streaks, a diagnosis may be confirmed by biopsy of a pre-existing scar[27].

Increased deposition of matrix proteins with a high degree of affinity for calcium is observed on an ultrastructural level; these proteins include osteonectin, fibronectin and vitronectin, as well as alkaline phosphatase and bone sialoprotein[28]. Serum levels of calcium and phosphate are normal[21].

Differential Diagnosis

Although the characteristic skin lesions of PXE are easily diagnosed in younger patients, actinic damage within chronically sun-exposed sites in older individuals can clinically mimic the yellowish, lax plaques of PXE. However, the latter involves the neck but not the axillae or groin. The differential diagnosis may also include late-onset focal dermal elastosis, elastoderma, perforating periumbilical calcific elastosis, and fibroelastolytic skin disorders (PXE-like papillary dermal elastolysis and white fibrous papulosis of the neck) (see Table 97.4)[29,30].

Skin lesions with the same morphology and distribution as PXE and similar histologic features have been observed in patients receiving D-penicillamine (which interferes with desmosine cross-linking in elastin; see below)[31], after local exposure to saltpeter[32,33], in longstanding end-stage renal disease[34] and (historically) in L-tryptophan-induced eosinophilia myalgia syndrome[35]. In patients with penicillamine-induced PXE-like skin changes, the von Kossa stain is negative, indicating no calcification of the abnormal fibers, whereas in saltpeter exposure and end-stage renal disease, calcification occurs and this stain is positive. Ophthalmologic and cardiovascular findings are absent and the skin lesions may resolve after cessation of the causative exposure or (in patients with renal disease) normalization of the serum calcium–phosphate product.

A PXE-like phenotype is present in up to 20% of the patients with β-thalassemia (Mediterranean populations) or sickle cell anemia[36]. Affected individuals may have characteristic cutaneous involvement as well as angioid streaks and vascular stigmata, but none of their siblings without a hematologic disorder have signs of PXE, and mutations in *ABCC6* have not been detected. Interestingly, down-regulation of ABCC6 expression in the liver has been observed in a mouse model of β-thalassemia, suggesting a possible pathogenic mechanism[37]. PXE-like skin lesions have also been encountered in amyloid elastosis, which typically occurs in the setting of primary systemic amyloidosis; histologic examination reveals amyloid deposits that encase dermal elastic fibers, which may be short and fragmented[38].

Treatment

An approach to the multidisciplinary management of PXE is presented in Table 97.5[39–43].

CUTIS LAXA

Synonyms: ■ Dermatochalasia ■ Dermatomegaly ■ Generalized elastolysis ■ Generalized elastorrhexis

Key features

- Group of conditions characterized by sparse and fragmented elastic fibers
- Both heritable (autosomal dominant or recessive) and acquired forms
- Features loose, sagging skin with reduced elasticity and resilience
- Extracutaneous manifestations include emphysema, hernias and diverticula

History

The clinical differences between cutis laxa (CL) and EDS were delineated in 1923 by F Parkes Weber[3], and the generalized nature of the elastolysis and potential for internal involvement were recognized by Goltz and co-workers in 1965[44].

Epidemiology

The heritable forms of CL are relatively rare and no precise estimate of their prevalence is available. There appears to be no racial or ethnic predilection, and inheritance can be autosomal dominant or autosomal recessive. Heritable CL is typically apparent at birth or during early childhood, but the development of lax skin is occasionally delayed until early adulthood in autosomal dominant forms. Acquired CL frequently has later onset.

Pathogenesis

CL represents a disorder of the elastic fiber network and can involve multiple tissues, including internal organs as well as the skin. Recent insights into the molecular bases of inherited forms of CL have refined the classification of this group of conditions (Table 97.6). Mutations in the elastin gene (*ELN*) that lead to qualitative as well as quantitative abnormalities in this protein have been identified as the cause of an autosomal dominant form of CL[45]. Defects in several genes can underlie autosomal recessive CL (ARCL), which tends to be more severe and is divided into two groups with different patterns of extracutaneous involvement. ARCL type I features potentially fatal involvement of the lungs, vascular abnormalities and gastrointestinal/genitourinary diverticula, whereas ARCL type II is characterized by craniofacial anomalies and delayed growth and development (see Table 97.6).

Initially, fibulin-5 "knockout" mice (see Ch. 3) were noted to develop a phenotype remarkably similar to human CL. In these mice, disorganization of elastic fibers resulted in loose skin, vascular abnormalities and emphysema. Fibulin-5 is a calcium-dependent elastin-binding protein that localizes to the surface of elastic fibers *in vivo*. Subsequently, homozygous fibulin-5 mutations were described in families with ARCL type I, and a heterozygous duplication within the fibulin-5 gene was also found in a sporadic case of CL[46,47]. Mutations in the fibulin-4 gene have also been identified in patients with ARCL type I, suggesting that fibulin-4 is necessary for elastic fiber formation[48]. Recently, mutations in the latent TGF-β binding protein-4 gene (*LTBP4*) were reported to underlie a lethal AR form of CL associated with severe pulmonary, gastrointestinal and genitourinary malformations[49]. The absence of LTBP4, an ECM protein that binds to fibrillin and controls the bioavailability of TGF-β, leads to aberrant TGF-β activity and defective elastic fiber assembly in many types of tissues.

Genetic defects in several intracellular proteins have been found to underlie ARCL type II. For example, mutations in both alleles of the *ATP6V0A2* gene, which encodes the A2 subunit of the vacuolar H^+-ATPase, produce a phenotypic spectrum that ranges from primarily "wrinkly skin" to severe CL in association with facial dysmorphism, microcephaly, joint laxity, and delayed growth and development[50]. ATP6V0A2 defects result in impaired N- and O-glycosylation, vesicular transport and secretion of tropoelastin, thereby reducing production of functional elastin. Interestingly, mutations in the pyrroline-5-carboxylate reductase 1 and pyrroline-5-carboxylate synthetase genes (*PYCR1* and *P5CS*, respectively) cause similar ARCL type II phenotypes[51]. These genes encode mitochondrial enzymes that are critical for the biosynthesis of proline, which is a major component of collagen and plays a role in an oxidative cycle important to cellular metabolism. PYCR1 deficiency causes abnormal mitochondrial morphology and increased apoptosis upon oxidative stress in fibroblasts, and it has been suggested that mitochondrial dysfunction is involved in the pathogenesis of these forms of CL, especially their progeroid and neurodegenerative manifestations (see Table 97.6).

An alternate pathogenic mechanism for CL, in particular acquired variants, is enhanced degradation of elastic fibers[52]. Sagging of the skin, usually with little or no associated internal organ involvement, can develop in the weeks to months following the onset of an inflammatory skin condition (e.g. a drug reaction, chronic urticaria, Sweet's syndrome). In these cases, release of elastases into the extracellular milieu by inflammatory cells (e.g. neutrophils, monocytes-macrophages) may lead to proteolytic degradation of elastic fibers[53]. Individuals with α_1-antitrypsin deficiency are especially susceptible to excessive proteolysis, and both generalized and localized (the latter following Sweet's syndrome [Marshall syndrome]) CL has been reported in these patients. Immunopathogenic mechanisms may play a role in some cases of acquired CL, as evidenced by the occurrence of acral or generalized CL in association with monoclonal gammopathies and observation of IgG, IgA or amyloid deposition on elastic fibers in lesional skin[54]. In addition, there may be an underlying genetic susceptibility for the development of CL, e.g. polymorphisms or "mild" mutations in the elastin and/or fibulin-5 genes[55].

Finally, CL-like cutaneous changes as well as elastosis perforans serpiginosa and PXE-like findings have been observed in patients treated for a prolonged period with high-dose D-penicillamine for conditions such as Wilson disease or cystinuria. D-Penicillamine can interfere with elastin cross-linking by two mechanisms. First, D-penicillamine is a copper chelator and can lower serum copper levels, which reduces the activity of lysyl oxidase, an enzyme required for elastin cross-linking (see Ch. 95)[56]. Second, D-penicillamine can chemically block the allysine and lysine residues that come together to form desmosine cross-links. As a result of these actions, newly synthesized elastin molecules do not become stably cross-linked. Instead, they are subject to rapid proteolysis, thus precluding the synthesis of functional elastic fibers.

Clinical Features

All forms of CL are characterized by loose, sagging skin with reduced elasticity and resilience. This often gives the affected patient an "aged" facial appearance with down-slanting palpebral fissures and a long philtrum (Fig. 97.9). Cutaneous findings are present at birth in most heritable forms of CL but may develop later in life in autosomal dominant as well as acquired variants. The laxity and wrinkling usually progress over time, although improvement of the skin with age has been noted in ARCL type II. Skin involvement is frequently generalized; however, it can be primarily acral in ARCL type II or acquired CL.

In some patients with CL, clinical manifestations are limited to the skin, and the phenotype is primarily of cosmetic concern. In other patients, the cutaneous findings are associated with prominent extracutaneous features, which can include emphysema, umbilical and inguinal hernias, gastrointestinal and genitourinary tract diverticula, cardiac or arterial abnormalities, skeletal or joint involvement, and delayed growth and development. The extracutaneous manifestations, particularly pulmonary complications, can cause considerable morbidity and mortality[44]. Association with congenital hemolytic anemia has also been reported[57]. The cutaneous and extracutaneous features of specific types of heritable CL are summarized in Table 97.6.

Generalized acquired CL without an identifiable trigger may be clinically indistinguishable from milder heritable forms of CL (e.g. late-onset autosomal dominant CL). Generalized or localized forms of acquired CL can also occur in association with a plasma cell dyscrasia (see Fig. 97.9B), as a consequence of drug intake (particularly penicillamine), and subsequent to a systemic or cutaneous inflammatory disorder (Table 97.7). In the latter situation, the inflammatory reaction is followed by progressive sagging of the skin, which can become extensive and lead to a prematurely aged appearance. Acquired CL most commonly develops in adults and presents with generalized skin involvement (often beginning on the face and neck), which can be associated with internal manifestations (e.g. emphysema, gastrointestinal and genitourinary diverticula). Occasionally, localized CL is found predominantly around the eyes (blepharochalasis) or on the distal extremities,

HERITABLE FORMS OF CUTIS LAXA AND RELATED CONDITIONS					
Disorder	**Inheritance**	**Gene***	**Protein**	**Distribution of cutis laxa**	**Additional features**
HERITABLE FORMS OF CUTIS LAXA					
AD cutis laxa	AD[†]	*ELN*	Elastin	Generalized	• Cardiac valve abnormalities, aortic dilatation (variable) • Emphysema (uncommon) • Hernias[‡]
		FBLN5	Fibulin-5		
AR cutis laxa type I[†]	AR	*FBLN4 (EFEMP2)*	Fibulin-4	Generalized	• Arterial/aortic tortuosity, aneurysms and stenoses • Emphysema (often severe/fatal) • GI and GU diverticula, hernias[‡] • Joint laxity, arachnodactyly, fractures (variable)
		FBLN5	Fibulin-5		
Cutis laxa with severe pulmonary, GI and GU abnormalities	AR	*LTBP4*	Latent TGF-β binding protein-4	Generalized	• Pulmonary malformations/emphysema (severe/fatal) • GI and GU malformations (diverticula, stenoses) • Facial dysmorphism[§], large fontanelles • Joint laxity, hypotonia
AR cutis laxa type IIA (including some patients with wrinkly skin syndrome)	AR	*ATP6V0A2*	Vacuolar H^+-ATPase A2 subunit	Generalized; improves over time	• Translucent skin with prominent veins (especially IIB) • Ocular abnormalities (strabismus & high myopia in IIA; corneal opacities & cataracts in DBS) • Facial dysmorphism[§], large fontanelles • Microcephaly • Partial pachygyria (IIA), absent corpus callosum (IIB) • Developmental delay ± neurologic degeneration; dystonia (DBS) • Congenital hip dislocation, joint laxity, hypotonia • Osteopenia, short stature (especially IIB) • Dental caries • O- and N-glycosylation defect (IIA[‖]) • Hyperammonemia (in a subset of the *ALDH18A1* type)
AR cutis laxa type IIB (including some patients with De Barsy syndrome [DBS] or a gerodermia osteodysplastica-like phenotype)	AR	*PYCR1*	Pyrroline-5-carboxylate reductase 1	Generalized, especially on dorsal hands and feet; improves over time	
		ALDH18A1 (rare variant)	Pyrroline-5-carboxylate synthetase		
Gerodermia osteodysplastica (geroderma osteodysplasticum)	AR	*GORAB (SCYL1BP1)*	Golgin, RAB6-interacting	Primarily on dorsal hands and feet	• Malar hypoplasia, prognathism, oblique furrow lateral to eyebrows • Joint laxity • Osteoporosis, fractures, dwarfism
Macrocephaly, alopecia, cutis laxa and scoliosis (MACS)	AR	*RIN2*	RAS and RAB interactor 2	Generalized, most pronounced on face	• Sparse hair • Gingival hypertrophy, facial dysmorphism • Macrocephaly • Scoliosis, joint laxity
Occipital horn syndrome	X-R	*ATP7A*	ATPase, Cu^{2+}-transporting, α-polypeptide	Generalized, most pronounced on face and neck	• Easy bruising, coarse hair (variable) • Arterial tortuosity • Chronic diarrhea; bladder diverticula • Long face, high forehead, hooked nose • Developmental delay • Wedge-shaped occipital calcifications • Joint laxity
RELATED HERITABLE CONDITIONS THAT FEATURE LAX AND/OR REDUNDANT SKIN					
Arterial tortuosity syndrome	AR	*SLC2A10*	Solute carrier family 2, member 10 (a glucose transporter)	Generalized	• Telangiectasias on cheeks (variable) • Arterial tortuosity • Long face, micrognathia, high-arched palate • Joint laxity and contractures

*A genetic defect has not been established for all patients classified in these subtypes.
[†]A recessive form of cutis laxa due to homozygous mutations in the elastin gene has been reported in a single family to date.
[‡]E.g. inguinal, umbilical, diaphragmatic.
[§]Features may include a broad forehead and midfacial hypoplasia as well as findings related to the lax skin (e.g. down-slanting palpebral fissures, long philtrum).
[‖]Can be assessed via analysis of the glycosylation of serum transferrin ± apolipoprotein C-III.

Table 97.6 Heritable forms of cutis laxa and related conditions. "Neonatal cutis laxa with a marfanoid phenotype" was described in an infant who lacked immunohistochemical evidence of laminin-β1 in the skin and had a heterozygous chromosomal break involving the *LAMB1* locus (which is near the *ELN* locus). Rare, autosomal recessive syndromes that can present with cutis laxa include transaldolase deficiency (also features hypertrichosis, hepatosplenomegaly, hemolytic anemia and GU malformations) and congenital disorders of glycosylation due to mutations in component of oligomeric Golgi complex 7 (*COG7*; fatal due to multiple-system malformations) or steroid 5-α-reductase 3 (*SRD5A3*; also features ichthyosis, ocular colobomas and midline brain malformations). AD, autosomal dominant; *ALDH18A1*, aldehyde dehydrogenase 18 family, member A1; AR, autosomal recessive; *EFEMP2*, EGF-containing fibulin-like extracellular matrix protein 2; GI, gastrointestinal; GU, genitourinary; TGF, transforming growth factor; X-R, X-linked recessive.

Continued

HERITABLE FORMS OF CUTIS LAXA AND RELATED CONDITIONS					
Disorder	**Inheritance**	**Gene***	**Protein**	**Distribution of cutis laxa**	**Additional features**
Costello syndrome	AR	*HRAS*	HRAS	Variable, especially on hands and feet	• Deep palmoplantar creases, acanthosis nigricans, periorificial papillomas • Curly or sparse hair, coarse facies • Cardiac malformations • Mental and growth retardation • Risk of malignancies, e.g. rhabdomyosarcoma
Donohue syndrome ("leprechaunism"; see Ch. 101)	AR	*INSR*	Insulin receptor	Variable	• Generalized lipodystrophy, hypertrichosis, acanthosis nigricans • Insulin resistance • Distinctive "elfin" facies • Severe growth retardation
Finnish-type amyloidosis	AD	*GSN*	Gelsolin	Generalized	• Corneal dystrophy • Polyneuropathy
"Michelin tire baby" syndrome (may represent multiple disorders with similar phenotypes; variant with extracutaneous findings also known as "circumferential skin creases Kunze type")	AD	?	?	Multiple circumferential creases/folds of skin on the extremities > neck > trunk (excess rather than lax skin)	• Affected skin may have excess fat or smooth muscle, and the latter is often associated with hypertrichosis; elastic fibers are usually normal (fragmentation noted in only one report) • Skin creases often resolve over time • Subset of patients has extracutaneous findings, most frequently cleft palate, thick/overfolded helices, dysmorphic facies (e.g. epicanthal folds, small eyes), and delayed growth and development

*A genetic defect has not been established for all patients classified in these subtypes.

Table 97.6 Heritable forms of cutis laxa and related conditions (cont'd). "Neonatal cutis laxa with a marfanoid phenotype" was described in an infant who lacked immunohistochemical evidence of laminin-β1 in the skin and had a heterozygous chromosomal break involving the *LAMB1* locus (which is near the *ELN* locus). Rare, autosomal recessive syndromes that can present with cutis laxa include transaldolase deficiency (also features hypertrichosis, hepatosplenomegaly, hemolytic anemia and GU malformations) and congenital disorders of glycosylation due to mutations in component of oligomeric Golgi complex 7 (*COG7*; also features ichthyosis, ocular colobomas and midline brain malformations) or steroid 5-α-reductase 3 (*SRD5A3*; fatal due to multiple-system malformations). AD, autosomal dominant; AR, autosomal recessive.

ACQUIRED CUTIS LAXA: ASSOCIATED CONDITIONS
SKIN DISORDERS
• Urticaria and/or angioedema • Drug eruptions (e.g. due to penicillin or an SSRI) • Sweet syndrome-like eruptions (Marshall syndrome*) • Arthropod bite reactions • Erythema multiforme • Dermatitis herpetiformis • Lupus panniculitis • Interstitial granulomatous dermatitis • Cutaneous mastocytosis • Cutaneous lymphoma
EXTRACUTANEOUS INFLAMMATORY DISORDERS
• Rheumatoid arthritis • Systemic lupus erythematosus • Nephrotic syndrome • Celiac disease • Sarcoidosis
HEMATOLOGIC DISORDERS
• Monoclonal gammopathy (especially acral CL; underlying plasma cell dyscrasia) • Congenital hemolytic anemia
INFECTIOUS DISEASES
• Febrile viral syndrome • *Borrelia burgdorferi* infection • Syphilis
DRUG INTAKE (ALSO SEE DRUG ERUPTIONS ABOVE)
• Penicillamine • Isoniazid (single report)
*Referred to as type II acquired CL, with other forms of acquired CL classified as type I.

Table 97.7 Acquired cutis laxa (CL): associated conditions. Generalized or localized CL (including Marshall syndrome) can occur in the setting of α_1-antitrypsin deficiency. SSRI, selective serotonin reuptake inhibitor.

particularly the palms and soles. Marshall syndrome refers to CL in association with a Sweet syndrome-like neutrophilic dermatosis, and it occurs primarily in infants and young children[58].

Pathology

In the skin of patients with CL, the characteristic histologic feature is sparse and/or fragmented elastic fibers (Fig. 97.10). This ranges from virtual absence of elastic fibers in a newborn with severe CL (e.g. ARCL type I) to fragmentation but a normal density of fibers in late-onset autosomal dominant CL. Electron microscopy shows irregular fragmentation of the elastic fiber structure. In some patients, elastic fiber abnormalities are accompanied by alterations in collagen fibers, which likely reflect a general perturbation of the ECM and mechanical properties of the skin due to the primary elastic fiber defect.

Differential Diagnosis

Clinical findings consistent with CL can develop as a consequence of the normal aging process of the skin. In contrast to CL, the hyperextensible skin of patients with EDS retains its elasticity and recoil, with the exception of lax as well as "doughy" and extremely fragile skin in the rare dermatosparaxis type of EDS. As in other forms of EDS, the primary pathology in dermatosparaxis resides in the collagen meshwork, and a diagnosis of CL should be reserved for conditions characterized by abnormalities in the structure or quantity of elastic fibers. In PXE and the related PXE-like disorder associated with coagulation factor deficiency, the skin can be loose and sagging without recoil; however, the primary papular lesions at the predilection sites distinguish these conditions from CL.

Mid-dermal elastolysis (see Ch. 99) is an acquired disorder with a predilection for young and middle-aged women that is characterized by circumscribed or diffuse areas of fine wrinkling, most often in sun-exposed sites on the upper trunk, lateral neck and upper arms[59]. It features the pathognomonic histopathologic finding of a band-like loss of elastic fibers in the mid dermis. Anetoderma presents as focal areas of flaccid skin (e.g. 1 to 2 cm in diameter) with loss of elastic tissue

Fig. 97.9 Clinical features in cutis laxa. **A** Loose skin and drooping jowls in an infant with heritable cutis laxa. **B** Sagging folds of skin giving a prematurely aged appearance to a man with acquired cutis laxa associated with multiple myeloma. *A, Courtesy, Thomas Schwarz, MD. B, Courtesy, Jeffrey P Callen, MD.*

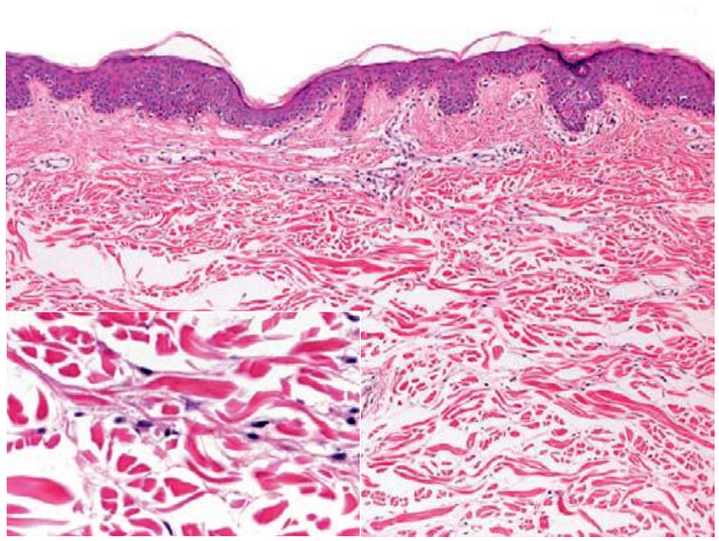


Fig. 97.10 Histologic features of cutis laxa. Dermal elastic fibers are sparse and fragmented. *Courtesy, Lorenzo Cerroni, MD.*

and may have an antecedent inflammatory process. It is histologically and ultrastructurally identical to CL and may be regarded as a variant of acquired localized CL with smaller, circumscribed lesions.

Several rare syndromes can present with lax skin and elastic fiber abnormalities characteristic of CL (see Table 97.6)[60]. The features of gerodermia osteodysplastica, wrinkly skin syndrome and De Barsy syndrome overlap considerably with those of ARCL type II, and many of the patients recently reported to have the latter condition (based on molecular testing as well as clinical findings) had previously been diagnosed with one or more of the former disorders. "Michelin tire baby" syndrome (see Table 97.6) presents with congenital circumferential skin creases on the extremities that may be reminiscent of CL, but the folds reflect excess tissue rather than cutaneous laxity.

Treatment

The redundant and sagging skin may be of major cosmetic concern to patients with CL, and reconstructive surgery can provide a dramatic improvement with significant psychosocial benefit. Surgical wounds heal with scars that have a normal appearance and tensile strength. However, sagging may reoccur, necessitating additional surgical procedures. The associated internal organ involvement requires appropriate care through a multidisciplinary approach.

REFERENCES

1. Sybert VP. Genetic Skin Disorders. Oxford Monographs on Medical Genetics, No. 33. Oxford: Oxford University Press, 1997.
2. Pulkkinen L, Ringpfeil F, Uitto J. Progress in heritable skin diseases: molecular bases and clinical implications. J Am Acad Dermatol. 2002;47:91–104.
3. McKusick VA. Heritable Disorders of Connective Tissue, 4th edn. St Louis: Mosby, 1972.
4. Beighton P, De Paepe A, Steinmann B, et al. Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). Am J Med Genet. 1998;77:31–7.
5. Burrows NP. The molecular genetics of the Ehlers-Danlos syndrome. Clin Exp Dermatol. 1999;24:99–106.
6. Mao JR, Bristow J. The Ehlers-Danlos syndrome: on beyond collagens. J Clin Invest. 2001;107:1063–9.
7. Pyeritz RE. Ehlers-Danlos syndrome. N Engl J Med. 2000;342:730–2.
8. Myllyharju J, Kivirikko KI. Collagens and collagen-related diseases. Ann Med. 2001;33:7–21.
9. Schalkwijk J, Zweers MC, Steijlen PM, et al. A recessive form of the Ehlers-Danlos syndrome caused by tenascin-X deficiency. N Engl J Med. 2001;345:1167–75.
10. Mao JR, Taylor G, Dean WB, et al. Tenascin-X deficiency mimics Ehlers-Danlos syndrome in mice through alteration of collagen deposition. Nat Genet. 2002;30:421–5.
11. Steinmann B, Royce PM. Connective Tissue and its Heritable Disorders. Molecular Genetic, and Medical Aspects. New York: Wiley-Liss, 1993.
12. Atzinger CL, Meyer RA, Khoury PR, et al. Cross-sectional and longitudinal assessment of aortic root dilation and valvular anomalies in hypermobile and classic Ehlers-Danlos syndrome. J Pediatr. 2011;158:826–30.
13. Pepin M, Schwarze U, Superti-Furga A, Byers PH. Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type. N Engl J Med. 2000;342:673–80.
14. Balzer F. Recherches sur les charactères anatomiques du xanthelasma. Arch Physiol. 1884;4:65–80.
15. Chauffard MA. Xanthelasma disséminé et symmétrique sans insufficiance hépatique. Bull Soc Med Hop Paris. 1889;6:412–19.
16. Darier J. Pseudo-xanthome élastique. IIIe Congrès Intern de Dermat de Londres. 1896;5:289–95.
17. Grönblad E. Angioid streaks – pseudoxanthoma elasticum. Acta Ophthalmol. 1929;7:329.
18. Strandberg J. Pseudoxanthoma elasticum. Z Haut Geschlechtskr. 1929;31:689–94.
19. Ringpfeil F, Lebwohl MG, Christiano AM, Uitto J. Pseudoxanthoma elasticum: mutations in the MRP6 gene encoding a transmembrane ATP-binding cassette (ABC) transporter. Proc Natl Acad Sci U S A. 2000;97:6001–6.
20. Ringpfeil F, McGuigan K, Fuchsel L, et al. Pseudoxanthoma elasticum is a recessive disease characterized by compound heterozygosity. J Invest Derm. 2006;126:782–6.
21. Neldner KH. Pseudoxanthoma elasticum. Clin Dermatol. 1988;6:1–159.
22. Martin L, Maître F, Bonicel P, et al. Heterozygosity for a single mutation in the *ABCC6* gene may closely mimic PXE: consequences of this phenotype overlap for the definition of PXE. Arch Dermatol. 2008;144:301–6.
23. Vanakker OM, Martin L, Gheduzzi D, et al. Pseudoxanthoma elasticum-like phenotype with cutis laxa and multiple coagulation factor deficiency represents a separate genetic entity. J Invest Dermatol. 2007;127:584–7.
24. Li Q, Grange DK, Armstrong NL, et al. Mutations in the *GGCX* and *ABCC6* genes in a family with pseudoxanthoma elasticum-like phenotypes. J Invest Dermatol. 2009;129:553–63.

25. Hendig D, Schulz V, Arndt M, et al. Role of serum fetuin-A, a major inhibitor of systemic calcification, in pseudoxanthoma elasticum. Clin Chem. 2006;52: 227–34.
26. Uitto J, Li Q, Jiang Q. Pseudoxanthoma elasticum: Molecular genetics and putative pathomechanisms. J Invest Dermatol. 2010;130:661–70.
27. Lebwohl M, Phelps RG, Yannuzzi L, et al. Diagnosis of pseudoxanthoma elasticum by scar biopsy in patients without characteristic skin lesions. N Engl J Med. 1987;317:347–50.
28. Contri MB, Boraldi F, Taparelli F, et al. Matrix proteins with high affinity for calcium ions are associated with mineralization within the elastic fibers of pseudoxanthoma elasticum dermis. Am J Pathol. 1996;148:569–77.
29. Lewis KG, Bercovitch L, Dill SW, Robinson-Bostom L. Acquired disorders of elastic tissue: Part I. Increased elastic tissue and solar elastosis syndromes. J Am Acad Dermatol. 2004;51:1–21.
30. Lewis KG, Bercovitch L, Dill SW, Robinson-Bostom L. Acquired disorders of elastic tissue: Part II. Decreased elastic tissue. J Am Acad Dermatol. 2004;51:165–85.
31. Bolognia JL, Braverman I. Pseudoxanthoma-elasticum-like skin changes induced by penicillamine. Dermatology. 1992;184:12–8.
32. Nielsen AO, Christensen OB, Hentzer B, et al. Salpeter-induced dermal changes electron-microscopically indistinguishable from pseudoxanthoma elasticum. Acta Derm Venereol. 1978;58:323–7.
33. Christensen OB. An exogenous variety of pseudoxanthoma elasticum in old farmers. Acta Derm Venereol. 1978;58:319–21.
34. Nickoloff BJ, Noodleman FR, Abel EA. Perforating pseudoxanthoma elasticum associated with chronic renal failure and hemodialysis. Arch Dermatol. 1985;121:1321–2.
35. Mainetti C, Masouye I, Saurat JH. Pseudoxanthoma elasticum-like lesions in the L-tryptophan-induced eosinophilia-myalgia syndrome. J Am Acad Dermatol. 1991;24:657–8.
36. Aessopos A, Farmakis D, Loukopoulos D. Elastic tissue abnormalities resembling pseudoxanthoma elasticum in beta thalassemia and the sickling syndromes. Blood. 2002;99:30–5.
37. Martin L, Douet V, VanWart CM, et al. A mouse model of β-thalassemia shows a liver-specific down-regulation of Abcc6 expression. Am J Pathol. 2011;178:774–83.
38. Sepp N, Pichler E, Breathnach SM, et al. Amyloid elastosis: analysis of the role of amyloid P component. J Am Acad Dermatol. 1990;22:27–34.
39. Viljoen DL, Bloch C, Beighton P. Plastic surgery in pseudoxanthoma elasticum: experience in nine patients. Plast Reconstr Surg. 1990;85:233–8.
40. Lim JI, Bressler NM, Marsh MJ, Bressler SB. Laser treatment of choroidal neovascularization in patients with angioid streaks. Am J Ophthalmol. 1993;116: 414–23.
41. Sawa M, Gomi F, Tsujikawa M, et al. Long-term results of intravitreal bevacizumab injection for choroidal neovascularization secondary to angioid streaks. Am J Ophthalmol. 2009;148:584–90.
42. Roth DB, Estafanous M, Lewis H. Macular translocation for subfoveal choroidal neovascularization in angioid streaks. Am J Ophthalmol. 2001;131:390–2.
43. LaRusso J, Li Q, Uitto J. Elevated dietary magnesium prevents connective tissue mineralization in a mouse model of pseudoxanthoma elasticum. J Invest Dermatol. 2009;129:1388–94.
44. Goltz RW, Hult AM, Goldfarb M, Gorlin RJ. Cutis laxa. A manifestation of generalized elastolysis. Arch Dermatol. 1965;92:373–87.
45. Tassabehji M, Metcalfe K, Hurst J, et al. An elastin gene mutation producing abnormal tropoelastin and abnormal elastic fibers in a patient with autosomal dominant cutis laxa. Hum Mol Genet. 1998;7:1021–8.
46. Loeys B, Van Maldergem L, Mortier G, et al. Homozygosity for a missense mutation in fibulin-5 (*FBLN5*) results in a severe form of cutis laxa. Hum Mol Genet. 2002;11:2113–18.
47. Elahi E, Kalhor R, Banihosseini SS, et al. Homozygous missense mutation in fibulin-5 in an Iranian autosomal recessive cutis laxa pedigree and associated haplotype. J Invest Dermatol. 2006;126:1506–9.
48. Hucthagowder V, Sausgruber N, Kim KH, et al. Fibulin-4: a novel gene for an autosomal recessive cutis laxa syndrome. Am J Hum Genet. 2006;78:1075–80.
49. Urban Z, Hucthagowder V, Schürmann N, et al. Mutations in *LTBP4* cause a syndrome of impaired pulmonary, gastrointestinal, genitourinary, musculoskeletal, and dermal development. Am J Hum Genet. 2009;85:593–605.
50. Kornak U, Reynders E, Dimopoulou A, et al. Impaired glycosylation and cutis laxa caused by mutations in the vesicular H+-ATPase subunit ATP6V0A2. Nat Genet. 2008;40:32–4.
51. Guernsey DL, Jiang H, Evans SC, et al. Mutation in pyrroline-5-carboxylate reductase 1 gene in families with cutis laxa type 2. Am J Hum Genet. 2009;85:120–9.
52. Anderson LL, Oikarinen AI, Ryhänen L, et al. Characterization and partial purification of a neutral protease from the serum of a patient with autosomal recessive pulmonary emphysema and cutis laxa. J Lab Clin Med. 1985;105:537–46.
53. Shapiro SD. Matrix metalloproteinase degradation of extracellular matrix: biological consequences. Curr Opin Cell Biol. 1998;10:602–8.
54. Krajnc I, Rems D, Vizjak A, Hodl S. Acquired generalized cutis laxa with paraproteinemia (IgG lambda). Immunofluorescence study, clinical and histologic findings with review of the literature. Hautarzt. 1996;47:545–9.
55. Hu Q, Reymond J-L, Pinel N, et al. Inflammatory destruction of elastic fibers in acquired cutis laxa is associated with missense alleles in the elastin and fibulin-5 genes. J Invest Dermatol. 2006;126:283–90.
56. Uitto J, Pulkkinen L. Heritable disorders affecting the elastic tissues: cutis laxa, pseudoxanthoma elasticum and related disorders. In: Rimoin DL, Connor JM, Pyeritz RE (eds). Emery and Rimoin's Principles and Practice of Medical Genetics, 3rd edn. London: Churchill Livingstone, 2002.
57. Anderson CE, Finklestein JZ, Nussbaum E, et al. Association of hemolytic anemia and early-onset pulmonary emphysema in three siblings. J Pediatr. 1984;105:247–51.
58. Marshall J, Heyl T, Weber HW. Post inflammatory elastolysis and cutis laxa. South Afr Med J. 1966,40: 1016–22
59. Rao BK, Endzweig CH, Kagen MH, et al. Wrinkling due to mid-dermal elastolysis: two cases and literature review. J Cutan Med Surg. 2000;4:40–4.
60. Morava E, Guillard M, Lefeber DJ, et al. Autosomal recessive cutis laxa syndrome revisited. Eur J Hum Genet. 2009;17:1099–110.

Dermal Hypertrophies 98

Marco Romanelli, Valentina Dini, Mariya Miteva and Paolo Romanelli

Chapter Contents

Hypertrophic scars and keloids 1621
Dupuytren's contracture 1625
Cutis verticis gyrata 1626
Juvenile hyaline fibromatosis and infantile systemic hyalinosis 1626
Elastic tissue-related disorders 1628

This chapter will discuss disorders in which there are increased amounts of collagen within the skin, followed by those with increased elastin.

HYPERTROPHIC SCARS AND KELOIDS

Key features

- Normal scars are preceded by injury, immediate in onset, flat and asymptomatic
- Hypertrophic scars are raised and confined to the wound margin. Sometimes they improve spontaneously and tend to have a good response to treatment
- Keloids extend beyond the wound margin and are delayed in onset. They seldom resolve spontaneously, and their response to treatment is often poor
- Compared to normal skin and normal scars, both hypertrophic scars and keloids have increased cellularity, vascularity and connective tissue

Introduction

Hypertrophic scars and keloids represent two forms of abnormal wound healing. Both are characterized by local fibroblast proliferation and excessive collagen production in response to cutaneous injury. However, their clinical and histopathologic features differ, as well as proposed pathogeneses. While keloids are often more elevated above the skin surface than hypertrophic scars, the key difference is that keloids extend beyond the original wound margin into adjacent normal skin, often with claw-like extensions resembling the pincers of a crab. Hypertrophic scars, on the other hand, remain confined to the site of the original injury. Both keloids and hypertrophic scars favor sites of increased tension, but keloids can also appear in sites such as the earlobe, where there is minimal tension.

Epidemiology

There is a higher incidence of keloids in darkly pigmented individuals of African ancestry. From 4.5% to 16% of predominantly black and Hispanic populations have keloids, with an incidence of up to 16% in black Africans[1]. Although the incidence of hypertrophic scars is probably higher than that of keloids, precise data are lacking. There is often a familial tendency to develop hypertrophic scars and keloids and possibly an autosomal dominant mode of inheritance with incomplete clinical penetrance and variable expression.

Keloids may occur at any age, but they tend to form in individuals between 10 and 30 years of age. Younger individuals are more frequently subjected to trauma and younger skin possesses greater tension, whereas older skin is less elastic and has more redundancy. The rate of collagen synthesis is also greater in younger persons[2].

Pathogenesis

Factors that play a major role in keloid development include genetic predisposition, typically coupled with some form of skin injury[3]. The latter include lacerations, burns, surgical excisions, skin piercings and injections (vaccines, tattoo inks) as well as cutaneous inflammation (e.g. acne vulgaris, insect bites). Whether the latter play a role in spontaneous keloids is a matter of debate.

Wound or skin tension has also been implicated as a critical factor in the formation of keloids and hypertrophic scars[4]. When there is loss of tissue as in a surgical excision, the attempt to close the wound creates tension. In addition, constant tension is transmitted to the skin from the underlying musculoskeletal structures. The possibility of hormonal influences has been raised[5] to provide an explanation for the appearance of keloids at or after puberty and their resolution following menopause, in addition to reports of the onset or enlargement of keloids during pregnancy.

Insight into the normal sequence of wound healing is important in understanding the pathophysiology of hypertrophic scars and keloids. Normal wound healing occurs in three phases: the inflammatory phase, the proliferative or granulation phase, and the maturation or remodeling phase (see Ch. 141). During the normal maturation phase, the nodularity and redness of the wound soften and flatten due to simultaneous collagen synthesis and degradation. In keloids, collagen

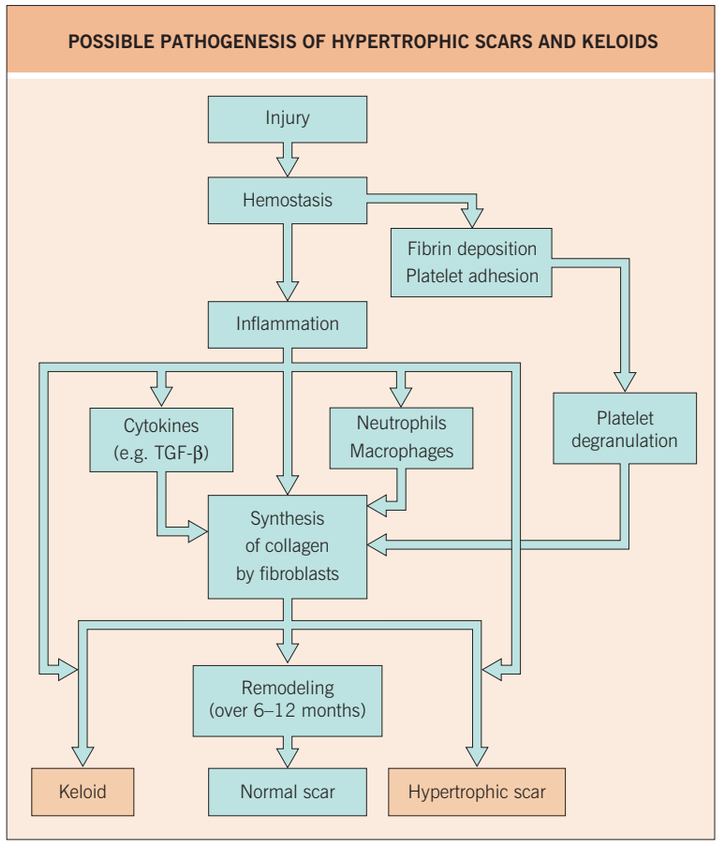


Fig. 98.1 Possible pathogenesis of hypertrophic scars and keloids. TGF, transforming growth factor. *Courtesy, Claude Burton, MD.*

DIFFERENCES IN ADULT VERSUS FETAL WOUND HEALING		
	Adult	**Fetal**
Fluid environment	No	Yes
Sterile environment	No	Yes
Inflammation	Yes	No
Scar formation	Yes	No
pO_2 (mmHg)	>60	20

Table 98.1 Differences in adult versus fetal wound healing.

synthesis is ~20 times and 3 times greater than in normal non-injured skin and hypertrophic scars, respectively. This collagen overproduction is attributed in large part to the activity of keloidal fibroblasts.

The influence of various growth factors on scar and keloid formation has been the subject of more recent studies[6]. As in systemic sclerosis, both transforming growth factor (TGF)-β and platelet-derived growth factor (PDGF) have been shown to play an integral role (Fig. 98.1). For example, the majority of cells involved in wound healing express TGF-β in an initially inactive form (which becomes active following its release from the latency associated protein; see Fig. 95.7) that strongly promotes the chemotaxis of fibroblasts to the site of injury. In keloidal tissue, TGF-β, which is known to play a critical role in fibroblast proliferation and collagen production, is overproduced and poorly regulated via autocrine signaling pathways. At the same time, keloidal fibroblasts have increased expression of growth factor receptors, including for TGF-β and PDGF, and therefore respond more intensely to these growth factors. Decreased production of molecules that promote matrix breakdown (e.g. matrix metalloproteinases [MMPs]) may also be occurring within keloids. Lastly, in comparison to normal dermal fibroblasts, keloidal fibroblasts exhibit a reduced rate of apoptosis[7].

Especially interesting is the observation that fetal wounds (prior to the third trimester) heal *without* scarring[8]. Scrutiny of the differences between adult and fetal wound healing suggests that both inflammation and cytokines unique to adult wound healing are likely to play a prominent role in the development of hypertrophic scars and keloids (Table 98.1).

Clinical Features

Both keloids and hypertrophic scars have a smooth surface and are firm to palpation. They may be pruritic or painful and can even inhibit normal motion of adjacent tissues. The color can vary from pink–purple (early lesions) to skin-colored to hypo- or hyperpigmented. While keloids may be more elevated above the skin surface than hypertrophic scars, the key difference is that keloids extend beyond the original wound margin into adjacent normal skin, often with claw-like extensions resembling the pincers of a crab (in Greek, *chelè* means claw; Figs 98.2 & 98.3). Hypertrophic scars, on the other hand, remain confined to the site of the original injury (Figs 98.4 & 98.5). Both keloids and hypertrophic scars favor sites of increased wound tension (e.g. upper trunk, deltoid region), but keloids can also appear in sites such as the earlobe, where there is minimal tension (Fig. 98.6). Additional clinical features are outlined in Table 98.2.

Scar assessment

Assessment of any scar begins with a determination of its extent, i.e. surface area or volume, based upon measurement of the maximum dimensions and thickness. In addition, subjective scales, such as the Vancouver Scar Scale (VSS), have been developed to provide an overall impression of the quality of the scar (Table 98.3)[9]. While the VSS is widely accepted, some authors have questioned its reliability and validity[10], and scales that incorporate both patient and observer scar assessments have subsequently been developed and shown to be reliable[11,12].

Non-invasive techniques can be used to measure scar color, blood flow, transcutaneous oxygen tension, skin hardness, elasticity and hydration[13]. In addition, skin imaging techniques such as dedicated scar photography, high-frequency ultrasound, laser Doppler perfusion imaging, confocal microscopy and magnetic resonance imaging can be employed to objectively evaluate scars[14]. However, the eventual goal is to create an easy-to-use and inexpensive system that monitors the qualitative and quantitative evolution of scars[15].

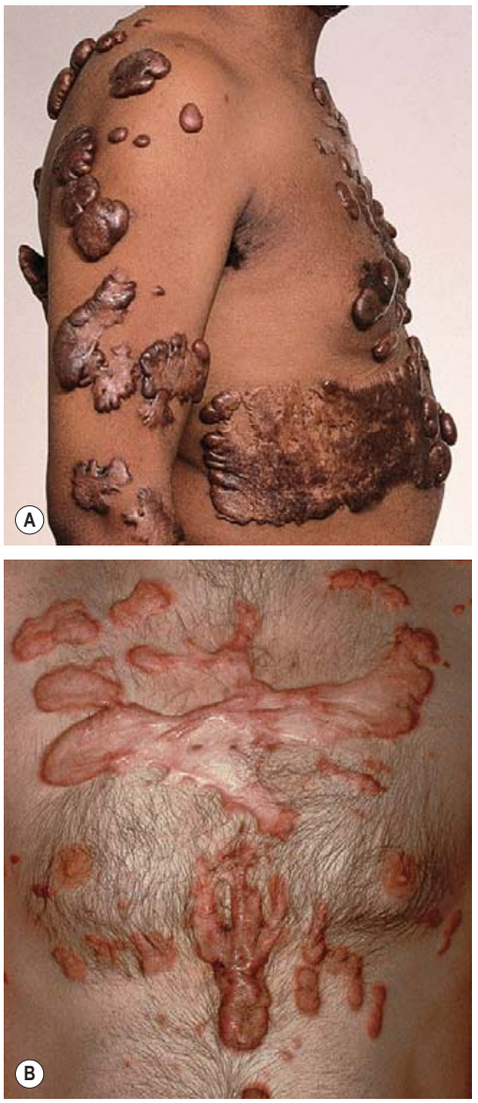


Fig. 98.2 Spontaneous generalized keloids. Extensive spontaneous keloids in a patient with darkly pigmented skin (**A**) and a patient with lightly pigmented skin (**B**). *A, Courtesy, Claude Burton, MD.*

Fig. 98.3 Keloid of the flexor arm in an African-American man. Note the extension of the keloid into the normal surrounding skin in a claw-like manner and the central involution. *Courtesy, Claude Burton, MD.*

Pathology

In hypertrophic scars, there is an increase in both the number of fibroblasts and density of collagen fibers within the dermis (Fig. 98.7). The orientation of both the cells, which are spindle-shaped, and the collagen becomes parallel to the skin surface[16,17]. Dermal blood vessels are vertically oriented (i.e. perpendicular to the skin surface; see Fig. 98.7B), and there may be a sparse perivascular inflammatory infiltrate. Elastic tissue is diminished or absent. Keloids are characterized by the presence of thick hyalinized collagen bundles in a haphazard array with mucinous

Fig. 98.4 Hypertrophic scar at the site of an excision of an atypical melanocytic nevus. The deltoid region is a common location for hypertrophic scars. *Courtesy, Jean L Bolognia, MD.*

KEY FEATURES OF NORMAL, HYPERTROPHIC AND KELOID SCARS			
	Normal scar	**Hypertrophic scar**	**Keloid**
Preceded by injury	Yes	Yes	Not always
Onset	Immediate	Immediate	Delayed (sometimes months)
Erythema	Temporary	Prominent	Varies
Profile	Flat	Raised	Raised
Symptomatic	No	Yes	Yes
Confined to wound margin	Yes	Yes	No
Increased mast cells	No	Yes	Yes
Contains myofibroblasts within nodules	N/A	Yes	No
Spontaneous resolution	N/A	Sometimes, gradual	Rare
Treatment response	N/A	Good	Poor

Table 98.2 Key features of normal, hypertrophic and keloid scars. N/A, not applicable.

Fig. 98.5 Multiple hypertrophic scars due to acne vulgaris. The posterior trunk is a common location for hypertrophic scars. *Courtesy, Julie V Schaffer, MD.*

Fig. 98.6 Keloid of the earlobe in an African-American woman. The earlobe, where piercing has been performed for placement of earrings, is a common site for keloid formation. *Courtesy, Joyce Rico, MD.*

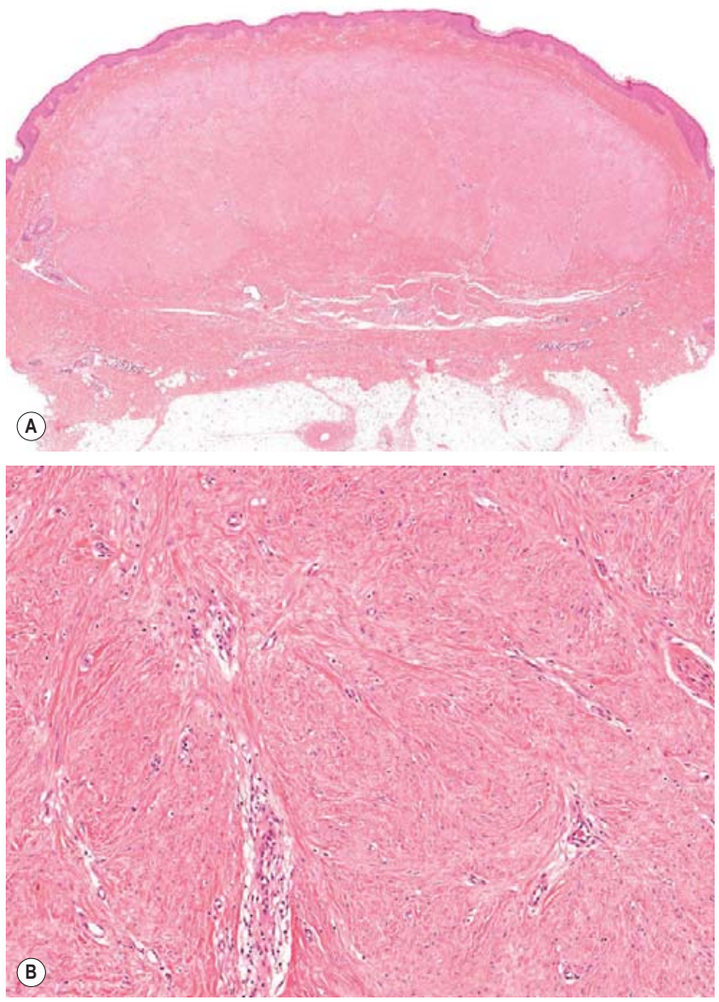


Fig. 98.7 Hypertrophic scar – histologic features. A Replacement of the dermis by hypertrophic bundles of collagen with increased numbers of fibroblasts. **B** Vertically oriented blood vessels, nodules of collagen and fibroblasts. *Courtesy, Lorenzo Cerroni, MD.*

VANCOUVER SCAR SCALE					
Score for each clinical feature	**0**	**1**	**2**	**3**	**4**
Pliability	Normal	Supple	Yielding	Firm	Adherent
Height	Normal	1–2 mm	3–4 mm	5–6 mm	>6 mm
Vascularity	Normal	Pink	Red	Purple	–
Pigmentation	Normal	Hypopigmentation	Hyperpigmentation	–	–

Table 98.3 Vancouver scar scale.

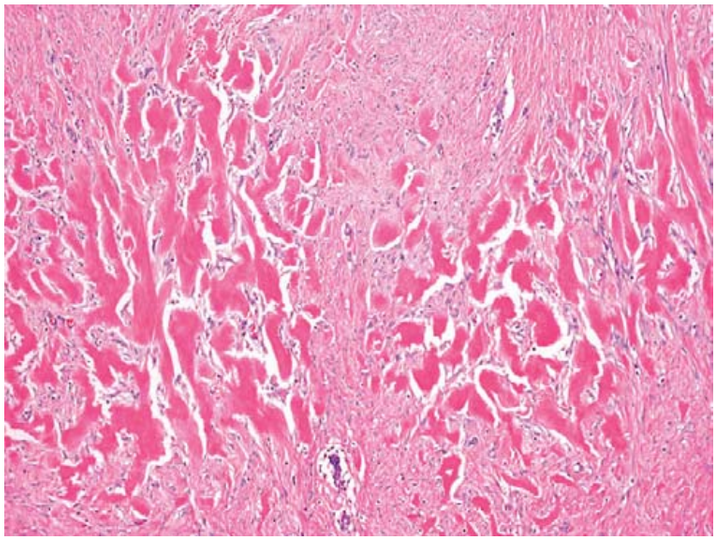


Fig. 98.8 Mature keloid – histologic features. Strikingly thick, glassy, homogeneous collagen bundles oriented haphazardly throughout the dermis.
Courtesy, Lorenzo Cerrroni, MD.

Fig. 98.9 Hidradenitis suppurativa of the axilla. In this patient, hypertrophic scars plus the formation of sinus tracts creates a keloid-like appearance.

ground substance and an increased number of fibroblasts. In general, the overlying epidermis and papillary dermis are uninvolved. Early on, there are abundant deposits of fibrillary collagen within the reticular dermis, while mature keloids often have strikingly thick, glassy, homogeneous collagen bundles; the latter are composed of multiple densely packed fibrils and are oriented *haphazardly* throughout the dermis (Fig. 98.8). In longstanding keloids, there may be a return to the earlier fibrillary pattern. There are fewer, if any, vertically oriented blood vessels, compared with hypertrophic scars[18]. Both keloids and hypertrophic scars have an absence of subepidermal adnexal structures.

Because keloidal collagen is not always present (absent in up to 45% of lesions, depending upon the series[16]), additional histologic findings may prove helpful in distinguishing keloids from hypertrophic scars. These include (in keloids) a tongue-like advancing edge as the scar tissue extends through the reticular dermis; a broad cellular fibrous band occupying the upper reticular dermis with a sharp demarcation from the normal-appearing papillary and reticular dermis; and fascia-like fibrous bands primarily in the deeper portion of the scar[16]. Occasionally, immunohistochemical stains are also employed, such as the α-smooth muscle actin (α-SMA) stain to identify myofibroblasts[17]. In one study, nodules of α-SMA-positive cells were observed only in hypertrophic scars[19].

To distinguish keloids and hypertrophic scars from spindle cell tumors, immunohistochemical stains may also be performed. In contrast to dermatofibrosarcoma protuberans, immunostaining for CD34 is negative in these scarring processes[20]. Staining for factor XIIIa, which highlights dermal dendrocytes, is also negative, allowing distinction from dermatofibromas, including the keloidal variant[21]. While there is little or no S100-staining in scars (<10% of cells in 2 of 25 cases[17]; 0% in 16 scars[22]), negative staining does not completely exclude desmoplastic melanoma; additional criteria such as cellular atypia and proliferation of atypical melanocytes within the epidermis need to be considered.

Differential Diagnosis

Perhaps the greatest difficulty lies in distinguishing hypertrophic scars, which may become enormous, from keloids (Fig. 98.9). By convention, a keloid extends into adjacent tissue, whereas a hypertrophic scar remains within the confines of the original injury. The sclerotic form of xanthoma disseminatum may be confused with keloids clinically but not histologically (see Fig. 91.18) – as may lobomycosis (keloidal blastomycosis; lacaziosis), which is due to infection with *Lacazia loboi* (see Ch. 77). There are also keloidal forms of scleroderma and morphea, in addition to the rare presentation of carcinoma *en cuirasse* as keloidal nodules and the keloidal plaques that can develop on the lower extremities of patients with type IV Ehlers–Danlos syndrome. Lastly, formation of keloids can be a clinical clue to rare inherited syndromes such as Rubenstein–Taybi and Goeminne syndromes. The histologic differential diagnosis is discussed in the Pathology section.

Treatment

The management of keloids and hypertrophic scars continues to challenge clinicians, for there is no universally accepted treatment protocol. Obviously, prevention remains the best strategy, with predisposed patients avoiding non-essential surgery. Potential treatments are outlined in Table 98.4[23–25]. Silicone elastomer sheeting, a simple intervention, is thought to work by increasing the temperature, hydration (reduces water vapor loss), and perhaps the oxygen tension of the occluded scar, which may decrease capillary activity, leading to a reduction in collagen deposition[26]. This sheeting is also used as a preventative measure immediately after healing in patients at risk for developing hypertrophic scars or keloids.

Keloids are thought to be best treated by a combination of surgery plus postoperative radiation therapy, although to date there have been no randomized controlled trials. Typically, a median cumulative dose of 28 Gy (range, 4–40 Gy) over a period of days (most often 2 or 3 consecutive days) is administered immediately following excision; complete flattening (68% of keloids) and flattening to <2 mm in height (an additional 11%) were observed in a retrospective series of 126 keloids in 83 patients[27]. In a recent literature review that focused on patients who had received radiation therapy for keloids, five radiotherapy-associated carcinomas were identified[28]. The authors concluded that the risk of inducing a malignancy is very low, especially when

TREATMENT OPTIONS FOR HYPERTROPHIC SCARS AND KELOIDS			
Treatment	**Study**	**HS**	**K**
Excision	2	✓	✓*
Triamcinolone acetonide (intralesional injection; 10–40 mg/ml)	1	✓	✓†
Interferon-α-2b (intralesional injection)	1		✓†,‡
Silicone gel sheets	2	✓	✓
Laser (pulsed dye)	1	✓	✓
Radiation	2		✓*
Topical imiquimod (5%)	2		✓*
5-Fluorouracil (intralesional injection)	2	✓†	✓†
Cryotherapy	2	✓†	✓†,§
Pressure	2	✓	✓†
Avotermin	1	✓	
Topical tacrolimus	3		✓
Topical retinoids	3	✓	✓
Intralesional verapamil	2		✓*

*As a component of combined therapy.
†Alone or as a component of combined therapy.
‡Several controlled studies have shown no benefit.
§One small, unblinded, controlled study showed a significant benefit of combination cryotherapy and intralesional triamcinolone over either alone.

Table 98.4 Treatment options for hypertrophic scars and keloids. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective trial or large case series; (3) small series or individual case reports. Radiofrequency treatment was found to have no effect (3). HS, hypertrophic scars; K, keloids.

surrounding tissues (e.g. thyroid, breasts) are adequately shielded, particularly in children.

Although TGF-β plays a key role in collagen production, research into mechanisms of skin scarring identified TGF-β_3 as a potential anti-scarring therapy; for example, in non-scarring fetal skin, the ratio of TGF-β_3: TGF-β_1 and -β_2 is high. In three double-blind, placebo-controlled studies, intradermal injections of avotermin (recombinant human TGF-β_3) along both margins of 1 cm, full-thickness skin incisions led to improvement of scar scores[29]. The injections were performed before wounding and 24 hours later and the assessment time points varied from week 6 to month 12. Erythema and edema were observed more frequently with avotermin than with placebo, and at the time of writing, avotermin is not an FDA-approved biologic agent. Lastly, in controlled trials, topical onion gel extract was not effective in reducing scar-associated erythema or pruritus[25].

DUPUYTREN'S CONTRACTURE

Synonyms: ■ Palmar fibromatosis ■ Dupuytren's disease/diathesis

Key features

- Thickening of the palmar and digital fascia
- Flexion contracture of affected digits
- Myofibroblast proliferation followed by excess collagen synthesis
- Treatments include injections of collagenase and surgical fasciectomy

History

In 1777, Henry Cline discovered that thickening of the palmar fascia produced this characteristic contracture, and, 2 years later, proposed palmar fasciotomy as a cure.

Epidemiology

Dupuytren's contracture is common in Caucasians of northern European ancestry, and it is rare in darkly pigmented populations. The prevalence approaches 30% in individuals over 60 years of age in Norway. This condition affects middle-aged to older individuals of both sexes, although men are affected about a decade earlier than women. Familial associations suggest an autosomal dominant inheritance, but sporadic cases are common. The lesion is associated with other fibromatoses, including Peyronie's disease, plantar fibromatosis (Ledderhose's disease), and knuckle pads (see Ch. 116). The condition has also been associated with alcoholism and diabetes mellitus.

Fig. 98.10 Dupuytren's contracture. There is greater involvement of the fifth finger than the fourth finger. Fibrotic cords can be felt and are accentuated by extension of the digits. Eventually, flexion contractures develop. *Courtesy, Jean L. Bolognia, MD.*

Pathogenesis

Fibrogenic cytokines (e.g. TGF-β_1 and TGF-β_2) are thought to be involved in the genesis of Dupuytren's contractures. They are able to induce the growth of fibroblasts and their differentiation into myofibroblasts, in addition to stimulating the production of extracellular matrix. In a recent genome-wide association study involving nearly 1000 individuals with Dupuytren's contracture, 9 different susceptibility loci were detected, with 6 of the 9 loci harboring genes that encode proteins in the Wnt-signaling pathway[29a]. This led the authors to conclude that aberrations in this signaling pathway will provide insights into the pathophysiology of this fibromatosis.

Clinical Features

Patients often present late in the course of their disease with flexion contractures of the affected digits. Most often, lesions develop in an ulnar distribution, and the ring finger is most commonly affected. The disorder begins with a nodule in the fascia of the palm, which grows at varying rates to produce a cord, and then it contracts, producing a flexion contracture (Fig. 98.10). Complications of Dupuytren's contracture include nerve injury, loss of joint mobility, and the development of reflex sympathetic dystrophy[30].

Pathology

Histologically, the nodular lesion consists of a proliferation of myofibroblasts, which subsequently align along lines of tension. As the cord develops, there is collagen thickening and myofibroblasts disappear.

Differential Diagnosis

Although usually a straightforward diagnosis, one must consider ganglion cysts, giant cell tumors of the tendon sheath, soft tissue sarcomas, calluses and tenosynovitis.

Fig. 98.11 Cutis verticis gyrata. Cerebriform folding of the skin of the scalp. Erythema in the posterior grooves is related to a previous superinfection.

CUTIS VERTICIS GYRATA – DISEASE ASSOCIATIONS
PRIMARY ESSENTIAL
• None
PRIMARY NON-ESSENTIAL
• Neurologic abnormalities (e.g. mental retardation, seizures) • Ophthalmologic abnormalities (e.g. cataracts, optic atrophy)
SECONDARY
• Acromegaly, pseudoacromegaly • Myxedema (including cretinism)* • Insulin resistance • Turner and Noonan syndromes (following resolution of intrauterine lymphedema)* • Fragile X syndrome • Klinefelter syndrome • Hereditary neuralgic amyotrophy • Tuberous sclerosis • Hyper-IgE syndrome • Graves' disease* • Paraneoplastic due to metastatic carcinoma
*Increased dermal mucin may also be observed.

Table 98.5 Cutis verticis gyrata – disease associations.

Treatment

Surgical approaches are the mainstay of therapy, with fasciectomy releasing the joint contracture in most patients. Postoperative splinting and range-of-motion exercises are important for a good outcome, and recurrences are common. Recently, injectable collagenase (from *Clostridium histolyticum*) was FDA-approved for the treatment of Dupuytren's contractures; up to three monthly injections are done per cord, followed by a finger-extension procedure the following day. In two placebo-controlled trials, reduction in the contracture (to 0–5°) was seen in 44% and 64% of collagenase-treated cords, compared to 5% and 7% in the placebo groups[31]. Possible complications include tendon, ligament or nerve injury, as well as urticaria and angioedema.

CUTIS VERTICIS GYRATA

Key features

- Hypertrophy and folding of the scalp
- Primary (idiopathic) form seen almost exclusively in males, with an onset at puberty
- Face not affected as in pachydermoperiostosis
- Underlying disorders in the secondary form include acromegaly, Turner syndrome and myxedema

Clinical Features

In primary cutis verticis gyrata, overgrowth of the scalp develops at puberty and progresses to produce symmetric gyrate or cerebriform folding of the skin (Fig. 98.11). The folds are usually aligned in an anterior–posterior direction on the crown and vertex and are soft to spongy on palpation. Terminal hair density may be reduced on the folds, but not in the furrows. *Primary* cutis verticis gyrata can be subdivided into essential (isolated) and non-essential (associated with neurologic and/or ophthalmologic abnormalities) forms, both of which have a male predominance. *Secondary* cutis verticis gyrata is less common and has a more equal sex distribution. Onset of the latter varies from birth to adulthood and secondary forms may be asymmetric, depending on the underlying etiology (Table 98.5).

Pathology

Biopsy specimens from cutis verticis gyrata typically show increased dermal collagen in otherwise normal-appearing skin.

Differential Diagnosis

An extensive congenital cerebriform melanocytic nevus of the scalp can have the appearance of cutis verticis gyrata. One must also differentiate the latter from pachydermoperiostosis, which is associated with facial involvement and thickening of the skin on the hands and feet, as well as clubbing of the digits[32]. Furrowed skin on the scalp, forehead, preauricular areas, neck, trunk, palms and soles in association with acanthosis nigricans, craniosynostosis and a prominent umbilical stump characterizes Beare–Stevenson cutis gyrata syndrome, an autosomal dominant condition caused by mutations in the fibroblast growth factor receptor 2 (*FGFR2*) gene. Dissecting cellulitis of the scalp, Darier disease or extensive AL amyloid deposition can lead to cerebriform folds of skin resembling cutis verticis gyrata. Less often, cutis verticis gyrata might be confused with a plexiform neurofibroma, nevus lipomatosus, connective tissue nevus, aggregated cylindromas, acanthosis nigricans or cutaneous leukemic infiltrates.

Treatment

This unusual morphologic syndrome is generally asymptomatic, and it requires no treatment. Occasionally, surgical excision is performed[33,34].

JUVENILE HYALINE FIBROMATOSIS AND INFANTILE SYSTEMIC HYALINOSIS

Synonyms: ■ Hyaline fibromatosis syndrome ■ Murray–Puretic–Drescher syndrome ■ Fibromatosis hyalinica multiplex juvenilis ■ (Juvenile) systemic hyalinosis

Key features

- Rare, allelic autosomal recessive disorders with clinical overlap
- Usually present during infancy or early childhood
- Clinical features include papulonodular lesions (favoring the ears, scalp, neck, hands and periorificial areas), gingival hypertrophy and flexion contractures of large joints; infantile systemic hyalinosis represents a more severe variant with internal organ involvement
- Mutations in the gene that encodes capillary morphogenesis protein-2 (CMG2) are responsible for both disorders
- Treatment consists of excision of nodules and gingivae as needed, but lesions often recur

Introduction

Both juvenile hyaline fibromatosis (JHF) and infantile systemic hyalinosis (ISH) are rare autosomal recessive genodermatoses characterized by hyaline accumulation in the dermis. They are allelic disorders, i.e. due to mutations in the same gene, but can differ with regard to severity and involvement of internal organs (Table 98.6). It has been suggested that JHF and ISH exist within a continuum of disease with varying phenotypic expression[35] and the encompassing term "hyaline fibromatosis syndrome" has been proposed.

History

As early as 1873, Murray had described a condition which he termed "molluscum fibrosum". In 1972, Kitano et al.[36] renamed the disorder "juvenile hyaline fibromatosis".

Epidemiology

Both JHF and ISH are rare disorders that present during infancy or early childhood. As expected given the autosomal recessive inheritance pattern, both sexes are equally affected.

Pathogenesis

The gene that encodes capillary morphogenesis protein-2 (CMG2) resides on chromosome 4q21. CMG2 is an integrin-like cell surface receptor that binds laminins and type IV collagen (as well as the anthrax toxin), and in the skin it is thought to play a role in cell–matrix interactions and basement membrane integrity[37]. Mutations in *ANTXR2* (*CMG2*) can lead to both JHF and ISH. Missense and other in-frame mutations that affect the cytoplasmic domain tend to cause JHF, whereas truncating mutations and missense mutations that affect the extracellular protein-binding domain tend to cause ISH[38]. However, the exact pathophysiology is still unclear.

Clinical Features

Initially, firm papules and nodules develop on the scalp, ears (Fig. 98.12), neck and face (particularly perinasal and perioral regions) as well as the perianal area; papulonodules also favor the hands. Affected children are of normal intelligence, but often suffer severe physical handicap from joint contractures and tumors. Gingival hyperplasia and osteolytic bone lesions may also occur. Infantile systemic hyalinosis is a more severe variant that is characterized by hyaline deposits in multiple internal organs, recurrent infections and, in most cases, death during early childhood.

Pathology

An increased number of fibroblasts are embedded in a hyalinized connective tissue stroma that is homogeneous, amorphous and acidophilic (stains positively with PAS)[36]. Mononuclear cells and $CD68^+$, osteoclast-like giant cells are also present in a perivascular location. Additional findings include intracytoplasmic and extracellular eosinophilic globules; over time, the lesions tend to become more paucicellular[39]. There is an accumulation of type VI collagen within the fibromas in JHF.

Differential Diagnosis

Winchester syndrome and nodulosis–arthropathy–osteolysis (NAO) syndrome share clinical features with JHF and ISH (e.g. nodules, joint contractures, osteopenia)[39]. The former are allelic autosomal recessive disorders due to mutations in the gene that encodes matrix metalloproteinase-2 (MMP2). Additional findings include coarse facies and hypertrichosis. Painful nodules on the palms and soles are observed in NAO syndrome, whereas thickened, hyperpigmented skin and gingival hypertrophy characterize Winchester syndrome. Histologically, both conditions feature a proliferation of fibroblasts and thickened col-

CLINICAL FEATURES OF JUVENILE HYALINE FIBROMATOSIS VERSUS INFANTILE SYSTEMIC HYALINOSIS

	Juvenile hyaline fibromatosis	Infantile systemic hyalinosis
Age of onset	Childhood (<5 years old)	Infancy
Cutaneous findings:		
• Firm, pearly papules (favoring the perinasal area and ears)	+	+
• Verrucous perianal nodules	+	+
• Firm nodules/tumors (favoring the scalp, neck, hands and trunk)	+	–
• Reddish-blue to brown plaques overlying extensor surfaces of joints	–	+
• Diffusely thickened skin	–	+
Gingival hypertrophy	+	+
Joint contractures	+	+
Osteopenia	+	+
Persistent diarrhea	–	+
Recurrent infections	–	+
Visceral involvement	–	+
Normal mental development	+	+
Survival into adulthood	+	–

Table 98.6 Clinical features of juvenile hyaline fibromatosis versus infantile systemic hyalinosis.

Fig. 98.12 Juvenile hyaline fibromatosis. Firm pearly papules favor the ears.

DISORDERS CHARACTERIZED BY INCREASED ELASTIC TISSUE FIBERS			
Disorder	**Clinical features**	**Histopathologic features**	**Comments**
Late-onset focal dermal elastosis	Multiple 1–3 mm yellow papules that may coalesce Favors the neck, axillae, groin, antecubital and popliteal fossae	Increased normal-appearing elastic fibers in the mid and deep reticular dermis	See Ch. 97
Linear focal elastosis (elastotic striae)	Multiple yellow, palpable, striae-like bands of the lumbosacral region	Focal increase in number of elongated or fragmented elastic fibers (thickened > thinned) within the mid dermis; the ends of the elastic fibers may be split with a "paintbrush" appearance	May represent an excessive regenerative process of elastic fibers, perhaps to repair striae distensae (see Ch. 99)
Elastoderma	Localized areas of lax, pendulous skin; neck, trunk, arm	Increased normal- and abnormal-appearing elastic fibers throughout the dermis	See Ch. 97
Elastofibroma dorsi	Large mass in the deep subcutaneous tissue of the infrascapular area	Arises within the fascia Increased elastic fibers with a globular and beaded morphology admixed with plump collagen bundles, fibroblasts and mature fat cells (Fig. 98.13)	Favors older women > men and Japanese Possibly related to chronic mechanical stress
Elastoma (nevus elasticus)	Firm, skin-colored to yellowish papule(s) which may be clustered Favors the trunk	Accumulation of broad, partially fragmented, branching elastic fibers within the mid and lower dermis	Type of connective tissue nevus (see Ch. 116) Associated with Buschke–Ollendorf syndrome
Elastosis perforans serpiginosa	Annular and polycyclic plaques composed of keratotic papules Favors the neck, face, antecubital fossae and other flexural areas	Perforating disorder with transepidermal channel that contains fragments of elastotic material Increased number of coarse elastic fibers in the superficial dermis	Associated with penicillamine (lumpy-bumpy fibers*), Down syndrome and connective tissue disorders (e.g. Ehlers–Danlos syndrome, Marfan syndrome; see Ch. 96)

*By electron microscopy

Table 98.7 Disorders characterized by increased elastic tissue fibers[41–51]. Actinic elastosis has masses of degenerated elastic fibers within the upper dermis, and when it forms a localized plaque, the term elastoma of Dubreuilh may be applied. Papillary dermal elastosis is considered a variant of papillary dermal elastolysis. Special stains for elastic fibers include Verhoeff–Van Gieson and orcein (acid orcein–Giemsa; see Ch. 0).

lagen bundles extending from the deep reticular dermis to the subcutaneous fat.

Treatment

Unfortunately, treatment options for JHF and ISH are limited. Surgical excision of nodules and gingival hypertrophy, as well as release of contractures, can be performed, but lesions often recur. Physiotherapy may slow the progression of joint contractures[39]. Injections of corticosteroids into fibromas have met with limited success. Systemic interferon-α-2b therapy was reported to improve the skin lesions, gingival hypertrophy and joint contractures in one patient.

ELASTIC TISSUE-RELATED DISORDERS

In general, mechanisms which lead to increased dermal elastic tissue are unknown, and the nosology of the elastic tissue-related disorders can be confusing[40]. There are several acquired disorders whose clinical appearance can overlap and their clinical as well as histologic features are outlined in Table 98.7.

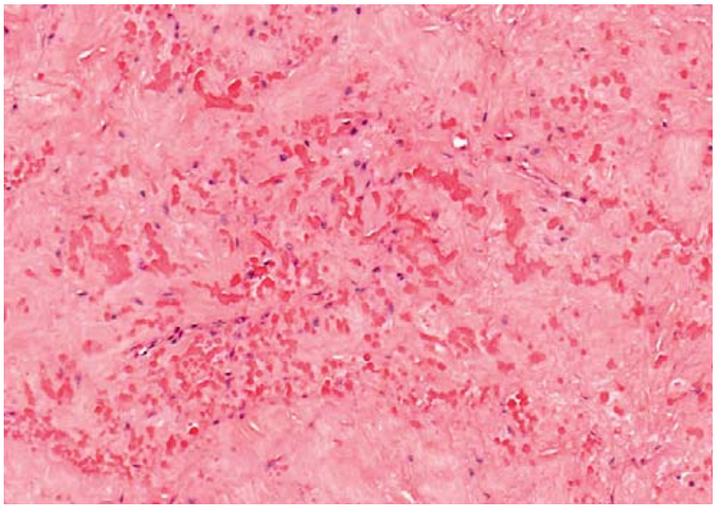


Fig. 98.13 Elastofibroma dorsi. Eosinophilic, irregular, partly fragmented elastic fibers admixed with swollen collagen bundles. *Courtesy, Lorenzo Cerroni, MD.*

REFERENCES

1. Robles DT, Berg D. Abnormal wound healing: keloids. Clin Dermatol. 2007;25:26–32.
2. English RS, Shenefelt PD. Keloid and hypertrophic scars. Dermatol Surg. 1999;25:631–8.
3. Alster TS, Tanzi EL. Hypertrophic scars and keloids: etiology and management. Am J Clin Dermatol. 2003;4:235–43.
4. Nemeth AJ. Keloids and hypertrophic scars. J Dermatol Surg Oncol. 1993;19:738–46.
5. Niessen FB, Spauwen PH, Schalkwijk J, Kon M. On the nature of hypertrophic scars and keloids: a review. Plast Reconstr Surg. 1999;104:1435–58.
6. Bran GM, Goessler UR, Hormann K, et al. Keloids: current concepts of pathogenesis. Int J Mol Med. 2009;24:283–93.
7. Mofikoya BO, Adeyemo WL, Abdus-Salam AA. Keloid and hypertrophic scars: a review of recent developments in pathogenesis and management. Nig Q J Hosp Med. 2007;17:134–9.
8. Shaw AM. Recent advances in embryonic wound healing. In: Garg HG, Longaker MT (eds). Scarless Wound Healing. New York: Marcel Dekker, 2000:227–37.
9. Sullivan T, Smith J, Kermode J, et al. Rating the burn scar. J Burn Care Rehabil. 1990;11:256–60.
10. Van Zuijlen P, Vloemans J, van Trier A, et al. Dermal substitute in acute burns and reconstructive surgery: a subjective and objective follow up. Plast Reconstr Surg. 2001;108:1938–46.
11. Draaijers L, Templeman F, Botman Y, et al. The patient and observer scar assessment scale: a reliable and feasible tool for scar evaluation. Plast Reconstr Surg. 2004;113:1960–5.
12. Van de Kar A, Corion L, Smeulders M, et al. Reliable and feasible evaluation of linear scars by the Patient and Observer Scar Assessment Scale. Plast Reconstr Surg. 2005;116:514–22.

13. Nguyen DQ, Potokar T, Price P. A review of current objective and subjective scar assessment tools. J Wound Care. 2008;17:101–2, 104–6.
14. Oliveira GV, Chinkes D, Mitchell C, et al. Objective assessment of burn scar vascularity, erythema, pliability, thickness and planimetry. Dermatol Surg. 2005;31:48–58.
15. Romanelli M, Gaggio G, Coluccia M, et al. Technological advances in wound bed measurements. WOUNDS. 2002;14:58–66.
16. Lee JY, Yang CC, Chao SC, Wong TW. Histopathological differential diagnosis of keloid and hypertrophic scar. Am J Dermatopathol. 2004;26:379–84.
17. Kamath NV, Ormsby A, Bergfeld WF, House NS. A light microscopic and immunohistochemical evaluation of scars. J Cutan Pathol. 2002;29:27–32.
18. Weedon D. Disorders of collagen. In: Weedon D (ed.). Weedon's Skin Pathology, 2nd edn. Edinburgh: Churchill Livingstone, 2002.
19. Ehrlich HP, Desmoulière A, Diegelmann RF, et al. Morphological and immunochemical differences between keloid and hypertrophic scar. Am J Pathol. 1994;145:105–13.
20. Haycox CL, Odland PB, Olbricht SM, Piepkorn M. Immunohistochemical characterization of dermatofibrosarcoma protuberans with practical applications for diagnosis and treatment. J Am Acad Dermatol. 1997;37:438.
21. Kuo T, Hu S, Chan H. Keloidal dermatofibroma: report of 10 cases of a new variant. Am J Surg Pathol. 1998;22:264.
22. Kaneishi NK, Cockerell CL. Histologic differentiation of desmoplastic melanoma from cicatrices. Am J Dermatopathol. 1998;20:128.
23. Ogawa R. The most current algorithms for the treatment and prevention of hypertrophic scars and keloids. Plast Reconstr Surg. 2010;125:557–68.
24. Darougheh A, Asilian A, Shariati F. Intralesional triamcinolone alone or in combination with 5-fluorouracil for the treatment of keloid and hypertrophic scars. Clin Exp Dermatol. 2009;34:219–23.
25. Mustoe TA, Cooter RD, Gold MH, et al. International clinical recommendations on scar management. Plast Reconstr Surg. 2002;110:560–71.
26. Berman B, Perez OA, Konda S, et al. A review of the biologic effects, clinical efficacy, and safety of silicone elastomer sheeting for hypertrophic and keloid scar treatment and management. Dermatol Surg. 2007;33:1291–302.
27. Klumpar DI, Murray JC, Anscher M. Keloids treated with excision followed by radiation therapy. J Am Acad Dermatol. 1994;31:225–31.
28. Ogawa R, Yoshitatsu S, Yoshida K, Mivashita T. Is radiation therapy for keloids acceptable? The risk of radiation-induced carcinogenesis. Plast Reconstr Surg. 2009;124:1196–201.
29. Ferguson MW, Duncan J, Bond J, et al. Prophylactic administration of avotermin for improvement of skin scarring: three double-blind, placebo-controlled, phase I/II studies. Lancet. 2009;373:1264–74.
29a. Dolmans GH, Werker PM, Hennies HC, et al. Wnt signaling and Dupuytren's disease. N Engl J Med. 2011;365:307–17.
30. Weinzweig N, Culver JE, Fleegler EJ. Severe contractures of the proximal interphalangeal joint in Dupuytren's disease: combined fasciectomy with capsuloligamentous release versus fasciectomy alone. Plast Reconstr Surg. 1996;97:560–6.
31. Gilpin D, Coleman S, Hall S, et al. Injectable collagenase *Clostridium histolyticum*: a new nonsurgical treatment for Dupuytren's disease. J Hand Surg Am. 2010;35:2027–38.e1.
32. Oikarinen A, Palatsi R, Kylmaniemi M, et al. Pachydermoperiostosis: analysis of the connective tissue abnormality in one family. J Am Acad Dermatol. 1994;31:947–53.
33. Zhao L, Fang F, Xu J, et al. Giant primary cutis verticis gyrata successfully treated with surgical excision and tissue expansion. Dermatol Surg. 2006;32:753–5.
34. Hsu YJ, Chang YJ, Su LH, Hsu YL. Using novel subcision technique for the treatment of primary essential cutis verticis gyrata. Int J Dermatol. 2009;48:307–9.
35. Shehab ZP, Raafat F, Proops DW. Juvenile hyaline fibromatosis. Int J Pediatr Otorhinolaryngol. 1995;33:179–86.
36. Kitano Y, Horiki M, Aoki T, et al. Two cases of juvenile hyaline fibromatosis: some histological, electron microscopic and tissue culture observations. Arch Dermatol. 1972;106:877–83.
37. El-Kamah GY, Fong K, El–Ruby M, et al . Spectrum of mutations in the *ANTXR2* (*CMG2*) gene in infantile systemic hyalinosis and juvenile hyaline fibrosis . Br J Dermatol. 2010;163:213–15.
38. Hanks S, Adams S, Douglas J, et al. Mutations in the gene encoding capillary morphogenesis protein 2 cause juvenile hyaline fibromatosis and infantile systemic hyalinosis. Am J Hum Genet. 2003;73: 791–800.
39. Thomas JE, Moossavi M, Mehregan DR, et al. Juvenile hyaline fibromatosis: a case report and review of the literature. Int J Dermatol. 2004;43:785–9.
40. Lewis KG, Bercovitch L, Dill SW, Robinson-Bostom L. Acquired disorders of elastic tissue: part I. Increased elastic tissue and solar elastotic syndromes. J Am Acad Dermatol. 2004;51:1–21.
41. Tajima S, Tanaka N, Ohnishi Y, et al. Analysis of elastin metabolism in patients with late-onset focal dermal elastosis. Acta Derm Venereol. 1999;79:285–7.
42. Tajima S, Shimizu K, Izumi T, et al. Late-onset focal dermal elastosis: clinical and histological features. Br J Dermatol. 1995;133:303–5.
43. Hashimoto K. Linear focal elastosis: keloidal repair of striae distensae. J Am Acad Dermatol. 1998;39:309–13.
44. Breier F, Trautinger F, Jurecka W, Honigsmann H. Linear focal elastosis (elastotic striae): increased number of elastic fibres determined by a video measuring system. Br J Dermatol. 1997;137:955–7.
45. Vieira AC, Vieira WT, Michalany N, et al. Elastoderma of the neck in a teenage boy. J Am Acad Dermatol. 2005;53(2 Suppl 1):S147–S149.
46. Harigopal M, Seshan SV, DeLellis RA, et al. Aspiration cytology of elastofibroma dorsi: case report with ultrastructural and immunohistochemical findings. Diagn Cytopathol. 2002;26:310–13.
47. Weedon D. Disorders of elastic tissue. In: Weedon D (ed.). Weedon's Skin Pathology, 2nd edn. Edinburgh: Churchill Livingstone, 2002.
48. de Almeida HL Jr, Breunig Jde A, Wolter M, et al. Light and electron microscopy of eruptive collagenoma. J Cutan Pathol. 2009;36(Suppl 1):35–8.
49. Fork HE, Sanchez RL, Wagner RF Jr, Raimer SS. A new type of connective tissue nevus: isolated exophytic elastoma. J Cutan Pathol. 1991;18:457–63.
50. Ledoux-Corbusier M, Achten G, De Dobbeleer G. Juvenile elastoma (Weidman). An ultrastructural study. J Cutan Pathol. 1981;8:219–27.
51. Wang AR, Lewis K, Lewis M, Robinson-Bostom L. Papillary dermal elastosis: a unique elastic tissue disorder or an unusual manifestation of pseudoxanthoma elasticum-like papillary dermal elastolysis? J Cutan Pathol. 2009;36:1010–13.

This page intentionally left blank

Atrophies of Connective Tissue 99

Catherine Maari and Julie Powell

Chapter Contents

Mid-dermal elastolysis 1631
Anetoderma 1632
Striae 1635
Idiopathic atrophoderma of Pasini and Pierini 1636
Follicular atrophoderma 1637
Atrophia maculosa varioliformis cutis 1639
Piezogenic pedal papules (piezogenic papules) 1639

Atrophies of the skin that are due to a diminution or loss of collagen and/or elastic fibers are discussed in this chapter. The areas of involvement can be quite large, as in mid-dermal elastolysis, or punctate, as in follicular atrophoderma. In most disorders, the underlying pathogenesis remains to be discovered.

MID-DERMAL ELASTOLYSIS

Key features

- Uncommon disorder with areas of fine wrinkling
- Usually affects Caucasian middle-aged women
- Selective loss of elastic tissue in the mid dermis

Introduction

Mid-dermal elastolysis is a rare acquired disorder of elastic tissue. It is characterized clinically by diffuse fine wrinkling, most often located on the trunk, neck and arms. Histologically, a clear band of elastolysis is present in the mid dermis.

History

In 1977, Shelley and Wood reported the first case of "wrinkles due to idiopathic loss of mid-dermal elastic tissue". Their patient, a 42-year-old woman, had circumscribed areas of fine wrinkles that gave her an inappropriately aged appearance[1].

Epidemiology

To date, approximately 80 cases have been reported in the literature. The vast majority of patients are Caucasian women between the ages of 30 and 50 years[2,3].

Pathogenesis

The cause of the acquired elastic tissue degeneration in mid-dermal elastolysis is still unclear. Exposure to UV light is thought to be a major contributing factor in the degeneration of elastic fibers[4] (as in annular elastolytic giant cell granuloma). There are reports of mid-dermal elastolysis developing after significant UV exposure, including natural sunlight, UVA (tanning salon) and narrowband UVB phototherapy[5].

Other possible mechanisms include defects in the synthesis of elastic fibers, autoimmunity against elastic fibers, and damage to elastic fibers via the release of elastase by inflammatory cells or fibroblasts. More recent studies have suggested that an altered balance between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) may be playing a role, in addition to $CD34^+$ dendritic fibroblasts[6].

Clinical features

Mid-dermal elastolysis is characterized by well-circumscribed or larger diffuse areas of fine wrinkling (Fig. 99.1), usually in a symmetric distribution pattern (type I). The wrinkles themselves tend to follow cleavage lines. Discrete perifollicular papules can be seen in some patients (type II), with the site of the central hair follicle being indented. Inconstant features include erythematous patches, telangiectasias and reticulated erythema (type III)[3]. Although in the majority of cases there is no history of a prior inflammatory dermatosis, some patients do report previous mild to moderate erythema and, rarely, the elastolysis is preceded by episodes of urticarial lesions or granuloma annulare.

The sites of predilection are the trunk, lateral neck and upper extremities. Once the patches of wrinkling have appeared, they usually remain stationary. They are asymptomatic and give the skin a prematurely aged appearance. The affected areas usually have normal pigmentation and no associated scaling, induration or herniation. There is neither associated systemic involvement nor a family history of similar lesions.

Pathology

The epidermis is normal in appearance and, occasionally, a mild perivascular infiltrate is noted in the dermis. Elastic tissue stains, such as Verhoeff–van Gieson or Weigert's stain, reveal a selective loss of elastic fibers in the mid dermis (Fig. 99.2). There is preservation of normal elastic tissue in the superficial papillary dermis above, in the reticular dermis below, and along adjacent hair follicles. The preservation of elastic tissue around the hair follicles explains the perifollicular papules that can be seen in some cases.

By electron microscopy, phagocytosis of normal as well as degenerated elastic fiber tissue by macrophages has been described[7]. Elastophagocytosis by macrophages is also occasionally observed by routine histology.

Differential diagnosis

Mid-dermal elastolysis must be differentiated from the other disorders of elastic tissue such as anetoderma, pseudoxanthoma elasticum (PXE), PXE-like papillary dermal elastolysis, elastoderma and cutis laxa, especially the acquired form (Table 99.1).

Clinically, anetoderma is characterized by smaller soft macules and papules that herniate upon palpation, as opposed to diffuse wrinkling. Histologically, elastolysis can occur in the papillary and/or mid-reticular dermis in anetoderma (see below). Patients with cutis laxa have loose, redundant skin, hanging in folds, and histologic examination shows elastolysis that frequently involves the entire dermis. There is also a form of postinflammatory elastolysis and cutis laxa that was originally described in young girls of African descent. An inflammatory phase consisting of indurated plaques or urticaria, malaise and fever preceded the diffuse wrinkling, atrophy and severe disfigurement. Insect bites may be the trigger for the initial inflammatory lesions[8].

Less often, mid-dermal elastolysis is confused with solar elastosis or perifollicular elastolysis that is usually seen on the trunk in association with acne vulgaris. Solar elastosis differs by its onset in an older age group, restriction to only sun-exposed areas, yellowish color and coarser wrinkling, as well as by hyperplasia of abnormal elastic fibers and basophilic degeneration of the collagen in the papillary dermis. Perifollicular elastolysis leads to a selective and almost complete loss of the

DISORDERS OF ELASTIC TISSUE			
Condition	**Clinical findings**	**Site of predilection**	**Pathology**
Anetoderma	Multiple circumscribed areas of flaccid skin; lesions are often elevated (protruding), but can be macular or depressed	Usually on trunk	Focal or complete loss of elastic tissue in the papillary and/or mid-reticular dermis
Mid-dermal elastolysis	Diffuse areas of fine wrinkling and occasional perifollicular papules in middle-aged women	Trunk, arms and lateral neck	Selective loss of elastic fibers within the mid dermis in a band-like pattern
Pseudoxanthoma elasticum (PXE; see Ch. 97)	Yellowish coalescing skin papules, "cobblestoning", and redundant folds in flexural sites; associated ocular and cardiovascular involvement	Lateral neck, axillae, and groin; scars	Calcified and clumped elastic fibers in the mid dermis
Cutis laxa (see Ch. 97)	Loose, sagging skin folds resulting in prematurely aged appearance. Hereditary or acquired. Internal organ involvement, e.g. pulmonary, in hereditary form and generalized acquired form	Eyelids, cheeks, neck, shoulder girdle and abdomen	Diminished and fragmented elastic fibers throughout the dermis
PXE-like papillary dermal elastolysis	Multiple 2–3 mm yellow or skin-colored papules that can coalesce into cobblestoned plaques	Neck, flexor forearms, axillae, lower abdomen, inframammary folds	Decreased elastic tissue in the papillary dermis (band-like pattern); clumping and fragmentation of elastic fibers

Table 99.1 Disorders of elastic tissue. For additional entities, see Tables 95.5, 97.4 and 97.6.

Fig. 99.1 Mid-dermal elastolysis. Large diffuse patch as well as reticulated areas of fine wrinkling on the upper trunk and proximal arm. The junction of involved and uninvolved skin is marked with an arrow. *Courtesy, Judit Stenn, MD.*

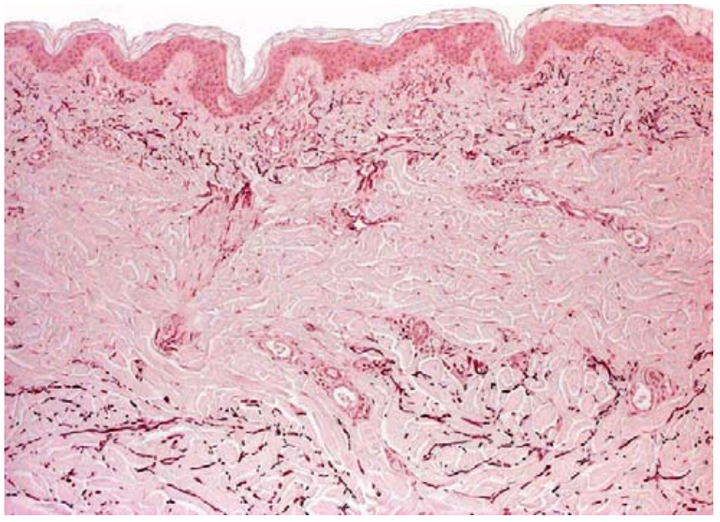


Fig. 99.2 Mid-dermal elastolysis – histologic features. A near absence of elastic fibers in a band-like distribution in the upper reticular dermis. Identification of these changes requires an elastic tissue stain (e.g. orcein). *Courtesy, Lorenzo Cerroni, MD.*

elastic fibers that surround hair follicles, compared with preservation of elastic fibers around follicles in mid-dermal elastolysis. In one report, elastase-producing *Staphylococcus epidermidis* was found within the hair follicles and postulated to be playing a role[9].

Treatment

Currently, there is no effective treatment for mid-dermal elastolysis. Sunscreens, colchicine, chloroquine, vitamin E and topical agents (retinoic acid, corticosteroids) have been tried without success[2].

ANETODERMA

Synonyms: ■ Macular atrophy ■ Anetoderma maculosa ■ Anetoderma maculosa cutis ■ Atrophia maculosa cutis

Key features

- Circumscribed 1–2 cm areas of flaccid skin, which may be elevated, macular or depressed
- *Primary* anetoderma has classically been divided into inflammatory and non-inflammatory
- *Secondary* anetoderma is associated with infectious and inflammatory cutaneous disorders as well as tumors and autoimmune disorders (e.g. antiphospholipid antibody syndrome)
- Focal dermal defect of elastic tissue

Introduction

The term "anetoderma" is derived from *anetos*, the Greek word for slack, and *derma* for skin. Anetoderma is an elastolytic disorder characterized by localized areas of flaccid skin, which may be depressed, macular or papular; the latter can reflect herniation of the subcutaneous tissue. Anetoderma may be idiopathic or associated with an inflammatory disorder of the skin.

History

The first case of primary inflammatory anetoderma was reported by Jadassohn in 1892, and it occurred in a 23-year-old woman who had depressed pink-to-red lesions on her elbows that were noted to have an atrophic, wrinkled appearance[10]. A year previously, Schweninger and Buzzi described a 29-year-old woman with multiple sac-like tumors that demonstrated herniation upon palpation; the lesions were located on the trunk and upper extremities but lacked inflammation[11].

Epidemiology

Several hundred cases of anetoderma have been reported in the world literature since the original report. Primary anetoderma favors young adults between 15 and 25 years of age and occurs more frequently in women than men. The epidemiology of secondary anetoderma reflects that of the underlying etiologies (see Table 99.3).

Pathogenesis

The pathogenesis of anetoderma is not known. These lesions could be considered unusual scars, since scars also have decreased elastic tissue. The loss of dermal elastin may reflect an impaired turnover of elastin, caused by either increased destruction or decreased synthesis of elastic fibers. There are a number of proposed explanations for the focal elastin destruction, e.g. the release of elastase from inflammatory cells, the release of cytokines such as interleukin-6, an increased production of progelatinases A and B[12], and the phagocytosis of elastic fibers by macrophages. In addition, immunologic mechanisms may play a role in anetoderma and may explain the occasional associated findings of antiphospholipid antibodies, antinuclear antibodies, false-positive serologic testing for syphilis or *Borrelia* spp., and positive direct immunofluorescence (see below).

True primary anetoderma occurs when there is no underlying associated disorder, and it arises within clinically normal skin. It can be classified into two major forms: those with preceding inflammatory lesions (the Jadassohn–Pellizzari type) and those without preceding inflammatory lesions (the Schweninger–Buzzi type) (Table 99.2). This clinical classification is primarily of historical interest, since the two types of lesions can coexist in the same patient and their histopathology is often the same (i.e. inflammation has been observed in both types of lesions); the presence or absence of clinical inflammation at the onset of the disease is not related to prognosis[13].

Secondary anetoderma can arise in the setting of a primary inflammatory dermatosis, skin infection or cutaneous tumor, as well as in patients with systemic disorders (e.g. autoimmune). Over the past decade, an association with antiphospholipid antibody syndrome has been highlighted. Although the vast majority of cases are sporadic, familial anetoderma has been described and is usually not associated with pre-existing lesions[14].

Clinical features

The characteristic lesions are flaccid circumscribed areas of slack skin that are a reflection of a marked reduction or absence of dermal elastic fibers; they can appear as depressions, wrinkling or sac-like protrusions (Fig. 99.3). These atrophic lesions can vary in number from a few to hundreds, and they typically measure 1–2 cm in diameter and are skin-colored to blue–white in color. The skin surface can be normal in appearance or wrinkled, and a central depression may be seen. Coalescence of smaller lesions can give rise to larger herniations.

The examining finger sinks into a distinct pit with sharp borders as if into a hernia ring. The bulge reappears when the pressure from the finger is released. This clinical finding is referred to as the "buttonhole" sign and is similar to that observed in neurofibromas.

Predilection sites for these asymptomatic lesions are the chest, back, neck and upper extremities. They usually develop in young adults, and new lesions often continue to form for many years as the older lesions fail to resolve.

CLASSIFICATION OF ANETODERMA	
Primary anetoderma	• Jadassohn–Pellizzari type: preceding inflammatory lesions • Schweninger–Buzzi type: no preceding inflammatory lesions
Secondary anetoderma	• Associated with a primary dermatosis or cutaneous tumor • Associated with a systemic disease (autoimmune, infectious) or drug
Familial anetoderma	

Table 99.2 Classification of anetoderma.

True secondary anetoderma implies that the characteristic atrophic lesion has appeared in the same site as a previous specific skin lesion (see Fig. 99.3D,E). Some authors also consider lesions associated with an underlying disease (e.g. HIV infection, antiphospholipid antibody syndrome) as secondary anetoderma; however, in this instance, the atrophic areas do not necessarily develop within areas of known inflammation. Evaluation for the presence of antiphospholipid antibodies should be performed before patients with idiopathic anetoderma are labeled as having true primary anetoderma[15]. The range of heterogeneous conditions associated with secondary anetoderma are outlined in Table 99.3. With the exception of distribution (and perhaps size), the clinical features are the same as those of primary anetoderma.

Anetoderma has also been described in premature infants. In some cases, it may have been related to the use of cutaneous monitoring leads or adhesives[16].

In patients with anetoderma, a variety of systemic abnormalities have been reported, including ocular, endocrinologic, skeletal, cardiac, pulmonary and gastrointestinal. Because there has been no consistency with regard to these associated abnormalities, they are probably coincidental, although the possibility exists that they may reflect a more generalized elastolytic disorder that has yet to be defined.

Pathology

In routinely stained sections, the collagen within the dermis of affected skin appears normal. Perivascular lymphocytes are often present but do not correlate with clinical findings of inflammation. Monoclonal antibody studies have shown that the majority of lymphocytes in these infiltrates are helper T cells.

The predominant abnormality (as revealed by elastic tissue stains) is a focal, more or less complete loss of elastic tissue in the papillary and/or mid-reticular dermis. There are usually some residual abnormal, irregular and fragmented elastic fibers (Fig. 99.4)[17]. Plasma cells and histiocytes with occasional granuloma formation can be seen.

SECONDARY ANETODERMA – ASSOCIATED CONDITIONS	
Infectious	• Varicella • Folliculitis • Syphilis (cutaneous) • Molluscum contagiosum • Tuberculosis (cutaneous) • Lepromatous leprosy • HIV infection • Acrodermatitis chronica atrophicans • Post-hepatitis B immunization
Drugs	• Penicillamine
Inflammatory	• Acne vulgaris • Mastocytosis • Lichen planus • Granuloma annulare • Juvenile xanthogranuloma • Cutaneous sarcoidosis • Cutaneous lymphoid hyperplasia (lymphocytoma cutis) • Prurigo nodularis • Insect bites
Autoimmune	• Discoid and systemic lupus erythematosus • Antiphospholipid syndrome • Primary Sjögren's syndrome • Addison's disease • Graves' disease
Tumors and depositions	• Involuted infantile hemangioma • Pilomatricoma • Melanocytic nevus • Dermatofibroma • Dermatofibrosarcoma protuberans • Primary cutaneous marginal zone B-cell lymphoma (primary cutaneous plasmacytoma or immunocytoma) • Nodular amyloidosis • Xanthoma

Table 99.3 Secondary anetoderma – associated conditions.

Fig. 99.3 Anetoderma – primary and secondary. Lesions can range from soft, skin-colored papules that herniate upon palpation (**A**) to flaccid papules that have a central depression (**B**). The upper trunk and neck is a common location for primary anetoderma (**C**). Wrinkling of the skin from secondary anetoderma due to sarcoidosis (**D**) and lepromatous leprosy (**E**). *A, Courtesy, Ronald P Rapini, MD; C, Courtesy, Thomas Schwarz, MD; E, Courtesy, Louis A Fragola, Jr, MD.*

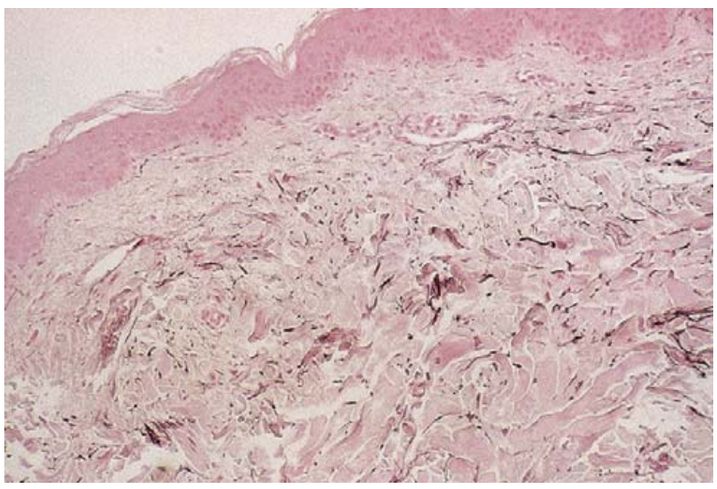


Fig. 99.4 Histology of anetoderma. A decrease of elastic fibers in both the papillary and reticular dermis (Weigert's stain).

Direct immunofluorescence sometimes shows linear or granular deposits of immunoglobulins and complement along the dermal–epidermal junction or around the dermal blood vessels in affected skin[18]. However, these findings are not helpful diagnostically.

Electron microscopy demonstrates that the elastic fibers are fragmented and irregular in shape and occasionally they are engulfed by macrophages.

Differential diagnosis

Anetoderma must be differentiated from other disorders of elastic tissue such as mid-dermal elastolysis (see Table 99.1) as well as atrophoderma (see below). However, the major differential diagnosis consists of post-traumatic scars and papular elastorrhexis. The latter is an acquired disorder characterized by firm, white, non-follicular papules that measure 2–5 mm in diameter and are evenly scattered on the trunk. The lesions usually appear during adolescence or early adulthood. Histology demonstrates focal degeneration of elastic fibers and normal collagen. There are no associated extracutaneous abnormalities. This disorder is believed by some authors to be a variant of connective tissue nevi[19] or an abortive form of the Buschke–Ollendorff syndrome[20], while others think that these lesions represent papular acne scars[21]. They are differentiated from anetoderma by being firm and non-compressible.

Less often, anetoderma is confused with perifollicular elastolysis (see above), nevus lipomatosus or focal dermal hypoplasia (Goltz syndrome). Nevus lipomatosus superficialis of Hoffman and Zurhelle presents as a clustered group of soft, skin-colored to yellow nodules, usually located on the lower trunk and present since birth (see Ch. 117). Histology shows ectopic mature lipocytes located within the dermis. The lesions of Goltz syndrome (including telangiectasias, vermiculate dermal atrophy, hypopigmentation, hyperpigmentation, and fatty herniations/hamartomas) are in a linear array along the lines of Blaschko (see Ch. 62). Histologically, a decrease in dermal content is seen as well as extension or deposition of subcutaneous fat into the dermis.

Treatment

Various therapeutic modalities have been tried, but have not resulted in improvement of existing atrophic lesions; these include intralesional

injections of triamcinolone and systemic administration of aspirin, dapsone, phenytoin, penicillin G, vitamin E and inositol niacinate. Some authors have reported improvement with hydroxychloroquine. Surgical excision of limited lesions may be helpful, with the patient aware of the possibility of scar formation.

STRIAE

Synonyms: ■ Striae distensae ■ Striae atrophicans ■ "Stretch marks" ■ Linear atrophy

Introduction

Striae are a very common condition in all age groups. They are linear atrophic depressions of the skin that form in areas of dermal damage produced by stretching of the skin. They are associated with various physiologic states, including puberty, pregnancy, growth spurts, rapid weight gain or loss, obesity[22], and disorders that lead to hypercortisolism.

History

Striae were first described by Roederer in 1773, and the first histologic descriptions were made by Troisier and Menetrier in 1889.

Epidemiology

Striae are very common and usually develop between the ages of 5 and 50 years. They are seen more commonly in Caucasians, and striae occur about twice as frequently in women as in men. They commonly develop during puberty, with an overall incidence of 25–35%[23], or during pregnancy, with an incidence of approximately 75%[24].

Pathogenesis

Factors leading to the development of striae have not been fully elucidated. Striae distensae are a reflection of "breaks" in the connective tissue that lead to dermal atrophy. A number of factors, including hormones (particularly corticosteroids), mechanical stress and genetic predisposition, appear to play a role.

Clinical features

Striae are usually multiple, symmetric, well-defined linear atrophic lesions that often follow the lines of cleavage. They are usually more of a cosmetic concern, but rarely they can ulcerate. Initially, striae appear as red-to-violaceous elevated lines that can be mildly pruritic and are called striae rubra (Fig. 99.5). Over time, the color gradually fades, and the lesions become atrophic, with the skin surface exhibiting a fine wrinkled appearance. These striae alba are usually permanent, but they may fade somewhat over time[23]. The striae can measure several centimeters in length and a few millimeters to a few centimeters in width.

During puberty, striae appear in areas where there is a rapid increase in size. In girls, the most common sites are the thighs, hips, buttocks and breasts, whereas in boys, they are seen on the shoulders, thighs and lumbosacral region (Fig. 99.6). Other less common sites include the abdomen, upper arms, neck and axillae.

Striae distensae are a common finding on the abdomen, and less so on the breasts and thighs, of pregnant women, especially during the last trimester. They are more common in younger primigravidas than in older pregnant women, in those who gained more weight during pregnancy, and/or those who had babies with a higher birth weight. One study showed that striae gravidarum are statistically significant predictors of lacerations during vaginal delivery[25]. More recently, the presence of striae was found to be a risk factor for the development of pelvic relaxation and clinical prolapse[26].

The striae associated with systemic corticosteroid therapy and Cushing's syndrome can be larger and more widely distributed (see Ch. 53). Flexural and intertriginous areas are particularly at risk for developing striae from the use of topical corticosteroids.

Atrophic striae may become elevated and even "worm-like" in the setting of severe edema, including lymphedema. In addition, there are diseases such as polymorphic eruption of pregnancy in which initial lesions arise within striae.

Fig. 99.5 Striae. A Linear erythematous lesions on the abdomen (striae rubra). **B** Atrophic linear lesions of striae alba in a teenager. **C** Large axillary striae in a patient receiving chronic, high-dose systemic corticosteroids. *B, Courtesy, Kalman Watsky, MD.*

Pathology

Histologic findings depend upon the stage of evolution of the striae at the time the biopsy is performed. The epidermis can be normal during

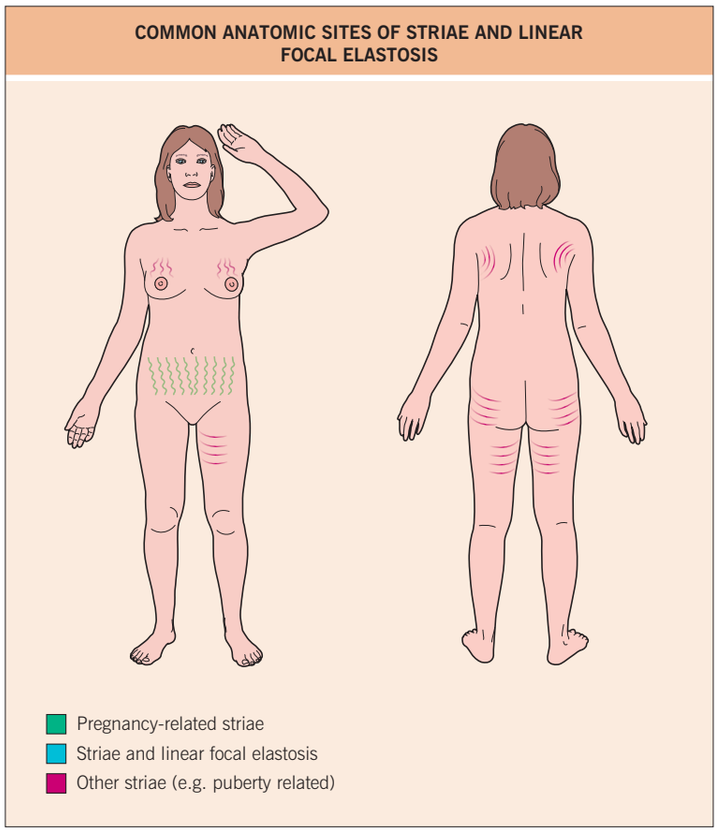


Fig. 99.6 Common anatomic sites of striae and linear focal elastosis. Striae associated with pregnancy are in green and lesions of linear focal elastosis are in blue.

the early stages, but eventually it becomes flattened and atrophic with blunted rete ridges. The dermal thickness is decreased, as is the collagen in the upper dermis. The collagen bundles are thinned and lie parallel to the epidermis, but they are also arranged transversely to the direction of the striae. Alterations in elastic fibers are variable, but dermal elastin can be fragmented, and specific elastin staining can demonstrate a marked reduction in visible elastin content compared with adjacent normal dermis[27]. There is an absence of both hair follicles and other adnexal structures.

Differential diagnosis

The diagnosis of striae distensae is usually straightforward, but the differential diagnosis does include linear focal elastosis (elastotic striae), an entity first described by Burket et al.[28] in 1989. Linear focal elastosis is characterized by rows of yellow, palpable, striae-like bands on the lower back. Unlike striae, the lesions are raised and yellow rather than depressed and white. Elderly men are most commonly affected, although such lesions have been described in teenagers. Linear focal elastosis is probably not an uncommon condition. Histologically, there is a focal increase in the number of elongated or fragmented elastic fibers as well as a thickened dermis. It is postulated that linear focal elastosis may represent an excessive regenerative process of elastic fibers and could be viewed as a keloidal repair of striae distensae[29].

Treatment

Striae distensae have no medical consequences, but they are frequently distressing to those afflicted. As stretch marks tend to improve spontaneously over time, the usefulness of treatments that have been tested without case controls is difficult to assess. Treatment of early-stage striae with tretinoin 0.1% cream can improve their appearance, and its application has been shown to decrease the length and width of striae[30]. Other topical treatments, including 0.05% tretinoin/20% glycolic acid and 10% L-ascorbic acid/20% glycolic acid, may also improve the appearance of stretch marks[31]. Several lasers have been used to treat striae: the 585 nm pulsed dye laser has been shown to lead to some improvement in the appearance of striae rubra, but it has no effect on striae alba; secondary pigmentary alterations in darker skin are a potential complication[32]. Improvement in the leukoderma of striae alba was noted with the 308 nm excimer laser, but maintenance treatment was required to sustain the cosmetic benefit[33]. Currently, there is no specific therapy that results in a complete response. Perhaps advances in laser technologies will provide better options in the future.

IDIOPATHIC ATROPHODERMA OF PASINI AND PIERINI

Synonyms: ■ Sclérodermie atrophique d'emblée ■ Morphea plana atrophica ■ Dyschromic and atrophic variation of scleroderma

Key features

- Depressed patches, usually on the posterior trunk and brown in color
- "Cliff-drop" or abrupt transition from normal to diseased skin
- Lesions are asymptomatic and lack induration
- Disorder lasts for many years but has a benign course

Introduction

Idiopathic atrophoderma of Pasini and Pierini is a form of dermal atrophy that presents as one or several sharply demarcated depressed patches, usually on the back of adolescents or young adults. Whether atrophoderma represents an atypical, primarily atrophic form of morphea or "burnt-out" morphea or a separate distinct entity is still debated.

History

In 1923, Pasini described atrophic cutaneous lesions on the trunk of a 21-year-old woman that he referred to as progressive idiopathic atrophoderma[34]. In 1936, and over the subsequent years, Pierini and associates extensively studied and defined the condition and its possible link to morphea. This prompted Canizares et al.[35] in 1958 to rename this entity "idiopathic atrophoderma of Pasini and Pierini".

Epidemiology

This disorder is more frequently encountered in women than in men, with a ratio of 6:1 in adults[36]. It usually starts insidiously in young individuals during the second or third decade of life. However, a number of cases have been described in children younger than 13 years of age. Recently, a rare congenital case was reported[37].

Pathogenesis

The etiology of atrophoderma of Pasini and Pierini remains as yet unknown. Some authors have suggested the possible role of infection with *Borrelia burgdorferi*, as in acrodermatitis chronica atrophicans, since a positive serology can be found in up to 40–50% of European patients[38]. However, false-positive results can occur, and results have varied widely. Given some overlap between atrophoderma and morphea, perhaps insights into the pathogenesis of the latter will provide clues to the former.

Clinical features

Lesions usually appear on the trunk, especially on the back and lumbosacral region, followed in frequency by the chest, arms and abdomen[38]. The face, hands and feet are usually spared. The distribution is often symmetric and bilateral, but a linear pattern along Blaschko's lines has been described (atrophoderma of Moulin; see Ch. 67).

The lesions are single or multiple and usually round or ovoid, ranging in size from a few centimeters to patches covering large areas of the trunk. They are usually asymptomatic and lack inflammation. When

lesions coalesce, they can form large irregular patches. The patches usually have a brown color (Fig. 99.7), but some are more blue to violet in color or even hypopigmented[39]. The surface of the skin is normal in appearance, as is the consistency upon palpation. There is a lack of cutaneous induration or sclerosis.

The borders or edges of these lesions are sharply defined, and they are usually described as abrupt "cliff-drop" borders ranging from 1 to 8 mm in depth, although they can have a gradual slant[35]. These depressed patches have a characteristic appearance and give the impression of inverted plateaus, or, if multiple lesions are present, they can have the appearance of Swiss cheese. The lesions are even more apparent when present on the back, because the dermis is thicker in this area. Occasionally, deep blood vessels may be seen running through the depressed patches.

The skin surrounding the patches is normal in appearance, and there is no erythema or lilac ring as in morphea. However, typical lesions of morphea, lichen sclerosus and atrophoderma have been observed to occur simultaneously in the same patient (but in different areas), supporting the view that these conditions are related[40]. In addition, sclerodermatous changes can occasionally appear years later in the center of the depressed lesions, leading to a white, shiny induration[35]. In a series of 139 patients, 17% had a white induration in the central portions of their atrophic lesions, and, in 22%, superficial plaques of morphea coexisted in sites separate from the atrophic foci[36].

Fig. 99.7 Atrophoderma of Pasini and Pierini. **A,B** Multiple light brown patches on the back; note the subtle depression of the lesions with a "cliff-drop" edge. In B, dermal blood vessels are easily seen within a few patches; the white papule is a healed biopsy site. *A, Courtesy, Catherine C McCuaig, MD; B, Courtesy, Julie V Schaffer, MD.*

The course of this benign disease is progressive, and lesions can continue to appear for decades before reaching a standstill. Transformation to generalized morphea has not been observed.

Pathology

In general, the histologic picture is not diagnostic, so the diagnosis is primarily a clinical one. The epidermis is usually normal or slightly atrophic. Pigmentation of the basal layer may be increased. A perivascular infiltrate consisting of T cells and histiocytes may be seen. Collagen bundles in the reticular dermis show varying degrees of homogenization and clumping. Dermal thickness is eventually reduced when compared with adjacent normal skin[41]. Dermal atrophy is difficult to evaluate on a punch biopsy, but it can be more easily demonstrated if an elliptical biopsy is taken in an area that includes the cliff-drop border and is then sectioned longitudinally to show the transition between normal and lesional skin. MRI performed in one patient with atrophoderma of Pierini and Pasini showed that the clinical depression was not secondary to subcutaneous atrophy[42]. In most series, no abnormality has been observed with elastic tissue stains[36,38]; however, a recent retrospective study described a spectrum of changes, ranging from normal to severe diminution and fragmentation of the elastic fiber network[39]. The diagnostic value of elastic tissue changes is still debatable. The adnexal structures are usually preserved.

If sclerodermatous changes appear in pre-existing patches, the histology reveals varying degrees of collagen sclerosis resembling morphea. Direct immunofluorescence may show nonspecific IgM and C3 staining in the dermal papillary blood vessels in early lesions or at the dermal–epidermal junction[43].

Differential diagnosis

Since the original description, there has been much discussion over whether idiopathic atrophoderma of Pasini and Pierini is a distinct entity or an atrophic, non-indurated, perhaps "burnt-out" variant of morphea (see Ch. 44). Active lesions of morphea present as indurated, often hyperpigmented plaques with a characteristic peripheral lilac rim.

Although atrophoderma of Pasini and Pierini lacks sclerosis[36,38,40,43], its relationship to morphea is favored by its striking clinical and histologic similarities to the atrophy seen at sites of regressing plaques of morphea. To some, the different course and outcome of atrophoderma of Pierini and Pasini as compared with morphea justifies preservation of a distinct name.

Anetoderma, also an atrophic dermal process, is easily differentiated by palpation and histology, which consistently shows a loss of elastic fibers in the dermis (as opposed to a loss of collagen).

Treatment

The natural course of the disease is often protracted (10–20 years) but self-healing, making the evaluation of therapy difficult. No treatment has been proven effective. In view of the possibility of an underlying *Borrelia* infection, penicillin has been used to treat atrophoderma of Pasini and Pierini, but the results have been inconclusive. A retrospective evaluation of 25 patients treated with oral penicillin (2 million IU/day) or oral tetracycline (500 mg three times daily) for 2–3 weeks reported clinical improvement and no evidence of new active lesions in 20 of the 25 patients. In the same study, four of six patients who did not receive treatment also had no evidence of progressive disease[38]. A dramatic response to oral hydroxychloroquine was recently reported in one patient[44], and three treatment sessions with the Q-switched alexandrite laser was effective in diminishing hyperpigmentation by 50% in another patient[45].

FOLLICULAR ATROPHODERMA

Follicular atrophoderma refers to dimple-like depressions at the follicular orifices. It can occur as an isolated defect of limited extent, in association with a variety of disorders in which hair follicles are plugged with keratin, or with rare genodermatoses.

In 1944, Miescher described follicular atrophoderma in an 8-year-old girl with atypical chondrodystrophy[46]. Six years later, Curth also used

the term follicular atrophoderma (although there was no evidence of follicular atrophy but rather follicular agenesis) and further reported in 1978 on the genetics of follicular atrophoderma[47].

Clinical features

Distinctive ice-pick depressions around hair follicles can be seen most commonly on the back of the hands and feet or on the cheeks. These pitted scars are often present at birth or during childhood. A family history may be present. Follicular atrophoderma can be associated with Bazex–Dupré–Christol syndrome or with Conradi–Hünermann–Happle syndrome. When the lesions are found exclusively on the cheeks, the term "atrophoderma vermiculatum" applies. Atrophoderma vermiculatum can in turn be associated with various disorders discussed in the next section.

Atrophoderma Vermiculatum

Atrophoderma vermiculatum, a disorder limited to the face, has been described under a variety of names, including ulerythema acneiforme, acne vermoulante, atrophoderma reticulata symmetrica faciei, folliculitis ulerythema reticulata, folliculitis ulerythemosa, and honeycomb atrophy ("ulerythema" means scar plus redness and "vermiculatum" means worm-eaten).

Atrophoderma vermiculatum is a condition that can: (1) occur sporadically; (2) be inherited as an autosomal dominant disorder; (3) be part of a group of related diseases that are referred to as "keratosis pilaris atrophicans" (see Table. 38.2); or (4) be associated with various syndromes.

Multiple symmetric inflammatory papules on the cheeks, presumably centered around hair follicles, may precede the atrophic lesions. These papules then go on to become pitted, atrophic and depressed scars in a reticulated or honeycomb pattern (Fig. 99.8). The severity of erythema varies, as does the presence of milia and horny follicular plugs. These lesions can extend to the forehead and preauricular regions. This condition usually has its onset during childhood or, less often, around puberty. Both sexes appear to be equally affected[48]. It usually has a slow progressive course.

Atrophoderma vermiculatum can be associated with a group of closely related disorders referred to as keratosis pilaris atrophicans (see Table. 38.2)[49]. This group also includes keratosis follicularis spinulosa decalvans and ulerythema ophryogenes. These conditions are characterized by keratotic follicular papules, variable degrees of inflammation, and secondary atrophic scarring. Ulerythema ophryogenes (or keratosis pilaris atrophicans faciei) differs from atrophoderma vermiculatum by affecting primarily the lateral portion of the eyebrows (ophryogenes) in the form of erythema, follicular papules and alopecia. The inheritance pattern is autosomal dominant with incomplete penetrance, and progression usually ceases after puberty. Keratosis follicularis spinulosa decalvans begins during childhood as keratotic follicular papules on the malar area and progresses to involve the eyebrows, scalp and extremities, with associated scarring alopecia. In most patients, this disorder is inherited in an X-linked recessive fashion.

The underlying pathogenesis in atrophoderma vermiculatum as well as the other disorders in the keratosis pilaris atrophicans group appears to be abnormal follicular hyperkeratinization. The latter occurs in the upper third of the hair follicle, leading to obstruction of the growing hair shaft and production of chronic inflammation. The end result is scarring below the level of obstruction.

Histopathology is usually not very helpful and shows dilated follicles, sometimes associated with plugging, inflammation and sclerosis of dermal collagen.

The various syndromes that include atrophoderma vermiculatum are Rombo syndrome (milia, telangiectasias, basal cell carcinomas [BCCs], hypotrichosis, acral cyanosis, and, rarely, trichoepitheliomas), Nicolau–Balus syndrome (syringomas and milia), Tuzun syndrome (fissured [scrotal] tongue), and, finally, the Braun–Falco–Marghescu syndrome (palmoplantar hyperkeratosis and keratosis pilaris).

The differential diagnosis of atrophoderma vermiculatum includes atrophia maculosa varioliformis cutis, keratosis pilaris rubra of the cheeks, and, in older adults, erythromelanosis faciei.

This disorder is primarily a cosmetic problem. Various topical treatments, including emollients, corticosteroids, tretinoin and keratolytics, have shown no consistent benefit. In some instances, systemic isotretinoin has been shown to stop progression and to induce remission[49]. Dermabrasion, laser therapy (e.g. CO_2 and 585 nm pulsed dye) and fillers (e.g. hyaluronic acid, autologous fat) are other options for improving the appearance of the atrophic scars[50].

Fig. 99.8 Atrophoderma vermiculatum. Multiple small pitted scars on the cheek of a young girl. Note the honeycomb pattern on the lower inner cheek; the skin is said to appear "worm-eaten". *Courtesy, Robert Hartman, MD.*

Bazex–Dupré–Christol Syndrome

Bazex, Dupré and Christol first described this genodermatosis in 1964, not to be confused with the other disease called Bazex syndrome (acrokeratosis paraneoplastica) in which hyperkeratotic plaques of the ears, nose, cheeks, hands, feet and knees are associated with carcinomas of the upper aerodigestive tract (see Ch. 53).

Bazex–Dupré–Christol syndrome is characterized by follicular atrophoderma, milia, multiple BCCs, hypotrichosis, and localized hypohidrosis (above the neck)[51]. It is inherited in an X-linked dominant fashion, and the gene has been linked to Xq24–q27[52]. Additional reported findings include facial hyperpigmentation, hair shaft anomalies and multiple trichoepitheliomas. Systemic manifestations are absent. Recently, it was suggested that this syndrome might better be classified as an ectodermal dysplasia[53].

The follicular atrophoderma, described as multiple ice-pick marks or patulous follicles, is found most commonly on the dorsal aspect of the hands, but can also be seen on the feet, lower back, elbows and, rarely, the face; it may be present at birth or appear later during childhood. No abnormalities of the elastic fibers have been found (nor any evidence of atrophy of the epidermis, hair or dermis), making the term "follicular atrophoderma" a misnomer. The histopathology usually shows hair follicles that are abnormally wide, plugged and surrounded by an inflammatory cell infiltrate and clusters of basaloid cells. Sweat glands can be absent.

The BCCs develop in about 40% of patients (primarily on the face) and they can resemble melanocytic nevi; the age of onset varies from 9 to 50 years of age. To date, approximately 20 families with this syndrome have been described.

The differential diagnosis includes other genodermatoses with multiple BCCs: nevoid basal cell carcinoma syndrome (Gorlin syndrome), an autosomal dominant disorder due to mutations in the *PTCH* gene, and Rombo syndrome, an autosomal dominant disorder characterized by BCCs, atrophoderma vermiculatum, milia, hypotrichosis, acrocyanosis, and, occasionally, trichoepitheliomas.

Conradi–Hünermann–Happle Syndrome (X-Linked Dominant Chondrodysplasia Punctata, CDPX2)

Conradi–Hünermann–Happle syndrome is an X-linked dominant disorder that occurs almost exclusively in girls, since it is usually lethal in hemizygous males. This form of chondrodysplasia punctata results from mosaicism for mutations in the gene on the X chromosome that

Fig. 99.9 Atrophia maculosa varioliformis cutis. Multiple linear scar-like depressions (between and above arrows) with no history of trauma. *Courtesy, Jean L Bolognia, MD.*

Fig. 99.10 Pedal papules of infancy. Soft nodules on the medial and plantar surfaces of the foot. *Courtesy, Julie V Schaffer, MD.*

encodes the emopamil-binding protein[54]. The clinical manifestations include ichthyosiform streaks (composed of erythema plus feathery, adherent scale) patterned along the lines of Blaschko; they usually resolve during the first year of life and are replaced by bands of follicular atrophoderma[55]. Hyperpigmentation, cataracts, scarring alopecia, saddle-nose deformity, asymmetric limb reduction defects, and stippled calcifications of the epiphyses can be seen (see Ch. 57). Within the ichthyosiform areas in newborns, keratotic follicular plugs containing dystrophic calcification is a distinctive histopathologic feature[54].

ATROPHIA MACULOSA VARIOLIFORMIS CUTIS

Atrophia maculosa varioliformis cutis was first described by Heidingsfeld in 1918[56] and is not as rare as the number of published cases would suggest. It consists of small round "varioliform" and linear facial depressions that are asymptomatic (Fig. 99.9)[57]. It occurs spontaneously on the cheeks and occasionally involves the forehead or chin. There is a gradual increase in the number of lesions, but in the absence of preceding trauma, acne or inflammatory lesions. A familial variant has been described. Pachydermodactyly and extrahepatic biliary atresia have been associated findings, but this association is probably fortuitous. The pathogenesis is unknown.

The histologic changes include a depression of the epidermis and normal collagen fibers, but a slightly decreased number of elastic fibers. There is usually little or no inflammation. The differential diagnosis includes simple scars, which can be differentiated by history and the presence histologically of dermal fibrosis, and atrophoderma vermiculatum. The latter is harder to differentiate, but it can present with inflammatory papules that are followed by pitted scars, and atrophoderma vermiculatum usually has a honeycombed (rather than sharply linear) pattern and is usually centered on hair follicles. There is no known treatment to prevent the occurrence of these lesions.

PIEZOGENIC PEDAL PAPULES (PIEZOGENIC PAPULES)

Piezogenic pedal papules were first described by Shelley and Rawnsley in 1968[58]. This term is somewhat of a misnomer as piezogenic means "producing pressure", when in fact these lesions are produced by pressure. It is postulated that pressure induces herniation of fat through connective tissue in the dermis of the heels.

These papules are common enough in the general population to be considered normal and have also been described in association with Ehlers–Danlos syndrome and Prader–Willi syndrome. An infantile variant characterized by larger nodules on the medial aspect of the heel (present without weight-bearing) has recently been reported (Fig. 99.10)[59].

Skin-colored papules and nodules are seen on the sides of the heels (see Ch. 88); they are induced by weight-bearing and disappear when the leg is raised. The lesions are usually asymptomatic, but pain has been described during weight-bearing, and, in these cases, an orthopedic shoe or surgical excision may help. Similar lesions have been described on the wrists[60].

OTHER ATROPHIES OF THE CONNECTIVE TISSUE

Many systemic conditions (scleroderma, lupus erythematosus, dermatomyositis) and genodermatoses (poikiloderma congenitale, dyskeratosis congenita, Cockayne syndrome, Hallermann–Streiff syndrome) have cutaneous atrophy (epidermal, dermal and/or subcutaneous) as an associated finding. Lichen sclerosus is discussed in Chapter 44, progeria in Chapter 63, Ehlers–Danlos syndrome and cutis laxa in Chapter 97, and acrodermatosis chronica atrophicans in Chapter 74. Cutaneous atrophy is also a well-known complication of prolonged use of either systemic or topical corticosteroids (see Ch. 125).

REFERENCES

1. Shelley WB, Wood MG. Wrinkles due to idiopathic loss of mid-dermal elastic tissue. Br J Dermatol. 1977;97:441–5.
2. Patroi I, Annessi G, Girolomoni G. Mid-dermal elastolysis: a clinical, histologic, and immunohistochemical study of 11 patients. J Am Acad Dermatol. 2003;48:846–51.
3. Gambichler T. Mid-dermal elastolysis revisited. Arch Dermatol Res. 2010;302:85–93.
4. Snider RL, Lang PG, Maize JC. The clinical spectrum of mid-dermal elastolysis and the role of UV light in its pathogenesis. J Am Acad Dermatol. 1993;28:938–42.
5. Vatve M, Morton R, Bilsland D. A case of mid-dermal elastolysis after narrowband ultraviolet B phototherapy Clin Exp Dermatol. 2009;34:263–4.
6. Gambichler T, Breuckmann F, Kreuter A, et al. Immunohistochemical investigation of mid-dermal elastolysis. Clin Exp Dermatol. 2004:29; 192–5.
7. Harmon CB, Su WPD, Gagne EJ, et al. Ultrastructural evaluation of mid-dermal elastolysis. J Cutan Pathol. 1994;21:233–8.
8. Verhagen AR, Woederman MJ. Post-inflammatory elastolysis and cutis laxa. Br J Dermatol. 1975;92:183–90.
9. Varadi DP, Saqueton AC. Perifollicular elastolysis. Br J Dermatol. 1970;83:143–50.
10. Jadassohn J. Uber eine eigenartige form von 'atrophica maculosa cutis! Arch Dermatol Syphilol. 1892;24:342–58.
11. Schweninger E, Buzzi F. Multiple benign tumor-like new growths of the skin. In: International Atlas Sellltener Hautkrankheiten, plate 15. Leipzig: L Voss, 1891.
12. Venencie PY, Bonnefoy A, Gogly B, et al. Increased expression of gelatinases A and B by skin explants from patients with anetoderma. Br J Dermatol. 1997;137:517–25.
13. Venencie PY, Winkelmann RK, Moore BA. Anetoderma: clinical findings, associations, and long-term follow-up evaluations. Arch Dermatol. 1984;120:1032–9.
14. Thomas JE, Mehregan DR, Holland J, et al. Familial anetoderma. Int J Dermatol. 2003;42:75–7.

15. Hodak E, Feureman H, David M. Primary anetoderma is a cutaneous sign of antiphospholipid antibodies. J Am Acad Dermatol. 2008;58:351.
16. Prizant TL, Lucky AW, Frieden IJ, et al. Spontaneous atrophic patches in extremely premature infants. Anetoderma of prematurity. Arch Dermatol. 1996;132:671–4.
17. Venecie PY, Wilkelmann RK. Histopathologic findings in anetoderma. Arch Dermatol. 1984;120:1040–4.
18. Bergman R, Friedman-Birnbaum R, Hazaz B, et al. An immunofluorescence study of primary anetoderma. Clin Exp Dermatol. 1990;15:124–30.
19. Sears J, Stone M, Argenyi Z. Papular elastorrhexis: a variant of connective tissue nevus: case reports and review of the literature. J Am Acad Dermatol. 1988;19:409–4.
20. Schirren H, Schirren C, Stolz W, et al. Papular elastorrhexis: a variant of dermatofibrosis lenticularis disseminata (Buschke-Ollendorff syndrome). Dermatology. 1994;189:368–72.
21. Wilson B, Dent C, Cooper P. Papular acne scars: a common cutaneous finding. Arch Dermatol. 1990;126:797–800.
22. Garda-Hidalgo L, Orozco-Topete R, Gonzalez-Barranco J, et al. Dermatoses in 156 obese adults. Obes Res. 1999;7:299–302.
23. Ammar NM, Rao B, Schwartz RA, et al. Adolescent striae. Cutis. 2000;65:69–70.
24. Muzaffar F, Hussain I, Haroon TS. Physiologic skin changes during pregnancy: a study of 140 cases. Int J Dermatol. 1998;37:429–31.
25. Wahman AJ, Finan MA, Emerson SC. Striae gravidarum as a predictor of vaginal lacerations at delivery. South Med J. 2000;93:873–6.
26. Salter SA, Batra RS, Rohrer TE, et al. Striae and pelvic relaxation: two disorders of connective tissue with a strong association. J Invest Dermatol. 2006;126:1745–8.
27. Arem A, Ward Kisher C. Analysis of striae. Plast Reconst Surg. 1980;65:22–9.
28. Burket JM, Zelickson AS, Padilla RS. Linear focal elastosis (elastotic striae). J Am Acad Dermatol. 1989;20;633–6.
29. Hashimoto K. Linear focal elastosis: keloidal repair of striae distensae. J Am Acad Dermatol. 1998;39:309–13.
30. Kang S. Topical tretinoin therapy for management of early striae. J Am Acad Dermatol. 1998;39:S90–2.
31. Ash K, Lord J, Zukowski M, McDaniel D. Comparison of topical therapy for striae alba (20% glycolic acid/0.05% tretinoin versus 20% glycolic acid/10% L-ascorbic acid). Dermatol Surg. 1998;24:849–56.
32. Jimenez GP, Flores F, Berman B, Gunja-Smith Z. Treatment of striae rubra and striae alba with the 585-nm pulsed-dye laser. Dermatol Surg. 2003;29:362–5.
33. Alexiades-Amenakas MR, Bernstein LJ, Friedman PM, Geronemus RG. The safety and efficacy of the 308-nm excimer laser for pigment correction of hypopigmented scars and striae alba. Arch Dermatol 2004;140:955–60.
34. Pasini A. Atrophoderma idiopathica progressiva. Gior Ital Derm Sif. 1923;58:785.
35. Canizares O, Sachs PM, Jaimovich L, Torres VM. Idiopathic atrophoderma of Pasini and Pierini. Arch Dermatol. 1958;77:42–60.
36. Kencka D, Blaszczyk M, Jablonska S. Atrophoderma Pasini-Pierini is a primary atrophic abortive morphea. Dermatology. 1995;190:203–6.
37. Kim SK, Rhee SH, Kim YC, et al. Congenital atrophoderma of Pasini and Pierini. J Korean Med Sci. 2006;21:169–71.
38. Buechner SA, Rufli T. Atrophoderma of Pasini and Pierini: clinical and histopathologic findings and antibodies to *Borrelia burgdorferi* in thirty-four patients. J Am Acad Dermatol. 1994;30:441–6.
39. Saleh Z, Abbas O, Dahdah MJ, et al. Atrophoderma of Pierini and Pasini: a clinical and histopathological study. J Cutan Pathol. 2008;35:1108–14.
40. Amano H, Nagai Y, Ishikawa O. Multiple morphea coexistent with atrophoderma of Pierini-Pasini (APP): APP could be abortive morphea. J Eur Acad Dermatol Venereol 2007;21:1254–6.
41. Yokoyama Y, Akimoto S, Ishikawa O. Disaccharide analysis of skin glycosaminoglycans in atrophoderma of Pasini and Pierini. Clin Exp Dermatol. 2000;25:436–40.
42. Franck JM, Macfarlan D, Silvers ON, et al. Atrophoderma of Pasini and Pierini: atrophy of dermis or subcutis? J Am Acad Dermatol. 1995;32:122–3.
43. Berman A, Berman GD, Kinnkelmann RK. Atrophoderma (Pasini-Pierini): findings on direct immunofluorescent, monoclonal antibody, and ultrastructural studies. Int J Dermatol. 1988;27:487–90.
44. Carter JD, Valeriano J, Vasey FB. Hydroxychloroquine as a treatment for atrophoderma of Pasini and Pierini. Int J Dermatol. 2006;45:1255–6.
45. Arpey CJ, Patel DS, Stone MS, et al. Treatment of atrophoderma of Pasini and Pierini-associated hyperpigmentation with Q-switched alexandrite laser: a clinical, histologic, and ultrastructural appraisal. Lasers Surg. 2000;27:206–12.
46. Miescher G. Atypische Chondrodystrophie, Typus morquino kombiniert mit follikularer atrophodermie. Dermatologica. 1944;89:38–51.
47. Curth HO. The genetics of follicular atrophoderma. Arch Dermatol. 1978;114:1479–83.
48. Luria RB, Conologue T. Atrophoderma vermiculatum: a case report and review of the literature on keratosis pilaris atrophicans. Cutis 2009;83:83–6.
49. Callaway SR, Lesher JL. Keratosis pilaris atrophicans: case series and review. Pediatr Dermatol. 2004;21:14–17.
50. Handrick C, Alster T. Laser treatment of atrophoderma vermiculata. J Am Acad Dermatol. 2001;44:693–5.
51. Torrelo A, Sprecher E, Medeiro IG, et al. What syndrome is this? Bazex-Dupré-Christol syndrome. Pediatr Dermatol. 2006;23:286–90.
52. Vabres P, Lacombe D, Rabinowitz LG, et al. The gene for Bazex-Dupré-Christol syndrome maps to chromosome Xq. J Invest Dermatol. 1995;105:87–91.
53. Castori M, Castiglia D, Passarelli F et al. Bazex-Dupré-Christol syndrome: an ectodermal dysplasia with skin appendage neoplasms. Eur J Med Genet. 2009:52:250–5.
54. Hoang MP, Carder KR, Pandya AG, Bennettt MJ. Ichthyosis and keratotic follicular plugs containing dystrophic calcification in newborns: distinctive histopathologic features of X-linked dominant chondrodysplasia punctata (Conradi-Hünermann-Happle syndrome). Am J Dermatopathol. 2004;26:53–8.
55. Jacyk WK. What syndrome is this? X-linked dominant chondroplasia punctata (Happle syndrome). Pediatr Dermatol. 2001;18:442–4.
56. Heidingsfeld ML. Atrophia maculosa varioliformis cutis. J Cutan Dis. 1918;36:285–8.
57. Kuflik JH, Schwartz RA, Becker KA, Lambert WC. Atrophia maculosa varioliformis cutis. Int J Dermatol. 2005;44:864–6.
58. Shelley WB, Rawnsley JM. Painful feet due to herniation of fat. JAMA. 1968;205:308–9.
59. Greenberg S, Krafchik BR. Infantile pedal papules. J Am Acad Dermatol. 2005;53:333–4.
60. Laing VB, Fleischer AB Jr. Piezogenic wrist papules: a common and symptomatic finding. J Am Acad Dermatol. 1991;24:415–17.

Panniculitis 100

James W Patterson

Chapter Contents

Erythema nodosum 1641
Morphea/scleroderma panniculitis 1645
Alpha$_1$-antitrypsin deficiency panniculitis 1646
Erythema induratum 1648
Pancreatic panniculitis 1649
Sclerema neonatorum, subcutaneous fat necrosis of the newborn, and post-steroid panniculitis 1650
Lupus erythematosus panniculitis (lupus panniculitis) 1653
Panniculitis of dermatomyositis 1654
Traumatic panniculitis 1655
Lipodermatosclerosis 1656
Infection-induced panniculitis 1658
Cytophagic histiocytic panniculitis 1659
Malignant subcutaneous infiltrates 1659

INTRODUCTION

Panniculitis is a diagnostically challenging arena for dermatologists and pathologists. Terminology is difficult, partly because various names have been applied to the same disorder (e.g. nodular vasculitis and erythema induratum), and partly because new discoveries have resulted in the introduction of new terms and the abandonment of others. For example, cases that might have previously been classified as Weber–Christian disease may now be categorized as α_1-antitrypsin deficiency panniculitis, lupus panniculitis, or pancreatic panniculitis. From a clinical standpoint, many forms of panniculitis with diverse etiologies closely resemble one another, presenting as tender, erythematous subcutaneous nodules. Some panniculitides can be a manifestation of different disease processes (erythema nodosum is the classic example), and, even if the type of panniculitis is correctly identified, this is only the first step in a series of clinical and laboratory investigations required to determine the underlying cause. From a pathologic standpoint, the subcutaneous fat responds to a variety of different insults in a limited number of ways, and, therefore, histopathologic differences among the various forms of panniculitis may be subtle. Management can also be difficult, since there are often at least two therapeutic desiderata:

- specific treatment of the panniculitis
- treatment of the underlying illness.

In this chapter, these issues will be addressed by introducing a schema for the classification of these disorders, recommending an approach to the histopathologic diagnosis, and providing information about the specific forms of panniculitis and their management.

Table 100.1 provides a working classification for the multiple forms of panniculitis. The categories are determined partly by clinical characteristics such as location (Fig. 100.1), partly by histopathology, and partly by etiology. A word should be said about *septal* versus *lobular* panniculitis. These are largely artificial constructs, since there is no purely septal or purely lobular panniculitis. Certain forms of panniculitis can be characterized as having predominantly septal involvement, and this finding can provide a useful clue to diagnosis when combined with other clinical and histopathologic features.

CLASSIFICATION OF THE PANNICULITIDES
PREDOMINANTLY SEPTAL PANNICULITIS
• Erythema nodosum
Erythema nodosum migrans (subacute nodular migratory panniculitis)
• Panniculitis of morphea/scleroderma
• Alpha$_1$-antitrypsin deficiency panniculitis*
LOBULAR AND MIXED SEPTAL–LOBULAR PANNICULITIS
• With vasculitis involving larger subcutaneous vessels
Erythema induratum (nodular vasculitis)
• With necrosis as an early finding
Pancreatic panniculitis
• With needle-shaped clefts within lipocytes
Sclerema neonatorum
Subcutaneous fat necrosis of the newborn
Post-steroid panniculitis
• Associated with autoimmune connective tissue disease
Lupus erythematosus panniculitis (lupus profundus)
Panniculitis of dermatomyositis
• Lipodystrophic panniculitis (see Ch. 101)
Lipoatrophy
Lipohypertrophy
• Traumatic panniculitis, including factitial panniculitis
Cold panniculitis (popsicle panniculitis, Haxthausen's disease)
Sclerosing lipogranuloma (including grease gun granuloma)
Panniculitis due to other injectable substances
Panniculitis due to blunt trauma
• Lipodermatosclerosis
• Infection-induced panniculitis
• Malignancy-related panniculitis-like infiltrates
Subcutaneous panniculitis-like T-cell lymphoma (see Ch. 120)
Other lymphomas with involvement of subcutaneous tissues
*Descriptions vary; some authors regard this as a lobular or mixed septal–lobular panniculitis.

Table 100.1 Classification of the panniculitides. The categories for classification of panniculitis are determined partly by clinical characteristics such as location and associated diseases and partly by histopathology. This classification scheme does not include Weber–Christian disease as cases initially assigned this designation have subsequently been reclassified as other forms of panniculitis, including α_1-antitrypsin deficiency, lipodermatosclerosis, lupus panniculitis and traumatic panniculitis.

Table 100.2 provides an approach to the histopathologic diagnosis of an unknown case of panniculitis. When performing a biopsy in a patient with panniculitis, it is absolutely critical that the specimen include a generous portion of subcutaneous fat. Therefore, excisional biopsies extending through the subcutis or narrow incisional biopsies that incorporate a broad expanse of subcutaneous fat are generally preferable to punch biopsies.

ERYTHEMA NODOSUM

Synonyms: ■ Erythema contusiformis ■ Erythema nodosum migrans (variant form)

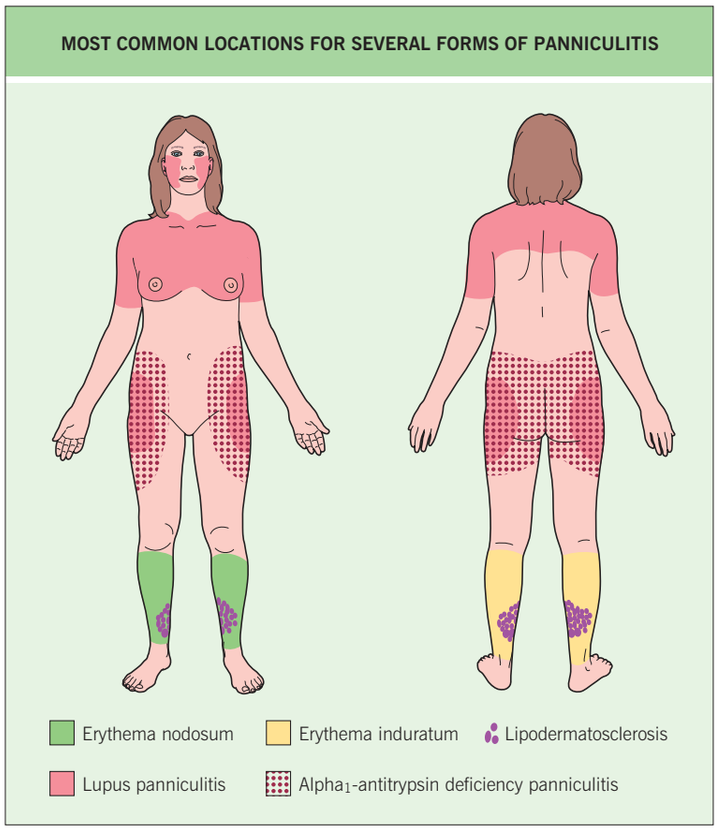


Fig. 100.1 Most common locations for several forms of panniculitis. Classification of panniculitis depends upon multiple factors, including clinical characteristics such as location and ulceration as well as histopathology and etiology.

Key features

- Tender, erythematous subcutaneous nodules
- Usually distributed symmetrically over pretibial areas; occasionally elsewhere
- In later stages, lesions acquire a bruise-like appearance
- May be accompanied by fever, arthralgias and malaise
- Associated with a wide variety of systemic disorders

Introduction

Erythema nodosum is probably the best known of the various forms of panniculitis, as well as the most common. It typically presents as an acute eruption of tender, erythematous subcutaneous nodules over the pretibial areas bilaterally. It is widely regarded as a delayed hypersensitivity response to a variety of antigenic challenges[1], although the mechanisms of its development are more complex than this statement would indicate. Histopathologically, it is the prototype of a "septal" panniculitis. Identification and treatment of the underlying disorder, if found, is of primary importance, but therapy directed toward the lesions themselves is also an option.

History

At the beginning of the eighteenth century, Robert Willan gave the first clear description of erythema nodosum, and he provided its name in his famous work, *On Cutaneous Disease*[2,3].

Epidemiology

Erythema nodosum can occur at any age, in both sexes, and in all racial groups. It is more common among women and is more frequently observed during the second through fourth decades of life[4,5]. The relative ranking of underlying causes may vary according to geographic location, for example, in areas where *Coccidioides immitis* is endemic and regions where Behçet's disease is more prevalent.

Pathogenesis

Erythema nodosum has been considered a delayed hypersensitivity response to a variety of antigenic stimuli, including bacteria, viruses and chemical agents[1,6]. Llorente et al.[7] observed expression of mRNA for Th1 cytokines (interferon-γ, interleukin-2) in the skin lesions and peripheral blood of patients with erythema nodosum, and a Th1 pattern of cytokine synthesis is associated with delayed-type hypersensitivity reactions. However, a complex series of intermediate steps is most assuredly involved in the development of these lesions. A variety of adhesion molecules and inflammatory mediators appear to be associated with erythema nodosum. For example, vascular cell adhesion molecule-1 (VCAM-1; CD106), platelet endothelial cell adhesion molecule-1 (PECAM-1; CD31), HLA-DR and E-selectin are expressed on endothelial cells (see Ch. 102), while intercellular adhesion molecule-1 (ICAM-1; CD54), very late antigen-4 (VLA-4), L-selectin and HLA-DR are expressed by inflammatory cells in erythema nodosum lesions[8].

Neutrophils are frequently numerous in early lesions, and it has been shown that a higher percentage of circulating neutrophils in patients with erythema nodosum leads to the production of reactive oxygen intermediates; these intermediates, in turn, may provoke inflammation and tissue damage[9]. Support for a pathogenic role for these cells and molecules is provided by studies of the effects of colchicine. This inhibitor of neutrophil chemotaxis is useful in treating inflammatory lesions of Behçet's disease and non-Behçet's-related erythema nodosum[10]. Among other effects, colchicine has been shown to diminish L-selectin expression on the neutrophil surface, inhibit E-selectin-mediated endothelial adhesiveness for neutrophils, and diminish stimulated expression of ICAM-1 on the endothelium[8].

Additional indirect evidence for the role of inflammatory cells and mediators includes reports of erythema nodosum following treatment with granulocyte colony-stimulating factor[11], and improvement (as well as flares) of erythema nodosum lesions with administration of tumor necrosis factor (TNF) inhibitors[12]. Erythema nodosum, especially in its chronic phase, is characterized by granuloma formation and TNF is known to play a role in granuloma formation. A link between deregulation of TNF-α production and granuloma formation is further supported by the strong correlation of a polymorphism in the promoter region of the gene that encodes TNF-α and the development of sarcoidosis-associated erythema nodosum[13].

A wide range of precipitating factors has been linked with erythema nodosum. Infectious causes are common, particularly upper respiratory infections (both streptococcal and non-streptococcal). Other commonly reported causes include sarcoidosis, inflammatory bowel disease, and certain medications. Table 100.3 lists the most well-known causes or associations as reported in several clinical series[4,5,14].

Clinical features

Erythema nodosum presents with bilateral, tender erythematous nodules. These arise in crops and clearly the most common sites are the shins (Fig. 100.2). Other locations are occasionally involved, particularly the thighs and forearms[4]. Nodules may appear on the trunk, neck and face[3], but this is sufficiently rare that development of lesions in these locations should prompt consideration of other diagnoses. Unlike other forms of panniculitis, ulceration is not a feature of erythema nodosum. Systemic symptoms may occur that are not necessarily related to a specific coexisting systemic disorder; these include arthritis, arthralgia, fever and malaise[3].

Because of its close association with a variety of disorders and infections, erythema nodosum is an important skin sign of systemic disease. For example, its development may precede or accompany a flare of inflammatory bowel disease[15]. It may also have some value as a prognostic indicator in certain disorders. For example, erythema nodosum is associated with a protective effect against disseminated disease in patients with coccidioidomycosis, and it is closely associated with a more benign and self-limited form of sarcoidosis[1,16]. Nevertheless, a significant percentage of cases – more than one-third – have no known disease association, even when followed for a year or more[5]. Clinical or laboratory data that tend to predict that a case of erythema nodosum may be secondary to a systemic disease are listed in Table 100.4.

AN APPROACH TO THE HISTOPATHOLOGIC DIAGNOSIS OF PANNICULITIS	
Histopathologic aspects to consider	**Conclusions**
Look for the "center of gravity" of the infiltrate	Recommended originally by Pinkus, the purpose is to determine whether or not the inflammatory process is centered in the subcutis (favoring a primary panniculitis), in the dermis, or in the fascia (in which case the panniculitis may be a secondary manifestation of a deeper inflammatory process)
Determine if the panniculitis is predominantly septal, predominantly lobular, or mixed	Generally, a predominantly septal panniculitis narrows the diagnostic considerations (see Table 100.1). If the panniculitis is lobular or mixed, look for other distinguishing features
Determine if there is vasculitis involving a medium-sized vessel, in the face of a lobular or mixed panniculitis	This is characteristic of **erythema induratum (nodular vasculitis);** caveat: deeper levels are often required in order to demonstrate the involvement of vessels
Look for fat necrosis with saponification and "calcium soap" formation	This is a feature of **pancreatic panniculitis**
Look for needle-shaped clefts within lipocytes	Their presence favors a diagnosis of **sclerema neonatorum, subcutaneous fat necrosis of the newborn**, or **post-steroid panniculitis**
Determine if the panniculitis has a lymphoplasmacytic predominance	This tends to be a feature of **panniculitis due to connective tissue disease**, including lupus erythematosus; beware of lymphocytic predominance in cases of subcutaneous panniculitis-like T-cell lymphoma
Check for a "central nidus" of inflammation or evidence of a needlestick injury. Look for vacuolated spaces or foreign material	These are clues to **traumatic panniculitis including factitial panniculitis**. Polarization microscopy can be helpful
Look for membranocystic changes in the subcutis	This change is characteristic of (though not pathognomonic for) **lipodermatosclerosis;** it can be observed in any panniculitis with prominent degenerative changes
Determine if the panniculitis is associated with substantial cellular necrosis, vascular proliferation, hemorrhage, sweat gland necrosis, or neutrophilic aggregates	These changes are often encountered in **infection-induced panniculitis**. Tissue cultures and special stains for organisms may be indicated
Determine if the infiltrating cells are particularly monotonous or atypical in appearance	Consider subcutaneous panniculitis-like T-cell lymphoma and other lymphomas with involvement of the subcutaneous fat. Rarely, non-hematologic malignancies mimic panniculitis. Immunohistochemical stains are mandatory for a precise diagnosis
Determine if there are large cells with cytophagic activity	Cytophagic activity (hematophagocytosis) observed primarily in subcutaneous infiltrates of primary cutaneous γ/δ T-cell lymphoma. This finding was previously termed "cytophagic histiocytic panniculitis"

Table 100.2 An approach to the histopathologic diagnosis of panniculitis.

Fig. 100.2 Erythema nodosum. Erythematous, tender nodules located bilaterally on the shins. *Courtesy, Kenneth E Greer, MD.*

Erythema nodosum lesions usually last a few days or weeks and then slowly involute, without scar formation. Discoloration suggestive of a bruise may be seen as erythema subsides. More chronic forms do occur, some of which show a tendency toward migration or centrifugal spread; the latter have been termed *subacute nodular migratory panniculitis* or *erythema nodosum migrans (*see below). Up to one-third of cases of erythema nodosum recur. Annual recurrences are particularly common among idiopathic cases[14].

Pathology

Erythema nodosum is the prototypic septal panniculitis, but this should not be taken to imply that histopathologic changes are entirely confined to subcutaneous septa[17]. Biopsy specimens of early lesions tend to show edematous septa and mild lymphocytic infiltrates (Fig. 100.3). Neutrophils may predominate in early lesions[8], and a variant with a predominance of eosinophils has been reported[18]. True vasculitis of the type seen in leukocytoclastic vasculitis is not demonstrable, and erythema nodosum is not generally regarded as a vasculitic process. However, "secondary" vasculitis may be observed in lesions when they contain relatively heavy, mixed or neutrophil-rich inflammatory infiltrates. Thrombophlebitis has been reported, and this change is apparently more frequent in erythema nodosum lesions associated with Behçet's disease[6,8].

In early lesions, one may also find Miescher's microgranulomas, a characteristic if not pathognomonic feature of erythema nodosum. These are small collections of macrophages, found within septa or at a septal–lobular interface, that tend to surround neutrophils or small cleft-like spaces[3]. Reported variations in the frequency of these granulomas in erythema nodosum[3,19] may result in part from differences in definition, in the acceptance of subtle changes, and in the rigor of the search. Miescher's microgranulomas can also be observed in older lesions, at which point the constituent cells have evolved into the appearance of epithelioid and multinucleated giant cells (Fig. 100.4).

As lesions progress, the septa become widened and contain a mixed, partly granulomatous infiltrate. These cells infiltrate the periphery of fat lobules in a lace-like configuration. The extent of lobular involvement may vary, and in some cases can be prominent[8]. Nevertheless, in the case of a lobular panniculitis without the characteristic septal changes, a diagnosis of erythema nodosum should be made with caution. There is also frequently a mild to moderate perivascular lymphocytic infiltrate in the overlying dermis. In later stages, the septa become fibrotic, partly replacing the fat lobules. Residual granulomas and lipophages can be observed, and a degree of vascular proliferation may be present[3]. Over the long term, a remodeling process takes place that usually results in minimal residual scarring[3].

CAUSES OF ERYTHEMA NODOSUM		
Incidence	**Cause**	**Comments**
Most common	Idiopathic	Still the largest single category, accounting for a third to a half of cases
	Streptococcal infections, especially of the upper respiratory tract	The largest single infectious cause
	Other infectious associations: Bacterial gastroenteritis – *Yersinia* > *Salmonella, Campylobacter* Viral upper respiratory tract infections	Overall, infection may account for a third or more of cases
	Coccidioidomycosis	Erythema nodosum is associated with a lower incidence of disseminated disease
	Drugs	Especially estrogens and oral contraceptive pills; also sulfonamides, penicillin, bromides, iodides; occasionally, TNF inhibitors
	Sarcoidosis*	10–20% of cases in some series
	Inflammatory bowel disease	Crohn's disease has a stronger association with erythema nodosum than does ulcerative colitis
Uncommon	Less common infectious associations: Brucellosis *Chlamydophila*† *pneumoniae* *Chlamydia trachomatis* *Mycoplasma pneumoniae* Tuberculosis Hepatitis B‡ Histoplasmosis	
	Neutrophilic dermatoses: Behçet's disease Sweet's syndrome	"Erythema nodosum" in Behçet's disease more closely resembles erythema induratum (nodular vasculitis)
	Pregnancy	
Rare	Rare infectious associations: Gonorrhea Meningococcemia *Escherichia coli* Pertussis Syphilis Cat scratch disease HIV infection Blastomycosis Giardiasis	*Erythema nodosum leprosum* is a different disease that is characterized by a cutaneous small vessel vasculitis
	Malignancy, most often acute myelogenous leukemia, Hodgkin disease	May overlap with Sweet's syndrome

*Löfgren's syndrome is an acute, spontaneously resolving form of sarcoidosis characterized by erythema nodosum, hilar lymphadenopathy, fever, polyarthritis and uveitis.
†Previously referred to as *Chlamydia*.
‡Erythema nodosum secondary to the hepatitis B vaccine has also been reported.

Table 100.3 Causes of erythema nodosum. TNF, tumor necrosis factor.

FINDINGS SUGGESTIVE OF A SYSTEMIC CAUSE FOR ERYTHEMA NODOSUM
• Synovitis • Diarrhea • Abnormal chest X-ray • Preceding upper respiratory tract infection • Elevated antistreptolysin O and/or anti-DNase B titers • Positive tuberculin skin test or QuantiFERON®-TB Gold test

Table 100.4 Findings suggestive of a systemic cause for erythema nodosum.

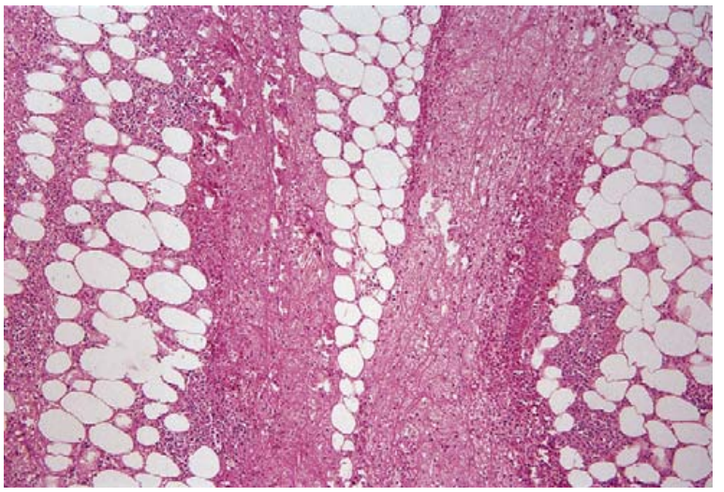


Fig. 100.3 Erythema nodosum. Septa are widened and edematous, and infiltrated by lymphocytes and neutrophils.

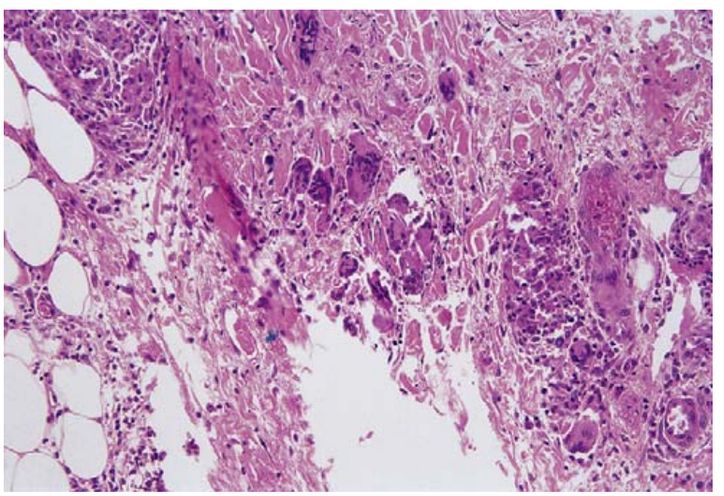


Fig. 100.4 Erythema nodosum. Miescher's microgranulomas within septa. Note the many multinucleated giant cells.

Differential diagnosis

The clinical picture of an acute eruption of tender subcutaneous nodules over both shins of a young person is highly characteristic of erythema nodosum. However, when lesions are few in number, are located in sites other than the lower legs, or are of longer duration (>6 weeks), erythema nodosum can be difficult to distinguish from other forms of panniculitis. Lesions of erythema induratum (nodular vasculitis) can resemble those of erythema nodosum, but they tend to occur on the posterior aspect of the lower legs and may ulcerate. Ulceration is also a feature of pancreatic panniculitis, which occurs more frequently in other locations (although still favoring the lower legs), is more likely to be accompanied by arthritis and serositis, and is associated with elevated serum amylase and lipase levels.

Histopathologically, the picture of a predominantly septal panniculitis usually limits the differential diagnosis and tends to exclude those conditions that are chiefly lobular or mixed. Pancreatic panniculitis may show predominantly septal changes in its earliest stages[20], but, eventually, these lesions exhibit the characteristic fat necrosis, with saponification and "ghost cell" formation. Infection-induced panniculitis can sometimes mimic erythema nodosum, but there are often

more extensive neutrophilic infiltrates, cellular necrosis (including sweat gland necrosis), vascular proliferation, and hemorrhage[21]. Special staining for organisms and microbiologic studies may be helpful if infection is a serious consideration.

Treatment

Treatments most often recommended for uncomplicated erythema nodosum include bed rest, salicylates, and nonsteroidal anti-inflammatory drugs (NSAIDs; Table 100.5)[2,15]. Potassium iodide has been used with success, with adult dosages ranging from 300 to 1500 mg/day (Table 100.6)[22]. Improvement may be seen within 2 weeks. Potassium iodide may work through inhibition of cell-mediated immunity, as well as via inhibition of neutrophil chemotaxis and suppression of neutrophil-generated oxygen intermediates[2]. In light of this treatment response, reports of erythema nodosum *triggered* by potassium iodide seem contradictory.

Treatment of erythema nodosum is influenced by underlying conditions. Thus, colchicine is useful in management of erythema nodosum that accompanies Behçet's disease[8]. Various treatments for inflammatory bowel disease are also effective in managing coexistent erythema nodosum[12]. Agents that have been employed in these circumstances include systemic corticosteroids, hydroxychloroquine, cyclosporine, thalidomide and infliximab[23]. Both etanercept and infliximab have been reported to be effective in treating erythema nodosum[24], but paradoxically both have been reported to produce erythema nodosum as a cutaneous side effect[25,26]. NSAIDs are to be avoided in treating the erythema nodosum of inflammatory bowel disease, since these may trigger a flare of the bowel disease or compromise maintenance therapy[15].

THERAPEUTIC LADDER FOR ERYTHEMA NODOSUM
Discontinue possible causative medications
Treatment of underlying infectious diseases
Bed rest and leg elevation
Nonsteroidal anti-inflammatory drugs (NSAIDs) (3)
Potassium iodide (2)
Colchicine (3) (esp. in the setting of Behçet's disease)
Prednisone (3)
Dapsone (3)
Hydroxychloroquine (3)
Mycophenolate mofetil (3)
Infliximab (3) (esp. in the setting of inflammatory bowel disease)
Thalidomide (3) (esp. in the setting of inflammatory bowel disease)*
Cyclosporine (3) (esp. in the setting of Behçet's disease)
*May transiently exacerbate erythema nodosum associated with Behçet's disease.

Table 100.5 Therapeutic ladder for erythema nodosum. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective trial or large case series; (3) small series or individual case reports.

USE OF POTASSIUM IODIDE (KI)
SATURATED SOLUTION OF POTASSIUM IODIDE (SSKI)
• 1000 mg/ml
• Droppers are supplied with calibrations for: 0.3 ml (300 mg)* 0.6 ml (600 mg)
• In adults and older children, common dose = 300 mg tid po with starting dose = 150–300 mg tid
• In infants and young children, common dose = 150 mg tid
• SSKI should be diluted in water or juice to try to minimize the bitter aftertaste
• Crystallization may occur with cold temperatures, but rewarming and shaking dissolves the crystals; discard if solution turns yellow–brown
SIDE EFFECTS OF SSKI
• Acute – nausea, bitter eructation, excessive salivation, urticaria, angioedema, cutaneous small vessel vasculitis
• Chronic – enlargement of salivary and lacrimal glands, acneiform eruption, iododerma, hypothyroidism, hyperkalemia, occasionally hyperthyroidism
*0.3 ml = 10 drops from the calibrated dropper supplied with SSKI.

Table 100.6 Use of potassium iodide (KI).

Subacute Nodular Migratory Panniculitis

Synonyms: ■ Erythema nodosum migrans ■ Chronic erythema nodosum

Key features

- Nodules on the lower extremities that migrate or undergo centrifugal spread, with central clearing
- Often unilateral
- Most cases are idiopathic; occasionally associated with streptococcal infection or thyroid disease
- More chronic course than typical erythema nodosum

Clinical features

This condition was first described by Bafverstedt in 1954[27] and was named *subacute nodular migratory panniculitis* by Vilanova and Piñol Aguade in 1956[28]. Some of its clinical and microscopic characteristics are similar to chronic erythema nodosum, and it is believed by many to represent a variant of the latter[3,27]; however, others consider it to be a separate disorder[29]. Subacute nodular migratory panniculitis is seen predominantly in women, is often unilateral, and is characterized by nodules that migrate or expand in a centrifugal manner (with central clearing)[3] and may assume a yellowish or morpheaform appearance[30]. Lesions tend to be less tender than those of classic erythema nodosum. There may be few, if any, associated systemic symptoms[27], though arthralgias have been reported and the ESR may be elevated[28]. Most cases are idiopathic, but some are associated with streptococcal infection (as evidenced by elevated antistreptolysin O and anti-DNase B titers) or thyroid disease[29].

Pathology

Microscopically, the changes are those of a chronic septal panniculitis[30]. However, in contrast to more classic forms of chronic erythema nodosum, subacute nodular migratory panniculitis shows greater septal thickening, more prominent granulomatous inflammation along the borders of widened subcutaneous septa, absence of phlebitis, and rare hemorrhage[29].

Treatment

Untreated, subacute nodular migratory panniculitis can last for months or years. However, treatment with potassium iodide is usually effective, resulting in clearing of lesions within several weeks[30].

MORPHEA/SCLERODERMA PANNICULITIS

(See also Chs 43 & 44)

Clinical features

Both morphea and scleroderma (systemic sclerosis) can affect the subcutaneous fat (Table 100.7), which is the primary site of involvement in deep morphea (morphea profunda)[36]. Subcutaneous extension also occurs in variants such as disabling pansclerotic morphea of childhood, generalized morphea, and linear morphea. In addition, eosinophilic fasciitis can involve the subcutaneous fat as well as the fascia[31]. These syndromes may be associated with peripheral eosinophilia, polyclonal gammopathy and serologic abnormalities[31,37]. Fleischmajer et al.[32] have proposed that the sclerosing process in scleroderma is initiated by the changes that take place in the subcutis.

Pathology

Table 100.7 outlines the microscopic changes in morphea and scleroderma. These conditions are associated with septal panniculitis (Fig. 100.5). Lymphocytes and plasma cells predominate[31,33,38], though macrophages and eosinophils may be present. In some cases, the number

CLINICAL AND MICROSCOPIC FEATURES OF CONNECTIVE TISSUE PANNICULITIS				
Disorder	**Clinical presentation**	**Lesion distribution**	**Relation to systemic disease**	**Histopathology of panniculitis**
Morphea and scleroderma	Indurated plaques	Extremities, trunk	Occurs in scleroderma, but usually more pronounced in morphea	Septal, with thickening and sometimes mucin deposition; inflammation especially at dermal–subcutaneous interface; lymphocytes and plasma cells; lymphoid follicles in morphea*
Lupus panniculitis	Tender subcutaneous nodules and plaques; may have overlying lesions of discoid LE	Face (especially cheeks), upper arms, shoulders, hips, breasts, trunk	Only minority of cases associated with systemic LE	Lobular or mixed lobular/septal; mucin deposition; hyaline necrosis of lobules; lymphocytes and plasma cells, sometimes with prominent nuclear dust; nodular lymphocytic aggregates or lymphoid follicles
Dermatomyositis	Indurated, painful plaques and nodules; may ulcerate	Buttocks, abdomen, thighs, arms	Can arise in patients with established dermatomyositis or precede other disease manifestations	Lobular or mixed septal/lobular; fat necrosis; lipomembranous changes; sometimes calcification; lymphocytes and plasma cells; sometimes nodular lymphocytic aggregates
Annular atrophic connective tissue panniculitis of the ankles	Subcutaneous atrophy, which may be preceded by induration and tenderness	Circumferential bands around the ankles	Patients often have antinuclear antibodies and/or autoimmune conditions such as thyroiditis or rheumatoid arthritis	Lobular or mixed septal/lobular lymphohistiocytic panniculitis with areas of fat necrosis
Atrophic connective tissue panniculitis	Erythematous, indurated plaques that resolve with subcutaneous atrophy	Favors extremities; may be widespread	As above	As above

*Less often than in lupus panniculitis.

Table 100.7 Clinical and microscopic features of connective tissue panniculitis. Based on refs 31–35. LE, lupus erythematosus.

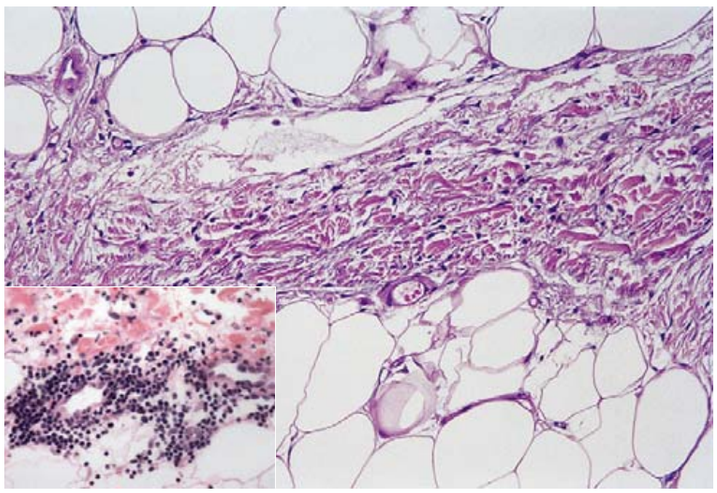


Fig. 100.5 Morphea panniculitis. Septal thickening, mucin deposition and mild lymphocytic infiltrate. Lymphoplasmacytic infiltrates concentrate at the dermal–subcutaneous interface (insert).

of plasma cells is striking[33]. In late stages of morphea, the subcutis is largely replaced by hyalinized connective tissue, quite often accompanied by changes of lipoatrophy.

Differential diagnosis

The combination of septal panniculitis with lymphoplasmacytic predominance and dermal and subcutaneous sclerosis is unique, and this helps to separate morphea/scleroderma panniculitis from other septal forms of panniculitis. Differentiation among the several variants outlined above is more difficult, requiring clinical data for accurate classification. Sclerosis with lesser degrees of subcutaneous inflammation characterizes scleroderma, while a predominance of fascial involvement with extension into the subcutis is more typical of eosinophilic fasciitis.

ALPHA$_1$-ANTITRYPSIN DEFICIENCY PANNICULITIS

Synonym: ■ Alpha$_1$-protease (proteinase) deficiency panniculitis

Key features

- Erythematous, painful subcutaneous nodules or plaques that often ulcerate and drain
- Associated with α_1-antitrypsin deficiency; patients with the most severe disease are homozygotes for the Z allele of the *SERPINA1* gene (PiZZ)
- A characteristic histologic finding is liquefactive necrosis of the dermis and subcutaneous septa, but lobular or mixed septal–lobular changes with neutrophils may occur

Introduction

Alpha$_1$-antitrypsin deficiency is a well-established but uncommon cause of panniculitis. The most severely affected individuals, with markedly decreased levels of the protease inhibitor, are most prone to the development of ulcerating neutrophilic panniculitis. Recognition of the disorder is important not only in the selection of appropriate therapy, but also in addressing other manifestations of the disease and in dealing with its genetic aspects.

History

Alpha$_1$-antitrypsin deficiency is an inborn error of metabolism that was first delineated by Eriksson and others in the early 1960s[39]. In 1972, Warter and colleagues identified members of a family with α_1-antitrypsin deficiency and "Weber–Christian syndrome". Subsequent investigations linked the clinical and microscopic findings to known effects of proteinase inhibitor deficiency.

Epidemiology

No apparent racial or geographic prevalence has been noted for α_1-antitrypsin deficiency panniculitis. The incidence of the disease is approximately equal in men and women[40,41]. Age of onset ranges from infancy to the eighth decade of life[41].

Pathogenesis

Alpha$_1$-antitrypsin, a glycoprotein produced in the liver, is the most abundant circulating *ser*ine *p*rotease *in*hibitor (serpin). The more than 120 different alleles of the gene that encodes this protein (SERPINA1;

formerly known as PI) are divided into categories based upon the electrophoretic mobility of their protein products (M = medium, S = slow, Z = very slow). The most common protease inhibitor (Pi) phenotype is MM (homozygous for M alleles), which is associated with normal serum levels of α_1-antitrypsin (120–200 mg/dl)[42]. Heterozygotes with one copy of the S or Z allele have mild to moderate deficiencies of the inhibitor (PiMS and PiMZ; prevalences of 1–3% in Caucasian populations). Patients who are homozygous for the Z allele (PiZZ; prevalence of 1:1500 – 1:5000 in Caucasian populations) have severe α_1-antitrypsin deficiency, with serum levels in the range of 20–45 mg/dl. In these individuals, most of the aberrant α_1-antitrypsin protein accumulates in the endoplasmic reticulum of hepatocytes, and the small amounts that enter the circulation have decreased function and a tendency to form inactive polymers that may stimulate neutrophil chemotaxis[43]. Of note, Z-type polymers have been detected in the skin of a patient with α_1-antitrypsin deficiency panniculitis, further suggesting a possible proinflammatory role[44].

Alpha$_1$-antitrypsin acts upon a wide range of proteolytic enzymes that play a direct role in degradation of tissues, including trypsin, collagenase, and elastase[45]. It also has important effects on immune function, e.g. inhibition of membrane-bound serine proteases involved in the activation of lymphocytes and macrophages[46]. It may also inhibit complement activation, both through a direct effect on complement-related proteases[47] and by inhibiting the neutrophil proteases that activate enzymes of the complement system[48].

In addition to panniculitis, the consequences of α_1-antitrypsin deficiency include chronic liver disease with cirrhosis (resulting from retention of the aberrant protein within the liver), emphysema, pancreatitis, membranoproliferative glomerulonephritis, rheumatoid arthritis, C-ANCA (cytoplasmic antineutrophil cytoplasmic antibody)-positive vasculitis, other cutaneous vasculitides, and angioedema (resulting from deficiency of the protease inhibitor)[40,48]. The initiating event in individuals who develop panniculitis is not always clear; trauma appears to play a role in some cases. Postpartum flares of the disease have been reported in genetically susceptible individuals. This is attributed to the estrogen-promoted increase in proteinase inhibitor levels during pregnancy, followed by a precipitous decline to subnormal levels postpartum[49]. Absence of the α_1-antitrypsin protease inhibitor results in activation of lymphocytes and macrophages, lack of restraint upon the complement cascade, release of chemotactic factors, accumulation of neutrophils with release of their proteolytic enzymes, and consequent attack upon fat and nearby connective tissues[43,45]. The subcutis may be particularly vulnerable to this process, since fatty acids make nearby elastin more susceptible to proteolytic degradation[48].

Clinical features

Large, erythematous to purpuric, tender nodules or plaques appear in a variety of sites (Fig. 100.6), especially the lower trunk and proximal extremities (flanks, buttocks and thighs)[40,43,45]. Ulcers develop that may be deep and necrotic, accompanied by an oily discharge[41,43,45]. Migration of lesions has been reported[40]. A history of antecedent trauma can be elicited in approximately one-third of cases[41]. Some patients with panniculitis also have fever, pleural effusions and pulmonary emboli[41]. The clinical course of the panniculitis is often prolonged, and lesions are resistant to therapy. Healing is accompanied by scarring and subcutaneous atrophy[41]. The most severe manifestations arise in those with profound proteinase inhibitor deficiency (PiZZ), although the panniculitis can also occur in heterozygotes[40].

Fig. 100.6 Alpha$_1$-antitrypsin deficiency panniculitis. Purpuric nodules on the ankle. *Courtesy, Kenneth E Greer, MD.*

Pathology

Descriptions of the pathology of α_1-antitrypsin deficiency panniculitis have varied. Early, there is a neutrophilic panniculitis, followed rapidly by necrosis and destruction of fat lobules[45]. Splaying of neutrophils between collagen bundles in the reticular dermis has been described as an early clue to the diagnosis[50]. Dissolution of dermal collagen, with resultant liquefactive necrosis and separation of fat lobules from adjacent septa, is a principal change in most cases[51]. Another characteristic feature is the presence of "skip areas" of normal fat adjacent to foci of severe necrotizing panniculitis[45]. Chronic inflammation and hemorrhage may be present at the periphery of areas of involvement[45]. Most authors have not found evidence for *primary* leukocytoclastic vasculitis, although there may be evidence for lymphocytic vasculitis, *secondary* vasculitis in areas of heavy neutrophilic infiltration, or thrombosis[45]. In individuals with intermediate levels of protease inhibitor deficiency, lipophage and giant cell accumulation may be prominent[45]. Lesions heal with scarring and obliteration of fat lobules.

Views differ on whether α_1-antitrypsin deficiency panniculitis should be regarded as a primarily septal or lobular panniculitis. Clearly, involvement of fat lobules can be significant, and, as a result, some authors have labeled the process a lobular panniculitis. On the other hand, some descriptions have emphasized early septal inflammation, collagenolysis of the fibrous septa[51], and the prominent septal fibrosis in late-stage lesions[50].

Differential diagnosis

Clinically, the degrees of inflammation, ulceration and drainage associated with α_1-antitrypsin deficiency panniculitis may actually raise a differential diagnosis more focused upon ulcerative skin disorders. The presence of ulcers with geometric patterns supports a diagnosis of factitial panniculitis. Ulcers associated with α_1-antitrypsin deficiency generally lack the necrotic, "undermined" borders associated with pyoderma gangrenosum[45].

Su et al.[45] have extensively reviewed the microscopic differential diagnosis for this disorder. Entities that are of particular importance for consideration include traumatic (factitial) panniculitis, infection-induced panniculitis, pancreatic panniculitis, and erythema induratum (nodular vasculitis). Each of these can be associated with infiltrates that include neutrophils and varying degrees of necrosis, yet each has other distinct findings (see below). In the appropriate clinical setting, subcutaneous Sweet's syndrome and neutrophilic panniculitis in patients with rheumatoid arthritis or inflammatory bowel disease may represent additional diagnostic considerations.

Treatment

Treatments that are usually ineffective include corticosteroids, immunosuppressants, cytotoxic agents, colchicine, danazol and hydroxychloroquine[40,45]. Doxycycline is sometimes effective, particularly in mild cases; one suggested dosage schedule is 200 mg twice daily for 3 months[47,52]. Dapsone may also be beneficial in mild cases, by suppressing neutrophil migration and inhibiting oxidation reactions induced by myeloperoxidase[40]. Reduction of alcohol intake has also been recommended, since ethanol (as a hepatotoxin) may precipitate α_1-antitrypsin-associated hepatitis[48].

The most effective therapeutic measure is replacement of α_1-antitrypsin via intravenous infusions. Dosages are generally 60 mg/kg per week, administered over a period of 3 to 7 weeks[40,41]. Improvement is relatively rapid, and clearing of the panniculitis can occur after three weekly doses[40]. Recurrences are possible when α_1-antitrypsin levels fall below 50 mg/dl[40], but these typically respond to further replacement therapy. Other successful therapies have included plasma exchange and liver transplantation (in appropriate clinical circumstances). In the future, autophagy-enhancing drugs such as carbamazepine may reduce systemic manifestations such as hepatic fibrosis[52a].

ERYTHEMA INDURATUM

Synonyms: ■ Nodular vasculitis ■ Erythema induratum of Bazin or Bazin's disease (tuberculous etiology) ■ Erythema induratum of Whitfield (non-tuberculous etiology)

Key features

- Erythematous nodules or plaques, usually on the posterior lower legs of young to middle-aged women
- Ulceration and drainage may occur
- Microscopic features of lobular or mixed panniculitis with evidence for vasculitis involving arteries or veins
- Classically associated with tuberculosis, but similar lesions can be idiopathic or induced by other infectious agents or drugs

Introduction

Erythema induratum is a condition characterized by nodules on the lower extremities, which may ulcerate and drain. Originally regarded as a tuberculid, its relationship to tuberculosis in a subset of patients has been solidified by several more recent studies detecting mycobacterial DNA in cutaneous lesions.

History

Erythema induratum was first described by Ernest Bazin in 1861. It was generally regarded as a tuberculid because of a strong association with tuberculosis, though Koch's postulates could not be fulfilled. In 1945, Montgomery and colleagues proposed the term *nodular vasculitis* for cases with similar clinical and pathologic features that were not of tuberculous origin. Since the early 1970s, erythema induratum and nodular vasculitis have generally been considered as synonyms referring to a clinicopathologic entity with several possible causes, one of which is tuberculosis. The detection of mycobacterial DNA in cutaneous lesions has confirmed a tuberculous origin in some patients[53]. There are some clinicians, however, who prefer to use the term nodular vasculitis when referring to individuals with a non-tuberculous etiology.

Epidemiology

In erythema induratum, an overwhelming female predominance is observed, but men can also develop the disease[54]. There is no apparent racial predilection, and although there is a wide age range among affected patients, the mean is between 30 and 40 years[54]. Erythema induratum of tuberculous etiology occurs more frequently in populations with a high prevalence of tuberculosis.

Pathogenesis

As mentioned, there has been a strong association of some cases with tuberculosis. This has now been substantiated by the detection of mycobacterial DNA in skin lesions by PCR[53,55,56]. Specific primers can be used to distinguish *M. tuberculosis* complex DNA from that of other mycobacterial pathogens[56]. Non-tuberculous cases have been related to other infectious agents (e.g. *Nocardia*[21]) or to drugs (e.g. propylthiouracil[57]). An example of erythema induratum in association with "red fingers" syndrome was described in a patient with chronic hepatitis C infection[58].

Although it has been suggested that erythema induratum results from an immune complex-mediated vasculitis[54], most investigators believe that the process represents a type IV, cell-mediated response to an antigenic stimulus[59]. Biopsy specimens show a predominance of T lymphocytes, macrophages and dendritic cells, including Langerhans cells[54,60,61]. One study of peripheral blood mononuclear cells from a patient with erythema induratum and active tuberculosis showed a high proliferative response to purified protein derivative (PPD) and marked production of interferon-γ, suggesting a pathogenic role for these PPD-specific T cells in a delayed hypersensitivity response to mycobacterial antigens[62].

Clinical features

Erythema induratum is characterized by tender, erythematous to violaceous nodules and plaques that most often develop on the lower legs, especially the calves[60,61]. Lesions have also been reported on the feet, thighs, buttocks and arms[54]. Annular arrangements of nodules have been described in *M. tuberculosis*-related cases[63]. Ulceration can occur (Fig. 100.7). Lesions are persistent, tend to heal with scarring, and are prone to recurrence[54,60,64]. In erythema induratum associated with *M. tuberculosis*, there may be clinical and radiographic evidence for active tuberculosis, positive skin tests to PPD or a positive QuantiFERON®-TB Gold test. Clinical differences between tuberculous and non-tuberculous cases are minor.

Pathology

Erythema induratum is generally described as a lobular or mixed septal/lobular panniculitis. Inflammation is mixed, and can include neutrophils, lymphocytes, macrophages and multinucleated giant cells. Vasculitis is identifiable in the vast majority of cases, and most frequently involves veins or arteries of connective tissue septa and small venules of the fat lobules[65] (Fig. 100.8). It may be predominantly neutrophilic[60], lymphocytic[64] or granulomatous. Necrosis with a coagulative or caseous appearance may be present, sometimes with palisading granulomas[60] (Fig. 100.9). Necrosis has been described in both tuberculous and non-tuberculous cases, and the incidence and degree of

Fig. 100.7 Erythema induratum. Nodular lesions on the lower leg, with evidence of ulceration. *Courtesy, Kenneth E Greer, MD.*

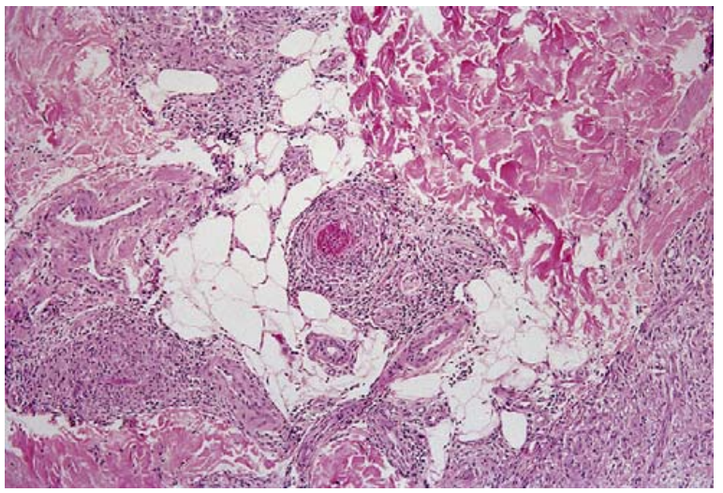


Fig. 100.8 Erythema induratum. Vasculitis involving a medium-sized vessel in the subcutis. The infiltrate is lymphocytic and granulomatous.

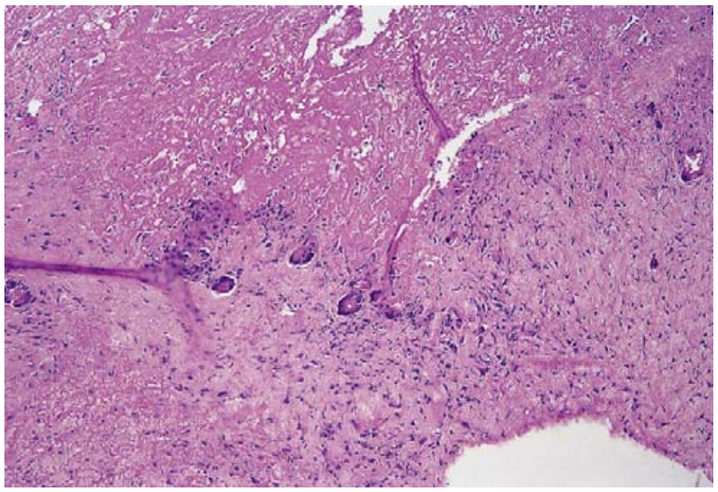


Fig. 100.9 Erythema induratum. Zone of caseous necrosis surrounded by a palisade of macrophages and multinucleated giant cells.

necrosis are greater in those cases that are positive for *M. tuberculosis* DNA by PCR methods[55]. However, this finding is absent in over half of cases.

Differential diagnosis

Infection-induced panniculitis tends to show a more prominent neutrophilic component, granular basophilic necrosis, sweat gland necrosis and proliferation of small vessels, and organisms may be identified on special staining. Lupus panniculitis tends to be less granulomatous, has a prominent lymphoplasmacellular infiltrate, may show mucin deposits, and sometimes has overlying epidermal and dermal changes typical for lupus erythematosus. Both polyarteritis nodosa and thrombophlebitis tend to show inflammation limited to the immediate perivascular zone, in contrast to the extensive lobular panniculitis often encountered in erythema induratum. Histologically, perniosis can be difficult to distinguish from erythema induratum, but there is typically a history of cold exposure[60], and on microscopic examination the vessels often show "fluffy edema" of their walls.

Treatment

Treatment should be directed at the underlying cause, if found. This includes multi-drug antituberculous therapy for those cases associated with *M. tuberculosis*[63] (see Ch. 75). Appropriate antimicrobial therapy is indicated for other infection-related cases, and possible inciting medications should be discontinued. Other helpful therapies have included corticosteroids, NSAIDs, potassium iodide, tetracycline, gold[64] and mycophenolate mofetil[66]. Supportive care includes bed rest, bandages, gradient support hose, and avoidance of aggravating factors such as smoking.

PANCREATIC PANNICULITIS

Synonyms: ■ Pancreatic fat necrosis ■ Enzymatic panniculitis

Key features

- Subcutaneous nodules, sometimes accompanied by fever, arthritis or abdominal pain
- Associated with pancreatic disorders, including acute and chronic pancreatitis and pancreatic carcinoma
- Mixed septal/lobular panniculitis featuring "ghost cell" formation and the deposition of basophilic material due to saponification of fat by calcium salts
- Treatment primarily directed towards the underlying pancreatic disorder

Introduction

Pancreatic panniculitis is an uncommonly reported complication of pancreatic disease. In addition to the symptoms associated with fat necrosis, its chief importance is as a sign of a significant systemic disorder, particularly because the panniculitis may be recognized prior to detection of the underlying pancreatic disease.

History

Chiari first described pancreatic panniculitis in 1883. By 1999, fewer than 100 cases had been reported[67,68].

Epidemiology

Panniculitis develops in up to 2% of patients with pancreatic disorders[69]. No geographic, racial or sex predilections have been reported.

Pathogenesis

There is considerable evidence that the enzymes lipase, amylase and trypsin are involved in producing the lesions of pancreatic panniculitis[67]. Elevated enzyme levels have been detected in the blood[68,69], urine[67] and skin lesions, even in the absence of detectable pancreatic disease. Lipase has the clearest relationship with the panniculitis, with a number of cases showing elevated serum lipase levels but normal amylase levels[68]. Amylase levels tend to peak 2–3 days after eruption of the skin lesions and return to normal 2–3 days after regression of the lesions. Trypsin and perhaps amylase may act by promoting increased permeability of vessel walls, thereby permitting lipase to hydrolyze neutral fat to form glycerol and free fatty acids, with resulting fat necrosis and inflammation[68,69]. Venous stasis may promote this process, possibly explaining the predilection for the lower extremities. Elevated enzyme levels may not be the complete explanation for the changes of pancreatic panniculitis[70]. Immunologic factors probably also play a role.

Clinical features

Subcutaneous nodules develop in association with acute or chronic pancreatitis, pancreatic carcinoma (acinar cell > other types [e.g. neuroendocrine carcinomas]), pancreatic pseudocysts, pancreas divisum, or traumatic pancreatitis[68,71]. Panniculitis developing in individuals with chronic pancreatitis is often associated with a pancreaticoportal fistula, and, in some of these patients, an acinar cell carcinoma can be found. Panniculitis may precede detection of pancreatic disease by 1–7 months[69], and in the case of pancreatic carcinoma, its onset may signal the presence of metastatic disease[68,69].

In pancreatic panniculitis, subcutaneous nodules develop, frequently on the legs (Fig. 100.10), but also on the abdomen, chest, arms and scalp[68,69]. Erythematous, edematous, sometimes painful lesions arise singly or in crops, and they may migrate. They can become fluctuant and ulcerate, discharging an oily material[68]. Panniculitis may also involve visceral fat, including the omentum and preperitoneal fat[68]. Associated findings include fever, abdominal pain, inflammatory polyarthritis, ascites and pleural effusions[68]. The association of subcutaneous nodules, polyarthritis and eosinophilia is known as Schmid's triad, and it is associated with a poor prognosis. Some patients have radiographic evidence of multiple lytic areas involving cortical bone near large joints. Cutaneous lesions may involute within a period of weeks, leaving hyperpigmented scars. In acute pancreatitis, the panniculitis resolves as the acute inflammatory phase passes[68]. However, lesions may also persist and expand until the underlying pancreatic abnormality has been treated.

Pathology

Pancreatic panniculitis may begin as a septal panniculitis[20], but with progression, the lesion takes on the appearance of a lobular or mixed septal/lobular process. Even in early stages, fat necrosis with liquefaction and microcyst formation is observed[67,70]. Lipocytes lose their nuclei and develop thick, shadowy walls, forming the characteristic "ghost cells". Saponification of fat by calcium salts results in deposition of granular or homogeneous basophilic material (Fig. 100.11). Neutrophils, occasional eosinophils, macrophages, and multinucleated giant cells are sometimes present and may encroach upon the septa. Fibrosis and lipoatrophy are seen in late stages as the process resolves.

Fig. 100.10 Pancreatic panniculitis. Multiple nodules on the legs. *Courtesy, Kenneth E Greer, MD.*

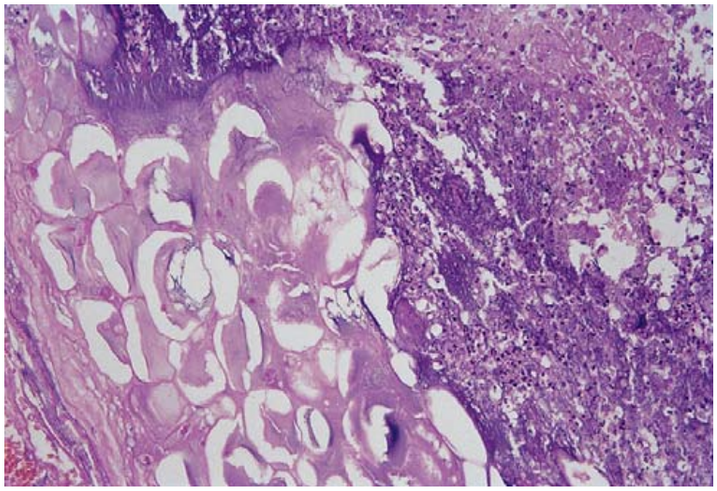


Fig. 100.11 Pancreatic panniculitis. Neutrophilic inflammation, cellular necrosis, and deposition of homogeneous basophilic material due to saponification of fat by calcium salts.

Differential diagnosis

Clinically, the nodules of pancreatic panniculitis can resemble those of a number of other forms of panniculitis. Ulceration and discharge would argue against erythema nodosum, and an association with fever, polyarthritis and/or abdominal pain should raise suspicion of associated pancreatic disease. Serum amylase and lipase levels, if elevated, may also be helpful. Histologic evidence of "ghost cell" formation and saponification of fat distinguishes pancreatic panniculitis from other panniculitides. Eosinophilic "hyaline necrosis" is seen in lupus panniculitis, rather than granular or homogeneous basophilic necrosis typical of pancreatic panniculitis.

Treatment

Although supportive measures such as compression and elevation can be helpful, effective management of pancreatic panniculitis is dependent upon treatment of the underlying pancreatic disease. In chronic pancreatitis, a pancreatic duct stent can be used to relieve obstruction, or, if a fistula or cyst is involved, biliary bypass surgery can be undertaken if simple drainage measures are unsuccessful. Octreotide, a synthetic somatostatin-like polypeptide, can be used to inhibit pancreatic enzyme production[68]. Resection of pancreatic cancer may be followed by regression of the panniculitis.

SCLEREMA NEONATORUM, SUBCUTANEOUS FAT NECROSIS OF THE NEWBORN, AND POST-STEROID PANNICULITIS

There are three entities – sclerema neonatorum, subcutaneous fat necrosis of the newborn, and post-steroid panniculitis – that are characterized histologically by formation of needle-shaped clefts within lipocytes. In contrast to adult fat, the subcutaneous fat of infants is thought to be prone to crystal formation because of a higher content of saturated fatty acids, including palmitic and stearic acids, and a relatively lower content of unsaturated fatty acids, such as oleic acid[72]. This increased saturated to unsaturated fatty acid ratio results in a higher melting point for stored fat and promotes crystallization under certain conditions. Microsized crystals (type A) apparently do not produce an inflammatory response; they are actually common (in a widely dispersed form) in healthy infants 6 months of age or less, but are more numerous in sclerema neonatorum. Larger, type B crystals that tend to be arranged in rosettes are capable of eliciting a granulomatous response; these larger crystals are most often seen in subcutaneous fat necrosis of the newborn and post-steroid panniculitis[72]. Crystallization and defects in fat mobilization account for the clinical findings in these disorders.

Sclerema Neonatorum

Key features

- Arises in premature infants
- Skin is diffusely cold, rigid, and board-like
- Microscopically, needle-shaped clefts are present within lipocytes with minimal inflammation
- Affected infants are often hypothermic and may have a variety of other medical problems; early death is common

History

Sclerema neonatorum was first recognized in 1722 by Uzembenzius, although the classic description is usually attributed to Underwood (1784). Ballantyne provided an early description of the histopathologic changes, and Knopfelmacher noted the presence of needle-shaped crystals in subcutaneous tissue in 1897.

Epidemiology

Sclerema neonatorum presents most often in premature, debilitated infants, usually during the first week of life. There is a slight male predominance, with no substantial difference in death rates between the sexes[73].

Pathogenesis

In infants who develop sclerema, crystallization and hardening of fat occur in the setting of an increased saturated:unsaturated fatty acid ratio and a defective ability to mobilize fatty acids. Precipitating factors, which may include subcutaneous ischemia due to perinatal asphyxia as well as hypothermia, are listed in Table 100.8[72].

Clinical features

The clinical features are outlined in Table 100.8[72–74]. Rapid hardening of the subcutaneous tissues leads to firm, rigid skin over most of the body. Low admission weight and temperature as well as hemorrhagic phenomena portend a particularly poor prognosis[73].

Pathology

Table 100.8 outlines the microscopic features. Inflammation is usually sparse, and most of the needle-shaped clefts are found within lipocytes rather than within giant cells (Fig. 100.12)[72,74]. At a later stage, thickened connective tissue bands may be the only histologic finding[74].

Differential diagnosis

In contrast to sclerema neonatorum, subcutaneous fat necrosis of the newborn is a localized process with a favorable prognosis; histologically,

PANNICULITIDES WITH NEEDLE-SHAPED CLEFTS IN THE SUBCUTIS						
Condition	**Patient characteristics**	**Onset**	**Cutaneous findings**	**Associated systemic findings**	**Histopathology**	**Possible precipitating factors**
Sclerema neonatorum	Severely ill premature neonates	First week of life	Widespread, diffuse hardening, sparing only the genitalia, palms and soles; cool, waxy, rigid and board-like skin with livid, mottled discoloration	Respiratory difficulties, congestive heart failure, intestinal obstruction, diarrhea; death, usually from septicemia, in three-quarters of cases	Needle-shaped clefts in lipocytes; septal thickening; inflammation sparse to absent (few neutrophils, eosinophils, macrophages or multinucleated giant cells may be seen)	Hypothermia, perinatal asphyxia, defective complement activity, dehydration
Subcutaneous fat necrosis of the newborn	Full-term neonates	First 2–3 weeks of life	Circumscribed, erythematous, indurated subcutaneous nodules favoring the cheeks, shoulders, back, buttocks, thighs; may become fluctuant	Hypercalcemia (onset may be delayed for several months), thrombocytopenia, hypertriglyceridemia	Lobular panniculitis with neutrophils, lymphocytes, macrophages; needle-shaped clefts in a radial array within lipocytes and giant cells; sometimes foci of calcification, hemorrhage	Hypothermia, hypoglycemia (e.g. due to gestational diabetes), perinatal hypoxemia (e.g. due to meconium aspiration, placenta previa, umbilical cord prolapse, pre-eclampsia), birth trauma
Post-steroid panniculitis	Children (ages 1–14 years)	1–40 days* after cessation of high-dose systemic corticosteroid therapy	Firm red plaques on cheeks, arms, trunk; small and discrete or large and confluent lesions; pruritic, tender or asymptomatic	Underlying conditions treated with systemic corticosteroids have included leukemia, cerebral edema, nephrotic syndrome, secretory diarrhea, acute rheumatic fever	Lobular panniculitis with lymphocytes, macrophages, multinucleated giant cells; needle-shaped clefts in lipocytes and giant cells	Follows rapid corticosteroid withdrawal

*Usually within 10 days.

Table 100.8 Panniculitides with needle-shaped clefts in the subcutis.

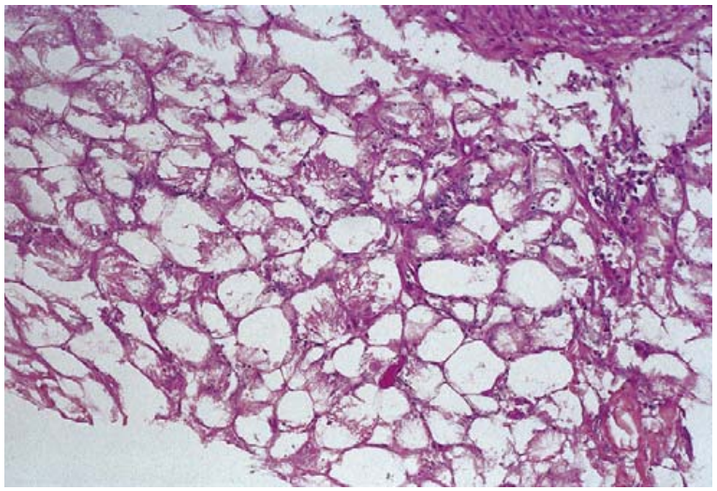


Fig. 100.12 Sclerema neonatorum. Needle-shaped clefts within lipocytes, in the absence of inflammation.

the latter is distinguished by more prominent inflammation and localization of needle-shaped clefts within giant cells. Scleredema neonatorum is a condition seen in premature infants with congenital heart disease. In this disorder, the skin is distended and wax-like, and on biopsy the dermis appears edematous, with increased amounts of mucin[72]. Other conditions that can present with diffusely indurated skin in the neonatal period include stiff skin syndrome (usually favoring the trunk, buttocks and thighs), restrictive dermopathy, and Hutchinson–Gilford progeria.

Treatment

Attempts to treat this disorder are disappointing[73]. Management includes treatment of sepsis, ventilatory support, correction of fluid and electrolyte imbalances, and maintenance of body temperature[72,75]. Exchange transfusions may be of value in selected instances[72,75]. Systemic corticosteroids are of questionable value[72,73].

Subcutaneous Fat Necrosis of the Newborn

Key features

- Development of one or more mobile, firm, subcutaneous nodules or plaques during the newborn period
- Sometimes associated with hypercalcemia or thrombocytopenia
- Granulomatous lobular panniculitis with needle-shaped clefts within lipocytes and giant cells
- Prognosis is usually favorable; spontaneous resolution is common

Introduction

In contrast to sclerema neonatorum, subcutaneous fat necrosis is a localized process. Although complications can arise, particularly in relation to hypercalcemia, most cases resolve spontaneously.

History

At the beginning of the twentieth century, Fabyan described "abscesses" that spontaneously resorbed, and provided the first microscopic description of subcutaneous fat necrosis.

Epidemiology

Subcutaneous fat necrosis of the newborn typically occurs in full-term neonates during the first 2 to 3 weeks of life[76].

Pathogenesis

It is believed that a variety of stresses imposed upon fetal fat, with its high ratio of saturated to unsaturated fatty acids, results in crystallization, adipocyte injury and granulomatous inflammation. Hypothermia is one potential eliciting factor, as illustrated by a case of subcutaneous fat necrosis that developed as a complication of hypothermic cardiac surgery[77]. Other proposed causes are listed in Table 100.8[72,76,78]. The role of birth trauma has been questioned, since many cases have occurred in infants delivered by cesarean section[76].

Clinical features

The clinical features are outlined in Table 100.8. Smooth, circumscribed, mobile, red to violaceous, subcutaneous nodules or plaques develop, sometimes in a symmetrical fashion[72,76] (Fig. 100.13). The areas of fat necrosis have been detected by CT[79] and MRI[80].

Some cases are associated with hypercalcemia or thrombocytopenia, and the former may develop 1–4 months after the onset of the skin lesions[78]. It is believed that the hypercalcemia results from extrarenal production of 1,25-dihydroxyvitamin D_3 (calcitriol) by activated macrophages (expressing 1-α-hydroxylase) within areas of granulomatous panniculitis, which stimulates calcium absorption from the gut and mobilization from the bones[76,81]. The mechanism for thrombocytopenia may be local sequestration in the subcutis, as studies have shown normal bone marrow findings and resolution of the platelet abnormality as the inflammatory process resolves[82]. Spontaneous resolution of lesions is the rule, sometimes in association with lipoatrophy. Deaths have been reported in patients with associated hypercalcemia[82].

Pathology

The microscopic changes are outlined in Table 100.8. Needle-shaped clefts are observed within both lipocytes and giant cells (Fig. 100.14). The crystals are doubly refractile and stain with oil red O[72]. Occasionally, however, needle-shaped clefts are not evident in otherwise typical cases. Eosinophilic granules are sometimes found within multinucleated giant cells; their origin is not entirely certain, but they may be derived from degranulating eosinophils[83].

Fig. 100.13 Subcutaneous fat necrosis of the newborn. Indurated plaques on the trunk.

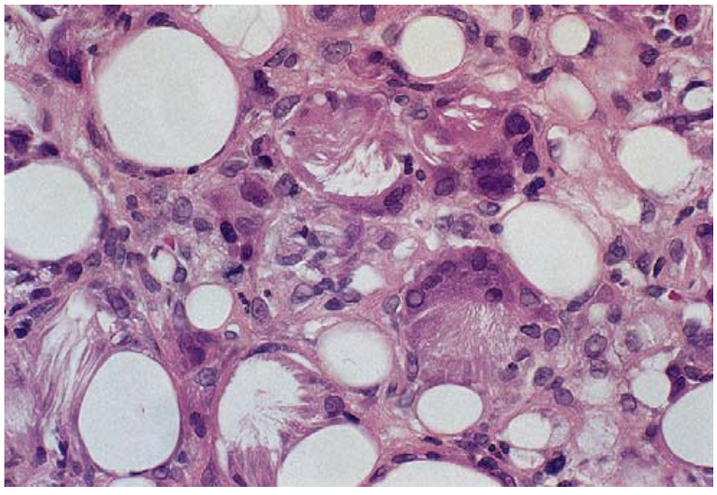


Fig. 100.14 Subcutaneous fat necrosis of the newborn. Needle-shaped clefts in a radial configuration are present within giant cells. Similar findings are seen in post-steroid panniculitis.

Differential diagnosis

The extensive cutaneous involvement in sclerema neonatorum is usually distinguishable from the localized, self-limited process of subcutaneous fat necrosis; histologically, inflammation in sclerema is minimal. Post-steroid panniculitis is microscopically indistinguishable from subcutaneous fat necrosis, but it arises in a different clinical setting (see below).

Treatment

Since many lesions resolve spontaneously, the emphasis is on supportive care. Systemic corticosteroids may be indicated to control the inflammation in severe cases[72]. Serial monitoring of calcium levels (for at least 4 months) is important. Hypercalcemia is managed by hydration, dietary restriction of both calcium and vitamin D, calcium-wasting diuretics (e.g. furosemide), calcitonin and bisphosphonates (e.g. etidronate, pamidronate)[76,78,84]. Corticosteroids may be helpful in managing hypercalcemia, by interfering with the metabolism of vitamin D to calcitriol, and by inhibiting calcitriol production by macrophages[78].

Post-steroid Panniculitis

Key features

- A rare complication of rapid systemic corticosteroid withdrawal
- Subcutaneous nodules develop on the cheeks, arms and trunk
- Lesions resolve spontaneously, or when corticosteroids are readministered
- Pathology consists of granulomatous lobular panniculitis with needle-shaped clefts within both lipocytes and giant cells

History

In 1956, Smith and Good[85] reported 11 children with acute rheumatic fever who were treated with large doses of corticosteroids that were rapidly tapered. Five children developed pruritic, erythema nodosum-like lesions.

Epidemiology

Post-steroid panniculitis is a disorder of children. It occurs in an older age group than either sclerema neonatorum or subcutaneous fat necrosis of the newborn, with reported ages ranging from 20 months to 14 years[86].

Pathogenesis

Post-steroid panniculitis occurs after rapid withdrawal of systemic corticosteroids that have been administered either orally or intravenously. For patients who had received prednisone, cumulative dosages ranged from 2000 to 6000 mg[86]. The precise mechanism by which the panniculitis arises is not known.

Clinical features

Patients who have developed this form of panniculitis received corticosteroid therapy for a variety of conditions[85–87], including those listed in Table 100.8. Lesions appear 1 to 40 days after rapid corticosteroid withdrawal and disappear spontaneously over a period of months to a year[87].

Pathology

Microscopic changes are outlined in Table 100.8[87]. Needle-shaped clefts, some with a "starburst" pattern, can be identified within lipocytes or giant cells.

Differential diagnosis

A less nodular presentation involving the cheeks can mimic non-panniculitic disorders such as erythema infectiosum, atopic dermatitis, lupus erythematosus or facial cellulitis. The microscopic changes in these conditions would be quite different from those of post-steroid panniculitis. Cold panniculitis has clinical and microscopic similarities, but the history of cold exposure and the lack of needle-shaped

clefts on biopsy permit distinction. The microscopic changes of post-steroid panniculitis are virtually identical to those of subcutaneous fat necrosis of the newborn, although calcification and hemorrhage are more commonly observed in the latter condition. Clinical history is decisive.

Treatment

Since spontaneous resolution is the rule, treatment is usually unnecessary. Readministration of corticosteroids followed by a more gradual taper may be helpful[87].

LUPUS ERYTHEMATOSUS PANNICULITIS (LUPUS PANNICULITIS)

Synonyms: ■ Lupus profundus ■ Subcutaneous lupus erythematosus

Key features

- Tender subcutaneous nodules and plaques arising on the face, proximal extremities and trunk
- Associated with discoid lupus erythematosus in at least one-third of patients; less often associated with systemic lupus erythematosus (10–15% of patients)
- Often precedes onset of other manifestations of lupus erythematosus
- Characteristic microscopic changes include lobular panniculitis with hyaline necrosis and a predominantly lymphoplasmacytic infiltrate; nodular aggregates of lymphocytes are common
- Overlying epidermal or dermal changes of lupus erythematosus are frequently present

History

Kaposi first described the clinical characteristics of lupus panniculitis in 1869. In 1940, it was recognized as a manifestation of lupus erythematosus (LE) by Irgang. Lupus panniculitis was firmly established as a specific subtype of LE in a 1956 paper by Arnold[88].

Epidemiology

Lupus panniculitis constitutes a small subset of all cases of cutaneous LE, representing 2–3% of this group[89]. It usually occurs in adults, with a median age of onset of 30–40 years[90]. Children can also develop lupus panniculitis, and an association with neonatal lupus has been described[88]. There is a predominance among women, with a female : male ratio ranging from 2 : 1 to 4 : 1[37,90]. Sometimes there is a family history of either LE or another autoimmune connective tissue disease[89].

Pathogenesis

The autoimmune basis of lupus panniculitis is thought to be similar to that of other types of LE (see Ch. 41). The cells comprising the infiltrates of lupus panniculitis are T lymphocytes and macrophages[91]. Lupus panniculitis (often with a childhood onset and widespread distribution) has been described in patients with partial C4 deficiency[92]. This complement deficiency causes defective opsonization of immune complexes, which may play a role in the pathogenesis of the disease[92]. Immunohistochemical analysis has shown an interferon-driven Th1-biased immune response in active lesions of lupus panniculitis; this may result in recruitment of cytotoxic CXCR3-positive lymphocytes[93].

Clinical features

Lupus panniculitis is characterized by tender subcutaneous nodules and plaques that may arise in crops (see Table 100.7). A history of trauma can sometimes be elicited. Lesions tend to develop on the face, upper arms, hips and trunk (Fig. 100.15). The lack of involvement of the distal extremities is noteworthy[90]. Changes in the overlying skin range from a light pink color to those of chronic cutaneous (discoid) LE (e.g. scaling, follicular plugging, dyspigmentation, telangiectasias, atrophy and scarring). At times, findings of discoid LE are too subtle to be recognized clinically but can be seen on microscopic examination of biopsy specimens. The overlying skin may also be "tethered" to the subcutaneous nodule or plaque, creating a surface depression, and ulceration occasionally occurs. Lupus panniculitis has a chronic, relapsing clinical course[94]. It usually eventuates in subcutaneous atrophy, which can be disfiguring (see Chs 41 & 101).

Fig. 100.15 Lupus panniculitis. Red–brown plaques on the upper outer arm. Note the significant subcutaneous atrophy and overlying lesions of discoid lupus erythematosus. *Courtesy, Kenneth E Greer, MD.*

Lupus panniculitis often occurs prior to other manifestations of LE and in the absence of other autoimmune connective tissue diseases[90]. For example, lesions of discoid LE have developed up to 10 years after the appearance of the panniculitis. However, manifestations of systemic LE or discoid LE can also occur long before (or at the same time as) the panniculitis[37]. There is a closer relationship of lupus panniculitis to other forms of chronic cutaneous LE (e.g. discoid LE) than to systemic LE. Coexistent discoid lesions are observed in at least one-third of patients, whereas only 10–15% meet the diagnostic criteria for systemic LE[34,90]. Most individuals in the latter group have relatively mild systemic manifestations, usually arthralgias or Raynaud's phenomenon[89]. It is common for patients to have low-titer antinuclear antibodies; they can also have other circulating autoantibodies (including those targeting double-stranded DNA or extractable nuclear antigens), leukopenia, hypocomplementemia, and an elevated ESR[89].

Pathology

Lupus panniculitis is a predominantly lobular process with a variable degree of inflammation (Fig. 100.16). The characteristic microscopic changes (e.g. hyaline necrosis of the fat lobules) are outlined in Table 100.7. Granulomas can occur and tend to encroach upon the septa, but they are usually not prominent. Other features include lymphocytic vasculitis and mucin or calcium deposition.

The subcutaneous findings alone are considered sufficiently characteristic to permit a diagnosis of lupus panniculitis. However, overlying epidermal or dermal changes of discoid LE occur in one-half to two-thirds of cases and are also helpful diagnostically[34,91,95]. With direct immunofluorescence, a positive lupus band can be identified in the overlying skin in a high percentage of cases, even in those where the histopathologic changes are nonspecific[95].

Differential diagnosis

Clinically, lesions of lupus panniculitis can resemble other forms of panniculitis. The rarity of involvement of the distal extremities helps to distinguish it from conditions such as erythema nodosum and

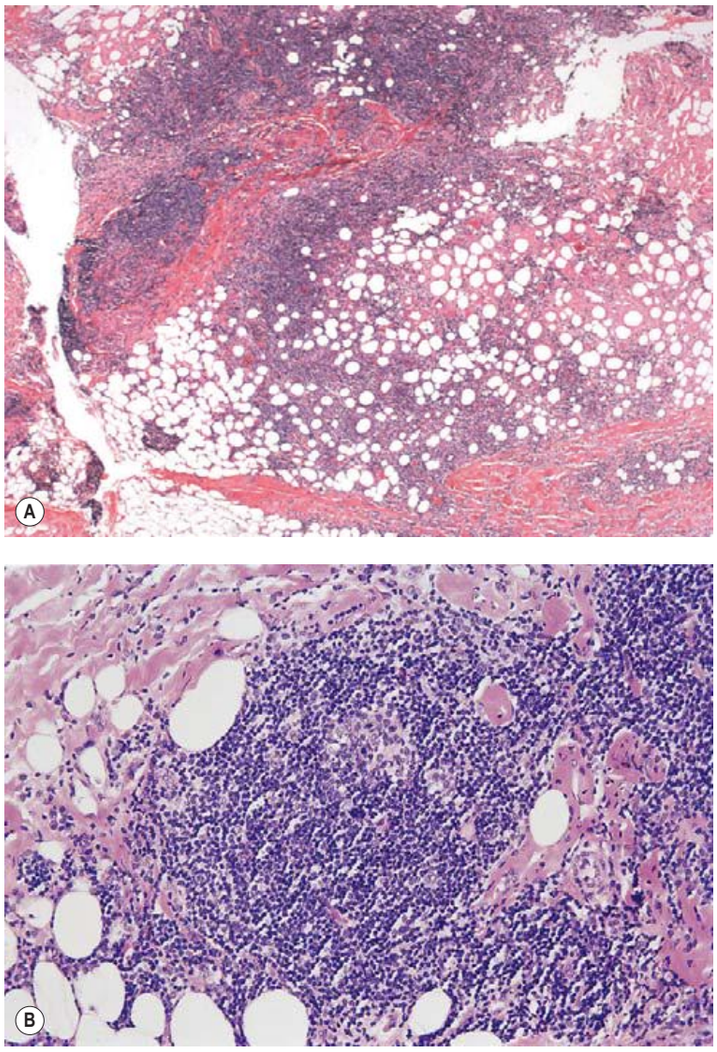


Fig. 100.16 Lupus panniculitis. A Septal and lobular panniculitis with hyaline necrosis of fat lobules. **B** Nodular aggregate of lymphocytes in the subcutis with lymphoid follicle formation.

erythema induratum. It should also be remembered that other forms of subcutaneous inflammation may occur in patients with LE, including erythema nodosum, thrombophlebitis, pancreatic panniculitis, and juxta-articular, rheumatoid nodule-like lesions.

Microscopically, lupus panniculitis can resemble the panniculitis associated with morphea and dermatomyositis (see Table 100.7), traumatic panniculitis (which often has evidence of foreign material) and, in its later stages, localized lipoatrophy due to other etiologies[89,94]. Overlying epidermal or dermal changes of LE, when present, can be of help in excluding other forms of panniculitis. However, a vacuolar interface dermatitis and abundant dermal mucin together with a lobular lymphocytic infiltrate have been described in cases of subcutaneous panniculitis-like T-cell lymphoma[96]. A lack of prominent $CD8^+$ T cells or cytophagia as well as the presence of lymphoid follicles with reactive germinal centers, a mixed infiltrate with conspicuous plasma cells, and polyclonal T-cell receptor gene rearrangement can help to establish a diagnosis of lupus panniculitis in patients lacking additional cutaneous or systemic manifestations of LE[35].

Treatment

Antimalarials are frequently used to treat lupus panniculitis, and they produce improvement in most patients[90]. Addition of a second antimalarial may prove useful in patients who do not respond to a single agent[94]. In view of the chronic, relapsing nature of the disease, treatment may be required for several years[89].

Systemic corticosteroids, when used, are often restricted to initial phases of the disease[89]. Other systemic therapies include dapsone, mycophenolate mofetil, cyclophosphamide, thalidomide and IVIg[90,92,97]. Overlying discoid lesions, if present, can be treated with potent topical or intralesional corticosteroids.

PANNICULITIS OF DERMATOMYOSITIS

Key features

- An uncommon manifestation of dermatomyositis
- Incidental microscopic changes of panniculitis (in the absence of clinical lesions) are seen more often
- Can precede or follow other manifestations of dermatomyositis
- Microscopically, it is a lobular or mixed panniculitis with lymphoplasmacytic predominance
- Usually responds well to therapy

Introduction

Panniculitis is a rare but established clinical manifestation of dermatomyositis. However, there is some evidence that microscopic involvement of subcutaneous fat without overt clinical features of panniculitis is more common.

Clinical features

The characteristic lesions are persistent, indurated, painful plaques and nodules that may ulcerate and lead to lipoatrophy (see Table 100.7)[98]. They can arise in the setting of established dermatomyositis[98] or represent the first manifestation of the disease[99]. The other clinical and laboratory features and the incidence of malignancy in affected individuals appear to be similar to those of dermatomyositis patients without panniculitis[98]. It has been suggested that panniculitis is a favorable prognostic sign, as good responses to therapy have generally been reported[100]. However, partial or generalized lipoatrophy without preceding clinical lesions of panniculitis (occasionally accompanied by increased abdominal fat) occurs in up to one-quarter of patients with juvenile dermatomyositis, and it is often associated with metabolic abnormalities such as hypertriglyceridemia and insulin resistance (see Ch. 101).

Pathology

The microscopic features are outlined in Table 100.7. Lymphocytic vasculitis has been described, and fat necrosis has been noted in several reports[98]. Lipomembranous changes have been observed in some cases (see section on lipodermatosclerosis), and lesions with these changes may be particularly resistant to therapy[98]. Calcification is variable and is an expected finding in cases of dermatomyositis associated with calcinosis of deep soft tissues and skeletal muscle[31]. Vacuolar alteration of the basal layer of the overlying epidermis has been described[98], and the dermis may be edematous or mucinous with perivascular lymphocytic inflammation[100]. Direct immunofluorescence is reported to be negative for deposits along the dermal–epidermal junction[98], although immunoreactants have been detected in vessel walls[100].

Differential diagnosis

Lupus panniculitis is more likely to show hyaline necrosis and lymphoid nodules, but clinical and laboratory findings may be needed to make a distinction. Overlying poikilodermatous changes can occur in both diseases, but lupus is more likely to show appendageal involvement and is associated with positive basement membrane zone fluorescence.

Treatment

Treatments include prednisone, methotrexate, azathioprine, cyclosporine and IVIg[98–100]. Panniculitis lesions have shown variable responses to hydroxychloroquine.

TRAUMATIC PANNICULITIS

Key features

- Inflammation in the subcutis resulting from external injury
- The injurious event may be accidental, purposeful or iatrogenic, and it may be a manifestation of an underlying psychiatric disturbance
- A variety of histopathologic changes are observed, depending upon the inciting agent
- Identification of foreign material is of greatest help in diagnosis

Introduction

Extrinsic injury of varying types can produce panniculitis. There are four broad categories: cold panniculitis (Haxthausen's disease), sclerosing lipogranuloma, panniculitis due to other injectable substances or therapies, and panniculitis due to blunt trauma.

History

Cold panniculitis was reported by Lemez in 1928, when he noted that newborns and infants up to 6 months of age were particularly susceptible to cold injury, as demonstrated by the production of a subcutaneous nodule following application of an ice cube[101]. In 1941, Haxthausen described a condition occurring in small children a few days after exposure to cold, consisting of firm infiltrated nodules of the cheeks and chin. A similar type of cold injury due to popsicles was reported by Epstein and Oren in 1970[102].

Injection of foreign lipid material into the skin for cosmetic or other purposes has been performed for centuries[103]. In 1950, Smetana and Bernhard reported 14 cases of what they termed *sclerosing lipogranuloma* of the male genitalia. They believed it was an endogenous process, but subsequent studies demonstrated the presence of mineral oil in similar cases[103].

Epidemiology

Infants and small children are most at risk for cold panniculitis. A form of the disease also occurs on the thighs of young women who are equestrians[104]. Sclerosing lipogranuloma of the male genitalia is seen mostly in young adults[105]. A sclerosing, pseudosclerodermatous panniculitis has been reported following megavoltage radiation for metastatic carcinoma[106] and as a radiation recall reaction after cyclophosphamide therapy[107].

Pathogenesis

Cold injury to fat favors small children, due in part to a higher ratio of saturated to unsaturated fatty acids that results in a higher solidification point for infantile fat[108]. Cold injury is also related to fluctuations in blood flow that occur with declining temperatures (the "hunting phenomenon"), ice crystal formation, and the changes that occur with thawing[108]. Injections of oils (and associated impurities) are known for producing subcutaneous inflammation. Substances include mineral oil (paraffin) as well as camphor, cottonseed and sesame oils. Even medical grade silicone may contain impurities, and, since encapsulation of this material is desirable when used for cosmetic purposes, fibrosis-inducing substances such as olive oil or castor oil are often added[103]. Injected substances responsible for factitial panniculitis have included milk and feces.

Panniculitis has been produced by numerous therapeutic agents, such as meperidine, morphine, tetanus antitoxoid, pentazocine, phytonadione (vitamin K)[109], povidone[110], aurothioglucose[111], interleukin-2 (IL-2)[112], and substances used for tissue augmentation such as bovine collagen[113] or poly-L-lactic acid. More recently, panniculitis due to "mesotherapy" (involves injection of substances such as phosphatidylcholine to treat localized fat accumulations; see Ch. 156)[114] and electroacupuncture[115] have been described. In addition to the foreign body response elicited by many of these agents, other immune mechanisms may also be involved. With blunt trauma, granulomas contain material that may be derived from the breakdown of erythrocyte membranes[116].

Clinical features

In cold panniculitis (including popsicle panniculitis), erythematous, firm nodules develop, particularly on the cheeks and chin[108]. In equestrian cold panniculitis, erythematous to violaceous, tender plaques appear on the thighs following exposure to cold while wearing tight-fitting clothing[104] (Fig. 100.17).

In lipogranuloma, nodules are sometimes migratory and can be accompanied by varying degrees of swelling, erythema, abscess formation, lymphangitis and fibrosis[103]. The term *sclerosing lipogranuloma* often refers to lesions arising on the male genitalia due to self-injection of oily materials (see Ch. 94). There has also been a report of a sclerosing lipogranuloma that apparently resulted from topical application of vitamin E cream[117]. In several Japanese patients, Y-shaped induration of the scrotum (in which exogenous lipids could not be detected) was described as eosinophilic sclerosing lipogranuloma[118]. Patients with sclerosing lipogranuloma frequently deny self-injection, making diagnosis difficult. Another variant of lipogranuloma is the *grease gun granuloma*, which results from accidental firing of the grease gun used by mechanics. This results in formation of a verrucous nodule, often on the dorsum of the hand[119].

Inflamed nodules with varying degrees of pain and fibrosis have been observed in other forms of panniculitis due to injection, with the distribution of lesions sometimes providing a clue to their cause. A dramatic example of this is *Texier's disease*, a panniculitis due to phytonadione (vitamin K) injections. In this disorder, sclerotic lesions with lilac-colored borders form on the buttocks and thighs, in a configuration resembling a "cowboy gunbelt and holster"[109]. Lesions due to blunt trauma often have an ecchymotic character and involve locations such as the arm or hand[116].

Pathology

Table 100.9 outlines the microscopic changes in various forms of traumatic panniculitis[105–107,119–122]. In addition, sclerosing lipogranuloma is discussed in Chapter 94.

Differential diagnosis

In cold panniculitis, the absence of needle-shaped clefts in lipocytes and location of the most intense inflammation near the dermal–subcutaneous interface help to distinguish this condition from subcutaneous fat necrosis of the newborn. In sclerosing lipogranuloma and related lipogranulomas, the large vacuoles found in the dermis and subcutis are distinctive (Fig. 100.18). Radiographs are sometimes useful in differentiating lipogranulomas from silicone granulomas, since only the latter are radio-opaque[123]. Mineral oil in non-processed tissue can be identified by infrared spectrophotometry[119].

Fig. 100.17 Cold panniculitis. Erythematous to violaceous plaques on the thighs of a young woman with equestrian cold panniculitis. *Courtesy, Kenneth E Greer, MD.*

MICROSCOPIC FEATURES OF TRAUMATIC PANNICULITIS		
Condition	**Microscopic features**	**Special considerations**
Cold panniculitis	Septal/lobular inflammation, especially at the dermal–subcutaneous border and periadnexally; lymphocytes, neutrophils, foamy macrophages, poorly developed granulomas; mucin, adipocyte necrosis, microcysts	Needle-shaped clefts are not observed
Lipogranuloma	*Sclerosing lipogranuloma* – granulomatous lobular panniculitis with marked fibrosis and numerous round or oval vacuoles of various sizes in the dermis and subcutis, producing a "Swiss cheese" appearance (Fig. 100.18); nodular aggregates of lymphocytes, plasma cells, eosinophils, macrophages or giant cells often present *Grease gun granuloma* – also pseudoepitheliomatous hyperplasia	Exogenous oils within the vacuoles can be identified in frozen sections stained with oil red O, silver bromide and osmium tetroxide
Injection-induced panniculitis	Central nidus of subcutaneous inflammation; sometimes fibrosis* or polarizing foreign material	*Povidone panniculitis* – gray–blue material within macrophages on routine staining that also stains with Congo red and chlorazol-fast pink *Cancer vaccines* – eosinophils may be numerous
Panniculitis due to aluminum in hyposensitization vaccines	Nonspecific lobular panniculitis with fibrosis; formation of numerous lymphoid follicles; may resemble lupus panniculitis, pseudolymphoma	Macrophages display greyish to violaceous, granular cytoplasm due to lysosomes that contain aluminum salts; can be identified using X-ray microanalysis or possibly aluminum staining
Panniculitis due to injectable aesthetic microimplants	Diffuse granulomatous infiltrate that may involve dermis and subcutis; focal areas of collagen degeneration	Different "fillers" can have specific histopathologic features (see Table 94.4)
Blunt trauma	Organizing hematoma, focal granuloma	Deposits of mucopolysaccharides and iron can be seen
Postirradiation or radiation recall panniculitis	Deep fibrosis, mixed inflammation	Inflammation includes lymphocytes, plasma cells, macrophages, eosinophils

*Especially with phytonadione (vitamin K) and pentazocine injections; lipid-containing vacuoles, fat necrosis, foam cells, thrombosis and endarteritis are also observed in the latter.

Table 100.9 Microscopic features of traumatic panniculitis.

Panniculitis due to injectable substances can be diagnosed when foreign material (often identified by polarization microscopy) is present. Cases with acute inflammation and necrosis may resemble infection-induced panniculitis, and, in fact, infection may accompany injection panniculitis[124]; special stains and cultures for organisms (including atypical mycobacteria) are useful in this regard. Sclerosing traumatic panniculitis (e.g. that due to phytonadione or pentazocine injections) may resemble morphea clinically, but would not present as a septal panniculitis histologically.

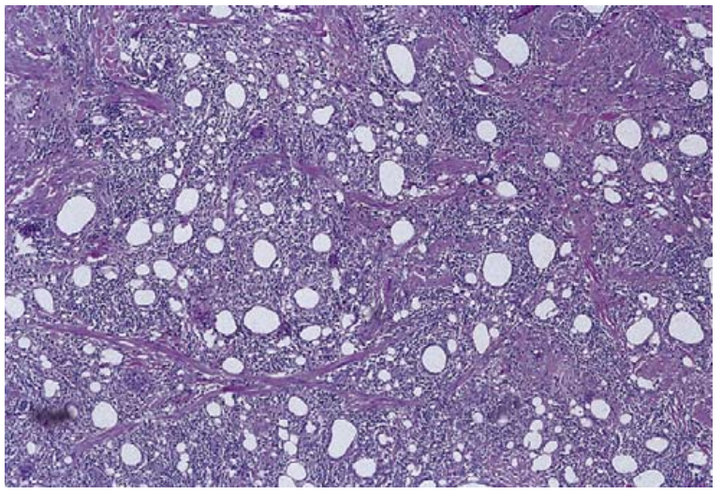


Fig. 100.18 Oil granuloma. Numerous vacuolated spaces, in this case due to grease gun injury.

Treatment

Treatment of these disorders mainly involves removal of the inciting stimulus and eradication of any associated infection. Intralesional or systemic corticosteroids can be helpful in controlling the inflammation, and they have been used in the management of sclerosing lipogranuloma[103] and granulomatous panniculitis due to bovine collagen injections[113]. Surgical excision may also be an option for sclerosing lipogranuloma[103].

LIPODERMATOSCLEROSIS

Synonyms: ■ Sclerosing panniculitis ■ Hypodermitis sclerodermiformis ■ Chronic panniculitis with lipomembranous changes

Key features

- Favors the medial aspect of the lower extremities above the malleolus
- Acute phase with erythema, warmth and tenderness, which may be misdiagnosed as infectious cellulitis
- Chronic phase with induration and red–brown to violet–brown discoloration
- Usually develops in the setting of chronic venous insufficiency
- Both septal and lobular panniculitis; lipomembranous changes are common, particularly in chronic lesions

Introduction

Erythema, induration and pigmentary changes have been known for many years to be associated with venous insufficiency. Because of the variety of clinical appearances and histopathologic findings that can occur at different stages of the disease, a number of diagnostic terms have been employed to explain the changes. Recently, the various manifestations of this panniculitis have been consolidated under the heading of *lipodermatosclerosis* or *sclerosing panniculitis*.

History

The cutaneous signs of venous insufficiency have long been recognized. In 1955, Huriez drew attention to a related indurated lesion, which he termed *hypodermitis sclerodermiformis*[125].

Epidemiology

Most patients are women over the age of 40 years, but cases appearing after the age of 75 years have also been reported[126,127].

Pathogenesis

There is considerable evidence for venous insufficiency in patients with lipodermatosclerosis[128], and fibrinolytic abnormalities are also present in these individuals. Venous hypertension leads to a compromised ability to reduce foot vein pressure during exercise. This results in increased capillary permeability, which causes leakage of fibrinogen, its polymerization to form fibrin cuffs around vessels, impedance of oxygen exchange, and tissue anoxia (see Ch. 105)[127]. Pericapillary fibrin deposits can be seen in uninvolved, clinically normal extremities of patients with healed venous ulcers of the opposite extremity, suggesting that this abnormality precedes the clinical changes of lipodermatosclerosis[129].

There may also be an abnormal regulation of angiogenesis within lesions of lipodermatosclerosis. In particular, increased expression of vascular endothelial growth factor receptor 1 (VEGFR-1), which can act as a negative regulator of VEGF-mediated angiogenesis, has been observed, along with increased expression of angiopoietin-2 (Ang-2)[130]. Additional factors contributing to the pathogenesis of lipodermatosclerosis may include protein C and S deficiencies[131], local stimulation of collagen synthesis[127], and obesity.

Clinical features

The acute phase of lipodermatosclerosis presents with pain, warmth, erythema and some induration (Fig. 100.19A), most often located on the medial lower leg above the malleolus. Other dependent sites such as the lower aspect of the abdominal pannus can also develop lipodermatosclerosis. At this point, the changes are relatively diffuse[127]. In the chronic phase, there is marked sclerosis of the dermis and subcutis, resulting in induration that is more sharply demarcated from the adjacent normal skin (Fig. 100.19B). Hyperpigmentation due to hemosiderin deposition may also be present[126]. These features give the affected leg the appearance of an inverted wine bottle[132].

Fig. 100.19 Lipodermatosclerosis. **A** Acute phase with tender erythematous plaques on both lower extremities. **B** Chronic phase with sclerotic red–brown plaque on the lower medial leg. *B, Courtesy, Kenneth E Greer, MD.*

Pathology

Early lesions show mid-lobular ischemic necrosis, a lymphocytic infiltrate in the septa that rims the fat lobules, variable degrees of capillary congestion and thrombosis, and hemorrhage with hemosiderin deposition. With progression, septal thickening, hyaline sclerosis involving lipocytes, lipophage formation, and mixed inflammatory cell infiltrates[126] appear. Advanced lesions show marked septal sclerosis and lipomembranous change in the face of markedly reduced inflammation.

Lipomembranous change has been emphasized as a key feature in lipodermatosclerosis[133]. This consists of thickened, undulating membranes that form cysts and papillary configurations (Fig. 100.20). The membranes are believed to result from degenerated cell membranes of lipocytes and/or macrophages. The material comprising the membranes is ceroid, an oxidation product of unsaturated fatty acids[134].

Pericapillary fibrin can be demonstrated in lesions of lipodermatosclerosis with phosphotungstic acid–hematoxylin stain or by immunofluorescent methods[133]. Dermal changes include fibrosis, tortuous thick-walled veins, and superficial and deep perivascular inflammation[126]. Biopsy should be avoided if the diagnosis is obvious, since poor wound healing and ulceration frequently result. When necessary, a thin elliptical excision should be obtained from the margin of a lesion.

Differential diagnosis

Difficulties in clinical diagnosis arise most often in early lesions, when the process is more diffuse and erythematous. At this stage, consideration is often given to cellulitis, erythema nodosum, or erythema induratum[126,127,132]. Persistence of a lesion, association with stasis changes, and lack of response to antimicrobials suggest the correct diagnosis, perhaps aided by studies of venous function[128].

As induration develops and progresses, differentiation from morphea and scleromyxedema may be necessary. In morphea, subcutaneous involvement is predominantly septal, and lipophagic and lipodystrophic changes are not as prominent as they are in lipodermatosclerosis[126]. Lipomembranous changes, when present, can be of great diagnostic help; however, these findings can occur in a variety of other conditions, including lupus and dermatomyositis panniculitis, liposarcoma, erythema nodosum, and diabetic dermopathy[134].

Treatment

Leg elevation and consistent compression therapy are the mainstays of treatment for lipodermatosclerosis[127]. Traditional anti-inflammatory therapies are usually ineffective in this condition[126], although intralesional corticosteroids (e.g. triamcinolone 5–10 mg/cc) may be of benefit when used in conjunction with compression therapy. Good results were reported with the anabolic steroid stanozolol[127], especially in the earlier phases of the disease, but this medication is no longer commercially available. As a result, danazol has been used (successfully) as a substitute[135]. Anabolic steroids enhance fibrinolysis, and they can reduce

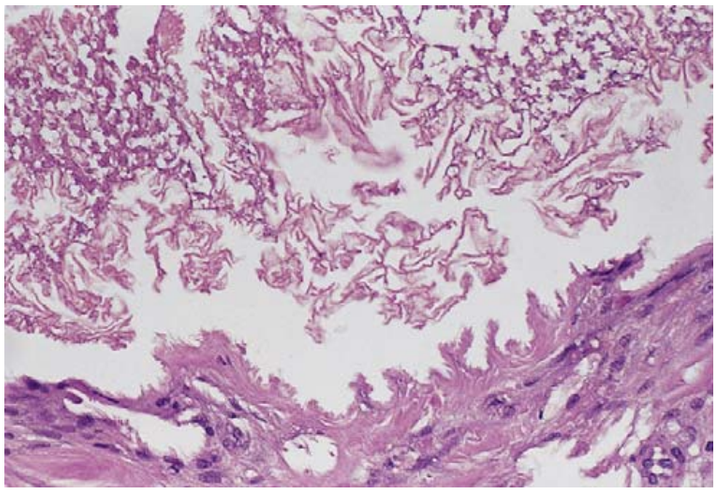


Fig. 100.20 Lipodermatosclerosis. Lipomembranous change, consisting of cystic formation with elaborate papillary configurations.

pain, extent of involvement, and induration of the skin. However, side effects of sodium retention, lipid profile abnormalities, hepatotoxicity, and virilization in women do limit their use. Oxandrolone, an anabolic steroid with less hepatotoxicity and fewer androgenic effects, represents another therapeutic option[132]. Other reported treatments include ultrasound, pentoxifylline, fasciotomy and phlebectomy[127,136].

INFECTION-INDUCED PANNICULITIS

Synonym: ■ Infective panniculitis

Key features

- A wide variety of infectious agents has been reported to produce panniculitis
- Some degree of immunosuppression is common, but not invariable
- Histopathologic findings vary, but often include mixed septal/lobular panniculitis, neutrophilic infiltration, hemorrhage and necrosis
- Special staining and culture studies can provide a definitive diagnosis

Introduction

Panniculitis can result from a distant focus of infection (a classic example being erythema nodosum) or panniculitis can be *directly* induced by an infectious agent. The latter can produce a variety of clinical and microscopic appearances, although there are some features that infection-induced lesions have in common, regardless of the etiologic agent.

History

Multiple case reports of panniculitis directly caused by infectious agents have been published[137,138], but most early studies of deep skin infections did not focus upon the changes in the subcutaneous fat. In 1989, Patterson et al.[21] studied 15 cases of infection-induced panniculitis, with an emphasis upon the histopathologic features in the subcutis. Since that time, additional reports of panniculitis due to infection have appeared.

Epidemiology

There appears to be no age, sex or racial predilection among cases of infection-induced panniculitis. Many of these patients are immunosuppressed[21] or have predisposing medical conditions such as diabetes mellitus[137].

INFECTION-INDUCED PANNICULITIS – REPORTED CAUSATIVE AGENTS
BACTERIA
Staphylococcus aureus
Group A *Streptococcus*
Pseudomonas aeruginosa
Nocardia asteroides
MYCOBACTERIA
M. tuberculosis
M. marinum
M. avium-intracellulare
M. chelonae
M. fortuitum
M. ulcerans
COXIELLA
C. burnetii
BORRELIA
B. burgdorferi
FUNGI
Blastomyces dermatitidis
Histoplasma capsulatum
Microsporum spp. (including *M. canis*)
Candida spp. (including *C. albicans*)
Cryptococcus neoformans
Fusarium spp.
Aspergillus spp. (including *A. flavus*)
Aureobasidium pullulans
HELMINTHS
Nematodes (*Gnathostoma* spp.)
Trematodes (*Fasciola hepatica*)

Table 100.10 Infection-induced panniculitis – reported causative agents.

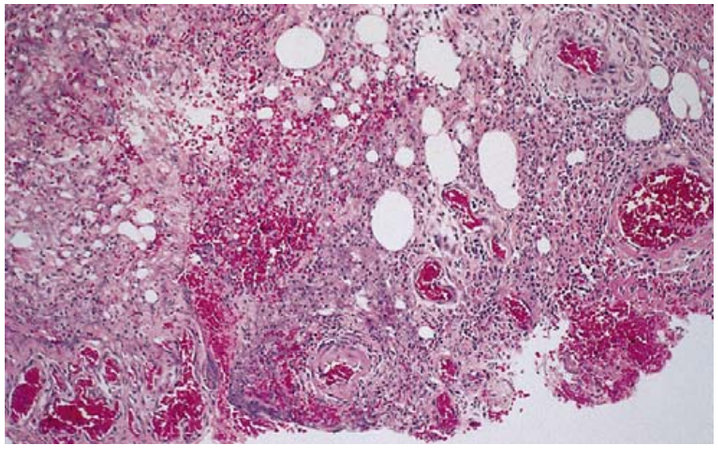


Fig. 100.21 Infection-induced panniculitis. Bacterial panniculitis, showing heavy neutrophilic infiltration, basophilic necrosis, vascular proliferation and hemorrhage.

Pathogenesis

In this group of disorders, infectious agents are considered to be directly responsible for the panniculitis. Examples of reported microorganisms to date are listed in Table 100.10[21,137–145].

Involvement of the subcutis can result from direct inoculation or septicemia. Other potential modes of spread include transfascial from an enteric source, in the case of abdominal panniculitis[144], or via "persorption", a proposed mechanism by which *Candida* migrates across intact endothelium from the gut to a subcutaneous site[145]. Immunosuppression is common, but not invariable, among individuals with infection-induced panniculitis.

Clinical features

Patients develop local swelling and erythema. There may be one or more fluctuant nodules that ulcerate and drain. Lesions on the legs and

Fig. 100.22 Cytophagic histiocytic panniculitis. Subcutaneous nodules with purpura. *Courtesy, Kenneth E Greer, MD.*

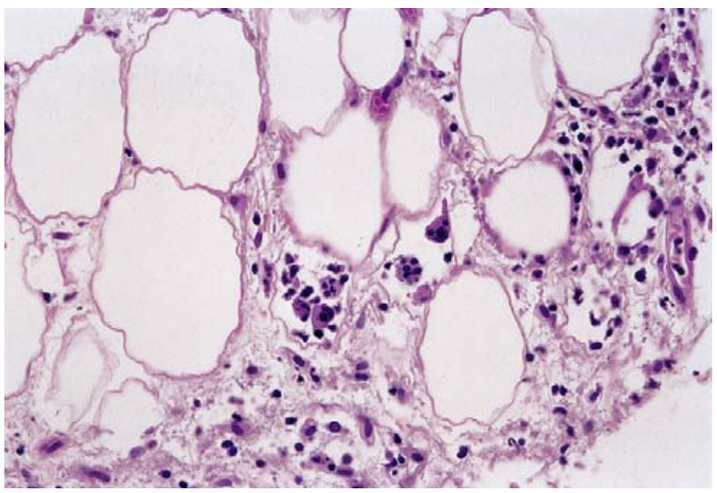


Fig. 100.23 Cytophagic histiocytic panniculitis. Macrophages engaged in cytophagic activity. Some of them have the appearance of "bean bag cells".

feet are common, but other sites of involvement include the gluteal region, abdomen, axillae, arm or hand. Underlying conditions include diabetes mellitus, leukemias or solid tumors, autoimmune connective tissue disease, AIDS and organ transplantation.

Pathology

Individual cases can mimic other primary forms of panniculitis. Common changes (regardless of the infectious agent) include a mixed septal/lobular panniculitis, neutrophilic infiltration, vascular proliferation, hemorrhage, and necrosis that involves lipocytes, inflammatory cells and eccrine sweat coils[21] (Fig. 100.21). In Q fever due to *Coxiella burnetii*, there may be a "doughnut-like" granulomatous lobular panniculitis, in which fibrin and inflammatory cells form a ring around a central clear space; similar changes have been found in the liver and bone marrow of patients with Q fever[140].

Differential diagnosis

Fluctuant, ulcerating nodules also occur in pancreatic panniculitis, traumatic panniculitis, and α_1-antitrypsin deficiency panniculitis. Clinical and laboratory data can usually permit distinction. Of note, traumatic panniculitis may be accompanied by infection. Examples of infection-induced panniculitis with predominantly septal involvement or with large vessel vasculitis could be confused with acute erythema nodosum or erythema induratum, respectively. Special stains for organisms and cultures are keys to the diagnosis. In one study, special stains were positive for organisms in 14 of 15 cases[21].

Treatment

Treatment consists of appropriate antimicrobial therapy. Surgery may be indicated for isolated lesions caused by grain-forming fungi or bacteria, such as mycetoma or botryomycosis[139]. A more radical surgical approach has been used successfully in treating abdominal panniculitis due to enteric bacteria[144].

CYTOPHAGIC HISTIOCYTIC PANNICULITIS

The term "cytophagic histiocytic panniculitis" has been used to describe subcutaneous nodules or plaques that on histiologic examination show infiltrates of macrophages containing erythrocytes, lymphocytes and/or karyorrhectic debris, i.e. exhibiting hematophagocytosis (Figs 100.22 & 100.23)[146]. These macrophages with cytophagic activity have been referred to as "bean bag" cells. With the advent of immunophenotyping and genetic techniques, it has become apparent that the vast majority of patients have lymphoma, with atypical lymphoid cells also present within the panniculus[147]. In general, the lymphomas represent subcutaneous involvement of primary cutaneous γ/δ T-cell lymphoma or EBV-associated extranodal NK/T-cell lymphoma, nasal type (see Ch. 120)[148]. Occasionally, patients have subcutaneous panniculitis-like T-cell lymphoma, and, rarely, no lymphoma[149]. Individuals in the latter group may still have a fatal course due to a hemophagocytic syndrome that involves the liver, spleen and bone marrow (leading to pancytopenia). Recently, a heterozygous nonsense mutation in the gene that encodes perforin, leading to a decrease in the expression of perforin by cytotoxic T cells, was reported in a child with these histologic findings (but no evidence of lymphoma)[150].

MALIGNANT SUBCUTANEOUS INFILTRATES

Malignant infiltrates may involve the subcutis, mimicking the clinical and microscopic appearance of panniculitis. The best known of these is subcutaneous panniculitis-like T-cell lymphoma (see Ch. 120). While cytophagia can be seen in the latter disorder, it is particularly characteristic of subcutaneous involvement of primary cutaneous γ/δ T-cell lymphoma and EBV-associated extranodal NK/T-cell lymphoma, nasal type. Other lymphomas (e.g. B-cell), leukemias, and metastatic solid tumors may infiltrate the subcutis. For example, a case of melanophagic panniculitis that obscured foci of metastatic melanoma has been reported[151]. Obviously, clinical information is crucial in such cases.

Histopathologic clues include the recognition of significant pleomorphism or monotony among infiltrating cells in the subcutis, infiltration between collagen bundles of the dermis or around adnexal structures, and supporting immunohistochemical studies. Of note, the diagnosis of subcutaneous panniculitis-like T-cell lymphoma can sometimes be elusive as the initial impression may be lupus panniculitis or even a nonspecific panniculitis with lipomembranous changes[152].

UNUSUAL OR NEWLY DESCRIBED FORMS OF PANNICULITIS

Table 100.11 lists several newly described or unusual forms of panniculitis[141,153–162]. When a patient presents with panniculitis that is not readily classifiable, it may be worthwhile to consider these alternative diagnoses. Several of them probably do not actually represent distinct entities, but rather represent overarching terms that include established forms of panniculitis. For example, plasma cell panniculitis could include not only morphea and postirradiation pseudoscleroderma tous

UNUSUAL OR NEWLY DESCRIBED FORMS OF PANNICULITIS			
Type of panniculitis	**Clinical features**	**Microscopic findings**	**Comments**
Crystal deposition panniculitis	Red nodules, sometimes with necrosis; may have drainage; legs and elsewhere	Necrotizing and/or granulomatous panniculitis; calcium oxalate crystals in subcutaneous vessels; subcutaneous deposits of sodium urate crystals	Oxalosis: primary (inherited) or secondary (chronic renal failure) Urate deposition: may be an isolated cutaneous finding in gout
Idiopathic palmoplantar hidradenitis	Sudden onset of painful erythematous nodules; soles > palms Self-limited	Neutrophilic eccrine hidradenitis	Precipitated by trauma (mechanical, thermal) Mimicked by erythema nodosum, cold panniculitis, pseudomonas hot-foot syndrome
Sweet's panniculitis (subcutaneous Sweet's syndrome)	Erythematous nodules that may be painful; extremities; associated with leukemias (e.g. AML, hairy cell leukemia), treatment of acute promyelocytic leukemia with all-*trans*-retinoic acid, and, rarely, solid tumors	Predominantly neutrophilic lobular panniculitis, without vasculitis; immature myeloid forms have been described	Must exclude other neutrophil-rich forms of panniculitis, such as α_1-antitrypsin deficiency and pancreatic panniculitis
Panniculitic bacterid	Sudden onset of tender subcutaneous nodules; lower extremities; polyclonal hypergammaglobulinemia, cold agglutinins, cryofibrinogens	Lobular panniculitis, predominantly neutrophils with microabscesses; angiopathy; extravascular granulomas	Triggered by non-tuberculous infections; underlying disorders include atopy, antiphospholipid antibody syndrome
Plasma cell panniculitis	Hyperpigmentation and induration; trunk and extremities	Sclerosis of subcutaneous septa; plasma cells prominent component of infiltrate	Not a single entity; manifestation of morphea profunda, other autoimmune connective tissue disorders, and post-irradiation pseudosclerodermatous panniculitis
Panniculitis of Lyme disease	Tender nodules or diffuse fasciitis; fever, chills, photophobia, polyarthritis	Acute septal panniculitis; may contain eosinophils, plasma cells; lymphocytic vasculopathy	Detection of *Borrelia* spp. in tissues; positive serologies confirm the diagnosis
Fasciitis–panniculitis syndrome	Subcutaneous induration, sometimes with regional pain	Chronic inflammation, accompanied by replacement of fat lobules by fibrous tissue; thickening of fascia	Term used primarily in the rheumatologic literature; encompasses several autoimmune connective tissue diseases; also described as a paraneoplastic syndrome with hematologic, pancreatic and gastrointestinal malignancies
Atypical lymphocytic lobular panniculitis	Recurrent, infiltrative plaques; lower extremities, abdomen	Interstitial subcutaneous infiltrate with well-differentiated lymphocytes; no significant fat necrosis	Molecular studies show clonal or oligoclonal profile; no progression to lymphoma; considered T-cell dyscrasia
Infantile-onset panniculitis with uveitis and systemic granulomatosis	High fever, anemia, hepatosplenomegaly, uveitis, arthritis	Histiocytic lobular panniculitis, with lymphocytes and neutrophils initially; granulomas in later stage	Resemblance to Blau syndrome, but lack *NOD2/CARD15* mutations; may respond to TNF inhibitors

Table 100.11 Unusual or newly described forms of panniculitis. AML, acute myelogenous leukemia; TNF, tumor necrosis factor.

panniculitis but also other autoimmune connective tissue diseases or infectious diseases. The fasciitis–panniculitis syndrome is a term that has appeared from time to time, primarily in the non-dermatology literature. While sometimes discussed as if it were a single entity, fasciitis–panniculitis syndrome has been used to include eosinophilic fasciitis, morphea profunda, lupus panniculitis, lipodermatosclerosis, and a variety of other conditions. Sweet's syndrome and Lyme disease are established entities that can occasionally have panniculitis as a significant finding. Two other recently described conditions, atypical lymphocytic lobular panniculitis and panniculitic bacterid, may require further study and experience before being widely accepted as distinct entities. No doubt this list will change as disease mechanisms are better understood and disorders are reclassified or absorbed into other classification schemes.

REFERENCES

1. Braverman IM. Protective effects of erythema nodosum in coccidioidomycosis. Lancet. 1999;353:168.
2. Cohen PR, Holder WR, Rapini RP. Concurrent Sweet's syndrome and erythema nodosum: a report, world literature review and mechanism of pathogenesis. J Rheumatol. 1992;19:814–20.
3. White WL, Hitchcock MG. Diagnosis: erythema nodosum or not? Semin Cutan Med Surg. 1999;18:47–55.
4. Cribier B, Caille A, Heid E, et al. Erythema nodosum and associated diseases. A study of 129 cases. Int J Dermatol. 1998;37:667–72.
5. Garcia-Porrua C, Gonzalez-Gay MA, Vazquez-Caruncho M, et al. Erythema nodosum: etiologic and predictive factors in a defined population. Arthritis Rheum. 2000; 43:584–92.
6. Honma T, Bang D, Lee S, et al. Ultrastructure of endothelial cell necrosis in classical erythema nodosum. Hum Pathol. 1993;24:384–90.
7. Llorente L, Richaud-Patin Y, Alvarado C, et al. Elevated Th1 cytokine mRNA in skin biopsies and peripheral circulation in patients with erythema nodosum. Eur Cytokine Netw. 1997;8:67–71.
8. Senturk T, Aydintug O, Kuzu I, et al. Adhesion molecule expression in erythema nodosum-like lesions in Behçet's disease. A histopathological and immunohistochemical study. Rheumatol Int. 1998;18:51–7.
9. Kunz M, Beutel S, Brocker E. Leucocyte activation in erythema nodosum. Clin Exp Dermatol. 1999;24:396–401.
10. Wallace SL. Erythema nodosum treatment with colchicine. JAMA. 1967;202:1056.
11. Nomiyama J, Shinohara K, Inoue H. Erythema nodosum caused by the administration of granulocyte colony-stimulating factor in a patient with refractory anemia. Am J Hematol. 1994;47:333.
12. Winter HS. Treatment of pyoderma gangrenosum, erythema nodosum, and aphthous ulcerations. Inflamm Bowel Dis. 1998;4:71.
13. Labunski S, Posern G, Ludwig S, et al. Tumor necrosis factor-alpha promoter polymorphism in erythema nodosum. Acta Dermatol Venereol. 2001;81:18–21.
14. Mert A, Ozaras R, Tabak F, et al. Erythema nodosum: an experience of 10 years. Scand J Infect Dis. 2004;36:424–7.
15. Hanauer SB. How do I treat erythema nodosum, aphthous ulcerations, and pyoderma gangrenosum? Inflamm Bowel Dis. 1998;4:70; discussion 73.

16. Arsura EL, Kilgore WB, Ratnayake SN. Erythema nodosum in pregnant patients with coccidioidomycosis. Clin Infect Dis. 1998;27:1201–3.
17. Thurber S, Kohler S. Histopathologic spectrum of erythema nodosum. J Cutan Pathol. 2006;33:18–26.
18. Winkelmann RK, Frigas E. Eosinophilic panniculitis: a clinicopathologic study. J Cutan Pathol. 1986;13:1–12.
19. Sanchez Yus E, Sanz Vico MD, de Diego V. Miescher's radial granuloma. A characteristic marker of erythema nodosum. Am J Dermatopathol. 1989;11:434–42.
20. Ball NJ, Adams SP, Marx LH, et al. Possible origin of pancreatic fat necrosis as a septal panniculitis. J Am Acad Dermatol. 1996;34:362–4.
21. Patterson JW, Brown PC, Broecker AH. Infection-induced panniculitis. J Cutan Pathol. 1989;16:183–93.
22. Horio T, Imamura S, Danno K, et al. Potassium iodide in the treatment of erythema nodosum and nodular vasculitis. Arch Dermatol. 1981;117:29–31.
23. Banks PA, Present DH. Treatment of erythema nodosum, aphthous stomatitis, and pyoderma gangrenosum in patients with IBD. Inflamm Bowel Dis. 1998;4:73.
24. Boyd AS. Etanercept treatment of erythema nodosum. Skinmed. 2007;6:197–9.
25. Rosen T, Martinelli P. Erythema nodosum associated with infliximab therapy. Dermatol Online J. 2008;14:3.
26. Rajakulendran S, Deighton C. Adverse dermatological reactions in rheumatoid arthritis patients treated with etanercept, an anti-TNFalpha drug. Curr Drug Saf. 2006;1:259–64.
27. Bafverstedt B. Erythema nodosum migrans. Acta Derm Venereol. 1954;34:181–93.
28. Vilanova X, Piñol Aguade J. Subacute nodular migratory panniculitis. Br J Dermatol. 1959;71:45–50.
29. de Almeida Prestes C, Winkelmann RK, Su WP. Septal granulomatous panniculitis: comparison of the pathology of erythema nodosum migrans (migratory panniculitis) and chronic erythema nodosum. J Am Acad Dermatol. 1990;22:477–83.
30. Ross M, White GM, Barr RJ. Erythematous plaque on the leg. Vilanova's disease (subacute nodular migratory panniculitis). Arch Dermatol. 1992;128: 1644–5, 1647.
31. Winkelmann RK. Panniculitis in connective tissue disease. Arch Dermatol. 1983;119:336–44.
32. Fleischmajer R, Damiano V, Nedwich A. Alteration of subcutaneous tissue in systemic scleroderma. Arch Dermatol. 1972;105:59–66.
33. Vincent F, Prokopetz R, Miller RA. Plasma cell panniculitis: a unique clinical and pathologic presentation of linear scleroderma. J Am Acad Dermatol. 1989;21:357–60.
34. Ng PP, Tan SH, Tan T. Lupus erythematosus panniculitis: a clinicopathologic study. Int J Dermatol. 2002;41: 488–90.
35. Massone C, Kodama K, Salmhofer W, et al. Lupus erythematosus panniculitis (lupus profundus): clinical, histopathological, and molecular analysis of nine cases. J Cutan Pathol. 2005;32:396–404.
36. Su WP, Person JR. Morphea profunda. A new concept and a histopathologic study of 23 cases. Am J Dermatopathol. 1981;3:251–60.
37. Peters MS, Su WP. Eosinophils in lupus panniculitis and morphea profunda. J Cutan Pathol. 1991;18:189–92.
38. Fleischmajer R, Nedwich A. Generalized morphea. I. Histology of the dermis and subcutaneous tissue. Arch Dermatol. 1972;106:509–14.
39. Eriksson S. Alpha 1-antitrypsin deficiency: lessons learned from the bedside to the gene and back again. Historic perspectives. Chest. 1989;95:181–9.
40. O'Riordan K, Blei A, Rao MS, et al. Alpha 1-antitrypsin deficiency-associated panniculitis: resolution with intravenous alpha 1-antitrypsin administration and liver transplantation. Transplantation. 1997;63: 480–2.
41. Pittelkow MR, Smith KC, Su WP. Alpha-1-antitrypsin deficiency and panniculitis. Perspectives on disease relationship and replacement therapy. Am J Med. 1988;84:80–6.
42. American Thoracic Society; European Respiratory Society. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. Am J Respir Crit Care Med. 2003;168:818–900.
43. Irvine C, Neild V, Stephens C, et al. Alpha-1-antitrypsin deficiency panniculitis. J R Soc Med. 1990;83:743–4.
44. Gross B, Grebe M, Wencker M, et al. New findings in PiZZ alpha1-antitrypsin deficiency-related panniculitis. Demonstration of skin polymers and high dosing requirements of intravenous augmentation therapy. Dermatology. 2009;218:370–5.
45. Su WP, Smith KC, Pittelkow MR, et al. Alpha 1-antitrypsin deficiency panniculitis: a histopathologic and immunopathologic study of four cases. Am J Dermatopathol. 1987;9:483–90.
46. Arora PK, Miller HC, Aronson LD. Alpha 1-antitrypsin is an effector of immunological stasis. Nature. 1978;274:589–90.
47. Breit SN, Penny R. The role of alpha 1 protease inhibitor (alpha 1 antitrypsin) in the regulation of immunologic and inflammatory reactions. Aust NZ J Med. 1980;10: 449–53.
48. Smith KC, Pittelkow MR, Su WP. Panniculitis associated with severe alpha 1-antitrypsin deficiency. Treatment and review of the literature. Arch Dermatol. 1987;123:1655–61.
49. Yesudian PD, Dobson CM, Wilson NJ. α 1-Antitrypsin deficiency panniculitis (phenotype PiZZ) precipitated postpartum and successfully treated with dapsone. Br J Dermatol. 2004;150:1222–3.
50. Geller JD, Su WP. A subtle clue to the histopathologic diagnosis of early alpha 1-antitrypsin deficiency panniculitis. J Am Acad Dermatol. 1994;31:241–5.
51. Hendrick SJ, Silverman AK, Solomon AR, et al. Alpha 1-antitrypsin deficiency associated with panniculitis. J Am Acad Dermatol. 1988;18:684–92.
52. Humbert P, Faivre B, Gibey R, et al. Use of anti-collagenase properties of doxycycline in treatment of alpha 1-antitrypsin deficiency panniculitis. Acta Derm Venereol. 1991;71:189–94.
52a. Hidvegi T, Ewing M, Hale P, et al. An autophagy-enhancing drug promotes degradation of mutant 1-antitrypsin Z and reduces hepatic fibrosis. Science. 2010;329:229–32.
53. Degitz K, Messer G, Schirren H, et al. Successful treatment of erythema induratum of bazin following rapid detection of mycobacterial DNA by polymerase chain reaction [letter]. Arch Dermatol. 1993;129: 1619–20.
54. Cho KH, Lee DY, Kim CW. Erythema induratum of Bazin. Int J Dermatol. 1996;35:802–8.
55. Baselga E, Margall N, Barnadas MA, et al. Detection of *Mycobacterium tuberculosis* DNA in lobular granulomatous panniculitis (erythema induratum–nodular vasculitis). Arch Dermatol. 1997;133: 457–62.
56. Tan SH, Tan BH, Goh CL, et al. Detection of *Mycobacterium tuberculosis* DNA using polymerase chain reaction in cutaneous tuberculosis and tuberculids. Int J Dermatol. 1999;38:122–7.
57. Wolf D, Ben-Yehuda A, Okon E, et al. Nodular vasculitis associated with propylthiouracil therapy. Cutis. 1992;49:253–5.
58. Gimenez-Garcia R, Sanchez-Ramon S, Sanchez-Antolin G, Velasco Fernandez C. Red fingers syndrome and recurrent panniculitis in a patient with chronic hepatitis C. J Eur Acad Dermatol Venereol. 2003;17:692–4.
59. Ollert MW, Thomas P, Korting HC, et al. Erythema induratum of Bazin. Evidence of T-lymphocyte hyperresponsiveness to purified protein derivative of tuberculin: report of two cases and treatment. Arch Dermatol. 1993;129:469–73.
60. Schneider JW, Jordaan HF. The histopathologic spectrum of erythema induratum of Bazin [see comments]. Am J Dermatopathol. 1997;19: 323–33.
61. Smolle J, Kneifel H. S-100-protein-positive dendritic cells in nodular vasculitis. Dermatologica. 1986; 172:139–43.
62. Koga T, Kubota Y, Kiryu H, et al. Erythema induratum in a patient with active tuberculosis of the axillary lymph node: IFN-gamma release of specific T cells. Eur J Dermatol. 2001;11:48–9.
63. Jacinto SS, Nograles KB. Erythema induratum of Bazin: role of polymerase chain reaction in diagnosis. Int J Dermatol. 2003;42:380–1.
64. Shaffer N, Kerdel FA. Nodular vasculitis (erythema induratum): treatment with auranofin. J Am Acad Dermatol. 1991;25:426–9.
65. Segura S, Pujol RM, Trindade F, Requena L. Vasculitis in erythema induratum of Bazin: a histopathologic study of 101 biopsy specimens from 86 patients. J Am Acad Dermatol. 2008;59:839–51.
66. Taverna JA, Radfar A, Pentland A, et al. Case reports: nodular vasculitis responsive to mycophenolate mofetil. J Drugs Dermatol. 2006;5:992–3.
67. Forstrom T, Winkelmann RK. Acute, generalized panniculitis with amylase and lipase in skin. Arch Dermatol. 1975;111:497–502.
68. Heykarts B, Anseeuw M, Degreef H. Panniculitis caused by acinous pancreatic carcinoma. Dermatology. 1999;198:182–3.
69. Francombe J, Kingsnorth AN, Tunn E. Panniculitis, arthritis and pancreatitis. Br J Rheumatol. 1995;34: 680–3.
70. Berman B, Conteas C, Smith B, et al. Fatal pancreatitis presenting with subcutaneous fat necrosis. Evidence that lipase and amylase alone do not induce lipocyte necrosis. J Am Acad Dermatol. 1987;17:359–64.
71. Preiss JC, Faiss S, Loddenkemper C, et al. Pancreatic panniculitis in an 88-year-old man with neuroendocrine carcinoma. Digestion. 2002;66: 193–6.
72. Fretzin DF, Arias AM. Sclerema neonatorum and subcutaneous fat necrosis of the newborn. Pediatr Dermatol. 1987;4:112–22.
73. Milunsky A, Levin SE. Sclerema neonatorum: a clinical study of 79 cases. S Afr Med J. 1966;40:638–41.
74. Pasyk K. Sclerema neonatorum. Light and electron microscopic studies. Virchows Arch A Pathol Anat Histol. 1980;388:87–103.
75. Ferguson CK. Care of the infant with sclerema neonatorum. JOGN Nurs. 1983;12:391–4.
76. Burden AD, Krafchik BR. Subcutaneous fat necrosis of the newborn: a review of 11 cases. Pediatr Dermatol. 1999;16:384–7.
77. Chuang SD, Chiu HC, Chang CC. Subcutaneous fat necrosis of the newborn complicating hypothermic cardiac surgery. Br J Dermatol. 1995;132:805–10.
78. Hicks MJ, Levy ML, Alexander J, et al. Subcutaneous fat necrosis of the newborn and hypercalcemia: case report and review of the literature. Pediatr Dermatol. 1993;10:271–6.
79. Norton KI, Som PM, Shugar JM, et al. Subcutaneous fat necrosis of the newborn: CT findings of head and neck involvement. AJNR Am J Neuroradiol. 1997;18: 547–50.
80. Anderson DR, Narla LD, Dunn NL. Subcutaneous fat necrosis of the newborn. Pediatr Radiol. 1999;29: 794–6.
81. Bachrach LK, Lum CK. Etidronate in subcutaneous fat necrosis of the newborn. J Pediatr. 1999;135:530–1.
82. Wolach B, Raas-Rothschild A, Vogel R, et al. Subcutaneous fat necrosis with thrombocytopenia in a newborn infant. Dermatologica. 1990;181:54–5.
83. Tajirian A, Ross R, Zeikus P, Robinson-Bostom L. Subcutaneous fat necrosis of the newborn with eosinophilic granules. J Cutan Pathol. 2007;34:588–90.
84. Khan N, Licata A, Rogers D. Intravenous bisphosphonates for hypercalcemia accompanying subcutaneous fat necrosis: a novel treatment approach. Clin Pediatr. 2001;40:217–19.
85. Smith RT, Good RA. Sequelae of prednisone treatment of acute rheumatic fever. Clin Res Proc. 1956;4:156–7.
86. Roenigk HH Jr, Haserick JR, Arundell FD. Poststeroid panniculitis. Arch Dermatol. 1964;90:387–91.
87. Silverman RA, Newman AJ, LeVine MJ, et al. Poststeroid panniculitis: a case report. Pediatr Dermatol. 1988;5: 92–3.
88. Nitta Y. Lupus erythematosus profundus associated with neonatal lupus erythematosus [see comments]. Br J Dermatol. 1997;136:112–14.
89. Peters MS, Su WP. Lupus erythematosus panniculitis. Med Clin North Am. 1989;73:1113–26.
90. Martens PB, Moder KG, Ahmed I. Lupus panniculitis: clinical perspectives from a case series. J Rheumatol. 1999;26:68–72.
91. Riccieri V, Sili Scavalli A, Spadaro A, et al. Lupus erythematosus panniculitis: an immunohistochemical study. Clin Rheumatol. 1994;13:641–4.
92. Burrows NP, Walport MJ, Hammond AH, et al. Lupus erythematosus profundus with partial C4 deficiency responding to thalidomide. Br J Dermatol. 1991;125: 62–7.
93. Wenzel J, Proelss J, Wiechert A, et al. CXCR3-mediated recruitment of cytotoxic lymphocytes in lupus erythematosus profundus. J Am Acad Dermatol. 2007;56:648–50.
94. Chung HS, Hann SK. Lupus panniculitis treated by a combination therapy of hydroxychloroquine and quinacrine. J Dermatol. 1997;24:569–72.
95. Sanchez NP, Peters MS, Winkelmann RK. The histopathology of lupus erythematosus panniculitis. J Am Acad Dermatol. 1981;5:673–80.
96. Pincus LB, LeBoit PE, McCalmont TH, et al. Subcutaneous panniculitis-like T-cell lymphoma with overlapping clinicopathologic features of lupus erythematosus: coexistence of 2 entities? Am J Dermatopathol. 2009;31:520–6.

97. Espirito Santo J, Gomes MF, Gomes MJ, et al. Intravenous immunoglobulin in lupus panniculitis. Clin Rev Allergy Immunol. 2010;38:307–18.
98. Lee MW, Lim YS, Choi JH, et al. Panniculitis showing membranocystic changes in the dermatomyositis. J Dermatol. 1999;26:608–10.
99. Solans R, Cortes J, Selva A, et al. Panniculitis: a cutaneous manifestation of dermatomyositis. J Am Acad Dermatol. 2002;46(5 suppl.):S148–50.
100. Molnar K, Kemeny L, Korom I, et al. Panniculitis in dermatomyositis: report of two cases. Br J Dermatol. 1998;139:161–3.
101. Lemez L. Beitrag zur Pathogenese der subcutanen Fettgewebsnekrose Neugeborener (Sog. Sclerodermia neonatorum) an der Hand. Einer Kalterreaktion des subcutanen Fettgewebes bei Neugeborenen und jungen Sauglingen. Zeitung der Kinderheilkunden. 1928;46.
102. Epstein EH Jr, Oren ME. Popsicle panniculitis. N Engl J Med. 1970;282:966–7.
103. Behar TA, Anderson EE, Barwick WJ, et al. Sclerosing lipogranulomatosis: a case report of scrotal injection of automobile transmission fluid and literature review of subcutaneous injection of oils. Plast Reconstr Surg. 1993;91:352–61.
104. Beacham BE, Cooper PH, Buchanan CS, et al. Equestrian cold panniculitis in women. Arch Dermatol. 1980;116:1025–7.
105. Oertel YC, Johnson FB. Sclerosing lipogranuloma of male genitalia. Review of 23 cases. Arch Pathol Lab Med. 1977;101:321–6.
106. Carrasco L, Moreno C, Pastor MA, et al. Postirradiation pseudosclerodermatous panniculitis. Am J Dermatopathol. 2001;23:283–7.
107. Borroni G, Vassallo C, Brazzelli V, et al. Radiation recall dermatitis, panniculitis, and myositis following cyclophosphamide therapy: histopathologic findings of a patient affected by multiple myeloma. Am J Dermatopathol. 2004;26:213–16.
108. Rajkumar SV, Laude TA, Russo RM, et al. Popsicle panniculitis of the cheeks. A diagnostic entity caused by sucking on cold objects. Clin Pediatr (Phila). 1976;15:619–21.
109. Pang BK, Munro V, Kossard S. Pseudoscleroderma secondary to phytomenadione (vitamin K1) injections: Texier's disease. Australas J Dermatol. 1996;37:44–7.
110. Kossard S, Ecker RI, Dicken CH. Povidone panniculitis. Polyvinylpyrrolidone panniculitis. Arch Dermatol. 1980;116:704–6.
111. McCain J, West TW, Vasey FB, et al. Intramuscular aurothioglucose (Solganal) leading to panniculitis. J Rheumatol. 1993;20:1632–3.
112. Baars JW, Coenen JL, Wagstaff J, et al. Lobular panniculitis after subcutaneous administration of interleukin-2 (IL-2), and its exacerbation during intravenous therapy with IL-2. Br J Cancer. 1992;66:698–9.
113. Garcia-Domingo MI, Alijotas-Reig J, Cistero-Bahima A, et al. Disseminated and recurrent sarcoid-like granulomatous panniculitis due to bovine collagen injection. J Investig Allergol Clin Immunol. 2000;10:107–9.
114. Tan J, Rao B. Mesotherapy-induced panniculitis treated with dapsone: case report and review of reported adverse effects of mesotherapy. J Cutan Med Surg. 2006;10:92–5.
115. Jeong KH, Lee MH. Two cases of factitial panniculitis induced by electroacupuncture. Clin Exp Dermatol. 2009;34:e170–3.
116. Winkelmann RK, Barker SM. Factitial traumatic panniculitis. J Am Acad Dermatol. 1985;13:988–94.
117. Foucar E, Downing DT, Gerber WL. Sclerosing lipogranuloma of the male genitalia containing vitamin E: a comparison with classical 'paraffinoma'. J Am Acad Dermatol. 1983;9:103–10.
118. Takihara H, Takahashi M, Ueno T, et al. Sclerosing lipogranuloma of the male genitalia: analysis of the lipid constituents and histological study. Br J Urol. 1993;71:58–62.
119. Henrichs WD, Helwig EB. Grease gun granulomas. Mil Med. 1986;151:78–82.
120. Kaufman HL, Harandi A, Watson MC, et al. Panniculitis after vaccination against CEA and MUC1 in a patient with pancreatic cancer. Lancet Oncol. 2005;6:62–3.
121. Chong H, Brady K, Metze D, Calonje E. Persistent nodules at injection sites (aluminum granuloma) – clinicopathological study of 14 cases with a diverse range of histological reaction patterns. Histopathology. 2006;48:182–8.
122. Requena C, Izguierdo MJ, Navarro M, et al. Adverse reactions to injectable aesthetic microimplants. Am J Dermatopathol. 2001;23:197–202.
123. Claudy A, Garcier F, Schmitt D. Sclerosing lipogranuloma of the male genitalia: ultrastructural study. Br J Dermatol. 1981;105:451–6.
124. Oh C, Ginsberg-Fellner F, Dolger H. Factitial panniculitis and necrotizing fasciitis in juvenile diabetes. Diabetes. 1975;24:856–8.
125. Huriez C. Ulceres de jambes et troubles trophiques d'origine veineuse (donnes tirees de l'etude d'un millier d'ulcereux hospitalises). Rev Pract. 1955;5: 2703–21.
126. Jorizzo JL, White WL, Zanolli MD, et al. Sclerosing panniculitis. A clinicopathologic assessment. Arch Dermatol. 1991;127:554–8.
127. Kirsner RS, Pardes JB, Eaglstein WH, et al. The clinical spectrum of lipodermatosclerosis. J Am Acad Dermatol. 1993;28:623–7.
128. Greenberg AS, Hasan A, Montalvo BM, et al. Acute lipodermatosclerosis is associated with venous insufficiency. J Am Acad Dermatol. 1996;35: 566–8.
129. Stacey MC, Burnand KG, Bhogal BS, et al. Pericapillary fibrin deposits and skin hypoxia precede the changes of lipodermatosclerosis in limbs at increased risk of developing a venous ulcer. Cardiovasc Surg. 2000;8:372–80.
130. Herouy Y, Kreis S, Mueller T, et al. Inhibition of angiogenesis in lipodermatosclerosis: implication for venous ulcer formation. Int J Mol Med. 2009;24: 645–51.
131. Falanga V, Bontempo FA, Eaglstein WH. Protein C and protein S plasma levels in patients with lipodermatosclerosis and venous ulceration. Arch Dermatol. 1990;126:1195–7.
132. Segal S, Cooper J, Bolognia J. Treatment of lipodermatosclerosis with oxandrolone in a patient with stanozolol-induced hepatotoxicity. J Am Acad Dermatol. 2000;43:558–9.
133. Alegre VA, Winkelmann RK, Aliaga A. Lipomembranous changes in chronic panniculitis. J Am Acad Dermatol. 1988;19:39–46.
134. Ishikawa O, Tamura A, Ryuzaki K, et al. Membranocystic changes in the panniculitis of dermatomyositis. Br J Dermatol. 1996;134:773–6.
135. Hafner C, Wimmershoff M, Landthaler M, Vogt T. Lipodermatosclerosis: successful treatment with danazol. Acta Derm Venereol. 2005;85:365–6.
136. Goldman MP. The use of pentoxifylline in the treatment of systemic sclerosis and lipodermatosclerosis: a unifying hypothesis? J Am Acad Dermatol. 1994;31: 135–6.
137. Maioriello RP, Merwin CF. North American blastomycosis presenting as an acute panniculitis and arthritis. Arch Dermatol. 1970;102:92–6.
138. Sanderson TL, Moskowitz L, Hensley GT, et al. Disseminated *Mycobacterium avium-intracellulare* infection appearing as a panniculitis. Arch Pathol Lab Med. 1982;106:112–14.
139. Farnsworth GA. Case for diagnosis. Panniculitis, pyogranulomatous, diffuse, severe, with numerous fungal aggregates; etiology consistent with deep dermatophytosis. Mil Med. 1990;155:618, 622.
140. Galache C, Santos-Juanes J, Blanco S, et al. Q fever: a new cause of 'doughnut' granulomatous lobular panniculitis. Br J Dermatol. 2004;151:685–7.
141. Kramer N, Rickert RR, Brodkin RH, Rosenstein ED. Septal panniculitis as a manifestation of Lyme disease. Am J Med. 1986;81:149–52.
142. Paredes CJ, Del Gordo EC, Torrado E, et al. Chronic septal panniculitis caused by Phaeohyphomycosis. J Clin Rheumatol. 1998;4:323–7.
143. Ollague Torres JM, Ollague Loaiza W. Histologic chronology of eosinophilic migratory nodular panniculitis (gnathostomiasis). Med Cutan Ibero Lat Am. 1987;15:85–8.
144. Nauta RJ. A radical approach to bacterial panniculitis of the abdominal wall in the morbidly obese. Surgery. 1990;107:134–9.
145. Ginter G, Rieger E, Soyer HP, et al. Granulomatous panniculitis caused by *Candida albicans*: a case presenting with multiple leg ulcers. J Am Acad Dermatol. 1993;28:315–17.
146. Winkelmann RK, Bowie EJ. Hemorrhagic diathesis associated with benign histiocytic, cytophagic panniculitis and systemic histiocytosis. Arch Intern Med. 1980;140:1460–3.
147. Wick MR, Patterson JW. Cytophagic histiocytic panniculitis – a critical reappraisal. Arch Dermatol. 2000;136:922–4.
148. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. Blood. 2005;105:3768–85.
149. Craig AJ, Cualing H, Thomas G, et al. Cytophagic histiocytic panniculitis – a syndrome associated with benign and malignant panniculitis: case comparison and review of the literature. J Am Acad Dermatol. 1998;39:721–36.
150. Chen RL, Hsu YH, Ueda I, et al. Cytophagic histiocytic panniculitis with fatal haemophagocytic lymphohistiocytosis in a paediatric patient with perforin gene mutation. J Clin Pathol. 2007;60: 1168–9.
151. Pierard GE. Melanophagic dermatitis and panniculitis. A condition revealing an occult metastatic malignant melanoma. Am J Dermatopathol. 1988;10:133–6.
152. Weenig RH, Ng CS, Perniciaro C. Subcutaneous panniculitis-like T-cell lymphoma: an elusive case presenting as lipomembranous panniculitis and a review of 72 cases in the literature. Am J Dermatopathol. 2001;23:206–15.
153. Buezo GF, Requena L, Fraga Fernandez J, et al. Idiopathic palmoplantar hidradenitis. Am J Dermatopathol. 1996;18:413–16.
154. Rabinowitz LG, Cintra ML, Hood AF, Esterly NB. Recurrent palmoplantar hidradenitis in children. Arch Dermatol. 1995;131:817–20.
155. Tomb R, Soutou B, Chehadi S. Plasma cell panniculitis: a histopathological variant of morphea profunda. Ann Dermatol Venereol. 2009;136:256–9.
156. Wouters CH, Martin TM, Stichweh D, et al. Infantile onset panniculitis with uveitis and systemic granulomatosis: a new clinicopathologic entity. J Pediatr. 2007;151:707–9.
157. Magro CM, Schaefer JT, Morrison C, et al. Atypical lymphocytic lobular panniculitis: a clonal subcutaneous T-cell dyscrasia. J Cutan Pathol. 2008;35:947–54.
158. Magro CM, Drysen ME, Crowson AN. Acute infectious id panniculitis/panniculitic bacterid: a distinctive form of neutrophilic lobular panniculitis. J Cutan Pathol. 2008;35:941–6.
159. Somach SC, Davis BR, Paras FA, et al. Fatal cutaneous necrosis mimicking calciphylaxis in a patient with type 1 primary hyperoxaluria. Arch Dermatol. 1995;131:821–3.
160. LeBoit PE, Schneider S. Gout presenting as lobular panniculitis. Am J Dermatopathol. 1987;9:334–8.
161. Jagdeo J, Campbell R, Long T, et al. Sweet's syndrome-like neutrophilic lobular panniculitis associated with chemotherapy in a patient with acute promyelocytic leukemia. J Am Acad Dermatol. 2007;56:690–3.
162. Naschitz JE, Yeshurun D, Zuckerman E, et al. The fasciitis-panniculitis syndrome: clinical spectrum and response to cimetidine. Semin Arthritis Rheum. 1992;21:211–20.

101 Lipodystrophies

Suat Hoon Tan, Priya Sen and Mark Tang

Synonyms: ■ Lipodystrophy: lipoatrophy, lipohypertrophy

Key features

- Lipodystrophies are inherited or acquired disorders characterized by a paucity or complete absence of fat that may be generalized, partial or localized; lipohypertrophy may accompany the lipoatrophy
- Though the terms lipodystrophy and lipoatrophy are often used interchangeably, lipoatrophy should be used specifically for selective loss of fat, with lipodystrophy implying a redistribution of fat, in part due to a hypertrophic compensation of the non-atrophic fat
- Lipodystrophy syndromes represent a heterogeneous group of disorders that are characterized by lipoatrophy and fat accumulation in characteristic body distribution patterns
- Fat is a metabolically active organ, thus fat loss is associated with metabolic derangements, which parallel the extent and duration of lipoatrophy
- Patients with lipodystrophy typically develop the metabolic syndrome, which includes insulin resistance, diabetes mellitus, hyperinsulinemia, hypertriglyceridemia, cardiovascular disease and hepatic steatosis. This association has provided insights into the pathogenesis of coronary artery disease and diabetes mellitus
- Systemic manifestations of generalized and partial lipodystrophy syndromes include medical complications of the metabolic syndrome, hormonal abnormalities, organ dysfunction, anabolic syndrome, glomerulonephritis and autoimmune disorders
- A distinct syndrome of peripheral lipoatrophy, central obesity, breast hypertrophy, dorsocervical fat pad enlargement, hyperlipidemia and insulin resistance occurs in patients with HIV infection undergoing treatment with antiretroviral therapy (ART)
- Isolated or localized lipoatrophy can occur at the site of medication injection, trauma or pressure, in association with autoimmune connective tissue disease, or following certain panniculitic inflammatory or neoplastic processes
- Microscopically, there may be a complete absence of subcutaneous fat or a decrease in adipocyte size and number. An inflammatory panniculitis may be seen in early disease

Introduction

Lipodystrophy is the term that describes a heterogeneous group of diseases characterized by a selective fat loss and secondary fat accumulation in a characteristic body distribution pattern in all but the more localized variants. Adipose tissue has crucial metabolic and endocrine functions, in addition to having a role in mechanical protection. The loss of peripheral subcutaneous fat and a compensatory accumulation of visceral fat is closely associated with insulin resistance, diabetes mellitus, dyslipidemia, hypertension and coronary artery disease. These metabolic abnormalities and their sequelae are now referred to as the metabolic syndrome and they underscore the important metabolic and endocrine functions of fat, in its role as a diverse and crucial body organ.

More than a century after the first description of lipodystrophy[1] and then delineation of generalized lipodystrophy into congenital and acquired forms[2], the genetic basis of several of the inherited lipodystrophies has now been elucidated. Mutations have been found in genes ranging from those encoding proteins essential for adipocyte differentiation to those encoding nuclear lamins (see below).

Clinically, lipodystrophy can be broadly classified into inherited or acquired forms and then further subclassified based on the extent of fat loss, in conjunction with genetic mutations, age of onset and systemic manifestations (Fig. 101.1 & Table 101.1). Based upon the distribution pattern, lipodystrophy may be subdivided into three major groups: (1) generalized; (2) partial (extensive, but not generalized); and (3) localized (limited to an isolated area).

Localized lipodystrophy is a commonly encountered form of lipoatrophy, which may be due to injections of medications or vaccines, pressure, previous surgery, trauma or panniculitis (see Ch. 100). Nowadays, lipodystrophy associated with antiretroviral therapy (ART; formerly referred to as highly active antiretroviral therapy [HAART]) for HIV infections has emerged as the most common non-localized form of acquired lipodystrophy[3]. It is important for dermatologists to recognize this drug effect and the associated metabolic syndrome, as there are profound social, psychological and medical implications. The dermatologist is also likely to occasionally encounter partial lipodystrophy that may be associated with glomerulonephritis or with autoimmune diseases such as dermatomyositis or lupus erythematosus. Finally, there are several rare genetic syndromes that will be discussed (see Table 101.1).

Pathogenesis

Adipose tissue functions as an endocrine organ via its secretion of hormones and adipocytokines, such as leptin, TNF-α, interleukin (IL)-6 and adiponectin. Altered expression and activity of these factors play a role in the development of insulin resistance and other metabolic changes seen in lipodystrophic syndromes, which are similar to those observed with obesity and the metabolic syndrome[4,5].

There appears to be a final common pathway of defective adipocyte triglyceride storage in conditions characterized by fat loss as well as fat excess. This defect can result from impaired triglyceride synthesis due to an enzyme deficiency (e.g. AGPAT2); defective adipocyte development caused by mutations in genes critical to adipocyte differentiation (e.g. *seipin, PPARG, AKT2, LMNA*); adipocyte apoptosis; or autoimmune- or drug-mediated adipocyte destruction. All of these processes can impair normal adipocyte differentiation, development, lifespan and/or function[6].

The destruction or impaired differentiation of adipocytes leads to a cascade of hormonal and metabolic consequences. Adiponectin, a product of the *apM1* gene, is expressed in and secreted exclusively by differentiated adipocytes. It plays a positive role in regulating insulin sensitivity and glucose and lipid homeostasis. Plasma adiponectin levels are inversely correlated with fasting insulin levels and insulin resistance[7]. Serum adiponectin and leptin levels are *reduced* both in murine models of lipoatrophy with insulin resistance and in humans with congenital and acquired lipodystrophies[8] as well as HIV/ART-related lipodystrophy[9,10]. As an example, the hyperphagia, reduced leptin levels, and deficiency in leptin signaling associated with generalized lipodystrophy results in an increased carbohydrate load, triglyceride accumulation in the muscle and liver, and, ultimately, insulin resistance, diabetes and hepatic steatosis. Of note, infusion of leptin reverses insulin resistance in mouse models with deficient messenger RNAs encoding leptin[11].

Lastly, a transgenic mouse model expressing a truncated version of nuclear *s*terol *r*egulatory *e*lement-*b*inding *p*rotein-1c (SREBP-1c) in

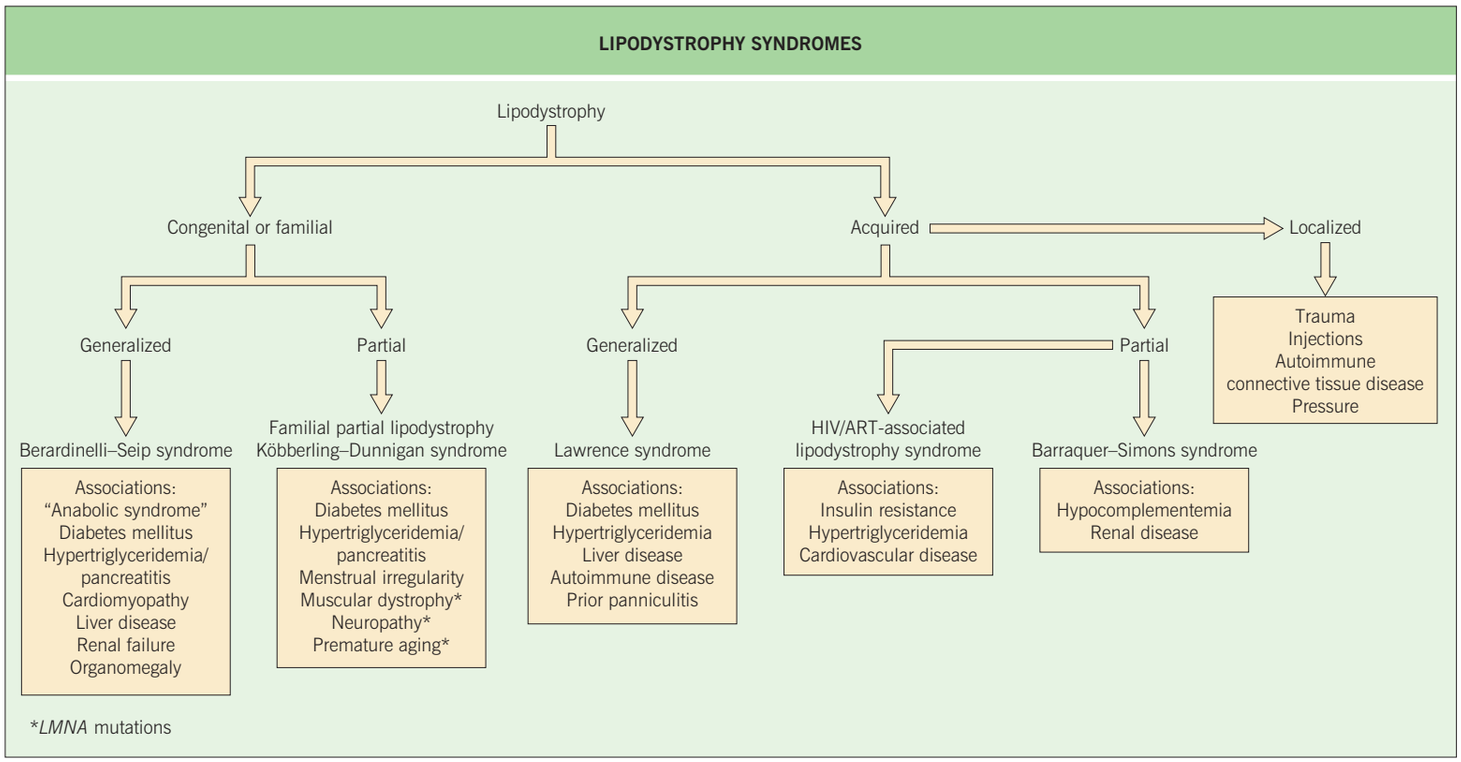


Fig. 101.1 Lipodystrophy syndromes.

adipose tissue exhibits features of generalized lipodystrophy (see below)[12].

Congenital generalized lipodystrophy (Berardinelli–Seip syndrome)

Congenital generalized lipodystrophy (CGL) is an autosomal recessive disorder, and two major genetic subtypes have been described – Berardinelli–Seip congenital lipodystrophy (BSCL) type 1, due to mutations in the gene that encodes 1-acylglycerol-3-phosphate *O*-acyltransferase 2 (*AGPAT2*), and BSCL type 2, due to mutations in *BSCL2/seipin* (see Table 101.1). It has been postulated that these genes cause lipodystrophy primarily by affecting adipocyte differentiation or lipid droplet formation in adipose tissue. In type 1, aberrant AGPAT2 enzyme activity causes a marked reduction in triglyceride and phospholipid synthesis, resulting in abnormal adipocyte function[13]. In type 2, *BSCL2* mutations affect the endoplasmic reticulum membrane protein seipin which is critical for lipid droplet morphology.

In some patients who do not have mutations in either gene, molecular screening has recently identified mutations in the gene that encodes caveolin 1 (*CAV1*). CAV1 is a key structural component of plasma membrane caveolae, which play an important role in human adipocyte function[14].

Differences in the molecular basis of CGL may account for the phenotypic heterogeneity[15]. *AGPAT2* has been found to be highly expressed in human omental adipose tissue, which may explain the preferential loss of metabolically active intra-abdominal adipose tissue but preservation of mechanical palmoplantar adipose tissue in patients with type 1 BSCL. *BSCL2* has been found to also be highly expressed in the brain[16], which may account for the higher prevalence of mental retardation in type 2 BSCL patients.

Familial partial lipodystrophy (including Dunnigan variety, Köbberling variety)

Familial partial lipodystrophy (FPLD) is a heterogeneous group of autosomal dominantly inherited disorders. The most prevalent subtype is the Dunnigan variety, which is due to mutations in *LMNA*[17,18]. *LMNA* encodes lamins A and C, and missense mutations in *LMNA* occur in patients with FPLD. Lamins belong to the intermediate filament family of structural proteins that compose the nuclear lamina. *LMNA* mutations lead to disruption of nuclear function, resulting in apoptosis and premature cell death of adipocytes. These mutations also alter plasma levels of leptin, with heterozygotes (mutation in one copy of *LMNA*) having decreased plasma leptin and increased fasting plasma insulin and C-peptide levels[19]. Of note, *LMNA* mutations are also responsible for a group of laminopathies that includes muscular dystrophy, cardiomyopathy, neuropathies, and syndromes of premature aging (see Table 63.9). The clinical phenotype/syndrome is determined by the site and type of *LMNA* mutations[20].

Another subtype of FPLD results from heterozygous missense mutations of the gene that encodes peroxisome proliferator-activated receptor-γ (*PPARG*)[21]. The PPAR-γ protein plays an essential role in adipogenesis (see Fig. 101.14), but the entire pathogenesis remains unclear. Although this subtype has a milder phenotype than the Dunnigan variety, with a later age of onset and involvement confined to the distal extremities, metabolic disturbances are more severe, suggesting that *PPARG* mutations may have additional direct effects.

Recently, FPLD due to heterozygous missense mutations in the gene that encodes v-AKT murine thymoma oncogene homolog 2 (*AKT2*) was described. AKT2, also known as protein kinase B, is involved in post-receptor insulin signaling and its dysfunction may lead to lipodystrophy secondary to abnormal adipocyte differentiation[22]. In addition, in three families with lipodystrophy (primarily of the lower extremities) as well as hypertension, insulin resistance, hypertriglyceridemia and acanthosis nigricans, heterozygous loss-of-function mutations were described in the gene that encodes perilipin (*PLIN1*)[22a]. Perilipin is responsible for the formation, maturation and function of lipid droplets within adipocytes.

Partial lipodystrophy may also be seen in association with mandibuloacral dysplasia (MAD), an autosomal recessive syndrome associated with mutations in the *LMNA* gene (type A), or with mutations in the gene *ZMPSTE24* which encodes a zinc metalloproteinase involved in post-translational proteolytic processing of prelamin A (type B)[23,24]. The latter has been associated with severe mandibuloacral dysplasia, premature aging and generalized lipodystrophy.

Mesangiocapillary glomerulonephritis type 2 (MCGN II) has been reported in a case of partial lipodystrophy due to a mutation in the *LMNA* gene, suggesting that partial lipodystrophy of both the sporadic and familial subtypes may predispose to this condition and the observed renal and complement abnormalities may be secondary to other factors associated with lipodystrophy[25].

LIPODYSTROPHY SYNDROMES							
Syndrome	**Age of onset**	**Sex**	**Genetics (chromosome)**	**Distribution of fat changes**	**Metabolic derangements**	**Systemic associations**	**Systemic complications**
INHERITED							
Congenital generalized lipodystrophy (Berardinelli–Seip syndrome)	Birth	F=M	AR Type 1: *AGPAT2* (9q34) Type 2: *BSCL2/seipin* (11q13) Type 3: *CAV1* (7q31)	↓ Fat: face, trunk, extremities, viscera Types 1 & 3: loss of metabolically active adipose tissue in the skin and viscera, but preservation of mechanical adipose tissue (palmoplantar, retro-orbital) Type 2: both metabolically active and mechanical adipose tissue are lost	+++: IR, DM, ↑ TG; anabolic syndrome; ↑ metabolic rate	Type 3: associated with vitamin D resistance	Hypertrophic cardiomyopathy, liver failure/cirrhosis, organomegaly, acute pancreatitis, proteinuric nephropathy (see Table 101.3) More severe disease in type 2, with higher incidence of mental retardation and cardiomyopathy
Familial partial lipodystrophy (Köbberling–Dunnigan syndrome)	Puberty	F>M	AD Dunnigan type: *LMNA* (lamin A/C; 1q21.2) *PPARG* (3p25) *AKT2* *PLIN1*	Dunnigan type: ↓ fat on extremities ± trunk, ↑ fat on face/neck (double chin), muscular hypertrophy *PPARG*-associated: ↓ fat on extremities/buttocks (less severe than Dunnigan type); trunk/viscera spared	IR, DM, ↑ TG, ↓ HDL (more severe in *PPARG*-associated type than Dunnigan type)	None preceding	Acute pancreatitis, hepatic steatosis/cirrhosis, menstrual abnormalities Clinical findings and metabolic complications more severe in women
Familial partial lipodystrophy with mandibuloacral dysplasia (MAD)	Childhood or puberty	M>F	AR Type A: *LMNA* Type B: *ZMPSTE24*	↓ fat on extremities Type B – may have generalized lipodystrophy	IR, DM, ↑ TG, ↓ HDL in some patients	None preceding	Premature aging, hypoplasia of mandible, clavicles and terminal digits, short stature, scleroderma-like skin lesions with mottled skin pigmentation
ACQUIRED							
Acquired generalized lipodystrophy (Lawrence syndrome)	Childhood or adolescence	F>M 3:1	None known	↓ Fat: face, trunk, extremities Preservation of fat within the bone marrow	++: IR, DM, ↑ TG (correlates with the degree of lipodystrophy)	1/3 have a preceding autoimmune disease (e.g. juvenile dermatomyositis, Sjögren's syndrome) or infection; 25% have a preceding panniculitis	Liver failure/cirrhosis, proteinuric nephropathy
Acquired partial lipodystrophy (Barraquer–Simons syndrome)	Childhood or adolescence Rarely adults	F>M 3:1	Sporadic or AD: *LMNB2* (Lamin B2; 19p13.3)	↓ Fat: face, upper extremities, trunk, with spread in a cephalocaudal direction Spares lower extremities ↑ Fat: hips and legs Hemilipodystrophic variants	Rare IR, DM, ↑ TG	Often preceded by a febrile illness; 1/5 have mesangiocapillary glomerulonephritis Almost all have low levels of C3 and presence of circulating C3 nephritic factor Autoimmune disease associations include SLE, dermatomyositis	Sequelae of renal abnormalities
HIV/ART-associated lipodystrophy syndrome	2 months–2 years after initiation of combination antiretroviral therapy Adults>children	M=F overall, F>M central adiposity	None known	↓ Fat: face, extremities ↑ Fat: central (trunk/viscera), dorsocervical ("buffalo hump"), breasts Lipomas (e.g. pubic)	++: IR, ↑ TG, ↑ LDL, ↓ HDL; ± DM	HIV infection	Cardiovascular disease

Table 101.1 Lipodystrophy syndromes. *AGPAT2*, 1-acylglycerol-3-phosphate O-acyltransferase-2 gene; AR, autosomal recessive; AD, autosomal dominant; *AKT2*, v-AKT murine thymoma oncogene homolog 2; *BSCL2*, Bernardinelli–Seip congenital lipodystrophy 2 (Seipin) gene; *CAV1*, caveolin 1 gene; DM, diabetes mellitus; ART, antiretroviral therapy; HDL, high-density lipoproteins; HIV, human immunodeficiency virus; LDL, low-density lipoproteins; IR, insulin resistance; PI, protease inhibitor; *PPARG*, peroxisome proliferator-activated receptor-γ; SLE, systemic lupus erythematosus; TG, triglycerides; *ZMPSTE24,* gene that encodes a zinc metallo-protease.

Acquired generalized lipodystrophy (Lawrence syndrome)

There is no known genetic defect. A third of patients have an antecedent autoimmune disease or viral or bacterial infection, but a causal relationship with the latter has not been established. Twenty-five percent of cases of acquired generalized lipodystrophy are heralded by panniculitis (see Table 101.1)[26].

The preceding panniculitis and the frequent association of autoimmune disease imply immunologically mediated fat cell lysis. Autoantibodies against the adipocyte membrane have been reported in one patient with this condition[27]. As with the other forms of lipodystrophy, most patients have low serum levels of leptin and adiponectin.

Acquired partial lipodystrophy syndrome (Barraquer–Simons syndrome)

This occurs sporadically or may be autosomal dominant. Subcutaneous fat is often lost acutely after a viral illness. The exact pathogenesis is not known, but it may be related to adipsin, a protein produced by adipocytes which is identical to factor D (a component of the alternative complement pathway; see Ch. 60), as well as C3 nephritic factor (C3NeF), an IgG autoantibody against an alternative pathway enzyme. There is dysregulated activation of the alternative pathway, associated with C3NeF binding to the rate-limiting C3 convertase enzyme (C3bBb). This results in unopposed activation of the alternative complement pathway, excessive consumption of C3, and complement-dependent lysis of adipocytes. Regional differences in factor D expression parallel the regional distribution of adipocyte loss in partial lipodystrophy, which may explain the cephalocaudal distribution of fat. Renal cells also express complement components, and a similar mechanism of complement-mediated injury may be responsible for the MCGN II seen in these patients[28].

Recently, mutations in *LMNB2* were described in four patients with acquired partial lipodystrophy[29].

Localized lipoatrophy

The pathogenesis of localized lipoatrophy is heterogeneous. Lipoatrophic plaques may be the result of direct sequelae of pyogenic abscesses, various lobular panniculitides, localized autoimmune connective tissue diseases such as lupus profundus and morphea, or panniculitic lymphoma. Atrophic connective tissue disease panniculitis is associated with systemic evidence of various autoimmune disorders such as systemic lupus erythematosus or dermatomyositis, implying an immunologic mechanism.

Iatrogenic causes include complications of injected medications (Table 101.2). The causes may be multifactorial, such as inflammatory responses to the injected medicines and/or trauma. In the case of insulin lipoatrophy, it may be induced by impurities and is significantly associated with the presence of anti-insulin antibodies[30]; perivascular mononuclear infiltrates and vascular immunoreactants near insulin injections suggest a localized immune response. Because repeated use of the same injection site increases the risk of lipoatrophy, the latter can be largely prevented by regular rotation of injection sites. Of note, lipoatrophy is rare with the use of human insulin and insulin pump therapy. Growth hormone injections may lead to lipoatrophy via a direct lipolytic effect. Panniculitis at the injection site may precede localized lipoatrophy due to glatiramer, and subcutaneous injections of methotrexate may cause semicircular lipoatrophy.

Lipoatrophia semicircularis may represent repetitive trauma or pressure-induced changes (Fig. 101.2), due to constant or intermittent pressure such as leaning against a desk or chair edge, basin, bathtub or counter, or from tight-fitting jeans or girdles. Support for microtrauma is demonstrated by resolution of the lesions when trauma is avoided, and the occurrence of similar lesions in multiple employees in the same workplace[31]. Others have implicated local hyperproduction of TNF-α by macrophages[32]. Localized lipoatrophy of the upper and lateral calf due to pressure is commonly observed in women who cross their legs when seated (Fig. 101.3).

Up to 60% of involutional lipoatrophy (see below) may be associated with prior local injections, suggesting a trauma-related phenomenon[33]. Lipophagocytizing macrophages seen by electron microscopy suggest an initial stimulation by injectable material; typically, an active foreign body reaction is absent.

Lipodystrophia centrifugalis abdominalis infantalis is usually idiopathic, but has been reported to be associated with mechanical trauma or focal infection. Predominance of this condition in East Asia is notable and reports in twins and siblings point to the possibility of an HLA predisposition. In one patient with lipodystrophia centrifugalis abdominalis infantilis, positive immunohistochemical staining for Fas, bcl-2 and p53 and terminal transferase-mediated dUTP nick end-labeling (TUNEL) in degenerating fatty tissue suggested apoptosis as a possible factor[34].

INJECTED MEDICATIONS THAT CAN CAUSE LOCALIZED LIPOATROPHY
MOST COMMON
Insulin • Non-human form primarily
Corticosteroids
LESS COMMON
Antibiotics • Benzathine penicillin
Growth hormone
Heparin
Iron
Immunomodulatory drugs • Glatiramer acetate (multiple sclerosis) • Methotrexate*
Vaccines • Diphtheria–pertussis–tetanus vaccine
Exogenous material
*Semicircular lipoatrophy.

Table 101.2 Injected medications that can cause localized lipoatrophy.

Fig. 101.2 Lipoatrophia semicircularis (semicircular lipoatrophy). Bilateral slightly curved depressions on the anterolateral thighs. *Courtesy, Diane Thaler, MD.*

Fig. 101.3 Localized lipoatrophy of the upper lateral calf. A common finding in women due to crossing the legs while seated. *Courtesy, Jean L Bolognia, MD.*

Clinical Features

Congenital generalized lipodystrophy (CGL)

CGL (BSCL types 1 and 2) is rare, with an estimated prevalence of less than 1 case in 10 million[35]. As an autosomal recessive disorder, there is often consanguinity. All subtypes are characterized by generalized loss or absence of metabolically active subcutaneous fat from birth, resulting in a cadaveric facies and distinctive muscular-appearing body habitus (Fig. 101.4). Features of anabolic syndrome are evident in early childhood (Table 101.3). There is also a deficiency of bone marrow and visceral fat. Type 2 BSCL also lacks mechanical fat, in addition to metabolically active fat. The inability to store sufficient fat in the adipocytes results in the metabolic syndrome (see Ch. 53), which becomes more profound during puberty[35]. Hepatosplenomegaly is typical, and may be associated with umbilical herniation. Diabetes mellitus is evident by adolescence, but the hyperinsulinemia can be detected as early as infancy. Enlarged genitalia are seen especially in women, and may be associated with polycystic ovarian syndrome and infertility. Dermatologic sequelae (see Table 101.3) include acanthosis nigricans, which is noted by adolescence and may be extensive. Serious medical complications and metabolic derangements include cirrhosis from fatty liver, premature atherosclerosis, sequelae of diabetes, pancreatitis from hypertriglyceridemia, and a high mortality rate from hypertrophic cardiomyopathy. The mean age of death is 32 years. Type 2 appears to be a more severe disorder that is associated with mental retardation, hypertrophic cardiomyopathy and a higher incidence of premature death.

Familial partial lipodystrophy

Familial partial lipodystrophy (FPLD) was first described by Dunnigan and Köbberling[36], who outlined the clinical characteristics of large Scottish and German pedigrees with familial syndromes of partial lipodystrophy. Nowadays, FPLD is classified based upon genetic mutations and clinical phenotype (see Table 101.1). This group of disorders differs from other forms of *inherited* lipodystrophy by a later onset (after puberty) and fat loss predominantly affecting the extremities, with sparing of the face[35,37]. FPLD is a rare disorder, with a prevalence of less than 1 in 15 million[35].

In *LMNA*-associated FPLD, a normal childhood is followed by a progressive, symmetric loss of subcutaneous fat; the latter uniformly involves the extremities and variably extends to the trunk (anterior > posterior). Compensatory accumulation of excess fat occurs and results in a fat head and neck, with a round face, as well as increased supraclavicular fat. Acromegalic facies with a double chin is characteristic. As a result of the loss of fat in the limbs, there is an accentuation of subcutaneous veins and an appearance of muscular hypertrophy

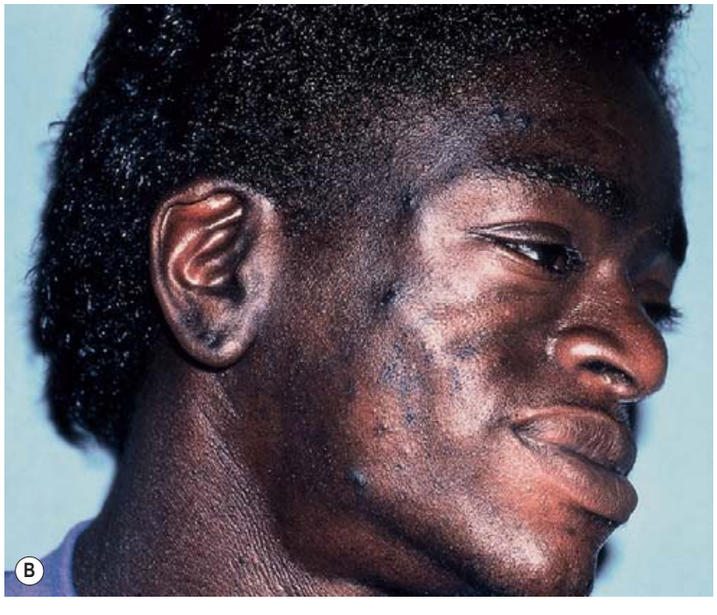


Fig. 101.4 Congenital generalized lipodystrophy syndrome. A Extensive acanthosis nigricans, facial and extremity lipodystrophy, and muscular habitus. **B** Close-up view demonstrating loss of Bichat's fat pad and buccal fat. *Courtesy, Kenneth E Greer, MD.*

FEATURES OF CONGENITAL GENERALIZED LIPODYSTROPHY
LIPODYSTROPHIC FEATURES
• Lack of Bichat's fat pad in the preauricular region, resulting in a cadaveric facies • MRI studies show near total absence of subcutaneous fat and other metabolically active adipose tissues • Preservation of fat deposits in "mechanical" sites (type 1): orbit, palms, soles, tongue, breasts, vulva and in periarticular and epidural regions • Muscular body habitus due to the extreme paucity of subcutaneous fat
ANABOLIC SYNDROME
• Muscular hypertrophy with prominent superficial veins • Acromegalic facial and acral features • Voracious appetite • Increased basal metabolic rate • Heat intolerance • Accelerated growth with a normal to slightly increased adult height • Advanced bone and dental age • Osteosclerotic and lytic skeletal changes • Masculine features in females (clitoromegaly rare) • Enlarged genitalia (usually limited to infancy and childhood)
METABOLIC DISTURBANCES
• Insulin resistance and severe fasting or postprandial hyperinsulinemia from early infancy • Insulin levels may decrease after several years, due to exhaustion of pancreatic β cells • Very insulin-resistant diabetes mellitus: noted at puberty with growth cessation • Impaired glucose tolerance is noted around age 8–10 years • Hypertriglyceridemia and sequelae (chylomicronemia, pancreatitis) • Hyperlipidemia accelerates at puberty (with growth cessation) • Low HDL-cholesterol levels (accurate assessment may be hindered by the increased TGs) • Low plasma leptin levels, corresponding to decreased body fat
DERMATOLOGIC MANIFESTATIONS
• Acanthosis nigricans (AN), often early onset and widespread • Hypertrichosis, including increased (often curly) scalp hair at birth • Hyperhidrosis • Coarse skin on the upper body • Hyperkeratotic epidermal papillomatosis (may represent an exaggerated form of AN) • Xanthomas
GYNECOLOGIC DISTURBANCES
• Oligomenorrhea • Polycystic ovaries • Infertility (females)
ORGANOMEGALY AND ORGAN DYSFUNCTION
• Hypertrophic cardiomyopathy (often fatal) • Fatty liver, hepatomegaly, cirrhosis, liver failure • Organomegaly: tonsils and adenoids, lymph nodes, spleen, kidneys, adrenals, pancreas, ovaries • Central nervous system abnormalities: hypothalamic–pituitary dysfunction, ventricular dilation, below average intelligence, +/– mild mental retardation • Proteinuric nephropathy

Table 101.3 Features of congenital generalized lipodystrophy[2,35]. HDL, high-density lipoprotein; TG, triglyceride.

Fig. 101.5 Lipoatrophy of the lower extremities, leading to the appearance of muscular hypertrophy. *Courtesy, William D James, MD.*

(Fig. 101.5). Although FPLD associated with mutations in *PPARG* has milder clinical features and an onset after the second decade of life, the metabolic disturbances may be more severe[35].

Metabolic disturbances in FPLD are similar to those in the generalized lipodystrophy syndromes. Glucose intolerance, ranging from mild to severe, develops during young adulthood. Acute pancreatitis and hepatic steatosis and cirrhosis may occur, with complications from diabetes mellitus, atherosclerotic cardiovascular disease or hypertrophic cardiomyopathy leading to premature death. When compared to men, affected women have been reported to have more severe triglyceride elevations. Dermatologic manifestations include tuberous xanthomas, acanthosis nigricans and hirsutism, while gynecologic findings include menstrual irregularities, polycystic ovaries, and fat hypertrophy within the labia majora.

Familial partial lipodystrophy with mandibuloacral dysplasia is a rare variant of partial lipodystrophy characterized by mandibular and clavicular hypoplasia, short stature, a high-pitched voice, and ectodermal abnormalities of the skin, teeth, nails and hair[23,35]. There are multiple craniofacial defects, including dental overcrowding and a bird-like facies with prominent eyes and a beaked nose. Skeletal abnormalities include osteolysis of the clavicles, acro-osteolysis, delayed closure of cranial sutures and joint contractures. Mottled hyperpigmentation, alopecia, atrophy of extremity skin and nail dysplasia are the characteristic cutaneous findings. Less common clinical features include sensorineural hearing loss, delayed puberty, a high-arched palate and cutaneous calcinosis. Features of the metabolic syndrome may be present (see Ch. 53).

Acquired generalized lipodystrophy

To date, approximately 80 cases of acquired generalized lipodystrophy (AGL; Lawrence or Lawrence–Seip syndrome) have been reported in the English literature. New diagnostic criteria for AGL have been proposed, as well as a subclassification into three subtypes (Table 101.4).

In approximately one-third to one-half of patients, there is a preceding systemic illness, in particular a viral or bacterial infection or an autoimmune disorder (e.g. a connective tissue disease, thyroiditis)[35]. Clinical features of AGL are similar to those of the congenital variant, but are of later onset and milder. The lipoatrophy typically does not become apparent until childhood or adolescence and rarely develops during adulthood; the disorder is approximately three times more common in women. Large areas of the face, trunk and extremities have fat loss (Fig. 101.6), and the palms and soles may even be involved. Loss of peripheral fat as well as perinephric and intra-abdominal fat can be documented by MRI scans, whereas bone marrow fat is preserved; the latter feature may be helpful in differentiating AGL from CGL.

Tender subcutaneous nodules of panniculitis may precede the lipoatrophy in the type 1 variant and there may be an overlap in the panniculitic and autoimmune varieties. Progression may occur rapidly or over an extended period. When the lipodystrophy becomes generalized, the systemic abnormalities become manifest. The extent of fat loss is closely related to the severity of insulin resistance and hypertriglyceridemia.

The associated metabolic syndrome is generally less severe than with CGL, in contrast to the liver sequelae, which are often lethal. The latency before the development of frank diabetes is shorter than with the congenital variant, that is, approximately 4 years after the loss of fat. If preceded by panniculitis, there may be less severe fat loss and a lower prevalence of diabetes and hypertriglyceridemia than with the other two varieties (see Table 101.4)[26]. The anabolic syndrome is

ACQUIRED GENERALIZED LIPODYSTROPHY: PROPOSED DIAGNOSTIC CRITERIA AND SUBTYPES

ESSENTIAL CRITERION

Selective loss of fat involving large regions of the body beginning during childhood or adolescence

SUPPORTIVE CRITERIA

Clinical
- Loss of subcutaneous fat from the palms and soles
- Acanthosis nigricans
- Hepatosplenomegaly
- Panniculitis prior to onset (by clinical history and/or histologic confirmation; see below)
- Associated autoimmune diseases (see below)

Laboratory
- Diabetes mellitus or impaired glucose tolerance
- Severe hyperinsulinemia (fasting and/or postprandial)
- Increased serum triglyceride and/or decreased HDL-cholesterol levels
- Reduced serum leptin and/or adiponectin levels
- Anthropometric or MRI evidence of large regions of fat loss
- MRI evidence of preserved bone marrow fat

SUBTYPES

Panniculitic variant (type 1)
- Panniculitis precedes the onset of lipoatrophy, which may be noted in the center of expanding annular lesions or at distant sites
- Mean age of onset is 7 years; slight female predominance (~1.5-fold)
- Associated symptoms include low-grade fever, malaise, arthralgias and abdominal pain
- May be associated with autoimmune diseases (see below)
- Relatively mild metabolic derangements and leptin abnormalities
- Histopathologic evaluation reveals a lymphohistiocytic subcutaneous infiltrate ± granulomatous foci

Autoimmune variant (type 2)
- Concurrent or prior autoimmune disease without preceding panniculitis; associated with juvenile dermatomyositis, Sjögren's syndrome, juvenile idiopathic arthritis, vitiligo, chronic urticaria/angioedema and autoimmune thyroiditis, hepatitis or hemolytic anemia
- Mean age of onset is 15 years; female predominance (~3-fold)
- Hepatomegaly is invariably present; hypertriglyceridemia and diabetes mellitus occur in most patients
- Laboratory abnormalities may be observed without clinical evidence of autoimmune disease, including antinuclear, anti-smooth muscle, anti-glomerular basement membrane, anti-salivary duct, antimitochondrial and anti-adrenal/ovary/placenta/testis antibodies

Idiopathic (type 3)
- No evidence of panniculitis or autoimmune disease
- Mean age of onset is 20 years (range, <2–60 years); female predominance (~3-fold)

Table 101.4 Acquired generalized lipodystrophy: proposed diagnostic criteria and subtypes. Adapted from reference 26.

variable and less prominent; its severity is less striking when the condition starts in later childhood or adulthood. Hepatic steatosis is commonly present in affected children, leading to a higher incidence of hepatomegaly, cirrhosis and liver-related mortality in AGL than in CGL. Gynecologic abnormalities include true or pseudo-clitoromegaly (the latter due to fat loss), polycystic ovarian syndrome, and menstrual irregularities. Premature coronary artery disease and carotid or peripheral vascular disease may occasionally be seen. Renal and central nervous system abnormalities are usually absent. Dermatologic features, in addition to panniculitis and lipoatrophic areas, include acanthosis nigricans, localized or generalized hyperpigmentation, eruptive xanthomas, telangiectases, mild palmar/plantar keratoderma, and hair abnormalities, including mild hirsutism, curly hair and occasional alopecia. The acanthosis nigricans begins in childhood and involves the neck, axillae, groin, umbilicus and nipples. Associated autoimmune diseases include juvenile dermatomyositis, Sjögren's syndrome, vitiligo, chronic urticaria and angioedema (see Table 101.4).

Fig. 101.6 Acquired generalized lipodystrophy. There is loss of subcutaneous fat, resulting in a muscular appearance of the legs and accentuation of the tendons. *Courtesy, Jacqueline Junkins-Hopkins, MD.*

Acquired partial lipodystrophy

Acquired partial lipodystrophy (Barraquer–Simons syndrome, progressive lipodystrophy, cephalothoracic lipodystrophy) is the most common type of non-localized lipodystrophy other than HIV/ART-related lipodystrophy. It has been reported worldwide, with more than 250 patients described in the literature[35,38].

Three phenotypic subtypes have been noted: (1) fat loss in the upper half of the body; (2) fat loss in the upper half of the body, with hypertrophy of adipose tissue in the lower half; and (3) hemilipodystrophy, where one half of the face or body is affected.

Lipodystrophy begins during childhood or pre-puberty (median age of diagnosis, 8–10 years), at times after a viral illness; it is characterized by a symmetric and insidious but progressive loss of subcutaneous fat in a cephalocaudal fashion starting on the face (Fig. 101.7) and scalp, and extending down to the pelvic girdle and mid thighs. Progression usually occurs within a 1–2-year period, but can occur over many years. Physical findings may be apparent by the teen years, although the onset may be delayed until 40 years of age. Women are affected three times more often than men.

The face is usually affected first, with sunken eyes due to loss of retro-orbital and periorbital tissue as well as loss of the preauricular (Bichat's) fat pads, resulting in a progeria-like or cadaveric appearance (Fig. 101.8). The hips and legs tend to be spared, and often demonstrate fat hypertrophy, especially in women. Growth delay or stunted growth is not characteristic of this disorder.

MCGN II with nephritic syndrome, seen in approximately one-fifth of patients, may occur many years, usually about eight, after the onset of lipodystrophy. Almost all patients with acquired partial lipodystrophy have low levels of C3 in addition to circulating C3 nephritic factor (C3NeF), composed of polyclonal IgG. This leads to unopposed activation of the alternative complement pathway (see above) and C3NeF-induced lysis of adipocytes. The low C3 level also predisposes these patients to recurrent *Neisseria meningitidis* infections and prophylactic antibiotics may be required.

Other autoimmune associations include systemic lupus erythematosus, juvenile dermatomyositis, scleroderma, Sjögren's syndrome, pernicious anemia, hypothyroidism, celiac disease, dermatitis herpetiformis, temporal arteritis and small vessel vasculitis. An association of acquired

Fig. 101.7 Acquired partial lipodystrophy syndrome in a patient with nephritic factor and renal disease. A Lipoatrophic features are most prominent on the face. **B** Closer view, demonstrating marked loss of buccal fat. Axillary acanthosis nigricans was present. *Courtesy, Kenneth E Greer, MD.*

Fig. 101.8 Acquired partial lipodystrophy syndrome in a patient with Sjögren's syndrome. Lipoatrophy of the face with sunken eyes and loss of temporal and preauricular (Bichat's) fat pads. The facial pigmentation is related to lichen planus. *Courtesy, Priya Sen, MD..*

Fig. 101.9 Lipoatrophy secondary to lupus panniculitis. A An area of depression on the cheek due to burnt-out lupus panniculitis; note the dyspigmentation and scarring from an overlapping lesion of discoid lupus erythematosus. **B** Circular depressions on the upper arm, a common location for lupus panniculitis. *A, Courtesy, National Skin Centre, Singapore.*

partial lipodystrophy with chronic sclerodermatous GVHD, POEMS syndrome and extrinsic allergic alveolitis have also been reported. CNS abnormalities such as mental retardation, epilepsy, and sensorineural deafness have been observed.

Metabolic syndrome is less common than in other lipodystrophies, but acanthosis nigricans, menstrual abnormalities, hirsutism, insulin resistance, type 2 diabetes mellitus, and hyperlipidemia may be seen.

Localized lipoatrophy

Localized lipoatrophy presents as one or multiple depressed areas (i.e. indentations), usually on the proximal extremities, ranging from under a few centimeters to greater than 20 cm in diameter. *Drug-induced lipoatrophy* is most commonly due to injections of corticosteroids and non-human insulin (see Table 101.2); it may be accompanied by local lipohypertrophy. Of note, multifocal lipoatrophy due to intravenous corticosteroid use has been described. *Involutional lipoatrophy* is an idiopathic lipoatrophy characterized clinically by non-inflammatory focal loss of fat. Based upon reported cases, there is a strong predominance of women. Focal oval areas of lipoatrophy, 2 to 8 cm in diameter, occur predominantly on the buttocks and proximal extremities, especially the upper arm, corresponding to locations frequently used as injection sites. Although it is estimated that up to 60% of cases of involutional lipoatrophy may be associated with prior local injections (see above), this type of lipoatrophy may occur without prior injections.

Atrophic connective tissue panniculitis is rare, and it often occurs on the upper or lower extremities. In "pure" cases of this condition, there is no prior clinical inflammation although there is evidence histologically of lymphocytic panniculitis. In other patients, the lipoatrophy may be the direct result of clinical panniculitis. The latter is common on the head and neck or proximal extremities if associated with lupus panniculitis (also referred to as lupus profundus; Fig. 101.9). Other associated autoimmune diseases include dermatomyositis, thyroiditis, juvenile idiopathic arthritis, vitiligo, and insulin-dependent diabetes mellitus.

Lipoatrophia semicircularis (semicircular lipoatrophy) has been reported primarily in women in their 20s to 30s and rarely in children. It presents as symmetric, asymptomatic, 4–8 cm linear horizontal depressions on the anterolateral thighs (see Fig. 101.2). Infrequent presentations include two or three parallel depressions, a unilateral distribution, or symptoms of cramps, pain after sports, heavy legs, or a burning sensation. The lesions usually appear over a few weeks and spontaneously resolve between 9 months to 4 years. The lipoatrophy may recur. MRI can assist in differentiating this from an inflammatory panniculitis.

Annular lipoatrophy presents with a deep, persistent, pseudosclerotic band approximately 9–11 cm in length that encircles the arm or ankle[39]. More extensive lesions have recently been reported that were 14–16 cm in length. It may be preceded by tenderness and swelling of the limb, or associated with discomfort and arthritis. This entity may represent a variant or end-stage presentation of atrophic connective tissue disease panniculitis. Thus, there may be patients with associated autoimmune diatheses.

Lipodystrophia centrifugalis abdominalis infantalis (centrifugal lipodystrophy) has largely been reported from East Asia, in particular Japan[40]. Onset is usually before 3 years of age, with more than 90% of patients presenting by age 5 years. In Koreans, there is a fourfold female predominance[41]. Although lipodystrophia centrifugalis abdominalis infantalis affects primarily Asian children, it may occasionally occur in Caucasians and in adults. There is a well-demarcated area of lipoatrophy with a periphery of erythema and scale on the trunk or abdomen, associated with regional lymphadenopathy. The lipoatrophy begins on the lower abdomen or in the groin region (and may include the genitalia) in about 80% of patients, and in the axillary region in about 20% of patients; it spreads onto the abdomen or chest, respectively, in a centrifugal fashion (Fig. 101.10). The underlying blood vessels become visible and ulceration may occur within the depressed areas. Contrary to its original name, this condition can affect non-abdominal sites such as the face, neck and lumbosacral region, and it is not limited to infants (Fig. 101.11). The lesions progress slowly over several years and spontaneous resolution has been observed in over 50% of patients by their teens[40]. Rarely, the disorder persists into adulthood.

Progressive hemifacial atrophy (Parry–Romberg syndrome) may be considered a form of severe morphea (see Ch. 44), and may be accompanied by atrophy of the underlying cartilage and bone, with potential ophthalmologic and dental consequences.

Non-progressive late-onset linear hemifacial lipoatrophy occurs on the malar cheek, primarily in elderly individuals.

Fig. 101.10 Lipodystrophia centrifugalis abdominalis infantalis (centrifugal lipodystrophy). A 5-year-old Malay boy with a two-year history of progressive lipoatrophy involving the groin bilaterally and the lower abdomen. The veins in the involved area are readily visible. *Courtesy, National Skin Centre, Singapore.*

Fig. 101.11 Lipodystrophia centrifugalis infantalis (centrifugal lipodystrophy) of the face. A A 2-year-old girl with a serpentine violaceous band involving the cheek in association with lipoatrophy. **B** The same child 2 years later, with spontaneous resolution. The most common location for lipodystrophia centrifugalis infantalis is the abdomen (see Fig. 101.10). *Courtesy, National Skin Centre, Singapore.*

Inflammatory reactions due to material injected for cosmetic purposes or due to self-inflicted injections of foreign material can lead to lipoatrophy which may be associated with scarring and dyschromia.

Lipohypertrophy

Lipohypertrophy remains a frequent complication of insulin therapy, irrespective of the insulin source and mode of administration[42]. As with insulin lipoatrophy, anti-insulin antibodies are associated with lipohypertrophy in children and adolescents with type 1 diabetes. The clinical consequence is that injection of insulin into a site of lipohypertrophy, while painless, may lead to erratic absorption of the insulin, with the potential for poor glycemic control. Injection of pegvisomant, a growth hormone receptor antagonist used to treat acromegaly, is another cause of lipohypertrophy (Table 101.5).

Pathology

Generally speaking, the histologic picture of the various lipodystrophy syndromes (see Table 101.1) is non-inflammatory. In *generalized lipodystrophy*, there is complete or near-complete loss of subcutaneous fat, with the dermis and fascia in direct apposition. Less often, biopsy specimens appear to have no overt abnormalities, except for an increased amount of collagen, which has replaced the subcutaneous fat. In contrast, biopsies of *acquired generalized lipodystrophy*, in particular type 1, may show a lobular panniculitis (Fig. 101.12; see Table 101.4).

In *acquired generalized lipodystrophy* and areas of lipoatrophy in some forms of *partial lipodystrophy*, two histologic patterns have been recognized: (1) non-inflammatory with involutional changes of the fat; and (2) inflammatory in the form of a lobular panniculitis with lymphocytes, lipophages and plasma cells[43]. Whether these two patterns are stage-related remains to be clarified, as even in patients without panniculitis clinically, biopsies of early lesions may show inflammation, but it is usually mild.

Involutional changes of the subcutaneous fat are characterized by small fat lobules with a reduction in the size and number of adipocytes (Fig. 101.13). *Involutional lipoatrophy* can be further divided into two histologic subtypes[33]. In the first type, the lobules may be composed of faintly acidophilic, small fat cells that retract from one another as well as the surrounding connective tissue, leading to an appearance similar to embryonic fat; the lobules often have an eosinophilic appearance. These histologic findings are more prominent at the periphery of the clinically depressed area, with tiny acidophilic fat cells present more centrally. Inflammation is absent to sparsely mononuclear. The second type, with indistinguishable clinical features, shows small atrophic adipocytes with a normal fat cell membrane surrounded by prominent vasculature. At scanning magnification, the lobules are collapsed (with an orientation parallel to the skin surface) and surrounded by numerous capillaries. Acid mucopolysaccharide deposition within the fat lobules and fibrosis of the septae may be seen, as well as occasionally lipomembranous changes.

Although birefringent non-crystalline foreign material may be observed, foreign body giant cells and lipophages are typically absent in both subtypes of involutional lipoatrophy. $CD68^+$ macrophages can be demonstrated with immunohistochemical staining. Ultrastructural studies have shown that these are lysosomally active macrophages

CAUSES OF LIPOHYPERTROPHY
Insulin therapy – risk factors include duration of therapy, frequent injections, failure to rotate sites of injections, and poor injection technique
Pegvisomant (growth hormone receptor antagonist) injections*
Growth hormone injections
Excess corticosteroids – includes Cushing's disease (excessive ACTH production by the pituitary gland) and Cushing's syndrome (iatrogenic, adrenal tumors, nodular adrenal hyperplasia, ectopic ACTH production)
HIV/ART-associated – risk factors include extended exposure to nucleoside reverse transcriptase inhibitors, exposure to protease inhibitors, age ≥40 years, longer duration of therapy, higher body mass index before onset of therapy, and presence of metabolic derangements (elevated serum triglyceride and insulin levels; depressed serum testosterone levels)
*Used to treat acromegaly.

Table 101.5 Causes of lipohypertrophy.

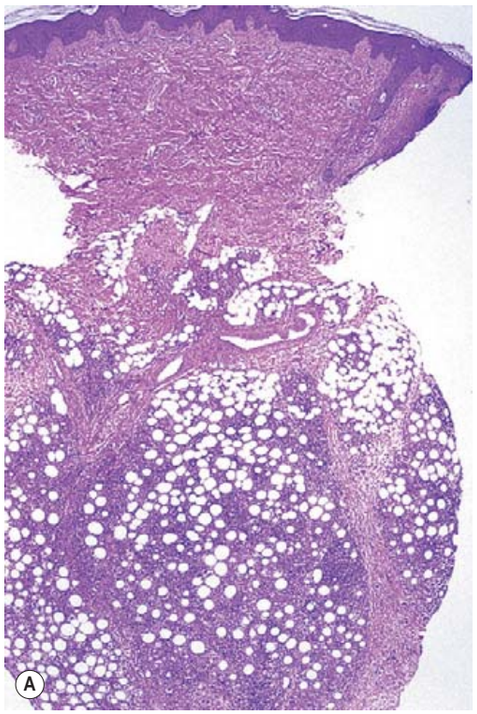
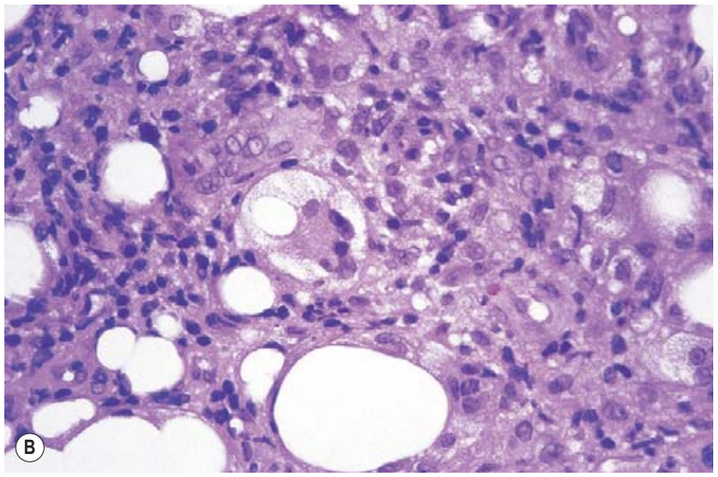
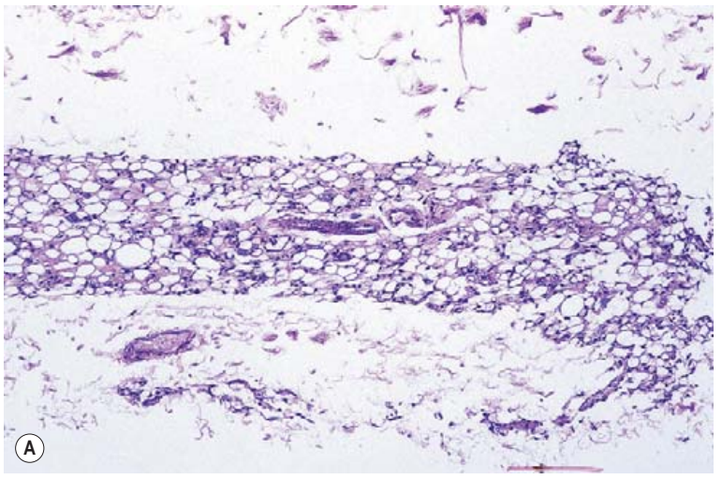


Fig. 101.12 Histopathologic features of the preceding panniculitis in type 1 acquired generalized lipodystrophy.
A, B Lobular panniculitis with infiltrate of lymphocytes, histiocytes, multinucleated giant cells, lipophages and phagocytized mucopolysaccharide. There is also microcystic alteration of the fat cells. *Courtesy, Jacqueline Junkins-Hopkins, MD.*





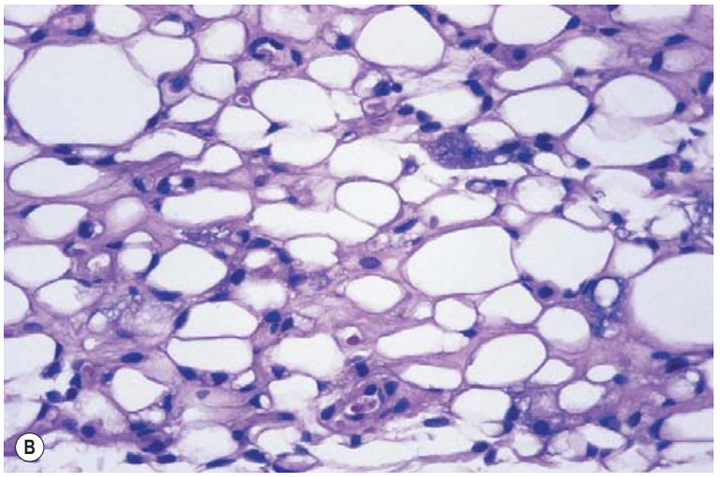


Fig. 101.13 Histopathologic features of involutional lipoatrophy secondary to corticosteroid injection. A There is marked diminution and collapse of the fat lobules, without inflammation. **B** Higher power demonstrates decreased size of fat cells with eosinophilic thickened cell walls with a hyalinized and mucinous stroma. *Courtesy, Jacqueline Junkins-Hopkins, MD.*

adjacent to lipocytes, and they may contain degenerated lipid[33]. In *localized lipodystrophy*, a loss of fatty tissue is seen, along with a variable degree of fibrosis. There is usually no inflammatory infiltrate, although panniculitis has been reported in a few cases. Deposits of immunoreactants can be seen within blood vessel walls or the basement membrane, particularly in the inflammatory type.

Histologically, well-developed areas of *lipodystrophia centrifugalis abdominalis infantilis* show a diminution of subcutaneous fat with scant or absent inflammation. The erythematous rim tends to correspond to a moderate or marked lymphohistiocytic infiltrate in the subcutaneous fat; a deep dermal and peri-eccrine lymphocytic infiltrate is an uncommon finding. There may be fibrosis and thickening of the septae within the subcutis. The few adipocytes that are present may have myxoid changes.

Other localized variants such as *lipoatrophia semicircularis* (semicircular lipoatrophy) and *drug-induced lipoatrophy* usually show a loss of fatty tissue and replacement by collagen, with no features of panniculitis. There are often scattered lipophages. Lastly, HIV/ART-associated lipodystrophy resembles the non-inflammatory pattern of lipodystrophy.

Differential Diagnosis

There are a variety of other complex syndromes that present with lipoatrophy along with a number of other physical and systemic features (see below). A detailed discussion of these syndromes is beyond the scope of this chapter.

The excessive fat accumulation seen in patients with familial partial lipodystrophy (Dunnigan variety) and HIV/ART-associated lipodystrophy could be confused with Cushing's syndrome. Acromegaly can have overlapping features with generalized lipodystrophy.

In an infant with generalized lipodystrophy, the following conditions should also be considered:

- *Leprechaunism* (Donohue syndrome) is included in some lipodystrophy classifications, as the patients present with generalized lipodystrophy, severe insulin resistance, acanthosis nigricans and hirsutism. In contrast to CGL, these patients have a distinct elfin facies, severe intrauterine growth retardation, prominent nipples, loose skin, a mutation in the insulin receptor gene, and death during infancy.
- *SHORT syndrome* (*s*hort stature, *h*yperextensible joints, *o*cular depression, *R*ieger anomaly [iridocorneal mesodermal dysgenesis], and *t*eething delay) is also included in some lipodystrophy classifications, as there is congenital lipoatrophy of the face and upper body. This is distinguished by the above-outlined associated abnormalities, intrauterine growth retardation, delayed bone age, and a dysmorphic facies which includes a triangular shape, micrognathia, deep-set eyes and anteverted ears. Carbohydrate metabolic abnormalities are rare to absent.
- *Progeria-type syndromes* are characterized by limb lipoatrophy, cardiovascular disease and diabetes, but they are accompanied by muscle wasting, sclerodermatous changes, cataracts and other signs of premature aging. Some of the progeric syndromes have

LMNA mutations similar to those associated with FPLD, and may be considered as part of a broader group of disorders, termed laminopathies (see Table 63.9).
- In *Cockayne syndrome*, lipoatrophic changes are accompanied by growth delay, retinal abnormalities, photosensitivity and defects in DNA repair (see Chs. 63 & 87).
- *AREDYLD syndrome*: congenital generalized lipoatrophic diabetes is associated with an acrorenal field defect and ectodermal dysplasia.

Localized lipodystrophies should be differentiated from initial phases of progressive lipodystrophy, morphea, lupus panniculitis, and atrophoderma of Pasini and Pierini. Although there is overlap amongst the various types of localized lipodystrophy, the distribution and morphology combined with a history of injections, the presence clinically or histologically of panniculitis, and associated autoimmune disorders may aid in the diagnosis.

Poland syndrome is a rare congenital disorder consisting of unilateral partial or total absence of a breast and/or pectoralis major muscle, and ipsilateral symbrachydactyly, which may simulate lipoatrophy. Lastly, MRI can help to differentiate loss of fat from other causes of localized depressions of the skin.

Treatment

Management issues for lipodystrophy syndromes are threefold: (1) cosmetic concerns; (2) metabolic derangements; and (3) systemic associations. Also, with better elucidation of the genetic basis of the various inherited lipodystrophy syndromes (see Table 101.1), determination of the underlying genetic mutation can have important implications for prognosis and genetic counseling.

Treatment options for the physical aspects of lipodystrophy are limited (see below). Localized lipodystrophy may resolve spontaneously, depending on the etiology and/or subtype. In trauma-induced cases, in particular lipoatrophia semicircularis, the depressions may normalize over a period of weeks. Switching to purified human insulin may improve insulin lipoatrophy, but it may take 1–3 years[42].

Surgical treatment has had variable and limited success. Persistent facial lipoatrophy may be amenable to flaps. Soft tissue augmentation using a variety of permanent and non-permanent fillers may be helpful (see Ch. 158). Solid synthetic volumetric midfacial implants, constructed using computer-aided design and manufacturing technology[44], may offer a more durable correction of the defects. A thoughtful assessment of possible long-term complications of permanent fillers is always mandatory prior to treatment. Fat transplantation via lipoinjection may also help facial defects[45].

While medical therapy is directed predominantly at the metabolic derangements in order to reduce the associated morbidity and mortality, it may also offer some benefit for the lipodystrophic features. Thiazolidinediones (TZDs; also referred to as glitazones), which are PPAR-γ agonists, have been used to increase insulin sensitivity, increase body fat, improve adipocytokine levels and lower triglyceride levels[46]. However, there have been concerns regarding the adverse side effects of this group of drugs, e.g. troglitazone was withdrawn from the market due to hepatotoxicity. In the US, prescribing the newer TZD rosiglitazone requires enrollment in a controlled access program and pioglitazone may exacerbate heart failure and increase the risk of bladder cancer. Fibrates are PPAR-α agonists that increase fatty acid oxidation and have been used to treat hypertriglyceridemia. Omega-3 polyunsaturated fatty acids can also lower circulating triglyceride levels by reducing hepatic triglyceride synthesis via competitive inhibition. To date, controlled trials supporting the efficacy of these various drugs in inherited lipodystrophies are lacking.

Therapy has also been targeted at the adipokine abnormalities, such as leptin deficiency. Treatment with recombinant methionyl human leptin (r-metHuLeptin) for generalized lipodystrophy, both congenital and acquired forms, has resulted in an improvement of glycemic control, hyperlipidemia, hepatomegaly, and diabetic complications such as proteinuria. The therapy is generally well tolerated, with no notable serious adverse effects[47,48]. Improvement has been documented after only 4 months of therapy[49]. In addition to correcting the metabolic derangements, leptin replacement may improve appetite regulation. With long-term treatment, benefits have been shown to persist[47].

Nutritional alteration (e.g. low-fat diet), exercise, and a weight-management program can further improve the hyperlipidemia and hyperglycemia. Management by an endocrinologist is recommended.

Acquired partial lipodystrophy

Management of patients with acquired partial lipodystrophy should include initial evaluation and continued monitoring for autoimmune disease (such as lupus and dermatomyositis), thyroid disease and renal disease. The latter should include evaluation for proteinuria, low C3, and C3 nephritic factor (C3NeF), and, if necessary, renal biopsy to exclude MCGN.

The presence of neutralizing antibodies against C3NeF in IVIg has led to treatment of a patient with MCGN II and C3NeF with IVIg, with encouraging results[50].

Genetic counseling should be considered for the familial variants.

Insulin lipodystrophy

While the incidence of insulin lipoatrophy has decreased significantly with the advent of purified human insulin, some patients may be injecting other forms. Switching to human insulin and changing the mode of delivery are helpful interventions (see above). For prevention, constant rotation of injection sites, such that the same site is not used more often than once a month, is recommended. Liposuction may lead to improvement in the hypertrophic form.

HIV/ART-ASSOCIATED LIPODYSTROPHY

HIV/ART-associated lipodystrophy has become the most common form of non-localized lipodystrophy. It is linked in particular to protease inhibitors (PI) and nucleoside analogue reverse transcriptase inhibitors (NRTIs), affecting up to 40% of patients within 1 to 2 years of initiation of ART[51].

The clinical findings in HIV/ART-associated lipodystrophy include:
- lipoatrophy of peripheral sites, primarily the face, limbs, heel pads, and buttocks
- central lipohypertrophy or adipose tissue accumulation, especially dorsocervical, supraclavicular, within the breasts, intra-abdominal and visceral (e.g. liver)
- metabolic abnormalities – insulin resistance, type 2 diabetes, dyslipidemia, hypertension, lactic acidosis.

The progressive body changes resulting from a combination of lipoatrophy and lipohypertrophy can be disfiguring and potentially stigmatizing, resulting in a loss of adherence to ART[52].

Pathogenesis

The etiology of HIV/ART-associated lipodystrophy is multifactorial and includes multiple sites of drug actions in metabolic pathways and within different tissues, all in a complex interplay with host-specific factors such as age, genetics, severity of HIV infection, and inflammatory states[52]. Proposed mechanisms for ART-induced subcutaneous fat loss include:
- impaired pre-adipocyte differentiation and increased adipocyte apoptosis[53,54]
- impaired insulin-stimulated lipogenesis and increased lipolysis[53], leading to decreased adipocyte size
- mitochondrial toxicity[55] (see Table 101.6 & Fig. 101.14).

HIV/ART-related lipodystrophy was initially considered a PI-mediated disease, but exposure to thymidine analogue NRTIs has been identified as an independent and significant risk factor for its development. In particular, stavudine, didanosine and zidovudine were more strongly associated with lipoatrophy[55,58].

Inhibition of DNA polymerase-γ within mitochondria is the proposed major site of action of NRTIs, leading to the mitochondrial dysfunction that has been observed in several tissues, including adipose tissue[55]. Of note, the latter has a high concentration of mitochondria. When the NRTI-induced mitochondrial DNA depletion reaches a threshold, this results in decreased adipocyte size[54] and increased adipocyte death, culminating in the development of lipoatrophy. Interference with the function of the respiratory chain complexes leads to impaired fatty acid

MECHANISMS OF ANTIRETROVIRAL THERAPY (ART)-ASSOCIATED LIPOATROPHY			
	HIV drugs implicated	**Drug-induced effect**	**Cellular response**
↓ Adipocyte differentiation*	PIs, NRTIs	Defect in lamin A/C processing and/or RXR-PPAR-γ heterodimer activation decreases function of SREBP-1c & other downstream transcription factors	↓ Production of new mature fat cells → ↓ fat cell number
↑ Adipocyte apoptosis*	PIs, NRTIs	↑ TNF-α signaling (as well as mechanism described above for ↓ differentiation)	↑ Fat cell death → ↓ fat cell number
↑ Lipolysis*	PIs, NRTIs	↓ Expression of perilipin	↑ Release of stored TGs as FFAs and glycerol into circulation → ↓ fat cell size
↓ Lipogenesis	PIs, NRTIs	↓ Expression and function of lipogenic SREBP-1c	↓ FFA uptake by adipocytes → ↓ fat cell size
Mitochondrial toxicity	NRTIs	Inhibition of mitochondrial DNA polymerase-γ	↑ Catabolic pathways (lipolysis), altered production of hormones and cytokines (↓ adiponectin, ↑ TNF-α), ↓ adipocyte differentiation, ↑ adipocyte apoptosis
*Also represent sequelae of mitochondrial toxicity.			

Table 101.6 Mechanisms of antiretroviral therapy (ART)-associated lipoatrophy. From refs 53–57. FFA, free fatty acids; HIV, human immunodeficiency virus; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PPAR-γ, peroxisome proliferator-activated receptor-γ; RXR, retinoid X receptor; SREBP-1c, sterol regulatory element-binding protein-1c; TG, triglycerides; TNF-α, tumor necrosis factor-α.

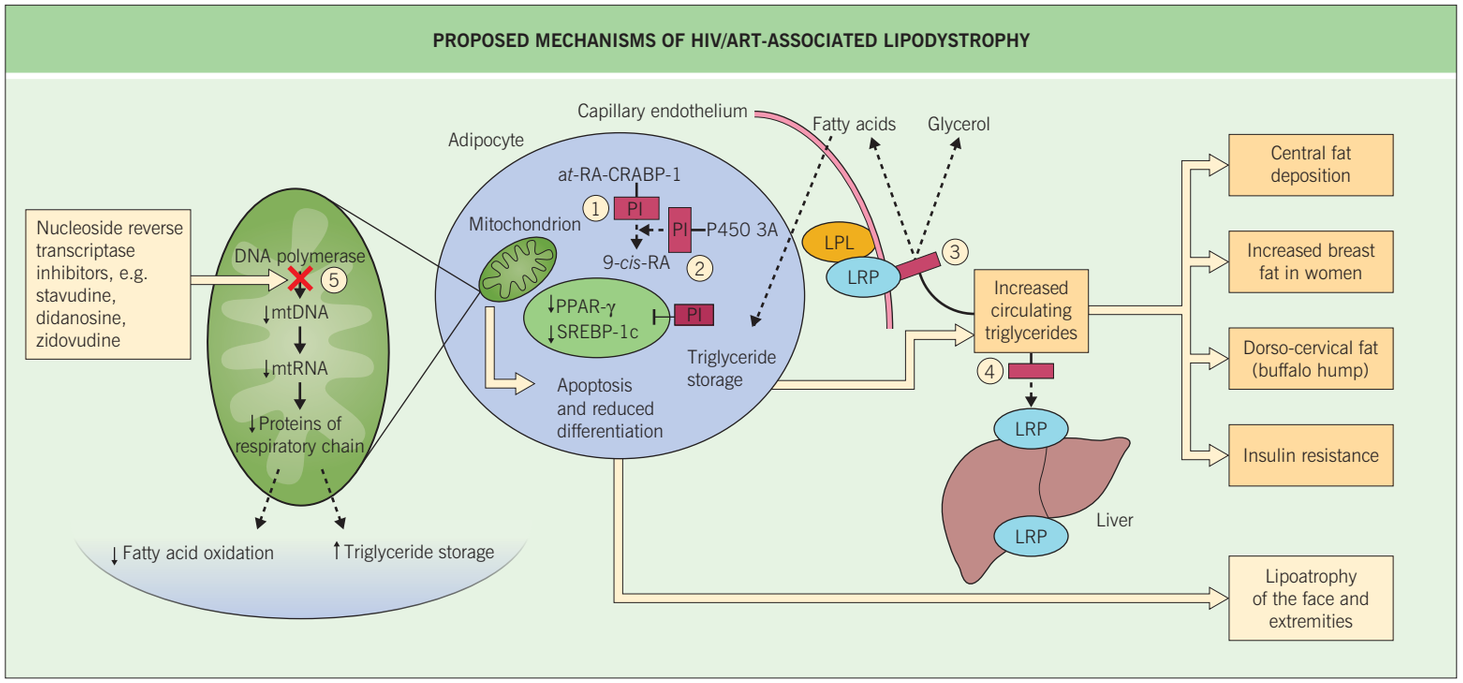


Fig. 101.14 Proposed mechanisms of HIV/ART-associated lipodystrophy. The combination of decreased PPAR-γ expression and decreased fatty acid oxidation capacity resulting from drug exposure could explain how these drugs cause adipocyte toxicity and lipoatrophy. ART, anti-retroviral therapy; *at*-RA, all-*trans*-retinoic acid; CRABP-1, cytoplasmic retinoic acid binding protein type 1; LPL, lipoprotein lipase; LRP, low-density lipoprotein receptor-related protein; mtRNA, mitochondrial RNA; mtDNA, mitochondrial DNA; PPAR-γ, peroxisome proliferator-activated receptor-γ; PIs, protease inhibitors; RXR, retinoid X receptor; SREBP-1c, sterol regulatory element-binding protein-1c. *Adapted from Carr A. HIV protease inhibitor-related lipodystrophy syndrome. Clin Infect Dis. 2000;30:S135–42.*

oxidation and intracellular accumulation of triglycerides and lactate, which can then enter the systemic circulation (see Fig. 101.14).

PIs cause adipose toxicity via their effects on *s*terol *r*egulatory *e*lement-*b*inding *p*roteins (SREBP) which function as transcription factors. In part, PIs prevent the cellular maturation of the SREBP-1c isoform to its active form in adipocytes[56], resulting in impairment of intracellular fatty acid and glucose metabolism as well as adipocyte differentiation (see Table 101.6). In addition, PIs decrease the expression of peroxisome proliferator-activated receptor-γ (PPAR-γ) and this can also lead to a reduction in differentiation of adipocytes[57]. These regulators of lipid metabolism, SREBP-1 and PPAR-γ, are linked through PPAR-γ coactivator-1. Decreases in PPAR-γ expression correlate with decreases in mitochondrial RNA expression, again providing a link between NRTI-induced mitochondrial toxicity and lipoatrophy. PPAR-γ expression is also decreased by the HIV viral protein R (vpr), lending support to a direct role of HIV itself in the pathogenesis of lipodystrophy.

Clinical Features

As in hereditary lipodystrophy syndromes, fat redistribution may precede the development of metabolic complications. HIV/ART-associated lipodystrophy usually has its onset during the first 6 to 12 months after commencing therapy. In cross-sectional studies using DEXA scans and computed tomography, a 14–65% prevalence of central lipohypertrophy was noted within 1 to 2 years of initiation of ART[60].

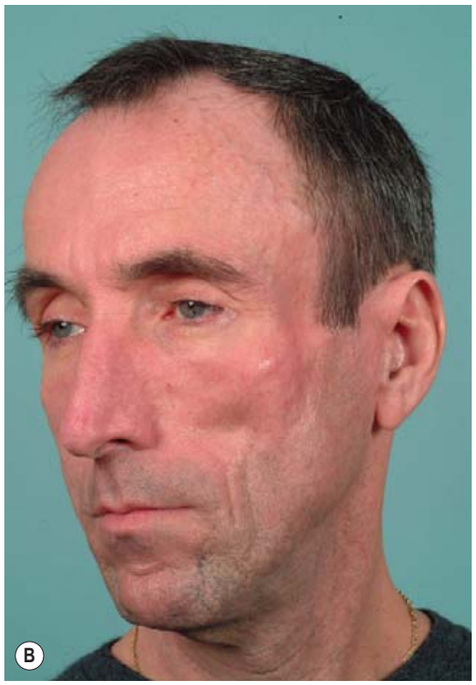


Fig. 101.15 HIV/ART-associated lipodystrophy. **A** There is symmetric loss of buccal, parotid and preauricular (Bichat's) fat pads, resulting in prominent zygomata, sunken eyeballs, and a cachectic appearance. **B** The side view highlights the loss of temporal fat. *Courtesy, Ken Katz, MD.*

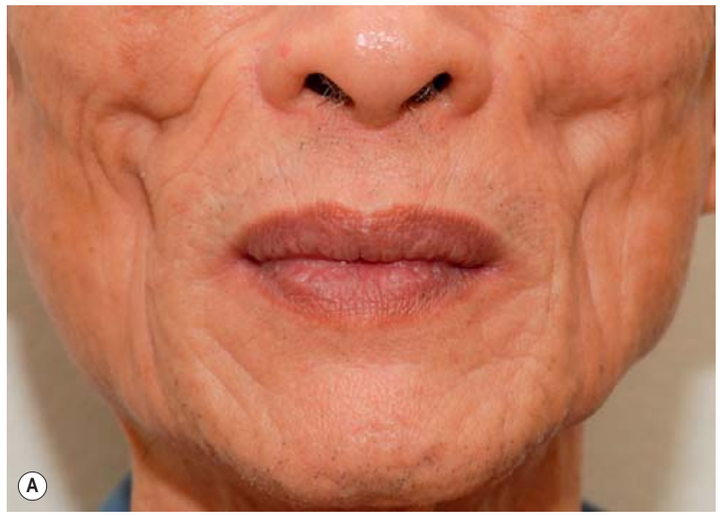


Fig. 101.16 HIV/ART-associated lipodystrophy. A Marked indentation of the medial cheeks in an older patient, with redundant melolabial folds. **B** Lower extremities with prominent veins and defined musculature. *A, Courtesy, Priya Sen, MD.*

However, patient self-report, in concert with physician examination, still remains the earliest and best indicator of body shape change.

Peripheral lipoatrophy occurs primarily in the face (Figs 101.15 & 101.16A), limbs (Fig. 101.16B), buttocks and heel pads. The loss of subcutaneous facial fat, in particular within the buccal, parotid and preauricular (Bichat) fat pads, results in prominent zygomata, sunken eyes, deepened and redundant melolabial folds, and a cachectic facies. Central lipohypertrophy presents as: (1) an accumulation of intra-abdominal fat (omental, mesenteric, retroperitoneal), resulting in abdominal protrusion ("protease paunch"; "Crix belly"); and/or (2) increased fat deposition within the dorsocervical fat pad ("buffalo hump"), breasts (gynecomastia in men, larger breasts in women), anterior neck and/or lateral mandibular region, and the muscles and liver. Lipoma formation has also been noted, and the presence of a "buffalo hump" has been shown to be associated with insulin resistance and diabetes mellitus. Of note, the cross-sectional Fat Redistribution and Metabolic Change in HIV Infection (FRAM) study found no correlation between changes in central fat and peripheral fat in HIV-infected men[59].

The use of different combinations of drugs in ART may lead to distinct clinical syndromes of fat redistribution. For example, PIs are more frequently associated with central fat hypertrophy and metabolic derangements, whereas treatment with NRTIs (stavudine in particular) is a stronger independent risk factor for the development of peripheral fat wasting and lipoatrophy. In addition, multiple NRTI-induced complications related to mitochondrial toxicity, including myopathy, polyneuropathy, liver steatosis, pancreatitis, hyperlactatemia, bone marrow toxicity and a Fanconi-like syndrome, can also develop.

HIV-related lipodystrophy is clearly associated with metabolic abnormalities[61], including insulin resistance, diabetes, dyslipidemia (hypertriglyceridemia, decreased high-density lipoproteins), and bone disorders, e.g. osteopenia, osteoporosis and avascular necrosis. Insulin resistance in HIV/ART-associated lipodystrophy arises via direct effects

of PIs on insulin-mediated whole-body glucose uptake as well as the indirect effects of dyslipidemia, mitochondrial toxicity, and changes in body composition on whole-body insulin sensitivity. Adipocytokines, in particular leptin and adiponectin, affect insulin sensitivity and low levels of both factors have been observed in HIV/ART-associated lipodystrophy[5,9]. In HIV-infected patients receiving ART, the prevalence of metabolic syndrome has been reported to be 16–24%, resulting in an increased risk for cardiovascular disease[62]. The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study found a 26% increase in the rate of myocardial infarction per year of ART during the first 4–6 years of exposure[63].

The most common significant risk factors for the development of lipoatrophy or lipohypertrophy are age (>40 years), disease severity at the onset of therapy (CD4 count <200/μl; higher nadir viral load), and longer duration of therapy with either PIs and/or NRTIs[60,64]. The risk of developing lipoatrophy appears higher in individuals with less subcutaneous fat pre-ART, whereas fat accumulation is more likely in those with more fat at baseline. Combination therapy consisting of two NRTIs and a PI has a strong association with severe lipoatrophy, and HIV-infected men have a lower risk of presenting with lipohypertrophy than do women[51]. In summary, the body fat changes in HIV/ART-associated lipodystrophy reflect an interplay of multiple influences: type of ART prescribed, viral-induced effects, and other host factors.

Treatment

The use of ART has significantly reduced HIV morbidity and mortality; however, the morphologic changes of lipodystrophy are quite stigmatizing and can cause pain, disability and psychosocial distress. Unfortunately, this can result in reduced compliance or even discontinuation of an effective therapeutic regimen. Lipoatrophy, once established, is largely irreversible in the majority of patients and it remains the most difficult manifestation of the lipodystrophy syndrome to manage.

HIV/ART-associated lipoatrophy

In antiretroviral therapy-naïve patients, selection of initial regimens that are less frequently associated with lipoatrophy can reduce the incidence of lipodystrophy. When initial regimens include tenofovir/emtricitabine as opposed to zidovudine/lamivudine, there is less lipoatrophy[65]. In both the RAVE[66] and MITOX[67] studies, switching from a thymidine analogue to either tenofovir or abacavir significantly improved peripheral lipoatrophy of the limbs, although there was no difference in visceral adipose tissue or buffalo hump development. Metabolic parameters improved following a switch to tenofovir, with modest reductions in serum levels of total cholesterol, low-density lipoproteins and triglycerides.

In general, the use of systemic medications to reverse the lipoatrophy has been disappointing. For example, even though the thiazolidinedione rosiglitazone, a PPAR-γ agonist, can reverse *in vitro* the block in adipocyte differentiation induced by PIs, randomized controlled studies have shown that rosiglitazone did not improve fat mass in HIV/ART-associated lipoatrophy. It actually worsened the dyslipidemia, despite an improvement in insulin sensitivity and adiponectin levels[68].

This lack of a beneficial effect on lipoatrophy was independent of background therapy. Use of pioglitazone, which unlike rosiglitazone is metabolized by cytochrome P450 3A4 enzymes, has shown some increase in limb fat. In vitro, uridine supplementation can abrogate thymidine analogue-induced adipocyte toxicities. Pilot studies have shown increases in fat mass in patients who take uridine supplements while continuing the thymidine analogues[69].

Particularly stigmatizing is the emaciated facies of facial lipoatrophy, and injectable fillers can help restore the facial fullness that has been lost. In 2004, the FDA approved poly-L-lactic acid fillers for this indication. Even though the lipoatrophic process is ongoing, facial volume can be restored by increasing the thickness of the dermis and the effects may last up to 2 years. Injectable calcium hydroxylapatite has also been FDA-approved for the treatment of HIV/ART-associated lipoatrophy. Its effects last up to 12 months. These fillers are generally safe and well tolerated, with nodule formation being a possible long-term complication. The transfer of autologous fat to the face also leads to improvement, but a donor site may be lacking in patients with significantly reduced body fat.

HIV/ART-associated lipohypertrophy

Switching from a PI to an alternative antiretroviral regimen has not been shown to reverse visceral abdominal fat accumulation. Diet and exercise modifications reduce overall and truncal fat, but as in the general population, adherence to these lifestyle changes is difficult. Use of thiazolidinediones, metformin and testosterone has not shown any beneficial effect on visceral adipose tissue.

Patients with central lipohypertrophy have reduced growth hormone secretion, reduced response to growth hormone-releasing hormone, and increased somatostatin tone (which inhibits growth hormone secretion). As a result of these findings and the known fat-oxidizing and lipolytic properties of growth hormone, the use of daily subcutaneous injections of recombinant growth hormone was investigated. There was some evidence of a reduction in both visceral adipose tissue and abdominal subcutaneous fat; however, its use was associated with a loss of peripheral limb fat and insulin resistance. There was no clear reduction in cardiovascular risk[70]. Liposuction may be beneficial, especially for dorsocervical and submental fat accumulation.

Metabolic derangements

The metabolic derangements in HIV/ART-associated lipodystrophy may be severe and unresponsive to intervention. Patients should be screened and assessed for dyslipidemia, diabetes mellitus, hypertension and change in body shape at regular intervals. Diet, exercise and cessation of smoking may improve metabolic parameters and reduce cardiovascular risk. Serum low-density lipoprotein (LDL) levels are used to monitor the need for further interventions. The latter include switching to antiretroviral drugs with no adverse effect on circulating lipid levels and the initiation of lipid-lowering medication(s). Statins are recommended as first-line therapy for reducing elevated LDL-cholesterol levels. Fibrates (gemfibrozil, fenofibrate) are recommended when there is an elevation in both LDL-cholesterol and triglyceride levels. Metformin and glitazones are used to manage type 2 diabetes[70].

REFERENCES

1. Mitchell SW. Singular case of absence of adipose matter in the upper half of the body. Am J Med Sci. 1885;90:105–6.
2. Seip M, Trygstad O. Generalized lipodystrophy, congenital and acquired (lipoatrophy). Acta Paediatr Suppl. 1996;413:2–28.
3. Carr A, Samaras K, Burton S, et al. A syndrome of peripheral lipodystrophy, hyperlipidemia and insulin resistance in patients receiving HIV protease inhibitors. AIDS. 1998;12:F51–8.
4. Wauters M, Considine RB, van Gaal LF. Human leptin: from an adipocyte hormone to an endocrine mediator. Eur J Endocrinol. 2000;143:293–311.
5. Vigouroux C, Maachi M, Nguyen TH, et al. Serum adipocytokines are related to lipodystrophy and metabolic disorders in HIV-infected men under antiretroviral therapy. AIDS. 2003;17:1503–11.
6. Simha V, Garg A. Lipodystrophy: lessons in lipid and energy metabolism. Curr Opin Lipidol. 2006;17:162–9.
7. Weyer C, Funahashi T, Tanaka S, et al. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab. 2001;86:1930–5..
8. Haque WA, Shimomura I, Matsuzawa Y, Garg A. Serum adiponectin and leptin levels in patients with lipodystrophies. J Clin Endocrinol Metab. 2002;87:2395–8.
9. Addy CL, Gavrila A, Tsiodras S, et al. Hypoadiponectinemia is associated with insulin resistance, hypertriglyceridemia, and fat redistribution in human immunodeficiency virus-infected patients treated with highly active antiretroviral therapy. J Clin Endocrinol Metab. 2003;88:627–36.
10. Nagy S, Tsiodras S, Martin L, et al. Leptin is independently associated with lipodystrophy in HIV-1 infected patients treated with HAART. Clin Infect Dis. 2003;36:795–802.
11. Shimomura I, Hammer RE, Ikemoto S, et al. Leptin reverses insulin resistance and diabetes mellitus in mice with congenital lipodystrophy. Nature. 1999;401:73–6.
12. Shimomura I, Hammer RE, Richardson RE, et al. Insulin resistance and diabetes mellitus in transgenic mice expressing nuclear SREBP-1c in adipose tissue: model for congenital generalized lipodystrophy. Genes Dev. 1998;12:3182–94.
13. Agarwal AK, Garg A. Genetic basis of lipodystrophies and management of metabolic complications. Annu Rev Med. 2006;57:297–311.
14. Kim CA, Delepine M, Boutet E, et al. Association of a homozygous nonsense caveolin-1 mutation with

Berardinelli-Seip congenital lipodystrophy. J Clin Endocrinol Metab. 2008;93:1129–34.
15. Agarwal AK, Simha V, Oral SA, et al. Phenotypic and genetic heterogeneity in congenital generalized lipodystrophy. J Clin Endocrinol Metab. 2003;88:4840–7.
16. van de Warrenburg BP, Scheffer H, van Eijk JJ, et al. *BSCL2* mutations in two Dutch families with overlapping Silver syndrome-distal hereditary motor neuropathy. Neuromuscul Disord. 2006;16:122–5.
17. Peters JM, Barnes R, Bennett L, et al. Localization of the gene for familial partial lipodystrophy (Dunnigan variety) to chromosome 1q21–22. Nat Genet. 1998;18:292–5.
18. Shackleton S, Lloyd DJ, Jackson SNJ, et al. *LMNA*, encoding lamin A/C, is mutated in partial lipodystrophy. Nat Genet. 2000;24:153–6.
19. Hegele RA, Cao H, Huff MW, Anderson CM. *LMNA* R482Q mutation in partial lipodystrophy associated with reduced plasma leptin concentration. J Clin Endocrinol Metab. 2000;855:3089–93.
20. Garg A, Vinaitheerthan M, Weatherall PT, Bowcock AM. Phenotypic heterogeneity in patients with familial partial lipodystrophy (Dunnigan variety) related to the site of missense mutations in lamin A/C gene. J Clin Endocrinol Metab. 2001;86:59–65.
21. Agarwal AK, Garg A. A novel heterozygous mutation in peroxisome proliferator-activated receptor-gamma gene in a patient with familial partial lipodystrophy. J Clin Endocrinol Metab. 2002;87:408–11.
22. George S, Rochford JJ, Wolfrum C, et al. A family with severe insulin resistance and diabetes due to a mutation in *AKT2*. Science. 2004;304:1325–8.
22a. Gandotra S, Le Dour C, Bottomley W, et al. Perilipin deficiency and autosomal dominant partial lipodystrophy. N Engl J Med. 2011;364:740–8.
23. Simha V, Agarwal AK, Oral EA, et al. Genetic and phenotypic heterogeneity in patients with mandibuloacral dysplasia-associated lipodystrophy. J Clin Endocrinol Metab. 2003;88:2821–4.
24. Agarwal AK, Fryns JP, Auchus RJ, Garg A. Zinc metalloproteinase, ZMPSTE24, is mutated in mandibuloacral dysplasia. Hum Mol Genet. 2003;12:1995–2001.
25. Owen KR, Donohoe M, Ellard S, et al. Mesangiocapillary glomerulonephritis type 2 associated with familial partial lipodystrophy (Dunnigan-Kobberling syndrome). Nephron Clin Pract. 2004;96:c35–8.
26. Misra A, Garg A. Clinical features and metabolic derangements in acquired generalized lipodystrophy: case reports and review of the literature. Medicine (Baltimore). 2003;82:129–46.
27. Hubler A, Abendroth K, Keiner T, et al. Dysregulation of insulin like growth factors in a class of generalized acquired lipoatrophic diabetes mellitus (Lawrence syndrome) connected with autoantibodies against adipocyte membranes. Exp Clin Endocrinol Diabetes. 1998;106:79–84.
28. Mathieson PW, Peters DK. Lipodystrophy in MCGN type II: the clue to links between the adipocyte and the complement system. Nephrol Dial Transplant. 1997;12:1804–6.
29. Hegele RA, Cao H, Liu DM, et al. Sequencing of the reannotated *LMNB2* gene reveals novel mutations in patients with acquired partial lipodystrophy. Am J Hum Genet. 2006;79:383–9.
30. Raile K, Noelle V, Landgraf R, Schwarz HP. Insulin antibodies are associated with lipoatrophy but also with lipohypertrophy in children and adolescents with type 1 diabetes. Exp Clin Endocrinol Diabetes. 2001;109:393–6.
31. Gómez-Espejo C, Pérez-Bernal A, Camacho-Martínez F. A new case of semicircular lipoatrophy associated with repeated external microtraumas and review of the literature. J Eur Acad Dermatol Venereol. 2005;19:459–61.
32. Becker C, Barbulescu K, Hildner K, et al. Activation and methotrexate-mediated suppression of the TNF alpha promoter in T cells and macrophages. Ann N Y Acad Sci. 1998;859:311–14.
33. Dahl PR, Zalla MJ, Winkelmann RK. Localized involutional lipoatrophy: a clinicopathologic study of 16 patients. J Am Acad Dermatol. 1996;35:523–8.
34. Okita H, Ohtsuka T, Yamakage A, Yamazaki S. Lipodystrophia centrifugalis abdominalis infantilis – immunohistochemical demonstration of an apoptotic process in the degenerating fatty tissue. Dermatology. 2000;201:370–2.
35. Garg A. Acquired and inherited lipodystrophies. N Engl J Med. 2004;350:1220–34.
36. Köbberling J, Dunnigan MG. Familial partial lipodystrophy: two types of an X linked dominant syndrome, lethal in the hemizygous state. J Med Genet. 1986;23:120–7.
37. Garg A, Peshock RM, Fleckenstein JL. Adipose tissue distribution pattern in patients with familial partial lipodystrophy (Dunnigan variety). J Clin Endocrinol Metab. 1999;84:170–4.
38. Misra A, Peethambaram A, Garg A. Clinical features and metabolic and autoimmune derangements in acquired partial lipodystrophy. Report of 35 cases and review of the literature. Medicine (Baltimore). 2004;83:18–34.
39. Dimson OG, Esterly NB. Annular lipoatrophy of the ankles. J Am Acad Dermatol. 2006;54:S40–2.
40. Imamura S. Skin diseases first described in Japan. Clin Dermatol. 1999;17:117–26.
41. Chang SE, Bae GY, Jeong YI, et al. Lipodystrophia centrifugalis abdominalis in Korea. Pediatr Dermatol. 2004;21:538–41.
42. Herold DA, Albrecht G. Local lipohypertrophy in insulin treatment. Hautarzt. 1993;44:40–2.
43 Peters MS, Winklemann RK. The histopathology of localized lipoatrophy. Br J Dermatol. 1986;114:27–36.
44. Binder WJ, Bloom DC. The use of custom-designed midfacial and submalar implants in the treatment of facial wasting syndrome. Arch Facial Plast Surg. 2004;6:394–7.
45. Wolfort FG, Cetrulo CL, Nevarre DR. Suction-assisted lipectomy for lipodystrophy syndromes attributed to HIV-protease inhibitor use. Plast Reconstr Surg. 1999;104:1814–20.
46. Arioglu E, Duncan-Morin J, Serbring N, et al. Efficacy and safety of troglitazone in the treatment of lipodystrophy syndromes. Ann Intern Med. 2000;133:263–74.
47. Ebihara K, Kusakabe T, Hirata M, et al. Efficacy and safety of leptin-replacement therapy and possible mechanisms of leptin actions in patients with generalized lipodystrophy. J Clin Endocrinol Metab. 2007;92: 532–41.
48. Guettier J-M, Park JY, Cochran EK, et al. Leptin therapy for partial lipodystrophy linked to a PPAR-γ mutation. Clin Endocrinol. 2008;68:547–54.
49. Oral EA, Simha V, Ruiz E, et al. Leptin-replacement therapy for lipodystrophy. N Engl J Med. 2002;346:570–8.
50. Levy Y, George J, Yona E, Shoenfeld Y. Partial lipodystrophy, mesangiocapillary glomerulonephritis, and complement dysregulation. An autoimmune phenomenon. Immunol Res. 1998;18:55–60.
51. Heath KV, Hoggs RS, Singer J, et al. Antiretroviral treatment patterns and incident HIV-associated morphologic and lipid abnormalities in a population-based cohort. J Acquir Immune Defic Syndr. 2002;30: 440–7.
52. Sattler FR. Pathogenesis and treatment of lipodystrophy: what clinicians need to know. Top HIV Med. 2008;16: 127–33.
53. Grigem S, Fischer-Posovszky P, Debatin KM, et al. The effect of the HIV protease inhibitor ritonavir on proliferation, differentiation, lipogenesis, gene expression and apoptosis of human preadipocytes and adipocytes. Horm Metab Res. 2005;37:602–9.
54. Caron M, Auclair M, Lagathu C, et al. The HIV-1 NRTI stavudine and zidovudine alter adipocyte functions *in vitro*. AIDS. 2004;18:2127–36.
55. Brinkman K, Smeitink I, Romijn J, Reiss P. Mitochondrial toxicity induced by NRTI is a key factor in the pathogenesis of ART-related lipodystrophy. Lancet. 1999;354:1112–15.
56. Caron M, Auclair M, Sterlingot H, et al. Some HIV protease inhibitors alter lamin A/C maturation and stability, SREBP-1 nuclear localization and adipocyte differentiation. AIDS. 2003;17:2437–44.
57. Lenhard J, Furfine E, Jain R, et al. HIV PI block adipogenesis and increase lipolysis *in vitro*. Antiviral Res. 2000;47:121–9.
58. Bogner J, Vielhauer V, Beckmann R, et al. Stavudine versus zidovudine and the development of lipodystrophy. J Acquir Immune Defic Syndr. 2001;27:237–44.
59. Tien PC, Benson C, Zolopa AR, et al. The Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM): methods, design, and sample characteristics. Am J Epidemiol. 2006;163:860–9.
60. Miller J, Carr A, Emery S, et al. HIV lipodystrophy: prevalence, severity and correlates of risk in Australia. HIV Med. 2003;4:293–301.
61. Mallon P. Pathogenesis of lipodystrophy and lipid abnormalities in patients taking antiretroviral therapy. AIDS Rev. 2007;9:3–15.
62. Friis-Moller N, Sabin CA, Weber R, et al. Combination antiretroviral therapy and the risk of myocardial infarction. N Engl J Med. 2003;349:1993–2003.
63. Friis-Møller N, Weber R, Reiss P, et al. DAD study group. Cardiovascular disease risk factors in HIV patients – association with antiretroviral therapy. Results from the DAD study. AIDS. 2003;17:1179–93.
64. Lichtenstein KA. Refining lipodystrophy syndrome. J Acquir Immune Defic Syndr. 2005;39:395–400.
65. Pozniak AL, Gallant JE, DeJesus E, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz versus fixed-dose zidovudine/lamivudine and efavirenz in antiretroviral-naive patients: virologic, immunologic, and morphologic changes – a 96-week analysis. J Acquir Immune Defic Syndr. 2006;43(5):535–40.
66. Moyle GJ, Sabin CA, Cartledge J, et al. A randomized comparative trial of tenofovir DF or abacavir as replacement for a thymidine analogue in persons with lipoatrophy. AIDS. 2006;20:2043–50.
67. Martin A, Smith D, Carr A, et al. for the Mitochondrial Toxicity Study Group. Reversibility of lipoatrophy in HIV-infected patients 2 years after switching from a thymidine analogue to abacavir: the MITOX Extension Study. AIDS. 2004;18:1029–36.
68. Carr A, Workman C, Carey D, et al. No effect of rosiglitazone for treatment of HIV-1 lipoatrophy: randomized, double-blind placebo controlled trial. Lancet. 2004;363:429–38.
69. Sutinen J, Walker UA, Sevastianova K, et al. Uridine supplementation for the treatment of antiretroviral therapy-associated lipoatrophy: a randomized double-blind, placebo-controlled trial. Antivir Ther. 2007;12:97–105.
70. Lundgren JD, Battegay M, Behrens G, et al. European AIDS Clinical Society (EACS) guidelines on the prevention and management of metabolic diseases in HIV. HIV Med. 2008;9: 72–81.

This page intentionally left blank

Vascular Biology 102

Michael Detmar and Satoshi Hirakawa

Chapter Contents

Structure and function of cutaneous blood vessels *1679*
Vascular development *1681*
Structure and function of the cutaneous lymphatic system *1685*
Related diseases *1687*
Current trends in antiangiogenesis *1688*

Key features

- Cutaneous blood vessels and lymphatic vessels play important roles in skin inflammation and tumor progression
- Vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) are major skin angiogenesis factors
- Expression of VEGF and PlGF by keratinocytes is upregulated in psoriasis, healing wounds and cutaneous squamous cell carcinomas
- VEGF-C and VEGF-D induce skin lymphangiogenesis via interaction with VEGF receptor-3 on lymphatic endothelium. Inactivating VEGF receptor-3 mutations have been found in congenital lymphedema
- Cutaneous lymphatic vessels can be specifically visualized in skin sections due to their selective expression of the glycoprotein podoplanin and of the hyaluronan receptor LYVE-1

INTRODUCTION

The blood vessels of the skin are involved in the control of body temperature and provide a conduit for the supply of nutrients and oxygen to the skin and for the rapid disposal of metabolic waste products. Recent scientific progress in the field of vascular biology has provided ample evidence that both blood vessels and lymphatic vessels also play essential roles in the development and progression of skin tumors, in the mediation and perpetuation of cutaneous inflammation, as well as in physiologic processes such as tissue repair and hair follicle growth. An increased knowledge about markers for specific types of vessels, together with the identification of key molecules that control vascular growth and function, has led to an in-depth understanding of the mechanisms that control the function of the cutaneous vascular system in health and disease, with important implications for the development of novel therapeutic strategies for the treatment of skin diseases.

STRUCTURE AND FUNCTION OF CUTANEOUS BLOOD VESSELS

Blood vessels are essential in order to: supply sufficient oxygen and nutrients to the skin, maintain normal tissue homeostasis and function, and meet the increased nutritional needs of the skin in various pathologic conditions. Blood flows from arteries and arterioles through capillary loops to postcapillary venules and veins. For practical and didactic purposes, the vascular system of the skin has been divided into a superficial and a deep vascular plexus (Fig. 102.1), with additional vascular networks surrounding sweat glands and hair follicles. The architecture of the cutaneous vascular system varies in different areas of the body. In the presence of pronounced epidermal rete ridges, such as in the skin overlying the extensor aspects of the joints or on the palms and soles, straight capillary loops extend into the elongated dermal papillae. In contrast, rete ridge formation and papillary loop formation are less pronounced in the abdominal skin. In fact, it appears that the shape of the papillary microvessels exactly reflects the three-dimensional architecture of the epidermal rete ridges, with only one loop within each papilla[1]. The inner diameter of papillary blood vessels averages between 5 and 10 microns. In contrast to the idealized architectural model of the cutaneous vascular system, vascular perfusion studies (Fig. 102.2) and immunofluorescent studies (Fig. 102.3) reveal a rather continuous, sometimes irregular meshwork of interconnecting cutaneous blood vessels. Consistently, blood vessels are found immediately below the non-vascularized epidermis and surrounding anagen hair follicles.

It has been thought that hair follicles and other skin appendages are predominantly supplied from the lower vascular plexus, whereas the papillary vessels originate from the superficial vascular plexus. Immunohistochemical and perfusion studies suggest that while the frequently single blood vessel within the mesenchymal hair papilla is derived from the lower vascular plexus, the dense vascular network surrounding the hair follicle is predominantly derived from the upper vascular plexus (Fig. 102.4). The relatively small blood vessels that are found during the telogen resting phase of the follicle elongate and enlarge during the anagen growth phase, and then extend towards the subcutis together with the growing hair follicle. During the catagen phase, hair follicle involution is associated with regression of perifollicular blood vessels and with increased rates of endothelial cell apoptosis[2]. Whereas the richness of the follicular blood supply depends on the size of the hair follicles, recent studies suggest that, conversely, the extent

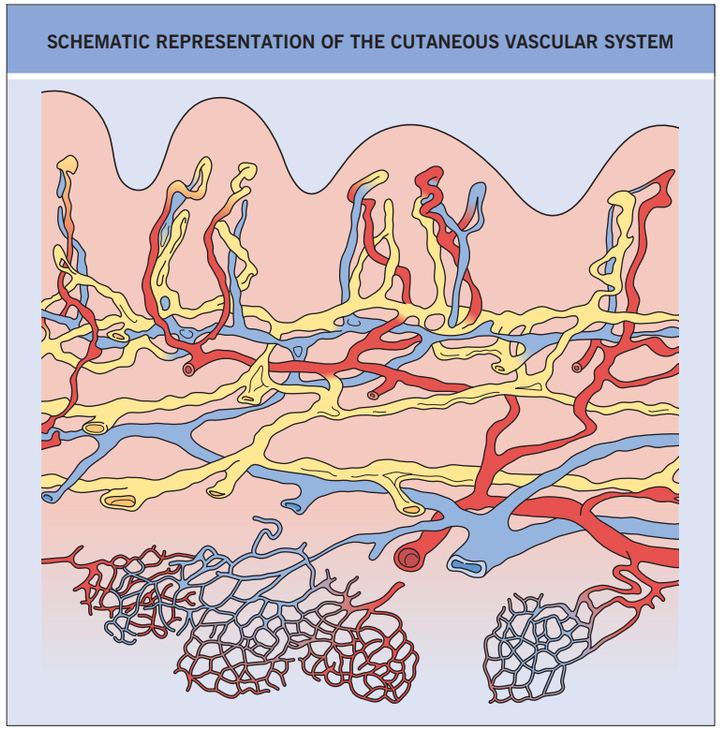


Fig. 102.1 Schematic representation of the cutaneous vascular system. The superficial vascular plexus feeds vessels in the dermal papillae; arteries (red) and veins (blue) are closely associated with lymphatic vessels (yellow). The capillary networks of the subcutaneous adipose tissue are depicted at the base of the schematic.

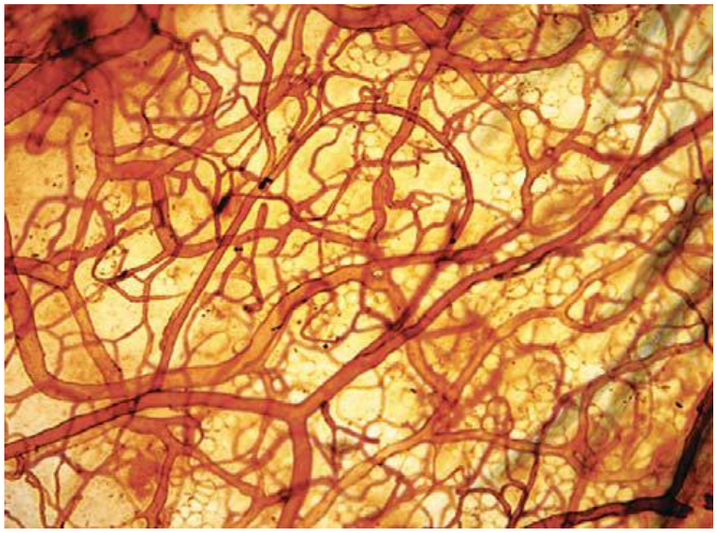


Fig. 102.2 Intravascular perfusion of murine skin with the lectin *Leucopersicon esculentum*. The perfusion highlights dense irregular vascular networks.

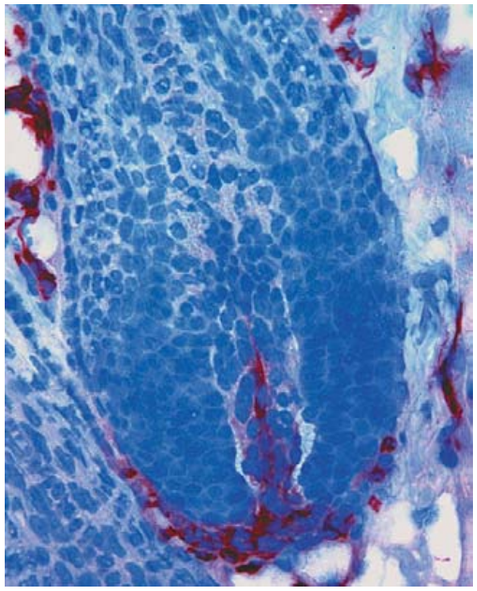


Fig. 102.4 Blood supply of the hair follicle. A single vascular loop extends into the dermal papilla of the hair follicle, while a mesh of blood vessels surrounds the anagen hair follicle (CD31 immunohistochemical stain).

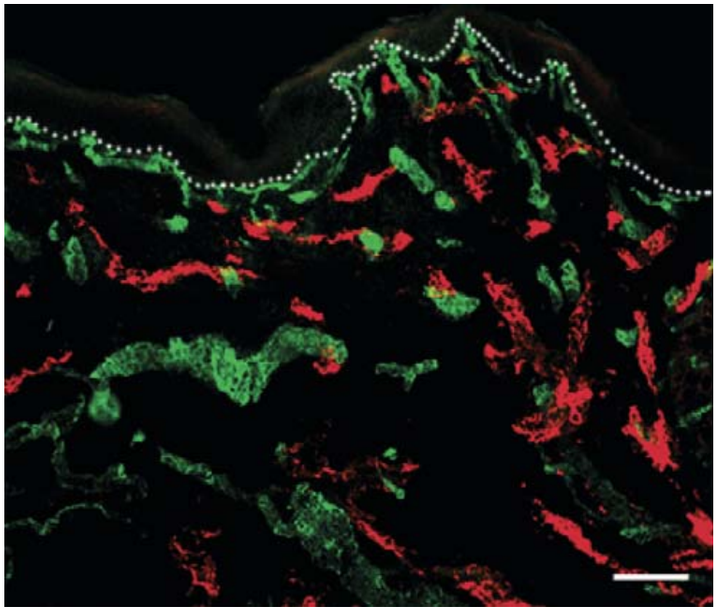


Fig. 102.3 Distinct staining of cutaneous blood vessels (PAL-E; green) and lymphatic vessels (LYVE-1; red) in human neonatal foreskin. The dotted line indicates the approximate location of the basement membrane. The white bar represents 50 microns.

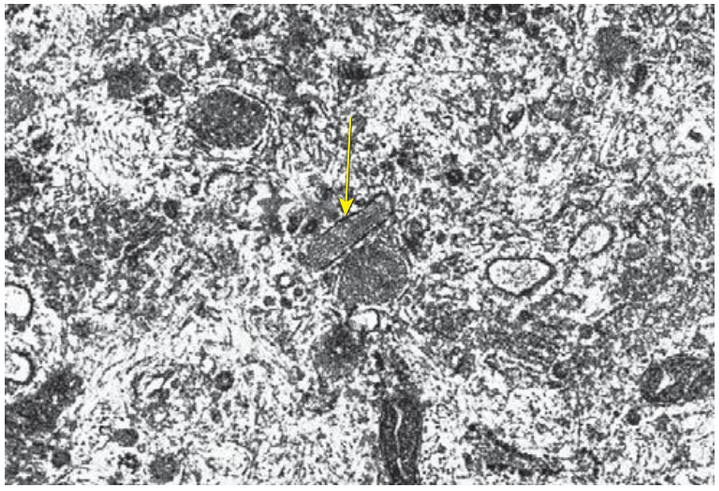


Fig. 102.5 Ultrastructural visualization of a rod-shaped Weibel–Palade body (WPB; arrow) within the cytoplasm of a human endothelial cell.

of perifollicular vascularization may directly influence the size of the hair follicles[2].

In addition to its importance for the nutritional support of the skin, the cutaneous vasculature also plays a systemic role in regulating body temperature and blood pressure. Arterioles possess precapillary muscular sphincters that, upon contraction, can shunt the blood via arteriovenous anastomoses directly to venules, thereby bypassing the capillary networks. Arteriovenous anastomoses are frequently found in the fingertips, where they form the glomi or glomus bodies[1]. Glomi have autonomous innervation and are able, via modulation of their muscular contraction levels, to control peripheral blood flow. The density and importance of arteriovenous anastomoses in other body areas remains unclear.

All blood vessels contain a continuous inner monolayer of flat endothelial cells that are surrounded, on the external side, by a continuous basement membrane. Smaller vessels contain a second, sometimes discontinuous, layer of perivascular cells, called pericytes, which are also surrounded by a basement membrane. Pericytes play an important role in the maintenance of mature blood vessels, and detachment of pericytes from endothelial cells is an early event during sprouting angiogenesis (outgrowth of new capillaries from pre-existing blood vessels). Arterioles and venules are also surrounded by pericytes, which can be visualized by staining for α-smooth muscle actin and desmin. The walls of most arterioles and larger venules and veins contain contractile smooth muscle cells that are surrounded by a basement membrane. Vascular basement membranes contain collagen types IV, XV and XVIII, laminin, fibronectin, and other extracellular matrix proteins. Electron microscopy studies have shown that the basement membrane of endothelial cells in the arterial side of the cutaneous vasculature is rather homogeneous, whereas multilayered basement membranes have been described surrounding venous capillaries[3].

At the ultrastructural level, vascular endothelial cells are characterized by tight junctions between neighboring cells and by a specialized organelle, the rod-shaped Weibel–Palade body (Fig. 102.5), which serves as a storage organelle for the coagulation factor von Willebrand factor, also known as factor VIII-related antigen. Weibel–Palade bodies also contain P-selectin, tissue plasminogen activator, angiopoietin-2 and endothelin-1. Activation of endothelial cells by proinflammatory cytokines or pro-angiogenic factors readily leads to translocation of these storage organelles to the cell membrane, with consecutive enhanced membrane expression of P-selectin and release of von Willebrand factor. Other characteristic ultrastructural features include caveolae (minute invaginations) of the membrane surface, pinocytotic vesicles, and the formation of vesiculo-vacuolar organelles (VVOs)[4]. Circulating macromolecules cross the endothelium through interendothelial cell gaps and transendothelial cell pores, some of which arise

from VVOs. Endothelial cell fenestrations, areas with direct apposition of the endothelial cell membranes without intervening cytoplasm, are rarely seen in normal skin except in angiogenic perifollicular blood vessels during the growth phase of the hair follicle. However, fenestrated endothelial cells are frequently seen in skin diseases with pronounced angiogenesis and vascular hyperpermeability, including psoriasis.

Several markers for blood vascular endothelial cells have been identified (see Table 102.3). However, some of these markers (e.g. CD31, CD34) can also be detected on other dermal cells such as lymphatic endothelial cells (CD31) or fibrocytes (CD34). In normal skin, the most specific markers for cutaneous blood vessels appear to be CD34 and PAL-E (see Fig. 102.3). Double immunofluorescence stains for both the pan-endothelial cell marker CD31 (PECAM-1) and for the lymphatic vascular endothelium-specific hyaluronan receptor LYVE-1 also allow for the selective visualization of LYVE-1-negative blood vessels in the skin (see Fig. 102.15). In addition, differential immunostains for CD31 as well as vascular basement membrane markers (e.g. laminin, collagen IV, collagen XVIII) can be used to visualize cutaneous blood vessels[5].

VASCULAR DEVELOPMENT

During embryogenesis, the first blood vessels are formed through *vasculogenesis*, the differentiation of undifferentiated angioblasts into endothelial cells that form a primitive vascular network. Angioblasts originate from blood islands in the extraembryonic mesoderm of the yolk sac. Blood islands are clusters of epithelioid cells; the outer cells differentiate into angioblasts, whereas the inner cells differentiate into primitive hematopoietic cells, suggesting that both cell types originate from a common embryonic precursor cell, the hemangioblast[6], which is formed from earlier precursor cells under the influence of fibroblast growth factors (Fig. 102.6). Hemangioblasts already express the high-affinity receptor for vascular endothelial growth factor (VEGF), vascular endothelial growth factor receptor-2 (VEGFR-2; KDR [human]; Flk-1 [murine]; see Fig. 102.8); under experimental conditions, early VEGFR-2-positive cells can give rise to both endothelial cells and blood cells[7].

Angioblasts develop under the influence of stimulation by VEGF and express several vascular endothelial cell markers, including the Tie-1 and Tie-2 receptors, vascular endothelial (VE)-cadherin, and the high-affinity VEGF receptors 1 (Flt-1), 2 (KDR) and 3 (Flt-4). Angioblasts within the embryo appear along the anterior intestinal portal and along the lateral edges of the somites, later coalescing to form the dorsal aorta and the large vessel primordia of the body. Angioblasts are highly migratory "prevascular" endothelial cells and are found throughout the embryo with the exception of tissues such as cartilage and epithelia[6].

When angioblasts form a lumen, they become endothelial cells with a polarized phenotype and production of a basal lamina. Interactions of integrin receptors on the endothelial surface with the basement membrane are of paramount importance for the formation of the primordial vascular plexus, and establishment of interendothelial adherence junctions requires the vascular endothelial (VE)-cadherin. The early vascular system consists of sinusoidal capillaries that are arranged in a polygonal honeycomb pattern (see Fig. 102.6). The primordial vascular plexus then becomes surrounded by mesenchymal cells that give rise to pericytes and vascular smooth muscle cells. In a next step, under the influence of VEGF, angiopoietins (see Fig. 102.7) and ephrins, profound remodeling of the primordial vascular plexus takes place. Remodeling involves both the formation and the regression of blood vessels and apoptosis of vascular endothelial cells.

Angiogenesis, the sprouting of new blood vessels from existing primordial vessels, represents the major mechanism for new blood vessel formation. In addition, intussusception, the non-sprouting generation of new blood vessels, involves the formation of intravascular endothelial pillars, leading to the division of the vascular lumen and to the formation of a new vascular space. The Tie-2 receptor tyrosine kinase, expressed on vascular endothelial cells, plays a crucial role in vascular sprouting and remodeling during early embryonic angiogenesis. Pericyte-derived angiopoietin-1 (Ang-1) activates the Tie-2 receptor, whereas Ang-2 can act as an inhibitor of Ang-1 (Fig. 102.7).

Ephrin–Eph receptor interactions, via bidirectional signaling, also play an important role in vascular remodeling and in the determination of vascular identity. Ephrin B2 is specifically expressed by arterial endothelium, whereas its receptor, Eph-B4, is expressed by venous endothelium. Both molecules are involved in the definition of boundaries between arterial and venous endothelial cells. Additional molecules are involved in the control of embryonic angiogenesis and vascular remodeling, including transforming growth factor-β (TGF-β), its low-affinity receptor endoglin, and activin receptor-like kinase-1. Of note, dysfunction of the latter two proteins is seen in hereditary hemorrhagic telangiectasia (see below). Platelet-derived growth factor-β (PDGF-β), secreted by endothelial cells, plays a critical role in the recruitment and differentiation of pericytes and periendothelial smooth muscle cells that contribute to the stability of mature blood vessels[8].

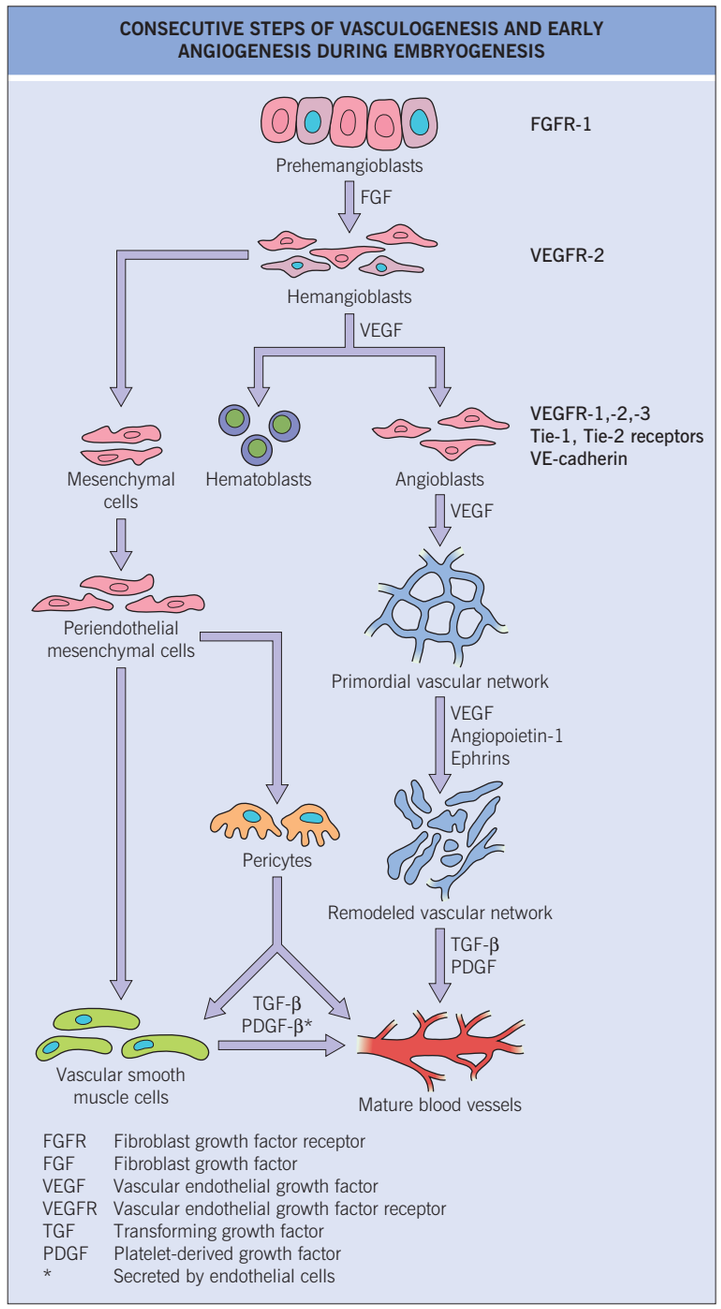


Fig. 102.6 Consecutive steps of vasculogenesis and early angiogenesis during embryogenesis: formation and remodeling of primordial vascular networks.

Regulation of Skin Angiogenesis

Angiogenesis is a common feature of developing skin during embryogenesis. In contrast, the blood vessels in healthy adult skin are predominantly quiescent, with the exception of the cyclic expansion and involution of perifollicular blood vessels during the hair cycle[2]. However, adult skin retains the capacity for brisk initiation of angiogenesis during

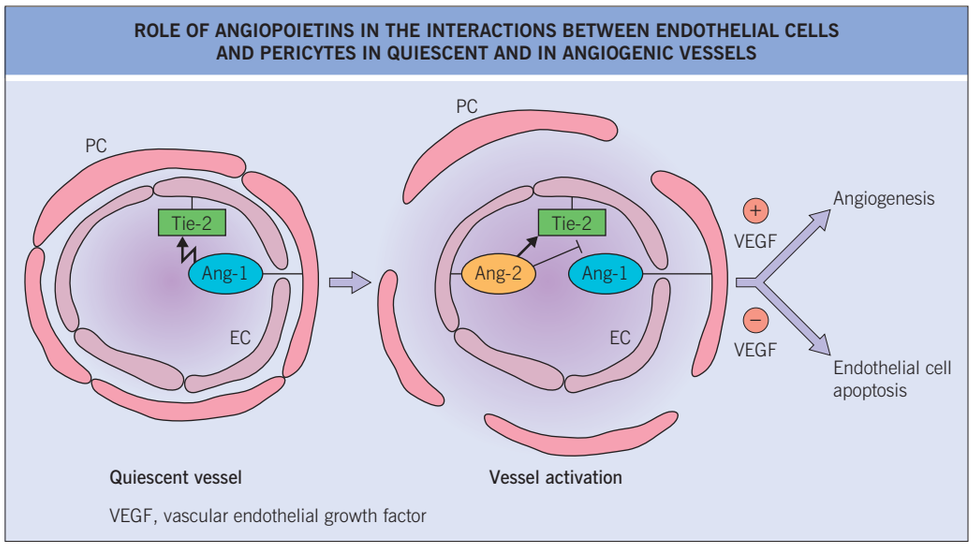


Fig. 102.7 Role of angiopoietins in the interactions between endothelial cells and pericytes in quiescent and in angiogenic vessels. Activation of the endothelial Tie-2 receptor by pericyte (PC)-derived angiopoietin-1 (Ang-1) is thought to result in vessel maturation. Upregulation of angiopoietin-2 (Ang-2) in angiogenic endothelial cells (EC) blocks the vessel-stabilizing effect of pericyte-derived Ang-1 via the endothelial Tie-2 receptor. Both VEGF and Ang-2 expression are upregulated in angiogenic skin diseases, including psoriasis.

THE STEPWISE INDUCTION OF ANGIOGENESIS
1. Induction of microvascular hyperpermeability
2. Enzymatic degradation of vascular basement membrane and interstitial matrix
3. Endothelial cell migration via integrin receptors on activated endothelial cells interacting with native or degraded matrix molecules
4. Endothelial cell proliferation
5. Formation of mature blood vessels

Table 102.1 The stepwise induction of angiogenesis.

wound healing, in the setting of inflammation, and during neoplastic growth. Angiogenesis occurs as: (1) the sprouting outgrowth of new capillaries from pre-existing postcapillary venules; or (2) non-sprouting remodeling of pre-existing blood vessels either through circumferential growth/vascular enlargement or through the formation of intravascular endothelial cell pillars (intussusception). Angiogenesis is a multistep process (Table 102.1) that often involves as a first step the induction of microvascular hyperpermeability, i.e. increased vascular leakage, leading to extravasation of plasma proteins such as fibrinogen and prothrombin. Fibrinogen is then further processed to fibrin and serves as a provisional matrix for migrating endothelial cells, whereas the generation of thrombin acts as an initiator of the extrinsic coagulation cascade, leading to cleavage and activation of several matrix proteins[9]. Together, these processes lead to the generation of a highly angiogenic stroma.

The distinct biologic functions of pericytes during angiogenesis have not been completely elucidated. Although in some experimental angiogenesis models pericytes may lead endothelial cells in the formation of vascular sprouts, a major function of pericyte coverage appears to be the maintenance of mature and quiescent blood vessels (a function which is interrupted during tumor angiogenesis). In normal adult skin, pericytes secrete Ang-1, which leads to phosphorylation of the Tie-2 receptor (a receptor exclusively expressed on vascular endothelial cells) and maintenance of the mature vascular architecture (see Fig. 102.7). In turn, endothelial cells secrete growth factors that mediate the recruitment of pericytes, including PDGF (see above). During the early stages of angiogenesis, endothelial cells express high amounts of Ang-2, a functional antagonist of Ang-1, thereby blocking the maturation-inducing effect of Ang-1 and leading to detachment of pericytes from vascular endothelial cells[10]. In the presence of VEGF, endothelial cells then undergo the consecutive steps of angiogenesis, whereas in the absence of VEGF, vascular endothelial cells undergo apoptosis (see Fig. 102.7). Both VEGF and Ang-2 expression are upregulated in angiogenic skin diseases, including psoriasis, and keratinocyte-derived VEGF and placental growth factor (PlGF; see below) both potently induce the expression of Ang-2 in dermal microvascular endothelial cells. There is evidence that bone marrow-derived progenitor cells also contribute to the angiogenic response. Most of these cells differentiate into perivascular macrophages that secrete angiogenic factors including VEGF, whereas some progenitor cells might adopt endothelial cell differentiation and become incorporated into the vessel wall.

The vascular basement membrane serves as a natural barrier that prevents sprouting of endothelial cells from quiescent, non-angiogenic vessels, with pericytes assisting in the maintenance of the quiescent state. An early step in the angiogenic response involves the degradation of vascular basement membrane components such as collagen type IV through the concerted action of activated proteases, including matrix metalloproteinase (MMP)-2 and MMP-9. Integrin receptors on the surface of activated endothelial cells, in particular the $\alpha_1\beta_1$, $\alpha_2\beta_1$ and $\alpha_v\beta_3$ integrins, then interact with either native or degraded matrix molecules (e.g. collagen type I, fibronectin) in order to facilitate endothelial cell migration[11]. The migration of endothelial cells in the skin is directed towards a gradient of angiogenesis factors that are most commonly produced by the epidermis, but that can also be secreted by macrophages. Endothelial cells then undergo a series of cell divisions, promoted by potent angiogenesis factors such as VEGF and basic fibroblast growth factor (bFGF). Finally, endothelial cells form vascular lumina and mature new blood vessels with basement membrane and pericyte coverage.

In normal skin, vascular quiescence is maintained by the dominant influence of potent endogenous angiogenesis inhibitors over angiogenic stimuli, whereas angiogenesis is induced by increased secretion of angiogenic factors and/or by down-regulation of angiogenesis inhibitors. Several factors that control angiogenesis within the skin have been identified. The major skin angiogenesis factor, VEGF, was originally discovered as vascular permeability factor (VPF), due to the activity of tumor cell-conditioned media to induce accumulation of ascites fluid[12]. VEGF is a homodimeric, heparin-binding glycoprotein occurring in at least four isoforms of 121, 165, 189 and 201 amino acids, due to alternative splicing. VEGF binds to two type III tyrosine kinase receptors that are expressed predominantly on vascular endothelial cells, Flt-1/VEGF receptor-1 (VEGFR-1) and KDR/Flk-1/VEGFR-2 (Fig. 102.8). In addition, VEGF165 also binds to the neuropilin-1 receptor on endothelial and other cells.

In vitro, VEGF acts as a specific mitogen for human dermal microvascular endothelial cells and also induces endothelial cell migration towards several extracellular matrices. *In vivo*, VEGF enhances microvascular permeability and angiogenesis. VEGF is expressed at low levels in normal epidermis, whereas healing wounds and skin diseases associated with angiogenesis and vascular hyperpermeability, particularly psoriasis, show prominent upregulation of VEGF expression by epidermal keratinocytes[13]. The expression and biologic activity of VEGF are controlled by several distinct molecular mechanisms. Hypoxia and low intracellular glucose concentrations result in transcriptional activation (via hypoxia-inducible factors) and stabilization of VEGF mRNA. Skin

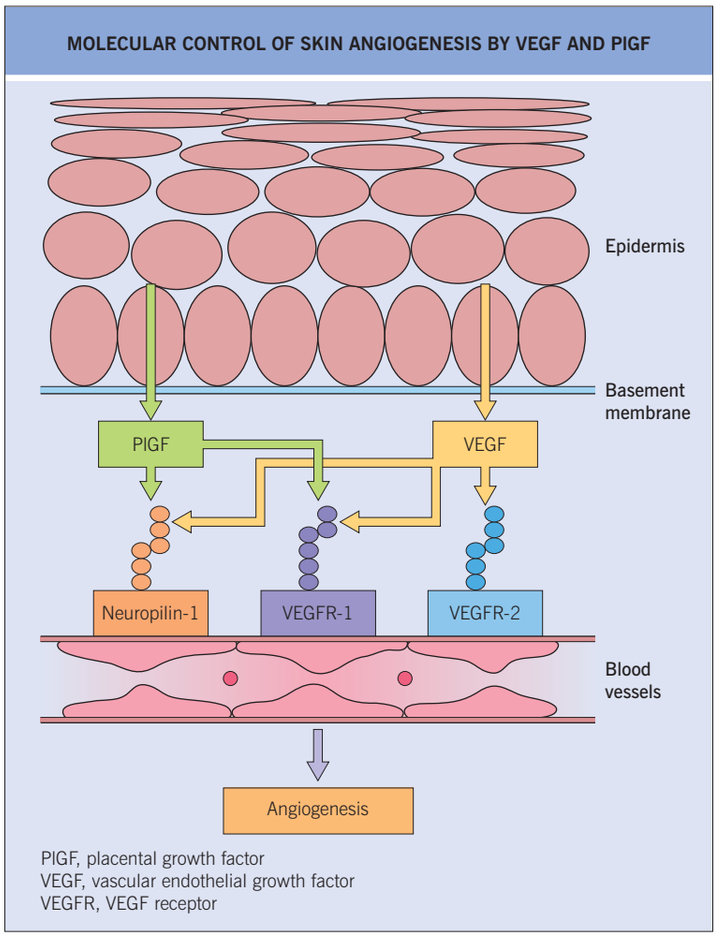


Fig. 102.8 Molecular control of skin angiogenesis by vascular endothelial growth factor (VEGF) and placental growth factor (PlGF).

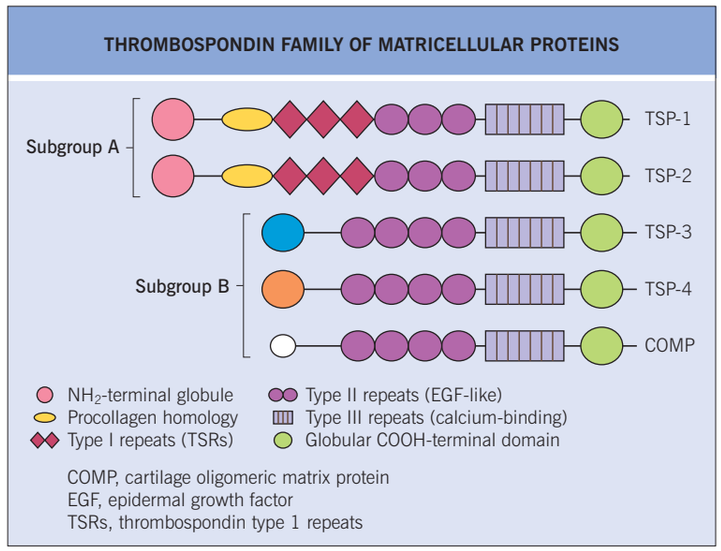


Fig. 102.9 The thrombospondin (TSP) family of matricellular proteins. TSP-1 and TSP-2 are potent endogenous inhibitors of skin angiogenesis.

hypoxia directly leads to upregulation of VEGF expression by epidermal keratinocytes, dermal fibroblasts and dermal endothelial cells. This mechanism is likely important in the induction of epidermal VEGF expression during wound healing and in areas of skin cancers adjacent to tumor necrosis.

Keratinocyte VEGF expression is also induced by several growth factors that mediate epidermal hyperplasia. In psoriasis, healing wounds and squamous cell carcinomas, TGF-α and other ligands of the epidermal growth factor receptor (EGFR) are released by suprabasal keratinocytes. In an autocrine loop, these growth factors induce hyperplasia of the epidermis. Simultaneously, they induce VEGF gene expression and protein secretion by epidermal keratinocytes, which lead to paracrine induction of angiogenesis through interaction with VEGF receptors on cutaneous microvessels (see Fig. 102.8). This mechanism links epidermal hyperplasia with increased vascularization, thereby providing enhanced vascular support to meet the enhanced nutritional needs of proliferating keratinocytes[13]. It also provides a molecular explanation for the reported association of thickened acanthotic epidermis with elongated capillary vessels[1]. Several other growth factors that stimulate keratinocyte proliferation, including keratinocyte growth factor (KGF), bFGF and hepatocyte growth factor (HGF), have recently joined the group of VEGF-inducing molecules.

The biologic importance of epidermis-derived VEGF for cutaneous angiogenesis *in vivo* has been confirmed in transgenic mouse models, using the keratin 14 promoter to selectively target expression of murine VEGF164 to basal epidermal keratinocytes and to keratinocytes of the outer root sheath of the hair follicle. VEGF transgenic mice are characterized by elongated and tortuous dermal blood vessels that are hyperpermeable to circulating plasma proteins[14]. VEGF-overexpressing mice are unable to down-regulate experimentally induced cutaneous inflammation and develop chronic inflammatory skin lesions that closely resemble those of human psoriasis[15].

The majority of human cancers studied thus far are characterized by overexpression of VEGF by tumor cells and by overexpression of VEGF receptors on tumor-associated blood vessels; blocking of VEGF function inhibits angiogenesis and suppresses tumor growth *in vivo*. However, in humans, the responses have ranged from none to modest (see below). VEGF also promotes skin carcinogenesis, since selective transgenic overexpression of VEGF in epidermal keratinocytes resulted in enhanced tumor development and metastasis[16].

Placental growth factor (PlGF) is a more recently identified member of the VEGF family of angiogenesis factors, with considerable sequence homology with VEGF. PlGF occurs in at least three different isoforms of 149 (PlGF-1), 170 (PlGF-2) and 221 (PlGF-3) amino acids. Both PlGF-1 and PlGF-2 are expressed in human skin. Similar to VEGF, the expression of PlGF is upregulated in cutaneous squamous cell carcinomas, in epidermal keratinocytes at the advancing wound edge, and in the hyperplastic psoriatic epidermis. In contrast to VEGF, PlGF does not activate VEGFR-2 (KDR), but selectively binds to VEGFR-1 (see Fig. 102.8). In addition, the heparin-binding isoform PlGF-2, but not PlGF-1, binds to the neuropilin-1 receptor. Evidence from genetic mouse models indicates that PlGF and VEGF act in synergy to induce both angiogenesis and vascular leakage and PlGF exerts proinflammatory effects[17,18]. A number of additional pro-angiogenic molecules are upregulated in angiogenic skin conditions, including interleukin-8, PDGF, FGF and angiogenic chemokines. However, the distinct contributions of each of these factors to the cutaneous vascular response remain to be characterized in more detail.

Thrombospondin (TSP)-1 and TSP-2 are major endogenous inhibitors of skin angiogenesis and are expressed in normal human skin. Thrombospondins are matricellular proteins that mediate interactions between extracellular matrix molecules and cellular integrin receptors (Fig. 102.9). TSP-1, a 450 kD modular, homotrimeric glycoprotein, contains a procollagen homology region, three properdin-like type I repeats, three epidermal growth factor-like repeats, and seven Ca^{2+}-binding repeats. TSP-1 is involved in a large number of biologic processes, including proliferation, migration and differentiation of various cell types; moreover, TSP-1 inhibits endothelial cell proliferation *in vitro* and angiogenesis *in vivo*. In normal human skin, TSP-1 is expressed by dermal cells and by epidermal keratinocytes, and it is deposited within the dermo-epidermal basement membrane zone, contributing to the barrier that prevents ingrowth of blood vessels into the epidermis. In contrast, TSP-1 expression is down-regulated in squamous cell carcinomas of the skin. Reintroduction of the *TSP-1* gene into squamous cell carcinomas inhibits tumor growth in mice, associated with inhibition of tumor angiogenesis and enhanced tumor cell necrosis[19]. The potential mechanisms by which TSP-1 inhibits skin angiogenesis include the induction of endothelial cell apoptosis through specific interactions with the endothelial CD36 receptor, the activation

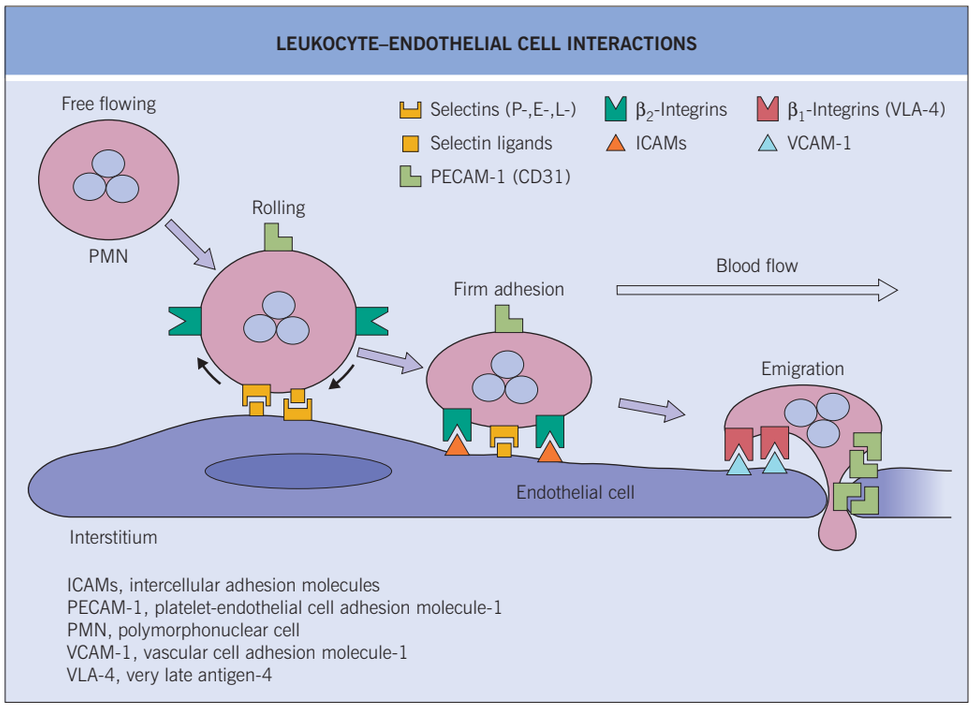


Fig. 102.10 The multistep process of leukocyte–endothelial cell interactions that leads to leukocyte recruitment into inflamed skin. Examples of selectin ligands on leukocytes are cutaneous lymphocyte-associated antigen (CLA) and P-selectin glycoprotein ligand (PSGL).

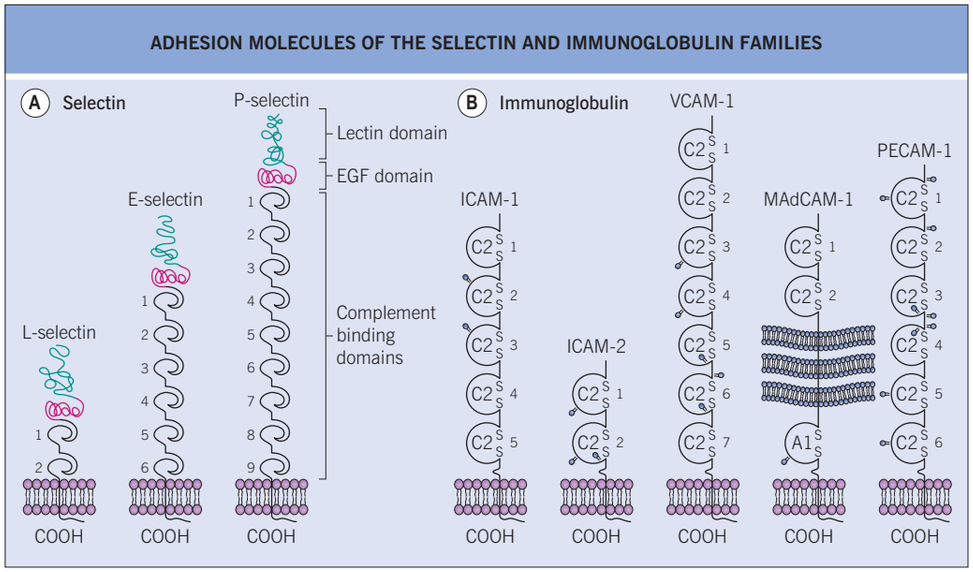


Fig. 102.11 Adhesion molecules of the selectin (A) and immunoglobulin (B) families. EGF, epidermal growth factor; MAdCAM, mucosal addressin cell adhesion molecule; ICAM, intercellular adhesion molecule; PECAM, platelet–endothelial cell adhesion molecule; VCAM, vascular cell adhesion molecule.

of latent TGF-β, and the inhibition of matrix metalloproteinase activity[19]. Overexpression of TSP-1 in the skin of transgenic mice results in impaired granulation tissue formation and wound vascularization, delayed and reduced skin carcinogenesis, and diminished photodamage induced by chronic UVB irradiation of the skin[20].

A second member of the thrombospondin family, TSP-2, is also expressed in normal human skin and acts as an endogenous inhibitor of angiogenesis. The expression of TSP-2 is down-regulated in epithelial squamous cell carcinoma cells, whereas a strong upregulation of TSP-2 is found in the mesenchymal stroma during skin carcinogenesis, representing a natural tumor defense mechanism[21]. Mice that are deficient in TSP-2 show increased skin vascularization, enhanced and prolonged inflammatory reactions, and enhanced skin carcinogenesis, confirming the important role of endogenous TSP-2 in the control of skin angiogenesis. Accordingly, targeted overexpression of TSP-2 within murine epidermis protects from skin cancer development and inhibits the growth of established skin cancers[19].

A number of additional endogenous inhibitors of angiogenesis are likely involved in the maintenance of normal vascular quiescence in the skin, most prominently interferons. Moreover, antiangiogenic activity has been reported for several cleavage products of molecules that are expressed in the vascular basement membrane, including fragments of collagens type IV (tumstatin), XV, and XVIII (endostatin).

Regulation of Leukocyte–Endothelial Cell Interactions

Accumulation of leukocytes in the skin is a prominent feature of acute and chronic inflammatory skin diseases and represents a rate-limiting step in the inflammatory response. Leukocyte recruitment is a multistep process that is controlled by the sequential activation of a number of adhesion molecules on both leukocytes and vascular endothelial cells, as well as by several inflammatory cytokines and chemokines. Predominantly, leukocyte extravasation occurs in the postcapillary venules of the skin that are particularly sensitive to the induction of adhesion molecules. As a first step, relatively weak adhesive leukocyte–endothelial cell interactions, involving distinct selectins and their ligands, result in the tethering and rolling of leukocytes on the vessel wall (Fig. 102.10). In a second step, leukocytes become firmly attached to the vessel wall, mainly mediated through the interaction of adhesion molecules of the immunoglobulin superfamily and their ligands. Finally, leukocytes migrate into the dermis through spaces between adjacent endothelial cells, involving interactions between junctional adhesion molecules. The molecular structure of the major adhesion molecules involved in leukocyte–endothelial cell interactions is shown in Figure 102.11, and the localization, ligand binding specificity, and function of each adhesion molecule are summarized in Table 102.2.

MAJOR ADHESION MOLECULES INVOLVED IN LEUKOCYTE–ENDOTHELIAL CELL INTERACTIONS: CELL-TYPE-SPECIFIC EXPRESSION, LIGANDS AND FUNCTION			
Adhesion molecule	**Cell type**	**Ligands**	**Function**
		INTEGRIN FAMILY	
LFA-1 (CD11a/CD18)	Leukocytes	ICAM-1, ICAM-2	Adhesion, emigration
Mac-1 (CD11b/CD18)	Granulocytes, monocytes	ICAM-1, iC3b	Adhesion, emigration
VLA-4 (CD49d/CD29)	Lymphocytes, monocytes, eosinophils, basophils	VCAM-1	Adhesion
		SELECTIN FAMILY	
E-selectin (CD62E)	Endothelial cells	L-selectin, CLA, SSEA-1	Rolling
P-selectin (CD62P)	Endothelial cells	L-selectin, PSGL-1	Rolling
L-selectin (CD62L)	Leukocytes	E-selectin, CD14, P-selectin, GlyCAM, MAdCAM	Rolling
		IMMUNOGLOBULIN SUPERGENE FAMILY	
ICAM-1 (CD54a)	Endothelial cells, monocytes	LFA-1, Mac-1, CD43	Adhesion, emigration
ICAM-2 (CD102)	Endothelial cells	LFA-1	Adhesion, emigration
VCAM-1 (CD106)	Endothelial cells	VLA-4	Adhesion
PECAM-1 (CD31)	Endothelial cells	PECAM-1	Adhesion, emigration

Table 102.2 Major adhesion molecules involved in leukocyte–endothelial cell interactions: cell-type-specific expression, ligands and function. CLA, cutaneous lymphocyte-associated antigen; Gly-CAM, glycosylation-dependent cell adhesion molecule; ICAM, intercellular adhesion molecule; LFA, lymphocyte function-associated antigen; MAdCAM, mucosal addressin cell adhesion molecule; PECAM, platelet–endothelial cell adhesion molecule; PSGL, P-selectin glycoprotein ligand; SSEA, stage-specific embryonic antigen; VCAM, vascular cell adhesion molecule; VLA, very late activation antigen.

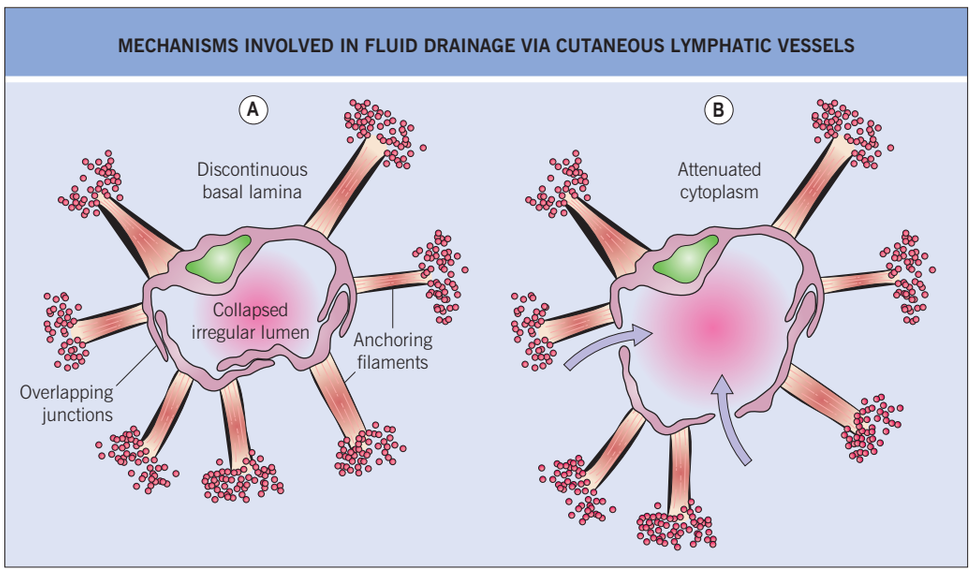


Fig. 102.12 Mechanisms involved in fluid drainage via cutaneous lymphatic vessels. A Normal skin. **B** Skin with increased interstitial fluid content.

STRUCTURE AND FUNCTION OF THE CUTANEOUS LYMPHATIC SYSTEM

Lymphatic vessels were first described in the seventeenth century by Gasparo Aselli as "lacteae venae" (milky veins). The cutaneous lymphatic system develops in parallel with the blood vascular system through a process termed lymphangiogenesis, and lymphatic vessels are not present in avascular structures such as epidermis, hair and nails[22]. The lymphatic system is composed of a vascular network of thin-walled capillaries that drain protein-rich lymph from the extracellular space and play a crucial role in the maintenance of normal tissue pressure. Lymphatic vessels also play an important role in mediating the trafficking of immune cells from the skin to the regional lymph nodes, and in the metastatic spread of cutaneous malignancies[22].

Lymphatic capillaries are lined by a continuous single-cell layer of overlapping endothelial cells and lack a continuous basement membrane. In initial lymphatics, overlapping flaps at the borders of oak leaf-shaped endothelial cells lack junctions at their tips but are anchored on the sides by discontinuous button-like junctions; the latter differ from the conventional, continuous, zipper-like junctions found in larger collecting lymphatics and blood vessels[23]. Lymph returns to the venous circulation via larger lymphatic collecting vessels, which contain a muscular and adventitial layer as well as numerous valves, and the thoracic duct.

The lymphatic vessels of the skin form two horizontal plexuses. The superficial plexus collects lymph from lymphatic capillaries that can extend into the dermal papillae and is located in close vicinity to the superficial cutaneous arterial plexus. Vertical lymphatic vessels connect the superficial plexus with the larger collecting vessels in the lower dermis and upper subcutis, whereas few lymphatics are found within the subcutis (see Fig. 102.1). The deep lymphatic vessels are located below the deep arterial system and contain valves to ensure unidirectional fluid transport.

The structure of the cutaneous lymphatics is dependent on the structure of the skin at a particular site and can vary significantly. Lymphatic vessels have a regular, uniform shape where the skin is firm and thick, whereas the shapes are more variable in regions where the skin is thin and loose. Certain areas, such as the fingers, the palms and soles, the scrotum and the foreskin, appear to have a more abundant lymphatic network.

Lymphatic capillaries respond to increased tissue fluid content by widening their lumina (Fig. 102.12), an action mediated by anchoring

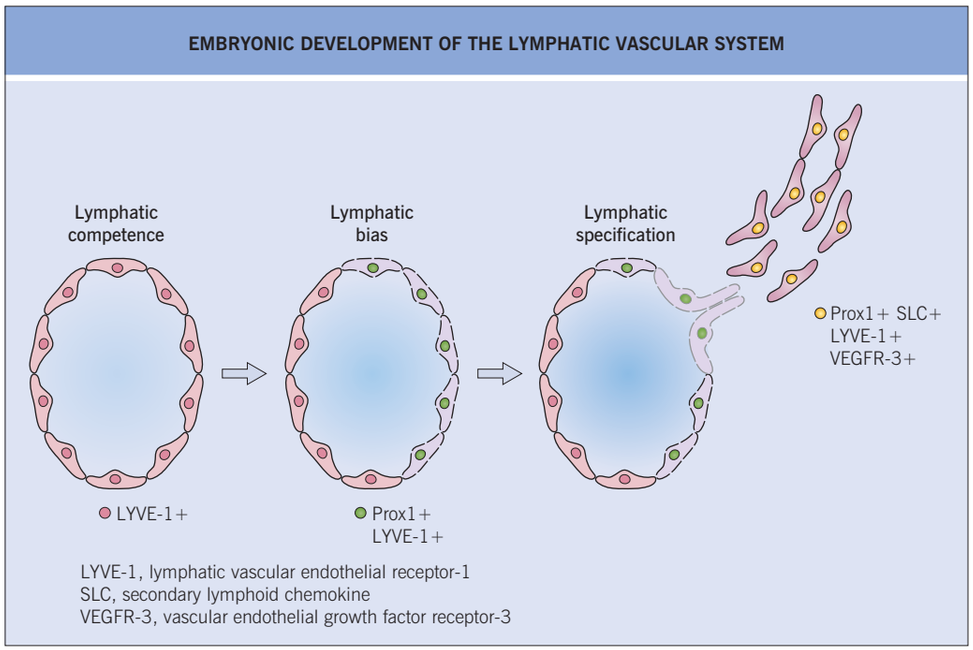


Fig. 102.13 Embryonic development of the lymphatic vascular system.

filaments that connect the lymphatic endothelial cells with the surrounding interstitium. In normal skin, the majority of lymphatic vessels are collapsed. Whereas elevation of the interstitial pressure up to + 2 mmHg results in distention of lymphatic vessels and in increased lymph flow, higher interstitial fluid pressure results in edema formation. The detection of enlarged lymphatics in the skin, however, does not allow predictions about their function, because overextended lymphatics can be dysfunctional, as in some types of lymphedema.

The first concept of lymphatic development was hypothesized by Florence Sabin, who proposed, based upon ink injection experiments, that isolated primitive lymph sacs originate from endothelial cells that bud from veins during early development. The peripheral lymphatic system originates from the primary lymph sacs and spreads by endothelial sprouting into the surrounding tissues and organs, where local capillaries are formed. As an alternative, it has been proposed that the primary lymph sacs arise in the mesenchyme, independent of the veins, and secondarily establish venous connections. Recent experimental evidence has supported the venous origin of the lymphatic system in mammals. The homeobox gene *Prox1* is a specific marker for lymphatic endothelial cells and is first expressed, during embryonic development, in a polarized manner by a subset of venous endothelial cells that consequently bud off from the cardinal veins, migrate through the tissues, and finally form lymphatic vessels (Fig. 102.13). Of note, Prox1 deficiency results in complete absence of a lymphatic system in mice, among other defects[24], and Prox1 activity is needed to maintain the lymphatic vessel phenotype after birth[25].

Until recently, studies of the lymphatic system were hampered by the lack of specific markers that reliably distinguish lymphatic from blood vascular endothelial cells. The endothelial marker PECAM-1 (platelet–endothelial cell adhesion molecule-1, CD31) is expressed by both blood vessel and lymphatic endothelial cells, although the expression levels are lower in lymphatics. Because of the absence or only rudimentary formation of a basement membrane, lymphatic vessels can be visualized by differential immunostaining for both CD31 and basement membrane components, such as collagen types IV and XVIII or laminin. Similarly, double stains for CD31 plus either the specific blood vascular marker PAL-E (only detectable on frozen sections; see Fig. 102.3) or the blood vascular marker CD34 can be used to specifically detect lymphatic vessels in the skin.

More recently, several new markers have been identified that are predominantly expressed by lymphatic endothelial cells in the skin (Table 102.3)[22]. *VEGFR-3* (vascular endothelial growth factor receptor-3, Flt-4) is expressed on lymphatic vessels in normal skin and serves as a receptor for the lymphangiogenesis factors VEGF-C and VEGF-D (Fig. 102.14). In addition, *podoplanin*, a surface glycoprotein, is a novel marker for the cutaneous lymphatic vasculature. The antibody D2-40 recognizes podoplanin and reliably and specifically stains lymphatic vessels (but not blood vessels) in normal and diseased human skin[26]. Of note, podoplanin deficiency results in congenital lymphedema formation as well as abnormal connections between lymphatic and blood vessels in mice[27,28].

The *lymphatic vascular endothelial hyaluronan receptor* (LYVE-1), a CD44 homologue, has been recently identified as a specific cell surface protein of lymphatic endothelial cells[22]. Although some specialized blood vascular endothelial cells that are involved in hyaluronic acid metabolism (e.g. sinusoidal endothelial cells in the liver, vascular endothelium in the lung) also express LYVE-1, its expression is highly specific for lymphatics in most organs, including the skin (Fig. 102.15). One has to keep in mind, however, that several of the markers discussed here, including

MARKERS FOR LYMPHATICS AND FOR BLOOD VESSELS

Marker	Lymphatics	Blood vessels
CD31 (PECAM-1)	+	++
CD34	–	+
PAL-E	–	+
Collagen type IV	–	+
Collagen type XVIII	–	+
Laminin	(+)	++
VEGFR-1	–	+
VEGFR-2	+	+
VEGFR-3	+	–
Podoplanin	++	–
LYVE-1	++	–
SLC/CCL21	+	–
Prox1	++	–

Table 102.3 Markers for lymphatics and for blood vessels. The shaded markers are expressed by lymphatics. PAL-E is only detectable on frozen sections. LYVE-1, lymphatic vascular endothelial receptor-1; PAL-E, pathologische anatomie Leiden-endothelium; PECAM-1, platelet–endothelial cell adhesion molecule-1; Prox1, prospero-related homeobox 1; SLC, secondary lymphoid chemokine; VEGFR, vascular endothelial growth factor receptor.

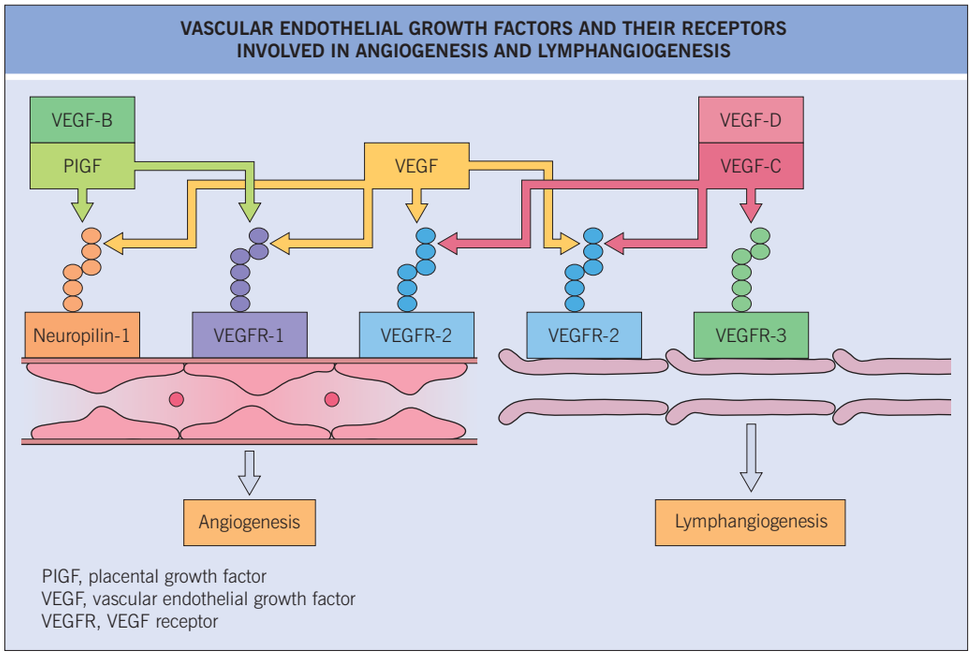


Fig. 102.14 Vascular endothelial growth factors and their receptors involved in angiogenesis and lymphangiogenesis. VEGF is also known as VEGF-A. Heterozygous inactivating missense mutations of the gene encoding VEGFR-3, the receptor for the lymphangiogenesis factors VEGF-C and VEGF-D, have been found in families affected by primary lymphedema (Milroy disease), which is characterized by chronic swelling of the extremities.

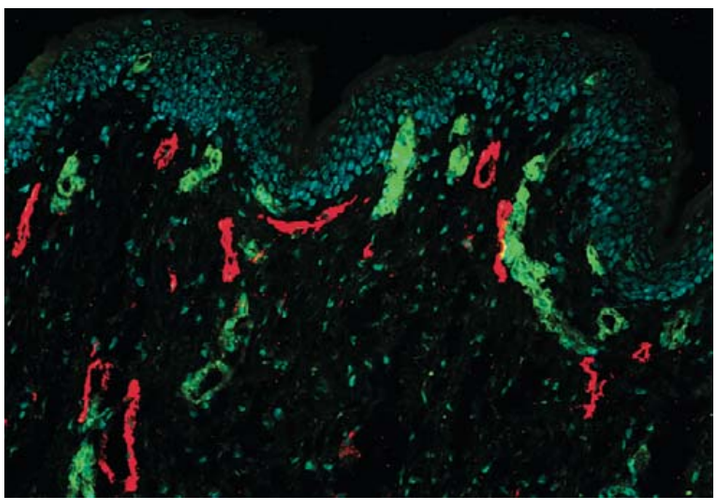


Fig. 102.15 Specific immunofluorescence staining of CD31-positive blood vessels (green) that are LYVE-1-negative and of CD31-positive/LYVE-1-positive lymphatic vessels (red) in human foreskin. Nuclei are stained blue.

VEGFR-3 and LYVE-1, can also be expressed by distinct subsets of leukocytes such as dermal dendritic cells and/or macrophages.

Secondary lymphoid chemokine (SLC; also termed CCL21) is specifically produced by lymphatic endothelial cells in the skin and binds to the CC chemokine receptor-7 (CCR-7) on dendritic cells and lymphocytes[22]. It serves an important role as a guidance molecule for the migration of dendritic and other cells via the lymphatics to the lymph nodes. Expression of CCR-7 in human melanoma cells resulted in increased lymph node metastasis of experimental melanomas in mice, suggesting that tumor cells may be able to take advantage of natural immune response mechanisms to further their metastatic spread[29]. The *chemokine receptor D6* – a receptor for several pro-inflammatory chemokines – has also been detected on lymphatic vessels, but not on blood vessels. Lastly, the homeobox gene *Prox1* is the earliest marker for lymphatic endothelial cells during embryonic development and its specific expression is maintained by cutaneous lymphatic endothelial cells in the adult. Prox1 appears to be the most specific marker for lymphatic vascular differentiation in the skin[22].

Until recently, the molecules regulating growth and function of lymphatic vessels have remained unknown. Over the past decade, two new members of the VEGF family of angiogenesis factors have been identified that are distinguished by their capacity to stimulate lymphangiogenesis. Both VEGF-C and VEGF-D activate the receptor tyrosine kinase VEGFR-3 (Flt-4) on lymphatic endothelial cells and, after cleavage, the receptor tyrosine kinase VEGFR-2 (KDR) that is expressed on blood vessels and lymphatic endothelium (see Fig. 102.14). Transgenic mice with targeted overexpression of either VEGF-C or VEGF-D in the skin were characterized by hyperplastic cutaneous lymphatic vessels, whereas no major abnormalities of blood vessels were found[30]. Conversely, blockade of both VEGF-C and VEGF-D by transgenic overexpression of a soluble VEGFR-3 in the skin has been shown to result in absence of a cutaneous lymphatic system and in the development of lymphedema[31]. Recently, additional lymphangiogenesis factors have been identified, including VEGF-A, angiopoietin-1, bFGF and hepatocyte growth factor (HGF)[32].

RELATED DISEASES

Angiogenesis is a characteristic feature of tissue repair and of numerous diseases, including inflammatory skin disorders such as psoriasis and contact dermatitis, cutaneous neoplasias including squamous cell carcinoma, melanoma and Kaposi sarcoma, and infantile hemangiomas. Moreover, several other diseases are characterized by prominent visible blood vessels, including rosacea and basal cell carcinomas. Genetic mutations that lead to dysfunction of the vascular Tie-2 receptor have been associated with vascular malformations (see Ch. 104), and mutations in the genes that encode the low-affinity TGF-β receptor endoglin and activin receptor-like kinase (ALK)-1 lead to the formation of vascular malformations in patients with hereditary hemorrhagic telangiectasia types I and II. Lastly, VEGF-C has been identified as a growth factor for HIV-associated Kaposi sarcomas that strongly express Flt-4/VEGFR-3, and infection of blood vascular endothelial cells with the Kaposi sarcoma-associated herpesvirus leads to their genetic reprogramming and to the adoption of a lymphatic endothelial cell phenotype[33].

Impairment of lymphatic function leads to the development of a number of diseases, most prominently to lymphedema of the skin, with associated impaired immune function and fibrotic changes[22,34]. Heterozygous inactivating missense mutations of the gene encoding VEGFR-3, the receptor for the lymphangiogenesis factors VEGF-C and VEGF-D, have been found in families affected by primary lymphedema (Milroy disease), which is characterized by chronic swelling of the extremities[35]. *VEGFR-3* mutations were also found in *Chy* mutant mice, the murine equivalent of Milroy disease, and both virus-mediated VEGF-C gene therapy and delivery of VEGF-C protein have been shown to induce

generation of functional lymphatic vessels in injured skin, indicating possible novel therapeutic strategies for congenital or acquired lymphedemas[30].

In lymphedema–distichiasis, lymphatic vessel function fails because of mutations affecting the function of the forkhead transcription factor FOXC2[36], and mutations in the transcription factor gene *SOX18* underlie recessive and dominant forms of hypotrichosis–lymphedema–telangiectasia[37]. Finally, tumor-associated lymphangiogenesis has been found to promote sentinel lymph node metastasis and to reduce overall survival in human melanomas and in a number of other carcinomas[38,39].

In summary, the recent progress in our understanding of the molecular mechanisms that control blood vascular and lymphatic development and function have led to novel insights into the pathogenesis of a number of skin diseases with vascular involvement, as well as to the development of novel therapeutic approaches to treat these diseases.

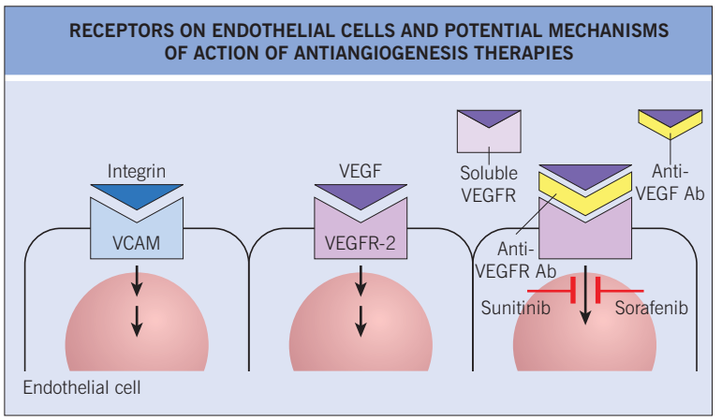


Fig. 102.16 Receptors on endothelial cells and potential mechanisms of action of antiangiogenesis therapies.

CURRENT TRENDS IN ANTIANGIOGENESIS

A large number of experimental studies have shown that the induction of angiogenesis is essential for tumor progression and that inhibition of blood vessel growth inhibits malignant tumor growth and metastasis in mice. Based upon these findings, inhibition of tumor angiogenesis has become a main target of anticancer strategies[40]. Despite the identification of several distinct tumor angiogenesis factors, including interleukin-8 and bFGF, the majority of current antitumor angiogenesis therapies are aimed at inhibiting the bioavailability or the receptor signaling of VEGF-A, generally considered to represent the major angiogenic factor in the majority of solid tumors.

The anti-VEGF-A antibody bevacizumab (Avastin®) – combined with chemotherapy – has shown modest beneficial effects in patients with metastatic colon cancer. However, in metastatic breast cancer, there are several studies that have failed to demonstrate a significant survival benefit with bevacizumab. Side effects include gastrointestinal perforation, delayed wound healing and hemorrhage (e.g. gastrointestinal, CNS). Additional clinical trials in human cancer patients are currently investigating the anticancer activity of VEGF receptor-blocking antibodies, PlGF-blocking antibodies and soluble VEGF receptor molecules, as well as small molecule tyrosine kinase inhibitors that block VEGF receptor signaling (Fig. 102.16).

Endogenous inhibitors of angiogenesis, including thrombospondin-1-derived peptides, are also under investigation in clinical trials. Several drugs that are already in clinical use have been found to exert mild antiangiogenic activities, including thalidomide and interferon-α and -β. The first two agents, for example, are used as second-line therapy for extensive Kaposi sarcoma. "Metronomic" or low-dose chemotherapy (e.g. with paclitaxel or vinblastine) has been proposed to exert antiangiogenic effects, and experimental tumor studies in mice have shown additive or synergistic effects of low-dose chemotherapy combined with angiogenesis inhibitors[41]. Unfortunately, there appears to be a number of potential mechanisms that lead to resistance to antiangiogenic therapy.

The recent discovery of active tumor- and lymph node-associated lymphangiogenesis, and its correlation with enhanced cancer metastasis, suggests that, at least in some types of cancer, anti-lymphangiogenic therapy might provide a novel strategy[5,38,39,42]. Moreover, *in vivo* imaging of tumor-induced lymphangiogenesis might provide a sensitive method for the early detection of lymph node metastases.

Although the efficacy of antiangiogenic therapy in the treatment of advanced melanoma or cutaneous squamous cell carcinoma still remains unclear, an increasing number of non-malignant skin diseases have emerged as potential targets for treatments aimed at vascular endothelium. For example, prior to the discovery of the efficacy of propranolol, steroid-unresponsive infantile hemangiomas were treated with interferon-α; additional vascular lesions that might respond to antiangiogenic treatment include angiokeratomas and kaposiform hemangioendotheliomas. Psoriasis is characterized by vascular enlargement and activation, and recent experimental data suggest that blockade of VEGF might represent a novel therapeutic strategy[43]. In fact, pulsed dye laser therapy has been used to effectively treat psoriatic skin lesions, predominantly by targeting cutaneous blood vessels. Similarly, telangiectasias, in particular in rosacea, would appear to represent prime targets for antiangiogenic therapy.

Blockade of angiogenesis and vascular activation might also represent a novel approach for preventing UVB-induced skin damage[44] as well as multistep skin carcinogenesis, indicating the potential use of angiogenesis inhibitors for chemoprevention. Of note, in solid organ transplant recipients, substituting sirolimus (rapamycin; an mTOR inhibitor) for cyclosporine has led to improvement of immunosuppression-associated Kaposi sarcoma, and in those transplant patients with multiple basal cell and squamous cell carcinomas, use of sirolimus may lead to a decrease in their formation.

Because systemic inhibition of angiogenesis might cause considerable side effects, including hypertension, proteinuria and interference with reproductive functions, the challenge and opportunity for dermatology will be to develop topical angiogenesis inhibitors that will be able to penetrate the skin but not reach potentially toxic systemic levels. Recent experimental data indicate the feasibility of this approach[45].

In addition to these potential dermatologic applications, antiangiogenesis has become a promising new therapeutic approach in ophthalmology. Diabetes mellitus is frequently associated with intraocular neovascularization, and new blood vessel growth is the principal cause of visual loss in the wet form of age-related macular degeneration, the most common cause of blindness in Western countries. Intravitreal injection of VEGF inhibitors has been successfully used to prevent progression of this disease and has been approved for clinical use by the Food and Drug Administration (FDA). Other potential therapeutic applications of antiangiogenesis include diseases of the female reproductive tract, such as polycystic ovary syndrome, endometriosis and ovarian hyperstimulation syndrome. The potential side effects of chronic, systemic angiogenesis inhibition are at present not well characterized and, therefore, it is difficult to predict whether systemic antiangiogenic therapies will be used for non-malignant conditions in the future.

REFERENCES

1. Ryan TJ. Cutaneous circulation. In: Goldsmith LA (ed.). Biochemistry and Physiology of the Skin. New York: Oxford University Press, 1983. 817–77.
2. Yano K, Brown LF, Detmar M. Control of hair growth and follicle size by VEGF-mediated angiogenesis. J Clin Invest. 2001;107:409–17.
3. Braverman IM, Yen A. Ultrastructure of the human dermal microcirculation. II. The capillary loops of the dermal papillae. J Invest Dermatol. 1977;68:44–52.
4. Dvorak HF, Brown LF, Detmar M, et al. Vascular permeability factor/vascular endothelial growth factor, microvascular hyperpermeability, and angiogenesis. Am J Pathol. 1995;146:1029–39.
5. Skobe M, Hawighorst T, Jackson DG, et al. Induction of tumor lymphangiogenesis by VEGF-C promotes breast cancer metastasis. Nat Med. 2001;7:192–8.

6. Flamme I. Molecular biology of vasculogenesis and early angiogenesis. In: Rubanyi GM (ed.). Angiogenesis in health and disease Basic mechanisms and clinical applications. New York: Marcel Dekker, 2000:1–30.
7. Nishikawa SI, Nishikawa S, Hirashima M, et al. Progressive lineage analysis by cell sorting and culture identifies FLK1+VE-cadherin+ cells at a diverging point of endothelial and hemopoietic lineages. Development (Cambridge, England). 1998;125:1747–57.
8. Andrae J, Gallini R, Betsholtz C. Role of platelet-derived growth factors in physiology and medicine. Genes Dev. 2008;22:1276–312.
9. Dvorak HF. Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing. N Engl J Med. 1986;315:1650–9.
10. Holash J, Maisonpierre PC, Compton D, et al. Vessel cooption, regression, and growth in tumors mediated by angiopoietins and VEGF. Science. 1999;284:1994–8.
11. Davis GE, Senger DR. Extracellular matrix mediates a molecular balance between vascular morphogenesis and regression. Curr Opin Hematol. 2008;15:197–203.
12. Senger DR, Galli SJ, Dvorak AM, et al. Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. Science. 1983;219:983–5.
13. Detmar M, Brown LF, Claffey KP, et al. Overexpression of vascular permeability factor/vascular endothelial growth factor and its receptors in psoriasis. J Exp Med. 1994;180:1141–6.
14. Detmar M, Brown LF, Schon MP, et al. Increased microvascular density and enhanced leukocyte rolling and adhesion in the skin of VEGF transgenic mice. J Invest Dermatol. 1998;111:1–6.
15. Kunstfeld R, Hirakawa S, Hong YK, et al. Induction of cutaneous delayed-type hypersensitivity reactions in VEGF-A transgenic mice results in chronic skin inflammation associated with persistent lymphatic hyperplasia. Blood. 2004;104:1048–57.
16. Hirakawa S, Kodama S, Kunstfeld R, et al. VEGF-A induces tumor and sentinel lymph node lymphangiogenesis and promotes lymphatic metastasis. J Exp Med. 2005;201:1089–99.
17. Carmeliet P, Moons L, Luttun A, et al. Synergism between vascular endothelial growth factor and placental growth factor contributes to angiogenesis and plasma extravasation in pathological conditions. Nat Med. 2001;7:575–83.
18. Oura H, Bertoncini J, Velasco P, et al. A critical role of placental growth factor in the induction of inflammation and edema formation. Blood. 2003;101:560–7.
19. Lawler J, Detmar M. Tumor progression: the effects of thrombospondin-1 and -2. Int J Biochem Cell Biol. 2004;36:1038–45.
20. Yano K, Oura H, Detmar M. Targeted overexpression of the angiogenesis inhibitor thrombospondin-1 in the epidermis of transgenic mice prevents ultraviolet-B-induced angiogenesis and cutaneous photo-damage. J Invest Dermatol. 2002;118:800–5.
21. Hawighorst T, Velasco P, Streit M, et al. Thrombospondin-2 plays a protective role in multistep carcinogenesis: a novel host anti-tumor defense mechanism. EMBO J. 2001;20:2631–40.
22. Cueni LN, Detmar M. The lymphatic system in health and disease. Lymphat Res Biol. 2008;6:109–22.
23. Baluk P, Fuxe J, Hashizume H, et al. Functionally specialized junctions between endothelial cells of lymphatic vessels. J Exp Med. 2007;204:2349–62.
24. Oliver G, Detmar M. The rediscovery of the lymphatic system: old and new insights into the development and biological function of the lymphatic vasculature. Genes Dev. 2002;16:773–83.
25. Johnson NC, Dillard ME, Baluk P, et al. Lymphatic endothelial cell identity is reversible and its maintenance requires Prox1 activity. Genes Dev. 2008;22:3282–91.
26. Schacht V, Dadras SS, Johnson LA, et al. Up-regulation of the lymphatic marker podoplanin, a mucin-type transmembrane glycoprotein, in human squamous cell carcinomas and germ cell tumors. Am J Pathol. 2005;166:913–21.
27. Schacht V, Ramirez MI, Hong YK, et al. T1alpha/podoplanin deficiency disrupts normal lymphatic vasculature formation and causes lymphedema. EMBO J. 2003;22:3546–56.
28. Uhrin P, Zaujec J, Breuss JM, et al. Novel function for blood platelets and podoplanin in developmental separation of blood and lymphatic circulation. Blood. 2010;115:3997–4005.
29. Wiley HE, Gonzalez EB, Maki W, et al. Expression of CC chemokine receptor-7 and regional lymph node metastasis of B16 murine melanoma. J Natl Cancer Inst. 2001;93:1638–43.
30. Tammela T, Alitalo K. Lymphangiogenesis: molecular mechanisms and future promise. Cell. 2010;140:460–76.
31. Makinen T, Jussila L, Veikkola T, et al. Inhibition of lymphangiogenesis with resulting lymphedema in transgenic mice expressing soluble VEGF receptor-3. Nat Med. 2001;7:199–205.
32. Jurisic G, Detmar M. Lymphatic endothelium in health and disease. Cell Tissue Res. 2009;335:97–108.
33. Hong YK, Foreman K, Shin JW, et al. Lymphatic reprogramming of blood vascular endothelium by Kaposi sarcoma-associated herpesvirus. Nat Genet. 2004;36:683–5.
34. Ryan TJ. The lymphatics of the skin. In: Jarrett A (ed.). Physiology and Pathophysiology of the Skin. New York: Academic Press, 1978:1755–811.
35. Karkkainen MJ, Ferrell RE, Lawrence EC, et al. Missense mutations interfere with VEGFR-3 signalling in primary lymphoedema. Nat Genet. 2000;25:153–9.
36. Petrova TV, Karpanen T, Norrmen C, et al. Defective valves and abnormal mural cell recruitment underlie lymphatic vascular failure in lymphedema distichiasis. Nat Med. 2004;10:974–81.
37. Irrthum A, Devriendt K, Chitayat D, et al. Mutations in the transcription factor gene SOX18 underlie recessive and dominant forms of hypotrichosis-lymphedema-telangiectasia. Am J Hum Genet. 2003;72:1470–8.
38. Dadras SS, Paul T, Bertoncini J, et al. Tumor lymphangiogenesis: a novel prognostic indicator for cutaneous melanoma metastasis and survival. Am J Pathol. 2003;162:1951–60.
39. Rinderknecht M, Detmar M. Tumor lymphangiogenesis and melanoma metastasis. J Cell Physiol. 2008;216:347–54.
40. Chung AS, Lee J, Ferrara N. Targeting the tumour vasculature: insights from physiological angiogenesis. Nat Rev. 2010;10:505–14.
41. Kerbel RS, Kamen BA. The anti-angiogenic basis of metronomic chemotherapy. Nat Rev. 2004;4:423–36.
42. Hirakawa S, Brown LF, Kodama S, et al. VEGF-C-induced lymphangiogenesis in sentinel lymph nodes promotes tumor metastasis to distant sites. Blood. 2007;109:1010–17.
43. Schonthaler HB, Huggenberger R, Wculek SK, et al. Systemic anti-VEGF treatment strongly reduces skin inflammation in a mouse model of psoriasis. Proc Natl Acad Sci U S A. 2009;106:21264–9.
44. Hirakawa S, Fujii S, Kajiya K, et al. Vascular endothelial growth factor promotes sensitivity to ultraviolet B-induced cutaneous photodamage. Blood. 2005;105:2392–9.
45. Halin C, Fahrngruber H, Meingassner JG, et al. Inhibition of chronic and acute skin inflammation by treatment with a vascular endothelial growth factor receptor tyrosine kinase inhibitor. Am J Pathol. 2008;173:265–77.

This page intentionally left blank

Infantile Hemangiomas 103

Anita N Haggstrom and Maria C Garzon

Synonyms: ■ Hemangioma of infancy ■ Hemangioma

Key features

- The most common soft tissue tumor of infancy
- Benign endothelial cell neoplasms
- Demonstrate a typical growth pattern characterized by early proliferation followed by gradual, spontaneous involution
- Distinct histopathologic and immunohistochemical features that differentiate them from other vascular anomalies in children
- May be associated with extracutaneous findings when occurring at certain anatomic sites, e.g. the face, neck and lumbosacral area
- Treatment choice, if any, depends on multiple factors and must be tailored to each individual patient

INTRODUCTION

Infantile hemangiomas are benign proliferations of endothelial tissue and represent the most common tumors arising in the neonatal period. They are characterized by significant growth during the first several months of life, followed by slow spontaneous involution over the ensuing years. This natural history differentiates them from vascular malformations (Table 103.1; see Fig. 104.1). During the past decade, elucidation of mechanisms governing growth and regulatory pathways of normal vascular development has led to new insights into the pathophysiology of infantile hemangiomas.

HISTORY

The terms "infantile hemangioma" and "hemangioma of infancy" are now used to describe a specific group of vascular tumors that arise during infancy and demonstrate characteristic clinical and histologic features. Infantile hemangiomas have been recognized in the medical literature for centuries, and they have been given various names such as *nevus maternus*, *angioma simplex*, *angioma cavernosum*, *angiodysplasia*, *strawberry nevus* and *capillary hemangioma*[1]. Despite early attempts to make distinctions among different types of vascular lesions of infancy, the term "hemangioma" was frequently applied in a generic manner to a wide variety of congenital and acquired vascular anomalies including vascular malformations, without consideration of differences in their biologic behavior.

One of the most important developments in the study of vascular "birthmarks" (including lesions that become apparent during early infancy) was the suggestion and acceptance of a biologic classification scheme. In 1982, Mulliken and Glowacki[2] first proposed that vascular birthmarks should be categorized according to their biologic and clinical behavior. The International Society for the Study of Vascular Anomalies modified this classification system slightly in 1996 (Table 103.2)[3].

Under this organization scheme, vascular birthmarks are divided into two broad categories: *vascular tumors* and *vascular malformations*. Vascular tumors are characterized by cellular proliferation and include infantile hemangiomas, the later-onset pyogenic granuloma, and less common neoplasms that may arise during infancy or early childhood, including tufted angioma and kaposiform hemangioendothelioma (see Table 103.2; see Ch. 114). Vascular malformations, on the other hand, are believed to represent errors in vascular morphogenesis. They are frequently noted during the neonatal period, but, unlike infantile hemangiomas, they do not rapidly proliferate in the first year of life nor do they resolve spontaneously (see Table 103.1). Vascular malformations are characterized by the type of dysplastic vessels they contain and their flow properties (see Ch. 104).

Adopting specific terminology has allowed investigators to better categorize vascular birthmarks and predict their clinical behavior and prognosis. The biologic classification was expanded to include histopathologic and immunohistochemical features that aid in distinguishing infantile hemangiomas from other vascular tumors (see Table 103.1). Despite the wide acceptance of the biologic classification scheme, nosologic confusion still persists in the medical community as well as in the literature. Even within the past decade, a review of genetic reference texts found the term "hemangioma" to be used imprecisely with great frequency[4].

EPIDEMIOLOGY

Infantile hemangiomas arise during the first year of life and are the most common tumor of infancy. They develop in 4–5% of infants, with the majority of lesions noted within the first several weeks of life[5]. Infantile hemangiomas may occur more commonly in Caucasian infants than in other racial groups, but this predilection has not been consistently observed[6]. This vascular tumor is clearly more common in girls than in boys, with a female : male ratio of 2–5 : 1 overall[7–9] and approximately 7 : 1 for severe, complicated lesions[10]. Infantile hemangiomas also develop more frequently in premature infants, affecting 23–30% of infants with birthweights less than 1000 g and 15% of those with birthweights between 1000 and 1500 g[6,11]. There is a threefold increased incidence in infants born following chorionic villus sampling compared to those born following amniocentesis or without a history of prenatal instrumentation[12]. A multicenter, prospective cohort study of over 1000 infants from the US with infantile hemangiomas found several important epidemiologic and demographic differences compared to US National Vital Statistics data for children born in the same period. Infants with hemangiomas were more likely to be female, Caucasian, low birthweight, premature, products of multiple gestation pregnancies, and born to older mothers[13].

Infantile hemangiomas typically arise sporadically, although Margileth and Museles[14] reported a 10% incidence of familial cases in their 1965 series. The frequent occurrence of hemangiomas in the general population makes it difficult to assess the true familial incidence. Autosomal dominant segregation of infantile hemangiomas was described in six kindreds, some of which included members who also had vascular malformations, and genetic mapping was performed (see below)[15,16].

PATHOGENESIS

Infantile hemangiomas represent localized or regional areas of abnormal vascular development and proliferation. Several hypotheses have been proposed to explain their pathogenesis, but no single theory accounts for all of their features. It is likely that several mechanisms under the control of multiple genes, in addition to local effects, play a role in the development, growth and involution of hemangiomas.

Hemangioma Endothelial Cells: Origin, Defects and Signaling

Recent evidence suggests that hemangiomas may be derived from endothelial progenitor cells or multipotent stem cells[17–19]. This implies

VASCULAR "BIRTHMARKS" IN CHILDREN		
	Infantile hemangioma	**Vascular malformation**
Clinical	• Usually absent at birth or subtle precursor lesion present (only occasionally well formed) • Rapid proliferation • Spontaneous involution over years	• Usually evident at birth • Slow expansion, proportionate with growth • Persists into adulthood
Epidemiology	More common in: • girls (2–5 : 1) • premature and/or low-birthweight infants • infants whose mothers were older or who underwent chorionic villus sampling	No gender or gestation predilection
Pathology	**Proliferating**: endothelial cell hyperplasia, lobule formation, mast cells, prominent basement membrane **Involuting**: fibrofatty tissue replacement, decreased mast cells when fully involuted	Dependent upon type, often irregular vascular channels
Immunohistochemistry	Positive for GLUT-1, Lewis Y antigen, merosin and FcγRII	Negative for GLUT-1, Lewis Y antigen, merosin and FcγRII

Table 103.1 Vascular "birthmarks" in children.

BIOLOGIC CLASSIFICATION OF VASCULAR BIRTHMARKS
VASCULAR TUMORS
• Infantile hemangioma • Congenital hemangioma (rapidly involuting or non-involuting variants) • Kaposiform hemangioendothelioma • Tufted angioma • Pyogenic granuloma • Congenital hemangiopericytoma • Spindle cell hemangioma
VASCULAR MALFORMATIONS
• Capillary malformations (slow flow) • Venous malformations (slow flow) – Typical – With glomus cells • Lymphatic malformations (slow flow) – Macrocystic – Microcystic • Arteriovenous malformations (fast flow) • Combined malformations (slow and/or fast flow)

Table 103.2 Biologic classification of vascular birthmarks.

that vasculogenesis (*de novo* formation of vessels from progenitor/stem cells) as well as angiogenesis (formation of new vessels from existing ones) might occur during hemangioma formation.

Hemangiomas have been shown to represent clonal expansions of endothelial cells[20], and *somatic* mutations in genes that encode proteins involved in vascular endothelial growth factor (VEGF) signaling (e.g. VEGF receptors [VEGFRs]; see Ch. 102) and other pathways that affect vascular development (e.g. dual-specificity phosphatase 5 [DUSP5]) have been identified in hemangioma tissue[18,21,22]. Heterozygous *germline* mutations in *VEGFR2* and *TEM8* (encodes an integrin-like receptor in endothelial cells) genes have also been found in a small subset of hemangioma patients and may represent hemangioma predisposition factors (Fig. 103.1)[23]. In addition, familial hemangiomas in several kindreds have been linked to chromosome 5q[16] and loss of heterozygosity (see Ch. 54) of 5q has been noted in sporadic hemangiomas[24], suggesting that gene(s) at this locus may be involved in hemangioma formation.

Recent studies have confirmed the importance of the VEGF pathway in infantile hemangiomas and provided evidence of a shift from VEGFR1 (which binds VEGF without transmitting a signal) to VEGFR2 (which stimulates endothelial cell proliferation upon VEGF binding) expression in hemangioma endothelial cells (see Fig. 103.1)[23]. Hemangiomas also have increased expression of the endothelial cell-specific Tie-2 tyrosine kinase receptor and dysregulated production of angiopoietin-2 (see Ch. 102)[25].

Placental Hypothesis

The shared immunohistochemical phenotype of hemangioma cells and human placental endothelium implies that hemangioma cells are either of placental origin (e.g. via embolization) or undergo differentiation toward a placental microvascular phenotype. North and co-workers[26,27] reported that glucose transporter protein-1 (GLUT-1) is expressed by infantile hemangiomas during all phases of their development (proliferating, involuting, involuted) as well as by the placenta, but not by other vascular tumors or malformations. Other placenta-associated vascular antigens, including merosin, FcγRII and Lewis Y antigen, are present in hemangioma specimens and placental chorionic villi but absent in microvessels of the normal skin and subcutis[27]. However, hemangiomas do not express placental *trophoblastic* markers (e.g. human placental lactogen)[28].

Hypoxia and Other Extrinsic Factors

A role for hypoxia in the pathogenesis of hemangiomas is supported by their association with hypoxic placental changes, prematurity/low birthweight (often caused by placental insufficiency), retinopathy of prematurity (GLUT-1-positive, hypoxia-induced neovascularization) and regional arterial insufficiency (e.g. PHACE[S] and LUMBAR syndromes; see below)[29,30]. Hypoxia upregulates expression of GLUT-1 and VEGF, leading to mobilization of endothelial progenitor cells. Moreover, the combination of hypoxia and estrogen (pertinent considering the predilection of hemangiomas for female infants) has a synergistic effect on hemangioma endothelial cell proliferation *in vitro*[29].

Other cell types in the hemangioma's environment, including monocytes, fibroblasts, mesenchymal cells, adipocytes and mast cells, can influence endothelial cell proliferation and may have a role in hemangioma formation and/or involution.

Factors Influencing Natural History

Hemangiomas have been studied during different phases of their clinical course to gain insights into the mechanisms that govern their growth and involution. In the proliferative phase, hemangiomas express markers of proliferation (e.g. proliferating cell nuclear antigen [PCNA]) and increased levels of pro-angiogenic molecules such as VEGF and basic fibroblast growth factor (bFGF)[31–33]. In addition, other angiogenesis mediators, proteins found within the perivascular extracellular matrix, and enzymes involved in matrix remodeling are produced at higher levels during proliferation (Table 103.3)[31,34–41].

The factors that govern the transition of hemangiomas from proliferation to involution, which is associated with decreased production of pro-angiogenic factors, are not fully understood[31,36,37]. Indoleamine 2,3-dioxygenase (IDO), an enzyme that degrades tryptophan and (through tryptophan starvation and immunosuppressive effects of its metabolites) inhibits T-cell activation, is highly expressed by macrophages, dendritic cells, the placenta (where it is believed to protect the fetus from rejection) and *proliferating* hemangiomas. It has been hypothesized that increased IDO activity protects proliferating hemangiomas from immune surveillance, and subsequent downregulation of IDO production may therefore have a role in involution[18,42]. Increased expression of angiogenesis inhibitors and apoptosis promoters has been observed in involuting hemangiomas (see Table 103.3)[31,43–46]. Loss of DUSP5 function increases apoptosis in human umbilical vein endothelial cells, leading to speculation that somatic mutations in this gene (recently found in hemangiomas; see above) may contribute to hemangioma involution as well as proliferation[22].

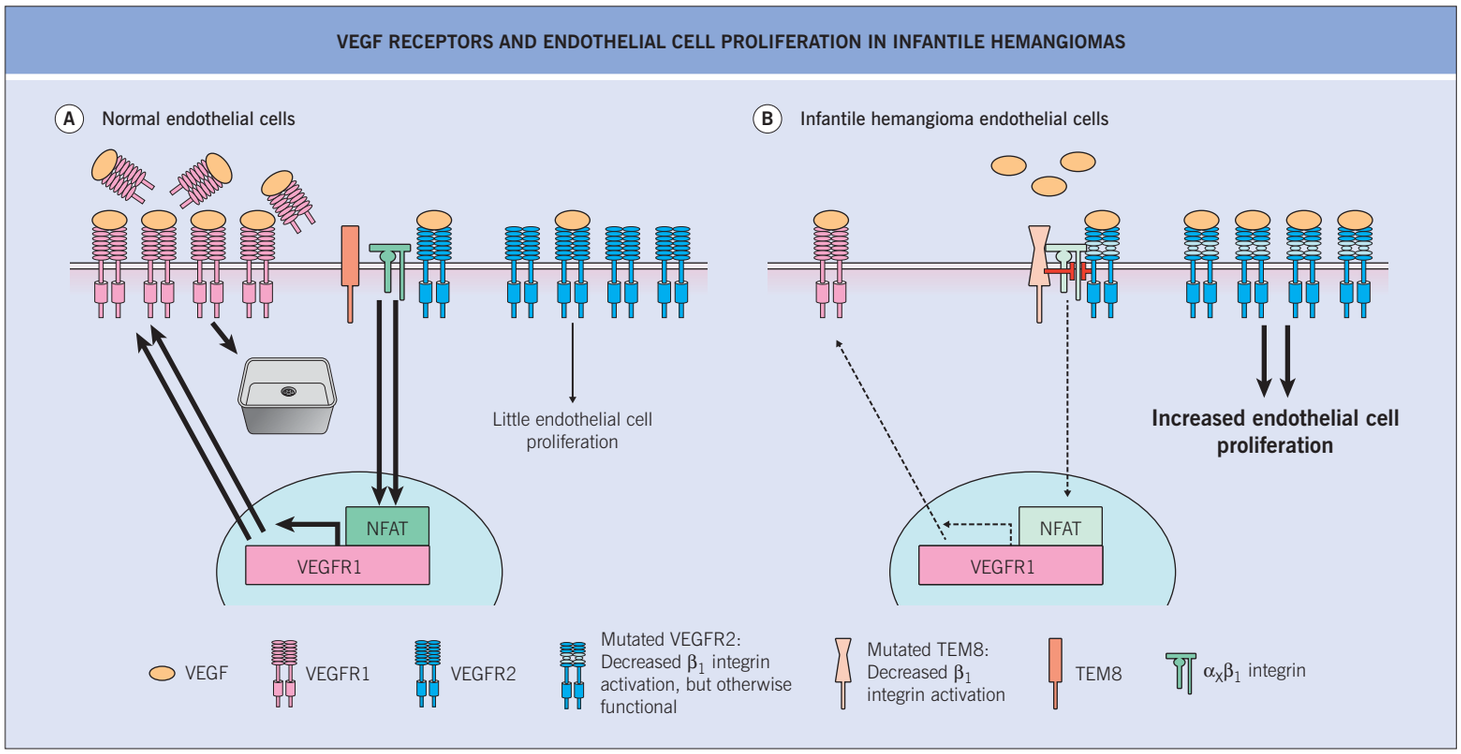


Fig. 103.1 VEGF receptors and endothelial cell proliferation in infantile hemangiomas. A In normal endothelial cells, β_1-integrin (which forms a complex with the integrin-like receptor TEM8 and VEGFR2) increases transcription of VEGFR1 via activation of NFAT. Binding of VEGF to VEGFR2 stimulates endothelial cell proliferation, but VEGF binding to VEGFR1 (which exists in soluble and transmembrane forms) is of higher affinity and does not transmit a signal. VEGFR1 thereby acts as a VEGF "sink" or decoy receptor that decreases the amount of VEGF available to activate VEGFR2. **B** Hemangioma endothelial cells have decreased β_1-integrin activity and, as a consequence, markedly reduced expression of VEGFR1. This leads to increased VEGF-dependent activation of VEGFR2 and enhanced endothelial cell proliferation. In a subset of hemangioma patients, the low β_1-integrin activity can be explained by a germline mutation in the *VEGFR2* or *TEM8* gene; such mutations result in increased interactions among β_1-integrin, TEM8 and VEGFR2 as well as inhibition of β_1-integrin function. NFAT, nuclear factor of activated T cells; TEM8, tumor endothelial marker 8; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

MARKERS OF PROLIFERATING AND INVOLUTING HEMANGIOMAS

PROLIFERATIVE PHASE

- General markers of proliferation, e.g. proliferating cell nuclear antigen (PCNA)
- Vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF)*,†
- Monocyte chemoattractant protein-1†
- Adhesion molecules on endothelial cells – E-selectin, ICAM-3†
- Matrix metalloproteinase-2 and -9 (extracellular matrix remodeling)‡
- Vitronectin (found in the perivascular extracellular matrix)
- Indoleamine 2,3-dioxygenase (inhibits T-cell activation)
- Apoptosis inhibitors

INVOLUTION

- Interferon-regulated gene products (interferons are known to inhibit angiogenesis)
- bFGF (early in involution)
- Increased mast cells (early in involution)
- Tissue inhibitor of matrix metalloproteinases-1 (inhibits angiogenesis)
- Apoptosis promoters

*VEGF and bFGF (but not the angiogenesis inhibitor interferon-β) are also expressed by the hyperplastic epidermis overlying proliferating hemangiomas.
†Angiogenesis mediators.
‡Increased levels also found in blood and urine.

Table 103.3 Markers of proliferating and involuting hemangiomas. Lymphatic vessel endothelial hyaluronan receptor (LYVE)-1 has been identified in perivascular dendritic cells in hemangiomas of various stages. ICAM, intercellular adhesion molecule.

CLINICAL FEATURES

Presentation

Most infantile hemangiomas have a typical presentation and growth pattern. Lesions usually become apparent during the first few weeks of life, although the proportion of hemangiomas that were "congenital" in published series has ranged from 15% to 60%[9,47]. There are several distinct subgroups of hemangiomas evident in the immediate newborn period: (1) infantile hemangioma precursor lesions; (2) occasional typical infantile hemangiomas that are relatively well formed at birth and subsequently demonstrate a natural history (variable proliferation then slow involution) similar to those that arise later; and (3) an uncommon subset of congenital hemangiomas that demonstrate intrauterine proliferation, little if any postnatal growth, and then either early rapid involution in postnatal life or minimal to absent involution. The third group includes the rapidly involuting congenital hemangioma (RICH) and the non-involuting congenital hemangioma (NICH), which are considered as separate entities from infantile hemangiomas and are discussed below.

Reports of significant numbers of hemangiomas being noted at birth probably included precursor lesions. Telangiectasias surrounded by a vasoconstricted halo, areas of pallor, pink macules, and blue bruise-like patches are the most common precursor lesions (Fig. 103.2). Pink macules and patches may mimic a capillary malformation, and repeat examination over the ensuing weeks is essential to determine the diagnosis (Fig. 103.3). Rarely, an area of ulceration on the lip or perineum may herald the onset of an infantile hemangioma, and in a newborn infant these lesions may be confused with bacterial or viral infections. Biopsy of the ulcerated lesion may not be clearly diagnostic of an infantile hemangioma, but continued observation of the site usually clarifies the diagnosis[48].

Hemangiomas may occur anywhere on the skin and mucosal surfaces, with approximately 50% of those in infants who present to a pediatric dermatologist being located on the head and neck[13]. The clinical appearance of a hemangioma is determined by its location within the skin and subcutaneous tissues. Superficial hemangiomas are situated in the superficial dermis and are bright red in color during their proliferating phase. The surface is finely lobulated, and the term "strawberry hemangioma" has been used to describe them[2]. The majority of superficial hemangiomas are focal lesions (Fig. 103.4A,B). Less common

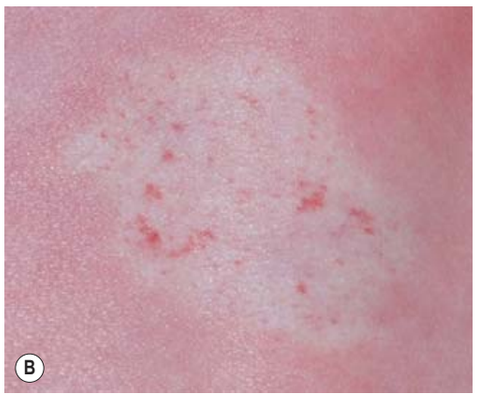


Fig. 103.2 Hemangioma precursors. These premonitory lesions can have a "bruised" (**A**) or blanched (**B**) appearance. *B, Courtesy, Julie V Schaffer, MD.*

Fig. 103.3 Superficial hemangioma mimicking a capillary malformation. This lesion's segmental configuration would warrant a consideration of PHACE(S) syndrome.

Fig. 103.4 Superficial hemangioma. Lesions can be focal (**A**, **B**) or have a broader segmental distribution (**C**). Note the bright red color and finely lobulated surface, irrespective of size. Involvement may be diffuse or broken-up. *Courtesy, Julie V Schaffer, MD.*

and more worrisome is the larger plaque-type or segmental pattern of superficial hemangiomas (Fig. 103.4C). These lesions may begin as broad erythematous patches that are confluent, reticulated or telangiectatic. Within a few weeks, bright red papules and plaques arise on the surface.

Deep hemangiomas are located in the deep dermis and/or subcutis. They usually are not apparent in the immediate newborn period, often becoming evident after a few weeks of age. They present as warm, ill-defined, light blue–purple masses with minimal or no overlying skin changes (Fig. 103.5), making them more difficult to diagnose than superficial or mixed hemangiomas[49]. The presence of dilated veins or telangiectasias overlying a deep hemangioma provides a clue that the lesion is of vascular origin. Larger deep hemangiomas often have significant arterial blood supply during their peak growth phase. A thrill may be felt or a bruit auscultated, and high flow can be documented by Doppler ultrasonography. Mixed hemangiomas have both superficial and deep components, often presenting during the proliferative phase as a well-delineated red vascular plaque overlying a larger, poorly circumscribed light blue nodule.

Superficial hemangiomas are the most common type, accounting for approximately 50–60% of infantile hemangiomas. An additional 25–35% of hemangiomas are mixed and 15% are deep[7]. Approximately 25% of patients have multiple lesions, which are occasionally associated with visceral hemangiomatosis (see below).

Several studies have characterized hemangiomas based upon the pattern of involvement in the skin and subcutaneous tissues, and these features may be useful for predicting prognosis[50,51]. Pattern subtypes include: (1) *focal* lesions that appear to arise from a single localized nidus; and (2) *segmental* lesions that cover a broad area or developmental unit (the terms "plaque-like" or "diffuse" are also used to describe this group). Lesions that are difficult to classify are designated as *indeterminate*. Segmental hemangiomas are more likely to be associated with regional extracutaneous anomalies, including PHACE(S) and LUMBAR syndromes (see below)[51]. The distribution patterns of segmental hemangiomas on the face correlate somewhat with classic embryonic facial prominences, differing the most on the upper face. Investigators have identified four primary segments for facial hemangiomas, S1 to S4 (Fig. 103.6)[52]. Involvement of these segments may be incomplete, and some hemangiomas encompass more than one segment.

Natural History

Studies have documented the typical growth pattern of infantile hemangiomas. The phases include *early proliferation* (rapid increase in size), *late proliferation* (continued growth at a slower rate), *plateau* (existence as a distinct phase debated), and *involution*[53]. Hemangiomas tend to "mark out their territory" early on, subsequently

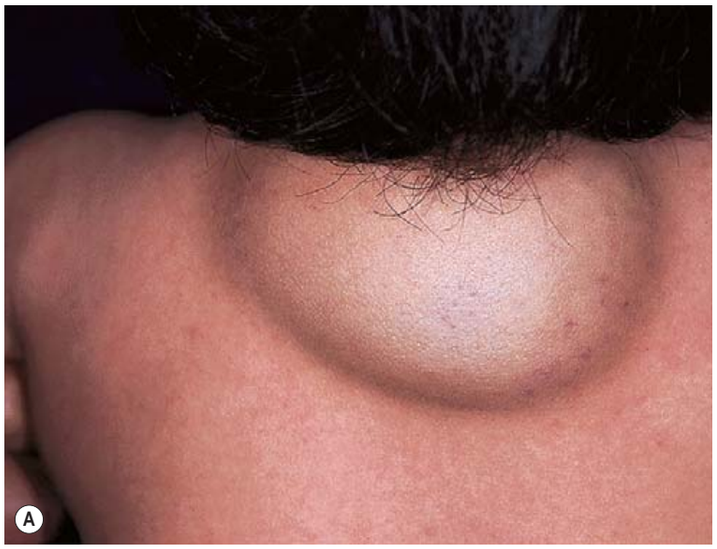


Fig. 103.5 Deep hemangiomas. Note the skin-colored to bluish hue with scattered telangiectasias. *A, Courtesy, Anthony J Mancini, MD.*

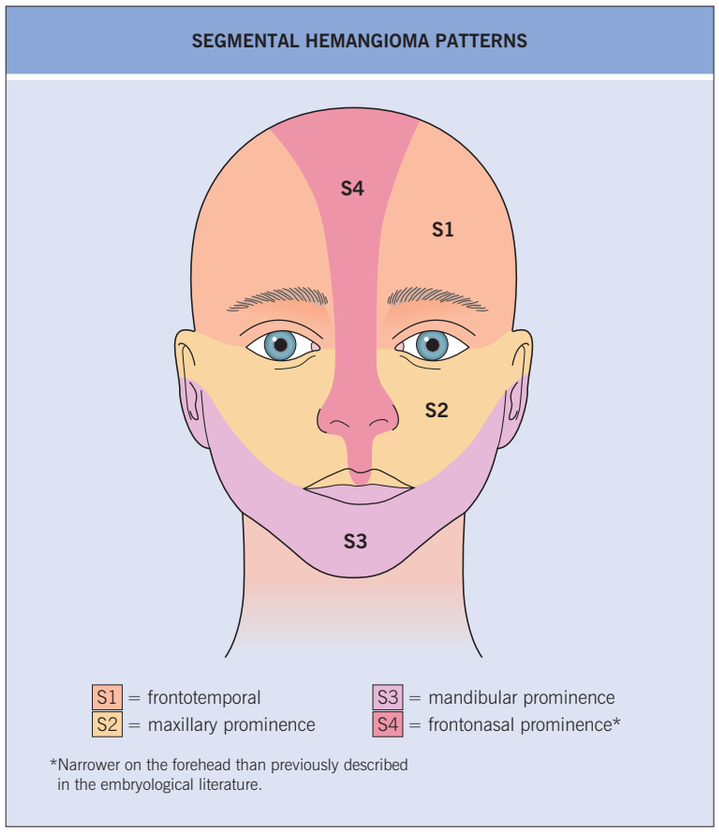


Fig. 103.6 Segmental hemangioma patterns. Based upon a prospective study (n = 165) of image analyses of hemangiomas. Adapted with permission from ref. 52.

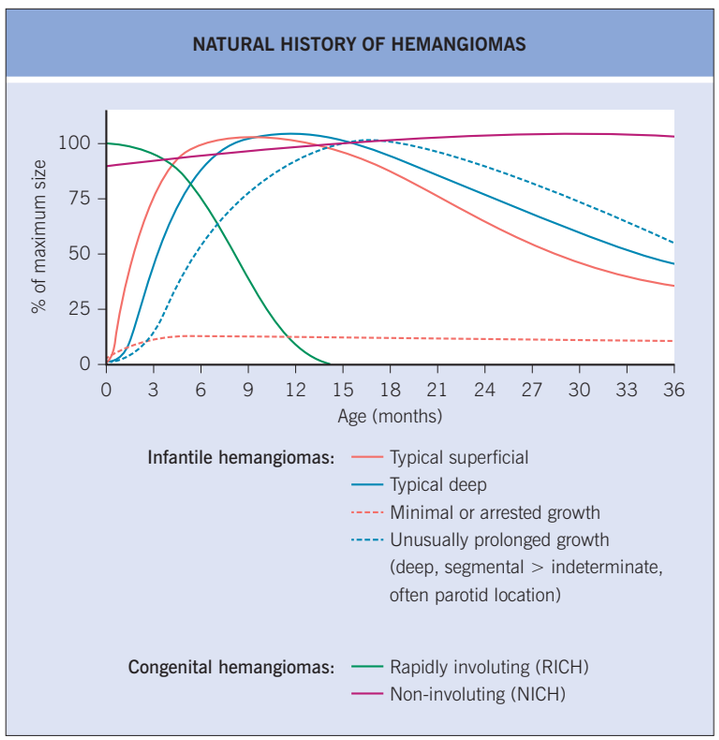


Fig. 103.7 Natural history of hemangiomas.

undergoing primarily volumetric rather than centrifugal growth[53]. During the proliferative phase, hemangiomas frequently become warmer and firmer in texture, and the surface of superficial hemangiomas may appear tense. Mixed and deep hemangiomas in the proliferative phase often feel firmer with crying or activity. Deep hemangiomas tend to proliferate for approximately a month longer than superficial hemangiomas, and the deep component of mixed lesions often continues to grow even after the superficial component has plateaued (Fig. 103.7).

A recent large prospective cohort study found that, on average, hemangiomas achieved 80% of their final size by the end of the early proliferative phase, which occurred at a mean age of 3.2 months (standard deviation ±1.7 months)[53]. Less than 5% of hemangiomas in this study had documented growth after 9 months of age, and most of these lesions had a deep component (70%) and a segmental or indeterminate morphology (70%)[53]. A retrospective series of 23 infants with hemangiomas exhibiting growth beyond 9 months of age (mean age of 17 months at last documented growth) showed that such lesions often have a location near the parotid gland (39%) as well as a deep component and segmental morphology[54].

A small subset of infantile hemangiomas (referred to as "*minimal or arrested growth*", "*abortive*" or "*reticular*") has little or no growth beyond patches of reticulated erythema with coarse and/or fine telangiectasias, often superimposed on a background of pallor (Fig. 103.8)[55,56]. They are GLUT-1-positive and involute at a pace similar to classic infantile hemangiomas (although larger ectatic vessels may persist), but a proliferative component is absent or accounts for <25% of the surface area, often presenting as small red papules at the periphery[55]. These hemangiomas favor the lower body and may develop recalcitrant ulceration or (if larger and segmental) be associated with LUMBAR syndrome (see below)[57].

Involution of infantile hemangiomas may begin as early as the first year of life and continues for several years. A color change from bright red to gray–purple (Fig. 103.9) and flattening of the surface are often the earliest signs of involution. Superficial plaques often break apart into smaller islands before clearing. As the tumor involutes, the mass becomes less firm and assumes a fatty consistency. During involution,

Fig. 103.8 Minimal/arrested growth (reticular) infantile hemangiomas. Telangiectasias and larger ectatic vessels are evident. Note the focal crusting (**A**) and small bright red papules behind the ear (**B**, arrow). Presence of the latter (which may be subtle or absent), reticulated erythema and characteristic telangiectasias (often both fine and coarse) help to distinguish these lesions from capillary–venous malformations. *B, Courtesy, Julie V Schaffer, MD.*

Fig. 103.9 Hemangioma during involution. Note the lightening (gray color) and softening of the hemangioma during involution.

larger lesions demonstrate less change in consistency and size with crying and activity[6,58].

Natural history studies of untreated hemangiomas demonstrate that 30% of lesions involute fully by 3 years of age, 50% by 5 years, 70% by 7 years, and over 90% by 9 years[6,9,58]. Some hemangiomas involute completely, while others may leave atrophic, fibrofatty or telangiectatic residua (Fig. 103.10). Predicting whether the residual lesion will be of cosmetic significance is one of the most challenging aspects of hemangioma management.

Complications

The majority of hemangiomas are small lesions that require little or no intervention. However, certain hemangiomas are problematic owing to their size, location or association with other anomalies. The age of the patient and the growth pattern of the hemangioma are crucial factors in predicting complications.

Ulceration

Ulceration occurs in up to 10% of all infantile hemangiomas and represents the most common complication[59]. Although hemangiomas in any location can be affected, those on the lip and in the anogenital region or other skin folds (e.g. the neck) have the greatest tendency to ulcerate (Fig. 103.11). Ulceration appears to develop more commonly within large, mixed (superficial and deep; see Fig. 103.11C) and segmental hemangiomas[59]. In addition, infantile hemangiomas with minimal or arrested growth are prone to ulceration (see Figs 103.8A & 103.11A), which may be recalcitrant. Although overall the median age at ulceration is 4 months[59], whitish discoloration of hemangiomas in infants younger than 3 months of age may be a sign of impending ulceration[60]. In addition to causing pain, ulcers increase the risk of infection and result in scarring with textural change. The management of ulcerated hemangiomas can be challenging (see below)[61]. Of note, significant bleeding is a rare complication of proliferating hemangiomas, including ulcerated lesions. Most bleeding episodes are minor and can be controlled with firm pressure.

Disfigurement and interference with function because of large size

Large hemangiomas can distort tissues, interfere with function, and lead to significant long-term sequelae. In addition, high-output congestive heart failure (which is most frequent in the setting of visceral hemangiomatosis) and regional extracutaneous abnormalities (especially for broad segmental lesions) may complicate the course of large hemangiomas.

Disfigurement and interference with function because of location

Even small lesions may cause complications if they arise in vulnerable locations[62]. *Periocular* hemangiomas are often associated with ophthalmologic complications (Fig. 103.12). Most commonly, periocular hemangiomas cause astigmatism by compressing the globe and deforming the cornea, which results in asymmetric refractive errors. They may also cause visual abnormalities by obstructing the visual axis as they proliferate or by invading the orbital musculature, which can lead to light-deprivation amblyopia and strabismus. Lesions located on the upper lid are most problematic, but visual obstruction can complicate lesions on the lower lid as well. Proptosis is a rare presentation of an orbital hemangioma and may develop gradually or suddenly. In these cases, the diagnosis of hemangioma may be difficult to establish clinically when a cutaneous lesion is not present. Infantile hemangiomas associated with proptosis may cause corneal exposure even after the mass has involuted. All infants with periocular hemangiomas should be evaluated by an ophthalmologist at baseline and closely thereafter during the proliferative stage[63–65].

Hemangiomas located on the *nasal tip* are particularly challenging. Deep and mixed hemangiomas can distort the underlying cartilage and leave significant fibrofatty residua. The resultant "Cyrano-nose" deformity may require reconstructive surgery. In rare cases, superficial hemangiomas located along the *columella* may ulcerate and lead to destruction of underlying cartilage, which may be heralded by the appearance of a horizontal crease in the inferior columella.

Lip hemangiomas are often superficial or mixed lesions; painful ulceration is common as they proliferate, which leads to feeding difficulties. Local factors, including recurrent trauma and the commensal bacterial flora, may increase the incidence of this complication. Even small hemangiomas crossing the vermilion border (Fig. 103.13) can leave significant cosmetic residua.

Hemangiomas located on the *pinna* may ulcerate and become infected, increasing the risk of scarring and distortion of normal structures. Conductive hearing loss can result from obstruction of the external auditory canal by a hemangioma[6].

Hemangiomas located on the *breast* pose a particular challenge in girls. These lesions may affect the underlying breast bud, and residual masses may lead to the appearance of breast asymmetry. Early surgical

Fig. 103.10 Residua of hemangiomas. Hemangioma with ulcer (**A**), which involuted leaving minimal hypopigmentation (arrows) and a circular scar at site of ulceration in the same patient 20 years later (**B**); **C, D** telangiectasias; and **E** atrophy and fibrofatty changes. *A, B, E, Courtesy, Ronald P Rapini, MD. D, Courtesy, Jean L Bolognia, MD.*

Fig. 103.11 Ulcerated hemangiomas. A Ulcerated minimal/arrested growth hemangioma on the buttock. Because the hemangioma component may not be obvious, this diagnosis should be considered when an infant presents with an ulcer in the diaper area. **B** Ulcerated superficial hemangioma above the ear. Note the distortion of the pinna. **C** Ulcerated mixed hemangioma on the upper back. *A, B, Courtesy, Julie V Schaffer, MD.*

intervention is ill advised as it may ultimately affect normal breast development.

Anogenital hemangiomas are often complicated by ulceration (associated with painful urination and defecation; see Fig. 103.11A) and infection. Wound care may be difficult in this region. Large hemangiomas of the *limbs* may also be complicated by ulceration, and when they resolve, residual excess tissue and rarely limb-length discrepancy can remain.

Systemic involvement

Large facial hemangiomas, specifically segmental lesions, can pose challenges beyond the complications noted above. They are often

Fig. 103.12 Segmental hemangioma partially obstructing the visual axis. *Courtesy, Julie V Schaffer, MD.*

Fig. 103.13 Infantile hemangioma on the lip. This is a cosmetically sensitive site, especially when lesions cross the vermilion border, and hemangiomas in this location are prone to ulceration. *Courtesy, Julie V Schaffer, MD.*

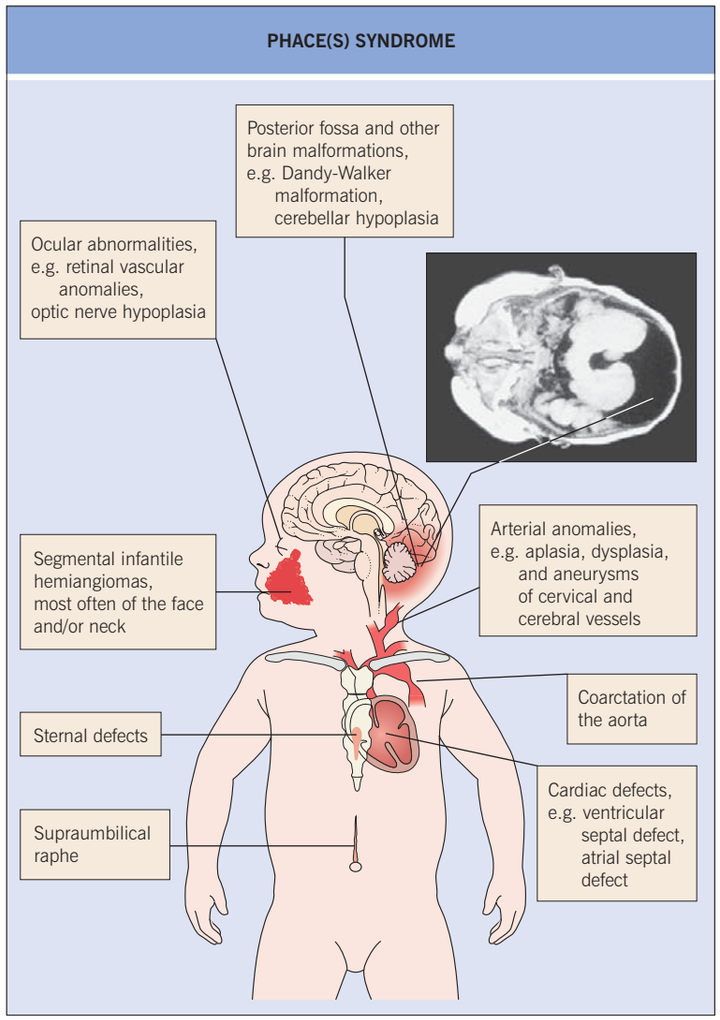


Fig. 103.14 PHACE(S) syndrome. Major clinical features are illustrated.

associated with extracutaneous anomalies, especially in female infants (~6:1 female:male ratio in PHACE[S] syndrome; see below)[66]. These hemangiomas may present as segmental telangiectatic patches (e.g. "minimal growth" lesions), vascular plaques or deep masses. A relationship between facial hemangiomas and CNS anomalies (structural and vascular) was recognized over 30 years ago[67]. Since then, other associated congenital anomalies have been identified. In 1996[68], the acronym ***PHACE(S)*** *syndrome* was coined for this spectrum of findings: ***P****, p*osterior fossa and other structural brain malformations; ***H****, h*emangioma; ***A****, a*rterial anomalies of cervical and cerebral vessels; ***C****, c*ardiac defects (especially *c*oarctation of the aorta); ***E****, e*ye anomalies; ***S****, s*ternal defects and *s*upraumbilical raphe (Fig. 103.14). Recently, diagnostic criteria for PHACE(S) syndrome were established by a multidisciplinary group of specialists[69] (Table 103.4).

In a prospective study of 108 infants (age <1 year; mean age 3 months) with large facial hemangiomas (≥22 cm^2), 31% had PHACE(S) syndrome. The vast majority (91%) of those with this syndrome had more than one extracutaneous manifestation (major ± minor criteria), and the most common findings were cerebrovascular (91%), cardiovascular (67%) and structural brain (52%) anomalies[66]. Recommendations for evaluation of infants at risk for PHACE(S) syndrome are presented in Figure 103.15. Cerebrovascular and cardiovascular changes may be progressive, with potential complications including ischemic stroke, and affected infants should be followed by neurologists and cardiologists as clinically appropriate[70].

Lower facial or "beard" hemangiomas often serve as markers of laryngeal hemangiomatosis, and the risk can be estimated by the extent of cutaneous involvement in this region (Fig. 103.16)[71]. However, airway hemangiomas are occasionally associated with segmental hemangiomas that primarily involve the upper face or small hemangiomas in the "beard" area[72]. Airway hemangiomas are typically subglottic. The onset of symptoms, which include noisy breathing and biphasic stridor, ranges from a few weeks to several months of age[71]. Infants with lower facial hemangiomas of concern should be referred for otolaryngologic evaluation.

Hemangiomas located in the *midline lumbosacral area* (Fig. 103.17) are a marker for occult spinal dysraphism. The risk of spinal dysraphism in an infant or child with an isolated midline lumbosacral hemangioma (or residuum of an involuted hemangioma) >2.5 cm in diameter is approximately 35%[73]. Factors that further increase the risk include a larger or ulcerated hemangioma and the presence of additional cutaneous markers (e.g. a deviated gluteal cleft, lipoma or skin appendage; see Ch. 64)[73].

Large hemangiomas on the lower body, especially extensive segmental lesions with "minimal growth", have been associated with a broad spectrum of regional extracutaneous abnormalities (analogous to those of the upper body in PHACE[S] syndrome). Several acronyms have been proposed for this group of findings (see Fig. 103.15), and the most

DIAGNOSTIC CRITERIA FOR PHACE(S) SYNDROME

Definite PHACE(S): Facial hemangioma >5 cm in diameter plus 1 major criterion or 2 minor criteria
Possible PHACE(S):
- Facial hemangioma >5 cm plus 1 minor criterion; *or*
- Hemangioma of the neck or upper torso plus 1 major criterion or 2 minor criteria; *or*
- 2 major criteria in the absence of a hemangioma

Organ system	Major criteria	Minor criteria
Cerebrovascular	• Anomalies of major cerebral arteries* (e.g. dysplasia, hypoplasia, stenosis, aneurysm, aberrant origin/course) • Persistent trigeminal artery	• Persistent embryonic arteries (other than trigeminal artery) • Intracranial hemangioma
Structural brain	• Posterior fossa anomalies (e.g. Dandy–Walker complex, cerebellar hypoplasia/dysplasia)	• Midline anomalies • Neuronal migration disorder
Cardiovascular	• Aortic arch anomalies • Anomalous origin of subclavian artery ± vascular ring	• Ventricular septal defect • Right aortic arch
Ocular	• Posterior segment anomalies (e.g. retinal vascular anomalies, optic nerve hypoplasia)	• Anterior segment anomalies (e.g. sclerocornea, cataract, coloboma)
Ventral or midline	• Sternal defect • Supraumbilical raphe	• Hypopituitarism • Ectopic thyroid

*Major cerebral arteries include: internal carotid artery; middle, anterior, or posterior cerebral artery; and vertebrobasilar system.

Table 103.4 Diagnostic criteria for PHACE(S) syndrome[69].

recent and inclusive is ***LUMBAR*** *syndrome*: ***L***, *l*ower body/*l*umbosacral hemangioma and *l*ipomas or other cutaneous anomalies (e.g. "skin tags"); ***U***, *u*rogenital anomalies and *u*lceration; ***M***, *m*yelopathy (spinal dysraphism); ***B***, *b*ony deformities; ***A***, *a*norectal and *a*rterial anomalies; and ***R***, *r*enal anomalies[74]. Recommendations for evaluation of infants with hemangiomas with a midline lumbosacral location and/or a segmental distribution on the lower body are summarized in Figure 103.15.

Multiple lesions are found in 10–25% of infants with hemangiomas and may be associated with visceral hemangiomatosis[75]. Most infants with both internal and skin involvement have many small, superficial cutaneous hemangiomas (Fig. 103.18) that range from a few millimeters to a few centimeters in diameter. Evaluation for visceral involvement is recommended when five or more skin lesions are present. Historically, the terms *"diffuse"* and *"benign" neonatal hemangiomatosis* were used for infants who had multiple cutaneous hemangiomas with or without visceral lesions, respectively[76–78]. However, some cases reported as diffuse neonatal hemangiomatosis actually represented other entities such as multifocal lymphangioendotheliomatosis with thrombocytopenia (see Ch. 114). To avoid further confusion, it has been recommended that patients simply be categorized as having *multiple cutaneous hemangiomas with or without systemic hemangiomas*.

The liver is the most common site of visceral hemangiomas in patients with multiple skin lesions (Fig. 103.19)[76,78]. Although they may be asymptomatic, hepatic hemangiomas can result in significant morbidity from complications such as high-output cardiac failure due to arteriovenous or arterioportal shunts (most often with multifocal hepatic lesions), abdominal compartment syndrome related to massive hepatomegaly (typically with diffuse hepatic involvement) and hypothyroidism (see below)[79–81]. Gastrointestinal tract hemangiomas (which may be associated with bleeding) have been described in patients with multiple or segmental skin lesions, but some reported cases might represent other types of multifocal vascular anomalies. True infantile hemangiomas within the CNS are rare, affecting only 1% (15/1454) of patients seen at a vascular anomalies referral center over a 10-year period[82]. Most of these cases represented intracranial or intraspinal extension of an overlying infantile hemangioma (some of which were segmental lesions); a few patients had hydrocephalus, but invasion into the CNS parenchyma was not observed[82]. Hemangiomas may also develop in a variety of other sites, including mucosal surfaces and the eyes.

In addition to their association with multiple small cutaneous lesions, visceral hemangiomas sometimes occur in infants with solitary large cutaneous hemangiomas, most often segmental facial lesions (with or without associated PHACE[S] syndrome). In such patients, hepatic, gastrointestinal, CNS and mediastinal hemangiomas have been observed[10,83,84]. However, no hepatic hemangiomas were found via ultrasound in a recent prospective study of 60 infants with at least one large (>30 cm^2) hemangioma and fewer than five lesions in total[85]. Of note, visceral hemangiomas occasionally occur in the absence of cutaneous lesions.

Increased levels of type 3 iodothyronine deiodinase, an enzyme that deactivates thyroid hormone, have been identified in tissue from proliferating hemangiomas. This can lead to hypothyroidism in infants with large-volume proliferative-phase lesions[86]. The consumptive nature of the hypothyroidism often makes it difficult to correct, but it resolves as the tumor regresses. Screening for hypothyroidism in the immediate neonatal period is inadequate, as hemangiomas are typically only beginning to develop at that time. Although most reported cases have been associated with hepatic hemangiomatosis, type 3 iodothyronine deiodinase activity has been noted in cutaneous hemangiomas. Consequently, it has been recommended that evaluation for hypothyroidism be considered in infants with large cutaneous hemangiomas or hepatic hemangiomatosis[86,87].

Infants with multiple cutaneous hemangiomas should be monitored for signs or symptoms of visceral involvement with periodic physical examinations. Radiologic evaluation, most often abdominal ultrasonography to screen for hepatic lesions[88], may be indicated to assess for systemic involvement in some patients (e.g. those with five or more cutaneous lesions) (see Fig. 103.15). Infants with hepatic hemangiomatosis should be followed closely with serial ultrasounds, clinical assessments and laboratory evaluation for hypothyroidism, with potential additional investigations including a cardiac evaluation (especially if high-flow shunting is identified) and further imaging with CT and/or MRI[89]. Not all infants with hepatic hemangiomatosis require treatment, but it is often difficult to determine those who will at initial presentation[88]. Typically, infantile hemangiomas located within the viscera follow the same course of proliferation and involution as cutaneous lesions.

Rapidly Involuting and Non-involuting Congenital Hemangiomas

Infrequently, infants present with a fully developed "hemangioma" in the immediate newborn period. These congenital hemangiomas have features that are clinically, histologically and immunohistochemically distinct from infantile hemangiomas (Table 103.5), most notably that they are GLUT-1-negative[47,90–92].

One subset of such tumors is referred to as the *rapidly involuting congenital hemangioma (RICH*; also reported as *congenital nonprogressive hemangioma* in a series where the lesions were excised during early infancy). RICHs are characterized by significant intrauterine growth, little if any postnatal growth, and rapid involution within the first year of life[47,91]. They are equally common in boys and girls. Intrauterine growth may be noted by prenatal ultrasonography as early as 12 weeks' gestation, and prenatal Doppler ultrasonography may reveal high vascularity and fast flow[90,91]. This tumor can appear at birth as a raised violaceous mass with prominent radiating veins, a hemispheric nodule with coarse telangiectasias surrounded by a pale rim, or a firm, pink to violaceous plaque that is often located on the lower extremity. Small, firm, violaceous papules may be present on the surface, and superimposed milia or hypertrichosis are occasionally noted. Ulceration, hemorrhage and necrosis can occur within the tumor, and rapid regression is evident within the first year of life[3,90] (Fig. 103.20). Transient thrombocytopenia may develop during the neonatal period[93].

Another type of congenital hemangioma is the *non-involuting congenital hemangioma (NICH)*[92]. These lesions occur slightly more often in male infants. They typically present at birth as well-circumscribed,

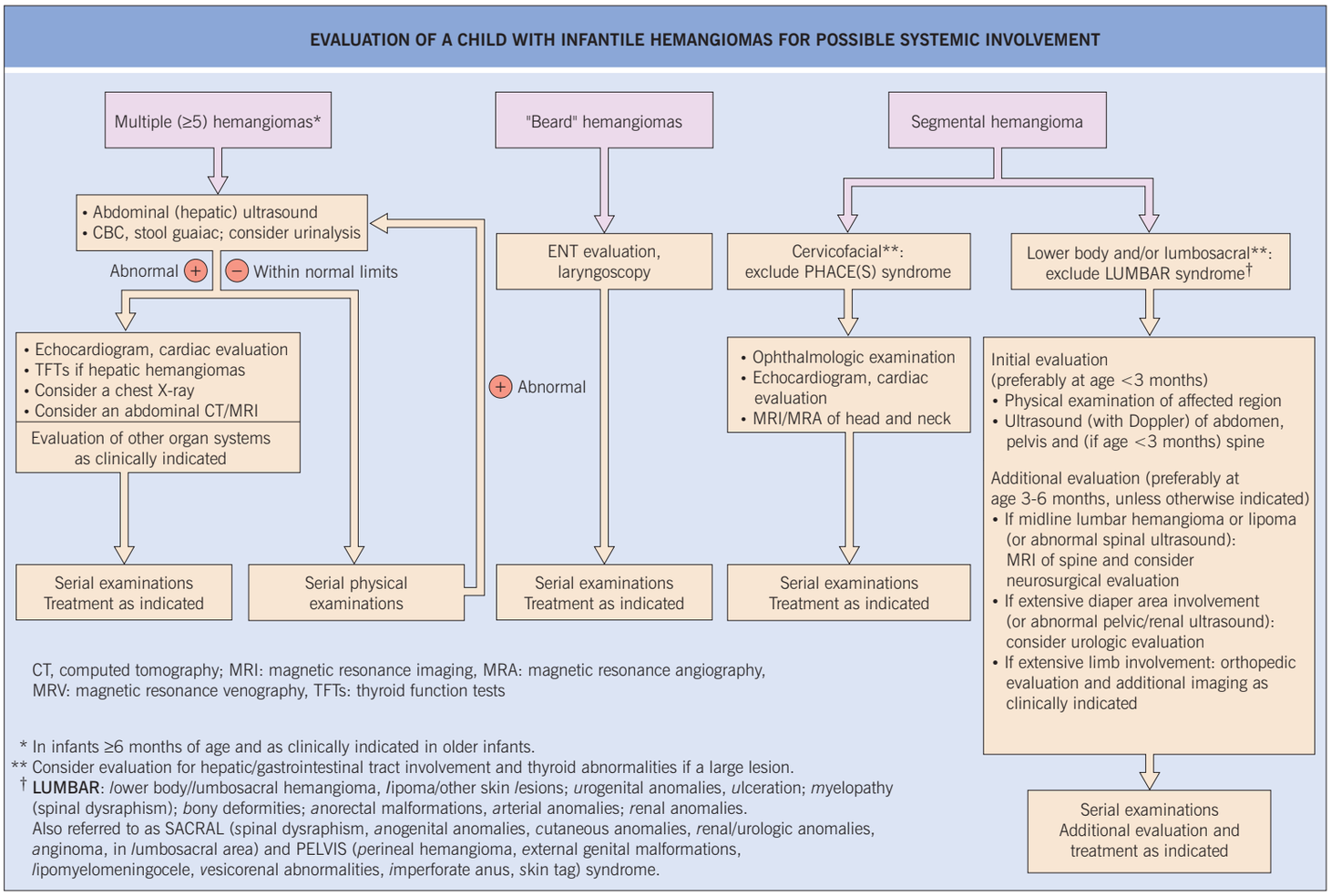


Fig. 103.15 Evaluation of a child with infantile hemangiomas for possible systemic involvement.

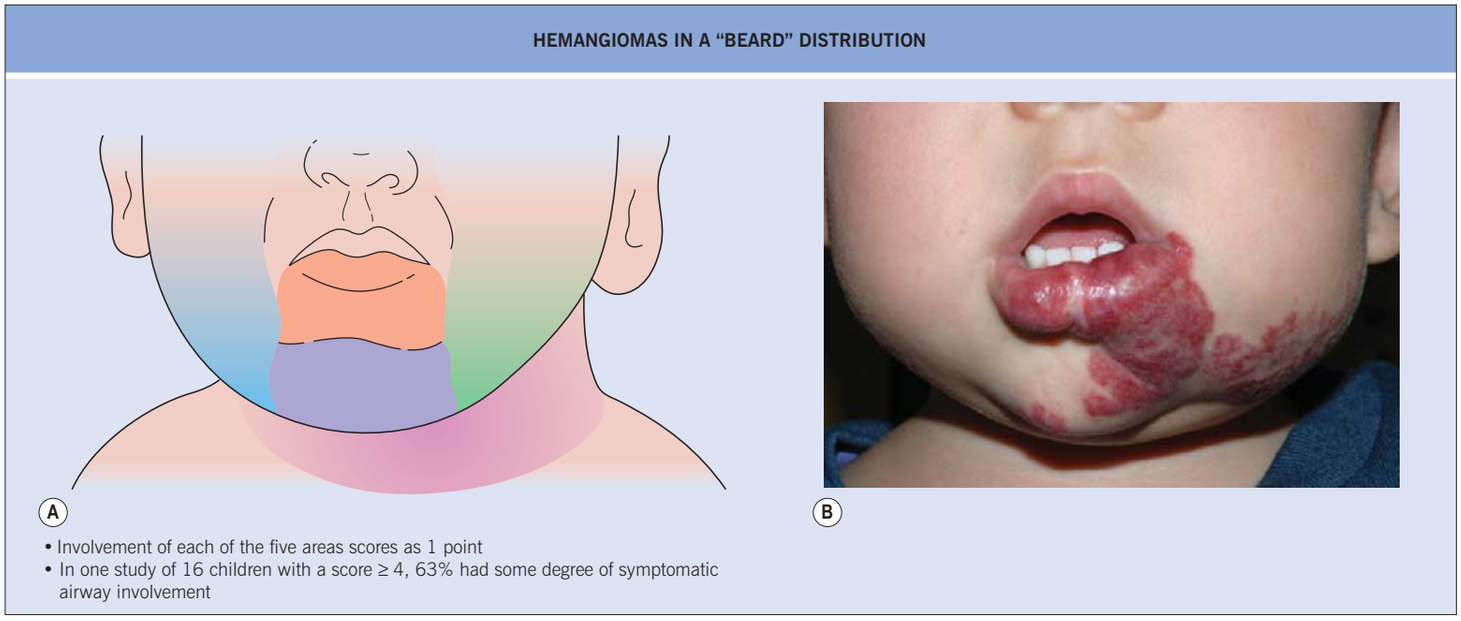


Fig. 103.16 Hemangiomas in a "beard" distribution. A Anatomic sites associated with risk of an airway hemangioma. **B** Infant with a laryngeal hemangioma in addition to cutaneous lesions in a "beard" distribution. *A, Adapted, with permission, from ref. 71. B, Courtesy, Julie V Schaffer, MD.*

pink to blue–violet masses or plaques with overlying coarse telangiectasias, surrounded by a pale or bluish rim (Fig. 103.21). NICHs are warm to palpation and, unlike infantile hemangiomas, grow proportionately with the child. The lesions may worsen with maturity and do not involute spontaneously. The diagnosis is often established retrospectively after the lesion is excised because involution fails to occur. Whether NICH and RICH represent distinct entities or exist on a spectrum remains unclear, and patients with coexistent congenital hemangiomas and common infantile hemangiomas have been described[91,94].

Fig. 103.17 Segmental lumbosacral hemangioma. This child is at risk for LUMBAR syndrome. *Courtesy, Julie V Schaffer, MD.*

Fig. 103.18 Multiple cutaneous hemangiomas in a child with hepatic involvement ("diffuse neonatal hemangiomatosis"). Many small, superficial skin lesions were present. *Courtesy, Ronald P Rapini, MD.*

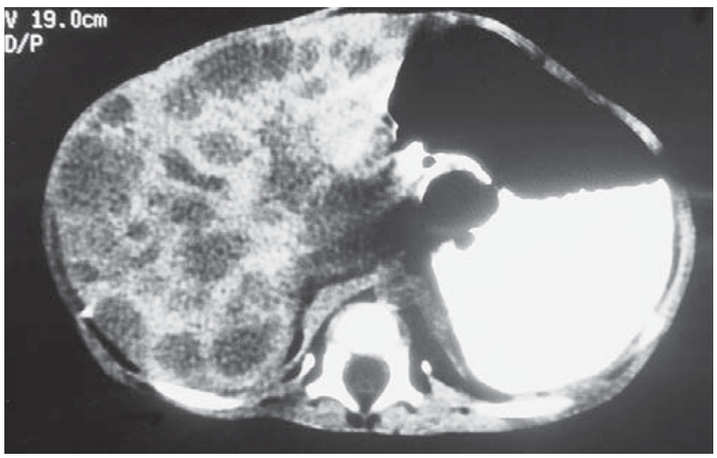


Fig. 103.19 Hepatic hemangiomatosis. CT scan demonstrating multiple hepatic hemangiomas in a child with multiple cutaneous hemangiomas ("diffuse neonatal hemangiomatosis"). *Courtesy, Amy Paller, MD.*

KEY FEATURES OF INFANTILE AND CONGENITAL HEMANGIOMAS		
Infantile hemangioma	**Rapidly involuting congenital hemangioma (RICH)**	**Non-involuting congenital hemangioma (NICH)**
Usually absent or precursor lesion at birth	Fully developed at birth	Fully developed at birth
Rapid postnatal proliferation	Intrauterine proliferation	Intrauterine proliferation then proportionate postnatal growth
Slow spontaneous involution	Rapid involution during the first year*	Do not involute spontaneously
More common in girls	Equal prevalence or slightly more common in girls	Slightly more common in boys
Lobular endothelial proliferation during proliferative phase; fibrofatty tissue during involution	Capillary lobules within fibrotic stroma containing thin-walled vessels, hemosiderin	Lobules of small, thin-walled vessels with large central vessel; dilated, dysplastic veins between lobules; "hobnailed" endothelial cells lining intralobular vessels
Positive GLUT-1 and Lewis Y antigen	Negative GLUT-1 and Lewis Y antigen	Negative GLUT-1

*Occasionally associated with thrombocytopenia during the neonatal period.

Table 103.5 Key features of infantile and congenital hemangiomas.

Kasabach–Merritt Phenomenon

Kasabach–Merritt phenomenon (KMP) is the association of a vascular tumor with a thrombocytopenic coagulopathy. Kasabach and Merritt reported the first case in 1940 and classified the tumor as a "capillary hemangioma". For decades thereafter, it was assumed that thrombocytopenic coagulopathy was a rare complication of typical hemangiomas[95]. However, data have shown that the tumors linked with this life-threatening complication are not true infantile hemangiomas. Rather, the histopathologic features of the tumors most commonly associated with KMP are those of kaposiform hemangioendothelioma (KHE) and tufted angioma (see Ch. 114)[96,97].

KMP typically presents during the first months to year of life with a rapidly enlarging, ecchymotic mass (Fig. 103.22) associated with thrombocytopenia and a consumptive coagulopathy. This syndrome is equally common in boys and girls. The clinical appearance of the tumor prior to the development of KMP is variable. Some patients have skin-colored, red or violaceous plaques, while others have masses that resemble lymphatic malformations or deep lesions within the neck, mediastinum or retroperitoneum. Many of these tumors are evident at birth. When the coagulopathy develops, the tumor becomes indurated as well as enlarged, and petechiae and purpura appear locally or (less commonly) in a widespread distribution.

Tumors associated with KMP do not typically respond well to treatment, and the coagulopathy may continue for months to years. Residual masses often persist after the coagulopathy resolves and occasionally worsen with maturity. Residual lesions frequently have a port-wine stain-like appearance with superimposed papules and a fibrotic texture upon palpation[98]. Telangiectatic streaks with associated swelling and irregular firm subcutaneous masses may also remain. Residual involvement of muscles and joints can impair mobility and cause painful contractures. Histologic examination of residual lesions has revealed features of tufted angioma and/or KHE with prominent fibrosis[98].

RADIOLOGIC FEATURES

Ultrasonography, CT and MRI can play important roles in the diagnosis and evaluation of infantile hemangiomas. Most superficial and mixed infantile hemangiomas are diagnosed based upon their clinical

Fig. 103.21 Non-involuting congenital hemangioma (NICH) in a school-aged child. This lesion was fully formed at birth and remained warm and firm to palpation. Note the coarse telangiectasias and pallor. *Courtesy, Julie V Schaffer, MD.*

Fig. 103.20 Rapidly involuting congenital hemangioma (RICH). A Violaceous tumor on the upper extremity with surface telangiectasias in a neonate. **B** Spontaneous involution at 5 months of age, with fibrofatty residua. *Courtesy, Annette Wagner, MD.*

Fig. 103.22 Kaposiform hemangioendothelioma associated with Kasabach–Merritt phenomenon in a 5-week-old boy. Progressive induration and ecchymosis developed rapidly over a 24-hour period. An eczematous eruption is also evident. *Courtesy, Julie V Schaffer, MD.*

features. However, imaging may be useful for defining the extent and depth of the deep component of mixed lesions. Radiologic evaluation is particularly helpful for confirming the diagnosis of deep infantile hemangiomas that lack superficial changes. It is important to consider the phase of growth when assessing hemangiomas radiographically, because proliferating hemangiomas demonstrate different characteristics than their involuting and involuted counterparts. The findings from MRI, Doppler sonography and CT of the various phases of hemangiomas as well as in KMP are presented in Table 103.6.

MRI is the most useful imaging technique for helping to define the extent and tissue characteristics of vascular tumors, and the use of contrast can help to differentiate an infantile hemangioma from other tumors. If MRI does not confirm the diagnosis of infantile hemangioma or there are concerns regarding a possible malignancy, histologic examination of the tumor is recommended. MRI and/or MR angiography (MRA) can also be used to determine the presence of hemangiomas within internal organs and to detect other structural anomalies, including CNS malformations and arterial anomalies[99].

A RICH may demonstrate distinct radiographic features. Although they can be recognized by prenatal ultrasonography during the second and third trimester, misdiagnosis as other vascular anomalies such as lymphatic or arteriovenous malformations is common[100]. Postnatal ultrasonographic evaluation of a RICH reveals uniformly hypoechoic lesions mostly confined to the subcutaneous fat. Diffuse vascularity is typical, with vessels showing venous or low-resistance arterial flow[101]. Doppler evaluation of a NICH demonstrates fast-flow vessels, and MRI reveals features similar to infantile hemangiomas[92].

MRI of vascular tumors associated with KMP shows diffuse soft tissue masses that enhance after contrast administration (see Table 103.6). Ill-defined margins, involvement of multiple tissue planes, overlying cutaneous thickening, edema, subcutaneous stranding and signal voids caused by hemosiderin deposits may help to differentiate KHEs from infantile hemangiomas[97].

PATHOLOGY

The histopathologic features of infantile hemangioma correlate with the stage of hemangioma development (see Tables 103.1 & 103.5). Infantile hemangiomas may extend from the superficial dermis to the deep subcutaneous tissue, and in some locations there may be involvement of surrounding tissues such as salivary glands and muscle. Biopsy

IMAGING FINDINGS IN SELECTED PEDIATRIC VASCULAR TUMORS						
Lesion	**Magnetic resonance imaging**				**Doppler sonography**	**Computed tomography**
	T1-weighted	**Contrast enhancement**	**T2-weighted**	**Gradient**		
Infantile hemangiomas:						
Proliferating	STM, iso- or hypointense to muscle Flow voids	Uniform intense enhancement	Lobulated STM Increased signal Flow voids	HFV within and around STM	Discrete STM containing HFV Decreased arterial resistance	Uniformly enhancing STM Dilated feeding and draining vessels
Involuting	Variable fat content	As above	Variable fat content	As above	As above	Variable fat content
Involuted	High signal (fat)	No enhancement	Decreased signal (fat)	No HFV	Echogenic avascular STM	Fat density No enhancement
Kasabach–Merritt phenomenon	Diffuse STM STT and skin thickening	Diffuse enhancement	Diffuse increased signal SQ stranding	Mildly dilated in/ around STM	Diffuse infiltrating STM with HFV	Diffuse enhancing STM SQ stranding

Table 103.6 Imaging findings in selected pediatric vascular tumors. HFV, high-flow vessels; SQ, subcutaneous; STM, soft tissue mass; STT, soft tissue thickening. Adapted with permission from ref. 99.

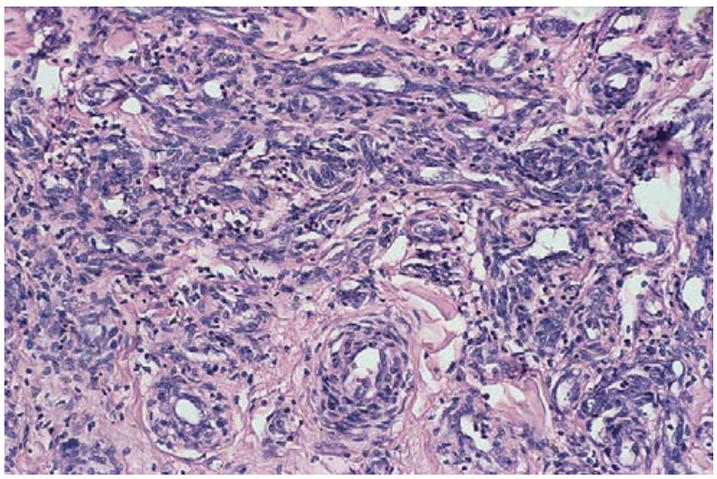


Fig. 103.23 Histologic features of a proliferating hemangioma. Collections of endothelial cells and pericytes are seen, as well as the formation of vascular lumens. *Courtesy, Ronald P Rapini, MD.*

specimens obtained from superficial and deep lesions show the same features. Well-defined non-encapsulated masses composed of proliferating plump endothelial cells and pericytes characterize proliferating hemangiomas (Fig. 103.23). Small vascular lumens may be noted focally throughout the tumor, but lumen formation may be more difficult to appreciate in early proliferating lesions.

Later in the proliferating stage, lobules of endothelial masses separated by fibrous septae become more prominent. Larger feeding and draining vessels are noted within the septae, and mitotic figures and apoptotic bodies may be present within the tumor mass. Although abnormal mitotic figures are not typical of proliferating hemangiomas, some authors have noted that mitotic activity and mild nuclear pleomorphism may be present in infantile hemangiomas and should not be a cause for concern if other typical histopathologic features are also present. An increased number of mast cells is often present within proliferating hemangiomas, and some studies have found even higher numbers of mast cells during early involution[39].

As the lesion matures, proliferation ceases and involution progresses; in some lesions, histologic features of both phases may be evident. The involuting phase is marked by flattening of the endothelium and reduced numbers of mitotic figures. Eventually, the vessels decrease in number and lose their tightly packed appearance, with fibrofatty tissue separating the vessels within and between lobules. The feeding and draining vessels within the septae may persist, but mast cells decrease in number. Fully involuted lesions display fibrofatty tissue and a few persistent vessels at sites where tumor lobules and septae previously existed.

Immunohistochemical analysis is useful for confirming the diagnosis of infantile hemangioma. As noted above, GLUT-1 expression is normally restricted to vessels with blood–tissue barrier functions, such as the brain and placenta. A high level of GLUT-1 immunoreactivity is present in the endothelia within infantile hemangiomas of all phases[25]. GLUT-1 staining is absent in other types of vascular tumors and vascular malformations. In addition, other placenta-associated vascular proteins, including FcγRII, merosin and Lewis Y antigen, are present in infantile hemangiomas but absent in vascular malformations and pyogenic granulomas. These placental markers are also absent in normal vessels of the skin and subcutis[26,39].

Histologically and immunophenotypically, congenital hemangiomas have several features that are distinct from infantile hemangiomas (see Table 103.5). These include striking lobularity with densely fibrotic stroma, stromal hemosiderin deposits, focal thrombosis and sclerosis of capillary lobules, lack of infiltration of surrounding tissues, fewer mast cells, and the coexistence of proliferating vasculature with multiple thin-walled vessels. Moreover, congenital hemangiomas lack immunoreactivity to GLUT-1 and Lewis Y antigen[47,91]. Some tumors do, however, demonstrate zones of involution[91].

DIFFERENTIAL DIAGNOSIS

Superficial and mixed hemangiomas are usually diagnosed based upon their characteristic clinical features. Hemangioma precursors and early proliferating lesions may sometimes be misdiagnosed as capillary malformations or telangiectasias. Deep lesions provide a greater challenge, and radiographic evaluation may be helpful. The differential diagnosis of a deep hemangioma may include a vascular malformation (particularly venous, lymphatic or combined venous–lymphatic malformations; see Ch. 104) and kaposiform hemangioendothelioma. Pyogenic granulomas occur commonly in children and may mimic a superficial hemangioma. They typically arise after the first few months of life and are pedunculated. Other vascular lesions of infancy that may represent diagnostic considerations include tufted angioma, multifocal lymphangioendotheliomatosis with thrombocytopenia, infantile hemangiopericytoma, spindle cell hemangioma, verrucous "hemangioma" and eccrine angiomatous hamartoma.

A congenital fibrosarcoma may mimic a hemangioma because the former are often firm and blue–purple in color and can have ectatic superficial veins. In addition, some patients with this malignancy present with disseminated intravascular coagulation, which further confuses the clinical picture. Rhabdomyosarcoma, neuroblastoma, primitive neuroectodermal tumor, lymphoblastic lymphoma and dermatofibrosarcoma protuberans are other neoplasms that may have a vascular appearance due to overlying telangiectasias or a blue to red color. Additional entities that may be mistaken for a hemangioma include: infantile myofibromatosis, which can present as solitary or multiple red to pink plaques or nodules; lipoblastoma, which presents as an enlarging skin-colored or (less often) erythematous mass; and

REASONS TO CONSIDER SYSTEMIC THERAPY FOR INFANTILE HEMANGIOMAS
Threatened vital functions
• Vision
• Airway
Potential for disfigurement
• Nasal tip/columella
• Lip, especially if the lesion crosses the vermilion border
• Large/rapidly growing lesion, especially if on the face
Severe/recalcitrant ulceration
High-output cardiac failure

Table 103.7 Reasons to consider systemic therapy for infantile hemangiomas.

nasal glioma, often presenting as a congenital blue–red mass on the bridge of the nose. Radiographic studies, especially MRI, may be useful in differentiating these tumors from a hemangioma. However, if the diagnosis is not clarified by clinical and radiographic examinations, or if the lesions are atypical, then histologic examination is indicated.

TREATMENT

Infantile hemangiomas manifest with a wide spectrum of clinical severity, and their management needs to be individualized. Most therapeutic recommendations are based on anecdotal experience. In the last few decades, upon identification of subgroups of infantile hemangiomas with a greater risk of developing complications, indications for active intervention have been proposed (Table 103.7)[102]. The major goals of management include: (1) preventing or reversing life- or function-threatening complications; (2) treating ulcerations; (3) preventing permanent disfigurement; (4) minimizing psychosocial distress to patients and their families; and (5) avoiding overly aggressive, potentially scarring procedures for lesions that have a strong probability of involuting without significant residua[103].

Active Non-intervention

Small hemangiomas that carry an excellent prognosis for spontaneous resolution with a good cosmetic outcome are usually managed with active non-intervention. Physicians should recognize that small, seemingly trivial lesions may be troubling to parents and cause significant distress. Parents of children with facial hemangiomas demonstrate reactions similar to those seen in parents of children with permanent deformities. They may feel that their concerns about the hemangioma have been inadequately addressed and express dissatisfaction with their child's medical care[104]. Use of the internet has increased parental access to information (albeit of variable quality) about hemangiomas and their treatment.

Active non-intervention includes discussing information that parents have learned about hemangiomas. Indications for treatment, types of therapy, and why they are or are not appropriate for their child must be reviewed. Close observation with periodic photography to monitor the hemangioma is essential. Reviewing photographic examples of the evolution of hemangiomas is helpful for families. Many parents are fearful of bleeding and ulceration; therefore, reviewing the care for superficial bleeding (along with reassurance that it is rarely problematic) or ulceration in anticipation of these potential complications, is worthwhile.

Management of Ulceration

Ulceration is the most frequent complication of infantile hemangiomas (see Fig. 103.11). Management should be directed at healing the ulceration, preventing infection and reducing pain. A review of 60 infants with ulcerations found that multiple modalities were often used concurrently, and that no single therapy proved most effective[61]. Components of management include local wound care, treatment of infection (relatively uncommon), specific therapies (e.g. pulsed dye laser, β-blockers, corticosteroids) and pain management. Superficial ulcerations can frequently be managed with local wound care. Saline or Burow's solution compresses may be used to gently debride thick crusts, and topical antibiotics such as mupirocin and bacitracin ointments are applied, followed by occlusive dressings.

In open trials, metronidazole gel has been useful for ulcers in intertriginous and moist areas such as the perineum. Although the safety of metronidazole gel has not been established in young children, systemic metronidazole has been used safely to treat parasitic infections in this age group. Kim et al.[61] calculated that it would require relatively large amounts of topical gel to reach systemic levels of the drug or toxicity from its propylene glycol vehicle; nonetheless, they recommended limited application of small amounts of metronidazole gel when it is used in this setting. Oral antibiotics are often prescribed to treat presumed infections of ulcerated hemangiomas. Antibiotics that cover staphylococci and streptococci, such as first-generation cephalosporins, are commonly employed (see Ch. 127). A bacterial culture should be obtained from the wound. Occlusive dressings such as Duoderm®, Duoderm Extra Thin®, Vigilon® or Omniderm® can be applied after application of the topical antibiotic at sites that are amenable (see Ch. 145). Thin hydrocolloid dressings are often favored because of the ease of application and the ability to leave them in place for a few days. Petrolatum-impregnated gauze may also be used for perineal ulcers but needs to be changed frequently. Compression dressings such as Coban® elastic bandage are useful for extremity hemangiomas, and parents should be instructed in their proper application.

A variety of modalities that are used to treat hemangiomas for other indications (see below) may be helpful for treating ulcerated lesions. Pulsed dye laser has been widely used for the treatment of ulcerated hemangiomas. Some uncontrolled studies demonstrated healing of ulcerations and resolution of pain after two to three treatments with the pulsed dye laser performed at 2-week intervals[105–108]. However, others observed mixed results, with 50% showing improvement and 5% experiencing worsening of the ulceration[61]. Excisional surgery may be considered as a means to manage small or pedunculated ulcerated lesions.

Improvement of chronically ulcerated, treatment-resistant facial and diaper-area hemangiomas was observed after application of becaplermin (recombinant platelet-derived growth factor) 0.01% gel[109,110]. This preparation is FDA-approved, but only for the treatment of diabetic ulcers in adults; in these patients, use of three or more 15 g tubes of becaplermin gel was associated with increased mortality from (but not incidence of) malignancy. Becaplermin's mechanism of action includes promotion of angiogenesis, which raises questions regarding the potential for stimulation of growth and worsening of hemangiomas. Further studies are indicated to determine the effectiveness and safety of this modality.

An important consideration in the treatment of ulcerated hemangiomas is pain, which is a commonly associated symptom. Local wound care, and especially occlusive dressings, can provide some pain relief. Oral acetaminophen and topical lidocaine ointment may also help to alleviate the discomfort, although the latter must be used sparingly to prevent systemic lidocaine toxicity. In some patients, narcotic analgesics (e.g. acetaminophen with codeine) may be necessary for short periods of time. Eutectic mixture of local anesthetics is not recommended for the treatment of ulcerated hemangiomas because it should not be applied to eroded or ulcerated skin[61].

Local Medical Therapies

Intralesional corticosteroids

Intralesional corticosteroids are usually used to treat localized lesions, such as small lip hemangiomas. Systemic absorption likely occurs, but it is believed to be less than with oral corticosteroids when small lesions are treated. As with oral corticosteroids, there is no well-established dosage regimen. Concentrations of triamcinolone acetonide between 5 and 40 mg/ml have been reported in the literature[61,111,112]. Shorter-acting corticosteroid preparations, such as dexamethasone or betamethasone acetate, are sometimes administered in combination with triamcinolone. It is recommended that the total maximum dose of triamcinolone not exceed 3–5 mg/kg per treatment session[62], thereby reducing the chance of HPA axis suppression and excessive exposure to the preservative benzyl alcohol. The interval between treatment sessions is also not well established. Some patients require repeat treatments at approximately monthly intervals, while others respond after a single treatment. The need for repeat therapy will depend upon the stage of proliferation of the hemangioma.

The use of intralesional corticosteroids to treat periorbital hemangiomas is controversial[113]. When the injection pressure exceeds the systemic arterial pressure, there can be retrograde arterial flow and presumably embolization of corticosteroid particles into the ocular circulation. Reports of serious complications, including retinal and ophthalmic artery occlusion leading to permanent vision loss, as well as local atrophy and necrosis, have limited the use of this modality in the periorbital area[112,114,115].

Topical corticosteroids

In a few case reports and one series of 34 patients, an ultrapotent class 1 topical corticosteroid was utilized to treat periocular hemangiomas and other lesions with a superficial component[116,117]. Cessation of growth, decreased size/thickness and/or lightening of the color of the hemangioma was observed in ~75% of the patients, and there were no significant side effects. Further studies are needed to assess the effectiveness of this modality and to identify the subset of hemangiomas (likely thinner superficial lesions) with the best response to such treatment.

Topical β-blockers

There have been anecdotal reports of improvement of superficial facial hemangiomas with topical application of timolol 0.5% gel or solution[118,118a]. Additional studies are needed to determine the potential benefits of this topical non-selective β-blocker (similar to the systemic agent propranolol; see below) in the treatment of superficial and ulcerated hemangiomas, with increased potential for systemic absorption in the latter setting (Fig. 103.24).

Topical imiquimod

There are a few case series and one small prospective study of 5% imiquimod cream (which has antiangiogenic as well as immune-modifying activity) for the treatment of proliferating hemangiomas[119,120]. Although improvement of the superficial component (fading of the color more than decreased volume) is often observed, an inflammatory reaction that may include erosion of the hemangioma surface frequently occurs[119,120]. Controlled studies are needed to further assess the risks and benefits of this modality.

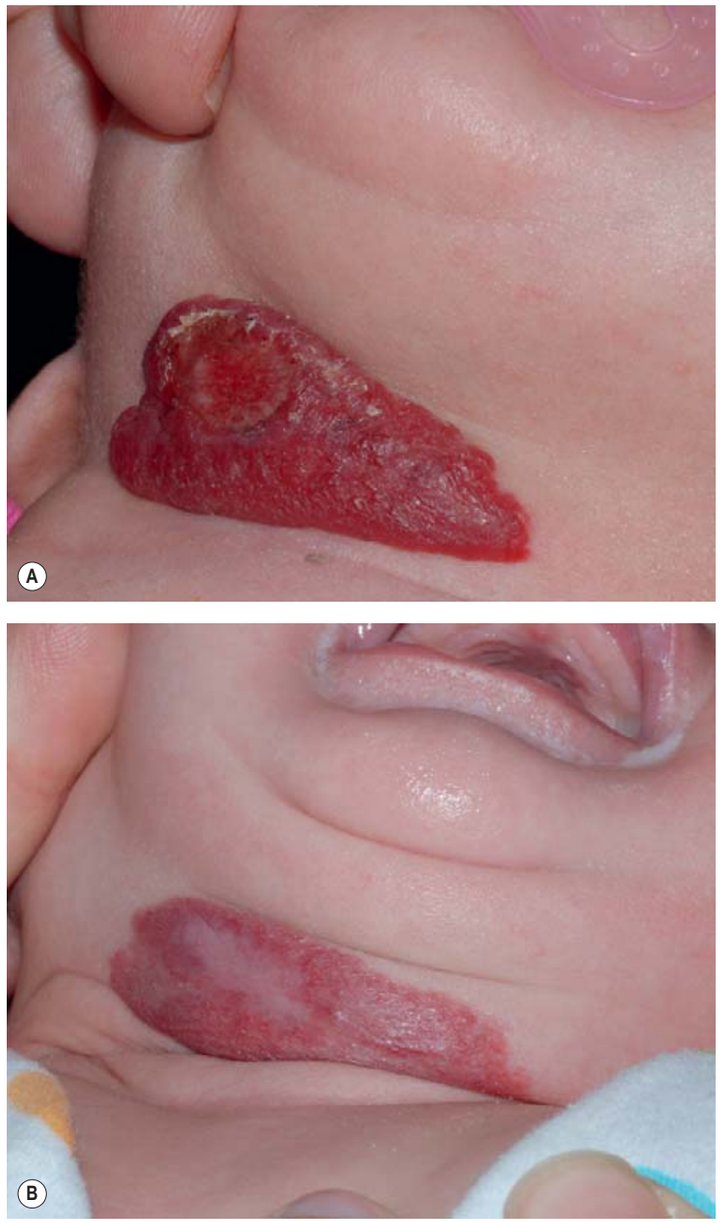


Fig. 103.24 Ulcerated superficial hemangioma treated with topical timolol. **A** An ulcerated superficial infantile hemangioma on the neck of a 10-week-old girl. **B** Four weeks after institution of topical timolol 0.5% gel, with one small drop applied twice daily. Note the healing of the ulcer, which occurred within two weeks, as well as the lighter color and decreased thickness of the hemangioma. *Courtesy, Julie V Schaffer, MD.*

Systemic Therapies

Systemic corticosteroids

Systemic corticosteroids, usually prednisolone or prednisone, have traditionally been the mainstay of treatment for life- or function-threatening hemangiomas (see Table 103.7). They are also used to treat hemangiomas that are highly likely to cause disfigurement and those that are persistently ulcerated. Corticosteroids have been shown to suppress VEGF production by hemangioma-derived stem cells and to inhibit vasculogenesis in a murine model[121].

Dosage recommendations, duration of therapy, tapering schedules and monitoring guidelines vary widely and no single standard exists. Initial dosages of prednisone (or its equivalent) of 2–3 mg/kg/day are most commonly used[62]. However, some authors have advocated higher dose regimens of 3–5 mg/kg/day because it is speculated that larger doses result in higher response rates[122]. Treatment is usually maintained at these doses until cessation of growth or shrinkage occurs, followed by a gradual taper. The taper schedule is determined by a variety of factors, including the age of the patient, hemangioma growth rate, reason for treatment, presence of adverse effects and rebound growth. The latter may occur if steroids are discontinued while the hemangioma is still in its proliferating phase; this should not be interpreted as a treatment failure but, rather, underscores the importance of recognizing the growth pattern of the hemangioma when making therapeutic decisions.

A literature review used strict inclusion and exclusion criteria to assess the effectiveness of systemic corticosteroids in proliferating infantile hemangiomas[123]. A mean dose of 2.9 mg/kg/day was used over a mean period of 1.8 months before tapering, with a response rate of 84%; cessation of growth was observed more often than shrinkage of the hemangiomas. Doses exceeding 3 mg/kg/day resulted in a response rate of 94% but with a greater incidence of adverse effects. Both this systematic review and a retrospective series of 62 children who received prednisone or prednisolone at an initial dosage of 2–3 mg/kg/day tapered over a mean period of 7.9 months found a low incidence of serious side effects[124]. Adverse reactions in children receiving systemic corticosteroids can include cushingoid facies, irritability, disruption of sleep, gastrointestinal symptoms, and a decreased growth rate (height and weight); however, the majority of children experience catch-up growth after cessation of therapy. In a series of 22 children with hemangiomas who were treated with systemic corticosteroids for a mean of 7 months, hypertension and hypothalamic–pituitary–adrenal (HPA) axis suppression (assessed via morning cortisol levels measured after tapering to a physiologic dose) were frequently observed[125]. However, in another study, only 1 of 16 infants whose hemangiomas were treated with systemic corticosteroids for a mean of 7 months had adrenal insufficiency (assessed with the more specific low-dose corticotropin stimulation test) following completion of therapy[126].

Immunosuppression is another potential side effect of systemic corticosteroid therapy for hemangiomas, although serious infections have

rarely been reported. *Pneumocystis jiroveci (carinii)* pneumonia has been described in a few infants receiving systemic corticosteroids for hemangiomas[127], leading some clinicians to recommend trimethoprim–sulfamethoxazole prophylaxis in this setting. The administration of live-virus vaccines (see Ch. 128) is a concern in children receiving systemic corticosteroids for more than 2 weeks at a dose equivalent to prednisone ≥2 mg/kg/day or ≥20 mg/day in those weighing more than 10 kg. The American Academy of Pediatrics' Committee on Infectious Disease recommends that the administration of live-virus vaccines (see Table 128.9) be avoided while an infant is receiving corticosteroids at these doses and until they have been discontinued for at least 1 month[128].

Recently, concerns have been raised about neurotoxicity in very premature infants treated with corticosteroids for other indications[129]. There is currently no evidence of similar effects in term infants, but this finding raises questions about long-term side effects. Controlled studies are needed to determine the optimal corticosteroid dosage regimen to achieve the desired response with the lowest incidence of adverse effects.

Systemic β-blockers

The non-selective β-blocker propranolol has recently been shown in a randomized controlled trial, several large series and multiple additional case reports to represent an effective systemic treatment for severe infantile hemangiomas[130,131,131a]. Hemangioma endothelial cells express β_2-adrenergic receptors, and effects of propranolol include vasoconstriction, decreased expression of pro-angiogenic factors (e.g. VEGF, bFGF), and induction of endothelial cell apoptosis. The original report in 2008 described the serendipitous discovery of rapid improvement of a hemangioma in an infant who was treated with propranolol for cardiac complications of corticosteroid therapy; this prompted the authors to initiate propranolol therapy in 10 additional infants with function-threatening or disfiguring proliferative-phase hemangiomas (some of whom had previously failed corticosteroid treatment), and marked improvement was again observed[130]. A more detailed follow-up study of these patients and 21 additional children treated with propranolol was subsequently published[131]. The infants in this uncontrolled series received 2–3 mg/kg/day (usually 2 mg/kg/day) of propranolol, divided into two or three oral doses. A color change from red to purple and softening of the hemangiomas were typically noted within a few days of initiating therapy, followed by progressive flattening and reduction in size over a period of weeks to months. Treatment was continued for an average of 6 months, with regrowth (sometimes requiring retreatment) in several hemangiomas when propranolol was stopped before age 12 months.

Additional case series and reports have described similar responses of infantile hemangiomas, including those involving the airway and liver, to treatment with propranolol[132,133]. Benefit for hemangiomas in the late proliferative phase or involution has also been noted[131]. The side-effect profile of propranolol is overall more favorable than that of systemic corticosteroids, and possible adverse reactions include hypotension, bradycardia, hypoglycemia (early signs blunted; can potentially lead to seizures), bronchospasm and sleep disturbances[134,135]. There have also been reports of β-blockers that do not cross the blood-brain barrier (i.e. are hydrophilic rather than lipophilic like propranolol) and/or are β_1-selective (e.g. atenolol) having efficacy for infantile hemangiomas, but controlled trials comparing different β-blockers have not yet been performed[135a].

There are currently no consensus guidelines regarding the use of propranolol for the treatment of infantile hemangiomas. Ongoing studies will help to determine optimal dosing (initial, escalation and tapering) and appropriate monitoring procedures; considerations regarding these issues are summarized in Table 103.8. Many experts advise a baseline cardiac assessment (including examination, electrocardiography, and, in some cases, echocardiography), often involving referral to a pediatric cardiologist, prior to propranolol therapy[134,135]. If clinically indicated (see above), patients should undergo evaluation for PHACE(S) syndrome (especially cardiovascular and cerebrovascular anomalies) or other potential extracutaneous involvement, before beginning propranolol, and its use in infants with PHACE(S) syndrome should be individualized based on consideration of potential complications. Following initiation of therapy and dose escalation, patients should be monitored for signs of bradycardia, hypotension and hypoglycemia[134]. Gradual tapering is recommended, in part to prevent rebound tachycardia.

Other systemic therapies

Vincristine is a chemotherapeutic agent that has been widely used for the treatment of childhood neoplasms. It is a vinca alkaloid that interferes with microtubule formation during mitosis, inducing apoptosis of tumor and endothelial cells[136]. There are reports of its use to treat life- or function-threatening infantile hemangiomas and other vascular tumors that are unresponsive to corticosteroids, as well as the Kasabach–Merritt phenomenon. Toxicities include peripheral neuropathy, constipation, jaw pain, and (uncommonly) anemia and leukopenia. Placement of a central venous catheter is required to administer vincristine, and participation of a pediatric oncologist/hematologist is advisable. Further studies are needed to determine its effectiveness, the incidence of adverse reactions, and optimal dosage regimens for the treatment of infantile hemangiomas[136–140].

Recombinant interferon-α (2a and 2b) can inhibit angiogenesis and was used in the past to treat life- or function-threatening infantile hemangiomas that were resistant to corticosteroid therapy[141–143]. Adverse effects include fever, irritability, diarrhea, neutropenia, elevated transaminases and skin necrosis[142–144]. The most worrisome potential side effect of interferon-α in infants is spastic diplegia, which has been reported in up to 20% of those undergoing treatment for hemangiomas[144,145]. Neurotoxicity does not appear to be dose-related and is potentially (but not always) reversible upon discontinuation of therapy. Because of this concerning possible complication, interferon is now rarely used for the treatment of infantile hemangiomas. When it is administered to infants, baseline neurologic assessment and serial examinations are essential.

Surgical and Laser Therapy

Pulsed dye laser (PDL) therapy (585–600 nm wavelength, usually 0.45–1.5 ms pulse duration) is effective for the treatment of capillary malformations. In the case of proliferating infantile hemangiomas, laser therapy appears to have the most benefit for superficial lesions[146–148]. Hemangiomas with deep dermal or subcutaneous involvement may show lightening of the superficial portion, but PDL therapy does not appear to alter the growth pattern of the deeper component[149]. Multiple treatment sessions, usually every few weeks, are required during the proliferating phase to improve the lesion and prevent rebound growth. Treatments are generally well tolerated, but adverse reactions can include pigmentary alteration, ulceration and atrophic scarring.

A randomized controlled study of early PDL treatment of uncomplicated infantile hemangiomas found no significant difference in the number of children with complete clearance of their hemangiomas at 1 year of age compared to the untreated control group. In the PDL-treated infants, redness was improved, but they were more likely to develop cutaneous atrophy and hypopigmentation than were the untreated cohort[150]. In addition, severe ulceration and scarring have been reported in young infants with large superficial hemangiomas following early laser treatment[151].

The PDL is effective for the treatment of telangiectasias on the surface of involuting and involuted hemangiomas. The Nd:YAG laser has also been used to treat infantile hemangiomas and may have greater efficacy than the PDL for deeper lesions, although there appears to be a higher risk of scarring. Percutaneous treatment utilizing bare fiber Nd:YAG has been reported for deep hemangiomas.

Surgical excision is usually employed to treat involuted or partially involuted lesions in order to remove fibrofatty tissue and redundant skin. The optimal timing for surgery depends upon many factors, including the location and size of the lesion. Surgical excision during the proliferating phase is controversial and reserved for specific situations, such as a function-threatening periorbital hemangioma that has failed to respond to pharmacologic therapy or in which pharmacologic therapy is believed to pose a greater risk to the patient than surgical excision. Other settings where early surgery may be appropriate include pedunculated lesions for which resection will be inevitable and small, persistently ulcerated lesions that have failed more conservative therapy. Excision can be considered in preschool children for involuting lesions when they are located in a cosmetically sensitive area (e.g. nasal tip,

ADMINISTRATION OF PROPRANOLOL FOR INFANTILE HEMANGIOMAS: CONSIDERATIONS REGARDING PRETREATMENT EVALUATION, DOSING AND MONITORING
PRETREATMENT EVALUATION
• In conjunction with a pediatrician and/or pediatric cardiologist: cardiac examination, heart rate, manual blood pressure, electrocardiogram (ECG), ± echocardiogram*
• If abnormalities on cardiac examination/ECG, at risk of PHACE(S) syndrome† or presence of hepatic hemangiomas, refer to a pediatric cardiologist and obtain echocardiogram ± Holter monitoring
• Consider blood glucose level (e.g. via fingerstick)
• Determine if history of bronchospasm/reactive airway disease (usually considered a contraindication to propranolol therapy)
• If at risk for PHACE(S) syndrome†, MRI/MRA of head and neck to exclude vascular anomalies (see Fig. 103.15 for additional information); if abnormal findings, obtain evaluation by a neuroradiologist familiar with PHACE(S) and consider referral to a pediatric neurologist
• If multiple (e.g. ≥5) hemangiomas, abdominal ultrasound to assess for hepatic hemangiomas (see Fig. 103.15 for additional information)
DOSING AND COURSE
• Initial: 0.5–1 mg/kg/day divided into 2 or 3 doses
• Increase as tolerated, usually with a goal of 2 mg/kg/day‡ divided into 2 or 3 doses§
• For a proliferating hemangioma, treatment is typically continued until 9–15 months of age (depending on the clinical setting and course)
– Based on the response to treatment and other characteristics of the hemangioma, dose increases as the child grows to maintain the same goal dose/kg may or may not be needed
– Dose should be lowered or therapy temporarily suspended during intercurrent illnesses, especially if decreased oral intake or vomiting
• Taper over ~2–4 weeks before discontinuing (primarily to prevent rebound tachycardia)
MONITORING
• Risks of propranolol include bradycardia, hypotension, hypoglycemia, sleep disturbances and bronchospasm‖
• Consider a brief *inpatient* stay (e.g. 1–2 days) with telemetry for initiation of treatment, especially if <2–3 months of age, history of preterm birth and/or complications (e.g. associated cardiovascular anomalies)
• Outpatient initiation of therapy with assessment of heart rate, blood pressure and blood glucose *in-office* or by a *visiting nurse* may otherwise be appropriate*
– Within one day of the first dose or a dose escalation (ideally 0.5–2 hours after administration)
– Every 3–6 weeks while on a stable dose
– Normal ranges for pediatric vital signs are available at: www.emedicinehealth.com/pediatric_vital_signs/article_em.htm
• Educate parents about signs of hypoglycemia (early¶: sweating, rapid heart rate, shakiness, fussiness; late: lethargy, poor feeding, hypothermia, seizures)
– Encourage parents to feed the infant before each dose and do not administer before bedtime without feeding
– Feed at least every 3–4 hours in younger infants and every 4–5 hours in older infants
*Holter monitoring can also be considered at baseline and/or periodically during treatment.
†Segmental cervicofacial hemangioma ≥5 cm in diameter.
‡Occasionally need to increase to 3 mg/kg/day, and doses as low as 1 mg/kg/day may be effective.
§An example protocol is an initial dose of 0.5 mg/kg/day divided into 2 or 3 doses (0.25 or 0.17 mg/kg/dose, respectively), then doubling of the dose every 3–7 *days* in an *out*patient setting or every 1–3 *doses* in an *in*patient setting until reaching 2 mg/kg/day.
‖To date there has been a single case report of hyperkalemia associated with treatment of a large, ulcerated hemangioma with propranolol.
¶May be masked with the β-adrenergic blockade.

Table 103.8 Administration of propranolol for infantile hemangiomas: considerations regarding pretreatment evaluation, dosing and monitoring. Practices vary widely, and some pediatric dermatologists/pediatric cardiologists recommend more or less intensive evaluation and monitoring. The patient's age, hemangioma-related issues, and medical comorbidities also affect management.

lip). The ultimate management goal is to achieve as normal an appearance as possible, considering the expected surgical scar as well as the predicted time course and outcome of involution. Therefore, just as with other treatment modalities, the surgical management of infantile hemangiomas needs to be individualized.

Arterial embolization has been used to treat life-threatening hemangiomas that are causing high-output congestive heart failure. It may be used concurrently with other modalities and prior to surgical resection in some cases[152].

Cryosurgery has also been used to treat infantile hemangiomas[153,154]. Contact cryosurgery is the method most commonly employed, and it is used mostly in Europe and Latin America. Adverse effects include scarring and pigmentary alteration.

Management of Kasabach–Merritt Phenomenon

KMP is a life-threatening disorder that represents a medical emergency. The associated vascular tumors respond less consistently to treatment than do infantile hemangiomas. Systemic corticosteroids, interferon-α, chemotherapeutic agents including vincristine and cyclophosphamide, ticlopidine and aspirin have been used alone and in combination, with a variable response rate[98]. A retrospective case series suggested that some patients may be successfully managed with vincristine[155]. Surgical excision, embolization and radiation have also been utilized[136,156], and supportive care is mandatory. Platelet transfusions may lead to enlargement of the tumor and worsening of the coagulopathy, possibly due to pro-angiogenic factors present in blood products[157].

REFERENCES

1. Mulliken, JB. Classification of vascular birthmarks. In: Mulliken JB, Young AE (eds). Vascular Birthmarks: Hemangiomas and Malformations. Philadelphia: WB Saunders, 1988:24–37.
2. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. Plast Reconstr Surg. 1982;69:412–20.
3. Enjolras O, Mulliken J. Vascular tumors and vascular malformations, new issues. Adv Dermatol. 1998;13:375–423.
4. Hand JL, Frieden IJ. Vascular birthmarks of infancy; resolving nosologic confusion. Am J Med Genet. 2002;108:257–64.
5. Kilcline C, Frieden IJ. Infantile hemangiomas: how common are they? A systematic review of the medical literature. Pediatr Dermatol. 2008;25:168–73.
6. Mulliken JB. Diagnosis and natural history of hemangiomas. In: Mulliken JB, Young AE (eds). Vascular Birthmarks: Hemangiomas and Malformations. Philadelphia: WB Saunders, 1988:41–62.
7. Esterly NB. Cutaneous hemangiomas, vascular stains and malformations, and associated syndromes. Curr Probl Dermatol. 1995;7:69–107.
8. Finn MC, Glowacki J, Mulliken JB. Congenital vascular lesions: clinical application of a new classification. J Pediatr Surg. 1983;18:894–900.
9. Moroz B. Long-term follow-up of hemangiomas in children. In: Williams HB (ed). Symposium on Vascular Malformations and Melanotic Lesions. St. Louis: CV Mosby, 1983:162–71.
10. Enjolras O, Gelbert F. Superficial hemangiomas: associations and management. Pediatr Dermatol. 1997;14:173–9.
11. Amir J, Metzker A, Krikler R, Reisner SH. Strawberry hemangioma in preterm infants. Pediatr Dermatol. 1986;3:331–2.
12. Burton BK, Schulz CJ, Angle B, Burd LI. An increased incidence of hemangiomas in infants born following chronic villus sampling (CVS). Prenat Diagn. 1995;15:209–14.

13. Hemangioma Investigator Group: Haggstrom AN, Drolet BA, Baselga E, et al. Prospective study of infantile hemangiomas: demographic, prenatal and perinatal characteristics. J Pediatr. 2007;150:291–4.
14. Margileth AM, Museles M. Cutaneous hemangiomas in children: diagnosis and conservative management. J Am Med Assoc. 1965;194:523–6.
15. Blei F, Walter J, Orlow SJ, Marchuk DA. Familial segregation of hemangiomas and vascular malformations as an autosomal dominant trait. Arch Dermatol. 1998;134:718–22.
16. Walter, JW, Blei F, Anderson JL, et al. Genetic mapping of a novel familial form of infantile hemangioma. Am J Med Genet. 1999;82:77–83.
17. Yu Y, Flint AF, Mulliken JB, et al. Endothelial progenitor cells in infantile hemangioma. Blood. 2004;103:1373–5.
18. Frieden IJ, Haggstrom AN, Drolet BA, et al. Infantile hemangiomas: current knowledge, future directions. Proceedings of a research workshop on infantile hemangiomas, April 7–9, 2005, Bethesda, Maryland, USA. Pediatr Dermatol. 2005;22:383–406.
19. Khan ZA, Boscolo E, Pcard A, et al Multipotential stem cells recapitulate human infantile hemangioma in immunodeficient mice. J Clin Invest. 2008;118:2592–9.
20. Boye E, Ying Y, Paranya G, et al. Clonality and altered behavior of endothelial cells from hemangiomas. J Clin Invest. 2001;107:745–52.
21. Walter JW, North PE, Waner M, et al. Somatic mutation of vascular endothelial growth factor receptors in juvenile hemangioma. Genes Chromosomes Cancer. 2002:33:295–303.
22. Pramanik K, Chun CZ, Garnaas MK, et al. Dusp-5 and Snrk-1 coordinately function during vascular development and disease. Blood. 2009;113:1184–91.
23. Jinnin M, Medici D, Park L, et al. Suppressed NFAT-dependent VEGFR1 expression and constitutive VEGFR2 signaling in infantile hemangioma. Nat Med. 2008;14:1236–46.
24. Berg JN, Walter JW, Thisanagayam U, et al. Evidence for loss of heterozygosity of 5q in sporadic hemangiomas: are somatic mutations involved in hemangioma formation? J Clin Pathol. 2001;54:249–52.
25. Yu Y, Brown LF, Mulliken JB, Bischoff J. Increased Tie2 expression, enhanced response to angiopoietin-1, and dysregulated angiopoietin-2 expression in hemangioma-derived endothelial cells. Am J Pathol. 2001;159:2271–80.
26. North PE, Waner M, Mizeracki A, Mihm MC. GLUT1: a newly discovered immunohistochemical marker for juvenile hemangiomas. Hum Pathol. 2000;31:11–22.
27. North PE, Waner M, Mizeracki A, et al. A unique microvascular phenotype shared by juvenile hemangiomas and human placenta. Arch Dermatol. 2001;137:559–70.
28. Bree AF, Siegfried E, Sotelo-Avila C, Nahass G. Infantile hemangiomas: speculation on placental trophoblastic origin. Arch Dermatol. 2001;137:573–7.
29. Drolet BA, Frieden IJ. Characteristics of infantile hemangiomas as clues to pathogenesis: does hypoxia connect the dots? Arch Dermatol. 2010;146:1295–9.
30. Colonna V, Resta L, Napoli A, Bonifazi E. Placental hypoxia and neonatal haemangioma: clinical and histological observations. Br J Dermatol. 2010;162:208–9.
31. Takahashi K, Mulliken JB, Kozakewich HPW, et al. Cellular markers that distinguish the phases of hemangiomas during infancy and childhood. J Clin Invest. 1994;93:2357–64.
32. Chang J, Most D, Bresnick S, et al. Proliferative hemangiomas: analysis of cytokine gene expression and angiogenesis. Plast Reconstr Surg. 1999;103:1–9.
33. Zhang L, Lin X, Wang W, et al. Circulating level of vascular endothelial growth factor in differentiating hemangioma from vascular malformation patients. Plast Reconstr Surg. 2005;116:200–4.
34. Isik FF, Rand RP, Gruss JS, et al. Monocyte chemoattractant protein-1 mRNA expression in hemangiomas and vascular malformations. J Surg Res. 1996;61:71–6.
35. Salcedo R, Ponce ML, Young HA, et al. Human endothelial cells express CCR2 and respond to MCP-1: direct role of MCP-1 in angiogenesis and tumor progression. Blood. 2000;96:34–40.
36. Kraling BM, Razon MJ, Boon LM, et al. E-selectin is present in proliferating endothelial cells in human hemangiomas. Am J Pathol. 1996;148:1181–91.
37. Verkarre V, Patey-Mariaud de Serre N, Vazeux R, et al. ICAM-3 and E-selectin endothelial cell expression differentiate two phases of angiogenesis in infantile hemangiomas. J Cutan Pathol. 1999;26:17–24.
38. Jang YC, Arumugam S, Ferguson M, et al. Changes in matrix composition during the growth and regression of human hemangiomas. J Surg Res. 1998;80:9–15.
39. Tan ST, Velickovic M, Ruger BM, Davis BF. Cellular and extracellular markers of hemangioma. Plast Reconstr Surg. 2000;106:529–38.
40. Marler JJ, Fishman SJ, Kilroy SM, et al. Increased levels of urinary matrix metalloproteinases parallels the extent and activity of vascular anomalies. Pediatrics. 2005;116:38–45.
41. Bielenberg DR, Bucana CD, Sanchez R, et al. Progressive growth of infantile cutaneous hemangiomas is directly correlated with hyperplasia and angiogenesis of adjacent epidermis and inversely correlated with expression of the endogenous angiogenesis inhibitor, IFN-beta. Int J Oncol. 1999;14:401–8.
42. Ritter MR, Moreno SK, Dorrell MI, et al. Identifying potential regulators of infantile hemangioma progression through large-scale expression analysis: a possible role of the immune system and indoleamine 2,3 dioxygenase (IDO) during involution. Lymphat Res Biol. 2003:1:291–9.
43. Ritter MR, Dorrell MI, Edmonds J, et al. Insulin-like growth factor 2 and potential regulators of hemangioma growth and involution identified by large-scale expression analysis. Proc Natl Acad Sci USA. 2002;99:7455–60.
44. Mancini AJ, Smoller BR. Proliferation and apoptosis within juvenile capillary hemangiomas. Am J Dermatopathol. 1996;18:505–14.
45. Razon MJ, Kraling BM, Mulliken JB, Bischoff J. Increased apoptosis coincides with onset of involution in infantile hemangiomas. Microcirculation. 1998;5:189–95.
46. Hasan Q, Ruger BM, Tan ST, et al. Clusterin/apoJ expression during the development of hemangiomas. Hum Pathol. 2000;31:691–7.
47. North PE, Waner M, James CA, et al. Congenital nonprogressive hemangiomas: a distinct clinicopathologic entity unlike infantile hemangioma. Arch Dermatol. 2002;137:1607–20.
48. Liang MG, Frieden IJ. Perineal and lip ulcerations as the presenting manifestation of hemangioma of infancy. Pediatrics. 1997;99:256–9.
49. Martinez-Perez D, Fein, N, Boon L, Mulliken JB. Not all hemangiomas look like strawberries: uncommon presentations of the most common tumor of infancy. Pediatr Dermatol. 1995;12:1–6.
50. Waner M, North PE, Scherer KA, et al. The nonrandom distribution of facial hemangiomas. Arch Dermatol. 2003;139:869–75.
51. Chiller KG, Passaro D, Frieden IJ. Hemangiomas of infancy: clinical characteristics, morphologic subtypes and their relationship to race, ethnicity and sex. Arch Dermatol. 2002;138:1567–76.
52. Haggstrom AN, Lammer EJ, Schneider RA, et al. Patterns of infantile hemangiomas: new clues to hemangioma pathogenesis and embryonic facial development. Pediatrics. 2006;117:698–703.
53. Chang LC, Haggstrom AN, Drolet BA, et al. Growth characteristics of infantile hemangiomas: implications for management. Pediatrics. 2008;122:360–7.
54. Brandling-Bennett HA, Metry DW, Baselga E, et al. Infantile hemangiomas with unusually prolonged growth phase: a case series. Arch Dermatol. 2008;144:1632–7.
55. Suh KY, Frieden IJ. Infantile hemangiomas with minimal or arrested growth: a retrospective case series. Arch Dermatol. 2010;146:971–6.
56. Corella F, Garcia-Navarro X, Ribe A, et al. Abortive or minimal-growth hemangiomas: immunohistochemical evidence that they represent true infantile hemangiomas. J Am Acad Dermatol. 2008;58:685–90.
57. Mulliken JB, Marler JJ, Burrows PE, et al. Reticular infantile hemangioma of the limb can be associated with ventral-caudal anomalies, refractory ulceration, and cardiac overload. Pediatr Dermatol. 2007;24: 356–62.
58. Bowers RE, Graham EA, Tomlinson KM. The natural history of the strawberry nevus. Arch Dermatol. 1960;82:667–80.
59. Chamlin SL, Haggstrom AN, Drolet BA, et al. Multicenter prospective study of ulcerated hemangiomas. J Pediatr. 2007;151:684–9.
60. Maguiness SM, Hoffman WY, McCalmont TH, Frieden IJ. Early white discoloration of infantile hemangioma: a sign of impending ulceration. Arch Dermatol. 2010;146:1235–9.
61. Kim HJ, Colombo M, Frieden IJ. Ulcerated hemangiomas: clinical characteristics and response to therapy. J Am Acad Dermatol. 2001;44:962–72.
62. Drolet BA, Esterly NB, Frieden IJ. Hemangiomas in children. N Engl J Med. 1999;341:173–81.
63. Haik BG, Jakobiec F, Ellsworth RM, et al. Capillary hemangiomas of the lid and orbit: an analysis of the clinical features and therapeutic results in 101 cases. Ophthamology. 1979;86:760–89.
64. Robb R. Refractive errors associated with hemangiomas of the eyelids and orbit in infancy. Am J Ophthamol. 1977;83:52–8.
65. Ceisler EJ, Santos L, Blei F. Periocular hemangiomas: what every physician should know. Pediatr Dermatol. 2004;21:1–9.
66. Haggstrom AN, Garzon MC, Baselga E, et al. Risk for PHACE syndrome in infants with large facial hemangiomas. Pediatrics. 2010;126:e418–26.
67. Pascual-Castroviejo I. Vascular and nonvascular intracranial malformations associated with external capillary hemangiomas. Neuroradiology. 1978; 16:82–4.
68. Frieden IJ, Reese V, Cohen D. PHACE syndrome: the association of posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities. Arch Dermatol. 1996;132:307–11.
69. Metry D, Heyer G, Hess C, et al. PHACE Syndrome Research Conference Consensus statement on diagnostic criteria for PHACE syndrome. Pediatrics. 2009;124:1447–56.
70. Burrows PE, Robertson RL, Mulliken JB, et al. Cerebral vasculopathy and neurologic sequelae in infants with cervicofacial hemangioma: report of eight patients. Radiology. 1998;207:601–7.
71. Orlow SJ, Isakoff MS, Blei F. Increased risk of symptomatic hemangiomas of the airway in association with cutaneous hemangiomas in a "beard" distribution. J Pediatr. 1997;131:643–6.
72. Haggstrom AN, Skillman S, Garzon MC, et al. Clinical spectrum and risk of PHACE syndrome in cutaneous and airway hemangiomas. Arch Otolaryngol Head Neck Surg. 2011;137:680–7.
73. Drolet BA, Chamlin SA, Garzon MC, et al. Prospective study of spinal anomalies in children with infantile hemangiomas of the lumbosacral skin. J Pediatr. 2010;157:789–94.
74. Iacobas I, Burrows PE, Frieden IJ, et al. LUMBAR: association between cutaneous infantile hemangiomas of the lower body and regional cutaneous anomalies. J Pediatr. 2010;157:795–801.
75. Achauer BM, Chang C, Vander Kam VM. Management of hemangiomas of infancy: review of 245 patients. Plast Reconstr Surg. 1997;99:1301–8.
76. Holden KR, Alexander F. Diffuse neonatal hemangiomatosis. Pediatrics. 1970;46:411–21.
77. Stern JK, Wolf JE, Jarratt M. Benign neonatal hemangiomatosis. J Am Acad Dermatol. 1981;4:442–5.
78. Golitz LE, Rudikoff J, O'Meara OP. Diffuse neonatal hemangiomatosis. Pediatr Dermatol. 1986;3:145–52.
79. Boon LM, Burrows PE, Paltiel HJ, et al. Hepatic vascular anomalies in infancy: a twenty-seven year experience. J Pediatr. 1996;129:346–54.
80. Kassarjian A, Zurakowski D, Dubois J, et al. Infantile hepatic hemangiomas: clinical and imaging findings and their correlation with therapy. AJR Am J Roentgenol. 2004;182:785–95.
81. Christison Lagay ER, Burrows PE, Alomari A, et al. Hepatic hemangiomas: subtype classification and development of a clinical practice algorithm and registry. J Pediatr Surg. 2007;42:62–8.
82. Viswanathan V, Smith ER, Mulliken JB, et al. Infantile hemangiomas involving the neuraxis: clinical and imaging findings. AJNR Am J Neuroradiol. 2009;30:1005–13.
83. Hughes JA, Hill V, Patel K et al. Cutaneous hemangioma: prevalence and sonographic characteristics of associated hepatic hemangioma. Clin Radiol. 2004;59:273–80.
84. Metry DW, Hawrot A, Altman C, et al. Association of solitary, segmental hemangiomas of the skin with visceral hemangiomatosis. Arch Dermatol. 2004;140:591–6.
85. Horii KA, Drolet BA, Baselga E, et al. Risk of hepatic hemangiomas in infants with large hemangiomas. Arch Dermatol. 2010;146:201–3.
86. Huang SA, Tu HM, Harney JW, et al. Severe hypothyroidism caused by type 3 iodothyronine deiodinase in infantile hemangiomas. N Engl J Med. 2000;343:185–9.
87. Konrad D, Ellis G, Perlman K. Spontaneous regression of severe acquired hypothyroidism associated with

multiple liver hemangiomas. Pediatrics. 2003;112:1424–6.
88. Sheu B, Shyu M, Lin Y, et al. Prenatal diagnosis and corticosteroid treatment of diffuse neonatal hemangiomatosis. J Ultrasound Med. 1994;13:495–9.
89. Dickie B, Dasgupta R, Nair R, et al. Spectrum of hepatic hemangiomas: management and outcome. J Pediatr Surg. 2009;44:125–33.
90. Boon, LM, Enjolras O, Mulliken JB. Congenital hemangioma: evidence of accelerated involution. J Pediatr. 1996;128:329–35.
91. Berenguer B, Mulliken JB, Enjolras O, et al. Rapidly involuting congenital hemangioma: clinical and histopathologic features. Pediatr Dev Pathol. 2003;6:495–510.
92. Enjolras O, Mulliken JB, Boon LM, et al. Noninvoluting congenital hemangioma: a rare cutaneous vascular anomaly. Plast Reconstr Surg. 2001;107:1647–54.
93. Baselga E, Cordisco MR, Garzon M, et al. Rapidly involuting congenital haemangioma associated with transient thrombocytopenia and coagulopathy: a case series. Br J Dermatol. 2008;158:1363–70.
94. Mulliken JB, Enjolras O. Congenital hemangiomas and infantile hemangioma: missing links. J Am Acad Dermatol. 2004;50:875–82.
95. Kasabach HH, Merritt KK. Capillary hemangioma with extensive purpura, report of a case. Am J Dis Child. 1940;59:1063–70.
96. Enjolras O, Wassef M, Mazoyer E, et al. Infants with Kasabach-Merritt syndrome do not have "true" hemangiomas. J Pediatr. 1997;130:631–40.
97. Sarkar M, Mulliken JB, Kozakewich HPW, et al. Thrombocytopenic coagulopathy (Kasabach-Merritt phenomenon) is associated with kaposiform hemangioenodothelioma and not with common infantile hemangioma. Plast Reconstr Surg. 1997;100:1377–86.
98. Enjolras O, Mulliken JB, Wassef M, et al. Residual lesions after Kasabach-Merritt phenomenon in 41 patients. J Am Acad Dermatol. 2000;42:225–35.
99. Burrows PE, Laor T, Paltiel H, et al. Diagnostic imaging in the evaluation of vascular birthmarks. Dermatol Clin. 1998;16:455–88.
100. Marler JJ, Fishman SJ, Upton J, et al. Prenatal diagnosis of vascular anomalies. J Pediatr Surg. 2002;37:318–26.
101. Rogers M, Lam A, Fischer G. Sonographic findings in a series of rapidly involuting congenital hemangiomas (RICH). Pediatr Dermatol. 2002;19:5–11.
102. Frieden IJ, Eichenfield LF, Esterly NB, et al. Guidelines of care for hemangiomas of infancy. J Am Acad Dermatol. 1997;37:631–7.
103. Frieden IJ. Which hemangiomas to treat and how? Arch Dermatol. 1997;133:1593–5.
104. Tanner JL, Dechert MP, Freiden IJ. Growing up with a facial hemangioma: parent and child coping and adaptation. Pediatrics. 1998;101:446–51.
105. Achauer BM, Vander Kam VM. Ulcerated anogenital hemangioma of infancy. Plast Reconstr Surg. 1991;87:861–6.
106. Morelli JG, Tan OT, Weston WL. Treatment of ulcerated hemangiomas with the pulsed tunable dye laser. Am J Dis Child. 1991;145:1062–4.
107. Scheepers JH, Quaba AA. Does the pulsed tunable dye laser have a role in the management of infantile hemangiomas? Observations based on 3 years' experience. Plast Reconstr Surg. 1995;95:305–12.
108. David LR, Malek MM, Argenta LC. Efficacy of pulse dye laser therapy for the treatment of ulcerated hemangiomas: a review of 78 patients. Br J Plast Surg. 2003;56:317–27.
109. Sugarman JL, Mauro TM, Frieden IJ. Treatment of an ulcerated hemangioma with recombinant platelet-derived growth factor. Arch Dermatol. 2002;138:314–16.
110. Metz BJ, Rubenstein MC, Levy ML, et al. Response of ulcerated perineal hemangiomas of infancy to becaplermin gel, a recombinant human platelet-derived growth factor. Arch Dermatol. 2004;140:867–70.
111. Chen MT, Yeong EK, Horng SY. Intralesional corticosteroid therapy in proliferating head and neck hemangiomas: a review of 155 cases. J Pediatr Surg. 2000;35:420–3.
112. Egbert JE, Schwartz GS, Walsh AW. Diagnosis and treatment of ophthalmic artery occlusion during an intralesional injection of corticosteroid into an eyelid capillary hemangioma. Am J Ophthamol. 1996;121:638–42.
113. Kushner BJ. Hemangiomas. Arch Ophthamol. 2000;118:835–6.
114. Schorr N, Seiff SR. Central retinal artery occlusion associated with periocular corticosteroid injection for juvenile hemangioma. Ophthamol Surg. 1986;17:229–31.
115. Sutula FC, Glover AT. Eyelid necrosis following intralesional corticosteroid injection for capillary hemangioma. Ophthamol Surg. 1987;18:103–5.
116. Garzon MC, Lucky AW, Hawrot A, et al. Ultrapotent topical corticosteroid treatment of hemangiomas of infancy. J Am Acad Dermatol. 2005;52:281–6.
117. Ranchod TM, Frieden IJ, Fredrick DR. Corticosteroid treatment of periorbital haemangioma of infancy: a review of the evidence. Br J Ophthalmol. 2005;89:1134–8.
118. Pope E, Chakkittakandiyil A. Topical timolol gel for infantile hemangiomas: a pilot study. Arch Dermatol. 2010;146:564–5.
118a. Ni N, Langer P, Wagner R, Guo S. Topical timolol for periocular hemangioma: report of further study. Arch Ophthalmol. 2011;129:377–9.
119. McCuaig CC, Dubois J, Powell J, et al. A phase II, open-label study of the efficacy and safety of imiquimod in the treatment of superficial and mixed infantile hemangioma. Pediatr Dermatol. 2009;26:203–12.
120. Ho NT, Lansang P, Pope E. Topical imiquimod in the treatment of infantile hemangiomas: a retrospective study. J Am Acad Dermatol. 2007;56:63–8.
121. Greenberger S, Boscolo E, Adini I, et al. Corticosteroid suppression of VEGF-A in infantile hemangioma-derived stem cells. N Engl J Med. 2010;362:1005–13.
122. Sadan N, Wolach B. Treatment of hemangiomas of infants with high doses of prednisone. J Pediatr. 1996;128:141–6.
123. Bennett ML, Fleischer AB Jr, Chamlin SL, Frieden IJ. Oral corticosteroid use is effective for cutaneous hemangiomas: an evidence-based evaluation. Arch Dermatol. 2001;137:1208–13.
124. Boon, LM, MacDonald DM, Mulliken JB. Complications of systemic corticosteroid therapy for problematic hemangioma. Plast Reconstr Surg. 1999;104:1616–23.
125. George ME, Sharma V, Jacobson J, et al. Adverse effects of systemic glucocorticosteroid therapy in infants with hemangiomas. Arch Dermatol. 2004;140:963–9.
126. Lomenick JP, Reifschneider KL, Lucky AW, et al. Prevalence of adrenal insufficiency following systemic glucocorticoid therapy in infants with hemangiomas. Arch Dermatol. 2009;145:262–6.
127. Aviles R, Boyce TG, Thompson DM. *Pneumocystis carinii* pneumonia in a 3-month-old infant receiving high-dose corticosteroid therapy for airway hemangiomas. Mayo Clin Proc. 2004;79:243–5.
128. Pickering LK (ed). Red Book: Report of the Committee on Infectious Diseases, 28th edn. Elk Grove Village, IL: American Academy of Pediatrics, 2009:78.
129. Halliday HL. The effect of postnatal steroids on growth and development. J Perinat Med. 2001;29:281–5.
130. Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, et al. Propranolol for severe hemangiomas of infancy. N Engl J Med. 2008;358:2649–51.
131. Sans V, de la Roque ED, Berge J, et al. Propranolol for severe infantile hemangiomas: follow-up report. Pediatrics. 2009;124:e423–31.
131a. Hogeling M, Adams S, Wargon O. A randomized controlled trial of propranolol for infantile hemangiomas. Pediatrics. 2011;128:e259–66.
132. Marsciani A, Pericoli R, Alaggio R. Massive response of severe infantile hepatic hemangioma to propanolol. Pediatr Blood Cancer. 2010;54:176.
133. Denoyelle F, Leboulanger N, Enjolras O, et al. Role of propranolol in the therapeutic strategy of infantile laryngotracheal hemangioma. Int J Pediatr Otorhinolaryngol. 2009;73:1168–72.
134. Lawley LP, Siegfried E, Todd JL. Propranolol treatment for hemangioma of infancy: risks and recommendations. Pediatr Dermatol. 2009; 26:610–14.
135. Frieden IJ, Drolet BA. Propranolol for infantile hemangiomas: promise, peril, pathogenesis. Pediatr Dermatol. 2009;26:642–4.
135a. Raphael MF, de Graaf M, Breugem CC, et al. Atenolol: a promising alternative to propranolol for the treatment of hemangiomas. J Am Acad Dermatol. 2011;65: 420–1.
136. Adams DM. The nonsurgical management of vascular lesions. Facial Plast Clin North Am. 2001;9:601–8.
137. Payarols P, Masferrer P, Bellvert G. Treatment of life-threatening hemangiomas with vincristine. N Engl J Med. 1995;333:69.
138. Hu B, Lachman R, Phillips J, et al. Kasabach-Merritt syndrome-associated kaposiform hemangioendothelioma successfully treated with cyclophosphamide, vincristine, and actinomycin D. J Pediatr Hematol Oncol. 1998;20:567–9.
139. Moore J, Lee M, Garzon M, et al. Effective therapy of a vascular tumor of infancy with vincristine. J Pediatr Surg. 2001;36:1273–6.
140. Fawcett SL, Grant I, Hall PN, et al. Vincristine as a treatment for a large haemangioma threatening vital functions. Br J Plast Surg. 2004;57:168–71.
141. Ezekowitz R, Mulliken JB, Folkman J. Interferon alfa-2a treatment for life threatening hemangiomas of infancy. N Engl J Med. 1992;326:1456–63.
142. Chang E, Boyd A, Nelson CC, et al. Successful treatment of infantile hemangiomas with interferon-alfa-2b. J Pediatr Hematol Oncol. 1997;19:237–44.
143. Tamayo L, Ortiz D, Orozco-Covarrubias L, et al. Therapeutic efficacy of interferon alfa-2b in infants with life-threatening giant hemangiomas. Arch Dermatol. 1997;133:1567–71.
144. Hershon DJ, Carman L, Belanger S, et al. Toxicity profile of interferon alfa-2b in children: a prospective evaluation. J Pediatr. 1999;135:782–5.
145. Barlow C, Priebe C, Mulliken JB, et al. Spastic diplegia as a complication of interferon alfa-2a treatment of hemangiomas of infancy. J Pediatr. 1998;132:527–30.
146. Ashinoff R, Geronemus RG. Capillary hemangiomas and treatment with flash lamp-pumped pulsed dye laser. Arch Dermatol. 1991;127:202–5.
147. Garden JM, Bakus AD, Paller AS. Treatment of cutaneous hemangiomas by the flashlamp-pumped pulsed dye laser: prospective analysis. J Pediatr. 1992;120:555–60.
148. Hohenleutner S, Badur-Ganter E, Landthaler M, Hohenleutner U. Long-term results in the treatment of childhood hemangioma with the flashlamp-pumped pulsed dye laser: an evaluation of 617 cases. Lasers Surg Med. 2001;28:273–7.
149. Ashinoff R, Geronemus RG. Failure of the flashlamp-pumped pulsed dye laser to prevent progression to deep hemangioma. Pediatr Dermatol. 1993;10:77–80.
150. Batta K, Goodyear HM, Moss C, et al. Randomised controlled study of early pulsed dye laser treatment of uncomplicated childhood haemangiomas: results of a 1-year analysis. Lancet. 2002;360:521–7.
151. Witman PM, Wagner AM, Scherer K, et al. Complications following pulsed dye laser treatment of superficial hemangiomas. Lasers Surg Med. 2006;38:116–23.
152. Burrows PE, Lasjaunias PL, Ter Brugge KG, Flodmark O. Urgent and emergent embolization of lesions of the head and neck in children: indications and results. Pediatrics. 1987;80;386–94.
153. Cremer H. Cryosurgery for hemangiomas. Pediatr Dermatol. 1998;15:173–9.
154. Reischle S, Schuller-Petrovic S. Treatment of capillary hemangiomas of early childhood with a method of cryosurgery. J Am Acad Dermatol. 2000;42:809–13.
155. Haisley-Royster C, Enjolras O, Frieden IJ, et al. Kasabach-Merritt phenomenon: a retrospective study of treatment with vincristine. J Pediatr Hematol Oncol. 2002;24:459–62. Erratum in: J Pediatr Hematol Oncol. 2002;24:794.
156. Drolet BA, Scott LA, Esterly NB, Gosain AK. Early surgical intervention in a patient with Kasabach-Merritt phenomenon. J Pediatr. 2001;138:756–8.
157. Phillips WG, Marsden JR. Kasabach-Merritt syndrome exacerbated by platelet transfusion. J R Soc Med. 1993;86:231–2.

This page intentionally left blank

Vascular Malformations 104

Odile Enjolras

Synonyms: ■ Mature angiomas [misnomer]; angiodysplasias; vascular birthmarks ■ Capillary malformation (CM): port-wine stain, nevus flammeus, telangiectasia ■ Venous malformation (VM): cavernous angioma [misnomer], cavernous hemangioma [misnomer], phlebectasia ■ Lymphatic malformation (LM): lymphangioma, lymphangioma circumscriptum, lymphangioma simplex, cystic hygroma, cavernous lymphangioma ■ Arteriovenous malformation (AVM): cirsoid aneurysm, cirsoid hemangioma

Key features

- Although both were once called "angiomas", vascular malformations clearly differ from the vascular tumors seen in infants and children
- In slow-flow malformations, capillaries, veins and/or lymphatic channels are anomalous; most lesions are either apparent at birth or become evident within the first few months or years of life
- In fast-flow malformations, there is arteriovenous shunting; some lesions are apparent at birth, but the majority become evident later in childhood or adulthood
- All vascular malformations are lifelong and may worsen, creating cosmetic consequences and functional impairment
- Vascular malformations are occasionally found together with other abnormalities as a part of a complex syndrome

INTRODUCTION

According to the classification system adopted by the International Society for the Study of Vascular Anomalies (ISSVA), there are two types of vascular anomalies: vascular tumors (most commonly the infantile hemangioma) and vascular malformations[1] (Table 104.1). Vascular malformations are localized defects of vascular morphogenesis, likely caused by dysfunction in pathways regulating the formation of vascular channels during embryonic development. True angiogenesis may occur in some of these lesions, potentially explaining their propensity to thicken and even expand over time. However, in general, vascular malformations have a quiescent endothelium, and they do not exhibit the markers of endothelial cell proliferation seen in infantile hemangiomas during their proliferative phase (Fig. 104.1)[2,3]. Because vascular malformations are not truly proliferating lesions with cellular hyperplasia, the suffix "oma" (meaning "tumor") has been deemed inaccurate. Thus, the terms "angioma", "lymphangioma" and "hemangioma" should no longer be used for vascular malformations.

Vascular malformations are subcategorized depending on the predominant anomalous channels and flow characteristics: slow-flow or fast-flow[2,3]. A slow-flow vascular malformation may be:

- capillary (CM), i.e. port-wine stain (PWS)
- venous (VM): a misnomer for this entity is "cavernous hemangioma", a term with a long history of use to describe deep infantile hemangiomas
- lymphatic (LM): this category includes microcystic and macrocystic lesions (formerly termed lymphangioma and cystic hygroma, respectively).

A fast-flow vascular malformation combines arterial anomalies and arteriovenous shunting, creating the nidus of an arteriovenous malformation (AVM).

Complex-combined vascular malformations are designated as capillary–venous (CVM), capillary–lymphatic (CLM), capillary–lymphatic–venous (CLVM), lymphatic–venous (LVM), capillary–arteriovenous (C-AVM) or lymphatic–arteriovenous (L-AVM), depending on the vessels involved. A few scenarios provide evidence of overlap (e.g. spindle cell hemangiomas and VMs in patients with Maffucci syndrome; pyogenic granulomas superimposed on a CM or AVM) or coexistence (e.g. familial co-segregation of infantile hemangiomas and vascular malformations) of vascular tumors and vascular malformations.

Vascular malformations may occur in any body part or organ system. They are most easily identified in the skin and mucous membranes, with some of these lesions invading deep into underlying muscles, bones or joints. Others are found in visceral locations. Vascular malformations can appear as localized lesions of varying sizes, occur within a segmental distribution, or be dispersed as multifocal or disseminated lesions. Vascular malformations are occasionally found together with other abnormalities as part of a complex syndrome, which may be referred to by an eponym (e.g. Klippel–Trenaunay syndrome; KTS).

Vascular malformations are persistent and tend to worsen over time if not treated. Categorizing a lesion as a CM, LM, VM or AVM is important, since diagnostic modalities as well as treatment will differ depending on the type of vessels involved[1]. In many patients, a multidisciplinary team is required to provide optimal management. Cure is rarely achievable. A realistic aim is improvement and minimization of cosmetic or functional consequences. Many patients require longitudinal care from infancy through adulthood[1].

HISTORY

In the medical literature addressing vascular malformations, lesions and syndromes were originally delineated based on clinical features. Many authors played a major role in their description, including Virchow, Trélat, Monod, Klippel, Trenaunay, Weber, Sturge, Bockenheimer, Maffucci, Bell and Malan. Unfortunately, pathologists and clinicians did not work together. Consequently, multiple nomenclatures became an obstacle to communication among physicians treating these patients. In 1976, John B Mulliken (a plastic surgeon in the US), Anthony E Young (a vascular surgeon in the UK) and Jean-Jaques Merland (a neurointerventional radiologist in France) joined forces to convene the first of many Workshops on Vascular Anomalies. The ISSVA, created in 1992, is dedicated to analyzing the clinical, radiologic, biologic and pathologic characteristics of vascular lesions and improving diagnosis and treatment via multidisciplinary and international collaboration[2].

EPIDEMIOLOGY

Little is known regarding the exact prevalence of vascular malformations in the general population. The most common types are CMs, then VMs. The least common are AVMs. Vascular malformations have no gender predilection. They appear to be less frequent in individuals of African and Asian descent.

PATHOGENESIS

An initial embryologic process, vasculogenesis, creates the primitive vascular plexus. Then angiogenesis, the secondary sprouting of mesoderm-derived endothelial cells, forms new vessels from existing ones, thereby generating most blood and lymphatic vessels. Endothelial

DIFFERENCES BETWEEN VASCULAR MALFORMATIONS AND INFANTILE HEMANGIOMAS		
Characteristics	**Vascular malformations**	**Infantile hemangiomas**
Clinical features	CM: red, macular during infancy VM: blue, compressible, fills with dependency LM: vesicles or large cysts AVM: four stages: stage 1 – dormant: red, warm; macular (mimics CM) or slightly infiltrated (mimics late involuting infantile hemangioma) stage 2 – expansion: warm mass with thrill/throbbing, dilated draining veins stage 3 – destruction: pain, ulceration; occasional bone lysis and fracture stage 4 – cardiac decompensation; high-output cardiac failure; also signs of stage(s) 2 ± 3	Premonitory markers at birth in 50%: red telangiectatic, bluish "bruise-like" or white "anemic" macules Superficial hemangioma: bright red, "strawberry"-like papules and plaques (during proliferative phase) Deep hemangioma: warm, rubbery mass under normal-colored or bluish skin
Sex prevalence	Female : male ratio 1 : 1	Female : male ratio 3 : 1 to 6 : 1
Natural history	Usually evident at birth Lifelong persistence, with commensurate growth during childhood and often slow worsening over time AVM: may worsen with puberty, trauma and pregnancy	Precursor lesion or no evidence at birth Postnatal proliferation over 6–12 months, then slow involution over years Reach stable involuted stage
Radiology	VM or LM (slow flow): hypersignal on MRI T2-weighted sequence VM: thrombi and phleboliths (MRI, CT); gadolinium enhancement on MRI AVM (fast flow): flow voids on MRI T1- and T2-weighted sequences; arteriovenous shunts on Doppler ultrasound	Well-defined mass Some flow voids on MRI T1-weighted sequences (high-flow vessels)
Pathology (see Fig. 104.22)	CM: ectatic capillaries VM or LM: distorted, interconnected malformed channels AVM: AV fistulae and increased capillaries Typically no increase in cellular turnover	Dense lobular proliferation of endothelial cells forming capillaries with tiny lumens Increased cellular turnover in proliferating lesions can be demonstrated by elevated levels of markers of proliferation (PCNA, Ki-67), ECM remodeling (collagenase, urokinase), and vascular growth (bFGF, VEGF)
Immunophenotype	GLUT-1-negative	GLUT-1-positive
Hematology	VM or LVM: chronic LIC, occasional DIC Treatment of flares with low-molecular-weight heparin Possible benefit of low-dose aspirin as prophylaxis	(Kasabach–Merritt syndrome is not linked to infantile hemangiomas, but to other vascular tumors such as kaposiform hemangioendotheliomas and tufted angiomas, both of which are GLUT-1-negative; see Ch. 114)
Molecular biology	Sporadic VMs: somatic *TEK* mutation in 50% Familial vascular malformations: see Table 104.2	Rare families with autosomal dominant inheritance linked to 5q, and *somatic* loss of heterozygosity of 5q in some hemangiomas *Germline* mutation in *VEGFR2* or *TEM8* in some patients *Somatic* mutation in *VEGFR2* or *FLT4/VEGFR3* (5q34) in some hemangiomas Clonality in some hemangiomas

Table 104.1 Differences between vascular malformations and infantile hemangiomas. AVM, arteriovenous malformation; bFGF, basic fibroblast growth factor; CM, capillary malformation; CT, computed tomography; DIC, disseminated intravascular coagulation; ECM, extracellular matrix; *FLT4*, fms-related tyrosine kinase 4; LIC, localized intravascular coagulation; LM, lymphatic malformation; MRI, magnetic resonance imaging; PCNA, proliferating cell nuclear antigen; *TEM8*, tumor endothelial marker 8; VEGF, vascular endothelial growth factor; VM, venous malformation.

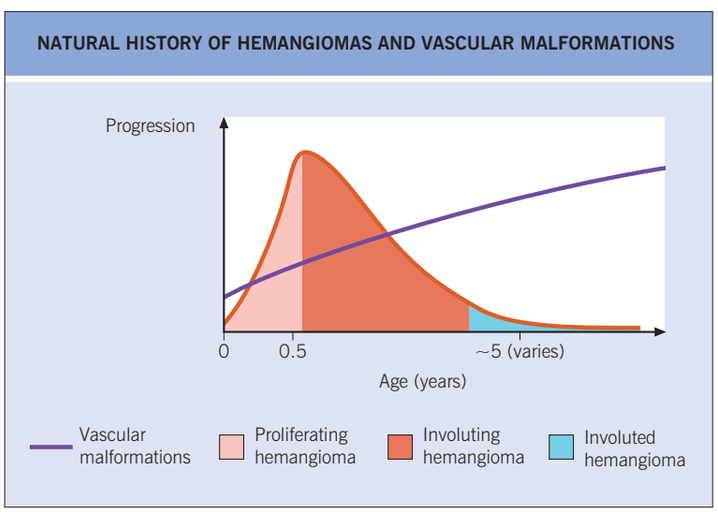


Fig. 104.1 Natural history of infantile hemangiomas and vascular malformations.

differentiation, recruitment of smooth muscle cell precursors to ensheathe endothelial cells and build vessel walls, and, finally, changes in channel size, morphology and rheology create capillaries, veins and arteries.

Vascular malformations constitute a heterogeneous group of disorders that result from alterations in formation of blood or lymphatic channels. Dysfunction in signaling processes that regulate migration, differentiation, maturation, adhesion and survival of the cells of vascular walls is thought to have a pathogenic role. Markers of cellular proliferation are not elevated in vascular malformations[3]. In the cephalic region of the embryo, mural cells associated with endothelial cells come from the neural crest; therefore, a vascular malformation complex such as Sturge–Weber syndrome (SWS) is likely caused by a somatic mutation in the embryo's anterior neural crest or adjacent cephalic mesoderm. Rare familial transmission of vascular malformations has allowed mapping of susceptibility to certain inherited lesions to precise chromosomal locations, identification of the associated gene(s) and disease-causing mutations, discovery of the function of the encoded proteins, and clarification of the role the dysfunction plays in regulatory pathways (Table 104.2). It remains to be determined if sporadic vascular malformations, which are far more frequent than familial ones, are caused by the same gene mutations. Some data support this hypothesis. For example, mutations in the *TEK* gene causing constitutive activation

VASCULAR ANOMALIES FOR WHICH THE MOLECULAR BASIS IS KNOWN				
Vascular malformation	**Mode of inheritance**	**Mutated gene(s)**	**Type of mutation**	**Protein and function**
CAPILLARY AND/OR ARTERIOVENOUS MALFORMATIONS				
Ataxia–telangiectasia	AR	*ATM* (11q22–23)	Loss-of-function	ATM protein is similar to phosphoinositol-3 kinase – regulates cell cycle, DNA repair, p53
Capillary malformation–arteriovenous malformation	AD	*RASA1* (5q13)	Loss-of-function	p120-Ras-GAP protein – involved in signaling by growth factor receptors
Cerebral capillary malformations (CCM; familial cerebral cavernomas)*	AD	CCM1: *KRIT1* (7q21–22) CCM2: *MGC4607* (7p15–13) CCM3: *PDCD10* (3q25.2–27)	Loss-of-function	KRIT-1 interacts with KREV-1, RAP-1A and malcavernin (the *CCM2* gene product) – roles in MAPK and integrin signaling
Hereditary hemorrhagic telangiectasia (HHT; Osler–Weber–Rendu)	AD	HHT1: *ENG* (9q3) HHT2: *ACVRL1/ALK1* (12q13) HHT3: (5q31–32) HHT4: (7p14)	Loss-of-function	Endoglin and activin receptor-like kinase 1 (ALK1) – two TGF-β receptors with roles in vessel wall integrity
Juvenile polyposis with HHT	AD	*SMAD4* (18q21.1)	Loss-of-function	SMAD4 tumor suppressor protein – role in TGF-β signaling
VENOUS MALFORMATIONS				
Cutaneous and mucosal venous malformations (VMCM)	AD; sporadic (with somatic mutations in lesional tissue)	*TEK* (9p21)	Gain-of-function	TIE-2, an endothelial cell-specific tyrosine kinase receptor that binds angiopoietins
Glomuvenous malformations (glomangiomatosis)	AD/"paradominant"	*GLMN* (1p21–22)	Loss-of-function (germline plus second hit within lesions)	Glomulin protein is a component of a multiprotein complex – role in vascular morphogenesis
LYMPHATIC ANOMALIES				
Milroy disease (familial congenital lymphedema)	AD†	*FLT4* (5q34)	Loss-of-function	VEGFR-3 – a tyrosine kinase receptor in lymphatic vessels
Lymphedema–distichiasis syndrome	AD	*FOXC2* (16q22–24)	Loss-of-function	Forkhead family transcription factor C2
Hypotrichosis–lymphedema–telangiectasia	AR, AD	*SOX18* (20q13.33)	Loss-of-function	SRY-box 18 transcription factor
Hennekam lymphangiectasia–lymphedema syndrome‡	AR	*CCBE1* (18q21)	Loss-of-function	Collagen & calcium-binding EGF domain-containing protein 1
Hereditary lymphedema	AD	*GJC2* (1q42.13)	Loss-of-function	Connexin 47 in gap junctions of lymphatic vessels
Lymphedema-choanal atresia	AR	*PTPN14* (1q32)	Loss-of-function	Protein tyrosine phosphatase that may interact with VEGFR-3
ARTERIOPATHY				
CADASIL	AD	*NOTCH3* (19q12)	Loss-of-function in a subset of cases	Accumulation of NOTCH-3 protein in vascular smooth muscle cells

Cutaneous vascular malformations, including hyperkeratotic capillary–venous malformations (associated with *KRIT1* mutations) and venous malformations (less common), occur in ~10% of patients.
†An autosomal *recessive* form of congenital lymphedema caused by hypomorphic *FLT4* mutations has also been described.
‡Presents with generalized lymphedema, lymphangiectasias (intestinal and pulmonary), facial anomalies (flat face, depressed nasal bridge, hypertelorism) and mental retardation.

Table 104.2 Vascular anomalies for which the molecular basis is known. Vascular malformations also occur in patients with PTEN hamartoma tumor syndrome (typically fast-flow lesions) and Proteus syndrome (due to mosaic activating *AKT1* mutations) (see text). AD, autosomal dominant; AR, autosomal recessive; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; *FLT4*, fms-related tyrosine kinase 4; MAPK, mitogen-activated protein kinase; *PDCD10*, programmed cell death 10; TGF-β, transforming growth factor-β; VEGFR-3, vascular endothelial growth factor receptor-3; VM, venous malformation.

of the endothelial cell tyrosine kinase receptor TIE-2 are found in lesional tissues but not the peripheral blood (indicative of a *somatic* mutation) in half of patients with sporadic VMs as well as in the *germline* of patients with familial cutaneous and mucosal VMs (VMCM)[4]. Such research brings hope of gene therapy or currently unimaginable novel treatment strategies[4–6].

CLINICAL FEATURES

With the expertise of multidisciplinary vascular clinics, >90% of vascular malformations can be correctly categorized on the basis of their clinical features. This helps in the selection of the best investigative tools (Table 104.3), avoiding redundant and unnecessary diagnostic imaging procedures.

Capillary Malformations

Two major types of CM exist: PWSs and telangiectasias. These lesions can represent the most obvious sign of a complex syndrome. An approach to the evaluation of a patient with a presumed CM of the head and neck region is shown in Figure 104.2.

Port-wine stain

PWSs typically present at birth as well-demarcated red macules and patches. PWS is *not* the correct term for the common congenital capillary stains located on the mid-face (forehead, glabella, tip of the nose and philtrum), eyelids, and nape or occiput (Fig. 104.3A&B). Such lesions are referred to as a *nevus simplex* or *salmon patch*; they are also known as an "angel kiss" or "aigrette" on the forehead and a "stork bite" on the neck. Many fade spontaneously between 1 and 3 years of age, the facial ones more often than those in the nape area.

The growth of PWSs is commensurate with the child's growth. They can be localized or have a segmental pattern, but they do not follow the lines of Blaschko. Some are multifocal and widespread. Facial PWSs are frequently distributed according to what has classically been considered the sensory trigeminal nerve dermatomes, with three areas recognized: V1 (ophthalmic region: forehead and upper eyelid), V2 (maxillary region; Fig. 104.3C) and V3 (mandibular region).

INVESTIGATIVE TOOLS FOR VASCULAR MALFORMATIONS				
Tool	**Vascular lesion**			
	Capillary malformation	**Lymphatic malformation**	**Venous malformation**	**Arteriovenous malformation**
Ultrasonography	+/–	++++	+++	++++
CT with contrast	–*	++	++	++
MRI with gadolinium	–*	+++ (no gadolinium enhancement)	++++ (gadolinium enhancement)	+++
3D-angio CT or 3D-angio MRI	–	–	++	++++
Arteriography	–	–	–	++++
Phlebography	–	–	+/–	–
Lymphography (isotopic)	–	+/–	–	–
Biopsy	+/–	+/–	–	–

*Brain studies are useful in the evaluation of possible Sturge–Weber syndrome (SWS); specific MRI techniques that may provide additional information in patients with SWS include dynamic contrast bolus MR perfusion imaging, susceptibility-weighted imaging (SWI), and MR diffusion tensor imaging (see text for details).

Table 104.3 Investigative tools for vascular malformations. A larger number of +'s indicates increased utility. CT, computed tomography; MRI, magnetic resonance imaging.

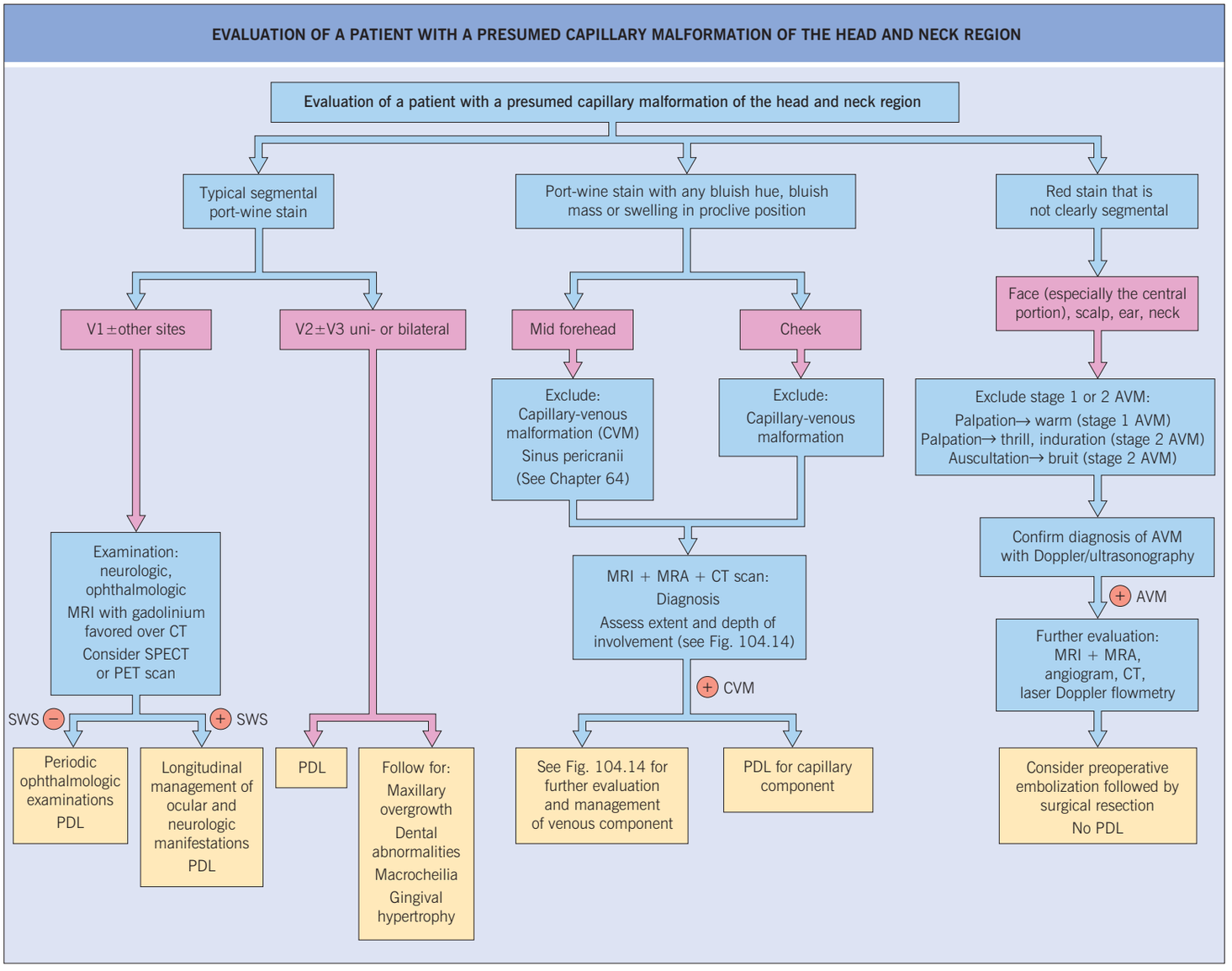


Fig. 104.2 Evaluation of a patient with a presumed capillary malformation of the head and neck region. AVM, arteriovenous malformation; CT, computed tomography; CVM, capillary venous malformation; PDL, flashlamp-pumped pulsed dye laser; MRA, magnetic resonance arteriography; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single photon emission computed tomography; SWS, Sturge-Weber syndrome.

Fig. 104.3 Salmon patches versus port-wine stain (PWS) in V2 distribution. A Involvement of the central face in a symmetric pattern is typical of a salmon patch; such lesions usually fade over the first few years of life but are sometimes misdiagnosed as a PWS. **B** Salmon patches in the nape area ("stork bites") tend to be more persistent. **C** In this young infant with a PWS, the skin is smooth. This lesion will be persistent. *B, Courtesy, Julie V Schaffer, MD.*

Over time, PWSs (especially those affecting the V2 and V3 areas) often develop a deeper red hue, changing from pinkish-red (at birth) to purplish-red (in adulthood). Affected skin may thicken and become nodular (Fig. 104.4), and superimposed pyogenic granulomas occasionally appear. In a study of 173 patients with PWSs, thickening was observed in 11% (median age 32 years), nodularity in 24% (median age 44 years), and both in 6% (median age 45 years)[7]. Overgrowth of the maxilla (Fig. 104.5) and other facial bones underlying a PWS can also occur, creating problems such as an open-bite deformity. Affected gums and lips may enlarge, potentially resulting in epulides, gingival bleeding, macrocheilia and lip incompetence. Hypertrophic skin changes are rare in PWSs on the trunk and limbs. Interestingly, when a child with a PWS has atopic dermatitis, eczematous lesions may have a predilection for areas of skin affected by the CM.

PWSs are congenital in the vast majority of patients. However, *acquired PWSs* have been described in adolescents and adults, and onset of such lesions may be precipitated by trauma. Of note, early morphea (especially the linear variant) occasionally presents with a red vascular patch that mimics an acquired PWS[7a].

A CM can be admixed with a network of blanched macules representing a nevus anemicus (Fig. 104.6), a phenomenon referred to as vascular twin spotting. The association of a CM with aberrant Mongolian spots (dermal melanocytosis) (Fig. 104.7) or a nevus spilus (speckled lentiginous nevus) is another example of twin spotting, which is referred to as *phakomatosis pigmentovascularis (PPV)* (Table 104.4)[8,9].

A dorsal midline PWS (e.g. of the lumbosacral area) is occasionally a hallmark for *occult spinal dysraphism*, particularly if the stain is associated with other cutaneous markers of dysraphism (see Ch. 64). In patients with clinically suspected dysraphism, ultrasound may be useful in infants <2–4 months of age, but MRI is a more sensitive study.

Fig. 104.4 Port-wine stain in V2 distribution in an adult. Hyperplasia and nodularity are prominent.

Fig. 104.5 Port-wine stain in V2 distribution. Note the enlarged gingiva on the right and overgrowth of the right maxilla.

Syndromic capillary malformations

Sturge–Weber syndrome

SWS is a sporadic neurologic disorder in which a facial CM is associated with ipsilateral ocular and leptomeningeal/brain anomalies. The facial PWS typically involves the V1 region (forehead and upper eyelid)[1], and it often extends unilaterally or bilaterally over more of the face (Fig. 104.8). Some SWS patients also have PWSs on the extremities and trunk, which may be associated with KTS (see below). In addition, SWS occasionally occurs in the setting of PPV.

Ocular involvement is more frequent when the PWS affects both the V1 and V2 regions. It may be detected at birth because of buphthalmos (congenital glaucoma). Acute glaucoma with a cloudy cornea can be an infantile emergency. Usually, however, increased eye pressure develops slowly. Glaucoma may become obvious only in late childhood; thus, periodic lifelong assessment of visual function and eye pressure is

Fig. 104.6 Phakomatosis pigmentovascularis type 2b (cesioflammea; associated with Sturge–Weber syndrome). A port-wine stain and nevus anemicus are intermingled on the shoulder of this man.

Fig. 104.7 Phakomatosis pigmentovascularis type 2a (cesioflammea). A large port-wine stain and extensive dermal melanocytosis are seen.

PHAKOMATOSIS PIGMENTOVASCULARIS (PPV)				
Type	**Descriptive name**	**Proportion of reported cases**	**Major cutaneous components**	**Other reported cutaneous components**
Ia/b	*	<5%*	Epidermal nevus + **PWS**	
IIa/b	Phakomatosis cesioflammea	75%	Dermal melanocytosis (aberrant Mongolian spots) + **PWS**	Nevus anemicus, hypotrichosis, lipohypoplasia, hypoplastic nails
IIIa/b	Phakomatosis spilorosea	10%	Nevus spilus (macular type) + **PWS/"nevus roseus"**†	Nevus anemicus, lymphedema, hypotrichosis
IVa/b	Phakomatosis pigmentovascularis, unclassifiable	10%	Variable, sometimes with features of II + III or II + V	Nevus anemicus, nevoid hyper- or hypopigmentation, nevus sebaceus
Va/b	Phakomatosis cesiomarmorata	<5%	Dermal melanocytosis + **cutis marmorata telangiectatica congenita**	

*Existence as a type of PPV has been challenged considering that epidermal nevi are not melanocytic lesions; epidermal nevi can occur together with vascular malformations in Proteus, *PTEN* hamartoma tumor and CLOVES syndromes (see text), which are not generally considered as PPV.
†Capillary malformation with a pale pink color; "rosé-wine" rather than port-wine stain.

Table 104.4 Phakomatosis pigmentovascularis (PPV). a = cutaneous abnormalities only; b = cutaneous and extracutaneous abnormalities (e.g. of Sturge–Weber syndrome, Klippel–Trenaunay syndrome, or ocular as well as cutaneous nevus of Ota). PWS, port-wine stain.

Fig. 104.8 Infant at risk for Sturge–Weber syndrome. Port-wine stain with involvement of V1 as well as V2 and V3.

mandatory to recognize and treat glaucoma before it results in loss of vision. A choroidal vascular malformation may also be detected in the affected eye.

Neurologic symptoms are due to the presence of a CVM within the pia mater ipsilateral to a V1 PWS; over time, cerebral hemiatrophy and calcifications may develop in association with the leptomeningeal vascular malformation. The occipital region of the brain is the most common location. Neurologic consequences can include seizures, either affecting the side of the body opposite to the vascular anomaly or generalized. Epilepsy typically develops in the first year of life, and the seizures may be difficult to control with anticonvulsants, especially early on. Additional findings can include contralateral hemiparesis or hemiplegia, developmental delays (e.g. in motor and cognitive skills), emotional and behavioral problems, attention deficits and migraine headaches.

The risk of ocular and neurologic manifestations of SWS is ≤10% when a unilateral PWS affects the full V1 region; it is lower when the PWS involves only a portion of the V1 area and much higher (>50%) for a bilateral PWS covering the forehead and both upper eyelids[1,10]. In a study of 55 patients with the leptomeningeal vascular anomalies of SWS, the associated cutaneous CM was unilateral in 63.5%, bilateral in 31%, and absent in 5.5%[11]. All three tissues involved in SWS – namely, all the cellular components of the V1 facial skin (except for the endothelial cells), the ocular choroid and the pia mater – are cephalic neural crest derivatives, originating from a common precursor in the anterior neural primordium. An early somatic mutation, prior to

migration of embryonic neural crest derivatives, has been hypothesized. Regionalization of the cephalic neural crest cells to specific areas of the face is not strict, explaining some fluidity in the distribution of the facial CM, especially at the internal and external eyelid canthi (V1–V2 watershed).

Early neuroimaging can identify and delineate the extent of central nervous system (CNS) abnormalities in infants with a V1 PWS. CT with iodinated contrast and MRI with gadolinium can detect pial and brain lesions as well as enlargement of the ipsilateral choroid plexus. Before 6 months of age, MRI may demonstrate advanced myelination in the involved hemisphere. Gyriform calcifications develop during childhood in SWS patients and are visible by various neuroimaging modalities. MRI may also reveal developmental venous anomalies of the brain (see cephalic VM section below).

Some infants and children with SWS have cognitive deficits that are more severe than anticipated based upon their limited cortical involvement on conventional MRI studies. Functional cerebral imaging, such as SPECT (single photon emission computed tomography, which evaluates regional cerebral blood flow) or PET (positron emission tomography, which shows the metabolism of glucose), can permit early and more precise evaluation of the location of brain lesions and their consequences. Newer, less invasive MRI techniques also enable early evaluation of brain anomalies. Susceptibility-weighted imaging (SWI), which detects deoxygenated blood with extremely high sensitivity, provides detailed assessment of venous abnormalities without contrast injection. In children with SWS, SWI also shows a gyriform pattern of cortical signal intensity loss that correlates well with hypometabolic areas on PET scans[12]. MR diffusion tensor imaging can identify microstructural changes in the white matter in children with SWS[12]. Lastly, dynamic contrast bolus magnetic resonance perfusion imaging can visualize cerebral perfusion defects in SWS patients[13].

Endocrine dysfunction may occur due to effects of SWS on the hypothalamic–pituitary axis. Examples include growth hormone deficiency in 0.5% (9/1653) of patients from a SWS registry (compared to 0.03% in the general population) and central hypothyroidism in ~2% (2/84) of patients evaluated at a SWS referral center[14].

Klippel–Trenaunay syndrome

Klippel–Trenaunay syndrome (KTS) is defined as a limb CVM or CLVM associated with progressive overgrowth of the affected extremity. Additional findings can include extension of the vascular malformation to the truncal skin, lipomatosis, lymphedema, and vascular lesions of the gastrointestinal (GI) and urinary tracts (which may bleed intermittently). The cutaneous CM presents either as: (1) a pink-to-red, blotchy stain in an apparently haphazard distribution over the affected extremity; or (2) a red-to-purple, sharply demarcated geographic stain that tends to affect the lateral aspect of the thigh, knee and leg (Fig. 104.9). Geographic stains often have a lymphatic component, and superimposed purple or clear vesicles (representing angiokeratomas or microcystic LMs) frequently develop[15]. KTS patients with a geographic stain have an increased risk of complications such as massive limb overgrowth and cellulitis[15]. Like "pure" VMs (see below), the anomalous venous network in KTS may be associated with a chronic intravascular coagulopathy with high D-dimer and low fibrinogen levels, and patients are at risk of deep vein thrombosis, chronic thromboembolic pulmonary hypertension or even life-threatening pulmonary embolism[16]. Foot and hand malformations in KTS are usually associated with deep venous system anomalies[17].

Duplex ultrasonography is useful in investigating the vascular anomalies underlying KTS, and MRI can delineate the extent of soft tissue and bone involvement (see Table 104.3). Lymphoscintigraphy is occasionally indicated. In patients with GI bleeding, colonoscopy or capsule endoscopy may reveal capillary patches, extensive dilated venous channels and microcystic LM in the intestines.

Fig. 104.9 Klippel–Trenaunay syndrome. Geographic capillary stain on the thigh associated with lymphatic vesicles, dilated incompetent veins and enlarged lower limb.

Fig. 104.10 Plantar cerebriform connective tissue nevus in a man with Proteus syndrome.

Proteus syndrome

Proteus syndrome is characterized by progressive worsening over time and a mosaic distribution of anomalies (see Ch. 62)[18]. It was recently found to be caused by mosaic activating mutations in the *AKT1* gene, which encodes a protein that positively regulates cellular growth and proliferation[18a]. Asymmetric, disproportionate overgrowth leads to severe deformity and disabling orthopedic consequences (e.g. hyperostoses that distort the skull and other bones, megaspondylodysplasia with scoliosis). Cutaneous features include epidermal nevi, cerebriform connective tissue nevi of the palms and soles (Fig. 104.10), patchy dermal hypoplasia, dysregulated adipose tissue (lipomas, regional absence of fat) and slow-flow vascular anomalies (CMs, VMs, LMs). Pulmonary cysts and a distinctive facial phenotype (e.g. a long face, ptosis, anteverted nares) represent additional manifestations. The differential diagnosis of Proteus syndrome includes the next three entities.

CLOVES syndrome

This "Proteus-like" syndrome is characterized by asymmetric ***C***ongenital ***L***ipomatous ***O***vergrowth (infiltrative, typically truncal), ***V***ascular anomalies (slow- or fast-flow), ***E***pidermal nevi and ***S***coliosis/other ***S***keletal abnormalities (especially broad hands and feet)[19,20].

CLAPO syndrome

CLAPO syndrome features ***C***Ms and ***L***Ms (particularly of the lower lip, tongue and neck) together with ***A***symmetry and ***P***artial ***O***vergrowth of the face and extremities[21].

Macrocephaly–capillary malformation

Macrocephaly–CM, previously known as macrocephaly–cutis marmorata telangiectatica congenita (CMTC), manifests with pinkish-red, finely reticulated or confluent PWSs (Fig. 104.11) rather than true CMTC (see below). Additional features include persistent mid-facial capillary stains (especially on the philtrum), developmental delay, neurologic anomalies (e.g. ventriculomegaly, acquired cerebellar tonsillar herniation), asymmetric overgrowth, syndactyly (especially 2nd–3rd toes), polydactyly, joint laxity and hyperelastic skin[22].

Telangiectasias

Telangiectasias (see Ch. 106) are dilated capillary-type blood vessels. These punctate, stellate, or linear red lesions may have a localized, segmental or widespread distribution. In some disorders they tend to affect particular anatomic sites. For example, *angioma serpiginosum* features clusters of tiny punctate telangiectasias in serpiginous patterns with a predilection for the extremities, whereas *unilateral nevoid telangiectasia* has a segmental configuration favoring the face, neck, chest and arms. The lesions of *hereditary benign telangiectasia* (HBT) may mimic those of hereditary hemorrhagic telangiectasia (HHT; see below), but the former is not associated with epistaxis or visceral hemorrhage. In addition, some kindreds initially reported as having HBT actually had capillary malformation–arteriovenous malformation (CM-AVM; see below)[23].

Cutis marmorata telangiectatica congenita

Cutis marmorata telangiectatica congenita (CMTC) is characterized by a dark purple to red–purple, broad reticulated vascular pattern intermingled with telangiectasias and (occasionally) prominent veins (Fig. 104.12). It commonly affects one or more limbs and the corresponding quadrant(s) of the trunk. Unlike cutis marmorata, CMTC persists upon warming the affected infant. Atrophic depressions may be evident within the net-like pattern, especially over joints, and can result in ulceration and scarring. CMTC often lightens after the first year of life, but some residual violaceous network is common[1,24]. Up to 50% of patients have associated abnormalities, most often hypoplasia (girth > length) of the affected limb(s) and additional vascular malformations. Other skeletal (e.g. syndactyly), ocular (e.g. glaucoma associated with facial CMTC) and neurologic defects are occasionally observed, especially in patients with generalized CMTC. *Adams–Oliver syndrome* combines distal transverse limb defects, scalp skin and skull defects (aplasia cutis congenita; see Ch. 64) and variable cardiac malformations with CMTC or a reticulated CM. Macrocephaly–CMTC has been reclassified as *macrocephaly–CM* (see above). Lastly, relatively short-lived "pseudo"-CMTC has been described in infants with neonatal lupus erythematosus.

Hereditary hemorrhagic telangiectasia

Hereditary hemorrhagic telangiectasia (HHT; Osler–Weber–Rendu disease) is an autosomal dominant disorder characterized by mucocutaneous telangiectasias (which actually represent small AVMs) and

Fig. 104.11 Reticulated port-wine stain (PWS) in a patient with macrocephaly–capillary malformation syndrome. This boy has hemihypertrophy of the side of the body *opposite* to the PWS. *Courtesy, Julie V Schaffer, MD.*

Fig. 104.12 Cutis marmorata telangiectatica congenita (CMTC) with atrophy of the affected limb. The color of the broad vascular network can be red–purple (**A**) or, as seen in this infant of Caribbean descent, brownish-purple (**B**).

visceral AVMs that have a propensity to bleed. Phenotypes vary considerably, even within a given family[25–27]. The first manifestation of HHT is usually epistaxis during childhood or adolescence (mean age of onset = 12 years)[27]. Telangiectasias of the skin and oral mucosa typically appear after puberty and may not be noticed until adulthood. They most commonly affect the face, lips, tongue, palms and fingers (including periungual areas and the nail bed). These dark red lesions are either round, slightly elevated papules or ill-defined, stellate macules.

It is important to screen individuals suspected to have HHT for visceral AVMs (Table 104.5). In particular, AVMs in the lungs and brain are often asymptomatic prior to the sudden development of life-threatening complications[25–27]. Pulmonary AVMs can result in hypoxemia, hemorrhage, and (because of the lack of capillary bed filtering) cerebral abscesses or strokes due to paradoxical emboli. Transcatheter embolotherapy of pulmonary AVMs is recommended[27]. Lethal intracranial hemorrhage from cerebral AVMs can occur as early as infancy[26], and acute paraplegia due to spinal AVMs has also been described in children with HHT. Treatment strategies for AVMs of the CNS include embolization, microsurgery and stereotactic radiation. Gastrointestinal or (less often) genitourinary tract bleeding typically occurs in mid adulthood and often presents as iron deficiency anemia. Lastly, hepatic AVMs may lead to high-output heart failure, portal hypertension and biliary disease.

Mutations in two different genes are known to cause classic HHT: *ENG* (endoglin; HHT1) and *ALK1* (activin receptor-like kinase 1, also known as *ACVRL1*; HHT2). Both genes encode glycoprotein components of endothelial transforming growth factor-β (TGF-β) receptors. A genotype–phenotype correlation has been established, with a higher risk of pulmonary (especially in women) and cerebral AVMs in HHT1 and a higher risk of liver AVMs in HHT2. Two other HHT loci have been described, but the associated genes have not yet been identified (see Table 104.2). In addition, mutations in the *SMAD4* gene (which encodes a protein that transmits signals from the TGF-β receptor) underlie a disorder that features juvenile gastrointestinal polyposis and HHT. Genetic testing can establish the diagnosis of HHT in children and young adults who do not yet meet clinical criteria (see Table 104.5). Information on medical centers and laboratories that specialize in HHT is available at www.hht.org.

Ataxia–telangiectasia

Ataxia–telangiectasia is an autosomal recessive disorder that occurs in approximately 1 in 40 000 births and is due to mutations in the *ATM* gene (see Ch. 60). Ataxia is the initial symptom and usually presents in toddlers. Telangiectasias typically begin to appear at 4–6 years of age, primarily on the conjunctivae, face and ears. Immunoglobulin deficiencies (e.g. IgA, IgG) and defective cell-mediated immunity explain the frequent sinopulmonary infections. Patients are at high risk for the development of lymphoma and leukemia. Elevated levels of circulating α-fetoprotein are found in affected individuals. Heterozygote carriers of a mutated *ATM* gene also have an increased risk of breast cancer and hematologic malignancies.

Angiokeratomas

Angiokeratomas (see Ch. 114) consist of ectasias of dermal capillaries associated with an acanthotic and hyperkeratotic overlying epidermis. These dark red-to-purple, papular vascular anomalies can vary considerably in size, depth and location[1]. The two most common types are *solitary papular angiokeratoma* and *angiokeratomas of the scrotum and vulva*. The former is often found on the lower extremity, and it may be mistaken for a melanoma. In *angiokeratoma circumscriptum*, clusters of ectasias form a plaque or linear array, usually on an extremity, that is often present at birth. Congenital hyperkeratotic vascular anomalies resembling angiokeratoma circumscriptum but with a deeper dermal component consisting of small, thick-walled blood vessels

STUDIES RECOMMENDED TO SCREEN FOR SYSTEMIC INVOLVEMENT AND ASSIST IN THE DIAGNOSIS OF HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT)

Study	Indication(s)	Purpose of study	Intervention(s) if positive study
Transthoracic contrast echocardiography (bubble study)*	Suspected or confirmed HHT†	Detect **pulmonary** AVMs, which lead to right-to-left shunting (15–50% of HHT patients)	• Confirmation with unenhanced multidetector CT of the thorax with thin-cut reconstructions • Transcatheter embolotherapy for all adults and symptomatic children (and on a case-by-case basis for asymptomatic children) • Antibiotic prophylaxis for procedures with risk of bacteremia, precautions to avoid air bubbles during intravenous access, and avoidance of SCUBA diving
Brain MRI with and without gadolinium‡	Suspected or confirmed HHT†	Detect **cerebral** AVMs and other vascular malformations (~25% of HHT patients)	• Consideration of invasive testing and treatment • Referral to a center with neurovascular expertise
Annual hemoglobin and hematocrit testing	HHT patients >35 years of age	Detect substantial bleeding related to **gastrointestinal** AVMs (~25% of HHT patients; rare before age 40 years)	• Upper endoscopy if anemia disproportionate to epistaxis • Iron supplementation • Treatment considerations include endoscopic cauterization and systemic hormonal or antifibrinolytic therapy
Doppler ultrasonography or triphasic spiral CT of liver	(1) HHT patients with signs/symptoms of heart failure or hepatobiliary disease; or (2) an uncertain HHT diagnosis†	Detect **hepatic** AVMs (present in 30–80% but symptomatic in <10% of HHT patients)	• Additional testing and treatment (directed by findings) in symptomatic patients; liver biopsy should be avoided • Further screening for systemic involvement if diagnosis established
Genetic analysis of *ENG* and/or *ACVRL1* (then *SMAD4* if negative)	(1) "Index case" in HHT family (2) Patients who do not meet HHT criteria† but are at risk because of an affected first-degree relative§ or clinically suspected to have HHT	Detect underlying *ENG* or *ACVRL1* mutation (~75% of HHT patients) or, rarely, *SMAD4* mutation (1–3% of HHT patients)	• Identification of a specific mutation facilitates genetic analysis in family members (including prenatal testing) • Further screening for systemic involvement if diagnosis established

*If negative, repeat screening should be considered after puberty, within the 5 years preceding a planned pregnancy, after pregnancy, and otherwise every 5–10 years.
†Clinical diagnostic criteria are: spontaneous recurrent epistaxis, characteristic mucocutaneous telangiectasias, visceral telangiectasias/AVMs, and HHT in a first-degree relative; definite HHT if ≥3 criteria (met by ≥90% of HHT patients by age 40 years) and possible/suspected HHT if 1–2 criteria (especially for children and young adults).
‡Some authors have recommended omission of gadolinium in the initial MRI screening of children (especially those <2 years of age), and repeat screening with gadolinium at ~age 18 can be considered for children with negative studies; MRI screening for spinal AVFs can also be considered in children.
§The causative mutation should first be identified in an "index case" from the family.

Table 104.5 Studies recommended to screen for systemic involvement and assist in the diagnosis of hereditary hemorrhagic telangiectasia (HHT). Based on 2009 international guidelines[27]. AVF, arteriovenous fistula; AVM, arteriovenous malformation; CT, computed tomography; MRI, magnetic resonance imaging.

(larger than normal capillaries) have been referred to as "*verrucous hemangiomas*" but behave clinically as vascular malformations. Grouped tiny lesions are also seen in *angiokeratoma of Mibelli*, which favors the toes, fingers, knees and elbows. *Angiokeratoma corporis diffusum* is characterized by more widespread lesions, often in a bathing trunk distribution, and it can be associated with several hereditary lysosomal storage disorders such as *Fabry disease* (an X-linked recessive condition due to deficiency of α-galactosidase A) and *α-fucosidase deficiency* (see Table 63.6). Angiokeratomas (as well as microcystic lymphatic lesions) may develop on the surface of geographic CMs in KTS (see above).

Cerebral capillary malformation and hyperkeratotic cutaneous capillary–venous malformation

A distinctive hyperkeratotic cutaneous capillary–venous malformation (HCCVM) occurs in a subgroup of patients with inherited cerebral capillary malformations (CCMs), also referred to as familial cerebral cavernomas[28,29]. Neurologic manifestations, which develop at a mean age of 30 years (range, 2–72 years), may include headaches, seizures and cerebral hemorrhage[28]. This autosomal dominant disorder can be caused by mutations in three different genes (see Table 104.2): *KRIT1* (*CCM1*), *MGC4607* (malcavernin; *CCM2*) and *PDCD10* (*CCM3*). Among the ~10% of familial CCM patients who have *cutaneous* vascular malformations, ~90% have a *KRIT1* mutation[29]. HCCVMs have thus far been described exclusively in patients with *KRIT1* mutations. These irregularly shaped, dark crimson or reddish-purple plaques with surrounding bluish discoloration are typically congenital and located on the extremities. Smaller reddish-brown macules with peripheral telangiectatic puncta have also been observed[29]. Less frequently, children and adults with mutations in any of the three genes develop dark blue cutaneous papules and nodules reminiscent of blue rubber bleb nevus syndrome (BRBNS), which represent VMs[29].

Venous Malformations

VMs are commonly confused with deep infantile hemangiomas or, when they involve a large portion of an extremity, KTS. VMs are recognized clinically by their blue hue, softness, compressibility and tendency to fill with dependency (Fig. 104.13). They can occur in a focal, segmental or (especially in forms with autosomal dominant inheritance) widespread distribution. VMs are best imaged using T2-weighted MRI (see Table 104.3)[1]. Figure 104.14 provides an approach to the evaluation and management of patients with VMs.

Cephalic venous malformation

These lesions frequently lead to cosmetic and functional problems that worsen over time[1]. In addition to the skin, they may affect the lips, oral mucosa, and deeper structures such as muscles, the infratemporal fossa and the orbit (see Fig. 104.13). Cephalic VMs expand when the head is in dependent position. With time, distortion of facial features often becomes conspicuous. Patients with parapharyngeal and laryngeal VMs should be monitored for sleep apnea, which can put them at risk of sudden death during sleep. Approximately 20% of patients with extensive cephalic VMs have defects of the underlying skull[1], which must be identified before performing sclerotherapy, to avoid embolization through the defect.

In the author's experience, 25% of patients with extensive cephalic VMs have developmental venous anomalies (previously referred to by the misnomer "venous angiomas"), compared to <1% of the general population[1]. These are uncommon functional trajectories of venous

Fig. 104.13 Venous malformations (VMs). **A** Distortion of the tongue and lower lip has lead to an open bite. **B** The skin and muscles of the entire arm are affected, with soft bluish nodules and obvious swelling in the dependent position. **C** This VM has a segmental distribution on the right trunk and involvement of the ipsilateral arm.

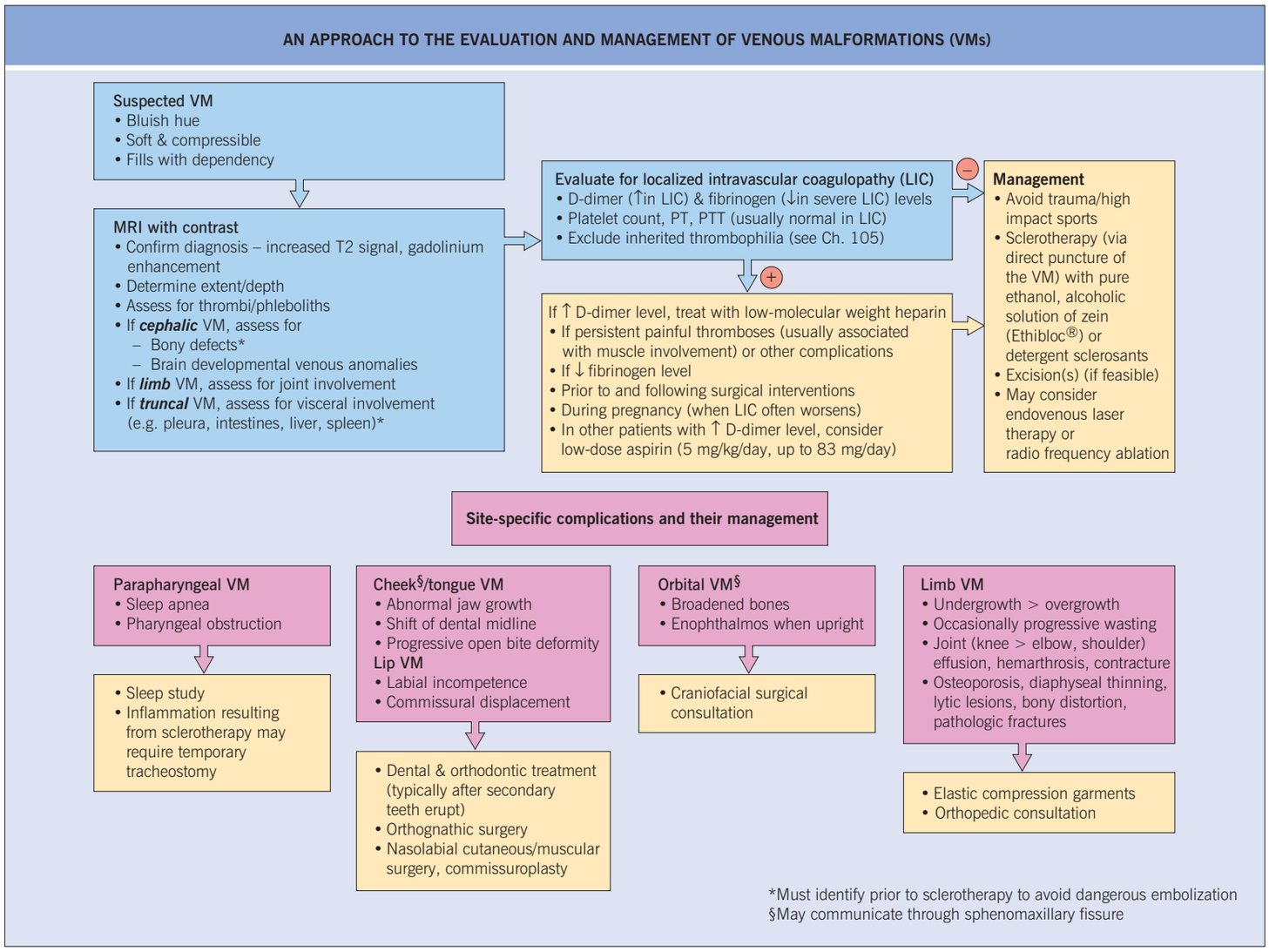


Fig. 104.14 An approach to the evaluation and management of venous malformations (VMs). In the inset, T2-weighted magnetic resonance imaging (MRI) clearly shows VM in the neck (white hypersignals); black dots within the white areas represent phleboliths.

drainage from the brain, usually with enlarged deep venous channels. Developmental venous anomalies may cause headaches, but they do not confer risk of cerebral hemorrhage and treatment is not needed. Of note, patients with cephalic VMs are not at increased risk of CCM-type cerebral vascular malformations (see above).

Trunk and limb venous malformation

VMs of the trunk and limbs often have cosmetic and functional consequences (see Fig. 104.14). VMs form spongy masses of saggy ectatic venous channels, which are easily emptied by elevating and massaging the affected region (see Fig 104.13). However, permeation deep into muscles, joints and bones is common[1]. Muscle involvement is associated with episodes of pain after motion and in the morning. The pain is linked to thromboses inside the low-flow channels, leading to phlebolith formation (round calcifications). Half of patients with large VMs have a chronic localized intravascular coagulopathy with elevated D-dimer levels[30,31]. Joint involvement usually becomes symptomatic before 10 years of age with complications such as effusions and hemarthrosis. Limb VMs are commonly misdiagnosed as KTS. However, the latter does not have muscle or joint involvement (other than that related to an associated VM), and undergrowth of a limb affected by a pure VM is more common than overgrowth.

Sinusoidal hemangioma

Sinusoidal "hemangioma" (see Ch. 114) is a misnomer for a distinctive vascular malformation that typically presents in adults (especially middle-aged women) with deep bluish nodules, often on the breast or extremities. Diagnosis is based on histologic features: well-circumscribed lobules composed of densely packed, large, thin-walled, blood-filled venous channels. Sinusoidal patterns have also been observed in congenital VMs.

Syndromes associated with venous malformations

Familial cutaneous and mucosal venous malformation (VMCM)

Familial VMCM is an autosomal dominant condition in which multiple VMs affect the skin, oral mucosa and muscles. Visceral VMs (e.g. of intestines, lungs, CNS) and cardiac malformations have been observed in a few families[32]. The disorder is caused by heterozygous germline mutations in the *TEK* gene that result in hyperphosphorylation and constitutive activation of TIE-2, a vascular endothelium-specific tyrosine kinase receptor; the downstream signaling of this receptor is also altered[5,32]. Interestingly, approximately half of *sporadic* VMs have *somatic* activating mutations in the *TEK* gene within lesional tissue[5].

Blue rubber bleb nevus syndrome (BRBNS; Bean syndrome)

BRBNS is a sporadic disease characterized by widely distributed dark blue papules and nodules and skin-colored compressible protuberances ("rubber blebs") as well as larger VMs (Fig. 104.15) or LVMs affecting the skin and muscle. Gastrointestinal lesions bleed and result in iron deficiency anemia. Other sites of visceral involvement (CNS, lungs, heart) are uncommon. To date, *TEK* mutations have not been identified in patients with classic BRBNS.

Fig. 104.15 Blue rubber bleb nevus syndrome. Small blue venous nodules are superimposed on a large subcutaneous venous malformation in this girl.

Fig. 104.16 Plaque-type glomuvenous malformation on the distal lower extremity.

Fig. 104.17 Maffucci syndrome. A Both nodular venous malformations and enchondromas distort the hand. **B** A radiograph demonstrates an enchondroma and multiple phleboliths.

Glomuvenous malformation

Glomuvenous malformations (GVMs; previously known as glomangiomas) represent a variant of VM with rows of glomus cells around distorted venous channels (see Ch. 114). They occur as small solitary lesions, widely scattered blue–purple nodules, or (less commonly) large segmental plaques (Fig. 104.16). GVMs may be evident at birth (especially plaque-type lesions) or appear during childhood or adolescence, and they often worsen over time[33,34]. In contrast to classic VMs, GVMs tend to be painful when palpated, partially (rather than fully) compressible, and hyperkeratotic (especially on the extremities) with a cobblestone-like appearance. GVMs do not typically affect viscera or joints; mucosal involvement (deep intraoral lesions) or superficial invasion of muscles occasionally occurs. Approximately two-thirds of patients with glomuvenous malformations, but only 1% of those with classic VMs, have a family history of similar lesions. GVMs have a dominant (sometimes referred to as paradominant) mode of inheritance that results from heterozygous germline mutations in the glomulin (*GLMN*) gene passed from generation to generation plus a somatic "second hit" in this gene within lesional skin (see Table 104.2)[35].

Maffucci syndrome

Maffucci syndrome features a combination of VMs (blue to skin-colored nodules) and enchondromas (similar to those of Ollier disease), leading to orthopedic and cosmetic consequences (Fig. 104.17). It most commonly affects the extremities; however, cephalic lesions with severe neuro-ophthalmologic complications may also occur. Histologically, the cutaneous nodules demonstrate features of both a VM and a vascular tumor, the spindle cell hemangioma (see Ch. 114). Maffucci syndrome is a sporadic condition that is distinct from Ollier disease, with mutations in the *PTHR1* gene identified in the latter but not the former disorder.

Lymphatic Anomalies

Lymphedema results from hypoplasia, aplasia or disruption of lymphatic channels, whereas LMs are due to hyperplasia of the lymphatic network. LMs may be microcystic, macrocystic or combined. They can have superficial (skin and mucous membranes), deep (e.g. muscles, bone), or visceral (<10% of patients) involvement[1]. Lymphedema is divided into primary (abnormal development of the lymphatic system) and secondary (acquired disruption of lymphatic channels) forms (see Ch. 105).

Primary lymphedema

Patients with primary lymphedema usually accumulate lymph fluid in the extremities (lower > upper); cephalic and genital involvement occasionally occurs. Affected individuals are at risk for bacterial infections and septicemia. Generalized lymphedema may be associated with intestinal or pulmonary lymphangiectasias, exudative enteropathy, and pleural effusions.

Genetic forms of lymphedema (see Table 104.2) manifest at birth or later in life (ranging from childhood to adulthood). Congenital or childhood-onset lymphedema can occur in the setting of *Turner syndrome* (see Ch. 55) and *Noonan syndrome*. *Milroy disease*, which

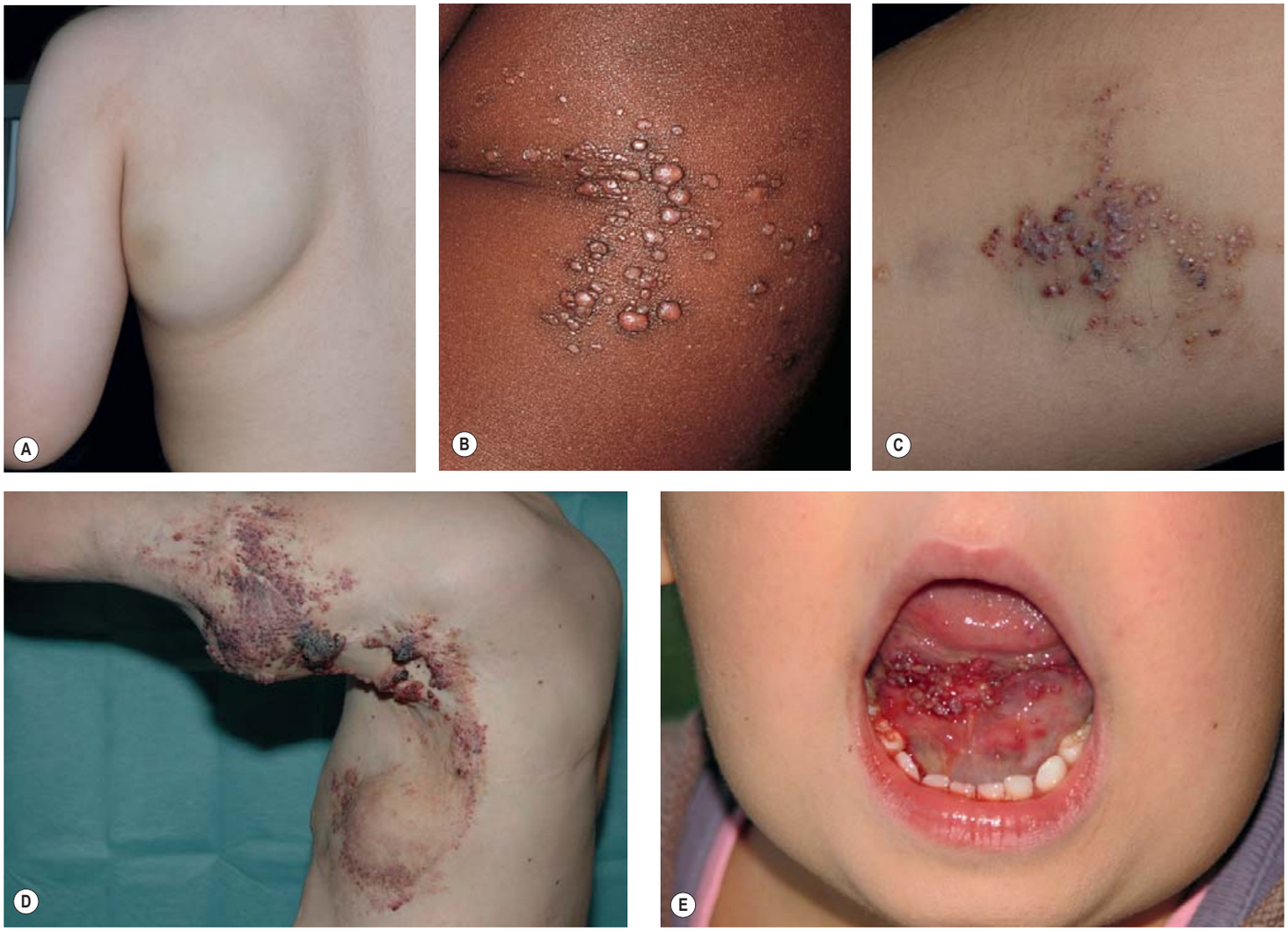


Fig. 104.18 Lymphatic malformations (LMs). A Macrocystic LM on the lateral trunk. The mass was soft except for a focal firm area of hemorrhage associated with bruise-like discoloration of the overlying skin. **B–E** Microcystic LMs presenting as clusters of clear or hemorrhagic vesicles, with active bleeding from lesions in the mouth (**E**). The crops of vesicles in (**D**) recurred years after surgical resection (utilizing grafting and linear closure) of a large microcystic LM affecting the skin and deeper structures of the arm and thorax. *A, C, Courtesy, Julie V Schaffer, MD.*

presents with congenital lymphedema of the lower extremities (especially below the knees), is an autosomal dominant disorder caused by mutations in the *FLT4* gene that encodes vascular endothelial growth factor receptor-3 (see Ch. 102). Autosomal dominant inheritance of lymphedema with peripubertal onset occurs in *Meige disease* (the etiology of which is currently unknown) and *lymphedema–distichiasis syndrome*. The latter also features congenital distichiasis (aberrant eyelashes arising from the meibomian glands) and venous varicosities, and it is caused by mutations in the *FOXC2* gene. *Aagenaes syndrome* is an autosomal recessive disorder that manifests with infantile cholestasis and childhood-onset lymphedema. Other familial lymphedema syndromes with a known molecular basis are presented in Table 104.2.

Macrocystic lymphatic malformation ("cystic hygroma")

Macrocystic LMs represent collections of large, interconnected lymphatic cysts lined by a thin endothelium. The most common locations are the neck, axilla and lateral chest wall (Fig. 104.18A). Prenatal detection by ultrasound is possible as early as the first trimester of pregnancy. Some patients who are diagnosed prenatally have malformation syndromes caused by chromosomal abnormalities or other genetic defects (Down syndrome, Turner syndrome, Noonan syndrome). A macrocystic LM appears as a large, soft, translucent mass under normal skin. The diagnosis can be confirmed by ultrasound, CT or MRI (see Table 104.3) as well as by direct puncture and cytologic analysis of the fluid. Hemorrhage inside a cyst can create sudden swelling, with the mass becoming tense, firm, purple or yellowish in color, and tender.

Microcystic lymphatic malformation ("lymphangioma circumscriptum")

These ill-defined aggregates of relatively small, abnormal lymphatic channels are the most common type of LMs. They can occur anywhere on the skin (favoring the proximal limbs and chest) or in the mouth (including the buccal mucosa, lips, tongue and oral floor). Plaques with crops of clear or hemorrhagic vesicles scattered on their surface (Fig. 104.18B–E) vary in size and appearance (e.g. the number and color of superimposed vesicles) over time. Additional clinical findings are intermittent swelling, hemorrhage and leakage of lymph from superficial vesicles. Lesions are often much more extensive than clinically expected from the number of vesicles. Complications include erysipelas-like reactions following minor injuries, other inflammatory flares and infections.

Combined microcystic and macrocystic lymphatic malformation

Extensive cervicofacial combined LMs commonly have bony involvement. This can lead to mandibular overgrowth and prognathism, resulting in a long or asymmetric face, bite deformities and abnormal occlusal planes[36]. Intraoral combined LMs are frequently complicated

by inflammatory flares or spontaneous bleeding in the setting of upper respiratory or dental infections. This can result in sudden expansion of the lesions, particularly those in the tongue. Local infections can lead to cellulitis or even septicemia. In some patients with massive oropharyngeal combined LMs, airway compromise (extrinsic or intrinsic) requires tracheostomy. Hypersalivation and dental caries are common, with the potential for loss of teeth. Speech, mastication and swallowing may be impaired. In addition to swelling, pain and infections, specific complications of combined LMs in the orbital region include chemosis, strabismus, amblyopia, proptosis and visual loss[37].

On the trunk and limbs, combined LMs tend to worsen as the child grows. When a minor wound on the affected extremity becomes infected, the inflammatory reaction results in expansion of the LM (just as in patients with limb lymphedema). Perineal and gluteal cleft LMs, which are particularly prone to fluid leakage and infection, severely impair quality of life. Rare multifocal abdominal and thoracic LMs that extend into viscera (often categorized as "lymphangiomatosis") may have a lethal outcome due to expansion and visceral complications. In *Gorham–Stout (disappearing bone) disease*, an LM creates progressive radiolucent bone lesions and eventually massive osteolysis, which results in pathological fractures and deformity; involvement of the thoracic skeleton may be associated with pulmonary lymphangiectasia. Lastly, patients with extensive combined LMs, in particular those that have a venous component, may have a chronic localized intravascular coagulopathy with elevated D-dimer levels.

Arteriovenous Malformations

AVMs are fast-flow vascular malformations with direct communications (AV shunting) between arteries and veins creating a nidus (AV nidus). They are rare and constitute the most dangerous group of vascular anomalies. Schobinger's staging was adopted by the ISSVA in order to classify AVMs according to their clinical severity[1,2,38]. The stages are: (1) *quiescent/dormant* – macular or slightly infiltrated, red, warm lesions mimicking a PWS (Fig. 104.19A&B); (2) *expansion* – warm masses with throbbing and thrills over dilated draining veins (Fig. 104.19C); (3) *destruction* – necrosis, hemorrhage, ulceration and (occasionally) lytic bone lesions (plus findings of stage 2) (Fig. 104.19D); (4) *cardiac decompensation* (plus findings of stage 2 ± 3). Initial evaluation with ultrasonography and MRI studies can confirm the diagnosis and delineate the extent of the lesion (see Table 104.3).

In 40% of patients, AVMs are visible at birth; the remainder appear later in life. The most frequent location is cephalic (~70% of patients in the author's experience; Fig. 104.20)[38]. Puberty (75% of patients), pregnancy (25% of women) and trauma may result in worsening of AVMs[38]. In an analysis of 65 patients with cephalic AVMs (unpublished personal data), 39 were centrofacial and 7 were hemifacial; 10 affected the forehead, 10 the ear and 4 the scalp. Stage 3 cephalic AVMs are disfiguring and function- or even life-threatening lesions, and those on an ear or extremity may lead to amputation[39]. Multifocal AVMs affecting an extremity can lead to cardiac overload and distal ischemia.

Fig. 104.19 Arteriovenous malformations (AVMs). A, B Dormant (stage 1) AVMs mimicking a port-wine stain (**A**) and infantile hemangioma (**B**). **C** Expanding (stage 2) centrofacial AVM associated with AVMs of the retina and brain in a boy with Bonnet–Dechaume–Blanc syndrome. **D** Destructive (stage 3) AVM that has led to cutaneous necrosis.

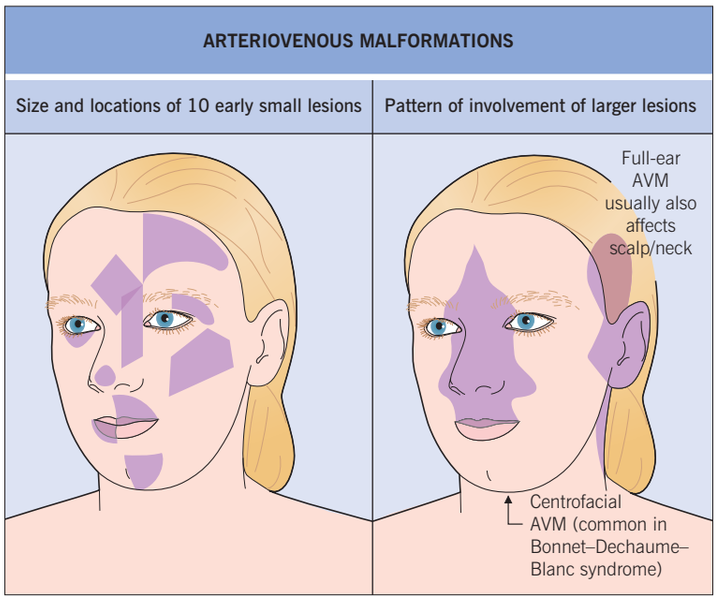


Fig. 104.20 Arteriovenous malformations – size, locations and patterns.

Fig. 104.21 Cobb syndrome. This stain on the nape has an appearance reminiscent of a salmon patch, but it was warm and superimposed darker red macules progressively appeared. Doppler ultrasonography, MRI and arteriography confirmed the presence of a metameric arteriovenous malformation of the skin and spine.

Attempted treatment with arterial or venous ligatures, partial excision, or proximal (rather than selective distal) embolization often precipitates complications. *Stewart–Bluefarb syndrome* represents *acroangiodermatitis* (pseudo-Kaposi sarcoma; see Ch. 105) occurring in association with an AVM of the lower extremity.

Syndromes associated with arteriovenous malformations

Cobb syndrome

This rare sporadic condition features cutaneous, intraspinal (intramedullary ± meningeal), and vertebral AVMs in the same metamere. Congenital red or red–brown vascular stains mimicking a PWS (actually a stage 1 AVM) (Fig. 104.21) or throbbing masses with dilated veins (stage 2 AVM) are present in 20% of patients with spinal AVMs. Neurologic deficits typically develop during young adulthood due to a mass effect of the expanding AVM on the spinal cord and subarachnoid hemorrhage. Neurologic signs range from back pain and radiculalgia to rectal and bladder dysfunction to paraparesis and paraplegia. MRI and angiography establish the presence of the spinal AVM. Endovascular embolization of the spinal AVM may improve the prognosis.

Bonnet–Dechaume–Blanc syndrome (BDBS; Wyburn–Mason syndrome)

This rare metameric AVM extends from the craniofacial region to the orbit and brain. Incomplete forms of the disease also exist. The brain AVM may remain asymptomatic or manifest as seizures or hemiparesis/hemiplegia. In 12 BDBS patients (personal observations) between 5 to 51 years of age, their facial AVMs (stage 1, 2 or 3) were midfacial in 3 (see Fig. 104.19B–D), hemifacial in 3, and both midfacial and hemifacial in 6. The presence of an orbital AVM was an inconsistent finding (4 patients), but brain AVMs (of the chiasm, choroid plexus, or thalamus) were present in all 12 individuals and led to cerebral hemorrhage in 4 patients. In a second series of 15 patients with BDBS[40], orbital AVMs were present in 14 and frequently affected the optic nerve (13 patients) and retina (11 patients); symptoms in this group included reduced visual acuity or fields, blindness, recurrent epistaxis, nasal obstruction and gingival hemorrhage.

Parkes Weber syndrome

In this rare *fast-flow* vascular malformation syndrome, limb overgrowth (in length and girth) occurs secondary to arteriovenous fistulae (AVF); this must be differentiated from the purely *slow-flow* malformations of KTS. A diffuse red CM, excess fat, and lymphatic anomalies may also be observed in Parkes Weber syndrome. Lytic bone lesions and cardiac failure often develop, and prognosis is poor after puberty. Parkes Weber syndrome can occur in association with multifocal CMs as a component of the familial CM-AVM syndrome (see below)[6,22].

Capillary malformation–arteriovenous malformation (CM-AVM)

This autosomal dominant disorder is caused by mutations in the *RASA1* gene (see Table 104.2). Multiple small cutaneous CMs are evident at birth or appear during childhood, presenting as pink to red–brown macules (often with a narrow blanched border) in a haphazard distribution. Approximately 30% of affected individuals also have high-flow lesion(s)[6,22]. Among 140 patients from 50 families with CM-AVM, 90% had multifocal small CMs, 6% had a solitary "atypical" CM, 12% had Parkes Weber syndrome, 11% had an AVM of the skin/subcutaneous tissue (most often a solitary facial lesion), and 7% had a cerebral AVM/AVF[22].

PTEN hamartoma tumor syndrome (PHTS)

PHTS, which encompasses Bannayan–Riley–Ruvalcaba and Cowden syndromes, is an autosomal dominant condition caused by mutations in the *PTEN* gene (see Ch. 63)[41,42]. Affected individuals are often macrocephalic, and they are predisposed to the development of malignancies (especially of the breast and thyroid). Cutaneous manifestations with onset at birth or in childhood include genital pigmented macules, segmental excess of hypervascularized fat, and vascular malformations. The latter are typically multifocal, intramuscular fast-flow lesions that are associated with ectopic fat and focal segmental dilatation of draining veins[43]. Cerebral developmental venous anomalies are also common in PHTS patients.

PATHOLOGY

The histologic characteristics of the four major types of vascular malformations are illustrated in Figure 104.22[1].

Capillary Malformations

A CM is composed of ectatic capillaries within the papillary and reticular dermis, lined by a flat continuous endothelium. Thickening of affected skin can occur over time due to a progressive increase in the diameter of the capillaries, involvement of the dermis and subcutis, fibrosis of the dermis, and, occasionally, venous channels in the subcutis.

Venous Malformations

Large convoluted and interconnected anomalous venous channels dissect the normal connective tissues and muscles. Organized thrombi,

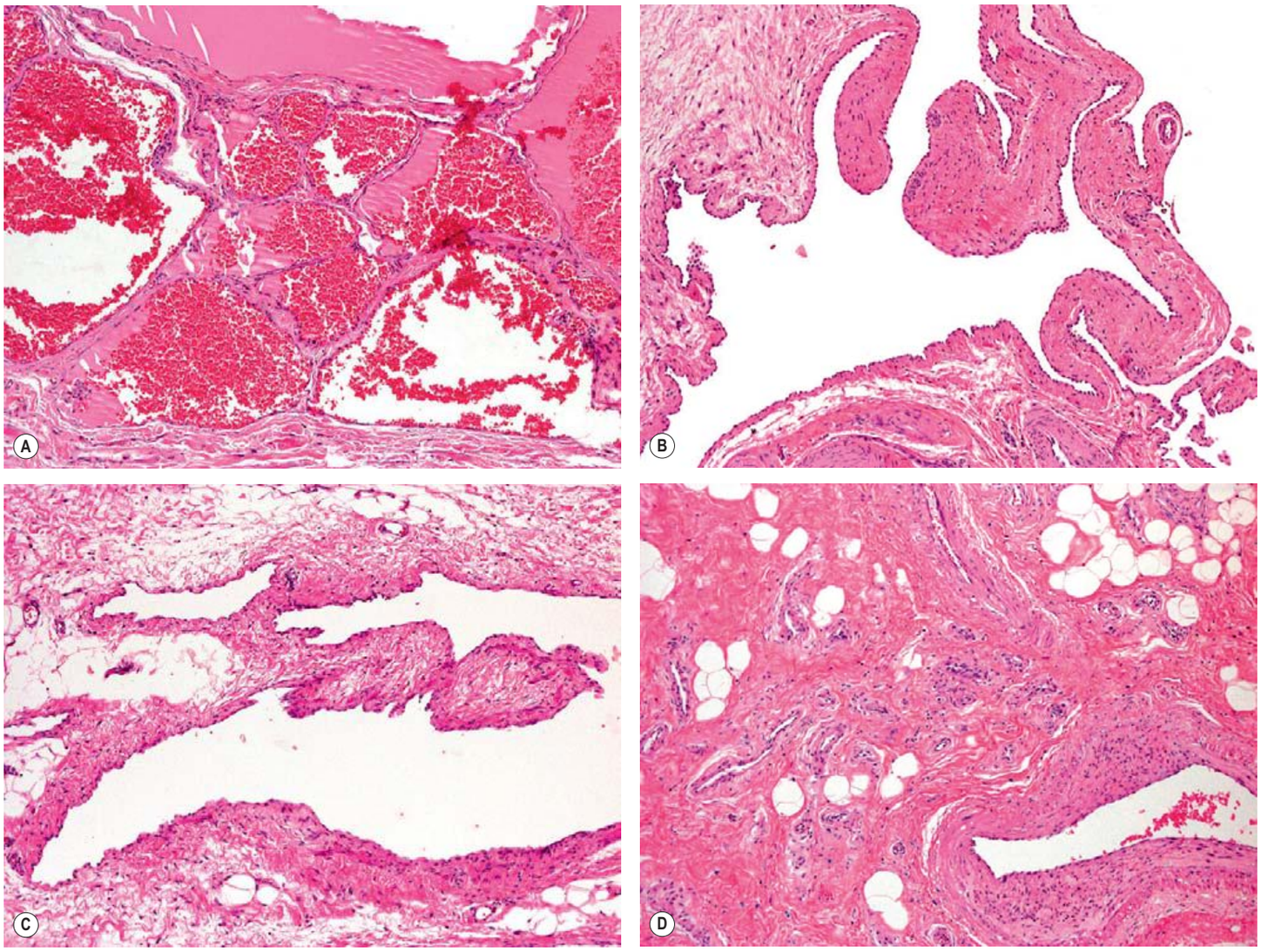


Fig. 104.22 Histologic features of vascular malformations. A Capillary malformation in an adult that was thickened and nodular. An increased number of dilated capillaries are present in the dermis. **B** Venous malformation composed of large, irregularly shaped, thin-walled channels. **C** Lymphatic malformation with large, irregularly shaped channels. **D** Arteriovenous malformation demonstrating an area of intense capillarogenesis near the AV nidus. This finding is sometimes misinterpreted as a "capillarovenous" malformation. *A–D, Courtesy, Lorenzo Cerroni, MD.*

phleboliths (round calcifications) and Masson's papillary endothelial hyperplasia are frequently observed. Anomalous vessels of a VM have a continuous flat endothelium and a thin basement membrane. Their walls have discontinuous media due to foci with a relative lack or absence of smooth muscle cells.

Lymphatic Malformations

LMs of the microcystic type ("lymphangioma") exhibit enlarged, distorted, irregular lymphatic channels with varying numbers of smooth muscle cells in their walls and a very thin endothelium, sometimes barely visible. Larger polyhedral lymphatic vessels may exhibit valves, and they are usually separated by fibrous septa. Lymphatic clefts dissect the host connective tissues. Hyperkeratotic epidermis may overlie some clusters of dermal lymphatic vesicles. LMs of the macrocystic type ("hygroma") are composed of large lymphatic cisterns, often interconnected with thinner channels. Vesicles and large cysts in LMs usually contain watery fluid, lymphocytes, and macrophages; hemorrhage can also be seen.

Arteriovenous Malformations

AVMs have irregularly thickened walls and are usually randomly distributed in the dermis and other involved tissues. Direct communications between vessels with different elastic components, typically arteries and veins, may be evident. A capillary component is often obvious in the overlying papillary dermis, and it may have a lobular architecture.

DIFFERENTIAL DIAGNOSIS

Vascular malformations must be distinguished from vascular neoplasms. Early or "arrested growth" ("abortive") superficial infantile hemangiomas may resemble CMs, whereas deep infantile hemangiomas and other vascular tumors (e.g. kaposiform hemangioendothelioma, infantile hemangiopericytoma) can mimic VMs, LMs and LVMs (see Chs 103 & 114). Multifocal lymphangioendotheliomatosis with thrombocytopenia should be considered in patients with multiple vascular malformations, especially when associated with gastrointestinal bleeding (see Ch. 114).

Occasionally, other neoplasms and inflammatory disorders are misdiagnosed as vascular anomalies. A red or blue color and/or a mass underneath normal skin can represent potentially misleading clinical signs. For example, erythematous lesions of lupus erythematosus, plaque-type angiofibromas, telangiectasia macularis eruptiva perstans and other telangiectatic conditions (see Ch. 106) can mimic CMs. Dermal melanocytosis (e.g. nevus of Ota, Mongolian spot) has a deep blue color that may lead to misdiagnosis as a VM. Masses beneath normal skin that may be erroneously diagnosed as a macrocystic LM in infants and children include a lipoblastoma, teratoma, bronchogenic

CAUSES OF ACQUIRED CUTANEOUS LYMPHANGIECTASIA
INFLAMMATORY CAUSES
Crohn's disease (favors perineal area) Morphea profunda Systemic sclerosis
INFECTIOUS CAUSES
Tuberculosis (e.g. scrofuloderma) Recurrent erysipelas/cellulitis
NEOPLASTIC CAUSES
Intralymphatic metastases (e.g. breast carcinoma, melanoma)
IATROGENIC CAUSES
Surgical resection, lymphadenectomy, and/or radiotherapy for cancer (e.g. of the breast, prostate, bladder, cervix) Amputations Corticosteroid-induced atrophy ± photoaging Penicillamine-induced dermopathy
OTHER CAUSES
Pregnancy (vulvar) Cirrhotic ascites (abdominal) Porphyrias (e.g. porphyria cutanea tarda, variegate porphyria; centrofacial) Spontaneous development in elderly patients (genital)

Table 104.6 Causes of acquired cutaneous lymphangiectasia.

cyst, branchial cleft cyst, thyroglossal duct cyst, myofibroma, rhabdomyosarcoma and fibrosarcoma.

Acquired cutaneous lymphangiectasia imitating a LM can develop in several settings (Table 104.6).

TREATMENT

No single treatment exists for this heterogeneous group of lesions.

Capillary Malformations

PWSs and telangiectasias are currently best treated with a flashlamp-pumped pulsed dye laser (PDL; see Ch. 137)[44–46]. This treatment of PWSs, which is typically initiated early in life (especially for facial lesions) to decrease potential psychosocial distress and avoid lesional thickening, is often very effective. However, not all lesions respond well; PWSs on the central face and distal limbs tend to be more resistant to therapy than those in other sites. PDL treatment is safe, producing temporary purpura but a low risk of hypo- or hyperpigmentation and scarring[45]. Although the latter side effects are more common in individuals with darkly pigmented skin (e.g. skin type V), these patients may have a good response and should not be excluded from PDL treatment.

Intervention during infancy with modified PDL therapy using a longer wavelength, increased pulse duration, higher fluence (11–12 J/cm^2) and dynamic cooling spray can maximize lightening or clearing of PWSs[46]. Use of a topical anesthetic (see Ch. 143), together with the anesthetic effect of the cryogen spray, helps to reduce the need for general anesthesia in children. In a longitudinal study of 51 patients whose facial CM was treated with classic PDL, redarkening was evident in one-third of the lesions after a median follow-up period of 10 years[47]. Relapses may be less common in patients treated at a younger age. If treatment is delayed, facial and gingival PWSs may develop hyperplastic changes that require additional dermatologic (e.g. dermabrasion prior to PDL treatment) as well as orthodontic and surgical interventions (e.g. to correct open-bite deformities and macrocheilia).

Multidisciplinary care is necessary for patients with SWS. Anticonvulsants are the mainstay of treatment for seizures, although selected patients with severe, uncontrolled seizures may benefit from surgical management. Glaucoma usually responds to medical or surgical treatment. As discussed above, PDL therapy for PWSs can begin during infancy. Psychological counseling may be helpful for patients and families affected by SWS, and support is also available through the Sturge–Weber Foundation (www.sturge-weber.org).

Venous Malformations

Satisfactory treatment of a cephalic VM typically requires multiple sclerotherapy procedures over a period of years (often spanning from childhood to adulthood) combined with surgical excisions (see Fig. 104.14)[1]. The aims are to maintain facial symmetry, preserve muscular functions and restore the dynamics of the smile. Limb VMs may also benefit from sclerotherapy and resection; however, many are too extensive and invasive for such interventions to be advisable. Use of elastic compression garments helps to reduce swelling and pain in the affected extremity. Treatment with low-molecular-weight heparin can control chronic coagulopathy associated with VMs, especially before surgery and during painful thrombotic events[30,31]. Low-dose aspirin (5 mg/kg/day, up to 83 mg/day) may be of some benefit in patients with a mild coagulopathy.

Lymphatic Malformations

The choice and outcome of treatment depend on the type and extent of the LM[36,37]. Macrocystic LMs are best treated with percutaneous sclerotherapy utilizing agents such as killed bacteria (picibanil/OK-432), alcoholic solution of zein (Ethibloc®), sodium tetradecyl sulfate, pure ethanol, doxycycline and bleomycin. This creates an inflammatory reaction with subsequent fibrosis and shrinkage of the treated cyst; repeated procedures are usually necessary. Surgical therapy is employed if sclerotherapy fails or gives incomplete results.

Surgical excision is the treatment of choice for microcystic LMs, either with direct closure or (for large lesions) use of skin grafts or tissue expanders. However, incomplete excisions are a common problem, whether because of concern regarding functional consequences of extensive surgeries or underestimation of the extent of the LM (see Fig. 104.18D). Other techniques (often used in combination) to reduce the extent of these lesions include laser therapy (e.g. CO_2, surface application or intralesional bare fiber Nd:YAG, diode), radiofrequency ablation, cryoablation and sclerotherapy[48–50]. Microcystic LMs of the tongue and floor of the mouth are particularly difficult to treat, and careful dental hygiene is important. Transient inflammatory swelling of LMs usually responds to therapy with nonsteroidal anti-inflammatory drugs, corticosteroids and/or antibiotics.

Arteriovenous Malformations

In general, stage 2 and 3 AVMs of the head and neck should be excised completely after careful preoperative embolization (using arterial ± direct puncture approaches) to prevent excessive intraoperative bleeding. Reconstruction often requires techniques such as skin grafting, preoperative tissue expansion, and free tissue transfer[1,38]. Subtotal excision frequently results in subsequent progression of the AVM, with recruitment of adjacent vessels and apparent angiogenesis. Stage 1 and early stage 2 AVMs are often managed conservatively if postsurgical cosmetic results might be worse than the lesion itself. However, resection of early-stage AVMs can prevent further progression.

Embolization alone usually cannot cure a superficial AVM. The most effective embolic agent, pure ethanol, poses substantial risks (especially at higher doses) that include renal or pulmonary toxicity and cardiac arrest. For AVMs that begin to hemorrhage, embolization may be lifesaving. Distal hand or foot AVMs are rarely controlled long-term by embolotherapy, and ischemic complications resulting in extreme pain, necrosis and bleeding may require amputation. In one report, treatment of a diffuse AVM in the arm of a young girl using a metalloproteinase inhibitor (Marimastat®) with antiangiogenic effects produced sustained improvement (including reconstruction of affected bones) over a 12-year period without adverse effects[51].

Complex-Combined Malformations

A complex-combined vascular malformation of a limb requires an individualized management plan. Longitudinal orthopedic evaluation is essential for lower extremity lesions in growing children. Carefully timed epiphysiodesis (before the end of the growth period) can potentially correct a leg-length discrepancy in KTS, but it may worsen vascular disease in Parkes Weber syndrome. Treatment of a component of the vascular malformation (e.g. surgery for varicose veins in KTS or embolization of the AV nidus in Parkes Weber syndrome) often has suboptimal results. Elastic support garments and a compensatory shoe-lift are indispensable conservative interventions.

REFERENCES

1. Enjolras O, Wassef M, Chapot R. A Color Atlas of Vascular Tumors and Vascular Malformations. New York: Cambridge University Press, 2007.
2. Enjolras O, Mulliken JB. Vascular tumors and vascular malformations (new issues). Adv Dermatol. 1997;13: 375–423.
3. Wassef M, Vanwijck R, Clapuyt P, et al. Tumeurs et malformations vasculaires, classification anatomopathologique et imagerie. Ann Chir Plast Esthet. 2006;51:263–81.
4. Limaye N, Wouters V, Uebelhoer M, et al. Somatic mutations in angiopoietin receptor gene *TEK* cause solitary and multiple sporadic venous malformations. Nat Genet. 2009;41:118–24.
5. Irrthum A, Brouillard P, Enjolras O, et al. Linkage disequilibrium narrows locus for venous malformation with glomus cells (VMGLOM) to a single 1.48 Mbp YAC. Eur J Hum Genet. 2001;9:34–8.
6. Eerola L, Boon LM, Mulliken JB, et al. Capillary malformation-arteriovenous malformation: a new clinical and genetic disorder caused by *RASA1* mutations. Am J Hum Genet. 2003;73:1240–9.
7. Klapman MH, Yao JF. Thickening and nodules in port-wine stains. J Am Acad Dermatol. 2001;44:300–2.

7a. Nijhawan RI, Bard S, Blyumin M, et al. Early localized morphea mimicking an acquired port-wine stain. J Am Acad Dermatol. 2011;64:779–82.

8. Fernández-Guarino M, Boixeda P, de Las Heras E, et al. Phakomatosis pigmentovascularis: clinical findings in 15 patients and review of the literature. J Am Acad Dermatol. 2008;58:88–93.
9. Happle R. Phacomatosis pigmentovascularis revisited and reclassified. Arch Dermatol. 2005;141:385–8.
10. Mazereeuw-Hautier J, Syed S, Harper J. Bilateral facial capillary malformation associated with eye and brain abnormalities. Arch Dermatol. 2006;142:994–8.
11. Pascual-Castroviejo I, Pascual-Pascual SI, Velazquez-Fragua R, et al. Sturge-Weber syndrome: study of 55 patients. Can J Neurol Sci. 2008;35:301–7.
12. Juhàsz C, Haacke EM, Hu J, et al. Multimodality imaging of cortical and white matter abnormalities in Sturge-Weber syndrome. AJNR Am J Neuroradiol. 2007;28: 900–6.
13. Evans AL, Widjaja E, Connolly DJ, Griffiths PD. Cerebral perfusion abnormalities in children with Sturge-Weber syndrome shown by dynamic contrast bolus magnetic resonance perfusion imaging. Pediatrics. 2006;117: 2119–25.
14. Miller RS, Ball KL, Comi AM, Germain-Lee EL. Growth hormone deficiency in Sturge–Weber syndrome. Arch Dis Child. 2006;91:340–1.
15. Maari C, Frieden IJ. Klippel-Trenaunay syndrome: the importance of "geographic stains" in identifying lymphatic disease and risk of complications. J Am Acad Dermatol. 2004;51:391–8.
16. Huiras EE, Barnes CJ, Eichenfield LF, et al. Pulmonary thromboembolism associated with Klippel-Trenaunay syndrome. Pediatrics. 2005;116:e596–600.
17. Redondo P, Bastarrika G, Aguado L, et al. Foot or hand malformations related to deep venous system anomalies of the lower limb in Klippel-Trénaunay syndrome. J Am Acad Dermatol. 2009;61:621–8.
18. Turner JT, Cohen MM, Biesecker LG. Reassessment of the Proteus syndrome literature: application of diagnostic criteria to published cases. Am J Med Genet. 2004;130A: 111–22.

18a. Lindhurst MJ, Sapp JC, Teer JK, et al. A mosaic activating mutation in AKT1 associated with the Proteus syndrome. N Engl J Med. 2011;365:611–19.

19. Sapp JC, Turner JT, van de Kamp JM, et al. Newly delineated syndrome of congenital lipomatous overgrowth, vascular malformations, and epidermal nevi (CLOVE syndrome) in seven patients. Am J Med Genet. 2007;143A:2944–58.
20. Alomari AT. Characterization of a distinct syndrome that associates complex truncal overgrowth, vascular, and acral anomalies: a descriptive study of 18 cases of CLOVES syndrome. Clin Dysmorphol. 2009;18:1–7.
21. López-Gutiérrez JC, Lapunzina P. Capillary malformation of the lower lip, lymphatic malformation of the face and neck, asymmetry and partial/generalized overgrowth (CLAPO): report of six cases of a new syndrome/ association. Am J Med Genet. 2008;146A:2583–8.
22. Wright DR, Frieden IJ, Orlow SJ, et al. The misnomer "macrocephaly-cutis marmorata telangiectatica congenita syndrome": report of 12 new cases and support for revising the name to macrocephaly-capillary malformations. Arch Dermatol. 2009;145:287–93.
23. Revencu N, Boon LM, Mulliken JB, et al. Parkes Weber syndrome, vein of Galen aneurysmal malformation and other fast-flow vascular anomalies are caused by *RASA1* mutations. Hum Mutat. 2008;29:959–65.
24. Ben Amitai D, Fichman S, Merlob P. Cutis marmorata telangiectatica congenita: clinical findings in 85 patients. Pediatr Dermatol. 2000;17:100–4.
25. Sabbà C, Pasculli G, Lenato GM, et al. Hereditary hemorrhagic telangiectasia: clinical features in *ENG* and *ALK1* mutation carriers. J Thromb Haemost. 2007;5: 1149–57.
26. Morgan T, McDonald J, Anderson C, et al. Intracranial hemorrhage in infants and children with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome). Pediatrics. 2002;109:e12.
27. Faughnan ME, Palda VA, Garcia-Tsao G, et al. International guidelines for the diagnosis and management of hereditary hemorrhagic telangiectasia. J Med Genet. 2011;48:73–87.
28. Revencu N, Vikkula M. Cerebral cavernous malformation: new molecular and clinical insights. J Med Genet. 2006; 43:716–21.
29. Sirvente J, Enjolras O, Wassef M, et al. Frequency and phenotypes of cutaneous vascular malformations in a consecutive series of 417 patients with familial cerebral cavernous malformations. J Eur Acad Dermatol Venereol. 2009;23:1066–72.
30. Mazoyer E, Enjolras O, Bisdorff A, et al. Coagulation disorders in patients with venous malformation of limbs and trunk (a study in 118 patients). Arch Dermatol. 2008;144:861–7.
31. Dompmartin A, Acher A, Thibon P, et al. Association of localized intravascular coagulopathy with venous malformations. Arch Dermatol. 2008;144:873–7.
32. Wouters V, Limaye N, Uebelhoer M, et al. Hereditary cutaneomucosal venous malformations are caused by *TIE2* mutations with widely variable hyper-phosphorylating effects. Eur J Hum Genet. 2010;18: 414–20.
33. Boon LM, Mulliken JB, Enjolras O, Vikkula M. Glomuvenous malformation (glomangioma) and venous malformation: distinct clinicopathologic and genetic entities. Arch Dermatol. 2004;140:971–6.
34. Mallory SB, Enjolras O, Boon LM, et al. Congenital plaque-type glomuvenous malformations presenting in childhood. Arch Dermatol. 2006;142:892–6.
35. Brouillard P, Ghassibé M, Penington A, et al. Four common glomulin mutations cause two thirds of glomuvenous malformations ("familial glomangiomas"): evidence for a founder effect. J Med Genet. 2005;42: e13:1–8.
36. Edwards PD, Rahbar R, Ferraro NF, et al. Lymphatic malformation of the lingual base and oral floor. Plast Reconstr Surg. 2006;115:1906–15.
37. Greene AK, Burrows PE, Smith L, Mulliken JB. Periorbital lymphatic malformation: clinical course and management in 42 patients. Plast Reconstr Surg. 2005;115:22–30.
38. Enjolras O, Logeart I, Gelbert F, et al. Malformations artérioveineuses: étude de 200 cas. Ann Dermatol Venereol. 2000;127:17–22.
39. Wu JK, Bisdorff A, Gelbert F, et al. Auricular arteriovenous malformation: evaluation, management, and outcome. Plast Reconstr Surg. 2005;115: 985–95.
40. Bhattacharya JJ, Luo CB, Suh DC, et al. Wyburn-Mason or Bonnet-Dechaume-Blanc as cerebrofacial arteriovenous metameric syndromes (CAMS). Intervent Neuroradiol. 2001;7:5–17.
41. Wanner M, Celebi JT, Peacocke M. Identification of a PTEN mutation in a family with Cowden syndrome and Bannayan-Zonana syndrome. J Am Acad Dermatol. 2001;44:183–7.
42. Pezzolesi MG, Li Y, Zhou XP, et al. Mutation-positive and mutation-negative patients with Cowden and Bannayan-Riley-Ruvalcaba syndromes associated with distinct 10q haplotypes. Am J Hum Genet. 2006;79: 923–34.
43. Tan WH, Baris HN, Burrows PE, et al. The spectrum of vascular anomalies in patients with PTEN mutations: implications for diagnosis and management. J Med Genet. 2007;44:594–602.
44. Nguyen CM, Yohn JJ, Huff C, et al. Facial port wine stains in childhood: prediction of the rate of improvement as a function of the age of the patient, size and location of the port wine stain and the number of treatments with the pulsed dye (585nm) laser. Br J Dermatol. 1998;138: 821–5.
45. Seukeran DC, Collins P, Sheehan-Dare RA. Adverse reactions following pulsed tunable dye laser treatment of port wine stains in 701 patients. Br J Dermatol. 1997;136:725–9.
46. Chapas AM, Eickhorst K, Geronemus RG. Efficacy of early treatment of facial port wine stains in newborns: a review of 49 cases. Lasers Surg Med. 2007;39:563–8.
47. Huikeshoven M, Koster PH, de Borgie CA, et al. Redarkening of port-wine stains 10 years after pulsed-dye-laser treatment. N Engl J Med. 2007;356: 1235–40.
48. Peters DA, Courtemanche DJ, Heran MKS, et al. Treatment of cystic lymphatic vascular malformations with OK-432 sclerotherapy. Plast Reconstr Surg. 2006;118:1441–46.
49. Leboulanger N, Roger G, Caze A, et al. Utility of radiofrequency ablation for haemorrhagic lingual lymphangioma. Int J Pediatr Otorhinolaryngol. 2008;72:953–8.
50. Shiels WE 2nd, Kenney BD, Caniano DA, Besner GE. Definitive percutaneous treatment of lymphatic malformations of the trunk and extremities. J Pediatr Surg. 2008;43:136–9.
51. Burrows PE, Mulliken JB, Fishman SJ, et al. Pharmacological treatment of a diffuse arteriovenous malformation of the upper extremity in a child. J Craniofac Surg. 2009;20:1597–2002.

CM in the so-called V1 area. This needs early neuroradiological and ophthalmologic evaluation; of note, as the skin of color darkens after birth, this will partly mask the CM.

Severe, gingival and bone hypertrophy in a child with diffuse facial CM. It creates open bite and a mess of both primary and secondary teeth. Notice the poor discoloration of the CM with FPDL.

Phacomatosis pigmentovascularis IIa with diffuse CM and Mongolian spots.

KT syndrome with CVL and huge lipomatosis.

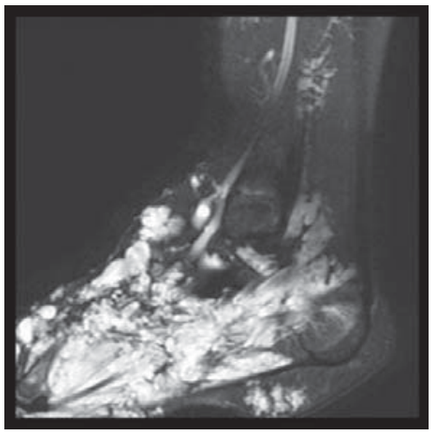
Massively nodular CM of the ear and peri-auricular skin. A biopsy ruled out an epithelioid hemangioma (Angiolymphoid Hyperplasia with Eosinophilia).

Hemi corporeal CMTC at birth. Purple reticulated CM. *(Courtesy, Dr Rosa Maria Cordisco)*

SWS: A The brain CT scan shows gyriform calcifications moulding the involved hemisphere; in (**B**) (same patient) MRI illustrates the corresponding cerebral hemiatrophy and vascular anomaly.

Various patterns of VM.

Various patterns of VM.



MRI, T2 – SE sequence. A swollen tender foot reveals diffuse skin but also intramuscular VM locations (hypersignals on T2).

Bean syndrome. This in 12a, this infant displays at birth a huge VM of a full arm, gut VMs, tiny cutaneous blue papules (knee and foot), and coagulopathy *(Courtesy, Pr Aïcha Salhi).*

GVM, various patterns (**A,B,C** = extent and color)

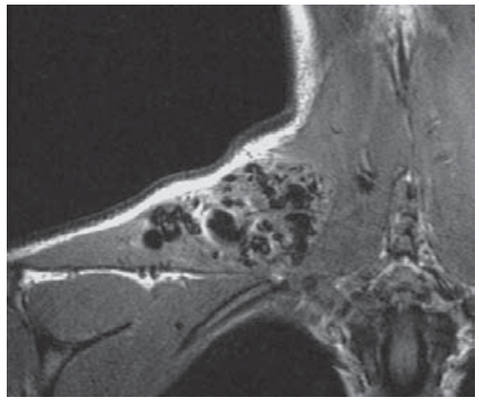
Massive congenital macrocystic LM, involving all soft tissues and some bones of the left neck, thorax, and arm; she died from uncontrolled LM-associated coagulopathy.

Cherry-like combined capillaro-lymphatic lesions in a setting of Gorham syndrome with several evanescent bones

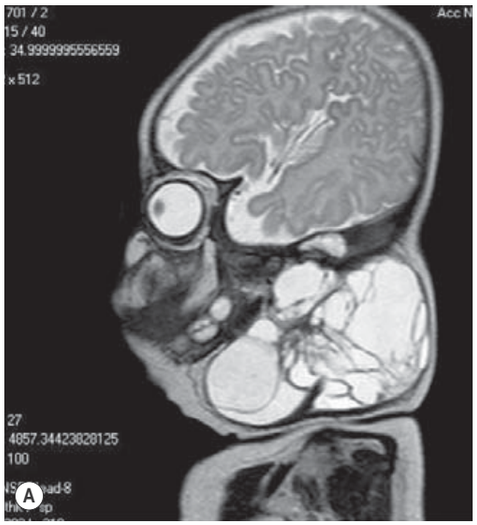
Easy bleeding of LM vesicles in the mouth.

Stage 3 facial AVM. This man needed multiple palliative embolizations, and, due to important exposure to X rays during them, he developed permanent alopecia and a temporal spindle cell carcinoma.

Arteriovenous malformation in necrotic stage 3. Shortening of the phalanx and miniaturization of the nail announce the unavoidable amputation of the finger.



AVM. MRI shows flow voids corresponding to high-flow vessels



MRI of some LMs. A infant at birth with well delineated, hyper T2, macrocysts of LM; **B** prenatal 2nd trimester MRI–T2 imaging of a diffuse head-and-neck, lungs and abdomen LM; death in utero occurred later; **C** MRI- T2 shows the massive microcystic LM blurring soft-tissues and distorting bones of the mouth and pharynx; **D** MRI-T1 with contrast indicates a diffuse LM of the abdomen with ascites, a condition often mislabeled lymphangiomatosis, with a poor prognosis.

105 Ulcers

Ariela Hafner and Eli Sprecher

Chapter Contents

Venous ulcers 1729
Lymphedema 1737
Arterial ulcers 1738
Diabetic (and neuropathic) ulcers 1740
Ulcers due to physical factors 1741
Other causes of skin ulceration 1744

Synonyms: ■ Ulcer – wound, sore ■ Venous ulcer – ulcer due to venous insufficiency/venous hypertension ■ Arterial ulcer – ulcer due to atherosclerosis ■ Neuropathic ulcer – mal perforans ■ Livedoid vasculopathy – atrophie blanche, livedoid vasculitis ■ Pressure ulcer – decubitus ulcer, pressure sore, bed sore

Key features

- The history should include onset, course, symptoms, exacerbating and alleviating factors, past medical history, family history, social history, travel and medications
- Important aspects of the physical examination include location, size and shape of the ulcer, characteristics of the ulcer edge and base, and associated physical findings
- Helpful laboratory evaluation includes vascular studies, blood tests, cultures and biopsy
- A biopsy of non-healing chronic ulcers is indicated to exclude carcinoma or other underlying diseases
- In addition to local care, therapy of ulcers should aim to correct or treat the underlying cause:
  - Venous insufficiency: compression
  - Arterial insufficiency: surgery
  - Neuropathic or pressure ulcer: relief of pressure
  - Infection: antibiotics
  - Neoplasm: surgery, chemotherapy, radiotherapy
  - Vasculopathy: treat the underlying cause of the occlusive disorder
  - Vasculitis or other inflammatory process (e.g. pyoderma gangrenosum): corticosteroids, immunosuppressive agents
- A key factor in therapy is the promotion of wound healing:
  - Debridement: mechanical, enzymatic, autolytic
  - Dressings: maintain a moist wound environment
  - Infection control: antibiotics
  - Skin grafting or skin substitutes
  - Growth factors

INTRODUCTION

A chronic wound is defined as one that fails to progress through a normal orderly and timely sequence of repair or a wound that passes through the repair process without restoring a functional result[1]. An ulcer is a wound that is associated with loss of both epidermal and dermal tissues, and chronic ulcers, which are due to a variety of systemic and/or local factors, represent a diagnostic and therapeutic challenge to the dermatologist. The majority of ulcers occur on the lower extremities, and most are related to venous hypertension and insufficiency, peripheral artery disease or peripheral neuropathy (Table 105.1). Less common causes are outlined in Figure 105.1 and sites other than the legs may be involved (e.g. pressure-induced ulcers).

Wound therapy has advanced considerably over the past few decades with the advent of innovative dressings and technologies, but the key factor in the management of chronic ulcers remains proper patient evaluation and correction of the underlying cause, once identified. This chapter addresses both common and unusual causes of cutaneous ulceration as well as appropriate evaluation and management.

VENOUS ULCERS

Chronic venous disease is a common problem in adults, with its prevalence increasing with age. However, the prevalence varies considerably amongst studies, i.e. from <1% to 17% in men and from <1% to 40% in women. This variability is due in large part to a lack of standardized diagnostic criteria[2].

Risk factors for chronic venous disease include family history, age, female gender, obesity, pregnancy, prolonged standing and height[3]. Venous hypertension and venous insufficiency represent the most common cause of chronic leg ulcerations. Venous ulcers tend to recur, are sometimes painful, and clearly have an impact on quality of life[4]. Because of their prevalence and chronicity, there are significant healthcare costs, estimated to be approximately $3 billion per year in the US[3].

Pathogenesis

The venous system of the lower extremities consists of an interconnected network of superficial veins, deep veins, and perforator or communicating veins which connect the superficial and deep systems[5] (see Ch. 155). Throughout the superficial, communicating and deep veins, one-way bicuspid valves ensure unidirectional flow toward the deep system, thus allowing blood to flow in a cephalad direction and preventing reflux (Fig. 105.2A). It is primarily the contraction of calf muscles that drives blood from the leg toward the heart[4].

During standing, as leg muscles relax, venous pressure in the legs may reach up to 80 to 90 mmHg[3]. Calf muscle contractions, as during ambulation, transiently increase pressure within the deep leg veins, propelling blood towards the heart. When pressure rises within the deep system, the valves close, preventing retrograde flow and transmission of high pressure to the superficial system[4]. When the deep system empties, the deep vein pressure abruptly falls to <30 mmHg and the valves open, enabling flow from the superficial into the deep system[3,4].

In the absence of competent valves, however, the decrease in venous pressure with leg movements is attenuated, and high pressures generated in the deep veins by calf muscle contraction are transmitted to the superficial venous system and to the microcirculation within the skin[3]. A sustained elevation in venous pressure is responsible for the typical clinical picture seen in chronic venous disease and is termed *venous hypertension* or *venous insufficiency*.

In most patients, venous hypertension is caused by reflux through incompetent valves (Fig. 105.2B), whether primary (congenital) or secondary to deep vein thromboses or recurrent trauma. Additional causes of venous hypertension include venous outflow obstruction and failure of the calf muscle pump due to obesity or leg immobility[3].

Although venous hypertension appears to be central to the skin changes seen in chronic venous disease, the exact pathogenic cascade

COMPARISON OF CLINICAL FINDINGS IN THE THREE MAJOR TYPES OF LEG ULCERS			
	Venous	**Arterial**	**Neuropathic/mal perforans***
Location	Medial malleolar region	Pressure sites Distal points (toes)	Pressure sites
Morphology	Irregular borders Yellow fibrinous base	Dry, necrotic base Well-demarcated ("punched out")	"Punched out"
Surrounding skin	Yellow–brown to brown discoloration due to hemosiderin deposits Pinpoint petechiae ("stasis purpura") Lipodermatosclerosis	Shiny atrophic skin with hair loss	Thick callus
Other physical examination findings	Varicosities Leg/ankle edema ± Stasis dermatitis ± Lymphedema	Weak/absent peripheral pulses Prolonged capillary refill time (>3–4 seconds) Pallor on leg elevation (45° for 1 min) Dependent rubor	Peripheral neuropathy with decreased sensation ± Foot deformities
*Most commonly due to diabetes mellitus.			

Table 105.1 Comparison of clinical findings in the three major types of leg ulcers. *Adapted from Phillips TJ, Dover JS. Leg ulcers. J Am Acad Dermatol. 1991;25:965–87.*

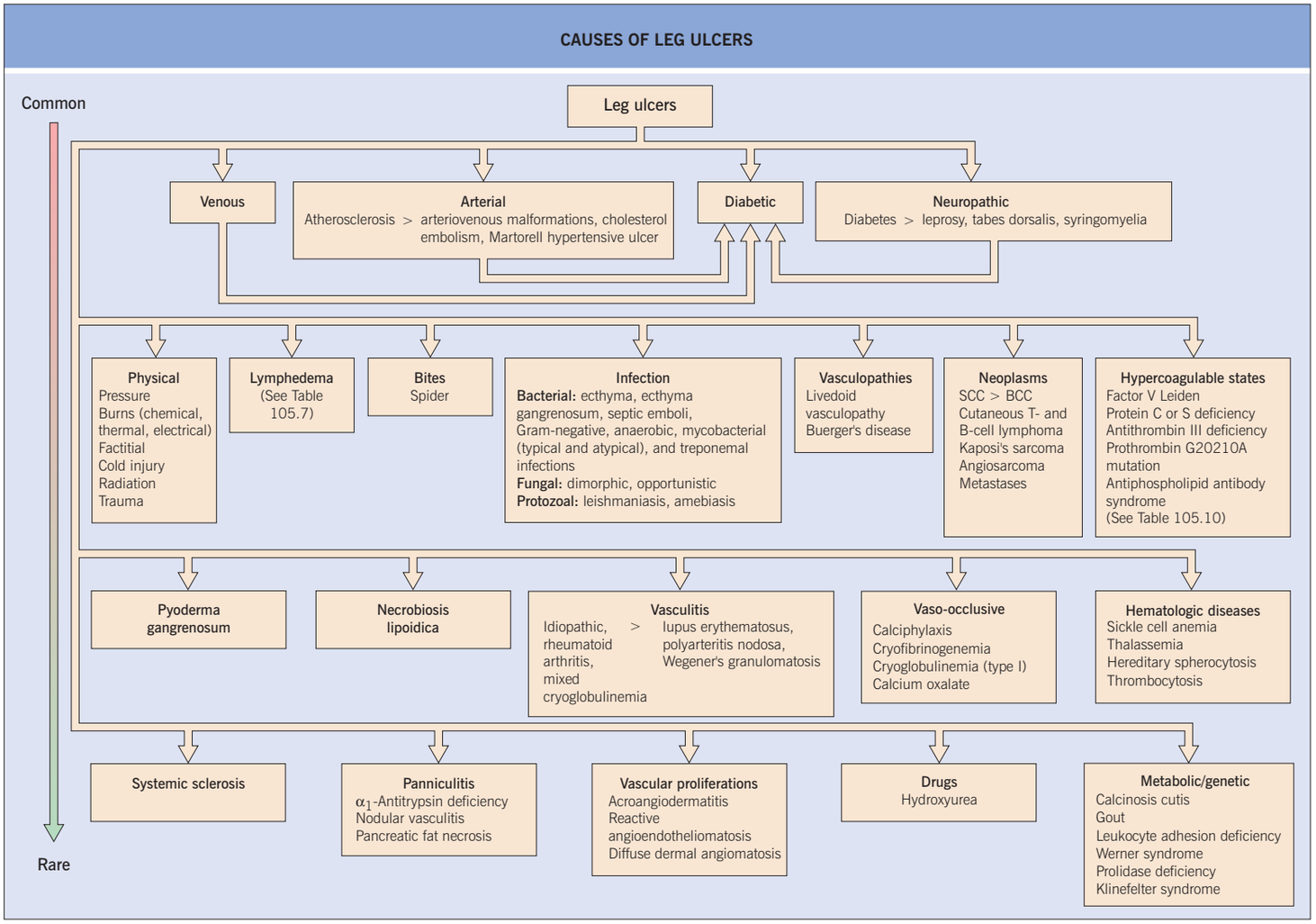


Fig. 105.1 Causes of leg ulcers. Patients with Behçet's disease also develop lower extremity ulcers due to vasculitis and/or venous insufficiency related to deep vein thromboses, and, occasionally, erosive pustular dermatosis is a cause of leg ulcers. Hydroxyurea-induced leg ulcers are often on the malleolus or tibial crest, exceedingly painful and surrounded by atrophic skin. Additional genetic syndromes associated with ulceration are listed in Table 105.10.

from valvular incompetence to frank ulceration remains obscure. A few pathomechanisms have been suggested, but it is still unclear whether they represent causative factors or epiphenomena[6]. For example, Browse and Burnand[7] proposed that cuffs of fibrin around dermal capillaries (due to leakage of fibrinogen) could impede the diffusion of oxygen and nutrients to surrounding tissues and lead to degenerative skin changes. Falanga and Eaglstein[8] postulated that venous pooling induced inter-endothelial space widening and deposition of fibrin and other macromolecules that then "trapped" growth factors, rendering them unavailable for wound repair.

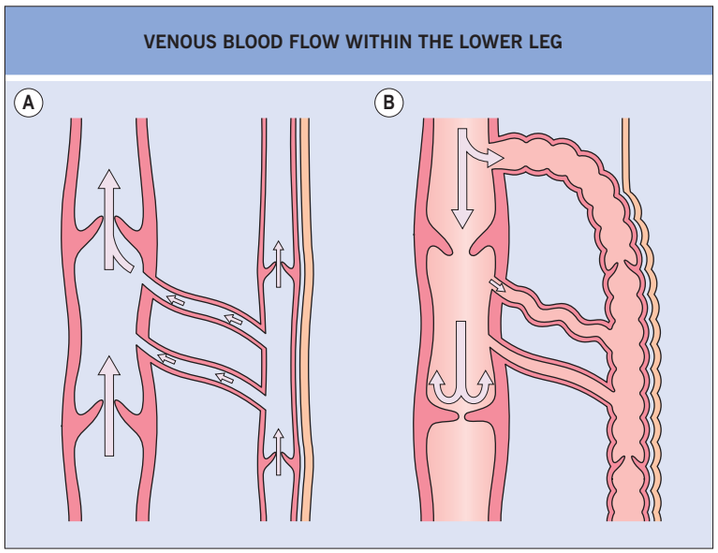


Fig. 105.2 Venous blood flow within the lower leg. A Under normal circumstances, blood is pumped against gravity towards the heart by the calf muscles. Blood flows from the superficial veins to the deep venous system via the perforating veins. Bicuspid valves ensure the unidirectionality of the blood flow. **B** When the valves are incompetent and/or hydrostatic pressure is elevated, blood flows back into the superficial venous system, leading to the formation of varicose veins.

Nowadays, however, the predominant theory is that chronic inflammation plays a key role in chronic wounds[3]. In the setting of elevated venous pressure, there is entrapment of leukocytes within small blood vessels and the skin of the lower extremity (referred to as the microvascular leukocyte-trapping hypothesis; Fig. 105.3)[9]. These trapped leukocytes become activated and they initiate an inflammatory response that leads to cellular and tissue dysfunction, resulting in the dermal changes often observed in patients with chronic venous insufficiency.

Expression of specific adhesion molecules on endothelial cells attracts various leukocytes (e.g. macrophages, T lymphocytes, mast cells) into the dermis via diapedesis (see Ch. 102), where they further promote inflammatory responses via the release of cytokines and activated proteinases[10]. Specifically, increased expression and activity of matrix metalloproteinases (MMPs) contribute to the breakdown of the extracellular matrix, which promotes the formation of ulcers and impairs healing. Elevated levels of cytokines such as transforming growth factor-beta (TGF-β) and vascular endothelial growth factor (VEGF) translate into increased dermal fibrosis and proliferation of dermal capillaries, respectively. Capillary hyperpermeability and extravasation of red blood cells lead to deposition of ferric iron within affected skin, resulting in brown discoloration. A persistent inflammatory response can eventually give rise to ulcer formation, as continued production of MMPs and cytokines (e.g. interleukin-1 and tumor necrosis factor-alpha [TNF-α]) leads to impaired fibroblast function and increased degradation of growth factors necessary for wound healing. In addition, oxidative stress-induced premature aging and dysfunction of wound fibroblasts contribute to the chronicity of venous ulcers[11,12].

Clinical Features

Chronic venous disease is associated with a wide spectrum of clinical findings, ranging from uncomplicated telangiectasias and varicose veins to lipodermatosclerosis and large chronic ulcerations[5]. Patients with

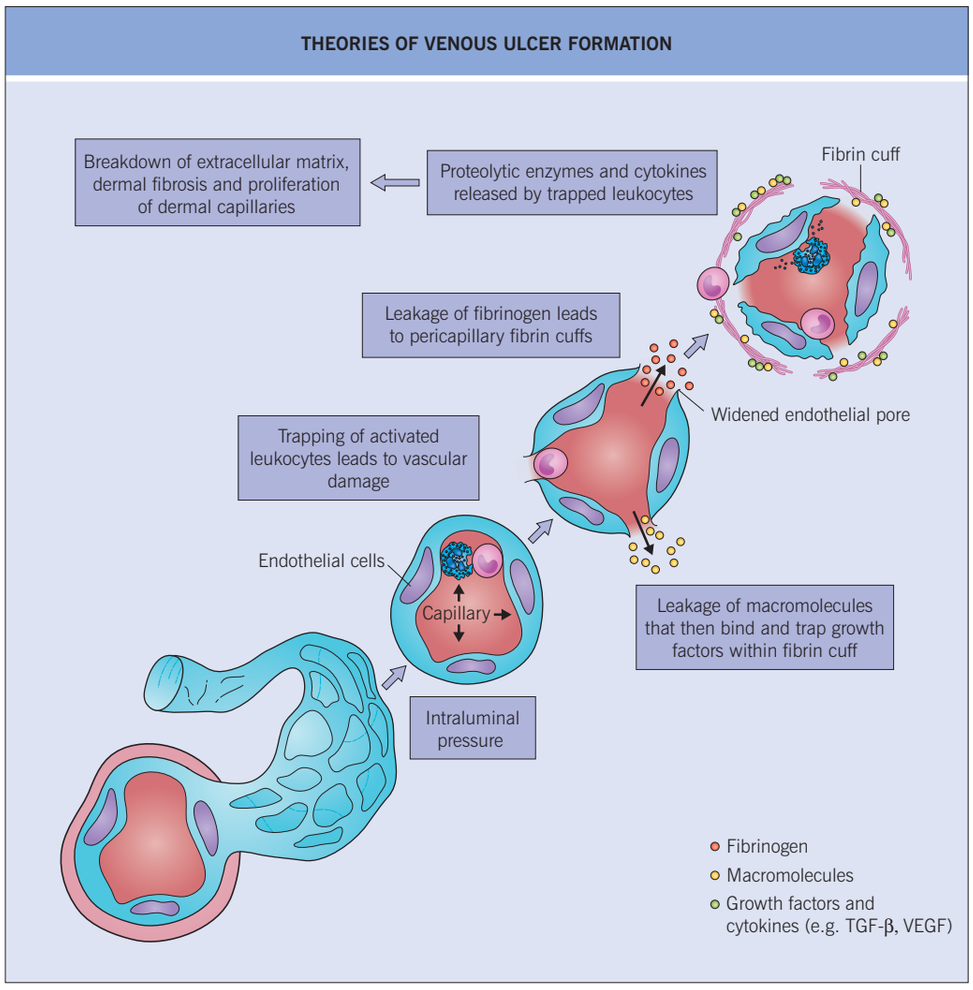


Fig. 105.3 Theories of venous ulcer formation. The theories include the presence of pericapillary cuffs due to leakage of fibrinogen, binding of growth factors by leaked molecules, and the trapping of leukocytes with subsequent chronic inflammation, dermal changes and ulcer formation. TGF, transforming growth factor; VEGF, vascular endothelial growth factor.

venous ulcers often complain of swelling and aching of the legs, typically worsened by dependency and prolonged standing but improved by leg elevation, use of gradient support stockings or walking, all of which decrease venous pressure. Additional symptoms sometimes ascribed to chronic venous disease include muscle cramps, pruritus and restless legs[4,5].

Most commonly, venous ulcers are located above the medial malleolus (Fig. 105.4). The ulcer is usually shallow with a border that is typically irregular; the wound bed is often covered by a yellow, fibrinous exudate. If the latter is appropriately debrided, a base of healthy, non-ischemic granulation tissue is usually seen. When untreated, venous ulcers tend to become larger than most other chronic wounds and can even become circumferential on the lower extremity[4]. Pedal pulses are usually palpable. If they are not palpable because of induration or edema, an ankle–brachial index (see below) should be obtained to exclude concomitant peripheral artery disease[5].

Characteristic associated features include (Fig. 105.5): (1) varicose veins of varying severity (see Ch. 155); (2) pinpoint petechiae superimposed on a yellow–brown discoloration due to extravasation of red blood cells and deposition of hemosiderin within macrophages (see Fig. 22.5), which is sometimes accompanied by hyperpigmentation; (3) edema; and (4) stasis dermatitis with pruritus, erythema, scaling and weeping (see Ch. 13). Of note, stasis dermatitis is sometimes aggravated by allergic contact dermatitis to topically applied medications, e.g. neomycin. The smooth, ivory-white, sclerotic plaques of atrophie blanche that are often surrounded by punctate telangiectasias and/or brown discoloration are observed in up to 40% of patients with chronic venous insufficiency[13] (Fig. 105.6).

Patients with longstanding venous hypertension and insufficiency may develop chronic lipodermatosclerosis (sclerosing panniculitis) with induration and fibrosis that begins on the lower medial aspect of the leg above the malleolus (see Fig. 105.5C, D). Eventually, the entire

Fig. 105.4 Venous ulcer and stasis dermatitis. Note the erythema, crusting and scaling of the skin surrounding the ulcer of the medial malleolus. There is a yellowish fibrinous exudate and granulation tissue is seen in approximately 15% of the ulcer bed.

Fig. 105.5 Associated findings in patients with venous hypertension and venous insufficiency. A Venulectasias of the instep. **B** Brown discoloration of the foot and ankle due to hemosiderin deposits within dermal macrophages in addition to hyperpigmentation. Note the cut-off at Wallace's line. **C** Lipodermatosclerosis with violet–brown discoloration, tenderness and induration that typically begins above the medial malleolus.
A, B, Courtesy, Jean L Bolognia, MD. C, Courtesy, Kalman Watsky, MD.

Continued

Fig. 105.5 Associated findings in patients with venous hypertension and venous insufficiency (cont'd). **D** Stasis dermatitis and chronic lipodermatosclerosis with serous crusts and the "inverted champagne bottle" or "bowling pin" configuration. **E** Acroangiodermatitis (pseudo-Kaposi sarcoma). Violaceous plaque in a patient with venous hypertension. Histologically, these lesions can resemble Kaposi sarcoma.

Fig. 105.6 Livedoid vasculopathy. A Multiple hemorrhagic crusts and small, very painful ulcers associated with brown discoloration due to hemosiderin deposits. **B** Stellate, porcelain-white atrophic scars with peripheral telangiectatic papules, referred to as atrophie blanche.
B, Courtesy, Julie V Schaffer MD.

lower third of the leg may become involved, leading to an appearance that has been likened to an "inverted champagne bottle". Some authors believe the degree of lipodermatosclerosis correlates with delayed wound healing. Chronic lipodermatosclerosis may be preceded by an acute inflammatory stage characterized by warm, erythematous, firm plaques that are tender and painful and are often misdiagnosed as cellulitis or another type of panniculitis, especially erythema nodosum[4].

Lipodermatosclerosis, along with ulcerations, is not limited to the lower extremities, as these changes can be seen in other sites such as the most dependent portion of the pannus (Fig. 105.7).

Laboratory Evaluation

Standardized evaluation of patients with chronic venous disease is based on the CEAP classification system which generates scores derived from objective clinical signs (C), etiology (E), anatomical (A) location of the affected veins, and pathophysiology (P) (reflux, obstruction or both)[14]. Table 155.1 outlines the details of the CEAP classification system.

Duplex ultrasonography, preferably performed with the patient in a standing position, is useful for assessing both reflux and obstruction within the deep, superficial and perforating veins, from the inferior vena cava to the calf veins. It provides information that is necessary for determining the CEAP score. In general, venography is performed if an intervention is planned. *Ascending* venography is recommended for patients with post-thrombotic disease as it gives a detailed anatomic map of the venous return of the lower extremity, whereas *descending* venography is helpful in assessing valvular disease and estimating reflux severity. Experience with high-resolution magnetic resonance venography and computed tomography venography is still limited, but should increase over the next decade[5,14].

Fig. 105.7 Lipodermatosclerosis, chronic ulceration and lymphedema of the dependent portion of the pannus. The changes are similar to those seen on the distal lower extremities.

POINTS TO INCLUDE IN THE HISTORY AND PHYSICAL EXAMINATION OF PATIENTS WITH A LEG ULCER

History	Physical examination
• Onset and clinical course of ulcer • Symptoms, including those of vascular disease or neuropathy • Alleviating factors • Exacerbating factors • Past medical history, e.g. diabetes mellitus, ASCVD, autoimmune CTD • Family history • Medications, topical and systemic • Personal habits (e.g. smoking, alcohol intake)	General, emphasizing the following: • Ulcer characteristics – Location and size – Morphology, including depth, shape, border and base – Surrounding skin, e.g. edema, dermatitis, fibrosis, cellulitis, necrosis • Peripheral pulses • Capillary refill time • Evidence of peripheral neuropathy • Deep tendon reflexes

Table 105.2 Points to include in the history and physical examination of patients with a leg ulcer. ASCVD, atherosclerotic cardiovascular disease; CTD, connective tissue disease. *Adapted from Kanj LF, Phillips TJ. Management of leg ulcers. Fitpatrick's J Clin Dermatol. 1994;Sept/Oct:52–60.*

Pathology

Within the dermis surrounding the ulceration, there is fibrosis, a proliferation of capillaries, and deposits of hemosiderin within macrophages. Extravasation of red blood cells may also be seen.

Differential Diagnosis

A significant number of patients may have a combination of venous and arterial insufficiency, so before treatments such as compression stockings are prescribed, the latter should be excluded (see below). In patients with livedoid vasculopathy or recurrent deep vein thromboses, the possibility of hypercoagulability as a contributing factor needs to be considered (see Table 105.9 & Ch. 23). Additional clues from the history, e.g. rate of expansion, or physical examination aid in narrowing the differential diagnosis (Table 105.2) Histologic examination of a longstanding or recalcitrant ulcer is recommended to exclude other diagnoses, such as squamous cell carcinoma[13] or atypical mycobacterial infection (see Fig. 105.1), and the biopsy specimen should include surrounding non-ulcerated skin.

Treatment

Most of the therapeutic principles described in the following sections can be applied to the care of other types of cutaneous ulcers, unless otherwise specified. In general, normal wound healing requires adequate perfusion, good nutritional and immune status, and avoidance of deleterious mechanical forces[15]. The initial step in the approach to an ulcer should be to address all systemic and local factors that may impair healing.

Moisture and occlusion

In the past, the mainstay of wound management was to dry the wound bed with absorptive gauzes. A major breakthrough in the management of chronic wounds was the realization that a moist environment is critical for wound healing and occlusive dressings do not increase the risk of infection[16]. Moist retentive wound dressings stimulate collagen synthesis, promote angiogenesis by creating an hypoxic environment, encourage re-epithelialization, and decrease pain. By serving as a barrier against external contamination and by lowering wound pH, occlusive dressings actually decrease wound infection rates[15].

Dressings should be changed based on their potential for absorbency and the amount of exudate, with attention to the delicate balance between overhydration and excessive dryness. For example, occlusive dressings applied to highly exudative wounds may cause maceration and erosion of the surrounding skin, possibly leading to further deterioration of the wound. In addition, chronic wound fluid can perpetuate cytokine and MMP production (see above), thereby affecting the function of fibroblasts and growth factors and contributing to chronicity. It is therefore important to protect the skin surrounding the wound bed with an ointment in order to preserve barrier integrity[15].

Debridement

Debridement consists of the removal of necrotic, non-viable or infected tissue from the wound bed in order to promote healing. In a sense, debridement is an attempt to shift the wound from a chronic state (with a milieu characterized by an abnormal extracellular matrix, an excess of proteolytic enzymes and senescent cells) into an acute state. Debridement can be surgical (sharp debridement), mechanical (wet to dry), autolytic, chemical (enzymatic) and biologic (maggot therapy)[17].

Sharp debridement with surgical instruments represents the most rapid method for debriding a wound and is most appropriate for large necrotic and/or infected wounds. It also enables the clinician to estimate the extent and severity of a wound. Although damage to viable tissue is possible, sharp debridement performed by a skilled physician is usually highly selective[17]. Caution is advised in the case of arterial ulcers because of the potential risk for tissue desiccation and ulcer enlargement[15]. Sharp debridement may be associated with bleeding and pain and may necessitate analgesia.

Wet-to-dry (mechanical) debridement consists of placing gauze moistened with saline over the wound, allowing the gauze to dry, and then removing the dry gauze along with adherent non-viable tissue. It is relatively fast and easy to perform, but is painful and does not discriminate between viable and non-viable tissue. It is indicated for wounds with large amounts of necrotic tissue.

Autolytic debridement is the process by which the body uses its own proteolytic enzymes and phagocytic cells to clear necrotic debris. The process is enhanced by moist retentive wound dressings and may require weeks to accomplish. Autolytic debridement is selective, painless, and suited primarily for wounds with minimal debris. It is contraindicated if the wound is infected[17].

Enzymatic (chemical) debridement utilizes topically applied proteolytic enzyme preparations such as papain–urea or collagenase to digest necrotic tissue, collagen, fibrin and wound exudate. Chemical debridement is a gradual process. The papain–urea preparation contains papain, which is derived from the plant *Carica papaya* and is a non-selective cysteine protease. It is active over a broad pH range and is associated with an intense inflammatory response and digestion of viable tissue; local pain or a burning sensation is often described. Therefore, the product should be applied only to the wound bed and not to the surrounding intact skin. Collagenase preparations are derived from *Clostridium histolyticum*; they specifically target native collagen and are active within a narrow pH range of 6 to 8. These preparations are highly selective and do not harm viable cells[16]. Prior to application, it is advisable to cross-hatch the eschar, if present, in order to increase penetration[15].

For therapy-resistant, chronic ulcers with marked necrosis and slough, *maggot debridement* therapy can be considered. Essentially, it

exploits the ability of maggots to decompose necrotic tissue (benign myasis), but the debridement is done in a controlled manner so as to avoid undesirable effects on healthy tissues[18]. Degradation via proteinases that are in larval excretory/secretory products is thought to contribute to wound debridement[19]. It is important to select larval strains that feed preferentially on necrotic tissue and to avoid applying too many larvae to a wound. The flies most often employed are facultative calliphorids, in particular the green bottle blowfly, *Lucilia sericata*[18].

Maggots are used to treat various types of chronic ulcers, including pressure ulcers, venous ulcers, neurovascular diabetic ulcers, and traumatic and postsurgical wounds. In a recent multicenter, randomized, open study that compared the clinical effectiveness of larval therapy to a standard debridement technique (hydrogel) for "sloughy" or necrotic leg ulcers, larval therapy did not improve the rate of healing or reduce bacterial load, but it did significantly reduce the time to debridement and increase ulcer pain[20].

Wound dressings

The ideal wound dressing should: (1) provide a moist retentive environment; (2) absorb excess exudate without causing maceration of surrounding skin; (3) protect against bacteria; (4) leave no residual debris but cause no trauma when removed; (5) decrease odor; and (6) relieve pain. In addition, the ideal wound dressing should be cost-effective, easy to handle, and be neither irritating nor allergenic. Obviously, there is no single dressing that can fulfill all these criteria throughout the entire healing process. A vast array of dressings exists and the choice of a dressing depends upon the wound type and its characteristics at a given time (Table 105.3)[15,16].

Management of wound infection

The presence of a microbial infection is always detrimental to wound healing. However, all chronic open wounds are colonized with bacteria and it is important, although often difficult, to distinguish true infection from bacterial colonization. Of note, colonization is defined by the presence of replicating bacteria and adherent microorganisms, but without evidence of tissue damage.

Critical colonization is a relatively new concept in which the bacterial burden within a chronic wound does not elicit the typical symptoms or signs of an infection, but does delay healing. The presence of 10^6 or more colony-forming units of bacteria per gram of tissue predicts delayed wound healing and a high risk for developing an infection[16]. Recent studies have demonstrated that in many chronic wounds, bacteria persist in the form of biofilms. The latter represent communities of bacteria protected by an adhesive polymeric matrix cover that communicate with each other via water channels. Through these communication channels, bacteria are able to regulate the transcription of genes and protein products in a manner that is beneficial to them, but which can delay healing (quorum sensing)[16]. Biofilms are particularly resistant to antimicrobial therapy.

Wounds become clinically infected when host defenses are overwhelmed. Signs and symptoms of infection include an increased exudate, purulent discharge, pain, and surrounding erythema and swelling. However, sometimes an increase in ulcer size and malodorous or friable granulation tissue are the only clues to the presence of an active infection within a chronic wound. Systemic signs of infection such as fever, chills, tachycardia and leukocytosis may suggest that the infection has progressed to a bacteremia or septicemia, although the former may be subtle in elderly patients, necessitating a high index of suspicion.

Most chronic wounds have a polymicrobial flora. Bacterial cultures usually grow aerobic Gram-positive cocci, which are often mixed with Gram-negative bacilli and sometimes anaerobes[21]. Clinically infected wounds should be cultured and treated initially with broad-spectrum systemic antibiotics. The antibiotic regimen is then adjusted based on the results of sensitivity testing.

In properly treated, non-healing wounds that demonstrate critical colonization, topical antimicrobials should be considered. Topical

TYPES OF WOUND DRESSINGS

Dressing type	Properties	Disadvantages	Indications
Gauzes	• Good absorption • Can be impregnated with: – NaCl to become highly absorbent, discourage bacterial overgrowth and prevent formation of excess granulation tissue – petrolatum so less drying and adherent, but then less absorbent – iodine or silver as an antiseptic	• Adhere to wound bed and promote desiccation • Can cause pain and trauma, including removal of epithelium, upon removal	• Wet wounds with heavy exudate • May serve as a secondary dressing
Films	• Semi-occlusive, thin polyurethane membranes • Maintain moisture • Permeable only to vapors, not to liquids • Transparency enables wound visualization	• Non-absorbent • Can cause maceration if applied to wounds with heavy exudate	• Wounds with minimal exudate • As a secondary dressing
Hydrogels	• Maintain a moist environment • Promote autolytic debridement • Non-adhesive • Relieve pain	• Can lead to maceration of skin surrounding wound if used in exudative wounds	• Dry wound • Wound with minimal exudate
Hydrocolloids	• Adhesive, occlusive dressings that absorb exudates with the formation of hydrophilic gel • Provide a moist environment	• Not suitable for wounds with heavy exudate or infected wounds • May produce a brown, malodorous exudate • May be traumatic on removal	• Wounds with a mild to moderate exudate
Alginates	• Fibrous dressings derived from brown seaweed • Highly absorbent and require moisture to function • Ion exchange between calcium in the alginate and sodium in the wound fluid leads to the formation of a moist retentive gel • Hemostatic	• May adhere to dry wounds • May leave fibrous debris in the wound • Can lead to maceration around the wound unless cut to the size of the wound bed	• Wounds with a moderate to heavy exudate • Undermined or tunneling wounds
Foams (polyurethane)	• Good absorbance capacity • Non-traumatic upon removal • Provide thermal and shear protection	• May produce malodorous drainage • Maceration around wound possible	• Wounds with a moderate to heavy exudate
Collagens	• Collagen matrix that physically entraps MMPs and facilitates growth factor activity	• Nonspecific inhibition of MMPs	• Clean, non-infected, recalcitrant chronic wounds

Table 105.3 Types of wound dressings. For additional details, see Chapter 145. MMPs, matrix metalloproteinases.

antimicrobial agents are divided into two major categories: antiseptics and antibiotics. Antiseptics have a broad antimicrobial spectrum as well as multiple microbial targets, but they are often toxic to host tissues. Topical antibiotics have specific cellular targets and a narrower spectrum of activity; they are not toxic to human cells but are more likely to induce bacterial resistance. Commonly used topical antibiotics include bacitracin, neomycin, mupirocin, retapamulin, gentamicin and fusidic acid. Topical antibiotics can cause allergic contact dermatitis, in particular neomycin and bacitracin. It is also preferable to avoid topical antimicrobials that have a systemic counterpart[21].

Commonly used antiseptics include hydrogen peroxide, chlorhexidine, iodine-based preparations (e.g. povidone-iodine, cadexomer iodine), and silver-releasing agents. Hydrogen peroxide and povidone-iodine have a broad antimicrobial spectrum with minimal resistance but may be cytotoxic. Cadexomer iodine is a complex of 0.9% elemental iodine plus cadexomer microbeads which are composed of a modified starch-based polymer. Upon absorption of exudate, the cadexomer beads swell and slowly release iodine into the wound bed, thus maintaining non-toxic iodine concentrations[22].

Silver is an effective antiseptic agent with broad-spectrum activity, including against methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and extended-spectrum β-lactamase producers. Resistance has rarely been reported, primarily with Gram-negative species[21]. Only the ionized form of silver (Ag^+) has antimicrobial properties, so exposure to wound fluid or exudate is required if the source is metallic silver[23]. Silver ions kill bacteria by damaging bacterial cell walls and intracellular and nuclear membranes as well as denaturing bacterial DNA, RNA and key enzymes (e.g. respiratory enzymes)[15,23]. Silver may also promote cellular proliferation and re-epithelialization by inducing the production of metallothionein by epidermal cells. Metallothionein increases zinc- and copper-dependent enzymes required for cellular proliferation and matrix remodeling[23]. Silver has been incorporated into various dressing products (e.g. gauzes, hydrocolloids, alginates, foams) in addition to creams, gels and barrier protectants which differ in their solubility and the rate at which silver ions are released into the wound bed[15]. Disadvantages of silver products include potential irritation, permanent blue–gray discoloration (localized argyria) and cost. Topical silver sulfadiazine has induced neutropenia in children which was reversible once the cream was discontinued[16].

Lastly, as chronic wounds may serve as a portal of entry for *Clostridium tetani*, it is recommended that the tetanus immune status of patients with chronic leg ulcers be assessed[23a].

Adjuncts to wound care

Compression

Compression therapy is a mainstay in the treatment of venous insufficiency. Compression stockings improve venous return, reduce edema, stimulate healthier granulation tissue within venous ulcers[15] and improve quality of life[15]. A Cochrane meta-analysis of 39 randomized controlled trials concluded that compression therapy increased ulcer healing rates as compared to no compression[24].

Elastic stockings, preferably with graduated compression, are available in a wide range of compressive pressures (15 to 60 mmHg), lengths and materials (Table 105.4). Lower levels of compression (20 to 30 mmHg) are sufficient for preventing mild edema, whereas higher levels of compression (30 to 40 mmHg) are required to control stasis dermatitis or lead to the healing of ulcers. Compression stockings also prevent the recurrence of venous ulcers once healed. Therefore, life-long use of compression is recommended for patients with a history of venous ulcers[5]. In addition to stockings, there are other forms of compression such as bandages and wraps, as outlined in Tables 105.5 and 105.6. Of note, surgical correction of superficial venous reflux (plus compression) does not improve ulcer healing but does reduce the recurrence of ulcers[25].

It is important to remember that compression therapy in patients with undiagnosed arterial insufficiency can lead to ulcer worsening, gangrene or even limb amputation. As many patients with venous disease have concomitant arterial insufficiency, clinically significant arterial disease must be excluded before prescribing compression therapy. The latter is also relatively contraindicated in patients with uncompensated congestive heart failure[15].

CLASSES OF COMPRESSION STOCKINGS

Class	Pressure at the ankle	Indication
I	20–30 mmHg	Simple varicose veins Mild edema Leg fatigue
II	30–40 mmHg	Moderate edema Severe varicosities Moderate venous insufficiency
III	40–50 mmHg	Severe edema Severe venous insufficiency Post-thrombotic lymphedema
IV	50–60 mmHg	Elephantiasis

Table 105.4 Classes of compression stockings. *Adapted from Phillips TJ. Current approaches to venous ulcers and compression. Dermatol Surg. 2001;27:611–21.*

Manual lymph drainage

Edema is a significant cause of delayed healing of venous ulcers. Identifying the cause of the edema is instrumental in choosing the appropriate therapy, which in turn is critical for ulcer resolution. However, even with identification and treatment of contributing factors (e.g. afterload reduction, diuretics), edema may be persistent.

Manual lymph drainage is a massage technique in which lymph conduits are contracted more frequently and lymphatic fluid is moved away from affected lymphedematous regions toward more centrally located, functioning lymph basins, thereby reducing edema volume. This manual drainage is employed during the early, intensive phase of lymphedema therapy and is combined with short-stretch compression bandaging applied immediately after treatment. The regimen also includes a series of exercises to increase lymphatic flow through functioning collateral pathways, skin care, and sometimes the use of intermittent pneumatic compression. This intensive, short-term therapy is referred to as "complete decongestive physiotherapy" and is followed by a maintenance phase that consists of skin care, elastic compression and exercise[26,27].

Topical negative pressure therapy

In topical negative pressure therapy, ideally performed using a vacuum-assisted closure (VAC) system, negative pressure is applied to hasten wound healing. It is used primarily for ulcers that are due to venous disease or diabetes. The system includes an open pore foam conduit (cut to the wound size) sealed with a semi-occlusive drape which is then attached to a vacuum source via a tube. When subatmospheric pressure (100–125 mm Hg) is applied to the foam–wound interface (continuously or intermittently), accumulated fluid is transferred to a canister. Topical negative pressure therapy promotes wound healing by creating mechanical forces that stimulate a biological response while maintaining a moist environment. It also removes exudate, reduces edema, increases local perfusion, decreases the bacterial count and enhances granulation tissue formation[15,28].

Before application, the wound must be debrided of necrotic tissue in order to prevent infection. Topical negative pressure therapy is contraindicated for ischemic wounds and ulcerated malignancies because it may cause necrosis of the wound edges and tumor growth, respectively. The foam should be changed every 48 to 72 hours. Sometimes, new granulation tissue grows into the foam, which can result in pain during foam changing. If this occurs, then the foam should be changed more frequently or a denser foam employed. In up to 25% of patients, there are complications such as pain, odor, periwound irritation or maceration, infection, bleeding and necrosis; most of these problems can be avoided with careful patient selection and skilled management[28,29].

Skin substitutes

Patients with recalcitrant chronic ulcers can sometimes benefit from autologous skin grafting, especially when the ulcers are due to venous disease (see Ch. 148). However, there has been an increase in the use of biological dressings and synthetic skin substitutes in such patients. Living skin substitutes are tissue-engineered products that contain a cellular component of autologous or allogeneic origin plus a biodegradable scaffold, and they serve as a replacement for the epidermis, dermis

TYPES OF COMPRESSION THERAPY		
Bandage	**Advantages**	**Disadvantages**
Elastic wraps	Inexpensive Can be reused	Often applied incorrectly by the patient Tend to unravel Do not maintain sustained compression Lose elasticity after washing
Self-adherent wraps	Self-adherent Maintain compression	Expensive Cannot be reused
Unna boot	Comfortable Protects against trauma Full maintenance of ambulatory outpatient status Minimal interference with regular activities Substitutes for a failing pump	Pressure changes over time Needs to be applied by well-trained physicians and nurses Does not accommodate highly exudative wounds
Four-layer bandage	Comfortable Can be left in place for 7 days Protects against trauma Maintains a constant pressure for 7 days because of the overlap and elasticity of the bandages Useful for highly exudative wounds	Needs to be applied by well-trained physicians and nurses Expensive
Graduated compression stockings	Reduce the ambulatory venous pressure Increase venous refilling time Improve calf pump function Different types of stockings accommodate different types of leg disorders Dressings underneath can be changed frequently	Often cannot monitor patient compliance Difficult to put on
Orthotic device	Adjustable compression Sustained pressure Easily put on and removed Comfortable	Expensive Bulky appearance
Compression pump	Augments venous return Improves hemodynamics and microvascular functions Enhances fibrinolytic activity Prevents postoperative thromboembolic complications in high-risk patients	Expensive Requires immobility for a few hours per day

Table 105.5 Types of compression therapy. *Adapted from Choucair M, Phillips TJ. Compression therapy. Dermatol Surg. 1998;24:141–8.*

CLASSES OF COMPRESSION BANDAGES	
Class	**Properties**
Class I	Lightweight and conforming Stretch and simple dressing retention properties
Class II	Also known as short stretch bandages Act like rigid, non-elastic bandages Used for light support
Class III • Class IIIA • Class IIIB • Class IIIC	 Light compression bandages Moderate compression bandages Extra-high performance Achieve 40 mmHg at the ankle Useful for: • Severe varicosities • Severe edema • Postphlebitic syndrome

Table 105.6 Classes of compression bandages.

or both. These skin mimetics provide temporary wound coverage, but serve primarily as a source for growth factors and extracellular matrix. Although effective in wound repair, their clinical use is still limited due to their high cost and complex technology (see Ch. 145)[30]. In general, these living skin substitutes are indicated for venous and diabetic ulcers.

There are also biological dressings that consist of just an extracellular matrix (i.e. they have no cellular component). Structural extracellular matrix components, such as collagen, fibronectin and proteoglycans, provide a temporary scaffold that supports cellular proliferation and migration. In addition, they contain cytokines, e.g. TGF-beta and bFGF, which promote wound healing. These dressings are also used for diabetic and venous ulcers.

Another approach is a bio-inspired artificial hydrogel matrix that utilizes natural enzymatic reactions to become bioactive. It is able to incorporate and then deliver biomolecules (e.g. MMPs, growth factors) and at the same time be degraded and remodeled by them, ultimately being replaced by newly formed tissue.

Topical and oral medications

Daily, short-contact application of topical tretinoin solution (0.05%) was reported to stimulate granulation tissue formation and healing of chronic leg ulcers[31]. Fonder et al.[15] also reported that application of small amounts of 0.025% tretinoin cream can induce neovascularization in ischemic wound beds.

Pentoxifylline, a drug that targets inflammatory cytokine release, leukocyte activation and platelet aggregation at the microcirculatory level, is occasionally a component of the treatment regimen for chronic venous insufficiency. Although evidence of a beneficial effect when the drug is used as monotherapy is largely lacking, pentoxifylline has been shown (at a dose of 1200 mg per day), in conjunction with compression therapy, to modestly improve ulcer healing as compared to compression plus placebo[32]. This effect has been attributed to the drug's fibrinolytic properties, antithrombotic effects, and/or ability to inhibit the production of proinflammatory cytokines.

LYMPHEDEMA

Lymphedema is the accumulation of lymph fluid within the interstitium that is due to a reduction in lymph drainage in the presence of *normal* capillary filtration. Lymphedema should be differentiated from edema which results from an imbalance between capillary filtration and lymph drainage.

Lymphedema can be primary or secondary (Table 105.7). Primary lymphedema can be further subdivided based on age at time of clinical presentation[33]. *Congenital lymphedema* usually appears before 1 year of age and is sporadic or familial (e.g. Nonne–Milroy disease; Fig. 105.8). Meige disease, a type of *lymphedema praecox*, is the most common form of primary lymphedema and it usually presents around puberty and more often affects girls. *Lymphedema tarda* usually presents after 35 years of age and is probably the result of an environmental

CAUSES OF LYMPHEDEMA	
Primary lymphedema	**Secondary lymphedema**
Congenital lymphedema (presents at birth or within first 1–2 years of life) • Congenital aplasia of the thoracic duct • Hypoplasia of peripheral lymphatics • Congenital abnormalities of the abdominal or thoracic lymphatics • Hereditary (Nonne–Milroy disease; type 1A) – AD; caused by *VEGFR3 (FLT4)* mutations in some families • Turner syndrome • Noonan syndrome	• Recurrent lymphangitis and cellulitis • Parasitic infections, e.g. filariasis • Lymph node dissection, e.g. for melanoma or breast cancer • Malignant obstruction, e.g. lymphoma, Kaposi sarcoma, retroperitoneal sarcoma • Radiation injury • Obesity • Surgical excisions, e.g. mastectomy, prostatectomy • Podoconiosis (exposure to mineral microparticles in volcanic soils) • Acne vulgaris and acne rosacea (midface) • Granulomatous disease
Lymphedema praecox (presents around puberty) • Meige disease (type II); lymphedema – distichiasis syndrome; yellow nail syndrome – AD; caused by *FOXC2* mutations in some families • Hypotrichosis–lymphedema–telangiectasia syndrome – AD or AR; caused by *SOX18* mutations	
Lymphedema tarda (presents after age 35 years)	

Table 105.7 Causes of lymphedema. In distichiasis, there is abnormal growth of eyelashes from the orifices of meibomian glands, leading to a double row of eyelashes. AD, autosomal dominant; AR, autosomal recessive.

Fig. 105.8 Bilateral primary lymphedema due to Nonne–Milroy disease.

trigger such as trauma or infection superimposed on inherently weakened lymphatics.

Common causes for secondary or acquired lymphedema are malignancy, radiation and surgical lymph node dissection, as well as chronic venous insufficiency, trauma, recurrent cellulitis, filariasis and obesity (Fig. 105.9). Filariasis, due to infection of the lymphatics by the nematode *Wuchereria bancrofti*, is the most common cause of lymphedema in low-income tropical and subtropical countries.

Clinically, lymphedema begins as painless pitting edema of the dorsal aspect of the foot which then progresses proximally. Over time, the skin becomes indurated due to fibrosis, and the affected areas are prone to ulceration and secondary infection. Recurrent infections lead to worsening of the lymphedema and a vicious cycle is established[26].

Elephantiasis nostras verrucosa is a complication of chronic lymphedema and most commonly affects the feet and distal lower extremities. In addition to profound non-pitting edema and progressive fibrosis of the dermis and subcutaneous tissue, there are verrucous changes with papillomatosis and hyperkeratosis (Fig. 105.10). The skin acquires a mossy or cobblestone appearance and discrete firm fibrous papules may develop. Colonization with bacteria and fungi often results in ulcers becoming crusted and malodorous[34].

Elephantiasis nostras verrucosa is difficult to treat. Compression stockings, pneumatic pumps and massage are used to decrease lymph

Fig. 105.9 Lymphedema secondary to morbid obesity associated with myxedema.

Fig. 105.10 Elephantiasis nostras verrucosa. The patient had both lymphedema and venous insufficiency.

accumulation. Topical keratolytics or humectants, such as salicylic acid and urea, may improve the hyperkeratosis[34]. Oral retinoids have been reported to be of benefit for both the verrucous changes and the lymphedema[35]. Surgical debridement can be considered for patients who do not respond to more conservative therapies[36].

The differential diagnosis includes lipedema[37], in which there is an abnormal deposition of subcutaneous fat with sparing of the feet (Fig. 105.11), and obesity-associated lymphedematous mucinosis, where there can be dermal mucin deposition in the absence of thyroid disease.

ARTERIAL ULCERS

Peripheral arterial disease (PAD) is a common manifestation of atherosclerosis. Cigarette smoking and diabetes mellitus are the strongest risk factors for the development of PAD, with hypertension, dyslipidemia and hyperhomocysteinemia representing additional risk factors[38]. Up to 25% of patients with leg ulcers have PAD, and a significant number of patients have a combination of arterial and venous insufficiencies[15].

Pathogenesis

A lack of blood perfusion decreases tissue resilience and leads to tissue necrosis; it also impedes wound healing by reducing the supply of oxygen, nutrients and soluble mediators involved in the repair process. Although PAD alone infrequently precipitates ulceration, arterial insufficiency plays a major role in delayed wound healing and complications

Fig. 105.11 Lipedema. This middle-aged woman has bilateral "stovepipe" enlargement of the legs and minimal involvement of the feet. Note the sharp demarcation between normal and abnormal tissue at the ankle, referred to as the "cuff sign". *Courtesy, Jean L Bolognia, MD.*

DETERMINATION AND INTERPRETATION OF THE ANKLE–BRACHIAL INDEX

- With the patient in a supine position, the systolic blood pressure is measured in the:
  - brachial arteries (right and left)
  - dorsalis pedis and posterior tibial arteries (right and left)
- The ABI is determined by:

$$\frac{\text{the highest of the systolic pressures from the dorsalis pedis or posterior tibial arteries}}{\text{the higher of the brachial artery systolic pressures}}$$

- Interpretation of the ABI:
  - 0.91–1.30 = normal range
  - >1.30 = suggests incompressible tibial arteries due to medial calcification (diabetes mellitus, chronic renal insufficiency)
  - <0.9 = indicative of peripheral artery disease (PAD)
  - 0.41–0.90 = mild to moderate PAD
  - 0.00–0.40 = severe PAD

Table 105.8 Determination and interpretation of the ankle–brachial index (ABI).

Fig. 105.12 Arterial ulcer. The punched-out appearance and surrounding smooth shiny skin are common features.

Fig. 105.13 Cholesterol emboli. Ischemia of the toes and necrosis with early ulcer formation.

including gangrene. Ischemic foot ulcers are often precipitated by trauma in a patient with relatively mild symptoms of arterial insufficiency. In such an individual, the degree of skin perfusion is sufficient to maintain cutaneous integrity, but is not adequate enough to support proper wound healing. In such a setting, the ulcer will inevitably progress into a chronic wound or gangrene unless perfusion is restored[39].

Clinical Manifestations

Although most patients with significant PAD are symptom-free, intermittent claudication, defined as leg pain induced by ambulation and relieved by resting, is the earliest and the most common presenting symptom of PAD of the lower extremities. With disease progression, patients begin to complain of pain at rest, especially when the legs are elevated in bed at night, which is ameliorated by dependency. While symptoms of claudication are usually localized to the calf or the thigh, pain at rest is often felt in the feet. In advanced stages of PAD, the reduction in cutaneous blood supply may lead to ischemic ulceration and gangrene, and this may necessitate amputation[40].

Arterial ulcers are usually round with a sharply demarcated border and are characterized by an absence of bleeding (Fig. 105.12). These wounds typically occur on the distal lower extremities, often over bony prominences (e.g. the first and fifth metatarsal heads). The surrounding skin may be hairless, shiny and atrophic. Wound pain is often significant and is exacerbated by limb elevation. Additional manifestations of impaired arterial perfusion to the foot include diminished or absent pedal pulses, cool feet, pallor of the foot with elevation of the leg and then subsequent redness with lowering (dependent rubor), sluggish refilling of toe capillaries, thickened nails and absence of toe hair (see Table 105.1)[15,39].

Laboratory Evaluation

The ankle–brachial pressure index, more commonly referred to as the ankle–brachial index (ABI), is a simple, non-invasive test that is widely used for diagnosis of PAD and to assess its severity. The ABI is calculated by dividing the systolic blood pressure in the ankle by the systolic blood pressure in the arm while the patient is in a resting supine position (Table 105.8). A decrease in arterial blood pressure at the ankle (relative to the central blood pressure) implicates arterial stenosis at any point between the aorta and the ankle[41]. The normal range for the ABI is 0.91 to 1.30, with a reading <0.9 being indicative of PAD[42].

Depending on the patient's presentation and symptoms, further non-invasive imaging techniques may be employed, including duplex ultrasound, computed tomography angiography (CTA), and magnetic resonance angiography (MRA). Both CTA and MRA produce images of vascular structures in cross-sectional slices that can be reconfigured into three-dimensional angiographic images. CTA is less expensive than MRA, with higher spatial resolution. However, CTA involves ionizing radiation and the use of iodinated contrast material. The gold standard for diagnosis and evaluation of PAD is invasive digital subtraction angiography, which can also be used to guide endovascular intervention[38].

Differential Diagnosis

Patients with PAD can also develop cutaneous ulcers due to cholesterol emboli (Fig. 105.13) and risk factors include arterial or coronary catheterization and anticoagulation (see Ch. 23). In Buerger's disease, ulcers occur distally on both the upper and lower extremities, with

smoking as a risk factor. Additional disorders to consider are in Figure 105.1, including diffuse dermal angiomatosis (see below).

Treatment

Arterial ulcers can benefit from restoration of peripheral arterial blood flow, either by surgical reconstruction (e.g. femoral popliteal bypass) or by less invasive endovascular interventions (e.g. femoral angioplasty)[15]. In principle, local treatment of arterial ulcers is similar to that of other types of skin ulcers, with two major exceptions: (1) sharp debridement should be performed very cautiously or avoided in order to prevent further necrosis and ulcer enlargement; and (2) VAC therapy should be avoided as it can lead to worsening of the ulcer.

DIABETIC (AND NEUROPATHIC) ULCERS

Patients with diabetes mellitus have a 12–25% lifetime risk of developing a foot ulcer. These foot ulcers constitute a major medical and economical burden, with a substantial morbidity and impaired quality of life. Approximately 15% of diabetic patients with foot ulcers will eventually undergo a lower extremity amputation. The rising incidence of both type 1 and type 2 diabetes has made diabetic foot ulcers the most important risk factor for lower extremity amputation in high-income countries[43,44].

Pathogenesis

The etiology of diabetic ulcer formation is multifactorial. Although ischemia, trauma and infection have traditionally been incriminated as underlying pathogenic factors, nowadays diabetic neuropathy is considered to be the major cause of foot ulcers in diabetic patients[45].

Diabetic neuropathy typically involves the sensory, motor and autonomic nerves, with *sensory* neuropathy substantially impairing the patient's perception of touch, deep pressure, temperature and joint position. With the loss of protective sensation, foot trauma is unrecognized and this can lead to ulceration. Peripheral *motor* neuropathy results in weakness and atrophy of the intrinsic muscles of the feet, producing altered biomechanics and structural deformities that, in the presence of sensory neuropathy, increase the risk for skin injury and ulceration from repetitive mechanical stress. Continuous pressure to the skin overlying bony prominences typically results in the formation of a thick, keratotic plaque (callus), which eventually breaks down and ulcerates[15,45]. *Autonomic* neuropathy also plays a role because it can lead to a loss of sweating, with the resultant dry skin being susceptible to cracks and fissures that serve as a portal of entry for bacteria[45]. In addition, a potential consequence of autonomic neuropathy is arteriovenous shunting within the skin microcirculation which results in decreased cutaneous perfusion and oxygen saturation, thus contributing to ulceration and an impaired response to infection[44]. Moreover, this abnormal vascular autoregulation, coupled with sensory neuropathy, contributes to the development of Charcot joints (degenerative arthropathy), further adding to the risk of ulceration from an abnormal distribution of pressure forces and foot deformities[46].

Diabetes is also associated with an increased risk of developing PAD, which characteristically affects vessels between the knee and the ankle[43]. Although microcirculatory dysfunction occurs early on in the course of diabetes, it is primarily atherosclerotic macrovascular disease that accounts for ischemic complications in these patients[44]. In general, diabetic foot ulcers are not purely related to vascular occlusion; rather, mechanical damage that typically occurs to the insensate foot, in the presence of a decreased blood supply, rapidly results in ischemic ulcers. PAD also contributes to an altered response to foot infections and poor wound healing. The combination of a depressed immune response plus a decrease in cutaneous blood supply plays a key role in the development of cellulitis, abscesses and osteomyelitis, all of which increase the risk of limb amputation[46].

Occasionally, patients with diabetes develop ulcerations within lesions of necrobiosis lipoidica as well as ulcers due to streptococcal infections.

Clinical Features

Diabetic ulcers are usually located on pressure points and bony prominences such as the metatarsal heads, great toes and heels. They often arise within exuberant, moist, malodorous calluses (mal perforans) (Fig. 105.14). In the absence of peripheral atherosclerotic disease, the diabetic foot is warm, with good color and palpable pulses, but with decreased sensation. Foot deformities are frequently present, e.g. hammer toes, claw toes, and a high or flattened arch (Charcot foot).

Fig. 105.14 Neuropathic ulcers (mal perforans) in patients with diabetes mellitus and peripheral neuropathy. Common locations are the plantar surface of the heel (**A**) and the great toe (**B**). Note the thick rim of callus.

Laboratory Evaluation

Because diabetic ulcers are heterogeneous in nature, a thorough evaluation of the patient is crucial in determining the underlying causes. More specifically, peripheral neuropathy can be detected via a neurologic examination of the lower extremities that includes the use of a 10 g monofilament to test for sensation[47]. More invasive testing, i.e. nerve conduction studies/electromyography, is sometimes required. The degree to which vascular perfusion is compromised can be assessed via determination of the ABI (see above).

A complete blood count, ESR, C-reactive protein level and blood glucose level are obtained when assessing for a possible associated infection. Of note, sometimes an elevated blood glucose level is the only sign of infection. Microbial cultures (bacterial, mycobacterial and fungal) should be obtained from the wound bed. Although swabs are often used, deep tissue specimens, obtained aseptically, are preferable[47].

Diagnostic imaging, including plain radiographs of both feet, bone scintigraphy, MRI, CT and sometimes ultrasound, is used to better define the presence or absence of a bone or deep soft tissue infection. Of these, MRI is the most accurate test for diagnosing osteomyelitis. If osteomyelitis is suspected, a bone biopsy processed for culture and histology is the gold standard[43,45].

Treatment

Conservative treatment of diabetic foot ulcers consists of providing a proper wound healing environment, eradication of infection, and avoidance of repetitive trauma by alleviating the mechanical load on ulcers

(off-loading). Methods of off-loading include bed rest and the use of a wheelchair, crutches, total contact casting, cast walkers, felted foam, half-shoes or therapeutic shoes. Total contact casting is considered the best approach as it enables pressure redistribution and continuous off-loading of the ulcer area. The inability of the patient to remove the cast ensures compliance and reduces the level of activity[47,48]. However, total contact casting is somewhat impractical because it is expensive and requires skill and experience. In addition, as the edema subsides, cast changing and size adjustments are often required (usually twice a week or more often). Total contact casting is contraindicated if the wound is infected or has a significant exudate and it can lead to new ulcerations over bony prominences[45].

Another approach to off-loading is the use of specialized shoes that reduce pressure about the forefoot and heel and multilayered insoles that enhance shock absorption[45]. Half-shoes assist in off-loading forefoot plantar ulcers as they support only the rear and mid foot, while the forefoot is left suspended in the air[47].

Initial wound management consists of cleansing the wound and proper debridement of any necrotic material, including the callus; the latter can contribute to increased pressure on the insensate foot. In addition, debridement promotes wound healing at the cellular level by removing excess extracellular matrix, thus liberating trapped growth factors and facilitating cell migration[46]. Moist wound healing is recommended as with other types of chronic ulcers but avoidance of maceration of surrounding skin is of particular importance.

Apart from standard therapies (see above), hyperbaric oxygen has been shown to be of specific benefit to patients with diabetic foot ulcers. While it is unclear to what extent it benefits other types of ulcers[49], hyperbaric oxygen therapy has been shown to be effective in the treatment of diabetic foot ulcers, with a decrease in healing time and amputation rate. Oxygen (100%) at supra-atmospheric pressures is intermittently inhaled, either in a full-body (monoplace) chamber or in a multiplace chamber via a gas mask. In theory, tissue hypoxia impairs wound healing and hyperbaric oxygen therapy leads to an increase in the blood oxygen level within the wound. In addition, there is reallocation of blood flow to hypoxic areas due to hyperoxic vasoconstriction of surrounding normal tissue[50]. Side effects include oxygen toxicity to the brain (e.g. seizures) and lungs and barotrauma to the lungs, ears, sinuses and eyes (transient myopia)[15].

As endogenous growth factors are often degraded or trapped within chronic wounds, genetically engineered exogenous growth factors have been used to try to enhance wound healing. Becaplermin gel (Regranex®) is recombinant platelet-derived growth factor whose biologic activity is similar to its endogenous counterpart, with stimulation of granulation tissue production and release of other growth factors important to wound repair. It is the only growth factor approved for use in chronic neuropathic diabetic ulcers[15]. In the setting of best wound care, becaplermin gel has been shown to increase healing rates and shorten healing time of diabetic ulcers[51]. However, in routine clinical practice, becaplermin has not been as successful and it has an FDA black box warning of an increased risk of cancer mortality (when exposed to three or more tubes). More recently, strategies have focused on improving growth factor activity and protecting these factors from degradation[30].

Living skin equivalents (e.g. Apligraf™, Dermagraft™) are bioengineered products that act as delivery systems for growth factors and extracellular matrix (see Ch. 145)[52–54]. Both are indicated for recalcitrant diabetic foot ulcers that have no exposed muscle, bone or tendon, are not infected and have had aggressive debridement.

Prevention

Preventing wound recurrence is of critical importance. The risk of ulceration and/or amputation is increased in patients who have had diabetes for ≥10 years, are male, have poor glucose control, or have target organ complications. Foot-related conditions that are associated with an increased risk of amputation are peripheral neuropathy, altered biomechanics, evidence of increased pressure, foot deformity, PAD, history of an ulcer or previous amputation, and severe nail pathology[55]. Tight control of glucose levels is required in order to prevent diabetic complications that are due to microvascular changes, as the latter predispose the patient to neuropathy, ischemia and infection. Lower HgbA1c values are associated with a decrease in healing times for leg and foot ulcers[56]. Smoking cessation and control of low-density lipoprotein (LDL) and total cholesterol levels are also important in the prevention of atherosclerotic vascular disease.

All diabetic patients should receive an annual foot examination to assess neurologic and vascular status, biomechanics, skin integrity, and the presence and types of foot deformities. Patients with significant risk factors for ulcer formation should be evaluated more frequently. Education regarding daily foot care that includes inspection for any scratch, blister or erythema, daily washing in warm water, appropriate footwear selection (e.g. avoiding pointed shoes), skin moisturizing, and treatment of nail and foot fungal infection should be provided.

ULCERS DUE TO PHYSICAL FACTORS

Any form of mechanical trauma to the skin can result in the formation of an ulcer if factors that compromise the skin's ability to recover from physical insults are present. The most common form of physical injury which leads to ulceration is prolonged pressure due to immobilization. The resultant ulcer is commonly referred to as a *pressure ulcer* or *decubitus ulcer* (decubitus means lying down in Latin). These ulcers are caused by unrelieved pressure to soft tissues compressed between a bony prominence and an external surface. The most common bony prominences involved are the sacrum, ischial tuberosities, greater trochanters, heels and lateral malleoli[57] (Fig. 105.15).

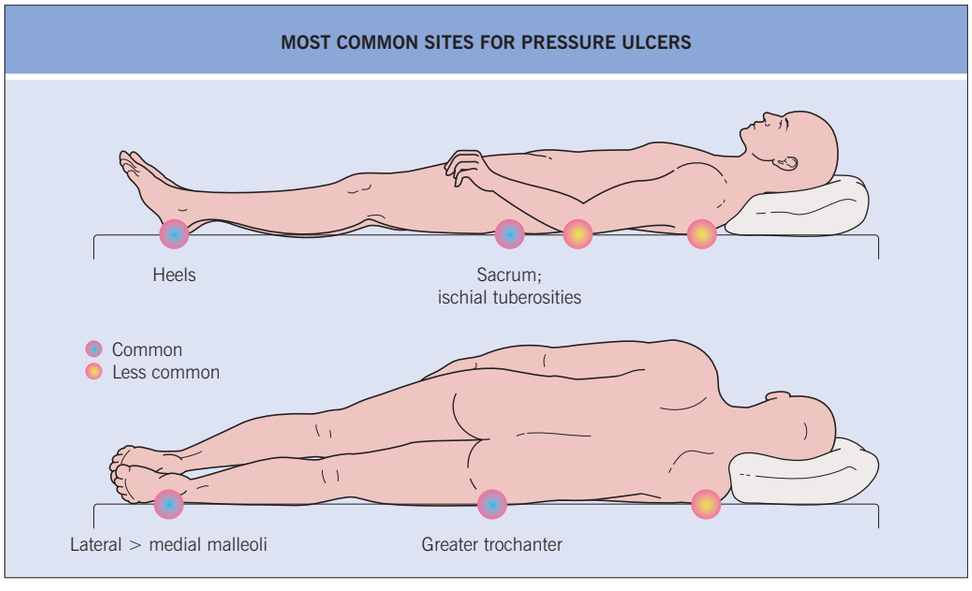


Fig. 105.15 Most common sites for pressure ulcers.

Fig. 105.16 Pressure ulcer (stage III) over the sacral area.

Fig. 105.17 Black eschar of the heel at site of pressure necrosis.

Approximately 1.5–3 million people in the US have pressure ulcers with an annual cost of treatment of up to $5 billion[57]. It has also been estimated that 10% of hospitalized patients and 25% of nursing home residents have pressure ulcers, with most developing during the first few weeks of hospitalization. An estimated 70% of pressure ulcers occur in patients over 70 years of age; 95% are located on the lower portion of the body: 65% in the pelvic girdle area (Fig. 105.16) and 30% on the lower limbs (Fig. 105.17). Risk factors that predispose to the development of pressure ulcers include prolonged immobility, sensory deficit, circulatory disturbance and poor nutrition[57].

Pathogenesis

Four major etiologic factors have been identified as playing an important role in the development of pressure ulcers: external pressure, shearing forces, friction and moisture.

Interstitial pressures >32 mmHg (normal capillary pressure range = 12–32 mmHg) usually compromise oxygenation and microcirculation. There is an inverse time–pressure curve, with slow ulcer formation at low pressures and rapid ulcer formation at high pressures (≥70 mmHg). The length of continuous exposure of the skin to pressure is also of critical importance, thus explaining why intermittent relief of the pressure can prevent ulcer formation. Because subcutaneous tissues are most susceptible to the damaging effects of prolonged exposure to pressure, deep tissue trauma can occur with relatively little superficial damage that would alert caregivers to the extent of tissue injury[57].

Shearing forces result from the sliding and relative displacement of two apposing surfaces. Although externally applied pressure is more effective than shearing forces alone in reducing skin arteriolar blood flow, these two factors can combine to enhance vascular occlusion. When the head of a supine patient is raised more than 30°, shearing forces occur in the sacral and coccygeal areas. Sliding of the torso transmits pressure to the sacrum and deep fascia, as the outer sacral skin is fixed because of friction with the bed. Vessels within the deeper portion of the superficial fascia angulate and thrombose, which manifests clinically as undermining of the ulcer[57].

Friction is often associated with shearing and it reflects the degree of resistance generated when two surfaces move across each other. When a bedridden patient is dragged across the bed sheets, friction is produced. Damage to the protective stratum corneum enhances ulcer formation by compromising the skin barrier.

Moisture results from perspiration due to fevers and from urine and feces. It has been shown to increase the risk of pressure ulcer formation fivefold[57].

Clinical Features

Pressure ulcers are usually classified according to a four-stage system designed by the National Pressure Ulcer Advisory Panel (NPUAP) (Fig. 105.18). Of note, the ulcers do not necessarily progress sequentially from stage I to stage IV, nor do they necessarily heal from stage IV to stage I[58].

- *Stage I*: non-blanchable erythema of intact skin which heralds skin ulceration. For darker-skinned individuals, warmth, edema, discoloration of the skin and induration may serve as indicators of impending ulceration[57,58].
- *Stage II*: partial-thickness skin loss involving the epidermis, dermis or both. This superficial lesion presents as an erosion, blister or shallow ulcer[57,58].
- *Stage III*: full-thickness skin loss with damage to the subcutaneous tissue, extending down to (but not including) the underlying fascia. This deep lesion presents as a crater-like ulcer and sometimes involves adjacent tissue[57,58].
- *Stage IV*: full-thickness skin loss and extensive tissue necrosis with destruction extending to muscle, bone, or supporting structures such as tendons or joint capsules. Undermining or sinus tracts can be present[57,58].

As mentioned previously, a major limitation in the clinical classification of pressure ulcers stems from the fact that extensive deep tissue damage may be accompanied initially by minimal superficial manifestations. Adequate evaluation may also be hampered by the presence of an eschar, which should be debrided for full assessment[57].

Pathology

When the diagnosis is in doubt or when a secondary malignancy is suspected in the setting of a longstanding lesion, histologic examination is indicated. When there is *blanchable* erythema clinically, the superficial dermal capillaries and venules are dilated. Mild to moderate edema within the papillary dermis is seen in association with a mild perivascular lymphocytic infiltrate. The epidermis, pilosebaceous structures and reticular dermis remain normal. At the stage of *non-blanchable* erythema, engorgement of capillaries and venules with red blood cells, platelet thrombi, and hemorrhage are observed in the papillary dermis. Although the epidermis still appears normal, sweat gland and subcutaneous fat degeneration is often present[57]. Subepidermal separation can occur with formation of a subepidermal bulla. In early ulcers, the epidermis is lost and acute inflammation of the papillary and reticular dermis is seen. Chronic ulcers have a diffusely fibrotic dermis with a loss of adnexa. The surface may have a hemorrhagic crust containing acute inflammatory cells or a thin zone of coagulation necrosis. In the black eschar stage, full-thickness destruction of the skin occurs. General dermal architecture is preserved, but there is obliteration of cellular details.

Treatment

As a rule, pressure ulcers are preventable. The mainstay of prevention is relief of pressure on the skin. This can be accomplished by frequent

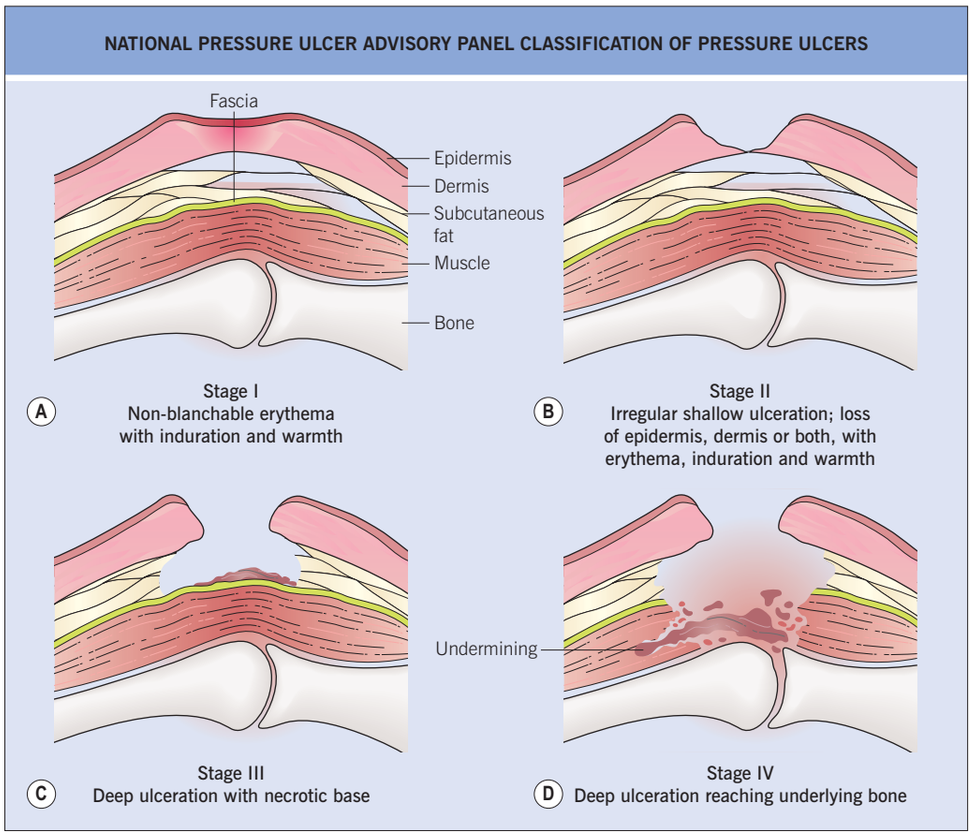


Fig. 105.18 National Pressure Ulcer Advisory Panel classification of pressure ulcers. A Stage I: non-blanchable erythema of intact skin. This lesion is the heralding sign of impending skin ulceration. For darker-skinned individuals, other signs may be indicators and include warmth, edema, discoloration of the skin, and induration. **B** Stage II: partial-thickness skin loss involving the epidermis, dermis or both. This superficial lesion presents as an abrasion, blister or shallow crater. **C** Stage III: full-thickness skin loss, in which subcutaneous tissue is damaged or necrotic and may extend down into, but not including, the underlying fascia. This deep lesion presents as a crater and sometimes involves adjacent tissue. **D** Stage IV: full-thickness skin loss and extensive tissue necrosis, destruction to muscle, bone, or supporting structures such as a tendon or joint capsule. Undermining or sinus tracts can be present.

Fig. 105.19 Additional causes of ulcers. A Systemic sclerosis with an ulcer of the fingertip. **B** Multiple ulcers secondary to sickle cell anemia.

position changes in addition to use of a variety of support surfaces to relieve pressure; the latter include air- or liquid-filled flotation devices, foam products, and pillows or foam wedges as positioning devices. Adequate nutrition, education, pain management and psychosocial support are also important interventions. Causes of immobility and systemic conditions that interfere with wound healing or decrease tissue perfusion must be addressed, including congestive heart failure, diabetes and/or spastic paresis.

The general principles of ulcer and chronic wound care discussed previously also apply to pressure ulcer management. Briefly, debridement may be accomplished via mechanical, enzymatic and/or autolytic means. Wounds should be cleansed as non-traumatically as possible, and normal saline for irrigation is preferred rather than cytotoxic agents such as hydrogen peroxide or povidone-iodine. As always, bacterial colonization and infection must be controlled. Dressings should provide a moist, but not macerated, environment and occlusive dressings are often utilized.

In general, stage I, II and III pressure ulcers are more likely to heal with local therapy, whereas stage IV ulcers, particularly those over the ischial tuberosities, often require surgical intervention. Adjuvant therapies such as laser, ultrasound, hyperbaric oxygen, and UV irradiation are investigational and to date cannot be considered as standard of care. The

EVALUATION FOR HYPERCOAGULABILITY			
Disorder	**%***	**Screening tests**	**Potential confounding conditions**
		INHERITED	
Factor V Leiden	5	Activated protein C (APC) resistance†	Warfarin, heparin, OCP, pregnancy, ↑ factor VIII level, lupus anticoagulant†
	5	Factor V Leiden mutation (AD)	–
Prothrombin G20210A	2	Prothrombin G20210A mutation (AD)	–
Hyperhomocysteinemia	>5	↑ Homocysteine level (may have homozygous *MTHFR* C677T mutation > heterozygous *CBS* mutation)	Deficient folate, B_{12} or B_6; older age, smoking
Protein C deficiency	0.3	↓ Protein C activity (AD)	Warfarin, OCP, pregnancy, liver disease, ↑ factor VIII level, lupus anticoagulant
Protein S deficiency	0.05	↓ Free protein S antigen level and/or activity (AD)	Warfarin, OCP, pregnancy, liver disease, ↑ factor VIII level, lupus anticoagulant, acute thrombosis
Antithrombin III deficiency	0.1	↓ Antithrombin III activity (AD)	Heparin, liver disease, acute thrombosis
Excess factor VIII	10	↑ Factor VIII level	Acute phase response, OCP, pregnancy, old age
Excess fibrinogen	ND	↑ Fibrinogen level	Acute phase response, pregnancy, smoking, older age
Dysfibrinogenemia	ND	↓ Functional fibrinogen; ↑ thrombin time	Recent birth, liver disease
Excess factor IX or XI	ND	↑ Factor IX or XI level	Warfarin (factor IX)
Plasminogen deficiency	ND	↓ Plasminogen	–
Excess plasminogen activator inhibitor-1 (PAI-1)	ND 10	↑ PAI-1 *PAI* 4G/4G polymorphism	Wide range of normal values
Excess lipoprotein (a)	10	↑ Lipoprotein (a) level	–
Tissue factor pathway inhibitor (TFPI)	10	↓ TFPI	–
Thrombin-activatable fibrinolysis inhibitor	ND	↑ Thrombin-activatable fibrinolysis inhibitor	–
Thrombomodulin deficiency	ND	↓ Thrombomodulin	–
		ACQUIRED	
Lupus anticoagulant‡	ND	↑ RVVT (dilute), sensitive PTT, or kaolin clotting time§	Warfarin, heparin
Anticardiolipin antibodies‡	ND	IgG or IgM anticardiolipin antibodies at moderate–high levels, on ≥2 occasions ≥6 weeks apart	Various infectious diseases
Cryoglobulinemia, type I	ND	Type I cryoglobulins present	–
Anti-β_2-glycoprotein I antibodies‡	ND	Anti-β_2-glycoprotein I antibodies present	–
Cryofibrinogenemia	ND	Cryofibrinogens present	Acute phase response

*Approximate percentage of general population with the defect.
†Factor V Leiden accounts for ~95% of patients with APC resistance when the latter is assessed by "second generation" assays, which are not limited by most potential confounding conditions.
‡Antiphospholipid antibodies.
§Confirmed by: (1) failure to correct the prolonged coagulation time in mixing studies; and (2) correction with the addition of excess phospholipids.

Table 105.9 Evaluation for hypercoagulability. Shaded areas represent first-tier screening tests. The initial laboratory evaluation should also include a complete blood count with differential and platelet count, examination of a peripheral blood smear, ESR, activated partial thromboplastin time (PTT), and hepatic and renal function panels. Testing for antineutrophil cytoplasmic antibodies (ANCA) can be considered for patients with retiform purpura, as ANCA-positive vasculitides occasionally present with minimally inflammatory lesions. Additional inherited causes of hypercoagulability include polymorphisms in the genes encoding the endothelial protein C receptor, the protein Z-dependent protease inhibitor, and E-selectin. AD, autosomal dominant; CBS, cystathionine β-synthase; MTHFR, methylenetetrahydrofolate reductase; ND, not determined; OCP, oral contraceptive pills; RVVT, Russell viper-venom time.

application of growth factors, cultured keratinocyte grafts and skin substitutes is promising, but these are also still in the investigational stage.

OTHER CAUSES OF SKIN ULCERATION

Diffuse Dermal Angiomatosis

Diffuse dermal angiomatosis is a rare manifestation of vascular atherosclerosis. There is rapid development of one or several violaceous, ill-defined plaques, often with central ulceration. The lesions are typically painful and are usually located on the lower extremities, but they may appear elsewhere (e.g. breast, forearm). Histologically, a diffuse interstitial proliferation of CD31-positive endothelial cells is present within the papillary and reticular dermis, with focal formation of small vascular channels. Cytologic atypia and atypical mitoses are absent.

Interventions to correct the underlying PAD, such as femoral popliteal bypass surgery or femoral artery angioplasty, lead to rapid resolution. Less often, lesions resolve without therapy[59].

Hematologic Disorders

Anemia is a major and often unrecognized cause for delayed wound healing. It prevents proper tissue oxygenation. In addition, some forms of anemia are associated with a marked tendency for ulcer formation, such as the hemoglobinopathies (Fig. 105.19)[60]. Hematologic malignancies are also associated with ulcerative processes including pyoderma gangrenosum, vasculitis and cryoglobulinemia (type I). Clotting abnormalities can play a direct role in the formation of ulcers (e.g. antiphospholipid antibody syndrome)[57,58], as well as serving as a predisposing factor for more common types of cutaneous ulcerations such as venous ulcers[61,62]. Table 105.9 summarizes the recommended evaluation when hypercoagulability is suspected.

Additional Causes

A variety of physical, inflammatory, infectious, metabolic and inherited disorders are also associated with cutaneous ulceration and they are discussed elsewhere in the textbook (Table 105.10).

ADDITIONAL CAUSES OF CUTANEOUS ULCERATION		
Cause	**Favored anatomic site**	**Location of review**
	PHYSICAL	
Burns – thermal, electrical, chemical	Site of exposure	Chapters 15, 16, 88
Cold injury (e.g. frostbite)	Acral	Chapter 88
Radiation (e.g. orthovoltage)	Site of exposure	Chapter 139
	INFLAMMATORY	
Vasculitis (small and medium-sized vessels, primary and secondary)	Lower extremities	Chapter 24; Fig. 105.1
Pyoderma gangrenosum	Lower extremities, sites of trauma	Chapter 26
Behçet's disease	Lower extremities	Chapter 26
	VASCULAR	
Raynaud's phenomenon and systemic sclerosis	Digital, extensor surface of joints	Chapter 43
	INFECTIOUS	
Bacterial (e.g. *Streptococcus* spp., *Treponema* spp.), mycobacterial, viral (e.g. chronic HSV), fungal, parasitic	Exposed sites Pressure sites in the case of leprosy and tertiary syphilis*	Chapters 74–83; Fig. 105.1
	BITES AND STINGS	Chapter 85
	NEOPLASTIC	
BCC, SCC > metastases or other primary cutaneous carcinomas	For BCC and SCC, sites of chronic sun exposure For SCC, chronic ulcers, scars, sites of chronic inflammation or oncogenic HPV infection	Chapters 108, 120, 122
	METABOLIC	
Examples: calcinosis cutis, calciphylaxis, gout	Varies from juxta-articular (calcinosis cutis, gout) to "fatty" areas (calciphylaxis)	Chapters 48, 50
	GENODERMATOSES	
Examples: Adams–Oliver syndrome, prolidase deficiency, laryngo-oculo-cutaneous syndrome, familial tumoral calcinosis, Werner syndrome, Flynn–Aird syndrome, chilblain lupus (*TREX1* mutations), Klinefelter syndrome	Varies from scalp due to aplasia cutis congenita to lower extremity	Chapters 41, 50, 63, 64; Fig. 105.1
	DRUGS	
Examples: hydroxyurea, methotrexate, interferon (IFN), anticoagulants	Varies from lower extremities (hydroxyurea) to sites of injection (IFN) to "fatty" areas (warfarin)	Chapters 21, 23
	PHOTODAMAGE	
Erosive pustular dermatosis	Usually hairless scalp, but occasionally lower extremity	Chapter 87
*Due to neuropathy.		

Table 105.10 Additional causes of cutaneous ulceration. In addition to lower extremity ulcers, patients with prolidase deficiency develop diffuse telangiectasias, dermatitis, lymphedema and manifestations of systemic lupus erythematosus. BCC, basal cell carcinoma; HPV, human papillomavirus; HSV, herpes simplex virus; SCC, squamous cell carcinoma.

REFERENCES

1. Lazarus GS, Cooper DM, Knighton DR, et al. Definitions and guidelines for assessment of wounds and evaluation of healing. Arch Dermatol. 1994;130:489–93.
2. Beebe-Dimmer JL, Pfeifer JR, Engle JS, Schottenfeld D. The epidemiology of chronic venous insufficiency and varicose veins. Ann Epidemiol. 2005;15:175–84.
3. Bergan JJ, Schmid-Schonbein GW, Smith PD, et al. Chronic venous disease. N Engl J Med. 2006;355:488–98.
4. Valencia IC, Falabella A, Kirsner RS, Eaglstein WH. Chronic venous insufficiency and venous leg ulceration. J Am Acad Dermatol. 2001;44:401–21.
5. Raju S, Neglen P. Clinical practice. Chronic venous insufficiency and varicose veins. N Engl J Med. 2009;360:2319–27.
6. Mekkes JR, Loots MA, Van Der Wal AC, Bos JD. Causes, investigation and treatment of leg ulceration. Br J Dermatol. 2003;148:388–401.
7. Browse NL, Burnand KG. The cause of venous ulceration. Lancet. 1982;2:243–5.
8. Falanga V, Eaglstein WH. The "trap" hypothesis of venous ulceration. Lancet. 1993;341:1006–8.
9. Thomas PR, Nash GB, Dormandy JA. White cell accumulation in dependent legs of patients with venous hypertension: a possible mechanism for trophic changes in the skin. Br Med J (Clin Res Ed). 1988;296:1693–5.
10. Raffetto JD. Dermal pathology, cellular biology, and inflammation in chronic venous disease. Thromb Res. 2009;123(Suppl 4):S66–71.
11. Wall IB, Moseley R, Baird DM, et al. Fibroblast dysfunction is a key factor in the non-healing of chronic venous leg ulcers. J Invest Dermatol. 2008;128:2526–40.
12. Clark RA. Oxidative stress and "senescent" fibroblasts in non-healing wounds as potential therapeutic targets. J Invest Dermatol. 2008;128:2361–4.
13. Barron GS, Jacob SE, Kirsner RS. Dermatologic complications of chronic venous disease: medical management and beyond. Ann Vasc Surg. 2007;21:652–62.
14. Meissner MH, Gloviczki P, Bergan J, et al. Primary chronic venous disorders. J Vasc Surg. 2007;46(Suppl S):54S–67S.
15. Fonder MA, Lazarus GS, Cowan DA, et al. Treating the chronic wound: a practical approach to the care of nonhealing wounds and wound care dressings. J Am Acad Dermatol. 2008;58:185–206.
16. Panuncialman J, Falanga V. The science of wound bed preparation. Surg Clin North Am. 2009;89:611–26.
17. Falabella AF. Debridement and wound bed preparation. Dermatol Ther. 2006;19:317–25.
18. Sherman RA, Hall MJ, Thomas S. Medicinal maggots: an ancient remedy for some contemporary afflictions. Annu Rev Entomol. 2000;45:55–81.
19. Chambers L, Woodrow S, Brown AP, et al. Degradation of extracellular matrix components by defined proteinases from the greenbottle larva *Lucilia sericata* used for the clinical debridement of non-healing wounds. Br J Dermatol. 2003;148:14–23.
20. Dumville JC, Worthy G, Bland JM, et al. Larval therapy for leg ulcers (VenUS II): randomised controlled trial. BMJ. 2009;338:b773.
21. Lipsky BA, Hoey C. Topical antimicrobial therapy for treating chronic wounds. Clin Infect Dis. 2009;49:1541–9.
22. Zhou LH, Nahm WK, Badiavas E, et al. Slow release iodine preparation and wound healing: in vitro effects consistent with lack of in vivo toxicity in human chronic wounds. Br J Dermatol. 2002;146:365–74.
23. Lansdown AB. A review of the use of silver in wound care: facts and fallacies. Br J Nurs. 2004;13:S6–19.
23a. Korber A, Graue N, Rietkotter J, et al. Insufficient tetanus vaccination status in patients with chronic leg ulcers. Results of a prospective investigation in 100 patients. Dermatology. 2008;217:69–73.
24. O'Meara S, Tierney J, Cullum N, et al. Four layer bandage compared with short stretch bandage for venous leg ulcers: systematic review and meta-analysis of randomised controlled trials with data from individual patients. BMJ. 2009;338:b1344.
25. Barwell JR, Davies CE, Deacon J, et al. Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomised controlled trial. Lancet. 2004;363:1854–9.
26. Kerchner K, Fleischer A, Yosipovitch G. Lower extremity lymphedema update: pathophysiology, diagnosis, and treatment guidelines. J Am Acad Dermatol. 2008;59:324–31.

27. Mayrovitz HN. The standard of care for lymphedema: current concepts and physiological considerations. Lymphat Res Biol. 2009;7:101–8.
28. Hunter JE, Teot L, Horch R, Banwell PE. Evidence-based medicine: vacuum-assisted closure in wound care management. Int Wound J. 2007;4:256–69.
29. Venturi ML, Attinger CE, Mesbahi AN, et al. Mechanisms and clinical applications of the vacuum-assisted closure (VAC) device: a review. Am J Clin Dermatol. 2005;6:185–94.
30. Rizzi SC, Upton Z, Bott K, Dargaville TR. Recent advances in dermal wound healing: biomedical device approaches. Expert Rev Med Devices. 2010;7:143–54.
31. Paquette D, Badiavas E, Falanga V. Short-contact topical tretinoin therapy to stimulate granulation tissue in chronic wounds. J Am Acad Dermatol. 2001;45:382–6.
32. Jull A, Waters J, Arroll B. Pentoxifylline for treatment of venous leg ulcers: a systematic review. Lancet. 2002;359:1550–4.
33. Brice G, Child AH, Evans A, et al. Milroy disease and the VEGFR-3 mutation phenotype. J Med Genet. 2005;42:98–102.
34. Sisto K, Khachemoune A. Elephantiasis nostras verrucosa: a review. Am J Clin Dermatol. 2008;9:141–6.
35. Zouboulis CC, Biczo S, Gollnick H, et al. Elephantiasis nostras verrucosa: beneficial effect of oral etretinate therapy. Br J Dermatol. 1992;127:411–6.
36. Iwao F, Sato-Matsumura KC, Sawamura D, Shimizu H. Elephantiasis nostras verrucosa successfully treated by surgical debridement. Dermatol Surg. 2004;30:939–41.
37. Langendoen SI, Habbema L, Nijsten TEC, Neumann HAM. Lipoedema: from clinical presentation to therapy. A review of the literature. Br J Dermatol. 2009;161:980–6.
38. White C. Clinical practice. Intermittent claudication. N Engl J Med. 2007;356:1241–50.
39. Sumpio BE. Foot ulcers. N Engl J Med. 2000;343: 787–93.
40. Ouriel K. Peripheral arterial disease. Lancet. 2001;358:1257–64.
41. Al-Qaisi M, Nott DM, King DH, Kaddoura S. Ankle brachial pressure index (ABPI): an update for practitioners. Vasc Health Risk Manag. 2009;5:833–41.
42. Grenon SM, Gagnon J, Hsiang Y. Video in clinical medicine. Ankle-brachial index for assessment of peripheral arterial disease. N Engl J Med. 2009; 361:e40.
43. Cavanagh PR, Lipsky BA, Bradbury AW, Botek G. Treatment for diabetic foot ulcers. Lancet. 2005;366:1725–35.
44. Kalish J, Hamdan A. Management of diabetic foot problems. J Vasc Surg. 2010;51:476–86.
45. Andersen CA, Roukis TS. The diabetic foot. Surg Clin North Am. 2007;87:1149–77, x.
46. Falanga V. Wound healing and its impairment in the diabetic foot. Lancet. 2005;366:1736–43.
47. Boulton AJ. Pressure and the diabetic foot: clinical science and offloading techniques. Am J Surg. 2004;187:17S–24S.
48. Boulton AJ, Kirsner RS, Vileikyte L. Clinical practice. Neuropathic diabetic foot ulcers. N Engl J Med. 2004;351:48–55.
49. Kranke P, Bennett M, Roeckl-Wiedmann I, Debus S. Hyperbaric oxygen therapy for chronic wounds. Cochrane Database Syst Rev. 2004;(2):CD004123.
50. Thackham JA, McElwain DL, Long RJ. The use of hyperbaric oxygen therapy to treat chronic wounds: a review. Wound Repair Regen. 2008;16:321–30.
51. Steed DL. Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity ulcers. Plast Reconstr Surg. 2006;117:143S–9S; discussion 150S–151S.
52. White R, McIntosh C. A review of the literature on topical therapies for diabetic foot ulcers. Part 2: Advanced treatments. J Wound Care. 2009;18:335–41.
53. Dinh TL, Veves A. The efficacy of Apligraf in the treatment of diabetic foot ulcers. Plast Reconstr Surg. 2006;117:152S–7S; discussion 8S–9S.
54. Marston WA. Dermagraft, a bioengineered human dermal equivalent for the treatment of chronic nonhealing diabetic foot ulcer. Expert Rev Med Devices. 2004;1:21–31.
55. Mayfield JA, Reiber GE, Sanders LJ, et al. Preventive foot care in diabetes. Diabetes Care. 2004;27(Suppl 1):S63–4.
56. Markuson M, Hanson D, Anderson J, et al. The relationship between hemoglobin A(1c) values and healing time for lower extremity ulcers in individuals with diabetes. Adv Skin Wound Care. 2009;22:365–72.
57. Nakano J, Nakamura M, Ito T, et al. A case of antiphospholipid syndrome with cutaneous ulcer and intrauterine fetal growth retardation. J Dermatol. 2003;30:533–7.
58. Schwartzfarb EM, Romanelli P. Hyperhomocysteinemia and lower extremity wounds. Int J Low Extrem Wounds. 2008;7:126–36.
59. Draper BK, Boyd AS. Diffuse dermal angiomatosis. J Cutan Pathol. 2006;33:646–8.
60. Trent JT, Kirsner RS. Leg ulcers in sickle cell disease. Adv Skin Wound Care. 2004;17:410–6.
61. Darvall KA, Sam RC, Adam DJ, et al. Higher prevalence of thrombophilia in patients with varicose veins and venous ulcers than controls. J Vasc Surg. 2009;49:1235–41.
62. Hafner J, Kuhne A, Schar B, et al. Factor V Leiden mutation in postthrombotic and non-postthrombotic venous ulcers. Arch Dermatol. 2001;137:599–603.

Other Vascular Disorders 106

Robert Kelly and Christopher Baker

Chapter Contents

Livedo reticularis 1747
Flushing 1750
Erythromelalgia 1751
Telangiectasias 1753
Venous lakes 1755
Nevus anemicus 1755
Angiospastic macules (Bier spots) 1756

INTRODUCTION

This chapter will cover several disorders of the skin vasculature, including livedo reticularis, flushing and erythromelalgia, as well as vascular ectasias such as telangiectasias and venous lakes. Some of the diseases described here are important skin signs of systemic disease, while others are incidental findings. Additional disorders of blood vessels are covered elsewhere, e.g. infantile hemangiomas (Ch. 103), vascular malformations (Ch. 104), and vascular neoplasms and proliferations (Ch. 114).

LIVEDO RETICULARIS

Key features

- A common physiologic finding consisting of a mottled reticulated vascular pattern
- May occur secondarily due to an underlying disease, e.g. autoimmune connective tissue disease, antiphospholipid antibody syndrome
- The pattern varies depending on the underlying cause
- Appropriate investigations depend on the clinical context and associated findings

Introduction

Livedo reticularis (LR) is an extremely common finding and usually results from a physiologic vasospastic response to cold exposure. Among normal healthy individuals, the predisposition to LR will vary. It can also be a reflection of a number of underlying systemic diseases. LR resulting from any cause can vary to some degree with changes in external temperature. Physiologic LR will usually disappear with warming and reappear with cooling. Other variants may persist to varying degrees with warming.

History

The term "livedo reticularis" was first used by Hebra over a century ago to describe a violaceous skin discoloration caused by an abnormality of the cutaneous circulation. Renault (1883) and later Unna (1896) and Spalteholz (1927) suggested that a cone arrangement of the cutaneous microvasculature served as an explanation for the occurrence and pattern of LR[1].

Pathogenesis

LR results from alterations in blood flow through the cutaneous microvasculature system (Fig. 106.1). The latter consists of arterioles that are oriented perpendicularly to the skin surface. The vessels then divide into capillary beds that in turn drain into a subpapillary plexus. It has been proposed that this arrangement of vessels gives rise to a series of 1 to 3 cm cones with the ascending arteriole at the apex of each cone. At the edge of the cone, the venous plexus is more prominent and the arterial bed is diminished. Any process that either reduces blood flow to and through the skin or reduces drainage of blood out of the skin will result in the accumulation of deoxygenated blood in the venous plexus, leading to the clinical appearance of LR[1–3].

There are a number of causes of LR (Table 106.1) and the clinical pattern of LR can vary with the nature of the underlying cause. A complete fine network is indicative of alterations in blood flow caused by vasospasm or by factors within the blood that alter the viscosity and the flow through the vessels. Vessel wall pathology and intraluminal obstruction are more likely to result in a patchy distribution of LR, depending on the distribution of the underlying pathology.

Livedo racemosa (Fig. 106.2) refers to a distinct pattern of LR consisting of a large branching pattern that is usually situated on the trunk and proximal limbs. It is generally indicative of Sneddon syndrome, which is associated with multiple strokes that lead to progressive neurologic impairment[4]. Similar findings may also be seen in the antiphospholipid antibody syndrome (APS)[5].

Clinical Features

Congenital livedo reticularis

Cutis marmorata telangiectatica congenita

Cutis marmorata telangiectatica congenita (CMTC) is characterized by a persistent reticulated vascular pattern that is often limited to one extremity (see Ch. 104), but can be more widespread. Lesions are usually noted at birth, and, when the trunk is involved, there may be a sharp cut-off at the midline. Associated anomalies include other vascular malformations, limb asymmetry and, occasionally, neurologic or ocular abnormalities[6,7]. Cutaneous vascular changes can improve during the first few years of life, with 20% of patients showing complete resolution.

Acquired livedo reticularis

Livedo reticularis without systemic associations

Physiologic livedo reticularis/cutis marmorata

These terms are synonymous and refer to a normal pattern of LR that occurs in response to cold (Fig. 106.3A). It is often more marked in neonates, infants and young children[2,3]. In adults, it may be associated with a tendency towards acrocyanosis and chilblains.

Primary/idiopathic livedo reticularis

This refers to a persistent fine network of LR that is often widespread, particularly on the lower extremities. While there is some fluctuation with temperature, the LR will usually persist with warming (Fig. 106.3B). It is due to persistent vasospasm of arterioles and is not secondary to any underlying cause. However, primary LR is a diagnosis of exclusion and it is important to consider secondary causes (see Table 106.1). This is especially true when the LR is extensive[2,3].

Livedo reticularis secondary to systemic disease

Livedo reticularis due to vasospasm

Vasospasm is the most common cause of LR, including that seen in association with autoimmune connective tissue diseases (CTD; Fig.

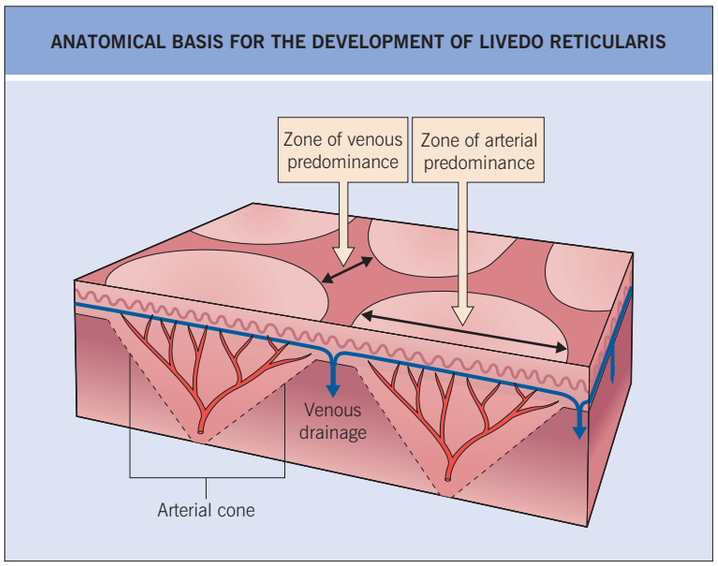


Fig. 106.1 Anatomical basis for the development of livedo reticularis.

106.3C). Reflecting a vasospastic tendency, it occurs more commonly in patients with Raynaud's phenomenon.

Livedo reticularis due to vessel wall pathology

Vasculitis is the most common cause of vessel wall pathology associated with LR. In general, LR will only occur if medium-sized arterioles at the dermal–subcutaneous border or in the deep dermis are affected. Cutaneous polyarteritis nodosa (PAN) always involves these vessels and is therefore invariably associated with LR[8]. Systemic PAN, cryoglobulinemic vasculitis and autoimmune CTD-related vasculitis may also affect these arterioles. The pattern of LR seen is usually a larger network that may be continuous or patchy depending on the distribution of vessel involvement.

Calciphylaxis consists of calcium deposition in the walls of blood vessels (see Ch. 50). It is most commonly seen in the setting of chronic renal failure complicated by hyperparathyroidism. Calciphylaxis may initially commence with LR that then becomes purpuric and subsequently necrotic (Fig. 106.4).

Sneddon syndrome is a rare syndrome consisting of widespread livedo racemosa (Fig. 106.5A) in conjunction with multiple cerebral ischemic episodes leading to progressive neurologic impairment[4,5] (see Ch. 23). It remains uncertain as to whether the vascular pattern results from vasculopathy, vasculitis or coagulopathy, but characteristic changes are seen within affected vessels (Fig. 106.5B; see below).

Livedo reticularis due to intraluminal pathology

LR can result either from factors (e.g. within the blood) that slow intravascular blood flow or from complete obstruction of the vessel lumen. Altered blood flow due to an increase in blood viscosity may be secondary to abnormal circulating proteins (e.g. cryoglobulins[9], cryofibrinogens, cold agglutinins, paraproteins) or an increase in normal blood components (e.g. polycythemia vera[10], thrombocytosis). A fine, evenly distributed pattern of LR is usually seen. Hypercoagulable states can also be associated with LR, including the APS[11] and protein C[12], protein S or antithrombin III deficiencies[13]. LR of the lower extremities is often seen in patients with neurologic conditions that lead to immobility of the lower limbs and stasis.

Complete obstruction of the vessel lumen can result from either emboli (e.g. cholesterol emboli derived from atheromata[14]) or thromboses within vessels (e.g. APS, heparin or warfarin necrosis). Intracellular crystal deposition is seen in hyperoxaluria and this also gives rise to luminal obstruction and LR[15]. A patchy, discontinuous-pattern LR is seen with intraluminal obstruction and it may subsequently become purpuric with areas of infarction and necrosis.

A combination of intraluminal obstruction and vessel wall pathology is seen in livedoid vasculopathy. This is an uncommon condition that is sometimes associated with LR. It consists of multiple, recurrent, painful ulcers on the lower extremities that heal slowly with residual atrophie blanche. Histologically, vessel lumina are filled with hyaline

CAUSES OF LIVEDO RETICULARIS
CONGENITAL LIVEDO RETICULARIS
• Cutis marmorata telangiectatica congenita
ACQUIRED LIVEDO RETICULARIS
Vasospasm
• Cutis marmorata/physiologic livedo reticularis • Primary (idiopathic) livedo reticularis • Autoimmune connective tissue diseases (e.g. SLE) • Raynaud's phenomenon/disease
Vessel wall pathology
• Vasculitis – Cutaneous polyarteritis nodosa – Systemic polyarteritis nodosa – Cryoglobulinemic vasculitis – Autoimmune connective tissue disease-associated vasculitis (e.g. rheumatoid arthritis, SLE, Sjögren's syndrome) • Calciphylaxis • Sneddon syndrome • Livedoid vasculopathy (also intraluminal obstruction)
Intraluminal pathology
• Increased normal blood components – Thrombocythemia – Polycythemia vera • Abnormal proteins – Cryoglobulinemia – Cryofibrinogenemia – Cold agglutinins – Paraproteinemia • Hypercoagulability (see Table 105.9) – Antiphospholipid syndrome – Protein S and C deficiencies – Antithrombin III deficiency – Factor V Leiden mutation – Homocystinuria, hyperhomocysteinemia – Disseminated intravascular coagulation • Thrombotic thrombocytopenic purpura • Embolic – Cholesterol emboli – Septic emboli – Atrial myxoma – Nitrogen (decompression sickness) – Carbon dioxide arteriography • Hyperoxaluria
Other
• Medications (e.g. amantadine, norepinephrine, interferon) • Infections (e.g. hepatitis C [vasculitis], *Mycoplasma* spp. [cold agglutinins], syphilis) • Neoplasms (e.g. pheochromocytoma) • Neurologic disorders (e.g. reflex sympathetic dystrophy, paralysis) • Moyamoya disease

Table 106.1 Causes of livedo reticularis. SLE, systemic lupus erythematosus.

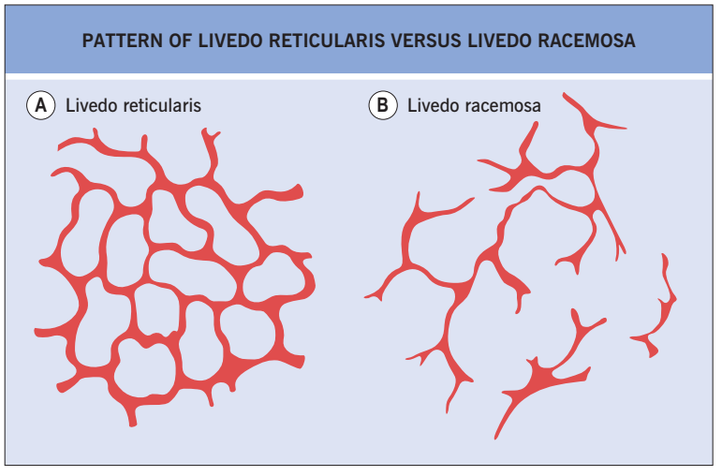


Fig. 106.2 Pattern of livedo reticularis (A) versus livedo racemosa (B).

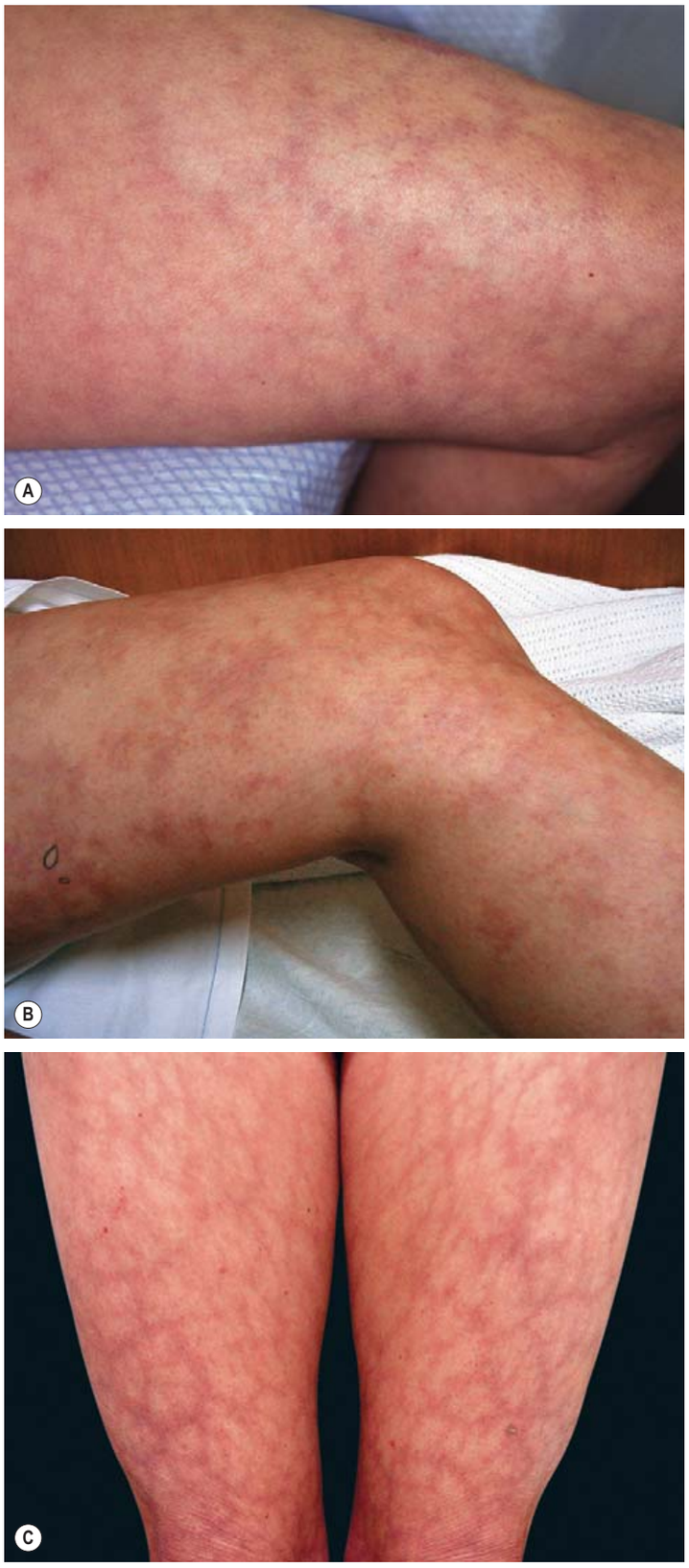


Fig. 106.3 Livedo reticularis. A An even, net-like pattern is seen on the thigh in physiologic livedo reticularis. **B** In primary (idiopathic) livedo reticularis, the pattern persists with warming. **C** Livedo reticularis in a patient with systemic lupus erythematosus. *C, Courtesy, Jeffrey Callen, MD.*

thrombi, and fibrinoid material is also present in the walls of these vessels and in the perivascular stroma[16].

Other causes of livedo reticularis

There are numerous causes of LR cited in the literature, and, in most, one of the above mechanisms can generally be implicated. The other causes include drugs such as amantadine[17] and norepinephrine (noradrenaline), as well as infections. The latter can lead to: the production of cryoglobulins, cold agglutinins or antiphospholipid antibodies; the induction of immune vasculitis; or septic vasculitis or septic emboli. Neoplasms may also be associated with LR via hypercoagulability or paraproteinemia as well as vasospasm (e.g. pheochromocytoma). Lastly, LR may be seen in several neurologic conditions (e.g. reflex sympathetic dystrophy) as a result of vasospasm or vasodilation (this is in addition to stasis arising from immobility).

Fig. 106.4 Reticulate purpura and cutaneous necrosis due to calciphylaxis. These patients also often have patchy areas of livedo reticularis. *Courtesy, Norbert Sepp, MD.*

Differential Diagnosis

Erythema ab igne is a heat-induced skin disease that begins as a reversible LR, then, with continued heat exposure, evolves into a fixed reticulated hyperpigmentation in the same pattern. When present on the anterior thighs, the possibility of direct contact with a laptop computer should be considered. Various cutaneous eruptions may have a reticulated pattern and might be confused with LR, including reticulated erythematous mucinosis (favors mid central trunk) and some viral exanthems (e.g. erythema infectiosum). Poikilodermatous conditions may also have a reticulate pattern (e.g. dermatomyositis, mycosis fungoides); however, the presence of epidermal changes and telangiectasias will help distinguish these conditions from LR.

Pathology

The histology of LR varies depending on the underlying cause. In idiopathic or physiologic forms resulting from vasospasm, no abnormality will be evident. With secondary causes of LR, a number of abnormalities may be seen, including vasculitis, calcium deposition within vessel walls (calciphylaxis), intravascular eosinophilic plugging (monoclonal cryoglobulinemia), intraluminal thromboses (hypercoagulable states), cholesterol clefting (cholesterol emboli) and crystal deposition (oxalosis). In Sneddon syndrome, vessel walls demonstrate endothelial inflammation and subendothelial myointimal hyperplasia with partial or complete occlusion of affected arterioles (see Fig. 106.5B). In order to locate the histopathologic changes, it is necessary to sample the affected arterioles. A moderately large elliptical biopsy from the non-discolored skin in the center of the net pattern is necessary and serial sectioning may be required.

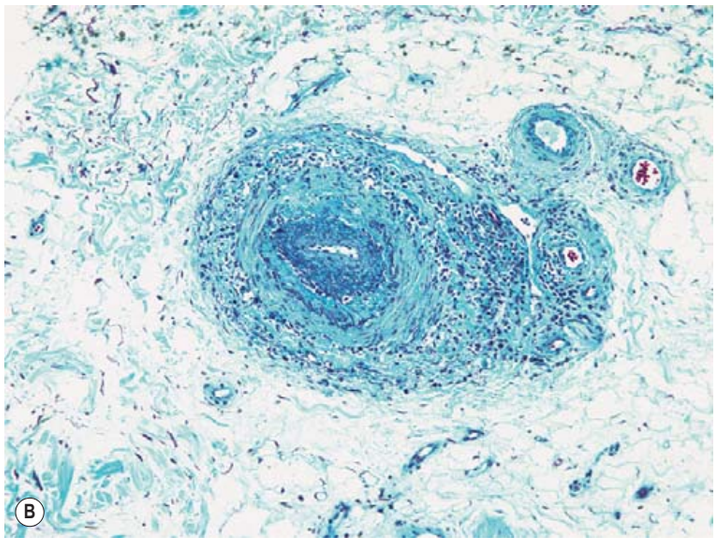


Fig. 106.5 Sneddon syndrome. A The characteristic irregular, broken, branching pattern of livedo racemosa is seen on the back and arms. **B** A connective tissue stain highlights a subcutaneous artery with subendothelial proliferation of smooth muscle, leading to almost complete luminal occlusion.

Treatment

LR is a clinical sign and does not require treatment per se. It is unresponsive to treatments such as vascular laser therapy or vasodilatory medications. Underlying causes require identification and appropriate treatment.

FLUSHING

Key features

- Flushing is a physiologic response, but in an exaggerated form causes clinical symptoms
- Common triggers (e.g. heat, emotion, exercise and some foods) will exacerbate flushing of any cause
- Causes of excessive flushing include exogenous medications, menopause, neurologic disorders and systemic diseases (e.g. carcinoid syndrome)

Introduction

Flushing is the term used to describe transient and episodic reddening of the skin, most commonly of the face, and less often the neck, ears and upper chest. It is the visible sign of a generalized increase in cutaneous blood flow. The greater visibility and capacitance of the superficial cutaneous vasculature of the face and adjacent areas accounts for the limited distribution[18]. In the evaluation of an affected patient, there are a number of causes to consider, including underlying systemic disorders (Table 106.2).

CAUSES OF FLUSHING
• Physiologic
• Exogenous agents (see Table 106.3)
• Menopause
• Neurologic disorders
– Anxiety
– Autonomic dysfunction
– Tumors (e.g. hypogonadal pituitary tumors)
– Migraine
– Frey's syndrome (auriculotemporal syndrome)
• Systemic diseases
– Carcinoid syndrome
– Mastocytosis
– Pheochromocytoma
– Medullary carcinoma of the thyroid
– Thyrotoxicosis
– POEMS syndrome
– Pancreatic tumors (e.g. VIPomas)
– Prostaglandin-secreting renal cell carcinoma

Table 106.2 Causes of flushing. POEMS, *p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *M*-protein (monoclonal gammopathy), *s*kin changes; VIP, vasoactive intestinal polypeptide.

EXOGENOUS AGENTS THAT CAN CAUSE FLUSHING
• Alcohol
• Drugs
– Angiotensin-converting enzyme (ACE) inhibitors
– Calcium channel blockers
– Calcitonin
– Chlorpropamide*
– Cholinergic agonists (e.g. pilocarpine)
– Cyclosporine
– Disulfiram*
– Fumaric acid esters
– Gold ("nitritoid reactions")
– Hydralazine
– Nicotinic acid
– Nitrates (e.g. glyceryl trinitrate)
– Opiates
– Prostaglandins
– Sildenafil, tadalafil, vardenafil
– Tamoxifen
• Foods
– Spoiled scombroid fish
• Foods additives
– Monosodium glutamate (MSG), sodium nitrite, sulfites
*With alcohol intake.

Table 106.3 Exogenous agents that can cause flushing.

Pathogenesis

An increase in cutaneous blood flow occurs with relaxation of vascular smooth muscle. This may occur via the autonomic nervous system[19] (usually leading to active vasodilation), endogenous vasoactive agents (such as histamine and serotonin) or exogenous agents (Table 106.3). Alcohol-induced flushing may result from the direct effect of alcohol as well as cutaneous vasodilation from elevated blood levels of acetaldehyde; the latter occurs in those with alcohol dehydrogenase deficiency (prevalent in Asians) and in the "disulfiram reaction" induced by some medications. Flushing from fermented alcoholic drinks may be caused by vasoactive substances such as tyramine[20]. Vasodilation mediated by the autonomic nervous system is often accompanied by eccrine

SIGNS AND SYMPTOMS OF THE CARCINOID SYNDROME
• Cutaneous – Flushing – Vascular rosacea-like changes – Pellagra – Edema and induration of the face > extremities • Bronchospasm • Diarrhea • Cardiac dysfunction (right-sided) • Hypotension • Peptic ulcers

Table 106.4 Signs and symptoms of the carcinoid syndrome.

sweating due to a direct effect on both sweat glands and blood vessels (wet flush)[21]. Direct vasodilation by vasoactive agents is usually not associated with increased sweating (dry flush).

Clinical Features

Blushing is a common emotionally triggered form of flushing associated with embarrassment and anxiety and is considered an exaggerated physiologic response. *Physiologic flushing* also occurs as part of normal thermoregulation in response to heat or exercise. *"Hot flashes"* refer to flushing associated with menopause, which lasts for a few minutes and is usually associated with sweating[22]. Flushing of any cause may be exacerbated or triggered by a number of common factors such as heat, hot drinks, exercise, anxiety, food additives (e.g. sulfites) and alcohol. Affected patients often report a feeling of heat and burning of the skin during episodes and find the color change a social hindrance. Some patients become anxious that they will flush at inopportune times and this further exacerbates the problem. Repeated flushing may lead to fixed erythema and telangiectasias.

Those carcinoid tumors that secrete vasoactive agents (e.g. serotonin) are associated with the carcinoid syndrome (Table 106.4). Flushing, often severe, is present in the majority of patients with carcinoid syndrome[23] and it may be precipitated by the common triggers of flushing. The classic "carcinoid flush", seen with approximately 10% of *midgut* tumors (small intestine, appendix, proximal colon), lasts minutes and consists of erythema and pallor as well as a cyanotic hue. Of note, liver metastases are required. Type III *gastric* carcinoid tumors are associated with a pruritic, patchy, bright red flush admixed with white patches and probably mediated by histamine. *Bronchial* tumors are associated with a prolonged (hours to days), intensely red to purple flush. Hindgut tumors (distal colon, rectum) are rarely, if ever, associated with the carcinoid syndrome and flushing, even with liver metastases.

An approach to the clinical assessment of flushing and relevant investigations are listed in Table 106.5.

Differential Diagnosis

Fixed erythema, and sometimes telangiectasia, of the face and neck are seen in fair-skinned individuals with photodamage as well as patients with seborrheic dermatitis, photosensitivity disorders or autoimmune CTD. Affected individuals may complain of the persistent redness and burning of the skin rather than actual flushing. Rosacea may be associated with pronounced flushing, but, usually, fixed erythema, papulopustules, edema and/or telangiectasia are present to some degree.

Treatment

The clinician should consider and eliminate any suspected exogenous cause (see Table 106.3). Underlying systemic causes, although rare, should be considered (see Table 106.2). Triggers of flushing are likely to be clinically relevant in most patients and should be avoided where possible. Non-selective β-blockers (e.g. nadolol, propranolol) or clonidine may be effective in idiopathic flushing. Anxiolytics may be helpful, particularly if emotional symptoms or anxiety are evident. Menopausal flushing may respond to hormone replacement therapy, clonidine or selective serotonin reuptake inhibitors (SSRIs). In troublesome cases unresponsive to these measures, transthoracic endoscopic sympathectomy may be considered.

CLINICAL APPROACH TO THE EVALUATION OF FLUSHING
1. Identify provocative factors • Direct questioning • Patient diary (food, medications, activities) 2. Check for associated symptoms • Sweating • Urticaria • Diarrhea • Bronchospasm 3. Investigation Not required in all cases Indicated if flushing: • Of sudden or recent onset • Severe • Associated with systemic symptoms Investigations to consider: • Complete blood count with differential and platelets • Thyroid function tests • Serum tryptase, histamine and/or chromogranin A levels; plasma free metanephrines • 24-hour urine collection for – Serotonin metabolites such as 5-hydroxyindole acetic acid (5-HIAA) – Fractionated metanephrines – Histamine metabolites such as methylimidazole acetic acid (MIAA) • CT/MRI scans; somatostatin receptor scintigraphy (using radiolabeled analogue of somatostatin) 4. Elimination • Exclude suspected drugs and food additives

Table 106.5 Clinical approach to the evaluation of flushing.

ERYTHROMELALGIA

Synonyms: ■ Erythermalgia ■ Erythralgia

Key features

- Characterized by painful burning and erythema of the distal extremities (lower > upper)
- Precipitated by heat and relieved by cooling
- May be idiopathic, familial or arise secondarily due to an underlying condition (e.g. thrombocythemia)

Introduction

Erythromelalgia (EM) is an episodic condition characterized by a burning sensation, erythema and increased skin temperature. It affects acral sites, particularly the lower extremities. Classically, there are three major forms, including:

- type 1 associated with thrombocythemia
- type 2 primary or idiopathic form
- type 3 associated with underlying causes other than thrombocythemia.

History

The term "erythromelalgia" was first coined by Mitchell in 1878. It was used to describe redness (erythos), involvement of extremities (melos), and pain (algos). The diagnostic criteria were established by Thompson[24] in 1979: (1) burning pain in the extremities; (2) pain aggravated by warming; (3) pain relieved by cooling; (4) erythema of affected skin; and (5) increased temperature of affected skin.

Epidemiology

In Norway, the estimated incidence of EM is 0.25/100 000 with a prevalence of 2/100 000[25]. While types 1 and 3 usually appear during adulthood, type 2 may appear in childhood and may be familial. The female : male incidence varies from 2 : 1 to almost 3 : 1. In one study,

the mean age of onset was 56 years (range, 5–91 years) with 4% having their symptoms begin in childhood.

Pathogenesis

While the discovery of *SCN9A* mutations in patients with primary familial EM has provided insights into this disorder, in general, the pathogenesis of EM is not entirely understood. Firstly, it may vary depending on the underlying cause and between different patient subgroups. In patients with thrombocythemia, the pathophysiology is likely to be related to both increased numbers of platelets as well as abnormalities in platelet function. Of note, one explanation for why type 1 EM does not respond to heparin or warfarin is that the microthrombi that form do not require thrombin activation[26].

In other types of EM, changes in vascular dynamics may be a factor. It has been proposed that hyperemia results from increased blood flow through arteriovenous shunts with a resultant reduction in blood flow within nutritional vessels, thus leading to cutaneous hypoxia[25,27]. Another proposed mechanism is vasoconstriction (as occurs in Raynaud's phenomenon), but in EM this is followed by a prolonged phase of hyperemia[28]. A temperature-triggered release of vasoactive substances and chemical pain mediators may also play a role.

In 2004, gain-of-function missense mutations in *SCN9A*, which encodes the voltage-gated sodium channel alpha subunit Na(v)1.7, were first described in patients with primary familial EM[29]. Na(v)1.7 produces threshold currents and is expressed primarily within dorsal root ganglia of sensory neurons (especially nociceptors) and sympathetic ganglion neurons. Mutations lead to lowered thresholds and "overexcitability" of pain-signaling sensory neurons[30] while at the same time producing "under-excitability" of sympathetic neurons. Certain mutations that produce a lesser effect on sodium channel activation and subsequent neuron excitability are associated with a later onset of clinical signs and symptoms[31].

Interestingly, another dominantly inherited pain syndrome, paroxysmal extreme pain disorder, has also been found to be due to gain-of-function mutations in *SCN9A*, whereas loss-of-function mutations in both copies of this gene lead to a recessively inherited insensitivity to pain[32]. Lastly, there exist additional families that are not linked to chromosome 2q31–32 (*SCN9A* locus), suggesting genetic heterogeneity[33].

Associations in secondary EM include myelodysplastic syndromes, diabetes mellitus, peripheral vascular disease, vasculitis, systemic lupus erythematosus and other autoimmune CTDs.

Clinical Features

EM is characterized by burning, erythema and warmth of acral sites (Fig. 106.6). Attacks most commonly occur late in the day, last through the night, and frequently impair sleep. The symptoms are usually episodic, though occasionally they may be continuous. The feet are involved in 90% of patients, whereas the hands are affected in 25%. Less commonly, there is also involvement of the head and neck. Type 1 EM may be unilateral and is more frequently associated with progression to ischemic necrosis. In contrast, the idiopathic type is more likely to be bilateral. The pain is precipitated by minor elevations in temperature (between 32°C and 36°C). Other exacerbating factors include exercise, standing, walking, fever, and limb dependency. Cooling and limb elevation generally reduce the symptoms.

The affected areas will often appear red and swollen. Other findings include acrocyanosis, livedo reticularis, facial flushing, cutaneous necrosis and ulceration. In up to 40% of patients, the limb may appear normal between attacks. Prolonged immersion in water can lead to extensive maceration and contribute to ulcer formation.

Prognosis is variable. In one long-term study, approximately 30% of patients fell into each of three categories: worsening, no change, and improvement. A further 10% had complete resolution of their symptoms[34].

Pathology

In type 1 EM, vessels may show intimal proliferation and occlusive thrombosis. In general, however, biopsies are not required and histology is nonspecific.

Fig. 106.6 Erythromelalgia. Red hot painful hand (**A**) and legs (**B**) in two patients with erythromelalgia.
A, Courtesy, Agustin Aloma, MD.

Differential Diagnosis

Complex regional pain syndrome (CRPS; reflex sympathetic dystrophy) may sometimes have features similar to EM (see Ch. 6). Abnormal warmth, erythema and burning pain may be seen in both, but CRPS does not have the characteristic close relationship to temperature and tends to be constant rather than episodic. Peripheral neuropathy may also cause tingling and burning and may require differentiation by nerve conduction studies. Calcium channel blockers, autonomic dysfunction, acrodynia and mushroom poisoning, as well as occlusive vascular diseases such as thromboangiitis obliterans, may be associated with EM-like symptoms. It is important to consider underlying causes of EM – in particular, chronic myeloproliferative disorders – as EM may be the first sign of the latter.

Treatment

Although numerous treatments have been reported as possible therapies for EM, no single therapy is consistently effective and many cases can prove difficult to control. The assistance of a specialist pain clinic can be valuable. Various methods of cooling the limbs during attacks, such as fans, wet dressings, and ice packs wrapped in towels, should be explored and have often already been tried by the time of presentation. Frequent periods of leg elevation can be helpful in reducing both discomfort and leg edema, whereas prolonged periods of leg dependency should be avoided. Simple oral analgesia is also important.

Aspirin can be effective for type 1 EM and treatment for the thrombocythemia with medications such as hydroxyurea should also be considered. Topical therapies include 10% capsaicin cream, 1%

amitriptyline/0.5% ketamine gel and lidocaine patches, while possible oral medications include SSRIs (e.g. venlafaxine), tricyclic antidepressants (e.g. amitriptyline), anticonvulsants (e.g. gabapentin, carbamazepine), calcium channel blockers (e.g. diltiazem), the prostaglandin analogue misoprostol, and, especially in primary inherited EM, sodium channel blocking agents (e.g. mexiletine, flecainide)[35,36]. With the report of functional expression studies (based upon a specific mutation) correlating with clinical responsiveness to carbamazepine, the possibility exists of utilizing such assays in the future to guide therapy.

Several intravenous therapies have been used for more severe cases, including nitroprusside, prostaglandin E1, and lidocaine (combined with oral mexiletine). More invasive approaches include epidural infusions of bupivacaine and opiates, lumbar sympathetic blocks and bilateral lumbar sympathectomies[37]. Oral medications should be tried initially, but more invasive procedures may be necessary for more severe cases.

TELANGIECTASIAS

Key features

- Telangiectasia is due to persistently dilated dermal vessels and not angiogenesis
- Can occur as a primary process, a result of cutaneous damage, or secondary to systemic disease

Introduction

Telangiectasia refers to abnormal, small, persistently dilated blood vessels visible in the skin (Fig. 106.7). Individual vessels can be discerned and range in color from light red to deep purple and will usually empty with pressure. They occur as a result of vascular dilation rather than new vessel growth and are thought to arise from capillaries, venules or small arteriovenous malformations. Telangiectasias are seen in a range of clinical settings (Table 106.6).

Treatment is often not required; however, options include cosmetic camouflage, light or fine wire diathermy, injection sclerotherapy, and laser or intense pulsed light therapies.

Spider Telangiectasia

Synonyms: ■ Nevus araneus ■ Spider nevus ■ Spider angioma

This localized lesion has a slightly raised central red papule (which often becomes more prominent with time) and multiple small, radiating, dilated vessels ("legs")[38] (Fig. 106.8). The lesion can vary from several millimeters to more than a centimeter in diameter. They are commonly located on the face, neck, upper trunk and hands.

Spider telangiectasias represent a form of telangiectasia with a central feeding arterial vessel. They are usually seen in otherwise healthy individuals, especially women and children. Lesions, often multiple, commonly occur with pregnancy, liver disease and oral contraceptive pills (OCPs). Spontaneous resolution may occur, especially after pregnancy. Treatment options include electrosurgery or vascular lasers.

Generalized Essential Telangiectasia

This is a primary disorder that typically affects adult women but may commence during childhood. Initially, the limbs are affected, especially the distal lower extremities, with sheets of asymptomatic blanchable telangiectasias[39,40]. The involvement is usually symmetric. Over time, there is often a progression proximally such that the telangiectasias become more widespread. Although the telangiectasias are persistent, patients do not have associated systemic illnesses.

The differential diagnosis includes cutaneous collagenous vasculopathy; typically it is not confused with telangiectasia macularis eruptiva perstans. While improvement with vascular lasers is possible, the progressive nature must be considered and the cost of treating extensive involvement may prove prohibitive.

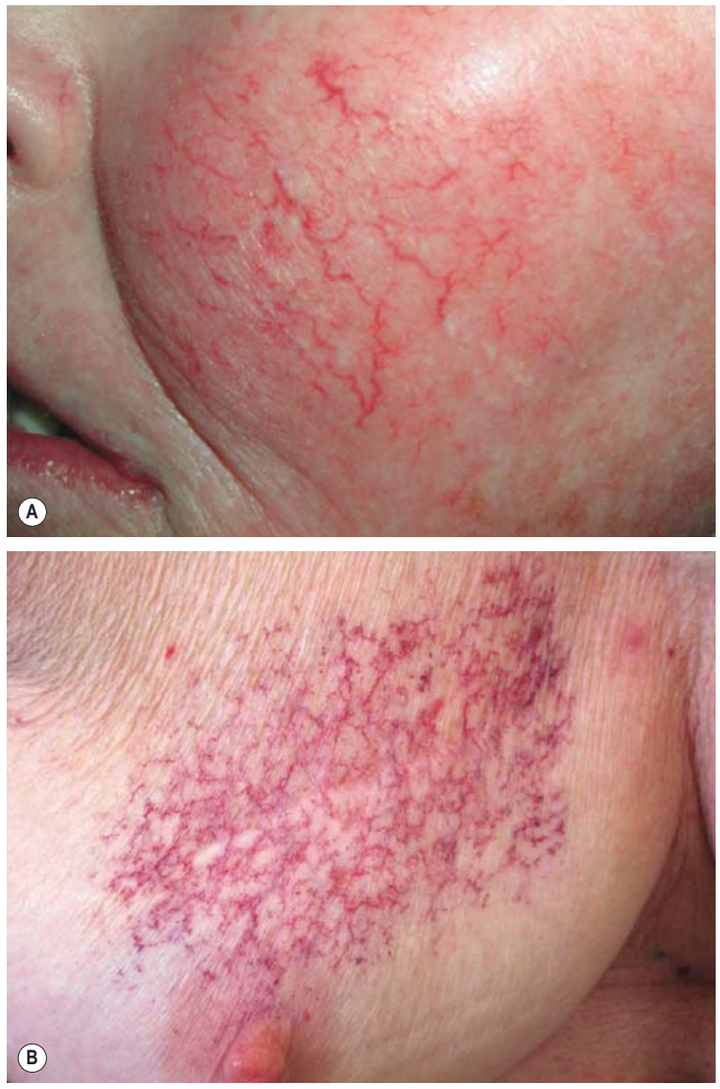


Fig. 106.7 Telangiectasias. A Sun-induced telangiectasias on the cheek. **B** Prominent telangiectasias on the breast following radiation therapy.

Cutaneous Collagenous Vasculopathy

Cutaneous collagenous vasculopathy (CCV) was first described in 2000[41]. Clinically, it can resemble generalized essential telangiectasia (GET). However, based upon the limited number of reported cases, there is not a female predominance, the telangiectasias may involve just the trunk and/or proximal extremities (Fig. 106.9A), and history of an "upward march" of lesions is lacking[42]. The etiology is unknown and there is no clear association with any underlying systemic illness or medication.

CCV does have unique histologic findings consisting of ectatic superficial blood vessels with hyalinized and laminated, concentric concretions surrounding the basement membrane of affected vessels. With special staining, this material is PAS-positive and diastase-resistant, and by immunohistochemistry, it reacts with antibodies against collagen type IV (Fig. 106.9B). Ultrastructurally, the deposits have been shown to consist of collagen with abnormal banding patterns (Luse bodies)[42].

This condition, like GET, is benign in nature. To date, responsiveness to vascular laser therapy has not been reported.

Unilateral Nevoid Telangiectasia

Telangiectasias in this condition are usually confined to the trigeminal or upper cervical dermatomes (Fig. 106.10) and may follow Blaschko's lines[43,44]. Congenital and acquired forms are recognized. It has been proposed that an increase in estrogen receptors on blood vessels in affected areas and/or an increase in estrogen levels is causative.

CAUSES OF TELANGIECTASIAS
PRIMARY
• Spider telangiectasias (also associated with estrogen excess) • Hereditary benign telangiectasia* • Costal fringe • Angioma serpiginosum • Unilateral nevoid telangiectasia • Generalized essential telangiectasia • Cutaneous collagenous vasculopathy
SECONDARY TO PHYSICAL CHANGES OR DAMAGE
• Photodamage • Post radiation therapy • Traumatic • Venous hypertension
SKIN DISEASE
• Telangiectatic rosacea • Incipient or involuted infantile hemangiomas
HORMONAL/METABOLIC
• Estrogen-related – Liver disease – Pregnancy – Exogenous estrogens • Corticosteroids
SYSTEMIC CONDITIONS
• Carcinoid syndrome • Mastocytosis (telangiectasia macularis eruptiva perstans) • Autoimmune connective tissue diseases – Lupus erythematosus – Dermatomyositis – CREST syndrome/systemic sclerosis • Mycosis fungoides, including poikilodermatous • B-cell lymphomas • Angiolupoid sarcoidosis • GVHD (in the context of poikiloderma) • HIV infection (anterior chest)
CONGENITAL MALFORMATIONS AND GENODERMATOSES
• Cutis marmorata telangiectatica congenita • Klippel–Trenaunay syndrome • Hereditary hemorrhagic telangiectasia • Ataxia–telangiectasia • Hypotrichosis–lymphedema–telangiectasia syndrome • Rombo syndrome • Bloom syndrome • Rothmund–Thomson syndrome • Poikiloderma with neutropenia • Dyskeratosis congenita • Xeroderma pigmentosum • Goltz syndrome (in Blaschko's lines) • GM1-gangliosidosis (also associated with angiokeratoma corporis diffusum) • Prolidase deficiency
*Childhood onset of multiple punctate, linear or arborizing telangiectasias favoring sun-exposed areas of the face and upper extremities; the vermilion lips and palate are occasionally affected, but there is no visceral involvement.

Table 106.6 Causes of telangiectasias. GVHD, graft-versus-host disease.

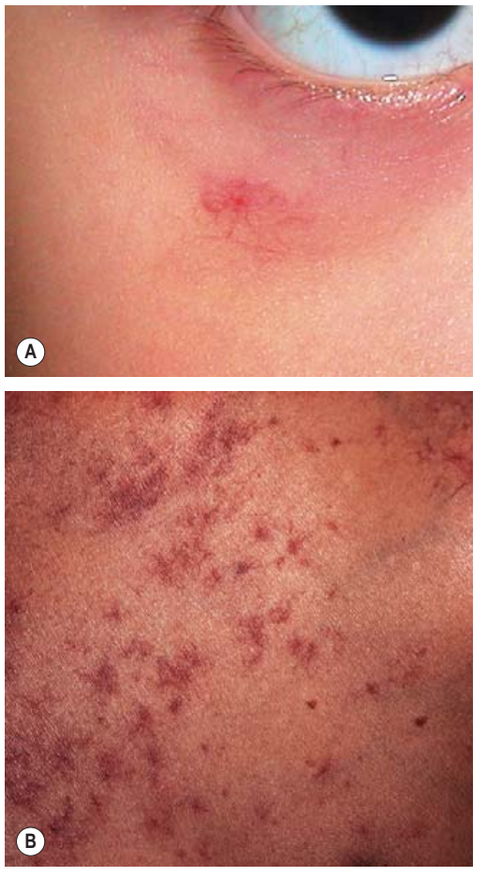


Fig. 106.8 Spider telangiectasias. **A** Central arteriole with radiating telangiectatic "legs" on the cheek of a young child. **B** Multiple lesions in a jaundiced patient with liver disease. *A, Courtesy, Phillip Bekhor, MD. B, Courtesy, Ronald P Rapini, MD.*

Situations of relative estrogen excess such as pregnancy, puberty and liver disease are associated with the acquired form.

Angioma Serpiginosum

Angioma serpiginosum is a rare vascular disorder with a characteristic appearance[45,46]. It is usually sporadic, but familial cases have been reported. Typically, the condition affects female patients and commences during the first two decades of life. Multiple, small, asymptomatic, non-palpable, deep-red to purple puncta occur in small clusters and sheets (Fig. 106.11). The arrangement and extension of the lesions may produce a serpiginous pattern. The extremities are most commonly affected, initially with a unilateral distribution; over months to years, the involvement may become more widespread. The palms, soles and mucous membranes are not involved.

The puncta represent dilated non-inflamed capillaries within the dermal papillae. These can be seen with dermoscopy. Incomplete blanching occurs with pressure, but lesions are not purpuric. The differential diagnosis includes pigmented purpuric eruptions, particularly the Majocchi's variant (purpura annularis telangiectoides), which is more likely to be bilateral and on biopsy has perivascular lymphocytes and extravasated erythrocytes. Treatment is not necessary, but lesions can be improved with the pulsed dye laser.

Hereditary Hemorrhagic Telangiectasia

Synonym: ▪ Osler–Weber–Rendu disease

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant condition in which there are multiple mucocutaneous and gastrointestinal telangiectasias (which are actually arteriovenous malformations) as well as variable visceral involvement (lung, liver and CNS). The diagnosis may first be suspected in children who have repeated episodes of epistaxis; however, the initial presentation can occur during the second or third decades of life. The characteristic mat-like and papular telangiectasias on the mucous membranes are first seen during adolescence[47]. Cutaneous lesions usually appear after puberty or even later in life.

Lesions, which increase in size and number as the patient ages, are most commonly seen on the face, tongue, lips, nasal mucosa, hands and fingertips. They frequently occur throughout the gastrointestinal tract and may result in obvious hemorrhage or iron deficiency anemia. Hemorrhage from vascular lesions in the lung, liver, CNS, spleen and urinary tract may occur, as well as paradoxical emboli due to pulmonary arteriovenous malformations.

HHT can result from mutations in several genes, most commonly *HHT1* and *HHT2* which encode endoglin and ALK-1, respectively (see

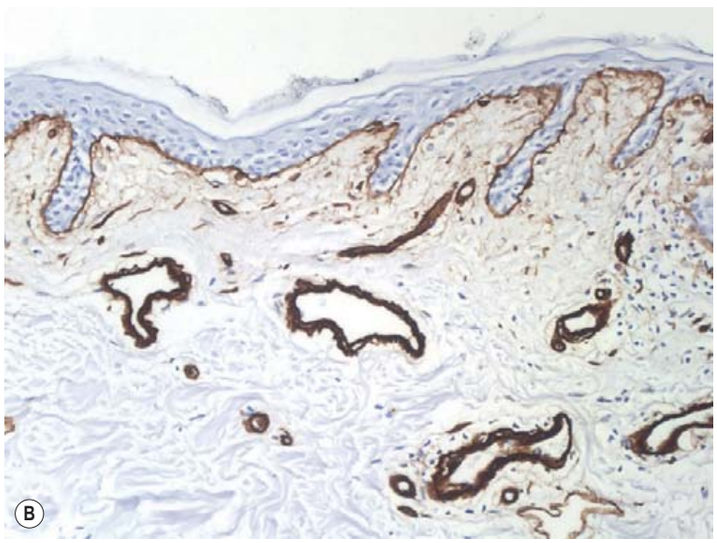


Fig. 106.9 Cutaneous collagenous vasculopathy – clinical and histologic features. A Multiple blanchable telangiectasias of the abdomen; the patient also had involvement of the thighs, back and hands. **B** Immunohistochemical staining with antibodies to collagen type IV demonstrating focal splitting and reduplication of the basement membrane zone surrounding dilated blood vessels. *Courtesy, Artur Zembowicz, MD. With permission from Davis TL, Mandal RV, Bevona C, et al. Collagenous vasculopathy: a report of three cases. J Cutan Pathol. 2008;35:967–70.*

Fig. 106.10 Unilateral nevoid telangiectasia. Note the segmental, unilateral distribution pattern of discrete telangiectasias. *Courtesy, Robert Hartman, MD.*

Fig. 106.11 Angioma serpiginosum. Grouped dark red puncta on the arm in a serpiginous pattern.

Table 104.2). Both of these glycoproteins are TGF-β receptors expressed by vascular endothelium, and they are thought to play a role in angiogenesis and vessel wall integrity.

Treatment of the mucocutaneous vascular lesions may not be required. Destructive treatments such as diathermy, cautery or laser may be used to treat individual lesions. Surgical management or embolization may be required for uncontrolled hemorrhage from mucosal lesions or complications arising from visceral lesions. Initial and longitudinal evaluation of patients with HHT is outlined in Table 104.5.

Ataxia–Telangiectasia

Synonym: ■ Louis-Bar syndrome

Ataxia–telangiectasia was first described by Louis-Bar in 1941. It is an autosomal recessive disorder characterized by cerebellar ataxia, chromosomal instability (frequent translocations between chromosomes 7 and 14), growth retardation, oculocutaneous telangiectasias, pulmonary infections (including bronchiectasis), immunodeficiency and the development of lymphomas[48].

It is covered in more detail in Chapter 60. Linear telangiectasias first appear on the bulbar conjunctivae between 4 and 6 years of age. Cutaneous telangiectasias favor the head and neck region, and they are most common on the malar prominences, ears and eyelids in addition to the popliteal and antecubital fossae. Patients may have poikiloderma (hypopigmentation, hyperpigmentation, atrophy, telangiectasia), premature hair graying, and decreased subcutaneous fat.

VENOUS LAKES

Venous lakes are small, dark-blue, slightly elevated, soft lesions that are predominantly localized on the lips (Fig. 106.12), ears or face of older adults. They can usually be emptied of most of their blood content by persistent pressure[49,50]. Pathologically, venous lakes represent telangiectasias in the dermis. Either one great, dilated venule or several communicating dilated spaces that contain erythrocytes are seen. Thrombosis is sometimes present. Optional treatment with electrosurgery or a hemoglobin-targeting laser is usually effective.

NEVUS ANEMICUS

Nevus anemicus is a congenital pale area of skin, most commonly found on the upper to mid trunk. These patches have an irregular border and an average diameter of 5–10 cm (Fig. 106.13). Within the body of the lesion, local blood vessels are very sensitive to endogenous catecholamines and are permanently vasoconstricted[51]. The border and extent of the lesion become imperceptible with pressure (or diascopy)

Fig. 106.12 Venous lake on the lip. The lesion is soft and, with compression, can be emptied of most of its blood content. *Courtesy, Ronald P Rapini, MD.*

Fig. 106.13 Nevus anemicus. Pale area of vasoconstriction with irregular borders on the back.

sufficient to cause blanching of surrounding skin. Conversely, application of heat or an ice cube will often accentuate the lesion; the border becomes hyperemic during warming, while the lesion stays pale. The pale appearance of the lesion (rather than an absence of pigmentation) and the results of the above clinical maneuvers allow nevus anemicus to be differentiated from vitiligo and nevus depigmentosus, respectively. Interestingly, islands of sparing may be present within the lesion, and skin transplanted within the nevus anemicus retains the characteristics of the donor site (donor dominance). No histologic abnormalities have been reported. No treatment is required or effective.

Fig. 106.14 Angiospastic macules (Bier spots). Multiple pale spots with an erythematous background on the forearm.

ANGIOSPASTIC MACULES (BIER SPOTS)

These were first described by Bier in 1898 and represent a pattern of vascular mottling consisting of white macular areas surrounded by a red to occasionally blue cyanotic background. Bier spots most commonly occur on the arms and legs of young adults (Fig. 106.14), but may also occur on the trunk. They are more noticeable in patients with lightly pigmented skin. Angiospastic macules may be induced by venous congestion and can be elicited by placing a limb in a dependent position or by placing a tourniquet around a limb. The spots disappear with limb elevation or release of the tourniquet. As with nevus anemicus, the border of the lesions becomes imperceptible with pressure (diascopy). The vascular pattern is thought to result from a benign physiological response consisting of vasoconstriction. Bier spots have also been associated with pregnancy and cryoglobulinemia.

REFERENCES

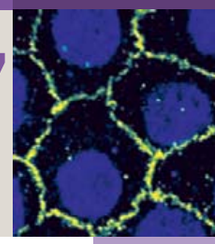
1. Fleischer AB Jr, Resnick SD. Livedo reticularis. Dermatol Clin. 1990;8:347–54.
2. Gibbs MB, English JC, Zirwas MJ. Livedo reticularis: an update. J Am Acad Dermatol. 2005;52:1009–19.
3. Dowd PM. Reactions to cold. In: Burns T, Breathnach S, Cox N, Griffiths C (eds). Textbook of Dermatology, 7th edn. Blackwell Science, 2004:23.7–23.12.
4. Francés C, Piette JC. The mystery of Sneddon syndrome: relationship with antiphospholipid syndrome and systemic lupus erythematosus. J Autoimmun. 2000;15:139–43.
5. Francés C, Papo T, Wechsler B, et al. Sneddon syndrome with or without antiphospholipid antibodies: a comparative study in 46 patients. Medicine (Baltimore). 1999;78:209–19.
6. Devillers AC, de Waard-van der Spek FB, Oranje AP. Cutis marmorata telangiectatica congenita: clinical features in 35 cases. Arch Dermatol. 1999;135:34–8.
7. Gerritsen MJP, Steijlen PM, Brunner HG, Rieu P. Cutis marmorata telangiectatica congenita: report of 18 cases. Br J Dermatol. 2000;142:366–9.
8. Bauzá A, España A, Idoate M. Cutaneous polyarteritis nodosa. Br J Dermatol. 2002;146:694–9.
9. Speight EL, Lawrence CM. Reticulate purpura, cryoglobulinaemia and livedo reticularis. Br J Dermatol. 1993;129:319–23.
10. Filo V, Brezová D, Hlavcák P, Filová A. Livedo reticularis as a presenting symptom of polycythemia vera. Clin Exp Dermatol. 1999;24:428.
11. Gibson GE, Su WPD, Pittelkow MR. Antiphospholipid syndrome and the skin. J Am Acad Dermatol. 1997;36:970–82.
12. Weir NU, Snowden JA, Greaves M, Davies-Jones GAB. Livedo reticularis associated with hereditary protein C deficiency and recurrent thromboembolism. Br J Dermatol. 1995;132:283–5.
13. Donnet A, Khalil R, Terrier G, et al. Cerebral infarction, livedo reticularis, and familial deficiency in antithrombin-III. Stroke. 1992;23:611–2.
14. Rosman HS, Davis TP, Reddy D, Goldstein S. Cholesterol embolization: clinical findings and implications. J Am Coll Cardiol. 1990;15:1296–9.
15. Spiers EM, Sanders DY, Omura EF. Clinical and histologic features of primary oxalosis. J Am Acad Dermatol. 1990;22:952–6.
16. Yamamoto M, Danno K, Shio H, Imamura S. Antithrombotic treatment in livedo vasculitis. J Am Acad Dermatol. 1988;18:57–62.
17. Sladden MJ, Nicolaou N, Johnston GA, Hutchinson PE. Livedo reticularis induced by amantadine. Br J Dermatol. 2003;149:655–80.
18. Wilkin JK. Why is flushing limited to a mostly facial cutaneous distribution? J Am Acad Dermatol. 1988;19:309–13.
19. Freeman R, Waldorf HA, Dover JS. Autonomic neurodermatology (Part II): Disorders of sweating and flushing. Semin Neurol. 1992;12:394–407.
20. Mooney E. The flushing patient. Int J Dermatol. 1985;24:549–54.
21. Wilkin JK. The red face: flushing disorders. Clin Dermatol. 1993;11:211–23.
22. Wilkin JK. Flushing reactions. Recent Adv Dermatol. 1983;6:157–87.

23. Hurst E, Heffernan M. Cutaneous changes in the flushing disorders and the carcinoid syndrome. In: Freedberg I, Eisen A, Wolff K, et al. (eds). Dermatology in General Medicine, 6th edn. New York, NY: McGraw-Hill 2003:1673–75.
24. Thompson GH, Hahn G, Rang M. Erythromelalgia. Clin Orthop Rel Res. 1979:144:249–54.
25. Kvernebo K. Erythromelalgia: a condition caused by microvascular arteriovenous shunting. Vasa. 1998;Suppl. 51:1–40.
26. van Genderen PJ, Lucas IS, van Strik R, et al. Erythromelalgia in essential thrombocythemia is characterized by platelet activation and endothelial cell damage but not by thrombin generation. Thromb Haemost. 1996;76:333–8.
27. Mork C, Asker CL, Salerud EG, Kvernebo K. Microvascular arteriovenous shunting is a probable pathogenetic mechanism in erythromelalgia. J Invest Dermatol. 2000;114:643–6.
28. Berlin AL, Pehr K. Coexistence of erythromelalgia and Raynaud's phenomenon. J Am Acad Dermatol. 2004;50:456–60.
29. Yang Y, Wang Y, Li S, et al. Mutations in *SCN9A*, encoding a sodium channel alpha subunit, in patients with primary erythermalgia. J Med Genet. 2004;41:171–4.
30. Choi JS, Dib-Hajj SD, Waxman SG. Inherited erythermalgia: limb pain from an S4 charge-neutral Na channelopathy. Neurology. 2006;67:1563–7.
31. Han C, Dib-Hajj SD, Lin Z, et al. Early- and late-onset inherited erythromelalgia: genotype-phenotype correlation. Brain. 2009;132:1711–22.
32. Fischer TZ, Waxman SG. Familial pain syndromes from mutations of the NaV1.7 sodium channel. Ann N Y Acad Sci. 2010;1184:196–207.
33. Burns TM, Te Morsche RH, Jansen JB, Drenth JP. Genetic heterogeneity and exclusion of a modifying locus at 2q in a family with autosomal dominant primary erythermalgia. Br J Dermatol. 2005;153:174–77.
34. Davis MDP, O'Fallon WM, Rogers RS III, Rooke TW. Natural history of erythromelalgia. Arch Dermatol. 2000;136:330–6.
35. Iqbal J, Bhat MI, Charoo BA, et al. Experience with oral mexiletine in primary erythromelalgia in children. Ann Saudi Med. 2009;29:316–8.
36. Natkunarajah J, Atherton D, Elmslie F, et al. Treatment with carbamazepine and gabapentin of a patient with primary erythermalgia (erythromelalgia) identified to have a mutation in the *SCN9A* gene, encoding a voltage-gated sodium channel. Clin Exp Dermatol. 2009;34:e640–2.
37. Cohen JS. Erythromelalgia: new theories and new therapies. J Am Acad Dermatol. 2000;43:841–7.
38. Bean WB. Vascular Spiders and Related Lesions of the Skin. Oxford: Blackwell Scientific, 1958.
39. Rothe MJ, Grant-Kels JM. Nomenclature of the primary telangiectasias. Int J Dermatol. 1992;31:320.
40. McGrae JD Jr, Winkelmann RK. Generalized essential telangiectasia: report of a clinical and histochemical study of 13 patients with acquired cutaneous lesions. J Am Med Assoc. 1963;185:909–13.
41. Salama S, Rosenthal DJ. Cutaneous collagenous vasculopathy with generalized telangiectasia: an immunohistochemical and ultrastructural study. J Cutan Pathol. 2000;27:40–8.
42. Davis TL, Mandal RV, Bevona C, et al. Collagenous vasculopathy: a report of three cases. J Cutan Pathol. 2008;35:967–70.
43. Wilken JK. Unilateral dermatomal superficial telangiectasia. Arch Dermatol. 1984;120:579–80.
44. Uhlin SR, McCarty KS Jr. Unilateral nevoid telangiectatic syndrome: the role of estrogen and progesterone receptors. Arch Dermatol. 1983;119:226–8.
45. Hunt SJ, Santa Cruz DJ. Acquired benign and 'borderline' vascular lesions. Dermatol Clin. 1992;10:97–115.
46. Marriott PJ, Munro DD, Ryan T. Angioma serpiginosum: familial incidence. Br J Dermatol. 1975;93:701–6.
47. Abrahamian LM, Rothe MJ, Grant-Kels JM. Primary telangiectasia of childhood. Int J Dermatol. 1992;31:307–13.
48. Smith LL, Conerly SL. Ataxia-telangiectasia or Louis-Bar syndrome. J Am Acad Dermatol. 1985;12:681–96.
49. Bean WB, Walsh JR. Venous lakes. Arch Dermatol. 1956;74:459–63.
50. Alcalay J, Sandbank M. The ultrastructure of cutaneous venous lakes. Int J Dermatol. 1987;26:645–46.
51. Mountcastle EA, Diestelmeier MR, Lupton GP. Nevus anemicus. J Am Acad Dermatol. 1986;14:628–32.

This page intentionally left blank

Principles of Tumor Biology and Pathogenesis of BCCs and SCCs

107



Edel A O'Toole, Fredrik Pontén, Joakim Lundeberg and Anna Asplund

Chapter Contents

Structure and function of p53 ..... *1764*
Structure and function of Patched *1765*
Pathogenesis of BCC *1768*
Pathogenesis of SCC *1769*

Key features

- Oncogenes act in a dominant fashion and gain-of-function results in increased proliferation
- Tumor suppressor genes act in a recessive fashion and loss of normal function results in uncontrolled growth
- The *p53* gene, the single most frequently mutated gene in human cancer, controls signaling pathways involved in cell division and apoptosis
- Mutations in either apoptosis- or senescence-regulating genes are considered "driver" mutations and are uniformly present in cancers.
- The *PTCH* gene controls proliferation and differentiation, and disruption of normal function is required for the development of basal cell carcinoma (BCC)
- BCCs, the most frequent cancer in humans, grow in skin that contains hair follicles, arise without precursors, and show no sign of progression
- BCCs are stroma-dependent and are locally invasive without producing metastasis (with rare exceptions)
- Squamous cell carcinomas (SCCs) arise in chronically sun-exposed skin and originate from epidermal keratinocytes
- SCC develops through a series of progressive stages, including actinic keratosis, invasive cancer and eventual metastasis

INTRODUCTION

No definition of cancer is entirely satisfactory from a cell biology point of view, despite the fact that cancer is essentially a cellular disease, characterized by a transformed cell population with autonomous cell growth and invasive behavior. Microscopic evaluation of a tissue section taken from an excised skin tumor remains the gold standard for determining the diagnosis of skin cancer. Analysis of genomic DNA, transcribed genes and expressed proteins adds important information to the histologic features detected by light microscopy. In the future, diagnosis and prognostic information and choice of treatment will most likely be based upon a synoptic evaluation of morphology in conjunction with an analysis of nucleic acids and proteins. Even today, evolving knowledge based on the human genome sequence and biochemical pathways, including signaling within and between cells, enables us to dissect some of the mechanisms that underlie different stages in tumor formation as well as the variation of phenotypes which define the different types of cancer.

Carcinogenesis

Malignant transformation represents the transition to a malignant phenotype and is based on the progressive accumulation of genetic alterations. Although not formally proven, malignant transformation takes place in one cell from which a subsequently developed tumor originates (the clonality of cancer dogma). Carcinogenesis is the process by which cancer is generated and is generally accepted to include multiple events which ultimately lead to growth of a malignant tumor[1]. This multistep process includes several rate-limiting steps, representing the addition of mutations and epigenetic events, which eventually lead to the formation of cancer (after various stages of precancerous proliferation).

The most common forms of cancer arise in somatic cells and are predominantly of epithelial origin (skin, prostate, breast, colon and lung), followed by cancers originating from hematopoietic lineage (leukemia and lymphoma) and mesenchymal cells (sarcomas). The stepwise changes involve an accumulation of errors (mutations) in vital regulatory pathways that control cell division, apoptosis, senescence, cell–cell and cell–matrix interactions, and cell death. Each of these changes provides a selective Darwinian growth advantage compared to surrounding cells, resulting in a net growth of the tumor cell population. A certain degree of genomic instability is probably required to attain a sufficient number of mutations. The spontaneous mutation rate is not high enough to explain the speed with which a cancer develops and thus tumor cells display a "mutator phenotype" with a higher mutation rate compared to neighboring normal cells. Decreased efficiency in DNA repair systems is one important mechanism leading to a "mutator phenotype"[2].

Knowledge of the events involved in carcinogenesis has been obtained from experimental cell culture and animal studies, as well as from clinicopathologic studies in humans. Information regarding cellular, molecular and genetic changes that represent tumor initiation and progression can be linked to histopathologic correlations. Primary genetic alterations leading to initiation of cancer can be identified and validated in experimental systems, but in clinical investigations this is not feasible. Progression is ascribed to the events that occur after malignant transformation and can in part be defined by histology. This multistep model includes defined stages of tumor development accompanied by features that include multiple genetic and epigenetic events involving different signalling pathways. Specific changes in DNA, signifying different steps in cancer development, were first described for colorectal cancer[3]. This model illustrates distinct genetic hits acquired during the passage from normal epithelium to metastatic cancer and provides support for the multi-hit carcinogenesis hypothesis.

The hallmarks of cancer have also been described from a functional perspective and consist of a number of molecular, biochemical and cellular traits that are shared by most human cancers. Six traits have been proposed and include self-sufficiency with regard to growth signals, insensitivity to antigrowth signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, and tissue invasion/metastasis[4]. Self-sufficiency with regard to growth signals can be achieved by activation of oncogenes. Loss of function of tumor suppressor genes results in uncontrolled proliferation due to insensitivity to antigrowth signals. Evasion of apoptosis can be accomplished via inactivation of the *p53* tumor suppressor gene and production of survival factors. Constitutively active telomerase can render limitless replicative potential. The production of vascular endothelial growth factors results in sustained angiogenesis, and inactivation of cellular adhesion molecules, e.g. E-cadherin, facilitates the cell migration necessary for tissue invasion and metastasis. The order in which these capabilities are acquired is not static and varies between different forms of cancer.

Several traits can be achieved through a single genetic change, whereas a certain trait may require several genetic alterations. For example, inactivation of the *p53* tumor suppressor gene can result in insensitivity to antigrowth signals, resistance to apoptosis and increased

angiogenesis. In addition, impairment of cell cycle control and apoptotic pathways contributes to the "mutator phenotype". In individuals predisposed to cancer at an early age, certain traits result from alterations in the germline and are thus carried in every cell. Xeroderma pigmentosum ("mutator phenotype"; mutations in nuclear excision repair genes; Ch. 86), familial melanoma (defect in cell cycle control; *CDKN2A [INK4A]* mutations), Li–Fraumeni syndrome (defect in cell cycle control/apoptosis; *p53* mutations) and Gorlin syndrome (defect in control of proliferation/differentiation; *PTCH* gene mutations) are examples of how mutations within single genes in the germline promote development of cancer.

The Cell Cycle

Normal cell growth and cell mass are influenced by several internal factors, including signals which regulate proliferation, differentiation and cell death. These factors are in part triggered by blood supply and the external environment, including soluble molecules as well as matrix–cell and cell–cell contacts. Proliferation involves DNA replication and mitosis in a series of events termed the cell cycle (Fig. 107.1). Three primary checkpoints (G1, G2 and M), which act to ensure successful cell division, have been identified in the cell cycle[5]. Regulation of these G1, G2 and M transitions involves three major protein families: cyclins, cyclin-dependent kinases (CDKs) and cyclin-dependent kinase inhibitors (CKIs). CDKs regulate the phosphorylation of key proteins involved in cell cycle progression, e.g. the retinoblastoma (Rb) protein. The concentration and balance of cyclins versus CKIs in turn regulate CDK activity. CDKs are activated by mitogenic growth factors and are removed by ubiquitin-mediated proteolysis in a cyclic manner correlating to the different phases of the cell cycle.

The G1 transition is a critical one and is regulated by a complex interplay of macromolecules influenced by growth factors, hormones and cell contacts. The key factor is the degree of phosphorylation of Rb. If, at the G1 checkpoint, Rb is underphosphorylated, then cell proliferation is blocked and the cell is arrested in G1. The repression can be reversed by CDK-mediated phosphorylation. This phosphorylation/dephosphorylation cycle can thus reversibly regulate cell cycle progression and rate of proliferation (see Fig 107.1).

There are two major families of CKIs, and both are involved in the G1 checkpoint. The family of inhibitors of CDK4, also referred to as INK4, consists of p15, p16, p18 and p19; these inhibitors specifically bind to CDK4 and CDK6. The other family of CKIs is less specific with respect to the type of CDK they bind and includes the general CDK–cyclin complex inhibitors p21, p27 and p57. Expression of these CKIs is in part tissue-specific.

The *CDKN2A (INK4A)* gene locus, which is involved in familial melanoma (see Ch. 113), has an extraordinary feature; it encodes two different mRNAs by shifting the reading frame (hence the term ARF or alternative reading frame) and these two mRNAs are independently regulated. As a result, the two protein products (p16 and $p14^{ARF}$) have different amino acid sequences and different functions. p16 is a CKI that blocks Rb phosphorylation, whereas $p14^{ARF}$ binds MDM2, resulting in an increase in p53 through interference with the p53–MDM2 feedback loop. Thus, both p16 activation and $p14^{ARF}$ activation lead to cell cycle arrest through different pathways and their dysfunction can lead to cell proliferation. In carcinomas, cyclin and CKI alterations are common, whereas activating mutations in CDKs are rare, e.g. only a few families with familial melanoma have been described with mutations in *CDK4*. p53 and Rb alterations are also common events in human cancer.

Cancer Genes – Oncogenes and Tumor Suppressor Genes

With advances in technology, it is now possible to catalogue genome-wide changes in DNA, at unparalleled resolution. In breast and colon cancer, sequencing the exomes (coding exons) of tumors has revealed an average of 50 to 100 somatic mutations in "cancer genes" in each tumor[6]. Are these all significant? The answer is, probably, no. Somatic alterations in tumor DNA are called either *driver mutations* that confer a selective growth advantage to the cancer cells or *passenger mutations* that have no effect on tumorigenesis. Somatic copy number alterations can also occur[7,8]. Increase of gene function (oncogenes) as well as loss of gene function (tumor suppressor genes) will affect cell proliferation and can lead to uncontrolled growth. These two categories of genes,

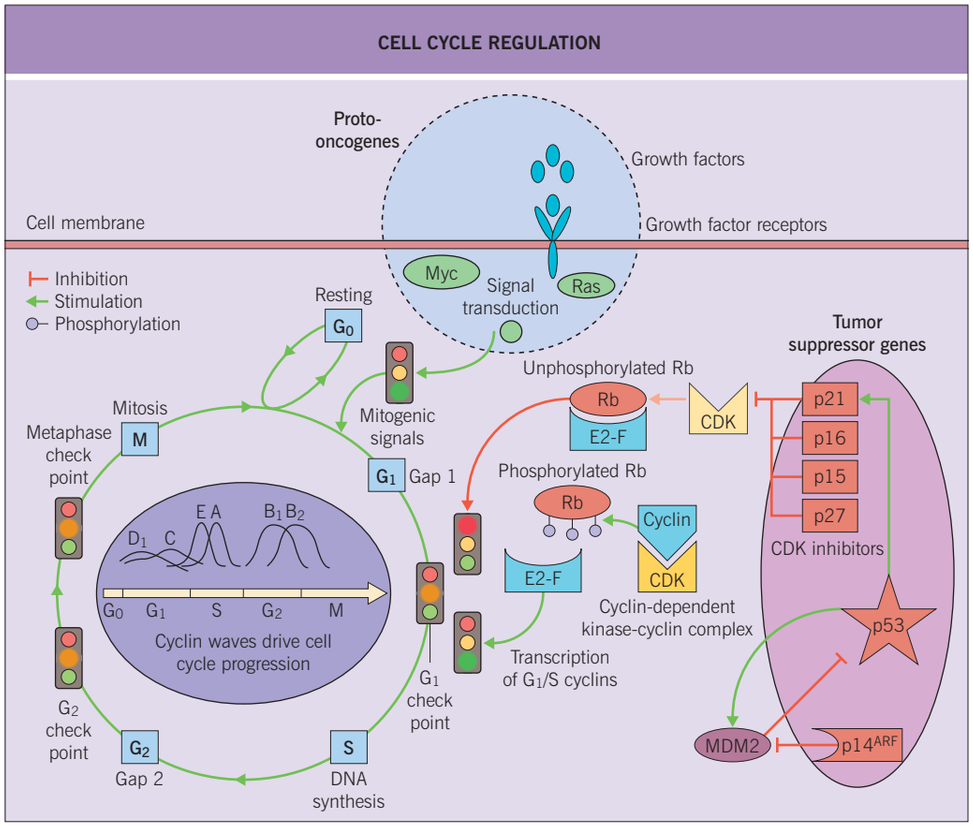


Fig. 107.1 The cell cycle. In normally dividing cells, the first gap (G1 phase, 8–30 h) prepares the cell for DNA synthesis (S phase, 8 h). The G1 gap includes a connection to a resting state (G0 phase) representing quiescent cells capable of entering into G1 after appropriate stimuli. Certain cells that exit the cell cycle and enter G0 phase are destined for terminal differentiation or senescence, irreversibly locked out of the cell cycle. After S phase, reorganization of the chromatin occurs in a second gap (G2 phase, 3 h) prior to mitosis (M, 1 h). Differentiation, which has a reciprocal correlation to proliferation, takes place in G0 after exit from G1. Cyclin waves, an underlying mechanism for cell cycle progression, are illustrated inside the cell cycle. Proto-oncogenes acting as driving forces on the cell cycle (green traffic lights), are depicted in green. Tumor suppressor genes, regulating the G1 checkpoint (red traffic light) of the cell cycle, are depicted in red. Yellow traffic light symbols represent checkpoints in the cell cycle. CDK, cyclin-dependent kinase; E2-F, a transcription factor that controls transcription of cyclins; Rb, retinoblastoma protein.

EXAMPLES OF ONCOGENES AND TUMOR SUPPRESSOR GENES IMPLICATED IN CARCINOGENESIS				
Gene			Protein product	
Name	Function	Chromosome	Location	Function
sis	Oncogene	22	Extracellular	Platelet-derived growth factor (PDGF)
ras	Oncogene	11	Membrane	GTPase
src	Oncogene	20	Cytoplasm/ membrane	Tyrosine kinase
raf	Oncogene	3	Cytoplasm/ membrane	Serine/threonine kinase
myc	Oncogene	8	Nucleus	Transcription factor
fos	Oncogene	14	Nucleus	Transcription factor
Rb	Suppressor gene	13	Nucleus	Cell cycle regulator
p53	Suppressor gene	17	Nucleus	DNA repair, apoptosis
bcl-2	Suppressor gene	18	Mitochondria	Apoptosis

Table 107.1 Examples of oncogenes and tumor suppressor genes implicated in carcinogenesis. A non-mutated oncogene is often referred to as a "proto-oncogene" and it encodes a protein that is part of the necessary network for cellular regulation.

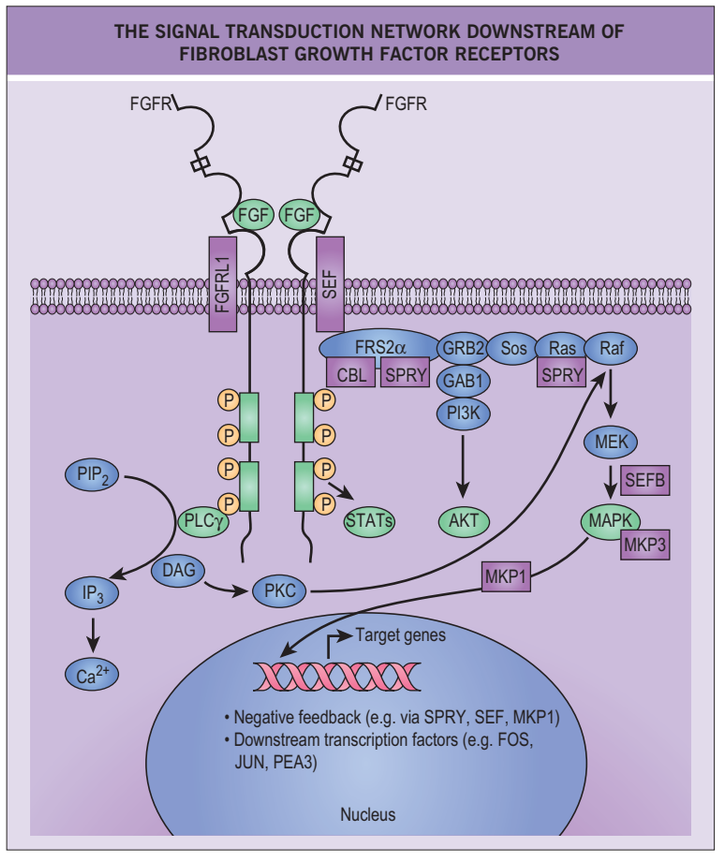


Fig. 107.2 The signal transduction network downstream of fibroblast growth factor (FGF) receptors (FGFRs), along with negative regulators. Following ligand binding and receptor dimerization, the kinase domains transphosphorylate each other, leading to the docking of adaptor proteins and the activation of four key downstream pathways: (1) RAS–RAF–MAPK; (2) PI3K–AKT; (3) signal transducer and activator of transcription (STAT); and (4) phospholipase Cγ (PLCγ) (all shown in green). Negative regulators are shown in purple, e.g. Sprouty (SPRY) and similar expression to FGF (SEF). DAG, diacylglycerol; FGFRL1, fibroblast growth factor receptor-like 1; FRS2α, FGFR substrate 2α; GAB1, GRB2-associated binding protein 1; GRB2, growth factor receptor-bound 2; IP_3, inositol triphosphate; MAPK, mitogen-activated protein kinase; MEK, MAPK kinase; MKP1/MKP3, MAPK phosphatase 1/3; P, phosphorylation; PI3K, phosphatidylinositol-3-kinase; PIP_2, phosphatidylinositol-4, 5-biphosphate; PKC, protein kinase C; Sos, son of sevenless. The abbreviations AKT, CBL and Raf are related to viral-associated nomenclature. *Adapted with permission from MacMillan Publishers Ltd: Turner N, Grose R. Nat Rev Cancer. Fibroblast growth factor signalling: from development to cancer. 2010;10:116–29.*

and their encoded proteins, represent the functional features that drive carcinogenesis at a molecular level. Oncogenes, described by a three-letter code (*ras, myc, src, fos*), are genes that gain oncogenic or transforming potential as a result of genetic changes[9]. More than 400 "cancer genes" have been identified that participate in diverse regulatory pathways that control cell fate (see examples in Table 107.1).

Extracellular signals such as growth factors and extracellular matrix components determine if cells move from a quiescent state into a proliferative state. These signals are transmitted into the cell through transmembrane structures that have distinct features (e.g. receptors) and the signals are then propagated into the nucleus by a multitude of interacting pathways (i.e. signal transduction). Increased production of growth factors and growth factor receptors is frequently observed in cancer cells and this results in an autocrine loop leading to enhanced cell proliferation[10]. Upon ligand binding, growth receptors mediate signals via tyrosine kinases or serine/threonine kinases on the cytosolic side of the membrane. As an example, the fibroblast growth factor signaling pathway is depicted in Figure 107.2. Cancer cells can also alter receptor activity via "activating" mutations in the genes that encode the receptors, thus generating constitutively active, ligand-independent receptor molecules (e.g. KIT in acral melanoma).

The *ras* proto-oncogene, which is mutated in approximately 40% of human cancers, plays a key role in signal transduction pathways between the cell membrane and the nucleus, communicating signals to a number of effector pathways. The ras family members are *H-ras, K-ras* and *N-ras*, and the 21 kDa Ras protein is a GTP-binding protein with latent GTPase activity, active when bound to GTP and inactive when GTP is hydrolyzed to GDP. The *ras* oncogene acts as a multifunctional modulator capable of redirecting input signals from growth receptors to alternative pathways. The end result of the signal cascade following Ras activation is increased transcription due to an alteration in the quantity or function of nuclear transcription factors.

For oncogenes, a change in one of the two inherited alleles leads to a gain-of-function that is dominant (over that of the unaffected allele). In contrast, tumor suppressor genes act in a recessive manner, i.e. a mutation in one allele has no effect (see Fig. 107.3). The biologic consequence of a recessive mutation becomes apparent when the second, normal (wild-type) allele is lost. Loss of this allele is termed loss of heterozygosity (LOH) and represents alteration from a heterozygous to a homozygous state for a gene (Fig. 107.4).

The tumor suppressor genes are of critical importance in human carcinogenesis. In contrast to the diverse interactions of oncogenes converging to stimulate growth, tumor suppressor genes act by inhibiting proteins that control cell cycle progression. Inactivation of both alleles of a suppressor gene (one of which may be inherited in an inactivated state as in familial cancer syndromes) is required to inactivate the normal repressive function. In normal cells, inactivation of the protein products of tumor suppressor genes is achieved via binding to other proteins or by phosphorylation. In tumor cells, inactivation is often due to mutations, insertions and/or deletions (allelic loss).

The Rb protein serves as a classic example for examining the functions of tumor suppressor genes. Underphosphorylated Rb protein blocks proliferation in normal cells by binding to, and thereby inactivating, a transcription factor (E2F) necessary for propagation of the cell cycle (see Fig. 107.1). Serine/threonine phosphorylation of the Rb protein disrupts this binding, releasing E2F and enabling cell cycle progression. Genes that control the levels of Rb phosphorylation (e.g. *CDKN2A*) act as tumor suppressor genes and are often inactivated in cancer by mutation or promoter methylation.

The *p53* gene is frequently inactivated by a point mutation, and as opposed to classic tumor suppressor genes (that act in a recessive manner), *p53* mutations can act in a dominant-negative manner (see Ch. 54 & Fig. 107.4). This is because the p53 protein is a tetrameric protein and oligomerization of a mutant allele product and a normal allele product results in an inactive protein.

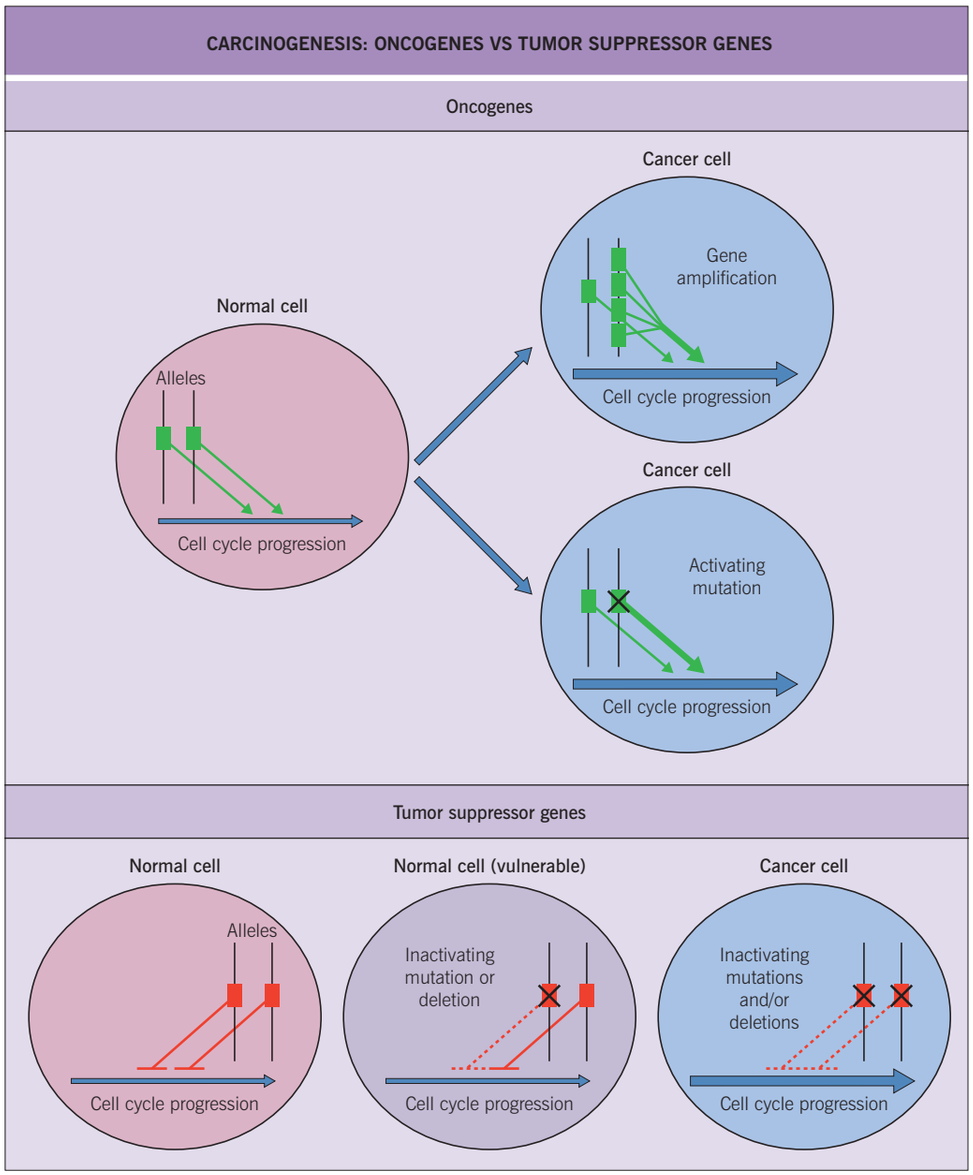


Fig. 107.3 Carcinogenesis: oncogenes vs tumor suppressor genes. An oncogene acts as an accelerator on the cell cycle, increasing cell proliferation. Oncogenes are proto-oncogenes that have acquired activating mutations or gene amplifications. Oncogenes function in a dominant fashion, meaning that activating alterations in only one allele are sufficient for the gene to gain oncogenic potential. A tumor suppressor gene acts as a brake on the cell cycle, decreasing cell proliferation. Tumor suppressor genes are inactivated by mutations in both alleles. Tumor suppressor genes function in a recessive manner, meaning that a mutation in only one allele is not sufficient for loss of gene function. Fig. 107.4 demonstrates the various mechanisms by which the "second hit" occurs in tumor suppressor genes.

MicroRNA (miRNA) is non-coding RNA that regulates translation and degradation of specific mRNAs (see Fig. 3.15). Dysregulation of miRNA expression has been associated with oncogenic transformation and miRNAs whose actions mimic oncogenes or tumor suppressors have been identified in human cancer. For example, miRNA-31 has been identified as a metastasis suppressor[11].

Epigenetic change is a modification to DNA or associated histone proteins, without variation in DNA sequence. There are two major mechanisms of epigenetic modification, DNA methylation (addition of a methyl [CH_3] group) and chromatin or histone modification. DNA methylation occurs in cytosines that precede guanines, known as dinucleotide CpGs or CpG islands, which occur in the promoter regions of many genes and generally results in gene silencing. However, changes in methylation may also occur in non-CpG-island regions, usually in close proximity to CpG islands. In cancer, methylation of cancer genes is more common than loss-of-function mutations or deletions[12].

Apoptosis

An equilibrium between proliferation and cell death is essential for normal homeostasis, and an imbalance can lead to abnormal growth. Cell death is important for tissue remodeling during embryogenesis and for maintaining homeostasis in normal adult tissues. Cell death is equally crucial for the removal of damaged cells, and this can occur via two different mechanisms – necrosis or apoptosis[13]. Necrosis involves poor nutrient supply leading to membrane disruption and cell lysis without *de novo* protein synthesis.

In contrast, apoptosis is regulated and requires mRNA and protein synthesis. Microscopically, apoptosis is characterized by the appearance of apoptotic bodies composed of cell membrane remnants and condensed chromatin. Apoptosis-related proteases, termed caspases, become activated and affect signal transduction pathways by activation of: (1) enzyme precursors that digest genomic DNA into 200 base pair (bp) units; and (2) proteases that degrade structurally important proteins such as lamins and actin (Fig. 107.5). Apoptosis can be induced by several different stimuli, including DNA damage (e.g. due to radiation, chemicals), withdrawal of growth cytokines (e.g. EGF, TGF-α, IGF, PDGF) and death-promoting agents (e.g. TNF) (see Fig. 107.5). Conflicts between different signaling pathways can also provoke apoptosis.

Independent of triggering apoptotic stimuli, apoptosis converges into a common series of molecular events that lead to irreversible morphologic changes and ultimately cell death. The regulation of apoptosis is under the strict control of proteins, including Bcl-2, BAX and Bad families that are capable of regulatory cross-talk by heterodimerization of protein subunits. The mitochondrial membranes contain proteins that either activate apoptosis (BAX, Bad) or inhibit apoptosis (Bcl-2). Overexpression of the survival factor Bcl-2 blocks apoptosis and thus protects the cells against radiation and chemotherapeutic agents. The p53 protein activates transcription of BAX and inhibits transcription of

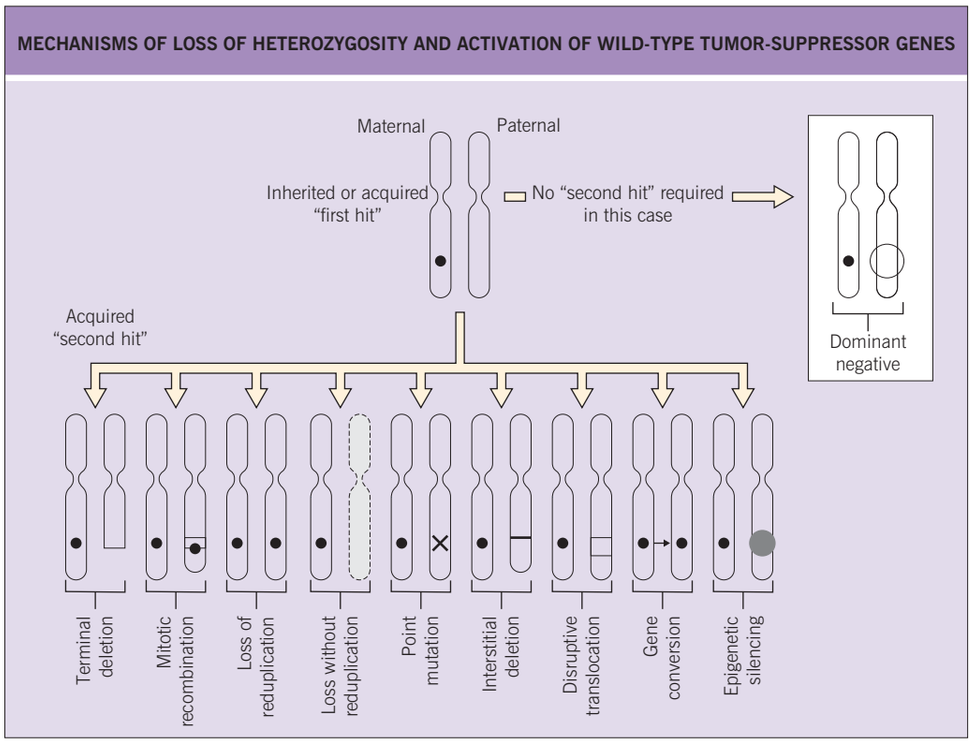


Fig. 107.4 Mechanisms of loss of heterozygosity and inactivation of wild-type tumor suppressor genes. Mechanisms depicted by which both copies of a gene can be inactivated (bottom). With loss of heterozygosity (LOH), the resultant changes are best explained by the absence of wild-type protein. While translocations usually activate oncogenes or generate new fusion proteins, they can also be associated with microdeletions. A common mechanism of epigenetic silencing is methylation of the promoter region of a gene. An alternative mechanism exists (right) in which the wild-type allele is rendered non-functional. That is, some mutations can lead to expressed truncated proteins, and the latter may have dominant negative effects or may be partially functional. An example would be the p53 protein. *Adapted and redrawn from Foulkes WD, Inherited susceptibility to common cancers, N Engl J Med. 2008;359:2143–53.*

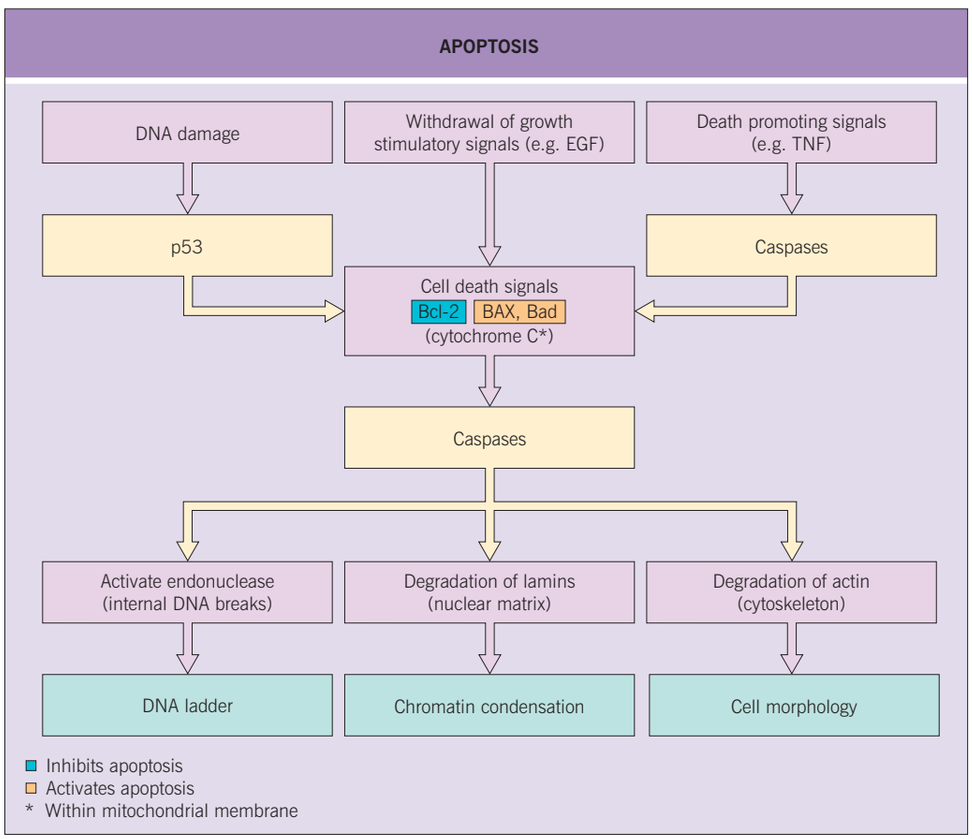


Fig. 107.5 Apoptosis. Various triggering events are depicted above the factors involved in the apoptotic pathways. Consequences of induced apoptosis are shown at the bottom of the figure. Fragmentation of genomic DNA by endonucleases results in a discrete ladder of DNA fragments of decreasing lengths. EGF, epidermal growth factor; TNF, tumor necrosis factor.

bcl-2, the net result favoring apoptosis. Thus, the p53 protein is a key factor for integrating pathways regulating DNA synthesis, DNA repair and apoptosis.

Limitless Replicative Potential

The number of mutations in a cell increases with time and partially explains the increasing risk for acquiring cancer as we age. The increased number of mutations is evident in normal cultured cells, which undergo approximately 60–70 doublings before reaching senescence and then death as a consequence of accumulating mutations and telomere shortening. Senescent cells are viable, but they are incapable of proliferation. During senescence, abnormal chromosomes accumulate and the telomere sequences diminish, eventually resulting in a crisis that leads to apoptosis.

The progressive erosion of telomere sequences (50–100 bp per mitosis) through successive cycles of replication eventually precludes protection of the ends of the chromosomes (see Fig. 67.21). This

facilitates end-to-end chromosomal fusions, resulting in karyotypic disarray and then apoptosis. Carcinogenesis involves disruption of these normal apoptotic events, yielding limitless replicative potential for the tumor cells. Up to 90% of all cancers exhibit increased levels of telomerase, the enzyme required for maintenance of telomere sequences in normal cells; this leads to retention of telomeres irrespective of the number of cell divisions[14].

Cancer cell populations also contain a subpopulation of self-renewing cells called cancer stem cells. These latter cells can increase in number as tumors enlarge and they can give rise to progeny that have the ability to invade locally as well as metastasize to distant sites, referred to as tumor-propagating cells (TPCs)[15]. Markers such as CD133, CD44 and ALDH (aldehyde dehydrogenase) are expressed by TPCs, and this population can be expanded within tumors by symmetrical division of TPCs and by cancer cells undergoing epithelial–mesenchymal transition.

Angiogenesis

Formation of new blood vessels (angiogenesis) is essential for tumor mass expansion, in order to provide adequate levels of oxygen and nutrients[16]. Endothelial cells are normally quiescent, with low proliferation rates and mitoses rarely being observed (aside from the setting of wound healing). Angiogenesis is initiated by growth factors, e.g. fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF), acting in a paracrine fashion and stimulating local endothelial proliferation (see Ch. 102). Sprouts from surrounding vasculature migrate toward the tumor via protease-mediated remodeling of extracellular matrix (e.g. serine proteases and metalloproteinases) and thereby establish new matrix–cell contacts. Of note, cancer cells express increased levels of VEGF and FGF. Inhibitors of angiogenesis, e.g. angiostatin, endostatin and thrombospondin, have been identified in plasma and extracellular matrix. Because thrombospondin is activated by p53, inactivation of p53 facilitates angiogenesis.

Invasion/Metastasis

Cell–cell interactions and extracellular glycoprotein matrix recognition are achieved by four classes of membrane-bound receptors, consisting of integrins, cadherins, selectins and members of the immunoglobulin family. All of these cellular adhesion molecules have an extracellular domain that binds ligands, leading to a conformational change in the cytoplasmic tail of the receptor. Upon ligand binding, internal regions of the receptors bind to specific cytoplasmic proteins influencing various pathways involved in proliferation, cell migration, differentiation and apoptosis. The extracellular ligands for integrins are matrix components composed of collagen, fibronectin or laminin (see Fig. 141.11) and immunoglobulin family members (see Table 102.2). Cadherins bind to cadherins present on adjacent cells and selectins bind to carbohydrate chains.

Disruption of tissue organization is a hallmark of cancer and is the result of alterations in cellular adhesion receptors resulting in selective growth advantage. In cell cultures, dysregulation of cell adhesion pathways underlies anchorage-independent growth. Metastases from epithelial cancers often lose E-cadherin expression, facilitating the escape of cells from the primary site to other locations. E-cadherin expression can be inactivated by hypermethylation of regulatory regions as well as mutations in the coding sequence. Alternatively, inactivation occurs through proteolysis of the extracellular domain of E-cadherin or mutations in the gene encoding E-cadherin's intracellular ligand, β-catenin.

Signaling from normal neighboring cells, e.g. fibroblasts and endothelial cells, appears to be equally important for the growth of a tumor and is often induced by signals from the tumor cells. Reciprocal release of abundant growth-stimulating signals creates amplifying loops enabling growth of both the tumor and its cognate stroma. Inflammatory cells have also been shown to be involved in a similar cross-talk between normal and malignantly transformed cells[17].

In humans, the most common cancers are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), often termed "non-melanoma skin cancer". Although BCCs and SCCs possess many similar features, there are fundamental biologic differences, justifying a distinction between the two and rendering "non-melanoma skin cancer" a poor conceptual term. In the remainder of this chapter, BCC and SCC will be described with an emphasis on the similarities and the differences between their tumor biology. Disruption of the Hedgehog–Patched signaling pathway is closely linked to development of BCC and the *p53* gene is often mutated in both BCC and SCC. The *Patched (PTCH)* and *p53* genes will serve as a model to illustrate some of the basic features of epithelial skin carcinogenesis.

STRUCTURE AND FUNCTION OF *p53*

Background

The *p53* tumor suppressor gene was first described in 1979 and was initially erroneously classified as an oncogene due to its ability to transform cells. The wild-type p53 protein is involved in a multitude of cellular events and illustrates the complex molecular machinery within a cell[18]. The p53 protein is regarded as the "guardian of the genome" as it protects DNA integrity in response to cytotoxic stress, including radiation. Protection is achieved by management of signaling pathways that regulate cell cycle progression, DNA repair and apoptotic cell death. The ability of p53 to induce apoptosis by transactivation of target genes is critical for its function as a tumor suppressor gene. Aside from genomic alterations, p53 protein can also be inactivated by binding to other proteins, such as the viral proteins adenovirus E1B, human papillomavirus E6 and the SV40 T-antigen.

The *p53* Gene, Protein and Regulation

The *p53* gene is located on the long arm of chromosome 17 and contains 11 exons spanning some 20 000 bp of genomic sequence. The gene encodes a 53 kDa nuclear phosphoprotein of 393 amino acid residues. Four functional domains involved in the regulation of transcription, DNA binding, oligomerization and auto-inhibition are recognized (Fig. 107.6). Transcription is indirectly regulated within the transactivation domain (42 amino acid residues) either by binding to other proteins or by phosphorylation. For example, the nuclear protein Mdm2 is capable of inactivating wild-type p53 protein by binding to the transactivation domain. Subsequent to binding to Mdm2, p53 is degraded via the ubiquitin-mediated proteolysis pathway. In normal cells containing latent p53 protein bound to Mdm2, the half-life of p53 is approximately 2 minutes.

Interaction between Mdm2 and the p53 protein is dependent upon phosphorylation of the p53 transactivation domain as well as interactions with other proteins. Upon DNA damage, serine protein kinases are activated that readily phosphorylate p53 and release it from Mdm2 binding. Up to a 100-fold increased cellular content of functional p53

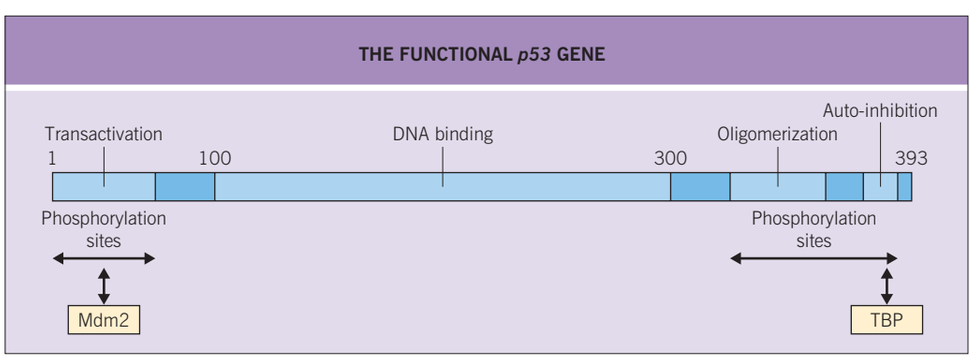


Fig. 107.6 The functional *p53* gene. There are four functional domains and they are involved in transactivation, sequence-specific DNA binding, oligomerization and auto-inhibition. Binding sites for Mdm2 and TBP proteins are noted. TBP, TATA box-binding protein.

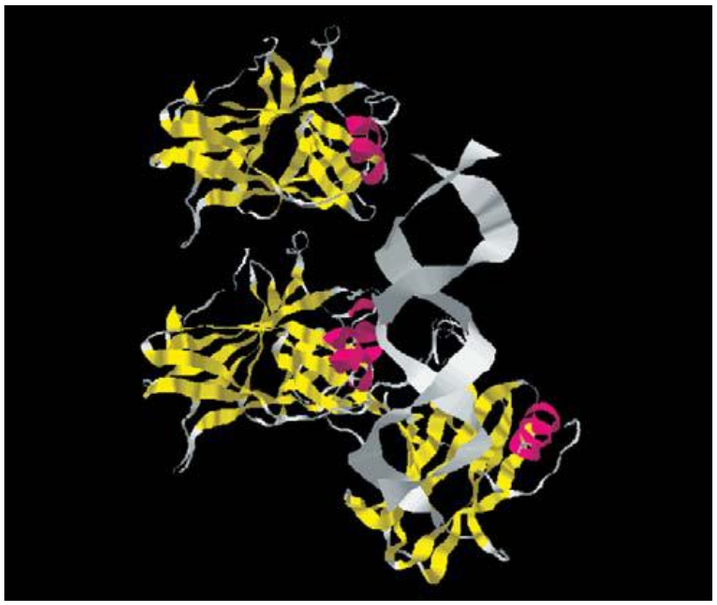


Fig. 107.7 Three-dimensional view of the p53 protein. Three units of the normally tetramerized active p53 are shown surrounding the DNA double helix (gray). The β-sheets are shown in yellow and α-helices are depicted in red. *From Sayle RA, Milner-White EJ. RASMOL: biomolecular graphics for all. Trends Biochem Sci. 1995;20:374; Cho Y, et al. Crystal structure of a p53 tumor suppressor-DNA complex: understanding tumorigenic mutations. Science. 1994;265:346–55.*

is thus obtained without a requirement for protein synthesis. p53 protein is a transcription factor for Mdm2, thus creating a feedback loop between p53 and Mdm2. Mdm2 protein levels are further regulated by binding to the $p14^{ARF}$ protein (see Fig. 107.1), which translocates Mdm2 to the nucleolus and thus prevents Mdm2–p53 interaction.

The structure of the DNA-binding domain has been shown to consist of a scaffold with three loops (Fig. 107.7). The first loop binds to the major groove of the target DNA sequence. The second loop has contact with the minor groove, and the third loop stabilizes the second loop via a zinc atom. The majority (80–90%) of detected *p53* mutations involve the sequence-specific DNA-binding domain. The distribution of reported mutations is shown in Figure 107.8 and depicts a number of hot spots within this region.

The p53 protein requires a tetramer configuration for DNA binding. The oligomerization domain is responsible for assembly of the protein. Because both normal and mutant allele products can be assembled together, this leads to the dominant-negative phenotype (see Ch. 54) that is characteristic of the mutant p53 protein. The auto-inhibitory domain of 30 basic amino acid residues is thought to block the DNA-binding domain and can be removed by phosphorylation or binding to other proteins such as TATA box-binding proteins (TBP). The p53 protein exerts its effects predominantly (but not exclusively) at the level of transcription. Genes that increase their transcription due to interaction with p53 contain a promotor (response) element for binding to the p53 tetramer (Table 107.2). The transactivation domain of p53 can also recruit additional transcription factors required for transcription.

The Cellular Response to DNA Damage

p53 is a general sensor of cytotoxic stress and can be activated by several types of DNA insults that create single- and double-strand breaks as well as cyclobutane pyrimidine dimers and 6-4 photoproducts, e.g. chemicals or gamma and UV radiation (see Ch. 86). In response to DNA damage, the level of p53 protein increases rapidly within the cell and exerts multiple, complex functions, including protection of DNA integrity and cellular proofreading[18]. The former involves cell cycle arrest at G1 in order to facilitate the repair of damaged DNA prior to cell division. The pathway downstream of p53 involves upregulation of p21, which, in turn, inhibits cyclin-dependent kinases and subsequent phosphorylation of Rb protein (see Fig. 107.1). Underphosphorylated Rb protein binds the transcription factor E2F and prevents the cell from entering into the S phase. Cellular proofreading involves apoptosis as a response to irreversible damage of genomic DNA and prevents survival of cells with severe genetic alterations. Sunburn cells in the epidermis represent apoptotic keratinocytes and can frequently be observed in normal skin subjected to sunburn.

EXAMPLES OF GENES WHERE TRANSCRIPTION IS INFLUENCED BY THE p53 TETRAMER

Gene (protein)	Regulation	Function
p21 (p21)	Activation	Proliferation
GADD45 (GADD45)	Activation	Proliferation
bax (Bax)	Activation	Apoptosis
thrombospondin (Thrombospondin)	Activation	Angiogenesis
mdm2 (Mdm2)	Inhibition	Regulatory
bcl-2 (Bcl-2)	Inhibition	Apoptosis
fos (Fos)	Inhibition	Proliferation
jun (Jun)	Inhibition	Proliferation

Table 107.2 Examples of genes where transcription is influenced by the p53 tetramer.

Mutated *p53*

The *p53* gene is the most frequently altered gene in human cancer. A majority of *p53* mutations are missense mutations leading to an altered amino acid sequence. Missense mutations are primarily found in the DNA-binding domain between codons 112 and 286 (see Fig. 107.8). Mutations in the DNA-binding domain do not affect oligomerization; thus, mutant p53 can still form tetramers with normal p53 protein derived from the intact *p53* allele. The formed heterodimers are, however, incapable of binding to promotor sequences.

The addition of small peptides (corresponding to the C-terminal domain) can potentially disrupt the auto-inhibitory binding of the C-terminal region to the DNA-binding domain of the mutant heterodimers and thereby reactivate the function of mutated p53. This observation may eventually translate into a therapeutic intervention. At the time of writing, drugs that disrupt p53–Mdm2 or p53–Mdm4 interactions are in clinical trials[19].

Clandestine proliferations of keratinocytes overexpressing p53 protein are evident in normal, chronically sun-exposed skin of Caucasians[20]. The pattern and degree of overexpression are distinctly different from the dispersed pattern of p53-immunoreactive keratinocytes following a single exposure to UV irradiation (Fig. 107.9). A recent study, using next-generation sequencing of sun-exposed versus shielded mid-life skin, revealed that persistent *p53* mutations had accumulated in 14% of epidermal cells in phenotypically normal skin, with no apparent evidence of a growth advantage[21]. Six percent of the mutated cells encoded for a truncated p53 protein. The authors estimated the accumulation of ~35 000 protein-altering *p53* mutations annually in the sun-exposed skin of a single individual, suggesting that UV-induced *p53* mutations are tolerated and not as hazardous as previously thought.

STRUCTURE AND FUNCTION OF PATCHED

Background

The Hedgehog signaling pathway plays a critical role during normal development, regulating both proliferation and cell fate. Initially, *patched* and *hedgehog* genes were identified in *Drosophila melanogaster*, where members of this complex signaling pathway were found to act as segment polarity genes involved in embryonic development. In recent years, it has become evident that Hedgehog is also involved in driving tumorigenesis[22]. When screening candidate genes for the hereditary nevoid basal cell carcinoma syndrome (Gorlin syndrome), the human homologue of the *patched* gene, *PTCH1*, was identified as a tumor suppressor gene associated with this syndrome[23]. The *PTCH1* gene encodes a receptor that mediates Hedgehog signaling (Fig. 107.10). Later studies have shown that inactivating mutations in the *PTCH1* gene are also common events in sporadic BCC. The significant cellular effects of Hedgehog signaling are mediated by proteins encoded by the *GLI* gene family.

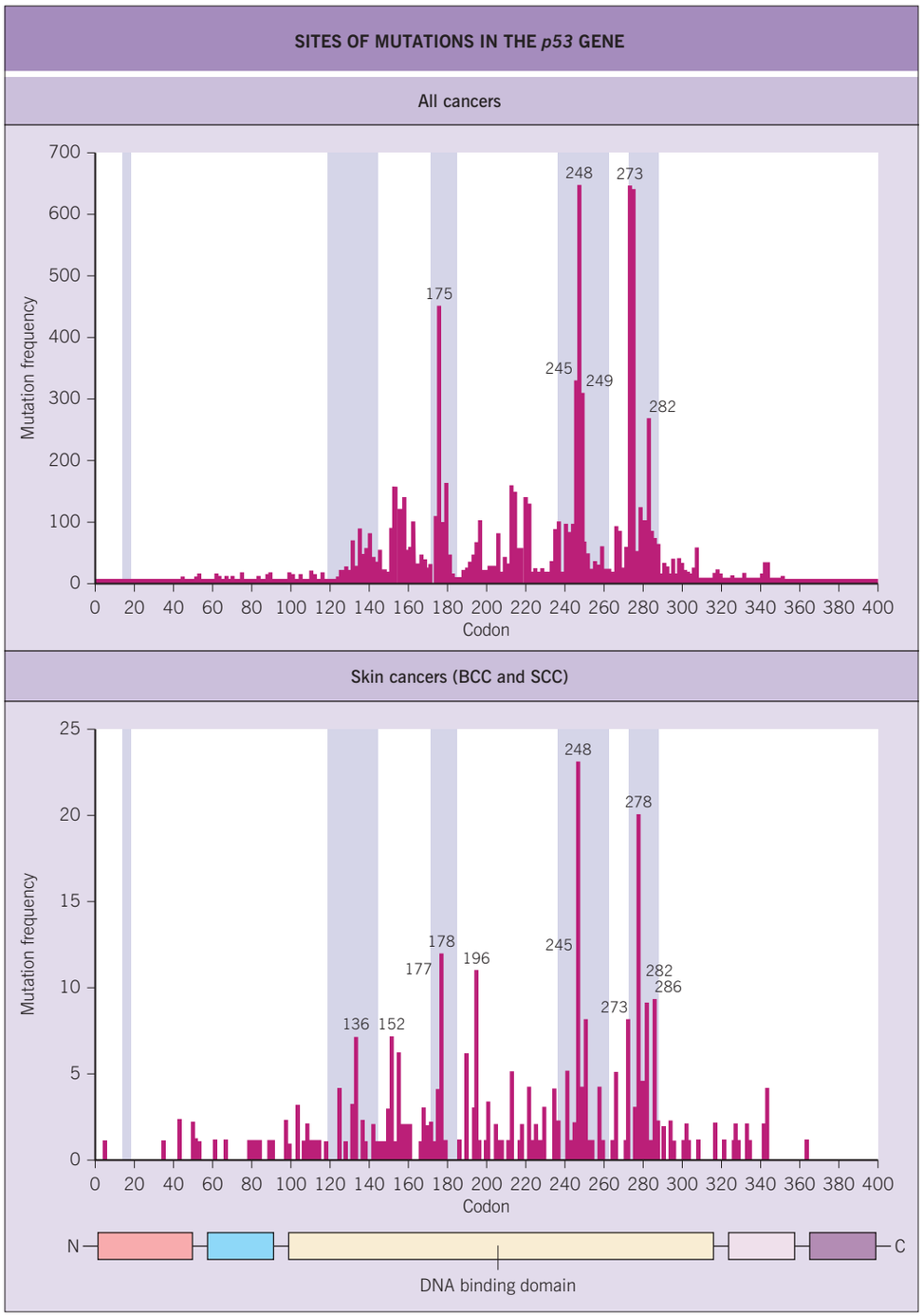


Fig. 107.8 Sites of mutations in the *p53* gene. The frequencies of mutations are shown with respect to specific codons within the *p53* gene in all cancers (top panel) and skin cancer (basal cell carcinoma + squamous cell carcinoma; bottom panel). Numbers represent hotspots for *p53* mutations. The gray bars represent evolutionary conserved regions of the *p53* gene. *From Hernandez-Boussard T, et al. IARC p53 mutation database. Hum Mutat. 1999;14:1–8.*

The human Hedgehog signaling pathway is complex, with three identified *hedgehog* genes (*sonic hedgehog* [*SHH*], *Indian hedgehog* [*IHH*] and *desert hedgehog* [*DHH*]), two *PTCH* genes (*PTCH1* and *PTCH2*) and three *GLI* genes (*GLI1*, *GLI2* and *GLI3*). The encoded proteins within these families are similar, although they display variations in expression levels in different cells and tissues as well as slightly different modes of interactions. In the skin, the SHH pathway is responsible for maintaining the stem cell niche and controlling development of sebaceous glands and hair follicles[24]. In the next section, a simplified scheme using Hedgehog, Patched and Gli as common denominators will be used to illustrate interactions and effects in this important pathway.

PTCH Gene

The human *PTCH1* gene was cloned and identified in 1996. Positional cloning was used to search the region within 9q22.3 in order to identify the gene responsible for Gorlin syndrome. The gene is 35 kb in length and consists of 23 exons. The first exon has three splice variants, 1, 1A and 1B. The different transcripts have been identified in human epidermis.

PTCH Protein Product (Patched)

The protein product of the human *PTCH* gene is the sonic hedgehog (SHH) receptor, which is an integral membrane protein with 12 predicted transmembrane regions and two large extracellular loops as well as a putative sterol-sensing domain. Patched protein normally binds and inhibits a seven-pass transmembrane G-protein receptor named Smoothened (SMO). SMO has been shown to be constitutively active when not bound to Patched (see Fig. 107.10).

Normal Function of Patched

By controlling proliferation, differentiation and cell fate, the SHH–Patched signaling pathway is critical for early embryologic development, including formation of the neural tube, musculoskeletal system, hematopoietic cells, skin and teeth. Mutations in the SHH pathway cause

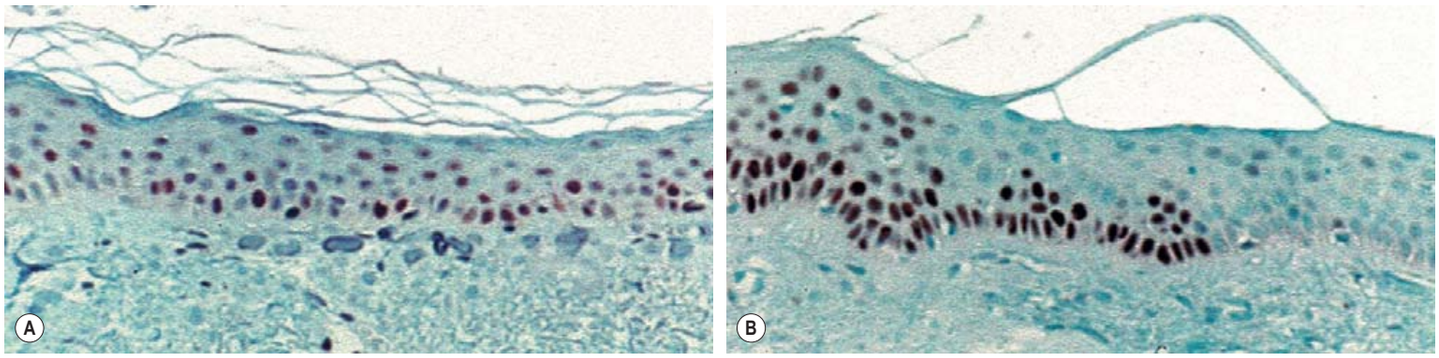


Fig. 107.9 p53 immunoreactivity. Photomicrographs of two different patterns of p53 immunoreactivity found in normal skin. **A** Dispersed pattern of p53 positivity representing a normal reactive response to DNA damage (e.g. single exposure to UVB). **B** Epidermal p53 clone representing a clonal expansion of morphologically normal keratinocytes with a *p53* mutation. The latter is seen in chronically sun-exposed skin. Of note, mutated p53 protein has an extended half-life as compared to wild-type protein (due to a less efficient MDM2/ubiquitin degradation pathway) and this property is used as a semiquantitative surrogate marker for altered p53 in immunohistochemical examination of tissue.

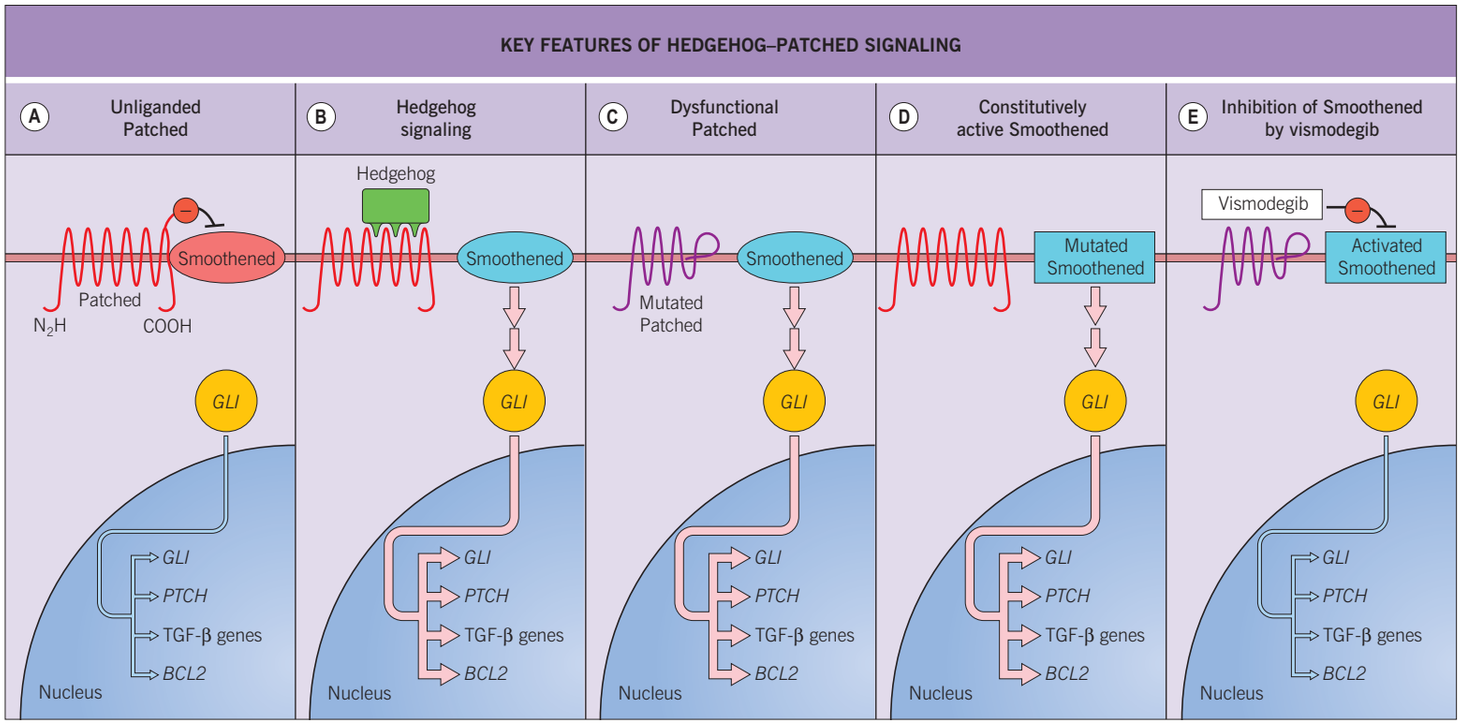


Fig. 107.10 Key features of Hedgehog–Patched signaling. A Unbound Patched silences Smoothened (SMO) signaling. **B** As Hedgehog binds to its receptor (Patched), the repression of SMO is removed and signals are transduced via Gli to the nucleus. **C** Inactivating mutations in *PTCH* simulate Hedgehog binding and result in constitutive activation of Gli and downstream target genes. **D** An activating mutation in *SMO* results in constitutive signaling to Gli and downstream target genes. **E** Vismodegib is an inhibitor of SMO that has been used to treat patients with nevoid BCC syndrome as well as metastatic or locally advanced BCCs (see Ch. 108).

holoprosencephaly, a Cyclops-like phenotype with severe congenital abnormalities.

Patched function is mediated via release of suppression of SMO. SMO signaling is then transduced and executed through the transcription factor Gli (see Fig. 107.10). Active Gli serves as a transcription factor for *GLI* itself as well as inducing transcription of *PTCH1*, thus creating a negative feedback loop. Other genes induced via the SHH–Patched signaling pathway include those that encode platelet-derived via factor-α (PDGFRA), the DNA-binding protein MYCN, β-catenin, members of the forkhead box (FOX) family, cyclins and runt-related transcription factor 3, a nuclear effector of the TGF-β family.

Regulation of Patched

Knowledge about genes and molecules involved in SHH–Patched signaling has been obtained mainly by genetic analyses in *Drosophila*. The signaling pathway is well conserved, although with increasing complexity, from insects to vertebrates, including humans. The SHH–Patched signaling pathway induces transcription of *PTCH* itself, creating a negative feedback loop for *PTCH*. Unliganded Patched interacts with and suppresses signaling by the co-receptor SMO. SHH signaling accordingly induces transcription of target genes by opposing the repressive activity of Patched. In other words, when SHH binds to the receptor Patched, repression of SMO is relieved and downstream target genes are induced. In a simplified scheme (see Fig. 107.10B), secreted SHH proteins bind to the receptor protein Patched and upon binding to the ligand, Patched dissociates from its co-receptor Smoothened.

Inactivating mutations of *PTCH1* simulate SHH signaling due to the failure of mutated Patched protein to suppress SMO (see Fig. 107.10C). The loss of negative autoregulation leads to increased transcription of non-functional PTCH mRNA. In carcinogenesis, several lines of evidence (including experiments using transgenic mice) suggest that the critical cellular effect is stimulation of proliferation as opposed to differentiation, and that this effect is mediated by upregulation of Gli.

PTCH Mutations

An early onset of multiple BCCs is a hallmark of Gorlin syndrome (also known as nevoid BCC syndrome), a rare autosomal dominant disease. The *PTCH* gene is mutated in patients with Gorlin syndrome and thus

strongly linked to the development of BCCs. Additional features that constitute Gorlin syndrome include skeletal abnormalities, jaw cysts, macrocephaly and palmoplantar pits. A majority of the germline mutations in *PTCH* are truncating, suggesting that haploinsufficiency underlies the developmental abnormalities. Both alleles of *PTCH* are often inactivated in both familial and sporadic cases of BCC, as would be expected for a classic tumor suppressor gene. Most tumors where *PTCH* is inactivated display a truncating mutation in one allele and deletion of the other allele, i.e. loss of heterozygosity (LOH). Alternatively, point mutations in both alleles can occur in tumors without LOH in the *PTCH* locus.

Constitutive activation of SHH signaling by inactivating mutations in *PTCH* or activating mutations in *SMO* appear to be required, and possibly also sufficient, for development of BCC. Disruption of the SHH–Patched pathway has also been found in other tumors such as medulloblastoma, as well as ovarian and cardiac fibromas, which are common in patients with Gorlin syndrome. In addition, *PTCH* mutations have been found in sporadic trichoepitheliomas, bladder carcinoma and SCC of the esophagus. Mutational analysis has shown that two-thirds of reported mutations were truncating or affected splicing.

PATHOGENESIS OF BCC

Sun exposure and anatomic site appear to be of etiologic importance in the development of BCC. Intermittent, recreational sun exposure, more so than cumulative UV radiation, is a significant risk factor[25]. The development of BCCs is restricted to skin containing pilosebaceous units. The fact that BCCs commonly develop on the face, and in particular on the nose, suggests that anatomic site, i.e. specific areas of skin that contain a higher number of target progenitor cells, plays an important role. Analogous to other malignancies, BCC appears to have a capacity for infinite growth and spontaneous regression is not a feature. Sophisticated studies of tumor biology have been sparse due to difficulties in establishing good experimental models, and *in vitro* culture of BCC cells from explanted tumors has in general been unsuccessful. Transplantation of BCC into athymic mice has been more successful, although extensive studies of long-term effects have been sparse. The development of transgenic mice as a model to study BCC has been rewarding, especially with regard to elucidating the role of different components of the SHH–Patched signaling pathway[26]. A recent study suggested that BCCs arise from interfollicular epidermis or the follicular infundibulum rather than the hair follicle bulge, as had been previously proposed[27].

Precursors

Perhaps the most striking feature of BCCs is that tumors virtually never develop metastases. Although tumors can grow for many years in the setting of sustained exposure to mutagenic UV radiation, the tumors remain indolent. Non-aggressive forms of BCC, such as superficial and nodular BCC, appear to develop *de novo* and continue to grow without progressing to more aggressive forms of BCC. Aggressive forms of BCC, e.g. morpheaform BCC, also show an unusual genomic stability, with a persistent pattern of locally invasive growth and tissue destruction, but without progression to metastatic disease. This also holds true for BCCs that develop in xeroderma pigmentosum patients, where there is a high number of unrepaired mutations. It is unclear why BCC cells are resistant to acquiring additional genetic hits leading to more autonomous growth.

Cancer

BCC is a tumor with unique growth characteristics. It is dependent on a specific loose connective tissue stroma for its continued growth, and one hypothesis for the inability of a BCC to transform into a metastasizing tumor is an unconditional dependence on a stroma produced by dermal fibroblasts. In an experiment where autotransplantation of BCC with and without its cognate stroma was performed, it became evident that BCC devoid of its stroma failed to proliferate and instead differentiated into keratin-filled cysts[28].

The loose connective tissue stroma that characteristically surrounds nests of BCC cells consists of dermal fibroblasts and thin collagen fibers. The cross-talk between tumor cells and mesenchymal cells of the cognate stroma simulates the epithelial–stromal interactions found in normal developing and adult cycling hair follicles. For example, the growth factor receptors for PDGF are upregulated in BCC stroma whereas the ligand, PDGF, is expressed primarily in tumor cells. In morpheic or infiltrative BCCs, the stroma is myofibroblast-rich as compared with nodular BCCs. These myofibroblasts secrete hepatocyte growth factor which promotes invasion of epithelial cells via its binding to c-Met, a tyrosine kinase receptor expressed in the epithelium of morpheic BCCs[29]. The invasive nature of BCCs can be explained in part by proteolytic activity of the tumor. Increased expression of enzymes such as metalloproteinases and collagenases, which degrade pre-existing dermal tissue and facilitate spread of tumor cells, can be found in both BCC cells and stromal cells.

Microscopically, BCCs often appear as multicentric tumors. In superficial BCCs, nests of tumor cells connected to the basal cell layer of the overlying epidermis appear as discontinuous buds of tumor cells. More recent studies based on microdissection, gene amplification and gene sequencing have shown that BCCs develop as a monoclonal proliferation consistent with a unicellular origin. Interestingly, BCCs often consist of subclones (Fig. 107.11). Using *p53* mutations as a marker for clonality, it was shown that different parts of a tumor share a common mutation but differ with respect to second, third or even fourth mutations within the two alleles of the *p53* gene[30].

Although BCC appears as a tumor with extraordinary genomic stability, a large number of tumors are aneuploid. Analyses of LOH have shown allelic loss of chromosome 9q, while LOH involving other chromosomes was observed infrequently[31]. Of note, the gene most often altered in BCCs is the *PTCH* gene, which is located on chromosome 9q. Two out of three BCCs show LOH and/or truncating mutations in the *PTCH* gene. In tumors where the *PTCH* gene is intact, other mutations such as activating mutations in *SMO* (up to 20%) have been detected. Accumulating data suggest that a sufficiently elevated expression level of Gli, by homozygous inactivation of *PTCH* or by activating mutations of *SMO*, in a responding cell is necessary and perhaps also sufficient to drive the formation of BCC. Constitutive SHH signaling has also been demonstrated to be required for growth of *established* BCCs (see Fig. 107.10)[32].

The second most common genetic alteration found in BCCs is point mutations in the *p53* gene. *p53* mutations appear early during carcinogenesis and at least 50% of BCCs have a mutated *p53* gene. The vast majority of *p53* mutations are missense mutations that carry a UV signature (see Ch. 86)[33]. In many BCCs, both *p53* alleles are affected by point mutations, unlike the more common combination of a point mutation and a deletion (LOH) observed in most other solid tumors. The role of *p53* mutations in the carcinogenesis of BCCs could be based on the expansion of the number of target cells, i.e. epidermal p53 clones, susceptible to transformation.

Mutations in the *CDKN2A (INK4A)* locus, which encodes both p16 and $p14^{ARF}$ (see above), have also been detected in a smaller number of sporadic BCCs. In contrast to tumor suppressor genes (e.g. *PTCH*, *p53*), oncogenes appear to play a lesser role in the development of BCC. *ras* genes are the most studied oncogenes and the frequency of *ras* mutations in BCC has varied between 0 and 30%, usually within the *H-ras* gene. Alterations in other oncogenes and tumor suppressor genes have only sporadically been recorded. Genome-wide association studies in the Icelandic population have revealed genetic susceptibility variants in the keratin 5 gene in patients with BCC[34].

Limitless replicative potential is essential for the malignant phenotype, and telomere maintenance is also evident in BCCs, due to high telomerase activity. Interestingly, BCCs express equal or higher levels of telomerase when compared to high-grade malignancies. The presence of intact DNA repair genes is also of critical importance. The detrimental effect of insufficient repair of UV-induced DNA damage is well illustrated in patients with xeroderma pigmentosum, who develop numerous BCCs at an early age.

Metastasis

Although BCCs virtually never metastasize, there have been a few reports in the literature of BCCs that developed metastases, and the incidence has been estimated to be 1:1000 to 1:35 000. It appears as if these rare cases represent aggressive tumors with perineural spread of tumor cells. Lymph node metastasis followed by lung and bone metastasis is the most common progression. The diagnosis has been

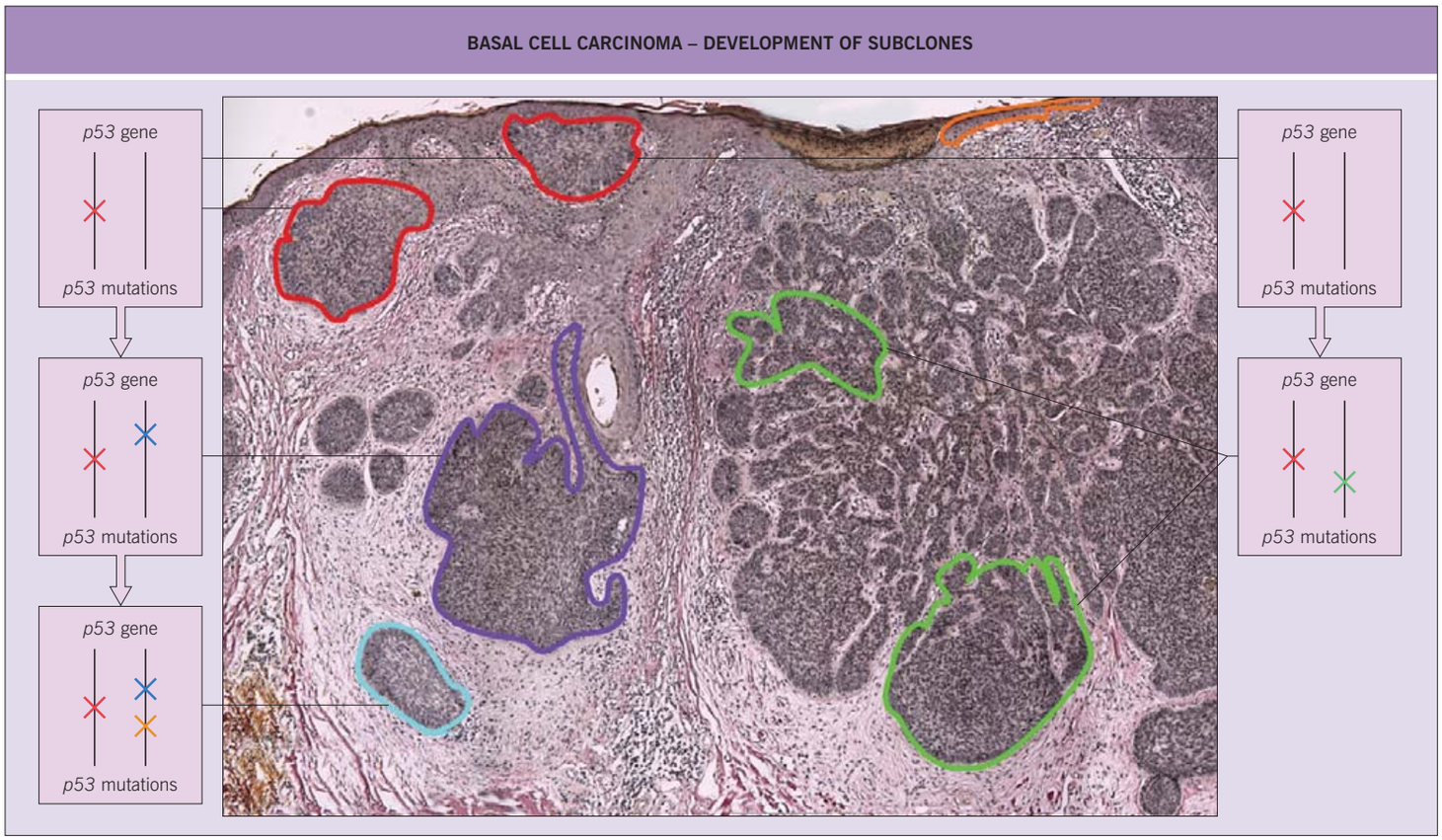


Fig. 107.11 Basal cell carcinoma (BCC) – development of subclones. A common *p53* mutation (red cross) is found in different parts of the tumor. Despite indistinguishable morphology, different parts of individual BCCs have acquired additional mutations in the *p53* gene (blue, orange and green crosses). Boxes illustrate the two *p53* alleles. Note normal *p53* status (outlined in orange) in overlying epidermal keratinocytes.

based on morphology, and the possibility that some of these cases represent poorly differentiated variants of SCCs cannot be excluded.

In summary, BCC is a common, locally invasive tumor of the skin, for which UV radiation and alterations in the *PTCH* gene are important etiologic factors. BCC is stroma-dependent for its growth, arises without precursors, and shows continuous growth without progression to metastatic disease.

PATHOGENESIS OF SCC

UV solar radiation is also a major etiologic factor in the development of cutaneous SCC. The cumulative dose of UV radiation received over time is a significant risk factor, in contrast to the more complex relationship between BCC and sun exposure early in life or cutaneous melanoma and sunburns[25]. SCC of the skin is a "classic cancer", as it has precursor lesions, tumor progression and the potential to develop metastatic disease. SCC can develop in different regions of the skin as well as other sites lined by squamous epithelia, e.g. mouth, esophagus, vagina. The biology of cutaneous SCC differs in part from that of SCCs that arise in other tissues. In particular, SCC in areas of chronically sun-exposed skin exhibits a relatively indolent behavior and the development of metastases is infrequent (less than 5% overall). There is a strong correlation between tumor thickness and metastasis (2.1–6 mm, 4% metastasize; >6 mm, 16% metastasize)[35]. Secondary risk factors for metastasis include immunosuppression and location on the lips or the ear. Desmoplastic SCCs have a higher recurrence rate. SCCs arising on the genitalia and perianal area are also more aggressive, with a higher risk of metastasis.

Precursors

The current opinion regarding cutaneous SCC is that the cancer is derived from a single transformed cell of keratinocytic lineage. The precise genetic events and number of mutations required for malignant transformation are unknown. However, cutaneous SCC develops through the addition of genetic alterations leading to a selective growth advantage. In this scheme of events, several stages can be defined. An attractive model (supported by studies in hairless mice) includes epidermal p53 clones as forerunners to squamous cell dysplasia (Fig. 107.12)[36]. According to the dogma, slight dysplasia precedes moderate and severe dysplasia (which is seen in SCC *in situ*) and invasive SCC then develops from carcinoma *in situ*. Further genetic alterations and selection leads to the final stage, where a locally invasive SCC gives rise to metastases in regional lymph nodes and distant organs.

Clinical precursor lesions associated with cutaneous SCC include actinic keratoses and Bowen's disease. Microscopically, actinic keratoses display signs of chronic sun damage, i.e. solar elastosis and a slight to severe grade of squamous cell dysplasia within the epidermis, especially in its lowermost portions. Bowen's disease also displays squamous cell dysplasia, which is full-thickness and often high-grade. Actinic keratoses are exceedingly common in chronically sun-exposed skin of older Caucasians. Lesions occur primarily on the face, hairless scalp, dorsal aspects of the hands, and helices of the ears (primarily in men). The risk for an individual actinic keratosis to progress into an invasive cancer is low, probably less than 1 in 1000 per year. The risk of SCC *in situ* progressing to invasive cancer is considered to be higher.

Cancer

UV solar radiation is accepted as a major risk factor for SCC. Numerous experiments using chemical multistage carcinogenesis models have been performed in mice, yielding SCC-like tumors. A typical protocol consists of a single application of an initiating compound, e.g. 7,12-dimethylbenz[a]anthracene (DMBA), which leads to irreversible activating mutations in *H-ras* genes within basal cells of the epidermis. In a second step, repetitive doses of a tumor-promoting agent, e.g. 12-O-tetradecanoylphorbol 13-acetate (TPA), induces a hyperproliferative response. Through partly epigenetic mechanisms, this leads to the development of squamous cell papillomas. Conversion of benign papillomas into malignant SCCs then involves a number of chromosomal and genetic alterations required for the acquisition of the

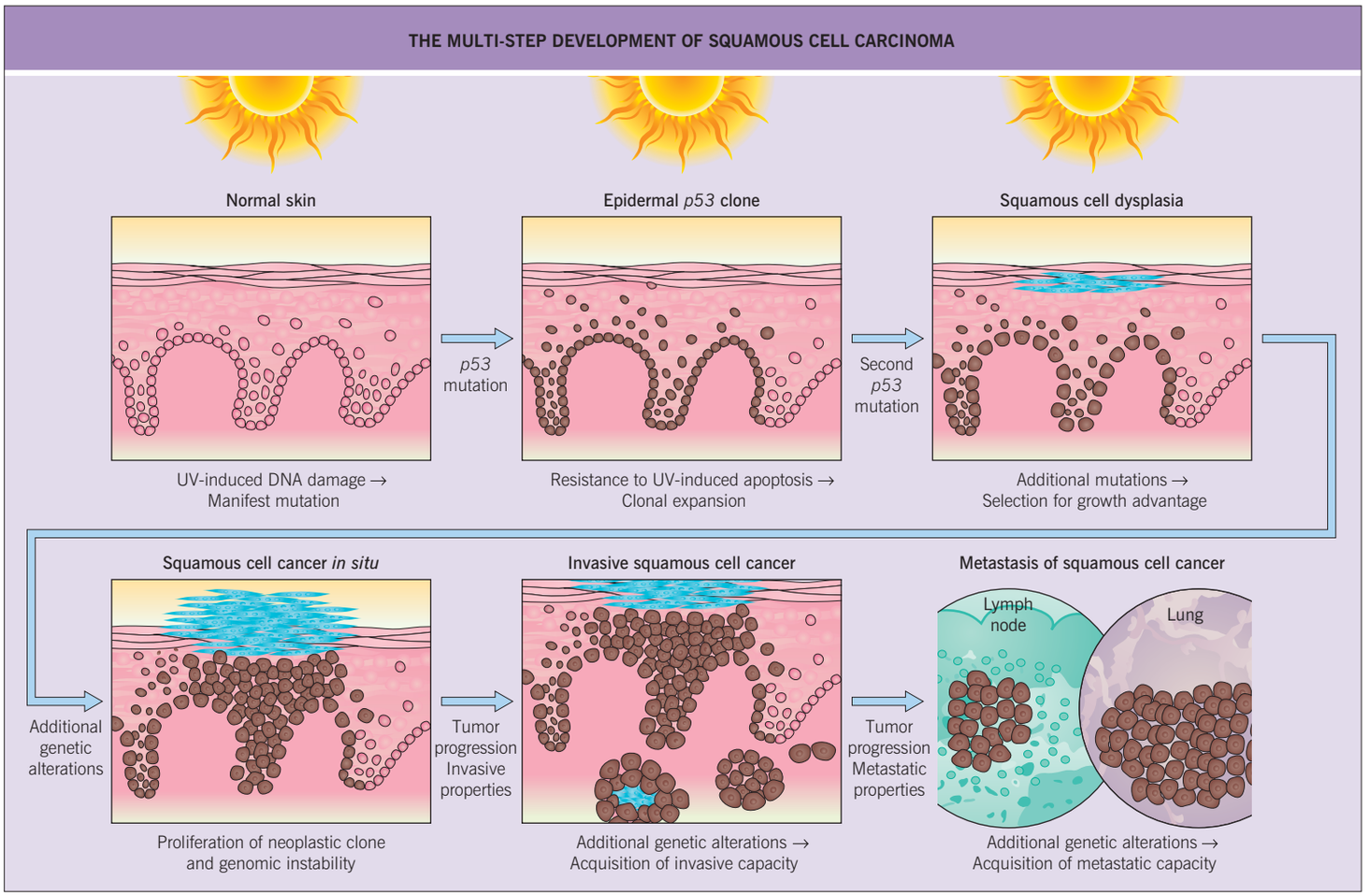


Fig. 107.12 The multistep development of squamous cell carcinoma. UV irradiation of normal skin induces mutations in keratinocytes and facilitates clonal expansion of keratinocytes with a mutated *p53* gene. Additional mutations (including a second *p53* mutation) that affect genes controlling proliferation, cell migration and cell death provide for selective growth advantage and cause genomic instability. The final result is metastatic tumor cells, capable of growing in regional lymph nodes and internal organs.

malignant phenotype. A limitation of the chemical carcinogenesis model is that it is different from UV-induced carcinogenesis, in particular *H-ras* is not implicated as a key oncogene in human SCC. A second murine skin carcinogenesis model is UVB-induced SCC in the hairless, SKH-1 mouse. Skin tumors in this model have a high frequency of *p53* mutations and low incidence of *Ras* mutations.

Invasive SCCs can have different degrees of differentiation. Highly differentiated tumors show features of keratinization and often invade the dermis with a broad rounded tumor margin. Papillomatous extensions and cords of slightly atypical squamous epithelia grow down into the dermis. Verrucous SCC, which very rarely metastasizes, is considered a special variant of highly differentiated SCC. Poorly differentiated SCCs show more anaplastic cytologic features and the squamous cell phenotype can sometimes only be verified via immunohistochemistry with antikeratin antibodies.

In general, poorly differentiated desmoplastic SCC exhibits a higher grade of malignancy[35]. However, biologic behavior can rarely be predicted by the degree of differentiation alone. SCC is dependent on a supportive stroma, as are all other solid tumors, and a vasculature induced by angiogenic signals is needed for the tumor to enlarge. Unlike the stroma surrounding a BCC, the SCC stroma is considered nonspecific and cell–cell interactions between tumor cells and stromal cells are not well characterized. SCC thus has the potential to grow at sites distant from the primary tumor.

Alterations in the *p53* gene are the most common genetic abnormalities found in actinic keratoses, SCC *in situ* and invasive SCC, and dysregulation of p53 pathways appears to be an early event in carcinogenesis of SCC. In typical cases, one allele contains a missense point mutation with a UV signature at dipyrimidine sites, while the remaining *p53* allele is deleted. Studies utilizing *p53* mutations as a clonality marker have suggested a direct relationship between actinic keratoses, SCC *in situ* and invasive SCC. By studying individual patients with lesions (e.g. SCC) adjacent to various morphologic entities (e.g. actinic keratoses), a genetic link has been found between coexisting lesions. The conclusion from these studies is that coexisting lesions represent different stages in SCC development.

One possible role for early *p53* mutations in SCCs (analogous to the situation in BCCs) is resistance to apoptosis, allowing for clonal expansion at the expense of neighboring keratinocytes containing a normal (wild-type) *p53* gene. Another common genetic aberration is mutation or epigenetic silencing of the *CDKN2A* locus. The most common mechanism of inactivation is promoter methylation[37]. The frequency of activating mutations in the oncogene *ras* ranges from 10% to 50%, depending on the experimental technique used and the site of the tumors analyzed. Amplification of the *c-Myc* oncogene has been reported in up to 50% of SCCs from immunosuppressed patients, often as a result of amplification of the chromosomal locus[38].

Loss of heterozygosity has been studied in different chromosomes, and unlike the case in BCC, where LOH is mainly restricted to chromosome 9q, actinic keratoses and SCCs demonstrate a more widespread LOH pattern with deletions in several chromosomes, e.g. 3p, 4p, 9p, 9q, 13q, 17p and 17q34 and gains of 3q, 8q and 20q. A recent study using high-resolution single nucleotide polymorphism microarrays of 60 SCC tumors showed that the most frequent aberrations were LOH at 3p and 9p, observed in 65% and 75% of tumors, respectively[39]. Three tumors had homozygous deletions within the fragile histidine triad (*FHIT*) gene at 3p14 and homozygous and heterozygous deletions were also found in the protein tyrosine phosphatase receptor type D (*PTPRD*) gene at 9p23 in 9 of 60 tumors. This study also revealed uniparental disomy (UPD) as a mechanism of copy number-neutral LOH in SCC.

Of note, UPD results in loss of one allele and subsequent duplication of the remaining allele (see Ch. 54). Poorly differentiated tumors had a greater number of chromosomal aberrations than well-differentiated tumors[39].

Recently, loss-of-function mutations in *NOTCH1* or *NOTCH2* were identified in 75% of cutaneous SCCs[39a]. These genes encode cellular receptors whose signalling pathways interact with that of the Wnt/β-catenin pathway (see Fig. 113.3).

Summary

In summary, SCC arising in chronically sun-exposed skin is a common tumor for which cumulative sun exposure is an important etiologic factor. SCC arises through a series of stages involving precursor lesions, such as actinic keratoses, and in high-risk cases results in metastasis to regional lymph nodes and elsewhere.

RELATED DISEASES

Adnexal Tumors

Tumors that mimic cutaneous adnexal differentiation display a multitude of different phenotypes (see Ch. 111). A majority of these tumors are benign, although malignant counterparts do exist. The degree of differentiation allows these tumors to be distinguished from BCC and SCC. An organoid nevus, e.g. nevus sebaceus of Jadassohn, represents a cutaneous malformation that includes pilosebaceous structures. Such lesions harbor an increased risk for the development of BCC and other adnexal tumors (e.g. trichoblastoma). The genetic background of a BCC arising in an organoid nevus is unclear, but one can speculate that such a developmental malformation contains an increased number of stem cells that could act as target cells for transformation into BCC.

Keratoacanthoma

Keratoacanthomas represent tumors characterized by the proliferation of atypical, highly differentiated squamous epithelia. Clinically, and even more so microscopically, keratoacanthomas resemble SCC. Clear distinction from a highly differentiated SCC is often impossible. However, the clinical course is usually benign and lesions are believed to undergo spontaneous regression if not excised. Sporadic cases with *p53* mutations and/or overexpression of p53 protein have been reported. Although microsatellite instability and LOH have been reported in keratoacanthomas from patients with the mismatch repair-deficient and cancer-prone Muir–Torre syndrome, sporadic keratoacanthomas appear to be more genetically stable. Ferguson–Smith syndrome, an autosomal dominant condition characterized by multiple keratoacanthomas, has recently been shown to be due to mutations in the *TGFBR1* gene[40].

Xeroderma Pigmentosum

Xeroderma pigmentosum (XP) represents a family of DNA repair syndromes, some of which are caused by inherited defects in nucleotide excision repair (NER) genes (see Ch. 86), resulting in a complex skin pathology including lentigines, epidermal hyperplasias, BCCs, SCCs and cutaneous melanomas triggered by exposure to the sun. Due to the deficient DNA repair, the rate at which skin cancers develop in young XP patients is increased at least 1000-fold. The variant form of XP is caused by mutations in DNA polymerase eta (Poleta) which has been recently shown to act like a "molecular splint" to stabilize damaged DNA[41].

Li–Fraumeni Syndrome

The Li–Fraumeni syndrome is a rare familial cancer syndrome where germline mutations of the *p53* gene play an important role. The syndrome is characterized by an autosomal dominant inheritance pattern and affected individuals display an early onset of various tumors, including breast cancer, brain tumors, osteosarcoma and leukemia. Excessive genomic DNA copy number variation has recently been described in this syndrome, accounting for variation in phenotypes in affected families[42]. However, skin cancer is not a typical feature of Li–Fraumeni syndrome, despite the fact that *p53* mutations are frequently observed in BCCs and SCCs.

Gorlin Syndrome

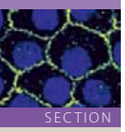
The most common inherited disorder associated with BCCs is the Gorlin syndrome (see above); it is transmitted in an autosomal dominant fashion. Affected individuals have a wide range of developmental anomalies, including skeletal abnormalities, craniofacial dysmorphism and macrocephaly. Multiple BCCs with an early onset are a hallmark of the syndrome which also includes features such as odontogenic keratocysts, palmoplantar pits and calcification of the falx cerebri. In addition to BCCs, patients have an increased incidence of medulloblastomas, meningiomas, ovarian fibromas and ovarian cancer, as well as cardiac fibromas. Germline mutations in the *PTCH* gene are found in the vast majority of patients with this syndrome.

Bazex Syndrome

Bazex syndrome is a rare genodermatosis characterized by follicular atrophoderma and the early onset of multiple BCCs. The responsible gene has been linked to Xq24–q27 and there is no male-to-male transmission. It should not be confused with acrokeratosis paraneoplastica, also known as Bazex syndrome, which occurs most commonly in the setting of carcinomas of the upper aerodigestive tract (see Ch. 53).

REFERENCES

1. Kinzler KW, Vogelstein B. Life (and death) in a malignant tumour. Nature. 1996;379:19–20.
2. Loeb LA, Bielas JH, Beckman RA. Cancers exhibit a mutator phenotype: clinical implications. Cancer Res. 2008;68:3551–7.
3. Vogelstein B, Fearon ER, Hamilton SR, et al. Genetic alterations during colorectal-tumor development. N Engl J Med. 1988;319:525–32.
4. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000;100:57–70.
5. Malumbres M, Barbacid M. Cell cycle, CDKs and cancer: a changing paradigm. Nat Rev Cancer. 2009;9:153–66.
6. Wood LD, Parsons DW, Jones S, et al. The genomic landscapes of human breast and colorectal cancers. Science. 2007;318:1108–13.
7. Beroukhim R, Mermel CH, Porter D, et al. The landscape of somatic copy-number alteration across human cancers. Nature. 2010;463:893–8.
8. Bignell GR, Greenman CD, Davies H, et al. Signatures of mutation and selection in the cancer genome. Nature. 2010;463:899–905.
9. Land H, Parada LF, Weinberg R. Cellular oncogenes and multistep carcinogenesis. Science. 1983;222:771–8.
10. Turner N, Grose R. Fibroblast growth factor signalling: from development to cancer. Nat Rev Cancer. 2010;10:116–29.
11. Dykxhoorn DM. MicroRNAs and metastasis: little RNAs go a long way. Cancer Res. 2010;70:6401–6.
12. Cowin PA, Anglesio M, Etemadmoghadam D, et al. Profiling the cancer genome. Annu Rev Genomics Hum Genet. 2010;11:133–59.
13. Letai AG. Diagnosing and exploiting cancer's addiction to blocks in apoptosis. Nat Rev Cancer. 2008;8:121–32.
14. Murnane JP. Telomere loss as a mechanism for chromosome instability in human cancer. Cancer Res. 2010;70:4255–9.
15. Alison MR, Islam S, Wright NA. Stem cells in cancer: instigators and propagators? J Cell Sci. 2010;123:2357–68.
16. Lichtenberger BM, Tan PK, Niederleithner H, et al. Autocrine VEGF signaling synergizes with EGFR in tumor cells to promote epithelial cancer development. Cell. 2010;140:268–79.
17. Erez N, Truitt M, Olson P, et al. Cancer-associated fibroblasts are activated in incipient neoplasia to orchestrate tumor-promoting inflammation in an NF-kappaB-dependent manner. Cancer Cell. 2010;17:135–47.
18. Lane DP. p53, guardian of the genome. Nature. 1992;358:15–16.
19. Lane D, Levine A. p53 research: the past thirty years and the next thirty years. Cold Spring Harb Perspect Biol. 2010;2:a000893.
20. Jonason AS, Restifo RJ, Spinelli HM, et al. Frequent clones of p53-mutated keratinocytes in normal human skin. Proc Natl Acad Sci U S A. 1996;93:14025–9.
21. Ståhl PL, Stranneheim H, Asplund A, et al. Sun-induced nonsynonymous p53 mutations are extensively accumulated and tolerated in normal appearing human skin. J Invest Dermatol. 2011;131:504–8.
22. Epstein EH. Basal cell carcinomas: attack of the hedgehog. Nat Rev Cancer. 2008;8:743–54.
23. Hahn H, Wiking C, Zaphiropoulos PG, et al. Mutations of the human homolog of Drosophila patched in the nevoid basal cell carcinoma syndrome. Cell. 1996;85:841–51.
24. Blanpain C, Fuchs E. Epidermal homeostasis: a balancing act of stem cells in the skin. Nat Rev Mol Cell Biol. 2009;10:207–17.
25. Armstrong BK, Kricker A. The epidemiology of UV induced skin cancer. J Photochem Photobiol B. 2001;63:8–18.



26. Fan H, Oro AE, Scott MP, Khavari PA. Induction of basal cell carcinoma features in transgenic human skin expressing Sonic Hedgehog. Nat Med. 1997;3: 788–92.
27. Youssef KK, Van Keymeulen A, Lapouge G, et al. Identification of the cell lineage at the origin of basal cell carcinoma. Nat Cell Biol. 2010;12:299–305.
28. van Scott EJV, Reinertson RP. The modulating influence of stromal environment on epithelial cells studied in human autotransplants. J Invest Dermatol. 1961;36:109–17.
29. Marsh D, Dickinson S, Neill GW, et al. alpha vbeta 6 Integrin promotes the invasion of morphoeic basal cell carcinoma through stromal modulation. Cancer Res. 2008;68:3295–303.
30. Pontén F, Berg C, Ahmadian A, et al. Molecular pathology in basal cell cancer with p53 as a genetic marker. Oncogene. 1997;15:1059–67.
31. Teh MT, Blaydon D, Chaplin T, et al. Genomewide single nucleotide polymorphism microarray mapping in basal cell carcinomas unveils uniparental disomy as a key somatic event. Cancer Res. 2005;65:8597–603.
32. Hutchin ME, Kariapper MS, Grachtchouk M, et al. Sustained Hedgehog signaling is required for basal cell carcinoma proliferation and survival: conditional skin tumorigenesis recapitulates the hair growth cycle. Genes Dev. 2005;19:214–23.
33. Brash DE, Rudolph JA, Simon JA, et al. A role for sunlight in skin cancer: UV-induced p53 mutations in squamous cell carcinoma. Proc Natl Acad Sci U S A. 1991;88: 10124–8.
34. Stacey SN, Sulem P, Masson G, et al. New common variants affecting susceptibility to basal cell carcinoma. Nat Genet. 2009;41:909–14.
35. Brantsch KD, Meisner C, Schönfisch B, et al. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. Lancet Oncol. 2008;9:713–20.
36. Kramata P, Lu YP, Lou YR, et al. Patches of mutant p53-immunoreactive epidermal cells induced by chronic UVB irradiation harbor the same p53 mutations as squamous cell carcinomas in the skin of hairless SKH-1 mice. Cancer Res. 2005;65: 3577–85.
37. Brown VL, Harwood CA, Crook T, et al. p16INK4a and p14ARF tumor suppressor genes are commonly inactivated in cutaneous squamous cell carcinoma. J Invest Dermatol. 2004;122:1284–92.
38. Pelisson I, Soler C, Chardonnet Y, et al. A possible role for human papillomaviruses and c-myc, c-Ha-ras, and p53 gene alterations in malignant cutaneous lesions from renal transplant recipients. Cancer Detect Prev. 1996; 20:20–30.
39. Purdie KJ, Harwood CA, Gulati A, et al. Single nucleotide polymorphism array analysis defines a specific genetic fingerprint for well-differentiated cutaneous SCCs. J Invest Dermatol. 2009;129:1562–8.
39a. Wang NJ, Sanborn Z, Arnett KL, et al. Loss-of-function mutations in Notch receptors in cutaneous and lung squamous cell carcinoma. Proc Natl Acad Sci USA. 2011;108:17761–6.
40. Goudie DR, D'Alessandro M, Merriman B, et al. Multiple self-healing squamous epithelioma is caused by a disease-specific spectrum of mutations in TGFBR1. Nat Genet. 2011;43:365–9.
41. Silverstein TD, Johnson RE, Jain R, et al. Structural basis for the suppression of skin cancers by DNA polymerase eta. Nature. 2010;465:1039–43.
42. Shlien A, Tabori U, Marshall CR, et al. Excessive genomic DNA copy number variation in the Li-Fraumeni cancer predisposition syndrome. Proc Natl Acad Sci U S A. 2008;105:11264–9.

Actinic Keratosis, Basal Cell Carcinoma and Squamous Cell Carcinoma

108

H Peter Soyer, Darrell S Rigel and Elisabeth MT Wurm

Chapter Contents

Actinic keratosis and squamous cell carcinoma *1777*
Basal cell carcinoma *1784*

Synonyms: ■ Solar keratosis and senile keratosis are non-preferred synonyms for actinic keratosis (solar keratosis is abbreviated to SK, causing confusion with seborrheic keratosis) ■ Bowen's disease – squamous cell carcinoma *in situ* ■ Basal cell epithelioma and rodent ulcer are antiquated synonyms for basal cell carcinoma ■ Basal cell nevus syndrome is a non-preferred synonym for nevoid basal cell carcinoma syndrome (Gorlin syndrome)

Key features

- Non-melanoma skin cancer (NMSC) represents the most frequently observed malignancy amongst Caucasians
- The major risk factor for NMSCs is UV light exposure; other factors include exposure to ionizing radiation, arsenic or organic chemicals, human papillomavirus infection, immunosuppression, and genetic predisposition
- Prevention efforts are aimed at lowering incidence and mortality via educational programs and sun protection campaigns
- NMSC, if neglected or inappropriately managed, can cause significant morbidity and even death
- Surgery is the mainstay of treatment, but promising new modalities include immunomodulators, photodynamic therapy, and drugs that address genetic defects

INTRODUCTION

Non-melanoma skin cancer (NMSC), specifically basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), represents the most frequently observed malignancy amongst Caucasians. In individuals with fair skin, approximately 75–80% of NMSCs are BCCs and up to 25% are SCCs[1]. Because the incidence of NMSC continues to rise, these neoplasms represent a significant health problem from the standpoint of patients' well-being and from the perspective of healthcare expenditures.

HISTORY

In 1775, Sir Percivall Pott noted an etiologic relationship between SCC and chimney soot exposure in his short treatise *Chirurgical Observations Relative to the Cancer of the Scrotum*. During the Industrial Revolution, links to arsenic, coal tar, shale oil and creosote were also identified. In the late 1800s, Paul Unna noted a connection to UV light, when he described skin cancer development in chronically sun-exposed sites in sailors.

Evidence of the nevoid basal cell carcinoma syndrome, consisting of jaw cysts, syndactyly and bifid ribs, has been identified in Egyptian mummies almost 4000 years old. In the 1850s, H Lebert first used the term "rodent ulcer" to describe untreated BCCs of long duration. Several years later, Sir Jonathan Hutchinson published a review of 42 cases of BCCs, identifying the tumor as a single entity with many different clinical and histopathologic forms. Krompecher first suggested that a BCC arose from the cells of the basal layer of the epidermis, but there were additional theories regarding the site of origin of this tumor, including from the hair follicle and other adnexal structures. Some authors hypothesized that a BCC was not a carcinoma but rather a nevoid tumor or hamartoma or that a BCC was derived from immature pluripotential cells which formed continuously during one's lifetime.

EPIDEMIOLOGY

NMSC occurs worldwide in all races. It is estimated that more than 3.5 million NMSCs occurred in approximately 2.5 million individuals in the US in 2006[2]. There are more skin cancers in the US population than there are all other cancers combined and it is estimated that one in five Americans will develop skin cancer during their lifetime[3] (over 95% will be NMSC). The most important factor related to development of these neoplasms appears to be skin phenotype (Table 108.1)[4–11], but other factors also play a significant role. As an example, the incidence of NMSC is about ten times higher in white versus Hispanic men and five times higher in white versus Hispanic women[12].

The exact incidence of NMSC may be difficult to determine due to issues such as diagnostic accuracy and diagnostic criteria (e.g. differentiation between AKs and SCC *in situ*). In addition, deriving precise data on NMSC is hampered by the fact that these neoplasms are not routinely included in state cancer registries (which often rely upon hospital data). Even if NMSCs were included, they would still be significantly underreported, given the number treated in private offices.

The amount of average annual UV radiation correlates with the incidence of skin cancer. There is also a direct relationship between the incidence of NMSC and latitude (Table 108.2), in that the closer individuals are to the equator, the greater their exposure to UV radiation. In Australia, the cumulative risk by age 70 years of having at least one NMSC is 70% for men and 58% for women. Incidence of NMSC increases with age, with a sharp increase in BCCs in men after the age of 60 years. In those under 40 years of age, the majority of NMSC is found in women, but, by age 80, the incidence in men exceeds that in women by a 2–3 : 1 ratio[12].

Actinic keratoses (AKs) are most often found in fair-skinned individuals, but can be seen in all races. AKs are so common that it has been estimated that currently up to 12% of individuals in the US have them[14]. In the UK, incidence rates for AKs are approximately 15 times those for BCC and SCC. Over 80% of AKs occur on the head, neck and upper extremities (dorsal hands and forearms). AKs develop much more often in individuals with a prior history of AKs, with increasing age, and in men. AKs are also markers for an increased risk for developing invasive SCC[15].

The demographics of ***SCC*** are similar to those of AKs, with the majority of SCC occurring on the head, neck and upper extremities[16]. In light-skinned populations, the degree of UV exposure is related to SCC development. On the other hand, in darkly pigmented populations, the pathogenesis of SCC may be unrelated to sun exposure, but rather may relate to chronic irritation or injury. SCC is found more frequently in men (3 : 1 male : female) and the incidence increases significantly after age 60 years[12]. The incidence of SCC has been rising worldwide in all age groups over the last several decades at an estimated 3–10% per year, with over 250 000 cases of invasive SCC diagnosed annually in the US. Similar incidence trends have been noted worldwide.

Weinstock[17] reported an age-adjusted mortality rate for confirmed cases of SCC in Rhode Island of 0.26/100 000. SCC-associated

INFLUENCE OF SKIN COLOR ON EPIDEMIOLOGY OF NMSC		
Characteristic	**Lightly pigmented individuals**	**Darkly pigmented individuals**
NMSC incidence	230 per 100 000	3.4 per 100 000
BCC:SCC ratio	4:1	1.1:1
BCC male:female ratio	1.5:1	1.3:1
SCC male:female ratio	2:1–5:1	1.3:1
% of BCCs developing in the head and neck region	60–80	90
% of SCCs developing in the head and neck region	65	35
% of SCCs developing in scars and chronic non-healing ulcers	<2	30–40
NMSC incidence rates	Increasing	?
NMSC mortality rates	Decreasing	Decreasing
% of skin cancer deaths due to NMSC in persons <50 years of age	10*	70
% of skin cancer deaths due to NMSC in persons >85 years of age	55	60

*Majority due to cutaneous melanoma.

Table 108.1 Influence of skin color on epidemiology of non-melanoma skin cancer (NMSC). BCC, basal cell carcinoma; SCC; squamous cell carcinoma. From refs 3–11.

COMPARISON OF LATITUDE AND INCIDENCE (PER 100 000) OF BASAL CELL CARCINOMA (BCC) AND SQUAMOUS CELL CARCINOMA (SCC)				
Geographic area (year of report)	**Latitude**	**BCC male/female**	**SCC male/female**	**Total (NMSC) male/female**
Townsville, Australia (1998)	19° S	2058/1195	1332/755	3390/1950
Nambour, Australia (1996)	27° S	2074/1579	1035/472	3109/2051
Nambour, Australia (2006)	27° S	1813/1269	–	–
Arizona (2001)	31° N	936/497	270/112	1206/609
New Hampshire (1999)	42° N	310/165	97/32	407/197
Rochester, MN (1997/1990)	43° N	175/124	155/71	330/195
Vaud, Switzerland (2001)	46° N	75/66	29/17	104/83
British Columbia, Canada (1990)	49° N	120/92	31/7	151/99
West Glamorgan, Wales (2000)	51° N	128/105	25/9	153/114
Netherlands (1991)	52° N	46/32	11/3	57/35
Hull, England (1994)	53° N	116/103	29/21	145/124
Finland (1999)	62° N	49/45	7/4	56/49

Table 108.2 Comparison of latitude and incidence (per 100 000) of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). All these data refer to Caucasian populations. Adapted from ref. 13. NMSC, non-melanoma skin cancer.

mortality is higher in whites and older persons, and men have a 3:1 greater SCC mortality rate as compared to women[17]. SCCs located on the ear, lip and genitalia appear to have a higher risk of death. While melanoma among whites is responsible for 90% of skin cancer deaths before 50 years of age (see Table 108.1), in adults over 85 years of age, the majority of skin cancer deaths are attributable to SCC[5].

BCC is the most common skin cancer in humans, and men generally have higher rates of BCC than do women (1.5–2:1)[18]. Over the last 30 years, it is estimated that incidence rates have risen between 20% and 80%. In the US, a disproportionate increase has been observed in young women. Similar increases in incidence rates have been noted worldwide, with the incidence doubling in Finland and Switzerland and increasing in Wales by 50% over the past two decades.

Incidence rates for BCC also increase with age and the median age at diagnosis is 68 years. In Queensland, Australia, age-adjusted incidence rates for BCC in 1996 were 2074 and 1579 per 100 000 per year for men and women, respectively – the highest rates for any specific cancer ever reported. In this geographic location, SCC occurred at half the rate of BCC among men and at about one-third the rate among women (see Table 108.2).

Mortality from BCC is quite rare and occurs primarily in immunocompromised patients and individuals with nevoid basal cell carcinoma (NBCC) syndrome. Cases of metastatic BCC are more likely from tumors with aggressive histopathologic patterns (morpheaform, infiltrating, metatypical, basosquamous). Perineural growth may be an indicator of aggressive disease. Metastases often involve regional lymph nodes, lungs, bone and skin. The mean age at the time of death is higher than with SCC, and the age-adjusted mortality rate for BCC has been estimated at 0.12 per 100 000. Mortality risk is related to increasing age, Caucasian race and male gender (>2× compared to women).

PATHOGENESIS

See Chapter 107.

RISK FACTORS (Table 108.3)

Environmental Exposures

UV radiation

UV exposure is the predominant cause of BCC and cutaneous SCC as evidenced by migrant studies, the correlation of incidence to latitude, and animal studies. There is, however, a difference in the type of UV exposure (see Table 108.3). For BCCs, intermittent intense episodes of UV exposure and sunburns at any age appear to increase risk, whereas cumulative long-term UV exposure and childhood sunburns increase the risk for developing SCCs and AKs[13,19].

As outlined in Table 108.2, the incidence of NMSC is inversely related to latitude. In addition, sun exposure early in life appears to have a greater influence on subsequent skin cancer risk than at a later age. For example, individuals born in countries with high ambient UV radiation such as Australia have significantly higher incidence rates of NMSC as compared to those with a similar genetic background (e.g. British, northern Europeans) who migrated to these locales later in life from countries with lower ambient UV radiation[13,20,21].

Tanning lamp usage

Several studies have demonstrated an increased risk for the development of NMSC in those who are exposed to artificial sources of UV radiation. Intentional tanning has been shown to increase the risk of SCC development[22] and Karagas et al.[23] demonstrated that any use of tanning devices was associated with odds ratios of 2.5 for SCC and 1.5 for BCC, even after adjustment for history of sunburns, sunbathing and sun exposure. In one study, women with BCCs had on average twice as many visits to tanning beds than did matched controls[24].

Therapeutic UV exposure

Individuals with psoriasis have been shown to be at increased risk for the development of NMSC. While long-term follow-up of psoriasis patients who underwent UV plus tar (Goeckerman) therapy found no increase in NMSC risk, long-term PUVA therapy was associated with a significant, dose-related risk of SCC development (adjusted relative risk = 8.6 for an accumulated exposure of between 100 and 337 treatments)[25]. With prolonged therapy, a slightly increased risk for BCC development was noted as well. In addition to the direct effects of PUVA, PUVA-induced immunosuppression may also play a role.

Ionizing radiation

Exposure to ionizing radiation leads to a threefold increased risk of NMSC[26]. The risk is in proportion to the radiation dose. Larger fractionated doses (>12–15 Gy) are thought to be necessary to induce tumor

RISK FACTORS FOR THE DEVELOPMENT OF BASAL CELL CARCINOMAS (BCCS) AND SQUAMOUS CELL CARCINOMAS (SCCS)	SCC	BCC
ENVIRONMENTAL EXPOSURES		
Cumulative/occupational sun exposure	+	
Intermittent/recreational sun exposure		+
Other exposures to UV light (PUVA, tanning beds)	+	+
Ionizing radiation	+	+
Chemicals (arsenic)	+	(+)
HPV	+	
Cigarette smoking	+	
PIGMENTARY PHENOTYPE		
Fair skin	+	+
Always burns, never tans	+	+
Freckling	+	+
Red hair	+	+
GENETIC SYNDROMES		
Xeroderma pigmentosum	+	+
Oculocutaneous albinism	+	(+)
Epidermodysplasia verruciformis	+	
Dystrophic epidermolysis bullosa (primarily recessive)	+	
Ferguson–Smith syndrome	+	
Muir–Torre syndrome	+*	(+)*
Nevoid basal cell carcinoma syndrome		+
Bazex and Rombo syndromes		+
PREDISPOSING CLINICAL SETTINGS		
Chronic non-healing wounds	+	
Longstanding discoid lupus erythematosus, lichen planus (erosive) or lichen sclerosus	+	
Porokeratosis (especially linear)	+	
Nevus sebaceus		+†
IMMUNOSUPPRESSION		
Organ transplantation	+	(+)
Other (e.g. chronic lymphocytic leukemia treated with fludarabine, AIDS patients with HPV infection)	+	

*Both SCCs (keratoacanthoma type) and BCCs typically have sebaceous differentiation.
†More often trichoblastomas.

Table 108.3 Risk factors for the development of basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs). HPV, human papillomavirus.

CHEMICALS ASSOCIATED WITH THE DEVELOPMENT OF NON-MELANOMA SKIN CANCER
Mineral oil
Coal tar
Soot
Polychlorinated biphenyls
Arsenic
4,4′ bipyridyl
Psoralen (plus UVA)
Nitrogen mustard

Table 108.4 Chemicals associated with the development of non-melanoma skin cancer. Based on ref. 30.

formation, so the risk with a given total dose may be less if a larger number of smaller fractionated doses are given. Most SCCs and BCCs that arise after exposure to ionizing radiation do so after a long latency period of up to several decades, with most tumors appearing ~20 years after the initial exposure.

Treatment of tinea capitis with radiation (prior to the discovery of effective systemic antifungal medications) has been linked to the development of multiple BCCs. In a study of 2224 children given X-ray therapy for tinea capitis (compared to a control group of 1380 tinea capitis patients given only topical medications), the relative risk for developing BCC of the head and neck among irradiated Caucasians was 3.6[27]. BCCs have been observed in radiation fields following treatment of port-wine stains and Hodgkin disease as well as after accidental exposure[28].

Occupational risk factors

Persons with outdoor occupations have a higher risk of developing NMSC. Airline pilots, who are exposed to ionizing radiation at flight altitudes, have been shown to have an elevated risk for both BCC and SCC[29]. Other occupations associated with an increased risk for NMSC include textile workers, sailors, locomotive engineers and agricultural workers.

Chemical exposures

Multiple organic chemicals have been associated with an increased risk for the development of NMSC[30] (Table 108.4). Occupational chemical exposures which can lead to skin cancer most commonly involve pesticides, asphalt, tar and polycyclic aromatic hydrocarbons, and they typically result in SCC. NMSCs induced by chemical exposures are usually localized, most often on the arms, and are usually multiple[31].

Arsenic is a well-defined cause of SCC (see Ch. 88). A clue to arsenic exposure is the presence of palmoplantar arsenical keratoses. The SCCs that arsenic induces are often multiple[28]. Increasing evidence indicates that arsenic acts as a tumor promoter by modulating the signaling pathways responsible for cell growth[32]. BCC has also been reported with extensive arsenic exposure. The typical latency period from exposure to clinical appearance of NMSC is 20–40 years[33].

Human papillomavirus infection

Human papillomaviruses (HPV) represent a large group of DNA tumor viruses that infect the epithelia of both skin and mucosae, inducing hyperproliferative lesions, most commonly warts. In addition to the association between HPV and anogenital SCCs, including in HIV-infected patients, individuals with epidermodysplasia verruciformis (EV) are known to have a significantly increased risk of developing SCCs, especially in sun-exposed sites (see below). Infection with the HPV types referred to as EV- or beta-types (see Table 79.1) is also observed in the general population, in particular in immunosuppressed organ transplant recipients[34]. Because specific HPV subtypes are thought to act as co-carcinogens in conjunction with UV in the early development of SCC[35], a current focus of research is the development of HPV vaccines that address this issue[36].

Immunosuppression

Organ transplantation

Organ transplant recipients have a markedly increased incidence of NMSC, primarily SCC. The incidence of BCC in organ transplant recipients is up to five to ten times greater than in the general population, while the incidence of SCC is 40–250 times greater. Risk factors include skin type, cumulative sun exposure, age at transplantation, and the degree and the length of immunosuppression.

SCC is a significant cause of morbidity and mortality in transplant recipients[37,38]. The pathogenesis of skin cancer in transplant recipients is multifactorial, involving decreased immunity, direct carcinogenic effects of immunosuppressive medications, HPV infection and UV light exposure. Transplant recipients are prone to develop numerous lesions and are more likely to suffer local and regional recurrences and metastases (Fig. 108.1)[37]. AKs and SCCs begin to appear with increasing frequency several years after transplantation. Lesions are often multiple, and usually develop in sun-exposed areas. HPV DNA is found in approximately 70–90% of transplant-associated SCCs. Tumors from transplant recipients contain HPV strains that occur in common benign cutaneous warts (HPV types 1 and 2), EV (HPV-5 and others), high-risk oncogenic warts (HPV types 16 and 18) and low-risk oncogenic genital warts (HPV types 6 and 11). Sometimes, several HPV types are detected within a single tumor.

In one series of renal transplant patients from the US, 5% of the patients died of skin cancer. In another series of heart transplant patients from Australia, 27% died of skin cancer. Two-thirds of these deaths were due to SCC. Patients who receive hematopoietic transplants do not experience this marked increase in skin cancer incidence (unless they have received long-term voriconazole), presumably because of a shorter duration of immunosuppression.

Fig. 108.1 Recurrent squamous cell carcinoma in a patient who had received a solid organ transplant. *Courtesy, John Carucci, MD.*

Immunosuppressive drugs

Use of immunosuppressive drugs, other than for organ transplantation as discussed previously, also increases the risk for the development of NMSC (particularly SCC). Risk of SCC development is directly related to length of immunosuppressive drug usage. In one study, the risk of SCC was significantly increased among recipients of oral glucocorticoids (odds ratio = 2.31) and the risk of BCC was also elevated (odds ratio = 1.49)[39].

HIV infection

Patients with HIV infection are at increased risk for the development of several cancers, including cutaneous SCC[40]. The incidence of HPV-related SCC of the anus is significantly increased in this population. Serial examinations and anal cytologies are recommended for surveillance. The biologic behavior of these SCCs can be aggressive.

Other risk factors

Other possible risk factors include residence at high altitudes, thermal burns, chronic ulcers and tobacco abuse[41]. While evidence from animal models suggested a relationship between fat intake and skin cancer incidence, results from subsequent epidemiologic studies were inconsistent and failed to show any strong evidence for either this association or for other dietary factors (e.g.vitamins, minerals)[34,42–44].

Genetic Risk Factors

Genetic predisposition

Phenotypic characteristics such as red hair, light skin, poor ability to tan and freckling have been identified as risk factors for melanoma as well as NMSC[13]. Pigmentation is a polygenic trait, with polymorphisms in several genes leading to the variation observed in the human race (see Table 65.5). A key gene encodes the human melanocortin-1 receptor (MC1R) which is expressed on the cell surface of melanocytes. Population-based studies in diverse ethnic groups have shown that the coding region of the human *MC1R* is remarkably polymorphic (see Fig 65.14). In Caucasians, there is a strong association between nine common *MC1R* variant alleles and the red hair/fair skin phenotype, thus placing these individuals at higher risk of photocarcinogenesis[45].

Genetic syndromes associated with increased NMSC risk

Xeroderma pigmentosum

Xeroderma pigmentosum (XP) consists of a group of autosomal recessive disorders characterized by defects in unscheduled DNA repair (see Ch. 86). A markedly increased incidence of NMSC and melanoma is observed in these individuals, if they are exposed to sunlight. NMSCs appear at an early age (median age, 8 years) and the risk of NMSC in affected individuals who are <20 years of age is 4800 times that of the general population. Strict UV avoidance can significantly decrease NMSC formation.

Oculocutaneous albinism

Oculocutaneous albinism encompasses a group of autosomal recessive disorders in which there is a variable degree of pigmentary dilution of the skin, eyes and hair (see Ch. 66). At a relatively early age, NMSC, especially SCC, and cutaneous melanoma develop with increased frequency. As in XP, strict sun avoidance for life can greatly minimize tumor development. However, metastatic cutaneous SCC is still a significant problem in areas of the world such as equatorial Africa.

Epidermodysplasia verruciformis

Epidermodysplasia verruciformis (EV) is a rare, usually recessively inherited disorder in which there is widespread colonization of the skin by HPVs of multiple subtypes (see Ch. 79). Evidence for an association between cutaneous HPV infection and SCC was first reported in these patients. One-third to one-half of patients will develop SCCs as adults, usually in sun-exposed regions, and several decades earlier than is typical for SCC development in the general population. Aggressive biologic behavior, including perineural spread, metastases and death, have been reported. HPV subtypes most frequently identified in the SCCs that arise in EV patients are 5 and 8.

Dystrophic epidermolysis bullosa

Dystrophic epidermolysis bullosa associated with significant scarring can result from both dominant and recessive mutations in the type VII collagen gene. SCCs more commonly appear in the recessive forms, where they are the most common cause of death. Tumors usually develop during the third to fifth decades of life, are frequently multiple, and demonstrate aggressive behavior in terms of recurrences and metastases. Whether this aggressive biologic behavior is due to tumor development within scars and chronic non-healing wounds, to specific mutations in the type VII collagen gene, or to elevated levels of basic fibroblast growth factor, is uncertain.

Nevoid basal cell carcinoma (NBCC) syndrome

Nevoid basal cell carcinoma syndrome (NBCC syndrome; Gorlin syndrome) is a rare, autosomal dominant disorder due to a mutation in the human *PTCH* gene[46].

Manifestations of the syndrome include multiple or early-onset BCCs, odontogenic keratocysts of the jaw, palmoplantar pits, calcification of the falx cerebri, and skeletal anomalies (Table 108.5). Affected individuals may develop specific neoplasms such as medulloblastomas, meningiomas, (bilateral) ovarian fibromas and cardiac fibromas. Of note, the medulloblastomas usually arise during early childhood, so suspicion of NBCC syndrome at early age allows screening of at-risk individuals[46].

BCCs usually appear after puberty, but they may develop during childhood. The number of BCCs in a single patient varies from a few to more than a thousand (Fig. 108.2). The BCCs favor the sun-exposed areas of the face, neck and upper trunk, but may occur in sun-protected sites. As in the general population, nodular BCCs usually occur on the face, while superficial BCCs are found primarily on the torso. Individual lesions may be papulonodular, pedunculated, pigmented, eroded, ulcerated, or have a combination of these features. The BCCs are sometimes mistakenly diagnosed clinically as melanocytic nevi, angiomas or even skin tags. The clinical course of the cutaneous tumors is usually indolent prior to puberty, after which they enlarge and eventually ulcerate, as in the general population. Individuals with NBCC syndrome are exquisitely sensitive to ionizing radiation, and hundreds of tumors can develop in children within radiation ports following radiotherapy for medulloblastoma. Additional cutaneous findings include epidermoid inclusion cysts and facial milia.

Bazex syndrome and Rombo syndrome

Bazex syndrome is a rare condition, consisting of follicular atrophoderma (usually occurring as circumscribed areas on the dorsal aspect of the hands and feet), hypotrichosis, localized hypohidrosis, milia, epidermoid cysts, and multiple, primarily facial, BCCs. Genetic transmission in most families appears to occur in an X-linked dominant fashion. Sometimes a source of confusion is the completely different

DIAGNOSTIC CRITERIA FOR NEVOID BASAL CELL CARCINOMA (NBCC) SYNDROME
MAJOR CRITERIA
1. More than two BCCs or one BCC before the age of 20 years
2. Odontogenic keratocysts of the jaw (proven by histology)
3. Three or more palmar or plantar pits
4. Bilamellar calcification of the falx cerebri
5. Bifid, fused or markedly splayed ribs
6. First-degree relative with NBCC syndrome
MINOR CRITERIA
1. Macrocephaly (determined after adjustment for height)
2. Congenital malformations: cleft lip or palate; frontal bossing; "coarse face"; moderate or severe hypertelorism
3. Other skeletal abnormalities: Sprengel deformity*; marked pectus deformity; marked syndactyly of the digits
4. Radiographic abnormalities: bridging of the sella turcica; vertebral anomalies such as hemivertebrae and fusion or elongation of the vertebral bodies; modeling defects of the hands and feet; flame-shaped lucencies of the hands or feet
5. Bilateral ovarian fibroma
6. Medulloblastoma
*Unilateral elevation of smaller-sized scapula.

Table 108.5 Diagnostic criteria for nevoid basal cell carcinoma (NBCC) syndrome. The diagnosis of NBCC syndrome requires ***two major or one major and two minor criteria***. BCC, basal cell carcinoma. Adapted from ref. 46.

Fig. 108.2 Nevoid basal cell carcinoma (NBCC) syndrome. A Numerous small and several large nodular BCCs on the face. **B** Three superficial BCCs and one large nodular BCC on the chest of a younger man.

Bazex syndrome (acrokeratosis paraneoplastica), in which psoriasiform plaques of the fingers, toes, ears and nose are often associated with SCC of the upper aerodigestive tract. In the follicular atrophoderma form of Bazex syndrome, BCCs develop in the second decade of life and frequently have a trichoepithelioma-like histopathologic appearance.

The so-called Rombo syndrome has many of the features of Bazex syndrome. Patients have an atrophoderma vermiculatum-like appearance on the cheeks, with evidence of sweat duct proliferation histologically. In addition, they often have hypotrichosis, blepharitis, peripheral (facial/acral) telangiectatic erythema, milia, trichoepitheliomas, and BCCs.

Risk of Additional Cancers

Individuals who have had a BCC or SCC are at increased risk for the development of additional BCCs and SCCs[47], compared to the general population. Patients with NMSC are also at increased risk for developing cutaneous melanoma[48]. In addition, persons with a history of NMSC are at increased risk for developing and dying from other (non-skin) cancers[49,50].

ACTINIC KERATOSIS AND SQUAMOUS CELL CARCINOMA

Clinical Features

Actinic keratosis

AKs were initially described as solar keratoses (due to their suspected cause) and senile keratoses (due to the age of onset). The term "actinic keratosis" is relatively recent. The latter term is preferred over solar keratosis, partly because the abbreviation SK also stands for seborrheic keratosis.

AKs have historically been characterized as being "precancerous" or "premalignant" because the atypical keratinocytes within these lesions are confined to the epidermis. There is no risk of metastasis until these lesions evolve into invasive carcinoma. An alternative minority view is that it is not accurate to deem them "premalignant" because they are malignant in the same sense as Bowen's disease (SCC *in situ*) or intraepithelial melanoma (melanoma *in situ*). The likelihood of an invasive SCC evolving from a given AK has been estimated to occur at a rate of 0.075–0.096% per lesion per year. For example, for a person with 7.7 AKs, the average number present on the skin of an affected individual, SCC would develop at a rate of 10.2% over 10 years. Other estimates are even higher, with rates of 13–20% over a 10-year period (if the lesions were left untreated). These rates are similar to those that have been determined for intraepithelial neoplasia of other sites. In the uterine cervix, approximately 15% of all untreated low- and moderate-grade cervical intraepithelial neoplasia lesions (CIN I and II) will progress to carcinoma *in situ* (CIN III) and to more advanced carcinoma involving deeper tissues, if left untreated. This process generally occurs over 10 to 20 years, although in some patients this interval may be as short as 6 months. Because of this continuum of progression of AKs in the skin, the analogous term keratinocytic intraepithelial neoplasia (KIN I, II and III) has been proposed, but has not gained widespread use. Possible explanations for this include the common phenomenon of spontaneous resolution of AKs, the very low rate of progression to invasive SCC, and concern regarding overaggressive therapies being employed.

AKs are amongst the most frequently encountered skin lesions in clinical practice. They present on sun-damaged skin of the head, neck, upper trunk and extremities (Fig. 108.3A). Individuals at higher risk of developing AKs include the elderly, those with lighter skin phototypes and those with a history of chronic sun exposure. The primary lesion

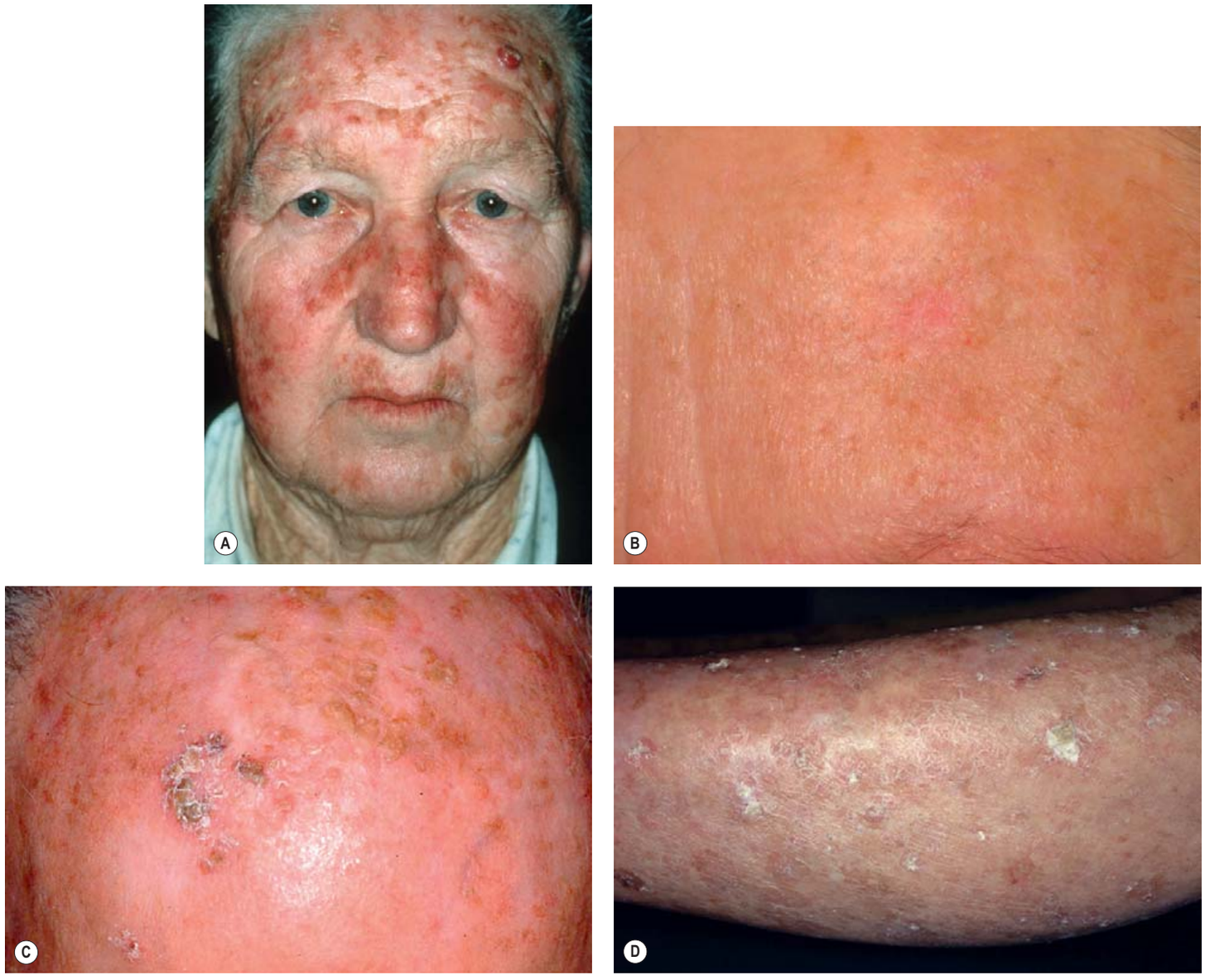


Fig. 108.3 Actinic keratoses (AKs). A Multiple AKs on the face of an elderly woman with fair complexion, blue eyes, and moderate to severe photodamage; the AKs vary in size from a few millimeters to over a centimeter. On the left forehead, the red nodule with slight scale-crust represents a well-differentiated SCC. **B** Pink-colored atrophic AK with minimal scale on the forehead. **C** Numerous hypertrophic AKs on the bald scalp with hypopigmentation at sites of previous treatment. **D** Multiple, large hypertrophic AKs on the shin of an elderly woman; note the thick scale. *B, Courtesy, Iris Zalaudek, MD; D, Courtesy, Jean L Bolognia, MD.*

is a rough erythematous papule with white to yellow scale. Patients may report tenderness. AKs can range in size from a few millimeters to large confluent patches several centimeters in diameter, especially in patients with severe photodamage. One of the earliest signs is slight erythema with almost imperceptible scale (Fig. 108.3B), although some lesions are devoid of visible erythema and present only as slight scale with indistinct borders. A clue to their presence is background photodamage, i.e. dyspigmentation, telangiectasia and wrinkling (see Ch. 87). Advanced lesions are typically thicker and well-defined with more visible hyperkeratosis and erythema. Lesions typically are clustered in areas of highest sun exposure, such as the superior helices of the ears, upper forehead, supraorbital ridge, nasal bridge, malar eminences, dorsal hands, extensor forearms, shins and the bald scalp (Fig. 108.3C).

Any region of the body can be affected if enough actinic damage has occurred. Visual inspection is best performed with simultaneous palpation to detect lesions that may not be readily apparent. This is especially true in individuals with significant background erythema from chronic sun exposure or rosacea. Tenderness on palpation should alert the clinician to the possibility that the lesion has evolved into carcinoma. Clinical subtypes of AKs include the classic variant already described, hyperplastic (or hyperkeratotic), pigmented, lichenoid, atrophic, bowenoid, and actinic cheilitis.

Hyperkeratotic (hypertrophic) AKs are easily identified on visual inspection as papules and plaques with scale or scale-crust and an erythematous base (Fig. 108.3D). The erythematous base often extends beyond the overlying hyperkeratosis. The hyperkeratotic scale can become white or yellow–brown over time (see Fig. 108.3C). Patients often find these lesions annoying due to their thickness. Sometimes, distinction from SCC can be difficult and biopsy is warranted. Occasionally, hyperkeratotic AKs may develop cutaneous horns which manifest as columns of thick cornified material that protrude above the skin. These should be biopsied to exclude the possibility of an underlying malignancy, as approximately 15% of cutaneous horns have invasive SCC at their bases[51].

Pigmented AKs, sometimes called superficial pigmented AKs (SPAKs), represent a subtype that often lacks associated erythema and has a hyperpigmented or reticulated appearance. These lesions can at times be difficult to distinguish from reticulated seborrheic keratoses, lentigines, or even the lentigo maligna subtype of cutaneous melanoma. Dermoscopy may be a useful adjunct in these situations. Clinical clues are the location on sun-exposed skin, background solar changes, and hyperkeratosis that is sometimes appreciable by palpation. In cases in which the diagnosis is questionable, a biopsy is required to exclude the possibility of melanoma.

Lichenoid AK is characterized histopathologically by the presence of a dense band-like inflammatory infiltrate. Clinically, this lesion is similar to the classic form of AK but has more erythema surrounding the base of the lesion. Patients may relate pruritus or tenderness that coincides with the onset of the lichenoid infiltrate in a pre-existing AK.

Atrophic AKs usually have minimal surface change but are appreciated as pink to red, slightly scaly macules or patches (see Fig. 108.3B) that are found by histopathologic examination to have an atrophic epidermis.

Actinic cheilitis is the term used to describe the characteristic changes that occur on the lower vermilion lip of individuals with moderate to severe photodamage. Actinic cheilitis may resemble the classic form of AK, with well-demarcated, erythematous papules or thin plaques with scale. In other patients, the erythema and especially the scale is more diffuse and can involve the entire lower vermilion lip; areas of leukoplakia may also be present. When clinical distinction between actinic cheilitis and SCC of the lip is not possible, a biopsy should be performed.

Squamous cell carcinoma in situ

SCC *in situ* is commonly called Bowen's disease. The most common presentation of SCC *in situ* is an erythematous scaly patch or slightly elevated plaque (Fig. 108.4) that arises within sun-exposed skin of an elderly individual. However, it can develop in younger individuals with significant photodamage. Bowen's disease may arise *de novo* or from a pre-existing AK. The head and neck, followed by the extremities and trunk, are the most common sites. Lesions can become crusted and in SCC *in situ* of anogenital mucosa, erosions may be prominent (Fig. 108.5).

Clinical distinction of SCC *in situ* from AK, superficial BCC, psoriasis or chronic eczema may at times be difficult (see Fig. 108.4D). Generally, AKs are smaller lesions and superficial BCCs often have a more translucent quality with slight elevation of the leading edge. Patients with psoriasis and diffuse actinic damage can pose a diagnostic dilemma, as concomitant psoriatic papules and plaques may clinically resemble AKs and Bowen's disease.

Arsenic-induced SCC *in situ* resembles the classic variety clinically but has a marked tendency to be multifocal and to arise on non-sun-exposed areas of the trunk. Associated findings include palmoplantar keratoses and guttate hypopigmentation superimposed on hyperpigmentation (see Ch. 88).

Bowenoid papulosis is a term used when histopathologic changes of SCC *in situ* are found within genital warts, usually due to infection with an oncogenic strain such as HPV-16 or -18. Dermatologists often prefer to use this term when multiple papules are present, as opposed to calling all of them SCC *in situ*, because the lesions rarely become invasive. The clinical appearance can vary from small brown papules of the penis to perianal pink papules to corrugated pink to brown plaques of

Fig. 108.4 Squamous cell carcinomas *in situ*, Bowen's type. A Scaly red plaque on the chest with skip areas. **B** Bright red, well-demarcated plaque on the proximal nail fold with associated horizontal nail ridging; the possibility of HPV infection needs to be considered. **C** Dermoscopic examination of a pink scaly plaque on the chest, with tiny dotted vessels in the upper half of the lesion. **D** Extensive involvement of the finger which is often misdiagnosed clinically as psoriasis or chronic eczema and therefore treated for years with corticosteroid creams (as was this patient). *C, Courtesy, Iris Zalaudek, MD.*

Fig. 108.5 Squamous cell carcinoma *in situ*, erythroplasia of Queyrat type. Large, eroded erythematous plaque with well-demarcated borders. The lesion began on the shaft of the penis.

the inguinal creases (see Chs 73 & 79). Whether this entity represents true SCC *in situ*, or is a histopathologic simulant, is a matter of debate.

Other variants of SCC *in situ* include a pigmented variant often seen in individuals with darker skin types and a verrucous form. Pigmented SCC *in situ* may be mistaken for a pigmented AK or a melanocytic lesion and verrucous SCC *in situ* may simulate a verruca clinically.

Invasive cutaneous squamous cell carcinoma

Invasive cutaneous SCC usually arises within a background of sun-damaged skin, most commonly on the bald scalp, face, neck, extensor forearms, dorsal hands and shins (Fig. 108.6A–D). The color usually varies from erythematous to skin-colored; rarely there are pigmented variants. SCCs are often papulonodular, but can be plaque-like, papillomatous or exophytic. The degree of associated scale varies, with some lesions becoming quite hyperkeratotic (see Fig. 108.6A); other secondary changes include crusting, erosions and ulcerations (Fig. 108.6E,F).

The natural history of SCCs also varies, from slowly enlarging to rapidly growing with significant tenderness and even pain. Of note, paresthesias, anesthesia and pain may be signs of perineural invasion.

Fig. 108.6 Clinical spectrum of cutaneous squamous cell carcinoma (SCC). A A large keratotic nodule of the supraorbital region in an elderly woman; note the coarse wrinkling and solar elastosis of the face. **B** Eroded and keratotic nodule that developed rapidly at the site of trauma on the shin. **C** Large, fungating nodule on the dorsum of the hand. **D** Multiple eroded superficial SCCs in association with hypertrophic AKs on the cheek and neck of an elderly man. **E** Erosive, slightly vegetating, thick plaque arising within lichen sclerosis of the vulva. **F** Firm, eroded, red plaque on the scrotum; histopathologically, the SCC was moderately differentiated. *B, Courtesy, Jean L Bolognia, MD.*

In general, invasive SCCs tend to have more "tumor volume" than classic AKs, but they can resemble hyperkeratotic (hypertrophic) AKs or inflamed seborrheic keratoses or verrucae.

Staging of SCC takes into account tumor volume as measured by diameter (≤2 cm vs >2 cm) and depth of invasion (>2 mm), and SCCs arising within sun-damaged skin are often early stage, i.e. T1/AJCC Stage I (Table 108.6). Anatomic sites with a greater risk of aggressive biologic behavior include the ear[52], the lips (Fig. 108.7), and mucosal sites including the vulva and penis (see Fig. 108.6E,F). Clinical examination of patients with invasive SCC includes palpation of regional lymph nodes for enlargement and firmness, followed by assessment of size if enlarged.

STAGING OF CUTANEOUS SQUAMOUS CELL CARCINOMA (SCC)

T, N, M			
	Primary tumor (T)		
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma *in situ*		
T1	Tumor ≤2 cm in greatest dimension with <2 high-risk features*		
T2	Tumor >2 cm in greatest dimension *or* Tumor any size with ≥2 high-risk features†		
T3	Tumor with invasion of maxilla, orbit or temporal bone		
T4	Tumor with invasion of skeleton (axial or appendicular) or perineural invasion of skull base		
	Regional lymph nodes (N)		
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension		
N2	Metastasis in a single ipsilateral lymph node, >3 cm but <6 cm in greatest dimension (2a); or in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension (2b); or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension (2c)		
N3	Metastasis in a lymph node, >6 cm in greatest dimension		
	Distant metastasis (M)		
M0	No distant metastasis		
M1	Distant metastasis		
STAGE			
	T	**N**	**M**
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IV	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T Any	N3	M0
	T4	N Any	M0
	T Any	N Any	M1

*High-risk features for the primary tumor (T) staging:
Depth/invasion: >2 mm thickness, Clark level ≥IV, perineural invasion
Anatomic location: primary site ear, primary site hair-bearing lip
Differentiation: poorly differentiated or undifferentiated
†Excludes cutaneous SCC of the eyelid.

Table 108.6 Staging of cutaneous squamous cell carcinoma (SCC). Adapted from American Joint Committee on Cancer, 2010.

Keratoacanthoma

Keratoacanthomas (KAs) are considered by some to be a variant of SCC and by others to represent benign tumors (i.e. pseudomalignancy). The exact nosology is still uncertain, although there are some data that support its differentiation from "conventional" SCC. Typically, a rapidly enlarging papule evolves into a sharply circumscribed, crateriform nodule with a keratotic core over a period of a few weeks (Fig. 108.8A,B), and then it may resolve slowly over months to leave an atrophic scar[53]. Most lesions occur on the head and neck or in sun-exposed areas of the extremities, with or without symptoms of pain or tenderness.

There are several distinct clinical presentations of KA, including solitary, multiple, grouped, keratoacanthoma centrifugum marginatum (Fig 108.8C), giant (Fig 108.8D), subungual, intraoral, multiple spontaneously regressing (Ferguson–Smith), multiple non-regressing, generalized eruptive (Grzybowski), KAs associated with Muir–Torre syndrome (may have sebaceous differentiation ["seboacanthoma"]; see Ch. 63), and KAs associated with chemical exposure, immunosuppression[30] and HPV infection[54].

By far the most common presentation is the solitary KA. While most of these tumors are small (5 to 15 mm), some KAs (e.g. keratoacanthoma centrifugum marginatum [see Fig. 108.8C]) may reach several centimeters in diameter, persist for months before resolution, and heal with prominent scarring. Grouped KAs may resolve more slowly than solitary KAs, while subungual KAs have been associated with underlying bony destruction.

The Ferguson–Smith syndrome is an autosomal dominant condition. Multiple KAs develop within sun-exposed areas, usually beginning in the third decade of life. Lesions typically regress over weeks to months, but rare examples of metastases have been reported.

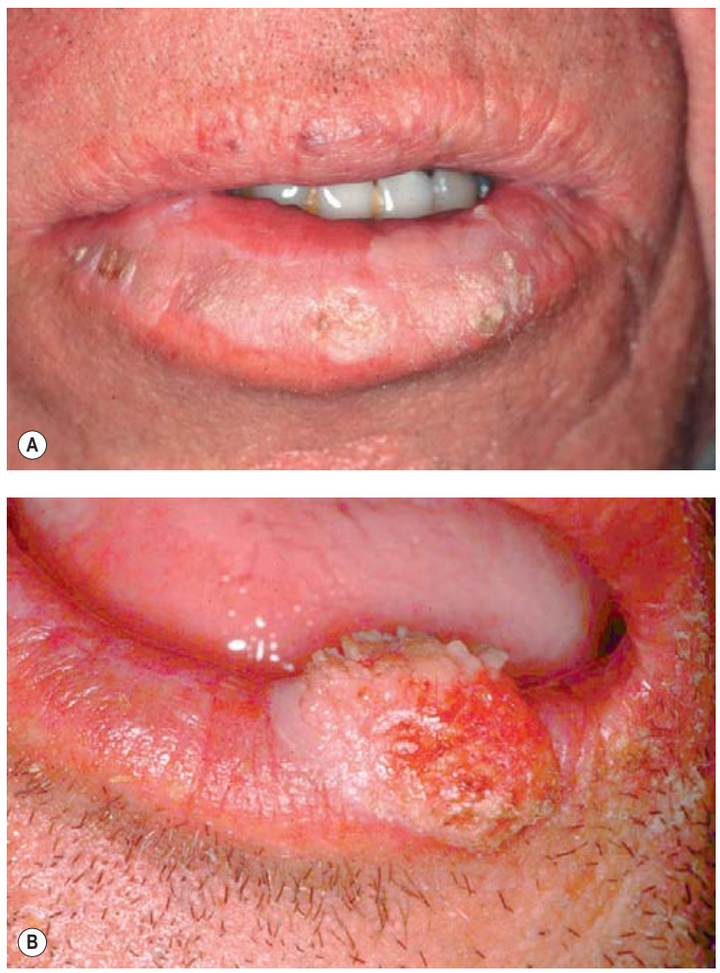


Fig. 108.7 Squamous cell carcinoma (SCC) of the lower lip. A Extensive hyperkeratosis and leukoplakia of the lower vermilion lip; histopathologically, the SCC was superficially invasive and well-differentiated. **B** Verrucous and eroded nodule on the lower vermilion lip in a heavy smoker.

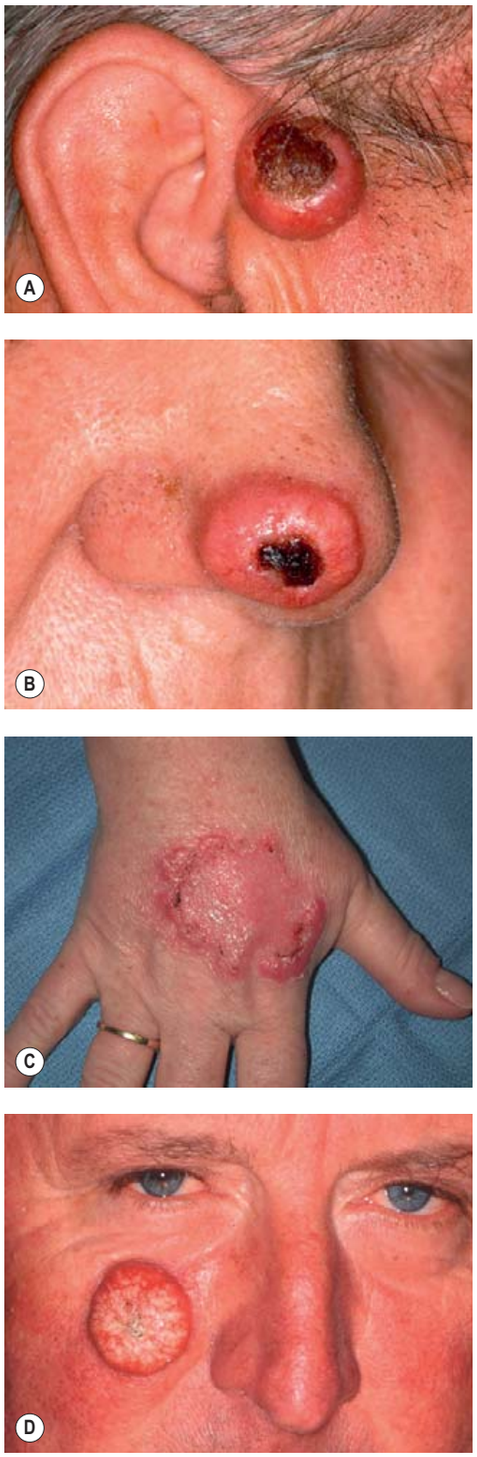


Fig. 108.8 Clinical spectrum of keratoacanthomas. **A, B** Rapidly growing, erythematous crateriform nodules with a rolled border and central keratotic core. **C** Progressive peripheral expansion and central involution with residual atrophy characterize keratoacanthoma centrifugum marginatum. **D** Giant keratoacanthoma with a yellow–red color and a history of rapid growth.

Fig. 108.9 Verrucous carcinoma. **A** Longstanding large nodule on the plantar surface with a rabbit burrow-like appearance; such a tumor is also referred to as an epithelioma cuniculatum. **B** Keratotic and ulcerated plaque on the ventromedial aspect of the great toe. **C** A classic location in an amputation stump. In general, these well-differentiated SCCs enlarge slowly.

Multiple KAs of the Grzybowski type present as thousands of papules resembling milia or early eruptive xanthomas. They develop rapidly and may slowly resolve over a period of months[53]. Patients often have scarring, ectropion and a mask-like facies.

Verrucous carcinoma

Verrucous carcinoma is a rare, well-differentiated variant of SCC which tends to occur in middle-aged and older adults. It is considered a low-grade malignancy with three major subtypes: (1) epithelioma cuniculatum (plantar surface of the foot); (2) giant condyloma acuminatum of the genitalia (also known as Buschke–Löwenstein tumor; see Ch. 79); and (3) oral florid papillomatosis (oral mucosa). Of note, the "cuniculatum" refers to the rabbit burrow-like appearance with crevices.

Clinically, verrucous carcinomas present as large (sometimes huge), exophytic tumors with a papillomatous or verrucous surface (Fig. 108.9A,B). They are commonly associated with HPV infection, and distinguishing between a verrucous carcinoma and a large wart or condyloma acuminatum can be difficult. Gradual penetration of verrucous carcinomas into underlying tissues can result in destruction of subcutis, fascia and bone. These tumors can arise within scars and amputation stumps (Fig. 108.9C) and in association with osteomyelitis fistulae and chronic venous insufficiency. Verrucous carcinomas often recur after attempted removal, but they usually do not metastasize, except for recurrent or irradiated tumors with anaplastic transformation.

Some authors consider subungual keratoacanthomas, proliferating tricholemmal cysts (proliferating pilar tumors) and papillomatosis cutis carcinoides to be subtypes of verrucous carcinoma.

Lymphoepithelioma-like carcinoma of the skin

Lymphoepithelioma-like carcinoma of the skin (LELCS) is an uncommon neoplasm that shows histopathologic similarities to lymphoepithelioma-like carcinoma (LELC), an undifferentiated

nasopharyngeal carcinoma associated with EBV infection. It has been suggested that LELCS has "the potential for both sweat glandular and follicular differentiation"[55]. Clinically, it presents as a dermal papule or nodule arising in the head and neck region[56]. In contrast to LELC, EBV genome integration is not found in LELCS, and metastases are rare. Evidence of HPV infection is also usually absent. LELCS is considered by some to be a variant of cutaneous SCC.

Histologically, LELCSs are localized within the dermis or subcutis; involvement of the overlying epidermis having been observed in only a few cases[57]. The tumor consists of clusters of epithelial cells (with large vesicular nuclei and prominent nucleoli) intermingled with lymphocytes and plasmacytoid cells. However, classic signs of squamous differentiation such as keratin "pearls", dyskeratotic cells or intercellular bridges are absent[56]. By immunohistochemistry, there is expression of cytokeratin and epithelial membrane antigen in the neoplastic cells; stromal lymphocytes express leukocyte common antigen (CD45). The histopathologic differential diagnosis includes cutaneous lymphadenoma, lymphocytoma cutis, follicle center lymphoma, and carcinoma with thymus-like differentiation.

In Vivo Imaging Methods

Dermoscopy

Dermoscopy of invasive SCC reveals linear-irregular vessels, elongated vessels resembling hairpins, dotted vessels or a combination of these findings (polymorphous or atypical vascular pattern). Typically, vessels are surrounded by a whitish halo; the latter is the dermoscopic hallmark of all keratinizing tumors and is also found in KAs and in seborrheic keratoses (see Table 0.38). Ulceration and hemorrhagic crusts appear as red-, brown- or black-colored surface blotches. Rare pigmented SCCs may have a scaly surface, diffuse or homogenous blue pigmentation and/or irregularly distributed blue–gray granular structures. AKs on the face demonstrate a so-called "strawberry pattern" (an erythematous pseudonetwork surrounding hair follicle orifices filled with yellowish keratotic plugs)[58], whereas in other body sites they often display surface scales and dotted vessels. Bowen's disease typically has a scaly surface and glomerular vessels.

Reflectance confocal microscopy

Reflectance confocal microscopy (RCM) is an imaging technique which allows non-invasive horizontal imaging of the epidermis and superficial dermis at almost the same resolution as routine histology. RCM (and dermoscopic) features of keratinizing tumors are often difficult to visualize due to the surface scaling which obscures underlying structures. Although to date, only a few publications have described the RCM features of AKs and SCCs, a recent study suggested that a disarranged pattern and/or an atypical honeycomb pattern, in conjunction with round nucleated cells at the level of the spinous/granular layer, were key features of SCC[59].

Pathology

Actinic keratosis

Several histopathologic variants of AK have been described, including pigmented, acantholytic, atrophic, bowenoid, lichenoid, hypertrophic (hyperkeratotic) and actinic cheilitis types. All are characterized by atypical keratinocytic proliferation, beginning in the basal layer and confined to the epidermis (Fig. 108.10).

Microscopic changes consist of partial-thickness atypical keratinocytes displaying nuclear pleomorphism (especially in the basal layer), and disordered maturation. The lesion may be acanthotic, often with an increased number of buds protruding into the papillary dermis, or atrophic with loss of rete ridges. Hyperkeratosis and parakeratosis are a constant finding. Acrosyringia and acrotrichia are often uninvolved, resulting in orthokeratosis at the ostia of these structures. This produces a characteristic pattern of alternating ortho- and parakeratosis, often referred to as the "flag" or "pink and blue" sign, since the color of the stratum corneum shows alternation of a more eosinophilic column (parakeratosis) with a basophilic one (orthokeratosis) (see Fig. 108.10A). AKs are associated with solar elastosis in the dermis (Fig. 108.10C).

The keratinocytic atypia of an AK is usually confined to the lower portion of the epidermis, as opposed to full-thickness atypia in SCC *in situ*. Diagnostic difficulty arises when the presence of small foci of full-thickness atypia occur in a lesion with otherwise characteristic features of an AK. Some pathologists may use the term "bowenoid AK" in this setting. A histopathologic grading system for AKs has been proposed as follows: grade 1, the presence of atypical cells within the basal or suprabasal layer only, without budding, involvement of the hair follicles or full-thickness atypia; grade 2, grade 1 plus budding and/or involvement of the hair follicles; and grade 3, characterized by full-thickness atypia (SCC *in situ*)[60].

In hyperkeratotic AKs, marked hyperkeratosis with associated parakeratosis is evident. If pronounced, this can lead to cutaneous horn formation. Pigmented AKs additionally show basilar pigmentation in a pattern similar to a solar lentigo (see Fig. 108.10C). Lichenoid lesions demonstrate a band-like infiltrate of lymphocytes in the papillary dermis directly beneath the dermal–epidermal junction. Actinic cheilitis arises on paramucosal skin, usually the lower vermilion lip, and may or may not show accompanying inflammation.

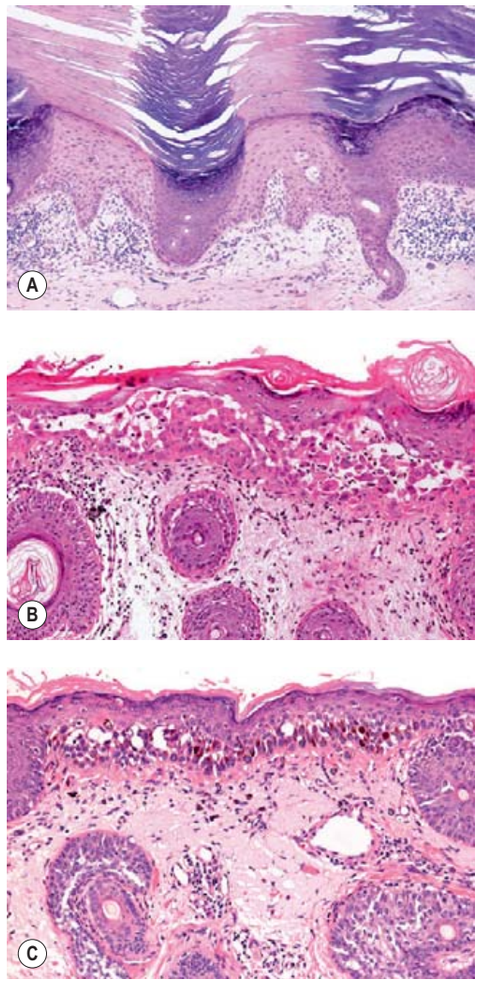


Fig. 108.10 Histopathology of actinic keratoses (AKs). **A** Hyperkeratotic AK with alternating pink and blue colors in the cornified layer; the pink-colored parakeratotic columns within the stratum corneum are located above the atypical keratinocytes in the spinous layer, while the blue-colored columns of orthohyperkeratosis are above the acrosyringia. Atypical epidermal keratinocytes also display a pinkish color that contrasts with the color of the basophilic, normal keratinocytes of the acrosyringia. **B** Acantholytic variant with clefts within the stratum spinosum. **C** Pigmented actinic keratosis with increased melanin pigmentation within the basal layer. Note the solar elastosis in the dermis.

Squamous cell carcinoma in situ

SCC *in situ* (Bowen's disease), by definition, demonstrates full-thickness atypia of the epidermis over a broad zone (Fig. 108.11). Nuclear pleomorphism and apoptosis are often more florid than in AKs, and mitoses are frequent. The epidermis commonly exhibits acanthosis. Atypical keratinocytes more commonly extend down the adnexa than in an AK. Diffuse confluent parakeratosis is also observed more often than the focal parakeratosis seen in an AK.

A number of different histopathologic variants have been described. The "pagetoid" variant demonstrates large keratinocytes with abundant, pale-staining cytoplasm scattered throughout the epidermis, simulating melanoma *in situ*, Paget's disease or extramammary Paget's disease (see Fig. 73.16). Immunohistochemistry may be necessary to make a distinction, although the location of the lesion on sun-damaged skin (as opposed to Paget's disease), the presence of desmosomal spines,

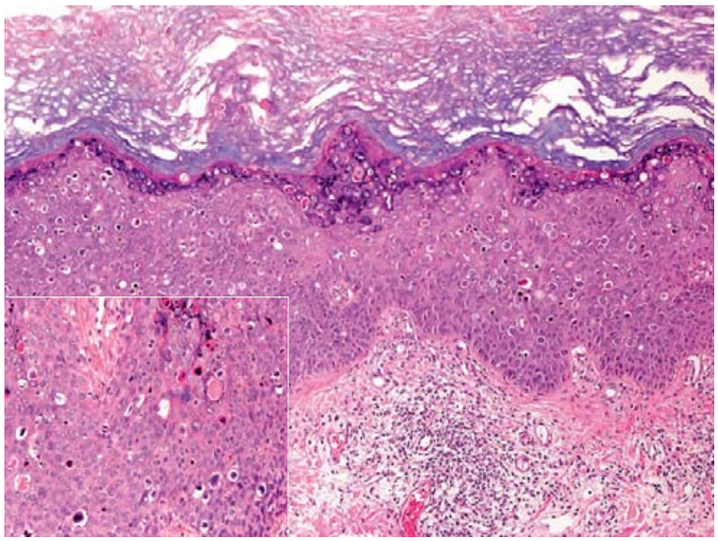


Fig. 108.11 Histopathology of Bowen's disease (squamous cell carcinoma *in situ*). Irregular epidermal hyperplasia with atypical pleomorphic keratinocytes throughout the entire epidermal thickness. Note several necrotic keratinocytes (insert).

and the presence of many apoptotic cells can be helpful. Another subtype is the pigmented variant, in which there is abundant melanin in the epidermis.

Invasive squamous cell carcinoma

Well-differentiated SCC generally arises in the setting of epidermal changes consistent with AK. In addition, there is a downward proliferation of lobules and detached aggregations of glassy, brightly eosinophilic keratinocytes containing nuclei with some degree of pleomorphism and mitoses (Fig. 108.12A). Nucleoli may be prominent. Intercellular bridges (desmosomes) are often apparent, along with keratin pearls and apoptotic cells. The degrees of nuclear atypia and cellular differentiation vary within and among tumors (Fig. 108.12B). The pink quality of the cytoplasm arises from abundant high-molecular-weight keratin. As a rule, aggregations of atypical keratinocytes are present within the dermis at varying levels. The inflammatory infiltrate varies considerably in intensity and consists primarily of lymphocytes and plasma cells. Invasive SCC arising from Bowen's disease is characterized by islands of tumor cells in the dermis that have a strikingly similar appearance to the atypical cells within the epidermis, i.e. a more basophilic appearance and an absence of clear-cut keratinization.

Poorly differentiated SCCs display progressive and overlapping features, ending in highly infiltrative tumors that lack overt keratinization and sometimes have a spindle cell morphology. Perineural infiltration (Fig. 108.12C) and desmoplastic or sclerotic stromal change become more common in these forms. Neurotropic SCCs behave in a more aggressive manner, with local recurrence rates approaching 50%[61]. Poorly differentiated tumors (cytokeratin-positive) generally require immunohistochemistry to distinguish them from spindle-cell melanoma (generally S100-positive), atypical fibroxanthoma (cytokeratin- and S100-negative, vimentin-positive) and leiomyosarcoma (smooth muscle actin- and desmin-positive).

There are several variants of SCC. The acantholytic type (Fig. 108.12D) and the related adenoid (pseudoglandular) SCC possibly have a worse prognosis. Other variants include bowenoid SCC, SCC with overlying cutaneous horn formation, and desmoplastic, mucinous, or pigmented SCC. Marjolin's ulcer is a SCC that occurs in a chronic wound or scar, including scars from a burn.

A recent large, prospective study focusing on risk factors that predict metastasis and local recurrence in cutaneous SCC reported overall rates of 4% for metastasis and 3% for local recurrence[52] . Only tumors >2 mm in vertical thickness had a significant risk of developing metastases. For SCCs whose thickness was between 2.1 and 6 mm, the metastatic rate was 4%, and it was 16% for lesions thicker than 6 mm. Other risk factors for metastasis included location on the ear, increased horizontal size, and immunosuppression (Table 108.7). Tumor thickness and the presence of a desmoplastic stroma were found to be risk factors for local recurrence. For example, of the 51 patients with desmoplastic SCC, 24% developed local recurrences, compared to 1% of the 564 patients with non-desmoplastic SCCs.

RISK FACTORS FOR METASTASIS OF INVASIVE SQUAMOUS CELL CARCINOMA
Tumor thickness >2 mm (high risk: tumor thickness >6 mm)
Diameter >2 cm
Location: ear, lips, mucosae including tongue, vulva, penis (perineural growth may be an additional risk factor in these locations)
Arising within a scar (e.g. burn, radiation)
Histopathologically, poorly differentiated or undifferentiated; acantholytic features; developing within Bowen's disease
Immunosuppression

Table 108.7 Risk factors for metastasis of invasive squamous cell carcinoma. Based in part upon ref. 52.

Keratoacanthoma

A KA typically has a "volcano-like" architecture. The tumor is comprised of well-differentiated keratinocytes with a brightly eosinophilic glassy cytoplasm, surrounding a core filled with cornified material (Fig. 108.13). An inflammatory infiltrate of lymphocytes, and often eosinophils, is usually present. Small intratumoral abscesses of neutrophils are common, and neurotropism may be observed. As the lesion regresses, the dome-shaped architecture flattens and fibrosis develops at the base of the lesion. Cytologic atypia is usually minimal in a KA. If hyperchromatic nuclei or abnormal mitoses are prominent, then the diagnosis of an invasive KA-like SCC should be rendered.

Verrucous carcinoma

Verrucous carcinoma is defined as a well-differentiated and distinct clinicopathologic variant of SCC. However, this term is not correctly used for any SCC that has a warty appearance. Cytologic atypia is minimal, and the tumor has a pushing border as opposed to an infiltrating invasive edge. Verrucous carcinoma can be associated with HPV infection, and histopathologic distinction from a large wart is often difficult and may be impossible if the entire tumor is not available for microscopic examination. The major distinguishing features of a verrucous carcinoma are the massiveness and depth of the lesion, as well as the more pronounced irregular architecture.

Histologic simulators of SCC

There are a number of histologic simulators of SCC, including irritated seborrheic keratosis, verruca vulgaris, warty dyskeratoma, inverted follicular keratosis, prurigo nodularis, hypertrophic lichen planus, hypertrophic lupus erythematosus, atypical mycobacterial or "deep" fungal infections, granular cell tumor, and pseudocarcinomatous hyperplasia (e.g. in a healing wound). Architectural pattern and recognition of cellular and nuclear features of malignancy are critical in establishing a diagnosis. In some cases, only clinical correlation allows a distinction between SCC and some of these conditions.

BASAL CELL CARCINOMA

Clinical Features

BCC is a tumor that arises within sun-damaged skin. It rarely develops on the palms and soles or mucous membranes. Currently, despite the description of more than 26 different subtypes of BCC, a universally accepted classification scheme is lacking[62]. In the view of the authors, there are four major distinctive clinicopathologic types, namely, nodular (Fig. 108.14), superficial (Fig. 108.15), morpheaform (Fig. 108.16), and fibroepithelial (also referred to as fibroepithelioma of Pinkus; Fig. 108.17)[63]. Combinations of the latter three types with nodular BCC may occur. While all types of BCC may ulcerate, ulceration is observed

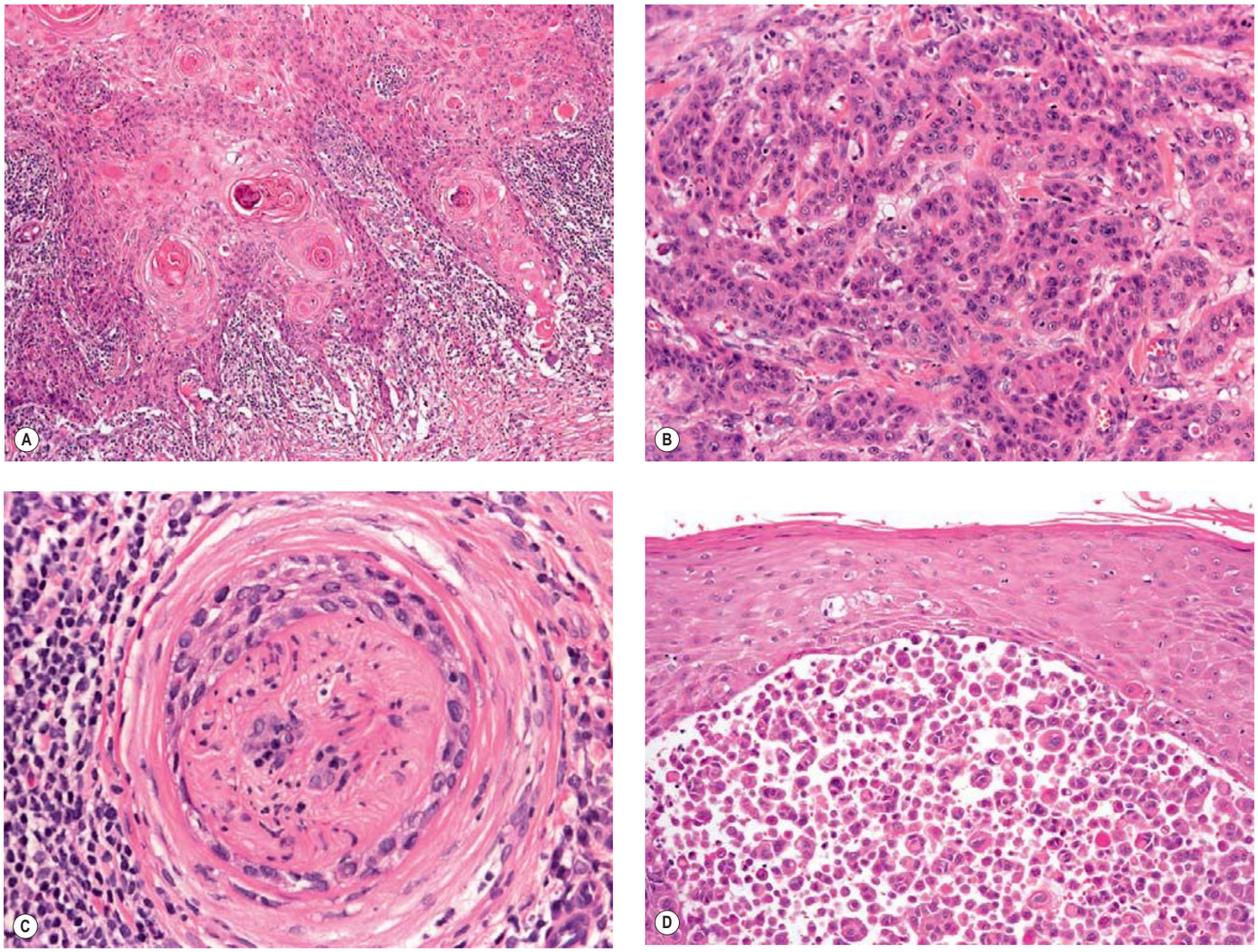


Fig. 108.12 Squamous cell carcinoma (SCC): range of histopathologic findings. A Well-differentiated SCC with numerous horn pearls (eosinophilic parakeratotic keratinization). **B** Poorly differentiated SCC with strands and cords of epithelial cells with prominent nuclear atypia and no signs of keratinization. **C** Perineural growth and neurotropism of a poorly differentiated SCC. **D** Acantholytic SCC characterized by epithelial aggregations composed of atypical keratinocytes with acantholysis. *Courtesy, Lorenzo Cerroni, MD*

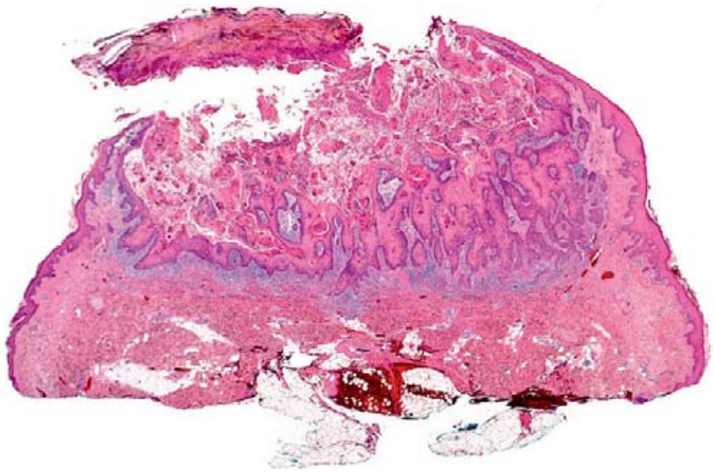


Fig. 108.13 Histopathology of keratoacanthoma. Scanning magnification of a stereotypical keratoacanthoma with a keratin-filled crater encompassed by epithelial lips.

more often in the nodular type. Also, variable amounts of melanin may be present within these tumors (Fig. 108.18), even though the majority of BCCs are amelanotic; pigmented BCCs are observed more commonly in those with darker skin phototypes[64]. A significant confounding factor when one attempts to classify BCCs is the number of different histopathologic patterns that become entwined with clinical subtypes. Examples are cystic, micronodular and basosquamous BCCs. A more complete list of histopathologic patterns is presented in Table 108.8. Although these patterns may be seen in all four major clinicopathologic types of BCC, they are observed more frequently in the nodular type.

Nodular basal cell carcinoma

Nodular BCC is the most common subtype, accounting for approximately 50% of all BCCs. Lesions typically present as a shiny, pearly papule or nodule with a smooth surface and the presence of arborizing telangiectasias (see Fig. 108.14A). With time, the tumor can enlarge and ulcerate (rodent ulcer, phagedenic ulcer), but an elevated rolled border usually remains and is a clinical clue to the diagnosis (see Fig. 108.14E). Sites of predilection are the face, especially the cheeks, nasolabial folds, forehead and eyelids, but nodular BCCs may arise in any hair-bearing area of the skin. They are rarely seen in non-hair-bearing sites, e.g. genital mucosa.

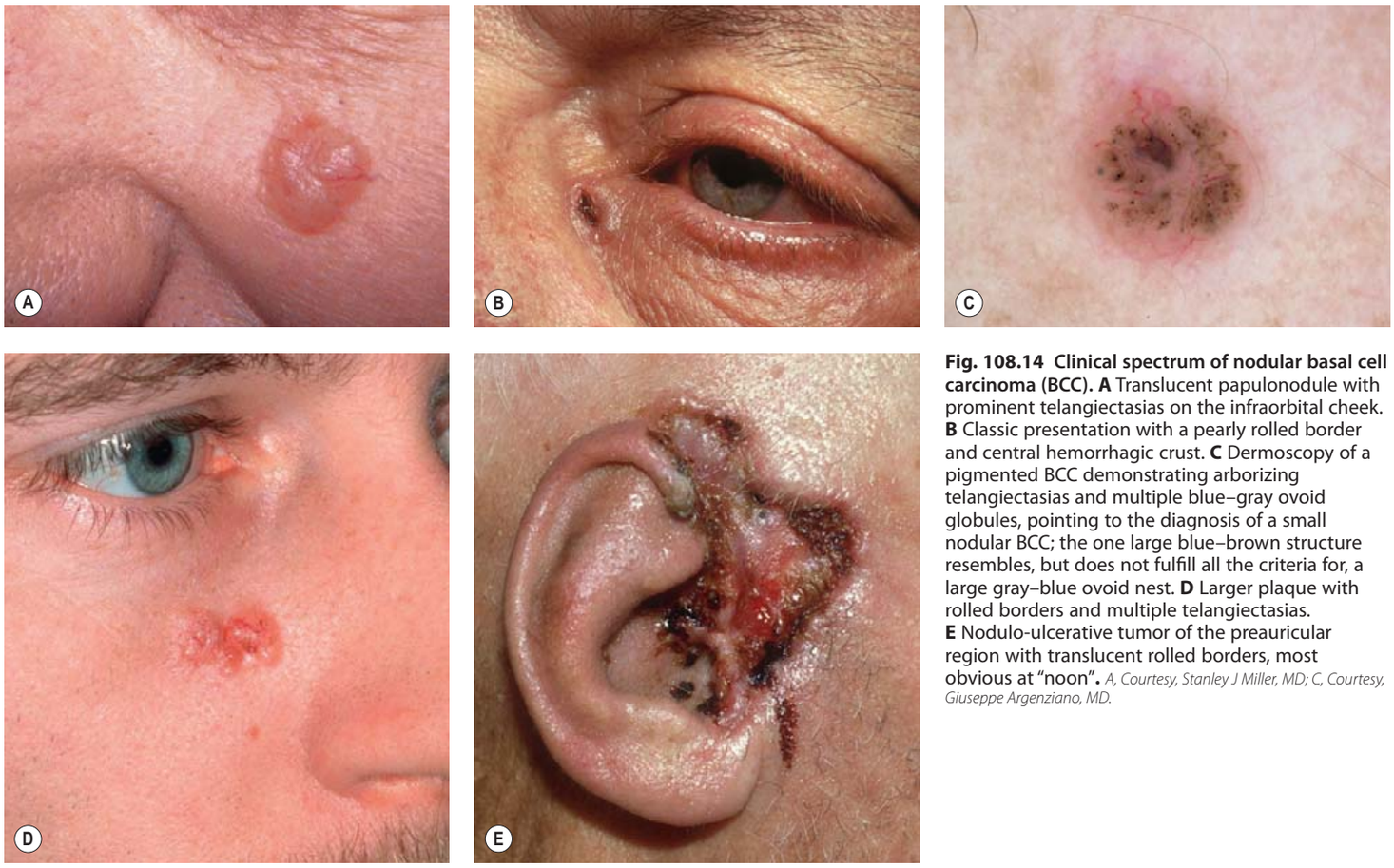


Fig. 108.14 Clinical spectrum of nodular basal cell carcinoma (BCC). A Translucent papulonodule with prominent telangiectasias on the infraorbital cheek. **B** Classic presentation with a pearly rolled border and central hemorrhagic crust. **C** Dermoscopy of a pigmented BCC demonstrating arborizing telangiectasias and multiple blue–gray ovoid globules, pointing to the diagnosis of a small nodular BCC; the one large blue–brown structure resembles, but does not fulfill all the criteria for, a large gray–blue ovoid nest. **D** Larger plaque with rolled borders and multiple telangiectasias. **E** Nodulo-ulcerative tumor of the preauricular region with translucent rolled borders, most obvious at "noon". *A, Courtesy, Stanley J Miller, MD; C, Courtesy, Giuseppe Argenziano, MD.*

Fig. 108.15 Superficial basal cell carcinoma. A Numerous erythematous patches and thin plaques on the back of a man with a history of arsenic exposure decades previously. **B** A solitary large, thin, dark pink plaque. There are scattered areas of fine scaling and small foci of brown pigment within the rolled border. As a rule, these lesions are neither pruritic nor tender.

The clinical differential diagnosis of non-ulcerated lesions includes adnexal neoplasms (see Ch. 109), intradermal melanocytic nevi (softer and comma vessels by dermoscopy), Merkel cell carcinoma, and cutaneous melanoma (amelanotic more often than melanotic); for ulcerated lesions, see Table 45.3 and Figure 105.1.

Superficial basal cell carcinoma

Superficial BCCs typically present as a well-circumscribed, erythematous, macule/patch or thin papule/plaque, with the diameter varying from a few millimeters to several centimeters (see Fig. 108.15). Additional findings include focal scale and/or crusts, a thin rolled border, and variable amounts of melanin; in larger lesions, areas of spontaneous regression may be present, characterized by atrophy and hypopigmentation. The mean age at diagnosis is 57 years, a younger age than for other types of BCC[43], and in younger age groups, superficial BCC is the most common subtype[65]. This BCC variant favors the trunk and extremities; less often, it occurs in the head and neck region. Multiple lesions may be present.

The growth pattern of superficial BCCs is primarily horizontal, but tumors may occasionally become deeply invasive, with induration, ulceration, and nodule formation. Extensive subclinical lateral spread accounts for the significant recurrence rate of these tumors after routine surgical treatment. The clinical differential diagnosis includes solitary lichenoid keratosis and Bowen's disease (more scale) as well as inflammatory diseases such as psoriasis, dermatitis and cutaneous lupus erythematosus.

Morpheaform basal cell carcinoma

This less common subtype of BCC frequently presents as a slightly elevated to even depressed area of induration that is usually light pink to white in color and has ill-defined borders (see Fig. 108.16); it often resembles a scar or plaque of morphea. The surface of the lesion is typically smooth, although crusts with underlying erosions or ulcerations as well as superimposed papules may be observed. While an elevated pearly border is typically absent, telangiectasias may be present.

Fig. 108.16 Morpheaform basal cell carcinoma (BCC). **A** Recurrent tumor 2 years after microscopically controlled surgery; note the scar-like appearance with superimposed glassy pink and brown papules. **B** Oval hypopigmented firm plaque that resembles a scar (e.g. post electrodessication and curettage). While there is a light pink color between 6 and 9 o'clock, no translucency or rolled border is present. **C** A classic example with indistinct borders and scar-like appearance. *A, Courtesy, Darrell S Rigel, MD.*

Fig. 108.17 Fibroepithelioma of Pinkus. This soft, skin-colored to light pink, broad, sessile nodule on the lower back representing a fibroepithelial BCC is adjacent to a classic nodular BCC.

The biologic behavior is usually more aggressive, with extensive local destruction.

Fibroepithelial basal cell carcinoma

This rare variant of BCC usually presents as a skin-colored or pink, sessile plaque or pedunculated papulonodule with a smooth surface (see Fig. 108.17). It favors the trunk, especially the lower back. Fibroepithelial BCCs often occur in individuals with multiple superficial BCCs. The clinical differential diagnosis includes a large fibroepithelial polyp (skin tag) or intradermal nevus.

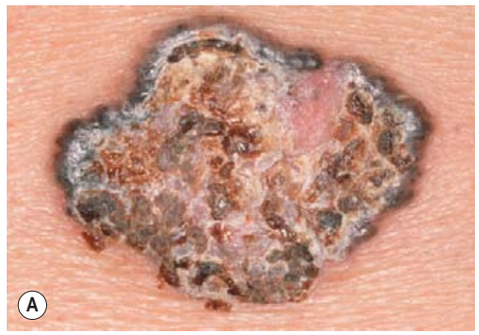


Fig. 108.18 Pigmented basal cell carcinoma. **A** In addition to the admixture of scale and hemorrhagic crusts centrally, there is a translucent and black rolled border superiorly. **B** The clinical differential diagnosis of this small nodular pigmented BCC includes nodular melanoma. However, the glassy translucency, in concert with characteristic dermoscopic features, will point to the diagnosis of pigmented BCC.

HISTOPATHOLOGIC PATTERNS OBSERVED IN NODULAR BASAL CELL CARCINOMAS

I. Epithelial patterns		II. Cytologic characteristics	
Adamantinoid	Labyrinthine	**Nuclear features**	**Cytoplasmic features**
Adenoid	Macronodular	Bowenoid	Basosquamous
Adenoid-cystic (adeno-cystic)	Micronodular	Cuboid	Clear
Anastomosing	Multimicrocystic	Oval	Granular
Arboriform	Nodular	Round	Signet-ring
Cribriform (sieve-like)	Petaloid	Spindle	Scant
Columnar	Racemiform	**III. Non-epithelial (stromal) findings**	
Cord-like	Retiform (reticulated)	Amyloid	Keloidal tissue
Comedo-like	Strand-like	Calcification	Mucin deposition
Cystic	Trabecular	Cartilaginous metaplasia	Osseous metaplasia
Frond-like	Tubular	Fibrosis (fibroplasia)	Sclerosis
Fenestrated		Granulation tissue-like	

Table 108.8 Histopathologic patterns observed in nodular basal cell carcinomas. Adapted from ref. 63.

Additional histopathologic subtypes of BCC

Basosquamous carcinoma

Basosquamous carcinoma (metatypical BCC) is a tumor that has histologic features of both BCC and SCC. These tumors may behave biologically more like a SCC than a BCC, i.e. have more aggressive behavior with a greater likelihood of recurring after treatment and metastasizing[66]. It has been estimated that this variant constitutes 1% of all NMSC. When metastases occur, they may have the same microscopic appearance as the original tumor or may resemble a poorly

differentiated SCC. The incidence of metastases with this variant of BCC has been estimated to be greater than 5%.

Micronodular basal cell carcinoma

This histopathologic term applies to BCCs in which smaller aggregations of basaloid cells infiltrate the dermis. Micronodular BCCs have a destructive behavior, with subclinical spread and high rates of recurrence. Clinically, they may present as macules, papules or slightly elevated plaques and may be difficult to differentiate from nodular BCC.

In Vivo Imaging Methods

Dermoscopy

Dermoscopy provides a demonstrated benefit in the diagnosis of non-pigmented and pigmented BCCs. The dermoscopic hallmark of BCC is the presence of well-focused arborizing vessels in conjunction with foci of microulceration. Additional dermoscopic findings with a high specificity for BCC include large blue-gray ovoid nests, multiple blue-gray globules, leaf-like structures and spoke-wheel areas (see Table 0.12). As expected, there is no pigment network[64]. In a recent publication, the presence of short, fine superficial telangiectasias as well as concentric structures and multiple, "in-focus" blue–gray dots was described (see Fig. 108.14C)[67].

Reflectance confocal microscopy

The following RCM features (see above for description of technique) have been described for all BCCs, regardless of subtype[68,69]: (1) variable architectural disarray of the epidermis; (2) a streaming pattern of elongated monomorphic nuclei that are polarized along the same axis; (3) tightly packed cells in the papillary dermis with a nodular/cord-like growth pattern; (4) palisading of tumor cell nuclei; (5) peri-tumoral dark cleft-like spaces (representing peri-tumoral mucinous edema); and (6) the presence of bright dendritic cells and melanophages (in pigmented BCC)[68].

Pathology

All types of BCC have as a least common denominator the presence of aggregations of basaloid keratinocytes within a variably fibromyxoid stroma (Fig. 108.19). A connection to the epidermis is usually observed, at least focally. The cells are characterized by large, relatively uniform nuclei and scant cytoplasm. Cellular borders are indistinct and desmosomes are inapparent. Apoptotic cells are common. The fibromyxoid stroma is intimately associated with the tumor islands, often showing increased cellularity. A characteristic feature of BCC is retraction of the stroma around the tumor islands, creating microscopically visible clefts (see Fig. 108.19B,D). Although this latter feature may not be seen in all instances, when present it is useful in differentiating BCCs from histopathologic simulators.

In nodular BCC (see Fig. 108.19D), large, round or oval aggregations of basaloid keratinocytes extend from the epidermis into the dermis. Overlying ulceration with an associated inflammatory response may be present. Peripheral palisading is usually prominent and peri-tumoral clefts are often conspicuous in nodular BCC. Centrally, the nuclei lack organization and are more randomly distributed. In larger tumor islands, central areas of necrosis may develop, leading to the formation of cystic spaces. True cystic or nodulocystic BCCs have mucin pools within the tumors (see Fig. 108.19E). Micronodular BCCs are composed of tumor islands much smaller than those of nodular BCC (see Fig 108.19I). The cellular features are similar.

Superficial BCCs are characterized by small, superficially located buds of basaloid cells extending no more deeply than the papillary dermis, with or without clefting (see Fig. 108.19A,B). In a given two-dimensional plane of section, there are skip areas along the epidermis, hence the synonym "superficial multifocal BCC". There is evidence that many of these multifocal buds connect in a net-like pattern, such that most tumors are not truly multifocal.

Keratotic BCCs or BCCs with follicular differentiation contain small keratinized cysts that lack a granular layer within the aggregates of neoplastic cells. These lesions display differentiation towards hair follicle structures. They can be difficult to differentiate from trichoepithelioma or other follicular adnexal neoplasms. Prominent clefting between the palisaded tumor islands and the stroma, as well as a myxoid (rather than a fibrocellular) stroma, characterize these BCCs. Infundibulocystic BCC is similar in appearance to the follicular variant of BCC, but usually has a more anastomosing pattern of tumor nests.

Pigmented BCCs usually have the overall architecture of a nodular BCC. They contain aggregates of melanin, often irregularly distributed, and melanocytes (see Fig. 108.19F). Melanophages are frequently dispersed within the dermis.

Morpheaform, sclerosing and infiltrative BCCs share similar histopathologic features. A common finding is a pattern of strands and cords of basaloid keratinocytes extending between collagen bundles (see Fig. 108.19J). These tumor islands may be composed of very few cells and may surround nerves. A peripheral palisaded pattern of tumor cells is absent and stromal retraction (cleft formation) is also frequently not evident.

Fibroepithelioma of Pinkus is a variant of BCC characterized by thin anastomosing strands and cords of tumor cells that project downward from the epidermis in a fenestrated pattern and are embedded in a fibrous stroma (see Fig. 108.19K). Both peripheral palisading and peritumoral retraction are less prominent. The differential diagnosis includes eccrine syringofibroadenoma and reticulated seborrheic keratosis.

The diagnosis of basosquamous carcinoma has been variably defined and applied. To some, these tumors are characterized by an admixture of typical BCC with zones of keratinization (positive for high-molecular-weight keratin), while to others, basosquamous carcinoma is characterized by histopathologic features of both BCC and SCC (see Fig. 108.19G). To some extent, use of the term may reflect diagnostic uncertainty between BCC and SCC. The diagnosis should be made sparingly, and not for any BCC that has some increased keratinization.

Histologic simulators of BCC

Of the other basaloid tumors that may simulate BCC (Table 108.9), adnexal neoplasms (see Ch. 111) cause the most difficulties, in particular trichoblastoma. In contrast to BCC, clefts in trichoblastoma are located within the stroma and not in direct proximity to the tumor, and follicular germs and papillae, simulating rudimentary hair follicles, are commonly found. Basaloid induction within dermatofibromas and nevus sebaceus may also simulate BCC histopathologically.

TREATMENT

The National Comprehensive Cancer Network (NCCN) has established guidelines of care for NMSCs. These guidelines are not strictly evidence-based, but developed through consensus by a working group of expert clinicians who review, interpret and synthesize the existing literature. For the most current version, see www.nccn.org/professionals/physician_gls/f_guidelines.asp.

Evaluation and risk assessment

Evaluation of a suspected NMSC requires a history, physical examination and biopsy of the suspicious lesion. The history should assess duration, rate of growth, and any prior therapy, as well as any personal or family history of prior skin cancers. Localized neurologic symptoms, although rare, may suggest the possibility of perineural involvement. Any history of prior radiation therapy to the area should be elicited. Current medical problems (e.g. chronic lymphocytic leukemia), medications (e.g. voriconazole) and allergies should be reviewed. Evidence of immunosuppression (i.e. organ transplantation, underlying hematologic malignancy, immunosuppressive medications or HIV infection) should be determined, and any of the risk factors listed in Table 108.3 identified.

Physical examination should include observation and palpation of the tumor to determine exact location and size, and whether it appears to have any connection to underlying structures such as muscle, cartilage or bone. How well or poorly defined the tumor borders are, whether there is physical evidence of prior surgery or other treatment modality (indicating the possibility of recurrence), and development within a site of chronic inflammation or scar should all be assessed. Careful inspection of the surrounding skin to exclude the presence of satellite lesions is necessary, as is examination of the draining lymph nodes, especially

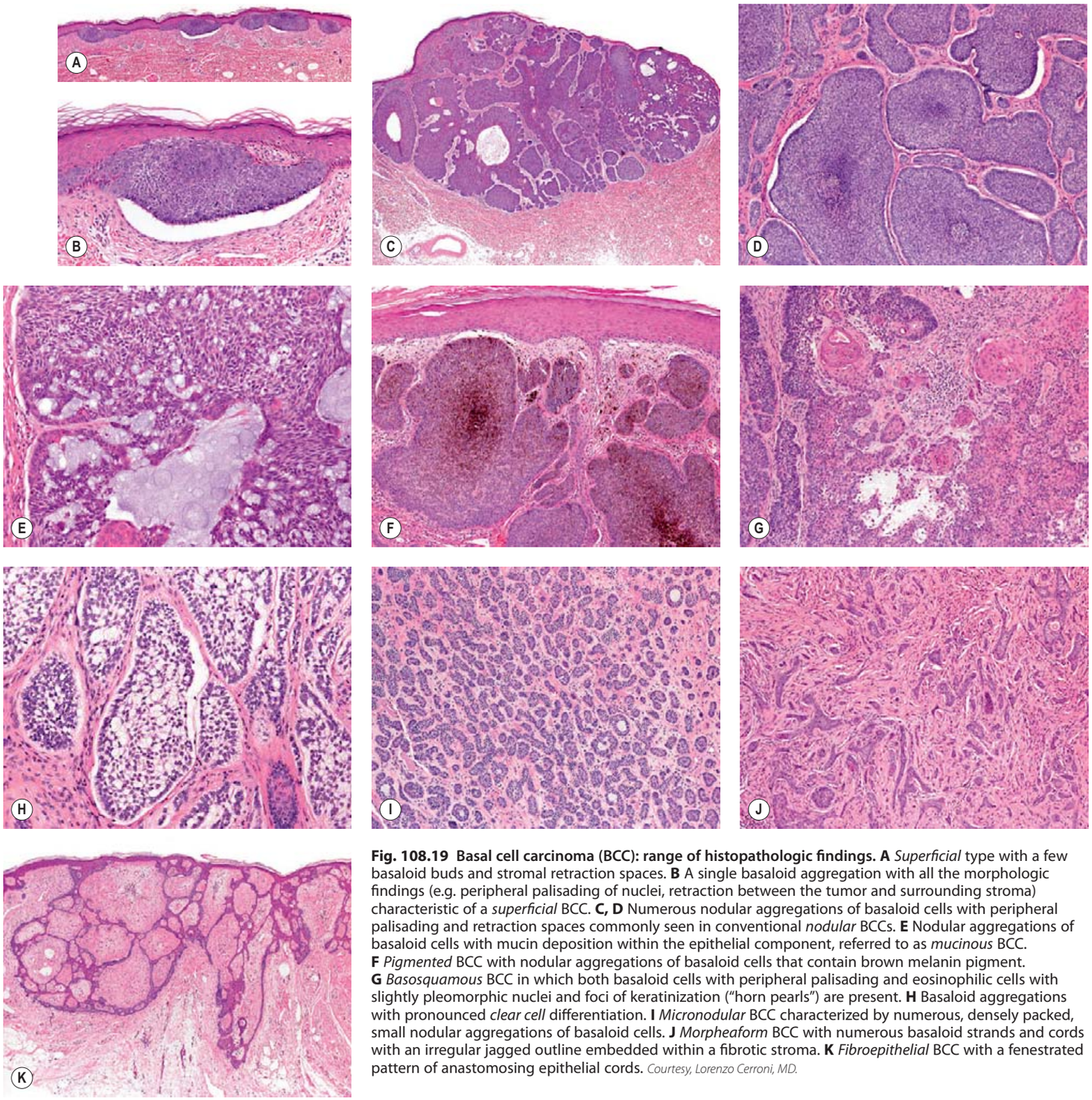


Fig. 108.19 Basal cell carcinoma (BCC): range of histopathologic findings. A *Superficial* type with a few basaloid buds and stromal retraction spaces. **B** A single basaloid aggregation with all the morphologic findings (e.g. peripheral palisading of nuclei, retraction between the tumor and surrounding stroma) characteristic of a *superficial* BCC. **C, D** Numerous nodular aggregations of basaloid cells with peripheral palisading and retraction spaces commonly seen in conventional *nodular* BCCs. **E** Nodular aggregations of basaloid cells with mucin deposition within the epithelial component, referred to as *mucinous* BCC. **F** *Pigmented* BCC with nodular aggregations of basaloid cells that contain brown melanin pigment. **G** *Basosquamous* BCC in which both basaloid cells with peripheral palisading and eosinophilic cells with slightly pleomorphic nuclei and foci of keratinization ("horn pearls") are present. **H** Basaloid aggregations with pronounced *clear cell* differentiation. **I** *Micronodular* BCC characterized by numerous, densely packed, small nodular aggregations of basaloid cells. **J** *Morpheaform* BCC with numerous basaloid strands and cords with an irregular jagged outline embedded within a fibrotic stroma. **K** *Fibroepithelial* BCC with a fenestrated pattern of anastomosing epithelial cords. *Courtesy, Lorenzo Cerroni, MD.*

for high-risk tumors, since in-transit[70] and distant metastases[71] are more common in these patients. In all patients, a full skin examination is required, to exclude other cutaneous malignancies.

Skin cancers are often identifiable visually by an experienced clinician. Nevertheless, a properly performed biopsy is essential to the diagnosis and management of any lesion. Numerous biopsy techniques, including excisional, incisional, shave, saucerization and punch, may be employed (see Ch. 146). For obvious skin cancers, especially in elderly patients, sometimes a tissue specimen can be obtained at the same time as definitive therapy. If a superficial process (such as a superficial BCC or SCC *in situ*) is suspected, or if shallow therapy (such as curettage and electrodesiccation) is being contemplated, a shave biopsy is usually adequate for establishing a diagnosis. In most other instances, a punch biopsy or deep saucerization that extends to subcutaneous fat is preferred. AKs, on the other hand, are often treated without prior biopsy unless invasive NMSC is suspected; clinical judgment determines which AKs require treatment and which can be left untreated.

The biopsy report should include an assessment of histopathologic subtype in both BCC and SCC, and degree of differentiation in SCC. Presence of ulceration and perineural or vascular involvement should be indicated. In SCC, histopathologic assessment of tumor depth, as either an anatomic estimate of depth or an actual measurement of tumor thickness in millimeters, appears to be prognostically useful[52].

Using these data, stratification of a specific tumor into a low- or high-risk category may be made (Table 108.10). High-risk tumors,

HISTOLOGIC SIMULANTS OF BASAL CELL CARCINOMA (BCC)	
	Major distinguishing features
Adenoid cystic carcinoma	Cribriform pattern, EMA-positive
Ameloblastoma	Location in mouth
Basaloid follicular hamartoma	Multiple small papules, positive family history
Cloacogenic carcinoma	Anal location
Dermatofibroma	Basaloid induction in overlying epidermis
Eccrine carcinoma	Small sweat ducts
Folliculocentric basaloid proliferation	Focal follicular budding
Merkel cell carcinoma	Punctate keratin (CK20-positive) in cytoplasm, expression of neuroendocrine markers
Metastatic breast carcinoma	History, single filing, expression of CK7, mammoglobulin, gross cystic disease fluid protein-15
Microcystic adnexal carcinoma	Small keratin cysts, absent stromal retraction, ductal differentiation
Mucinous carcinoma	Pools of mucin with floating basaloid islands
Nevus sebaceus	Basaloid induction; trichoblastomas and BCCs may arise within a nevus sebaceus
Sebaceous carcinoma	Oil red O-positive sebocytes on histochemical staining
Trichoblastoma	Clefts within the stroma; hair germs and papillae
Trichoepithelioma and desmoplastic trichoepithelioma	Horn cysts, absent stromal retraction, papillary mesenchymal bodies, peritumoral CD34 positivity; positive family history when multiple

Table 108.9 Histologic simulants of basal cell carcinoma (BCC). CK, cytokeratin; EMA, epithelial membrane antigen.

RISK FACTORS FOR RECURRENCE OF NMSC		
	Low risk	**High risk**
CLINICAL RISK FACTORS		
Location/size	Area L <20 mm	Area L ≥20 mm
	Area M <10 mm	Area M ≥10 mm
	Area H <6 mm	Area H ≥6 mm
Borders	Well defined	Poorly defined
Primary vs recurrent	Primary	Recurrent
Tumor at site of prior radiation therapy	Negative	Positive
Tumor at site of chronic inflammatory process (SCC only)	Negative	Positive
Rapidly growing tumor (SCC only)	Negative	Positive
Neurologic symptoms: pain, paresthesia, paralysis (SCC only)	Negative	Positive
Immunosuppression	Negative	Positive
PATHOLOGIC RISK FACTORS		
Perineural involvement	Negative	Positive
Subtype (BCC only)	Nodular, superficial	Micronodular, infiltrating, sclerosing
Degree of differentiation (SCC only)	Well differentiated	Moderately or poorly differentiated
Desmoplasia (SCC only)	Negative	Positive
Adenoid, adenosquamous or desmoplastic (SCC only)	Negative	Positive
Tumor thickness (SCC only)	<2 mm	≥ 2 mm (see text)

Area L: low risk for recurrence: trunk, extremities.
Area M: middle risk for recurrence: cheeks, forehead, neck, scalp.
Area H: high risk for recurrence: "mask areas" of face (central face, eyelids, eyebrows, periorbital, nose, lips, chin, mandible, preauricular and postauricular skin/sulci, ear, temple), genitalia, hands and feet.

Table 108.10 Risk factors for recurrence of non-melanoma skin cancer (NMSC). BCC, basal cell carcinoma; SCC, squamous cell carcinoma. Adapted from Miller SJ. The National Comprehensive Cancer Network guidelines of care for nonmelanoma skin cancers. Dermatol Surg. 2000;26:289–92 and Brantsch KD, Meisner C, Schonfisch B, et al. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. Lancet Oncol. 2008;9:713–20.

particularly SCCs, need to be treated aggressively[72]. For larger and deeper tumors, the possible need for multispecialty collaboration or preoperative imaging studies should be considered. On the basis of this assessment, a rational therapeutic plan is designed. Because of the risk of post-therapeutic tumor recurrence and the elevated risk for subsequent NMSC and melanoma, patients with NMSC are typically followed regularly for life.

Standard excision

Standard surgical excision is effective for most primary BCCs; however, cure rates are inferior to those achieved with Mohs surgery in the case of recurrent BCC, infiltrative BCC, and BCC arising in high-risk (H) anatomic sites. It has been demonstrated that 4 mm margins are adequate for removal in 98% of cases of non-morpheaform BCC <2 cm in diameter. However, for facial lesions, simple excision with narrow margins is often not adequate for effective removal[73]. High-risk SCC requires 6 mm margins, with size >2 cm, poor differentiation, invasion to fat, and location in high-risk areas associated with a greater risk of subclinical tumor extension. Incompletely excised lesions, especially those involving high-risk sites or those involving the deep margin, should be re-treated. Re-excision or Mohs micrographic surgery are the treatments of choice in these cases[74].

Curettage with electrodesiccation

Curettage with electrodesiccation is frequently used by dermatologists to treat BCCs. Cure rates as high as 97–98% have been reported[75], but careful selection of appropriate lesions (e.g. those without extension into the deep dermis) is necessary. In terminal hair-bearing sites, extension of neoplastic cells down follicular structures could also lead to incomplete removal. Curettage and electrodesiccation can be used for small SCCs *in situ* and well-differentiated primary SCCs <1 cm in diameter. With a 4-year follow-up, Honeycutt and Jansen reported a 99% cure rate for 281 SCCs treated with this technique[76]; two recurrences were noted in lesions >2 cm in diameter.

Curettage alone

Barlow et al.[77] reported a 5-year cure rate of 96% for 302 biopsy-proven BCCs treated by a single investigator with curettage alone, with minimal complications (hypopigmentation, scarring). Tumors involving more than 50% of the deep edge of the shave biopsy specimen had an increased risk of recurrence.

Mohs micrographic surgery

Mohs surgery (see Ch. 150) for NMSC results in superior histopathologic verification of complete removal, can allow maximum conservation of tissue, and remains cost-effective when compared to either some excisions (such as those done in a surgical center or hospital operating room) or radiation therapy. Rowe and colleagues[78] reported a recurrence rate for BCC treated with Mohs surgery of only 1% over 5 years. This was superior to all other modalities, including excision (10%), curettage and desiccation (7.7%), radiation therapy (8.7%), and cryotherapy (7.5%). However, percentages do vary amongst studies, depending in part on the physicians involved and the types of lesions selected for inclusion. Although direct comparison of different studies is difficult, Mohs surgery clearly has the highest cure rate when all tumor types are included. In a similar study of treatment of recurrent BCC, Mohs surgery showed a long-term recurrence rate of 5.6%, superior to all other modalities, including excision (17.4%), radiation therapy (9.8%),

and curettage with electrodesiccation (40%). Mohs surgery is the preferred treatment for morpheaform, recurrent, poorly demarcated, high-risk (defined earlier), or incompletely removed BCC, and for those sites in which tissue conservation is paramount and there is a need for reliable clear margins. Mohs surgery is similarly indicated in cases of primary or recurrent SCC.

Radiation therapy

Radiation therapy (see Ch. 139) is a primary option for treating BCC or SCC if surgery is contraindicated. In choosing candidates for this therapy, consideration is given to function, cosmetic outcome and patient preference, but because of concerns regarding potential long-term sequelae, patients over the age of 60 years are preferred candidates. Advantages include avoidance of an invasive procedure in a patient who may not be able to tolerate or is unwilling to undergo surgery. Disadvantages include lack of margin control, poor cosmesis in some patients, prolonged course of therapy, and increased risk for future skin cancers. Radiation therapy is associated with higher recurrence rates than surgery for BCC[79]. Scars from radiation therapy tend to worsen with time, in contrast to surgical scars, which improve over time. Radiation is often used as an adjuvant modality following treatment of aggressive or high-risk SCC with surgery, especially when perineural involvement is identified, although to date no controlled studies have proven its usefulness[80]. Verrucous carcinomas, which are well differentiated and rarely metastasize, are usually not treated with radiation therapy, since there is concern that cellular transformation may result in a worse prognosis.

Cryosurgery

Cryosurgery (see Ch. 138) is a mainstay of treatment for AKs, but has also been used to treat NMSCs. It has the advantage of being fast (particularly in the case of AKs), and is advantageous for those patients wishing to avoid invasive surgery. Complications may include hypertrophic scarring and postinflammatory pigmentary changes. A serious potential adverse outcome is recurrent carcinoma that can become extensive because of concealment by the fibrous scar tissue.

Photodynamic therapy

Photodynamic therapy (see Ch. 135) is most often used for patients with multiple AKs and multiple small NMSCs. Reports of high recurrence rates[81,82] for NMSC suggest that this method may be best reserved for selected tumors when better-established methods are not feasible.

Laser

Laser surgery is an uncommon treatment for NMSCs, with limited data in the literature. One small study involving three patients with NBCC syndrome showed that carbon dioxide laser was effective in treating small, low-risk BCCs[83].

Medical treatment

Non-surgical treatment is employed primarily for AKs and superficial NMSCs. Topical 5-fluorouracil has been used for the treatment of AKs, superficial BCCs, and selected SCCs *in situ*[84]. Side effects are usually limited to local skin reactions (see Ch. 129). Topical diclofenac, a nonsteroidal anti-inflammatory drug (NSAID), is also an effective option for the treatment of AKs[85].

Imiquimod cream (see Ch. 128) has been used for the treatment of AKs and low-risk NMSC[86]. Imiquimod is a Toll-like receptor 7 (TLR7) agonist which induces interferon-α (IFN-α) and other cytokines and promotes Th1-type immunity. Cure rates for nodular BCC range from 53% to 75%, with higher rates for superficial BCC. The major advantage is a superior cosmetic result[87]. In general, adverse side effects are limited to local skin reactions. Topical imiquimod 5% cream has also proven to be a fairly effective treatment for cutaneous SCC *in situ*; in a placebo-controlled trial, 11 of 15 lesions resolved as compared to 0% in the placebo-treated group[88].

Intralesional injection of interferon-α-2b may be used to treat BCC as an alternative to surgical or destructive methods. Tucker et al.[89] reported clinical cures in 95 of 98 BCCs (51 nodular and 44 superficial), with a mean follow-up period of 10.5 years. The main advantage is probably a superior cosmetic result, but the treatment is laborious, because usually nine injections are given (three times weekly for 3 weeks). Intralesional fluorouracil or methotrexate has been more commonly used for KA than for BCC or other forms of invasive SCC.

A new therapeutic concept for patients with advanced or metastatic BCC that cannot be treated with conventional therapeutic methods is the use of hedgehog pathway inhibitors. Mutations that lead to activation of the hedgehog-patched signaling pathway have been associated with the development of BCC (see Ch. 107). Vismodegib (GDC-0449), a selective inhibitor of hedgehog pathway activation via binding to the protein smoothened, was first reported to have antitumor activity in locally advanced or metastatic BCC in 2009[90]. Of the 33 patients with metastatic or locally advanced BCC in this phase I trial, 2 had a complete response while 16 had a partial response. In a randomized, placebo-controlled, phase II trial that enrolled 41 patients with NBCC syndrome, the number of new BCCs per month was 0.07 in those receiving 150 mg/day of oral vismodegib for at least a month, compared to 1.74 in the placebo group[90a]. Side effects included loss of taste, muscle cramps and weight loss, with 20% of patients discontinuing the medication because of side effects.

Combination therapy

Combining more than one therapeutic modality has the potential advantage of enhancing the cure rate while minimizing adverse effects and maximizing cosmetic results. Both topical 5-fluorouracil cream and 5% imiquimod cream have been used to pretreat BCC sites prior to Mohs surgery, leading to a decrease in wound size[91]. Imiquimod cream has also been used, in conjunction with topical fluorouracil cream, for the treatment of SCC *in situ* in transplant recipients. Excellent cosmetic results have been reported when BCCs were treated with just curettage followed by 6 weeks of topical 5% imiquimod cream (applied five times per week).

Metastatic NMSC

Cutaneous SCC of the head and neck most commonly metastasizes to parotid and cervical lymph nodes, and the development of metastases is associated with poor survival[92]. Aggressive local surgery, lymph node dissection, and postoperative radiation therapy are often needed. Chemotherapy for metastatic SCC is usually administered by oncologists and nowadays includes EGFR inhibitors. For metastatic BCC, the use of vismodegib can be considered (see above).

Prophylaxis

Retinoids have been used as prophylaxis against skin cancer development in solid organ transplant recipients, patients with multiple KAs or NBCC syndrome, and those with multiple NMSCs. Studies favor the use of acitretin over isotretinoin due to a better side-effect profile. Low-dose retinoid therapy (0.2–0.4 mg/kg/day) has been associated with lower rates of SCC[93]. Triglyceride levels and liver function should be monitored during therapy (see Ch. 126)[94].

A novel approach for chemoprevention of SCC in transplant patients is low-dose oral capecitabine, a prodrug of 5-flourouracil.

Reduction of immunosuppression in high-risk SCC

Reduction or cessation of immunosuppressive drug therapy has been associated with decreased numbers of future skin cancers and improved outcome in patients with pre-existing skin cancers[95]. This strategy may be useful in patients with many lesions or in cases of metastatic disease. Any alteration of the immunosuppressive regimen, including substitution with sirolimus, must be done in consultation with the primary physician.

Prevention and early detection

Primary prevention programs focused on lowering UV exposure appear to be having a positive effect in reducing the incidence of skin cancer. Consistent use of sunscreens (see Ch. 132) has been shown to decrease the incidence of SCC, but to have no effect or only a weak effect on the incidence of BCC in both immunocompetent individuals and immunocompromised organ transplant recipients[96]. As a side effect, sunscreens decrease pre-vitamin D_3 synthesis. Since vitamin D has been found to reduce non-skin cancer risk[97], the delicate balance between beneficial sun exposure that produces vitamin D and sun exposure that induces skin damage has become a controversial issue.

Marks[98] noted that the regular wearing of a hat with a 10 cm brim could lower lifetime NMSC rates by 40%, yet fewer than half of those watching outdoor sport events wear hats[99]. Other chemopreventive agents currently being evaluated are retinoids, difluoromethylornithine, T4 endonuclease V, polyphenolic antioxidants such as epigallocatechin gallate found in green tea and grape seed extract, silymarin, isoflavone genistein, curcumin, lycopene, vitamin E, beta-carotene, and selenium[100]. Use of NSAIDs did not significantly reduce the number of BCCs and SCCs[101].

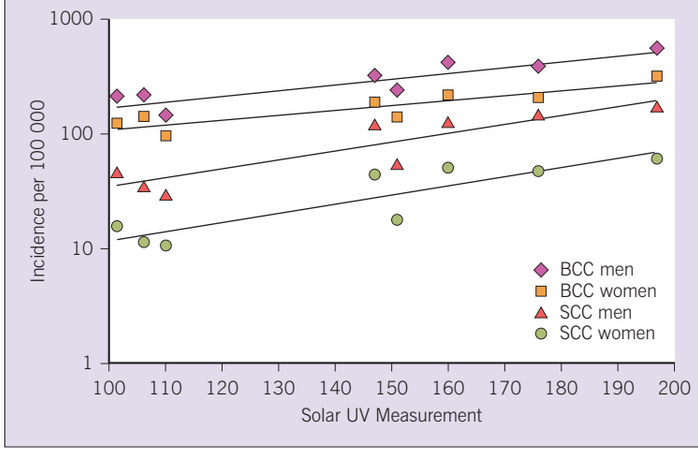
Since fewer than 20% of medical students receive training in skin cancer examination[102], programs need to be developed to educate medical professionals in order to increase NMSC diagnostic skills. New non-invasive diagnostic techniques such as RCM may lead to enhanced diagnostic accuracy in the near future[102].

REFERENCES

1. Staples MP, Elwood M, Burton RC, et al. Non-melanoma skin cancer in Australia: the 2002 national survey and trends since 1985. Med J Aust. 2006;184:6–10.
2. Rogers HW, Weinstock MA, Harris AR, et al. Incidence estimate of nonmelanoma skin cancer in the United States, 2006. Arch Dermatol. 2010;146:283–7.
3. Rigel DS, Friedman RJ, Kopf AW. Lifetime risk for development of skin cancer in the U.S. population: current estimate is now 1 in 5. J Am Acad Dermatol. 1996;35:1012–3.
4. Hannuksela-Svahn A, Pukkala E, Karvonen J. Basal cell skin carcinoma and other nonmelanoma skin cancers in Finland from 1956 through 1995. Arch Dermatol. 1999;135:781–6.
5. Weinstock MA. Death from skin cancer among the elderly: epidemiological patterns. Arch Dermatol. 1997;133:1207–9.
6. Stern RS. The mysteries of geographic variability in nonmelanoma skin cancer incidence. Arch Dermatol. 1999;135:843–4.
7. Halder RM, Bridgeman-Shah S. Skin cancer in African Americans. Cancer. 1995;75:667–73.
8. Alam M, Ratner D. Cutaneous squamous-cell carcinoma. N Engl J Med. 2001;344:975–83.
9. Halder RM, Bang KM. Skin cancer in blacks in the United States. Dermatol Clin. 1988;6:397–405.
10. Bang KM, Halder RM, White JE, et al. Skin cancer in black Americans: a review of 126 cases. J Natl Med Assoc. 1987;79:51–8.
11. Kwa RE, Campana K, Moy RL. Biology of cutaneous squamous cell carcinoma. J Am Acad Dermatol. 1992;26:1–26.
12. Harris RB, Griffith K, Moon TE. Trends in the incidence of nonmelanoma skin cancers in southeastern Arizona, 1985–1996. J Am Acad Dermatol. 2001;45:528–36.
13. Almahroos M, Kurban AK. Ultraviolet carcinogenesis in nonmelanoma skin cancer. Part I: incidence rates in relation to geographic locations and in migrant populations. Skinmed. 2004;3:29–35.
14. Bickers DR, Lim HW, Margolis D, et al. The burden of skin diseases: 2004 a joint project of the American Academy of Dermatology Association and the Society for Investigative Dermatology. J Am Acad Dermatol. 2006;55:490–500.
15. Chen GJ, Feldman SR, Williford PM, et al. Clinical diagnosis of actinic keratosis identifies an elderly population at high risk of developing skin cancer. Dermatol Surg. 2005;31:43–7.
16. Lebwohl M. Actinic keratosis: epidemiology and progression to squamous cell carcinoma. Br J Dermatol. 2003;149(Suppl 66):31–3.
17. Weinstock MA. Controversies in the public health approach to keratinocyte carcinomas. Br J Dermatol. 2006;154(Suppl 1):3–4.
18. Scrivener Y, Grosshans E, Cribier B. Variations of basal cell carcinomas according to gender, age, location and histopathological subtype. Br J Dermatol. 2002; 147:41–7.
19. Zanetti R, Rosso S, Martinez C, et al. Comparison of risk patterns in carcinoma and melanoma of the skin in men: a multi-centre case-case-control study. Br J Cancer. 2006;94:743–51.
20. Kricker A, Armstrong BK, English DR, Heenan PJ. Pigmentary and cutaneous risk factors for non-melanocytic skin cancer – a case-control study. Int J Cancer. 1991;48:650–62.
21. Dallas R, English DR, Armstrong BK, et al. Demographic characteristics, pigmentary and cutaneous risk factors for squamous cell carcinoma of the skin: a case-control study. Int J Cancer. 1998;76:628–34.
22. Hemminki K, Zhang H, Czene K. Time trends and familial risks in squamous cell carcinoma of the skin. Arch Dermatol. 2003;139:885–9.
23. Karagas MR, Stannard VA, Mott LA, et al. Use of tanning devices and risk of basal cell and squamous cell skin cancers. J Natl Cancer Inst. 2002;94:224–6.
24. Boyd AS, Shyr Y, King LE Jr. Basal cell carcinoma in young women: an evaluation of the association of tanning bed use and smoking. J Am Acad Dermatol. 2002;46:706–9.
25. Stern RS, Liebman EJ, Vakeva L. Oral psoralen and ultraviolet-A light (PUVA) treatment of psoriasis and persistent risk of nonmelanoma skin cancer. PUVA Follow-up Study. J Natl Cancer Inst. 1998;90: 1278–84.
26. Lichter MD, Karagas MR, Mott LA, et al. Therapeutic ionizing radiation and the incidence of basal cell carcinoma and squamous cell carcinoma. The New Hampshire Skin Cancer Study Group. Arch Dermatol. 2000;136:1007–11.
27. Shore RE, Moseson M, Xue X, et al. Skin cancer after X-ray treatment for scalp ringworm. Radiat Res. 2002;157:410–8.
28. Stante M, Salvini C, De Giorgi V, Carli P. Multiple synchronous pigmented basal cell carcinomas following radiotherapy for Hodgkin's disease. Int J Dermatol. 2002;41:208–11.
29. Ott C, Huber S. [The clinical significance of cosmic radiation in aviation]. Praxis (Bern 1994). 2006;95:99–106.
30. Yuspa SH. Cutaneous chemical carcinogenesis. J Am Acad Dermatol. 1986;15:1031–44.
31. Lei U, Masmas TN, Frentz G. Occupational non-melanoma skin cancer. Acta Derm Venereol. 2001;81:415–17.
32. Simeonova PP, Luster MI. Mechanisms of arsenic carcinogenicity: genetic or epigenetic mechanisms? J Environ Pathol Toxicol Oncol. 2000;19:281–6.
33. Wong SS, Tan KC, Goh CL. Cutaneous manifestations of chronic arsenicism: review of seventeen cases. J Am Acad Dermatol. 1998;38:179–85.
34. Cancer Council Australia/Australian Cancer Network. Basal cell carcinoma, squamous cell carcinoma (and related lesions) – a guide to clinical management in Australia. Sydney: Cancer Council Australia/Australian Cancer Network, 2008.
35. Nindl I, Gottschling M, Stockfleth E. Human papillomaviruses and non-melanoma skin cancer: basic virology and clinical manifestations. Dis Markers. 2007;23:247–59.
36. Trimble CL, Frazer IH. Development of therapeutic HPV vaccines. Lancet Oncol. 2009;10:975–80.
37. Berg D, Otley CC. Skin cancer in organ transplant recipients: epidemiology, pathogenesis, and management. J Am Acad Dermatol. 2002;47:1–17.
38. Comeau S, Jensen L, Cockfield SM, et al. Non-melanoma skin cancer incidence and risk factors after kidney transplantation: a Canadian experience. Transplantation. 2008;86:535–41.
39. Karagas MR, Cushing GL Jr, Greenberg ER, et al. Non-melanoma skin cancers and glucocorticoid therapy. Br J Cancer. 2001;85:683–6.
40. Clifford GM, Polesel J, Rickenbach M, et al. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. J Natl Cancer Inst. 2005;97:425–32.
41. Freiman A, Bird G, Metelitsa AI, et al. Cutaneous effects of smoking. J Cutan Med Surg. 2004;8:415–23.
42. Granger RH, Blizzard L, Fryer JL, Dwyer T. Association between dietary fat and skin cancer in an Australian population using case-control and cohort study designs. BMC Cancer. 2006;6:141.
43. McNaughton SA, Marks GC, Green AC. Role of dietary factors in the development of basal cell cancer and squamous cell cancer of the skin. Cancer Epidemiol Biomarkers Prev. 2005;14:1596–607.
44. Ibiebele TI, van der Pols JC, Hughes MC, et al. Dietary fat intake and risk of skin cancer: a prospective study in Australian adults. Int J Cancer. 2009;125:1678–84.
45. Sturm RA. Skin colour and skin cancer – MC1R, the genetic link. Melanoma Res. 2002;12:405–16.
46. Kimonis VE, Goldstein AM, Pastakia B, et al. Clinical manifestations in 105 persons with nevoid basal cell carcinoma syndrome. Am J Med Genet. 1997; 69:299–308.
47. Marcil I, Stern RS. Risk of developing a subsequent nonmelanoma skin cancer in patients with a history of nonmelanoma skin cancer: a critical review of the literature and meta-analysis. Arch Dermatol. 2000;136:1524–30.
48. Marghoob AA, Slade J, Salopek TG, et al. Basal cell and squamous cell carcinomas are important risk factors for cutaneous malignant melanoma. Screening implications. Cancer. 1995;75:707–14.
49. Nugent Z, Demers AA, Wiseman MC, et al. Risk of second primary cancer and death following a diagnosis of nonmelanoma skin cancer. Cancer Epidemiol Biomarkers Prev. 2005;14:2584–90.
50. Chen J, Ruczinski I, Jorgensen TJ, et al. Nonmelanoma skin cancer and risk for subsequent malignancy. J Natl Cancer Inst. 2008;100:1215–22.
51. Yu RH, Pryce DW, MacFarlane AQ, Stewart TW. A histopathological study of 643 cutaneous horns. Br J Dermatol. 1991, 24:449–52.
52. Brantsch KD, Meisner C, Schonfisch B, et al. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. Lancet Oncol. 2008;9:713–20.
53. Schwartz RA. Keratoacanthoma. J Am Acad Dermatol. 1994;30:1–19.
54. Norgauer J, Rohwedder A. Human papillomavirus and Grzybowski's generalized eruptive keratoacanthomas. J Am Acad Dermatol. 2003, 49:771–2.
55. Wick MR, Swanson PE, LeBoit PE, et al. Lymphoepithelioma-like carcinoma of the skin with adnexal differentiation. J Cutan Pathol. 1991;18: 93–102.
56. Lind AC, Breer WA, Wick MR. Lymphoepithelioma-like carcinoma of the skin with apparent origin in the epidermis – a pattern or an entity? A case report. Cancer. 1999;85:884–90.
57. Lopez V, Martin JM, Santonja N, et al. Lymphoepithelioma-like carcinoma of the skin: report of three cases. J Cutan Pathol. 2011;38:54–8.
58. Zalaudek I, Giacomel J, Argenziano G, et al. Dermoscopy of facial nonpigmented actinic keratosis. Br J Dermatol. 2006;155:951–6.
59. Rishpon A, Kim N, Scope A, et al. Reflectance confocal microscopy criteria for squamous cell carcinomas and actinic keratoses. Arch Dermatol. 2009;145:766–72.
60. Röwert-Huber J, Patel MJ, Forschner T, et al. Actinic keratosis is an early in situ squamous cell carcinoma: a proposal for reclassification. Br J Dermatol. 2007;156:8–12
61. Rowe DE, Carroll RJ, Day CL Jr. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. Implications for treatment modality selection. J Am Acad Dermatol. 1992;26:976–90.
62. Wade TR, Ackerman AB. The many faces of basal-cell carcinoma. J Dermatol Surg Oncol. 1978;4:23–8.
63. Ackerman AB, Reddy VB, Soyer HP. Neoplasms with Follicular Differentiation. New York: Ardor Scribendi, 2001.
64. Menzies SW. Pigmented basal cell carcinoma. In: Soyer HP, Argenziano G, Hofmann-Wellenhof R, Johr R (eds). Melanocytic Lesions of the Skin. Berlin: Springer, 2007:179–285.
65. McCormack CJ, Kelly JW, Dorevitch AP. Differences in age and body site distribution of the histological subtypes of basal cell carcinoma. A possible indicator of differing causes. Arch Dermatol. 1997;133:593–6.
66. Costantino D, Lowe L, Brown DL. Basosquamous carcinoma – an under-recognized, high-risk cutaneous neoplasm: case study and review of the literature. J Plast Reconstr Aesthet Surg. 2006;59:424–8.

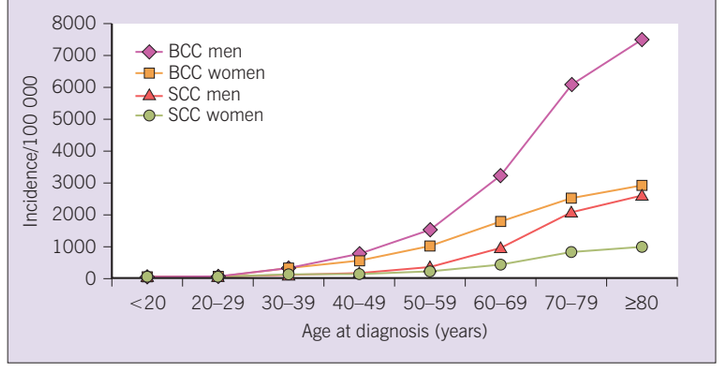
67. Altamura D, Menzies SW, Argenziano G, et al. Dermatoscopy of basal cell carcinoma: morphologic variability of global and local features and accuracy of diagnosis. J Am Acad Dermatol. 2010;62:67–75.
68. Agero AL, Busam KJ, Benvenuto-Andrade C, et al. Reflectance confocal microscopy of pigmented basal cell carcinoma. J Am Acad Dermatol. 2006;54: 638–43.
69. Gonzalez S, Tannous Z. Real-time, in vivo confocal reflectance microscopy of basal cell carcinoma. J Am Acad Dermatol. 2002;47:869–74.
70. Carucci JA, Martinez JC, Zeitouni NC, et al. In-transit metastasis from primary cutaneous squamous cell carcinoma in organ transplant recipients and nonimmunosuppressed patients: clinical characteristics, management, and outcome in a series of 21 patients. Dermatol Surg. 2004;30:651–5.
71. Martinez JC, Otley CC, Stasko T, et al. Defining the clinical course of metastatic skin cancer in organ transplant recipients: a multicenter collaborative study. Arch Dermatol. 2003;139:301–6.
72. Stasko T, Brown MD, Carucci JA, et al. Guidelines for the management of squamous cell carcinoma in organ transplant recipients. Dermatol Surg. 2004;30:642–50.
73. Kimyai-Asadi A, Alam M, Goldberg LH, et al. Efficacy of narrow-margin excision of well-demarcated primary facial basal cell carcinomas. J Am Acad Dermatol. 2005;53:464–8.
74. Telfer NR, Colver GB, Morton CA. British Association of Dermatologists. Guidelines for the management of basal cell carcinoma. Br J Dermatol. 2008;159:35–48.
75. Spiller WF, Spiller RF. Treatment of basal cell epithelioma by curettage and electrodesiccation. J Am Acad Dermatol. 1984;11:808–14.
76. Honeycutt WM, Jansen GT. Treatment of squamous cell carcinoma of the skin. Arch Dermatol. 1973;108:670–2.
77. Barlow JO, Zalla MJ, Kyle A, et al. Treatment of basal cell carcinoma with curettage alone. J Am Acad Dermatol. 2006;54:1039–45.
78. Rowe DE, Carroll RJ, Day CL Jr. Mohs surgery is the treatment of choice for recurrent (previously treated) basal cell carcinoma. J Dermatol Surg Oncol. 1989,15:424–31.
79. Bath FJ, Bong J, Perkins W, Williams HC. Interventions for basal cell carcinoma of the skin. Cochrane Database Syst Rev. 2003;(2):CD003412.
80. Barrett TL, Greenway HT Jr, Massullo V, Carlson C. Treatment of basal cell carcinoma and squamous cell carcinoma with perineural invasion. Adv Dermatol. 1993;8:277–304.
81. Marmur ES, Schmults CD, Goldberg DJ. A review of laser and photodynamic therapy for the treatment of nonmelanoma skin cancer. Dermatol Surg. 2004;30:264–71.
82. Rhodes LE, de Rie M, Enstrom Y, et al. Photodynamic therapy using topical methyl aminolevulinate vs surgery for nodular basal cell carcinoma: results of a multicenter randomized prospective trial. Arch Dermatol. 2004;140:17–23.
83. Nouri K, Chang A, Trent JT, Jimenez GP. Ultrapulse CO2 used for the successful treatment of basal cell carcinomas found in patients with basal cell nevus syndrome. Dermatol Surg. 2002;28:287–90.
84. Jorizzo JL, Carney PS, Ko WT, et al. Fluorouracil 5% and 0.5% creams for the treatment of actinic keratosis: equivalent efficacy with a lower concentration and more convenient dosing schedule. Cutis. 2004;74:18–23.
85. Nelson C, Rigel D, Smith S, et al. Phase IV, open-label assessment of the treatment of actinic keratosis with 3.0% diclofenac sodium topical gel (Solaraze). J Drugs Dermatol. 2004;3:401–7.
86. Saldanha G, Fletcher A, Slater DN. Basal cell carcinoma: a dermatopathological and molecular biological update. Br J Dermatol. 2003;148:195–202.
87. Peris K, Campione E, Micantonio T, et al. Imiquimod treatment of superficial and nodular basal cell carcinoma: 12-week open-label trial. Dermatol Surg. 2005;31:318–23.
88. Patel GK, Goodwin R, Chawla M, et al. Imiquimod 5% cream monotherapy for cutaneous squamous cell carcinoma in situ (Bowen's disease): a randomized, double-blind, placebo-controlled trial. J Am Acad Dermatol. 2006;54:1025–32.
89. Tucker SB, Polasek JW, Perri AJ, Goldsmith EA. Long-term follow-up of basal cell carcinomas treated with perilesional interferon alfa 2b as monotherapy. J Am Acad Dermatol. 2006;54:1033–8.
90. Von Hoff DD, LoRusso PM, Rudin CM, et al. Inhibition of the hedgehog pathway in advanced basal-cell carcinoma. N Engl J Med. 2009;361:1164–72.
90a. Tang JY, Mackay-Wiggan JM, Aszterbaum M, et al. An investigator-initiated, phase II randomized, double-blind, placebo-controlled trial of GDC-0449 for prevention of BCCs in basal cell nevus syndrome (BCNS) patients. AACR 102nd Annual Meeting, Abstract LB-1. Presented April 3, 2011.
91. Ceilley RI, Del Rosso JQ. Current modalities and new advances in the treatment of basal cell carcinoma. Int J Dermatol. 2006;45:489–98.
92. Moore BA, Weber RS, Prieto V, et al. Lymph node metastases from cutaneous squamous cell carcinoma of the head and neck. Laryngoscope. 2005;115: 1561–7.
93. Harwood CA, Leedham-Green M, Leigh IM, Proby CM. Low-dose retinoids in the prevention of cutaneous squamous cell carcinomas in organ transplant recipients: a 16-year retrospective study. Arch Dermatol. 2005;141:456–64.
94. Neuhaus IM, Tope WD. Practical retinoid chemoprophylaxis in solid organ transplant recipients. Dermatol Ther. 2005;18:28–33.
95. Otley CC, Maragh SL. Reduction of immunosuppression for transplant-associated skin cancer: rationale and evidence of efficacy. Dermatol Surg. 2005; 31:163–8.
96. Ulrich C, Jurgensen JS, Degen A, et al. Prevention of non-melanoma skin cancer in organ transplant patients by regular use of a sunscreen: a 24 months, prospective, case-control study. Br J Dermatol. 2009;161(Suppl 3): 78–84.
97. Grant WB, Garland CF, Gorham ED. An estimate of cancer mortality rate reductions in Europe and the US with 1,000 IU of oral vitamin D per day. Recent Results Cancer Res. 2007;174:225–34.
98. Marks R. Photoprotection and prevention of melanoma. Eur J Dermatol. 1999;9:406–12.
99. Rigel AS, Lebwohl MG. Hat-wearing patterns in persons attending baseball games. J Am Acad Dermatol. 2006;54:918–19.
100. Wright TI, Spencer JM, Flowers FP. Chemoprevention of nonmelanoma skin cancer. J Am Acad Dermatol. 2006;54:933–46.
101. Grau MV, Baron JA, Langholz B, et al. Effect of NSAIDs on the recurrence of nonmelanoma skin cancer. Int J Cancer. 2006;119:682–6.
102. Moore MM, Geller AC, Zhang Z, et al. Skin cancer examination teaching in US medical education. Arch Dermatol. 2006;142:439–44.

RELATIONSHIP OF INCIDENCE RATES OF BASAL CELL CARCINOMA (BCC) AND SQUAMOUS CELL CARCINOMA (SCC)



Relationship of incidence rates of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) to estimated ambient erythemal UV radiation as measured in ten cities in the US. *From Armstrong BK, Kricker A. J Photochem Photobiol B. 2001;63:8–18.*

INCIDENCE OF BASAL CELL CARCINOMA (BCC) AND SQUAMOUS CELL CARCINOMA (SCC)



Incidence of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) by age and gender.

This page intentionally left blank

Benign Epidermal Tumors and Proliferations

109

Luis Requena, Celia Requena and Clay J Cockerell

Chapters Contents

Seborrheic keratosis 1795
Lichenoid keratosis 1798
Dermatosis papulosa nigra 1799
Stucco keratosis 1800
Porokeratosis 1801
Flegel disease 1803
Acrokeratosis verruciformis 1804
Cutaneous horn 1805
Clear cell acanthoma 1805
Inverted follicular keratosis 1806
Warty dyskeratoma 1806
Acantholytic (dyskeratotic) acanthoma 1807
Epidermolytic acanthoma 1808
Large cell acanthoma 1808
Epidermal nevus 1809
Inflammatory linear verrucous epidermal nevus 1810
Nevus comedonicus 1811
Acanthosis nigricans 1812
Confluent and reticulated papillomatosis 1812
Clear cell papulosis 1813

The majority of the entities in this chapter can be further classified according to the algorithm in Figure 109.1.

SEBORRHEIC KERATOSIS

Key features

- Common benign lesions that typically begin to appear during the fourth decade of life
- Solitary or multiple, tan to black, macular, papular or verrucous lesions
- Often have a waxy or verrucous, "stuck-on" appearance
- May occur anywhere except mucous membranes, palms and soles
- Large variation in clinical appearance and may simulate melanocytic neoplasms
- In the very rare sign of Leser–Trélat, an abrupt increase in size or number of seborrheic keratoses is associated with an internal malignancy

Introduction

Seborrheic keratoses (SKs) are common benign skin lesions that are almost ubiquitous among older individuals. They only occur on hair-bearing skin, invariably sparing the mucosal surfaces and the palms and the soles. SKs can develop on the face, neck and trunk (especially the upper back), as well as the extremities.

Many clinical and histologic variants of SK have been described, and although they are usually easily recognized clinically, some lesions may prove difficult to diagnose by inspection alone, so biopsy for histopathologic examination may be required. This is especially true when there is a history of recent change or if there is inflammation. Larger dark lesions are sometimes biopsied when there is concern about the possibility of melanoma, but with the advent of dermoscopy, this occurs less frequently.

History

The date of the initial description of SKs is uncertain. In 1927, Fruedenthal delineated their clinical and histologic features.

Epidemiology

An apparent familial predisposition with a postulated autosomal dominant inheritance with incomplete penetrance has been described for the development of SKs. Despite their frequent occurrence, there are few statistics on prevalence, gender or racial predilection, or geographic distribution. Almost all epidemiologic studies have noted SKs as coincidental findings. They have been reported to be more common in Caucasian populations and to affect men and women with equal incidence[1]. Their appearance prior to the fourth decade is uncommon. Usually, additional lesions develop throughout the course of the life of the individual.

Pathogenesis

Although SKs are common in areas covered by clothing, sun exposure has been implicated in their development. Supporting evidence comes from the more frequent occurrence and earlier age of onset of SKs in individuals residing in tropical climates. An Australian study found a higher prevalence of SKs within sun-exposed areas such as the head and neck in contrast to non-sun-exposed areas in the same subjects. The authors also reported a more frequent occurrence and an earlier age of onset in their Australian study group population compared to a UK study group[2].

Based upon analysis of androgen receptor polymorphisms, a clonal origin was detected in over half of lesions evaluated, suggesting a neoplastic as opposed to hyperplastic origin[3]. An alteration in the distribution of epidermal growth factor receptors has also been observed. In irritated SKs, apoptosis within areas of squamous differentiation has been implicated as a cause of the irritation[4]. More recently, *somatic activating* mutations in *FGFR3* which encodes fibroblast growth factor receptor 3[5] and *PIK3CA* (whose protein product is the alpha subunit of phosphoinositide-3-kinase)[6] have been demonstrated within SKs.

Although SKs are often clinically verrucous, human papillomavirus (HPV) has been detected infrequently, except in lesions in the genital region. It is likely that these latter lesions actually represent condyloma acuminatum, as the two entities may appear similar both clinically and histologically[7].

Clinical Features

Occasionally solitary, SKs more commonly present as multiple, pigmented, sharply marginated lesions. They may be macules, papules or even plaques, depending on their stage of development (Fig. 109.2). Even within the same lesion there may be a great variation in color. They are usually light brown but may appear waxy yellow to brown–black in color. SKs typically evolve from a macule and may progress to become papular or verrucous. Keratotic plugging with follicular prominence, a velvety surface, a "stuck-on" appearance and/or hyperkeratotic scale are helpful features in distinguishing SKs from other pigmented

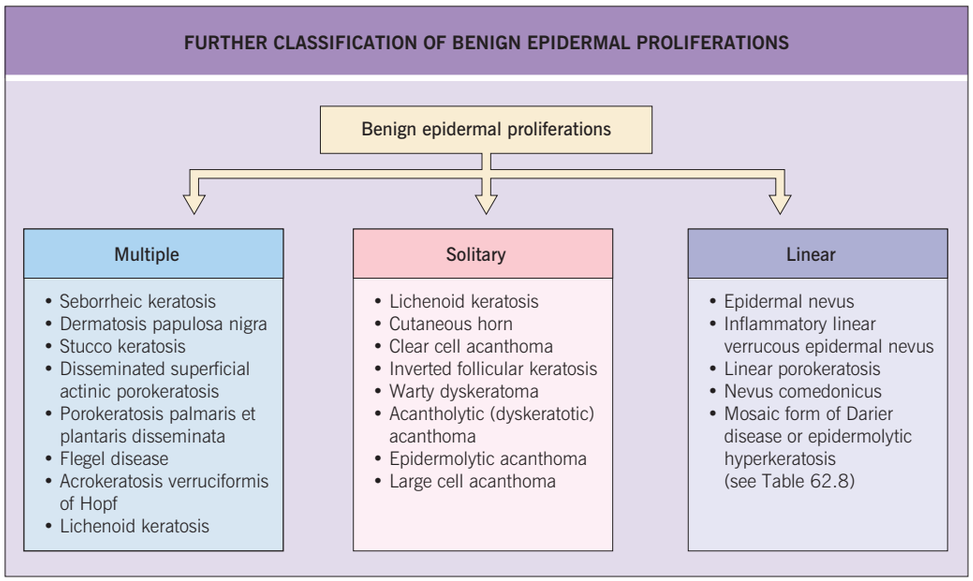


Fig. 109.1 Further classification of benign epidermal proliferations. Although the term solitary lichenoid keratosis is sometimes used, patients may develop multiple lesions, especially those with skin phototypes I or II and significant actinic damage.

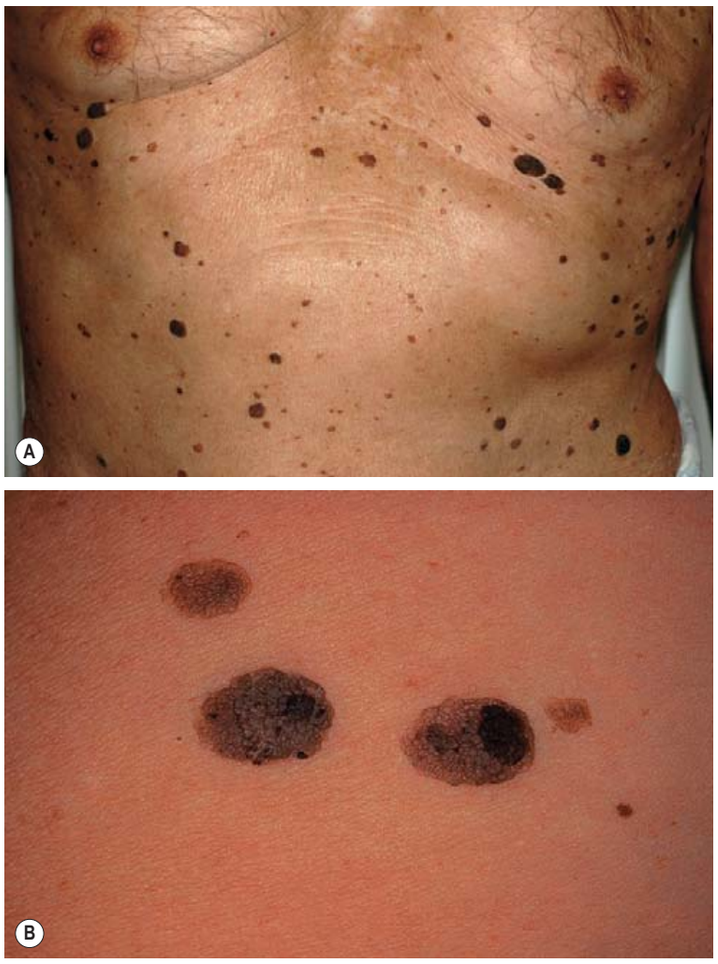


Fig. 109.2 Seborrheic keratoses. A Multiple seborrheic keratoses of the anterior trunk that vary in size and color. **B** Sharply demarcated, pigmented papule and plaques with a papillomatous surface and horn pseudocysts. Note the "stuck-on" appearance.

lesions. Individual lesions may be of any size but usually measure about 1 cm in diameter. They can become quite large, i.e. greater than 5 cm in diameter. Lesions may become inflamed due to rupture of the small pseudocysts they contain or from trauma, or rarely from infection with microorganisms such as *Staphylococcus aureus*. Although usually asymptomatic, traumatized or inflamed lesions may become tender, pruritic, erythematous, crusted and, rarely, pustular.

"Spontaneous regression", although observed, is not a common feature of SKs, even following inflammation. Conditions associated with an abrupt "flare" of lesions followed by regression include pregnancy, coexisting inflammatory dermatoses (in particular erythroderma) and malignancy[8].

Seborrheic Keratosis and Malignancy

Instances of malignant neoplasms arising within and adjacent to SKs were reported as early as 1932[9]. Invasive squamous cell carcinoma (SCC), cutaneous melanoma, basal cell carcinoma (BCC), keratoacanthoma, and SCC *in situ* have all been observed in association with SKs. This likely represents a coincidental neoplasm developing in adjacent skin, although it is possible that the various cell types present in an SK could develop into their respective neoplasms. In theory, the basaloid cells could give rise to BCC, the spinous cells to SCC, and melanocytes to melanoma[9]. BCC is thought to be the most frequent neoplasm seen in association with SKs[9–11], although one prospective study identified only SCC *in situ* when 4310 cases accessioned as SK clinically were evaluated histologically. SCC *in situ* was seen histologically in 60 of these specimens (1.4%)[12]. In another investigation, 4.6% of SCCs were clinically diagnosed as SKs, and in some of these, features of SK were seen in association with the SCC. The "collision" theory, when two distinct neoplasms develop separately at the same site, was entertained as a possible cause for this occurrence, especially given the prevalence of both of these lesions in the population at large[10]. Others believe that BCCs and SKs are both derived from the infundibular portion of the hair follicle, cells of which could evolve into either neoplasm, and in some cases, both concurrently.

The sign of Leser–Trélat is a rare cutaneous marker of internal malignancy (in particular gastric or colonic adenocarcinoma, breast carcinoma, and lymphoma). It is considered to be a paraneoplastic cutaneous syndrome characterized by an abrupt and striking increase in the number and/or size of SKs occurring before, during or after an internal malignancy has been detected[13–15]. Associated pruritus has been documented in over 40% of cases and the majority of the lesions are located on the back, followed by the extremities, face and abdomen[16,17]. Malignant acanthosis nigricans, another paraneoplastic syndrome, may appear at the same time or shortly after the sign of Leser–Trélat in approximately 20% of patients[16]. Rarely, in other conditions such as inflammatory dermatoses (see Ch. 10) and pregnancy[18,19], an abrupt appearance or increase in the number and size of SK lesions has also been reported.

The sign of Leser–Trélat was first described in 1900. Its validity as a reliable marker of internal malignancy has been challenged, given the frequency of both neoplasia and SKs in the elderly population, in whom

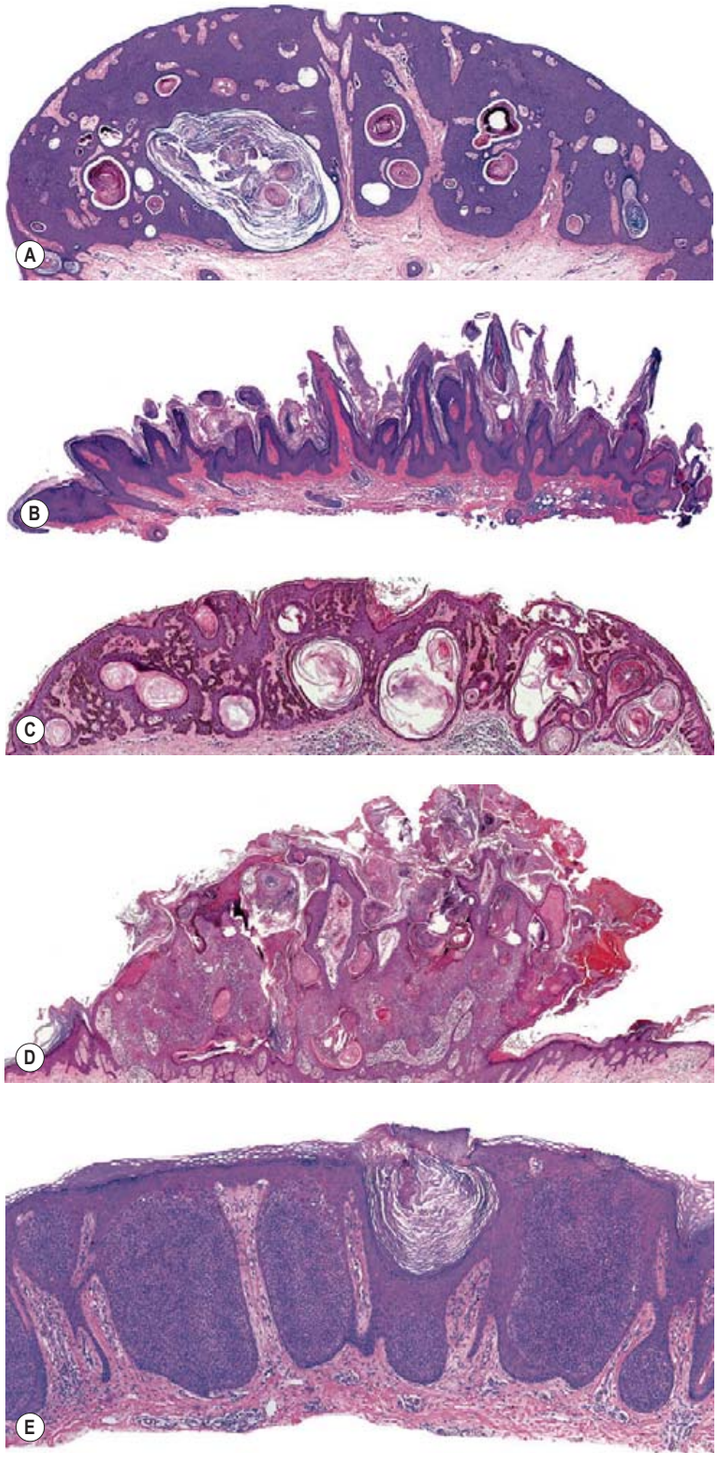


Fig. 109.3 Seborrheic keratoses – spectrum of histologic subtypes. A Acanthotic type with lobular hyperplasia with prominent horn cysts. **B** Papillomatous or hyperkeratotic type with church spires of papillomatosis and hyperkeratosis. **C** Reticulated or adenoid type with delicate, lace-like strands of interconnecting epithelium and interspersed horn pseudocysts. **D** Irritated seborrheic keratosis. Exophytic lesion with papillomatosis, hyperkeratosis, hemorrhagic crust and dermal inflammation. **E** Clonal type with Borst–Jadassohn phenomenon characterized by well-demarcated nests of keratinocytes within the epidermis. *C, D, Courtesy, Lorenzo Cerroni, MD.*

the condition is usually observed[17]. Its description is also loosely defined, which is problematic as there are no standards that quantify the number of lesions required for the diagnosis. The few studies investigating SKs and their link with internal malignancy have largely been inconclusive. One retrospective review examined 1752 consecutive patients with the diagnosis of SK, and of these, 62 individuals were diagnosed with an internal malignancy within 1 year before or after the diagnosis of SK. Of those 62 patients, six patients presented with findings consistent with the sign of Leser–Trélat. However, an age- and sex-matched control group demonstrated similar findings[20].

The pathogenesis of the sign of Leser–Trélat is uncertain, but it is thought to be related to secretion of a growth factor by the neoplasm which leads to epithelial hyperplasia[16]. To qualify as a paraneoplastic process, the cutaneous findings need to coincide with the presence of the malignancy, resolving when the primary tumor is excised or successfully treated and reappearing with its recurrence or metastasis.

Pathology

There are at least six histologic types of SK: acanthotic, hyperkeratotic, reticulated, irritated, clonal and melanoacanthoma. Different histologic features are often present in the same lesion, resulting in diverse appearances. There are varying degrees of hyperkeratosis, acanthosis and papillomatosis. Horn pseudocysts, the product of cross-sectioned epidermal invaginations, are highly characteristic, though not invariably present. Generally, the base of an SK lies on a flat horizontal plane flanked by normal epidermis. The characteristic acanthosis is the result of an accumulation of benign squamous and basaloid keratinocytes, typically projecting outward and upward in an irregular fashion. The sharp demarcation at the base of most lesions has been called the "string" sign. The marked papillomatosis and hyperkeratosis are often likened to "church spires" with shadows of retained cornified material at their peaks.

The squamous cells of many SKs are representative of those found in the normal-appearing epidermis, but some SKs may contain basaloid cells that have a smaller size, uniform appearance and large oval-shaped nuclei. When slight intercellular edema is present, intercellular bridges are easily visualized. Cytologic atypia is usually not a feature of most SKs. Mild keratinocyte atypia and mitotic figures, when present, are usually associated with irritation and inflammation. The papillary dermis in most instances is unremarkable.

The *acanthotic* SK is the most common histologic type. It usually presents as a smooth-surfaced, dome-shaped papule. Slight hyperkeratosis and papillomatosis are often present, while the greatly thickened epidermis typically contains a preponderance of basaloid cells (Fig. 109.3A). Papillae may be narrow in some lesions, while others may be composed of interwoven aggregates of epithelial cells surrounding islands of connective tissue in a retiform pattern. Invaginated horn pseudocysts are most prevalent in this variant. Melanin is often increased in the acanthotic type of SK; it is primarily concentrated in keratinocytes and is transferred from neighboring melanocytes. Deeply pigmented lesions contain abundant melanin in basaloid cells.

The *hyperkeratotic* type of SK, also known as a digitated, serrated or papillomatous type, is almost the morphologic reverse of the acanthotic type. There is acanthosis but there is more prominent hyperkeratosis and papillomatosis (Fig. 109.3B). A preponderance of squamous cells relative to basaloid cells is seen. Abundant pigmentation is unusual, and keratinizing pseudocysts are observed less frequently than in acanthotic SKs. The hyperkeratotic type is the variant often described as having epidermal projections resembling "church spires", a finding also seen in acrokeratosis verruciformis.

The *reticulated* or *adenoid* type of SK is characterized histologically by delicate strands of epithelium that extend from the epidermis in an interlacing pattern (Fig. 109.3C). They are composed of a double row or more of basaloid cells that may be hyperpigmented. Horn pseudocysts, although less common than in the acanthotic variant, may be observed. Often, a solar lentigo is seen at the lateral margins of the lesion, supporting the notion that reticulated SK evolves from a solar lentigo.

A lymphoid infiltrate is often present in the dermis of *inflamed* or *irritated* SKs (Fig. 109.3D). It may be perivascular, diffuse or lichenoid. Spongiosis is often present and there may be necrosis of keratinocytes. Squamous eddies are common findings as well. These consist of whorls of eosinophilic keratinocytes. Irritated SKs often lack the sharply demarcated horizontal base seen with most SKs.

Clonal SKs are considered by some to represent a variant of irritated SK. The clonal, or nested, type of SK is characterized by having well-defined nests of loosely packed cells in the epithelium (Fig. 109.3E). The nests are composed predominantly of variably sized keratinocytes

that are often paler than adjacent cells and have a uniform appearance. They may also contain melanocytes.

Differential Diagnosis

Most SKs are easily identified clinically, although there are entities that may have a similar appearance. Conditions thought to be variants of SKs include dermatosis papulosa nigra, stucco keratoses and inverted follicular keratoses. They are discussed in this chapter under their respective headings. The clinical differential diagnosis includes acrochordon, verruca vulgaris, condyloma acuminatum, acrokeratosis verruciformis, tumor of the follicular infundibulum, eccrine poroma, Bowen's disease, SCC, solar lentigo, melanocytic nevus and melanoma.

Clinical differentiation between macular SKs, solar lentigines, and melanocytic neoplasms such as melanoma may at times be impossible. Solar lentigines are neither hyperkeratotic nor elevated and some are considered to represent an incipient reticulated type of SK. Over time, these lesions can develop into SKs as the buds of pigmented basaloid cells become thicker and there is greater acanthosis. Dermoscopy may be useful in distinguishing these entities (see Chs. 0 and 112).

A recent review of 20 cases of verrucous melanoma demonstrated how difficult it may be to distinguish between benign and malignant tumors. Of interest, 50% of these verrucous melanomas were thought to represent SKs clinically and a histopathologic diagnosis of a benign nevus was assigned to 10%. A broad spectrum of histopathologic findings, including hyperkeratosis, pseudoepitheliomatous hyperplasia, asymmetry and exophytic papillomatous growth pattern, were present in these cases[21].

Acanthotic and irritated types of SK should be delineated from eccrine poroma. On occasion, SKs may demonstrate "poroid" differentiation. Clinically, poromas are skin-colored, brown, pink or sometimes red papules or nodules that may be pedunculated and multilobular. Histologically, poromas are comprised of homogeneous, small basophilic cells with a delicate fibrovascular stroma and narrow ductal lumina with eosinophilic, PAS-positive, diastase-resistant cuticles (see Ch. 111).

Differentiation between an irritated SK, an SCC *in situ* (Bowen's disease) and SCC may require histopathologic examination. An irritated SK may be misdiagnosed as a carcinoma if atypia is present. Although squamous eddies may be abundant in both tumors, there should be no evidence of involvement of the dermis in irritated SKs. Bowen's disease demonstrates a preponderance of atypical keratinocytes with vacuolated cytoplasm, close crowding of nuclei, abundant mitoses and parakeratosis. The adnexal epithelium is also involved.

The Borst–Jadassohn pattern of clonal SK is also seen in some examples of Bowen's disease. In general, Bowen's disease with a clonal or nested pattern has greater atypia of the individual keratinocytes.

Melanoacanthoma was originally described by Bloch and named "non-nevoid melano-epithelioma, type 1"[22]. It is now regarded as a heavily pigmented SK by most authorities. In this variant, melanocytes are distributed throughout the lesion. While the keratinocytes contain melanin, the bulk of the pigment is present within melanocytes, many of which also have long dendrites[23]. Although the melanocytes are prominent, there is no significant increase in their number. The heavy pigmentation of melanoacanthoma has been explained by the blockage of transfer of melanin to keratinocytes, perhaps leading to an increase in the amount of melanin within melanocytes.

Intraoral melanoacanthoma or melanoacanthosis was first described in 1979. These lesions bear a striking clinical resemblance to the melanoacanthoma type of SK. Histologically, they are distinct from the cutaneous variant by having only minimal epithelial hyperplasia. Their histologic features are most like those of a heavily pigmented lentigo simplex, with a proliferation of dendritic melanocytes within the basal layer of the epithelium[24].

Verruca and condyloma acuminatum are hyperplasias caused by HPV. Both can clinically mimic SKs but differ in that they most frequently occur in younger individuals. Verrucae often present as rough papules with red or black dots that represent dilated or thrombosed capillary loops at the tips of the underlying dermal papillae. Verrucae favor acral locations, while condylomata acuminata occur in the genital region and rarely on the buccal mucosa. HPV has been reported in anogenital lesions with histologic features of SK[25] (see above). Koilocytic changes of perinuclear vacuolization with nuclear pyknosis in the superficial epidermis may not be present in some verrucae, but are helpful if present. An SK generally tends to be oriented in a more horizontal than vertical fashion, often has horn pseudocysts, and lacks koilocytes.

Tumor of the follicular infundibulum is distinguished from an SK by a superficial distinct plate-like epithelial proliferation. The latter consists of multiple slender epidermal connections composed of basaloid or pale cells, without as much hyperkeratosis as an SK. The reticulated type of SK has a similar pattern but lacks the distinct plate-like growth. Lightly pigmented SKs can easily be mistaken for an acrochordon, which has a pedunculated shape and is usually smoother and smaller in size.

Other conditions with papillated epidermal hyperplasia histologically are readily distinguished on a clinical basis. Some of these include acanthosis nigricans, epidermal nevus, and confluent and reticulated papillomatosis. Epidermal nevi tend to follow Blaschko's lines, appearing in a linear arrangement on the extremities and a whorled pattern on the trunk. Although histologic sections of epidermal nevi typically exhibit acanthosis and hyperkeratosis, they usually lack the pseudocysts seen in many SKs. Epidermal nevi are also usually apparent at birth or shortly thereafter, unlike SKs, which are seen in adults.

Acrokeratosis verruciformis of Hopf has a "church spire" configuration similar to that described for hyperkeratotic SK[26], but it is an autosomal dominant disorder (see Ch. 59) and lesions are usually limited to the distal extremities. Acanthoma fissuratum may clinically resemble a large SK, but histologic analysis reveals irregular epidermal hyperplasia.

Treatment

Treatment of asymptomatic SKs is largely performed for cosmetic reasons. Symptomatic lesions are usually removed by destruction, curettage or shave excision. The most common method of destruction is cryotherapy. Other methods include laser vaporization (pulsed CO_2, erbium:YAG) or electrodesiccation.

LICHENOID KERATOSIS

Synonyms: ■ Lichen planus-like keratoses (LPLK) ■ Solitary lichen planus ■ Solitary lichenoid keratosis (SLK) ■ Benign lichenoid keratosis (BLK)

Key features

- A solitary, pink to red–brown, scaly papule, most common on the upper chest or forearms
- Histologically, it appears almost identical to lichen planus, but is distinguished by clinical correlation
- Represents an inflammatory stage of a solar lentigo, actinic keratosis or SK

History

In 1966, two independent groups reported lesions with the histologic features of lichen planus but, unlike lichen planus, they occurred as solitary asymptomatic lesions. These two groups referred to these lesions as solitary lichen planus and solitary lichen planus-like keratosis.

Epidemiology

Eighty-five percent of lichenoid keratoses (LKs) develop between the ages of 35 and 65 years[27]. Women are diagnosed with the condition twice as frequently as men, and the vast majority of lesions are seen in Caucasians.

Pathogenesis

LKs have been thought to represent inflammation of a benign lentigo, actinic keratosis or SK. Because at least half of the lesions are related to "precancerous" actinic keratoses, the term lichenoid keratosis is preferred over the term benign lichenoid keratosis (BLK). Lesions are best referred to as lichenoid actinic keratosis when there is significant keratinocyte cytologic atypia or other classic features of an actinic keratosis, and as irritated SK when a lichenoid infiltrate is associated with other features of an SK. The authors prefer to use the term BLK only when the lesion is associated with a lentigo, with no evidence of actinic keratosis or SK.

Increased numbers of Langerhans cells have been observed in the epidermis of LKs. This has led to the suggestion that the lichenoid infiltrate of lymphocytes is secondary to a stimulus from Langerhans cells after their processing of an unidentified epidermal antigen. This mechanism is similar to that proposed for lichen planus. Constant pressure has been incriminated as an etiologic factor in some cases.

Clinical Features

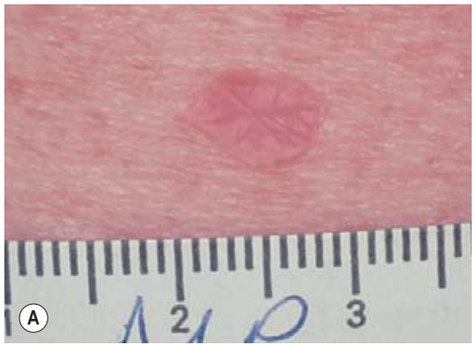
LKs occur primarily as solitary pink to red–brown, often scaly, papules ranging from 0.3 to 1.5 cm in diameter (Fig. 109.4A). An astute clinician can oftentimes suspect the diagnosis before the biopsy is performed. LK most closely resembles a BCC or Bowen's disease, and for this reason, these lesions are frequently biopsied. They are usually asymptomatic, although occasionally patients complain of slight pruritus or stinging[28]. The most common sites are the forearm and upper chest, with less frequent occurrence on the shins (in women) and other chronically sun-exposed sites.

Pathology

LK has a lichenoid infiltrate composed mainly of lymphocytes with scattered histiocytes (Fig. 109.4B). Eosinophils and plasma cells are sometimes present. All other elements of an interface dermatitis are observed, including basal vacuolar alteration, melanin incontinence, and colloid bodies. When melanin incontinence is prominent, and the lesion is clinically pigmented, sometimes the term pigmented lichenoid keratosis is used. Parakeratosis may be seen, unlike typical lichen planus. Sometimes there is frank separation of the epidermis from the infiltrate in the dermis, giving rise to a subepidermal blister or cleft. Basal cell proliferation is absent, and keratinocyte atypia is either mild or absent. Changes of a solar lentigo are often present at the periphery of the specimen. In some cases, a macular SK is observed.

Occasionally, lesions of LK may mimic mycosis fungoides, because of the presence of Pautrier-like microabscesses, alignment of lymphocytes along the basal layer and epidermotropism of the infiltrate. There are also atrophic and bullous variants, and sometimes the lesion may mimic lupus erythematosus or toxic epidermal necrolysis histopathologically[29].

LKs may undergo regression, and histologically, the appearance of a regressed keratosis may be confused with other regressing tumors, especially melanoma. The regressed LK usually displays a loosely fibrotic papillary dermis with scattered lymphocytes and melanophages. Regressed melanoma typically has a dense band of melanophages with lymphocytes and dilated blood vessels; there is also usually a thin epidermis overlying effaced rete ridges. In states of partial regression, remaining histologic clues to the proper diagnosis remain. The end stages of both tumors may not be distinguishable. Careful search for elements of superficial BCC is also advisable.



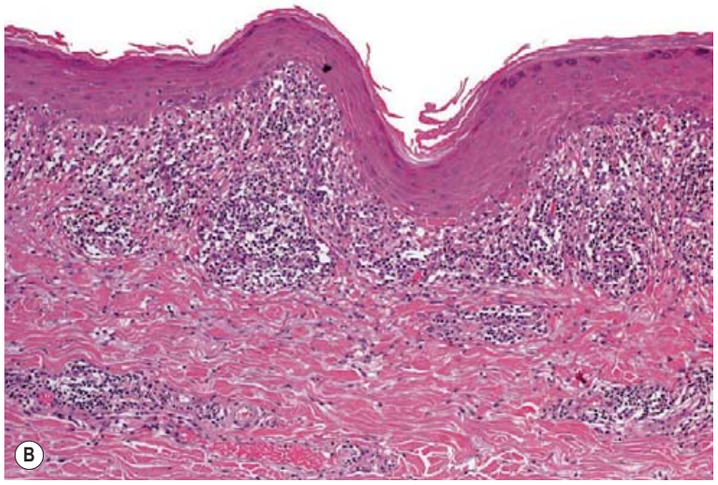


Fig. 109.4 Lichenoid keratosis. A Pink, flat-topped papule in a fair-skinned individual. **B** A lichenoid infiltrate beneath the epidermis with formation of Civatte bodies. Compact hyperkeratosis is also present. *A, Courtesy, Jean L Bolognia, MD. B, Courtesy, Lorenzo Cerroni, MD.*

Differential Diagnosis

Frequently cited clinical impressions include BCC, Bowen's disease, actinic keratosis, irritated SK, melanoma (including amelanotic), and nevus. A recent change in pigmentation of a lesion often leads the clinician to suspect an atypical melanocytic nevus or melanoma[27]. There is frequently melanin incontinence in the dermis associated with the vacuolar alteration of the basal cell layer and damage to melanocytes. The pathologist must take care to ensure that the lichenoid infiltrate is not obscuring melanoma *in situ* or even melanoma involving the superficial dermis, as these tumors may become heavily inflamed.

LK resembles other conditions with a band-like inflammatory (lichenoid) reaction pattern, including lichen planus, "lichenoid" lupus erythematosus, and lichenoid fixed drug reactions. Clinical correlation is very useful in excluding these conditions. Although lichen planus may be virtually identical to LK histologically, there is usually more wedge-shaped hypergranulosis and less parakeratosis in lichen planus. Clinically, in contrast to lichen planus, LK occurs as a single lesion in an overwhelming majority of patients.

Treatment

Once the diagnosis of LK is made, no further therapy is necessary. Any remaining lesion may be destroyed by any method.

DERMATOSIS PAPULOSA NIGRA

Key features

- Most common in individuals of African descent with darkly pigmented skin
- Multiple hyperpigmented papules on the face
- Considered to be a variant of SK
- Cryotherapy can result in hypopigmentation; best treatment is scissor snip, curettage or electrodesiccation, when desired

Introduction

Dermatosis papulosa nigra (DPN) is characterized by the presence of multiple, hyperpigmented, sessile to filiform, smooth-surfaced papules measuring from 1 to 5 mm, typically occurring on the face of darkly pigmented individuals (Fig. 109.5).

History

DPN was first described by Castellani in 1925 based on his observations during visits to Central America and Jamaica.

Fig. 109.5 Dermatosis papulosa nigra. Multiple hyperpigmented papules with typical location on the cheeks.

Epidemiology

DPN has a strong familial predisposition and has been reported to have an incidence in selected study populations ranging from 10% to 75%. This variability in incidence may be a reflection of sampling, as lighter-skinned blacks are affected less commonly[30]. In addition to those with African heritage, the condition has also been reported in Filipinos, Vietnamese, Europeans and Mexicans[30]. Rarely, it may be seen in children. Women are twice as likely to be affected as men. DPN is not related to any systemic disease or syndrome.

Pathogenesis

The cause of DPN is unknown. It tends to have an earlier age of onset than that of SKs, but otherwise is similar and probably is a variant of SK. Others view it as a variant of multiple fibroepithelial papillomata (acrochordons). There are ongoing molecular studies evaluating the potential role of circulating growth factors and receptor interactions in the development of DPN.

Clinical Features

Pigmented papules are distributed symmetrically across the malar eminences and forehead. Less often, lesions are on the neck, chest and back. The papules usually appear during adolescence, gradually increasing in size and number over time, and peaking in the sixth decade.

Pathology

DPN is characterized by acanthosis, papillomatosis and hyperkeratosis in a pattern quite similar to the acanthotic type of SK. Horn pseudocysts, however, are not a common feature.

Differential Diagnosis

The differential diagnosis of DPN includes primarily multiple SKs and acrochordons. Occasionally, melanocytic nevi, lentigines, verrucae, trichoepitheliomas, trichilemmomas, follicular hamartomas, syringomas and angiofibromas might be considered clinically.

Treatment

Treatment of DPN is generally performed only for cosmetic purposes, although individual lesions may be troublesome. Care should be exercised to avoid treatments that may result in dyspigmentation, so it may be best at first to only treat a small number of lesions. Snip excision with scissors, curettage and light electrodesiccation are the most common treatment modalities. Hypopigmentation after cryotherapy can be particularly problematic, since melanocytes are more sensitive to freeze damage than are keratinocytes.

Fig. 109.6 Stucco keratoses. Multiple gray–white keratotic papules on the ankle and dorsal foot. *Courtesy, Jean L Bolognia, MD.*

STUCCO KERATOSIS

Synonym: ■ Keratosis alba

Key features

- Gray–white papules or small plaques
- Typically on the lower extremities of older adults, especially the ankles
- Lesions are "stuck on", and when scraped off, there is minimal bleeding
- Probably is a white variant of SK

Introduction

Stucco keratoses are discrete gray–white papules and small plaques that are hard and opaque, with the latter reflecting focal accumulations of cornified material. They are usually distributed symmetrically below the knee, especially on the dorsal and lateral aspects of the foot and ankle (Fig. 109.6). Occasionally, they may also be noted on the thighs and the forearms.

History

Kocsard was the first to characterize stucco keratoses in 1958 based on his observations in 24 affected men in an Australian study group of 240 geriatric participants. The term stucco keratosis was coined by Kocsard in 1966, alluding to its "stuck-on" appearance. Although early accounts of stucco keratoses described elastotic changes in the upper dermis, this has been shown to represent solar elastosis.

Epidemiology

There is no familial predilection for stucco keratoses. They are noted more frequently during cold winter months, which is probably a manifestation of them being more overt with lower humidity and dry skin. They are seen most commonly in middle-aged to elderly individuals and are usually first observed after the age of 40. Men are four times more likely to be affected than women. Most patients are Caucasian, although information regarding racial or ethnic background is minimal. There are no known associated diseases or syndromes.

Pathogenesis

The cause of stucco keratosis remains unknown. Histochemical studies suggest an acquired focal abnormality of keratinization. Ultrastructural

examination has revealed no viral particles[31]. However, one immunocompetent patient with extensive stucco keratoses was shown to have multiple HPV types within various lesions using PCR technology[32]. The significance of this finding is not known, as HPV is purported to occur in about 20% of normal skin specimens[33].

Sun exposure has been proposed to be a factor in the formation of stucco keratosis, as most affected individuals present with manifestations of solar damage. However, this may be a reflection of the age and phototype of the patients. Heat and petroleum products such as tar have also been implicated.

Clinical Features

Gray–white papules or small plaques are typically present on the lower extremities of older adults. Lesions on the upper extremity are less common and the palms and soles are not involved. The papules may number in the hundreds. They are usually small, measuring from 1 to 4 mm, but rarely individual plaques may be as large as a few centimeters. Occasionally, brown, pink and deep yellow shades have been described. The lesions may be scraped or flicked off the skin surface with a fingernail and there is usually minimal, if any, bleeding. A collarette of dry scale may remain.

Pathology

Stucco keratoses display prominent orthokeratotic hyperkeratosis and papillomatosis, often imparting a peaked "church spire" pattern. Acanthosis is usually present, but to a lesser degree than in some SKs. The granular layer may be thickened. Horn cysts are usually absent and cytologic atypia is not a feature.

Differential Diagnosis

Stucco keratoses may resemble SKs, acrokeratosis verruciformis of Hopf, epidermodysplasia verruciformis, or verrucae plana. SKs tend to be larger and pigmented with a surface that appears "greasy", in contrast to stucco keratoses, which are smaller and have a dry, rough surface. Histologically, stucco keratoses resemble hyperkeratotic SKs and acrokeratosis verruciformis. All three may demonstrate papillomatosis and digitation, giving an appearance similar to "church spires" under the microscope. Acrokeratosis verruciformis differs from stucco keratoses in that it is an autosomal dominant disorder and involves the dorsal aspects of the hands (as well as the feet).

Treatment

As with SKs, treatment is generally for cosmetic reasons, although symptomatic lesions may require removal. Curettage, or local destruction with cryosurgery or electrodesiccation, are the usual forms of treatment. Some lesions soften with application of urea, lactic or α-hydroxy acids, or retinoid preparations, although these agents do not usually lead to their removal.

POROKERATOSIS

Key Features

- At least five clinical variants of porokeratosis are recognized
- The prototype, porokeratosis of Mibelli, is a plaque that appears during infancy or childhood
- Disseminated superficial actinic porokeratosis (DSAP) is the most common type, with multiple thin papules appearing most commonly on the legs of adult women
- Linear porokeratosis develops during infancy or childhood and follows the lines of Blaschko
- Punctate porokeratosis appears during or after adolescence as 1–2 mm papules of the palms and soles
- Porokeratosis palmaris et plantaris disseminata (PPPD) is a variation of punctate porokeratosis, with lesions also present on other areas of the body
- Some forms are inherited in an autosomal dominant fashion, but many patients have no family history
- A thread-like raised hyperkeratotic border is characteristic
- Histologically, a thin column of parakeratosis, the cornoid lamella, is seen in all variants and corresponds to the raised hyperkeratotic border seen clinically
- Development of SCC is possible but rare

Introduction

Porokeratosis presents as a hyperkeratotic papule or plaque, with an annular appearance due to its thread-like elevated border that expands centrifugally. The disorder was erroneously named porokeratosis because the column of parakeratosis known as the cornoid lamella was initially described as being present over a sweat pore, which of course is a fixed structure that cannot expand peripherally. At least five types of porokeratosis have been recognized. The different varieties of porokeratosis are likely related, as evidenced by reports of more than one type of porokeratosis developing in the same patient[34] and in multiple members of an affected family[35].

History

In 1893, Mibelli first described what is now considered classic porokeratosis: one to several discrete plaques that may occur anywhere on the skin or mucous membranes, usually appearing during infancy or childhood. That same year, Respighi reported a superficial and disseminated form of the disease. Descriptions of linear porokeratosis first appeared in 1918. Disseminated superficial actinic porokeratosis (DSAP) was detailed by Chernosky in 1966. Guss, in 1971, was the first to report porokeratosis palmaris et plantaris disseminata (PPPD). In 1977, Rahbari proposed that punctate porokeratosis be added to the group of diseases already classified as variations of porokeratosis.

Epidemiology

Porokeratosis is sometimes inherited as an autosomal dominant disorder, but most cases appear to be sporadic. Porokeratosis of Mibelli affects boys more than girls, but DSAP is more common in women. PPPD is inherited in an autosomal dominant manner yet is twice as common in males than in females, perhaps reflecting an environmental factor. DSAP is more common in Caucasians and is rare in blacks. Linear porokeratosis has been reported in monozygotic twins[36], and it has been seen in families with other types of porokeratosis (see below)[37], but a specific heritable pattern has thus far not been identified.

Pathogenesis

Although porokeratosis is thought to be a disorder of keratinization, the definitive pathogenesis remains unclear. In the case of DSAP, there are four possible genetic loci: 12q23.3 (DSAP1)[38], 15q25.1–26.1 (DSAP2)[39], and 1p31.3–p31.1 (DSAP3)[40], and 18p11.3 (DSAP4). For DSAP1, candidate genes include *SART3*[41] (encodes a tumor rejection antigen involved in the regulation of messenger RNA splicing), *SSH1*[42], and *ARPC3*[43]; the latter two are involved in polymerization and dynamics of actin filaments. The proposed genetic locus for PPPD1 is 12q24.1–q24.2.

An old hypothesis set forth by Reed proposes that lesions of porokeratosis represent an expanding mutant clone of keratinocytes. In Reed's view, the characteristic cornoid lamella, seen histologically, represents the border between normal epidermis and the mutant clone of cells. A dermal lymphocytic infiltrate beneath the cornoid lamella or in the central zone of the lesion is considered to be an immunologic response. Supporting this theory is the finding of abnormal DNA ploidy in keratinocytes of porokeratosis[44]. Triggering factors such as UV exposure[45] or immunosuppression due to AIDS[46] or organ transplantation[47] may induce porokeratosis in individuals who are genetically predisposed to developing abnormal clones of keratinocytes. A second, less accepted, theory suggests that the dermal lymphocytic infiltrate may be directed against an unidentified epidermal antigen and that this population of inflammatory cells releases mediators that provide a mitotic stimulus for epidermal cells[48]. A relationship between porokeratosis and HPV has not been established.

Clinical Features

Classic *porokeratosis of Mibelli* is a rare condition, beginning during infancy or childhood as an asymptomatic, small, brown to skin-colored keratotic papule that gradually enlarges over a period of years to form a plaque that may measure several centimeters in diameter. There is a raised, sharply demarcated, keratotic, thready border with a longitudinal furrow (Fig. 109.7A). The center of the lesion may be hyperpigmented, hypopigmented, atrophic and/or anhidrotic. Lesions may occur anywhere on the body, including mucous membranes, but the extremities are most frequently involved. Multiple lesions may appear, but they are almost always regionally localized and unilateral. It can be inherited in an autosomal dominant fashion.

Disseminated superficial porokeratosis and *disseminated superficial actinic porokeratosis* (DSAP) are actually more common than the Mibelli type. Small asymptomatic or mildly pruritic keratotic papules, usually ranging from 2 to 7 mm in diameter, appear during the third to fourth decades of life. They are often skin-colored to tan to pink or red in color. As the lesions progress, they expand radially, and the older, central area becomes atrophic while the well-demarcated border develops a thin, elevated, furrowed keratotic rim (Fig. 109.7C,D). Lesions occur in a more widespread pattern than other types of porokeratosis. Disseminated superficial porokeratosis usually involves the extremities bilaterally and symmetrically, sparing the palms, soles and mucous membranes, while the actinic form (DSAP) occurs exclusively in sun-exposed areas, most commonly the legs below the knees.

A majority of patients with DSAP report that the lesions become more prominent and erythematous during the summer[49]. Chernosky coined the term DSAP to distinguish this variant from the non-actinic disseminated superficial porokeratosis. He was able to induce lesions by exposing patients to UV light. Other investigators have not been able to reproduce these results and have questioned whether these lesions are really actinically induced. While many patients with DSAP have involvement of the shins and extensor forearms without involvement of other areas of sun damage (analogous to idiopathic guttate hypomelanosis), there are individuals with widespread involvement who clearly have sparing of non-sun-exposed sites. In addition, there are case reports of patients with psoriasis receiving UVB or PUVA treatments developing DSAP. DSAP may resemble and coexist with actinic keratoses, but, unlike actinic keratoses, DSAP almost always involves the legs and rarely the face whereas patients with actinic keratoses on the legs almost always have them on the face as well[50]. Rarely, DSAP has been reported in association with hepatitis C infection or systemic lupus erythematosus.

Linear porokeratosis arises in infancy or childhood, and it consists of one or more plaques that are similar in appearance to classic porokeratosis; however, the plaques follow the lines of Blaschko, most commonly on the extremities (Fig. 109.7E). Some patients have both DSAP and linear porokeratosis and the latter may represent loss-of-heterozygosity (i.e. type 2 mosaicism; see Fig. 62.2).

PPPD is uncommon and individual lesions resemble those of porokeratosis of Mibelli except they are smaller and have a less pronounced keratotic border. They may be asymptomatic or pruritic, and generally arise during childhood or adolescence. As the name suggests, the palms and soles are initially affected, but any surface, including mucous membranes, may be involved.

Fig. 109.7 Porokeratoses. A Porokeratosis of Mibelli on the hand of a child. **B** Actinic porokeratosis in a renal transplant patient with significant solar damage. Note the narrow, elevated rim. **C, D** Multiple lesions of disseminated superficial actinic porokeratosis (DSAP) with obvious peripheral keratotic rims; lesions can range in color from light brown to pink. **E** Several streaks of linear porokeratosis on the lower extremity. **F** Multiple keratotic papules of the plantar surface due to punctate porokeratosis. *B, C, D, Courtesy, Jean L Bolognia, MD. F, Courtesy, Kalman Watsky, MD.*

Punctate porokeratosis is the most difficult type to recognize clinically because of the small size of the lesions. It appears during adolescence or adulthood as small "seed-like" keratotic papules with a peripheral raised rim on the palms and/or soles[51] (Fig. 109.7F). It may clinically resemble punctate keratoderma, Darier disease, Cowden disease and arsenical keratoses, but a biopsy will usually confirm the diagnosis of punctate porokeratosis with its characteristic cornoid lamella. However, parakeratotic columns can be seen in spiny keratoderma in which the lesions resemble the spines of an old-fashioned music box.

Development of SCC in lesions of porokeratosis has been reported in all variants except the punctate form. Lesions in older patients, those of longstanding duration, and linear variants all have higher rates of malignant degeneration. DSAP has the lowest risk of malignant change[52]. SCC generally appears as a papule or plaque arising in contiguity with the individual lesion of porokeratosis, leading to asymmetry.

Other unusual or rare forms of porokeratosis include lesions that simulate porokeratosis of Mibelli, given their large diameter, but occur in immunocompromised adult patients (Fig. 109.7B). Porokeratosis can also develop within body folds, especially the gluteal cleft, termed porokeratosis ptychotropica.[53] Other uncommon clinical variants of porokeratosis include a reticular form[54] and a follicular variant[55]. In CDAGS syndrome, a very rare autosomal recessive disorder, patients develop erythematous plaques on the face and extremities that histologically resemble porokeratosis. *C*raniosynostosis and clavicular hypoplasia, *d*elayed closure of the fontanelle, *a*nal anomalies, and genitourinary malformations are additional findings to this *s*kin eruption[56].

Pathology

Identification of the cornoid lamella is the *sine qua non* for the histologic diagnosis of porokeratosis, although it may be seen in other conditions such as verruca vulgaris and actinic keratosis. It is characterized by a thin column of tightly packed parakeratotic cells extending from an invagination of the epidermis through the adjacent stratum corneum, often protruding above the surface of the adjacent skin (Fig. 109.8). Under the cornoid lamella, the granular layer is either absent or markedly attenuated, but it is of normal thickness in other areas of the lesion. Dyskeratosis and pyknotic keratinocytes with perinuclear edema are present in the spinous layer beneath the cornoid lamella. The superficial portion of the cornoid lamella trails toward the center of the lesion in a pattern that has been likened to smoke coming out of a moving train as the "clone" of epidermal cells advances centrifugally. The cornoid lamella corresponds to the clinically observed raised hyperkeratotic border. The clinician should include this portion of the lesion in the biopsy to establish the diagnosis. Sometimes, cornoid lamellae are found in multiple locations throughout the lesion in addition to the periphery. The invagination from which the cornoid lamella extends is less pronounced in varieties other than classic porokeratosis of Mibelli. Corresponding with the less prominent border seen in DSAP, the cornoid lamella in DSAP often does not protrude above the surface of the adjacent stratum corneum. The epidermis in the central portion of the porokeratotic lesion may be normal, hyperplastic or atrophic, with effacement of rete ridges. The dermis contains lymphocytes that may be perivascular, localized beneath the cornoid lamella, or lichenoid in the central portion of the lesion.

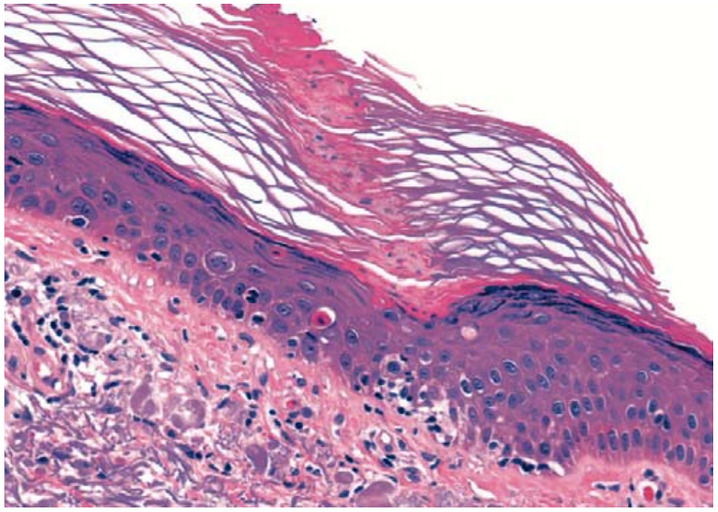


Fig. 109.8 Porokeratosis – histologic features. The cornoid lamella, a narrow column of parakeratotic cells, is the typical histologic feature of porokeratosis. Note both the absence of the granular layer and the vacuolar change at the dermo-epidermal junction beneath the cornoid lamella.

Differential Diagnosis

Porokeratosis can resemble other annular lesions (see Table 19.1) as well as actinic keratoses, but dermoscopy can assist in detection of the furrowed keratotic rim. Linear porokeratosis may be confused with other linear lesions (see Ch. 62) such as inflammatory linear epidermal nevus, incontinentia pigmenti (stage II) and linear lichen planus, none of which have a cornoid lamella. Cornoid lamellae can be found in actinic keratoses, but, in the latter, partial epidermal cytologic atypia is invariably present. Verruca vulgaris often has mounds of parakeratosis that are sometimes identical to cornoid lamellae, but koilocytosis is usually present along with other histologic features of warts. Porokeratotic eccrine ostial and dermal duct nevus is a separate entity (see Ch. 111).

Treatment

Cryotherapy[49], topical 5-fluorouracil (5-FU)[50], topical retinoids in combination with 5-FU, topical imiquimod, photodynamic therapy, CO_2 and other lasers, shave excision, curettage, linear excision[57], and dermabrasion[58] have all been used with variable degrees of success in treating porokeratosis. The abnormal clone of keratinocytes must be destroyed lest lesions recur. Porokeratosis is more difficult to eradicate than both actinic keratoses and SKs. In widespread or refractory lesions, administration of oral acitretin may be beneficial, although the disease will recur following its discontinuation[59]. Photoprotection should be recommended for patients who experience photoinduced aggravation.

FLEGEL DISEASE

Synonym: ■ Hyperkeratosis lenticularis perstans

Key features

- Very rare disorder, possibly autosomal dominant inheritance
- Multiple keratotic papules with a disc-like appearance in a symmetric distribution
- Predilection for the dorsal aspect of the feet and the distal extremities of adults

Introduction

In 1958, Flegel described this rare disorder in which asymptomatic, disc-shaped keratotic papules appear most commonly on the distal extremities of adults. The name hyperkeratosis lenticularis perstans refers to the disc or lens shape (lenticularis) of the papules and their persistent nature (perstans).

Epidemiology

Flegel disease is possibly inherited in an autosomal dominant pattern, although it also presents sporadically. Lesions are usually not evident until mid to late adulthood, but they have been described in individuals as young as 13 years of age[60,61]. No racial predilection has been reported.

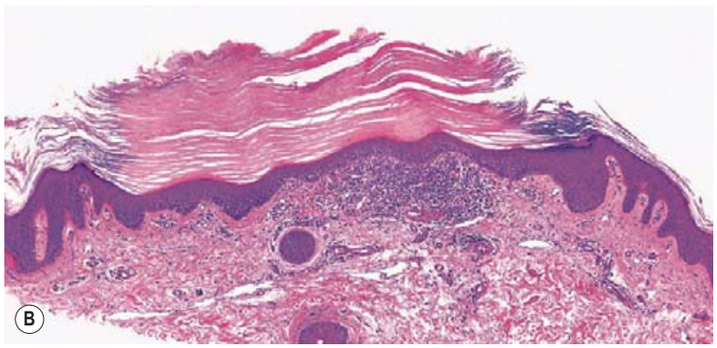


Fig. 109.9 Flegel disease. A Multiple symmetric hyperpigmented keratotic papules are present on the shins. **B** Thinned and flattened epidermis with overlying marked hyperkeratosis and an underlying patchy lichenoid infiltrate within the papillary dermis.

Pathogenesis

Lamellar granules (Odland bodies) have been shown to be either absent or altered on electron microscopic examination[62]. The lipid byproducts within lamellar granules influence stratum corneum desquamation, and, if they are absent or abnormal, hyperkeratosis may develop.

Clinical Features

Flegel disease is characterized by numerous symmetric keratotic papules (Fig. 109.9A). Lesions are most commonly observed on the dorsal aspect of the feet and the distal arms and legs, including the palms and soles. Lesions of the pinna and oral mucosa have also been documented. Individual papules are small, typically measuring from 1 to 5 mm in size. There is attached scale which may be more prominent at the peripheral margin. Removal of this scale can result in bleeding. Although most lesions are asymptomatic, patients occasionally complain of pruritus. While most lesions are small papules, those on the palms or soles often appear as fine pits. Flegel disease has been reportedly associated with endocrine disorders such as diabetes mellitus and hyperthyroidism[63].

Pathology

The papules consist of a discrete zone of ortho-hyperkeratosis, contrasting with the normal basket-weave cornified layer of the surrounding normal epidermis in most locations (Fig. 109.9B). There is often focal parakeratosis and hypogranulosis. The thin atrophic stratum spinosum is usually sharply indented or depressed at its lateral margin. A lichenoid infiltrate of lymphocytes is often present in the papillary dermis, along with dilated blood vessels[64]. A slight degree of hyperchromatism or nuclear infoldings, resembling Sézary cells, has been described in some cases of Flegel disease[65].

Differential Diagnosis

Stucco keratoses present as whitish-gray papules on the legs, but they typically do not bleed easily when scraped off and histologically there is papillomatosis not atrophy of the epidermis. There is no inflammation unless lesions have become irritated. Perforating disorders (see Ch. 96) have more prominent central keratotic plugs instead of disc-shaped hyperkeratosis, and there is a transepidermal elimination of connective tissue. With the exception of perforating granuloma annulare, perforating diseases rarely, if ever, occur on the palms or soles. Disseminated superficial actinic porokeratosis usually occurs on the legs, and a cornoid lamella is present. Other lichenoid diseases (see Ch. 11) can resemble the dermal changes in Flegel disease, but the clinical presentation allows differentiation. On a histopathologic basis, in the absence of clinical correlation, cases with lymphocyte atypia may be misdiagnosed as a cutaneous T-cell lymphoma.

Treatment

Treatment of Flegel disease is problematic as lesions tend to resist all but destructive therapy. Application of topical 5-fluorouracil cream is moderately effective, although it may not be well tolerated because of irritation. Other options include PUVA in combination with calcipotriol. Oral administration of retinoids has been attempted with inconsistent results.

ACROKERATOSIS VERRUCIFORMIS

Key features

- Multiple skin-colored, small, warty papules on the dorsal aspect of the hands and feet
- Rare autosomal dominant disorder of keratinization, often associated with Darier disease
- "Church spire" hyperkeratosis, papillomatosis and acanthosis

Clinical Features

Acrokeratosis verruciformis of Hopf is a rare autosomal dominant disorder, and it is often recognized during early childhood. Multiple skin-colored, small, warty papules appear on the dorsal aspect of the hands and feet and less commonly the extensor surfaces of the forearms and legs (see Fig. 59.14). It is often seen in patients with Darier disease, and patients with acrokeratosis verruciformis can have small, keratin-filled depressions on the palms and soles, as well as nail involvement. These observations are not surprising given that both Darier disease and acrokeratosis verruciformis can be due to mutations in the gene *ATP2A2* (see Fig. 59.1).

Pathology

There is hyperkeratosis, papillomatosis and acanthosis, often with hyperpigmentation. The hyperkeratosis may be quite prominent, and this lesion is often described as having a "church spire" configuration similar to that described for hyperkeratotic SK and stucco keratosis.

Differential Diagnosis

Histologic features similar to those of SK include hyperkeratosis, papillomatosis and acanthosis as well as some degree of hyperpigmentation. Clinicopathologic correlation is necessary to distinguish between these disorders. The name acrokeratosis verruciformis should not be confused with the unrelated epidermodysplasia verruciformis, a form of HPV infection (see Ch. 79) which usually has koilocytosis and cytologic atypia.

Treatment

Treatment is similar to that described for SKs and stucco keratoses.

CUTANEOUS HORN

Key features

- Clinical term for a firm, white to yellow, conical, markedly hyperkeratotic papule, plaque or nodule
- Most common in sun-exposed areas and arising from a hyperkeratotic actinic keratosis
- SCC is present at the base of the lesion in up to 20% of patients
- Other common causes include verruca and SK

Clinical Features

Cutaneous horn (cornu cutaneum) is a clinical term for a firm, white to yellow, conical, keratotic papule or plaque ranging from a few millimeters to several centimeters in size (Fig. 109.10A). These lesions result from abnormal accumulation of keratin in an elongated, vertically oriented column overlying an abnormality of the underlying spinous layer. Cutaneous horns may arise anywhere on the body, but sun-exposed areas are the most common locations. Men are affected more frequently than women. Individuals with a fair complexion and the elderly are particularly predisposed[66].

Pathology

A cutaneous horn consists of hyperkeratosis and parakeratosis associated with variable acanthosis (Fig. 109.10B), usually in association with the atypical keratinocytes of an actinic keratosis. Up to 20% of cutaneous horns arise over *in situ* or invasive SCCs[66]. Other lesions that may give rise to cutaneous horns include verrucae and SKs. Less common are other epithelial neoplasms, including tumors derived from follicular epithelium, especially trichilemmoma. A keratoacanthoma may produce a horn, but usually there is more of an endophytic keratinous plug.

Treatment

Shave excision with local destruction is the most common treatment. This must be done deeply enough to allow the pathologist to see the dermis beneath the horn in order to evaluate the possibility of dermal involvement by invasive carcinoma. Excision to adipose is best when invasion is suspected. In that case, induration of the dermis is detected, as opposed to the thickness related only to the horn. Treatment of malignant lesions is as described in Chapter 108. Cryotherapy alone may fail because the base may not be adequately treated unless the horn is pared first.

Fig. 109.10 Cutaneous horn. A This cutaneous horn arose from an actinic keratosis. **B** Striking column of hyperkeratosis with hyperplasia of the underlying epidermis.

CLEAR CELL ACANTHOMA

Synonym: ■ Degos' acanthoma

Key features

- Uncommon, usually solitary, papule or plaque on the leg
- Lesions are blanchable, erythematous and discrete; they may have attached "wafer-like" scale at their periphery
- Psoriasiform histology with well-demarcated zone containing clear to pale keratinocytes that stain positively with PAS

Introduction

First described by Degos in 1962, clear cell acanthoma is an uncommon red papule or plaque of the leg that may be suspected by astute clinicians, but usually a biopsy is required to establish the diagnosis.

Epidemiology

Clear cell acanthoma shows no sexual predilection and generally develops during middle-age, peaking in incidence by 50 to 60 years of age. It has not been described in children and neither an ethnic nor racial preference has been identified. Familial predisposition is rare, although there is one report of a French kinship with multiple affected family members having disseminated lesions[67].

Pathogenesis

The etiology of clear cell acanthoma is unknown. It was once thought to be induced by crude coal tar and UV light, although research has failed to demonstrate any link with environmental trauma, drugs, toxic substances or viruses. Given its abundant clear cytoplasm, it was originally thought to exhibit eccrine differentiation, although immunohistochemical and ultrastructural findings are more consistent with trichilemmal differentiation or features of the interfollicular epidermis[68,69]. It may be regarded as a variant of SK in which there are abundant glycogen-containing keratinocytes[70].

Others have proposed that clear cell acanthoma may actually be a localized, nonspecific, reactive inflammatory dermatosis. Several benign hyperproliferative dermatoses, including psoriasis, share a cytokeratin staining pattern similar to that seen in clear cell acanthoma. Furthermore, similarities in the histopathologic features between psoriasis and clear cell acanthoma suggest a common abnormality in the maturation of keratinocytes[71]. However, clear cell acanthomas do not develop following trauma and do not exhibit koebnerization, suggesting they are not simply a variant of localized psoriasis.

Clinical Features

Clear cell acanthoma presents as an erythematous, rounded papule or plaque that appears "stuck on" similar to an SK (Fig. 109.11A)[72]. A "wafer-like" scale is often appreciated, especially at the periphery[73]. The majority of clear cell acanthomas are solitary papules on the legs, but they may be found on the face, forearm, trunk and inguinal region. Lesions are almost always asymptomatic. Occasionally they are slightly eroded and a serous exudate may be present on the surface. There is often prominent vascularity that occasionally simulates a pyogenic granuloma, although the erythema can be blanched with application of pressure. By dermoscopy, the looped blood vessels within the dermal papillae create red dots in lines.

Clear cell acanthomas usually develop slowly, most commonly over a period of 2–10 years. They range in size from 0.3 to 2 cm in diameter,

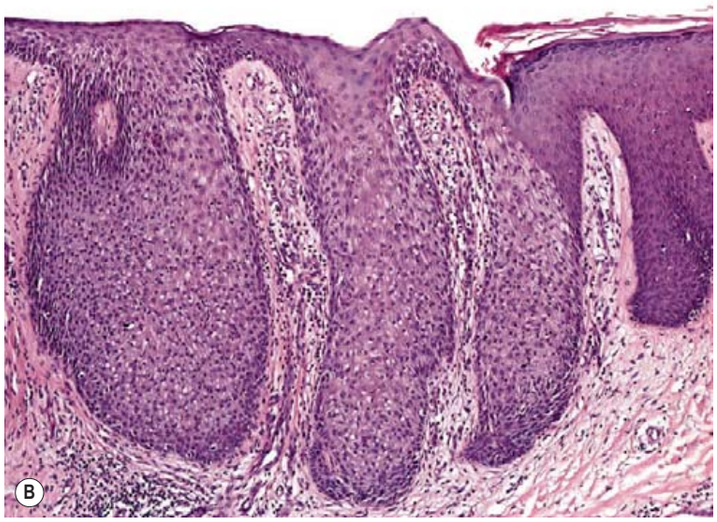


Fig. 109.11 Clear cell acanthoma. A Well-demarcated, dark red, shiny papule with a wafer-like collarette of scale. **B** Epidermal hyperplasia consisting of large pale keratinocytes. Note the sharp transition to normal skin. *B, Courtesy, Lorenzo Cerroni, MD.*

although larger lesions have been reported rarely, one of which had a diameter of 6 cm. Multiple lesions are rare, with only about 25 cases reported in the English literature, and these may either be few in number or numerous and widespread[74]. Disseminated forms have been categorized as either discrete (<12 lesions) or eruptive (>30 lesions)[75]. One patient had approximately 400 lesions[74]. Multiple lesions show a predilection for the lower extremities and may occur in conjunction with SKs, some forms of ichthyosis, and varicose veins[74]. Clear cell acanthomas with cystic, pigmented and polypoid features have been described, but these are uncommon. They have also been noted to develop in areas of pre-existing dermatoses, epidermal nevi, after trauma and following insect bites[76]. SCC *in situ* has also been rarely documented in association with clear cell acanthoma.

Pathology

Clear cell acanthoma displays a zone of sharply demarcated thickened epidermis with regular psoriasiform hyperplasia composed of enlarged pale keratinocytes (Fig. 109.11B). The epidermis is eroded and neutrophils extend from the papillary dermis into the stratum spinosum, aggregating in the overlying thin crust. The granular layer is diminished. PAS stains the pale cytoplasm of the keratinocytes red. The material that stains with PAS is diastase-sensitive, confirming it is glycogen. Electron microscopy also demonstrates abundant glycogen within the cytoplasm. Epidermal rete ridges are elongated. The dermis contains dilated blood vessels and sparse perivascular lymphocytes.

Differential Diagnosis

Clear cell acanthoma may be clinically confused with a pyogenic granuloma, traumatized hemangioma, dermatofibroma, verruca, BCC, SCC, amelanotic melanoma, inflamed SK, or psoriasis; dermoscopy can assist in making the diagnosis. Other clear cell neoplasms may occasionally cause confusion histologically, although the overall psoriasiform pattern of a clear cell acanthoma usually allows for distinction. Trichilemmomas usually appear on the face and consist of an inwardly growing lobule of pale keratinocytes lacking other features of psoriasis. The sebocytes of sebaceous neoplasms have a multiloculated cytoplasm containing lipid instead of glycogen, and are positive with oil red O, epithelial membrane antigen or adipophilin.

Treatment

Simple destruction or excision is adequate for removal. Shave excision or curettage combined with electrofulguration is a common form of treatment. Most lesions do not recur.

INVERTED FOLLICULAR KERATOSIS

Key features

- Asymptomatic, firm, white–tan to pink papule
- Typically solitary; most commonly on the face and neck of middle-aged and older adults
- Benign endophytic variant of irritated SK
- Histologically, squamous eddies and inflammation are common

History

Helwig was the first to delineate the features of inverted follicular keratosis (IFK) in 1955.

Epidemiology

IFK is seen most commonly in middle-aged to older Caucasian individuals. Men are affected twice as frequently as women.

Pathogenesis

In 1963, Duperrat and Mascaro proposed that the tumor was derived from the infundibulum of the hair follicle, although the cause is unclear.

Clinical Features

IFK is typically an asymptomatic, firm, white–tan to pink papule. It is found on the face in approximately 85% of cases, in particular on the cheek and upper lip. Other sites within the head and neck region are also affected. IFKs are usually less than 1 cm in diameter, but rarely they may reach up to 8 cm. They are typically stable and persistent lesions, but may regress.

Pathology

IFK exhibits an endophytic, somewhat bulbous proliferation of eosinophilic keratinocytes with basaloid or squamous differentiation (Fig. 109.12). The keratinocyte proliferation seems to surround one or several follicular canals that open to the surface. There may be inflammation. Squamous eddies are commonly seen.

Differential Diagnosis

The clinical differential diagnosis of IFK includes verruca, SK, trichilemmoma and other follicular adnexal tumors, BCC and SCC. Trichilemmoma has a predominance of clear cells, often with a palisade of basal cells and a thickened basement membrane. Rare mitotic figures may be appreciated in IFK, but overt cellular atypia as in SCC is absent.

WARTY DYSKERATOMA

Key features

- Uncommon, usually solitary papule or nodule with a central keratotic plug
- Usually located on the head or neck
- Acantholytic dyskeratosis seen at the base and sides of a cup-like epidermal invagination

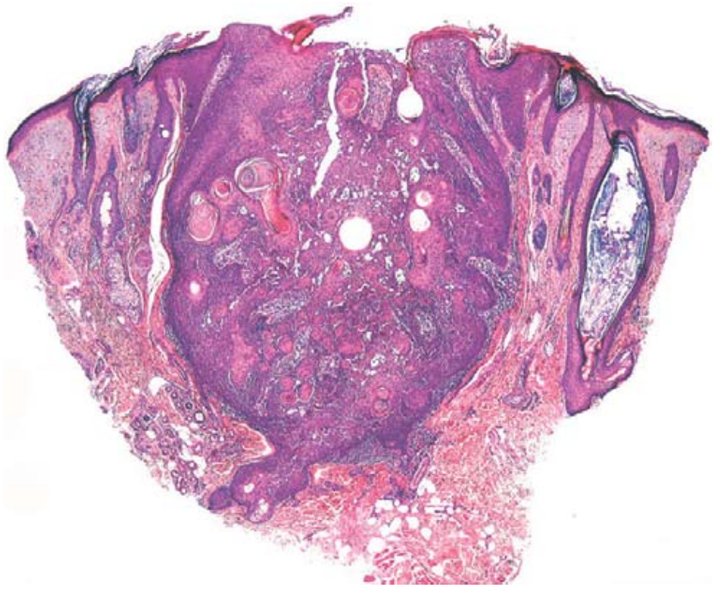


Fig. 109.12 Inverted follicular keratosis. An endophytic proliferation of keratinocytes with prominent squamous eddies is seen.

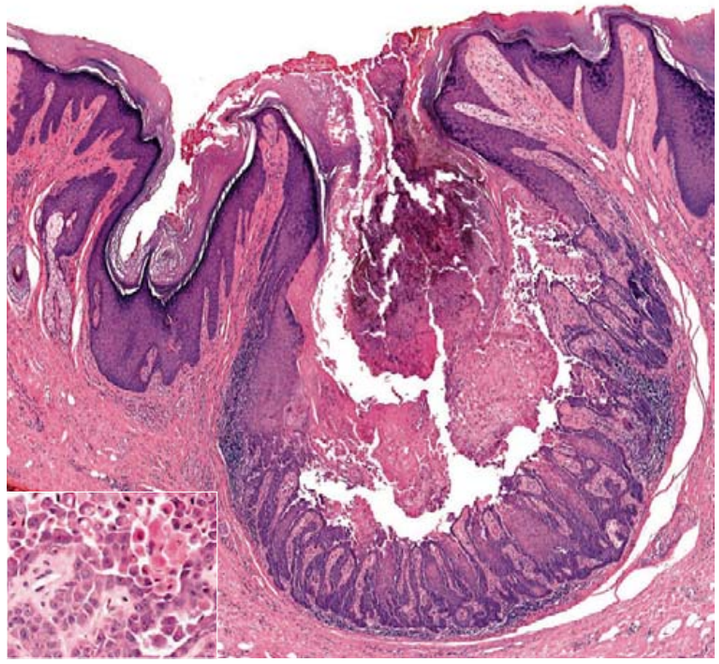


Fig. 109.13 Warty dyskeratoma. A cup-shaped invagination with a central keratotic plug. The lower portion of the wall has multiple villi. The epithelium demonstrates acantholysis and dyskeratosis (insert). *Courtesy, Lorenzo Cerroni, MD.*

Introduction

Warty dyskeratoma is an uncommon solitary papule or nodule usually found on the head or neck with a comedo-like plug and acantholysis with dyskeratosis histologically.

History

Helwig coined the term "isolated Darier's disease" in 1954. Three years later, the lesion was given the name warty dyskeratoma to indicate its solitary verrucous nature.

Epidemiology

Warty dyskeratoma is uncommon and demonstrates no genetic predisposition. It is more prevalent in men, usually appearing between the fifth and seventh decades of life. It is seen more commonly in Caucasians[77].

Pathogenesis

The pathogenesis of the acantholytic dyskeratosis in warty dyskeratomas has not been elucidated, although abnormal adhesion of keratinocytes has been demonstrated. Now that the gene responsible for Darier disease has been cloned, abnormalities in the function of its protein product could potentially be investigated in related entities like warty dyskeratoma.

Clinical Features

Warty dyskeratoma presents as a solitary, rarely multiple, verrucous, often crusted, skin-colored to red–brown papule or nodule with a central pore and a keratotic plug. Lesions grow slowly, and they are located most commonly on the scalp, cheek, temple, forehead, postauricular area and nose. Lesions have been found beneath the nail plate and in the mouth, especially on the hard palate and alveolar ridge. Warty dyskeratomas typically range in size from several millimeters to 2 cm in diameter.

Most warty dyskeratomas are asymptomatic, but patients may rarely complain of pruritus or burning. Bleeding and discharge of foul-smelling cornified material may occur. Warty dyskeratoma has been reported to coexist with other skin lesions, including verruciform xanthoma, actinic keratosis, SCC, BCC and adnexal carcinomas. Malignant degeneration in warty dyskeratoma has not been reported[77].

Pathology

Warty dyskeratoma is well circumscribed, and usually involves at least one dilated folliculosebaceous unit. There is a central cup-like invagination lined with epithelium displaying acantholysis and individual cell necrosis, corps ronds and grains, most closely resembling Darier disease (Fig. 109.13). The central crater is filled with cornified debris. Villous-like papillae, sometimes composed of only a single layer of basal cells, often project upward from the invaginated hyperplastic base.

Differential Diagnosis

Warty dyskeratoma may resemble other epithelial neoplasms and proliferations such as verruca, epidermal inclusion cyst, SK, hypertrophic actinic keratosis and SCC. Histologically, other conditions with suprabasilar acantholytic dyskeratosis must be excluded, such as Darier disease, Grover's disease, Hailey–Hailey disease, acantholytic acanthoma, familial dyskeratotic comedones, acantholytic actinic keratosis, and acantholytic SCC. Most of these are quite different clinically.

Treatment

Warty dyskeratoma is benign, so treatment depends upon the clinical situation. Most lesions are biopsied to exclude the possibility of a malignancy. Excision is curative.

ACANTHOLYTIC (DYSKERATOTIC) ACANTHOMA

Key features

- Often a solitary papule on the trunk of adults; may present as multiple lesions in the genital area
- Variant of a solitary keratosis with histopathologic findings of acantholysis with or without dyskeratosis in a hyperplastic epidermis with an overall flat architecture

Acantholytic (dyskeratotic) acanthoma is often a solitary papule on the trunk of adults, and biopsy is often performed to exclude a basal cell carcinoma. Occasionally, there are multiple lesions in the genital area. Histologically, there is acantholysis with or without dyskeratosis. Unlike warty dyskeratoma, there is neither a cup-shaped architecture nor an association with a hair follicle. In contrast to acantholytic actinic keratosis, there is not keratinocyte atypia.

EPIDERMOLYTIC ACANTHOMA

Key features

- Discrete keratotic papules in adults, with epidermolytic hyperkeratosis seen histologically
- Two varieties: an isolated form and a disseminated form

Epidemiology

Epidermolytic acanthomas may appear any time during adulthood. No particular race or gender is favored. There are no reports of familial epidermolytic acanthoma.

Pathogenesis

Because its clinical and histologic features may resemble those of verrucae, a viral origin was originally suspected, but HPV DNA has not been detected in skin lesions[78]. Gene mutations and exogenous factors such as UV light, other viruses[79], and trauma[80] have all been suggested as causes of acquired epidermolytic hyperkeratosis. Other theories include increased keratinocyte metabolic activity and aberrant keratin gene expression[81].

Clinical Features

Isolated epidermolytic acanthoma was initially described in 1970, while the disseminated form was described in 1973. Both the solitary and disseminated forms present as pigmented keratotic papules that may resemble verrucae or SKs (Fig. 109.14A). Individual lesions are generally 1 cm or less in diameter. Isolated epidermolytic acanthoma may appear on any body site. Lesions are discrete but they may occur in clusters and still be considered to represent the isolated variant. The disseminated form has a predilection for the trunk, especially the back[82]; it has also been reported in the genital region. Lesions are usually asymptomatic, but they may be pruritic.

Pathology

The histologic pattern of epidermolytic hyperkeratosis (Fig. 109.14B) consists of four components:

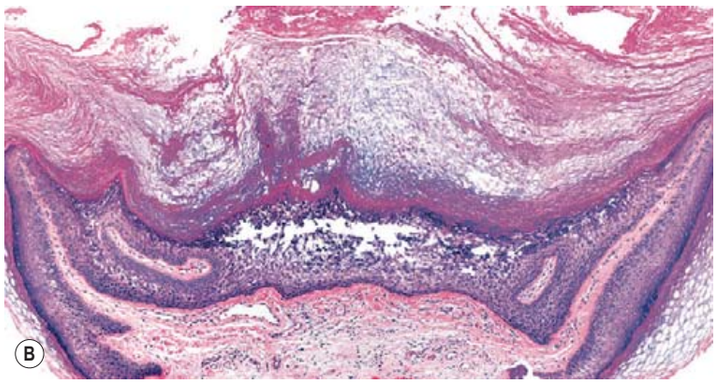


Fig. 109.14 Solitary epidermolytic acanthoma. A Keratotic papulonodule on the chest. **B** Marked hyperkeratosis and epidermolytic hyperkeratosis within the underlying epidermis.

- clear spaces of varying size surrounding nuclei in the stratum spinosum and stratum granulosum
- indistinct cellular boundaries consisting of reticulated, lightly staining material
- a markedly thickened granular zone containing an increased number of small and large, irregularly shaped, basophilic keratohyaline-like bodies
- compact hyperkeratosis.

The basal layer is normal. Epidermolytic acanthoma generally demonstrates more papillomatosis than is typically seen in other conditions with the histologic pattern of epidermolytic hyperkeratosis. There is often a slight superficial perivascular lymphocytic infiltrate in the dermis.

Differential Diagnosis

Conditions resembling epidermolytic acanthoma clinically include verrucae and SKs. Because the former does not have a characteristic clinical appearance, the diagnosis is not usually made until after a biopsy is performed. Epidermolytic hyperkeratosis is a histologic finding common to several conditions, including epidermolytic ichthyosis (bullous congenital ichthyosiform erythroderma), some epidermal nevi, and Vörner's palmoplantar keratoderma, and it is seen incidentally in normal skin and in lesions such as follicular cysts, SKs, atypical nevi, actinic keratoses and cutaneous horns[82].

Treatment

Treatment is not required as the lesions are benign. Destruction, shave excision or linear excision is successful, although recurrence may follow superficial removal.

LARGE CELL ACANTHOMA

Key features

- Small, skin-colored, hyper- or hypopigmented papule or plaque
- Located on sun-exposed skin of older individuals
- Likely a variant of solar lentigo or SK

Introduction

Large cell acanthoma is a benign keratinocytic lesion that is asymptomatic and often ignored[83,84]. Some dermatopathologists make the diagnosis frequently, while others do not believe that this is a specific entity.

History

Pinkus first described the lesion in 1967 during a lecture on benign epidermal neoplasms where he coined the term. He published his observations in 1970, noting its resemblance to solar keratosis[85].

Epidemiology

Large cell acanthoma is seen most commonly on sun-damaged skin of middle-aged to elderly individuals, with ages at diagnosis ranging from 28 to 89 years, and a mean age in the mid-60s. Women have a slightly higher incidence and most affected patients are Caucasian[85].

Pathogenesis

The pathogenesis of large cell acanthoma is unknown. Genetic studies have demonstrated low-grade aneuploidy, a finding typically associated with malignancy. Nevertheless, large cell acanthoma has generally been considered to be clinically benign. Some investigators have proposed that it is a variant of Bowen's disease[86]. Still others classify it as a variant of solar lentigo in a stage evolving into a reticulated SK or lichen planus-like keratosis[87].

Clinical Features

Large cell acanthoma characteristically presents as an asymptomatic, sharply demarcated, solitary, skin-colored, hyper- or hypopigmented papule or plaque (Fig. 109.15A) on the face or neck, including the

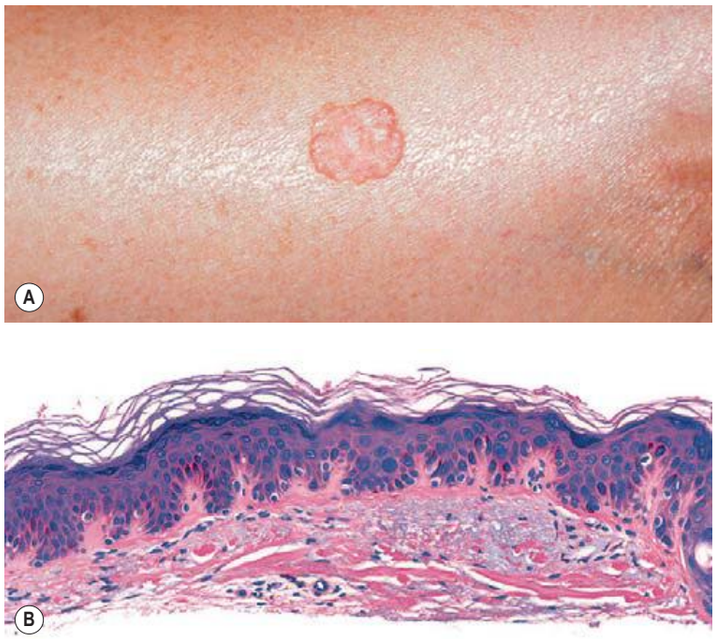


Fig. 109.15 Large cell acanthoma. A Well-demarcated, thin, pink–brown plaque. **B** Slight epidermal hyperplasia with foci of enlarged keratinocytes centrally.

eyelid[88]. It also may be found on the upper or lower extremities and the trunk[86]. Rarely, multiple lesions scattered on the extremities are observed.

As it is asymptomatic and often ignored, the time to diagnosis is quite variable, ranging from 3 months to 15 years[83,84].

Pathology

Histologically, large cell acanthomas are well demarcated, with uniform large keratinocytes with abundant cytoplasm and enlarged nuclei (Fig. 109.15B). Mild cytologic atypia may be appreciated. There is variable hyperkeratosis, epidermal rete ridge elongation, papillomatosis, or basal layer hyperpigmentation. Some lesions have minimal hyperkeratosis with flattened rete ridges and only small dermal papillae[86].

Differential Diagnosis

The differential diagnosis includes solar lentigo (histologically), solar keratosis, SK, Bowen's disease and melanoma.

Treatment

Shave or simple excision as well as destruction are options.

EPIDERMAL NEVUS

Synonym: ■ Nevus verrucosus

Key features

- Onset usually within the first year of life with "nevus" referring to a hamartoma of the epidermis and papillary dermis
- Most commonly, hyperpigmented papillomatous papules and plaques appear in a linear array along Blaschko's lines
- In nevus unius lateris (unilateral) and ichthyosis hystrix (bilateral), there are multiple lesions in streaks and whorls
- Patients with epidermal nevus syndrome have associated abnormalities, especially of the musculoskeletal and neurologic systems

Introduction

The word nevus (plural, nevi) is derived from Latin and, as currently used, has three definitions: (1) a congenital lesion (birthmark) or lesion arising early in life; (2) a benign tumor of melanocytes; or (3) a hamartoma. The latter is a benign malformation with an excess or deficiency of structural elements normally found in the affected area (e.g. epidermis, connective tissue, adnexa). In most hamartomas, one element is predominant.

Epidemiology

The incidence of epidermal nevus is estimated to be 1 in 1000 infants. The majority of epidermal nevi develop sporadically, although familial cases have been reported[89,90]. Males and females are equally affected.

Pathogenesis

Epidermal nevi are thought to originate from pluripotent cells in the basal layer of the embryonic epidermis. While mosaicism is thought to be responsible for most epidermal nevi (see Ch. 62), until recently only those nevi associated histologically with epidermolytic hyperkeratosis or acantholytic dyskeratosis had been shown to be due to genetic mosaicism (i.e. mutations in *KRT1* or *KRT10* versus *ATP2A2* that are limited to involved epidermis). In 2006, mosaicism for activating mutations in the gene that encodes fibroblast growth factor receptor 3 (*FGFR3*) were demonstrated in "common" epidermal nevi (i.e. those with acanthosis, papillomatosis and hyperkeratosis; see Table 62.8)[91]. Of note, similar germline mutations in *FGFR3* lead to skeletal dysplasia syndromes associated with acanthosis nigricans. As in SKs, activating mutations in *PIK3CA*, which encodes the alpha subunit of phosphoinositide-3-kinase which functions downstream of FGFR3, have been detected in epidermal nevi[6], in addition to an oncogenic mutation in *KRAS* in the latter[91a]. The possibility exists that additional genetic mutations in keratinocytes or fibroblasts within epidermal nevi may be detected in the future, including those that encode proteins involved in differentiation or other growth factor receptors.

While these lesions are classically referred to as "epidermal" nevi, the hamartomatous process also involves at least some portion of the dermis, especially the papillary dermis. This is evident when treatment directed purely at destruction of the epidermis fails to eradicate the lesion, which invariably recurs unless there is ablation or destruction of the upper dermis.

Clinical Features

In a review of 131 patients with epidermal nevi, the age of onset ranged from birth to 14 years, with 80% occurring within the first year of life[92]. They may occasionally appear during adulthood[93]. Epidermal nevi most commonly present as a single linear lesion, but sometimes multiple unilateral or bilateral linear plaques are seen. Most lesions consist of well-circumscribed, hyperpigmented, papillomatous papules or plaques that are usually asymptomatic (Fig. 109.16). The earliest lesions may be macular and confused with linear and whorled nevoid hypermelanosis. Rarely, epidermal nevi are hypopigmented. Once developed, the nevi may thicken and become more verrucous, especially over joints and in flexural areas such as the neck. Lesions occur most commonly on the trunk, extremities or neck[92] and their size and distribution are highly variable. Epidermal nevi follow Blaschko's lines (see Ch. 62) and may have an abrupt midline demarcation.

Nevus verrucosus is a term used for localized lesions that have a warty appearance. Nevus unius lateris, first named in 1863 by von Baerensprung, is a variant in which there are extensive unilateral plaques, often involving the trunk. Ichthyosis hystrix (systematized epidermal nevus) is a variant with extensive bilateral involvement, also usually on the trunk[94].

Epidermal nevus syndrome, a concept proposed by Solomon and Esterly in 1968, is diagnosed when epidermal nevi occur in combination with other developmental anomalies (see Ch. 62). These abnormalities most commonly involve the neurologic or musculoskeletal systems. Excluding cutaneous manifestations, a study of 119 patients with epidermal nevi found that 33% had abnormalities in one organ system, 6% in two, 5% in three, and 5% in five or more. Individuals with SOLAMEN and Proteus syndromes also develop epidermal nevi.

Fig. 109.16 Epidermal nevi. A, B Verrucous hyperpigmented plaques that follow the lines of Blaschko. Note the midline demarcation in B. *A, Courtesy, Kalman Watsky, MD. B, Courtesy, Kathyrn Schwarzenberger, MD.*

Pathology

At least ten histologic patterns have been observed in epidermal nevi, and more than one may be present in the same lesion[95,96]. Virtually all are characterized by epidermal hyperplasia, hyperkeratosis, acanthosis, papillomatosis, and variable parakeratosis (Fig. 109.17). Other findings such as epidermolytic hyperkeratosis and focal acantholytic dyskeratosis may be prominent features. Inflammatory linear verrucous epidermal nevus (ILVEN) may have clinical and histologic features very similar to psoriasis (see the following section).

Neoplasms such as BCC, SCC and keratoacanthoma may rarely develop in association with epidermal nevi. This malignant change occurs less commonly in epidermal nevus than in the closely related nevus sebaceus. Malignancy in epidermal nevus, when it does occur, typically develops after puberty[97]. Examples of BCC arising in epidermal and sebaceous nevi may actually be trichoblastomas, representing a manifestation of the hamartomatous nature of the neoplasm[98–100].

Differential Diagnosis

Nevus sebaceus (see Ch. 111), usually found on the head instead of the trunk or extremities, can be considered a subtype of epidermal nevus with additional hamartomatous components of sebaceous and apocrine glands accompanying the papillomatous epidermis. Organoid nevi combine features of both epidermal nevus and nevus sebaceus, with variation often depending upon anatomic site (e.g. head and neck versus trunk). Lichen striatus is an acquired lesion, has less papillomatosis and acanthosis as well as more dyskeratosis and spongiosis, and does not persist indefinitely. There are other nevoid conditions that are distributed along Blaschko's lines and therefore may simulate epidermal nevi, depending on the type and degree of epidermal proliferation.

Fig. 109.17 Epidermal nevus – most common histologic pattern. Epidermal hyperplasia with papillomatosis and hyperkeratosis.

Examples include porokeratotic eccrine ostial and dermal duct nevus, linear lichen planus and X-linked dominant chondrodysplasia punctata. Small lesions must be distinguished from SKs, verrucae vulgares and psoriasis, especially if there is Koebner phenomena.

Treatment

Infants and children with epidermal nevi, particularly multiple or extensive lesions, require a thorough evaluation for systemic abnormalities in conjunction with a pediatrician (see Ch. 62). Full-thickness surgical excision is curative, but recurrence is common when only the epidermis is removed (e.g. by shave excision or curettage). Surgical excision of larger lesions can be complicated by hypertrophic scars or keloid formation[101]. Topical therapies such as corticosteroids, retinoic acid, tars, anthralin, 5-fluorouracil and podophyllin have all been used, but they are of limited benefit. Chronic therapy with oral retinoids has been reported to be effective at decreasing the thickness of systematized epidermal nevi, although it does not result in resolution. Laser ablation may also be undertaken, but, to be effective, it must induce scarring and fibrosis of at least the papillary dermis. Therefore, this treatment is often not cosmetically acceptable to patients and test sites are recommended.

INFLAMMATORY LINEAR VERRUCOUS EPIDERMAL NEVUS

Synonym: ■ Dermatitic epidermal nevus

Key features

- Linear, psoriasiform papules or plaques, usually on one extremity
- 75% of nevi appear before the age of 5 years
- Four times more common in girls
- Usually persists for years despite attempts at treatment
- Histologically, psoriasiform hyperplasia with alternating parakeratosis and orthokeratosis

Introduction

Inflammatory linear verrucous epidermal nevus (ILVEN) is a relatively rare, linear, psoriasiform plaque that usually presents during childhood.

History

Altman and Mehregan are credited with the first description of ILVEN in 1971[102].

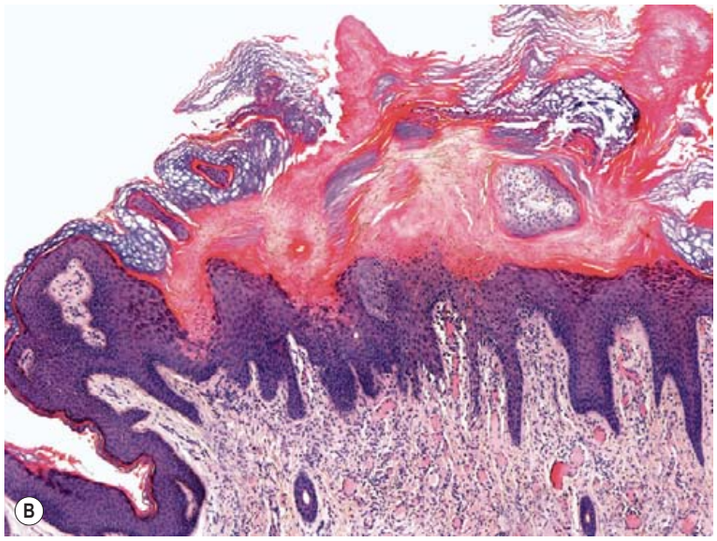


Fig. 109.18 Inflammatory linear verrucous epidermal nevus (ILVEN). A Linear erythematous scaly plaques on the medial aspect of the right thigh. Some of the lesions have a psoriasiform appearance. **B** Epidermal hyperplasia and broad zones of parakeratosis alternating with ortho-hyperkeratosis.

Pathogenesis

The definitive cause is unknown. As it bears some resemblance to psoriasis histologically, some believe that the two conditions share a common pathogenesis[103]. Involucrin, a structural component of mature squamous epithelium, is expressed in ILVEN in increased amounts within the orthokeratotic epithelium, but is minimally expressed within keratinocytes underlying areas of parakeratosis. However, in psoriasis, involucrin is expressed in all layers of the epidermis except the basal layer[104]. While there are similarities to psoriasis, others propose that ILVEN represents a clonal dysregulation of keratinocyte growth[103].

Clinical Features

ILVEN has a psoriasiform appearance and may be associated with significant pruritus. Scaly, erythematous papules coalesce to form a linear plaque, usually on a limb (Fig. 109.18A), although occasionally the trunk may be involved. Lesions are almost always unilateral. The left leg is reportedly more frequently affected than the right[102]. In 75% of patients, the age of onset is before the age of 5 years. Isolated instances of adult onset have been reported[105] and, rarely, there may be a familial predisposition. ILVEN has a 4:1 female-to-male predilection. Most lesions spontaneously resolve by adulthood[106]. A possible association of ILVEN with arthritis has been described[107].

Pathology

The psoriasiform histology of ILVEN correlates with its psoriasiform clinical appearance. Epidermal rete ridges are elongated, and broad zones of parakeratosis without an underlying granular layer alternate abruptly with depressed regions of orthokeratosis and hypergranulosis (Fig. 109.18B). There is often exocytosis of lymphocytes and neutrophils into the spongiotic papillomatous epidermis and occasionally Munro's microabscesses may be seen.

Differential Diagnosis

At least three other variants of epidermal nevi with inflammation have been described, including lichenoid epidermal nevus, psoriasis superimposed on an epidermal nevus, and epidermal nevi in *c*ongenital *h*emidysplasia with *i*chthyosiform nevus and *l*imb *d*efects (CHILD) syndrome (see Ch. 57). Lichenoid epidermal nevus is typically a verrucous plaque with a lichenoid lymphocytic dermal infiltrate. It is debatable whether lichenoid epidermal nevus truly represents linear lichen planus. The age of onset, distribution, lack of development of additional lesions of psoriasis over time, resistance to therapy, and lack of family history are all features of ILVEN. Patients with linear (nevoid) psoriasis can have or develop classic plaques of psoriasis elsewhere.

It has been suggested that ILVEN may be a form fruste of CHILD syndrome because rarely, ipsilateral skeletal anomalies are seen in patients with ILVEN. Also, although large areas of ichthyosiform erythema characteristically involve one-half of the body with an affinity for skin folds (ptychotropism), patients with CHILD syndrome can have linear keratotic plaques along Blaschko's lines that have an appearance similar to ILVEN. CHILD syndrome differs histologically from ILVEN in that it has features of verruciform xanthoma with elongated dermal papillae and cells with foamy cytoplasm in the upper papillary dermis[108], as well as vacuoles within the cells of the lower stratum corneum ultrastructurally.

Treatment

As with other epidermal nevi, ILVEN is difficult to treat. Treatments that are successful in psoriasis are only partially effective for ILVEN[107]. Surgical excision is effective but results in scarring. The pulsed dye laser (see Ch. 137) has been used successfully in some cases. Its mechanism of action is thought to involve destruction of small blood vessels in the papillary dermis that supply the overlying epidermis[109]. Combination therapy with topical tretinoin and 5-fluorouracil creams has also been employed with beneficial results, but long-term success can only be achieved with maintenance therapy[110]. Topical synthetic derivatives of vitamin D_3, such as calcipotriol, may also be partially effective[111,112]. There are anecdotal reports of improvement with etanercept.

Arthritis in association with ILVEN, although rare, can lead to significant morbidity. Early recognition is critical. Treatment is the same as for psoriatic arthritis[107].

NEVUS COMEDONICUS

Synonym: ■ Comedo nevus

Key features

- Benign hamartoma, usually arising before the age of 10 years
- Multiple grouped comedones in a linear array, most commonly on the face, trunk or neck
- Histologically, underdeveloped hair shafts and epidermal invaginations containing a keratin plug

Introduction

Nevus comedonicus is a rare hamartoma of the folliculosebaceous unit resulting in numerous dilated, keratin-filled comedones.

History

Kofmann, in 1895, was the first to delineate the features of nevus comedonicus. In 1914, White attempted to change the name to "nevus follicularis keratosis" as he considered the comedo-like lesions not to represent true comedones, as sebaceous glands were either rudimentary or absent in most cases.

Epidemiology

Approximately half of the cases of nevus comedonicus are evident at birth, with others appearing during childhood, usually before the age of 10 years. Onset in adulthood, albeit rare, is often associated with irritation or trauma. There is no racial or sexual predilection. Although most cases arise sporadically, familial clustering has been reported[113].

Pathogenesis

Nevus comedonicus is thought to represent growth dysregulation affecting the mesodermal portion of the pilosebaceous unit. The epithelial-lined invaginations, incapable of forming mature terminal hairs and sebaceous glands, accumulate a soft cornified ostial product resulting in a comedo-like plug. In 1998, *FGFR2* mutations were detected in a nevus comedonicus and not in the adjacent normal skin, providing evidence for genetic mosaicism (see Table 62.8)[114]. Of note, patients with Apert syndrome, sporadic or inherited in an autosomal dominant manner and due to mutations in *FGFR2*, may have comedones and severe cystic acne (see Table 62.8).

Clinical Features

There is usually a single circumscribed area (Fig. 109.19A) or linear streak composed of clusters of dilated follicular ostia that contain firm, darkly pigmented, cornified material. Occasionally, multiple linear plaques may be seen with midline demarcation. Their size is variable and they can range from a few centimeters in diameter to extensive lesions affecting half of the body. The site most commonly affected is the face, followed by the trunk, neck and upper extremity. These nevi may also arise in areas that are devoid of hair follicles such as the palms, soles and glans penis. When present on the elbows and knees, lesions can be verrucous in appearance. Inflammatory papules and cysts can be admixed with the comedones. Hormonal influences of puberty often worsen the condition.

Pathology

Nevus comedonicus consists of grouped undeveloped hair follicles, presenting as dilated invaginations filled with cornified debris devoid of hair shafts (Fig. 109.19B). Epidermolytic hyperkeratosis may sometimes be present in the follicular epithelium.

Differential Diagnosis

Many skin conditions present with comedones, and these must be differentiated from nevus comedonicus. Infantile acne typically presents on the face between the ages of 3 and 24 months. The comedones, pustules and papules in this disorder are not linear, and they are self-limited. Chloracne is associated with exposure to toxins that lead to the formation of comedones, generally located on both sides of the face and commonly behind the ears.

Familial dyskeratotic comedones is a rare autosomal dominant disorder in which comedones arise during childhood or adolescence and are widely scattered on the trunk and extremities without a linear configuration. Histologically, acantholytic dyskeratosis in the comedo wall is seen.

The dilated pore nevus resembles nevus comedonicus clinically but differs histologically by containing dilated follicular cysts. Porokeratotic eccrine ostial and dermal duct nevi also may be confused with nevus comedonicus, especially when the latter involves the palms or soles. These lesions are comprised of dilated eccrine ducts containing parakeratotic debris. The keratinocyte cytoplasm is typically vacuolated and the granular layer is absent.

Treatment

As with other epidermal nevi, treatment of nevus comedonicus is problematic. Localized lesions can be surgically excised, although it is often difficult to excise larger lesions. Manual comedo extraction, dermabrasion, and the use of keratolytic agents (e.g. salicylic acid, tretinoin and ammonium lactate[115]) may be helpful, but they are not curative. Isotretinoin is not usually recommended owing to the long-term treatment required, but it may be beneficial in preventing cyst formation. Antibiotics may be necessary to treat secondary infections.

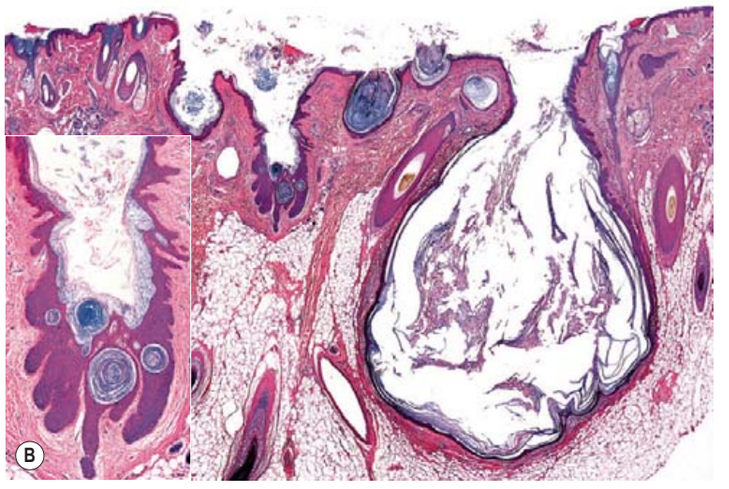


Fig. 109.19 Nevus comedonicus. **A** Numerous comedones within a broad streak along the lines of Blaschko. **B** Dilated infundibula filled with orthokeratotic keratin. Occasionally, the wall of the comedo will display epithelial hyperplasia (insert).

ACANTHOSIS NIGRICANS

Acanthosis nigricans is discussed in detail in Chapter 53. Histologically, it may be misinterpreted as SK, acrochordon, epidermal nevus, or confluent and reticulated papillomatosis, unless appropriate clinical correlation is provided.

CONFLUENT AND RETICULATED PAPILLOMATOSIS

Synonym: ■ Confluent and reticulated papillomatosis of Gougerot and Carteaud

Key features

- Onset typically during puberty
- Multiple brown verrucous papules or patches in a confluent and/or reticulated pattern, most commonly on the central chest and upper abdomen
- Oral minocycline is effective in approximately 50% of patients

History

Confluent and reticulated papillomatosis of Gougerot and Carteaud (CARP) was first described in 1927.

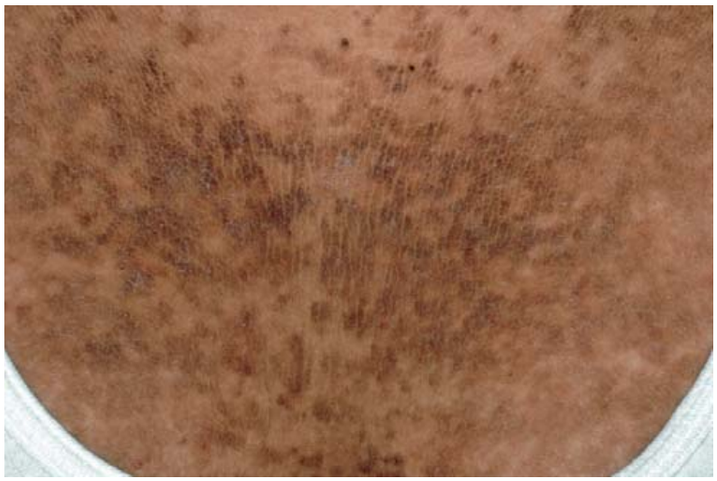


Fig. 109.20 Confluent and reticulated papillomatosis (CARP). Multiple hyperpigmented papules that are confluent centrally and assume a reticulated pattern laterally. *Courtesy, Julie V Schaffer, MD.*

Epidemiology

The typical onset of CARP is during puberty. Young women are affected 2.5 times more frequently than young men, and blacks are twice as likely to have CARP as whites. Occurrence of CARP is mostly sporadic, although familial cases have been reported[116].

Pathogenesis

Some think CARP may be caused by an endocrine imbalance, especially insulin resistance, because of its association with conditions such as obesity, menstrual irregularities and diabetes mellitus as well as pituitary and thyroid disorders. In addition, there is a clinical resemblance to acanthosis nigricans. However, most patients are otherwise healthy. Another hypothesis is that CARP is a disorder of keratinization. This theory arose because a number of patients have been successfully treated with topical and systemic retinoids[117]. An abnormal host response to *Malassezia furfur* has also been suggested, because this organism is sometimes prevalent within areas of involvement in its yeast (and, less often, hyphal) forms and because treatment with topical selenium sulfide has sometimes been successful[118]. The majority of cases, however, demonstrate no evidence of *M. furfur* proliferation.

Clinical Features

The initial lesions of CARP are 1–2 mm papules, first appearing in the intermammary area or less frequently the interscapular or epigastric regions. Lesions rapidly enlarge to 4–5 mm and become brown, hyperkeratotic, verrucous papules or patches. The papules coalesce and become confluent centrally and reticulated peripherally (Fig. 109.20). Involvement of the neck, shoulders and back can develop. Oral lesions have not been reported. The eruption is asymptomatic or, rarely, mildly pruritic.

Pathology

There is hyperkeratosis, acanthosis and papillomatosis. Sparse superficial perivascular lymphocytes are also seen. A characteristic feature is the club-shaped, bulbous epidermal rete ridges that protrude slightly into the papillary dermis with pigment at their bases ("dirty feet").

Differential Diagnosis

CARP can clinically resemble acanthosis nigricans, pseudoacanthosis nigricans, Darier disease and tinea versicolor. Acanthosis nigricans has thicker, more velvety plaques involving intertriginous areas; it also lacks the reticulated pattern of CARP. Although pseudoacanthosis nigricans, like CARP, has a predilection for darkly pigmented individuals, it is characteristically associated with weight gain and disappears with weight loss. Tinea versicolor may be related to CARP because of its brownish scale and association with *M. furfur*, but it is neither reticulated nor papillomatous.

Histologically, CARP may be misinterpreted as an SK, acrochordon, epidermal nevus, acanthosis nigricans, or other papillomatous epithelial proliferation, unless appropriate clinical information is provided.

Treatment

Treatment of CARP is often frustrating because it may not respond to therapeutic interventions or recurs after cessation of therapy. No single agent has been uniformly successful at providing long-term resolution. Temporary improvement has been reported with the use of various antibiotics, isotretinoin[119], etretinate[117] and acitretin as well as topical salicylic acid, hydroquinone, antifungals[118], and 5-fluorouracil[118]. Oral minocycline has been reported to be effective in about 50% of patients. Many reported no recurrences, while others experienced disease-free intervals for up to 18 months[120]. Oral retinoids are no more successful than oral antibiotics at maintaining a disease-free state, and, given their potential for causing hypertriglyceridemia and teratogenicity, they are generally considered to be second- or third-line agents.

CLEAR CELL PAPULOSIS

Key features

- Extremely rare condition, mainly described in Asian children
- Hypopigmented macules and papules arranged along the milk lines
- Histopathologically, large clear cells scattered along the basal layer of the epidermis and within the malpighian layer

Epidemiology

Clear cell papulosis (CCP) is an extremely rare condition that preferentially affects Chinese and other Asian children[121].

Pathogenesis

The pathogenesis of CCP is unknown. The arrangement of lesions along the so-called milk lines and the appearance of clear cells in lesional skin suggest a histogenetic relationship with Toker cells. Some authors have considered this process as the benign counterpart of extramammary Paget disease[122].

Clinical Features

CCP is characterized by multiple, asymptomatic, white macules or papules that are 2–10 mm in diameter, involving the anterior chest, abdomen and lumbar region. The lesions are often arranged along the milk lines. In rare cases, the face may be also involved.

Pathology

Lesions of CCP are mildly acanthotic and show a slightly disorganized arrangement of epidermal keratinocytes. Numerous clear cells are scattered primarily along the basal layer of the epidermis, but also within its upper layers. These clear cells are larger than adjacent keratinocytes and have cytoplasmic vacuolization due to abundant mucin contained within their cytoplasm; the latter may be better demonstrated with PAS, mucicarmine, alcian blue or colloidal iron stains. Immunohistochemically, clear cells of CCP express carcinoembryonic antigen, cytokeratins (CK7-, AE1/AE3-, and CAM5.2-positive), epithelial membrane antigen (EMA) and gross cystic fluid disease protein-15 (GCDFP-15), but are negative for expression of CD1a, S100 protein and HMB45[121].

Differential Diagnosis

Clinically, CCP should be differentiated from hypopigmented lesions of tinea versicolor, pityriasis lichenoides chronica, guttate lichen

sclerosus and confetti-type vitiligo (see Table 66.7). Histologically, CCP needs to be distinguished from extramammary Paget's disease and pagetoid dyskeratosis. Neoplastic cells of extramammary Paget's disease are more atypical and pleomorphic than those of CCP. Pagetoid dyskeratosis is a disorder of keratinization characterized by clear and pale eosinophilic keratinocytes scattered within the epidermis[123]; it is an incidental histopathologic finding without any clinical significance.

Treatment

CCP is a benign process and no treatment is necessary. Lesions may spontaneously resolve over time.

REFERENCES

1. Verhagen ARHB, Koten JW, Chaddah VK, Patel RI. Skin diseases in Kenya: a clinical and histopathological study of 3,168 patients. Arch Dermatol. 1968;98:577–86.
2. Yeatman J, Kilkenny M, Marks R. The prevalence of seborrhoeic keratoses in an Australian population: does exposure to sunlight play a part in their frequency? Br J Dermatol. 1997;137:411–4.
3. Nakamura H, Hirota S, Adachi S, et al. Clonal nature of seborrheic keratosis demonstrated by using the polymorphism of the human androgen receptor locus as a marker. J Invest Dermatol. 2001;116:506–10.
4. Pesce C, Scalora S. Apoptosis in the areas of squamous differentiation of irritated seborrheic keratosis. J Cutan Pathol. 2000;27:121–3.
5. Hafner C, Hartmann A, van Oers JMM, et al. *FGFR3* mutations in seborrheic keratoses are already present in flat lesions and associated with age and localization. Mod Pathol. 2007;20:895–903.
6. Hafner C, López-Knowles E, Luis NM, et al. Oncogenic *PIK3CA* mutations occur in epidermal nevi and seborrheic keratoses with a characteristic mutation pattern. Proc Natl Acad Sci USA. 2007;104:13450–4.
7. Leonardi C, Zhu W, Kinsey W, Penneys N. Seborrheic keratoses from the genital region may contain human papillomavirus DNA. Arch Dermatol. 1991;127:1203–6.
8. Winkelmann R. Superficial spreading (and disappearing) seborrheic keratosis. Cutis. 1999;63:235–7.
9. Díaz-Cascajo C, Reichel M, Sanchez J. Malignant neoplasms associated with seborrheic keratoses. An analysis of 54 cases. Am J Dermatopathol. 1996;18:278–82.
10. Rao B, Freeman R, Poulos E, et al. The relationship between basal cell epithelioma and seborrheic keratosis. A study of 60 cases. J Dermatol Surg Oncol. 1994;20:761–4.
11. Zabel R, Vinson R, McCollough M. Malignant melanoma arising in a seborrheic keratosis. J Am Acad Dermatol. 2000;42:831–3.
12. Sloan J, Jaworsky C. Clinical misdiagnosis of squamous cell carcinoma in situ as seborrheic keratosis. A prospective study. J Dermatol Surg Oncol. 1993;19:413–6.
13. Vielhauer V, Herzinger T, Korting HC. The sign of Leser-Trélat: a paraneoplastic cutaneous syndrome that facilitates early diagnosis of occult cancer. Eur J Med Res. 2000;5:512–6.
14. Heaphy MR Jr, Millns JL, Schroeter AL. The sign of Leser-Trélat in a case of adenocarcinoma of the lung. J Am Acad Dermatol. 2000;43:386–90.
15. Grob JJ, Rava MC, Gouvernet J, et al. The relation between seborrheic keratoses and malignant solid tumours. A case-control study. Acta Derm Venereol. 1991;71:166–9.
16. Yeh J, Munn S, Plunkett T, et al. Coexistence of acanthosis nigricans and the sign of Leser-Trélat in a patient with gastric adenocarcinoma: a case report and literature review. J Am Acad Dermatol. 2000;42:357–62.
17. Schwartz R. Sign of Leser-Trélat. J Am Acad Dermatol. 1996;35:88–95.
18. Schwengle L, Rampen F. Eruptive seborrheic keratoses associated with erythrodermic pityriasis rubra pilaris: possible role of retinoid therapy. Acta Derm Venereol. 1988;68:443–5.
19. Garcia R, Bishop M. The rapid onset of seborrheic keratosis of the breast during pregnancy. J Assoc Mil Dermatol. 1977;3:13–14.
20. Lindelof B, Sigurgeirsson B, Melander S. Seborrheic keratoses and cancer. J Am Acad Dermatol. 1992;26:947–50.
21. Blessing K, Evans AT, al-Nafussi A. Verrucous naevoid and keratotic malignant melanoma: a clinico-pathological study of 20 cases. Histopathology. 1993;23:453–8.
22. Mishima Y, Pinkus H. Benign mixed tumor of melanocytes and malpighian cells. Arch Dermatol. 1960;81:539–50.
23. Simón P, Requena L, Sánchez Yus E. How rare is melanoacanthoma? Arch Dermatol. 1991;127:583–4.
24. Tomich C, Zunt S. Melanoacanthosis (melanoacanthoma) of the oral mucosa. J Dermatol Surg Oncol. 1990;16:231–6.
25. Li J, Ackerman AB. "Seborrheic keratoses" that contain human papillomavirus are condylomata acuminata. Am J Dermatopathol. 1994;16:398–405.
26. Schueller W. Acrokeratosis verruciformis of Hopf. Arch Dermatol. 1972;106:81–3.
27. Berger TG, Graham JH, Goette DK. Lichenoid benign keratosis. J Am Acad Dermatol. 1984;11:635–8.
28. Prieto VG, Casal M, McNutt NS. Lichen planus-like keratosis: a clinical and histologic reexamination. Am J Surg Pathol. 1993;259–63.
29. Morgan MB, Stevens GL, Switlyk S. Benign lichenoid keratosis. A clinical and pathologic reappraisal of 1040 cases. Am J Dermatopathol. 2005;27:387–92.
30. Grimes P, Arora S, Minus H, Kenney J. Dermatosis papulosa nigra. Cutis. 1983;32:385–6, 392.
31. Shall L, Marks R. Stucco keratoses. A clinico-pathological study. Acta Derm Venereol. 1991;71:258–61.
32. Stockfleth E, Rowert J, Arndt R, et al. Detection of human papillomavirus and response to topical 5% imiquimod in a case of stucco keratosis. Br J Dermatol. 2000;143:846–50.
33. Astori G, Lavergne D, Benton C, et al. Human papillomaviruses are commonly found in normal skin of immunocompetent hosts. J Invest Dermatol. 1998;110:752–5.
34. Dover JS, Phillips TJ, Burns DA. Disseminated superficial actinic porokeratosis: coexistence with other porokeratotic variants. Arch Dermatol. 1986;122:887–9.
35. Lucker GP, Steiflen PM. The coexistence of linear and giant porokeratosis associated with Bowen's disease. Dermatology. 1994;189:78–80.
36. Guillot P. Porokeratose de Mibelli lineaire chez des jumelles monozygotes. Ann Dermatol Venereol. 1991;118:519–24.
37. Commens CA, Shumack SP. Linear porokeratosis in two families with disseminated superficial actinic porokeratosis. Pediatr Dermatol. 1987;4:209–14.
38. Wu LQ, Yang YF, Zheng D, et al. Confirmation and refinement of a genetic locus for disseminated superficial actinic porokeratosis (DSAP1) at 12q23.2-24.1. Br J Dermatol. 2004;150:999–1004.
39. Xia K, Deng H, Xia JH, et al. A novel locus (DSAP2) for disseminated superficial actinic porokeratosis maps to chromosome 15q25.1-26.1. Br J Dermatol. 2002;147:650–4.
40. Liu P, Zhang S, Yao Q, et al. Identification of a genetic locus for autosomal dominant disseminated superficial actinic porokeratosis on chromosome 1p31.3-p31.1. Hum Genet. 2008;123:507–13.
41. Zhang ZH, Niu ZM, Yuan WT, et al. A mutation in *SART3* gene in Chinese pedigree with disseminated superficial actinic porokeratosis. Br J Dermatol. 2005;52:658–63.
42. Zhang Z, Niu Z, Yuan W, et al. Fine mapping and identification of a candidate gene *SSH1* in disseminated superficial actinic porokeratosis. Hum Mutat. 2004;24:438.
43. Zhang ZH, Huang W, Niu ZM, et al. Two closely linked variations in actin cytoskeleton pathway in a Chinese pedigree with disseminated superficial actinic porokeratosis. J Am Acad Dermatol. 2005;52:972–6.
44. Otsuka F, Chi HI, Shima A. Cytological demonstration of abnormal DNA ploidy in the epidermis of porokeratosis. Arch Dermatol Res. 1988;230:61–3.
45. Cockerell CJ. Induction of disseminated superficial actinic porokeratosis by phototherapy for psoriasis. J Am Acad Dermatol. 1991;24:301–2.
46. Kanitakis J. Disseminated superficial porokeratosis in a patient with AIDS. Br J Dermatol. 1994;131:284–9.
47. Fields LL. Rapid development of disseminated superficial porokeratosis after transplant induction therapy. Bone Marrow Transplant. 1995;15:993–5.
48. Raychaudhuri SP, Smoller BR. Porokeratosis in immunosuppressed and nonimmunosuppressed patients. Int J Dermatol. 1992;31:781–2.
49. Shumack SP, Commens CA. Disseminated superficial actinic porokeratosis: a clinical study. J Am Acad Dermatol. 1989;20:1015–22.
50. McDonald SG, Peterka ES. Porokeratosis (Mibelli): treatment with topical 5-fluorouracil. J Am Acad Dermatol. 1983;8:107–10.
51. Rahbari H, Cordero A, Mehregan A. Punctate porokeratosis. A clinical variant of porokeratosis of Mibelli. J Cutan Pathol. 1977;4:338–41.
52. Sasson M, Krain A. Porokeratosis and cutaneous malignancy: a review. Dermatol Surg. 1996;22:339–42.
53. Tallon B, Blumental G, Bhawan J. Porokeratosis ptychotropica: a lesser known variant. Clin Exp Dermatol. 2009;34:e895–7.
54. Helfman RJ, Poulos EG. Reticulated porokeratosis: a unique variant of porokeratosis. Arch Dermatol. 1985;121:1542–3.
55. de Almeida HL Jr, Guarenti MIM, de Castro LAS, Rocha NM. Follicular involvement in porokeratosis. J Eur Acad Dermatol Venereol. 2007;21:109–11.
56. Mendoza-Londono R, Lammer E, Watson R, et al. Characterization of a new syndrome that associates craniosynostosis, delayed fontanel closure, parietal foramina, imperforate anus, and skin eruption: CDAGS. Am J Hum Genet. 2005;77:161–8.
57. Rabbin PE, Baldwin HE. Treatment of porokeratosis of Mibelli with CO_2 laser vaporization versus surgical excision with split-thickness skin graft: a comparison. J Dermatol Surg Oncol. 1993;19:199–202.
58. Spencer JM, Katz BE. Successful treatment of porokeratosis of Mibelli with diamond fraise abrasion. Arch Dermatol. 1992;128:1187–8.
59. Goldman GD, Milstone LM. Generalized linear porokeratosis treated with etretinate. Arch Dermatol. 1995;131:496–7.
60. Bean S. Hyperkeratosis lenticularis perstans: a clinical, histopathologic, and genetic study. Arch Dermatol. 1969;99:705–9.
61. Miranda-Romero A, Sanchez Sambucety P, Bajo del Pozo C, et al. Unilateral hyperkeratosis lenticularis perstans (Flegel's disease). J Am Acad Dermatol. 1998;39:655–7.
62. Jang K, Choi J, Sung K, et al. Hyperkeratosis lenticularis perstans (Flegel's disease): histologic, immunohistochemical, and ultrastructural features in a case. Am J Dermatopathol. 1999;21:395–8.
63. Pearson LH, Smith JG, Chalker DK. Hyperkeratosis lenticularis perstans (Flegel's disease): case report and literature review. J Am Acad Dermatol. 1987;16:190–5.
64. Ando K, Hattori H, Yamauchi Y. Histopathological differences between early and old lesions of hyperkeratosis lenticularis perstans (Flegel's disease). Am J Dermatopathol. 2006;28:122–6.
65. Langer K, Zonzits E, Konrad K. Hyperkeratosis lenticularis perstans (Flegel's disease). J Am Acad Dermatol. 1992;27:812–6.
66. Korkut T, Tan NB, Oztan Y. Giant cutaneous horn: a patient report. Ann Plast Surg. 1997;39:654–5.
67. Balus L, Cainelli T, Cristiani R, et al. Multiple familial clear cell acanthoma. Ann Dermatol Venereol. 1984;111:665–6.
68. Hashimoto T, Inamoto N, Nakamura K, et al. Involucrin expression in skin appendage tumours. Br J Dermatol. 1987;117:325–32.
69. Akiyama M, Hayakawa K, Watanabe Y, et al. Lectin-binding sites in clear cell acanthoma. J Cutan Pathol. 1990;17:197–201.

70. Kwittken J. Clear cell acanthoma: a metabolic variant of seborrheic keratosis. Mt Sinai J Med. 1980;47:49–51.
71. Finch TM, Tan CY. Clear cell acanthoma developing on a psoriatic plaque: further evidence of an inflammatory aetiology? Br J Dermatol. 2000;142:842–4.
72. Degos R, Civatte J. Clear-cell acanthoma. Experience of 8 years. Br J Dermatol. 1970;83:248–54.
73. Fine R, Chernosky M. Clinical recognition of clear-cell acanthoma (Degos'). Arch Dermatol. 1969;100: 559–63.
74. Innocenzi D, Barduagni F, Cerio R, et al. Disseminated eruptive clear cell acanthoma – a case report with review of the literature. Clin Exp Dermatol. 1994;19:249–53.
75. Naeyaert J, de Bersaques J, Geerts M, et al. Multiple clear cell acanthomas. A clinical, histological, and ultrastructural report. Arch Dermatol. 1987;123: 1670–3.
76. Yamasaki K, Hatamochi A, Shinkai H, et al. Clear cell acanthoma developing in epidermal nevus. J Dermatol. 1997;24:601–5.
77. Tanay A, Mehregan A. Warty dyskeratoma. Dermatologica. 1969;138:155–64.
78. Leonardi C, Zhu W, Kinsey W, et al. Epidermolytic acanthoma does not contain human papillomavirus DNA. J Cutan Pathol. 1991;18:103–5.
79. Metzler G, Sonnichsen K. Disseminated epidermolytic acanthoma. Hautarzt. 1997;48:740–2.
80. Banky JP, Turner RJ, Hollowood K. Multiple scrotal epidermolytic acanthomas; secondary to trauma? Clin Exp Dermatol. 2004;29:489–91.
81. Hirone T, Fukushiro R. Disseminated epidermolytic acanthoma. Acta Derm Venereol. 1973;53:393–402.
82. Knipper JE, Hud JA, Cockerell CJ. Disseminated epidermolytic acanthoma. Am J Dermatopathol. 1993;15:70–2.
83. Sanchez Yus E, de Diego V, Urrutia S. Large cell acanthoma. A cytologic variant of Bowen's disease? Am J Dermatopathol. 1988;10:197–208.
84. Rabinowitz A, Inghirami G. Large-cell acanthoma. A distinctive keratosis. Am J Dermatopathol. 1992;14:136–8.
85. Pinkus H. Epidermal mosaic in benign and precancerous neoplasia (with special reference to large-cell acanthoma). Acta Dermatol (Kyoto). 1970;65:75–81.
86. Sanchez Yus E, del Rio E, Requena L. Large-cell acanthoma is a distinctive condition. Am J Dermatopathol. 1992;14:140–8.
87. Roewert H, Ackerman A. Large-cell acanthoma is a solar lentigo. Am J Dermatopathol. 1992;14:122–32.
88. Chevez P, Patrinely J, Font R. Large-cell acanthoma of the eyelid. Report of two cases. Arch Ophthalmol. 1991;109:1433–4.
89. Alsaleh Q, Nanda A, Hassab-el-Naby H, et al. Familial inflammatory linear verrucous epidermal nevus (ILVEN). Int J Dermatol. 1994;33:52–4.
90. Goldman K, Don P. Adult onset of inflammatory linear verrucous epidermal nevus in a mother and her daughter. Dermatology. 1994;189:170–2.
91. Hafner C, van Oers JMM, Vogt T, et al. Mosaicism of activating *FGFR3* mutations in human skin causes epidermal nevi. J Clin Invest. 2006;116:2201–6.
91a. Bourdeaut F, Hérault A, Gentien D, et al. Mosaicism for oncogenic G12D KRAS mutation associated with epidermal nevus, polycystic kidneys and rhabdomyosarcoma. J Med Genet. 2010;47:859–62.
92. Rogers M, McCrossin I, Commens C. Epidermal nevi and the epidermal nevus syndrome. A review of 131 cases. J Am Acad Dermatol. 1989;20:476–88.
93. Adams B, Mutasim D. Adult onset verrucous epidermal nevus. J Am Acad Dermatol. 1999;41:824–6.
94. Loff H, Bardenstein D, Levine M. Systematized epidermal nevi: case report and review of clinical manifestations. Ophthal Plast Reconstr Surg. 1994;10:262–6.
95. Su W. Histopathologic varieties of epidermal nevus. A study of 160 cases. Am J Dermatopathol. 1982;4: 161–70.
96. Submoke S, Piamphongsant T. Clinico-histopathological study of epidermal naevi. Australas J Dermatol. 1983;24:130–6.
97. Solomon L, Esterly N. Epidermal and other congenital organoid nevi. Curr Probl Pediatr. 1975;6:1–56.
98. Willis D, Rapini RP, Chernosky ME. Linear basal cell nevus. Cutis. 1990;46:493–4.
99. Levin A, Amazon K, Rywlin A. A squamous cell carcinoma that developed in an epidermal nevus. Report of a case and a review of the literature. Am J Dermatopathol. 1984;6:51–5.
100. Braunstein B, Mackel S, Cooper P. Keratoacanthoma arising in a linear epidermal nevus. Arch Dermatol. 1982;118:362–3.
101. Dellon AL, Luethke R, Wong L, Barnett N. Epidermal nevus: surgical treatment by partial-thickness skin excision. Ann Plast Surg. 1992;28:292–6.
102. Altman J, Mehregan A. Inflammatory linear verrucose epidermal nevus. Arch Dermatol. 1971;104:385–9.
103. Welch M, Smith K, Skelton H, et al. Immunohistochemical features in inflammatory linear verrucous epidermal nevi suggest a distinctive pattern of clonal dysregulation of growth. Military Medical Consortium for the Advancement of Retroviral Research. J Am Acad Dermatol. 1993;29:242–8.
104. Ito M, Shimizu N, Fujiwara H, et al. Histopathogenesis of inflammatory linear verrucose epidermal naevus: histochemistry, immunohistochemistry and ultrastructure. Arch Dermatol Res. 1991;283:491–9.
105. Kawaguchi H, Takeuchi M, Ono H, et al. Adult onset of inflammatory linear verrucous epidermal nevus. J Dermatol. 1999;26:599–602.
106. Morag C, Metzker A. Inflammatory linear verrucous epidermal nevus: report of seven new cases and review of the literature. Pediatr Dermatol. 1985;3:15–8.
107. Al-Enezi S, Huber A, Krafchik B, et al. Inflammatory linear verrucous epidermal nevus and arthritis: a new association. J Pediatr. 2001;138:602–4.
108. Happle R. How many epidermal nevus syndromes exist? A clinicogenetic classification. J Am Acad Dermatol. 1991;25:550–6.
109. Altster T. Inflammatory linear verrucous epidermal nevus: successful treatment with the 585 nm flashlamp-pumped pulsed dye laser. J Am Acad Dermatol. 1994;31:513–4.
110. Kim J, Chang M, Shwayder T. Topical tretinoin and 5-fluorouracil in the treatment of linear verrucous epidermal nevus. J Am Acad Dermatol. 2000;43: 129–32.
111. Gatti S, Carrozzo AM, Orlandi A, et al. Treatment of inflammatory linear verrucous epidermal naevus with calcipotriol. Br J Dermatol. 1995;132:837–9.
112. Mitsuhashi Y, Katagiri Y, Kondo S. Treatment of inflammatory linear verrucous epidermal naevus with topical vitamin D3. Br J Dermatol. 1997;136: 134–5.
113. Patrizi A, Neri I, Fiorentini C, Marzaduri S. Nevus comedonicus syndrome: a new pediatric case. Pediatr Dermatol. 1998;15:304–6.
114. Munro CS, Wilkie AO. Epidermal mosaicism producing localised acne: somatic mutation in *FGFR2*. Lancet. 1998;352:704–5.
115. Inoue Y, Miyamoto Y, Ono T. Two cases of nevus comedonicus: successful treatment of keratin plugs with a pore strip. J Am Acad Dermatol. 2000;43: 927–9.
116. Henning JP, de Wit RFE. Familial occurrence of confluent and reticulated papillomatosis. Arch Dermatol. 1981;117:809–10.
117. Buynzeel-Koomen CAFM, de Wit RFE. Confluent and reticulated papillomatosis successfully treated with aromatic etretinate. Arch Dermatol. 1984;120: 1236–7.
118. Nordby AC, Mitchell AJ. Confluent and reticulated papillomatosis responsive to selenium sulfide. Int J Dermatol. 1986;25:194–9.
119. Lee MP, Stiller MJ, McClain SA, et al. Confluent and reticulated papillomatosis: response to high-dose oral isotretinoin therapy and reassessment of epidemiologic data. J Am Acad Dermatol. 1994;31:327–31.
120. Chang SN, Kim SC, Lee SH, Lee WS. Minocycline treatment for confluent and reticulated papillomatosis. Cutis. 1996;57:454–7.
121. Kuo T-T, Chan H-L, Hsueh S. Clear cell papulosis of the skin. Am J Surg Pathol. 1987;11:827–34.
122. Yu Y, Sukhatme S, Loo DS. Clear cell papulosis: a connection of clear cells to Toker cells or Paget disease. Arch Dermatol. 2009;145:1066–8.
123. Tschen JA, McGavran MH, Kettler AH. Pagetoid dyskeratosis: a selective keratinocytic response. J Am Acad Dermatol. 1988;19:891–4.

This page intentionally left blank

110 Cysts

Mary S Stone

Chapter Contents

Cysts with a lining of stratified squamous epithelium *1817*
Cysts lined with non-stratified squamous epithelium..... *1823*
Cysts without an epithelial lining *1826*

Key features

- Multiple types of cutaneous cysts have been described
- Cutaneous cysts present as circumscribed dermal or subcutaneous papules or nodules
- Histologic features of the cyst lining and the anatomic location determine the type of cyst
- Cysts may be lined by stratified squamous epithelium, non-stratified squamous epithelium, or no epithelium at all
- Treatment of cysts, when indicated, is primarily surgical

INTRODUCTION

Cysts are common cutaneous lesions. Patients with cysts may present to clinicians because of medical or cosmetic concerns, or due to discomfort from mechanical irritation or inflammation of the cyst. The definitive diagnosis of a cyst requires histologic examination, as many other dermal and subcutaneous tumors can form cyst-like nodules. Cysts can be classified by anatomic location (as they may occur in virtually any organ of the body), by embryologic derivation, or by histologic features. As the histologic features determine the definitive diagnosis, that scheme will be used in this chapter, which is limited to cutaneous cysts.

True cysts have an epithelial lining that may be composed of stratified squamous epithelium or other forms of epithelia. Some "cysts" have no epithelial lining at all. Cutaneous cysts can be divided into three main categories based on the presence or absence and composition of the cyst wall (Table 110.1; Fig. 110.1). Many non-dermatologists refer to epidermoid and pilar cysts as "sebaceous cysts", believing erroneously that the hydrated white keratinized contents of many epithelial-lined cysts is of sebaceous origin. The only true sebaceous cyst is the steatocystoma. Because of the confusion, the term "sebaceous cyst" is best avoided.

CYSTS WITH A LINING OF STRATIFIED SQUAMOUS EPITHELIUM

Epidermoid Cyst

Synonyms: ■ Epidermoid inclusion cyst ■ Infundibular cyst ■ Epidermal cyst ■ Epidermal inclusion cyst

Epidermoid cysts are the most common cutaneous cysts. They can occur anywhere on the skin, but are most common on the face and upper trunk. These lesions are well-demarcated, skin-colored to yellowish dermal nodules, and they may have a clinically visible punctum representing the follicle from which the cyst is derived (Fig. 110.2). These cysts range from a few millimeters to several centimeters in diameter. Tiny superficial epidermoid cysts are known as milia (see below). Epidermoid cysts derive from the follicular infundibulum (hence the synonym infundibular cysts; Fig. 110.3). They may be primary, or they may arise from disrupted follicular structures or traumatically implanted epithelium (hence the synonym epidermal "inclusion" cyst).

As follicular disruption is important in the pathogenesis of many epidermoid cysts, multiple epidermoid cysts may occur in individuals with a history of significant acne vulgaris. Multiple cysts may also occur in the setting of Gardner syndrome (familial adenomatous polyposis) and in nevoid basal cell carcinoma (BCC) syndrome[1,2]. Multiple scrotal cysts (Fig. 110.4) may lead to scrotal calcinosis via dystrophic calcification[3].

Non-inflamed epidermoid cysts are usually asymptomatic, but, with pressure, cyst contents may be expressed that may have an objectionable odor. Rupture of the cyst wall can result in an intensely painful inflammatory reaction, and this is a common reason for presentation to a physician (Fig. 110.5). Development of a BCC or squamous cell carcinoma (SCC) within an epidermoid cyst is a very rare event[4].

THE THREE MAIN CATEGORIES OF CUTANEOUS CYST

Category	Type	Most common location
Stratified squamous epithelium	Epidermoid cyst	Face; upper trunk
	Milium	Face
	Trichilemmal cyst	Scalp
	Proliferating trichilemmal cyst	Scalp (favors the elderly)
	Proliferating epidermoid cyst	Pelvic (anogenital)
	Vellus hair cyst	Trunk (chest)
	Steatocystoma	Trunk; axillae; groin
	Cutaneous keratocyst	No characteristic location
	Pigmented follicular cyst	Face (men)
	Dermoid cyst	Face along embryonic fusion planes, e.g. lateral eyebrow (infants)
	Verrucous cyst	Face, upper trunk (HPV-infected epidermoid cysts)
	Ear pit cyst	Preauricular
	Pilonidal cyst	Upper gluteal cleft; sacrococcygeal area
Non-stratified squamous epithelium	Hidrocystoma	
	• Eccrine	Face (lower eyelid, cheek)
	• Apocrine	Face (eyelid margin)
	Bronchogenic cyst	Suprasternal notch (infants)
	Thyroglossal duct cyst	Midline anterior neck
	Branchial cleft cyst	Lateral neck; preauricular; mandibular (teenagers, young adults)
	Cutaneous ciliated cyst	Lower extremities (young women)
	Ciliated cyst of the vulva	Labia majora
	Median raphe cyst	Ventral glans of penis
	Omphalomesenteric duct cyst	Umbilical; periumbilical
Absence of epithelium	Mucocele	Oral mucosa (lower labial)
	Digital mucous cyst	Dorsal aspect of distal phalanx of finger (occasionally toe)
	Ganglion	Wrist
	Pseudocyst of the auricle	Scaphoid fossa of the ear (adult men)
	Cutaneous metaplastic synovial cyst	Sites of surgical trauma

Table 110.1 The three main categories of cutaneous cyst.

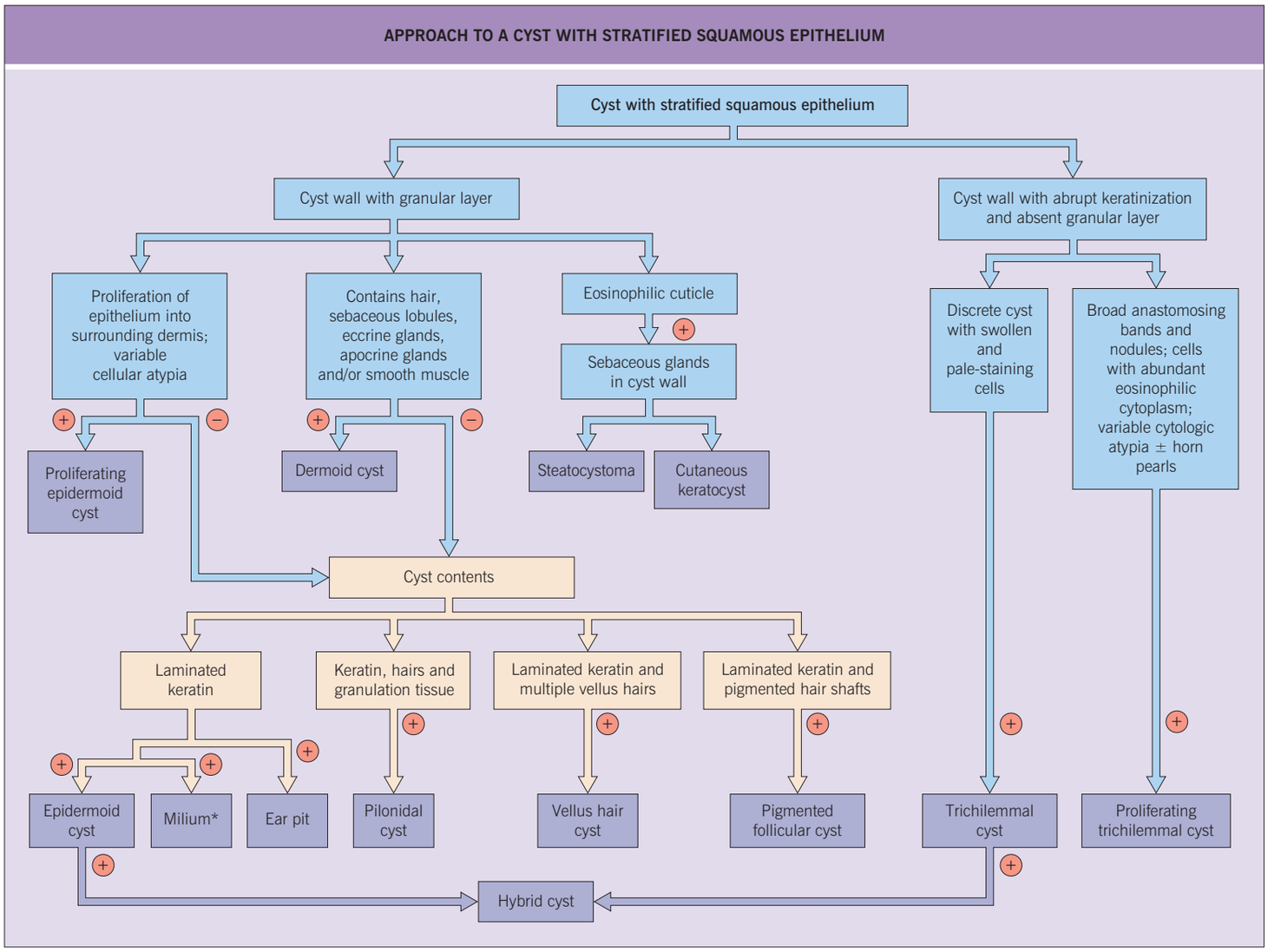


Fig. 110.1 Approach to a cyst with stratified squamous epithelium. *Diameter 1–2 mm.

Fig. 110.2 Epidermoid cyst. Typical clinical appearance of an epidermoid cyst with a yellowish hue. Two pores are present in this example.

Pathology

Histologic examination shows a cystic cavity filled with laminated keratin lined by a stratified squamous epithelium including a granular layer (Fig. 110.6). A surrounding inflammatory response with both acute and chronic granulomatous inflammation may be seen as evidence of prior rupture. In individuals with Gardner syndrome, some cysts show, as a characteristic feature, columns of pilomatricoma-like shadow cells projecting into the cyst cavity[1]. Infection of the cyst's epithelium with human papillomavirus can lead to irregular acanthosis with a verrucous appearance to the cyst wall ("verrucous cyst").

Treatment

If treatment is desired, excision is curative. Removal may be accomplished by simple excision, or incision and expression of the cyst contents and wall through the surgical defect. If the entire cyst wall is not removed, the cyst may recur. Inflamed epidermoid cysts may require incision and drainage, and, occasionally, antibiotic therapy. Intralesional triamcinolone may be helpful in speeding the resolution of the inflammation.

Dilated Pore of Winer and Pilar Sheath Acanthoma

Dilated pore of Winer and pilar sheath acanthoma are very similar lesions that present primarily on the face of adults (the upper lip in the case of pilar sheath acanthoma). While both have an obvious central keratin-filled opening ("pore"), the pilar sheath acanthoma has a more papular component. A large-pore BCC or large-pore trichoblastoma may have a similar appearance.

Pathology

Both lesions are cystic invaginations that are connected to the surface (like an open comedone) and have a stratified squamous epithelial lining. The wall is acanthotic with bulbous proliferations pushing into the surrounding dermis. Pilar sheath acanthoma has a more proliferative wall and a wider opening to the epidermis.

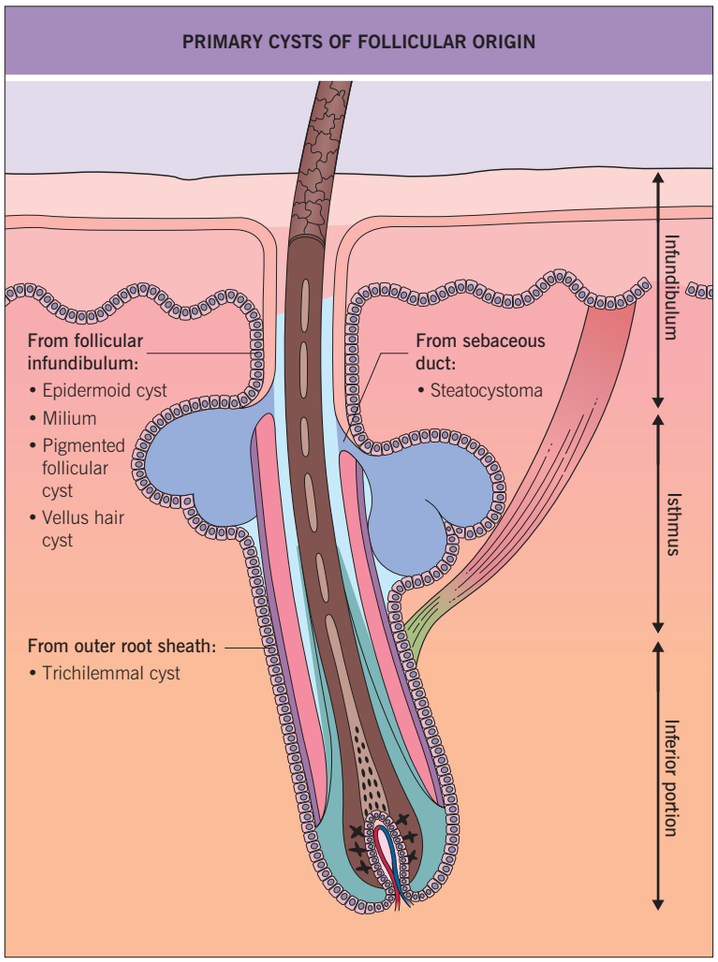


Fig. 110.3 Primary cysts of follicular origin. Anatomic origin of cysts derived from the pilosebaceous unit. *Adapted from Requena L, Sanchez Yus E. Follicular hybrid cysts. An expanded spectrum. Am J Dermatopathol. 1991;13:228–33.*

Fig. 110.4 Multiple scrotal cysts. They may be associated with dystrophic calcification. *Courtesy, Joyce Rico, MD.*

Treatment

If treatment is desired, excision is curative.

Milium

Milia are small epidermoid cysts and are quite common, occurring in individuals of all ages. Milia present as 1–2 mm white to yellow subepidermal papules (Fig. 110.7). Between 40% and 50% of infants will have milia, most commonly on the face. Most milia in newborns will resolve spontaneously during the first 4 weeks of life. Milia in newborns may also occur on the hard palate (Bohn's nodules) or on the gum margins (Epstein's pearls). These also resolve spontaneously. Milia may occur as a primary phenomenon, especially on the face, or as secondary phenomena following blistering processes or superficial ulceration from trauma or cosmetic procedures. Milia may also occur in areas of topical corticosteroid-induced atrophy[5].

Milia en plaque is characterized by multiple milia within an erythematous edematous plaque. Milia en plaque most often occurs in the postauricular area, but may also occur on or anterior to the ear. Persistent widespread milia in an infant may be a sign of hereditary trichodysplasia (Marie–Unna hypotrichosis) or oral–facial–digital syndrome type 1, an X-linked disorder that is lethal in males, in which milia are

Fig. 110.5 Inflamed epidermoid cyst. Such painful inflammatory reactions to cyst rupture are a frequent cause for presentation to a physician.

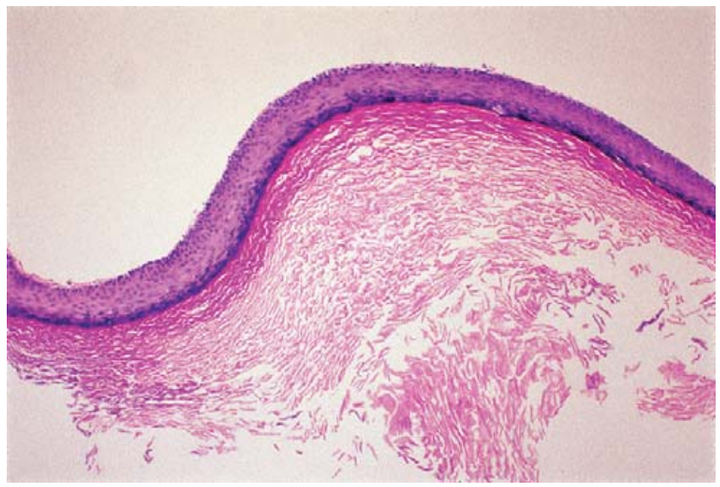


Fig. 110.6 Histology of an epidermoid cyst. The cyst wall shows epidermal keratinization including a granular layer. Laminated keratin cyst contents are seen.

Fig. 110.7 Milia. Tiny (1–2 mm), white, dome-shaped papules on the face.

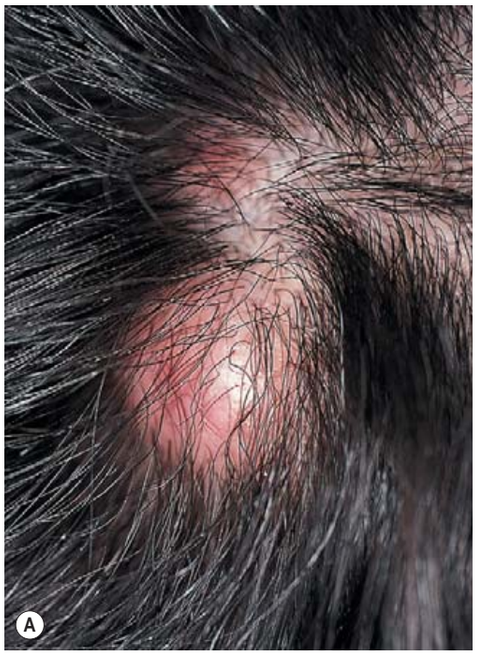


Fig. 110.8 Trichilemmal cyst versus proliferating trichilemmal cyst. A A non-inflamed trichilemmal cyst is skin-colored, mobile and has a smooth surface. **B** A proliferating trichilemmal cyst presenting as an enlarging cystic nodule in an elderly woman. Both types of cyst favor the scalp.

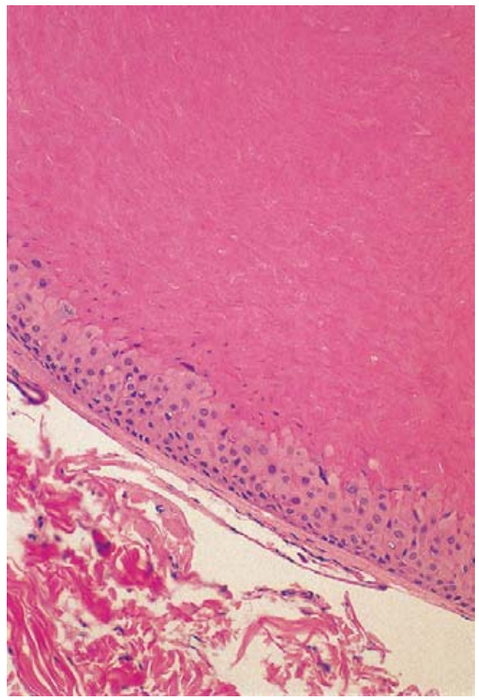


Fig. 110.9 Histology of a trichilemmal cyst. The cyst wall shows swollen keratinocytes with abrupt keratinization without formation of a granular layer. Homogeneous keratin fills the cyst.

associated with facial and skull malformations, cleft lip and palate, a lobulated tongue, mental retardation and polycystic kidneys; the associated alopecia follows the lines of Blaschko on the scalp. Milia are also seen in the setting of a number of other syndromes, including the BCC-associated syndromes, Rombo syndrome and Bazex syndrome.

Pathology

Histologic features are those of a small epidermoid cyst with a stratified squamous epithelial lining including a granular layer and laminated keratin cyst contents.

Treatment

Milia may be removed by incising the epidermis over the milium with a needle, scalpel or lancet and expressing the milium. The latter can be aided by the use of a comedo extractor. Laser ablation and electrodesiccation are also reported options. For multiple facial milia, topical retinoid therapy may be helpful in reducing the number of milia and aiding in the ease of removal.

Trichilemmal Cyst

Synonyms: ■ Pilar cyst ■ Wen ■ Isthmus–catagen cyst

Trichilemmal cysts are clinically indistinguishable from epidermoid cysts, but they are fourfold to fivefold less common. Ninety percent of trichilemmal cysts are located on the scalp (Fig. 110.8A). They may be solitary, but frequently they are multiple. Trichilemmal cysts may be inherited as an autosomal dominant trait.

Pathology

Trichilemmal cyst walls show keratinization analogous to that of the outer root sheath of the hair follicle at the isthmus *and* the sac surrounding catagen and telogen hairs (hence the synonym isthmus–catagen cyst). Trichilemmal cysts are lined by stratified squamous epithelial cells without visible intracellular bridges that become swollen and pale close to the cystic cavity and show abrupt keratinization without an intervening granular layer (Fig. 110.9). The cyst contents consist of homogeneous eosinophilic material that frequently shows foci of calcification. A foreign body giant cell response may surround the cyst if prior wall rupture has occurred.

Treatment

Treatment is by excision. Trichilemmal cysts typically "deliver" themselves through an incision without rupture more easily than do epidermoid cysts, and, therefore, the distinction between a trichilemmal cyst and an epidermoid cyst can often be correctly made at the time of excision.

Proliferating Trichilemmal Cyst

Synonyms: ■ Proliferating trichilemmal tumor ■ Proliferating pilar tumor ■ Proliferating follicular cystic neoplasm

A proliferating trichilemmal cyst classically occurs as a slow-growing nodule on the scalp in elderly women (see Fig. 110.8B). In fact, 90% occur on the scalp, and 84% occur in women with a median age of 63 years[6]. Proliferating trichilemmal cysts vary in size from a few millimeters to up to 25 cm in diameter. These tumors generally behave in a benign fashion, although, on occasion, aggressive local growth with

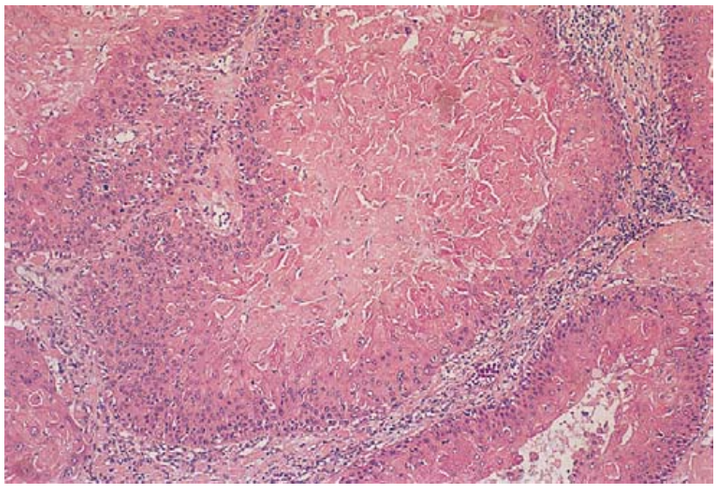


Fig. 110.10 Histology of a proliferating trichilemmal cyst. Irregular bands and nodules of squamous epithelium show central areas of abrupt keratinization.

Fig. 110.11 Eruptive vellus hair cysts. Pigmented small papules on the thigh of a young woman.

recurrences and metastases has been observed[6]. Extremely rarely, spindle cell carcinomas may develop within a proliferating trichilemmal cyst[7,8]. Distant metastases are rare in proliferating trichilemmal cysts, but over 30 such cases have been reported[9]. Whether a proliferating trichilemmal cyst represents a variant of SCC is an area of controversy[10].

Pathology

The histologic features of a proliferating trichilemmal cyst consist of broad anastomosing bands and nodules of squamous epithelium. The epithelium shows a proliferation of cells with abundant eosinophilic cytoplasm showing abrupt keratinization forming dense homogeneous keratin that fills cystic spaces. There may be areas of epidermoid keratinization with formation of horn pearls (Fig. 110.10) as well as areas of foreign body giant cell reaction. One-quarter of cases show an epidermal connection[6]. Cytologic atypia may vary markedly. Most tumors show well-circumscribed, pushing borders surrounded by compressed collagen. The lack of infiltrative growth into the surrounding stroma and abrupt trichilemmal keratinization helps in differentiation from SCC. Areas of marked atypia and infiltrative borders are features associated with a potential for aggressive behavior[11].

Treatment

Treatment is by complete surgical excision.

Proliferating Epidermoid Cyst

Synonym: ■ Proliferating epithelial cyst

Proliferating epidermoid cysts were first described in detail in 1995[6]. Unlike proliferating trichilemmal cysts, proliferating epidermoid cysts are observed more commonly in men and only 20% occur on the scalp. They range in size from 0.4 to 15 cm. In the 30 patients reported by Sau et al.[6] for whom follow-up was available, 20% of the cysts recurred, some multiple times, and one patient died of intractable local disease. None of the patients developed metastatic disease.

Pathology

Histologically, almost half of cases show an epidermal connection, usually with a narrow opening or connection to a dilated follicle. Most tumors show areas of typical epidermoid cyst wall. In addition, areas of squamous proliferation with squamous eddy formation are seen, with formation of a granular layer and production of loose laminated keratin. The epithelium tends to proliferate peripherally into the surrounding dermis, rather than centrally as seen in proliferating trichilemmal cysts. Degrees of cellularity and atypia are variable, and frank carcinomatous change with an infiltrative growth pattern may be seen.

Treatment

Treatment is by complete surgical excision.

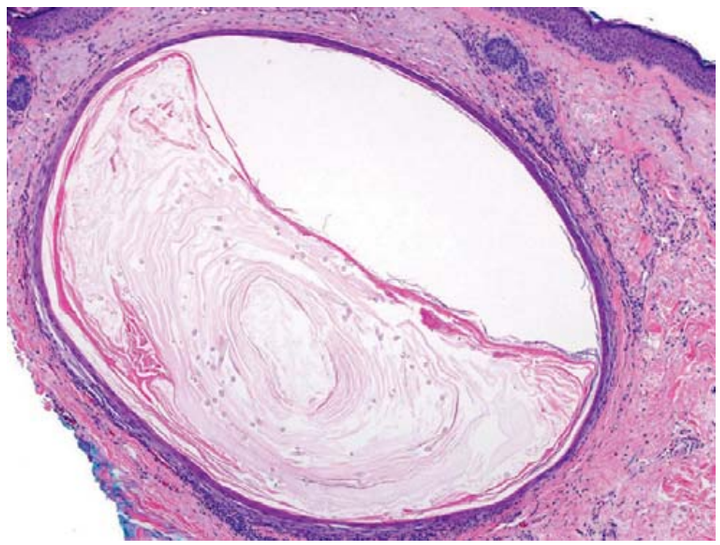


Fig. 110.12 Histology of a vellus hair cyst. A small cyst shows epidermoid keratinization of the cyst wall and numerous vellus hairs in the lumen.

Vellus Hair Cysts

Vellus hair cysts, described by Esterly, Fretzin and Pinkus in 1977[12], most commonly present as numerous, small, dome-shaped papules, ranging from skin-colored to darkly pigmented (Fig. 110.11). These cysts are most commonly located on the trunk, and they may be inherited in an autosomal dominant pattern. Multiple lesions are known as "eruptive" vellus hair cysts; occasionally, solitary cysts are seen. Although some lesions may resolve via transepidermal elimination of cyst products, most lesions persist indefinitely. Vellus hair cysts may become inflamed, but, in general, they are asymptomatic except for cosmetic concerns.

Eruptive vellus hair cysts may be seen in conjunction with steatocystoma multiplex, and both types of cysts have been reported in the setting of pachyonychia congenita (primarily type 2 [PC-2]; see Table 58.3). PC-2 can result from mutations in the genes that encode keratin 17 (*KRT17*) or keratin 6B (*KRT6B*)[13], whereas, to date, patients with inherited steatocystoma multiplex have been found to have mutations in *KRT17* (see below). Keratin 17 is expressed in the nail bed, hair follicles and sebaceous glands, but not in stratified squamous epithelium[14].

Pathology

Histologically, one sees a small cystic structure lined by stratified squamous epithelium with epidermoid keratinization. The cysts contain loose laminated keratin and numerous vellus hairs (Fig. 110.12). A follicle may be found entering the lower portion of the cyst.

Treatment

Vellus hair cysts may be treated by a number of modalities, including incision and drainage, needle evacuation, puncture followed by forceps-assisted extraction, topical retinoic or lactic acid, and laser ablation.

Steatocystoma

Steatocystomas occur as single (steatocystoma simplex) or multiple (steatocystoma multiplex) lesions. They tend to be a few millimeters to a centimeter in diameter and appear as cysts in the dermis that drain oily fluid if punctured (Fig. 110.13A,B). Steatocystomas are most numerous on the chest and in the axillae and groin. There are unusual facial and acral variants as well as a rare congenital linear form. Steatocystomas persist indefinitely, and they are usually asymptomatic except for cosmetic concerns.

Steatocystoma multiplex can be inherited as an autosomal dominant condition, and is due to mutations in the *KRT17* gene. It may occur in association with eruptive vellus hair cysts and pachyonychia congenita, primarily type 2 (see Table 58.3)[13,14]. Of note, all patients with pachyonychia congenita can develop epidermoid and pilar cysts, and there is a movement towards classifying patients based upon their *KRT* mutations, rather than clinical subtypes. For example, PC-2 is referred to as PC-6b/17.

Pathology

Biopsy specimens show a dermal cyst lined by a thin stratified squamous epithelium, without a granular layer and surmounted by a thin, irregular, corrugated eosinophilic cuticle (Fig. 110.13C). Small sebaceous lobules are found in or immediately adjacent to the cyst wall.

Treatment

Lesions can be excised or incised with removal of the cyst wall.

Cutaneous Keratocyst

Synonyms: ▪ Sebaceous duct cyst ▪ Isthmic-anagen cyst

Cutaneous keratocysts have been reported primarily in patients with the nevoid BCC syndrome. Their clinical appearance is similar to epidermoid cysts and there is no characteristic clinical location.

Pathology

These cysts have a stratified squamous epithelial wall without a granular layer and an eosinophilic cuticle, like a steatocystoma. However, no associated sebaceous lobules are seen[15].

Follicular Hybrid Cyst

Synonym: ▪ Hybrid cyst

Follicular hybrid cysts are not distinctive clinically, but rather represent a histologic variant of cysts with a stratified squamous lining in which there is transition in the cell wall between epidermoid keratinization and trichilemmal or pilomatrical keratinization[16,17]. They were originally described by Brownstein[17].

Pigmented Follicular Cyst

Pigmented follicular cysts, described by Mehregan and Medenica[18], are solitary and occur primarily on the face of men. They are often deeply pigmented and may be confused clinically with a nevus.

Histologically, these cysts have a pore-like connection to the epidermis, are lined by stratified squamous epithelium including a granular layer, and contain pigmented hair shafts. The clinical presentation, epidermal connection, and pigmented hair shafts distinguish the pigmented follicular cyst from vellus hair cysts.

Dermoid Cyst

Cutaneous dermoid cysts typically present in an infant along an embryonic fusion plane as a discrete, subcutaneous nodule. Dermoid cysts are usually 1–4 cm in diameter. The most common location is around the eyes (see Ch. 64).

Fig. 110.13 Steatocystoma multiplex. A,B Numerous cystic papules on the trunk and multiple cystic nodules on the neck. **C** Histology of steatocystoma. The cyst wall is characterized by an undulated, thin stratified epithelium lacking a stratum granulosum and lined by an eosinophilic cuticle. A search may be required to identify small sebaceous lobules in or immediately adjacent to the cyst wall (insert). *C, Courtesy, Lorenzo Cerroni, MD.*

Pathology

Histologically, dermoid cysts are lined by stratified squamous epithelium including a granular layer. They contain other normal cutaneous structures such as hair, sebaceous lobules, eccrine glands, apocrine glands, or smooth muscle.

Treatment

Treatment is by excision. However, as the differential diagnosis includes neural heterotopias, imaging studies may be appropriate prior to excision, to exclude a connection to the CNS (see Ch. 64).

Ear Pit

Synonyms: ■ Preauricular cyst ■ Congenital auricular fistula ■ Preauricular fistula

Ear pits are congenital defects, and they may present as a true cystic nodule or an invagination in the preauricular area (Fig. 110.14). During development, the ear is formed by the fusion of six tubercles: three each from the first two branchial arches. Preauricular cysts reflect defective embryologic fusion with epithelial entrapment. These defects are relatively common, occurring in approximately 0.5–1% of the normal population, and they may be transmitted in an autosomal dominant fashion[19]. Ear pits are usually unilateral and right-sided. Infection with tenderness and purulent drainage may prompt presentation to a physician.

Although ear pits are usually not associated with other significant abnormalities, they can occur in conjunction with deafness or with deafness plus renal anomalies in the branchio-otic syndrome and branchio-oto-renal dysplasia, respectively. Ear pits are also seen in a number of other congenital syndromes that are characterized by major morphologic anomalies, including Treacher Collins–Franceschetti syndrome, Goldenhar syndrome, Lowry–MacLean syndrome and cat-eye syndrome[20].

Pathology

Histologically, preauricular pits or cysts are lined by stratified squamous epithelium with a granular layer.

Treatment

If removal is desired, simple excision is curative. Although most ear pits are incidental findings, in a newborn, a physical examination to exclude one of the associated syndromes and an evaluation for hearing loss is indicated. Infected lesions may require antibiotic therapy.

Fig. 110.14 Ear pit.
Courtesy, Julie V Schaffer, MD.

Pilonidal Cyst

Synonyms: ■ Pilonidal sinus ■ Pilonidal disease ■ Barber's interdigital pilonidal sinus (when located in the interdigital spaces)

Pilonidal cysts typically present as an inflamed, painful cystic swelling in the upper gluteal cleft or sacrococcygeal area, but they have been described in many other locations. They are most common in men (at a ratio of 3–4 : 1) and in Caucasians. They occur most commonly in hirsute individuals[21]. Pilonidal cysts typically present near the end of the first decade of life and were a significant source of morbidity and hospitalization during World War II[21].

The etiology of pilonidal cysts and sinuses has been a controversial issue. Some authors have argued that they are congenital, essentially representing a dermoid cyst, whereas most authors now believe that the vast majority of lesions are acquired, representing a foreign body response to entrapped hair. A pilonidal cyst can be seen as part of the "follicular inclusion tetrad" which consists of acne conglobata, hidradenitis suppurativa, perifolliculitis capitis abscedens et suffodiens, and pilonidal cyst (see Ch. 38). Persistent exogenous hairs in the interdigital space of barbers or dog groomers may incite an encompassing epidermal proliferation, giving rise to a pilonidal cyst.

Pathology

Histologic features are those of an epidermal-lined cyst or sinus tract. Cyst cavities are lined with granulation tissue and mixed inflammation, with hair and keratin debris.

Treatment

Treatment is surgical and may include excision, marsupialization, or incision and curettage.

CYSTS LINED WITH NON-STRATIFIED SQUAMOUS EPITHELIUM

Hidrocystoma

Synonyms: ■ Cystadenoma ■ Sudoriferous cyst ■ Moll's gland cyst

Hidrocystomas typically present as translucent, skin-colored to bluish cysts on the face, although they may occur in other sites. Hidrocystomas are traditionally divided into apocrine and eccrine hidrocystomas by histologic features, and as solitary (Smith type) or multiple (Robinson type). Hidrocystomas may be associated with specific syndromes of ectodermal dysplasia, including Schöpf–Schulz–Passarge syndrome.

Apocrine hidrocystomas are usually solitary (Fig. 110.15), whereas eccrine hidrocystomas may be solitary or multiple and are occasionally quite numerous (Fig. 110.16). Eccrine hidrocystomas can enlarge with heat exposure or during the summer and regress with cooler temperatures. In general, eccrine hidrocystomas are thought to develop from cystic dilation of eccrine ducts due to retention of eccrine secretions,

Fig. 110.15 Apocrine hidrocystoma. A single, slightly bluish, translucent papule on the lower eyelid near the lateral canthus.

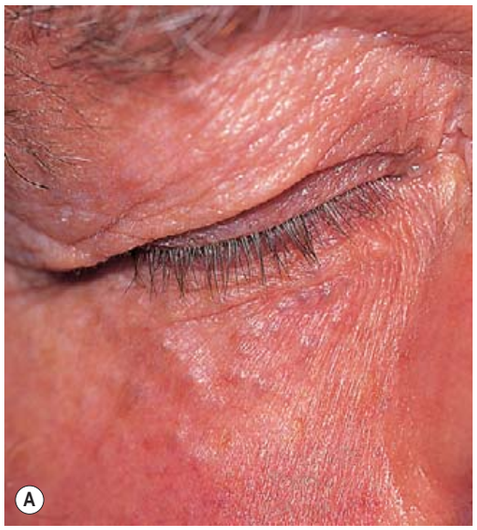


Fig. 110.16 Eccrine hidrocystomas. Numerous, tiny, translucent or bluish papules on the lower eyelid (**A**) or the cheek (**B**).

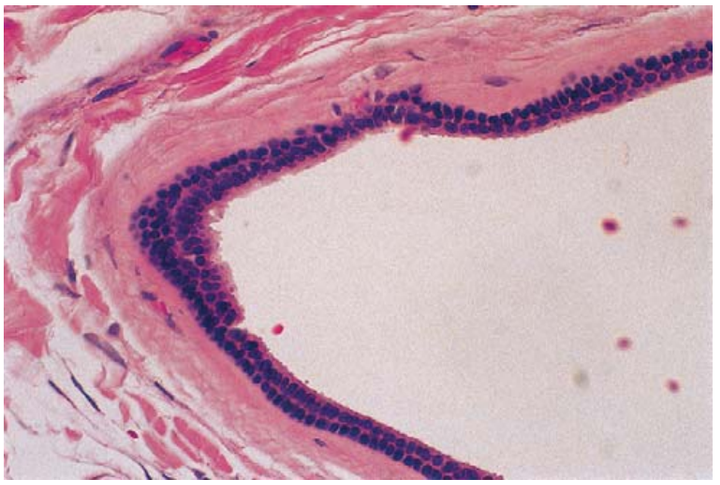


Fig. 110.17 Histology of apocrine hidrocystoma. The cyst wall shows typical apocrine decapitation secretion.

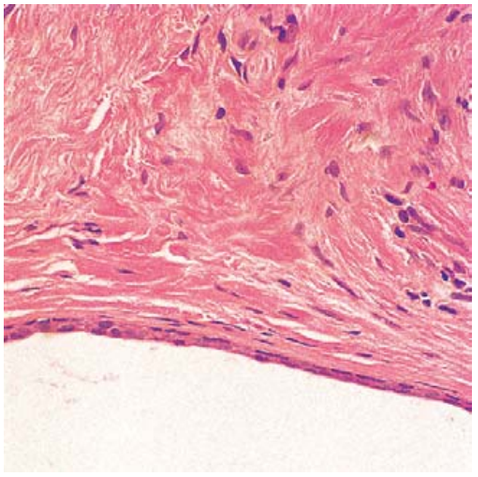


Fig. 110.18 Histology of eccrine hidrocystoma. Two layers of flattened epithelium form the cell wall.

while apocrine hidrocystomas are thought to represent adenomas of apocrine sweat gland coils[22]. Apocrine hidrocystomas are sometimes referred to as cystadenomas, although it has been recommended that this term be reserved for lesions with true papillomatous projections histologically[23]. Lesions along the lower eyelid margin are also known as Moll's gland cysts.

Pathology

Histologically, apocrine hidrocystomas are unilocular to multilocular dermal cysts lined by one to several layers of epithelial cells that show bulbous protrusions ("snouting") and luminal decapitation secretion (Fig. 110.17). Similarly lined papillary projections may extend into the cyst lumen. Histologic features of eccrine hidrocystomas are those of a uniloculate cyst containing clear fluid, lined by two layers of cuboidal to flattened epithelium (Fig. 110.18). Apocrine hidrocystomas express human milk-fat globulin antigen, while "true" eccrine hidrocystomas do not. Hidrocystomas that appear by light microscopy to be eccrine include a subset of lesions that mark immunohistochemically as apocrine hidrocystomas, despite a flattened wall[22].

Treatment

Hidrocystomas may be removed by simple excision, electrodesiccation or CO_2 laser. Multiple eccrine hidrocystomas may also be treated with daily application of topical 1% atropine in aqueous solution, although lesions reappear within days of discontinuing therapy[24]. Flattening after botulinum toxin A injections has been reported[25].

Bronchogenic Cyst

Cutaneous bronchogenic cysts are most commonly found in the suprasternal notch and, rarely, on the anterior neck or chin (see Fig. 64.2). A fistulous tract may connect to the epidermis. Rarely, they present as a pedunculated growth[26]. Bronchogenic cysts are solitary, and they are typically found at birth. Malignant transformation is very rare. They represent respiratory epithelium sequestered during embryologic development of the tracheobronchial tree.

Pathology

Bronchogenic cysts are lined by pseudostratified ciliated columnar epithelium with interspersed goblet cells. The cyst wall often contains smooth muscle and mucous glands, and, rarely, cartilage.

Treatment

Treatment is by excision.

Thyroglossal Duct Cyst

Thyroglossal duct cysts present as midline cystic nodules on the anterior neck in children or young adults (see Fig. 64.2). During development, the thyroid gland descends from the floor of the pharynx to the anterior neck. The tract it forms is known as the thyroglossal duct. Thyroglossal duct cysts arise from remnants of the thyroglossal duct. A tract connecting these cysts to the hyoid bone is frequently present, resulting in characteristic movement of the cyst with swallowing. Rarely, thyroid carcinoma may originate in a thyroglossal duct cyst[27].

Pathology

Histologically, thyroglossal duct cysts may be lined with cuboidal, columnar or stratified squamous epithelium and may contain some ciliated columnar cells. The characteristic histologic feature is the presence of thyroid follicles, characterized by low cuboidal cells surrounding homogeneous pink material, in the cyst wall (Fig. 110.19).

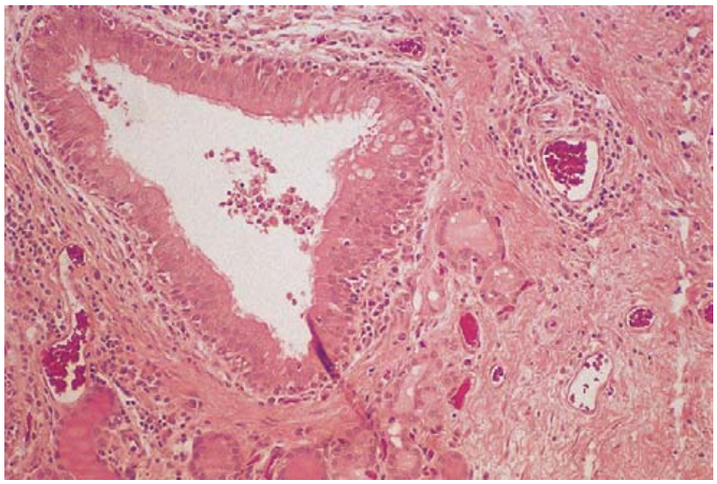


Fig. 110.19 Histology of thyroglossal duct cyst. Thyroid follicles are seen adjacent to a cyst lined by ciliated epithelium.

Treatment

Treatment is surgical, with excision of the cyst and any residual tract.

Branchial Cleft Cyst

Synonyms: ■ Lymphoepithelial cyst ■ Lateral cervical cyst

Branchial cleft cysts occur in the preauricular area, mandibular region, or along the anterior border of the sternocleidomastoid muscle (see Fig. 64.2). The origin of these cysts is controversial. There are two major theories regarding their origin:

- they arise from branchial cleft remnants
- they represent cystic alteration of embryologic epithelium or tonsillar epithelium within cervical lymph nodes[28].

Branchial cleft cysts most commonly present during the second or third decade of life. Infection of these cysts is a frequent cause of presentation to a physician.

Pathology

Histologically, these cysts are lined by stratified squamous epithelium or by pseudostratified ciliated columnar epithelium, and they are surrounded by lymphoid tissue.

Treatment

Treatment is by excision of the cyst and its associated tract after delineation of the extent of the lesion by CT or MRI[29].

Cutaneous Ciliated Cyst and Ciliated Cyst of the Vulva

Synonyms: ■ Cutaneous müllerian cyst ■ Cutaneous ciliated cystadenoma ■ Paramesonephric mucinous cyst of the vulva

Cutaneous ciliated cysts are uncommon cysts that typically occur on the lower extremities of young women, although a few cases have been reported in men. They are usually a few centimeters in diameter and, on rupture, drain clear to amber fluid. The histogenesis of these cysts is controversial. Most authors have suggested a müllerian duct origin. However, the few occurrences in men have led to the alternative hypothesis that some cases represent ciliated metaplasia of eccrine glands[30].

Ciliated cysts of the vulva are müllerian heterotopias, and they are located, as their name implies, on the vulva (most commonly on the labia majora). They usually measure between 1 and 3 cm in diameter. It has been suggested that both ciliated cyst of the vulva and the cutaneous ciliated cyst should be called cutaneous müllerian cysts, as their presumed origin is the same[31].

Fig. 110.20 Histology of a ciliated cyst of the vulva. The cyst wall is composed of columnar ciliated epithelium with papillary projections into the lumen.

Pathology

Cutaneous ciliated cysts may be unilocular or multiloculated. The cyst wall is composed of simple cuboidal to columnar ciliated epithelium that may have papillary projections into the cyst lumen (Fig. 110.20).

Treatment

Excision is curative.

Median Raphe Cyst

Synonym: ■ Apocrine cystadenoma of the penis

Median raphe cysts are solitary and usually only a few millimeters in diameter, although they may extend over several centimeters linearly. They occur in young men on the ventral aspect of the penis, most commonly on or near the glans. These cysts are thought to develop from aberrant urethral epithelium, but do not connect to the urethra[32].

Pathology

Histologically, median raphe cysts are lined by stratified columnar epithelium (one to four cell layers thick) without a connection to the overlying epithelium. Occasional mucin-containing cells are seen in the lining. Very rarely, a ciliated lining has been observed[33].

Treatment

Excision is curative.

Omphalomesenteric Duct Cyst

Synonyms: ■ Vitelline cyst ■ Omphalomesenteric duct remnant

Omphalomesenteric duct cysts represent a developmental defect in the closure of the omphalomesenteric duct. The omphalomesenteric duct is the fetal connection between the midgut and the yolk sac. It is usually obliterated and loses its intestinal attachment by 6 weeks of gestation[34]. Remnants of this duct may occur anywhere along its course between the intestines and the umbilicus. The spectrum of defects resulting from this faulty closure includes Meckel's diverticulum, umbilical–enteric fistulae, umbilical sinuses and omphalomesenteric duct cysts (internal or external); the latter can present as an umbilical polyp (Fig. 110.21).

Fig. 110.21 Omphalomesenteric duct cyst. This pink papule in the umbilicus of this infant showed gastrointestinal epithelium histologically. The clinical differential diagnosis includes an umbilical (pyogenic) granuloma and urachal cyst/remnant.

Pathology

These lesions are characterized histologically by ectopic gastrointestinal mucosa and must be distinguished from umbilical metastases of gastrointestinal adenocarcinomas.

Treatment

Management of omphalomesenteric duct cysts includes appropriate radiologic studies to exclude communication to the gastrointestinal tract prior to surgical excision.

Urachal Cyst

The urachus is a tube connecting the fetal bladder to the umbilicus and it normally closes during development, resulting in a fibrous tract. A persistent urachus presents during infancy with urine leakage from the umbilicus. A urachal cyst results from an incomplete urachal duct remnant. Urachal cysts are rare, and they usually present as a painful umbilical mass due to secondary infection. The diagnosis can be established by ultrasound in the majority of patients[35].

Pathology

These cysts are characterized by a urothelial lining of cuboidal or columnar cells.

Treatment

Excision is recommended to prevent secondary infections as well as late development of adenocarcinoma[35].

CYSTS WITHOUT AN EPITHELIAL LINING

Synonyms: ■ Mucous cyst of oral mucosa ■ Ranula (when located on the floor of the mouth)

Mucocele

Mucoceles most frequently develop on the lower labial mucosa, but they also occur on the floor of the mouth, buccal mucosa, and tongue. They appear as dome-shaped, bluish, translucent papules or nodules that range in size from a few millimeters to over a centimeter (Fig. 110.22). Mucoceles arise as a result of disruption of the ducts of minor salivary glands. This disruption leads to an accumulation of mucinous material, a reactive inflammatory response, and the development of surrounding granulation tissue.

A variant of mucocele, superficial mucocele, presents as a clear tense vesicle that is a few millimeters in diameter. Superficial mucoceles are most commonly found on the retromolar pad, posterior buccal mucosa, and soft palate. These lesions are short-lived, asymptomatic and recurrent. They may be confused clinically with an immunobullous or viral process.

Fig. 110.22 Mucocele. A bluish translucent papule on the lower mucosal lip.

Pathology

Biopsy specimens of mucoceles show one or several spaces within the connective tissue filled with mucinous material, but without an epithelial lining. The spaces are surrounded by chronic inflammation, mucin-containing macrophages, and granulation tissue. A salivary duct may be seen at the periphery of these findings. Adjacent minor salivary glands may show chronic inflammation and fibrosis. The mucinous material is sialomucin, and the latter contains both neutral and acid mucopolysaccharides, which stain with PAS (diastase-resistant) and with Alcian blue or colloidal iron, respectively.

Histologically, a superficial mucocele shows a subepithelial vesicle filled with mucin and a surrounding sparse to moderate mixed inflammatory infiltrate. Salivary gland ducts are seen opening into the vesicle or immediately adjacent to the vesicle.

Treatment

Mucoceles may resolve spontaneously. If they do not, treatment options include excision, marsupialization, electrodesiccation, intralesional corticosteroid injection, cryosurgery, and CO_2 laser therapy.

Digital Mucous Cyst

Synonyms: ■ Digital myxoid cyst ■ Cutaneous myxoid cyst

Digital mucous cysts most commonly occur on the dorsal surface of the distal phalanx of the finger. Toe lesions are less commonly observed. A characteristic depressed nail deformity may be seen distal to the cyst (Fig. 110.23). These cysts are skin-colored to bluish and drain clear gelatinous material when punctured. The etiology of digital mucous cysts is controversial, with some authors stating that they are degenerative in origin while others believe they extend from the distal interphalangeal joint space. A pedicle connecting the cyst to the adjacent joint space can usually be demonstrated[36].

Pathology

Histologically, clefts are seen in the dermis without an epithelial lining (Fig. 110.24). The clefts and the surrounding loose connective tissue contain abundant acid mucopolysaccharides, which can be highlighted by Alcian blue or colloidal iron stains.

Treatment

Resolution may be seen after intralesional injection of corticosteroids. Repeated puncture and drainage of a digital mucous cyst leads to resolution in up to 70% of patients[37]. Surgical excision may give even higher success rates. De Berker and Lawrence[36] reported a technique for identification and ligature of the connection to the joint capsule. This technique was curative in 94% of finger lesions and 57% of those on the toes.

Fig. 110.23 Digital mucous cyst. A translucent papule on the dorsal distal phalanx of the finger causing a depression in the nail plate.

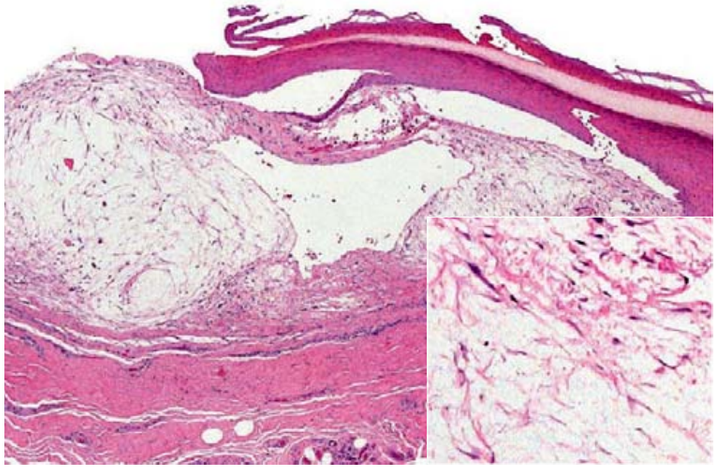


Fig. 110.24 Histology of a digital mucous cyst. A subepidermal cystic cavity is surrounded by mucin-rich dermis (insert). Note the prominent stratum lucidum of acral skin. *Courtesy, Lorenzo Cerroni, MD.*

Ganglion

Synonyms: ■ Ganglion cyst ■ Synovial cyst

Ganglia are soft cystic masses up to 4 cm in diameter that most commonly occur on the dorsal aspect of the wrist; they may also be found on the volar wrist or fingers, the dorsal aspect of the feet, or the knees. Ganglia rarely develop on the lateral elbow or anterior shoulder. They occur more commonly in women and may cause discomfort with activity, impairment of mobility, or cosmetic concerns. In the rare disorder cystic ganglionosis, multiple lesions appear during childhood or adolescence.

Ganglia are frequently attached to a tendon sheath or the joint capsule, but usually do not communicate with the joint space[38]. The mucin present within a ganglion is thought to be produced by local fibroblasts.

Pathology

Myxoid change is seen within the connective tissue that ultimately forms cystic spaces. These spaces coalesce into a dominant cystic space lined by fibrous tissue (Fig. 110.25), sometimes with a synovial lining.

Treatment

Early lesions may respond to several weeks of compression therapy[38]. Other options include aspiration plus intralesional corticosteroid injection or excision. Recurrences are common, even with excisional therapy.

Fig 110.25 Histology of a ganglion (cyst). A cystic space of acral skin is surrounded by fibrous tissue. *Courtesy, Lorenzo Cerroni, MD.*

Fig. 110.26 Pseudocyst of the auricle. Erythematous firm nodule on the ear.

Pseudocyst of the Auricle

Synonyms: ■ Endochondral pseudocyst ■ Cystic chondromalacia ■ Intracartilaginous cyst

Pseudocyst of the auricle usually arises in the scaphoid fossa of the ear in middle-aged men. Lesions are usually unilateral. They present as a painless swelling (Fig. 110.26), and they tend to arise over the course of a few weeks. The etiology of pseudocyst of the auricle is unknown, but chronic trauma as well as a developmental defect have been suggested.

Pathology

Biopsy specimens show a cavity within the auricular cartilage (without an epithelial lining) that contains clear fluid. Fibrous tissue and granulation tissue may be found in the cavity as well. The cartilage lining the cavity may show degenerative changes. No inflammation is seen within the cartilage, a feature that distinguishes a pseudocyst from relapsing polychondritis, which is frequently in the clinical differential diagnosis.

Treatment

Treatment options include aspiration, with or without intralesional injection of corticosteroids, as well as incision and drainage with

destruction of the cavity. Each of these modalities should be followed by pressure dressings[39].

Cutaneous Metaplastic Synovial Cyst

Cutaneous metaplastic synovial cysts typically present as a solitary tender subcutaneous nodule, although multiple lesions have been reported[40]. They occur primarily in areas of prior trauma, particularly prior surgical trauma. Frequently, the preoperative diagnosis is that of a suture granuloma.

Pathology

A cystic cavity is seen within the dermis that is not lined by epithelium. The cavity may communicate with the overlying epidermis via fistulas. Variably cellular villous structures mimicking hyperplastic synovium protrude into the cavity. These villi are covered with a fibrinous exudate. The base of the villi tends to merge with surrounding scar tissue.

Treatment

Excision is curative.

REFERENCES

1. Cooper PH, Fechner RE. Pilomatricoma-like changes in the epidermal cysts of Gardner's syndrome. J Am Acad Dermatol. 1983;8:639–44.
2. Gorlin RJ. Nevoid basal cell carcinoma syndrome. Dermatol Clin. 1995;13:113–25.
3. Sha V, Shet, T. Scrotal calcinosis results from calcification of cysts derived from hair follicles: a series of 20 cases evaluating the spectrum of changes resulting in scrotal calcinosis. Am J Dermatopathol. 2007;29:172–5.
4. Lopez-Rios F, Rodriguez-Peralto JL, Castano E, Benito A. Squamous cell carcinoma arising in a cutaneous epidermal cyst: case report and literature review. Am J Dermatopathol. 1999;21:174–7.
5. Langley RG, Walsh NM, Ross JB. Multiple eruptive milia: report of a case, review of the literature, and a classification. J Am Acad Dermatol. 1997;37:353–6.
6. Sau P, Graham JH, Helwig EB. Proliferating epithelial cysts. Clinicopathological analysis of 96 cases. J Cutan Pathol. 1995;22:394–406.
7. Alvarez-Quinones M, Garijo MF, Fernandez F, et al. Malignant aneuploid spindle-cell transformation in a proliferating trichilemmal tumour. Acta Derm Venereol. 1993;73:444–6.
8. Mori O, Hachisuka H, Sasai Y. Proliferating trichilemmal cyst with spindle cell carcinoma. Am J Dermatopathol. 1990;12:479–84.
9. Lopez-Rios F, Rodriguez-Peralto JL, Aguilar A, et al. Proliferating trichilemmal cyst with focal invasion: report of a case and a review of the literature. Am J Dermatopathol. 2000;22:183–7.
10. Mones JM, Ackerman AB. Proliferating trichilemmal cyst is squamous cell carcinoma. Dermatopathology: Practical & Conceptual. 1998;4:295–310.
11. Ye J, Nappi O, Swanson PE, et al. Proliferating pilar tumors: a clinicopathologic study of 76 cases with a proposal for definition of benign and malignant variants. Am J Clin Pathol. 2004;122:566–74.
12. Esterly NB, Fretzin DF, Pinkus H. Eruptive vellus hair cysts. Arch Dermatol. 1977;113:500–3.
13. Sharma VM, Stein SL. A novel mutation in K6b in pachyonychia congenita type 2. J Invest Dermatol. 2007;127:2060–2.
14. McLean WH, Rugg EL, Lunny DP, et al. Keratin 16 and keratin 17 mutations cause pachyonychia congenita. Nat Genet. 1995;9:273–8.
15. Cassarino DS, Linden KG, Barr RJ. Cutaneous keratocyst arising independently of the nevoid basal cell carcinoma syndrome. Am J Dermatopathol. 2005;27:177–8.
16. Requena L, Sanchez Yus E. Follicular hybrid cysts. An expanded spectrum. Am J Dermatopathol. 1991;13:228–33.
17. Brownstein MH. Hybrid cyst: a combined epidermoid and trichilemmal cyst. J Am Acad Dermatol. 1983;9:872–5.
18. Mehregan AH, Medenica M. Pigmented follicular cysts. J Cutan Pathol. 1982;9:423–7.
19. Scheinfeld NS, Silverberg NB, Weinberg JM, Nozad V. The preauricular sinus: a review of its clinical presentation, treatment, and associations. Pediatr Dermatol. 2004;21:191–6.
20. McKusick VA (ed). OMIM™ Online Mendelian Inheritance in Man. National Center for Biotechnology Information. www.ncbi.nlm.nih.gov/Omim/
21. da Silva JH. Pilonidal cyst: cause and treatment. Dis Colon Rectum. 2000;43:1146–56.
22. de Viragh PA, Szeimies RM, Eckert F. Apocrine cystadenoma, apocrine hidrocystoma, and eccrine hidrocystoma: three distinct tumors defined by expression of keratins and human milk fat globulin 1. J Cutan Pathol. 1997;24:249–55.
23. Sugiyama A, Sugiura M, Piris A, et al. Apocrine cystadenoma and apocrine hidrocystoma: examination of 21 cases with emphasis on nomenclature according to proliferative features. J Cutan Pathol. 2007;34:912–17.
24. Sanz-Sanchez T, Dauden E, Perez-Casas A, et al. Efficacy and safety of topical atropine in treatment of multiple eccrine hidrocystomas. Arch Dermatol. 2001;137:670–1.
25. Woolery-Lloyd H, Rajpara V, Nijhawan RI. Treatment for multiple periorbital eccrine hidrocystomas: botulinum toxin A. J Drugs Dermatol. 2009;8:71–3.
26. Miller OF III, Tyler W. Cutaneous bronchogenic cyst with papilloma and sinus presentation. J Am Acad Dermatol. 1984;11:367–71.
27. Dedivitis RA, Guimaraes AV. Papillary thyroid carcinoma in thyroglossal duct cyst. Int Surg. 2000;85:198–201.
28. Golledge J, Ellis H. The aetiology of lateral cervical (branchial) cysts: past and present theories. J Laryngol Otol. 1994;108:653–9.
29. Thaller SR, Bauer BS. Cysts and cyst-like lesions of the skin and subcutaneous tissue. Clin Plast Surg. 1987;14:327–40.
30. Fontaine DG, Lau H, Murray SK, et al. Cutaneous ciliated cyst of the abdominal wall: a case report with a review of the literature and discussion of pathogenesis. Am J Dermatopathol. 2002;24:63–6.
31. Kurban RS, Bhawan J. Cutaneous cysts lined by nonsquamous epithelium. Am J Dermatopathol. 1991;13:509–17.
32. Asarch RG, Golitz E, Sausker WF, Kreye GM. Median raphe cysts of the penis. Arch Dermatol. 1979;115:1084–6.
33. Fernandez Acenera MF, Garcia-Gonzales J. Median raphe cyst with ciliated cells: report of a case. Am J Dermatopathol. 2003;251:175–6.
34. Larralde de Luna M, Cicioni V, Herrera A, et al. Umbilical polyps. Pediatr Dermatol. 1987;4:341–3.
35. Ekwueme KC, Parr NJ. Infected urachal cyst in an adult: a case report and review of the literature. Cases J. 2009;2:6422.
36. de Berker D, Lawrence C. Ganglion of the distal interphalangeal joint (myxoid cyst): therapy by identification and repair of the leak of joint fluid. Arch Dermatol. 2001;137:607–10.
37. Epstein E. A simple technique for managing digital mucous cysts. Arch Dermatol. 1979;115:1315–16.
38. Soren A. Clinical and pathologic characteristics and treatment of ganglia. Contemp Orthop. 1995;31:34–8.
39. Secor CP, Farrell HA, Haydon RC III. Auricular endochondral pseudocysts: diagnosis and management. Plast Reconstr Surg. 1999;103:1451–7.
40. Singh SR, Ma AS, Dixon A. Multiple cutaneous metaplastic synovial cysts. J Am Acad Dermatol. 1999;41:330–2.

Adnexal Neoplasms 111

Timothy H McCalmont

Chapter Contents

Neoplasms and proliferations of follicular lineage *1829*
Neoplasms and proliferations with sebaceous differentiation .. *1839*
Neoplasms and proliferations with apocrine differentiation *1840*
Neoplasms and proliferations with eccrine differentiation..... *1847*

Key features

- Terminology and classification of adnexal tumors has varied considerably according to different authorities
- Combinations of follicular, sebaceous and apocrine differentiation occur commonly
- Many tumors historically classified as eccrine are probably apocrine

The nosology of adnexal neoplasms has been confused for decades, and a key problem has been the lack of a logical classification scheme. Postulated classifications and inferences regarding lineage have often been contradictory, a reflection of the fact that broad conclusions regarding lineage and classification were formerly based on enzyme histochemical attributes of dubious specificity[1,2].

The crucial principle to keep in mind when considering adnexal neoplasms is that the development of the eccrine apparatus is distinct from the folliculosebaceous-apocrine unit. Eccrine glands develop directly from the embryonic epidermis in early months of fetal development[3]. Follicles arise directly from the epidermis concurrently, but their development differs in that mesenchymal cells, precursors of the follicular papilla, descend jointly into the dermis with the developing follicle. Subsequently, sebaceous and apocrine glands and their ducts elaborate as secondary structures from bulges on the side of the developing follicle.

These ontogenetic relationships reflect relationships observed repeatedly in clinical disease[1]. As one would expect from ontogeny, follicular, sebaceous and apocrine differentiation occur conjointly, and combinations of eccrine and folliculosebaceous differentiation probably do not exist.

The topography of adnexal structures also offers insight into logical classification. There is striking variation in anatomic distribution among adnexal neoplasms, and some of these differences hold implications regarding lineage. Based on topography, it is nonsensical to pigeonhole spiradenoma, a tumor that commonly occurs within apocrine skin and rarely, if ever, develops acrally, as an eccrine tumor. In contrast, an acral predilection suggests that poroma is commonly of eccrine lineage[4].

Lastly, microscopy and morphology play a role in the assessment of lineage. For some lines of differentiation, the meaning ascribed to specific attributes is indisputable. Cells with coarsely vacuolated cytoplasm and scalloped nuclei signify sebaceous differentiation. Follicular differentiation is established by the presence of bulbar basaloid cells accompanied by mesenchymal cells resembling the follicular papilla. Follicular lineage is also connoted by matrical or outer sheath differentiation. In contrast, there are no specific attributes that permit recognition of eccrine or apocrine differentiation.

NEOPLASMS AND PROLIFERATIONS OF FOLLICULAR LINEAGE

Follicular and Folliculosebaceous-apocrine Hamartomas

Hamartomas are benign proliferations composed of cellular elements, native to a site, in aberrant proportion. A congenital hamartoma, such as nevus sebaceus, is properly referred to as a *nevus*. Hamartomas can be acquired and present in tumor-like fashion, although such lesions do not represent authentic neoplasms.

Proliferations of the folliculosebaceous-apocrine unit are commonly hamartoma-like. The folliculosebaceous-apocrine unit incorporates follicular epithelial, follicular mesenchymal, sebaceous and apocrine elements, and thus its microscopically diverse progeny is not surprising. Many follicular proliferations that we consider neoplastic, such as trichoblastoma, have integral stroma, and thus the distinction between follicular hamartoma and follicular neoplasm is sometimes blurred.

Hair follicle nevus

Introduction

Hair follicle nevi are authentic hamartomas, usually congenital, in which hairs and the follicles that ensheath them have abnormal morphology or size or are present in increased numbers.

Clinical features

Hair follicle nevus, also known as *vellus hamartoma*, presents as a small papule from which fine hairs protrude evenly from the surface. Lesions typically involve the face and commonly reside near the ear[5]. *Accessory tragus* overlaps with hair follicle nevus, and it has been suggested that the two entities are the same[6,7]. *Nevus pilosus* designates hamartomas characterized by closely set, non-vellus hairs.

Pathology

Microscopically, hair follicle nevi display a domed surface with an increase in normally formed vellus follicles. The configuration may resemble normal skin. Accessory tragi exhibit an identical pattern but are uniquely identifiable if deep subjacent hyaline cartilage can be found. Nevus pilosus is characterized by closely set terminal follicles.

Treatment

No therapy is required. Excision can be considered for cosmesis. In the evaluation of a hair follicle nevus or accessory tragus in a small child, parents can be counseled that the relative size of the lesion will diminish with time. The child will grow faster than the lesion, which may become inconspicuous by adolescence.

Trichofolliculoma

Introduction

Trichofolliculoma does not represent an authentic neoplasm. Rather, the term designates a group of follicular hamartomas in which fully formed follicular structures emanate from a central dilated infundibular space.

Clinical features

Trichofolliculoma presents as a papule or nodule involving the face, scalp or upper trunk. Many examples are not clinically distinctive. Sometimes, a central follicular ostium or punctum may be identifiable

Fig. 111.1 Trichofolliculoma. Wispy vellus hairs emerge from a skin-colored papule with a dilated central pore.

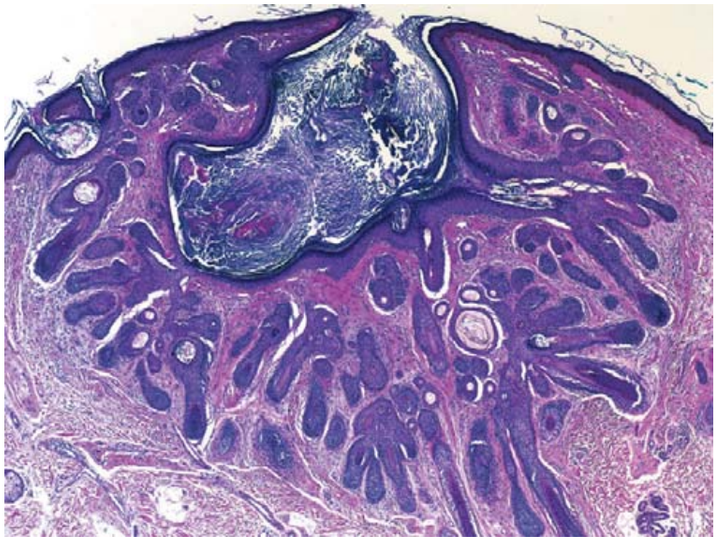


Fig. 111.2 Trichofolliculoma, viewed at scanning magnification. There is a central patulous follicular infundibulum, from which fully formed or nearly fully formed follicles radiate.

and it may harbor a small tuft of hairs (Fig. 111.1). Rarely, the clinical presentation will be as a large nodule or cyst.

Pathology

Prototypically, a trichofolliculoma consists of a central cystic space with infundibular cornification and central orthokeratin. Sometimes, cross-sections of hair shafts are identifiable within the cyst. Relatively well-developed and occasionally oddly formed vellus follicles protrude in radial fashion from the central structure (Fig. 111.2). The follicles usually display a bulb and papilla and exhibit inner and outer sheath and isthmic differentiation. The entire structure, including the central cyst and its associated radiating follicles, is enveloped by a vascularized fibrous (angiofibroma-like) stroma.

The radiating follicles are frequently cut on tangent, thus creating considerable microscopic variation, and deeper sections through the tissue block sometimes are required for diagnosis. If the radiating follicles are accompanied by sebaceous glands, the hamartoma can be termed a *sebaceous trichofolliculoma*[8]. This diagnostic embellishment is not of any clinical import.

The term *folliculosebaceous cystic hamartoma* has been applied to a group of nodular and cystic lesions described independently from trichofolliculoma[9–11]. Folliculosebaceous cystic hamartoma shows a central infundibular cyst from which follicular and sebaceous elements emanate, and the encompassing stroma may be fibrous or myxoid and often contains adipocytes. Rather than a unique entity, is seems likely that folliculosebaceous cystic hamartoma represents a large cystic sebaceous trichofolliculoma[9].

Treatment

Trichofolliculoma is wholly benign and no treatment is needed. If a trichofolliculoma is discovered by biopsy, no further intervention is required.

Fibrofolliculoma, perifollicular fibroma and trichodiscoma

Introduction

Fibrofolliculoma represents an adnexal hamartoma that includes both follicular epithelial and mesenchymal elements. Perifollicular fibroma and trichodiscoma were described independently but probably represent purely mesenchymal proliferations on the same spectrum as fibrofolliculoma. Some authorities consider perifollicular fibroma to be related to angiofibroma.

Clinical features

Fibrofolliculomas (Fig. 111.3), perifollicular fibromas and trichodiscomas are not clinically distinctive. All present as small, skin-colored to hypopigmented papules that involve the head and neck or upper trunk. The papules commonly present in multiplicity. In this context, strong consideration should be given to the possibility of the Birt–Hogg–Dubé syndrome (Fig. 111.4), an autosomal dominant disorder typified by multiple fibrofolliculomas, trichodiscomas and acrochordon-like lesions. Other associated phenomena include chromophobe renal cell carcinoma, colonic adenomas, pulmonary cysts and spontaneous pneumothoraces, medullary thyroid carcinoma, and connective tissue nevi.

Pathology

At low magnification, fibrofolliculoma displays slender strands of follicular mantle cells that emanate from a folliculosebaceous unit at the level of the isthmus. Usually, the strands are composed of cells with a slightly basaloid appearance, and sometimes, tiny integrated collections of mature sebocytes are identifiable. The epithelial component may assume a mitt-like morphology in some instances. The entire structure is encased by vascularized fibrous stroma.

Perifollicular fibroma consists almost exclusively of stroma that is identical to the stromal elements of fibrofolliculoma and angiofibroma. Lesions consist of spindled and stellate cells arrayed concentrically around follicles and distributed amongst thickened collagen bundles with a proportionate number of intervening small thin-walled vessels. Sometimes, a concurrent component of follicular epithelial hyperplasia is identifiable, although the epithelium tends to be inconspicuous in comparison to fibrofolliculoma. Trichodiscoma was thought by Pinkus to represent a unique proliferation with differentiation toward the *haarscheibe* (hair disk), which is probably a mythical structure. More recently, trichodiscomas have been interpreted as fibrofolliculomas or perifollicular fibromas with myxoid rather than fibrous stroma.

Treatment

Fibrofolliculomas, perifollicular fibromas and trichodiscomas are all benign and require no surgical treatment. Superficial electrodesiccation, carbon dioxide laser ablation, or dermabrasion can be utilized to ameliorate multiple lesions.

Nevus sebaceus

Introduction

Originally known as *organoid nevus*, nevus sebaceus is commonly thought of as a sebaceous lesion and historically has been the first entity discussed in chapters describing sebaceous tumors. In truth, nevus sebaceus is a non-neoplastic malformation that includes follicular, sebaceous and apocrine elements[12].

Clinical features

Nevus sebaceus represents a classic *nevus* or congenital malformation. At birth, lesions are only slightly raised and subtly discernible. Nevus sebaceus involves the scalp or face commonly, the neck occasionally, and the trunk rarely. Lesions that are linear are distributed along the lines of Blaschko, although this may be difficult to appreciate if small. On the scalp, a nevus will remain hairless, or mostly so, as the infant's hair grows around it. During childhood, the nevus thickens slightly and assumes a yellow or orange hue (Fig. 111.5). At adolescence, progressive thickening occurs and the surface becomes pebbly or verrucous.

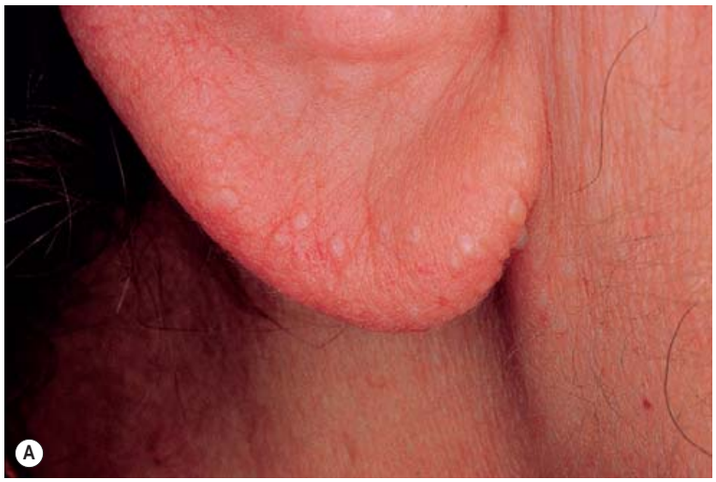
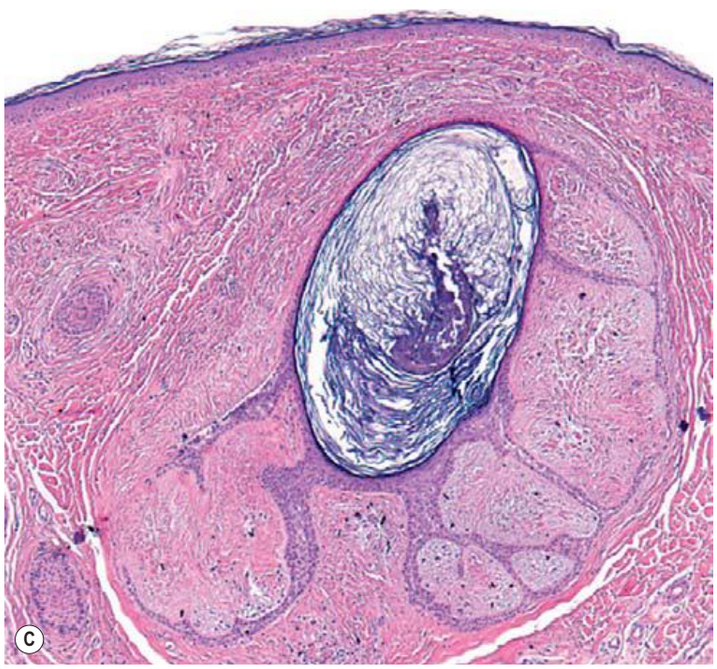


Fig. 111.3 Fibrofolliculomas in association with Birt–Hogg–Dubé syndrome. A Multiple small skin-colored to white papules on the ear. **B** Multiple smooth papules of the lateral cheek that are relatively hypopigmented and lack the telangiectasias of the background skin. **C** Histology from a patient with Birt–Hogg–Dubé syndrome showing a mitt-like configuration with a retiform array of isthmic keratinocytes flanked by delicate mucinous stroma.



Especially when there is more extensive involvement with nevus sebaceus, the possibility of Schimmelpenning syndrome or phakomatosis pigmentokeratotica needs to be considered (see Table 62.8).

Nevus sebaceus represents a fertile field for the development of secondary adnexal neoplasms, commonly benign but occasionally malignant[13–15]. A past generation of dermatologists was taught that secondary carcinoma develops in 10% or more of these lesions over time, although this figure was poorly substantiated. The vast majority of secondary proliferations represent benign follicular germinative (trichoblastoma-like) foci (Fig. 111.6); the actual incidence of secondary basal cell carcinoma (BCC) is less than 1%[13,14]. Historically, syringocystadenoma papilliferum (papillary syringoadenoma) was believed to represent the most common secondary proliferation, but recent analysis indicates that trichoblastoma holds this role[13,14]. Other common secondary neoplasms include trichilemmoma, desmoplastic trichilemmoma, sebaceous adenoma, apocrine adenoma, and poroma. Only rarely does secondary sebaceous carcinoma or apocrine carcinoma arise in a nevus sebaceus. Malignancy probably develops only in longstanding or neglected lesions but exceptionally can be a source of mortality.

Pathology

In nevus sebaceus, the principal malformation is of individual folliculosebaceous units. An infantile nevus sebaceus can be microscopically subtle, particularly if the biopsy specimen includes only lesional skin, as the malformed follicular units are small and deviate little from normal. In an excisional specimen from the scalp during later childhood, tiny misshapen lesional follicles provide a stark contrast to normal terminal follicles at the periphery of the biopsy. Small apocrine glands may be identifiable in a specimen of sufficient depth. The epidermis also thickens and becomes progressively more papillated, gradually assuming a configuration akin to an epidermal nevus.

By late adolescence, nevus sebaceus displays an epidermal pattern identical to that of an epidermal nevus, typified by acanthosis and fibroplasia of the papillary dermis. There may be enlarged sebaceous glands in contiguity with the epidermal–dermal junction. Buds of follicular germinative cells may jut from the junction as well (Fig. 111.7). The underlying follicular units remain smallish and appear distorted but their sebaceous lobules increase in prominence. Dilated apocrine glandular structures with inspissated secretions are not uncommonly identifiable in the reticular dermis. This histopathology remains stable into adulthood.

Over time, some patients develop exaggerated verrucous epidermal hyperplasia much like a verruca vulgaris. It has been suggested that this represents a consequence of human papillomavirus infection[16]. Secondary neoplasms are common, and trichoblastoma, trichilemmoma and syringocystadenoma are frequently observed[13,14]. The strong association between syringocystadenoma and nevus sebaceus warrants careful scrutiny any time the diagnosis of syringocystadenoma is rendered, to ascertain whether a nevus sebaceus can be found in the same specimen.

Treatment

As carcinoma was formerly reputed to commonly develop within nevus sebaceus, the risk of transformation was used as justification for complete excision. In truth, the risk of development of secondary carcinoma is low[16]. However, the risk for the development of a secondary benign neoplasm, such as syringocystadenoma or trichoblastoma, is relatively high. In addition, it is clear that nevus sebaceus becomes increasingly verrucous and unsightly over time. In light of this, conservative complete excision in late childhood represents a commonly utilized approach. Lesions within the scalp may be difficult to follow clinically and extirpation will prevent the development of occult secondary changes. For facial lesions, consideration should be given to excision during childhood, before the development of secondary verrucous alteration, at a time when the risk of scarring is reduced compared to adulthood. The excisional margins can be minimal. Removal by shave or laser ablation is usually not successful.

Mixed tumor (chondroid syringoma)

Introduction

Cutaneous mixed tumor, also known as *chondroid syringoma*, represents an acquired hamartoma with folliculosebaceous-apocrine differentiation that has been interpreted as an adnexal adenoma since its description. Despite this legacy, mixed tumor is best pigeonholed as a hamartoma. The stroma of mixed tumor is always abundant and generally comprises half of the surface area of a given lesion in conventional sections, and the epithelial component is commonly heterogeneous[17].

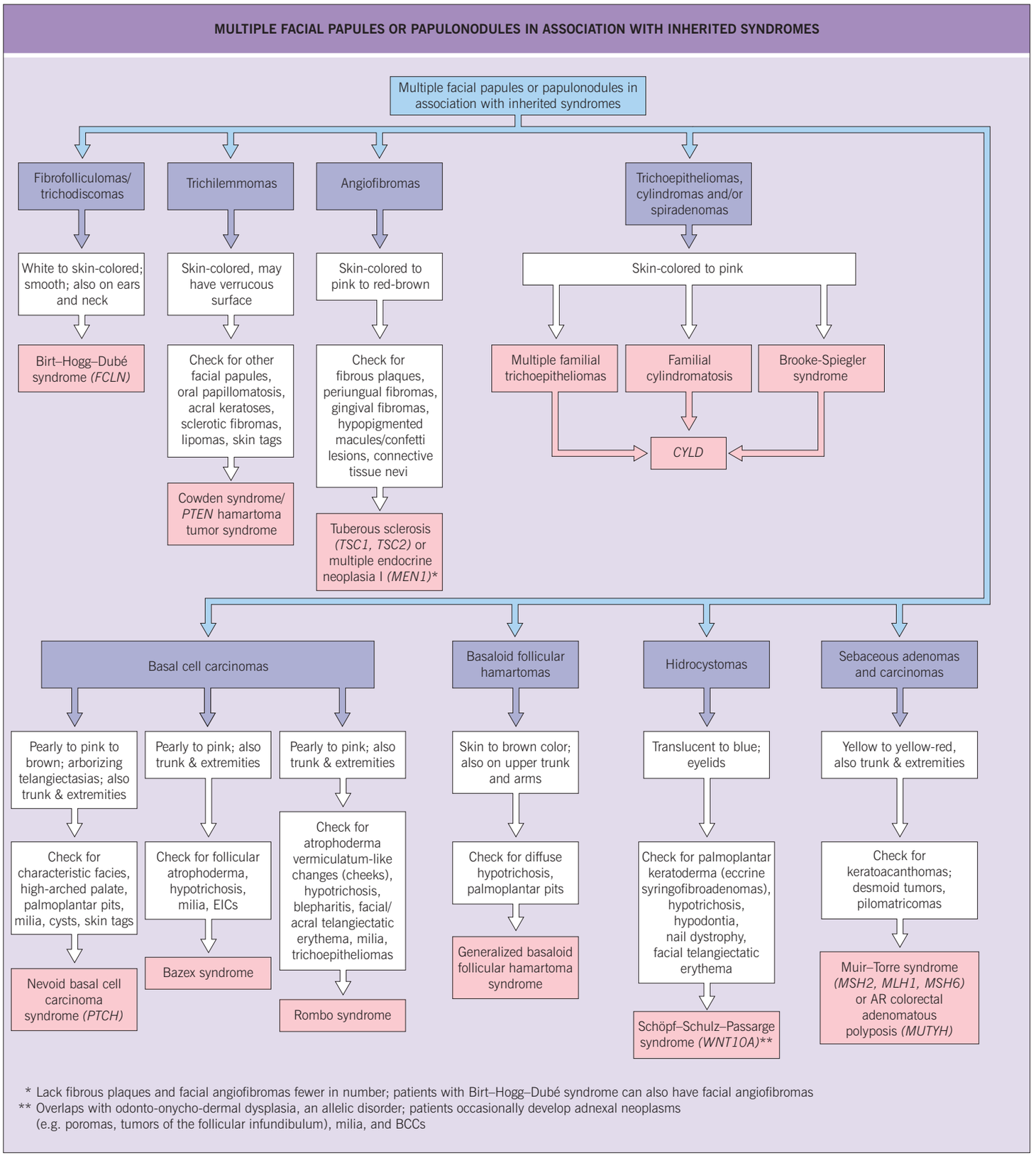


Fig. 111.4 Multiple facial papules or papulonodules in association with inherited syndromes. Patients with Gardner syndrome can develop multiple epidermoid inclusion cysts (sometimes with foci of pilomatrical differentiation) and osteomas in the head and neck region. AR, autosomal recessive; EICs, epidermoid inclusion cysts.

Fig. 111.5 Nevus sebaceus. An oval yellow-pink verrucous plaque on the scalp. Note the alopecia.

Fig. 111.6 Nevus sebaceus. Yellow–brown verrucous plaque in which a bluish "basal cell carcinoma" developed. *Courtesy, Ronald P Rapini, MD.*

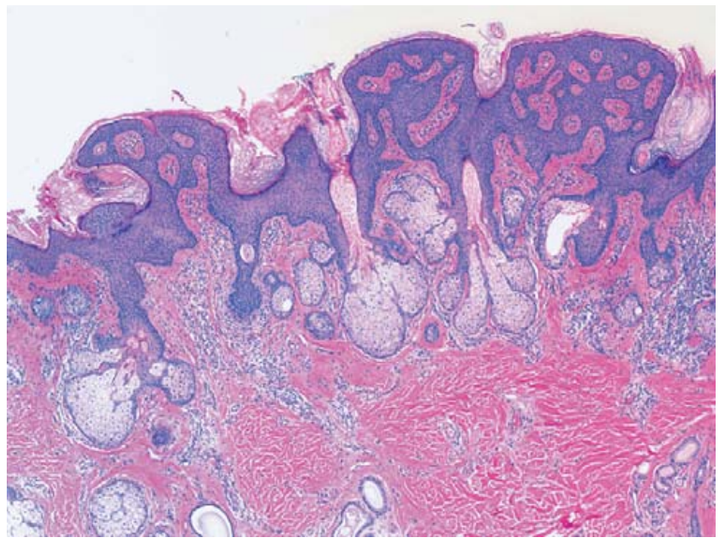


Fig. 111.7 Nevus sebaceus. Medium magnification reveals expansion of the epidermis in a papillated fashion, much like the pattern of an epidermal nevus. This is accompanied by adnexal malformation, with enlarged sebaceous lobules and clusters of follicular germinative cells positioned along the dermal–epidermal junction.

Fig. 111.8 Chondroid syringoma. Nodule on chin. *Courtesy, Ronald P Rapini, MD.*

An analogy has been drawn between cutaneous mixed tumor and mixed tumor (pleomorphic adenoma) of the salivary gland. While the comparison has some validity, it is important to note that pleomorphic adenoma of the salivary gland functions as a neoplasm in a biological sense, as it holds a tendency for local recurrence if incompletely extirpated as well as the potential for evolution to malignancy. In contrast, chondroid syringoma represents an indolent process virtually devoid of proliferative capacity. It rarely recurs after enucleation. Some authors consider chondroid syringoma and cutaneous myoepithelioma to represent two ends of a spectrum, and this concept is supported by the fact that some chondroid syringomata are particularly rich in myoepithelial (indeterminate) cells.

Clinical features

The clinical presentation of mixed tumor is indistinctive (Fig. 111.8). The lesions present as cutaneous nodules that are often misconstrued as cysts. Involvement of the head and neck is common and lesions may also develop on the trunk or within axillary or genital skin.

Pathology

Mixed tumor presents pathologically as a well-circumscribed nodule that resides within the deep reticular dermis or subcutis. Its biphasic morphology includes epithelial structures encompassed by ample varied stroma[17]. There is always a prominent collagenous component to the stroma, but myxoid and lipocytic zones can also be found. Despite its name, stromal hyaline cartilage is found in less than half of all chondroid syringomata.

The epithelial component of a mixed tumor displays two primary patterns. Most mixed tumors demonstrate large interanastomosing and branching tubules lined by columnar cells with decapitation secretion apparent at the luminal border; this configuration has been dubbed apocrine mixed tumor[18] (Fig. 111.9). Less commonly, mixed tumors show an epithelial component that includes many small rounded cuticulated ducts (Fig. 111.10). Such lesions have been interpreted by some as eccrine. Rather, it seems likely that all mixed tumors are hamartomas of folliculosebaceous-apocrine lineage and that the configuration of the epithelial component can vary.

The epithelial component of mixed tumor also commonly includes follicular and sebaceous elements[17,19]. Follicular differentiation can consist of small clusters of follicular germinative cells, lobules of outer sheath cells, cystic foci with isthmic or infundibular keratinization, and

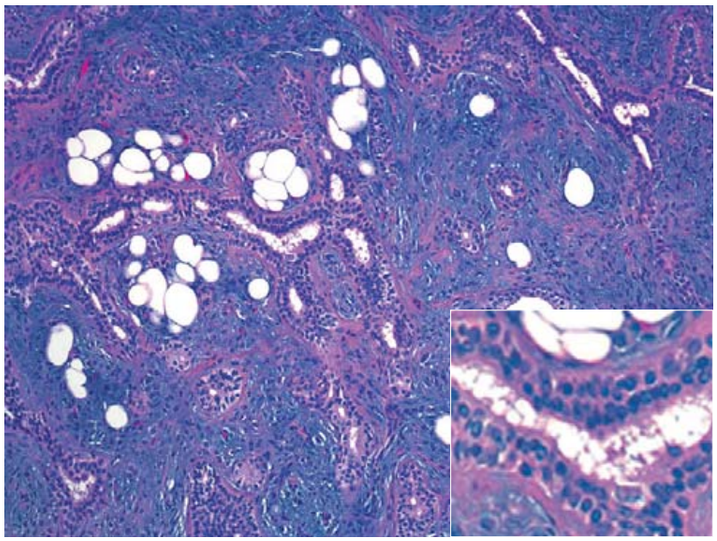


Fig. 111.9 Mixed tumor (chondroid syringoma) with overt apocrine differentiation. At medium magnification, there is a hamartomatous pattern, with large branching tubules arrayed within a mucinous stroma that contains lipocytes. Conspicuous apocrine differentiation with a "decapitation" pattern is evident in the insert.

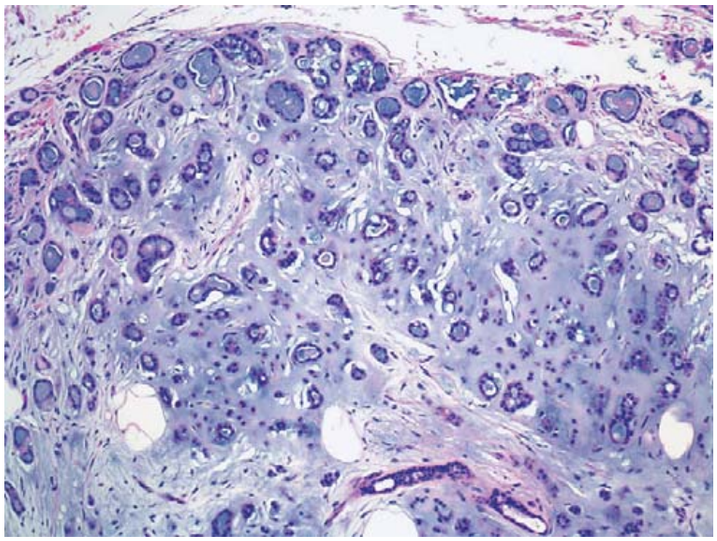


Fig. 111.10 Mixed tumor (chondroid syringoma) with ductal differentiation. This pattern, commonly referred to as the "eccrine" type of mixed tumor, shows small syringoma-like ducts positioned in ample stroma reminiscent of hyaline cartilage.

clusters of matrical cells. Small collections of sebocytes may also be found.

The number of myoepithelial cells in chondroid syringomas varies. Rare tumors composed exclusively of myoepithelial cells are classified as cutaneous myoepithelioma.

Treatment

Mixed tumor is benign and indolent. Most lesions are treated by simple enucleation, and the risk for persistence/recurrence is minimal. In contrast to mixed tumors of salivary origin, there is no need for excision with margins.

Neoplasms and Proliferations with Follicular Germinative Differentiation

Trichoepithelioma/trichoblastoma

Introduction

Trichoepithelioma and trichoblastoma are terms that refer to benign neoplasms with mostly follicular germinative differentiation[20]. Historically, the term *trichoepithelioma* is older and represents the name ascribed to a solitary lesion of the familial multiple form of trichoepithelioma (epithelioma adenoides cysticum), and thus the term trichoepithelioma is clinically useful in this context. The designation *trichoblastoma* was coined more recently and was originally applied to neoplasms that showed follicular bulbar differentiation almost exclusively. Although trichoepithelioma is still used, *trichoblastoma* has evolved to be an overarching label for benign proliferations with follicular germinative differentiation[20]. For many, in the current dermatopathologic lexicon, trichoepithelioma represents a variant of trichoblastoma.

Many authors have described subtle variations within the spectrum of follicular germinative neoplasms, thereby birthing terms such as trichogerminoma, trichoblastic fibroma, and lymphadenoma (adamantinoid trichoblastoma)[20]. For purposes of this discussion, these variants will be considered as falling within the larger spectrum of trichoblastoma.

Clinical features

Classic trichoepithelioma usually presents as a skin-colored papule or nodule on the face or upper trunk. Lesions have a predilection for the nose (Fig. 111.11). When in multiplicity, constituting epithelioma adenoides cysticum or Brooke's disease, lesional density is always greatest in the central face. The cylindromatosis (*CYLD*) gene, whose protein product functions as a tumor suppressor, underlies Brooke's disease. *CYLD* encodes a deubiquitinating enzyme that impedes the nuclear factor (NF)-κB and c-Jun N-terminal kinase (JNK) pathways[21]. Specifically, missense mutations lead to amino acid substitutions within the ubiquitin (Ub)-specific protease (USP) domain of the CYLD protein. Brooke's disease can be cosmetically troublesome and is associated with a risk of secondary BCC[22]. Patients can also develop cylindromas and spiradenomas (see Fig. 111.4). Lesions described historically as *trichoblastoma* were often larger and deeper than simple trichoepithelioma.

Pathology

All trichoepitheliomas and trichoblastomas have in common the architectural attributes of a benign neoplasm – namely, relative symmetry, circumscription and a lack of substantial cytologic atypicality. In addition, all are linked by prominence of follicular germinative cells with enveloping fibrocytic stroma that varies in degree[20,23]. In classic trichoepithelioma, the fibrocytic stroma is conspicuous and constitutes as much as half of the cellularity of the lesion in a given cross-section. In other lesions that simulate BCC, follicular germinative cells may be arrayed as either small or large nodules with only scant intervening sclerotic stroma. The coarse fibrous stroma typically maintains tightly adherent contact to the lesional follicular germinative cells[23]. This is in distinct contrast to the pattern of BCC, in which clefts between basaloid cells and stromal elements often serve as a diagnostic clue.

In classic trichoepithelioma, follicular germinative cells are often disposed as small clusters or as reticulate and cribriform cords (Fig. 111.12). There are usually foci of pronounced bulbar differentiation, emulating the follicular bulb and papilla; these structures have been termed *papillary mesenchymal bodies*[23,24]. Classic trichoepithelioma does not typically show follicular germinative differentiation exclusively. Rather, small cornifying cystic spaces with surrounding pinkish keratinocytes, reflecting concurrent infundibular or isthmic differentiation, are also apparent.

In small or large nodular trichoblastoma, follicular germinative cells comprise the majority of the surface area, papillary mesenchymal bodies may be inconspicuous, and superficial follicular differentiation may be absent. *Trichoblastic fibroma* is a designation used to characterize small nodular trichoblastomas with exaggerated fibrous stroma that often constitutes over half of the cross-sectional area of the lesion[25–27]. Papillary mesenchymal bodies may be conspicuous in trichoblastic fibroma. With close scrutiny, other modes of differentiation can occasionally be found in a trichoblastoma. There may be tiny collections of mature sebocytes, reflecting concurrent sebaceous differentiation, and (apocrine) ductal differentiation may also be noted.

Treatment

Trichoblastoma is benign and provokes no imperative for surgical treatment. Multiple facial trichoepitheliomas can be cosmetically disabling and many affected patients desire some type of intervention. Close

Fig. 111.11 Multiple familial trichoepitheliomas. Numerous skin-colored papules and nodules on the midface.

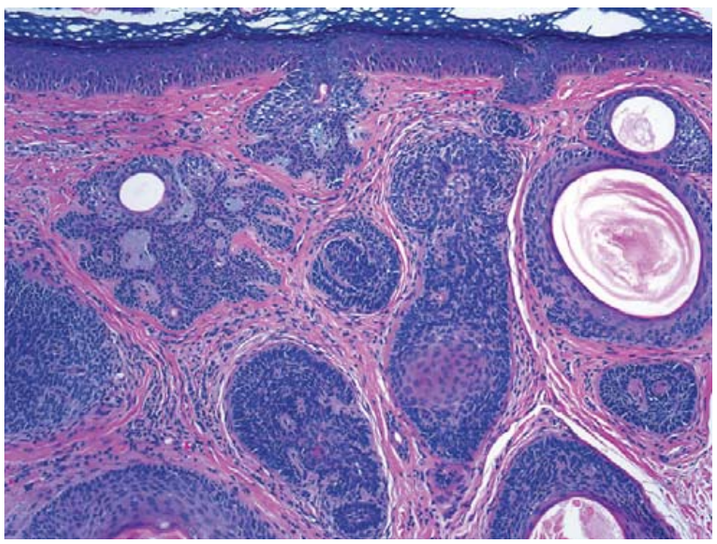


Fig. 111.12 Trichoepithelioma (trichoblastoma). This "classic" trichoepithelioma is composed mostly of clusters of follicular germinative cells but also shows superficial follicular differentiation, with small keratinizing cystic spaces. Note that clefts within the proliferation are between stromal elements, in contrast to the clefts between tumor and stroma that are characteristic of basal cell carcinoma.

followup for the possibility of secondary BCC is warranted[22]. Because of the number of lesions, conventional excision is not indicated. Other ablative approaches, including laser or electrosurgical destruction, have been employed with some success[28,29].

Desmoplastic trichoblastoma (desmoplastic trichoepithelioma)

Introduction

Originally termed *sclerosing epithelial hamartoma*, desmoplastic trichoepithelioma represents a variant of trichoblastoma with exaggerated stromal sclerosis (desmoplasia)[30]. It can easily be misinterpreted as morpheaform BCC by the uninitiated.

Clinical features

Desmoplastic trichoepithelioma commonly presents as a firm skin-colored to erythematous annular plaque with a central dell. The cheek of a woman represents a stereotypical context[30]. Most examples do not exceed 1 cm in diameter. Nearly all desmoplastic trichoepitheliomas are solitary. Multiplicity is a rarity.

Pathology

Desmoplastic trichoepitheliomas are composed of cords of basaloid cells, often two cells wide, arrayed interstitially amongst coarsened collagen bundles[20,30] (Fig. 111.13). The lesions are relatively circumscribed and are often confined to the upper two-thirds of the reticular dermis, although this is difficult to appreciate in biopsies *en parte*. Small cystic foci of isthmic or infundibular keratinization may be present, and if these cystic spaces are predominant, the designation *trichoadenoma* is apt. The cornifying cysts can rupture and elicit a granulomatous reaction, and small secondary foci of calcification may also be identified[20,30].

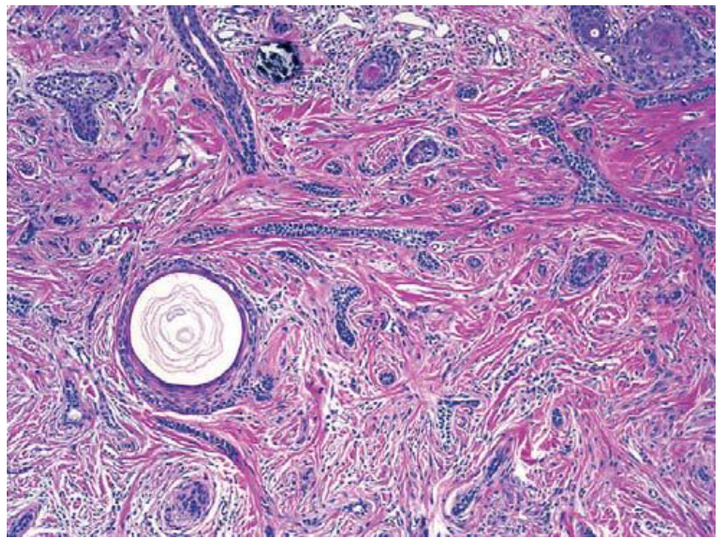


Fig. 111.13 Desmoplastic trichoepithelioma. It is composed of thin strands of basaloid (follicular germinative) cells, arrayed in sclerotic stroma. Much like conventional trichoepithelioma, there are foci of superficial follicular keratinization.

Treatment

Desmoplastic trichoepithelioma is benign. Small or partial biopsies may yield diagnostic uncertainty with respect to morpheaform BCC or microcystic adnexal carcinoma as a consideration in the differential diagnosis, and re-excision or resampling may be necessary when the interpretation is ambiguous.

Neoplasms and Proliferations with Matrical Differentiation

Pilomatricoma

Introduction

Pilomatricoma (pilomatrixoma, trichomatrioma, calcifying epithelioma) is a benign neoplasm or cyst typified by follicular matrical cornification. It has been demonstrated that mutations in *CTNNB1*, the gene that encodes β-catenin, a component of a key signaling pathway that influences cell differentiation and proliferation, are generally present in matrical neoplasms, including pilomatricomas[31]. Pilomatricomas also commonly demonstrate trisomy 18[32].

Clinical features

Pilomatricoma usually presents as a solitary skin-colored or bluish nodule (Fig. 111.14). Rarely, multiple lesions are evident, sometimes in association with myotonic dystrophy, Turner syndrome or Gardner syndrome (when cystic). Firmness is typical and reflects secondary calcification as well as accompanying fibrosis and granulomatous inflammation. Some lesions are "rock-hard" and plate-like on palpation. Pilomatricomas may occur on any hair-bearing surface, but most involve the head or upper trunk[33]. Most common in childhood and adolescence, pilomatricomas may develop at any age and can simulate BCC, clinically or microscopically, in later adulthood. Occasionally, the dermis overlying a pilomatricoma will develop anetoderma.

Pathology

Histopathologically, an early pilomatricoma frequently presents as a cyst with central matrical cornification. The cyst wall consists of basaloid matrical cells that show an abrupt transition to central eosinophilic cornified matrical cells in which barely discernible nuclear outlines remain. Sometimes, pink trichohyalin granules, illustrative of matrical cornification, are identifiable at the transition point. The

Fig. 111.14 Pilomatricoma. A nodule on the cheek of a child.

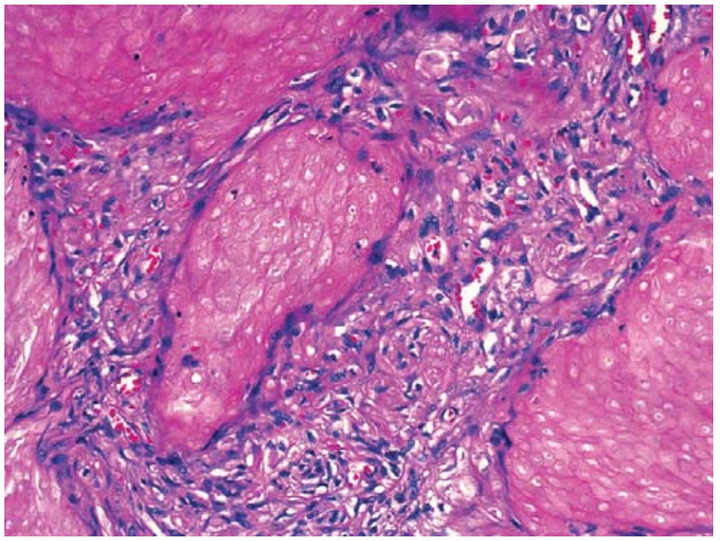


Fig. 111.15 Pilomatricoma. At high magnification, this longstanding example is notable for anucleate keratinized matrical cells ("shadow" cells) and a surrounding granulomatous reaction.

central anucleate cornified cells are commonly referred to as *ghost* or *shadow* cells.

In fully developed pilomatricomas, a cystic configuration is commonly lost. Solid collections of basaloid matrical cells and matrical corneocytes are present in varying degrees (Fig. 111.15). The cornified matrical cells elicit considerable fibrosis and a secondary granulomatous infiltrate, which can become predominant in longstanding lesions. Matrical cells have a proliferative capacity as high as any human tissue and can display numerous cells in mitosis. The designation *proliferative pilomatricoma* refers to a pilomatricoma with a high mitotic index. At times, such lesions can be misinterpreted as carcinoma[34]. In late lesions, basaloid matrical cells may be lacking. An involutional pilomatricoma at times can present with only a few shadow cells buried in a larger fibrosing granulomatous reaction. Calcification and ossification also ensue in late lesions.

Treatment

Pilomatricoma is a benign lesion that is usually treated by simple enucleation. A pilomatricoma may recur after limited excision. If multiple recurrences are observed, complete excision (with negative margins) should be performed to exclude pilomatrical carcinoma.

Pilomatrical carcinoma

Introduction

Pilomatrical (matrical) carcinoma is an uncommon malignancy that exhibits matrical cornification, much like pilomatricoma[35]. Mutations in the *CTNNB1* gene (coding for β-catenin) are common in matrical carcinoma[31]. This suggests a partial common pathogenesis for pilomatricoma and matrical carcinoma. Although on a practical basis no clear association exists, there is theoretical risk for the possibility of matrical carcinoma developing from conventional pilomatricoma.

Clinical features

Matrical carcinoma is typically a disease of adulthood. Lesions develop on the head and neck, often in the retroauricular area. Although a pathogenic link with ultraviolet irradiation has not been established, many matrical carcinomas develop within severely sun-damaged skin. If a diagnosis of matrical carcinoma is offered in a child or young adult at an age when the diagnosis is improbable, the case should be reassessed for the possibility of pilomatricoma.

Pathology

Much like pilomatricoma, matrical carcinomas include both basaloid matrical cells and anucleate matrical corneocytes. In contrast to pilomatricoma, the matrical carcinoma cells usually display nuclear pleomorphism. An infiltrative configuration or poor circumscription may be apparent, especially in an excisional biopsy. There may be considerable squamous cornification as well, and parts of a given lesion may resemble conventional squamous cell carcinoma (SCC).

Matrical carcinoma should be distinguished microscopically from BCC with matrical differentiation[36,37]. Histopathologically, the latter entity represents an otherwise conventional BCC in which small foci of matrical cornification are identifiable. The clinical behavior of this variant is thought to be identical to that of conventional BCC.

Treatment

Matrical carcinoma is a low-grade form of adnexal carcinoma that poses some risk for metastasis, although the risk is believed to be low[35]. Complete extirpation with negative margins represents standard care.

Neoplasms and Proliferations with Follicular Sheath (Trichilemmal) Differentiation

Trichilemmoma

Introduction

Trichilemmoma (tricholemmoma) constitutes a form of benign adnexal neoplasm with differentiation toward the follicular outer sheath[38]. Some have averred that trichilemmoma is merely a viral wart based upon conventional histopathology[20]. Generally, molecular analysis has failed to demonstrate intralesional papillomavirus DNA and thus viral causation seems unlikely[39].

Clinical features

Trichilemmomas may arise as simple or as multiple[38,40] papules that usually have similar coloration to surrounding normal skin (see Fig. 63.3). Individual lesions may display hyperkeratosis or a verrucous surface. Most are distributed on the central face, including the nose or upper lip, but any non-glabrous site may be affected. Trichilemmomas can also present on genital skin and simulate condylomata if multiple. Trichilemmoma may occur as a secondary neoplasm within nevus sebaceus. The variant *desmoplastic trichilemmoma* is especially common in this context[41].

Multiple trichilemmomas typically present on facial or genital skin. Multiple trichilemmomas are a common manifestation of Cowden syndrome (see Ch. 63 & Fig. 111.4)[38,42]. In addition to trichilemmomas, manifestations of Cowden disease include sclerotic fibromas, acral keratoses, and adenocarcinoma of the breast, thyroid gland or gastrointestinal tract[43].

Pathology

Microscopically, trichilemmomas present as small circumscribed lobular proliferations composed of pallid, glycogen-containing outer sheath cells. There is often a broad connection to the surface epidermis[38,40,42]. A papillated surface is common, and there may be verrucous hyperplasia with hypergranulosis, thereby simulating the pattern of a verruca in a superficial biopsy. Squamous eddies are not uncommon. There is a palisade of small, compact basal keratinocytes at the periphery of a lesional lobule, and a flanking thickened basement membrane that is PAS-D (periodic acid–Schiff with diastase)-positive is commonly present (Fig. 111.16). Outer sheath differentiation can also be recognized through use of CD34 immunostaining.

In desmoplastic trichilemmoma, small central angular clusters of outer sheath cells are arrayed in an infiltrative pattern with enveloping sclerotic stroma. This creates a configuration that at times simulates carcinoma[41,44,45]. Most commonly, a desmoplastic focus is accompanied

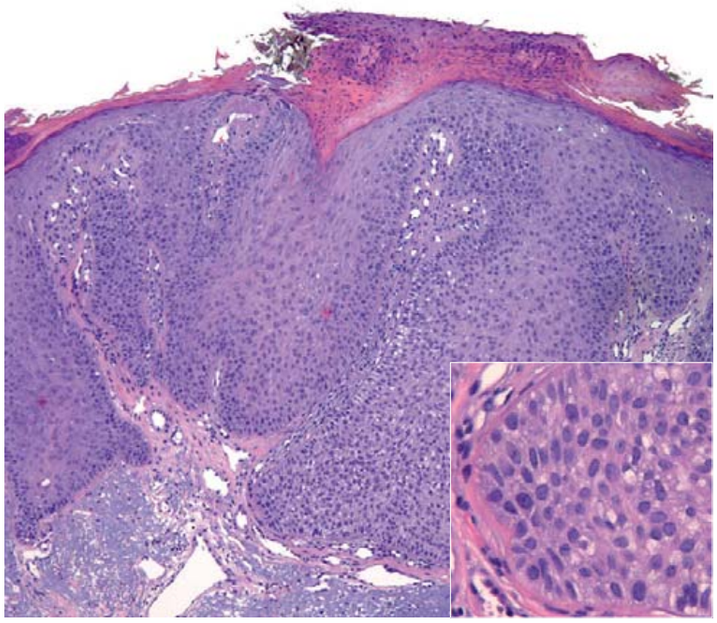


Fig. 111.16 Trichilemmoma. A benign neoplasm with a verrucous appearance arising within sun-damaged skin. Sometimes these lesions are misdiagnosed as actinic keratoses or superficial carcinomas. A thickened basement membrane flanks an area with follicular outer sheath differentiation (insert).

or surrounded by areas of conventional trichilemmoma that serve as the basis for accurate interpretation, but the diagnosis can be deceptive in partial or superficial biopsies.

Treatment

Trichilemmoma is a benign adnexal neoplasm with limited proliferative capacity. After recognition by biopsy, no further treatment is needed unless there is uncertainty regarding the diagnosis. If there is a desire for ablation, cryotherapy, electrosurgical destruction, shave, curettage or excision may be employed.

Trichilemmal carcinoma

This malignant analogue of trichilemmoma represents an invasive lesion composed in part of glycogen-containing clear cells, similar to cells of the follicular outer sheath. If a thickened, PAS-positive prominent basement membrane can be identified peripheral to areas of clear cell change, it is probably of considerable diagnostic significance. CD34 immunopositivity may also be of potential diagnostic value. Many of these carcinomas show accompanying keratinization and thus there is considerable overlap with lesions that have been pigeonholed as clear cell SCC.

Treatment

Trichilemmal carcinoma represents a carcinoma with limited metastatic potential. These lesions are probably best considered equivalent to SCC and treated as such.

Neoplasms and Proliferations with Superficial Follicular (Infundibular and Isthmic) Differentiation

Tumor of follicular infundibulum (isthmicoma)

Introduction

This benign lesion is commonly known as *tumor of follicular infundibulum (TFI)* or *infundibuloma*, but the designation *isthmicoma* is more apt, as the proliferation primarily shows follicular isthmic differentiation.

Clinical features

TFI prototypically presents clinically as a subtle macule, thin papule or plaque[46,47]. Lesions are skin-colored or sometimes slightly hypopigmented and may appear slightly atrophic[46]. Many examples are diagnosed incidentally within skin cancer excision specimens where no known clinical lesion was even identifiable. TFI may occur in multiplicity (Fig. 111.17A), and patients with this presentation may defy diagnosis for a time because of the subtlety of both the clinical and the microscopic findings[46–49]. Patients with multiple atrophic-appearing TFI may display a clinical pattern reminiscent of disseminated superficial porokeratosis or multiple actinic keratoses. TFI is occasionally present in Cowden disease.

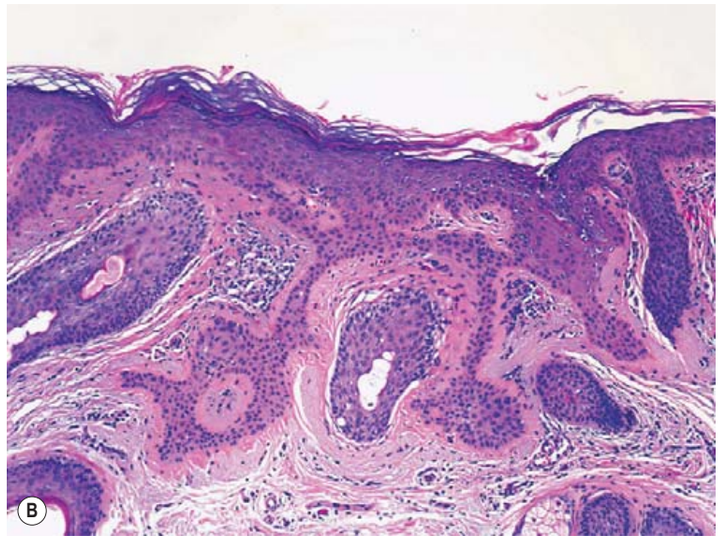


Fig. 111.17 Tumor of follicular infundibulum. A Multiple hypopigmented thin papules on the cheek. **B** The microscopic pattern is subtle, resembling a reticulated seborrheic keratosis. Strands of pale eosinophilic keratinocytes display multifocal attachment to the epidermal surface and also commonly interconnect with existent follicular structures.

Pathology

TFI consists of a plate-like proliferation of eosinophilic isthmic keratinocytes arrayed in reticulate fashion in the superficial dermis, in broad but intermittent continuity with both the surface epidermis and extant follicular structures[46]. Most of the constituent keratinocytes have cytoplasm similar to keratinocytes of the follicular isthmus, follicles in catagen phase, or the cells of an isthmic (pilar) cyst (Fig. 111.17B). The keratinocytes are paler than those of the surface epidermis, and sometimes a few scattered dyskeratotic keratinocytes are present. Some lesions will display trichilemmal foci in which pallid keratinocytes or a thickened basement membrane can be found, and occasionally a hybrid of TFI and trichilemmoma may be encountered. Additionally, small buds of follicular germinative cells may jut from the undersurface of a TFI.

Rarely, small clusters of sebocytes may be found within TFI[50]. Sebaceous or apocrine ducts have also been documented[49].

Treatment

TFI is a benign adnexal proliferation with negligible proliferative capacity. If desired, lesions may be removed by cryotherapy, shave, or electrosurgical destruction. For multiple lesions, superficial laser ablation can be considered[46].

Trichoadenoma (trichoadenoma of Nikolowski)

Introduction

The term *trichoadenoma* is a misnomer, as there are no adenomas of follicular lineage since the hair follicle is not a structure that exhibits glandular differentiation. Trichoadenoma represents a benign follicular neoplasm with sclerotic stroma that consists largely of small cystic spaces that exhibit infundibular and isthmic differentiation[51].

Clinical features

The clinical presentation of trichoadenoma is not distinctive. The neoplasm presents as a skin-colored papule or small plaque.

Pathology

Trichoadenoma is usually positioned in the superficial dermis. Cornifying cysts with infundibular or isthmic keratinization comprise the bulk of the proliferation[51]. The sclerotic stroma is often accompanied by thin strands of basaloid cells, similar to the cords observed in desmoplastic trichoepithelioma (Fig. 111.18). The degree of microscopic overlap between trichoadenoma and desmoplastic trichoepithelioma can be remarkable, and "pure" trichoadenomas may represent one pole of the spectrum of histopathologic findings that can be seen.

Treatment

Trichoadenoma is a benign adnexal neoplasm with negligible proliferative capacity. No further treatment is necessary unless the patient desires removal.

Proliferating pilar tumor (proliferating follicular-cystic neoplasm)

Introduction

Known for decades as *proliferating pilar tumor (PPT)* or *proliferating pilar cyst*, the designation *proliferating follicular-cystic neoplasm (PFCN)* was proposed by Ackerman as a more apt designation[20]. This term describes a group of nodular/cystic neoplasms characterized microscopically by abrupt keratinization akin to that of the follicular isthmus or in a follicle in catagen phase[52]. In the past, it was known that PPT could simulate SCC microscopically, but the entity was generally regarded as a benign process, although it was recognized that, occasionally, locally destructive behavior could occur[52].

Recently, this concept has been called into question, and a proposal has been issued that PFCN represents a mix of benign and malignant neoplasms grouped together under one rubric[20]. The proposal further iterates that a benign PFCN should be designated as *proliferating follicular-cystic acanthoma (PFCA)*, while a malignant PFCN should be designated as *proliferating follicular-cystic carcinoma (PFCC)*. As some examples of PFCN share features with carcinoma, including clinical characteristics such as locally destructive behavior, microscopic characteristics such as nuclear atypicality and molecular characteristics such as aberrations in ploidy, this proposal seems diagnostically practical[53–55].

Clinical features

PPT presents as a nodule, usually no more than a few centimeters in size, although there have been reports of lesions exceeding 20 cm in diameter. The lesions can develop in men but a female predominance is seen in most series. Roughly 90% of cases arise in the scalp, probably as a reflection of the density of follicles at that locale. The prototypical presentation is as a nodule on the scalp of an elderly woman. The lesions are usually well circumscribed but may be multinodular. Their circumscription is reflected in smooth borders and the fact that lesions generally shell out from adjacent tissues during surgical excision.

Pathology

PPT consists of a large and/or deep nodule that resides in the dermis or subcutis[52]. Because of its large size, the laboratory commonly receives fragmented specimens. Both solid and cystic patterns are usually evident at low magnification, with cystic areas exhibiting the pattern of an isthmic (pilar) cyst. The constituent keratinocytes are mostly isthmic keratinocytes with dense eosinophilic cytoplasm, and centrally there is an abrupt transition to compact keratin with little intervening granular layer (Fig. 111.19). Rarely, shadow cells, implying matrical keratinization, can be found. There may be focal necrosis and calcification.

The degree of cytologic atypicality varies among lesions and amongst different areas of a given lesion. Commonly, the neoplastic cells contain enlarged vesicular nuclei with prominent nucleoli and some degree of nuclear hyperchromasia, and mitotic figures are usually identified, but overt anaplasia is usually not present. Since some examples of PPT represent low-grade forms of carcinoma, tumors with marked cytologic atypicality, extensive necrosis, a lack of circumscription, or

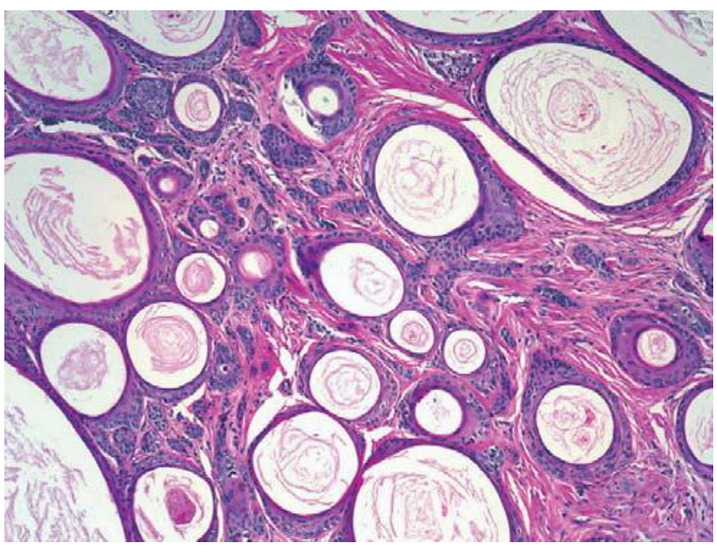


Fig. 111.18 Trichoadenoma. This lesion consists almost exclusively of small keratinizing cystic spaces. There are also a few strands of basaloid cells and sclerotic stroma, similar to the pattern observed in desmoplastic trichoepithelioma.

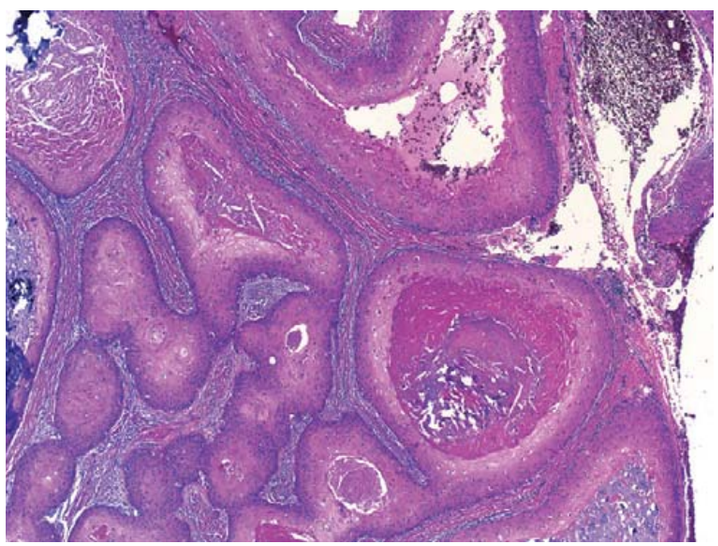


Fig. 111.19 Proliferating follicular-cystic neoplasm. This complex multicystic neoplasm shows abrupt keratinization, similar to the pattern exhibited at the follicular isthmus. Although it can be difficult to determine whether these lesions are benign or malignant, this example was well circumscribed and was eradicated by simple enucleation.

extraordinary numbers of mitotic figures warrant designation as PFCC[53,55].

Treatment

As noted, some examples of PPT may represent carcinoma. If a lesion has been enucleated in its entirety or near entirety, is circumscribed, and lacks substantial cytologic atypism, it can be interpreted as PFCA and additional surgical therapy is not necessary. If a given lesion lacks circumscription, shows substantial cytologic atypism or necrosis, or has been sampled *en parte*, then complete excision is warranted, as PFCC remains a concern.

NEOPLASMS AND PROLIFERATIONS WITH SEBACEOUS DIFFERENTIATION

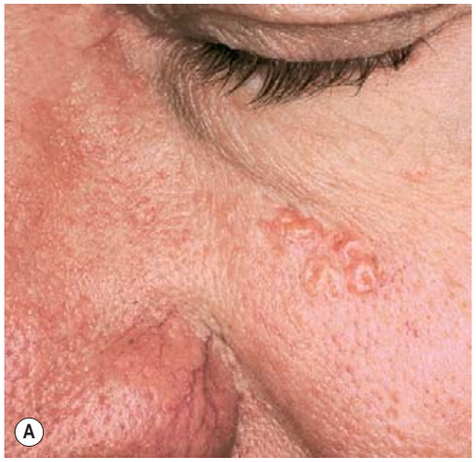
Sebaceous gland hyperplasia

Introduction

Sebaceous gland hyperplasia (SGH) does not represent a true neoplasm. It represents benign enlargement of sebaceous glands.

Clinical features

SGH is relatively common and presents with one or multiple yellowish, occasionally telangiectatic papules, usually on the central or upper face (Fig. 111.20) and sometimes on the upper trunk. Commonly, the clinical lesions display a central dell that corresponds to a central follicular infundibular ostium. *Beaded lines* represent a unique expression of SGH in which a linear array of hyperplastic sebaceous glands is present in the vicinity of the clavicle or on the neck[56]. Biopsy is occasionally indicated to exclude BCC.



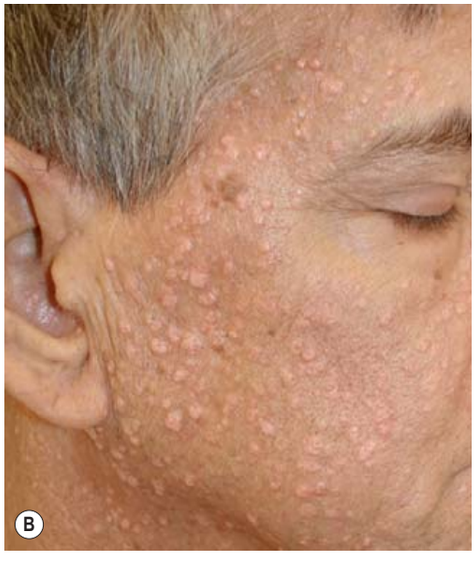


Fig. 111.20 Sebaceous hyperplasia. A Skin-colored to yellowish papules with a central dell. **B** Numerous lesions of sebaceous hyperplasia in a solid organ transplant recipient receiving long-term cyclosporine. *B, Courtesy, Oscar Colegio, MD, PhD.*

Pathology

The sebaceous gland in SGH shows normal morphology, with a thin rim of seboblasts surrounding the remainder of the gland, composed of mature sebocytes. The enlarged sebaceous lobules usually circumferentially surround a central infundibulum.

Treatment

If treatment is desired, lesions can be removed or diminished by shave, light electrosurgical destruction, cryotherapy, or laser ablation[57]. Long-term topical retinoid application may be beneficial. Oral isotretinoin has been utilized for patients with extensive disfiguring lesions.

Sebaceous adenoma, sebaceous epithelioma and sebaceoma

Introduction

The term *adenoma* designates a benign neoplasm with glandular differentiation, and any benign proliferation with predominance of sebaceous differentiation can be grouped under this rubric. Commonly, the term sebaceous adenoma has been applied to superficial benign sebaceous neoplasms with a predominance of mature sebocytes, while sebaceous epithelioma and sebaceoma have been applied to sebaceous neoplasms with a predominance of seboblasts. Troy and Ackerman[58] coined *sebaceoma* as an alternative to describe a group of benign sebaceous proliferations that were generally more deeply situated than superficial sebaceous adenomas and in which a vertically oriented microscopic pattern was identifiable.

The dated term sebaceous epithelioma is inherently confusing, as the diagnosis has been utilized differently by various authorities. To some, a sebaceous epithelioma represents a low-grade form of sebaceous carcinoma or BCC with sebaceous differentiation. Others have utilized the term to characterize sebaceoma or sebaceous proliferations of uncertain potential. We believe that the designation sebaceous epithelioma should be abandoned.

In this chapter, the term *sebaceous adenoma* is used in broad fashion to encompass both conventional sebaceous adenoma and sebaceoma.

Clinical features

Sebaceous adenomas present clinically as papules or nodules, usually less than a centimeter in diameter, distributed on the head or neck and sometimes on the upper trunk. The lesions are not clinically distinctive except when there is a yellowish color, which is often not apparent. Superficial sebaceous adenomas are usually relatively small and papular, while sebaceomas may present as a deep nodule[58,59]. Multiple sebaceous neoplasms, especially cystic ones, may serve as a presenting sign of the Muir–Torre syndrome (see Ch. 63 & Fig. 111.4), characterized also by multiple keratoacanthomas and visceral carcinomas, especially colonic adenocarcinoma[60,61].

Pathology

Conventional sebaceous adenoma is usually captured in continuity with the surface epidermis and is relatively small and circumscribed. The relative proportions of basaloid seboblastic cells and mature sebocytic cells varies, but sebocytes usually predominate. Seboblasts comprise a thin multilayer of cells at the periphery of each lobule. Mitotic figures can be found in seboblasts but are not conspicuous. Necrosis is not typically evident in an adenoma unless the lesion has been traumatized. Significant necrosis, whether of single cells or *en masse*, raises concern for the possibility of carcinoma.

Sebaceoma is usually more deeply situated, often involving the deep reticular dermis and sometimes the superficial subcutis[58]. The lesions are sharply circumscribed in an excisional specimen, but this may be difficult to fully appreciate in a biopsy *en parte*. Seboblasts predominate in sebaceoma and sebocytic differentiation may be only focal, yielding a microscopic pattern not unlike large nodular trichoblastoma (Fig. 111.21). If sebaceous differentiation is only focal, then epithelial membrane antigen (EMA) or adipophilin immunoperoxidase staining can be considered as a diagnostic supplement. EMA labels mature sebocytes in the normal sebaceous gland, while adipophilin labels fat-containing cells.

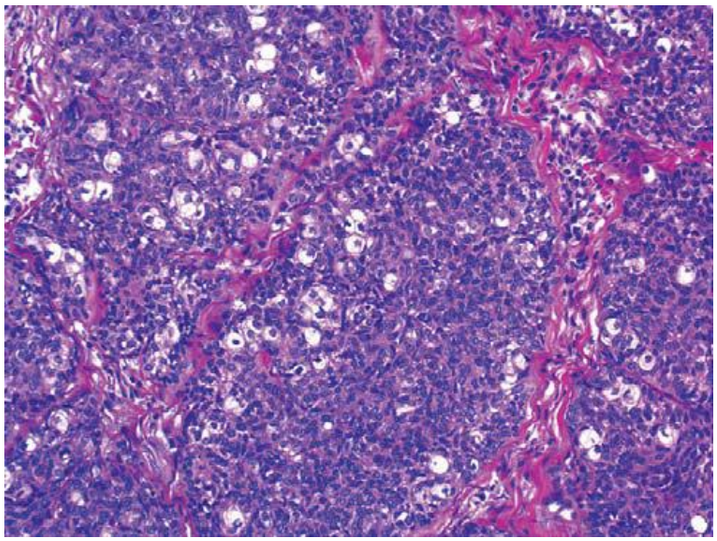


Fig. 111.21 Sebaceous adenoma (sebaceoma). This high-magnification view shows a background of basaloid seboblastic cells punctuated by scattered mature sebocytes with coarsely vacuolated cytoplasm. The neoplasm was large but sharply circumscribed at low magnification.

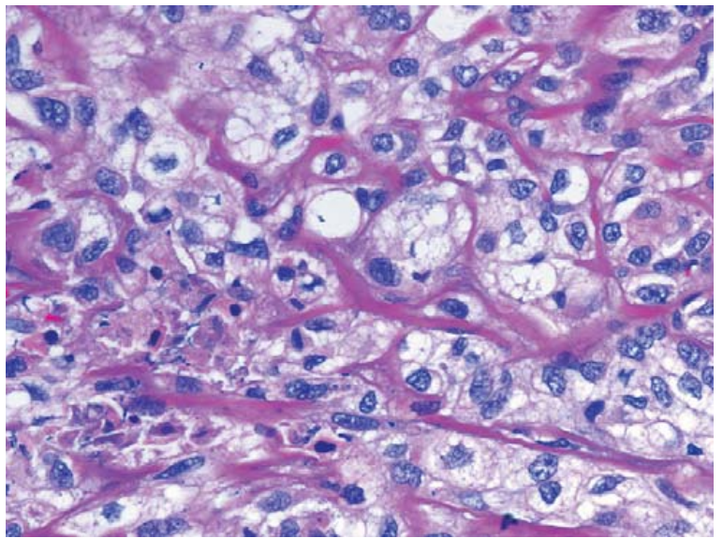


Fig. 111.22 Sebaceous carcinoma. At high magnification, there are cells with atypical nuclei and ample coarsely vacuolated cytoplasm. There are also many necrotic cells with pyknotic nuclei.

Treatment

Once a definite microscopic diagnosis has been achieved, no further treatment is obligatory. It is often difficult to establish the circumscription of lesions captured in superficial or partial biopsies. Complete excision of such lesions is appropriate to exclude the possibility of BCC with sebaceous differentiation or sebaceous carcinoma. Deeply situated lesions of Muir–Torre syndrome may be prone to rapid growth.

Sebaceous carcinoma

Introduction

The term sebaceous carcinoma designates an adenocarcinoma with sebaceous differentiation. By historical convention, these carcinomas have been separated into ocular and extraocular types. Extraocular sebaceous carcinoma is thought to hold a graver prognosis, although the data behind this belief are old and have been questioned[62].

Clinical features

The clinical presentation of sebaceous carcinoma is not distinctive. Typical clinical lesions include erythematous nodules or plaques that may be ulcerated or crusted and only occasionally display yellowish coloration. More commonly, the lesions display an erythematous or pearly morphology that is indistinguishable from common forms of non-melanoma skin cancer. Early in presentation, ocular lesions are very commonly misdiagnosed as blepharitis or ocular rosacea.

Sebaceous carcinomas commonly develop in the periorbital area but also occur elsewhere on the head and neck and less commonly on the trunk. Carcinomas from the trunk commonly display a nodular pattern, and superficial biopsies from such lesions may be deceptive and can be misinterpreted[62]. Sebaceous carcinoma can occur in patients with Muir–Torre syndrome, but the identification of a sebaceous carcinoma alone is not sufficient to diagnose the syndrome[60]. However, any unusual sebaceous neoplasm is probably sufficient provocation for consideration of the disease.

Pathology

Like many malignancies, sebaceous carcinoma often exhibits asymmetry, a lack of circumscription, and areas with an infiltrative pattern. In nodular sebaceous carcinoma, cells are arrayed as large nests and lobules. In infiltrative sebaceous carcinomas, jagged nests and thin strands are found. Sebaceous carcinoma can involve the surface epidermis or conjunctiva, in a pagetoid pattern, especially in ocular lesions[63,64]. This can be confused with Bowen's disease or melanoma.

The degree of sebaceous differentiation in sebaceous carcinoma varies greatly, as does the degree of nuclear atypicality (Fig. 111.22). Some carcinomas display obvious sebocytic differentiation, while other examples may be largely seboblastic or undifferentiated in appearance.

Stains for lipid, such as oil red O or Sudan black, have been utilized in the past as a tool to confirm sebaceous differentiation through labeling of cytoplasmic fat. However, such stains have little routine practical applicability as they require the use of frozen tissue substrate. EMA and adipophilin immunoperoxidase staining represent the best supplemental tests for confirmation of sebaceous differentiation. When authentic sebaceous differentiation is present, coarsely vacuolated cytoplasmic positivity can be seen with either stain.

Crateriform or cystic sebaceous neoplasms that display a clinical and microscopic pattern reminiscent of keratoacanthoma are uncommon lesions that probably represent low-grade carcinomas[60]. Sebaceous neoplasms with a keratoacanthoma-like pattern probably only occur in the context of Muir–Torre syndrome.

Treatment

Sebaceous carcinoma is an adnexal carcinoma with significant albeit variable metastatic potential. The primary treatment remains surgical extirpation. Although the risk of metastatic disease was formerly believed to be high, particularly for ocular carcinomas, the data contained within many older reports may be skewed by inclusion of carcinomas diagnosed late in their evolution. Extensive disease of the eye has been treated with ocular enucleation, especially when ocular conjunctival involvement was present. The metastatic potential of both superficial sebaceous carcinoma and sebaceous carcinoma with an infiltrative pattern may be limited, although additional study will be necessary to fully establish this.

NEOPLASMS AND PROLIFERATIONS WITH APOCRINE DIFFERENTIATION

In most textbooks, adnexal neoplasms with glandular and ductular differentiation have been rigorously separated into eccrine and apocrine neoplasms. Commonly, the distinction was based upon enzyme histochemistry, an imprecisely applied technique that is no longer available. Discrimination has also been based upon conventional microscopic assessment, a useful but imprecise tool, at least for the distinction of eccrine and apocrine attributes.

A few authorities have responded to this difficulty by grouping apocrine and eccrine neoplasms together, in recognition of the fact that it is impossible to determine whether a given lesion, such as a given syringoma, is of apocrine or eccrine lineage. In the sections that follow, the traditional categorization as apocrine or eccrine will be maintained, but areas of overlap will be expressly noted. For entities such as syringoma, poroma and hidradenoma, which can be of either apocrine or

eccrine lineage, the presentation will be included in the discussion of apocrine lesions.

Benign Neoplasms and Proliferations with Apocrine Ductular and Tubular Differentiation

Syringoma

Introduction

Syringoma represents a benign adnexal neoplasm with mostly ductal (syringeal) differentiation. Historically, syringomas have been interpreted as neoplasms of eccrine lineage[65,66]. The term syringoma can be used to describe neoplasms of either apocrine or eccrine lineage, and it is currently impossible to judge the lineage of any given lesion other than by its context[1,2].

Clinical features

A syringoma manifests clinically as a small, firm, skin-colored papule. Syringomas commonly present in multiplicity (Fig. 111.23) and may be eruptive[67,68]. The lesions are removed from women more commonly than men, although it is not clear that this represents authentic gender predilection. There is an increased incidence in Asian populations as well as an association with Down syndrome. Clear cell syringomas are associated with diabetes mellitus.

Syringomas may occur at any site on the body but are prone to occur in the periorbital area, especially the eyelids. Sometimes, lesions involve the upper trunk, favoring the ventral surface, or genital skin[67–69]. Eruptive syringomas most commonly involve the trunk but may involve the extremities, including the palms and soles. Acral syringomas, which are rare, are those that are most clearly of eccrine lineage, as the acini of glabrous (non-hair-bearing) skin are exclusively eccrine[70].

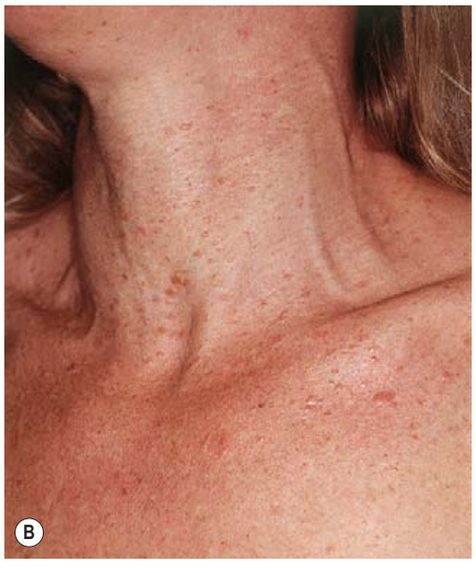


Fig. 111.23 Syringomas. **A** Aggregated skin-colored papules on the eyelids. **B** Multiple skin-colored to pink, smooth papules on the neck and upper chest. The lesions favor the ventral surface of the trunk, a distribution pattern referred to as *"en demicuirasse".* *B, Courtesy, Jean L Bolognia, MD.*

Pathology

From scanning magnification, a syringoma is small and circumscribed and is usually confined to the superficial dermis. The encompassing stroma is sclerotic. The epithelial component of the proliferation is composed of cells with pale or pinkish cytoplasm forming nests and tubules of relatively uniform size. Depending upon the exact plane of section, the nests of a syringoma vary in shape, and some nests may assume a morphology that resembles a comma or a tadpole (Fig. 111.24). Tubular areas exhibit ductular differentiation with central lumina lined by a compact eosinophilic cuticle. Typically, half or more of the nests in a given plane of section will show central ductal differentiation.

Usually, a syringoma lacks keratinization, although at times superficial cornification can be seen. Syringomas also typically lack evidence of follicular differentiation. If either follicular differentiation or keratinization is identified, other differential diagnostic possibilities should be strongly considered. The combination of superficial cornification, poor circumscription, and extension into the deep reticular dermis (or subcutis) favors microcystic adnexal carcinoma over syringoma. A lesion with strands of basaloid cells, focal superficial cornification and focal calcification probably represents desmoplastic trichoepithelioma rather than syringoma. If there are only cornifying cysts present and authentic ductal differentiation is lacking, then the most likely diagnosis is trichoadenoma.

Treatment

Syringoma is a benign adnexal neoplasm with negligible proliferative capacity. After definitive diagnosis, no further surgical intervention is needed unless adnexal carcinoma remains a clinicopathologic consideration. Syringomas may be treated with careful application of trichloroacetic acid, cryotherapy, punch excision, or electrosurgical destruction, with variable results. This can be difficult in the common situation in which multiple lesions are present on eyelids. Disseminated lesions can be cosmetically disabling and therapeutically challenging, and laser ablation might be the best choice[71].

Poroma

Introduction

Poroma designates a group of benign adnexal neoplasms with poroid (terminal ductal) differentiation. Like syringomas, poromas were widely interpreted historically as neoplasms of eccrine lineage because of dubious enzyme histochemistry[65,66]. The words *eccrine* and *poroma* became seemingly inextricably linked in the dermatologic lexicon, and thus poromas are often referred to as eccrine in reflexive fashion[2]. Poroma can be a proliferation of either apocrine or eccrine lineage[72–75]. Eccrine and apocrine poromas probably occur in nearly equal numbers.

The term *acrospiroma* is used by some authorities as a synonym for poroma and is used by other authorities as a broad designation that encompasses both poroma and hidradenoma.

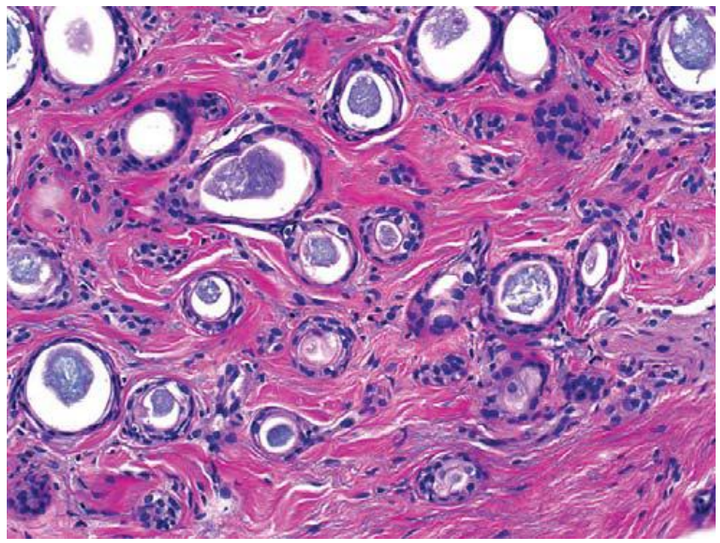


Fig. 111.24 Syringoma. This superficial adnexal neoplasm consists of nests of cells with pale cytoplasm positioned within sclerotic stroma. Many nests show central ductal differentiation with a compact eosinophilic cuticle.

Clinical features

Poromas usually present as solitary papules, plaques or nodules (Fig. 111.25)[4]. When sessile vascular plaques surrounded by thin indented moats appear on the palms and soles, an astute dermatologist can strongly suspect the diagnosis. They can appear on any cutaneous surface, where they are less readily identified with specificity. The scalp is another common site, with or without an associated nevus sebaceus[13]. Presumably, poromas arising secondarily within nevus sebaceus represent apocrine poromas. Occasionally, a poroma will be pigmented. Poromas commonly display highly vascularized stroma, and a clinical pattern suggestive of pyogenic granuloma is common, especially in poromas that involve acral skin. Rarely, multiple poromas will develop, either in an acral or in a widespread distribution, a clinical pattern referred to as poromatosis.

Pathology

The principal finding in all forms of poroma consists of a circumscribed proliferation of compact cuboidal keratinocytes with small monomorphous nuclei and scant eosinophilic cytoplasm. Poromas can be wholly intraepidermal, a pattern known historically as hidroacanthoma simplex; can occur in broad continuity with the epidermis (juxta-epidermal poroma; Fig. 111.26); or can develop wholly (or nearly so) within the dermis (intradermal poroma; Fig. 111.27), a pattern known historically as dermal duct tumor[3]. Accompanying stroma may be scant in association with intraepidermal poroma.

The degree of ductal differentiation varies greatly in individual neoplasms. Some poromas display innumerable foci in which poroid cells form small cuticulated ductal spaces. In other lesions, ducts may be difficult to identify, and a resemblance to seborrheic keratosis may ensue. Carcinoembryonic antigen (CEA) immunostaining, which labels the luminal surface of both apocrine and eccrine ducts, can be employed as a tool to confirm the presence of ductal differentiation. Poromas may occasionally display tubular (rather than ductular) foci in which a central cuticle is lacking. If such tubular foci are lined by columnar cells with holocrine secretion at the luminal border, a presumptive diagnosis of apocrine poroma can be offered.

At times, a poroma may display striking clear cell change. The constituent nuclei in such lesions are small but are surrounded by ample pale cytoplasm. Poromas are an exception to the rule that necrosis *en masse* is a clue to a malignancy. Curiously, poromas commonly display small collections of cells in coagulation necrosis. In malignant tumors, necrosis is usually a consequence of rapid growth (growth beyond the capacity of perfusion), but this is an unlikely explanation for necrosis in poroma, in which cellular proliferation is low. Poromas may occasionally display small foci of sebaceous differentiation, which usually consists of clusters of mature sebocytes near the lesion base[72,76,77].

Treatment

Poroma is a benign adnexal neoplasm and thus treatment is optional. Superficial lesions may be treated by shave or electrosurgical destruction. Superficial or deeper lesions may also be treated with simple excision.

Fig. 111.25 Poroma. A biopsy specimen is necessary to establish a definitive diagnosis.

Hidradenoma

Introduction

Hidradenoma is a form of benign adnexal neoplasm that is a close relative of poroma but is usually characterized by cells with ample cytoplasm, is never wholly intraepidermal, and does not commonly have a broad-based connection to the epidermis. As has been mentioned, some authorities use the broad designation *acrospiroma* to refer to both hidradenoma and poroma jointly. Although commonly classified as an eccrine neoplasm, hidradenomas are currently thought to be of either apocrine or eccrine lineage[65,66]. The vast majority of hidradenomas are believed to be of apocrine lineage[1,78].

Clinical features

Hidradenoma lacks any distinctive clinical attributes. The lesion presents as a solitary dermal or subcutaneous nodule; sometimes, a cystic quality or serous drainage can be detected.

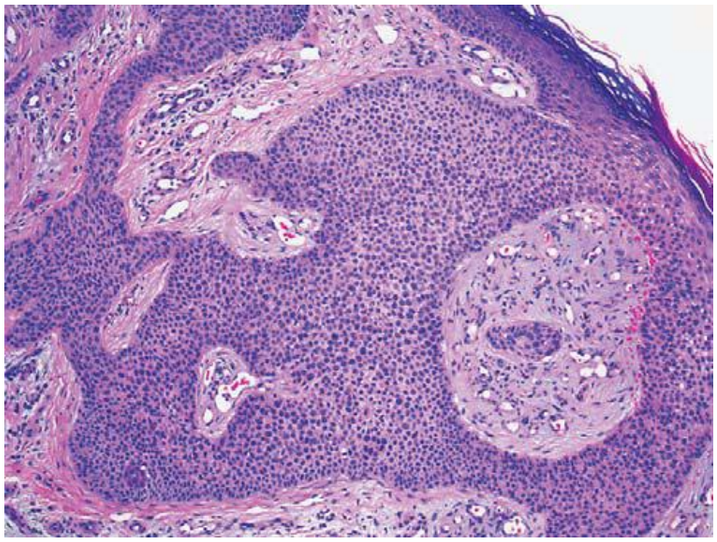


Fig. 111.26 Poroma, juxta-epidermal pattern. This poroma displays a pattern common to both eccrine and apocrine poroma. There are interanastomosing cords composed of small compact "poroid" cells, and the intervening stroma is highly vascularized and resembles granulation tissue.

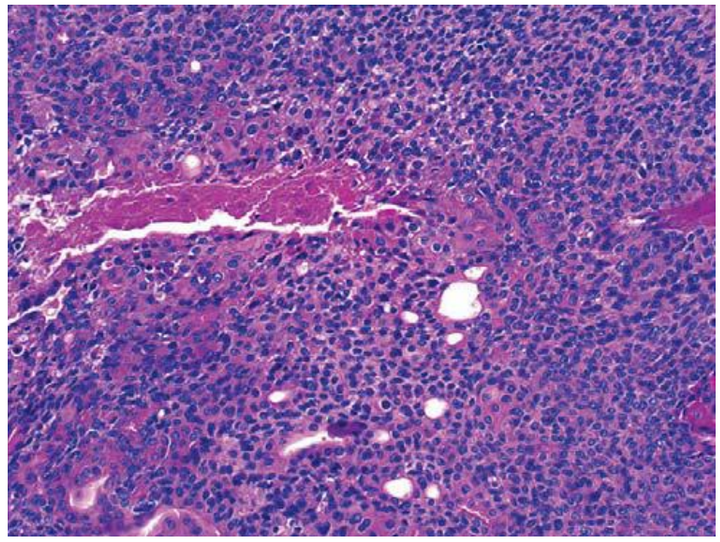


Fig. 111.27 Poroma, intradermal pattern. At low magnification, this lesion was a well-circumscribed dermal nodule. This high magnification shows conspicuous foci of ductal differentiation and also a focus of necrosis *en masse,* a finding common to poroma that is uncommon in other benign neoplasms.

Pathology

Hidradenomas are mostly dermal neoplasms with a nodular, sharply circumscribed pattern when viewed at low magnification. Some hidradenomas may display a juxta-epidermal pattern superficially with multifocal attachment to the epidermis, much like poroma. Although the stroma of hidradenoma is commonly sclerotic and may contain ectatic vessels, usually the granulation tissue-like quality that typifies the stroma of a poroma is not present. If desmoplastic stroma is conspicuous and exaggerated, the designation *desmoplastic hidradenoma* is recommended. The cells of hidradenoma are large with ample cytoplasm but uniform nuclei, which are generally somewhat larger than the nuclei of poroma. Overt clear cell change (clear cell hidradenoma) is common, as is cystic degeneration (solid-cystic hidradenoma)[79,80] (Fig. 111.28). Ductal differentiation can be found with scrutiny, although the degree observed may be minimal. Some lesions contain tubules lined by columnar cells with a decapitation pattern along their luminal border; such lesions can be designated as apocrine hidradenoma without question. Not surprisingly, hybrid lesions with features of both hidradenoma and poroma can be encountered, and the intermediate term *poroid hidradenoma* has been applied in this setting[81].

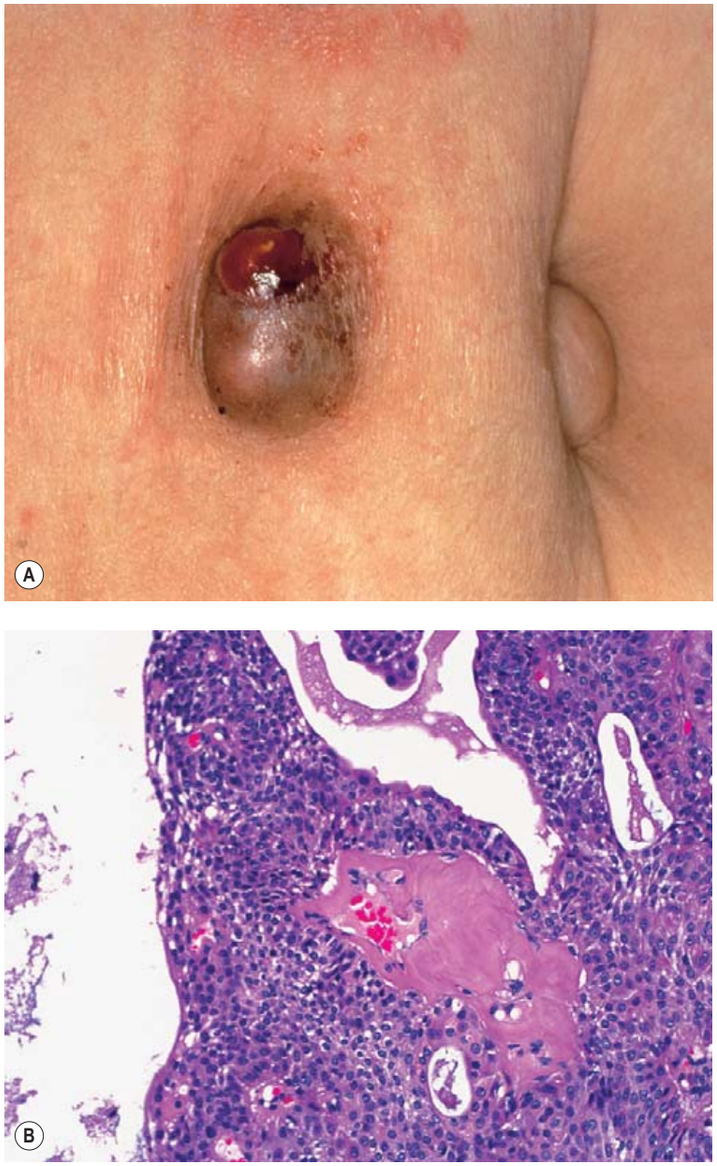


Fig. 111.28 Hidradenoma. A Solitary violaceous nodule on the abdomen with serous drainage. **B** This well-circumscribed nodule is composed of cells with small uniform nuclei and ample cytoplasm that often is pale or shows overt clear cell change. A cystic focus is present; lesions that display prominent cystic change have been referred to as "solid-cystic" hidradenoma.

Treatment

Hidradenoma is a benign adnexal neoplasm. Complete conservative excision is curative.

Apocrine adenoma

Introduction

Any benign neoplasm with apocrine differentiation, including poroma and hidradenoma, could be grouped under the broad roof of this rubric. On a practical basis, only adenomas with conspicuous glandular differentiation are included in this category. Usually, these proliferations exhibit abundant apocrine epithelium and conspicuous decapitation secretion, in which part of the cytoplasm pinches off into a lumen. Apocrine adenomas may present with a tubular or papillary microscopic pattern or a combination of the two. Entities within this conglomeration include *tubular adenoma, papillary adenoma, syringocystadenoma papilliferum* and *hidradenoma papilliferum*. The latter entity, also known as *papillary hidradenoma*, is a source of potential semantic confusion with conventional hidradenoma. Papillary hidradenoma (hidradenoma papilliferum) is an apocrine adenoma that usually exhibits a pronounced frond-like pattern with apocrine epithelium lining the constituent papillae. In contrast, conventional hidradenoma (acrospiroma) exhibits a mostly solid configuration.

Tubular, papillary or tubulopapillary adenomas with conspicuous apocrine differentiation may develop within the parenchyma or secretory apparatus of the breast. Apocrine adenomas in continuity with the nipple commonly exhibit a tubulopapillary pattern and have been referred to as *erosive adenomatosis*[82–84]. In addition to a tubulopapillary pattern, apocrine adenomas of the nipple may display small foci with solid and cribriform patterns, but usually necrosis is not identifiable. As such lesions are usually solitary, as erosion is commonly not present, and as the designation erosive adenomatosis is somewhat provocative, it is probably best to employ the simple term *nipple adenoma* in this context. The distinction between nipple adenoma and ductal adenocarcinoma can sometimes be challenging, and consultation with an experienced breast pathologist should be sought in difficult cases.

Clinical features

The presentation of tubular or papillary adenoma is not distinctive. These tumors present as smooth papules or nodules, and biopsy is required for diagnosis.

Syringocystadenoma papilliferum presents as a papule or plaque almost exclusively on the head or neck (Fig. 111.29). Syringocystadenomas usually exhibit a crusted surface that may ooze serosanguinous fluid; this is a reflection of the fact that the papillae of a syringocystadenoma are in continuity with the epidermal surface, permitting extrusion of secretory products. Most papillary syringoadenomas present on the scalp in association with nevus sebaceus[13,85].

Hidradenoma papilliferum usually presents as a smooth dermal or subcutaneous nodule, usually no more than a centimeter in diameter. Most papillary hidradenomas arise on the vulva, but development

Fig. 111.29 Syringocystadenoma papilliferum. Grouped papules and nodules with scale-crust. The possibility of an associated nevus sebaceus needs to be considered.

within skin of the breast, axilla, and inguinal or perianal areas has also been documented[86].

Pathology

At low magnification, tubular and papillary adenomas are usually well-circumscribed neoplasms positioned within the dermis, the superficial subcutis, or a combination of the two. Adenomas with a tubular pattern are composed mostly of rounded glandular spaces that vary in size and are lined by one or several layers of cuboidal cells with pale cytoplasm and small nuclei. Most spaces have small lumina and some display columnar apocrine cells apically. Papillary adenomas contain conspicuous tufts, with luminal cells that display an apocrine pattern. A combination of tubular and papillary patterns is not uncommon.

Papillary syringocystadenoma (syringocystadenoma papilliferum) is distinctive for its wide papillary fronds that are in continuity with the surface squamous epithelium. Syringocystadenomas are only rarely cystic. The fronds are lined by a bilayer, with basal cuboidal cells and apical columnar apocrine cells, and the cores of fronds virtually always contain a dense infiltrate of lymphocytes and plasmacytes (Fig. 111.30). A plasmacytic infiltrate commonly accompanies neoplasms of apocrine lineage, and thus the mere presence of plasma cells in a given lesion is not sufficient to confirm a diagnosis of syringocystadenoma.

At low magnification, papillary hidradenoma (hidradenoma papilliferum) consists of a well-circumscribed nodule within the dermis and usually lacks both a connection to the surface epithelium and the prominent plasmacytic infiltrate of syringocystadenoma papilliferum. Both tubules and papillary fronds are usually present, and broad elongated fronds with delicate fibrous cores are usually identifiable (Fig. 111.31). Both tubules and fronds are usually lined by a bilayer, with basal cuboidal myoepithelial cells and apical apocrine cells, and the apical cells usually display a conspicuous holocrine secretion. At least some of the basal layer cells represent authentic myoepithelial cells with contractile function, and labeling of the myoepithelial layer through immunoperoxidase staining for actin filaments can sometimes be of diagnostic value in the distinction from adenocarcinoma, which often lacks a complete myoepithelial layer.

Treatment

Apocrine adenomas are completely benign lesions. Complete conservative excision is curative.

Undifferentiated Neoplasms of Apocrine Lineage

Most adnexal neoplasms contain foci of differentiation that may be rudimentary but that are readily interpretable as representing normal structures. For example, while trichoblastoma is largely undifferentiated, it contains foci such as papillary mesenchymal bodies that clearly indicate follicular germinative lineage. In contrast, two closely-related entities, spiradenoma and cylindroma, display either a general lack of differentiation or display differentiation not readily identifiable as indicative of a normal structure. Both spiradenoma and cylindroma occasionally display tubular foci with a decapitation luminal pattern, suggesting apocrine lineage, but mostly these neoplasms display uninterpretable/unrecognizable differentiation.

Spiradenoma

Definition

The term *spiradenoma* connotes a benign adnexal neoplasm that has been historically designated as being of eccrine lineage, although reassessment indicates an apocrine process[1,65,66]. Spiradenoma not uncommonly occurs jointly with cylindroma and both occur jointly with trichoepithelioma/trichoblastoma (see Fig. 111.4); the most parsimonious explanation for this complex juxtaposition is that both spiradenoma and cylindroma are of folliculosebaceous-apocrine lineage[87,88]. Both spiradenoma and cylindroma occur jointly with trichoepithelioma in the Brooke–Spiegler syndrome that is due to mutations in *CYLD*, again implying kinship rather than disparate lineage. Spiradenoma has never been observed on glabrous (non-hair-bearing) skin. If spiradenoma were truly eccrine, occurrence on the palm or sole would be the rule and not the exception.

Clinical features

Spiradenoma typically presents as a dermal or subcutaneous papule or nodule on nearly any location; extraordinary lesions may achieve a diameter of several centimeters. Sometimes, spiradenomas are painful. The clinical lesions are not distinctive and biopsy is required for diagnosis, although an astute dermatologist can suspect the diagnosis in the setting of a painful nodule with a bluish hue. Spiradenomas may occur in multiplicity and in concert with cylindroma and trichoblastoma, and multiple lesions should prompt consideration of a diagnosis of Brooke–Spiegler syndrome.

Pathology

At low magnification, spiradenoma assumes a multinodular pattern with relatively large nodules positioned within the dermis and subcutis. Although the nodules may be asymmetrically distributed, each is sharply circumscribed. The nodules are composed of basaloid cells without obvious differentiation, although tubular apocrine foci can be observed on occasion. Upon close scrutiny, individual nodules exhibit a trabecular internal morphology, with compact basophilic cells lining the borders of trabeculae and larger cells with scant pale cytoplasm within their centers (Fig. 111.32). Usually, small lymphocytes

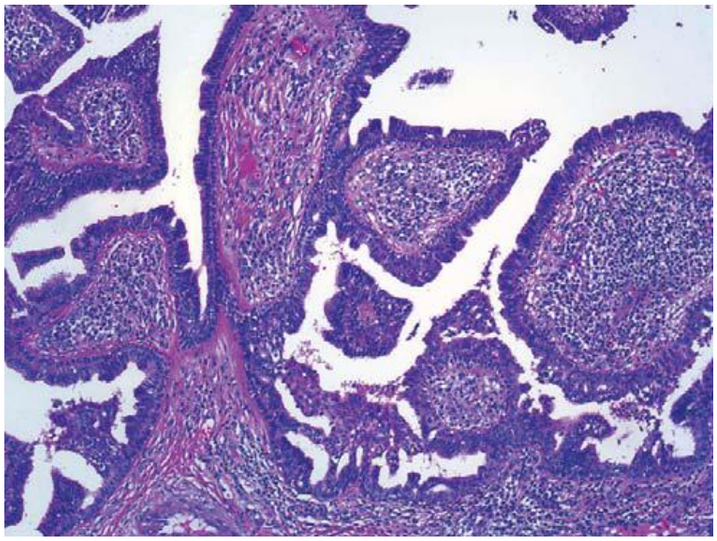


Fig. 111.30 Syringocystadenoma papilliferum. This neoplasm consists of papillary foci lined by columnar cells that usually display overt apocrine differentiation. The dermal cores of papillae are usually stuffed with lymphocytes and many plasma cells.

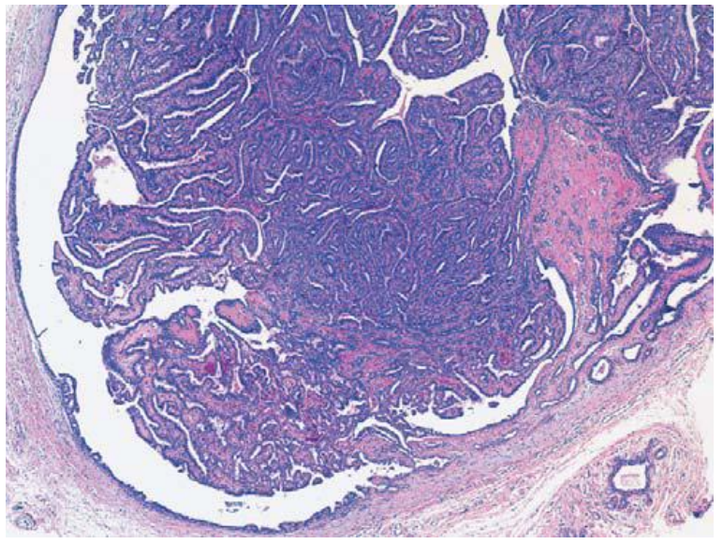


Fig. 111.31 Hidradenoma papilliferum. This well-circumscribed dermal nodule is composed of fronds and papillae with a connective tissue core lined by a bilayer of cells, with columnar apocrine cells positioned above a cuboidal monolayer of myoepithelial cells.

are scattered throughout trabecular areas. Some large (giant) spiradenomas develop cystic areas of degeneration or striking vascular ectasia as secondary events. Compact eosinophilic basement membrane material, arrayed either as tiny PAS-positive droplets or as circumferential bands, can occasionally be found within a spiradenoma, although such deposits are more commonplace in cylindroma. Spiradenoma can occur jointly with cylindroma, at least some of the time[87,88].

Treatment

Spiradenoma is a benign adnexal neoplasm. Despite its basaloid appearance, spiradenoma holds negligible proliferative capacity and recurrence is uncommon after simple enucleation or conservative excision.

Cylindroma

Introduction

The term *cylindroma* describes a form of benign adnexal neoplasm that is closely related to spiradenoma.

Clinical features

Cylindromas can present singly or in multiplicity and are not clinically distinctive; thus a biopsy is required for diagnosis. Solitary lesions commonly involve the head and neck area, especially the scalp (Fig. 111.33), and can also develop within skin of the trunk or genitalia. Multiple cylindromas may coalesce and form giant mosaic plaques on the scalp, which has been pejoratively referred to as turban tumor[89–91]. The recognition of multiple cylindromas should prompt consideration of the Brooke–Spiegler syndrome or multiple cylindromatosis (both autosomal dominant conditions), most examples of which are associated with *CYLD* gene mutations.

Pathology

At low magnification, cylindroma consists of sharply circumscribed nodules arrayed within the dermis and/or subcutis. The nodules are composed of nests of basaloid cells in close apposition, arrayed in a complex pattern that has been likened to a jigsaw puzzle. A rim of densely eosinophilic, PAS-positive basement membrane material commonly envelops the individual nests, and droplets of similar composition are often scattered in the centers of small nests (Fig. 111.34). Foci of ductular and apocrine tubular differentiation can sometimes be found but are inconspicuous.

Treatment

Cylindroma is a benign adnexal proliferation. Despite its basaloid appearance, cylindroma holds negligible proliferative capacity and recurrence is uncommon after complete excision.

Carcinomas of apocrine lineage

Introduction

Adnexal carcinomas with tubular and ductular differentiation (adnexal adenocarcinomas) are relatively uncommon, and their rarity has contributed to confusion with respect to diagnosis, classification and therapy. Adnexal carcinomas can develop *de novo* or they can arise in association with extant benign adnexal neoplasms. The semantics of carcinomas that arise in association with benign neoplasms has been problematic, as there has been a historical tendency to create an oxymoronic nomenclature by modifying the name of the benign analogue with the simple addition of the adjective *malignant*. Going forward, correct designations such as porocarcinoma and spiradenocarcinoma should be employed while the oxymoronic designations malignant poroma and malignant spiradenoma should be eschewed[2].

For certain types of adnexal carcinoma, such as spiradenocarcinoma or cylindrocarcinoma, the adenocarcinomas that develop from the benign neoplasm often lack a decisive pattern of differentiation and may only be specifically diagnosable through recognition of a remnant

Fig. 111.33 Cylindroma. While numerous tumors aggregated on the scalp are called turban tumors, solitary lesions usually present as smooth erythematous nodules.

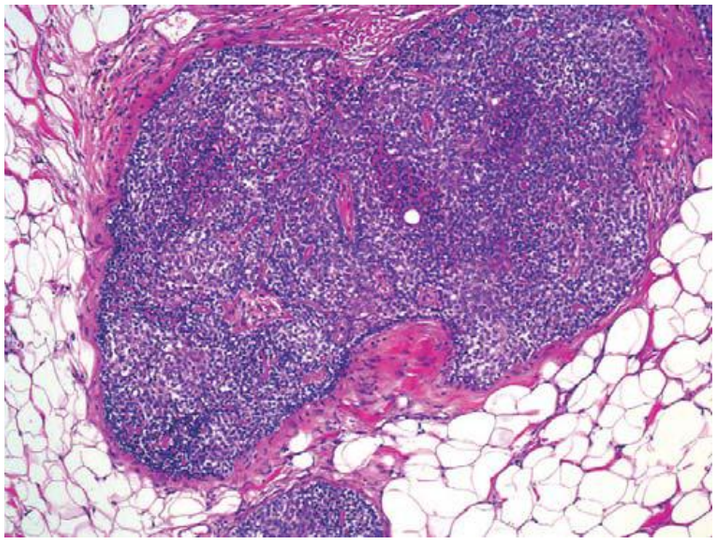


Fig. 111.32 Spiradenoma. This subcutaneous nodule shows multinodular basaloid aggregates with the typical trabecular pattern. Darkly staining cells line trabeculae and pale cells with pink cytoplasm are present in their centers, admixed with lymphocytes.

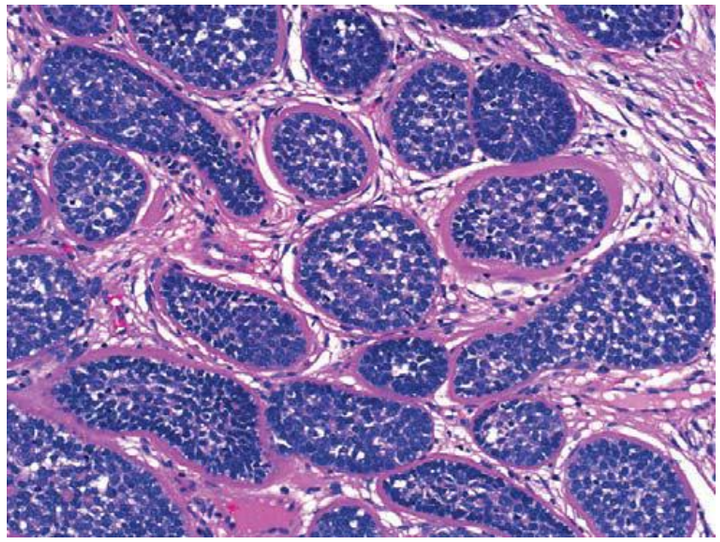


Fig. 111.34 Cylindroma. Nests of basaloid cells in a jigsaw puzzle-like pattern. Many nests are circumferentially enveloped by a dense eosinophilic cylinder of basement membrane material.

of the residual benign lesion. A spiradenocarcinoma in the absence of detectable spiradenoma will likely only be recognizable as poorly differentiated adenocarcinoma. Some forms of adnexal adenocarcinoma, such as porocarcinoma, display distinctive differentiation that is recognizable in a *de novo* lesion or in a carcinoma that developed within an existent tumor.

Clinical features

In general, the presentation of adnexal adenocarcinomas is not distinctive. Patients who develop adnexal carcinoma within an existent benign neoplasm often relate a history of recent rapid (or explosive) enlargement of a previously stable, longstanding plaque or nodule (Fig. 111.35). Ulceration and bleeding are common associated findings. Adnexal adenocarcinoma presents as a plaque or nodule, and biopsy and microscopy are required for diagnosis.

Perhaps the most is known about the presentation of *microcystic adnexal carcinoma* (MAC), a low-grade form of adnexal carcinoma (also known as *sclerosing sweat duct carcinoma*) that has been carefully evaluated in several large series[92]. MAC typically presents in young or middle-aged adults, most commonly in women and occasionally in children, and lesions slowly enlarge over years and are often misdiagnosed prior to the time of definitive recognition (Fig. 111.36)[92]. The most common location is the lip. Curiously, a left-sided predominance was noted in the largest series from the US, suggesting that UV light exposure (from driving) might be contributory to carcinogenesis, much like common forms of non-melanoma skin cancer.

Fig. 111.35 Porocarcinoma. Rapid growth and erosion or ulceration accompany this malignant adnexal tumor.

Fig. 111.36 Microcystic adnexal carcinoma. This tumor presents as a slowly expanding, firm plaque.

Pathology

All forms of adnexal adenocarcinoma share architectural attributes of malignancy, such as asymmetry, lack of circumscription, and an infiltrative configuration. There is considerable variability in the degree of cytologic atypicality, and no standard currently exists for the grading of these neoplasms. Some forms of adnexal carcinoma may display overtly anaplastic cytomorphology while other carcinomas, such as MAC or syringomatous carcinoma, display very subtle nuclear atypism.

Syringomatous carcinoma refers to a rare form of carcinoma with distal ductal differentiation[93,94]. Syringomatous carcinoma may be of either apocrine or eccrine lineage, and generally lineage cannot be discerned microscopically. Syringomatous carcinoma is characterized by poor circumscription, an infiltrative pattern at low magnification, and composition of small nests and tubules of pale cells with central cuticulated ducts. The degree of nuclear atypicality is usually modest, and thus a superficial biopsy, which hides the lack of circumscription, can lead to misinterpretation as syringoma. Syringomatous carcinoma has only been observed as a *de novo* malignancy.

MAC is a close relative of syringomatous carcinoma that is distinctive for biphasic or multiphasic differentiation. MAC displays a ductal component identical to that of syringomatous carcinoma coupled with follicular and (sometimes) sebaceous differentiation[92,95] (Fig. 111.37). The follicular component of MAC consists most notably of small cystic (microcystic) foci with follicular infundibular and isthmic keratinization, similar to the superficial follicular keratinization observed in desmoplastic trichoepithelioma or trichoadenoma. Areas resembling the follicular outer sheath may also be present. Extensive infiltration of the reticular dermis and perineural extension of tumor cells are common findings. Although desmoplastic trichoepithelioma and MAC exhibit overlapping features and both are characterized by foci of superficial follicular keratinization, follicular germinative (basaloid) cells are a hallmark of trichoepithelioma but are rarely, if ever, present in MAC.

Porocarcinoma may develop *de novo* or in association with an existent poroma[96]. Like poroma, porocarcinoma may be of apocrine or eccrine lineage, and it is generally impossible to determine the exact lineage of any given tumor. Some examples of porocarcinoma display little cytologic atypism and thus close attention must be paid to other attributes of malignancy, and small or partial biopsies may defy exact diagnosis. However, the degree of cytologic atypism is variable[94,97]. Porocarcinoma is composed of nests of eosinophilic or pallid cuboidal cells that infiltrate the dermis and perhaps subjacent deeper tissues, and ductal differentiation is usually conspicuous (Fig. 111.38). Porocarcinoma may display intraepidermal growth, with a pagetoid or nested pattern within the epidermis in some cases[94,97].

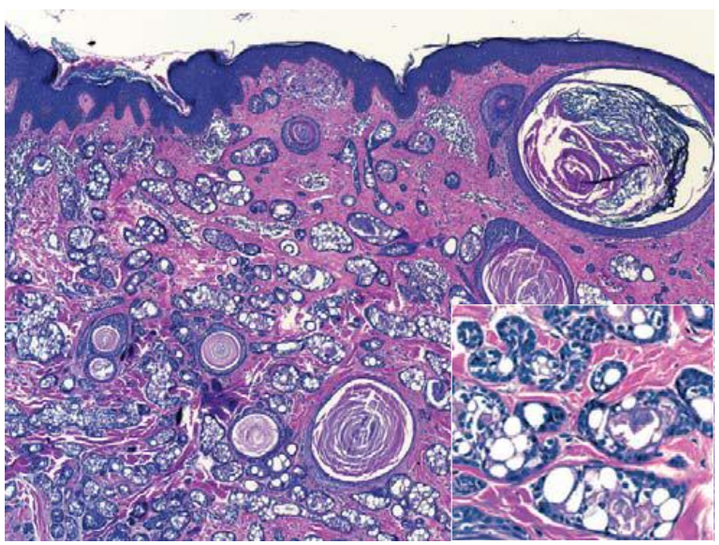


Fig. 111.37 Microcystic adnexal carcinoma. This deeply infiltrative carcinoma shows a biphasic microscopic pattern, with both ductular differentiation and superficial follicular keratinization. The high-magnification insert shows conspicuous ductal differentiation without cytologic atypism, which sometimes leads to misdiagnosis as a benign lesion.

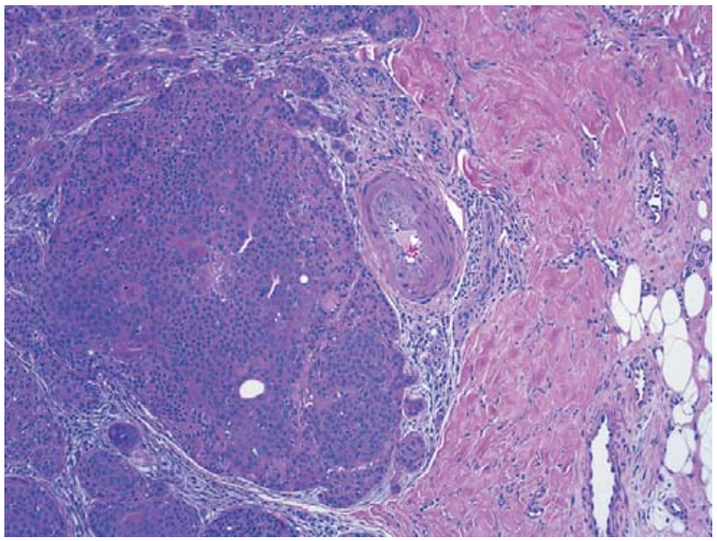


Fig. 111.38 Porocarcinoma. There are irregularly shaped nests of neoplastic cells that infiltrate deeply, with this image obtained at the level of the superficial subcutis. The largest nest shows central foci of ductular differentiation.

Hidradenocarcinoma may develop *de novo* or in association with an existent hidradenoma. Hidradenocarcinoma may be of apocrine or eccrine lineage. Cases reported in the older literature were notable for the presence of marked clear cell change, much like clear cell hidradenoma.

Spiradenocarcinoma and *cylindrocarcinoma* are usually poorly differentiated carcinomas that develop *de novo* or more commonly in association with an existent spiradenoma or cylindroma[98–100]. Both are extremely rare and may come to medical attention late in their course, as their evolution within longstanding stable lesions may contribute to a delay in pursuit of care by the patient.

Adenoid cystic carcinoma is a type of relatively undifferentiated adnexal carcinoma that resembles micronodular BCC but is generally distinctive for the presence of cribriform (net-like) glandular differentiation and a paucity of accompanying myxoid stroma. Primary cutaneous adenoid cystic carcinomas have been misinterpreted as metastatic lesions. Although initially postulated to represent a type of eccrine carcinoma, most authorities believe the entity represents a neoplasm of apocrine lineage. Adenoid cystic carcinoma tends to display considerable local invasiveness and most examples remain confined to the skin over years or even decades, but metastasis to lymph nodes and parenchymal organs can also rarely occur[101]. CD117 immunopositivity has been reported in association with adenoid cystic carcinoma and may be of value in providing additional diagnostic support.

Treatment

As a generality, the majority of adnexal adenocarcinomas are low-grade forms of carcinoma that are locally invasive but pose a low risk for metastasis. Many adnexal carcinomas that yield metastatic spread are large or were diagnosed late in their evolution. Surgical extirpation, including removal via Mohs micrographic surgery, remains the primary therapeutic modality. Careful microscopic classification is crucial to developing experience with larger groups of histopathologically homogeneous lesions to enable careful assessment of natural history as well as proper medical and surgical care.

NEOPLASMS AND PROLIFERATIONS WITH ECCRINE DIFFERENTIATION

Eccrine nevus (hamartoma)

Nevi or malformations with an eccrine glandular component are extremely uncommon. The clinical morphology of such lesions is not distinctive. Some lesions are alleged to maintain function of the eccrine apparatus. This can manifest clinically as mucinous discharge or localized hyperhidrosis.

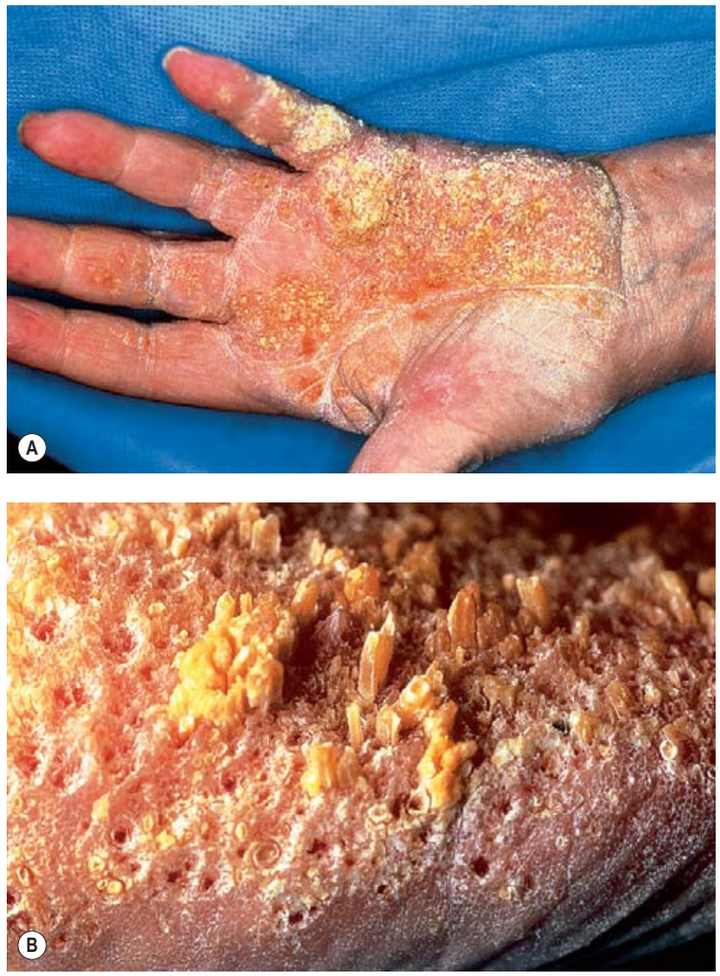


Fig. 111.39 Porokeratotic eccrine ostial and dermal duct nevus. Markedly hyperkeratotic spines arise from dilated eccrine ostia, corresponding to the histologic findings of coronoid lamellae.

Microscopically, the judgment as to whether eccrine glands are normal in number or increased can be difficult, especially in a partial biopsy. The absolute number of eccrine units is increased and the constituent units are of increased size in eccrine nevi. The surrounding stroma may be exclusively fibrotic or may include adipocytes. When the stroma also harbors an increase in small vascular channels, the designation eccrine angiomatous hamartoma can also be applied (see Fig. 39.5). For skin tag-like lesions on the coccygeal area, the term *coccygeal polypoid eccrine nevus* has been applied.

So-called porokeratotic eccrine ostial and dermal duct nevi are probably not eccrine nevi at all. These lesions are typically congenital and present as papules or plaques on the hands or feet, with punctate hyperkeratosis. The focal hyperkeratosis corresponds to cornoid lamellae that are often situated within acanthotic acrosyringia (Fig. 111.39). Eccrine acini are qualitatively and quantitatively normal in porokeratotic nevi, suggesting that these lesions should not be classified as a form of adnexal nevus. From the standpoint of nosology, these lesions probably fit best on the spectrum of epidermal nevi.

Treatment

Eccrine nevi are benign and require no treatment. Excision can be completed as an optional step.

Syringoma, poroma, hidradenoma, adnexal adenocarcinoma (see above)

Syringofibroadenoma

Syringofibroadenomas are rare tumors, usually located on the limbs. They may be associated with Clouston syndrome or Schöpf–Schulz–Passarge syndrome. They are characterized by an irregular

network of thin cords and strands of epithelial cells extending down from the epidermis. Ductal structures are usually present. A similar pattern may be observed in some cases of chronic stasis dermatitis. This has prompted some authorities to view syringofibroadenoma as a reactive process rather than an authentic neoplasm.

Papillary adenoma and adenocarcinoma

Introduction

The concept of *papillary adenoma* was originally put forth under the designation *aggressive digital papillary adenoma*[102–104]. These neoplasms are uncommon and commonly occur on acral skin of the fingers, toes, palms and soles, a topographic restriction that suggests that many or most are of eccrine lineage. Papillary adenoma was deemed aggressive because the neoplasms were prone to local recurrence if not completely excised, and some lesions were found to erode bone or infiltrate adjacent soft tissue[103]. Some neoplasms first classified as aggressive papillary adenoma have metastasized[104], and thus it appears this spectrum includes both adenomas and adenocarcinomas. It has also been suggested that all acral papillary lesions represent adenocarcinomas, but this seems biologically unlikely.

Clinical features

Papillary adenoma/adenocarcinoma presents as a solitary nodular lesion in an adult of any age. Lesions up to several centimeters in diameter have been observed. There is a male predilection. The lesions may be deeply situated and can impinge upon or erode underlying bone. The favored metastatic route appears to be hematogenous, and metastases involving the lung can occur.

Pathology

Papillary adenocarcinomas are extraordinarily cellular and display a combination of solid and papillary areas and are occasionally cystic[103]. A cribriform pattern can occasionally be found. For carcinomas with a largely cribriform or tubular configuration, the designation tubulopapillary carcinoma can be employed. Irrespective of the architecture of the lesion, its constituent cells have hyperchromatic nuclei and relatively little cytoplasm, and mitotic figures are usually readily identifiable (Fig. 111.40). There may be necrosis of individual cells or necrosis *en masse*. The enveloping stroma is commonly sclerotic. In overtly malignant lesions, vascular invasion or infiltration of bone may be observed.

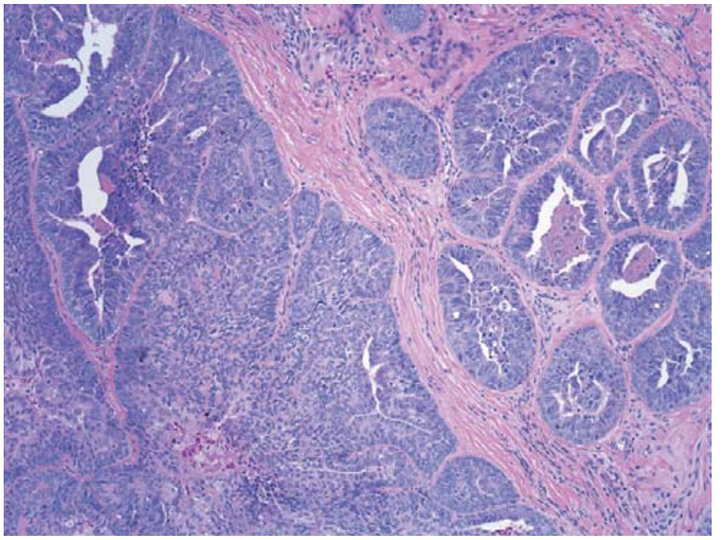


Fig. 111.40 Papillary adenocarcinoma of the digit. Solid, tubular and papillary foci, with small foci of necrosis. Mitotic figures are easily identified.

Treatment

It is difficult to predict the clinical course based upon the microscopic pattern. Complete surgical extirpation of papillary adenocarcinoma remains the standard of care. Because of diagnostic ambiguity, any papillary adenoma should also be fully excised.

REFERENCES

1. McCalmont TH. A call for logic in the classification of adnexal neoplasms. Am J Dermatopathol. 1996;18:103–9.
2. McCalmont TH. Batman and adnexal tumors. J Cutan Pathol. 2010;37:401–2.
3. Montagna W. Embryology and anatomy of the cutaneous adnexa. J Cutan Pathol. 1984;11:350–1.
4. Hyman AB, Brownstein MH. Eccrine poroma. An analysis of forty-five new cases. Dermatologica. 1969;138:29–38.
5. Labandeira J, Peteiro C, Toribio J. Hair follicle nevus: case report and review. Am J Dermatopathol. 1996;18:90–3.
6. Ban M, Kamiya H, Yamada T, Kitajima Y. Hair follicle nevi and accessory tragi: variable quantity of adipose tissue in connective tissue framework. Pediatr Dermatol. 1997;14:433–6.
7. Brownstein MH, Wanger N, Helwig EB. Accessory tragi. Arch Dermatol. 1971;104:625–31.
8. Plewig G. Sebaceous trichofolliculoma. J Cutan Pathol. 1980;7:394–403.
9. Schulz T, Hartschuh W. Folliculo-sebaceous cystic hamartoma is a trichofolliculoma at its very late stage. J Cutan Pathol. 1998;25:354–64.
10. Kimura T, Miyazawa H, Aoyagi T, Ackerman AB. Folliculosebaceous cystic hamartoma. A distinctive malformation of the skin. Am J Dermatopathol. 1991;13:213–20.
11. Bolognia JL, Longley BJ. Genital variant of folliculosebaceous cystic hamartoma. Dermatology. 1998;197:258–60.
12. Prioleau PG, Santa Cruz DJ. Sebaceous gland neoplasia. J Cutan Pathol. 1984;11:396–414.
13. Jaqueti G, Requena L, Sanchez Yus E. Trichoblastoma is the most common neoplasm developed in nevus sebaceus of Jadassohn: a clinicopathologic study of a series of 155 cases. Am J Dermatopathol. 2000;22:108–18.
14. Cribier B, Scrivener Y, Grosshans E. Tumors arising in nevus sebaceus: a study of 596 cases. J Am Acad Dermatol. 2000;42:263–8.
15. Alessi E, Wong SN, Advani HH, Ackerman AB. Nevus sebaceus is associated with unusual neoplasms. An atlas. Am J Dermatopathol. 1988;10:116–27.
16. Carlson JA, Cribier B, Nuovo G, Rohwedder A. Epidermodysplasia verruciformis-associated and genital-mucosal high-risk human papillomavirus DNA are prevalent in nevus sebaceus of Jadassohn. J Am Acad Dermatol. 2008;59:279–94.
17. Akasaka T, Onodera H, Matsuta M. Cutaneous mixed tumor containing ossification, hair matrix, and sebaceous ductal differentiation. J Dermatol. 1997;24:125–31.
18. Hassab-el-Naby HM, Tarn S, White WL, Ackerman AB. Mixed tumors of the skin. A histological and immunohistochemical study. Am J Dermatopathol. 1989;11:413–28.
19. Gianotti R, Coggi A, Alessi E. Cutaneous apocrine mixed tumor: derived from the apocrine duct of the folliculo-sebaceous-apocrine unit? Am J Dermatopathol. 1998;20:53–5.
20. Ackerman AB, Reddy VB, Soyer HP. Neoplasms with Follicular Differentiation, 2nd edn. New York: Ardor Scribendi, 2001:1109.
21. Blake PW, Toro JR. Update of cylindromatosis gene (*CYLD*) mutations in Brooke-Spiegler syndrome: novel insights into the role of deubiquitination in cell signaling. Hum Mutat. 2009;30:1025–36.
22. Pincus LB, McCalmont TH, Neuhaus IM, et al. Basal cell carcinomas arising within multiple trichoepitheliomas. J Cutan Pathol. 2008;35:59–64.
23. Bettencourt MS, Prieto VG, Shea CR. Trichoepithelioma: a 19-year clinicopathologic re-evaluation. J Cutan Pathol. 1999;26:398–404.
24. Brooke JD, Fitzpatrick JE, Golitz LE. Papillary mesenchymal bodies: a histologic finding useful in differentiating trichoepitheliomas from basal cell carcinomas. J Am Acad Dermatol. 1989;21:523–8.
25. Escalonilla P, Requena L. Plaque variant of trichoblastic fibroma. Arch Dermatol. 1996;132:1388–90.
26. Altman DA, Mikhail GR, Johnson TM, Lowe L. Trichoblastic fibroma. A series of 10 cases with report of a new plaque variant. Arch Dermatol. 1995;131:198–201.
27. Requena L, Renedo G, Sarasa J, et al. Trichoblastic fibroma. J Cutan Pathol. 1990;17:381–4.
28. Sajben FP, Ross EV. The use of the 1.0 mm handpiece in high energy, pulsed CO_2 laser destruction of facial adnexal tumors. Dermatol Surg. 1999;25:41–4.
29. Shaffelburg M, Miller R. Treatment of multiple trichoepithelioma with electrosurgery. Dermatol Surg. 1998;24:1154–6.
30. Brownstein MH, Shapiro L. Desmoplastic trichoepithelioma. Cancer. 1977;40:2979–86.
31. Lazar AJ, Calonje E, Grayson W, et al. Pilomatrix carcinomas contain mutations in *CTNNB1*, the gene encoding beta-catenin. J Cutan Pathol. 2005;32:148–57.
32. Agoston AT, Liang CW, Richkind KE, et al. Trisomy 18 is a consistent cytogenetic feature in pilomatricoma. Mod Pathol. 2010;23:1147–50.
33. Danielson-Cohen A, Lin SJ, Hughes CA, et al. Head and neck pilomatrixoma in children. Arch Otolaryngol Head Neck Surg. 2001;127:1481–3.
34. Kaddu S, Soyer HP, Wolf IH, Kerl H. Proliferating pilomatricoma. A histopathologic simulator of matrical carcinoma. J Cutan Pathol. 1997;24:228–34.
35. Hardisson D, Linaves MD, Cuevas-Santos, J, Contreas F. Pilomatrix carcinoma: a clinicopathologic study of six cases and review of the literature. Am J Dermatopathol. 2001;23:394–401.
36. Ambrojo P, Aguilar A, Simon P, et al. Basal cell carcinoma with matrical differentiation. Am J Dermatopathol. 1992;14:293–7.

37. Aloi FG, Molinero A, Pippione M. Basal cell carcinoma with matrical differentiation. Matrical carcinoma. Am J Dermatopathol. 1988;10:509–13.
38. Brownstein MH. Trichilemmoma. Benign follicular tumor or viral wart? Am J Dermatopathol. 1980;2:229–31.
39. Leonardi CL, Zhu WY, Kinsey WH, Penneys NS. Trichilemmomas are not associated with human papillomavirus DNA. J Cutan Pathol. 1991;18:193–7.
40. Brownstein MH, Shapiro L. Trichilemmoma. Analysis of 40 new cases. Arch Dermatol. 1973;107:866–9.
41. Roson E, Gomez Centeno P, Sanchez-Aguiler D, et al. Desmoplastic trichilemmoma arising within a nevus sebaceus. Am J Dermatopathol. 1998;20:495–7.
42. Brownstein MH, Mehregan AH, Bikowski JB, et al. The dermatopathology of Cowden's syndrome. Br J Dermatol. 1979;100:667–73.
43. Requena L, Gutierrez J, Sanchez Yus E. Multiple sclerotic fibromas of the skin. A cutaneous marker of Cowden's disease. J Cutan Pathol. 1992;19:346–51.
44. Hunt SJ, Kilzer B, Santa Cruz DJ. Desmoplastic trichilemmoma: histologic variant resembling invasive carcinoma. J Cutan Pathol. 1990;17:45–52.
45. Tellechea O, Reis JP, Baptista AP. Desmoplastic trichilemmoma. Am J Dermatopathol. 1992;14:107–14.
46. Vin-Christian K, Grekin R, McCalmont T. Hypopigmented papules of the cheeks, neck, and shoulders. Arch Dermatol. 1999;135:463–4, 466–7.
47. Kolenik SA 3rd, Bolognia JL, Castiglione FM Jr, Longley BJ. Multiple tumors of the follicular infundibulum. Int J Dermatol. 1996;35:282–4.
48. Kossard S, Finley AG, Poyzer K, Kocsard E. Eruptive infundibulomas. A distinctive presentation of the tumor of follicular infundibulum. J Am Acad Dermatol. 1989;21:361–6.
49. Horn TD, Vennos EM, Bernstein BD, Cooper PH. Multiple tumors of follicular infundibulum with sweat duct differentiation. J Cutan Pathol. 1995;22:281–7.
50. Mahalingam M, Bhawan J, Finn R, Stefanato CM. Tumor of the follicular infundibulum with sebaceous differentiation. J Cutan Pathol. 2001;28:314–17.
51. Rahbari H, Mehregan A, Pinkus A. Trichoadenoma of Nikolowski. J Cutan Pathol. 1977;4:90–8.
52. Brownstein MH, Arluk DJ. Proliferating trichilemmal cyst: a simulant of squamous cell carcinoma. Cancer. 1981;48:1207–14.
53. Sethi S, Singh UR. Proliferating trichilemmal cyst: report of two cases, one benign and the other malignant. J Dermatol. 2002;29:214–20.
54. Sleater J, Beers B, Stefan M, et al. Proliferating trichilemmal cyst. Report of four cases, two with nondiploid DNA content and increased proliferation index. Am J Dermatopathol. 1993;15:423–8.
55. Lopez-Rios F, Rodriguez-Peralto JR, Aguilar A, et al. Proliferating trichilemmal cyst with focal invasion: report of a case and a review of the literature. Am J Dermatopathol. 2000;22:183–7.
56. Finan MC, Apgar JT. Juxta-clavicular beaded lines: a subepidermal proliferation of sebaceous gland elements. J Cutan Pathol. 1991;18:464–8.
57. Bader RS, Scarborough DA. Surgical pearl: intralesional electrodesiccation of sebaceous hyperplasia. J Am Acad Dermatol. 2000;42:127–8.
58. Troy JL, Ackerman AB. Sebaceoma. A distinctive benign neoplasm of adnexal epithelium differentiating toward sebaceous cells. Am J Dermatopathol. 1984;6:7–13.
59. Misago N, Narisawa Y. Rippled-pattern sebaceoma. Am J Dermatopathol. 2001;23:437–43.
60. Rutten A, Burgdorf W, Hugel H, et al. Cystic sebaceous tumors as marker lesions for the Muir-Torre syndrome: a histopathologic and molecular genetic study. Am J Dermatopathol. 1999;21:405–13.
61. Misago N, Narisawa Y. Sebaceous neoplasms in Muir-Torre syndrome. Am J Dermatopathol. 2000;22:155–61.
62. Wick MR, Goellner JR, Wolfe JT 3rd, Su WP. Adnexal carcinomas of the skin. II. Extraocular sebaceous carcinomas. Cancer. 1985;56:1163–72.
63. Kohler S, Rouse RV, Smoller BR. The differential diagnosis of pagetoid cells in the epidermis. Mod Pathol. 1998;11:79–92.
64. Nguyen GK, Mielke BW. Extraocular sebaceous carcinoma with intraepidermal (pagetoid) spread. Am J Dermatopathol. 1987;9:364–5.
65. Hashimoto K, Lever WF. Histogenesis of skin appendage tumors. Arch Dermatol. 1969;100: 356–69.
66. Hashimoto K, Lever WF. Skin appendage tumors. Arch Dermatol. 1970;101:252–3.
67. Patrizi A, Neri I, Marzaduri S, et al. Syringoma: a review of twenty-nine cases. Acta Derm Venereol. 1998;78:460–2.
68. Soler-Carrillo J, Estrach T, Mascara JM. Eruptive syringoma: 27 new cases and review of the literature. J Eur Acad Dermatol Venereol. 2001;15:242–6.
69. Di Lernia V, Bisighini G. Localized vulvar syringomas. Pediatr Dermatol. 1996;13:80–1.
70. Garcia C, Krunic AL, Grichnik J, et al. Multiple acral syringomata with uniform involvement of the hands and feet. Cutis. 1997;59:213–14, 216.
71. Goyal S, Martins CR. Multiple syringomas on the abdomen, thighs, and groin. Cutis. 2000;66:259–62.
72. Harvell JD, Kerschmann RL, LeBoit PE. Eccrine or apocrine poroma? Six poromas with divergent adnexal differentiation. Am J Dermatopathol. 1996;18:1–9.
73. Azma A, Tawfik O, Casparian JM. Apocrine poroma of the breast. Breast J. 2001;7:195–8.
74. Groben PA, Hitchcock MG, Leshin B, et al. Apocrine poroma: a distinctive case in a patient with nevoid basal cell carcinoma syndrome. Am J Dermatopathol. 1999;21:31–3.
75. Kamiya H, Oyama Z, Kitajima Y. 'Apocrine' poroma: review of the literature and case report. J Cutan Pathol. 2001;28:101–4.
76. Lee NH, Lee SH, Ahn SK. Apocrine poroma with sebaceous differentiation. Am J Dermatopathol. 2000;22:261–3.
77. Mahalingam M, Byers HR. Intra-epidermal and intra-dermal sebocrine adenoma with cystic degeneration and hemorrhage. J Cutan Pathol. 2000;27:472–5.
78. Gianotti R, Alessi E. Clear cell hidradenoma associated with the folliculo-sebaceous-apocrine unit. Histologic study of five cases. Am J Dermatopathol. 1997;19:351–7.
79. Wolff K, Winkelmann RK, Decker RH. Solid-cystic hidradenoma: an enzyme histochemical, biochemical, and electron microscopic study. Acta Dermatol Kyoto Engl Ed. 1968;63:309–22.
80. Ohnishi T, Watanabe S. Histogenesis of clear cell hidradenoma: immunohistochemical study of keratin expression. J Cutan Pathol. 1997;24:30–6.
81. Requena L, Sanchez M. Poroid hidradenoma: a light microscopic and immunohistochemical study. Cutis. 1992;50:43–6.
82. Brownstein MH, Phelps RG, Magnin PH. Papillary adenoma of the nipple: analysis of fifteen new cases. J Am Acad Dermatol. 1985;12:707–15.
83. Diaz NM, Palmer JO, Wick MR. Erosive adenomatosis of the nipple: histology, immunohistology, and differential diagnosis. Mod Pathol. 1992;5:179–84.
84. Miller L, Tyler W, Maroon M, et al. Erosive adenomatosis of the nipple: a benign imitator of malignant breast disease. Cutis. 1997;59:91–2.
85. Koga T, Kubota Y, Nakayama J. Syringocystadenoma papilliferum without an antecedent naevus sebaceous. Acta Derm Venereol. 1999;79:237.
86. Vang R, Cohen PR. Ectopic hidradenoma papilliferum: a case report and review of the literature. J Am Acad Dermatol. 1999;41:115–18.
87. Goette DK, McConnell MA, Fowler VR. Cylindroma and eccrine spiradenoma coexistent in the same lesion. Arch Dermatol. 1982;118:273–4.
88. Michal M, Lamovec J, Mukensnabl P, Pizinger K. Spiradenocylindromas of the skin: tumors with morphological features of spiradenoma and cylindroma in the same lesion: report of 12 cases. Pathol Int. 1999;49:419–25.
89. Nerad JA, Folberg R. Multiple cylindromas. The 'turban tumor'. Arch Ophthalmol. 1987;105:1137.
90. Freedman AM, Woods JE. Total scalp excision and auricular resurfacing for dermal cylindroma (turban tumor). Ann Plast Surg. 1989;22:50–7.
91. Reingold IM, Keasbey LE, Graham JH. Multicentric dermal-type cylindromas of the parotid glands in a patient with florid turban tumor. Cancer. 1977;40:1702–10.
92. Chiller K, Passaro D, Scheuller M, et al. Microcystic adnexal carcinoma: forty-eight cases, their treatment, and their outcome. Arch Dermatol. 2000;136: 1355–9.
93. Hoppenreijs VP, Reuser TT, Mooy CM, et al. Syringomatous carcinoma of the eyelid and orbit: a clinical and histopathological challenge. Br J Ophthalmol. 1997;81: 668–72.
94. Urso C, Bondi R, Paglierani M, et al. Carcinomas of sweat glands: report of 60 cases. Arch Pathol Lab Med. 2001;125:498–505.
95. Nickoloff BJ, Fleischmann HE, Carmel J, et al. Microcystic adnexal carcinoma. Immunohistologic observations suggesting dual (pilar and eccrine) differentiation. Arch Dermatol. 1986;122:290–4.
96. Spencer DM, Bigler LR, Hearne DW, et al. Pedal papule. Eccrine porocarcinoma (EPC) in association with poroma. Arch Dermatol. 1995;131:211, 214.
97. Robson A, Greene J, Ansari N, et al. Eccrine porocarcinoma (malignant eccrine poroma): a clinicopathologic study of 69 cases. Am J Surg Pathol. 2001;25:710–20.
98. Granter SR, Seeger K, Calonje E, et al. Malignant eccrine spiradenoma (spiradenocarcinoma): a clinicopathologic study of 12 cases. Am J Dermatopathol. 2000;22: 97–103.
99. Biernat W, Wozniak L. Spiradenocarcinoma: a clinicopathologic and immunohistochemical study of three cases. Am J Dermatopathol. 1994;16:377–82.
100. Durani BK, Kurzen H, Jaeckel A, et al. Malignant transformation of multiple dermal cylindromas. Br J Dermatol. 2001;145:653–6.
101. Kato N, Yasukawa K, Onozuka T. Primary cutaneous adenoid cystic carcinoma with lymph node metastasis. Am J Dermatopathol. 1998;20:571–7.
102. Smith KJ, Skelton HG, Holland TT. Recent advances and controversies concerning adnexal neoplasms. Dermatol Clin. 1992;10:117–60.
103. Kao GF, Helwig EB, Graham JH. Aggressive digital papillary adenoma and adenocarcinoma. A clinicopathological study of 57 patients, with histochemical, immunopathological, and ultrastructural observations. J Cutan Pathol. 1987;14:129–46.
104. Duke WH, Sherrod TT, Lupton GP. Aggressive digital papillary adenocarcinoma (aggressive digital papillary adenoma and adenocarcinoma revisited). Am J Surg Pathol. 2000;24:775–84.

This page intentionally left blank

Benign Melanocytic Neoplasms 112

Harold S Rabinovitz and Raymond L Barnhill

Chapter Contents

Ephelides ... 1851
Café-au-lait macules ... 1851
Becker's melanosis (nevus) ... 1853
Solar lentigines ... 1854
Lentigo simplex and mucosal melanotic lesions ... 1855
Dermal melanocytosis ... 1858
Nevus of Ota and related conditions ... 1858
Blue nevus and its variants ... 1860
Common acquired melanocytic nevi ... 1861
Melanocytic nevi of genital and flexural skin ... 1863
Melanocytic nevus of acral skin ... 1864
Spitz (spindle and epithelioid cell) nevus/tumor ... 1864
Pigmented spindle cell nevus ... 1867
Atypical (dysplastic) melanocytic nevus ... 1868
Congenital melanocytic nevus ... 1871
Nevus spilus ... 1874
Halo nevus ... 1875
Combined nevus ... 1876
Recurrent melanocytic nevus ... 1877

EPHELIDES

Synonym: ■ Freckles

Key features

- Small, well-circumscribed, pigmented macules found only on sun-exposed skin of individuals with fair skin

Epidemiology and Pathogenesis

Ephelides are common in individuals with blond or red hair[1–6]. They are not present at birth, but usually appear during the first 3 years of life. Hyperpigmentation in ephelides is the result of increased sun-induced melanogenesis and transport of an increased number of fully melanized melanosomes from melanocytes to keratinocytes. Variants of the gene that encodes the melanocortin-1 receptor play a role in the development of red hair and ephelides (see Ch. 65)[7].

Clinical Features

Ephelides occur only on sun-exposed areas of the body, in particular the face, dorsal aspects of the arms, and upper trunk. They do not occur on mucous membranes. Ephelides are well demarcated and round, oval or irregular in shape. They are usually 1 to 3 mm in diameter, but are occasionally larger. Depending on the intensity of sun exposure, ephelides vary in color from light to dark brown, but almost never become as dark as lentigines or junctional nevi. They may increase in number and distribution and show a tendency for confluence, but they can fade over time with aging.

Ephelides are benign and show no propensity for malignant transformation[4]. While they are not a direct precursor of melanoma, ephelides are a marker of ultraviolet (UV)-induced damage and, hence, a marker for increased risk of UV-induced neoplasia[5]. In a study of 195 patients diagnosed with melanoma in England, the density of freckles on the face and arms was found to be more strongly associated with cutaneous melanoma than the number of melanocytic nevi. When adjusted for other factors (nevi, sunburns, skin type), those with a high freckle density had an odds ratio of 6.0 for developing melanoma compared with those without freckles. Some ephelides may represent a subtype of solar lentigo[5].

Pathology

The epidermis exhibits a normal configuration. The keratinocytes show an increase in melanin content, predominantly in the basal cell layer[6]. Occasionally, melanophages are seen in the papillary dermis. The density of melanocytes within ephelides does not differ significantly from normal. Compared to adjacent uninvolved epidermis, the melanocytes in ephelides are larger and have more branching of dendrites and a higher DOPA positivity, apparently indicating greater functional activity.

Differential Diagnosis

Ephelides must be distinguished from simple lentigines, solar lentigines, small café-au-lait macules and junctional nevi. In general, ephelides are lighter in color than simple lentigines, are confined to sun-exposed skin, and are responsive to solar exposure. In contrast, simple lentigines may occur on any site and are persistent. Table 112.1 compares ephelides and solar lentigines. Café-au-lait macules are usually solitary and larger than ephelides.

Treatment

Since darkening of ephelides depends on UV radiation, sun exposure should be minimized and use of sunscreens, hats and protective clothing recommended. Although topical retinoids and hydroquinone may lighten lesions, it is difficult to achieve an even clinical effect. Pigment-specific lasers and cryotherapy represent additional treatment options. Of note, any resulting dyspigmentation from these destructive therapies can be more disturbing to the patient than the original lesion.

CAFÉ-AU-LAIT MACULES

Key features

- Well-circumscribed, uniformly light to dark brown macules or patches that often range from 2 to 5 cm (in adults)
- Usually noted during infancy or early childhood
- Found in 10–20% of the normal population but can serve as a marker of an underlying genodermatosis, especially when multiple

COMPARATIVE CLINICAL FEATURES OF EPHELIDES AND SOLAR LENTIGINES		
	Ephelides (freckles)	**Solar lentigines**
EPIDEMIOLOGY		
Age of appearance	Early childhood	By 20–30 years (I, II)
Skin color	Light pigmentation	Light to dark pigmentation
Hair color	Often red or blond hair	Any type
Skin phototype	More common in I, II	More common in I and II, but also in III and IV
HISTORY		
Precipitating factors	Bursts of high-intensity sun exposure convert latent predetermined melanocytes to permanent freckles	Repeated sun exposure over time alters melanocytes within a circumscribed area to overproduce melanin
Duration of lesions	Fade without sun exposure	Persist for life
Relation to season	Much darker in summer, fade in winter and over time with aging	May darken in summer but do not fade in winter
Heredity	Probably AD; also AR when related to *MC1R* variants	No data
PHYSICAL EXAMINATION		
Type of lesion	Macule	Macule
Size	1–5 mm	5–15 mm or larger
Color	Light or medium brown	Medium or dark brown
Shape	Round to oval	Oval to irregular
Border	Smooth to jagged	Smooth to jagged
Distribution	Favor the face, forearms and back; rare on the dorsal aspect of the hands	Sites of chronic sun exposure, especially the face, arms (including dorsal aspect of the hands) and upper trunk
DERMOSCOPIC FEATURES		
	Uniform pigmentation and a moth-eaten edge	Diffuse light brown structureless areas, sharply demarcated and/or moth-eaten borders, fingerprinting, and a reticular pattern with thin lines that are occasionally short and interrupted

Table 112.1 Comparative clinical features of ephelides and solar lentigines. I, II, III, IV = skin phototypes (see Ch. 134); AD, autosomal dominant; AR, autosomal recessive; MC1R, melanocortin-1 receptor.

Fig. 112.1 Café-au-lait macule. Large tan patch in a geographic pattern on the lateral trunk. The patient did not have McCune-Albright syndrome.

Epidemiology

In an individual, the number of café-au-lait macules (CALM) can vary from one to more than a dozen. When multiple, the possibility of a genetic syndrome, such as neurofibromatosis 1 (NF1), needs to be considered[8,9] (see Table 61.4). Single CALM are found in 10% to 20% of the normal population, and up to 1% of healthy children have up to three CALM, especially African-American children. The lesions may be present at birth, but usually become clinically obvious during the first year of life and then increase proportionately in size with age.

Pathogenesis

The hyperpigmentation observed in CALM is due to increased melanogenesis and an increased melanin content within keratinocytes. While the underlying pathogenesis has not been elucidated in patients with isolated lesions, biallelic *NF1* inactivation has been identified in melanocytes from CALM in patients with NF1, and in McCune–Albright syndrome, affected skin contains an activating mutation in the gene that encodes $G_s\alpha$ (see Chs 61 & 65).

Clinical Features

The term café-au-lait refers to the lesion's characteristic homogeneous color of coffee with milk, which can be light to dark brown, depending upon the level of constitutive pigmentation. CALM are completely macular (Fig. 112.1), and they often have an overall oval morphology with margins that are well defined and regular ("typical" CALM)[10,11]. They may be located anywhere on the body, with the exception of the mucous membranes. CALM are usually 2–5 cm in diameter in adults, but may vary from freckle-like lesions (≤2 mm) to patches that are >20 cm in diameter. CALM enlarge proportionately with overall body growth and then remain stable in size during adulthood.

Compared with NF1, the CALM of McCune–Albright syndrome are typically fewer in number, larger, and have a midline demarcation; they usually have a segmental distribution pattern or present as broad bands along Blaschko's lines[12]. These CALM favor the head, neck, trunk and buttocks. They also tend to be unilateral, often involving the same side as the bone lesions and situated in proximity. They can, however, be indistinguishable both clinically and histologically from the CALM of neurofibromatosis. If present, superimposed lentigines (due to diffuse "freckling") can point to NF1-associated CALM.

Pathology

Light microscopy shows a normally configured epidermis with a slightly increased melanin content in the basilar keratinocytes. The adnexal epithelium is spared of hyperpigmentation, and melanophages are rarely found in the dermis. In DOPA-stained epidermis from most patients with neurofibromatosis, the density of melanocytes is higher in both CALM and normal adjacent skin, in comparison with healthy individuals. The melanocytic density in isolated CALM of otherwise normal persons, however, is usually less than in surrounding skin. Melanin macroglobules (large pigment particles) may be found in CALM but they are not specific for neurofibromatosis, as they are occasionally found in isolated CALM (without any underlying disease) and occur in several other conditions such as simple lentigines, Becker's melanosis, congenital melanocytic nevi, and sometimes even normal skin. By electron microscopy, the melanosomes are usually dispersed singly within melanocytes and are usually homogeneous, electron-dense, and ellipsoidal when fully melanized[9,13,14].

Differential Diagnosis

Hyperpigmented macules or patches that might be confused with CALM include linear nevoid hyperpigmentation (pigmentary mosaicism), early nevus spilus (before the "speckles" have appeared), Becker's

melanosis (without obvious hypertrichosis), mastocytomas, postinflammatory hyperpigmentation and phytophotodermatitis. Smaller lesions may resemble lentigines or acquired melanocytic nevi, while larger lesions may be confused with relatively flat congenital melanocytic nevi. Café-noir spots are hyperpigmented patches that have an even darker hue (relative to background skin) than CALM and are seen in LEOPARD syndrome and the Carney complex.

Treatment

CALM have never been reported to undergo malignant change. Topical agents (e.g. hydroquinone) and sun protection will have no effect on CALM. A variety of lasers have been used to treat CALM, with variable success[15,16]. The risks of laser surgery include transient hyperpigmentation or hypopigmentation, slight scarring, permanent hyperpigmentation, incomplete clearance, and especially recurrence. Typically, between 1 and 14 treatments are required, and responses are difficult to predict. For instance, of 12 CALM treated with a Q-switched ruby laser in one study, 50% developed repigmentation within 6 months. Responses to frequency-doubled Nd:YAG are also quite variable.

BECKER'S MELANOSIS

Synonyms: ■ Becker's nevus ■ Becker's pigmentary hamartoma ■ Nevoid melanosis ■ Pigmented hairy epidermal nevus

Key features

- Unilateral, hyperpigmented and often hypertrichotic patch or slightly elevated plaque
- Usually on the shoulder of male patients
- Onset during adolescence

Epidemiology

Becker's melanosis has been described in all races[17]. Although it is usually acquired, some cases are congenital. The lesions most often appear during the second and third decades of life and are six times more common in males than in females. Familial occurrence has been reported. In one study, the prevalence among 19 302 army recruits ages 17 to 26 years was 0.52%.

Pathogenesis

The pathogenesis of Becker's melanosis remains unclear. It is believed to be an organoid hamartoma of ectodermally and mesodermally derived tissues. An increase in androgen receptors and probable heightened sensitivity to androgens have been postulated. The latter characteristics would explain its onset during or after puberty, as well as its clinical and histologic manifestations, which include hypertrichosis, dermal thickening, acne and hypertrophic sebaceous glands. Androgen stimulation could also explain the accentuated smooth muscle elements often found in the dermis of Becker's melanosis[18].

Clinical Features

The onset of Becker's melanosis is usually noted during the second or third decade of life, sometimes following intense sunbathing. Lesions commonly have a unilateral distribution and involve an upper quadrant of the anterior or posterior chest plus the shoulder, but they also have been described on the forehead, face, neck, lower trunk, extremities (Fig. 112.2) and buttocks[17]. Normally, Becker's melanosis appears as a single lesion, but multiple lesions have occasionally been observed. The diameter ranges from a few centimeters to >15 cm, and the most common configuration is block-like, although linear patterns have been described.

The hyperpigmentation varies from uniformly tan to dark brown and the lesions are well demarcated, but the margins are usually irregular. The center of the lesion may show slight thickening and corrugation of the skin. Hypertrichosis usually develops after the hyperpigmentation, and the hairs become coarser and darker with time. Sometimes, the hypertrichosis is subtle and can only be appreciated by comparison with the contralateral side. The hypertrichosis and pigmentation may not overlap completely.

Fig. 112.2 Becker's melanosis (nevus). Large patch of hyperpigmentation on the leg which is medium brown in color. These lesions may be misdiagnosed as café-au-lait macules or congenital melanocytic nevi, especially when they do not occur on the upper trunk. *Courtesy, Jean L Bolognia, MD.*

Firmness to palpation may point to an associated smooth muscle hamartoma. In some patients, perifollicular papules may be a sign of coexistent proliferation of the arrector pili muscle. Acneiform lesions strictly limited to the area of hyperpigmentation have also been reported. Normally, Becker's melanosis is asymptomatic, but some patients report pruritus. After its initial appearance, the lesion may enlarge slowly for a year or two but then remains stable in size. The color can fade with time, but hypertrichosis usually persists.

Becker's melanosis is a benign lesion, and malignant transformation has not been reported. In contrast to the hyperplasia of the ectodermal and mesodermal tissues in Becker's melanosis, developmental anomalies that are generally hypoplastic in nature have occasionally been associated with Becker's melanosis. These abnormalities include hypoplasia of the ipsilateral breast, areola, nipple and arm, ipsilateral arm shortening, lumbar spina bifida, thoracic scoliosis and pectus carinatum, as well as enlargement of the ipsilateral foot. Accessory scrotum and supernumerary nipples have also been reported. In cases of Becker's melanosis with associated abnormalities (also referred to as "Becker's nevus syndrome"), the male:female ratio is reversed at 2:5 (in comparison to 6:1 in those without abnormalities)[19].

Pathology

There is variable papillomatosis, acanthosis and hyperkeratosis[17]. Regular elongation of the rete ridges and hyperplasia of the pilosebaceous unit may be observed. The melanin content of the keratinocytes is increased, whereas the number of melanocytes is normal or only slightly increased, without nesting. Melanophages may be found in the papillary dermis. A concomitant smooth muscle hamartoma is often, but not invariably, present in the dermis.

Differential Diagnosis

The differential diagnosis primarily includes CALM, congenital melanocytic nevus, plexiform neurofibroma and congenital smooth muscle hamartoma. The latter tends to be smaller in size but some authors consider Becker's melanosis and congenital smooth muscle hamartoma to be two ends of a clinical spectrum (see Ch. 117). A congenital melanocytic nevus, plexiform neurofibroma and congenital smooth muscle hamartoma can all have cutaneous hyperpigmentation and hypertrichosis. By dermoscopy, Becker's melanosis is less likely to have focal thickening of network lines, globules or homogeneous diffuse pigmentation, when compared to congenital nevi. The presence of

multiple CALM and axillary freckling can be helpful in establishing the diagnosis of neurofibromatosis, and unlike Becker's melanosis, CALM do not have corrugation on side-lighting. In an occasional patient, histologic evaluation is required to confirm the diagnosis, especially if the lesion is in an unusual location and there is an associated smooth muscle hamartoma.

Treatment

Patients with Becker's melanosis should be examined for possible soft tissue and bony abnormalities (see above). Electrolysis, waxing, camouflage makeup, and laser treatments may be recommended. The hyperpigmented component has been successfully treated with Q-switched ruby and frequency-doubled Nd:YAG[20], but recurrence rates are high. The hypertrichosis can be addressed with one of several lasers designed for this purpose (see Ch. 137).

SOLAR LENTIGINES

Synonyms: ■ Lentigo senilis ■ Liver spot ■ Old age spot ■ Senile freckle

Key feature

■ Tan to dark brown or black macules due to exposure to UV radiation

Epidemiology

Solar lentigines are found in 90% of the Caucasian population older than 60 years of age, and their incidence increases with advancing age[21,22]. They can also be found in younger individuals after acute or chronic sun exposure. Lentigines are more common in Caucasians, but also occur in Asians. Inherited patterned lentiginosis favors more lightly pigmented African-Americans, including those with mixed American Indian heritage.

Pathogenesis

Solar lentigines result from epidermal hyperplasia with variable proliferation of melanocytes and accumulation of melanin within keratinocytes in response to chronic UV radiation exposure. Associated mutations have not been elucidated. As with ephelides, variants in the melanocortin-1 receptor gene are linked to the development of solar lentigines[7].

Clinical Features

Solar lentigines are well-circumscribed, round, oval or irregularly shaped macules that vary in color from tan to dark brown or black. More lightly pigmented lesions are usually homogeneous (Fig. 112.3), whereas darker ones tend to have a mottled appearance. Solar lentigines almost always appear as multiple lesions. They usually vary from about 3 mm to 2 cm in diameter and can become confluent. Solar lentigines occur on sun-exposed areas, predominantly the dorsal aspects of hands and forearms, the face, the upper chest and back.

Solar lentigines have an irregular border and a reticulated pigment pattern when examined by tangential lighting and hand lens magnification. They may also be visible under Wood's lamp illumination when not apparent in normal light. The dermoscopic features of a solar lentigo may include the following: a diffuse light brown structureless area, sharply demarcated and/or moth-eaten borders, fingerprinting, and a reticular pattern with thin lines that are occasionally short and interrupted[23] (Fig. P1 [Appendix]). A particular variant that may be termed hypermelanotic or "ink spot" solar lentigo is characterized by a striking jet-black color and a stellate outline. By dermoscopy, a black branching pattern is seen.

Solar lentigines may develop at almost any age and may fade slightly with age or after the cessation of UV exposure. Most, however, persist indefinitely. The occasional development of melanocyte cytologic atypia in solar lentigines suggests a relationship of solar lentigines to lentigo maligna, but clear progression to lentigo maligna has not been established. Solar lentigines have been shown to be an independent risk factor for the development of melanoma. Histologic overlap suggests that solitary lichen planus-like keratosis and reticulated seborrheic keratosis can evolve from solar lentigines.

Fig. 112.3 Solar lentigines. Numerous light brown macules, some of which have an irregular border, on chronically sun-exposed skin.

Associated diseases and special forms

A *PUVA (psoralen + ultraviolet A)* lentigo is a well-defined hyperpigmented macule that commonly develops in individuals undergoing long-term PUVA chemotherapy (see Ch. 134). Up to 50% of PUVA-treated patients develop PUVA lentigines after an average of 5 to 7 years of photochemotherapy. The frequency and severity of the lesions are positively correlated with greater numbers of treatments, age of starting therapy, and male sex. There is a negative association with skin phototypes V and VI. In contrast to typical solar lentigines, PUVA lentigines also occur in sun-protected skin subjected to PUVA treatment. These lesions usually exhibit darker pigmentation and more of a stellate appearance in contrast to solar lentigines. PUVA lentigines often persist for years beyond the discontinuation of PUVA therapy. Histologically, the PUVA-induced lesions display lentiginous hyperplasia of large melanocytes that often exhibit mild cytologic atypia. On ultrastructural examination, the melanosomes in PUVA lentigines are usually larger in comparison with the melanosomes in solar lentigines[21]. Patients treated with PUVA should be monitored for the development of melanoma. Solar lentigines are also found in patients with *xeroderma pigmentosum* (see Ch. 87), a rare genetic disease in which clinical and cellular hypersensitivity to UV radiation and defective DNA repair are associated with skin malignancies.

Pathology

The rete ridges often have club-shaped or bud-like extensions and branching or fusing of rete ridges, forming a reticulated pattern (Fig. 112.4). The epidermis between the rete ridges may appear thinned. There is increased basal layer pigmentation, especially in the basaloid cells of the rete ridges. In some (but not all) cases, the melanocytes are increased in number. Melanocytes in dopa-stained sections of solar lentigines exhibit increased melanogenesis, and these cells have more numerous as well as longer and thicker dendritic processes than the melanocytes of normal skin. The superficial dermis often contains melanophages and occasionally a mild perivascular infiltrate of lymphocytes. Electron microscopic studies reveal abundant melanosome complexes in keratinocytes which appear to be larger than in normal surrounding skin[22].

Differential Diagnosis

The differential diagnosis of solar lentigines includes ephelides, macular seborrheic keratoses, simple lentigines, pigmented actinic keratoses, lentigo maligna, junctional melanocytic nevi and large cell acanthomas.

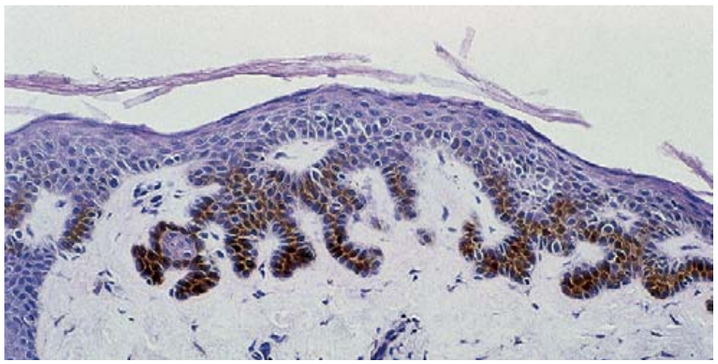


Fig. 112.4 Histology of a solar lentigo. Hyperpigmented elongated rete ridges with a diffuse increase in non-nested melanocytes, in addition to solar elastosis. *Courtesy, Ronald P Rapini, MD.*

Fig. 112.5 Anogenital lentiginosis. Biopsy of the darkest lesion (at 7 o'clock) showed no cellular atypia. Over a period of 10 years, several of the macules faded. *Courtesy, Jean L Bolognia, MD.*

Table 112.1 outlines the similarities and differences between solar lentigines and ephelides. There is essentially a continuum extending from solar lentigo to macular varieties of seborrheic keratosis. Demonstration of a keratotic surface with horn cysts is consistent with seborrheic keratosis. Pigmented actinic keratosis is more likely to have a scaly rough surface. Lentigo maligna often exhibits greater variation in pigmentation and irregularity of borders compared with solar lentigo, and by dermoscopy, rhomboid structures can be seen, in particular on the face. Simple lentigines are often smaller and more heavily pigmented than solar lentigines, and they arise during childhood with less relationship to UV exposure.

Treatment

Patients with PUVA lentigines should be monitored for the development of melanoma. Although a solar lentigo is a benign lesion of cosmetic concern only, it is an indication of chronic UV exposure which dictates monitoring of the patient for non-melanoma skin cancer and melanoma. Bleaching agents (e.g. hydroquinone) are not effective. Cryotherapy and laser surgery have been shown to be equally effective, but caution must be used to prevent post-treatment dyspigmentation. Preventive measures include sunscreens, physical barriers and limitation of sun exposure[22].

LENTIGO SIMPLEX AND MUCOSAL MELANOTIC LESIONS

Synonyms:
- Lentigo simplex: • Simple lentigo • Lentiginosis (multiple)
- Mucosal melanotic lesions: • Melanosis • Mucosal melanotic macules • Genital lentiginosis • Lentiginosis

Key feature

- A lentigo simplex is a brown macule with an early age of onset (as compared with a solar lentigo) and little or no relationship to sun exposure

Epidemiology

The frequency of lentigo simplex in children and adults is unknown. Lentigines are found in all races and seem to occur equally in both sexes. Isolated lesions may be present at birth, more commonly in darkly pigmented than lightly pigmented newborns. These lentigines may increase in number during childhood or puberty and sometimes occur in an eruptive form called lentiginosis with or without obvious precipitating factors. After melanocyte activation, lentigo simplex represents the next most common histology in matrix biopsies of longitudinal melanonychia (see Ch. 71). In darkly pigmented races, lentigo simplex is the most common histologic pattern for pigmented lesions in acral cutaneous sites.

Oral melanotic macules are found primarily in adults over 40 years of age. Some authors report a slight female predilection, whereas others describe both sexes being affected equally. The most common sites are the vermilion border, followed by the gingiva, the buccal mucosa and the palate. Up to 30% of melanomas in the oral cavity of Caucasians are preceded by melanosis for several months or years[23a]. In Japanese patients, two-thirds of infiltrative oral melanomas arise in association with oral melanosis. The labial (lip) melanotic macule usually appears between the second and fourth decades of life and has a strong predilection for Caucasian women.

The incidence of lentiginosis or melanosis of the female genital area is probably higher than reported. For example, 15% of 106 females between the ages of 16 and 42 years had genital "nevi", and in a study of 100 random autopsies, three cases showed melanosis of the genitalia, and all three were elderly women. Most lesions are found on the labia minora (Fig. 112.5), but they can also occur on the labia majora, the vaginal introitus, the cervix, the periurethral area and the perineum as well as perianally. In general, lentiginosis and melanosis of the female genitalia are benign conditions; atypia is uncommon and progression to melanoma has not been reported.

In a study of 10 000 men between 17 and 25 years of age, 14.2% were noted to have "pigmented nevi" of the genitalia[24]. It is uncertain what proportion represented penile lentiginosis or melanosis since no clinical descriptions or histologic studies were reported. In the literature, the ages of patients with penile lentiginosis or melanosis range from 15 to 75 years. The lesions occur on both the glans penis and penile shaft. Men can also develop lentigines perianally.

The incidence of conjunctival melanosis is unknown, but it can be assumed that primary acquired melanosis is a precursor lesion of melanoma in this area, since a significant number of conjunctival melanomas are associated with it. Lentigo simplex occasionally develops within scars following excision of cutaneous melanoma as do pigmented streaks due to basilar hyperpigmentation; the latter favors individuals with numerous solar lentigines.

Pathogenesis

An increased number of melanocytes within the basal layer of the epidermis leads to an increased production of melanin, resulting in hyperpigmented macules. To date, insights into lentigo formation have not been forthcoming despite the discovery of the genetic bases of several syndromes associated with lentiginosis (see Ch. 55). Some

penile lesions have been reported to follow injury, irritation or PUVA therapy. In women, hormonal factors are thought to play a role. Acral lentigines may be influenced by genetic factors, since they are frequently found in darkly pigmented individuals.

Clinical Features

Lentigines simplex are light brown to black, homogeneous pigmented macules occurring anywhere on the body, including mucous membranes and palmoplantar skin, without any predilection for sun-exposed areas. They are well circumscribed, round or oval, have regular borders, and are usually less than 5 mm (often <3 mm) in diameter. Lesions on the mucous membranes frequently have irregular, ill-defined borders and mottled non-homogeneous pigmentation with areas devoid of pigment (see Fig. 112.5). The latter may be several centimeters in diameter and may resemble early melanoma.

Lentigines simplex occur as solitary or multiple lesions. Generalized lentigines may be an isolated phenomenon without an underlying disease, either present at birth or appearing during childhood or adulthood, or it may be a sign of a genetic disorder (Table 112.2).

In contrast to lentigo simplex occurring on the skin, lesions on mucous membranes can slowly increase in size over months to years, with or without changes in the degree of pigmentation. The relationship between acral or anogenital lentigines and acrolentiginous melanoma requires more investigation.

Special forms and associated syndromes

Multiple lentigines may or may not be associated with other systemic manifestations. In *LEOPARD syndrome* (multiple lentiginosis syndrome, progressive cardiomyopathic lentiginosis, cardiocutaneous syndrome) the acronym refers to: *l*entigines, *e*lectrocardiographic conduction defects, *o*cular hypertelorism, *p*ulmonary stenosis, *a*bnormalities of genitalia, *r*etardation of growth, and *d*eafness (see Table 112.2). Multiple lentigines are present at birth or appear during early infancy and may increase in number during childhood. The lesions are generalized, occurring in both sun-exposed and sun-protected sites, including genitalia, palms and soles.

The *Carney complex* is an autosomal dominant syndrome characterized by multiple lentigines and multiple neoplasias, including: myxomas of the skin, heart (atrial) and breast; psammomatous melanotic schwannomas; epithelioid blue nevi of skin and mucosae; growth hormone-producing pituitary adenomas; and testicular Sertoli cell tumors. Components of the Carney complex have been described previously as the *NAME (n*evi, *a*trial myxoma, *m*yxoid neurofibroma, *e*phelides) and *LAMB* (*l*entigines, *a*trial myxoma, *m*ucocutaneous myxoma, *b*lue nevi) syndromes.

Peutz–Jeghers syndrome is also an autosomal dominant disorder characterized by mucocutaneous lentigines which are present at birth or appear during childhood in combination with intestinal polyposis. The skin lesions have an acrofacial distribution pattern and favor the perioral region. Mucosal lesions may affect the palate, tongue, buccal mucosa and conjunctivae. The major entity in the differential diagnosis is Laugier–Hunziker syndrome (Fig. 112.6).

In *partial unilateral lentiginosis*, also referred to as segmental lentiginosis, there is unilateral clustering of lentigines, suggesting a developmental abnormality of melanocytes. The onset is often during childhood and the individual lentigines are well circumscribed, varying from 2 to 10 mm in diameter. There is no background hyperpigmentation (as in nevus spilus) and the lesion can expand in a wavefront-like manner. Patients with facial lesions may have ocular involvement and CALM may also be present. Partial unilateral lentiginosis may be associated with segmental NF1.

Pathology

Lentigo simplex exhibits increased numbers of melanocytes in the basal layer of elongated epidermal rete ridges. Increased melanin in the basal layer and sometimes even in the upper layers of the epidermis and stratum corneum is commonly observed. Melanophages and a mild inflammatory infiltrate are often present in the superficial dermis.

Lesions on mucous membranes, including the lips, show acanthosis with or without elongation of the rete ridges (Fig. 112.7). Slight melanocytic hyperplasia is usually observed, but may be absent. Hyperkeratosis, telangiectasia, activated fibroblasts, and large dendritic melanocytes have been described in labial melanotic macules. Some acral and mucosal lesions have been reported to exhibit cytologic atypia of the melanocytes. Ultrastructurally, melanin macroglobules have been observed within the melanocytes, as well as in keratinocytes and melanophages. These are not specific for lentigo simplex, since they have been described in other pigmented lesions (see above).

Fig. 112.6 Labial lentigines. Multiple hyperpigmented macules on the lower lip in a patient with Laugier–Hunziker syndrome. Additional lesions are present on the tongue. Peutz–Jeghers syndrome can have a similar clinical appearance.

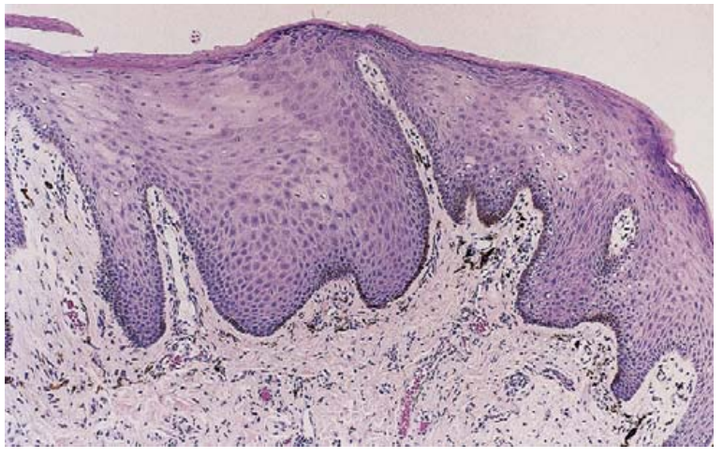


Fig. 112.7 Histology of a labial lentigo (melanotic macule). Hyperpigmented rete ridges are broader than in the typical lentigo.

Differential Diagnosis

The differential diagnosis of the solitary lentigo simplex involves primarily the junctional and relatively flat forms of compound melanocytic nevus, solar lentigo and ephelis. In some instances, cutaneous melanoma, pigmented spindle cell nevus, and cutaneous intracorneal hemorrhage might enter into the differential diagnosis.

Although there is a continuum from simple lentigo to junctional melanocytic nevus, the simple lentigo is distinguished from melanocytic nevi by the absence of distorted skin markings when viewed with side-lighting. Lentigo simplex is often smaller than a melanocytic nevus, but histopathologic examination may be required for discrimination. Lentigo simplex is usually distinguished from a solar lentigo by its smaller size, symmetry, uniform pigmentation, and lack of relationship to sun-exposed sites. However, this clinical distinction may not be possible in some instances.

Treatment

In general, there is no need to treat a benign-appearing lentigo simplex. Lesions on acral or mucous membranes should be evaluated carefully and, if clinically atypical, should be considered for biopsy to assess for

DISORDERS ASSOCIATED WITH MULTIPLE LENTIGINES			
Disorder	**Comments**	**Disorder**	**Comments**
GENERALIZED		**LOCALIZED**	
LEOPARD syndrome	• Autosomal dominant inheritance (high penetrance, variable expressivity); mutations in *PTPN11* gene • *L*entigines present in infancy/early childhood • Café-noir macules • *E*CG changes (conduction defects, hypertrophic cardiomyopathy), *o*cular hypertelorism, *p*ulmonary stenosis, *a*bnormal genitalia, growth *r*etardation and *d*eafness	**Head and neck (including oral mucosa) ± acral**	
		Peutz–Jeghers syndrome	• Autosomal dominant inheritance; mutations in *STK11* gene • Lentigines favor perioral region†, oral mucosa‡ and hands; longitudinal melanonychia • Multiple hamartomatous GI polyps • Pancreatic carcinoma; ovarian (adenoma malignum)/testicular tumors
Generalized lentigines	• Autosomal dominant inheritance; mapped to 4q21.1–q22.3 • Café-au-lait macules	Bandler syndrome*	• Autosomal dominant inheritance • Distribution of lentigines similar to Peutz–Jeghers • GI bleeding with small intestine hemangiomas rather than polyps
Deafness plus lentiginosis*	• ? Forme fruste of LEOPARD syndrome		
Carney complex (NAME/LAMB syndrome)	• Autosomal dominant inheritance; mutations in *PRKAR1A* gene • Lentigines, mucocutaneous myxomas, blue nevi (including epithelioid) • Psammomatous melanotic schwannomas • Atrial myxoma • Myxoid mammary fibroadenomas • Pigmented nodular adrenocortical disease; testicular (calcifying Sertoli cell), thyroid, and pituitary tumors	Laugier–Hunziker syndrome	• Similar distribution of lentigines as in Peutz-Jeghers, including lips, oral mucosa and digits • Longitudinal melanonychia and genital melanosis
		Cantú (hyperkeratosis–hyperpigmentation) syndrome	• Autosomal dominant inheritance • Punctate palmoplantar keratoderma • Multiple small (1 mm) macules on the face, forearms, hands/feet
Arterial dissection plus lentiginosis	• ? Inheritance pattern • Cutaneous lentigines with onset in childhood • Dissection of aortic, internal carotid and vertebral arteries	Cowden disease	• Autosomal dominant inheritance; mutations in *PTEN* gene • Periorificial and acral pigmented macules (see Table 63.3)
Gastrocutaneous syndrome*	• Autosomal dominant inheritance; see Table 61.4 for details	Centrofacial lentiginosis	• Autosomal dominant inheritance • Lentigines in a butterfly distribution on the nose, cheeks > forehead, eyelids, upper lip • Onset in infancy; increase in number in childhood • Possibly associated with neuropsychiatric illness and osseous anomalies
Tay syndrome*	• ? Autosomal recessive inheritance • Growth retardation, mental retardation; triangular face; cirrhosis; trident hands • Café-au-lait macules; premature canities; vitiligo		
Pipkin syndrome*	• Autosomal dominant inheritance • Nystagmus; strabismus	Inherited patterned lentiginosis	• Autosomal dominant inheritance • African-Americans with light brown skin • Pigmented macules appear in early childhood • Present on central face and lips > buttocks, elbows, hands/feet • Occasional oral mucosal involvement
		Cronkhite–Canada syndrome	• Typically affects older men • Lentigines of buccal mucosa, face, hands/feet • Alopecia (diffuse, non-scarring), nail dystrophy, intestinal polyposis
		Genital	
		Bannayan–Riley–Ruvalcaba syndrome	• Autosomal dominant inheritance; mutations in *PTEN* gene • Penile > vulvar pigmented macules (see Table 63.3)
		Lentiginosis perigenito-axillaris	• Genital and acral pigmented macules
		"Photodistribution"	
		Xeroderma pigmentosum	• Autosomal recessive inheritance; mutations in genes encoding proteins that repair UV-induced DNA damage • Lentigines favor, but are not limited to, chronically sun-exposed sites • Multiple skin cancers
		Segmental	
		Partial unilateral lentiginosis	• Multiple lentigines in a segmental distribution • Café-au-lait macules in same distribution

*To date, observed in a single family
†May fade.
‡Persists.

Table 112.2 Disorders associated with multiple lentigines. ECG, electrocardiogram; GI, gastrointestinal; LEOPARD, *l*entigines/*E*CG abnormalities/*o*cular hypertelorism/*p*ulmonary stenosis/*a*bnormalities of genitalia/*r*etardation of growth/*d*eafness syndrome; NAME, *n*evi/*a*trial myxoma/*m*yxoid neurofibroma/*e*phelides syndrome; LAMB, *l*entigines/*a*trial myxoma/*m*ucocutaneous myxoma/*b*lue nevi syndrome. *Adapted from Bolognia JL. Disorders of hypopigmentation and hyperpigmentation. In: Harper J, Oranje A, Prose N (eds). Textbook of Pediatric Dermatology, 2nd edn. Oxford: Blackwell Science, 2006;997–1040.*

melanocytic atypia. Patients with both generalized and localized lentiginosis should undergo investigation to exclude systemic disease (see Table 112.2).

DERMAL MELANOCYTOSIS

Synonyms: ■ Congenital dermal melanocytosis ■ Mongolian spot

Key features

- Blue to blue–gray patch present at birth, whose primary location is lumbosacral
- More common in Asians
- Usually resolves during childhood
- Sparse dendritic melanocytes in the deeper dermis

Epidemiology

Dermal melanocytosis is usually present at birth or appears within the first weeks of life; rarely lesions appear after early childhood[25–27]. Both sexes seem to be affected equally. Dermal melanocytosis usually regresses during early childhood, but it can persist and was seen in 4.1% of 9996 Japanese males between 18 and 22 years of age. It occurs in all races, with a frequency in one study of 100% in Malaysians, 90–100% in Mongolians, Japanese, Chinese and Koreans, 87% in Bolivian Indians, 65% of blacks in Brazil, 17% of whites in Bolivia, but only 1.5% of whites in Brazil. The racial differences in the frequency of this abnormality suggest that genetic factors influence survival of dermal melanocytes (see Ch. 65). Microscopically, histologic findings consistent with dermal melanocytosis can be found in 100% of newborns, irrespective of race[25,26].

Pathogenesis

The blue color in dermal melanocytosis is secondary to melanin-producing melanocytes residing in the middle to lower dermis. Melanocytes appear in the dermis during the 10th week of gestation, and then either migrate into the epidermis or undergo cell death, except for melanocytes in the dermis of the scalp, extensor aspects of the distal extremities, and the sacral area. The latter is the most common site for dermal melanocytosis. The bluish coloration of dermal melanocytosis results from the Tyndall phenomenon: dermal pigmentation appears blue because of decreased reflectance of light in the longer-wavelength region compared with the surrounding skin. Longer wavelengths, such as red, orange and yellow, are not reflected, compared with the shorter wavelengths of blue and violet, which are reflected[27].

Clinical Features

The classic location is the sacrococcygeal and lumbar regions and the buttocks, followed by the back (Fig. 112.8). Dermal melanocytosis may consist of a single or multiple patches and usually involves <5% of the body surface area. The lesions are macular and have a round, oval or angulated shape. The size varies from a few to more than 20 cm. The color varies from light blue to dark blue to blue–gray. Extrasacral (aberrant) variants tend to be more persistent and there is overlap amongst persistent and adult-onset dermal melanocytoses, nevus of Ito and patch blue nevus. Extensive dermal melanocytosis should raise the possibility of phakomatosis pigmentovascularis types II and IV (see Ch. 104). When CALM and satellite congenital melanocytic nevi reside within areas of dermal melanocytosis, there may be a rim that lacks dermal melanocytes around each lesion (see Fig. 112.8).

Pathology

Bipolar dendritic melanocytes are dispersed singly in the lower half or two-thirds of the dermis. These melanocytes are DOPA-positive and lie parallel to the epidermis between the collagen bundles without disturbing the normal architecture of the skin. Occasionally, persistent dermal melanocytosis has the histology of a blue nevus with involvement of the subcutis, muscle and fascia by melanocytes. On electron microscopy, dermal melanocytosis shows fully developed melanocytes with exclusively mature, electron-dense melanosomes and very few premelanosomes.

Fig. 112.8 Dermal melanocytosis (Mongolian spots) in a child with neurofibromatosis 1. Surrounding each café-au-lait macule there is an absence of the characteristic blue discoloration.

Differential Diagnosis

The differential diagnosis of dermal melanocytosis includes primarily nevus of Ota (if there is facial involvement), nevus of Ito, and patch blue nevus. The latter has many names in the literature, including dermal melanocyte hamartoma, acquired dermal melanocytosis and acquired linear dermal melanocytosis; clearly there is overlap with the rare adult-onset dermal melanocytosis. The differential diagnosis also includes venous malformations or deep hemangiomas and a contusion. Although the distinctive clinical presentation of dermal melanocytosis generally allows easy distinction from these entities, there have been reports of the misdiagnosis of child abuse.

Treatment

Persistent lesions may be treated with cover-up cosmetics or lasers (see nevus of Ota).

NEVUS OF OTA AND RELATED CONDITIONS

Synonyms:
- Nevus of Ota: • Nevus fuscoceruleus ophthalmomaxillaris
- Oculodermal melanocytosis • Congenital melanosis bulbi
- Oculomucodermal melanocytosis
- Nevus of Ito: • Nevus fuscoceruleus acromiodeltoideus
- Nevus of Ota-like macules: • Hori's nevus

Key features

- Blue–brown unilateral or occasionally bilateral facial patch
- More common in Asians and blacks
- More dermal dendritic melanocytes than in congenital dermal melanocytosis, but less than in blue nevus

Epidemiology

Nevus of Ota occurs predominantly in more darkly pigmented individuals, especially in Asians and blacks, but has also been described in Caucasians as well[28,29]. Approximately 80% of all reported cases have been in women; however, this figure may be somewhat skewed as a result of greater cosmetic concerns in women. In Japan, nevus of Ota is seen in ~0.4–0.8% of all dermatologic patients. The lesion has two peaks of onset: the first (~50–60% of all cases) during infancy (before the age of 1 year), with the majority present at birth, and the second (40–50%) around puberty. Onset between the ages of 1 and 11 years and after 20 years is unusual. Although rare familial forms of nevus of Ota have been reported, the condition is generally not considered hereditary.

Pathogenesis

The blue to blue–gray color in nevus of Ota is due to melanin-producing melanocytes in the dermis. The larger concentration of melanocytes in nevus of Ota in comparison with congenital dermal melanocytosis is thought to indicate a hamartoma. The possibility of a hormonal influence in women has been raised. Somatic activating mutations in *GNA11* and *GNAQ* were detected in up to 15% of cases of nevus of Ota, as compared to 65–75% of blue nevi (primarily *GNAQ*) and 83% of primary uveal melanomas[30]. Both of these genes encode α-subunits of G proteins (see Ch. 65). In mice, germline mutations that increase the activity of closely related GTPases lead to an increase in dermal pigmentation.

Clinical Features

Nevus of Ota is usually characterized by a confluence of individual macules varying from pinhead-sized to several millimeters in diameter. The shape of the individual macules may be round, oval or serrated, whereas the overall appearance is that of an irregularly demarcated and often mottled patch. The overall size varies from a few centimeters to extensive unilateral and occasionally bilateral involvement (Fig. 112.9). The color varies from shades of tan and brown to gray, blue, black and purple.

Nevus of Ota is usually unilateral and favors the distribution of the first two branches of the trigeminal nerve. The periorbital area, temple, forehead, malar area, earlobe, pre- and retroauricular regions, nose and conjunctivae are the most common sites of involvement. A characteristic feature, which is seen in about two-thirds of patients, is the involvement of the ipsilateral sclera; rarely, nevus of Ota affects the cornea, iris, fundus oculi, retrobulbar fat, periosteum, retina and optic nerve. Iris mammillations and glaucoma (~10% of patients)[31] have been reported, but vision is usually not impaired. Other frequent sites of involvement are the tympanum (55%), nasal mucosa (30%), pharynx (25%) and palate (20%). Occasionally, the external auditory canal, mandibular area, lips, neck and thorax are involved. In 5% to 15% of patients, the lesion is bilateral.

Fig. 112.9 Nevus of Ota (oculodermal melanocytosis). Unilateral blue–gray discoloration of the face, which is either mottled or confluent. There is also involvement of the sclera.

Nevus of Ota may extend over time and it persists for life. Fluctuations in the intensity of the color have been described, especially in association with periods of hormonal flux such as menstruation, puberty or menopause.

Malignancies arising within nevi of Ota are rare, estimated at 1 in 400 in Caucasians. As of 2010, eleven cases of cutaneous melanoma arising within a nevus of Ota had been reported in the literature[32,33]. These typically presented in Caucasian patients as new subcutaneous nodules and did not adhere to the ABCD rules of melanoma. Other tumors such as atypical and borderline cellular blue nevi also have been described[33,34]. Multiple examples of primary melanoma of the choroid, orbit, iris, chiasma and meninges have been observed in association with nevus of Ota that exhibited eye involvement. It is one of the entities that can have associated neuromelanosis.

Related conditions

Nevus of Ito differs from nevus of Ota primarily in its area of involvement; the former corresponds to the distribution of the posterior supraclavicular and lateral cutaneous brachial nerves (which encompasses the supraclavicular, scapular and deltoid regions). The clinical and histologic picture is the same as in nevus of Ota. There is a mottled appearance with bluish and brownish macules. Nevus of Ito may occur as an isolated lesion or in association with an ipsilateral or bilateral nevus of Ota. *Acquired nevus of Ota-like macules* (Hori's nevus) are characterized by bilateral blue–gray to gray–brown macules of the zygomatic area (less often the forehead, upper outer eyelids and nose). Primarily Chinese or Japanese women ranging in age from 20 to 70 years have been reported with this condition. The eye and oral mucosa are not involved. It may also be misdiagnosed as melasma. A *patch blue nevus*, which overlaps with the rare adult-onset dermal melanocytosis, presents as a diffusely gray–blue area that may have superimposed darker macules. The age of onset and sites of involvement vary, with some lesions having a linear distribution.

Pathology

The non-infiltrated areas in nevus of Ota show pigmented, elongated, dendritic melanocytes scattered among the collagen bundles. In comparison with dermal melanocytosis, the cells are more numerous and are located in the upper third of the reticular dermis. Occasionally, cells are found in the papillary dermis or even deep in the subcutaneous fat.

Hypermelanosis of the lower epidermis and an increase in basilar melanocytes may occur. The DOPA reactivity of the melanocytes in nevus of Ota varies: slightly pigmented cells are often strongly reactive, whereas heavily pigmented melanocytes often are not reactive, indicating minimal residual enzymatic activity. Melanocytes can be found clustering around blood vessels and sweat and sebaceous glands; occasionally, they are seen within vessel walls or in sweat ducts. Raised or infiltrated areas show a larger number of dendritic melanocytes forming cellular aggregates or clumps resembling blue nevi histologically.

Differential Diagnosis

The differential diagnosis of nevus of Ota and related conditions includes congenital dermal melanocytosis (Mongolian spot), adult-onset dermal melanocytosis, blue nevus (patch or plaque), melasma, partial unilateral lentiginosis (when it involves the face), a nevus spilus that develops blue nevi, venous malformations and ecchymosis. Congenital dermal melanocytosis differs from nevus of Ota and other dermal melanocytoses due to its location in the lumbosacral region and its spontaneous regression during childhood.

Treatment

Nevus of Ota and nevus of Ota-like macules have been treated successfully by Q-switched ruby, alexandrite and Nd:YAG lasers[35,36]. Although malignant changes are rare in patients with nevus of Ota, patients with eye involvement should be followed more carefully by an ophthalmologist, since the majority of associated melanomas are ocular in origin and some patients develop glaucoma. Suspicious lesions, especially a new subcutaneous nodule, should be biopsied. Any complaint of neurologic symptoms requires further investigation.

BLUE NEVUS AND ITS VARIANTS

Synonyms: ■ Blue nevus of Jadassohn–Tièche ■ Nevus bleu ■ Blue neuronevus ■ Dermal melanocytoma

Key features

- Blue to blue–black firm papule, nodule or plaques, often with an onset during childhood or adolescence
- Aggregates of dermal, dendritic, heavily pigmented melanocytes

Epidemiology

Blue nevi are usually acquired with an onset during childhood or adolescence, although up to a quarter arise in middle-aged adults. A congenital common blue nevus is unusual but approximately 25% of cellular blue nevi are congenital.

Pathogenesis

Blue nevi represent benign tumors of dermal melanocytes[37–45]. In general, melanocytes disappear from the dermis during the second half of gestation, but some residual melanin-producing cells remain in the scalp, sacral region, and dorsal aspect of the distal extremities. These are the sites where blue nevi most commonly occur. The blue coloration of these nevi is the result of the Tyndall phenomenon (see above). As noted previously, somatic activating mutations in *GNA11* and *GNAQ* (primarily the latter) have been detected in 65–75% of blue nevi. As a consequence, the intrinsic GTPase activity of encoded α-subunits is blocked and the G protein becomes locked in a GTP-bound, constitutively active state[30].

Clinical Features

Common blue nevi

Common blue nevi are well-circumscribed, dome-shaped papules that are blue, blue–gray or blue–black in color (Fig. 112.10A). They are usually 0.5 to 1.0 cm in diameter, rarely larger. The lesions may occur anywhere, but about 50% are found on the dorsal aspect of the hands and feet, with the face and scalp being other common sites. Blue nevi have been described in the vagina, cervix, prostate, spermatic cord and lymph nodes. Over time, hypopigmentation can appear centrally within common blue nevi.

Usually, blue nevi are solitary, but they may be multiple or agminated or may arise with a nevus spilus or plaque blue nevus. Concentric, target-like lesions (target blue nevus) have been described as well. Dermoscopically, a blue nevus is characterized by homogeneous blue–gray to blue–black pigmentation (see Ch. 0).

Cellular blue nevi

Cellular blue nevi are blue to blue–gray or black nodules or plaques, generally 1 to 3 cm in diameter but sometimes larger (Fig. 112.11A)[37–39]. Their surface is often smooth but sometimes irregular. The most common sites are the buttocks, sacrococcygeal area and scalp, followed by the face and feet. Congenital cellular blue nevi, some with satellite lesions, have been reported, as have benign or malignant cellular blue nevi arising within congenital melanocytic nevi. The ratio of common blue nevus to cellular nevus is at least 5:1.

Epithelioid blue nevi

Epithelioid blue nevi were first reported as a feature of the Carney complex (see Table 112.2); however, they also may occur sporadically[46]. These lesions have a predilection for the trunk and extremities and rarely develop on orogenital mucosa. Histologically, they may be indistinguishable from pigmented epithelioid melanocytoma.

Pigmented epithelioid melanocytoma

This somewhat controversial term has been proposed as one that unifies epithelioid blue nevi (described above) and lesions previously reported as "animal-type", "melanophagic" or "pigment synthesizing" melanomas. The latter are characterized by marked melanin production and a resemblance to certain melanizing tumors in animals[47]. The lesions seem to have a low-grade potential for regional metastases, but rarely non-regional metastases; they almost never result in overt malignant behavior and death of patients. In one study, all eight epithelioid blue nevi that arose in patients with Carney complex (with confirmed *PRKAR1A* mutations) showed loss of expression of protein kinase

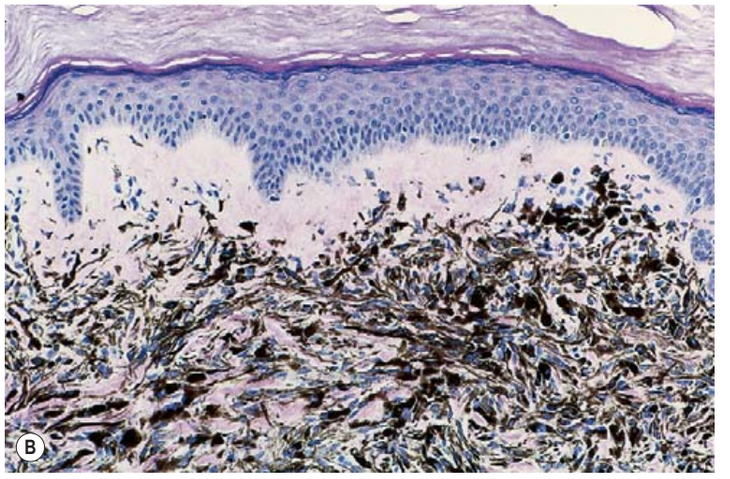
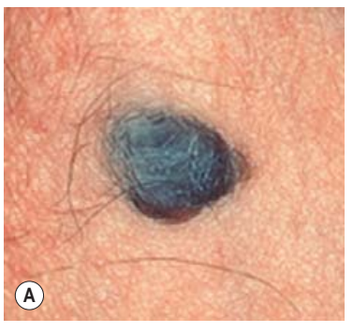


Fig. 112.10 Common blue nevus. **A** A well-circumscribed, blue, dome-shaped papule. **B** Histologically, there are heavily pigmented, spindle-shaped melanocytes as well as melanophages within the dermis; the melanocytes are denser than in dermal melanocytosis or nevus of Ota.



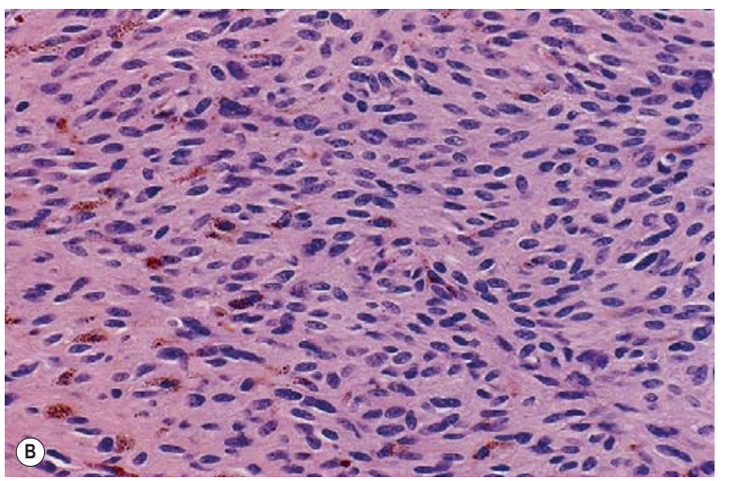


Fig. 112.11 Cellular blue nevus. **A** A firm blue plaque is a common presentation. **B** Histologically, there are plump spindled melanocytes devoid of melanin pigment and arranged within bundles. *A, Courtesy, Jean L Bolognia, MD.*

A regulatory subunit 1-α (the product of *PRKAR1A*) as did 28 (82%) of 34 sporadic pigmented epithelioid melanocytomas, suggesting a relationship[48].

Malignant blue nevi (cutaneous melanoma arising in or having features of blue nevus)

Malignant blue nevi are rare forms of cutaneous melanoma most commonly arising within cellular blue nevi[45,49]. They tend to show progressive enlargement, often measuring several centimeters in diameter, and have a multinodular or plaque-like appearance. The scalp is the most common site of occurrence and lymph nodes are the most common sites of metastasis. Malignant blue nevi can arise in a previously benign cellular blue nevus, in a nevus of Ota or Ito, or *de novo*.

Pathology

The *common* or *ordinary blue nevus* is composed of elongated and often slightly wavy melanocytes with long, branching dendrites (Fig. 112.10B). The melanocytes, with their long axes parallel to the epidermis, lie grouped or in bundles in the upper and mid dermis. Occasionally, they extend into the subcutaneous tissue or approach the epidermis, but do not alter it. Most of the melanocytes are filled with numerous fine melanin granules, often completely obscuring their nuclei as well as extending into their dendrites. Variable numbers of melanin-laden macrophages are also present. The amount of collagen is usually increased, giving the lesion a fibrotic appearance.

In the *cellular blue nevus*, one often observes deeply pigmented dendritic melanocytes (as in a common blue nevus) in addition to nests and fascicles of spindle-shaped cells with abundant pale cytoplasm containing little or no melanin (Fig. 112.11B). The aggregates of spindle cells may be arranged in intersecting bundles extending in various directions, a disposition resembling the storiform pattern of neurofibroma. Penetration of rounded, well-defined cellular islands into subcutaneous tissue is frequently noted. Some of the cells may appear atypical, with nuclear pleomorphism accompanied by multinucleated giant cells, rare mitoses and inflammatory infiltrates.

Occasionally, lymph nodes draining the anatomic site of a cellular blue nevus contain atypical cells. The foci, found either in the marginal sinuses or in the capsule, are usually small, discrete and peripherally located. They may result from passive transport or represent arrested migration from the neural crest. These "benign metastases" are found in 5% of the reported cases of cellular blue nevi. Electron microscopy reveals that the spindle-shaped cells in cellular blue nevi contain melanosomes with little or no melanization. Melanin production in these cells and a transition to bipolar dendritic nevus cells have been documented.

Atypical cellular blue nevi demonstrate one or more of the following features compared to conventional cellular blue nevi: larger size (e.g. >1–2 cm), asymmetry, ulceration, infiltrating features, cytologic atypia, mitoses and necrosis[50–52]. Such lesions have been associated with lymph node metastases and evolution to frank melanoma. These lesions require further study since their biologic potential is difficult to predict.

Epithelioid blue nevi and *pigmented epithelioid melanocytomas* are typified by dermal (and sometimes junctional) aggregates of enlarged epithelioid melanocytes often containing coarsely granular melanin pigment and prominent nucleoli. These cells are often admixed with heavily pigmented spindled and dendritic melanocytes as well as melanophages. Cytologic atypia and dermal mitoses may be present.

Differential Diagnosis

The differential diagnosis of a common blue nevus includes traumatic tattoo, combined nevus, vascular lesions including venous lake and angiokeratoma, sclerosing hemangioma, primary and metastatic melanoma, atypical nevus, pigmented spindle cell nevus, dermatofibroma, papular pigmented basal cell carcinoma and glomus tumor. For cellular blue nevus, especially with satellitosis, malignant blue nevus needs to be considered, and when the lesion is on the face, nevus of Ota. Blue nevi also need to be distinguished from a cutaneous neurocristic hamartoma, a complex proliferation of nevus cells, Schwann cells, and pigmented dendritic and spindled cells. Histologically, epithelioid blue nevi and pigmented epithelioid melanocytomas must be differentiated from primary or metastatic melanoma as well as tumoral melanosis due to complete or almost complete regression of melanoma.

Treatment

Blue nevi that are <1 cm in diameter, are clinically stable, do not have atypical features and are located in a typical anatomic site do not require removal. On the other hand, histologic evaluation should be strongly considered for lesions that appear *de novo*, are multinodular or plaque-like, or have undergone change. Atypical cellular blue nevi and pigmented epithelioid melanocytomas should be resected completely in order to prevent recurrence and because of their risk for malignant transformation or metastases. The approach to typical cellular blue nevi varies, but if observation is difficult (e.g. lesions on the scalp), excision can be considered.

COMMON ACQUIRED MELANOCYTIC NEVI

Synonyms: ■ Nevocellular nevus ■ "Mole"

Key features

- A junctional nevus is a brown to black macule with melanocytic nests at the junction of the epidermis and dermis
- An intradermal nevus is a skin-colored or light brown papule with nests of melanocytes in the dermis
- A compound nevus is a brown papule with combined histologic features of junctional and intradermal nevi

Epidemiology

The prevalence of melanocytic nevi is related to age, race, and perhaps genetic and environmental factors. A few nevi are present in early childhood, but their number then increases, reaching a peak during the third decade of life; thereafter, nevi tend to disappear with increasing age[53–55]. There is a period of particularly rapid development of nevi at puberty. A study in Scotland noted that, in the first decade of life, females had an average of three nevi and males two nevi. For the peak age interval 20 to 29 years, women and men had mean nevu counts of 33 and 22, respectively. Reflecting the progressive decline thereafter, women had a mean of six nevi and men four nevi in the seventh decade of life.

Caucasians in general have greater numbers of nevi than do darker-skinned populations, i.e. African-Americans and Asians. Furthermore, a greater prevalence of nevi is associated with lighter skin color in whites, with a peak in nevi number in those with skin phototype II. The frequency of melanocytic nevi (includes lentigines) on the palms and soles, nail beds and conjunctivae is also related to race; nevi on these surfaces are more prevalent in blacks and Asians than in whites. The mean acral nevus count for Africans in Uganda was 11, versus 2 to 8 for African-Americans.

Genetic factors may be operative in the prevalence of nevi: increased numbers of nevi have been shown to cluster in families, especially in those with familial melanoma. Although an autosomal dominant mode of inheritance has been postulated for clinically atypical nevi in hereditary melanoma families, the pattern of inheritance may be more complex. Environmental factors such as sun exposure influence the development of melanocytic nevi. However, genetic factors seem to directly determine an individual's potential for the development of melanocytic nevi, and the final expression of this potential is influenced by solar exposure. In addition, individuals appear to inherit different propensities for nevogenesis[55].

Pathogenesis

Melanocytic nevi are thought to originate from neural crest stem cells that migrate from the neural crest to the epidermis. Nevi are hypothesized to result from the proliferation of slightly altered melanocytes or "nevus cells" within the epidermis, producing junctional nevi. It is

TRIGGERS FOR THE DEVELOPMENT AND/OR GROWTH OF MELANOCYTIC NEVI
LIGHT EXPOSURE
• Sun exposure leading to multiple or severe sunburns* • Intermittent intense sun exposure (e.g. on sunny holidays) • Chronic moderate sun exposure (e.g. residence at lower latitudes) • Neonatal phototherapy
CUTANEOUS INJURY
Blistering processes (other than severe sunburns) • Toxic epidermal necrolysis/Stevens–Johnson syndrome* • Epidermolysis bullosa – junctional (particularly generalized atrophic benign) > recessive dystrophic > recessive simplex* • Bullae secondary to sulfur mustard (mustard gas) exposure*
Severe sunburn*
Scarring processes • Lichen sclerosus†
SYSTEMIC IMMUNOSUPPRESSION
• Chemotherapy, particularly for childhood hematologic malignancies*,†,‡ • Allogeneic bone marrow transplantation‡ • Solid organ transplantation, particularly renal*,‡ • HIV infection/AIDS* • Chronic myelogenous leukemia* • TNF inhibitor therapy*,‡ • Cyclosporine*
INCREASED HORMONE LEVELS
• Pregnancy*,§ • Growth hormone (increased size, not number, of nevi) • Addison's disease* • Thyroid hormone* • α-Melanocyte stimulating hormone analogue*
OTHER
• Sorafenib* • Atopic dermatitis in children (conflicting results in different studies) • Postoperative fever* • Seizures or electroencephalographic abnormalities*
*Eruptive nevi have been reported. †An increased number of atypical nevi may also be seen. ‡Nevi have a predilection for the palms and soles. §Relative immunosuppression may also play a role; an increase in the size or number of nevi has not been clearly demonstrated for pregnant women in general.

Table 112.3 Triggers for the development and/or growth of melanocytic nevi. TNF, tumor necrosis factor. *Adapted from Schaffer JV, Bolognia JL. The biology of melanocytic nevi. In: Nordlund JJ, Boissy RE, Hearing VJ, et al. (eds). The Pigmentary System: Physiology and Pathophysiology, 2nd edn. Oxford: Blackwell Publishing, 2006;1092–125.*

Fig. 112.12 Acquired melanocytic nevi. **A** Junctional nevus – dark brown macule with lighter brown rim. **B** Compound nevus – light to medium brown papule. **C** Intradermal nevus – soft light pink papule.

believed that such nevus cells subsequently migrate into the dermis, giving rise to compound nevi and ultimately dermal nevi when there are no longer residual nevus cells within the epidermis. Nevi are thought to be either developmental malformations (hamartomas) or benign proliferations with some growth advantage over surrounding basilar melanocytes. Of note, subclinical nests have been described in normal-appearing skin.

Factors leading to the onset of melanocytic nevi are poorly understood but could include the genetic influences alluded to earlier and environmental agents, principally UV exposure (Table 112.3). As in melanomas arising in sites of intermittent sun exposure, somatic mutations in *BRAF* are often detected in common acquired melanocytic nevi, including intradermal nevi, with *NRAS* mutations present in a small minority of acquired nevi[56]. In nevi, the *BRAF* mutations are thought to induce senescence.

Clinical Features

Melanocytic nevi are well-circumscribed, round to ovoid lesions, generally measuring from 2 to 6 mm in diameter. They appear orderly and symmetric overall. Although many nevi display slight asymmetry, the borders are usually regular and well defined. The junctional nevus is a macular lesion with slight accentuation of skin markings visible with side-lighting. Junctional nevi are also characterized by a uniform, medium to dark brown color (Fig. 112.12A). The dermoscopic features of a junctional nevus include a uniform pigment network thinning out towards the periphery (see Tables 0.12 & 0.13) (Fig. P2). Compound nevi show variable degrees of elevation and in general somewhat lighter shades of brown than do junctional nevi (Fig. 112.12B). Dermoscopically, they are characterized by a globular architecture with multiple round to ovoid globules sometimes forming a cobblestone pattern (see Ch. 0). Dermal nevi (Fig. 112.12C) are usually more elevated and show lighter shades of brown or even skin-colored tones compared with compound nevi. The dermoscopic features of an intradermal nevus predominantly consist of focal globules or globular-like structures. In addition, there may be pale to whitish structureless areas and fine linear or comma vessels (Fig. P3).

In addition to clinical and dermoscopic overlap amongst all three types of nevi, dermal nevi (and to a lesser degree compound nevi) may be papillomatous with pseudo-horn cysts. Nevi, especially acquired "congenital-appearing" nevi, contain hairs that are coarse and dark compared with those in surrounding skin. Nevi of the palms and soles are often macular or only slightly raised, have regular and well-defined borders, and show uniform or linear brown coloration (see below).

Melanocytic nevi of the nail matrix usually present as uniformly pigmented brown to dark brown longitudinal bands (melanonychia striata) with regular and distinct margins (see Ch. 71).

An important aspect of melanocytic nevi is their relationship to melanoma. A significant proportion of melanoma patients report the prior presence of a longstanding melanocytic nevus at the site of melanoma development. Histologic studies also have documented that approximately one-third of melanomas are associated with nevus remnants (but this figure is probably lower nowadays because of the increased incidence of lentigo maligna melanoma which rarely demonstrates an associated nevus). An increased number of melanocytic nevi correlates with increased melanoma risk.

Melanocytic nevi associated with epidermolysis bullosa

Distinctive melanocytic nevi termed "epidermolysis bullosa (EB) nevi" or "EB nevi" may develop at the sites of antecedent bullae or erosions primarily in patients with forms of EB that are recessively inherited[57]. These nevi can have a strikingly large size (up to 3 cm) as well as asymmetry, border irregularity, dark color, and satellitosis. Their development may be related to repetitive disruption of the basement membrane zone with the promotion of nevus cell proliferation or the dispersion of nevus cells into the blister cavity with their subsequent proliferation in its floor. To date, there are no reports of cutaneous melanoma developing at the sites of EB nevi, but longitudinal observation is warranted.

Melanocytic nevi associated with lichen sclerosus

Occasionally, melanocytic nevi develop in sites of genital lichen sclerosus[58,59]. The lesions are often dark brown to black in color, irregular in outline and can measure ≥6 mm. As a result, the possibility of melanoma is frequently considered and histologic distinction is not always simple.

Pathology

Melanocytic nevi contain intraepidermal or dermal collections of nevus cells or both (Fig. 112.13). The cells within the junctional nests have round, ovoid or fusiform shapes and are arranged in cohesive nests; with the exception of unusual amelanotic variants, these cells contain melanin. In the superficial dermis, the cells in general have epithelioid cell characteristics and contain amphophilic cytoplasm and, frequently, granular melanin. The nuclei have uniform chromatin with a slightly clumped texture. Deeper in the dermis, there is a diminished content of cytoplasm, such that the cells resemble lymphocytes; they are frequently arranged in linear cords. There may be a further transition to cells separated by fine connective tissue and assuming a spindled configuration, similar to fibroblasts or Schwann cells.

EB nevi are best considered exaggerated variants of recurrent/persistent melanocytic nevi (see below). Thus they usually exhibit asymmetry and considerable variation in the overall architecture of the nevus, including the junctional nests. Pagetoid melanocytosis and cytologic atypia may be present, as well as fibroplasia, a lymphocytic infiltrate, and melanophages.

In *melanocytic nevi associated with lichen sclerosus* (LS), the features of a genital nevus are superimposed on the changes of LS, which can vary from subtle to obvious. Irregular and confluent junctional nests are often accompanied by cytologic atypia. The changes of LS may suggest regression, and if the inflammatory component is significant, it may hinder assessment of the nevus cells. Findings that favor a genital nevus (rather than melanoma) include a diameter <5 mm, symmetry, sharp circumscription, nests predominantly at the dermal–epidermal junction, low-grade cytologic atypia of melanocytes, a conventional dermal nevus component, an absence of significant dermal mitoses, and limitation of the nevus to the area of LS.

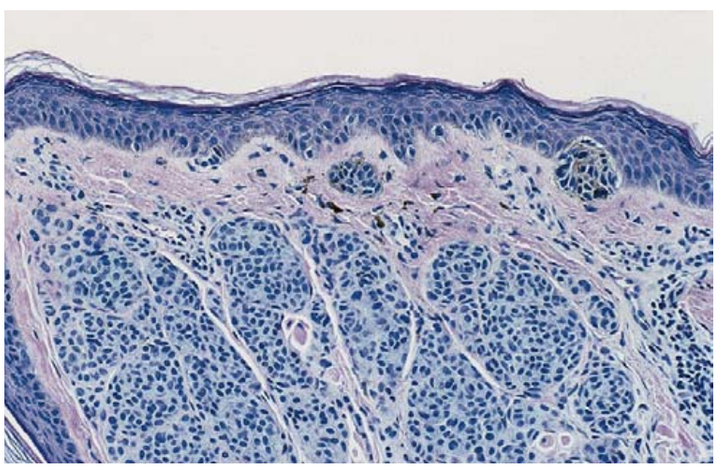


Fig. 112.13 Histology of a compound nevus. Nests of melanocytes within the dermis and at the dermal–epidermal junction. *Courtesy, Ronald P Rapini, MD.*

Differential Diagnosis

The differential diagnosis of melanocytic nevi includes the entire gamut of pigmented and skin-colored lesions (see Ch. 0). Raised nevi, potentially confused with seborrheic keratoses, are less likely to have a verrucoid surface and pseudo-horn cysts and dermoscopy can assist in the distinction. Dermatofibromas are usually differentiated from nevi by their very firm consistency, "dimpling" with lateral compression, preference for the lower extremities, and central white patch by dermoscopy. Both neurofibromas and fibroepithelial polyps may be indistinguishable from skin-colored or slightly pigmented, pedunculated dermal nevi. In general, typical melanocytic nevi are distinguishable from atypical nevi and melanoma by smaller size, overall symmetry and orderly appearance, homogeneous coloration, and regular, well-defined borders. Furthermore, red, blue, gray and black colors are not usually seen in common acquired nevi and should alert one to a potentially atypical lesion.

Treatment

Indications for removing melanocytic nevi are as follows: (1) a changing lesion; (2) atypical clinical appearance suspicious for melanoma; (3) repeated irritation; and (4) cosmetic concerns. Beyond these indications, there is no reason to remove nevi on a routine basis.

MELANOCYTIC NEVI OF GENITAL AND FLEXURAL SKIN

Key feature

- Nevi in "special sites", including genitalia, sometimes have atypical histologic changes, making distinction from melanoma difficult

Clinical Features

Melanocytic nevi occurring in genital sites, especially the vulva, are thought to have rather distinctive histopathologic features compared to most nevi from non-genital sites[60–62]. However, similar nevi may occur in other locations such as the scrotum, perineum, umbilicus or axilla[62]. In general, premenopausal women (ages 14 to 40 years) present with this type of vulvar lesion[60]. These nevi appear to be uncommon, perhaps accounting for <10% of nevi removed, but data could be biased by selection factors. In a series of 36 cases, more than half of the nevi were macular clinically, with the remainder elevated. These nevi are often larger in size (mean 5.9 mm, range of about 2–24 mm) than non-genital ordinary nevi, usually have fairly regular borders, and often have a complex mahogany color, i.e. an admixture of tan, brown and red[61].

Pathology

In general, these nevi are characterized by an overall symmetry and a frequent absence of lateral extension of intraepidermal melanocytic components beyond the dermal nevus elements (if present), and they are well circumscribed[60–62]. Many have a mushroom-like polypoidal morphology, with the rather distinctive junctional elements overlying a prominent dermal nevus component. Notably, there are architectural and cytologic features similar to atypical melanocytic nevi.

Differential Diagnosis

The differential diagnosis includes primarily melanoma, Spitz nevus, and nevi associated with genital LS (see above). Vulvar melanoma tends to occur in older women (average age ~65 years).

MELANOCYTIC NEVUS OF ACRAL SKIN

Synonyms: ■ Melanocytic nevus with intraepidermal ascent of cells (MANIACS) ■ Acral nevus

Key feature

- About one-third of acral nevi have intraepidermal upward migration of melanocytes and other architectural changes that can resemble melanoma

Clinical Features

Acral nevi are usually macular or only slightly elevated. They may display uniform brown or dark brown color, but often have linear striations (Fig. P4). The characteristic dermoscopic features of benign melanocytic nevi of the palms and soles are due to the unique anatomy of acral skin. The palms and soles consist of parallel ridges (mountains) and furrows (valleys). The intraepidermal eccrine ducts pass through the ridges (Fig. 112.14). In benign melanocytic nevi, the nests of nevus cells are situated around the furrows. The three major dermoscopic patterns seen in benign melanocytic nevi are the parallel furrow (Fig. 112.15), the lattice-like (see Fig. P4), and the fibrillar pattern (Table 112.4)[63].

Pathology

Acral nevi are usually relatively small (<5–6 mm), well-circumscribed and symmetric compound nevi. On occasion, the junctional nests are somewhat enlarged, but they usually have a fairly uniform round or oval shape and are similar in size and spacing. Lentiginous melanocytic proliferation and some degree of upward migration of melanocytes are features commonly observed in acral nevi [64–66]. One should be cautious in over-interpreting the latter changes unless prominent architectural disorder and cytologic atypia are also present. The dermal component of acral nevi is often characterized by round nests of type A cells.

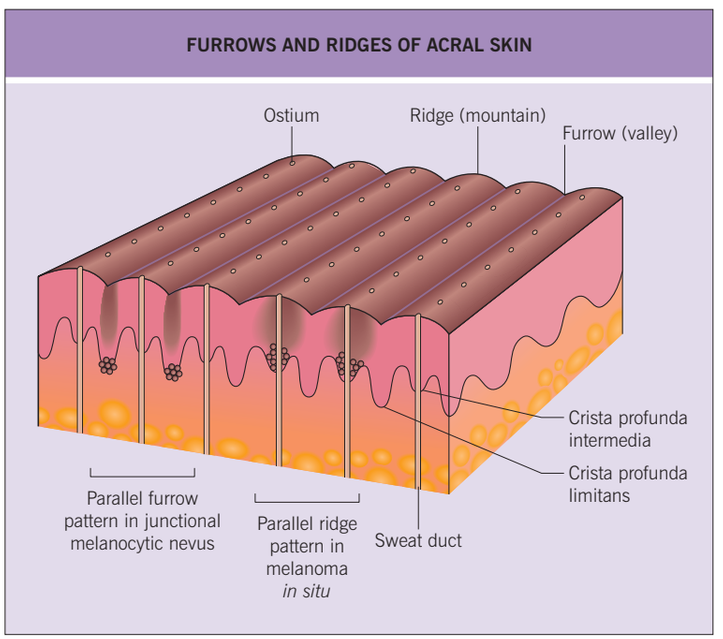


Fig. 112.14 Furrows and ridges of acral skin.

SPITZ (SPINDLE AND EPITHELIOID CELL) NEVUS/TUMOR

Synonyms: ■ Spitz's juvenile melanoma ■ Benign juvenile melanoma

Key features

- Red or pigmented papule or nodule, usually in children or young adults
- Prominent epithelioid and/or spindled melanocytes
- Mimic of melanoma histologically

Epidemiology

The prevalence of Spitz nevus in the general population has not been accurately documented[67,68]. However, among melanocytic lesions that have been surgically excised, approximately 1% exhibit the histologic characteristics of Spitz nevus. In data from Australia, it has been estimated that Spitz nevus accounts for 1.4 cases per 100 000 population, as compared with an annual incidence of 25.4 melanomas per 100 000 population. The vast majority of Spitz nevi are acquired, but up to 7% may be congenital. Spitz nevi occur in all age groups but are uncommon beyond 40 to 50 years of age. In the series of Weedon and Little[67], 36% of the individuals with Spitz nevi were under the age of 10 years, 33% were between the ages of 10 and 20 years, and 31% were older than 20 years of age. There is no gender predilection.

Pathogenesis

No particular etiologic factors that might account for the characteristic histologic changes found in Spitz nevi have been identified (see below regarding chromosome 11p). Widespread eruptive Spitz nevi have been associated with HIV infection, Addison's disease, chemotherapy, pregnancy, puberty and trauma, many of the same triggers as for common acquired nevi (see Table 112.3). The eruption of Spitz nevi with pregnancy and puberty suggests that dormant nevi may become hormonally activated. Many Spitz nevi, however, have no identified precipitating cause. To date, mutations in *BRAF* have not been detected in Spitz nevi,

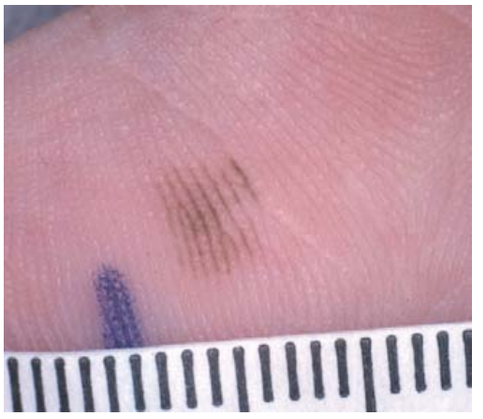


Fig. 112.15 Acral melanocytic nevus. The parallel furrow pattern is evident with a small focus of the lattice pattern. The ostia of the eccrine ducts within the epidermal ridges can also be seen, especially at the site of blue ink. *Courtesy, Jean L Bolognia, MD.*

ACRAL NEVI – COMMON DERMOSCOPIC PATTERNS	
Pattern	**Dermoscopy features**
Parallel furrow (most common)	Parallel rows of linear pigmentation along furrows/valleys (sulci of the surface skin markings; see Figs 112.14 & 112.15)
Lattice-like	Parallel furrows plus lines of pigmentation crossing the parallel lines (see Fig. P4)
Fibrillar	Densely packed, fine parallel lines of pigmentation, often set in a direction that crosses the skin markings

Table 112.4 Acral nevi – common dermoscopic patterns.

Fig. 112.16 Spitz nevus. Red dome-shaped papule on the ear of a child. *Courtesy, Ronald P Rapini, MD.*

Fig. 112.17 Agminated Spitz nevi. The grouped papules have arisen on normally pigmented skin.

in contrast to common melanocytic nevi (e.g. dermal). Recently, two families with multiple epithelioid and atypical nevi were found to have inactivating germline mutations in *BAP1*, which encodes a ubiquitin carboxy-terminal hydrolase[67a].

Clinical Features

Spitz nevi vary in size from 2 mm to >2 cm, with an average diameter of ~8 mm[67–70]. Typically, they are well-circumscribed, dome-shaped papules or nodules varying in color from pink to tan to dark brown (Fig. 112.16). Generally, the color is homogeneous and the margins are well defined. The surface topography may be smooth or, in some instances, verrucous. Relatively flat, polypoid and pedunculated morphologies have also been described. Occasional lesions may have erosions and scale-crust while others may be firm due to sclerosis and resemble dermatofibromas (i.e. desmoplastic)[71–73]. Telangiectasia is a frequent finding.

Although Spitz nevi may involve any part of the body, the head and neck area is probably the most common site, accounting for 42% of lesions in one series. There is a rather even distribution of lesions over the remainder of the body. In most instances, there is a history of recent onset, but a small percentage of Spitz nevi have been present for many years. Multiple Spitz nevi may occur in an agminated (grouped) or disseminated pattern[74,75]. *Disseminated* Spitz nevi can number in the hundreds, erupt suddenly, and involve the entire integument except for the palms, soles and mucous membranes. The papules tend to be polymorphous, affect adults, and spontaneously regress over several years. To date, no case reports of malignant degeneration of grouped or disseminated Spitz nevi have been published, although disseminated Spitz nevi have been associated with seizures.

Agminated (grouped) Spitz nevi are characterized by varying numbers of individual, raised nevi occurring in a localized or segmental distribution, and arising in otherwise clinically normal skin (Fig. 112.17). There has been some confusion in the literature where lesions arising with a CALM-like tan background have been referred to as agminated Spitz nevi; however, these lesions would be better termed Spitz nevi within a nevus spilus (speckled lentiginous nevus). Solitary or multiple spindle and epithelioid cell proliferations developing within a large congenital nevus exhibit the features of typical Spitz nevi.

Pigmented spindle cell nevus (see below) is classified by some authors as a subtype of Spitz nevi.

Atypical Spitz nevi refer to lesions demonstrating one or more (usually a constellation of) features that deviate from conventional Spitz nevi[76]. The features may include: large size (e.g. >1 cm in diameter); asymmetry; deep involvement of the dermis or subcutis; ulceration; easily found dermal mitoses (>2–3 mitoses/mm^2), especially deep; significant pagetoid spread; prominent confluence and high cellular density of melanocytes in the dermis; and lack of maturation. A grading protocol for atypical Spitz nevi in childhood and adolescence has been formulated (Table 112.5)[77]. Studies utilizing comparative genomic hybridization and fluorescence *in situ* hybridization techniques have identified copy number increases of chromosome 11p, sometimes accompanied by *HRAS* mutations (*HRAS* is located on 11p), in subgroups of Spitz nevi[78]. Additional chromosomal abnormalities (e.g. gain of 1p) have been found in atypical Spitz tumors[78a]. However, more studies are needed before the identification of such genetic alterations can be used to predict the biologic behavior of Spitz nevi.

ASSESSMENT OF ATYPICAL SPITZ NEVUS (TUMOR) IN CHILDREN AND ADOLESCENTS FOR RISK FOR METASTASIS	
Parameter	**Score**
AGE (YEARS)	
0–10 (pre-pubertal)	0
11–17 (post-pubertal)	1
DIAMETER (mm)	
0–10	0
>10	1
INVOLVEMENT OF SUBCUTANEOUS FAT	
Absent	0
Present	2
ULCERATION	
Absent	0
Present	2
MITOTIC ACTIVITY (per mm^2)	
0–5	0
6–8	2
≥9	5

Table 112.5 Assessment of atypical Spitz nevus (tumor) in children and adolescents for risk for metastasis. Total score and risk for metastasis: 0–2, low risk; 3–4, intermediate risk; 5–11, high risk.

Malignant or metastasizing Spitz nevi are exceedingly rare lesions with features of atypical Spitz nevi that have been reported to result in a single regional lymph node metastasis, but no subsequent disease progression. Since such lesions are only rarely encountered, they have not been sufficiently studied to know their biologic nature and how (and if) they differ from conventional melanomas.

Pathology

Typically, these lesions display striking nests of large epithelioid cells, spindle cells or both, usually extending from the epidermis into the reticular dermis in an inverted-wedge configuration. The closely apposed nests of cells within a uniformly hyperplastic epidermis often contribute to a so-called "raining-down" appearance (Fig. 112.18). Both mononuclear and multinucleate giant epithelioid cells are frequently observed. These cells extend into the subjacent dermis both as single

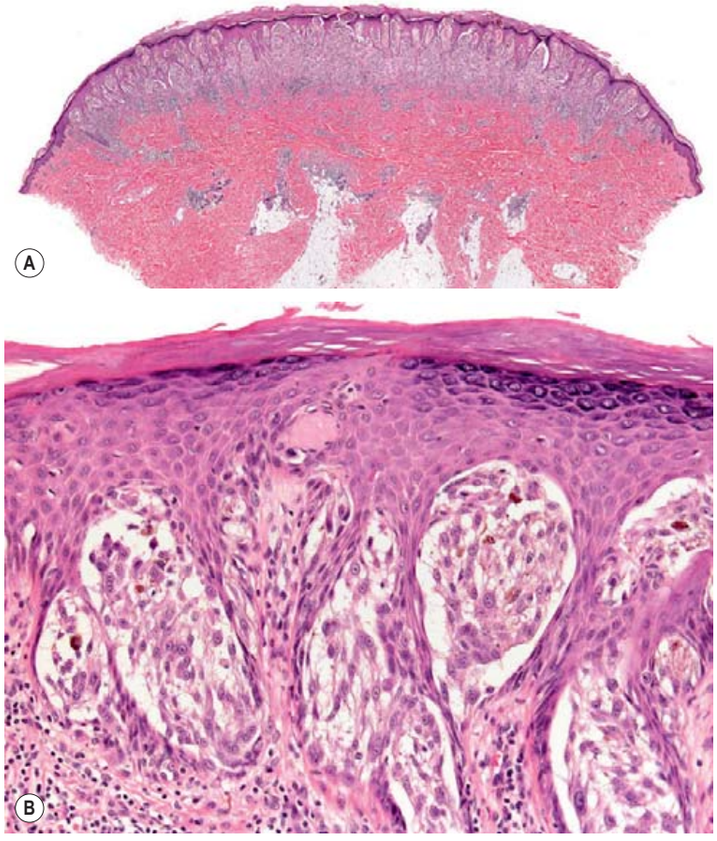


Fig. 112.18 Histology of Spitz nevus. A Dome-shaped with sharply demarcated and symmetric proliferation of spindled and epithelioid melanocytes at the dermo-epidermal junction and within the papillary dermis; there is also epidermal hyperplasia. **B** Nests of cohesive spindled and epithelioid melanocytes with clefts between the nests and the hyperplastic epidermis. *Courtesy, Lorenzo Cerroni, MD.*

cells and as nests or fascicles. In general, there is orderly infiltration of the dermal collagen by these nests or cells with so-called maturation, i.e. gradual diminution of nuclear and cellular sizes. The individual cells usually have abundant cytoplasm that stains slightly bluish or pink and nuclei with open chromatin patterns. Rather uniform nucleoli are usually also noted. Occasionally, bizarre cytologic features, necrotic cells and mitotic figures are found within even the most banal lesions.

Differential Diagnosis

The clinical differential diagnosis of Spitz nevi is wide and includes other melanocytic nevi, particularly dermal nevi, hemangiomas, pyogenic granuloma, verrucae, molluscum contagiosum, juvenile and adult xanthogranulomas, dermatofibroma, mastocytoma and adnexal tumors. The fundamental diagnostic problem is the histologic differentiation of Spitz nevus from cutaneous melanoma. The latter distinction is one of the most difficult problems in all of pathology and at present is subjective, based on the experience of the pathologist, and the careful weighing of a number of clinical and histopathologic parameters summarized in Table 112.6.

Treatment

Because of the frequent diagnostic difficulty in classifying these lesions, histologic evaluation of the entire lesion is highly recommended. Recurrence rates from 7% to 16% have been observed when lesions were incompletely excised. In the authors' opinion, complete excision with margins free of tumor is recommended for all Spitz nevi. However, there are clinicians, including pediatric dermatologists, who reserve this recommendation for lesions with any atypical features (clinically or histologically) or for Spitz nevi in adults. Margins of approximately 1 cm are advised for markedly atypical or histologically ambiguous variants. It is also advisable that patients with atypical lesions have periodic evaluations every 6 to 12 months. Although controversial, sentinel lymph biopsy may be considered on a case-by-case basis for markedly atypical lesions with a Breslow depth ≥1 mm. However, there is mounting evidence that sentinel lymph node involvement by Spitz tumors is not necessarily analogous to conventional metastatic melanoma[76], as almost all of the cases studied to date have not shown progression of

COMPARISON OF SPITZ NEVUS AND MELANOMA

Parameter	Spitz nevus	Melanoma
Age	Young age, especially <10 years, favors a benign process	Exceedingly rare under age 10 years (pre-pubertal); outnumber Spitz nevi in patients >30 to 40 years of age
Anatomic site	Head and neck > extremities (especially thighs) are preferential sites, but may occur anywhere	Most often on the trunk (back) in men and distal lower extremities in women; favor intermittently sun-exposed skin, but may occur anywhere
Size	Often <5–6 mm, usually <10 mm	Often >6 mm, but early lesions may be smaller; large size favors melanoma
Symmetry	Usually symmetric	Increasing asymmetry favors melanoma
Architecture	Dome-shaped, plaque-like, wedge-shaped in dermis, plexiform	Heterogeneous and complex (with exceptions)
Circumscription	Usually well demarcated with peripheral junctional nests	Often poorly demarcated ending in single-cell patterns
Maturation	Overall reduction in cellular density with depth; orderly dispersion and regular spacing of nests and cells among collagen bundles with depth; nests become progressively smaller, finally resulting in single melanocytes at the base of lesion; cells and nuclei also diminish in size with depth; maturation may be absent in a subset of Spitz nevi	Little or no maturation; confluence of melanocytes is not lost with depth; irregular spacing and disorderly arrangements of cells
Pagetoid spread	Less frequent than in melanoma; orderly; often confined to the epidermis over the central part of the lesion; nested patterns may be more frequent than single cells	Common; disorderly; the melanoma cells often reach the granular layer; higher cellular density
Zonation	Uniformity of cytologic features across horizontal strata of lesion	Heterogeneity of features
Mitotic figures in dermal component	Limited in number, superficial, usually not atypical	Greater in number, deeply located, atypical
Cytologic features	Abundant ground-glass or opaque cytoplasm; polyangular, rhomboidal; occasional dendrites	Variable amount of cytoplasm; often granular or "dusty" and abundant in epithelioid cells; scant cytoplasm in spindled cells
Nuclear features	Enlarged nuclei; uniform dispersed chromatin pattern; nucleoli may be prominent but usually uniform; reniform, multilobulated, multinucleate and giant bizarre forms occur	Pleomorphism; often high nuclear to cytoplasmic ratios; hyperchromatism; prominent variable nucleoli commonly multiple; thickened nuclear membranes

Table 112.6 Comparison of Spitz nevus and melanoma.

disease beyond the sentinel lymph nodes. In sum, further research into understanding and predicting the biologic behavior of atypical or ambiguous Spitz tumors is needed.

PIGMENTED SPINDLE CELL NEVUS

Synonyms: ■ Pigmented spindle cell tumor of Reed ■ Pigmented variant of Spitz nevus

Key features

- Dark brown to black macule or papule, usually <6 mm in diameter
- Found in children or young adults
- They are a spindle cell variant of Spitz nevus

Epidemiology

Pigmented spindle cell nevi occur less frequently than other forms of spindle and epithelioid cell nevi[79–82]. A few have been noted at birth; however, the mean age at diagnosis is 25 years (the age range in one series was 3 to 66 years). Women are affected more often than men. Pigmented spindle cell nevi are most commonly located on the extremities (70% of cases in one study), with the thigh being the most frequent site. About 20% of pigmented spindle cell nevi are found on the trunk, and 9% occur in the head and neck region.

Pathogenesis

As with other melanocytic nevi, pigmented spindle cell nevi are thought to be derived from cells migrating from the neural crest. The reasons for the prominent spindle cell features are not understood.

Clinical Features

The pigmented spindle cell nevus is usually a relatively flat or slightly raised, well-circumscribed lesion averaging about 3 mm in diameter (range 1.5 to 10 mm). The color is usually dark brown or black and is homogeneous. The most common dermoscopic patterns include the following: a dark structureless area almost to the periphery of the lesion, a central dark structureless area with symmetric pseudopods or radial streaming (starburst pattern), and/or a peripheral globular pattern (see Ch. 0). Irregularity of pigmentation is not common but may be found in atypical variants of pigmented spindle cell nevi. There is often a history of recent development or alteration. In one study, lesions had been present on average for about 6 months, although some were of longstanding duration. There is usually no family history of melanoma or atypical nevi.

The natural history is largely unknown. As has been mentioned, the vast majority of pigmented spindle cell nevi have been present for only a short time, usually less than a year. Congenital forms of pigmented spindle cell nevi, although uncommon, have been recognized. The occurrence of atypical varieties of pigmented spindle cell nevi and the presence of remnants of pigmented spindle cell nevi in association with cutaneous melanoma are circumstantial evidence that pigmented spindle cell nevi can undergo rare transformation to cutaneous melanoma. In a long-term (mean 8.8 years) follow-up of 15 patients with excised pigmented spindle cell nevi, there was no evidence of recurrence. In our experience, these lesions have almost never recurred. Thus, unless a lesion has been incompletely excised, recurrence strongly suggests an atypical process, possibly cutaneous melanoma.

Deep penetrating nevus (plexiform pigmented spindle cell nevus), which was previously thought to be a variant of cellular blue nevus by many, is more closely related to pigmented spindle cell nevi[83,84]. These lesions do not show *GNAQ* mutations typical of blue nevi. Pleomorphic spindle cells and variably present epithelioid cells extend vertically into the deep dermis or fat in plexiform aggregates.

Pathology

The pigmented spindle cell nevus displays a well-circumscribed and orderly appearance (Fig. 112.19A). The lesions are usually only slightly raised with nevus cells confined to the epidermis, but may involve the papillary dermis. The lesion is typified by fascicles of uniform, slender spindle cells that are closely aggregated (Fig. 112.19B). The cells usually contain fine, granular melanin. The nuclei contain delicate chromatin and small inconspicuous nucleoli and overall have a monotonous appearance. There may be clefting about the intraepidermal fascicles. Numerous melanophages are usually present in the papillary dermis. Upward migration of nevus cells throughout the epidermis is sometimes noted, but these cells are usually confined to the lower half of the epidermis. Atypical variants exhibit prominent single-cell hyperplasia extending peripherally along the basal layer of the epidermis and in a pagetoid pattern throughout the epidermis. Cytologic atypia also may be present in a varying degree in these atypical variants.

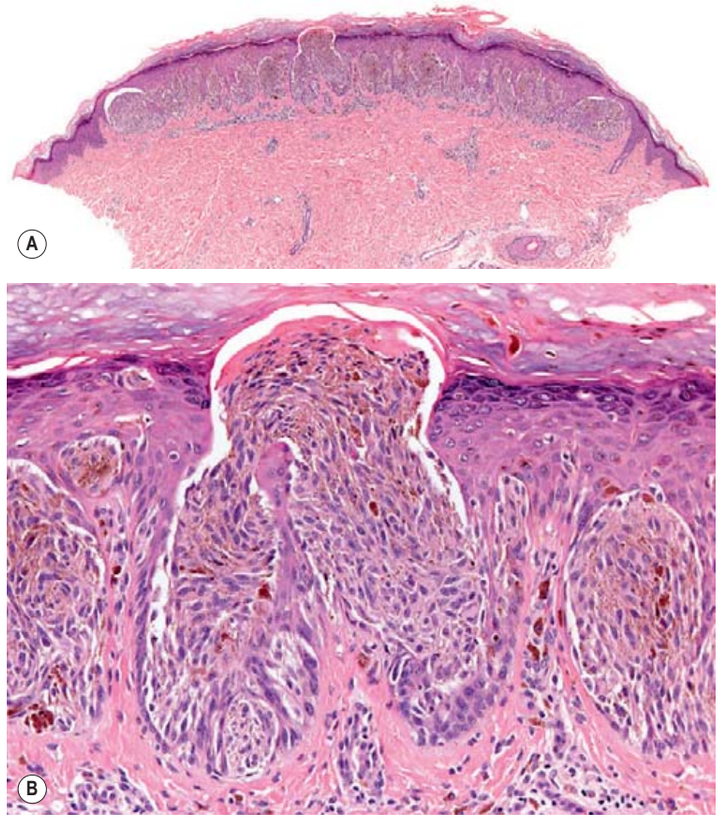


Fig. 112.19 Histology of a pigmented spindle cell nevus. A A predominantly junctional melanocytic proliferation that is characterized by well-defined margins, symmetry and an overall plate-like configuration. Several nests have a vertical configuration. **B** The melanocytes are spindle-shaped and heavily pigmented. *Courtesy, Lorenzo Cerroni, MD.*

Differential Diagnosis

The clinical differential diagnosis of pigmented spindle cell nevi includes early melanoma, atypical nevus, blue nevus, angiokeratoma and pigmented basal cell carcinoma. In general, the borders of pigmented spindle cell nevi are regular and well defined. The color is also homogeneous in most instances. However, atypical forms of pigmented spindle cell nevi may exhibit irregular borders and variation in color. Although spindle cell nevi have a characteristic dermoscopic pattern, histopathologic examination is required for diagnosis. It must be stressed, however, that the clinicopathologic presentation of typical pigmented spindle cell nevi is distinctive. Its history is that of a recently developed or changing, small, well-circumscribed, black lesion on the thigh of a young woman (usually in her 20s). These lesions are often conspicuous because of the dearth of pigmented lesions elsewhere on the body.

Treatment

The proper treatment of pigmented spindle cell nevi is complete excision with clear margins. The reason for this recommendation is to prevent recurrence, since the pathology of recurring lesions may be

alarming and difficult to distinguish from melanoma. For pigmented spindle cell nevi with atypical features, wider surgical margins are advised. For example, we advocate resection margins of 5 to 10 mm for markedly atypical forms of pigmented spindle cell nevus. Periodic follow-up, i.e. every 6 to 12 months, is also strongly advised for patients with atypical variants of pigmented spindle cell nevus.

ATYPICAL (DYSPLASTIC) MELANOCYTIC NEVUS

Synonyms: ■ Atypical nevus ■ Clark's nevus ■ Atypical mole ■ "Dysplastic" melanocytic nevus ■ Nevus with architectural disorder ■ B-K mole ■ The mole of FAMM (familial atypical mole and melanoma syndrome)

The US National Institutes of Health Consensus Conference held in January 1992 recommended that the histologic term "nevus with architectural disorder" replace dysplastic melanocytic nevus

Key features

- A controversial clinical designation for various nevi that have morphologic changes such as asymmetry, irregular borders and color variation
- Also a controversial pathologic term used for nevi with certain architectural changes and/or cytologic atypia
- The relationship to melanoma is complex

History

Since the description of atypical or "dysplastic" melanocytic nevi in the setting of melanoma-prone families over 30 years ago and subsequently in individuals outside such kindreds, these lesions have remained highly controversial[56,85–121]. This has largely resulted from the failure to reach a consensus regarding the nature of these lesions, an inability to formulate precise criteria for recognition, and, finally, a lack of understanding about their biologic significance. Specifically, this relates to criteria for individual lesions and for the so-called "dysplastic nevus syndrome", i.e. how many clinically atypical melanocytic nevi are needed and what are the minimal essential gross morphologic criteria required for diagnosis of an individual lesion? One particular problem, dating back to the original studies on atypical melanocytic nevi ("dysplastic nevi") in hereditary kindreds, has been the tendency to consider the histopathologic diagnosis of atypical melanocytic nevi ("dysplastic nevi") as the gold standard. However, it has been shown that the histopathologic features ascribed to atypical melanocytic nevi ("dysplastic nevi") lack specificity (see below).

Many studies have established that, irrespective of histology, melanoma risk is directly related to numbers of ordinary nevi (> 50 or 100 on the total skin surface) as well as the presence and number of atypical nevi, as defined by size (e.g. > 5, 6 or 8 mm), irregular or ill-defined borders, variation in color, macular component, etc. (Tables 112.7 & 112.8)[87–93]. Despite the seemingly logical conclusion that histopathologically atypical nevi should be associated with increased melanoma risk, only limited data thus far have shown such a relationship. Furthermore, studies examining the relationship between clinically atypical melanocytic nevi and histopathologically atypical melanocytic nevi have shown a poor correlation. Therefore, the "dysplastic" nevus cannot be considered a distinct clinicopathologic entity. At present, melanoma risk assessment of patients is based almost solely on gross morphologic parameters of nevi, i.e. total numbers of nevi on the skin surface and the presence and number of clinically atypical melanocytic nevi, along with other factors such as personal or family history of melanoma.

The term "atypical melanocytic nevus" undoubtedly encompasses a large and heterogeneous group of nevi including:

- nevi with atypical clinical features, which have been termed simply "atypical nevi"; in general, these atypical nevi can simulate melanoma clinically; this group of nevi includes not only "atypical" or "dysplastic" nevi, but also some congenital and combined melanocytic nevi, as well as Spitz/pigmented spindle cell nevi
- nevi with abnormal histopathologic features
- nevi with *both* abnormal clinical and histopathologic features
- nevi with histopathologic features that are equivocal or of unknown significance.

The latter group of nevi may demonstrate findings that may be reactive or proliferative in nature rather than neoplastic[85–121].

Epidemiology

Estimates of the incidence of atypical melanocytic nevi cover a wide range, as would be expected given the lack of consensus regarding definitions. Most estimates are in the 10% range, but estimates as high as 53% have been reported for the US population.

Atypical melanocytic nevi may be single or multiple. In the general population, atypical nevi may arise in a "sporadic" fashion, i.e. without a history of familial melanoma, versus in the context of a family history of atypical moles and/or melanoma. In both clinical settings, there is

MELANOCYTIC NEVUS PHENOTYPES		
	Common pattern	**Atypical pattern**
Number	None to few (<25) nevi	Many (>50) nevi
Size	<5 mm	Variable: small to large, often several >5 mm
Color	Uniform, homogeneous color	Some to many nevi with irregular or haphazard color, erythema
Borders	Well circumscribed	Irregular or ill-defined borders

Table 112.7 Melanocytic nevus phenotypes.

MELANOMA RISK ASSOCIATED WITH CLINICALLY ATYPICAL MELANOCYTIC NEVI: COMPARISON OF OCCURRENCE IN MELANOMA PATIENTS VERSUS CONTROLS					
Study	**Country**	**Definition**	**Melanoma patients (%)**	**Controls (%)**	**Relative risk**
Roush et al. & Nordlund et al.	Australia	>5 mm, irregular border, and haphazard pigmentation	34	7	7.7
MacKie et al.	Scotland	>5 mm and either irregular pigmentation or inflammation	38	20	2.1–4.5*
Holly et al.	US	At least 3 of 6 criteria: ill-defined border, irregular border, irregular pigmentation, >5 mm, erythema, accentuated skin margins	55	17	3.8–6.3†
Halpern et al.	US	>4 mm, macular component, variegation of color, and irregular or indistinct border	39	7	8.8
Garbe et al.	Germany	At least 3 of 5 criteria: >5 mm, irregular margins, ill-defined border, color variation, macular and papular components	45	5	7

*Relative risk for one or two atypical nevi, 2.1; for three or more atypical nevi, 4.5.
†Relative risk for one to five atypical nevi, 3.8; for six or more atypical nevi, 6.3.

Table 112.8 Melanoma risk associated with clinically atypical melanocytic nevi: comparison of occurrence in melanoma patients versus controls[87–93].

agreement that these nevi indicate some increase in melanoma risk[113]. More recently, objective evidence was presented that "dysplastic" nevi with moderate to severe atypia histologically represented a risk factor for the development of melanoma[121].

Sporadic atypical melanocytic nevi may occur at any time, while persons with a family history of atypical melanocytic nevi and/or melanoma usually manifest their atypical lesions by the end of the second decade. In contrast to common acquired moles that tend to appear in clusters around puberty, atypical melanocytic nevi may appear, even in an eruptive fashion, as late as the sixth decade. Histologic contiguity of atypical melanocytic nevi to melanomas was frequently observed in several studies of melanoma kindreds, but the development of melanoma in association with an individual atypical melanocytic nevus in the sporadic setting seems to be an uncommon event.

Clinical Features

Nevi as described below can occur anywhere on the cutaneous or mucosal surfaces of Caucasians as well as on the acral and mucosal surfaces of other races. Of note, other authors believe that distinct atypical melanocytic proliferations apart from atypical melanocytic nevi occur on acral and mucosal sites. Atypical nevi occupy an intermediate position on a continuum with common nevi at one end and cutaneous melanoma at the other end, and, as a result, they overlap with both. No single feature is diagnostic of atypical melanocytic nevi; rather, a constellation of clinical and dermoscopic findings is required for their recognition (see Figs P9, P10). However, the greater the number of clinical abnormalities present, the greater is the likelihood that the lesion will prove to be histologically atypical, but there are many exceptions.

The following gross morphologic features are commonly observed in atypical melanocytic nevi:

- *Asymmetry*: atypical melanocytic nevi often lack mirror-image symmetry. Greater asymmetry suggests greater likelihood of atypicality.
- *Size*: atypical melanocytic nevi may be of any size but generally range from 3 to 15 mm in greatest diameter. There is generally a positive correlation between increasing size and likelihood of atypia.
- *Borders*: atypical melanocytic nevi often exhibit irregular and ill-defined borders, but not typically the notched or scalloped borders of melanoma.
- *Coloration*: atypical melanocytic nevi often have many colors. They commonly exhibit irregularity of pigmentation with two or three shades of brown, e.g. tan, brown and dark brown (Fig. 112.20). They may also have areas that are skin-colored, pink, gray or brown–black. Of note, some atypical melanocytic nevi present with fairly uniform coloration and an erythematous appearance.

Fig. 112.20 Atypical melanocytic nevus. There is asymmetry as well as several shades of brown, simulating the clinical features seen in cutaneous melanoma.

Atypical melanocytic nevi most frequently involve the trunk and also show a striking (though less common) predilection for the scalp and for doubly covered areas of the body (breasts in women and bathing-trunk area in men). Their numbers may range from one or two to hundreds (Fig. 112.21). When multiple large lesions are present, their prominence is noteworthy, and while there may be variability, patients often have a "signature" nevus, clinically and histologically. Localized patterns such as linear tracts, clusters or figurate arrays may also be seen in patients with numerous nevi.

The overwhelming majority of atypical melanocytic nevi are clinically stable. However, there is definite evidence that some lesions eventuate in cutaneous melanoma. Progressive abnormalities in DNA content, cytogenetic alterations, and increased expression of melanocyte-associated antigens by immunohistochemistry have been correlated with progressive degrees of histologic atypia. Although these latter findings suggest a progression of atypical melanocytic nevi toward melanoma, atypical melanocytic nevi are not inevitable precursors to melanoma, and their presence can be viewed as a phenotypic marker of "skin at risk".

Pathology

Prototypic atypical melanocytic nevi are described as having several noteworthy architectural features (Fig. 112.22). Such nevi are often larger (commonly >5 to 6 mm in diameter), are more poorly circumscribed, are slightly more asymmetric, are relatively flat, particularly at the peripheries of the lesion, and often show heterogeneity as compared

Fig. 112.21 Atypical melanocytic nevi. Multiple pigmented macules and papules of varying sizes on the back.

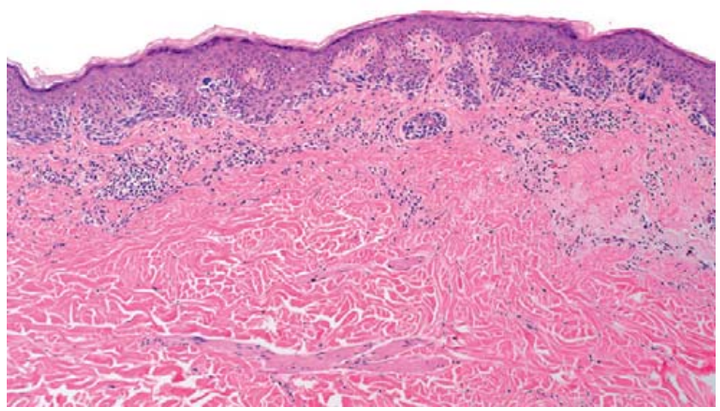


Fig. 112.22 Histology of an atypical melanocytic nevus. Note confluent nests of melanocytes at the dermo-epidermal junction and scattered solitary melanocytes in the lower portion of the epidermis. *Courtesy, Lorenzo Cerroni, MD.*

to ordinary nevi. In atypical melanocytic nevi, the junctional nests frequently extend beyond the dermal component (the "shoulder" phenomenon).

Of particular importance are abnormalities of the intraepidermal component. Architectural or organizational disorder occurs in two patterns that are often present simultaneously to a varying extent. The first is lentiginous melanocytic proliferation that is almost always associated with elongated epidermal rete ridges. In general, the basilar melanocytes are concentrated in the lowermost portions of the rete ridges, and the frequency of basilar melanocytes varies greatly, e.g. from one melanocyte per one to two keratinocytes to the melanocytes replacing the basilar keratinocytes and resulting in a confluent, clustered, or multilayered cellular appearance.

The second pattern includes nests of melanocytes irregularly disposed along and between the rete ridges in a more haphazard fashion as compared to ordinary nevi. These nests vary in size and shape, are frequently elongated, commonly have their long axes oriented along the dermal–epidermal junction, and contain variable numbers of cells. Colliding nests of melanocytes frequently fuse or "bridge". Dyscohesion of cells within these nests is also common; this feature contrasts with the cohesive appearance of junctional nests of melanocytes in ordinary nevi. Often, atypical nevi have a higher density or concentration of melanocytes in the intraepidermal component than do banal nevi, and this may be a helpful feature in their recognition.

Atypical melanocytic nevi with the latter two patterns usually exhibit cytologic atypia of their melanocytes. Such change is discontinuous and variable, from only a small percentage of cells demonstrating nuclear atypia to most cells being atypical. Cytologic atypia often has a general correlation with the degree of architectural abnormality present in a particular lesion. Pleomorphism of the nuclei (i.e. variation in size, shape and staining properties) is perhaps the most characteristic attribute of the nuclear changes in atypical melanocytic nevi. However, nuclear enlargement and hyperchromatism also occur. The cells are frequently typified by a perinuclear clear space resulting from cytoplasmic shrinkage, an artifact of tissue processing. Criteria for grading the degree of cytologic atypia and even architectural abnormality have been proposed, but there is currently no consensus.

Atypical melanocytic nevi may also contain a proliferation of atypical epithelioid melanocytes that resembles the epithelioid melanocytes in some forms of melanoma. This is characterized by prominent junctional nests of cells that are predominantly epithelioid in appearance, with round nuclei and finely granular melanin in their cytoplasm. The cells may also be disposed singly along the dermal–epidermal junction, with occasional pagetoid spread. Epithelioid cell proliferation may occur in a normal epidermis or in a hyperplastic epidermis, but the normal rete ridge pattern is retained. Cytologically, the melanocytes are enlarged and have variable degrees of nuclear enlargement, pleomorphism, hyperchromatism and, occasionally, prominent nucleoli. When these cells are in nests, they show some dyscohesion, but on the whole fill the nests completely. Mixtures of these intraepidermal patterns are common.

The dermal component of atypical melanocytic nevi may be composed of typical nevus cells, such as those in any acquired nevus, or of cells that may exhibit atypia. In addition to the abnormal proliferative patterns described above, other frequent alterations, in particular changes related to host response, characterize intermediate nevi. Two forms of collagenous change occur in the papillary dermis. Most common is a condensation of dense, acellular collagen around the elongated epidermal rete; this is known as concentric eosinophilic fibrosis. A less common pattern consists of delicately layered, or laminated, collagen subjacent to the rete tips with fibroblasts disposed along the laminated collagen fibers in a linear array. This pattern is referred to as lamellar fibroplasia. A mixture of the two collagen patterns is not uncommon.

Lymphocytic infiltrates, which usually are distributed in a perivascular fashion and less commonly in a band-like pattern, are also frequently observed in atypical melanocytic nevi. Finally, atypical melanocytic nevi usually have prominent vascularity throughout the papillary dermis, which is secondary to dilation and hypertrophy of existing vascular channels, rather than significant angiogenesis. The histopathologic criteria for atypical melanocytic nevi are still evolving, and, as already mentioned, many questions relating to the histopathology of these lesions are still unanswered.

Differential Diagnosis

The differential diagnosis of pigmented lesions approximately 4 to 15 mm in size includes both melanocytic and keratinocytic lesions. Among melanocytic proliferations, the principal diagnostic considerations lie among common acquired nevi, small congenital nevi, and cutaneous melanoma. The atypical melanocytic nevus is characterized by haphazard, irregular coloration, including hues of pink, tan, brown and even black, and irregularity in shape (features it shares with melanoma). The other nevic lesions either show symmetry and/or uniformity of coloration or, when irregularly colored, show orderly gradations or patterns of pigmentation.

Dermoscopy may also play an important role in evaluating atypical melanocytic nevi (Fig. P5). Although atypical melanocytic nevi can clinically resemble melanoma, many of these lesions fall into one of the benign dermoscopic melanocytic patterns (see Fig. P9). The features employed to evaluate a melanocytic nevus include colors, symmetry and organization. Benign melanocytic lesions tend to have few colors and are symmetric with regard to the distribution of colors and structures. Organization refers to the distribution of structures in a lesion. When these structures are symmetrically distributed and there are fewer than three colors (light brown, dark brown and black) noted, they create a pattern seen in many benign lesions. The most common benign patterns are reticular, globular and homogeneous. In addition, there are the subset patterns of reticular–homogeneous, reticular–globular and globular–homogeneous (see Fig. P9)[120].

Of particular note, a subset of atypical melanocytic nevi may demonstrate a "malignant" melanocytic dermoscopic pattern (see Fig. P10). These lesions often have many colors and are asymmetric and disorganized with respect to a non-uniform distribution of colors and structures. It is recommended that these lesions be biopsied.

Finally, another subset of atypical melanocytic nevi is characterized by uncertain melanocytic dermoscopic patterns. Just as the clinical and histologic features of atypical melanocytic nevi are a continuum, so too are the features with dermoscopy. These lesions should either be serially monitored or undergo biopsy.

Pigmented seborrheic keratoses, solar lentigines, lichen planus-like keratoses, pigmented actinic keratoses, pigmented Bowen's disease and basal cell carcinoma may exhibit pink, tan, brown or dark brown coloration.

Treatment

As within any area of medicine, the physician is first obliged to do no harm. Such an approach is particularly germane to patients with atypical melanocytic nevi, in order to avoid overly aggressive procedures, surgery and follow-up. Common sense should prevail at all times and consideration given as to whether the intervention will have any impact on potentially reducing mortality from melanoma. Treatment depends, on whether the patient presents with one or a few nevi or with numerous nevi and whether there is a personal history of melanoma, as well as on whether there exists a familial setting of atypical melanocytic nevi and/or melanoma. A gradient of melanoma risk has been clearly established for these various subsets of patients. Melanoma risk is probably continuous and increases with progressive increases in numbers of nevi, clinical atypia of nevi, and personal and familial occurrence of atypical nevi and melanoma.

Regardless of the risk group, any pigmented lesion suspicious for melanoma and any persistently and significantly changing lesion should, in the authors' opinion, be excised completely with approximately 2 mm margins for histopathologic examination. Some authors have advocated "deep" shave excision (saucerization) for superficial lesions, as long as the base of the lesion is removed. As opposed to partial punch biopsy, the latter allows for assessment of the overall architecture of the lesion and leads to less sampling error. A helpful rule of thumb in following patients with many atypical melanocytic nevi is to search for lesions that clearly stand out as different from the patient's other (baseline) nevi; such lesions should be examined carefully. It should be kept in mind that new nevi will continue to develop and nevi may enlarge and change with time, especially in young individuals. One must use common sense in assessing this normal evolution of nevi and not be overly aggressive in removing such nevi. It is not mandatory to remove clinically atypical nevi simply to confirm or exclude atypical melanocytic nevi histologically. An acceptable

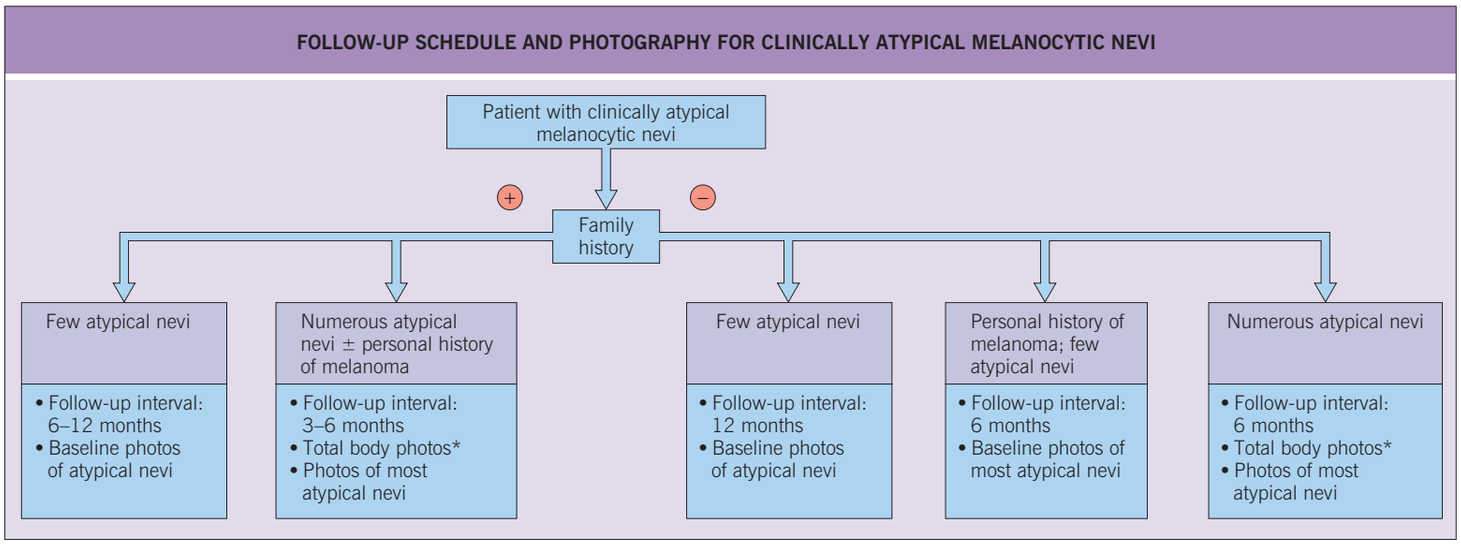


Fig. 112.23 Follow-up schedule and photography for clinically atypical melanocytic nevi. *Advocated by some authors, but not standard of care.

practice is to follow such patients on a regular schedule with a total body skin examination plus dermoscopy, baseline photography, and/or digital dermoscopy, as preferred by the clinician. The frequency of follow-up examinations is individualized and is based on the previously mentioned risk factors, i.e. numbers and clinical atypia of nevi, lesion stability, and personal and family history of melanoma (Fig. 112.23).

For patients having clinically suspicious lesions removed, narrow surgical margins are advised. If "severe" cytologic atypia is present in the lesion, re-excision is recommended because of frequent overlap with melanoma *in situ*. For atypical melanocytic nevi with lesser degrees of melanocytic atypia, the question of re-excision for a nevus not completely removed is controversial. One reason for the latter statement is that there is currently neither consensus about the grading of atypia in nevi nor sufficient data regarding the significance of melanocytic atypia in nevi. However, as with any melanocytic lesion, it is important to know if the lesion has been adequately sampled and also if the lesion was considered to be clinically atypical. If lesions are "slightly" atypical, no re-excision is recommended, as long as no residuum of the nevus is clinically apparent. If lesions are "moderately" atypical and present in the margins, even when no residual lesion is clinically obvious, a re-excision with clear margins might be considered, depending upon the degree of concern clinically, the site, the size of the nevus (versus the size of the biopsy), the patient's ability and interest in following the site, and color (more inclined with amelanotic lesions as assessing residuum is more difficult during healing phase).

In general, follow-up of patients with multiple atypical nevi, especially in the context of a personal or family history of melanoma, should be every 3 to 12 months, depending on the clinical situation. One should consider documentation of nevi by body charts and clinical photography as judged appropriate, with periodic updating. The authors have found that individual photographs of the most atypical or difficult-to-follow nevi are particularly helpful. Additional tools such as dermoscopy and/or digital imaging devices may be useful diagnostic aids.

Finally, individuals presenting with atypical melanocytic nevi should have a family history taken for the presence of atypical melanocytic nevi and/or melanoma. First-degree blood relatives should be examined both for documentation and to assess and potentially diminish their own risks of developing melanoma.

CONGENITAL MELANOCYTIC NEVUS

Synonyms: ■ Congenital nevomelanocytic nevus ■ Large congenital melanocytic nevi: • Giant pigmented nevus • Giant hairy nevus • Bathing trunk nevus • Garment nevus

Key features

- Small congenital nevi are <1.5 cm in diameter (in adults)
- Medium-sized congenital nevi are between 1.5 and 19.9 cm in diameter (in adults)
- Only the large (or giant) congenital nevi >20 cm in diameter (in adults) have a significantly higher risk for developing melanoma than do ordinary nevi

Introduction

Congenital melanocytic nevi are melanocytic nevi present at birth[122–141]. They consist of proliferations of benign melanocytes that may be intraepidermal, dermal, or both. Rarely, lesions appear after birth or within 2 years which are not otherwise remarkably different from congenital nevi and are therefore referred to as *congenital nevus tardive*. Some congenital melanocytic nevi may be just a few millimeters in size and appear clinically indistinguishable from common acquired nevi. In general, congenital melanocytic nevi are classified as small, intermediate- or medium-sized, and large or giant. For practical purposes, small congenital nevi are <1.5 cm in greatest diameter, medium-sized congenital nevi are from 1.5 to 19.9 cm, and large (or giant) congenital nevi are >20 cm (in adults; 9 cm on the scalp and 6 cm on the trunk in newborns). The latter often cover large areas of the body such as the arm, scalp, or even the entire dorsal surface from the scalp to the feet. Some authors base the distinction between small, intermediate and large congenital nevi on their ease of removal. In this scheme, small congenital nevi generally may be removed by simple excision, medium-sized nevi often require staged excisions for closure, and giant nevi often cannot be removed or require multiple staged excisions. A fourth category, garment nevus, is sometimes used to distinguish nevi that are >40 cm in diameter (in adults), given the greater risk for developing complications.

Neurocutaneous melanosis, also referred to as neurocutaneous melanocytosis, is a rare congenital syndrome characterized by: (1) the presence of either a large (>20 cm) congenital melanocytic nevus or multiple (more than three) usually smaller congenital melanocytic nevi (or both), in association with meningeal melanosis or melanoma; (2) an absence of cutaneous melanoma except in patients with histologically benign meningeal lesions; and (3) an absence of meningeal melanoma except in patients with histologically benign cutaneous lesions[137–140].

Epidemiology

Estimates of the incidence of congenital nevi are imprecise since distinctions between relatively "small" congenital melanocytic nevi and

acquired nevi are not well defined and histologic patterns vary considerably among congenital melanocytic nevi. When histologic confirmation is a criterion, the incidence may be as low as 0.6%; series based on clinical criteria have found an incidence as high as 2.5%. Giant congenital nevi are rare, with an estimated incidence of 0.005% (1 in 20 000). Patients with giant nevi often have multiple smaller (satellite) nevi as well, with greater numbers correlating with an increased risk of neurocutaneous melanosis. Familial aggregation of congenital nevi has occasionally been reported.

Pathogenesis

The precise pathogenesis of congenital melanocytic nevi has not been established. In one study of 32 truly congenital nevi, no *BRAF* mutations were detected, but 81% (26/32) harbored mutations in *NRAS*[142]. An origin from neural crest stem cells that have migrated to the skin appears almost certain. Individual melanocytes begin to appear in fetal skin before 40 days' gestation. Given the observation of congenital divided nevi of the eyelid and the fact that the eyelids open during the sixth month of gestation, it appears that congenital melanocytic nevi develop some time during this interval. Patients with either a large congenital nevus or multiple satellite-like lesions should be thought of as having a systemic disease, as nevus cells can be found in sites beyond the skin and central nervous system (CNS), such as the retroperitoneum.

Clinical Features

Small and medium-sized congenital melanocytic nevi are usually round or oval and fairly symmetric (Fig. P6). These lesions are usually slightly raised at birth and may be tan in color. They may or may not have associated hypertrichosis, and perifollicular hypo- or hyperpigmentation may be seen. Some congenital melanocytic nevi have rugose or pebbly surfaces (Fig. 112.24). Lesions that begin as slightly raised tend with age to become more elevated; color darkening and the assumption of a verrucous appearance are also common. After an initial darkening during the first year or so of life, some congenital melanocytic nevi may actually become lighter in color with aging, including satellites. In addition, congenital nevi can develop the halo phenomenon (see below), and occasionally, congenital nevi completely regress, even without forming a halo. As hamartomas, congenital nevi can exhibit asymmetry and variation in color, develop papules and nodules (e.g. proliferative nodules), and undergo change over time; however, histologic examination of any concerning areas is recommended (see Table 112.9).

The dermoscopic structures seen in congenital nevi may include the following: globules, diffuse background pigmentation (structureless), milia-like cysts, hypertrichosis, hyphae-like structures and perifollicular pigment changes. Congenital nevi have repeatable dermoscopic patterns. The most common patterns are the reticular, globular, reticular–globular (see Fig. P6), diffuse brown pigmentation, and multicomponent. The multicomponent pattern is often difficult to distinguish from melanoma and requires either monitoring or biopsy.

Varying numbers of so-called satellite congenital melanocytic nevi often accompany giant congenital melanocytic nevi (Fig. 112.25). In one study, at least 80% of patients with large congenital melanocytic nevi had satellite congenital melanocytic nevi. Such lesions typically resemble small or medium-sized congenital melanocytic nevi. Of note, some patients present with multiple satellite-like lesions in the absence of a large congenital nevus (see Fig. 112.25A), and these individuals are at greatest risk for neurocutaneous melanosis.

Neurocutaneous melanosis (melanocytosis)

In one series of 33 patients with neurocutaneous melanosis associated with large congenital melanocytic nevi (>20 cm), all nevi had a posterior axial location (involving the head, neck, back and/or buttocks); 31 of 33 patients had satellite nevi. In another study, 80% had posterior axis involvement and 55% had more than 20 satellite nevi. Neurocutaneous melanosis is divided into symptomatic and asymptomatic (noted on screening MRI). Symptomatic neurocutaneous melanosis presents with signs and symptoms of increased intracranial pressure, often due to hydrocephalus or mass effect, and it is associated with a poor prognosis. By MRI, there are several presentations of neurocutaneous melanosis, including: (1) multiple obvious postgadolinium-enhancing masses; (2) diffusely thickened leptomeninges noted by gadolinium enhancement; and (3) focal areas of increased signal on T1-weighted images. The first two forms are associated with a poor prognosis.

Melanoma

Although all sizes of congenital melanocytic nevi may be associated with melanoma, historical estimates of melanoma risk have been exaggerated because of referral bias and misdiagnosing the atypical melanocytic proliferations that develop in congenital melanocytic nevi as melanoma. The potential risk is probably related to size of the congenital melanocytic nevi, i.e. the larger the nevus, the greater the risk. At present it is thought that the melanoma risk associated with small congenital melanocytic nevi is low and probably not much more than that associated with acquired nevi. A prospective study of 230 medium-sized congenital melanocytic nevi in 227 patients, followed on average for 6.7 years, failed to document the development of a single case of

Fig. 112.24 Small congenital melanocytic nevus. Note the hypertrichosis and slight heterogeneity in pigmentation, reflecting its hamartomatous nature.
Courtesy, Lorenzo Cerroni, MD.

MANAGEMENT OF CHILDREN WITH GIANT CONGENITAL MELANOCYTIC NEVI
SURGICAL EXCISION VERSUS LONG-TERM CLINICAL EXAMINATION
• Consider surgical excision of the nevus (staged and/or with tissue expanders) in children at least 6 months of age in order to avoid the period of highest general anesthesia risk • If not excised or partial excision, lifelong examination of the nevus (including palpation) every 6 to 12 months plus baseline photography • Histologic examination of enlarging firm papulonodules and new areas of induration or ulceration*
MRI OF HEAD AND SPINE FOR THE DETECTION OF NEUROCUTANEOUS MELANOSIS† (NCM) AND OTHER CNS ABNORMALITIES‡
• Risk factors for NCM – multiple satellite lesions (>20)§, giant/"garment" nevus (>40 cm projected adult size), posterior axial location • In patients with no risk factors and no neurologic symptoms, MRI not necessary • In asymptomatic patients with at least one risk factor, MRI should be considered and it has a higher sensitivity prior to 4–6 months of age • In asymptomatic patients with intermediate risk (e.g. <10–20 satellites, 20–40 cm nevus as adult), MRI can be considered on a case-by-case basis • Repeat MRIs and neurodevelopmental evaluation performed based upon initial findings and neurologic symptoms • Patients with symptomatic NCM, in particular with multiple gadolinium-enhancing nodules, should not undergo surgical excision of the GCMN because of the associated poor prognosis
*Ulceration at birth or during the first week of life in areas prone to trauma may be due to immaturity of the skin but should heal over a few weeks. †Also referred to as neurocutaneous melanocytosis. ‡Need to check renal function given association with genitourinary malformations. §Highest risk of NCM in those with multiple satellite nevi but no giant congenital nevus.

Table 112.9 Management of children with giant congenital melanocytic nevi (GCMN). CNS, central nervous system; MRI, magnetic resonance imaging.

Fig. 112.25 Congenital melanocytic nevi. **A** Multiple medium-sized nevi. The patient had 25–30 such lesions. This presentation can be associated with neurocutaneous melanosis. **B** Large congenital nevus in an axial location with numerous satellite nevi, some of which have hypertrichosis. This patient died of intractable ascites due to the migration of melanocytes from the brain to the peritoneal cavity via his VP shunt. In the perianal region, the nevus was softer and somewhat "boggy" due to neurotization. *A, Courtesy, Jean L Bolognia, MD.*

melanoma. Similarly, in a longitudinal cohort study of 265 patients with medium-sized congenital melanocytic nevi, none developed melanoma. Thus, in general, the latter studies suggest that medium- (and small-) sized congenital melanocytic nevi are not associated with significantly increased risk for melanoma.

On the other hand, several studies have noted substantial melanoma risk linked to large or giant (>20 cm) congenital melanocytic nevi. In the same cohort study referred to above, Swerdlow, English and Qiao[128] estimated that patients with congenital melanocytic nevi >20 cm had a standardized morbidity ratio of 1224 for the development of melanoma. In a prospective study of 92 patients with large/giant congenital melanocytic nevi[134], three patients developed melanoma in extracutaneous sites (brain, CNS, retroperitoneum) during follow-up averaging 5.4 years. The latter authors calculated the cumulative 5-year life-table risk for melanoma to be 4.5%. The standardized morbidity ratio, which was calculated to be 239, was highly significant.

In a study of 289 patients with large congenital melanocytic nevi culled from the world literature[135], 34 patients (12%) developed primary cutaneous melanoma within their nevi. All of the patients developing these melanomas had congenital melanocytic nevi in an axial location, i.e. the head and neck and/or trunk. No melanomas were associated with an extremity or satellite congenital melanocytic nevus. The median age at diagnosis of melanoma was 4.6 years (range: birth to 52 years; average age: 13.2 years). Twenty-one patients developed primary melanomas in the CNS; all of the latter patients had neurocutaneous melanosis and large congenital melanocytic nevi in a posterior axial location. The median age at diagnosis was 3 years (range: 1 month to 50 years; average age: 11.6 years) for the latter group. An additional 10 patients presented with metastatic melanoma with unknown primary. All of the latter patients had axial congenital melanocytic nevi. A study based on a database of 1008 patients with large congenital melanocytic nevi or multiple medium-sized congenital melanocytic nevi found a significantly lower risk than in previous publications: 2.9% developed cutaneous melanoma associated with 0.8% deaths[141]. Recently, a comprehensive review of 14 studies that examined the development of melanoma in patients with congenital melanocytic nevi reported an overall risk of melanoma of 0.7% (in those with congenital melanocytic nevi of all types), with a risk of 2.5% and 3.1% in large and garment nevi, respectively[142a].

When a cutaneous melanoma develops in a relatively small congenital melanocytic nevus, it appears most commonly at the dermal–epidermal junction in a fashion similar to that of other conventional melanomas. However, up to two-thirds of cutaneous melanomas arising in larger congenital melanocytic nevi develop in the dermis, subcutaneous fat, or even deeper, as a distinct nodule. Rarely, other malignant tumors may arise in these lesions, including neurogenic sarcomas, fibrosarcomas, leiomyosarcomas, rhabdomyosarcomas, osteogenic sarcomas, and liposarcomas.

Leptomeningeal melanomas can arise in patients with neurocutaneous melanosis and most commonly involve the frontal and temporal lobes. As expected, these melanomas have a very poor prognosis.

Pathology

In contrast to common acquired nevi, which are confined to the papillary and upper reticular dermis, congenital nevi may exhibit infiltration of the lower reticular dermis, subcutaneous fat, fascia, and even deeper (Fig. 112.26). It is characteristic to observe nevus cells in a single-cell array throughout the middle or lower reticular dermis and even extending into the septa of the subcutis. Especially helpful is the presence of nevus cells surrounding (cuffing) and within the walls of blood vessels, within adnexal structures such as hair follicles and sweat glands, and within cutaneous nerves, particularly when observed in the lower half of the reticular dermis. Nevus cells may be found in the papillae and epithelium of hair follicles, in the sebaceous glands, in arrector pili muscles, and in the eccrine ducts of the lower dermis. There is often diminished cellularity (or maturation) with depth in the dermis. Uncommonly, congenital melanocytic nevi may show striking neural differentiation suggesting a peripheral nerve sheath tumor such as a neurofibroma. Structures resembling Meissner's corpuscles, Verocay bodies or neuroid tubules may be observed. Neurocutaneous melanosis is defined by the proliferation of benign "melanotic cells" (a term used to avoid a more precise designation such as melanocyte or melanoblast) in the meninges. This melanosis may involve the convexities and base of the brain, the ventral surfaces of the pons and medulla, as well as the upper cervical and lumbosacral spinal cord.

Differential Diagnosis

Although giant congenital melanocytic nevi are quite distinctive, occasionally they are confused with plexiform neurofibromas, as the latter can have both hyperpigmentation and hypertrichosis. The differential diagnosis of small congenital nevi includes congenital smooth muscle hamartoma, atypical nevus, and melanoma. For medium-sized congenital nevi, an additional entity to consider is Becker's melanosis. Of course, the possibility of melanoma exists for any clinically atypical area (e.g. darkening, nodularity) within a congenital nevus.

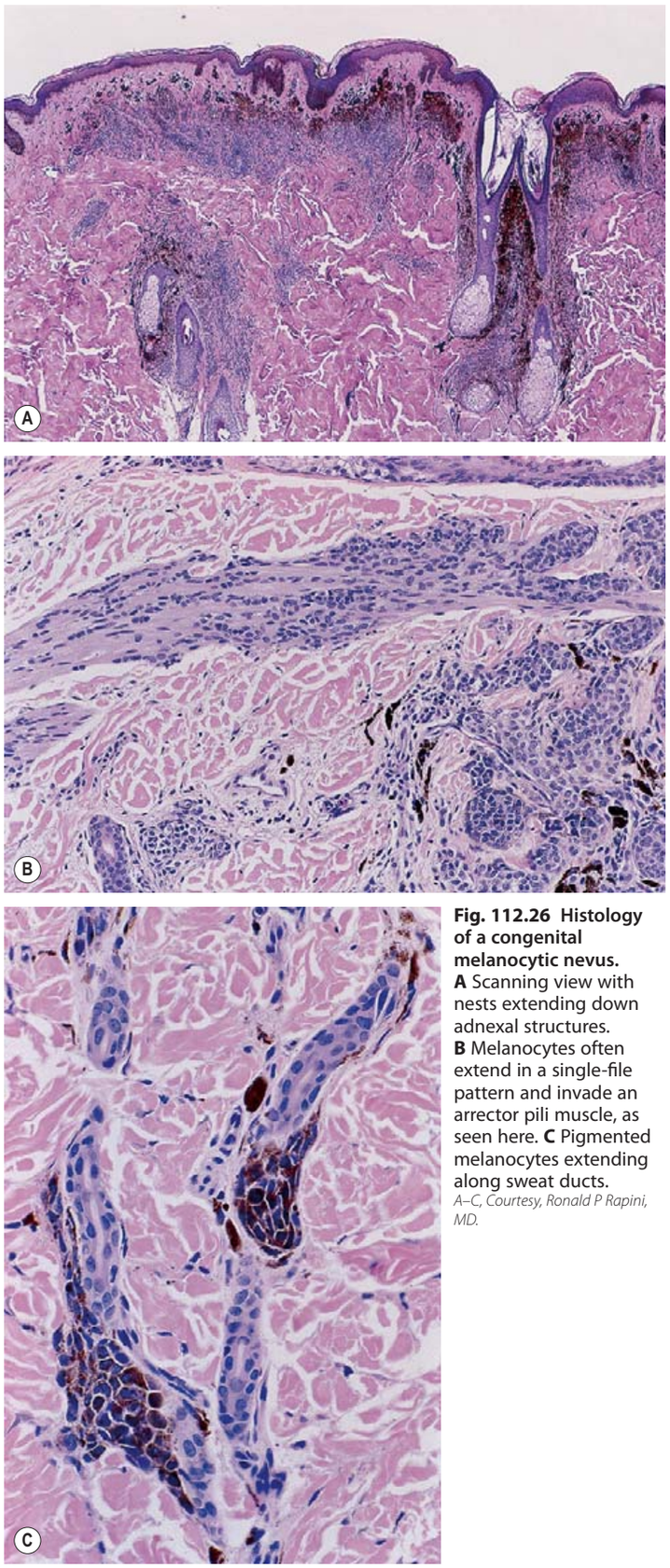


Fig. 112.26 Histology of a congenital melanocytic nevus. **A** Scanning view with nests extending down adnexal structures. **B** Melanocytes often extend in a single-file pattern and invade an arrector pili muscle, as seen here. **C** Pigmented melanocytes extending along sweat ducts. *A–C, Courtesy, Ronald P Rapini, MD.*

Treatment

The treatment of congenital melanocytic nevi is primarily related to two factors: their increased risk for progression to melanoma and their cosmetically disfiguring appearance. The decision to remove a congenital nevus is individualized and based on melanoma risk, age of the individual, anatomic location (proximity to vital structures), presence or absence of neurocutaneous melanosis, cosmetic outcome, and complexity of removal. The routine excision of uniform-appearing small and medium-sized congenital nevi no longer seems justified due to the low melanoma risk. An acceptable alternative to surgical excision is baseline photography, education and yearly examination.

The treatment of giant congenital nevi is more problematic, since melanoma risk is present from birth. If such giant nevi are to be excised, most authorities recommend delaying the procedure for at least 6 months so as to decrease the risk from general anesthesia (Table 112.9). Since the prognosis of patients with symptomatic neurocutaneous melanosis is so poor, surgical removal of large congenital melanocytic nevi should be delayed in such individuals. MRI of the CNS should be considered for neonates with large posterior axial congenital melanocytic nevi and with multiple satellite nevi, in order to screen for neurocutaneous melanosis. For patients with asymptomatic neurocutaneous melanosis, repeat scans and individualized care is indicated.

In the past, dermabrasion was sometimes performed, resulting in a more lightly pigmented and less elevated congenital nevus. More recently, especially in Europe, repeat curettage performed during the first few weeks of life (when there is a cleavage plane in the upper dermis) has led to similar results. Scarring and prolonged healing in the case of large lesions are the drawbacks. Lasers (e.g. Q-switched ruby, Q-switched alexandrite) have also been used to treat congenital nevi, but recurrence of pigmentation is an issue as is persistence of nevus cells[142b].

As mentioned previously, when melanoma supervenes in a large congenital nevus, it may involve the dermal or subcutaneous component and be difficult to detect early. Cutaneous melanoma arising in the smaller types of congenital melanocytic nevi usually begins in the epidermis and can be detected more readily.

NEVUS SPILUS

Synonyms: ■ Speckled lentiginous nevus ■ Zosteriform lentiginous nevus

Key features

- Tan patch with superimposed "speckles" that develop over time
- The darker macules and papules vary from lentigines and junctional and compound nevi to Spitz and blue nevi
- Occasionally, atypical nevi and small and medium-sized congenital nevi are seen within a larger nevus spilus
- There is a small risk of cutaneous melanoma

Epidemiology

There is some controversy as to whether nevus spilus is congenital or acquired and this is explained in part by the initial appearance of a nevus spilus – a uniformly tan-colored, CALM-like patch. There are several lines of evidence to suggest that nevus spilus is a type of congenital melanocytic nevus[143]. In one series, a nevus spilus was noted in approximately 2% of white adults. Males and females are equally affected.

Pathogenesis

A nevus spilus often has an oval shape, but it may have a block-like configuration or follow the lines of Blaschko (see Ch. 62); nevi in the latter patterns are sometimes referred to as zosteriform speckled lentiginous nevi and their configuration suggests a molecular event during embryogenesis. This type of nevus is thought to represent a localized "field defect" and has been likened to a garden of melanocytes in which any type of nevus can develop, simultaneously or sequentially[143].

Clinical Features

These lesions most commonly affect the trunk and extremities. The tan macular area typically ranges from 1 to 4 cm in diameter

Fig. 112.27 Nevus spilus (speckled lentiginous nevus) versus agminated nevi. A Multiple brown macules and papules superimposed upon a tan patch. **B** Grouped brown macules and papules in the absence of background hyperpigmentation. *B, Courtesy, Jean L. Bolognia, MD.*

(Fig. 112.27), but it may measure >20 cm and involve an entire extremity or half the trunk[143–145]. Although the darker speckles are usually macules or papules that are 1–6 mm in diameter, larger lesions that resemble small and medium-sized congenital nevi are occasionally seen.

A nevus spilus persists indefinitely and increased degrees of speckling over time have been documented by serial photography. There are reports of cutaneous melanoma arising within a nevus spilus[146] and on occasion melanocytic dysplasia has been noted in the nevus spilus adjacent to the site of melanoma development. As with conventional congenital melanocytic nevi, the risk of melanoma may be related to size[146], but it may also be related to the type of "speckles".

Nevus spilus is also seen in patients with phakomatosis pigmentovascularis types III and IV (see Ch. 104) as well as those with phakomatosis pigmentokeratotica. The latter patients also have organoid nevi, which combine features of epidermal nevi and sebaceous nevi. Patients with speckled lentiginous nevi may have ipsilateral dysesthesia, muscular weakness or hyperhidrosis, a combination referred to as the "speckled lentiginous nevus syndrome".

Pathology

The tan macule or patch of nevus spilus is characterized by lentiginous melanocytic hyperplasia associated with elongated epidermal rete ridges. The hyperpigmented macular foci are also characterized by lentiginous melanocytic hyperplasia or junctional nevi, whereas the papular foci represent compound, dermal, blue, Spitz, and/or atypical nevi. Histologic features associated with congenital melanocytic nevi can also be seen.

Differential Diagnosis

Agminated nevi (junctional, compound > Spitz, blue) and partial unilateral lentiginosis represent the major entities in the differential diagnosis. However, neither has an associated tan patch as a background and agminated nevi have less variation in the types of nevi present. Sometimes Wood's lamp examination is required to make the distinction.

Treatment

Because of reports of cutaneous melanoma developing within a nevus spilus, it seems advisable that patients be followed on a periodic basis (photography may be helpful). Individual pigmented lesions with atypical features or suspicious change should be evaluated histologically.

HALO NEVUS

Synonyms: ■ Leukoderma acquisitum centrifugum ■ Sutton's nevus ■ Perinevoid vitiligo

Key features

- White halo around a nevus
- Most common on the back in teenagers with an increased number of nevi
- Lymphocytes infiltrate the nevus

Epidemiology

Halo nevi generally affect individuals under the age of 20 years. Although the mean age is approximately 15 years, these nevi have been noted to appear from the first to the fifth decade of life[147]. The overall incidence of halo nevi in individuals under age 20 is probably <1%. There is no gender predilection, but those patients who develop halo nevi in general have an overall increased number of melanocytic nevi. Approximately 20% of individuals with halo nevi have vitiligo and they are less often associated with atypical features.

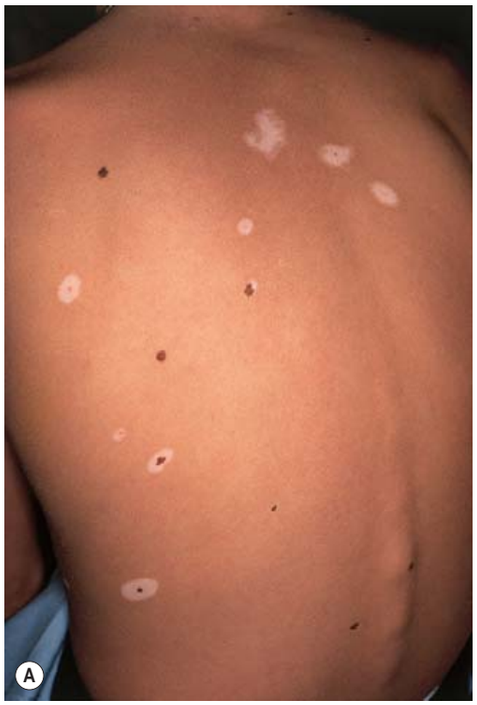
Pathogenesis

The basis for the development of a halo of depigmentation is thought to be either: (1) an immune response against antigenically altered nevus cells associated with tumor progression (dysplasia); or (2) a cell-mediated and/or humoral (antibody-mediated) reaction against non-specifically altered nevomelanocytes and possible cross-reactivity with nevomelanocytes at a distant site or sites. The first hypothesis holds that all halo nevi are atypical, but this has not been supported by histologic evaluations. The second theory holds that halo nevi are the result of a host response directed against non-specifically altered nevomelanocytes in response to a physical, chemical or other insult or perhaps result from an autoimmune pathogenesis, as in vitiligo. The second is favored nowadays.

The basis for nevus cell destruction in halo nevi is poorly understood, but both humoral and cellular immunologic factors have been implicated. Individuals with regressing halo nevi (but not other types of conventional nevi) have antibodies directed against melanoma cells, and lymphocytes isolated from patients with halo nevi and from melanoma patients are cytotoxic to melanoma cells in culture. However, it is not known whether the preceding observations are important in the pathogenesis of halo nevi or are merely epiphenomena. While the central nevus component of an active halo nevus is usually associated with a dense mononuclear cell infiltrate, the peripheral white halo has little or no such infiltrate. Perhaps destruction of melanocytes within the depigmented zone is secondary to the diffusion of a cytotoxic factor.

Clinical Features

Halo nevi are characterized by a central melanocytic nevus component that may be relatively flat or raised and dark brown to pink in color. The nevus may exhibit surface scale or crusting. Surrounding the central nevus is a well-circumscribed annulus of hypo- or depigmented skin (Fig. 112.28A). Erythema occasionally precedes the development of the depigmented halo, which is thought to appear over a period of weeks to months. In typical halo nevi, the central nevus often measures 3–6 mm in diameter, has smooth and well-defined borders, and has a homogeneous color. By dermoscopy, globular and/or homogeneous patterns that typify benign nevi in children and young adults are usually observed[148]. The white halo is often symmetric with a uniform width that may vary from a few millimeters up to several centimeters



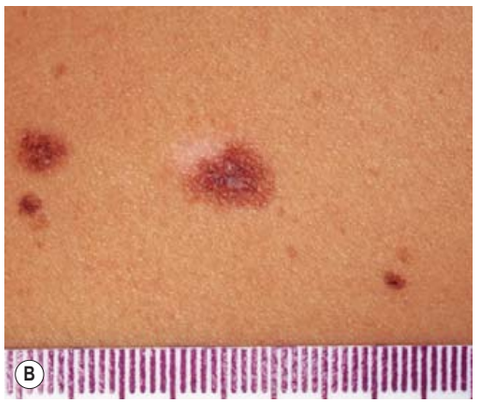


Fig. 112.28 Halo melanocytic nevi. **A** Stage I (central brown nevus), II (central pink nevus), III (depigmented macule), and early IV (partially repigmented) halo nevi are present. Multiple halo nevi are seen most commonly in children and young adults with numerous nevi. **B** A benign compound nevus with an asymmetric halo. *B, Courtesy, Jean L Bolognia, MD.*

(uncommon), but it can be asymmetric (Fig. 112.28B). A Wood's lamp may enhance or discern the halo. Dermoscopically, it is white and structureless (Fig. P7).

Halo nevi are most typically located on the upper back, but may be found in any location. Approximately 25% to 50% of affected individuals have two or more halo nevi. Rarely, large numbers of halo nevi occur, sometimes with a rapid onset. After the development of a halo nevus, its subsequent course is variable. Rarely, the central nevus persists indefinitely (and the halo repigments); usually the nevus regresses over months to years, leaving a white macule. The central nevus may first become irregular or pink in color. Complete repigmentation of the skin is seen in the vast majority of patients, but the process may take years.

A relationship to vitiligo, melanoma and atypical nevi has been well documented. A new onset of multiple halo nevi may be a sign of an ocular or cutaneous melanoma elsewhere, especially in older adults.

Pathology

The halo nevus may be junctional, compound or dermal. In the fully evolved stages, the central nevus is associated with a well-circumscribed, dense, somewhat band-like infiltrate of mononuclear cells, almost exclusively lymphocytes and histiocytes, which occupies the papillary dermis and penetrates nests of nevus cells. The latter change can be so prominent that nevus cells are difficult to distinguish from surrounding lymphoid cells without special stains. Degenerating nevus cells can sometimes be identified in this zone.

Differential Diagnosis

Common acquired melanocytic nevi with the halo phenomenon must be distinguished from: (1) other melanocytic proliferations with halos, such as congenital melanocytic nevi, atypical nevi, blue nevi, Spitz nevi, and primary melanomas or melanoma metastases; and (2) non-melanocytic lesions with halos, such as dermatofibromas, seborrheic keratoses, flat warts, molluscum contagiosum, basal cell carcinoma, lichen planus, psoriasis and sarcoidosis. An asymmetric, irregular halo may be seen with melanoma, as compared with the symmetry usually found in a halo nevus, but asymmetry does not equate with malignancy (see Fig. 112.28B). The clinical characteristics of the central melanocytic lesions determine whether a biopsy is performed, but halo nevi are exceedingly more common than halo primary melanomas, especially in adolescents.

Treatment

The approach to patients with halo nevi is individualized and depends upon the clinical setting. All persons with halo nevi should be questioned regarding a personal or family history of cutaneous melanoma, atypical nevi and vitiligo. Each halo nevus should be inspected carefully for features of an atypical melanocytic nevus or melanoma. The patient also should undergo a comprehensive skin examination for evidence of other halo nevi, atypical nevi, melanoma or vitiligo. If no atypical features are observed, the patient should be followed with periodic skin examinations. In general, clinically atypical halo nevi should be examined histologically. Halo nevi with a benign clinical appearance need not be removed. Individuals beyond 40 years of age with new-onset halo nevi should be examined carefully for melanoma (ocular and cutaneous).

COMBINED NEVUS

Synonyms: ■ Melanocytic nevus with phenotypic heterogeneity ■ One variant: • Clonal nevus • Inverted type A nevus

Key features

- Usually < 5–6 mm in diameter
- Frequently blue–gray in color when combination of blue nevus plus conventional nevus
- Another clinical presentation is the presence of a dark brown or black focus within a common nevus
- Presence of two or more distinct nevus components histologically

Introduction and Epidemiology

Combined melanocytic nevus refers to the simultaneous presence of at least two distinct nevus components in a single melanocytic neoplasm[149–153]. Any combination of conventional nevus, blue nevus or Spitz nevus may potentially be observed; however, one of the more common combinations is a conventional nevus plus a population of enlarged, pigmented, polygonal/epithelioid melanocytes and/or spindled melanocytes within the dermis, in association with melanophages. The incidence of combined nevi has been estimated to be ~1% of all melanocytic nevi sampled for histopathologic examination.

Clinical Features

The clinical features are directly related to the types of nevus components present. Combined nevi may arise at any site, but they have a predilection for the head and neck region (especially those with a blue nevus component), followed by the trunk. A smooth, blue–gray to blue–brown to blue–black papule or nodule is a common presentation, as is a discrete dark brown to black focus within an otherwise uniformly tan or brown banal nevus (Fig. 112.29). Some clinicians refer to the latter as a clonal nevus.

Fig. 112.29 One variant of combined melanocytic nevus. Dark brown to black papule within an otherwise uniformly pigmented light brown nevus. The differential diagnosis includes the possibility of a melanoma developing in a nevus. Some clinicians refer to nevi with this clinical appearance and the histologic features seen in Fig. 112.30 as clonal nevi. *Courtesy, Lorenzo Cerroni, MD.*

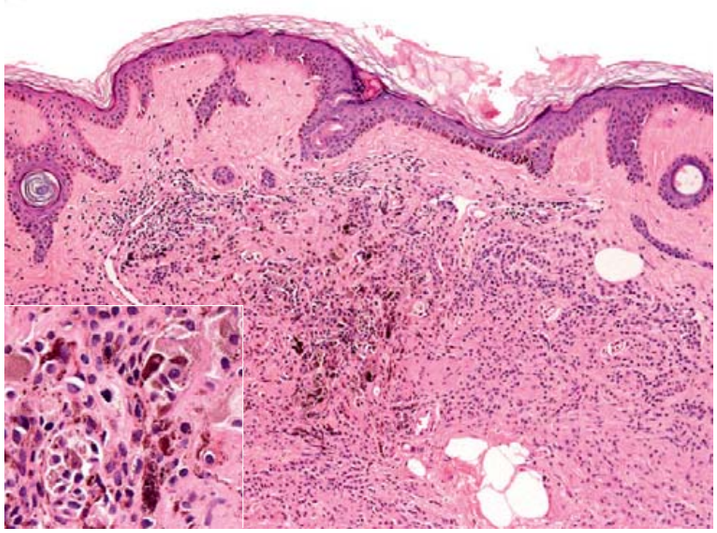


Fig. 112.30 Histology of a combined nevus. Within this intradermal nevus is a focal collection of pigmented dermal melanocytes and melanophages. The cells are benign in appearance (insert). Close examination of the focal proliferation of pigmented cells is recommended to exclude the possibility of melanoma. *Courtesy, Lorenzo Cerroni, MD.*

Pathology

The histologic features also vary depending on the types of nevi present. Most often, a banal compound or dermal nevus is either admixed with a dermal population of pigmented epithelioid or spindled melanocytes or it overlies a more discrete pigmented spindle and epithelioid component (Fig. 112.30). When there is extension into the deep dermis or subcutaneous fat, the term "deep penetrating nevus" or "plexiform pigmented spindle cell nevus" is sometimes applied.

Differential Diagnosis and Treatment

Both clinically and histologically, the presence of two or more components in a melanocytic lesion raises the possibility of melanoma, including one arising within a nevus. The clinical differential diagnosis also includes blue nevus, pigmented Spitz nevus, pigmented basal cell carcinoma, benign vascular tumor, the hemosiderotic variant of dermatofibroma, and melanoma metastasis. Careful histologic examination to exclude melanoma is required. If the lesion is sufficiently suspicious, a biopsy is performed.

RECURRENT MELANOCYTIC NEVUS

Synonyms: ■ Persistent melanocytic nevus ■ Pseudomelanoma

Key features

- Recurrent melanocytic nevi are fairly common following shave excision
- Heavily pigmented melanocytes proliferate within the epidermis, often with upward migration, and may resemble melanoma histologically

Epidemiology

In a series of 175 cases[154] recurrent nevi were most often noted in relatively young women, reflecting the greater number of nevi removed from women and a higher prevalence in younger patients. Recurrent nevi are most commonly observed on the trunk, followed by the head and neck region. Most of the recurrences have followed a shave excision, at an estimated rate of 10–30%. Approximately 50% of the recurrences were noted within 6 months of the surgical procedure[154].

Pathogenesis

The recurrence of melanocytic nevi reflects an intraepidermal proliferation of residual melanocytes, possibly originating from nearby sweat ducts, hair follicles or intraepidermal melanocytes. Trophic factors stimulating melanocyte migration, melanocyte proliferation, or both, may be related to mechanisms of wound healing or scar formation.

Clinical Features

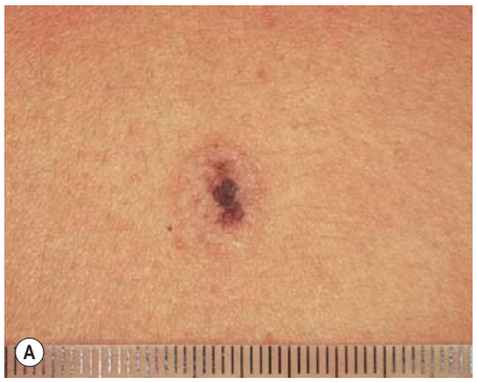
These lesions are characterized by circumscribed hyperpigmentation within a scar that is due to a previous surgical procedure for nevus removal (Fig. 112.31A). In most instances, the lesion is macular and exhibits variable irregularity of its border and pigment pattern. Stippling, mottling and a perifollicular distribution may be observed. Most recurrent nevi measure 2 to 5 mm in diameter. The dermoscopic features of persistent nevi are sometimes difficult to distinguish from melanoma. As a general rule, in recurrent nevi, the pigment will not extend beyond the white scar (Fig. P8). Most recurrent nevi are stable for years after development and then may fade. No increased melanoma risk has been associated with recurrent nevi.

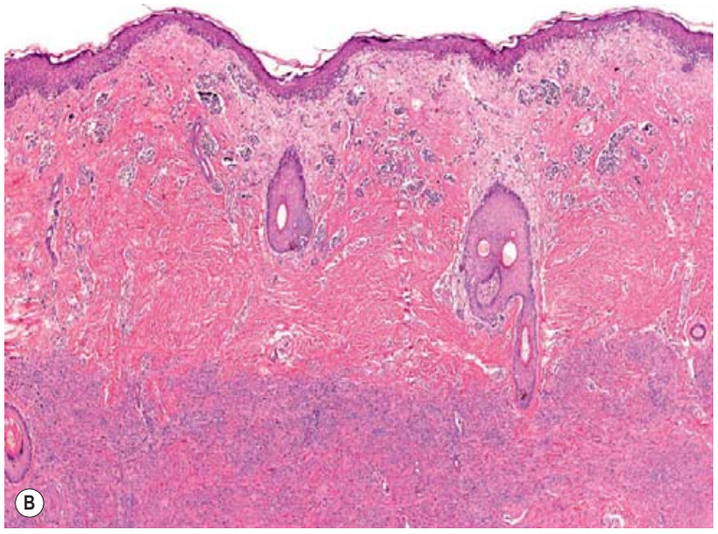
Pathology

Corresponding to the clinical features, one frequently observes intraepidermal melanocytic proliferation confined to the area above a dermal scar (Fig. 112.31B,C). The epidermis usually exhibits effacement of the rete pattern and variable lentiginous or nested proliferation of melanocytes. Often, the cells contain abundant melanin and have relatively uniform nuclei. However, occasionally, low-grade cytologic atypia is noted. Upward migration of epidermal melanocytes may also occur. Frequently, there are residual dermal nevus cells beneath the superficial dermal scar (see Fig. 112.31B).

Differential Diagnosis

The differential diagnosis of recurrent nevi includes the lentiginous melanocytic proliferations and the pigmented streaks due to basilar hyperpigmentation that can both develop in surgical excision scars (including those for melanoma). Additional entities to consider are traumatized nevi, recurrent atypical melanocytic nevi, and recurrent melanoma. In general, a recurrent melanocytic nevus is confined to the area of the surgical scar, appears within 6 months of surgery, and





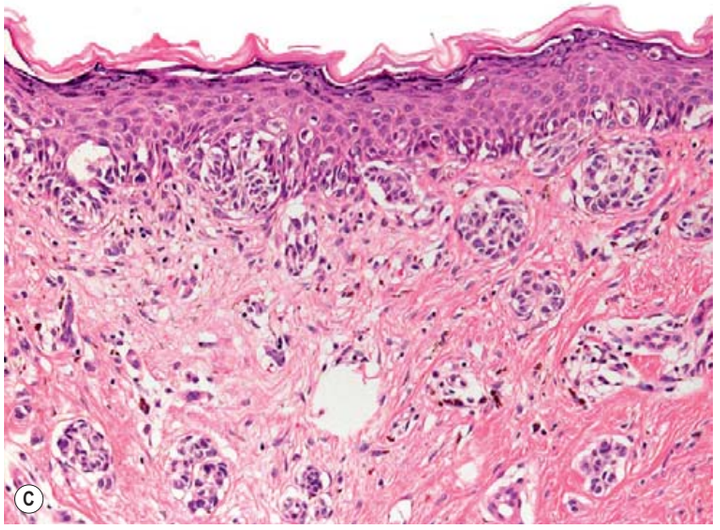


Fig. 112.31 Recurrent melanocytic nevus. A Dark brown pigmentation within the center of a circular scar; the pigmentation reflects the proliferation of melanocytes within the epidermis. **B** Histologically, an irregular junctional and superficial dermal melanocytic proliferation overlies a dermal scar and more deeply located residual dermal nevus. **C** At higher magnification, both junctional nests of melanocytes and single melanocytes are noted along the flattened dermal–epidermal junction. The melanocytes are enlarged polygonal cells and show some low-grade nuclear pleomorphism. *A, Courtesy, Jean L Bolognia, MD. B, C, Courtesy, Lorenzo Cerroni, MD.*

exhibits a banal histologic picture. Recurrent atypical nevi may have more disordered intraepidermal melanocytic proliferation (even a pagetoid pattern) and greater cytologic atypia than conventional recurrent nevi. Clinical features suggesting melanoma include irregular pigmentation, progressive enlargement, extension beyond the confines of the surgical scar, and a longer time interval before recurrence (>6 months).

Treatment

Establishing that a previous surgical procedure has occurred is integral to the diagnosis. Review of the previous biopsy specimen is mandatory if any atypicality is noted histologically. Excision of a recurrent nevus is not necessary unless abnormal clinical features are present, e.g. extension of the lesion beyond the surgical scar.

REFERENCES

1. Bataille V, Snieder H, MacGregor AJ, Spector T. Genetics of risk factors for melanoma: an adult twin study of nevi and freckles. J Natl Cancer Inst. 2000;92:457–63.
2. McLean DI, Gallagher RP. "Sunburn" freckles, café-au-lait macules, and other pigmented lesions of schoolchildren: the Vancouver Mole Study. J Am Acad Dermatol. 1995;32:565–70.
3. Brues AM. Linkage of body build with sex, eye color and freckling. Am J Hum Genet. 1950;2:215–39.
4. Bliss JM, Ford D, Swerdlow AJ, et al. Risk of cutaneous melanoma associated with pigmentation characteristics and freckling: systematic overview of 10 case-control studies. Int J Cancer. 1995;62:367–76.
5. Rhodes AR, Albert LS, Barnhill RL, Weinstock MA. Sun-induced freckles in children and young adults: a correlation of clinical and histopathologic features. Cancer. 1991;67:1990–2001.
6. Breathnach AS. Melanocyte distribution in forearm epidermis of freckled human subjects. J Invest Dermatol. 1957;29:253–61.
7. Bastiaens M, ter Huurne J, Gruis N, et al. The melanocortin-1-receptor gene is the major freckle gene. Hum Mol Genet. 2001;10:1701–8.
8. Landau M, Krafchik BR. The diagnostic value of café-au-lait macules. J Am Acad Dermatol. 1999;40:877–90.
9. Nakagawa H, Hori Y, Sato S, et al. The nature and origin of the melanin macroglobule. J Invest Dermatol. 1983;83:134–9.
10. Korf BR. Diagnostic outcome in children with multiple café au lait spots. Pediatrics. 1992;90:924–7.
11. Sigg C, Pelloni F, Schnyder UW. Frequency of congenital nevi, nevi spili and café-au-lait spots and their relation to nevus count and skin complexion in 939 children. Dermatologica. 1990;180:18–23.
12. Rieger E, Kofler R, Borkenstein M, et al. Melanotic macules following Blaschko's lines in McCune-Albright syndrome. Br J Dermatol. 1994;130:215–20.
13. Jimbow K, Szabo G, Fitzpatrick TB. Ultrastructure of giant pigment granules (macromelanosomes) in the cutaneous pigmented macules of neurofibromatosis. J Invest Dermatol. 1973;61:300–9.
14. Silvers DN, Greenwood RS, Helwig EB. Café-au-lait spots without giant pigment granules: occurrence in suspected neurofibromatosis. Arch Dermatol. 1974;110:87–8.
15. Carpo GB, Grevelink JM, Grevelink SV. Laser treatment of pigmented lesions in children. Semin Cutan Med Surg. 1999;18:233–43.
16. Goldberg DJ. Laser treatment of pigmented lesions. Dermatol Clin. 1997;15:397–407.
17. Cohen PR. Becker's nevus. Am Fam Physician. 1988;37:221–6.
18. Danari R, Konig A, Salhi A, et al. Becker's nevus syndrome revisited. J Am Acad Dermatol. 2004:51:965–9.
19. Glinick SE, Alper JC, Bogaars H, Brown JA. Becker's melanosis: associated abnormalities. J Am Acad Dermatol. 1983;9:509–14.
20. Tse Y, Levine VJ, McClain SA, Ashinoff R. The removal of cutaneous pigmented lesions with the Q-switched ruby laser and the Q-switched Nd:YAG laser: a comparative study. J Dermatol Surg Oncol. 1994;20:795–800.
21. Rhodes AR, Harrist TJ, Momtaz TK. The PUVA-induced pigmented macule: a lentiginous proliferation of large, sometimes cytologically atypical, melanocytes. J Am Acad Dermatol. 1983;9:47–58.
22. Todd MM, Rallis TM, Gerwels JW, Itata TR. A comparison of three lasers and liquid nitrogen in the treatment of solar lentigines. Arch Dermatol. 2000;136:841–6.
23. Wang SQ, Rabinovitz H, Oliviero MC. Dermoscopic patterns of solar lentigines and seborrheic keratosis. In: Marghoob AA, Braun B, Kopf AW (eds). Atlas of Dermoscopy. London: Taylor & Francis, 2005:60–71.

23a. Rapini RP, Golitz LE, Gree RO, et al. Primary malignant melanoma of the oral cavity: A review of 177 cases. Cancer. 1985;55:1543–51.

24. Barnhill RL, Albert LS, Shama SK, et al. Genital lentiginosis: a clinical and histopathologic study. J Am Acad Dermatol. 1990;22:453–6.
25. Cordova A. The Mongolian spot. Clin Pediatr. 1981;20:714–9.
26. Kikuchi I. The biological significance of the Mongolian spot. Int J Dermatol. 1989;28:513–4.
27. Gilchrest BA, Fitzpatrick TB, Anderson RR, Parrish JA. Localization of melanin pigmentation in the skin with Wood's lamp. Br J Dermatol. 1977;96:245–8.
28. Mishima Y, Mevorah B. Nevus of Ota and nevus of Ito in American Negroes. J Invest Dermatol. 1961;36:133–54.

29. Hidano A, Kajima H, Ikeda S, et al. Natural history of nevus of Ota. Arch Dermatol. 1967;95:187–95.
30. Van Raamsdonk CD, Griewank KG, Crosby MB, et al. Mutations in *GNA11* in uveal melanoma. N Engl J Med 2010;363:2191–9.
31. Teekhasaenee C, Ritch R, Rutnin U, Leelawongs N. Ocular findings in oculodermal melanocytosis. Arch Ophthalmol. 1990;108:1114–20.
32. Patel BC, Egan CA, Lucius RW, et al. Cutaneous malignant melanoma and oculodermal melanocytosis (nevus of Ota): report of a case and review of the literature. J Am Acad Dermatol. 1998;38:862–5.
33. Gerami P, Pouryazdanparast P, Venmula S, Bastian BC. Molecular analysis of a case of nevus of Ota showing progressive evolution to a melanoma with intermediate stages resembling cellular blue nevus. Am J Dermatopathol. 2010;32:301–5.
34. Balmaceda CM, Fetell RM, O'Brien JL, Housepian EH. Nevus of Ota and leptomeningeal melanocytic lesions. Neurology. 1993;43:381–6.
35. Chan HH, Leung RS, Ying SY, et al. A retrospective analysis of complications in the treatment of nevus of Ota with the Q-switched alexandrite and Q-switched Nd:YAG lasers. Dermatol Surg. 2000;26:1000–6.
36. Chan HH, Ying SY, Ho WS, et al. An in vivo trial comparing the clinical efficacy and complications of Q-switched 755 nm alexandrite and Q-switched 1064 nm Nd:YAG lasers in the treatment of nevus of Ota. Dermatol Surg. 2000;26:919–22.
37. Dorsey CS, Montgomery H. Blue nevus and its distinction from Mongolian spot and the nevus of Ota. J Invest Dermatol. 1954;22:225–36.
38. Lund HZ, Kraus JM. Melanotic Tumors of the Skin. Atlas of Tumor Pathology. Washington, DC: Armed Forces Institute of Pathology, 1962:104–6.
39. Rodriguez HA, Ackerman LV. Cellular blue nevus. Clinicopathologic study of forty-five cases. Cancer. 1968;21:393–405.
40. Gonzalez-Campora R, Galera-Davidson H, Vazquez-Ramirez FJ, Diaz-Cano S. Blue nevus: classical types and related entities. A differential diagnostic review. Pathol Res Pract. 1994;190:627–35.
41. Murali R, McCarthy SW, Scolyer RA. Blue nevi and related lesions: a review highlighting atypical and newly described variants, distinguishing features and diagnostic pitfalls. Advan Anat Pathol. 2009: 16:365–82.
42. Hendricks WM. Eruptive blue nevi. J Am Acad Dermatol. 1981;4:50–3.
43. Hendrickson MR, Ross JC. Neoplasms arising in congenital giant nevi. Am J Surg Pathol. 1981;5: 109–35.
44. Lambert WC, Brodkin RH. Nodal and subcutaneous cellular blue nevi: a pseudometastasizing pseudomelanoma. Arch Dermatol. 1984;120:367–70.
45. Temple-Camp CR, Saxe N, King H. Benign and malignant cellular blue nevus: a clinicopathological study of 30 cases. Am J Dermatopathol. 1988;10:289–96.
46. Carney JA, Ferreiro JA. The epithelioid blue nevus: a multicentric familial tumor with important associations, including cardiac myxoma and psammomatous melanotic schwannoma. Am J Surg Pathol. 1996;20:259–72.
47. Zembowicz A, Carney JA, Mihm MC. Pigmented epithelioid melanocytoma: a low-grade melanocytic tumor with metastatic potential indistinguishable from animal-type melanoma and epithelioid blue nevus. Am J Surg Pathol. 2004;28:31–40.
48. Zembowicz A, Knoepp SM, Bei T, et al. Loss of expression of protein kinase A regulatory subunit 1 alpha in pigmented epithelioid melanocytoma but not in melanoma or other melanocytic lesions. Am J Surg Pathol. 2007;31:1764–75.
49. Goldenhersh MA, Savin RC, Barnhill RL, Stenn KS. Malignant blue nevus. J Am Acad Dermatol. 1988;19:712–22.
50. Tran TA, Carlson JA, Barsaca PC, Mihm MC. Cellular blue nevus with atypia (atypical cellular blue nevus): a clinicopathologic study of nine cases. J Cutan Pathol. 1998;25:252–8.
51. Maize JC Jr, McCalmont TH, Carlson JA, et al. Genomic analysis of blue nevi and related dermal melanocytic proliferations. Am J Surg Pathol. 2005;29:1214–24.
52. Barnhill RL, Argenyi Z, Berwick M, et al. Atypical cellular blue nevi (cellular blue nevi with atypical features): lack of consensus for diagnosis and distinction from cellular blue nevi and malignant melanoma ("malignant blue nevus"). Am J Surg Pathol. 2008;32:36–44.
53. Lund HS, Stobbe GD. The natural history of the pigmented nevus; factors of age and anatomic location. Am J Pathol. 1949;25:1117–55.
54. Maize JC, Foster G. Age-related changes in melanocytic naevi. Clin Exp Dermatol. 1979;4:49–58.
55. Whiteman DC, Pavan WJ, Bastian BC. The melanomas: a synthesis of epidemiological, clinical, histopathological, genetic, and biological aspects, supporting distinct subtypes, causal pathways, and cells of origin. Pigment Cell Melanoma Res. 2011;24:879–97.
56. Elder DE. Dysplastic naevi: an update. Histopathology. 2010;56:112–20.
57. Lanschuetzer CM, Laimer M, Nischler E, Hintner H. Epidermolysis bullosa nevi. Dermatol Clin. 2010;28:179–83.
58. Carlson JA, Mu XC, Slominski A, et al. Melanocytic proliferations associated with lichen sclerosus. Arch Dermatol. 2002;138:77–87.
59. El Shabrawi-Caelen L, Soyer HP, Schaeppi H, et al. Genital lentigines and melanocytic nevi with superimposed lichen sclerosus: a diagnostic challenge. J Am Acad Dermatol. 2004;50:690–4.
60. Clark WH Jr, Hood AF, Tucker MA, Jampel RM. Atypical melanocytic nevi of the genital type with a discussion of reciprocal parenchymal-stromal interactions in the biology of neoplasia. Hum Pathol. 1998;29:S1–S24.
61. Rongioletti F, Ball RA, Marcus R, Barnhill RL. Histopathological features of flexural melanocytic nevi: a study of 40 cases. J Cutan Pathol. 2000;27:215–7.
62. Gleason BC, Hirsch MS, Nucci MR, et al. Atypical genital nevi. A clinicopathologic analysis of 56 cases. Am J Surg Pathol. 2008;32:51–7.
63. Grin, CM, Saida, T. Pigmented nevi of the palms and soles. In: Marghoob AA, Braun B, Kopf AW (eds). Atlas of Dermoscopy. London: Taylor & Francis, 2005:271–9.
64. McCalmont TH, Brinsko R, LeBoit PE. Melanocytic acral nevi with intraepidermal ascent of cells (MANIACs): a reappraisal of melanocytic lesions from acral sites. J Cutan Pathol. 1991;18:378.
65. Boyd AS, Rapini RP. Acral melanocytic neoplasms: a histologic analysis of 158 lesions. J Am Acad Dermatol. 1994;31:740–5.
66. Signoretti S, Annessi G, Puddu P, Faraggiana T. Melanocytic nevi of palms and soles: a histological study according to the plane of section. Am J Surg Pathol. 1999;23:283–7.
67. Weedon D, Little J. Spindle and epithelioid cell nevi in children and adults. A review of 211 cases of the Spitz nevus. Cancer. 1977;40:217–25.
67a. Wiesner T, Obernauf AC, Murali R, et al. Germline muations in BAP1 predispose to melanocytic tumors. Nature Genet. 2011;43:1018–21.
68. Paniago-Pereira C, Maize J, Ackerman A. Nevus of large spindle and/or epithelioid cells (Spitz's nevus). Arch Dermatol. 1978;114:1811–23.
69. Busam KJ, Barnhill RL. The spectrum of Spitz tumors. In: Kirkham N, Lemoine NR (eds). Progress in Pathology. Vol. 2. Edinburgh, Churchill Livingstone, 1995:31–46.
70. Schaffer JV, Bolognia JL. The clinical spectrum of pigmented lesions. Clin Plast Surg. 2000;27:391–408, viii.
71. Barr R, Morales R, Graham J. Desmoplastic nevus. A distinct histologic variant of mixed spindle and epithelioid cell nevus. Cancer. 1980;46:557–64.
72. MacKie RM, Doherty VR. The desmoplastic melanocytic naevus: a distinct histological entity. Histopathology. 1992;20:207–11.
73. Harris GR, Shea CR, Horenstein MG, et al. Desmoplastic (sclerotic) nevus an underrecognized entity that resembles dermatofibroma and desmoplastic melanoma. Am J Surg Pathol. 1999;23:786–94.
74. Dawe RS, Wainwright NJ, Evans AT, Lowe JG. Multiple widespread eruptive Spitz naevi. Br J Dermatol. 1998;138:872–4.
75. Lancer H, Muhlbauer JE, Sober AJ. Multiple agminated spindle cell nevi: unique clinical presentation and review. J Am Acad Dermatol. 1983;8:707–11.
76. Ludgate MW, Fullen DR, Lee J, et al. The atypical Spitz tumor of uncertain biologic potential. a series of 67 patients from a single institution. Cancer. 2009;115:631–41.
77. Spatz A, Calonje E, Handfield-Jones S, Barnhill RL. Spitz tumors in children: a grading system for risk stratification. Arch Dermatol. 1999;135:282–9.
78. Bastian BC, Wesselmann U, Pinkel D, Leboit PE. Molecular cytogenetic analysis of Spitz tumors shows clear differences to melanoma. J Invest Dermatol. 1999;113:1065–9.
78a. Raskin L, Ludgate M, Iyer RK, et al. Copy number variations and clinical outcome in atypical spitz tumors. Am J Surg Pathol. 2011;35:243–252.
79. Sagebiel R, Chinn E, Egbert B. Pigmented spindle cell nevus. Clinical and histologic review of 90 cases. Am J Surg Pathol. 1984;8:645–53.
80. Smith N. The pigmented spindle cell tumor of Reed: an underdiagnosed lesion. Semin Diagn Pathol. 1987; 4:75–87.
81. Barnhill RL, Mihm MC Jr. The pigmented spindle cell naevus and its variants: distinction from melanoma. Br J Dermatol. 1989;121:717–25.
82. Barnhill RL, Barnhill MA, Berwick M, Mihm MC Jr. The histologic spectrum of pigmented spindle cell nevus: a review of 120 cases with emphasis on atypical variants. Hum Pathol. 1991;22:52–8.
83. Seab JA Jr, Graham JH, Helwig EB. Deep penetrating nevus. Am J Surg Pathol. 1989;13:39–44.
84. Barnhill RL, Mihm MC Jr, Magro CM. Plexiform pigmented spindle cell naevus: a distinctive variant of plexiform melanocytic naevus. Histopathology. 1991;18:243–7.
85. Clark WH Jr, Reimer RR, Greene M, et al. Origin of familial malignant melanomas from heritable melanocytic lesions. "The B-K mole syndrome." Arch Dermatol. 1978;114:732–8.
86. Ackerman AB, Mihara L. Dysplasia, dysplastic melanocytes, dysplastic nevi, the dysplastic nevus syndrome, and the relation between dysplastic nevi and malignant melanomas. Hum Pathol. 1985;16:87–91.
87. Roush GC, Nordlund JJ, Forget B, et al. Independence of dysplastic nevi from total nevi in determining risk for nonfamilial melanoma. Prev Med. 1988;17: 273–9.
88. Nordlund JJ, Kirkwood J, Forget BM, et al. Demographic study of clinically atypical (dysplastic) nevi in patients with melanoma and comparison subjects. Cancer Res. 1985;45:1855–61.
89. MacKie RM, Freudenberger T, Aitchison TC. Personal risk-factor chart for cutaneous melanoma. Lancet. 1989;2:487–90.
90. Holly EA, Kelly JW, Shpall SN, Chiu SH. Number of melanocytic nevi as a major risk factor for malignant melanoma. J Am Acad Dermatol. 1987;17:459–68.
91. Halpern AC, Guerry D 4th, Elder DE, et al. Dysplastic nevi as risk markers of sporadic (nonfamilial) melanoma. A case-control study. Arch Dermatol. 1991;127:995–9.
92. Garbe C, Buttner P, Weiss J, et al. Risk factors for developing cutaneous melanoma and criteria for identifying persons at risk: multicenter case-control study of the central malignant melanoma registry of the German Dermatological Society. J Invest Dermatol. 1994;102:695–9.
93. Garbe C, Buttner P, Weiss J, et al. Associated factors in the prevalence of more than 50 common melanocytic nevi, atypical melanocytic nevi, and actinic lentigines: multicenter case-control study of the central malignant melanoma registry of the German Dermatological Society. J Invest Dermatol. 1994;102:700–5.
94. Barnhill RL. Current status of the dysplastic melanocytic nevus. J Cutan Pathol. 1991;18:147–59.
95. Clark WH Jr, Elder DE, Guerry D 4th, et al. A study of tumor progression: the precursor lesions of superficial spreading and nodular melanoma. Hum Pathol. 1984;15:1147–65.
96. Clemente C, Cochran AJ, Elder DE, et al. Histopathologic diagnosis of dysplastic nevi: concordance among pathologists convened by the World Health Organization Melanoma Programme. Hum Pathol. 1991;22:313–9.
97. Crutcher WA, Sagebiel RW. Clinical diagnosis of dysplastic melanocytic nevi. J Am Acad Dermatol. 1986;14:1044–52.
98. Piepkorn M, Meyer U, Goldgar D, et al. The dysplastic melanocytic nevus: a prevalent lesion that correlates poorly with clinical phenotype. J Am Acad Dermatol. 1989;20:407–15.
99. Weinstock MA, Barnhill RL, Rhodes AR, et al. Reliability of the histopathologic diagnosis of melanocytic dysplasia. Arch Dermatol. 1997;133:953–8.
100. Duray PH, DerSimonian R, Barnhill RL, et al. An analysis of interobserver recognition of the histopathologic features of dysplastic nevi from a mixed group of nevomelanocytic lesions. J Am Acad Dermatol. 1992;27:741–9.
101. Mihm MC Jr, Barnhill RL, Sober AJ, Hernandez MH. Precursor lesions of melanoma: do they exist? Semin Surg Oncol. 1992;8:358–65.

102. Barnhill RL. Melanocytic nevi and tumor progression: perspectives concerning histomorphology, melanoma risk, and molecular genetics. Dermatology. 1993;187:86–90.
103. Duncan LM, Berwick MA, Bruijn JA, et al. Histopathologic recognition and grading of dysplastic melanocytic nevi: an inter-observer agreement study. J Invest Dermatol. 1993;100(suppl.);318S–21S.
104. Kenet RO, Kang S, Kenet BJ, et al. Clinical diagnosis of pigmented lesions using digital epiluminescence microscopy: grading protocol and atlas. Arch Dermatol. 1993;129:157–74.
105. Roush GC, Dubin N, Barnhill RL. Prediction of histologic melanocytic dysplasia from clinical observation. J Am Acad Dermatol. 1993;29:555–62.
106. Kang S, Barnhill RL, Mihm MC Jr, et al. Melanoma risk in individuals with clinically atypical nevi. Arch Dermatol. 1994;130:999–1001.
107. Piepkorn MW, Barnhill RL, Cannon-Albright LA, et al. A multiobserver, population-based analysis of histologic dysplasia in melanocytic nevi. J Am Acad Dermatol. 1994;30:707–14.
108. Schmidt B, Hollister K, Weinberg D, Barnhill RL. Analysis of melanocytic lesions by DNA image cytometry. Cancer. 1994;73:2971–7.
109. Gruber SB, Barnhill RL, Stenn KS, Roush GC. Nevomelanocytic proliferations in association with cutaneous malignant melanoma: a multivariate analysis. J Am Acad Dermatol. 1989;21:773–80.
110. Barnhill RL, Roush GC. Histopathologic spectrum of clinically atypical melanocytic nevi: studies of nonfamilial melanoma, II. Arch Dermatol. 1990;126:1315–8.
111. Barnhill RL, Roush GC, Duray PH. Correlation of histologic architectural and cytoplastic features with nuclear atypia in atypical (dysplastic) nevomelanocytic nevi. Hum Pathol. 1990;21:51–8.
112. Barnhill RL, Kiryu H, Sober AJ, Mihm MC Jr. Frequency of dysplastic nevi among nevomelanocytic lesions submitted for histopathologic examination: time trends over a 37-year period. Arch Dermatol. 1990;126:463–5.
113. Tucker MA, Halpern A, Holly EA, et al. Clinically recognized dysplastic nevi. A central risk factor for cutaneous melanoma. JAMA. 1997;277:1439–44.
114. Annesi G, Cattaruzza MS, Abeni D. Correlation between clinical atypia and histologic dysplasia in acquired melanocytic nevi. J Am Acad Dermatol. 2001;45:77–85.
115. Blessing K. Benign atypical naevi: diagnostic difficulties and continued controversy. Histopathology. 1999;34:189–98.
116. Shea CR, Vollmer RT, Prieto VG. Correlating architectural disorder and cytological atypia in Clark (dysplastic) melanocytic nevi. Hum Pathol. 1999;30:500–5.
117. Pozo L, Naase M, Cerio R, et al. Critical analysis of histologic criteria for grading atypical (dysplastic) melanocytic nevi. Am J Clin Pathol. 2001;115: 194–204.
118. Slade J, Marghoob AA, Salopek TG, et al. Atypical mole syndrome: risk factor for cutaneous malignant melanoma and implications for treatment. J Am Acad Dermatol. 1995;32:479–94.
119. Marghoob AA, Kopf AW, Rigel DS, et al. Risk of cutaneous malignant melanoma in patients with "classic" atypical-mole syndrome: a case-control study. Arch Dermatol. 1994;130:993–8.
120. Hoffman-Wellenhof R, Blum A, Wolf IH, et al. Dermoscopic classification of atypical melanocytic nevi. Arch Dermatol. 1992;137:1575–80.
121. Shors AR, Kim S, White E, et al. Dysplastic naevi with moderate to severe histological dysplasia: a risk factor for melanoma. Br J Dermatol. 2006;155:988–93.
122. Castilla EE, da Graca Dutra M, Orioli-Parreiras IM. Epidemiology of congenital pigmented naevi: incidence rates and relative frequencies. Br J Dermatol. 1981;104:307–15.
123. Everett MA. Histopathology of congenital pigmented nevi. Am J Dermatopathol. 1989;1:11–2.
124. Illig L, Weidner F, Hundeiker M, et al. Congenital nevi less than or equal to 10 cm as precursors to melanoma. Arch Dermatol. 1985;121:1274–81.
125. Lorentzen M, Pers M, Bretteville-Jensen G. The incidence of malignant transformation in giant pigmented nevi. Scand J Plast Reconstr Surg. 1977;71:163–7.
126. Rhodes AR. Congenital nevomelanocytic nevi: histologic patterns in the first year of life and evolution during childhood. Arch Dermatol. 1986;122:1257–62.
127. Rhodes AR, Sober AJ, Day CL, et al. The malignant potential of small congenital nevocellular nevi: an estimate of association based on a histologic study of 234 primary cutaneous melanomas. J Am Acad Dermatol. 1982;6:230–41.
128. Swerdlow AJ, English JSC, Qiao Z. The risk of melanoma in patients with congenital nevi: a cohort study. J Am Acad Dermatol. 1995;32:595–9.
129. Shpall S, Frieden I, Chesney M, Newman T. Risk of malignant transformation of congenital melanocytic nevi in blacks. Pediatr Dermatol. 1994;11:204–8.
130. Barnhill RL, Aguiar M, Cohen C, et al. Congenital melanocytic nevi and DNA content an analysis by flow and image cytometry. Cancer. 1994;74:2935–43.
131. Bouffard D, Barnhill RL, Mihm MC Jr, Sober AJ. Very late metastasis (27 years) of cutaneous malignant melanoma arising in a halo giant congenital nevus. Dermatology. 1994;189:162–6.
132. Barnhill RL, Fleischli M. Pathology of congenital melanocytic nevi in infants less than a year of age. J Am Acad Dermatol. 1995;33:780–5.
133. Sahin S, Levin L, Kopf AW, et al. Risk of melanoma in medium-sized congenital melanocytic nevi: a follow-up study. J Am Acad Dermatol. 1998;39:428–33.
134. Marghoob AA, Schoenbach SP, Kopf AW, et al. Large congenital melanocytic nevi and the risk for the development of malignant melanoma. A prospective study. Arch Dermatol. 1996;132:170–5.
135. DeDavid M, Orlow SJ, Provost N, et al. A study of large congenital melanocytic nevi and associated malignant melanomas: review of cases in the New York University Registry and the world literature. J Am Acad Dermatol. 1997;36:409–15.
136. Dawson HA, Atherton DJ, Mayou B. A prospective study of congenital melanocytic naevi: progress report and evaluation after 6 years. Br J Dermatol. 1996;134:617–23.
137. DeDavid M, Seth JO, Provost N, et al. Neurocutaneous melanosis: clinical features of large congenital melanocytic nevi in patients with manifest central nervous system melanosis. J Am Acad Dermatol. 1996;35:529–38.
138. Kadonaga JN, Frieden IJ. Neurocutaneous melanosis: definition and review of the literature. J Am Acad Dermatol. 1991;24:747–55.
139. Agero ALC, Benvenuto-Andrade C, Dusza SW, et al. Asymptomatic neurocutaneous melanocytosis in patients with large congenital melanocytic nevi: a study of cases from an Internet-based registry. J Am Acad Dermatol. 2005;53:959–65.
140. Lovett A, Maari C, Decarie JC, et al. Large congenital melanocytic nevi and neurocutaneous melanocytosis: one pediatric center's experience. J Am Acad Dermatol. 2009;61:766–74.
141. Bett BJ. Large or multiple congenital melanocytic nevi: occurrence of cutaneous melanoma in 1008 persons. J Am Acad Dermatol. 2005;52:793–7.
142. Bauer J, Curtin JA, Pinkel D, Bastian BC. Congenital melanocytic nevi frequently harbor *NRAS* mutations but no *BRAF* mutations. J Invest Dermatol. 2007;127:179–82.
142a. Krengel S, Hauschild A, Schäfer T. Melanoma risk in congenital melanocytic naevi: a systematic review. Br J Dermatol. 2006;155:1–8.
142b. Kishi K, Okabe K, Ninomiya R, et al. Early serial Q-switched ruby laser therapy for medium-sized to giant congenital melanocytic naevi. Br J Dermatol. 2009;161:345–52.
143. Schaffer JV, Orlow SJ, Lazova R, Bolognia JL. Speckled lentiginous nevus: within the spectrum of congenital melanocytic nevi. Arch Dermatol. 2001;137:172–8.
144. Cohen HJ, Minkin W, Frank SB. Nevus spilus. Arch Dematol. 1970;102:433–7.
145. Falo LD, Sober AJ, Barnhill RL. Evolution of nevus spilus. Dermatology. 1994;189:382–3.
146. Abecassis S, Spatz A, Cazeneuve C, et al. Melanoma within naevus spilus: 5 cases. Ann Dermatol Venerol. 2006;133:323–8.
147. Wayte DM, Helwig EB. Halo nevi. Cancer. 1968;22:69–90.
148. Kolm I, Di Stefani A, Hofmann-Wellenhof R, et al. Dermoscopy patterns of halo nevi. Arch Dermatol. 2006;142:1627–32.
149. Fletcher V, Sagebiel RW. The combined nevus: mixed patterns of benign melanocytic lesions must be differentiated from malignant melanomas. In: Ackerman AB, (ed). Pathology of Malignant Melanoma. New York: Masson, 1981:273–83.
150. Rogers GS, Advani H, Ackerman AB. A combined variant of Spitz's nevi. How to differentiate them from malignant melanomas. Am J Dermatopathol. 1985;7:61–78.
151. Pulitzer DR, Martin PC, Cohen AP, Reed RJ. Histologic classification of the combined nevus. Analysis of the variable expression of melanocytic nevi. Am J Surg Pathol. 1991;15:1111–22.
152. Scolyer RA, Zhuang L, Palmer AA, et al. Combined naevus: a benign lesion frequently misdiagnosed both clinically and pathologically as melanoma. Pathology. 2004;36:419–27.
153. Barnhill RL, Cerroni L, Cook M, et al. State of the art, nomenclature, and points of consensus and controversy concerning benign melanocytic lesions: outcome of an international workshop. Adv Anat Pathol. 2010;17:73–90.
154. Park HK, Leonard DD, Arrington JH 3rd, Lund HZ. Recurrent melanocytic nevi: clinical and histologic review of 175 cases. J Am Acad Dermatol. 1987;17:285–92.

Fig. P1 Solar lentigines. Sharply demarcated, uniform, tan macules on sun-exposed skin. Dermoscopically, moth-eaten borders, fingerprinting, and a reticular pattern with thin lines, short and interrupted.

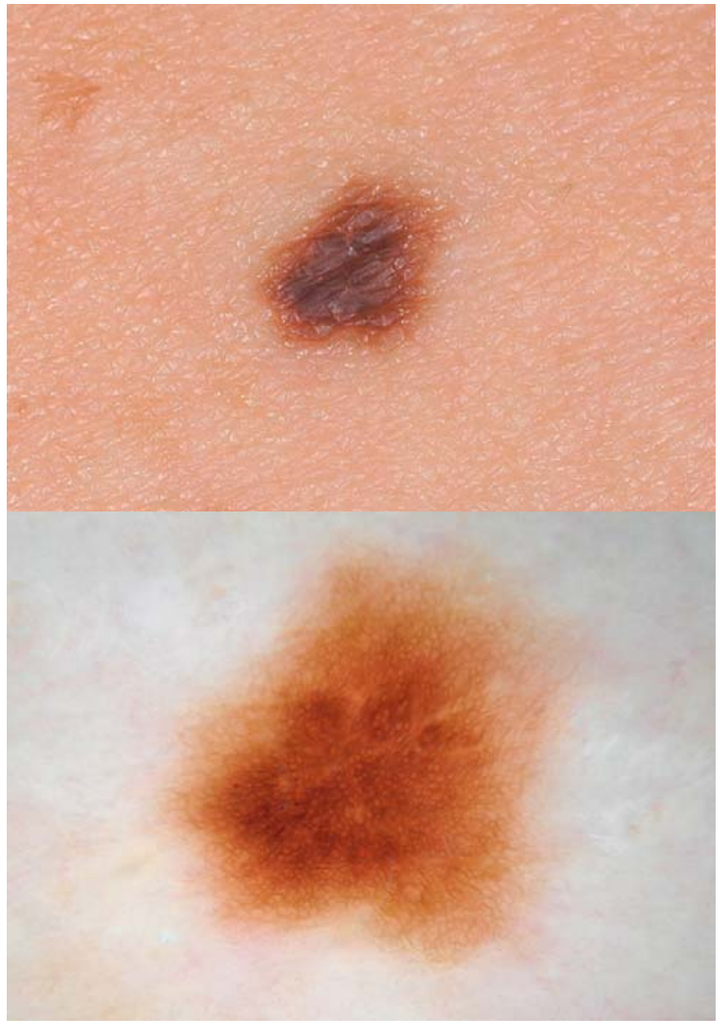


Fig. P2 Junctional nevus. Clinically, a brown macule with central hyperpigmentation. Dermoscopically, a uniform pigment network.

Fig. P3 Dermal nevus. A light tan, soft, raised papule. Dermoscopically, focal globular-like structures, whitish structureless areas, and fine comma vessels.

Fig. P4 Melanocytic nevus of acral skin. A brown macule on the sole of the foot. Dermoscopically, a lattice-like pattern.

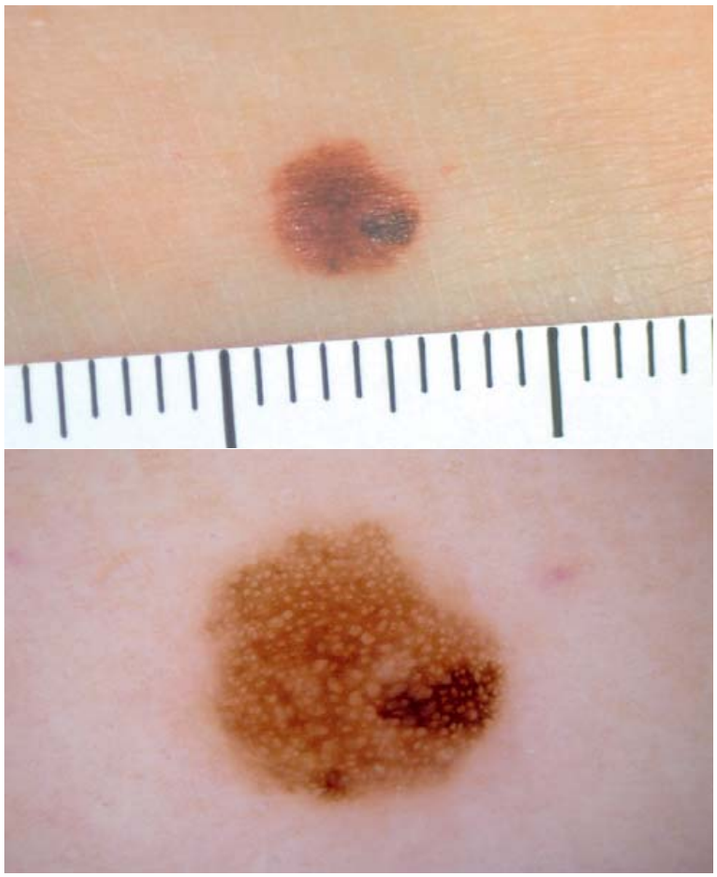


Fig. P5 Clinically atypical melanocytic nevus. The dermoscopy pattern is reticular–disorganized and can be seen with uncertain lesions.

Fig. P6 Medium-sized congenital nevus. Dermoscopically, a globular pattern with hyphae-like structures.

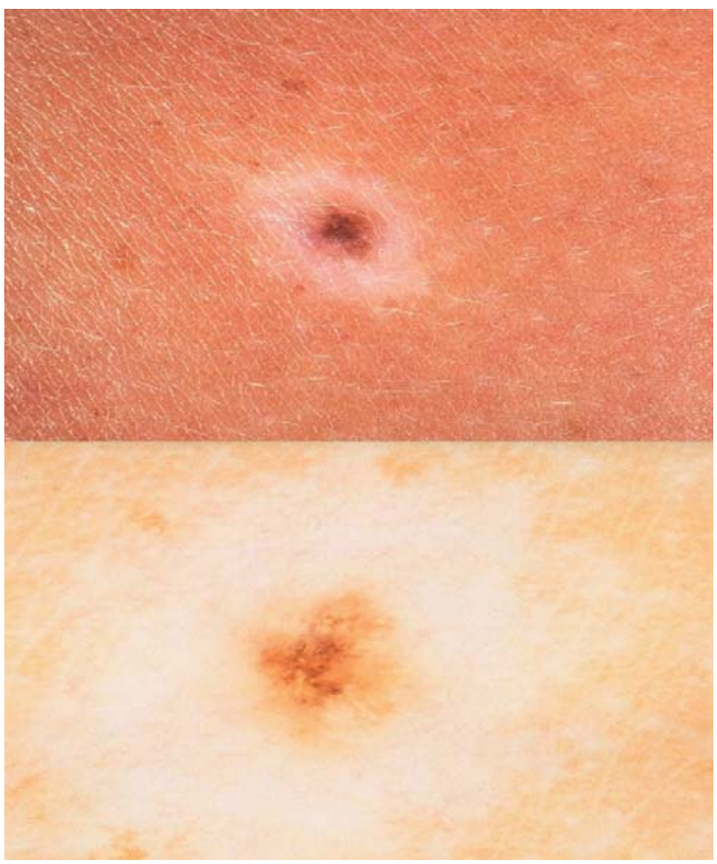


Fig. P7 Halo nevus. A depigmented macular halo surrounding a central dark brown papule. Dermoscopically, a symmetric white structureless area surrounding the remaining network of the nevus.

Fig. P8 Recurrent melanocytic nevus. A brown papule with areas of scarring. Dermoscopically, asymmetric pigmentation within the confines of the scar.

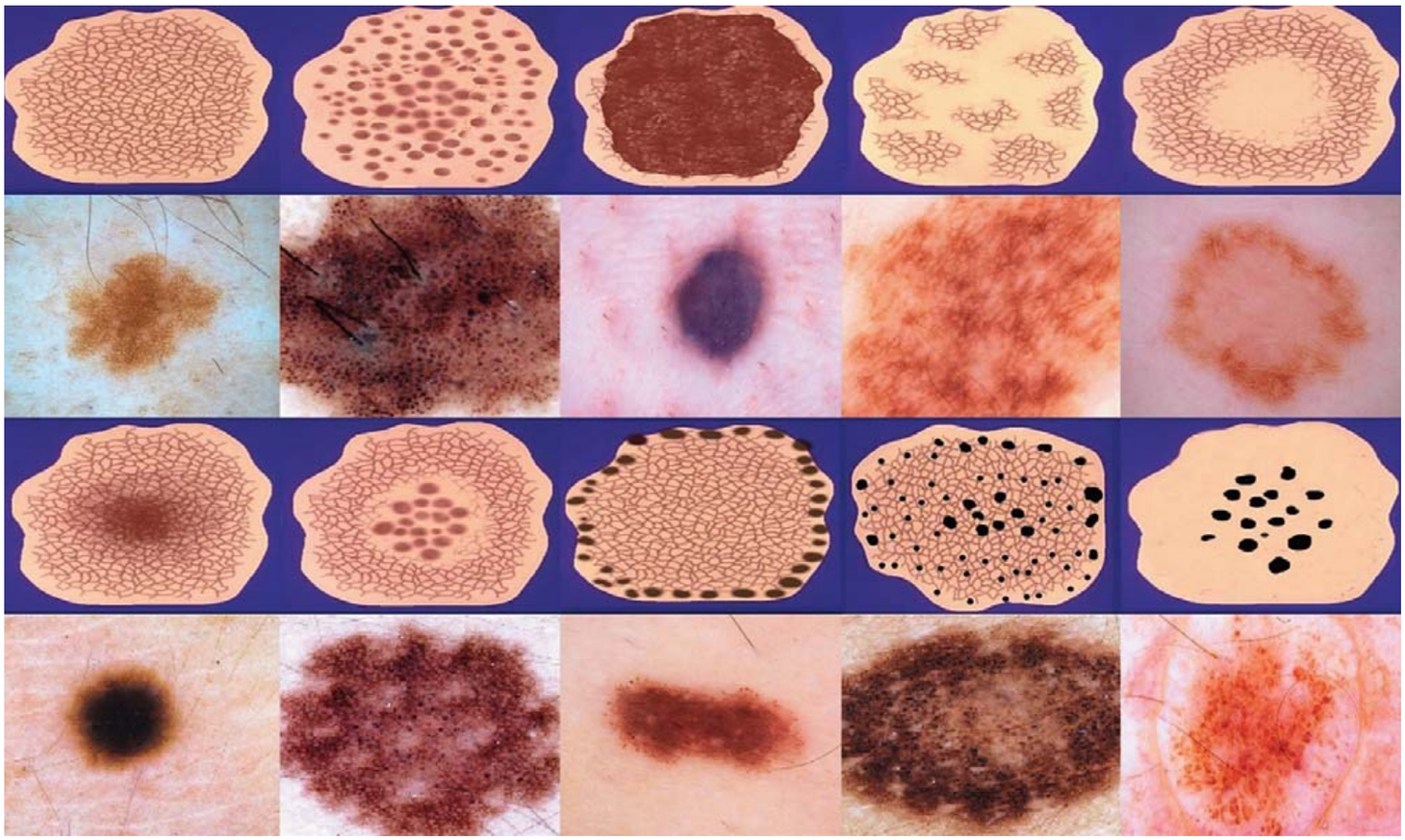


Fig. P9 Atypical melanocytic nevi with dermoscopic patterns commonly seen in benign melanocytic nevi. *Courtesy of the AAD dermoscopy group.*

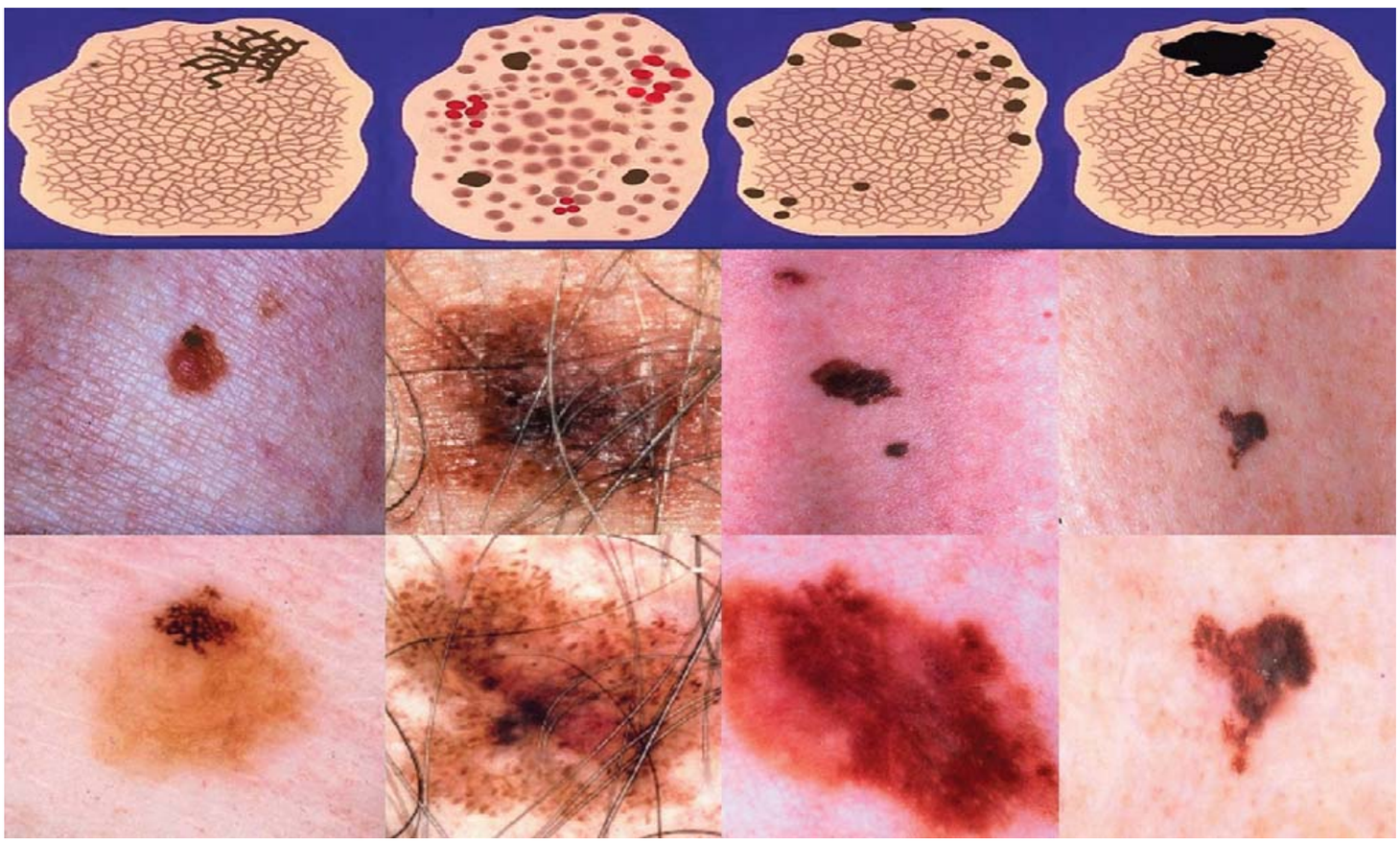


Fig. P10 Atypical melanocytic nevi with dermoscopic patterns often associated with melanoma. From top to bottom, schematic, normal illumination, and dermoscopy. *Courtesy of the AAD dermoscopy group.*

This page intentionally left blank

Melanoma 113

Claus Garbe and Jürgen Bauer

Chapter Contents

Molecular pathogenesis *1885*
Host immune response to melanoma *1887*
Epidemiology *1888*
Risk factors *1889*
Types of primary melanomas *1892*
Other melanoma variants *1894*
Melanoma and pregnancy *1896*
Childhood melanoma *1897*
Diagnosis *1897*
Histopathology *1899*
Staging *1902*
Prognosis *1903*
Evaluation of a patient with suspected melanoma *1904*
Management *1905*
Melanoma surveillance *1910*

Key features

- Melanoma represents a malignant tumor that arises from melanocytes, and, due to its metastatic potential, leads to >75% of skin cancer deaths
- The incidence rates of melanoma have increased over the past four decades by three- to five-fold, whereas mortality rates began to stabilize in the early 1990s
- *In situ* and early invasive cutaneous melanoma can be subtle in appearance but dermoscopy has led to an improvement in diagnostic accuracy
- Early-stage melanomas are often curable by surgical excision
- For metastatic melanoma, immunotherapies (e.g. ipilimumab) and targeted therapies (e.g. vemurafenib) can be tried

INTRODUCTION

Melanoma is a malignant tumor that arises from melanocytes and is most commonly cutaneous in origin. It can also arise on mucosal surfaces (e.g. oral, conjunctival, vaginal) and within the uveal tract of the eye as well as the leptomeninges. While the majority of melanomas are brown-black in color due to melanin deposition, some are skin-colored to pink-red, i.e. amelanotic.

Rising incidence rates of cutaneous melanoma have been observed worldwide over the past four decades in white populations[1–3]. While mortality rates increased slightly in the US and Europe during the 1970s and 1980s, a stabilization of mortality rates was observed in a number of countries during the 1990s, due primarily to the early detection of thinner cutaneous melanomas. Melanoma is also one of the most common forms of cancer in young adults[4]. It therefore represents a significant public health problem, especially with respect to years of life lost.

MOLECULAR PATHOGENESIS

There are several hallmarks of cancer, including self-sufficiency with regard to growth signals, insensitivity to antigrowth signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis[5,6]. As depicted in Figures 107.3 and 107.4, this set of properties can be acquired by the activation of oncogenes or the inactivation of tumor suppressor genes via molecular mechanisms such as point mutations, deletions and translocations as well as epigenetic mechanisms such as microRNA expression and promoter methylation. Genome-wide analysis of genetic aberrations has revolutionized our understanding of the complex interplay of signaling pathways, including in melanoma[7].

Carcinomas usually develop through a stepwise, evolutionary process. Tumor progression involves both genetic instability[8] and selective growth of cells with advantageous mutations[9]. Additional factors include genetic predisposition, mutagenic environmental events, and antitumor host response. For example, melanomas from different body sites and from locations with different amounts of ultraviolet radiation (UVR) damage also differ genetically (Fig. 113.1). Based upon different patterns of DNA copy number changes and varying frequencies of oncogene mutations, the molecular classification of melanoma was thus redefined[10], providing a rationale for targeted therapy.

Cellular Signaling Pathways in Melanoma

Genetic aberrations in melanoma frequently affect signaling pathways that play an essential role in normal melanocyte biology. Discovery of specific sites of dysfunction within these pathways has led to the era of targeted therapies, e.g. the use of vemurafenib in patients with a somatic mutation in *BRAF* that leads to substitution of glutamic acid (E) for valine (V) at codon 600 (i.e. V600E) and subsequent activation of the mitogen-activated protein kinase (MAPK) pathway.

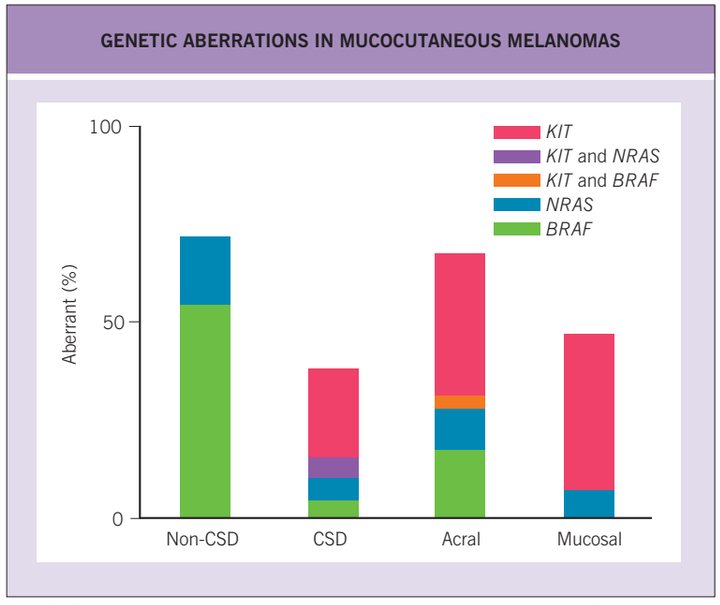


Fig. 113.1 Genetic aberrations in mucocutaneous melanomas. CSD, skin with chronic sun-induced changes such as marked solar elastosis; non-CSD, skin without chronic sun-induced damage. *From Curtin JA, Busam K, Pinkel D, Bastian BC. J Clin Oncol. 2006;24:4340–6.*

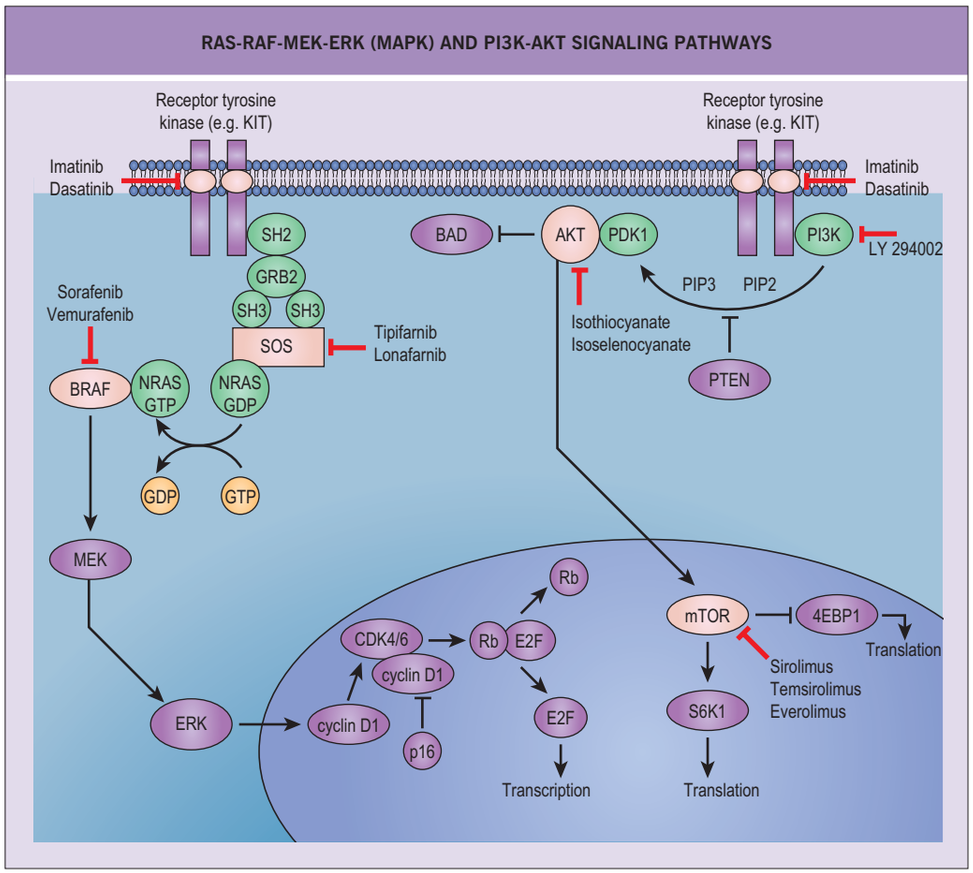


Fig. 113.2 RAS-RAF-MEK-ERK (MAPK) and PI3K-AKT signaling pathways The mitogen-activated protein kinase (MAPK) pathway is physiologically activated by growth factor binding to receptor tyrosine kinases. The stimulus is relayed to the nucleus via the GTPase activity of NRAS and the kinase activity of BRAF, MEK and ERK. Within the nucleus, this results in increased transcription of genes involved in cell growth, proliferation, and migration. The central role of this pathway in melanocytic neoplasia is highlighted by the fact that either *NRAS* or *BRAF* is mutated in approximately 80% of all cutaneous melanomas and melanocytic nevi. The PI3K-AKT pathway is another important regulator of cell survival, growth, and apoptosis. A key inhibitor of this pathway is PTEN and inactivation of the gene that encodes PTEN via mutations, deletions or promoter methylation also occurs in cutaneous melanomas. As a result, there is increased activity of the PI3K-AKT signaling pathway. 4EBP1, eIF-4E binding protein 1 (inhibits translation); CDK, cyclin-dependent kinase; E2F, transcription factor that controls transcription of cyclins; GDP, guanosine-5′-diphosphate; GRB2, growth factor receptor-bound protein 2, an adaptor protein that contains one Src homology 2 (SH2) domain and two SH3 domains; GTP, guanosine-5′-triphosphate; MEK, MAPK kinase; mTOR, mammalian target of rapamycin (aka sirolimus); PDK1, phosphoinositide-dependent kinase-1; PI3K, phosphoinositide 3-kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-triphosphate; PTEN, phosphatase and tensin homolog; Rb, retinoblastoma protein; S6K1, S6 kinase 1; SOS, son of sevenless.

MAPK signaling

The MAPK pathway regulates cellular proliferation, growth and migration. Via this pathway, interactions between growth factors (mitogens) and receptor tyrosine kinases (RTKs) such as the KIT receptor on the cell surface eventually lead to changes in the activity of transcription factors and gene expression within the nucleus (Fig. 113.2)[11]. Upon ligand binding, RTKs dimerize and become activated by autophosphorylation of intracellular tyrosine residues. The phosphorylation of tyrosine residues creates binding sites for adaptor proteins (e.g. GRB2, SOS) and initiates a signaling cascade that requires the GTPase activity of NRAS and the kinase activity of BRAF, MEK and ERK. Phosphorylated ERK activates nuclear cyclin D1 and a complex between cyclin D1 and cyclin-dependent kinases 4 and 6 (CDK4/6) is formed that phosphorylates retinoblastoma tumor suppressor protein (Rb), resulting in release of E2F from the Rb–E2F complex (see Fig. 107.1)[12]. E2F represents a family of transcription factors that play an important role in the regulation of cell cycle progression. An important tumor suppressor is p16, encoded by the *CDKN2A* gene. By binding to CDK4/6, p16 prevents the formation of the cyclin D1–CDK4/6 complex and as a result prevents Rb activation and E2F release.

The key role of the MAPK pathway in melanoma is highlighted by the high frequency of mutations in the genes that encode its components and its downstream targets. With regard to RTKs, 30% to 40% of acral and mucosal melanomas as well as melanomas from chronically sun-exposed skin harbor activating mutations or copy number amplifications of the *KIT* gene[13]. In addition, constitutively activating mutations are present in the *NRAS* gene (15–20% of melanomas overall)[10,14] and the *BRAF* gene (50–60%)[15,16] (Table 113.1). Of note, the frequency of *BRAF* mutations is high in melanomas from skin intermittently exposed to UV, yet low in melanomas with histopathologic evidence of significant UV damage[10,17], i.e. with increasing cumulative amounts of mutagenic UV radiation, the *BRAF* mutation frequency declines. MAPK pathway activation in melanoma can also be induced by inherited mutations in the *CDKN2A* gene that underlie familial melanoma[18], as well as by acquired inactivating mutations and deletions of *CDKN2A*[19].

PI3K signaling

Phosphoinositide 3-kinases (PI3Ks) are enzymes that regulate cell growth, proliferation, differentiation, motility and survival (see Fig. 113.2). PI3Ks are activated by RTKs and phosphorylate PIP2 (phosphatidylinositol 4,5-bisphosphate) to PIP3 (phosphatidylinositol 3,4,5-triphosphate). PIP3 then acts as a second messenger and AKT is activated via phosphorylation[20]. It is important to note that by converting PIP3 back to PIP2, AKT activation can be inhibited by PTEN[21]. Activated phospho-AKT inhibits apoptosis by phosphorylating BAD which leads to its loss of pro-apoptotic function (see Fig. 107.5), enhances survival by increasing the transcription of survival genes, and accelerates cell growth via mTOR (see Fig. 113.2)[22].

PI3K signaling is activated in a high percentage of melanomas by multiple mechanisms. Frequent activating events include inactivation of the gene that encodes the inhibitor PTEN via mutations, deletions or promoter methylation[23], activating mutations of *NRAS*[10], and overexpression of AKT[23]. However, direct activation of the PI3K pathway by activating mutations in the genes that encode PI3K subunits occurs infrequently[24].

WNT signaling

As a group, WNT signaling proteins are involved in cellular processes such as differentiation, migration, proliferation, and stem cell maintenance. When Frizzled (FZ)/LRP receptor complexes are *not* bound by ligand, the "destruction complex" that contains the adenomatous polyposis coli (APC) tumor suppressor protein phosphorylates β-catenin (Fig. 113.3). Phosphorylated β-catenin is ubiquitinated and as a result targeted by the proteasome for rapid destruction. Once bound by extracellular WNT, the FZ/LRP coreceptor complex activates dishevelled (DSH) which inhibits the β-catenin destruction complex, leading to the stabilization of β-catenin. Beta-catenin then translocates to the nucleus and promotes the transcription of WNT target genes via the TCF/LEF family of transcription factors[25–27].

The role of WNT signaling in melanoma is complex, as WNT signaling is tightly regulated. In melanoma, mutations that stabilize β-catenin

NEWER THERAPEUTIC APPROACHES TO MELANOMA		
IMMUNOTHERAPY		
Treatment rationale	**Clinical indication**	**Drug**
CTLA-4 inhibition	Unresectable or metastatic melanoma	• Ipilimumab: 3 mg/kg IV infusion (over 90 minutes) every 3 weeks for 4 total doses
MUTATED-ONCOGENE TARGETED THERAPY		
Mutated oncogene*	**Clinical associations**	**Drug (inhibitor)**
c-*KIT*	Found in site-specific melanomas: • Mucosal (~40%) • Acral (~35%) • Chronically sun-damaged skin (25-30%)	• Imatinib • Nilotinib • Dasatinib • Sunitinib
NRAS	Found in ~15–20% of melanomas Most often seen in later age-at-onset melanomas	• R115777
BRAF	Found in ~40–60% of melanomas Most often seen in younger age-at-onset melanomas Most common in melanomas arising in intermittently sun-exposed, non-chronically sun damaged skin	Non selective: • Sorafenib • XL-281 • RAF-265
BRAF (V600E)	Of melanomas with *BRAF* mutations, ~80% are of the V600E subtype	Selective for V600E: • Vemurafenib (PLX4032) • GSK2118436
GNAQ	Uveal melanomas (45%); "malignant" blue nevi (melanoma arising within a cellular blue nevus)	
CDK4	Germline in a few families with inherited melanoma	• PD0332991
ERBB4	Found in ~20% of melanomas	• Lapatinib
MEK	Can be seen in patients who develop resistance to vemurafenib	• AZD6244 • GSK1120212 • PD0325901
PI3K		• GDC0941 • XL147
AKT		• MK-2206 • GSK690693

*Somatic (acquired) unless other noted under clinical associations. IV, intravenous.

Table 113.1 Newer therapeutic approaches to melanoma. Ipilimumab has also been administered intravenously at 10 mg/kg for four doses and once every 12 weeks as maintenance therapy. Side effects, related to autoimmunity, include enterocolitis, hypophysitis, thyroiditis, primary adrenal insufficiency, dermatitis (sometimes severe) and toxic epidermal necrolysis. The mechanism of action of ipilimumab is depicted in Fig. 128.8E. Use of targeted therapies has followed the discovery of mutations in the genes that encode the components of several signal transduction pathways including RAS-RAF-MEK-ERK (MAPK) and PI3K-AKT (see Fig. 113.2). Mechanisms of resistance to BRAF inhibitors include mutational activation of MEK (downstream of BRAF in the MAPK pathway), overexpression of COT which leads to an increase in MEK activity, and expression of truncated forms of BRAF (which can dimerize and activate the MAPK pathway) in addition to overexpression of platelet-derived growth factor. As a result, in the future, multi-drug regimens will be utilized from the onset and include inhibitors of BRAF and MEK as well as inhibitors of the PIP3/AKT pathway. One possible explanation for the induction of cutaneous keratoacanthomas and squamous cell carcinomas by BRAF inhibitors such as vemurafenib is the presence of *RAS* mutations plus wild-type BRAF (leading to activation of the MAPK pathway) in the keratinocytes of sun-damaged skin. Figure 107.1 illustrates the role of CDK4 in cell cycle regulation.

and increase intracellular β-catenin have been described[28]. However, β-catenin and *APC* mutations are rare events in melanoma[29,30]. The controversial role of β-catenin signaling in melanoma is highlighted by the observation that gene silencing of β-catenin in melanoma cells slows their growth but promotes the formation of pulmonary metastases in mice[31]. In sum, WNT signaling can promote tumor growth by activating proliferation and cell migration, but it can also inhibit tumor growth by inducing cell differentiation and acting as a tumor suppressor[32].

MC1R-MITF signaling

The melanocortin 1 receptor (MC1R) is a G-protein-coupled receptor that is activated by melanocortins (ACTH, α-MSH; see Table 65.4). MC1R is one of the key receptors involved in regulating skin and hair color[33]. When bound to its ligands, MC1R activates adenylate cyclase and cAMP is formed as a second messenger (see Fig. 65.15). cAMP activates protein kinase A (PKA) and PKA activates the cAMP response-element binding protein (CREB); the latter is a transcription factor that enhances expression of microphthalmia-associated transcription factor (MITF; see Fig. 65.4)[34,35]. MITF is also a transcription factor and it regulates expression of a number of melanocyte lineage specific genes that encode enzymes of the melanin biosynthetic pathway (e.g. tyrosinase, tyrosinase-related proteins) as well as other genes such as *CDK2*, *CDKN2A* and *BCL2*. MITF signaling is also tightly linked and regulated by MAPK and WNT signaling.

MCIR variants have been associated with a red hair/fair skin phenotype, and independent of phenotype, have been found to be a risk factor for the development of cutaneous melanoma (see Fig. 65.14 and Table 65.5)[37]. In addition, MITF has been shown to be an oncogene amplified in melanoma[38]. However, MITF can also act as an antiproliferative transcription factor by inducing cell cycle arrest[39,40]. Interestingly, mutant oncogenic BRAF can regulate MITF expression to ensure that its protein levels are compatible with proliferation and survival of melanoma cells[41].

Better understanding of the molecular mechanisms of melanoma development will hopefully translate into improvements in melanoma risk assessment, prevention, diagnosis, and molecularly targeted therapies.

HOST IMMUNE RESPONSE TO MELANOMA

Clinical observations such as incomplete or complete regression of melanoma (Fig. 113.4), associated development of vitiligo-like depigmentation and halo nevi, and a higher incidence of melanoma in immunosuppressed patients point to the fact that melanoma is an immunogenic tumor[42]. Numerous melanoma antigens recognized by autologous T cells or antibodies have been described including: (1) mutant tumor antigens (e.g. mutant p16 [*CDKN2A*]); (2) shared tumor-specific antigens of the cancer/testis family (e.g. MAGE-1, MAGE-3, NY-ESO-1); and (3) cell type-specific differentiation antigens (e.g. tyrosinase, gp100/Pmel17, Melan-A/MART-1). These proteins are processed and presented on the melanoma cell surface as MHC/peptide complexes. $CD8^+$ cytotoxic T cells recognize these antigens and, if appropriately activated, are able to kill tumor cells. In addition to $CD8^+$ T cells, $CD4^+$ helper T cells as well as antibodies also play a critical role.

Activation of melanoma-specific $CD8^+$ T cells is dependent on the migration of tumor antigen-loaded dendritic cells to a draining lymph node. Here, melanoma antigens are presented to $CD8^+$ T cells in the

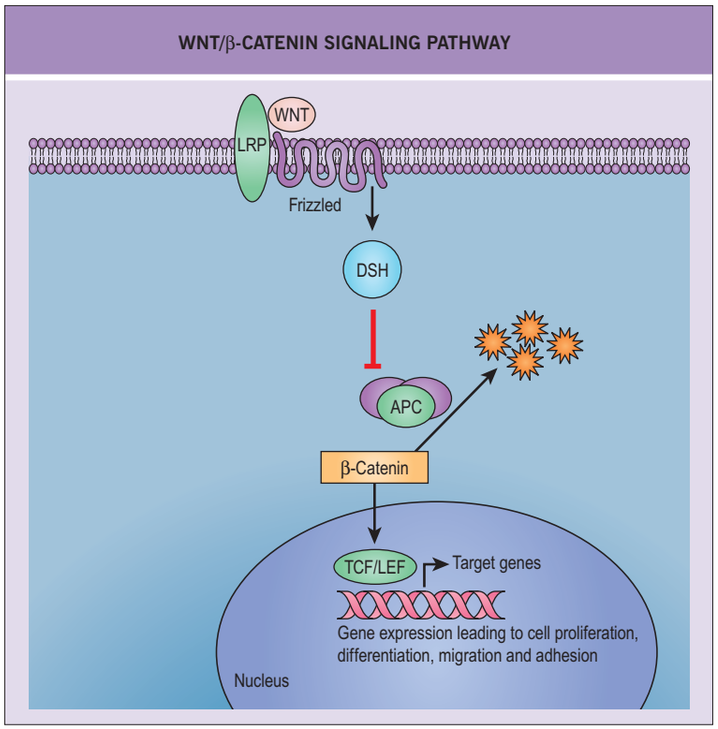


Fig. 113.3 WNT/β-catenin signaling pathway. When extracellular WNT binds to the Frizzled/LRP receptor complex, the cytosolic protein dishevelled (DSH) is activated and can inhibit the "destruction complex". The latter complex contains the adenomatous polyposis coli (APC) tumor suppressor protein and it can phosphorylate β-catenin. Phosphorylated β-catenin becomes ubiquitinated and then is targeted by the proteosome for destruction. Therefore, when DSH is activated by WNT binding, β-catenin is not phosphorylated and it accumulates and is translocated to the nucleus. There, it induces the transcription of target genes via the T-cell factor/lymphoid enhancer factor (TCF/LEF) family of transcription factors. LRP, low-density lipoprotein-receptor-related protein.

presence of a costimulatory signal provided by the binding of B7 on the antigen-presenting cell to CD28 on the T cell (see Ch. 4). Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) is an inhibitory homologue of CD28 that is upregulated following T-cell activation and acts as natural inhibitor of T-cell activation by removing the costimulatory signal. Recently, immunotherapy based upon CTLA-4 blockade was introduced for the treatment of melanoma (see below).

Fig. 113.4 Cutaneous melanoma with regression. An asymmetric, irregularly pigmented melanocytic lesion. The central depigmented zone is due to tumor regression and histopathologically, an inflammatory infiltrate can be seen.

A variety of immune escape mechanisms may be found in advanced tumors, including melanoma. These include loss of tumor-specific antigens, loss of MHC class I molecules, and secretion of immunoinhibitory cytokines such as interleukin (IL)-10 and TGF-β[43]. Downregulation of a melanoma-specific immune response might also involve naturally occurring $CD4^+/CD25^+$ regulatory T cells, inducible IL-10-producing regulatory T cells, or negative signals delivered via cell surface CTLA-4[44]. New insights into mechanisms of melanoma-specific host immune responses and immune escape will hopefully lead to more successful immunotherapy, including more effective vaccines.

EPIDEMIOLOGY

Over the past several decades, the incidence rates of cutaneous melanoma have increased significantly (Fig. 113.5)[2,45,47]. It develops almost exclusively in Caucasian populations, with its incidence remaining very low amongst darkly pigmented populations of African, Asian and Hispanic origin[46].

The annual increase in melanoma incidence varies depending upon the populations, but in general it has been estimated to be between 3% and 7%[48–53]. These estimates predict a doubling of rates every 10–20 years, making cutaneous melanoma the most rapidly increasing cancer in white populations. For example, in the US, over a period of 30 years, an increase in incidence rates of at least three-fold was observed[49,54,55] (see Fig. 113.5). Cohort studies from several countries indicate that the trend of increasing incidence rates will continue for at least the next two decades.

Based upon data from the Surveillance Epidemiology and End Results (SEER) database, an estimated 62 480 men and women in the US were expected to be diagnosed with melanoma in 2008 and an estimated 8420 were expected die from melanoma that same year[55]. In Europe, the highest incidence rates were noted in Scandinavian countries[48,56,57], while the lowest incidence rates were observed in Mediterranean countries[58,59]. One explanation for this North–South gradient is a darker skin phototype (types III–IV) in the Mediterranean populations. Worldwide, the highest incidence rates have been reported in Australia and New Zealand, with 30 to 60 cases per 100 000 inhabitants per year. Within Australia, the highest incidence rates were found in the northern equatorial regions of the country (e.g. Queensland)[60].

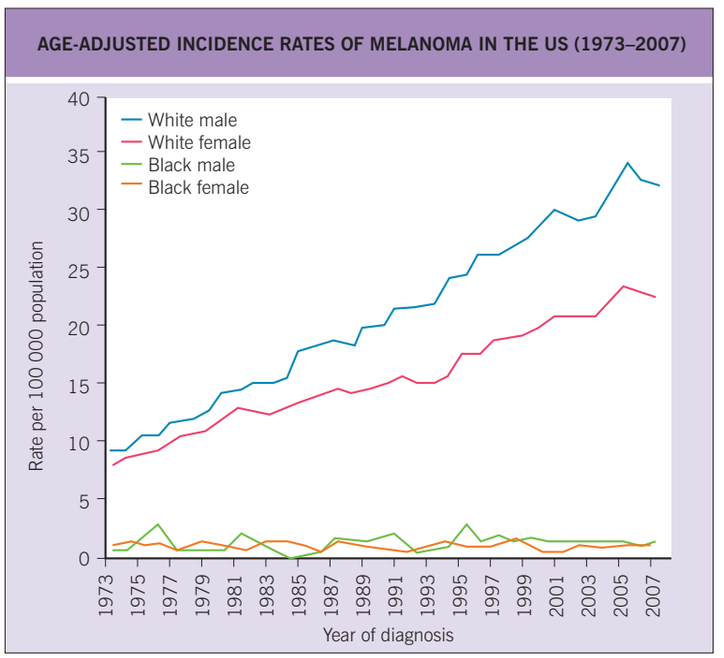


Fig. 113.5 Age-adjusted incidence rates of melanoma in the US (1973–2007). The incidence has increased in the male and female Caucasian populations over the past three decades and this trend has not yet stopped. The African-American population shows a constant low incidence, mostly caused by acral and mucosal melanomas. *Data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute.*

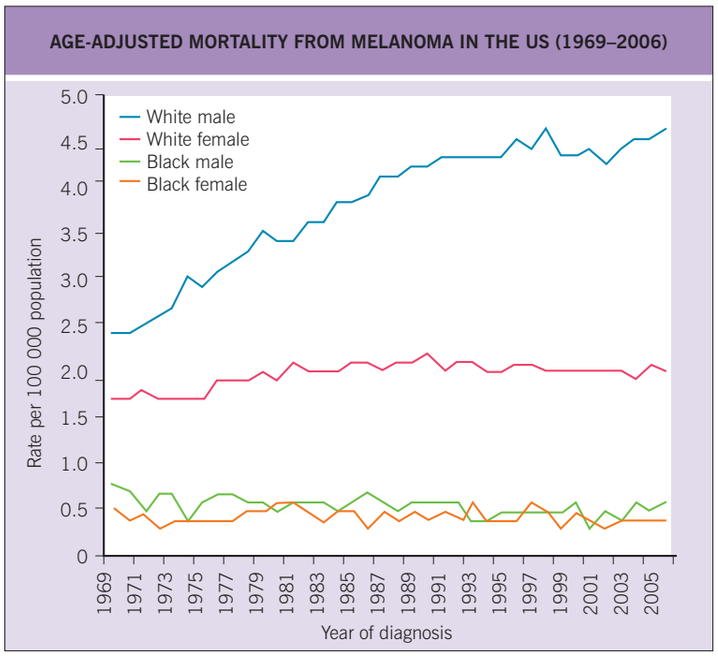


Fig. 113.6 Age-adjusted mortality from melanoma in the US (1969–2006). The mortality has increased, especially for the male Caucasian population, over the past three decades. For females, the increase was less pronounced and has leveled off since the 1980s. *Data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute.*

RISK FACTORS FOR THE DEVELOPMENT OF CUTANEOUS MELANOMA
GENETIC FACTORS
• Family history of cutaneous melanoma • Lightly pigmented skin • Tendency to burn, inability to tan • Red hair color • DNA repair defects (e.g. xeroderma pigmentosum)
ENVIRONMENTAL FACTORS
• Intense intermittent sun exposure • Chronic sun exposure • Residence in equatorial latitudes • PUVA (possible) • Tanning bed use, especially under the age of 35 years • Iatrogenic or acquired immunosuppression
PHENOTYPIC EXPRESSIONS OF GENE/ENVIRONMENT INTERACTIONS
• Melanocytic nevi and solar lentigines: – Increased total number of acquired melanocytic nevi (MN) >100 MN, relative risk ~ 8–10-fold increased – Atypical melanocytic nevi (AMN) > 5 AMN, relative risk ~ 4–6-fold increased – Multiple solar lentigines (SL) Multiple SL, relative risk ~3–4-fold increased Relative risks (RR) are multiplicative: e.g. a person with >100 MN + >5 AMN + multiple SL has a relative risk ~ 10 × 5 × 3 = 150-fold • Personal history of cutaneous melanoma

Table 113.2 Risk factors for the development of cutaneous melanoma.

Mortality rates from melanoma increased throughout the 1980s in most European countries[1,47,52,61], as well as in North America (Fig. 113.6), Australia and New Zealand[4,62,63]. Mortality rates peaked around 1988–1990. Subsequently, trends have been less uniform, with mortality rates still rising in several European countries among middle-aged adults, but with more favorable trends in women and some stabilization in young adults; rates have remained relatively constant among men[64].

The vertical tumor thickness (Breslow depth) is the most important local prognostic factor in primary cutaneous melanoma[65–67]. Therefore, tumor thickness serves as an indicator of the effectiveness of early detection of melanoma[68,69]. In a number of countries, there is an ongoing trend for the diagnosis of thinner melanomas[68,70,71]. For example, in Germany, such a trend has been observed since the 1980s, with the median tumor thickness decreasing from 1.81 mm (1980s) to 0.53 mm (2000). The percentages of *in situ* and level II melanoma also increased[68]. The diagnosis of thinner tumors should translate into stable or decreasing mortality rates, despite the increase in incidence rates.

The tumor thickness at the time of primary diagnosis is also age-dependent. In general, there are significantly fewer melanomas ≤1.0 mm in older age groups. As a corollary, the percentage of thick melanomas increases significantly with age and reaches 20% by age 80 years in both genders[72].

RISK FACTORS FOR CUTANEOUS MELANOMA

Recognition of risk factors for the development of melanoma is important from a public health and a clinical care perspective (Table 113.2). Identification of high-risk cohorts improves the efficiency and efficacy of public health efforts. Individual risk assessment influences clinical decision-making including the threshold for performing a biopsy, prevention counseling, and surveillance. Risk factors may be divided into three categories: (1) genetic factors, (2) phenotypic manifestations of gene–environment interactions, and (3) environmental factors.

Genetic Risk Factors

Germline genetic mutations and polymorphisms can predispose individuals to melanoma. The genes involved range from the rare high-penetrance genes responsible for some familial clustering of melanoma to the very common pigmentation genes responsible for the relative propensity for fair-skinned individuals to develop melanoma[73].

The major high-penetrance susceptibility gene locus associated with familial melanoma is *CDKN2A*. Approximately 2% of cutaneous melanomas can be specifically attributed to pathogenic germline mutations in *CDKN2A*[74]. This locus encodes two distinct protein products, p16 and $p14^{ARF}$, with the latter via an alternative reading frame, hence the designation ARF. p16 and $p14^{ARF}$ exert regulatory effects on cell cycle progression through the retinoblastoma protein (Rb) and p53 pathways, respectively (see Fig. 107.1)[75,76]. Germline *CDKN2A* mutations are observed in ~25% of familial melanoma kindreds[77]. The penetrance of *CDKN2A* mutations is modified by germline variants of other genes, including *MC1R*[78,79]. In some families, carriers of germline *CDKN2A* mutations are also at increased risk of developing pancreatic cancer[80].

While assays for these *CDKN2A* mutations have been commercialized and have been advocated by some in the field, it is the recommendation of the International Melanoma Genetics Consortium that at present genetic testing for *CDKN2A* mutations be done only as part of research protocols[81]. However, a recent study suggested that individuals with three or more primary invasive melanomas or families with at least one invasive melanoma and two or more other diagnoses of invasive melanoma or pancreatic cancer among first- or second-degree relatives (on the same side of the family) were appropriate candidates for referral for genetic consultation and possible testing[74].

Among pigmentation genes, specific germline variants of the melanocortin 1 receptor (*MC1R*) gene have been found to correlate with melanoma risk above and beyond clinically apparent skin phenotype[82]. Recently, a strong association between *MC1R* as a susceptibility gene and risk of developing *BRAF*-mutant melanomas was observed. While the risk of developing any cutaneous melanoma lies between 1.5-fold and 3-fold for individuals with *MC1R* variants, the risk of developing *BRAF*-mutant melanomas was as high as 17-fold for those with two *MC1R* germline variants[83,84]. In addition to *MC1R*, single nucleotide polymorphisms in the tyrosinase (*TYR*) gene, the tyrosinase-related protein 1 (*TYRP1*) gene, and the *SLC45A2* gene are significantly associated with melanoma risk (see Table 65.5)[85].

Phenotypic Risk Factors Reflecting Gene/Environment Interactions

The strongest independent risk factors for the development of cutaneous melanoma are those that reflect both genetic susceptibility and environmental exposure: melanocytic nevi, atypical melanocytic

nevi[86,87], ephelides and solar lentigines. Both an increased number of common melanocytic nevi and the presence of atypical melanocytic nevi are independent risk factors for melanoma, as is the presence of solar lentigines. Acquired melanocytic nevi play a dual role as a risk factor: (1) they are indicators of UV exposure and DNA damage; and (2) they can be formal precursors of melanoma. However, remnants of benign melanocytic nevi are found in only a minority of melanomas[88,89]. Based on epidemiologic data, the risk of malignant transformation in an individual melanocytic nevus has been estimated to be one melanoma in hundreds of atypical nevi and one in thousands of common nevi[90,91]. Consequently, prophylactic removal of clinically unsuspicious melanocytic nevi is not justified.

Common melanocytic nevi

Although performed on populations from different regions and with varying skin phototypes, studies have consistently reported a continuous and almost linear increase in melanoma risk with greater numbers of common melanocytic nevi[92–98] (Fig. 113.7). It has been speculated that the increased risk may be attributed to higher numbers of melanocytes in patients with numerous common nevi or with large congenital melanocytic nevi[99].

Light-skinned populations have higher melanocytic nevus counts than do darker-skinned populations. The relative melanoma risk for greater than 50 common melanocytic nevi has ranged from 6.9 in southern Spain[97] to 53.9 in Scotland[100]. Nonetheless, the dose-dependent relationship between number of common melanocytic nevi and risk of cutaneous melanoma holds true for all Caucasian populations.

The association of increased nevus counts and melanoma risk is strongest for superficial spreading melanoma and nodular melanoma, in contrast to lentigo maligna melanoma which is highly correlated with skin type and hair color[100,101]. This suggests there are additional genetic susceptibility factors and molecular mechanisms involved in the formation of melanoma in chronically versus intermittently sun-exposed skin (see Fig. 113.1). Melanoma at a particular anatomic site is more strongly related to the number of melanocytic nevi at that respective site than to the number of nevi in other body sites[97,100], highlighting the key role of local mutagenic effects of UV radiation in addition to genetic susceptibility.

Atypical melanocytic nevi

Since the original description of BK-mole syndrome in 1978[86], several definitions of atypical melanocytic nevi and of the atypical mole syndrome have been published[93,102–104]. A relative risk of up to 500-fold for developing cutaneous melanoma has been described for specific subgroups of the atypical mole syndrome[105]. However, sporadic atypical melanocytic nevi are often diagnosed in "normal" individuals outside of the setting of the atypical mole syndrome. One possible explanation for the range of estimates of risk is the use of different definitions of clinically "atypical" melanocytic nevi by various investigators.

Several studies have found clinically atypical nevi to be associated with increased melanoma risk outside of the context of familial melanoma[92–95,98,106,107] (Fig. 113.8). The maximum reported relative risk for developing melanoma was as high as 32-fold when there were 10 or more atypical melanocytic nevi[98]. The consistency of these findings among multiple studies and across geographic locations supports the significance of atypical melanocytic nevi as an independent risk marker for sporadic melanoma.

In contrast to the continuous increase in melanoma risk with greater numbers of common melanocytic nevi, for atypical melanocytic nevi a threshold level of five or more such lesions was associated with a clearly higher relative risk in several studies; however, there was no significant increase in the risk beyond this number[93]. This finding suggests that at least five atypical melanocytic nevi are needed to establish the diagnosis of atypical mole syndrome. In patients with familial melanoma, atypical melanocytic nevi are an indicator of a markedly elevated melanoma risk[108,109].

Ephelides and solar lentigines

Ephelides (freckles) have been reported to be a risk factor independent of numbers of common melanocytic nevi[106,110,111]. The independence of freckling and common melanocytic nevi indicates that these cutaneous findings represent separate host characteristics, both of which are related to sun exposure[112]. Additional studies found that solar lentigines were a risk factor for the development of cutaneous melanoma, independent of the number of common melanocytic nevi[93].

Environmental Risk Factors

Ultraviolet radiation

It is widely believed that the total risk for developing melanoma is determined by the interplay between genetic factors and exposure to UVR[113]. Approximately 80% of cutaneous melanomas develop in intermittently sun-exposed regions, and both intermittent sun exposure and sunburn history have been identified as risk factors in epidemiologic studies[2,114].

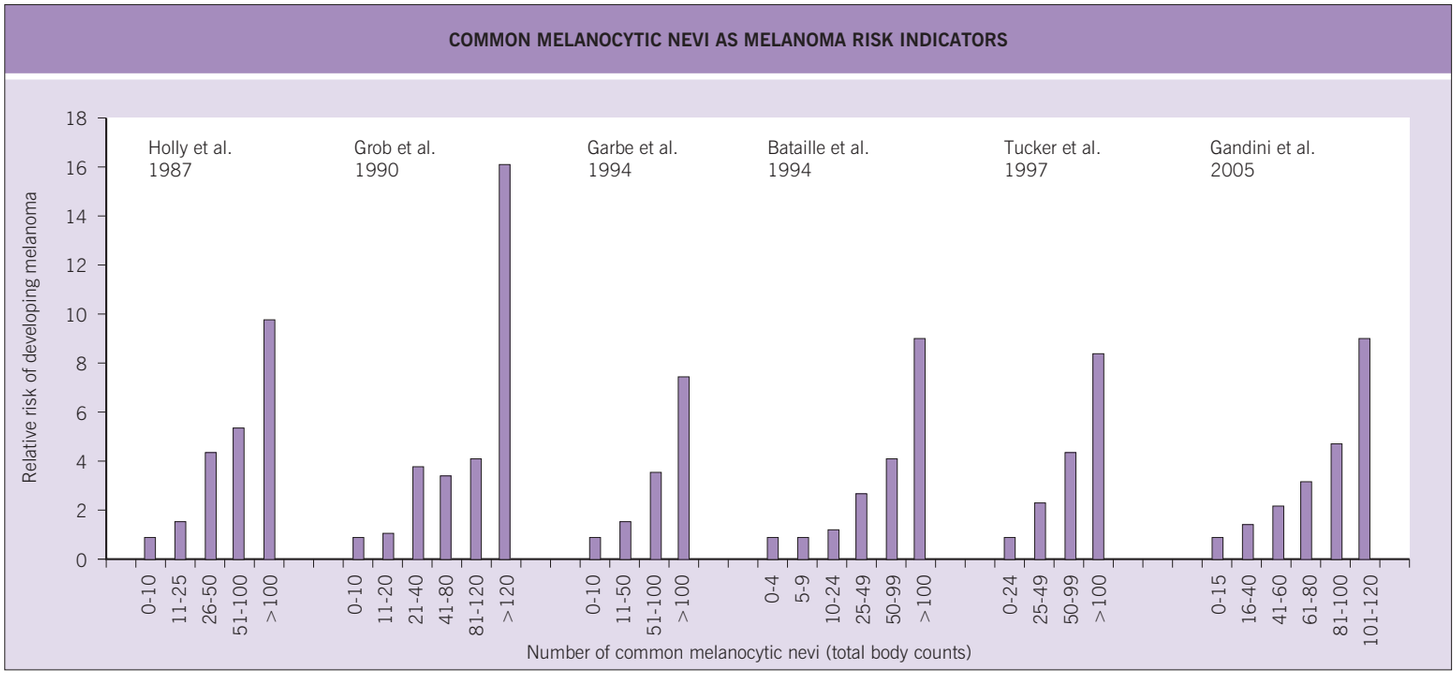


Fig. 113.7 Common melanocytic nevi as melanoma risk indicators. Relative risk of developing melanoma for a given number of common melanocytic nevi (total body counts) as determined by five epidemiologic studies and one meta-analysis (Gandini et al.). Melanoma risk increases almost linearly with the number of common melanocytic nevi, rendering common nevi valuable as risk indicators.

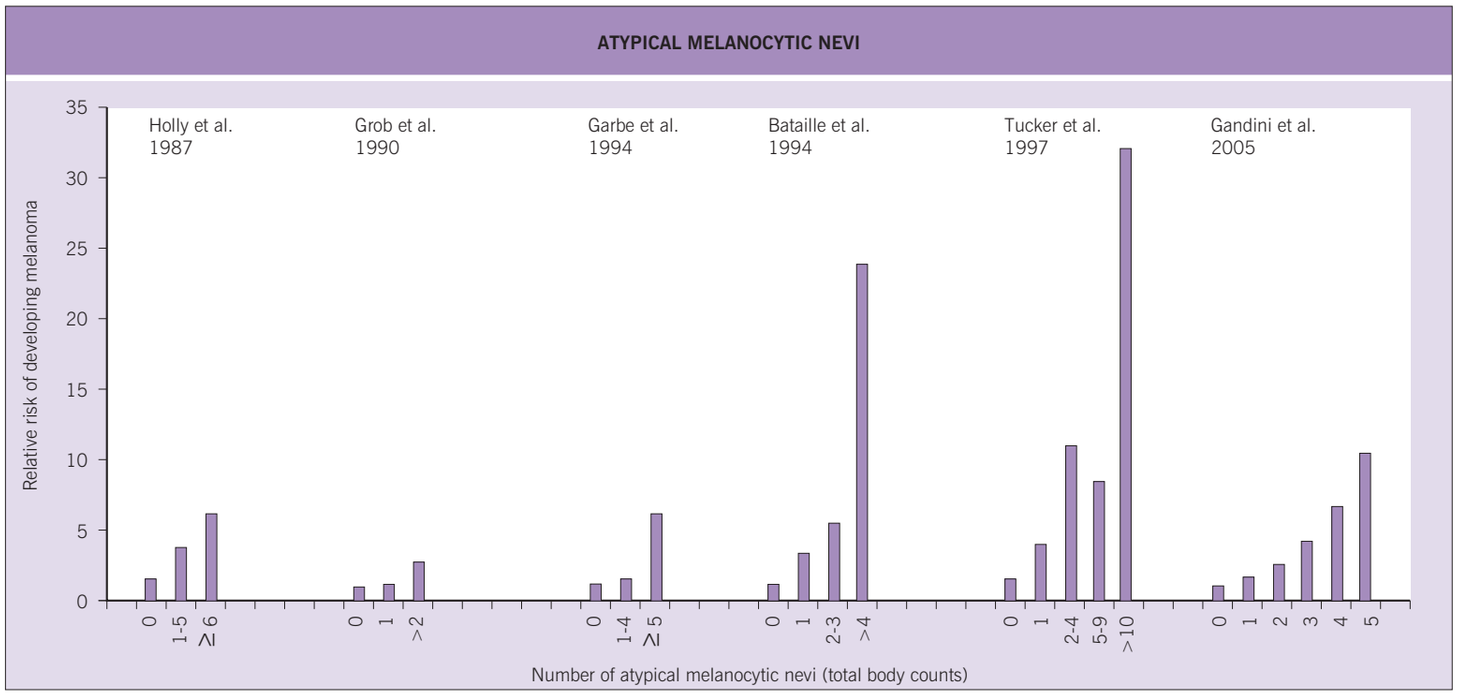


Fig. 113.8 Atypical melanocytic nevi as melanoma risk indicators. Relative risk of developing melanoma for a given number of atypical melanocytic nevi (total body counts) as determined by five epidemiologic studies and one meta-analysis (Gandini et al.). An elevated risk is associated with relatively small numbers of atypical nevi. The relative risk as indicated by the number of atypical nevi is independent from the total number of melanocytic nevi, and it is related in a multiplicative fashion to the risk based on the total number of nevi. In other words, the individual risk for developing melanoma is calculated by multiplying the risk related to the total number of nevi times that due to the number of atypical nevi (see Table 113.2).

The role of sunlight in melanoma development has been a matter of debate for decades, in part because the etiologic role of sunlight is far less clear than in other tumors such as cutaneous squamous cell carcinoma (SCC)[115,116]. Also, melanoma is clearly a multi-factorial disease and forcing an all-or-none stance regarding sun exposure represents an erroneous oversimplification. That said, the following clinical and epidemiologic features have raised doubts regarding the impact of sunlight on melanoma development:

- With the exception of lentigo maligna melanoma, the anatomic distribution of melanoma does not closely match sites of greatest cumulative sun exposure as in cutaneous SCC.
- Melanoma most commonly develops in middle-aged adults, not the elderly with the greatest cumulative sun exposure.
- In most of the reported case-control studies, neither greater cumulative sun exposure during adulthood nor sunburns during the preceding years was associated with an elevation in melanoma risk.

Initial indications of an etiologic role for sunlight came from the observation that melanoma incidence was increased in white populations living closest to the equator. This was most striking when melanoma incidence and mortality rates in Europe versus Australia were compared, with both variables being 5–10 times higher in Australia[117,118]. Furthermore, case–control studies demonstrated that melanoma risk was closely associated with the number of melanocytic nevi and with the occurrence of sunburns in childhood[112,119,120]. Interestingly, sunburns during childhood and adolescence significantly elevated the risk for melanoma development, but additional sunburns during adulthood did not contribute to any further risk elevation. This was in agreement with previous findings that melanoma risk is mainly acquired during childhood.

The total number of melanocytic nevi has been identified as the most important risk factor for cutaneous melanoma, and as the number of melanocytic nevi increases, the melanoma risk increases nearly linearly (see Fig. 113.7)[93,95,121]. Therefore, to gain more insight into the relationship between sun exposure and nevus development, epidemiologic studies have been performed in young children. With exposure to intense UVR, children in Australia developed melanocytic nevi early in life and in large numbers[122]; of note, duration of sun exposure was a stronger risk factor than the occurrence of sunburns. In a study of 1812 German nursery school children, high nevus counts in children were preferentially associated with the number of weeks on sunny holidays and with outdoor activities at home that were linked to moderate sun exposure[123,124]. These findings suggested that sunburns were not required and that moderate sun exposure appeared to be sufficient for the induction of melanocytic nevi in children.

A possible explanation for the differences in the epidemiology of melanoma as compared with non-melanoma skin cancer involves apoptosis[125]. After exposure to UVR, the most severely damaged keratinocytes undergo apoptosis (sunburn cells), with the less damaged keratinocytes upregulating their DNA-repair capacities and undergoing nearly perfect DNA repair. As a result, the development of non-melanoma skin cancer would favor elderly adults. In contrast, melanocytes do not undergo apoptosis as readily. Their function is to provide protective melanin to the surviving cells and so they are retained within the epidermis, even with damage. In addition, some UVR-induced mutations are thought to enable melanocytes to proliferate and give rise to junctional nevi. Subsequently, melanoma could arise in anatomic sites with intermittent sun exposure, with the sites of melanoma development reflecting the distribution pattern of melanocytic nevi[126,127]. This hypothesis might also explain why melanomas tend to develop in a younger age group (i.e. middle-aged adults).

Both UVB and UVA radiation are thought to be associated with the development of cutaneous melanoma, with UVB believed to be the stronger risk factor. Data supporting UVB as a causative factor come from: (1) animal studies in which UVB was shown to induce melanoma in susceptible mice and in xenografted human skin engineered to express melanocytic growth factors[128,129]; and (2) the fact that there is a higher incidence of cutaneous melanoma in equatorial regions where UVB is most intense. Data implicating UVA in the development of cutaneous melanoma derive from: (1) animal studies in which UVA was shown to initiate melanoma (fish) and melanocytic hyperplasia (pigmented opossums)[130–133]; and (2) recent studies showing an increased incidence of melanoma developing in users of tanning beds and perhaps recipients of PUVA. In 2009, the World Health Organization (WHO)

International Agency for Research on Cancer (IARC) categorized tanning beds as a human carcinogen. Of note exposure to tanning beds before the age of 35 years has a statistically significant association with melanoma development.

Sun protection

With regard to sun protection, there is a significant misunderstanding by the public that avoidance of sunburns and use of sunscreens is sufficient to prevent skin cancer. It is well established that sub-erythemal doses of UVR cause DNA mutations. Chronic irradiation with 10–20% of the minimal erythema dose of UVB induced DNA damage in mouse skin and this damage persisted in the dermis and epidermis for several weeks following discontinuation[134]. Therefore, low-dose UVB exposure in a repeated fashion could cause skin cancer.

Regular use of sunscreen has been shown to decrease the development of actinic keratoses and cutaneous SCCs, but evidence regarding its ability to prevent cutaneous melanoma has been controversial to non-existent, until recently (see Ch. 132). In 2010, a randomized sunscreen trial in Australia found that the regular application of SPF 15+ sunscreen in 1621 adults over 5 years reduced the incidence of new primary cutaneous melanoma, even 10 years after completion of the trial. Whether or not the regular use of sunscreen in children, when sun exposure is thought to be critical for the development of cutaneous melanoma, will be beneficial is less clear[135].

There are additional sun-protective measures that should be encouraged, including physical means of blocking the sun (e.g. non-transparent clothing, hats[136]) and reducing UVR exposure (e.g. shade coverings, limiting outdoor activities between the hours of 10:00 AM and 4:00 PM).

TYPES OF PRIMARY MELANOMAS

Until the 1960s, melanoma was regarded as a large black nodule that, as a rule, metastasized and caused death. Therefore, the recognition of early-stage melanoma was a major advancement. Four major subtypes (growth patterns) of primary cutaneous melanoma have been described[137] (Table 113.3). These different growth patterns characterize the early phase of development, but do not predict the prognosis.

DIFFERENT TYPES OF PRIMARY CUTANEOUS MELANOMA			
Clinico-histopathologic subtype	**Abbreviation**	**Percentage**	**Median age**
Superficial spreading melanoma	SSM	57.4%	51 years
Nodular melanoma	NM	21.4%	56 years
Lentigo maligna melanoma	LMM	8.8%	68 years
Acral lentiginous melanoma	ALM	4%	63 years
Unclassifiable melanoma	UCM	3.5%	54 years
Others		5%	54 years

Table 113.3 Different types of primary cutaneous melanoma. Data from the German Central Malignant Melanoma Registry (N = 30 015).

Fig. 113.9 Superficial spreading melanoma (SSM). Note asymmetry, irregular borders, variation in colors, scar-like regression zones, and an inferior pink papule, indicating vertical growth phase.

Superficial Spreading Melanoma

Superficial spreading melanoma (SSM) is the most common type of cutaneous melanoma in fair-skinned individuals (Fig. 113.9) and it is diagnosed most frequently between the ages of 40 and 60 years. It accounts for approximately 60–70% of all melanomas and occurs at any site, but is most frequently seen on the trunk of men and the legs of women. It begins as an asymptomatic brown to black macule with color variations and irregular, notched borders (Fig. 113.10). SSM can arise *de novo* or in a pre-existing nevus (Fig. 113.11). When *in situ*, the melanoma is usually macular with an irregular outline and variable pigmentation (Fig. 113.12). SSMs may have a diameter ≤5 mm (Fig. 113.13). After a typically slow horizontal (radial) growth phase limited to the epidermis or focally within the papillary dermis, a more rapid vertically oriented growth phase, which presents clinically with the development of a papule or nodule, can then occur. In up to two-thirds of tumors, regression (visible as gray, hypo- or depigmentation) of part of the lesion is observed, reflecting the interaction of the host immune system with the progressing tumor. About half of SSMs arise in a pre-existing nevus[138], although the likelihood of an individual nevus progressing to melanoma is exceedingly low.

Nodular Melanoma

Nodular melanoma is the second most common type of cutaneous melanoma in fair-skinned individuals and is diagnosed most frequently in patients in their sixth decade of life. It accounts for approximately 15% to 30% of all melanomas and occurs at any body site, but is most frequently seen on the trunk, head and neck. Nodular melanomas are observed more frequently in men than in women. They usually present as a blue to black, but sometimes pink to red, nodule which may be ulcerated or bleeding and in some patients have developed rapidly over months (Fig. 113.14). Nodular melanoma is believed to arise as a *de novo* vertical growth phase tumor without the pre-existing horizontal growth phase that characterizes the other histologic types. These melanomas tend to be diagnosed at a thicker, more advanced stage, with an associated poorer prognosis. The incidence of nodular melanoma has remained fairly stable in recent decades[139].

Lentigo Maligna Melanoma

Lentigo maligna melanoma (LMM) represents a minority of cutaneous melanomas (around 10%) and it is diagnosed most frequently during the seventh decade of life. It occurs in chronically sun-damaged skin, most commonly on the face, with a preference for the nose and cheek. LMM usually develops as a slowly growing, asymmetric, brown to black macule with color variation and an irregular, indented border (Fig. 113.15). Invasive LMM arises in a precursor lesion termed lentigo maligna (*in situ* melanoma in sun-damaged skin). It has been estimated that 5% of lentigo maligna lesions progress to invasive melanoma[140]. Because lentigo maligna typically arises within a background of severely sun-damaged skin, it can be difficult to histologically distinguish lentigo maligna from the atypical melanocytic hyperplasia seen in severely sun-damaged skin[141](see Fig. 150.5).

Lentigo maligna displays characteristic features on dermoscopic examination (Fig. 113.16). Hyperpigmented follicular openings of the facial skin (circle in a circle), are slowly overgrown by irregular pigmented dots around the follicles (annular granular pattern)[142,143] Rhomboidal structures can also be seen (see Table 0.13).

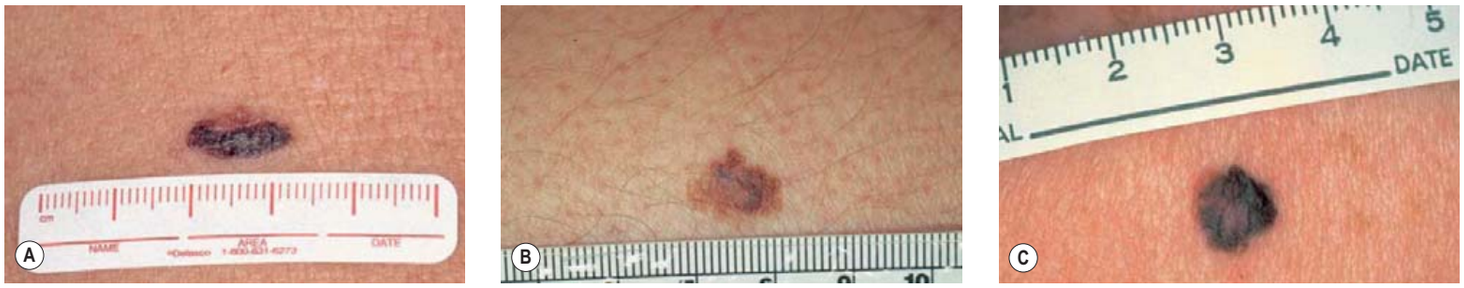


Fig. 113.10 Early superficial spreading melanomas. All of these lesions demonstrate asymmetry due to variation in color and irregularity in outline. In addition, there is pink discoloration in **C**. **A,B** were less than 0.5 mm in thickness and **C** was 0.8 mm. *A, Courtesy, Kalman Watsky MD. B & C, Courtesy, Jean L Bolognia, MD.*

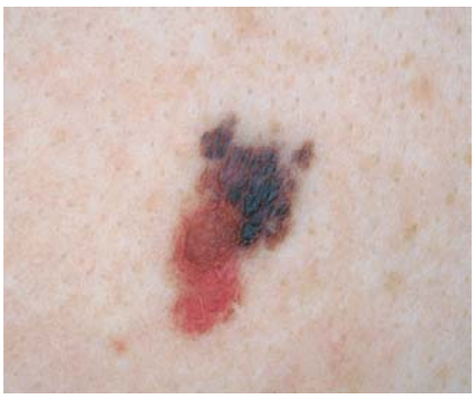


Fig. 113.11 Superficial spreading melanoma (SSM) arising in a pre-existing nevus. Note the irregular outline and variable pigmentation.

Fig. 113.12 Melanoma *in situ*. A Note the asymmetry, border irregularity, color variation, and erythema ("Little Red Riding Hood" sign). **B** The dermoscopic findings include a broadened network, dots and some globules inside this asymmetric lesion.

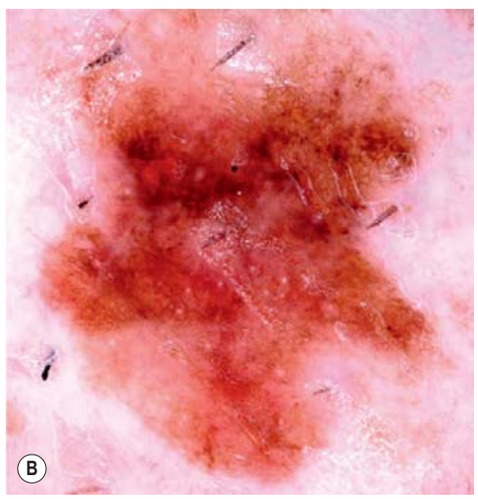


Fig. 113.13 Melanoma *in situ*. This melanoma *in situ* measured less than 3 mm in diameter. Small melanomas can be easily overlooked, especially if they are less heavily pigmented. This lesion was the "ugly duckling" of all of this patient's nevi. Dermoscopy assists in making an earlier diagnosis.

Acral Lentiginous Melanoma

Acral lentiginous melanoma (ALM) is a relatively uncommon type of cutaneous melanoma and is diagnosed most frequently in the seventh decade of life. It typically occurs on the palms and soles or in and around the nail apparatus. ALM accounts for approximately 5% of all melanomas and the incidence of ALM is similar across all racial and ethnic groups. As more darkly pigmented Africans and Asians do not typically develop sun-related melanomas, ALM represents a disproportionate percentage of melanomas diagnosed in blacks (up to 70%) and Asians (up to 45%)[144].

ALM typically presents as an asymmetric, brown to black macule with color variation and irregular borders (Fig. 113.17). A disproportionate percentage of ALMs are diagnosed at an advanced stage. This is likely the result of the difficulty of clinically distinguishing many ALMs from benign lesions and traumatic skin changes, as well as an elevated threshold for biopsy due to the morbidity associated with surgery at acral sites. Primary misdiagnosis of ALM occurs in about one-third of all patients and leads to substantial delay in establishing the correct diagnosis[145].

Melanoma of the nail matrix can present as longitudinal melanonychia (Fig. 113.18) or as hyperpigmentation extending onto the hyponychium or beyond the lateral or proximal nail fold (Hutchinson sign) (see Ch. 71). The possibility of melanoma should be considered for all pigmented nail bands in fair-skinned individuals, especially if they are darkly pigmented, have irregular pigmentation and/or have a width ≥3 mm.

Fig. 113.14 Nodular melanoma (NM). Rapidly growing black nodule that was >15 mm in diameter on the back of a male patient.

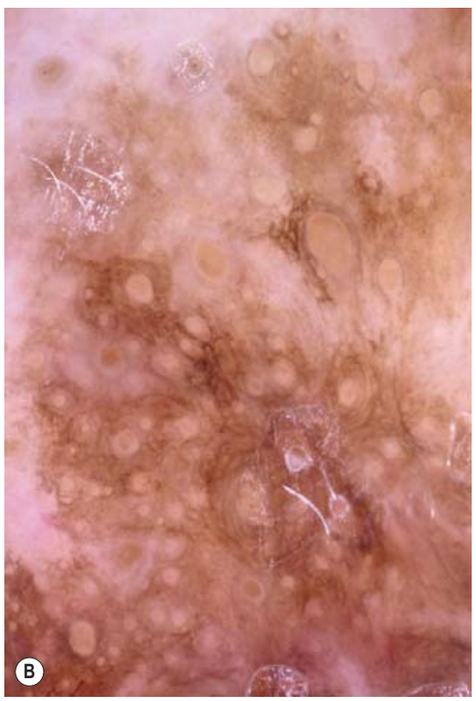


Fig. 113.16 Lentigo maligna melanoma (LMM). A A pigmented lesion on the dorsal nose, with irregular borders, light to dark brown pigmentation and marked asymmetry. **B** Dermoscopy demonstrating annular structures corresponding to follicular openings surrounded by melanoma cells ("circle in a circle").

Fig. 113.15 Lentigo maligna versus lentigo maligna melanoma. A Large-sized brown patch with mild variation in color representing lentigo maligna. **B** Similarly sized lesion, but with marked variation in color and topography. There was invasion to a depth of 1.1 mm within the blue-gray papules.
B, Courtesy, Kalman Watsky, MD.

ALM is a genetically distinct subtype of melanoma and clearly differs from the other types of cutaneous melanoma. It harbors more and different genetic changes than the other types and can display activating *KIT* mutations in exons 11, 13 and 17, which can make the tumor sensitive to KIT-inhibiting drugs (e.g. imatinib; see Table 113.1)[10,146].

OTHER MELANOMA VARIANTS

There are cutaneous melanomas that may present with unusual manifestations. Some of these are defined by clinical features, others by histologic findings.

Amelanotic Melanomas

Fortunately, the overwhelming majority of melanomas are pigmented, aiding visual diagnosis. Melanomas lacking clinically evident pigment are termed "amelanotic" (Fig. 113.19). All four histologic subtypes of melanoma discussed above can occur as amelanotic variants that largely defy clinical diagnosis. Amelanotic SSMs, nodular melanomas and LMMs are often biopsied due to clinical suspicion of basal cell carcinoma. Amelanotic ALMs are especially challenging and may be mistaken for warts or squamous cell carcinoma. Amelanotic melanomas do not differ from pigmented melanomas in terms of prognosis or therapy.

Fig. 113.17 Acral lentiginous melanoma (ALM). Irregularly pigmented lesion on the plantar surface of the foot. These tumors may become amelanotic and are then easily overlooked or misdiagnosed as verrucae or other benign lesions, often resulting in a significantly delayed diagnosis.

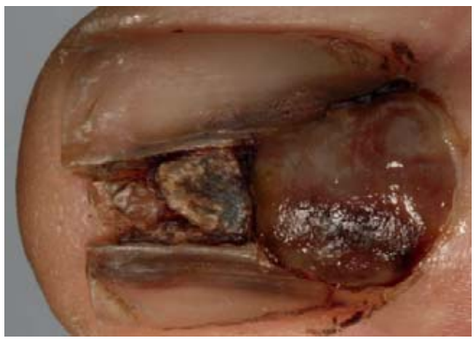


Fig. 113.18 Melanoma of the nail matrix. Ulcerated tumor destroying the nail plate. The longitudinal pigmentation of the nail plate adjacent to the nodular portion is a clue to the diagnosis of melanoma.

Fig. 113.19 Amelanotic melanoma. A, B Skin-colored to light pink nodule on the right scapula of a female patient. Pathology revealed an amelanotic nodular melanoma with a tumor thickness of 4 mm.

Melanoma with Features of a Spitz Nevus ("Spitzoid" Melanoma)

This variant shows histologic features suggestive of Spitz nevus (Fig. 113.20) with overall symmetry and a dermal nodule of epithelioid melanocytes that do not mature with progressively deeper dermal extension. Other important histologic clues that point to the diagnosis of melanoma are sheets of atypical melanocytes in the dermis and mitotic figures at the base of the lesion. While several approaches have been taken to distinguish spitzoid melanomas from benign Spitz nevi (e.g. immunohistochemistry, fluorescence in situ hybridization [FISH], comparative genomic hybridization [CGH] analysis), some of these lesions continue to defy definitive histologic diagnosis[147].

Desmoplastic Melanoma

While this type of melanoma is histologically defined, the typical clinical lesion consists of a skin-colored, red or brown–black nodule or plaque, usually in sun-exposed sites. It may develop *de novo*, but more commonly arises in conjunction with a lentigo maligna, ALM or mucosal radial growth phase melanoma. Deep tissue samples are necessary to establish the diagnosis (Fig. 113.21), as superficial portions of the tumor show subtle or non-diagnostic findings which may be mistaken for the fibrosis of a scar or other spindle cell neoplasms. Metastasis to lymph nodes is uncommon, but the tumor is highly infiltrative and, thus, locally aggressive, with recurrence being common after incomplete excision. While these tumors do have significant potential for distant metastasis, conventional T staging tends to overestimate the likelihood for metastasis of these tumors, which are typically quite deep at the time of diagnosis[148,149].

Clear Cell Sarcoma: Melanoma of Soft Parts

Clear cell sarcoma most often presents on the distal extremities of adolescents and young adults. The tumors usually arise in association with tendons and aponeuroses, and they are composed of nests and fascicles of oval to spindled cells with vesicular nuclei, basophilic nucleoli, and eosinophilic to clear cytoplasm. Multinucleated giant cells and melanin can frequently be seen. Despite its unique clinical and histologic presentation, several lines of evidence, including immunohistochemical studies, presence of melanosomes on electron microscopy, and gene profiling, support the classification of clear cell sarcoma as a subset of melanoma[150,151]. Clear cell sarcoma pathogenesis differs from that of other melanoma subtypes by a frequent and characteristic reciprocal translocation t(12;22)(q13;q12) that results in fusion of the *EWS* and *ATF1* genes[150]. The clinical course of these lesions resembles that of other soft tissue sarcomas, with a high likelihood of regional and distant metastasis.

Malignant Blue Nevus

Malignant blue nevus is a rare dermal tumor of melanocytes, most commonly located on the head and particularly the scalp (Fig. 113.22). It appears as a blue–black, deeply situated nodule, generally >1 cm in diameter. Histologically, elements of a benign cellular blue nevus are associated with nodular areas of atypical spindle-shaped and bipolar dendritic melanocytes, mitotic figures, necrosis and melanophages[152].

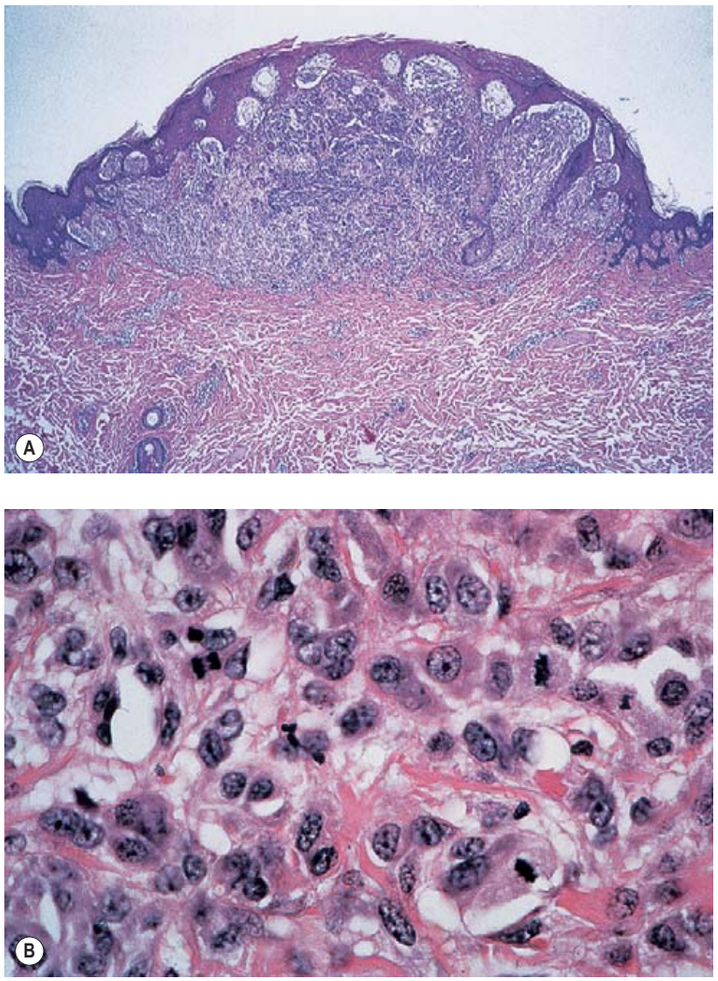


Fig. 113.20 Histopathology of "spitzoid" melanoma, histopathologically simulating a Spitz nevus. This neoplasm could be misdiagnosed as a Spitz nevus because the lesion is symmetrical and well circumscribed (**A**). This is a melanoma because: nests of melanocytes have become confluent with formation of sheets; there is no distinct maturation of melanocytes; nuclei of melanocytes are atypical; and melanocytes are in mitosis at the base of the neoplasm (**B**). *Courtesy, Helmut Kerl, MD.*

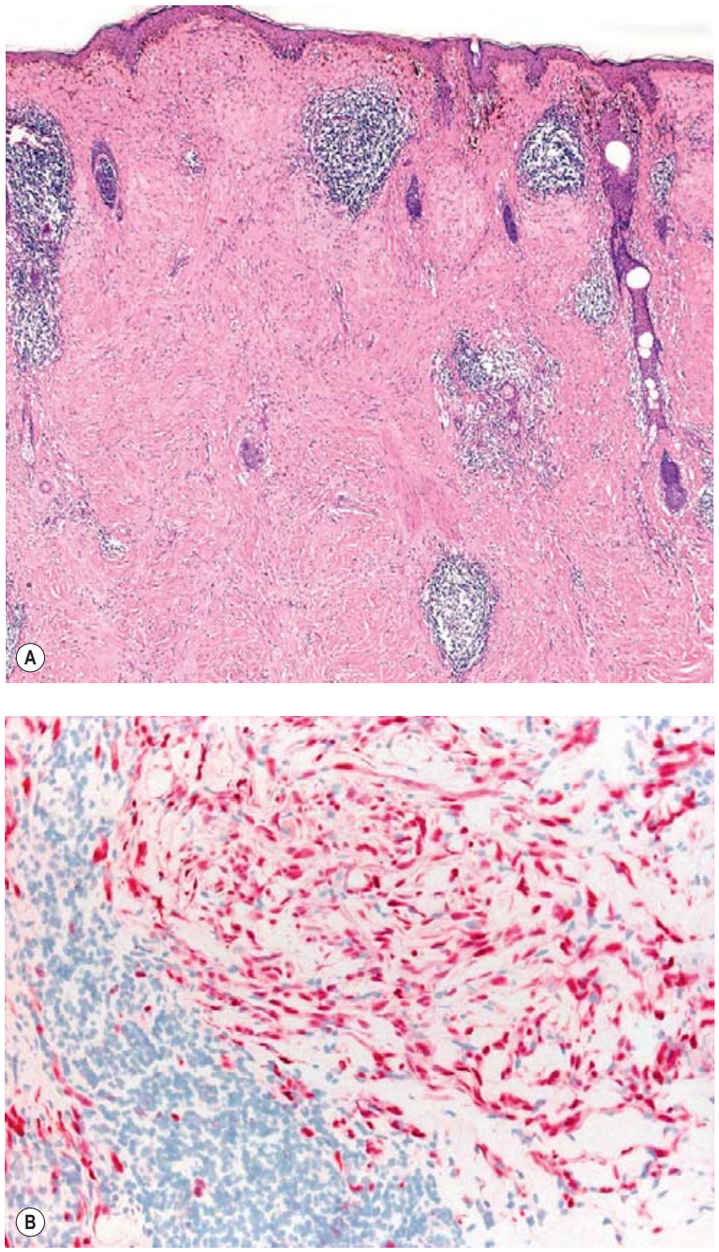


Fig. 113.21 Histopathology of desmoplastic melanoma. A Loosely textured spindle cells within fibroblastic stroma. In the epidermis and follicular epithelium, there are changes of melanoma *in situ* with proliferation of atypical melanocytes. Note the lymphoid infiltrates. **B** S100-positive spindle cells within the dermis. *Courtesy, Lorenzo Cerroni, MD.*

The clinical course is characterized by a high rate of recurrence and metastasis.

Ocular Melanoma

Primary ocular melanomas, which are relatively rare (5% of all melanomas), can be divided into conjunctival melanomas and uveal melanomas (iris, choroidal and ciliary body melanomas). Uveal melanomas frequently (80–85%) harbor somatic activating mutations in *GNA11* or *GNAQ*. These genes encode members of the q class of G protein α-subunits. Heterotrimeric G proteins are involved in mediating signals between G-protein-coupled receptors (GPCRs) and downstream effectors (see Fig. 65.15)[153]. Of note, *GNAQ* (more frequently than *GNA11*) mutations have been detected in blue nevi but not in cutaneous melanomas. Chromosomal changes of prognostic significance in ocular melanoma have been described and include monosomy 3 and alterations of 8q and 6p. Monosomy 3 reduces the 5-year survival from approximately 100% to less than 50%. A particularly poor outcome has been associated with combined abnormalities in chromosomes 3 and 8[154]. The management of uveal melanoma has shifted to eye-sparing approaches without significant impact on patient survival. Radiotherapy with proton beams has replaced eye enucleation as the standard treatment for uveal melanoma[155].

Mucosal Melanoma

Mucosal melanomas are rare lesions that may occur in the mouth, nasopharynx, larynx, vagina and anus. They tend to occur near the mucocutaneous junctions of squamous and columnar epithelia and account for ~1% of melanomas. As many as 35% of mucosal melanomas are reportedly amelanotic, further complicating a difficult clinical diagnosis[156]. Not surprisingly, these tumors tend to be diagnosed at a locally advanced stage with associated poor prognosis. Similar to ALM, mucosal melanomas are a genetically distinct subtype of melanoma. They harbor more and different DNA copy number changes than do cutaneous melanomas and they can harbor activating *KIT* mutations, which can make the tumor sensitive to KIT-inhibiting drugs (e.g. imatinib; see Table 113.1)[10,146].

MELANOMA AND PREGNANCY

During pregnancy, levels of hormones and growth factors that stimulate melanocytes are elevated and increased pigmentation occurs in some women. More than 10% of women experience darkening of melanocytic nevi during the first 3 months of pregnancy[157]. However, an association

Fig. 113.22 Melanoma in association with a cellular blue nevus (malignant blue nevus). Satellite metastases are also present. *Courtesy, Frank Nestlé, MD.*

between hormonal changes during pregnancy and development of melanoma or worsening of the prognosis of an existing melanoma has not been demonstrated[158]. Transplacental metastases are very rare in pregnant women with melanoma and only a limited number of cases have been described in the literature[159]. Surgical excision and sentinel lymph node biopsy (if chosen by the patient) are performed as indicated, based upon stage of disease and current recommendations (see below). In more advanced stages, the advantages and disadvantages of immunotherapy and chemotherapy should be discussed with the patient. Ultrasound and magnetic resonance imaging can be performed in pregnant patients, but computerized tomography (CT) scans should be avoided. In women with a history of high-risk melanoma, it may be reasonable to wait 2 years after diagnosis before becoming pregnant again, because two-thirds of recurrences occur within this period. Lastly, there have been no studies demonstrating an adverse effect of hormonal contraception on melanoma development[160].

CHILDHOOD MELANOMA

Childhood melanoma is very rare. Approximately 2% of melanomas occur in patients younger than 20 years of age, and 0.3% in those younger than 14 years[161]. The risk factors for melanoma in children parallel those in adults. The exceedingly rare conditions of xeroderma pigmentosum and giant congenital melanocytic nevi contribute minimally to the prepubertal incidence of melanoma. Histologically, melanomas in children may resemble those of adults, but melanomas with features of Spitz nevus are reported to be more common in this age group[162]. As noted above, the differentiation of melanoma from atypical Spitz nevus and from deep penetrating nevus remains a major challenge, and overdiagnosis of childhood melanoma may result from this uncertainty[163,164]. Overall survival and prognosis appears to be stage-dependent and similar to that in adults[165]. Treatment follows the same rationale as in adults.

DIAGNOSIS

Early detection is a key factor in improving survival in patients with melanoma. The clinical diagnosis of cutaneous melanoma continues to be based on visual inspection and dermoscopy. A history of change in the color, shape or size of a pigmented skin lesion over the course of months or years is the most sensitive clinical sign for melanoma, and may be detected by the patient himself or by serial screening examinations based on dermoscopy with image storing or on lesional or total body photography[166,167].

Public awareness campaigns have highlighted the ABCD's of melanoma: **A**symmetry, **B**order irregularity, **C**olor variegation, and **D**iameter greater than 5 mm. However, the ABCD rule widely overlaps with the definition of benign atypical melanocytic nevi[168]. Furthermore, it has been shown that patients recognize a melanoma by the development of a new pigmented lesion or by an increase in size or change in color of a pre-existing lesion instead of by the ABCD features[169]. Thus, an '**E,**' for **E**volving, has been added to highlight the importance of a changing lesion.

Dermatologists seem to unconsciously rely on cognitive (overall pattern) and comparative (ugly duckling sign) processes rather than an algorithm of morphologic criteria (ABCD)[170]. A diagnostic clue is the so-called *"ugly duckling" sign*, which focuses on the morphologic differences between a single striking lesion and the surrounding benign "signature" nevi[171]. There is a good inter-observer reproducibility of this sign[172].

Two other helpful clinical clues are the *"Little Red Riding Hood" sign* and the *"EFG" rule*. The former represents the finding of erythema or inflammation that at times will surround a cutaneous melanoma. "EFG" stands for an **E**levated, **F**irm, or **G**rowing lesion and is helpful to keep in mind for accurately diagnosing an amelanotic or nodular melanoma.

It is important to keep in mind that not all cutaneous melanomas present with these typical clinical clues. Diagnostic accuracy for the clinical diagnosis of melanoma does not exceed 75% and may be increased to up to 90% with the use of dermoscopy by experts. However, 10–25% of melanomas may still be missed despite all these diagnostic efforts. The term "featureless melanoma" has been coined for early and difficult-to-diagnose melanomas and may partially explain this statistic[173,174]. Sometimes, patients are the first to recognize these featureless cutaneous melanomas and infrequently patients are very suspicious about a single such skin lesion. Therefore, the following principle for the management of skin cancer patients is suggested, which may be called "Garbe's rule": *If a patient is worried about a single skin lesion, do not ignore their suspicion and have a low threshold for performing a biopsy.*

Differential Diagnosis

A variety of conditions may simulate melanoma, either clinically or histopathologically, or both. Awareness of these simulators is of great practical importance in order to avoid misdiagnosis or overdiagnosis of melanoma[175]. Tables 113.4 and 113.5 list several melanocytic and non-melanocytic lesions that can mimic melanomas. Occasionally, a primary melanoma arising in the dermis with no epidermal component is diagnosed as a dermal metastasis of melanoma.

Dermoscopy

Dermoscopy, also known as skin surface microscopy or epiluminescence microscopy (ELM), is a helpful non-invasive tool for diagnosing pigmented skin lesions and for recognizing cutaneous melanoma (Fig. 113.23)[176]. Clinical diagnostic sensitivity is significantly enhanced by the use of dermoscopy and the correct diagnosis of melanoma is improved by nearly 50% by utilizing this diagnostic technique[177].

In one form of dermoscopy, a magnifying lens system is combined with a fluid interface in order to eliminate skin surface reflection. Hand-held lenses or cameras equipped with lenses and coupled with digital imaging systems are used. A glass plate makes direct contact with the skin and for the fluid interface, ultrasound contact gel or a disinfectant spray can be used. Morphologic structures within the epidermis, the dermal–epidermal junction and the superficial dermis can be visualized with this technique. An alternative form of dermoscopy employs polarized light to eliminate the surface reflection so that neither a liquid interface nor direct skin contact is required. The magnifications of these instruments range from 6- to 100-fold, but the most widely used dermoscope provides a 10-fold magnification, which is sufficient for routine assessment of pigmented skin lesions.

The dermoscopic evaluation of cutaneous pigmented lesions involves a two-step algorithm. First, the observer determines whether the lesion under investigation is of melanocytic origin or not. For a lesion to be considered melanocytic, it needs to have at least one of the following dermoscopic structures/features: pigment network, streaks, aggregated globules, homogeneous blue pigment, or parallel pattern (acral lesions). If the lesion does not possess one of the aforementioned melanocytic features, then it needs to be evaluated further to determine if it has any dermoscopic characteristics consistent with other entities such as a seborrheic keratosis, dermatofibroma or pigmented basal cell carcinoma (see Ch. 0). However, if the lesion does not have any features of

MELANOCYTIC LESIONS THAT SIMULATE MELANOMAS
CLINICAL SIMULATORS
• Acral nevi • Atypical (dysplastic, Clark's) nevi • Black (hypermelanotic) nevi • Blue nevi and variants • Combined nevi • Congenital nevi • Halo nevi • Longitudinal melanonychia • Melanosis of mucosal regions • Nevi and lentigines in genital regions • Nevi in patients with epidermolysis bullosa • Pigmented streaks in melanoma scars • Recurrent nevi • Reticulated (ink-spot) lentigo • Spitz nevi and variants
HISTOPATHOLOGIC SIMULATORS
• Acral nevi • Ancient nevi • Atypical (dysplastic, Clark's) nevi • Atypical Spitz nevi and variants • Congenital nevi biopsied shortly after birth • Deep penetrating nevi • Hyperplasia of melanocytes in sun-damaged skin • Melanocytic proliferation overlying a benign neoplasm • Nevi arising within areas of lichen sclerosus • Nevi exposed to UV radiation • Nevi in genital regions (including milk-line nevi and flexural nevi) • Nevi in patients with epidermolysis bullosa • Nevi on or around the ear • Pigmented streaks in melanoma scars • Proliferating nodules in giant congenital nevi in neonates • Recurrent nevi

Table 113.4 Melanocytic lesions that simulate melanomas.

NON-MELANOCYTIC CLINICAL SIMULATORS OF MELANOMA
SIMULATING SUPERFICIAL SPREADING MELANOMA
• Seborrheic keratosis • Thrombosed hemangioma, angiokeratoma • Pigmented basal cell carcinoma • Pigmented actinic keratosis • Extramammary Paget's disease • Bowen's disease including pigmented variant
SIMULATING NODULAR MELANOMA
• Seborrheic keratosis • Pyogenic granuloma • Dermatofibroma • Thrombosed hemangioma, angiokeratoma • Pigmented basal cell carcinoma • Pigmented poroma and pigmented porocarcinoma • Pigmented pilomatricoma • Pigmented dermatofibrosarcoma protuberans (Bednar tumor)
SIMULATING LENTIGO MALIGNA MELANOMA
• Macular seborrheic keratosis • Solar keratosis, including the pigmented variant • Pigmented basal cell carcinoma
SIMULATING ACRAL LENTIGINOUS MELANOMA OF THE PALMS AND SOLES
• Black heel (hemorrhage in stratum corneum caused by trauma) • Plantar warts • Trophic ulcers • Plantar callosity • Tinea nigra
SIMULATING SUBUNGUAL ACRAL LENTIGINOUS MELANOMA
• Subungual hematoma • Bowen's disease • Verruca • Paronychia • Drug-induced nail pigmentation
SIMULATING AMELANOTIC MELANOMA
• Superficial basal cell carcinoma • Bowen's disease • Benign lichenoid keratosis • Isolated patch of psoriasis

Table 113.5 Non-melanocytic clinical simulators of melanoma.

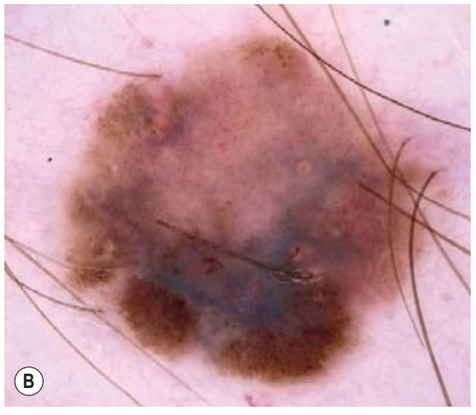


Fig. 113.23 Illustration of dermoscopy. This pair of images illustrates the clinical appearance (**A**), and the same lesion viewed with dermoscopy (**B**). Greater detail can be appreciated at 10- to 20-fold magnification. This lesion is an early invasive melanoma with sharp demarcation, asymmetry, and a central blue-whitish veil.

a melanocytic lesion *and* it does not have any features of a non-melanocytic tumor, then, by default, the lesion is considered to be of melanocytic origin.

Once a lesion is deemed to be of melanocytic origin, the second step of the algorithm is to differentiate between benign melanocytic nevi and melanoma. To this end, multiple algorithms have been created, including pattern analysis, the ABCD rule, Menzies method, and the 7-point checklist, among others, which assist the clinician in deciding which lesions require a biopsy (see Tables 0.15–0.18)[142].

The major dermoscopic criteria for melanoma can be broken down into global features, patterns and local features (Fig. 113.24). Global features of melanoma include dermoscopic asymmetry and the presence of multiple colors. Patterns seen by dermoscopy include reticular, globular, reticular–globular, homogeneous, reticular–homogeneous, and starburst. In melanoma, the most common patterns are the multi-component pattern (three or more dermoscopic structures distributed asymmetrically), asymmetric starburst pattern, and nonspecific pattern (does not fit one of the known benign patterns). Lastly, the presence of any of the following local features should raise concern for melanoma: atypical network, streaks, atypical dots or globules, irregular blood vessels, regression structures and blue-white veil (Table 113.6).

Over the past several years, dermoscopy has been further refined in order to recognize difficult-to-diagnose melanomas such as ALMs and subungual melanomas[178–180]. Additionally, diagnostic clues for early nodular melanomas and for amelanotic melanomas have been described, as these melanomas do not display the classic features (see above)[181,182].

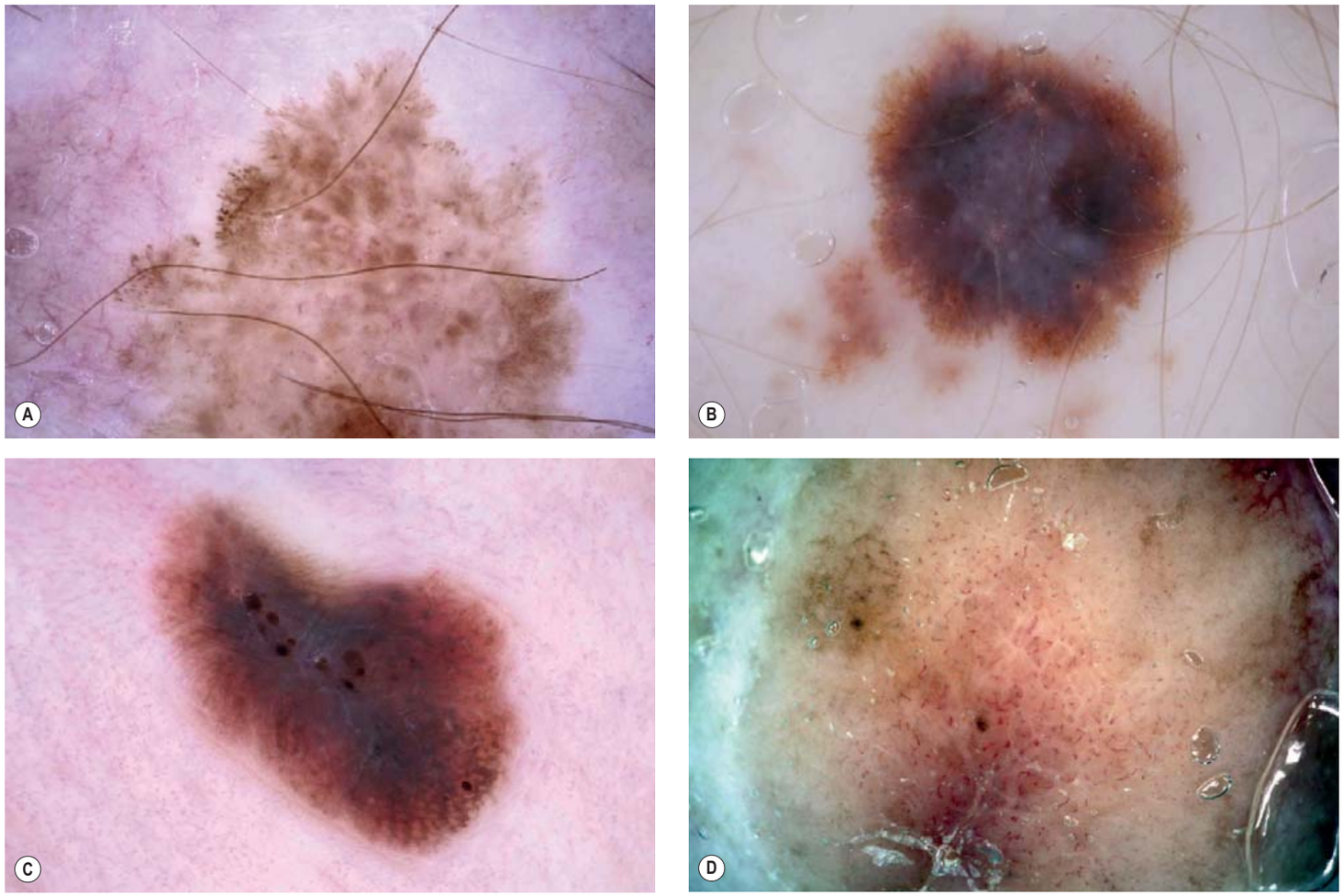


Fig. 113.24 Dermoscopic appearance of primary cutaneous melanomas. A Superficial spreading melanoma (SSM) with striking asymmetry, and streaks at the periphery. The latter have also been called radial streaming and pseudopods. **B** SSM with streaks and blue-whitish veil. **C** SSM with streaks, blue-whitish veil, and irregular blotches. **D** Dermoscopy of a clinically amelanotic melanoma (Fig. 113.19) reveals some pigmented globules that allow one to identify the tumor as a melanocytic lesion. Dotted, point and linear-irregular vessels are suggestive of melanoma.

It is noteworthy that not all melanomas can be clearly recognized by dermoscopy and that "featureless" melanomas exist[174].

Photography

In high-risk patients, especially those with complex mole patterns, baseline photographs can be a helpful adjunct in the identification of new and changing lesions[183]. The advent of digital photography and computerized image archives has improved the practicality of this approach. The availability of baseline images for comparison, including dermoscopic images, permits the detection of melanomas that are growing or changing without manifesting obvious clinical characteristics, while simultaneously avoiding the excision of stable, albeit clinically concerning, atypical nevi[184].

HISTOPATHOLOGY

Histopathology remains the gold standard for melanoma diagnosis. While most melanomas are readily distinguished from melanocytic nevi based on standard criteria (Table 113.7), some melanocytic lesions remain diagnostically challenging despite the advent of immunohistochemical and molecular techniques. There is significant variability in the application of diagnostic criteria for thin and *in situ* melanomas among pathologists[185].

It has been proposed that melanomas progress through two phases[186]. The first is the *r*adial (horizontal) *g*rowth *p*hase (RGP), characterized by centrifugal spread of neoplastic melanocytes within the epidermis and infiltration of the papillary dermis by single cells or small nests. The second, *v*ertical *g*rowth *p*hase (VGP), is characterized by the presence of dermal nests/nodules of atypical melanocytes that are larger than and/or cytologically distinct from their intraepidermal counterparts. It has been further postulated that the RGP lacks metastatic potential even in the presence of dermal invasion, whereas the VGP correlates with the capacity for metastasis. The major histologic types of melanoma described above differ with regard to the presence and morphology of the RGP.

Typically, cutaneous melanoma (Fig. 113.25)[137,187] is asymmetric, poorly circumscribed, and characterized by nests of melanocytes within the epidermis that are not equidistant from one another, vary in size and shape, and focally become confluent. Within the epidermis, solitary melanocytes predominate over nests. Some solitary melanocytes and nests of melanocytes are found well above the dermal–epidermal junction, at times extending into the upper epidermis, even the cornified layer. These findings define melanoma *in situ* (Fig. 113.26). One element of this histologic asymmetry is the extension of the intraepidermal tumor cells far from the invasive intradermal component. Similar findings are present in the adnexal epithelium of pilosebaceous units and eccrine ducts. Within the dermis, nests of melanocytes do not become smaller with progressive descent (absence of maturation). In parallel, nuclei of melanocytes do not become smaller in deeper portions of the tumor.

Lentigo maligna melanoma differs from the prototypic melanoma by its presence within sun-damaged skin, and the tendency to have little pagetoid spread within the epidermis. Tumor cells show lentiginous spread, i.e. solitary tumor cells predominate over tumor cell nests within the epidermis (Fig. 113.27). The atypical melanocytes are commonly present within the epithelium of adnexal structures, especially

DERMOSCOPIC CRITERIA AND THEIR CORRESPONDING HISTOPATHOLOGIC FEATURES			
Criterion	**Morphologic definition**	**Associated histopathologic changes**	**Diagnosis**
Pigment network	Network of brownish lines over a diffuse tan background	Pigmented rete ridges	Melanocytic lesion
Typical network	Brown-colored, regularly meshed and narrowly spaced network	Regular and elongated rete ridges	Benign melanocytic lesion
Atypical network	Black, brown or gray network with irregular meshes and thick lines	Irregular and broadened rete ridges	Melanoma
Dots/globules	Black, brown and/or gray, round to oval, variably sized structures regularly or irregularly distributed within the lesion	Pigment aggregates within the stratum corneum, epidermis, dermal–epidermal junction or papillary dermis	If regular: benign melanocytic lesion; if irregular: melanoma
Streaks	Irregular, linear structures not clearly combined with pigment network lines at the margins	Confluent junctional nests of melanocytes	Melanoma
Blue-whitish veil	Irregular, confluent, gray–blue to whitish-blue diffuse pigmentation	Acanthotic epidermis with focal hypergranulosis above sheets of heavily pigmented melanocytes in the dermis	Melanoma
Blotches	Black-, brown- and/or gray-colored areas with regular or irregular shape/distribution	Hyperpigmentation throughout the epidermis and/or upper dermis	If regular: benign melanocytic lesion; if irregular: melanoma
Regression structures	White (scar-like) areas, blue (pepper-like) areas or combinations of both	Thickened papillary dermis with fibrosis and/or variable amounts of melanophages	Melanoma
Milia-like cysts	White-yellowish, roundish dots	Intraepidermal horn globules, also called horn pseudocysts	Seborrheic keratosis (occasionally observed in papillomatous melanocytic nevi)
Comedo-like openings	Brown-yellowish, round to oval or even irregularly shaped, sharply circumscribed structures	Keratin plugs situated within dilated follicular openings	Seborrheic keratosis
Leaf-like areas	Brown–gray to gray–black patches revealing a leaf-like configuration	Pigmented, solid aggregations of basaloid cells in the papillary dermis	Basal cell carcinoma
Red–blue lacunas	Sharply demarcated, roundish to oval areas with a reddish, red-bluish, or red–black color	Dilated vascular spaces situated in the upper dermis	Vascular lesion
Vascular structures	Comma-like vessels Arborizing vessels Hairpin vessels Dotted or irregular vessels		Benign melanocytic lesion Basal cell carcinoma Seborrheic keratosis Melanoma

Table 113.6 Dermoscopic criteria and their corresponding histopathologic features. *With permission from Argenziano & Soyer, Lancet Oncol. 2001;2:443–9. © 2001 Elsevier.*

CRITERIA FOR THE HISTOPATHOLOGIC DIAGNOSIS OF MELANOMA
ARCHITECTURAL PATTERN
• Asymmetry • Poor circumscription of intraepidermal melanocytic component • Silhouette of tumor base is uneven (except in nevoid melanoma) • No maturation of melanocytes with progressive descent into the dermis • Nests of melanocytes within the epidermis are not equidistant from one another • Nests of melanocytes vary in size and shape • Some nests of melanocytes become confluent • Scatter of melanocytes above the dermal–epidermal junction • Melanocytes arranged as solitary units predominate over nests within the epidermis • Melanocytes in some nests are not cohesive • Melanocytes extend down adnexal epithelium • Sheets of melanocytes within the dermis • Nests at the base of lesions are occasionally large
CYTOMORPHOLOGY
• Atypical melanocytes (with pleomorphic nuclei) • Mitotic figures • Necrotic melanocytes
OTHER FEATURES
• Signs of regression • Actinic elastosis • "Dusty" melanin within tumor cells • Melanin is not distributed in a uniform fashion • Plasma cells at the base of the lesion

Table 113.7 Criteria for the histopathologic diagnosis of melanoma. *Adapted from Ackerman A, Cerroni L, Kerl H. Pitfalls in Histopathologic Diagnosis of Malignant Melanoma. Philadelphia: Lea & Febiger, 1994.*

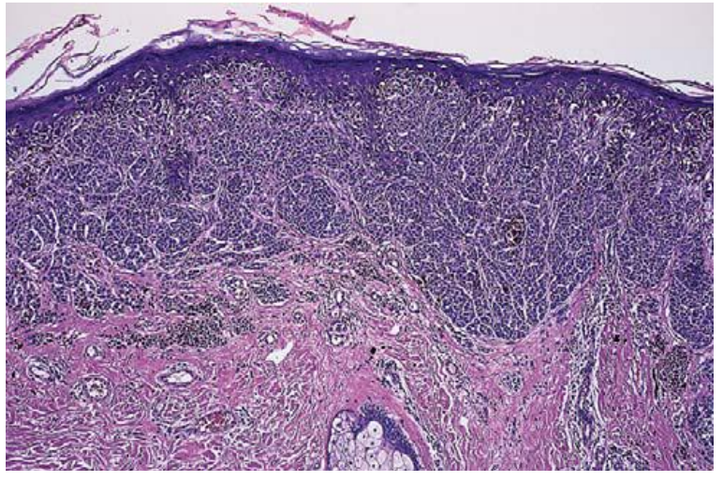


Fig. 113.25 Histopathology of a typical melanoma. Pagetoid melanocytes organized as solitary units and nests varying in size and shape are present throughout the entire epidermis. Neoplastic melanocytes extend into the dermis. There is absence of maturation at deeper levels of the dermis. *Courtesy, Helmut Kerl, MD.*

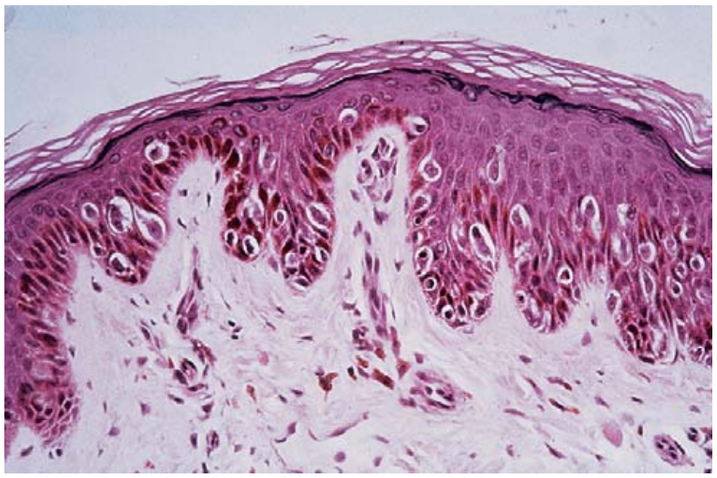


Fig. 113.26 Histopathology of a melanoma *in situ*. Increased number of melanocytes with atypical nuclei not only in the basal zone, but also at the upper levels of the epidermis. *Courtesy, Helmut Kerl, MD.*

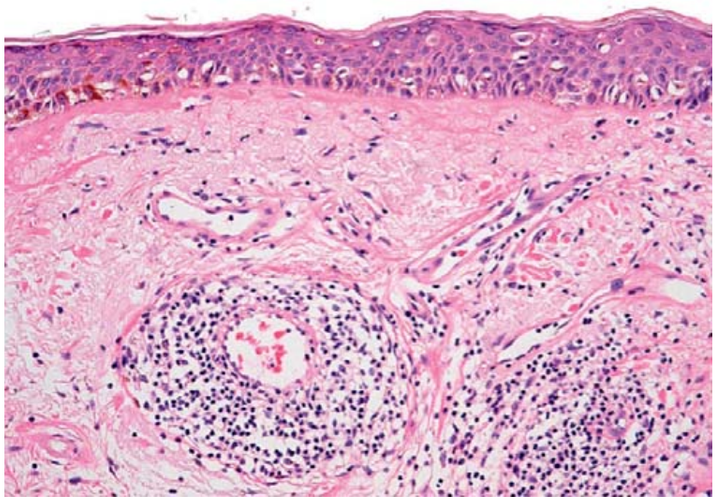


Fig. 113.27 Histopathology of a lentigo maligna melanoma. Proliferation of atypical melanocytes within the epidermis, with single cells predominating over nests. Note the flattened appearance of the epidermis and the solar elastosis in the dermis. *Courtesy, Lorenzo Cerroni, MD.*

along the outer root sheath of hair follicles. The invasive component is more often composed of spindle cells. Desmoplastic stromal change and neurotropism of tumor cells are additional findings. Epidermal atrophy and signs of solar elastosis are often observed in the upper dermis.

ALM often has a proliferation of atypical melanocytes within the basal layer of a hyperplastic epidermis, i.e. a lentiginous spread of single melanoma cells. Atypical melanocytes are arranged singly and in irregularly shaped nests at all levels of the epidermis ("pagetoid scatter"), with predominance of single cells. In the cornified layer, numerous melanocytes and melanin granules are found in a diffusely scattered distribution (Fig. 113.28). Notably, melanomas in volar and subungual sites display strikingly dendritic melanocytes.

Microstaging

Of the histologic features of a primary cutaneous melanoma, the Breslow depth or tumor thickness (depth of invasion) is the strongest predictor of survival. Melanoma thickness is measured in millimeters from the top of the granular cell layer of the epidermis (or the base of an ulcer) to the deepest point of tumor penetration, using an ocular micrometer (Fig. 113.29). In addition to tumor thickness, a number of other histologic features should be noted (Table 113.8)[188]. Tumor thickness, ulceration, and mitoses/mm^2 are major determinants of T stage

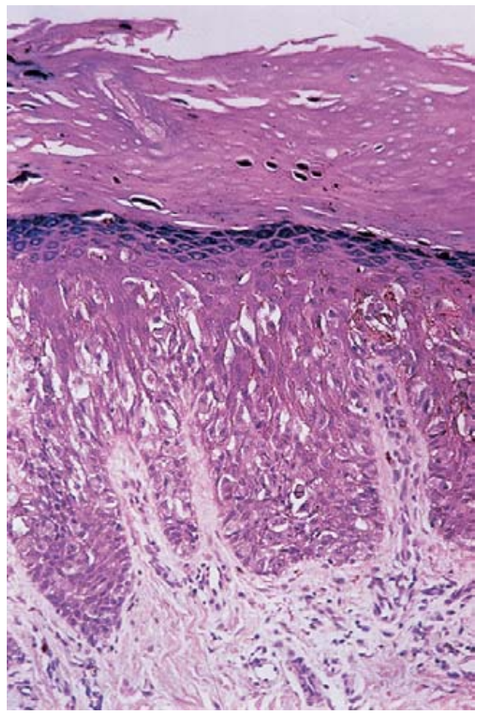


Fig. 113.28 Histopathology of an acral melanoma. Atypical melanocytes are scattered throughout the hyperplastic epidermis including the cornified layer. Note the presence of dendritic melanocytes. *Courtesy, Helmut Kerl, MD.*

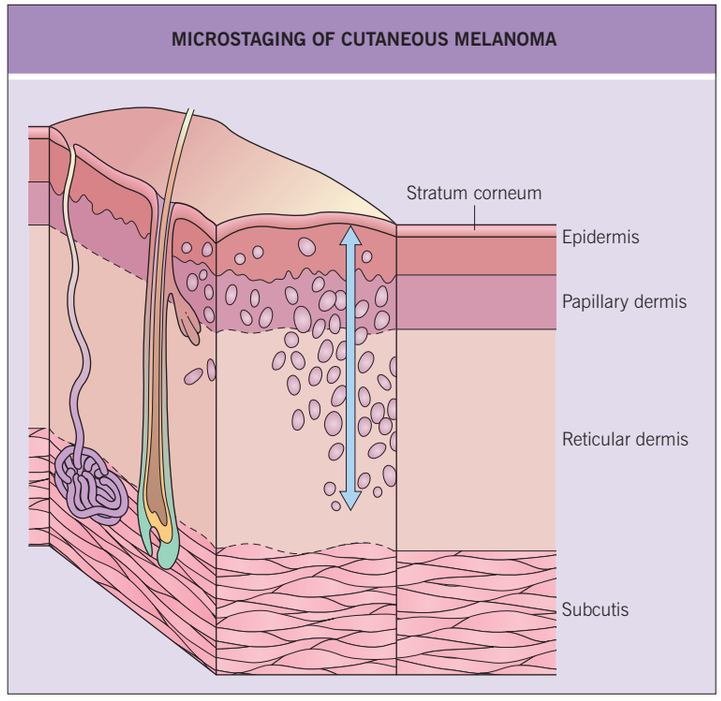


Fig. 113.29 Microstaging of melanoma: Breslow tumor thickness. Breslow method: measure from the granular layer of the epidermis to the deepest part of the tumor.

in the current staging system, with ulceration defined as the absence of an intact epidermis overlying a major portion of the primary tumor, based on microscopic examination.

Immunohistopathology

Immunohistochemical studies can be helpful in the assessment of diagnostically difficult cases of primary melanoma as well as in the assessment of metastatic tumors of unknown origin (see Table 0.11). However, the diagnosis of cutaneous melanoma is made on the basis of routine H&E staining, as no immunostaining pattern exists which on its own allows a clear differentiation between benign and malignant

lesions. A wide range of melanoma-associated antigens have been identified for which immunohistochemical stains are available. Melanocyte differentiation antigens, e.g. gp100 (HMB45), tyrosinase and Melan-A/MART-1, are useful for distinguishing cells of melanocytic lineage from other tumor types, for visualizing the full extent of tumor cells of a primary melanoma, and for the identification of minute foci of melanoma in sentinel lymph node biopsies. Staining for S100, a calcium-binding protein, has high sensitivity for melanocytes and melanoma, but this protein is also expressed by Langerhans cells, other dendritic cells, eccrine glands, Schwann cells, chondrocytes and adipose tissue. Of note, S100 is the most reliable marker for identifying the spindled component of a melanoma. HMB45, which recognizes the melanosome-specific glycoprotein gp100/Pmel17, has high specificity for melanocytes and nevus cells, but its utility is limited by its heterogeneous staining pattern and limited sensitivity. Staining for MITF expression can assist in distinguishing solar lentigo from lentigo maligna. The use of panels of these antibodies improves sensitivity and specificity, but remains diagnostically imperfect[189].

CUTANEOUS MELANOMA – COMPONENTS OF THE HISTOPATHOLOGIC REPORT
MANDATORY
Diagnosis of malignant melanoma
Thickness (Breslow depth)
Ulceration
Mitoses/mm^2 (for melanomas ≤ 1 mm)
Margins
DESIRABLE
Histopathologic subtype of melanoma
Level of invasion (Clark), if mitotic rate can not be determined (T1 melanomas)
Regression, tumor-infiltrating lymphocytes, presence of plasma cells
Vascular invasion
Microscopic satellites
Associated nevus

Table 113.8 Cutaneous melanoma – components of the histopathologic report.

Molecular Analysis

Some cutaneous melanomas are very difficult to diagnose, and the differentiation between atypical Spitz nevus and spitzoid melanoma or between deep penetrating blue nevus and melanoma can be difficult based upon histopathology. It has been suggested that these lesions be called melanocytic tumors of uncertain malignant potential (MELTUMP)[190]. In such cases, comparative genomic hybridization and fluorescence *in situ* hybridization may be helpful[147].

Comparative genomic hybridization (CGH) is a method for the genome-wide assessment of DNA copy number changes in tumor cells[191]. Fluorescence-labeled tumor DNA and reference DNA from a healthy donor are hybridized onto metaphase chromosomes or on arrays of oligonucleotides (array-CGH) (Fig. 113.30). From the relative fluorescence copy number, gains or losses within the tumor can be calculated (see Ch. 3). The oligonucleotide spots on the array can be mapped to the respective position within the human genome. CGH analysis of benign melanocytic nevi typically shows no clonally expanded chromosomal aberrations, while in the vast majority of melanomas, gains and losses of particular segments of chromosomes or entire chromosomes are found. As an exception, ~20% of Spitz nevi show an increase in copy number of chromosome 11p, an aberration not found in melanoma. CGH can be used as an adjunct for the difficult-to-diagnose melanocytic tumors described above.

Fluorescence *in situ* hybridization (FISH) can also assist in differentiating between benign and malignant melanocytic tumors. FISH assays focus on chromosomal loci that are frequently affected by copy number changes in melanoma. Studies have shown that a FISH assay that targets 6p25, 6q23, 11q13 and CEP6 (centromere of chromosome 6) discriminates between benign nevi and melanoma with high sensitivity and specificity[192,193]. The disadvantage of this approach is that only gains and losses involving two chromosomes are detected, whereas CGH examines the entire genome.

STAGING

Prior staging systems categorized melanoma into local, regional or distant disease, which strongly correlates with survival. The present

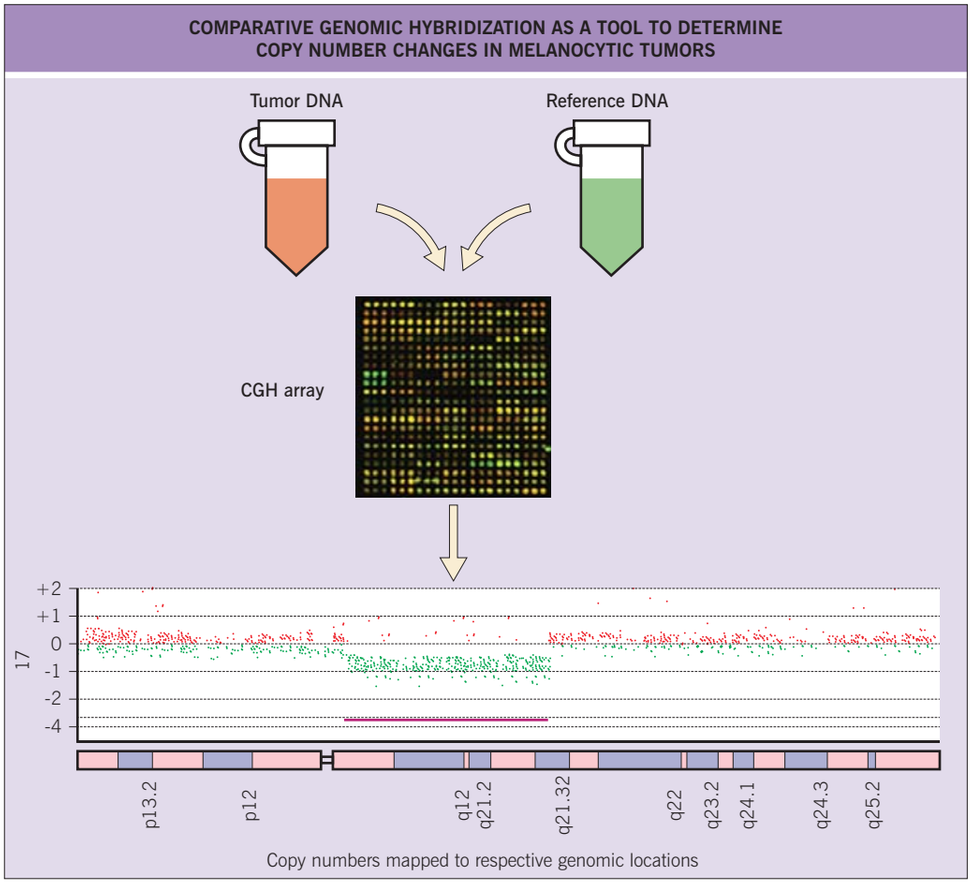


Fig. 113.30 Comparative genomic hybridization (CGH) as a tool to determine copy number changes in melanocytic tumors. Total genomic DNA is isolated from the tumor and from healthy reference samples, and labeled with fluorescent dyes. The mixture of test and reference DNA is hybridized onto a genome-wide microarray of oligonucleotides. Tumor and reference DNA bind to the complementary oligonucleotides and the ratio of their fluorescence intensities is approximately proportional to the ratio of the copy numbers of the corresponding DNA sequences in the tumor and reference genomes. The copy number ratio can be mapped to the genomic location of the array element.

MELANOMA TNM CLASSIFICATION		
T classification	**Thickness**	**Ulceration status/ Mitoses**
Tis	NA	NA
T1	≤1.0 mm	a: Without ulceration and mitosis <1/mm^2 b: With ulceration or mitoses ≥1/mm^2
T2	1.01–2.0 mm	a: Without ulceration b: With ulceration
T3	2.01–4.0 mm	a: Without ulceration b: With ulceration
T4	>4.0 mm	a: Without ulceration b: With ulceration
N classification	**Number of metastatic nodes**	**Nodal metastatic mass**
N0	0	NA
N1	1 node	a: Micrometastasis* b: Macrometastasis†
N2	2–3 nodes	a: Micrometastasis* b: Macrometastasis† c: In-transit met(s)/ satellite(s)‡ without metastatic node(s)
N3	4 or more metastatic nodes, matted nodes, or in-transit met(s)/satellite(s)‡ with metastatic node(s)	
M classification	**Site**	**Serum lactate dehydrogenase**
M0	No distant metastases	NA
M1a	Distant skin, subcutaneous or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases Any distant metastasis	Normal Elevated

*Micrometastases are diagnosed after sentinel or elective lymphadenectomy.
†Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.
‡In-transit metastases are >2 cm from the primary tumor but not beyond the regional lymph nodes, while satellite lesions are within 2 cm of the primary.

Table 113.9 Melanoma TNM classification. For defining T1 melanomas, Clark level of invasion is used as default criterion only if mitotic rate cannot be determined. Histologic evaluation of lymph nodes must include at least one immunohistochemical marker (e.g. HMB45, Melan-A/MART-1). NA, not applicable. *Adapted from Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009;27: 6199–6206. Reprinted with permission from the American Society of Clinical Oncology.*

STAGE GROUPINGS FOR CUTANEOUS MELANOMA							
	Survival (%)*	**Clinical staging†**			**Pathologic staging‡**		
		T	**N**	**M**	**T**	**N**	**M**
0		Tis	N0	M0	Tis	N0	M0
IA	97	Tia	N0	M0	Tla	N0	M0
IB	93	T1b T2a	N0	M0	T1b T2a		
IIA	82 79	T2b T3a	N0	M0	T2b T3a	N0	M0
IIB	68 71	T3b T4a	N0	M0	T3b T4a	N0	M0
IIC	53	T4b	N0	M0	T4b	N0	M0
III§		Any T	N1 N2 N3	M0			
IIIA	78				T1-4a T1-4a	N1a N2a	M0
IIIB	59				T1-4b T1-4b T1-4a T1-4a T1-4a	N1a N2a N1b N2b N2c	M0
IIIC	40				T1-4b T1-4b T1-4b Any T	N1b N2b N2c N3	M0
IV	9–27‖	Any T	Any N	Any M1	Any T	Any N	Any M1

*Approximate 5-year survival (%), modified from Balch et al.[194]
†Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.
‡Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic stage 0 or stage IA patients are the exception.
§There are no stage III subgroups for clinical staging.
‖Higher survival rate associated with normal serum LDH levels and lower rate with elevated LDH levels.

Table 113.10 Stage groupings for cutaneous melanoma. *Adapted from Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009;27:6199–6206. Reprinted with permission from the American Society of Clinical Oncology.*

tumor–node–metastases (TNM) staging system was introduced by the American Joint Committee on Cancer (AJCC) in 2000, and then revised in 2009 (Table 113.9)[66,194].

The three main factors that determine the **T** classification are: (1) Breslow depth; (2) primary tumor mitotic rate; and (3) histopathologic evidence of ulceration. The **N** classification is determined by the extent of tumor within the regional lymph node basin. The most important prognostic factors in the **N** classification are: (1) the number of metastatic lymph nodes; (2) the presence of microscopic versus macroscopic nodal tumor burden; and (3) the presence or absence of satellite or in-transit metastases. The **M** classification refers to metastatic disease and is based on two important features: (1) the anatomic site of the distant metastases; and (2) the serum lactate dehydrogenase (LDH) level. When the **T**, **N**, **M** classifications are combined, placement into one of the four stages in the current AJCC staging system can be accomplished (Table 113.10; www.cancerstaging.org/staging/index.html) and then treatment can be determined and survival predicted (Fig. 113.31).

Stage 0 represents melanoma *in situ*. Stages I and II represent localized disease, but a distinction is often made between low-risk stage I patients (Breslow depth <1 mm) and higher-risk stage II patients (>2 mm or >1 mm plus ulceration). Stage III represents regional nodal and/or intralymphatic metastases. Stage IV represents distant metastases.

PROGNOSIS

The prognosis of a patient with melanoma depends upon the stage at diagnosis. Prognosis for patients with localized primary cutaneous melanoma and no nodal or distant metastases (stage I or II) is generally favorable. Patients with stage IA melanoma have a 10-year survival expectancy of >95%, whereas patients with thick (>4 mm) melanoma and ulceration (T4b) have a 10-year survival rate of ~50%. In addition to the microstaging variables discussed above, clinical variables with prognostic significance in stage I/II disease include sex, age and anatomic site[65,195,196] (Table 113.11). For example, women with stage I/II disease tend to have a better survival rate than men. Location of the primary melanoma on the trunk, head or neck portends a poorer prognosis than when located on the extremities.

Stage III melanoma patients are a heterogeneous group with respect to their risk for distant metastases and melanoma-specific mortality.

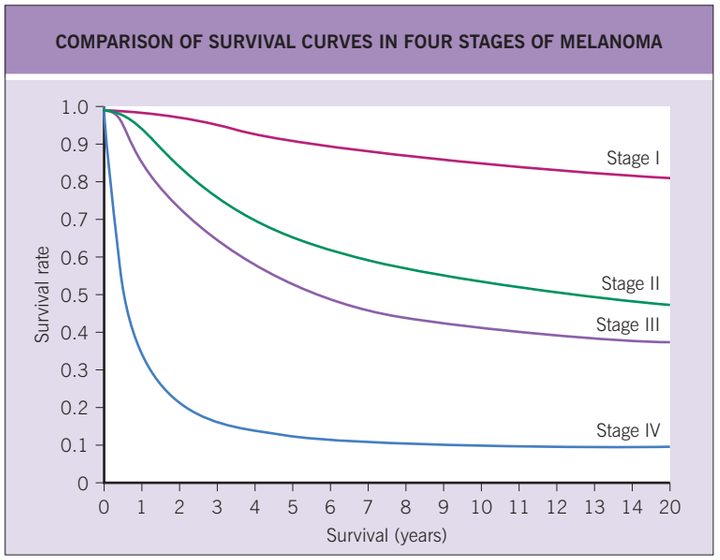


Fig. 113.31 Comparison of survival curves in four stages of melanoma.
Redrawn from Balch CM. Melanoma of the skin. In: Edge SB, Byrd DR, Compton CC, et al., eds. AJCC Cancer Staging Manual, 7th edn. New York: Springer Verlag, 2009.

MAJOR INDEPENDENT PROGNOSTIC FACTORS FOR SURVIVAL IN MULTIVARIATE ANALYSES

Prognostic factor	Commentary
Tumor thickness	≤1 mm, low risk; >1 mm, higher risk melanoma
Ulceration	Worse prognosis with ulceration
Mitotic rate	Worse prognosis with ≥1 mitoses/mm^2
Age	Worse prognosis with higher age
Sex	Men have poorer prognosis (only for localized disease)
Anatomic site	Trunk, head and neck associated with poorer prognosis than extremities
Number of involved lymph nodes	Cut-off points: 1, 2–3, 4 or more lymph nodes (see Table 113.9)
Regional lymph node tumor burden	Macroscopic (palpable) nodal metastases with poorer prognosis than microscopic (non-palpable) nodal metastases
Site of distant metastases	Visceral metastases associated with poorer prognosis than non-visceral metastases (skin, subcutaneous, distant lymph nodes)

Table 113.11 Major independent prognostic factors for survival in multivariate analyses.

The 5-year survival rates range from 70% for patients with non-ulcerated melanomas and a single nodal micrometastasis (T1–4N1aM0), to a low of 39% for patients with ulcerated primary melanomas and four or more lymph nodes with clinically apparent metastases (T1–4N3M0)[65]. Major prognostic factors in this group are the number of metastatic lymph nodes and the tumor burden. Tumor burden is reflected by whether the nodal metastases are clinically occult (micrometastases, as detected by sentinel or elective lymph node dissection) or clinically palpable (macrometastases).

In stage IV patients, the major prognostic factor is the site of distant metastases, with a poorer prognosis for visceral than for non-visceral (e.g. skin, subcutaneous, and distant lymph node) metastases. The median survival time for stage IV patients is 9 months, and the estimated 5-year survival rate is 10% when the serum LDH level is abnormally elevated. The main variables that predict survival are initial site of metastasis, disease-free interval before distant metastases, and stage of disease preceding distant metastases.

EVALUATION OF A PATIENT WITH SUSPECTED MELANOMA

Medical History

A thorough medical history should be taken, focusing especially on risk factors for the development of melanoma (see above), such as a personal or family history of melanoma, skin phototype I/II, extensive tanning bed use or PUVA treatment, childhood history of sunburns, genetic syndromes with skin cancer predisposition (e.g. xeroderma pigmentosum), and iatrogenic or acquired immunosuppression (e.g. solid organ transplant recipients, HIV infection). A detailed history of the specific lesion in question should be obtained. Was the lesion present at birth? Did the lesion develop in a pre-existing mole? Did it change in size or shape? Did it change in color or ulcerate? Was there itching or bleeding? What is the time course of change? Are there systemic symptoms such as weight loss, fatigue, headache or cough?[197] Other family members should be screened if either melanoma or atypical melanocytic nevi are present. All individuals at risk should be educated about the clinical features of melanoma and about sun protection measures.

Skin Investigation and Clinical Diagnosis

A total body skin examination (TBSE) has to be performed. An estimation of the total number of melanocytic nevi and of the number of clinically atypical melanocytic nevi should be noted, as well as the presence of congenital nevi. Atypical pigmented lesions should be examined by dermoscopy. Any lesion suspected of being melanoma should undergo biopsy. Excisional biopsy with narrow 1–2 mm margins is the preferred method of biopsy, as it prevents sampling error (e.g. missing a focus of melanoma arising in a precursor benign lesion) and enables the pathologist to assess the overall architecture of the lesion and accurately microstage the tumor. Superficial shave biopsies should be avoided, but deeper saucerization biopsies may be used for flat lesions or if the clinical suspicion of cutaneous melanoma is not high. The specimen should be sent to an individual experienced in the diagnosis of melanocytic tumors. A second opinion is sometimes necessary for difficult cases. Examination of lymph node basins should also be routinely performed.

Laboratory Investigations and Imaging

The evidence-based clinical practice guidelines (2008) for the management of melanoma in Australia and New Zealand had the following recommendation: following the diagnosis of localized primary cutaneous melanoma (stages I, II), routine laboratory investigations and imaging (e.g. chest radiography) are not required for asymptomatic patients. Additional investigators noted that such tests have limited, if any, value in the initial evaluation of asymptomatic patients with primary cutaneous melanoma 4 mm or less in thickness[198]. An American Academy of Dermatology task force recommended that initial imaging studies and blood work should be optional and most appropriately directed based on findings of a thorough medical history and physical examination[199]. In a study involving more than 200 asymptomatic patients with localized melanomas initially examined with chest radiography, the true-positive radiograph rate for lung metastases was 0%, with a false-positive rate of 7%[198].

A simple and effective examination technique which was first introduced in Europe is lymph node ultrasound[200]. The scar of the primary cutaneous melanoma, the lymphatic drainage areas, and the regional lymph node basin are examined by ultrasound with a 7.5–10 MHz probe. In one-third of patients, metastases can be detected before they become palpable with this technique. In some European countries, lymph node ultrasound is recommended for staging and follow-up of patients with melanomas >1 mm in thickness[201,202].

Serum markers for metastatic melanoma have been examined and the two most frequently employed markers are protein S100B and melanoma inhibitory activity (MIA). Comparative studies found a higher diagnostic sensitivity for protein S100B than for MIA[203]. A large US study found that for patients with surgically resected high-risk melanoma, a high baseline or increasing serum S100B level was an independent prognostic marker of risk for mortality[204]. Primarily in Europe, protein S100B is currently the most widely used serum marker

SYMPTOMS AND DIAGNOSTIC TESTS FOR METASTATIC MELANOMA		
Metastatic site (TNM)	**Symptoms**	**Diagnostic tests***
Skin, soft tissue metastasis (TxNxM1a), in-transit metastasis (TxN2cM0)	Papules or nodules that vary in color from skin-toned to pink–red to blue, brown or black; secondary ulceration or bleeding	Histopathologic examination
Brain metastasis (TxNxM1c)	Headache, nausea, seizures, focal weakness, visual disturbance, paresthesias	MRI, CT or PET-CT
Lung metastasis (TxNxM1b)	Chest pain, dyspnea, cough, hemoptysis	Chest radiograph, CT or PET-CT
Gastrointestinal or liver metastasis (TxNxM1c)	• GI: abdominal pain, signs of anemia (e.g. fatigue, chest pain), vomiting, constipation, melena • Liver: abdominal pain, jaundice	• CBC, CT or PET-CT; colonoscopy • Liver function tests, LDH; CT, PET-CT or MRI
Bone metastasis (TxNxM1c)	Pain, spontaneous fractures	Bone scan or PET-CT

*Always include a thorough medical history and physical examination as well as complete blood count (CBC) and blood chemistry including lactate dehydrogenase (LDH). Special procedures such as detection of soluble melanoma markers (e.g. S100, melanoma inhibitory activity [MIA] protein) are performed at selected melanoma referral centers, especially in Europe.

Table 113.12 Symptoms and diagnostic tests for metastatic melanoma. CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

SURGICAL TREATMENT OF PRIMARY CUTANEOUS MELANOMA		
Tumor thickness	**Excision margins (cm)**	**Comments**
In situ	0.5	Lentigo maligna of the face may be excised with 1 cm margins (especially when lesions are >1.5–2 cm in diameter) or treated by Mohs micrographic surgery or radiotherapy; postoperative topical imiquimod is often used
≤1 mm	1.0	Mohs micrographic surgery may be necessary in acral and facial melanomas
1.01–2 mm	1.0–2.0	
>2 mm	2.0	

Table 113.13 Surgical treatment of primary cutaneous melanoma. Evidence from available randomized trials is insufficient to address the optimal margins for the excision of primary cutaneous melanoma, but multiple expert international committees have produced fairly consistent guidelines, as summarized here. Of note, further investigative efforts will likely alter the standards of care over time. *Adapted from Sladden MJ, et al. Surgical excision margins for primary cutaneous melanoma. Cochrane Database Syst Rev. 2009;(4):CD004855.*

for the detection of melanoma metastasis, both at the time of staging and in conjunction with surveillance examinations, in patients with elevated risk for recurrence[201,202]. Of note, detection of circulating melanoma cells in the blood by tyrosinase/MART-1 reverse transcription–polymerase chain reaction (RT-PCR) was found by several investigators to have no predictive value.

Investigation of stage III/IV melanoma patients may include radiologic investigations such as CT of the chest, abdomen and pelvis and CT or MRI of the brain as well as positive emission tomography (PET)-CT (Table 113.12). For routine examinations and staging, CT remains the imaging technique of choice. Whereas CT is the most sensitive technique for the detection of lung metastases, intra-abdominal and soft tissue metastases are better detected by MRI, and the latter is often chosen for special clinical situations such as deciding on the operability of soft tissue metastases[205]. A significant advance in imaging for metastasis detection is PET scanning using 18F-fluorodeoxyglucose (FDG)[206]. It is based on the assumption that melanoma metastases have a higher metabolic rate than does normal tissue and utilize more glucose. PET is now being combined with CT technology and whole body PET-CT is the most sensitive technique for the detection of melanoma metastasis[207]. As PET-CT is an expensive examination technique, it should not be used indiscriminately.

MANAGEMENT

Management of the Primary Melanoma (Stage I and II)

Following histologic diagnosis, the primary cutaneous melanoma site should be re-excised with an appropriate margin determined by the Breslow depth (Table 113.13). The rationale for excisional margins is based on the capacity of melanoma cells to migrate away from the tumor origin, i.e. melanoma may extend wider or deeper than is visibly apparent. The major goal is to prevent local recurrence or persistent disease.

Excisional margins for primary cutaneous melanoma have changed remarkably over the past several decades. Until the 1980s, melanoma was often excised with a margin of 5 cm, independent of its tumor thickness. A WHO randomized trial demonstrated that 1 cm excisional margins were safe and effective for melanomas with a Breslow depth <1 mm[208]. A randomized trial focusing on intermediate-thickness melanoma (1 to 4 mm in depth) found that 2 cm margins were as effective as 4 cm margins in preventing local recurrences[209]. While current randomized trial evidence is insufficient with regard to optimal excisional margins, expert international committees have produced fairly consistent guidelines, as summarized in Table 113.13[202,210,211].

Margins of excision are also limited by surgically difficult anatomic sites such as the distal extremities, the mucous membranes and the face. Often, an individualized surgical approach must be undertaken[212]. For instance, lentigo maligna melanoma on the face may necessitate narrower margins and Mohs micrographic control of excisional margins may be employed to conserve anatomic structures. Lentiginous acral and mucosal melanomas are often poorly defined and multifocal with discrepancies between the clinically visible and histopathologic margins. As a result, local recurrences are more frequent in these types of melanoma. Therefore, removal can be achieved with increased safety margins (at least 1 cm) or by narrow margins with micrographic control (e.g. in subungual melanoma)[213,214,215].

Treatment of lentigo maligna with topical imiquimod rather than surgical excision is an area of debate. While some clinicians limit its use as a primary therapy to elderly patients with serious comorbidities or facial lesions whose surgical removal would lead to mutilation, others use it more routinely. Initial case series reported histologic clearance rates of 80-90%, but a recent study from Australia observed histologic clearance in only 53% of patients (20/38) when used for 12 weeks following excision of lentigo maligna with 5 mm margins[215a].

Local Recurrences

Local recurrence is defined as any recurrence within 2 cm of the scar from the primary melanoma excision[66] (Fig. 113.32). Recurrence results from extension of the primary tumor or intralymphatic spread. The overall risk of recurrence is approximately 4%, and is increased in thicker or ulcerated tumors as well as melanomas located on the head and neck or distal lower extremity[216]. Local recurrence is strongly associated with the development of in-transit, regional and distant metastases but it is not an independent prognostic indicator of survival in multivariate analysis[216]. There is evidence that patients with local recurrence, satellites and in-transit metastases have similar outcomes[217]. There is no evidence that patient survival is adversely affected if local recurrence results from incomplete excision of the primary melanoma (i.e. persistent disease), provided that the residual tumor is *in situ* or in a radial growth phase, is promptly re-excised, and there is no distant disease at the time of re-excision[218].

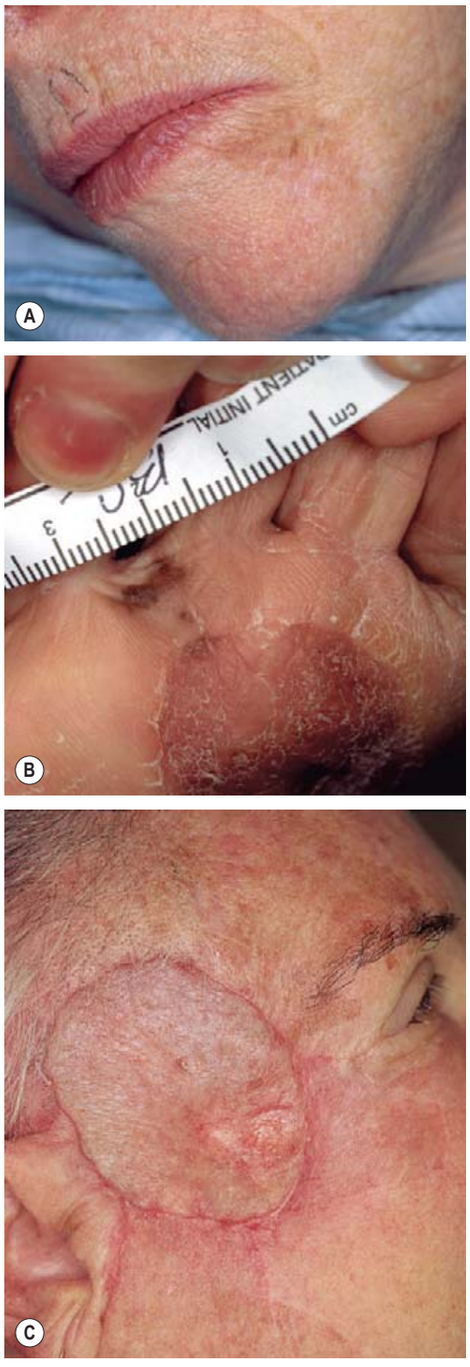


Fig. 113.32 Local recurrence of cutaneous melanoma. A Recurrent lentigo maligna along the upper lateral margin of the excision of the chin; inked lesion on the central upper lip is an actinic keratosis. **B** Recurrent *in situ* acral lentiginous melanoma at the 10 o'clock position on the split-thickness skin graft. **C** Amelanotic nodular recurrence of a desmoplastic melanoma within the skin graft. *Courtesy, Jean L Bolognia, MD.*

Management of Regional Metastatic Melanoma (Stage III)

Metastatic spread of melanoma is primarily regional in about 70% of patients, i.e. confined to the site of the primary melanoma and its draining lymph nodes. For example, metastasis may manifest as a clinically occult lymph node micrometastasis, as a rapidly growing clinically evident lymph node macrometastasis, or as in-transit metastasis.

Elective lymph node dissection and sentinel lymph node biopsy

Approximately 20% of patients with a cutaneous melanoma >1 mm in depth, plus no evidence (clinically or radiologically) of detectable nodal disease at presentation, will have microscopic lymph node involvement[219]. On the basis of a presumed migration of melanoma cells in an orderly fashion towards the draining lymph node, surgical resection of regional lymph nodes in all patients with intermediate- and high-risk tumors was previously recommended and was referred to as "elective lymph node dissection (ELND)". However, four multicenter, randomized, prospective trials in patients with primary melanoma did not show a survival benefit for patients treated with ELND plus wide re-excision as compared to wide re-excision alone[220–223].

As a consequence, a less traumatic procedure to identify regional metastatic disease was introduced, called the sentinel lymph node biopsy (SLNB)[224]. SLNB is based on the finding that the cutaneous site of the melanoma drains to one or more lymph node basins and particularly to one (or two but rarely more) lymph node, the sentinel node, which is the first site of deposition of metastatic cells. The draining lymph node basins for a given melanoma site and the approximate location of the sentinel node within that basin are identified and marked on the overlying skin preoperatively during lymphoscintigraphy performed in the nuclear medicine department. Intraoperatively, typically in conjunction with the wide local excision[206], technetium sulfur colloid and blue dye are injected into the skin surrounding the melanoma biopsy site. A small incision is made at the previously marked site overlying the sentinel node and a hand-held gamma counter and visual inspection are used to identify the "hot, blue" sentinel node(s), which is selectively biopsied and examined by serial sectioning using H&E stains combined with immunohistochemistry (S100, HMB45). If melanoma micrometastasis is identified, then a complete regional lymph node dissection is normally recommended. As the therapeutic benefit of complete lymphadenectomy after positive sentinel node(s) has not been demonstrated in clinical trials (as often the remainder of the lymph nodes have no evidence of metastasis), two large multicenter trials are presently being conducted to compare complete lymphadenectomy versus observation with lymph node ultrasound examinations in patients with lymph node micrometastasis.

Sentinel lymph node biopsy, followed by complete lymphadenectomy in the case of positive sentinel node(s), has meanwhile become a standard procedure in the staging and prognostication of primary cutaneous melanoma ≥1 mm in thickness. Numerous publications have identified the status of the sentinel lymph node as a strong prognostic factor for survival and recurrence[225–227], and the AJCC included it in the latest staging system for cutaneous melanoma (see Tables 113.9 & 113.10)[194]. In 2006, the randomized Multicenter Selective Lymphadenectomy Trial (MSLT-1) confirmed the prognostic value of SLNB, and found improved disease-free survival for the SLNB group and improved survival for SLNB-positive patients with complete lymphadenectomy as compared to patients developing macroscopic nodal metastasis in the control group, but no difference in overall survival[228].

Thus, based upon current data, SLNB is useful as a diagnostic and prognostic tool, but its usefulness as a therapeutic modality has not been established. Also, given the potential morbidity (chronic lymphedema) associated with the completion lymphadenectomy that is usually performed if the SLNB is positive, the question arises as to why SLNB should even be performed. There are basically four reasons to proceed with a SLNB in a person with a primary cutaneous melanoma >1 mm thick who has no clinically involved lymph nodes: (1) to obtain the most complete and accurate diagnostic and staging information possible for a patient who desires such data; (2) to institute early therapeutic complete lymph node dissection if there is evidence of micrometastases, providing improved disease-free survival but not overall survival; (3) to offer adjuvant therapy (interferon-α may slightly improve overall survival in selected patients); and (4) to gain entry into a clinical trial for new adjuvant therapies. Reasons *not* to proceed with SLNB include: (1) the patient is not interested in a complete lymphadenectomy or adjuvant therapy; and (2) he or she is content not knowing whether micrometastases exist.

Skin satellite and in-transit metastases

Satellite and in-transit metastases are recurrences that generally occur in the lymphatic vessels more proximally relative to the primary cutaneous melanoma and toward the regional lymph nodes. Patients generally have a poorer prognosis with frequent development of distant metastasis. However, occasionally, despite the development of numerous in-transit metastases, the disease remains localized to a lower extremity for years. The goal of treatment is maintenance of local control.

The treatment of choice for skin metastases is surgical, but systemic therapies should be considered if numerous or extensive lesions are not

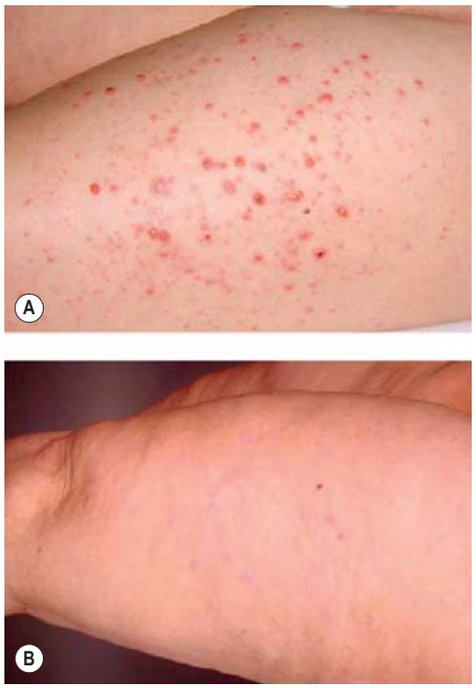


Fig. 113.33 Intralesional interleukin-2 (IL-2) treatment. A Multiple in-transit metastases were treated with intralesional low-dose IL-2 for 6 weeks. **B** Complete remission after 1 year, which persisted during the follow-up period of 7 years.

DOSAGE SCHEDULES FOR ADJUVANT THERAPY WITH INTERFERON-α

Schedule	Dose	Frequency	Duration	Indication
Low-dose	3 million IU sc	Days 1, 3 & 5 every week	18 months	Stage II–III
High-dose				
– Initiation	20 million IU/m^2 IV rapid infusion	Days 1–5 every week	4 weeks	Stage III
– Maintenance	10 million IU/m^2 sc	Days 1, 3 & 5 every week	11 months	Stage III
Pegylated				
– Initiation	6 mcg/kg body weight sc	Day 1 every week	8 weeks	Stage III
– Maintenance	3 mcg/kg body weight sc	Day 1 every week	Total 5 years	Stage III

Table 113.14 Dosage schedules for adjuvant therapy of melanoma with interferon-α. IV, intravenous; sc, subcutaneous.

amenable to surgery. For multiple lesions on a limb, isolated limb perfusion with melphalan, with or without tumor necrosis factor (TNF), has palliative value[229,230]. In stage III patients with satellite/in-transit metastases, the procedure may be curative, as indicated by reported 5- and 10-year survival rates of 40% and 30%, respectively. Alternative options include cryotherapy, laser therapy, and experimental approaches such as intralesional/topical IL-2 (Fig. 113.33), electrochemotherapy, miltefosine, interferon-α and imiquimod[231].

Clinically identified lymph node metastases

If lymph node metastasis is diagnosed clinically or by imaging techniques, complete lymph node dissection is considered standard therapy, which consists of an anatomically complete dissection of the involved nodal basin[202,210,211]. The extent of complete lymph node dissection is often modified according to the anatomic area of lymph node involvement, e.g. in the setting of inguinal lymphadenopathy, a deep groin dissection is recommended if the PET or pelvic CT scan reveals iliac and/or obturator lymphadenopathy.

Adjuvant therapy

The goal of adjuvant therapy is the elimination of clinically unapparent micrometastases. The major target population for adjuvant therapy is patients with resected high-risk stage II or III melanoma. Some trials have also targeted resected stage IV patients. A number of postsurgical adjuvant approaches have been tested, including systemic chemotherapy and immunotherapy using microbial agents such as bacille Calmette-Guérin (BCG) or *Corynebacterium parvum*[232]. None of these approaches were successful in randomized controlled trials.

The current recommendation is to include appropriate patients in well-controlled clinical studies in order to obtain valid data leading to recommendations regarding future adjuvant therapies. Currently, the major candidates for adjuvant therapy are recombinant biological response modifiers, in particular the intensively studied IFN-α. IFN-α is a type I member of the interferon family of proteins and has pleiotropic functions including induction of MHC class I expression, activation of natural killer (NK) cells and the maturation of dendritic cells; some of its activities may have direct or indirect antitumor effects[233]. It is important to distinguish high-dose IFN-α therapy with the aim of reaching maximally tolerated dosage (20 MIU/m^2 intravenously 5 days per week during the initiation phase, followed by 10 MIU/m^2 subcutaneously three times per week) from low-dose IFN-α therapy which is much better tolerated in terms of side effects (typically 3 MIU subcutaneously three times per week). Treatment regimens with pegylated IFN-α have also been established, which because of its prolonged half-life is given once weekly (Table 113.14).

High-dose IFN-α has demonstrated an improvement in relapse-free and overall survival compared to controls in two studies (ECOG 1684 and ECOG 1694). However, a beneficial effect on overall survival was not seen in a third high-dose IFN-α study (ECOG 1690). A recent study noted the association of the appearance of autoantibodies or clinical manifestations of autoimmunity during IFN-α-2b treatment with significant improvements in relapse-free survival and overall survival[234].

Toxicities from high-dose IFN-α include constitutional (flu-like) symptoms and neuropsychiatric (depression, suicidal intention), hematologic and hepatic side effects[235]. These toxicities have a major impact on the patient's quality of life and lead to dose modifications in two-thirds of patients during the first month of high-dose IFN-α therapy. IFN-α and now pegylated IFN-α are the only FDA-approved adjuvant therapies for melanoma in the US. The use of high-dose IFN-α adjuvant therapy has been questioned, especially in Europe, due to the inconsistent reports of its impact on overall survival and the considerable dose-dependent toxicity. For low-dose IFN-α, randomized studies have consistently reported a benefit with regard to relapse-free survival – and, in one trial, for overall survival – compared to untreated controls[236–238].

The large number of clinical trials with variations in dosage, schedule and duration of IFN-α administration, as well as different patient populations, has prompted several attempts to consolidate and review the available outcome data. A large meta-analysis of the available published data of 6067 patients from randomized clinical trials was reported in 2007, summarizing event-free survival (over 3700 events) and overall survival (over 3000 events) in patients with high-risk melanoma treated with IFN-α adjuvant therapy[239]. Clinical data were sorted by IFN dose: high (20 MIU/m^2), intermediate (5–10 MIU/m^2), low (3 MIU/m^2), and very low (1 MIU/m^2) doses. Groups were also stratified by duration of treatment (<6 months, 12–18 months, or >24 months). Although there was a statistically significant overall survival benefit for treatment of patients with IFN-α ($p = 0.008$), this assimilation did not find evidence of a clear difference in overall survival with different dose levels ($p = 0.8$) or durations of treatment ($p = 0.9$). Thus, adjuvant IFN improves overall survival of patients with stage II/III melanoma, though the absolute benefit in terms of survival rate at 5 years was small (~3%; 95% CI 1%–5%). In summary, there is a clear benefit for recurrence-free survival and a small benefit for overall survival with adjuvant IFN-α treatment regardless of dose, schedule, duration, or formulation (pegylation).

In spite of more than 20 years' experience with adjuvant IFN-α in melanoma, there are still some unanswered questions. *First*, the optimal dose remains unclear. It has been claimed that high-dose IFN-α leads to a higher rate of durable responses; however, this has

not been convincingly demonstrated. In the only randomized trial comparing high-dose versus low-dose IFN-α adjuvant treatment, improvement of recurrence-free survival was nearly identical for both regimens, and improvement of overall survival was not achieved by either regimen[240]. An initiation phase with modified high-dose IFN-α for 1 month followed by 18 months of low-dose IFN-α did not improve outcomes[241]. *Secondly*, the optimal treatment duration is unknown. The prolongation of low-dose IFN-α adjuvant treatment from 18 to 60 months was not associated with a survival benefit in a large randomized trial[242]. Interestingly, 1 month of treatment with a modified high-dose IFN-α regimen was not inferior as compared to a 1-year modified high-dose IFN-α treatment regimen in a randomized trial[243]. Presently, a large ECOG trial is looking at the reduction of high-dose IFN-α adjuvant treatment from 1 year to 1 month. *Thirdly*, the role of the pegylated formulation of IFN-α is not yet clear. A large EORTC trial tested pegylated IFN-α versus observation and found a benefit for disease-free but not for overall survival[244]. No superiority of pegylated IFN-α over classic IFN-α would be expected based on these results. Two large randomized multicenter trials in Europe are currently addressing this question. *Fourthly*, the optimal patient profile to benefit from adjuvant IFN-α therapy has not been clearly defined. Micrometastases in sentinel nodes and ulceration of the primary tumor were unequivocally associated with increased benefit in two large adjuvant IFN-α trials of the EORTC[244,245]. Therefore, patients fulfilling these criteria should be specifically offered adjuvant IFN-α treatment.

Management of Distant Metastases (Stage IV)

Despite new treatment options, the prognosis for patients with distant metastatic melanoma has not changed significantly over the past several decades, with 5-year survival rates of ~10% and a median survival time of around 9 months, with considerable inter-individual variation[246]. Differential survival is observed within the AJCC substages, that is soft tissue metastases only (M1a) versus lung metastasis (M1b) versus other visceral metastasis (M1c). For each of these disease sites, an abnormal LDH level is associated with a poorer prognosis (upstaging to M1c). By multivariate analysis, more than one metastasis, more than one organ involved, and older age at diagnosis are independently associated with poorer survival[246]. In a certain percentage of patients with few metastases and only one or two organs involved, surgical or other ablative treatment strategies with curative intent may be considered. When patients have failed to respond to previous therapies, a discussion regarding the option of enrolling in clinical trials is appropriate. In some patients, however, the focus is on palliative therapy with special emphasis on quality of life.

Surgery

Despite the well-known ability of melanoma to disseminate to multiple organs, resection of metastases may provide excellent palliation and, in selected patients, long-term survival[247]. Numerous studies have demonstrated clear and durable survival advantages for patients undergoing complete resection of metastatic melanoma. Factors that positively influence prognosis are isolated non-visceral metastasis and complete resection with free surgical margins. For certain indications, such as isolated lung metastases, median 5-year survival can approach 30% after surgical treatment. Patients rarely survive long-term with brain metastases but surgical resection may extend median survival to about 10 months, with a significant improvement in quality of life[248].

Radiation therapy

The efficacy of radiotherapy for melanoma is often understated due to unfavorable clinical results observed in early studies[249]. Radiotherapy can be administered to patients with unresectable disease, yielding relatively favorable results. Furthermore, radiotherapy is used successfully as a palliative maneuver for symptoms related to distant metastases in patients with incurable disease. Specific indications include pain control and stabilization of bones affected by metastases, spinal cord compression, brain metastases and local control of cutaneous disease. Studies do not support the administration of adjuvant radiotherapy following resection of regional lymph node metastases[250].

Whole brain radiotherapy combined with surgical resection has been the mainstay for treating cerebral metastases. This approach results in a median survival of about 10 months[251]. A newer development, providing at least similar results, is stereotactic radiosurgery utilizing either the so-called "Gamma Knife" or a linear accelerator. Up to five cerebral metastases can be treated, and the median survival was found to be 11.1 months from time of diagnosis. One-year and 2-year survival was 48% and 18%, respectively[252]. A benefit of radiosurgery is the virtual absence of perioperative complications, with a reduced adverse impact on quality of life compared to surgery or whole brain radiotherapy.

Systemic therapy

The mainstay of therapy in patients with distant metastases is systemic therapy. The systemic agents that have been used include chemotherapy, immunotherapy and combination biochemotherapy. A recent and very promising development has been the introduction of molecularly targeted therapy (see Table 113.1)[253,254]. Especially in the past, the overall results with many of these therapies have been sufficiently disappointing such that participation in clinical trials should be considered, if not encouraged, for this patient population.

Chemotherapy

Over the past four decades, cytotoxic chemotherapy has had a low but reproducible level of activity against metastatic melanoma (Table 113.15). Drugs employed include dacarbazine (DTIC)/temozolomide, carboplatin/cisplatin, vindesine/vinblastine, BCNU/fotemustine and paclitaxel/docetaxel[202]. Unfortunately, despite the identification of multiple chemotherapeutic agents with activity against melanoma as demonstrated *in vitro* and in phase I/II clinical trials[255,256], this has not translated into a significant impact on survival.

The most widely used single chemotherapeutic agent remains dacarbazine (DTIC). It has shown the greatest effectiveness as a single agent in most trials and was equally effective when combined with IFN-α or tamoxifen. With DTIC as a single agent, an approximately 10–15% response rate can be achieved with a median response duration of 5 to 6 months. The oral alkylating agent temozolomide (a prodrug of MTIC, the active metabolite of DTIC) has some efficacy in CNS metastasis and equal efficacy to DTIC[257,258]. Fotemustine is a member of the nitrosourea family and has some efficacy in melanoma, including brain metastases[259].

Combination chemotherapy regimens like CVD (cisplatin, vinblastine, DTIC) and BOLD (bleomycin, vincristine, lomustine, DTIC) have induced responses in metastatic lesions typically unresponsive to DTIC alone, including in the liver, bone and brain, but have failed to improve overall patient survival[260]. Another approach is chemohormonal therapy using tamoxifen in addition to chemotherapy. The four-drug combination cisplatin, carmustine (BCNU), DTIC and tamoxifen, also referred to as the "Dartmouth regimen", achieved high response rates in earlier trials (up to 55%), but a phase III trial did not show a statistical survival benefit compared to DTIC alone[261]. Therefore, DTIC remains the reference standard for chemotherapy in stage IV melanoma.

Immunotherapy

Immunotherapy builds on the concept that the immune system is able to fight cancer and melanoma is one of the prototypic immunogenic cancers. Therefore, a therapeutic effect might be achieved by infusing effectors of the immune system such as cytokines, killer cells or antibodies. Presently, high-dose IL-2 treatment, CTLA-4 blockade, cancer vaccination and adoptive T-cell transfer are the most promising strategies.

High-dose interleukin-2 treatment

High-dose recombinant IL-2 received US FDA approval for the treatment of metastatic melanoma in 1998. An objective response rate of approximately 16% was observed in phase II trials in patients with metastatic melanoma[262,263]. The inpatient high-dose regimen consisted of 600 000 U/kg of IL-2 every 8 hours for up to 14 doses. A small percentage of patients (~5%) experienced long-term, durable complete responses, which has been interpreted as potential cure. However, this therapy has not been shown to improve overall survival and has never been evaluated in a phase III setting. In addition, IL-2 treatment-related toxicity is severe and requires inpatient intensive care. A recent study combined a gp100 peptide vaccine with high-dose IL-2 and both the

MEDICAL TREATMENT OPTIONS FOR METASTATIC MELANOMA		
Medication	**Dose**	**Objective response rates***
	SINGLE AGENTS	
Dacarbazine (DTIC), 5 days	250 mg/m^2 IV daily for 5 days every 3–4 weeks	12–17%
Dacarbazine (DTIC), 1 day	800–1200 mg/m^2 IV on one day every 3–4 weeks	5–23%
Temozolomide	150–200 mg/m^2 po daily for 5 days every 4 weeks	13–21%
Fotemustine	100 mg/m^2 IV on days 1, 8 and 15; then 5-week pause, then repeat single dose every 3 weeks	7–24%
Vindesine	3 mg/m^2 IV every 14 days	12–26%
Interferon-α	9–18 million IU/m^2 sc 3× weekly	(13–25%)
Interleukin-2	600 000 IU/kg as 15-min infusion IV every 8 hours for 5 days (total of 14 doses). Repeat every 2 weeks, depending upon response and toxicity	(16–21%)
	COMBINED REGIMENS	
DTIC (or temozolomide) + interferon-α	DTIC 850 mg/m^2 IV day 1 (or temozolomide 150 mg/m^2 po days 1–5); interferon-α-2a/b 3 million IU/m^2 sc days 1–5, then 5 million IU/m^2 sc 3× weekly in weeks 2–4; repeat every 4 weeks	14–28%
Vindesine + interferon-α	Vindesine 3 mg/m^2 IV day 1; interferon-α-2a/b 5 million IU/m^2 sc 3× weekly; repeat every 2 weeks	24%
BHD	BCNU 150 mg/m^2 IV day 1 in every other cycle; hydroxyurea 1500 mg/m^2 po days 1–5; DTIC 150 mg/m^2 IV days 1–5 every 4 weeks	13–30%
BOLD	Bleomycin 15 mg IV days 1+4; vincristine 1 mg/m^2 IV days 1+5; CCNU 80 mg/m^2 po day 1; DTIC 200 mg/m^2 IV days 1–5; repeat every 4–6 weeks	20–40%
DVP	DTIC 250 mg/m^2 IV days 1–5; vindesine 3 mg/m^2 IV day 1; cisplatin 100 mg/m^2 IV day 1; repeat every 3–4 weeks	30–45%
DVP	DTIC 450 mg/m^2 IV days 1+8; vindesine 3 mg/m^2 IV days 1+8; cisplatin 50 mg/m^2 IV days 1+8; repeat every 3–4 weeks	25%
DBCT	DTIC 220 mg/m^2 IV days 1–3; BCNU 150 mg/m^2 IV day 1 of every other cycle; cisplatin 25 mg/m^2 IV days 1–3; tamoxifen 2 × 10 mg po daily; every 3–4 weeks	20–30%
CarboTax	Carboplatin AUC6 IV day 1, after four cycles reduce to AUC4; paclitaxel 225 mg/m^2 IV day 1 every 3 weeks, after four cycles reduce to 175 mg/m^2	12% (second line)

*Objective response rates were ascertained from randomized controlled clinical trials, or, if not available, from phase II trials or retrospective studies (in brackets). For details, see Garbe et al.[202,254a].

Table 113.15 Medical treatment options for metastatic melanoma. See Table 113.1 for newer therapeutic approaches to melanoma. IV, intravenous; po, orally; sc, subcutaneous.

response rates and progression-free survival were significantly improved[264].

Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) blockade

Seemingly one of the most potent immunotherapeutic approaches in melanoma is CTLA-4 blockade[265,266]. Full T-cell activation requires stimulation through the T-cell receptor as well as a costimulatory signal provided by the binding of B7 on an antigen-presenting cell to CD28 on the T cell. CTLA-4 is a homologue of CD28 and is an inhibitory T-cell receptor that is upregulated following T-cell activation. The normal function of CTLA-4 is to compete with CD28 to bind B7 in order to downregulate T-cell activation, acting as a natural "brake" by removing the costimulatory signal. The CTLA-4–B7 interaction can be blocked with an anti-CTLA-4 monoclonal antibody, which has a higher affinity for CTLA-4 than B7. Thus, the inhibitory signal is prevented and the "brake" on T-cell activation released. Two fully human anti-CTLA-4 monoclonal antibodies (mAbs) have been investigated, tremelimumab and ipilimumab, with the latter recently receiving US FDA approval for the treatment of metastatic melanoma[266a,266b]. As a single agent, objective response rates vary from 7–15%, with a median duration of 20 months. At three years, the survival rate for ipilimumab plus dacarbazine was 20.8% versus 12.2% for dacarbazine alone. Although responses to anti-CTLA-4 mAbs are durable, they may take as long as 12 weeks or even longer to develop[267]. Side effects with CTLA-4 blockade are autoimmune-related, but less acute than those observed with high-dose IL-2 therapy and are manageable. Presently, studies are ongoing to combine CTLA-4 blockade with vaccination treatments[268] and radiotherapy.

Cancer vaccines

Cancer vaccines have been pursued in hopes of enhancing immune recognition and effector antitumor immune responses via improved antigen presentation and the ability to elicit effector memory T-cell responses that are durable[269,270]. Increased knowledge of the relevant antigenic epitopes capable of eliciting antitumor immunity has prompted a variety of vaccine approaches. Although vaccines are well tolerated, they rarely have been monitored with methods that are now recognized to be critical for detecting whether or not the vaccine induced an immune response. Not surprisingly, the large phase III trials of older crude tumor cell vaccines have not demonstrated robust clinical evidence of antitumor activity either in advanced disease or in the adjuvant setting.

Peptide vaccines are a promising vaccine category. Peptide vaccines have been studied in large, multicenter ECOG trials in the US[271]. These studies in patients with advanced metastatic melanoma revealed the induction of immune responses, e.g. more than a third of vaccinated patients had increased T-cell production of IFN-γ as detected by ELISPOT. Of interest, those patients who demonstrated immune response to the triple peptide (gp100, MART-1/Melan-A, and tyrosinase HLA-A2 epitopes) had significantly improved survival that was nearly double that of patients who did not develop immunity to one or more of the peptide vaccine epitopes.

Adoptive cell therapy

To date, adoptive cell therapy has yielded some of the most dramatic responses among patients with metastatic melanoma. Objective response rates in a highly selected patient population have been stated to range between 49% and 72%[272,273]. Adoptive cell therapy as

undertaken by the group based at the National Cancer Institute is complex and costly, involving multiple steps: first, specifically sensitized antitumor lymphocytes must be isolated from the patient's tumor or stimulated *in vitro* with autologous melanoma cells. For this purpose, tumor-infiltrating lymphocytes are cultured *in vitro* in IL-2-containing media, exhibiting MHC-restricted recognition of the autologous melanoma cells. Secondly, the antitumor lymphocytes have to be expanded *in vitro* to large numbers as the efficacy of adoptive cell therapy depends on the presence of large numbers of antitumor lymphocytes capable of recognizing the melanoma cells and destroying the cancer cells *in vivo*. The ideal number for the adoptive transfer is more than 10^{11} cells. Because objective clinical responses have been associated with cells that were cultured for shorter time periods (14 days), a protocol for rapid expansion has been developed[274], utilizing IL-2, anti-CD3 antibodies, and irradiated allogeneic feeder cells.

The third step entails lymphodepletion which is performed to prepare the patient for adoptive cell transfer. Seven days before the adoptive transfer, a non-myeloablative lymphodepleting regimen consisting of cyclophosphamide and fludarabine is administered[272]. It has been suggested that this be supplemented with total body irradiation in single fractions of 2 Gy or with 12 Gy administered as 2 Gy twice a day for 3 days[273]. Fourthly, the adoptive cell transfer, accompanied by treatment with high-dose IL-2 for 3 days, is performed. The tumor-infiltrating lymphocytes are administered as a bolus intravenous infusion over 0.5–1 hours and the high-dose IL-2 treatment is then started within 24 hours. Patients who received total body irradiation additionally received autologous cryopreserved $CD34^+$ hematopoietic stem cells previously obtained from a granulocyte colony-stimulating factor-mobilized apheresis. After non-myeloablative but lymphodepleting chemotherapy, adoptive cell transfer therapy (n = 35) resulted in objective response rates of 51%[121]. By intensifying the lymphodepleting therapy through the addition of total body irradiation with a total dose of 12 Gy (n = 25), the response rate could be increased to 72%[273].

It is important to mention that this therapeutic approach is not generally available. It is performed primarily at the National Cancer Institute in the US and only a few other institutions in the world have developed these protocols[275–277]. The procedure is very complex and has several critical steps, such as the isolation of the tumor-infiltrating lymphocytes and their *in vitro* expansion, which is labor-intensive as well as costly. Finally, the patients must have an excellent performance status with no other severe co-morbidities. Therefore, only a few patients per year have been included in phase II studies, and, to date, no phase III study has been initiated.

Molecularly targeted therapy

As described above, ongoing molecular studies have identified the signaling pathways involved in melanoma progression and the genes that encode their components. These studies have provided molecular targets for melanoma therapy (see Table 113.1)[16,278,279].

Tumor genotyping indicates that between 50% and 60% of melanomas harbor activating mutations in *BRAF*, leading to constitutive activation of the RAS/RAF/MEK/ERK (MAPK) signaling pathway that regulates cell proliferation (see Fig. 113.2). A specific point mutation in *BRAF*, which leads to the substitution of glutamic acid (E) for valine (V) at codon 600, hence V600E, accounts for 90% of these mutations. Oral small molecule inhibitors that selectively target the mutant BRAF kinase have been developed and vemurafenib (PLX4032) was recently approved by the FDA based upon the results of a phase III clinical trial comparing it to DTIC[16,280,281,281a]. In patients with metastatic melanoma carrying the V600E mutation who received vemurafenib at the maximum tolerated dose of 960 mg twice daily, a 50% response rate was reported. Tumor responses were rapid with onset seen by PET scan as early as 2 weeks into treatment. Other similar compounds are under development by different pharmaceutical companies (see Table 113.1)[16,280], but there are issues with drug resistance due to alternative activation of the signaling pathway and the development of keratoacanthoma- and cutaneous SCC-like lesions.

For a smaller subgroup of melanoma patients, mutations in the KIT receptor gene represent another promising target for systemic melanoma therapy. Based on one analysis, KIT mutations and/or amplifications were found in about 30–40% of patients with chronic sun-damaged, mucosal or acral lentiginous melanomas (see Fig. 113.1)[273,282]. Anecdotal reports indicate that inhibitors of KIT, including imatinib, dasatinib and nilotinib, may benefit these patients who can be identified using commercially available assays. This hypothesis is currently being tested in several ongoing clinical trials.

In the further development of systemic targeted therapies for melanoma, combinations of selective BRAF inhibitors plus other targeted agents that inhibit downstream or parallel signaling molecules such as MEK, PI3 kinase, AKT and mTOR are considered the most promising at this time[283,284](see Fig. 113.2). It is very likely that combined treatments targeting several molecules simultaneously will be the treatment strategy in the future. Also, combinations of targeted molecules with cytotoxic agents is possible. Interestingly, blockade of the MAPK pathway did not show synergistic actions with cytotoxic drugs, whereas inhibition of the PI3K/AKT pathway appeared to lead to increased chemosensitivity[285,286].

MELANOMA SURVEILLANCE

Protocols for the longitudinal care of melanoma patients vary worldwide and there are no generally accepted guidelines. The primary objectives are to identify potentially curable locoregional recurrences and to identify additional primary cutaneous melanomas. Lifelong follow-up of these patients is important because of: (1) the significant risk of second primary cutaneous melanomas (3.5–4.5%); (2) the risk of local recurrence (~4%; greatest in the first 2–5 years after initial diagnosis and in thicker/ulcerated tumors and those on the head/neck/distal legs); (3) the risk of ultra-late recurrence (>15 years), which is unpredictable but does occur; and (4) the increased risk of other cutaneous and non-cutaneous malignancies.

Most stage I/II cutaneous melanomas will present with locoregional recurrence, while stage III/IV patients most often present with systemic metastases. The latter group is also typically followed by an oncologist. Recommendations for the frequency of dermatologic visits varies internationally and amongst practitioners. As 90% of all recurrences occur during the first 5 years following primary diagnosis (with the greatest risk in the first 2 years), most experts recommend dermatologic visits one to four times per year for 2 years after diagnosis (depending on risk factors and frequency of oncologic visits) and then every 6 to 12 months thereafter for life. The frequency is also influenced by the number of melanocytic nevi, common and atypical, and the number of primary cutaneous melanomas.

Dermatologic visits should include: (1) updates on the medical history; (2) review of systems (e.g. any new or changing lesions; new "lumps or bumps," weight loss, fatigue, headache or cough); (3) TBSE; (4) examination and palpation of the melanoma scar/excision site and surrounding area for local recurrences or in-transit metastases; (5) examination of lymph nodes; (6) laboratory and radiologic tests as indicated by signs and symptoms. Patients should be counseled to adhere to sun-protective measures; perform skin self-examinations at home; and to take an oral vitamin D supplement. Family members should also be encouraged to undergo TBSEs.

Although there has been an ongoing debate regarding the value of follow-up examinations[287] (some authors doubt that early detection of metastases has a beneficial effect on patient survival and that it may only prolong the patient's period of suffering), a review of the literature on early detection and on resection of melanoma metastases demonstrates the following[288]:

- For in-transit metastases and regional lymph node metastases, the tumor volume of the metastatic nodules at the time of diagnosis has prognostic significance. Either the number of nodes involved or the diameter of the largest node has demonstrated prognostic importance. Therefore, early detection appears to affect the cure rate in stage III disease.
- With distant metastases, surgical resection of all recognizable metastases (if possible) prolongs survival.

Therefore, early detection of melanoma metastases may contribute to prolongation of survival. Lastly, in a prospective follow-up study of more than 2000 patients, recurrences were classified as diagnosed in either an early or a late phase of development, and patients diagnosed in an early phase had significantly more favorable odds of recurrence-free and overall survival than those in a late phase[289,290].

REFERENCES

1. Lens MB, Dawes M. Global perspectives of contemporary epidemiological trends of cutaneous malignant melanoma. Br J Dermatol. 2004;150:179–85.
2. Garbe C, Leiter U. Melanoma epidemiology and trends. Clin Dermatol. 2009;27:3–9.
3. Leiter U, Garbe C. Epidemiology of melanoma and nonmelanoma skin cancer – the role of sunlight. Adv Exp Med Biol. 2008;624:89–103.
4. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. Ca Cancer J Clin. 2005;55:10–30.
5. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000;100:57–70.
6. Lazebnik Y. What are the hallmarks of cancer? Nat Rev Cancer. 2010;10:232–3.
7. Pleasance ED, Cheetham RK, Stephens PJ, et al. A comprehensive catalogue of somatic mutations from a human cancer genome. Nature. 2010;463:191–6.
8. Lengauer C, Kinzler KW, Vogelstein B. Genetic instabilities in human cancers. Nature. 1998;396: 643–9.
9. Goymer P. Natural selection: the evolution of cancer. Nature. 2008;454:1046–8.
10. Curtin JA, Fridlyand J, Kageshita T, et al. Distinct sets of genetic alterations in melanoma. N Engl J Med. 2005;353:2135–47.
11. Mckay MM, Morrison DK. Integrating signals from RTKS to ERK/MAPK. Oncogene. 2007;26:3113–21.
12. Giacinti C, Giordano A. Rb and cell cycle progression. Oncogene. 2006;25:5220–7.
13. Curtin JA, Busam K, Pinkel D, Bastian BC. Somatic activation of *KIT* in distinct subtypes of melanoma. J Clin Oncol. 2006;24:4340–6.
14. Ball NJ, Yohn JJ, Morelli JG, et al. Ras mutations in human melanoma: a marker of malignant progression. J Invest Dermatol. 1994;102:285–90.
15. Davies H, Bignell GR, Cox C, et al. Mutations of the *BRAF* gene in human cancer. Nature. 2002;417:949–54.
16. Gray-Schopfer V, Wellbrock C, Marais R. Melanoma biology and new targeted therapy. Nature. 2007;445:851–7.
17. Maldonado JL, Fridlyand J, Patel H, et al. Determinants of *BRAF* mutations in primary melanomas. J Natl Cancer Inst. 2003;95:1878–90.
18. Meyle KD, Guldberg P. Genetic risk factors for melanoma. Hum Genet. 2009;126:499–510.
19. Guldberg P, Thor SP, Birck A, et al. Disruption of the MMAC1/PTEN gene by deletion or mutation is a frequent event in malignant melanoma. Cancer Res. 1997;57:3660–3.
20. Cantley LC. The phosphoinositide 3-kinase pathway. Science. 2002;296:1655–7.
21. Salmena L, Carracedo A, Pandolfi PP. Tenets of PTEN tumor suppression. Cell. 2008;133:403–14.
22. Manning BD, Cantley LC. AKT/PKB signaling: navigating downstream. Cell. 2007;129:1261–74.
23. Madhunapantula SV, Robertson GP. The PTEN-AKT3 signaling cascade as a therapeutic target in melanoma. Pigment Cell Melanoma Res. 2009;22:400–19.
24. Curtin JA, Stark MS, Pinkel D, et al. PI3-kinase subunits are infrequent somatic targets in melanoma. J Invest Dermatol. 2006;126:1660–3.
25. Clevers H. WNT/beta-catenin signaling in development and disease. Cell. 2006;127:469–80.
26. Reya T, Clevers H. WNT signalling in stem cells and cancer. Nature. 2005;434:843–50.
27. Nelson WJ, Nusse R. Convergence of WNT, beta-catenin, and cadherin pathways. Science. 2004;303:1483–7.
28. Rubinfeld B, Robbins P, El-Gamil M, et al. Stabilization of beta-catenin by genetic defects in melanoma cell lines. Science. 1997;275:1790–2.
29. Worm J, Christensen C, Gronbaek K, et al. Genetic and epigenetic alterations of the APC gene in malignant melanoma. Oncogene. 2004;23:5215–26.
30. Reifenberger J, Knobbe CB, Wolter M, et al. Molecular genetic analysis of malignant melanomas for aberrations of the WNT signaling pathway genes CTNNB1, APC, ICAT and BTRC. Int J Cancer. 2002;100:549–56.
31. Takahashi Y, Nishikawa M, Suehara T, et al. Gene silencing of beta-catenin in melanoma cells retards their growth but promotes the formation of pulmonary metastasis in mice. Int J Cancer. 2008;123:2315–20.
32. O'connell MP, Weeraratna AT. Hear the WNT ROR: how melanoma cells adjust to changes in WNT. Pigment cell Melanoma Res. 2009;22:724–39.
33. Lin JY, Fisher DE. Melanocyte biology and skin pigmentation. Nature. 2007;445:843–50.
34. Steingrimsson E, Copeland NG, Jenkins NA. Melanocytes and the microphthalmia transcription factor network. Annu Rev Genet. 2004;38:365–411.
35. Widlund HR, Fisher DE. Microphthalmia-associated transcription factor: a critical regulator of pigment cell development and survival. Oncogene. 2003;22:3035–41.
36. Cheli Y, Ohanna M, Ballotti R, Bertolotto C. Fifteen-year quest for microphthalmia-associated transcription factor target genes. Pigment Cell Melanoma Res. 2010;23:27–40.
37. Valverde P, Healy E, Jackson I, et al. Variants of the melanocyte-stimulating hormone receptor gene are associated with red hair and fair skin in humans. Nat Genet. 1995;11:328–30.
38. Garraway LA, Widlund HR, Rubin MA, et al. Integrative genomic analyses identify mitf as a lineage survival oncogene amplified in malignant melanoma. Nature. 2005;436:117–22.
39. Carreira S, Goodall J, Aksan I, et al. MITF cooperates with rb1 and activates p21cip1 expression to regulate cell cycle progression. Nature. 2005;433:764–9.
40. Loercher AE, Tank EM, Delston RB, Harbour JW. MITF links differentiation with cell cycle arrest in melanocytes by transcriptional activation of ink4a. J Cell Biol. 2005;168:35–40.
41. Wellbrock C, Rana S, Paterson H, et al. Oncogenic *BRAF* regulates melanoma proliferation through the lineage specific factor MITF. Plos One. 2008;3:E2734.
42. Nestle FO, Burg G, Dummer R. New perspectives on immunobiology and immunotherapy of melanoma. Immunol Today. 1999;20:5–7.
43. Marincola FM, Jaffee EM, Hicklin DJ, Ferrone S. Escape of human solid tumors from T-cell recognition: molecular mechanisms and functional significance. Adv Immunol. 2000;74:181–273.
44. Antony PA, Restifo NP. Cd4+cd25+ T regulatory cells, immunotherapy of cancer, and interleukin-2. J Immunother. 2005;28:120–8.
45. Jemal A, Devesa SS, Hartge P, Tucker MA. Recent trends in cutaneous melanoma incidence among whites in the United States. J Natl Cancer Inst. 2001;93:678–83.
46. Mackie RM, Hauschild A, Eggermont AM. Epidemiology of invasive cutaneous melanoma. Ann Oncol. 2009;20(Suppl 6):vi1–7.
47. Garbe C, Blum A. Epidemiology of cutaneous melanoma in Germany and worldwide. Skin Pharmacol Appl Skin Physiol. 2001;14:280–90.
48. Mansson-Brahme E, Johansson H, Larsson O, et al. Trends in incidence of cutaneous malignant melanoma in a Swedish population 1976–1994. Acta Oncol. 2003;41:138–46.
49. Geller AC, Miller DR, Annas GD, et al. Melanoma incidence and mortality among US whites, 1969–1999. JAMA. 2002;288:1719–20.
50. De Vries E, Bray FI, Coebergh JW, Parkin DM. Changing epidemiology of malignant cutaneous melanoma in Europe 1953–1997: rising trends in incidence and mortality but recent stabilizations in western Europe and decreases in Scandinavia. Int J Cancer. 2003;107:119–26.
51. Pruthi DK, Guilfoyle R, Nugent Z, et al. Incidence and anatomic presentation of cutaneous malignant melanoma in central Canada during a 50-year period: 1956 to 2005. J Am Acad Dermatol. 2009;61:44–50.
52. Lasithiotakis KG, Leiter U, Gorkievicz R, et al. The incidence and mortality of cutaneous melanoma in southern Germany: trends by anatomic site and pathologic characteristics, 1976 to 2003. Cancer. 2006;107:1331–9.
53. De Vries E, Coebergh JW. Melanoma incidence has risen in Europe. BMJ. 2005;331:698.
54. [Anonymous]. Stat bite: incidence of and mortality from melanoma of the skin, 1975–2000. J Natl Cancer Inst. 2003;95:933.
55. [Anonymous]. Statbite: distribution of melanoma incidence and mortality by age, 2001–2005. J Natl Cancer Inst. 2008;100:1498.
56. Black RJ, Bray F, Ferlay J, Parkin DM. Cancer incidence and mortality in the European Union: cancer registry data and estimates of national incidence for 1990. Eur J Cancer. 1997;33:1075–107.
57. Stang A, Pukkala E, Sankila R, et al. Time trend analysis of the skin melanoma incidence of Finland from 1953 through 2003 including 16,414 cases. Int J Cancer. 2006;119:380–4.
58. Balzi D, Carli P, Giannotti B, et al. Cutaneous melanoma in the Florentine area, Italy: incidence, survival and mortality between 1985 and 1994. Eur J Cancer Prev. 2003;12:43–8.
59. Crocetti E, Carli P, Miccinesi G. Melanoma incidence in central Italy will go on increasing also in the near future: a registry-based, age-period-cohort analysis. Eur J Cancer Prev. 2007;16:50–4.
60. Whiteman DC, Bray CA, Siskind V, et al. Changes in the incidence of cutaneous melanoma in the west of Scotland and Queensland, Australia: hope for health promotion? Eur J Cancer Prev. 2008;17:243–50.
61. Mackie RM, Bray C, Vestey J, et al. Melanoma incidence and mortality in Scotland 1979–2003. Br J Cancer. 2007;96:1772–7.
62. Dennis LK. Analysis of the melanoma epidemic, both apparent and real: data from the 1973 through 1994 surveillance, epidemiology, and end results program registry. Arch Dermatol. 1999;135:275–80.
63. Hall HI, Miller DR, Rogers JD, Bewerse B. Update on the incidence and mortality from melanoma in the United States. J Am Acad Dermatol. 1999;40:35–42.
64. Bosetti C, La Vecchia C, Naldi L, et al. Mortality from cutaneous malignant melanoma in Europe. Has the epidemic levelled off? Melanoma Res. 2004;14: 301–9.
65. Balch CM, Soong SJ, Gershenwald JE, et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. J Clin Oncol. 2001;19:3622–34.
66. Balch CM, Buzaid AC, Soong SJ, et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. J Clin Oncol. 2001;19:3635–48.
67. Buttner P, Garbe C, Bertz J, et al. Primary cutaneous melanoma. Optimized cutoff points of tumor thickness and importance of Clark's level for prognostic classification. Cancer. 1995;75:2499–506.
68. Buettner PG, Leiter U, Eigentler TK, Garbe C. Development of prognostic factors and survival in cutaneous melanoma over 25 years: an analysis of the central malignant melanoma registry of the German Dermatological Society. Cancer. 2005;103:616–24.
69. Swetter SM, Soon S, Harrington CR, Chen SC. Effect of health care delivery models on melanoma thickness and stage in a university-based referral center: an observational pilot study. Arch Dermatol. 2007;143:30–6.
70. Baade PD, English DR, Youl PH, et al. The relationship between melanoma thickness and time to diagnosis in a large population-based study. Arch Dermatol. 2006;142:1422–7.
71. Bono A, Tolomio E, Bartoli C, et al. Metamorphosis of melanoma. Trends in size and thickness of cutaneous melanoma over one decade at the Istituto Nazionale Tumori, Milan. Tumori. 2008;94:11–3.
72. Lasithiotakis K, Leiter U, Meier F, et al. Age and gender are significant independent predictors of survival in primary cutaneous melanoma. Cancer. 2008;112:1795–804.
73. Hayward NK. Genetics of melanoma predisposition. Oncogene. 2003;22:3053–62.
74. Leachman SA, Carucci J, Kohlmann W, et al. Selection criteria for genetic assessment of patients with familial melanoma. J Am Acad Dermatol. 2009;61:677. E1–14.
75. Sharpless E, Chin L. The INK4A/ARF locus and melanoma. Oncogene. 2003;22:3092–8.
76. Yang G, Rajadurai A, Tsao H. Recurrent patterns of dual RB and p53 pathway inactivation in melanoma. J Invest Dermatol. 2005;125:1242–51.
77. Bataille V. Genetic epidemiology of melanoma. Eur J Cancer. 2003;39:1341–7.
78. Yang XR, Pfeiffer RM, Wheeler W, et al. Identification of modifier genes for cutaneous malignant melanoma in melanoma-prone families with and without *CDKN2A* mutations. Int J Cancer. 2009;125:2912–7.
79. Fargnoli MC, Gandini S, Peris K, et al. *MC1R* variants increase melanoma risk in families with *CDKN2A* mutations: a meta-analysis. Eur J Cancer. 2010;46:1413–20.
80. Goldstein AM, Chan M, Harland M, et al. Features associated with germline *CDKN2A* mutations: a genomel study of melanoma-prone families from three continents. J Med Genet. 2007;44:99–106.

81. Hansen CB, Wadge LM, Lowstuter K, et al. Clinical germline genetic testing for melanoma. Lancet Oncol. 2004;5:314–9.
82. Landi MT, Kanetsky PA, Tsang S, et al. *MC1R*, ASIP, and DNA repair in sporadic and familial melanoma in a Mediterranean population. J Natl Cancer Inst. 2005;97:998–1007.
83. Fargnoli MC, Pike K, Pfeiffer RM, et al. *MC1R* variants increase risk of melanomas harboring BRAF mutations. J Invest Dermatol. 2008;128:2485–90.
84. Landi MT, Bauer J, Pfeiffer RM, et al. *MC1R* germline variants confer risk for *BRAF*-mutant melanoma. Science. 2006;313:521–2.
85. Bishop DT, Demenais F, Iles MM, et al. Genome-wide association study identifies three loci associated with melanoma risk. Nat Genet. 2009;41:920–5.
86. Clark WHJ, Reimer RR, Greene M, et al. Origin of familial malignant melanomas from heritable melanocytic lesions. 'The B-K mole syndrome'. Arch Dermatol. 1978;114:732–8.
87. Reimer RR, Clark Whj, Greene MH, et al. Precursor lesions in familial melanoma. A new genetic preneoplastic syndrome. JAMA. 1978;239:744–6.
88. Stolz W, Schmoeckel C, Landthaler M, Braun-Falco O. Association of early malignant melanoma with nevocytic nevi. Cancer. 1989;63:550–5.
89. Stadler R, Garbe C. Nevus associated malignant melanomas – diagnostic validation and prognosis. Hautarzt. 1991;42:424–9.
90. Bauer J, Garbe C. Risk estimation for malignant transformation of melanocytic nevi. Arch Dermatol. 2004;140:127.
91. Tsao H, Bevona C, Goggins W, Quinn T. The transformation rate of moles (melanocytic nevi) into cutaneous melanoma. A population based estimate. Arch Dermatol. 2003;139:282–8.
92. Bataille V, Bishop JA, Sasieni P, et al. Risk of cutaneous melanoma in relation to the numbers, types and sites of naevi: a case-control study. Br J Cancer. 1996;73:1605–11.
93. Garbe C, Buttner P, Weiss J, et al. Risk factors for developing cutaneous melanoma and criteria for identifying persons at risk: multicenter case-control study of the central malignant melanoma registry of the German Dermatological Society. J Invest Dermatol. 1994;102:695–9.
94. Grob JJ, Gouvernet J, Aymar D, et al. Count of benign melanocytic nevi as a major indicator of risk for nonfamilial nodular and superficial spreading melanoma. Cancer. 1990;66:387–95.
95. Holly EA, Kelly JW, Shpall SN, Chiu SH. Number of melanocytic nevi as a major risk factor for malignant melanoma. J Am Acad Dermatol. 1987;17:459–68.
96. Naldi L, Lorenzo IG, Parazzini F, et al. Pigmentary traits, modalities of sun reaction, history of sunburns, and melanocytic nevi as risk factors for cutaneous malignant melanoma in the Italian population: results of a collaborative case-control study. Cancer. 2000;88:2703–10.
97. Rodenas JM, Delgado-Rodriguez M, Farinas-Alvarez C, et al. Melanocytic nevi and risk of cutaneous malignant melanoma in southern Spain. Am J Epidemiol. 1997;145:1020–9.
98. Tucker MA, Halpern A, Holly EA, et al. Clinically recognized dysplastic nevi. A central risk factor for cutaneous melanoma. JAMA. 1997;277:1439–44.
99. Evans RD, Kopf AW, Lew RA, et al. Risk factors for the development of malignant melanoma – i: review of case-control studies. J Dermatol Surg Oncol. 1988;14:393–408.
100. Swerdlow AJ, English J, Mackie RM, et al. Benign melanocytic naevi as a risk factor for malignant melanoma. Br Med J (Clin Res Ed). 1986; 292:1555–9.
101. Weiss J, Bertz J, Jung EG. Malignant melanoma in southern Germany: different predictive value of risk factors for melanoma subtypes. Dermatologica. 1991;183:109–13.
102. Kopf AW, Friedman RJ, Rigel DS. Atypical mole syndrome. J Am Acad Dermatol. 1990;22:117–8.
103. Kraemer KH, Greene MH, Tarone R, et al. Dysplastic naevi and cutaneous melanoma risk. Lancet. 1983;2:1076–7.
104. Newton JA, Bataille V, Griffiths K, et al. How common is the atypical mole syndrome phenotype in apparently sporadic melanoma? J Am Acad Dermatol. 1993;29:989–96.
105. Kraemer KH, Tucker M, Tarone R, et al. Risk of cutaneous melanoma in dysplastic nevus syndrome types a and b. N Engl J Med. 1986;315:1615–6.
106. Mackie RM, Freudenberger T, Aitchison TC. Personal risk-factor chart for cutaneous melanoma. Lancet. 1989;2:487–90.
107. Augustsson A, Stierner U, Rosdahl I, Suurkula M. Common and dysplastic naevi as risk factors for cutaneous malignant melanoma in a Swedish population. Acta Derm Venereol. 1991;71:518–24.
108. Greene MH, Clark Whj, Tucker MA, et al. High risk of malignant melanoma in melanoma-prone families with dysplastic nevi. Ann Intern Med. 1985;102:458–65.
109. Novakovic B, Clark WHJ, Fears TR, et al. Melanocytic nevi, dysplastic nevi, and malignant melanoma in children from melanoma-prone families. J Am Acad Dermatol. 1995;33:631–6.
110. Elwood JM, Williamson C, Stapleton PJ. Malignant melanoma in relation to moles, pigmentation, and exposure to fluorescent and other lighting sources. Br J Cancer.1986;53:65–74.
111. Osterlind A, Tucker MA, Hou-Jensen K, et al. The Danish case-control study of cutaneous malignant melanoma. I. Importance of host factors. Int J Cancer. 1988;42:200–6.
112. Osterlind A, Tucker MA, Stone BJ, Jensen OM. The Danish case-control study of cutaneous malignant melanoma. II. Importance of UV-light exposure. Int J Cancer. 1988;42:319–24.
113. Miller AJ, Mihm MC jr. Melanoma. N Engl J Med. 2006;355:51–65.
114. Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. Eur J Cancer. 2005;41:45–60.
115. Shuster S. Is sun exposure a major cause of melanoma? No. BMJ. 2008;337:A764.
116. Menzies SW. Is sun exposure a major cause of melanoma? Yes. BMJ. 2008;337:A763.
117. Mcgovern VJ, Mackie BS. The relationship of solar radiation to melanoblastoma. Aust N Z J Surg. 1959;28:257–62.
118. Mcgovern VJ. Epidemiological aspects of melanoma: a review. Pathology. 1977;9:233–41.
119. Elwood JM, Gallagher RP, Hill GB, et al. Pigmentation and skin reaction to sun as risk factors for cutaneous melanoma: western Canada melanoma study. Br Med J (Clin Res Ed). 1984;288:99–102.
120. Green A, Maclennan R, Siskind V. Common acquired naevi and the risk of malignant melanoma. Int J Cancer. 1985;35:297–300.
121. Garbe C, Buttner P, Weiss J, et al. Associated factors in the prevalence of more than 50 common melanocytic nevi, atypical melanocytic nevi, and actinic lentigines: multicenter case-control study of the central malignant melanoma registry of the German Dermatological Society. J Invest Dermatol. 1994;102:700–5.
122. Harrison SL, Maclennan R, Speare R, Wronski I. Sun exposure and melanocytic naevi in young Australian children. Lancet. 1994;344:1529–32.
123. Bauer J, Buttner P, Wiecker TS, et al. Risk factors of incident melanocytic nevi: a longitudinal study in a cohort of 1,232 young German children. Int J Cancer. 2005;115:121–6.
124. Wiecker TS, Luther H, Buettner P, et al. Moderate sun exposure and nevus counts in parents are associated with development of melanocytic nevi in childhood: a risk factor study in 1,812 kindergarten children. Cancer. 2003;97:628–38.
125. Gilchrest BA, Eller MS, Geller AC, Yaar M. The pathogenesis of melanoma induced by ultraviolet radiation. N Engl J Med. 1999;340:1341–8.
126. Rieger E, Soyer HP, Garbe C, et al. Overall and site-specific risk of malignant melanoma associated with nevus counts at different body sites: a multicenter case-control study of the German Central Malignant-Melanoma Registry. Int J Cancer. 1995;62:393–7.
127. Whiteman DC, Stickley M, Watt P, et al. Anatomic site, sun exposure, and risk of cutaneous melanoma. J Clin Oncol. 2006;24:3172–7.
128. De Fabo EC, Noonan FP, Fears T, Merlino G. Ultraviolet B but not ultraviolet A radiation initiates melanoma. Cancer Res. 2004;64:6372–6.
129. De Fabo EC. Initial studies on an in vivo action spectrum for melanoma induction. Prog Biophys Mol Biol. 2006;92:97–104.
130. Ley RD. Dose response for ultraviolet radiation a-induced focal melanocytic hyperplasia and nonmelanoma skin tumors in monodelphis domestica. Photochem Photobiol. 2001;73:20–3.
131. Wood SR, Berwick M, Ley RD, et al. UV causation of melanoma in xiphophorus is dominated by melanin photosensitized oxidant production. Proc Natl Acad Sci U S A. 2006;103:4111–5.
132. Mitchell D, Paniker L, Sanchez G, et al. The etiology of sunlight-induced melanoma in xiphophorus hybrid fish. Mol Carcinog. 2007;46:679–84.
133. Setlow RB, Grist E, Thompson K, Woodhead AD. Wavelengths effective in induction of malignant melanoma. Proc Natl Acad Sci U S A. 1993;90: 6666–70.
134. Mitchell DL, Greinert R, De Gruijl FR, et al. Effects of chronic low-dose ultraviolet B radiation on DNA damage and repair in mouse skin. Cancer Res. 1999;59:2875–84.
135. Green AC, Williams GM, Logan V, Strutton GM. Reduced melanoma after regular sunscreen use: randomized trial follow-up. J Clin Oncol. 2011;29:257–63.
136. Dadlani C, Orlow SJ. Planning for a brighter future: a review of sun protection and barriers to behavioral change in children and adolescents. Dermatol Online J. 2008;14:1.
137. Clark WH Jr, From L, Bernardino EA, Mihm MC. The histogenesis and biologic behavior of primary human malignant melanomas of the skin. Cancer Res 1969;29:705–27.
138. Skender-Kalnenas TM, English DR, Heenan PJ. Benign melanocytic lesions: risk markers or precursors of cutaneous melanoma? J Am Acad Dermatol. 1995;33:1000–7.
139. Demierre MF, Chung C, Miller DR, Geller AC. Early detection of thick melanomas in the United States: beware of the nodular subtype. Arch Dermatol. 2005;141:745–50.
140. Weinstock MA, Sober AJ. The risk of progression of lentigo maligna to lentigo maligna melanoma. Br J Dermatol .1987;116:303–10.
141. Tannous ZS, Lerner LH, Duncan LM, et al. Progression to invasive melanoma from malignant melanoma in situ, lentigo maligna type. Hum Pathol. 2000;31: 705–8.
142. Argenziano G, Soyer HP, Chimenti S, et al. Dermoscopy of pigmented skin lesions: results of a consensus meeting via the internet. J Am Acad Dermatol. 2003;48:679–93.
143. Stolz W, Schiffner R, Burgdorf WH. Dermatoscopy for facial pigmented skin lesions. Clin Dermatol. 2002;20:276–8.
144. Cress RD, Holly EA. Incidence of cutaneous melanoma among non-hispanic whites, hispanics, asians, and blacks: an analysis of California Cancer Registry data, 1988–93. Cancer Causes Control. 1997;8:246–52.
145. Metzger S, Ellwanger U, Stroebel W, et al. Extent and consequences of physician delay in the diagnosis of acral melanoma. Melanoma Res. 1998;8:181–6.
146. Torres-Cabala CA, Wang WL, Trent J, et al. Correlation between KIT expression and KIT mutation in melanoma: a study of 173 cases with emphasis on the acral-lentiginous/mucosal type. Mod Pathol. 2009;22:1446–56.
147. Bastian BC. Molecular cytogenetics as a diagnostic tool for typing melanocytic tumors. Recent Results Cancer Res. 2002;160:92–9.
148. De Almeida LS, Requena L, Rutten A, et al. Desmoplastic malignant melanoma: a clinicopathologic analysis of 113 cases. Am J Dermatopathol. 2008;30:207–15.
149. Zettersten E, Sagebiel RW, Miller Jr III, et al. Prognostic factors in patients with thick cutaneous melanoma (>4 mm). Cancer. 2002;94:1049–56.
150. Hantschke M, Mentzel T, Rutten A, et al. Cutaneous clear cell sarcoma: a clinicopathologic, immunohistochemical, and molecular analysis of 12 cases emphasizing its distinction from dermal melanoma. Am J Surg Pathol. 2010;34:216–22.
151. Hisaoka M, Ishida T, Kuo TT, et al. Clear cell sarcoma of soft tissue: a clinicopathologic, immunohistochemical, and molecular analysis of 33 cases. Am J Surg Pathol. 2008;32:452–60.
152. Koch H, Zelger B, Cerroni L. Malignant blue nevus: malignant melanoma in association with blue nevus. Eur J Dermatol. 1996;6:335–8.
153. Van Raamsdonk CD, Bezrookove V, Green G, et al. Frequent somatic mutations of GNAQ in uveal melanoma and blue naevi. nature. 2009;457: 599–602.
154. Schoenfield L, Pettay J, Tubbs RR, Singh AD. Variation of monosomy 3 status within uveal melanoma. Arch Pathol Lab Med. 2009;133:1219–22.
155. Skalicky SE, Holt PE, Giblin M, et al. Australian cancer network clinical practice guidelines for the management of ocular and periocular melanoma: an evidence-based literature analysis. Clin Experiment Ophthalmol. 2008;36:646–58.

156. Tomicic J, Wanebo HJ. Mucosal melanomas. Surg Clin North Am. 2003;83:237–52.
157. Sanchez JL, Figueroa LD, Rodriguez E. Behavior of melanocytic nevi during pregnancy. Am J Dermatopathol. 1984;6(Suppl):89–91.
158. Driscoll MS, Grant-Kels JM. Nevi and melanoma in the pregnant woman. Clin Dermatol. 2009;27:116–21.
159. Pages C, Robert C, Thomas L, et al. Management and outcome of metastatic melanoma during pregnancy. Br J Dermatol. 2010;162:274–81.
160. Grin CM, Driscoll MS, Grant-Kels JM. The relationship of pregnancy, hormones, and melanoma. Semin Cutan Med Surg. 1998;17:167–71.
161. Pappo AS. Melanoma in children and adolescents. Eur J Cancer. 2003;39:2651–61.
162. Barnhill RL. Childhood melanoma. Semin Diagn Pathol. 1998;15:189–94.
163. Paradela S, Fonseca E, Pita S, et al. Spitzoid melanoma in children: clinicopathological study and application of immunohistochemistry as an adjunct diagnostic tool. J Cutan Pathol. 2009;36:740–52.
164. Ridha H, Ahmed S, Theaker JM, Horlock N. Malignant melanoma and deep penetrating naevus – difficulties in diagnosis in children. J Plast Reconstr Aesthet Surg. 2007;60:1252–5.
165. Saenz NC, Saenz-Badillos J, Busam K, et al. Childhood melanoma survival. Cancer. 1999;85:750–4.
166. Psaty EL, Halpern AC. Current and emerging technologies in melanoma diagnosis: the state of the art. Clin Dermatol. 2009;27:35–45.
167. Bauer J, Blum A, Strohhacker U, Garbe C. Surveillance of patients at high risk for cutaneous malignant melanoma using digital dermoscopy. Br J Dermatol. 2005;152:87–92.
168. Bauer J, Garbe C. Acquired melanocytic nevi as risk factor for melanoma development. A comprehensive review of epidemiological data. Pigment Cell Res. 2003;16:297–306.
169. Liu W, Hill D, Gibbs AF, et al. What features do patients notice that help to distinguish between benign pigmented lesions and melanomas?: the ABCD(E) rule versus the seven-point checklist. Melanoma Res. 2005;15:549–54.
170. Gachon J, Beaulieu P, Sei JF, et al. First prospective study of the recognition process of melanoma in dermatological practice. Arch Dermatol. 2005;141: 434–8.
171. Grob JJ, Bonerandi JJ. The "ugly duckling" sign: identification of the common characteristics of nevi in an individual as a basis for melanoma screening. Arch Dermatol. 1998;134:103–4.
172. Scope A, Dusza SW, Halpern AC, et al. The "ugly duckling" sign: agreement between observers. Arch Dermatol. 2008;144:58–64.
173. Menzies SW, Ingvar C, Crotty KA, Mccarthy WH. Frequency and morphologic characteristics of invasive melanomas lacking specific surface microscopic features. Arch Dermatol. 1996;132:1178–82.
174. Kittler H, Guitera P, Riedl E, et al. Identification of clinically featureless incipient melanoma using sequential dermoscopy imaging. Arch Dermatol. 2006;142:1113–9.
175. Cerroni L, Kerl H. Simulators of malignant melanoma of the skin. Eur J Dermatol. 1998;8:388–96.
176. Argenziano G, Soyer HP. Dermoscopy of pigmented skin lesions – a valuable tool for early diagnosis of melanoma. Lancet Oncol. 2001;2:443–9.
177. Kittler H, Pehamberger H, Wolff K, Binder M. Diagnostic accuracy of dermoscopy. Lancet Oncol. 2002;3:159–65.
178. Braun RP, Thomas L, Kolm I, et al. The furrow ink test: a clue for the dermoscopic diagnosis of acral melanoma vs nevus. Arch Dermatol. 2008;144:1618–20.
179. Phan A, Dalle S, Touzet S, et al. Dermoscopic features of acral lentiginous melanoma in a large series of 110 cases in a white population. Br J Dermatol. 2010;162:765–71.
180. Ronger S, Touzet S, Ligeron C, et al. Dermoscopic examination of nail pigmentation. Arch Dermatol. 2002;138:1327–33.
181. Kalkhoran S, Milne O, Zalaudek I, et al. Historical, clinical, and dermoscopic characteristics of thin nodular melanoma. Arch Dermatol. 2010;146: 311–8.
182. Menzies SW, Kreusch J, Byth K, et al. Dermoscopic evaluation of amelanotic and hypomelanotic melanoma. Arch Dermatol. 2008;144:1120–7.
183. Halpern AC. Total body skin imaging as an aid to melanoma detection. Semin Cutan Med Surg. 2003;22:2–8.
184. Feit NE, Dusza SW, Marghoob AA. Melanomas detected with the aid of total cutaneous photography. Br J Dermatol. 2004;150:706–14.
185. Crc Melanoma Pathology panel. A nationwide survey of observer variation in the diagnosis of thin cutaneous malignant melanoma including the min terminology. J Clin Pathol. 1997;50:202–5.
186. Clemente C, Cook M, Ruiter D, Mihm M. Histopathologic diagnosis of melanoma. World Health Organization melanoma programme publications. Milan: Trezzano SN, 2001.
187. Ackermann A, Cerroni L, Kerl H. Pitfalls in histopathologic diagnosis of malignant melanoma. Philiadelphia: Lea & Febiger, 1994.
188. Cochran AJ, Bailly C, Cook M, et al. Recommendations for the reporting of tissues removed as part of the surgical treatment of cutaneous melanoma. The association of directors of anatomic and surgical pathology. Am J Clin Pathol. 1998;110:719–22.
189. De Wit NJ, Van Muijen GN, Ruiter DJ. Immunohistochemistry in melanocytic proliferative lesions. Histopathology. 2004;44:517–41.
190. Elder DE, Xu X. The approach to the patient with a difficult melanocytic lesion. Pathology. 2004;36: 428–34.
191. Bauer J, Bastian BC. Distinguishing melanocytic nevi from melanoma by DNA copy number changes: comparative genomic hybridization as a research and diagnostic tool. Dermatol Ther. 2006;19:40–9.
192. Gerami P, Mafee M, Lurtsbarapa T, et al. Sensitivity of fluorescence in situ hybridization for melanoma diagnosis using RREB1, MYB, CEP6, and 11q13 probes in melanoma subtypes. Arch Dermatol. 2010;146:273–8.
193. Clemente C, Bettio D, Venci A, et al. A fluorescence in situ hybridization (FISH) procedure to assist in differentiating benign from malignant melanocytic lesions. Pathologica. 2009;101:169–74.
194. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009;27:6199–206.
195. Garbe C, Buttner P, Bertz J, et al. Primary cutaneous melanoma. Identification of prognostic groups and estimation of individual prognosis for 5093 patients. Cancer. 1995;75:2484–91.
196. Levi F, Randimbison L, La Vecchia C, et al. Prognostic factors for cutaneous malignant melanoma in Vaud, Switzerland. Int J Cancer. 1998;78:315–9.
197. Johnson TM, Chang A, Redman B, et al. Management of melanoma with a multidisciplinary melanoma clinic model. J Am Acad Dermatol. 2000;42:820–6.
198. Wang TS, Johnson TM, Cascade PN, et al. Evaluation of staging chest radiographs and serum lactate dehydrogenase for localized melanoma. J Am Acad Dermatol. 2004;51:399–405.
199. Sober AJ, Chuang TY, Duvic M, et al. Guidelines of care for primary cutaneous melanoma. J Am Acad Dermatol. 2001;45:579–86.
200. Blum A, Schlagenhauff B, Stroebel W, et al. Ultrasound examination of regional lymph nodes significantly improves early detection of locoregional metastases during the follow-up of patients with cutaneous melanoma: results of a prospective study of 1288 patients. Cancer. 2000;88:2534–9.
201. Garbe C, Hauschild A, Volkenandt M, et al. Evidence and interdisciplinary consensus-based German guidelines: diagnosis and surveillance of melanoma. Melanoma Res. 2007;17:393–9.
202. Garbe C, Peris K, Hauschild A, et al. Diagnosis and treatment of melanoma: European consensus-based interdisciplinary guideline. Eur J Cancer. 2010;46:270–83.
203. Garbe C, Leiter U, Ellwanger U, et al. Diagnostic value and prognostic significance of protein S-100beta, melanoma-inhibitory activity, and tyrosinase/MART-1 reverse transcription-polymerase chain reaction in the follow-up of high-risk melanoma patients. Cancer. 2003;97:1737–45.
204. Tarhini AA, Stuckert J, Lee S, et al. Prognostic significance of serum s100b protein in high-risk surgically resected melanoma patients participating in intergroup trial ECOG 1694. J Clin Oncol. 2009;27:38–44.
205. Muller-Horvat C, Radny P, Eigentler TK, et al. Prospective comparison of the impact on treatment decisions of whole-body magnetic resonance imaging and computed tomography in patients with metastatic malignant melanoma. Eur J Cancer. 2006;42:342–50.
206. Kumar R, Alavi A. Clinical applications of fluorodeoxyglucose–positron emission tomography In the management of malignant melanoma. Curr Opin Oncol. 2005;17:154–9.
207. Pfannenberg C, Aschoff P, Schanz S, et al. Prospective comparison of (18)f-fluorodeoxyglucose positron emission tomography/computed tomography and whole-body magnetic resonance imaging in staging of advanced malignant melanoma. Eur J Cancer. 2007;43:557–64.
208. Veronesi U, Cascinelli N, Adamus J, et al. Thin stage I primary cutaneous malignant melanoma. Comparison of excision with margins of 1 or 3 cm. N Engl J Med. 1988;318:1159–62.
209. Balch CM, Soong SJ, Smith T, et al. Long-term results of a prospective surgical trial comparing 2 cm vs. 4 cm excision margins for 740 patients with 1–4 mm melanomas. Ann Surg Oncol. 2001;8:101–8.
210. Guidelines Working Party. Clinical practice guidelines for the management of melanoma in Australia and New Zealand. Sydney & Auckland: www.cancer.org.au/skincancerguides; 2008.
211. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: melanoma, v.2.2009. www.nccn.org; 2009.
212. Ross M.I., Balch C. Surgical treatment of primary melanoma. In: Balch CM, Houghton AN, Sober AJ, Soong S-J (eds). Cutaneous Melanoma. St Louis: Quality Medical Publishing, 1998:141–53.
213. Breuninger H, Schlagenhauff B, Stroebel W, et al. Patterns of local horizontal spread of melanomas: consequences for surgery and histopathologic investigation. Am J Surg Pathol. 1999;23:1493–8.
214. Temple CL, Arlette JP. Mohs micrographic surgery in the treatment of lentigo maligna and melanoma. J Surg Oncol. 2006;94:287–92.
215. Moehrle M, Metzger S, Schippert W, et al. "Functional" surgery in subungual melanoma. Dermatol Surg. 2003;29:366–74.
215a. Ly L, Kelly JW, O'Keefe R, et al. Efficacy of imiquimod cream, 5%, for lentigo maligna after complete excision. Arch Dermatol. 2011;147:1191–5.
216. Karakousis CP, Bartolucci AA, Balch C. Local recurrence and its management. In: Balch CM, Houghton AN, Sober AJ, Soong S-J (eds). Cutaneous Melanoma. St Louis: Quality Medical Publishing, 1998:155–62.
217. Buzaid AC, Ross MI, Soong S-J. Classification and staging. In: Balch CM, Houghton AN, Sober AJ, Soong S-J (eds). Cutaneous Melanoma. St Louis: Quality Medical Publishing, 1998:37–49.
218. Kanzler MH, Mraz-Gernhard S. Primary cutaneous malignant melanoma and its precursor lesions: diagnostic and therapeutic overview. J Am Acad Dermatol. 2001;45:260–76.
219. Mraz-Gernhard S, Sagebiel RW, Kashani-Sabet M, et al. Prediction of sentinel lymph node micrometastasis by histological features in primary cutaneous malignant Melanoma. Arch Dermatol. 1998;134:983–7.
220. Veronesi U, Adamus J, Bandiera DC, et al. Delayed regional lymph node dissection in stage I melanoma of the skin of the lower extremities. Cancer. 1982;49:2420–30.
221. Veronesi U, Adamus J, Bandiera DC, et al. Inefficacy of immediate node dissection in stage 1 melanoma of the limbs. N Engl J Med. 1977;297:627–30.
222. Sim FH, Taylor WF, Pritchard DJ, Soule EH. Lymphadenectomy in the management of stage I malignant melanoma: a prospective randomized study. Mayo Clin Proc. 1986;61:697–705.
223. Balch CM, Soong SJ, Bartolucci AA, et al. Efficacy of an elective regional lymph node dissection of 1 to 4 mm thick melanomas for patients 60 years of age and younger. Ann Surg. 1996;224:255–63.
224. Morton DL, Chan AD. The concept of sentinel node localization: how it started. Semin Nucl Med. 2000;30:4–10.
225. Gershenwald JE, Thompson W, Mansfield PF, et al. Multi-institutional melanoma lymphatic mapping experience: the prognostic value of sentinel lymph node status in 612 stage I or II melanoma patients. J Clin Oncol. 1999;17:976–83.
226. Leiter U, Buettner PG, Bohnenberger K, et al. Sentinel lymph node dissection in primary melanoma reduces subsequent regional lymph node metastasis as well as distant metastasis after nodal involvement. Ann Surg Oncol. 2010;17:129–37.
227. Kettlewell S, Moyes C, Bray C, et al. Value of sentinel node status as a prognostic factor in melanoma: prospective Observational Study. BMJ. 2006;332:1423.
228. Morton DL, Thompson JF, Cochran AJ, et al. Sentinel-node biopsy or nodal observation in melanoma. N Engl J Med. 2006;355:1307–17.

229. Lienard D, Eggermont AM, Koops HS, et al. Isolated limb perfusion with tumour necrosis factor-alpha and melphalan with or without interferon-gamma for the treatment of in-transit melanoma metastases: a multicentre randomized phase II study. Melanoma Res. 1999;9:491–502.
230. Alexander HR Jr, Fraker DL, Bartlett DL, et al. Analysis of factors influencing outcome in patients with in-transit malignant melanoma undergoing isolated limb perfusion using modern treatment parameters. J Clin Oncol. 2010;28:114–8.
231. Hoekstra HJ. The european approach to in-transit melanoma lesions. Int J Hyperthermia. 2008;24: 227–37.
232. Eggermont AM, Testori A, Marsden J, et al. Utility of adjuvant systemic therapy in melanoma. Ann Oncol. 2009;20(Suppl 6):vi30–4.
233. Kirkwood JM. Adjuvant interferon in the treatment of melanoma. Br J Cancer. 2000;82:1755–6.
234. Gogas H, Ioannovich J, Dafni U, et al. Prognostic significance of autoimmunity during treatment of melanoma with interferon. N Engl J Med. 2006;354:709–18.
235. Hauschild A, Gogas H, Tarhini A, et al. Practical guidelines for the management of interferon-alpha-2b side effects in patients receiving adjuvant treatment for melanoma: expert opinion. Cancer. 2008;112:982–94.
236. Pehamberger H, Soyer HP, Steiner A, et al. Adjuvant interferon alfa-2a treatment in resected primary stage II cutaneous melanoma. Austrian Malignant Melanoma Cooperative Group. J Clin Oncol. 1998;16:1425–9.
237. Grob JJ, Dreno B, De La SP, et al. Randomised trial of interferon alpha-2a as adjuvant therapy in resected primary melanoma thicker than 1.5 mm without clinically detectable node metastases. French Cooperative Group on Melanoma. Lancet.1998;351:1905–10.
238. Garbe C, Radny P, Linse R, et al. Adjuvant low-dose interferon-α2a with or without dacarbazine compared with surgery alone: a prospective-randomized phase III DECOG trial in melanoma patients with regional lymph node metastasis. Ann Oncol. 2008;19:1195–201.
239. Wheatley K, Ives NJ, Eggermont A, et al. Interferon-α as adjuvant therapy for melanoma: an individual patient data meta-analysis of randomised trials. 2007 ASCO annual meeting proceedings part 1. J Clin Oncol. 2007;25:Abstr 8526.
240. Kirkwood JM, Ibrahim JG, Sondak VK, et al. High- and low-dose interferon alfa-2b in high-risk melanoma: first analysis of intergroup trial e1690/s9111/c9190. J Clin Oncol. 2000;18:2444–58.
241. Hauschild A, Weichenthal M, Rass K, et al. Prospective randomized multicenter adjuvant dermatologic cooperative oncology group trial of low-dose interferon alfa-2b with or without a modified high-dose interferon alfa-2b induction phase in patients with lymph node-negative melanoma. J Clin Oncol. 2009;27:3496–502.
242. Hauschild A, Weichenthal M, Rass K, et al. Efficacy of low-dose interferon-α2a 18 versus 60 months of treatment in patients with primary melanoma of >=1.5 mm tumor thickness: results of a randomized phase III DECOG trial. J Clin Oncol. 2010;28:841–6.
243. Pectasides D, Dafni U, Bafaloukos D, et al. Randomized phase III study of 1 month versus 1 year of adjuvant high-dose interferon alfa-2b in patients with resected high-risk melanoma. J Clin Oncol. 2009;27:939–44.
244. Eggermont AM, Suciu S, Santinami M, et al. Adjuvant therapy with pegylated interferon alfa-2b versus observation alone in resected stage III melanoma: final results of EORTC 18991, a randomised phase III trial. Lancet. 2008;372:117–26.
245. Eggermont AM, Suciu S, Mackie R, et al. Post-surgery adjuvant therapy with intermediate doses of interferon alfa 2b versus observation in patients with stage IIB/III melanoma (EORTC 18952): randomised controlled trial. Lancet. 2005;366:1189–96.
246. Neuman HB, Patel A, Ishill N, et al. A single-institution validation of the AJCC staging system for stage IV melanoma. Ann Surg Oncol. 2008;15:2034–41.
247. Young SE, Martinez SR, Essner R. The role of surgery in treatment of stage IV melanoma. J Surg Oncol. 2006;94:344–51.
248. Staudt M, Lasithiotakis K, Leiter U, et al. Determinants of survival in patients with brain metastases from cutaneous melanoma. Br J Cancer. 2010;102: 1213–8.
249. Schild SE. Role of radiation therapy in the treatment of melanoma. Expert Rev Anticancer Ther. 2009;9:583–6.
250. Fuhrmann D, Lippold A, Borrosch F, et al. Should adjuvant radiotherapy be recommended following resection of regional lymph node metastases of malignant melanomas? Br J Dermatol. 2001;144:66–70.
251. Young RF. Radiosurgery for the treatment of brain metastases. Semin Surg Oncol. 1998;14:70–8.
252. Samlowski WE, Watson GA, Wang M, et al. Multimodality treatment of melanoma brain metastases incorporating stereotactic radiosurgery (SRS). Cancer. 2007;109:1855–62.
253. Flaherty KT, Smalley KS. Preclinical and clinical development of targeted therapy in melanoma: attention to schedule. Pigment Cell Melanoma Res. 2009;22:529–31.
254. Ji Z, Flaherty KT, Tsao H. Molecular therapeutic approaches to melanoma. Mol Aspects Med. 2010;31:194–204.
254a. Garbe C, Eigentler TK, Keilholz U, et al. Systematic review of medical treatment in melanoma: current status and future prospects. Oncologist. 2011; 16:5–24.
255. Jilaveanu LB, Aziz SA, Kluger HM. Chemotherapy and biologic therapies for melanoma: do they work? Clin Dermatol. 2009;27:614–25.
256. Yang AS, Chapman PB. The history and future of chemotherapy for melanoma. Hematol Oncol Clin North Am. 2009;23:583–97, X.
257. Middleton MR, Grob JJ, Aaronson N, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. J Clin Oncol. 2000;18:158–66.
258. Quirt I, Verma S, Petrella T, et al. Temozolomide for the treatment of metastatic melanoma: a systematic review. Oncologist. 2007;12:1114–23.
259. Avril MF, Aamdal S, Grob JJ, et al. Fotemustine compared with dacarbazine in patients with disseminated malignant melanoma: a phase III study. J Clin Oncol. 2004;22:1118–25.
260. Eigentler TK, Caroli UM, Radny P, Garbe C. Palliative therapy of disseminated malignant melanoma: a systematic review of 41 randomised clinical trials. Lancet Oncol. 2003;4:748–59.
261. Chapman PB, Einhorn LH, Meyers ML, et al. Phase III multicenter randomized trial of the Dartmouth regimen versus dacarbazine in patients with metastatic melanoma. J Clin Oncol. 1999;17:2745–51.
262. Petrella T, Quirt I, Verma S, et al. Single-agent interleukin-2 in the treatment of metastatic melanoma: a systematic review. Cancer Treat Rev. 2007;33:484–96.
263. Tarhini AA, Agarwala SS. Interleukin-2 for the treatment of melanoma. Curr Opin Investig Drugs. 2005;6:1234–9.
264. Schwartzentruber DJ, Lawson DH, Richard JM, et al. Gp100 peptide vaccine and interleukin-2 in patients with advanced melanoma. N Engl J Med. 2011;364:2119–27.
265. Agarwala SS. Novel immunotherapies as potential therapeutic partners for traditional or targeted agents: cytotoxic t-lymphocyte antigen-4 blockade in advanced melanoma. Melanoma Res. 2010;20:1–10.
266. Robert C, Ghiringhelli F. What is the role of cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma? Oncologist. 2009;14:848–61.
266a. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363:711–23.
266b. Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med. 2011;364:2517–26.
267. Sarnaik AA, Weber JS. Recent advances using anti-CTLA-4 for the treatment of melanoma. Cancer J. 2009;15:169–73.
268. Ribas A, Comin-Anduix B, Chmielowski B, et al. Dendritic cell vaccination combined with CTLA4 blockade in patients with metastatic melanoma. Clin Cancer Res. 2009;15:6267–76.
269. Lens M. The role of vaccine therapy in the treatment of melanoma. Expert Opin Biol Ther. 2008;8:315–23.
270. Terando AM, Faries MB, Morton DL. Vaccine therapy for melanoma: current status and future directions. Vaccine. 2007;25(Suppl 2):B4–16.
271. Kirkwood JM, Lee S, Moschos SJ, et al. Immunogenicity and antitumor effects of vaccination with peptide vaccine+/-granulocyte-monocyte colony-stimulating factor and/or ifn-alpha2b in advanced metastatic melanoma: Eastern Cooperative Oncology Group phase II trial e1696. Clin Cancer Res. 2009;15: 1443–51.
272. Dudley ME, Wunderlich JR, Yang JC, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol. 2005;23:2346–57.
273. Dudley ME, Yang JC, Sherry R, et al. Adoptive cell therapy for patients with metastatic melanoma: evaluation of intensive myeloablative chemoradiation preparative regimens. J Clin Oncol. 2008;26:5233–9.
274. Dudley ME, Wunderlich JR, Shelton TE, et al. Generation of tumor-infiltrating lymphocyte cultures for use in adoptive transfer therapy for melanoma patients. J Immunother. 2003;26:332–42.
275. Besser MJ, Shapira-Frommer R, Treves AJ, et al. Clinical responses in a phase ii study using adoptive transfer of short-term cultured tumor infiltration lymphocytes in metastatic melanoma patients. Clin Cancer Res. 2010;16:2646–55.
276. Koike N, Pilon-Thomas S, Mule JJ. Nonmyeloablative chemotherapy followed by T-cell adoptive transfer and dendritic cell-based vaccination results in rejection of established melanoma. J Immunother. 2008;31: 402–12.
277. Wallen H, Thompson JA, Reilly JZ, et al. Fludarabine modulates immune response and extends in vivo survival of adoptively transferred CD8 T cells in patients with metastatic melanoma. Plos One. 2009;4:E4749.
278. Flaherty KT. New molecular targets in melanoma. Curr Opin Oncol. 2004;16:150–4.
279. Tuveson DA, Weber BL, Herlyn M. BRAF as. a potential therapeutic target in melanoma and other malignancies. Cancer Cell. 2003;4:95–8.
280. Smalley KS. Understanding melanoma signaling networks as the basis for molecular targeted therapy. J Invest Dermatol. 2010;130:28–37.
281. Lorigan P, Eisen T, Hauschild A. Systemic therapy for metastatic malignant melanoma – from deeply disappointing to bright future? Exp Dermatol. 2008;17:383–94.
281a. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364:2507–16.
282. Tawbi H, Nimmagadda N. Targeted therapy in melanoma. Biologics. 2009;3:475–84.
283. Lasithiotakis KG, Sinnberg TW, Schittek B, et al. Combined inhibition of MAPK and mTOR signaling inhibits growth, induces cell death, and abrogates invasive growth of melanoma cells. J Invest Dermatol. 2008;128:2013–23.
284. Meier F, Busch S, Lasithiotakis K, et al. Combined targeting of MAPK and AKT signalling pathways is a promising strategy for melanoma treatment. Br J Dermatol. 2007;156:1204–13.
285. Meier F, Guenova E, Clasen S, et al. Significant response after treatment with the mTOR inhibitor sirolimus in combination with carboplatin and paclitaxel in metastatic melanoma patients. J Am Acad Dermatol. 2009;60:863–8.
286. Sinnberg T, Lasithiotakis K, Niessner H, et al. Inhibition of PI3K-AKT-mTOR signaling sensitizes melanoma cells to cisplatin and temozolomide. J Invest Dermatol. 2009;129:1500–15.
287. Francken AB, Bastiaannet E, Hoekstra HJ. Follow-up in patients with localised primary cutaneous melanoma. Lancet Oncol. 2005;6:608–21.
288. Garbe C. A rational approach to the follow-up of melanoma patients. Recent Results Cancer Res. 2002;160:205–15.
289. Leiter U, Buettner PG, Eigentler TK, et al. Is detection of melanoma metastasis during surveillance in an early phase of development associated with a survival benefit? Melanoma Res. 2010;20:240–6.
290. Garbe C, Paul A, Kohler-Spath H, et al. Prospective evaluation of a follow-up schedule in cutaneous melanoma patients: recommendations for an effective follow-up strategy. J Clin Oncol. 2003;21:520–9.

Vascular Neoplasms and Neoplastic-like Proliferations

114

Paula E North and Jay Kincannon

Chapter Contents

Benign vascular neoplasms and reactive hyperplasias *1915*
Borderline and low-grade malignant vascular neoplasms *1928*
Malignant vascular neoplasms *1935*
Perivascular neoplasms and neoplastic-like proliferations *1937*

INTRODUCTION

In this chapter we use the term *neoplasm* synonymously with *tumor* in a general, albeit imperfect[1], sense, consistent with its common usage: *an abnormal proliferation ("new growth") of cells that appears to be relatively autonomous (i.e. not reactive)*. Of note, common infantile hemangiomas are discussed separately (see Ch. 103) as are telangiectatic lesions (see Ch. 106) and vascular malformations (see Ch. 104); the latter, however, may be associated, in some patients, with a number of the cellular vascular proliferations discussed herein. Several entities with established or suspected features of reactive processes that mimic neoplasms are included in this chapter (Table 114.1) as is Kaposi sarcoma, a virus-associated and possibly virus-induced process of as-yet-uncertain position on the hyperplasia–neoplasia spectrum, but with an associated mortality rate. Two benign vascular proliferations of more seemingly straightforward infectious etiology (bacillary angiomatosis and verruga peruana) are covered elsewhere (see Ch. 74). With these caveats in mind, a broad working classification of vascular neoplasms and neoplastic-like conditions is presented in Table 114.1. Vascular neoplasms with classic associations with syndromes or laboratory findings appear in Figure 114.1.

BENIGN VASCULAR NEOPLASMS AND REACTIVE HYPERPLASIAS

Intravascular Papillary Endothelial Hyperplasia (PEH)

Synonyms: ■ Masson's lesion ■ Masson's pseudoangiosarcoma ■ Masson's tumor ■ Masson's hemangio-endotheliome vegetant intravasculaire

Key features

- Not a specific disease entity, but rather a distinct histopathological pattern that can be confused with angiosarcoma
- The primary or "pure" form is not associated with a pre-existing vascular anomaly and appears as a solitary, slowly growing, often painful nodule located within a dilated dermal, subcutaneous or submucosal vein
- Secondary forms are associated with venous malformations and other vascular anomalies prone to thrombosis
- Rare forms are extravascular, probably arising within hematomas
- Thought to represent an unusual, exuberant response of endothelial cells to organizing thrombus

Introduction

Masson first described this process in 1923 in hemorrhoidal veins, terming it *hemangio-endotheliome vegetant intravasculaire*, and interpreted it as a neoplastic process mimicking angiosarcoma. In 1932, Henschen re-interpreted the process as reactive, and in 1971 Kauffman and Stout noted its occurrence not only in thrombosed vessels but also in a hematoma, further demonstrating the potential for confusion with soft tissue angiosarcoma. A lymphatic vessel counterpart of Masson's lesion was reported in 1979 in a cystic lymphatic malformation[2].

Epidemiology

Papillary endothelial hyperplasia (PEH) shows a slight female predominance, most pronounced for the rare extravascular examples[3]. Although lesions can occur at any age, most are in adults, with an average age of 34 years. A history of trauma was elicited in a small minority of patients[3].

Pathogenesis

Areas of papillary endothelial hyperplasia can, in most cases, be seen to merge with definitive thrombus material, in support of the notion that they represent an unusual form of thrombus organization.

Clinical features

Primary lesions of superficial tissues appear as solitary, firm masses, often with red or blue discoloration of the overlying skin or mucosa. The history is typically one of slow growth over a period of several months or years. These occur most commonly within veins of the head and neck and, interestingly, the fingers, but they may also arise elsewhere[3]. In a study of 314 cases, 56% were of the primary form, 40% were associated with other vascular lesions, and 4% appeared extravascularly[3]. Clinical features of the secondary forms are those of the underlying vascular anomaly.

Pathology

Intravascular examples may be limited to the confines of a single thin-walled vein or may arise, often multifocally, within pre-existing vascular lesions such as venous malformations, glomuvenous malformations (glomangiomas), spindle cell hemangiomas and pyogenic granulomas (Fig. 114.2). Foci of intravascular papillary endothelial hyperplasia are extremely common in venous malformations and serve to distinguish these low-flow lesions from high-flow arteriovenous malformations. Rarely, the involved vessel wall is ruptured, allowing the proliferative vascular process to spill out into the adjacent stroma. Extravascular examples that on serial sectioning show no evidence of a surrounding blood vessel wall may have arisen within an organizing hematoma[3].

Early lesions show growth of endothelial sprouts into fibrinous thrombus material, dividing it into papillary fronds lined by a single layer of plump endothelial cells with minimal mitotic activity and no significant cytologic atypia (Fig. 114.2, insert). The early fibrin cores of the papillae become collagenized and hyalinized with time, and the endothelial lining becomes thin and attenuated. Lesional papillae may fuse to form an anastomosing meshwork of vessels separated by connective tissue stroma that mimics angiosarcoma. However, the relatively high mitotic rate, striking pleomorphism and necrosis that characterize angiosarcoma are lacking[4].

Differential diagnosis

The clinical appearance of these lesions is nonspecific, and diagnosis relies on microscopic examination. The most important differential diagnostic consideration for the pathologist is well-differentiated angiosarcoma.

A WORKING CLASSIFICATION OF VASCULAR TUMORS AND ANOMALIES
REACTIVE CONDITIONS
• ***Intravascular papillary endothelial hyperplasia***
• ***Reactive angioendotheliomatosis***
– ***Intravascular reactive angioendotheliomatosis***
– ***Diffuse dermal angiomatosis***
• Eruptive pseudoangiomatosis (self-limited exanthem of bright-red angioma-like lesions, originally described in children)
VASCULAR AND LYMPHATIC MALFORMATIONS (see Ch. 104)
• Capillary malformation (port-wine stain)
• Venous malformation
• Lymphatic malformation (microcystic and macrocystic)
• Mixed capillary/venous/lymphatic malformation ("lymphangioma")
• Arteriovenous malformation
• Verrucous "hemangioma"
TELANGIECTASIAS (see Ch. 106)
• Generalized essential telangiectasia
• Unilateral nevoid telangiectasia
• Hereditary hemorrhagic telangiectasia
• Hereditary benign telangiectasia
• Angioma serpiginosum
• Spider nevus
• Venous lake
• ***Angiokeratoma*** (exception is angiokeratoma circumscriptum, which represents a capillary/lymphatic or capillary malformation)
BENIGN VASCULAR NEOPLASMS
• Infantile hemangioma (see Ch. 103)
• Congenital hemangioma (see Ch. 103)
• ***Cherry angioma***
• ***Sinusoidal hemangioma***
• ***Hobnail hemangioma (targetoid hemosiderotic hemangioma)***
• ***Tufted angioma***
• ***Multifocal lymphangioendotheliomatosis with thrombocytopenia***
• ***Glomeruloid hemangioma****
• ***Microvenular hemangioma****
• ***Angiolymphoid hyperplasia with eosinophilia (ALHE)****
• ***Pyogenic granuloma (lobular capillary hemangioma)****
• ***Spindle cell hemangioma***†
• Epithelioid angiomatous nodule (debate as to whether it is a variant of epithelioid hemangioma or ALHE)
• Papillary hemangioma
• Acquired elastotic hemangioma (hobnail endothelial pattern in association with solar elastosis)
• Cutaneous pseudoangiomatous stromal hyperplasia (primarily encountered in the breast)
BORDERLINE AND LOW-GRADE MALIGNANT VASCULAR NEOPLASMS
• ***Kaposiform hemangioendothelioma***
• ***Dabska-type hemangioendothelioma (papillary intralymphatic angioendothelioma [PILA])***
• ***Retiform hemangioendothelioma***
• ***Epithelioid hemangioendothelioma***
• ***Kaposi sarcoma***
MALIGNANT VASCULAR NEOPLASMS
• ***Angiosarcoma***
PERIVASCULAR NEOPLASMS AND NEOPLASTIC-LIKE CONDITIONS
• ***Glomus tumor (proper)***
• ***Glomuvenous malformation ("glomangioma")***
• ***Infantile-type hemangiopericytoma/myofibromatosis***
• Adult-type hemangiopericytoma
• Glomangiopericytoma
• Myopericytoma
• PEComa (*p*erivascular *e*pithelioid *c*ell tumor)‡
*Also viewed as a reactive condition.
†Also viewed as a vascular malformation.
‡A spectrum of mesenchymal tumors that includes clear cell "sugar" tumor of the lung, angiomyolipoma, lymphangiomyomatosis, clear cell myomelanocytic tumor, and the rare *cutaneous* tumors with a similar morphology and phenotype.

Table 114.1 A working classification of vascular tumors and anomalies. Entities covered in this chapter are in bold italics.

Treatment

Surgical excision is usually curative. Local recurrences may occur when the lesion is superimposed on a vascular malformation that may generate new foci of endothelial hyperplasia.

Reactive Angioendotheliomatosis

Key features

- Rare, self-limited process occurring exclusively in the skin and characterized histologically by a dense proliferation of small capillaries
- The most common form is predominantly intravascular, resulting in luminal obliteration of pre-existing dermal vessels; many of these patients have vaso-occlusive disorders or systemic infections
- Should be distinguished from *intravascular large cell lymphoma (B or NK/T)*, an angiotropic lymphoma erroneously termed *malignant angioendotheliomatosis* prior to the advent of discriminating immunohistochemistry

Introduction

Angioendotheliomatosis has historically been considered to be a single disease entity, divided into benign and malignant variants. As such, the large pleomorphic cells found within blood vessels in malignant angioendotheliomatosis were thought to be transformed endothelial cells. More recently, immunohistochemical studies have convincingly demonstrated that these cells are neoplastic lymphocytes. Accordingly, *malignant angioendotheliomatosis* has been renamed *intravascular large cell lymphoma (B or NK/T)* (see Ch. 119). The benign form is a true angioendotheliomatosis and is considered reactive.

Epidemiology

Reactive angioendotheliomatosis is rare and although it can occur at any age, the age of onset often reflects that of any associated systemic disorder. While many cases are idiopathic, this vascular proliferation is frequently associated with systemic disorders such as bacterial endocarditis, monoclonal gammopathies (including type I cryoglobulinemia), antiphospholipid syndrome, renal transplantation, hepatic disease and rheumatoid arthritis. The diffuse dermal angiomatosis variant, whether on the leg or the breast[5], is associated with atherosclerosis and cigarette smoking.

Pathogenesis

Reactive angioendotheliomatosis is a benign self-limited process. Its frequent association with various systemic conditions has led some investigators to propose that the capillary proliferation may be caused by a circulating angiogenic factor[6]. However, the fact that many of the disorders associated with this process cause vascular occlusion or tissue ischemia suggests that a local, hypoxia-induced increase in vascular endothelial growth factor (VEGF) may be playing a role. In addition, immunological factors may contribute to the proliferative process.

Clinical features

Although erythematous nodules or plaques, often with superimposed petechiae or ecchymoses, are the characteristic primary lesions, the spectrum ranges from erythematous macules to tumor-like masses. Sites of involvement can vary, but the most common is the lower extremities. Focal ulceration may be evident, especially in the diffuse dermal angiomatosis variant.

Pathology

In this predominantly dermal, but also occasionally subcutaneous, process, there is a poorly marginated proliferation of closely packed capillaries lined by plump endothelial cells rimmed by small numbers of pericytes. The pattern of proliferation is highly variable both within and between lesions and is typically described as diffuse and/or lobular[7]. Focally, more dilated capillaries may be present and foci of hemosiderin

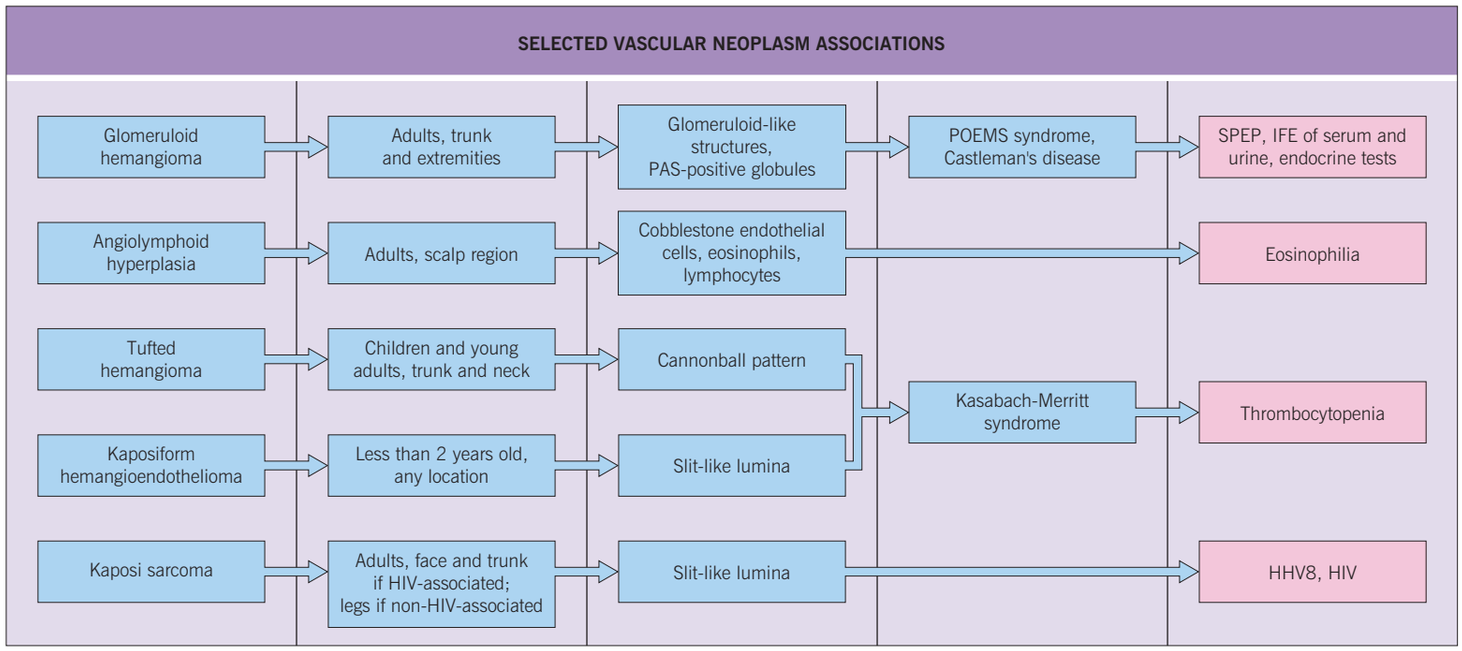


Fig. 114.1 Selected vascular neoplasm associations. IFE, immunofixation electrophoresis; SPEP, serum protein electrophoresis. HHV8, human herpesvirus 8; HIV, human immunodeficiency virus, PAS, periodic acid-Schiff stain.

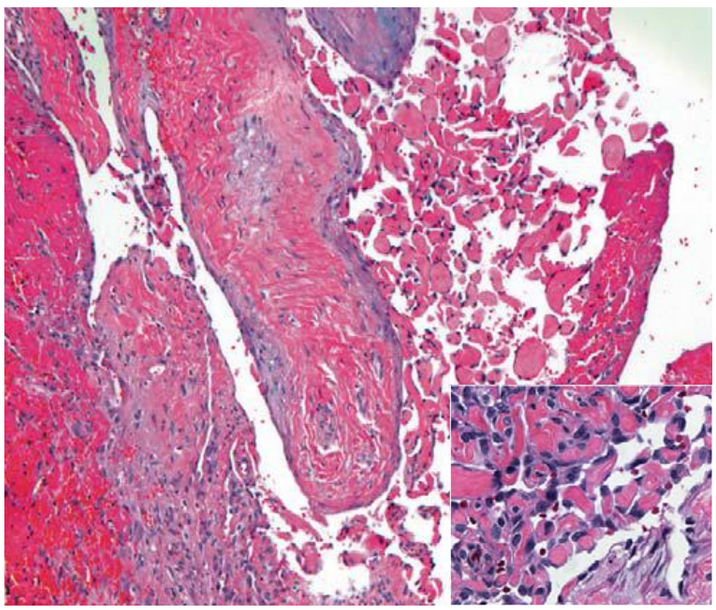


Fig. 114.2 Histology of papillary endothelial hyperplasia. Hyperplastic endothelial cells line stromal papillae formed within organizing thrombus material. Complex networks of recanalizing thrombus may mimic angiosarcoma (insert).

deposition, fibrin microthrombi and/or mild chronic inflammation are relatively common. Immunohistochemical positivity for endothelial markers such as CD31 and von Willebrand's factor, and focally for pericyte/smooth muscle-associated actins, confirms the cellular composition. Cytologic atypia is absent and mitotic figures are rare to absent.

The capillary lumina are small and may be occluded by fibrin thrombi and bulging endothelial cells (Fig. 114.3A). In many cases, the proliferating capillaries appear to be contained within a larger, pre-existing vessel, obliterating its lumen, but sometimes the proliferation extends directly between collagen bundles (Fig. 114.3B). Cases associated with cryoglobulinemia typically show intraluminal and intracellular eosinophilic globules, but this finding can also be seen in the absence of cryoglobulinemia.

Differential diagnosis

The clinical differential diagnosis includes vascular tumors (e.g. Kaposi sarcoma, angiosarcoma) as well as other causes of ulceration (see Fig. 105.1). Histologically, one must consider other forms of intravascular endothelial proliferation, including intravascular pyogenic granuloma, Dabska's tumor and intravascular papillary endothelial hyperplasia.

Treatment

Evaluation for known associated systemic disorders is important because lesions may regress upon resolution of the underlying condition, e.g. revascularization of an ischemic limb. In case reports, oral isotretinoin has led to improvement, possibly due to its antiangiogenic properties[8].

Glomeruloid Hemangioma

Key features

- A histologically distinct type of hemangioma that occurs in patients with POEMS syndrome
- In POEMS syndrome, presents as multiple, small, firm, angiomatous papules scattered primarily on the trunk and proximal extremities
- Characterized histologically by nests of capillaries within dilated dermal vessels, resembling renal glomeruli
- May be induced by increased circulating levels of vascular endothelial growth factor

Introduction and history

The term *glomeruloid hemangioma* was coined by Chan et al.[9] in 1990 to describe a distinctive vascular proliferation that occurs in patients with POEMS syndrome (*p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *m*onoclonal gammopathy, and *s*kin lesions), sometimes in association with multicentric Castleman's disease. Although there is some overlap with reactive angioendotheliomatosis, it is discussed separately because of its highly distinctive histologic features and well-recognized clinical association.

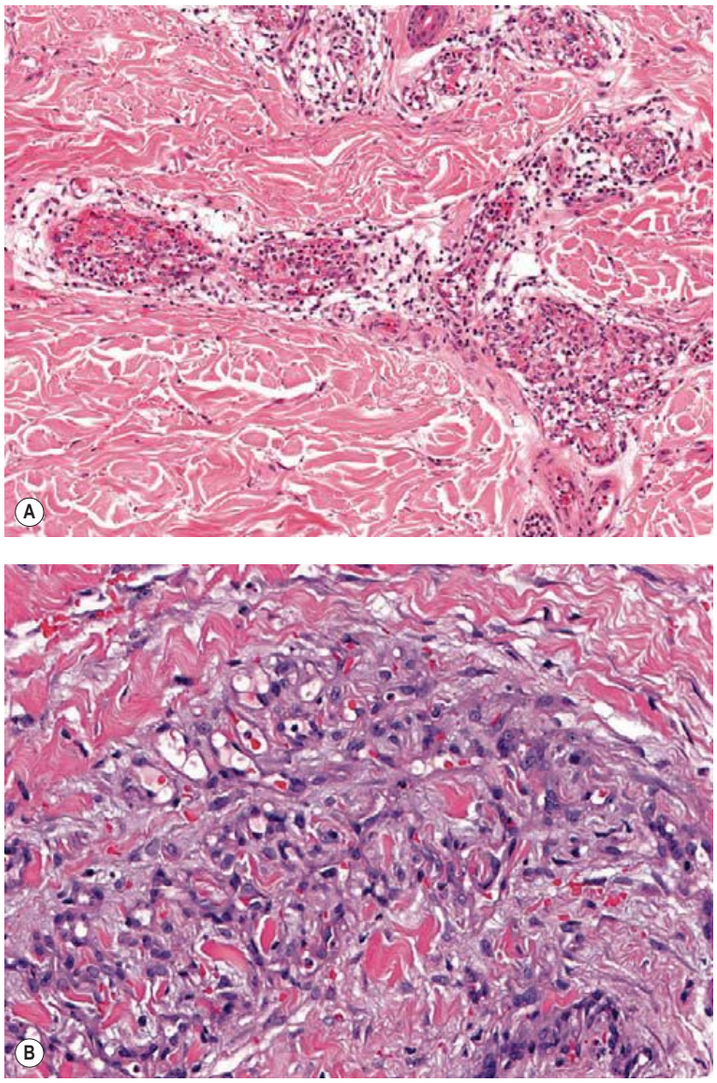


Fig. 114.3 Reactive angioendotheliomatosis. A Intravascular variant with proliferation of grouped capillaries along the course of a dermal blood vessel. The endothelial cells lack atypia and within several capillaries there is an intraluminal proliferation of endothelial cells admixed with erythrocytes occluding the lumina. **B** Diffuse dermal angiomatosis variant with proliferation of hyperplastic endothelial cells without atypical features infiltrating the dermis and forming small vascular lumina. *A, Courtesy, Heinz Kutzner, MD; B, Courtesy, Lorenzo Cerroni, MD.*

POEMS SYNDROME – CLINICAL CRITERIA, CUTANEOUS FINDINGS AND ASSOCIATED VASCULAR LESIONS
DIAGNOSTIC CRITERIA
***M*onoclonal plasmaproliferative disorder** – *and* – **Sensorimotor *p*olyneuropathy** *plus at least one other major and one minor criterion*
Major criteria
• Sclerotic bone lesions • Castleman's disease • Increased circulating levels of VEGF
Minor criteria
• Extravascular volume overload (peripheral edema, pleural effusions, ascites) • Thrombocytosis • Papilledema • *O*rganomegaly (hepatosplenomegaly) or lymphadenopathy • *E*ndocrinopathy (e.g. adrenal, pituitary, gonadal, parathyroid) • *S*kin changes (characteristic)
CUTANEOUS FINDINGS
• More common: diffuse hyperpigmentation, induration, hypertrichosis, hyperhidrosis • Less common: clubbing, livedo reticularis, acrocyanosis, flushing
TYPES OF VASCULAR LESIONS
• Cherry hemangiomas • Glomeruloid hemangiomas • Other: reactive angioendotheliomatosis, intravascular papillary endothelial hyperplasia, lobular capillary hemangiomas, microvenular hemangiomas

Table 114.2 POEMS syndrome – clinical criteria, cutaneous findings and associated vascular lesions. VEGF, vascular endothelial growth factor. *Adapted from Dispenzieri A. Blood Rev. 2007;21:285–99.*

Clinical features

The reported incidences of angiomas in patients with POEMS syndrome range from 25% to 45%. These appear as multiple, firm, dome-shaped, red to purple papules ranging in diameter from a few millimeters to a few centimeters and are scattered predominantly over the trunk and proximal extremities (see Ch. 53). Additional cutaneous manifestations of POEMS syndrome are outlined in Table 114.2, as are the types of vascular lesions that occur in these patients. True glomeruloid hemangiomas appear to be fairly specific for POEMS syndrome, although rarely they may appear years prior to recognition of the syndrome[10]. In addition, there are reports of a solitary variant that is not associated with POEMS syndrome.

Pathogenesis

Glomeruloid hemangiomas are thought to be reactive, rather than neoplastic. Patients with POEMS syndrome often have increased circulating levels of VEGF[11] such that this elevation represents a major diagnostic criterion (see Table 114.2). Most cases of POEMS syndrome associated with multicentric Castleman's disease (~90%) have evidence of human herpesvirus-8 (HHV-8) infection by PCR. It is suspected that viral interleukin (IL)-6 produced by the HHV-8 may indirectly promote angiogenesis by inducing VEGF expression[12].

Pathology

Most of the angiomas seen in patients with POEMS syndrome are found upon histologic examination to be consistent with common cherry angiomas, with numerous dilated dermal capillaries lined by flattened endothelial cells (see below). Only a few demonstrate the distinctive features of glomeruloid hemangioma. These consist of dilated dermal vessels filled by small, well-formed capillary loops that lead to structures reminiscent of renal glomeruli (Fig. 114.4).

The capillaries comprising these glomeruloid formations are lined by flat endothelial cells surrounded by an outer layer of pericytes and are separated by a scant stroma containing large cells with lightly eosinophilic cytoplasm and multiple eosinophilic globules. The latter are PAS-positive, diastase-resistant, and immunopositive for polytypic immunoglobulin, presumably derived from the associated paraprotein[9]. Of note, these interstitial, immunoglobulin-containing cells are of endothelial derivation. Lastly, since many POEMS syndrome patients have both cherry angiomas and glomeruloid hemangiomas, and the cherry angiomas may display focal glomeruloid formation, it is likely that these two histologic subsets reflect different stages of the same process[9].

Differential diagnosis

The clinical differential diagnosis includes other vascular proliferations and tumors (see Table 114.1) while the histologic differential diagnosis of glomeruloid hemangioma is essentially that described above for reactive angioendotheliomatosis. A more recently described entity, *papillary hemangioma*, also enters the histologic differential diagnosis[13]. The latter is characterized by intravascular papillary growths of capillaries, pericytes and stromal cells within ectatic dermal vessels, accompanied by hyaline globules (features reminiscent of glomeruloid hemangioma), but it differs by being solitary, being confined to the head and neck region, and having neither a true glomeruloid architecture nor an association with POEMS syndrome.

Treatment

Treatment is not required, although shave excision, cryosurgery, electrodesiccation, or pulsed dye laser surgery will remove the vascular tumors.

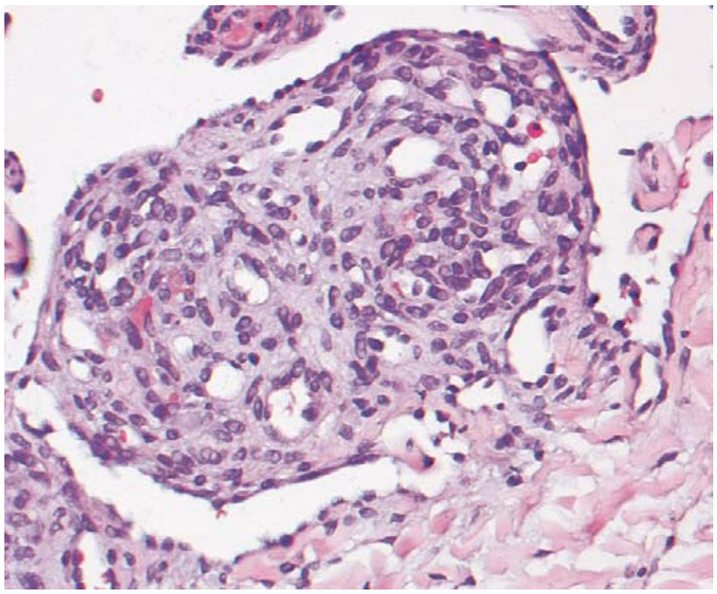


Fig. 114.4 Histology of a glomeruloid hemangioma in a patient with POEMS syndrome. Dilated dermal vessels are filled with congeries of small capillaries reminiscent of renal glomeruli.

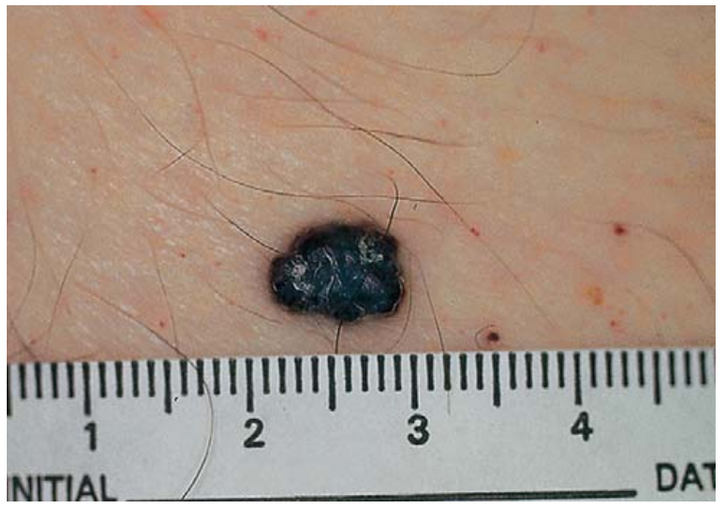


Fig. 114.5 Solitary angiokeratoma. Because of their dark color, these lesions may resemble cutaneous melanoma. Dermoscopy will readily distinguish between these two entities. *Courtesy, Jean L Bolognia, MD.*

Fig. 114.6 Scrotal angiokeratomas. These lesions typically arise along superficial vessels.

Angiokeratomas

Key features

- Small, dark, vascular and variably keratotic lesions that result from dilation of superficial vessels
- Angiokeratoma circumscriptum is a capillary–lymphatic or capillary malformation
- Angiokeratoma corporis diffusum results from several lysosomal storage disorders and is associated with systemic manifestations

Introduction

Angiokeratomas are well-circumscribed vascular lesions consisting of superficial vascular ectasia and hyperkeratosis. Five variants have been recognized. With the exception of angiokeratoma circumscriptum (which represents a capillary–lymphatic or capillary malformation), angiokeratomas result from ectatic dilation of pre-existing vessels in the papillary dermis.

Clinical features

Solitary or multiple angiokeratomas

Most commonly, they present as a small, warty, black papule on the lower extremities, but may occur anywhere on the body (Fig. 114.5). The lesions are thought to result from injury/trauma to or chronic irritation of the wall of a venule in the papillary dermis. Solitary lesions may be confused with melanoma due to their dark color. Dermoscopy will readily distinguish between these two entities (see Ch. 0).

Angiokeratomas of the scrotum and vulva

Synonym: ■ Angiokeratoma of Fordyce

These angiokeratomas may arise in the second or third decade but are most commonly seen in older age groups. The lesions are red-purple to black in color, may be single or multiple, and arise along superficial vessels (Fig. 114.6). In some patients, they may be associated with thrombophlebitis, varicoceles and inguinal hernias. Vulvar lesions may be associated with vulvar varicosities, hemorrhoids, oral contraceptive use, or increased venous pressure during pregnancy.

Angiokeratoma corporis diffusum

This disorder is characterized by the development of multiple, often clustered angiokeratomas, usually in a bathing trunk distribution. Lesions vary in number (from only a few to numerous) and usually begin to appear during late childhood or adolescence. X-linked recessive Fabry disease is the best known entity with this clinical presentation and results from a deficiency of the lysosomal enzyme α-galactosidase A (see Ch. 63). This leads to the accumulation of the neutral glycolipid ceramide trihexidose within lysosomes of multiple cell types. Other enzyme deficiencies associated with angiokeratoma corporis diffusum are outlined in Table 63.6.

Angiokeratoma of Mibelli

Lesions usually develop between the ages of 10 and 15 years and are most commonly situated on the dorsal and lateral aspects of the fingers and toes. They may also occur on the dorsa of the hands and feet and rarely on the elbows and knees. Angiokeratoma of Mibelli may be associated with chilblains and acrocyanosis. In rare instances, ulceration of the fingertips can occur. There is a familial predisposition and the disorder may be transmitted in an autosomal dominant fashion with variable penetrance.

Fig. 114.7 Angiokeratoma circumscriptum. These grouped red–violet papules had been present since childhood. *Courtesy, Jean L Bolognia, MD.*

Angiokeratoma circumscriptum

This entity usually develops during infancy or childhood as either a plaque of multiple discrete papules (Fig. 114.7) or hyperkeratotic papules and nodules that often become confluent. They occur on the trunk, arms or legs and are unilateral in most patients. There is a female predominance.

Pathology

Marked dilatation of the papillary dermal vessels is seen in association with an acanthotic, variably hyperkeratotic epidermis. Elongated rete ridges may partially or completely enclose vascular channels, and a collarette may be present at the margin of the lesions. In Fabry disease, vacuoles can be detected within endothelial cells and pericytes. The amount of glycolipid is small and may be difficult to detect in routinely prepared sections. However, the deposits are PAS-positive and Sudan black-positive and these stains can therefore assist in diagnosis. They can also be demonstrated by electron microscopy.

Differential diagnosis

Angiokeratomas should be distinguished from other vascular lesions. In particular, darkly colored or thrombosed angiokeratomas may resemble cutaneous melanoma.

Treatment

Patients may request removal for cosmetic reasons. This may be achieved by shave excision, diathermy or laser therapy, the choice of which would largely depend on the size of the lesion.

Microvenular Hemangioma

Synonym: ■ Microcapillary hemangioma

Key features

- An uncommon, acquired, slowly growing, benign vascular tumor of young to middle-aged adults of both genders
- Presents as a small, usually solitary, sharply circumscribed red papulonodule or plaque on the trunk or extremities, with a predilection for the forearms
- Consists of small branching capillaries and venules with collapsed lumina and conspicuous pericytes infiltrating the full thickness of the reticular dermis
- May be subject to hormonal influences in some women

Introduction and history

Microvenular hemangioma was first described by that name in 1991 by Hunt, Santa Cruz and Barr[14], although cases reported as microcapillary hemangiomas are probably identical.

Epidemiology

Reported cases have been in young and middle-aged adults of both sexes. Some cases in women have been temporally related to pregnancy or oral contraceptive use, although this has not been widely corroborated.

Pathogenesis

Microvenular hemangiomas have been reported in patients with POEMS syndrome[15], suggesting that these lesions, like glomeruloid hemangiomas, may be of reactive etiology. Observations that some microvenular hemangiomas affecting women present in association with pregnancy or oral contraceptive use arguably suggest a hormonal influence.

Clinical features

Microvenular hemangioma typically presents as a solitary, purple to red, slowly enlarging papule, plaque or small nodule on the trunk or extremities (rarely the face). There appears to be a particular predilection for the forearms, and most lesions are less than 2 cm in diameter[15]. Although the majority are asymptomatic, mild erythema and tenderness have been reported.

Pathology

Histologically, lesions are poorly circumscribed proliferations of small, relatively monomorphous, branching capillaries and venules involving the full thickness of the reticular dermis. Unlike port-wine stains, in which vascular ectasia is prominent, the vascular lumina of this tumor are inconspicuous and often collapsed. Cells lining the vessels show no atypia and are strongly positive for endothelial markers and are associated with smooth muscle actin-positive pericytes. The vessels are not as delicate or angulated as the lymphatic-like vessels of Kaposi sarcoma or vessels of microcystic lymphatic malformations and often contain red blood cells. The pericytic component is obvious even in routine H&E-stained sections.

Differential diagnosis

The major histologic differential diagnostic consideration for these acquired lesions is patch-stage Kaposi sarcoma. Kaposi sarcoma differs by the presence of delicate lymphatic-like vessels, plasma cells, eosinophilic globules, and interstitial fascicles of spindle cells.

Treatment

Surgical excision has been effective in reported cases.

Angiolymphoid Hyperplasia with Eosinophilia (AHE)

Synonyms: ■ Epithelioid hemangioma ■ Pseudopyogenic granuloma ■ Inflammatory angiomatous nodule ■ Papular angioplasia ■ Inflammatory arteriovenous hemangioma ■ Intravenous atypical vascular proliferation ■ Nodular angioblastic hyperplasia with eosinophilia and lymphofolliculosis ■ Histiocytoid hemangioma[16]

Key features

- Benign angiomatous nodules or plaques, often multiple and grouped, usually located in the head and neck region, especially around the ears
- May be painful, pruritic or pulsatile, and often recur after excision
- Characterized histologically by proliferations of capillary-sized vessels with epithelioid endothelial cells surrounding larger, thick-walled vessels, accompanied by eosinophils and lymphocytes
- May be associated with arteriovenous shunts
- Kimura's disease now thought to be a separate clinicopathological entity

Introduction and history

Angiolymphoid hyperplasia with eosinophilia (AHE) was first described in 1969 by Wells and Whimster[17]. They considered AHE to be a late stage of Kimura's disease, described in the Japanese literature in 1948. It is now generally accepted that these are two separate entities[18].

Epidemiology

AHE occurs in young to middle-aged adults without gender predilection. Previous reports of a female predominance are not supported by more recent series. A history of trauma can be elicited in some patients[19].

Pathogenesis

The frequent presence of mural damage or rupture in intralesional large vessels of AHE has suggested a role for trauma or arteriovenous shunting in its pathogenesis[19]. Cases have been described in association with arteriovenous fistulas and malformations. These findings suggest that in some patients AHE may be reactive, rather than neoplastic, especially in those with this latter type of lesion.

Clinical features

AHE typically presents as papules or nodules that are tan, brown, pink or dull red in color and are located predominantly in the head and neck region, especially around the ears and on the forehead and scalp (Fig. 114.8). Less commonly, lesions have been observed in the mouth and on the trunk, distal extremities, vulva and penis. Most papulonodules are dermal in location, but some are subcutaneous; occasionally, AHE involves deeper soft tissues or arises from vessels[4]. Approximately half of patients have multiple lesions, generally in a clustered pattern[4]. AHE can be either asymptomatic or painful, pruritic or pulsatile[19]. Some patients have regional lymph node enlargement and peripheral eosinophilia.

Fig. 114.8 Angiolymphoid hyperplasia with eosinophilia. Multiple pink papulonodules are often seen on the scalp.

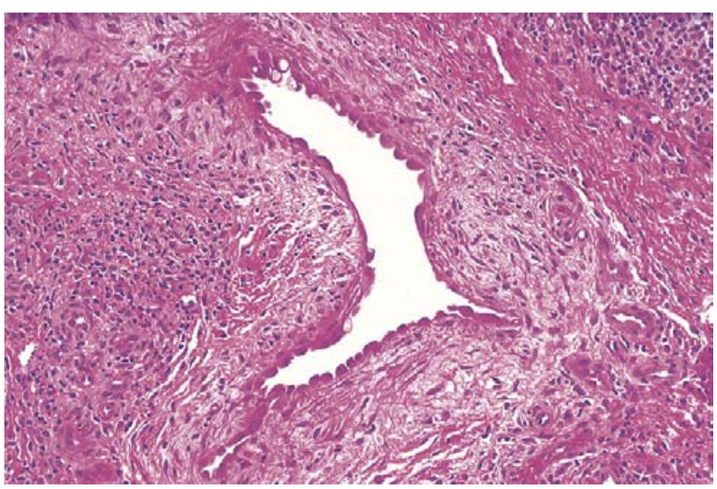


Fig. 114.9 Histology of angiolymphoid hyperplasia with eosinophilia. Enlarged endothelial cells protrude into the lumen of the central blood vessel, producing a scalloped or "cobblestone" appearance. An infiltrate of lymphocytes and eosinophils surrounds the vessel. *Courtesy, Ronald P Rapini, MD.*

Pathology

Typical lesions involving the dermis and subcutaneous tissue are well circumscribed and show vaguely lobular proliferations of capillary-sized vessels surrounding larger central blood vessels, with a variably dense perivascular inflammatory infiltrate rich in lymphocytes and eosinophils (Fig. 114.9). Scattered ectatic lymphatic vessels are variably present. Mast cells and plasma cells are usually also present, and nodular lymphoid aggregates, with or without germinal centers, may be prominent in subcutaneous lesions. The stroma is fibrous, and the larger vessels have thick walls with prominent myxoid degeneration.

Many of the vessels, particularly the larger ones, are lined by enlarged endothelial cells that protrude into the lumen, producing a scalloped or "cobblestone" appearance. These epithelioid endothelial cells are responsible for the synonym *epithelioid hemangioma*. Inflammatory infiltration of medium- to large-sized arteries, with variable luminal occlusion, damage to elastic laminae, and even mural rupture, is common. In older lesions, fibrosis is more prominent, with a reduction in the inflammatory and vascular elements.

Differential diagnosis

AHE may resemble cutaneous lymphoid hyperplasia, lymphoma cutis, sarcoidosis, angiosarcoma, Kimura's disease, and richly vascularized metastatic tumors. Angiosarcoma lacks the eosinophils and is usually cytologically more atypical and hemorrhagic. Although AHE was previously postulated to be a variant of Kimura's disease, current opinion is that these represent distinct entities. Kimura's disease has much larger lymphoid follicles and is usually located on the posterior neck.

Treatment

Although rare instances of spontaneous regression have been reported, surgical excision is generally required. About one-third of lesions recur after excision[4], sometimes due to incomplete excision of an underlying nidus of arteriovenous (AV) shunting (e.g. an AV malformation, an acquired AV fistula). Intraoperative bleeding can be problematic. Various lasers (e.g. CO_2, pulsed dye, copper vapor) have been used with variable success. In a small case series, treatment with polidocanol sclerotherapy (for the deep vascular component) plus radiofrequency ablation was reportedly successful[20].

Spindle Cell Hemangioma

Synonym: ■ Spindle cell hemangioendothelioma

Key features

- Blue–red nodules that typically appear in the dermal and subcutaneous tissue of the distal extremities of young adults and children and tend to multiply locally
- Composed of thin-walled cavernous veins containing organizing thrombi, interspersed with fascicles of spindle cells resembling Kaposi sarcoma
- Originally interpreted as a low-grade angiosarcoma (*spindle cell hemangioendothelioma*), but now viewed as a benign lesion without metastatic potential (*spindle cell hemangioma*)
- Currently viewed by many as a vascular malformation complicated by thrombosis and irregular vascular collapse
- Tends to recur following resection

Introduction and history

This entity was first described by Weiss and Enzinger in 1986 as *spindle cell hemangioendothelioma* in order to recognize its spindle cell morphology and the fact that one case from their series of 26 had metastasized to a regional lymph node[21]. Results of larger studies with

extended follow-up have led to the current view that this tumor has no inherent malignant potential[4,22]. Based on these observations, Perkins and Weiss suggested in 1996 that the entity be renamed *spindle cell hemangioma*[22].

Epidemiology

Spindle cell hemangiomas usually occur in children and young adults, although in a series of 78 cases compiled by Perkins and Weiss[22], patient ages ranged from 8 to 78 years, with a median age of 32 years. However, those presenting during late adulthood appear to represent previously occult, longstanding lesions. There is no gender predilection. Spindle cell hemangiomas are occasionally associated with Maffucci syndrome[21–23], Klippel–Trenaunay syndrome[23], congenital lymphedema[21,23], and, rarely, epithelioid hemangioendothelioma.

Pathogenesis

This vascular proliferation[23–25] is thought to probably be a vascular malformation altered by thrombosis and irregular vascular collapse[4,22]. The typical development of multiple nodules over time within a given anatomic region may represent intravascular propagation[22].

Clinical features

Most spindle cell hemangiomas begin as a solitary, firm, red–blue nodule in the subcutaneous tissue and dermis of the distal upper or lower extremity, then slowly develop multifocally within a localized area (Fig. 114.10). Rarely there is involvement of skeletal muscle and occasionally tumors develop on the trunk, head and neck, or proximal limbs. Spindle cell hemangiomas are largely asymptomatic, but ~60% recur following resection[22].

Fig. 114.10 Spindle cell hemangioma. Clustered blue–red multifocal nodules are typical.

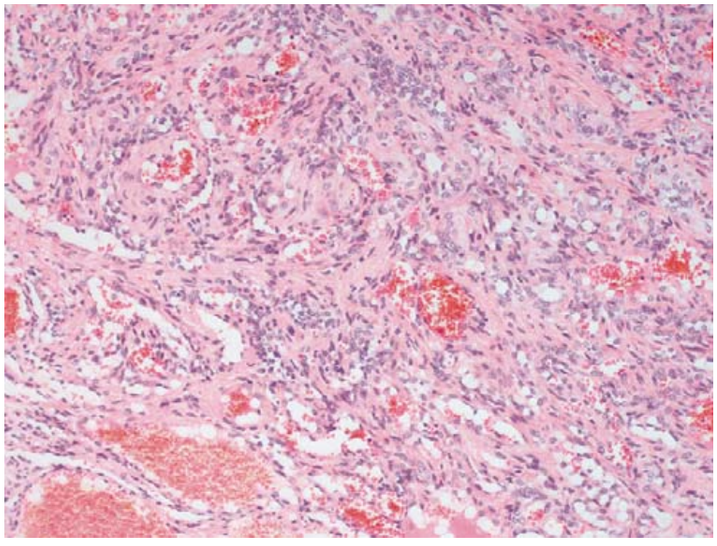


Fig. 114.11 Histology of spindle cell hemangioma. Collapsed veins containing organizing thrombi alternate with more cellular spindled areas and occasional vacuolated epithelioid cells.

Pathology

Hemorrhagic, often multiple, nodules are see within the dermis and subcutaneous tissue and are composed of two basic histologic elements (in variable combinations): (1) thin-walled, cavernous spaces containing organizing thrombi; and (2) more cellular areas containing spindle cells and occasional aggregates of vacuolated epithelioid cells (Fig. 114.11). The spindled areas stain focally for actin, form slit-like vascular spaces, and appear to consist of fibroblastic cells, pericytes and collapsed vessels[4]. The epithelioid interstitial cells, as well as the flattened cells lining the cavernous spaces, immunoreact positively for endothelial markers[23]. Cavernous vessels may show foci of intravascular papillary endothelial hyperplasia consistent with the presence of organizing thrombus material (see above). Frequently, remnants of residual vascular walls rim the lesion, suggesting intravascular development.

Differential diagnosis

These tumors may resemble nodular lesions of Kaposi sarcoma, but the latter lack cavernous vascular spaces and vacuolated epithelioid endothelial cells. The frequent presence of foci of intravascular papillary endothelial hyperplasia (Masson's lesion) within a spindle cell hemangioma may lead to misdiagnosis. A primary Masson's lesion is solitary and lacks epithelioid endothelial cells.

Treatment

Based upon the large series of Perkins and Weiss[22], simple surgical excision is successful in some patients (approximately 40%). The frequent local recurrences may reflect the inherent multifocality, with growth within vessels leading to discontinuous locoregional sites[22]. There is one report of the successful use of intralesional and intra-arterial IL-2, with no signs of recurrence at 24 months[26].

Pyogenic Granuloma

Synonyms: ■ Lobular capillary hemangioma ■ Granuloma pyogenicum ■ Tumor of pregnancy ■ Eruptive hemangioma ■ Granulation tissue-type hemangioma

Key features

- Rapidly growing, friable, red papule or polyp of skin or mucosa that frequently ulcerates; most common in children and young adults
- Examples arising on the gingiva of pregnant women (*granuloma gravidarum*) are considered a separate subgroup, but are histologically indistinguishable
- Consist of lobules of small capillaries set in a fibromyxoid matrix, often distinctly exophytic and bounded by collarettes of hyperplastic epithelium
- Occasionally found in subcutaneous or intravascular locations
- Neither infectious in etiology nor granulomatous histologically; often considered a reactive vascular hyperplasia rather than a neoplasm

Introduction and history

Poncet and Dor are credited with the initial description in 1897, and they believed the cause was a *Botryomyces* infection. The term *granuloma pyogenicum* was coined in 1904 by Hartzell to describe four similar cases that he thought represented a nonspecific granulation tissue-type response to any type of pyogenic agent[27]. Although the etiology of these common lesions remains uncertain today, the term *pyogenic granuloma* is clearly a misnomer. There is no evidence to

implicate any infectious agent, and the histologic appearance is not granulomatous.

Epidemiology

Pyogenic granulomas can develop at any age but are more common in children and young adults. There may be a slight male predominance, but no racial or familial predisposition. Gingival lesions are relatively common during pregnancy.

Pathogenesis

Pyogenic granulomas exhibit a number of clinical features suggestive of reactive neovascularization, including a common association with a pre-existing injury or irritation, limited capacity for growth, and a propensity for multiple eruptions that may be localized or disseminated. The occasional eruption of pyogenic granulomas within pre-existent port-wine stains[28] and other vascular malformations suggests that abnormalities in blood flow may be etiologically important in some cases.

Clinical features

The lesion presents as a solitary red papule or polyp that grows rapidly over the course of several weeks or months, stabilizes and then may decrease in size (Fig. 114.12). Its final size is rarely >1 cm, and it may persist indefinitely if not removed. Approximately one-third develop following minor trauma. In one series of 289 cases, the most common sites, in decreasing order of frequency, were the gingiva, fingers, lips, face and tongue[29]. They are extremely friable, frequently ulcerate and may bleed profusely with minor trauma. Multiple satellite lesions occasionally develop near a primary pyogenic granuloma, usually after destruction of that lesion[30]. Rarely, pyogenic granulomas arise within the subcutis, develop intravascularly or erupt in a disseminated fashion[31]. Pyogenic granulomas have been reported in association with systemic retinoids[32], indinavir, and EGFR inhibitors, but in some cases this may represent excessive granulation tissue.

Pathology

The quintessential lesion is a well-circumscribed, exophytic, sometimes pedunculated, proliferation of small capillaries, often arranged in a lobular pattern (Fig. 114.13). Lesional capillaries are lined by flattened to slightly plump endothelial cells, rimmed by pericytes, and surrounded by a variably edematous fibromyxoid interstitial stroma containing fibroblasts. Endothelial and stromal cell mitotic activity is highly variable and depends on the stage of growth; a scant infiltrate of lymphocytes, plasma cells and mast cells may be present. Capillary lumina within the lobules vary from small and angular to branching and ectatic, and foci of thrombosis and intravascular papillary endothelial hyperplasia may be present. A few larger vessels with smooth muscle walls, usually venous (but often including a small ascending arterial feeder), are frequently present at the base of the lesion. Thick, intervening bands of dense fibrous tissue sharply define the lobularity and help distinguish pyogenic granuloma from other lobular forms of capillary proliferation such as infantile hemangioma.

The lateral margins are often defined by prominent epithelial "collarettes" resulting from peripheral adnexal hyperplasia or, in some cases, from downward growth of rete ridges, bridged by flattened epidermis. The histology of many early lesions is altered by ulceration and secondary inflammatory change, leading to an appearance similar to granulation tissue, with radially oriented capillaries, fibrin deposition and a loss of lobularity. Intravascular and subcutaneous forms demonstrate features similar to superficial lesions, but without the inflammatory complications. Late-stage lesions are characterized by increased *intra*lobular and *inter*lobular fibrosis, as well as quiescent, flattened capillary endothelia.

Differential diagnosis

The diagnosis of pyogenic granuloma can be made clinically if the red, bleeding papule is coupled with the characteristic location and history. Otherwise they can be easily confused with amelanotic melanoma and, in the immunosuppressed patient, bacillary angiomatosis or Kaposi sarcoma. Glomus tumors, hemangiomas, and irritated melanocytic nevi and warts can all mimic pyogenic granulomas. Histologic conformation is always helpful in cases where the diagnosis is in question.

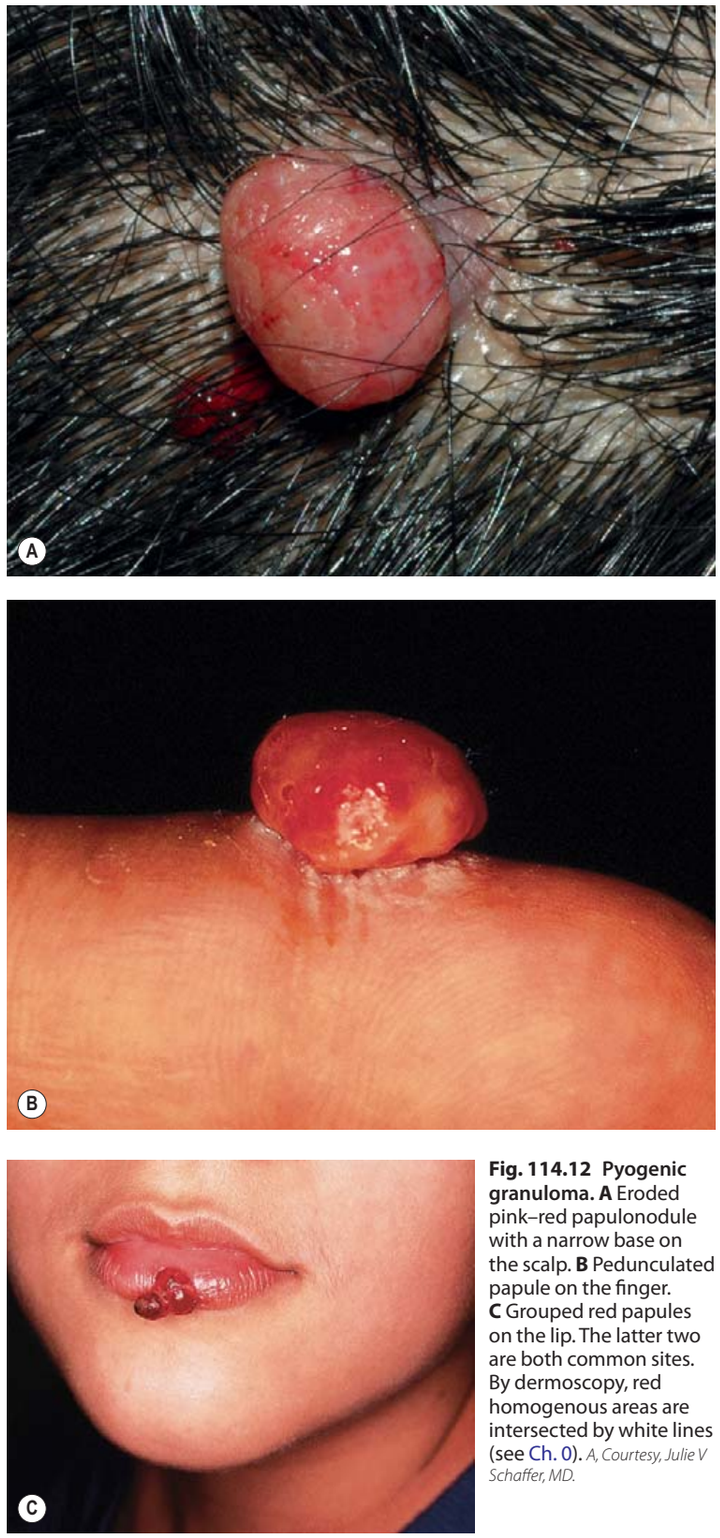


Fig. 114.12 Pyogenic granuloma. A Eroded pink–red papulonodule with a narrow base on the scalp. **B** Pedunculated papule on the finger. **C** Grouped red papules on the lip. The latter two are both common sites. By dermoscopy, red homogenous areas are intersected by white lines (see Ch. 0). *A, Courtesy, Julie V Schaffer, MD.*

Treatment

Shave excision followed by electrosurgery of the base under local anesthesia is sufficient for most lesions. Patients and parents should be alerted to the possibility of recurrence after removal. Excision with suturing may result in less postoperative bleeding and a lower recurrence rate.

Pulsed dye laser has also been shown to be a safe and effective treatment for small pyogenic granulomas and may be particularly useful in children[33]. There is a report of successful sclerotherapy in nine patients using monoethanolamine oleate, with inconspicuous scar formation and no recurrence[34].

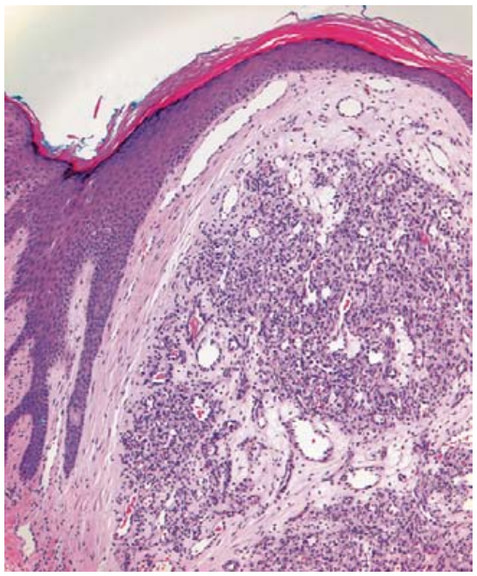


Fig. 114.13 Histology of pyogenic granuloma. Proliferating capillaries are often grouped into lobules by dense fibrous bands, hence the synonym lobular capillary hemangioma. The lesion is often clutched by an epithelial collarette.

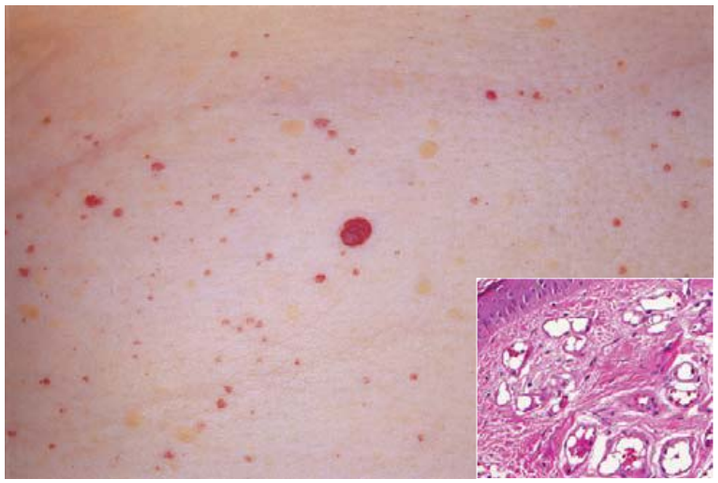


Fig. 114.14 Cherry angioma. Multiple compressible red papules. Histologically, congested capillaries and postcapillary venules expand the papillary dermis (insert). *Courtesy, Jean L Bolognia, MD.*

Cherry Angioma

Synonyms: ■ Cherry hemangioma ■ Senile angioma ■ Campbell–De Morgan spot

Key features

- Bright red, dome-shaped to polypoid papules up to several millimeters in diameter that begin appearing during adult life, most commonly on the trunk and upper extremities
- A common, benign lesion found in most individuals by the age of 60 years, often in large numbers
- Consist of dilated, congested capillaries and postcapillary venules within the papillary dermis

Introduction and history

Cherry angiomas are the most common of the acquired cutaneous vascular proliferations. They can be unattractive and rarely when eruptive herald an underlying systemic abnormality.

Epidemiology

Both sexes are affected equally. Although they may occasionally develop during adolescence, cherry hemangiomas usually first appear during the third decade of life or later, and then increase in number over time. Most people over 60 years of age have one or more such lesions.

Pathogenesis

An increased number of cherry angiomas often appear during pregnancy and may involute in the postpartum period, suggesting that hormonal factors may be important in their pathogenesis. Two women with hundreds of eruptive cherry hemangiomas, both of whom had increased serum levels of prolactin, have also been reported[15]. Most angiomas that appear in the setting of POEMS syndrome are cherry angiomas, often in association with glomeruloid hemangiomas.

Clinical features

Cherry angiomas are round to oval, bright red, dome-shaped papules ranging in size from barely visible to several millimeters in diameter (Fig. 114.14). Well-developed lesions may be polypoid. They most commonly develop on the trunk and proximal extremities and are rare on the hands, feet and face. It is not unusual for elderly adults to have 50–100 cherry angiomas on their trunk. Patients are usually aware of the benign nature of these extremely common lesions and bring them to a physician's attention only when concerned about their appearance. They are generally asymptomatic, but may occasionally bleed when traumatized.

Pathology

Histologically, congested, ectatic capillaries and postcapillary venules are seen within the papillary dermis and superficial reticular dermis (Fig. 114.14, insert). Early lesions are characterized by small lumina and plump endothelial cells. With maturation, the vessels dilate and the endothelial cell cytoplasm flattens, often producing slightly hobnailed nuclei. Vessel diameter decreases with descent into the reticular dermis. There is loss of epidermal ridges centrally and peripherally adnexal epithelial collarettes are seen.

Differential diagnosis

The distinctive clinical and dermoscopic finding (see Ch. 0) limit other diagnostic considerations. Glomeruloid hemangiomas, although similar in clinical appearance, can be distinguished histologically. Tiny cherry angiomas may resemble petechiae.

Treatment

Patients may request removal of cosmetically undesirable or chronically traumatized cherry angiomas. This can be accomplished by shave excision, electrodesiccation or laser ablation, with recurrences unusual.

Sinusoidal Hemangioma

Synonyms: ■ Variant sinusoidal hemangioma ■ Sinusoidal venous malformation

Key features

- Relatively rare, small, well-demarcated acquired lesion most commonly seen in the subcutis of middle-aged women and traditionally described as a variant of "cavernous hemangioma" (venous malformation)
- Probably malformative with a delayed presentation, rather than neoplastic or reactive in etiology
- Histologically distinguished by dilated, interconnecting venous channels exhibiting a prominent sieve-like or sinusoidal pattern
- Similar sinusoidal patterns are seen focally in many venous malformations
- May be confused with well-differentiated angiosarcoma, but distinguished from the latter by lack of significant cytologic atypia, infiltrative growth and endothelial multilayering

Introduction and history

In 1991, sinusoidal hemangioma was described as a distinctive subset of so-called "cavernous hemangioma" (historic term as now recognized to be a venous malformation)[35]. In contrast to typical venous malformations of childhood, sinusoidal hemangiomas presented during adulthood and had an unusually prominent sinusoidal or sieve-like histologic pattern.

Epidemiology

These adult-onset lesions have most commonly been observed in middle-aged women and are relatively rare. Their not uncommon occurrence in breast subcutaneous tissue has emphasized the need to differentiate these lesions from angiosarcoma.

Pathogenesis

Because of the typical presentation during adulthood, a neoplastic or reactive etiology has been suggested. However, the strong histologic parallels with venous malformations of childhood suggests that these mitotically quiescent vascular lesions are probably congenital developmental disorders that become evident later in life due to remodeling, thrombosis, recanalization and progressive vascular dilation. Focal sinusoidal patterns have also been described in congenital venous malformations.

Clinical features

Sinusoidal hemangiomas, as traditionally defined, are relatively well-demarcated, solitary, deep dermal or subcutaneous papulonodules that are freely mobile. The color varies from red (superficial lesions) to bluish or skin-colored (subcutaneous lesions). They most commonly develop in adult women and favor the arms and torso (including the breast). Longitudinal studies have revealed no evidence of metastasis or of local recurrence following resection.

Pathology

Generally well-defined lobules of dilated, thin-walled veins with scant mural smooth muscle form characteristic interconnected, "emphysematous", sieve-like spaces. Lining endothelial cells are flattened, single-layered, and mitotically inactive. Organizing thrombi are common, with occasional superimposed changes of papillary endothelial hyperplasia. There is no significant cytologic atypia. Central infarction and necrosis have been reported.

Differential diagnosis

Given the typical presentation during adulthood and anastomosing vascular pattern, the most clinically significant simulant is well-differentiated angiosarcoma. The latter is distinguished by a more infiltrative pattern, endothelial multilayering, mitotic activity and cytologic atypia.

Treatment

Complete surgical resection, which is facilitated by the typical well demarcation, is curative.

Hobnail Hemangioma

Synonym: ■ Targetoid hemosiderotic hemangioma

Key features

- Uncommon, acquired, benign vascular lesion that usually presents as a red–blue or brown papule on the trunk or extremities of children and young to middle-aged adults
- The papule is sometimes surrounded by a pale ring and then an ecchymotic halo
- Biphasic pattern of dilated, thin-walled vessels with hobnail endothelial cells in the superficial dermis, transitioning to smaller, slit-like vessels in the deeper dermis
- Lesional endothelial cells strongly express the lymphoendothelial marker podoplanin and poorly express CD34, suggesting lymphatic differentiation

Introduction and history

The original description in 1988 coined the term *targetoid hemosiderotic hemangioma* to emphasize the targetoid clinical appearance and hemosiderin deposition seen in a series of eight cases. Since then it has become apparent that only a minority of these lesions demonstrate the ecchymotic halo and hemosiderin deposition is variable. The term *hobnail hemangioma* has been proposed to encompass lesions with the characteristic biphasic growth pattern and marked hobnail endothelial morphology, with or without a targetoid clinical appearance and/or marked hemosiderin deposition[36,37]. More than 100 cases have now been reported[37,38], and all have had a benign clinical course.

Epidemiology

There is an equal male : female distribution[37]. In the largest series to date (62 cases), patients ranged in age from 6 to 72 years (median, 32 years)[38].

Pathogenesis

It has been proposed that this tumor represents the benign end of a spectrum of vascular tumors with hobnail endothelial cells that also includes Dabska's tumor and retiform hemangioendothelioma[36]. However, recent demonstration of markers of lymphatic derivation in hobnail hemangioma and Dabska's tumor, but not retiform hemangioendothelioma, suggests that the underlying pathogenesis of this histologic spectrum is not uniform. Trauma may stimulate the appearance of a hobnail hemangioma, and microshunts between small lesional blood vessels and adjacent lesional lymphatic vessels may explain the presence of erythrocytes within lymphatic vessels and hemosiderin deposits[39].

Clinical features

Most lesions are asymptomatic, solitary, well-circumscribed, red–blue to brown papules that are initially 2 to 3 mm in diameter and then slowly increase in size. In some cases, the papule is surrounded by a thin, pale area and then an ecchymotic ring (Fig. 114.15). The ecchymotic halo may fade and eventually disappear over time, and some lesions have been reported to undergo cycles of spontaneous regression and recurrence[31]. Favored sites, in decreasing order of frequency, are the lower extremities, upper extremities, back, buttock and hip, and chest wall. Lesions have also been reported on the tongue and gingiva[37].

Pathology

A biphasic histologic pattern is observed, consisting of a superficial dermal complement of dilated, thin-walled vessels containing small numbers of red blood cells and lined by prominent hobnail endothelial cells, which then merge with smaller, more slit-like vessels that dissect between collagen bundles in deeper areas of the dermis (Fig. 114.16). Extravasated red blood cells and hemosiderin deposits are common, but may be absent. Although the superficial vessels occasionally show delicate intraluminal papillary fronds, the more complex, multilayered endothelial tufts of Dabska's tumor are lacking. The endothelial cells of both the dilated and slit-like vessels immunoreact positively for the lymphoendothelial markers VEGF-3 and podoplanin (see Ch. 102), but show little, if any, reactivity for the blood vascular marker CD34[38,39].

Fig. 114.15 Hobnail hemangioma (targetoid hemosiderotic hemangioma). Note the target-like appearance. *Courtesy, Ronald P Rapini, MD.*

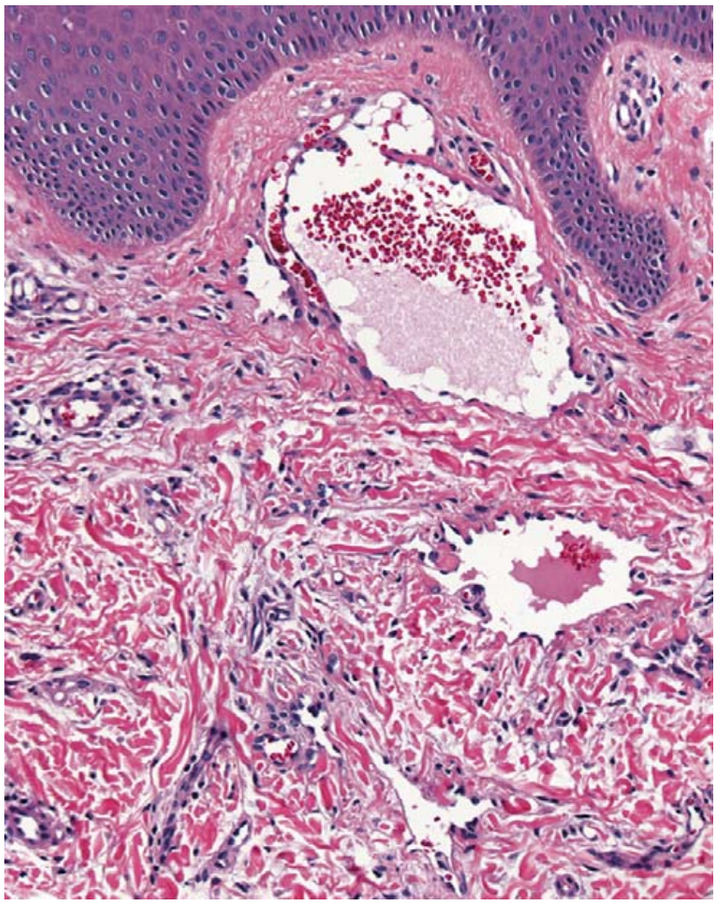


Fig. 114.16 Histology of hobnail hemangioma. Dilated superficial dermal vessels lined by hobnailed endothelial cells, merging with smaller slit-like vessels in the lower dermis.

Differential diagnosis

Hobnail hemangiomas are benign in clinical appearance and may resemble a melanocytic nevus or a sclerosing hemangioma as well as other benign vascular proliferations[37]. The histopathologic differential diagnosis is much more complex and includes patch-stage and lymphangioma-like variants of Kaposi sarcoma, well-differentiated angiosarcoma, retiform hemangioendothelioma, Dabska's tumor and microcystic lymphatic malformation.

Treatment

Hobnail hemangioma is successfully treated by simple excision. Longitudinal evaluation of 35 patients, ranging from 1 to 4 years, revealed no local recurrence or systemic metastasis[38].

Tufted Angioma

Synonyms: ■ Acquired tufted angioma ■ Angioblastoma of Nakagawa ■ Tufted hemangioma ■ Hypertrophic hemangioma ■ Progressive capillary hemangioma

Key features

- Inhomogeneous pink to red patches and plaques with superimposed papules that spread slowly, often to involve large areas, then stabilize; rarely may regress
- Most commonly located on neck or trunk
- Usually presents as an acquired lesion in children and young adults, but may be congenital or appear late in life
- When congenital, may be associated with Kasabach–Merritt phenomenon
- Characterized histologically by tightly packed tufts of tiny capillaries distributed within the dermis and subcutis in a "cannonball" pattern; foci of spindled endothelial cells may also be present

Introduction

Tufted angioma has often been lumped erroneously with infantile hemangioma under the generic term "capillary hemangioma". However, a distinction is important given its association with Kasabach–Merritt syndrome in some infants. In older children and adults, it may clinically mimic Kaposi sarcoma. Current opinion is that it represents a mild, superficial form of kaposiform hemangioendothelioma (KHE).

History

Tufted angioma was first described in 1989 by Wilson-Jones and Orkin[40]. Apparently identical lesions had been described many years previously as angioblastoma[41] and progressive capillary hemangioma[42]. The association of tufted angioma with Kasabach–Merrit phenomenon, shared by KHE, has relatively recently been recognized[43].

Epidemiology

Most lesions occur in young adults and children, many during the first year of life. Over 50% present before 5 years of age[40], and approximately 15% are congenital[40]. Rarely, lesions appear late in life[44]. Although one family with several affected family members has been reported[45], the vast majority of cases are sporadic.

Pathogenesis

Tufted angioma and KHE have a significant degree of overlap in histologic features, with resection specimens of KHE often demonstrating dermal changes that would have been interpreted in small biopsy specimens as tufted angioma. In light of the virtually exclusive association of these two entities with Kasabach–Merritt phenomenon, this histologic overlap suggests that tufted angioma may represent a more superficial, milder form of KHE[43,46,47].

Clinical features

Tufted angiomas appear as mottled red patches or plaques with superimposed angiomatous papules, typically on the neck, trunk or shoulders, that grow slowly by lateral extension over a period of 5 months to 10 years[40] (Fig. 114.17). Occasionally, lesions have an associated growth of lanugo hair or port-wine-like stain[48]. Platelet trapping (Kasabach–Merritt phenomenon) may develop in congenital cases, although less commonly than in KHE. Lesions eventually stabilize in size, then may persist unchanged, shrink or leave a fibrotic residuum. Rarely, complete spontaneous regression has been observed[48]. Occasional lesions are painful, and this may be exacerbated during periods of uncontrolled platelet trapping[49].

Pathology

Tufted angiomas are characterized by multiple discrete lobules of capillaries set within the dermis and often the subcutis in a so-called "cannonball" pattern (Fig. 114.18). Borders of the area of tissue involvement are poorly defined. Dermal collagen and subcutis separating capillary lobules may be histologically normal, but are often fibrotic. The lobules are composed of tiny capillaries with pinpoint lumina, occasionally containing fibrin microthrombi, tightly packed together without intervening stroma and frequently bulging into peripherally placed thin-walled vessels. Mitotic figures are rare.

Foci of spindled endothelial cells that coexpress the lymphatic markers podoplanin, LYVE-1 and Prox1, in addition to the blood vascular marker CD34, may be present within the tumor lobules, but this feature is typically not prominent[50]. Of note, the endothelial cells of tufted angioma do not immunoreact for infantile hemangioma-associated antigens such as GLUT-1 and Lewis Y antigen[51]. Ultrastructural studies have demonstrated classical Weibel-Palade bodies. In cases

Fig. 114.17 Tufted angioma. A Mottled red patches and superimposed papules are typical clinical features. **B** Dark-red to violet plaque in an infant.

associated with Kasabach–Merritt phenomenon, platelet trapping has been confirmed with CD61 immunoreaction[52].

Differential diagnosis

Congenital tufted angiomas must be differentiated from infantile hemangiomas, the most common tumors of infancy (see Ch. 103). The latter are positive for placental capillary-associated endothelial markers (e.g. GLUT-1) and show more rapid growth (without lateral extension) during the first year of life, followed by spontaneous, slow involution[51]. Infantile hemangiomas are transiently positive for the lymphatic-associated marker LYVE-1 early in their course, presumably as an expression of their embryonic, cardinal vein-type endothelial phenotype[50], but lack the definitive mixed lymphatic–blood endothelial phenotype described above[53,54].

Other entities that may mimic the clinical appearance of tufted angioma include pyogenic granuloma arising within a vascular malformation and Kaposi sarcoma. Pyogenic granuloma can be distinguished histologically by its characteristic edematous stroma, granulation tissue-type changes, lack of association with lymphatic markers, and generally larger, more loosely packed lesional vessels. Kaposi sarcoma differs in its lack of tufting, presence of a plasma cell infiltrate and prominence of fascicles of spindle cells forming slit-like spaces. KHE, although overlapping in histology and likely in pathogenesis, is traditionally described as a more bulky, deeply seated lesion that tends to infiltrate across multiple tissue planes and has more prominent spindled endothelial cells[50].

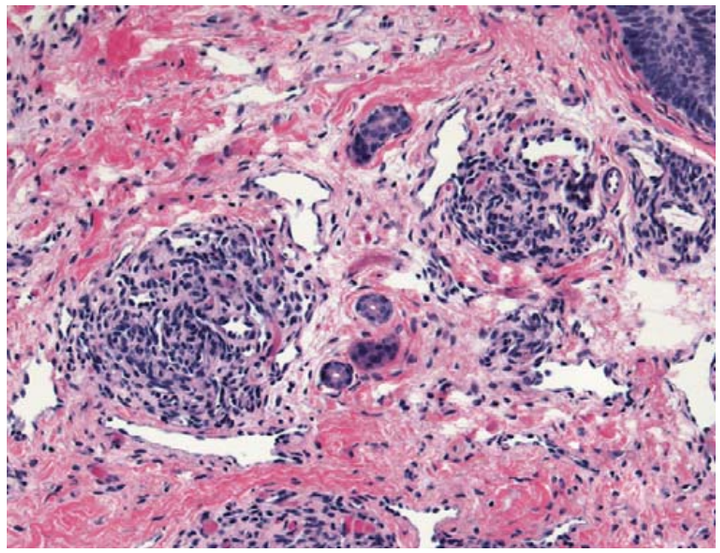


Fig. 114.18 Histology of tufted angioma. A cannonball distribution of dense capillary lobules in the dermis is classic.

Treatment

Complete surgical excision is the treatment of choice for small tufted angiomas, although recurrence is common. Use of the pulsed dye laser has been ineffective[49,55], although the argon tunable dye laser has been used successfully but with the risk of scarring. Both aggravation and improvement have been reported with the Nd:YAG laser. High-dose systemic corticosteroids may be useful[56], and interferon-α has produced partial regression (for side effects, see Ch. 103)[55]. Currently, vincristine is the preferred treatment for Kasabach–Merritt syndrome[57]. Aspirin may help control the platelet interaction, pain and growth of tufted angiomas that develop this complication[49].

Multifocal Lymphangioendotheliomatosis with Thrombocytopenia

Synonyms: ■ Congenital cutaneovisceral angiomatosis with thrombocytopenia

Key features

- Multiple congenital and progressive vascular lesions involving the skin and viscera, complicated by chronic mild to moderate thrombocytopenia
- Skin lesions consist of red–brown plaques and they may be numerous
- Clinically significant gastrointestinal bleeding appears universal and may be life-threatening
- Distinctive histopathological features that resemble benign lymphangioendothelioma, with variable expression of lymphatic-associated immunohistochemical markers (e.g. LYVE-1, podoplanin)

Introduction and history

This distinctive, but only recently recognized, clinicopathological entity was first described in 2004 by North et al.[58] as *multifocal lymphangioendotheliomatosis with thrombocytopenia* (MLT), based upon the highly characteristic histology, multifocal tissue involvement, and consistent expression of the lymphatic-associated marker LYVE-1. An equivalent series of cases was reported by Prasad et al.[59] in 2005 using the term *congenital cutaneovisceral angiomatosis with thrombocytopenia* (CCAT).

Epidemiology

Most cases are evident at birth, although many lesions are slowly progressive and increase in number with time. No clear racial or sexual predilections have emerged.

Pathogenesis

Reported cases are sporadic and it is not yet clear if the lesions are best considered tumors or malformations. Lesional endothelial cells coexpress CD34 and LYVE-1 and may focally express podoplanin, making blood-vascular versus lymphatic-vascular differentiation ambiguous[60]. The association with selective thrombocytopenia draws parallels with KHE and tufted angioma – two vascular entities uniquely linked to the Kasabach–Merritt phenomenon that also express mixed blood vascular and lymphatic endothelial markers[43,47,58].

Clinical features

Cutaneous lesions, often numbering in the hundreds at birth, are flat or indurated red–brown to burgundy plaques or papules, often with central pallor and occasionally central scar-like areas. Slow progression of pre-existing lesions and progressive appearance of new lesions is typical, without evidence of regression. Similar lesions in the gastrointestinal tract cause severe gastrointestinal bleeding beginning in infancy. Some patients have extensive pulmonary involvement complicated by hemoptysis; rarely, other sites are affected (e.g. muscle, synovium)[47,48,58,59,61]. Thrombocytopenia is mild to moderate, chronic and fluctuating, with essentially normal prothrombin time (PT), partial thromboplastin time (PTT) and serum fibrinogen levels.

Pathology

Lesions are composed of thin-walled vessels scattered throughout the dermis and subcutis and lined by a monolayer of slightly hobnailed endothelial cells that focally form papillary projections (Fig. 114.19). Some of the papillary formations are complex and appear to float in the luminal plane of section (Fig. 114.19, insert). Many vessel lumens, especially the smaller ones, are largely devoid of red blood cells. Endothelial cells show strong immunopositivity for CD31, CD34, and LYVE-1, light to absent positivity for D2-40 (podoplanin), and negativity for GLUT-1[58]. Mitotic figures are rare or absent.

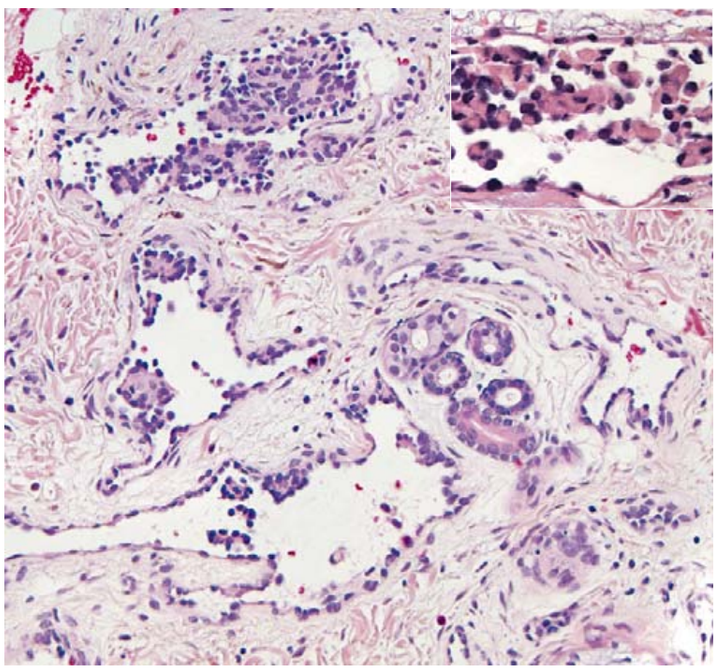


Fig. 114.19 Histology of multifocal lymphangioendotheliomatosis with thrombocytopenia. Thin-walled vessels focally forming intraluminal papillary projections scattered throughout the dermis and subcutis. Complex papillary projections lined by endothelium may appear to float in the lumen (insert).

Differential diagnosis

This entity must be differentiated from other multifocal vascular skin disorders presenting during infancy or childhood, including diffuse neonatal hemangiomatosis, blue rubber bleb nevus syndrome, glomuvenous malformations (glomangiomas), and Maffuci syndrome. The differential diagnosis also includes other causes of a "blueberry muffin baby", such as extramedullary hematopoiesis and leukemia cutis (see Table 121.4). The skin lesions of MLT, however, are unique in their clinical and histologic appearance, and are far more numerous than would be typical for any of the other vascular conditions except diffuse neonatal hemangiomatosis.

Treatment

Gastrointestinal bleeding may spontaneously stabilize or require colectomy for effective control. Corticosteroids, interferon-α, thalidomide and bevacizumab have been reported to be of possible value in some, but not all, cases[58,59,62].

BORDERLINE AND LOW-GRADE MALIGNANT VASCULAR NEOPLASMS

Kaposiform Hemangioendothelioma

Synonyms: ■ Infantile kaposiform hemangioendothelioma ■ Kaposi-like infantile hemangioendothelioma

Key features

- A rare vascular tumor of childhood that presents as an ill-defined violaceous plaque and in some patients is associated with a life-threatening platelet-trapping syndrome (Kasabach–Merritt phenomenon)
- Locally aggressive and occasionally multifocal along lymphatic pathways, but thought not to truly metastasize
- Classically, a deeply seated, infiltrative tumor that crosses tissue planes and may involve the skin and subcutaneous as well as deep soft tissues, bone and even viscera
- Overlapping histologic features (e.g. expression of mixed blood vascular and lymphatic endothelial markers) and likely synonymous in pathogenesis with tufted angioma, with the latter being more superficial in location
- Unlike common infantile hemangioma, does not spontaneously involute
- Complete surgical excision is recommended where feasible

Introduction and history

Kaposiform hemangioendothelioma (KHE) was described as such by Zukerberg et al.[46] in 1993, although equivalent lesions had been previously reported as "hemangioma with Kaposi's sarcoma-like features"[63] and "Kaposi-like infantile hemangioendothelioma"[64]. Many lesions of this type were previously misdiagnosed as infantile hemangioma.

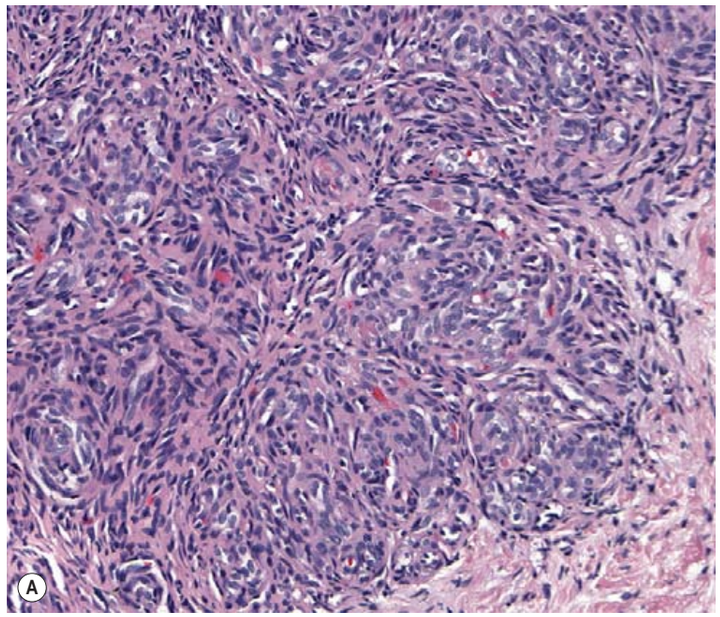
Epidemiology

Most tumors present in children less than 2 years of age, and some are congenital. Occasionally they have been reported in adults, all to date without evidence of Kasabach–Merritt syndrome[65]. There is no gender predilection.

Pathogenesis

Recent studies have demonstrated expression of several lymphatic endothelium-associated antigens (including the master regulator of lymphatic differentiation Prox1) in KHEs, supporting the concept that these tumors, like tufted angioma, Kaposi sarcoma and a subset of angiosarcomas, have at least a partial lymphatic endothelial phenotype[50,66]. Coexpression of the blood vascular marker CD34 with these

Fig. 114.20 Kaposiform hemangioendothelioma complicated by Kasabach–Merritt phenomenon. A large red–purple mass on the upper flank of an infant.



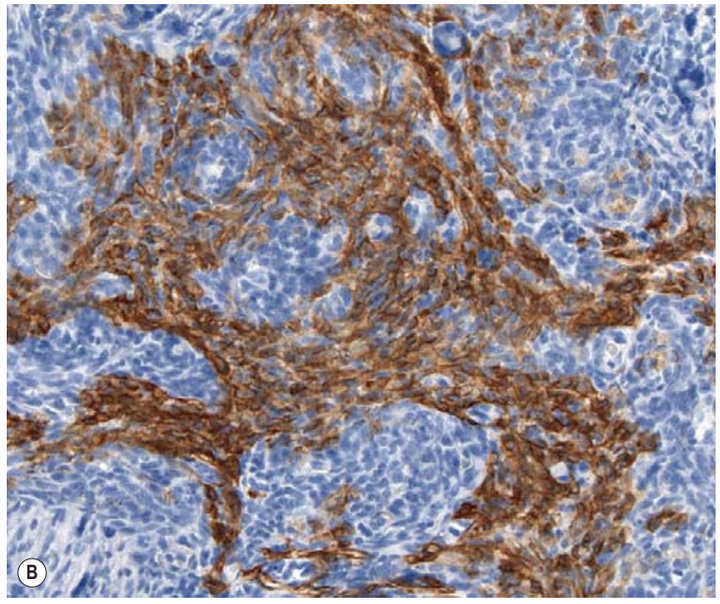


Fig. 114.21 Histology of kaposiform hemangioendothelioma. A Fascicles of spindled endothelial cells forming slit-like lumina surround nests of more epithelioid areas rich in pericytes. **B** The endothelial cells show evidence of lymphatic differentiation, here evidenced by positivity for podoplanin.

lymphatic markers in both KHE and tufted angioma, together responsible for the vast majority of cases of Kasabach–Merritt phenomenon, suggests that this aberrant, ambiguous lymphatic–blood vascular phenotype (at least when present in infants) may promote intratumoral platelet trapping[58].

Although platelet transfusions may be necessary for acute management, they have in some patients paradoxically worsened the coagulopathy[43,67]. Based on these observations plus the rapid tumor shrinkage that can follow pharmacologic control of platelet trapping, it has been suggested that intratumoral platelet activation may "add fuel to the fire" by stimulating vascular proliferation[43], presumably by the release of angiogenic agonists such as platelet-derived growth factor. A self-sustaining cycle of platelet trapping and tumor growth may thus be important for development of the full-blown Kasabach–Merritt phenomenon.

Histologic and immunohistochemical similarities between Kaposi sarcoma and KHE suggested that these entities might be etiologically related. However, HHV-8 sequences have not been identified in KHE[68], and children with coincident KHE and HIV infection have not been reported.

Clinical features

Cutaneous forms present as locally infiltrative vascular macules or plaques that may develop nodules. Deeper soft tissue lesions may present as bulging, indurated masses (Fig. 114.20) or be undetected on physical examination. Untreated lesions do not appear to regress, and patients with tumors complicated by Kasabach–Merritt phenomenon often have purpura and ecchymoses. In a compilation of reported cases with skin involvement[68], the initial average age at presentation was 43 months, which is significantly later than that of classic infantile hemangioma. More deeply seated tumors, particularly those in the retroperitoneum, are more likely to cause Kasabach–Merritt phenomenon[68].

The two most common causes of death from KHE are complications of thrombocytopenia and direct tumor infiltration[68]. No distant metastases have been reported to date, although one patient had spread to regional lymph nodes[69]. Clinical evaluation of suspected cases, for instance new-onset vascular tumors in children >3 months of age[68], should include magnetic resonance imaging (MRI), a complete blood cell count, coagulation studies to detect coexistent Kasabach–Merritt phenomenon, and, if not prohibited by severe thrombocytopenia, biopsy for histopathologic diagnosis. MRI typically shows ill-defined tumor margins with the involvement of multiple tissue layers.

Pathology

Kaposiform hemangioendotheliomas are characterized by ill-defined, frequently coalescing nodules composed of fascicles of moderately plump spindled endothelial cells with eosinophilic to clear cytoplasm and bland nuclei that form elongated, slit-like lumina containing erythrocytes, reminiscent of Kaposi sarcoma (Fig. 114.21A). The spindle cells often encompass nests of more epithelioid endothelial cells and pericytes that are surrounding platelet-rich microthrombi (highlighted by CD61 immunostaining). At the margin of the lesion, the spindle cells may infiltrate into the surrounding adipose tissue and between collagen bundles, or they may be encased by desmoplastic stroma. The spindle cells are strongly immunoreactive for the pan-endothelial marker CD31, the blood vascular marker CD34, and the lymphatic endothelial markers podoplanin (Fig. 114.21B), LYVE-1, VEGFR-3 and Prox1[50].

Mitotic activity is variable, but generally low. Focally, lobules of small, rounded capillaries lined by flat endothelia merge with the spindled areas. Extravasated erythrocytes and hemosiderin granules are typically present, and tumor cells may contain intracytoplasmic erythrocyte fragments and hyaline globules. Often there is a prominent component of dilated vessels with a lymphatic morphology that intermingles with the tumor lobules, but these vessels are often most obvious within the marginal soft tissues. Residual KHE, i.e. remaining after successful

medical treatment, represents a dormant, often sclerotic, version of the original disease process.

Differential diagnosis

The most important differential considerations are common infantile hemangioma, tufted angioma and Kaposi sarcoma. Infantile hemangiomas, unlike KHE, express an unusual and complex endothelial phenotype shared only by placental capillaries, most commonly manifested by immunohistochemical staining for GLUT-1[51,70]. Infantile hemangiomas also lack both fascicles of spindle cells and foci with a mixed lymphatic–blood vascular phenotype. Tufted angioma is thought to be a milder, more superficial form of KHE that is distinguished by a relative scarcity of endothelial spindling and an absence of pericyte-rich epithelioid nodules. Kaposi sarcoma, which is rare in children (outside of Africa), lacks the lobularity of KHE and characteristically contains plasma cell infiltrates.

Treatment

Tumors that are localized and superficial can be cured by wide local excision. However, tumors in the mediastinum or retroperitoneum are often large and unresectable. Evidence-based treatment regimens for unresectable tumors with associated Kasabach–Merritt syndrome are not available. Based upon case series, the following, alone or in combination[71], may be helpful therapeutically: interferon-α-2a[72], vincristine[73], radiation therapy, and aspirin plus ticlopidine, as well as chemotherapeutic regimens (e.g. cyclophosphamide, vincristine and actinomycin D)[74]. Currently, vincristine is the recommended first-line treatment for associated Kasabach–Merritt syndrome[57]. Corticosteroids alone do not appear to be effective[68].

Dabska-type Hemangioendothelioma

Synonyms: ■ Papillary intralymphatic angioendothelioma (PILA) ■ Dabska tumor ■ Endovascular papillary angioendothelioma ■ Malignant endovascular papillary angioendothelioma ■ Hobnail hemangioendothelioma

Key features

- Rare neoplasm of at least partial lymphatic differentiation and very low metastatic potential that occurs primarily in children
- Enlarging dermal or subcutaneous mass or plaque, primarily in children and often on distal extremities
- Histologically defined by prominent papillary intralymphatic growth and peculiar rosette-like clusters of hobnail, columnar endothelial cells
- Arguably related to retiform hemangioendothelioma, a histologically similar tumor occurring mainly in adults

Introduction and history

Maria Dabska first described tumors of this type as *malignant endovascular papillary angioendothelioma* in 1969 based on a series of six cases, all in children. Two patients in this original series had lymph node metastases, and one of these later developed distant metastases and died[75]. Subsequently reported cases have behaved in a benign fashion, although follow-up for some has been limited[76]. Based on the prominent presence of lymphatic vessels, the tentative potential for malignant or borderline clinical behavior, and the defining presence of papillary intravascular proliferation, another designation for this tumor is *papillary intralymphatic angioendothelioma* (PILA)[76]; this latter term has been adopted by the WHO[77]. Because of their shared hobnail endothelial morphology, lymphatic differentiation and similar biologic behavior, Weiss and Goldblum[4] have suggested that the term *hobnail hemangioendothelioma* be used to embrace both Dabska-type hemangioendothelioma and retiform hemangioendothelioma. However, detection of lymphatic differentiation in retiform hemangioendothelioma has been inconsistent, bringing into question the relatedness of these two entities[78–80].

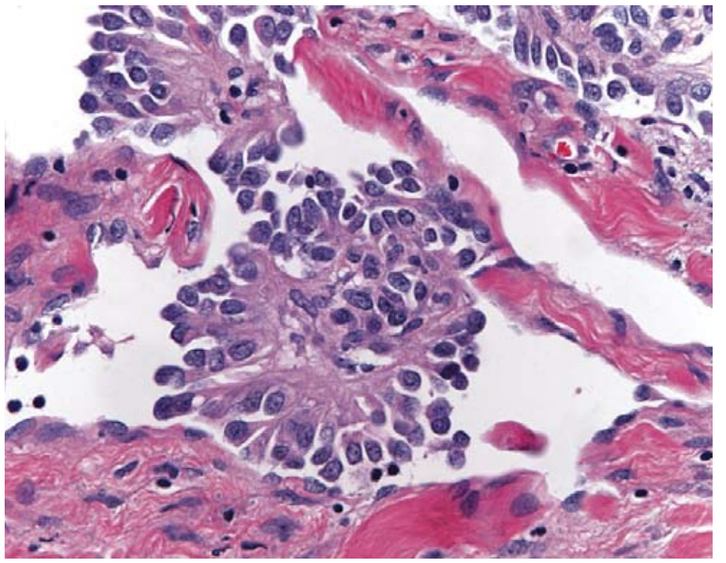


Fig. 114.22 Histology of Dabska-type hemangioendothelioma. Rosette-like intravascular clusters of hobnailed, columnar endothelial cells.

Epidemiology

Compilations of reported cases have shown no clear gender predilection, with approximately 75% of patients being children and the remainder primarily young adults. Tumors may be present at birth. A more recent series of 12 patients in which the mean age was 30 years suggests a wider age range for Dabska-like hemangioendotheliomas[76].

Clinical features

Most of these tumors originate within the soft tissues of an extremity and rarely other sites such as bone or spleen. Lesions can present as either enlarging, diffuse, firm swellings of skin and subcutaneous tissue or as soft intradermal plaques; sometimes there is also a pink or blue discoloration of the skin. The size range is wide (up to 40 cm)[76]. A number of cases appear to have arisen within pre-existing lymphatic malformations ("lymphangiomas"). Involvement of superficial tissues has been observed on the extremities, head and neck, and trunk. Local recurrences are relatively common (about 40%).

Pathology

The unifying microscopic feature is a presence within the dermis and/or subcutis of intercommunicating, thin-walled vessels lined by hobnail endothelial cells, with the latter forming characteristic intraluminal papillary projections that focally assume a rosetting or matchstick-like pattern (Fig. 114.22). Lesional vessels are variable in size. Hyaline papillary stromal cores are immunoreactive for collagen type IV, and, in some cases, focal actin-positive pericytes may be present within the papillary projections[76]. Lymphocytes may cluster along the endothelial lining of the vessels and infiltrate into the surrounding stroma; large lymphoid aggregates are common. Recent studies have shown strong endothelial immunopositivity for VEGFR-3 and podoplanin in the hobnail endothelial proliferations of these tumors[52,62,66,76,77], indicative of lymphatic differentiation. CD34 expression is low.

Differential diagnosis

Dabska-type hemangioendotheliomas must be differentiated histologically from other entities with hobnail endothelial architecture, including hobnail hemangioma (targetoid hemosiderotic hemangioma), retiform hemangioendothelioma, and well-differentiated angiosarcoma. Hobnail hemangioma is a smaller, more superficial dermal process, without exuberant papillary tufts. Retiform hemangioendotheliomatosis usually occurs in adults and intravascular papillary tufts are infrequent and poorly developed. Of note, regional lymph node disease has been documented in both Dabska-type and retiform hemangioendothelioma. Angiosarcoma, even when well differentiated, may display intravascular papillary growths that suggest Dabska-type

hemangioendothelioma, but classic hobnail endothelial cells are absent. Angiosarcomas are extremely uncommon in children and are usually visceral (especially cardiac or pericardial).

Treatment

Dabska tumors are rare, typically indolent lesions with rare examples of regional lymph node spread. Optimal therapy is relatively conservative surgical excision with clear margins, supplemented by close follow-up.

Retiform Hemangioendothelioma

Synonym: ■ Hobnail hemangioendothelioma

Key features

- Rare neoplasm with very low metastatic potential that occurs primarily in adults
- Presents as a slow-growing exophytic tumor or plaque on the trunk or extremities, especially the distal lower extremities
- Characterized histologically by a diffuse infiltration of the dermis and/or subcutis by elongated vessels with hobnail endothelial cells arborizing in a pattern similar to that of the normal rete testis
- Local recurrence following excision occurs in about 60% of cases but regional lymph node spread is rare
- Proposed, but still unclear, relationship to Dabska-type hemangioendothelioma, a histologically similar tumor occurring mainly in children

Introduction and history

Retiform hemangioendothelioma was first described as an entity in 1994 by Calonje et al.[36] based on a series of 15 cases, and was interpreted as a low-grade angiosarcoma. Fewer than a dozen additional cases have subsequently been reported. Similarities in histology and clinical behavior to Dabska-type hemangioendothelioma, a tumor mainly affecting children, have led to a proposal that these two entities be jointly described by the term *hobnail hemangioendothelioma*[4], not to be confused with hobnail hemangioma discussed previously. However, reported cases of retiform hemangioendothelioma, unlike hobnail hemangioma and Dabska-type hemangioendothelioma which show clear lymphatic differentiation, have shown variable expression of lymphatic markers[78–80].

Epidemiology

Men and women are equally affected. The patient age range for reported cases is 9 to 78 years.

Clinical features

The clinical appearance of retiform hemangioendothelioma is not specific and its vascular nature may not be suspected clinically. Lesions present as solitary, slowly growing plaques, exophytic masses or dermal/subcutaneous nodules, and they most commonly develop on the extremities. In the series of Calonje et al.[36], nearly 60% of cases recurred locally, and 1 of 14 patients followed longitudinally developed lymph node involvement. To date, there have been no tumor-related deaths.

Pathology

Retiform hemangioendothelioma is one of a small group of vascular tumors that also includes hobnail hemangioma and Dabska's tumor which is characterized by endothelial cells with a so-called hobnail appearance. Overall, there is a diffuse infiltration of the reticular dermis and/or subcutis by an arborizing network of elongated, thin-walled vessels forming a pattern reminiscent of normal rete testis. The margins are ill defined. Higher magnification of the lesional vessels reveals a lining of bland endothelial cells with prominent apical nuclei that protrude into the lumina in a hobnail or "matchstick" fashion. Mitotic figures are rare, and cytologic atypia is minimal, or rarely, mild. Solid foci of spindle cells expressing endothelial markers are often present, as are occasional intravascular papillae. The cavernous lymphatic-like vessels and prominent intravascular proliferations characteristic of Dabska-type hemangioendothelioma tumor are absent. Most, but not all, cases of retiform hemangioendothelioma that have been assessed for markers of lymphatic endothelial differentiation (e.g. VEGFR-3, podoplanin) have proved to be negative[66,76,78,79].

Differential diagnosis

The most important entity to exclude is well-differentiated angiosarcoma, which is distinguished by cytologic atypia, multilayed endothelial cells, increased mitotic activity, and lack of hobnail endothelial cells.

Treatment

Wide excisional biopsy with follow-up is appropriate.

Epithelioid Hemangioendothelioma

Key features

- Vascular tumor of adults with intermediate malignant potential
- Skin involvement is uncommon and is usually associated with more deeply seated disease, often associated with a vein
- Characterized histologically by cords and nests of epithelioid endothelial cells in a myxoid or hyalinized background
- Approximately 30% of patients develop metastases within regional nodes, lung, liver or bone
- Fewer than 50% of patients with metastases die of their disease

Introduction and history

Epithelioid hemangioendothelioma is a low-grade angiosarcoma (hemangioendothelioma) first described by Weiss and Enzinger in 1982. It has more metastatic potential than other lesions classified as hemangioendotheliomas[81]. Most arise within deep soft tissues, but lesions can occur in the skin, viscera and bone. Since its original description, approximately 20 cutaneous cases have been reported in the literature[81,82].

Epidemiology

Epithelioid hemangioendothelioma typically occurs in adults. There is no gender predilection.

Pathogenesis

Epithelioid hemangioendotheliomas are clonal neoplastic proliferations of endothelial cells with low to intermediate potential to metastasize. Chromosomal translocation has been reported[83].

Clinical features

Most tumors present as a solitary, slightly painful, soft tissue mass. Skin involvement is often associated with an underlying soft tissue or bone tumor, but purely cutaneous examples also occur[81]. The most frequently reported sites of cutaneous involvement are the extremities. Some cases are closely associated with or arise from a vessel, usually a vein[84]. Occlusion of that vessel may cause secondary symptoms, such as edema or thrombophlebitis. Overall, approximately 30% of patients develop metastatic disease involving regional nodes, lung, liver or bone, and fewer than 50% of these patients with metastases have died of their disease[84]. One study of 30 patients suggested that dermal tumors may have a better prognosis than more deeply seated lesions[76].

Pathology

Like their more common counterparts involving soft tissue and bone, epithelioid hemangioendotheliomas involving the skin show an infiltrative growth pattern of epithelioid tumor cells with eosinophilic cytoplasm that form poorly canalized nests and cords within a distinctive myxohyaline stroma. An important clue to their endothelial origin is the presence of small intracytoplasmic vacuoles containing red blood cells (Fig. 114.23). Nuclei are vesicular with little or no atypia and

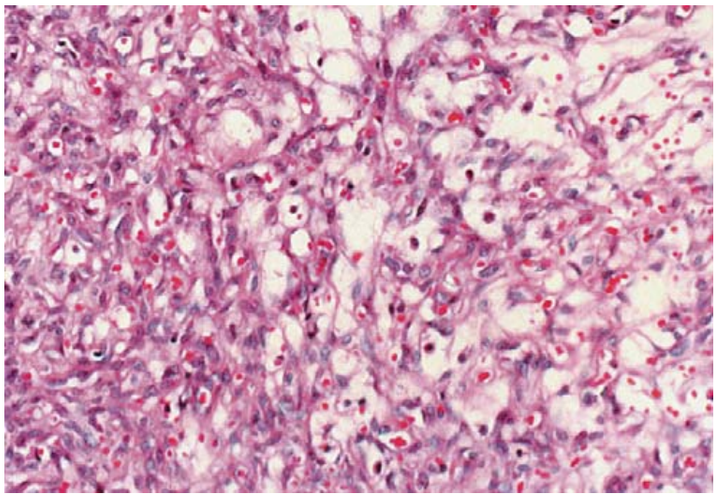


Fig. 114.23 Histology of epithelioid hemangioendothelioma. Poorly canalized cords and nests of endothelial cells in a myxoid background form small intracytoplasmic vacuoles containing red blood cells.

contain small, inconspicuous nucleoli. An angiocentric growth pattern may be present, but is less commonly observed in cutaneous tumors. Unlike epithelioid hemangioma (angiolymphoid hyperplasia with eosinophilia), inflammation is sparse. Mitotic rate is variable and only weakly correlated with clinical outcome[81].

Differential diagnosis

The differential diagnosis is wide and includes epithelioid sarcoma, metastatic carcinoma, melanoma and epithelioid angiosarcoma. An essential criterion for diagnosis of epithelioid hemangioendothelioma is immunohistochemical evidence of endothelial differentiation[81]. Differentiation from epithelioid angiosarcomas may be problematic and relies upon recognition of the typical architectural pattern of epithelioid hemangioendothelioma throughout the lesion.

Treatment

Appropriate therapy involves wide local excision without adjuvant chemotherapy or radiotherapy, given the typically low-grade nature of these tumors. Regional lymph nodes should be evaluated since these represent a common metastatic site. In case reports, stabilization of disease has been observed with antiangiogenic agents such as interferon, celecoxib and thalidomide[85].

Kaposi Sarcoma

Key features

- It is controversial whether Kaposi sarcoma (KS) represents neoplasia or hyperplasia; all clinical variants are viewed as a virally induced disease, with human herpesvirus-8 (HHV-8) the implicated agent
- A multifocal systemic disease with four principal clinical variants: (1) chronic or classic KS; (2) African endemic KS, including a fulminant lymphadenopathic type; (3) KS due to iatrogenic immunosuppression; and (4) AIDS-related epidemic KS
- Cutaneous lesions can vary from pink patches to dark violet plaques, nodules or polyps, depending on clinical variant and stage
- The histologic features of KS do not vary significantly between clinical subtypes, but do vary with stage of the lesion
- Most cases in children, with or without HIV infection, are of the lymphadenopathic type and are rapidly fatal due to visceral dissemination
- Because of multifocality, treatment with chemotherapy and/or radiation is favored over surgery

EPIDEMIOLOGIC ASPECTS OF THE FOUR MAJOR TYPES OF KAPOSI SARCOMA
CLASSIC
• Predominantly in individuals of Jewish (Ashkenazi) descent and/or of Mediterranean/Eastern European descent • Male : female (M : F) ratio varies from 15 : 1 (older literature) to 3 : 1 or 1 : 1 (more recent observations) • Two-thirds of patients develop disease after the age of 50 years
AFRICAN ENDEMIC
• Incidence amongst black Africans ranges from 1% to 10%, with a clear male predominance • Accounts for up to 9% of all reported cancers in equatorial Africa • The lymphadenopathic variant affects primarily children, with a M : F ratio of approx. 1 : 1
DUE TO IATROGENIC IMMUNOSUPPRESSION
• Individuals are immunosuppressed secondary to systemic medications, e.g. calcineurin inhibitors, prednisone, cytotoxic agents • Cyclosporine is associated with a higher incidence and more rapid onset of disease • Lesions can regress following cessation of immunosuppressive therapy • Estimated incidences of post-transplantation KS in Western countries and the Near East are <1% and 4%, respectively • Men are slightly more often affected than women
AIDS-RELATED EPIDEMIC
• Occurs primarily in men who have sex with men • To a lesser degree, seen in female partners of affected men and in women from certain regions of Africa and the Caribbean who became HIV-infected via heterosexual contact • Up to 40% of men who have AIDS and became HIV-infected via homosexual contact can develop KS, compared with <5% in other risk groups and 4% in children

Table 114.3 Epidemiologic aspects of the four major types of Kaposi sarcoma (KS).

Introduction and history

In 1872 Moritz Kaposi described five men with an unusual multifocal sarcoma of the skin which he termed "idiopathic multiple pigmented sarcoma of the skin". This disease entity became known as *Kaposi sarcoma* and historically has been considered a chronic, protracted disease primarily affecting elderly men, generally Jewish (Ashkenazi) or of Mediterranean/Eastern European descent. Despite occasional reports regarding its occurrence in organ transplant recipients and its endemic form in Africa, KS received little attention until it became epidemic among men who have sex with men and was recognized as a sign of acquired immunodeficiency syndrome (AIDS). A new human herpesvirus (HHV-8) was recognized as the probable inductive agent of all clinical variants of KS. The mechanisms that control the clinical variability of KS are likely to involve a number of interrelated factors modulated by the patient's immune status and have yet to be fully defined.

Epidemiology

The epidemiologic aspects of the four major types of Kaposi sarcoma are outlined in Table 114.3.

Pathogenesis

Immunohistochemical and ultrastructural studies have firmly established the endothelial nature of KS, but it remains controversial whether this endothelial phenotype is vascular, lymphatic or perhaps a composite of both. Moreover, many, if not most cells forming the substance of a plaque or nodule of KS are spindled cells distinctly unlike normal endothelial cells in morphology, although expressing pan-endothelial markers like CD31. These spindled cells also coexpress markers of blood vascular differentiation (CD34) and lymphatic differentiation (VEGFR-3[66,86], podoplanin[87] and LYVE-1[88]). A seminal discovery was that, *in vitro*, HHV-8 can infect both lymphatic and blood vascular endothelial cells and induce transcriptional reprogramming, leading to expression of lymphangiogenic molecules in infected blood vascular endothelial cells[89] and a more blood vascular profile in infected

Fig. 114.24 Classic Kaposi sarcoma. Red macules and patches on the plantar surface of the foot, with violaceous plaques on the ankle.

Fig. 114.25 Kaposi sarcoma in a patient with AIDS. Violet–red papules or nodules are often oval to lanceolate and are usually more widely distributed than in classic KS.

lymphatic endothelial cells[90]. This potentially explains the mixed lymphatic/blood vascular phenotype of KS, but also emphasizes the difficulty in precisely assigning endothelial cell derivation based solely on marker studies[91].

It also remains unclear whether KS is essentially hyperplastic or neoplastic in nature. While some studies employing X-chromosome inactivation (methylation) patterns have supported singular, presumably disseminated, clones[92], others utilizing the same methodology in examining sets of multiple lesions from single patients have found either oligoclonal composition within a given lesion or dissimilar, presumably independently developing, clones[93].

Despite these lingering uncertainties about endothelial phenotype and clonality, it is noteworthy how much compelling molecular, clinical and epidemiological evidence has accumulated to confirm that infection with HHV-8 causes, or at least strongly influences, the development of KS[94]. This virus was first identified in KS cells of a patient with AIDS and now is known to be present in most patients with all clinical types of KS. Seroreactivity to HHV-8 is not present to a significant degree in the normal population. The HHV-8 genome, when detected in the blood of HIV-positive men, strongly predicts their subsequent development of KS. HHV-8 contains homologues of cellular genes that can stimulate cell proliferation, inflammation and angiogenesis and perhaps inhibit apoptosis[95]. The host immune response and cytokines (particularly fibroblast growth factor) released by the virally infected cells may further support tumor growth in an autocrine and paracrine manner[77,78,96,97]. The role of inflammation in KS is supported by the observation that in patients with AIDS, pre-existing KS can get worse, at least transiently, in the setting of the immune reconstitution inflammatory syndrome (IRIS; see Ch. 78)[98].

Clinical features

Classic KS typically presents as slowly growing, pink to red–violet macules on the distal lower extremities that may coalesce to form large plaques (Fig. 114.24), or develop into nodules or polypoid tumors. Initially unilateral lesions progress to a more widely disseminated multifocal pattern. Early lesions may regress, while others evolve, leading to lesions of different stages at the same time. Patients with longstanding KS may have lesions in the mouth and gastrointestinal tract that are usually asymptomatic.

African endemic KS can be classified into four subgroups: nodular, florid, infiltrative and lymphadenopathic. The nodular variant resembles classic KS in course and appearance, whereas the florid and infiltrative types are more biologically aggressive. The lymphadenopathic type is notably different in several regards: it predominantly affects children, the primary tumors involve the lymph nodes (although skin and mucosal lesions may also be present), and its course is fulminant and fatal.

KS due to iatrogenic immunosuppression (transplantation-associated KS) is generally clinically similar to classic KS. It may resolve completely upon removal of immunosuppressive therapy. KS associated with prolonged high-dose immunosuppression may behave in a more aggressive fashion, causing death in patients who develop internal involvement.

AIDS-related epidemic KS most commonly affects HIV-infected patients with advanced immune impairment and $CD4^+$ T cell counts of fewer than 500 cells per cubic millimeter[99]. Clinical features of KS in the HIV-infected patient are protean. While some patients experience only a single lesion, others have disseminated cutaneous disease. Individual lesions range from faint erythematous macules, papules and plaques, to purple–black tumors and nodules. Macules and plaques are frequently oval to lanceolate and may array along lines of cleavage of the skin (Fig. 114.25). Coalescing papules and plaques occasionally form extensive armor-like constricting plaques that may impair the function of extremities and cause lymphedema.

While any skin surface may be involved, the trunk and midface (particularly the nose) are common sites, causing significant cosmetic disfigurement (see Ch. 78) . Bluish to violaceous macules, plaques and tumors can arise intraorally. Plaques and tumors at any site may ulcerate and become secondarily infected. KS frequently involves the viscera, including the gastrointestinal tract, lymph nodes and lungs. The prognosis of pulmonary disease is grave.

Pathology

The histologic appearance of KS does not vary significantly between the different clinical subtypes, but does vary with stage of the lesion. The *patch* stage is characterized by a superficial dermal proliferation of small, angulated vessels lined by inconspicuous endothelial cells, suggestive of lymphatics (Fig. 114.26). These delicate but "jagged" vessels tend to separate collagen bundles and are accompanied by a sparse infiltrate of lymphocytes and plasma cells as well as small numbers of spindle cells expressing endothelial markers. In the more advanced *plaque* stage, the vascular proliferation extends to include the deeper dermis and may involve the subcutis. The spindled endothelial cell population also expands among the ramifying small vessels.

In the *nodular* phase, there is replacement of dermal collagen by these spindled endothelial cells. Pleomorphism and significant numbers of mitotic figures are absent. The spindle cells form intersecting fascicles and are separated by characteristic slit-like spaces containing erythrocytes (Fig. 114.27). The resulting sieve-like pattern of vascular spaces is highly characteristic of KS. Intracellular and extracellular hyaline globules are thought to represent degenerated erythrocytes[4]. The tumor nodules are often rimmed by ectatic or crescentic vessels, hemosiderin

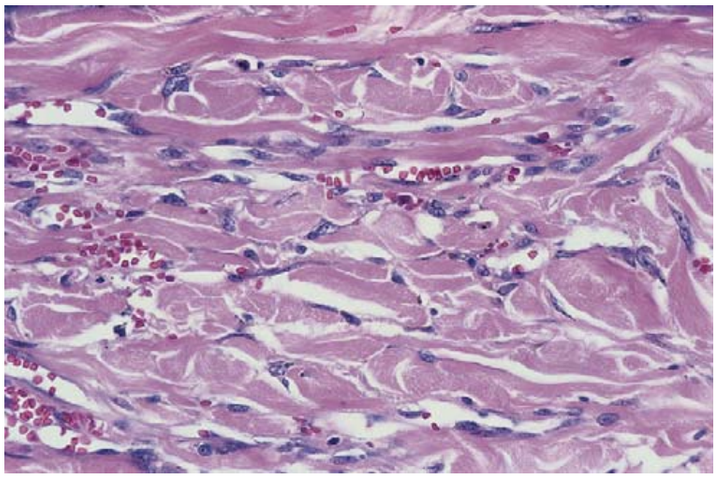


Fig. 114.26 Histology of Kaposi sarcoma – patch stage. Slit-like vascular spaces are present. *Courtesy, Ronald P Rapini, MD.*

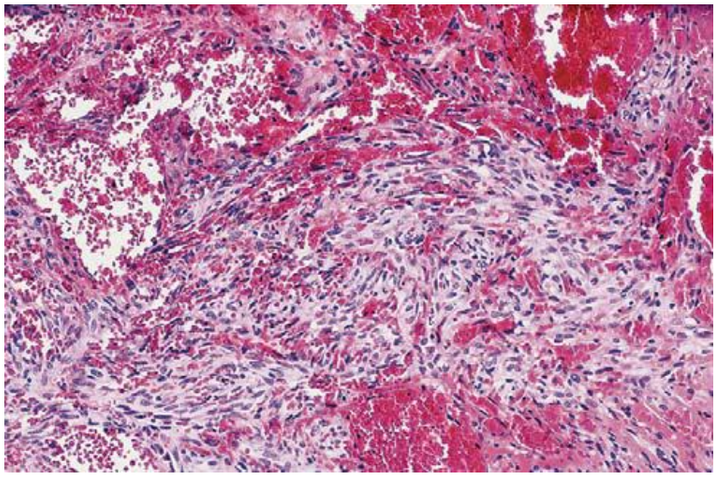


Fig. 114.27 Histology of Kaposi sarcoma – nodular stage. Dilated blood vessels and solid areas of bland spindle cells, slit-like spaces, and hemorrhage.

deposits, lymphocytes and plasma cells, and may be compartmentalized by fibrous bands. Some tumors contain prominent ectatic meshworks of vessels and have been referred to as "lymphangioma-like" KS. Tumors with a frankly sarcomatous appearance, nuclear pleomorphism and brisk mitotic activity may occur either as a late stage within previously indolent lesions or as an initial presentation, the latter most commonly in African endemic cases.

Demonstration of expression of the latency-associated nuclear antigen (LANA-1) of HHV-8 has proved in a number of studies to be a highly sensitive and specific marker of KS and other HHV-8-associated disorders such as multicentric Castleman's disease and primary effusion lymphoma in both HIV-positive and HIV-negative patients (see Ch. 80)[100,101]. Immunohistochemical detection of this antigen in vascular tumors is more diagnostically useful than detection of the HHV-8 genome by PCR since a few non-KS vascular tumors in both immunocompromised and immunocompetent patients have been found to be positive for HHV-8 by PCR, but not by LANA-1 immunohistochemistry, presumably due to detection of HHV-8 within blood cells circulating through the tumors[100].

Differential diagnosis

Lesions of KS may resemble a number of other diseases clinically and histologically, especially early and late stage lesions. The clinical differential for macular stage KS includes well-differentiated angiosarcoma, capillary malformation, microvenular hemangioma and hobnail hemangioma. These can be distinguished histologically, with the plasma cell-rich infiltrate of KS being an important discriminating factor.

The most important differential diagnostic considerations in nodular stage KS are KHE, spindle cell hemangioma and moderately differentiated angiosarcoma. Although KS and spindle cell hemangioma are both characterized by proliferations of spindle cells, KS lacks the cavernous spaces of the latter. KHE is almost exclusively a disease of infancy and childhood and is distinguished from KS by a strongly lobular architecture and lack of plasma cell infiltrates. Angiosarcoma is characterized by endothelial atypia and mitotic activity, both absent in KS.

Late stage KS may both clinically and histologically resemble acroangiodermatitis of chronic venous insufficiency and Stewart–Bluefarb syndrome (pseudo-Kaposi sarcoma). These reactive, hyperplastic entities differ from KS in that the hyperplasia can be seen to derive from pre-existing vasculature. Late stage KS lesions can also be confused histologically with a number of non-vascular spindle cell sarcomas such as fibrosarcoma and leiomyosarcoma. In these cases, demonstration of CD31 immunoreactivity helps confirm the vascular differentiation of KS.

Other entities that can mimic KS clinically but which can be easily distinguished on the basis of histologic features include cutaneous metastases, leukemia or lymphoma cutis, venous and lymphatic malformations, and the cutaneous manifestations of polyarteritis nodosa and erythema elevatum diutinum.

Treatment

In many patients with KS, obtaining a complete cure may be an unrealistic expectation, since recurrence rates are high. Treatment of visible lesions, even in HIV-positive patients with widely disseminated disease, improves appearance, heightens self-esteem and provides patients with a sense of control in an otherwise difficult situation. In older immunocompetent patients with static disease, observation and close follow-up is an option. Surgery is only useful for tissue diagnosis and removal of solitary lesions. Cryotherapy, laser surgery, photodynamic therapy and topical alitretinoin have been used to treat superficial macules and plaques. Freezing must usually be sufficiently vigorous to cause epidermal ulceration, and the resulting scar seems to replace the vascular proliferation of KS. Extensive, multifocal disease often requires chemotherapy.

Radiation therapy is a treatment option for the patient presenting with multifocal but relatively localized KS. Regimens reported to be successful include single-dose radiation (8 to 12 Gy) delivered to an extended field and total body electron beam therapy (4 Gy) once a week for 6 to 8 weeks. Radiation therapy clearly plays a role in the treatment of localized cutaneous and oral KS, but may have a briefer effect in AIDS-related KS than in classic KS[102].

Rapidly progressive KS (defined by development of 10 or more new cutaneous lesions per month), pulmonary KS, symptomatic visceral involvement and lymphedema are indications for systemic chemotherapy. Doxorubicin, vincristine, etoposide and bleomycin are administered singly or in combination[103], with liposomal preparations of anthracyclines employed to try to reduce side effects. The taxanes paclitaxel and docetaxel are used for the treatment of disseminated KS not responsive to anthracyclines and, depending upon comorbitities, may be used initially. Gemcitabine, an analogue of deoxycytidine, has shown some promise in the treatment of classic KS, with limited side effects[104].

For treatment of individual lesions, intratumoral vinblastine (0.1 mg/ml) or vincristine (0.001 mg/ml)[105] causes a slow fading of erythema and thickness. High concentrations or volumes of injection may cause ulceration of the overlying epidermis, but lesions still resolve with adequate cosmesis.

Interferon-α is a biological response modifier that has been proven effective as a systemic therapy for KS. It is administered either intravenously or as daily subcutaneous injections, with the dose required to achieve success in the treatment of disseminated KS approaching 30 million units per day. However, patients may not tolerate the interferon, given its multiple side effects at this dose[106].

Systemic therapies that inhibit angiogenesis or target HHV-8 are also being investigated. These include thalidomide, bevacizumab (anti-VEGF), the matrix metalloproteinase inhibitor COL-3, and TNP-470 (fumagillin analogue)[83,84]. Additional potential therapies are tyrosine kinase inhibitors (imatinib, sorafenib, gefitinib), pentosan polysulfate, IL-12 and topical halofuginone[104,107,108]. Antiretroviral therapy has clearly helped to alleviate AIDS-related KS, probably indirectly by

decreasing viral load and by increasing the CD4 count, but the exact mechanism is unclear. As noted previously, flares of KS can occur as a manifestation of IRIS (see Ch. 78), but this does not necessarily translate into a poor prognosis.

Organ transplant patients with KS pose a particular therapeutic challenge, that of balancing the risk of graft rejection with the benefit of improvement in KS. In addition to reduction of immunosuppression[109], substitution of sirolimus (rapamycin; mTOR inhibitor) for cyclosporine can also lead to clinical improvement of KS. In 15 renal transplant recipients, this substitution led to resolution of all of the KS lesions in all of the patients, both clinically (by 3 months) and histologically (by 6 months). The authors observed neither episodes of rejection nor changes in kidney graft function[110]. This observation has been independently corroborated by additional studies, albeit not always with equally impressive response rates[111]. It is not yet clear if the beneficial effect of sirolimus reflects lessened immunosuppression or possibly a more direct antitumor effect related to inhibition of HHV-8-induced effects (e.g., PI3K and AKT phosphorylation)[91]. Organ transplant patients with KS also respond to conventional local and systemic therapies used in other forms of KS. There are few published studies on the treatment of African endemic KS.

MALIGNANT VASCULAR NEOPLASMS

Angiosarcoma

Synonyms: ■ Malignant hemangioendothelioma ■ Hemangiosarcoma ■ Lymphangiosarcoma

Key features

- Uncommon malignant neoplasm of endothelium, accounting for <1% of all sarcomas
- Unlike most sarcomas, has a predilection for skin and superficial soft tissue
- Most commonly affects the scalp and face of the elderly and areas of chronic lymphedema or radiodermatitis; rare in children
- Cutaneous forms are usually well to moderately differentiated lesions composed of anastomosing vessels that dissect between bundles of collagen
- Approximately 50% of cases express markers of lymphatic differentiation
- Prognosis is extremely poor, with fewer than 15% of patients surviving 5 years
- Most long-term survivors received early radical ablative surgery

Introduction and history

The term *angiosarcoma* is traditionally used to denote all biologically high-grade malignant neoplasms of endothelial derivation, regardless of the evidence of lymphatic or blood vascular differentiation. Endothelial tumors of low or intermediate malignant potential are designated *hemangioendotheliomas*, although in the past these borderline tumors were often referred to as *low-grade angiosarcomas*. An exception to this rule is KS, a virus-associated disease of highly variable behavior that maintains a controversial place on the spectrum between neoplasia and hyperplasia. Angiosarcomas were first described systematically by Caro and Stubenrauch in 1945. Only 3 years later, Stewart and Treves described the association between angiosarcoma and post-mastectomy lymphedema[112]. The cutaneous form of angiosarcoma that primarily affects the face and scalp of the elderly was characterized by Wilson-Jones in 1964[113].

Epidemiology

Angiosarcomas are unusual neoplasms that occur primarily in adults. Those rare examples that occur during childhood or adolescence are more likely to arise within viscera (especially the heart or pericardium)[114] or in association with other disease states[115], including chronic or congenital lymphedema, chronic radiodermatitis and immunosuppression. Among elderly patients with angiosarcomas of the face and scalp, there is a strong predilection for Caucasians compared to individuals of African or Asian descent, and approximately a 2:1 male:female ratio[116].

Pathogenesis

Angiosarcomas are clonal proliferations of malignantly transformed cells expressing endothelial differentiation. Mechanisms of the association between chronic lymphedema and angiosarcoma remain uncertain. Theories include induction of neoplastic change by unknown carcinogens in accumulated lymphatic fluid[112] and the idea that areas with chronic lymphedema are "immunologically privileged sites" due to loss of afferent lymphatic connections. Although angiosarcomas arising in the setting of chronic lymphedema have often been presumed to originate from lymphatics, this has not been definitively proven. In one series in which cases associated with lymphedema and prior irradiation were excluded, expression of the lymphatic endothelium-associated antigen VEGFR-3 was observed in 8 of 16 angiosarcomas[66]. Another series found VEGFR-3 positivity in only 1 of 2 spindled angiosarcomas and in 0 of 4 epithelioid angiosarcomas[76]. Most angiosarcomas in a third series were found to coexpress podoplanin and podocalyxin, thought to be markers of lymphatic and vascular endothelium, respectively[87]. In sum, this suggests that many angiosarcomas are of mixed lineage. Until this issue is further clarified, use of the more generic term *angiosarcoma,* rather than *lymphangiosarcoma* or *hemangiosarcoma*, seems prudent.

Radiotherapy has been shown to be an independent risk factor for angiosarcoma development, best exemplified in breast cancer patients (see below). Gene amplification of *MYC* and *FLT4* has been implicated in the pathogenesis of secondary angiosarcoma, but not other types[117,118]. Environmental chemical exposures linked to angiosarcoma, particularly of the liver, include vinyl chloride, thorium dioxide, arsenic, radium, and anabolic steroids[119]. Lastly, neither HHV-8 infection nor cumulative sun exposure appears to be associated with angiosarcoma.

Clinical features

The most common form of angiosarcoma is cutaneous angiosarcoma (without lymphedema) in the elderly. Approximately 70% of these tumors occur in patients over 40 years of age, with the highest incidence in those >70 years of age. About 50% involve the head and neck (Fig. 114.28). Lesions typically present as a deceptively benign-appearing bruise-like patch on the central face, forehead or scalp. Facial swelling and edema may be present. More advanced lesions are violaceous, elevated nodules that bleed easily. Ulceration may be present. The area of involvement spreads centrifugally, eventually covering large portions of the head and neck. The prognosis is invariably poor, with a less than 15% survival over a 5-year period[116].

Fig. 114.28 Angiosarcoma. Erythematous and purple hemorrhagic plaques as well as grouped vesicles with clear or hemorrhagic fluid (reminiscent of microcystic lymphatic malformation) are present. There is also induction and a pink hue to the left side of the face in addition to evidence of previous excisions and radiotherapy. *Courtesy, Lorenzo Cerroni, MD.*

Angiosarcomas that arise in the setting of chronic lymphedema present as firm, coalescing violaceous nodules or an indurated plaque on a background of brawny, non-pitting edema. More than 90% of all angiosarcomas associated with lymphedema arise after mastectomy and lymph node dissection (Stewart–Treves syndrome). In these cases, the inner aspect of the upper arm is the most common site of involvement. Other forms of chronic lymphedema are associated with angiosarcoma, including congenital, filarial, traumatic and idiopathic. The duration of lymphedema prior to appearance of angiosarcoma ranges from 4 to 27 years.

Even though the incidence is very low (<0.05% in a recent survey of breast cancer patients)[120], the greater use of breast-sparing surgery paired with irradiation has translated into an increase in post-irradiation sarcomas. The latter arise within breast parenchyma and overlying skin, with an average post-treatment interval of 6 years. Post-irradiation angiosarcomas appear as infiltrative plaques or nodules in or near the area of tissue irradiated and share the poor prognosis of all forms of angiosarcoma. These are aggressive, infiltrative, multicentric tumors that enlarge incessantly. Local recurrence and metastasis to regional lymph nodes and lung are common.

Angiosarcomas of skin and soft tissue have also been reported in association with benign and malignant nerve sheath tumors[121], defunctionalized arteriovenous shunts in renal transplant patients[122], long-term exposure to various foreign materials[123], xeroderma pigmentosum[124] and bilateral retinoblastoma[125]. MRI, which shows a nonspecific decreased or variable signal intensity in T1 images, an increased signal in T2 images, and enhancement with gadolinium, is more useful than CT in accurately delineating the extent of local disease, including involvement of neurovascular structures and joints. It is also the imaging modality of choice for evaluating tumor response to preoperative radiation or chemotherapy.

Pathology

Angiosarcomas involving the skin, although highly variable in degree of endothelial differentiation both between and within individual tumors, do not vary in histology as a class between those of the "usual type" not associated with lymphedema, those associated with chronic lymphedema, and those associated with chronic radiodermatitis. Well-differentiated areas display an anastomosing network of sinusoidal vessels, often bloodless, lined by a single layer of endothelial cells of slight to moderate nuclear atypia. These exhibit a highly infiltrative pattern, splitting apart collagen bundles and groups of adipose cells (Fig. 114.29). In less well-differentiated areas, the endothelial cells with more pronounced nuclear pleomorphism and mitotic activity pile up and form papillary projections. In poorly differentiated areas, luminal formation may be non-apparent and mitotic activity may be high, mimicking other high-grade sarcomas, carcinoma or melanoma. Hemorrhage and blood-filled cavities may be present.

In tumors associated with chronic lymphedema, networks of small lymphatics lined by endothelial cells with hyperchromatic nuclei may ramify through adjacent soft tissues and have been interpreted as premalignant change. Angiosarcomas developing in this setting may retain lymphatic characteristics (Fig. 114.30). Most angiosarcomas immunoreact positively for CD31 and CD34, with CD31 being the more sensitive and endothelium-specific of the two. Immunohistochemical detection of factor VIII-related antigen, although highly specific for endothelial cells, lacks sensitivity for vascular neoplasms and is negative or very weak even in well-differentiated angiosarcomas. Highly aggressive angiosarcomas with an epithelioid appearance occasionally occur in the skin[126], although this variant is more common in deep soft tissues. These so-called "epithelioid angiosarcomas" consist of large rounded cells with prominent eosinophilic nucleoli in which the only morphologic evidence of vascular differentiation may be the presence of occasional intracytoplasmic vacuoles. Cytokeratin positivity is present in about one-third of epithelioid angiosarcomas[127,128], making distinction from carcinoma problematic. Fortunately, this distinction can be accomplished by demonstration of coexistent CD31 expression.

Differential diagnosis

Early recognition and histologic diagnosis are crucial in the treatment of angiosarcoma. Well-differentiated angiosarcomas, which display only slight cytologic atypia despite their high-grade biologic behavior, may closely resemble microcystic lymphatic malformation. Other vascular neoplasms that must be distinguished from angiosarcoma histologically include Dabska-like and retiform hemangioendothelioma, epithelioid hemangioendothelioma and tufted angioma. Intravascular proliferation of atypical endothelial cells is not a feature of KS.

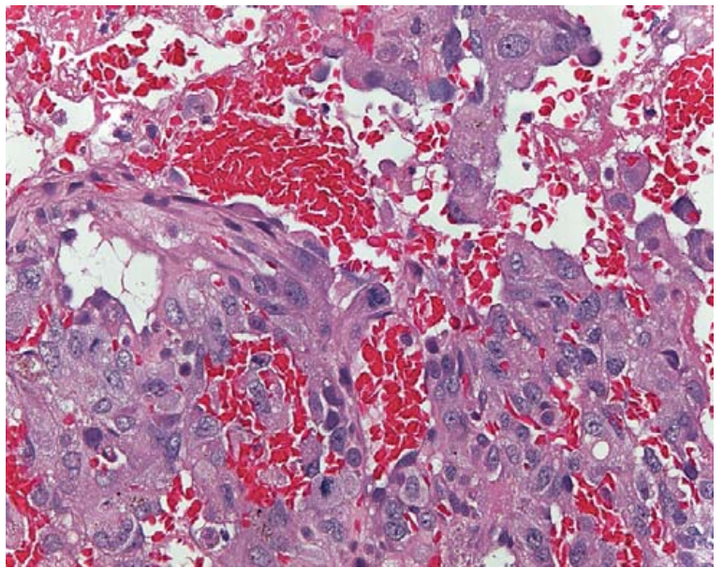


Fig. 114.29 Histology of angiosarcoma. Infiltration of the dermis by ill-defined vascular spaces lined by atypical, piled-up endothelial cells.

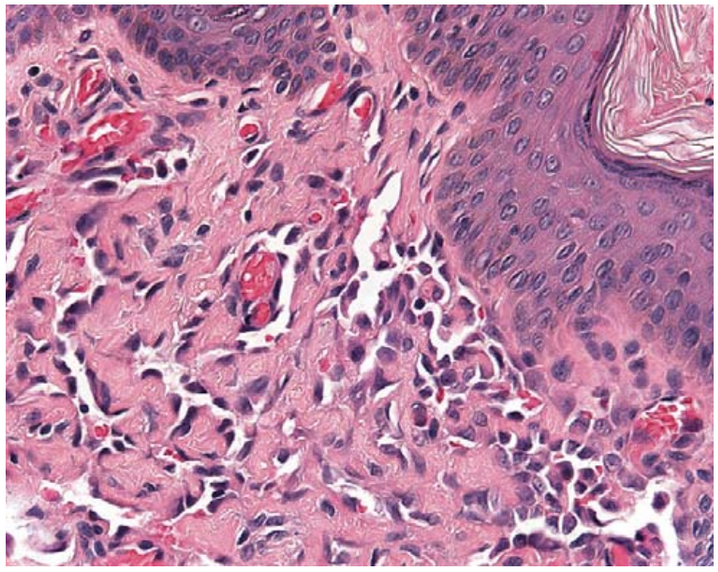


Fig. 114.30 Histology of angiosarcoma with lymphatic characteristics ("lymphangiosarcoma"). Some of the vascular channels are angular and lack erythrocytes. Also note the hyperchromatic atypical endothelial cells.

Treatment

Surgical excision with wide margins is indicated. Even with negative margins by histologic examination, the recurrence rate and chance of metastatic disease are high. This may in part reflect the tendency for multifocality. In a recent retrospective review, 10 of 13 patients showed a response to weekly paclitaxel versus 14 of 27 for non-paclitaxel regimens, but the difference was not statistically significant (p=0.18)[129]. There are also isolated reports of successful thalidomide therapy. Radiotherapy may be palliative, but does not improve survival.

PERIVASCULAR NEOPLASMS AND NEOPLASTIC-LIKE PROLIFERATIONS

Glomus Tumors and Glomuvenous Malformations (Glomangiomas)

Synonyms: ■ Glomus tumor: solitary glomus tumor, solid glomus tumor ■ Glomuvenous malformation: glomangioma, infiltrating glomus tumor, multiple glomus tumors

Key features

- A heterogeneous group of benign tumors and malformations characterized by presence of glomus cells
- The two major subgroups are *glomus tumor* and *glomuvenous malformation (glomangioma)*
- The glomus tumor typically presents in young adults, is a *solitary*, *painful* papule or nodule on the extremities with a predilection for subungual sites, and consists of a relatively *solid proliferation of glomus cells* associated with *small vessels*
- The less common glomuvenous malformation ("glomangioma") typically presents in infancy or childhood, is often *multiple* and *asymptomatic* and histologically resembles a venous malformation in which *dilated vessels* are rimmed by a *few glomus cells*
- Histologic variants in which glomus cells merge with well-differentiated smooth muscle cells are referred to as glomangiomyomas
- Extremely rare atypical and malignant forms have been described

Introduction

Tumors distinguished by the presence of benign glomus cells have been subclassified in the past into a number of descriptive types, such as solid, solitary, multiple, adult, pediatric and diffuse. Current evidence supports division of these tumors into two major disparate categories: (1) the glomus tumor proper, a cellular lesion that tends to be well circumscribed, solitary and subungual; and (2) the glomuvenous malformation, a frequently multifocal lesion, traditionally termed a "glomangioma", that most commonly presents in infants or children and histologically resembles a venous malformation in which lesional vessels are rimmed by glomus cells.

Epidemiology

Solitary glomus tumors can occur at any age, but are most common in young adults. Although these tumors in general show no gender predilection, subungual lesions are more common in women. Glomuvenous malformations are less common (accounting for 10–20% of all glomus cell lesions) and typically present in children; many are congenitally evident.

Pathogenesis

The fact that the most common site of occurrence of glomus tumors (the subungual region of the finger) corresponds to one of the densest areas of distribution of the normal glomus body suggests that many glomus tumors represent neoplastic proliferations originating from pre-existing normal glomus cell populations. However, the occasional occurrence of glomus tumors at sites where normal glomus bodies may not be found, including bone, gastrointestinal tract, trachea and nerve, suggests that some glomus tumors may arise from pluripotent mesenchymal cells or even ordinary smooth muscle cells.

Despite their shared compliment of benign glomus cells, glomus tumors and glomuvenous malformations differ widely in clinical and histopathologic features and are likely unrelated in pathogenesis. The resemblance to venous malformations plus the early presentation of glomuvenous malformations strongly supports their now widely accepted malformative etiology, thus the recent abandonment of the traditional term *glomangioma*. Although a number of glomuvenous malformations are sporadic, a recent large cohort study found that approximately two-thirds of cases are familial[130], with an autosomal dominant pattern of inheritance[131,132]. Multiple loss-of-function mutations in the glomulin gene (*GLMN*) have been identified in patients with familial glomuvenous malformations[133–135].

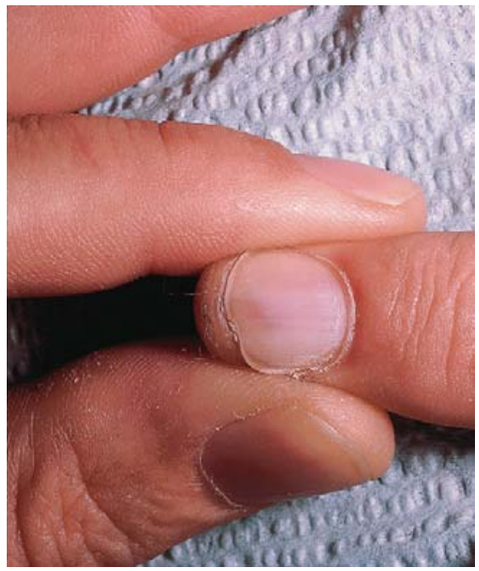


Fig. 114.31 Glomus tumor. The lesion presented with pain and ill-defined subungual erythema. *Courtesy, Ronald P Rapini, MD.*

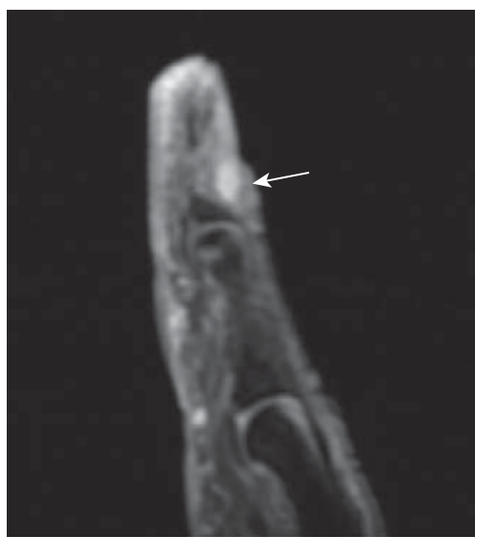


Fig. 114.32 MRI of a glomus tumor located in the proximal portion of the nail bed and matrix. While there was a low signal lesion noted in T1-weighted images of the left index finger, the lesion was very bright in T2-weighted images with diffuse homogeneous enhancement with gadolinium (arrow). *Courtesy, Kalman Watsky, MD.*

Clinical features

The glomus tumor is a benign lesion that usually presents in young adults (20–40 years of age) as a small (<2 cm), blue–red papule or nodule in the deep dermis or subcutis of the distal upper or lower extremities. They are tender to touch, and may be associated with severe paroxysmal pain in response to temperature changes and pressure. The hand, especially the nail beds and palm, is most commonly affected (Fig. 114.31), but lesions can also occur at other cutaneous locations. Unusual extracutaneous glomus tumors have been reported in the gastrointestinal tract, bone, mediastinum, trachea, mesentery, cervix and vagina. Extremely rare instances of malignant transformation within glomus tumors, with documented metastasis, have been described[136]. Radiographs are of limited usefulness in diagnosis, but subungual tumors often show bony erosion and may show increased distance between the nail and the dorsum of the phalanx. MRI is frequently the primary diagnostic imaging modality of choice (Fig. 114.32), followed by contrast-enhanced CT. Glomus tumors are strongly enhancing masses by both CT and MRI.

Glomuvenous malformations arise in children and adolescents and tend to be multiple. They are generally asymptomatic lesions that appear either as multiple, soft, red to blue nodules that may be widely distributed or confluent, or as pink to deep blue plaque-like lesions (Figs 114.33 & 114.34), also multifocal. Although they clinically

Fig. 114.33 Glomuvenous malformation ("glomangioma"). Note the cluster of slightly compressible blue papules.

Fig. 114.34 Glomuvenous malformation ("glomangioma"). Large cluster of blue papulonodules becoming confluent centrally.

resemble venous malformations, glomuvenous malformations differ in appearance from the latter in a number of aspects[137]: they tend to be more nodular or cobblestone-like in appearance, more blue and less compressible, and they do not swell with exercise or dependency. Lesions typically thicken and become more blue in color with time. Although less painful than the glomus tumor, glomuvenous malformations may be tender to palpation, and attacks of pain may occur in association with menstruation and pregnancy. All reported cases have behaved in a benign fashion.

Pathology

The common glomus tumor is a generally well-circumscribed proliferation of solid sheets and clusters of uniform glomus cells focally clustering around a variable complement of capillary-sized, endothelium-lined vessels (Fig. 114.35). The stroma is typically myxoid or hyalinized and may contain numerous small nerve twigs. A dense fibrous pseudocapsule may be present. The glomus cells are distinctive in their uniformly rounded or polygonal shape, centrally placed, rounded nuclei, and pale eosinophilic cytoplasm. PAS staining reveals basement membrane material around individual tumor cells. Mitotic figures may be present, but are normally configured. The ultrastructural features of these cells are consistent with modified smooth muscle cells, replete with relatively abundant myofilaments that focally condense to form dense bodies and pinocytotic vesicles[138]. Immunohistochemical studies have revealed consistent expression of vimentin and muscle actin isoforms, and variably reported expression of desmin. Examples demonstrating gradual transition from rounded glomus cells to elongated, well-differentiated smooth muscle cells have been termed glomangiomyomas[139].

Although the great majority of glomus tumors display no significant cytologic atypia, some have atypical or frankly malignant features.

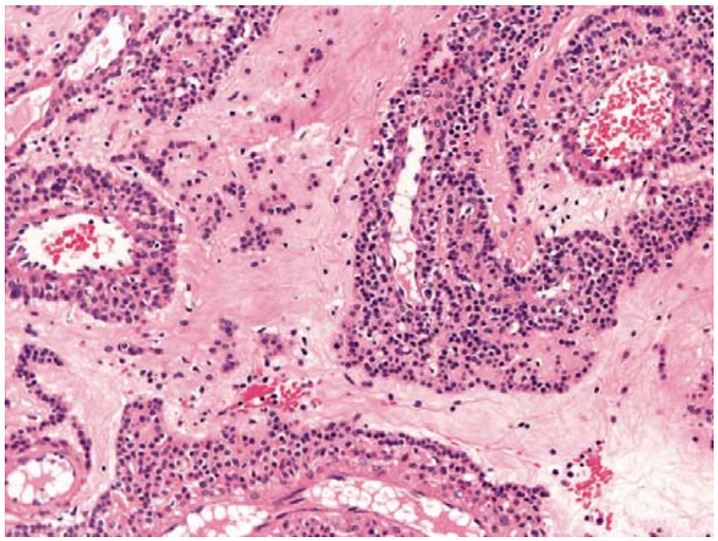


Fig. 114.35 Histology of glomus tumor. Proliferation of rounded, homogeneous, hyperchromatic glomus cells surrounding vascular lumina. *Courtesy, Lorenzo Cerroni, MD.*

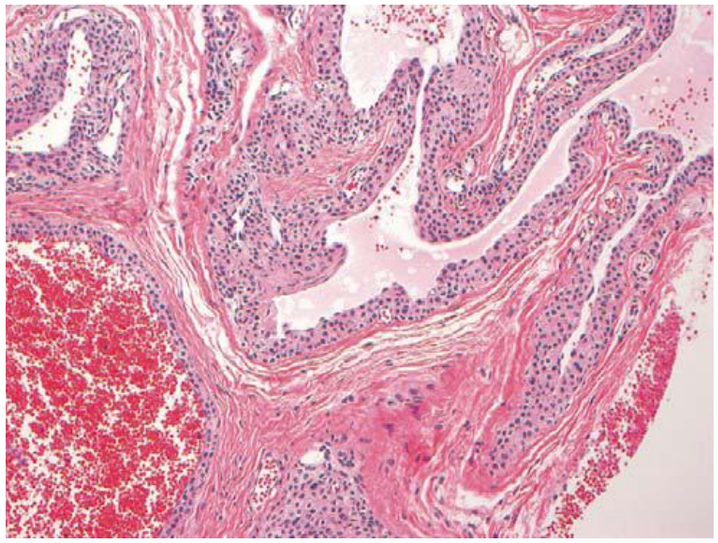


Fig. 114.36 Histology of glomuvenous malformation ("glomangioma"). One or more, often incomplete, layers of glomus cells rim abnormal venous channels that are otherwise histologically consistent with a venous malformation.

Based on an analysis of 53 atypical and malignant glomus tumors[140], a histopathologic classification of glomus tumors with unusual features has been proposed, with malignant glomus tumors defined as those of large size (>2 cm) and deep location, or those with marked atypia and a high mitotic rate (≥5/50 HPF), or those with atypical mitotic figures. Malignant examples show a compressed rim of benign glomus tumor around the malignant areas in about one-half of cases, consistent with malignant transformation from a pre-existing benign tumor.

Glomuvenous malformations consist of large, dilated, thin-walled veins in the dermis and subcutaneous tissue, histologically equivalent to those comprising venous malformations, but surrounded by one or more layers of uniform, cuboidal glomus cells (Fig. 114.36). Some microscopic fields may lack the glomus cells and be indistinguishable from common venous malformations. They are less circumscribed than solitary glomus tumors and may be distributed as separate nodules in the same anatomic area. Like venous malformations without glomus cells, many glomuvenous malformations contain organizing thrombi or phleboliths.

Differential diagnosis

Solitary glomus tumors may clinically be confused with other painful nodules such as eccrine spiradenomas and leiomyomas which can readily be distinguished from glomus tumors histologically and immunohistochemically. From a histologic point of view, solid forms of hidradenoma may closely resemble glomus tumors, especially when sweat ducts acquire erythrocytes, but can be distinguished by their keratin expression. Cellular glomus tumors are occasionally mistaken for pseudoangiomatous intradermal nevi, but the latter are positive for S100.

Glomuvenous malformations must be distinguished from ordinary venous malformations that lack glomus cells by histologic examination, although several clinical features of these lesions help make this distinction (see section above). It is likely that many cases of the so-called blue rubber bleb nevus syndrome, a familial disorder characterized by multiple venous malformations, actually represent examples of multiple glomuvenous malformations (glomangiomatosis).

Treatment

Solitary glomus tumors can be treated successfully by local surgical excision. Other options include electrodesiccation and sclerotherapy.

Glomuvenous malformations are less amenable to surgery than are common glomus tumors, due to their more extensive and multifocal nature. In a series of large facial "glomangiomas"[137], MRI was the best modality for definition of the extent of the lesions and their relationship to other anatomic structures. In this same series, surgical resection reduced the area of discoloration and improved facial contour, while sclerotherapy was less effective than for venous malformations[137]. Laser surgery employing CO_2, KTP, Nd:YAG and pulsed dye lasers may also be helpful. Residual lesions following subtotal resections may slowly re-expand[137].

Infantile Hemangiopericytoma

Synonym: ■ Congenital hemangiopericytoma

Key features

- Benign neoplasm of perivascular myoid differentiation that usually presents at birth or in the first years of life
- Clinical appearance is that of single or multiple dermal and subcutaneous nodules that may be alarmingly large at birth or grow rapidly
- Differs in both histology and clinical behavior from adult-type hemangiopericytoma, which rarely involves the skin
- Multilobulated tumor with cellular areas of spindle cells and antler-like branching blood vessels, merging with less cellular areas containing plump myofibroblasts
- Closely related to infantile myofibromatosis
- Behaves in a benign fashion, despite frequent focal necrosis and increased mitotic activity

Introduction and history

The concept of hemangiopericytoma as an entity has been controversial since these tumors were described in 1942 by Stout and Murray, who considered them to be composed mainly of pericytes. Congenital or infantile hemangiopericytoma was recognized as a separate entity from adult-type hemangiopericytoma in 1976 by Enzinger and Smith[141] in consideration of its distinguishing clinical and histologic features. Classic adult-type hemangiopericytomas will not be discussed here because of their extreme rarity in superficial tissues.

Epidemiology

Infantile hemangiopericytomas are uncommon tumors that typically appear in the first year of life and are usually congenital. There is a male predominance by approximately 2 : 1. Examples in older children have occasionally been reported.

Pathogenesis

The frequent zonal pattern of myofibroblastic differentiation in infantile hemangiopericytomas has led to the proposal that infantile hemangiopericytoma and infantile myofibromatosis may lie upon a continuous spectrum of myofibroblastic lesions[142]. A family of adult tumors with perivascular myoid differentiation has been described that overlaps histologically with infantile myofibromatosis and includes two newer entities, termed *glomangiopericytoma* and *myopericytoma*. Granter et al.[143], in support of similar observations by Requena and colleagues[144], have proposed that this widening spectrum of tumors and their distinctive cellular components might be better explained by derivation from a pluripotent periendothelial cell capable of differentiating along smooth muscle, pericytic and glomus cell lines, rather than from myofibroblasts.

Clinical features

Infantile hemangiopericytomas are nodules that primarily occur in the subcutaneous and dermal tissues of the head and neck. Congenital examples may be alarming in size at birth or grow rapidly thereafter. Multicentric cases have been reported and have in some instances been misinterpreted as examples of distant metastasis. Although benign behavior appears to be the rule, large tumors may be problematic if they hemorrhage or threaten vital structures. Lesions in deeply seated sites, such as the tongue, mediastinum and abdomen, have been reported. Rare multisystemic forms in neonates may be lethal. Local recurrence after excision is common, although spontaneous tumor regression has also been documented.

Pathology

Infantile-type hemangiopericytomas, unlike the adult type, are usually dermal or subcutaneous in location and are often multilobulated. They typically show a biphasic growth pattern in which primitive, hemangiopericytomatous areas resembling the adult tumors (short spindle cells arranged around thin-walled, branching vessels) blend with less cellular areas containing plump, myofibroblast-like cells set within a collagenous matrix. Focal necrosis and significant mitotic activity may be present, but are not indicative of poor prognosis.

Differential diagnosis

Infantile hemangiopericytomas demonstrate nonspecific clinical and radiologic features and require histologic examination for definitive diagnosis. They may be confused clinically with an infantile hemangioma due to rapid postnatal growth, and large congenital lesions may suggest a rapidly involuting congenital hemangioma or infantile fibrosarcoma. Further diagnostic considerations include infantile myofibromatosis and subcutaneous pyogenic granuloma.

Treatment

Conservative treatment following establishment of the diagnosis via histologic examination is generally recommended given the potential for spontaneous regression. Complete surgical resection is a reasonable option in some cases, although there appears to a conflicting tendency of these tumors to both locally recur and spontaneously regress.

REFERENCES

1. Ackerman AB. Resolving Quandaries in Dermatology, Pathology, and Dermatopathology. New York: Ardor Scribendi, 2001.
2. Kuo T, Gomez LG. Papillary endothelial proliferation in cystic lymphangiomas. A lymphatic vessel counterpart of Masson's vegetant intravascular hemangioendothelioma. Arch Pathol Lab Med. 1979;103:306–8.
3. Pins MR, Rosenthal DI, Springfield DS, Rosenberg AE. Florid extravascular papillary endothelial hyperplasia (Masson's pseudoangiosarcoma) presenting as a soft-tissue sarcoma. Arch Pathol Lab Med. 1993;117:259–63.
4. Weiss SW, Goldblum JR. Enzinger and Weiss's Soft Tissue Tumors, 4th edn. St Louis: Mosby, 2001.
5. Yang H, Ahmed I, Verghese M, Schroeter AL. Diffuse dermal angiomatosis of the breast. Arch Dermatol. 2006;142:343–7.
6. Pasyk K, Depowski M. Proliferating systematized angioendotheliomatosis of a 5-month-old infant. Arch Dermatol. 1978;114:1512–5.

7. McMenamin ME, Fletcher CDM. Reactive angioendotheliomatosis: a study of 15 cases demonstrating a wide clinicopathologic spectrum. Am J Surg Pathol. 2002;26:685–97.
8. McLaughlin ER, Morris R, Weiss SW, Arbiser JL. Diffuse dermal angiomatosis of the breast: response to isotretinoin. J Am Acad Dermatol. 2001;45: 462–5.
9. Chan JK, Fletcher CD, Hicklin GA, Rosai J. Glomeruloid hemangioma. A distinctive cutaneous lesion of multicentric Castleman's disease associated with POEMS syndrome. Am J Surg Pathol. 1990;14:1036–46.
10. Chung W-K, Lee D-W, Yang J-H, et al. Glomeruloid hemangioma as a very early presenting sign of POEMS syndrome. J Cutan Pathol. 2009;36;1126–8.
11. Watanabe O, Maruyama I, Arimura K, et al. Overproduction of vascular endothelial growth factor/ vascular permeability factor is causative in Crow-Fukase (POEMS) syndrome. Muscle Nerve. 1998;21:1390–7.
12. Belec L, Mohamied AS, Authier F-J, et al. Human herpesvirus 8 infection in patients with POEMS syndrome-associated multicentric Castleman's disease. Blood. 1999;93:3643–53.
13. Suurmeijer AJH, Fletcher CDM. Papillary hemangioma: a distinctive cutaneous hemangioma of the head and neck area containing hyaline globules. Histopathology. 2007;51:638–48.
14. Hunt SJ, Santa Cruz DJ, Barr RJ. Microvenular hemangioma. J Cutan Pathol. 1991;18:235–40.
15. Requena L, Sangueza OP. Cutaneous vascular proliferation. Part II. Hyperplasias and benign neoplasms. J Am Acad Dermatol. 1997;37:887–919.
16. Allen PW, Ramakrishna B, MacCormac LB. The histiocytoid hemangiomas and other controversies. Pathol Ann. 1992;27:51–87.
17. Wells GC, Whimster IW. Subcutaneous angiolymphoid hyperplasia with eosinophilia. Br J Dermatol. 1969;81:1–14.
18. Googe PB, Harris NL, Mihm MC Jr. Kimura's disease and angiolymphoid hyperplasia with eosinophilia: two distinct histopathological entities. J Cutan Pathol. 1987;14:263–71.
19. Olsen TG, Helwig EB. Angiolymphoid hyperplasia with eosinophilia. A clinicopathologic study of 116 patients. J Am Acad Dermatol. 1985;12:781–96.
20. Khunger N, Pahwa M, Jain RK. Angiolymphoid hyperplasia with eosinophilia treated with a novel combination technique of radiofrequency ablation and sclerotherapy. Dermatol Surg. 2010;36:422–5.
21. Weiss SW, Enzinger FM. Spindle cell hemangioendothelioma. A low-grade angiosarcoma resembling a cavernous hemangioma and Kaposi's sarcoma. Am J Surg Pathol. 1986;10:521–30.
22. Perkins P, Weiss SW. Spindle cell hemangioendothelioma. An analysis of 78 cases with reassessment of its pathogenesis and biologic behavior. Am J Surg Pathol. 1996;20:1196–204.
23. Fletcher CD, Beham A, Schmid C. Spindle cell haemangioendothelioma: a clinicopathological and immunohistochemical study indicative of a non-neoplastic lesion. Histopathology. 1991;18: 291–301.
24. Imayama S, Murakamai Y, Hashimoto H, Hori Y. Spindle cell hemangioendothelioma exhibits the ultrastructural features of reactive vascular proliferation rather than of angiosarcoma. Am J Clin Pathol. 1992;97:279–87.
25. Battocchio S, Facchetti F, Brisigotti M. Spindle cell haemangioendothelioma: further evidence against its proposed neoplastic nature. Histopathology. 1993;22:296–8.
26. Setoyama M, Shimada H, Miyazono N, et al. Spindle cell hemangioendothelioma: successful treatment with recombinant interleukin-2. Br J Dermatol. 2000;142:1238–9.
27. Hartzell MB. Granuloma pyogenicum (botryomycosis of French authors). J Cutan Dis. 1904;22:520–3.
28. Katta R, Bickle K, Hwang L. Pyogenic granuloma arising in port-wine stain during pregnancy. Br J Dermatol. 2001;144:644–5.
29. Kerr DA. Granuloma pyogenicum. Oral Surg Oral Med Oral Pathol. 1951;4:158.
30. Warner J, Jones EW. Pyogenic granuloma recurring with multiple satellites. A report of 11 cases. Br J Dermatol. 1968;80:218–27.
31. Wilson BB, Greer KE, Cooper PH. Eruptive disseminated lobular capillary hemangioma (pyogenic granuloma). J Am Acad Dermatol. 1989;21:391–4.
32. Campbell JP, Grekin RC, Ellis CN, et al. Retinoid therapy is associated with excess granulation tissue responses. J Am Acad Dermatol. 1983;9:708–13.
33. Tay YK, Weston WL, Morelli JG. Treatment of pyogenic granuloma in children with the flashlamp-pumped pulsed dye laser. Pediatrics. 1997;99:368–70.
34. Matsumoto K, Nakanishi H, Seike T, et al. Treatment of pyogenic granuloma with a sclerosing agent. Dermatol Surg. 2001;27:521–3.
35. Calonje E, Fletcher CD. Sinusoidal hemangioma. A distinctive benign vascular neoplasm within the group of cavernous hemangiomas. Am J Surg Pathol. 1991;15:1130–5.
36. Calonje E, Fletcher CD, Wilson-Jones E, Rosai J. Retiform hemangioendothelioma. A distinctive form of low-grade angiosarcoma delineated in a series of 15 cases. Am J Surg Pathol. 1994;18:115–25.
37. Guillou L, Calonje E, Speight P, et al. Hobnail hemangioma: a pseudomalignant vascular lesion with a reappraisal of targetoid hemosiderotic hemangioma. Am J Surg Pathol. 1999;23:97–105.
38. Mentzel T, Partanen TA, Kutzner H. Hobnail hemangioma ('targetoid hemosiderotic hemangioma'): clinicopathologic and immunohistochemical analysis of 62 cases. J Cutan Pathol. 1999;26:279–86.
39. Franke FE, Steger K, Marks A, et al. Hobnail hemangiomas (targetoid hemosiderotic hemangiomas) are true lymphangiomas. J Cutan Pathol. 2004;31: 362–7.
40. Wilson-Jones E, Orkin M. Tufted angioma (angioblastoma). A benign progressive angioma, not to be confused with Kaposi's sarcoma or low-grade angiosarcoma. J Am Acad Dermatol. 1989;20:214–25.
41. Nakagawa K. Case report of angioblastoma of the skin. Nippon Hifuka Gakkai Zasshi. 1949;59:92–4.
42. Macmillan A, Champion RH. Progressive capillary haemangioma. Br J Dermatol. 1971;85:492–3.
43. Enjolras O, Wassef M, Mazoyer E, et al. Infants with Kasabach-Merritt syndrome do not have 'true' hemangiomas. J Pediatr. 1997;130:631–40.
44. Hebeda CL, Scheffer E, Starink TM. Tufted angioma of late onset. Histopathology. 1993;23:191–3.
45. Heagerty AH, Rubin A, Robinson TW. Familial tufted angioma. Clin Exp Dermatol. 1992;17:344–5.
46. Zukerberg LR, Nickoloff BJ, Weiss SW. Kaposiform hemangioendothelioma of infancy and childhood. An aggressive neoplasm associated with Kasabach-Merritt syndrome and lymphangiomatosis. Am J Surg Pathol. 1993;17:321–8.
47. Sarkar M, Mulliken JB, Kozakewich HP, et al. Thrombocytopenic coagulopathy (Kasabach-Merritt phenomenon) is associated with Kaposiform hemangioendothelioma and not with common infantile hemangioma. Plast Reconstr Surg. 1997;100:1377–86.
48. Browning J, Frieden I, Baselga E, et al. Congenital self-regressing tufted angioma. Arch Dermatol. 2006;142:749–51.
49. Leaute-Labreze C, Bioulac-Sage P, Labbe L, et al. Tufted angioma associated with platelet trapping syndrome: response to aspirin. Arch Dermatol. 1997;133:1077–9.
50. Le Huu AR, Jokinen CH, Ruben BP, et al. Expression of Prox1, lymphatic endothelial nuclear transcription factor, in kaposiform hemangioendothelioma and tufted angioma. Am J Surg Pathol. 2010;34:1563–73.
51. North PE, Waner M, Mizeracki A, et al. A unique microvascular phenotype shared by juvenile hemangiomas and human placenta. Arch Dermatol. 2001;137:559–70.
52. Seo SK, Suh JC, Na GY, et al. Kasabach-Merritt syndrome: identification of platelet trapping in a tufted angioma by immunohistochemistry technique using monoclonal antibody to CD61. Pediatr Dermatol. 1999;16:392–4.
53. Dadras SS, North PE, Bertoncini J, et al. Infantile hemangiomas are arrested in an early developmental vascular differentiation state. Mod Pathol. 2004;17: 1068–79.
54. North PE. Vascular tumors and malformations of infancy and childhood. Pathol Case Rev. 2008;13:213–35.
55. Suarez SM, Pensler JM, Paller AS. Response of deep tufted angioma to interferon alfa. J Am Acad Dermatol. 1995;33:124–6.
56. Munn SE, Jackson JE, Jones RR. Tufted haemangioma responding to high-dose systemic steroids: a case report and review of the literature. Clin Exp Dermatol. 1994;19: 511–14.
57. Fahrtash F, McCahon E, Arbuckle S. Successful treatment of kaposiform hemangioendothelioma and tufted angioma with vincristine. J Pediatr Hematol Oncol. 2010;32:506–10.
58. North PE, Kahn T, Cordisco MR, et al. Multifocal lymphangioendotheliomatosis with thrombocytopenia: a newly recognized clinicopathological entity. Arch Dermatol. 2004;140:599–606.
59. Prasad V, Fishman SJ, Mulliken JB, et al. Cutaneovisceral angiomatosis with thrombocytopenia. Pediatr Dev Pathol. 2005;8:407–19.
60. North PE. Vascular tumors and malformations. Surg Pathol Clin. 2010;3:455–94.
61. Maronn M, Catrine K, North P, et al. Expanding the phenotype of multifocal lymphangioendotheliomatosis with thrombocytopenia. Pediatr Blood Cancer. 2009;52:531–4.
62. Kline RM, Buck LM. Bevacizumab treatment in multifocal lymphangioendotheliomatosis with thrombocytopenia. Pediatr Blood Cancer. 2009;52:534–6.
63. Niedt GW, Greco MA, Wieczorek R, et al. Hemangioma with Kaposi's sarcoma-like features: report of two cases. Pediatr Pathol. 1989;9:567–75.
64. Tsang WY, Chan JK. Kaposi-like infantile hemangioendothelioma. A distinctive vascular neoplasm of the retroperitoneum. Am J Surg Pathol. 1991;15:982–9.
65. Mentzel T, Mazzoleni G, Dei Tos AP, Fletcher CD. Kaposiform hemangioendothelioma in adults. Clinicopathologic and immunohistochemical analysis of three cases. Am J Clin Pathol. 1997;108:450–5.
66. Folpe AL, Veikkola T, Valtola R, Weiss SW. Vascular endothelial growth factor receptor-3 (VEGFR-3): a marker of vascular tumors with presumed lymphatic differentiation, including Kaposi's sarcoma, kaposiform and Dabska-type hemangioendotheliomas, and a subset of angiosarcomas. Mod Pathol. 2000;13: 180–5.
67. Phillips WG, Marsden JR. Kasabach-Merritt syndrome exacerbated by platelet transfusion. J R Soc Med. 1993;86:231–2.
68. Vin-Christian K, McCalmont TH, Frieden IJ. Kaposiform hemangioendothelioma. An aggressive, locally invasive vascular tumor that can mimic hemangioma of infancy. Arch Dermatol. 1997;133:1573–8.
69. Lai FM, Allen PW, Yuen PM, Leung PC. Locally metastasizing vascular tumor. Spindle cell, epithelioid, or unclassified hemangioendothelioma? Am J Clin Pathol. 1991;96:660–3.
70. North PE, Waner M, Mizeracki A, Mihm MC Jr. GLUT1: a newly discovered immunohistochemical marker for juvenile hemangiomas. Hum Pathol. 2000;31:11–22.
71. Blei F, Karp N, Rofsky N, et al. Successful multimodal therapy for kaposiform hemangioendothelioma complicated by Kasabach-Merritt phenomenon: case report and review of the literature. Pediatr Hematol Oncol. 1998;15:295–305.
72. Deb G, Jenkner A, De Sio L, et al. Spindle cell (Kaposiform) hemangioendothelioma with Kasabach-Merritt syndrome in an infant: successful treatment with alpha-2A interferon. Med Pediatr Oncol. 1997;28:358–61.
73. Enjolras O, Wassef M, Dosquet C, et al. Kasabach-Merritt syndrome on a congenital tufted angioma. Ann Dermatol Venereol. 1998;125:257–60.
74. Hu B, Lachman R, Phillips J, et al. Kasabach-Merritt syndrome-associated kaposiform hemangioendothelioma successfully treated with cyclophosphamide, vincristine, and actinomycin D. J Pediatr Hematol Oncol. 1998;20:567–9.
75. Argani P, Athanasian E. Malignant endovascular papillary angioendothelioma (Dabska tumor) arising within a deep intramuscular hemangioma. Arch Pathol Lab Med. 1997;121:992–5.
76. Fanburg-Smith JC, Michal M, Partanen TA, et al. Papillary intralymphatic angioendothelioma (PILA): a report of twelve cases of a distinctive vascular tumor with phenotypic features of lymphatic vessels. Am J Surg Pathol. 1999;23:1004–10.
77. Fletcher CDM, Unni KK, Mertens F. Tumors of Soft Tissue and Bone. World Health Organization Classification of Tumours. Lyon, France: IARC Press, 2002:163–77.
78. Parsons A, Sheehan DJ, Sangueza OP: Retiform hemangioendotheliomas usually do not express D2-40 and VEGFR-3. Am J Dermatopathol. 2008;30:31–3.
79. Emberger M, Laimer M, Steiner H, Zelger B. Retiform hemangioendothelioma: presentation of a case expressing D2-40. J Cutan Pathol. 2009;36:987–90.
80. Stratton JS, Billings SD. Vascular tumors of intermediate malignancy: a review and update. Dermatologica Sinica. 2009;27:140–53.
81. Mentzel T, Beham A, Calonje E, et al. Epithelioid hemangioendothelioma of skin and soft tissues:

clinicopathologic and immunohistochemical study of 30 cases. Am J Surg Pathol. 1997;21:363–74.
82. Quante M, Patel NK, Hill S, et al. Epithelioid hemangioendothelioma presenting in the skin: a clinicopathologic study of eight cases. Am J Dermatopathol. 1998;20:541–6.
83. Mendlick MR, Nelson M, Pickering D, et al. Translocation t(1;3)(p36.3;q25) is a nonrandom aberration in epithelioid hemangioendothelioma. Am J Surg Pathol. 2001;25:684–7.
84. Weiss SW, Ishak KG, Dail DH, et al. Epithelioid hemangioendothelioma and related lesions. Semin Diagn Pathol. 1986;3:259–87.
85. Park MS, Ravi V, Araujo DM. Inhibiting the VEGF-VEGFR pathway in angiosarcoma, epithelioid hemangioendothelioma, and hemangiopericytoma/solitary fibrous tumor. Curr Opin Oncol. 2010;22:351–5.
86. Jussila L, Valtola R, Partanen TA, et al. Lymphatic endothelium and Kaposi's sarcoma spindle cells detected by antibodies against the vascular endothelial growth factor receptor-3. Cancer Res. 1998;58:1599–604.
87. Weninger W, Partanen TA, Breiteneder-Geleff S, et al. Expression of vascular endothelial growth factor receptor-3 and podoplanin suggests a lymphatic endothelial cell origin of Kaposi's sarcoma tumor cells. Lab Invest. 1999;79:243–51.
88. Xu H, Edwards JR, Espinosa O, et al. Expression of a lymphatic endothelial cell marker in benign and malignant vascular tumors. Hum Pathol. 2004;35:857–61.
89. Carroll PA, Brazeau E, Lagunoff M. Kaposi's sarcoma-associated herpesvirus infection of blood endothelial cells induces lymphatic differentiation. Virology. 2004;328:7–18.
90. Wang H-W, Trotter MWB, Lagos D, et al. Kaposi sarcoma herpesvirus-induced cellular reprogramming contributes to the lymphatic gene expression in Kaposi sarcoma. Nat Genet. 2004;36:687–93.
91. Ganem D. KSHV and the pathogenesis of Kaposi sarcoma: listening to human biology and medicine. J Clin Invest. 2010;120:939–49.
92. Rabkin CS, Janz S, Lash A, et al. Monoclonal origin of multicentric Kaposi's sarcoma lesions. N Engl J Med. 1997;336:988–93.
93. Duprez R, Lacoste V, Brière J, et al. Evidence for a multiclonal origin of multicentric advanced lesions of Kaposi sarcoma. J Natl Cancer Inst. 2007;99:1086–94.
94. Weiss RA, Whitby D, Talbot S, et al. Human herpesvirus type 8 and Kaposi's sarcoma. J Natl Cancer Inst Monogr. 1998;(23):51–4.
95. Moore PS, Chang Y. Kaposi's sarcoma-associated herpesvirus-encoded oncogenes and oncogenesis. J Natl Cancer Inst Monogr. 1998;(23):65–71.
96. Sciacca FL, Sturzl M, Bussolino F, et al. Expression of adhesion molecules, platelet-activating factor, and chemokines by Kaposi's sarcoma cells. J Immunol. 1994;153:4816–25.
97. Masood R, Cai J, Tulpule A, et al. Interleukin 8 is an autocrine growth factor and a surrogate marker for Kaposi's sarcoma. Clin Cancer Res. 2001;7:2693–702.
98. Bower M, Nelson M, Young AM, et al. Immune reconstitution inflammatory syndrome associated with Kaposi's sarcoma. J Clin Oncol. 2005;23:5224–8.
99. Tappero JW, Conant MA, Wolfe SF, Berger TG. Kaposi's sarcoma. Epidemiology, pathogenesis, histology, clinical spectrum, staging criteria and therapy. J Am Acad Dermatol. 1993;28:371–95.
100. Hammock L, Reisenauer A, Wang W, et al. Latency-associated nuclear antigen expression and human herpesvirus-8 polymerase chain reaction in the evaluation of Kaposi sarcoma and other vascular tumors in HIV-positive patients. Mod Pathol. 2005;18:463–8.
101. Dupin N, Fisher C, Kellam P, et al. Distribution of human herpesvirus-8 latently infected cells in Kaposi's sarcoma, multicentric Castleman's disease, and primary effusion lymphoma. Proc Natl Acad Sci U S A. 1999;96:4546–51.
102. Antman K, Chang Y. Kaposi's sarcoma. N Engl J Med. 2000;342:1027–38.
103. Krown SE. Acquired immunodeficiency syndrome-associated Kaposi's sarcoma. Biology and management. Med Clin North Am. 1997;81:471–94.
104. Vanni T, Sprinz E, Machado MW, et al. Systemic treatment of AIDS-related Kaposi sarcoma: current status and perspectives. Cancer Treat Rev. 2006;32:445–55.
105. Brambilla L, Bellinvia A, Tourlaki A, et al. Intralesional vincristine as first-line therapy for nodular lesions in classic Kaposi sarcoma: a prospective study in 151 patients. Br J Dermatol. 2009;162:854–9.
106. Gascon P, Schwartz RA. Kaposi's sarcoma. New treatment modalities. Dermatol Clin. 2000;18:169–75.
107. Di Lorenzo G, Konstantinopoulos PA, Pantanowitz L, et al. Management of AIDS-related Kaposi's sarcoma. Lancet Oncol. 2007;8:167–76.
108. Koon HB, Fingleton B, Lee JY, et al. Phase II AIDS Malignancy Consortium trial of topical halofuginone in AIDS-related Kaposi sarcoma. J Acquir Immune Defic Syndr. 2011;56:64–8.
109. Qunibi WY, Barri Y, Alfurayh O, et al. Kaposi's sarcoma in renal transplant recipients: a report on 26 cases from a single institution. Transplant Proc. 1993;25:1402–5.
110. Stallone G, Schena A, Infante B, et al. Sirolimus for Kaposi sarcoma in renal-transplant patients. N Engl J Med. 2005;352:1317–23.
111. Lebbe C, Euvrard S, Barrou B, et al. Sirolimus conversion for patients with post-transplant Kaposi's sarcoma. Am J Transplant. 2006;6:2164–8.
112. Stewart FW, Treves N. Lymphangiosarcoma in postmastectomy lymphedema. Cancer. 1948;1:64–81.
113. Wilson-Jones E. Malignant angioendothelioma of the skin. Br J Dermatol. 1964;76:21–39.
114. Deyrup AT, Miettinen M, North PE, et al. Angiosarcomas arising in the viscera and soft tissue of children and young adults. Am J Surg Pathol. 2009;33:264–9.
115. Deyrup AT, Miettinen M, North PE, et al. Pediatric cutaneous angiosarcomas: a clinicopathological study of 10 cases. Am J Surg Pathol. 2011;35:70–5.
116. Holden CA, Spittle MF, Jones EW. Angiosarcoma of the face and scalp, prognosis and treatment. Cancer. 1987;59:1046–57.
117. Manner J, Radlwimmer B, Hohenberger P, et al. *MYC* high level gene amplification is a distinctive feature of angiosarcomas after irradiation or chronic lymhedema. Am J Surg Pathol. 2010;176:34–9.
118. Guo T, Zhang L, Chang N-E, et al. Consistent *MYC* and *FLT4* gene amplification in radiation-induced angiosarcoma but not in other radiation-associated atypical vascular lesions. Genes Chromosomes Cancer. 2011;50:25–33.
119. Young RJ, Brown NJ, Reed MW, et al. Angiosarcoma. Lancet Oncol 2010;11:983–91.
120. Marchal C, Weber B, de Lafontan B, et al. Nine breast angiosarcomas after conservative treatment for breast carcinoma: a survey from French comprehensive Cancer Centers. Int J Radiat Oncol Biol Phys. 1999;44:113–19.
121. Brown RW, Tornos C, Evans HL. Angiosarcoma arising from malignant schwannoma in a patient with neurofibromatosis. Cancer. 1992;70:1141–4.
122. Bessis D, Sotto A, Roubert P, et al. Endothelin-secreting angiosarcoma occurring at the site of an arteriovenous fistula for haemodialysis in a renal transplant recipient. Br J Dermatol. 1998;138:361–3.
123. Jennings TA, Peterson L, Axiotis CA, et al. Angiosarcoma associated with foreign body material. A report of three cases. Cancer. 1988;62:2436–44.
124. Leake J, Sheehan MP, Rampling D, et al. Angiosarcoma complicating xeroderma pigmentosum. Histopathology. 1992;21:179–81.
125. Dunkel IJ, Gerald WL, Rosenfield NS, et al. Outcome of patients with a history of bilateral retinoblastoma treated for a second malignancy: the Memorial Sloan-Kettering experience. Med Pediatr Oncol. 1998;30:59–62.
126. Suchak R, Thway K, Zelger B, et al. Primary cutaneous epithelioid angiosarcoma: a clinicopathological study of 13 cases of rare neoplasm occurring outside the setting of conventional angiosarcomas and with predilection for the limbs. Am J Surg Pathol. 2011;35:60–9.
127. Gray MH, Rosenberg AE, Dickersin GR, Bhan AK. Cytokeratin expression in epithelioid vascular neoplasms. Hum Pathol. 1990;21:212–17.
128. Meis-Kindblom JM, Kindblom LG. Angiosarcoma of soft tissue: a study of 80 cases. Am J Surg Pathol. 1998;22:683–97.
129. Saroha S, Litwin S, von Mehren M. Retrospective review of treatment for angiosarcoma at Fox Chase Cancer Center over the past 15 years. J Clin Oncol. 2007:25(18S):10034.
130. Boon LM, Mulliken JB, Enjolras O, Vikkula M. Glomuvenous malformation (glomangioma) and venous malformation: distinct clinicopathologic and genetic entities. Arch Dermatol. 2004;140:971–6.
131. Rycroft RJ, Menter MA, Sharvill DE, et al. Hereditary multiple glomus tumours. Report of four families and a review of literature. Trans St Johns Hosp Dermatol Soc. 1975;61:70–81.
132. Wood WS, Dimmick JE. Multiple infiltrating glomus tumors in children. Cancer. 1977;40:1680–5.
133. Brouillard P, Boon LM, Mulliken JB, et al. Mutations in a novel factor, glomulin, are responsible for glomuvenous malformations ("glomangiomas"). Am J Hum Genet. 2002;70:866–74.
134. Brouillard P, Ghassibe M, Penington A, et al. Four common glomulin mutations cause two thirds of glomuvenous malformations ("familial glomangiomas"): evidence for a founder effect. J Med Genet. 2005;42:e13–20.
135. Limaye N, Boon LM, Vikkula M. From germline towards somatic mutations in the pathophysiology of vascular anomalies. Hum Mol Genet. 2009;18:R65–74.
136. Brathwaite CD, Poppiti RJ Jr. Malignant glomus tumor. A case report of widespread metastases in a patient with multiple glomus body hamartomas. Am J Surg Pathol. 1996;20:233–8.
137. Mounayer C, Wassef M, Enjolras O, et al. Facial 'glomangiomas': large facial venous malformations with glomus cells. J Am Acad Dermatol. 2001;45:239–45.
138. Gould EW, Manivel JC, Albores-Saavedra J, Monforte H. Locally infiltrative glomus tumors and glomangiosarcomas. A clinical, ultrastructural, and immunohistochemical study. Cancer. 1990;65:310–18.
139. Yang JS, Ko JW, Suh KS, Kim ST. Congenital multiple plaque-like glomangiomyoma. Am J Dermatopathol. 1999;21:454–7.
140. Folpe AL, Fanburg-Smith JC, Miettinen M, Weiss SW. Atypical and malignant glomus tumors: analysis of 52 cases, with a proposal for the reclassification of glomus tumors. Am J Surg Pathol. 2001;25:1–12.
141. Enzinger FM, Smith BH. Hemangiopericytoma. An analysis of 106 cases. Hum Pathol. 1976;7:61–82.
142. Mentzel T, Calonje E, Nascimento AG, Fletcher CD. Infantile hemangiopericytoma versus infantile myofibromatosis. Study of a series suggesting a continuous spectrum of infantile myofibroblastic lesions. Am J Surg Pathol. 1994;18:922–30.
143. Granter SR, Badizadegan K, Fletcher CD. Myofibromatosis in adults, glomangiopericytoma, and myopericytoma: a spectrum of tumors showing perivascular myoid differentiation. Am J Surg Pathol. 1998;22:513–25.
144. Requena L, Kutzner H, Hugel H, et al. Cutaneous adult myofibroma: a vascular neoplasm. J Cutan Pathol. 1996;23:445–57.

This page intentionally left blank

Neural and Neuroendocrine Neoplasms (Other than Neurofibromatosis)

115

Zsolt B Argenyi

Chapter Contents

Classification, terminology and histogenesis *1943*
Neuromas *1944*
Schwannoma *1948*
Neurofibroma *1949*
Nerve sheath myxoma and cellular neurothekeoma *1951*
Granular cell tumor *1952*
Perineurioma *1953*
Malignant peripheral nerve sheath tumor *1953*
Merkel cell carcinoma *1954*
Heterotopic neuroglial tissue *1955*
Heterotopic meningeal tissue *1957*
Heterotopic neuroblastic tissues and their tumors *1957*

For decades, neural tumors were often misdiagnosed histopathologically because of confusing classifications; as a result, their clinical relevance was poorly understood. Clinically, cutaneous neural tumors often look alike and most of them are benign. However, their correct diagnosis can be helpful in recognizing important clinical syndromes and can contribute to better patient management. Moreover, with the advancement of immunohistochemistry, new variants of cutaneous neural neoplasms have been described[1].

CLASSIFICATION, TERMINOLOGY AND HISTOGENESIS

Cutaneous neural tumors can be classified into two major groups: those derived from peripheral nerves and those derived from ectopic or heterotopic neural tissue (Table 115.1). The former group is often subdivided into true nerve sheath neoplasms and hamartomatous tumors, although this classification may not be universally accepted[2].

Cutaneous neural tumors either arise from or differentiate toward one or more elements of the nervous system. During their differentiation, neural neoplasms often recapitulate to varying degrees the morphogenesis of normal peripheral nerves. Therefore, knowledge of the organization of the normal peripheral nerve is crucial to understanding the histogenesis of tumors that arise from it[3]. The peripheral nerve can be compared to a conventional telephone cable, in which each axon and its surrounding Schwann cell layer correspond to a telephone wire and its insulation, respectively (Fig. 115.1).

The basic units of a peripheral nerve are nerve fibers, composed of axons and the surrounding Schwann cells. These fibers form nerve fascicles and are held together by a sheath of specialized cells, which is called the perineurium. The space between the individual nerve fibers is called the endoneurium. As in a telephone cable system where the smaller cable units are separated, protected and held together by an outer wrapping, bundles of nerve fascicles are also encased in a supportive fibrous sheath that is called the epineurium. To a variable extent, this architectural arrangement is recognizable in many cutaneous neural neoplasms.

The most important constituent cells are the Schwann cell, the perineurial cell, and the various nonspecific mesenchymal cells, such as fibroblasts and mast cells. These cells are capable of proliferation and malignant transformation. Other elements of the peripheral nerve, which are cell parts or products (i.e. axons and myelin), cannot duplicate. Schwann cells are derived from the neural crest, and there is evidence that perineurial cells are modified fibroblasts of mesodermal origin. This difference in histogenesis is also reflected in the distinct antigenic expression of these cells. Schwann cells express S100 protein but not epithelial membrane antigen, whereas perineurial cells stain for epithelial membrane antigen but not for S100 protein. Axons contain a specific type of intermediate filament called neurofilament, and myelinated axons contain myelin basic protein, both of which can be detected by immunohistochemistry. These and other immunohistochemical markers often can help to establish the correct diagnosis.

In the following sections, each clinically relevant neural neoplasm is discussed (Tables 115.2–115.4; Fig. 115.2).

CLASSIFICATION OF CUTANEOUS NEURAL TUMORS

Peripheral nerve sheath tumors	Neural heterotopias
Hamartomas	**Meningeal**

• Neuromas
  • Traumatic (amputation)
  • Spontaneous
  • Solitary, palisaded encapsulated
  • Multiple, non-encapsulated
  • Variants
	• Meningocele
	• Rudimentary meningocele
	• Meningioma

	Neuroglial
	• Nasal glioma
True nerve sheath neoplasms	**Neuroblastic/ganglionic**

• Schwannomas
  • Common, solitary
  • Ancient
  • Cellular
  • Plexiform
  • Variants
• Neurofibromas
  • Superficial/solitary
  • Deep
  • Diffuse
  • Pigmented
  • Plexiform
  • Variants
• Nerve sheath myxoma
• Cellular neurothekeoma
• Perineurioma
• Malignant peripheral nerve sheath tumor
	• Neuroblastoma
	• Primary primitive neuroectodermal tumor
	• Ganglioneuroma

	Miscellaneous
	• Pigmented neuroectodermal tumor of infancy
Miscellaneous	
• Neuroendocrine carcinoma of the skin (Merkel cell carcinoma) • Granular cell tumor	

Table 115.1 Classification of cutaneous neural tumors.

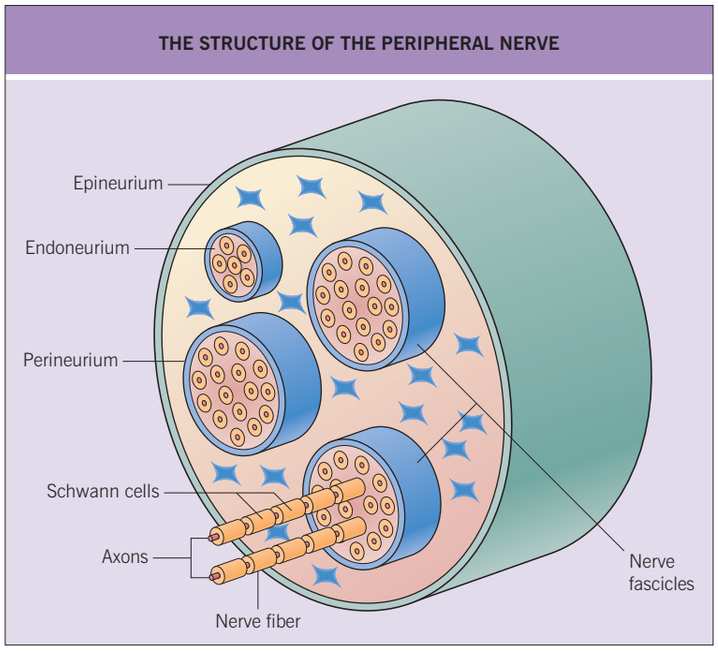


Fig. 115.1 The structure and components of the peripheral nerve.

NEUROMAS

Key features

Traumatic neuroma

- At the site of previous trauma
- Skin-colored papule or nodule
- Often painful or sensitive
- Circumscribed histologically, but not encapsulated
- Regenerative proliferation of axons and Schwann cells with fibrous tissue

Palisaded encapsulated neuroma (PEN)

- Usually on the face of adults
- Solitary
- Skin-colored papule or nodule
- Circumscribed histologically; partly or completely encapsulated
- Compactly arranged fascicles of spindle cells with vague palisading of nuclei

Introduction

Neuromas are proliferations of neural tissue in which Schwann cells and axon components are found in roughly equal numbers. There are two major subtypes: *traumatic* or *amputation neuroma* and *palisaded encapsulated neuroma* (PEN). Traumatic or amputation neuromas are complex regenerative proliferations of nerve fibers secondary to injury. Palisaded encapsulated or solitary circumscribed neuromas are complex hamartomatous proliferations of nerve fibers without apparent previous tissue injury.

History

The current view of traumatic neuroma was introduced by Huber and Lewis based on the concept of Wallerian degeneration[4]. PEN was described by Reed and co-workers in 1972[5].

Epidemiology

Traumatic neuromas are relatively uncommon but can occur at any age and in either sex. They are more prevalent in professions with a high probability of physical injuries. The solitary form of PEN develops spontaneously and gradually without evidence of obvious previous trauma. These tumors appear during adulthood (mean age, 45.5 years) with about equal occurrence in men and women[5]. With the solitary form, there is no specific association with neurofibromatosis or multiple endocrine neoplasia syndrome type 2B (MEN 2B).

Pathogenesis

Any extrinsic damage to nerve fibers can cause a traumatic neuroma. Amputation neuroma is considered the most common form and represents an attempted, but failed, regeneration of nerve fibers following transection. After transection, the distal segments of the nerve fibers degenerate, whereas the proximal segments regenerate in an attempt to reunite with the distal portion of the transected nerve fibers[6]. In cases of severe trauma, this regenerative process is unsuccessful and the growing nerve fibers form a tangle of fascicles within fibrotic tissue. Despite marked variations in arrangement, size and shape of the regenerating fascicles, in traumatic neuromas the constituent fibers have a Schwann cell to axon ratio close to normal (1 : 1), which helps to distinguish true neuromas from other nerve sheath neoplasms[7].

In PEN there is an overgrowth of axons and their sheath cells within the confinement of the perineurium. This benign tumor most likely represents a hamartomatous growth in which there is a close reduplication of the normal axon to Schwann cell ratio[5]. The cause of the overgrowth of neurites is unknown. Although minor tissue injury such as inflammation induced by acne has been suggested as a cause, to date a definite traumatic origin has not been established[7].

Clinical Features

Traumatic neuromas are usually solitary, skin-colored or reddish purple, firm papules or nodules at sites of wounds, surgical scars and amputations[8,9] (Fig. 115.3). On the lower extremities they tend to be multiple[8]. Early lesions are asymptomatic, but after a few months they gradually become painful, frequently with a lancinating character. Variable tingling and itching can be associated with the pain.

In neonates and young infants, lesions may be located on the lateral surface of a normal digit, most commonly the ulnar side of the fifth digit. Here, they represent amputation neuromas secondary to amputation *in utero* of supernumerary digits[10] (see Ch. 64). These tumors are occasionally referred to as "rudimentary supernumerary digits"; however, on histologic examination, they do not contain either normal or rudimentary elements of a digit.

In the solitary form of PEN, the individual lesions are asymptomatic, rubbery, firm, skin-colored to pink papules or nodules ranging in size from 0.2 to 0.6 cm in diameter[5]. Approximately 90% are located on the face, primarily around the nose, but they also occur on the cheek, chin and lips[11]. The remaining 10% occur elsewhere, including the trunk and extremities.

In MEN 2B, also referred to as multiple mucosal neuroma syndrome or MEN type 3, numerous soft, skin- or mucosa-colored papules and nodules appear on the lips, tongue and conjunctivae, as well as in the nasal and laryngeal mucosa. Patients also develop pheochromocytomas, medullary carcinoma of the thyroid, and gastrointestinal ganglioneuromas (see Table 63.2); therefore, early recognition of this syndrome can be life-saving. Multiple mucocutaneous neuromas with a predilection for the face and distal extremities can also be a manifestation of the PTEN hamartoma tumor syndrome, which includes Cowden disease and Bannayan–Riley–Ruvalcaba syndrome (see Table 63.3).

Pathology

Traumatic or amputation neuromas are usually well-circumscribed nodules located at any level of the dermis or the subcutis. They are encased by a fibrous sheath, although the distal end can be poorly defined. The proliferation is composed of a chaotic, poorly organized tangle of fascicles of various sizes and shapes (Fig. 115.4). Between the fibers are variable amounts of fibrous tissue with or without inflammatory cells or mucin[7]. The constituent cells are Schwann cells and perineurial cells with spindle-shaped nuclei and cytoplasm (Fig. 115.5). Special stains show many axons in an irregular, haphazard pattern[1,5].

Solitary PENs are well-circumscribed, ovoid or round tumors located in the mid dermis, although some lesions may extend into the subcutis. The tumor appears encapsulated by a thick condensation of collagen

CLINICAL FEATURES OF BENIGN NEURAL NEOPLASMS							
	Traumatic neuroma	**Palisaded encapsulated neuroma (PEN)**	**Schwannoma (neurilemmoma)**	**Neurofibroma**	**Nerve sheath myxoma***	**Cellular neurothekeoma***	**Granular cell tumor**
Incidence	Uncommon	Rare	Uncommon	Very common	Rare	Rare	Rare
Age	Any	Adults (mean age, 45.5 years)	Adults (20–50 years)	Adults (20–60 years)	Adults (mean age, 48 years)	Early adulthood (mean age, 24 years)	Adults (30–50 years)
Gender	Any	M:F = 1:1	F > M	M:F = 1:1	M:F = 1:2	F > M	M:F = 1:3
Number	Usually solitary	Usually solitary	Usually solitary (>90%)	Usually solitary	Usually solitary	Usually solitary	Usually solitary
Location	At sites of trauma, surgical scars, amputations	90% face, 10% elsewhere	Flexor aspect of an extremity, head	Trunk, head (solitary type)	Head and upper extremities	Predominantly on head, but also elsewhere	30% tongue, 70% elsewhere, mainly head and neck
Size	0.5–2.0 cm	0.2–0.6 cm	0.5–3.0 cm	0.2–2.0 cm	0.5–1.0 cm	0.5–3.0 cm	0.5–3.0 cm
Clinical appearance	Skin-colored to reddish purple, firm papule or nodule	Skin-colored or pink, rubbery, firm papule or nodule	Soft, skin-colored to pink or yellow, smooth-surfaced nodule or tumor	Skin-colored, soft or rubbery papule or nodule, sometimes pedunculated	Soft, skin-colored papule or nodule	Pink, red or brown, firm papule or nodule	Skin-colored to brownish red, firm papulonodule; may have ulceration or verrucous surface
Symptoms	Variable; tingling, pruritus, lancinating pain	Asymptomatic	Asymptomatic; occasionally painful or tender; rarely paresthetic; occasionally freely movable	Asymptomatic; "buttonhole" sign may be present	Asymptomatic	Usually asymptomatic, rarely sore or pruritic	Asymptomatic or occasionally tender or pruritic
Association	NA	Multiple (non-encapsulated) neuromas in MEN 2B (mucosal) and PTEN hamartoma tumor syndrome (mucocutaneous)	Neurofibromatosis (primarily type 2)	If multiple, may be sign of one of the various forms of neurofibromatosis (see Ch. 61)	NA	NA	10% multiple; predilection for blacks; rare in children
Clinical differential diagnosis	Hypertrophic scar, dermatofibroma, foreign body granuloma, granular cell tumor, neurothekeoma	Basal cell carcinoma, adnexal tumor, IDN, neurofibroma, schwannoma, nerve sheath myxoma	Neurofibroma, lipoma, angiolipoma, cyst (epidermoid, pilar, dermoid, ganglion), IDN, adnexal tumor (including sebaceous), PEN, leiomyoma	IDN, soft fibroma, schwannoma, fibrolipoma, PEN, nerve sheath myxoma, anetoderma, lipoma, cyst (epidermoid, pilar)	IDN, neurofibroma, schwannoma, lipoma, cyst (myxoid, ganglion, epidermoid, pilar)	Dermatofibroma (including sclerosing hemangioma variant), adnexal tumor, hypertrophic scar, keloid, granular cell tumor, PEN, fibrosed dermal or compound melanocytic nevus, pyogenic granuloma	Tongue: irritation (traumatic) fibroma, verruca, SCC Elsewhere: dermatofibroma, regressing verruca, adnexal tumor, prurigo nodularis, fibrosed melanocytic nevus, SCC
Other	"Rudimentary supernumerary digit" is considered a variant	May be induced by minor trauma	May be multiple; "schwannomatosis"	Plexiform variant is pathognomonic for neurofibromatosis type 1			Visceral forms occur; malignant transformation may occur (3%)

*Some authors view as ends of a spectrum.

Table 115.2 Clinical features of benign neural neoplasms. NA, not applicable; IDN, intradermal melanocytic nevus; MEN 2B, multiple endocrine neoplasia, type 2B; SCC, squamous cell carcinoma.

fibers that surround it, and there is often some clefting from the adjacent dermis[5] (Fig. 115.6). The parenchyma is composed of interwoven fascicles of spindled cells. The fascicles are compactly and relatively uniformly arranged, separated only by clefts. There is no evidence of extensive fibrosis, inflammation, granulation tissue, degenerative changes or foreign bodies, in contrast to traumatic neuromas[7].

The nuclei of the spindle-shaped tumor cells are elongated and wavy with tapered ends, and have an evenly basophilic chromatin pattern. Occasionally, a parallel arrangement of the nuclei is present, but, despite its name, distinct palisading or Verocay body formation is rare[12–14]. There is no appreciable nuclear pleomorphism, and mitotic figures are scant or absent. Special stains show abundant axons in a variable pattern[12]. The tumors of MEN 2B may be considered to be a variant of PEN but are not encapsulated and are multiple.

Differential Diagnosis

The diagnosis of traumatic neuroma is usually suspected by the history of a painful or symptomatic papulonodule at a site of injury and is confirmed by pathologic examination.

A PEN can resemble a BCC, adnexal tumor, intradermal melanocytic nevus or neurofibroma (see Table 115.2). The diagnosis is seldom made clinically and depends upon histologic examination (see Table 115.3).

Treatment

Surgical excision of traumatic neuromas is recommended, with an attempt to reposition the proximal nerve stump into a scar-free area[8].

PENs are easily excised, and some can even be enucleated from the surrounding dermis or subcutaneous tissue[5].

HISTOLOGIC DIFFERENTIAL DIAGNOSTIC FEATURES OF COMMON CUTANEOUS NEURAL NEOPLASMS				
	Traumatic neuroma	**Palisaded encapsulated neuroma**	**Schwannoma**	**Neurofibroma**
Location in the skin	Any level of dermis or subcutis	Mid dermis, occasionally extending into subcutis	Deep dermis or subcutis	Any location in the dermis
Growth pattern	Usually well circumscribed but may be poorly defined at the distal end	Well circumscribed, nodular, rarely plexiform	Well circumscribed, nodular or ovoid	Poorly to well circumscribed
Encapsulation	Usually encased by a fibrous sheath	Yes, by perineurium	Yes, by perineurium	Not encapsulated in the dermis
Architecture	Chaotic, poorly organized tangle of fascicles of various sizes and shapes	Compactly arranged fascicles; frequent clefts between fascicles	Hypercellular areas (Antoni A), fascicles in various patterns, hypocellular areas (Antoni B), edematous, myxoid	Fine fibrillary lattice of haphazardly arranged spindle cells in variably dense matrix
Constituent cell types	Schwann cells, fibroblasts, perineurial cells, inflammatory cells, macrophages	Schwann cells (99%), perineurial cells (in capsule only)	Schwann cells (99%), perineurial cells (in capsule only)	Schwann cells, perineurial cells, fibroblasts, mast cells
Cytologic features	Spindle cells with indistinct cytoplasmic contours and tapered slender nuclei	Spindle cells with indistinct cytoplasmic contours and tapered slender nuclei	Spindle cells with indistinct cytoplasmic contours and slender nuclei	Spindle cells with slender nuclei, plump fibroblasts
Nuclear palisading	None	Usually present, but indistinct	Yes, prominent in Antoni A areas	Rarely
Verocay bodies	None	None	Often	None
Nerve fibers (axons)	Yes; abundant, irregular pattern	Yes; abundant, often in a parallel arrangement	None or only at the site of the connecting nerve	Yes; rare, scattered
Other important features	Nerve of origin frequently present, extensive fibrosis	Nerve of origin frequently present, no fibrosis	Mast cells; may have extensive degenerative changes (e.g. hyalinization, hemorrhage) in Antoni B areas ("ancient changes")	Variable fibrosis and myxoid changes, mast cells, occasional blood vessels
Histopathologic differential diagnosis	Hypertrophic scar, neurofibroma, schwannoma	Traumatic neuroma, schwannoma, angioleiomyoma, myofibroma	Palisaded encapsulated neuroma, angiomyoma, fibrous histiocytoma	Neural nevus, dermatofibroma, hypertrophic scar, dermatofibrosarcoma protuberans, traumatic neuroma

Table 115.3 Histologic differential diagnostic features of common cutaneous neural neoplasms.

TUMORS AND TUMOR-LIKE CONDITIONS OF ECTOPIC AND HETEROTOPIC NEURAL TISSUE INVOLVING THE SKIN				
	Nasal glioma*	**Rudimentary meningocele**	**Cutaneous meningioma (Types II and III)**	**Peripheral neuroblastoma**
Incidence	Rare	Rare	Extremely rare	Extremely rare
Age	Neonates	Neonates or infants	Usually adults	Late adulthood
Location	Most commonly near the root of the nose but can be intranasal	Scalp, forehead, paravertebral area	Scalp	Head and trunk
Size	1.0–3.0 cm	0.5–3.0 cm	0.5–4.0 cm	0.5–5.0 cm
Clinical appearance	Firm, smooth, skin-colored to red–purple nodule	Soft to firm nodule, often with alopecia or the "hair collar" sign; occasionally cystic; blue–red hue common	Soft to firm nodule, often with alopecia	Soft, skin-colored to red, often ulcerated nodule
Clinical differential diagnosis	Infantile hemangioma, nasal polyp, juvenile xanthogranuloma, dermoid cyst	Membranous aplasia cutis, heterotopic brain tissue, dermoid cyst, infantile hemangioma	Epidermoid or pilar cyst, adnexal tumor, cutaneous metastasis	Adnexal tumor, lymphoma, soft tissue sarcoma, cutaneous metastasis
Associations	Intracranial connection in ~20% ("atretic" encephalocele)	An intracranial connection may be present ("atretic" meningocele)	May be associated with neurofibromatosis (types I and II)	NA
Other	NA	NA	Metastasis of CNS meningioma must be excluded	Metastasis of ganglionic or adrenal neuroblastoma and extension of olfactory neuroblastoma must be excluded, especially in children
Histopathologic features	Lobulated neural tissue (glial cells, astrocytes, rarely true neurons)	Cystic or cavernous spaces, scattered meningothelial cells, pseudovascular pattern, psammoma bodies	Solid nests and strands, whorls of epithelioid or spindle cells, psammoma bodies	Rosette-like (Homer Wright type) structures of small, round, blue cells, extensive infiltration and necrosis
Biologic course	Benign	Benign	Locally aggressive and destructive	Extremely malignant with widespread metastases
*Heterotopic brain tissue can also be located in the midline scalp, orbit, lip and oropharynx.				

Table 115.4 Tumors and tumor-like conditions of ectopic and heterotopic neural tissue involving the skin. NA, not applicable.

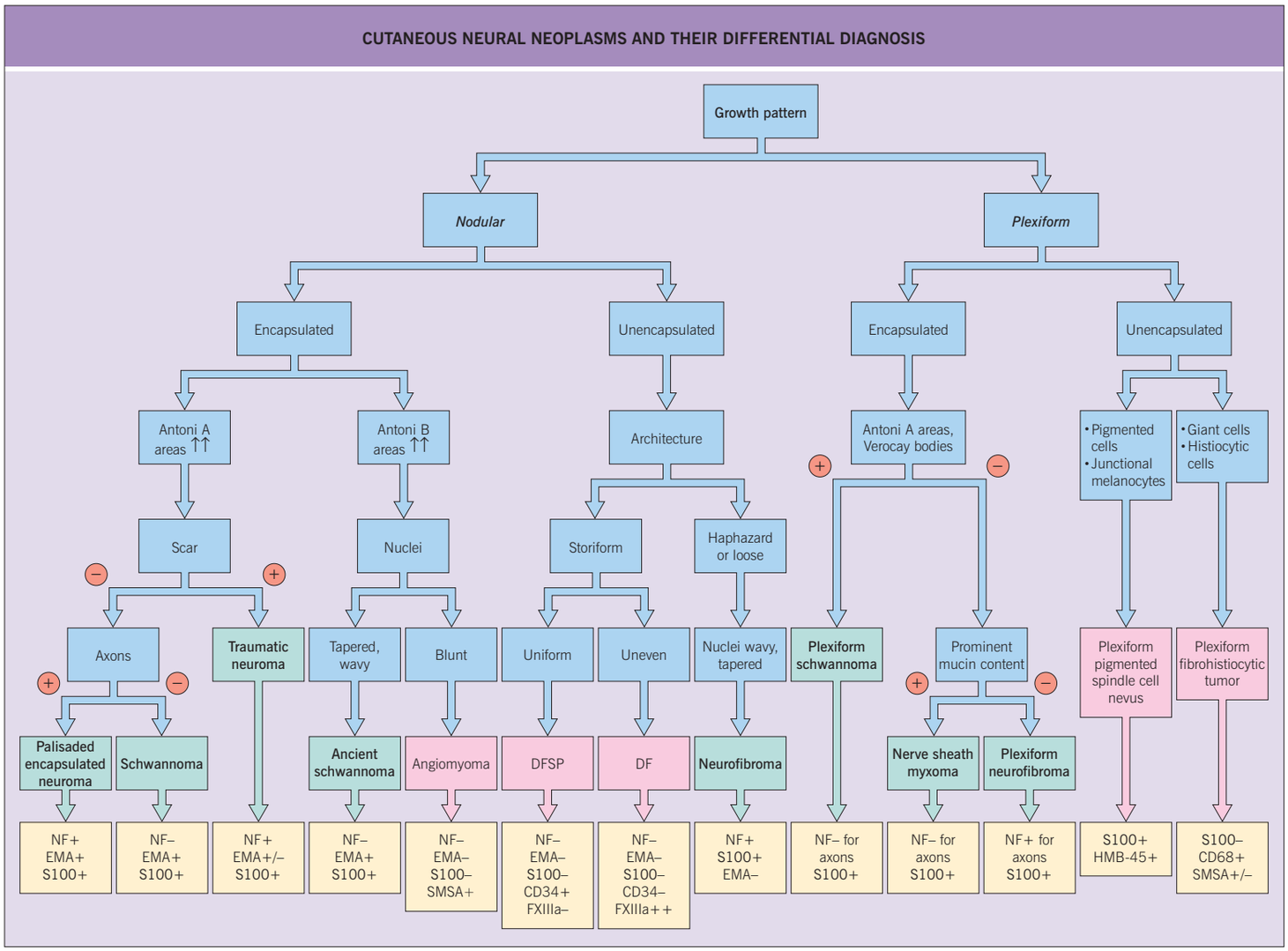


Fig. 115.2 Cutaneous neural neoplasms and their differential diagnosis. DF, dermatofibroma; DFSP, dermatofibrosarcoma protuberans; EMA, epithelial membrane antigen; FXIIIa, Factor XIII antigen; HMB45, melanocyte-related antibody; NF, neurofilament; S100, S100 protein; SMSA, smooth muscle-specific actin; +, positive; –, negative.

Fig. 115.3 Traumatic neuroma. A painful, firm papule that appeared after a deep puncture injury.

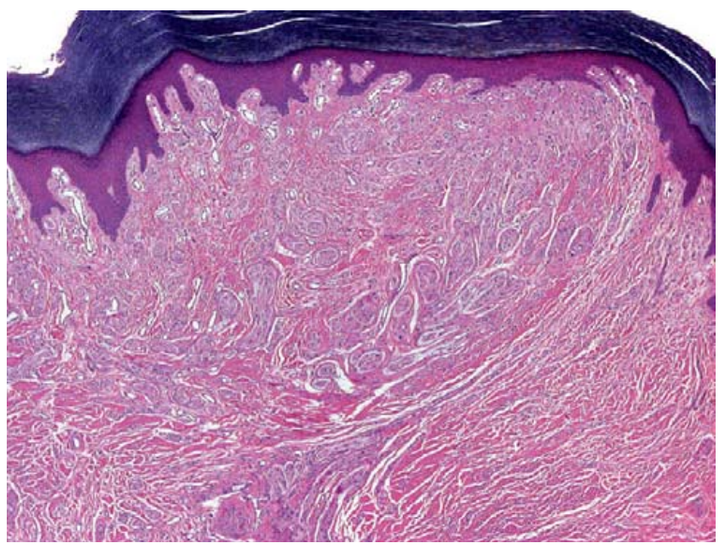


Fig. 115.4 Traumatic neuroma. Acral lesion with a chaotic proliferation of nerve fascicles is embedded in a fibrous stroma. *Courtesy, Lorenzo Cerroni, MD.*

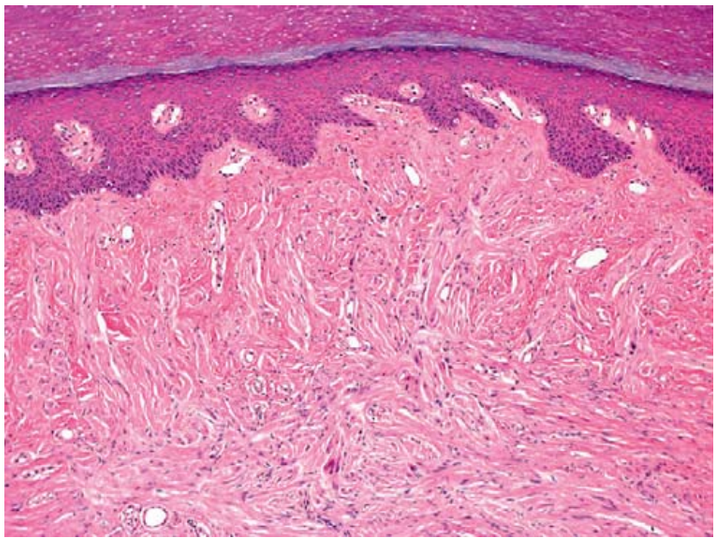


Fig. 115.5 Amputation neuroma (digit). Note the proliferation of nerve fascicles within a fibrotic stroma and the lack of bony structures. *Courtesy, Lorenzo Cerroni, MD.*

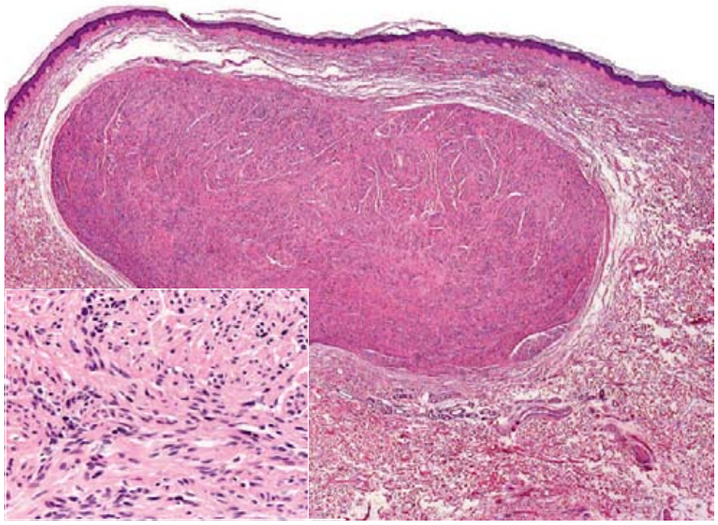


Fig. 115.6 Palisaded encapsulated neuroma. The well-circumscribed dermal nodule appears encapsulated. Note nerve fascicles (insert). *Courtesy, Lorenzo Cerroni, MD.*

SCHWANNOMA

Synonyms: ■ Neurilemmoma ■ Neurolemmoma ■ Schwann cell tumor ■ Acoustic neuroma

Key features

- Solitary papulonodule that usually appears on the flexural aspect of an extremity, along a peripheral nerve
- Occasionally painful or tender
- Deep dermal or subcutaneous location
- Histologically, there is an encapsulated spindle cell proliferation with biphasic Antoni A and B areas, palisading of nuclei, and Verocay bodies; axons are usually absent

Fig. 115.7 Solitary schwannoma. Skin-colored nodule on the plantar surface of the great toe. *Courtesy, Julie V Schaffer, MD.*

Introduction

Schwannomas are benign true nerve sheath neoplasms composed entirely of a Schwann cell proliferation.

History

Stout coined the term "neurilemoma", referring to the closely applied sheath and covering of the tumor[15]. Verocay suggested nerve sheath tumor as a general classification[16]. Because nearly the entire tumor is composed of Schwann cells, the designation "schwannoma" is now preferred.

Epidemiology

Schwannomas are relatively uncommon tumors that can occur at any age, but they are seen most often in adults and slightly more frequently in women than in men. Approximately 90% of schwannomas are solitary and not associated with any specific syndrome[2]. That said, schwannomas are seen in patients with neurofibromatosis (primarily type 2) and therefore can be associated with bilateral acoustic neuromas and meningiomas (see Table 61.5)[2]. Rare cases of multiple schwannomas have been referred to as "neurilemmomatosis" or "schwannomatosis"; sometimes there is a familial occurrence[17,18] or features that overlap with neurofibromatosis type 2 (NF2)[19,20]. Germline mutations in *INII/SMARCB1* have been described in familial schwannomatosis[21].

Pathogenesis

Schwannomas are derived from a proliferation of periaxonal or endoneurial Schwann cells. As a result of the Schwann cell proliferation, the remaining normal nerve fibers are displaced to the periphery of the tumor, creating an absence of the other components of a peripheral nerve[2]. Only after careful dissection can the attached nerve trunk be demonstrated. Since only the Schwann cells proliferate, the neoplasm remains within the confines of the perineurium, forming an encapsulated tumor. The exact cause of the exclusive Schwann cell proliferation is unknown, but in some patients it is related to mutations in both alleles of *NF2*[22].

Clinical Features

Schwannomas present as a solitary, soft, skin-colored to pink or yellow, smooth-surfaced dermal or subcutaneous papulonodule (Fig. 115.7). In general, their size ranges between 0.5 and 3.0 cm in diameter[23]. They are most commonly found on the flexor aspect of an extremity along a larger nerve trunk, followed by the head and neck region[24,25]. The tumors are usually asymptomatic, but occasionally pain and tenderness occur, in particular if the tumor is forcefully moved and the attached nerve is placed under tension. Motor disturbances and paresthesias are extremely rare[26].

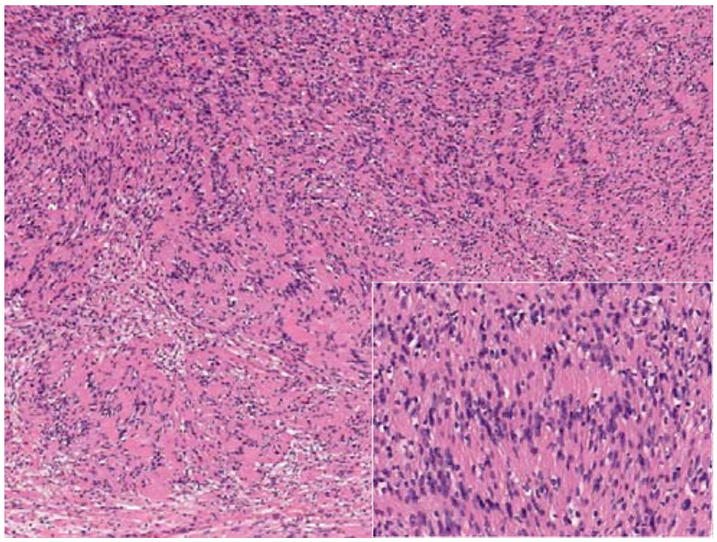


Fig. 115.8 Solitary cutaneous schwannoma. Hypercellular areas often show nuclear palisading and Verocay bodies. Detail of Verocay bodies (insert). *Courtesy, Lorenzo Cerroni, MD.*

Pathology

Schwannomas are well-circumscribed, nodular or ovoid tumors located in the deep dermis or subcutis. They are almost always encapsulated. The tumors are composed of hypercellular (also called Antoni A-type tissue) and hypocellular (Antoni B-type tissue) areas[2]. The hypercellular areas show proliferation of spindle cells with indistinct cytoplasmic contours and uniform nuclei[27]. Nuclear palisading and arrangement of palisaded nuclei in double rows, so-called "Verocay bodies", are characteristic features of these tumors[15,28] (Fig. 115.8). Mitotic figures are absent or rare.

The hypocellular areas show variable degrees of degeneration, including cystic, edematous, mucinous, fibrotic and vascular changes. Degenerative changes are often associated with some degree of cytologic atypia. These so-called *ancient schwannomas* should not be confused with the more specific entity of cellular schwannomas, which may display similar degenerative changes but rarely occur in the skin[29]. As a general rule, schwannomas are devoid of axons or the latter can only be detected at the site at which they are attached to a nerve[2]. There are additional less common subtypes of schwannomas, e.g. plexiform (no association with neurofibromatosis), pigmented, epithelioid and glandular[2,30–34].

Differential Diagnosis

The clinical differential diagnosis includes neurofibroma, lipoma, angiolipoma, adnexal tumor, cyst (epidermoid, pilar, dermoid, ganglion), and intradermal melanocytic nevus. The diagnosis is made by histopathologic examination.

Treatment

This tumor is benign and a simple excision is curative. If the clinical diagnosis is suspected, the lesion should be removed by enucleation, preserving normal nerve function.

NEUROFIBROMA

Variants/synonyms: ■ Solitary neurofibroma – sporadic neurofibroma, solitary nerve sheath tumor ■ Deep neurofibroma – subcutaneous neurofibroma ■ Plexiform neurofibroma

Key features

Solitary type

- Skin-colored to tan–violet papule or nodule
- May be pedunculated or have the "buttonhole" sign
- Predilection for the trunk and head
- Spindle cell proliferation with variable mixture of the components of the peripheral nerve, including residual axons
- Fibrosis and mucinous changes are common

Plexiform type

- Pathognomonic of NF1
- Large, occasionally pigmented, bag-like mass
- Favors the trunk and proximal extremities
- The plexiform variant has similar cytologic constituents as the solitary or sporadic type

Introduction

Neurofibromas are benign tumors composed of a complex proliferation of neuromesenchymal tissue (Schwann cells, perineurial cells, fibroblasts and mast cells), with residual nerve fibers (axons)[2]. Cutaneous neurofibromas are common, especially as solitary lesions. The presence of multiple neurofibromas raises the possibility of one of the several types of neurofibromatosis (including the mosaic form; see Ch. 61). Plexiform neurofibromas are seen in patients with neurofibromatosis type 1 (NF1).

History

Neurofibromas were originally described as fibrous tumors by von Recklinghausen. Subsequently, a neuroectodermal origin was suggested by Verocay[35], which was eventually confirmed by immunohistochemical and ultrastructural studies.

Epidemiology

Solitary cutaneous neurofibromas are relatively common, especially in adults, and have no gender preferences. The presence of a plexiform neurofibroma almost always indicates that the patient has NF1.

Pathogenesis

Neurofibromas differ from schwannomas in that several cell types are involved in their histogenesis. Regardless of the various histologic subtypes of neurofibromas (e.g. solitary, diffuse, combined, plexiform), the basic process is proliferation of the entire "neuromesenchyme", which includes Schwann cells, endoneurial fibroblasts, perineurial cells, mast cells, and cell types with intermediate features[2]. Since the extent of proliferation of each cell line often differs, the resultant histologic composition and architecture will vary. As stated earlier, axons do not duplicate; therefore, the relative ratio of axons to Schwann cells will be less than 1:1. Studies in patients with NF1 indicate that their mutations lead to inactivation of one copy of *NF1* (i.e. haploinsufficiency); however, tumorigenesis requires a somatic mutation that inactivates the remaining allele, i.e. a "second hit" leading to loss of heterozygosity (see Ch. 54). While nullizygosity ($NF^{-/-}$) of Schwann cells is necessary, it may not be sufficient for neurofibroma formation; the latter may require an $NF^{+/-}$ environment, in particular $NF^{+/-}$ mast cells (see Ch. 61). The pathogenesis of isolated solitary neurofibromas is unclear.

Clinical Features

Neurofibromas are usually solitary, skin-colored, soft or rubbery papulonodules. They range in size from 0.2 to 2.0 cm and may become pedunculated[2]. They grow slowly and are asymptomatic. The "buttonhole" sign is often present[2], i.e. the tumor is easily invaginated. Approximately 10% of patients with common neurofibromas will have multiple lesions, and some of these patients have one of the several types of neurofibromatosis (see Ch. 61). There are several clinical and pathologic subtypes of neurofibroma, such as diffuse, pigmented and

Fig. 115.9 Plexiform neurofibroma in a child with neurofibromatosis. Bag-like mass with overlying patches of hyperpigmentation.

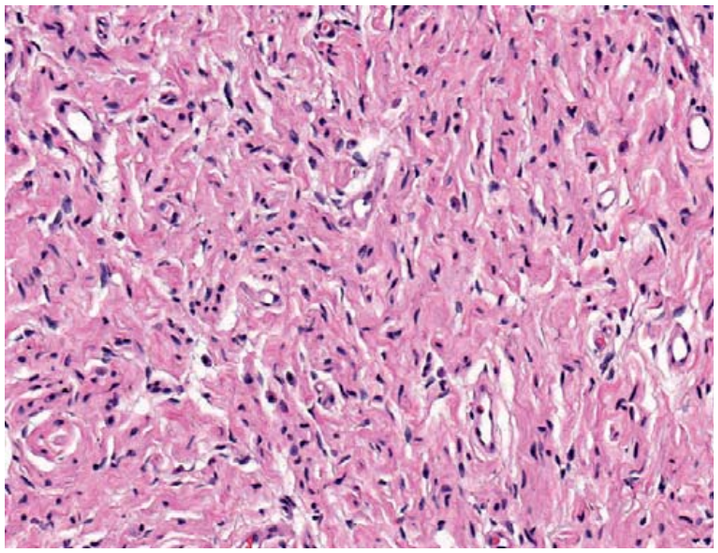


Fig. 115.10 Neurofibroma. The tumor contains a diffuse proliferation of spindle cells with slender, ovoid nuclei in a fibrillary matrix. Note several mast cells. *Courtesy, Lorenzo Cerroni, MD.*

plexiform variants. The diffuse and pigmented subtypes may present as indurated or soft nodules and plaques, with or without hyperpigmentation. Except for the plexiform variant, these subtypes of neurofibromas rarely undergo malignant change.

The plexiform neurofibroma is especially important because it is considered pathognomonic of von Recklinghausen disease (NF1) and carries a higher probability of malignant transformation[2]. Typically, these tumors are baggy or pedunculated dermal and subcutaneous masses that can feel rope-like on palpation and are sometimes hyperpigmented (Fig. 115.9). Recognition and correct patient management is crucial in these cases, especially in subtle forms of NF1, where the other cutaneous stigmata may not be obvious[36]. The exact incidence of malignant transformation of plexiform neurofibromas is not known; it ranges from 2% to 13% (the lower percentage cited more recently).

Pathology

Neurofibromas are poor- to well-circumscribed, usually nonencapsulated, nodular or oblong tumors that can be located anywhere within the dermis and subcutis[2,37]. The common solitary variant is usually present in the superficial dermis, creating a dome-shaped or polypoid elevation of its surface. The tumor is composed of a fine fibrillary lattice of haphazardly arranged slender spindle cells[38] (Fig. 115.10). The stroma can be variably vascular, fibrotic, edematous or myxomatous. In addition to Schwann cells and perineurial cells, plump fibroblasts and mast cells are present. Palisading of nuclei can occur, but true Verocay body formation is rare[37,38]. Mitotic figures are absent or rare. The diffuse form has an essentially similar cytology, but lacks a well-defined growth pattern as it infiltrates adjacent structures. Atypical forms of neurofibromas have been described[39].

As opposed to superficial, solitary and diffuse forms, neurofibromas which are seated within the deep dermis, subcutis and other deep soft tissues are usually encapsulated by perineurium or epineurium and may show a plexiform growth pattern (Fig. 115.11)[2]; the latter is defined as irregularly expanded, twisted and interconnected nerve fascicles arranged in lobular structures. Variants with a combined diffuse and plexiform growth pattern usually occur in NF1. By utilizing special stains, rare scattered axons can be demonstrated in both the superficial and deep variants of neurofibroma.

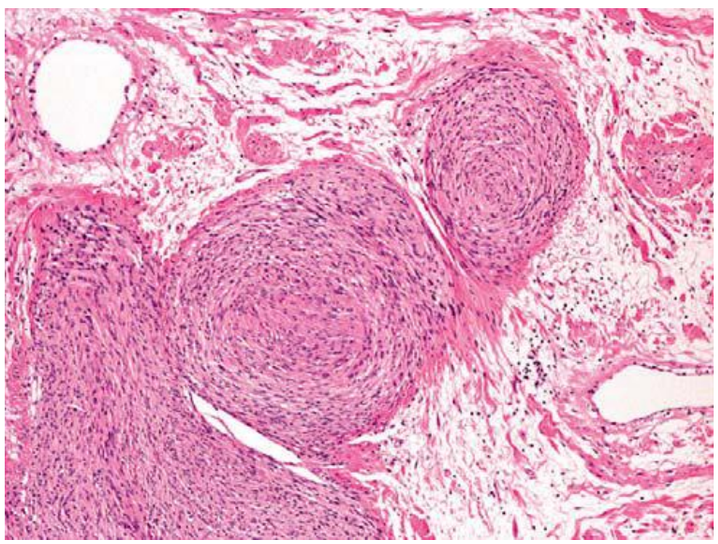


Fig. 115.11 Plexiform neurofibroma. Irregularly expanded, twisted nerve fascicles arranged in lobular structures. *Courtesy, Lorenzo Cerroni, MD.*

Differential Diagnosis

The clinical differential diagnosis of a solitary neurofibroma includes a dermal melanocytic nevus, schwannoma, soft fibroma and fibrolipoma (see Table 115.2). The majority of solitary or sporadic neurofibromas have similar clinical and histologic features as the multiple papular neurofibromas seen in patients with NF1. Plexiform neurofibromas with overlying hyperpigmentation and hypertrichosis can resemble congenital melanocytic nevi. As the latter can undergo neurotization, examination of the patient for Lisch nodules, axillary freckling and café-au-lait macules is essential. Histologically, a plexiform neurofibroma must be differentiated from other plexiform tumors, including a plexiform schwannoma.

Treatment

Neurofibromas are usually treated by simple excision. The evaluation and management of plexiform neurofibromas and neurofibromatosis is discussed in Chapter 61.

NERVE SHEATH MYXOMA AND CELLULAR NEUROTHEKEOMA

Synonyms: ■ Neurothekeoma ■ Myxoma of the nerve sheath

Key features

- Occurs most commonly in young and middle-aged women
- A skin-colored to red–brown papule or nodule with a predilection for the head and neck region
- Histologically, a lobular and fascicular pattern with a lack of axons
- There is a hypocellular myxomatous pattern as well as a cellular type with scant mucin
- Benign behavior, but local recurrences may occur

Introduction

Nerve sheath myxoma and cellular neurothekeoma refer to a spectrum of neuromesenchymal tumors that are characterized by the proliferation of nerve sheath cells in a variably myxomatous stroma. Nerve sheath myxomas have been traditionally classified into a *classic myxoid type* and a *cellular type* (cellular neurothekeoma)[40,41], based on the degree of cytologic differentiation and the relative amount of myxomatous stroma. Nevertheless, recently there has been a growing body of evidence that there are myxoid variants of cellular neurothekeoma which are histogenetically different from nerve sheath myxoma[42].

History

Nerve sheath myxoma was first described as a specific entity by Harkin and Reed in 1969[43]. The term "cellular neurothekeoma" was coined by Rosati et al. in 1986[44].

Epidemiology

The classic or myxoid type of nerve sheath myxoma occurs commonly in middle-aged adults (mean age, 48 years) with an approximate 1:2 male–female ratio[45,46].

The cellular form of nerve sheath myxoma (cellular neurothekeoma) is also a tumor of adulthood, but it usually affects younger adults (mean age, 24 years) and is also more common in women[47,48].

Pathogenesis

Both Schwann cells and perineurial cells are present in a classic nerve sheath myxoma[40,41]. The reason for extreme mucin production is unknown, although mucin is part of the normal endoneurium. Some authors speculate that a nerve sheath myxoma could represent a variant of neurofibroma with extreme myxoid degeneration[45]. This degeneration may explain the virtual lack of axons in these tumors. The available immunohistochemical and ultrastructural data support nerve sheath differentiation in the classic myxoid variant. The cellular neurothekeoma has a controversial histogenesis. Despite its having some similarities to the mucin-rich variant of a classic nerve sheath myxoma, only partial or indirect markers of neural differentiation are detected in a cellular neurothekeoma[42,49].

Clinical Features

A classic nerve sheath myxoma is a soft, skin-colored papule or nodule, generally 0.5 to 1.0 cm in diameter and typically located on the head and upper extremities[45].

Although cellular neurothekeomas also favor the head, cases from a variety of anatomic sites have been reported. These tumors are described as firm papulonodules that are pink, red or brown in color and range in size from 0.5 to 3.0 cm (Fig. 115.12). Symptoms are nonspecific and seem to relate to the size and firmness of the tumor[47,48].

Fig. 115.12 Cellular neurothekeoma of the scalp, presenting as an erythematous, firm papule.

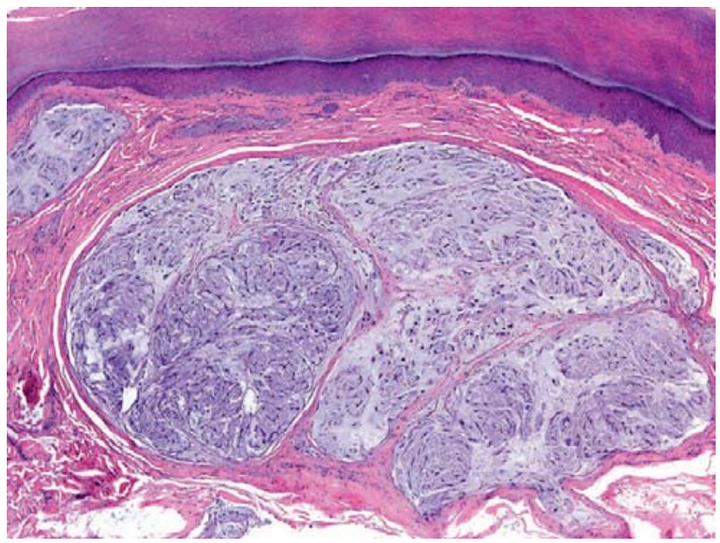


Fig. 115.13 Nerve sheath myxoma. Well-defined fascicles with myxoid stroma. *Courtesy, Lorenzo Cerroni, MD.*

Pathology

The classic myxoid type of nerve sheath myxoma is a well-defined, lobular or plexiform neoplasm that is usually located in the reticular dermis (Fig. 115.13). It often appears encapsulated by a compression of the surrounding fibrous tissue[40]. There is a hypocellular myxoid stroma with rare, scattered, spindled, stellate or dendritic cells. The cells usually have scant, pale cytoplasm with indistinct cytoplasmic contours and hyperchromatic, ovoid or angulated nuclei[40,45]. Nucleoli are small and mitotic figures are rare or absent. On occasion, multinucleated giant cells with eosinophilic cytoplasm can be identified. Histochemically, the myxoid stroma stains strongly positive for acidic mucopolysaccharides (see Ch. 46)[45]. While entrapped nerves in and around the tumor can be identified, the presence of scattered axons or direct continuity of axons with tumor cells has not been established[40,41]. The tumor cells are positive for S100 protein and collagen type IV and the capsule can express epithelial membrane antigen (EMA).

A cellular neurothekeoma is composed of ill-defined multilobular masses or fascicles in the reticular dermis[40] (Fig. 115.14). In some cases, the growth pattern can be frankly infiltrative or dissecting without any hint of a residual capsule, and there may be involvement of the superficial subcutis[7]. Cytologically, the predominant cell types are epithelioid or polygonal cells with ample eosinophilic cytoplasm and round nuclei with an open chromatin pattern[48,50]. Many cells have prominent nucleoli. Less often, the constituent cells are spindle-shaped with hyperchromatic nuclei, as are seen in the classic form of nerve sheath myxoma. Mitotic figures are often present but are usually normal morphologically. Rare cases with increased mitotic figures and cytologic atypia have been reported[51]. The stroma can be markedly fibrotic or even hyalinized. An obvious direct connection with peripheral nerves has not been established, but branches of pre-existing nerve

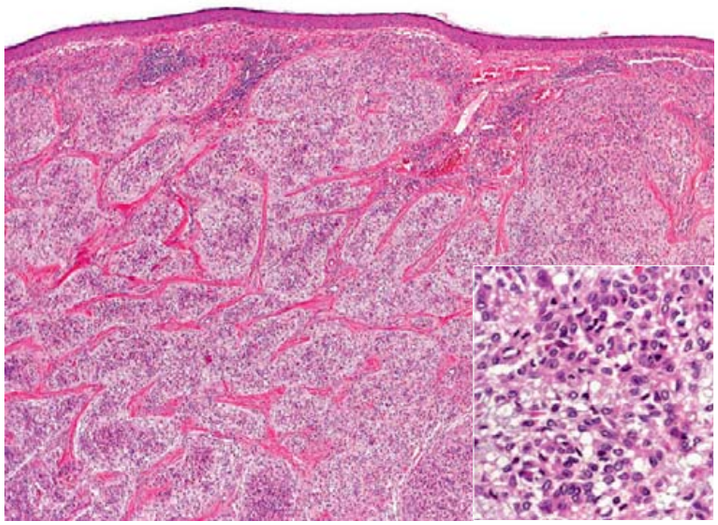


Fig. 115.14 Cellular neurothekeoma. Epithelioid nests are dispersed in a hyalinized stroma. Whorl-like arrangement of epithelioid cells with nuclear pleomorphism (insert). *Courtesy, Lorenzo Cerroni, MD.*

fibers can be demonstrated by special stains. The tumor does not have a consistent immunohistochemical profile, with NKI/C3, PGP9.5 (neuron-specific peptide), microphthalmia transcription factor (see Ch. 65), and smooth muscle-specific actin the most commonly expressed markers. While the lack of S100 protein expression can help to differentiate it from a classic nerve sheath myxoma, S100A6 may be expressed[52].

Differential Diagnosis

A nerve sheath myxoma is usually asymptomatic and clinically is often mistaken for a dermal melanocytic nevus, neurofibroma, lipoma or cyst (e.g. myxoid, ganglion) (see Table 115.2). Clinically, a cellular neurothekeoma usually resembles a dermatofibroma (including the sclerosing hemangioma variant), hypertrophic scar, keloid or granular cell tumor.

Treatment

These lesions are usually treated by simple excision; however, if incompletely removed, a nerve sheath myxoma may recur. There have been a few case reports of atypical variants of cellular neurothekeoma with postulated uncertain behavior, in which case complete excision is recommended.

GRANULAR CELL TUMOR

Synonym: ■ Abrikossoff's tumor

Key features

- Seen more commonly in adults, women and darkly pigmented individuals of African descent
- Predilection for the tongue, but can occur anywhere, including the viscera
- Malignant transformation is rare and usually occurs with deep-seated lesions
- Histologically, an ill-defined, infiltrative tumor, often with associated pseudoepitheliomatous hyperplasia
- Large polygonal cells with finely granular eosinophilic cytoplasm; the granules are PAS-positive, diastase-resistant

Introduction

Granular cell tumor is a descriptive term for a heterogeneous group of neoplasms composed of cells with granular cytoplasm due to the accumulation of lysosomal granules. Most cutaneous granular cell neoplasms are of neural origin, but granular cell change occurs in a variety of neoplasms (see below).

History

This tumor was originally thought by Abrikossoff to be derived from muscle, who used the term "granular cell myoblastoma"[53]. Feyrter first suggested a neural origin[54].

Epidemiology

Granular cell tumor is a relatively rare tumor that occurs primarily in adults (age 30–50 years) with a 1 : 3 male–female ratio. The tumor is characteristically solitary, and 70% of them are located in the head and neck region, including 30% on the tongue[53]. Other common locations are the breast (5–15%) and the proximal extremities. Rare visceral lesions have also been reported. In approximately 10% of patients, the lesions are multiple, especially in darkly pigmented individuals of African descent.

Pathogenesis

The neural origin of this tumor has been a subject of controversy, and it was originally based on the observation that granular cells are sometimes intimately associated with nerves and other neural tumors[55–57]. In addition, granular cells express S100 protein and CD57 (a neuronally expressed adhesion molecule), as do many Schwann cell tumors[58]. However, the classic form of this tumor does not resemble any other type of peripheral nerve sheath tumor. More recent immunohistochemical studies suggest that this tumor is neural crest-derived with peripheral nerve-related cellular differentiation[59]. Despite the controversy regarding its histogenesis, the granular cell tumor is histologically distinct and rarely presents a diagnostic problem.

Clinical Features

A granular cell tumor presents as an asymptomatic or occasionally tender or pruritic, skin-colored to brownish-red, firm dermal or subcutaneous papulonodule, ranging in size from 0.5 to 3.0 cm in diameter. Occasionally, the surface will be ulcerated or verrucous. Granular cell tumors are slowly growing and in general have a benign behavior. In approximately 3% of cases, malignant behavior may ensue (local infiltration or metastasis), usually when the tumor arises from a visceral or deep location.

Pathology

The dermis contains a poorly circumscribed nodule composed of polygonal, pale-staining cells that may infiltrate into the adjacent dermis. The cells have abundant, granular, faintly eosinophilic cytoplasm with round, dark nuclei (Fig. 115.15)[60]. Characteristic larger cytoplasmic granules are called pustulo-ovoid bodies. With the PAS reaction, the granules are positive, but they are diastase-resistant. Occasionally, a perineurial growth pattern is present; however, the tumor is devoid of axons. Increased numbers of mast cells are present in some lesions[55]. The overlying epidermis is frequently acanthotic. Rarely, a plexiform growth pattern has been described[61]. Histologic criteria that can prospectively identify the rare aggressive tumors are not well established[62]. The presence of necrosis, an increased mitotic rate, and spindling of the cells has been suggested as predictive of aggressive behavior[63].

Differential Diagnosis

The clinical differential diagnosis of lingual lesions includes an irritation fibroma, verruca and squamous cell carcinoma (SCC). Elsewhere, this tumor may resemble a dermatofibroma, regressing verruca or adnexal neoplasm (see Table 115.2). Granular cell tumors can induce considerable pseudocarcinomatous hyperplasia of the overlying epithelium, and superficial biopsy samples have been mistaken for SCC, especially on the tongue[64]. A variety of epithelial and mesenchymal neoplasms can show granular cell change, including BCCs, leiomyomas and leiomyosarcomas[60,65].

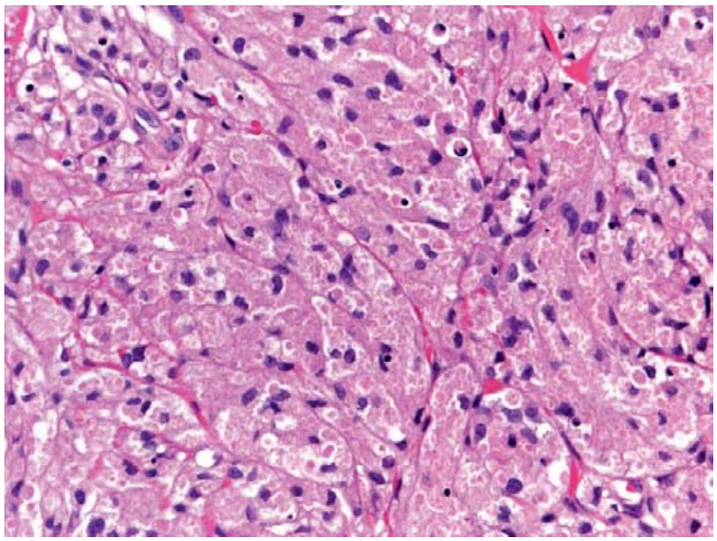


Fig. 115.15 Granular cell tumor. The tumor may show a nodular or infiltrative growth pattern. The large polygonal cells have finely granular cytoplasm and round nuclei. *Courtesy, Lorenzo Cerroni, MD.*

Treatment

The treatment is complete excision. If incompletely excised, this tumor has a high local recurrence rate, due to the plexiform or perineurial growth pattern.

PERINEURIOMA

Synonyms ■ Storiform perineurial fibroma ■ Fibrolamellar nerve sheath tumor ■ Localized hypertrophic neuropathy

Introduction

Perineuriomas represent a proliferation of perineurial cells, with both intraneural and extraneural growth patterns. Because of their rarity, only the extraneural variants that are pertinent to dermatologists are summarized in Table 115.5.

PERINEURIOMAS – KEY FEATURES OF EXTRANEURAL VARIANTS OF INTEREST TO DERMATOLOGISTS
CLINICAL FEATURES
• Solitary, non-descript, skin-colored, soft tissue mass • Occurs primarily on the trunk and extremities of adults, with the sclerosing type favoring the hands of young men
HISTOPATHOLOGIC FEATURES
• Predominant cell type is the perineurial cell, with an admixture of fibroblasts • The two most common variants are: "soft tissue" and "sclerosing type" • In the "soft tissue" variant, there is a well-circumscribed (but non-encapsulated) proliferation of slender, elongated spindle cells within the dermis and/or subcutis; the latter form tightly woven fascicles (sometimes with a lamellar or storiform pattern; Fig. 115.16) and the intertwining stroma can be hyalinized or myxoid • In the "sclerosing type", there may be epithelioid cells alternating with spindle cells, intermixed with thick collagen bundles • No significant atypia or mitotic activity
IMMUNOHISTOCHEMISTRY
• Cells stain positively for EMA, claudin 1, type IV collagen and laminin
CLINICAL DIFFERENTIAL DIAGNOSIS
• Benign soft tissue tumors (e.g. lipoma) and soft tissue sarcomas
HISTOLOGIC DIFFERENTIAL DIAGNOSIS
• Neurofibromas with extensive fibrosis (S100-positive and NF-positive), DFSP (EMA-negative; CD34-positive), sclerosing fibroma (EMA-negative)
TREATMENT
• Complete excision – biologic behavior usually benign, rarely malignant

Table 115.5 Perineuriomas – key features of extraneural variants of interest to dermatologists. Based upon refs 66 & 67. DFSP, dermatofibrosarcoma protuberans; EMA, epithelial membrane antigen; NF, neurofilament. Claudin-1 is a tight junction-associated protein.

MALIGNANT PERIPHERAL NERVE SHEATH TUMOR

Synonyms: ■ Neurosarcoma ■ Malignant schwannoma

The term "malignant peripheral nerve sheath tumor" is preferable to the widely used but confusing synonyms above. This is because any cellular component of the peripheral nerve can give rise to these tumors. In the majority of cases, perineurial or endoneurial fibroblasts (rather than Schwann cells) form the bulk of the tumor[68–70].

Malignant peripheral nerve sheath tumor is a tumor of deep soft tissues and rarely involves the skin. A definitive diagnosis requires histologic examination, usually in conjunction with immunohistochemistry and molecular biologic analysis. Histologically, in the most common form, there is a proliferation of atypical spindle cells, often arranged in a "herring-bone" pattern. There is variable cytologic atypia, numerous abnormal mitotic figures, and areas of necrosis and hemorrhage (Fig. 115.17)[69–71]. Despite its rarity,

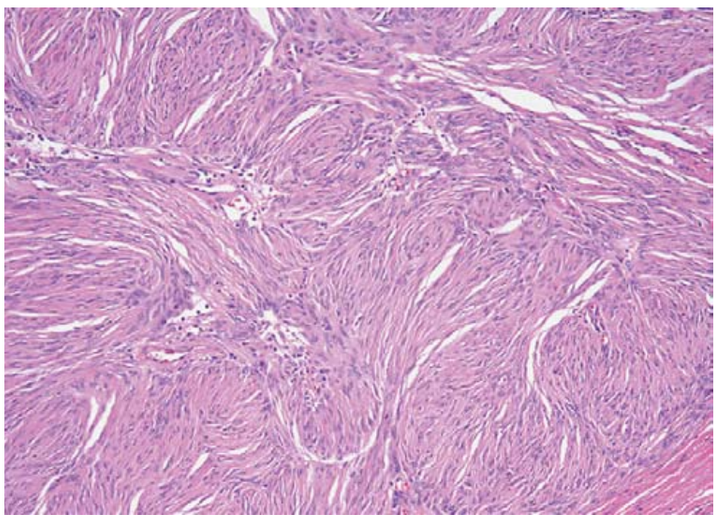


Fig. 115.16 Soft tissue perineurioma. Compact proliferation of spindle cells with lobular and storiform pattern.

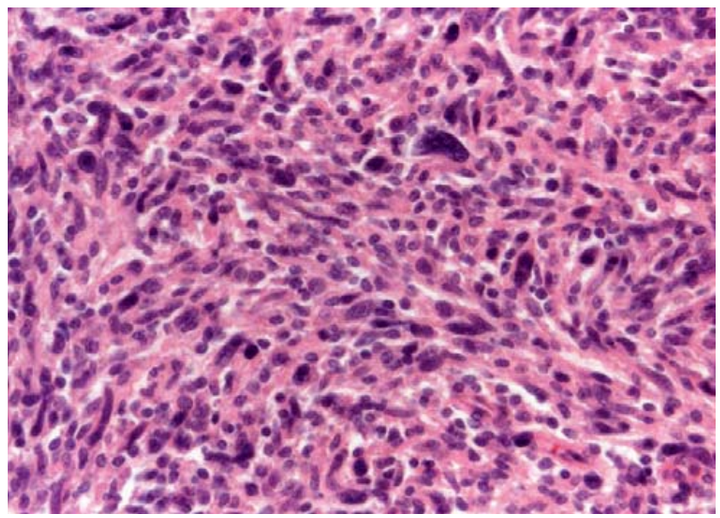


Fig. 115.17 Malignant peripheral nerve sheath tumor. Marked cellular pleomorphism with cytologic atypia and mitotic activity. Overall, the intersecting fascicles create a "herring-bone" pattern.

malignant peripheral nerve sheath tumor has clinical relevance for the dermatologist, because this malignancy develops within 2–13% of plexiform neurofibromas, which are associated with neurofibromatosis[71] (Ch. 61).

MERKEL CELL CARCINOMA

Synonyms: ■ Primary neuroendocrine carcinoma of the skin ■ Trabecular carcinoma of the skin ■ Primary small cell carcinoma of the skin ■ Cutaneous apudoma

Key features

- Predilection for the head and neck region of older adults
- Solitary, rapidly growing nodule
- Histologically, tumor is composed of small, round blue cells, often with a nested or trabecular growth pattern
- High mitotic rate, frequent single-cell necrosis, and often zonal necrosis
- Aggressive, malignant behavior

Introduction

Merkel cell carcinoma is a malignant proliferation of highly anaplastic cells which share structural and immunohistochemical features with various neuroectodermally derived cells, including cutaneous Merkel cells. These tumors display nonspecific clinical features and highly aggressive behavior. Early recognition and adequate therapy are therefore critical.

History

This tumor was originally described by Toker and given the name "trabecular carcinoma" based on its lattice-like and infiltrative growth pattern[72]. Subsequently, the neuroendocrine nature of this tumor was recognized, with similarities to the normal Merkel cell of the skin[73].

Epidemiology

Merkel cell carcinoma most commonly occurs in the elderly, and it is slightly more prevalent in women[74].

Pathogenesis

Although the cells of this tumor and the normal Merkel cell, which is a specialized receptor cell of touch located in the basal layer of the epidermis, share several morphologic, immunohistochemical and ultrastructural features, there is little evidence for a direct histogenetic relationship between the two[73]. Furthermore, extracutaneous neuroendocrine tumors display similar features. Therefore, the conceptually more unifying term "primary neuroendocrine carcinoma of the skin" (PNECS) is preferred by pathologists over Merkel cell carcinoma[4], as it indicates the tumor's relationship with neuroendocrine tumors of other origins. Clinicians seem to prefer the shorter term Merkel cell carcinoma, which appears entrenched in the lexicon.

In 2008, the first report appeared of the association of polyomavirus and PNECS[75]. This polyomavirus, now referred to as Merkel cell polyomavirus, infects approximately 80% of these carcinomas[76]. Notably, there is monoclonal integration of viral DNA into the host genome (rather than existing as a plasmid), suggesting that this is an early event. Inhibition of viral oncoproteins in polyomavirus-infected tumor cells leads to their death while this has no effect on uninfected tumor cells, pointing to a causal relationship.

Clinical Features

The tumor favors the head and neck region, followed by the extremities and the buttocks. It usually presents as a pink–red to violaceous, firm, dome-shaped, solitary nodule that has grown rapidly (Fig. 115.18)[74]. Ulceration can occur. Overall, the behavior is that of an aggressive tumor, with significant risk of recurrence after excision.

Tumor diameter at the time of diagnosis influences prognosis, with lesions >2 cm having a 51% relative survival rate at 5 years (compared to 66% for tumors ≤2 cm; Table 115.6)[77]. In a series of 5823 prospectively enrolled patients followed for a median of 64 months[77], 27% had lymph node involvement and 7% had distant metastatic disease at the time of presentation.

Fig. 115.18 Merkel cell carcinoma (primary neuroendocrine carcinoma). A A rapidly growing, violaceous nodule on the toe. **B** Eroded erythematous nodule arising within sun-damaged skin of the cheek. *B, Courtesy, Lorenzo Cerroni, MD.*

MERKEL CELL CARCINOMA – FOUR-STAGE SYSTEM AND PROGNOSIS

Criterion	Stage	Relative survival* at 5 years (%)
Primary lesion ≤2 cm	I	66
Primary lesion >2 cm	II	51
Regional lymph node disease	III	39
Distant metastatic disease	IV	18

*Compared with age- and sex-matched population data.

Table 115.6 Merkel cell carcinoma – four-stage system and prognosis. Relative survival data are based upon 5823 prospectively enrolled patients followed for a median of 64 months[77]. Patients with a primary tumor ≤2 cm *and* histologically negative regional lymph node(s) had a 5-year relative survival rate of 79%. For the more detailed AJCC staging system, see Merkel cell carcinoma. In: Edge SB, Byrd DR, Compton CC, et al. (eds). AJCC Cancer Staging Manual, 7th edn. New York, NY: Springer, 2010, pp 315–23, or www.cancer.gov. AJCC, American Joint Committee on Cancer.

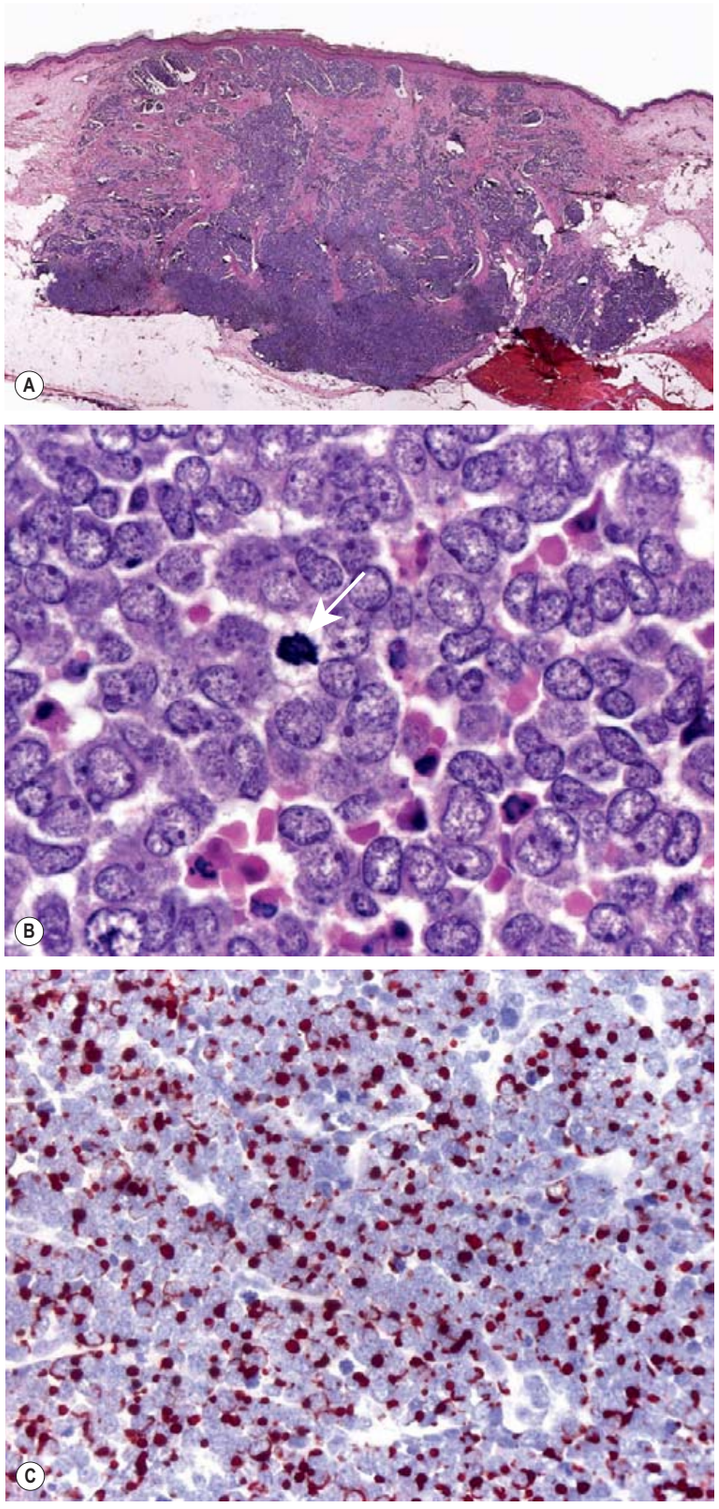


Fig. 115.19 Primary neuroendocrine carcinoma of the skin (Merkel cell carcinoma). A Nodular infiltrate of basaloid cells with focally small "trabecular" structures within the entire dermis and superficial subcutis. **B** Small, round to ovoid basaloid cells with vesicular nuclei and small nucleoli; note several necrotic (apoptotic) cells and a mitotic figure (arrow). **C** Immunohistochemical stain for cytokeratin 20 demonstrates a characteristic perinuclear dot pattern. *Courtesy, Lorenzo Cerroni, MD.*

Pathology

The tumor appears as a poorly defined dermal mass, frequently infiltrating the subcutaneous fat, fascia and muscle. While it may show various growth patterns, a sheet-like growth pattern is seen most commonly, followed by nested and trabecular patterns (Fig. 115.19A)[78]. Characteristically, the edge of the tumor shows a trabecular infiltrating pattern[72]. The tumor is composed of monotonously uniform, small, round to oval cells that are about two to three times larger than mature lymphocytes[72,73]. The nuclei of these cells are ovoid with a finely dispersed chromatin pattern and distinct nuclear membranes (Fig. 115.19B). Nucleoli are usually not prominent. Mitotic figures are abundant. The cytoplasm is scant and faintly amphophilic. Extensive areas of necrosis, individual cell necrosis and characteristic crush artifact are common[78].

Various types of differentiation have been described in Merkel cell carcinoma, including rosette-like structures resembling Homer Wright rosettes of neuroblastoma, epidermotropic involvement with pagetoid spread, and eccrine and squamoid differentiation[79,80]. Immunohistochemically, there is a characteristic perinuclear globule upon staining for low-molecular-weight cytokeratins (CK) such as CK20, CK5/6 and CK7 (Fig. 115.19C). This corresponds to the ultrastructural distribution of paranuclear whorls of intermediate filaments[78,79]. In addition, there is positive staining for various neuroendocrine markers, including chromogranin, synaptophysin, somatostatin, calcitonin and vasoactive intestinal peptide[79]. These peptides are associated with ultrastructurally demonstrable, membrane-bound, dense-core secretory granules. The tumor also expresses neuron-specific enolase and, occasionally, neural filaments and CD56; however, immunostaining for S100 protein is characteristically negative[79]. Likewise, a negative reaction for thyroid transcription factor 1 (TTF-1) helps to differentiate Merkel cell carcinoma from cutaneous metastases of other small cell carcinomas (pulmonary and extrapulmonary); the latter are characteristically positive for this marker[79]. Recent recognition of Merkel cell polyomavirus, which can be detected by immunohistochemical (e.g. T antigen) and molecular biologic methods[81], provides an additional tool for diagnosis; however, false-positive PCR results are possible given the ubiquitous nature of the virus. For prognostication, increased p63 expression may portend a clinically aggressive behavior[82].

Differential Diagnosis

Common clinical diagnoses are BCC, SCC, amelanotic melanoma and adnexal tumor. Due to the violaceous, sometimes hemorrhagic, appearance of some tumors, the differential diagnosis also includes pyogenic granuloma, abscess, angiosarcoma and lymphoma. Histologically, there is a broad spectrum of small, round, blue cell tumors of diverse histogenesis that can be confused with PNECS[79]. These include metastatic neuroendocrine carcinoma of the lung (small cell or oat cell carcinoma), poorly differentiated eccrine carcinoma, lymphoma, metastatic neuroblastoma, primary peripheral primitive neuroectodermal tumor, Ewing's sarcoma, melanoma, and poorly differentiated SCC[78,79].

Treatment

Surgery is the primary approach. However, owing to the aggressive nature of this tumor, adjuvant chemotherapy and radiation therapy are often administered simultaneously[83]. To aid in treatment decisions and for prognosis, sentinel lymph node mapping has been recommended[84,85] (Fig. 115.20).

TUMORS AND TUMOR-LIKE CONDITIONS OF ECTOPIC AND HETEROTOPIC NEURAL TISSUE OF THE SKIN

These rare lesions develop from embryologically misplaced neural tissue within the skin. They range from benign malformations to cellular proliferations with potential for metastasis. There are three major clinicopathologic manifestations of neural heterotopias in the skin: (1) neuroglial; (2) meningeal; and (3) neuroblastic/ganglionic abnormalities.

HETEROTOPIC NEUROGLIAL TISSUE

Synonyms: ■ Nasal glioma ■ Brain-like heterotopia ■ Glial hamartoma

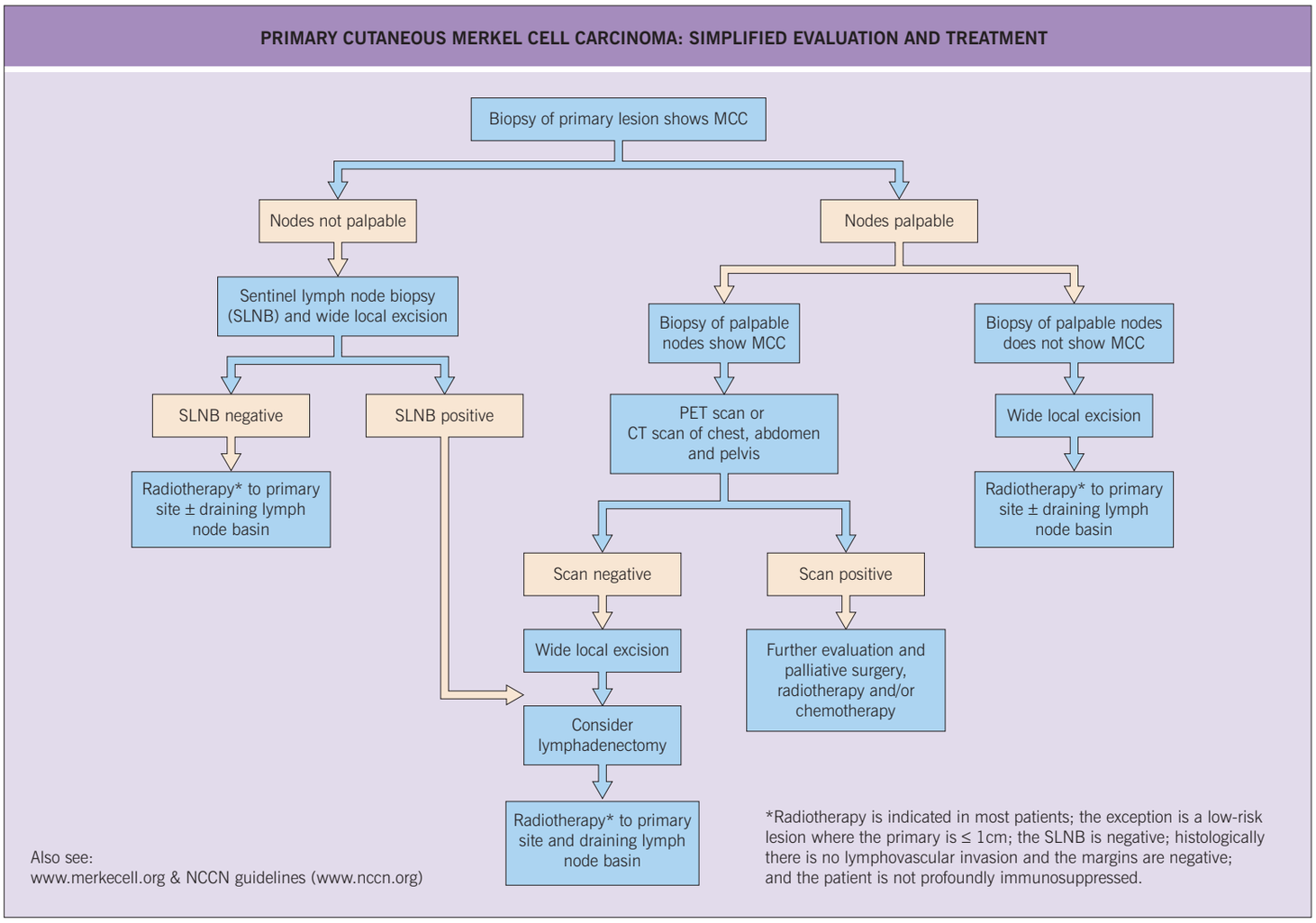


Fig. 115.20 Primary cutaneous Merkel cell carcinoma (MCC): simplified evaluation and treatment algorithm. NCCN, National Comprehensive Cancer Network; PET, positron emission tomography. *Courtesy, Paul Nghiem, MD PhD. Based upon: Gupta SG, Wang LC, Penas PF, et al. Sentinel lymph node biopsy for evaluation and treatment of patients with Merkel cell carcinoma: The Dana-Farber experience and meta-analysis of the literature. Arch Dermatol. 2006;142:685–90.*

Key features

- Rare, benign, congenital lesion
- Most common near the root of the nose, but can be intranasal
- Solitary, firm, smooth, skin-colored to red–purple papulonodule
- May be associated with an encephalocele
- Microscopically, lobulated neuroglial tissue

History

The term "nasal glioma" was introduced by Schmidt in 1900[86].

Epidemiology

These tumors are rare and usually manifest at the time of birth.

Pathogenesis

A nasal glioma is the result of embryologic displacement of brain tissue, usually along the cranial closure lines and without apparent communication with underlying structures[87]. It has a predilection for the perinasal area; therefore, it is commonly referred to as a nasal glioma. As this is not a true neoplasm, the term is misleading[88].

Clinical Features

Nasal gliomas are firm, smooth-surfaced, skin-colored to red–violet papulonodules that may have obvious telangiectasias and range in size from 1 to 3 cm. Approximately 60% are located on the bridge of the nose (Fig. 115.21), with the remainder usually located intranasally or in both locations[88,89].

Pathology

In a nasal glioma, an ill-defined, non-encapsulated neuropil-like mass is seen within the dermis and subcutis. The neuropil-like tissue is composed of nests and strands of pale-staining, finely vacuolated or fibrillary matrix in which various types of astrocytes can be found[87]. Gemistocytic astrocytes, with polygonal, eosinophilic cytoplasm and eccentric nuclei, as well as multinucleated giant cells, are relatively common. Mature neurons are present in variable numbers[88]. Occasionally, residual meningoendothelial cells, ependymal cells, choroid plexus-like structures and pigmented cells can be identified[89]. No mitotic activity or aggressive growth pattern has been described.

Differential Diagnosis

Clinically, the lesion must be differentiated from other facial midline lesions (see Ch. 64)[88,90] as well as an infantile hemangioma, juvenile xanthogranuloma, dermoid cyst and nasal polyp.

Treatment

Most cutaneous neural malformations can be effectively treated by excision. Cranial imaging is recommended before these lesions are biopsied or removed[91], because nasal gliomas can communicate with the intracranial space, and cerebrospinal fluid leakage and subsequent

Fig. 115.21 Nasal glioma in a newborn. Pink to violet soft nodule.

meningoencephalitis and other neurologic damage may occur after biopsy[88].

HETEROTOPIC MENINGEAL TISSUE

Synonyms: ■ Cutaneous meningioma ■ Rudimentary meningocele

Key features

- Rare disorder that usually presents in neonates and infants and favors the scalp, forehead and paravertebral region
- Soft to firm, skin-colored nodule, often with partial alopecia or the "hair collar" sign
- Can be associated with neurofibromatosis or other developmental anomalies
- Histologically, solid nests and strands, whorls of epithelioid or spindle cells, and psammoma bodies

History

The rare cutaneous presentation of meningioma was first reported by Winkler[92] in 1904, and the concept of rudimentary meningocele was introduced by Lopez et al.[93].

Epidemiology

Meningeal heterotopias are rare lesions, usually apparent at or shortly after birth[93].

Pathogenesis

Rudimentary meningoceles are thought to result from herniation of the meningeal lining into the skin and subcutaneous tissues during embryologic development, usually with no residual communication with the CNS (see Ch. 64)[94]. Cutaneous meningiomas have three major forms of histogenesis[93]. In type I, the tumors are composed of arachnoid lining cells that were misplaced during embryogenesis. These lesions are usually congenital, and considering their non-neoplastic nature, they are better classified as rudimentary meningoceles[94]. In type II, the tumors develop along the course of the cranial nerves. Type III lesions represent cutaneous "metastasis" or direct extension of primary meningiomas of the arachnoid lining[95,96].

Clinical Features

Rudimentary meningoceles most commonly present on the scalp of neonates and infants at the sites of cranial closure. Less often they occur on the forehead (midline) or in a paravertebral location. Skin-colored papules or nodules on the scalp are often associated with alopecia or the "hair collar" sign[95]. Type II and type III meningiomas usually develop on the head of adults[93]. Their clinical appearance is similar to rudimentary meningoceles. Cutaneous meningioma has been reported in association with neurofibromatosis[97].

Pathology

A rudimentary meningocele is an ill-defined mass of cavernous, pseudovascular spaces embedded in a markedly collagenous stroma[94,98]. The spaces may be lined by elongated meningoendothelial cells characterized by eosinophilic cytoplasm, round or ovoid nuclei, and a fine chromatin pattern. Similar cells dissect or wrap around collagen fibers, producing "collagen bodies". No significant cytologic atypia or mitotic activity is present. Focal calcification and psammoma bodies (eosinophilic laminated and whorled structures with variable calcification) may occur.

A cutaneous meningioma is composed of a multinodular mass in the deep dermis or subcutis, often with an infiltrative growth pattern[99–101]. Depending on their histogenesis, the cells may show a variable degree of differentiation. In the most common form, the spindle cells show a concentric, whorl-like arrangement[99]. The cells have oval nuclei with a vesicular chromatin pattern. Mitotic figures are rare in type II and variably increased in type III. Psammoma bodies are often present[99–101].

Differential Diagnosis

Rudimentary meningoceles must be distinguished from "atretic" meningoceles (an intermediate form with an intracranial connection), membranous aplasia cutis congenita, heterotopic brain tissue, dermoid cysts and infantile hemangiomas. Clinically, cutaneous meningiomas may resemble cysts and other adnexal neoplasms as well as metastatic tumors.

Treatment

As with heterotopic neuroglial tissue (nasal glioma), imaging studies are required prior to biopsy or excision. The latter is usually performed by neurosurgeons.

HETEROTOPIC NEUROBLASTIC TISSUES AND THEIR TUMORS

Synonyms: ■ Neuroblastoma (primary or metastatic) ■ Primitive neuroectodermal tumor ■ Neuroepithelioma

Key features

- The third most common malignant neoplasm in children
- Cutaneous metastases (children) are seen more frequently than primary cutaneous tumors (adults)
- Cutaneous metastases present as multiple, blue to purple dermal nodules in association with elevated serum and urine catecholamines
- Histologically, small, round, blue cells in a nested or infiltrative growth pattern, with formation of Homer Wright rosettes
- Prognosis depends on the patient's age, clinical stage and specific genetic abnormalities (e.g. *MYCN* oncogene amplification)

Introduction

Neuroblastic–ganglionic tumors are derived from the germinal neuroepithelium and/or from the neural crest. They display a wide spectrum of clinicopathologic features based on their relative degree of differentiation, ranging from very primitive neuroectodermal tumors to more mature forms such as neuroblastomas.

History

The concept of neuroectodermal tumors was introduced by Stout in 1918[102]. Since then, different terms have been used for tumors with cytologically similar features, reflecting the controversy regarding this entity. Dehner performed a comprehensive review of the nosology of this diverse group of lesions, suggesting the term "primitive neuroectodermal tumors" (PNET)[103].

Epidemiology

Neuroblastoma is the third most commonly observed childhood malignancy, and cutaneous metastases are frequent[3]. Most neuroblastomas develop as sporadic tumors, although familial cases have been reported. Primary cutaneous PNETs are tumors of adulthood (mean age, 40 years) and are exceedingly rare[3].

Pathogenesis

PNETs of the skin either represent metastases from a PNET of the adrenals and/or ganglionic chain (traditionally designated as neuroblastomas) or develop *de novo* from heterotopic neural crest cells[3]. In the latter case, they are referred to as peripheral PNETs or as peripheral neuroblastomas. Recent studies have implicated the anaplastic lymphoma kinase gene in the tumorigenesis of many familial and some sporadic cases of neuroblastoma. In addition, specific genetic abnormalities, such as *MYCN* oncogene amplification or aberrations of chromosomes 1p or 11q, influence prognosis[104].

Clinical Features

In children, the cutaneous metastases of neuroblastoma often manifest as multiple, blue to purple, dermal papules or nodules that resemble the "blueberry muffin" lesions seen with congenital infections or hematologic disorders[5] (see Ch. 121). These nodules may blanch upon stroking and develop an erythematous halo[105,106]. Serum and urine catecholamine levels are typically elevated. Spontaneous regression has been described in stage IV-S[7], but rarely occurs in other stages.

In adults, PNETs are rapidly growing dermal or subcutaneous nodules that favor the trunk or head. Ulceration is common. These highly aggressive neoplasms have an almost invariably fatal outcome[107].

Pathology

In metastatic neuroblastoma, an ill-defined or infiltrative mass is present in the dermis and/or the subcutis. However, when smaller and more superficial, deposits are more well defined. The tumor mass is composed of atypical, small, dark cells with scant cytoplasm[3,103]. The cells have larger nuclei than mature lymphocytes (with a coarse chromatin pattern) and they form irregular nests, cords or poorly cohesive sheets. Rosette formation, by concentrically arranged tumor cells in double or multiple circles, is common. The center of the rosettes contains converging fine fibrillary material characteristic of Homer Wright-type rosettes[3] (Fig. 115.22). Mitotic activity is high, and abnormal mitoses are abundant. Extensive areas of necrosis and hemorrhage are common.

As the tumor differentiates, the relative proportion of neuroblastoma components decreases, and the ganglioneuromatous elements increase. Eventually, the tumor may become a ganglioneuroma[107]. Immunohistochemically, the cells react variably with neural and neuroendocrine markers, depending on their state of differentiation. These markers include neuron-specific enolase, S100 protein, neurofilaments, synaptophysin, chromogranin and CD99 (see Ch. 0)[104].

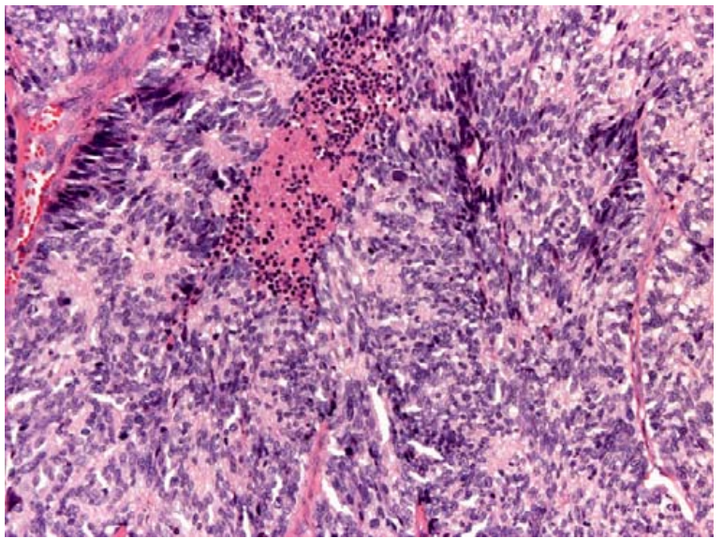


Fig. 115.22 Cutaneous neuroblastoma. The tumor is composed of small cells with small, round to ovoid nuclei that can be arranged in rosettes. The fibrillary material in the center of Homer Wright-type rosettes is characteristic. *Courtesy, Lorenzo Cerroni, MD.*

Primary PNETs have similar histopathologic features to those of the classic neuroblastoma, but ganglionic or neuromatous differentiation is not characteristic. PNET and classic neuroblastoma also share major immunohistochemical features. However, MIC-2(013) is commonly expressed by PNETs, but not by neuroblastomas, facilitating their distinction[104,108–111].

Differential Diagnosis

In children, the clinical differential diagnosis includes other types of cutaneous metastasis, extramedullary hematopoiesis and mastocytosis, whereas in adults it includes adnexal tumors, lymphoma and soft tissue sarcomas. Histologically, both metastatic neuroblastoma and primary cutaneous neuroectodermal tumor must be differentiated from other rosette-forming small, round, blue cell tumors that may involve the skin[109–111] (see Merkel cell carcinoma).

Treatment

The effective treatment of neuroblastoma requires an interdisciplinary team that includes oncologists, surgeons and radiation therapists. The overall prognosis of localized tumor involvement has recently improved with combined surgical excision, multiagent chemotherapy, differentiating agents (e.g. 13-cis-retinoic acid), radiopharmaceuticals, and small molecule inhibitors of signal transduction pathways[104]. Important prognostic factors include the age, stage, histologic differentiation, specific genetic abnormalities (e.g. *MYCN* oncogene amplification, 11q aberration), and response to initial chemotherapy[3].

REFERENCES

1. Argenyi ZB. Recent developments in cutaneous neural neoplasms. J Cutan Pathol. 1993;20:97–108.
2. Scheithauer BW, Woodruff JM, Erlandson RA. Tumors of the peripheral nervous system. In: Atlas of Tumor Pathology, 3rd series, Fascicle 24. Washington, DC: Armed Forces Institute of Pathology, 1999:1–415.
3. Enzinger FM, Weiss SW. Benign tumors of peripheral nerves. In: Soft Tissue Tumors, 4th edn. St. Louis: Mosby, 2001:1111–207.
4. Huber CC, Lewis LD. Amputation neuroma: their development and prevention. Arch Surg. 1920;1:85–9.
5. Reed RJ, Fine RM, Meltzer HD. Palisaded, encapsulated neuromas of the skin. Arch Dermatol. 1972;106:865–70.
6. Lundborg G. Nerve regeneration and repair: a review. Acta Orthop Scand. 1987;58:145–69.
7. Argenyi ZB, Santa Cruz D, Bromley C. Comparative light-microscopic and immunohistochemical study of traumatic and palisaded, encapsulated neuromas of the skin. Am J Dermatopathol. 1992;14:504–10.
8. Matthews GJ, Osterholm JL. Painful traumatic neuromas. Surg Clin North Am. 1972;51:1313–24.
9. Burtner DD, Goodman M. Traumatic neuroma of the nose. Arch Otolaryngol. 1972;103:108–9.
10. Shapiro L, Juklin EA, Brownstein HM. Rudimentary polydactyly. Arch Dermatol. 1973;108:223–5.
11. Dakin MC, Leppard B, Theaker JM. The palisaded, encapsulated neuroma (solitary circumscribed neuroma). Histopathology. 1992;20:405–10.
12. Argenyi ZB. Immunohistochemical characterization of palisaded encapsulated neuroma. J Cutan Pathol. 1990;17:329–35.
13. Argenyi ZB, Cooper PH, Santa Cuz D. Plexiform and other unusual variants of palisaded encapsulated neuroma. J Cutan Pathol. 1993;20:34–9.
14. Argenyi ZB. Newly recognized neural neoplasms relevant to the dermatopathologist. Dermatol Clin. 1992;10:219–34.

15. Stout AP. The peripheral manifestations of specific nerve sheath tumor (neurilemoma). Am J Cancer. 1935;24:751–96.
16. Verocay J. Multiple Geschwülste als Systemerkrankung am nervösen Apparate. Festschrift Hans Chiari aus Anlasz Seines 25 Jèhrigen Professoren-Jubilaüms Gewidmet. W. Braumüller, Wein and Leipzig, 1908:378–415.
17. Izumi AK, Rosato FE, Wood MG. Von Recklinghausen's disease associated with multiple neurilemomas. Arch Dermatol. 1971;104:172–6.
18. Shishiba T, Niimura M, Ohtsuka F, et al. Multiple cutaneous neurilemomas as a skin manifestation of neurilemmomatosis. J Am Acad Dermatol. 1984;10:744–54.
19. Purcell SM, Dixon SL. Schwannomatosis: an unusual variant of neurofibromatosis or a distinct clinical entity? Arch Dermatol. 1989;125:390–3.
20. Reith JD, Goldblum JR. Multiple cutaneous plexiform schwannomas: report of a case and review of the literature with particular reference to the association with types 1 and 2 neurofibromatosis and schwannomatosis. Arch Pathol Lab Med. 1996;120:399–401.
21. Hulsebos TJM, Plomp AS, Wolterman RA, et al. Germline mutations of *INII/SMARCB1* in familial schwannomatosis. Am J Human Genet. 2007;80:805–10.
22. Sainz J, Huynh PD, Figueroa K, et al. Mutations of the neurofibromatosis type 2 gene and lack of the gene product in vestibular schwannomas. Hum Mol Genet. 1994;3:885–91.
23. Das Gupta TK, Brasfield RD, Strong EW, et al. Benign solitary schwannomas (neurilemomas). Cancer. 1969;24:355–66.
24. White NB. Neurilemomas of the extremities. J Bone Joint Surg Am. 1967;49:1605–10.
25. Whitaker WG, Droulias C. Benign encapsulated neurilemoma: a report of 76 cases. Am Surg. 1976;42:675–8.
26. Jacobs RL, Barmada R. Neurilemoma: a review of the literature with six case reports. Arch Surg. 1971;102:181–6.
27. Vilanova JR, Burgos-Bretones JJ, Alvarez JA, et al. Benign schwannomas: a histopathological and morphometric study. Pathology. 1982;137:281–6.
28. Dahl I, Hagmar B, Idvall I. Benign solitary neurilemoma (schwannoma): a correlative cytological and histological study of 28 cases. Acta Pathol Microbiol Immunol Scand. 1984;92:91–101.
29. Argenyi ZB, Balogh K, Abraham AA. Degenerative ("ancient") changes in benign cutaneous schwannoma: a light microscopic, histochemical and immunohistochemical study. J Cutan Pathol. 1993;20:148–53.
30. Berg JC, Schethauer BW, Spinner RJ, et al. Plexiform schwannoma: a clinicopathologic overview with emphasis on the head and neck region. Human Pathol. 2008;39:633–40.
31. Kao GF, Laskin WB, Olsen TG. Solitary cutaneous plexiform neurilemmoma (schwannoma): a clinicopathologic, immunohistochemical and ultrastructural study of 11 cases. Mod Pathol. 1986;2:20–6.
32. Argenyi ZB, Goodenberger ME, Strauss JS. Congenital neural hamartoma ("fascicular schwannoma"): a light microscopic, immunohistochemical, and ultrastructural study. Am J Dermatopathol. 1990;12:283–93.
33. Woodruff JM, Susin M, Godwin TA, et al. Cellular schwannoma: a variety of schwannoma sometimes mistaken for a malignant tumor. Am J Surg Pathol. 1981;5:733–44.
34. Hajdu SI. Schwannomas. Mod Pathol. 1995;8:109–14.
35. Verocay J. Zur kenntnis der Neurofibrome. Beitr Pathol Annat Allg Pathol. 1910;48:1–69.
36. Riccardi VM. Neurofibromatosis: the importance of localized or otherwise atypical forms. Arch Dermatol. 1987;123:882–3.
37. Lassmann H, Jurecka W, Lassmann W, et al. Different types of benign nerve sheath tumors: light microscopy, electron microscopy, and autoradiography. Virchows Arch A Pathol Anat Histol. 1977;375:197–210.
38. Megahed M. Histopathological variants of neurofibroma. A study of 114 lesions. Am J Dermatopathol. 1994;16:486–95.
39. Lin BT, Weiss LM, Medeiros LJ. Neurofibroma and cellular neurofibroma with atypia: a report of 14 tumors. Am J Surg Pathol. 1997;21:1443–9.
40. Argenyi ZB, LeBoit PE, Santa Cruz D, et al. Nerve sheath myxoma (neurothekeoma) of the skin: light microscopic and immunohistochemical reappraisal of the cellular variant. J Cutan Pathol. 1993;20:294–303.
41. Argenyi ZB, Kutzner H, Seaba MM. Ultrastructural spectrum of cutaneous nerve sheath myxoma/cellular neurothekeoma. J Cutan Pathol. 1995;22:137–45.
42. Fetsch JF, Laskin WB, Hallman JR, et al. Neurothekeoma: an analysis of 178 tumors with detailed immunohistochemical data and long-term patient follow-up information. Am J Surg Pathol. 2007;31:1103–14.
43. Harkin JC, Reed RJ. Tumors of the peripheral nervous system. In: Atlas of Tumor Pathology, 2nd series, Fascicle 3. Washington, DC: Armed Forces Institute of Pathology, 1969:60–4.
44. Rosati LA, Fratamico FCM, Eusebi V. Cellular neurothekeoma. Appl Pathol. 1986;4:186–91.
45. Angervall L, Kindblom LG, Haglid K. Dermal nerve sheath myxoma. A light and electron microscopic, histochemical and immunohistochemical study. Cancer 1984;53:1752–9.
46. Aronson PJ, Fretzin DF, Potter BS. Neurothekeoma of Gallagher and Helwig (dermal nerve sheath myxoma variant): report of a case with electron microscopic and immunohistochemical studies. J Cutan Pathol. 1985;12:506–19.
47. Barnhill RL, Mihm MC Jr. Cellular neurothekeoma. A distinctive variant of neurothekeoma mimicking nevomelanocytic tumors. Am J Surg Pathol. 1990;14:113–20.
48. Barnhill RL, Dickersin GR, Nickeleit V, et al. Studies on the cellular origin of neurothekeoma: clinical, light microscopic, immunohistochemical and ultrastructural observations. J Am Acad Dermatol. 1991;25:80–8.
49. Hornick JL, Fletcher CD. Cellular neurothekeoma: detailed characterization in a series of 133 cases. Am J Surg Pathol. 2007;31:329–40.
50. Fletcher CD, Chan JK, McKee PH. Dermal nerve sheath myxoma: a study of three cases. Histopathology. 1986;10:135–45.
51. Busam KJ, Mentzel T, Colpaert C, et al. Atypical or worrisome features in cellular neurothekeoma. A study of 10 cases. Am J Surg Pathol. 1998;22:1067–72.
52. Plaza JA, Torres-Cabala C, Evans H, et al. Immunohistochemical expression of S100A6 in cellular neurothekeoma: clinicopathologic and immunohistochemical analysis of 31 cases. Am J Dermatopathol. 2009;31:419–22.
53. Abrikossoff A. Myomas originating from transversely striated voluntary musculature. Virchow Arch. 1926;260:215–33.
54. Feyrter F. Uber die granularen neurogenen Gewachse. Beitr Pathol Anat. 1949;110:181–208.
55. Abenoza P, Sibley RK. Granular cell myoma and schwannoma: fine structural and immunohistochemical study. Ultrastruct Pathol. 1987;11:19–28.
56. Bedetti CD, Martinez AJ, Beckford NS, May M. Granular cell tumor arising in myelinated peripheral nerves. Light and electron microscopy and immunoperoxidase study. Virchows Arch. 1983;402:175–83.
57. Fisher ER, Wechsler H. Granular cell myoblastoma – a misnomer. Electron-microscopic and histochemical evidence concerning its Schwann cell derivation and nature (granular cell schwannoma). Cancer. 1962;15:936–54.
58. Armin A, Connelly EM, Rowden G. An immunoperoxidase investigation of S-100 protein in granular cell myoblastomas: evidence for Schwann cell derivation. Am J Clin Pathol. 1983;79:37–44.
59. Filie AC, Lage JM, Azumi N. Immunoreactivity of S-100 protein, alpha-1 antitrypsin, and CD68 in adult and congenital granular cell tumors. Mod Pathol. 1996;9:888–92.
60. Mentzel T, Wadden C, Fletcher CD. Granular cell change in smooth muscle tumors of skin and soft tissue. Histopathology. 1994;24:223–31.
61. Lee J, Bhawan J, Wax F, Farber J. Plexiform granular cell tumor. A report of two cases. Am J Dermatopathol. 1994;16:537–41.
62. Simsir A, Osborne BM, Greenebaum E. Malignant granular cell tumor: a case report and review of the recent literature. Hum Pathol. 1996;27:853–8.
63. Fanburg-Smith JC, Meis-Kindblom JM, Fante R, Kindblom LG. Malignant granular cell tumor of soft tissue. Diagnostic criteria and clinicopathologic correlation. Am J Surg Pathol. 1998;22:779–94.
64. Apisarnthanarax P. Granular cell tumor. An analysis of 16 cases and review of the literature. J Am Acad Dermatol. 1981;5:171–82.
65. Suster S, Rosen LB, Sanchez JL. Granular cell leiomyosarcoma of the skin. Am J Dermatopathol. 1988;10:234–9.
66. Macarenco RS, Ellinger F, Oliveira AM. Perineuroma. A distinctive and underrecognized peripheral nerve sheath neoplasm. Arch Pathol Lab Med. 2007;131:625–36.
67. Fetsch JF, Miettinen M. Sclerosing perineurioma: a clinicopathologic study of 19 cases of a distinctive soft tissue lesion with a predilection for the fingers and palms of young adults. Am J Surg Pathol. 1997;21:1433.
68. Erlandson RA, Woodruff JM. Peripheral nerve sheath tumors: an electron microscopic study of 43 cases. Cancer. 1982;49:273–87.
69. Wanebo JE, Malik JM, Vandenberg SE, et al. Malignant peripheral nerve sheath tumors: a clinicopathologic study of 28 cases. Cancer. 1993;71:1247–53.
70. Hirose T, Hasegawa T, Kudo E. Malignant peripheral nerve sheath tumors: an immunohistochemical study in relation to ultrastructural features. Hum Pathol. 1992;23:865–70.
71. Wick MR, Swanson PE, Scheithauer BW, et al. Malignant peripheral nerve sheath tumor: an immunohistochemical study of cases. Am J Clin Pathol. 1987;87:425–33.
72. Toker C. Trabecular carcinoma of the skin. Arch Dermatol. 1972;105:107–10.
73. Sibley RK, Dehner LP, Rosai J. Primary neuroendocrine (Merkel cell?) carcinoma of the skin. I. Am J Surg Pathol. 1985;9:95–108.
74. Ratner D, Nelson BR, Brown MD, et al. Merkel cell carcinoma. J Am Acad Dermatol. 1993;29:143–56.
75. Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. Science. 2008;319:1096–100.
76. Kassem A, Schöpflin A, Diaz C, et al. Frequent detection of Merkel cell polyomavirus in human Merkel cell carcinomas and identification of a unique deletion in the *VP1* gene. Cancer Res. 2008;68:5009–13.
77. Lemos BD, Storer BE, Iyer JG, et al. Pathologic nodal evaluation improves prognostic accuracy in Merkel cell carcinoma: analysis of 5823 cases as the basis of the first consensus staging system. J Am Acad Dermatol. 2010;63:751–61.
78. Wick MR, Scheithauer BW. Primary neuroendocrine carcinoma of the skin. In: Wick MR (ed.). Pathology of Unusual Malignant Cutaneous Tumors. New York: Marcel Dekker, 1985:107–72.
79. Cheuk W, Kwan MY, Suster S, Chan JK. Immunostaining for thyroid transcription factor 1 and cytokeratin 20 aids the distinction of small cell carcinoma from Merkel cell carcinoma, but not pulmonary from extrapulmonary small cell carcinomas. Arch Pathol Lab Med. 2001;125:228–31.
80. LeBoit PE, Crutcher WA, Shapiro PE. Pagetoid intraepidermal spread in Merkel cell (primary neuroendocrine) carcinoma of the skin. Am J Surg Pathol. 1992;16:584–92.
81. Duncavage EJ, Le BM, Wang D, Pfeifer JD. Merkel cell polyomavirus: a specific marker for Merkel cell carcinoma in histologically similar tumors. Am J Surg Pathol. 2009;33:1771–7.
82. Asioli S, Righi A, Volante M, et al. p63 expression as a new prognostic marker in Merkel cell carcinoma. Cancer. 2007;110:640–7.
83. Medina-Franco H, Urist MM, Fiveash J, et al. Multimodality treatment of Merkel cell carcinoma: case series and literature review of 1024 cases. Ann Surg Oncol. 2001;8:204–8.
84. Duker I, Starz H, Bachter D, Balda BR. Prognostic and therapeutic implications of sentinel lymphonodectomy and S-staging in Merkel cell carcinoma. Dermatology. 2001;202:225–9.
85. Gupta SG, Wang LC, Penas LC, et al. Sentinel lymph node biopsy for evaluation and treatment of patients with Merkel cell carcinoma: The Dana-Farber experience and meta-analysis of the literature. Arch Dermatol. 2006;142:771–4.
86. Schmidt MB. Über seltene Spaltbildungen im Bereiche des mittleren Stirnfortsatzes. Virchow Arch Pathol Anat. 1900;162:340–70.
87. Patterson K, Kapur S, Chandra RS. "Nasal gliomas" and related brain heterotopias: a pathologist's perspective. Pediatr Pathol. 1986;5:353–62.
88. Yeoh GPS, Bale PM, de Silva M. Nasal cerebral heterotopia: the so-called nasal glioma or sequestered encephalocele and its variants. Pediatr Pathol. 1989;9:531–49.

89. Orkin M, Fisher I. Heterotopic brain tissue (heterotopic neural rest): case report with review of related anomalies. Arch Dermatol. 1966;94:699–708.
90. Fletcher CDM, Carpenter G, McKee PH. Nasal glioma: a rarity. Am J Dermatopathol. 1986;8:341–6.
91. Kennard CD, Rasmussen JE. Congenital midline nasal masses: diagnosis and management. J Dermatol Surg Oncol. 1990;16:1025–36.
92. Winkler M. Ueber Psammome der Haut und des Unterhautgewebes. Arch Pathol Anat. 1904;178: 323–50.
93. Lopez DA, Silvers DN, Helwig EB. Cutaneous meningiomas: a clinicopathologic study. Cancer. 1974; 34:728–44.
94. Sibley DA, Cooper PH. Rudimentary meningocele: a variant of "primary cutaneous meningioma". J Cutan Pathol. 1989;16:72–80.
95. Berry AD III, Patterson W. Meningoceles, meningomyeloceles, and encephaloceles: a neuro-dermatopathologic study of 132 cases. J Cutan Pathol. 1991;18:164–77.
96. Argenyi ZB. Cutaneous neural heterotopias and related tumors relevant for the dermatopathologist. Semin Diagn Pathol. 1996;13:60–71.
97. Argenyi ZB, Thielberg MD, Hayes CM, Whitaker DC. Primary cutaneous meningioma associated with von Recklinghausen disease. Cutan Pathol. 1994;21:549–56.
98. Marrogi AJ, Swanson PE, Kyriakos M, et al. Rudimentary meningocele of the skin: clinicopathologic features and differential diagnosis. J Cutan Pathol. 1991;18:178–88.
99. Nochomovitz LE, Jannotta F, Orenstein JM. Meningioma of the scalp: light and electron microscopic observations. Arch Pathol Lab Med. 1985;109:92–5.
100. Theaker JM, Fleming KA. Meningioma of the scalp: a case report with immunohistological features. J Cutan Pathol. 1987;14:49–53.
101. Gelli MC, Pasquinelli G, Martinelli G, et al. Cutaneous meningioma: histochemical, immunohistochemical and ultrastructural investigation. Histopathology. 1993;23: 576–8.
102. Stout AP. A tumor of the ulnar nerve. Proc NY Pathol Soc. 1918;18:2–12.
103. Dehner LP. Peripheral and central primitive neuroectodermal tumors: a nosologic concept seeking a consensus. Arch Pathol Lab Med. 1986;110: 997–1005.
104. Mueller S, Matthay KK. Neuroblastoma: biology and staging. Curr Oncol Rep. 2009;11:431–8.
105. Shown TE, Durfee MF. Blueberry muffin baby: neonatal neuroblastoma with subcutaneous metastases. J Urol. 1970;104:193–5.
106. Hawthorne HC, Nelson JS, Witzelben CL, et al. Blanching subcutaneous nodules in neonatal neuroblastoma. J Pediatr. 1970;77:297–300.
107. Evans AE, Chatten J, D'Angio GD, et al. A review of 17 IV-S neuroblastoma patients at the Children's Hospital of Philadelphia. Cancer. 1980;45:833–9.
108. Argenyi ZB, Bergfeld WF, McMahon JT, et al. Primitive neuroectodermal tumor in the skin with features of neuroblastoma in an adult patient. J Cutan Pathol. 1986;13:420–30.
109. Nguyen AV, Argenyi ZB. Cutaneous neuroblastoma: peripheral neuroblastoma. Am J Dermatopathol. 1993; 15:7–14.
110. Joshi VV, Silverman JF. Pathology of neuroblastic tumors. Semin Diagn Pathol. 1994;11:107–17.
111. Banerjee SS, Agbamu DA, Eyden BP, Harris M. Clinicopathological characteristics of peripheral primitive neuroectodermal tumour of skin and subcutaneous tissue. Histopathology. 1997;31: 355–66.

Fibrous and Fibrohistiocytic Proliferations of the Skin and Tendons

116

Hideko Kamino, Vijaya B Reddy and John Pui

Chapter Contents

Skin tags ... *1961*
Cutaneous angiofibroma ... *1961*
Dermatofibroma ... *1962*
Acral fibrokeratoma ... *1964*
Superficial acral fibromyxoma ... *1965*
Sclerotic fibroma of the skin ... *1965*
Pleomorphic fibroma of the skin ... *1966*
Epithelioid fibrous histiocytoma ... *1966*
Multinucleate cell angiohistiocytoma ... *1966*
Dermatomyofibroma ... *1967*
Giant cell tumor of tendon sheath ... *1967*
Fibroma of tendon sheath ... *1968*
Nodular fasciitis ... *1968*
Connective tissue nevus ... *1969*
Infantile digital fibroma ... *1969*
Infantile myofibromatosis ... *1970*
Calcifying aponeurotic fibroma ... *1971*
Fibrous hamartoma of infancy ... *1971*
Fibromatoses ... *1971*
Plexiform fibrohistiocytic tumor ... *1972*
Atypical fibroxanthoma ... *1973*
Dermatofibrosarcoma protuberans ... *1973*
Giant cell fibroblastoma ... *1974*
Fibrosarcoma ... *1975*
Epithelioid sarcoma ... *1975*

Key features

- Fibrous and fibrohistiocytic proliferations of the skin and tendons are common lesions that include both neoplastic and "reactive" processes
- Common benign fibrous and fibrohistiocytic proliferations, some of their atypical variants that could be misdiagnosed as malignant tumors, and corresponding malignant neoplasms are reviewed
- These tumors are composed of fibroblasts, myofibroblasts, histiocytes, dermal dendritic cells, collagen fibers, elastic fibers and connective tissue mucin, each present in variable proportions depending upon the particular lesion
- Immunohistochemical stains for vimentin (for nonspecific mesenchymal components); factor XIIIa and CD34 (for dermal dendritic cells); CD68 and α1-antichymotrypsin (for histiocytes); and muscle-specific actin (for myofibroblasts) are helpful in evaluating these lesions

SKIN TAGS

Synonyms: ■ Acrochordons ■ Fibroepithelial polyps ■ Soft fibromas

Clinical Features

Skin tags are very common, presenting as soft, skin-colored to slightly hyperpigmented, pedunculated papules that favor the neck, axilla and groin (Fig. 116.1). They may be single or multiple and vary from 1–2 mm papules on the eyelids to 1–2 cm baggy polyps on the trunk. Skin tags are usually asymptomatic, but can become painful secondary to irritation or infarction.

Clinically, they can resemble intradermal melanocytic nevi, neurofibromas and pedunculated seborrheic keratoses.

Epidemiology

The incidence increases with age. Men and women are equally affected, and close to 50% of all individuals have at least one skin tag[1]. Although skin tags were once thought to be associated with colonic polyps, more recent studies have not confirmed this relationship[2]. Skin tags have also been reported as a cutaneous marker for diabetes mellitus[3].

Pathology

Histologically, skin tags are polypoid with loose to dense collagenous stroma and thin-walled blood vessels. The overlying epidermis may be hyperpigmented and hyperplastic. Adipocytes are sometimes seen within larger skin tags (lipofibroma or fibroma molle). The histopathologic differential diagnosis includes seborrheic keratosis, nevus lipomatosus superficialis, and angiofibroma.

In Birt–Hogg–Dubé syndrome and Cowden syndrome, patients can have typical skin tags, but sometimes the "skin tags" represent fibrofolliculomas, trichodiscomas or perifollicular fibromas, versus sclerotic fibromas, respectively[4].

Treatment

Unless irritated or infarcted, skin tags are more of a cosmetic issue than a clinical concern and can be removed by scissor excision.

CUTANEOUS ANGIOFIBROMA

Synonyms: ■ Fibrous papule ■ Pearly penile papule ■ Periungual fibroma

Cutaneous angiofibroma is a descriptive term for a group of lesions with different clinical presentations and implications, but similar histologic findings.

Clinical Features

Fibrous papules are solitary, dome-shaped and shiny, skin-colored to reddish papules located on the face of adults, most commonly on the nose (Fig. 116.2)[5]. Clinically, they can mimic small intradermal melanocytic nevi, basal cell carcinomas (BCCs) or adnexal tumors. They are often sampled to exclude a BCC. Removal consists of shave excision and electrodesiccation.

Pearly penile papules are pearly, white, dome-shaped, closely aggregated small papules located on the glans penis, commonly in a multilayered and circumferential manner on the corona (Fig. 116.3). They are found in up to 30% of young postpubertal adults, and are more common in uncircumcised men[6]. They can be mistaken for condyloma acuminata or hypertrophied sebaceous glands. They are sometimes of significant cosmetic concern to the patient, but no treatment is needed, only reassurance.

Fig. 116.1 Multiple skin tags in the axilla. The lesions are skin-colored, soft and pedunculated.

Fig. 116.2 Fibrous papule of the nose. A smooth, dome-shaped, skin-colored papule.

Fig. 116.3 Pearly penile papules. Multiple small white papules along the corona of the glans penis. Note the multilayered distribution. *Courtesy, Kalman Watsky, MD.*

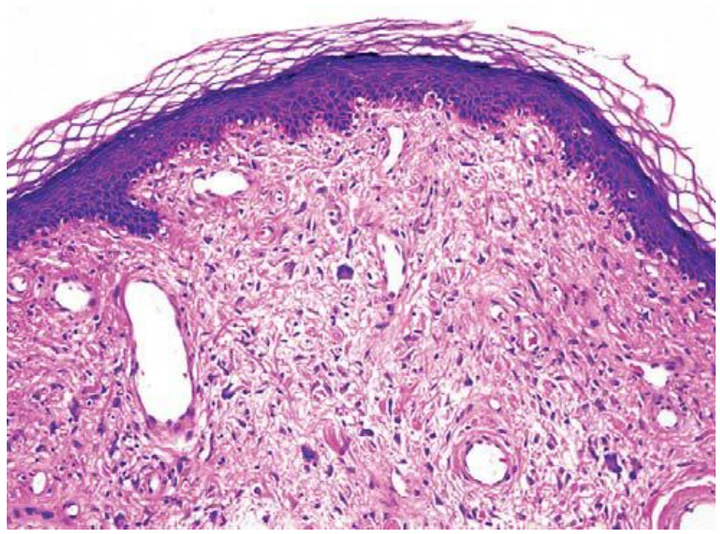


Fig. 116.4 Angiofibroma. Dermal fibroplasia with dilated, thin-walled vessels and large stellate fibroblasts is seen.

Multiple facial angiofibromas are seen in tuberous sclerosis (TS), multiple endocrine neoplasia type 1 and Birt–Hogg–Dubé syndrome[7] (see Ch. 61). They are usually distributed bilaterally on the cheeks, nasolabial folds, nose and chin. In TS, facial angiofibromas usually appear during early to mid childhood, with 75% of individuals eventually developing these lesions. Patients with TS can also have multiple *periungual angiofibromas*; they are less common in children but increase in incidence with age to 40% in adults. Both facial and periungual angiofibromas represent major diagnostic criteria for TS (see Table 61.8).

Pathology

All angiofibromas are dome-shaped lesions composed of a dermal proliferation of fibroblasts in a collagenous stroma with an increase in the number of thin-walled, dilated blood vessels (Fig. 116.4). The collagen fibers can be arranged in a concentric fashion around hair follicles and blood vessels (a variant known as perifollicular fibroma). Elastic fibers are decreased in number. Some fibroblasts are stellate in shape and can be multinucleated. By immunohistochemistry, these cells are positive for factor XIIIa and negative for S100 protein. The overlying epidermis is sometimes slightly atrophic. The histopathologic differential diagnosis includes skin tags and intradermal melanocytic nevi.

DERMATOFIBROMA

Synonyms: ■ Fibroma simplex ■ Benign fibrous histiocytoma ■ Nodular subepidermal fibrosis ■ Histiocytoma ■ Sclerosing hemangioma ■ Dermal dendrocytoma

Clinical Features

Dermatofibromas are the second most common fibrohistiocytic tumor of the skin (after skin tags). They are seen primarily in adults and favor the lower extremities. They are firm, minimally elevated to dome-shaped papules that usually measure from a few millimeters to 1 cm in diameter, but occasionally are up to 2 cm in size. The lesions are commonly hyperpigmented (Fig. 116.5), but in patients with lightly pigmented skin may appear tan to pink. On palpation, they may seem attached to the subcutaneous tissue; pinching the lesion gently usually results in apparent downward movement of the tumor, also known as the "dimple sign".

Although some dermatofibromas are thought to arise at sites of trauma or arthropod bites, their precise etiology is not known. Multiple eruptive dermatofibromas have been observed in patients with autoimmune disorders (e.g. lupus erythematosus), atopic dermatitis and in the

Fig. 116.5 Dermatofibroma. Hyperpigmented firm papule on the lower extremity. *Courtesy, Jean L Bolognia, MD.*

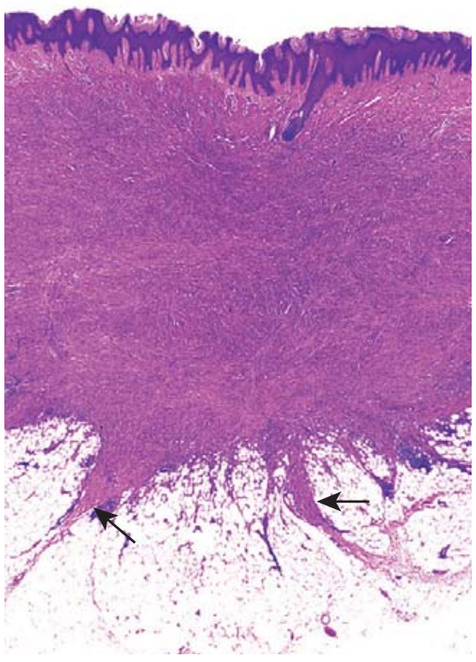


Fig. 116.6 Dermatofibroma. There is a nodular proliferation of spindled fibroblasts and histiocytes in the reticular dermis, with hyperplasia and hyperpigmentation of the overlying epidermis. Extension into the subcutaneous tissue occurs in a radial pattern (arrows).

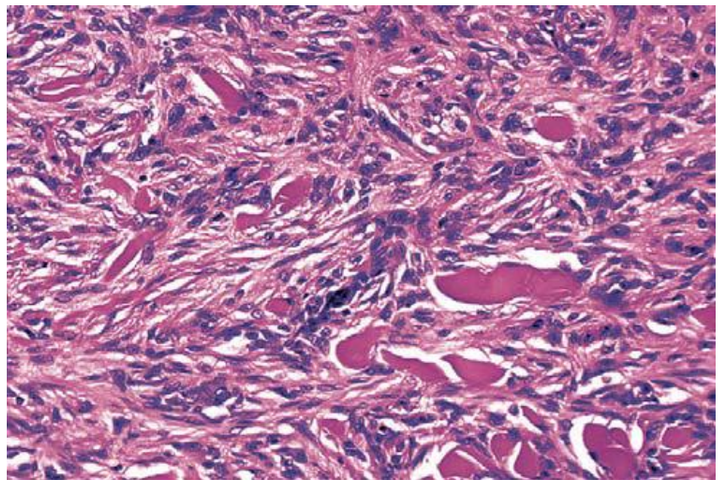


Fig. 116.7 Dermatofibroma. The fibroblasts are arranged in broad intersecting fascicles with entrapment of thick collagen bundles.

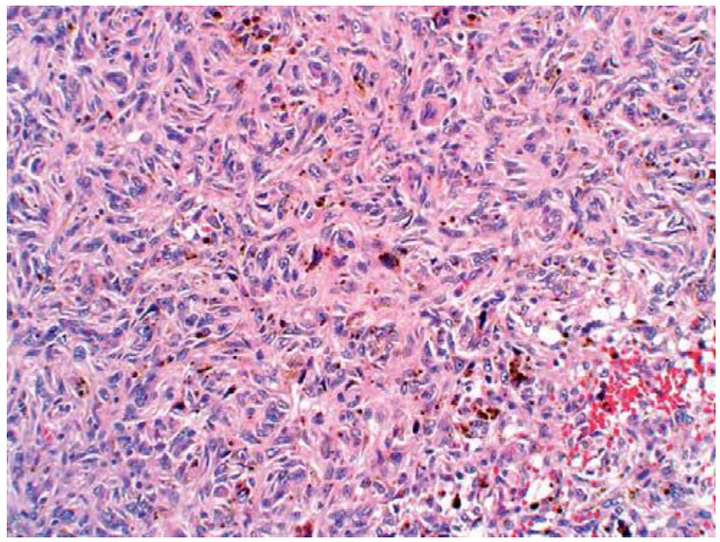


Fig 116.8 Dermatofibroma, sclerosing hemangioma pattern. In addition to plump fibroblasts and blood vessels, there are extravasated red blood cells and abundant hemosiderin pigment.

setting of immunosuppression (e.g. HIV infection)[8]. Clinically, dermatofibromas can be confused with cysts or melanocytic nevi, especially those with fibrosis. In the case of larger lesions, the possibility of dermatofibrosarcoma protuberans (DFSP), which is less well defined and multilobulated, may be considered.

Pathology

Dermatofibromas are characterized by a nodular dermal proliferation, predominantly of spindle-shaped fibroblasts and myofibroblasts arranged as short intersecting fascicles (Fig. 116.6). The fibroblasts and myofibroblasts have plump oval nuclei with small nucleoli; mitoses may be present. There may be a component of mono- or multinucleated histiocytes with vacuolated (xanthomatous) cytoplasm (hence the synonym benign fibrous histiocytoma). "Keloidal" collagen bundles, which are refractile with polarized light, are seen at the periphery (Fig. 116.7). An increased number of small blood vessels and a perivascular infiltrate of lymphocytes and plasma cells may be present. Hemorrhage into a dermatofibroma (sclerosing hemangioma) explains the common finding of hemosiderin (Fig 116.8).

The overlying epidermis is usually hyperplastic with flat confluent rete ridges and hyperpigmentation of the basal layer (so-called "dirty fingers"). Adnexal structures are usually absent at the center of the lesion; however, very often, small follicular or sebaceous structures are connected to the epidermis. Sometimes there are aggregates of basaloid cells with follicular differentiation emanating from the epidermis, which may be confused with a superficial BCC. There are, however, a few reported cases of true BCCs evolving within longstanding dermatofibromas[9]. Histologic variants of dermatofibroma are listed in Table 116.1.

MAJOR HISTOLOGIC VARIANTS OF DERMATOFIBROMA
With atypical ("monster") cells*
Atrophic
Extending into the subcutaneous tissue (deep dermatofibroma)
Palisading
Aneurysmal (hemosiderotic sclerosing hemangioma)
With osteoclast-like cells
Ossifying
Clear cell
Xanthomatous†
With granular cells
Cellular
Myxoid
*Also referred to as atypical (pseudosarcomatous) cutaneous histiocytoma.
†May be yellow in color.

Table 116.1 Major histologic variants of dermatofibroma.

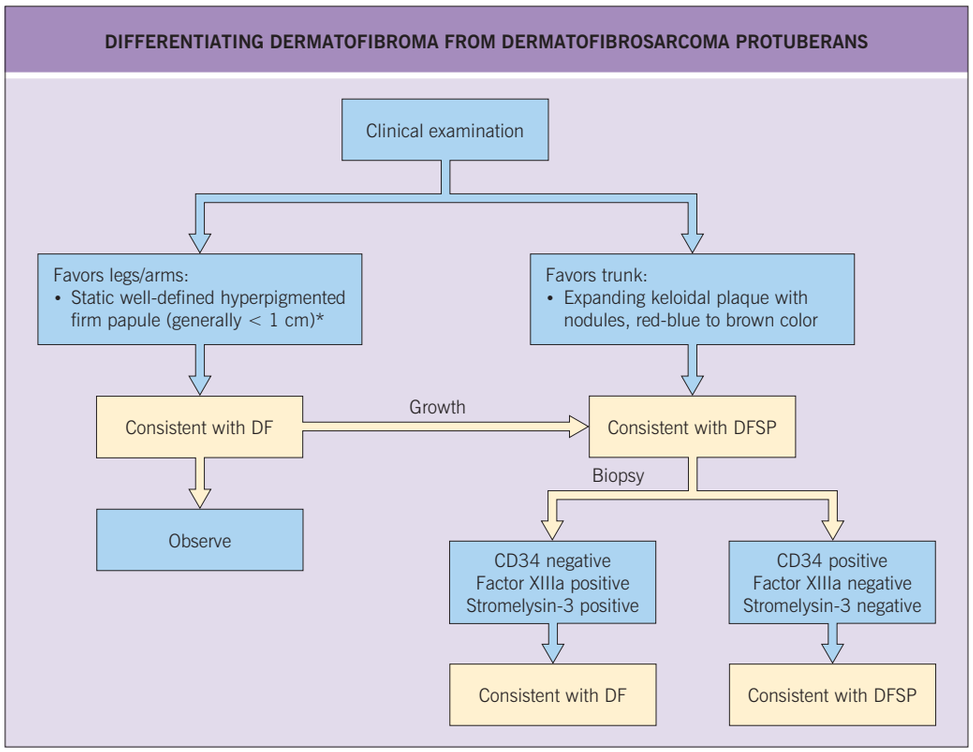


Fig. 116.9 Differentiating dermatofibroma (DF) from dermatofibrosarcoma protuberans (DFSP). At the periphery of dermatofibromas, there may be an increased number of CD34-positive cells, most likely representing pre-existing dendritic cells that were displaced by the cells of the dermatofibroma. *In patients with skin phototype I, it may be pink in color.

Positive immunohistochemical reactions for vimentin, factor XIIIa[10–12], stromelysin-3[13], muscle-specific actin, and CD68, as well as a negative reaction for CD34, support a diagnosis of dermatofibroma (Fig. 116.9). The histologic differential diagnosis includes keloid, scar, dermatomyofibroma, DFSP ($CD34^+$) and nodular Kaposi sarcoma. Whether dermatofibromas are reactive or neoplastic has been an area of controversy. More recent studies have reported evidence of clonality in dermatofibromas, supporting the neoplastic nature of this tumor[14,15].

Treatment

Dermatofibromas may be biopsied or excised to exclude a melanocytic proliferation, a fibrosed cyst or other mesenchymal neoplasm. Excision for cosmetic purposes is of questionable value, as the resultant scar is sometimes more noticeable than the original lesion, especially on the legs. However, some patients find the lesions bothersome or may wish to have histologic confirmation of the diagnosis. Undisturbed, dermatofibromas usually persist, but with time may undergo partial regression, especially centrally.

Histologic Variants of Dermatofibroma (Table 116.1)

Dermatofibroma with atypical cells

Dermatofibromas with atypical cells usually present in middle-aged adults and are slightly larger than 1 cm in diameter. Clinical follow-up in three studies showed no evidence of recurrence after simple excision[16–18].

Dermatofibromas with atypical cells have the architectural pattern and components of common dermatofibromas. In addition, they have atypical mono- and multinucleated cells with large pleomorphic and hyperchromatic nuclei, some of which have prominent nucleoli (Fig. 116.10). The cells have abundant vacuolated cytoplasm, often with hemosiderin deposits. Mitotic figures are rare, and atypical mitoses are not seen. The histopathologic differential diagnosis includes atypical fibroxanthoma and pleomorphic fibroma.

Deep dermatofibroma extending into the subcutaneous tissue

Deep dermatofibromas are usually seen on the trunk and proximal extremities of young to middle-aged patients and tend to be larger than the common variety, measuring 1–2 cm in diameter. The skin surface may be depressed, flat or dome-shaped, and on palpation the tumor is attached to the underlying subcutaneous tissue. The clinical differential diagnosis includes a cyst, lipoma and DFSP.

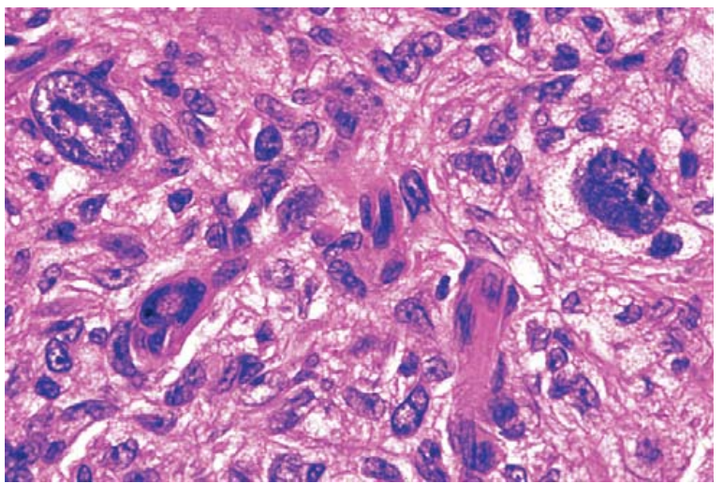


Fig. 116.10 Dermatofibroma with atypical cells. There are histiocyte-like cells with large hyperchromatic nuclei as well as scattered fibroblasts.

The deep variant has histopathologic features similar to those of the common dermal dermatofibroma, but with extensions into the subcutaneous tissue in two main patterns[19]. In approximately 70% of cases, the dermatofibroma extends in a vertical or radial fashion, predominantly along the septae, which have a wedge-shaped appearance (see Fig. 116.6). In approximately 30% of cases, the base is well circumscribed, with a smooth deep margin. All the components present within the dermis extend into the subcutaneous tissue. These patterns are different from the multilayered and "honeycomb" patterns characteristic of DFSP. The histologic differential diagnosis includes DFSP and malignant fibrous histiocytoma.

ACRAL FIBROKERATOMA

Synonym: ■ Acquired digital fibrokeratoma

Fig. 116.11 Acral fibrokeratoma. A light pink exophytic papule arising from the dorsal surface of the finger.

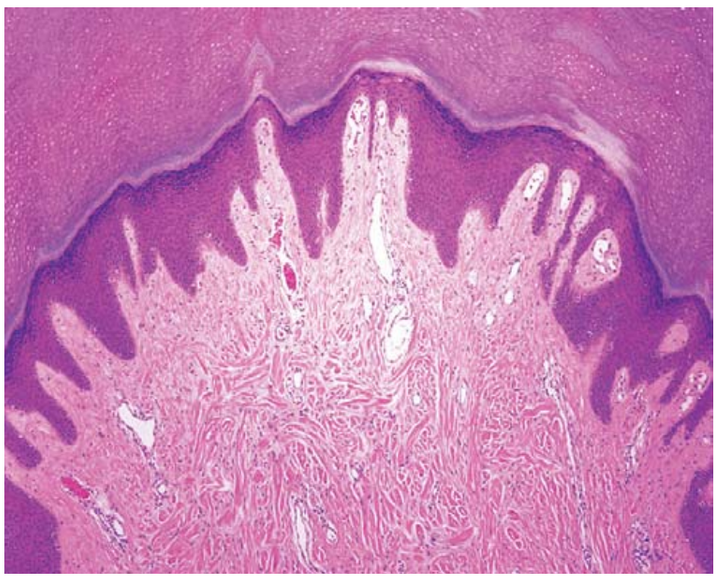


Fig. 116.12 Acral fibrokeratoma. There is a digitated fibrovascular core with vertically arranged collagen bundles lined by epidermal hyperplasia. Note the thick stratum corneum.

Clinical Features

These uncommon lesions present as a solitary, skin-colored to pink, slightly keratotic, exophytic papulonodule with a collarette of elevated skin (Fig. 116.11). Acquired fibrokeratomas usually occur in middle-aged adults and the most common site is the finger[20]. Clinically, they can resemble a supernumerary digit (see Ch. 64), periungual fibroma or verruca. Fibrokeratomas are benign and can be removed by shave excision.

Pathology

Acral fibrokeratomas are composed of thick collagen bundles surrounded by blood vessels, oriented perpendicularly to the epidermis. There is orthokeratosis with variable epidermal hyperplasia, and elastic fibers are decreased (Fig. 116.12)[21]. The histopathologic differential diagnosis includes periungual fibroma and supernumerary digit[22].

SUPERFICIAL ACRAL FIBROMYXOMA

Clinical Features

Superficial acral fibromyxoma is a rare tumor of acral sites, first described by Fetsch et al.[23] in 2001. There is a 2:1 male:female ratio, with a broad range for age of onset. The tumor presents as a slowly enlarging mass, attaining an average size of 2 cm. It usually develops on the toes or fingers, with two-thirds of tumors occurring close to or involving the nail bed. Less common sites include the palm or heel[24]. The clinical differential diagnosis includes periungual fibroma, verruca, giant cell tumor of the tendon sheath, squamous cell carcinoma (SCC), glomus tumor and pyogenic granuloma.

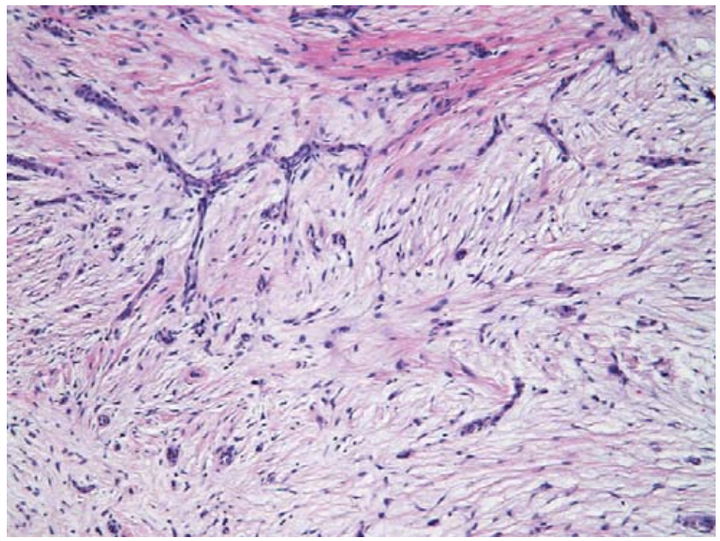


Fig. 116.13 Superficial acral fibromyxoma. The lesion is composed of spindled and stellate cells arranged in a loose storiform pattern with a myxoid collagenous matrix. *Courtesy, Shane Meehan, MD.*

Pathology

Superficial acral fibromyxomas are located within the dermis with extension into the subcutis. There are non-encapsulated masses composed of spindled to stellate cells arranged in a vague storiform or fascicular pattern (Fig. 116.13). The stroma is myxoid to fibromyxoid with prominent blood vessels and frequent mast cells. Mitotic figures are rare and necrosis is not seen. In cases involving the nail bed, there is often papillary hyperplasia of the nail bed epithelium[24].

The majority of these tumors stain strongly for CD34 and frequently for CD99, with focal expression of epithelial membrane antigen[24]. The histologic differential diagnosis includes myxoid neurofibroma, superficial angiomyxoma, DFSP and acral myxoinflammatory fibroblastic sarcoma.

Treatment

These tumors follow a benign course with only rare recurrences after complete excision. Malignant transformation has not been reported.

SCLEROTIC FIBROMA OF THE SKIN

Clinical Features

This distinct, very collagenous variant of fibroma was originally reported as a component of Cowden disease (PTEN hamartoma tumor syndrome). However, a sporadic solitary form has also been described[25].

In Cowden disease, the sclerotic fibromas can be solitary or multiple. They appear on the skin and/or mucous membranes as pearly papules or nodules that measure from a few to up to 10 mm in diameter. Sclerotic fibromas usually develop during adulthood, and there is no gender predominance. In the sporadic form, there is no predilection for any particular anatomic site.

Pathology

Sclerotic fibromas are well-circumscribed, dome-shaped, dermal hypocellular nodules composed predominantly of sclerotic thick collagen bundles arranged as short intersecting stacks in a parallel arrangement and separated by spaces containing connective tissue mucin (plywood-like or whorl-like pattern; Fig. 116.14). Between the collagen bundles, there are thin spindled cells with scanty cytoplasm and small

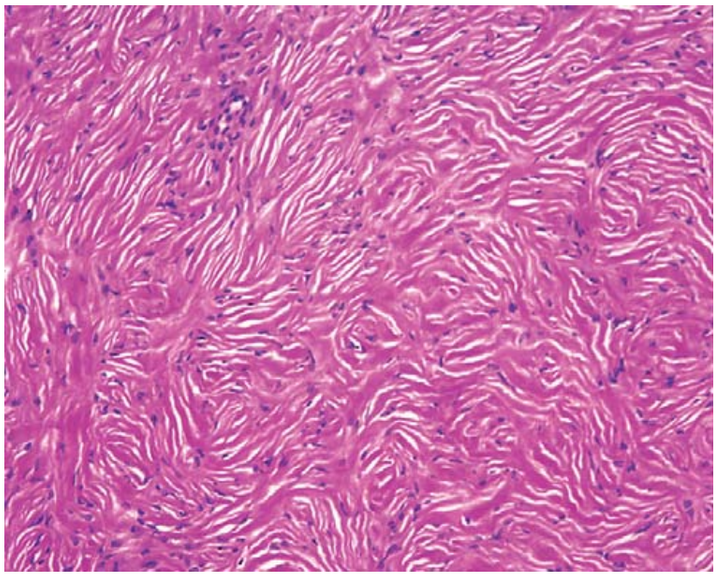


Fig. 116.14 Sclerotic fibroma. The collagen bundles in this hypocellular tumor are arranged in short parallel bundles, leading to a laminated or "plywood" appearance.

nuclei. The blood vessels are inconspicuous, and the overlying epidermis is usually thin. The spindle cells react positively for vimentin, muscle-specific actin, and CD34[26]. Positivity for CD34 may result in the misdiagnosis of early DFSP. The differential diagnosis includes keloid and early DFSP.

PLEOMORPHIC FIBROMA OF THE SKIN

Clinical Features

This unusual variant of a fibroma was described by Kamino et al.[27] in 1989. Pleomorphic fibromas of the skin usually present in adults, with a slight preponderance in women. They favor the extremities and appear as asymptomatic, solitary, skin-colored, dome-shaped or polypoid papules which measure from a few millimeters to nearly 2 cm in diameter. Clinically, they resemble skin tags, neurofibromas or intradermal melanocytic nevi. Treatment is simple excision, and to date there have been no reports of recurrence.

Pathology

Pleomorphic fibromas are polypoid or dome-shaped, well-circumscribed dermal lesions characterized by low cellularity with a predominance of thick collagen bundles in a haphazard array. There are scattered spindled cells and irregularly shaped multinucleated cells with scanty cytoplasm, indistinct cellular borders, and large pleomorphic and hyperchromatic nuclei. Some of the multinucleated cells have multilobed nuclei (Fig. 116.15). Mitotic figures are rare. In some cases, moderate amounts of connective tissue mucin and scattered adipocytes are present. The overlying epidermis is thinned.

The spindle-shaped cells and the irregularly shaped, multinucleated cells are positive for vimentin and CD34[28], and the spindle-shaped cells react positively for muscle-specific actin. The differential diagnosis includes dermatofibroma with atypical cells, atypical fibroxanthoma, and neurofibroma with atypical cells.

EPITHELIOID FIBROUS HISTIOCYTOMA

This benign epithelioid cell mesenchymal neoplasm was originally described as epithelioid cell histiocytoma by Wilson Jones and co-workers in 1989[29].

Clinical Features

Epithelioid fibrous histiocytomas commonly present in adults during the fifth decade of life, with a slight predominance in women. They

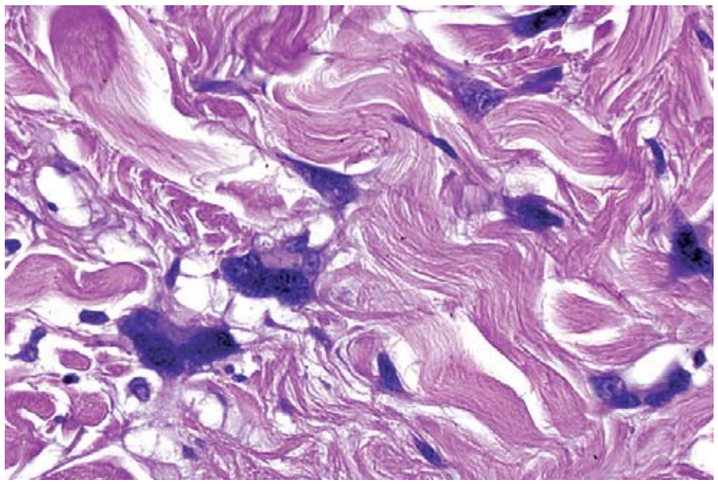


Fig. 116.15 Pleomorphic fibroma. There are interwoven coarse collagen bundles with a few interspersed large mono- and multinucleated atypical fibroblasts.

favor the extremities, and the thigh is the most frequent location. They are firm, sessile or polypoid papules or nodules measuring 0.5–1.5 cm in diameter. Because this neoplasm can be vascular in appearance, common clinical diagnoses are pyogenic granuloma and dermatofibroma (sclerosing hemangioma). The treatment consists of simple excision.

Pathology

Epithelioid fibrous histiocytomas are dome-shaped or polypoid dermal nodules with a well-demarcated base and a collarette of epithelium at their periphery. They are cellular lesions comprised of a monomorphous population of large, epithelioid stellate and triangular cells with angulated borders. The cells have abundant eosinophilic cytoplasm and oval nuclei with small nucleoli; some cells have two or more nuclei. Mitotic figures are rare. The cells are separated by delicate collagen fibers and variable amounts of connective tissue mucin, with no evidence of nesting. A proliferation of small blood vessels can be seen.

The neoplastic cells react positively for vimentin and factor XIIIa[29,30]. Most of the epithelioid cells are negative for CD68 and α_1-antichymotrypsin. The differential diagnosis includes intradermal Spitz nevus and cellular neurothekeoma.

MULTINUCLEATE CELL ANGIOHISTIOCYTOMA

Clinical Features

The typical clinical presentation of multinucleate cell angiohistiocytomas is that of slowly growing, multiple, discrete but grouped, red to violaceous papules, usually on the lower extremities (Fig. 116.16) or the dorsal aspect of the hands. The lesions may be unilateral or bilateral, and typically affect women over 40 years of age[31]. A generalized form has also been described in a young man[32]. Clinically, lesions may resemble Kaposi sarcoma, granuloma annulare or sarcoidosis.

Pathology

These lesions are composed of a proliferation of dilated capillaries and small venules in the superficial to mid dermis within thickened collagen bundles. The characteristic cell is a multinucleated giant cell, sometimes with peripheral palisading of the nuclei within eosinophilic cytoplasm (Fig. 116.17). By immunohistochemistry, these cells are positive for vimentin and factor XIIIa and negative for S100 protein. Mast cells and a mixed inflammatory cell infiltrate can also be seen. The overlying epidermis may be hyperplastic, with hyperpigmentation and orthokeratosis. The histopathologic differential diagnosis includes dermatofibroma, angiofibroma, hemangioma and interstitial granuloma annulare.

Treatment

These lesions are benign and can be removed by simple excision. If left untreated, most cases progress slowly without evidence of spontaneous resolution.

Fig. 116.16 Multinucleate cell angiohistiocytoma. Grouped erythematous macules and papules on the thigh. Hemorrhagic crust represents biopsy site.

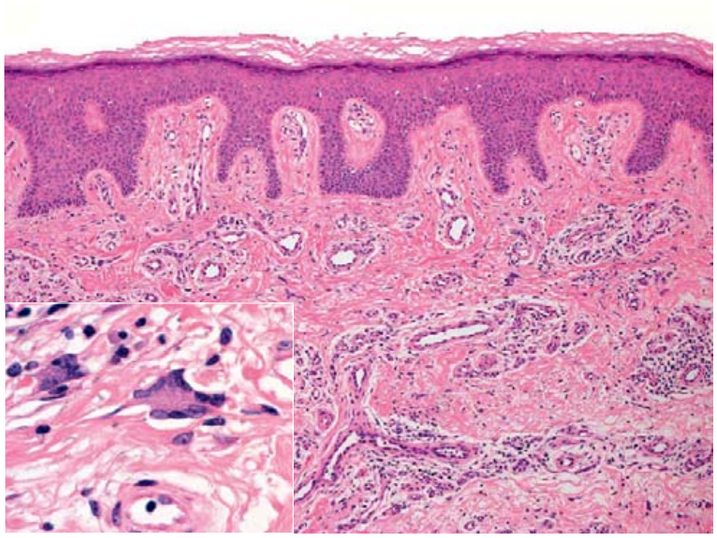


Fig. 116.17 Multinucleate cell angiohistiocytoma. There is a proliferation of dilated blood vessels with a sparse inflammatory infiltrate, an increase in fibroblasts, and the presence of angulated multinucleated giant cells (insert). *Courtesy, Lorenzo Cerroni, MD.*

DERMATOMYOFIBROMA

This tumor was described as plaque-like dermal fibromatosis in 1991 by Hugel[33] and as dermatomyofibroma by Kamino et al.[34] the following year.

Clinical Features

Dermatomyofibromas are lesions predominantly of young women and usually involve the shoulder area, axilla, upper arm and neck. Occasionally, these tumors arise during childhood. They are asymptomatic, well-circumscribed, oval or annular, skin-colored to red–brown plaques measuring 1–2 cm in greatest diameter, with a smooth skin surface. The clinical differential diagnosis includes dermatofibroma, fibrosed cyst, granuloma annulare, pseudolymphoma and DFSP.

Pathology

Dermatomyofibromas are well-circumscribed plaques involving the reticular dermis and the upper portion of the subcutaneous septae; they are composed of well-defined, long fascicles of spindle-shaped cells parallel to the skin surface (Fig. 116.18). The cells have a very uniform appearance, with elongated nuclei having rounded or pointed ends and one or two small nucleoli. There is no evidence of nuclear atypia, and mitoses are rare. The cells are separated by thin collagen fibers and elastic fibers are preserved. The fascicles, spindle-shaped cells, collagen fibers and elastic fibers may have a wavy appearance. The adnexal structures are spared.

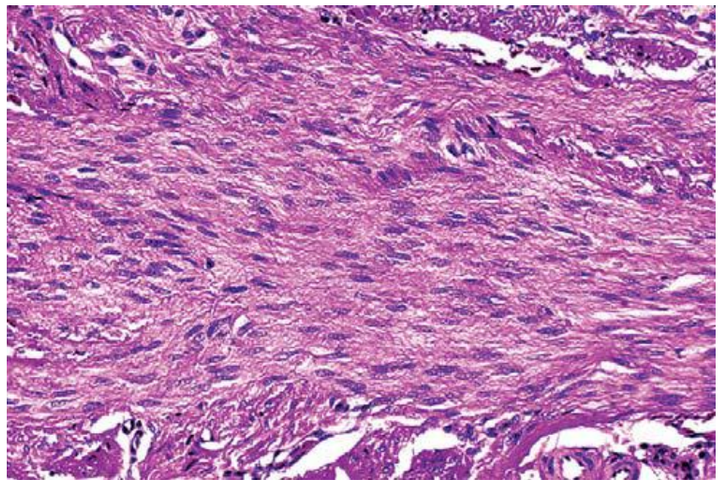


Fig. 116.18 Dermatomyofibroma. The myofibroblasts are arranged in long intersecting fascicles that are parallel to the skin surface.

Masson's trichrome stain highlights the presence of thin collagen fibers between the spindle cells. With Verhoeff–van Gieson's stain, the elastic fibers appear slightly increased in number compared with the surrounding uninvolved dermis. The spindle-shaped cells react positively for vimentin and muscle-specific actin. They are variably positive for smooth muscle actin and negative for desmin, factor XIIIa and CD34. These results support a fibroblastic–myofibroblastic differentiation rather than smooth muscle differentiation[33,34]. On electron microscopy, the myofibroblasts contain prominent rough endoplasmic reticulum and intracytoplasmic myofilaments[34]. The histologic differential diagnosis includes dermatofibroma, leiomyoma and neurofibroma.

Treatment

The treatment is simple excision. Recurrence is uncommon even when marginally or incompletely excised[35].

GIANT CELL TUMOR OF TENDON SHEATH

Synonyms: ■ Localized nodular tenosynovitis ■ Giant cell synovioma ■ Pigmented villonodular synovitis

Clinical Features

This tumor usually presents as a firm nodule on the hand or finger (Fig. 116.19), but can also occur on the toes and other periarticular sites. It is typically slow growing and fixed to subcutaneous structures without attachment to the overlying skin, except on the distal fingers and toes. Although usually asymptomatic, there can be pain, numbness or stiffness of the affected digit.

Giant cell tumor of tendon sheath is the most common tumor of the hand and can present at any age, but usually appears in adults 30 to 50 years of age and is more common in women than in men[36]. The clinical differential diagnosis is broad and includes rheumatoid nodule, ganglion cyst, subcutaneous granuloma annulare, fibroma of tendon sheath, and the rare entity epithelioid sarcoma.

Pathology

These tumors have a lobular outline and are attached to the tendon sheath. They have a biphasic appearance, with moderately cellular areas of rounded to polygonal cells blending into hypocellular collagenized areas with spindle cells. The characteristic multinucleated giant cells are scattered throughout the tumor in variable densities.

Fig. 116.19 Giant cell tumor of tendon sheath. A skin-colored nodule on the lateral aspect of the index finger.

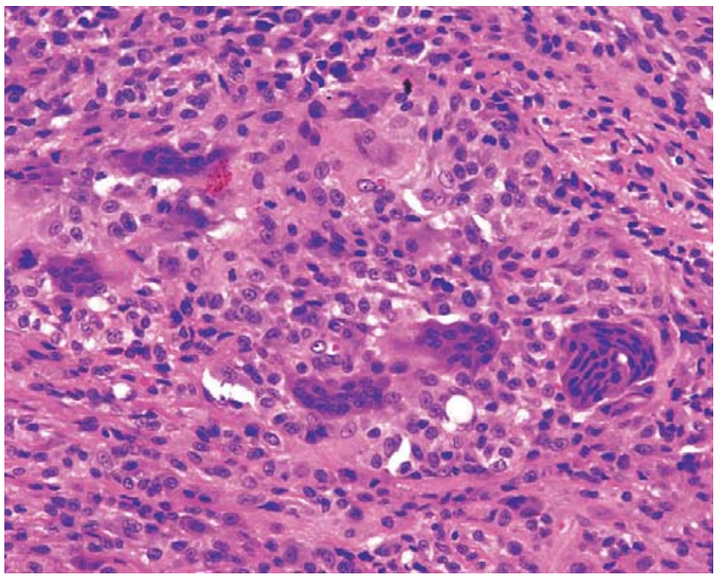


Fig. 116.20 Giant cell tumor of tendon sheath. The tumor is composed of sheets of epithelioid histiocytes with a variable number of the characteristic multinucleated osteoclast-like giant cells. Some of the histiocytes may have pale foamy cytoplasm. *Courtesy, Jacqueline M Wharton, MD.*

These cells have eosinophilic cytoplasm and from a few to 50 nuclei (Fig. 116.20). There are also mononucleated histiocytes with abundant vacuolated cytoplasm containing variable amounts of hemosiderin deposits. Stromal clefts, mitotic figures, and, rarely, vascular involvement may be observed. The histologic differential diagnosis includes subcutaneous granuloma annulare, rheumatoid nodule, epithelioid sarcoma, synovial sarcoma, deep dermatofibroma, fibroma of tendon sheath, and foreign body granuloma.

Treatment

This tumor is benign, with a local recurrence rate of 30%. It can be treated by a simple excision[36]. Whether this tumor is reactive or neoplastic in nature remains controversial. Although karyotypic abnormalities have been reported by some, others have found that the tumors are polyclonal[37].

FIBROMA OF TENDON SHEATH

Clinical Features

This benign tumor presents as a small subcutaneous nodule. It is most frequently found on the hands and feet, with the thumb being the most common site of involvement. They are usually asymptomatic, but there can be limitation in the range of motion of involved joints[38].

The usual age of presentation is between 20 and 50 years. Men develop these tumors three times more often than women. The clinical differential diagnosis includes giant cell tumor of tendon sheath, neuroma, ganglion cyst, rheumatoid nodule and subcutaneous granuloma annulare.

Pathology

The tumor has a well-circumscribed lobular appearance and is attached to a tendon sheath. It is composed of dense hyalinized collagen with scattered spindle-shaped fibroblasts and stromal clefts. There are occasional giant cells and foci of myxoid change. The histopathologic differential diagnosis includes giant cell tumor of tendon sheath, fibromatosis, nodular fasciitis, benign fibrous histiocytoma, synovial sarcoma and fibrosarcoma.

Treatment

This tumor is benign, with a recurrence rate of about 25%. Treatment is usually simple excision. Some authors believe that this tumor may represent a sclerotic end-stage of giant cell tumor of tendon sheath[39].

NODULAR FASCIITIS

Synonyms: ■ Subcutaneous pseudosarcomatous fibromatosis ■ Pseudosarcomatous fasciitis

Clinical Features

Nodular fasciitis is a benign reactive process seen in young to middle-aged adults. The upper extremity is the most common site. In children, the head and neck region is the most frequent location[40]. There is no gender predominance. Nodular fasciitis presents as a rapidly growing (but self-limited) subcutaneous nodule measuring from 1 to 5 cm in diameter, which may be tender. Some lesions are triggered by trauma.

Pathology

There is a well-circumscribed subcutaneous, fascial or intramuscular nodule with a stellate appearance. Dermal and intravascular variants have been reported[41]. A proliferation of plump spindle and stellate fibroblasts and myofibroblasts with oval nuclei that have a fine chromatin pattern and prominent nucleoli is seen. In early lesions, the cells are loosely arranged in an edematous, myxomatous stroma imparting a "feathered" appearance (Fig. 116.21), with a proliferation of small

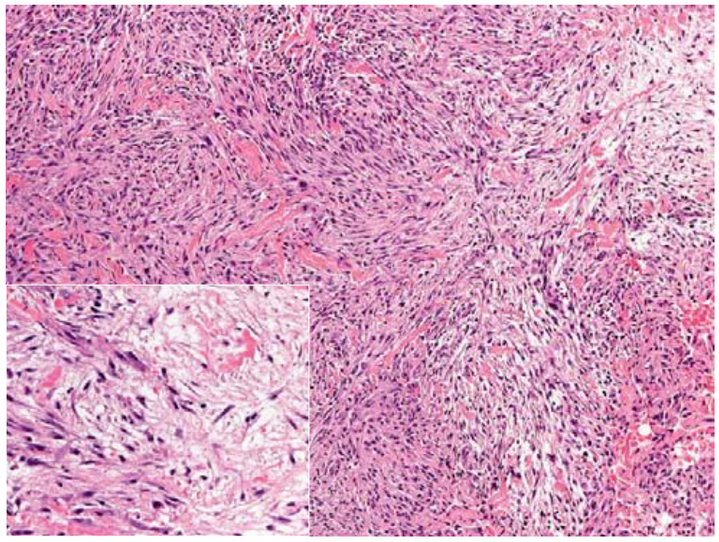


Fig. 116.21 Nodular fasciitis. Proliferation of spindle-shaped and plump fibroblasts arranged in a haphazard array with focally myxoid stroma. The plump and spindle-shaped fibroblasts within the myxoid stroma have a vague "tissue culture-like" appearance (insert). *Courtesy, Lorenzo Cerroni, MD.*

blood vessels, scattered lymphocytes and extravasated erythrocytes. Mitoses are frequent. Occasionally, clusters of siderophages may be present. Older lesions show hyalinized collagen bundles.

The fibroblasts and myofibroblasts react positively for vimentin and muscle-specific actin and, to a lesser degree, for smooth muscle actin. Some cells are positive for CD68[42]. The histologic differential diagnosis includes fibrosarcoma and malignant fibrous histiocytoma.

Treatment

Nodular fasciitis is treated with a conservative excision. The recurrence rate is approximately 1%[43].

CONNECTIVE TISSUE NEVUS

Synonyms: ■ Collagenoma ■ Elastoma ■ Shagreen patch (tuberous sclerosis) ■ Dermatofibrosis lenticularis disseminata (Buschke-Ollendorf syndrome)

Clinical Features

Connective tissue nevi are firm, solitary or multiple, skin-colored papules, nodules or plaques that usually present at birth or arise during childhood (Fig. 116.22). A linear arrangement occasionally occurs. These nevi may represent hamartomas rather than neoplasms. Clinically and histologically, they may be subtle and even resemble normal skin. There are several variants, including the shagreen patch of tuberous sclerosis (see Ch. 61), which most commonly presents as a pebbly plaque with a "pigskin" appearance on the lower back.

In the Buschke–Ollendorf syndrome, multiple skin-colored or slightly yellowish papules are seen and are referred to as dermatofibrosis lenticularis disseminata. The disease is due to loss-of-function mutations in the *LEMD3* gene which then lead to loss of antagonism of the TGF-β and bone morphogenic protein signaling pathways[44]. The disorder is inherited in an autosomal dominant pattern and the papules begin at an early age. In radiograms, a characteristic stippled appearance to the bone is seen, called osteopoikilosis (Fig. 116.23). This abnormality is asymptomatic.

Connective tissue nevus is a specific criterion (category A) for Proteus syndrome. The nevi occur most commonly on the plantar surface and acquire a cerebriform appearance, but can be seen elsewhere (e.g. hands, abdomen).

Pathology

There is usually a poorly demarcated area of increased dermal collagen bundles (some of which are oriented perpendicular to the skin surface), without an apparent increase in fibroblasts. These lesions are designated collagenomas. A variant with increased elastic fibers has been called elastoma. Many of the cutaneous lesions in Buschke–Ollendorf syndrome tend to have increased elastic fibers, but some appear to be primarily collagenous. Elastoma should not be confused with elastofibroma, which is a large mass in the deep subcutaneous tissue or fascia of the infrascapular area that is rarely treated by dermatologists. In many examples of connective tissue nevi, the connective tissue alterations may not be readily apparent unless the surrounding normal skin is examined histologically for comparison or special stains are performed (e.g. Verhoeff–van Gieson).

Fig. 116.22 Connective tissue nevus. Coalescence of multiple tan papules and plaques on the lower back. The lesion was firm to palpation and histologically had increased collagen.

Fig. 116.23 Osteopoikilosis. In this radiograph, multiple asymptomatic round to oval areas ("islands") of increased bone density are seen in the tibia. *Courtesy, Jean L Bolognia, MD.*

Differential Diagnosis

Although the differential diagnosis includes fibromatoses, fibrous hamartoma of infancy, infantile myofibromatosis and dermatofibromas, clinicopathologic correlation usually establishes the diagnosis fairly easily.

INFANTILE DIGITAL FIBROMA

Synonyms: ■ Recurring digital fibrous tumor of childhood ■ Inclusion body fibromatosis

Clinical Features

Infantile digital fibromas commonly present as multiple, firm, smooth, skin-colored, dome-shaped nodules on the dorsolateral aspects of the fingers and toes (Fig. 116.24). They can be up to several centimeters in diameter, and tend to spare the thumb and great toe.

Almost all cases occur in infants under 1 year of age, and boys and girls are equally affected. Rare adult cases of a histologically similar tumor have been reported at extradigital sites[45]. The smaller tumors can resemble acral fibrokeratomas, periungual fibromas and supernumerary digits.

Pathology

Infantile digital fibromas are poorly circumscribed proliferations of spindle-shaped myofibroblasts, arranged as interwoven fascicles with a collagenous stroma within the dermis or subcutaneous tissue. The cells have uniform spindle-shaped wavy nuclei without nuclear atypia or mitoses. The pathognomic feature is the presence of eosinophilic intracytoplasmic inclusions (Fig. 116.25), which are often perinuclear. These inclusions stain red with Masson's trichrome and purple with

Fig. 116.24 Infantile digital fibroma. Firm skin-colored nodule on the dorsolateral aspect of the second toe in a young child.

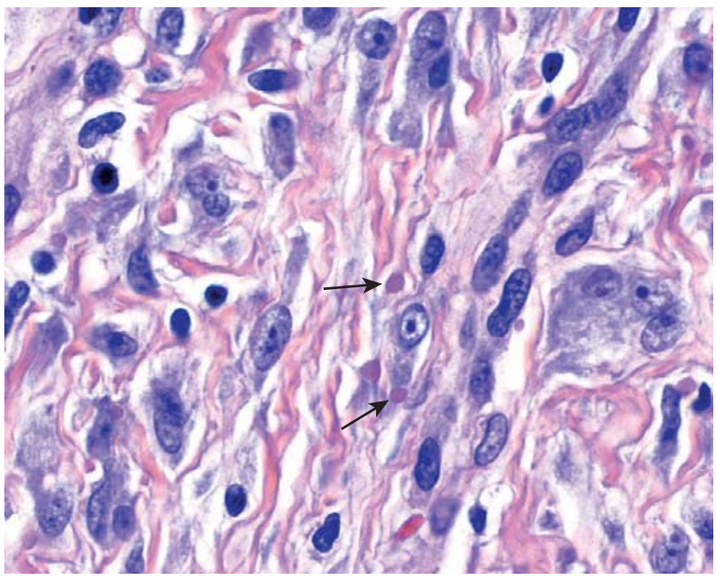


Fig. 116.25 Infantile digital fibroma. Myofibroblasts have pathognomonic cytoplasmic eosinophilic hyalin globules (arrows).

phosphotungsten acid–hematoxylin (PTAH). Ultrastructurally, the inclusions are composed of bundles of actin-like filaments. The histopathologic differential diagnosis includes scar, dermatofibroma, angiofibroma, neurofibroma and angiofibromatous verruca vulgaris.

Treatment

In general, the clinical course is benign, although functional impairment is possible. Spontaneous regression within 2–3 years is the usual natural history[46]. Contractures can be problematic. Recommended treatment options include conservative excision or observation (after histologic confirmation), with additional surgery as necessary for recurrences[47].

INFANTILE MYOFIBROMATOSIS

Synonyms: ■ Congenital multicentric fibromatosis ■ Congenital generalized fibromatosis

Fig. 116.26 Infantile myofibromatosis. Multiple firm violaceous papulonodules on the scalp.

Clinical Features

Although this entity is rare, it is the most common of the juvenile fibromatoses. Clinically, it presents as one or more, firm to rubbery, skin-colored to purple, dermal or subcutaneous nodules, commonly located in the head and neck region (Fig. 116.26) or on the trunk. Skeletal involvement in the form of lytic metaphyseal lesions occurs in half of the patients, and the tumors can involve multiple internal organs, including the gastrointestinal tract, kidneys, lungs and heart.

Approximately 50% of patients have lesions present at birth, with more appearing during the first 2 years of life. Familial cases have been reported, but with an unclear inheritance pattern, and female infants have a greater tendency for visceral involvement[48]. When there are multiple myofibromas, the clinical differential diagnosis includes multiple juvenile xanthogranulomas (JXG), hemangiomatosis, mastocytomas, and cutaneous metastases; when the lesion is solitary, it may resemble a mastocytoma, nodular JXG, nasal glioma, soft tissue sarcoma (e.g rhabdomyosarcoma), or vascular tumor (e.g. infantile hemangiopericytoma).

Solitary myofibromas may also develop in older children or adults and have a good prognosis[49].

Pathology

These tumors are composed of circumscribed nodules with a biphasic appearance. Areas of plump spindle-shaped myofibroblasts, with abundant cytoplasm arranged in fascicles within a collagenous stroma, blend with more cellular areas of smaller, rounder cells having less cytoplasm and an associated stag-horn pattern of dilated branching blood vessels. Mitotic figures, necrosis, intravascular growth and stromal hyalinization can be present.

Immunohistochemically, the spindle and rounded cells are positive for vimentin and actin, with negative staining for desmin, as is seen in myofibroblasts. The histologic differential diagnosis includes infantile hemangiopericytoma (which some authors suggest exists on a continuum with myofibromatosis), fibrosarcoma, leiomyosarcoma, leiomyoma, juvenile hyaline fibromatosis, nodular fasciitis and fibrous hamartoma of infancy.

Treatment

Patients with only soft tissue and bony involvement have a good prognosis, as the tumors regress spontaneously within months via massive apoptosis[50]. Those with visceral involvement have a high mortality rate within the first 4 months owing to the compromise of vital organ function (e.g. cardiopulmonary failure). However, if patients survive beyond this period to when the tumors begin to regress, the prognosis is much improved. Because the tumors tend to regress, debulking surgery is recommended only for symptomatic lesions. Combination chemotherapy has been used in severe cases[48].

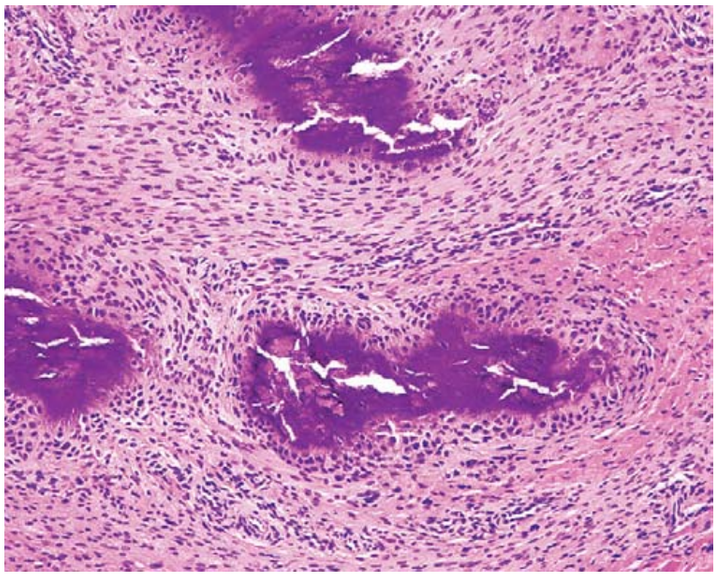


Fig. 116.27 Calcifying aponeurotic fibroma. Islands of calcification are surrounded by palisaded and osteoclast-like fibroblasts. In between these areas are sheets of spindled and epithelioid fibroblasts in a collagenous stroma.

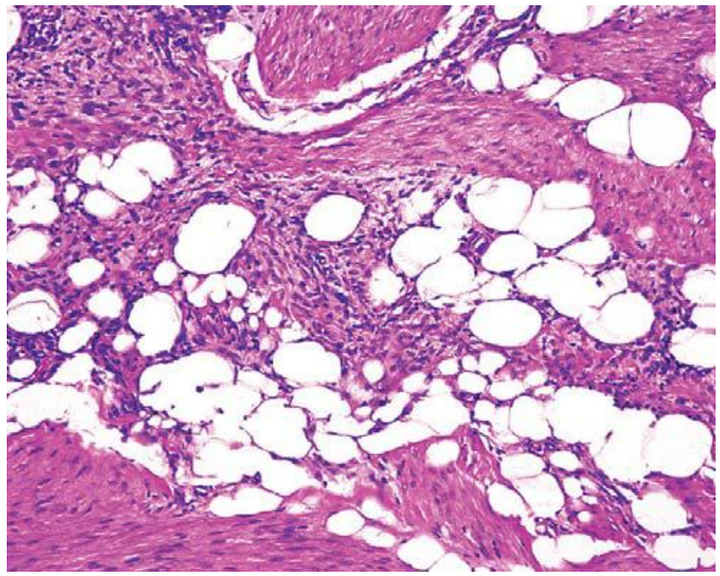


Fig. 116.28 Fibrous hamartoma of infancy. It is composed of a mixture of elongated bundles of spindle-shaped myofibroblasts, clusters of smaller immature mesenchymal cells in a myxoid stroma, and mature adipocytes.

CALCIFYING APONEUROTIC FIBROMA

Synonyms: ▪ Juvenile aponeurotic fibroma ▪ Calcifying fibroma ▪ Cartilage analogue of fibromatosis

Clinical Features

This is a very rare entity that presents as a slowly growing, asymptomatic, solitary, firm, subcutaneous nodule that is usually fixed to underlying structures. It occurs primarily on the hands, and sometimes on the feet. A characteristic radiologic finding is the presence of stippled calcifications. Most cases occur in young children and adolescents, and boys are affected more frequently than girls[51]. The clinical differential diagnosis includes giant cell tumor of tendon sheath, fibroma of tendon sheath, neuroma and rheumatoid nodule.

Pathology

The tumor is poorly circumscribed with an infiltrating border. It is composed of sheets of spindled and epithelioid fibroblasts with parallel nuclei in a collagenous stroma. There are characteristic islands of calcifications surrounded by palisaded epithelioid fibroblasts (Fig. 116.27). In older lesions, these areas of calcification can undergo chondroid and osseous metaplasia. Occasional multinucleated giant cells may also be present. The histopathologic differential diagnosis includes palmar and plantar fibromatosis, chondroma and pseudogout.

Treatment

These tumors are benign, with a local recurrence rate of ~50%[51]. Treatment consists of local excision, with re-excision for recurrences.

FIBROUS HAMARTOMA OF INFANCY

Synonym: Subdermal fibromatous tumor in infancy

Clinical Features

This tumor typically presents as a painless, solitary, skin-colored, subcutaneous nodule. It favors the axilla, shoulder and upper arm, although it can appear in other sites such as the groin[52,53]. There is a variable rate of growth, and the fibrous hamartoma can become quite large. Fixation to underlying structures may be observed. Occasionally, hypertrichosis is present[54].

Most of these tumors appear within the first year of life, but some are congenital. Boys are affected three times as often as girls[52,55]. They may mimic other subcutaneous malignancies of infancy such as rhabdomyosarcoma and cutaneous metastases (e.g. neuroblastoma, leukemia) as well as other fibromatoses and subcutaneous fat necrosis.

Pathology

This tumor is not well circumscribed, and it is composed of three distinctive elements in variable proportions: (1) a proliferation of spindle-shaped myofibroblasts arranged as broad fascicles within a collagenous stroma; (2) nests and aggregates of smaller, round to plump, spindle-shaped, immature mesenchymal cells within a myxoid matrix; and (3) mature adipocytes (Fig. 116.28). The histopathologic differential diagnosis includes infantile myofibromatosis, embryonal rhabdomyosarcoma, neurofibroma, early calcifying aponeurotic fibroma, fibrolipoma and lipoblastoma.

Treatment

Fibrous hamartoma is benign and the usual treatment is local excision, with recurrence being fairly uncommon[55]. If left untreated, the tumor continues to grow and stabilizes in size by mid-childhood.

FIBROMATOSES

Synonyms/subtypes:
- Superficial fascial fibromatosis:
  - palmar fibromatosis (Dupuytren's disease)
  - plantar fibromatosis (Ledderhose's disease)
  - penile fibromatosis (Peyronie's disease)
  - knuckle pads (holoderma)
  - pachydermodactyly
- Deep musculoaponeurotic fibromatosis:
  - desmoid tumor (extra-abdominal)

Clinical Features

Fibromatoses are slowly growing tumors. The superficial variants may reach up to several centimeters in greatest diameter[56]. They appear as firm nodules, plaques, or cord-like tumors along the flexor tendons (see Ch. 98).

Palmar and plantar fibromatoses usually appear during adulthood and the incidence increases with age. Flexion contractures, especially of the fourth and fifth fingers, can result. Penile fibromatosis is more common

Fig. 116.29 Knuckle pads. Note the localization to the skin overlying the knuckles. *Courtesy, Ronald P Rapini, MD.*

Fig. 116. 30 Pachydermodactyly. A form of digital fibromatosis characterized by soft tissue swelling of the lateral aspects of the fingers, usually in the area of the proximal interphalangeal joints of the second to fourth fingers. *Courtesy, Julie V Schaffer, MD.*

in middle-aged to elderly men; pain and erectile dysfunction are common.

Knuckle pads affect the extensor surfaces of the interphalangeal and metacarpophalangeal joints (Fig. 116.29) and may be associated with palmar and plantar fibromatosis. While often idiopathic, they may also be a reflection of trauma. In Bart–Pumphrey syndrome, knuckle pads are seen in association with palmoplantar keratoderma, hearing loss and leukonychia (see Ch. 58).

Pachydermodactyly is an uncommon form of digital fibromatosis. It typically presents in adolescent boys as soft tissue swelling of the lateral aspects of the proximal interphalangeal joints of the second to fourth fingers (Fig. 116.30). This disorder may be related to mechanical trauma[57].

Deep musculoaponeurotic fibromatoses or desmoid tumors are usually rather large – up to 25 cm in diameter. There are abdominal and extra-abdominal variants. They may present after pregnancy in the abdominal wall, in postsurgical scars, and as mesenteric fibromatosis in Gardner syndrome (see Ch. 63). Trauma and cytogenetic

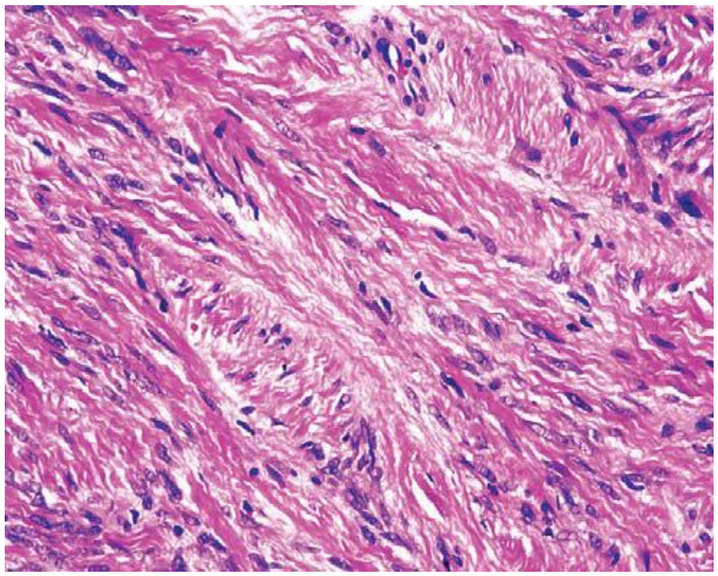


Fig. 116.31 Fibromatosis. Slender spindle-shaped fibroblasts and collagen strands are arranged in broad sweeping fascicles.

abnormalities, including trisomies of chromosomes 8 and 14 (in plantar fibromatosis), may play a role in the pathogenesis of these tumors[58].

Pathology

Fibromatoses consist of large, poorly circumscribed, dermal and subcutaneous plaques and nodules composed of long fascicles of monomorphous fibroblasts and myofibroblasts (Fig. 116.31); the nuclei are elongated with a fine chromatin pattern and small nucleoli. Mitotic figures are rare. There are cellular foci in which the cells are scattered between thin collagen fibers. In hypocellular areas, the cells are separated by thick collagen fibers. The neoplastic cells usually infiltrate the adjacent aponeurosis, fascia and skeletal muscle. The histopathologic differential diagnosis includes fibrosarcoma, dermatomyofibroma, DFSP and keloid.

Cytogenetic abnormalities have been identified less frequently in superficial fibromatoses as compared to their deep counterparts, and, in the former, usually exhibit simple numerical changes, especially gains of chromosome 8[59].

Treatment

Surgical excision with fasciectomy is standard therapy for palmar and plantar fibromatosis, with the goal of reducing functional impairment rather than complete disease removal. More recently, injectable collagenase (from *Clostridium histolyticum*) was approved by the FDA for the treatment of Dupuytren's contractures, based upon response rates of 45–65%[60]. Penile fibromatoses may resolve spontaneously in approximately a third of patients[61]. Therefore, a waiting period is recommended before surgical excision or laser treatment. The deep musculoaponeurotic fibromatoses have a higher recurrence rate and appropriate treatment of these is beyond the scope of this book.

PLEXIFORM FIBROHISTIOCYTIC TUMOR

Clinical Features

A plexiform fibrohistiocytic tumor typically presents as a slowly growing, firm, painless mass in a child or young adult[62]. It is usually less than 3 cm in diameter and favors the wrists and hands; there is a striking female predominance. This tumor is regarded as being of intermediate malignancy, with a tendency to recur locally but only rarely metastasizing.

Pathology

Within the dermis and subcutaneous fat, a multinodular mass is seen composed of nodules of histiocytes and fascicles of spindled cells intersecting the stroma in a plexiform pattern. Multinucleated giant cells

are frequently present. Mitotic figures and mild nuclear pleomorphism may be seen. Immunohistochemical and ultrastructural studies confirm histiocytic and myofibroblastic differentiation. The histopathologic differential diagnosis includes cellular dermatofibroma, dermatomyofibroma, fibromatoses, and nodular fasciitis; the latter lacks a plexiform pattern. Based on shared morphologic and phenotypic features, there is growing evidence to suggest that cellular neurothekeoma and plexiform fibrohistiocytic tumor exist on a continuum[63].

Treatment

These tumors are locally aggressive with high rates of recurrence, requiring excision with wider margins and long-term evaluation[64].

ATYPICAL FIBROXANTHOMA

Synonym: ■ Superficial variant of malignant fibrous histiocytoma

Clinical Features

Atypical fibroxanthoma is a low-grade sarcoma that occurs in the sun-damaged skin of the head and neck in elderly patients. It usually presents as a rapidly growing, dome-shaped nodule that measures from 1 to 2 cm in diameter (Fig. 116.32). Secondary changes include serosanguineous crusts and ulceration[65]. A few cases have been reported in children with xeroderma pigmentosum[66], and a rare variant can develop in non-sun-damaged skin of the trunk or extremities in younger patients. The clinical differential diagnosis includes BCC, SCC, amelanotic melanoma, Merkel cell carcinoma, and cutaneous metastasis.

Pathology

A thin epidermis covers a dome-shaped nodule composed of both atypical spindle-shaped cells with moderate amounts of cytoplasm and large atypical cells with abundant pale-staining vacuolated cytoplasm. The cells have large pleomorphic and hyperchromatic nuclei and some of them are multinucleated (Fig. 116.33). There are numerous typical and atypical mitotic figures. A rare variant with scattered osteoclast-like multinucleated giant cells has been reported[67].

Both the spindle-shaped cells and the histiocyte-like cells react positively for vimentin. The spindle-shaped cells are positive for muscle-specific actin, while the large histiocyte-like cells react positively for α_1-antichymotrypsin, CD68 and CD10[68]. The differential diagnosis includes spindle cell SCC, spindle cell melanoma, dermatofibroma with atypical cells, and pleomorphic fibroma. Atypical fibroxanthoma is considered to be a superficial form of malignant fibrous histiocytoma, which typically presents as a deep subcutaneous or visceral mass that regularly metastasizes.

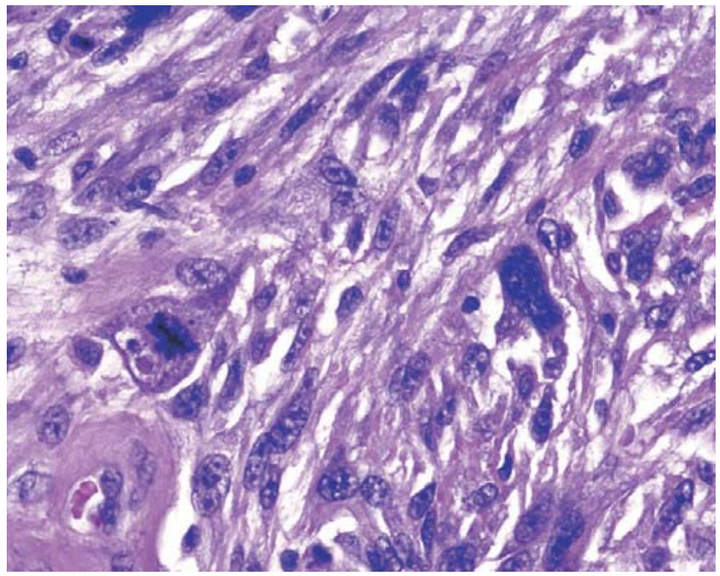


Fig. 116.33 Atypical fibroxanthoma. The spindled cells have pale foamy cytoplasm and hyperchromatic nuclei with small nucleoli. There is also a large atypical giant cell with darker nuclear chromatin as well as a cell in atypical mitosis.

Treatment

Atypical fibroxanthoma is a low-grade superficial sarcoma that usually is cured by complete excision. It has a very low incidence of local recurrence, and metastases are rare[68].

DERMATOFIBROSARCOMA PROTUBERANS

Clinical Features

Dermatofibrosarcoma protuberans (DFSP) is a locally aggressive sarcoma of intermediate malignancy that favors young to middle-aged adults. Lesions that are present at birth or with an onset during childhood have also been reported. DFSP occurs on the trunk in 50–60% of patients, the proximal extremities in 20–30%, and the head and neck in 10–15%. There is a predilection for the shoulder or pelvic region. Initially, it presents as a slowly growing, asymptomatic, skin-colored, indurated plaque that eventually develops violaceous to red–brown nodules measuring from one to several centimeters in diameter (Fig. 116.34)[69]. On palpation, the lesion is firm and attached to the subcutaneous tissue. There are reports of accelerated growth during pregnancy[70].

Fig. 116.32 Atypical fibroxanthoma. A red, dome-shaped nodule on the nose of an elderly man. *Courtesy, Lorenzo Cerroni, MD.*

Fig. 116.34 Dermatofibrosarcoma protuberans. A broad, pink–brown, multinodular, firm plaque on the back.

The early plaque stage may be misdiagnosed as a benign tumor and incompletely excised. Moreover, superficial samples may not yield diagnostic material. The clinical differential diagnosis includes keloid, large dermatofibroma, dermatomyofibroma and morphea. Congenital and childhood-onset DFSP (and occasionally early lesions in adults) may have an atrophic appearance and/or hypopigmented to blue–red color, with the latter potentially leading to misdiagnosis as a vascular malformation or tumor.

Pathology

Early plaque lesions are characterized by a flat surface and low cellularity and are comprised of slender spindle-shaped cells arranged as long fascicles parallel to the skin surface. The cells are scattered between thin collagen fibers and infiltrate thick collagen bundles which appear cellular and wavy. Nuclear atypia is minimal and mitotic figures are rare. Adnexal structures are infiltrated and obliterated. The spindle cells infiltrate into the subcutaneous tissue, very often in a multilayered pattern (Fig. 116.35)[19].

In the nodular stage, the tumor becomes more cellular, with the cells arranged as short fascicles in a "storiform" or mat-like arrangement (Fig. 116.36). The cells infiltrate the subcutaneous tissue in a "honeycomb" pattern. Nuclei are hyperchromatic, and mitotic figures are easily identified. The nodules may develop myxomatous areas, characterized by more rounded to stellate cells in a highly vascular myxomatous stroma. Less differentiated fibrosarcomatous foci have a more cellular appearance, with intersecting fascicles in a "herringbone" pattern, with increased cytologic atypia and frequent mitoses.

Less than 5% of DFSPs contain melanin-producing cells with schwannian differentiation, and they are referred to as Bednar tumors[71].

In plaque-stage tumors, the spindle-shaped cells are strongly positive for CD34[10,72,73] (see Fig. 116.9). The reaction is stronger within the plaque areas than in the nodular foci[74]. Plaque and nodular areas are negative for factor XIIIa[10]. The general immunostaining pattern of DFSP – CD34-positive, factor XIIIa-negative – serves to distinguish it from large and/or highly cellular dermatofibromas, which are CD34-negative and factor XIIIa-positive.

Unique cytogenetic abnormalities have been reported, such as reciprocal t(17;22) translocations (see below) and supernumerary ring chromosomes containing sequences from chromosomes 17 and 22[75]. Overexpression of *p53* has been found in the fibrosarcomatous foci of DFSP that have higher proliferative activity and aneuploidy[76].

The pathologic differential diagnosis of the plaque stage of DFSP includes atrophic dermatofibroma, dermatomyofibroma and neurofibroma. For the nodular stage, it includes deep dermatofibroma extending to the subcutaneous tissue, fibrosarcoma and malignant peripheral nerve sheath tumor. Incisional biopsy specimens, including ample subcutaneous tissue, are optimal for diagnosis.

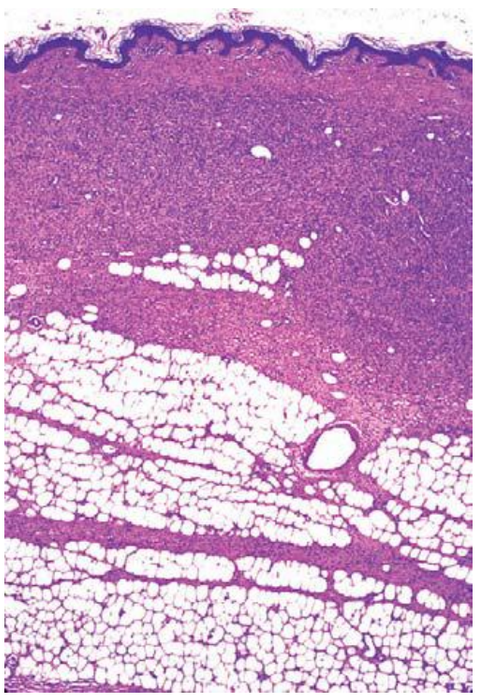


Fig. 116.35 Dermatofibrosarcoma protuberans, plaque stage. Characteristic mutilayered pattern of infiltration into the subcutaneous tissue.

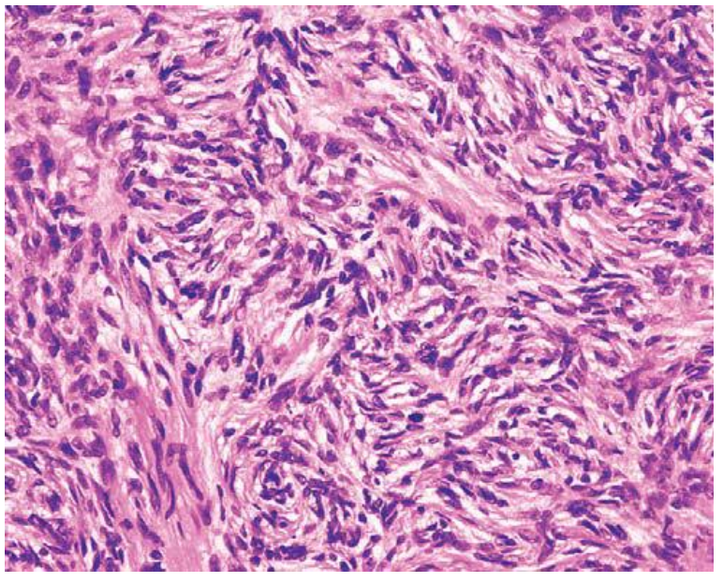


Fig. 116.36 Dermatofibrosarcoma protuberans, nodular stage. The spindle-shaped cells are arranged in a "storiform" pattern.

Treatment

Complete surgical excision, including Mohs micrographic surgery, is the standard treatment for DFSP[77]. This tumor is characterized by its local invasion and tendency to recur. In rare cases, recurrent tumors with fibrosarcomatous areas have metastasized to the lungs[78]. Because the translocation (17;22) places the platelet-derived growth factor (PDGF) β-chain gene under the control of the collagen 1A1 promoter, imatinib mesylate (which targets the PDGF receptor [as well as other proteins with tyrosine kinase activity, e.g. KIT and BCR-ABL]), was tried in patients with DFSP. It is currently FDA-approved for adults with unresectable, recurrent and/or metastatic DFSP (800 mg daily). In two phase II trials with a total enrollment of 24 patients with DFSP, there was a partial response in 46% of individuals[79].

GIANT CELL FIBROBLASTOMA

Clinical Features

This is a rare, solitary, slow-growing, asymptomatic, skin-colored, dermal or subcutaneous nodule involving the neck, trunk or groin. It usually appears during early childhood, with a strong predilection for boys[80]. Clinically, these tumors can mimic cystic hygromas, lipomas or other juvenile subcutaneous tumors (see fibrous hamartoma of infancy section).

Pathology

This lesion is composed of diffusely infiltrating sheets of spindle-shaped fibroblasts and multinucleated cells with hyperchromatic nuclei within a slightly myxoid matrix. Irregular "angiectoid" or pseudovascular spaces lined by multinucleated giant cells are present throughout the tumor (Fig. 116.37). These giant cells do not react with markers for endothelial differentiation, but do react with anti-CD34 antibodies[81]. Similar-appearing giant cells can also be seen in the solid portions of the tumor. On occasion, some tumors have hypercellular spindle cell areas with a storiform pattern similar to that seen in DFSP[81], and some authors consider giant cell fibroblastoma to be the juvenile form of DFSP[82]. More recent molecular studies have revealed that giant cell fibroblastoma and DFSP share the same t(17;22) chromosomal translocation which places the PDGF β-chain gene under the control of the promoter of the collagen 1A1 gene[83].

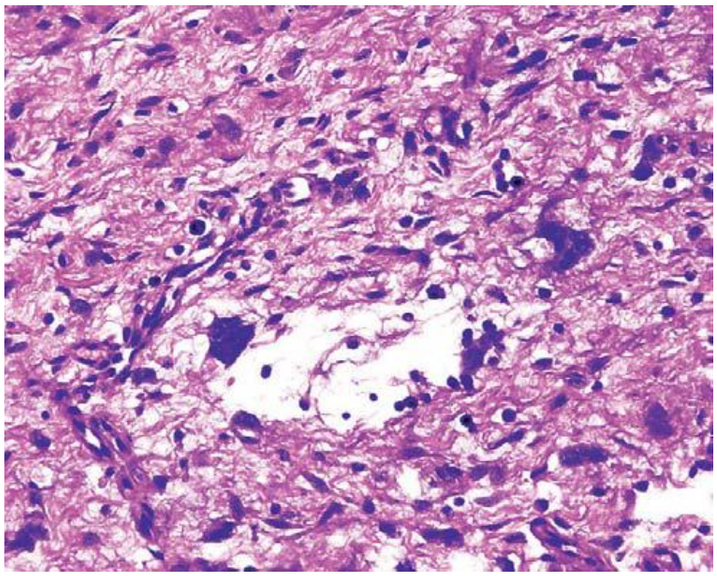


Fig. 116.37 Giant cell fibroblastoma. This pseudovascular or "angiectoid" space lined by giant cells with hyperchromatic nuclei is characteristic of this tumor.

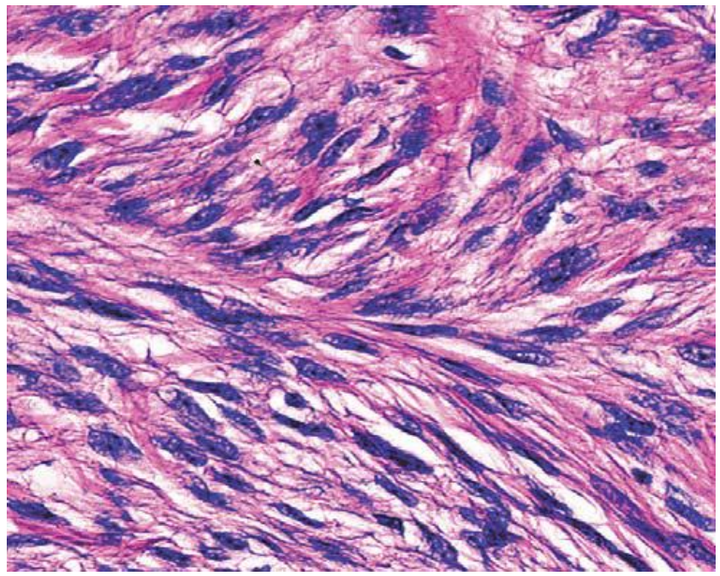


Fig. 116.38 Fibrosarcoma. Cellular fascicles of atypical spindle-shaped fibroblasts with coarse nuclear chromatin are arranged in a "herringbone" pattern.

Treatment

Giant cell fibroblastoma is a low-grade sarcoma with occasional recurrences following local excision[80].

FIBROSARCOMA

Clinical Features

Fibrosarcoma usually affects young to middle-aged adults. The most common location is the lower extremities, followed by the upper extremities, trunk, and head and neck region. This is a neoplasm predominantly of the deep soft tissues, with secondary involvement of the overlying subcutis and skin. Fibrosarcoma is a slowly growing tumor that measures from 1 to 10 cm in diameter and is usually diagnosed when it becomes a palpable painful nodule[84]. They may appear in old burn scars and in areas of prior irradiation[85].

Pathology

The tumor is composed of a proliferation of atypical spindle-shaped cells arranged as intersecting fascicles in a "herringbone" pattern (Fig. 116.38). There are thin collagen bundles between the cells which have scanty cytoplasm and elongated hyperchromatic nuclei. Mitotic figures are easily identified and myxomatous foci may be present. A sclerosing epithelioid variant that simulates an infiltrating carcinoma has been described[86]. High-grade fibrosarcomas are characterized by increased cellularity with more atypical nuclei, a higher mitotic rate, foci of necrosis, and a less distinct "herringbone" pattern. In most cases, the constituent cells only react positively for vimentin (nonspecific) and, to a lesser degree, for muscle-specific actin.

The histopathologic differential diagnosis includes nodular fasciitis, fibromatoses, DFSP, malignant fibrous histiocytoma, and malignant peripheral nerve sheath tumor (see Ch. 115).

Treatment

The treatment for fibrosarcoma is wide excision. When wide free margins cannot be achieved, adjuvant radiation therapy and amputation are additional options. In high-grade fibrosarcomas, adjuvant systemic chemotherapy is given. Hematogenous metastases to the lung, and, less often, to the bones, develop in patients with high-grade or poorly differentiated fibrosarcomas. The overall 5-year survival rate is approximately 40%[84]. There are rare cases of congenital or infantile fibrosarcomas that tend to be less aggressive[87].

EPITHELIOID SARCOMA

Synonym: ■ Epithelioid cell sarcoma

Clinical Features

This rare tumor presents as a slow-growing, firm, subcutaneous nodule of the distal extremities, usually the hands and fingers. There may be associated ulceration if the tumor involves the dermis. Advanced disease can present as a linear arrangement of ulcerated nodules extending from distal to proximal sites on affected extremities. If there is involvement of a large nerve, associated pain, paresthesias and muscle wasting can occur[88].

The majority of patients are between 20 and 40 years of age, and men are affected twice as often as women. Hand and finger lesions may resemble giant cell tumor of tendon sheath, fibroma of tendon sheath, nodular fasciitis, subcutaneous granuloma annulare, rheumatoid nodule or ganglion cyst. Penile lesions can mimic Peyronie's disease[88].

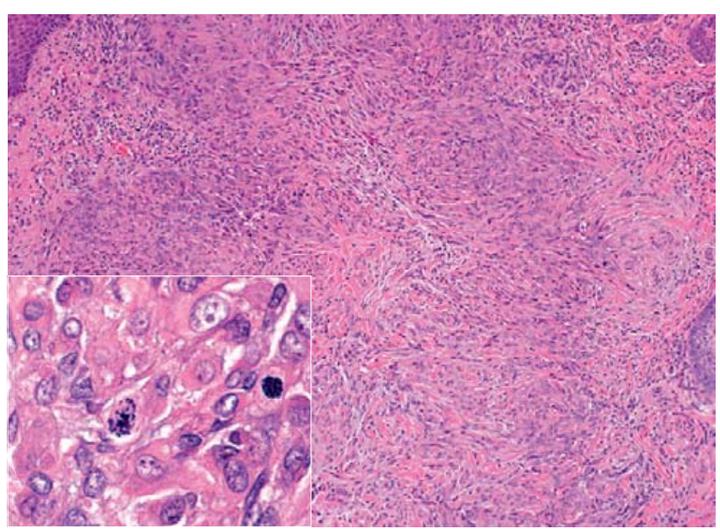


Fig. 116.39 Epithelioid sarcoma. Palisading of atypical epithelioid cells. Pleomorphism and mitoses are present (insert). *Courtesy, Lorenzo Cerroni, MD.*

Pathology

The tumor is composed of a nodular proliferation of spindle-shaped to round or polygonal cells with abundant eosinophilic cytoplasm and small uniform nuclei without prominent nucleoli (Fig. 116.39). The tumor is frequently associated with fascia, periosteum, tendons and nerves. The larger tumor nodules have zones of central necrosis surrounded by palisaded tumor cells and a mixed chronic inflammatory cell infiltrate. Distinction from other tumors usually requires immunohistochemical analysis. The tumor cells are positive for both keratins (hence "epithelioid") and vimentin (hence "sarcoma"). They are also positive for epithelial membrane antigen and negative for S100, HMB45 and CD31. The histopathologic differential diagnosis includes granuloma annulare, necrobiosis lipoidica, rheumatoid nodule, infectious granuloma, giant cell tumor of tendon sheath, SCC, fibrosarcoma, melanoma, synovial sarcoma, epithelioid angiosarcoma, epithelioid hemangioendothelioma, and malignant fibrous histiocytoma.

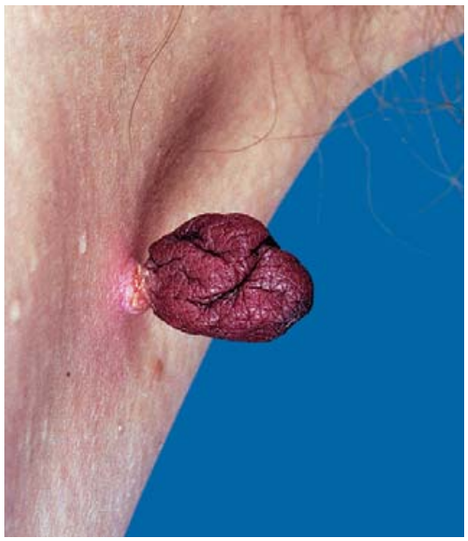
Treatment

Epithelioid sarcoma tends to be multifocal, with an infiltrating growth pattern along tendons, nerves and fascia. Although earlier therapeutic approaches involved radical surgery, including amputation, there has been a movement toward more conservative surgery with adjuvant radiation therapy[89]. Local recurrences are frequent, as are pleuropulmonary metastases (seen in 50% of patients)[88]. The 5-year survival rate is 50%, and metastases can present as late as two decades after the initial diagnosis[88,90].

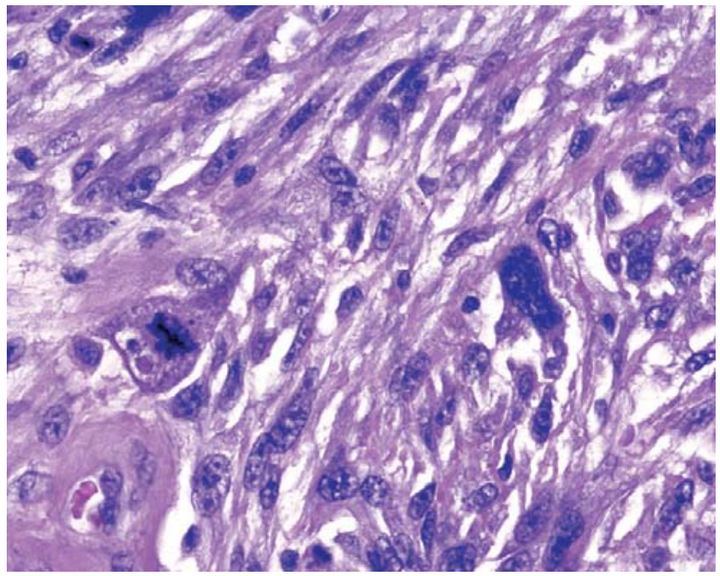
REFERENCES

1. Banik R, Lubach D. Skin tags: localization and frequencies according to sex and age. Dermatologica. 1987;174:180–3.
2. Gould BE, Ellison RC, Greene HL, Bernhard JD. Lack of association between skin tags and colon polyps in a primary care setting. Arch Intern Med. 1988;148:1799–800.
3. Kahana M, Grossman E, Feinstein A, et al. Skin tags: a cutaneous marker for diabetes mellitus. Acta Derm Venereol. 1987;67:175–7.
4. De la Torre C, Ocampo C, Doval IG, et al. Acrochordons are not a component of the Birt-Hogg-Dube syndrome: does this syndrome exist? Case reports and review of the literature. Am J Dermatopathol. 1999;21:369–74.
5. Meigel WN, Ackerman AB. Fibrous papule of the face. Am J Dermatopathol. 1979;1:329–40.
6. Rehbein HM. Pearly penile papules: incidence. Cutis. 1977;19:54–7.
7. Schaffer JV, Gohara MA, McNiff JM, et al. Multiple facial angiofibromas: a cutaneous manifestation of Birt-Hogg-Dubé syndrome. J Am Acad Dermatol. 2005;53(Suppl 1):S108–11.
8. Yazici AC, Baz K, Ikizoglu G, et al. Familial eruptive dermatofibromas in atopic dermatitis. J Eur Acad Dermatol Venereol. 2006;20:90–2.
9. Goette DK, Helwig EB. Basal cell carcinomas and basal cell carcinoma-like changes overlying dermatofibromas. Arch Dermatol. 1975;111:589–92.
10. Abenoza P, Lillemoe T. CD34 and factor XIIIa in the differential diagnosis of dermatofibroma and dermatofibrosarcoma protuberans. Am J Dermatopathol. 1993;15:429–34.
11. Cerio R, Spaull J, Oliver GF, Wilson Jones E. A study of factor XIIIa and MAC 387 immunolabeling in normal and pathological skin. Am J Dermatopathol. 1990;12:221–33.
12. Reid MB, Gray C, Fear JD, Bird CC. Immunohistological demonstration of factors XIIIa and XIIIs in reactive and neoplastic fibroblastic and fibrohistiocytic lesions. Histopathology. 1986;10:1171–8.
13. Kim HJ, Lee JY, Kim SH, et al. Stromelysin-3 expression in the differential diagnosis of dermatofibroma and dermatofibrosarcoma protuberans: comparison with factor XIIIa and CD34. Br J Dermatol. 2007;157:319–24.
14. Vanni R, Fletcher CD, Sciot R, et al. Cytogenetic evidence of clonality in benign fibrous histiocytoma: a report of the CHAMP study group. Histopathology. 2000;37:212–17.
15. Chen TC, Kuo T, Chan HL. Dermatofibroma is a clonal proliferative disease. J Cutan Pathol. 2000;27:36–9.
16. Fukamizu H, Oku T, Inoue K, et al. Atypical ("pseudosarcomatous") cutaneous histiocytoma. J Cutan Pathol. 1983;10:327–33.
17. Leyva WH, Santa Cruz DJ. Atypical cutaneous fibrous histiocytoma. Am J Dermatopathol. 1986;8:467–71.
18. Tamada S, Ackerman AB. Dermatofibroma with monster cells. Am J Dermatopathol. 1987;9:380–7.
19. Kamino H, Jacobson M. Dermatofibroma extending into the subcutaneous tissue. Differential diagnosis from dermatofibrosarcoma protuberans. Am J Surg Pathol. 1990;14:1156–64.
20. Cooper PH, Mackel SE. Acquired fibrokeratoma of the heel. Arch Dermatol. 1985;121:386–8.
21. Kint A, Baran R, De Keyser H. Acquired (digital) fibrokeratoma. J Am Acad Dermatol. 1985;12:816–21.
22. Kint A, Baran R. Histopathologic study of Koenen tumors. Are they different from acquired digital fibrokeratoma? J Am Acad Dermatol. 1988;18:369–72.
23. Fetsch JF, Laskin WB, Miettinen M. Superficial acral fibromyxoma: a clinicopathologic and immunohistochemical analysis of 37 cases of a distinctive soft tissue tumor with a predilection for the fingers and toes. Hum Pathol. 2001;32:704–14.
24. Al-Daraji WI, Miettinen M. Superficial acral fibromyxoma: a clinicopathological analysis of 32 tumors including 4 in the heel. J Cutan Pathol. 2008;35:1020–6.
25. Rapini RP, Golitz LE. Sclerotic fibromas of the skin. J Am Acad Dermatol. 1989;20:266–71.
26. Hanft VN, Shea CR, McNutt NS, et al. Expression of CD34 in sclerotic ("plywood") fibromas. Am J Dermatopathol. 2000;22:17–21.
27. Kamino H, Lee JY, Berke A. Pleomorphic fibroma of the skin: a benign neoplasm with cytologic atypia. A clinicopathologic study of eight cases. Am J Surg Pathol. 1989;13:107–13.
28. Rudolph P, Schubert C, Zelger BG, et al. Differential expression of CD34 and Ki-Mlp in pleomorphic fibroma and dermatofibroma with monster cells. Am J Dermatopathol. 1999;21:414–19.
29. Wilson Jones E, Cerio R, Smith NP. Epithelioid cell histiocytoma: a new entity. Br J Dermatol. 1989;120:185–95.
30. Dezfoulian B, Nikkels AF, Pierard-Franchimont C, Pierard GE. Epithelioid cell histiocytoma: a report of two cases. Dermatology. 1995;190:349–50.
31. Wilson Jones E, Cerio R, Smith NP. Multinucleate cell angiohistiocytoma: an acquired vascular anomaly to be distinguished from Kaposi's sarcoma. Br J Dermatol. 1990;122:651–63.
32. Chang SN, Kim HS, Kim SC, Yang WI. Generalized multinucleate cell angiohistiocytoma. J Am Acad Dermatol. 1996;35:320–2.
33. Hugel H. Plaque-like dermal fibromatosis/dermatomyofibroma. Hautzart. 1991;42:223–6.
34. Kamino H, Reddy VB, Gero M, Greco MA. Dermatomyofibroma. A benign cutaneous, plaque-like proliferation of fibroblasts and myofibroblasts in young adults. J Cutan Pathol. 1992;19:85–93.
35. Mentzel T, Kutzner H. Dermatomyofibroma: clinicopathologic and immunohistochemical analysis of 56 cases and reappraisal of a rare and distinct cutaneous neoplasm. Am J Dermatopathol. 2009;31:44–9.
36. Rao AS, Vigorita VJ. Pigmented villonodular synovitis (giant-cell tumor of the tendon sheath and synovial membrane). A review of eighty-one cases. J Bone Joint Surg Am. 1984;66:76–94.
37. Vogrincic GS, O'Connell JX, Gilks CB. Giant cell tumor of tendon sheath is a polyclonal cellular proliferation. Hum Pathol. 1997;28:815–19.
38. Chung EB, Enzinger FM. Fibroma of tendon sheath. Cancer. 1979;44:1945–54.
39. Satti MB. Tendon sheath tumours: a pathological study of the relationship between giant cell tumour and fibroma of tendon sheath. Histopathology. 1992;20:213–20.
40. Sarangarajan R, Dehner LP. Cranial and extracranial fasciitis of childhood: a clinicopathologic and immunohistochemical study. Hum Pathol. 1999;30:87–92.
41. Price SK, Kahn LB, Saxe N. Dermal and intravascular fasciitis. Unusual variants of nodular fasciitis. Am J Dermatopathol. 1993;15:539–43.
42. Montgomery EA, Meis JM. Nodular fasciitis. Its morphologic spectrum and immunohistochemical profile. Am J Surg Pathol. 1991;15:942–8.
43. Bernstein KE, Lattes R. Nodular (pseudosarcomatous) fasciitis, a nonrecurrent lesion: clinicopathologic study of 134 cases. Cancer. 1982;49:1668–78.
44. Hellemans J, Preobrazhenska O, Willaert A, et al. Loss-of-function mutations in *LEMD3* result in osteopoikilosis, Buschke-Ollendorff syndrome and melorheostosis. Nat Genet. 2004;36:1213–18.
45. Viale G, Doglioni C, Iuzzolino P, et al. Infantile digital fibromatosis-like tumour (inclusion body fibromatosis) of adulthood: report of two cases with ultrastructural and immunocytochemical findings. Histopathology. 1988;12:415–24.
46. Niamba P, Léauté-Labrèze C, Boralevi F. Further documentation of spontaneous regression of infantile digital fibromatosis. Pediatr Dermatol. 2007;24:280–4.
47. Laskin WB, Mettinen M, Fetsch JF. Infantile digital fibroma/fibromatosis: a clinicopathologic and immunohistochemical study of 69 tumors from 57 patients with long-term follow-up. Am J Surg Pathol. 2009;33:1–13.
48. Stanford D, Rogers M. Dermatological presentations of infantile myofibromatosis: a review of 27 cases. Australas J Dermatol. 2000;41:156–61.
49. Beham A, Badve S, Suster S, Fletcher CD. Solitary myofibroma in adults: clinicopathological analysis of a series. Histopathology. 1993;22:335–41.
50. Fukasawa Y, Ishikura H, Takada A, et al. Massive apoptosis in infantile myofibromatosis. A putative mechanism of tumor regression. Am J Pathol. 1994;144:480–5.
51. Fetsch JF, Miettinen M. Calcifying aponeurotic fibroma: a clinicopathologic study of 22 cases arising in uncommon sites. Hum Pathol. 1998;29:1504–10.
52. Paller AS, Gonzalez-Crussi F, Sherman JO. Fibrous hamartoma of infancy. Eight additional cases and a review of the literature. Arch Dermatol. 1989;125:88–91.
53. Popek EJ, Montgomery EA, Fourcroy JL. Fibrous hamartoma of infancy in the genital region: findings in 15 cases. J Urol. 1994;152:990–3.
54. Yoon TY, Kim JW. Fibrous hamartoma of infancy manifesting as multiple nodules with hypertrichosis. J Dermatol. 2006;33:427–9.
55. Sotelo-Avila C, Bale PM. Subdermal fibrous hamartoma of infancy: pathology of 40 cases and differential diagnosis. Pediatr Pathol. 1994;14:39–52.
56. Allen PW. The fibromatoses: a clinicopathologic classification based on 140 cases. Am J Surg Pathol. 1977;1:255–70.
57. Beltraminelli H, Itin P. Pachydermodactyly – just a sign of emotional distress. Eur J Dermatol. 2009;19:5–13.
58. Breiner JA, Nelson M, Bredthauer BD, et al. Trisomy 8 and trisomy 14 in plantar fibromatosis. Cancer Genet Cytogenet. 1999;108:176–7.
59. De Wever I, Dal Cin P, Fletcher CDM, et al. Cytogenetic, clinical and morphologic correlations in 78 cases of fibromatosis: a report from the CHAMP study group. Mod Pathol. 2000;13:1080–5.
60. Desai SS, Hentz VR. The treatment of Dupuytren disease. J Hand Surg Am. 2011;36:936–42.
61. Gelbard MK, Dorey F, James K. The natural history of Peyronie's disease. J Urol. 1990;144:1376–9.
62. Enzinger FM, Zhang RY. Plexiform fibrohistiocytic tumor presenting in children and young adults. An analysis of 65 cases. Am J Surg Pathol. 1988;12:818–26.
63. Jaffer S, Ambrosini-Spaltro A, Mancini AM, et al. Neurothekeoma and plexiform fibrohistiocytic tumor: mere histologic resemblance or histogenetic relationship? Am J Surg Pathol. 2009;33:905–13.

64. Moosavi C, Jha P, Fanburg-Smith JC. An update on plexiform fibrohistiocytic tumor and addition of 66 new cases from the Armed Forces Institute of Pathology, in honor of Franz M. Enzinger, MD. Ann Diagn Pathol. 2007;11:313–19.
65. Fretzin DF, Helwig EB. Atypical fibroxanthoma of the skin. A clinicopathologic study of 140 cases. Cancer 1973;31:1541–52.
66. Dilek FH, Akpolat N, Metin A, Ugras S. Atypical fibroxanthoma of the skin and the lower lip in xeroderma pigmentosum. Br J Dermatol. 2000;143:618–20.
67. Ferrara N, Baldi G, Di Marino MP, et al. Atypical fibroxanthoma with osteoclast-like multinucleated giant cells. In Vivo. 2000;14:105–7.
68. Mirza B, Weedon D. Atypical fibroxanthoma of the skin: a clinicopathological study of 89 cases. Australas J Dermatol. 2005;46:235–8.
69. Taylor HB, Helwig EB. Dermatofibrosarcoma protuberans: a study of 115 cases. Cancer. 1962;15:717–25.
70. Parlette LE, Smith CK, Germain LM, et al. Accelerated growth of dermatofibrosarcoma protuberans during pregnancy. J Am Acad Dermatol. 1999;41:778–83.
71. Ding JA, Hashimoto H, Sugimoto T, et al. Bednar tumor (pigmented dermatofibrosarcoma protuberans). An analysis of six cases. Acta Pathol Jpn. 1990;40:744–54.
72. Aiba S, Tabata N, Ishii H, et al. Dermatofibrosarcoma protuberans is a unique fibrohistiocytic tumour expressing CD34. Br J Dermatol. 1992;127:79–84.
73. Kutzner H. Expression of the human progenitor cell antigen CD34 (HPCA-1) distinguishes dermatofibrosarcoma protuberans from fibrous histiocytoma in formalin-fixed, paraffin-embedded tissue. J Am Acad Dermatol. 1993;28:613–17.
74. Kamino H, Burchette J, Garcia J. Immunostaining for CD34 in plaque and nodular areas of dermatofibrosarcoma protuberans. J Cutan Pathol. 1992;19:530.
75. Pedeutour F, Simon MP, Minoletti F, et al. Translocation, t(17;22)(q22;q13), in dermatofibrosarcoma protuberans: a new tumor-associated chromosome rearrangement. Cytogenet Cell Genet. 1996;72:171–4.
76. Hisaoka M, Okamoto S, Morimitsu Y, et al. Dermatofibrosarcoma protuberans with fibrosarcomatous areas. Molecular abnormalities of the p53 pathway in fibrosarcomatous transformation of dermatofibrosarcoma protuberans. Virchows Arch. 1998;433:323–9.
77. Gloster HM Jr, Harris KR, Roenigk RK. A comparison between Mohs micrographic surgery and wide surgical excision for the treatment of dermatofibrosarcoma protuberans. J Am Acad Dermatol. 1996;35:82–7.
78. Mentzel T, Beham A, Katenkamp D, et al. Fibrosarcomatous ("high-grade") dermatofibrosarcoma protuberans: clinicopathologic and immunohistochemical study of a series of 41 cases with emphasis on prognostic significance. Am J Surg Pathol. 1998;22:576–87.
79. Rutkowski P, Van Glabbeke M, Rankin J, et al. Imatinib mesylate in advanced dermatofibrosarcoma protuberans: pooled analysis of two phase II clinical trials. J Clin Oncol. 2010;28:1772–9.
80. Jha P, Moosavi C, Fanburg-Smith JC. Giant cell fibroblastoma: an update and addition of 86 new cases from the Armed Forces Institute of Pathology, in honor of Dr. Franz M Enzinger. Ann Diagn Pathol. 2007;11:81–8.
81. Harvell JD, Kilpatrick SE, White WL. Histogenetic relations between giant cell fibroblastoma and dermatofibrosarcoma protuberans. CD34 staining showing the spectrum and a simulator. Am J Dermatopathol. 1998;20:339–45.
82. Shmookler BM, Enzinger FM, Weiss SW. Giant cell fibroblastoma. A juvenile form of dermatofibrosarcoma protuberans. Cancer. 1989;64:2154–61.
83. Simon MR, Pedeutour F, Sirvent N, et al. Deregulation of the platelet-derived growth factor B-chain gene via fusion with collagen gene *COL1A1* in dermatofibrosarcoma protuberans and giant-cell fibroblastoma. Nat Genet. 1997;15:95–8.
84. Scott SM, Reiman HM, Pritchard DJ, Ilstrup DM. Soft tissue fibrosarcoma. A clinicopathologic study of 132 cases. Cancer. 1989;64:925–31.
85. Wiklund TA, Blomqvist CP, Raty J, et al. Postirradiation sarcoma. Analysis of a nationwide cancer registry material. Cancer. 1991;68:524–31.
86. Meis-Kindblom JM, Kindblom LG, Enzinger FM. Sclerosing epithelioid fibrosarcoma. A variant of fibrosarcoma simulating carcinoma. Am J Surg Pathol. 1995;19:979–93.
87. Soule EH, Pritchard DJ. Fibrosarcoma in infants and children: a review of 110 cases. Cancer. 1977;40:1711–21.
88. Chase DR, Enzinger FM. Epithelioid sarcoma. Diagnosis, prognostic indicators, and treatment. Am J Surg Pathol. 1985;9:241–63.
89. Callister MD, Bailo MT, Pisters PW, et al. Epithelioid sarcoma: results of conservative surgery and radiotherapy. Int J Radiat Oncol Biol Phys. 2001;51:384–91.
90. Evans HL, Baer SC. Epithelioid sarcoma: a clinicopathologic and prognostic study of 26 cases. Semin Diagn Pathol. 1993;10: 286–91.

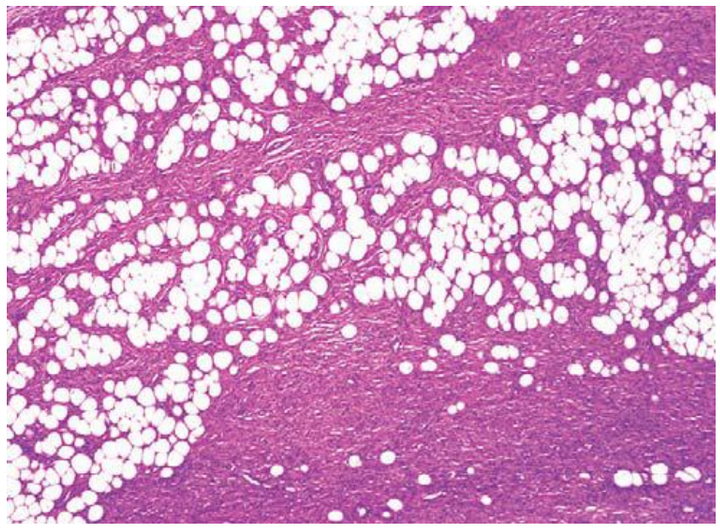


Infarcted skin tag. A pedunculated dark-red papule in the axilla.
Courtesy of the Ronald O. Perelman Department of Dermatology, New York University.



Atypical fibroxanthoma. The spindle cells have pale foamy cytoplasm and hyperchromatic nuclei with small nucleoli. There is also a large atypical giant cell with darker nuclear chromatin as well as a cell in atypical mitosis.

Facial angiofibromas of tuberous sclerosis. There are multiple firm papules of the nose and cheek.
Courtesy of the Ronald O. Perelman Department of Dermatology, New York University.



Dermatofibrosarcoma protuberans, nodular stage. At the base of the tumor, the neoplastic cells infiltrate the subcutaneous tissue to produce a honeycomb pattern.

Dermatofibrosarcoma protuberans. A broad red-brown plaque on the abdomen, with superimposed nodules.

This page intentionally left blank

Muscle, Adipose and Cartilage Neoplasms 117

Steven Kaddu and Sabine Kohler

In this chapter, benign and malignant neoplasms of muscle, adipose tissue and cartilage will be reviewed (Fig. 117.1). The entities include:

- leiomyoma
- leiomyosarcoma
- smooth muscle hamartoma
- lipoma
- angiolipoma
- spindle cell/pleomorphic lipoma
- hibernoma
- nevus lipomatosus superficialis
- lipoblastoma/lipoblastomatosis
- liposarcoma/atypical lipomatous tumor
- extraskeletal chondroma

TUMORS OF SMOOTH MUSCLE

Leiomyoma

Synonyms: ■ Superficial leiomyoma ■ Leiomyoma cutis ■ Superficial benign smooth muscle tumor

Key features

- Three distinct variants: piloleiomyoma, genital leiomyoma and angioleiomyoma
- A solitary or multiple clustered (piloleiomyomas) papules or nodules in an adult
- Piloleiomyomas may be painful
- Multiple piloleiomyomas may be a manifestation of Reed syndrome (multiple cutaneous and uterine leiomyomatosis)
- Smooth muscle cells (myocytes) are fusiform cells with centrally located, cigar-shaped nuclei

Introduction

Superficial (cutaneous) leiomyomas represent benign smooth muscle tumors that can arise from arrector pili muscles, the dartoic, vulvar or mammary smooth muscles, or the muscles enveloping dermal blood vessels. Thus, they are subclassified into piloleiomyomas (solitary or multiple), leiomyomas of the external genitalia, and angioleiomyomas. Some authors categorize vulvar and scrotal leiomyomas separately, based upon distinctive clinical and histologic features[1].

History

In an early review article, Arthur Purdy Stout[2] cites an 1854 publication of Rudolf Virchow as the first case report of multiple leiomyomas involving the skin near the areola in a 32-year-old man.

Epidemiology

Cutaneous leiomyomas are relatively uncommon neoplasms, but their exact incidence is not known[3]. Angioleiomyomas appear to be more common than piloleomyomas[4], with genital leiomyomas the least common variant.

Pathogenesis

The exact pathogenesis of superficial leiomyomas has yet to be determined. Piloleiomyomas are thought to arise from the smooth muscle cells within the arrector pili muscle of the pilosebaceous unit. Leiomyomas of the external genitalia are probably derived from the network of smooth muscles in the external genitalia (e.g. scrotum, vulva) and areolae. Angioleiomyomas are believed to originate from the smooth muscle within the walls of arteries and veins.

Multiple piloleiomyomas may occur sporadically or they may be inherited in an autosomal dominant manner (with variable penetrance) as a component of the multiple cutaneous and uterine leiomyomatosis syndrome, also referred to as Reed syndrome[5] (Table 117.1). Although the molecular basis of Reed syndrome is known (mutations in the gene that encodes fumarate hydratase), how this translates into smooth muscle tumors is not understood.

Clinical features

Piloleiomyomas can be solitary or multiple, and in an occasional patient may even number in the hundreds. They present as firm, reddish-brown to skin-colored papules or nodules. Solitary piloleiomyomas develop primarily during adulthood and there is an approximately equal sex distribution[6]; rare congenital or pediatric cases have been reported. When multiple, the distribution pattern is most often clustered (Fig. 117.2), linear or along Blaschko's lines, but widespread lesions are observed occasionally. Most piloleiomyomas measure 1–2 cm in diameter, and they usually develop on the extremities and trunk (especially the shoulder), with solitary lesions favoring the limbs and multiple lesions the trunk[6]. Piloleiomyomas are often associated with spontaneous or induced pain, e.g. following cold exposure, but the explanation is still unclear[6].

Genital leiomyomas are most often solitary and painless. They can develop on the vulva, penis, scrotum, nipple or areola and usually measure less than 2 cm in diameter. Occasionally, lesions are pedunculated.

Angioleiomyomas most commonly present as a solitary, firm subcutaneous nodule on the lower extremity. They often develop in women during the fourth to sixth decades of life[4]. Approximately 50% of angioleiomyomas are painful.

Pathology

Piloleiomyomas are typically centered within the reticular dermis, with focal extension into the subcutaneous fat in some cases. They are composed of interlacing fascicles of relatively bland smooth muscle cells (myocytes) which peripherally tend to ramify between surrounding dermal collagen bundles (Fig. 117.3); often there is a close relationship to hair follicles[4]. Occasionally, the overlying epidermis is hyperplastic. Smooth muscle cells have abundant brightly eosinophilic cytoplasm and blunt-ended, cigar-shaped nuclei.

Mitotic figures are rare. In the presence of bland cytology, one or two morphologically normal mitotic figures per 10 high-power fields may be seen, which does not signify aggressive behavior. Cases with nuclear pleomorphism and atypical nuclei, but without mitotic activity (symplastic leiomyomas), have also been described[7].

In leiomyomas, smooth muscle differentiation is usually obvious in H&E-stained sections. Sometimes, special stains for smooth muscle cells are utilized, including Masson's trichrome stain (cells stain red) and immunohistochemical stains for smooth muscle actin and desmin (cells are consistently positive). Other smooth muscle-associated markers include smooth muscle myosin (SMS), calponin and h-caldesmon, but the first two markers in particular may also be expressed in other spindle cell tumors[8]. In contrast to uterine leiomyomas, smooth muscle tumors of the skin do not express receptors for estrogen or progesterone[9].

Genital leiomyomas of the scrotum or vulva tend to be larger and better circumscribed than piloleiomyomas. Scrotal leiomyomas are

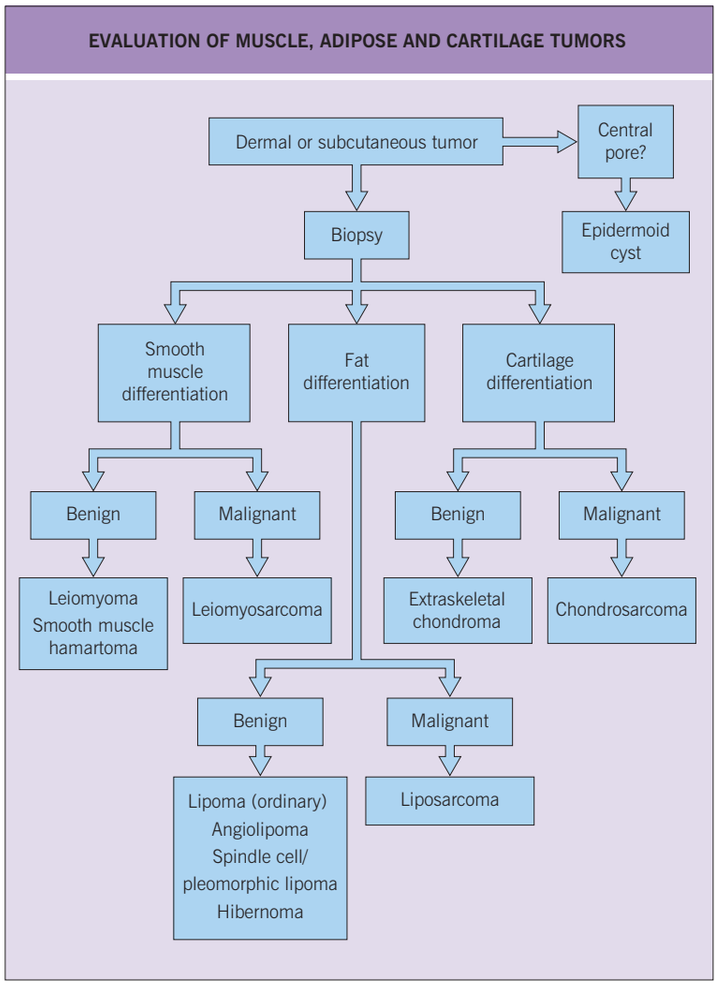


Fig. 117.1 Evaluation of muscle, adipose and cartilage tumors.

CLINICAL FEATURES OF MULTIPLE CUTANEOUS AND UTERINE LEIOMYOMATOSIS (REED SYNDROME)	
Genetic aspects	• Autosomal dominant • Mutations in the gene that encodes fumarate hydratase, an enzyme in the mitochondrial Krebs cycle
Clinical features	• Cutaneous leiomyomas: appear during the second to fourth decade and multiple painful, grouped, skin-colored to red-brown papules during the second to fourth decades • Uterine leiomyomas: >90% of affected women; menorrhagia and pelvic pressure or pain • Renal cell cancer: 1–17% of families with syndrome; most commonly type II papillary renal cell carcinomas that are often early-onset and aggressive (metastases in >50% of patients)
Screening of individuals with multiple cutaneous leiomyomas	• Abdominal and pelvic ultrasound (or CT scan) • Complete history and physical examination, including pelvic examination in women • Genetic testing for mutations in the fumarate hydratase gene
Patients with confirmed Reed syndrome	• Complete history and physical examination yearly, including pelvic examination in women • Repeat abdominal and pelvic ultrasound (or CT scan or MRI) every 2 years • Complete physical examination (including pelvic examination in women) of first-degree family members and other family members as indicated; abdominal and pelvic ultrasound as indicated

Table 117.1 Clinical features of multiple cutaneous and uterine leiomyomatosis (Reed syndrome). Other reported features that may not be directly related to the syndrome include tumors of the breast, prostate, bladder and testis, Leydig cell tumors, adrenal gland adenomas, ovarian and kidney cysts, and cerebral cavernomas.

Fig. 117.2 Clustered piloleiomyomas on the back. The trunk is a common location for multiple piloleiomyomas. Patients with this clinical presentation need to be evaluated for the possibility of Reed syndrome (see Table 117.1).

usually homogeneous spindle cell tumors, while vulvar lesions may demonstrate an epithelioid cytology, myxoid changes, and/or hyalinization[1]. Leiomyomas of the nipple closely resemble piloleiomyomas.

Angioleiomyomas are usually well-circumscribed tumors centered within the superficial subcutis. They are composed of bland smooth muscle cells compactly arranged into bundles and whorls around thick-walled vascular channels[4] (Fig. 117.4). Degenerative changes including hyalinization, focal thrombosis, myxoid changes, dystrophic calcification, pyknotic nuclear atypia and fat foci may be present.

Differential diagnosis

For single lesions, the clinical differential diagnosis includes other dermal nodules such as a dermatofibroma, adnexal tumor or fibrosed epidermoid inclusion cyst and the diagnosis is based upon histologic findings. When a lesion is painful or there is clustering of multiple red–brown papulonodules, the diagnosis may be strongly considered prior to biopsy.

Histopathologically, leiomyomas need to be distinguished from other spindle cell tumors with fibrohistiocytic or peripheral nerve sheath differentiation. The differences between leiomyomas and leiomyosarcomas are discussed below.

Treatment

Simple excision is usually curative for solitary or limited tumors. For those tumors that are not amenable to surgery because of their number or location, treatment with gabapentin, medications that reduce smooth muscle contraction (e.g. nifedipine, nitroglycerin, doxazosin), cryotherapy or CO_2 laser ablation may provide relief from pain[10,11]. The experience with mitotically active leiomyomas is very limited. There are no definitive criteria for distinguishing mitotically active leiomyomas from leiomyosarcomas and there is significant overlap between these two entities. It would, therefore, appear prudent to completely excise mitotically active leiomyomas.

Leiomyosarcoma

Synonyms: ■ Superficial leiomyosarcoma ■ Superficial malignant smooth muscle tumor

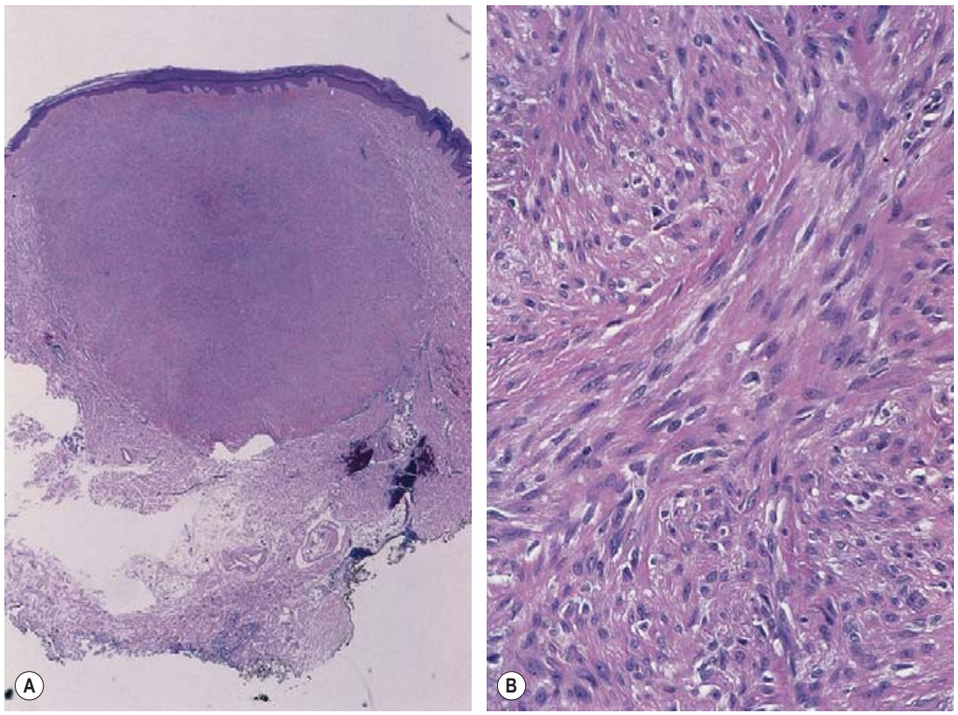


Fig. 117.3 Piloleiomyoma. A Piloleiomyoma centered in the reticular dermis forming a nodule with fascicles of myocytes interdigitating between collagen bundles at its periphery. **B** The center of the lesion shows intersecting fascicles of smooth muscle cells which have eosinophilic cytoplasm and elongated nuclei. The latter are described as cigar-shaped.

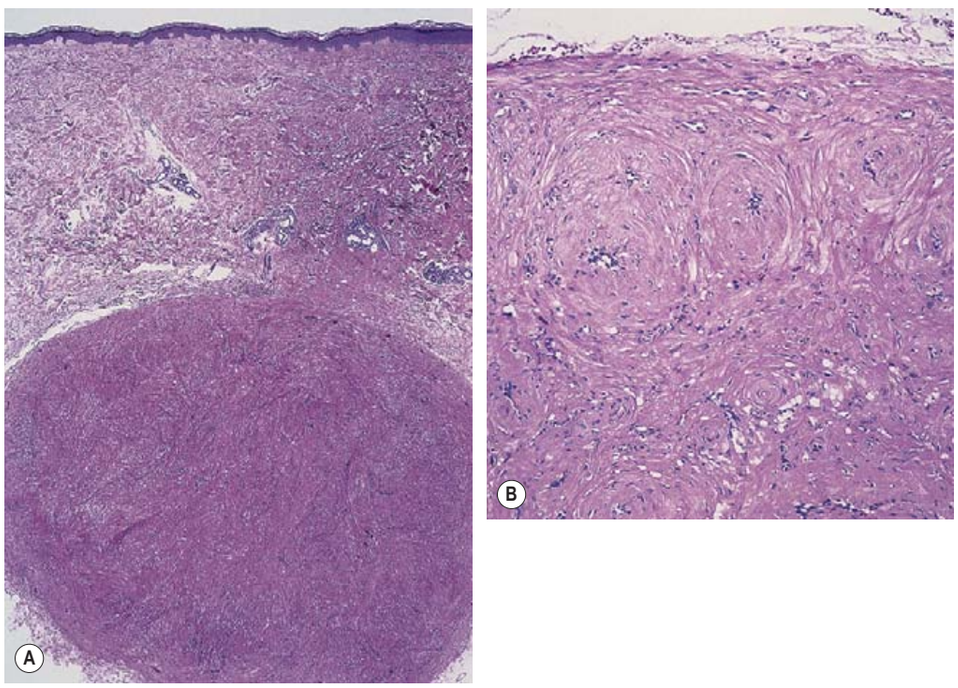


Fig. 117.4 Angioleiomyoma. A Angioleiomyomas are well circumscribed and often located in the deep dermis, extending into the subcutis. **B** At higher magnification, thick-walled vessels are surrounded by bundles of smooth muscle cells.

Key features

- Malignant smooth muscle neoplasms
- Occur primarily in adults older than 50 years of age
- Most commonly located on the extremities, in particular the lower leg
- *Dermal* leiomyosarcomas are typically cured by simple excision and rarely metastasize; *subcutaneous* leiomyosarcomas require wide excision and have a 25–40% risk of metastasis

Introduction

For management and prognostic reasons, it is important to differentiate between "superficial leiomyosarcomas" that are limited to the dermis, and lesions that primarily arise in or extensively involve the subcutis. The former have a favorable prognosis, can recur, but very rarely metastasize. Subcutaneous leiomyosarcomas, in contrast, metastasize in approximately 25–40% of cases[12,13].

Epidemiology

Cutaneous and subcutaneous leiomyosarcomas are rare neoplasms, comprising only 4.0–6.5% of soft tissue sarcomas[14,15].

Pathogenesis

Dermal leiomyosarcomas are thought to arise from either arrector pili or genital smooth muscles. Subcutaneous leiomyosarcomas probably originate from vascular smooth muscle. Anecdotal reports describe a rare association with trauma and radiation[15,16].

Clinical features

Cutaneous and subcutaneous leiomyosarcomas classically present as a solitary, firm, skin-colored to red–brown nodule or plaque. Dermal tumors range from 0.5 to 4 cm in diameter[17], while subcutaneous lesions tend to be larger. Sometimes the tumors are painful or become ulcerated. Leiomyosarcomas favor the extremities, in particular the lower leg of older adults (Fig. 117.5)[4,17,18]. There is a slight male preponderance[4]. Patients with multiple tumors should be evaluated to exclude the possibility of metastases due to a primary retroperitoneal or visceral leiomyosarcoma.

Pathology

The histopathologic features of leiomyosarcomas span a morphologic continuum that, at the well-differentiated end, demonstrates an overlap with leiomyomas, while poorly differentiated lesions closely resemble atypical fibroxanthomas or "malignant fibrous histiocytomas". Leiomyosarcomas of moderate differentiation are comprised of cells that cytologically resemble normal smooth muscle cells. Compared with leiomyomas, malignant smooth muscle tumors are more cellular, exhibit cytologic atypia, and contain easily identifiable mitotic figures (Fig. 117.6). At least focally, the spindle cells are arranged in fascicles. Cytologically, poorly differentiated leiomyosarcomas may resemble myofibroblastic or fibrohistiocytic tumors. Notably, the degree of differentiation may vary within a single tumor.

While a leiomyoma is usually recognized morphologically, the diagnosis of leiomyosarcoma often requires adjuvant special stains and/or immunohistochemical studies to support the cell lineage. Historically, red staining of the cytoplasm on Masson's trichrome stain was used to support smooth muscle differentiation. Nowadays, immunophenotypic studies with antibodies to smooth muscle actin and desmin represent the standard of care. Of the two markers, actin is more sensitive and desmin is somewhat more specific. Unfortunately, neither of these markers is entirely specific for smooth muscle differentiation, and reactivity (especially for actin) may also be observed in myofibroblasts and fibroblasts. However, negative staining with an antibody to smooth muscle actin would strongly argue against smooth muscle differentiation. Additional smooth muscle-associated markers include smooth muscle myosin (SMS), calponin and h-caldesmon, but the first two markers in particular may also be expressed in myofibroblastic tumors[8,17]. Careful consideration of morphologic features and use of multiple immunohistochemical stains are essential for the diagnosis of leiomyosarcoma.

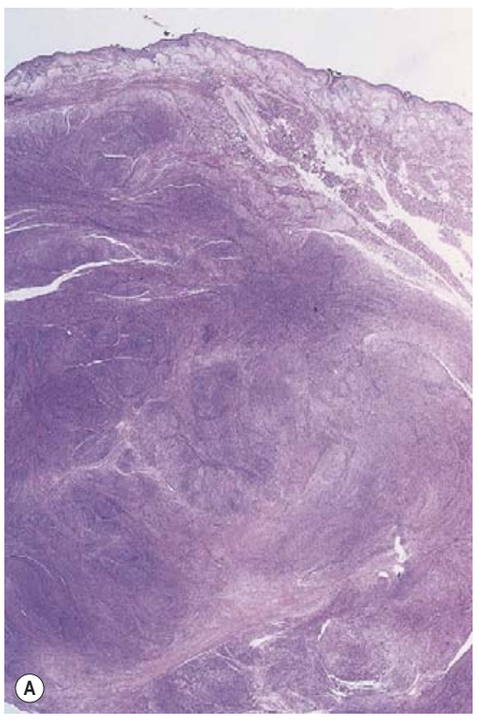
Rarely, leiomyosarcomas have an epithelioid cytology[19]. These neoplasms are usually actin-positive and desmin-negative, but they seem to possess a clinical behavior similar to that of ordinary leiomyosarcomas.

By definition, dermal leiomyosarcomas are superficial malignant smooth muscle neoplasms with at least 90% of the tumor confined to the dermis[20]. They are usually poorly circumscribed and are composed of spindle cells; the latter are focally arranged in fascicles that infiltrate between adjacent collagen bundles. In comparison, subcutaneous leiomyosarcomas tend to be better circumscribed and may be surrounded by a pseudocapsule of compressed tissue.

Fig. 117.5 Leiomyosarcoma. Two hyperpigmented tumor nodules on the lower extremity. *Courtesy, Lorenzo Cerroni, MD.*

Differential diagnosis

Because the clinical features are not unique, the differential diagnosis includes a number of tumors that can present as a solitary firm nodule or plaque (e.g. dermatofibrosarcoma protuberans, other soft tissue



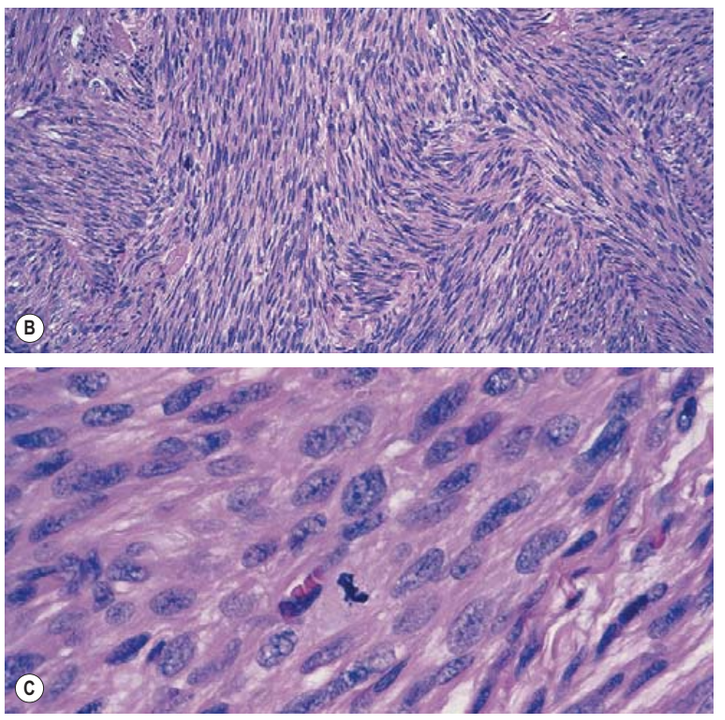


Fig. 117.6 Leiomyosarcoma. A A large tumor extending from the upper reticular dermis deep into the subcutis. **B** At higher magnification, this neoplasm is more cellular than a leiomyoma. The nuclei are pleomorphic, more hyperchromatic, and have coarse chromatin. **C** Mitotic figures are numerous and are easily identified.

IMMUNOHISTOCHEMICAL FINDINGS IN LEIOMYOSARCOMA RELATIVE TO OTHER SPINDLE CELL TUMORS					
	Leiomyosarcoma	SCC	Melanoma	Nerve sheath tumors	AFX/MFH
Actin	+	–	–	–	±
Desmin	±	–	–	–	–
Cytokeratin	–	+	–	–	–
S100 protein	–	–	+	+	–
CD68	–	–	±	–	±

Table 117.2 Immunohistochemical findings in leiomyosarcoma relative to other spindle cell tumors. AFX, atypical fibroxanthoma; MFH, malignant fibrous histiocytoma; SCC, spindle cell squamous carcinoma. CD68 is a glycoprotein expressed by monocytes and macrophages.

sarcomas), a fibrosed epidermoid inclusion cyst, and, less often, panniculitis (e.g. lipodermatosclerosis).

The histopathologic differential diagnosis usually raises two problems: the differentiation of leiomyosarcoma from leiomyoma and its delineation from other spindle cell neoplasms. Traditionally, the number of mitotic figures is used as the most reliable diagnostic criterion when trying to predict clinical behavior. In the presence of cytologic atypia, a mitotic rate of one or more mitotic figures per high-power field is generally considered to be indicative of malignancy[14]. It is important to remember, however, that the prognosis of leiomyosarcomas appears to depend more on the depth of involvement (dermal vs subcutaneous), and that the extent of mitotic activity is probably more important in subcutaneous lesions. Necrosis and angiolymphatic invasion are generally not useful for predicting prognosis of patients with dermal and subcutaneous leiomyosarcomas.

The distinction of leiomyosarcoma from other dermal spindle cell neoplasms nearly always requires immunophenotyping. This is best approached by using a panel of antibodies that examine the neoplasm for its line of differentiation (Table 117.2). A standard panel consists of antibodies to actin, desmin, keratin, S100 protein and CD68. Leiomyosarcoma will usually be actin-positive and desmin-positive, but negative for keratin, S100 protein and CD68. Other dermal and subcutaneous spindle cell neoplasms that are often in the differential diagnosis include spindle cell squamous carcinoma (keratin-positive), spindle cell and desmoplastic melanoma (S100-positive), nerve sheath tumors (S100-positive), atypical fibroxanthoma (AFX)/malignant fibrous histiocytoma (MFH), and nodular fasciitis. It is important to remember that cutaneous leiomyosarcomas can rarely express cytokeratins[4].

Treatment

Wide excision with meticulous examination of all surgical margins is crucial in order to prevent recurrence. Recurrent tumors tend to infiltrate more deeply, and they are often less well differentiated. They are more difficult to treat and carry a higher risk of metastasis. Several authors have reported successful treatment with Mohs micrographic surgery[15], allowing for complete margin control.

Complete surgical excision of a primary dermal leiomyosarcoma can be curative. Local recurrences, due to incompletely excised tumors, are unusual and metastases rarely, if ever, develop. Recently, some authors have even suggested using the term "atypical intradermal smooth muscle neoplasm".[20a] Subcutaneous leiomyosarcomas metastasize in 25–40% of patients. The risk of metastasis appears to be related to size, as metastasis is unlikely in tumors <5 cm in diameter. Metastatic spread occurs hematogenously to the lung and, less often, other visceral organs, or via the lymphatics to regional lymph nodes[16,20].

Smooth Muscle Hamartoma

Key features

- Congenital or acquired skin-colored to hyperpigmented plaque on the trunk or proximal extremities
- Commonly exhibit follicular prominence and/or hypertrichosis
- Clinical and histopathologic overlap with Becker's nevus (melanosis)

Fig. 117.7 Smooth muscle hamartoma. This infant presented with a firm plaque on the thigh. *Courtesy, Ronald P Rapini, MD.*

Introduction

Hamartoma is derived from the Greek word *hamartanein*, which means "to err" or "to fail". Hamartomas are defined as lesions that are: (1) most commonly present at birth, but can also be acquired; and (2) are composed of aberrant mature or nearly mature structures. The term hamartoma is synonymous with "nevus", for example, nevus sebaceus, apocrine nevus, eccrine nevus. A smooth muscle hamartoma may be congenital or acquired and may be associated with a Becker's nevus (melanosis).

History

The first description of a smooth muscle hamartoma is attributed to Stokes in 1923[21].

Epidemiology

The estimated incidence ranges from 1 : 1000 to 1 : 27 000 live births.

Clinical features

Smooth muscle hamartomas not associated with a Becker's nevus present as firm, skin-colored or hyperpigmented plaques, most commonly located on the trunk, buttocks or proximal extremities (Fig. 117.7). Surface changes may be present in the form of small follicular papules or hypertrichosis. Lesions with hypertrichosis and hyperpigmentation overlap with a Becker's nevus (see Ch. 112). These hamartomas are most often solitary, but may be multiple. Extensive lesions can present as large areas of hypertrichotic skin with dimpling (accentuated upon exposure to cold) and/or folding, and generalized involvement may produce a "Michelin tire baby" phenotype (see Table 97.6)[22]. Rubbing of the plaque may result in a pseudo-Darier's sign, consisting of transient induration of the affected area.

Pathology

Well-defined and thickened bundles of smooth muscle are haphazardly distributed throughout the dermis. Connections with hair follicles may

be present. The epidermis is often acanthotic and has hyperpigmentation of the basal layer.

Differential diagnosis

Clinically and histologically, smooth muscle hamartomas demonstrate overlap with Becker's nevus, and the two lesions possibly represent a spectrum of phenotypic expression of the same process. Leiomyomas usually present as papulonodules rather than plaques. Additional entities in the clinical differential diagnosis are congenital melanocytic nevus and neurofibroma. Histologically, the smooth muscle fibers in a piloleiomyoma aggregate to form dermal tumors with irregular margins, but they are not haphazardly scattered throughout the dermis as in a smooth muscle hamartoma.

Treatment

Therapy may be indicated for cosmetic reasons. A small lesion may be amenable to excision. Treatment of Becker's nevi with lasers that target melanin (e.g. Q-switched ruby laser) lead to modest, if any, improvement[23].

Fig. 117.8 Familial multiple lipomatosis. Several discrete lipomas are present on the forearm.

TUMORS OF FAT

Lipoma

Key features

- Common benign tumor of mature fat
- Asymptomatic, soft, subcutaneous nodule arising at any site
- Multiple lipomas are seen in familial multiple lipomatosis, Madelung's disease, adiposis dolorosa, Gardner syndrome, Bannayan–Riley–Ruvalcaba syndrome and Proteus syndrome

Introduction

(Ordinary) lipomas are benign tumors composed of mature lipocytes. They are among the most common neoplasms in humans, and they represent the most common mesenchymal neoplasm[24]. Lipomas are often solitary, but 5–10% of patients have multiple lipomas, usually in the setting of a lipomatosis or less often a multisystem syndrome.

Epidemiology

Lipomas develop at any age, but they usually become clinically apparent between the fourth and sixth decades of life. Most studies report the incidence of lipomas to be slightly higher in men than in women[24].

Pathogenesis

Little is known about the pathogenesis of lipomas and the vast majority represent an incidental finding. Of note, the incidence of lipomas is increased in overweight individuals, diabetics, and patients with elevated serum cholesterol[24]. In familial multiple lipomatosis, there is clearly a genetic component.

Clonal chromosomal aberrations are found within lipomas in approximately two-thirds of patients. The abnormalities are heterogeneous and most commonly consist of translocations between 12q13–15 and various other chromosomes. This 12q13–15 region contains the gene *HMGA2* (*HMGIC*) which encodes a transcriptional regulatory factor that is a member of the *h*igh-*m*obility *g*roup (non-histone chromosomal) protein family[25]; of note, this region is amplified in well-differentiated liposarcomas.

Clinical features

Classically, lipomas present as solitary, painless, soft (to rubbery), mobile, subcutaneous nodules, with a normal overlying epidermis[4]. They are often oval in shape and may feel multilobular. Most lipomas measure a few centimeters in diameter, but occasionally reach over 10 cm in size. Although lipomas may develop within any fatty tissue, sites of predilection are the neck, proximal extremities, forearms and buttocks; lipomas also occur on the trunk, but are very rarely seen on the hands and feet. They present primarily in adults over the age of 30 years.

Lipomas usually exhibit an initial slow growth phase, then remain stable in size with no tendency to involute. The rate of growth may accelerate during periods of weight gain, but weight loss, even when extreme, does not seem to affect their size. Weight loss, however, may result in lipomas becoming more clinically apparent.

Multiple lipomas may be observed in patients with a lipomatosis or in the setting of a multisystem syndrome, such as Proteus syndrome.

Infiltrating or diffuse lipomatosis is characterized by non-encapsulated mature fat infiltrating subcutaneous tissue, muscle, skin, and, at times, even fascia and bone. This entity usually occurs before 30 years of age and is rarely congenital. Diffuse lipomatosis has been described in association with tuberous sclerosis (see Ch. 61) and paralytic poliomyelitis[26–28]. The lower extremities are most commonly affected, but involvement of the head, neck, face and upper extremities have all been reported. Pelvic involvement may lead to urinary tract, intestinal, and even vena caval obstruction[29].

Familial multiple lipomatosis is also known as familial multiple lipomas, multiple circumscribed lipomas, hereditary multiple lipomas, and discrete lipomatosis (Fig. 117.8). This disorder is characterized by multiple lipomas occurring in several members of one kindred. In contrast to benign symmetric lipomatosis (Madelung's disease), the tumors are discrete, mobile, and surrounded by a capsule, as opposed to the diffuse and infiltrative tumor growth observed in Madelung's disease[30]. Favored sites include, but are not limited to, forearms and thighs. The neck and shoulders are generally spared.

Proteus syndrome is a complex disorder due to mosaicism for an activating mutation in the **AKT1** oncogene. It is characterized by asymmetric, disproportionate (i.e. progressive and distorting) overgrowth of multiple tissues and multiple hamartomatous malformations (see Ch. 62). Although this syndrome has a highly variable phenotype[31], clinical criteria include a mosaic distribution of lesions, progressive course, and sporadic occurrence. The tissue overgrowth is progressive until after adolescence, but then seems to plateau.

Lipomatosis arising in the setting of Proteus syndrome is associated with overgrowth of multiple tissues in a mosaic pattern, and this can lead to partial gigantism of the head or limbs, vascular malformations and skeletal deformities as well as areas of lipoatrophy[32]. Connective tissue nevi (particularly cerebriform lesions on the palms and soles) and epidermal nevi are also commonly observed in these patients.

Hemihyperplasia–multiple lipomatosis syndrome is a related but distinct condition characterized by multiple lipomas in association with asymmetric (but non-progressive and non-distorting) overgrowth, mild macrodactyly, cutaneous capillary malformations, and thickened plantar skin with prominent creases. Additional entities with lipomatosis include **CLOVE syndrome**, which is characterized by *c*ongenital *l*ipomatous *o*vergrowth (typically not progressive), *v*ascular malformations and *e*pidermal nevi, and individuals with Proteus-like features who have germline mutations in *PTEN* (plus a second hit in affected

Fig. 117.9 Benign symmetric lipomatosis (Madelung's disease). Large symmetric fatty deposits in the supraclavicular region, lateral chest, and abdomen.

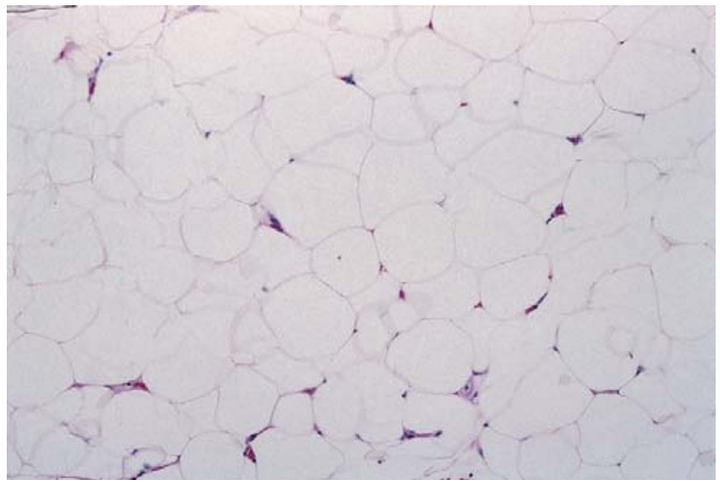


Fig. 117.10 Lipoma (ordinary). A uniform population of mature adipocytes with small and eccentric nuclei is seen.

tissues) and develop *s*egmental *o*vergrowth, *l*ipomatosis, *a*rteriovenous *m*alformations, and *e*pidermal *n*evi (**SOLAMEN**)[33].

Benign symmetric lipomatosis is also known as Madelung's disease in the American literature[34] and as benign symmetric lipomatosis of Launois–Bensaude in the European literature[35]. It consists of extensive symmetric fat deposits in the head, neck, and shoulder girdle area (Fig. 117.9). When the mediastinum is involved, complications related to a space-occupying mass may ensue. Most patients are men, and a high percentage suffer from alcoholism; this may account for several disorders reported in association with benign symmetric lipomatosis, such as peripheral neuropathy, squamous cell carcinomas of the head and neck, and macrocytic anemia. Mutations in the mitochondrial tRNA lysine gene (which also result in neuropathy) have been described in a subset of patients with benign symmetric lipomatosis.

Multiple painful lipomas are present primarily on the arms, trunk, and in the periarticular soft tissue in **adiposis dolorosa (Dercum disease)**. This disease most commonly affects postmenopausal women, and it is associated with weakness and psychiatric symptoms such as depression[36]. Pain is intermittent, but it may be debilitating, necessitating sophisticated pain management. Pain is caused by lipomas compressing adjacent nerves. Lipomas may be part of **Gardner syndrome**. This syndrome consists of polyposis of the colon (eventuating in colonic carcinoma unless there is surgical intervention), odontomas, multiple epidermoid cysts, osteomas, leiomyomas and desmoid fibromatosis (see Ch. 63). Congenital hypertrophy of the retinal pigment epithelium (CHRPE) is an early characteristic finding in Gardner syndrome. Mutations in the *APC* gene are responsible for this syndrome as well as familial adenomatous polyposis.

Multiple lipomas are also seen in **Bannayan–Riley–Ruvalcaba syndrome**, an autosomal dominantly inherited hamartoma syndrome. The characteristic constellation of findings has been described under at least five different eponyms, including Riley–Smith syndrome (1960), Bannayan–Zonana syndrome (1971), Ruvalcaba–Myre syndrome (1980) and Bannayan–Riley–Ruvalcaba syndrome (1980). Cutaneous manifestations include pigmented macules on the penis, multiple acrochordons, multiple lipomas, and "hemangiomas" (which actually represent vascular anomalies)[37,38].

Bannayan–Riley–Ruvalcaba syndrome and Cowden disease are allelic genetic disorders. Both are due to mutations in the tumor suppressor gene *PTEN* (*p*hosphatase and *ten*sin homolog deleted from chromosome 10). As outlined in Table 63.3, these two disorders have overlapping features, including lipomas, and exist along a disease spectrum[27]. Nowadays they are often referred to as the PTEN hamartoma tumor syndrome.

Pathology

Lipomas are composed of a uniform population of mature fat cells with small, uniform and eccentric nuclei (Fig. 117.10). The fat cells are arranged in lobules with capillaries scattered throughout the lesion. Mitotic figures are absent. Microscopically, lipomas may be indistinguishable from mature adipose tissue. Some lipomas contain lipocytes with intranuclear vacuoles that need to be distinguished from lipoblasts. Fibrolipoma and myxolipoma represent lipomas with an admixture of significant amounts of fibrous tissue and myxoid stroma, respectively. Occasionally, foci of cartilaginous tissue and osseous metaplasia may be present. Secondary changes, due primarily to trauma, include focal fat necrosis and/or aggregates of foamy macrophages and these changes may pose diagnostic difficulties.

Differential diagnosis

Clinically, lipomas may be mistaken for epidermoid cysts, hibernomas, and other special variants of benign fatty tumors. On the forehead, for example, a subfrontalis lipoma is often misdiagnosed as an epidermoid inclusion cyst. As lipomas are histologically indistinguishable from normal fat, a definitive diagnosis may not be possible in some patients.

Treatment

Small solitary lipomas are usually cured by simple excision. Local recurrence after excision is more common with larger-sized lipomas. Larger lesions, or systemic lipomatoses, may be amenable to liposuction.

Angiolipoma

Key features

- Soft subcutaneous nodule, usually less than 2 cm in diameter
- Typically located on the forearms of young adults
- More often painful than ordinary lipomas
- Well-circumscribed lesion composed of mature fat cells intermingled with small, focally thrombosed vessels

Introduction

Angiolipomas are benign subcutaneous tumors composed of mature fat and a vascular component.

Epidemiology

Patients with angiolipomas are typically young adults in their late teens or early twenties. About 5% of cases are familial.

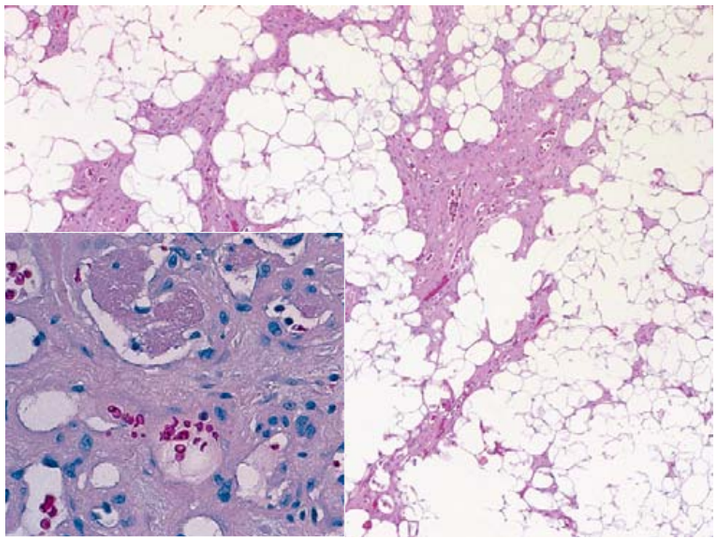


Fig. 117.11 Angiolipoma. In angiolipomas, mature fat is admixed with a variable number of small vessels. Occasional vessels are occluded by fibrin thrombi (insert).

Pathogenesis

The pathogenesis of angiolipomas is not known. A small number of cases are familial, thus suggesting a genetic component. Unlike lipomas, hibernomas and many other fatty tumors, angiolipomas have a normal karyotype.

Clinical features

Angiolipomas usually measure less than 2 cm in diameter and are clinically similar to ordinary lipomas. However, they may be painful. In approximately two-thirds of patients, the tumors are found on the forearms. Other, less common, sites include the trunk and upper arms. An estimated two-thirds of patients have multiple tumors[24].

Pathology

On cut sections, angiolipomas are well-circumscribed or encapsulated yellow tumors with a reddish tinge. Histologically, mature adipose tissue is admixed with a variable number of small vessels (Fig. 117.11). Occasional blood vessels are occluded by fibrin thrombi. The degree of vascularity varies among different lesions and within different areas of the same tumor. Tumors with a predominantly vascular component may be difficult to distinguish from a vascular neoplasm. There is a cellular variant which is characterized by dense cellular angiomatous tissue with a prominent number of spindle cells. Mast cells are more numerous than in ordinary lipomas, and older lesions may contain areas of fibrosis.

Differential diagnosis

Clinically, angiolipomas cannot be reliably distinguished from other benign fatty tumors, although the presence of pain may hint towards a diagnosis of angiolipoma. The histopathologic differential diagnosis includes ordinary lipoma, and no lower threshold exists for the minimal number of vessels required to warrant the diagnosis of angiolipoma. The identification of thrombosed vessels may be helpful in this situation, as they are usually not seen in ordinary lipomas. Highly vascular or cellular angiolipomas may be difficult to distinguish from Kaposi sarcoma, spindle cell lipoma and spindle cell hemangioendothelioma.

Treatment

Surgical excision is curative and, to date, no malignant transformation has been reported. Angiolipomas tend to be more circumscribed than ordinary lipomas and are therefore more readily excised *in toto*.

Spindle Cell/Pleomorphic Lipoma

Key features

- Solitary, subcutaneous nodule on the upper back of middle-aged to older men
- Histologic triad of spindle cells, mature fat cells, and strands of dense collagen
- Pleomorphic lipomas also contain an admixture of floret-like cells

Introduction

Spindle cell and pleomorphic lipomas represent a group of histologically distinct tumors composed of mature fat cells, a population of spindle cells, and strands of dense collagen. Pleomorphic lipomas also contain an admixture of bizarre, often multinucleated cells ("floret-like cells"). Not only do spindle cell and pleomorphic lipomas share common karyotypic abnormalities (rearrangements of 13q and 16q), but tumors with intermediate histopathologic features (between classic spindle cell lipoma and pleomorphic lipoma) are sometimes observed. Spindle cell/pleomorphic lipomas usually develop on the posterior neck, upper back and shoulders of middle-aged and older men, and their clinical appearance is similar to other fatty tumors.

History

Spindle cell lipoma was first described by Enzinger and Harvey in 1975[39].

Epidemiology

Although these tumors have occasionally been reported in women and young men, the vast majority of spindle cell and pleomorphic lipomas have been observed in middle-aged to older men[39].

Pathogenesis

The pathogenesis of spindle cell and pleomorphic lipomas is unknown. Only a small fraction of cases occurs in a familial setting. The spindle cells in spindle cell and pleomorphic lipomas probably represent undifferentiated mesenchymal cells. The causal relationship between the chromosomal abnormalities and tumor formation is not known.

Clinical features

A spindle cell/pleomorphic lipoma presents as a solitary, slowly growing, mobile and painless subcutaneous nodule without epidermal changes. The most common locations are the posterior neck, upper back and shoulders, but these tumors can develop in other sites, including the breast, upper aerodigestive tract, and orbit[24]. Multiple spindle cell lipomas and familial cases are rare.

Pathology

Histopathologically, the diagnosis of spindle cell lipoma requires the presence of three components, admixed in varying proportions: (1) mature fat cells; (2) small, uniform spindle cells; and (3) strands of dense, eosinophilic ("ropey") collagen[40] (Fig. 117.12). In some tumors, variable myxoid areas are seen, whereas in others, spindle cells may predominate; mature fat cells may even be inconspicuous or absent. The spindle cells have bland, uniform nuclei and pale eosinophilic "bipolar" cytoplasm. Other possible histologic features include foci with nuclear palisading, cleft-like spaces and numerous mast cells.

Pleomorphic lipomas are characterized by the presence of mature adipocytes admixed with a variable number of bizarre, multinucleated cells ("floret-like cells") and occasional lipoblasts (Fig. 117.13). By immunohistochemistry, the spindle cells in both spindle cell and pleomorphic lipomas are CD34-positive and rarely S100-positive.

Differential diagnosis

Clinically, spindle cell/pleomorphic lipomas are indistinguishable from other benign superficial lipomatous tumors, with anatomic location being the most characteristic finding. The histopathologic appearance

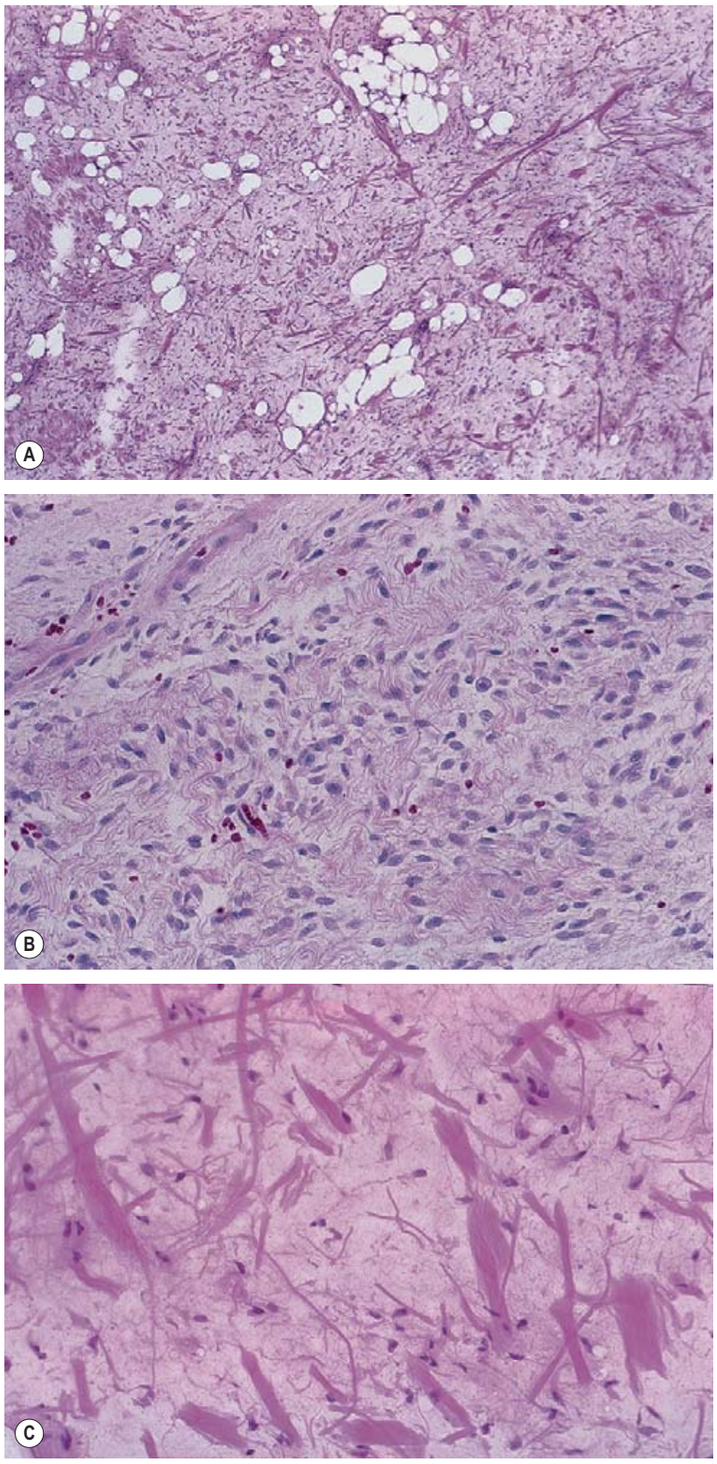


Fig. 117.12 Spindle cell lipoma. A This low-power photomicrograph shows all three components of a spindle cell lipoma – spindle cells, mature fat cells, and "ropey" collagen. **B** The spindle cells are small, uniform, bland, and have inconspicuous cytoplasm. **C** High magnification of thick, "ropey" collagen.

is characteristic, and diagnostic problems should arise only when the spindle cell population is predominant. In the latter situation, immunophenotyping may be helpful. Nodular fasciitis is actin-positive and CD34-negative. Neurofibroma and schwannoma are also in the differential diagnosis, but these tumors are S100-positive.

Treatment

Surgical excision is curative for this benign tumor. It is rare for spindle cell lipomas to recur after complete excision.

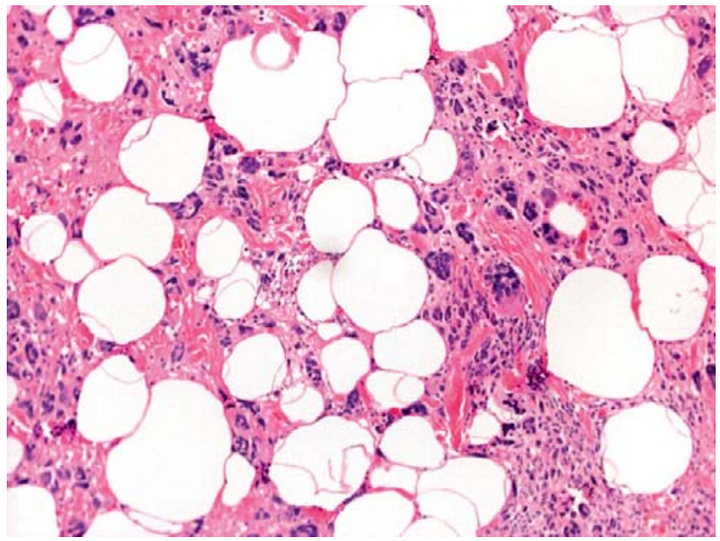


Fig. 117.13 Pleomorphic lipoma. Numerous floret-like multinucleate cells are present in this tumor. Sometimes only a few floret-like multinucleate cells are seen and the majority of cells are mature adipocytes.

Hibernoma

Synonyms: ■ Lipoma of immature adipose tissue ■ Lipoma of embryonic fat ■ Fetal lipoma

Key features

- Rare benign fatty tumor derived from brown fat
- Except for a larger average size, clinically indistinguishable from a lipoma
- The most common locations are the interscapular area, thighs, neck and chest

Introduction

A hibernoma is a rare benign tumor that is derived from brown fat. Brown fat is prominent in hibernating animals, but it is also found in humans. Brown fat first appears in the human fetus and persists into childhood. In children, brown fat is most prominent in the interscapular area, neck, mediastinum, anterior abdominal wall, and around some of the intraperitoneal and retroperitoneal organs. Brown fat gradually disappears with increasing age, and, in adults, it only persists in the neck and around the kidneys, adrenal glands and aorta. The main function of brown fat is heat production.

History

This neoplasm was first described in 1906 by Merkel[41] as a pseudolipoma of the breast. The term hibernoma was first introduced by Gery in 1914[42].

Epidemiology

Hibernomas occur primarily in adults. Individuals who develop these tumors are younger than patients with ordinary lipomas, and are typically in their thirties. In a series of 170 hibernomas, patient ages ranged from 2 to 75 years, with a mean age of 38 years. The series included nine children[43].

Pathogenesis

Little is known about the pathogenesis of hibernoma. Characteristic clonal chromosomal abnormalities consist of structural rearrangements of 11q13 and 11q21.

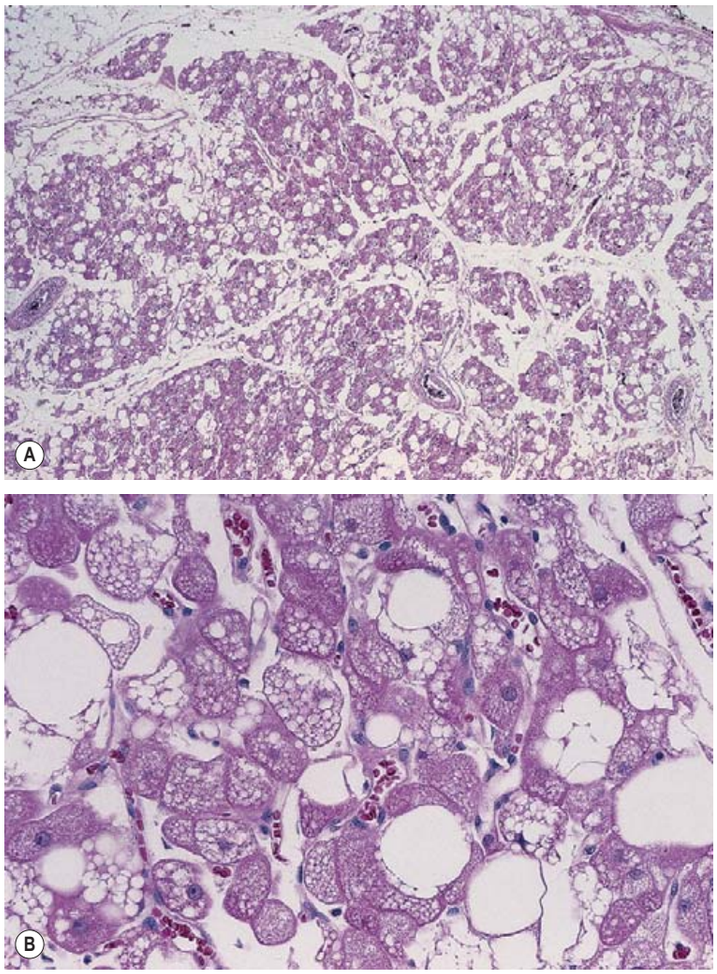


Fig. 117.14 Hibernoma. A Hibernoma with characteristic lobulation. **B** The cytoplasm of hibernoma cells ranges from multivacuolated to granular.

Clinical features

Hibernomas are slow-growing tumors located in the subcutis or, occasionally, within skeletal muscle. On examination, they are indistinguishable from a lipoma, i.e. they consist of a soft, mobile, round to oval subcutaneous nodule. The most common anatomic locations are the interscapular area, thighs, shoulder, neck, chest, arms and abdominal cavity/retroperitoneum. They can measure up to 25 cm in diameter, with an average size of 10 cm[43].

Pathology

On cut section, hibernomas have a characteristic tan to deep red–brown color. Histologic examination shows pronounced lobulation. Highly vascular interlobular septa surround individual lobules (Fig. 117.14). Common to hibernomas are the characteristic brown fat cells with a small central nucleus and multivacuolated to granular eosinophilic cytoplasm. The cellular membrane is distinct. These typical hibernoma cells are admixed with variable numbers of mature fat cells and pale multivacuolated cells. Rare cases have a myxoid stroma or have features of both spindle cell lipoma and hibernoma[43].

Differential diagnosis

Except for a larger average size, hibernomas are clinically indistinguishable from lipomas. However, their histopathologic features are characteristic.

Treatment

Surgical excision is curative. In a clinicopathologic study of 66 cases, none recurred after complete excision[43].

Nevus Lipomatosus Superficialis

Synonym: ■ Nevus lipomatosis of Hoffman and Zurhelle

Key features

- Grouped soft papulonodules on the hips and upper thighs
- Hamartomatous lesion with onset during the first two decades of life
- Mature fat cells in the dermis are the defining histopathologic feature

Introduction

Nevus lipomatosus superficialis of Hoffman and Zurhelle is a connective tissue nevus or hamartoma that is characterized by grouped soft papulonodules. It is most commonly located on the buttocks or upper thighs.

History

Nevus lipomatosus was first described by Hoffman and Zurhelle in 1921[44].

Epidemiology

This rare hamartoma develops shortly after birth or during the first two decades of life, and no gender preference has been observed.

Pathogenesis

The pathogenesis of nevus lipomatosus superficialis is unknown. There is speculation that precursor cells around dermal blood vessels give rise to mature fat cells in a mosaic pattern.

Clinical features

Nevus lipomatosus superficialis consists of soft, clustered papulonodules that are usually present at birth, or appear during childhood or adolescence. Initial presentation in adults has been described. The lesions consist of soft, yellow to skin-colored papules or nodules that are clustered, do not cross the midline, and may follow Blaschko's lines (Fig. 117.15A). Individual lesions may be sessile or pedunculated, and they have a smooth or cerebriform surface. The pelvic girdle area and upper thighs are the most common locations.

Pathology

The defining histopathologic feature consists of mature fat cells in the dermis (Fig. 117.15B). Skin appendages are not displaced.

Differential diagnosis

A solitary acquired papilloma that contains fat cells but no adnexal structures in the dermis is a variant of a skin tag known as a lipofibroma, not a nevus lipomatosus superficialis. The congenital circumferential folds of excess skin in patients with the "Michelin tire baby" phenotype can have the histologic findings of nevus lipomatosus superficialis (see Table 97.6)[45]. In focal dermal hypoplasia (Goltz syndrome), the dermis is either absent and completely replaced by fat cells, or significantly thinned. Adnexal structures are missing. Clinically, agminated neurofibromas may be mistaken for nevus lipomatosus.

Treatment

Most lesions are amenable to excision.

Lipoblastoma/Lipoblastomatosis

Synonym: ■ Embryonic lipoma

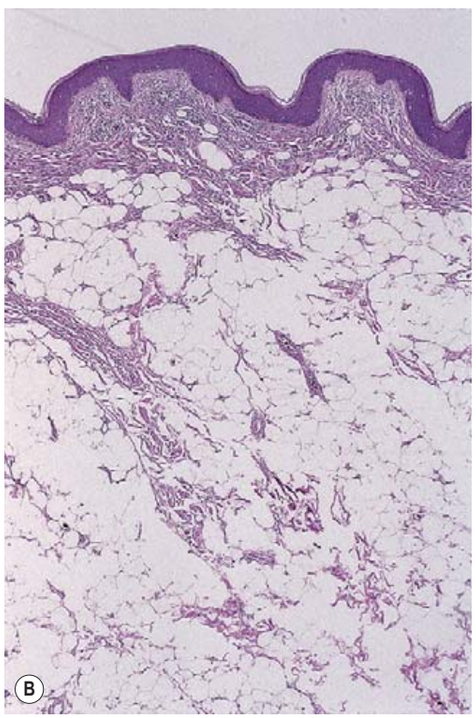


Fig. 117.15 Nevus lipomatosus superficialis. A This hamartoma is characterized by grouped, soft, pedunculated, skin-colored tumors; a partial resection had been performed. **B** Histopathologically, mature fat cells seen in the dermis are pathognomonic. *A, with permission from Kopf AW and Bart RS. J Dermatol Surg Oncol 9:279–281, 1983.*

Key features

- Benign neoplasm of immature fat cells that arises primarily on the extremities of children
- The circumscribed form is termed lipoblastoma, and the diffuse form is termed lipoblastomatosis
- Histopathologically, indistinguishable from myxoid liposarcoma

Introduction

This is a rare variant of lipoma, and it represents a benign tumor of immature fat cells that occurs almost exclusively in children. When circumscribed, this neoplasm is termed lipoblastoma, and, when diffuse, it is known as lipoblastomatosis.

History

The term lipoblastoma was coined by Vellios et al.[46] in 1958 when they reported a case of lipoblastomatosis.

Epidemiology

Lipoblastoma and lipoblastomatosis are tumors of infancy. Occasionally, these neoplasms are described in older children, or even teenagers, but the majority occur before the age of 3 years. Congenital tumors have been observed. Boys are affected twice as often as girls.

Pathogenesis

Lipoblastomas are neoplasms of immature white fat, and they probably represent residual areas of immature fat. The latter is suggested by sequential biopsies showing maturation to mature fat and by the almost exclusive occurrence in infancy and childhood. On the other hand, the presence of chromosomal rearrangements affecting chromosome 8q argues for a clonal neoplasm.

Clinical features

The majority of lipoblastomas present before the age of 3 years, and they are twice as common in boys as in girls. The upper and lower extremities are the sites of predilection. Most tumors are circumscribed and limited to the subcutis, and hence represent lipoblastomas. In addition to the extremities, lipoblastomas may be found in the head and neck region as well as on the trunk. These superficial lesions clinically simulate ordinary lipomas, presenting as slow-growing, soft, mobile, painless nodules, measuring 3–5 cm in diameter.

Lipoblastomatosis affects the deeper soft tissue and often diffusely infiltrates adjacent skeletal muscle. This process can occur in the mediastinum, mesentery and retroperitoneum. Rare tumors weigh up to 1 kg. Depending on the location, the tumor may result in symptoms of local obstruction or compression.

Pathology

Grossly, lipoblastomas are paler than ordinary lipomas, and they have a myxoid quality. Histologically, it is a lobulated neoplasm. The stroma is often myxoid, contains a plexiform vascular network, and is divided into lobules by connective tissue septa. Deep-seated tumors often lack the lobulation, and they may grow in a diffuse pattern. The tumors are composed of fat cells spanning the range of maturation from immature stellate and spindled mesenchymal cells, to lipoblasts with a single cytoplasmic vacuole that indents a peripherally located nucleus, to small and mature adipocytes. Lipoblastomas are paucicellular, cytologically bland, and lack mitotic activity. Serial biopsies of a lipoblastoma may show gradual maturation to a mature fatty tumor.

Differential diagnosis

Histopathologically, lipoblastoma and myxoid liposarcoma can be indistinguishable. Clinical parameters that aid in the differential diagnosis are the age of the patient and the location of the tumor. Myxoid liposarcomas almost always develop in individuals older than 20 years of age, and they are located in the deep soft tissue, rather than the subcutis. Nevertheless, in a child, an immature fat tumor that contains areas of marked cellularity, loss of lobulation, and mitotic figures should raise concern for a myxoid liposarcoma.

Treatment

Lipoblastoma, if treated with complete excision, rarely recurs. Unusual cases of spontaneous resolution without treatment exist[47]. In a series of 14 patients with lipoblastomas/lipoblastomatosis, 22% recurred after excision[48]. Wide excision is the therapy of choice for the diffuse form of the disease.

Liposarcoma/Atypical Lipomatous Tumor

Synonym: ■ Atypical lipoma

Key features

- Sarcoma of deep soft tissue that is only rarely limited to the skin
- Five major histologic subtypes, ranging from locally aggressive tumors without metastatic potential to malignant neoplasms with a significant risk of metastatic dissemination
- Cutaneous involvement may represent superficial extension of a deeply situated tumor

Fig. 117.16 Liposarcoma. Note the large mass in the right buttock. *Courtesy, Ronald P Rapini, MD.*

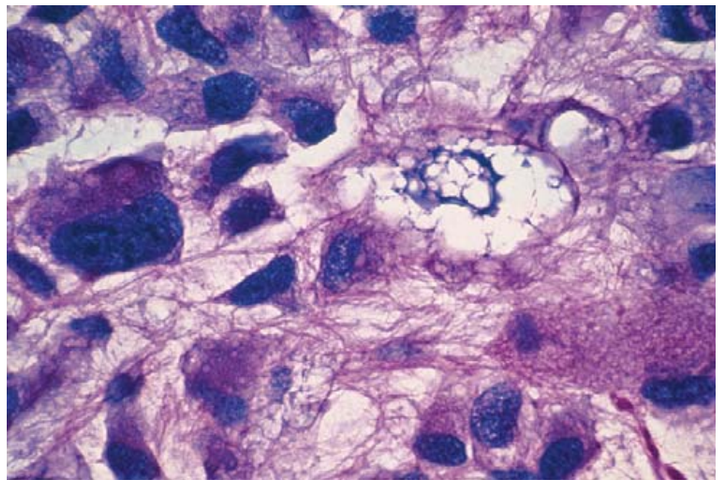


Fig. 117.17 Liposarcoma. Lipoblasts are immature fat cells, with a hyperchromatic nucleus that is scalloped by cytoplasmic fat vacuoles. Their presence is mandatory for a diagnosis of liposarcoma. *Courtesy, Richard Kempson, MD.*

Introduction

Liposarcoma is the second most common soft tissue sarcoma after malignant fibrous histiocytoma. Five histopathologic subtypes are recognized by the World Health Organization (WHO), with important prognostic, cytogenetic, molecular and epidemiologic differences. The biologic behavior of the subtypes ranges from locally aggressive tumors without metastatic potential to highly malignant neoplasms with a significant risk of systemic spread. There is considerable controversy among soft tissue pathologists regarding the nomenclature of this tumor. Some experts prefer the term atypical lipomatous tumor for all liposarcomas in the subcutis, because these tumors recur but have virtually no metastatic potential[49,50]. Others prefer to retain the term liposarcoma because histologically and cytogenetically these tumors are the same, regardless of location, and also because these tumors carry a small risk for dedifferentiation, which confers metastatic potential[51].

Epidemiology

The annual incidence of all types of soft tissue liposarcoma is estimated at 2.5 per million, based on a Swedish study. The average age at presentation is 50 years. Rare cases arise in children older than 10 years of age, but virtually never in children younger than 10 years of age.

Pathogenesis

It appears that liposarcomas arise *de novo*, rather than from preexisting lipomas. A reciprocal translocation between chromosomes 12 and 16 is consistently present in myxoid and round cell liposarcomas, and this results in expression of the TLS/FUS-DDIT3 fusion protein; the latter plays an important role in oncogenesis. Well-differentiated liposarcomas have giant and ring chromosomes that are derived from chromosome 12 and can result in amplification of the 12q13–15 region. Unlike for other soft tissue sarcomas, radiation does not appear to play a role in their pathogenesis.

Clinical features

Liposarcoma is a tumor primarily of the deep soft tissue of the extremities and retroperitoneum. Legs and buttocks are more frequently affected than the upper extremities (Fig. 117.16). It originates in, and is limited to, the dermis or subcutis only in exceptional circumstances[52,53]. Primary cutaneous liposarcomas are described as dome-shaped or polypoid, and they measure between 1 and 20 cm[53]. If a liposarcoma presents in the subcutis, this will often be due to direct extension from an underlying sarcoma of the deep soft tissue.

Tumors limited to the dermis or subcutis can recur, but they do not metastasize or cause patient death. Liposarcomas of the deep soft tissue and retroperitoneum are malignant neoplasms, capable of recurrence, metastasis, and causing patient death. The prognosis depends on the location, degree of differentiation, and the histopathologic subtype.

Pathology

The *sine qua non* for the diagnosis of liposarcoma is the presence of lipoblasts. Lipoblasts are immature fat cells, characterized by a hyperchromatic nucleus that is indented or scalloped by cytoplasmic fat vacuoles (Fig. 117.17). However, the lipoblasts need to be present in the appropriate histopathologic context, as they are not specific for liposarcomas, but can also be found in lipoblastomas and pleomorphic lipomas, or can closely resemble histiocytes found in fat necrosis or fat atrophy.

The histopathologic appearance is highly variable and depends on the particular subtype (Fig. 117.18). A **well-differentiated** liposarcoma consists of mature fat with a variable number of lipoblasts and cells with hyperchromatic nuclei. **Myxoid** liposarcoma resembles immature fat and can be histologically indistinguishable from a lipoblastoma. Small and uniformly bland spindle cells are set in a myxoid matrix with plexiform vessels. In the more cellular areas, myxoid liposarcoma merges with **round cell** liposarcoma, which is characterized by sheets of primitive round cells. Several classification schemes recognize round cell liposarcoma as a part of the spectrum of myxoid liposarcoma. **Pleomorphic** liposarcoma is the least common subtype; it exhibits an extreme degree of nuclear pleomorphism and resembles a malignant fibrous histiocytoma. **Dedifferentiated** liposarcoma is a biphasic tumor comprised of areas of well-differentiated liposarcoma/atypical lipomatous tumor and areas of a non-lipogenic sarcoma.

Differential diagnosis

Liposarcomas of the skin and superficial subcutaneous tissue are exceedingly rare, and they should be diagnosed only after histopathologic mimics, metastases, and direct extension from a deep soft tissue sarcoma have been excluded. In addition, these tumors need to be distinguished from a spindle cell/pleomorphic lipoma, a benign lipomatous tumor that commonly arises on the upper back and posterior neck of older men and is characterized histopathologically by the presence of a variable number of floret-like cells and occasional lipoblasts, admixed with mature adipocytes.

Myxoid liposarcoma can be histologically indistinguishable from lipoblastoma and lipoblastomatosis. This differential diagnosis relies on clinical parameters and is discussed above under lipoblastoma.

Treatment

Wide excision is the treatment of choice. Tumors limited to the dermis and subcutis may be treated by dermatologists. The treatment of most liposarcomas, however, will require an oncologic soft tissue surgeon. It is not uncommon for liposarcomas to have a multinodular growth pattern and extend into muscle and fascial planes. Excision needs to be carefully planned using MRI and radiographic information.

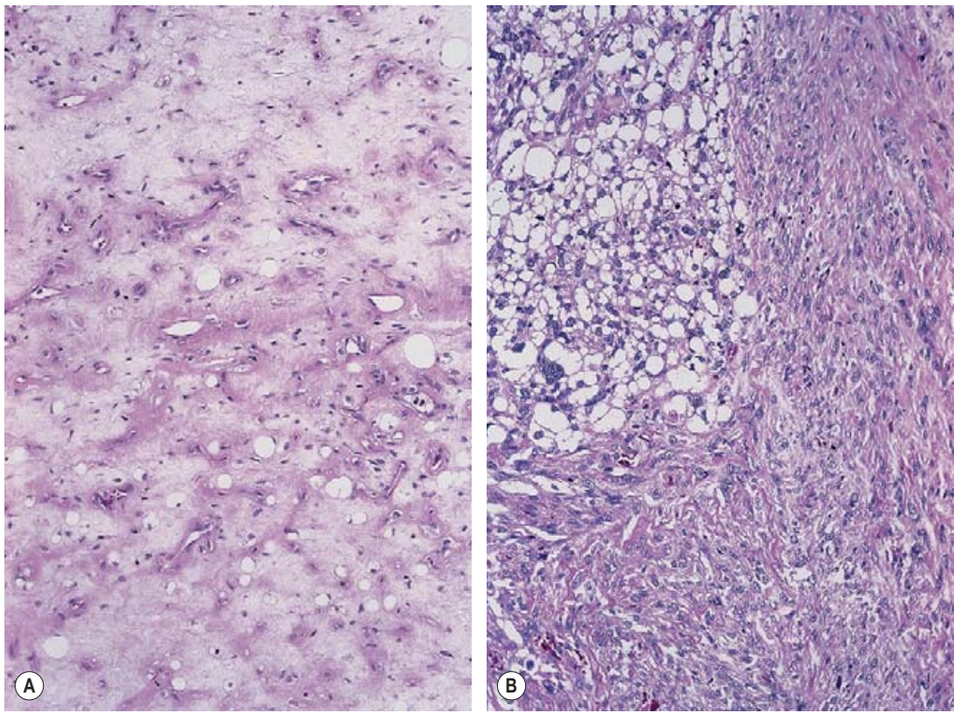


Fig. 117.18 The varied histopathologic features of liposarcoma. A Myxoid liposarcoma – without the clinical context, this tumor can be indistinguishable from lipoblastoma. Bland spindle cells occur in a myxoid matrix with plexiform vessels. **B** Pleomorphic liposarcoma – anaplastic and cellular neoplasm. Lipoblasts may be difficult to find.

TUMORS OF CARTILAGE

Extraskeletal Chondroma

Synonym: ■ Chondroma of soft parts

Key features

- Rare benign tumor of mature cartilage
- Most commonly located near the small joints of the hands and feet

Introduction

Cartilage can be found in the skin as a result of metaplasia, as a component of chondroid syringomas, and as the exclusive component of extraskeletal chondromas. By definition, extraskeletal chondromas are not attached to bone and occur outside the synovial space. With the exception of two clinical series[54,55], most of the experience with extraskeletal chondromas is in the form of case reports.

Epidemiology

Extraskeletal chondromas are rare tumors that occur in children as well as adults, but most patients are beyond their third decade.

Clinical features

Extraskeletal chondromas present as solitary painless nodules on the hands and feet and, most frequently, on the fingers. They grow slowly and are often associated with tendons. Other, rare locations include the trunk, head, neck, oropharynx and larynx.

Pathology

On gross examination, chondromas are sharply circumscribed and often lobulated. Most measure less than 2 cm, but larger lesions can occur. Histopathologically, they consist of hyaline cartilage that may be admixed with variable amounts of fibrous tissue or myxoid stroma. The cartilage may compose only a small portion of the tumor. Mature hyaline cartilage displays a dense basophilic matrix with nuclei in lacunae. Calcification is common, preferentially affecting the center of the tumor, and it may be extensive. Like normal chondrocytes, the lesional cells of chondroma are reactive for S100 protein.

Differential diagnosis

Synovial chondromatosis consists of multiple discrete osteocartilaginous nodules and favors the large joints, such as the knee, hip and elbow. Histologic differentiation from grade I chondrosarcoma or myxoid chondrosarcoma may be difficult, but chondrosarcomas rarely affect hands and feet, and they are in continuity with bone and cartilage.

Treatment

Local excision is usually curative. Up to 20% of extraskeletal chondromas may recur. To the best of our knowledge, malignant transformation to chondrosarcoma does not occur.

REFERENCES

1. Newman PL, Fletcher CD. Smooth muscle tumours of the external genitalia: clinicopathological analysis of a series. Histopathology. 1991;18:523–9.
2. Stout AP. Solitary cutaneous and subcutaneous leiomyoma. Am J Cancer. 1937;29:435–69.
3. Orellana-Diaz O, Hernandez-Perez E. Leiomyoma cutis and leiomyosarcoma: a 10-year study and a short review. J Dermatol Surg Oncol. 1983;9:283–7.
4. Fletcher CDM. Soft tissue tumors. In: Fletcher CDM (ed.). Diagnostic Histopathology of Tumors, 3rd edn. Philadelphia: Churchill Livingstone, 2007:1527–93.
5. Badeloe S, Frank J. Clinical and molecular genetic aspects of hereditary multiple cutaneous leiomyomatosis. Eur J Dermatol. 2009;19:545–51.
6. Raj S, Calonje E, Kraus M, et al. Cutaneous pilar leiomyoma: clinicopathologic analysis of 53 lesions in 45 patients. Am J Dermatopathol. 1997;19:2–9.
7. Mahalingam M, Goldberg LJ. Atypical pilar leiomyoma: cutaneous counterpart of uterine symplastic leiomyoma? Am J Dermatopathol. 2001;23:299–303.
8. Perez-Montiel MD, Plaza JA, Dominguez-Malagon H, et al. Differential expression of smooth muscle myosin, smooth muscle actin, h-caldesmon, and calponin in the diagnosis of myofibroblastic and smooth muscle lesions of skin and soft tissue. Am J Dermatopathol. 2006;28:105–11.

9. McGinley KM, Bryant S, Kattine AA, et al. Cutaneous leiomyomas lack estrogen and progesterone receptor immunoreactivity. J Cutan Pathol. 1997;24:241–5.
10. Thompson JA Jr. Therapy for painful cutaneous leiomyomas. J Am Acad Dermatol. 1985;13:865–7.
11. Christenson LJ, Smith K, Arpey CJ. Treatment of multiple cutaneous leiomyomas with CO_2 laser ablation. Dermatol Surg. 2000;26:319–22.
12. Svarvar C, Bohling T, Berlin O, et al. Clinical course of nonvisceral soft tissue leiomyosarcoma in 225 patients from the Scandinavian Sarcoma Group. Cancer. 2007; 109:282–91.
13. Hornick JL, Fletcher CD. Criteria for malignancy in nonvisceral smooth muscle tumors. Ann Diagn Pathol. 2003;7:60–6.
14. Fields JP, Helwig EB. Leiomyosarcoma of the skin and subcutaneous tissue. Cancer. 1981;47:156–69.
15. Bernstein SC, Roenigk RK. Leiomyosarcoma of the skin. Treatment of 34 cases. Dermatol Surg. 1996;22:631–5.
16. Weiss SW, Goldblum JR. Leiomyosarcoma. In: Weiss SW (ed). Soft Tissue Tumors, 4th edn. St Louis: Mosby, 2001: 727–48.
17. Massi D, Franchi A, Alos L, et al. Primary cutaneous leiomyosarcoma: clinicopathological analysis of 36 cases. Histopathology. 2010;56:251–62.
18. Kaddu S, Beham A, Cerroni L, et al. Cutaneous leiomyosarcoma. Am J Surg Pathol. 1997;21:979–87.
19. Suster S. Epithelioid leiomyosarcoma of the skin and subcutaneous tissue. Clinicopathologic, immunohistochemical, and ultrastructural study of five cases. Am J Surg Pathol. 1994;18:232–40.
20. Kempson RL, Fletcher CDM, Evans HL, et al. Smooth muscle tumors. In: Rosai J, Sobin LH (eds). Tumors of Soft Tissues. Washington, DC: Armed Forces Institute of Pathology, 2001:239–56.
20a. Kraft S, Fletcher CD. Aytpical intradermal smooth muscle neoplasms: clinicopathologic analysis of 84 cases and a reappraisal of cutaneous "leiomyosarcoma". Am J Surg Pathol. 2011;35:599–607.
21. Stokes JH. Nevus pilaris with hyperplasia of no-striated muscle. Arch Dermatol Syph. 1923;7:479–81.
22. Glover MT, Malone M, Atherton DJ. Michelin-tire baby syndrome resulting from diffuse smooth muscle hamartoma. Pediatr Dermatol. 1989;6:329–31.
23. Nanni CA, Alster TS. Treatment of a Becker's nevus using a 694-nm long-pulsed ruby laser. Dermatol Surg. 1998; 24:1032–4.
24. Weiss SW, Goldblum JR. Benign lipomatous tumors. In: Weiss SW (ed.). Soft Tissue Tumors, 4th edn. St. Louis: Mosby, 2001:571–639.
25. Ashar HR, Fejzo MS, Tkachenko A, et al. Disruption of the architectural factor HMGI-C: DNA-binding AT hook motifs fused in lipomas to distinct transcriptional regulatory domains. Cell. 1995;82:57–65.
26. Karademir M, Kocak M, Usal A, et al. A case of infiltrating lipomatosis with diffuse, symmetrical distribution. Br J Clin Pract. 1990;44:728–30.
27. Klein JA, Barr RJ. Diffuse lipomatosis and tuberous sclerosis. Arch Dermatol. 1986;122:1298–302.
28. Kindblom LG, Moller-Nielsen J. Diffuse lipomatosis in the leg after poliomyelitis. Acta Pathol Microbiol Scand A. 1975;83:339–44.
29. Klein FA, Smith MJ, Kasenetz I. Pelvic lipomatosis: 35-year experience. J Urol. 1988;139:998–1001.
30. Leffell DJ, Braverman IM. Familial multiple lipomatosis. Report of a case and a review of the literature. J Am Acad Dermatol. 1986;15:275–9.
31. Biesecker LG, Happle R, Mulliken JB, et al. Proteus syndrome: diagnostic criteria, differential diagnosis, and patient evaluation. Am J Med Genet. 1999;84: 389–95.
32. Biesecker LG. The multifaceted challenges of Proteus syndrome. JAMA. 2001;285:2240–3.
33. Zhou X, Hampel H, Thiele H, et al. Association of germline mutation in the *PTEN* tumour suppressor gene and Proteus and Proteus-like syndromes. Lancet. 2001; 358:210–11.
34. Enzi G. Multiple symmetric lipomatosis: an updated clinical report. Medicine (Baltimore). 1984;63:56–64.
35. Ruzicka T, Vieluf D, Landthaler M, et al. Benign symmetric lipomatosis Launois-Bensaude. Report of ten cases and review of the literature. J Am Acad Dermatol. 1987;17: 663–74.
36. Reece PH, Wyatt M, O'Flynn P. Dercum's disease (adiposis dolorosa). J Laryngol Otol. 1999;113:174–6.
37. Bannayan GA. Lipomatosis, angiomatosis, and macrencephalia. A previously undescribed congenital syndrome. Arch Pathol. 1971;92:1–5.
38. Wanner M, Celebi JT, Peacocke M. Identification of a *PTEN* mutation in a family with Cowden syndrome and Bannayan-Zonana syndrome. J Am Acad Dermatol. 2001;44:183–7.
39. Enzinger FM, Harvey DA. Spindle cell lipoma. Cancer. 1975;36:1852–9.
40. Kempson RL, Fletcher CDM, Evans HJ, et al. Lipomatous tumors. In: Rosai J, Sobin LH (eds). Tumors of Soft Tissues. Washington, DC: Armed Forces Institute of Pathology, 2001:187–238.
41. Merkel H. On a pseudolipoma of the breast (peculiar fat tumor). Beitr Pathol Anat. 1906;39:152–7.
42. Gery L. Discussions. Bull Mem Soc Anat (Paris). 1914: 111–12.
43. Furlong MA, Fanburg-Smith JC, Miettinen M. The morphologic spectrum of hibernoma: a clinicopathologic study of 170 cases. Am J Surg Pathol. 2001;25:809–14.
44. Hoffman E, Zurhelle E. Über einen Nävus lipomatosus cutaneous superficialis der linken Glutealgegend. Arch Dermatol. 1921;130:327.
45. Ross CM. Generalized folded skin with an underlying lipomatous nevus. "The Michelin Tire baby". Arch Dermatol. 1969;100:320–3.
46. Vellios F, Baez JM, Schumacker HB. Lipoblastomatosis: a tumor of fetal fat different from hibernoma: report of a case with observations on embryogenesis of human adipose tissue. Am J Pathol. 1958;34:1149.
47. Mognato G, Cecchetto G, Carli M, et al. Is surgical treatment of lipoblastoma always necessary? J Pediatr Surg. 2000;35:1511–13.
48. Mentzel T, Calonje E, Fletcher CD. Lipoblastoma and lipoblastomatosis: a clinicopathological study of 14 cases. Histopathology. 1993;23:527–33.
49. Azumi N, Curtis J, Kempson RL, et al. Atypical and malignant neoplasms showing lipomatous differentiation. A study of 111 cases. Am J Surg Pathol. 1987;11:161–83.
50. Evans HL, Soule EH, Winkelmann RK. Atypical lipoma, atypical intramuscular lipoma, and well differentiated retroperitoneal liposarcoma: a reappraisal of 30 cases formerly classified as well differentiated liposarcoma. Cancer. 1979;43:574–84.
51. Weiss SW, Rao VK. Well-differentiated liposarcoma (atypical lipoma) of deep soft tissue of the extremities, retroperitoneum, and miscellaneous sites. A follow-up study of 92 cases with analysis of the incidence of "dedifferentiation". Am J Surg Pathol. 1992;16: 1051–8.
52. Yoshikawa H, Ueda T, Mori S, et al. Dedifferentiated liposarcoma of the subcutis. Am J Surg Pathol. 1996; 20:1525–30.
53. Dei Tos AP, Mentzel T, Fletcher CD. Primary liposarcoma of the skin: a rare neoplasm with unusual high grade features. Am J Dermatopathol. 1998;20:332–8.
54. Dahlin DC, Salvador AH. Cartilaginous tumors of the soft tissues of the hands and feet. Mayo Clin Proc. 1974; 49:721–6.
55. Chung EB, Enzinger FM. Chondroma of soft parts. Cancer. 1978;41:1414–24.

118 Mastocytosis

Michael D Tharp

Key features

- The onset of mastocytosis can occur from birth to adulthood and may involve only the skin (most children and some adults) or multiple organs such as the bone marrow, liver, spleen and/or lymph nodes (primarily adults)
- Childhood disease is more common and often presents with one or more tan to brown papules or plaques *(urticaria pigmentosa)* that frequently resolve during late adolescence or early adulthood
- Mastocytomas are thicker plaques or nodules that occur primarily in children
- Adults with mastocytosis may or may not have cutaneous lesions; when present, they appear as 2–5 mm red–brown macules or papules. Adult disease persists throughout life
- Stroking of lesions of mastocytosis often causes urtication (Darier's sign), which is more pronounced in children due to a higher density of mast cells
- Activating mutations in codon 816 of c-*KIT* are detected in the majority of adults and up to 40% of children with mastocytosis; extracellular domain mutations occur more frequently in childhood-onset disease
- Patients may be asymptomatic or have accompanying symptoms of mast cell mediator release such as pruritus, flushing, headaches, abdominal pain, diarrhea and syncope

INTRODUCTION

Mastocytosis represents a spectrum of clinical disorders with a common phenotype of tissue mast cell hyperplasia. Patients with this disorder were initially thought to have only cutaneous disease, but it was then discovered that mastocytosis patients could have involvement of multiple organs. Although the clinical aspects of the disorder have been well documented for decades, the last 10 years have brought significant advances in understanding its pathogenesis. Nonetheless, explanations for the differences in clinical presentations and course between childhood-onset and adult-onset disease (Fig. 118.1) are still needed. Therapy for mastocytosis currently centers on inhibiting the effects of secreted mast cell mediators, with cladribine reserved for advanced systemic disease. Only a small subgroup of patients responds to the tyrosine kinase inhibitor imatinib.

HISTORY

The original description of mastocytosis was by Nettleship and Tay, who reported on a 2-year-old girl with hyperpigmented papules that spontaneously urticated[1]. Eight years later, in 1877, Paul Ehrlich formally discovered the mast cell. The next year, Sangster suggested the name "urticaria pigmentosa"[2]. Unna was the first to demonstrate that mast cells were responsible for the cutaneous eruption in mastocytosis patients.

EPIDEMIOLOGY

Mastocytosis can present in neonates or develop any time thereafter into late adulthood. Childhood mastocytosis is defined as that with an onset before puberty. Approximately 55% of mastocytosis patients develop their disease by 2 years of age, and another 10% experience disease onset between the ages of 2 and 15 years. This disorder has no gender preference, and it has been reported in all races[3]. While most patients with mastocytosis have no family history of the disorder, to date there have been approximately 70 familial cases of mastocytosis reported, including at least 15 sets of monozygotic twins (although several monozygotic twin pairs discordant for mastocytosis have also been described). Familial mastocytosis has been documented in three generations of a single kindred[4].

PATHOGENESIS

Mast cells are derived from pluripotent $CD34^+$ precursors in the bone marrow and circulate in the peripheral blood as agranular, monocytic-appearing cells. After migrating into tissues, these immature mast cells assume their typical granular morphology (see Ch. 18). Circulating mast cell precursors express CD34, the tyrosine kinase KIT (CD117), and IgG receptors (FcγRII), but not high-affinity IgE receptors (FcεRI)[5]. KIT is the protein product of the proto-oncogene c-*KIT* located on chromosome 4q12, and it belongs to the type III receptor tyrosine kinase subfamily. KIT is expressed on mast cells, melanocytes, primitive hematopoietic stem cells, primordial germ cells, and interstitial cells of Cajal. Activation of KIT induces cellular growth and extends cell survival by preventing apoptosis. The ligand for KIT is stem cell factor (SCF), which is an important growth factor for mast cells. The gene for SCF is located on chromosome 12, and encodes a protein that localizes to the cell membrane. A membrane-bound and a soluble form of SCF exist, and both induce KIT activation; the latter is thought to arise via enzymatic cleavage of the former[6]. SCF is produced by bone marrow stromal cells, fibroblasts, keratinocytes, endothelial cells, and reproductive Sertoli and granulosa cells. Peripheral blood mast cell precursors cultured in the presence of SCF and other cytokines (e.g. interleukin [IL]-3, -4, -6, -9) become $KIT^+/CD34^-/Fc\gamma RII^-/Fc\varepsilon RI^+$ and develop characteristic cytoplasmic mast cell granules, as seen in mature tissue mast cells[5,7].

Alterations in KIT structure and activity are central to the pathogenesis of several forms of mastocytosis. *Somatic* mutations involving codon 816 of the c-*KIT* gene represent the most common genetic abnormality in patients with sporadic mastocytosis. The result is a substitution of the amino acid aspartic acid (D) with valine (V) or another amino acid; examples include D816V, D816Y, D816F and D816H (Fig. 118.2). These particular mutations are activating mutations and lead to constitutive ligand-independent activation of the receptor. Additional, less common mutations that have been identified in children and adults with mastocytosis are outlined in Table 118.1[4,8]. As noted, non-D816 mutations can also be activating and there are examples of dominant inactivating mutations (e.g. E839K).

In a recent study of 50 children (0–16 years of age) with mastocytosis in whom the entire c-*KIT* sequence was analyzed, activating mutations were found in 86% of the patients – 42% in codon 816 and the remainder elsewhere, in particular within the portion of the gene that encodes the proximal extracellular region (fifth immunoglobulin-like domain)[8]. Examples of the latter are del419 and K509I (see Fig. 118.2). The majority of the children in this study had urticaria pigmentosa and the results have led to a shift in thinking about the basis for spontaneously resolving childhood-onset mastocytosis. For example, functional studies have been designed and differences in signaling properties between extracellular domain mutations and phosphotransferase domain mutations (i.e. D816) have been observed[9]. Lastly, in a study of 114 adults with childhood-onset mastocytosis in whom seven exons of c-*KIT* were sequenced, 42% had D816 mutations while 23% had other activating mutations[10]. Further insights will surely emerge from long-term studies of children with known mutations.

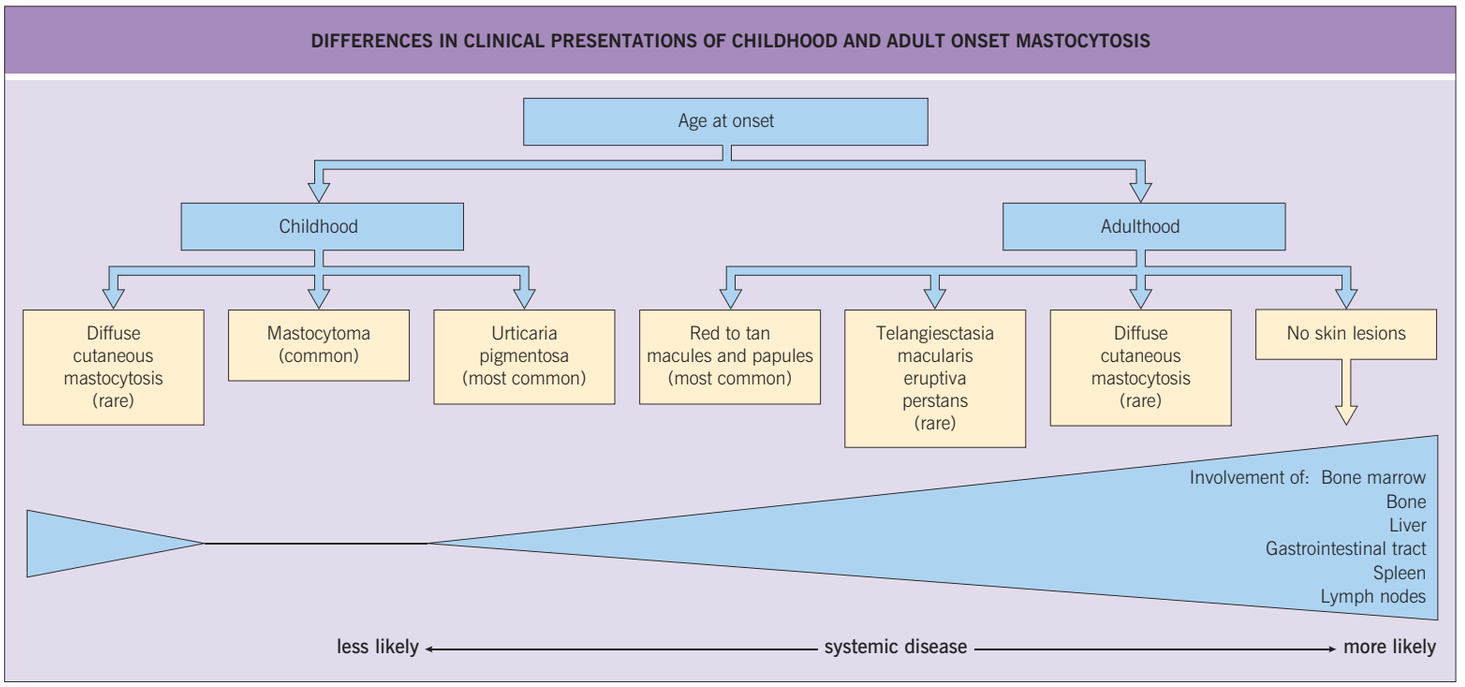


Fig. 118.1 Differences in clinical presentations of childhood and adult-onset mastocytosis. Based upon the WHO classification scheme (see Tables 118.2 & 118.3), most children and some adults have cutaneous mastocytosis. Those with indolent systemic mastocytosis and smoldering systemic mastocytosis often have cutaneous lesions, while individuals with systemic mastocytosis with associated clonal hematological non-mast cell-lineage disease, aggressive mastocytosis or mast cell leukemia often do not have cutaneous lesions. Only a few children with TMEP have been reported. In general, children have a more benign course with a tendency for spontaneous remission of cutaneous and extracutaneous disease.

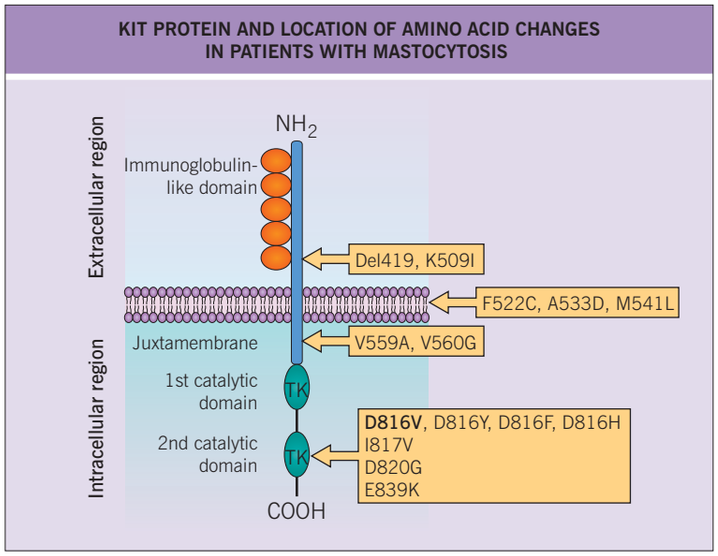


Fig. 118.2 KIT receptor and location of amino acid changes (due c-*KIT* mutations) in patients with mastocytosis. For example, D816V means that because of a mutation in codon 816, valine (V) has replaced aspartic acid (D). The plasma membrane-bound KIT receptor is composed of three distinct regions: (1) the extracellular region (five immunoglobulin-like repeats [orange]); (2) the transmembrane region; and (3) the intracellular region (two tyrosine kinase domains [green]). The most common site for activating mutations is exon 17, which contains codon 816. The result is constitutive ligand-independent activation of the receptor (see Table 118.1). TK, tyrosine kinase domain (one binds ATP and the other has phosphotransferase activity).

MUTATIONS IN c-*KIT* IN PATIENTS WITH MASTOCYTOSIS
CHILDHOOD-ONSET DISEASE
No activating mutation (minority*) Activating mutations (majority*; e.g. D816V†, del419‡, K509I‡, A533D) Inactivating mutations (rare; e.g. E839K) Other mutations (rare; e.g. M541L‡)
ADULT-ONSET DISEASE
D816 activating mutations (most; D816V†, D816Y, D816F, D816H) Activating mutations, non-D816 (few; e.g. V560G‡, del419‡, K509I‡, D820G) Other mutations, some of which are activating (rare; e.g. F522C‡, V533D, V559A‡, I817V, E839K)
FAMILIAL DISEASE
No activating or inactivating mutation (some) Other mutations (few; e.g. del419‡, K509I‡, F522C‡, A533D)
FAMILIAL GASTROINTESTINAL STROMAL TUMORS (GISTS) PLUS HYPERPIGMENTATION OR MAST CELL DISEASE
Examples: deletion of V559 & V560; V559A‡; L576_P577insQL; del419‡)
*In one series of 50 children and adolescents (the majority of whom had urticaria pigmentosa or diffuse cutaneous disease), 86% had an activating mutation[8]. †For example, when it leads to an Asp/Val substitution, the abbreviation is D816V, and when it leads to an Asp/Phe substitution, D816F. ‡Disease responsive to imatinib.

Table 118.1 Mutations in c-*KIT* in patients with mastocytosis.

Recently, a transgenic mouse model of mastocytosis was developed via the expression of human activated (D816V) c-*KIT*[11]. Among the 28 genetically identical animals studied, only eight had clinical findings of mastocytosis, and the disease ranged from indolent mast cell hyperplasia to an invasive mast cell tumor. This diverse phenotypic expression of mastocytosis in genetically identical animals, along with the finding of inactivating or no c-*KIT* mutations in some patients with mastocytosis, especially children, points to additional factors beyond an abnormal KIT receptor.

CLINICAL FEATURES

Signs and Symptoms

Many children and adults have few, if any, symptoms. When symptoms do occur, they are due to the diverse physiologic effects of secreted mast cell mediators, such as histamine, eicosanoids and cytokines

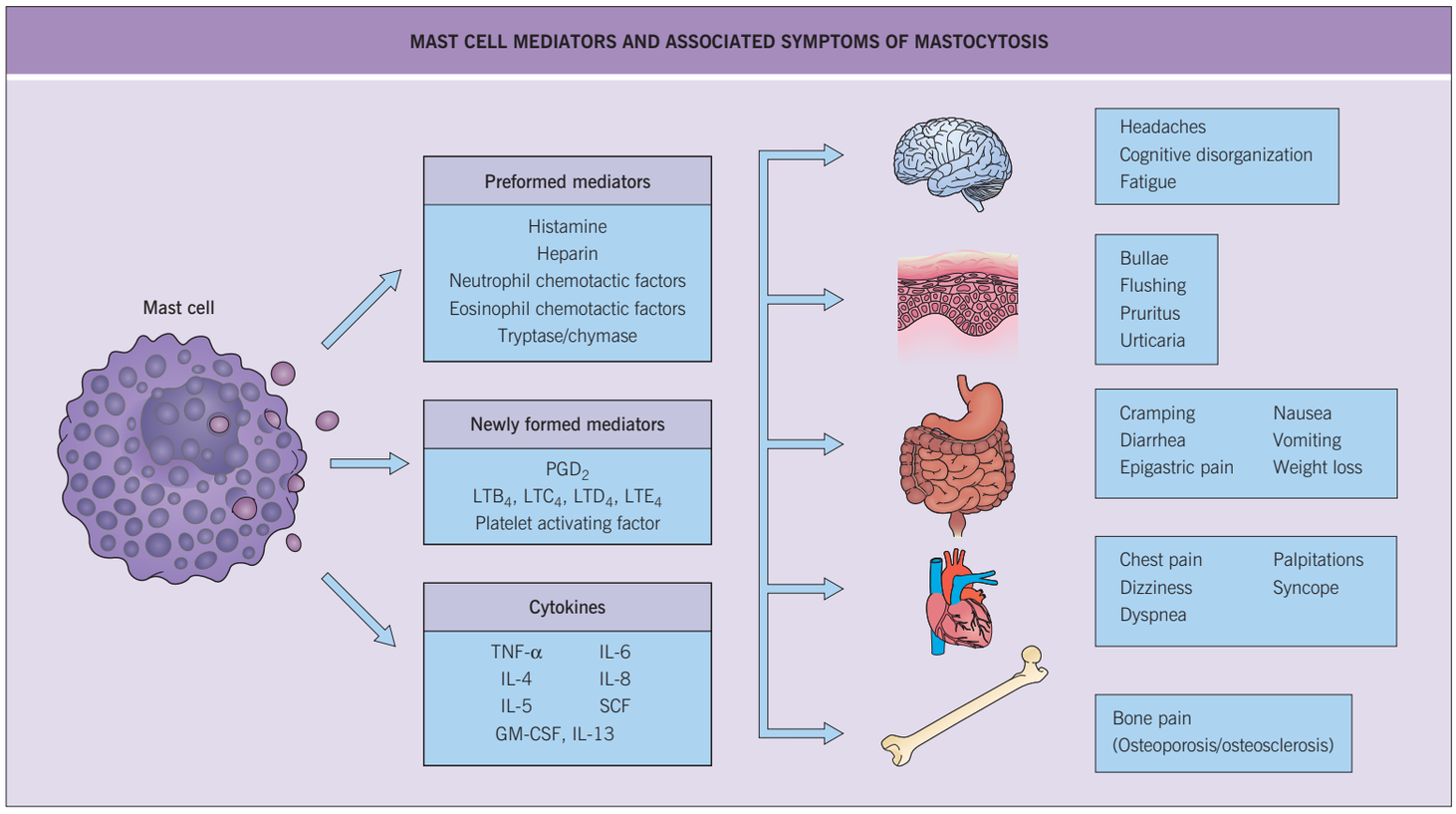


Fig. 118.3 Mast cell mediators and associated symptoms of mastocytosis. GM-CSF, granulocyte–macrophage colony-stimulating factor; IL, interleukins; LT, leukotrienes; PGD_2, prostaglandin D_2; SCF, stem cell factor; TNF, tumor necrosis factor.

(Fig. 118.3). These complaints and findings may range from pruritus and flushing to abdominal pain and diarrhea to palpitations, dizziness and syncope. Of interest is the relative absence of pulmonary symptoms in mastocytosis. Complaints of fever, night sweats, malaise, weight loss, bone pain, epigastric distress, and problems with mentation (cognitive disorganization) often signal the presence of extracutaneous disease. Deaths associated with extensive mast cell mediator release also are rare, but have been reported in both children and adults. Symptoms of mastocytosis can be exacerbated by exercise, heat, or local trauma to skin lesions. In addition, alcohol, narcotics, salicylates and other nonsteroidal anti-inflammatory drugs (NSAIDs), polymyxin B, and anticholinergic medications have been implicated in precipitating symptoms of mastocytosis. Some systemic anesthetic agents may precipitate anaphylaxis (see Treatment).

Cutaneous Lesions

The two common clinical presentations of **childhood mastocytosis** are a solitary tan, yellow–tan or brown plaque or nodule (mastocytoma; Fig. 118.4) and variable numbers of tan to brown macules or papules (urticaria pigmentosa, UP; Fig. 118.5). Mastocytomas may be present at birth or may appear during infancy, and they favor the distal extremities[12]. An estimated 10–35% of patients with childhood-onset mastocytosis have mastocytomas while ~65% have UP. The lesions of UP usually develop during early childhood and most commonly appear on the trunk, classically sparing the central face, scalp, palms and soles.

While telangiectatic macules (telangiectasia macularis eruptiva perstans, TMEP) are a rare manifestation of mastocytosis in children, at least three children have been reported with this type of lesion. A form of childhood mastocytosis with little clinical resemblance to lesions of UP or TMEP is diffuse cutaneous mastocytosis. The skin of patients with this form of mastocytosis has numerous erythematous to yellow–tan papules and plaques with areas of confluence that have a leathery texture. Some infants and children with UP and diffuse cutaneous mastocytosis develop non-scarring vesicles or bullae (Fig. 118.6; see Ch. 34). Bullous lesions of mastocytosis usually resolve by 3 to 5 years of age, and are believed to result from the release of mast cell serine proteases.

Fig. 118.4 Mastocytoma in an infant. Note the leathery appearance of the skin and the two erosions.

Skin lesions in **adult mastocytosis** patients differ significantly from those in children. The most common cutaneous lesions of mastocytosis in adults are reddish-brown macules and papules that measure 1 cm or less in diameter (Fig. 118.7), and in patients with skin type I, they may be pink to red in color. These lesions are most numerous on the trunk and proximal extremities and appear less frequently on the face, distal extremities or palms and soles. Individual lesions can resolve, but the total number usually increases over time. Close inspection reveals variable hyperpigmentation and fine telangiectasias.

A more rare form of adult cutaneous mastocytosis is TMEP, which is characterized by macules and patches composed of telangiectasias without significant hyperpigmentation (Fig. 118.8). While there have been several reports of mastocytomas in adults, these are extremely rare. Diffuse cutaneous mastocytosis has also been documented in adults. The skin of these patients has a doughy consistency, and the presence of numerous, confluent, yellow–tan papules has led to the descriptive term xanthelasmoidal mastocytosis. In more advanced stages, skin folds of patients with diffuse disease become markedly thickened and can distort facial features. Another rare variant, nodular mastocytosis, was recently described in an adult who had red–purple

Fig. 118.5 Urticaria pigmentosa in children. Both papular (**A**) and papulonodular (**B**) lesions are seen. As in mastocytomas, the degree of associated hyperpigmentation can vary. *A, Courtesy, Julie V Schaffer, MD.*

Fig. 118.6 Diffuse cutaneous mastocytosis in infants. A Diffuse infiltration with multiple erosions. **B** Spontaneous blister superimposed on a plaque; note the leathery appearance of the lesions on the shin.

nodules of the axillae and inguinal region; the mast cells had the V560G c-*KIT* mutation[13].

The presence of mast cell hyperplasia in the skin of mastocytosis patients can be confirmed clinically by firmly rubbing a characteristic lesion. The formation of an urticarial wheal (Darier's sign; Fig. 118.9) at the lesion site is indicative of mast cell mediator release. Darier's sign is readily demonstrated in mastocytomas and childhood UP lesions, whereas it may be less apparent in common adult mastocytosis lesions and barely detectable in TMEP. This can be explained from studies quantifying mast cells in the skin of children and adults with mastocytosis. Mast cell concentrations in mastocytomas and childhood UP have been reported to be 150-fold and 40-fold greater than normal skin, respectively, whereas the mast cell content of lesional skin in adult mastocytosis patients was only 8-fold greater than normal skin[14].

Systemic Manifestations

Skeletal lesions are detected more commonly in adult patients with mastocytosis and are reported as rare in children[12]. In one study of 142 adults with mastocytosis, 40% had skeletal involvement, with a similar frequency in those with childhood-onset and adult-onset disease[10]. Bony lesions may appear as radio-opacities, radiolucencies, or a mixture of the two. The skull, spine and pelvis are most commonly involved. In an earlier study of 58 adult systemic mastocytosis patients, 57% had diffuse bone involvement, whereas only 2% had focal lesions. Demineralization was the most common change in patients with diffuse skeletal disease, followed by osteosclerosis and mixed lesions of osteosclerosis and osteoporosis[15]. Patients can complain of skeletal pain.

Undecalcified iliac crest biopsies from adult mastocytosis patients have demonstrated increased numbers of mast cells and evidence of

Fig. 118.7 Adult mastocytosis – typical reddish-brown macules and papules.

Fig. 118.8 Telangiectasia macularis eruptiva perstans. Multiple lesions composed of telangiectasias are present.

Fig. 118.9 Darier's sign in mastocytosis. An infant with extensive cutaneous involvement (**A**) and an adult with macular and papular lesions (**B**). *A, Courtesy, Julie V Schaffer, MD. B, Courtesy, Thomas Horn, MD.*

enhanced cortical and trabecular bone turnover. These observations have led to the hypothesis that mast cells and their mediators are directly responsible for the associated skeletal changes. For example, mast cell-derived heparin and SCF have been implicated in promoting osteoporosis via stimulation of osteoclastic activity. Osteoclasts have been shown to express KIT on their surface and to be activated by SCF. Mast cell histamine, however, is capable of promoting bone sclerosis through activation of fibroblasts, and mast cell-derived IL-6 appears to induce both bone resorptive and fibrotic activities[16,17].

The bone marrow is commonly involved in adult patients with mastocytosis. In a report of 71 adults with mastocytosis, 90% had increased numbers of spindle-shaped bone marrow mast cells with focal perivascular, peritrabecular and/or intertrabecular accumulations[18]. Of the 114 patients with adult-onset mastocytosis in the previously cited study[10], 70% had bone marrow involvement. When bone marrow biopsies were performed in 19 children with mastocytosis, only focal perivascular mast cell aggregates were observed in 10 of the patients. Eight of the remaining nine children had normal marrow cellularity, and the ninth child had hypocellular changes[18a]. These and similar observations have led to the recommendation that bone marrow biopsies should not be routinely performed in children with mastocytosis. Also, in patients with indolent mastocytosis and normal hematologic parameters, especially those with limited cutaneous disease, bone marrow biopsies are not required (in the opinion of the author and editors). Of note, some groups have recommended performing a bone marrow biopsy in all adult mastocytosis patients as well as anyone with a serum tryptase level >100 ng/ml (including children)[20].

Splenomegaly, detected either clinically or by CT scan, has been reported in 50% to 60% of adult systemic mastocytosis patients[18,19]. However, in two recent larger studies, each with over 140 adult mastocytosis patients, splenomegaly was observed in only 8–9% of individuals[10,21]. Increased numbers of mast cells and eosinophils are frequently observed in the spleen, as are various degrees of fibrosis and hematopoiesis. Lymph node enlargement is uncommon in most mastocytosis patients, but occurs in patients with more advanced systemic disease. Among 58 systemic mastocytosis patients, 26% had peripheral lymphadenopathy, whereas 19% had central nodal disease[22]. Histologically, early involvement of lymph nodes often consists of only clusters of mast cells, while in more advanced disease, mast cell infiltrates involve the paracortex, and are often accompanied by eosinophils[18,22].

Gastrointestinal (GI) symptoms that are due to mast cell mediator release, such as abdominal pain, diarrhea, nausea and vomiting, may occur spontaneously or may be precipitated by alcohol, aspirin, NSAIDs or certain foods[15,18,20]. Diarrhea in patients with mastocytosis is usually episodic; it can result from malabsorption, increased motility and/or acid hypersecretion, with the former due to infiltration and the latter two probably a result of the release of mast cell histamine and prostaglandins. GI hemorrhage has been reported in some patients with systemic mastocytosis and is often secondary to gastritis or peptic ulcers. A number of radiographic changes in the GI tract have been described and they include urticaria-like lesions and thickened gastric, duodenal and jejunal folds, as well as mucosal nodules and/or peptic ulcers. Biopsies of mucosal nodules have demonstrated numerous mast cells with varying numbers of eosinophils. Hepatomegaly has also been documented in several large series of systemic mastocytosis patients, ranging from 12% to 40%; however, abnormal liver function tests were detected less frequently[10,19,21].

A mixed organic brain syndrome with a constellation of symptoms – including irritability, fatigue, headache, poor attention span and motivation, limited short-term memory, inability to work effectively, and difficulty in interacting with other people – has been described in patients with mastocytosis[23]. It has been hypothesized that these symptoms may be secondary to released mast cell mediators. Electroencephalographic studies in these patients range from normal to changes consistent with a toxic or metabolic process.

Classification of Mastocytosis

In 2001, the World Health Organization (WHO) proposed a classification scheme, with seven disease variants (Table 118.2)[24]. *Cutaneous mastocytosis* represents the largest group and includes children and some adults. Most children with cutaneous mastocytosis have a limited course, with approximately 50% experiencing resolution of their disease by adolescence and the remainder noting a marked reduction in lesion number[3,12]. With the discovery of c-*KIT* mutations in the majority of children with urticaria pigmentosa or diffuse mastocytosis[8], there has been a change in thinking about why most patients experience

WHO CLASSIFICATION OF MASTOCYTOSIS	
Variants (abbreviation)	**Subvariants**
Cutaneous mastocytosis (CM)	Urticaria pigmentosa (maculopapular), diffuse, mastocytoma
Indolent systemic mastocytosis (ISM)	Smoldering systemic mastocytosis (SSM), isolated bone marrow mastocytosis
Systemic mastocytosis with *a*ssociated clonal *h*ematological *n*on-*m*ast cell-lineage *d*isease (AHNMD)*	Associated with myeloproliferative disorder, CMML, myelodysplastic disorder, AML, non-Hodgkin lymphoma, HES†
Aggressive systemic mastocytosis (ASM)	Lymphadenopathic with eosinophilia‡
Mast cell leukemia (MCL)	Aleukemic
Mast cell sarcoma (e.g. larynx, colon, brain)	
Extracutaneous mastocytoma (e.g. lung)	

*Some patients have *JAK2* V617F mutations.
†Myeloproliferative form of HES characterized by *FIP1L1/PDGFRA* fusion gene (see Ch. 25).
‡Some patients have *FIP1L1/PDGFRA* fusion gene.

Table 118.2 WHO classification of mastocytosis. Patients with disorders in shaded boxes often do not have cutaneous lesions. While both are extremely rare, mast cell sarcomas have a poor prognosis while extracutaneous mastocytomas appear to have a good prognosis. AML, acute myelogenous leukemia; CMML, chronic myelomonocytic leukemia; HES, hypereosinophilic syndrome. From ref. 24.

WHO CRITERIA FOR THE DIAGNOSIS OF SYSTEMIC MASTOCYTOSIS
Requires either the major criterion plus one minor criterion* or *three minor criteria
MAJOR CRITERION
• Multifocal dense infiltrates of mast cells (aggregates of ≥15 mast cells) in bone marrow or extracutaneous tissues
MINOR CRITERIA
• >25% of mast cells in bone marrow samples or extracutaneous tissues are spindle-shaped or otherwise atypical • Extracutaneous mast cells (CD117⁺) express CD2, CD25 or both (often bone marrow; determined via flow cytometry) • Presence of c-*KIT* codon 816 mutation in blood, bone marrow or extracutaneous tissues • Serum total tryptase level is persistently >20 ng/ml (unless there is an associated clonal myeloid disorder, in which case this parameter is not valid)

Table 118.3 WHO criteria for the diagnosis of systemic mastocytosis. From ref. 24.

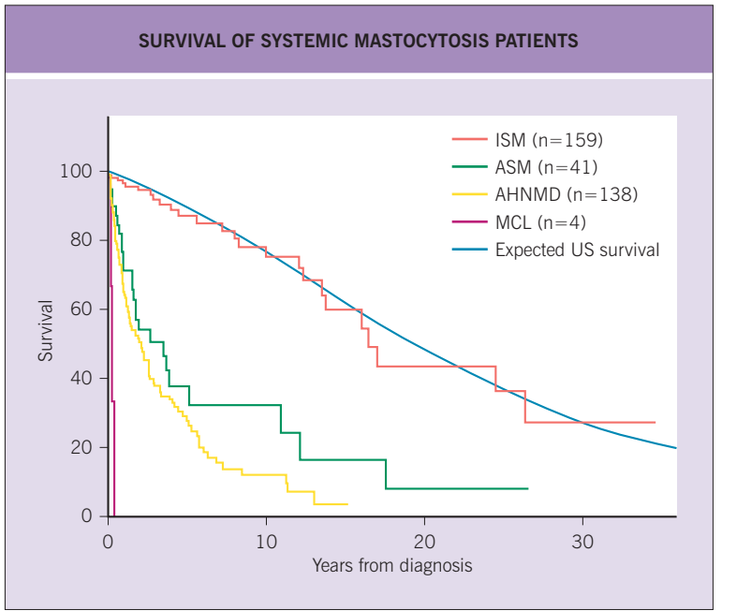


Fig. 118.10 Survival of systemic mastocytosis patients. The life expectancy of patients with indolent systemic mastocytosis (ISM) was not significantly different from the age- and sex-matched US population from the appropriate time period, and leukemic transformation rarely occurred. Based upon these data, the authors recommended that, in general, therapy for ISM should be symptom-directed with avoidance of potentially leukemogenic and immunosuppressive therapies. ASM, aggressive systemic mastocytosis; AHNMD, systemic mastocytosis with *a*ssociated clonal *h*ematological *n*on-*m*ast cell-lineage *d*isease; MCL, mast cell leukemia. *From Lim K-H, Tefferi A, Lasho TL, et al. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. Blood. 2009;113:5727–36.*

spontaneous resolution of childhood-onset mastocytosis and the disease persists into adulthood in only 10–15% (see above).

The WHO has also established criteria for the diagnosis of systemic mastocytosis (SM; Table 118.3)[20,24]. From a dermatologic perspective, appreciation of indolent and smoldering SM is important as these patients frequently have cutaneous lesions. Although mast cell infiltrates can be detected in multiple organs (e.g. bone marrow, liver, spleen and/or lymph nodes) in patients with *indolent SM* (ISM), organ impairment is usually absent and they have few, if any, systemic symptoms. Progression to more severe forms of SM appears to be limited; in a study of 145 adults with ISM, the cumulative probabilities of disease progression to aggressive SM at 10 and 25 years were 1.7% and 8.4%, respectively[21].

Compared to those individuals with ISM, patients with *smoldering SM* (SSM) have more disease burden, e.g. hepatosplenomegaly, lymphadenopathy, serum tryptase levels >200 ng/ml. The overall prognosis for SSM patients is unknown, but they do have the potential to progress to aggressive SM[24]. Recently, a revised classification system was proposed for SM: indolent, smoldering, aggressive, and associated with an unclassifiable myeloproliferative neoplasm (with mast cell leukemia classified under acute leukemias)[25]. The distinction between the first two categories (ISM vs SSM) was based upon the absence or presence, respectively, of "B" symptoms.

Patients with *SM-AHNMD* (systemic mastocytosis-associated clonal hematological non-mast cell-lineage disease) often do not have cutaneous lesions, but they may have liver, spleen and/or lymph node involvement, in addition to the associated hematologic disorder (see Table 118.2). The overall prognosis of SM-AHNMD patients appears directly dependent upon the severity of the hematologic disease[20,24].

Patients with *aggressive SM* have symptomatic disease due to mast cell infiltrates in the liver (hepatomegaly, functional impairment), bone (pain, pathologic fractures), gastrointestinal tract (malabsorption) and spleen (hypersplenism), in addition to cytopenias, leukocytoses (eosinophilia, basophilia, monocytosis) and thrombocytosis as a reflection of bone marrow involvement and abnormal myelopoiesis. The serum tryptase level is often high, reflecting a significantly increased total body mast cell burden. The overall prognosis appears to be dependent upon the response to treatment[20,21,24], and in one study, the median survival was 3.5 years (Fig. 118.10)[26].

Mast cell leukemia (MCL) is rare. Diagnosis requires the peripheral blood nucleated cell population to be composed of at least 10% mast cells and bone marrow smears to contain at least 20% mast cells[20,21,24]. However, because mature mast cells are rarely observed in the peripheral blood of normal individuals, their presence should raise the suspicion of MCL. Most patients do not have cutaneous lesions, but frequently experience recurrent fever, weight loss, abdominal pain, diarrhea, nausea and vomiting. Multiorgan failure, including the bone marrow, often occurs over weeks to a few months. Prognosis is extremely poor, with an expected survival of a year or less from the time of diagnosis[20,24].

With the detection of c-*KIT* mutations (see Table 118.1), an alternative classification for childhood, adult-onset, and familial mastocytosis may become more clinically relevant (e.g. D816 mutations versus extracellular domain mutations). However, in a recent study of 165 adults with systemic mastocytosis, the presence of the D816V mutation did not correlate with survival, but it did correlate with mast cell burden[26].

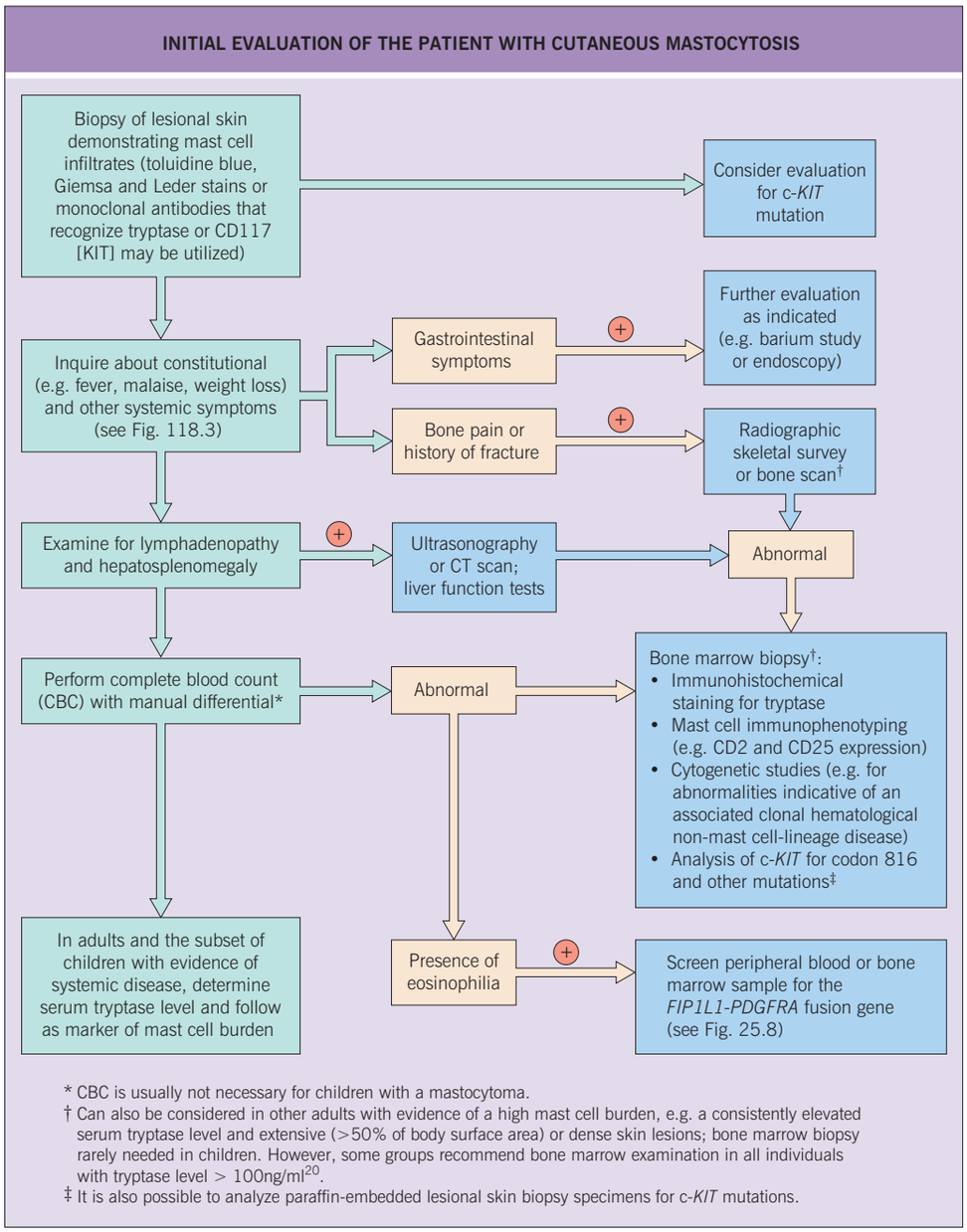


Fig. 118.11 Initial evaluation of the patient with cutaneous mastocytosis. A proposed scheme for the diagnosis of mastocytosis of the skin requires one major criterion (typical skin lesions clinically) plus one or two minor criteria. The minor criteria are: (1) monomorphic mast cell infiltrate that consists of either large aggregates of tryptase-positive mast cells (>15 cells/cluster) or scattered mast cells exceeding 20 cells per microscopic high power field (40×); and (2) detection of a c-*KIT* mutation at codon 816 in lesional skin[20].

Interestingly, patients with familial disease often lack c-*KIT* mutations. The clinical course and overall prognosis of familial disease appears good, but is less well defined.

An approach to the initial evaluation of a patient with mastocytosis is presented in Figure 118.11.

PATHOLOGY

Direct Studies

The diagnosis of mastocytosis is established by demonstrating characteristic mast cells in one or more organs. For patients with cutaneous lesions, mast cell infiltrates can be demonstrated in a biopsy of lesional skin (Fig. 118.12). Eosinophils are also commonly found within the dermis and hyperpigmentation of the basal layer of the epidermis is often seen, especially in lesions of urticaria pigmentosa. Special stains, such as toluidine blue, Giemsa and Leder, or monoclonal antibodies that recognize tryptase or CD117 (KIT) are helpful for identifying tissue mast cells (Fig. 118.13). Mast cells in nodular, papular and macular lesions (including TMEP) of mastocytosis have been quantified using a morphometric technique and shown to contain mean mast cell densities of 63.2% (± 8.2% SEM), 16.1% (± 4.8% SEM) and 3.5% (± 1.8% SEM), respectively[27]. In contrast, the mast cell content of normal skin

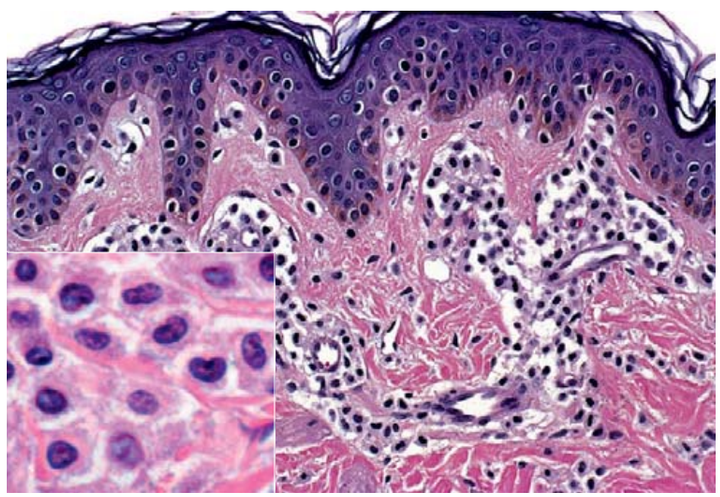


Fig. 118.12 Cutaneous mastocytosis – histologic features. Mast cells within the dermis have a "fried egg" appearance. Granules are seen within the amphophilic cytoplasm (insert). *Courtesy, Lorenzo Cerroni, MD.*

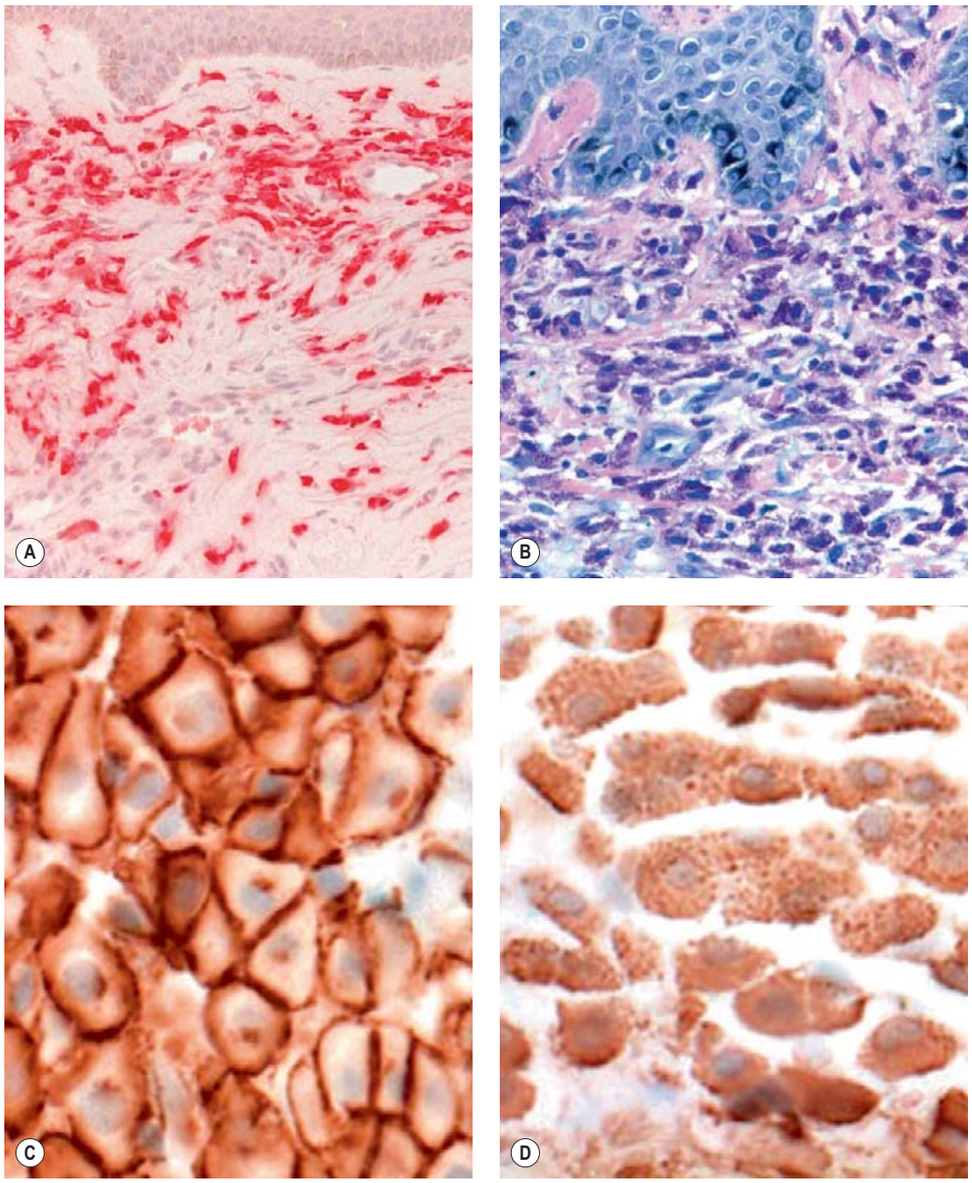


Fig. 118.13 Special stains to detect dermal mast cells. A The Leder method utilizes naphthol AS-D chloroacetate esterase and the mast cell granules appear red. **B** With the Giemsa stain, the mast cell granules stain metachromatically purple. Immunohistochemical staining with monoclonal antibodies that recognize CD117/KIT receptor (**C**) or tryptase (**D**) can also be employed. *A,B, Courtesy, Lorenzo Cerroni, MD. C,D, Courtesy, Antonio Subtil, MD.*

was reported to be 0.4% (± 0.1% SEM). In cases of adult mastocytosis with cutaneous lesions that contain only borderline numbers of mast cells, molecular diagnostic studies for c-*KIT* mutations may help confirm or establish a diagnosis. However, these studies are not routinely available. Immunohistochemical staining for CD117 (KIT) can prove helpful in establishing the diagnosis in more subtle forms of mastocytosis[20,28].

Biopsy specimens of normal-appearing skin from patients with mastocytosis have normal concentrations of mast cells, and thus are not helpful in establishing the diagnosis. A biopsy of the bone marrow or GI tract may be indicated for patients in whom the diagnosis of SM is a possibility, but who lack skin lesions. Increased mast cell numbers in association with variable numbers of eosinophils are observed in these tissue specimens. In addition, the combination of monoclonal antibodies against CD117 (KIT) and tryptase may be particularly useful for identifying atypical mast cells in various tissues[20,28]. WHO criteria for the diagnosis of SM are listed in Table 118.3.

Indirect Studies

Detection of circulating mast cell mediators and/or their metabolites can offer indirect evidence of mastocytosis. Two forms (α and β) of mast cell tryptase have been identified[29]. Alpha-tryptase is elevated in patients with SM, regardless of whether or not they are experiencing acute symptoms, and therefore may be useful in assessing total body mast cell burden. Beta-tryptase, however, is often detected both in mastocytosis patients and in patients without mastocytosis who are experiencing anaphylactic symptoms. Total (α and β) serum tryptase levels have been correlated with the extent of mast cell disease. Fifty percent of patients with total serum tryptase levels between 20 and 75 ng/ml had evidence of SM, whereas all patients with levels >75 ng/ml had proven systemic involvement. Of note, a total serum tryptase level >20 ng/ml represents one of the minor criteria for SM[24] (see Table 118.3).

Urinary histamine and its metabolites have also been measured in mastocytosis patients. In many instances, unmetabolized urinary histamine levels may be normal in asymptomatic SM patients, whereas the major metabolite of histamine, 1,4-methylimidazole acetic acid (MeImAA), is often persistently elevated. When urinary MeImAA levels were correlated with the extent of mast cell disease, patients with widespread systemic involvement had the highest concentrations, and patients with only cutaneous disease had normal or only slightly elevated MeImAA[30]. It is important to note that certain foods with high histamine content, such as spinach, eggplant, cheeses (Parmesan, Roquefort and blue) and red wines, can artificially elevate the levels of urinary histamine and its metabolites.

The urinary excretion of the major urinary metabolite of prostaglandin D_2 (PGD_2), 9α,11β-dihydroxy-15-oxo-2,3,18,19-tetranorprost-5-ene-1,20-diolic acid (PGD_2M), has also been reported to be increased in some systemic mastocytosis patients[31]. In one study of 17 patients with mastocytosis, the levels of PGD_2M were compared to urinary

methylhistamine concentrations. In all patients, urinary PGD_2M levels were increased to a greater extent than those of methylhistamine, and markedly elevated PGD_2M levels were detected in four patients with a normal concentration of urinary methylhistamine. Urinary PGD_2M levels have not been compared to urinary MeImAA or serum α-tryptase determinations, and as a result it is unclear whether measuring PGD_2M offers any advantage over obtaining commercially available urinary MeImAA or serum tryptase levels. Plasma levels of IL-6 have also been shown to be elevated in patients with mastocytosis, correlating with severity of bone marrow pathology, organomegaly and extent of skin involvement[32].

DIFFERENTIAL DIAGNOSIS

The lesions of childhood and adult mastocytosis are so characteristic that they are only occasionally confused with other skin disorders. Childhood lesions of UP may spontaneously urticate and thus may be mistaken for urticaria. However, lesions of urticaria last only a few hours and do not have the associated hyperpigmentation seen in UP. Some childhood mastocytosis patients may develop bullae. Therefore, the differential diagnosis for blisters in these children includes bullous arthropod bites, bullous impetigo, herpes simplex viral infection, linear IgA bullous dermatosis and, less often, other autoimmune bullous dermatoses. In addition, children with diffuse cutaneous mastocytosis may develop widespread blisters early in their course, which may be mistaken for epidermolysis bullosa or toxic epidermal necrolysis. Demonstration of increased mast cells in either the blister fluid or skin biopsy of the mastocytosis patient helps to establish the correct diagnosis. Rarely, nodular scabies has been misdiagnosed as mastocytosis. Lastly, if mast cells are not readily detected due to the presence of other leukocytes within the dermis, the patient may be misdiagnosed as having a histiocytic disorder or vasculitis[33].

Skin lesions of adult mastocytosis patients may at first glance appear as lentigines or melanocytic nevi, but mastocytosis lesions usually have an associated erythema. Mastocytomas in children may be confused with café-au-lait macules, arthropod bites, Spitz or congenital melanocytic nevi, pseudolymphomas and juvenile xanthogranulomas.

TREATMENT

Treatment of patients with mastocytosis is directed primarily at alleviating symptoms, since there is no cure for this disorder. Many patients with CM and ISM have few, if any, symptoms, and therefore require little or no therapy. Mastocytosis patients should be cautioned to avoid potential mast cell degranulating agents and environmental triggers (Table 118.4). A number of systemic anesthetic agents that have been directly or indirectly implicated in precipitating anaphylactoid reactions in mastocytosis patients are listed in Table 118.4. In contrast to systemic anesthetics, local injections of lidocaine can be used safely in these patients, and recent reports indicate that fentanyl, sufentanil, remifentanil, midazolam, propofol, ketamine, desflurane, sevoflurane, cisatracurium, pancuronium and vecuronium bromide are safe alternative systemic anesthetics for patients with mastocytosis. It has been recommended that mastocytosis patients undergoing general anesthesia be monitored postoperatively for at least 24 hours since delayed anaphylaxis has occurred hours after surgery in some of these patients[34,35].

Histamine type 1 (H_1) receptor antagonists, or combined H_1 and H_2 receptor antagonists, are often helpful in controlling many of the symptoms associated with mastocytosis. The second-generation antihistamines cetirizine, loratadine and fexofenadine have distinct advantages over first-generation antihistamines because they have longer half-lives and are more specific H_1 antagonists. In some instances, the addition of an H_2 antagonist (cimetidine, ranitidine, famotidine or nizatidine) may prove beneficial, especially in patients with gastric acid hypersecretion. Oral cromolyn sodium (disodium cromoglycate; 400–800 mg/day) may alleviate GI, cutaneous and CNS symptoms associated with mastocytosis.

Psoralen plus UVA (PUVA) therapy given up to four times a week can help to control the pruritus and cutaneous whealing in patients with mastocytosis[36,37]. While PUVA is capable of reducing skin mast cell histamine content, it does not permanently eliminate cutaneous mast cell infiltrates.

THERAPEUTIC LADDER FOR MASTOCYTOSIS
AVOIDANCE OF POTENTIAL MAST CELL STIMULI
Alcohol Anticholinergic medications Aspirin Nonsteroidal anti-inflammatory drugs Heat Friction Narcotics (e.g. morphine, codeine) Polymyxin B sulfate Systemic anesthetics, including lidocaine, d-tubocurarine, metocurine, etomidate, thiopental, succinylcholine hydrochloride (suxamethonium chloride), enflurane, isoflurane (see text for alternatives)
LOCAL THERAPY FOR SYMPTOM CONTROL
Potent and superpotent topical corticosteroids, including under occlusion (2) Intralesional corticosteroids (3)
SYSTEMIC THERAPY FOR SYMPTOM CONTROL
Oral H_1 and H_2 receptor antagonists (2) Oral cromolyn sodium (1) Oral PUVA [psoralens plus ultraviolet A] (2) Oral corticosteroids (3) UVA1 (3) Pre-measured epinephrine with auto-injector (EpiPen®) (3)
SYSTEMIC THERAPY FOR AGGRESSIVE/SEVERE MASTOCYTOSIS
Interferon-α-2b (2; limited success) Cladribine (2) Imatinib mesylate or other KIT inhibitors, depending upon type of mutation (3)

Table 118.4 Therapeutic ladder for mastocytosis. Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

Potent topical corticosteroids under occlusion for 6 weeks or more eliminate pruritus and cutaneous whealing and reduce histamine levels and the number of lesional skin mast cells, but they can lead to skin atrophy[38]. Intralesional injections of triamcinolone acetonide have also been successful in clearing mast cell infiltrates in the skin of mastocytosis patients. The use of systemic corticosteroids in SM patients has been anecdotal, but relief of both cutaneous and GI symptoms has been reported using prednisone, alone or in combination with cyclosporine, for more severe disease[39,40].

Some patients with systemic mastocytosis may experience recurrent, life-threatening episodes of hypotension following mast cell mediator release, and therefore should be provided with a premeasured epinephrine (adrenaline) preparation (EpiPen®) for emergency use. In some instances, these patients may experience recurrent similar attacks within hours of the initial event; when this occurs, prednisone (20–40 mg/day for 2–4 days) should be initiated, since it often suppresses these recurrent reactions.

Interferon-α-2b has been used with limited success in patients with aggressive forms of mastocytosis. Of the various chemotherapeutic agents that have been tried for severe mastocytosis, intravenous cladribine (2-chlorodeoxyadenosine [2-CDA]) has been shown to effectively eliminate skin lesions and markedly reduce the number of bone marrow mast cells in patients with advanced SM, including those with the D816 c-*KIT* mutation. Because this latter group of patients does not respond to imatinib mesylate (see below), for them 2-CDA represents first-line therapy[41,42]. For patients with SM-AHNMD, chemotherapy should be directed at treating the associated hematologic disorder. Local radiation therapy (approximately 20 to 40 Gy over a 7- to 14-day period) may benefit patients with bone pain. Splenectomy may be indicated for mastocytosis patients with hypersplenism who experience significant cytopenia, and it appears to improve survival in patients with more aggressive disease. Non-myeloablative allogeneic hematopoietic stem cell transplantation for life-threatening disease is still under investigation.

Imatinib mesylate is a tyrosine kinase inhibitor that can inhibit the KIT and PDGF receptors, as well as the BCR-ABL oncoprotein

associated with chronic myelogenous leukemia. However, the active site for imatinib within the KIT receptor is at a distance from the location of the amino acid substitutions that result from the most common mutation, D816 (see Table 118.1), and the latter are thought to hamper the binding ability of imatinib. As a result, imatinib does not alter the clinical course of patients with mutations at this codon[43]. On the other hand, it does appear to alleviate the signs and symptoms of mastocytosis in patients with rare c-*KIT* mutations (e.g. del419, V560G, F522C and K509I; see Fig 118.2)[43–45], in addition to those with the *FIP1L1-PDGFRA* fusion gene who are D816-negative[46]. Dasatinib, a dual SRC/ABL kinase inhibitor, reduces the proliferation of D816V-expressing mastocytosis mast cell lines *in vitro*; however, this agent does not appear to be effective as monotherapy for mastocytosis patients who have this mutation[47].

REFERENCES

1. Nettleship E, Tay W. Rare forms of urticaria. Br Med J. 1869;2:323–4.
2. Sangster A. An anomalous mottled rash accompanied by pruritus, factitious urticaria and pigmentation. Urticaria pigmentosa? Trans Clin Svc. London. 1878;11:161–3.
3. Caplan RM. The natural course of urticaria pigmentosa. Arch Dermatol. 1963;87:146–57.
4. Longley BJ, Metcalfe DD, Tharp MD, et al. Activating and dominant inactivating c-*KIT* catalytic domain mutations in distinct clinical forms of human mastocytosis. Proc Natl Acad Sci USA. 1999;96:1609–14.
5. Rottem M, Okada T, Goff JP, et al. Mast cells cultured from the peripheral blood of normal donors and patients with mastocytosis originate from a CD34+/FcεRI– cell population. Blood. 1994;84:2489–96.
6. Longley BJ, Tyrrell L, Ma Y, et al. Chymase cleavage of stem cell factor yields a bioactive, soluble product. Proc Natl Acad Sci USA. 1998;94:9017–21.
7. Anderson DM, Lyman SD, Baird A, et al. Molecular cloning of mast cell growth factor, a hematopoietin that is active in both membrane bound and soluble forms. Cell. 1990;63:235–43.
8. Bodemer C, Hermne O, Palmérini F, et al. Pediatric mastocytosis is a clonal disease associated with $D^{816}V$ and other activating c-*KIT* mutations. J Invest Dermatol. 2010;130:804–15.
9. Yang Y, Létard S, Borge L, et al. Pediatric mastocytosis-associated KIT extracellular domain mutations exhibit different functional and signaling properties compared with KIT-phosphotransferase domain mutations. Blood. 2010;116:1114–23.
10. Lanternier F, Cohen-Akenine A, Palmérini F, et al. Phenotypic and genotypic characteristics of mastocytosis according to the age of onset. PLos ONE. 2008;3:1–6.
11. Zappulla JP, Dubreuil P, Desbois S, et al. Mastocytosis in mice expressing human Kit receptor with the activating Asp816Val mutation. J Exp Med. 2005;202:1635–41.
12. Heide R, Tank B, Oranje AP. Mastocytosis in childhood. Ped Dermatol. 2002;19:375–81.
13. Kasprowicz S, Chan IJ, Tharp MD. Nodular mastocytosis. Arch Dermatol. 2006;55;347–9.
14. Kasper CS, Tharp MD. Quantification of cutaneous mast cells using morphometric point counting and a conjugated avidin stain. J Am Acad Dermatol. 1987;16:326–31.
15. Travis W, Li C-Y, Bergstrahl E, et al. Systemic mast cell disease. Medicine (Baltimore). 1988;67:345–68.
16. Andrew SM, Freemont AJ. Skeletal mastocytosis. J Clin Pathol. 1993;46:1033–5.
17. Linkhart TA, Linkhart SG, MacCharles DC, et al. Interleukin-6 messenger RNA expression and interleukin-6 protein secretion in cells isolated from normal human bone: regulation by interleukin-1. J Bone Miner Res. 1991;6:1285–94.
18. Sagher F, Even-Paz Z. Mastocytosis and the mast cell. Chicago: Yearbook Medical, 1967;10–291.
18a. Parker RI. Hematologic aspects of mastocytosis: I: Bone marrow pathology in adult and pediatric systemic mast cell disease. J Invest Dermatol. 1991;96:47S–51S.
19. Metcalfe DD. The liver, spleen, and lymph nodes in mastocytosis. J Invest Dermatol. 1991;96:45S–46S.
20. Valent R, Akin C, Escribano M, et al. Standards and standardization in mastocytosis: consensus statements on diagnostic, treatment recommendations and response criteria. Eur J Clin Invest. 2007;37:435–53.
21. Escribano L, Alvarez-Twose I, Sanchez-Munoz L, et al. Prognosis in adult indolent systemic mastocytosis: a long-term study of the Spanish network on mastocytosis in a series of 145 patients. J Allergy Clin Immunol. 2009;124:514–21.
22. Travis WD, Li C-Y. Pathology of the lymph node and spleen in systemic mast cell disease. Mod Pathol. 1986;1:4–14.
23. Rogers M, Bloomingdale K, Murawski B, et al. Mixed organic brain syndrome as a manifestation of systemic mastocytosis. Psychosomatic Med. 1986;48:437–47.
24. Horny H-P, Akin C, Metcalfe DD, et al. Mastocytosis. In: Swerdlow SH, Campo E, Harris NL, et al. (eds). WHO Classification of Tumours of Haematopoetic and Lymphoid Tissues. Lyon, France: IARC Press, 2008:54–63.
25. Pardanani A, Tefferi A. Proposal for a revised classification of systemic mastocytosis. Blood. 2010;115:2720–1.
26. Lim K-H, Tefferi A, Lasho TL, et al. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. Blood. 2009;113:5727–36.
27. Kasper C, Freeman RG, Tharp MD. Diagnosis of mastocytosis subsets using a morphometric point counting technique. Arch Dermatol. 1987;123:1017–21.
28. Lee HW, Jeong YI, Choi JC, et al. Two cases of telangiectasia macularis eruptiva perstans demonstrated by immunohistochemistry for c-KIT (CD117). J Dermatol. 2005;32:817–20.
29. Schwartz LB, Sakai K, Bradford TR, et al. The α form of human tryptase is the predominant type present in blood at baseline in normal subjects and is elevated in those with systemic mastocytosis. J Clin Invest. 1995;96:2702–10.
30. Keyzer JL, DeMonchy JGR, van Doormaal JJ, et al. Improved diagnosis of mastocytosis by measurement of urinary histamine metabolites. N Engl J Med. 1983;309:1603–5.
31. Morrow J, Guzo C, Lazarus G, et al. Improved diagnosis of mastocytosis by measurement of the major urinary metabolite of prostaglandin D2. J Invest Dermatol. 1995;104:937–40.
32. Theoharides TC, Boucher W, Speark K. Serum interleukin-6 reflects disease severity and osteoporosis in mastocytosis patients. Int Arch Allergy Immunol. 2002;128:344–50.
33. Dunst KM, Huemer GM, Zelger BG, et al. A new variant of mastocytosis: report of three cases clinicopathologically mimicking histiocytic and vasculitic disorders. Br J Dermatol. 2005;153:642–6.
34. Borgeat A, Ruetsch YA. Anesthesia in a patient with malignant systemic mastocytosis using a total intravenous anesthetic technique. Anesth Analg. 1998;86:442–4.
35. Konrad FM, Schroeder TH. Anaesthesia in patients with mastocytosis. Acta Anaesth Scand. 2009;53;207–10.
36. Kolde G, Frosch P, Czarnetzki B. Response of cutaneous mast cells to PUVA in patients with urticaria pigmentosa: histomorphometric, ultrastructural, and biochemical investigations. J Invest Dermatol. 1984;83:175–8.
37. Godt O, Proksch E, Streit V, et al. Short- and long-term effectiveness of oral and bath PUVA therapy in urticaria pigmentosa and systemic mastocytosis. Dermatology. 1997;195:35–9.
38. Barton J, Lavker RM, Schechter NM, et al. Treatment of urticaria pigmentosa with corticosteroids. Arch Dermatol. 1985;121:1516–23.
39. Kurosawa M, Amano H, Kanbe N, et al. Response to cyclosporin and low dose methylprednisolone in aggressive systemic mastocytosis. J Allergy Clin Immunol. 1999;103:S412–20.
40. Butterfield JH. Response of severe systemic mastocytosis to interferon-alpha. Br J Dermatol. 1998;138:489–95.
41. Teferi A, Li CY, Butterfield, JH, Hoagland HC. Treatment of systemic mast cell disease with cladribine. N Engl J Med. 2001;344:307–8.
42. Pardanani A, Hoffbrand AV, Butterfield JH, et al. Treatment of systemic mast cell disease with 2-chlorodeoxyadenosine. Leuk Res. 2004;28;127–31.
43. Vega-Ruiz A, Cortes JE, Sever M, et al. Phase II study of imatinib mesylate as therapy for patients with systemic mastocytosis. Leuk Res. 2009;33;1481–4.
44. Zhang LY, Smith ML, Schultheis B, et al. A novel K509I mutation of *KIT* identified in familial mastocytosis – in vitro and in vivo responsiveness to imatinib therapy. Leuk Res. 2006;30:373–8.
45. Hoffman KM, Moser A, Lhose P, et al. Successful treatment of progressive cutaneous mastocytosis with imatinib in a 2 year old boy carrying a somatic *KIT* mutation. Blood. 2008;112;1655–7.
46. Pardanani A, Ketterling R, Brockman SR, et al. *CHIC2* deletion, a surrogate for *FIP1L1-PDGFRA* fusion, occurs in systemic mastocytosis associated with eosinophilia and predicts response to imatinib mesylate therapy. Blood. 2003;102;3093–6.
47. Purtill D, Cooney J, Sinnian R, et al. Dasatinib therapy for systemic mastocytosis: four cases. Eur J Haematol. 2008;80;456–8.

B-Cell Lymphomas of the Skin 119

Lorenzo Cerroni

Synonyms: ■ Cutaneous B-cell lymphomas ■ *S*kin-*a*ssociated *l*ymphoid *t*issue (SALT)-related B-cell lymphomas

Key features

- Cutaneous B-cell lymphomas represent a group of lymphomas whose primary site is the skin; they are derived from B lymphocytes in different stages of differentiation. The skin can also be the site of secondary involvement by extracutaneous (usually nodal) B-cell lymphomas
- Most primary cutaneous B-cell lymphomas (>80%) are low-grade malignancies, and they are characterized by indolent behavior and a good prognosis
- The widespread use of immunohistochemical and molecular genetic techniques has shown that many of the cases previously classified as cutaneous B-cell pseudolymphomas actually represent low-grade malignant B-cell lymphomas of the skin
- Precise classification can be achieved only after a complete synthesis of clinical, histopathologic, immunophenotypic and molecular features. The WHO-EORTC and new WHO classifications provide the basis for a consistent classification of patients
- Treatment options for low-grade types include primarily "watchful waiting" and local radiotherapy; when solitary lesions are present, surgical excision is an option. Systemic or intralesional anti-CD20 antibody may be used in some patients, while systemic chemotherapy is usually required in only a small proportion of patients with high-grade tumors

INTRODUCTION

Although B-cell lymphomas represent the majority of non-Hodgkin lymphomas arising within lymph nodes, they represent only a minority of the non-Hodgkin lymphomas whose primary site is the skin. In the classification of cutaneous lymphomas published by the World Health Organization (WHO) and the European Organization for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Project Group (Table 119.1), B-cell lymphomas represented 22.5% of all cutaneous lymphomas[1]. A similar figure was derived from a large series of patients observed in Graz between 1960 and 1999, in which B-cell lymphomas represented 26.4% of all cases of primary cutaneous lymphoma[2]. The WHO-EORTC classification has been integrated with only minor changes into the new WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues published in 2008 (see Table 119.1)[3].

Primary cutaneous lymphomas are defined as *malignant lymphomas confined to the skin at presentation after complete staging procedures*[1,4]. In general, most patients with primary cutaneous B-cell lymphoma are diagnosed by dermatologists, as extracutaneous symptoms and signs are observed only very rarely at the onset of the disease. Consequently, dermatologists should be conversant with the clinicopathologic features of this group of diseases, in order to be able to establish the diagnosis in its early stages. Additionally, as aggressive treatment modalities are needed only in selected cases, these patients should be managed primarily in dermatology departments with special expertise in cutaneous lymphomas.

HISTORY

In the past, cutaneous B-cell lymphomas were thought to be invariably secondary, that is, due to dissemination of extracutaneous (usually nodal) B-cell lymphomas to the skin. In recent years, it was recognized that B-cell lymphomas whose primary site is the skin, i.e. primary cutaneous B-cell lymphomas (pCBCLs), represent a distinct and very important group of extranodal lymphomas[4]. The widespread use of immunohistochemical and molecular genetic techniques that can establish clonality has shown that many of the cases previously classified as cutaneous B-cell pseudolymphomas actually represent low-grade malignant B-cell lymphomas of the skin[4,5].

The WHO-EORTC and WHO 2008 classification schemes provide a valid basis for a uniform classification of pCBCLs and should be used consistently, in order to allow comparison of data amongst different centers.

EPIDEMIOLOGY

Although reports of single cases or small series of pCBCL have been published from around the world, there are only a few studies of large series of patients. Consequently, epidemiologic data are still fragmentary and are based primarily on the experience of two major centers in the Netherlands and Austria[1,2].

pCBCLs may occur more frequently in specific regions of the world. For example, analysis of data from four academic centers in the US showed that they represented only 4.5% of all the cases of primary cutaneous lymphoma registered in those centers[6]. In contrast, pCBCL represented 22.5% of all the cases of primary cutaneous lymphoma in the Dutch and Austrian registries for cutaneous lymphomas[1].

Regional variations have also been observed with regard to the incidence of specific types of pCBCL. In the two largest series published to date, the relative frequencies of follicle center lymphoma and marginal zone lymphoma varied considerably. For example, follicle center lymphoma represented 71% of all pCBCLs in the Netherlands, but only 41% in Graz; conversely, marginal zone lymphoma represented 42% of all cases of pCBCL in Graz, but only 10% in the Netherlands. On the other hand, the relative frequency of the third most common type of pCBCL, the diffuse large B-cell lymphoma, leg type, was similar in the two series (~15%), indicating that, in these two series, differences in the relative frequencies were confined to B-cell lymphomas characterized by an indolent behavior. This suggests that these variations may be due, at least in part, to a different classification of patients in different centers.

Although variations in the relative frequency of pCBCLs, and of specific subtypes, may be explained by differences in diagnostic and classification standards, true regional variations in the incidence of special types of pCBCL may be due to the presence of different etiologic factors. For example, the association between pCBCL and infection with specific *Borrelia* species in endemic areas has been known for many years (see Ch. 74). This association may explain, in part, regional differences in the incidence of pCBCLs, but the relatively low percentage of such cases (even in countries with endemic *Borrelia* infections) suggests that other etiologies are also involved in regional variations.

pCBCL affects adults of both sexes. In a study of 147 patients, there was a slight predominance of men (male : female = 1.1 : 1)[2]. With the exception of precursor B lymphoblastic lymphoma/leukemia (which

WHO-EORTC 2005 CLASSIFICATION OF B-CELL LYMPHOMAS WITH PRIMARY CUTANEOUS MANIFESTATIONS [CORRESPONDING ENTITY IN THE WHO 2008 CLASSIFICATION]
• Primary cutaneous follicle center lymphoma (PCFCL) [same]
• Primary cutaneous marginal zone B-cell lymphoma (PCMZL)* [Extranodal marginal zone lymphoma of *m*ucosa-*a*ssociated *l*ymphoid *t*issue – MALT lymphoma]
• Primary cutaneous diffuse large B-cell lymphoma, leg type (DLBCLLT) [same]
• Primary cutaneous diffuse large B-cell lymphoma, other [Diffuse large B-cell lymphoma, NOS]
• Intravascular diffuse large B-cell lymphoma [same]
*Includes cases previously designated as primary cutaneous immunocytoma and primary cutaneous plasmacytoma.

Table 119.1 WHO-EORTC 2005 and corresponding WHO 2008 classification of B-cell lymphomas with primary cutaneous manifestations. NOS, not otherwise specified.

only rarely represents an example of true pCBCL), only a few cases have been observed in patients less than 20 years of age.

ETIOLOGY AND PATHOGENESIS

The pathogenesis of pCBCL is unknown. In contrast to the many nodal B-cell lymphomas that have been linked to specific genetic alterations (e.g. nodal follicular lymphomas and interchromosomal 14;18 translocations), there are relatively limited data on the specific genetic features of pCBCLs, especially for low-grade subtypes (for details see below).

Some similarities to the clinicopathologic features observed in B-cell lymphomas arising in the gastric mucosa (so-called *mucosa-associated lymphoid tissue* [MALT] lymphomas) led to the hypothesis that pCBCLs are caused by longstanding antigenic stimulation, possibly due to chronic infection with specific microorganisms. In fact, it has been long established that MALT lymphomas originating in the stomach are linked to chronic antigenic stimulation due to infection with *Helicobacter pylori*. As previously mentioned, *Borrelia* spp. are thought to play a role in the etiology of a minority of cases of pCBCL, particularly in Europe. In patients from a region in Austria with endemic *Borrelia* infections, specific DNA sequences of *Borrelia* were detected in 18% of all cases of pCBCL[7]; similar findings have been reported from Scotland[8].

At present, no other microorganism has been convincingly linked to the development of pCBCL. However, it should be noted that pCBCLs have been described in patients with AIDS, and reversible pCBCLs have been observed in patients undergoing therapy with methotrexate (in particular those with rheumatoid arthritis), thus suggesting that immune dysregulation may play a role in the development of this disease[9,10].

CLINICAL FEATURES

In the WHO-EORTC 2005 classification scheme, pCBCLs have been divided into four major types (see Table 119.1)[1]; these subtypes are also included in the WHO 2008 classification scheme. Follicle center lymphoma and marginal zone B-cell lymphoma are characterized by an indolent clinical behavior, whereas diffuse large B-cell lymphoma, leg type, and intravascular diffuse large B-cell lymphoma have a more aggressive clinical behavior. It must be emphasized that, in addition to pCBCLs, the skin can be a site of secondary involvement for practically all types of extracutaneous (usually nodal) B-cell lymphomas and leukemias. Consequently, complete staging must be performed in all patients with a confirmed diagnosis of B-cell lymphoma involving the skin. This includes a complete blood examination, flow cytometry of peripheral blood, and CT examination of the chest, abdomen and pelvis. Gallium scans have been replaced by positron emission tomography (PET). Bone marrow biopsy (with flow cytometry of the aspirate) is recommended in follicle center lymphoma, diffuse large B-cell lymphoma, leg type, and intravascular diffuse large B-cell lymphoma, but seems to be of limited value in cutaneous marginal zone lymphoma[11].

In the following two sections, the clinicopathologic features of the main types of pCBCL will be discussed. In addition, the cutaneous manifestations of precursor B lymphoblastic lymphoma/leukemia will be presented.

Primary Cutaneous Follicle Center Lymphoma

*P*rimary *c*utaneous *f*ollicle *c*enter *l*ymphoma (PCFCL) is defined as a neoplastic proliferation of germinal center cells confined to the skin. It represents a common subtype of pCBCL.

Clinically, patients present with solitary or grouped, pink- to plum-colored papules, plaques or tumors, which, especially on the trunk, can be surrounded by patches of erythema (Figs 119.1 & 119.2). Ulceration is uncommon. Preferential locations are the scalp and forehead or the back. In the past, lesions located on the back were referred to as Crosti's lymphoma or reticulohistiocytoma of the dorsum[12]. The skin lesions are usually asymptomatic, and, as a rule, symptoms are rare. The serum level of lactate dehydrogenase (LDH), which is a powerful prognostic factor in systemic lymphomas, is within normal limits.

The prognosis is favorable[1,13,14]. Recurrences are observed in up to 50% of patients, but dissemination to lymph nodes or internal organs is rare.

Primary Cutaneous Marginal Zone B-Cell Lymphoma

*P*rimary *c*utaneous *m*arginal *z*one B-cell *l*ymphoma (PCMZL) has been recognized as a distinct variant of low-grade malignant pCBCL[5,15]. In the WHO classification of 2008[3], it has been grouped with other extranodal marginal zone lymphomas of *m*ucosa-*a*ssociated *l*ymphoid *t*issue

Fig. 119.1 Cutaneous follicle center lymphoma. Large ulcerated tumors on the scalp surrounded by infiltrated erythematous nodules and plaques.

Fig. 119.2 Cutaneous follicle center lymphoma. Large ulcerated tumor on the back. Note surrounding erythematous papules, patches and plaques (Crosti's lymphoma).

(i.e. MALT lymphomas). Of note, cases classified in the past as *primary cutaneous immunocytoma* or *primary cutaneous plasmacytoma* represent examples of PCMZL with prominent lymphoplasmacytic or plasmacytic differentiation, respectively, and the terms cutaneous immunocytoma and cutaneous plasmacytoma are not used in the WHO-EORTC and WHO 2008 classification schemes[1,3].

Clinically, patients present with recurrent pink–violet to red–brown papules, plaques and nodules localized preferentially on the extremities (upper more so than lower) or trunk (Figs 119.3 & 119.4). Generalized lesions can be observed in a small number of patients. Ulceration rarely, if ever, occurs and skin lesions are usually asymptomatic. As a rule, systemic signs and symptoms, such as fever, night sweats, weight loss and malaise (B-symptoms), are not present. The serum level of LDH is within normal limits. In some instances, resolution of lesions may be accompanied by secondary anetoderma due to loss of elastic fibers in the area of the tumor infiltrate.

The prognosis of PCMZL is excellent. In a study of 32 patients with PCMZL, none of them developed lymph node or internal involvement during a mean follow-up of more than 4 years[5].

Fig. 119.3 Cutaneous marginal zone B-cell lymphoma. Two well-circumscribed, erythematous nodules on the shoulder.

Fig. 119.4 Cutaneous marginal zone B-cell lymphoma. Dome-shaped erythematous nodule with smooth surface. The surrounding area shows features of acrodermatitis chronica atrophicans. This tumor, which demonstrated prominent lymphoplasmacytic differentiation histologically, was classified as cutaneous immunocytoma in the past.

Of note, PCMZL can arise in areas affected by acrodermatitis chronica atrophicans (see Fig. 119.4), and it may be linked to infection by *Borrelia* spp. more frequently than are other types of pCBCL, particularly in Europe[7].

Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type

Primary cutaneous *d*iffuse *l*arge *B-c*ell *l*ymphoma, *l*eg *t*ype (DLBCLLT), represents a form of pCBCL that is characterized by a predominance of large round cells (centroblasts, immunoblasts) positive for Bcl-2, MUM1 (*mu*ltiple *m*yeloma oncogene *1* or interferon regulatory factor 4 [expressed by germinal center B cells and plasma cells]) and FOX-P1[1]. It has an intermediate prognosis and occurs almost exclusively in elderly patients, predominantly women[16].

Clinically, patients present with solitary or clustered erythematous to red–brown nodules, located primarily on the distal aspect of one leg (Fig. 119.5). In some patients, lesions may arise on both lower extremities contemporaneously or within a short interval of time. Ulceration may occur. Small erythematous papules can be seen adjacent to larger nodules. It must be emphasized that in approximately 20% of patients, tumors with similar morphologic and phenotypic features can arise in areas other than the lower extremities[17].

The prognosis of DLBCLLT is less favorable than that of other types of pCBCL, with a 5-year survival rate of approximately 50%[1,2]. In the past, the prognosis of cutaneous diffuse large B-cell lymphomas had been linked to several factors, including Bcl-2 expression, morphology of the cells, number of lesions at presentation, and location on the legs[18,19]. A large study, however, demonstrated that accurate classification based upon the WHO-EORTC categories was the single most important prognostic criterion, and other features were of little or no relevance when patients were stratified into these specific categories[17]. Recent data revealed that 9p21 deletions, possibly due to loss of function of *CDKN2A* (encodes p16 and $p14^{ARF}$), are associated with a worse prognosis[20,21].

It must be stressed that some patients with nodal large B-cell lymphoma can present with secondary cutaneous lesions located exclusively on the legs, underlying the need for complete staging investigations before a diagnosis of DLBCLLT can be established. The addition of PET scans to CT studies is a useful way of discovering evidence of systemic disease.

Intravascular Diffuse Large B-Cell Lymphoma

*I*ntra*v*ascular *d*iffuse *l*arge *B-c*ell *l*ymphoma (IVDLBCL) is a malignant proliferation of large B lymphocytes within blood vessels[22]. Most patients have a B-cell phenotype, but a T-cell variant has been reported. In occasional patients, the skin may be the only affected site, although more often there is systemic involvement (including the CNS) from the

Fig. 119.5 Cutaneous diffuse large B-cell lymphoma, leg type. Multiple red–brown papulonodules and tumor on the lower leg.

onset. Clinically, patients present with indurated, erythematous or violaceous patches and plaques, preferentially located on the trunk and thighs. The clinical appearance is not typical of cutaneous lymphoma, and it may sometimes suggest a diagnosis of panniculitis or vascular tumors. Interestingly, IVDLBCL has been observed to be confined to cherry angioma lesions[23]. The prognosis of IVDLBCL limited to the skin has been reported to be better than that of the systemic (disseminated) form, but only a limited number of cases have been studied.

Precursor B Lymphoblastic Lymphoma/Leukemia

B-cell lymphoblastic lymphomas/leukemias are malignant proliferations of precursor B lymphocytes. Reports of patients whose primary site is the skin have been rare. It should be emphasized, however, that all patients should be assumed to have, and treated for, systemic disease, even in the absence of documented systemic involvement at the time of presentation.

In contrast to the other cutaneous B-cell lymphomas, this disease shows a clearcut predilection for children and young adults[24,25]. Clinically, patients present with solitary large erythematous tumors, commonly located on the head (Fig. 119.6) and neck. Patients with primary skin disease often have asymptomatic lesions of a few weeks' duration. Those with secondary skin lesions may have systemic symptoms (e.g. weight loss, fever, fatigue, malaise, night sweats). The serum level of LDH is often elevated, reflecting the aggressive and often systemic nature of the disease. The disease is highly aggressive, and the prognosis of untreated patients is poor.

Other Cutaneous B-Cell Lymphomas

Rare cases of pCBCL do not fit within the subtypes reviewed above. They are therefore placed in the category of primary cutaneous large B-cell lymphoma, other (WHO-EORTC classification)[1]. In the new WHO 2008 classification, these patients are divided amongst several categories, including (but not limited to) large B-cell lymphomas arising in the setting of immune suppression, EBV-associated diffuse large B-cell lymphoma of the elderly, and diffuse large B-cell lymphoma, NOS[3].

Plasmablastic lymphoma is a rare lymphoma that usually arises within the oral cavity in patients with severe immunosuppression, especially HIV-related. It is often associated with infection by human herpesvirus-8 (HHV-8) and EBV. EBV-associated diffuse large B-cell lymphoma of the elderly is an aggressive large B-cell lymphoma occurring in patients >50 years of age[26]. The disease is commonly extranodal, including the skin as the primary site, but prognosis is poor irrespective of the primary site.

Fig. 119.6 Precursor B lymphoblastic lymphoma/leukemia. Large erythematous tumor on the face of a small child.

PATHOLOGY

Primary Cutaneous Follicle Center Lymphoma

In PCFCL, nodular or diffuse infiltrates are seen within the entire dermis, often extending into the subcutaneous fat (Fig. 119.7A)[3]. The epidermis is usually spared. A clearcut follicular pattern with formation of neoplastic germinal centers was observed in only a minority of cases (25%) in the series from Graz[2,13]. However, a higher percentage of cases may show at least some follicular architecture. In those with a follicular pattern, the neoplastic follicles show morphologic features of malignancy, including the presence of a reduced or absent mantle zone, the lack of tingible body macrophages, and a monomorphism of the follicles – so-called "dark" and "clear" areas are no longer recognizable (Fig. 119.8)[13].

In both the follicular and diffuse variants, centroblasts (large, noncleaved follicle center cells with prominent nucleoli) and centrocytes (small to large, cleaved follicle center cells) predominate within the neoplastic infiltrate, admixed with a variable number of immunoblasts, small lymphocytes, histiocytes, and, in some cases, eosinophils and plasma cells (see Fig. 119.7B). On a cytomorphologic basis, some cases of PCFCL with a diffuse pattern of growth have the appearance of a large cell lymphoma, but the prognosis of these cases is similar to that of lesions without the large cell morphology[1,17]. An accompanying infiltrate of small T lymphocytes and histiocytes/macrophages is usually present, and, in some instances, these cells can be predominant.

In addition to cases characterized by numerous large cells, other morphologic variants of PCFCL include those with a predominant

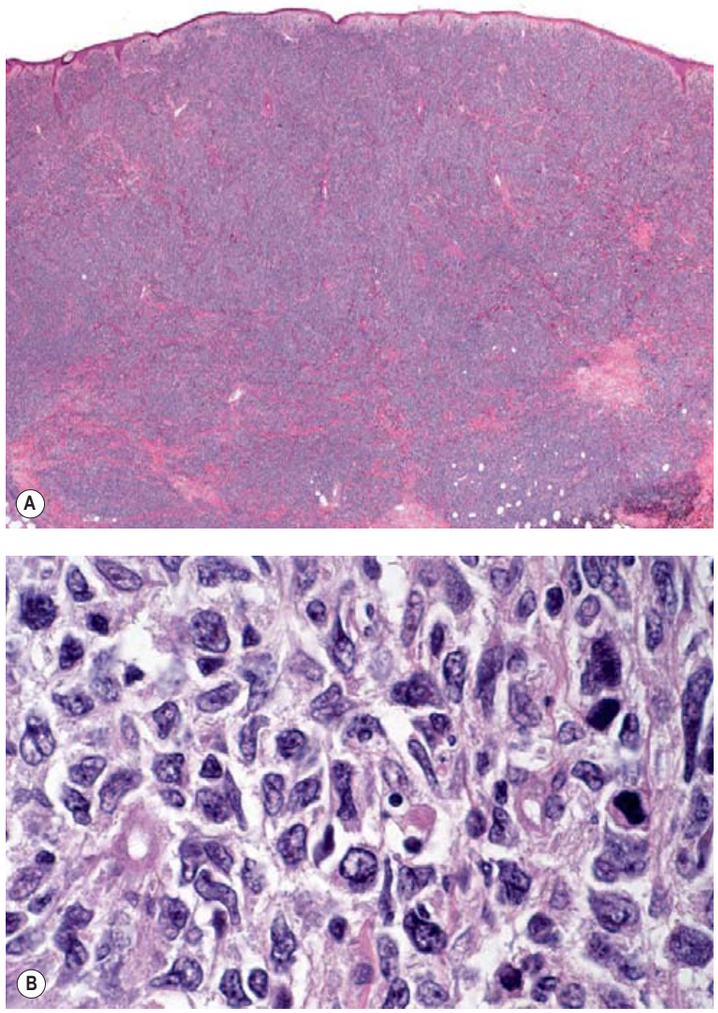


Fig. 119.7 Cutaneous follicle center lymphoma, diffuse type. A Diffuse infiltrate without follicular pattern. **B** Centroblasts and medium- and large-sized centrocytes (cleaved cells) predominate.

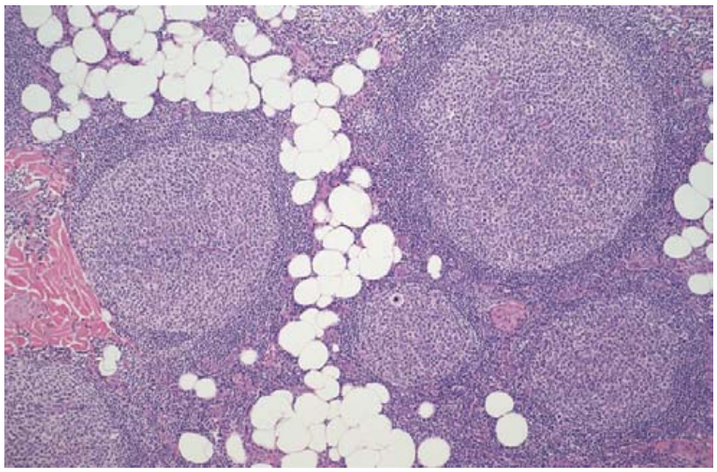


Fig. 119.8 Cutaneous follicle center lymphoma, follicular type. Neoplastic follicles with monomorphous morphology.

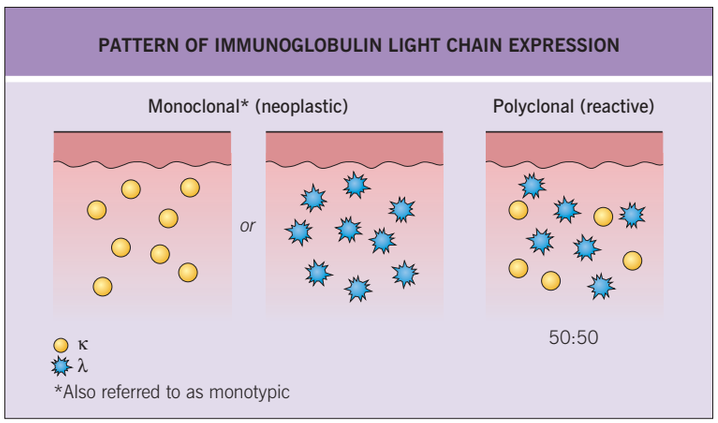


Fig. 119.9 Pattern of immunoglobulin light chain expression.

spindle cell morphology, which can simulate sarcomas or other spindle cell tumors histopathologically, thus representing a diagnostic pitfall[27]. Lesions in which a few B-cell blasts are admixed with numerous T lymphocytes have been classified as "T-cell/histiocyte-rich B-cell lymphomas", and in the skin probably represent another rare morphologic variant of PCFCL[3].

The tumor cells express monotypic surface immunoglobulins (e.g. all the neoplastic cells stain positively for either κ or λ light chains; Fig. 119.9) as well as B-cell-associated antigens (CD20, CD79a); they are $CD5^-$ and $CD43^-$ (see Table 0.11 for the specificities of CD markers). When follicles are present, they are characterized by an irregular network of $CD21^+$ follicular dendritic cells. Bcl-6 (a marker of germinal center cells and other blastic cells) is positive in virtually all cases, irrespective of the pattern of growth. In all cases with a follicular growth pattern, and in a minority of those with a diffuse growth pattern, neoplastic cells also stain positively for CD10. The presence of small clusters of $Bcl\text{-}6^+$ cells outside the follicles is considered strongly suggestive of a diagnosis of PCFCL[13].

In the overwhelming majority of cases, staining for the protein product of *bcl-2* (Bcl-2) yields negative results, representing a major difference from follicular lymphomas arising within lymph nodes[28]. A useful, though somewhat counterintuitive, distinguishing immunohistochemical feature is the *lower* degree of proliferative activity within *malignant* follicles as detected by the MIB-1 antibody (which detects the Ki-67 antigen expressed by proliferating cells), in contrast to the strong MIB-1-positivity in *reactive* follicles[13,29]. In cases with large cell morphology (predominance of large cleaved cells), immunohistochemical staining for MUM1 is usually either negative or is positive in a minority of neoplastic cells (in contrast to strong expression of MUM1 by DLBCLLT; see below)[1,17].

The interchromosomal 14;18 translocation, typically found in *nodal* follicular lymphomas, is present in a minority of PCFCLs[28]. Therefore, the presence of the 14;18 translocation and/or expression of Bcl-2 should raise suspicion that the patient has a systemic lymphoma involving the skin. Analysis of the genes that encode the joining segment (J_H) and other regions of the immunoglobulin heavy chain (IGH) reveals the presence of a monoclonal rearrangement in the majority of patients (60–70%). In cases of PCFCL with a follicular growth pattern, monoclonality of the follicular structures has been proven by PCR analysis of J_H gene rearrangements after microdissection of the follicular cells[15]. When gene expression in PCFCLs was analyzed via cDNA microarrays, a germinal center cell signature pattern was observed.

Analysis of morphologic, immunohistochemical and molecular data suggests that follicular lymphomas originating in the lymph nodes and the skin, although characterized by a similar morphologic pattern, have different pathogenic mechanisms.

Primary Cutaneous Marginal Zone B-Cell Lymphoma (Extranodal Marginal Zone Lymphoma of the Mucosa-Associated Lymphoid Tissue – MALT Lymphoma)

Histology of PCMZL shows a patchy, nodular or diffuse infiltrate involving the dermis and subcutaneous fat. The epidermis is spared. A characteristic pattern can be observed at scanning magnification: nodular infiltrates (sometimes containing reactive germinal centers) are surrounded by a pale-staining population of small- to medium-sized cells with indented nuclei, inconspicuous nucleoli and abundant pale cytoplasm (Fig. 119.10A) – variously described as marginal zone cells, centrocyte-like cells or monocytoid B cells (Fig. 119.11A)[3,5]. In addition, plasma cells (at the margins of the infiltrate), lymphoplasmacytoid cells, small lymphocytes and occasional large blasts are observed. Eosinophils are also a common finding. In some patients, there may be a granulomatous reaction with epithelioid and giant cells. Cases with a predominance of lymphoplasmacytoid lymphocytes were once classified as cutaneous immunocytomas[30], but are now considered variants of PCMZL. PAS-positive intranuclear inclusions (Dutcher bodies) are sometimes observed and represent a valuable clue to the diagnosis (Fig. 119.11B). Occasionally, the predominant cell type is a plasma cell (Fig. 119.11C), and although such cases used to be classified as primary cutaneous plasmacytomas, they are now also considered to be variants of PCMZL[1].

The centrocyte-like cells stain positively for CD20, CD79a and Bcl-2, and they are negative for CD5, CD10 and Bcl-6. In the overwhelming majority of cases, intracytoplasmic monotypic expression of immunoglobulin light chains (either κ or λ, but not both) can be observed (see Fig. 119.9). The monoclonal population of B lymphocytes is often characteristically arranged at the periphery of the cellular aggregates (Fig. 119.10B). Staining for proliferation markers also shows increased positivity at the periphery of the nodules (Fig. 119.10C). Monoclonal rearrangement of the *IGH* genes can be observed in the majority of cases (60–80%).

PCMZLs express class-switched immunoglobulins[31] (class-switching allows a B lymphocyte to change antibody production from one class to another, e.g. from an IgG to an IgM isotype; after class-switching, the cell retains affinity for the same antigen, but can interact with different effector molecules) and are characterized by aberrant somatic hypermutations[32]. A particular translocation, t(14;18)(q32;21), that involves the *IGH* and *MALT1* genes has been detected recently in a subset of PCMZL as well as MALT lymphomas arising in organs other than the skin. In gene expression studies utilizing cDNA microarrays, PCMZLs had a plasma cell signature pattern. Other genetic aberrations include trisomy 3 and rarely an 11;18 or a 3;14 translocation. However, in more than 50% of patients, no molecular abnormalities have been found.

Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type

In DLBCLLT, a dense diffuse infiltrate is seen within the dermis and subcutis. The infiltrate usually involves the entire papillary dermis

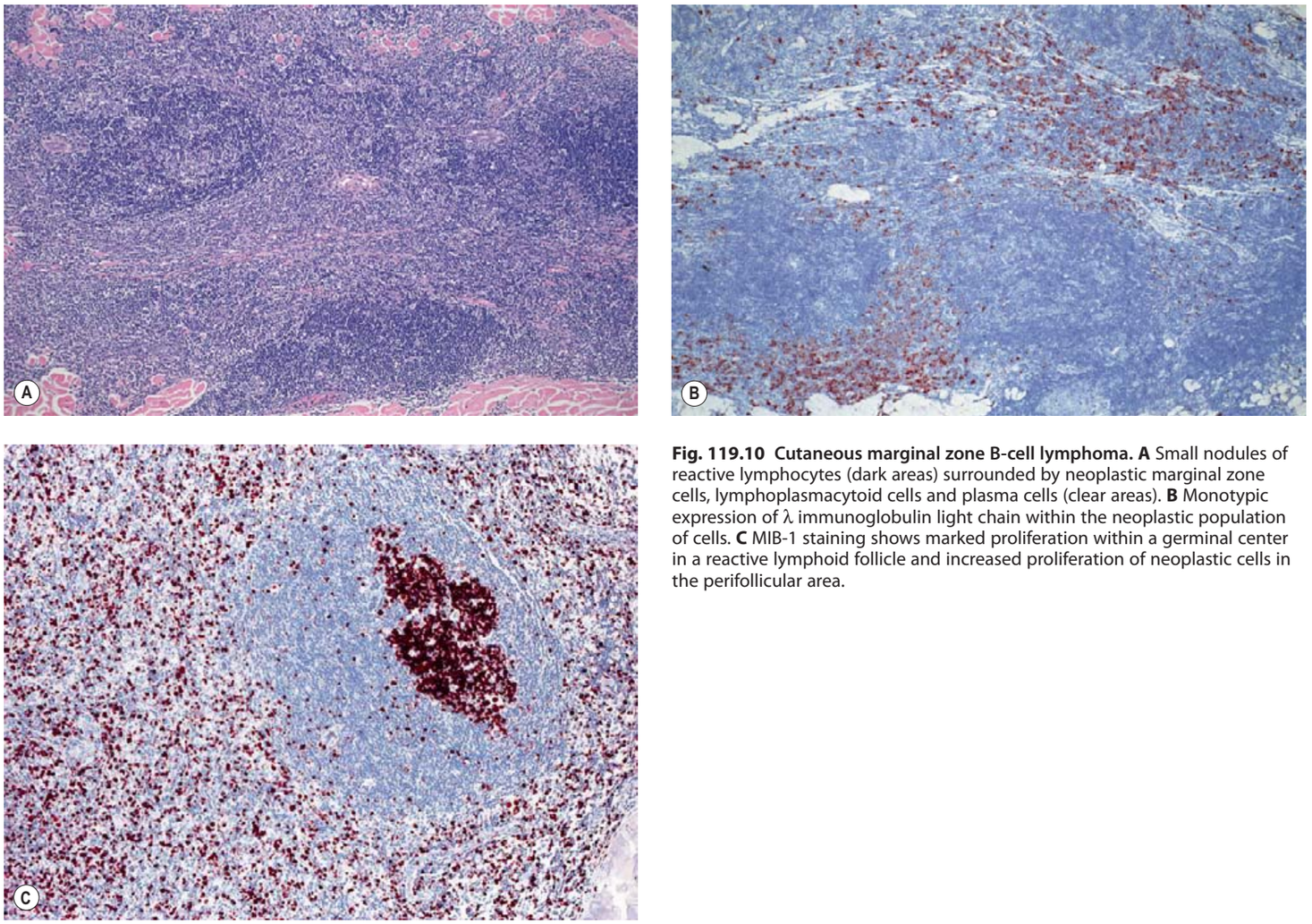


Fig. 119.10 Cutaneous marginal zone B-cell lymphoma. A Small nodules of reactive lymphocytes (dark areas) surrounded by neoplastic marginal zone cells, lymphoplasmacytoid cells and plasma cells (clear areas). **B** Monotypic expression of λ immunoglobulin light chain within the neoplastic population of cells. **C** MIB-1 staining shows marked proliferation within a germinal center in a reactive lymphoid follicle and increased proliferation of neoplastic cells in the perifollicular area.

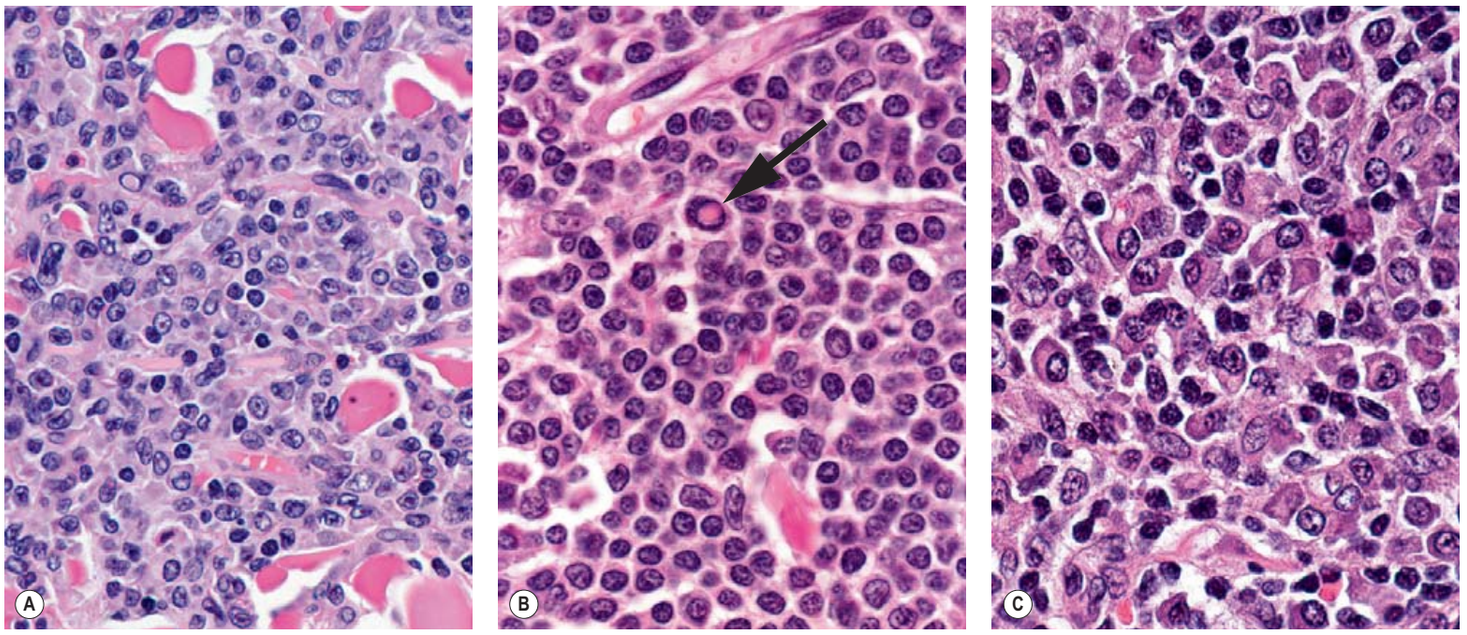


Fig. 119.11 Cutaneous marginal zone B-cell lymphoma – spectrum of cell types. A Admixture of marginal zone cells, plasmacytoid cells and plasma cells. **B** Predominance of lymphoplasmacytoid cells (formerly classified as cutaneous immunocytoma; note an intranuclear eosinophilic inclusion [Dutcher body, arrow]). **C** Predominance of plasma cells (formerly classified as cutaneous plasmacytoma).

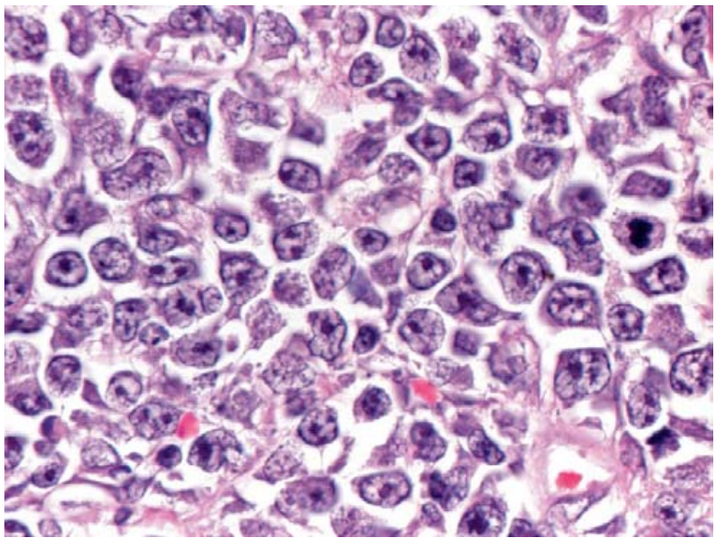


Fig. 119.12 Cutaneous diffuse large B-cell lymphoma, leg type. Large cells with a round morphology (mainly immunoblasts) predominate.

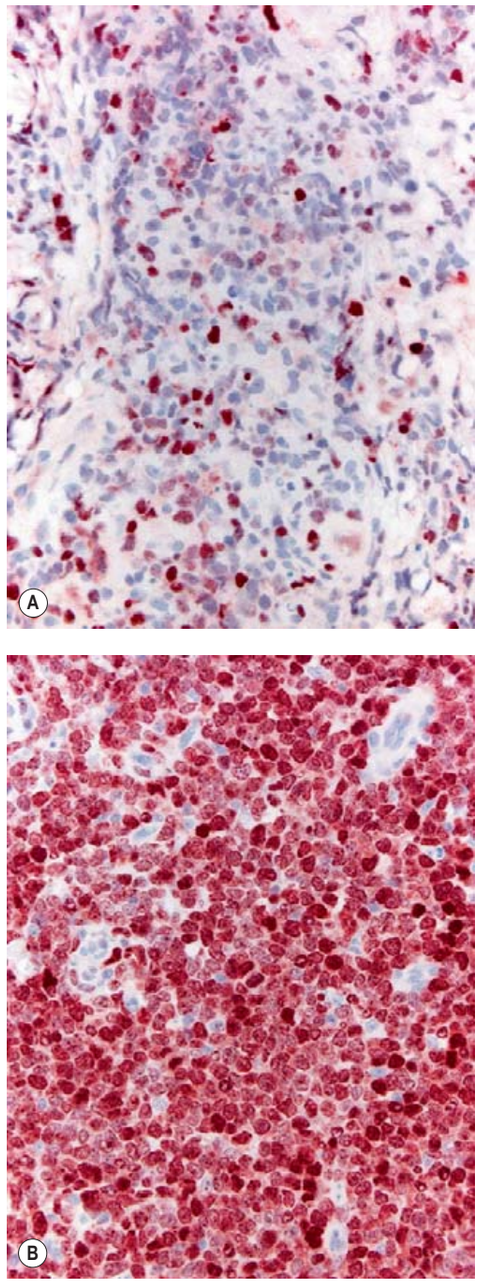


Fig. 119.13 Immunohistochemical staining with the anti-MUM1 antibody. **A** Only a minority of cells are positive in primary cutaneous follicle center lymphoma, diffuse type. **B** Virtually all tumor cells are positive in primary cutaneous diffuse large B-cell lymphoma, leg type.

extending to the dermal–epidermal junction. Involvement of the epidermis by clusters of large atypical cells, simulating the Pautrier's microabscesses found in cutaneous T-cell lymphoma, can be observed in some cases (B-cell epidermotropism), representing a potential diagnostic pitfall[3]. The neoplastic infiltrate consists predominantly of immunoblasts (large round cells with abundant cytoplasm and prominent nucleoli) and centroblasts (Fig. 119.12). Of note, cases of diffuse large B-cell lymphoma with a predominance of large cleaved cells are classified among the PCFCLs[1]. Reactive small lymphocytes are few or absent, and mitoses are frequent. Based on the common finding of immunoglobulin gene hypermutations, it has been proposed that most cases of DLBCLLT represent large cell lymphomas originating from lymphocytes of the germinal center.

Neoplastic cells express monoclonal surface immunoglobulins and/or cytoplasmic immunoglobulins. They are positive for B-cell markers (CD20, CD79a), but there can be (partial) loss of antigen expression. MUM1 (see above) and FOX-P1 are strongly expressed by neoplastic cells in most patients[1,17]. These markers are useful in the differential diagnosis of DLBCLLT from PCFCL, diffuse type; in the latter, MUM1 and FOX-P1 are usually either negative or expressed by a small minority of cells (Fig. 119.13). The tumors demonstrate monoclonal rearrangement of the *IGH* genes. The interchromosomal 14;18 translocation is not present. Staining for Bcl-2 is positive in all patients with primary cutaneous DLBCLLT, and an algorithmic approach to the diagnosis of cutaneous diffuse large B-cell lymphomas is provided in Figure 119.14.

Rare cases of otherwise typical cutaneous DLBCLLT show expression of CD30 by neoplastic cells[17]. In contrast to cutaneous T-cell lymphomas, prognosis in large B-cell lymphomas (both cutaneous and extracutaneous) is not related to CD30 expression. Hypermethylation of the genes that encode p15 and/or p16 (*CDKN2B*, *CDKN2A*), resulting in decreased expression of these proteins, has been observed in some patients. 9p21 deletions, possibly due to loss of function of *CDKN2A*, are associated with a worse prognosis[21]. However, 9p21 deletions may not be detected by some of the standard fluorescent *in situ* hybridization (FISH) probes[33].

Genetic data obtained by FISH or microarray chip technologies have confirmed that DLBCLLTs show clear molecular differences from PCFCL, diffuse type, confirming the need of classifying these cases separately[34,35]. Some of the aberrations found in DLBCLLT are similar to those observed in diffuse large B-cell lymphomas of the lymph nodes.

Intravascular Diffuse Large B-Cell Lymphoma

IVDLBCL is characterized by a proliferation of large atypical lymphocytes that fills dilated blood vessels within the dermis and subcutaneous tissues (Fig. 119.15A). The malignant cells are large with scanty cytoplasm and often have prominent nucleoli. They are positive for B-cell-associated markers (Fig. 119.15B) as well as for Bcl-2, MUM1 and FOX-P1. Staining with endothelial cell-related antibodies (e.g. CD31, CD34) highlights the characteristic intravascular location of the cells (Fig. 119.15C). Molecular analysis shows monoclonal rearrangement of the *IGH* genes.

Precursor B Lymphoblastic Lymphoma/Leukemia

Histologically, precursor B lymphoblastic lymphoma/leukemia shows a monomorphous proliferation of medium-sized cells with scanty cytoplasm and round or convoluted nuclei with fine chromatin (Fig. 119.16). A "starry sky" pattern is commonly seen at low power, due to the presence of macrophages with inclusion bodies ("tingible bodies"). Another characteristic feature is the arrangement of neoplastic cells in a "mosaic-stone" pattern. Mitoses and necrotic cells are abundant. It must be stressed that histologic features alone do not allow differentiation of lymphoblastic lymphomas of B-cell phenotype from those of T-cell

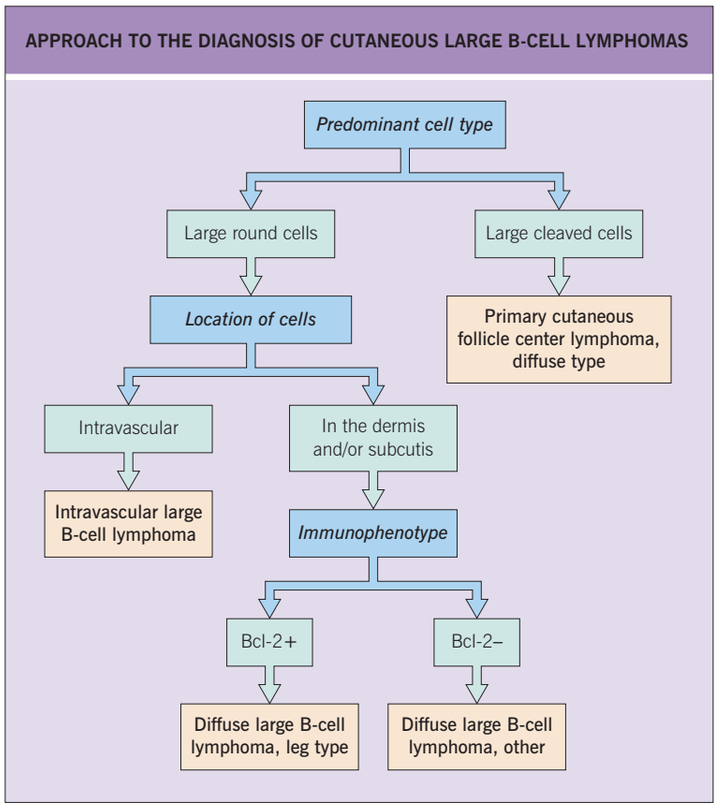


Fig. 119.14 Approach to the diagnosis of cutaneous large B-cell lymphomas. In most patients with primary cutaneous diffuse large B-cell lymphoma, leg type, the neoplastic cells strongly express MUM1 and FOX-P1, whereas in primary cutaneous follicle center lymphoma, diffuse type, these stains are usually either negative or expressed by a small minority of cells.

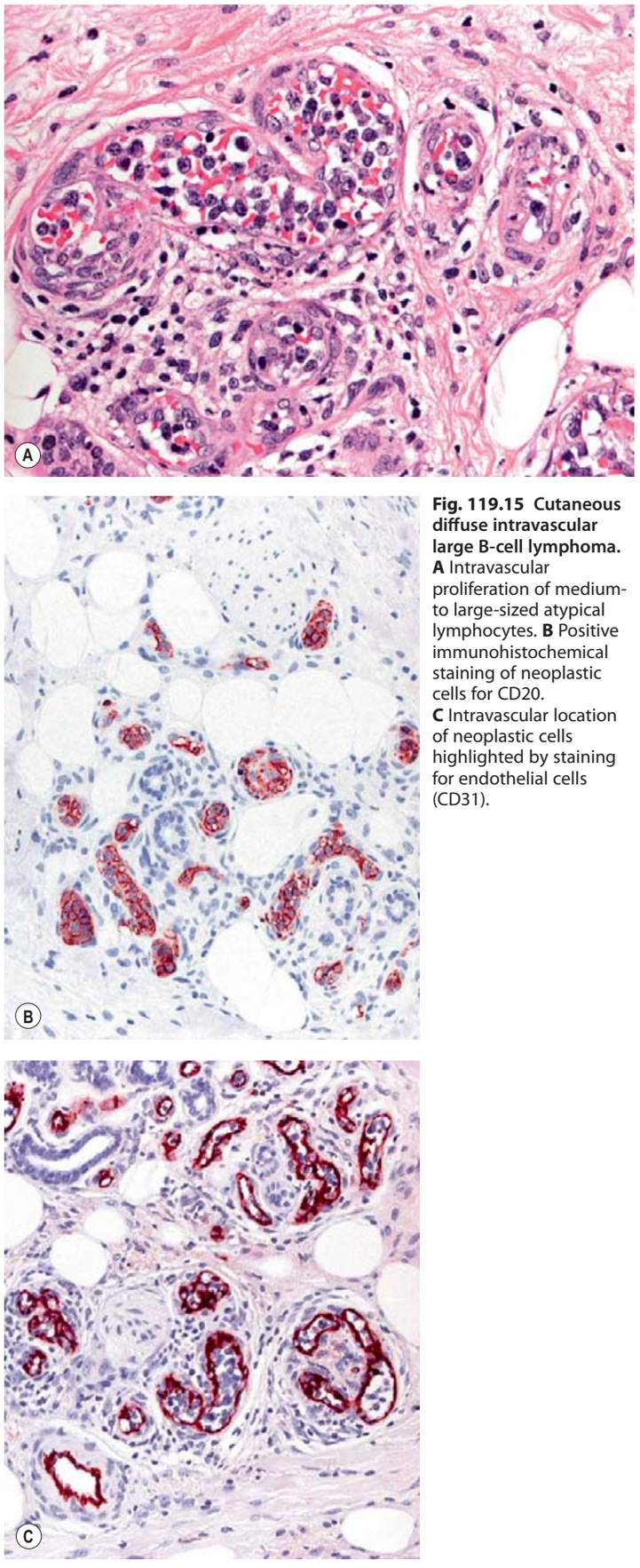


Fig. 119.15 Cutaneous diffuse intravascular large B-cell lymphoma. **A** Intravascular proliferation of medium- to large-sized atypical lymphocytes. **B** Positive immunohistochemical staining of neoplastic cells for CD20. **C** Intravascular location of neoplastic cells highlighted by staining for endothelial cells (CD31).

lineage. Immunohistology demonstrates positive staining for TdT (terminal deoxynucleotidyl transferase; present on precursor T and B cells), CD10 and the cytoplasmic μ-chain of immunoglobulins and, in most cases, CD20 and CD79a. CD20 is negative in the pre-pre-B-cell variant, which is $CD34^+$. Molecular analyses usually show a monoclonal rearrangement of the *IGH* genes and a polyclonal pattern for the T-cell receptor (*TCR*) genes, but a lack of rearrangement of the *IGH* genes or monoclonal rearrangement of both the *TCR* and *IGH* genes may be observed.

Other Cutaneous B-Cell Lymphomas

Plasmablastic lymphoma is characterized by a proliferation of plasmablasts with large eccentric nuclei, abundant cytoplasm and prominent nucleoli. The neoplastic cells are positive for CD38 and CD138, and they express monotypic immunoglobulin light chains.

Cutaneous EBV-associated diffuse large B-cell lymphoma of the elderly is characterized by a predominance of large rounded B cells. In contrast to DLBCLLT, these lesions may show loss of CD20 expression, thus representing a potential diagnostic pitfall. CD79a is usually positive on neoplastic cells, as well as MUM1. Detection of EBV by *in situ* hybridization is a prerequisite for the diagnosis.

DIFFERENTIAL DIAGNOSIS

Differential diagnoses of pCBCLs vary according to the type of lymphoma and include primarily inflammatory processes that may simulate malignant lymphomas either clinically, histopathologically, or both (cutaneous lymphoid hyperplasia or "pseudolymphoma"; see Ch. 121). It must be emphasized that a definitive diagnosis of pCBCL can be reached only after careful examination of the clinical, histopathologic, immunophenotypic and molecular features; in some cases, only

repeated examination of the patient and sequential biopsy specimens will allow the correct classification[3,29]. A schematic diagram with examples of the use of immunohistochemical stains and PCR in the differential diagnosis of pCBCLs is presented in Figure 119.17.

Patients for whom no definitive diagnosis can be established at the time of presentation should provisionally be classified as having "cutaneous atypical lymphoid proliferation of B-cell lineage", and they should be re-examined at regular intervals[3]. A complete staging investigation does not belong in the diagnostic evaluation of these patients; that is, patients without a definitive diagnosis of cutaneous B-cell lymphoma should not be screened for extracutaneous disease until the diagnosis is established with certainty[3]. In contrast, once the diagnosis of cutaneous B-cell lymphoma has been established, complete staging is mandatory, as clinicopathologic features alone do not allow the differentiation of primary from secondary cutaneous B-cell lymphomas. A diagnostic algorithm for evaluation of patients at first presentation is provided in Figure 119.18. In the following section, the major differential diagnoses of each of the main types of pCBCL are outlined separately, as they differ according to the lymphoma type.

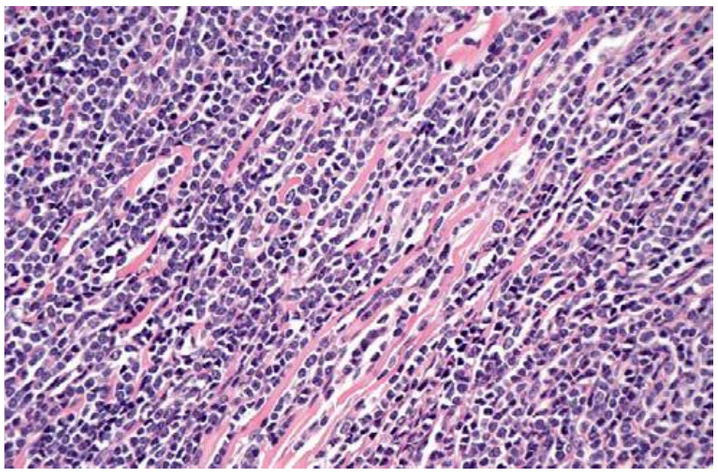


Fig. 119.16 Precursor B lymphoblastic lymphoma/leukemia. Medium-sized blasts with the characteristic "mosaic-stone" linear arrangement.

PCFCL with a follicular pattern of growth should be differentiated from B-cell pseudolymphomas with prominent germinal centers, such as *Borrelia*-induced lymphocytoma cutis (cutaneous lymphoid hyperplasia)[13,36]. Lymphocytoma cutis often occurs in children, and it shows a predilection for particular body sites such as the earlobes, nipples and scrotum[36]. Clinically, lesions are usually solitary and relatively small. Although histologically a follicular pattern is almost always observed, germinal centers in lymphocytoma cutis are reactive, and they are accompanied by inflammatory infiltrates with small lymphocytes, plasma cells and often eosinophils[3,36]. The germinal centers in *Borrelia*-induced lymphocytoma cutis are often devoid of a clearcut mantle, but they are characterized by the presence of: many tingible body macrophages, "clear" and "dark" areas, and a normal (high) proliferation rate[36].

Rare cases of cutaneous PCMZL can have a prominent presence of reactive germinal centers, and they should be differentiated from the follicular type of PCFCL. In these cases, so-called follicular colonization

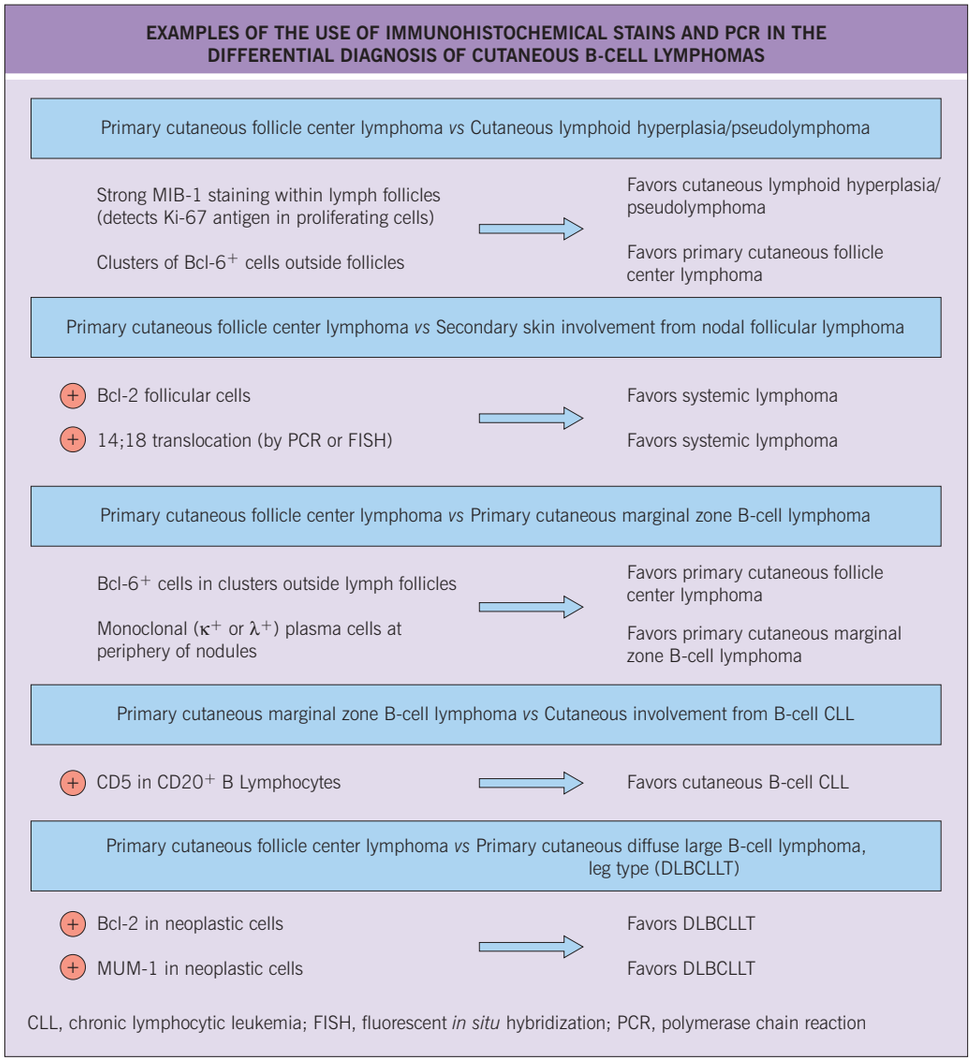


Fig. 119.17 Examples of the use of immunohistochemical stains and PCR in the differential diagnosis of cutaneous B-cell lymphomas. This does represent a simplification and is intended to assist dermatologists in their interpretation of pathology reports. $CD20^+/CD5^+$ infiltrates are also seen in secondary skin involvement from mantle cell lymphoma, but in contrast to CLL, mantle cell lymphoma is also positive for cyclin D.

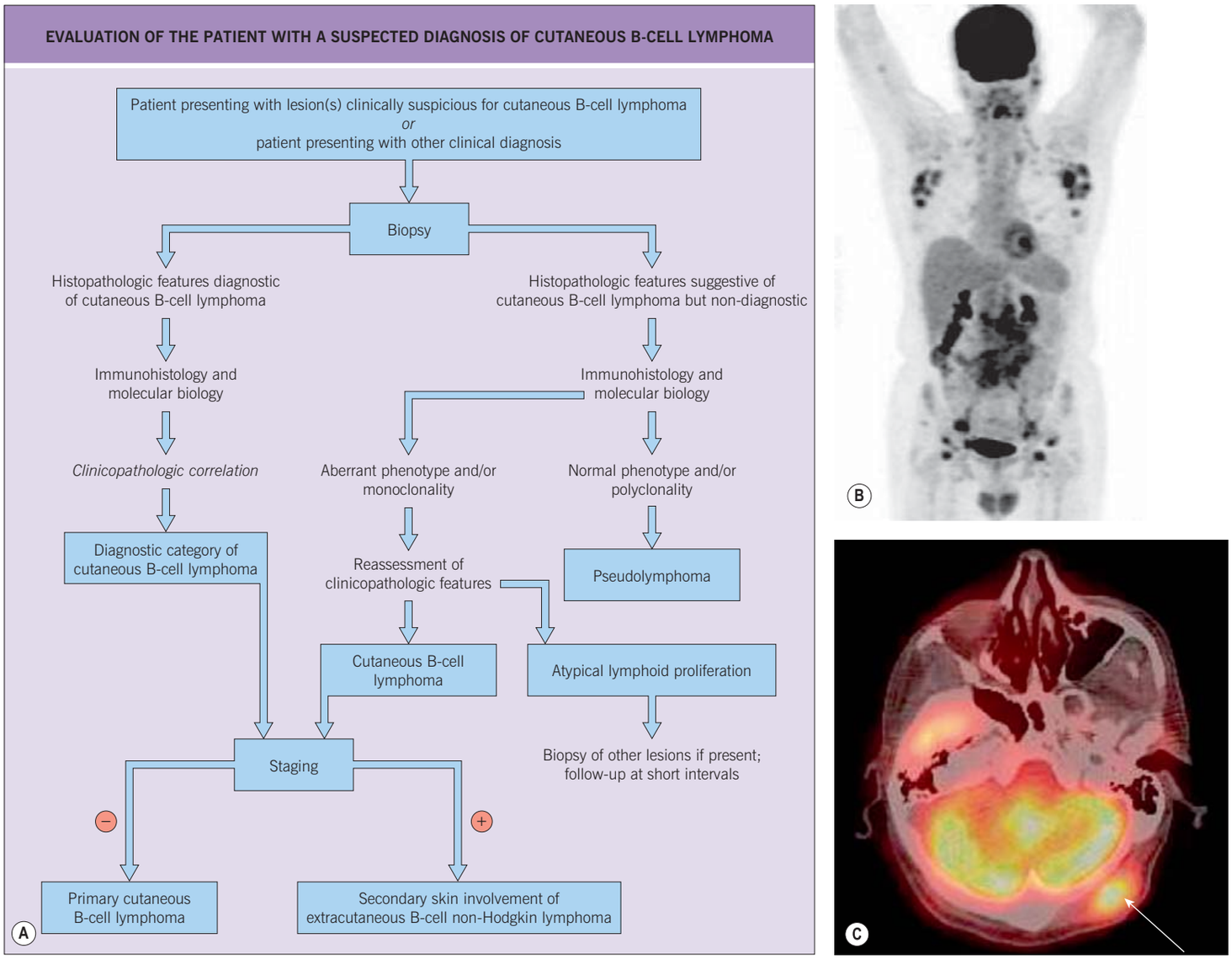


Fig. 119.18 Evaluation of the patient with a suspected diagnosis of cutaneous B-cell lymphoma. A Algorithm outlining approach to the patient. **B, C** Positron emission tomography (PET) scans in a 66-year-old patient with stage IV non-Hodgkin B-cell lymphoma. He had a 1-year history of a cutaneous nodule of the scalp that was originally diagnosed as an epidermoid inclusion cyst. Biopsy of the nodule showed a diffuse large B-cell lymphoma ($CD10^+$, $CD20^+$, variably $Bcl\text{-}2^+$, $MUM1^-$) and a PET/CT scan was performed for staging. There is evidence of widespread disease involving multiple lymph node basins in the dedicated (MIP) image (**B**) as well as a scalp lesion in a PET/CT fusion image (**C**; arrow). *B, C, Courtesy, Dennis Cooper, MD.*

by neoplastic marginal zone cells can indeed cause significant problems in histopathologic differential diagnosis, similar to what happens in B-cell lymphomas of the MALT type. However, the overall architecture of the infiltrate, the presence of a population of monoclonal plasma cells belonging to the neoplastic clone, and the negativity of neoplastic cells for CD10 and Bcl-6 usually allow the diagnosis of cutaneous PCMZL to be established.

As mentioned previously, secondary cutaneous involvement by primary extracutaneous follicular lymphomas has morphologic and phenotypic features similar or identical to those observed in primary cutaneous B-cell lymphoma, except for the usual positivity of neoplastic cells for Bcl-2 in secondary cutaneous lesions. Consequently, the occurrence of a cutaneous follicular lymphoma with clearcut positivity for Bcl-2 within neoplastic follicles should be considered as a strong hint (although exceptions can be encountered) for the diagnosis of secondary skin lesions of nodal lymphoma.

The differential diagnosis of **PCMZL** consists primarily of reactive processes and other types of low-grade pCBCL. Benign, reactive processes do not have monotypic restriction of immunoglobulin light chain expression, in contrast to what is observed in the great majority of cases of PCMZL. PCFCL, diffuse type, can be differentiated from PCMZL by the architectural pattern and cytomorphology, the former being characterized by a diffuse infiltrate of B lymphocytes with a predominance of centrocytes and centroblasts. Moreover, in contrast to PCMZL, neoplastic cells in PCFCL express Bcl-6.

PCMZL should also be distinguished from secondary cutaneous lesions of B-cell chronic lymphocytic leukemia (B-CLL), a condition in which neoplastic B lymphocytes display positivity for CD20 and CD43, and usually for CD5. Helpful diagnostic features are: (1) the absence, in B-CLL, of plasma cells belonging to the neoplastic clone; and (2) the positivity for CD5 observed in most cases of cutaneous B-CLL, but practically never in PCMZL. $CD20^+/CD5^+$ infiltrates are also seen in secondary skin involvement from mantle cell lymphoma, but in contrast to CLL, mantle cell lymphoma is also positive for cyclin D. Finally, it seems likely that cases classified in the past as "cutaneous lymphoid hyperplasia with monotypic plasma cells" represent, in fact, examples of PCMZL with prominent plasma cell differentiation.

PCMZL with prominent plasma cell differentiation must be differentiated from reactive plasma cell proliferations and from inflammatory pseudotumors (plasma cell granulomas). In reactive conditions, plasma cells are not atypical, and they display a polyclonal pattern of immunoglobulin light chain expression. Besides inflammatory pseudotumors, reactive skin diseases with a predominance of plasma cells are very rare, with the exception of lesions arising on mucosal surfaces, spirochetal infections (e.g. syphilis, pinta, yaws), and cutaneous and systemic plasmacytosis. The latter disorder displays a polyclonal

pattern of immunoglobulin light chain expression. A silver stain (e.g. Warthin-Starry) or immunohistochemical staining for *Treponema pallidum* can help to highlight the microorganisms in cases of syphilis (see Fig. 0.32).

DLBCLLT must be differentiated from a number of entities, including cutaneous involvement from systemic lymphomas as well as specific infiltrates of acute myelogenous leukemia and non-lymphoid tumors (e.g. solid organ metastases; see Ch. 122). The clinicopathologic pattern together with phenotypic and molecular features allow correct classification of these lesions in most instances. In order to avoid diagnostic errors, detailed immunophenotyping is mandatory in all cases of cutaneous lymphoma, especially in those showing medium- to large-sized cell morphology.

The differential diagnosis of **IVDLBCL** is not a problem in typical cases. The large number of atypical cells within blood vessels is pathognomonic of this condition. Distinction between T- and B-cell types cannot be achieved on morphologic grounds alone. IVDLBCL should be distinguished from so-called intravascular histiocytosis, a condition in which the vessels in the dermis show intraluminal collections of histiocytes. Morphologic, immunophenotypic and molecular features allow one to distinguish these entities with confidence. Intravascular histiocytosis has been observed in different clinical settings, including chronic erysipelas.

Cases of precursor B lymphoblastic lymphoma/leukemia should be differentiated from other cutaneous lymphomas and from non-lymphoid tumors such as Ewing's sarcoma and small cell lung carcinoma. Positivity for TdT represents the most important immunohistochemical feature for the diagnosis of cutaneous lymphoblastic lymphoma. Histologic features of cutaneous lesions do not allow the differentiation of T-cell from B-cell lymphoblastic lymphomas, thus emphasizing the importance of complete immunophenotypic and genotypic analyses.

TREATMENT

The most appropriate treatment modality for patients with a pCBCL is selected after exact classification of the lymphoma, analysis of results of staging investigations, and consideration of the overall condition of the patient[3]. Those patients with secondary cutaneous lesions of extracutaneous B-cell lymphoma should be treated in a hemato-oncologic, not dermatologic, setting[3,37,38].

Before reviewing the major therapeutic strategies, it must be emphasized that many patients with low-grade pCBCL can be managed conservatively with a so-called watchful-waiting strategy, similar to what is often adopted for indolent B-cell lymphomas and leukemias at extracutaneous sites[3,39]. Follow-up examinations in these patients should be performed at least every 6 months or at the onset of new lesions and/or new symptoms, in order to treat the patient as soon as it is necessary. Many patients managed conservatively with a watchful-waiting strategy experience a prolonged course and long survival, and they do not need aggressive treatment. Especially if only a few lesions are present, some of the patients in the watchful-waiting group may choose to have injections of intralesional corticosteroids into their papulonodules.

Most patients with pCBCLs that are low-grade (PCFCL, PCMZL) and who have a solitary or few lesions can be treated by local radiotherapy, simple surgical excision, or surgical excision followed by radiotherapy of the surgical field[3,37,39,40]. It has been reported that recurrences are less frequently seen in patients treated by radiotherapy with wide margins (about 10–20 cm beyond clinically apparent lesions); this approach seems to be justified for so-called Crosti's lymphoma, a type of PCFCL arising on the back, in which erythematous nodules, papules and patches surrounding the tumor represent specific infiltrates that can extend far beyond the main bulk of the lesion[41]. Radiotherapy with wide margins, however, does not seem to be justified for lesions other than Crosti's lymphoma, as margins of about 3–5 cm usually suffice (depending on the size of the lesion). Surgical excision with narrow margins is a valuable therapeutic modality for patients with solitary well-circumscribed lesions. In these patients, relapse rates do not seem to be higher than in patients treated with more time-intensive modalities such as local radiotherapy.

A few reports have appeared in which low-grade pCBCLs were treated with systemic antibiotics, achieving a complete resolution in at least a percentage of the patients[38,42,43]. This type of treatment is conceptually analogous to that adopted for *Helicobacter pylori*-associated MALT lymphomas of the stomach, which in their early stages can be cured by eradication of *H. pylori* infection. Complete response to antibiotic therapy has been observed in some patients with *Borrelia*-associated pCBCL. Although not yet corroborated by adequate data, antibiotic treatment of patients with pCBCLs should be considered before more aggressive therapeutic options are employed, particularly in European countries endemic for *Borrelia* infections. It is important to treat patients at the onset of the disease, because, in later stages, lesions may no longer be sensitive to systemic antibiotics. PCR analysis of *Borrelia* DNA is a rapid test that should be performed in all patients with pCBCL from endemic areas, in order to identify those who would more likely benefit from early antibiotic treatment.

Another treatment modality for low-grade pCBCL is subcutaneous or intralesional interferon, particularly interferon-α-2a[38]. Although some favorable results have been reported, it seems that treatment with interferon is associated with a complete response in about 50% of patients. Therapy with interferon should be considered for patients presenting with multiple lesions at different body sites, such that local radiotherapy becomes difficult to administer.

Intralesional or systemic injection of anti-CD20 monoclonal antibody (rituximab) has been used to induce tumor reduction in patients with indolent pCBCLs[44,45]. Intralesional administration should be considered in patients presenting with a few, localized lesions. Therapy with intravenous rituximab represents a valid alternative to established treatments, especially in patients who present with disseminated skin lesions or relapse after radiotherapy. Rituximab can also be administered in combination with other treatment modalities for pCBCLs with more aggressive behavior (e.g. DLBCLLT). Anti-CD20 monoclonal antibody has also been conjugated to radioisotopes (e.g. I-131, Y-90), in an attempt to provide selective irradiation of tumor cells.

Patients with disseminated lesions of PCFCL, diffuse type, or with DLBCLLT need more aggressive treatment modalities (e.g. systemic chemotherapy plus rituximab). This treatment, however, is usually necessary in only a small proportion of patients with PCFCL[38,46,47]. The regimen used most frequently is cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) plus rituximab, and it represents the standard of care for DLBCLLT. In the absence of signs of transformation into high-grade lymphoma, aggressive treatment is not indicated in patients with PCMZL. In the setting of significant co-morbidities, rituximab alone or in combination with local radiotherapy may be administered.

Systemic chemotherapy plus rituximab is the treatment of choice for patients with IVDLBCL, regardless of results of staging investigations. As with DLBCLLT, the addition of rituximab to anthracycline-based chemotherapy significantly improves outcome in "Western" patients with this lymphoma[48]. Finally, patients with precursor B lymphoblastic lymphoma/leukemia should be treated with aggressive modalities (chemotherapy plus rituximab; hematopoietic stem cell transplantation) by a hematologist.

PLASMA CELL DYSCRASIAS, INCLUDING MULTIPLE MYELOMA

A plasma cell dyscrasia represents a clonal proliferation of plasma cells and it can lead to a monoclonal gammopathy composed of intact immunoglobulins, isolated light chains (15% of patients) or, rarely, isolated heavy chains. The term plasma cell dyscrasia encompasses a number of entities, including monoclonal gammopathy of undetermined significance (MGUS), smoldering/asymptomatic myeloma and active/symptomatic myeloma, as well as light and heavy chain deposition disease and amyloidosis (AL). While proliferations of plasma cells within the skin are rare, an understanding of the spectrum and natural history of plasma cell dyscrasias is important for dermatologists given the number of cutaneous disorders associated with monoclonal gammopathies (Table 119.2). Table 119.3 outlines the differences between MGUS and smoldering myeloma in addition to the risk factors for progression to symptomatic myeloma. The diagnosis of symptomatic myeloma requires the presence of CRAB: *c*alcium elevation, *r*enal insufficiency, *a*nemia and/or *b*one lesions (osteolytic > osteosclerotic) due to the myeloma.

CUTANEOUS CONDITIONS ASSOCIATED WITH MONOCLONAL GAMMOPATHY
PROLIFERATION OF LYMPHOPLASMACYTIC CELLS IN THE SKIN
• Extramedullary cutaneous plasmacytoma*
• Cutaneous Waldenström's macroglobulinemia†
DEPOSITION OF THE MONOCLONAL PROTEIN IN THE SKIN, BY DEFINITION
• Primary systemic amyloidosis (light chains)
• Cryoglobulinemic occlusive vasculopathy (type I cryoglobulins‡)
• Hyperkeratotic spicules (follicular > non-follicular)
• Crystal-storing histiocytosis
• IgM storage papules (cutaneous macroglobulinosis)†
• Subepidermal bullous dermatosis associated with IgM gammopathy†
DEPOSITION OF THE MONOCLONAL PROTEIN IN THE SKIN FREQUENTLY OBSERVED
• Plasma cell dyscrasia-associated acquired cutis laxa, acral or generalized (amyloid and/or IgG)
• Plasma cell dyscrasia-associated reactive angioendotheliomatosis (type I cryoglobulins or amyloid)
ALMOST ALWAYS ASSOCIATED WITH MONOCLONAL GAMMOPATHY
• Scleromyxedema
• POEMS syndrome§
• AESOP syndrome – *a*denopathy and *e*xtensive *s*kin patch *o*verlying a *p*lasmacytoma; may coexist with POEMS syndrome†
• Schnitzler's syndrome
• Necrobiotic xanthogranuloma
FREQUENTLY ASSOCIATED WITH MONOCLONAL GAMMOPATHY
• Normolipemic plane xanthoma
• Scleredema (type 2; see Ch. 46)
• Angioedema secondary to acquired C1 esterase inhibitor deficiency
• Clarkson's syndrome (idiopathic systemic capillary leak syndrome)
SIGNIFICANT ASSOCIATION WITH MONOCLONAL GAMMOPATHY (AT LEAST 15% OF CASES)
• Erythema elevatum diutinum
• Subcorneal pustular dermatosis (SPD) and SPD-type IgA pemphigus
• Pyoderma gangrenosum
OCCASIONALLY ASSOCIATED WITH MONOCLONAL GAMMOPATHY
• Sweet's syndrome
• Cutaneous small vessel vasculitis‡,‖
• Xanthoma disseminatum
• Epidermolysis bullosa acquisita
• Paraneoplastic pemphigus
• Atypical scleroderma¶
*In the current WHO-EORTC classification (see Table 119.1), primary cutaneous plasmacytoma is classified as primary cutaneous marginal zone B-cell lymphoma.
†IgM monoclonal gammopathy is present by definition; in Schnitzler's syndrome, IgG gammopathy has occasionally been observed; Waldenström's macroglobulinemia is due to a lymphoplasmocytic lymphoma.
‡Cryoglobulinemic vasculitis can occur secondary to type II cryoglobulins.
§Polyneuropathy (P), organomegaly (O), endocrinopathy (E), M-protein (M), skin changes (S; see Ch. 53 for list of skin changes); diagnosis requires monoclonal plasmaproliferative disorder & neuropathy + one other major criterion (sclerotic bone lesions, Castleman's disease, increased VEGF levels) and one minor criterion (extravascular volume overload, papilledema, O, E, S, thrombocytosis/polycythemia).
‖Henoch–Schönlein purpura in adults is occasionally associated with an IgA monoclonal gammopathy.
¶Possible association; sclerodermoid changes can also occur in the setting of primary systemic amyloidosis.

Table 119.2 Cutaneous conditions associated with monoclonal gammopathy.

RELATIONSHIP OF MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE TO MYELOMA	
MGUS	• Serum monoclonal protein <3 g/dl • <10% plasma cells in the bone marrow • No end-organ damage (*h*ypercalcemia, *r*enal insufficiency, *a*nemia and/or *b*one lesions [CRAB]) that is associated with symptomatic myeloma • Prevalence: 3% in those ≥50 yrs; 5% in those ≥70 yrs
Risk factors for progression of MGUS to myeloma or lymphoproliferative disorder*	• Increase in serum free light chains • MGUS of non-IgG origin (e.g. IgA, IgM) • Serum monoclonal protein ≥1.5 g/dl • Chance of progression from MGUS to myeloma (at 20 yrs): – 58% if 3 risk factors – 37% if 2 risk factors – 21% if 1 risk factor – 5% if 0 risk factors
Smoldering (asymptomatic) myeloma	• Serum monoclonal protein ≥3 g/dl – *or* – • ≥10% plasma cells in the bone marrow • No end-organ damage (see above) • Cumulative probability of progression to symptomatic myeloma or amyloidosis: – 51% at 5 yrs – 66% at 10 yrs – 73% at 15 yrs
*2–3% of monoclonal gammopathies are due to lymphoproliferative disorders, e.g. CLL, and approximately 3% represent Waldenström's macroglobulinemia (IgM) which is due to a lymphoplasmacytic lymphoma.	

Table 119.3 Relationship of monoclonal gammopathy of undetermined significance (MGUS) to myeloma. CLL, chronic lymphocytic leukemia. Adapted from references 49 & 50.

Of note, the level of circulating monoclonal protein associated with several of the skin disorders listed in Table 119.2 may be so low as to fall below the detection limit of a serum protein electrophoresis. As a result, the more sensitive serum immunofixation electrophoresis (IFE) is required to detect an intact immunoglobulin (e.g. IgG or IgA) paraprotein. In patients with primarily light chain disease (e.g. systemic amyloidosis), the serum free light chain (SFLC) ratio is much more sensitive than even the serum IFE. Because light chains are rapidly excreted into the urine, a urine IFE in addition to SFLC assay is necessary to exclude a light chain-producing plasma cell dyscrasia.

Histopathology

In specific skin lesions (see Table 119.2), diffuse infiltration of the dermis by atypical plasma cells or lymphoplasmacytoid cells is present, usually with prevalent mitoses. Multinucleated plasma cells may be found. The infiltrating cells can be difficult to recognize as plasma cells, and CD45 and CD20 are negative as a rule. Neoplastic plasma cells can be stained with CD38 and CD138, and they express monotypic immunoglobulins. Intracytoplasmic eosinophilic inclusions (Russell bodies) are often present; the cells are called Mott cells when these bodies form grape-like clusters. PAS-positive eosinophilic inclusions in the nucleus (Dutcher bodies) can also be observed. These are thought to be immunoglobulin or glycoprotein accumulations, and can be found in other neoplastic conditions in which plasma cells are prevalent (plasma cell-rich PCMZL; see Fig. 119.11B).

Differential Diagnosis

The differential diagnosis of PCMZL with prominent plasma cell differentiation (formerly called cutaneous plasmacytoma) is discussed above. Waldenström's macroglobulinemia has histologic features similar to PCMZL with prominent lymphoplasmacytic differentiation (formerly called cutaneous immunocytoma), except that direct immunofluorescence demonstrates monoclonal IgM within and around the infiltrating cells. Immunofixation electrophoresis of the serum detects the circulating monoclonal protein as IgM.

REFERENCES

1. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. Blood. 2005;105:3768–85.
2. Fink-Puches R, Zenahlik P, Bäck B, et al. Primary cutaneous lymphomas: applicability of current classification schemes (EORTC, WHO) based on clinicopathologic features observed in a large group of patients. Blood. 2002;99:800–5.
3. Swerdlow SH, Campo E, Harris NL, et al. (eds). WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon: IARC Press, 2008.
4. Cerroni L, Gatter K, Kerl H. Skin Lymphoma – The Illustrated Guide, 3rd edn. Oxford: Wiley-Blackwell, 2009.
5. Cerroni L, Signoretti S, Höfler G, et al. Primary cutaneous marginal zone B-cell lymphoma: a recently described entity of low-grade malignant cutaneous B-cell lymphoma. Am J Surg Pathol. 1997;21:1307–15.
6. Zackheim HS, Vonderheid EC, Ramsay DL, et al. Relative frequency of various forms of primary cutaneous lymphomas. J Am Acad Dermatol. 2000;43:793–6.
7. Cerroni L, Zöchling N, Pütz B, Kerl H. Infection by *Borrelia burgdorferi* and cutaneous B-cell lymphoma. J Cutan Pathol. 1997;24:457–61.
8. Goodlad JR, Davidson MM, Hollowood K, et al. Primary cutaneous B-cell lymphoma and *Borrelia burgdorferi* infection in patients from the highlands of Scotland. Am J Surg Pathol. 2000;24:1279–85.
9. Viraben R, Brousse P, Lamant L. Reversible cutaneous lymphoma occurring during methotrexate therapy. Br J Dermatol. 1996;135:116–18.
10. Beylot-Barry M, Vergier B, Masquelier B, et al. The spectrum of cutaneous lymphomas in HIV infection. A study of 21 cases. Am J Surg Pathol. 1999;23:1208–16.
11. Senff NJ, Kluin-Nelemans JC, Willemze R. Results of bone marrow examination in 275 patients with histological features that suggest an indolent type of cutaneous B-cell lymphoma. Br J Haematol. 2008;142:52–6.
12. Berti E, Alessi E, Caputo R, et al. Reticulohistiocytoma of the dorsum. J Am Acad Dermatol. 1988;19:259–72.
13. Cerroni L, Arzberger E, Pütz B, et al. Primary cutaneous follicle center cell lymphoma with follicular growth pattern. Blood. 2000;95:3922–8.
14. Pimpinelli N, Santucci M, Bosi A, et al. Primary cutaneous follicular centre-cell lymphoma: a lymphoproliferative disease with favourable prognosis. Clin Exp Dermatol. 1989;14:12–9.
15. Bailey EM, Ferry JA, Harris NL, et al. Marginal zone lymphoma (low-grade B-cell lymphoma of mucosa-associated lymphoid tissue type) of skin and subcutaneous tissue. A study of 15 patients. Am J Surg Pathol. 1996;20:1011–23.
16. Vermeer MH, Geelen FAMJ, van Haselen CW, et al. Primary cutaneous large B-cell lymphomas of the legs. A distinct type of cutaneous B-cell lymphoma with an intermediate prognosis. Arch Dermatol. 1996;132:1304–8.
17. Kodama K, Massone C, Chott A, et al. Primary cutaneous large B-cell lymphomas: clinicopathologic features, classification, and prognostic factors in a large series of patients. Blood. 2005;106:2491–7.
18. Grange F, Bekkenk MW, Wechsler J, et al. Prognostic factors in primary cutaneous large B-cell lymphomas: a European multicenter study of 145 cases. J Clin Oncol. 2001;19:3602–10.
19. Grange F, Petrella T, Beylot-Barry M, et al. Bcl-2 protein expression is the strongest independent prognostic factor of survival in primary cutaneous large B-cell lymphomas. Blood. 2004;103:3662–8.
20. Dijkman R, Tensen CP, Jordanova ES, et al. Array-based comparative genomic hybridization analysis reveals recurrent chromosomal alterations and prognostic parameters in primary cutaneous large B-cell lymphoma. J Clin Oncol. 2006;24:296–305.
21. Senff NJ, Zoutman WH, Vermeer MH, et al. Fine-mapping chromosomal loss at 9p21: correlation with prognosis in primary cutaneous diffuse large B-cell lymphoma, leg type. J Invest Dermatol. 2009;129:1149–55.
22. Perniciaro C, Winkelmann RK, Daoud MS, et al. Malignant angioendotheliomatosis is an angiotropic intravascular lymphoma. Immunohistochemical, ultrastructural, and molecular genetics studies. Am J Dermatopathol. 1995;17:242–8.
23. Cerroni L, Zalaudek I, Kerl H. Intravascular large B-cell lymphoma colonizing cutaneous hemangiomas. Dermatology. 2004;209:132–4.
24. Chimenti S, Fink-Puches R, Peris K, et al. Cutaneous involvement in lymphoblastic lymphoma. J Cutan Pathol. 1999;26:379–85.
25. Sander CA, Medeiros LJ, Abruzzo LV, et al. Lymphoblastic lymphoma presenting in cutaneous sites: a clinicopathologic analysis of six cases. J Am Acad Dermatol. 1991;25:1023–31.
26. Oyama T, Yamamoto K, Asano N, et al. Age-related EBV-associated B-cell lymphoproliferative disorders constitute a distinct clinicopathologic group: a study of 96 patients. Clin Cancer Res. 2007;13:5124–32.
27. Cerroni L, El-Shabrawi-Caelen L, Fink-Puches R, et al. Cutaneous spindle-cell B-cell lymphoma. A morphologic variant of cutaneous large B-cell lymphoma. Am J Dermatopathol. 2000;22:299–304.
28. Cerroni L, Volkenandt M, Rieger E, et al. bcl-2 protein expression and correlation with the interchromosomal 14;18 translocation in cutaneous lymphomas and pseudolymphomas. J Invest Dermatol. 1994;102: 231–5.
29. Leinweber B, Colli C, Chott A, et al. Differential diagnosis of cutaneous infiltrates of B lymphocytes with follicular growth pattern. Am J Dermatopathol. 2004;26:4–13.
30. Rijlaarsdam JU, van der Putte SCJ, Berti E, et al. Cutaneous immunocytomas: a clinicopathologic study of 26 cases. Histopathology. 1993;23:117–25.
31. van Maldegem F, van Dijk R, Wormhoudt TAM, et al. The majority of cutaneous marginal zone B-cell lymphomas expresses class-switched immunoglobulins and develops in a T-helper type 2 inflammatory environment. Blood. 2008;112:3355–61.
32. Deutsch AJA, Frühwirth M, Aigelsreiter A, et al. Primary cutaneous marginal zone B-cell lymphomas are targeted by aberrant somatic hypermutation. J Invest Dermatol. 2009;129:476–9.
33. Wiesner T, Obenauf AC, Geigl JB, et al. 9p21 deletion in primary cutaneous large B-cell lymphoma, leg-type, may escape detection by standard FISH assays. J Invest Dermatol. 2009;129:238–40.
34. Hoefnagel JJ, Dijkman R, Basso K, et al. Distinct types of primary cutaneous large B-cell lymphoma identified by gene expression profiling. Blood. 2005;105:3671–8.
35. Wiesner T, Streubel B, Huber D, et al. Genetic aberrations in primary cutaneous large B-cell lymphoma. A fluorescence in situ hybridization study of 25 cases. Am J Surg Pathol. 2005;29:666–73.
36. Colli C, Leinweber B, Müllegger R, et al. *Borrelia burgdorferi*-associated lymphocytoma cutis: clinicopathologic, immunophenotypic, and molecular study of 106 cases. J Cutan Pathol. 2004;31:232–40.
37. Parry EJ, Stevens SR, Gilliam AC, et al. Management of cutaneous lymphomas using a multidisciplinary approach. Arch Dermatol. 1999;135:907–11.
38. Zenahlik P, Fink-Puches R, Kapp KS, et al. Therapy of primary cutaneous B-cell lymphomas. Hautarzt. 2000;51:19–24.
39. Senff NJ, Noordijk EM, Kim YH, et al. European Organization for Research and Treatment of Cancer and International Society for Cutaneous Lymphoma consensus recommendations for the management of cutaneous B-cell lymphomas. Blood. 2008;112: 1600–9.
40. Senff NJ, Hoefnagel JJ, Neelis KJ, et al. Results of radiotherapy in 153 primary cutaneous B-cell lymphomas classified according to the WHO-EORTC classification. Arch Dermatol. 2007;143:1520–6.
41. Piccinno R, Caccialanza M, Berti E, Baldini L. Radiotherapy of cutaneous B cell lymphomas: our experience in 31 cases. Int J Radiat Oncol Biol Phys. 1993;27:385–9.
42. Kütting B, Bonsmann G, Metze D, et al. *Borrelia burgdorferi*-associated primary cutaneous B cell lymphoma: complete clearing of skin lesions after antibiotic pulse therapy or intralesional injection of interferon α-2a. J Am Acad Dermatol. 1997;36: 311–14.
43. Roggero E, Zucca E, Mainetti C, et al. Eradication of *Borrelia burgdorferi* infection in primary marginal zone B-cell lymphoma of the skin. Hum Pathol. 2000;31:263–8.
44. Heinzerling LM, Urbanek M, Funk JO, et al. Reduction of tumor burden and stabilization of disease by systemic therapy with anti-CD20 antibody (rituximab) in patients with primary cutaneous B-cell lymphoma. Cancer. 2000;89:1835–44.
45. Fink-Puches R, Wolf IH, Zalaudek I, et al. Treatment of primary cutaneous B-cell lymphoma with rituximab. J Am Acad Dermatol. 2005;52:847–53.
46. Bekkenk MW, Vermeer MH, Geerts ML, et al. Treatment of multifocal primary cutaneous B-cell lymphoma: a clinical follow-up study of 29 patients. J Clin Oncol. 1999;17:2471–8.
47. Rijlaarsdam JU, Toonstra J, Meijer CJLM, et al. Treatment of primary cutaneous B-cell lymphomas of follicle center cell origin: a clinical follow-up study of 55 patients treated with radiotherapy or polychemotherapy. J Clin Oncol. 1996;14:549–55.
48. Ferreri AJM, Dognini GP, Bairey O, et al. The addition of rituximab to anthracycline-based chemotherapy significantly improves outcome in "Western" patients with intravascular large B-cell lymphoma. Br J Haematol. 2008;143:253–7.
49. Kyle RA, Remstein ED, Therneau TM, et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. N Engl J Med. 2007;356:2582–90.
50. Kyle RA, Rajkumar SV. Monoclonal gammopathy of undetermined significance and smouldering multiple myeloma: emphasis on risk factors for progression. Br J Haematol. 2007;139:730–43.

Cutaneous diffuse large B-cell lymphoma, leg type. Multiple red-brown tumors on the lower leg.

This page intentionally left blank

Cutaneous T-Cell Lymphoma 120

Rein Willemze

Chapter Contents

Mycosis fungoides 2019
Variants of mycosis fungoides 2025
Sézary syndrome 2027
Adult T-cell leukemia/lymphoma 2028
Primary cutaneous CD30-positive lymphoproliferative disorders 2029
Subcutaneous panniculitis-like T-cell lymphoma 2032
Extranodal NK/T-cell lymphoma, nasal type 2033
Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma 2033
Primary cutaneous gamma/delta T-cell lymphoma 2034
Primary cutaneous CD4-positive small/medium pleomorphic T-cell lymphoma 2034
Primary cutaneous peripheral T-cell lymphoma, unspecified 2034

Introduction

The term cutaneous T-cell lymphoma (CTCL) describes a heterogeneous group of neoplasms of skin-homing T cells that show considerable variation in clinical presentation, histologic appearance, immunophenotype and prognosis. CTCL represents approximately 75–80% of all primary cutaneous lymphomas, whereas primary cutaneous B-cell lymphomas (CBCL) account for approximately 20–25%[1]. For many years, mycosis fungoides (MF) and Sézary syndrome (SS) were the only known types of CTCL. Over the past two decades, based on a combination of clinical, histologic and immunophenotypical criteria, new types of CTCL and CBCL have been defined and new classifications for the group of primary cutaneous lymphomas have been formulated[1–4]. A major advantage in the management of primary cutaneous lymphomas compared with lymphomas arising at other sites is that the former can be seen and can be biopsied easily, giving the dermatologist the unique opportunity to correlate the clinical appearance and clinical behavior with histologic, immunophenotypical and genetic aspects of these conditions. Hence, the dermatologist can play a key role in the diagnosis, classification and treatment of these diseases.

History

In 1806, a French physician, Jean Louis Alibert, was the first to describe a patient with MF. This case was designated *pian fungoïde* in his atlas, but in 1835 it was renamed *mycosis fungoïde* because of the resemblance of some skin tumors to mushrooms. In 1870, Bazin described the natural progression from a nonspecific premycotic phase to plaque lesions and finally to tumors, which probably represents one of the first descriptions of the "multistep model" in the development of a malignancy. In 1885, Vidal and Brocq used the term "mycosis fungoides d'emblée" for patients presenting with skin tumors not preceded by patches or plaques. It has now become clear that such cases represent another type of CTCL or a CBCL. The erythrodermic form of MF was described in 1892 by Besnier and Hallopeau. These early descriptions of the main clinical forms of MF were followed by descriptions of Sézary syndrome by Sézary and Bouvrain in 1938, pagetoid reticulosis by Woringer and Kolopp in 1939, and lymphomatoid papulosis (LyP) by Macaulay in 1968.

Thus, in the early 1970s, MF and some related conditions were the only types of cutaneous lymphoma that had been rather well described. Reports on cutaneous lymphomas other than MF/SS, commonly designated in the past as malignant reticulosis or reticulum cell sarcoma, were few. Moreover, they were firmly believed to represent skin manifestations of a systemic lymphoma and treated as such.

The CTCL concept

In 1968, Lutzner and Jordan described the ultrastructural features of the circulating atypical cells in SS. Characteristically, the nuclei of these cells had deep and narrow indentations, giving them a cerebriform appearance. In 1971, similar cells were found in the skin and lymph nodes of patients with MF. In 1975, based on the observation that the neoplastic cells in MF, SS and related conditions not only had the same morphology but also a common T-cell phenotype, the term "CTCL" was suggested for this group of diseases[5]. Within a short time, this term gained wide acceptance, particularly in the US. The introduction of the CTCL concept can be considered as a landmark in the history of this group of diseases. However, a major disadvantage has been that in many subsequent studies, distinction was no longer made between MF, SS and other T-cell neoplasms, entities which may vary considerably in clinical presentation and clinical behavior.

The concept of primary cutaneous lymphomas

At about the same time that the CTCL concept was introduced, several European groups started to classify cutaneous lymphomas according to the criteria of the Kiel classification, a system used by hematopathologists for the categorization of nodal lymphomas. It was then determined that many types of CBCL and CTCL (other than classical MF and SS) can present in the skin without any evidence of extracutaneous disease at the time of diagnosis. It appeared that these primary cutaneous lymphomas often have a completely different clinical behavior and prognosis when compared to morphologically similar lymphomas arising in lymph nodes, and therefore require different types of treatment[1]. In addition, differences in the presence of specific chromosomal translocations and in the expression of oncogenes, viral sequences or antigens (e.g. EBV), and adhesion receptors involved in tissue-related lymphocyte homing were found[1].

Such differences underscored that primary cutaneous lymphomas represent a distinct group and may explain, at least in part, their different clinical behavior. For instance, the observation that the neoplastic T cells in most CTCLs express cutaneous lymphocyte antigen (CLA) and the CC-chemokine receptors 4 (CCR4) and 10 (CCR10), indicates that they are the neoplastic counterparts of normal skin-homing T cells, and this explains why these CTCLs present in the skin. Perhaps most important, it appeared that different types of CTCL and CBCL with different clinical behaviors and different therapeutic requirements may have an identical histologic appearance. This implies that histologic features should always be combined with clinical and immunophenotypical data, before a definite diagnosis (classification) can be made.

Over the past two decades, such an approach resulted in the delineation of several new types of CTCL and CBCL, and it formed the basis of the European Organization for Research and Treatment of Cancer (EORTC) classification for primary cutaneous lymphomas[1].

EORTC, WHO and WHO-EORTC classification schemes

The EORTC classification scheme was the first one that was specifically designed for the group of primary cutaneous lymphomas. It contained

a limited number of well-defined types of CTCL and CBCL, which together accounted for more than 95% of all primary cutaneous lymphomas, in addition to some provisional entities, which were not yet fully defined clinically. A distinction was made between cutaneous lymphomas with indolent, intermediate or aggressive clinical behavior. By including well-defined and recognizable disease entities, this classification provided the clinician with detailed information on staging, preferred mode of treatment, clinical behavior and prognosis, serving as a useful guide to optimal management and treatment.

The third edition of the World Health Organization (WHO) classification for malignant lymphomas adopted the most common types of CTCL from the EORTC classification, but there was controversy with regard to the categorization of some rare types of CTCL[2]. In addition, the WHO classification contained some new entities not yet included in the EORTC scheme. In 2004, representatives from both organizations reached an agreement on a new classification scheme for the group of cutaneous lymphomas: the WHO-EORTC classification[3]. Importantly, the fourth edition of the WHO classification for malignant lymphomas, published in 2008, which is used by pathologists and hematologists worldwide, has adopted the terminology and definitions of the WHO-EORTC classification, and therefore, it now includes all the types of CTCL and CBCL included in previous classifications of primary cutaneous lymphomas[4]. The frequency and survival of patients with the different types of CTCL recognized in the WHO-EORTC classification are presented in Table 120.1. Following a description of practical guidelines for diagnosis, classification and staging, relevant features of the different types of CTCL included in this classification are presented.

WHO-EORTC CLASSIFICATION FOR CUTANEOUS T-CELL LYMPHOMAS

WHO-EORTC classification	Frequency (%)*	5-year survival rate (%)*
INDOLENT CLINICAL BEHAVIOR		
Mycosis fungoides (MF)	54	88
Mycosis fungoides variants and subtypes		
• Folliculotropic MF	6	80
• Pagetoid reticulosis	1	100
• Granulomatous slack skin	<1	100
Primary cutaneous CD30-positive lymphoproliferative disorders		
• Primary cutaneous anaplastic large cell lymphoma (C-ALCL)	10	95
• Lymphomatoid papulosis (LyP)	16	100
Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)	1	82
Primary cutaneous CD4-positive small/medium pleomorphic T-cell lymphoma‡	3	75
AGGRESSIVE CLINICAL BEHAVIOR		
Sézary syndrome (SS)	4	24
Adult T-cell leukemia/lymphoma (ATLL)	NDA	NDA
Extranodal NK/T-cell lymphoma, nasal type	1	<5
Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma‡	<1	18
Primary cutaneous gamma/delta T-cell lymphoma (PCGD-TCL)‡	1	<5
Primary cutaneous peripheral T-cell lymphoma (PTCL), unspecified§	3	16

*Data are based on 1476 CTCL patients registered by the Dutch and Austrian Cutaneous Lymphoma Groups[3].
†α/β T-cell phenotype.
§Primary cutaneous T-cell lymphoma, unspecified, excluding the three provisional entities indicated by ‡.

Table 120.1 WHO-EORTC classification for cutaneous T-cell lymphomas[3]. NDA, no data available.

Practical Guidelines for Diagnosis, Classification and Staging of CTCL

Diagnosis

The first step in the evaluation of a patient suspected of having CTCL is to decide if it represents a lymphoma or a benign condition. Skin biopsies – preferably deep punch biopsies 4–6 mm wide or an excisional or incisional biopsy from the most representative skin lesions – should be performed.

Since prior treatment with topical corticosteroids or PUVA may change the original histology profoundly, biopsies from untreated skin lesions are preferred. Even if an adequate biopsy specimen is obtained, a definite diagnosis is not always possible. First, several types of CTCL, such as MF, are often preceded for years by skin lesions that are neither clinically nor histologically diagnostic. The gradual progression from this prediagnostic phase to overt lymphoma explains why it has always been so difficult to reach a consensus on the minimal histologic criteria needed for an unequivocal diagnosis of MF[6]. Because of the indolent clinical behavior of the disease in such patients, a conservative approach is justified. In most cases, repeated biopsies, when appropriate, will ultimately result in the correct diagnosis.

Secondly, atypical T-cell infiltrates are found not only in CTCL but also in reactive conditions, e.g. lymphomatoid drug eruptions (pseudo-T-cell lymphomas)[7]. Therefore, a definite diagnosis should always be based on a combination of clinical, histologic and, in most cases, immunophenotypical criteria, and it may be supplemented with the results of gene rearrangement analysis[8].

Immunophenotyping

Immunohistochemical studies on paraffin or frozen sections using antibodies reactive with cell-surface or cytoplasmic molecules are extremely important in the diagnosis and classification of cutaneous lymphomas. Using a panel of such antibodies (see Ch. 0), distinction can be made between neoplasms of T-cell, B-cell, NK-cell and myeloid or monocytic origin. Within the group of CTCLs, such studies have contributed to the delineation of new subtypes and provided important diagnostic and prognostic criteria.

With respect to the diagnosis of CTCL, demonstration of an aberrant phenotype, i.e. loss of one or more T-cell-associated antigens, such as CD2, CD3, CD4 or CD5, by the neoplastic T cells, can be considered as an important additional criterion in establishing a definite diagnosis of CTCL[8]. However, loss of CD7 expression, which may be caused by chronic T-cell stimulation and is commonly observed in benign dermatoses as well, is not a reliable marker. Recently, new antibodies have become available, which, in combination with antigen retrieval techniques, now also allow demonstration of "marker loss" on paraffin sections.

T-cell receptor gene rearrangement analysis

In the past decade, T-cell receptor gene rearrangement analysis, either by Southern blot analysis or by more sensitive polymerase chain reaction (PCR)-based techniques, has increasingly been used in the diagnosis and staging of malignant lymphomas[9]. However, caution is warranted in interpreting the results of such analyses. Clonal T-cell populations have been detected not only in skin lesions, lymph nodes and peripheral blood of patients with CTCL, and in cases of chronic dermatitis preceding MF ("clonal dermatitis"; see Ch. 9), but also in skin lesions of patients with apparently benign conditions, such as pityriasis lichenoides et varioliformis acuta, lichen planus, lichen sclerosus and some pseudolymphomas[9,10].

Demonstration of clonal T-cell populations can therefore not be used as an absolute criterion of malignancy, but should always be considered in conjunction with clinical and histologic features, which together remain the "gold standard". If the clinical and histologic findings are not consistent, and an aberrant phenotype is not detected, a definite diagnosis of CTCL should not be made.

Classification

Once a diagnosis of CTCL has been made, the type of CTCL should be determined. As noted before, the histologic diagnosis is not the final diagnosis, which means that CTCL cannot be classified on the basis of histologic criteria alone. For instance, in the case of a skin biopsy showing a dermal infiltrate which is composed predominantly of CD30-positive large anaplastic or pleomorphic T cells, the *histologic diagnosis* will be (CD30-positive) anaplastic large cell lymphoma (ALCL). However, depending upon the clinical presentation, the *definite diagnosis* may be a primary cutaneous ALCL; cutaneous involvement of a systemic ALCL; large cell transformation of MF with expression of CD30; or LyP (in cases of recurrent self-healing papules). Obviously, each of these conditions requires a different approach in terms of staging and treatment.

In Table 120.2, the differential diagnosis of four histologic categories has been elaborated. This histologic subdivision into epidermotropic CTCL, CTCL with diffuse pleomorphic infiltrates, CD30-positive CTCL and subcutaneous CTCL is neither complete nor meant as an alternative classification. It is only presented as an illustration of how histology should be combined with clinical and immunophenotypical data to arrive at a definite diagnosis.

Practical guidelines

For those not regularly involved in the diagnosis and classification of CTCL and perhaps overwhelmed by the many new types of CTCL introduced in recent years, a stepwise approach, as presented in Figure 120.1, may serve as a practical guide.

Step one: Based on a combination of clinical, histologic and immunophenotypical criteria, distinction is first made between classic MF, MF variants and SS on the one hand *and* CTCL other than these conditions on the other. The rationale for this first step is that dermatologists are familiar with the former set of conditions, which comprise approximately 65% of CTCLs, and these lymphomas require a different clinical approach in terms of staging and therapy compared to the other forms of CTCL. Cases of unequivocal LyP can be included in this first step.

Step two: The second category to be considered is the group of *primary* cutaneous CD30-positive lymphoproliferative disorders. It implies that evaluation of skin biopsies from patients with (suspected) CTCL should always include CD30 immunostaining. This group includes cases of cutaneous ALCL (C-ALCL) and LyP, which together represent the second most common group of CTCL (see Table 120.1). Patients within this spectrum of disease generally have an excellent prognosis, and most individuals can be managed easily by dermatologists.

Step three: With the first two steps, approximately 90% of CTCL will be classified correctly. The remaining group (10% of patients) contains rare types of CTCL, including subcutaneous panniculitis-like T-cell lymphoma (SPTCL), extranodal NK/T-cell lymphoma, nasal type, and the broad group of primary cutaneous peripheral T-cell lymphoma (PTCL), unspecified. From the latter group, primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma, primary cutaneous gamma/delta T-cell lymphoma (PCGD-TCL) and primary cutaneous CD4-positive small/medium pleomorphic T-cell lymphoma have been separated out as provisional entities (see Table 120.1)[3]. In the WHO-EORTC classification, the term PTCL, unspecified, is maintained for remaining cases that do not fit into any of the provisional entities.

Apart from SPTCL and primary cutaneous CD4-positive small/medium pleomorphic T-cell lymphomas, lymphomas included in this third category have an aggressive clinical course, and should be treated by, or in close collaboration with, a hemato-oncologist. It should be emphasized that distinction between these different types of aggressive CTCL is sometimes very difficult, because of overlapping clinicopathologic features and highly aberrant phenotypes. Distinction between primary and secondary cutaneous involvement is less important than in other types of cutaneous lymphoma. Patients presenting with only skin lesions generally develop extracutaneous disease within a short period of time and have a poor prognosis as well.

Staging

Apart from CTCL, a term preferably used only for *primary* CTCL, systemic T-cell lymphomas frequently present or relapse in the skin. Adequate staging procedures are required to differentiate between CTCL and these systemic lymphomas secondarily involving the skin. The extent of staging procedures is dependent on the type of (suspected) CTCL, and, in the case of classical MF, on the clinical stage of the disease[11]. In cases of early patch/plaque stage MF, unequivocal cases of LyP and probably pagetoid reticulosis as well, staging procedures are generally not worthwhile. In cases of suspected SS, adequate staging with special emphasis on assessment of peripheral blood involvement by cytology, immunophenotyping (flow cytometry) and TCR gene rearrangement analysis is essential. In all other types of CTCL, routine hematological staging, including complete and differential blood cell counts, a blood chemistry panel, computed tomographic (CT) scans of the chest and abdomen, and bone marrow sampling, are required[12].

MYCOSIS FUNGOIDES

Definition

Mycosis fungoides (MF) represents the most common type of CTCL and accounts for approximately 50% of all primary cutaneous lymphomas (see Table 120.1). The term MF should be restricted to the classic "Alibert–Bazin" type characterized by the typical evolution of patches, plaques and tumors, or for clinicopathologic variants showing a similar clinical course.

Epidemiology

MF has an incidence of about 0.4 per 100 000 inhabitants per year in the US[13]. MF typically affects older adults (median age at diagnosis: 55–60 years), but it may occur in children and adolescents as well. Men are affected more often than women, with a male-to-female ratio of 1.6–2.0 : 1.

Pathogenesis

The etiology and the pathogenetic mechanisms involved in the development and stepwise progression of MF are largely unknown. Genetic, environmental and immunologic factors have all been considered.

Genetic factors

Lymphomagenesis is considered to be a multifactorial process, in which a stepwise accumulation of genetic abnormalities may result in clonal proliferation, malignant transformation and, ultimately, progressive and widely disseminated disease. Although the successive clinical steps of tumor progression were described more than a century ago, the molecular events underlying the different steps of tumor progression have not been identified. Many genetic abnormalities have been reported in patients with MF, but a consistent pattern has not emerged[14]. Constitutive activation of *STAT3* and inactivation or loss of *CDKN2A*, *PTEN* and *p53* have been identified in advanced, but not early, stages of MF, suggesting that these are secondary genetic events[15–17]. Gene expression profiling studies have shown activation of the tumor necrosis factor (TNF) antiapoptotic pathway in the tumorigenesis of MF[18].

Environmental factors

Persistent antigenic stimulation has been demonstrated to play a crucial role in the development of various malignant lymphomas, including *m*ucosa-*a*ssociated *l*ymphoid *t*issue (MALT) lymphomas (*Helicobacter pylori* infection), CBCL (*Borrelia burgdorferi* infection) and enteropathy-type T-cell lymphoma (celiac disease). In MF, persistent antigenic stimulation has also been proposed as an initial event, but the nature of the antigen(s) involved is unknown. Large case–control studies do not support a relationship between industrial or environmental exposure and the development of MF[19]. Whereas the etiologic roles of human T-cell leukemia virus 1 (human T-cell lymphotropic virus 1; HTLV-1) in adult T-cell leukemia/lymphoma and Epstein-Barr virus (EBV) in nasal NK/T-cell lymphoma have been firmly established, conclusive evidence for a primary etiologic role of these viruses in MF is lacking[20].

Immunological factors

Recent studies suggest that $CD8^+$ cytotoxic T cells (CTL) play a crucial role in the antitumor response in MF. A relationship between high percentages of $CD8^+$ CTL in the dermal infiltrates and better survival has been described[21]. These $CD8^+$ T cells exert their antitumor effect

DIFFERENTIAL DIAGNOSIS OF COMMON HISTOLOGIC PATTERNS IN CUTANEOUS T-CELL LYMPHOMA		
Histologic category	**Differential diagnosis**	**Diagnostic criteria/clues**
Epidermotropic CTCL (simulating or consistent with plaque stage MF)	Mycosis fungoides (MF)	• Characteristic patches and plaques • Most atypical cells within the epidermis (basal layer)
	Pagetoid reticulosis	• Solitary plaque, commonly on distal extremities • Neoplastic cells confined to an often acanthotic epidermis • Often $CD8^+$ phenotype; CD30 expression common
	Lymphomatoid papulosis (LyP), type B or type D	• Recurrent, self-healing papular eruption • Sometimes extension of infiltrate into lower dermis • In some cases admixture with large atypical cells as in type A LyP (mixed type A and B) • LyP type D is $CD8^+$
	Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma	• Infiltrated plaques, but often eruptive nodules and tumors with ulceration • Intraepidermal accumulation of medium-sized pleomorphic T cells or small blast cells; no typical cerebriform appearance • Phenotype: $CD8^+$, TIA-1^+, granzyme B^+, $CD45RA^+$, $CD7^{-/+}$
	Sézary syndrome	• Often more monotonous infiltrate histologically • Erythroderma • Peripheral blood involvement
	Adult T-cell leukemia/lymphoma	• Sometimes clinically and histologically identical to MF • Check HTLV-1 status in patients from endemic areas
CTCL with diffuse pleomorphic infiltrates ($CD30^-$) (simulation or consistent with tumor stage MF; few $CD30^+$ tumor cells may be present)	Tumor stage MF	• Concurrent patches and plaques • Variable numbers of small, medium-sized and/or large cerebriform T cells and/or blast cells and variable admixture with inflammatory cells
	Primary cutaneous peripheral T-cell lymphoma, unspecified	• Histologically, often indistinguishable from MF with blastic transformation • No prior or concurrent patches and plaques
	Primary cutaneous CD4-positive small/medium pleomorphic T-cell lymphoma	• Less than 30% large neoplastic T cells • Histologically, sometimes indistinguishable from tumor stage MF • No prior or concurrent patches and plaques
	Pseudo-T-cell lymphoma	• Presentation with solitary plaque or tumor (2–3 cm) • Scattered medium-sized to large pleomorphic T cells (no clusters) • Many admixed $CD8^+$ T cells, B cells and histiocytes • No aberrant phenotype ("marker loss") • Clonal T-cell population uncommon
CD30-positive CTCL (see Fig. 120.11)	Lymphomatoid papulosis, type A/C	• Recurrent self-healing papules and nodules • Histologic spectrum (from typical LyP to C-ALCL)
	Primary cutaneous anaplastic large cell lymphoma (C-ALCL)	• Generally, solitary or localized nodules or tumors • No evidence of prior or concurrent MF or another type of CTCL • No extracutaneous disease (staging negative) • Histologic spectrum (from typical C-ALCL to LyP) • Phenotype: CLA^+, EMA^-, ALK^-
	Systemic ALCL with secondary skin involvement	• Prior or concurrent extracutaneous involvement (exception: involvement of one regional lymph node basin) • Often generalized skin lesions • Phenotype: CLA^-, EMA^+, ALK^+ (mainly in pediatric subgroup)
	MF with blastic transformation	• Histologically, an admixture with typical cerebriform cells, but sometimes indistinguishable from C-ALCL • Prior or concurrent patches and plaques
CTCL with subcutaneous involvement	Subcutaneous panniculitis-like T-cell lymphoma	• Infiltrates confined to subcutis • Characteristic rimming of individual fat cells by neoplastic T cells • Deeply seated nodules and plaques, mainly involving the legs and trunk • Characteristic $CD3^+$, $CD4^-$, $CD8^+$, $CD56^-$, $\beta F1^+$ T-cell phenotype
	Other types of CTCL	• Subcutaneous infiltrates represent extension from dermal infiltrates • For specific features: see text

Table 120.2 Differential diagnosis of common histologic patterns in cutaneous T-cell lymphoma (CTCL). ALK, anaplastic lymphoma kinase; CLA, cutaneous lymphocyte antigen; C-ALCL, cutaneous anaplastic large cell lymphoma; EMA, epithelial membrane antigen; TIA, T-cell restricted intracellular antigen; βF1, positivity reflects α/β T-cell origin.

both by a direct cytotoxic effect and by the production of cytokines, particularly interferon (IFN)-γ. They can mediate tumor cell lysis by exocytosis of cytotoxic granules containing perforin, granzymes and T-cell-restricted intracellular antigen (TIA-1), and by expression of Fas ligand (FasL), which interacts with Fas (CD95; APO-1) on the neoplastic T cells[21]. Both pathways ultimately lead to activation of caspase 3 and tumor cell death. Loss of Fas expression or function by the neoplastic T cells is one of the many mechanisms by which tumor cells can escape from an effective antitumor response[22].

More recent studies suggest that the neoplastic T cells in SS and tumor stage MF are derived from $CD4^+$ T cells with a Th2 cytokine profile (production of IL-4, IL-5 and IL-10), whereas the cytotoxic T cells are the main producers of IFN-γ, which plays an important role in augmenting T-cell- and NK-cell-mediated killing. In accordance with this

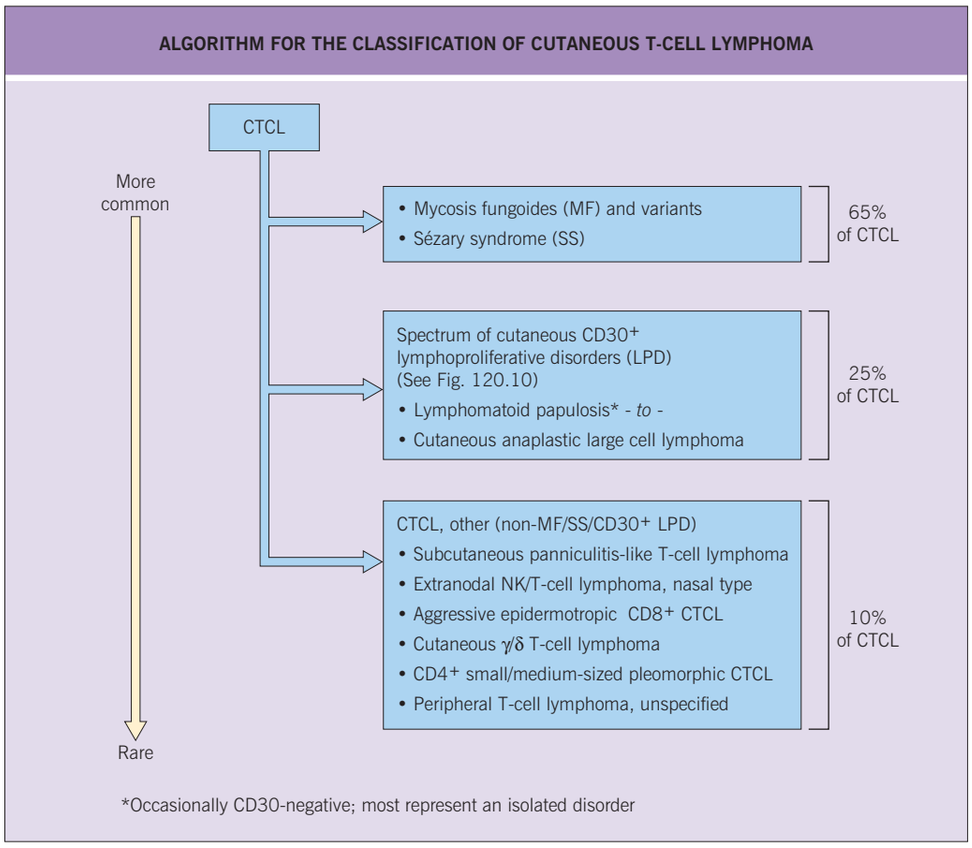


Fig. 120.1 Algorithm for the classification of cutaneous T-cell lymphoma (CTCL). *Adapted from Willemze R, Beljaards RC, Meijer CJLM. Classification of primary cutaneous T-cell lymphoma. Histopathology. 1994;24:405–15.*

concept, a gradual shift from a predominantly type 1 cytokine profile in MF plaques to a predominantly type 2 cytokine profile in MF tumors has been suggested[23]. Increased levels of Th2 cytokines may impair the Th1 cell-mediated antitumor response and contribute to the immunosuppression seen in patients with advanced MF.

Clinical features

Characteristically, patients with classical MF progress from patch stage to plaque stage and finally to tumor stage disease, and they have a protracted clinical course over years or even decades. Before a definite diagnosis is made, patients generally have many years of nonspecific eczematous or psoriasiform skin lesions and non-diagnostic biopsies. The median duration from onset of skin lesions to the diagnosis of MF is 4–6 years, but it may vary from several months to more than five decades[24,25].

Early patch stage MF is characterized by the presence of variably sized erythematous, finely scaling lesions, which may be mildly pruritic (Fig. 120.2A). These early lesions may show variable degrees of atrophy, and a poikilodermatous variant consisting of patches with mottled hyper- and hypopigmentation, atrophy and telangiectasia has been described (formerly called poikiloderma vasculare atrophicans). Generalized hypopigmented lesions may be observed in patients with darkly pigmented skin, and this is also a common presentation of juvenile-onset MF (Fig. 120.3). The initial skin lesions have a predilection for the buttocks and other covered sites of the trunk and limbs. With progression, more infiltrated reddish-brown, scaling plaques develop, which gradually enlarge and may have an annular, polycyclic or typical horseshoe-shaped configuration (Fig. 120.4A). It should be stressed that many patients never progress beyond the plaque stage of the disease. However, a number of patients may develop nodules or tumors. These patients with tumor stage MF characteristically show a combination of patches, plaques and tumors (Fig. 120.5A); the latter often show ulceration.

If only skin tumors are present without preceding or concurrent patches or plaques, a diagnosis of MF is highly unlikely and another type of CTCL should be considered. The risk of developing extracutaneous disease correlates with the extent and type of skin lesions. It is exceedingly rare in patients with limited patch/plaque stage disease, relatively uncommon in patients with generalized plaques, and most likely in patients with skin tumors or erythroderma[24,25]. Extracutaneous dissemination, almost without exception, first involves the regional lymph nodes draining areas of extensive skin involvement. Visceral involvement may develop subsequently and can involve any organ. The bone marrow is rarely involved.

Pathology

Early patch lesions in MF show superficial band-like or lichenoid infiltrates, mainly consisting of lymphocytes. Atypical cells, with small to medium-sized, highly convoluted (cerebriform) and sometimes hyperchromatic nuclei, are few in number and are mostly confined to the epidermis (epidermotropism). These lymphocytes characteristically colonize the basal layer of the epidermis as single cells surrounded by vacuolated halos, often in a linear configuration (see Fig. 120.2B)[8,26]. In plaques, epidermotropism is generally more pronounced (see Fig. 120.4B). The presence of intraepidermal nests of atypical cells (Pautrier's microabscesses) is a highly characteristic feature, but is observed in only a minority of cases. The epidermis may show acanthosis and elongated rete ridges, but spongiosis is generally mild or absent. The dermal infiltrates are also more pronounced, and they may contain a higher number of atypical cells with cerebriform nuclei and occasional blast cells, as well as admixed eosinophils and plasma cells. With progression to tumor stage, the dermal infiltrates can involve the entire dermis and extend into the subcutaneous tissue. Epidermotropism may no longer be present. The tumor cells increase in number and size, showing variable proportions of small, medium-sized or large cells with cerebriform nuclei, blast cells with prominent nuclei and intermediate forms (Fig. 120.5B). Large cell transformation, defined by the presence of CD30-negative or CD30-positive large cells exceeding 25% of the infiltrate or forming microscopic nodules, may occur and is generally associated with a poor prognosis[27].

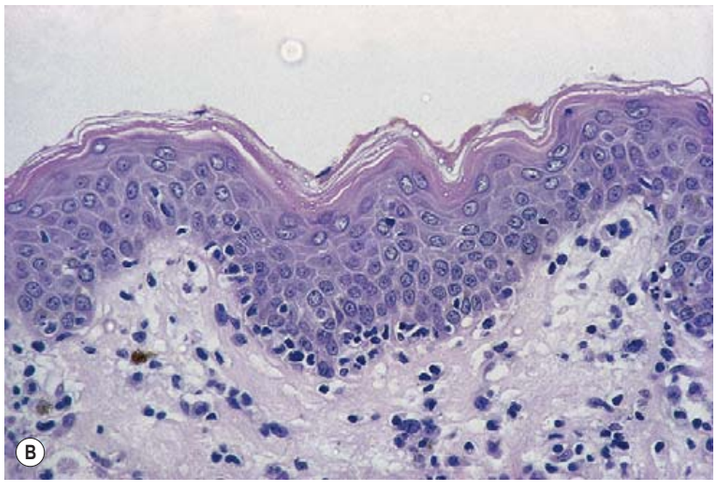
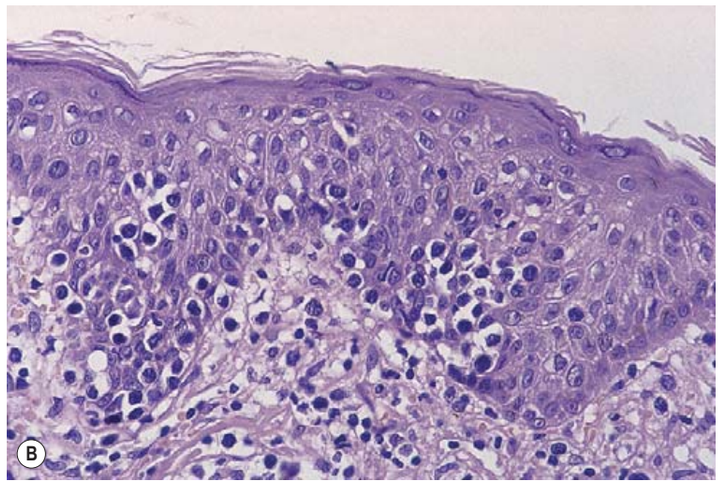


Fig. 120.2 Mycosis fungoides, limited patch/plaque stage disease (stage 1A). A Patches on the buttocks involving less than 10% of the skin surface. **B** Atypical lymphocytes in a typical linear configuration along the epidermal basal layer.

Fig. 120.3 Mycosis fungoides (stage 1B). Generalized hypopigmented lesions as well as pink-colored plaques.

Fig. 120.4 Mycosis fungoides, generalized patch/plaque stage disease (stage 1B). A Extensive patches and plaques involving more than 10% of the skin surface. **B** Pronounced epidermotropism with the formation of small nests of atypical cells (Pautrier's microabscesses).



Immunophenotype

The neoplastic cells in MF have a mature $CD3^{+}$, $CD4^{+}$, $CD45RO^{+}$, $CD8^{-}$ memory T-cell phenotype. In rare cases of otherwise classic MF, a $CD3^{+}$, $CD4^{-}$, $CD8^{+}$ mature T-cell phenotype may be seen. Immunophenotyping may demonstrate an aberrant phenotype in plaque or tumor stage MF, but rarely in early patch lesions, and is therefore of little help in early diagnosis.

Differential diagnosis

Regarding the differential diagnosis of MF, three categories should be considered. The first category contains a diverse group of benign dermatoses, which early MF may resemble clinically, and it includes several types of eczema, psoriasis, superficial fungal infections and drug reactions. These specific diagnoses can generally be excluded by histologic and other standard dermatological examinations. This category may also include patients with *large plaque parapsoriasis* (parapsoriasis en plaque) who show slightly scaly, sometimes atrophic, erythematous patches or plaques, which are commonly located on the trunk and buttocks (see Ch. 9). Whereas large plaque parapsoriasis cannot be distinguished clinically from early patch or plaque stage MF, the histologic features are often not consistent with MF. Long-term follow-up studies have documented progression of large plaque parapsoriasis to overt MF in approximately 10% of cases. One prevailing opinion is that large plaque parapsoriasis should be considered a form of MF, rather than a potential precursor of MF, but the author feels there is no consensus. There is even less consensus about whether small plaque parapsoriasis represents MF.

A second category includes several benign conditions with histologic features highly suggestive of MF. Examples of these are lymphomatoid

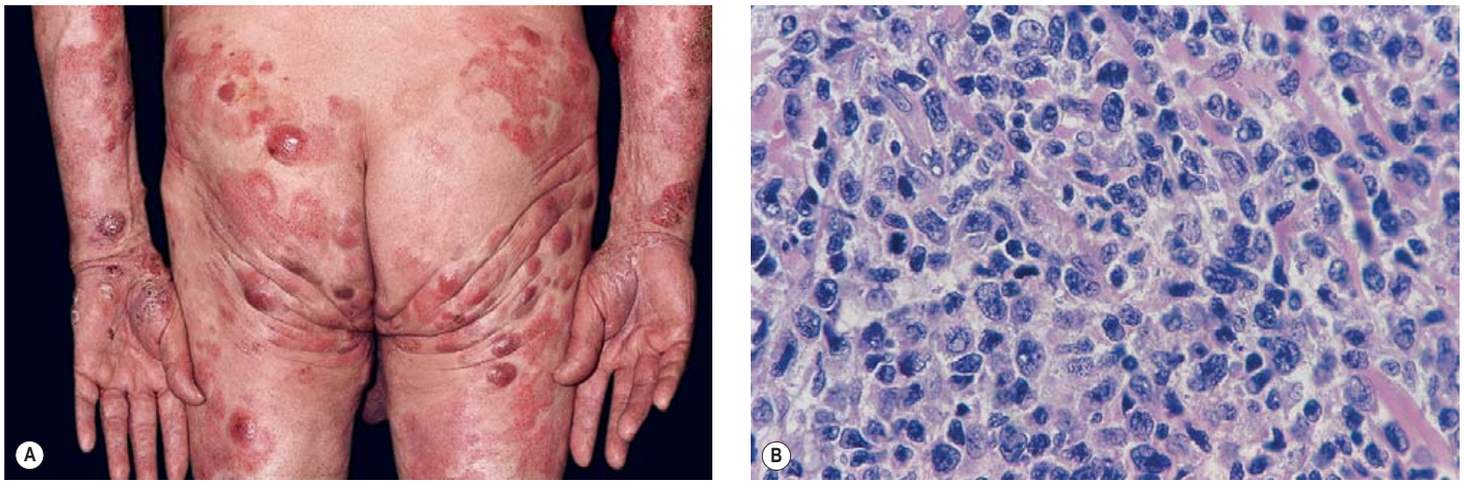


Fig. 120.5 Mycosis fungoides, tumor stage. A Multiple skin tumors in combination with typical patches and plaques. **B** Diffuse dermal infiltrates of medium-sized to large neoplastic T cells.

contact dermatitis, lymphomatoid drug reactions, and actinic reticuloid. Apart from subtle histologic differences (e.g. the predominance of atypical T cells in the dermal infiltrates rather than in the epidermis), careful evaluation of the clinical features, which are generally not consistent with MF, often results in a correct diagnosis[7].

The third category includes other types of (epidermotropic) CTCL, which may resemble MF histologically. Diagnostic features of these entities are presented in Table 120.2.

Staging systems and staging procedures

Staging patients with MF and SS is important, since it determines management and treatment and has prognostic significance. Recently, a revised clinical staging system for MF and SS was proposed, which is based on the TNM (tumor–node–metastasis) classification system and takes into account the type and extent of skin lesions (T1–4) as well as the presence or absence of nodal (N0–3), visceral (M0–1) and peripheral blood involvement (B0–2) (Tables 120.3 & 120.4)[11].

Evaluation of patients suspected of having MF should include a thorough physical examination with special attention to the type and extent of skin lesions and the presence of palpable lymph nodes, as well as skin biopsies, complete blood counts and serum chemistries. Enlarged lymph nodes should be biopsied. Histologically, distinction can be made between lymph nodes showing dermatopathic lymphadenopathy without involvement by MF (N1), dermatopathic lymphadenopathy with early MF involvement (N2), and lymph nodes showing effacement of the normal lymph node architecture by neoplastic T cells (N3). The prognostic significance of such a subdivision has been well established.

No further examinations are recommended for patients with stage IA–B disease. CT scans of the chest and abdomen are recommended in patients in whom extracutaneous disease is suspected, but they are less useful in patients with limited patches and/or plaques without lymphadenopathy. Examination of other organs, including the bone marrow, should only be performed if clinically indicated.

Treatment

The choice of an initial treatment in MF depends on the stage of the disease and the general condition and age of the patient[28,29]. Given the chronic and recurrent nature of MF, treatment should be aimed at improving symptoms while limiting toxicity. Following the traditional "stage-based" approach, skin-directed therapies are preferred in the early stages of MF (stages IA–IIA) and even in patients with limited tumor stage MF (IIB) (Table 120.5). These skin-directed therapies include topical or intralesional corticosteroids, topical cytotoxic agents (e.g. nitrogen mustard [mechlorethamine]), phototherapy and radiotherapy. The efficacy of skin-directed therapies in MF is explained by the preferential localization of the neoplastic skin-homing T cells to the epidermis and superficial dermis. Systemic multi-agent chemotherapy is not useful in these early stages, since it does not improve survival and is associated with considerable morbidity[30]. In patients with refractory or progressive skin disease, skin-directed therapies can be combined with IFN-α or systemic retinoids. Alternatively, novel agents such as denileukin diftitox or *h*istone *deac*etylase *i*nhibitors (HDACi) can be used, before systemic chemotherapy is considered. In general, systemic chemotherapy is only indicated in advanced stages when there is nodal or visceral involvement or in patients with rapidly progressive tumors unresponsive to less aggressive therapies.

Skin-directed therapies

Topical corticosteroids

In many MF patients with only patches and thin plaques, application of topical corticosteroids is effective in controlling disease activity. In patients with limited patch/plaque stage disease (mainly patches), complete remissions in up to 60% of patients have been reported[31]. In the more advanced stages, they continue to be an important adjuvant therapy.

Topical chemotherapy

Topical application of the chemotherapeutic agents mechlorethamine (nitrogen mustard) and carmustine (bis-chloronitrosourea [BCNU]) has proven to be an effective treatment for early stage MF. Nitrogen mustard, either dissolved in water or compounded in an ointment-based preparation, results in complete remissions in approximately 60–80% of patients with stage IA-B[32]. Most patients with early MF remain clear on maintenance therapy. Side effects include skin irritation, allergic contact dermatitis and an increased risk for the development of skin cancer related to long-term use. The complete remission rate with BCNU is similar to that of nitrogen mustard[33]; side effects include telangiectasias and myelosuppression, which requires careful monitoring of the complete blood count.

Radiotherapy

Total skin electron beam irradiation (TSEB) with an energy of 4–6 MeV is a highly effective treatment in patients with skin-limited MF (see Ch. 139)[29–34]. The total dose is generally 36 Gy administered in fractions of 1.5–2 Gy over an 8–10-week period. TSEB is most effective in patients with stage IA–B disease, with complete response rates of more than 80%. However, in most centers, such patients are treated with PUVA or topical chemotherapy. TSEB is particularly useful in patients with tumor stage MF, where complete response rates of approximately 40% have been reported. Side effects are generally mild and include erythema, scaling, and temporary loss of hair, nails and sweat gland function.

Local radiotherapy with X-ray or preferably electron beam may be considered for single tumors in patients with plaque stage disease, either in combination with other modalities (e.g. PUVA) as an alternative for TSEB, or for new tumors following TSEB. A dose of 10–20 Gy suffices. In patients with unilesional MF, local radiotherapy may be curative.

TNMB CLASSIFICATION OF MYCOSIS FUNGOIDES AND SÉZARY SYNDROME	
T (SKIN)	
T_1	Limited patch/plaque (involving <10% of total skin surface)
T_2	Generalized patch/plaque (involving ≥10% of total skin surface)
T_3	Tumor(s)
T_4	Erythroderma
N (LYMPH NODE)	
N_0	No enlarged lymph nodes
N_1	Enlarged lymph nodes, histologically uninvolved
N_2	Enlarged lymph nodes, histologically involved (nodal architecture uneffaced)
N_3	Enlarged lymph nodes, histologically involved (nodal architecture [partially] effaced)
M (VISCERA)	
M_0	No visceral involvement
M_1	Visceral involvement
B (BLOOD)	
B_0	No circulating atypical (Sézary) cells (or <5% of lymphocytes)
B_1	Low blood tumor burden (≥5% of lymphocytes are Sézary cells, but not B_2)
B_2	High blood tumor burden (≥1000/μl Sézary cells + positive clone)

Table 120.3 TNMB classification of mycosis fungoides and Sézary syndrome.

CLINICAL STAGING SYSTEM FOR MYCOSIS FUNGOIDES AND SÉZARY SYNDROME				
CLINICAL STAGE				
IA	T_1	N_0	M_0	$B_{0–1}$
IB	T_2	N_0	M_0	$B_{0–1}$
IIA	$T_{1–2}$	$N_{1–2}$	M_0	$B_{0–1}$
IIB	T_3	$N_{0–1}$	M_0	$B_{0–1}$
III	T_4	$N_{0–2}$	M_0	$B_{0–1}$
IVA_1	$T_{1–4}$	$N_{0–2}$	M_0	B_2
IVA_2	$T_{1–4}$	N_3	M_0	$B_{0–2}$
IVB	$T_{1–4}$	$N_{0–3}$	M_1	$B_{0–2}$

Table 120.4 Clinical staging system for mycosis fungoides and Sézary syndrome.

TREATMENT OF MYCOSIS FUNGOIDES
PREMYCOTIC PHASE
• Topical or intralesional corticosteroids; UVB • If former not effective, PUVA
STAGE IA–IIA (PATCHES/PLAQUES)
• PUVA; HN2; topical BCNU • UVB (if only patches) • Topical corticosteroids or topical bexarotene (if only limited patches/thin plaques as second-line therapy) • RT (if single lesion) • TSEB (if generalized thick plaques)
STAGE IIB (SKIN TUMORS)
• PUVA or HN2 + RT (if only a few tumors) • TSEB (followed by skin-directed therapies) • Relapse: PUVA + IFN-α; PUVA + retinoids (acitretin; oral bexarotene*); second-line therapy: denileukin diftitox*; HDACi* • Add RT (if persistent tumors); consider second course of TSEB (10–20 Gy)
STAGE III (ERYTHRODERMA)
• ECP; if not effective, add IFN-α • Low-dose chlorambucil and prednisone; low-dose methotrexate • Add skin-directed therapies (PUVA; HN2; RT), if necessary • Second-line therapy: oral bexarotene*; denileukin diftitox*; HDACi*
STAGE IV (NODAL, VISCERAL INVOLVEMENT)
• Multi-agent chemotherapy (e.g. CHOP) • Biological response modifiers (denileukin diftitox; IFN-α; oral retinoids) • Add skin-directed therapies (PUVA; HN2), if necessary • Allogeneic hematopoietic stem cell transplantation (in selected cases)
*Efficacy compared to traditional treatments yet to be determined.

Table 120.5 Treatment of mycosis fungoides. BCNU, topical bis-chloronitrosourea (carmustine); CHOP, cyclophosphamide, hydroxydaunomycin (doxorubicin), Oncovin® (vincristine) and prednisone; ECP, extracorporeal photopheresis; HDACi, histone deacetylase inhibitors; HN2, topical nitrogen mustard (mechlorethamine); IFN, interferon; RT, local radiotherapy; TSEB, total skin electron beam.

Phototherapy

Several types of phototherapy can be used in the treatment of MF (Ch. 134). These include UVA irradiation following photosensitization with 8-methoxypsoralen (PUVA therapy), broadband and narrowband UVB therapy, and, more recently, UVA1 therapy. Extracorporeal photopheresis (ECP) may be effective in patients with erythrodermic MF (see the section on Sézary syndrome).

PUVA treatment has become a standard therapy for the early stages of MF[35]. In patients with stages IA–IIA, complete response rates of 80–90% have been reported. In many centers, maintenance PUVA therapy (every 2 to 4 weeks) is given to prolong remission. Although sustained complete remissions have been reported, most patients will relapse after cessation of PUVA therapy or during maintenance treatment. Recurrent or persistent lesions particularly favor UV-shielded areas, such as the inner thighs and the gluteal cleft. In tumor stage MF, PUVA therapy alone is unlikely to result in complete responses, but favorable results may be achieved when combined with IFN-α, systemic retinoids or radiotherapy.

In patients with only patches, broadband UVB therapy (300–320 nm) has been reported as a safe and effective alternative, with complete response rates of up to 75%[36]. Recent studies reported favorable results with narrowband UVB (311 nm) and UVA1 therapy in the early stages of MF, but it remains to be determined how these new therapies compare to the established forms of phototherapy.

Systemic therapies (other than chemotherapy)

Most agents within this category are biological response modifiers aimed at potentiating the host's immune response to the neoplastic T cells. They include cytokines (e.g. IFN-α, IL-12), retinoids, immunotoxins (e.g. denileukin diftitox), and monoclonal antibodies such as zanolimumab (anti-CD4) and alemtuzumab (anti-CD52). Current evidence suggests that biological response modifiers are most effective when combined with (or preceded by) traditional therapies aimed at tumor cell eradication. HDACi represent a new class of drugs being employed for the treatment of MF and SS.

Interferons

The most commonly prescribed biological response modifier is interferon-alpha (IFN-α). In most centers, IFN-α is administered subcutaneously in doses of 3 to 9 million units three times a week. Side effects are generally mild and reversible, and they include flu-like symptoms, hair loss, nausea, depression and bone marrow suppression. The overall response rate of IFN-α, when used as a single agent, is approximately 50%, with 17% representing complete remissions[37]. The combination of PUVA and IFN-α appears to produce higher response rates than PUVA alone, and this combination may also be considered in patients with early tumor stage disease, when PUVA therapy alone is insufficient.

Retinoids

When used as a single agent, the overall and complete response rates of several first- and second-generation oral retinoids (isotretinoin, etretinate, acitretin) and a novel RXR-selective retinoid (bexarotene) are

roughly similar to those of IFN-α[29,38]. A combination of retinoids and PUVA (RePUVA) produces response rates similar to those of PUVA alone, although patients treated with RePUVA require fewer treatments and a significantly lower cumulative UVA dose. In many centers, bexarotene has replaced the earlier-generation retinoids, but comparative studies have never been performed. In patients with patches or thin plaques, topical bexarotene may be considered, but cost is an issue.

Denileukin diftitox

Denileukin diftitox is a fusion protein, in which diphtheria toxin is linked to IL-2. It binds to the high-affinity IL-2 receptor expressed by the neoplastic T cells in MF, and internalization of the toxin results in inhibition of protein synthesis and cell death. Overall and complete clinical response rates are approximately 30% and 10%, respectively[28,29,39]. Denileukin diftitox can have substantial side effects, including capillary leak syndrome, fever, and fluid retention.

Histone deacetylase inhibitors

HDACi, such as vorinostat and depsipeptide, represent a novel class of drugs used in cancer therapy. Inhibition of the enzyme HDAC affects the expression of many genes (and their protein products) that are involved in cellular proliferation, differentiation, migration and apoptosis. Recent studies of both vorinostat and depsipeptide report overall response rates of approximately 35% in patients with MF and SS, but complete responses are rare[29,40]. The most common side effects are fatigue, gastrointestinal symptoms and reversible thrombocytopenia. It remains to be determined which patients are most likely to benefit from this therapy.

Systemic chemotherapy

Systemic multi-agent chemotherapy should only be used in patients with unequivocal lymph node or visceral involvement, or in patients with progressive skin tumors that have failed to respond to other therapies[28,29]. In many centers, the standard treatment in such cases is the administration of six cycles of CHOP (*c*yclophosphamide, *h*ydroxydaunomycin [doxorubicin], *O*ncovin® [vincristine] and *p*rednisone). With this and other combination regimens, high response rates can be achieved for extracutaneous involvement, but the responses are generally short-lived. Moreover, concurrent patches and plaques are often less responsive, and may require additional treatment with PUVA or nitrogen mustard. Recent studies utilizing pentostatin, gemcitabine and liposomal doxorubicin have demonstrated high overall response rates in patients with advanced MF, but controlled studies are still lacking.

In young patients with refractory and/or progressive MF and SS, an allogeneic hematopoietic stem cell transplantation may be considered. Durable responses have been reported, but experience is still limited and the optimal conditioning regimen and optimal timing for the transplant are currently unknown. Results with autologous hematopoietic stem cell transplantation in MF and SS have been disappointing[41], suggesting the need for a graft-versus-tumor response.

Prognosis

The prognosis of patients with MF is dependent on the stage, and in particular the type and extent of skin lesions and the presence of extracutaneous disease[24,25]. Patients with limited patch/plaque stage MF have a similar long-term life expectancy as an age-, sex-, and race-matched control population. In a study of 309 Dutch MF patients, the disease-related 10-year survival for those with limited patch/plaque disease, generalized patch/plaque disease, and tumor stage disease (without concurrent lymph node involvement) was 97%, 83% and 42%, respectively, but it was only 20% for patients with histologically documented lymph node involvement[25]. An aggressive clinical course is seen in patients with effaced lymph nodes, visceral involvement, and large cell transformation. Patients usually die of systemic involvement or infections.

VARIANTS OF MYCOSIS FUNGOIDES

Apart from the classical Alibert–Bazin type of MF, many clinical and/or histologic variants have been reported. Clinical variants, such as bullous and hyper- or hypopigmented MF, have clinical behavior similar to that of classic MF, and they are therefore not considered separately. In contrast, folliculotropic MF, pagetoid reticulosis, and granulomatous slack skin have distinctive clinicopathologic features, and therefore they have been included as distinct variants or subtypes of MF in the WHO-EORTC classification scheme.

Folliculotropic MF

Synonyms: ■ MF-associated follicular mucinosis ■ Folliculocentric or pilotropic MF

Definition

Folliculotropic MF is a distinct variant of MF characterized by the presence of folliculotropic infiltrates, often with sparing of the epidermis and preferential involvement of the head and neck region. Most cases show mucinous degeneration of the hair follicles (follicular mucinosis; Ch. 46) and are traditionally designated as MF-associated follicular mucinosis. Similar cases, but without follicular mucinosis, have been reported as folliculocentric or pilotropic MF. From a biologic point of view, the most relevant feature (irrespective of the presence or absence of follicular mucinosis) is the deep, follicular and perifollicular localization of the neoplastic infiltrates, which makes them less accessible to skin-directed therapies. For both groups, the term folliculotropic MF is therefore preferred[3].

Epidemiology

This variant is found in approximately 10% of MF patients[25]. It occurs mostly in adults, but may occasionally affect children and adolescents. Men are affected more often than women.

Clinical features

Patients may present with (grouped) follicular papules, acneiform lesions, indurated plaques and sometimes tumors, which preferentially involve and are most pronounced in the head and neck area. The skin lesions are often associated with alopecia, and sometimes with mucinorrhea. Infiltrated plaques in the eyebrow region with concurrent alopecia are a common and highly characteristic finding (Fig. 120.6A). Pruritus is often more severe than in classic MF and may represent a reliable parameter of disease activity. Secondary bacterial infections are frequently observed.

It should be stressed that the clinical staging systems for MF are not very helpful in patients with folliculotropic MF. Because of the perifollicular localization of the neoplastic infiltrates, patients presenting with one or a few plaques on the face do not have stage IA disease, but should always be considered as having tumor stage disease. Consistently, the survival of patients with folliculotropic MF is similar to that of classic tumor stage MF[42,43].

Pathology

Characteristic findings include primarily perivascular and periadnexal localization of the dermal infiltrates, with variable infiltration of the follicular epithelium by small, medium-sized or sometimes large T cells with hyperchromatic and cerebriform nuclei, and sparing of the epidermis (folliculotropism instead of epidermotropism) (Fig. 120.6B). Most cases show mucinous degeneration of the follicular epithelium (follicular mucinosis), as assessed with Alcian blue or colloidal iron staining. There is often a considerable admixture with eosinophils and sometimes plasma cells. In the perifollicular infiltrates, the neoplastic T cells may be blast cells rather than cerebriform cells, and therefore may be easily mistaken for histiocytes. In most cases, the neoplastic T cells have a $CD3^+$, $CD4^+$, $CD8^-$ phenotype as in classic MF. Admixture with CD30-positive blast cells is common.

Differential diagnosis

The distinctive clinical and histologic features should facilitate an early and correct diagnosis. However, because of the preferential involvement of the head and neck area, the absence of patches and plaques on the trunk and buttocks, and particularly because of the absence of epidermotropic atypical T cells, the diagnosis of MF or CTCL is often not considered and is misinterpreted as seborrheic dermatitis or atopic dermatitis. Clinicopathologic correlation is also required to

Fig. 120.6 Folliculotropic mycosis fungoides. **A** Infiltrated plaques on the forehead and eyebrow with concurrent hair loss. **B** Characteristic perifollicular infiltrates with extensive follicular mucinosis (asterisks). Note absence of epidermotropism.

differentiate folliculotropic MF from other types of CTCL[42]. The relationship between folliculotropic MF and the so-called benign or idiopathic form of follicular mucinosis (alopecia mucinosa) resembles the relationship between classic MF and "parapsoriasis". In the case of persistent lesions of the idiopathic form, patients should be monitored regularly, since progression into overt folliculotropic MF has been frequently reported.

Treatment

Because of the perifollicular localization of the dermal infiltrates, folliculotropic MF is often less responsive to skin-directed therapies, such as PUVA and topical nitrogen mustard, than is classic plaque stage MF. In the case of unresponsive disease, a combination of PUVA with either IFN-α or retinoids, local radiotherapy or TSEB can be used, although sustained complete remissions are rarely achieved[42,43].

Pagetoid Reticulosis

Synonyms: ■ Woringer–Kolopp disease ■ Unilesional MF

Definition

This is a rare variant of MF, characterized by the presence of localized patches or plaques with an intraepidermal proliferation of neoplastic T cells. The term pagetoid reticulosis should only be used for the localized type (Woringer–Kolopp type) and not for the disseminated type (Ketron–Goodman type). Nowadays, patients with generalized disease would most likely be classified as primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma, primary cutaneous gamma/delta T-cell lymphoma, or tumor stage MF[3].

Epidemiology

Pagetoid reticulosis is extremely rare, and it accounts for fewer than 1% of CTCL cases. It mostly affects adults.

Clinical features

Patients present with a solitary psoriasiform or hyperkeratotic patch or plaque, which is usually localized on an extremity and slowly progressive (Fig. 120.7A). In contrast to classic MF, extracutaneous dissemination or disease-related deaths have never been reported.

Pathology

The typical histologic picture consists of a hyperplastic epidermis with marked infiltration by large atypical pagetoid cells, arranged singly or in nests or clusters (Fig. 120.7B). The atypical cells have medium-sized or large, sometimes hyperchromatic and cerebriform nuclei and abundant, vacuolated cytoplasm. The superficial dermis may have an infiltrate of mostly small lymphocytes, but rarely contains neoplastic T cells.

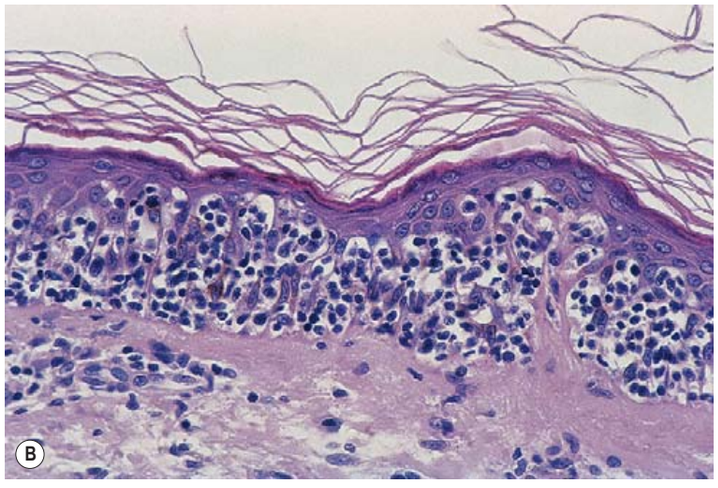


Fig. 120.7 Pagetoid reticulosis. **A** Solitary plaque on the left upper leg. **B** Purely intraepidermal proliferation of atypical T cells.

Immunophenotype

The neoplastic T cells may show either a $CD3^+$, $CD4^+$, $CD8^-$ or a $CD3^+$, $CD4^-$, $CD8^+$ phenotype. CD30 is often expressed[44].

Differential diagnosis

Pagetoid reticulosis should be differentiated from other types of epidermotropic CTCL, such as MF, LyP type B, and primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma (see Table 120.2). Useful criteria for pagetoid reticulosis include the characteristic clinical presentation and the often strictly epidermal localization of the neoplastic T cells.

Treatment

The preferred mode of treatment is radiotherapy or surgical excision.

Granulomatous Slack Skin

Definition

This is an extraordinarily rare type of CTCL, characterized by the slow development of folds of lax skin and a granulomatous infiltrate with clonal T cells[45].

Epidemiology

This is an extremely rare type of CTCL, with approximately 60 cases reported. It typically affects adolescents and adults, and mostly occurs in men.

Clinical features

This condition is characterized by circumscribed areas of pendulous lax skin with a predilection for the axillae and groin (Fig. 120.8A). In approximately one-third of the reported patients, an association with Hodgkin lymphoma was observed. Most patients have an indolent clinical course.

Pathology

Fully developed lesions show dense granulomatous dermal infiltrates containing atypical T cells with cerebriform nuclei, macrophages and often many multinucleated giant cells, as well as destruction of elastic tissue and elastophagocytosis by the multinucleated cells (Fig. 120.8B). The epidermis may be infiltrated by small atypical T cells with cerebriform nuclei, as in classic MF. The atypical T cells have a $CD3^+$, $CD4^+$, $CD8^-$ phenotype. A recent study noted overlapping histologic features between granulomatous slack skin and granulomatous MF[46].

Treatment

Radiotherapy may be effective, but experience is still limited. Rapid recurrences after surgical excision have been reported.

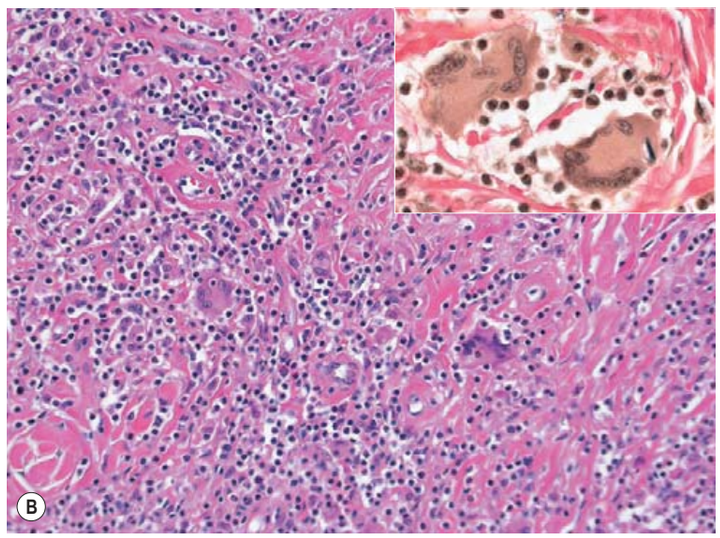


Fig. 120.8 Granulomatous slack skin. A Pendulous fold of atrophic lax skin in the right inguinal area. **B** Multinucleated giant cells with intracellular leukocytes (emperipolesis), surrounded by a dense leukocytic infiltrate. Inset: Elastic tissue stain showing a multinucleated giant cell containing an elastic fiber (elastophagocytosis).

SÉZARY SYNDROME

Definition

Sézary syndrome (SS) is defined historically by the triad of erythroderma, generalized lymphadenopathy, and the presence of neoplastic T cells (Sézary cells) in the skin, lymph nodes and peripheral blood (Fig. 120.9). Criteria recommended for the diagnosis of SS include demonstration of a T-cell clone in the peripheral blood by molecular or cytogenetic methods, demonstration of immunophenotypical abnormalities (an expanded $CD4^+$ T-cell population resulting in a CD4/CD8 ratio greater than 10 and/or aberrant expression of pan-T-cell antigens), and an absolute Sézary cell count of least 1000 cells per µl[47]. In the WHO-EORTC classification, demonstration of a T-cell clone (preferably the same T-cell clone in skin and peripheral blood) in combination with one of the aforementioned cytomorphologic or immunophenotypical criteria are suggested as minimal criteria for the diagnosis of SS, so as to exclude patients with a benign inflammatory condition simulating SS.

Epidemiology

SS is a rare disease accounting for less than 5% of all CTCL (see Table 120.1). It occurs exclusively in adults.

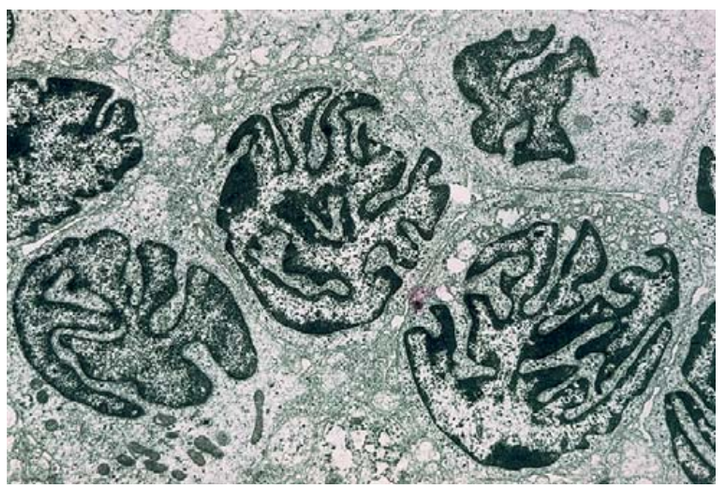


Fig. 120.9 Sézary syndrome. Electron photomicrograph of a skin biopsy showing characteristic Sézary cells.

Fig. 120.10 Sézary syndrome. Erythroderma with diffuse scaling.

Clinical features

SS is characterized by erythroderma, which may be associated with marked exfoliation, edema and lichenification; it is intensely pruritic (Fig. 120.10). Lymphadenopathy, alopecia, onychodystrophy and palmoplantar hyperkeratosis are common findings. The overt clinical picture may be preceded by a non-diagnostic dermatitis. The prognosis is generally poor, with an overall 5-year survival of approximately 25%. Most patients die of opportunistic infections due to immunosuppression.

Pathology

The histologic features in SS may be similar to those in MF. However, the cellular infiltrates in SS are more often monotonous, and epidermotropism may sometimes be absent. In up to one-third of skin biopsies from patients with otherwise classic SS, the histologic findings may be nonspecific[48]. Involved lymph nodes characteristically show a dense, monotonous infiltrate of Sézary cells with effacement of the normal lymph node architecture. The bone marrow may be involved, but the infiltrates are often sparse and mainly interstitial. The neoplastic T cells have a $CD3^+$, $CD4^+$, $CD8^-$ phenotype and characteristically lack CD7 and CD26 expression[48].

Pathogenesis

The pathogenesis of SS is unknown. Conclusive evidence of an etiological role for HTLV-1 is lacking. Recurrent chromosomal translocations have not been detected in SS, but complex karyotypes are common. Several studies have identified a consistent pattern of identical chromosomal abnormalities in SS, with deletions involving chromosomes 10q and 17p and gains involving chromosomes 8q, 10p and 17q being the most common findings[49–51]. While SS is often designated as a leukemic phase or variant of MF, recent studies have revealed major genomic and phenotypical differences between these two conditions, suggesting that SS and MF should be considered as separate lymphomas arising from distinct functional T-cell subsets[51a,51b].

Differential diagnosis

Differentiation between SS and non-neoplastic forms of erythroderma may be extremely difficult. The differential diagnosis includes erythroderma secondary to psoriasis, atopic dermatitis or other forms of dermatitis, pityriasis rubra pilaris and drug reactions as well as idiopathic erythroderma (see Ch. 10). Demonstration of clonal T cells in the peripheral blood is considered an important diagnostic criterion favoring SS. Demonstration of a predominant $CD3^+$, $CD4^-$, $CD8^+$ T-cell population in the skin and peripheral blood is highly suggestive of actinic reticuloid (see Ch. 87)[52].

Treatment

Being a systemic disease (leukemia) by definition, systemic treatment is required. Skin-directed therapies like PUVA or potent topical corticosteroids may be used as adjuvant therapy. Extracorporeal photopheresis (ECP), either alone or in combination with other treatment modalities, has been suggested as the treatment of choice in SS and erythrodermic MF, with overall response rates of 30–80%, and complete response rates of 14–25%[53,54]. This great variation in response rates may reflect differences in patient selection and/or concurrent therapies. The suggested superiority of ECP over traditional low-dose chemotherapy regimens has not yet been substantiated by randomized controlled trials[54]. Beneficial effects have also been reported with IFN-α (either alone or in combination with PUVA therapy), prolonged treatment with low-dose chlorambucil plus prednisone, or methotrexate, but complete responses are uncommon. CHOP or CHOP-like regimens may produce higher response rates, but these responses are generally short-lived. Recent studies have observed possible benefits with bexarotene, denileukin diftitox, HDACi and alemtuzumab (anti-CD52), but the long-term effects of these therapies remain to be established[28,29].

ADULT T-CELL LEUKEMIA/LYMPHOMA

Definition

Adult T-cell leukemia/lymphoma (ATLL) is a type of T-cell neoplasm etiologically associated with HTLV-1. Skin lesions are generally a manifestation of widely disseminated disease. However, a slowly progressive form that sometimes has only skin lesions has been described (smoldering variant)[55].

Epidemiology

ATLL is endemic in areas with a high prevalence of HTLV-1 in the population, such as southwestern Japan, the Caribbean Islands and parts of Central Africa. In addition, a high prevalence is seen in Jewish individuals whose ancestors were from Mashad, Iran. However, only a minor proportion of seropositive patients eventually develops ATLL. The disease occurs in adults, and men are affected more frequently than women. Vertical transmission is more common than horizontal transmission.

Clinical features

Most patients present with acute ATLL characterized by the presence of leukemia, lymphadenopathy, organomegaly, hypercalcemia and frequently skin lesions; it has a poor prognosis. Chronic and smoldering variants often present with patches, plaques and papular skin lesions, which may closely resemble MF, and circulating neoplastic T cells are few or absent. Such cases have a more protracted clinical course, but progression to a high-grade malignant disseminated form of the disease may occur.

Pathology

Skin lesions demonstrate a superficial or more diffuse infiltration of small, medium-sized or large pleomorphic T cells, which often display marked epidermotropism. The histologic picture may be indistinguishable from MF. Skin lesions in the smoldering type may have sparse dermal infiltrates with only slightly atypical cells. The neoplastic T cells express a $CD3^+$, $CD4^+$, $CD8^-$, $CD25^+$ phenotype.

Differential diagnosis

Differentiation between chronic or smoldering variants of ATLL and MF may be extremely difficult, particularly in endemic areas. In such cases, a definite diagnosis of ATLL requires demonstration of clonally integrated HTLV-1.

Treatment

ATLL may be treated with a combination of zidovudine and IFN-α, but in most cases, systemic chemotherapy is required[56]. In chronic and smoldering cases mainly affecting the skin, skin-directed therapies as in MF are preferred.

PRIMARY CUTANEOUS CD30-POSITIVE LYMPHOPROLIFERATIVE DISORDERS

Primary cutaneous CD30-positive lymphoproliferative disorders represent the second most common group of CTCL, accounting for approximately 25% of CTCL (see Table 120.1). This group includes primary cutaneous anaplastic large cell lymphoma (C-ALCL), lymphomatoid papulosis (LyP), and borderline cases. C-ALCL and LyP have overlapping clinical, histologic and immunophenotypical features and form a spectrum of disease. Thus, histologic criteria alone are often insufficient to distinguish between the two ends of the spectrum. In the end, the clinical appearance and course are used as decisive criteria for the definite diagnosis and choice of treatment. The term "borderline case" refers to patients in whom, despite careful clinicopathologic correlation, a definite distinction between C-ALCL and LyP cannot be made. Longitudinal clinical evaluation will generally disclose whether the patient has C-ALCL or LyP[57]. Cases previously designated as *regressing atypical histiocytosis*, as well as rare cases of primary cutaneous Hodgkin lymphoma with an indolent clinical course, also belong to this spectrum[57].

Primary cutaneous CD30-positive lymphoproliferative disorders should be differentiated from: (1) skin involvement by systemic ALCL; (2) CD30-positive transformed MF; (3) other well-defined types of CTCL, which may sometimes express the CD30 antigen; and (4) reactive skin conditions with infiltrates containing CD30-positive blast cells, including various viral infections, arthropod bite reactions, scabies and atopic dermatitis[58] (see Table 120.2). Guidelines for the diagnosis and treatment of primary cutaneous CD30-positive lymphoproliferations are provided in Figure 120.11.

Primary Cutaneous Anaplastic Large Cell Lymphoma

Definition

Primary cutaneous anaplastic large cell lymphoma (C-ALCL) is composed of large cells with an anaplastic, pleomorphic or immunoblastic cytomorphology and expression of the CD30 antigen by the majority (greater than 75%) of tumor cells. Patients should not have clinical evidence or a history of MF. In such individuals, a diagnosis of tumor stage MF with blastic transformation is more likely.

Epidemiology

These lymphomas account for approximately 12% of all CTCLs (see Table 120.1). They predominantly affect adults and are rare in children or adolescents. The male-to-female ratio is approximately 2:1.

Clinical features

Most patients present with solitary or localized nodules or tumors (sometimes papules) that often develop ulceration (Fig. 120.12A). Multifocal lesions are seen in about 20% of the patients. The skin lesions may show partial or complete spontaneous regression, as in LyP. These lymphomas frequently relapse in the skin. Extracutaneous dissemination occurs in approximately 10% of the patients, and it mainly

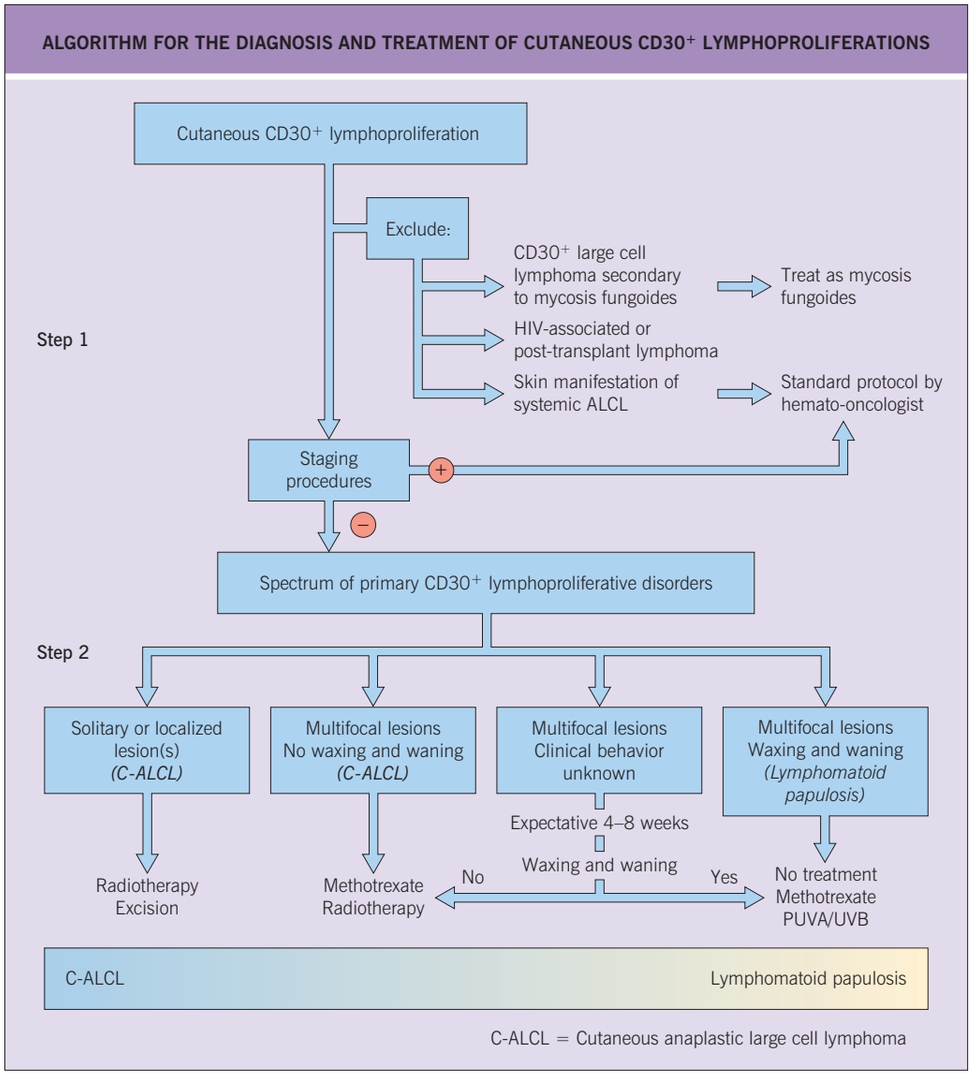


Fig. 120.11 Algorithm for the diagnosis and treatment of primary cutaneous CD30-positive lymphoproliferations. Cases previously designated as regressing atypical histiocytosis, as well as rare cases of primary cutaneous Hodgkin lymphoma with an indolent clinical course, also belong to this spectrum. From ref. 57.

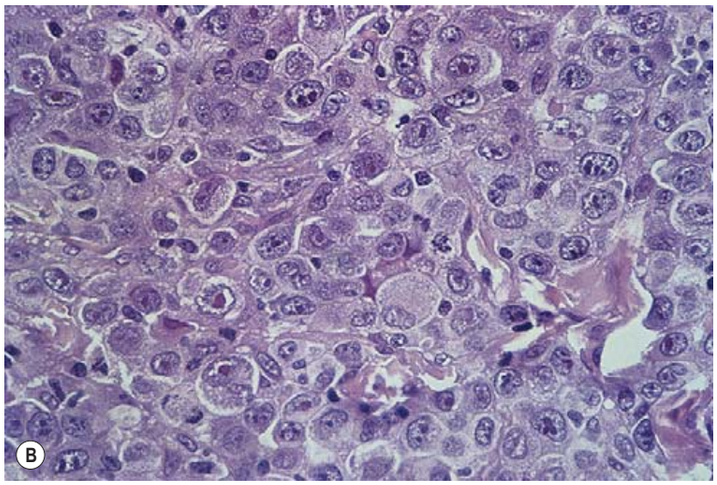


Fig. 120.12 Primary cutaneous anaplastic large cell lymphoma. **A** Characteristic clinical presentation with a solitary ulcerating tumor. **B** Detail of dermal infiltrate showing cohesive clusters of large (CD30-positive) anaplastic cells with pronounced eosinophilic nucleoli and abundant cytoplasm.

involves the regional lymph nodes. The prognosis is usually favorable, with a 10-year disease-related survival exceeding 85%[57,59].

Pathology

Histologically, these lymphomas show diffuse non-epidermotropic infiltrates with cohesive sheets of large CD30-positive tumor cells (Fig. 120.12B). In most cases, the tumor cells have the characteristic morphology of anaplastic cells, with round, oval or irregularly shaped nuclei, prominent (eosinophilic) nucleoli and abundant cytoplasm. Less commonly (20–25%), tumor cells have a pleomorphic, immunoblastic or Reed–Sternberg cell-like appearance. The mitotic index is generally high. Reactive lymphocytes are often present at the periphery of the tumor. Ulcerating lesions may show an LyP-like histology with an abundant inflammatory infiltrate of reactive T cells, histiocytes, eosinophils, neutrophils, and relatively few CD30-positive cells. In such cases, epidermal hyperplasia may be prominent.

Immunophenotype

The neoplastic cells often express a $CD4^+$ T-cell phenotype with variable loss of CD2, CD5 and/or CD3. Some cases (<5%) have a $CD8^+$ T-cell phenotype. CD30 must be expressed by the majority of neoplastic cells. Expression of cytotoxic proteins (granzyme B, TIA-1, perforin) is noted in approximately 70% of cases, while MUM1/IRF4 (multiple myeloma oncogene 1/interferon regulatory factor 4) is expressed in almost all cases[60]. Unlike systemic ALCL, most C-ALCLs express CLA (cutaneous lymphocyte antigen), but do not express EMA (epithelial membrane antigen) and ALK (anaplastic lymphoma kinase); the latter is indicative of the t(2;5) chromosomal translocation[61]. Coexpression of CD56 is observed in rare cases, but does not appear to be associated with an unfavorable prognosis[62].

Genetic features

The t(2;5) translocation, which is found predominantly in systemic ALCL in children, is rarely, if ever, found in C-ALCL[60]. Recent studies demonstrated a recurrent translocation of *IRF4* in a subset of C-ALCL[63,64].

Treatment

Radiotherapy is the initial choice of treatment in patients presenting with a solitary or a few localized nodules or tumors. However, if a solitary lesion has been excised completely or disappeared spontaneously, no further therapy is required. Patients presenting with multifocal skin lesions can best be treated with radiotherapy (if there are only a few lesions) or with low-dose methotrexate as in LyP[57,65]. Patients who present with or develop extracutaneous disease or those rare patients with rapidly progressive skin disease should be treated with doxorubicin-based multi-agent chemotherapy. Early systemic chemotherapy may also be considered in patients presenting with extensive skin lesions on one or both legs, since they often have an aggressive clinical course and the prognosis is unfavorable[66,67].

Lymphomatoid Papulosis

Definition

Lymphomatoid papulosis (LyP) is defined as a chronic, recurrent, self-healing papulonecrotic or papulonodular skin disease with histologic features suggestive of a (CD30-positive) malignant lymphoma. Since the introduction of the term LyP in 1968 by Macaulay[68], there has been continued discussion as to whether LyP is a malignant, premalignant or benign condition. Because of the overlapping clinical and histologic features between LyP and C-ALCL, including the presence of an aberrant T-cell phenotype, the presence of clonally rearranged TCR genes in 60–70% of the patients, and the presence of identical T-cell clones in LyP lesions and associated lymphoma lesions, LyP is best regarded as a low-grade variant of CTCL.

Pathogenesis

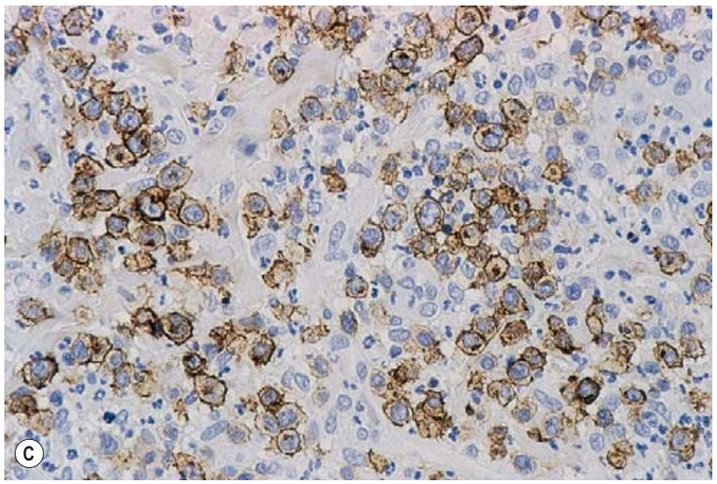
The initiating event in LyP is unknown. Several authors have suggested a viral etiology. However, studies searching for an etiologic role for HTLV-1, EBV and other herpes viruses, including herpes simplex virus types 1 and type 2 and human herpesvirus-6, have been consistently negative. The mechanisms involved in the spontaneous disappearance of skin lesions, or in the tumor progression observed in some patients with LyP, have not yet been identified. It has been suggested that interactions between CD30 and its ligand (CD30L) may contribute to apoptosis of the neoplastic T cells and the subsequent regression of the skin lesions, but the exact mechanism is as yet unknown[69]. Unresponsiveness to the growth inhibitory effect of transforming growth factor-β (TGF-β) due to a mutation in the gene that encodes the TGF-β type I receptor on the CD30-positive tumor cells has been suggested as one of the possible mechanisms in tumor progression[70].

Epidemiology

LyP accounts for approximately 15% of all CTCL (see Table 120.1). It may occur at any age. The youngest patient reported to date was 8 months old, and the oldest was 84 years of age. In large series, the average age of onset varies between 35 and 45 years. The male-to-female ratio is approximately 1.5:1.

Clinical features

The typical skin lesions in LyP are red–brown papules and nodules that may develop central hemorrhage, necrosis and crusting; they subsequently disappear spontaneously within 3 to 8 weeks. Characteristically, skin lesions in different stages of evolution coexist (Fig. 120.13A). The papulonodules may leave transient hypopigmented or hyperpigmented macules and, occasionally, superficial atrophic (varioliform) scars, or they may disappear without ulceration or sequelae. The



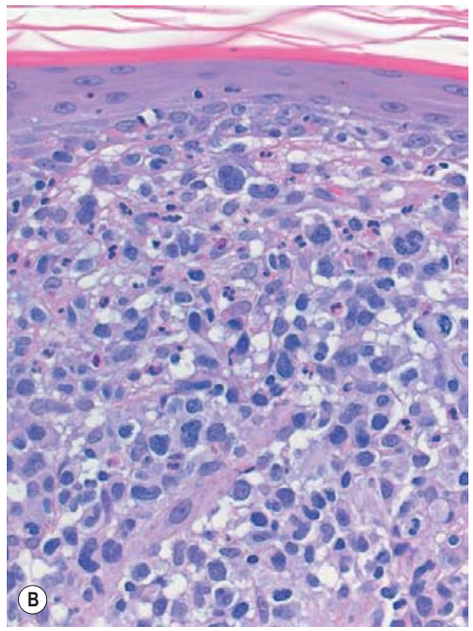


Fig. 120.13 Lymphomatoid papulosis (LyP). A Clinical presentation with papulonecrotic skin lesions at different stages of evolution. **B** Diffuse infiltrate with many large atypical lymphocytes. Scattered neutrophils are seen both in the epidermis and dermis. **C** Detail of dermal infiltrate showing a mixed inflammatory infiltrate with scattered (CD30-positive by immunohistochemistry) large anaplastic T cells (LyP, type A).

number of lesions varies from several to more than one hundred. Lesions may be localized, sometimes clustered within rather well-defined areas, or generalized. The predominant sites of involvement are the trunk and limbs. The eruption is generally asymptomatic.

The duration of the disease ranges from several months to more than 40 years. In up to 20% of patients, LyP may be preceded by, associated with, or followed by another type of cutaneous or systemic lymphoma, generally MF, C-ALCL or Hodgkin lymphoma[71]. However, the prognosis is usually excellent. In a recent study of 118 patients with LyP, only five patients (4%) developed a systemic lymphoma, and only two patients (2%) died of systemic disease over a median follow-up period of 77 months[57]. Risk factors for the development of a systemic lymphoma are unknown.

Pathology

The histologic picture of LyP is extremely variable, but in part it correlates with the age of the sampled skin lesion. In addition, four histologic types of LyP have been described: types A, B, C and D.

LyP type A lesions show a wedge-shaped, initially non-epidermotropic, infiltrate with scattered or small clusters of large atypical, sometimes multinucleated or Reed–Sternberg-like, CD30-positive T cells, interspersed in an extensive inflammatory infiltrate composed of small lymphocytes, neutrophils and/or eosinophils (Fig. 120.13B,C). The large atypical cells, which have the morphologic and immunophenotypical characteristics of the neoplastic cells in C-ALCL, are relatively few in early lesions and more numerous in fully developed lesions, but they may be completely absent in resolving lesions. The presence of scattered neutrophils within a moderately acanthotic and parakeratotic, but otherwise unaffected, epidermis is a characteristic finding.

LyP type B lesions are relatively uncommon (<10%) and are characterized by superficial perivascular to band-like lymphocytic infiltrates, which show early infiltration of the basal and parabasal layers of the epidermis. Occasionally, these perivascular infiltrates can also be found in the lower dermis. The infiltrates are composed predominantly of small to medium-sized atypical cells with cerebriform nuclei and the phenotype of $CD3^+$, $CD4^+$, $CD30^-$ or $CD30^+$ T cells, similar to those observed in MF.

LyP type A and type B may occur in different but concurrent lesions, and occasionally a single LyP lesion shows histologic features characteristic of both type A and type B[57].

LyP type C lesions demonstrate a monotonous population or large clusters of large CD30-positive T cells with relatively few admixed inflammatory cells, a histologic appearance typically found in C-ALCL.

Recently, a type of LyP that simulates $CD8^+$ aggressive epidermotropic T-cell lymphoma has been described and termed *LyP type D*. The intraepidermal cells express CD8 and CD30 with the usual loss of some pan-T-cell antigens[71a].

Recognition of these four histologic types has contributed to our understanding of the relationship between LyP and other types of CTCL and to the definition of the spectrum of primary cutaneous $CD30^+$ lymphoproliferations. However, from a practical point of view, histologic subtyping is not necessary, since the four histologic subtypes do not differ clinically.

Differential diagnosis

LyP is often diagnosed clinically as more common entities. Small recurrent LyP lesions on the trunk are frequently misinterpreted as folliculitis or arthropod bites for years. On the other hand, because of the presence of multifocal skin lesions with the histologic features of CD30-positive CTCL, LyP patients are regularly treated unnecessarily with multi-agent chemotherapy by physicians not familiar with this condition. Obviously, when the clinical features are taken into account, differentiation between LyP and the malignant lymphomas it may resemble histologically is not difficult.

Because of the clinical similarities between LyP and pityriasis lichenoides, a relationship between the two conditions was initially suggested. In addition, more recent studies have demonstrated clonal T-cell populations in skin biopsies of both conditions. However, differentiation is generally not difficult. Pityriasis lichenoides occurs more often in younger patients, is often relatively short-lived, does not develop nodular lesions, and rarely, if ever, progresses to a lymphoma. Histologically, the diseases are usually easily distinguished, and CD30-positive blast cells are generally not seen in pityriasis lichenoides[72].

Treatment

The treatment of patients with LyP is unsatisfactory. Topical or systemic corticosteroids or antibiotics are not effective. Aggressive treatment modalities such as systemic chemotherapy or TSEB irradiation may produce complete remissions, but after discontinuation of therapy, the LyP lesions generally reappear within weeks or months, and the disease follows its natural course. Since a curative therapy is not available and none of the available treatment modalities affects the natural course of the disease, the short-term benefits of active treatment should be balanced carefully against potential side effects[57]. In patients with relatively few non-scarring lesions, active treatment is not necessary. In the case of cosmetically disturbing lesions (e.g. scarring or many papulonodules), low-dose oral methotrexate (5–20 mg/week) is the most effective therapy for reducing the number of skin lesions[65]. Beneficial effects have been reported from PUVA, topical mechlorethamine or carmustine, and low-dose etoposide. When larger skin tumors develop in the course of LyP, they can be observed for a period of 4 to 12 weeks for the possibility of spontaneous remission. If spontaneous resolution does not occur, such lesions can be excised or treated with radiotherapy. Because of the potential risk for developing a systemic lymphoma, long-term follow-up is required in all patients with LyP.

SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA

Definition

In the WHO-EORTC classification (2004) and the most recent WHO classification (2008), subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is defined as a cytotoxic T-cell lymphoma characterized by the presence of primarily subcutaneous infiltrates of small, medium-sized or large pleomorphic T cells with an α/β^+ T-cell phenotype, in association with many macrophages[3,4]. In past classification schemes, the SPTCL category included cases with an α/β T-cell phenotype (75%) *and* cases with a γ/δ T-cell phenotype (25%)[1,2]. However, recent studies have shown clinical, histologic and immunophenotypical differences between cases of SPTCL with an α/β T-cell phenotype and those with a γ/δ T-cell phenotype, suggesting that they may represent different entities. Whereas SPTCLs with an α/β T-cell phenotype are homogeneous with a rather indolent clinical behavior in many patients, SPTCL with a γ/δ T-cell phenotype overlaps with other types of γ/δ-positive T-cell lymphoma and invariably runs a very aggressive clinical course[73,74]. Therefore, in both the WHO-EORTC classification and the most recent WHO classification, the term SPTCL is only used for cases with an α/β^+ T-cell phenotype, whereas cases with a γ/δ^+ T-cell phenotype are included in the category of primary cutaneous gamma/delta T-cell lymphoma (Table 120.6).

Epidemiology

SPTCL is a rare condition, accounting for less than 1% of all CTCL. It may occur in adults as well as in young children, and both sexes are equally affected.

Clinical features

Patients generally present with a solitary or multiple nodules or deeply seated plaques with a diameter varying from 1 to 20 cm. The skin lesions involve primarily the extremities and the trunk and less commonly the face; when the nodules and plaques resolve, they may be replaced by areas of lipoatrophy (Fig. 120.14A). Ulceration is uncommon. Systemic symptoms such as fever, fatigue and weight loss may be present in over half of the patients. Laboratory abnormalities including cytopenias and elevated liver function tests are common, but

COMPARISON OF SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA AND PRIMARY CUTANEOUS GAMMA/DELTA T-CELL LYMPHOMA WITH SUBCUTANEOUS INVOLVEMENT

	SPTCL	PCGD-TCL with subcutaneous involvement
Phenotype	α/β T-cell phenotype	γ/δ T-cell phenotype
T-cell receptor	$\beta F1^+$, $TCR\delta1^-$	$\beta F1^-$, $TCR\delta1^+$
T-cell phenotype	$CD3^+$, $CD4^-$, $CD8^+$	$CD3^+$, $CD4^-$, $CD8^-$
Coexpression of CD56	Absent	Common
Architecture	Subcutaneous	Subcutaneous and epidermal/dermal
Clinical features	Nodules and plaques Rarely ulceration	Nodules and plaques Ulceration common
Hemophagocytic syndrome	Uncommon	Common
Survival (5-year)	>80%	<10%
Treatment	Systemic corticosteroids	Systemic chemotherapy
WHO-EORTC classification (2004)[3] WHO classification (2008)[4]	Subcutaneous panniculitis-like T-cell lymphoma	Primary cutaneous gamma-delta T-cell lymphoma

Table 120.6 Comparison of subcutaneous panniculitis-like T-cell lymphoma (SPTCL) and primary cutaneous gamma-delta T-cell lymphoma (PCGD-TCL) with subcutaneous involvement[1,2]. βF1, positivity reflects α/β T-cell origin; TCR, T-cell receptor.

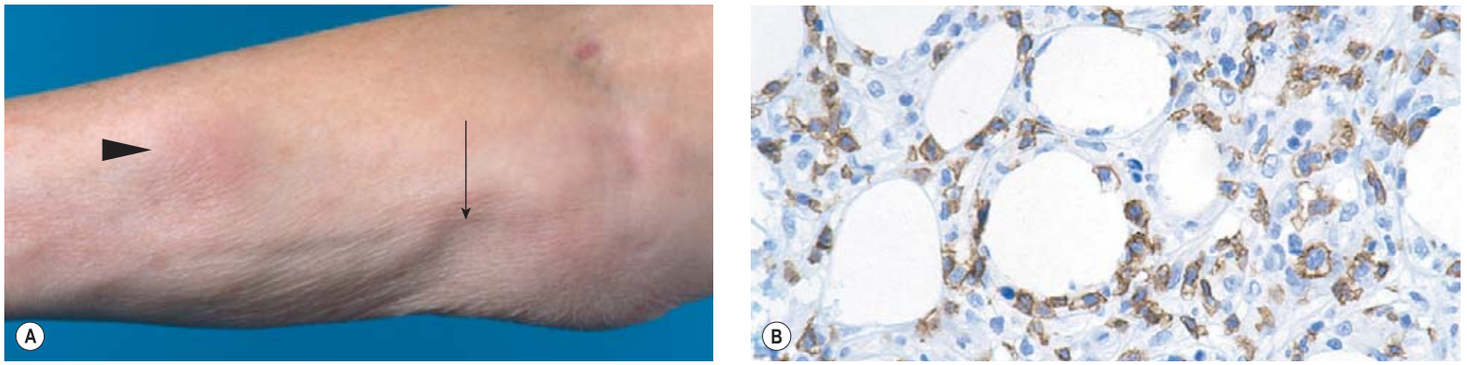


Fig. 120.14 Subcutaneous panniculitis-like T-cell lymphoma (SPTCL). A Pink nodular skin lesions (arrowhead) as well as an area of lipoatrophy (arrow) at the site of a resolved nodule. **B** Subcutaneous infiltration with rimming of CD8-positive neoplastic T cells around adipocytes. *B, Courtesy, Lorenzo Cerroni, MD.*

a frank hemophagocytic syndrome is observed in only ~15% of patients[74]. Dissemination to extracutaneous sites is rare and while hepatosplenomegaly may be seen, it is generally not due to lymphomatous involvement.

SPTCL may be preceded for years or decades by a seemingly benign panniculitis. Up to 20% of patients have an associated autoimmune disease, most commonly systemic lupus erythematosus. Recent studies have suggested overlapping features between SPTCL and lupus profundus[75]. SPTCL has a favorable prognosis with a 5-year overall survival of approximately 80%[74]. However, the presence of hemophagocytic syndrome is associated with a more unfavorable prognosis. In a recent study, patients with or without an associated hemophagocytic syndrome had a 5-year overall survival of 46% and 91%, respectively[74].

Pathology

Subcutaneous infiltrates simulating a lobular panniculitis are seen in SPTCL. Small, medium-sized or sometimes large pleomorphic T cells with hyperchromatic nuclei are present and are often admixed with many macrophages. The overlying epidermis and dermis are typically uninvolved. Rimming of individual fat cells by neoplastic T cells is a helpful, although not entirely specific, diagnostic feature (Fig. 120.14B). Necrosis, karyorrhexis and cytophagocytosis are common findings. In the early stages, the neoplastic infiltrates may lack significant atypia and a heavy inflammatory infiltrate may predominate.

Immunophenotype

These lymphomas have a TCR-α/β$^+$, CD3$^+$, CD4$^-$, CD8$^+$ T-cell phenotype, with expression of cytotoxic proteins. The neoplastic T cells express βF1 and are negative for CD56, facilitating differentiation from primary cutaneous gamma/delta T-cell lymphoma with subcutaneous involvement and panniculitis-like lesions (see Table 120.6). CD30 is rarely, if ever, expressed.

Treatment

While doxorubicin-based chemotherapy has traditionally been used, recent studies suggest that more conservative immunosuppressive regimens (e.g. prednisone, cyclosporine) may be effective and should initially be considered in patients with SPTCL without an associated hemophagocytic syndrome. In patients presenting with a solitary lesion, local radiotherapy may be effective[74].

EXTRANODAL NK/T-CELL LYMPHOMA, NASAL TYPE

Definition

Extranodal NK/T-cell lymphoma, nasal type is nearly always an EBV-positive lymphoma with an NK-cell, or more rarely a cytotoxic T-cell, phenotype. The skin is the most common site of involvement after the nasal cavity/nasopharynx, and skin involvement may be a primary or secondary manifestation of the disease.

Epidemiology

Extranodal NK/T-cell lymphoma is a rare disease, particularly in Europe and the US. It is more common in Asia, Central America and South America. Patients are adults, with a predominance of males.

Clinical features

Patients generally present with multiple plaques or tumors on the trunk and extremities or, in the case of nasal NK/T-cell lymphoma, with a midfacial destructive tumor (previously referred to as lethal midline granuloma)[76,77] (Fig. 120.15). Ulceration is common. Although patients presenting with only skin lesions have a somewhat better prognosis than patients presenting with both cutaneous and extracutaneous disease, the disease in both groups has a very aggressive clinical behavior and requires the same type of treatment.

Pathology

These lymphomas are characterized by dense infiltrates involving the dermis and often the subcutis. Prominent angiocentricity and angiodestruction are often accompanied by extensive necrosis[76,77]. NK/T-cell lymphoma has a broad cytologic spectrum ranging from small to large cells, with most cases consisting of medium-sized cells with irregular or oval nuclei, moderately dense chromatin and pale cytoplasm. In some cases, a heavy inflammatory infiltrate of small lymphocytes, histiocytes, plasma cells and eosinophils can be seen. The T-cell receptor usually has a germline configuration, but can be clonally rearranged in the rare tumors with a cytotoxic T-cell phenotype.

Fig. 120.15 Nasal NK/T-cell lymphoma. An extensive ulceronecrotic nasal mass, previously referred to as lethal midline granuloma.

Immunophenotype

The neoplastic cells express CD2, CD56, cytoplasmic CD3ε and cytotoxic proteins (TIA-1, granzyme B, perforin), but they lack surface CD3. In rare CD56-negative cases, detection of EBV by *in situ* hybridization and expression of cytotoxic proteins is required for diagnosis.

Treatment

In patients with localized disease, radiotherapy is the preferred treatment. For individuals with advanced disease, systemic chemotherapy is recommended, but the results are disappointing.

PRIMARY CUTANEOUS CD8-POSITIVE AGGRESSIVE EPIDERMOTROPIC CYTOTOXIC T-CELL LYMPHOMA

These tumors are characterized by a proliferation of epidermotropic CD8-positive cytotoxic T cells and an aggressive clinical behavior[78,79]. Differentiation from other types of CTCL expressing a CD8-positive cytotoxic T-cell phenotype – more than 50% of patients with pagetoid reticulosis and rare cases of MF, LyP and C-ALCL – is based on the clinical presentation and clinical behavior. In the latter conditions, no differences in clinical presentation or prognosis are observed between CD4$^+$ and CD8$^+$ cases.

Clinically, these lymphomas are characterized by the presence of localized or disseminated eruptive papules, nodules and tumors with central ulceration and necrosis *or* by superficial, hyperkeratotic patches and plaques (Fig. 120.16). They may disseminate to other visceral sites (lung, testis, central nervous system, oral mucosa), but lymph nodes are often spared[78].

Histologically, these lymphomas show strongly epidermotropic, band-like to diffuse infiltrates of small, medium-sized or large pleomorphic T cells with a CD3$^+$, CD4$^-$, CD8$^+$, CD7$^{-/+}$, CD45RA$^+$, granzyme B$^+$, perforin$^+$, TIA-1$^+$ phenotype[78]. The epidermis may be acanthotic or atrophic, and there may be necrotic keratinocytes, ulceration and variable spongiosis, sometimes with blister formation. Invasion and destruction of cutaneous adnexal structures are commonly seen. Angiocentricity and angioinvasion may be present.

These lymphomas run an aggressive clinical course and should be treated with systemic chemotherapy.

Fig. 120.16 Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma. Generalized skin tumors with central ulceration. Previously, such cases were designated as disseminated pagetoid reticulosis (Ketron–Goodman type).

Fig. 120.17 Primary cutaneous peripheral T-cell lymphoma, unspecified. Rapidly growing nodules and tumors. Note: the skin lesions in the left upper corner do not represent patches, but rather deep plaques present for 2 weeks.

PRIMARY CUTANEOUS GAMMA/DELTA T-CELL LYMPHOMA

Primary cutaneous gamma/delta T-cell lymphoma (PCGD-TCL) is a lymphoma composed of a clonal proliferation of mature, activated gamma/delta T cells with a cytotoxic phenotype. This group includes cases previously known as SPTCL with a gamma/delta T-cell phenotype.

PCGD-TCL generally presents with disseminated plaques and/or ulceronecrotic nodules or tumors, particularly on the extremities[74,80]. Involvement of mucosal and other extranodal sites is frequently observed, but involvement of lymph nodes, spleen or bone marrow is uncommon. In patients with panniculitis-like tumors, a hemophagocytic syndrome may occur.

Histologically, three major patterns of involvement can be seen: epidermotropic, dermal and subcutaneous. Often more then one histologic pattern is present within a single biopsy specimen or in different biopsy specimens from the same patient. The epidermal pattern can vary from mild epidermotropism to a marked pagetoid reticulosis-like infiltrate. Rimming of fat cells may be observed when there is subcutaneous involvement, similar to SPTCL. Angiocentricity and angiodestruction are commonly seen. The neoplastic cells are generally medium to large in size with coarsely clumped chromatin, and they have a $\beta F1^-$, $CD3^+$, $CD2^+$, $CD4^-$, $CD5^-$, $CD7^{+/-}$, $CD8^-$, $CD56^+$ phenotype with strong expression of cytotoxic proteins. In frozen sections, the cells are strongly positive for TCR-delta.

Most patients have aggressive, often rapidly fatal disease, which is resistant to multi-agent chemotherapy. Patients with subcutaneous fat involvement may have a worse prognosis in comparison to patients with epidermal or dermal disease only[80].

PRIMARY CUTANEOUS CD4-POSITIVE SMALL/MEDIUM PLEOMORPHIC T-CELL LYMPHOMA

These lymphomas are defined as CTCL with a predominance of small to medium-sized CD4-positive pleomorphic T cells without (a history of) patches and plaques typical of MF and, in most cases, a favorable clinical course. In contrast to the EORTC classification, the WHO-EORTC classification restricts the term primary cutaneous small/medium pleomorphic T-cell lymphoma to cases with a $CD4^+$ T-cell phenotype. Cases with a $CD3^+$, $CD4^-$, $CD8^+$ phenotype usually have a more aggressive clinical course similar to that of primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma[81].

Characteristically, these lymphomas present with a solitary plaque or tumor, generally on the face, the neck or the upper trunk. Less commonly, they present with generalized skin lesions[82–84]. Histologically, these lymphomas have dense, diffuse or nodular infiltrates within the dermis with a tendency to infiltrate the subcutis. Epidermotropism may be present focally. There is a predominance of small/medium-sized $CD3^+$, $CD4^+$, $CD8^-$, $CD30^-$ pleomorphic T cells. A small proportion (<30%) of large pleomorphic cells may be present. The proliferative rate is generally low. In most cases, a considerable admixture with reactive CD8-positive T cells, B cells, plasma cells and histiocytes is observed. Demonstration of an aberrant T-cell phenotype and clonality has been considered as helpful in differentiating small/medium pleomorphic T-cell lymphomas from pseudo-T-cell lymphomas, but the reported clinicopathologic features of these two entities do have considerable overlap[7,84]. For example, clonal T cells have been found in pseudo-T-cell lymphomas, and the large atypical cells in both conditions express programmed death-1 (PD-1), Bcl-6 and CXCL13, suggesting a common follicular helper T-cell phenotype[84a,84b].

Patients presenting with a solitary lesion have an excellent prognosis. In contrast, those with rapidly evolving tumors, a high proliferation index and few admixed $CD8^+$ T cells have been reported to be at risk for a more aggressive clinical course[82]. Surgical excision or radiotherapy is the preferred mode of treatment for a solitary skin lesion. Cyclophosphamide (as a single agent) and IFN-α have been reported to be effective in patients with more generalized skin disease[85]. However, the optimal treatment for this group has yet to be defined.

PRIMARY CUTANEOUS PERIPHERAL T-CELL LYMPHOMA, UNSPECIFIED

The designation "primary cutaneous peripheral T-cell lymphoma (PTCL), unspecified" is maintained for CTCLs that do not fit into any of the better-defined subtypes outlined in Table 120.1. It is therefore a diagnosis of exclusion. Clinically, these patients present with solitary or localized, but more frequently generalized, nodules or tumors[81] (Fig. 120.17).

Histologically, there are nodular or diffuse infiltrates with variable numbers of medium-sized to large pleomorphic or immunoblast-like T cells. Epidermotropism is generally mild or absent. Most cases have an aberrant $CD4^+$ T-cell phenotype with variable loss of pan-T-cell antigens. CD30 staining is negative or restricted to a few scattered tumor cells. Rare cases may show coexpression of CD56.

Patients should be treated with systemic chemotherapy, but the prognosis is generally poor, with a 5-year survival of less than 20%[81].

REFERENCES

1. Willemze R, Kerl H, Sterry W, et al. EORTC classification for primary cutaneous lymphomas. A proposal from the Cutaneous Lymphoma Study Group of the European Organization for Research and Treatment of Cancer (EORTC). Blood. 1997;90:354–71.
2. Jaffe ES, Harris NL, Stein H, Vardiman JW (eds). World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. Lyon: IARC Press, 2001.
3. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005;105:3768–85.
4. Swerdlow A, Campo E, Harris NL, et al. World Health Organization Classification of Tumours of

Haematopoietic and Lymphoid Tissue. Lyon: IARC Press, 2008.
5. Lutzner MA, Edelson RL, Schein P, et al. Cutaneous T-cell lymphomas: the Sézary syndrome, mycosis fungoides and related disorders. Ann Intern Med. 1975;83:534–52.
6. Santucci M, Burg G, Feller AC. Interrater and intrarater reliability of histologic criteria in early cutaneous T-cell lymphoma: an EORTC Cutaneous Lymphoma Project Study Group. Dermatol Clin. 1994;12:323–7.
7. Rijlaarsdam JU, Scheffer E, Meijer CJLM, Willemze R. Cutaneous pseudo-T-cell lymphomas. A clinicopathologic study of 20 patients. Cancer. 1992;69:717–24.
8. Pimpinelli N, Olsen EA, Santucci M, et al. Defining early mycosis fungoides. J Am Acad Dermatol. 2005;53:1053–63.
9. Wood GS. T-cell receptor and immunoglobulin gene rearrangements in diagnosing skin disease. Arch Dermatol. 2001;137:1503–6.
10. Lukowski A, Muche JM, Sterry W, Audring H. Detection of expanded T-cell clones in skin biopsy samples of patients with lichen sclerosus et atrophicus by T-cell receptor-gamma polymerase chain reaction assays. J Invest Dermatol. 2000;115:254–9.
11. Olsen E, Vonderheid E, Pimpinelli N, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). Blood. 2007;110:1713–22.
12. Kim YH, Willemze R, Pimpinelli N, et al. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). Blood. 2007;110:479–84.
13. Criscione VD, Weinstock MA. Incidence of cutaneous T-cell lymphoma in the United States, 1973–2002. Arch Dermatol. 2007;143:854–9.
14. Smoller BR, Santucci M, Wood GS, Whittaker SJ. Histopathology and genetics of cutaneous T-cell lymphoma. Hematol Oncol Clin North Am. 2003;17:1277–311.
15. Sommer VH, Clemmensen OJ, Nielsen O, et al. In vivo activation of STAT3 in cutaneous T-cell lymphoma. Evidence for an antiapoptotic function of STAT3. Leukemia. 2004;18:1288–95.
16. Scarisbrick JJ, Woolford AJ, Russell-Jones R, Whittaker SJ. Loss of heterozygosity on 10q and microsatellite instability in advanced stages of primary cutaneous T-cell lymphoma and possible association with homozygous deletion of PTEN. Blood. 2000;95: 2937–42.
17. Navas JC, Ortiz-Romero PL, Villuendas R, et al. P16(INK4a) gene alterations are frequent in lesions of mycosis fungoides. Am J Pathol. 2000;156:1565–72.
18. Tracey L, Villuendas R, Dotor AM, et al. Mycosis fungoides shows concurrent deregulation of multiple genes involved in the TNF signaling pathway: an expression profile study. Blood. 2003;102:1042–50.
19. Whitmore AS, Holly EA, Lee IM, et al. Mycosis fungoides in relation to environmental exposure and immune response. J Natl Cancer Inst. 1989;81:1560–7.
20. Li G, Vowels BR, Benoit BM, et al. Failure to detect human T-lymphotropic virus type I (HTLV-I) proviral DNA in cell lines and tissues from patients with cutaneous T-cell lymphoma. J Invest Dermatol. 1996;7:308–13.
21. Vermeer MH, van Doorn R, Dukers D, et al. $CD8^+$ T-cells in cutaneous T-cell lymphoma: expression of cytotoxic proteins, FAS ligand and killing inhibitory receptors and relationship with clinical behaviour. J Clin Oncol. 2001;19:4322–9.
22. van Doorn R, Dijkman R, Vermeer MH, et al. A novel splice variant of the *fas* gene in patients with cutaneous T-cell lymphoma. Cancer Res. 2002;62:5389–92.
23. Kim EJ, Hess S, Richardson SK, et al. Immunopathogenesis and therapy of cutaneous T-cell lymphoma. J Clin Invest. 2005;115:798–812.
24. Kim YH, Liu HL, Mraz-Gernhard S, et al. Long-term outcome of 525 patients with mycosis fungoides and Sezary syndrome: clinical prognostic factors and risk for disease progression. Arch Dermatol. 2003;139:857–66.
25. van Doorn R, van Haselen CW, van Voorst PC, et al. Mycosis fungoides: disease evolution and prognosis of 309 Dutch patients. Arch Dermatol. 2000;136:504–10.
26. Smoller BR, Bishop K, Glusac E, Warnke R. Reassessment of histologic parameters in the diagnosis of mycosis fungoides. Am J Surg Pathol. 1995;19:1423–30.
27. Diamandidou E, Colome-Grimmer M, Fayad L, et al. Transformation of mycosis fungoides/Sézary syndrome: clinical characteristics and prognosis. Blood. 1998;92:1150–9.
28. Trautinger F, Knobler R, Willemze R, et al. EORTC consensus recommendations for the treatment of mycosis fungoides/Sezary syndrome. Eur J Cancer. 2006;42:1014–30.
29. Prince HM, Whittaker S, Hoppe RT. How I treat mycosis fungoides and Sézary syndrome. Blood. 2009;114:4337–53.
30. Kaye FJ, Bunn PA, Steinberg SM, et al. A randomized trial comparing combination electron beam radiation and chemotherapy with topical therapy in the initial treatment of mycosis fungoides. N Engl J Med. 1989;321:784–90.
31. Zackheim HS, Kashani-Sabet M, Amin S. Topical corticosteroids for mycosis fungoides. Experience in 79 patients. Arch Dermatol. 1998;134:949–54.
32. Vonderheid EC, Tan E, Kantor AF, et al. Long-term efficacy, curative potential and carcinogenicity of topical mechlorethamine chemotherapy in cutaneous T-cell lymphoma. J Am Acad Dermatol. 1989;20: 416–28.
33. Zackheim HS, Epstein EH, Crain WR. Topical carmustine (BCNU) for cutaneous T-cell lymphoma: a 15-year experience in 143 patients. J Am Acad Dermatol. 1990;22:802–10.
34. Jones GW, Kacinski BM, Wilson LD, et al. Total skin electron radiation in the management of mycosis fungoides: consensus of the European Organization for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Project Group. J Am Acad Dermatol. 2002;47:364–70.
35. Querfeld C, Rosen ST, Kuzel TM, et al. Long-term follow-up of patients with early-stage cutaneous T-cell lymphoma who achieved complete remission with psoralen plus UV-A monotherapy. Arch Dermatol. 2005;141:305–11.
36. Ramsey D, Lish K, Yalowitz C, et al. Ultraviolet-B phototherapy for early stage cutaneous T-cell lymphoma. Arch Dermatol. 1992;128:931–3.
37. Olsen EA. Interferon in the treatment of cutaneous T-cell lymphoma. Dermatol Ther. 2003;16:311–21.
38. Stadler R, Kremer A. Therapeutic advances in cutaneous T-cell lymphoma (CTCL): from retinoids to rexinoids. Semin Oncol. 2006;(1 Suppl 3):S7–10.
39. Foss F. Clinical experience with denileukin diftitox. Semin Oncol. 2006;33(1 Suppl 3):S11–16.
40. Prince HM, Bishton MJ, Harrison SJ. Clinical studies of histone deacetylase inhibitors. Clin Cancer Res. 2009;15:3958–69.
41. Duarte RF, Schmitz N, Servitje O, Suerda A. Haematopoietic stem cell transplantation for patients with primary cutaneous T-cell lymphoma. Bone Marrow Transplant. 2008;41:597–604.
42. van Doorn R, Scheffer E, Willemze R. Follicular mycosis fungoides: a distinct disease entity with or without associated follicular mucinosis. Arch Dermatol. 2002;138:191–8.
43. Gerami P, Rosen S, Kuzel T, et al. Folliculotropic mycosis fungoides: an aggressive variant of cutaneous T-cell lymphoma. Arch Dermatol. 2008;144:738–46.
44. Haghighi B, Smoller BR, LeBoit PE, et al. Pagetoid reticulosis (Woringer-Kolopp disease): an immunophenotypic, molecular and clinicopathologic study. Mod Pathol. 2000;13:502–10.
45. LeBoit PE. Granulomatous slack skin. Dermatol Clin. 1994;12:375–89.
46. Kempf W, Ostheeren-Michaelis S, Paulli M, et al. Granulomatous mycosis fungoides and granulomatous slack skin: a multicenter study of the Cutaneous Lymphoma Histopathology Task Force Group of the European Organization for Research and Treatment of Cancer (EORTC). Arch Dermatol. 2008;144:1609–17.
47. Vonderheid EC, Bernengo MG, Burg G, et al. Update on erythrodermic cutaneous T-cell lymphoma: report of the International Society for Cutaneous Lymphomas. J Am Acad Dermatol. 2002;46:95–106.
48. Trotter MJ, Whittaker SJ, Orchard GE, Smith NP. Cutaneous histopathology of Sezary syndrome: a study of 41 cases with a proven circulating T-cell clone. J Cutan Pathol. 1997;24:286–91.
49. Vermeer MH, van Doorn R, Dijkman R, et al. Novel and highly recurrent chromosomal alterations in Sezary syndrome. Cancer Res. 2008;68:2689–98.
50. Caprini E, Cristofoletti C, Arcelli D, et al. Identification of key regions and genes important in the pathogenesis of Sezary syndrome by combining genomic and expression arrays. Cancer Res. 2009;69:8438–46.
51. Laharanne E, Oumouhou N, Bonnet F, et al. Genome-wide analysis of cutaneous T-cell lymphomas identifies three clinically relevant classes. J Invest Dermatol. 2010;130:1707–18.
51a. van Doorn R, van Kester MS, Dijkman R, et al. Oncogenomic analysis of mycosis fungoides reveals major differences with Sézary syndrome. Blood. 2009;113:127–36.
51b. Campbell JJ, Clark RA, Watanabe R, Kupper TS. Sézary syndrome and mycosis fungoides arise from distinct T-cell subsets: a biologic rationale for their distinct clinical behaviors. Blood. 2010;116:767–7.
52. Toonstra J, Henquet CJM, van Weelden H, et al. Actinic reticuloid: a clinical, photobiologic, histopathologic and follow-up study of 16 cases. J Am Acad Dermatol. 1989;21:205–14.
53. Edelson R, Berger C, Gasparro F, et al. Treatment of cutaneous T-cell lymphoma by extracorporeal photochemotherapy. N Engl J Med. 1987;316: 297–303.
54. Russell-Jones R. Extracorporeal photopheresis in cutaneous T-cell lymphoma. Inconsistent data underline the need for randomized studies. Br J Dermatol. 2000;142:16–21.
55. Shimoyama M. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukemia-lymphoma: a report from the Lymphoma Study Group (1984–1987). Br J Haematol. 1991;79:428–37.
56. Yamada Y, Tomonaga M. The current status of therapy for adult T-cell leukemia- lymphoma in Japan. Leukemia Lymphoma. 2003;44:611–18
57. Bekkenk M, Geelen FAMJ, van Voorst Vader PC, et al. Primary and secondary cutaneous CD30-positive lymphoproliferative disorders: long term follow-up data of 219 patients and guidelines for diagnosis and treatment. A report from the Dutch Cutaneous Lymphoma Group. Blood. 2000;95:3653–61.
58. Werner B, Massone C, Kerl H, Cerroni L. Large CD30-positive cells in benign, atypical lymphoid infiltrates of the skin. J Cutan Pathol. 2008;35: 1100–7.
59. Liu HL, Hoppe RT, Kohler S, et al. $CD30^+$ cutaneous lymphoproliferative disorders: The Stanford experience in lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma. J Am Acad Dermatol. 2003;49:1049–58.
60. Benner MF, Jansen PM, Meijer CJ, Willemze R. Diagnostic and prognostic evaluation of phenotypic markers TRAF1, MUM1, BCL2 and CD15 in cutaneous CD30-positive lymphoproliferative disorders. Br J Dermatol. 2009;161:121–7.
61. DeCouteau JF, Butmarc JR, Kinney MC, Kadin ME. The t(2;5) chromosomal translocation is not a common feature of primary cutaneous $CD30^+$ lymphoproliferative disorders: comparison with anaplastic large cell lymphoma of nodal origin. Blood. 1996;87:3437–41.
62. Natkunam Y, Warnke RA, Haghighi B, et al. Co-expression of CD56 and CD30 in lymphomas with primary presentation in the skin: clinicopathologic, immunohistochemical and molecular analyses of seven cases. J Cutan Pathol. 2000;27:392–9.
63. Feldman AL, Law M, Remstein ED, et al. Recurrent translocations involving the IRF4 locus in peripheral T-cell lymphomas. Leukemia 2009;23:574–80.
64. Pham-Ledard A, Prochazkova-Carlotti M, Laharanne E, et al. IRF4 gene rearrangements define a subgroup of $CD30^+$ cutaneous T-cell lymphoma: a study of 54 cases. J Invest Dermatol. 2010;130:816–25.
65. Vonderheid EC, Sajjadian A, Kadin ME. Methotrexate is effective therapy for lymphomatoid papulosis and other primary cutaneous CD30-positive lymphoproliferative disorders. J Am Acad Dermatol. 1996;34:470–80.
66. Woo DK, Jones CR, Vanoli-Storz MN, et al. Prognostic factors in primary cutaneous anaplastic large cell lymphoma. Arch Dermatol. 2009;145:667–74.
67. Benner MF, Willemze R. Applicability and prognostic value of the new TNM classification system in 135 patients with primary cutaneous anaplastic large cell lymphoma. Arch Dermatol. 2009;145:1399–404
68. Macaulay WL. Lymphomatoid papulosis. A continuing self-healing eruption, clinically benign: histologically malignant. Arch Dermatol. 1968;97:23–30.
69. Mori M, Manuelli C, Pimpinelli N, et al. CD30–CD30L interaction in primary cutaneous $CD30^+$ T-cell lymphomas: a clue to the pathophysiology of clinical regression. Blood. 1999;94:3077–83.
70. Schieman WP, Pfeifer WM, Levi E, et al. A deletion in the gene for transforming growth factor beta type I receptor

abolishes growth regulation by transforming growth factor beta in cutaneous T-cell lymphoma. Blood. 1999:94:2854–61.
71. Beljaards RC, Willemze R. The prognosis of patients with lymphomatoid papulosis associated with malignant lymphomas. Br J Dermatol. 1992;126: 596–602.
71a. Saggini A, Gulia A, Argenyi Z, et al. A variant of lymphomatoid papulosis simulating primary cutaneous aggressive epidermotropic CD8$^+$ cytotoxic T-cell lymphoma. Description of 9 cases. Am J Surg Pathol. 2010;34:1168–75.
72. Varga FJ, Vonderheid EC, Olbricht SM, et al. Immunohistochemical distinction of lymphomatoid papulosis and pityriasis lichenoides et varioliformis acuta. Am J Pathol. 1990;136:979–87.
73. Santucci M, Pimpinelli N, Massi D, et al. Cytotoxic/natural killer cell cutaneous lymphomas. Report of EORTC Cutaneous Lymphoma Task Force Workshop. Cancer. 2003;97:610–27.
74. Willemze R, Jansen PM, Cerroni L, et al. Subcutaneous panniculitis-like T-cell lymphoma: definition, classification, and prognostic factors: an EORTC Cutaneous Lymphoma Group Study of 83 cases. Blood. 2008;111:838–45.
75. Magro CM, Crowson AN, Kovatich AJ, Burns F. Lupus profundus, indeterminate lymphocytic lobular panniculitis and subcutaneous T-cell lymphoma: a spectrum of subcuticular T-cell lymphoid dyscrasia. J Cutan Pathol. 2001;28:235–47.
76. Cheung MMC, Chan JKC, Lau WH, et al. Primary non-Hodgkin lymphoma of the nose and nasopharynx: clinical features, tumor immunophenotype, and treatment outcome in 113 patients. J Clin Oncol. 1998;16:70–7.
77. Chan JK, Sin VC, Wong KF, et al. Nonnasal lymphoma expressing the natural killer cell marker CD56: a clinicopathologic study of 49 cases of an uncommon aggressive neoplasm. Blood. 1997;89:4501–13.
78. Berti E, Tomasini D, Vermeer MH, et al. Primary cutaneous CD8-positive epidermotropic cytotoxic T-cell lymphoma: a distinct clinicopathologic entity with an aggressive clinical behavior. Am J Pathol. 1999;155:483–92.
79. Agnarsson BA, Vonderheid EC, Kadin ME. Cutaneous T-cell lymphoma with suppressor/cytotoxic (CD8) phenotype: identification of rapidly progressive and chronic subtypes. J Am Acad Dermatol. 1990;22:569–77.
80. Toro JR, Liewehr DJ, Pabby N, et al. Gamma-delta-T-cell phenotype is associated with significantly decreased survival in cutaneous T-cell lymphoma. Blood. 2003;101:3407–12.
81. Bekkenk MW, Vermeer MH, Jansen PM, et al. Peripheral T-cell lymphomas unspecified presenting in the skin: analysis of prognostic factors in a group of 82 patients. Blood. 2003;102:2213–19.
82. Garcia-Herrera A, Colomo L, Camos M, et al. Primary cutaneous small/medium CD4$^+$ T-cell lymphomas: a heterogeneous group of tumors with different clinicopathologic features and outcome. J Clin Oncol. 2008;26:3364–71.
83. Grogg KL, Jung S, Erickson LA, et al. Primary cutaneous CD4-positive small/medium-sized pleomorphic T-cell lymphoma: a clonal T-cell lymphoproliferative disorder with indolent behavior. Mod Pathol. 2008;21:708–15.
84. Beltraminelli H, Leinweber B, Kerl H, Cerroni L. Primary cutaneous CD4$^+$ small/medium-sized pleomorphic T-cell lymphoma: a cutaneous nodular proliferation of pleomorphic T-lymphocytes of undetermined significance? A study of 136 cases. Am J Dermatopathol. 2009;31:317–22.
84a. Rodriguez Pinilla SM, Roncador G, Rodriguez-Peralto JL, et al. Primary cutaneous CD4$^+$ small/medium-sized pleomorphic T-cell lymphoma expresses follicular T-cell markers. Am J Surg Pathol. 2009;33:81–90.
84b. Çetinözman F, Jansen PM, Willemze R. Expression of Programmed Death-1 (PD-1) in primary cutaneous CD4-positive small/medium-sized pleomorphic T-cell lymphoma, cutaneous pseudo-T-cell lymphoma and other types of cutaneous T-cell lymphoma. Am J Surg Pathol. 2012;36:109–16.
85. Friedmann D, Wechsler J, Delfau MH, et al. Primary cutaneous pleomorphic small T-cell lymphoma. Arch Dermatol. 1995;31:1009–15.

Other Lymphoproliferative and Myeloproliferative Diseases

121

Harry L Winfield and Bruce R Smoller

Chapter Contents

Benign lymphocytic infiltrates *2037*
Malignant hematopoietic infiltrates *2041*

BENIGN LYMPHOCYTIC INFILTRATES

LYMPHOCYTIC INFILTRATE OF JESSNER

Synonyms: ■ Benign lymphocytic infiltration of the skin ■ Jessner's lymphocytic infiltration of the skin ■ Jessner's lymphocytic infiltrate of the skin ■ Jessner–Kanof lymphocytic infiltration of the skin

Key features

- Erythematous papules, plaques and, less commonly, nodules
- Most common on the head, neck and back
- Dermal infiltrate of lymphocytes without epidermal involvement

History

Lymphocytic infiltrate of Jessner (LIJ) was initially described in 1953 by Jessner and Kanof[1] as circinate papules on the face, surrounding a central area of clearing.

Epidemiology

Lymphocytic infiltrate of Jessner occurs primarily in middle-aged adults. There is no gender predilection.

Pathogenesis

Lymphocytic infiltrate of Jessner remains a controversial entity. Some authors believe it is a variant of either lupus erythematosus (LE), cutaneous lymphoid hyperplasia or polymorphic light eruption[2], while in Europe, it has been associated with *Borrelia burgdorferi* infection[3]. There are cases of co-occurrence with LE and with polymorphic light eruption, further raising the possibility that these entities are related. Lastly, rare cases of drug-induced LIJ (e.g. angiotensin-converting enzyme [ACE] inhibitors, glatiramer acetate) have been described[4,5].

Clinical features

Lymphocytic infiltrate of Jessner occurs primarily on the head, neck and upper back as one or several asymptomatic erythematous papules, plaques and, less commonly, nodules, with an absence of secondary changes such as scale (Fig. 121.1). Annular plaques with central clearing are commonly observed and individual lesions last several weeks to months. There are no associated systemic manifestations. Emotional stress has been associated with exacerbation of the eruption in a minority of patients. The eruption resolves spontaneously and without sequelae in most patients.

Pathology

The epidermis is unremarkable, with little evidence of lymphocytic exocytosis or interface dermatitis. There is a superficial and deep, primarily perivascular, lymphocytic infiltrate that may surround hair follicles (Fig. 121.2). By immunohistochemistry, a mixed T-cell infiltrate with a predominance of $CD8^+$ lymphocytes is seen[6], admixed with small clusters of $CD123^+$ plasmacytoid dendritic cells. An increase in reticular dermal mucin may be seen.

Fig. 121.1 Lymphocytic infiltrate of Jessner. Annular erythematous plaque on the face.

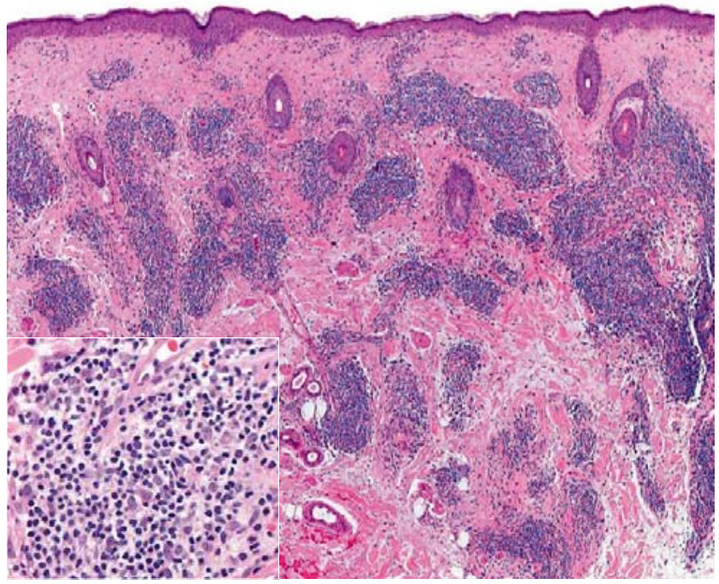


Fig. 121.2 Lymphocytic infiltrate of Jessner. A superficial and deep perivascular infiltrate without an interface component is characteristic. The infiltrate is composed of lymphocytes (insert).

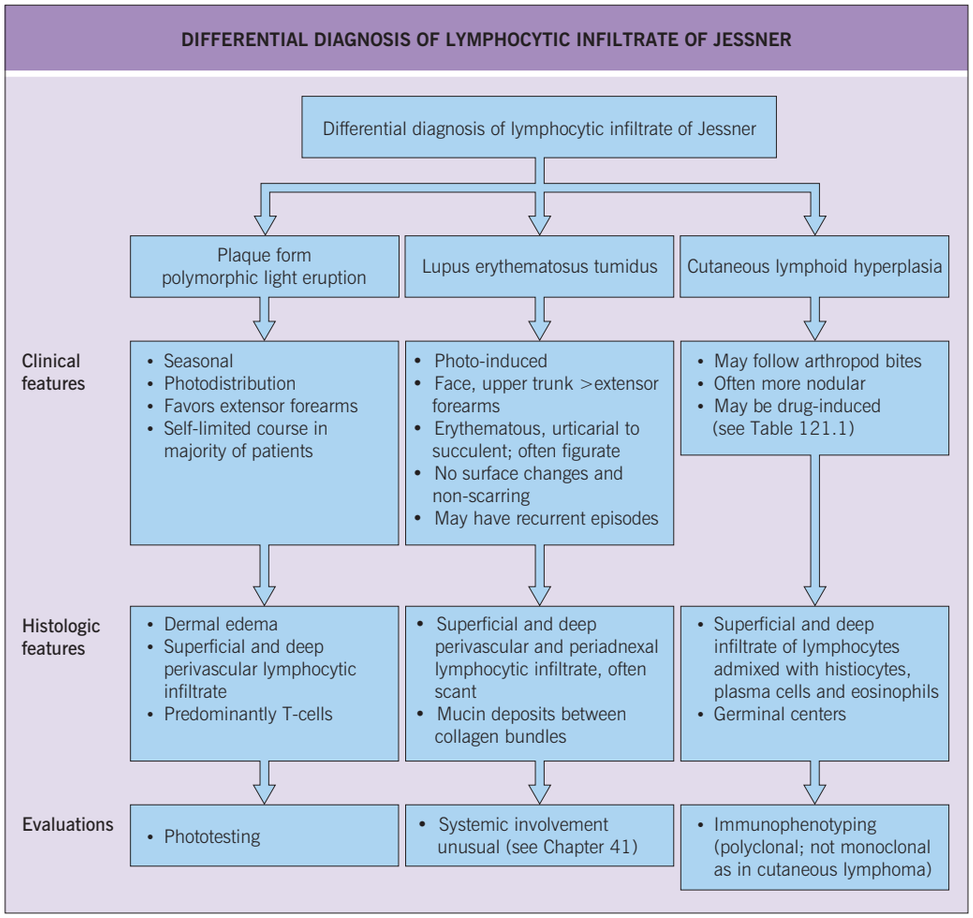


Fig. 121.3 Differential diagnosis of lymphocytic infiltrate of Jessner. Reticular erythematous mucinosis can also be considered in the differential diagnosis; histologically, abundant dermal mucin is observed. Some authors consider lymphocytic infiltrate of Jessner, lupus erythematosus tumidus and reticular erythematous mucinosis to be similar entities along a clinical spectrum.

Differential diagnosis

The differential diagnosis includes the plaque form of polymorphic light eruption, LE tumidus, cutaneous lymphoid hyperplasia (see below), reticular erythematous mucinosis, and cutaneous lymphoma (Fig. 121.3). In contrast to LIJ, subacute and chronic cutaneous LE have secondary changes, including scale, follicular plugging and central hypopigmentation, along with interface changes histologically. However, in LE tumidus, interface changes are sparse, if present at all, and distinction is more difficult. Reticular erythematous mucinosis, which is considered by some as synonymous with LE tumidus, also has abundant dermal mucin.

Polymorphic light eruption is associated with sun exposure and usually has a self-limited clinical course. Histologically, papillary dermal edema is often seen, a feature not present in LIJ. For some patients, it may be difficult to distinguish between these entities and phototesting may prove helpful (see Fig. 121.3).

Cutaneous lymphomas can have significant clinical and histopathologic overlap with LIJ. If the dermal lymphocytic infiltrate is extensive, immunophenotypic analyses may help to distinguish between the two entities (see Chs 119 & 120).

Treatment

The cutaneous manifestations of LIJ resolve spontaneously within months to years, without scarring. Oral antibiotics and topical or intralesional corticosteroids have been used with limited success. Up to 50% of patients may improve with hydroxychloroquine. In general, LIJ is resistant to radiation therapy. A crossover study of oral thalidomide (100 mg/day) versus placebo in 25 patients resulted in a clinical response of 76% for thalidomide and 16% for placebo. In isolated case reports, improvement following pulsed dye (595 nm) laser treatment or chemotherapy (for an unrelated malignancy) has been described[7,8].

CUTANEOUS LYMPHOID HYPERPLASIA (LYMPHOCYTOMA CUTIS)

Synonyms: ■ Lymphocytoma cutis ■ Pseudolymphoma ■ Lymphadenosis benigna cutis (LABC) ■ Spiegler–Fendt sarcoid ■ Miliary lymphocytoma

Key features

- Erythematous to violaceous nodule or plaque
- Most common on the face and upper trunk
- Mixed dermal infiltrate of lymphocytes, plasma cells and eosinophils
- Follicular/germinal centers with tingible-body macrophages are common
- Polyclonal inflammatory infiltrate

History

Cutaneous lymphoid hyperplasia (CLH) was first reported by Spiegler in 1894. He described patients who presented with clinical features of a sarcoma but experienced a benign clinical course. Subsequent investigators recognized the reactive lymphocytic nature of the process.

Epidemiology

CLH is seen most often in adults and may be slightly more common in women. The disorder has been reported in children.

MEDICATIONS ASSOCIATED WITH CUTANEOUS LYMPHOID HYPERPLASIA	
Anticonvulsants	*Carbamazepine*, *phenobarbital*, *phenytoin*, *ethosuximide*, *lamitrogine*, *valproic acid*, ethotoin
Antiarrhythmics	*Mexiletine*, procainamide
Antibiotics	*Trimethoprim-sulfamethoxazole*, *cefixime*, cefuroxime, *nitrofurantoin*, clarithromycin
Antidepressants	*Amytriptyline*, desipramine, fluoxetine, clomipramine, lithium
Antihistamines	Cimetidine, ranitidine, nizatidine, doxepin
Antihypertensives (including diuretics)	*Atenolol*, *captopril*, lisinopril, *diltiazem*, amlodipine, furosemide, amiloride, losartan, valsartan, clonidine patch
Antipsychotics	Chlorpromazine, perphenazine, thioridazine
Chemotherapeutic agents	*Imatinib*, fluorouracil, gemcitabine, oxaliplatin, tamoxifen, leucovorin
Lipid-lowering agents	Gemfibrozil, lovastatin
Nonsteroidal anti-inflammatory drugs (NSAIDs)	*Aspirin*, *ibuprofen*, *naproxen*, diclofenac, indomethacin, ketoprofen, sulindac, diflunisal, oxaprozin, nabumetone
Rheumatologic agents	*Allopurinol*, *dapsone*, *sulfasalazine,* etanercept, methotrexate, gold, D-penicillamine
Sedatives	Benzodiazepines
Steroid hormones	Estrogen, progesterone
Stimulants	Methylphenidate
Vaccines	Hepatitis A, hepatitis B
Miscellaneous	Cyclosporine, interferon-alpha, adesleukin (interleukin-2), glatiramer acetate, bromocriptine, black cohosh

Table 121.1 Medications associated with cutaneous lymphoid hyperplasia (CLH)[9–12]. The lesions are similar clinically and histologically to idiopathic CLH (T-cell, B-cell, and mixed). For patients with the drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS) who have atypical lymphocytes in the blood and skin, the term pseudolymphoma is sometimes applied; however, this is a separate entity (see Ch. 21). The drugs in italics have also been reported to cause DRESS/DIHS. Adapted from references 10-12.

ENTITIES IN WHICH CUTANEOUS LYMPHOID HYPERPLASIA CAN OCCUR		
Common entities	**Less common entities**	**Rare entities**
Arthropod bites or stings, scabies	Post herpes zoster infection (dermatomal)	APACHE syndrome
Borrelia infection (Europe)	Folliculitis (pseudolymphomatous)	Kikuchi–Fujimoto disease
Tattoo reactions	Vaccinations	Sjögren's syndrome (cutaneous)
Drugs (see Table 121.1)		
Infections, e.g. herpes simplex		

Table 121.2 Entities in which cutaneous lymphoid hyperplasia can occur. APACHE, acral pseudolymphomatous angiokeratoma of children.

Pathogenesis

CLH does not represent a single disease state, but rather reflects an exaggerated local immunologic reaction to a stimulus, often unrecognized. The possibility of a hapten-driven immunologic response to cells damaged by a direct toxic effect of stimuli has been suggested[9]. Inciting agents include arthropod bites, metal implants, tattoos, vaccinations and medications (Table 121.1)[9–12]. In addition, several infections and reactive disorders have been associated with CLH (Table 121.2).

Clinical features

Classically, CLH presents as firm, erythematous to violaceous papules, plaques or nodules located on the head, neck or upper extremities. The lesions are often solitary, but may be multiple and grouped (Fig. 121.4). Although the vast majority of papulonodules lack surface changes, occasionally there is scale or follicular accentuation, including in the variant termed "pseudolymphomatous folliculitis". The latter presents as a solitary facial lesion and has rather unique histologic features (see below)[13].

Fig. 121.4 Cutaneous lymphoid hyperplasia (lymphocytoma cutis). A Violet papulonodules on the helix and lobe of the ear (unknown etiology). **B** Multiple red–brown to violet papules at the sites of *Hirudo medicinalis* (medicinal leech) application. *B, Courtesy, Josef Smolle, MD.*

Pathology

The histologic features are variable and the pattern may resemble mycosis fungoides, a B-cell lymphoma or a $CD30^+$ anaplastic large cell lymphoma. Pseudolymphomas with a *mycosis fungoides-like* pattern are most often encountered in drug-induced pseudolymphomas. Histologically, epidermotropism, spongiosis, vacuolar degeneration of the basal layer, papillary dermal edema, and red cell extravasation may be seen. Prominent papillary dermal fibrosis, commonly seen in mycosis fungoides, is absent, but T-cell clonality may be present (see below).

In CLH with *B-cell predominance*, there is typically a single lesion with a superficial and deep nodular or diffuse infiltrate of lymphocytes, admixed with histiocytes and occasional plasma cells and eosinophils. The dermal infiltrate is dense and recapitulates nodal architecture (Fig. 121.5). In florid cases, germinal centers have prominent tingible-body macrophages. A mantle zone surrounds the lymphoid follicles. Differentiation from cutaneous lymphoma may be difficult; however, in most cases, the distinction can be made on routine histologic sections or with the addition of immunohistochemical stains (Table 121.3). Clonality, based upon IgH gene rearrangements, is not seen in CLH[9].

B-cell-predominant infiltrates express a mixture of both kappa and lambda light chains (see Fig. 119.9). In T-cell-predominant infiltrates,

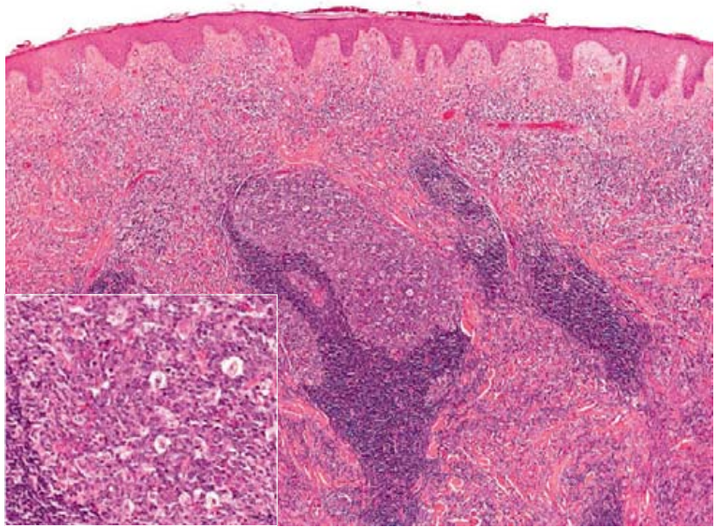


Fig. 121.5 Cutaneous lymphoid hyperplasia (lymphocytoma cutis). Lymphoid cells throughout the dermis in a nodular and diffuse pattern. There is germinal center formation and tingible-body macrophages are present within the germinal centers (insert). *Courtesy, Lorenzo Cerroni, MD.*

MICROSCOPIC DIFFERENCES BETWEEN CUTANEOUS LYMPHOID HYPERPLASIA AND CUTANEOUS FOLLICLE CENTER B-CELL LYMPHOMA	
Cutaneous lymphoid hyperplasia	**Cutaneous follicle center B-cell lymphoma**
HISTOLOGIC FEATURES	
Mixed cellular infiltrate, including eosinophils and plasma cells	Predominantly lymphocytic infiltrate
Reactive germinal centers Mantle zone present Tingible-body macrophages present Polarization of follicles with light and dark areas	Neoplastic germinal centers No or reduced mantle zone No tingible-body macrophages Monomorphous appearance of follicles without polarization
IMMUNOPHENOTYPIC FEATURES	
T and B lymphocytes	Predominance of B lymphocytes ($CD20^+$)
$Bcl\text{-}6^+$ cells restricted to lymph follicles	Clusters of $Bcl\text{-}6^+$ cells outside of lymph follicles
Bcl-2 only on T lymphocytes	Bcl-2 on neoplastic B cells (small minority of cases)
High proliferation of germinal centers	Reduced proliferation of germinal centers
Mixed κ and λ expression	Restricted κ or λ expression (some cases, frozen sections)
*Exception is T-cell-rich B-cell lymphoma.	

Table 121.3 Microscopic differences between cutaneous lymphoid hyperplasia and cutaneous follicle center B-cell lymphoma.

$CD4^+$ T helper lymphocytes are commonly observed within the dermis, beneath a minority population of $CD8^+$ cytotoxic/suppressor T cells in the epidermis. A small proportion of cases have clonal T-cell receptor (TCR) gene rearrangements, and CLH rarely may eventuate into overt cutaneous lymphoma. Whether the presence of clonal populations is a marker for progression to lymphoma, or constitutes a lymphoma at the outset, remains uncertain[14].

In the variant pseudolymphomatous folliculitis, the infiltrate is predominantly perifollicular and periadnexal and is typically mixed, with a predominance of T or B cells. Lymphocyte atypia may be seen. Irregular hyperplasia and distortion of the follicular epithelium, with blurring of the dermal–epidermal junction, are seen. Characteristically, infiltrates of $CD1a^+/S100^+$ mononuclear cells surround and infiltrate the distorted follicles. Granulomas may be variably present[13,15,16].

Differential diagnosis

The clinical differential diagnosis usually includes lymphoma cutis, non-lymphoid metastatic disease, and lymphocytic infiltrate of Jessner. Histologically, the differential diagnosis includes primarily cutaneous lymphoma, lymphocytic infiltrate of Jessner, polymorphic light eruption, and LE tumidus (see Fig. 121.3).

Cutaneous lymphoid hyperplasia may be difficult to differentiate from cutaneous lymphomas (see Pathology section). Features that differentiate CLH from cutaneous follicle center B-cell lymphoma are outlined in Table 121.3. Although the presence of clonality may aid in distinguishing reactive from neoplastic processes, it should not be used to establish malignancy.

Acral pseudolymphomatous angiokeratoma of children (APACHE), originally thought to represent a vascular nevus, is now categorized as a pseudolymphoma. In contrast to CLH, it favors the extremities of children between the ages of 2 and 16 years, usually presenting as a unilateral grouping of small, red to violet, "angiomatous" papules. Histologically, there is a dermal infiltrate of lymphocytes, histiocytes and plasma cells accompanied by prominently thickened capillaries.

Kikuchi–Fujimoto disease, also known as histiocytic necrotizing lymphadenitis, is an idiopathic systemic inflammatory disease most commonly seen in young adult women. It is associated with a variety of viral and bacterial infections (e.g. Epstein-Barr virus, cytomegalovirus) as well as autoimmune diseases (e.g. systemic lupus erythematosus). In addition to fevers, malaise, weight loss and gastrointestinal symptoms, patients develop cervical lymphadenopathy. Histologically, there is necrosis and histiocytic infiltration of the paracortical areas of involved lymph nodes, without an identifiable pathogen. Cutaneous findings, present in 40% of patients, include acneiform eruptions, urticaria, ulcers and indurated erythematous plaques. Histologically, dense superficial and deep perivascular lymphohistiocytic infiltrates with nuclear debris (in the absence of neutrophils) are seen; interface changes are commonly present[17,18].

Treatment

Cutaneous lymphoid hyperplasia is a benign, reactive condition and it should be treated conservatively. Spontaneous resolution may occur without scarring. For persistent lesions, topical and/or intralesional corticosteroids may lead to improvement. Simple excision, cryosurgery, laser ablation and radiation therapy are other options. Thalidomide has been utilized with success in recalcitrant cases[19]. Performance of a biopsy, even if partial, can be followed by spontaneous regression.

EXTRAMEDULLARY HEMATOPOIESIS

Key features

- Evidence of bone marrow dysfunction
- Most common associations are TORCH (*to*xoplasmosis, *r*ubella, *c*ytomegalovirus and *h*erpes virus) infections in neonates and myelofibrosis in adults
- Widely disseminated erythematous to violaceous papules and nodules, with neonatal form referred to as "blueberry muffin baby"
- Diffuse dermal infiltrate of immature erythrocytes, leukocytes and megakaryocytes

Epidemiology

Extramedullary hematopoiesis (EMH) is most commonly seen in neonates secondary to underlying bone marrow dysfunction. It may occur in adults with myeloproliferative disorders such as myelofibrosis or after splenectomy.

Pathogenesis

Cutaneous EMH occurs normally during early embryogenesis and abates prior to birth. Thereafter, it occurs only as a secondary phenomenon in response to altered bone marrow function. Rarely, primary cutaneous neoplasms such as pilomatricomas, nevus sebaceus, hemangiomas, and pyogenic granulomas may be associated with localized extramedullary hematopoiesis[20].

Clinical features

The clinical presentation consists of erythematous to violaceous papules and nodules which may ulcerate. When widely disseminated in neonates, it leads to the classic "blueberry muffin baby" (Fig. 121.6). This can be seen in association with congenital viral infections and prenatal anemias (Table 121.4). Dermal hematopoiesis is most often seen with rubella and cytomegalovirus, and serologic titers for TORCH infections can aid in diagnosis.

Pathology

Extramedullary hematopoiesis is characterized by a dermal infiltrate of immature red and white blood cell precursors and megakaryocytes, centered around vessels of the superficial vascular plexus. It may also extend into the deeper reticular dermis and exhibit a diffuse pattern. All three hematopoietic cell lines are present in varying ratios, depending upon the underlying disease process.

Fig. 121.6 Extramedullary hematopoiesis. "Blueberry muffin baby" secondary to congenital rubella. *Courtesy, James Graham, MD.*

DIFFERENTIAL DIAGNOSIS OF "BLUEBERRY MUFFIN BABY"

- Disseminated extramedullary hematopoiesis
  - Prenatal infections
    - TORCH
      - Congenital rubella
      - Cytomegalovirus
      - Toxoplasmosis
    - Coxsackievirus
    - Parvovirus
  - Severe and chronic prenatal anemias
    - Severe hemolytic anemias
      - Congenital spherocytosis
      - Rhesus hemolytic disease
      - ABO incompatibility
    - Twin–twin transfusion
    - Chronic fetomaternal hemorrhage
    - Severe internal bleeding (e.g. intracranial)
    - Myelodysplasia, congenital leukemia
- Congenital leukemia cutis
- Neonatal neuroblastoma
- Congenital Langerhans cell histiocytosis
- Congenital alveolar cell rhabdomyosarcoma
- Hemangiomatosis, other vascular lesions (e.g. multifocal lymphangioendotheliomatosis, glomuvenous malformations)

Table 121.4 Differential diagnosis of "blueberry muffin baby".

Differential diagnosis

Histologically, the differential diagnosis is limited. Distinguishing EMH from disseminated congenital leukemia cutis and neonatal neuroblastoma is important. Whereas all three hematopoietic cell lines (erythrocytes, leukocytes and megakaryocytes) are represented in EMH, there is an atypical infiltrate of immature leukocytes in leukemia cutis. Patients with overwhelming marrow involvement by leukemia may have both EMH and leukemic involvement of the skin, further complicating the diagnosis.

Treatment

Treatment of the underlying bone marrow dysfunction results in reversal of the cutaneous process. Spontaneous resolution can occur with some viral infections.

MALIGNANT HEMATOPOIETIC INFILTRATES

LEUKEMIA CUTIS

Key features

- Red to purple papules and nodules; hemorrhagic ulcers
- Diffuse dermal infiltrate of neoplastic leukocytes
- Immature precursor cells in some types

Epidemiology

Multiple types of leukemia exist, each with its own epidemiologic characteristics. Acute lymphoblastic leukemia (ALL) tends to be a neoplasm of childhood. Acute myelogenous leukemia (AML) and chronic myelogenous leukemia (CML) occur primarily in adults, and chronic lymphocytic leukemia (CLL) and hairy cell leukemia are most common in elderly patients.

Pathogenesis

Specific chromosomal abnormalities are associated with particular subtypes of leukemia. The Philadelphia chromosome, the primary diagnostic feature of CML, represents a translocation between chromosomes 9 and 22 [t(9;22)]. This translocation results in fusion of the two genes *BCR* and *ABL*, with constitutive activation of the tyrosine kinase activity of the fusion oncoprotein. It is this kinase activity that is selectively inhibited by imatinib mesylate (Gleevec®). Additionally, 95% of patients with promyelocytic leukemia have a t(15;17) translocation, which leads to abnormal expression of a fusion retinoic acid receptor that is the target of all-*trans* retinoic acid therapy. A variety of non-random chromosomal abnormalities exists in ALL and AML. Table 121.5 outlines the relationship between specific abnormalities and prognosis in CLL.

Clinical features

Leukemia can lead to nonspecific reactive skin lesions (Table 121.6) or specific infiltrates. The latter most commonly present as firm papules

RELATIONSHIP BETWEEN SPECIFIC CHROMOSOMAL ABNORMALITIES AND PROGNOSIS IN CHRONIC LYMPHOCYTIC LEUKEMIA

Chromosomal abnormalities	Prognosis
13q deletion	Good
Trisomy 12	Intermediate
6q deletion	Poor
11q deletion	Poor
17p deletion	Poor

Table 121.5 Relationship between specific chromosomal abnormalities and prognosis in chronic lymphocytic leukemia.

"INFLAMMATORY" DISORDERS ASSOCIATED WITH ACUTE AND CHRONIC LEUKEMIAS	
Disorder	**Associated leukemias**
NEUTROPHILIC DERMATOSES	
Sweet's syndrome	AML > CML, hairy cell leukemia, CNL > ALL, CLL
Pyoderma gangrenosum*	AML, CML, hairy cell leukemia > ALL, CLL
Neutrophilic eccrine hidradenitis	AML >> ALL, CML, CLL
REACTIVE ERYTHEMAS	
Exaggerated arthropod reactions	CLL
Erythroderma	CLL†
VASCULITIS	
Polyarteritis nodosa	Hairy cell leukemia >> CMML
Vasculitis (small vessel/ leukocytoclastic)	Hairy cell leukemia, CLL > AMML, ALL
Erythema elevatum diutinum	Hairy cell leukemia, CLL
PANNICULITIS	
Erythema nodosum‡	AML, CML, CMML
Other panniculitides§	Hairy cell leukemia, AML, CMML
OTHER	
Erythema multiforme#	CLL
Urticaria	CLL, hairy cell leukemia
Paraneoplastic pemphigus	CLL
Recalcitrant adult-onset eczema	CLL (T cell)
Acral ischemia with lividity	CML¶

*Especially bullous.
†Many probably represented Sézary syndrome.
‡Isolated case reports; may occur concomitantly with Sweet's syndrome.
§Sweet's syndrome may have a subcutaneous component.
#May have represented paraneoplastic pemphigus.
¶Leukostasis/hyperleukocytosis syndrome.

Table 121.6 "Inflammatory" disorders associated with acute and chronic leukemias[21–25]. ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; AMML, acute myelomonocytic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; CMML, chronic myelomonocytic leukemia; CNL, chronic neutrophilic leukemia.

and nodules (Fig. 121.7) that are frequently hemorrhagic; thrombocytopenia often plays a role in this associated hemorrhage. Ulcerative and rarely bullous lesions occur. Leukemia cutis can develop in any location, but the head, neck and trunk are most commonly involved. Leukemic infiltrates may arise at sites of trauma or scars.

Rarely, myelogenous leukemias may present with dermal nodules known as chloromas, granulocytic sarcomas or extramedullary myeloid tumors. Granulocytic sarcomas may precede the development of systemic leukemia by months. Gingival hyperplasia, secondary to leukemic infiltrates, favors acute monocytic or acute myelomonocytic leukemia.

In one series, cutaneous eruptions of leukemia accounted for 30% of all skin biopsy specimens in patients with leukemia[21]. Other diagnoses included GVHD, drug eruptions, infectious processes, purpura and small vessel vasculitis. In most patients with acute leukemia, cutaneous lesions are present at the time of diagnosis or recurrence, but, occasionally, skin involvement precedes the appearance of leukemia in the peripheral smear ("aleukemic" leukemia cutis). Rarely, leukemia cutis predates apparent bone marrow involvement by months or even years. Of note, asymptomatic dermal leukemic infiltrates of CLL may be evident in biopsy specimens of primary cutaneous neoplasms (e.g. squamous cell carcinoma) and inflammatory disorders[22].

The characteristics of the different forms of leukemia cutis are summarized in Table 121.7.

Fig. 121.7 Leukemia cutis. Multiple red–brown papules and plaques in a patient with hairy cell leukemia.

Pathology

Histologic features of leukemia cutis vary with the type of leukemia. The neoplastic infiltrate may be perivascular, nodular and diffuse, or densely surrounding the eccrine glands[23,24].

AML represents a neoplastic proliferation of immature myeloid cells and encompasses multiple subtypes[26]. In general, the neoplastic cells recapitulate myeloid precursor cells in their immature stages of development. In many cases, cytoplasmic granules can be found. A chloroacetate esterase stain is helpful in detecting myeloid differentiation, but in very immature precursor cells, granules may not be present. The most common forms of AML that involve the skin and present *de novo* (without previous evidence of systemic disease) are the more mature subtypes – acute myelomonocytic and acute monocytic leukemia. Immunohistochemically, the infiltrates of AML are positive for myeloid markers such as myeloperoxidase, CD13, CD33 and CD68.

ALL represents a clonal expansion of immature lymphocytes, most commonly of B-cell lineage and less commonly T-cell lineage. Rarely, cytoplasmic granularity may be present, and this corresponds with a precursor B-cell immunophenotype. Cells of ALL may be difficult to identify in skin biopsy specimens and immunostaining for terminal deoxytransferase may prove helpful.

CML demonstrates a range of myeloid precursors, including promyelocytes, metamyelocytes, bands and mature neutrophils. Although cutaneous lesions of CML are rare, they are typically seen in patients with chronic myelomonocytic leukemia and are associated with blast transformation and a poor prognosis.

Cutaneous CLL is characterized by a dense infiltrate of uniform-appearing, small, round lymphocytes of B-cell lineage (Fig. 121.8). The infiltrating cells appear mature, but the monomorphous nature and paucity of other cell types within the infiltrate suggest a leukemic infiltrate. The lymphocytes often surround adnexal and vascular structures with the infiltrates having prominent crush artifact. Immunohistochemically, CLL shows positivity for CD5, CD20, and CD43[25].

Differential diagnosis

The clinical differential diagnosis includes lymphoma cutis, infectious emboli, vasculitis and drug eruptions. The histologic differential diagnosis of leukemia cutis depends upon the type of leukemia present. Distinguishing some cases of leukemia cutis from lymphomas involving the skin can be difficult. For myeloid leukemias, the differential diagnosis includes extramedullary hematopoiesis (see above), Sweet's syndrome, cutaneous small vessel vasculitis and other neutrophilic dermatoses. Recognizing immature and atypical granulocytic precursors within leukemic infiltrates allows the distinction from reactive neutrophilic infiltrates.

CHARACTERISTICS OF DIFFERENT TYPES OF LEUKEMIA CUTIS				
SUBTYPE OF LEUKEMIA	**ALL**	**CLL**	**AML**	**CML**
Characteristic age	Predominantly <6 years of age	6th decade or older	Variable, most commonly 5th decade	Variable, most commonly 5th–6th decade
Presenting anatomic site	Variable	Predominantly head and neck, but can occur at any site	Variable	Variable
Clinical course	Aggressive	Indolent	Aggressive	Intermediate*
Subtype of leukemia/ immunophenotype	• Predominantly B-cell ALL (TdT^+/ $CD5^+$/$CD19^+$/$CD20^+$/$CD10^+$) • Rarely T-cell ALL (TdT^+/$CD1a^+$/ $CD2^+$/$CD3c^+$/$CD5^+$/$CD7^+$)	• B-cell type ($CD5^+$/ $CD20^+$/ $CD43^+$)	• Most commonly, AMML (M4) & AMoL (M5) • $CD13^+$/$CD33^+$/$CD68^+$/ myeloperoxidase-positive	• Most commonly, CMML • Cutaneous involvement associated with blast transformation
Incidence of cutaneous involvement	Rare	Rare†	• More common than other types • May be presenting sign	Rare
Time of presentation	Late	Late‡	Early	Late
Clinical appearance	• Large, nonulcerated tumors • Nonspecific papulonodules	• Nonspecific papulonodules • Rarely, erythroderma	Nonspecific papulonodules	• Nonspecific pruritic papules, plaques and nodules • Rarely, vitiligo-like presentation unless patient is receiving imatinib

*When acceleration or blast transformation occurs, becomes aggressive.
†Often an incidental finding in biopsy specimens of primary cutaneous neoplasms (e.g. squamous cell carcinoma) and inflammatory disorders.
‡Unless incidental finding.

Table 121.7 Characteristics of different types of leukemia cutis. Most patients with CML who develop vitiligo-like changes are receiving imatinib. ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; AMML, acute myelomonocytic leukemia; AMoL, acute monocytic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; CMML, chronic myelomonocytic leukemia.

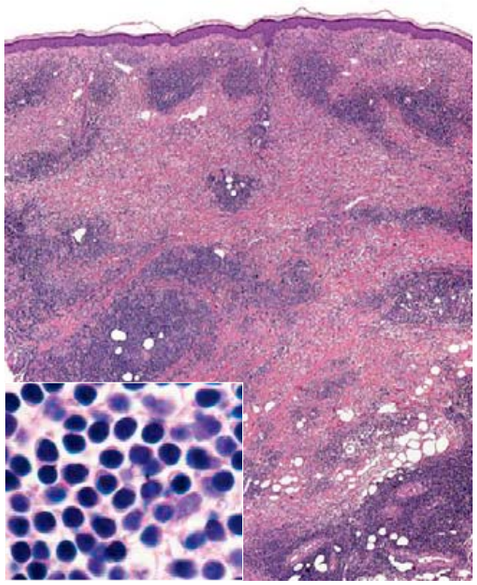


Fig. 121.8 Chronic lymphocytic leukemia (CLL). Nodular-diffuse CLL infiltrates within the entire dermis and superficial subcutis. The cells in CLL are small, monomorphous, hyperchromatic lymphocytes that lack significant cytologic atypia (insert). *Courtesy, Lorenzo Cerroni, MD.*

Treatment

No specific treatment for leukemia cutis currently exists. The cutaneous eruptions typically resolve following successful treatment of the leukemia.

NON-B-CELL, NON-T-CELL LYMPHOMAS

Hodgkin Disease

Synonym: ■ Hodgkin lymphoma

Key features

- Advanced stage in most patients with skin involvement
- Dermal nodules and plaques, sometimes ulcerated
- Dense dermal infiltrate with lymphocytes and eosinophils
- Atypical cells (lacunar cells, Reed–Sternberg cells)

History

In 1832, Thomas Hodgkin described a series of patients with lymphadenopathy, splenomegaly and weight loss, all of whom died of their disease. Wilks reported a subsequent series of patients in 1885, and designated the illness Hodgkin's disease.

Epidemiology

Isolated cutaneous involvement by Hodgkin disease (HD), termed "specific cutaneous Hodgkin's" by Grosz in 1906, is unusual[27]. In one large study, only 0.5% of patients with HD had cutaneous involvement and the development of specific skin lesions prior to apparent nodal disease is rare[28]. Individuals with isolated (primary) cutaneous HD may follow a more indolent course than their systemic counterparts, even with the subsequent development of nodal involvement. In the majority of patients, however, cutaneous involvement occurs in the setting of advanced systemic disease and is a marker of poor prognosis.

The incidence of HD peaks in young adults, with a second, smaller peak in individuals in their fifties. Of note, compared to the general population, mycosis fungoides is seen at higher rates in patients with HD. This reflects the increased incidence of non-Hodgkin lymphomas in general in HD patients. The underlying reason for this phenomenon is not known[29].

Pathogenesis

The pathogenesis of HD is unknown, although Epstein–Barr virus (EBV) has been detected in a minority of cases[30]. Evidence suggests that in the majority of patients with classic HD, the Reed–Sternberg cell represents a malignant B lymphocyte; however, in isolated cutaneous cases, evidence suggests that the malignant cells are of a T-cell lineage[31].

Clinical features

Isolated cutaneous HD presents as one or several papules, plaques or ulcerated nodules with no site predilection. Signs of systemic involvement (e.g. hepatosplenomegaly, lymphadenopathy) and constitutional symptoms (e.g. fevers, chills, night sweats) may not develop. There are scattered reports of spontaneous regression of primary lesions.

The most common presentation is that of multiple, disseminated papulonodules and plaques appearing rapidly in a patient with known, advanced disease. Cutaneous lesions often occur at sites distal to

affected lymph nodes. The trunk is the most common site of involvement (Fig. 121.9).

In 20–50% of patients with HD, paraneoplastic cutaneous disorders can develop. These include primary pruritus, acquired ichthyosis, persistent dermatitis, hyperpigmentation and, occasionally, erythema nodosum.

Pathology

The histologic features of cutaneous HD (primary or secondary) are similar to affected lymph nodes. A dermal infiltrate consisting of lymphocytes with occasional eosinophils and plasma cells is present; epidermotropism is not seen. Depending upon the histologic subtype, Reed–Sternberg cells (or mononuclear variants) (Fig. 121.10) and lacunar cells may be present. The latter, most common in the nodular sclerosing subtype of HD, are large cells with abundant eosinophilic cytoplasm. The retraction of this cytoplasm from adjacent cells during fixation gives rise to a giant cell residing within a clear space. Areas of dermal sclerosis may be seen and extension into the subcutaneous fat is common.

Reed–Sternberg cells express CD30 (Ki-1), fascin and CD15, but not CD45RB (leukocyte common antigen) or CD20. The background infiltrate of lymphocytes is composed predominantly of T cells[31]. In lymphocyte-predominant HD, the malignant cells may stain positively for CD20.

Fig. 121.9 Cutaneous Hodgkin disease. A large pink plaque with central clearing is noted on the lower abdomen. The small ulceration represents the site of a previous skin biopsy.

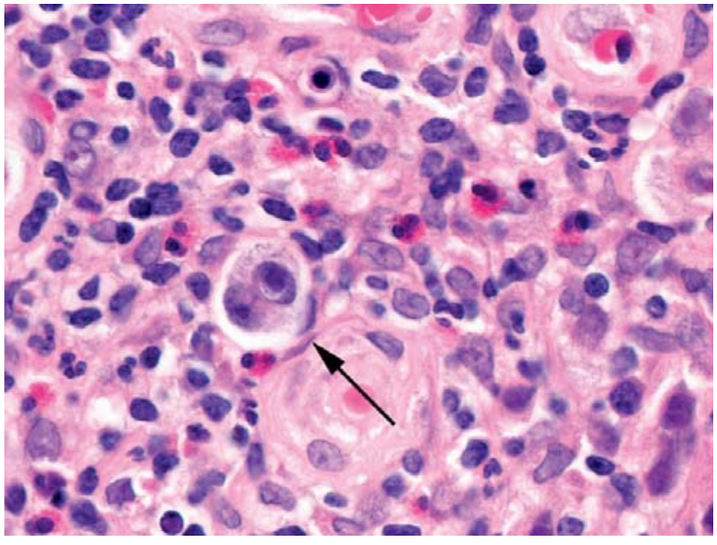


Fig 121.10 Cutaneous Hodgkin disease. Polymorphic infiltrate with lymphocytes, eosinophils, histiocytes, and a Reed–Sternberg cell (arrow). *Courtesy, Lorenzo Cerroni, MD.*

Differential diagnosis

The histologic differential diagnosis of HD includes primary cutaneous anaplastic large cell lymphoma (C-ALCL) and lymphomatoid papulosis (LyP) (see Ch. 120). Clinicopathologic correlation is important in differentiating between these entities. Both LyP and C-ALCL can present with variably ulcerated papules and nodules, but patients with LyP do not have evidence of systemic involvement (unless there is a concomitant lymphoma) and crops of their lesions appear and then spontaneously resolve. Patients with C-ALCL rarely have nodal involvement. In contrast, primary cutaneous HD is not just very rare, but nearly all patients with cutaneous involvement have advanced systemic disease.

All three entities demonstrate a mixed infiltrate with varying numbers of large $CD30^+$ atypical cells, but, in HD, unlike the other two, the cells also express CD15. In C-ALCL, the majority of the infiltrate is composed of malignant cells (with a relatively small number of reactive inflammatory cells) and the infiltrate tends to be deeper than in LyP. The majority of the neoplastic cells of C-ALCL are $CD4^+$; ALK expression is variable. In LyP, the infiltrate is more heterogeneous, with fewer large atypical cells. Like in C-ALCL, the atypical cells in LyP are $CD4^+$, $CD45^+$ and $CD30^+$, but $CD15^-$.

Treatment

Although the number of cases reported is small, the prognosis for patients with primary cutaneous HD appears to be similar to (or perhaps better than) that of patients with classic early-stage HD. Many patients do not develop systemic disease. Patients with stage IV HD, who may have secondary cutaneous disease, have a cure rate of approximately 60–70% following combination chemotherapy[32].

Blastic Plasmacytoid Dendritic Cell Neoplasm

Synonyms: ■ Blastic plasmacytoid dendritic cell lymphoma ■ $CD4^+$/$CD56^+$ hematodermic neoplasm ■ Blastic NK-cell lymphoma

Key features

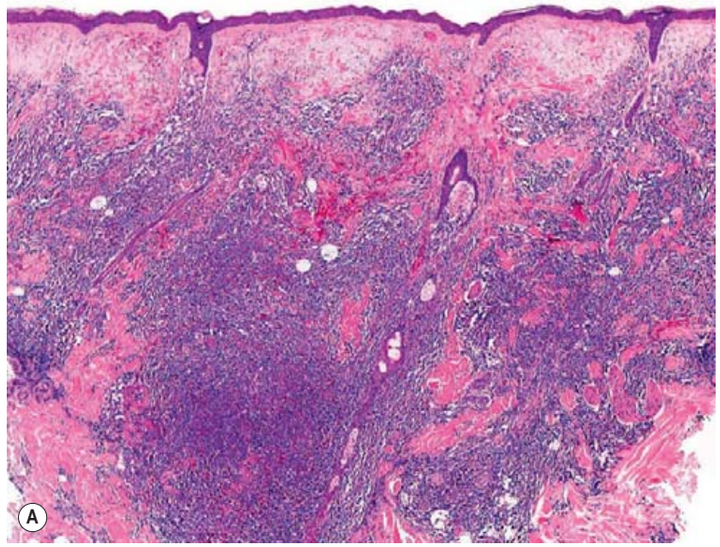
- Single to multiple, non-tender papules, nodules and plaques
- At initial presentation, skin is the most common site of involvement
- Dense perivascular infiltrate of uniformly atypical medium-sized mononuclear cells
- Immunohistochemical profile: $CD123^+$, $CD4^+$, $CD56^+$
- T-cell receptor (TCR) and IgH gene rearrangements are not present
- Predictable good initial response to chemotherapy, with relapses common and poor survival

History and epidemiology

In 1994, blastic plasmacytoid dendritic cell neoplasm (BPDCN) was described by Adachi et al.[33] as a $CD4^+$/$CD56^+$ lymphoma presenting predominantly in the skin. Initially classified as blastic NK-cell lymphoma due to its CD56 expression, this rare tumor was subsequently reclassified, first as a hematodermic neoplasm and then as a neoplasm of plasmacytoid dendritic cells.

BPDCN is a disease of adults, usually those over the age of 50 years. The male-to-female ratio is 3:1 and rare pediatric cases have been reported.

Fig. 121.11 Blastic plasmacytoid dendritic cell neoplasm. Two firm violaceous nodules on the cheek. *Courtesy, Lorenzo Cerroni, MD.*



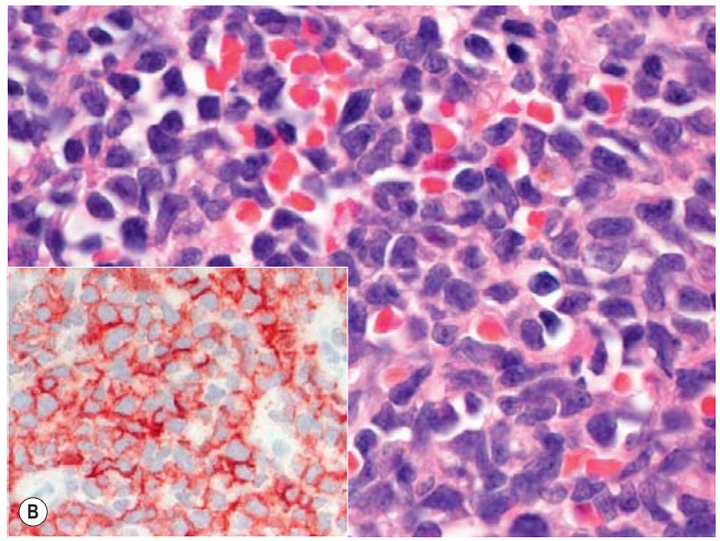


Fig. 121.12 Blastic plasmacytoid dendritic cell neoplasm. A Dense diffuse infiltrates of monomorphous blastoid cells within the entire dermis, without involvement of the epidermis. **B** Diffuse infiltrate of medium-sized blastoid mononuclear cells admixed with extravasated erythrocytes; positive immunohistochemical staining for CD56 (insert). *Courtesy, Lorenzo Cerroni, MD.*

Pathogenesis

A BPDCN arises within the interfollicular zones of peripheral lymphoid tissue, an area that plays a crucial role in the first-line response to various pathogens. Plasmacytoid dendritic cells produce large amounts of type I interferons (IFN), specifically IFN-α, and they express several Toll-like receptors (e.g. TLR7, TLR9), making them critical in the defense against viruses and other pathogens[34].

Clinical features

Clinically, BPDCN presents as solitary or multiple, non-tender, variably pruritic, erythematous to violaceous papules, plaques or nodules (Fig. 121.11). In 50% of patients, the skin is the presenting site of involvement. However, further evaluation usually reveals subclinical regional lymph node, peripheral blood and bone marrow involvement in a majority of patients[35]. Symptoms of fevers, chills, night sweats or weight loss are uncommon at presentation but may develop with disease progression.

Pathology

A diffuse dermal infiltrate of monotonous, atypical, medium-sized mononuclear cells is seen (Fig. 121.12). These cells have fine blastic chromatin, indistinct nucleoli and scant agranular eosinophilic cytoplasm. There are numerous mitoses, but neither necrosis nor angioinvasion. In early lesions, the dense infiltrate may be perivascular and periadnexal. A grenz zone is often present and the infiltrate commonly extends into the subcutis.

Immunohistochemical studies are necessary to establish the diagnosis. The cells are $CD4^+$, $CD56^+$, $CD123^+$, $TCL1^+$, $BDCA2^+$, and myeloperoxidase-negative; TdT is variably positive. TCL1, an Akt kinase regulator expressed in non-neoplastic B cells and plasmacytoid dendritic cells, is positive in 90% of BPDCNs. These tumors have nonspecific chromosomal aberrations[36] and are negative for EBV. There are descriptions of aberrant $CD4^-$ or $CD56^-$ cases[36].

Differential diagnosis

The differential diagnosis includes AML and other cutaneous lymphomas. BPDCN, however, lacks IgH and TCR gene rearrangements and has a characteristic immunohistochemical profile (see above). In addition, there are subtypes of AML that may express CD4 and CD56 and can present in the skin (without evidence of systemic disease), but expression of CD123, TCL1, BDCA2 and CD2-associated protein (CD2AP) points to the diagnosis of BPDCN[37]. Of note, there are isolated reports of patients with BPDCN developing associated AML.

Treatment

Initial treatment of BPDCN usually consists of multidrug chemotherapeutic regimens. Although response rates are high (up to 80%), relapse followed by progression is common, with the overall survival rate ranging from 12 to 17 months. For that reason, eligible patients are offered autologous or allogeneic hematopoietic stem cell transplantation. Favorable prognostic factors include a $CD7^-/TdT^+$ phenotype, a young age, and disease limited to the skin[38].

ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA

Synonyms: ■ Angioimmunoblastic lymphadenopathy ■ Angioimmunoblastic lymphadenopathy with dysproteinemia ■ Immunoblastic lymphadenopathy ■ Lymphogranulomatosis X

Key features

- Constitutional symptoms (fever, sweats, weight loss)
- Variable cutaneous manifestations, including morbilliform erythema, urticaria and, rarely, erythroderma
- Polyclonal gammopathy, autoantibodies, hemolytic anemia, thrombocytopenia, eosinophilia and pleural effusions
- Generalized lymphadenopathy and hepatosplenomegaly
- Most commonly, a superficial perivascular infiltrate with eosinophils, but not atypia of the lymphocytes

History

This disease was initially described in 1974 as angioimmunoblastic lymphadenopathy with dysproteinemia, and its features included generalized lymphadenopathy, hepatosplenomegaly, polyclonal hypergammaglobulinemia, and a hemolytic anemia[39].

Epidemiology

Angioimmunoblastic T-cell lymphoma (AITCL) is a rare disease of the middle-aged and elderly, with a nearly equal incidence in men and women[26].

Pathogenesis

Formerly, AITCL was considered to be an atypical reactive process or an abnormal immunologic reaction, until non-random chromosomal abnormalities, clonal rearrangements of the TCR, and progression to an aggressive lymphoma were frequently noted. Currently, it is classified as a subtype of peripheral T-cell lymphoma in the World Health Organization (WHO) Classification of Haematopoietic Tumours[26].

Clinical features

Patients with AITCL usually present at an advanced stage with fever, weight loss, night sweats, generalized lymphadenopathy, and hepatosplenomegaly[26,40]. Approximately one-half of the patients have cutaneous manifestations. The most common presentation is a widespread morbilliform erythema that resembles a viral exanthem[41]. Other cutaneous findings include petechiae (often associated with thrombocytopenia), urticaria, purpura and, rarely, erythroderma. Generalized pruritus may be a presenting symptom. AITCL has an aggressive behavior, with a median survival of <3 years[26].

Pathology

The histopathologic features vary[41], with five patterns described to date. These include: (1) a superficial perivascular infiltrate composed of eosinophils and lymphocytes that lack atypia (most common pattern); (2) a sparse perivascular infiltrate with atypical lymphocytes; (3) a dense superficial and deep infiltrate of pleomorphic lymphocytes; (4) a vasculitis, with or without atypical lymphocytes; and (5) necrotizing granulomas[42]. Similar to involved lymph nodes, the skin may have increased vascularity with hyperplastic endothelial cells. The immunohistochemical profile supports a nonspecific T-cell phenotype ($CD2^+/CD3^+/CD5^+$ with $CD4^+$ lymphocyte predominance). Although EBV-positive B cells are frequently seen within involved lymph nodes, EBV is rarely detected in the skin[40,42].

Differential diagnosis

The morbilliform nature of the eruption belies its malignant nature. Consequently, confusion with a drug eruption or viral exanthem is common. As cutaneous histologic changes are subtle, a specific diagnosis often cannot be rendered.

Treatment

Few prognostic factors exist and the majority of patients present with stage III–IV disease[40,43]. In a recent prospective, randomized clinical trial, in which most of the 157 patients received various intensive anthracycline-based chemotherapeutic regimens, there were no observable differences amongst the varying regimens, even with the addition of hematopoietic stem cell transplantation[43]. Despite achieving a complete response in 46% of patients following induction therapy, the 5- and 7-year survival rates were 33% and 29%, respectively.

LYMPHOMATOID GRANULOMATOSIS

Key features

- EBV-driven angiocentric/destructive lymphoproliferative disorder
- Presents with cough, dyspnea, chest pain and constitutional symptoms
- Cavitary pulmonary nodules on chest radiograph
- Nodular or ulcerative cutaneous lesions in 25–50% of patients

History

Lymphomatoid granulomatosis was first described in 1972 as a pulmonary angiitis/granulomatosis mimicking Wegener's granulomatosis. Initially thought to represent a reactive process, subsequent studies demonstrated a malignant clonal B-cell population admixed with an abundant, polyclonal, reactive T-cell population[44].

Epidemiology

Lymphomatoid granulomatosis is a rare disease of adults, usually presenting in the fifth to sixth decade of life. The male-to-female ratio is approximately 2 : 1. The disease can affect children, most commonly in the setting of immunodeficiency syndromes.

Pathogenesis

The pathogenesis of lymphomatoid granulomatosis is often related to EBV infection, occasionally in combination with immunosuppression. Based upon case reports, immunosuppressive factors associated with lymphomatoid granulomatosis include renal transplantation, Wiskott–Aldrich syndrome, HIV infection and X-linked lymphoproliferative syndrome[44].

Clinical features

Patients with lymphomatoid granulomatosis present with symptoms related to pulmonary involvement, such as cough, dyspnea and chest pain. Constitutional symptoms include fever, weight loss, malaise, arthralgias and myalgias. Cutaneous lesions develop in 25–50% of patients and usually present as nodules or ulcerated plaques (Fig. 121.13). Rarely, lymphomatoid granulomatosis may present as an exanthem of macules and papules. The kidney, brain and gastrointestinal tract may be affected. In contrast to angioimmunoblastic T-cell lymphoma, the lymph nodes and spleen are rarely involved.

Pathology

Lesions of lymphomatoid granulomatosis show nodular lymphoid infiltrates composed of lymphocytes, plasma cells and large atypical mononuclear cells with convoluted nuclei and prominent nucleoli. These infiltrates surround and invade arteries and veins. Granulomatosis, as defined by necrosis within lymphoid aggregates in the absence of granuloma formation, is a distinct and prominent feature. The atypical cells stain with the B-cell markers CD20 and CD79a, and EBV DNA can be detected via *in situ* hybridization.

Differential diagnosis

The clinical differential diagnosis includes various forms of cutaneous lymphoma, as well as infectious and inflammatory disorders (e.g.

Fig. 121.13 Lymphomatoid granulomatosis. Ulcerated violaceous plaque in the popliteal fossa. *Courtesy, Jean L Bolognia, MD.*

medium vessel vasculitis, pyoderma gangrenosum). The histologic differential diagnosis is broad and encompasses most of the lymphoproliferative disorders mentioned above, including B-cell and T-cell lymphomas. Other disorders with histologic evidence of granulomatosis (as defined above) include Wegener's granulomatosis, sarcoidosis and infectious processes. Diagnosis is based upon histopathologic findings plus immunohistochemical and molecular analyses.

Treatment

Lymphomatoid granulomatosis follows an aggressive course, with 5-year mortality ranging from 60% to 90%. Treatment commonly involves multidrug chemotherapy and/or rituximab (anti-CD20 monoclonal antibody), and, for milder cases, IFN-α. Reversal of exogenous immunosuppression may also lead to clinical improvement[44].

REFERENCES

1. Jessner M, Kanof NB. Lymphocytic infiltration of the skin. Arch Dermatol. 1953;68:447–9.
2. Toonstra J, Wildschut A, Boer J, et al. Jessner's lymphocytic infiltration of the skin. A clinical study of 100 patients. Arch Dermatol. 1989;125:1525–30.
3. Ziemer M, Eisendle K, Muller H, Zelger B. Lymphocytic infiltration of the skin (Jessner-Kanof) but not reticular erythematous mucinosis occasionally represents clinical manifestations of *Borrelia*-associated pseudolymphoma. Br J Dermatol. 2009;161:583–90.
4. Noider S, Casper C, Kuhn A, Petereit HF. Jessner-Kanof lymphocytic infiltration of the skin associated with glatiramer acetate. Mult Scler. 2005;11:245–8.
5. Schepis C, Lentini M, Siragusa M, Batolo D. ACE-inhibitor-induced drug eruption resembling lymphocytic infiltration (of Jessner-Kanof) and lupus erythematosus tumidus. Dermatology. 2004;208:354–5.
6. Poenitz N, Dippel E, Klemke CD, et al. Jessner's lymphocytic infiltration of the skin: a CD8+ polyclonal reactive skin condition. Dermatology. 2003;207:276–84.
7. Ardavanis A, Orphanos G, Skafida S, et al. Coincidental successful treatment of Jessner–Kanof disease with chemotherapy. Ann Oncol. 2008;19:1360–1.
8. Borges da Costa J, Boixeda P, Moreno C. Pulsed-dye laser treatment of Jessner lymphocytic infiltration of the skin. J Eur Acad Dermatol Venereol. 2008;23:595–6.
9. Albrecht J, Fine LA, Piette W. Drug-associated lymphoma and pseudolymphoma: recognition and management. Dermatol Clin. 2007;25:233–44.
10. Albrecht J, Fine LA, Piette W. Drug-associated lymphoma and pseudolymphoma: Recognition and management. Dermatol Clin. 2007;25:233–44.
11. Litt's Drug Eruption and Reference Manual Database. Available at: www.drugeruptiondata.com/. Accessed April 12, 2011.
12. Callot V, Roujeau J-C, Bagot M, et al. Drug-induced pseudolymphoma and hypersensitivity syndrome: Two different clinical entities. Arch Dermatol. 1996;132:1315–21.
13. Arai E, Shimizu M, Hirose T. A review of 55 cases of cutaneous lymphoid hyperplasia: reassessment of the histopathologic findings leading to reclassification of 4 lesions as cutaneous marginal zone lymphoma and 19 as pseudolymphomatous folliculitis. Hum Pathol. 2005;36:505–11.
14. Nihal M, Mikkola D, Horvath N, et al. Cutaneous lymphoid hyperplasia: a lymphoproliferative continuum with lymphomatous potential. Hum Pathol. 2003;34:617–22.
15. Arai E, Okubo H, Tsuchida T, et al. Pseudolymphomatous folliculitis: a clinicopathologic study of 15 cases of cutaneous pseudolymphoma with follicular invasion. Am J Surg Pathol. 1999;23:1313–19.
16. Kazakov DV, Belousova IE, Kacerovska D, et al. Hyperplasia of hair follicles and other adnexal structures in cutaneous lymphoproliferative disorders. Am J Surg Pathol. 2008;32:1468–78.
17. Atwater AR, Longley BJ, Aughenbaugh WD. Kikuchi's disease: case report and systematic review of cutaneous and histopathologic presentations. J Am Acad Dermatol. 2008;59:130–6.
18. Paradela S, Lorenzo J, Martinez-Gomez W, et al. Interface dermatitis in skin lesions of Kikuchi-Fujimoto's disease: a histopathological marker of evolution into systemic lupus erythematosus? Lupus. 2008;17:1127–35.
19. Benchikhi H, Bodemer C, Fraitag S, et al. Treatment of cutaneous lymphoid hyperplasia with thalidomide: report of two cases. J Am Acad Dermatol. 1999;40:1005–7.
20. Vega Harring SM, Niyaz M, Okada S, Kudo M. Extramedullary hematopoiesis in a pyogenic granuloma: a case report and review. J Cutan Pathol. 2004;31:555–7.
21. Desch JK, Smoller BR. The spectrum of cutaneous disease in leukemias. J Cutan Pathol. 1993;20:407–10.
22. Cerroni L, Zenahlik P, Höfler G, et al. Specific cutaneous infiltrates of B-cell chronic lymphocytic leukemia. A clinicopathologic and prognostic study of 42 patients. Am J Surg Pathol. 1996;20:1000–10.
23. Traweek ST, Arber DA, Rappaport H, Brynes RK. Extramedullary myeloid cell tumors. An immunohistochemical and morphologic study of 28 cases. Am J Surg Pathol. 1993;17:1011–19.
24. Longacre TA, Smoller BR. Leukemia cutis. Analysis of 50 biopsy-proven cases with an emphasis on occurrence in myelodysplastic syndromes. Am J Clin Pathol. 1993;100:276–84.
25. Plaza JA, Comfere NI, Gibson LE, et al. Unusual cutaneous manifestations of B-cell chronic lymphocytic leukemia. J Am Acad Dermatol. 2009;60;772–80.
26. Jaffe ES, Harris NL, Stein H, Vardiman JW. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. World Health Organization Classification of Tumours. Lyon, France: IARC Press, 2001.
27. Introcaso CE, Kantor J, Porter DL, Junkins-Hopkins JM. Cutaneous Hodgkin's disease. J Am Acad Dermatol. 2008;58:295–8.
28. Smith JL Jr, Butler JJ. Skin involvement in Hodgkin's disease. Cancer. 1980;45:354–61.
29. Rubenstein M, Duvic M. Cutaneous manifestations of Hodgkin's disease. Int J Dermatol. 2006;45:251–6.
30. Vasef MA, Kamel OW, Chen Y-Y, et al. Detection of Epstein-Barr virus in multiple sites involved by Hodgkin's disease. Am J Pathol. 1995;147:1408–15.
31. Kadin ME, Drews R, Samel A, et al. Hodgkin's lymphoma of T cell type: clonal association with a CD30+ cutaneous lymphoma. Hum Pathol. 2001;32:1269–72.
32. Tesch H, Diehl V, Lathan B, et al. Moderate dose escalation for advanced stage Hodgkin's disease using the bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone scheme and adjuvant radiotherapy: a study of the German Hodgkin's Lymphoma Study Group. Blood. 1998;92:4560–7.
33. Adachi M, Maeda K, Takekawa M, et al. High expression of CD56 (N-CAM) in a patient with cutaneous CD4-positive lymphoma. Am J Hematol. 1994;47:278–82.
34. Marafioti T, Paterson JC, Ballabio E, et al. Novel markers of normal and neoplastic human plasmacytoid dendritic cells. Blood. 2008;111:3778–92.
35. Cota C, Vale E, Viana I, et al. Cutaneous manifestations of blastic plasmacytoid dendritic cell neoplasm – morphologic and phenotypic variability in a series of 33 patients. Am J Surg Pathol. 2010;34:75–87.
36. Kaune KM, Baumgart M, Bertsch HP, et al. Solitary cutaneous nodule of blastic plasmacytoid dendritic cell neoplasm progressing to overt leukemia cutis after chemotherapy: immunohistology and FISH analysis confirmed the diagnosis. Am J Dermatopathol. 2009;31:695–701.
37. Ascani S, Massone C, Ferrara G, et al. CD4-negative variant of CD4+/CD56+ hematodermic neoplasm: description of three cases. J Cutan Pathol. 2008;35:911–15.
38. Weaver J, Hsi ED. CD4+/CD56+ hematodermic neoplasm (blastic NK-cell lymphoma). J Cutan Pathol. 2008;35:975–7.
39. Frizzera G, Moran EM, Rappaport H. Angio-immunoblastic lymphadenopathy with dysproteinemia. Lancet. 1974;1:1070–3.
40. Park B-B, Ryoo B-Y, Lee JH, et al. Clinical features and treatment outcomes of angioimmunoblastic T-cell lymphoma. Leuk Lymphoma. 2007;48:716–22.
41. Martel P, Laroche L, Courville P, et al. Cutaneous involvement in patients with angioimmunoblastic lymphadenopathy with dysproteinemia: a clinical, immunohistological, and molecular analysis. Arch Dermatol. 2000;136:881–6.
42. Jayaraman AG, Cassarino D, Advani R, et al. Cutaneous involvement by angioimmunoblastic T-cell lymphoma: a unique histologic presentation, mimicking an infectious etiology. J Cutan Pathol. 2006;33:6–11.
43. Mourad N, Mounier N, Briere J, et al. Clinical, biologic, and pathologic features in 157 patients with angioimmunoblastic T-cell lymphoma treated within the Groupe d-Etude des Lymphomes de l'Adulte (GELA) trials. Blood. 2008;111:4463–70.
44. Jaffe ES, Wilson WH. Lymphomatoid granulomatosis: pathogenesis, pathology and clinical implications. Cancer Surv. 1997;30:233–48.

This page intentionally left blank

Cutaneous Metastases 122

Matthew B Zook, Hong Wu and Stuart R Lessin

Key features

- Cutaneous metastases are uncommon and rarely they may be the presenting sign of an internal malignancy
- In general, cutaneous metastases are associated with a poor prognosis
- In women, breast carcinoma and melanoma are the most common malignancies that metastasize to the skin
- In men, melanoma and head and neck, lung and colon carcinomas are the most common malignancies that metastasize to the skin
- Among common malignancies, breast carcinoma is the most likely and prostate carcinoma is the least likely to metastasize to the skin
- The most common clinical presentation for a cutaneous metastasis is a firm, painless, erythematous nodule
- Cutaneous metastases may arise in the anatomic vicinity of the primary cancer
- Cutaneous metastases typically have histologic features similar to, but not identical to, those of the primary malignancy
- Treatments include excision, chemotherapy, immunotherapy and radiotherapy; the latter is often administered for palliation

INTRODUCTION

Given their prognostic implications, cutaneous metastases represent an important dermatologic entity. The skin is not a particularly common site for metastatic spread, and because the clinical appearance of cutaneous metastases can mimic more common disorders, e.g. epidermoid inclusion cysts (inflamed and non-inflamed), lipomas, cellulitis, there may be a delay in diagnosis. An understanding of the clinical spectrum as well as advances in histological assessment of skin metastases is vital to establishing the correct diagnosis.

EPIDEMIOLOGY

Depending upon the series, cutaneous metastases occur in 1% to 10% of patients with metastatic disease (to any organ)[1,2]. While unusual, their recognition is important because they can be the first sign of extranodal metastatic disease and, as a result, have profound prognostic implications. The proportion of patients with metastatic disease who have cutaneous metastases depends upon the particular malignancy, e.g. the highest incidence is in individuals with metastatic melanoma, where up to 45% of patients can develop skin metastases (Table 122.1)[2]. Gender-specific cancer rates also influence the frequency of the various types of cutaneous metastases. In women, skin metastases from breast carcinoma (70%) and melanoma (12%) are the most common, followed by carcinomas originating from the ovary, head and neck (SCC), and lung[2]. In men with skin metastases, melanoma (32%) and head and neck (16.5%), lung (12%), and colon (11%) carcinoma are the most common primary malignancies. In addition, the overall prevalence of a cancer is an important determinant. For instance, although skin metastases develop in only 2.5% of patients with metastatic lung cancer, they account for 12% of all cutaneous metastases in men due to the high prevalence of lung cancer[2]. Similarly, the age of the patient plays a role, with rhabdomyosarcoma, leukemia and neuroblastoma responsible for the majority of cutaneous "metastases" seen in children[3].

Cutaneous metastases develop an average of 36 months[4] (range, 1 to 177 months)[5] after the initial diagnosis of the primary malignancy. Unfortunately, the vast majority (~95%) of patients with cutaneous metastases have advanced, stage III or IV disease. Rarely, cutaneous metastases can be the presenting sign of an internal malignancy (<1% of all new cancer diagnoses).

PATHOGENESIS

In 1889, Dr Stephen Paget espoused the "seed and soil" hypothesis as the paradigm of metastatic disease – a malignancy must develop the capability to dissociate from its native environment, survive during transit, and then propagate in a new milieu (detachment, intravasation, circulation, stasis, extravasation, and finally proliferation; Table 122.2)[6,7]. It is estimated that that ≤0.01% of tumor cells shed into the vasculature form metastatic foci at distant sites[3,8].

The ability of a malignancy to acquire metastatic potential is thought to occur via one of two mechanisms[9]. In the clonal expansion or linear progression model, selective growth advantages are acquired during the course of tumor development. Over time, subpopulations of cells acquire genetic characteristics that enable them to dissociate and then propagate in distant tissues. In this model, metastatic foci have similar phenotypes and genotypes to the original tumor. Alternatively, in the

CUTANEOUS METASTASES IN PATIENTS WITH METASTATIC CANCER

Primary malignancy	Percentage of all patients with metastatic disease who developed cutaneous metastases*	Percentage of all patients with cutaneous metastases*
Melanoma	45	18
Breast	30	50
SCC (head and neck)†	13	7
Endocrine glands	12.5	1
Esophagus	8.5	1
Urinary bladder	8	1.5
Unknown	7.5	4.5
Gallbladder/bile ducts	5.5	<1
Liver	5	<1
Kidney	4.5	<1
Colon/rectum	4.5	4
Ovary	4	2.5
Lung	2.5	5
Endometrium	2	<1
Stomach	2	<1
Pancreas	2	<1
Uterine cervix	1	<1
Prostate	<1	<1
Testes	<1	<1

*The percentages are for men and women combined.
†Larynx, oropharynx, nasal sinuses.

Table 122.1 Cutaneous metastases in patients with metastatic cancer. Rates of metastatic spread do vary depending upon the series. Adapted from ref. 2.

DIFFERENT STAGES OF METASTASIS – UNDERLYING FACTORS	
Stage of metastasis	**Factors**
Detachment	E-cadherin, integrins
Intravasation	Matrix metalloproteinases, other proteases, N-cadherin
Circulation	Vascular endothelial growth factor (VEGF)
Stasis	Mechanical forces
Extravasation	Pseudopod formation
Proliferation	Chemokines, growth factors, genetic & epigenetic changes

Table 122.2 Different stages of metastasis – underlying factors.

rare variant or parallel progression model, rare, highly aggressive stem cell-like clones with high metastatic potential exist within the tumor and can cause dissemination at any point during tumorigenesis.

It is generally accepted that certain cancers tend to metastasize to distinct tissues. The mechanism by which they choose their final destination is related to hemostatic forces and surface protein expression patterns. When tumor emboli lodge in the first vascular bed they encounter, adhesion molecule interactions (e.g. integrins) facilitate extravasation and account for the commonly noted involvement of regional nodal basins. Yet, certain cancers have an affinity for specific tissues that are not anatomically convenient, such as prostate cancer spreading to bone or ocular melanoma to the liver[1]. Adhesion molecule expression seems likely to influence this tissue-specific homing of metastases. However, these mechanisms may be attenuated in highly aggressive, undifferentiated tumors that display a random distribution of metastases.

ANATOMIC LOCATION OF CUTANEOUS METASTASES			
Anatomic site	**Primary malignancy (men)**	**Primary malignancy (women)**	**Comments**
Scalp	Lung, renal	Breast	Can lead to alopecia
Face & neck	SCC of the head & neck*, lung	Breast	Eyelid metastases from breast carcinoma have been reported; breast & lung metastases can lead to a "clown nose"
Upper extremities	Lung, kidney, colon	Breast	Uncommon site in men and usually occurs late during disease
Lower extremities	Melanoma > lung, kidney	Melanoma > lung, kidney	Uncommon site: 36% of BSA but site of only 4% of metastases
Chest	Lung	Breast	
Abdomen	Colon, lung, stomach	Colon, ovary, breast	Sister Mary Joseph nodule: most commonly gastric, colon, ovarian or pancreatic cancers
Back	Lung	Breast	20% of BSA, but site of 8% of metastases
Pelvis	Colon	Colon, ovary	Site of 8% of cutaneous metastases

*e.g. larynx, oropharynx, nasal sinuses.

Table 122.3 Anatomic location of cutaneous metastases. The trunk is the most common site (~55% of metastases) and the scalp is the site of ~15% of metastases[1]. BSA, body surface area; SCC, squamous cell carcinoma. Adapted from refs 9 & 10.

CLINICAL FEATURES

When a patient with a known history of cancer presents with an extremely firm and rapidly growing erythematous nodule or an eruption of multiple nodules, the diagnosis of cutaneous metastasis is relatively straightforward. However, the clinical lesions may be more slowly progressive or they may mimic more common entities, from lipomas or dermatitis to erysipelas and ulcers. Occasionally, cutaneous metastases may even be the presenting sign of an unknown primary tumor. Therefore, for a number of reasons, there may be a delay in diagnosis. Hopefully, an appreciation of the spectrum of clinical presentations will lead to an improvement in diagnostic accuracy.

Location can be a clue to the diagnosis of cutaneous metastases. For example, in patients with cutaneous melanoma, satellitosis and in-transit metastases have a clear relationship to the primary site and its lymphatic drainage (see Ch. 113). Papules vary in color from pink to blue to black and initially may require palpation for detection. In addition to hematogenous and lymphatic spread of metastases, there can also be direct extension of a malignancy, especially SCC of the head and neck and breast carcinoma; in this situation, the site of involvement aids in the differential diagnosis (Table 122.3). Occasionally, implantation of tumor occurs at the time of a surgical procedure, e.g. chest tube placement for a malignant pleural effusion due to lung cancer, and the location plus the relationship to a scar point to the correct diagnosis. Lastly, certain malignancies favor particular anatomic sites, e.g. the periumbilical region (Sister Mary Joseph nodule; Fig. 122.1) for gastrointestinal malignancies.

As discussed in the section on epidemiology, the propensity of a particular malignancy to metastasize to the skin (see Table 122.1), prevalence of the specific carcinoma in the population, gender and age all play a significant role in determining which malignancies are most likely to metastasize to the skin. In addition, certain metastases can have a more unique clinical appearance, e.g. both Paget's disease and extramammary Paget's disease may resemble dermatitis, and renal carcinoma metastases may have the appearance of bright red vascular tumors and/or bleed easily (Table 122.4). However, "classic" presentations are not necessarily the most common presentation and a more generic clinical appearance is always possible (e.g. pink papulonodules). Occasionally, cutaneous metastases, including those of renal origin, may have a zosteriform distribution pattern (Fig. 122.2).

Fig. 122.1 Cutaneous metastasis of colon carcinoma. A Sister Mary Joseph nodule presenting as a pink plaque with scale-crust.

Of all the carcinomas metastatic to the skin, breast cancer may be the one with the widest range of clinical presentations (see Table 122.4). Due to its high prevalence in the population and its propensity to metastasize to the skin (lymphatic, hematogenous and direct extension), breast cancer accounts for 70% of cutaneous metastases in women[2]. The presentations vary from papulonodules to patches of erythema mimicking erysipelas (inflammatory carcinoma) to marked induration with a *peau d'orange* appearance (given the name "*en*

CLINICAL PRESENTATIONS OF CUTANEOUS METASTASES AND HISTOLOGIC CORRELATES			
Type	**Clinical description**	**Histology**	**Associated primary malignancy**
Dermal or subcutaneous nodules	Small miliary lesions to large tumors; single or multiple	Tumor cells infiltrating among collagen bundles or replacing dermis; Grenz zone often present	Most common presentation; any type
Inflammatory carcinoma (carcinoma erysipeloides)	Erythematous patch with spreading border; resembles erysipelas	Tumor cells within dilated lymphatic vessels	Breast >> lung, ovary, prostate, GI, others
En cuirasse	Morpheaform or sclerodermoid, depending upon extent; indurated with *peau d'orange* appearance	Fibrosis with infiltrating tumor cells	Breast >> lung, GI, kidney, others
Carcinoma telangiectodes	Red–violet papules	Tumor cells within superficial lymphatics and RBC sludging	Breast
Paget's disease*	Patches extending from the nipple and areola that resemble dermatitis	Large, atypical epithelial cells with abundant pale cytoplasm arranged in solitary units and small nests within all layers of the epidermis	Breast
Alopecia neoplastica	Nodules or plaques on the scalp in association with alopecia	Cords of tumor cells between collagen bundles	Breast > lung, renal, others
Pyogenic granuloma-like	Rapidly growing nodule resembling a vascular tumor (particularly a pyogenic granuloma)	Neoplastic cells in cords and lobules admixed with prominent hemorrhage and "pseudovascular" spaces	Renal clear cell carcinoma, hepatocellular carcinoma > others

*Lesions of extramammary Paget's disease share similar histopathologic features with those of Paget's disease of the breast, but usually represent (>75% of patients) primary cutaneous adenocarcinomas (see Ch. 73); an underlying visceral malignancy is most likely when there is perianal involvement.

Table 122.4 Clinical presentations of cutaneous metastases and histologic correlates. An individual patient can have an admixture of the various types. Occasionally, cutaneous metastases have a zosteriform distribution pattern and clinically they can resemble dermatoses, including eczema, vasculitis and erythema annulare centrifugum. Obviously, they can also mimic cutaneous tumors, including non-melanoma skin cancers, epidermoid or pilar cysts, lipomas, granular cell tumors or angiosarcoma[5]. GI, gastrointestinal; RBC, red blood cell.

Fig 122.2 Cutaneous metastases of renal cell carcinoma. Pink plaques in a zosteriform pattern on the flank.

HISTOLOGIC CLUES TO THE DIAGNOSIS OF CUTANEOUS METASTASES
Well-circumscribed dermal or subcutaneous nodules of atypical cells with numerous mitoses and without connection to the epidermis
Presence of atypical cells within lymphatic vessels (differential diagnosis: intravascular lymphoma, intravascular histiocytosis)
Atypical cells arranged in lines within the dermis ("Indian files") (differential diagnosis: myelogenous leukemia)
Presence of necrosis *en masse* at the center of a nodule of atypical cells (differential diagnosis: some lymphomas, some primary cutaneous adnexal carcinomas)

Table 122.5 Histologic clues to the diagnosis of cutaneous metastases. *Courtesy, Lorenzo Cerroni, MD.*

cuirasse" due to its resemblance to the armor of a cavalry soldier [*cuirassier*][1]) (Fig. 122.3). In addition, intralymphatic metastases can lead to vascular-appearing papules that may be confused clinically with the vascular proliferations (including angiosarcoma) that can follow breast irradiation (see Ch. 114).

In addition to metastases from solid organs, patients can also have involvement of the skin by systemic lymphomas and leukemias (see Chs 119–121). The lesions are often pink–violet to red–brown papulonodules and therefore can have an appearance similar to the most common clinical presentation of cutaneous metastases. Distinction of metastases of SCC to the skin and primary cutaneous SCCs can sometimes prove challenging, especially in patients with SCC of the oropharynx or larynx[11].

PATHOLOGY

The initial step in establishing the histologic diagnosis of a cutaneous metastasis is to exclude other entities that may share some common features, e.g. primary cutaneous adnexal carcinomas, cutaneous involvement with myelogenous leukemia[12], and intravascular histiocytosis (benign angioendotheliomatosis) or intravascular lymphoma. Histologic clues to the diagnosis of cutaneous metastases are outlined in Table 122.5. Once the diagnosis of a cutaneous metastasis is suspected, the next step is to try to determine the underlying primary malignancy. The two most common histologic patterns for a cutaneous metastasis are: (1) nodules of tumor cells within the dermis, and possibly the panniculus; and (2) cords of tumors cells admixed with a fibrotic stroma[5]. When these findings are not accompanied by any unique or distinguishing features (Table 122.6), precise identification via routine histology may prove difficult. The clinical analogy would be a patient with a cutaneous metastasis presenting as an erythematous nodule on the trunk. The reason for the difficulty is the number of primary malignancies that can give rise to this histologic picture. If available, a comparison should be made with tissue from previously diagnosed primary tumors. While separation of carcinomas into broad categories, e.g. adenocarcinoma versus SCC, can often be accomplished via routine histology, complete evaluation usually requires the application of a panel of histochemical stains (see Table 122.6).

When evaluating cutaneous metastases histologically, the presence of tumor cells within lymphatics or blood vessels should be noted (Fig. 122.4)[5]. While this pattern is commonly the pathologic correlate of

Fig. 122.3 Various presentations of cutaneous metastases of breast carcinoma. A Eroded erythematous nodules in the axilla. **B** Inflammatory form (carcinoma erysipeloides) with patches of erythema that may initially be misdiagnosed as infectious cellulitis. **C** Primarily *en cuirasse* form with obvious induration and *peau d'orange* appearance in addition to papulonodules. **D** Mixed pattern – reticulated erythema of carcinoma erysipeloides as well as *peau d'orange* appearance near the areola.

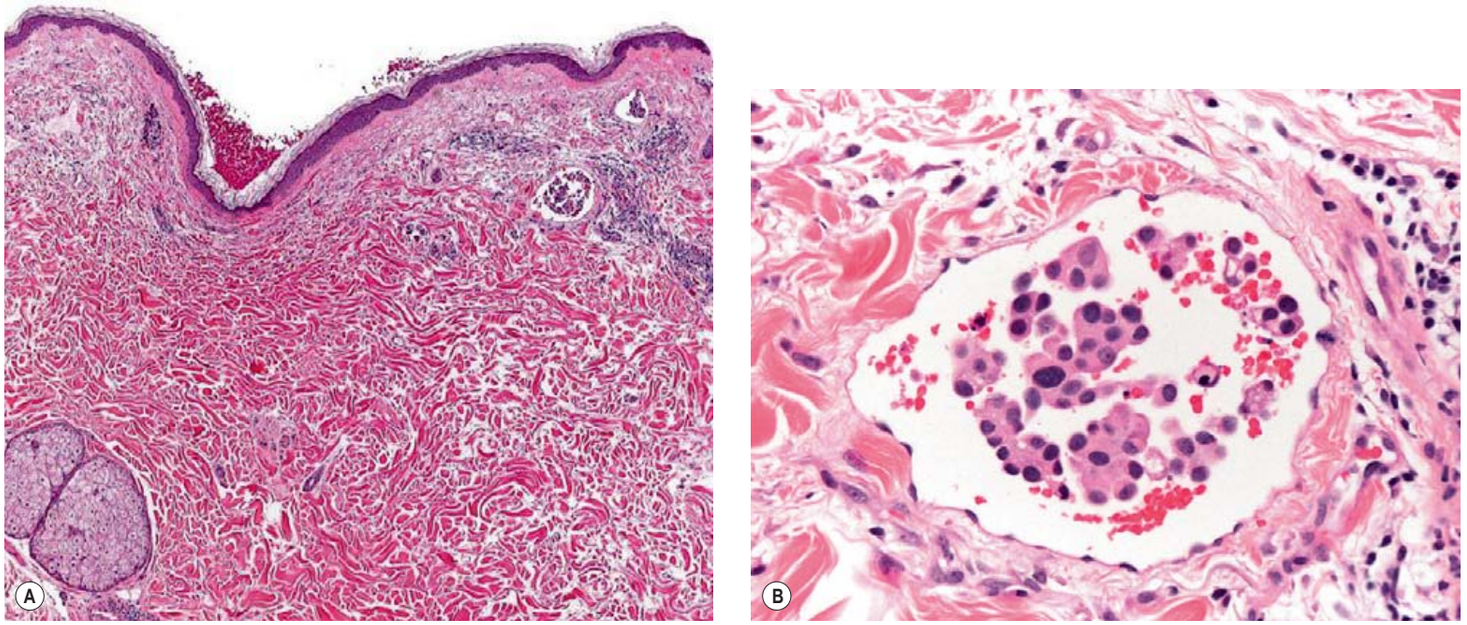


Fig. 122.4 Histopathologic features of cutaneous metastasis of urothelial micropapillary bladder carcinoma. A Complexes of neoplastic cells within dilated lymphatic spaces in the dermis. **B** Detail of a lymphatic space with intravascular tumor complexes admixed with erythrocytes. Neoplastic urothelial (transitional) cells exhibit round–ovoid nuclei and abundant eosinophilic cytoplasm, and they form small rosette-like aggregates. These histopathologic features may simulate a benign condition, namely, intravascular histiocytosis. *Courtesy, Lorenzo Cerroni, MD.*

PATHOLOGIC FINDINGS IN CUTANEOUS METASTASES			
Malignancy	**Histological features**	**Immunohistochemical markers**	**Comments**
Breast	Single filing or cords of cells (lobular CA); tumor cells form glandular structures (ductal CA)	CK7, ER/PR, mammoglobulin, gross cystic disease fluid protein-15 (GCDFP-15)	Breast CA can be ER/PR-negative; GCDFP-15 positivity also seen in cutaneous adnexal and salivary gland tumors; occasionally, ER/PR positivity in non-breast CA
Colon	Columnar cells with basally oriented nuclei and intracytoplasmic mucin production; gland formation; "dirty" necrosis	CK20, CK7, CDX2, villin	Mucinous CA can develop from other tissues (lung, ovary, uterine cervix)
Small cell (including lung)	Nuclear molding, scant cytoplasm, indistinct nucleoli	Keratins, TTF-1, CD56, neuron-specific enolase, chromogranin, synaptophysin	Some small cell CAs, including lung, may not express neuroendocrine markers
Non-small cell lung (adenocarcinoma)	Gland formation	CK7, TTF-1	Non-small cell lung CA can be TTF-1-negative; TTF-1 positivity not limited to lung or thyroid CA
Prostate	Glandular structures formed by cells with prominent nucleoli	PSA, PSAP	High-grade CA may lose glandular differentiation as well as PSA & PSAP expression
Thyroid	Thyroid follicle formation (follicular CA); papillary structure, psammoma bodies (papillary CA)	TTF-1, thyroglobulin	High-grade tumors (insular CA, anaplastic CA) may lose characteristic thyroid gland morphology
Neuroendocrine	Nests of cells with neuroendocrine morphology	Neuroendocrine markers (CD56, chromogranin); medullary thyroid CA: calcitonin & TTF-1	Poorly preserved tissue may resemble lymphoma, carcinoma or small cell CA
Renal (clear cell)	Clear cytoplasm, highly vascular	Coexpression of EMA and vimentin, CD10, RCC-Ma	Other types of renal cell CA do not have prominent clear cells (e.g. sarcomatoid CA)
Ovarian	Psammoma bodies can be seen in papillary serous CA	CA125, CK7, ER/PR, WT-1 (serous CA)	Mucinous ovarian CA may closely resemble other types of mucinous CA
Melanoma	Epithelioid cells with prominent nucleoli	Vimentin, S100, tyrosinase, Melan-A (MART-1), HMB45, MITF	Great morphological mimicker of other tumors; rare undifferentiated melanoma may lose all melanocytic markers
Pancreatobiliary	Well-differentiated glands formed by cells with abundant cytoplasm	CK7, CK20, CA19.9, CA125	CA19.9 is not specific for pancreatobiliary tumors
Stomach	Signet ring cells (signet ring type)	CK7, CK20, CDX2	Non-signet ring cell type gastric CA may not have distinct morphology; signet ring cell CA is not limited to the stomach (e.g. can be seen in breast CA)
Bladder / urothelial	Medium-sized tumor cells arranged in nests or sheets	p63, CK5/6, CK7, CK20	May resemble high-grade cutaneous adnexal CA
SCC	Large cells with intercelllar bridges; keratin pearls	CK5/6, p63, CK903	Small cell SCC variant resembles small cell CA

Table 122.6 Pathologic findings in cutaneous metastases. p63 negativity strongly favors metastases (with the exception of mucinous eccrine carcinoma); for p63-positive tumors, a combined pattern of D2-40 (podoplanin)$^+$, B72.3$^+$, CK5/6$^+$, and calretinin$^-$ immunostains favors metastases[5]. CA, carcinoma; CDX2, homeobox protein CDX2; CK, cytokeratin; EMA, epithelial membrane antigen; ER, estrogen receptor; MITF, microphthalmia transcription factor; PR, progesterone receptor; PSA, prostate-specific antigen; PSAP, prostatic-specific acid phosphatase; RCC-Ma, renal cell carcinoma marker – detects a renal tubule antigen (highly specific); SCC, squamous cell carcinoma; TTF-1, thyroid transcription factor 1; WT-1, product of Wilms tumor gene.

"inflammatory carcinoma" (carcinoma erysipeloides), it can also be seen in other forms of cutaneous metastases, in particular carcinoma "*en cuirasse*". In addition, a search for the presence of distinguishing features such as signet ring cells (most commonly, gastric adenocarcinoma or breast carcinoma; Fig. 122.5)[13], clear cell differentiation (renal clear cell carcinoma; Fig. 122.6), or psammoma bodies (ovarian carcinoma), is always performed. Occasionally, the metastasis may show epidermotropism and the neoplastic cells are contained within the epidermis. In addition to melanoma, this may be seen with metastases from carcinomas of the prostate, breast, colon, larynx, penis and vagina[13]. In rare instances, epidermotropic metastases (particularly from breast carcinoma) may contain pigment and even an intratumoral increase in melanocytes, leading to the misdiagnosis of a melanocytic tumor.

As noted previously, the use of a panel of immunohistochemical stains can assist in determining the underlying primary malignancy and while it is not a substitute for diagnostic imaging and procedures, the resulting information provides direction and can be invaluable in those patients with an unknown primary (so-called cancer of unknown primary [CUP] syndrome). A panel also aids in differentiating a primary cutaneous carcinoma from a metastasis. In the latter situation, a helpful initial panel includes p63, CK5/6, D2-40 (podoplanin), B72.3 (an antibody that stains adenocarcinomas originating from several different organs) and calretinin immunostains in conjunction with appropriate organ-restricted markers (e.g. TTF-1, CDX2; Figs 122.6C & 122.7). In general, p63 negativity strongly favors a metastasis (with the exception of mucinous eccrine carcinoma). For p63-positive tumors, a combined pattern of D2-40$^+$, B72.3$^+$, calretinin$^-$ and CK5/6$^+$ would favor a metastasis[5]. However, panels of immunostains are no substitute for the clinician informing the dermatopathologist of known primary malignancies in a particular patient and diagnostic imaging[14].

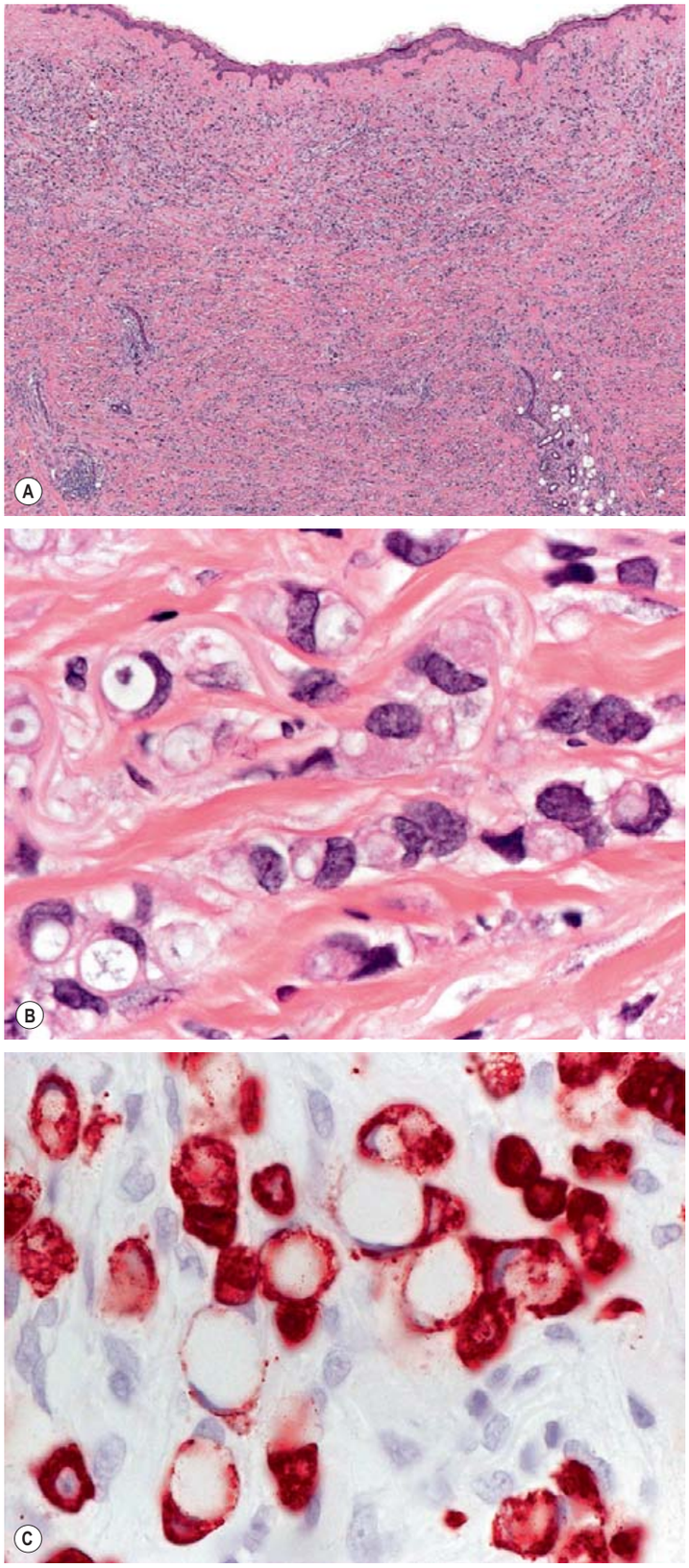


Fig. 122.5 Histopathologic features of cutaneous metastases of signet ring adenocarcinoma of the breast (A,B) and stomach (C). A Diffuse infiltration of neoplastic cells throughout the entire dermis. **B** Detail of neoplastic cells with signet ring cell morphology due to intracellular mucin accumulation. **C** Signet ring cells are not unique to breast carcinoma and may be observed in a variety of adenocarcinomas, particularly those from the gastrointestinal tract; a cytokeratin stain in this metastatic signet ring cell carcinoma of the stomach highlights the peculiar morphology of the cells, with intracellular mucin pressing the nuclei and distorting them, thus conferring the characteristic shape similar to that of a signet ring. *Courtesy, Lorenzo Cerroni, MD.*

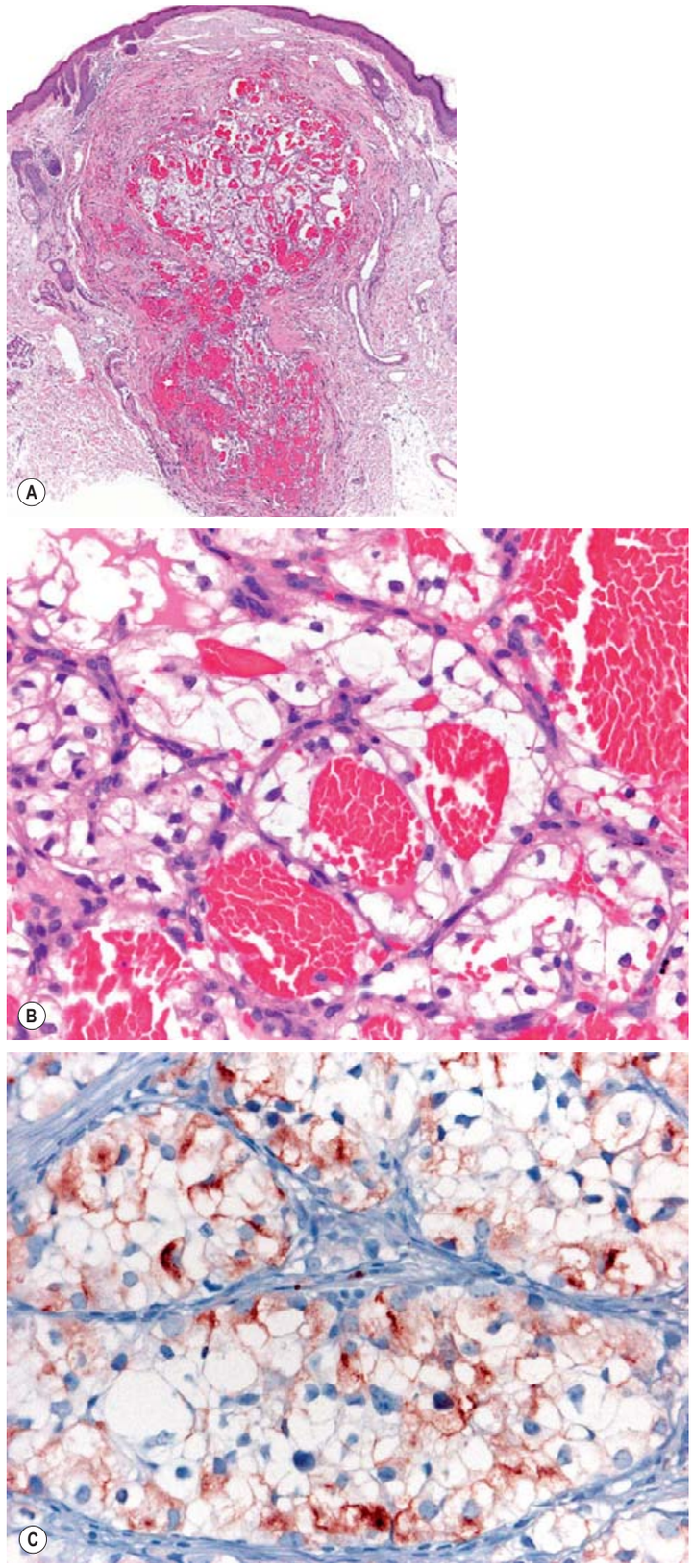


Fig. 122.6 Histopathologic features of cutaneous metastasis from renal clear cell carcinoma. A Vertically oriented hemorrhagic tumor within the dermis resembling an angiomatous tumor. **B** Tumor cells with clear cytoplasm arranged as fine trabecular structures and lobules surrounding hemorrhagic areas. The lack of prominent atypia can be misleading and lead to the erroneous diagnosis of hemangioma. **C** Positive immunohistochemical staining with RCC-Ma (renal cell carcinoma marker), a monoclonal antibody directed against a proximal tubule antigen and highly specific for clear cell renal carcinoma. *Courtesy, Lorenzo Cerroni, MD.*

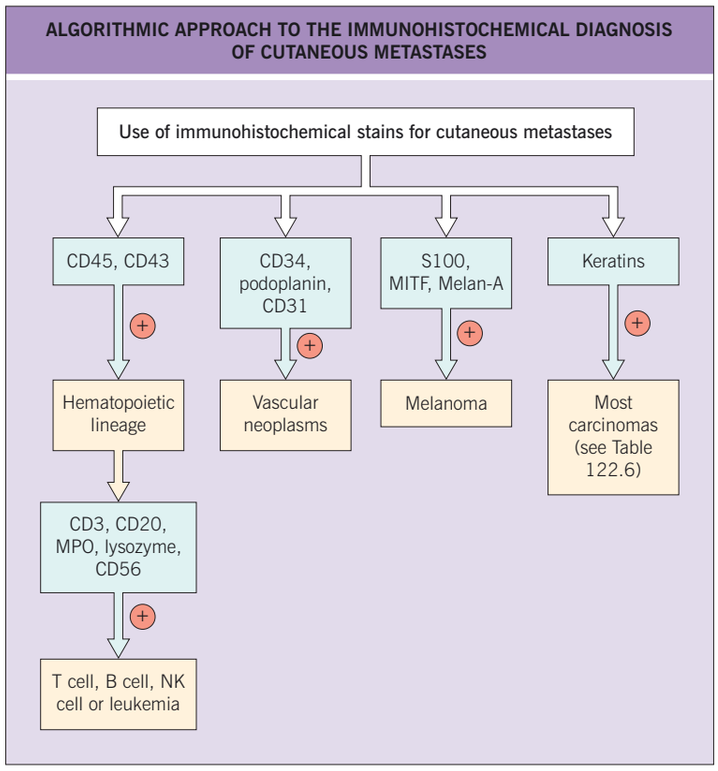


Fig. 122.7 Algorithmic approach to the immunohistochemical diagnosis of cutaneous metastases. See Chapter 0 for explanation of CD markers; MPO, myeloperoxidase. A combination of hematopoietic, vascular, melanocytic and keratinocytic markers allows one to identify the lineage of neoplastic cells in most cases. A more precise classification, particularly of hematopoietic neoplasms and of carcinomas, relies on detailed phenotypic analyses.

TREATMENT AND PROGNOSIS

Typically, cutaneous metastases are a harbinger of late-stage or progressive disease and as such portend a poor prognosis. The average survival time following the initial diagnosis of cutaneous metastasis is 7.5 months[15] and half of the patients expire within the first 6 months[16]. Whether the patient has a known or unknown primary malignancy, the development of cutaneous metastases calls for a multidisciplinary approach, including medical and surgical oncologists, radiation oncologists, and mental health care providers when appropriate. Localized treatment of cutaneous metastases can be undertaken for functional, palliative or cosmetic indications. When feasible, surgical excision is performed; however, radiation and focal chemotherapeutics or immunotherapies can be considered on a case-by-case basis. Systemic therapies are indicated for immuno- or chemotherapy-responsive tumors. When malodorous, topical metronidazole solution (supplied for intravenous use) can be applied via cotton gauze or pump spray once to twice daily.

REFERENCES

1. Rolz-Cruz G, Kim CC. Tumor invasion of the skin. Dermatol Clin. 2008;26:89–102.
2. Lookingbill DP, Spangler N, Helm KF. Cutaneous metastases in patients with metastatic carcinoma: a retrospective study of 4020 patients. J Am Acad Dermatol. 1993;29:228–36.
3. Hussein MRA. Skin metastasis: a pathologist's perspective. J Cutan Pathol. 2009;17:1–20.
4. Nashan D, Lucas Muller M, Braun-Falco M, et al. Cutaneous metastases of visceral tumors: a review. J Cancer Res Clin Oncol. 2009;135:1–14.
5. Sariya D, Ruth K, Adams-McDonnell R, et al. Clinicopathologic correlation of cutaneous metastases: experience from a cancer center. Arch Dermatol. 2008;144:1155–62.
6. Brodland DG, Zitelli JA. Mechanisms of metastasis. J Am Acad Dermatol. 1992;27:1–10.
7. Brodland DG. The life of a skin cancer. May Clinic Proc. 1997;72:475–78.
8. Morgan-Parkes JH. Metastases: mechanisms, pathways, and cascades. Adv Clin Med. 1995;164:1075–82.
9. Klein CA. Parallel progression of primary tumours and metastases. Nat Rev Cancer. 2009;9:302–12.
10. Provost T. Cutaneous metastasis. In: Provost T, Flynn J (eds). Cutaneous Medicine, Cutaneous Manifestations of Systemic Disease. Hamilton, Ont: BC Decker, 2001:357–67.
11. Schwartz RA. Cutaneous metastatic disease. J Am Acad Dermatol. 1995;33:161–82.
12. Wick M. Metastatic neoplasms. In: Patterson J, Wick M (eds). Armed Forces Institute of Pathology Atlas of Tumor Pathology, Series 4. Silver Springs: ARP Press, 2006:201–14.
13. Schwartz RA. Histopathologic aspects of cutaneous metastatic disease. J Am Acad Dermatol. 1995;33:649–57.
14. Azoulay S, Adem C, Pelletier F, et al. Skin metastases from unknown origin: role of immunohistochemistry in the evaluation of cutaneous metastases of carcinoma of unknown origin. J Cutan Pathol. 2005;32:561–6.
15. Saeed S, Keehn CA, Morgan MB. Cutaneous metastasis: a clinical, pathological, and immunohistochemical appraisal. J Cutan Pathol. 2004;31:419–30.
16. Schoenlaub P, Sarraux A, Grosshans E, et al. Survival after cutaneous metastasis: a study of 200 cases. Ann Dermatol Venereol. 2001;128:1310–15.

Localized melanoma metastases. Discrete black papules are present within and at the periphery of the skin graft placed at the excision site. *Courtesy of Ronald P Rapini MD.*

This page intentionally left blank

Public Health and Dermatology 123

Sarah Nakib and Abrar A Qureshi

INTRODUCTION

As a dermatologist walks into the examination room of the patient in Figure 123.1, several differential diagnoses likely come to mind. The patient's history, additional examination findings, and other clues help narrow the differential. In this case, knowing the patient's history of atopic dermatitis lends context to the appearance of punched-out erosions and allows one to arrive at the diagnosis of eczema herpeticum. Therefore, awareness of the epidemiology of a disease, how it is distributed in populations and the factors that influence its distribution can assist with making a diagnosis[1–2a].

Considering the high prevalence of skin conditions, dermatologists have the potential to play an important role in public health research and policy. This chapter seeks to highlight the relevance of dermatologic conditions to public health, the impact epidemiology can have on a dermatology practice, major types of public health studies and terminology used in epidemiology.

THE PUBLIC HEALTH IMPORTANCE OF DERMATOLOGY

Office visits to a dermatologist account for 4% of all outpatient visits, representing the third most common subspecialty ambulatory visit (after ophthalmology and orthopedics). In addition, dermatologic conditions account for approximately 5% to 8% of primary care visits[3–5] and 4% of primary diagnoses made in the emergency room[6]. Additional data on skin conditions addressed in various medical settings are presented in Table 1.

Not only are dermatologic conditions common, but some are becoming more common, with rapidly rising incidence rates. The rate of melanoma increased by approximately 2.6% per year in the US from 1985 to 2007[8]. In addition, some countries have experienced an increase in non-melanoma skin cancers, such as basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs)[9–11].

ROLE OF EPIDEMIOLOGY IN DERMATOLOGY

Epidemiologic studies have yielded information on the etiology, risk factors, natural history, prognosis, incidence, prevalence, and effective treatments of dermatologic diseases. The impact that epidemiologic data can have on patient care and systems-based practice in dermatology is outlined in Table 123.2.

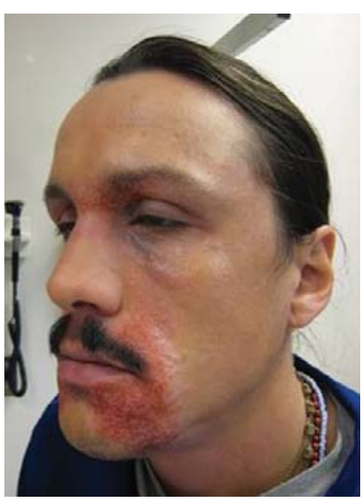


Fig. 123.1 Eczema herpeticum: diagnosis facilitated by knowledge of epidemiology. Grouped vesicles and punched-out erosions are evident. Based on this information alone, eczema herpeticum is in the differential diagnosis. However, awareness of the patient's history of atopic dermatitis, in combination with knowledge regarding the epidemiology of eczema herpeticum, allows for greater certainty in establishing the diagnosis.

OBSERVATIONAL STUDIES

Participants in observational studies are observed and certain outcomes are measured, without external manipulation or an attempt to affect the outcome. Characteristics of different types of observational studies, including the "level of evidence" provided[12,13], are summarized in Table 123.3.

Descriptive Studies

Many of the studies currently being done in dermatology are descriptive. These include case reports and case series. A *case report* is a detailed description of an individual patient's clinical presentation, characteristics (e.g. demographic information), diagnosis, treatment, and disease course. A *case series* reports on some aspect(s) of a disease, diagnostic procedure or treatment in a group of patients with common characteristics[12]. Case reports and series are useful for determining the manifestations of rare conditions, reporting the preliminary outcomes of experimental therapies, and generating hypotheses for larger studies. A major limitation of case series is the lack of a control group, although previous data (e.g. on the prevalence of risk factors in the general population) can sometimes be utilized for comparison.

PUBLIC HEALTH IMPORTANCE OF DERMATOLOGY
• Dermatologist visits account for 4% of all outpatient visits are dermatologist visits (third most common subspecialty visit) • 4.7% to 8.4% of primary care visits are related to dermatologic conditions – Most common conditions addressed (in decreasing frequency) are eczema, infections, benign neoplasms, acne, psoriasis and skin cancer. • 4.2% of primary diagnoses in the ER are diseases of the skin and subcutaneous tissue • In pediatric patients (age < 15 years), "skin rash" accounts for 3.4% of visits to the ER – Common conditions include viral exanthems, urticaria, atopic dermatitis, varicella, diaper dermatitis, herpetic gingivostomatitis

Table 123.1 Public health importance of dermatology. ER, emergency room.

USES FOR EPIDEMIOLOGY IN DERMATOLOGY
EPIDEMIOLOGY APPLIED AT THE PATIENT CARE LEVEL
• Provide context to assist with diagnosis • Give guidance to patients on avoiding triggers and modifiable risk factors for their disease • Provide evidence for management strategies • Prevent associated comorbidities for patients and their families through early screening
EPIDEMIOLOGY APPLIED AT THE SYSTEMS LEVEL
• Raise awareness of the burden and distribution of skin disease in the community • Allow for appropriate allocation of resources for common and emerging conditions • Help in anticipating and addressing future needs • Affect public policy

Table 123.2 Uses for epidemiology in dermatology.

STUDY TYPES AND THEIR CHARACTERISTICS						
Type of study	**Study group**	**Control group**	**Association measure frequently used**	**Advantages**	**Limitations**	**Level of evidence for whether a therapy is efficacious***
Case series	Persons with disease	None	Varies (e.g. percentile)	• Describes rare conditions and therapies	• No control group, no information on background level of exposure for comparison	4
Case–control	Persons with disease	Persons without disease	OR (approximates the RR in rare diseases)	• Can study rare diseases • Short duration, inexpensive, small size	• Potential for bias and confounding because sampling two different populations • Does not establish causal relationship • Limited to one disease	3
Cohort	Persons exposed	Persons not exposed	RR or absolute risk†	• *Causal inference* • Can evaluate a number of diseases • Yields *incidence* of disease • Can study rare exposures	• Often requires a large sample size • Less feasible for rare diseases	2**
Cross-sectional	Persons with disease or exposed	Either of the above	OR or relative prevalence	• Can study several exposures and diseases • Relatively short duration • Yields *disease and exposure prevalence*	• Does not establish causality • Less feasible for rare diseases	2**
Randomized controlled trials (RCTs)	Persons randomized to treatment	Persons randomized to control	Varies (e.g. RR or percentiles)	• Ability to demonstrate causality • Randomization and blinding help to decrease bias or confounding	• Expensive • Can expose participants to potential harm • Answers a narrow clinical question	1

*The level of evidence for a therapeutic efficacy has a scale of 1–5, 1 being the best. Expert opinions represent level 5. The level of evidence for therapeutic efficacy for a systematic review depends on the types of studies it reviews. A systematic review of RCTs with good homogeneity ranks above an individual RCT.

**In general, a cohort study (2b) is ranked as better than a cross-sectional study (2c).

†***Absolute risk reduction*** is the incidence rate of disease in the exposed group subtracted by that of the unexposed group. This is affected by the rate of disease in the population; the greater the prevalence of disease, the higher the absolute risk reduction. The reciprocal of absolute risk reduction is the ***number needed to treat*** to avoid one person getting the disease.

Table 123.3 Study types and their characteristics[2,13,14]. OR odds ratio; RR, relative risk.

An example of a valuable case series is the description of scalp involvement in patients with dermatomyositis by Kasteler and Callen[15]. Fourteen of the 17 patients with dermatomyositis who were seen in the authors' practice over a 5-year period had scalp involvement, manifesting as atrophic, erythematous, scaly plaques. Five of the 14 affected individuals had previously been diagnosed with scalp psoriasis or seborrheic dermatitis. This study helped raise awareness of scalp involvement as a manifestaton of dermatomyositis.

Using Epidemiology to Identify the Cause of Disease

Case–control, cohort, and cross-sectional studies are often performed to help elucidate the etiology and risk factors of a disease. These methods involve studying a disease of interest (e.g. SCC) and an exposure that is suspected of being a risk factor for the disease (e.g. ultraviolet [UV] radiation), so that the study participants can be categorized as having the disease or not and as being exposed to the potential risk factor or not (Table 123.4).

CATEGORIZATION OF STUDY PARTICIPANTS, BASED ON THEIR DISEASE AND EXPOSURE		
	Disease (e.g. SCC)	**No disease (e.g. no SCC)**
Exposed (e.g. high-dose UV)	a	b
Non-exposed (e.g. no high-dose UV)	c	d

Table 123.4 Categorization of study participants, based on their disease and exposure. SCC, squamous cell carcinoma; UV, ultraviolet radiation.

Case–control study

A case–control study identifies a group of individuals with a disease, as well as a comparison group without the disease from the same population. The study design retrospectively evaluates the level of exposure in the disease group (cases), as compared to that in the group without disease (controls). To ensure that those with disease and without are comparable, both types of participants should be sampled from a single population and data collected in the same way for each group[14]. In addition, cases and controls should be matched on possible confounding factors; for example, if there is a 60-year-old female case, then a 60-year-old female control from the same general population would be selected.

A *confounder* is an extraneous variable that is associated with both the exposure and disease being studied; it could therefore account for a part or all of the relationship between the exposure and disease. Although the confounder may be a contributing factor to the disease, it is not caused by the exposure and thus is not along the "causal pathway" between the exposure and disease[1,2] (Figure 123.2). Age and gender are examples of possible confounders. These and other baseline characteristics that may be associated with both the exposure and disease should also be recorded and placed in the statistical model. If an association remains after accounting for confounders, it is more likely to be a true one.

In a case–control study, one can calculate the odds of having had the exposure among those with disease (a/c), as compared to the odds of having had the exposure among those without disease (b/d) (see Table 123.4). The association measure used for case–control studies is an *odds ratio* (OR), which equals (a/c)/(b/d) or ad/bc. An OR = 1 denotes a null association. If it is statistically significantly greater or less than 1, then there is a positive or negative association, respectively. An OR is different from a *relative risk* (RR), the rate of disease among those exposed divided by that among those unexposed, (a/a+b)/(c/c+d), see Cohort study section below. While the RR cannot be directly calculated

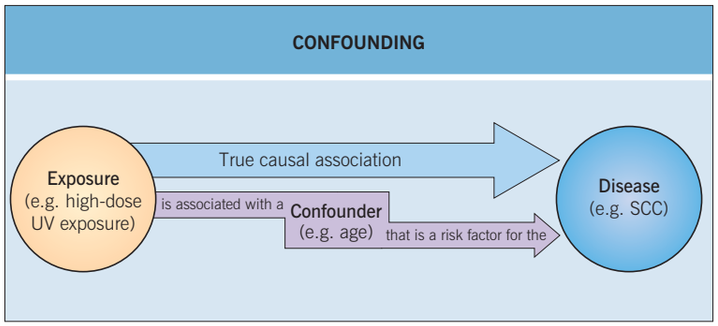


Fig. 123.2 Confounding. The blue arrow represents a true association, in this case a causal one. The purple arrow does not represent a true association, but one found because of confounding. SCC, squamous cell carcinoma; UV, ultraviolet radiation.

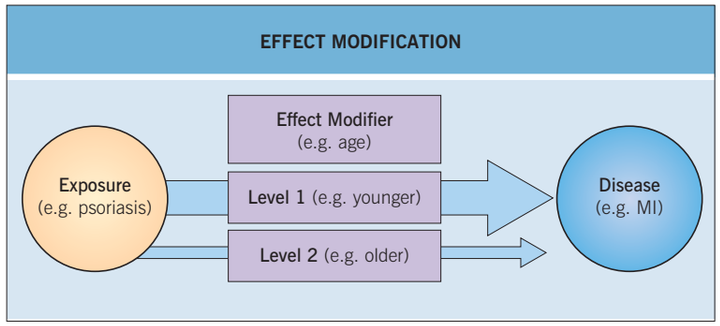


Fig. 123.3 Effect modification. The blue arrow represents a true association, in this case a causal one; the thicker it is, the stronger the association. If a variable causes effect modification, the strength of the association between exposure and disease varies across levels of the effect modifier. In some cases, there may not be an association for a given level of the effect modifier. Age is an effect modifier for many conditions. Interaction represents a similar concept that occurs when the exposure and another variable are interdependent in their effect on disease. MI, myocardial infarction.

from a case–control study, the OR approximates the RR when the disease is rare.

One of the major advantages of a case–control study is that it can yield information on a disease with many possible predictors, using only a limited number of participants. Therefore, it works well for rare conditions. Also, these studies are relatively inexpensive and time-efficient. One of the disadvantages of a case–control study is that it is not clear if the exposure preceded the disease, so causality cannot be established. In addition, this type of study has several potential biases. *Sampling bias* can occur when cases and controls are collected separately and may not be comparable. Because of the retrospective ascertainment of exposure, *recall bias* can occur; for example, those with disease may recall the exposure with greater detail because they have been contemplating the potential causes of their condition. Of note, a case–control study does not yield information on the incidence or prevalence of a disease.

An example of a recent case–control study is that by Lazovich et al.[16], which compared the amount of indoor tanning exposure in patients with cutaneous melanoma (aged 25–59, selected from a statewide cancer registry) to that in age- and gender-matched controls (randomly selected from state driver's license lists). The investigators found that 62.9% of cases and 51.1% of controls had tanned indoors, with an adjusted OR of 1.74 (95% confidence interval [CI] of 1.42–2.14). In other words, after adjusting for potential confounders (e.g. sun exposure and other melanoma risk factors), those with melanoma had a 1.74 times or 74% greater odds of having tanned indoors, when compared to those without melanoma. The 95% CI shows that the OR is statistically significant because it does not include 1.

Cohort study

A cohort study recruits its participants from the general population, and those recruited must be without the disease of interest. Using the example given in Table 123.4, all participants would need to be SCC-free at the onset of the study. They are categorized as having or not having high-dose UV exposure and are then followed over time. At the end of the study, one can calculate the rate of SCC among those with high-dose UV exposure (a/a+b) and compare it to the rate of SCC among those without high-dose UV exposure (c/c+d). Therefore, a cohort study compares the incidence of disease between those exposed and not exposed to particular risk factor(s). This is usually expressed in terms of a RR (see definition above). Similar to an OR, a RR of 1 represents a null association, whereas an RR statistically significantly greater or less than 1 indicates a positive or negative association, respectively. A cohort study can be done prospectively, allowing for more control over measuring outcomes (preferred particularly for fatal diseases), or retrospectively, which is less expensive and requires less time.

One of the advantages of a cohort study is that it can determine the *incidence* of a disease, which is the number of new cases divided by the total number of people at risk in a particular population (e.g. participants in the study) over a specified time period (e.g. length of study)[1]. It also gives information on the natural history of a disease, since it captures data from the time of disease onset. Another advantage is that a cohort study establishes temporality, as the exposure precedes the outcome, and therefore allows for causal inference between the exposure and disease. The disadvantages are that a cohort study often requires a large sample size and is less feasible for rare outcomes.

An example of a recent cohort study is one by Gelfand et al.[17], which looked at the association between psoriasis and risk of myocardial infarction (MI). Here, psoriasis was the "exposure" and MI was the "disease". Their study population comprised persons aged 20 to 90 years of age who saw a general practitioner in the UK. Their results revealed that the incidence of MI per 1000 person-years was 3.58 (95% CI, 3.52–3.65) for the control group, 4.04 (95% CI, 3.88–4.21) for the group with mild psoriasis, and 5.13 (95% CI, 4.22–6.17) for the group with severe psoriasis. After adjusting for potential confounders (e.g. age, gender, smoking, hypertension, diabetes), they found that psoriasis was significantly associated with MI. They also found that age was an effect modifier (see below) in the association between psoriasis and MI. Therefore, they reported the association across strata of age. The adjusted RRs of an MI for 30-year-old patients with mild or severe psoriasis were 1.29 (95% CI, 1.14–1.46) and 3.10 (95% CI, 1.98–4.86), respectively, as compared to controls. In contrast, the adjusted RRs of an MI for 60-year-old patients with mild or severe psoriasis were 1.08 (95% CI, 1.03–1.13) and 1.36 (95% CI, 1.13–1.64), respectively, as compared to controls. This means that a 30-year-old patient with mild psoriasis has a risk of MI that is 1.29 times or 29% greater than that of a 30-year-old person without psoriasis, after controlling for confounding factors.

Effect modification or *interaction* occurs when the association between the exposure and disease varies across levels of a variable (e.g. age; Fig. 123.3). Therefore, the exposure and effect modifier have an interdependent role in their effect on the disease. When this happens, the association between exposure and disease should be displayed at various levels or strata of the effect modifier[1,2].

Cross-sectional study

A cross-sectional study is similar to a cohort study, except that the initial population does not need to be free of the disease of interest and both the exposure and disease are measured in a single time point, without a follow-up period. It yields information on the *prevalence* of disease, which is the number of affected individuals divided by the number of people in the population at risk (e.g. total number of study participants), at a given time. It allows one to study the association between exposure and disease, but it does not provide information about which preceded the other. Its results are often expressed in terms of ORs or *relative prevalence*, which compares the prevalence rate of a disease among those exposed to that among the unexposed. While mathematically it is represented by (a/a+b)/(c/c+d) (see Table 123.4), here a/a+b and c/c+d are prevalence rates, rather than incidence rates as in a cohort study.

The advantages of a cross-sectional study are that it is relatively fast, without requiring follow-up time, and inexpensive. It is the only epidemiologic study that gives the prevalence of a disease, exposure, or other risk factor. One of its weaknesses is that it does not demonstrate temporality, and so it does not establish a causal relationship between the exposure and disease. Also, it is not practical for rare diseases or rare exposures, which would require a very large study population.

An example of a cross-sectional study is one by Love et al.[18], which used a national database representative of the non-institutionalized civilian US population, the National Health and Nutrition Examination Survey. It found that the prevalence of metabolic syndrome was 40% among psoriasis cases, compared to 23% among controls. After adjusting for age, sex, race/ethnicity, smoking status, and C-reactive protein levels, the OR for the association between psoriasis and metabolic syndrome was 1.96 (95% CI 1.01–3.77). Therefore, those with psoriasis had a 1.96 times or 96% greater odds of having metabolic syndrome, as compared to those without psoriasis.

ASSESSING THE EFFICACY OF A PREVENTIVE OR THERAPEUTIC INTERVENTION

Clinical Trials

Unlike most observational studies, clinical trials involve an intervention. In a randomized controlled trial (RCT), participants are randomized to receive the intervention or placebo. Participants can be blinded to their group, as can the observers (double-blinded). The participants are followed for a given period of time, during which disease outcomes and safety are measured. Table 123.5 presents the four phases for testing of new drug therapies. *Intention-to-treat analysis* is then performed, which classifies participants into the intervention group that they were assigned through randomization, rather than the actual intervention that they received (which may vary if participants crossed over into the other intervention group because of non-compliance, side effects, or other reasons). This preserves the randomization of the study design. However, an analysis taking into account the actual intervention received is done as well, for comparison. The outcome measures for a RCT vary according to the outcome of interest (e.g. relative risk, percentile improvement comparison across groups, prognosis measures; Table 123.6). The concept of statistical significance is applied to assess whether the outcomes differed in the treatment and control groups.

The major advantage of a controlled trial is its ability to demonstrate causality (see Table 123.7). Randomization can eliminate confounding effects and blinding can eliminate bias. The disadvantages of this kind of study are that they are relatively expensive and can expose participants to potential harm. In addition, they answer a narrow clinical question. Therefore, RCTs are often reserved for well-developed research questions that are based on previous evidence from smaller or observational studies. Generally, participants in clinical trials should be easy to recruit and have be likely to benefit and unlikely to be harmed from the intervention; participants with a high level of adherence to the treatment and follow-up plan are also desirable. The design of the intervention should balance efficacy and safety, with interim monitoring during the trial to ensure that participants are not exposed to a harmful intervention, denied a beneficial intervention, or continued in a trial that cannot answer the question it was intended to answer. Whenever possible, trials should include comparison with placebo. When comparing active treatments in an equivalence or superiority trial, comparison with the gold-standard treatment for the patient population being studied can maximize the relevance to clinical practice. A well-designed blinded RCT is thought of as the gold standard for study design[13] (see Table 123.3).

An example of a recent RCT was that by Paller et al.[19] to assess the efficacy and safety of etanercept in children and adolescents with moderate to severe plaque psoriasis. It involved randomizing 211 pediatric patients (4 to 17 years of age) with psoriasis to a double-blinded trial of once-weekly subcutaneous injections of etanercept or placebo, for 12 weeks. The primary endpoint was ≥75% improvement from baseline in the psoriasis area and severity index (PASI 75). The patients randomized to receive etanercept were significantly more likely to achieve a PASI 75 (57%) than those receiving placebo (11%) ($P < 0.001$). The authors were able to conclude that etanercept significantly reduced disease severity in children and adolescents with moderate to severe plaque psoriasis.

Systematic Reviews

A systematic review identifies completed studies that address a specific research question and then aggregates and statistically analyzes the

FIVE WAYS OF EXPRESSING PROGNOSIS AND SURVIVAL DATA	
Case-fatality rate	The number who died from the disease of interest divided by the number of those with the disease, used more for short-term acute conditions
Five-year survival	The percentage of patients who are alive 5 years after diagnosis or after treatment begins, often used in evaluating cancer research
Observed survival rate	Expressed in probability of survival each year of the study (e.g. a life table) or based on the time interval from baseline to when a study participant dies (e.g. a Kaplan-Meier plot)
Median survival rate	The length of time at which half of the study population survives, which can be useful for diseases with extremes in survival
Relative survival rate	The observed survival in those with the disease divided by expected survival if the disease were absent

Table 123.6 Five ways of expressing prognosis and survival data. Considering that there are some dermatologic conditions that are fatal, being aware of survival measures is useful[2].

THE FOUR PHASES OF TESTING A NEW DRUG	
Phase I	An unblinded, uncontrolled study, involving a few volunteers, that focuses on a drug's safety and pharmacologic profile
Phase II	A small randomized trial that tests for efficacy, as well as relative safety
Phase III	A larger randomized trial that tests for effectiveness and safety
If the drug passes phase III, it can be approved by the FDA	
Phase IV	A trial or observational study used for post-marketing surveillance to assess the rate of serious side effects and evaluate for additional therapeutic uses

Table 123.5 The four phases of testing a new drug[2,14].

FACTORS THAT STRENGTHEN CAUSAL INFERENCE
Evidence of temporality – i.e. the exposure preceded the disease or outcome
Consistent across other studies and reproducible
A strong association (e.g. the further the RR or OR is from 1), given that it is statistically significant in a well-powered study
A dose–response relationship – i.e. the greater the exposure, the greater the risk of disease
Cessation of the exposure is associated with *decreased risk of disease*
Biological plausibility and *consistency with other scientific knowledge* – i.e. there is a mechanism linking the exposure to the disease that makes sense

Table 123.7 Factors that strengthen causal inference. A well-designed randomized controlled trial provides the best evidence for establishing causality. Cohort studies can infer causality, as the exposure precedes the disease in these studies[2,14]. OR, odds ratio, RR, relative risk.

results across studies, to arrive at a conclusion about a body of research[1]. Although traditionally applied to RCTs, systematic reviews can also be used for observational studies. A systematic review should have a written protocol addressing the research question it seeks to answer, comprehensive and unbiased methods for identifying studies, and a display of the statistical aspects of the review, i.e. meta-analysis. It should also include a summary estimate of effect and confidence interval based on the findings of all eligible studies (Fig. 123.4). In addition, it should have an assessment of heterogeneity across the studies used, to indicate the degree of variability in the findings in different studies. It should address publication bias, to ensure that it has taken into account unpublished studies, as positive studies are more likely to get published. It also usually includes subgroup analyses based on additional measures done by some or all of the studies that are supplemental to the main research question. Analyses to assess how sensitive the findings of the meta-analysis are to decisions taken in designing the study or inclusion of certain studies should be done if any of the design decisions were questionable or arbitrary. Here, the less sensitive the study the better. The characteristics and the findings of individual studies should be displayed clearly in tables and figures to allow the reader to visualize the data and not rely solely on the conclusions of the meta-analysis[2,14].

The advantage of a systematic review is that it enables the integration of the results of multiple studies, allowing for greater power. While it is often time-consuming, it does not require significant financial or other resources. Because it involves intimate knowledge of the literature related to the research question, it can establish the investigator as an expert in the area. In addition, the results are sometimes used to develop practice guidelines. It must be noted that a systematic review is only as valuable as the quality of the studies it is based on. Caution must be exercised in interpreting systematic reviews, with recognition that they may not take into account unpublished studies, the quality of all of the studies may not be equal, studies may not be comparable (e.g. different outcome measures), and adjusting for biases can be a formidable task. In addition, having a single estimate of risk based on that of several studies may give a false sense of certainty regarding the magnitude of the risk[2,14]. A systematic review of RCTs that have homogeneous results gets the highest ranking of all study types[13] (see Table 123.3) however, the level of evidence is considerably lower for systematic reviews limited by the factors discussed above.

The Cochrane Skin Group, which stems from the larger Cochrane Collaboration Group that reviews a variety of healthcare studies, is dedicated to the production of systematic reviews on dermatologic topics[20]. Another example of a systematic review is that done by Warycha et al.[21], which sought to estimate the risk, potential predictors, and outcomes of a positive sentinel lymph node (SLN) biopsy among patients with thin (≤1 mm) melanomas. The rate of SLN positivity was the primary outcome. To conduct this study, the authors searched large databases (MEDLINE, EMBASE and Cochrane databases) for studies on SLN positivity in patients with thin melanoma. They assessed the methodologic quality of studies, heterogeneity, and publication bias through established criteria. They found that there were 34 studies, with 3651 patients, that met inclusion criteria. These studies were mostly descriptive. The pooled SLN positivity rate was 5.6%. There was significant heterogeneity among studies (P=0.005), but no statistical evidence of publication bias (P=0.21). They did a subgroup analysis on 18 studies, and reported the clinical and histopathologic features of thin melanomas in 113 SLN-positive patients. They concluded that relatively few patients with thin melanoma have a positive SLN and that there are no clinical or histopathologic criteria that can reliably predict which patients with thin melanomas will have a positive SLN.

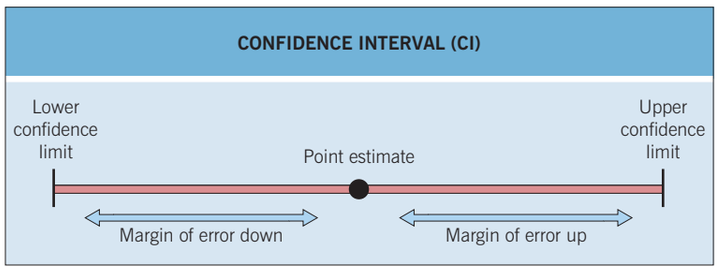


Fig. 123.4 Confidence interval (CI). A confidence interval derived from a valid analysis will, over unlimited repetitions of the study, contain the true parameter 95% of the time.

GENETIC EPIDEMIOLOGY

When considering the etiology of a disease, it is important to account for not only environmental factors but also genetic susceptibility. Because of recent advances in molecular and genetic techniques, epidemiologic studies have expanded to include use of biologic samples. With the completion of the Human Genome Project in 2003 and the International HapMap Project in 2005, researchers in genetic epidemiology are using a technique known as the genome-wide association study (GWAS; see Ch. 54). This technique examines the association between single nucleotide polymorphisms (SNPs), markers for groups of DNA variation inherited together in blocks (haplotypes), and a variety of diseases. Findings from these studies can be used to investigate the molecular pathways of disease. One can look for associations in a hypothesis-driven or non-hypothesis-driven manner.

A study by Petukhova et al.[22] illustrates the use of GWAS techniques to elucidate the pathogenesis of alopecia areata (AA). Using genetic samples from 1054 cases and 3278 controls, they identified 139 SNPs significantly associated with AA ($P \leq 5\times10^{-7}$). They found an association between these SNPs and the genomic regions containing several genes that control the activation of T cells and the production of cytokines. The results of the study implicated both innate and acquired immunity in the pathogenesis of AA and suggested potential autoimmune mechanisms for this condition.

HEALTH SERVICES RESEARCH

The field of health services research applies techniques of epidemiologic investigation to assess the association between health services provided in the community and disease outcomes. Outcomes for this kind of research include traditional endpoints such as mortality and morbidity, as well as others such as usage and access, patient satisfaction, quality of life, and disability measures. It involves the concepts of efficacy, effectiveness and efficiency. *Efficacy* is where an association is demonstrated in an ideal, controlled situation; for example, showing that skin cancer screening in a dermatology office is associated with early detection of skin cancer. *Effectiveness* is finding an association in a "real life", uncontrolled environment, e.g. skin cancer screening in a community setting, such as a booth at the state fair. There may be factors in this environment (but not an ideal setting) that decrease compliance. Finally, once efficacy and then effectiveness are demonstrated, *efficiency*, i.e. cost–benefit ratios, can be evaluated[2].

Quality-of-Life Measures

Quality of life (QOL) has been defined by the World Health Organization (WHO) as "the individuals' perception of their position in life, in the context of the cultural and value systems in which they live and in relation to their goals, expectations, standards and concerns". QOL is an important outcome measure for dermatologic conditions because, while many conditions are not fatal, they can cause significant morbidity in the form of decreased QOL. Patients may place different weights on various QOL measures depending on their personal values, background and education. Therefore, development of a QOL measure that is valid can be challenging. The most commonly used QOL instrument in dermatology is the Dermatology Life Quality Index (DLQI), which has been employed for numerous conditions. It is a self-administered, 10-item questionnaire about the patients' perception of the impact of skin diseases on different aspects of their QOL over the last week[23]. The DLQI has been validated for dermatology patients aged 16 years and above. Its internal consistency has been rated as good to excellent, its test–retest reliability has a high Spearman's correlation coefficient, and the results correlate with those of other QOL instruments (although less so for mental and emotional aspects[24]). Another commonly used QOL instrument in dermatology is the Skindex-29, a 30-item questionnaire that is more comprehensive than

the DLQI. The Skindex-29 is often used in cross-sectional studies for a variety of conditions, especially psoriasis[24].

IMPORTANT CONCEPTS WHEN DESIGNING AND REVIEWING A STUDY

Research Question and Design

There are important concepts to consider when thinking about one's own research and in reviewing that published by others in the literature. These concepts apply to both observational studies and clinical trials (Table 123.8). First, it is important to be aware of the study design needed to best answer the research question of interest. Alternatively, given a certain study design, one must recognize the questions that it can and cannot answer (e.g. a case–control study cannot answer a question about causality).

Methods

When designing or reviewing the methods, it is important to have a control group whenever possible. Also, it is important to consider the types of errors that can affect the study. There are two types of errors, random (due to chance) and systematic. *Systematic errors* are due to bias, "sources of variation that distort the study findings in one direction"[14]. The opposite of systematic errors is validity. Several types of bias that can occur in epidemiologic studies are described in Table 123.9. Some studies are particularly prone to certain types of bias. For example, retrospective studies are especially susceptible to recall bias, a type of information bias (see section on Case–control study). An effort should be made in the study design to decrease systematic errors.

The baseline patient characteristics, exposures, other risk factors, and disease characteristics should be measured reliably and accurately (Fig. 123.5). Information on validity (accuracy) is often expressed using sensitivity and specificity or predictive values. *Sensitivity* represents the likelihood of testing positive for someone who has the disease (a/a+c) (Table 123.10). *Specificity* is the likelihood of testing negative for someone who does not have the disease (d/b+d). These measures yield information on how well we are able to identify those who have or do not have the disease, when we test the general population. A different perspective on the validity of a test is gained through measuring predictive value. This allows us to inform individual patients about what their test results mean. The *positive predictive value* is the likelihood of having the disease when testing positive (a/a+b). The *negative predictive value* is the likelihood of not having the disease when testing negative (d/c+d). Predictive values depend on the prevalence of a disease

IMPORTANT CONSIDERATIONS WHEN REVIEWING A STUDY

Research question and study design	Given the study design, what are the questions it can and cannot answer? See Table 123.3
Methods	• ***Is there a control group?*** • Was an effort made to decrease systematic errors? • Were exposure and disease measured reliably and accurately? • ***Were potential confounders included in the statistical model for the association between exposure and disease?*** • Were tests done looking for effect modification or interaction between the exposure and other study variables (see Fig. 123.3)?
Results	• Are baseline characteristics significantly different across exposure groups, as well as across outcome groups? If so, were these variables adjusted for in the statistical model? • ***Was the correct outcome measure for a given study design used?*** • Is the association statistically significant? (e.g. P value >0.05 or a 95% CI that does not include 1, in the case of a ratio) • Did the study have enough power, usually referring to number of participants, to detect statistical significance?
Conclusions	• ***How strong is the evidence for a causal association?*** (see Table 123.7) • Could a type I error have occurred (false positive) • Could a type II error have occurred (false negative)? • ***What conclusions can be drawn given the type of the study design, its strengths and limitations, including biases*** (see Table 123.3)? • How generalizable are the findings? • Was the study industry-sponsored? • Are the findings compelling enough to affect current clinical practice and the direction of future research?

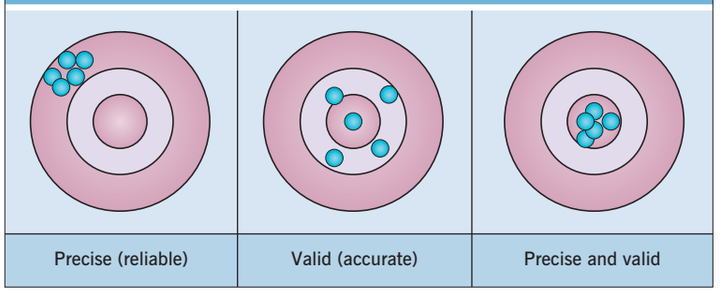
Table 123.8 Important considerations when reviewing a study. Common pitfalls are in bold italics.CI, confidence interval; OR, odds ratio[2,14].

TYPES OF ERRORS AND BIAS

- **Random errors**
- **Systematic errors**
  - *Ascertainment bias* is when not all of those who are supposed to be represented in a population are represented
  - *Selection bias* occurs when participants are selected differently across exposure or disease categories.
  - *Misclassification bias* occurs when participants are wrongfully thought to belong to one category of exposure or disease, when they actually belong to another
  - *Information bias* relates to inaccuracies in the collection of data on the exposure or disease (e.g. *recall bias*).

Table 123.9 Types of errors and bias. There are two types of errors: random (due to chance) and systematic.

PRECISION AND VALIDITY



Precise (reliable) | Valid (accurate) | Precise and valid

Fig. 123.5 Precision and validity. Precision (reliability) is the relative lack of random error, and validity (accuracy) is the relative lack of systematic error[1].
From Porta, Miquel. Dictionary of Epidemiology (5th Edition). Cary, NC, USA: Oxford University Press, 2008. p 2. Copyright © 2008. Oxford University Press. All rights reserved.

CONCEPTS OF SENSITIVITY, SPECIFICITY, POSITIVE PREDICTIVE VALUE, AND NEGATIVE PREDICTIVE VALUE

	True condition (as determined by gold standard)		
Result of screening test	**Disease**	**No disease**	
Positive	a (true positives)	b (false positives)	Positive predictive value = a/a+b (increases with increased disease prevalence)
Negative	c (false negatives)	d (true negatives)	Negative predictive value = d/c+d (decreases with increased disease prevalence)
	Sensitivity = a/a+c	Specificity = b/b+d	

Table 123.10 Concepts of sensitivity, specificity, positive predictive value, and negative predictive value.

– the higher the prevalence, the higher the positive predictive value and the lower the negative predictive value.

Statistical methods should include adjustment for potential confounders in the statistical model for the association between exposure and disease (see Fig. 123.2). If not adjusted for, confounders may be the reason the exposure and disease are associated. It is also important to test for effect modification between the exposure and other study variables suspected of playing an interdependent role with the exposure in affecting the disease outcome (see Fig. 123.3). If there is a significant effect modification variable for an association, then the association measure should be presented for different levels of the effect modification variable.

Results

In thinking about the display of results, it is important to assess whether baseline characteristics significantly differ across exposure groups, as well as across outcome groups. If they differ significantly across both exposure and outcome categories, then they could be confounders and need to be placed in the statistical model for the association between the exposure and disease so that they may be adjusted for. Next, it is important to use the correct outcome measure for a given study design (e.g. the outcome measure for a case–control study is an OR). Associated with each outcome measure is an indication of whether it is statistically significant. This is indicated by a P value or a 95% CI. *Statistical significance* is shown by a P value less than or equal to 0.05 (in most cases) and or by a 95% CI that does not include 1 within the interval for measures that represent a ratio (zero for measures that represent a difference). A *95% CI* that shows significance indicates that there is 95% confidence that the association is not due to chance alone (see Fig. 123.4). It is also important to note whether the study was powered enough to detect a statistically significant difference. *Power* is affected by the number of participants. One can do a power calculation when planning a study to attempt to include enough participants to detect a statistically significant difference between study groups. The variables included in the calculation vary according to study design, but they always include the expected magnitude of the association being measured, desired level of significance, and sample size.

Conclusions

In drawing conclusions about the results, it is important to consider those factors that support causality and how many are satisfied for the association in question (see Table 123.7). If statistical significance is found, one needs to determine whether the association makes biological and clinical sense. If it does not make sense, a *type I error* may have occurred, where a statistically significant association is found when one does not truly exist (false positive). It is important to note that the more statistical tests done for a study, the more likely a statistically significant association will be found based on chance alone. Alternatively, if an association is not found when one would be expected, a *type II error* may have occurred, where no statistical significance is found when one truly exists (false negative). This can be caused by a study not having enough power.

It is again important to consider what conclusions can be drawn given the type of study design, taking into account its strengths and limitations, including potential biases. In extrapolating the results, the *generalizability* of the study must also be considered. This pertains to how applicable the results are to the greater population and groups that did not participate in the study. It should also be noted if a trial was industry-sponsored. Lastly, it is important to consider the implications of the study on current clinical practices and the direction of future research.

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and the Consolidated Standards for Reporting Trials (CONSORT)

There is currently a need to improve reporting of findings in dermatologic studies. A study by Langan et al.[25] found that dermatologic papers infrequently reported sample size calculations, missing data, losses to follow-up, and statistical methods. Another paper by Ubriani et al.[26] found that only 20–49% of articles in three prominent dermatology journals reported the design of their study in the title or abstract of the paper.

In order to improve the quality of reporting of observational studies in medical research, criteria for reporting have been suggested in the form of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist. The items marked as critical for inclusion include the design of the study in the title or abstract and an informative summary of what was done in the abstract. Also, the methods section should have a description of: eligibility criteria for participants, sources of participants, methods of participant selection, methods of follow-up, matching criteria (if this was done), numbers of exposed and unexposed individuals, all outcomes measured, all exposures measured, all predictors, potential confounders, effect modifiers, diagnostic criteria, all statistical methods (including those dealing with confounding), whether subgroups and interactions were examined, how missing data was addressed, how losses to follow-up were addressed, and any sensitivity analysis[27]. A similar initiative for improving the quality of reporting of RCTs exists, with the Consolidated Standards for Reporting Trials (CONSORT) statement. This is a 25-item checklist that emphasizes reporting on how the trial was designed, analyzed, and interpreted. It also includes a flow diagram that displays the progress of all participants through the trial[28].

OPPORTUNITIES FOR RESEARCH IN DERMATO-EPIDEMIOLOGY

While each of the above study types provides valuable information, there appears to be a paucity of studies that include a control group or a large study population in dermatologic research. Considering the high prevalence of skin conditions and the rising incidence of diseases such as melanoma, the field of dermatology is likely to play a bigger role in public health research in the future. Therefore, it will be important for dermatologists to gain a greater understanding of epidemiologic and clinical research techniques. Also, it will be important to advocate for the inclusion of dermatology-related questions in local, state, and national surveys, allowing for larger epidemiologic studies to be conducted with limited resources.

There are currently some sources of data that can be analyzed for information on skin conditions, including national databases and disease registries (e.g. the National Alopecia Areata Foundation patient registry). Other options for getting involved in epidemiologic research include conducting a systematic review or enrolling one's clinic in a drug trial. There are also new molecular technologies on the horizon that warrant further research. Dermatologists interested in gaining greater experience in epidemiologic research may consider enrolling in a public health class, connecting with a mentor in the field, or getting involved with a community of researchers in this area. There are several funding sources currently available for dermato-epidemiology research, including those from dermatologic societies or foundations and national grants. As dermatologists become more active in these arenas, patients will be more likely to reap the benefits of research in dermato-epidemiology.

REFERENCES

1. Porta MI. Dictionary of Epidemiology, 5th edn. Cary, NC: Oxford University Press, 2008.
2. Gordis L. Epidemiology, 4th edn. Philadelphia: Elsevier/Saunders, 2009.
2a. Barzilai DA, Freiman A, Dellavalle RP, et al. Dermatoepidemiology. J Am Acad Dermatol. 2005;52:559–73.
3. Feldman SR, Fleischer AB Jr, McConnell RC. Most common dermatologic problems identified by internists, 1990–1994. Arch Intern Med. 1998;158:726–30.
4. Awadalla F, Rosenbaum DA, Camacho F, et al. Dermatologic disease in family medicine. Fam Med. 2008;40:507–11.
5. Kerr OA, Tidman MJ, Walker JJ, et al. The profile of dermatological problems in primary care. Clin Exp Dermatol. 2010;35:380–3.
6. Centers for Disease Control and Prevention. National Ambulatory Medical Care Survey: 2008 Summary Tables. www.cdc.gov/nchs/data/ahcd/namcs_summary/namcssum2008.pdf

7. Auvin S, Imiela A, Catteau B, et al. Paediatric skin disorders encountered in an emergency hospital facility: a prospective study. Acta Derm Venereol. 2004;84:451–4.
8. Altekruse SF, Kosary CL, Krapcho M, et al (eds). SEER Cancer Statistics Review, 1975–2007. Bethesda, MD: National Cancer Institute. http://seer.cancer.gov/csr/1975_2007/, based on November 2009 SEER data submission, posted to the SEER website 2010.
9. Brewster DH, Bhatti LA, Inglis JH, et al. Recent trends in incidence of nonmelanoma skin cancers in the East of Scotland, 1992–2003. Br J Dermatol. 2007;156:1295–300.
10. Birch-Johansen F, Jensen A, Mortensen L, et al. Trends in the incidence of nonmelanoma skin cancer in Denmark 1978–2007: rapid incidence increase among young Danish women. Int J Cancer. 2010;127:2190–8.
11. Holterhues C, Vries E, Louwman MW, et al. Incidence and trends of cutaneous malignancies in the Netherlands, 1989–2005. J Invest Dermatol. 2010;130:1807–12.
12. Nijsten T, Stern RS. How epidemiology has contributed to a better understanding of skin disease. J Invest Dermatol. 2012 [epub ahead of print]
13. OCEBM Levels of Evidence Working Group. The Oxford 2011 Levels of Evidence. Oxford Centre for Evidence-Based Medicine. www.cebm.net/index.aspx?o=5653
14. Hulley SB, Cummings SR, Browner WS, et al. Designing Clinical Research, 2nd edn. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2001.
15. Kasteler JS, Callen JP. Scalp involvement in dermatomyositis. Often overlooked or misdiagnosed. JAMA. 1994;272:1939–41.
16. Lazovich D, Vogel RI, Berwick M, et al. Indoor tanning and risk of melanoma: a case-control study in a highly exposed population. Cancer Epidemiol Biomarkers Prev. 2010;19:1557–68.
17. Gelfand JM, Neimann AL, Shin DB, et al. Risk of myocardial infarction in patients with psoriasis. JAMA. 2006;296:1735–41.
18. Love TJ, Qureshi AA, Karlson EW, et al. Prevalence of the metabolic syndrome in psoriasis: results from the National Health and Nutrition Examination Survey, 2003–2006. Arch Dermatol. 2011;147:419–24.
19. Paller AS, Siegfried EC, Langley RG, et al. Etanercept Pediatric Psoriasis Study Group. Etanercept treatment for children and adolescents with plaque psoriasis. N Engl J Med. 2008;358:241–51.
20. Collier A, Johnson KR, Delamere F, et al. The Cochrane Skin Group: promoting the best evidence. J Cutan Med Surg. 2005;9:324–31.
21. Warycha MA, Zakrzewski J, Ni Q, et al. Meta-analysis of sentinel lymph node positivity in thin melanoma (<or=1 mm). Cancer. 2009;115:869–79.
22. Petukhova L, Duvic M, Hordinsky M, et al.Genome-wide association study in alopecia areata implicates both innate and adaptive immunity. Nature. 2010;466:113–7.
23. Basra MKA, Fenech R, Gatt RM, et al. The Dermatology Life Quality Index 1994–2007: a comprehensive review of validation data and clinical results. . Br J Dermatol. 2008;159:997–1035.
24. Both H, Essink-Bot ML, Busschbach J, Nijsten T. Critical review of generic and dermatology-specific health-related quality of life instruments. J Invest Dermatol. 2007;127:2726–39.
25. Langan S, Schmitt J, Coenraads PJ, et al.; European Dermato-Epidemiology Network (EDEN). The reporting of observational research studies in dermatology journals: a literature-based study. Arch Dermatol. 2010;146:534–41.
26. Ubriani R, Smith N, Katz KA. Reporting of study design in titles and abstracts of articles published in clinically oriented dermatology journals. Br J Dermatol. 2007;156:557–9.
27. von Elm E, Altman DG, Egger M, et al; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Epidemiology. 2007;18:800–4.
28. Altman DG, Schulz KF, Moher D, et al; CONSORT GROUP (Consolidated Standards of Reporting Trials). The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Intern Med. 2001;134:663–94

Skin Barrier and Transdermal Drug Delivery

124

Mark R Prausnitz, Peter M Elias, Thomas J Franz, Matthias Schmuth, Jui-Chen Tsai, Gopinathan K Menon, Walter M Holleran and Kenneth R Feingold

Chapter Contents

Structure and origin of the skin barrier *2065*
Parameters affecting skin permeability *2068*
Strategies to enhance transdermal drug delivery *2070*

The skin provides the largest interface between the human body and the external environment. Therefore, one of its most important functions is to regulate what enters the body via the skin, as well as what exits. In general, the skin is designed to let very little enter, since other tissues, such as the permeable epithelia of the gastrointestinal tract and lung, provide the primary means of regulated entry into the body. Likewise, the skin must prevent excessive loss of water and other bodily constituents.

The skin's remarkable barrier properties are due in large part to the stratum corneum, which represents the thin outer layer of the epidermis[1]. In contrast to other tissues in the body, the stratum corneum consists of corneocytes (composed primarily of aggregated keratin filaments encased in a cornified envelope) that are surrounded by an extracellular milieu of lipids organized as multiple lamellar bilayers. These structured lipids prevent excessive loss of water from the body and likewise block entry of most topically applied drugs, other than those that are lipid-soluble and of low molecular weight. This poses a significant challenge to administering medications via the skin either for local cutaneous effects or as systemic therapy following their entry into superficial dermal capillaries.

STRUCTURE AND ORIGIN OF THE SKIN BARRIER

Stratum Corneum Structure and Organization

The stratum corneum is a composite material made of proteins and lipids structurally organized as "bricks and mortar" (Fig. 124.1; Table 124.1)[2]. Instead of being uniformly dispersed, the highly hydrophobic lipids in normal stratum corneum are sequestered within the extracellular spaces, where this lipid-enriched matrix is organized into lamellar membranes that surround the corneocytes[3]. Hence, rather than stratum corneum thickness, variations in number of lamellar membranes (= lipid weight %), membrane structure, and/or lipid composition provide the structural and biochemical basis for site-related variations

FEATURES OF THE STRATUM CORNEUM
• Primary barrier to drug absorption into skin
• Two-compartment organization: "bricks and mortar"
• Microheterogeneity within extracellular spaces: "There's more to the mortar than lipid"
• Persistent metabolic activity: dynamic changes in cytosol, cornified envelope, and interstices from inner to outer stratum corneum
• Homeostatic links to the nucleated cell layers: barrier function regulates epidermal DNA and lipid synthesis
• Pathophysiologic links to deeper skin layers: barrier abrogation and/or epidermal injury initiates epidermal hyperplasia and inflammation
• Stratum corneum as a biosensor: changes in external humidity alone regulate proteolysis of filaggrin, epidermal DNA/lipid synthesis, and initiation of inflammation

Table 124.1 Features of the stratum corneum.

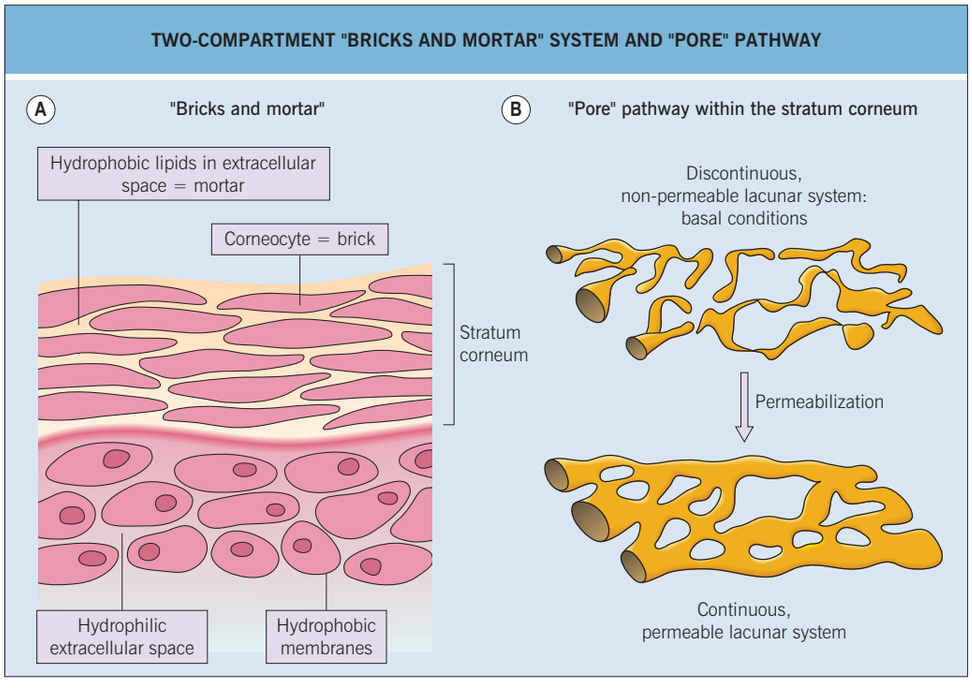


Fig. 124.1 Two-compartment "bricks and mortar" system and "pore" pathway. A The stratum corneum is a unique two-compartment system, analogous to a brick wall. Whereas lipids are sequestered extracellularly within the stratum corneum, the corneocyte is lipid-depleted but protein-enriched. **B** The degradation of corneodesmosomes results in discontinuous lacunar domains, which represent the likely aqueous "pore" pathway. These lacunae can enlarge and extend, forming a continuous but collapsible network under certain conditions, e.g. occlusion, prolonged hydration, sonophoresis.

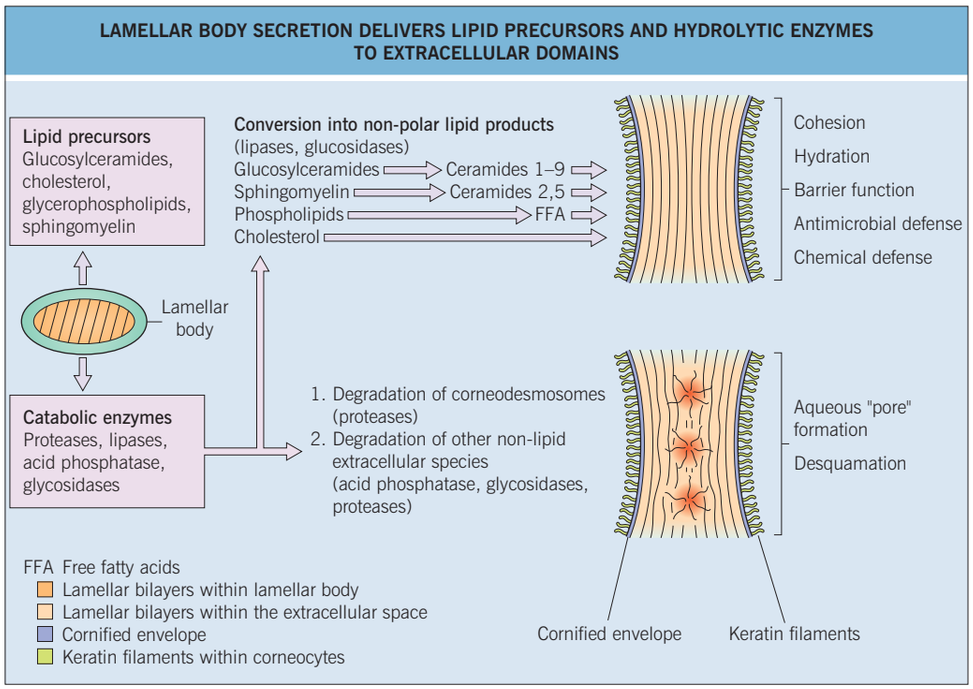


Fig. 124.2 Lamellar body secretion delivers not only lipid precursors, but also several hydrolytic enzymes to extracellular domains. These organelles also release antimicrobial peptides, including human β-defensin 2 and LL-37 (the carboxy-terminal fragment of human cathelicidin). As a result, the antimicrobial barrier is intimately linked to the permeability barrier. In atopic dermatitis, for example, there is both an impaired permeability barrier and reduced expression of antimicrobial peptides, explaining in part the predisposition to colonization with *Staphylococcus aureus*.

FACTORS AFFECTING HOW STRATUM CORNEUM LIPIDS MEDIATE BARRIER FUNCTION
• Extracellular localization: only intercellular lipids play a role
• Amount of lipid (lipid weight %)
• Elongated, tortuous pathway: increases diffusion length
• Organization into lamellar membrane structures
• Hydrophobic composition: absence of polar lipids and presence of very-long-chain saturated fatty acids
• Correct molar ratio: approximately 1:1:1 of three key lipids: ceramides, cholesterol and free fatty acids
• Unique molecular structures (e.g. acylceramides)

Table 124.2 Factors affecting how stratum corneum lipids mediate barrier function.

in permeability[4]. It follows, then, that the extracellular, lipid-enriched matrix of the stratum corneum comprises not only the structure that limits transdermal delivery of hydrophilic drugs, but also the so-called stratum corneum "reservoir"[5], within which lipid-soluble drugs, such as topical corticosteroids, can accumulate and be slowly released.

Human stratum corneum is typically comprised of about 20 corneocyte cell layers, which differ in their thickness, packing of keratin filaments, filaggrin content, and number of corneodesmosomes, depending on body site. Corneocytes are surrounded by a highly cross-linked, resilient sheath, the cornified envelope, while the cell interior is packed with keratin filaments embedded in a matrix composed mainly of filaggrin and its breakdown products (the latter are also referred to as "natural moisturizing factors"). As noted above, individual corneocytes, in turn, are surrounded by a lipid-enriched extracellular matrix, organized largely into lamellar membranes, which derive from secreted lamellar body precursor lipids (Fig. 124.2). Following secretion, lamellar body contents fuse end-to-end, forming progressively elongated membrane sheets[3], a sequence requiring the action of a battery of lipolytic "processing" enzymes (see below). Although corneocytes play a role both as spacers and as a scaffold for the extracellular matrix, transdermal drug delivery strategies have focused primarily on manipulations of the extracellular lipid milieu[6,7]. Lastly, the existence of aqueous pores within the extracellular matrix[8] not only adds further complexity to the extracellular pathway (see Fig. 124.1), but also provides additional opportunities for novel delivery strategies.

The exceptionally low permeability of normal stratum corneum to water-soluble drugs is the consequence of several characteristics of the lipid-enriched, extracellular matrix (Table 124.2), including its organization into a highly convoluted and tortuous extracellular pathway imposed by geometrically arrayed corneocyte "spacers"[9]. Moreover, not only the paired-bilayer arrangement of extracellular lipids, but also their extreme hydrophobicity and the composition and distribution of the three key species (ceramides, cholesterol and free fatty acids) in a critical (1:1:1) molar ratio are further characteristics that provide for barrier function.

Ceramides account for approximately 50% of the total stratum corneum lipid mass[10,11], and are crucial for the lamellar organization of the stratum corneum barrier[12]. Of the nine ceramide classes, acylceramides or ceramides 1, 4 and 7 (which contain ω-hydroxy-linked, essential fatty acids in an ester linkage) are epidermis-unique compounds, known to be important for the barrier[13]. *Cholesterol*, the second most abundant lipid by weight in the stratum corneum, promotes the intermixing of different lipid species and regulates its "phase" behavior[14]. *Free fatty acids*, which account for 10–15% of stratum corneum lipids, consist predominantly of very-long-chain, saturated species with ≥18 carbon atoms[10]. A decrease in the concentrations of any of these critical lipid species compromises barrier integrity, by altering the molar ratio of the membranes that mediate normal barrier function.

The "domain-mosaic model" advocates a meandering, polar (pore) pathway for water transport through lamellar boundaries within the lipid mosaic[15], adding potential complexity to the already tortuous, extracellular pathway. An alternative model is based upon the presence of lacunar domains embedded within the lipid bilayers[8] (see Fig. 124.1). These lacunae correspond to sites of subjacent corneodesmosome degradation (see Fig. 124.2), and presumably they contain the hydrophobic degradation products of corneodesmosomes[16]. Whereas these lacunae are scattered and discontinuous under basal conditions, following certain types of permeabilization (e.g. occlusion, prolonged hydration, sonophoresis, iontophoresis), they are thought to expand until they interconnect, forming a continuous "pore pathway" (see Fig. 124.1). The pore pathway can revert back to its original, discontinuous state once the permeabilizing stimulus disappears.

Epidermal Lipid Metabolism and the Skin Barrier

Biosynthetic activities

Epidermal differentiation is a vectorial process that is accompanied by dramatic changes in lipid composition, including loss of phospholipids with the emergence of ceramides, cholesterol and free fatty acids in the stratum corneum[11,13] (see Fig. 124.2). Although epidermal lipid synthesis is both highly active and largely autonomous from

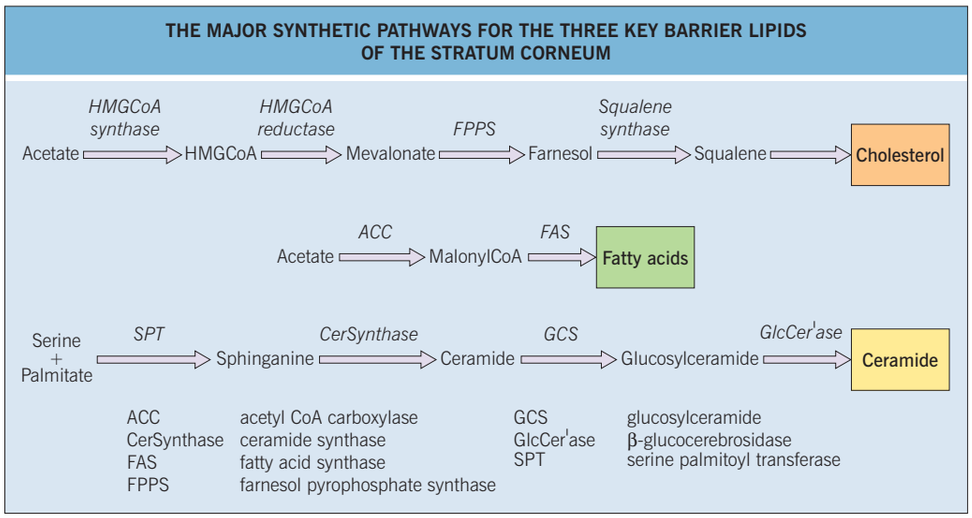


Fig. 124.3 The major synthetic pathways that lead to the generation of the three key barrier lipids of the stratum corneum. The rate-limiting enzymes in each pathway are shown. Applications of specific, conduritol-type inhibitors of β-glucocerebrosidase to intact skin lead to a progressive abnormality in barrier function. In both a transgenic murine model of Gaucher disease (GD) (produced by targeted disruption of the β-glucocerebrosidase gene) and in the severe, type 2 neuronopathic form of GD, infants present with a barrier abnormality. This was attributable to accumulation of glucosylceramides, depletion of ceramides, and persistence of immature lamellar bodies within the interstices of the stratum corneum.

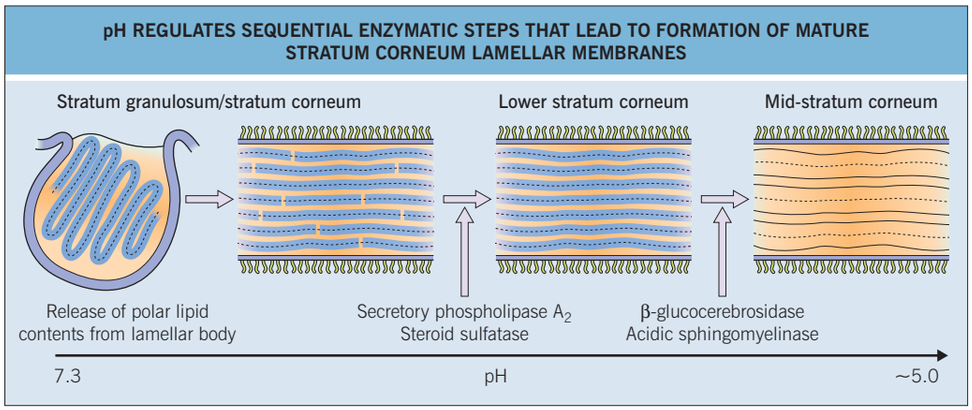


Fig. 124.4 pH regulates sequential enzymatic steps that lead to formation of mature stratum corneum lamellar membranes. The process begins at the stratum granulosum–stratum corneum interface. Of note, in atopic dermatitis, a higher pH is observed.

systemic influences, it can be regulated by external influences, i.e. changes in the status of the permeability barrier[17]. Acute perturbations of the permeability barrier stimulate a characteristic recovery sequence that leads to restoration of normal function over about 72 hours in young skin (the cutaneous stress test). This sequence includes an increase in cholesterol, free fatty acid and ceramide synthesis that is restricted to the underlying epidermis, and attributable to a prior increase in mRNA and enzyme activity/mass for each of the key synthetic enzymes (Fig. 124.3). Furthermore, synthesis of each of the three key lipids is required for normal barrier homeostasis, i.e. topically applied inhibitors of the key enzymes in each pathway produce abnormalities in permeability barrier homeostasis[17].

Lamellar body secretion

The unique two-compartment organization of the stratum corneum is attributable to the secretion of lamellar body-derived lipids and co-localized hydrolases at the stratum granulosum–stratum corneum interface[3]. Under basal conditions, lamellar body secretion is slow, but sufficient to provide for barrier integrity. Following acute barrier disruption, calcium is lost from the outer epidermis, and much of the preformed pool of lamellar bodies in the outermost cells of the stratum granulosum is quickly secreted[18–20]. Calcium is an important regulator of lamellar body secretion, with the high levels of Ca^{2+} in the stratum granulosum restricting lamellar body secretion to low, maintenance levels[21].

Extracellular processing

Extrusion of the polar lipid contents of lamellar bodies at the stratum granulosum–stratum corneum interface is followed by the processing of those lipids into more hydrophobic species that form mature, lamellar membranes[8] (Fig. 124.4). The extracellular processing of glucosylceramides, phospholipids and cholesterol sulfate with accumulation of ceramides, free fatty acids and cholesterol in the stratum corneum is attributable to the co-secretion of a set of hydrolytic enzymes[3] (see Fig 124.2).

Extracellular processing of *glucosylceramides* plays a key role in barrier homeostasis (see legend to Fig. 124.3). In addition, phospholipid hydrolysis, catalyzed by one or more secretory phospholipases (e.g. $sPLA_2$), generates a family of non-essential free fatty acids, which are required for barrier homeostasis[22–24]. Since applications of either bromphenacylbromide or MJ33 (chemically unrelated $sPLA_2$ inhibitors) modulate barrier function in intact skin, $sPLA_2$ appears to play a critical role in barrier homeostasis[22–24]. Moreover, applications of either inhibitor to perturbed skin sites delay barrier recovery.

Sphingomyelin hydrolysis by acidic sphingomyelinase generates two of the nine ceramides required for normal barrier homeostasis (see Fig 124.2). Moreover, patients with mutations in the gene encoding acidic sphingomyelinase (Niemann–Pick, Type A) that lead to low enzyme activity display an ichthyosiform dermatosis, and transgenic mice with an absence of acidic sphingomyelinase also demonstrate a barrier abnormality. Finally, applications of nonspecific inhibitors of acidic sphingomyelinase to perturbed skin sites lead to a delay in barrier recovery[25].

Just as with glucosylceramides and sphingomyelin, *cholesterol sulfate* content increases during epidermal differentiation, and then decreases progressively as the latter is desulfated during passage from the inner to the outer stratum corneum[26]. Both cholesterol sulfate and its processing enzyme, steroid sulfatase, are concentrated in membrane domains of the stratum corneum. Of note, the content of cholesterol sulfate in these sites increases by approximately 10-fold[26] in recessive X-linked ichthyosis (see Ch. 57). Not only is recessive X-linked ichthyosis characterized by a barrier defect[27], but also repeated applications of cholesterol sulfate to intact skin produce a barrier abnormality[28]. In both cases, the barrier abnormality is attributable to cholesterol sulfate-induced phase separation in lamellar membrane domains[27]. But the barrier defect may also be, in part, attributed to a reduction in

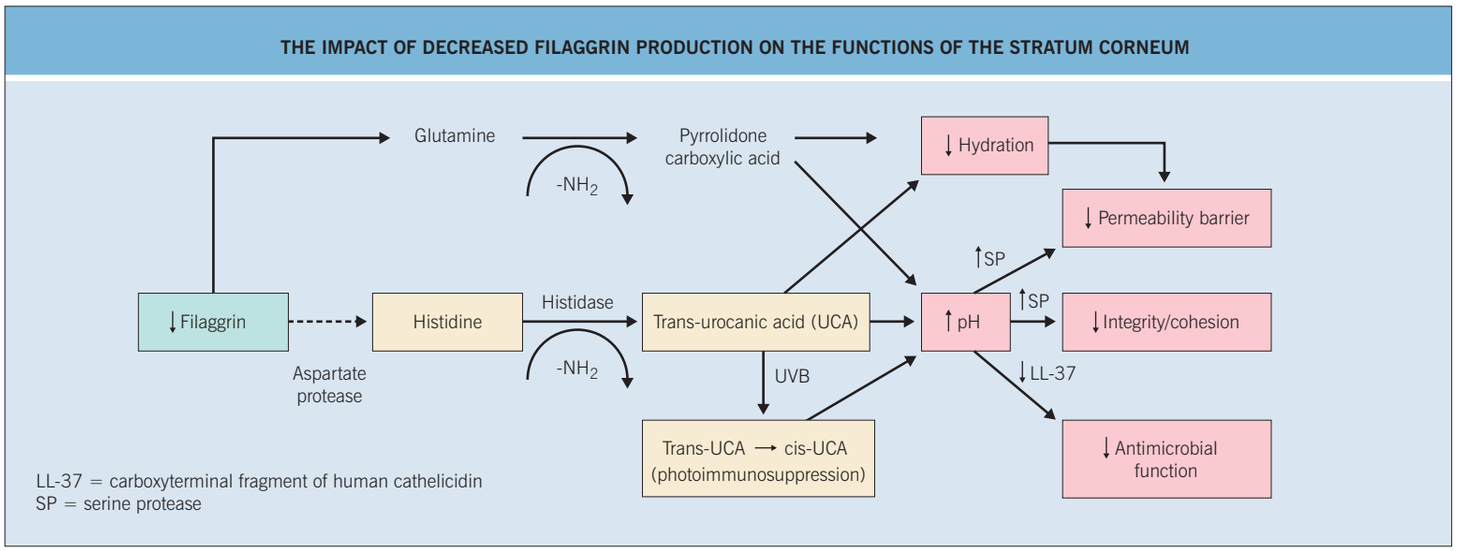


Fig. 124.5 The impact of decreased filaggrin production on the functions of the stratum corneum. UVB, ultraviolet B.

cholesterol content, since cholesterol sulfate is a potent inhibitor of HMG-CoA reductase (see Fig. 124.3).

In addition to lipid precursors and hydrolytic enzymes (e.g. steroid sulfatase, acidic sphingomyelinase), lamellar bodies contain proteases and antiproteases that orchestrate the orderly digestion of corneodesmosomes, allowing corneocyte shedding. These organelles also release antimicrobial peptides, including human β-defensin 2 and LL-37 (the carboxy-terminal fragment of human cathelicidin). As a result, the antimicrobial barrier is intimately linked to the permeability barrier. In atopic dermatitis, for example, there is both an impaired permeability barrier and reduced expression of antimicrobial peptides, explaining in part the predisposition to colonization with *Staphylococcus aureus* (see Table. 12.3). Inherited abnormalities in serine protease/antiprotease expression and filaggrin production are also observed in patients with atopic dermatitis and the impact of reduced filaggrin production on various functions of the stratum corneum is depicted in Figure 124.5.

Acidification

The fact that the stratum corneum displays an acidic external pH ("acid mantle") is well documented, but its origin is not fully understood. Extraepidermal mechanisms (including surface deposits of eccrine- and sebaceous gland-derived products as well as metabolites of microbial metabolism), endogenous catabolic processes (e.g. phospholipid-to-free fatty acid hydrolysis, deamination of histidine to urocanic acid; see Fig. 124.5), and local generation of protons within the lower stratum corneum (by sodium-proton antiporters [NHE_1] inserted into the plasma membrane[29,30]) could actively acidify the extracellular space. These mechanisms would explain not only the pH gradient across the interstices of the stratum corneum (see Fig. 124.4), but also selective acidification of membrane microdomains within the lower stratum corneum.

The concept that acidification is required for permeability barrier homeostasis is supported by the observation that barrier recovery is delayed when acutely perturbed skin sites are immersed in neutral pH buffers[31], or when either the sodium–proton exchanger/antiporter or $sPLA_2$-mediated phospholipid catabolism to free fatty acids is blocked[29]. Acidification appears to impact barrier homeostasis through regulation of enzymes involved in extracellular processing, such as β-glucocerebrosidase and acidic sphingomyelinase, which exhibit acidic pH optima (see Fig. 124.4).

PARAMETERS AFFECTING SKIN PERMEABILITY

As discussed in greater detail in the following sections, the skin is an attractive site for drug delivery[6,7]. However, normal skin provides a significant barrier to drug absorption. Understanding the parameters that affect the permeability of this barrier is essential for achieving successful drug therapy via the skin. While local cutaneous effects are generally achieved by dissolving or suspending the drug in a vehicle that is applied topically as a semi-solid formulation (e.g. cream or ointment)[32], administration of systemic therapy via the skin is typically accomplished through the use of a patch. In either situation, drug is supplied at the surface of the skin for diffusion across the stratum corneum, with the goal of reaching therapeutic targets within the skin and/or systemic uptake via superficial dermal capillaries.

Parameters Controlling Absorption

Conventional transdermal drug delivery is a passive process governed by Fick's law, that is, the rate of absorption or flux (J) of any substance across a barrier is proportional to its concentration difference across that barrier[33,34]. For topically applied drugs, the concentration difference can be simplified as the concentration of drug in the vehicle, C_v, and the proportionality constant relating flux to concentration is the permeability coefficient, K_p (equation 1). K_p is composed of factors that relate to both drug and barrier, as well as their interaction. These factors are: K_m, the partition coefficient; D, the diffusion coefficient; and L, the length of the diffusion pathway (equation 2). Thus, four factors control the kinetics of percutaneous drug absorption (equation 2); however, it is of great practical importance that two of the four (C_v, K_m) are highly dependent on one additional factor, the vehicle.

$$J = K_p C_v \quad (1)$$

$$J = \left(\frac{DK_m}{L}\right) C_v \quad (2)$$

Role of the Vehicle

The vehicle is an important link between drug potency and therapeutic effectiveness, since extensive pharmaceutical research has shown that the composition of the vehicle can profoundly influence the rate and extent of absorption (bioavailability). As illustrated by the potency ranking scale for glucocorticoids[35], the same drug appears in different potency classes when formulated in different vehicles (Table 124.3). It was once axiomatic that ointments were more potent than creams. Though true for the early glucocorticoid products, it is no longer generally applicable. Greater understanding of the science underlying topical formulations has allowed creams, gels, solutions and foams to be specifically formulated equipotent to ointments (see Table 124.3).

In the rational design of dermatologic vehicles that maximize bioavailability, two factors are of critical importance: (1) solubilizing the drug in the vehicle (C_v); and (2) maximizing movement (partitioning) of drug from vehicle to stratum corneum (K_m). The partition

EFFECT OF VEHICLE ON POTENCY	
Corticosteroid*	**Potency class**
BETAMETHASONE DIPROPIONATE	
• Diprolene ointment 0.05%	1
• Diprolene gel 0.05%	1
• Diprolene cream AF 0.05%	2
• Diprosone ointment 0.05%	2
• Diprosone cream 0.05%	3
• Diprosone lotion 0.05%	5
CLOBETASOL PROPIONATE	
• Temovate ointment 0.05%	1
• Temovate cream 0.05%	1
• Temovate gel 0.05%	1
• Temovate E cream 0.05%	1
• Olux foam 0.05%	1
• Temovate Scalp Application 0.05%	2
FLUOCINONIDE	
• Lidex ointment 0.05%	2
• Lidex cream 0.05%	2
• Lidex gel 0.05%	2
• Lidex solution 0.05%	2
• Lidex E cream 0.05%	3
TRIAMCINOLONE ACETONIDE	
• Aristocort A ointment 0.1%	3
• Kenalog cream 0.1%	4
• Kenalog lotion 0.1%	5
• Aristocort cream 0.1%	6

Table 124.3 Effect of vehicle on potency. *Generic name in header, followed by trade names.

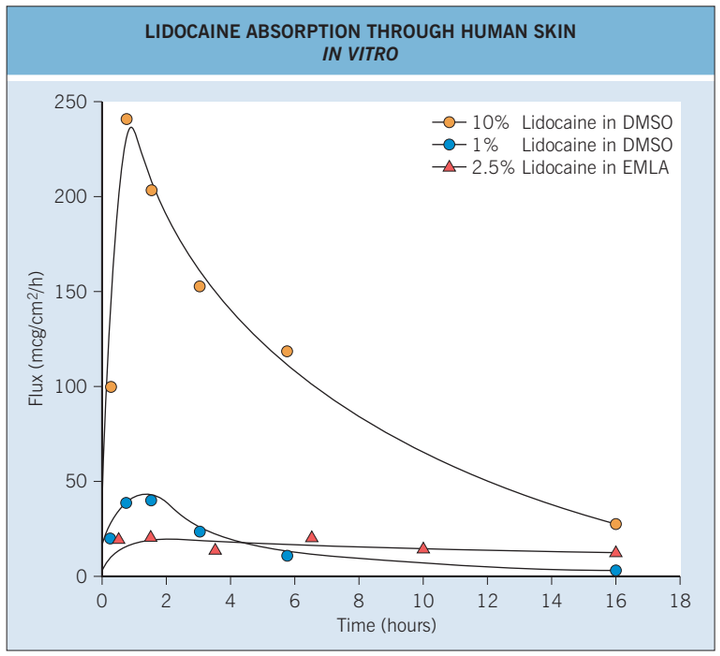


Fig. 124.6 Lidocaine absorption through human skin *in vitro*. Incorporation of DMSO as a co-solvent with ethanol results in both increased drug solubility (C_v) and partitioning (K_m). At 10% drug concentration, the maximum flux is 10-fold greater than that achieved in an emulsion formulation (eutectic mixture of lidocaine 2.5% and prilocaine 2.5% [EMLA]). At 1% drug concentration in DMSO the maximum flux is twofold greater than 2.5% drug in EMLA. *Reproduced from Mallory SB, et al. Topical lidocaine for anesthesia in patients undergoing pulsed dye laser treatment for vascular malformations. Pediatr Dermatol. 1993;10:370–5.*

coefficient describes the ability of a drug to escape from the vehicle and move into the outermost layer of the stratum corneum. It is defined as the equilibrium solubility of drug in the stratum corneum (sc) relative to its solubility in the vehicle ($K_m = C_{sc}/C_v$).

Drug Concentration

The driving force for percutaneous absorption is the concentration of *soluble* drug in the vehicle. Many older topical drug products were marketed with the expectation that higher concentrations were more potent. Although true for some products, e.g. tretinoin gels and creams (0.01–0.1%) in which the drug is completely solubilized at all concentrations, for others it is not. Hydrocortisone 1% and 2.5% in a cream formulation have been shown to be of equal potency, as have triamcinolone acetonide 0.025%, 0.1% and 0.5% creams[35]. One of the major advances in formulating glucocorticoids, as first shown with fluocinonide, came when it was discovered that the addition of propylene glycol to the vehicle could completely solubilize the drug. This led to corticosteroid products with greater potency, as demonstrated in the vasoconstrictor assay. Newer products are now tested during the development process to ensure that increased drug concentration results in increased bioavailability. However, excess non-dissolved drug can sometimes be advantageous, especially in transdermal patches worn for prolonged periods of time (e.g. up to a week). In this situation, as dissolved drug is absorbed into the body, non-dissolved drug can then become dissolved in order to maintain an equilibrium, thereby maintaining a constant dissolved drug concentration over time and providing a constant rate of delivery[36].

Partition Coefficient

In general, topically applied drugs are poorly absorbed because only a small fraction partitions into the stratum corneum. Most of the drug remains on the skin surface, subject to loss from a multitude of factors (exfoliation, sweating, wash-off, rub-off, adsorption onto clothing, and chemical or photochemical degradation). Even 10–12 hours following dosing, a drug that has not been lost by exfoliation or rub-off remains largely on the skin surface, and it is easily removed by a simple soap and water wash[37]. In the case of patches worn for several days, as much as half of the original amount of drug may still be present in the patch when it is removed, and this can pose a safety hazard upon disposal, especially with potentially dangerous drugs such as fentanyl[38].

A number of physical and chemical factors can improve partitioning. Hydration of the skin due to occlusion, either from a topical formulation or a patch, expands the reservoir volume available to drugs within the stratum corneum; this can increase absorption as much as five- to tenfold[39]. Common excipients such as ethanol and propylene glycol can also alter barrier structure so as to increase partitioning[40]. In addition, many excipients have good solvent properties and, as a result, positively affect C_v as well as K_m. The use of high concentrations of propylene glycol to maximize bioavailability has become pervasive among the super- and high-potency corticosteroids, but at a price. Adverse events such as burning and stinging are common when such preparations are applied to fissured or eroded skin, and contact dermatitis may occur.

A number of other compounds have been identified as enhancers. Dimethylsulfoxide (DMSO), the archetypical enhancer, exemplifies the effects that can be achieved (Fig. 124.6). As with ethanol and propylene glycol, both C_v and K_m are affected. Because DMSO is a superb solvent, higher drug concentrations can be achieved than with other solvents, but it also expands the stratum corneum barrier, permitting increased drug uptake and possibly an increased rate of diffusion (D) through the barrier. However, the use of powerful enhancers such as DMSO is constrained by excessive skin irritation or toxicity[41].

Regional Variation

All body sites are not equally permeable[42]. Variations in stratum corneum thickness, the number of sebaceous glands, and hydration status can all affect absorption. Current data and clinical experience suggest that one can crudely rank regional permeability as follows: nail < < palm/sole < trunk/extremities < face/scalp < < scrotum.

STRATEGIES TO ENHANCE TRANSDERMAL DRUG DELIVERY

Despite the significant permeability barrier of the stratum corneum, drug delivery via the skin is a very attractive option and is widely employed for both local and systemic therapy (Table 124.4; Fig. 124.7)[6,7]. Topical treatment of cutaneous disorders obviously targets the site of disease, thereby minimizing adverse side effects elsewhere within the body. Delivery of systemic therapies via the skin avoids degradation of the medication within the gastrointestinal tract and first-pass metabolism by the liver, both of which are associated with oral administration of drugs, in addition to evading the pain and safety issues associated with injections. Transdermal delivery of drugs, especially via long-acting patches, enables infrequent dosing and maintenance of steady-state drug levels.

Many dermatologic medications can be applied topically to the skin because the required dosage is often exceedingly small and therefore they can be effective even in the setting of highly inefficient absorption. In addition, a number of skin disorders are associated with compromised barrier function, which leads to enhanced drug uptake in sites of involvement[43].

In contrast, systemic drug delivery via the skin typically requires administration of larger doses through normal skin. As a result, at the time of writing, only ~20 drugs have been FDA-approved for transdermal administration. The drugs contained within these patches share several characteristics – they are low molecular weight (<400 Da), lipophilic (octanol–water partition coefficient up to 10 000), and relatively low dose (typically <10 mg per day)[44] (Table 124.5).

Significant efforts have been expended on the development of new approaches to enhance transdermal drug delivery and thereby increase the number of drugs administered via this route (Fig. 124.8). These strategies can be broadly subdivided into chemical, biochemical and physical approaches (Table 124.6).

TRANSDERMAL DRUG DELIVERY: THEORETICAL ADVANTAGES
• Improved patient compliance
• Improved efficacy, i.e. continuous release
• Reduced toxicity: (a) no "peaks" and (b) lower total absorbed dose
• Bypass hepatic first-pass metabolism
• Avoid local GI side effects/metabolism
• Decreased dosing frequency
• Avoid painful injections
• Decreased costs to patient due to decreased: (a) total dose and (b) dosing frequency (increased efficiency)

Table 124.4 Transdermal drug delivery: theoretical advantages.
GI, gastrointestinal.

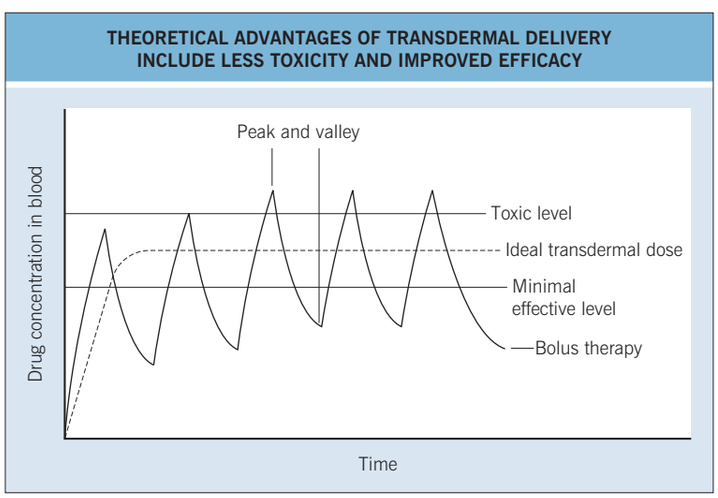


Fig. 124.7 Theoretical advantages of transdermal delivery include less toxicity and improved efficacy. This is due to a reduction in the "peaks" and "valleys" associated with bolus therapy.

Chemical Enhancement

Chemical enhancers include compounds that interact with the lipid matrix of the stratum corneum to alter its nanostructure and thereby increase permeability[7,40]. The major advantages of chemical enhancers are that they are typically low cost, can be incorporated into a conventional patch or topical formulation, and do not require the complexity of a battery-powered device. The primary disadvantage of chemical enhancers is that they are often associated with skin irritation or toxicity when present at high concentrations and with long exposure times[41]. Thus, chemical enhancers have been employed principally to increase permeability to compounds that already cross the skin reasonably well, but they have generally been unable to significantly impact delivery of new classes of molecules (e.g. highly water-soluble drugs) or macromolecules such as proteins, gene-based medicines and vaccines.

The most common chemical enhancer is water, which leads to hydration of the stratum corneum when it accumulates during prolonged occlusion; the occlusion can result from a topical formulation or a patch[39,45]. Following 24–48 hours of occlusion, corneocytes swell, the intercellular spaces become distended, and the lacunar network becomes dilated. Distention of lacunae is thought to eventually lead to connections within an otherwise discontinuous system, creating "pores" in the stratum corneum interstices through which polar and non-polar substances can penetrate more readily (see Fig. 124.1).

Solvents, such as ethanol, methanol, chloroform and acetone, as well as detergents can extract barrier lipids and/or disrupt their bilayer structures, which then permeabilizes the stratum corneum[7,40,41]. Morphologic changes in human stratum corneum following exposure

CONVENTIONAL TRANSDERMAL DRUG DELIVERY UTILIZING PATCHES
IDEAL DRUG CHARACTERISTICS
• Low dosage (<10 mg/day) • Low molecular weight (<400 Da) • Moderately lipophilic
EXAMPLES OF DRUGS AVAILABLE IN TRANSDERMAL PATCHES
Clonidine, estradiol*, ethinyl estradiol*, fentanyl, granisetron, levonorgestrel*, methylphenidate, nicotine, nitroglycerin, norelgestromin*, norethindrone*, oxybutynin, rivastigmine, rotigotine, scopolamine, selegiline, testosterone*
*Hormones.

Table 124.5 Conventional transdermal drug delivery utilizing patches.

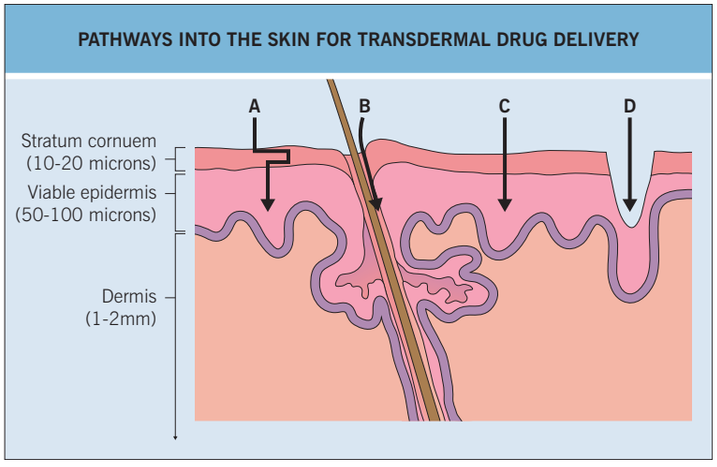


Fig. 124.8 Pathways into the skin for transdermal drug delivery.
A Transdermal transport via a tortuous pathway largely within extracellular lipids. This pathway is utilized during drug absorption in association with chemical, biochemical and some physical enhancers. **B** Transport through hair follicles and sweat ducts can be enhanced by iontophoresis and certain particulate formulations. **C** Transport directly across the stratum corneum is enabled by electroporation. **D** Stripping, ablation, abrasion and microneedles remove stratum corneum to make micron-scale (or larger) pathways into the skin. *Reproduced with permission from Prausnitz MR, et al. Current status and future potential of transdermal drug delivery. Nat Rev Drug Discov. 2004;3:115–24.*

to solvents[46] include phase separation and disruption of lamellar bilayers in addition to the creation of defects in corneocyte membranes (with detergents). Moreover, surfactants, such as sodium dodecyl (lauryl) sulfate, and vehicles (e.g. propylene glycol) extract lipids and create extensive expansion of pre-existing lacunar domains. Furthermore, solvent-based penetration enhancers, such as azone, sulfoxides, urea and free fatty acids, not only extract extracellular lipids, but they also alter stratum corneum lipid organization (phase behavior), thereby increasing transdermal delivery and expanding intercellular domains (Fig. 124.9; see Fig. 124.6). Recent work suggests that combinations of particular chemical enhancers that adhere to specific, narrow-range compositions can be especially effective[47].

Finally, *liposomes* represent yet another "chemical" method frequently employed to enhance delivery into the skin, especially in the case of cosmetics and moisturizers[48]. While intact liposomes probably do not penetrate the stratum corneum[49], they can be used to increase effective drug solubility in a vehicle (C_v) and facilitate partitioning into the skin (K_m).

STRATEGIES TO ENHANCE TRANSDERMAL DRUG DELIVERY
CHEMICAL
• Water • Solvents • Surfactants • Liposomes
BIOCHEMICAL
• Peptides • Metabolic inhibitors
PHYSICAL
• Stripping • Iontophoresis • Electroporation • Ultrasound (thermal) • Ultrasound (cavitational) • Thermal ablation • Mechanical abrasion • Microneedles

Table 124.6 Strategies to enhance transdermal drug delivery.

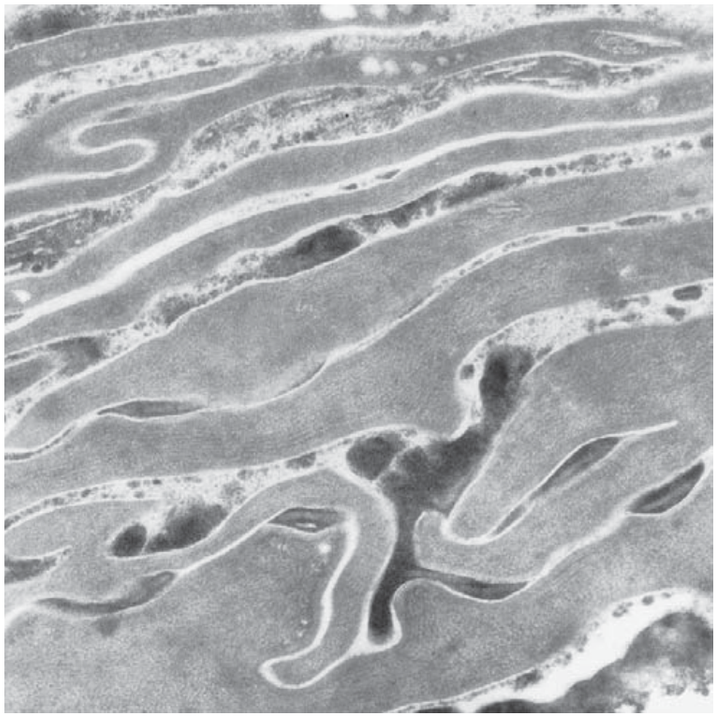


Fig. 124.9 Lipophilic agents (e.g. *n*-butanol) penetrate across the stratum corneum (SC) via the intercellular spaces. Note huge volume expansion of extracellular domains in this electron photomicrograph, representing the putative SC reservoir. *Method: n*-butanol precipitation *in situ* with osmium vapors.

Biochemical Enhancement

Biochemical methods have been developed to *directly* increase permeability of the stratum corneum lipid matrix as well as to *indirectly* affect skin permeability via alteration of lipid metabolism. Much of the work in this area has focused on peptides that are believed to disrupt or penetrate stratum corneum lipids. For example, polyarginine has been shown to ferry molecules attached to it across the stratum corneum and into the viable epidermis and dermis[50] (Fig. 124.10). Other peptides, identified by phage-display screening, appeared to target transfollicular pathways and did not require the drug to be attached[51]. Magainin, a naturally occurring pore-forming peptide, has been shown to increase skin permeability by direct interaction with and disruption of stratum corneum lipids[52].

In a related strategy, metabolically based approaches aim to enhance the efficacy of standard enhancers by biochemically inhibiting the repair (metabolic) response *in vivo* and thereby delaying barrier recovery[53]. This can be accomplished by altering the critical molar ratio of the three key stratum corneum lipids or by inducing discontinuities in the lamellar bilayer system. Both lipid synthesis inhibitors and agents that interfere with the assembly, secretion or extracellular processing of lamellar bodies have been examined, including brefeldin A, monensin, chloroquine, high Ca^{2+}/K^{+} levels and neutral pH buffers. Overall, biochemical enhancement methods are relatively new and to date they have not been used much in clinical drug delivery.

Physical Enhancement

There are a number of physical methods to increase drug delivery via the skin, many of which require the use of devices and some of which hold the promise to significantly expand the spectrum of drugs that can be administered transdermally to include water-soluble molecules and macromolecules[54,55].

Stripping is a simple technique used in research protocols to remove stratum corneum by sequential application of adhesive tape or cyanoacrylate glue[53,56]. Tape stripping removes both corneocytes and extracellular lipids, thereby reducing the elongated path length that drugs otherwise need to traverse, and it mechanically disrupts lamellar bilayers, even in the retained lower stratum corneum layers. Barrier disruption of human skin requires multiple strippings, which can lead to inflammation. More strippings are required to disrupt the barrier in skin phototypes V and VI (darkly pigmented) than in phototypes I and II (lightly pigmented) subjects[57].

Iontophoresis and electroporation represent electrically assisted, physical approaches to enhance delivery of drugs/macromolecules across the stratum corneum[58]. *Iontophoresis* uses low currents applied

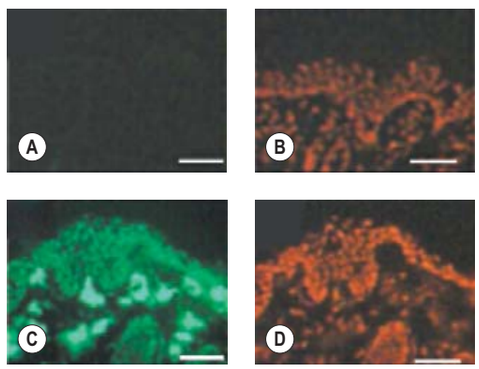


Fig. 124.10 Biochemical enhancement of drug delivery to the skin in mice. **A** Fluorescein does not penetrate intact skin. **C** Fluorescein conjugated to a heptamer of D-arginine penetrates extensively across the stratum corneum and localizes within viable epidermis and dermis. **B,D** Propidium iodide counter-staining shows tissue architecture in the same tissue sections as **A** and **C**. Scale bars are 20 microns. *Reproduced with permission from Rothbard JB, et al. Conjugation of arginine oligomers to cyclosporin A facilitates topical delivery and inhibition of inflammation. Nat Med. 2000;6:1253–7.*

for minutes to hours from an externally placed electrode (with the same charge as the drug) in order to drive these molecules across the stratum corneum, primarily by electrophoresis[59]. As the rate of drug delivery is generally proportional to the applied current, iontophoresis offers an opportunity for programmable drug delivery, especially with the recent development of miniaturized microprocessor systems. Clinically, iontophoresis has been employed to deliver: fentanyl and lidocaine for pain relief[60], pilocarpine to induce sweating (as a diagnostic test)[61], and tap water to treat hyperhidrosis[62]. Reverse iontophoresis has been used to extract glucose from the skin as a means of monitoring glucose levels in diabetic patients[63].

Electroporation (electropermeabilization) utilizes very short (microsecond to millisecond) and relatively high voltage (~100 V) electrical pulses to induce structural rearrangement of stratum corneum lipids, leading to pore formation[64,65]. Properly designed systems can minimize sensations from the pulses and facilitate delivery, especially of hydrophilic and charged molecules into the skin. Although only at the research stage with regard to transdermal delivery, electroporation is currently being used to drive chemotherapeutic agents into superficial skin tumors by applying surface or penetrating electrodes[66].

While *ultrasound* is widely and safely employed in both medical diagnostics and physical therapy, this technology can also be used to enhance transdermal delivery. When ultrasound is utilized in a manner that resembles medical imaging, it is not very effective at increasing skin permeability. However, ultrasound administered in the context of heating deep tissues, for example during physical therapy, has been shown to increase drug penetration into the skin, and this technique is actually used to increase local delivery of anti-inflammatory agents at the time of physical therapy[67]. With still different settings (in particular low frequencies such as <1 MHz), ultrasound can be used to generate bubble activity, referred to as "*cavitation*". Cavitation bubbles oscillating and imploding in the medium between the ultrasound transducer and the skin surface generate shockwaves that mechanically impact the skin, creating submicroscopic defects in stratum corneum structure. These defects increase skin permeability to water-soluble molecules and some macromolecules[68]. In a related approach, pulsed laser beams have also been used to generate photomechanical shockwaves at the skin surface, which also increase skin permeability[69]. Cavitational ultrasound of the skin has been approved as a pretreatment prior to the application of lidocaine as a means of accelerating local anesthesia.

In addition to the methods described above that disrupt stratum corneum structure on a nanometer scale, there are methods for producing micron-scale holes within the stratum corneum. This enables delivery of much larger molecules with much greater fluxes into the skin. With *thermal ablation*, microsecond- to millisecond-long pulses of heat are applied utilizing electrical filaments, radiofrequency electrodes or lasers which lead to micron-sized holes in the stratum corneum[70,71]. Because the pulses are so short, there is not enough time for heat to propagate deeply into the tissue, thereby localizing the ablation to the epidermis and minimizing pain; these latter effects have been demonstrated in clinical trials. An at least partial removal of the stratum corneum and an increase in skin permeability can also be accomplished via sandpaper abrasion and microdermabrasion[72,73].

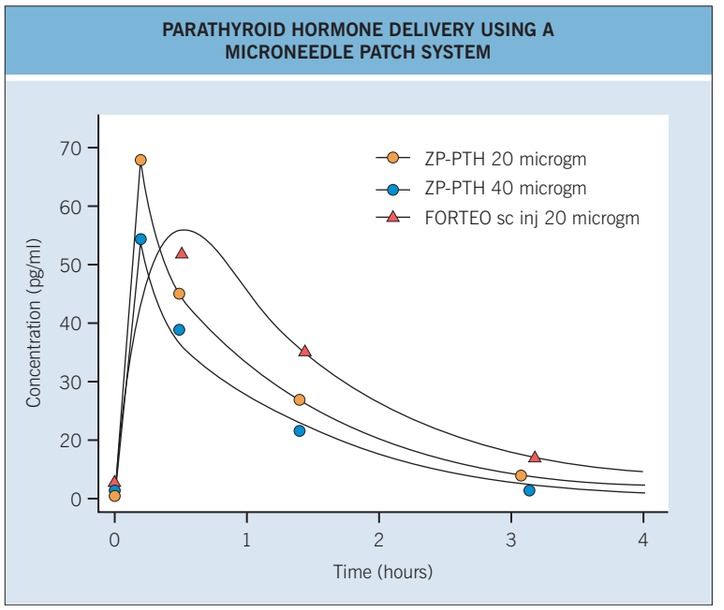


Fig. 124.11 Parathyroid hormone delivery to human subjects using a microneedle patch system. Subcutaneous (sc) injection of synthetic human parathyroid hormone 1-34 (FORTEO) achieved a peak drug concentration (T_{max}) at 23 min, whereas application of a microneedle patch coated with the same drug achieved a T_{max} of 8 min (ZP-PTH). *Reproduced with permission from Daddona PE, et al. Parathyroid hormone (1-34)-coated microneedle patch system: clinical pharmacokinetics and pharmacodynamics for treatment of osteoporosis. Pharm Res. 2011;28:159–65.*

Finally, *microneedles* represent another micron-scale approach to drug delivery via the skin[74]. Microneedles typically measure 0.1–1 mm in length; they can be solid or hollow and are manufactured by microfabrication tools similar to those used in the microelectronics industry. When solid, microneedles can be incorporated into patches that are applied to the skin and possibly worn for some time. In clinical trials, microneedles have been used to punch microscopic holes into the skin prior to the application of drug-loaded patches such as those containing naltrexone[75]. Drug-coated solid microneedles, designed to undergo dissolution upon insertion into the skin, have also been tested, and the efficacy of parathyroid hormone delivered in this manner for the treatment of osteoporosis has been demonstrated[76] (Fig. 124.11).

In contrast to the Mantoux technique, which requires clinical training to ensure an intradermal location for the needle injection[77], hollow microneedles enable simple and reliable intradermal injections. Clinical trials in patients with diabetes have shown accelerated pharmacokinetics of insulin after microneedle injections into the skin, when compared to conventional subcutaneous infusions[78]. Influenza vaccine that is approved for injection into the skin using a microneedle demonstrated increased immunogenicity in the elderly and a lower dose was effective in non-elderly adults[79]. This increased effectiveness of the vaccine is due to the highly immunoresponsive environment in the skin compared to muscle, the conventional site of vaccination.

REFERENCES

1. Scheuplein RJ, Blank IH. Permeability of the skin. Physiol Rev. 1971;51:702–47.
2. Elias PM. Epidermal lipids, barrier function, and desquamation. J Invest Dermatol. 1983;80(suppl.):44S–9S.
3. Elias PM, Menon GK. Structural and lipid biochemical correlates of the epidermal permeability barrier. Adv Lipid Res. 1991;24:1–26.
4. Lampe MA, Burlingame AL, Whitney J, et al. Human stratum corneum lipids: characterization and regional variations. J Lipid Res. 1983;24:120–30.
5. Rougier A, Dupuis D, Lotte C, et al. In vivo correlation between stratum corneum reservoir function and percutaneous absorption. J Invest Dermatol. 1983;81:275–8.
6. Prausnitz MR, Langer R. Transdermal drug delivery. Nat Biotechnol. 2008;26:1261–8.
7. Bronaugh RL, Maibach HI (eds). Percutaneous Absorption: Drugs-Cosmetics-Mechanisms-Methodology, 4th edn. New York: Marcel Dekker, 2005.
8. Menon GK, Elias PM. Morphologic basis for a pore-pathway in mammalian stratum corneum. Skin Pharmacol. 1997;10:235–46.
9. Potts RO, Francoeur ML. The influence of stratum corneum morphology on water permeability. J Invest Dermatol. 1991;96:495–9.
10. Wertz PH, Downing DL. Epidermal lipids. In: Goldsmith LA (ed.). Physiology, Biochemistry and Molecular Biology of the Skin. New York: Oxford University Press, 1991:205–36.
11. Schurer NY, Elias PM. The biochemistry and function of stratum corneum lipids. Adv Lipid Res. 1991;24:27–56.
12. Bouwstra JA, Gooris GS, Cheng K, et al. Phase behavior of isolated skin lipids. J Lipid Res. 1996;37:999–1011.
13. Wertz PW, Downing DT. Ceramides of pig epidermis: structure determination. J Lipid Res. 1983;24:759–65.
14. Norlen L, Nicander I, Lundh Rozell B, et al. Inter- and intra-individual differences in human stratum corneum lipid content related to physical parameters of skin barrier function in vivo. J Invest Dermatol. 1999;112:72–7.
15. Forslind B. A domain mosaic model of the skin barrier. Acta Derm Venereol. 1994;74:1–6.
16. Haftek M, Teillon MH, Schmitt D. Stratum corneum, corneodesmosomes and ex vivo percutaneous penetration. Microsc Res Tech. 1998;43:242–9.
17. Feingold KR. The regulation and role of epidermal lipid synthesis. Adv Lipid Res. 1991;24:57–82.

18. Menon GK, Elias PM, Lee SH, Feingold KR. Localization of calcium in murine epidermis following disruption and repair of the permeability barrier. Cell Tissue Res. 1992;270:503–12.
19. Menon GK, Feingold KR, Elias PM. Lamellar body secretory response to barrier disruption. J Invest Dermatol. 1992;98:279–89.
20. Menon GK, Elias PM, Feingold KR. Integrity of the permeability barrier is crucial for maintenance of the epidermal calcium gradient. Br J Dermatol. 1994;130:139–47.
21. Lee SH, Elias PM, Proksch E, et al. Calcium and potassium are important regulators of barrier homeostasis in murine epidermis. J Clin Invest. 1992;89:530–8.
22. Mao-Qiang M, Brown BE, Wu-Pong S, et al. Exogenous nonphysiologic vs physiologic lipids. Divergent mechanisms for correction of permeability barrier dysfunction. Arch Dermatol. 1995;131:809–16.
23. Mao-Qiang M, Feingold KR, Jain M, Elias PM. Extracellular processing of phospholipids is required for permeability barrier homeostasis. J Lipid Res. 1995;36:1925–35.
24. Mao-Qiang M, Jain M, Feingold KR, Elias PM. Secretory phospholipase A2 activity is required for permeability barrier homeostasis. J Invest Dermatol. 1996;106:57–63.
25. Schmuth M, Man MQ, Weber F, et al. Permeability barrier disorder in Niemann-Pick disease: sphingomyelin-ceramide processing required for normal barrier homeostasis. J Invest Dermatol. 2000; 115:459–66.
26. Elias PM, Williams ML, Maloney ME, et al. Stratum corneum lipids in disorders of cornification. Steroid sulfatase and cholesterol sulfate in normal desquamation and the pathogenesis of recessive X-linked ichthyosis. J Clin Invest. 1984;74:1414–21.
27. Zettersten E, Man MQ, Sato J, et al. Recessive X-linked ichthyosis: role of cholesterol-sulfate accumulation in the barrier abnormality. J Invest Dermatol. 1998;111:784–90.
28. Maloney ME, Williams ML, Epstein EH Jr, et al. Lipids in the pathogenesis of ichthyosis: topical cholesterol sulfate-induced scaling in hairless mice. J Invest Dermatol. 1984;83:252–6.
29. Behne MJ, Meyer JW, Hanson KM, et al. NHE1 regulates the stratum corneum permeability barrier homeostasis. Microenvironment acidification assessed with fluorescence lifetime imaging. J Biol Chem. 2002;277:47399–406.
30. Chapman SJ, Walsh A. Membrane-coating granules are acidic organelles which possess proton pumps. J Invest Dermatol. 1989;93:466–70.
31. Mauro T, Holleran WM, Grayson S, et al. Barrier recovery is impeded at neutral pH, independent of ionic effects: implications for extracellular lipid processing. Arch Dermatol Res. 1998;290:215–22.
32. Williams A. Transdermal and Topical Drug Delivery. London: Pharmaceutical Press, 2003.
33. Michaels AS, Chandrasekaran SK, Shaw JE. Drug permeation through human skin: theory and in vitro experimental measurement. AIChE J. 1975;21:985–96.
34. Franz TJ. Kinetics of cutaneous drug penetration. Int J Dermatol. 1983;22:499–505.
35. Stoughton RB. Vasoconstrictor assay: specific applications. In: Maibach HI, Surber C (eds). Topical Corticosteroids. Basel: Karger, 1992:42–53.
36. Gupta SK, Southam M, Gale R, Hwang SS. System functionality and physicochemical model of fentanyl transdermal system. J Pain Symptom Manage. 1992;7(3 Suppl):S17–S26.
37. Franz TJ, Lehman PA. Percutaneous absorption of sulconazole nitrate in man. J Pharm Sci. 1988;77:489–91.
38. US Food and Drug Administration. Guidance for Industry. Residual Drug in Transdermal and Related Drug Delivery Systems (Draft Guidance). Silver Spring, MD: Center for Drug Evaluation and Research (CDER), August 2010.
39. Van Den Merwe E, Ackermann C. Physical changes in hydrated skin. Int J Cosmet Sci. 1987;9:237–47.
40. Williams AC, Barry BW. Penetration enhancers. Adv Drug Deliv Rev. 2004;56:603–18.
41. Karande, P, Jain A, Ergun K, et al. Design principles of chemical penetration enhancers for transdermal drug delivery. Proc Natl Acad Sci USA. 2005;102: 4688–93.
42. Wester RC, Maibach HI. Regional variation in percutaneous absorption. In: Bronaugh RL, Maibach HI (eds). Percutaneous Absorption: Drugs, Cosmetics, Mechanisms, Methodology. New York: Marcel Dekker, 1999:107–16.
43. Bucks DAW. Permeability through diseased and damaged skin. In: Walters K, Roberts M, (eds). Dermatologic, Cosmeceutic and Cosmetic Development. New York: Informa Healthcare, 2008:157–67.
44. Choy YB, Prausnitz MR. The rule of five for non-oral routes of drug delivery: ophthalmic, inhalation and transdermal. Pharm Res. 2011;28:943–8.
45. Mikulowska A. Reactive changes in human epidermis following simple occlusion with water. Contact Dermatitis. 1992;25:224–7.
46. Menon GK, Lee SH, Roberts MS. Ultrastructural effects of some solvents and vehicles on the stratum corneum and other skin components: evidence for an "extended mosaic-partitioning model of the skin barrier". In: Robert MS, Walters KA (eds). Dermal Absorption and Toxicity Assessment. New York: Marcel Dekker, 1998: 727–51.
47. Karande P, Jain A, Mitragotri S. Discovery of transdermal penetration enhancers by high-throughput screening. Nat Biotechnol. 2004;22:192–7.
48. Sinico C, Fadda AM. Vesicular carriers for dermal drug delivery. Expert Opin Drug Deliv. 2009;6:813–25.
49. Lasch J, Laub R, Wohlrab W. How deep do intact liposomes penetrate into human skin? J Contr Rel. 1992;18:55–8.
50. Rothbard JB, Garlington S, Lin Q, et al. Conjugation of arginine oligomers to cyclosporin A facilitates topical delivery and inhibition of inflammation. Nat Med. 2000;6:1253–7.
51. Chen Y, Shen Y, Guo X, et al. Transdermal protein delivery by a coadministered peptide identified via phage display. Nat Biotechnol. 2006;24:455–60.
52. Kim YC, Ludovice PJ, Prausnitz MR. Transdermal delivery enhanced by magainin pore-forming peptide. J Control Release. 2007;122:375–83.
53. Tsai JC, Guy RH, Thornfeldt CR, et al. Metabolic approaches to enhance transdermal drug delivery. 1. Effect of lipid synthesis inhibitors. J Pharm Sci. 1996;85:643–8.
54. Arora A, Prausnitz MR, Mitragotri S. Micro-scale devices for transdermal drug delivery. Int J Pharm. 2008;364:227–36.
55. Banga AK. Transdermal and Intradermal Delivery of Therapeutic Agents: Application of Physical Technologies. Boca Raton, FL: CRC Press, 2011.
56. Spruit D, Malten KE. The regeneration rate of the water vapour loss of heavily damaged skin. Dermatologica. 1966;132:115–23.
57. Reed JT, Ghadially R, Elias PM. Skin type, but neither race nor gender, influence epidermal permeability barrier function. Arch Dermatol. 1995;131:1134–8.
58. Banga AK. Electrically-Assisted Transdermal and Topical Drug Delivery. London: Taylor & Francis, 1998.
59. Subramony JA, Sharma A, Phipps JB. Microprocessor controlled transdermal drug delivery. Int J Pharm. 2006:317:1–6.
60. Mayes S, Ferrone M. Fentanyl HCl patient-controlled iontophoretic transdermal system for the management of acute postoperative pain. Ann Pharmacother. 2006;40:2178–86.
61. Beauchamp M, Lands LC. Sweat-testing: a review of current technical requirements. Pediatr Pulmonol. 2005;39:507–11.
62. Kreyden OP. Iontophoresis for palmoplantar hyperhidrosis. J Cosmet Dermatol. 2004;3:211–4.
63. Tamada J, Garg S, Jovanovic L, et al. Noninvasive glucose monitoring: comprehensive clinical results. Cygnus Research Team. JAMA 1999:282:1839–44.
64. Prausnitz MR, Bose VG, Langer R, Weaver JC. Electroporation of mammalian skin: a mechanism to enhance transdermal drug delivery. Proc Natl Acad Sci USA. 1993;90:10504–8.
65. Denet AR, Vanbever R, Preat V. Skin electroporation for transdermal and topical delivery. Adv Drug Deliv Rev. 2004;56:659–74.
66. Gehl J. Electroporation for drug and gene delivery in the clinic: doctors go electric. Methods Mol Biol. 2008;423:351–9.
67. Machet L, Boucaud A. Phonophoresis: efficiency, mechanisms and skin tolerance. Int J Pharm. 2002;243:1–15.
68. Ogura M, Paliwal S, Mitragotri S. Low-frequency sonophoresis: current status and future prospects. Adv Drug Deliv Rev. 2008;60:1218–23.
69. Doukas AG, Kollias N. Transdermal drug delivery with a pressure wave. Adv Drug Deliv Rev. 2004;56:559–79.
70. Levin G, Gershonowitz A, Sacks H, et al. Transdermal delivery of human growth hormone through RF-microchannels. Pharm Res. 2005;22:550–5.
71. Bramson J, Dayball K, Evelegh C, et al. Enabling topical immunization via microporation: a novel method for pain-free and needle-free delivery of adenovirus-based vaccines. Gene Ther. 2003;10:251–60.
72. Glenn GM, Flyer DC, Ellingsworth LR, et al. Transcutaneous immunization with heat-labile enterotoxin: development of a needle-free vaccine patch. Expert Rev Vaccines. 2007;6:809–19.
73. Andrews S, Lee JW, Choi SO, Prausnitz MR. Transdermal insulin delivery using microdermabrasion. Pharm Res. 2011;28:2110–8.
74. Prausnitz MR, Mikszta JA, Cormier M, Andrianov AK. Microneedle-based vaccines. Curr Top Microbiol Immunol. 2009;333:369–93.
75. Wermeling DP, Banks SL, Hudson DA, et al. Microneedles permit transdermal delivery of a skin-impermeant medication to humans. Proc Natl Acad Sci USA. 2008;105:2058–63.
76. Cosman F, Lane NE, Bolognese MA, et al. Effect of transdermal teriparatide administration on bone mineral density in postmenopausal women. J Clin Endocrinol Metab. 2010;95:151–8.
77. Flynn PM, Shenep JL, Mao L, et al. Influence of needle gauge in Mantoux skin testing. Chest. 1994;106: 1463–5.
78. Pettis RJ, Ginsberg B, Hirsch L, et al. Intradermal microneedle delivery of insulin lispro achieves faster insulin absorption and insulin action than subcutaneous injection. Diabetes Technol Ther. 2011;13:435–42.
79. Atmar RL, Patel SM, Keitel WA. Intanza®: a new intradermal vaccine for seasonal influenza. Expert Rev Vaccines. 2010;9:1399–409.

This page intentionally left blank

Glucocorticosteroids 125

Scott M Jackson and Lee T Nesbitt Jr

Key features

- Glucocorticosteroids continue to be among the most commonly prescribed anti-inflammatory agents in dermatology and all of medicine, with a large number of disorders responding to these drugs
- Proper systemic use of glucocorticosteroids requires a working knowledge of the hypothalamic–pituitary–adrenal (HPA) axis
- Proper local (topical and intralesional) use of glucocorticosteroids requires awareness of their various formulations and potencies
- Glucocorticosteroids have a broad range of potential adverse effects that can be minimized by a variety of strategies
- Clinical usage guidelines facilitate proper dosing and administration of glucocorticosteroids for both short-term and long-term therapy

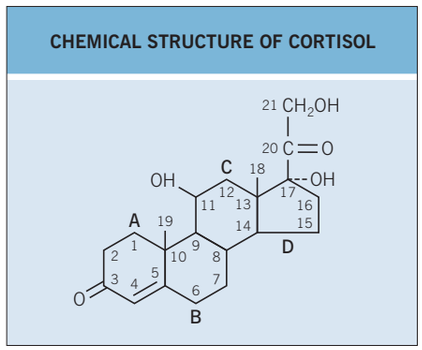


Fig. 125.1 Chemical structure of cortisol (hydrocortisone). Note the hydroxyl group at the 11 position.

INTRODUCTION

The Nobel Prize in Medicine was awarded in 1950 to Hench and associates[1] for their initial work on the beneficial effects and toxicities of glucocorticosteroids (glucocorticoids), which focused on rheumatic disorders. In 1951, Sulzberger and colleagues[2] first reported the use of systemic cortisone and adrenocorticotropic hormone (ACTH) as therapies for inflammatory skin diseases. One year later, Sulzberger and Witten successfully treated eczematous eruptions with topical hydrocortisone. In 1961, Reichling and Kligman[3] employed alternate-day oral glucocorticosteroid therapy for skin conditions. A novel method of high-dose glucocorticosteroid therapy was introduced to dermatology in 1982 by Johnson and Lazarus[4], who used pulse intravenous therapy for pyoderma gangrenosum. During the past 40 years, a variety of other anti-inflammatory/immunomodulatory drugs have been developed, allowing for a "corticosteroid-sparing" effect and minimization of risks from long-term therapy with systemic glucocorticosteroids.

PHARMACOLOGY AND MECHANISM OF ACTION

Structure and Metabolism

All steroids, including glucocorticosteroids, have the basic four-ring structure of cholesterol, with three hexane rings and one pentane ring. Figure 125.1 shows the chemical structure of hydrocortisone (cortisol). Modifications in the basic four-ring structure of glucocorticosteroids result in systemic agents that have different potencies, mineralocorticoid effects, durations of action (biologic half-life), and metabolism. Table 125.1 lists the key pharmacologic properties of the major systemic agents used today. Similar changes in the basic structure of the glucocorticosteroid molecule have resulted in various topical agents with differing solubilities, lipophilic properties, degrees of percutaneous absorption, and glucocorticoid receptor-binding activities.

When examining the chemical structure of glucocorticosteroids, it is important to recognize that active agents such as hydrocortisone (see Fig. 125.1) have a hydroxyl group at the 11 position. The corresponding inactive drug, cortisone, has a ketone group at the 11 position and must undergo hepatic conversion to hydrocortisone for biologic activity. The same is true for prednisone, which must undergo the identical 11-hydroxylation by the liver to produce an active agent, prednisolone. Since conversion of the inactive drug to its active analogue is impaired in patients who have severe hepatic disease, it is best to treat such individuals with a medication such as prednisolone that does not require metabolic alteration to be of therapeutic benefit[5].

In addition to indicating equivalent glucocorticosteroid doses in milligrams, Table 125.1 shows that these agents differ in their relative mineralocorticoid as well as glucocorticosteroid potencies. Cortisone and hydrocortisone have fairly significant mineralocorticoid potency, whereas prednisone and prednisolone have slight mineralocorticoid effects. A drug that has no mineralocorticoid activity, such as methylprednisolone, would be an excellent choice in situations in which mineralocorticoid effects must be avoided[5].

Plasma half-lives of the various systemic glucocorticosteroids vary from about 1 to 5 hours, as seen in Table 125.1. However, the plasma half-life is a poor indicator of the duration of action (biologic activity) of each drug. Duration of biologic effect is best assessed by the period of suppression of ACTH secretion by the pituitary gland after the administration of a single dose of a particular glucocorticosteroid. As seen in Table 125.1, short-acting glucocorticosteroids have an effect for 8–12 hours, intermediate-acting agents for 24–36 hours, and long-acting agents for more than 48 hours. Duration of biologic activity is a critical factor in choosing a glucocorticosteroid for alternate-day therapy. Intermediate-acting agents should be used for this purpose, with long-acting agents avoided because there would be no period for recovery of the hypothalamic–pituitary–adrenal (HPA) axis (see below)[5].

Absorption and Distribution

Oral glucocorticosteroids are absorbed in the jejunum, with peak plasma levels occurring 30–90 minutes after intake. Administration of these drugs with food may delay absorption but does not decrease the amount absorbed.

Once glucocorticosteroids reach the plasma, the primary carrier protein is corticosteroid-binding globulin (CBG), also known as transcortin. Most endogenous cortisol is bound to CBG, and low doses of exogenous glucocorticosteroids are initially primarily bound by this high-affinity, but low-capacity, carrier system. With larger glucocorticosteroid doses, some binding also occurs to albumin in a low-affinity fashion, but with a greater capacity because of the larger amount of albumin in the plasma. The avidity with which exogenous glucocorticosteroids bind to these two carrier proteins is less than that of endogenous cortisol. As exogenous glucocorticosteroids fill CBG binding

PHARMACOLOGY OF SYSTEMIC GLUCOCORTICOSTEROIDS					
	Equivalent GCS *dose* (mg)	GCS *potency* (relative)	Mineralocorticoid potency (relative)	Duration of action (hours)*	Plasma half-life (minutes)
SHORT-ACTING					
Cortisone	25	0.8	1.0	8–12	60
Hydrocortisone	20	1	0.8	8–12	90
INTERMEDIATE-ACTING					
Prednisone	5	4	0.25	24–36	60
Prednisolone	5	4	0.25	24–36	200
Methylprednisolone	4	5	0	24–36	180
Triamcinolone	4	5	0	24–36	300
LONG-ACTING					
Dexamethasone	0.75	25–30	0	36–54	200
Betamethasone	0.6	30–35	0	36–54	200

*Differs for intramuscular administration (see text).

Table 125.1 Pharmacology of systemic glucocorticosteroids (GCSs).

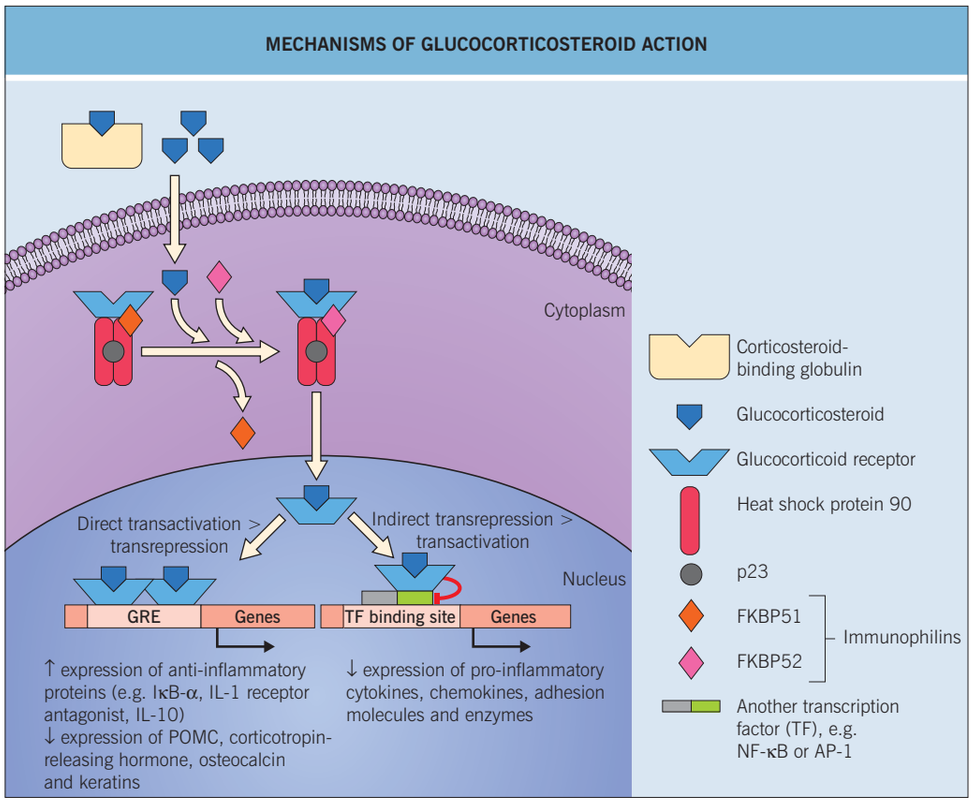


Fig. 125.2 Mechanisms of glucocorticosteroid action. "Free" glucocorticosteroid enters the cell and binds to the glucocorticoid receptor (which forms a complex that includes the 90 kDa heat shock protein and an immunophilin, FK506-binding protein 51 [FKBP51]) in the cytoplasm. After glucocorticosteroid binding, FKBP52 replaces FKBP51 and facilitates nuclear translocation. In the nucleus, ligand-bound glucocorticoid receptor homodimers directly bind to glucocorticoid response elements (GREs) in the promoter regions of target genes, which leads to activation or (less often) repression of transcription. Glucocorticoid receptor monomers can also indirectly affect gene expression by interacting with and inhibiting other transcription factors such as nuclear factor-κB (NF-κB) or activator protein 1 (AP-1), resulting in decreased transcription of proinflammatory genes. IL, interleukin; IκB-α, inhibitor κB-α; POMC, proopiomelanocortin.

sites, increased low-affinity binding to albumin leads to a greater fraction of free (unbound) glucocorticosteroid. The free fraction is biologically active, entering cells and mediating glucocorticosteroid effects[5]. Disorders that result in decreased binding proteins in the plasma, such as hepatic or renal disease, increase the free fraction of exogenous glucocorticosteroids and thereby augment the therapeutic effects and toxicities of these drugs.

The Hypothalamic–Pituitary–Adrenal (HPA) Axis

A working knowledge of the normal function of the HPA axis is required to understand glucocorticosteroid physiology. The hypothalamus produces corticotropin-releasing hormone, which is released in small pulses into the pituitary circulation. The anterior pituitary responds to corticotropin-releasing hormone with synthesis of ACTH and its subsequent pulsatile secretion into the peripheral circulation. ACTH is the hormone that stimulates the middle layer of the adrenal cortex to generate and release cortisol. In an individual with a normal sleep cycle, the greatest amount of cortisol is released during the early morning hours prior to waking. Under basal conditions, the adrenals produce approximately 20–30 mg of cortisol (equivalent to 5–7.5 mg of prednisone) per day in an adult, but this may increase up to 10-fold under times of maximal stress. ACTH also has some role in stimulating adrenal androgen production, but it is not significantly involved in the production of the major mineralocorticoid, aldosterone. The major mineralocorticoid control mechanisms are the renin–angiotensin system and serum potassium levels.

There are three main control mechanisms for endogenous cortisol secretion[6]. The first is a negative feedback effect by plasma cortisol, which inhibits the secretion of corticotropin-releasing hormone and ACTH by the hypothalamus and pituitary, respectively. The second method of regulation is the pulsatile secretion of ACTH, which is based on a circadian cycle, with increasing pulses beginning several hours

ANTI-INFLAMMATORY EFFECTS OF GLUCOCORTICOSTEROIDS
DECREASED PRODUCTION OF CYTOKINES AND OTHER PRO-INFLAMMATORY MOLECULES
• Tumor necrosis factor-α • Granulocyte–macrophage colony-stimulating factor • Interleukin (IL)-1, IL-2, IL-6 and IL-8 • Intercellular adhesion molecule (ICAM)-1, E-selectin • Leukotrienes and prostaglandins (due to decreased phospholipase A_2 and cyclooxygenase activity)
EFFECTS ON INFLAMMATORY CELLS
• **Neutrophils** – Increased release from the bone marrow, resulting in neutrophilia (due to larger circulating pool) – Decreased infiltration into sites of inflammation (due to reduced expression of endothelial adhesion molecules and chemoattractants) – Decreased apoptosis – Phagocytosis and bactericidal function less affected • **Lymphocytes** – Redistribution of T cells to lymphoid depots, resulting in transient lymphopenia – Decreased activation and proliferation of effector (helper > cytotoxic) T cells (related to decreased IL-2 signaling and antigen presentation) – Decreased B-cell function and antibody production (at high doses) – Increased apoptosis – Increased regulatory T-cell function • **Eosinophils** – Decreased release from bone marrow and recruitment to sites of inflammation – Increased apoptosis • **Monocytes/macrophages** – Decreased production, differentiation and antigen presentation • **Mast cells** – Decreased maturation, cytokine production, high-affinity IgE receptor (FcεRI) expression and mediator release • **Erythrocytes** – Decreased destruction (due to reduced autohemolysis and erythrophagocytosis)

Table 125.2 Anti-inflammatory effects of glucocorticosteroids.

MAJOR USES OF SYSTEMIC GLUCOCORTICOSTEROIDS IN DERMATOLOGY
SEVERE DERMATITIS
• Contact dermatitis (various forms) • Atopic dermatitis • Photodermatitis • Exfoliative erythrodermas
BULLOUS DERMATOSES
• Pemphigus (all forms) • Bullous pemphigoid • Mucous membrane (cicatricial) pemphigoid • Linear IgA bullous dermatosis • Epidermolysis bullosa acquisita • Gestational pemphigoid • Erythema multiforme (major)
VASCULITIS
• Cutaneous (various types) • Systemic (various types)
AUTOIMMUNE CONNECTIVE TISSUE DISEASES
• Lupus erythematosus • Dermatomyositis • Systemic sclerosis • Morphea (severe generalized and linear variants) • Eosinophilic fasciitis • Mixed connective tissue disease • Relapsing polychondritis
NEUTROPHILIC DERMATOSES
• Pyoderma gangrenosum • Sweet's syndrome (acute febrile neutrophilic dermatosis) • Behçet's disease
OTHER DISORDERS
• Sarcoidosis • Lichen planus • Panniculitis (some types) • Urticaria/angioedema (acutely) • Drug reaction with eosinophilia and systemic symptoms (DRESS) • Arthropod bites/stings • Infantile hemangiomas

Table 125.3 Major uses of systemic glucocorticosteroids in dermatology.

after the onset of sleep and reaching a maximum shortly before waking. From these ACTH pulses, the peak release of cortisol in a typical sleep cycle is at about 6–8 a.m. With other sleep cycles, the circadian pattern will adjust so that peak cortisol levels occur just prior to waking. The third form of control of endogenous cortisol production comes from neural effects on the HPA axis in response to various emotional or physical stresses. These neural stimuli include catecholamine production from the brainstem, corticotropin-releasing hormone from sites other than the hypothalamus, and vasopressin.

Molecular Mechanisms

As depicted in Figure 125.2, the glucocorticosteroid free (unbound) fraction enters cells and exerts its effects by binding to the glucocorticoid receptor, which is located in the cytoplasm of almost all cells of the body in a protein complex that includes the 90 kDa heat shock protein[7]. Binding of glucocorticosteroids to this receptor leads to their translocation into the nucleus and eventual release from the protein complex. In the nucleus, the glucocorticoid receptor forms a dimer that binds to glucocorticoid response elements in the promoter region of certain genes (see Fig. 125.2). Approximately 10–100 genes in each cell are regulated directly by glucocorticosteroids[8]. This binding affects the rate of transcription, inducing or (less often) repressing messenger RNA production and protein synthesis.

The glucocorticoid receptor also interacts with other transcription factors (see Fig. 125.2) that have a central role in the inflammatory response as well as their coactivator molecules, such as cAMP response element binding protein (CREB)-binding protein. Nuclear factor-κB (NF-κB) is an important transcription factor that induces the expression of many genes that play a significant role in chronic inflammation, encoding various cytokines, adhesion molecules, inflammatory enzymes, and growth factors. By indirectly and directly inhibiting NF-κB, the glucocorticoid receptor can dramatically reduce the inflammatory process[8]. The glucocorticoid receptor also has an inhibitory effect on activator protein 1 (AP-1; a collective term for the heterodimeric transcription factor composed of proteins such as c-jun, c-fos and activating transcription factor), which likewise controls expression of growth factor and cytokine genes. The key cytokines and other proinflammatory molecules that are inhibited by glucocorticosteroids and the effects of these drugs on inflammatory cells are summarized in Table 125.2[9,10].

CLINICAL INDICATIONS, DOSAGES AND CONTRAINDICATIONS

Table 125.3 lists major categories of dermatologic disease in which systemic glucocorticosteroids are used. There are many more skin conditions for which topical and intralesional glucocorticosteroids can be helpful, such as papulosquamous disorders and other localized inflammatory processes.

Oral Therapy

Dermatologists use glucocorticosteroids for short periods to treat acute conditions such as extensive allergic contact dermatitis and other acute eczematous disorders. Therapy is considered as short-term if it is administered for approximately 3 weeks or less. An oral agent with an intermediate duration of action, such as prednisone, is usually given in a single early-morning dose to achieve the least HPA axis suppression[11]. In some severe acute dermatoses, the dose can be divided and administered twice (or occasionally up to four times) daily for better initial

control, but conversion to a single early-morning dose should occur as soon as possible. Split-dose therapy results in parallel increases in efficacy and toxicity. Despite the same total number of milligrams, the split dose may simply be considered to represent the equivalent of a slightly higher single morning dose. The daily dose of prednisone can vary depending on the severity of the dermatosis, but for most moderate, self-limited conditions in average-weight adults, a common initial dose is 40–60 mg/day (corresponding to approximately 1 mg/kg/day in children).

Long-term therapy is usually defined as that lasting 4 weeks or more, but it often refers to treatment lasting for months to years[5]. In these situations, corticosteroid-sparing agents are usually added in an attempt to reduce the glucocorticosteroid dose required to control the disease process, or to eliminate the glucocorticosteroid altogether.

Prednisone is often the intermediate-acting glucocorticosteroid of choice for both short-term and long-term therapy. It is inexpensive and available in many dosage forms[6].

Methylprednisolone can be used if there is a need to eliminate all mineralocorticoid effects. Intermediate-acting drugs such as prednisone and methylprednisolone are also utilized for alternate-morning therapy (a common component of tapering regimens; see below), which allows the HPA axis to recover in the last 12 hours of the off-day of therapy. Other advantages of alternate-morning glucocorticosteroid therapy are listed in Table 125.4. Two important side effects of long-term glucocorticosteroid therapy that are not minimized by alternate-morning dosing are osteoporosis and cataracts (see below).

Although it may help to prevent a disease rebound, tapering of the glucocorticosteroid dose is not usually necessary from an adrenal recovery standpoint in short-term therapy. However, tapering to allow adrenal recovery is an important consideration when treatment is for longer than a few weeks. Manifestations of the glucocorticosteroid withdrawal syndrome include arthralgias, myalgias, mood changes, fatigue, headache, and gastrointestinal symptoms (e.g. nausea, vomiting, anorexia)[12]. When this syndrome occurs, a return to the previous dose of glucocorticosteroid, followed by more gradual tapering, is recommended. In general, the rate of prednisone tapering depends on both features of the dermatosis (e.g. type, activity, severity) and adrenal recovery issues. The prednisone dose can usually be tapered in 20 mg increments at doses greater than 60 mg/day, 10 mg increments between 30 and 60 mg/day, and 5 mg increments between 30 mg and the physiologic dose range. Once the physiologic dose range of 5–7.5 mg/day of prednisone is reached, a more gradual reduction (e.g. in 1–2.5 mg increments) may be necessary to allow adrenal recovery.

Another method of glucocorticosteroid dosage tapering is to convert from daily to alternate-day therapy once the prednisone dose is about 20–30 mg/day[5]. The simplest way to convert is to multiply the previous daily dose by 2–2.5 times for the on-day dose, and taper therapy rapidly on the off-day. An alternative method is to increase the on-day dose by 5 mg increments and decrease the off-day dose by a similar amount, until therapy is eventually doubled on the on-day and stopped on the off-day. Finally, simultaneous tapering and alternate-morning conversion can be accomplished by decreasing the dose by 5 mg on the alternate morning, with the patient eventually taking the same dose every other morning as they were taking daily.

ALTERNATE-MORNING GLUCOCORTICOSTEROID THERAPY
• "Off" days allow recovery of hypothalamic–pituitary–adrenal (HPA) axis
• Decreases risks of:
– Growth suppression
– Myopathy
– Hypertension
– Opportunistic infections
– Neuropsychiatric effects*
– Electrolyte imbalances (e.g. hypokalemia, hypocalcemia)
• Does *not* substantially alter risks of osteoporosis or cataracts
• Fluctuations in glucose levels can make diabetes mellitus more difficult to manage
*Except occasional worsening of bipolar behavior.

Table 125.4 Alternate-morning glucocorticosteroid therapy.

Intramuscular Therapy

Dermatologists occasionally use intramuscular administration of glucocorticosteroids for control of acute dermatoses[13]. Although some acute dermatoses respond very well to intramuscular glucocorticosteroid therapy, serious conditions such as pemphigus vulgaris or severe drug reactions are best treated by other routes of systemic administration because of the initial need for higher daily doses and the requirement for more control over dosage changes. Advantages of intramuscular glucocorticosteroid therapy include guaranteed compliance due to physician administration and an assured steady release of glucocorticosteroids achieved by depot preparations. Opponents of intramuscular therapy stress that oral morning doses are more physiologic, are absorbed more predictably, allow more precise tapering, and can be administered on alternate-morning schedules to further decrease HPA axis suppression. There also is the possibility of lipoatrophy or a sterile abscess at an injection site, especially with triamcinolone if the injection is not given deeply enough into the muscle. Intramuscular agents such as betamethasone and dexamethasone, which have a duration of action of less than 1 week, may be preferred in self-limited dermatoses. Longer-acting intramuscular agents that produce effects for about 3 weeks, such as triamcinolone acetonide and methylprednisolone acetate, should not be given more than about four to six times per year. The physician might be lulled into thinking that therapy is intermittent and relatively safe, while in fact it is continuous for ≥3 weeks per injection, necessitating time for HPA axis recovery.

Intravenous and Pulse Therapy

Intravenous doses of glucocorticosteroids may be necessary in life-threatening dermatologic conditions. A total daily dose of 2 mg/kg or more of methylprednisolone is given initially in divided doses every 6–8 hours in these acute and critical situations. Another method of dosing glucocorticosteroids in severe dermatologic disease is intravenous pulse therapy[14]. With this method, methylprednisolone is given intravenously in doses of 0.5–1 g over 2 hours daily for 1–5 days. This therapy was formerly given in an inpatient setting with cardiac monitoring because arrhythmias and rare cases of sudden death are possible if this treatment is given too quickly. Acute electrolyte shifts are a possible cause for these cardiac effects, so infusion of potassium during the methylprednisolone administration may prevent this problem. In addition, slow infusion of the methylprednisolone over 2 hours usually prevents cardiac effects and has allowed use of this therapy in an outpatient setting. Most commonly, oral doses are continued on a maintenance basis after pulse therapy is given. Pulse therapy allows for a dramatic acute effect in severe dermatoses, but hopes that it would greatly reduce the need or dose of maintenance therapy have not been realized.

Topical Therapy

For topical glucocorticosteroid therapy, there are many different medications available in a wide range of potencies and a variety of vehicles[15]. Topical glucocorticosteroids can be categorized into seven classes based on potency, ranging from the superpotent agents in class 1 to the very low potency agents in class 7. These classes have been developed based on vasoconstrictor assays and double-blind clinical studies[16]. A partial list of topical preparations in each class is shown in Table 125.5. The vehicle can greatly influence the percutaneous absorption and therapeutic efficacy of a particular glucocorticosteroid. In some instances, brand-name and generic formulations may have different potencies. As a result, in the era of generic substitutions and limited formularies, the clinician needs to consider these points, as well as non-compliance, as potential explanations for an unresponsive dermatosis.

In general, a glucocorticosteroid molecule in an ointment vehicle is more potent than the same molecule in a cream or lotion base, because occlusive vehicles enhance percutaneous absorption through increased hydration of the stratum corneum. Gel preparations also tend to be readily absorbed. In selecting a topical glucocorticosteroid preparation for clinical use, one must first choose the desired potency based on the type, location, thickness and extent of lesions. Next, one must select the proper vehicle based on the need for hydration or a drying effect,

POTENCY RANKING OF SOME COMMONLY USED TOPICAL GLUCOCORTICOSTEROIDS
CLASS 1 (SUPERPOTENT)
• Clobetasol propionate gel, ointment, cream, lotion, foam, spray and shampoo 0.05% • Betamethasone dipropionate gel* and ointment* 0.05% • Diflorasone diacetate ointment* 0.05% • Fluocinonide cream 0.1% • Flurandrenolide tape 4 mcg/cm^2 • Halobetasol propionate ointment and cream 0.05%
CLASS 2 (HIGH POTENCY)
• Amcinonide ointment 0.1% • Betamethasone dipropionate cream*, lotion*, gel and ointment 0.05% • Clobetasol propionate solution ("scalp application") 0.05% • Desoximetasone ointment and cream 0.25% and gel 0.05% • Diflorasone diacetate ointment and cream* 0.05% • Fluocinonide gel, ointment, cream and solution 0.05% • Halcinonide ointment, cream and solution 0.1% • Mometasone furoate ointment 0.1% • Triamcinolone acetonide ointment 0.5%
CLASS 3 (HIGH POTENCY)
• Amcinonide cream and lotion 0.1% • Betamethasone dipropionate cream and lotion 0.05% • Betamethasone valerate ointment 0.1% • Diflorasone diacetate cream 0.05% • Fluticasone propionate ointment 0.005% • Triamcinolone acetonide ointment 0.1% and cream 0.5%
CLASS 4 (MEDIUM POTENCY)
• Betamethasone valerate foam 0.12% • Desoximetasone cream 0.05% • Fluocinolone acetonide ointment 0.025% • Flurandrenolide ointment 0.05% • Hydrocortisone valerate ointment 0.2% • Mometasone furoate cream and lotion 0.1% • Triamcinolone acetonide ointment (Kenalog®) and cream 0.1% or spray 0.2%
CLASS 5 (MEDIUM POTENCY)
• Betamethasone dipropionate lotion 0.05% • Betamethasone valerate cream and lotion 0.1% • Clocortolone pivalate cream 0.1% • Fluocinolone acetonide cream 0.025% or oil and shampoo 0.01% • Fluticasone propionate cream and lotion 0.05% • Flurandrenolide cream and lotion 0.05% • Hydrocortisone butyrate ointment, cream and lotion 0.1% • Hydrocortisone probutate cream 0.1% • Hydrocortisone valerate cream 0.2% • Prednicarbate ointment and cream 0.1% • Triamcinolone acetonide ointment 0.025% and lotion 0.1%
CLASS 6 (LOW POTENCY)
• Alclometasone dipropionate ointment and cream 0.05% • Triamcinolone acetonide cream 0.1% (Aristocort®) • Betamethasone valerate lotion 0.1% • Desonide gel, ointment, cream, lotion and foam 0.05% • Fluocinolone acetonide cream and solution 0.01% • Triamcinolone acetonide cream and lotion 0.025%
CLASS 7 (LOW POTENCY)
• Topicals with hydrocortisone, dexamethasone and prednisolone
*Optimized vehicle.

Table 125.5 Potency ranking of some commonly used topical glucocorticosteroids.

OPHTHALMIC GLUCOCORTICOSTEROIDS
MAXIMUM STRENGTH
• Loteprednol suspension 0.5% • Prednisolone suspension and solution 1% • Rimexolone suspension 1%
MODERATE STRENGTH
• Fluorometholone ointment 0.1% and suspension 0.1% or 0.25% • Loteprednol suspension 0.2% • Prednisolone suspension and solution 0.125%
LOWER STRENGTH
• Betamethasone solution 0.1%* • Dexamethasone ointment 0.05%, suspension and solution 0.1% • Difluprednate emulsion 0.05% • Medrysone suspension 1%
*Not available in the US.

Table 125.6 Ophthalmic glucocorticosteroids.

location on the body, and potential for irritation or sensitization by components of the vehicle. Lotions are elegant for the face, creams rub in well, ointments are beneficial for dry lesions, and gels or foams are more useful in hairy areas or for a drying effect. For the face and body folds, high potency and superpotent glucocorticosteroid preparations should be avoided if possible due to the risks of epidermal atrophy in both locations and steroid rosacea/perioral dermatitis on the face. There is some evidence that pulse dosing (i.e. twice daily on the weekends only) may reduce the risk of epidermal atrophy with more potent corticosteroids. Other than decreasing the potency or the frequency of application, it is not certain that any modification reduces the risk of cutaneous atrophy or perioral dermatitis/steroid rosacea.

Innovative topical glucocorticosteroids such as mometasone furoate and fluticasone propionate have low percutaneous absorption and are rapidly metabolized in the liver, minimizing their systemic bioavailability[17]. The latter agent is highly lipophilic and has high affinity for the glucocorticoid receptor without significant binding to androgen, progesterone, estrogen or mineralocorticoid receptors.

Commonly prescribed ophthalmologic glucocorticosteroid preparations are listed in Table 125.6.

Intralesional Therapy

For many localized disorders, especially when topical therapy is not beneficial and systemic therapy is best avoided, intralesional glucocorticosteroid therapy can be very effective. With this method, triamcinolone acetonide is diluted to the desired concentration (which depends on the condition to be treated) and injected in small amounts into the lesion(s), usually with a 30-gauge needle. With thick dermal lesions such as keloids, concentrations as high as 20–40 mg/ml of triamcinolone may be injected, as the desired result is to decrease the excessive connective tissue. However, with other disorders, atrophy of the dermis or fat can occur as a side effect, and a more dilute concentration (as low as 2 mg/ml of triamcinolone acetonide) should be used. The ideal concentration varies depending on the type of lesion to be treated and its location. This method of administration allows the clinician to bypass the barrier of a thickened stratum corneum and/or to treat a dermal inflammatory process (e.g. sarcoidosis, granuloma annulare) directly with higher concentrations of corticosteroid at the site of the pathology, reducing the possibility of epidermal atrophy.

Contraindications

Finally, one must always consider contraindications to glucocorticosteroid therapy, whether it be systemic or local[6]. Herpes simplex keratitis is considered a contraindication to local glucocorticosteroid therapy of the eye. Also, active tuberculosis and systemic fungal infections are usually considered as contraindications to systemic glucocorticosteroid therapy. Previous history of hypersensitivity to an intravenous preparation, which is rare, should preclude further use of that particular intravenous drug. Many other situations, such as active peptic ulcer disease, severe depression or psychosis, and extensive chronic dermatoses (e.g. psoriasis) likely to flare with a rebound after rapid corticosteroid taper, should be relative contraindications to systemic glucocorticosteroid therapy, with these agents used only when necessary.

MAJOR SIDE EFFECTS

Short-term glucocorticosteroid therapy is usually extremely safe for self-limited and acute dermatoses. When side effects do occur with short courses of therapy, those listed in Table 125.7 are most common. With long-term glucocorticosteroid therapy at supraphysiologic doses, there is an increased incidence of more serious effects. Table 125.8 lists the major categories of complications and major adverse effects in each category. Most of these side effects are dose-related. As shown in Table 125.9, some patients have a higher risk of side effects from glucocorticosteroids[6]. The following discussion highlights selected toxicities of glucocorticosteroid therapy.

Osteoporosis

Osteoporosis is one of the most prevalent side effects in patients receiving long-term systemic glucocorticosteroid therapy. Without preventative measures, osteoporosis develops in 30–50% of all patients treated chronically with glucocorticosteroids[18]. The most significant demineralization occurs during the first 6–12 months of therapy, with slowing after this time. Postmenopausal women are most at risk for complications such as fractures, because they have the lowest bone mass before beginning therapy. The greatest amount of bone loss is usually observed in young men, because they have the highest pretreatment bone mass. The development of osteopenia and osteoporosis is not avoided by alternate-morning treatment schedules.

Trabecular bone, which is present in the axial skeleton (vertebrae, ribs), has a metabolic turnover rate eight times that of cortical bone (long bones), making trabecular bone much more prone to demineralization[19]. Although many patients with osteoporosis have no symptoms, more advanced disease can produce bone pain, fractures and vertebral collapse. The mechanism of glucocorticosteroid-induced bone loss includes both reduced intestinal absorption of calcium and decreased renal tubular resorption of calcium. A diet high in sodium may increase calcium loss even further. Decreased serum calcium results in parathyroid hormone release and produces a form of secondary hyperparathyroidism, stimulating osteoclast activity and resulting in bone resorption. Inhibition of osteoblasts in bone and collagen matrix synthesis also occurs through several mechanisms.

Although routine radiographs can detect vertebral compression fractures, these plain X-ray studies are not sensitive enough to detect osteoporosis until 20–60% of bone mass is lost (Fig. 125.3). Currently, the best measurement of osteoporosis is quantification of bone mineral density with dual-energy X-ray absorptiometry (DEXA), which is preferred because of its sensitivity, reproducibility and low radiation exposure. Ideally, patients on long-term glucocorticosteroids should have a baseline DEXA examination of the hip and lumbar spine, with a repeat study performed at least annually at the same sites (due to variability in density among different sites). In densitometry reports, T scores are used to connote a standard deviation from the mean of a healthy control population. Osteopenia is defined as a T score between –1 and –2.5 standard deviations below the mean, with a T score less than –2.5 defining osteoporosis[18]. For patients beginning long-term glucocorticosteroid therapy, risk factors for decreased bone density should be assessed and guidelines for the prevention and treatment of osteoporosis followed (Fig. 125.4)[20,21]. Endocrinologic consultation should be obtained in patients who develop significant osteopenia or osteoporosis. Further information on recommended regimens for osteoporosis prevention and treatment in patients receiving long-term glucocorticosteroid therapy is provided in Figure 125.4.

In general, experts agree that postmenopausal women, men over 50–65 years of age, and patients with a history of low-impact fractures should begin concomitant bisphosphonate therapy when started on long-term glucocorticosteroid treatment. Since the largest reduction in bone mass occurs during the first 6 months of glucocorticosteroid therapy, it is important to initiate this and other preventative measures promptly[20]. Alendronate or risedronate are first-line oral agents. They should be taken on an empty stomach, only with water, upon arising in the morning; patients should not lie flat for 1 hour after administration. Although generally well tolerated, gastrointestinal side effects can occur and, if severe, may necessitate changing to a different agent. Intravenous bisphosphonates such as pamidronate 30 mg IV every 3 months or zoledronate 4–5 mg IV once yearly are alternatives. Osteonecrosis of the jaw represents an occasional complication of bisphosphonate therapy, occurring most often with intravenous administration (especially in patients with an underlying malignancy such as multiple myeloma). Several case reports and small series have described atypical fractures of the subtrochanteric or diaphyseal femur in patients receiving long-term bisphosphonate therapy, but the larger studies performed to date have failed to confirm this association. All

SIDE EFFECTS OF SHORT-TERM SYSTEMIC GLUCOCORTICOSTEROID THERAPY
• Mood changes, anxiety insomnia
• Gastrointestinal intolerance (e.g. nausea, vomiting)
• Hyperglycemia
• Fluid/sodium retention
• Increased appetite, weight gain
• Acneiform eruptions
• Increased infections
• Amenorrhea
• Muscular weakness, muscle effects
• Wound healing effects

Table 125.7 Side effects of short-term systemic glucocorticosteroid therapy.

MAJOR SIDE EFFECTS OF LONG-TERM SYSTEMIC GLUCOCORTICOSTEROID THERAPY	
MUSCULOSKELETAL	**GYNECOLOGIC, OBSTETRIC**
Osteoporosis	Amenorrhea
Osteonecrosis (e.g. hip)	Fetal effects
Growth retardation	**HEMATOLOGIC, CELLULAR**
Muscle atrophy	Leukocytosis
Myopathy	Lymphopenia
OPHTHALMOLOGIC	Eosinopenia
Cataracts	Immunosuppression
Glaucoma	Impaired fibroplasia
Infection	Decreased mitotic rate
Hemorrhage	Infections
Exophthalmos	**NERVOUS SYSTEM**
GASTROINTESTINAL	Mood, personality changes
Nausea, vomiting	Psychiatric problems, psychosis
Gastroesophageal reflux	Seizures
Peptic ulcer disease	Pseudotumor cerebri
Intestinal perforation	Peripheral neuropathy
Pancreatitis	Epidural lipomatosis
Esophagitis (reflux or candidal)	**CUTANEOUS**
METABOLIC	Atrophy, striae, telangiectasias
Hyperglycemia	Vascular fragility, purpura
Hyperlipidemia	Acne, acneiform eruptions
Obesity	Hirsutism
Hypocalcemia	Infections
Hypokalemic alkalosis	**HYPOTHALAMIC–PITUITARY–ADRENAL (HPA) AXIS**
CARDIOVASCULAR	Suppression
Hypertension	Withdrawal syndrome
Peripheral edema	Adrenal crisis
Atherosclerosis	

Table 125.8 Major side effects of long-term systemic glucocorticosteroid therapy.

PATIENTS AT HIGHER RISK FOR TOXICITY FROM GLUCOCORTICOSTEROID THERAPY	
Patient group	**Concerns**
Female patients	• Slower metabolism/clearance of GCSs due to estrogen • Lower baseline bone density • Often given a higher dose per kg when not adjusted based on weight
Postmenopausal women, elderly patients	• Increased risk of osteoporosis, especially if limited physical activity
Pediatric patients	• Temporary retardation of growth • Increased likelihood of striae distensae in adolescents
Patients with SLE, (dermato)myositis or rheumatoid arthritis	• Long-term use associated with a higher risk of aseptic necrosis of bone, muscle atrophy and osteoporosis, respectively
Patients with hepatic disease (e.g. secondary to alcoholism)	• Decreased metabolism of GCSs and lipids, leading to high serum triglyceride levels
Patients with hypoalbuminemia	• Increased free fraction of GCSs results in greater side effects
Patients who smoke and/or have high alcohol intake	• Increased risk of osteoporosis and peptic ulcer disease

Table 125.9 Patients at higher risk for toxicity from glucocorticosteroid (GCS) therapy. SLE, systemic lupus erythematosus.

Fig. 125.3 Radiograph of the spine showing severe demineralization. This is indicative of advanced osteoporosis.

bisphosphonates, especially those with long half-lives (e.g. ibandronate), should be avoided in premenopausal women who might become pregnant, as these agents cross the placenta and produce teratogenicity, including fetal skeletal abnormalities. Although not as effective as bisphosphonates, intranasal calcitonin (200 IU daily) is a second-line agent when bisphosphonates are not tolerated or are contraindicated.

Hormonal therapy in women was once considered a treatment of choice for management of postmenopausal osteoporosis, and it is effective, as demonstrated by the Women's Health Initiative (WHI) study[22]. Unfortunately, the WHI also revealed increased breast cancer, stroke, thromboembolism and myocardial infarction in women on estrogen–progesterone hormonal therapy, with these risks outweighing the benefits of osteoporosis prevention. It is as yet unclear if low-dose estrogen without progesterone has the same risk profile. Raloxifene, a selective estrogen receptor modulator (SERM), is not as effective as estrogen in preventing osteoporosis but has beneficial effects in breast cancer prevention and treatment, making it a consideration for preventing bone loss in some women on long-term glucocorticosteroids. In men with low testosterone levels who are on long-term glucocorticosteroid therapy, testosterone replacement (250 mg intramuscularly once monthly) can be considered if there are no contraindications (e.g. a history of prostate or breast cancer, severe prostatic hyperplasia).

In patients who have a T score less than –2.5, a history of osteoporotic fractures, or previously failed bisphosphonates and other osteoporosis management, treatment with teriparatide, a fragmented portion of human parathyroid hormone (PTH), can be considered. The cost of teriparatide is a limiting factor, and it should not be used in combination with bisphosphonates, which may inhibit the effectiveness of teriparatide. Recently, denosumab, a monoclonal antibody directed against RANKL (receptor activator of NF-κB ligand), was approved for the treatment of osteoporosis in postmenopausal women who are at high risk for osteoporotic fractures or have failed other therapies. Activation of osteoclast maturation via the binding of this ligand (RANKL) to the RANK receptor on osteoclasts is interrupted by denosumab. Potential side effects include hypocalcemia, dermatitis, osteonecrosis of the jaw and an increased risk of infections.

Osteonecrosis

Osteonecrosis (also known as aseptic necrosis or avascular necrosis) has numerous causes, and it occasionally occurs as a complication of glucocorticosteroid treatment[23]. Co-risk factors include physical trauma, alcohol abuse, cigarette smoking and elevated serum triglycerides. The incidence of glucocorticosteroid-related osteonecrosis is higher in renal transplant recipients and patients with systemic lupus erythematosus (SLE), altered lipid metabolism, fatty degeneration of the liver or alcoholism.

Localized bone pain during activity is the usual initial symptom of osteonecrosis, with the pain eventually occurring at rest and requiring analgesics for relief. The proximal femur is the most common site, although the distal femur or humeral head may be affected. Most patients who develop osteonecrosis while on glucocorticosteroids have been treated for at least 6–12 months, paralleling the time needed to induce changes in bone marrow fat deposition.

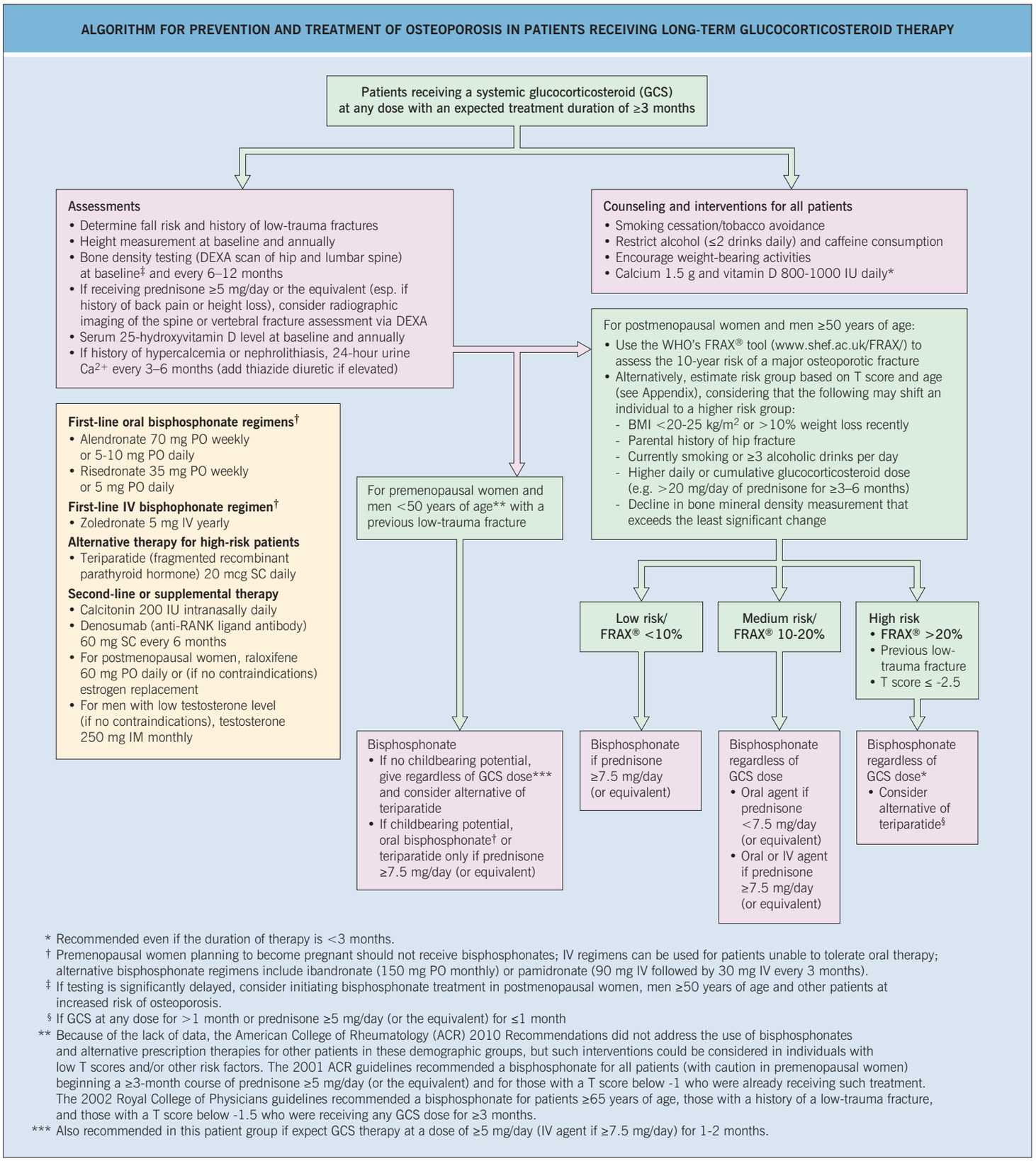
The mechanism of this condition is not completely understood, although intraosseous hypertension secondary to fat cell enlargement may compromise terminal arterioles at certain sites. Some investigators believe that fat emboli can originate from fatty deposits in the liver or from serum triglycerides, whereas others believe that only bone-derived fat emboli produce arterial occlusion with subsequent infarction.

Signs of osteonecrosis may not be evident on standard X-rays for as long as 6 months after bone pain begins (Fig. 125.5). Therefore, early MRI, the most specific and sensitive radiologic examination, is recommended for confirmation of diagnosis (Fig. 125.6). Initial medical treatment is conservative and consists of trauma prevention, rest, and modified weight bearing with the use of crutches[23]. More advanced cases in young patients may require hip salvaging procedures such as core decompression to reduce intraosseous pressure, vascularized fibular grafting, or electric stimulation. Eventual total joint arthroplasty is often unavoidable.

Growth Retardation

The doses of systemic glucocorticosteroids required to produce growth suppression are not much larger than physiologic doses. Alternate-morning therapy can minimize this effect but does not eliminate it completely[24]. Glucocorticosteroid therapy via inhalants or extensive, chronic use of topical agents may also rarely produce growth suppression. Once the glucocorticosteroid therapy is discontinued, there is often a compensatory growth spurt with normal development of height, except if chronic glucocorticosteroid therapy is given during the two major spurts of childhood – prior to age 2 years and at puberty. If glucocorticosteroids are given just before puberty, the usual compensatory growth may be negated by epiphyseal closure.

Glucocorticosteroids produce growth retardation by many mechanisms, including interference with nitrogen and mineral retention, inhibition of collagen and protein matrix synthesis, and a decreased effect of growth hormone[24]. Growth monitoring should be done every 3–6 months, and growth hormone therapy might be considered in certain situations to restore linear growth and reverse other catabolic effects.



* Recommended even if the duration of therapy is <3 months.
† Premenopausal women planning to become pregnant should not receive bisphosphonates; IV regimens can be used for patients unable to tolerate oral therapy; alternative bisphosphonate regimens include ibandronate (150 mg PO monthly) or pamidronate (90 mg IV followed by 30 mg IV every 3 months).
‡ If testing is significantly delayed, consider initiating bisphosphonate treatment in postmenopausal women, men ≥50 years of age and other patients at increased risk of osteoporosis.
§ If GCS at any dose for >1 month or prednisone ≥5 mg/day (or the equivalent) for ≤1 month
** Because of the lack of data, the American College of Rheumatology (ACR) 2010 Recommendations did not address the use of bisphosphonates and alternative prescription therapies for other patients in these demographic groups, but such interventions could be considered in individuals with low T scores and/or other risk factors. The 2001 ACR guidelines recommended a bisphosphonate for all patients (with caution in premenopausal women) beginning a ≥3-month course of prednisone ≥5 mg/day (or the equivalent) and for those with a T score below -1 who were already receiving such treatment. The 2002 Royal College of Physicians guidelines recommended a bisphosphonate for patients ≥65 years of age, those with a history of a low-trauma fracture, and those with a T score below -1.5 who were receiving any GCS dose for ≥3 months.
*** Also recommended in this patient group if expect GCS therapy at a dose of ≥5 mg/day (IV agent if ≥7.5 mg/day) for 1-2 months.

Fig. 125.4 Algorithm for prevention and treatment of osteoporosis in patients receiving long-term glucocorticosteroid therapy. Based on the American College of Rheumatology 2010 recommendations[20]. Androgen-deprivation therapy in men and medical conditions such as hyperthyroidism, hyperparathyroidism and (especially in women) rheumatoid arthritis represent additional risk factors for osteoporosis. BMI, body mass index; DEXA, dual-energy X-ray absorptiometry.

Myopathy

Myopathy is an uncommon complication of glucocorticosteroid therapy. The classic (chronic) form presents as painless, symmetrical proximal muscle weakness, most often of the lower extremities. It typically begins many weeks to months after systemic therapy is initiated, usually in patients treated with doses equivalent to >40 mg/day of prednisone. Although possibly more common with fluorinated glucocorticosteroids (e.g. dexamethasone, betamethasone, triamcinolone), the condition can occur with any agent[25]. Alternate-morning therapy might decrease its incidence. Diagnosis of myopathy may be difficult, as serum muscle enzyme levels and electromyographic studies tend to be normal. Muscle biopsy findings are relatively nonspecific, with

Fig. 125.5 Radiograph of the head of the femur, which fails to demonstrate early stages of osteonecrosis.

Fig. 125.6 MRI study of the head of the femur demonstrating osteonecrosis (arrows). (Same patient as in Fig. 125.5.)

FEATURES THAT DISTINGUISH GLUCOCORTICOSTEROID-RELATED MYOPATHY FROM MYOSITIS

Feature	Glucocorticosteroid-related myopathy	Myositis
Clinical setting	• More likely with a high GCS dose • Improves when the GCS dose is decreased	• Less likely with a high GCS dose • Worsens when the GCS dose is decreased
Clinical presentation	• Weakness, usually without myalgias	• Weakness, often associated with myalgias
Laboratory findings	• Normal serum creatine kinase • Elevated urine creatine, which decreases as the GCS dose is decreased	• Elevated serum creatine kinase • Elevated urine creatine, which increases as the GCS dose is decreased
EMG findings	• Normal	• Abnormal
MRI findings	• Signs of muscle atrophy	• Signs of muscle inflammation/edema
Muscle biopsy findings	• Atrophy	• Inflammation and necrosis

Table 125.10 Features that distinguish glucocorticosteroid (GCS)-related myopathy from myositis. EMG, electromyography; MRI, magnetic resonance imaging.

Fig. 125.7 A 12–year-old girl treated intermittently with systemic glucocorticosteroids for severe atopic dermatitis. Note lens opacity of the left eye, due to development of a cataract.

variable muscle fiber diameters and atrophy of type II fibers but no substantial inflammation or necrosis. Increased urinary creatine excretion can be a clue to the diagnosis. Gradual reduction of the glucocorticosteroid dose along with physical therapy is useful in managing this complication, although muscle function may not return to normal for many months.

When treating inflammatory muscle diseases such as dermatomyositis, glucocorticosteroids are vital for controlling the disorder but may actually increase the tendency for muscle atrophy. Corticosteroid-sparing agents are often utilized after initial control with glucocorticosteroids, especially if glucocorticosteroid tapering is not occurring at an acceptable rate[5] (see Ch. 42). Findings that help to distinguish glucocorticosteroid-related myopathy from myositis are presented in Table 125.10.

Cataracts

The cumulative dosage and duration of therapy are the most important factors in the development of posterior subcapsular cataracts in patients receiving systemic glucocorticosteroid therapy. This adverse effect has been noted in patients receiving as little as 10 mg/day of prednisone for 1 year. Cataract development is not reduced by alternate-morning schedules, although patients on continuous therapy are at higher risk than those receiving intermittent treatment. While there may be some individual susceptibility factors, children are at greatest risk, developing cataracts with lower doses and shorter treatment durations compared to adults. Cataracts that occur as a manifestation of the disease process in atopic dermatitis are usually anterior plaques in the papillary zone, but cataracts may occur in a posterior location and be indistinguishable from those associated with glucocorticosteroids (Fig. 125.7).

Ophthalmologic examinations are recommended every 6–12 months for patients on long-term systemic glucocorticosteroid therapy. Progression of cataracts can still occur despite decreasing or discontinuing glucocorticosteroid therapy, but discontinuing the glucocorticosteroids may occasionally deter further cataract formation or reverse lens opacification[26].

Metabolic Effects

Glucocorticosteroids produce hyperglycemia by affecting glucose metabolism through enhanced hepatic gluconeogenesis and decreased peripheral insulin-mediated glucose uptake. Relative insulin resistance is produced by decreasing the affinity of cellular receptors for insulin.

Although worsening of pre-existing or subclinical glucose intolerance is common, new-onset diabetes mellitus usually occurs only with high-dose therapy, and ketoacidosis is rare. Most patients will revert to their prior glucose status within a few months of discontinuing glucocorticosteroid therapy. Blood glucose levels should be assessed periodically during high-dose or long-term glucocorticosteroid therapy. Diabetic patients require closer monitoring, and they may need to be switched from oral antidiabetic agents to insulin or (because glucocorticosteroids induce relative insulin resistance) given higher insulin doses. Alternate-morning glucocorticosteroid schedules are usually not possible in diabetic patients because of the resulting fluctuations in insulin requirements.

Hyperlipidemia is a common side effect of glucocorticosteroid therapy, especially in patients with prior lipid abnormalities. Elevation of triglycerides is most frequently observed, but elevations of high- or low-density lipoproteins occur in some patients. The mechanism of hypertriglyceridemia is likely related to relative insulin insufficiency. A diet low in saturated fat and calories should be instituted in patients on long-term glucocorticosteroids.

Other metabolic effects from glucocorticosteroids include weight gain with central redistribution of fat (including the classic "buffalo hump" and "moon facies"), hypokalemic alkalosis (associated with high-dose therapy, especially with agents that have a substantial mineralocorticoid effect), and the uncommon development of hypocalcemia (a rare cause of tetany in children on high-dose therapy). Potassium supplementation may be necessary, and adequate calcium intake is mandatory.

Cardiovascular Effects

Although the majority of patients with endogenous glucocorticosteroid excess (Cushing's syndrome) have hypertension, administration of exogenous glucocorticosteroids produces hypertension in only about 20% of patients, because of the lower mineralocorticoid effect of these agents. Glucocorticosteroid therapy-associated hypertension is more common in patients with pre-existing hypertension or decreased renal function, in the elderly, and when glucocorticosteroids with greater mineralocorticoid activity are used[27]. Because glucocorticosteroids rarely affect blood pressure during the first 2 weeks of therapy, short courses of glucocorticosteroids in hypertensive patients almost never produce problems. When such patients receive long-term therapy, sodium restriction is important along with the possible institution of a thiazide diuretic. Alternate-morning therapy may reduce blood pressure elevation. The pathogenesis of glucocorticosteroid-induced hypertension is not totally understood, but it is likely related to vasoconstriction (from potentiation of catecholamines and inhibition of vasodilators), sodium retention (related to mineralocorticoid activity), and intravascular volume expansion.

Certain patients, including those with SLE, rheumatoid arthritis and renal transplants, have a tendency to develop accelerated atherosclerosis with long-term systemic glucocorticosteroid therapy. This adverse effect has also been observed in children treated with glucocorticosteroids, and it has long been noted in patients with Cushing's syndrome from chronic endogenous glucocorticosteroid excess. Instances of thromboembolic complications and atrioventricular conduction problems have also been reported with glucocorticosteroid therapy.

Gastrointestinal Effects

The relationship between glucocorticosteroid therapy and peptic ulcer disease (PUD) is controversial, with varying results in different published case series. There does seem to be an increased incidence of PUD in patients (such as those with rheumatoid arthritis) treated concomitantly with glucocorticosteroids and nonsteroidal anti-inflammatory drugs or aspirin[28]. Other additive risk factors include smoking, alcohol use, and a history of PUD. When PUD occurs in patients receiving glucocorticosteroids, it is more likely to be gastric than duodenal, with milder pain symptoms and a greater chance of a major complication such as hemorrhage or perforation. This is related to the tendency of glucocorticosteroids to mask signs and symptoms of inflammation and to inhibit wound healing. A possible mechanism of ulceration in these situations is decreased mucus production and mucosal cell renewal. The administration of oral glucocorticosteroids with food, as well as the use of H_2 receptor antagonists or proton pump inhibitors in higher-risk settings, decreases the likelihood of PUD in patients on glucocorticosteroids.

Other gastrointestinal side effects of glucocorticosteroids include nausea, vomiting and symptoms of gastroesophageal reflux (also minimized by administering with food and/or taking acid-suppressing medications); candidal esophagitis (especially in patients with an erosive oral mucosal disease such as pemphigus vulgaris), which requires treatment with oral antifungals (e.g. fluconazole); pancreatitis in patients with hypertriglyceridemia; fatty liver changes; and (rarely) intestinal perforation.

Infection

Patients receiving glucocorticosteroids have an increased susceptibility to many bacterial, viral, fungal and parasitic infections. Cutaneous staphylococcal and superficial fungal infections are extremely common. Fever and signs of inflammation may be masked in patients taking glucocorticosteroids, making early recognition of infection difficult. Alternate-morning therapy and doses equivalent to less than 10 mg/day of prednisone reduce the chance of opportunistic infection.

Reactivation of tuberculosis has long been a concern in patients on chronic glucocorticosteroid therapy, but this risk may be less than previously believed. A tuberculosis history should be taken and, if negative or uncertain, a tuberculin skin test or interferon-γ release assay performed prior to beginning therapy. A baseline chest radiograph should be obtained for patients with a positive tuberculin reaction (defined as ≥5 mm of induration in individuals receiving the equivalent of ≥15 mg/day of prednisone for a month or more) or interferon-γ release assay, a history of tuberculosis, or other risk factors (e.g. pre-existing immunosuppression). A 9-month course of isoniazid is recommended for those with an untreated latent tuberculosis infection.

An increased risk of *Pneumocystis jiroveci (carinii)* pneumonia has been observed in certain patient groups receiving systemic glucocorticosteroid therapy for longer than 2 months[29]. Susceptible individuals include those with systemic inflammatory disorders such as Wegener's granulomatosis or SLE, especially if they are receiving additional immunosuppressive agents and/or have comorbid medical conditions (e.g. pre-existing pulmonary disease, lymphopenia)[30]. Trimethoprim–sulfamethoxazole (TMP-SMX; typically one double-strength tablet three times weekly) can be used for prophylaxis in high-risk patients[31]. While HIV-positive patients with $CD4^+$ counts <200/ml routinely receive daily TMP-SMX prophylaxis, it should also be considered in HIV-positive individuals with $CD4^+$ counts >200/ml who are receiving systemic glucocorticosteroid therapy.

Patients receiving chronic glucocorticosteroid therapy at supraphysiologic doses may have inadequate antibody responses to immunizations. Live-virus vaccines (see Table 128.9) should not be given to children or adults during or (if treated for ≥2 weeks) within a month after discontinuing glucocorticosteroid therapy at a dose equivalent to ≥20 mg/day of prednisone (≥2 mg/kg/day in children weighing <10 kg)[32]. An increase in complications associated with naturally acquired varicella has also been reported in patients taking systemic glucocorticosteroids.

Obstetric and Gynecologic Effects

An increased incidence of cleft palate has been noted in rodents exposed to very large doses of glucocorticosteroids early in gestation; therefore, the safety of glucocorticosteroids during the first trimester of pregnancy has been debated. However, clinical experience and several clinical trials have shown minimal effects in the offspring of women treated with glucocorticosteroids during pregnancy[33]. Only small amounts of prednisone reach the fetus of a pregnant patient in an active form, because a placental enzyme, 11-hydroxysteroid dehydrogenase type 2, inactivates most prednisolone crossing into the fetal circulation. This enzyme has a limited ability to metabolize fluorinated glucocorticosteroids (e.g. betamethasone and dexamethasone), so greater amounts of these agents reach the fetus. Pregnant patients on glucocorticosteroids do have a slightly increased risk of both hypertension, which might account indirectly for smaller fetal gestational size, and gestational glucose intolerance, which is relatively common on moderate to high glucocorticosteroid doses. When large glucocorticosteroid doses are used near the time of delivery, fetal HPA axis suppression may occasionally occur, producing a pseudo-addisonian neonate. Even though glucocorticosteroids are excreted into breast milk, the American Academy of

Fig. 125.8 Striae in a patient on chronic oral prednisone therapy.

Fig. 125.9 Cutaneous atrophy due to topical corticosteroids. Note the prominent vascular pattern.

Fig. 125.10 Local side effects of intralesional glucocorticosteroids. Telangiectasias, dermal and subcutaneous atrophy, and yellow–white deposits of triaminolone acetonide (arrow). *Courtesy, Jean L Bolognia, MD.*

Pediatrics has determined that prednisone therapy is compatible with breastfeeding; if possible, nursing should be delayed for approximately 4 hours after prednisone administration.

In non-pregnant women, amenorrhea may occur from systemic therapy with glucocorticosteroids, most frequently with intramuscular injections. To prevent unnecessary concern, premenopausal women receiving systemic glucocorticosteroids should be alerted to this possibility. Decreased sperm counts have also been reported in men receiving systemic glucocorticosteroids.

Nervous System Effects

Mood changes, anxiety and insomnia are common dose-related side effects of glucocorticosteroids. Patients with a prior history of personality disorders are at a greater risk for glucocorticosteroid-related neuropsychiatric symptoms. Depression and fatigue are not uncommon during the tapering phase of glucocorticosteroid therapy.

Psychosis is an uncommon side effect that is dose-related and occurs more commonly in patients with a previous history of major psychiatric disease. When psychosis develops in patients with SLE on glucocorticosteroids, it may be difficult to determine if the psychosis is due to the underlying disease or the glucocorticosteroid. If glucocorticosteroid doses are reduced, steroid psychosis should improve, whereas lupus encephalopathy would be expected to worsen or remain the same.

Pseudotumor cerebri is a possible complication of high-dose or long-term glucocorticosteroid therapy and presents with headache, nausea, vomiting, visual changes and papilledema. It typically develops after rapid tapering or discontinuation of the glucocorticosteroid, so returning to a higher dose followed by more gradual tapering is recommended. Although the condition is reversible, there is potential for visual loss.

Seizures occur uncommonly, primarily affecting seizure-prone patients on high glucocorticosteroid doses. Other infrequent neurologic complications include electroencephalographic changes, enhancement of tremor, peripheral neuropathy and epidural lipomatosis. In treating neuropsychiatric complications, consultation with a psychiatrist or neurologist may be necessary and pharmacologic therapy with neuroleptics is sometimes needed. Tricyclic antidepressants may worsen symptoms and are best used under the recommendation of a specialist. Alternate-morning glucocorticosteroid therapy may be beneficial, but bipolar behavior has occasionally been noted to worsen with this schedule.

Cutaneous Effects

A host of cutaneous effects can occur in patients on systemic and topical glucocorticosteroids, many of which are similar to those associated with endogenous Cushing's syndrome. These include purpura, telangiectasias, atrophy, striae (Fig. 125.8), pseudoscars, acneiform or rosacea-like eruptions, and facial plethora. Localized development of telangiectasias, atrophy (Figs 125.9 & 125.10) and hypopigmentation (see Ch. 66) can result from topical (typically with chronic daily application of potent agents or use under occlusion) and intralesional glucocorticosteroid therapy; with intralesional administration, these findings occasionally occur in a linear pattern along pathways of lymphatic drainage.

Systemic glucocorticosteroid-induced acne or folliculitis characteristically presents with monomorphic papulopustules on the chest (Fig. 125.11) and back. Acne vulgaris itself is also frequently worsened by continuous glucocorticosteroid therapy, although inflammatory and cystic acne lesions may be temporarily improved by very short intermittent courses of systemic glucocorticosteroids, or by intralesional injections of cysts (see Ch. 36). An acneiform or rosacea-like perioral or periorbital eruption can also occur secondary to use of inhaled glucocorticosteroids or application of topical glucocorticosteroids (especially more potent agents) to the face (Fig. 125.12). Topical tacrolimus or pimecrolimus may be helpful in treating perioral dermatitis/steroid rosacea (see Ch. 37), although these agents have also been reported to exacerbate rosacea.

Other cutaneous effects from systemic glucocorticosteroids include acanthosis nigricans and telogen effluvium of scalp hair. Hirsutism and increased vellus hair growth can develop on other areas of the body.

Topical and systemic glucocorticosteroid therapy may impair wound healing by inhibiting fibroblast function and collagen production. Angiogenesis, production of the extrafibrillar matrix ("ground substance"), and re-epithelialization of wounds are also inhibited[5]. Some authors have advocated using vitamin C to improve wound healing in glucocorticosteroid-treated patients.

Fig. 125.11 Systemic glucocorticosteroid-induced acne. Note the monomorphic pink papulopustules.

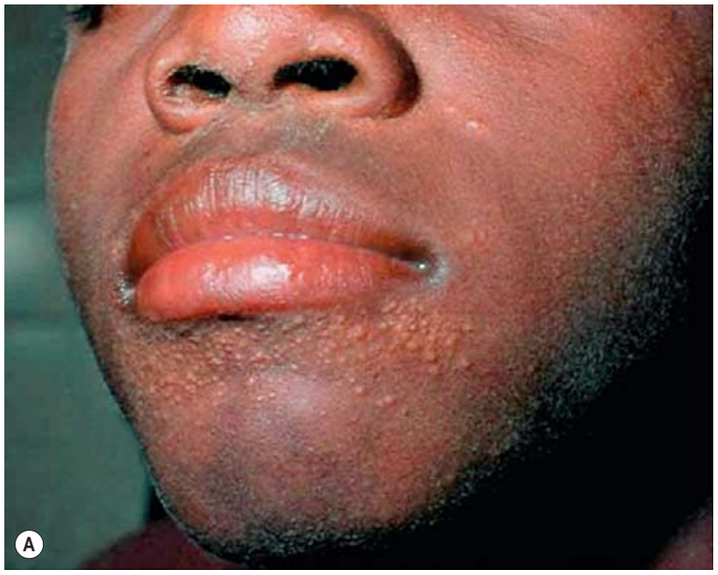


Fig. 125.12 Topical glucocorticosteroid-induced perioral eruptions. These monomorphic hypopigmented (**A**) and erythematous rosacea-like (**B**) papules resulted from the application of mid-potency topical glucocorticosteroids**.**
B, Courtesy, Kalman Watsky, MD.

GLUCOCORTICOSTEROID THERAPY: DOSING AND SIDE-EFFECT CONSIDERATIONS RELATED TO DRUG INTERACTONS AND MEDICAL CONDITIONS	
Increased dose of GCS required	Induction of cytochrome P450 metabolism* (particularly CYP3A4; see Table 131.8) • Phenytoin • Phenobarbital • Rifampin Decreased GI absorption, increased hepatic clearance, and lower prednisolone : prednisone ratio • Hyperthyroidism
Decreased dose of GCS required	Inhibition of cytochrome P450 metabolism (particularly CYP3A4; see Table 131.8) • Ketoconazole > other azole antifungals • Erythromycin > clarithromycin Altered protein binding and decreased hepatic metabolism (e.g. via competitive inhibition) • Estrogens/oral contraceptives Increased free (unbound) fraction of GCS • Hypoalbuminemia Renal function impaired Liver function impaired†
Specific side effect potentiated	Risk of GI side effects/peptic ulcer disease • NSAIDs Risk of infections • Other immunosuppressive agents Risk of hypokalemia • Potassium-depleting diuretics • Amphotericin B
Decreased levels/increased dose requirements of other drugs	• Insulin, oral hypoglycemic agents (due to GCS-related insulin resistance) • Isoniazid • Salicylates • Warfarin (variable; GCS can also increase vascular fragility)
Increased levels/decreased dose requirements of other drugs	• β-carotene • Cyclosporine

*Of note, dexamethasone itself may act as a CYP3A4 inducer.
†In patients with severe hepatic disease, conversion of prednisone to its active form (prednisolone) may be decreased.

Table 125.11 Glucocorticosteroid (GCS) therapy: dosing and side-effect considerations related to drug interactions and medical conditions. GI, gastrointestinal, NSAIDs, nonsteroidal anti-inflammatory drugs.

HPA Axis Suppression

Exogenous glucocorticosteroids can produce a secondary type of adrenal insufficiency that is related to both the dose and duration of treatment. Adrenal suppression occurs after 4 weeks of treatment with doses just above physiologic levels and earlier with higher doses. This effect is lessened by administering the glucocorticosteroid in a single morning dose and decreased even more by using an intermediate-acting agent on alternate mornings.

The entire HPA axis is affected by exogenous glucocorticosteroids. The hypothalamus is the first to be suppressed and the quickest to recover, whereas the adrenals are the last of the three glands to be suppressed and the slowest to recover. After high-dose therapy for months to years, ACTH levels may not return to normal for several months. Full recovery of the adrenal glands with normal serum cortisol levels may take even longer, sometimes up to 1 year[6]. There can be altered stress responsiveness in situations such as infection or surgery. Symptoms of weakness, fatigue, anorexia, nausea and fever may occur, and patients may even rarely develop hypotension or shock. Small doses of intravenous glucocorticosteroids may be needed prior to physically stressful situations such as major surgical procedures. Minor surgical procedures under local anesthesia do not require replacement therapy. Endocrinologic consultation should always be obtained if the rare addisonian crisis occurs.

A more common problem than adrenal crisis is the corticosteroid withdrawal syndrome. In this situation, the patient develops

arthralgias, headache, mood swings, lethargy and nausea upon rapid tapering of long-term glucocorticosteroid therapy. Low intracellular corticosteroid levels are thought to be the cause. A return to previous doses with slower tapering alleviates this syndrome.

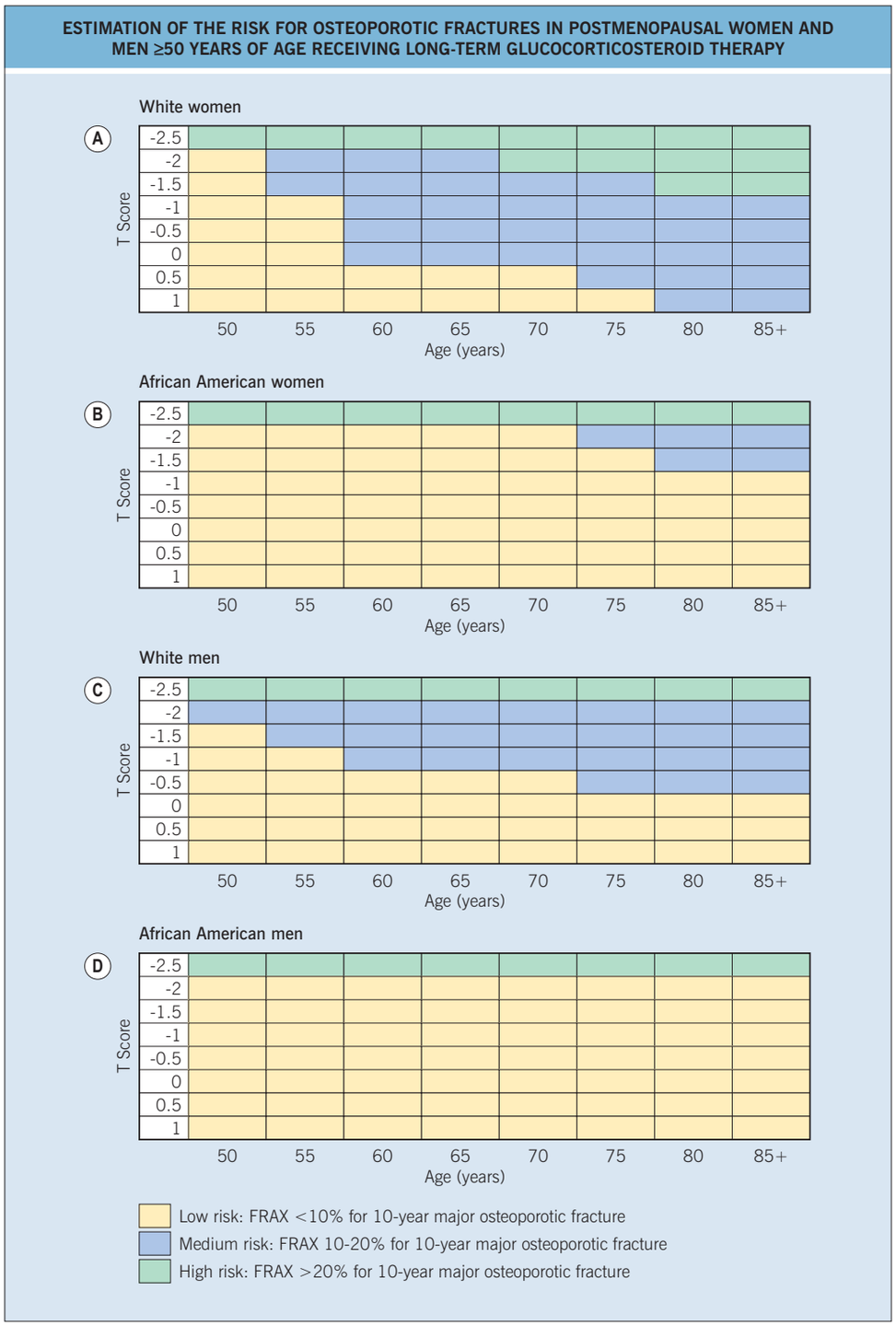
With regard to HPA axis suppression, the primary screening test for basal function of the entire axis is the morning serum cortisol level. The morning glucocorticosteroid dose should be omitted on the day the cortisol level is checked. Impaired basal HPA axis function is suggested by serum cortisol levels below 10 mcg/dl. Adrenal function alone can be tested by using the more specific ACTH stimulation test, in which serum cortisol levels are measured at baseline and then 30 and/or 60 minutes after parenteral administration of 250 mcg (standard-dose test; can be adjusted for weight in young children) or 1 mcg (low-dose test, which may be more sensitive) of ACTH[34]. If it is necessary to test stress responsiveness of the HPA axis or the adrenal glands in greater detail, endocrinologic consultation should be obtained for the ACTH stimulation test or for other evaluations including the corticotropin-releasing factor test, the insulin hypoglycemia test, or the metyrapone test.

INTERACTIONS AND DOSE ALTERATIONS

Considerations regarding interactions between glucocorticosteroids and other medications as well as medical conditions that may require alteration of the glucocorticosteroid regimen are presented in Table 125.11.

REFERENCES

1. Hench PS, Kendall EC, Slocumb CH, et al. Effects of cortisone acetate and pituitary ACTH on rheumatoid arthritis, rheumatic fever, and certain other conditions. Study in clinical physiology. Arch Intern Med. 1950;85:545–666.
2. Sulzberger MB, Witten VH, Yaffe SN. Cortisone acetate administered orally in dematologic therapy. Arch Dermatol Syphilol. 1951;64:573–8.
3. Reichling GH, Kligman AM. Alternate-day corticosteroid therapy. Arch Dermatol. 1961;83:980–3.
4. Johnson RB, Lazarus GS. Pulse therapy: therapeutic efficacy in the treatment of pyoderma gangrenosum. Arch Dermatol. 1982;118:76–84.
5. Jackson SM, Gilchrist HM, Nesbitt LT. Update on the dermatologic use of systemic glucocorticosteroids. Dermatol Ther. 2007;4:187–205.
6. Wolverton SE. Systemic corticosteroids. In: Wolverton SE (ed). Comprehensive Dermatologic Drug Therapy, 2nd ed. Philadelphia: WB Saunders, 2007;127–62.
7. Grad I, Picard D. The glucocorticoid responses are shaped by molecular chaperones. Mol Cell Endocrinol. 2007;274:2–12.
8. Fauci AS, Dale DC, Balow JE. Glucocorticosteroid therapy: mechanisms of action and clinical considerations. Ann Intern Med. 1976;84:304–15.
9. Boumpas DT, Chrousos GP, Wilder RL, et al. Glucocorticoid therapy for immune-mediated diseases: basic and clinical correlates. Ann Intern Med. 1993;119:1198–208.
10. Barnes PJ. Corticosteroid effects on cell signaling. Eur Respir J. 2006;27:413–26.
11. Myles AB. Single daily dose corticosteroid treatment. Ann Rheum Dis. 1971;30:149–53.
12. Dixon RB, Christy NP. On the various forms of corticosteroid withdrawal syndrome. Am J Med. 1980;68:224–30.
13. Robins DN. Intramuscular triamcinolone: a safe, effective and underutilized dermatologic therapy. J Drugs Dermatol. 2009;8:580–5.
14. Baethge BA, Lidsky MD, Goldberg JW. A study of adverse effects of high-dose intravenous (pulse) methylprednisolone therapy in patients with rheumatic disease. Ann Pharmacother. 1992;26:316–20.
15. Brazzini B, Pimpinelli N. New and established topical corticosteroids in dermatology: clinical pharmacology and therapeutic use. Am J Clin Dermatol. 2002;3:47–58.
16. Comell RC, Stoughton RB. Correlation of the vasoconstrictor assay and clinical activity. Arch Dermatol. 1985;121:63–7.
17. Chu AC, Munn S. Fluticasone propionate in the treatment of inflammatory dermatoses. Br J Clin Pract. 1995;49:131–3.
18. Iqbal MM. Osteoporosis: epidemiology, diagnosis and treatment. South Med J. 2000;93:2–18.
19. Lane NE, Lukert B. The science and therapy of glucocorticoid-induced bone loss. Endocrinol Metab Clin North Am. 1998;27:465–83.
20. Grossman JM, Gordon R, Ranganath VK, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Care Res. 2010;62:1515–26.
21. Qaseem A, Snow V, Shekelle P, et al. Pharmacologic treatment of low bone density or osteoporosis to prevent fractures: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2008;149:404–15.
22. Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: Women's Health Initiative randomized trial. JAMA. 2003;290:1729–38.
23. Mankin HJ. Nontraumatic necrosis of bone (osteonecrosis). N Engl J Med. 1992;326:1473–9.
24. Allen DB. Growth suppression by glucocorticoid therapy. Endocrinol Metab Clin North Am. 1996;25:699–717.
25. Lacomrs D, Samuels MA. Adverse neurologic effects of glucocorticosteroids. J Gen Intern Med. 1991;6: 367–77.
26. Renfro L, Snow JS. Ocular effects of topical and systemic steroids. Dermatol Clin. 1992;10:505–12.
27. Whitworth JA. Mechanisms of glucocorticoid-induced hypertension. Kidney Int. 1987;31:1213–24.
28. Piper JM, Ray WA, Daugherty JR, Griffin MR. Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. Ann Intern Med. 1991;114:735–40.
29. Yale SH, Limper AH. *Pneumocystis carinii* pneumonia in patients without acquired immunodeficiency syndrome: associated illnesses and prior corticosteroid therapy. Mayo Clin Proc. 1996;71:5–13.
30. Gerhart JL, Kalaaji AN. Development of *Pneumocystis carinii* pneumonia in patients with immunobullous and connective tissue disease receiving immunosuppressive medications. J Am Acad Dermatol. 2010; 62:957–61.
31. Green H, Paul M, Vidal L, Leibovici L. Prophylaxis of *Pneumocystis* pneumonia in immunocompromised non-HIV-infected patients: systematic review and meta-analysis of randomized controlled trials. Mayo Clin Proc. 2007;82:1052–9.
32. Pickering LK (ed). Red Book: Report of the Committee on Infectious Diseases, 28th edn. Elk Grove Village, IL: American Academy of Pediatrics, 2009:78.
33. Reed BR. Pregnancy, drugs, and the dermatologist. Curr Prob Dermatol. 1994;6:33–54.
34. Kazlauskaite R, Evans AT, Villabona CV, et al. Corticotropin tests for hypothalamic-pituitary-adrenal insufficiency: a metaanalysis. J Clin Endocrinol Metab. 2008;93:4245–53.



Appendix Estimation of the risk for osteoporotic fractures in postmenopausal women and men ≥50 years of age receiving long-term glucocorticosteroid therapy. The presence of additional risk factors (see Fig. 125.4) may shift an individual to a higher risk group.

Retinoids 126

Anne-Marie Thielen and *Jean-Hilaire Saurat*

Key features

- Retinoids are structural and functional analogues of vitamin A that exert multiple effects on cellular differentiation and proliferation, the immune system, and embryonic development
- Retinoic acid receptors (RARs) and retinoid X receptors (RXRs) are ligand-dependent transcription factors belonging to the steroid–thyroid hormone nuclear receptor superfamily
- Topical retinoids are used to treat acne, photoaging, psoriasis and a number of other conditions; the limiting factor is dose-related skin irritation, and teratogenicity risk is very low to non-existent
- Oral retinoids are the most effective drugs available for severe acne (isotretinoin) and many disorders of cornification (acitretin and isotretinoin). They are also helpful in the management of psoriasis, especially pustular and erythrodermic forms (acitretin > isotretinoin), pityriasis rubra pilaris (acitretin and isotretinoin), cutaneous T-cell lymphoma (bexarotene) and chronic hand eczema (alitretinoin)
- Systemic retinoid therapy requires careful patient selection and monitoring due to toxicities that can potentially result in laboratory abnormalities (e.g. hypertriglyceridemia, elevated transaminases); ocular, musculoskeletal, and (primarily for bexarotene) endocrinologic or hematologic adverse effects; and teratogenicity

INTRODUCTION

Vitamin A (retinol) and related compounds with either structural (retinol derivative) or functional (vitamin A activity) similarities are known as retinoids (Fig. 126.1). The importance of retinoids in cutaneous biology was first appreciated early in the twentieth century by Wolbach[1], who observed that vitamin A-deficient animals manifested altered keratinization, such as epidermal hyperkeratosis and squamous metaplasia of mucous membranes as well as certain precancerous conditions. The anti-keratinizing properties of vitamin A led von Stuettgen and Bollag to administer topical and systemic retinoids to treat disorders of keratinization. In initial clinical trials with oral vitamin A, it was either ineffective at tolerable doses or too toxic at higher dosage levels. Because of this narrow therapeutic window, a program was launched to engineer synthetic retinoids that would have higher therapeutic activity and lower toxicity. Although retinoids are produced naturally during vitamin A metabolism, most prescribed retinoids are synthetic. Parallel to efforts with systemic agents, a growing interest in topical retinoids emerged.

All-*trans*-retinoic acid (*at*-RA; tretinoin), a naturally occurring metabolite of retinol (see Fig. 126.1), was the first retinoid to be synthesized. Orally, it did not have significant advantages over vitamin A, and, as a result, the primary focus became its topical use, especially for acne vulgaris and photoaging. The ability of tretinoin to promote cellular differentiation has been exploited for the systemic treatment of patients with acute promyelocytic leukemia, but resistance eventually occurs in those who receive tretinoin monotherapy.

First synthesized in 1955, 13-*cis*-retinoic acid (13-*cis*-RA; isotretinoin) was tested years later in clinical trials. Its initial use was hampered by concerns regarding its teratogenicity, which were amplified because of the thalidomide tragedy. Initially, Orfanos and co-workers obtained equivocal results when they used isotretinoin to treat psoriasis, and etretinate was subsequently found to be more effective for psoriasis. This led to the temporary abandonment of studies of isotretinoin. Interest in isotretinoin was rekindled by the discovery of its effectiveness in the treatment of lamellar ichthyosis and other disorders of keratinization as well as its ability to produce complete responses with prolonged remissions in patients with previously treatment-resistant nodulocystic acne[2]. Topical isotretinoin has also been formulated and has efficacy similar to that of topical tretinoin for acne. In 1999, the US Food and Drug Administration (FDA) approved 9-*cis*-retinoic acid (9-*cis*-RA; alitretinoin) 0.1% gel for the topical treatment of cutaneous Kaposi sarcoma. Recently, systemic alitretinoin has been used to treat severe chronic hand eczema that is refractory to potent topical corticosteroids.

In 1972, Bollag developed two aromatic retinoids: etretinate and its free acid metabolite, acitretin. Both had a therapeutic index ten times more favorable than that of tretinoin in the chemically induced rodent papilloma test model. Etretinate and acitretin represent second-generation retinoids, and their development constituted a breakthrough in the systemic treatment of psoriasis and disorders of keratinization.

A major advance in understanding the molecular pharmacologic features and mechanisms of action of retinoids came with the discovery of nuclear receptors known as retinoic acid receptors (RARs) and retinoid X receptors (RXRs). This allowed the development of new retinoids that target specific retinoid receptors. Third-generation retinoids include topical adapalene (acne), topical tazarotene (psoriasis and acne) and oral as well as topical bexarotene (cutaneous T-cell lymphoma [CTCL]). Lastly, topical retinol and retinaldehyde, the precursors of retinoic acid, are included in cosmeceutical products.

MECHANISM OF ACTION

Retinoids are involved in the regulation of diverse biologic functions (Table 126.1). They affect cellular growth, differentiation and morphogenesis; inhibit tumor promotion and malignant cell growth; exert immunomodulatory actions; and alter cellular cohesiveness.

Vitamin A Metabolism

Vitamin A (retinol) must be acquired through the diet and is ingested as retinyl esters and provitamin A carotenoids; of the latter, beta-carotene is particularly efficient in its ability to be converted to vitamin A. Within the intestinal lumen, retinyl esters are hydrolyzed to retinol, which is then absorbed and stored in the liver in the ester form (especially retinyl palmitate; Fig. 126.2). Retinol and its esters represent the main dietary source, as well as transport and storage form, of vitamin A. Once inside the bloodstream, after release of the retinyl ester (storage form) from the liver, retinol is transported bound to a complex of retinol-binding protein (RBP) and transthyretin.

The cellular pathway leading to conversion of retinol to *at*-RA, the biologically active ligand that binds to nuclear receptors, consists of a two-step process (see Figs 126.1 & 126.2). Retinol (vitamin A alcohol) is first reversibly oxidized to retinaldehyde (vitamin A aldehyde), which is then irreversibly converted to retinoic acid (vitamin A acid). Cytosolic RBP (CRBP-I), facilitates these enzymatic reactions by delivering retinol to appropriate enzymes.

Two additional intracellular carriers, cytosolic retinoic acid-binding proteins (CRABP-I and CRABP-II), are thought to function in transporting retinoic acid to the nucleus as well as buffering the level of free *at*-RA in the cell. The latter is accomplished by sequestering *at*-RA and by promoting metabolism of *at*-RA by cytochrome P450 enzymes belonging to the CYP26 family (e.g. CYP26A1). CRABP-I regulates the metabolic fate of its ligands by directly affecting the activities of

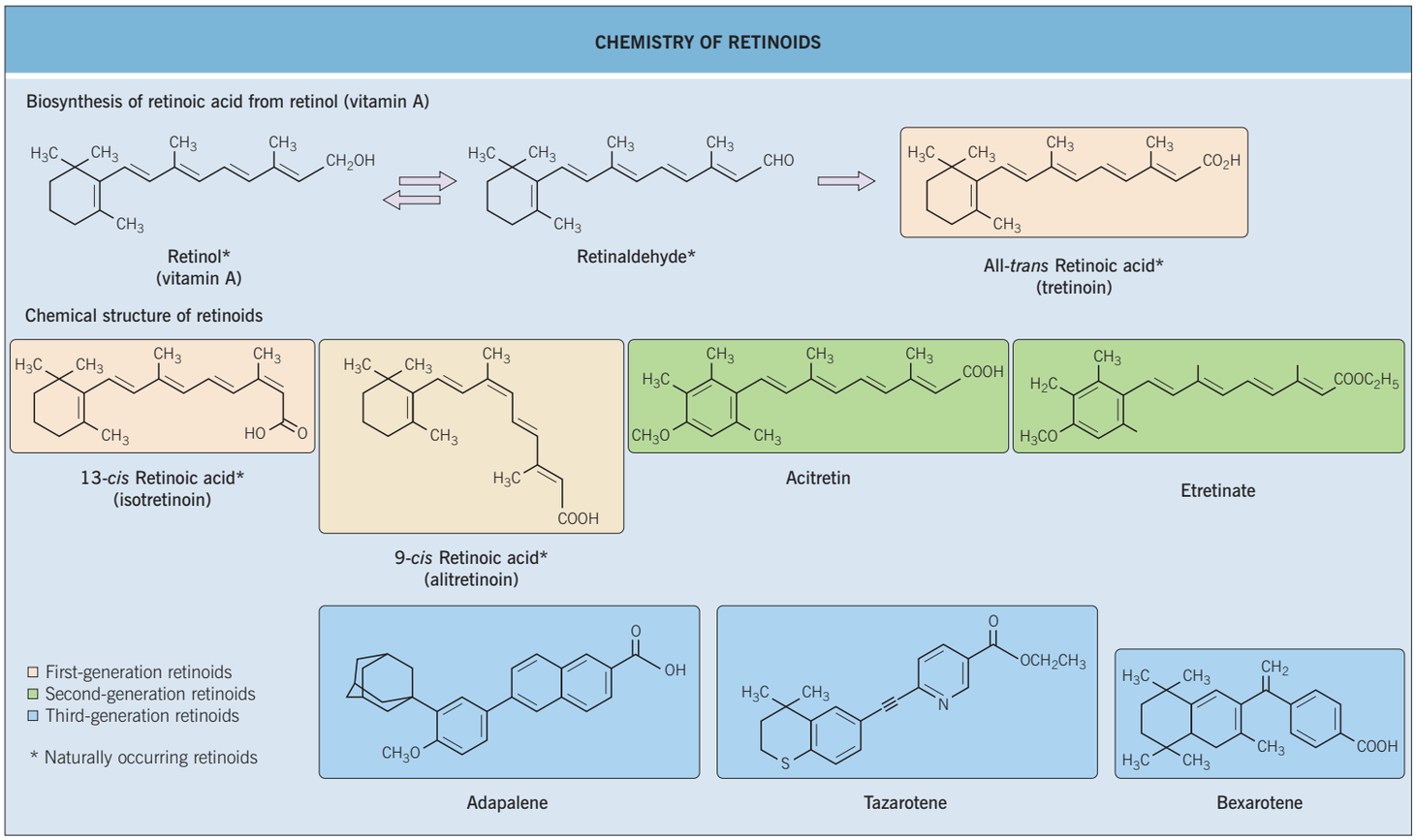


Figure 126.1 Chemistry of retinoids.

BIOLOGIC FUNCTIONS OF RETINOIDS
FUNCTIONS OF VITAMIN A (RETINOL)*
• Embryonic growth • Morphogenesis • Differentiation and maintenance of epithelial tissues • Reproduction (retinol) • Visual function (retinaldehyde)
BIOLOGIC EFFECTS OF RETINOIDS
• Modulation of proliferation and differentiation • Anti-keratinization • Alteration of cellular cohesiveness • Anti-acne and antiseborrheic effects • Immunologic and anti-inflammatory effects • Tumor prevention and therapy • Induction of apoptosis • Effects on extracellular matrix components
*Retinoic acid can substitute for retinol with regard to growth, morphogenesis and epithelial differentiation; it cannot substitute completely for retinol in reproductive function, nor can it replace retinaldehyde in the visual cycle.

Table 126.1 Biologic functions of retinoids.

RA-metabolizing cytochrome P450 enzymes, while CRABP-II markedly stimulates the RA-induced transcriptional activity of RAR through protein–protein interactions.

Intracellularly, retinoic acid is found in both all-*trans* and 9-*cis* configurations (see Fig. 126.2). Physiologically, at-RA is the predominant retinoic acid form, and only a very small fraction is isomerized into 13-*cis*-RA. at-RA is the primary active ligand that binds to the three known nuclear RARs, which mediate, at least in part, the molecular and cellular effects of retinoic acid.

Retinoid Receptors

Retinoids exert their physiologic effects on DNA transcription by binding to two distinct families of nuclear receptors, RARs and RXRs. These receptor families belong to a superfamily of nuclear receptors that act as ligand-activated transcription factors and include the steroid, vitamin D_3 and thyroid hormone receptors as well as peroxisome proliferator-activated receptors (PPAR). The RAR and RXR receptor families each contain three receptor isotypes (α, β and γ) encoded by different genes. at-RA (tretinoin) binds only to RARs, whereas 9-*cis*-RA (alitretinoin) binds both to RARs and RXRs (Table 126.2).

RARs function as heterodimers with RXRs, whereas RXRs may also act as homodimers or participate in the formation of heterodimers with a variety of other nuclear receptors, including vitamin D_3, thyroid hormone and peroxisome proliferator-activated receptors. Such heterodimers provide a mechanism for cross-talk between nuclear hormone signaling pathways. Dimers of retinoid receptors (RAR/RXR or RXR/RXR) are localized to the nucleus and bind, even in the unliganded state, to specific DNA regulatory sequences (called retinoid hormone response elements [RAREs]) in the promoter regions of retinoid-responsive genes (see Fig. 126.2). The unliganded receptors bind to co-repressor molecules and repress transcription. However, when the receptor binds its ligand, it undergoes a conformational change resulting in the release of co-repressors and recruitment of co-activators. These molecules include histone acetylases that change the conformation of chromatin and allow access to DNA by transcriptional machinery. The retinoid–receptor complex thereby modulates the transcription of specific sets of genes, and it is likely that many of the differentiation-inducing actions of retinoids are mediated by this mechanism.

In addition to *direct* upregulation of gene transcription via binding of retinoid–receptor complexes to RAREs, retinoids can have *indirect* effects on gene transcription that result from the downregulation of genes that do not contain RAREs in their promoter region. The retinoid–receptor complex is thought to antagonize transcription factors such as activator protein-1 (AP1) and nuclear factor-interleukin-6 (NF-IL6) by competing for the same set of required co-activator proteins, thereby

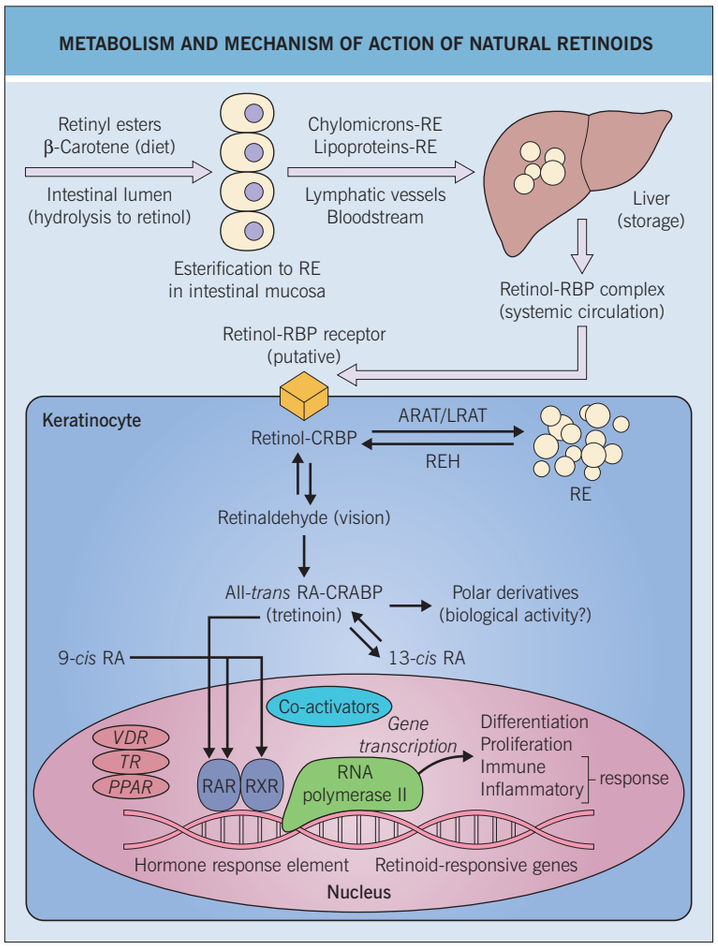


Figure 126.2 Metabolism and mechanism of action of natural retinoids. ARAT, acyl-CoA:retinol acyl transferase; CRABP, cytosolic retinoic acid-binding protein; CRBP, cytosolic retinol binding protein; LRAT, lecithin:retinol acyl transferase; PPAR, peroxisome proliferator-activated receptor; RA, retinoic acid; RAR, retinoic acid receptor; RBP, retinol binding protein; RE, retinyl esters; REH, retinyl ester hydrolase; RXR, retinoid X receptor; TR, thyroid receptor; VDR, vitamin D_3 receptor.

leading to decreased expression of AP1 and NF-IL6-responsive genes. The antiproliferative and anti-inflammatory actions of retinoids are believed to be mediated by this type of indirect negative gene regulation. AP1 and NF-IL6 are key transcription factors in proliferative and inflammatory responses, and "dissociating retinoids" have been synthesized that possess indirect anti-AP1 function but are not capable of direct gene transactivation. Retinoic acid was recently found to have important roles in inhibiting interleukin-6-driven induction of proinflammatory Th17 cells and in promoting differentiation of anti-inflammatory regulatory T cells[3]. The anti-inflammatory effects of *at*-RA (tretinoin) have also been associated with its ability to regulate the expression and activation of Toll-like receptors (TLRs; especially TLR2)[4]. The biologic relevance of non-genomic effects of retinoids (e.g. phosphorylation, membrane effects) is still a matter of investigation.

The existence of several types and varied distributions of receptors, dimers, hormone response elements, mechanisms of action, and regulatory proteins shows that retinoid action is mediated via multiple pathways and results in the complex activation or inhibition of a large set of coordinately regulated genes. However, the exact mechanism of retinoid action in many dermatologic conditions is still unknown, and, so far, the nuclear receptor concept does not fully explain the biologic diversity of retinoid effects.

Synthetic Retinoids

Three generations of synthetic retinoids have been developed (see Fig. 126.1). The first-generation monoaromatic retinoids (tretinoin, isotretinoin, alitretinoin) are produced by chemically modifying the polar end group and the polyene side chain of vitamin A. Second-generation monoaromatic retinoids (etretinate, acitretin) are formed by replacing the cyclic end group of vitamin A with different substituted and unsubstituted ring systems. The third-generation polyaromatic retinoids (adapalene, bexarotene, tazarotene), called arotinoids, are produced by cyclization of the polyene side chain.

Commercially available retinoids differ not only in their spectrum of clinical efficacy but also in their observed toxicity and pharmacokinetics. Each retinoid should be investigated as a unique drug, and the lack of disease response to one retinoid does not necessarily signify unresponsiveness to other retinoids.

The oral bioavailability of all retinoids is considerably enhanced when administrated with food, especially with a fatty meal, due to their lipophilic properties. Retinoid metabolism is predominantly hepatic. It involves oxidation and chain shortening to biologically inactive and polar metabolites, facilitating biliary and/or renal elimination. The oxidative metabolism is induced by the retinoids themselves and possibly also by other agents known to stimulate hepatic cytochrome P450 isoforms. Table 126.2 summarizes the key pharmacologic features and nuclear binding profile of retinoids used in dermatology.

Adapalene

Adapalene is a light-stable, rigid, and highly lipophilic synthetic retinoid with higher affinity for RAR-β/γ than for RAR-α. Since RAR-β is not expressed in keratinocytes, RAR-γ is the primary target receptor for adapalene in the epidermis. Adapalene does not bind to CRABPs but induces expression of CRABP-II. Due to its lipophilic properties, there is selective uptake into the pilosebaceous unit, which may contribute to topical adapalene's low systemic absorption (due to dissolution within the sebum) and anti-acne activity. Systemically absorbed adapalene is excreted through the hepatobiliary route and, given its negligible transdermal absorption, teratogenic risks appear to be minimal. Adapalene affects cellular differentiation, keratinization and inflammatory processes that are abnormal in acne. However, it has no sebostatic effect.

Tazarotene

Tazarotene is a prodrug that is rapidly converted by skin esterases to its free carboxylic acid (tazarotenic acid), which is the active metabolite. It has a higher affinity for RAR-β/γ than for RAR-α and no affinity for RXR. Because of its rapid metabolism, systemic exposure is low. Tazarotene appears to modulate the pathogenesis of psoriasis by regulating expression of retinoid responsive genes, including those involved in: (1) cell proliferation, which leads to downregulation of proliferation-associated proteins, including ornithine decarboxylase, hyperproliferative keratins (i.e. K6, K16) and epidermal growth factor receptor; (2) cell differentiation; and (3) inflammation, including downregulation of proinflammatory cytokine interleukin-6 and migration inhibition factor-related protein 8. Tazarotene's antiproliferative effects may occur via upregulation of *t*azarotene-*i*nducible genes (TIG-1,2,3)[5]. An oral form of tazarotene had beneficial effects for psoriasis patients in phase III clinical trials, but it is not approved by the FDA.

Acitretin

Acitretin is the major metabolite and the pharmacologically active form of etretinate. Although acitretin and etretinate are equally effective, acitretin has much more rapid elimination. Etretinate is approximately 50 times more lipophilic than acitretin and binds strongly to plasma proteins, particularly lipoproteins and albumin. Etretinate is stored in adipose tissue (including subcutaneous fat), from which it is released slowly, with a long terminal half-life of up to 120 days. Under identical conditions, acitretin carries a negatively charged group that makes it much less lipophilic than etretinate. As a result, acitretin does not accumulate in adipose tissue and is eliminated from the body more rapidly, with a half-life of 2 days.

The major serious adverse effect of oral retinoids is teratogenicity, and, therefore, the length of time that these drugs are present in the body is of great importance. Re-esterification of acitretin to etretinate may occur when acitretin is taken simultaneously with alcohol. This finding prompted the manufacturer to extend the time of contraception in patients taking acitretin to 2 years after discontinuation, as it is for

KEY PHARMACOLOGIC FEATURES AND NUCLEAR BINDING PROFILE OF RETINOIDS						
Retinoid	**Type**	**Systemic absorption* or bioavailability† (% dose)**	**Elimination half-life**	**Metabolism**	**Excretion**	**Nuclear receptor and binding protein profile**
TOPICAL RETINOIDS						
Tretinoin	Natural (1st generation)	<2% in normal skin	Normally present in the skin	Isomerization to 13-*cis*-RA (epidermis)	Desquamation, biliary	RAR; CRABP; not RXR
Alitretinoin (9-*cis*-retinoic acid)	Natural (1st generation)	Minimal	Normally present in the skin	Main metabolite: 4-oxo-9-*cis*-RA	Desquamation, biliary	RXR and RAR
Adapalene	3rd generation	Minimal	Unknown	Minimal biotransformation due to chemical rigidity	Desquamation, biliary	RAR-β, -γ > -α; not RXR
Tazarotene	3rd generation	<1–6% in normal skin	16 hours (tazarotenic acid)	Rapid (within 20 minutes) ester hydrolysis within the skin to form its active metabolite, tazarotenic acid; excreted metabolites: sulfoxides, sulfones	Desquamation, renal (within 3 days), biliary (within 7 days)	RAR-β, -γ > -α; not RXR
SYSTEMIC RETINOIDS						
Tretinoin	Natural (1st generation)	50%	1 hour	Hepatic; main metabolites: *cis*- and *trans*-4-oxo derivatives	Biliary, renal	RAR; CRABP; not RXR
Isotretinoin (13-*cis*-RA)	Natural (1st generation)	25%	20 hours	Hepatic, endogenous concentration reached within 2 weeks; main metabolite: 4-oxo-isotretinoin	Biliary, renal	–‡
Alitretinoin	Natural (1st generation)	Unknown	2–10 hours	Hepatic; main metabolite: 4-oxo-alitretinoin	Renal, biliary	RXR and RAR
Etretinate	2nd generation	40%	120 days	Hepatic, hydrolysis to acitretin	Biliary, renal (accumulation in fat)	–‡
Acitretin	2nd generation	60%	2 days	Hepatic, re-esterification to etretinate indirectly increased by alcohol consumption; main metabolite: *cis*-acitretin	Biliary, renal	–‡
Bexarotene	3rd generation	Unknown	7–9 hours	Hepatic	Biliary	RXR

*Limited propensity for distribution to systemic tissues.
†Increased with food intake, highly variable.
‡No clearly identified affinity for any retinoid receptor; acitretin and etretinate activate the RARs despite binding poorly to them.

Table 126.2 The key pharmacologic features and nuclear binding profile of retinoids. CRABP, cellular retinoic acid-binding protein; RA, retinoic acid; RAR, retinoic acid receptor; RXR, retinoid X receptor.

etretinate. The FDA advises a contraceptive period of at least 3 years for acitretin, based on the pharmacokinetics of acitretin and etretinate observed in clinical trials and on previous safety experience with etretinate. However, acitretin retains its shorter half-life in women who strictly avoid alcohol during treatment and for 2 months thereafter[6]. Because of its improved risk–benefit ratio, acitretin was approved by the FDA in 1996 as a substitute for etretinate, which is no longer commercially available[6].

Acitretin's mechanism of action is still not clearly understood. Paradoxically, it activates all three RAR subtypes despite binding poorly to them. Evidence supports a normalization of differentiation and proliferation as well as a modification of inflammatory responses and neutrophil function.

Isotretinoin (13-cis-retinoic acid)

Isotretinoin is a naturally occurring compound resulting from the metabolism of vitamin A (see Fig. 126.2). 13-*cis*-RA and a*t*-RA are two physiologically interconvertible isomers that differ in their elimination half-lives: approximately 20 hours and 1 hour, respectively. Isotretinoin undergoes first-pass metabolism in the liver and subsequent enterohepatic recycling. In plasma, more than 99% of isotretinoin is protein-bound, mainly to albumin. There is neither liver nor adipose tissue storage, in contrast to vitamin A. The major metabolite of isotretinoin (4-oxo-isotretinoin) is produced by oxidation. Isotretinoin and its metabolites are excreted in the urine and feces. After discontinuation of isotretinoin, natural concentrations of the drug and its major metabolites are reached within 2 weeks, ranging from 2 days for a*t*-RA to 10 days for 4-oxo-isotretinoin. Therefore, 1 month of post-therapy contraception provides an adequate safety margin to avoid teratogenicity.

Among natural and synthetic retinoids, only oral isotretinoin significantly suppresses sebum production, which explains its dramatic effects on acne. Since no clear affinity for isotretinoin has been identified for any known retinoid receptor[7], isotretinoin may target the sebaceous gland via other pathways or with its metabolites or isomers. Isotretinoin induces cell cycle arrest and apoptosis of sebocytes through what appears to be an RAR-independent mechanism; tretinoin and alitretinoin do not have these effects on sebocytes. Neutrophil gelatinase-associated lipocalin (NGAL), which functions in innate immune defense and induces apoptosis of murine B lymphocytes, was recently shown to mediate isotretinoin-induced sebocyte apoptosis[8]. Isotretinoin was found to upregulate NGAL expression in acne patients' sebaceous glands as well as in cultured human sebocytes, and recombinant NGAL led to apoptosis of cultured sebocytes. This suggests that strategies to selectively induce NGAL expression in sebaceous glands might be of benefit in the treatment of acne[8].

Bexarotene

Bexarotene, an RXR-selective retinoid (rexinoid), is FDA-approved in oral (1999) and topical (2000) forms for treatment of CTCL. This compound is about 100-fold more potent at binding to RXRs than to

RARs. In plasma, bexarotene is highly bound (>99%) to various proteins that have yet to be characterized. Both the ability of bexarotene to displace other drugs bound to plasma proteins and the ability of other drugs to displace bexarotene are unknown. Bexarotene has a clearance profile similar to that of isotretinoin, with a terminal half-life of between 7 and 9 hours[9]. Bexarotene is metabolized by CYP3A4 and generates its own oxidative metabolites via hepatic CYP3A4 induction. Neither bexarotene nor its metabolites are excreted in the urine; their elimination is thought to occur primarily via the hepatobiliary system[9]. The exact mechanism of action of bexarotene in CTCL is still unknown, but it probably acts through regulation of cellular differentiation and proliferation, and induction of apoptosis.

Alitretinoin (9-cis-retinoic acid)

Alitretinoin is a naturally occurring pan-agonist retinoid that binds to both RARs and RXRs[10], representing the endogenous ligand for the latter. Topical alitretinoin 0.1% gel is indicated for the treatment of cutaneous Kaposi sarcoma, whereas oral alitretinoin is a recently introduced therapy for refractory chronic hand eczema. The absorption of oral alitretinoin from the gastrointestinal tract is variable and dose-proportional over the therapeutic range of 10–30 mg daily; the absolute bioavailability of alitretinoin has not been determined. Alitretinoin is metabolized via oxidation by CYP3A4 enzymes of the liver into 4-oxo-alitretinoin, and both the parent drug and its metabolite also undergo isomerization into *at*-RA and 4-oxo-*at*-RA, respectively. Elimination is primarily renal, with the half-life of unchanged alitretinoin ranging between 2 and 10 hours. Alitretinoin concentrations return to normal within 1 to 3 days after treatment cessation.

The mechanism of action of alitretinoin in chronic hand eczema is unknown. Alitretinoin has immunomodulatory and anti-inflammatory effects that are relevant to cutaneous inflammation, including suppressing the expansion of cytokine-activated leukocyte subsets and antigen-presenting cells.

Retinoic acid metabolism blocking agents

*R*etinoic *a*cid *m*etabolism *b*locking *a*gents (RAMBAs) inhibit catabolism of *at*-RA by P450 enzymes in the CYP26 family, thereby raising the intracellular levels of endogenous *at*-RA in the skin and other targeted tissues[11]. This limits systemic exposure and the potential for toxicity, and *at*-RA levels return to the physiologic range within 24 hours of discontinuing these medications. Liarozole, an imidazole derivative without antifungal properties, is a RAMBA with low isoenzyme specificity that also inhibits P450-mediated pathways of steroid biosynthesis. Talarozole (R115866), a triazole derivative, is a more selective and highly active CYP26 enzyme inhibitor.

Both topical and oral forms of liarozole and talarozole have been developed, but they are not currently available in the US. However, liarozole has been granted orphan drug status for congenital ichthyosis by the European Commission and the FDA, and a randomized controlled trial showed that oral liarozole had equal efficacy to acitretin but greater tolerability in patients with moderate to severe forms of ichthyosis. Preliminary studies of talarozole have shown potential benefit for plaque-type psoriasis and acne.

INDICATIONS (Table 126.3)

Topical Retinoids

The most important element in topical therapy with retinoids is patient education. Local skin irritation can be expected, and noticeable beneficial effects may take weeks or months to appear. Administration of topical retinoids should be titrated depending on cutaneous irritation, which may mean decreasing the concentration or the frequency of application. It is generally wise to begin with the lowest-strength formulation and then increase the concentration as tolerance builds. Another tactic is to start by applying a given concentration every other day. Daytime moisturizers with sunscreen are important components of any topical retinoid regimen.

Acne

Topical retinoids, of which tretinoin is the prototype, are mainstays in the treatment of comedonal and inflammatory acne vulgaris. The primary mode of action in acne is normalization of differentiation and proliferation of the follicular epithelium (see Ch. 36), which leads to the loosening and unseating of microcomedones, thereby preventing obstruction of the pilosebaceous unit. In addition, topical retinoids may have anti-inflammatory activity and they decrease expression of potentially destructive matrix metalloproteinases (MMPs). The mechanism of action of topical isotretinoin (not available in the US) is similar to that of topical tretinoin because of intraepithelial isomerization of isotretinoin to tretinoin. Topical isotretinoin (in contrast to oral isotretinoin) fails to significantly suppress sebum production, and it is less irritating but probably somewhat less effective than tretinoin.

The newer topical synthetic retinoids, adapalene and tazarotene, are intended to have comparable or improved tolerability while maintaining efficacy similar to that of topical tretinoin. In company-sponsored studies of patients with acne, adapalene 0.1% gel was as effective as tretinoin 0.025% gel against open and closed comedones and more effective against inflammatory lesions, with less irritation[12]. Tazarotene 0.05% and 0.1% gels significantly decreased acne lesions in treated individuals compared with control patients, with clinical tolerability comparable to tretinoin.

Topical retinoids should be applied to the entire face or all acne-prone areas once a day (if tolerated), preferably in the evening to prevent inactivation by UV light. The medication should be applied to dry skin to minimize dermal absorption, which correlates with skin irritation. Patients should be advised that beneficial effects do not become evident for weeks to months. An apparent exacerbation may occur during the first month of therapy, representing the externalization of deeper-seated acne lesions as the follicular epithelium is loosening. With the exception of mild, primarily comedonal acne, topical retinoids should be used concomitantly with antibiotics (oral or topical) and/or benzoyl peroxide products, which have different modes of action that target inflammatory lesions.

Psoriasis

Topical application of tretinoin or isotretinoin has limited efficacy in psoriasis. However, topical tazarotene was shown to be effective in treating mild to moderate plaque-type psoriasis not exceeding 20% of the body surface area. When compared with twice-daily fluocinonide cream, tazarotene 0.05% and 0.1% gels applied once daily were found to produce similar reductions in plaque elevation, and tazarotene 0.1% gel carried a significantly lower risk of relapse than fluocinonide cream after 12 weeks off therapy[13]. A combination of tazarotene and a mid-potency topical corticosteroid improved efficacy and reduced the incidence of local adverse effects; this combination may also reduce the risk of corticosteroid-induced atrophy.

Photoaging

Photodamaged skin is characterized by fine and coarse wrinkling, a rough texture, a sallow color, and irregular pigmentation. Several controlled studies have clearly demonstrated that topical retinoids, including tretinoin and (more recently) tazarotene cream, can improve fine wrinkling and lighten uneven pigmentation. It generally takes 3–6 months of daily applications to see significant clinical improvement. Cutaneous irritation is usually the limiting factor. Retinaldehyde was found to be as effective as tretinoin in treating photodamage in less extensive trials[14], and it had a better tolerance profile that may reflect more controlled delivery of retinoic acid to target cells.

Photoaging is the consequence of UV radiation-induced damage to the skin, which is characterized by decreased expression of RXR-α and RAR-γ (the major retinoid receptors in keratinocytes) in the acute setting and by upregulation of AP1-driven MMPs. Topical retinoids promote cellular differentiation and extracellular matrix synthesis, including an increase in hyaluronic acid via a CD44-mediated mechanism and decreased MMP production[15]. Histologic findings after repeated topical application of tretinoin include compaction of the stratum corneum, epidermal hyperplasia (acanthosis), correction of atypia (e.g. actinic keratoses), dispersion of melanin granules, increased dermal collagen synthesis, and angiogenesis. These findings explain the reported smoother skin, rosy glow, decrease in blotchy pigmentation, and diminished fine lines and wrinkles.

CLINICAL INDICATIONS FOR RETINOIDS			
Topical retinoids	FDA-approved indications	Acne vulgaris (tretinoin, adapalene, tazarotene) Photoaging (wrinkling, mottled pigmentation, facial roughness) (tretinoin, tazarotene) Psoriasis (<20% of body surface area) (tazarotene) Cutaneous T-cell lymphoma (bexarotene) Kaposi sarcoma (alitretinoin)	
	Selected non-FDA-approved indications	Limited disorders of keratinization (Darier disease, ichthyoses) Pityriasis rubra pilaris Rosacea Pigmentary disorders (melasma, postinflammatory hyperpigmentation) Lentigines Actinic keratoses Striae Wound healing Lichen planus (oral and cutaneous) Verrucae planae (flat warts) Corticosteroid-induced atrophy Therapy and prevention of skin cancer (basal cell carcinoma; xeroderma pigmentosum)	
Systemic retinoids	FDA-approved indications	Psoriasis (acitretin)	Pustular psoriasis (localized and von Zumbusch) Erythrodermic psoriasis Severe and recalcitrant psoriasis
		Acne (isotretinoin)	Nodulocystic acne Recalcitrant acne with tendency for scarring
		Cutaneous T-cell lymphoma (bexarotene)	Resistant to at least one systemic therapy
	Selected non-FDA-approved indications	Rosacea and acne-related disorders	Hidradenitis suppurativa Eosinophilic pustular folliculitis (Ofuji's disease) AIDS-associated eosinophilic folliculitis Pyoderma faciale (rosacea fulminans) Acne with solid facial edema Dissecting cellulitis of the scalp
		Disorders of keratinization and related disorders	Ichthyosis, various forms (see Ch. 57) Darier disease Keratoderma Papillon-Lefèvre syndrome
		Inflammatory disorders	Chronic hand eczema Pityriasis rubra pilaris Lupus erythematosus Lichen planus
		Chemoprophylaxis of neoplastic processes	Xeroderma pigmentosum Nevoid basal cell carcinoma syndrome Skin cancer in solid organ transplant patients
		Treatment of neoplastic processes	Epithelial precancerous conditions Basal cell carcinoma Advanced squamous cell carcinoma Keratoacanthoma Kaposi sarcoma Sebaceous hyperplasia Muir–Torre syndrome Leukoplakia Langerhans cell histiocytosis
		Miscellaneous conditions	Atrophoderma vermiculatum Ulerythema ophryogenes Confluent and reticulated papillomatosis of Gougerot and Carteaud Bazex paraneoplastic acrokeratosis Follicular mucinosis Sarcoidosis Granuloma annulare Lichen sclerosus (genital or extragenital) Subcorneal pustular dermatosis Graft-versus-host disease (chronic sclerodermoid) Verruca vulgaris, condyloma

Table 126.3 Clinical indications for retinoids.

Other indications

Other FDA-approved indications for topical retinoids include alitretinoin 0.1% gel for cutaneous Kaposi sarcoma and bexarotene 1% gel for CTCL. In one study, 67 patients with early-stage (IA–IIA) CTCL achieved an overall response rate of 63% and a clinical complete response rate of 21% after using topical bexarotene for a median of 20 weeks[16]. There are also numerous "off-label" uses for topical retinoids (see Table 126.3).

Systemic Retinoids

Psoriasis

Several randomized, controlled multicenter trials have been performed to ascertain the efficacy of acitretin in plaque-type[17] and pustular psoriasis. Acitretin appears to be as effective as etretinate and can be used in the same combination regimens. Adverse effects appear to be similar in quality and incidence. The best results have been obtained in acral or generalized (von Zumbusch) pustular psoriasis, in which

acitretin is considered to be a first-line therapy. The lesions of both localized and generalized pustular psoriasis, as well as those of erythrodermic psoriasis, cleared more rapidly with etretinate or acitretin monotherapy than with most other therapies[18]. Rebound does not usually occur after stopping treatment, and reintroduction produces a beneficial response.

Plaque-type psoriasis responds variably to both drugs. Although complete clearance of plaques is achieved in only about 30% of treated patients, a significant improvement is obtained in an additional 50%[19]. The mean decrease in the Psoriasis Area and Severity Index (PASI) score is approximately 60–70%, depending on the dosage and duration of treatment. Many of the plaques may remain, but they are thinner with less scale and erythema. Approximately 20% of patients may be considered treatment failures[19].

One of the main reasons for treatment interruption is an initial worsening of the disease with an increase in erythema and/or the extent of involvement. This may occur within a few days of starting therapy at a dosage of 0.5–1 mg/kg/day (i.e. 30–70 mg/day in adults). Utilization of a low dose (10 mg/day) of acitretin initially, followed by progressively increasing the dose, helps to avoid this complication. In order to define the efficacy of acitretin as monotherapy for psoriasis, different doses (10–75 mg/day) were compared with placebo in a double-blind fashion. At the end of an 8-week treatment period in two studies, acitretin at doses of 25 to 75 mg/day was superior to placebo, whereas the efficacy of 10 mg/day was not significantly different from that of placebo[20,21].

Total clearance of psoriatic lesions usually requires a combination of retinoids with other treatments such as topical corticosteroids, topical vitamin D derivatives, anthralin (dithranol) or photo(chemo)therapy (narrowband UVB or psoralen plus UVA [PUVA]). The main advantages of the "Re-PUVA" combination, in which retinoids are given for 14 days before starting PUVA, are an accelerated response rate and resolution of lesions that would not clear with a retinoid or PUVA alone (Fig. 126.3). The cumulative radiation exposure required to produce a remission is also significantly lower with Re-PUVA, reducing the risk of PUVA-induced carcinogenesis which is UVA dose-dependent. Oral retinoids can also be combined with bath PUVA. Lastly, the combination of etretinate or acitretin with UVB phototherapy has been shown to be more effective than retinoid or UVB phototherapy alone in patients with psoriasis[22,23].

Isotretinoin is less effective than acitretin or etretinate for psoriasis, although some efficacy has been shown in combination with PUVA[24]. Isotretinoin is still occasionally used in women of childbearing age with psoriasis who need a systemic retinoid to avoid the long post-acitretin contraception period.

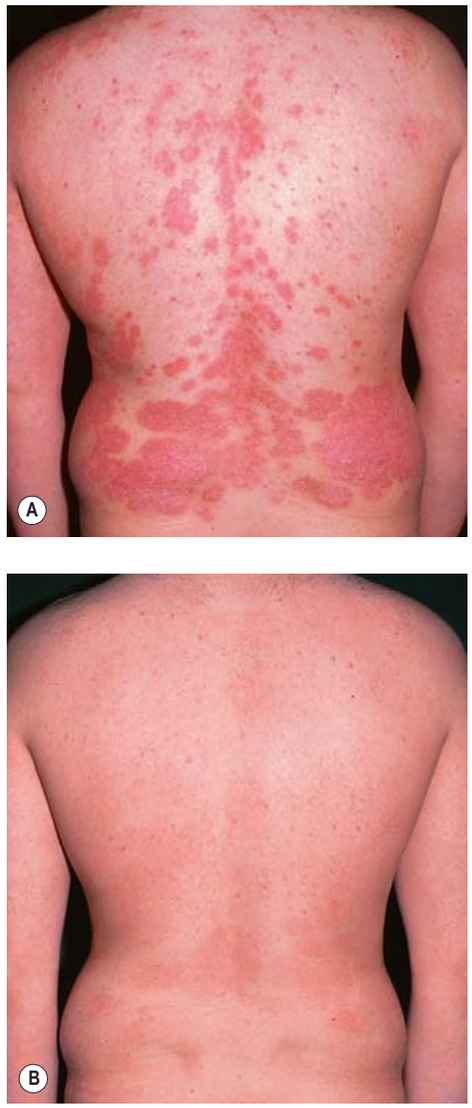


Figure 126.3 Chronic plaque-type psoriasis. Before (**A**) and after (**B**) treatment with a combination of acitretin and PUVA.

Acne

The introduction of isotretinoin was a key advance in dermatologic therapy. Isotretinoin is still the only treatment that has been shown to induce long-term remissions and even "cure" acne, because it is the only medication that affects, albeit not to the same degree or permanently, all the etiologic factors implicated in acne: sebum production, comedogenesis, and colonization with *Propionibacterium acnes* (Fig. 126.4). Among natural and synthetic retinoids studied in humans, only isotretinoin has been found to suppress sebum production (see above).

In the early 1980s, oral isotretinoin use was restricted to patients suffering from severe nodulocystic acne. With increasing experience, however, its use has been extended to patients with less severe disease who have responded unsatisfactorily to conventional therapies such as topical retinoids plus oral antibiotics. Patients with moderate acne that shows signs of scarring also represent candidates for oral isotretinoin therapy.

Acne morbidity extends beyond the aesthetics of physical appearance. Psychosocial consequences of acne range from depression and anxiety to interpersonal and work-related difficulties. Studies with quality-of-life instruments have shown that isotretinoin treatment significantly improves sociability and self-esteem.

It was initially considered that optimal benefit would be achieved with an isotretinoin dose of approximately 1 mg/kg/day[25]. However, this can induce undesirable dose-dependent effects, and similar short-term therapeutic results have been obtained with doses below 0.5 mg/kg/day. In order to avoid the higher incidence of relapses associated with lower-dose isotretinoin, treatment can be continued for a longer period of time in order to reach a critical cumulative dose threshold. The cumulative dose was first recognized to be important in isotretinoin therapy for acne by Harms et al. in 1989[26]; it refers to the total amount of oral isotretinoin taken by the patient over the entire course, divided by the body weight (mg/kg body weight). For example, a patient weighing 50 kg and receiving 25 mg/day of isotretinoin for 100 days would have received a cumulative dose of 50 mg/kg (25 mg × 100 = 2500 mg, divided by 50 kg = 50 mg/kg). Data from several studies have indicated that post-therapy relapse is minimized by a treatment course amounting to a total of at least 120 mg/kg[27], with no further therapeutic gain beyond about 150 mg/kg[28]. However, a 6-month course of low-dose isotretinoin (20 mg/day; mean cumulative dose = 70 mg/kg) was also found to be effective in the treatment of moderate acne, with a low incidence of severe side effects and a reduced cost compared to higher doses[29].

A lag period of 1–3 months may occur before the onset of the therapeutic effect, and continued healing after the discontinuation of therapy is frequently observed. Consequently, it is not necessary to maintain treatment until total clearance is achieved. Approximately one-third of patients with acne require a second course of isotretinoin therapy, either for persistent disease or for relapse. A major predictive factor of resistance to isotretinoin treatment is closed comedonal and microcystic acne[30]. Women with a history of acne that is refractory to isotretinoin or with repeated relapses should be examined for hirsutism, questioned regarding abnormal menstruation, and referred

Figure 126.4 Severe acne vulgaris. Before (**A**) and after (**B**) treatment with oral isotretinoin.

for an endocrinologic evaluation to exclude ovarian or adrenal dysfunction.

A flare of disease during the first few weeks of treatment, and subsequent evolution of acne cysts into lesions resembling pyogenic granulomas, is occasionally observed with isotretinoin treatment. The incidence of this side effect may be reduced by using lower doses of isotretinoin during the first 3–4 weeks of therapy.

Women of childbearing potential must have at least one (in the US, two) negative pregnancy test(s) and practice effective contraception for 1 month prior to therapy, during therapy, and for 1 month after completing therapy. To afford a sufficient safety margin, a 1-month post-therapy contraceptive period is mandatory because plasma concentrations of isotretinoin take approximately 10 days to return to physiologic levels after completing therapy.

Isotretinoin has a more limited effect on hidradenitis suppurativa and dissecting cellulitis of the scalp, disorders that may occur together with acne conglobata as part of the follicular occlusion tetrad. Some investigators recommend oral isotretinoin during the weeks or months preceding surgery for hidradenitis suppurativa, and sometimes also during the postoperative period.

Cutaneous T-cell lymphoma

Isotretinoin and etretinate are somewhat effective and are considered to be of equal potency in the treatment of mycosis fungoides (MF). Retinoids can be used in combination with PUVA, interferon or systemic chemotherapy. Despite initial improvement of the various stages of MF, it is often impossible to maintain remissions with these retinoids as monotherapy.

Both oral and topical bexarotene can produce responses in CTCL. Two multicenter clinical trials of oral bexarotene were conducted in patients with stage I–IIA (early) disease (n = 58)[31] or stage IIB–IVB (advanced) disease (n = 94)[32]. Patients in the early-stage study who were randomly assigned to a low-dose arm of 6.5 mg/m^2/day had a 20% response rate, in contrast to 54% and 67% for patients receiving starting doses of 300 mg/m^2/day and 650 mg/m^2/day (then decreased to 500 mg/m^2/day), respectively[31]. However, dose-dependent toxicity was a significant problem. Responses rates were approximately 50% for the patients with advanced CTCL, who all received doses of 300–650 mg/m^2/day[32,33].

The FDA approved bexarotene in December 1999 as oral therapy for CTCL that has been refractory to at least one systemic agent, and in June 2000 as a topical gel formulation for refractory early-stage CTCL. Given the high incidence of side effects, in particular hyperlipidemia (see below), a commonly recommended starting dose for oral bexarotene is 150 mg/m^2/day (Table 126.4). Combination therapies utilizing bexarotene together with PUVA, narrowband UVB, interferon-α, denileukin diftitox or methotrexate have also been evaluated in clinical trials and case series.

Chronic hand eczema

In a randomized, double-blind, placebo-controlled, multicenter study, 1032 adults with severe chronic hand eczema were treated with 30 or 10 mg of oral alitretinoin or placebo once daily for 12–24 weeks. Responses, defined as clear or almost clear hands, were achieved in 48%, 28% and 17% of the patients in the three groups, respectively. Treatment was well tolerated, with dose-dependent adverse events including headache, mucocutaneous side effects, hyperlipidemia and hypothyroidism. The median time to relapse, defined as recurrence of 75% of initial signs and symptoms, was 6 months in the absence of any further therapy[34].

Oral alitretinoin (which is not currently available in the US) therefore represents a therapeutic option for adults with severe, recalcitrant chronic hand eczema. Improvement is more rapid at higher doses (e.g. 30 mg daily) and typically develops after approximately 4 weeks of treatment. Because alitretinoin tends to induce remissions in hand eczema patients, intermittent 12- to 24-week courses may be suitable for long-term management of this condition.

Other "off-label" clinical uses

The pleomorphic effects of retinoids explain the potential benefits that they provide to patients with a broad spectrum of cutaneous disease. Although many skin disorders respond to retinoids (see Table 126.3), benefit has been established in controlled studies for relatively few conditions[35].

Ichthyosis

The best results can be obtained by using acitretin for non-bullous congenital ichthyosiform erythroderma and lamellar ichthyosis (Fig. 126.5). Good results have also been observed in patients with X-linked recessive ichthyosis and ichthyosis vulgaris; however, these diseases tend to be less severe and do not usually require systemic retinoid therapy. Given the lifelong duration of heritable ichthyoses, intermittent retinoid courses are sometimes prescribed.

Darier disease

Severe forms of Darier disease are often treated with systemic retinoids, but therapy should be initiated with a very low dose (e.g. acitretin 10 mg/day) in order to prevent an initial exacerbation of the disease; 20 mg/day of acitretin is usually sufficient for significant improvement.

APPROACH TO INITIATING ORAL BEXAROTENE THERAPY FOR CUTANEOUS T-CELL LYMPHOMA			
	Bexarotene administration	**Monitoring**	**Management of side effects**
Prior to treatment		Baseline CBC, basic metabolic panel, hepatic panel, TSH, free T4, fasting lipid panel, CK Determine if patient takes medications that inhibit or induce CYP3A4 (see Ch. 131)	Dietary and lifestyle modifications to minimize risk of hyperlipidemia If pre-existing laboratory abnormalities, administer: • Levothyroxine to achieve normal free T4 levels • A fibrate (e.g. fenofibrate)* to achieve triglyceride level <200 mg/dl and HDL level >50 mg/dl • A statin† to achieve LDL level <160 mg/dl
Day −7			Start fibrate (e.g. fenofibrate 145–200 mg daily)*
Day 0	Start bexarotene 150 mg/m^2 daily		Start levothyroxine 0.05 mg daily
Days 7 to 28		Free T4‡ & fasting lipid panel every 1–2 weeks	Adjust levothyroxine and fibrate doses and/or add statin† as required to keep laboratory values in target ranges above
Day 28§	Increase to bexarotene 300 mg/m^2 daily		
Day 29 onward	Adjust bexarotene dose as needed depending on disease response	Free T4‡ & fasting lipid panel every 1–2 weeks until in target range and after subsequent dose changes, otherwise every 1–2 months CBC every 1–2 months	As above; a triglyceride level <400 mg/dl may be a more realistic target for some patients

*Reduce dose for patients with decreased creatinine clearance; because gemfibrozil raises bexarotene levels, these medications should ***not*** be administered concomitantly.
†Niacin represents another option for patients with combined hyperlipidemia; patients receiving a fibrate and statin concomitantly may be at increased risk of rhabdomyolysis.
‡Monitor free T4 as indicator of hypothyroidism; bexarotene lowers TSH levels (central hypothyroidism)
§May increase dose as early as day 14 or, if more time is required to normalize lipid and free T4 levels, after day 28.

Table 126.4 Approach to initiating oral bexarotene therapy for cutaneous T-cell lymphoma. CBC, complete blood count; CK, creatine kinase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; T4, thyroxine; TSH, thyroid-stimulating hormone.

Figure 126.5 Lamellar ichthyosis. Before (**A**) and after (**B**) treatment with acitretin.

Pityriasis rubra pilaris

Treatment with an oral retinoid can lead to clearance of pityriasis rubra pilaris (PRP) (Fig. 126.6). In extensive cases, concomitant use of methotrexate may be advantageous. Etretinate and acitretin are considered to be superior to isotretinoin for the treatment of adult-onset PRP[36].

Rosacea

In severe or treatment-resistant rosacea, isotretinoin typically has a greater effect on inflammatory lesions than on vascular manifestations[37]. A low daily dose (10 mg) is often sufficient, although higher-dose acne vulgaris regimens are sometimes used for severe disease.

Premalignant and malignant skin lesions

Etretinate and acitretin were both shown to be effective in the treatment of premalignant skin lesions, including human papillomavirus-induced neoplasia and actinic keratoses. In patients with nevoid basal cell carcinoma syndrome and xeroderma pigmentosum, these drugs may reduce the development of skin cancers. A double-blind study demonstrated that acitretin (30 mg/day for 6 months) prevented the development of premalignant and malignant cutaneous neoplasms in renal transplant recipients[38].

Lupus erythematosus

Both isotretinoin and acitretin have been used successfully in patients with various forms of lupus erythematosus (LE). Recurrence of the

Figure 126.6 Pityriasis rubra pilaris. Before (**A**) and after (**B**) treatment with acitretin.

lesions after completion of the treatment is a limiting factor. Comparable therapeutic efficacy has been observed for acitretin and hydroxychloroquine in chronic and subacute cutaneous LE[39].

DOSAGE

The different formulations, strengths and standard dosage ranges of topical and systemic retinoids currently available for use in dermatology are outlined in Table 126.5.

CONTRAINDICATIONS

Topical Retinoids

Topical retinoids should be avoided during pregnancy and nursing, due primarily to medicolegal issues raised by the teratogenicity of oral isotretinoin. Concomitant use of irritating topical products (e.g. abrasive cleansers, astringents) should be avoided.

Systemic Retinoids

The absolute contraindications are pregnancy or women contemplating becoming pregnant, non-compliance with contraception, breastfeeding, and hypersensitivity to preservatives present in acitretin's capsule (parabens). Relative contraindications are leukopenia, moderate to severe hypercholesterolemia or hypertriglyceridemia, significant hepatic (especially for bexarotene) or renal dysfunction, hypothyroidism (especially for bexarotene), suicidal ideation and pseudotumor cerebri. Patients should be advised not to take vitamin A supplements in excess.

MAJOR SIDE EFFECTS

Topical Retinoids

By far the most common side effect of topical retinoids is skin irritation characterized by erythema and peeling (Table 126.6). This "retinoid dermatitis" typically occurs during the first month of treatment and tends to recede thereafter. It usually responds to a temporary reduction

VARIOUS FORMULATIONS OF TOPICAL AND SYSTEMIC RETINOIDS				
Retinoid	**Route (Pregnancy category)**	**Formulations**	**Standard dosage range**	**Major indications**
Retinol	Topical	Various (0.15%, 0.3%)		Cosmeceutical products
Retinaldehyde	Topical	Various (0.05–0.1%)		
Tretinoin	Topical (C)	Gel, cream, solution (0.1%, 0.05%, 0.04%, 0.025%, 0.02%, 0.01%)		Acne vulgaris Photoaging
	Oral (X)	10 mg capsules	45 mg/m^2/day	Acute promyelocytic leukemia
Tazarotene	Topical (X)	Gel, cream (0.05%, 0.1%)		Acne vulgaris Plaque-type psoriasis Photoaging
Adapalene	Topical (C)	Gel, cream, lotion (0.1%, 0.3%)		Acne vulgaris
Isotretinoin	Topical (C)	Gel (0.05%)		Acne vulgaris*
	Oral (X)	10, 20, 30, 40 mg capsules	0.5–2 mg/kg/day	Severe, recalcitrant acne; related dermatoses*
Acitretin	Oral (X)	10, 17.5, 22.5, 25 mg capsules	25–50 mg/day	Psoriasis Disorders of keratinization*
Bexarotene	Topical (C)	Gel (1%)		Cutaneous T-cell lymphoma
	Oral (X)	75 mg capsules	300 mg/m^2/day	
Alitretinoin	Topical (D)	Gel (0.1%)		Kaposi sarcoma
	Oral	10, 30 mg capsules	10–30 mg/day	Chronic hand eczema*
Motretinide (etretinate derivative)	Topical (C)	Cream, solution (0.1%)		Acne vulgaris*

*Not an FDA-approved indication.

Table 126.5 Various formulations of topical and systemic retinoids.

ADVERSE EFFECTS OF TOPICAL RETINOIDS	
Skin irritation (retinoid dermatitis)	Erythema Peeling, scaling Dryness Burning Pruritus Photosensitivity
Uncommon	Hypo- or hyperpigmentation Ectropion Allergic contact dermatitis Sticky skin

Table 126.6 Adverse effects of topical retinoids.

in the frequency, amount or duration (e.g. "short contact" therapy) of retinoid application and to the use of moisturizers. Desquamation and peeling correspond to the hyperproliferative response of the epidermis to tretinoin mediated by RARs, but the erythema does not seem to be receptor-mediated[40]. The perioral area of the face is most sensitive to peeling, and retinoid use in this region can be limited or avoided.

Although no photoallergic or phototoxic reactions have been proven for topical retinoids, many patients note a decreased tolerance to UV radiation. This reaction tends to develop shortly after sun exposure and is often accompanied by a sensation of heat, raising the question of involvement of infrared irradiation. The potential for teratogenicity from use of topical retinoids is very low. Systemic absorption of topically applied retinoids has been inconsequential in both animal and human studies[41], and there is no evidence that topical application of tretinoin during pregnancy causes congenital disorders. Temporary worsening of acne may occur within the first weeks of therapy. Uncommon side effects include transient hypo- or hyperpigmentation, koebnerization of psoriasis (especially with tazarotene), allergic contact dermatitis, and ectropion.

RETINOID EMBRYOPATHY
CRANIOFACIAL
• Atresia of the ear canal, microtia, anotia • Microphthalmia • Asymmetry of the face • Cleft palate • Micrognathia
CARDIOVASCULAR (ESPECIALLY CONOTRUNCAL AND AORTIC ARCH DEFECTS)
• Transposition of the great vessels • Tetralogy of Fallot • Truncus arteriosus • Supracristal ventricular septal defect • Interrupted aortic arch • Retroesophageal right subclavian artery • Hypoplastic aorta
CENTRAL NERVOUS SYSTEM
• Hydrocephalus • Microcephaly • Cortical agenesis • Cerebellar hypoplasia • Mental retardation • Difficulty with visual motor integration
THIRD AND FOURTH PHARYNGEAL POUCHES
• Thymic hypoplasia • Parathyroid hypoplasia
OTHER
• Limb anomalies • Anal and vaginal atresia

Table 126.7 Retinoid embryopathy.

Systemic Retinoids

Teratogenicity is the most concerning adverse effect of oral retinoids (Table 126.7). The side-effect profile of systemic retinoids (Table 126.8) resembles the toxic effects of vitamin A or hypervitaminosis A syndrome. Acute retinoid toxicity can include mucocutaneous (most common) and laboratory abnormalities, while chronic retinoid toxicity may occasionally produce bony changes.

Teratogenicity

Systemic retinoids are potent teratogens, and fetal deformities are the major concern in treating fertile women with oral retinoids. So far, with regard to teratogenicity, no safe minimal dose during pregnancy has been established. The defects seen in retinoid embryopathy can include craniofacial (microtia/anotia, micrognathia), cardiovascular, thymic and central nervous system (CNS; hydrocephalus, microcephaly) abnormalities (see Table 126.7)[42]. These malformations may lead to spontaneous abortion, premature birth, or fetal death. The putative mechanism involves toxic effects on neural crest cells, particularly with exposure during the fourth week of gestation. No typical retinoid embryopathy malformations have been reported in pregnancies where only the male partner was taking acitretin or isotretinoin at the time of conception. However, it is usually recommended that men who are actively trying to father children avoid systemic retinoid therapy.

In the US, physicians and patients (female or, to prevent sharing of medication, male) must register with a pregnancy risk management program (iPLEDGE) in order for isotretinoin to be prescribed. The program requires monthly office visits for all patients and monthly pregnancy testing for female patients with childbearing potential.

Skin and mucous membrane adverse effects

Dose-dependent mucocutaneous toxicity is the most commonly observed side effect of oral retinoids, and it reflects decreased production of sebum, reduced stratum corneum thickness, and altered skin barrier function (Fig. 126.7). Dry lips or cheilitis is the earliest and the most frequent finding (Fig. 126.8). Dryness of the mouth (accompanied by thirst), nasal mucosa (associated with fragility and epistaxis) and eyes (see below) are other potential manifestations.

Xerosis of the skin and associated pruritus, peeling (especially of the palms and soles) and fissuring (particularly of the fingertips) are frequent side effects. Exacerbations of atopic dermatitis may occur. Photosensitivity is occasionally observed, in particular with isotretinoin, and probably reflects a reduction in the thickness of the stratum corneum. *Staphylococcus aureus* colonization correlates with isotretinoin-induced reduction in sebum production and may lead to overt cutaneous infections. Diffuse hair loss (telogen effluvium) is a relatively common complaint, although objective alopecia tends to occur only at high dosage levels. Effects on the nail apparatus can include thinning, fragility and shedding of the nail plate as well as paronychia-like changes with periungual granulation tissue.

Mucocutaneous side-effect profiles vary among the systemic retinoids. Isotretinoin causes more mucosal dryness, and acitretin has been associated with higher incidences of alopecia and palmoplantar peeling, whereas bexarotene induces milder mucocutaneous and ocular side effects than other oral retinoids.

Systemic toxic effects

Bone toxicity

Bone pain can occur in retinoid-treated patients without objective evidence of any abnormalities and without sequelae. Several reports have also implicated therapy with oral retinoids, including etretinate and isotretinoin, in the formation of diffuse hyperostoses of the spine (diffuse idiopathic skeletal hyperostosis [DISH] syndrome-like changes) as well as calcification of tendons and ligaments, particularly in the ankles[43]. Specific findings include anterior spinal ligament calcification, osteophyte ("spur") formation, extraspinal calcifications, and bony bridges, but not narrowing of the disk space (Fig. 126.9). More rarely, ossification of the spinal posterior longitudinal ligament has been reported; this change, which can be progressive, may lead to spinal cord compression with signs of partial spastic paraplegia[44].

Based on data from retrospective studies, it was concluded that although many of the bone changes observed were common in the general population (especially adults) and could *not* be attributed with certainty to etretinate or acitretin therapy, spurs and interosseous membrane and tendon calcifications were probably treatment-related[45]. Of

ADVERSE EFFECTS OF SYSTEMIC RETINOIDS		
Acute effects	Mucocutaneous	Xerosis with pruritus* Cheilitis* Dry mucosa*: mouth, nose (epistaxis), eyes (see below) Skin fragility* Retinoid dermatitis (see Table 126.6)* Palmoplantar peeling* Photosensitivity Sticky sensation (palms, soles) Granulation tissue and pyogenic granuloma-like lesions Nail fragility with softening, onycholysis, paronychia Facial swelling *Staphylococcus aureus* infection Telogen effluvium, hair thinning
	Ocular	Xerophthalmia* Blepharoconjunctivitis, corneal ulceration Reduced night vision Blurred vision, photophobia, keratitis
	Systemic	Myalgias Arthralgias Anorexia, nausea, diarrhea, abdominal pain Headache, pseudotumor cerebri (rare) Fatigue, lethargy, irritability Depression, suicidal ideation (rare and controversial) Toxic hepatitis (rare) Clinical signs of hypothyroidism (with bexarotene*) Pancreatitis secondary to hypertriglyceridemia (rare) Hyperuricemia with gout (rare)
	Laboratory	Elevated liver function tests (usually transient, minor): AST, ALT, alkaline phosphatase, LDH, bilirubin Hyperlipidemia: hypertriglyceridemia*; increased cholesterol, VLDL and LDL; decreased HDL Decreased free thyroxine (T4) (with bexarotene*) Elevated creatine kinase Leukopenia (with bexarotene) Agranulocytosis (with bexarotene) Thrombocytosis, thrombocytopenia Hypercalcemia (rare)
Chronic effects	Mucocutaneous	Alopecia (rare) Dry eyes (rare)
	Systemic	DISH syndrome-like bone changes: Osteophyte and bony bridge formation, especially of vertebrae (rarely clinically significant at dosages for acne) Anterior > posterior spinal ligament calcification Extraspinal tendon and ligament calcification Osteoporotic changes in long bones (rare, with possible exception of long-term etretinate) Premature epiphyseal closure (rare) Periosteal thickening Myopathy (rare)
*Common adverse effects.		

Table 126.8 Adverse effects of systemic retinoids. See Table 126.7 for teratogenicity. ALT, alanine aminotransferase; AST, aspartate aminotransferase; DISH, diffuse idiopathic skeletal hyperostosis; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

Figure 126.7 Retinoid dermatitis: Xerosis, peeling and erythema of the face in a patient treated with oral isotretinoin.

Figure 126.8 Cheilitis in an isotretinoin-treated patient.

Figure 126.9 Osteophytes and bony ridges without narrowing of the disk spaces in an acne patient treated with a prolonged (several-year) course of isotretinoin.

note, prospective studies have shown that the effect of retinoids on bone, if present at all, is likely to involve worsening of pre-existing skeletal overgrowth rather than induction of *de novo* changes. Even long-term use of isotretinoin in acne patients rarely causes clinically significant radiologic abnormalities, as most hyperostoses are asymptomatic and clinically insignificant[46].

Osteoporosis has been observed with hypervitaminosis A and after long-term therapy with etretinate but not with isotretinoin[47]. A mean bone density loss of 4.4% in Ward's triangle of the femur was observed in 18 young men (without measurable alterations of calcium metabolism) after 6 months of isotretinoin use (1 mg/kg); bone changes differed compared with controls at this site ($p = 0.04$) but not in the humoral neck or lumbar spine[48]. Subsequent investigations in patients receiving similar isotretinoin regimens, including an open-label trial in 217 adolescents and two controlled studies in adolescents and young adults (21 and 36 patients), showed no significant change in bone mineral density[49,50]. In children, only a few cases of skeletal abnormalities, including osteoporosis, periosteal thickening, slender long bones and premature epiphyseal closure[51,52], have been reported. No baseline X-rays are required, although monitoring high-risk patients who require prolonged high-dose retinoid therapy may be useful.

Muscle effects

Although muscular pain and cramps can occur in patients taking etretinate or acitretin, these symptoms are more common with isotretinoin therapy, especially in individuals involved in vigorous physical activity. Occasionally, elevated creatine kinase levels may be observed. Increased muscle tone as well as axial muscle rigidity and myopathy have been reported in patients receiving etretinate and acitretin therapy, respectively[53].

Central nervous system and psychiatric effects

CNS side effects are rare. Although individual signs of increased intracranial pressure, such as headache, nausea and vomiting, are occasionally observed, the complete pseudotumor cerebri syndrome with papilledema and blurred vision is very rare[54]. Concomitant use of other drugs associated with intracranial hypertension (e.g. tetracyclines) is considered a risk factor for developing pseudotumor cerebri and should therefore be avoided[55]. Examination for papilledema should be performed immediately when a patient receiving retinoid therapy complains of a persistent headache, especially if it is accompanied by visual changes, nausea or vomiting, or when pseudotumor cerebri is otherwise suspected.

Although anecdotal reports have suggested a link between isotretinoin therapy in acne patients and depression, psychosis and suicide attempts, a causal association has not been established[56]. Multiple prospective studies have failed to find a significant increase in depressive symptoms or depression diagnoses following initiation of isotretinoin therapy for acne, and several studies actually noted a significant decrease in depressive symptoms compared to baseline or a control group receiving other acne therapies[57]. Among population-based studies, large case–control and prescription sequence symmetry analyses did not provide evidence of an association between isotretinoin exposure and depression or suicidal behavior, but a small case-crossover study showed a significant 2.8-fold higher likelihood of exposure to isotretinoin in the 5 months prior to (compared with the 7–12 months prior to) an initial diagnosis of depression in patients with acne[56]. Patients with depressive symptoms or suicidal ideation should be advised about the possible association with psychiatric effects prior to initiating treatment and carefully monitored[56].

Ophthalmologic side effects

The most common ocular retinoid effects are dryness and irritation. Xerophthalmia due to decreased meibomian gland secretions may prohibit the use of contact lenses and can lead to blepharoconjunctivitis or corneal ulceration. If artificial tears and topical ophthalmologic antibiotic ointment fail to alleviate the conjunctivitis, ophthalmologic consultation should be sought. Alterations in visual function, mainly nyctalopia (reduced night vision), excessive glare sensitivity, and changes in color perception, have also been reported[58]. Competitive inhibition of ocular retinol dehydrogenase by retinoids, resulting in decreased rhodopsin formation, may be the cause of nyctalopia.

Other systemic effects

Hypothyroidism

Clinical and biochemical central hypothyroidism occurred in 40% of patients in the CTCL trials with bexarotene and was rapidly and completely reversible with cessation of therapy, without any clinical sequelae[31,59]. This effect is probably mediated through suppression of thyroid-stimulating hormone β-subunit (TSH-β) secretion by the thyrotrope cells of the anterior pituitary, which express RXR-γ. Free T4 levels should be monitored before and during bexarotene therapy and normalized with thyroid hormone replacement as necessary (see Table 126.4)[33].

Gastrointestinal side effects

Uncommon nonspecific gastrointestinal complaints have been reported in association with retinoid therapy. Retinoids have been temporally linked with other gastrointestinal conditions, such as case reports of isotretinoin administration preceding the onset of inflammatory bowel disease. However, a cause-and-effect relationship has not been established to date. One recent large population-based study found that patients with inflammatory bowel disease were no more likely to have used isotretinoin prior to diagnosis than matched controls[60], but another large case-control study found that ulcerative colitis (but not Crohn's disease) was associated with previous isotretinoin use[60a].

Renal effects

Renal toxicity is not characteristic of retinoid therapy. Isotretinoin has been safely administered to patients with end-stage kidney disease who were undergoing hemodialysis. However, reversible renal dysfunction (with elevated creatinine levels) during etretinate therapy has been described. Renal function should be monitored in patients with a history of kidney disease[61].

Laboratory abnormalities

Dyslipidemia

Hypertriglyceridemia is the most frequently observed systemic effect of retinoid therapy. Isotretinoin and etretinate/acitretin elevate triglycerides in 50% and cholesterol in 30% of treated patients[62], whereas bexarotene induces elevated triglycerides and cholesterol in approximately 79% and 48% of patients, respectively[31]. In addition, a concomitant increase in total and low-density lipoprotein (LDL)

cholesterol is frequently observed. In cases of severe retinoid-induced hypertriglyceridemia, eruptive xanthomas and acute hemorrhagic pancreatitis may occur. A higher incidence of acute hemorrhagic pancreatitis has been encountered in patients taking bexarotene, as compared to first- or second-generation retinoids.

Baseline fasting serum lipid levels should be obtained before initiating bexarotene therapy and every 1 to 2 weeks during therapy until levels become stable (generally in 4 to 8 weeks) (see Table 126.4). For other oral retinoids, monitoring levels monthly for the first 2 months and then at 2- to 3-month intervals is adequate if baseline lipid levels are normal, there are no increases in dosage, and risk factors (obesity, high alcohol intake, diabetes) are absent. Discontinuation of therapy is suggested if fasting triglycerides reach 800 mg/dl (8 g/l). Less severe increases may be treated by dose reduction, withdrawing therapy until normalization of serum lipids occurs, and changes in diet or lifestyle. In some instances, lipid-lowering agents may be indicated[63]. Coadministration of bexarotene with a statin (e.g. atorvastatin) for hypercholesterolemia and/or fenofibrate for hypertriglyceridemia is recommended to treat retinoid-induced hyperlipidemia and to lower the risk of pancreatitis[6,64]. Some authors recommend starting all patients on fenofibrate 7 days before initiating bexarotene treatment (see Table 126.4)[33].

The effects of retinoid-induced hyperlipidemia during long-term therapy on the development of atherosclerotic cardiovascular disease is unknown. Retinoids probably cause hyperlipidemia by interfering with lipid clearance. Bexarotene increases the expression of apolipoprotein C-III, which prevents the uptake of lipids from very-low-density lipoproteins (VLDL) into cells[65]. Of note, individuals who develop hypertriglyceridemia during isotretinoin therapy for acne may be at increased risk for future metabolic syndrome.

Liver toxicity

Transitory elevations in serum transaminases occur in approximately 20% of patients treated with either etretinate or acitretin and much less frequently in those receiving isotretinoin or bexarotene therapy. Circulating levels of alkaline phosphatase, lactic dehydrogenase and bilirubin may also become elevated during retinoid therapy. Liver function test abnormalities are typically mild, usually developing between 2 and 8 weeks after starting therapy and then returning to normal within another 2–4 weeks despite continued therapy. Severe or persistent hepatotoxic reactions occur in fewer than 1% of patients. Acitretin therapy elicited no biopsy-proven hepatotoxicity in a 2-year prospective study, thus suggesting that periodic liver biopsy is not necessary[66]. No studies have specifically evaluated the use of retinoids in patients with hepatic insufficiency. However, since retinoids are metabolized by hepatic cytochrome P450 isoenzymes (e.g. CYP3A4) and undergo partial biliary elimination, significant hepatic insufficiency is likely to interfere with drug elimination. Transaminase elevations to greater than three times the upper limit of normal should prompt discontinuation of retinoid therapy. With two- to three-fold transaminase elevations, therapy should be withdrawn until normalization occurs[6]. Other causes of hepatic dysfunction should be excluded.

Hematologic toxicities

A high incidence (28%) of dose-related leukopenia was reported in studies of bexarotene for CTCL, occurring as early as 2–4 weeks, and characterized by a decrease in neutrophils rather than lymphocytes[31]. Hematologic abnormalities are much less common with other retinoids, but careful hematologic monitoring in HIV-infected patients is warranted.

Summary

Most adverse effects associated with retinoids are preventable or manageable through proper patient selection, diligent monitoring and dose adjustments (or occasionally discontinuation of treatment) as indicated.

INTERACTIONS

Concurrent use of retinoids with alcohol or other medications having similar side effects may increase the incidence of adverse events. The following should be avoided or used with caution:

- tetracycline, doxycycline, minocycline (may increase intracranial pressure)
- alcohol (increased conversion of acitretin to etretinate and hepatotoxicity)
- methotrexate (synergistic liver toxicity with retinoids; however, combination may be used with caution in patients with PRP or severe psoriasis)
- vitamin A supplements (risk of hypervitaminosis A).

Retinoid drug levels and resultant potential for toxicity may increase with CYP3A4 inhibitors such as azoles and macrolides. In contrast, antituberculosis drugs (rifampin) and anticonvulsants (phenytoin and carbamazepine) may decrease the drug levels of retinoids via CYP3A4 induction. Retinoids may also increase the drug levels of cyclosporine via competition for CYP3A4 metabolism[6]. Concomitant administration of bexarotene and gemfibrozil results in a substantial increase in plasma concentrations of bexarotene, at least partially because of cytochrome P450 CYP3A4 inhibition that is induced by gemfibrozil. Concomitant fenofibrate (for hypertriglyceridemia) or atorvastatin (for hypercholesterolemia) administration does not affect bexarotene plasma levels and, therefore, can be utilized together with bexarotene (see Table 126.4).

In rare instances, patients with diabetes mellitus may have more difficult glucose control while taking a retinoid; however, the causal relationship remains uncertain. Acitretin has been shown to possibly reduce the efficacy of progestin-only contraceptives. Also, unprotected UV radiation exposure or photosensitizing medications should be avoided because of increased photosensitivity caused by retinoid therapy. Since retinoids act through nuclear receptor dimers, cross-talk with other nuclear receptors may provide synergistic effects: for example, interactions between RXR and VDR positively influence the action of vitamin D_3; however, cross-talk with PPAR and its ligands is still under investigation.

USE IN PREGNANCY AND LACTATION

All systemic retinoids are teratogenic and are absolutely contraindicated during pregnancy and lactation (FDA category X), which should be excluded by pregnancy test(s) before considering retinoid therapy and then at regular intervals (e.g. monthly in the case of isotretinoin) during its administration. In the US, two pregnancy tests are required before instituting isotretinoin therapy. Pregnancy not only is an absolute contraindication to starting therapy; it must also be avoided throughout therapy and for an appropriate interval after completion of therapy. Adequate contraception for at least 1 month before therapy is required for all systemic retinoid therapy. Acitretin requires contraception for 3 years (US) or 2 years (Europe) after cessation of therapy, whereas isotretinoin, bexarotene and alitretinoin require contraception for just 1 month after cessation of therapy.

Although no evidence exists for teratogenicity of topical retinoids in humans, they are nevertheless not recommended for use during pregnancy. Since no dermatologic condition that is known to be responsive to topical retinoids is life-threatening to the mother or fetus, it is wiser to postpone treatment until after delivery (primarily due to medicolegal rather than scientific data in the opinion of the authors). The same recommendations are also valid for lactating women, as it is not known whether topical retinoids pass into the breast milk. Consequently, topical retinoid use is not recommended during breastfeeding.

REFERENCES

1. Wolbach SB, Howe PR. Tissue changes following deprivation of fat-soluble A vitamin. J Exp Med. 1925;42:753–78.
2. Peck GL, Olsen TG, Yoder FW, et al. Prolonged remissions of cystic and conglobata acne with 13-*cis*-retinoic acid. N Engl J Med. 1979;300:329–33.
3. Mucida D, Park Y, Kim G, et al. Reciprocal TH17 and regulatory T-cell differentiation mediated by retinoic acid. Science. 2007;317:256–60.
4. Liu PT, Krutzik SR, Kim J, Modlin RL. Cutting edge: all-trans retinoic acid down-regulates TLR2 expression and function. J Immunol. 2005;174:2467–70.
5. Duvic M, Nagpal S, Asano AT, et al. Molecular mechanisms of tazarotene action in psoriasis. J Am Acad Dermatol. 1997;37:S18–24.
6. Wiegand UW, Chou RC. Pharmacokinetics of acitretin and etretinate. J Am Acad Dermatol. 1998;39(2 Pt 3):S25–33.
7. Torma H. Interaction of isotretinoin with endogenous retinoids. J Am Acad Dermatol. 2001;45:S143–9.
8. Nelson AM, Zhao W, Gilliland KL, et al. Neutrophil gelatinase-associated lipocalin mediates 13-cis retinoic acid-induced apoptosis of human sebaceous gland cells. J Clin Invest. 2008;118:1468–78.
9. Ethan-Quan HN, Wolverton S. Systemic retinoids. In: Wolverton SE (ed). Comprehensive Dermatologic Drug Therapy. Philadelphia: WB Saunders, 2001:269–310.
10. Molin S, Ruzicka T. Alitretinoin. Die erste spezifisch zugelassene Therapie für das chronische Handekzem. Hautarzt 2008;59:703–9.
11. Verfaill CJ, Borgers M, van Steesel MAM. Retinoic acid metabolism blocking agents (RAMBAs): a new paradigm in the treatment of hyperkeratotic disorders. J Dtsch Dermatol Ges. 2008;6:355–64.
12. Cunliffe WJ, Caputo R, Dreno B, et al. Clinical efficacy and safety comparison of adapalene gel and tretinoin gel in the treatment of acne vulgaris: Europe and US multicenter trials. J Am Acad Dermatol. 1997;36: S126–34.
13. Lebwohl M, Ast E, Callen JP, et al. Once-daily tazarotene gel versus twice-daily fluocinonide cream in the treatment of plaque psoriasis. J Am Acad Dermatol. 1998;38:705–11.
14. Creidi P, Vienne M-P, Ochonisky S, et al. Profilometric evaluation of photodamage after topical retinaldehyde and retinoic acid treatment. J Am Acad Dermatol. 1998;39:960–5.
15. Calikoglu E, Sorg O, Tran C, et al. UVA and UVB decrease the expression of CD44 and hyaluronate in mouse epidermis, which is counteracted by topical retinoids. Photochem Photobiol. 2006;82:1342–7.
16. Breneman D, Duvic M, Kuzel T, et al. Phase 1 and 2 trial with bexarotene gel for skin-directed treatment of patients with cutaneous T cell lymphoma. Arch Dermatol. 2002;138:325–32.
17. Arechalde A, Saurat J-H. Management of psoriasis: the position of retinoid drugs. Bio Drugs. 2000;13:327–33.
18. White SI, Marks JM, Shuster S. Etretinate in pustular psoriasis of palms and soles. Br J Dermatol. 1985;113: 581–5.
19. Lowe NL. When systemic retinoids fail to work in psoriasis. In: Saurat JH (ed.). Retinoids: 10 Years On. Basel: Karger, 1991:341–9.
20. Lassus A, Geiger JM, Nyblom M, et al. Treatment of severe psoriasis with etretin (Ro 10–1670). Br J Dermatol. 1987;117:333–41.
21. Goldfarb MT, Ellis CN, Gupta AK, et al. Acitretin improves psoriasis in a dose-dependent fashion. J Am Acad Dermatol. 1988;18:655–62.
22. Saurat JH, Geiger JM, Amblard P, et al. Randomized double-blind multicenter study comparing acitretin-PUVA, etretinate-PUVA and placebo-PUVA in the treatment of severe psoriasis. Dermatologica. 1988;177:218–24.
23. Lebwohl M. Acitretin in combination with UVB or PUVA. J Am Acad Dermatol. 1999;41:S22–4.
24. Saurat JH. Systemic retinoids. What's new? Dermatol Clin. 1998;16:331–40.
25. Layton AM, Knaggs H, Taylor J, et al. Isotretinoin for acne vulgaris – 10 years later: a safe and successful treatment. Br J Dermatol. 1993;129:292–6.
26. Harms M, Duvanel T, Williamson C, et al. Isotretinoin for acne: should we consider the total cumulative dose? In: Marks R, Plewig G (eds). Acne and Related Disorders. London: Martin Dunitz, 1989:203–6.
27. Lehucher-Ceyrac D, Weber-Buisset MJ. Isotretinoin and acne: a prospective analysis of 188 cases over 9 years. Dermatology. 1993;186:123–8.
28. Cunliffe WJ, van de Kerkhof PCM, Caputo R, et al. Roaccutane treatment guidelines: results of an international survey. Dermatology. 1997;194:351–7.
29. Amichai B, Shemer A, Grunwald MH. Low-dose isotretinoin in the treatment of acne vulgaris. J Am Acad Dermatol. 2006;54:644–6.
30. Lehucher-Ceyrac D, de La Salmoniere P, Chastang C, et al. Predictive factors for failure of isotretinoin treatment in acne patients: results from a cohort of 237 patients. Dermatology. 1999;198:278–83.
31. Duvic M, Martin AG, Kim Y, et al. Phase 2 and 3 clinical trial of oral bexarotene (Targretin capsules) for the treatment of refractory or persistent early-stage cutaneous T-cell lymphoma. Arch Dermatol. 2001;137:581–93.
32. Duvic M, Hymes K, Heald P, et al. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results. J Clin Oncol. 2001;19:2456–71.
33. Gniadecki R, Assaf C, Bagot M, et al. The optimal use of bexarotene in cutaneous T-cell lymphoma. Br J Dermatol 2007;157:433–40.
34. Ruzicka T, Lynde CW, Jemec GBE, et al. Efficacy and safety of oral alitretinoin (9-*cis* retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo-controlled, multicentre trial. Br J Dermatol. 2008;158:808–17.
35. Arechalde A, Saurat JH. Retinoids: unapproved uses or indications. Clin Dermatol. 2000;18:63–76.
36. Clayton BD, Jorizzo JL, Hitchcock MG, et al. Adult pityriasis rubra pilaris: a 10-year case series. J Am Acad Dermatol. 1997;36:959–64.
37. Erdogan FG, Yurtsever P, Aksoy D, et al. Efficacy of low-dose isotretinoin in patients with treatment-resistant rosacea. Arch Dermatol. 1998;134:884–5.
38. Bavinck JNB, Tieben LM, Vanderwoude FJ, et al. Prevention of skin cancer and reduction of keratotic skin lesions during acitretin therapy in renal transplant recipients: a double-blind, placebo-controlled study. J Clin Oncol. 1995;13:1933–8.
39. Ruzicka T, Sommerburg C, Goerz G, et al. Treatment of cutaneous lupus erythematosus with acitretin and hydroxychloroquine. Br J Dermatol. 1992;127:513–18.
40. Kang S, Duell EA, Fisher GJ, et al. Application of retinol to human skin *in vivo* induces epidermal hyperplasia and cellular retinoid binding proteins characteristic of retinoic acid but without measurable retinoic acid levels or irritation. J Invest Dermatol. 1995;105:549–56.
41. Jick H. Retinoids and teratogenicity. J Am Acad Dermatol. 1998;39:S118–22.
42. Lammer EJ, Chen DT, Hoar RM, et al. Retinoic acid embryopathy. N Engl J Med. 1985;313:837–41.
43. Carey BM, Parkin GJ, Cunliffe WJ, et al. Skeletal toxicity with isotretinoin therapy: a clinico-radiological evaluation. Br J Dermatol. 1988;119:609–14.
44. Tfelt-Hansen P, Knudsen B, Petersen E, et al. Spinal cord compression after long-term etretinate. Lancet. 1989;2:325–6.
45. Kilcoyne RF. Effects of retinoids in bone. J Am Acad Dermatol. 1988;19:212–16.
46. Ling TC, Parkin G, Islam J, et al. What is the cumulative effect of long-term, low-dose isotretinoin on the development of DISH? Br J Dermatol. 2001;144:630–2.
47. DiGiovanna JJ, Sollitto RB, Abangan DL, et al. Osteoporosis is a toxic effect of long-term etretinate therapy. Arch Dermatol. 1995;131:1263–7.
48. Leachman SA, Insogna KL, Katz L, et al. Bone densities in patients receiving isotretinoin for cystic acne. Arch Dermatol. 1999;135:961–5.
49. DiGiovanna JJ, Langman CB, Tschen EH, et al. Effect of a single course of isotretinoin therapy on bone mineral density in adolescent patients with severe, recalcitrant, nodular acne. J Am Acad Dermatol. 2004;51:709–17.
50. Tekin NS, Ozdolap S, Sarikaya S, Keskin SI. Bone mineral density and bone turnover markers in patients receiving a single course of isotretinoin for nodulocystic acne. Int J Dermatol. 2008;47:622–5.
51. Halkier-Sörensen L, Laurberg G, Andersen J. Bone changes in children on long-term treatment with etretinate. J Am Acad Dermatol. 1987;16:999–1006.
52. Nishimura G, Mugishima H, Hirao J, et al. Generalized metaphyseal modification with cone-shaped epiphyses following long-term administration of 13-*cis*-retinoic acid. Eur J Pediatr. 1997;156:432–5.
53. Lister RK, Lecky BRF, Lewis-Jones MS, et al. Acitretin-induced myopathy. Br J Dermatol. 1996;134:989–90.
54. Bonnetblanc JM, Hugon J, Dumas M. Intracranial hypertension with etretinate. Lancet. 1983;2:974.
55. Lee AG. Pseudomotor cerebri after treatment with tetracycline and isotretinoin for acne. Cutis. 1995;55:165–8.
56. Bigby M. Does isotretinoin increase the risk of depression? Arch Dermatol. 2008;144:1197–9.
57. Marqueling AL, Zane LT. Depression and suicidal behavior in acne patients treated with isotretinoin: a systematic review. Semin Cutan Med Surg. 2007; 26:210–20.
58. Safran AB, Haliaoua B, Roth A, et al. Ocular side-effects of oral treatment with retinoids. In: Saurat JH (ed.). Retinoids: 10 Years On. Basel: Karger, 1991:315–26.
59. Sherman SI, Gopal J, Haugen BR, et al. Central hypothyroidism associated with retinoid X receptor-selective ligands. N Engl J Med. 1999;340:1075–9.
60. Sewell JL, Mahadevan U. Of blemishes and bowels: isotretinoin and inflammatory bowel disease. Gastroenterology. 2010;138:392–4.

60a. Crockett SD, Porter CQ, Martin CF, et al. Isotretinoin use and the risk of inflammatory bowel disease: a case-control study. Am J Gastroenterol. 2010;105: 1986–93.

61. Cribier B, Welsch M, Heid E. Renal impairment probably induced by etretinate. Dermatology. 1992;185:266–8.
62. Koo J, Nguyen Q, Gambla C. Advances in psoriasis therapy. Adv Dermatol. 1997;12:47–72.
63. Vahlquist C, Olsson A, Lindholm A, et al. Effects of gemfibrozil (Lopid®) on hyperlipidemia in acitretin-treated patients. Acta Derm Venereol. 1995;75:377–80.
64. Talpur R, Ward S, Apisarnthanarax N, et al. Optimizing bexarotene therapy for cutaneous T-cell lymphoma. J Am Acad Dermatol. 2002;47:672–84.
65. Vu Dac N, Gervois P, Torra IP, et al. Retinoids increase human apo C-III expression at the transcriptional level via the retinoid X receptor – contribution to the hypertriglyceridemic action of retinoids. J Clin Invest. 1998;102:625–32.
66. Roenigk HH Jr, Callen JP, Guzzo CA, et al. Effects of acitretin on the liver. J Am Acad Dermatol. 1999;41:584–8.

This page intentionally left blank

Antimicrobial Drugs 127

Jack L Lesher Jr and R Carol McConnell

Key features

- Bacterial, fungal and viral infections of the skin and soft tissue are very common
- Selection of the appropriate treatment depends on the infecting microbe, the site and extent of the infection, and patient characteristics (e.g. age, pregnancy/lactation, comorbid medical conditions)
- Physicians must be aware of the drug interactions and potential adverse effects of antimicrobial medications

ANTIBACTERIAL AGENTS

Introduction

The hundreds of antibiotics now available provide physicians with a formidable armamentarium against bacterial diseases. While physicians have gained abundant therapeutic options, some find the vast number of antibacterial medications confusing and overwhelming. Selection of the most appropriate antibiotic depends upon identification of the infecting organism and its sensitivity to antimicrobial agents. Often a patient will present with a clinical picture strongly suggestive of a particular organism. When possible and practical, a culture should be obtained prior to starting therapy.

In acutely ill patients, empiric therapy with broad-spectrum antibiotics may be necessary initially. Knowledge of local bacterial resistance patterns should guide antibiotic selection. Once the microbe is identified, preferably along with antibiotic sensitivities, the medication can be adjusted accordingly. Indiscriminate use of broad-spectrum antibiotics leads to the development of resistant bacteria[1,2]. The site and extent of the infection; the side effect profiles and costs of possible medication choices; and patient characteristics, including age and medical comorbidities (e.g. impaired renal or hepatic function) as well as pregnancy and lactation status, also influence drug selection.

Antibacterial drugs are characterized as being either bacteriostatic or bactericidal. Bacteriostatic drugs stop growth and replication of bacteria and limit spread of infection, allowing the immune system to eliminate the pathogen. Bactericidal agents kill bacteria directly. Table 127.1 outlines into which category commonly used antibiotics are classified.

BACTERIOSTATIC VERSUS BACTERICIDAL DRUGS

Bacteriostatic	Bactericidal
Chloramphenicol	Aminoglycosides
Clindamycin	Bacitracin
Erythromycin	Carbapenems
Sulfonamides	Monobactams
Tetracyclines	Penicillins
Trimethoprim	Polymyxin B
	Quinolones
	Vancomycin

Table 127.1 Bacteriostatic versus bactericidal drugs. Clindamycin may be either bacteriostatic or bactericidal depending on the susceptibility of the infecting organism and the concentration achieved at the site of infection. Factors such as the infecting organism and growth conditions can also affect whether other drugs are bacteriostatic or bactericidal.

Topical Antibacterial Agents

Introduction

Topical antibacterials are used to treat acne vulgaris, rosacea and superficial bacterial infections and to prevent infection after surgery or injuries. Topical antibacterials can easily be applied directly to the affected skin and thus deliver a high concentration of the medication locally with relatively little chance of adverse systemic effects. However, their utility is limited to localized superficial conditions.

Topical antibacterial agents used to treat acne vulgaris and rosacea

Table 127.2 lists topical antibiotics commonly used to treat acne vulgaris and rosacea. Topical antibiotics are used in these conditions for their anti-inflammatory properties as well as for their antibacterial effects. They have limited benefit for non-inflammatory, comedonal acne.

Mechanisms of action

Table 127.3 lists the mechanisms of action of topical antibacterials used to treat acne vulgaris and rosacea.

Azelaic acid (see Ch. 129) is a dicarboxylic acid derivative found in whole grain cereals and animal products, and it is normally present in human plasma. *In vitro*, azelaic acid has activity against *Propionibacterium acnes* and *Staphylococcus epidermidis*. It is usually bacteriostatic but may be bactericidal in high concentrations. Its activity may be due to inhibition of microbial cellular protein synthesis. Azelaic acid has anticomedonal effects by normalizing keratinization. It thins the stratum corneum, decreases the number and size of keratohyalin granules, and reduces the amount and distribution of filaggrin in the epidermis. Azelaic acid has antiproliferative effects against hyperactive and abnormal melanocytes, but it rarely causes hypo- or depigmentation of normally pigmented skin (see Table 127.4).

Benzoyl peroxide is bacteriostatic against *P. acnes*. Once absorbed by the skin, it is converted to benzoic acid. Its effects are believed to be due to oxidation of bacterial proteins by reactive oxygen species, which are released when the drug is decomposed by cysteine in the skin. Daily use of 10% benzoyl peroxide for 2 weeks decreases free fatty acids by 50% and *P. acnes* by 98%, which is comparable to results obtained after use of topical antibiotics for 4 weeks[3]. Benzoyl peroxide is also keratolytic and desquamative.

Clindamycin is a semisynthetic lincosamide antibiotic that is active against Gram-positive cocci and anaerobes including staphylococci, streptococci, *P. acnes, Corynebacterium* spp., *Clostridium* spp. and *Gardnerella vaginalis*. Clindamycin may be either bacteriostatic or bactericidal depending on the susceptibility of the infecting organism and the concentration achieved at the site of infection.

Erythromycin is a macrolide antibiotic that is active against Gram-positive cocci including group A β-hemolytic streptococci and *Staphylococcus aureus,* as well as some Gram-negative bacilli. Erythromycin also has anti-inflammatory properties.

Studies have shown that the combination of erythromycin and benzoyl peroxide is more effective for the treatment of acne than erythromycin alone both *in vivo* and *in vitro*[4–8]. Randomized, double-blind, controlled trials have also demonstrated that acne patients treated with the combination of clindamycin and benzoyl peroxide had a greater reduction in the number of inflammatory papules and pustules than did those treated with benzoyl peroxide alone, clindamycin alone or vehicle alone[9,10]. These synergistic combinations may also slow the development of antibiotic resistance. Several products containing erythromycin or clindamycin together with benzoyl peroxide are available.

TOPICAL ANTIBACTERIALS USED FOR ACNE VULGARIS AND ROSACEA				
Generic name	**Trade name(s)®**	**Formulations**	**Dosing frequency**	**FDA pregnancy category**
Azelaic acid	Azalea, Azelex, Cutacelan, Finacea, Finevin, Skinoderm, Skinoren	20% cream, 15% gel	bid	B
Benzoyl peroxide	Acetoxyl, Acne-Aid, Acnomel, Ambi, Benoxyl, Benzac, Benzagel, BenzaShave, BenzEFoam, Benziq, Brevoxyl, Clearasil, Clearplex, Clinac, Del-Aqua, Dermoxyl, Desquam-E, Desquam-X, Fostex, Inova, Lavoclen, Loroxide, Oxy, Oxyderm, NeoBenz, PanOxyl, Pacnex, Persa-Gel, Solugel, Triaz, Zapzyt	2.5–10% lotion, cream, gel, foam, solution, stick, cleansing bar, cleansing lotion, cloths, pads, mask, shaving cream	qd–tid; mask qwk	C
Clindamycin	Basocin, Cleocin T, Clinac, Clinda-Derm, Clindagel, Clindets, Cutaclin, Dalacin, Dalagis, Euroclin, Evoclin	1% gel, lotion, solution, foam, pledgets; 2% vaginal cream	bid	B
Erythromycin	Akne-Mycin, A/T/S, Emgel, Erycette, Eryderm, Erygel, Erymax, Ery-Sol, Erythra-Derm, ETS, Ilotycin, Sans-Acne, Staticin, Theramycin Z, T-Stat	1.5% or 2% solution; 2% pledgets, gel, ointment	bid	B
Sodium sulfacetamide	Klaron, Mexar, Ovace, Seb-Prev, Sebizon *With 5% sulfur:* Avar Cleanser, Clarifoam, Clenia, Novacet, Plexion, Prascion, Rosac, Rosaderm, Rosanil, Rosula, Sulfacet-R, Sulfatol, SulZee, Sumaxin, Suphera, Topisulf, Zetacet	10% lotion, cream, suspension, foam, wash/cleanser, cleansing cloths	bid	C
Metronidazole	MetroGel, MetroCream, MetroLotion, Noritate	0.75% or 1% gel, cream, lotion	qd–bid	B
Dapsone	Aczone	5% gel	bid	C
Benzoyl peroxide/erythromycin	Benzamycin	5%/3% gel	bid	C
Benzoyl peroxide/clindamycin	Acanya, Benzaclin, Duac, Z-Clinz	2.5–10%/1% gel	bid	C
Benzoyl peroxide/adapalene	Epiduo	2.5/0.1% gel	qd	C
Clindamycin phosphate/tretinoin	Veltin, Ziana	1.2/0.025% gel	qd	C

Table 127.2 Topical antibacterials used for acne vulgaris and rosacea. bid, twice daily; qd, daily; qwk, weekly; tid, three times daily.

Erythromycin (4%) has been combined with 1.2% zinc acetate, as has benzoyl peroxide (3–10%) with zinc lactate. The former product is not available in the US. Zinc has antiandrogen activity *in vitro* and suppresses sebum secretion[11]. Studies have shown erythromycin combined with zinc to be superior to placebo *in vivo*[12–15] and effective *in vitro* against erythromycin-resistant *P. acnes*[16]. However, it may be inferior to benzoyl peroxide combined with erythromycin[17].

Sodium sulfacetamide is bacteriostatic. It is active against some Gram-positive and Gram-negative organisms. Some topical preparations combine sodium sulfacetamide with sulfur, which acts as a keratolytic as well as antimicrobial agent (see Ch. 129).

Metronidazole is a nitroimidazole. Topical metronidazole has antioxidant and anti-inflammatory as well as antimicrobial effects.

Dapsone is a sulfone drug that, in addition to its antimicrobial properties, has anti-inflammatory effects that target neutrophils (e.g. inhibiting neutrophil chemotaxis, decreasing myeloperoxidase activity).

Indications

Azelaic acid, benzoyl peroxide, clindamycin, erythromycin, sodium sulfacetamide and dapsone can be used for mild to moderate inflammatory acne vulgaris. Azelaic acid may also be useful for melasma and other forms of hyperpigmentation. Benzoyl peroxide has been used for decubitus and stasis ulcers. Topical clindamycin and erythromycin can treat superficial bacterial infections of the skin, whereas topical clindamycin and metronidazole are both indicated for bacterial vaginosis. Sodium sulfacetamide and topical metronidazole are indicated for the treatment of rosacea.

Dosages

Topical antibacterial agents are usually used once or twice a day (see Table 127.2). A small amount of medication is applied in a thin layer onto clean, dry skin. Benzoyl peroxide cleansing bars and washes are used one to three times a day. Benzoyl peroxide shave cream is used like any other shaving cream, and the mask is applied in a thin layer once a week, left on for 15 to 25 minutes, and then rinsed off.

MECHANISMS OF ACTION OF TOPICAL ANTIBACTERIAL AGENTS USED TO TREAT ACNE VULGARIS AND ROSACEA		
Generic name	**Class**	**Mechanism of action**
Azelaic acid	Dicarboxylic acid derivative	Possibly inhibition of bacterial protein synthesis
Benzoyl peroxide	Oxidizing agent	Oxidation of bacterial proteins by reactive oxygen species
Clindamycin	Lincosamide	Inhibits protein synthesis by binding to the bacterial 50S ribosomal subunit
Erythromycin	Macrolide	Inhibits protein synthesis by binding to the bacterial 50S ribosomal subunit
Sodium sulfacetamide	Sulfonamide	Inhibits nucleic acid and protein synthesis and cell growth by impeding bacterial synthesis of dihydrofolic acid. Competitive inhibition of dihydropteroate synthetase prevents condensation of pteridine precursors with PABA (see Fig. 127.4)
Metronidazole	Nitroimidazole	May cause DNA strand breaking. Also has antioxidant and anti-inflammatory effects
Dapsone	Sulfone	Inhibits dihydropteroate synthase and prevents bacterial folic acid synthesis. Also decreases neutrophil chemotaxis and myeloperoxidase activity

Table 127.3 Mechanisms of action of topical antibacterial agents used to treat acne vulgaris and rosacea. PABA, para-aminobenzoic acid.

Contraindications

The chief contraindication for these medications is a history of hypersensitivity to any component of the formulation. Azelaic acid preparations contain propylene glycol, which may be a sensitizer. Topical clindamycin should be avoided in patients with a history of

SIDE EFFECTS OF TOPICAL ANTIBACTERIAL AGENTS USED FOR ACNE VULGARIS AND ROSACEA	
Generic name	**Side effects**
Azelaic acid	Pruritus, burning, stinging, tingling, erythema, xerosis, peeling, irritant contact dermatitis, allergic contact dermatitis Rarely reported: hypopigmentation, depigmentation, hypertrichosis, keratosis pilaris, exacerbation of recurrent herpes labialis
Benzoyl peroxide	Irritation; occasionally blistering, crusting, severe erythema, edema Bleaches hair and colored fabrics
Clindamycin	Gram-negative folliculitis Rare cases of pseudomembranous colitis (the suggested risk of pseudomembranous colitis from topical use appears not to be clinically significant[18])
Erythromycin	Eye irritation, skin tenderness, Gram-negative folliculitis, rarely generalized urticarial reactions Bacterial resistance
Sodium sulfacetamide	Xerosis, pruritus; may cross-react in patients allergic to related oral medications
Metronidazole	Watery eyes, metallic taste in the mouth, nausea, numbness and paresthesias have been reported with topical use[19]; may cross-react in patients allergic to the oral form
Dapsone	Dryness, peeling, erythema; in patients with G6PD deficiency, occasionally associated with a drop in the hemoglobin level

Table 127.4 Side effects of topical antibacterial agents used for acne vulgaris and rosacea. G6PD, glucose-6-phosphate dehydrogenase.

inflammatory bowel disease or antibiotic-associated colitis. These conditions may increase the chance of gastrointestinal side effects.

Major side effects

Adverse reactions to the topical antibacterial agents used to treat acne vulgaris and rosacea are usually mild and transient. Stinging is especially common with alcohol-containing solutions and pledgets. Table 127.4 lists side effects of individual drugs.

Interactions

Application of more than one topical medication simultaneously may increase or decrease the effect of one or both of the medications. Benzoyl peroxide may have additive irritant effects when used with other topical acne medications, and it can oxidize and thereby decrease the activity of tretinoin when these products are applied at the same time. Topically applied clindamycin may interact with other drugs as a result of systemic absorption. Clindamycin has neuromuscular blocking properties that may enhance the effects of similar agents. It should be used with caution in patients receiving neuromuscular blocking agents. Clindamycin, erythromycin and chloramphenicol may antagonize each other due to their similar mechanisms of action. Oral metronidazole may potentiate the anticoagulant effect of warfarin, resulting in a prolonged prothrombin time. It is not known whether topical preparations have the same effect. A temporary yellow–orange staining of the skin and hair occasionally occurs with concomitant use of topical dapsone and benzoyl peroxide, and systemic levels of dapsone increase if it is administered together with co-trimoxazole.

Pregnancy and lactation

Table 127.2 lists the FDA pregnancy categories of the topical antibacterial agents used to treat acne vulgaris and rosacea.

Azelaic acid has not been adequately studied in pregnant women. There is a small amount of systemic absorption of azelaic acid through topical application. Passage of azelaic acid into maternal milk may occur. There have been no reported problems due to azelaic acid in nursing infants.

Studies on the effects of benzoyl peroxide in pregnancy have not been done in either humans or animals. There may be systemic absorption of topically applied benzoyl peroxide. It is not known whether benzoyl peroxide is excreted in breast milk, but has not been reported to cause problems in nursing infants.

There are no adequate studies of topical clindamycin in pregnant or lactating women. It is not known whether topically applied clindamycin passes into breast milk. No serious adverse effects have been reported in nursing infants. Clindamycin vaginal cream is not recommended during pregnancy, except for women who are at high risk for a bad outcome due to bacterial vaginosis or in women who are at low risk of adverse pregnancy outcomes who also have symptomatic bacterial vaginosis.

Studies on the effects of topical erythromycin in pregnancy have not been done in humans or animals. Animal reproduction studies have not been done. Systemically administered erythromycin is excreted in breast milk, but it is not known whether topical erythromycin is excreted in breast milk. Erythromycin topical preparations have not been reported to cause problems in nursing infants.

Sulfonamides may increase the chance of kernicterus in newborns and should not be used late in pregnancy. Systemic sulfonamides are excreted in breast milk and may cause kernicterus, anemia and other adverse effects in nursing infants, especially those with glucose-6-phosphate dehydrogenase deficiency.

Topical metronidazole has not been studied in pregnant women. Systemic metronidazole crosses the placental barrier and enters the fetal circulation, and whether or not it has the potential to cause birth defects or other problems in animal studies has been the subject of controversy; it is generally recommended that systemic administration be avoided during the first trimester. Topical metronidazole results in blood levels much lower than those achieved with systemically administered metronidazole. The small amounts of this medication that are absorbed are unlikely to cause problems in nursing infants.

Topical antibacterial agents used to treat superficial infections

Table 127.5 lists antibacterial agents commonly used to prevent and treat superficial skin infections.

Mechanisms of action

The mechanisms of action of the topical antibacterial agents used to treat superficial infections are listed in Table 127.6.

Mupirocin (pseudomonic acid A) is derived from *Pseudomonas fluorescens*. It is clinically active against staphylococci, groups A, B, C and G streptococci, and some Gram-negative aerobic bacteria. It is usually bacteriostatic, but may be bactericidal at high concentrations.

Retapamulin is the first drug in the new pleuromutilin class, derived from fermentation of a mushroom, *Clitopilus passeckerianus*[20].

Neomycin and *gentamicin* are aminoglycoside antibiotics isolated from cultures of *Streptomyces fradiae* and *Micromonospora purpurea*, respectively. Neomycin is bactericidal against Gram-positive and Gram-negative bacteria including *S. aureus, Escherichia coli, Haemophilus influenzae, Proteus* spp. and *Serratia* spp. It is generally not effective against *Pseudomonas aeruginosa*. Gentamicin is effective against sensitive strains of group A β-hemolytic and α-hemolytic streptococci, *S. aureus* (coagulase-positive, coagulase-negative and some penicillinase-producing strains) and Gram-negative bacteria including *P. aeruginosa, Aerobacter aerogenes, E. coli, Proteus vulgaris* and *Klebsiella pneumoniae*.

Bacitracin is a cyclic polypeptide antibiotic produced by the Tracey I strain of *Bacillus subtilis*. It has a thiazolidine ring and peptide side chains. Bacitracin is active against Gram-positive organisms such as staphylococci, streptococci, corynebacteria and clostridia.

Polymyxin B is a cyclic lipopeptide antibiotic isolated from the aerobic Gram-positive rod *Bacillus polymyxa*, a soil organism. It is rapidly bactericidal for various Gram-negative organisms, including *P. aeruginosa, E. coli, K. pneumoniae, Enterobacter aerogenes, H. influenzae, Proteus mirabilis* and *Serratia marcescens*. It is not active against Gram-positive organisms.

Indications

Mupirocin, neomycin, gentamicin, bacitracin and combination products containing polymyxin B are all indicated for the treatment and prevention of superficial bacterial skin infections. The intranasal

TOPICAL ANTIBACTERIAL AGENTS USED FOR SUPERFICIAL INFECTIONS				
Generic name	**Trade name(s)®**	**Formulations**	**Dosing frequency**	**FDA pregnancy category**
Mupirocin	Bactoderm, Bactroban, Centany, Eismycin	2% ointment or cream	tid	B
Retapamulin	Altabax	1% ointment	bid	B
Neomycin	Myciguent	0.5% ointment or cream	qd–tid	C
Gentamicin	Garamycin, Gentamar, G-Myticin	0.1% ointment or cream	tid–qid	C
Bacitracin	Baciguent	400–500 units per gram ointment	tid	C
Polymyxin B	Polysporin ointment = bacitracin + polymyxin B Neosporin ointment = bacitracin, polymyxin B + neomycin Neosporin cream = polymyxin B + neomycin only	5000–10 000 units per gram ointment	qd–tid	C

Table 127.5 Topical antibacterial agents used for superficial infections. bid, twice daily; qd, daily; tid, three times daily.

MECHANISMS OF ACTION OF TOPICAL ANTIBACTERIAL AGENTS USED FOR SUPERFICIAL INFECTIONS		
Generic name	**Class**	**Mechanism of action**
Mupirocin	Unique	Inhibits protein synthesis by reversibly binding to bacterial isoleucyl transfer RNA synthetase
Retapamulin	Pleuromutilin	Selectively inhibits bacterial protein synthesis by interacting with the ribosomal protein L3 on the 50S ribosomal subunit
Neomycin	Aminoglycoside	Binds to the 30S subunit of the bacterial ribosome and causes misreading of the mRNA and inhibition of bacterial protein synthesis. May also inhibit bacterial DNA polymerase
Gentamicin	Aminoglycoside	Binds to the 30S subunit of the bacterial ribosome and causes misreading of the mRNA and inhibition of bacterial protein synthesis
Bacitracin	Cyclic polypeptide	Forms a complex with C55-phenol pyrophosphate, a component of the bacterial cell wall, impeding bacterial cell wall synthesis
Polymyxin B	Cyclic lipopeptide	Interacts with the phospholipids of bacterial cell membranes, increasing their cellular permeability

Table 127.6 Mechanisms of action of topical antibacterial agents used for superficial infections.

preparation made with the calcium salt of mupirocin is indicated for the eradication of nasopharyngeal carriage of *S. aureus*. Studies implicating nasal staphylococci as a potential source for wound infections and bacteremia suggest mupirocin intranasally may have an effect in decreasing the incidence of these bacterial infections in susceptible individuals (e.g. those with recurrent staphylococcal infections)[21]. Mupirocin has been shown to be as effective as systemic antibiotics for limited impetigo[22,23]. Retapamulin is indicated for the topical treatment of impetigo due to *Streptococcus pyogenes* and methicillin-susceptible *S. aureus* in patients as young as 9 months of age.

Dosages
Table 127.5 outlines the formulations and dosing for the antibacterial agents used for the treatment of superficial skin infections. Intranasal mupirocin is applied into the nares two to four times a day for 5 to 14 days.

Contraindications
As with all topical medications, the main contraindication is a history of hypersensitivity to any component of the formulations.

Major side effects
Potential side effects of mupirocin include burning, stinging, tenderness, pain and pruritus, as well as erythema, edema, increased exudate, allergic contact dermatitis, headache and nausea. Use of nasal mupirocin is occasionally associated with headaches, rhinitis, respiratory tract congestion, pharyngitis, taste perversion, burning, stinging and cough. Use of mupirocin on extensive areas of skin with decreased barrier function has been reported to cause systemic absorption of polyethylene glycol leading to renal toxicity. Retapamulin can cause application site irritation and pruritus.

Side effects of neomycin include allergic contact dermatitis in 5% to 15% of patients[19], in particular when neomycin is applied to cutaneous ulcerations and/or areas of chronic stasis dermatitis. The most common symptoms are pruritus, erythema and edema. The risk of side effects increases if the patient has impaired renal function; for example, patients with decreased renal function may develop irreversible ototoxicity manifested by hearing loss. Caution should be exercised if the medication is used over extensive areas. Nephrotoxicity, neuromuscular blockade and death have been reported after application of neomycin[19]. It may also cause mast cell degranulation and histamine release[3].

Possible side effects of gentamicin are erythema, pruritus, edema and photosensitization. There is a risk of producing gentamicin-resistant strains of *Pseudomonas* when this topical agent is applied to heavily colonized skin (e.g. leg ulcers).

Adverse effects of bacitracin include irritant and allergic contact dermatitis. Chronic stasis dermatitis predisposes to the latter. Anaphylaxis has been reported in patients with a history of multiple previous exposures when bacitracin was applied to open wounds.

There are very few side effects from polymyxin B. Contact sensitization has been reported. Of note, some cross-reactivity exists between bacitracin and polymyxin B because they are both derived from *Bacillus* species.

Interactions
In studies utilizing *E. coli*, chloramphenicol interferes with the effect of mupirocin on bacterial RNA synthesis. Otherwise, there are no known significant drug interactions with the topical antibiotics used for superficial skin infections.

Pregnancy and lactation
Table 127.5 lists the FDA pregnancy categories of the topical antibacterials used to treat superficial infections.

Neither topical nor nasal mupirocin has been adequately studied in pregnant women. It has not been shown to cause birth defects or other problems in animal studies using rats and rabbits. It is not known whether topical or nasal mupirocin is excreted in breast milk. There is very little systemic absorption of topically applied mupirocin. Topical neomycin has not been shown to cause birth defects in humans and has not been reported to cause problems in nursing infants. Animal studies have not been conducted with polymyxin B, and it is not known whether polymyxin B is excreted in breast milk.

Other topical antibacterial agents
Fusidic acid is a fusidane antibiotic isolated from the fungus *Fusidum coccineum*[24]. It is not approved in the US but is used in Europe and Canada for mild to moderately severe cutaneous infections, external eye infections and eradication of nasopharyngeal carriage of *S. aureus*. It is available as a 2% cream, ointment and impregnated gauze that is

applied three times a day. It may also be given orally or intravenously. It has a steroid-like structure but does not have any steroid effects[24,25]. Fusidic acid inhibits bacterial protein synthesis by interfering with elongation factor G. It is active against Gram-positive bacteria, especially *S. aureus*. This medication has a bacteriologic efficacy comparable to that of mupirocin for impetigo and may be more cost-effective[26–28]. When combined with topical corticosteroids, it is useful in treating atopic dermatitis with superimposed staphylococcal infection[25]; it is also effective in erythrasma[29,30]. Fusidic acid has few adverse effects, although allergic contact dermatitis has been reported.

Iodoquinol (1%) combined with 1% hydrocortisone has been commercially available for many years. Iodoquinol is a halogenated oxyquinoline with antibacterial and antifungal activity. Its mechanism of action is unknown. The combination product is applied three to four times a day for superficial bacterial and fungal skin infections. It is in FDA pregnancy category C and its safety during pregnancy is unknown. Topical iodoquinol (1%) preparations have a high iodine content. There is a systemic form of iodoquinol used for amebiasis, which is contraindicated in patients with iodine intolerance, may interfere with thyroid function tests, and may cause iododerma[31]. A related medication, topical *clioquinol* (iodochlorhydroxyquin), is used primarily for the treatment of superficial fungal infections (see below).

Mafenide acetate cream is a sulfonamide used for thermal burns and is applied once or twice daily. It has antibacterial and antifungal activity. The most common side effect is burning, and, less often, urticaria or facial edema can occur. Rarely, mafenide acetate may cause bone marrow suppression or lead to hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. It should be used with caution in patients with renal or pulmonary disease owing to its potential to cause metabolic acidosis. Furthermore, mafenide acetate may cause intense pain upon application and can be associated with *Candida* superinfection.

Nitrofurazone is used for thermal burns and skin grafting. It is available as a 0.2% cream, ointment and solution. Nitrofurazone is used once a day. It works by inhibiting bacterial metabolic enzymes and is effective against staphylococci, streptococci, *E. coli*, *Clostridium perfringens*, *Aerobacter enterogenes* and *Proteus* spp.

Silver sulfadiazine is a 1% cream applied once to twice a day for thermal burns. In addition to its sulfonamide properties, the silver interacts with bacterial cell walls and membranes. When used in conjunction with cimetidine, there is an increased risk of leukopenia. Silver sulfadiazine may interfere with collagenase (Santyl®), papain (Panafil®) and sutilains (Travase®). It is contraindicated in patients with a history of hypersensitivity to sulfonamides and should be used with caution in patients with G6PD deficiency, renal or hepatic disease, and porphyria. Sulfonamides can generate oxidants and induce an acute hemolytic anemia in patients with G6PD deficiency. They may precipitate an attack of pseudoporphyria or unmask a case of true porphyria. The mechanism for this is unclear, but may be direct hepatocellular damage, increased cytochrome P450 activity, or inhibition of liver enzymes leading to increased production of porphyrins. Localized argyria due to deposits of silver in the dermis can also occur.

Topical tetracyclines

Tetracycline hydrochloride is available as a 3% solution and as an ointment. It is applied twice a day for acne vulgaris and is also indicated for superficial skin infections. Meclocycline sulfosalicylate solution and cream are indicated for acne but are not available in the US. Chlortetracycline ointment is indicated for superficial skin infections. Topical tetracyclines may be less effective than topical clindamycin or erythromycin. They work by inhibition of protein synthesis and are bacteriostatic against a wide range of Gram-negative and Gram-positive bacteria. The products currently available have been formulated to reduce the yellow color associated with topical tetracyclines. Side effects include stinging, burning and an unpleasant odor. It is not known whether topically applied tetracyclines are excreted in breast milk. However, because tetracyclines can cause permanent yellow, gray or brown discoloration of the teeth, they should not be used in pregnant women, nursing mothers, or children under 8 years of age. Topical tetracycline contains sodium bisulfite, which may cause anaphylaxis in susceptible individuals.

Systemic Antibacterial Agents

Systemic antibacterial agents have the potential to cause a wide range of adverse effects and to have significant interactions with other systemic medications. For example, rifampin may reduce the efficacy of oral contraceptives. Bacteriostatic antibacterial agents can decrease the efficacy of bactericidal antibacterial agents, because the latter target actively dividing cells. In addition, use of systemic antibacterial agents is associated with a risk for the development of bacterial resistance. The mechanisms of action of the major classes of antibacterial drugs are listed in Table 127.7 and illustrated in Figure 127.1. Systemic antibiotics may be used perioperatively by dermatologic surgeons to prevent surgical site infections in high-risk situations such as procedures involving the lower extremity or groin, wedge excisions on the lip or ear, skin flaps on the nose, and skin grafts. Antibiotic prophylaxis is also recommended in patients at high risk for infective endocarditis or

SITES OF ACTION OF DIFFERENT CLASSES OF SYSTEMIC ANTIBACTERIAL DRUGS

Site of action	Drug class(es)
Cell wall	Penicillins Cephalosporins Carbapenems Monobactams Vancomycin β-lactamase inhibitors
Inhibit nucleic acid synthesis	Sulfonamides Trimethoprim
DNA gyrase	Quinolones
DNA strand breakage	Metronidazole
Ribosomal subunit	Aminoglycosides – 30S Tetracyclines – 30S Chloramphenicol – 50S Clindamycin – 50S Macrolides – 50S

Table 127.7 Sites of action of different classes of systemic antibacterial drugs.

SITES OF ACTION OF ANTIBACTERIAL DRUGS

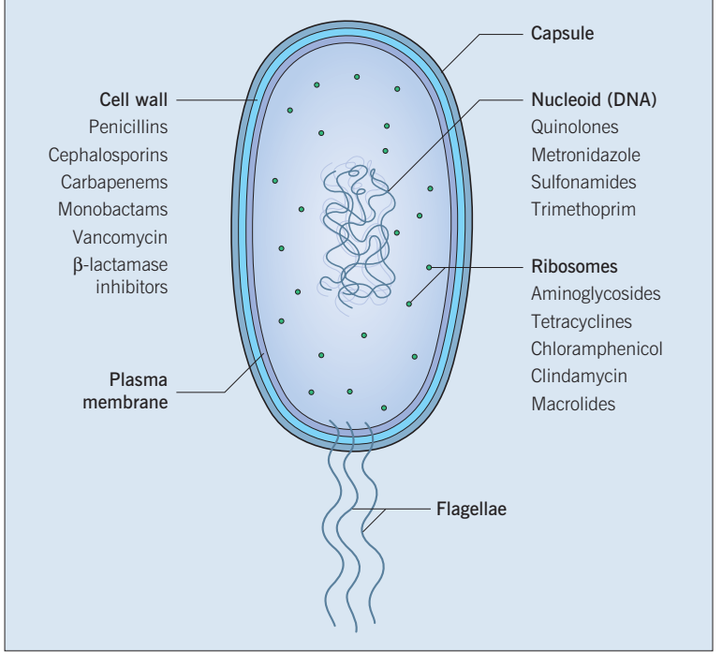


Fig. 127.1 Sites of action of antibacterial drugs. This figure illustrates a prototypical bacterial cell. Each class of antibacterial drug exerts its effect on a particular component of the cell.

hematogenous total joint infection who have surgery involving the oral mucosa or infected skin (see Ch. 151)[32].

Penicillins

Mechanism of action

Penicillins are β-lactam antibiotics that exert a bactericidal effect by binding to and inactivating penicillin-binding proteins in the bacterial cell wall. They are thought to inhibit bacterial cell wall synthesis by blocking the transpeptidase cross-linking of peptidoglycan chains (Fig. 127.2).

The natural penicillins (penicillin G and penicillin V) are active against Gram-positive and Gram-negative cocci, most Gram-positive bacilli, and spirochetes. Penicillinase-resistant penicillins or anti-staphylococcal penicillins (methicillin, nafcillin and dicloxacillin) have greater efficacy against *S. aureus*. Aminopenicillins (ampicillin, amoxicillin) have an extended spectrum to include *H. influenzae*, *E. coli*, *Salmonella* and *Shigella* spp. and some other Gram-negative bacteria, but not *Pseudomonas* spp. Antipseudomonal penicillins (carbenicillin, ticarcillin and piperacillin) cover *P. aeruginosa* and *B. fragilis*. Carbenicillin and ticarcillin have no activity against *Klebsiella* spp., whereas mezlocillin, azlocillin and piperacillin do. Addition of the β-lactamase inhibitors clavulanic acid, sulbactam and tazobactam extends the spectrum of penicillins to include staphylococci and other β-lactamase-producing bacteria (Fig. 127.3).

Indications

Penicillins are used for syphilis and streptococcal skin infections such as erysipelas and perianal disease as well as other cutaneous infections such as erysipeloid[33]. Amoxicillin with clavulanic acid is the drug of choice for cat, dog and human bites. It is useful also for acute paronychia. The penicillinase-resistant penicillins, e.g. dicloxacillin, are used for staphylococcal skin infections, including impetigo, folliculitis and furunculosis, although the incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) is rising and sensitivity testing should be obtained when MRSA is a clinical concern. Amoxicillin may be used for Lyme disease when tetracyclines are contraindicated. Penicillins are also used to treat non-cutaneous infections caused by susceptible bacteria, including pneumonia, gonorrhea, urinary tract infections, otitis media and sinusitis.

Dosages

The pediatric and adult dosages of commonly used penicillins are listed in Table 127.8. Amoxicillin and amoxicillin with clavulanic acid should be taken with food. Other penicillins should be taken on an empty stomach.

Contraindications

Penicillins are contraindicated in patients with known immediate-type (IgE-mediated) hypersensitivity to any penicillin (i.e. a history of urticaria, angioedema or anaphylaxis). However, it has been shown that only 10% to 20% of patients who report a history of allergy to penicillins have a true allergy proven by skin testing[34]. Cross-reaction with penicillins occurs in approximately 2–10% of patients allergic to cephalosporins. Benzylpenicilloyl polylysine, benzylpenicillin G, benzylpenicilloate and penicilloyl propylamine, as well as negative (saline) and positive (histamine) controls, are used to test for penicillin allergy. Antihistamines should be avoided prior to testing. Patients who have had a life-threatening reaction to penicillin should be tested with 100-fold dilutions of the allergens before being tested with full-strength allergens in a monitored setting where treatment for anaphylaxis is available. Epicutaneous (prick) testing may be performed by placing drops of antigen solutions on the volar forearm and using a 26-gauge needle to pierce the epidermis without drawing blood. An epicutaneous test is positive if, within 15 minutes, the average wheal diameter is 4 mm larger than the wheal of negative controls. For intradermal testing, antigen solutions and controls are injected in the volar forearm. An intradermal test is positive if, 15 minutes after injection, the average wheal diameter is at least 2 mm greater than the initial wheal size and is also at least 2 mm greater than the negative controls. Patients who report a history of penicillin allergy but are skin-test-negative to the entire battery of major (benzylpenicilloyl polylysine) and minor (benzylpenicillin G, benzylpenicilloate and penicilloyl propylamine) allergenic determinants can use penicillin in a monitored setting. Skin-test-positive patients may be desensitized orally or intravenously in a hospital setting in about 4 hours. Rarely, serious IgE-mediated allergic reactions can occur. Blood tests can also be used to detect specific IgE directed against penicillin, but this method is less sensitive and gives less information than skin tests.

Major side effects

Drugs in the penicillin group cause hypersensitivity reactions characterized by urticaria, flushing and pruritus in 7% to 15% of patients. In severe cases, they may give rise to anaphylaxis, shock and death. Penicillins may also cause delayed hypersensitivity reactions associated with fever, eosinophilia and (occasionally) serum sickness-like

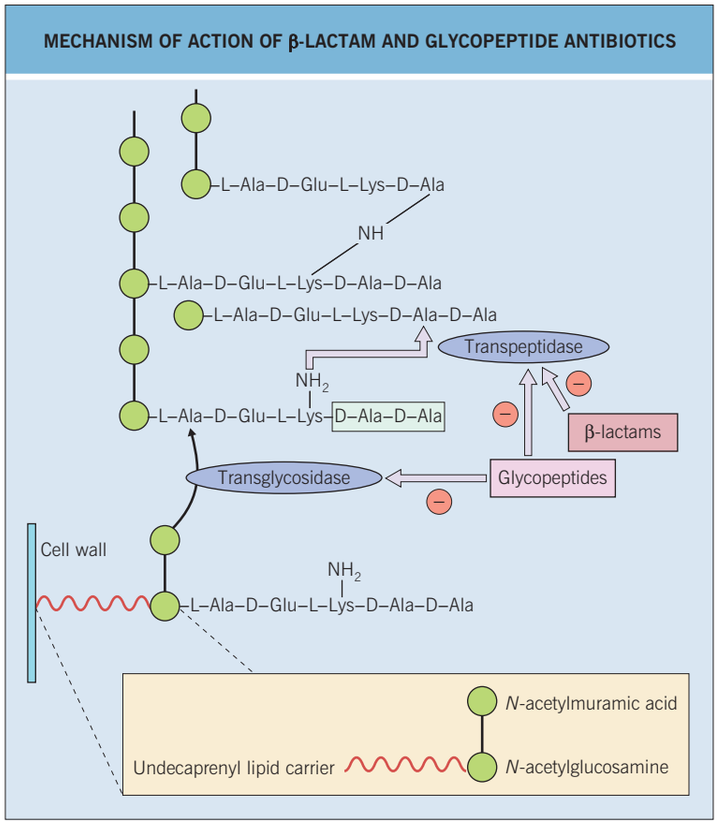


Fig. 127.2 Mechanism of action of β-lactam and glycopeptide antibiotics. Simplified schematic of mechanisms of action of β-lactam antibiotics (penicillins, cephalosporins) and glycopeptides (e.g. vancomycin, dalbavancin) in interfering with enzymatic steps in bacterial cell wall (peptidoglycan) synthesis.

DOSAGES OF COMMONLY USED PENICILLINS

Generic name	Pediatric oral dosage	Adult oral dosage
Penicillin V potassium	25–50 mg/kg/day divided q6–8 h	250–500 mg qid
Dicloxacillin	12.5–50 mg/kg/day divided q6 h	125–500 mg qid
Ampicillin	50–100 mg/kg/day divided q6 h	250–500 mg qid
Amoxicillin	25–50 mg/kg/day divided q8 h or q12 h	250–500 mg bid
Amoxicillin/clavulanate	20–40 mg/kg/day (of amoxicillin) divided q8 h or q12 h*	500–875 mg bid

*Do not double the dose of clavulanate if you double the amoxicillin dose, as this causes excessive clavulanate dosage and increased risk of gastrointestinal side effects like diarrhea.

Table 127.8 Dosages of commonly used penicillins. bid, twice daily; h, hours; q, every; qid, four times daily.

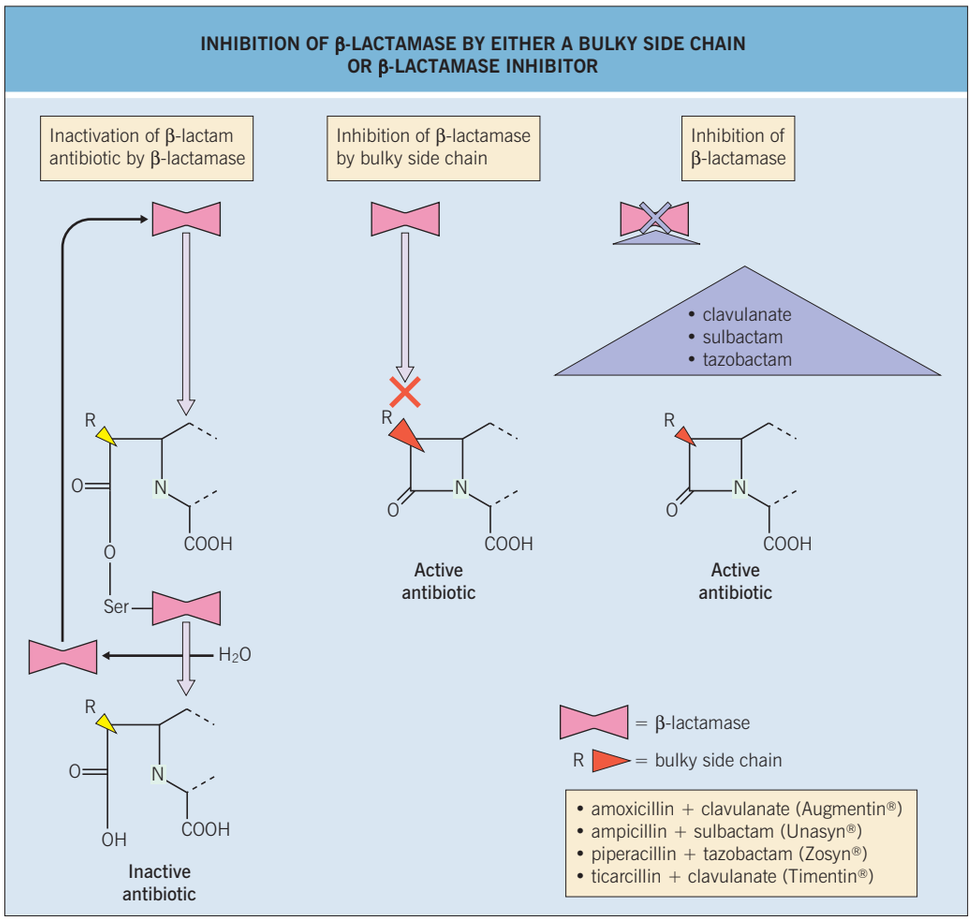


Fig. 127.3 Inhibition of β-lactamase by either a bulky side chain or β-lactamase inhibitor. Placement of a bulky side chain on the penicillin molecule (e.g. methicillin, nafcillin, dicloxacillin) can inhibit bacterial β-lactamase, as can the combination of a penicillin with a β-lactamase inhibitor (e.g. clavulanic acid, sulbactam, tazobactam). The latter group of drugs has no inherent antibacterial activity. Inhibition of β-lactamase allows the antibiotic to remain active and inhibit bacterial transpeptidase.

reactions. Stevens–Johnson syndrome, toxic epidermal necrolysis, and pustular eruptions such as acute generalized exanthematous pustulosis are also potential side effects. These drugs sometimes lead to autoimmune phenomena, including hemolytic anemia or vasculitis. Ampicillin and amoxicillin almost invariably cause a generalized morbilliform eruption when used in patients with infectious mononucleosis; this type of reaction is also more likely in patients with lymphocytic leukemia and those who are taking concomitant allopurinol. When administered in high doses to patients with renal insufficiency, penicillins may lead to neurotoxicity with hyperirritability, confusion, seizures and coma. Rapid infusion, high blood levels or intrathecal injection may also cause seizures.

Penicillins can induce an acute interstitial nephritis characterized by proteinuria, hematuria, renal casts, eosinophilia, eosinophiluria, fever, arthralgias and declining renal function. Prolonged use of penicillins may lead to reversible neutropenia, anemia, agranulocytosis and platelet dysfunction. Penicillins can cause diarrhea, pseudomembranous colitis and hepatic dysfunction. For example, oxacillin and carbenicillin are associated with "oxacillin hepatitis", an anicteric liver dysfunction with eosinophilia that may occur in as many as 15% of patients. Treatment with penicillins is associated with oral or vaginal overgrowth of *Candida* spp. in over 10% of patients.

Interactions
Because probenecid blocks the secretion of penicillins in the distal renal tubules, concomitant administration of these two drugs increases the serum levels and duration of action of the penicillins. When amoxicillin or ampicillin is used with allopurinol, there is an increased risk of morbilliform drug eruption, and when tetracyclines are used with penicillins, the bactericidal effect of penicillins is decreased.

Pregnancy and lactation
Penicillins are grouped in pregnancy category B and are considered to be safe for use in nursing mothers.

Cephalosporins

Mechanism of action
Like the penicillins, the cephalosporins (Table 127.9) are bactericidal β-lactam antibiotics that bind to penicillin-binding proteins and interfere with bacterial cell wall synthesis. First-generation cephalosporins are very effective against Gram-positive organisms (staphylococci and streptococci) and less effective against Gram-negative organisms; however, they are active against *E. coli, Klebsiella* and *Proteus* spp. Second-generation cephalosporins are equally effective against Gram-positive and Gram-negative bacteria. Their spectrum includes all of the organisms covered by first-generation cephalosporins plus *Enterobacter* spp., *Neisseria gonorrhea* and *H. influenzae*. Third-generation cephalosporins are more effective against Gram-negative bacteria than Gram-positive bacteria. Fourth-generation cephalosporins have an extended spectrum for Gram-negative and Gram-positive organisms, but have minimal resistance to β-lactamase. They are active against *Enterobacter* and *Klebsiella* spp. Cephamycins are resistant to β-lactamase and have a broad spectrum, including *E. coli, Klebsiella*, *Proteus*, *Serratia* and *Bacteroides* spp.

Indications
Cephalosporins are useful in staphylococcal and streptococcal skin and soft tissue infections. A first-generation agent such as cephalexin or cefadroxil is the cephalosporin of choice in uncomplicated skin infections[33]. These drugs are very useful for uncomplicated impetigo, cellulitis, furunculosis, erysipelas and ecthyma; however, strains of MRSA are resistant to cephalosporins as well.

Dosages
See Table 127.10 for dosages of the more commonly used cephalosporins.

Contraindications
Cephalosporins are contraindicated in patients with a history of an immediate-type (IgE-mediated) hypersensitivity to this class of drugs.

DIFFERENT CLASSES OF CEPHALOSPORINS AND ROUTES OF ADMINISTRATION		
Generic name	**Trade name(s)®**	**Route(s) of administration**
FIRST GENERATION		
Cefadroxil	Duracef, Ultracef	po
Cefazolin	Ancef, Kefzol, Zolicef	im, iv
Cephalexin	Keflex, Keftab, Biocef	po
Cephalothin*	Keflin, Seffin	im, iv
Cephapirin*	Cefadyl	im, iv
Cephradine*	Velosef, Anspor	po, im, iv
SECOND GENERATION		
Cefaclor	Ceclor, Ceclor CD	po
Cefamandole*	Mandol	im, iv
Cefmetazole*	Zefazone	iv
Cefonicid*	Monocid	im, iv
Cefprozil	Cefzil	po
Cefuroxime sodium	Zinacef, Kefurox	im, iv
Cefuroxime axetil	Ceftin	po
Loracarbef (a carbacephem)*	Lorabid	po
THIRD GENERATION		
Cefdinir	Omnicef	po
Cefditoren	Spectracef	po
Cefixime	Suprax	po
Cefoperazone*	Cefobid	im, iv
Cefotaxime	Claforan	im, iv
Cefpodoxime proxetil	Vantin	po
Ceftazidime	Ceptaz, Fortaz, Tazidime, Tazicef	im, iv
Ceftibuten	Cedax	po
Ceftizoxime	Cefizox	im, iv
Ceftriaxone	Rocephin	im, iv
FOURTH GENERATION		
Cefepime	Maxipime	im, iv
Ceftaroline	Teflaro	iv
CEPHAMYCINS		
Cefoxitin	Mefoxin	im, iv
Cefotetan	Cefotan	im, iv

*Not currently available in the US.

Table 127.9 Different classes of cephalosporins and routes of administration. im, intramuscularly; iv, intravenously; po, orally.

DOSAGES OF COMMONLY PRESCRIBED CEPHALOSPORINS		
Generic name	**Pediatric dosage**	**Adult dosage**
Cephalexin	25–100 mg/kg/day divided q6 h or q12 h	250–500 mg qid
Cefadroxil	30 mg/kg/day divided q12 h	1–2 g qd
Cefaclor	40 mg/kg/day divided q8 h or q12 h	250–500 mg tid
Cefprozil	30 mg/kg/day divided q12 h	250–500 mg qd
Cefuroxime axetil	20–30 mg/kg/day divided q12 h	250–500 mg bid
Cefpodoxime proxetil	10 mg/kg/day divided q12 h	100–400 mg bid
Ceftibuten	9 mg/kg/day divided q24 h	400 mg qd
Cefixime	8 mg/kg/day divided q12 h or q24 h	200 mg bid or 400 mg qd
Ceftriaxone	50 mg/kg im x 1 (max. 1 g)	1–4 g im qd; 250 mg im × 1 for uncomplicated gonorrhea
Cefdinir	14 mg/kg/day divided q12 h or q24 h	300 mg bid or 600 mg qd

Table 127.10 Dosages of commonly prescribed cephalosporins. Administration is oral unless otherwise noted. bid, twice daily; h, hours; im, intramuscularly; q, every; qd, daily; qid, four times daily; tid, three times daily.

Approximately 15% of patients allergic to penicillins have cross-reactivity to cephalosporins (2% in pediatric patients)[35].

Major side effects

Cephalosporins can cause morbilliform eruptions, urticaria, anaphylaxis, drug fever, eosinophilia, and acute generalized exanthematous pustulosis. Cutaneous reactions are similar to those seen with the penicillins. Approximately 2% of patients allergic to cephalosporins exhibit cross-reactivity with penicillins. Cefaclor has been reported to have a significantly higher rate of drug eruptions (especially serum sickness-like reactions) in children compared to other cephalosporins and other antibiotic classes[36]. Cephalosporins may also lead to neutropenia, thrombocytopenia, hemolytic anemia and a positive direct Coombs test, especially in the setting of renal insufficiency. They can cause diarrhea, nausea and pseudomembranous colitis. Certain cephalosporins with a methylthiotetrazole side group (e.g. cefotetan, cefoperazone, cefamandole) can cause a disulfiram-like effect when alcohol is ingested concomitantly and have anti-vitamin K effects leading to an enhanced risk of bleeding.

Interactions

Administration of oral cephalosporins together with aminoglycosides can increase the likelihood of nephrotoxicity. Probenecid may decrease renal clearance of cephalosporins. Antacids, didanosine and proton pump inhibitors may decrease absorption of some oral cephalosporins (e.g. cefuroxime).

Pregnancy and lactation

Cephalosporins are in FDA pregnancy category B. They have not shown any adverse effects during pregnancy or lactation. However, their safety has not been definitively established. Cephalosporins are excreted in breast milk.

Sulfonamides and co-trimoxazole

Mechanism of action

Sulfamethoxazole, *sulfasalazine* and *sulfisoxazole* are sulfonamides that compete with para-aminobenzoic acid (PABA) to be the substrate for the enzyme dihydropteroate synthetase (Fig. 127.4). Dihydropteroate synthetase catalyzes the reaction that combines pteridine precursors with PABA to make folic acid. Thus, sulfonamides prevent the synthesis of bacterial folic acid, an essential cofactor for bacterial nucleic acid synthesis. They have a bacteriostatic effect against Gram-positive bacteria (including *S. aureus* and *Str. pyogenes*), Gram-negative bacteria, *Chlamydia* and *Nocardia* spp.

Co-trimoxazole is a synergistic combination of sulfamethoxazole and trimethoprim. It blocks two consecutive steps in the biosynthesis of bacterial nucleic acids (see Fig. 127.4). The sulfonamide inhibits dihydropteroate synthetase and trimethoprim blocks the action of dihydrofolate reductase, which normally converts dihydrofolate to tetrahydrofolate (the active form of folic acid). This combination may be bactericidal or bacteriostatic depending on the concentration of the drug and the susceptibility of the infecting organism. It is active against most Gram-positive organisms and Gram-negative organisms.

Indications

Systemic sulfonamides are indicated for uncomplicated urinary tract infections. They are also used for *Chlamydia* conjunctivitis and

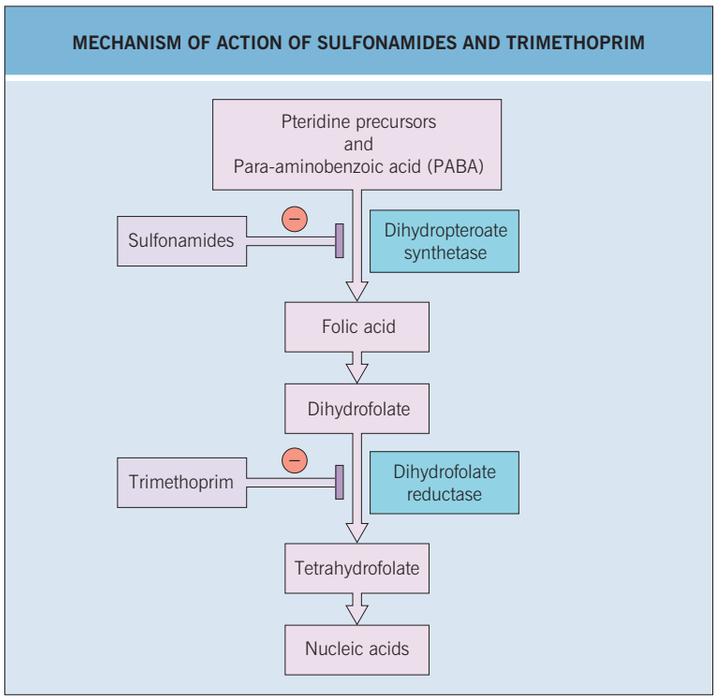


Fig. 127.4 Mechanism of action of sulfonamides and trimethoprim. Sulfonamides inhibit the conversion of pteridine precursors and PABA to folic acid by dihydropteroate synthetase. Trimethoprim inhibits the conversion of dihydrofolate to tetrahydrofolate by dihydrofolate reductase. The end result of both actions is inhibition of bacterial nucleic acid synthesis.

Nocardia infections. Sulfasalazine is commonly prescribed for ulcerative colitis. Co-trimoxazole is used to treat respiratory tract, prostate, urinary tract and gastrointestinal infections, as well as to treat, and as prophylaxis against, *Pneumocystis jiroveci* pneumonia. The latter indication is for patients who are immunosuppressed, e.g. as a result of HIV infection or systemic medications. Co-trimoxazole is also used for skin infections (e.g. furuncles or purulent cellulitis suspected to be due to MRSA), inflammatory acne vulgaris recalcitrant to other antibacterial agents, and granuloma inguinale.

Dosages
In pediatric patients, sulfadiazine and sulfisoxazole are given as 120–150 mg/kg/day divided every 4 to 6 hours. One double-strength capsule of co-trimoxazole contains 160 mg of trimethoprim and 800 mg of sulfamethoxazole, and in adults is given twice a day. In children, the dose is 6–12 mg/kg of trimethoprim and 30–60 mg/kg of sulfamethoxazole every 12 hours.

Contraindications
The sulfonamides and co-trimoxazole are contraindicated in patients with a history of hypersensitivity to this class of medications. Sulfonamides are contraindicated in the third trimester of pregnancy and in lactating patients (see below). They are also contraindicated in patients with porphyria. Sulfonamides can precipitate an acute attack of pseudoporphyria or true porphyria, possibly by increasing levels of porphyrins via hepatocellular damage, stimulating cytochrome P450 activity or inhibiting other liver enzymes. Co-trimoxazole is contraindicated in patients with megaloblastic anemia, folate deficiency or G6PD deficiency. It should be used cautiously in patients with impaired hepatic or renal function and in individuals with bone marrow suppression.

Major side effects
The sulfonamides and co-trimoxazole may cause fixed drug or morbilliform eruptions, urticaria, angioedema, photosensitivity, Stevens–Johnson syndrome, toxic epidermal necrolysis, exfoliative erythroderma and vasculitis. Additional cutaneous side effects include acute generalized exanthematous pustulosis, Sweet's syndrome, linear IgA bullous dermatosis, erythema nodosum and radiation recall. In HIV-infected patients, these drugs are common causes of cutaneous eruptions. Non-cutaneous side effects include hemolytic anemia in the setting of G6PD deficiency, agranulocytosis, thrombocytopenia, eosinophilia, methemoglobinemia, nephrotoxicity, hepatotoxicity, neurotoxicity and kernicterus in newborns. Co-trimoxazole may also cause nausea, vomiting, glossitis and stomatitis, as well as dizziness and headaches. Trimethoprim (alone or in combination with sulfamethoxazole) can induce a folate deficiency with megaloblastic anemia, leukopenia and granulocytopenia. It can also cause thrombocytopenia. Giving folinic acid, which does not impair antibacterial activity because it does not enter bacteria, can reverse all of the sequelae of folate deficiency.

Interactions
The sulfonamides and co-trimoxazole can potentiate the effects of oral hypoglycemics and the anticoagulant effect of warfarin. They should not be used in patients on methenamine for urinary tract infections. Sulfonamides decrease protein binding and renal clearance of methotrexate, leading to potentially life-threatening methotrexate myelosuppression toxicity. Monoamine oxidase (MAO) inhibitors and probenecid may increase sulfonamide adverse effects through altered hepatic metabolism and renal clearance, respectively.

Pregnancy and lactation
Co-trimoxazole must be avoided during pregnancy and lactation and for the first 2 months of life. The sulfonamides and co-trimoxazole are in pregnancy category C during the first two trimesters owing to their inhibition of folic acid, but they are in category D during the third trimester owing to the increased risk of kernicterus. Systemic sulfonamides are excreted in breast milk, and they may cause hepatic toxicity, anemia and other adverse effects in nursing infants.

Macrolides
Mechanism of action
Macrolides are bacteriostatic and inhibit bacterial protein synthesis by binding to the 50S ribosomal subunit. Erythromycin is effective against Gram-positive and Gram-negative cocci, most Gram-positive bacilli, and spirochetes. Clarithromycin has an expanded spectrum that includes *H. influenzae* and *Moraxella catarrhalis*. Azithromycin also covers *H. influenzae*. Clarithromycin and azithromycin are both effective against atypical mycobacteria, *Treponema pallidum* and *Borrelia burgdorferi*; however, they are not first-line agents for infections with the latter two organisms.

Macrolides also have anti-inflammatory effects, including inhibiting production of proinflammatory cytokines (e.g. interleukin [IL]-8, tumor necrosis factor-α [TNF-α]), reducing expression of matrix metalloproteinases, and decreasing leukocyte migration and adhesion.

Indications
Macrolides are commonly used for staphylococcal and streptococcal skin infections as they often represent a suitable treatment alternative for patients allergic to penicillin. However, there are regions where a significant percentage of *S. aureus* isolates are erythromycin-resistant. Erythromycin and azithromycin may be used for inflammatory acne, erythrasma, pitted keratolysis, bacillary angiomatosis and cat scratch disease. These agents also represent therapeutic options for several sexually transmitted diseases, e.g. chancroid, lymphogranuloma venereum, chlamydia and granuloma inguinale.

Erythromycin and azithromycin have been used for both the acute and chronic forms of pityriasis lichenoides, employing their anti-inflammatory properties. Macrolides are also indicated for pharyngitis, bacterial respiratory infections (including *Mycoplasma* pneumonia and Legionnaire's disease), diphtheria, pertussis and disseminated *Mycobacterium avium-intracellulare* complex treatment and prophylaxis.

Dosages
Table 127.11 outlines the dosages for commonly prescribed macrolides. Erythromycin base should be taken on an empty stomach; other formulations should be taken with food.

Contraindications
Macrolides are contraindicated in patients with hepatic dysfunction, renal dysfunction (clarithromycin) and hypersensitivity to the drug. Macrolides are also contraindicated in patients taking terfenadine, astemizole or cisapride (three drugs which have been removed from the

DOSAGES OF COMMONLY USED MACROLIDES		
Generic name	**Oral pediatric dosage**	**Oral adult dosage**
Azithromycin	Bacterial infections: 10 mg/kg (max 500 mg) on day 1, then 5 mg/kg (max 250 mg) qd on days 2–5	Bacterial infections: 500 mg on day 1, then 250 mg qd on days 2–5 Chancroid: 1 g once
Clarithromycin	15 mg/kg qd divided q12 h Maximum 1 g/day Adjust for decreased renal function	250–500 mg bid Adjust for decreased renal function
Erythromycin base	30–50 mg/kg qd divided q6–8 h Maximum 2 g/day	250–500 mg qid or 333 mg tid or 500 mg bid
Erythromycin estolate	20–50 mg/kg qd divided q6–12 h Maximum 2 g/day	250–500 mg bid–qid
Erythromycin ethyl succinate	20–50 mg/kg qd divided q8–12 h Maximum 2 g/day	400 mg qid
Erythromycin stearate	20–50 mg/kg qd divided q6 h	250–500 mg bid–qid

Table 127.11 Dosages of commonly used macrolides. bid, twice daily; h, hours; q, every; qd, daily; qid, four times daily.

US market and are banned or severely restricted in many other countries).

Major side effects

The use of erythromycin may be limited by gastrointestinal intolerance (e.g. nausea, vomiting, abdominal cramping). Erythromycin estolate can cause intrahepatic cholestasis in adults, and this risk increases during pregnancy. Less common side effects include stomatitis, jaundice, transient deafness and cardiac arrhythmias. Although hypersensitivity reactions to macrolides are uncommon, pustular eruptions (generalized exanthematous pustulosis) may occur; Stevens–Johnson syndrome, toxic epidermal necrolysis, urticaria and vasculitis are unusual complications.

Interactions

Macrolides have numerous significant drug interactions. Due to CYP3A4 inhibition (see Ch. 131), macrolides increase the risk of *torsades de pointes* when used with grepafloxacin, sparfloxacin, terfenadine, astemizole or cisapride. By the same mechanism, macrolides increase serum levels and potential toxicity of anticonvulsants, benzodiazepines, buspirone, corticosteroids, warfarin, HMG-CoA reductase inhibitors, oral contraceptives, cyclosporine, tacrolimus, disopyramide, felodipine and ergot alkaloids. Macrolides can increase serum levels of theophylline by inhibiting CYP1A2, leading to cardiac arrhythmias. Macrolides may also increase digoxin levels by altering gut flora, which metabolize digoxin.

Clarithromycin administered in conjunction with calcium channel blockers increases the risk of bradycardia and hypotension. Erythromycin used concomitantly with lovastatin has been reported to cause rhabdomyolysis. Macrolides may interfere with the effectiveness of chloramphenicol or clindamycin (see below), and antacids can decrease the absorption of azithromycin. Clarithromycin levels may be increased when this drug is administered with fluconazole, hexobarbital, alfentanil, disopyramide or bromocriptine. Of note, azithromycin has improved gastrointestinal tolerance and little potential for significant metabolism-based drug interactions[37].

Pregnancy and lactation

Erythromycin and azithromycin are in FDA pregnancy category B; clarithromycin is category C. The macrolides are generally considered safe during pregnancy, except for erythromycin estolate. This drug is contraindicated in pregnancy owing to the risk of maternal cholestatic hepatitis. The latter may represent a hypersensitivity reaction to the estolate component, and it can be accompanied by fever, leukocytosis and eosinophilia in addition to findings related to liver disease (nausea, vomiting, abdominal pain, jaundice, liver enzyme abnormalities); occasionally, a cutaneous eruption is seen.

DOSAGES AND ROUTES OF ADMINISTRATION OF THE TETRACYCLINES			
Generic name	**Trade name(s)®**	**Routes of administration**	**Adult dosage**
Demeclocycline	Declomycin, Declostatin, Ledermycin	po	300 mg q12 h
Doxycycline hyclate	Vibramycin, Vibra-Tabs, Periostat, Doxy-Caps, Microdox, Novo-Doxylin	po	50–100 mg qd– q12 h; 20 mg q12 h (sub-antimicrobial)
Doxycycline hyclate delayed release	Doryx	po	75–150 mg qd
Doxycycline monohydrate	Monodox, Adoxa, Doxyhexal	po	50–100 mg qd–q12 h
Doxycycline monohydrate immediate and delayed release	Oracea	po	40 mg qd
Minocycline	Minocin, Dynacin, Vectrin	po	50–100 mg qd–q12 h
Minocycline extended release	Solodyn	po	45–135 mg qd
Oxytetracycline	Terramycin	po, im	250–500 mg q6 h
Tetracycline	Sumycin, Achromycin, Robitet, Panmycin	po, iv	250–1500 mg/day divided into 2-4 doses

Table 127.12 Dosages and routes of administration of the tetracyclines. h, hours; im, intramuscularly; iv, intravenously; po, orally; q, every; qd, daily.

Tetracyclines

Mechanism of action

Tetracyclines (Table 127.12) inhibit bacterial protein synthesis by binding to the 30S ribosomal subunit. They are mainly bacteriostatic, but may be bactericidal at high concentrations. Tetracyclines are active against most bacteria, *Rickettsia*, *Chlamydia* and *Mycoplasma* spp. However, they are not active against *Proteus* spp. or *P. aeruginosa*. Tetracyclines also have anti-inflammatory effects, including decreasing matrix metalloproteinase activity, inhibiting leukocyte chemotaxis and reducing production of proinflammatory cytokines (e.g. TNF-α, IL-1β).

Indications

Tetracyclines are indicated for acne vulgaris, rosacea and perioral dermatitis, taking advantage of their anti-inflammatory as well as antimicrobial properties. They are first-line treatments for rickettsial infections (Rocky Mountain spotted fever, rickettsialpox, typhus, Q fever and trench fever), Lyme disease and ehrlichiosis. They are used in syphilis (in penicillin-allergic patients), granuloma inguinale, chlamydial infections (including lymphogranuloma venereum and psittacosis), actinomycosis, brucellosis, pulmonary infections (e.g. *Mycoplasma* pneumonia) and cholera. Tetracyclines are also useful for treating skin infections due to MRSA (e.g. furuncles or purulent cellulitis), *Vibrio vulnificus* or *Mycobacterium marinum*. Tetracyclines are used in conjunction with nicotinamide for bullous pemphigoid.

Dosages

Tetracycline should be taken 1 hour before or 2 hours after meals. Doxycycline and minocycline may be taken with or without food. To decrease the likelihood of esophagitis, the pills should not be "dry swallowed" and should be taken at least half an hour prior to bedtime. Table 127.12 lists the dosages of commonly prescribed tetracyclines.

Fig. 127.5 Minocycline pigmentation. Blue–gray macules and patches on the lower leg.

Contraindications
Tetracyclines should not be used in patients under 8 years of age (to avoid tooth discoloration) or in pregnant women. All tetracyclines except doxycycline should be avoided in patients with renal impairment, because they can accumulate; doxycycline has a compensatory gastrointestinal secretion.

Major side effects
Common side effects of tetracyclines include gastrointestinal upset, vaginal candidiasis and phototoxicity (especially doxycycline). Minocycline does not typically lead to overt phototoxicity but may cause diffuse "muddy brown" hyperpigmentation that is accentuated in sun-exposed areas as well as bluish discoloration of scars (including those due to acne) and normal skin (in particular on the shins)[33] (Fig. 127.5; see Table 67.3). Gray to blue–gray discoloration of the oral mucosa, sclerae, nails and teeth (including occasional tooth discoloration in adults) can also occur, as can black pigmentation of the thyroid gland. Deposition of tetracyclines in the teeth and bones occurs in children, causing discoloration and hypoplasia of the teeth (deciduous and permanent) and occasionally temporarily stunting growth. Dizziness is another potential side effect of minocycline.

Tetracyclines (especially minocycline) can cause allergic reactions, including urticaria and a minocycline "hypersensitivity syndrome" (drug reaction with eosinophilia and systemic symptoms [DRESS]; see Ch. 21) that often includes pneumonitis as well as hepatitis[38]; these reactions may occur more frequently in black patients[39]. Tetracyclines have also been associated with serum sickness-like reactions, esophageal ulcerations, infectious enterocolitis, blood dyscrasias, a pseudotumor cerebri-like syndrome (risk of which may be increased when given together with a systemic retinoid), nephrotoxicity, nephrogenic diabetes insipidus and even fatal fulminant hepatitis. Minocycline use has been linked to a variety of autoimmune conditions, including drug-induced lupus, polyarteritis nodosa, polyarthritis and autoimmune hepatitis[40,41]. These reactions often develop after a year or more of therapy, and affected individuals frequently have antineutrophil cytoplasmic antibodies (ANCA; usually with perinuclear staining and myeloperoxidase specificity) as well as antinuclear antibodies (ANA)[42].

Interactions
Food decreases the absorption of tetracycline by about 50%. Therefore, tetracycline should be taken 1 hour before or 2 hours after a meal. Minocycline and doxycycline may be taken with food to diminish the gastrointestinal upset caused by these medications. Absorption of tetracyclines is impaired by polyvalent cations such as calcium, aluminum, magnesium, iron, zinc and bismuth. Thus, antacids, some laxatives, medications containing magnesium (e.g. quinapril), dietary supplements and dairy products can inhibit absorption of tetracyclines (tetracycline > doxycycline > minocycline). Antacids, H_2 blockers and proton pump inhibitors increase stomach pH and thereby decrease tetracycline absorption. Tetracyclines increase the serum levels and potential toxicity of digoxin, lithium and warfarin, and they can reduce insulin requirements. Barbiturates, phenytoin and carbamazepine decrease the half-life of doxycycline. As noted above, bacteriostatic tetracyclines may interfere with the effectiveness of bactericidal penicillins.

Pregnancy and lactation
Systemic tetracyclines should not be used during pregnancy or lactation because they cross the placenta and are excreted in breast milk. They cause staining of the deciduous teeth and enamel hypoplasia and may impair skeletal growth in developing fetuses and in nursing infants[43]. They are designated pregnancy category D.

Clindamycin

Mechanism of action
Clindamycin is a lincosamide that suppresses bacterial protein synthesis by binding to the bacterial 50S ribosomal subunit. It is active against Gram-positive cocci including *S. aureus*, *Streptococcus pneumoniae*, *Str. pyogenes*, *Str. viridans* and anaerobic streptococci. It is not active against enterococci. Clindamycin is also active against anaerobes including peptostreptococci, peptococci, *Bacteroides* spp. and fusobacteria.

Indications
Clindamycin may be used in infections caused by susceptible bacteria, including anaerobic abscesses, chlamydial infections and bacterial vaginosis. Clindamycin can be effective in skin infections caused by MRSA as well as methicillin-sensitive *S. aureus* or *Str. pyogenes*, including impetigo, cellulitis, folliculitis, furunculosis and ecthyma. It may also be useful in necrotizing fasciitis and (considering its inhibition of protein production) toxin-mediated conditions such as toxic shock syndromes. Of note, staphylococci and β-hemolytic streptococci that are sensitive to clindamycin but resistant to erythromycin on initial susceptibility testing should be evaluated with the D (double-disk diffusion)-test for inducible clindamycin resistance. This occurs in bacteria that carry the *erm* gene encoding the erythromycin ribosomal methylase; when expression of this protein is induced (e.g. by erythromycin) or becomes constitutive (which commonly occurs and is selected for during clindamycin therapy), it modifies the bacterial ribosome and results in resistance to both macrolides and lincosamides (see Ch. 74).

Dosages
Clindamycin is formulated for oral, intravenous and intramuscular administration. It is typically dosed from 150 to 450 mg four times a day.

Contraindications
Clindamycin is contraindicated in patients with hypersensitivity to the drug and in patients with colitis.

Major side effects
Clindamycin carries a relatively high risk of pseudomembranous colitis. Studies have reported rates from 0.1% to 10%[44–46]. It occasionally increases serum levels of liver enzymes. Clindamycin may also cause hypersensitivity reactions, especially in HIV-positive patients. It may cause transient neutropenia or thrombocytopenia, eosinophilia and (possibly) neuromuscular blockade. Stevens–Johnson syndrome rarely occurs.

Interactions
Clindamycin binds at or near the sites of binding of erythromycin and chloramphenicol. These drugs should not be used concomitantly. It may potentiate the neuromuscular effect of botulinum toxin or neuromuscular blockers.

Pregnancy and lactation
Clindamycin is in pregnancy category B. There are no known adverse effects of systemic clindamycin on the developing fetus. In rat and mouse studies, oral and subcutaneous clindamycin have not been shown to cause birth defects. Clindamycin may modify the bowel flora of nursing infants and may interfere with the interpretation of bacterial culture results obtained during a fever evaluation of a nursing infant.

QUINOLONES		
Generic name	**Trade name(s)®**	**Routes of administration**
Alatrofloxacin*	Trovan IV	iv, im
Ciprofloxacin	Cipro	po, iv
Enoxacin*	Penetrex	po
Gatifloxacin*	Tequin	po, iv
Gemifloxacin	Factive	po
Levofloxacin	Levaquin	po, iv
Lomefloxacin*	Maxaquin	po
Moxifloxacin	Avelox	po
Norfloxacin	Chibroxin, Noroxin	po
Ofloxacin	Floxin	po, iv
Sparfloxacin*	Zagam	po
Trovafloxacin*	Trovan	po, iv
*Withdrawn from US market.		

Table 127.13 Quinolones. im, intramuscularly; iv, intravenously; po, orally.

Quinolones

Mechanism of action

Quinolones are rapidly bactericidal by inhibiting DNA gyrase (topoisomerase II). They are active against Gram-negative aerobes, staphylococci and streptococci, but not against anaerobes.

Table 127.13 lists the drugs in this class.

Indications

Quinolones are indicated for sinusitis, acute exacerbations of chronic bronchitis, community acquired pneumonia, urinary tract infections, gastrointestinal infections, chlamydia, osteomyelitis, and some skin and soft tissue infections. Second-generation quinolones (ciprofloxacin, ofloxacin, enoxacin, lomefloxacin and norfloxacin) have good coverage of Gram-negative rods and some Gram-positive coverage. They are the most potent antipseudomonal quinolones. Third-generation quinolones (levofloxacin, gatifloxacin and sparfloxacin) are broad spectrum, with coverage of Gram-negative rods and greater Gram-positive cocci coverage, especially of *Pneumococcus* spp. Fourth-generation quinolones (alatrofloxacin, moxifloxacin and trovafloxacin) are very broad spectrum, with coverage of Gram-negative rods, Gram-positive cocci, anaerobes and atypical bacteria. They have minimal antipseudomonal activity but cover streptococcus and *S. aureus*; however, quinolone resistance to the latter organism can develop rapidly.

Dosages

Ciprofloxacin and levofloxacin are dosed at 250 to 750 mg twice a day. Quinolones must be adjusted for renal impairment. The safety of quinolones in children has not been established, and their use in pediatric patients is generally avoided unless there is no safe and effective alternative[46a] (see below). However, ciprofloxacin has been given to children at levels of 20–30 mg/kg per day in divided doses.

Contraindications

Quinolones are contraindicated in pregnancy and in patients with QT prolongation or hypokalemia. Historically, quinolones have been avoided in patients under 18 years of age because of a potential risk of arthropathy or tendinopathy based on studies in animals. However, quinolones have been used to treat children with cystic fibrosis, and a recent systematic literature review found that joint changes (most often arthralgias or stiffness) were reversible and affected 1.4% (232/16 184) of pediatric patients treated with ciprofloxacin[46a,47].

Major side effects

In studies involving juvenile animals, quinolones have been shown to damage cartilage in weight-bearing joints[48]. Quinolones may cause gastrointestinal upset, changes in taste, abnormal liver function tests, phototoxicity, nephrotoxicity, headache, dizziness, lightheadedness, drowsiness and, rarely, increased intracranial pressure and seizures. Rupture of tendons, in particular the Achilles tendon, has been rarely observed. Exacerbation of myasthenia gravis has also been described.

Interactions

Cations (e.g. calcium, aluminum, magnesium, iron and zinc salts), antacids and sucralfate prevent absorption of quinolones. Quinolones increase serum levels and potential toxicities of caffeine, theophylline and aminophylline due to CYP1A2 inhibition. They may also increase serum levels of warfarin. Use of quinolones in combination with cyclosporine may increase serum creatinine levels in renal transplant patients. Quinolones can also increase circulating levels of procainamide by decreasing its renal clearance.

Quinolones should be used with caution in patients who are taking antiarrhythmics, erythromycin, antipsychotics, tricyclic antidepressants or other drugs that can cause QT prolongation or lower the seizure threshold. Quinolones may also increase seizure risk if administered with nonsteroidal anti-inflammatory drugs. Gatifloxacin can cause hypoglycemia when used with sulfonylureas.

Pregnancy and lactation

Quinolones are designated pregnancy category C. They should not be used during pregnancy or nursing because of the arthropathy found in animal studies.

Metronidazole

Mechanism of action

Metronidazole is an imidazole. Its mechanism of action is thought to be due to DNA strand breaking.

Indications

In addition to its antiprotozoal actions, metronidazole has activity against anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* spp.), anaerobic Gram-negative bacilli (including *Bacteroides* and *Fusobacterium* spp.) and anaerobic Gram-positive bacilli (including *Clostridium* spp.). It is indicated for trichomoniasis, amebiasis and anaerobic bacterial infections. Metronidazole has been used for skin and soft tissue infections, oral and dental infections, intra-abdominal, pelvic and brain abscesses, anaerobic pulmonary infections and osteomyelitis. It can be used in combination with a broad-spectrum β-lactamase inhibitor–penicillin combination to treat Fournier's gangrene. Metronidazole is also used to treat giardiasis, New World mucocutaneous leishmaniasis and bacterial vaginosis.

Dosages

Metronidazole is available for oral and intravenous administration. For bacterial infections, it is given as 500 mg orally every 6 to 8 hours for 7 to 14 days. For bacterial vaginosis or trichomoniasis, a single 2 g dose is given or 500 mg may be taken twice a day for 7 days. The pediatric dose is 30 mg/kg/day in divided doses every 6 hours.

Contraindications

Metronidazole is contraindicated in patients with prior hypersensitivity to the drug and during the first trimester of pregnancy. It should be used with caution in patients with impaired liver function.

Major side effects

Metronidazole can cause a morbilliform eruption, pruritus, fever, gastrointestinal disturbances, a metallic taste and xerostomia, in addition to thrombophlebitis, transient leukopenia, dark urine and neurologic symptoms (e.g. headache, confusion, syncope, seizures, sensory neuropathy).

Interactions

Metronidazole increases circulating levels of cyclosporine, tacrolimus and phenytoin; it may increase the anticoagulant effect of warfarin. Metronidazole can cause a disulfiram-like reaction when combined with ethanol or with protease inhibitors, and administration of metronidazole with disulfiram may precipitate psychosis. Metronidazole may increase the risk of neuropathy due to reverse transcriptase inhibitors.

Pregnancy and lactation

Metronidazole is pregnancy category B. It has been shown to be teratogenic in rodents, but it has no known adverse effects on the developing human fetus. It is contraindicated during the first trimester of

NEWER ANTIBACTERIAL AGENTS					
Generic name	**Trade name(s)®**	**Formulations**	**Indications and dosing**	**FDA pregnancy category**	**Major side effects**
Daptomycin	Cubicin	iv	Complicated Gram-positive skin infections: 4 mg/kg iv q24 h × 7–14 days Adjust dose for renal or hepatic impairment	B	Constipation, diarrhea, nausea/vomiting, headache, insomnia, morbilliform eruptions, infusion site reactions, elevated transaminase and creatine kinase levels, myopathy (at higher doses), nephrotoxicity, eosinophilic pneumonia (rare)
Linezolid	Zyvox	600 mg tablet 100 mg/5 ml oral suspension iv	Skin infections (e.g. with MRSA): 10 mg/kg up to 400–600 mg po or (if complicated) iv q12 h* × 7–14 days Adjust dose for renal impairment	C	Headache, insomnia, diarrhea (occasionally due to *Clostridium difficile*), nausea/vomiting, bone marrow suppression (thrombocytopenia > anemia or leukopenia; especially if treated >14 days), neuropathy (peripheral or optic; primarily if treated >28 days), pancreatitis, elevated transaminase levels, lactic acidosis (rare), serotonin syndrome (when taken concurrently with other MAOIs, SSRIs or tricyclics), hypertension (when taken with α-agonist drugs)
Quinupristin/dalfopristin	Synercid	iv	Serious skin infections due to *S. aureus* or *S. pyogenes*: 7.5 mg/kg iv q12 h	B	Hyperbilirubinemia, infusion site reactions, arthralgias/myalgias, headache, nausea/vomiting, diarrhea (occasionally due to *C. difficile*)
Telavancin	Vibativ	iv	Complicated skin infections due to MRSA or other Gram-positive bacteria: 10 mg/kg iv q 24 h × 7–14 days Adjust dose for renal impairment	C	Nephrotoxicity, infusion site reactions, "red-man" syndrome, QT prolongation, headache, insomnia, foamy urine, dysgeusia, nausea/vomiting, diarrhea (occasionally due to *C. difficile*)
Tigecycline	Tygacil	iv	Complicated skin infections: 50 mg iv q12 h × 5–14 days Adjust dose for hepatic impairment	D	Nausea/vomiting, diarrhea (occasionally due to *C. difficile*), abdominal pain, headache, infusion site reactions, tooth discoloration (if age <8 years), anaphylaxis/hypersensitivity†, photosensitivity, pancreatitis, hepatic dysfunction, pseudotumor cerebri

*Every 8 hours for children with complicated infections or who are <5 years of age.
†Cross-reacts with tetracyclines.

Table 127.14 Newer antibacterial agents. MAOI, monoamine oxidase inhibitor; MRSA, methicillin-resistant *Staphylococcus aureus*; SSRI, selective serotonin reuptake inhibitor. h, hours; iv, intravenous(ly); po, orally; q, every.

pregnancy based on scattered reports of fetal malformation in women exposed to metronidazole, despite the fact that there has never been a reported increase in the overall risk of birth defects. Metronidazole should be used with caution in nursing women.

New Antibacterial Agents

Linezolid and quinupristin/dalfopristin are useful in serious staphylococcal and streptococcal skin infections, including infections with MRSA. Both inhibit bacterial protein synthesis. Daptomycin is a cyclic lipopeptide used for complicated skin infections. It kills bacteria by binding to and depolarizing bacterial cell membranes, inhibiting protein and nucleic acid synthesis. Tigecycline interferes with protein synthesis by binding to the 30S ribosomal subunit and is also used in complicated skin infections. Table 127.14 outlines the indications, dosages and side effects of these newer antibacterial agents.

Dapsone

The oral form of dapsone, a sulfone drug that is a component of combination therapy for leprosy but also has anti-inflammatory effects that are useful in the treatment of neutrophlic dermatoses, is discussed in Chapters 31 and 130.

ANTIFUNGAL AGENTS

Superficial dermatophytoses usually respond to topical antifungal agents (Table 127.15), which rarely have serious side effects. Several of these products are available without a prescription. Fungal infections of the hair and nails as well as systemic mycoses generally necessitate treatment with systemic antifungal medications. Furthermore, fungal infections in patients who are immunocompromised or who have extensive skin involvement often require systemic treatment. In addition, systemic antifungal therapy is occasionally necessary for superficial infections resistant to topical treatments in immunocompetent individuals[49].

Mechanisms of action

The mechanisms of action of antifungal agents are outlined in Table 127.16 and illustrated in Figures 127.6 and 127.7. Most azoles are fungistatic, although some are fungicidal at high concentrations. Allylamines, benzylamines and ciclopirox olamine have both fungistatic and fungicidal effects. The polyene antifungal agents – nystatin and amphotericin B – are fungistatic at low concentrations and fungicidal at high concentrations. Amphotericin B is available in three lipid formulations (liposomal, a lipid complex and a cholesteryl complex [colloidal dispersion]) that are less nephrotoxic but more expensive than the conventional form of this agent.

The aforementioned classes of antifungal agents all have anti-inflammatory effects. For example, naftifine inhibits chemotaxis and the production of reactive oxygen intermediates by neutrophils[50]. Azoles inhibit neutrophil chemotaxis, calmodulin activity, synthesis of leukotrienes and prostaglandins, and histamine release from mast cells[51–53]. Ketoconazole has anti-inflammatory activity comparable to that of hydrocortisone[54]. Ciclopirox olamine is also anti-inflammatory due to its inhibition of prostaglandin and leukotriene synthesis[52,55].

Griseofulvin is fungistatic against *Trichophyton*, *Microsporum* and *Epidermophyton* spp. It is not active against yeast (including *Malassezia* spp.), dimorphic fungi, *Cryptococcus* spp. or the fungi that cause chromomycosis.

Indications

Topical azoles are indicated for tinea corporis, tinea pedis, tinea cruris, pityriasis versicolor and mucocutaneous candidiasis. Within this group, oxiconazole and sulconazole have relatively weak activity against *Candida* spp. Butoconazole, clotrimazole, econazole, miconazole, terconazole and tioconazole are available in vaginal preparations to treat *Candida* vaginitis. Ketoconazole is additionally indicated for seborrheic dermatitis.

Topical allylamines and benzylamines are indicated for tinea pedis, tinea cruris and tinea corporis. Butenafine has been shown, *in vitro*,

TOPICAL ANTIFUNGAL AGENTS				
Generic name	**Trade name(s)®**	**Formulation(s)**	**FDA pregnancy category**	**OTC/Rx**
IMIDAZOLES				
Butoconazole	Femstat-3, Gynazole-1, Mycelex-3	2% vaginal cream	C	OTC
Clotrimazole	Canesten, Clotrimaderm, Cruex, Desenex AF, FemCare, Gyne-Lotrimin, Lotrimin, Lotrimin AF, Mycelex, Mycelex Troches, Myclo, Myclo-Gyne, Neo-Zol	1% lotion, solution, cream, aerosol solution, lozenges, troches, powder	B	OTC, Rx
Econazole	Spectazole, Ecostatin	1% cream	C	Rx
Ketoconazole	Nizoral, Nizoral AD	1% and 2% cream, shampoo	C	OTC, Rx
Miconazole	Femizole-M, Micatin, Micozole, Monistat, Monistat-Derm, Vusion, Zeasorb AF	2% cream, lotion, powder, aerosol powder, aerosol solution; 0.25% ointment (with zinc oxide)	C	OTC, Rx
Oxiconazole	Derimine, Myfungar, Oceral, Oceral GB, Okinazole, Oxistat, Oxizole	1% cream, lotion	B	Rx
Sertaconazole	Ertaczo	2% cream	C	Rx
Sulconazole	Exelderm, Sulcosyn	1% cream, solution	C	Rx
Terconazole	Fungistat, Fungistat 3, Fungistat 5, Byno-Terazol, Cyno-Terazol 3, Terazol, Terazol 3, Terazol 7, Tercospor	0.4% and 0.8% vaginal cream, 80 mg vaginal suppositories	C	Rx
Tioconazole	GyneCure, Monistat 1, Trosyd AF, Trosyd J, Vagistat 1	20% nail lacquer, 6.5% vaginal cream, ointment	C	OTC
ALLYLAMINES				
Naftifine	Naftin	1% cream, gel	B	Rx
Terbinafine	Lamisil, Lamifen	1% cream, solution, aerosol solution	B	OTC
BENZYLAMINE				
Butenafine	Mentax, Lotrimin Ultra	1% cream	B	OTC, Rx
POLYENES				
Nystatin	Acronistina, Barstatin, Bio-Statin, Candacin, Candex, Candida-Lokalicid, Candio, Candio-Hermal, Canstat, Conio, Fongistat, Kandistatin, Korostatin, Lystin, Micostatin, Moronal, Mycastatin, Mycocide, Mycostatin, Mycostatine, Mykinac, Mytrex, Nadostine, Nilstat, Nyaderm, Nysert, Nystacid, Nystan, Nystaina, Nystex, Nystop, O-V Statin, Oranyst, Pedi-Dry, Scanytin, Statin, Vagistat	100 000 USP units/g cream, ointment, powder, oral suspension, lozenges (pastilles), vaginal tablets	C, Pastilles A	Rx
Amphotericin B*	Fungizone	3% cream, ointment, lotion	B	Rx
OTHERS				
Ciclopirox olamine	Batrafen, Batrafen Nail Lacquer, Brumixol, Ciclochem, Fungowas, Loprox, Miclast, Micoxolamina, Mycoster, Nail Batrafen, Penlac, Primax	0.77% and 1% cream, gel, lotion, solution, 8% nail lacquer	B	Rx
Tolnaftate	Aftate, Equate, Genaspore, NP-27, Pitrex, Tinactin, Ting	1% cream, gel, powder, solution, aerosol liquid, aerosol powder	–	OTC
Undecylenic acid	Caldesene, Cruex, Decylenes, Gordochom	20% cream, 25% ointment, solution, 15% powder, aerosol foam, aerosol powder	–	OTC
Clioquinol*	Vioform HC, Lococorten-Vioform	3% clioquinol with 1% hydrocortisone or 0.02% flumethasone in a cream or ointment	C	–
Iodoquinol (iodochlorhydroxyquin)†	Alcortin, Vytone	1% iodoquinol with 2% hydrocortisone gel	C	Rx

*Not currently available in the US.
†A synthetic hydroxyquinoline with both antifungal and antibacterial effects.

Table 127.15 Topical antifungal agents. Other topical agents with antifungal activity not listed in this table include Whitfield's ointment (benzoic acid and salicylic acid), selenium sulfide, sodium thiosulfate, salicylic acid plus sulfur, zinc pyrithione, haloprogin, mafenide, amorolfine, propylene glycol and benzoyl peroxide. OTC, over the counter.

to be 10 to 100 times more effective than azole antifungals against common dermatophytes[56]. Terbinafine is 2 to 30 times more potent than azole antifungal agents against common dermatophytes *in vitro*[57]. Clinical trials have shown that terbinafine, butenafine and naftifine are superior to azole antifungals for tinea pedis[58,59]. The mycologic cure rates are significantly higher a month after treatment has stopped[60]. Post-treatment relapse rates are also lower for allylamines and benzylamines than for azole antifungal drugs[58,61,62]. For example, butenafine 1% cream applied once a day for 2 weeks for tinea cruris resulted in an 81% mycologic cure rate 4 weeks after the end of treatment[63]. In addition, topical terbinafine and butenafine are indicated for *Candida* infections, though they have relatively weak anti-*Candida* action compared to the topical azoles.

Of the two topical polyenes, only nystatin is commonly used. It is indicated for mucocutaneous *Candida* infections. Polyenes are not effective against dermatophytes[64,65]. Nystatin is not well absorbed when taken orally. However, this fact may be used to an advantage in treating anogenital candidiasis and candidal diaper dermatitis[65,66].

Ciclopirox olamine is active against dermatophytes, *Malassezia* spp., *Candida*, actinomycetes, molds, and Gram-positive and Gram-negative

MECHANISM OF ACTION OF ANTIFUNGAL DRUGS	
Drug class(es)	**Mechanism of action**
Polyenes	Bind irreversibly to cell membrane sterols (e.g. ergosterol) and increase membrane permeability
Echinocandins	Interfere with cell wall synthesis/permeability via inhibition of β-(1,3)-D-glucan synthesis
Imidazoles Triazoles	Interfere with cell membrane synthesis via inhibition of the fungal cytochrome P450-dependent 14-α-demethylase, which normally converts lanosterol to 14-demethyl lanosterol; this leads to accumulation of toxic 14-α-methyl sterols and prevents synthesis of ergosterol, which is required for structural integrity of the fungal cell membrane; these drugs may also impair fungal triglyceride/phospholipid synthesis and inhibit fungal oxidative/peroxidase enzymes (resulting in accumulation of toxic levels of hydrogen peroxide)
Allylamines Benzylamines Tolnaftate (a thiocarbamate)	Interferes with cell membrane synthesis via inhibition of squalene epoxidase, which is required for lanosterol formation; the resultant accumulation of intracellular squalene is fungicidal
Flucytosine	Cytosine analogue that interferes with DNA synthesis
Griseofulvin	Disrupts mitotic spindle by interacting with microtubules, thereby inhibiting mitosis in dermatophytes
Ciclopirox olamine (a hydroxypyridone)	Chelates polyvalent cations (e.g. Fe^{3+}) that have important functions in fungal cytochromes, catalases and peroxidases; it thereby inhibits respiration, blocks transport of amino acids and alters cell membrane permeability
Selenium sulfide	Antimitotic properties; reduces cellular adhesion in the stratum corneum, facilitating shedding of fungi

Table 127.16 Mechanism of action of antifungal drugs. In addition to antifungal effects, these agents have anti-inflammatory properties (see text).

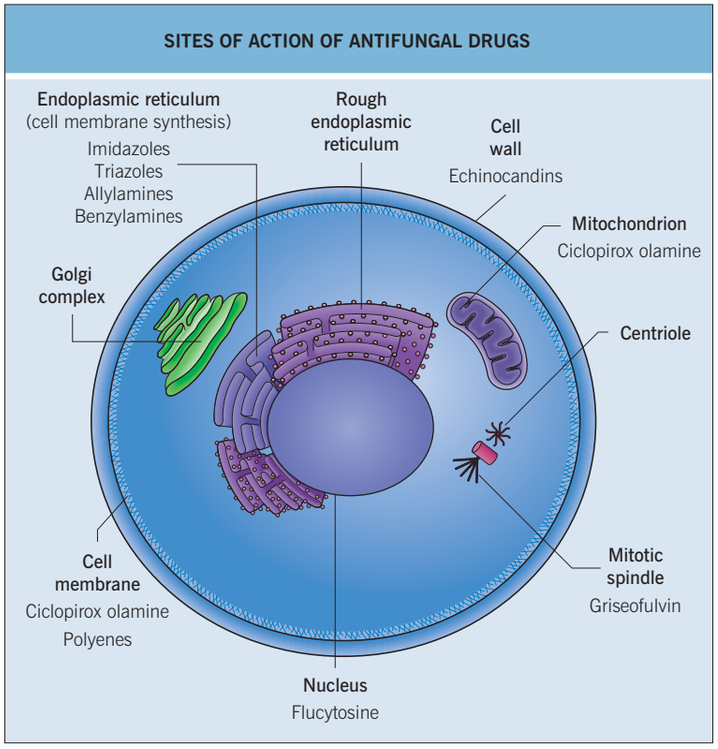


Fig. 127.6 Sites of action of antifungal drugs. Of note, ciclopirox olamine has more than one site of action.

bacteria. It is indicated for tinea corporis, tinea pedis, tinea cruris, pityriasis versicolor, mucocutaneous candidiasis and seborrheic dermatitis. *In vitro*, it is less potent against dermatophytes than the allylamine and benzylamine antifungals, but more potent than the azole antifungals. However, it is more effective than the azoles, allylamines or benzylamines against *Candida*.

Tolnaftate, undecylenic acid and clioquinol are indicated for dermatophyte infections, but they are less efficacious than the aforementioned topical agents; tolnaftate is also effective for *Malassezia* infections.

Indications for systemic antifungal agents are outlined in Table 127.17. Griseofulvin is classically the drug of choice for treating dermatophyte infections resistant to topical therapy in children. Mycologic cure rates are usually 80% to 95%. Terbinafine, itraconazole and fluconazole have also been successful in treating superficial dermatophyte infections of the skin, hair and nails in adults and children[49,67]. Terbinafine at standard doses results in a mycologic cure rate of approximately 70% for onychomycosis of the toenails and 80% for fingernails. Itraconazole, used continuously or in a pulse regimen, produces similar mycologic cure rates. Terbinafine has been shown to have a higher combined clinical and mycologic cure rate than itraconazole (38% versus 23%, $p = 0.004$) after 12 weeks of continuous oral therapy for toenail onychomycosis[68]. Fluconazole is generally the drug of choice for systemic candidiasis. However, cases of fungemia due to azole-resistant *Candida* have been reported[69]; amphotericin B is then the next best alternative. Fluconazole is relatively hydrophilic compared to other systemic azole antifungal drugs and thus is distributed to the cerebrospinal fluid and can be used to treat fungal meningitis. Flucytosine is generally used concomitantly with amphotericin B for a synergistic effect and to decrease the likelihood of resistance.

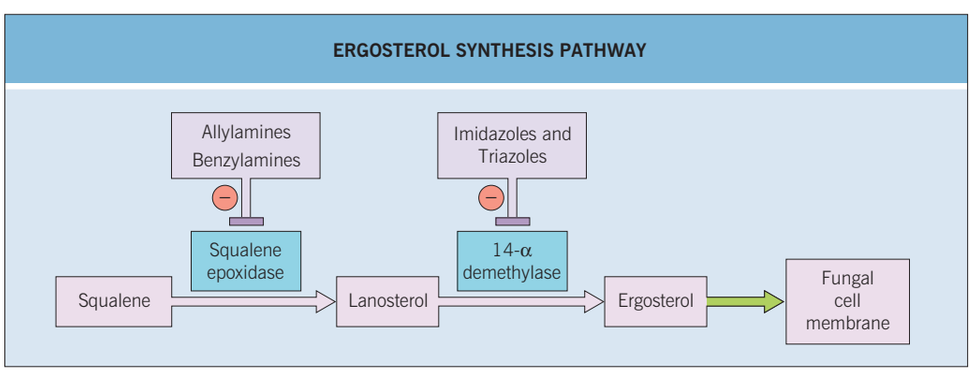


Fig. 127.7 Ergosterol synthesis pathway. Squalene is converted to lanosterol by squalene epoxidase. This enzyme is inhibited by the allylamine and benzylamine antifungals. 14-α demethylase converts lanosterol to ergosterol. Imidazole and triazole antifungals inhibit this conversion.

INDICATIONS FOR SYSTEMIC ANTIFUNGAL AGENTS			
Generic name	**Antifungal spectra**	**Indications**	**FDA pregnancy category**
Terbinafine	*Epidermophyton floccosum*, *Trichophyton mentagrophytes*, *T. rubrum*, *T. tonsurans*	Onychomycosis Superficial fungal infections: widespread, severe or resistant to topical antifungals*	B
Ketoconazole	Most dermatophytes, *Candida* spp.	Systemic fungal infections: histoplasmosis, non-meningeal cryptococcosis, blastomycosis, mucocutaneous candidiasis, oropharyngeal and esophageal candidiasis, vaginal candidiasis and nail candidiasis Superficial fungal infections: widespread, severe or resistant to topical antifungals*	C
Itraconazole	Dermatophytes, yeasts (*Candida*, *Pityrosporum* spp.), some molds	Blastomycosis, histoplasmosis and aspergillosis (oral and intravenous), onychomycosis (oral), oropharyngeal and esophageal candidiasis (solution) Superficial fungal infections: widespread, severe or resistant to topical antifungals*	C
Fluconazole	*Candida* spp., *T. tonsurans*, *T. rubrum*, *Microsporum canis*	Oropharyngeal, esophageal, vaginal and systemic candidiasis Cryptococcal meningitis Superficial fungal infections resistant to topical antifungals*	C
Voriconazole	*Aspergillus*, *Candida*, *Fusarium*, *Scedosporium* spp.	Invasive aspergillosis (superior to amphotericin B), esophageal candidiasis, serious infections caused by *Fusarium* and *Scedosporium apiospermum*	D
Posaconazole	*Candida*, *Aspergillus*, *Cryptococcus*, *Fusarium*, *Zygomycetes* spp.	Prevention of invasive aspergillosis and *Candida* infections in immunosuppressed hosts	C
Pramiconazole†	*Dermatophytes, Pityrosporum* spp.	Tinea capitis, tinea corporis, tinea cruris, tinea pedis, onychomycosis, tinea versicolor	NA
Griseofulvin	*Trichophyton*, *Microsporum*, *Epidermophyton* spp. (no activity against *Candida* or *Malassezia* spp.)	Tinea capitis and onychomycosis Superficial fungal infections: widespread, severe or resistant to topical antifungals	C
Amphotericin B	*Candida* spp., *Cryptococcus neoformans*, dimorphic fungi (*Histoplasma capsulatum*, *Coccidioides immitis* and *Blastomyces dermatitidis*), *Aspergillus* spp.	Severe fungal infections including disseminated systemic candidiasis, cryptococcal meningitis, blastomycosis, disseminated histoplasmosis, extracutaneous sporotrichosis, coccidioidomycosis, paracoccidioidomycosis, mucormycosis and aspergillosis	B
Flucytosine	*Candida*, *Cryptococcus*, *Aspergillus* spp., agents of chromomycosis	Second-line therapy for severe fungal infections including candidiasis, cryptococcosis, aspergillosis and chromomycosis	C
Caspofungin acetate**	*Aspergillus fumigatus*, *A. flavus*, *A. terrus*, *Candida* spp.	Invasive aspergillosis in patients refractory to or intolerant of other antifungals, candidemia, esophageal candidiasis	C
Micafungin**	*Candida*, *Aspergillus* spp.	Prophylaxis for *Candida* infections in hematopoietic stem cell transplant patients, esophageal candidiasis	C
Anidulafungin**	*Candida*, *Aspergillus* spp.	Candidemia, esophageal candidiasis, intra-abdominal *Candida* infections and peritonitis	C

*Resistant superficial fungal infections treated by systemic terbinafine and azole antifungals include tinea corporis, tinea cruris and tinea pedis. The azoles are also used for pityriasis versicolor.
†This drug is under development.
**Members of the echinocandin class of antifungal drugs.

Table 127.17 Indications for systemic antifungal agents. The use of flucytosine is declining, but it is still given in certain situations. NA, not applicable.

Dosages

Topical antifungal agents are generally applied twice a day until clinical signs and symptoms are improved, usually for 1 to 4 weeks. Occlusion should not be used. Shampoos are used every 3 to 4 days and are left in place for 5 minutes before rinsing. Nystatin oral suspension is held in the mouth for as long as possible before swallowing or expectorating, which is repeated four times a day. There is essentially no systemic absorption. The pastilles are allowed to dissolve slowly in the mouth four to five times a day for up to 14 days. Ciclopirox olamine nail lacquer is applied daily for 1 week and then removed with alcohol; this cycle is then repeated.

A typical treatment course of systemic terbinafine is 12 weeks for toenail onychomycosis or 6 weeks for fingernail onychomycosis, and 2 weeks for superficial tinea infections resistant to topical antifungal agents. Dosages are based on age and weight and are shown in Table 127.18[49]. For tinea capitis in children, terbinafine is given continuously for 3 to 4 weeks.

Ketoconazole is available in 200 mg tablets. Adults take one or two tablets daily. Children over 2 years of age take 6.6 mg/kg orally once daily (typically for 5 days) for pityriasis versicolor. For other tinea infections and cutaneous candidiasis, children over 2 years of age take 3.3 to 6.6 mg/kg/day orally for 2 to 4 weeks. For mucocutaneous candidiasis in children, the dose is 5 to 10 mg/kg/day divided into two doses; the maximum dose is 400 mg a day. Absorption is improved with an acidic stomach pH. The manufacturer suggests ketoconazole should be taken with food. However, some clinicians suggest plasma levels are higher when the drug is taken on an empty stomach.

Itraconazole is available as 100 mg capsules and a 10 mg/ml cherry-caramel-flavored solution. The solution should be taken on an empty stomach, and the capsules should be taken with a full meal to enhance absorption. Pediatric dosing is 3 to 5 mg/kg daily[67,70]. Doses over 200 mg should be divided into two doses per day. For tinea capitis in children, itraconazole may be given continuously for 2 to 4 weeks or as 1- to 3-week-long pulses (with 3 weeks without drug in between each pulse). Adult oral dosages for various indications are outlined in Table 127.19. Itraconazole is also available for intravenous infusion, given 200 mg intravenously twice a day for four doses and then 200 mg every day. The maximum length of intravenous treatment is usually 14 days. Treatment of oropharyngeal and esophageal candidiasis is for at least 3 weeks and should be continued for at least 2 weeks after symptoms resolve. Itraconazole solution is swished in the mouth, 10 mg at a time, for several seconds and then swallowed.

Fluconazole is available as 50 mg, 100 mg and 200 mg tablets and as an orange-flavored suspension in 10 mg/ml and 40 mg/ml strengths. Table 127.20 outlines the dosing of fluconazole. Unlike ketoconazole and itraconazole, fluconazole is not dependent on a low gastric pH for absorption.

Voriconazole is used for invasive aspergillosis at 4 mg/kg intravenously every 12 hours or 100 to 200 mg orally every 12 hours. A loading dose of 6 mg/kg intravenously, given twice, 12 hours apart, is administered prior to the intravenous or oral regimen. Dose adjustments must be made in patients with renal or hepatic dysfunction.

Posaconazole is a 40 mg/ml suspension, given with food. It is indicated for prophylaxis of invasive fungal infections in immunocompromised patients. The dosage is 200 mg orally three times daily in patients over 13 years of age. For oropharyngeal candidiasis, it may be given as 100 mg orally twice daily (on the first day) and then 100 mg daily for 12 days. In cases refractory to fluconazole or itraconazole, the dose is increased to 400 mg orally twice daily. Duration of treatment varies according to patient response[71].

Dosages for griseofulvin are shown in Table 127.21. In the US, increasing doses have been required for the treatment of tinea capitis

DOSING OF TERBINAFINE	
ORAL TABLETS	
Adults	250 mg qd
Children over 2 years old and under 20 kg	62.5 mg qd
Children over 2 years old and 20–40 kg	125 mg qd
Children over 2 years old and over 40 kg	250 mg qd
ORAL GRANULES FOR TINEA CAPITIS	
Children over 4 years old and under 25 kg	125 mg qd
Children over 4 years old and 25–35 kg	187.5 mg qd
Children over 4 years old and over 35 kg	250 mg qd

Table 127.18 Dosing of terbinafine. Terbinafine comes in 250 mg tablets and 125 mg or 187.5 mg packets of granules; the latter are taken after sprinkling on a non-acidic, non-fruity, soft food. qd, daily.

ADULT DOSING OF ORAL ITRACONAZOLE	
Indication	**Adult dosage**
Pityriasis versicolor	200 mg po qd for 5–7 days
Tinea corporis, tinea cruris	100 mg po qd for 2 weeks *or* 200 mg po qd for 1 week
Tinea pedis	100 mg po qd for 2 weeks *or* 200 mg po qd for 1 week
Blastomycosis, histoplasmosis	200 mg po qd May increase by 100 mg increments to a maximum of 400 mg po qd for at least 3 months
Cutaneous sporotrichosis	200 mg po qd for 3–6 months or until 2–4 weeks after all lesions have resolved
Aspergillosis	200–400 mg po qd for at least 3 months May give loading dose of 200 mg tid for first 3 days in life-threatening conditions
Onychomycosis of toenails	200 mg po qd for 12 weeks *or* 200 mg po bid for 1 week, then 3 weeks without treatment, repeated twice more for a total of three pulses of therapy
Onychomycosis of fingernails	200 mg po qd for 6 weeks *or* 200 mg po bid for 1 week, then 3 weeks without treatment, then 200 mg po bid for 1 week
Oropharyngeal candidiasis	Swish and swallow 200 mg qd for 1–2 weeks
Oropharyngeal candidiasis refractory to fluconazole	Swish and swallow 100 mg bid
Esophageal candidiasis	Swish and swallow 100–200 mg qd

Table 127.19 Adult dosing of oral itraconazole. Itraconazole is available in 100 mg capsules and a 10 mg/ml solution. The safety of itraconazole in children has not been established. Children 3 to 16 years old have been treated for systemic fungal infections with itraconazole capsules or solution, typically at a dose of 5 mg/kg/day, without any problems. Animal studies have shown teratogenicity at high doses, causing skeletal defects in rats. Of note, itraconazole oral solution contains the excipient hydroxypropyl-β-cyclodextrin, which produced pancreatic adenocarcinomas in rats (but not mice) when given for extended periods. bid, twice daily; po, orally; qd, daily; tid, three times daily.

DOSING OF ORAL FLUCONAZOLE		
Indication	**Pediatric dosage**	**Adult dosage**
Pityriasis versicolor		400 mg po once *or* 300 mg po once, with possible second dose in 1 week, depending on clinical response
Tinea corporis, tinea cruris		50–100 mg po qd *or* 150 mg po qwk for 2–4 weeks
Tinea pedis		Pulse doses of 150 mg po qwk for 2–6 weeks
Tinea capitis		6 mg/kg/day for 2–3 weeks
Oropharyngeal candidiasis	6 mg/kg on day 1 then 3 mg/kg q24–72 h for 14 days*	200 mg on day 1 then 100 mg qd for at least 2 weeks
Vaginal candidiasis		150 mg po once
Esophageal candidiasis	6 mg/kg on day 1 then 3–12 mg/kg q24–72 h for 21 days*	200 mg on day 1 then 100 mg qd for at least 3 weeks Treat for at least 2 weeks after symptoms resolve
Systemic candidiasis	6–12 mg/kg q24–72 h for 28 days*	Up to 400 mg qd
Prophylaxis of candidiasis in bone marrow transplantation	10–12 mg/kg q24 h (maximum 600 mg/day)	400 mg qd
Cryptococcal meningitis	12 mg/kg iv on day 1 then 6–12 mg/kg q24–72 h* (maximum 600 mg/kg iv qd; continue until 10–12 weeks after culture is negative)	400 mg on day 1 then 200–400 mg qd Continue until 10–12 weeks after spinal fluid is negative
Prevention of relapse of cryptococcal meningitis in HIV patients		200 mg po qd

*If the patient is less than 14 days old, dosing is every 24–72 h. If the patient is over 14 days old, dosing is every 24 h.

Table 127.20 Dosing of oral fluconazole. h, hours; iv, intravenously; po, orally; q, every; qd, daily; qwk, weekly.

ORAL DOSING OF GRISEOFULVIN			
Generic name	**Adult**		**Pediatric (over 2 years of age)**
	Tinea corporis, cruris	**Tinea pedis, manuum, unguium, capitis**	
Griseofulvin microsize* (125 mg/5 ml suspension; 250 and 500 mg tablets)	500–1000 mg daily	750–1500 mg daily	15–20 mg/kg daily (usual maximum 1 g); use higher range (20-25 mg/kg daily) for tinea capitis
Griseofulvin ultramicrosize* (125 and 250 mg tablets)	375–500 mg daily	500–750 mg daily	10–15 mg/kg/day (maximum usually 750 mg/day)
DURATION OF TREATMENT			
2–4 weeks for tinea corporis 6–12 weeks for tinea capitis 4–8 weeks for tinea pedis 4 months for fingernail onychomycosis† 6 months for toenail onychomycosis†			

*To increase absorption, griseofulvin should be taken with a fatty meal.
†No longer commonly used for this indication; may require a longer duration of treatment.

Table 127.21 Oral dosing of griseofulvin.

due to *Trichophyton tonsurans*. The long duration of therapy required with griseofulvin is a significant disadvantage and contributes to noncompliance. Absorption of griseofulvin is improved when it is administered with fatty foods. Drug particle size reduction through micronization and ultra-micronization has also significantly enhanced oral absorption.

Dosing of intravenous amphotericin B varies depending upon the formulation of the medication (e.g. 0.75–1 mg/kg/day of conventional amphotericin B versus 3–5 mg/kg/day of lipid formulations). In adults, flucytosine is given at a dose of 150 mg/kg orally daily, divided into four doses. Taking the medicine over 15 minutes decreases associated nausea. Doses of both drugs should be adjusted in patients with renal insufficiency.

Caspofungin acetate is given as a slow intravenous infusion over 1 hour. For treatment of *Aspergillus* infections, the loading dose on the first day is 70 mg. The dose is 50 mg intravenously per day thereafter. Patients who do not respond to this dose may respond to 70 mg intravenously per day. Caspofungin must not be mixed with solutions containing dextrose, and patients with moderate hepatic insufficiency should receive 35 mg per day after the 70 mg loading dose. This drug has not been adequately studied in children.

Micafungin is only available in an intravenous form. For esophageal candidiasis, it is administered as 150 mg intravenously daily. In hematopoietic stem cell transplant patients, as prophylaxis for *Candida* infections, it may be given at a dose of 50 mg intravenously daily. Anidulafungin is also available in an intravenous form for *Candida* infections[72]. In candidemia, the dose is 100 mg intravenously daily after a loading dose of 200 mg; treatment should continue until 2 weeks after the most recent positive blood culture. For esophageal candidiasis, the dose is 50 mg daily.

Contraindications

Topical and systemic antifungals are contraindicated in patients with hypersensitivity to any of the formulation components. Systemic antifungals are contraindicated in patients who are taking other drugs that may cause potentially serious interactions (see below). Itraconazole is contraindicated in patients with left-sided heart disease and should be avoided in pregnant or lactating patients. Ketoconazole and itraconazole may not be absorbed in patients with achlorhydria. Fluconazole absorption, however, is not dependent on a low gastric pH[73]. Griseofulvin is contraindicated in patients with acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda or liver failure. All systemic antifungal agents should be used with caution in patients with liver or kidney disease. Flucytosine should be used with caution in patients with bone marrow suppression.

Major side effects

The most common side effect of topical antifungal drugs is local skin irritation, which may be more severe with occlusion. Clinical manifestations include burning, stinging, pruritus, erythema, edema, peeling, blistering and allergic contact dermatitis. Clioquinol can cause discoloration of clothes, skin, hair and nails.

Oral terbinafine may cause a morbilliform eruption and, less commonly, urticaria, pruritus, alopecia or dermatitis. Severe cutaneous reactions that have been caused by systemic terbinafine include Stevens–Johnson syndrome and toxic epidermal necrolysis, as well as acute generalized exanthematous pustulosis, pustular psoriasis, flares of psoriasis and subacute cutaneous lupus erythematosus[74–78]. Non-cutaneous side effects of terbinafine include gastrointestinal disturbances, elevated liver enzymes, headaches, taste and visual disturbances, transient decreases in absolute lymphocyte count, and, rarely, neutropenia in immunosuppressed patients. This drug should be used with caution in patients with liver or kidney disease. It is recommended that liver enzyme tests be performed before and (for courses lasting >6 weeks or in patients at risk for hepatic disease) during treatment. The side effects of the systemic azole antifungals are listed in Table 127.22.

Griseofulvin has been used for over 40 years with infrequent adverse effects and is considered a very safe medication. Its most common side effects are headache and gastrointestinal disturbances. It also may cause a fixed drug eruption, photosensitivity, petechiae, pruritus, exfoliative dermatitis or urticaria, and it can precipitate or exacerbate lupus erythematosus or porphyria. Griseofulvin has occasionally been associated with enuresis, proteinuria, increased urinary frequency, arthralgias, fever, hypersensitivity reactions (including angioedema and serum sickness-like reactions), neurologic side effects (e.g. confusion, blurred vision, vertigo, depression, nightmares, insomnia, ataxia, paresthesias), syncope, epistaxis, estrogen-like effects, sore throat, hepatotoxicity and leukopenia.

Amphotericin B commonly causes fever, chills, nausea and vomiting. These side effects may be minimized by pretreatment with aspirin or acetaminophen, diphenhydramine and/or intravenous hydrocortisone. Less commonly, it may also cause anorexia, diarrhea, orthostatic hypotension or hypertension, tachycardia, dyspnea, headache and skin eruptions, including exanthems, exfoliative dermatitis, fixed drug eruption, flushing, urticaria, and infusion site reactions. Amphotericin B can produce hypokalemia, thrombocytopenia and renal toxicity characterized by increased BUN and creatinine. Damage to the kidney may be mediated directly or through vasoconstriction and can be severe and irreversible after high doses. Less commonly, amphotericin B can cause seizures, arrhythmias, agranulocytosis, liver failure or anaphylaxis.

Flucytosine can cause a number of neurologic side effects, including headaches, fatigue, vertigo, ataxia, paresthesias, confusion and hallucinations. In addition to gastrointestinal disturbances (e.g. nausea, vomiting, abdominal pain and diarrhea), hypokalemia and hypoglycemia may occur with use of this drug. Flucytosine can also cause more serious side effects, including cardiac and respiratory arrest, renal failure, aplastic anemia, agranulocytosis, thrombocytopenia, gastrointestinal bleeding and colitis.

Caspofungin acetate may cause headaches, fever, infusion site reactions, phlebitis, flushing, erythema, induration, facial swelling and pruritus as well as nausea and vomiting. Anaphylaxis has been reported. Laboratory abnormalities that have been encountered include increased alkaline phosphatase, hypokalemia, eosinophilia, proteinuria and hematuria. Micafungin may uncommonly cause anaphylaxis, liver or kidney dysfunction, thrombophlebitis or hemolytic anemia. It can also result in headaches, nausea, rigors and leukopenia. Skin reactions include "rash" and injection site reactions. Anidulafungin may cause liver toxicity, diarrhea, hypokalemia and infusion reactions.

SIDE EFFECTS OF SYSTEMIC AZOLE ANTIFUNGAL AGENTS

Generic name	Side effects
Ketoconazole	• Nausea, vomiting, abdominal pain, idiosyncratic hepatotoxicity • Anaphylaxis, urticaria, pruritus • At higher doses, suppresses testosterone and cortisol synthesis
Itraconazole	• Morbilliform eruption, pruritus, urticaria, alopecia, Stevens–Johnson syndrome (rarely); parenteral administration may result in infusion site reactions • Anorexia, nausea, vomiting, abdominal pain, hepatic dysfunction • Fatigue, headaches, dizziness • Fever, edema, hypokalemia, neutropenia (rarely) • Rarely causes congestive heart failure, pulmonary edema, anaphylaxis, peripheral neuropathy
Fluconazole	• Morbilliform eruption, exfoliative dermatitis (rarely) • Nausea, vomiting, abdominal pain, diarrhea, hepatotoxicity • Headache
Voriconazole	• Phototoxicity; this can lead to pseudoporphyria and (with chronic use) accelerated photoaging (Fig. 127.8), aggressive or multifocal cutaneous squamous cell carcinomas (especially in the setting of immunosuppression), and melanoma[79,80] • Visual disturbances (e.g. blurred vision, altered color perception, photophobia), headache, hallucinations • Nausea, vomiting, diarrhea, abdominal pain, hepatotoxicity • Fever, peripheral edema • QT prolongation

Table 127.22 Side effects of systemic azole antifungal agents.

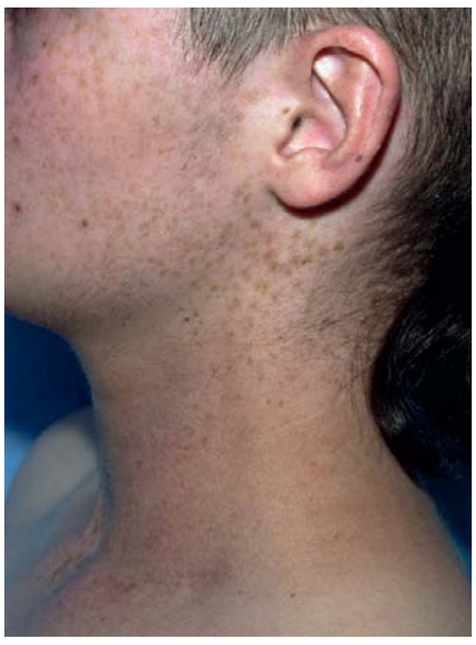


Fig. 127.8 Accelerated photoaging due to chronic voriconazole therapy. Note the solar lentigines in this young man with chronic granulomatous disease. *Courtesy, Edward Cowen, MD.*

Interactions

Systemic terbinafine inhibits the cytochrome P450 isoform CYP2D6. As such, it may increase serum levels and toxic effects of other drugs metabolized by this pathway, including β-blockers, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), MAO inhibitors, and type B and class IC antiarrhythmics. Terbinafine increases cyclosporine clearance by 15% and decreases caffeine clearance by 19%. It also decreases the efficacy of codeine. Terbinafine used with thioridazine may cause prolonged QT intervals and arrhythmias. Whereas cimetidine increases terbinafine levels, rifampin decreases terbinafine levels by doubling its rate of clearance.

Azole antifungal drugs exert their therapeutic effect by inhibiting cytochrome P450 enzymes (see above). Cytochrome P450 enzymes play a major role in transforming lipophilic drugs to more easily excreted metabolites[73]. Inhibition of this enzyme family is the cause of many of the azole antifungals' drug–drug interactions. These interactions have resulted in black box warnings in the package insert by the FDA in the US. The interactions are listed in Table 127.23.

Griseofulvin may decrease the levels and efficacy of warfarin and salicylates. Barbiturates may decrease griseofulvin efficacy by decreasing its absorption. Griseofulvin potentiates the effect of alcohol or may induce a disulfiram-like reaction[73]. It also increases estrogen-metabolizing liver enzymes, which may make oral contraceptives less effective or cause menstrual irregularities.

Systemic corticosteroids, loop diuretics and thiazide diuretics increase the risk of developing hypokalemia due to amphotericin B. Antipsychotics used concomitantly with amphotericin B may cause QT prolongation and cardiac arrhythmias. Nephrotoxic drugs such as cisplatin, flucytosine, gentamicin and vancomycin may compound the nephrotoxicity of amphotericin B. Amphotericin may increase digoxin levels. Cisplatin used in conjunction with flucytosine increases the risk for nephrotoxicity and bone marrow suppression.

Caspofungin acetate does not affect the cytochrome P450 system. It does decrease tacrolimus levels, and cyclosporine increases caspofungin levels. Phenytoin, rifampin, dexamethasone, carbamazepine and several antiretroviral drugs (efavirenz, nelfinavir, nevirapine) can decrease caspofungin levels.

Pregnancy and lactation

Topical imidazoles have not been shown to cause any problems during pregnancy; their pregnancy categories are listed in Table 127.15. Clotrimazole used intravaginally during the second and third trimesters has not been shown to cause birth defects or other problems in humans. Topical imidazoles have not been shown to cause any problems during breastfeeding. Topical oxiconazole is excreted in breast milk, but it is not known whether the other topical imidazoles are excreted in breast milk. Topical nystatin has not been shown to cause birth defects or other problems in humans; it is not known whether topically applied nystatin is excreted in breast milk. There are not adequate studies of ciclopirox olamine in pregnant women. Although a small amount of this drug is absorbed through the skin, animal studies involving mice, rats, rabbits and monkeys showed no impairment of fertility or harm to the fetus at doses 10 times higher than the topical human dose. It is not known whether ciclopirox olamine is secreted in breast milk. Tolnaftate and undecylenic acid have not been reported to cause problems during pregnancy or with breastfeeding.

The FDA pregnancy categories of the systemic antifungal drugs are listed in Table 127.17. These drugs should not be used to treat onychomycosis if the patient is pregnant or contemplating pregnancy. During pregnancy, they should be reserved for systemic fungal infections only if the benefit outweighs the risk. Although animal studies of oral terbinafine have shown no adverse effects during pregnancy, there are no adequate studies in pregnant women. Orally administered terbinafine is secreted in breast milk and is not recommended for use in nursing mothers.

There are no adequate human studies of the effects of azole antifungals during pregnancy or nursing. Itraconazole is contraindicated in lactating patients because it is excreted in human milk. Fluconazole is excreted in breast milk. Griseofulvin has been associated with fetal abnormalities in rats and dogs. Rare cases of conjoined twins have been reported in women taking griseofulvin in the first trimester of pregnancy. Patients should avoid pregnancy for at least 1 month after discontinuing griseofulvin[81]. There are no adequate studies of

DRUG INTERACTIONS OF SYSTEMIC AZOLE ANTIFUNGAL AGENTS		
Interacting drug	**Result**	**Azoles involved**
Astemizole, terfenadine, cisapride (banned or restricted)	Arrhythmia, torsade de pointes	K, I, F, V
Warfarin	Increased warfarin levels	K, I, F, V
Cyclosporine, tacrolimus	Increased cyclosporine or tacrolimus levels, nephrotoxicity, neurotoxicity, hypertension	K, I, F, V
Rifampin, rifamycin	Decreased plasma levels of azole antifungals (ketoconazole also decreases absorption of rifamycin)	K, I, F, V
Phenytoin	Phenytoin causes decreased levels of itraconazole, ketoconazole Fluconazole causes increased levels of phenytoin	K, I, F, V
Sildenafil (Viagra®)	Increased sildenafil levels	K, I, F, V
Oral hypoglycemics	Hypoglycemia	K, I, F, V
Oral contraceptives	Increased levels of estrogens & progestins; effects on contraception debated	K, I, F, V
Antacids, H_2 antihistamines, proton pump inhibitors, anticholinergics, didanosine	Decreased gastrointestinal absorption of azole antifungals Administration of omeprazole with voriconazole causes increased levels of both drugs	K, I, V
Benzodiazepines	Excessive sedation	K, I, F, V
Indinavir	Increased indinavir levels	K
Corticosteroids	Increased corticosteroid levels	K
Digoxin	Increased digoxin levels	I, F, V
HMG-CoA reductase inhibitors (e.g. atorvastatin, simvastatin)	Rhabdomyolysis, myopathy	I, V
Dihydropyridine calcium channel blockers	Edema	I, V
Phenobarbital, carbamazepine, isoniazid, revirapine	Decreased levels of itraconazole	I, V
Pimozide, buspirone, quinidine, vincristine	Increased levels of interacting drug	I, V
Thiazide diuretics (e.g. HCTZ)	Increased levels of fluconazole	F
Theophylline, nucleoside analogues	Increased levels of interacting drug	F, V
Ritonavir	Increased levels of interacting drug	I, K

Table 127.23 Drug interactions of systemic azole antifungal agents. K, ketoconazole; I, itraconazole; F, fluconazole; V, voriconazole.

amphotericin B or flucytosine in pregnant or lactating women. Flucytosine has been teratogenic in rat and mouse studies. Caspofungin acetate is toxic to rat and rabbit embryos and is excreted in breast milk in rats.

ANTIVIRAL AGENTS

This section reviews antiviral agents used for herpes simplex virus (HSV) and varicella–zoster virus (VZV) infections. Table 127.24 lists the topical antiherpetic antiviral medications. Antiretroviral medications (see Ch. 78) and immunomodulating medications (see Ch. 128) are addressed elsewhere in the text.

Mechanisms of action

Figure 127.9 illustrates the mechanism of action of the major antiherpetic drugs.

Valacyclovir is the prodrug of acyclovir. It is almost completely converted to acyclovir by valacyclovir hydrolase while passing through the gastrointestinal tract and liver. It has an oral bioavailability approximately three times greater than that of acyclovir (55% versus 15–30%) and is also more conveniently dosed than acyclovir.

Penciclovir is an acyclic guanosine analogue with a mechanism of action similar to acyclovir. It reaches higher intracellular concentrations and has a longer intracellular half-life than acyclovir (2.3–3 hours versus 1.3–1.5 hours). However, it is less potent because it does not cause chain termination of viral DNA, and it has a poor oral bioavailability. For these reasons, this medication is only available in topical form[82]. Famciclovir is the prodrug of penciclovir. The bioavailability of famciclovir is about 77%. Like valacyclovir, it is converted to its active form in the gastrointestinal tract and liver[83]. *In vitro* studies show that penciclovir is at least as effective as acyclovir against HSV-1 and HSV-2[84].

Docosanol, also known as behenyl alcohol, is a saturated 22-carbon aliphatic alcohol that exhibits antiviral activity against several lipid-enveloped viruses, including HSV. After the virus has attached to the host cell, n-docosanol prevents the fusion of the HSV envelope with the plasma membrane of uninfected cells[85].

Indications

Topical acyclovir is indicated for the initial episode of genital herpes. It decreases the duration of viral shedding from 7 days to 4 days[86]. In some studies it has also been shown to be effective in recurrent genital

TOPICAL ANTIHERPETIC ANTIVIRAL AGENTS				
Generic name	**Trade name(s)®**	**Formulations**	**FDA pregnancy category**	**OTC/Rx**
Acyclovir	Acic, Acicloftal, Aciclor, Aciclosina, Acivir, Acivir Eye, Aclovir, Acyclo-V, Acyvir, Avirax, Avorax, Azovir, Cicloferon, Cicloviral, Clinovir, Clovicin, Clovix, Cusiviral, Cyclivex, Cyclovir, Deherp, Eduvir, Entir, Herpefug, Herpex, Herpoviric Rp, Hexidol, Inmerax, Lisovyr, Lovir, Lovire, Maynor, Norum, Oppvir, Poviral, Quavir, Supra-Vir, Supraviran, Vacrovir, Vicorax, Virogon, Virex, Virless, Virobis, Zevin, Zoter, Zovir, Zovirax, Zyclir With 1% hydrocortisone: Xerese	5% ointment, cream	B	Rx
Penciclovir	Denavir, Vectavir	1% cream	B	Rx
Docosanol	Abreva	10% cream	B	OTC

Table 127.24 Topical antiherpetic antiviral agents. OTC, over the counter.

herpes[87]. Topical acyclovir is indicated for non-life-threatening mucocutaneous herpes simplex infections in immunocompromised patients, but these patients often require systemic therapy. In immunocompetent individuals, acyclovir ointment is less effective for orolabial herpes infections than for genital herpes; however, a topical combination of acyclovir and hydrocortisone can shorten healing time and is indicated for orolabial herpes in this group of patients.

Penciclovir is active against HSV-1, HSV-2, VZV and EBV. Penciclovir cream is indicated for treatment of recurrent orolabial herpes simplex infections. It has not been studied in immunocompromised patients. Compared to placebo, penciclovir shortens healing time and decreases pain and viral shedding in herpes labialis[82]. Docosanol is available in the US as a non-prescription drug and is also indicated for the topical treatment of recurrent orolabial herpes.

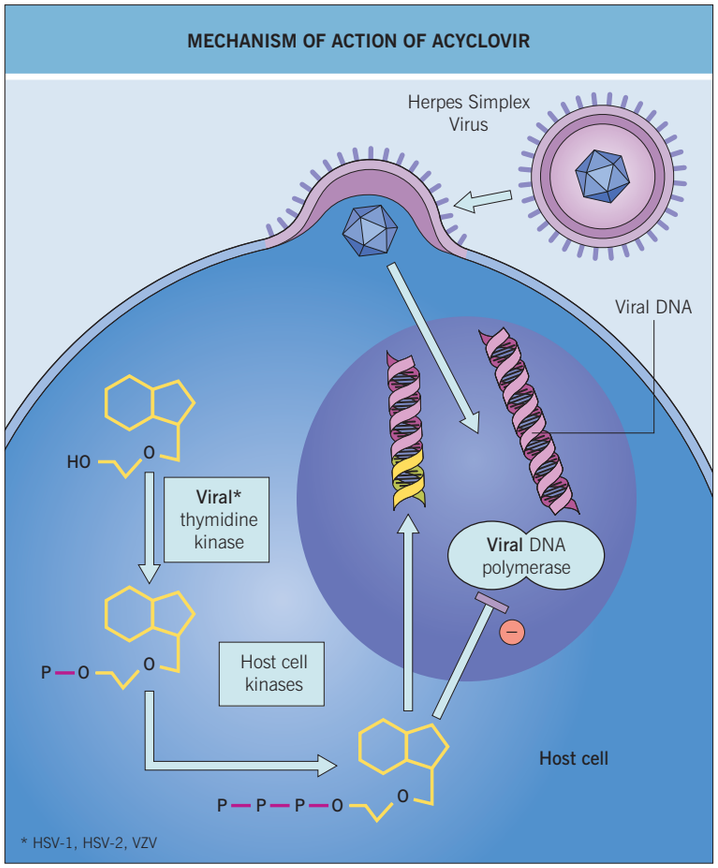


Fig. 127.9 Mechanism of action of acyclovir. Acyclovir is a synthetic purine nucleoside analogue (similar in chemical structure to deoxyguanosine) that has a high affinity for HSV-1, HSV-2 and VZV thymidine kinase, which phosphorylates and activates the drug. Human cellular guanylate kinase then phosphorylates acyclovir twice, to transform it into acyclovir triphosphate, which blocks viral DNA synthesis by competitively inhibiting and inactivating viral DNA polymerase and by becoming irreversibly incorporated into the viral DNA chain, causing DNA chain termination. Valacyclovir, penciclovir and famciclovir have similar mechanisms of action.

Systemic acyclovir and valacyclovir are indicated for primary and recurrent episodes of genital herpes simplex infection, herpes simplex suppression, varicella (acyclovir for both children and adults, valacyclovir for children) and herpes zoster. Acyclovir is also indicated for varicella. Intravenous acyclovir is used in immunocompromised patients with disseminated HSV or VZV and in patients with severe herpes zoster[88]. Other off-label uses of acyclovir are prevention of recurrent herpes-associated erythema multiforme and treatment of eczema herpeticum, primary herpes gingivostomatitis, herpetic whitlow and neonatal herpes. Famciclovir is indicated for herpes zoster, primary or recurrent genital herpes, herpes suppression in immunocompetent patients and recurrent herpes simplex in HIV-infected patients. Oral valganciclovir and valacyclovir are used for CMV prophylaxis in solid organ transplant patients.

Acyclovir, valacyclovir and famciclovir are considered equivalent in safety and efficacy (time to healing, duration of pain, and viral shedding) for initial episodes of genital herpes[89]. Famciclovir and valacyclovir have the advantage of greater oral bioavailability and more convenient dosing. Valacyclovir is at least as effective as acyclovir in decreasing the duration of pain in herpes zoster[90,91]. Table 127.25 lists the relative susceptibilities of herpes viruses to the antiviral drugs.

Dosages

Antivirals (topical or systemic) should be started as soon as possible after the onset of signs and symptoms. A glove or applicator should be used to apply topical antivirals to prevent autoinoculation of the finger. Table 127.26 details the dosing regimens of the topical antiviral drugs. Table 127.27 lists the available formulations of systemic antiviral medications. Table 127.28 outlines the dosages of the systemic antiherpetic medications for their various indications. Intravenous, rather than oral, treatment may be required in severely immunosuppressed patients, patients who cannot take medications orally, and those who cannot be relied upon to take the medication correctly[92].

The majority of people who are seropositive for HSV-2 are asymptomatic[93,94], and it is thought that asymptomatic viral shedding leads to most transmission of genital herpes. The physician must decide whether to treat on an episodic basis or in a continuous suppressive fashion. Factors that influence this decision include the number of outbreaks per year, the severity of outbreaks, a lack of prodromal symptoms, and an HSV-seronegative sexual partner[92]. Suppression with acyclovir 400 mg twice daily can decrease recurrences by 80–90% and asymptomatic shedding by 95%[95]. A year-long, double-blind, placebo-controlled study demonstrated that 1 g of valacyclovir taken daily reduced recurrence rates by 78%[96]. In addition, a multicenter, randomized, placebo-controlled study showed that daily valacyclovir significantly lowered the risk of transmission of genital herpes in heterosexual, immunocompetent, monogamous, HSV-2 discordant couples[97].

Acyclovir, valacyclovir and famciclovir are all effective against herpes labialis when used intermittently or suppressively, and they are all effective in treating herpes zoster. Treatment of varicella in children is controversial, but it does not alter antibody production at 28 days or at 1 year[98]. Oral therapy is recommended for healthy adolescents and adults as well as children with chronic skin or lung disease or on long-term salicylates; intravenous administration is indicated for

COMPARATIVE SUSCEPTIBILITY OF HERPESVIRUSES TO ANTIVIRAL DRUGS

Antiviral drug	Viral susceptibility				Main target organisms
	HSV-1	HSV-2	VZV	CMV	
Acyclovir, valacyclovir	+++	+++	++	–	HSV-1, HSV-2, VZV
Cidofovir	+	+	++	+++	CMV, resistant HSV
Famciclovir	+++	+++	++	–	HSV-1, HSV-2, VZV
Foscarnet	++	++	+	++	CMV, resistant HSV, VZV
Ganciclovir, valganciclovir	+	+	+	+++	CMV

Table 127.25 Comparative susceptibility of herpesviruses to antiviral drugs. CMV, cytomegalovirus; HSV, herpes simplex virus; VZV, varicella–zoster virus.

DOSING OF TOPICAL ANTIVIRAL DRUGS		
Antiviral drug	**Dosage**	**Side effects**
Acyclovir	q3 h, 6 times/day for 7 days In Canada: 4–6 times/day for up to 10 days Combined with hydrocortisone: 5 times/day for 5 days	Burning, stinging and discomfort at the application site; less commonly, pruritus, erythema, edema or mucosal irritation (when applied to genital lesions)
Penciclovir 1% cream	q2 h while awake (at least 6 times/day) for 4 days	Burning, stinging and discomfort at the application site; less commonly, erythema and decreased cutaneous sensation (particularly to touch); occasionally, headache and dysgeusia
Docosanol	5 times/day until episode is resolved	Burning, pruritus, xerosis, erythema, edema and acne

Table 127.26 Dosing of topical antiviral drugs. q, every; h, hours.

FORMULATIONS OF SYSTEMIC ANTIVIRAL DRUGS	
Antiviral drug	**Available formulations**
Acyclovir	200 mg capsules; 400 mg and 800 mg tablets; iv solution; 200 mg/5 ml banana-flavored suspension
Valacyclovir	500 mg and 1000 mg tablets*
Famciclovir	125 mg, 250 mg and 500 mg tablets
Ganciclovir	250 mg and 500 mg capsules; iv solution
Valganciclovir	450 mg tablets; 50 mg/ml oral solution
*Pharmacies can compound valacyclovir tablets into an oral suspension (25 or 50 mg/ml).	

Table 127.27 Formulations of systemic antiviral drugs. iv, intravenous.

immunocompromised individuals, including those receiving chronic systemic corticosteroid therapy[99].

Contraindications

As with other medications, antiviral agents are contraindicated in patients with hypersensitivity to any components of the formulation. Systemic antivirals need to be dose-adjusted for patients with impaired renal function (Table 127.29); renal function should be monitored in patients taking nephrotoxic medications. Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome have been reported in immunocompromised patients receiving valacyclovir[100].

Major side effects

Table 127.26 lists the side effects of topical antiviral agents, which have limited systemic absorption, and Table 127.30 lists the side effects of systemic antiherpetic medications.

Interactions

No clinically important drug interactions with topical antivirals have been identified. Table 127.31 lists the interactions of the systemic antiviral agents with other medications.

Pregnancy and lactation

There are no adequate studies of topical antiviral agents in pregnant or lactating women. Small amounts of topical acyclovir are absorbed through the skin and mucous membranes, and it is not known if topically applied antivirals are excreted in breast milk. Topical docosanol has not been shown to cause birth defects or other problems in animal studies using rats or rabbits. It is unknown whether docosanol passes into breast milk. To date, no problems in nursing infants due to topical antiviral agents have been reported.

Systemic antiviral drugs should not be used during pregnancy unless the benefit justifies the potential risk to the fetus. Systemic acyclovir is FDA pregnancy category C. Acyclovir crosses the placenta and is mutagenic at high doses *in vitro*[101]. However, it has not been shown to be teratogenic in animal studies, and a prospective registry of 756 pregnant patients who took acyclovir showed an incidence of birth defects similar to that in the general population[102]. Acyclovir is the drug of choice for primary genital herpes in pregnant women because it has been used safely more often than other antivirals. Recurrent herpes simplex during pregnancy is generally not an indication for acyclovir. Varicella in pregnant women should be treated with acyclovir due to the high risk of maternal mortality from varicella pneumonia as well as fetal death or premature delivery[103]. It is not known, however, whether acyclovir prevents congenital varicella syndrome. Acyclovir is excreted in breast milk, but no data are available regarding the risk to nursing infants. There are no adequate human studies of valacyclovir (pregnancy category B) in pregnancy or lactation.

Systemic famciclovir (pregnancy category B) and penciclovir have not been shown to be teratogenic in animal studies. Very high doses of penciclovir are mutagenic, and prolonged exposure to high-dose famciclovir is associated with benign mammary tumors in rats[101]. There is an ongoing registry maintained by the manufacturer to monitor pregnant patients exposed to famciclovir[19]. Penciclovir does pass into the milk in animals when given orally. The safety of famciclovir and penciclovir use during lactation has not been established.

INDICATIONS AND DOSAGES OF SYSTEMIC ANTIHERPETIC DRUGS	
Indication	**Dosage**
Primary genital herpes	Acyclovir 200 mg po 5 times a day for 10 days *or* 400 mg po tid for 10 days Valacyclovir 1 g po bid for 10 days Famciclovir 250 mg po tid for 10 days
Recurrent genital herpes	Acyclovir 400 mg po tid for 5 days *or* 800 mg po bid for 5 days *or* 800 mg po tid for 2 days Valacyclovir 500 mg po bid for 3 days *or* 1 g po qd for 5 days Famciclovir 125 mg po bid for 5 days *or* 1 g po bid × 1 day *or* 500 mg po × 1 dose then 250 mg bid for 2 days
Chronic suppression of herpes	Acyclovir 400 mg po bid Valacyclovir 500 mg (if <10 outbreaks/year) or 1 g (if ≥10 outbreaks/year) po qd Valacyclovir 1 g po qd for patients with over 10 recurrences per year Famciclovir 250 mg po bid
Herpes zoster	Acyclovir 800 mg po 5 times a day for 7–10 days Valacyclovir 1 g po tid for 7 days Famciclovir 500 mg po tid for 7 days
Varicella	Patients over 2 years of age, over 40 kg: Acyclovir 800 mg po qid for 5 days Patients over 2 years of age, under 40 kg: Acyclovir 20 mg/kg (800 mg max) po qid for 5 days Valacyclovir 20 mg/kg (1 g max) po tid for 5 days*
Mucocutaneous herpes simplex in immunocompromised patients, including HIV-infected	Acyclovir 5 mg/kg (if age ≥10 years) or 10 mg/kg (if age <10 years) iv q8 h for 7 days† Acyclovir 400 mg po 3–5 times a day for 14–21 days† Valacyclovir 1 g po bid–tid for 7 days† Famciclovir 500 mg po bid for 5–10 days†
HSV encephalitis	Acyclovir 10 mg/kg iv q8 h for 10 days
Disseminated herpes zoster	Acyclovir 5–10 mg/kg iv q8 h for 7–10 days
Recurrent orolabial herpes	Famciclovir 1500 mg po once Valacyclovir 2 g po bid × 1 day
*FDA-approved for ages 2–17 years. †Continue until lesions have all healed.	

Table 127.28 Indications and dosages of systemic antiherpetic drugs. Dosage frequency and amount must be adjusted for renal failure and dialysis (see Table 127.29). bid, twice daily; h, hours; iv, intravenously; po, orally; q, every; qd, daily; qid, four times daily; tid, three times daily.

Other antiviral agents

Herpes infection resistant to commonly used drugs is a problem in immunocompromised patients. Foscarnet and cidofovir are two alternative treatments in this situation (see Table 127.25).

DOSE REDUCTIONS FOR ACYCLOVIR, VALACYCLOVIR AND FAMCICLOVIR IN PATIENTS WITH RENAL DISEASE						
Indication	**Acyclovir**		**Valacyclovir**		**Famciclovir**	
	Creatinine clearance (ml/min)	**Adjusted dose**	**Creatinine clearance (ml/min)**	**Adjusted dose**	**Creatinine clearance (ml/min)**	**Adjusted dose**
Primary genital herpes	<10	200 mg po bid	10–29 <10	1 g qd 500 mg qd	20–39 <20	125 mg bid 125 mg qd
Recurrent genital herpes			<30	500 mg qd	40–59 20-39 <20	500 mg bid × 1 day 500 mg once 250 mg once
Chronic suppression of herpes			<30	500 mg q48 h or qd	20–39 <20	125 mg bid 125 mg qd
Herpes zoster	10–25 <10	800 mg po tid 800 mg po bid	30–49 10–29 <10	1 g bid 1 g qd 500 mg qd	40–59 20–39 <20	500 mg bid 500 mg qd 250 mg qd
Recurrent orolabial herpes (2 g bid × 1 day)			30–49 10–29 <10	1 g bid × 1 day 500 mg bid × 1 day 500 mg once	40–59 20–39 <20	750 mg once 500 mg once 250 mg once
Immunocompromised patients with mucocutaneous herpes; for acyclovir, also herpes encephalitis and disseminated zoster	25–50 10–24 <10	5–10 mg/kg iv q12 h 5–10 mg/kg iv q24 h 2.5–5 mg/kg iv q24 h			20–39 <20	500 mg qd 250 mg qd

Table 127.29 Dose reductions for acyclovir, valacyclovir and famciclovir in patients with renal disease. In hemodialysis patients, the medication should be administered after dialysis. bid, twice daily; h, hours; iv, intravenously; po, orally; q, every; qd, daily; tid, three times daily.

SIDE EFFECTS OF SYSTEMIC ANTIVIRAL AGENTS	
Acyclovir and valacyclovir	• Cutaneous: morbilliform eruption, Stevens–Johnson syndrome, injection site reaction, urticaria, angioedema • Gastrointestinal: nausea, vomiting, diarrhea, abdominal pain • Hematologic: aplastic anemia, leukopenia, thrombocytopenia • Neurologic: headaches, vertigo, lethargy, confusion, hallucinations, depression, seizures, encephalopathy, coma (CNS disturbances more likely in elderly patients) • Cardiovascular: hypertension, tachycardia, anaphylaxis • Other: malaise, arthralgia, myalgia, dyspnea, dysmenorrhea • Reversible crystalluria-induced nephropathy with intravenous acyclovir (typically in patients with pre-existing renal dysfunction or dehydration) • Thrombotic thrombocytopenic purpura or hemolytic uremic syndrome in immunocompromised patients with valacyclovir
Famciclovir	• Pruritus, paresthesias, headache, fatigue, nausea, vomiting, diarrhea, and flatulence

Table 127.30 Side effects of systemic antiviral agents.

DRUG INTERACTIONS OF SYSTEMIC ANTIVIRAL AGENTS	
Interacting drug	**Result**
Amphotericin	Increases serum acyclovir level
Cimetidine	Decreases rate of conversion of valacyclovir to acyclovir Increases serum levels of acyclovir and valacyclovir
Digoxin	Famciclovir increases digoxin levels
Glyburide with metformin (Glucovance®)	Acyclovir or valacyclovir may cause lactic acidosis in patients with decreased renal function
Interferon	May worsen potential neurotoxicity of acyclovir
Intrathecal methotrexate	May worsen potential neurotoxicity of acyclovir
Nephrotoxic drugs (i.e. cisplatin)	Acyclovir increases risk of nephrotoxicity
Probenecid	Decreases rate of conversion of valacyclovir to acyclovir Increases serum levels of acyclovir and valacyclovir
Theophylline	Acyclovir causes decreased metabolism and increased serum levels of theophylline Theophylline increases serum levels of acyclovir and valacyclovir
Zidovudine	Increases serum levels of acyclovir and valacyclovir

Table 127.31 Drug interactions of systemic antiviral agents.

Foscarnet is an intravenous antiviral used for CMV retinitis or CMV skin infection in HIV-infected patients and for acyclovir-resistant herpes simplex infections. Foscarnet is an inorganic pyrophosphate analogue that selectively inhibits viral DNA polymerase by blocking its pyrophosphate binding sites. This prevents the cleavage of pyrophosphate from deoxyadenosine triphosphate. Foscarnet does not require phosphorylation to be activated, and thus it circumvents the commonest mode of viral resistance involving viral thymidine kinase. Foscarnet is active against all herpesviruses. Side effects of the intravenous form include nephrotoxicity, anemia, erosive penile lesions, thrombophlebitis, seizures, gastrointestinal disturbances, and changes in serum calcium, magnesium and phosphate levels[104,105]. Topical formulations of the drug are being studied.

Cidofovir is an acyclic nucleoside phosphate analogue of deoxycytosine monophosphate. It inhibits viral DNA polymerase and causes DNA chain termination. It differs from acyclovir and penciclovir in that it does not require viral thymidine kinase to become activated[105]. It is also used for CMV retinitis in HIV-infected patients. Cidofovir is currently available in intravenous form only, and side effects include nephrotoxicity, iritis, neutropenia, metabolic acidosis and gastrointestinal disturbances. However, a compounded topical form has been used with some success for herpes simplex resistant to acyclovir, molluscum contagiosum, condyloma acuminata and verruca vulgaris[106,107]. *In vitro*, cidofovir is active against DNA viruses including monkeypox, variola and vaccinia.

Compounds that target the HSV helicase-primase complex (composed of three proteins that unravel DNA) have been shown to be effective *in vitro* as well as in animal models[108–110]. Resiquimod, a topical immune-response modifier, has been shown to reduce the number of recurrences of genital herpes.

REFERENCES

1. Espersen F. Resistance to antibiotics used in dermatological practice. Br J Dermatol. 1998;139(suppl. 53):4–8.
2. Veien NK. The clinician's choice of antibiotics in the treatment of bacterial skin infection. Br J Dermatol. 1998;139(suppl. 53):30–6.
3. Tunkel AR. Topical antibacterials. In: Mandell GL, Bennett JE, Dolin R (eds). Mandell, Douglas, and Bennett's Principles and Practice of Infectious Disease, 5th edn. Philadelphia: Churchill Livingstone, 2000;428–35.
4. Eady EA, Bojar RA, Jones CE, et al. The effects of acne treatment with a combination of benzoyl peroxide and erythromycin on skin carriage of erythromycin-resistant propionibacteria. Br J Dermatol. 1996;134:107–13.
5. Ross JL, Snelling AM, Eady EA, et al. Phenotypic and genotypic characterization of antibiotic-resistant Propionibacterium acnes isolated from acne patients attending dermatology clinics in Europe, the USA, Japan and Australia. Br J Dermatol. 2001;144:339–46.
6. Eady EA, Farmery MR, Ross JI, et al. Effects of benzoyl peroxide and erythromycin alone and in combination against antibiotic-sensitive and -resistant skin bacteria from acne patients. Br J Dermatol. 1994;131:331–6.
7. Harkaway KS, McGinley KJ, Foglia AN, et al. Antibiotic resistance patterns in coagulase-negative staphylococci after treatment with topical erythromycin, benzoyl peroxide, and combination therapy. Br J Dermatol. 1992;126:586–90.
8. Chalker DK, Shalita A, Smith JG Jr, Swann RW. A double-blind study of the effectiveness of a 3% erythromycin and 5% benzoyl peroxide combination in the treatment of acne vulgaris. J Am Acad Dermatol. 1983;9:933–6.
9. BenzaClin® topical gel (clindamycin – benzoyl peroxide gel). [Prescribing Information]. Bridgewater, NJ: Dermik Laboratories, 2006.
10. Lookingbill DP, Chalker DK, Lindholm JS, et al. Treatment of acne with a combination clindamycin/benzoyl peroxide gel compared with clindamycin gel, benzoyl peroxide gel and vehicle gel: combined results of two double-blind investigations. J Am Acad Dermatol. 1997;37:590–5.
11. Pierard GE, Pierard-Franchimont C. Effect of topical erythromycin-zinc formulation on sebum delivery. Evaluation by combined photometric-multi-step samplings with Sebutape. Clin Exp Dermatol. 1993;18:410–13.
12. Feucht CL, Allen BS, Chalker DK, Smith JG Jr. Topical erythromycin with zinc in acne. A double-blind controlled study. J Am Acad Dermatol. 1980;3: 483–91.
13. Pierard-Franchimont C, Goffin V, Visser JN, et al. A double-blind controlled evaluation of the sebosuppressive activity of topical erythromycin-zinc complex. Eur J Clin Pharmacol. 1995;49:57–60.
14. Schachner L, Eaglstein W, Kittles C, Mertz P. Topical erythromycin and zinc therapy for acne. J Am Acad Dermatol. 1990;22:253–60.
15. Strauss JS, Stanieri AM. Acne treatment with topical erythromycin and zinc: effect of *Propionibacterium acnes* and free fatty acid composition. J Am Acad Dermatol. 1984;11:86–9.
16. Holland KT, Bojar RA, Cunliffe WJ, et al. The effect of zinc and erythromycin on the growth of erythromycin-resistant and erythromycin-sensitive isolates of *Propionibacterium acnes*: an in-vitro study. Br J Dermatol. 1992;126:505–9.
17. Chu A, Huber FL, Plott RT. The comparative efficacy of benzoyl peroxide 5%/erythromycin 3% gel and erythromycin 4%/zinc 1.2% solution in the treatment of acne vulgaris. Br J Dermatol. 1997;136:235–8.
18. van Hoogdalem EJ. Transdermal absorption of topical anti-acne agents in man; review of clinical pharmacokinetic data. J Eur Acad Dermatol Venerol. 1998;11:S13–19.
19. McEvoy GK (ed). American Hospital Formulary Service (AHFS) Drug Information. Bethesda: American Society of Health-System Pharmacists, 2001;539–41, 3322–4.
20. Altabax ointment (retapamulin ointment), 1% [package insert]. Research Triangle Park, NC: GlaxoSmithKline, 2007.
21. von Eiff C, Becker K, Machka K, et al. Nasal carriage as a source of *Staphylococcus aureus* bacteremia. N Engl J Med. 2001;344:11–16.
22. Leyden JJ. Review of mupirocin ointment in the treatment of impetigo. Clin Pediatr. 1992;31:549–53.
23. Rice TD, Duggan AK, DeAngelis C. Cost-effectiveness of erythromycin versus mupirocin for the treatment of impetigo in children. Pediatrics. 1992;89:210–14.
24. Mandell LA. Fusidic acid. In: Mandell GL, Bennett JE, Dolin R (eds). Mandell, Douglas, and Bennett's Principles and Practice of Infectious Disease, 6th edn. Philadelphia: Churchill Livingstone, 2005:326–8.
25. Wilkinson JD. Fusidic acid in dermatology. Br J Dermatol. 1998;139(suppl. 53):37–40.
26. Sutton JB, Lagdon CG. An analysis of the cost effectiveness of fusidic acid cream and mupirocin ointment in the treatment of superficial skin sepsis in general practice. Br J Med Econ. 1993;6:367–43.
27. Sutton JB. Efficacy and acceptability of fusidic acid cream and mupirocin ointment in facial impetigo. Curr Ther Res. 1992;51:673–8.
28. Morley PAR, Munot LD. A comparison of sodium fusidate ointment and mupirocin ointment in superficial skin sepsis. Curr Med Res Opin. 1988;11:142–8.
29. Macmillan AL, Sarkany I. Specific topical therapy for erythrasma. Br J Dermatol. 1970;82:507–9.
30. Hamann K, Thorn P. Systemic or local treatment of erythrasma? A comparison between erythromycin tablets and fucidin cream in general practice. Scand J Prim Health Care. 1991;9:35–9.
31. Pearson RD. Agents active against parasites and *Pneumocystis carinii*. In: Mandell GL, Bennett JE, Dolin R (eds). Mandell, Douglas, and Bennett's Principles and Practice of Infectious Disease, 6th edn. Philadelphia: Churchill Livingstone, 2005:583.
32. Wright TI, Baddour LM, Berbari EF, et al. Antibiotic prophylaxis in dermatologic surgery: advisory statement 2008. J Am Acad Dermatol. 2008;59:464–73.
33. Darmstadt GL. Antibiotics in the management of pediatric skin disease. Dermatol Clin. 1998;16:509–25.
34. Salkind AR, Cuddy PG, Foxworth JW. Is this patient allergic to penicillin? An evidence-based analysis of the likelihood of penicillin allergy. JAMA. 2001;285:2498–505.
35. Anderson JA. Antibiotic drug allergy in children. Curr Opin Pediatr. 1994;6:656–60.
36. Ibia EO, Schwartz RH, Wiedermann BL. Antibiotic rashes in children. A survey in a private practice setting. Arch Dermatol. 2000;136:849–54.
37. Raimer SS. New and emerging therapies in pediatric dermatology. Dermatol Clin. 2000;18:73–8.
38. Sullivan JR, Shear NH. The drug hypersensitivity syndrome. What is the pathogenesis? Arch Dermatol. 2001;137:357–64.
39. Le Cleach L, Bocquet H, Roujeau JC. Reactions and interactions of some commonly used systemic drugs in dermatology. Dermatol Clin. 1998;16:421–9.
40. Shapiro LE, Knowles SR, Shear NH. Comparative safety of tetracycline, minocycline, and doxycycline. Arch Dermatol. 1997;133:1224–30.
41. Margolis DJ, Hoffstad O, Bilker W. Association or lack of association between tetracycline class antibiotics used for acne vulgaris and lupus erythematosus. Br J Dermatol. 2007;157:540–6.
42. El-Hallak M, Giani T, Yeniay BS, et al. Chronic minocycline-induced autoimmunity in children. J Pediatr. 2008;153:314–19.
43. Cohan S, Bevelander G, Tiamisc T. Growth inhibition of prematures receiving tetracycline. Am J Dis Child. 1963;105:1008.
44. Bartlett JG. Antimicrobial agents implicated in *Clostridium difficile* toxin-associated diarrhea or colitis. Johns Hopkins Med J. 1981;149:6–9.
45. Bartlett JG. Anti-anaerobic antibacterial agents. Lancet. 1982;2:478–81.
46. Tedesco FJ. Clindamycin and colitis: a review. J Infect Dis. 1977;135:S95–8.

46a. Adefurin A, Sammons H, Jacqz-Aigrain E, et al. Ciprofloxacin safety in paediatrics: a systematic review. Arch Dis Child. 2011;96:874–80.

47. Burkhardt JE, Walterspiel JN, Schaad UB. Quinolone arthropathy in animals versus children. Clin Infect Dis. 1997;25:1196–204.
48. Hooper DC. Quinolones. In: Mandell GL, Bennett JE, Dolin R (eds). Mandell, Douglas, and Bennett's Principles and Practice of Infectious Disease, 5th edn. Philadelphia: Churchill Livingstone, 2000;306–7.
49. Lesher JL Jr. Oral therapy of common superficial fungal infections of the skin. J Am Acad Dermatol. 1999;40:S31–4.
50. Evans EG, James IG, Seaman RA, Richardson MD. Does naftifine have anti-inflammatory properties? A double-blind comparative study with 1% clotrimazole/1% hydrocortisone in clinically diagnosed fungal infection of the skin. Br J Dermatol. 1993;129:437–42.
51. Hegemann L, Toso SM, Lahijani KI, et al. Direct interaction of antifungal azole-derivatives with calmodulin: a possible mechanism for their therapeutic activity. J Invest Dermatol. 1993;100:343–6.
52. Rosen T, Schell BJ, Orengo I. Anti-inflammatory activity of antifungal preparations. Int J Dermatol. 1997;36:788–92.
53. Bremm KD, Plempel M. Modulation of leukotriene metabolism from human polymorphonuclear granulocytes by bifonazole. Mycoses. 1991;34:41–5.
54. van Cutsem J, van Gerven F, Cauwenbergh G, et al. The anti-inflammatory effects of ketoconazole. A comparative study with hydrocortisone acetate in a model using living and killed *Staphylococcus aureus* on the skin of guinea-pigs. J Am Acad Dermatol. 1991;25:257–61.
55. Abrams BB, Hanel H, Hoehler T. Ciclopirox olamine: a hydroxypyridine antifungal agent. Clin Dermatol. 1991;9:471–7.
56. Arika T, Yokoo M, Yamaguchi H. Topical treatment with butenafine significantly lowers relapse rate in an interdigital tinea pedis model in guinea pigs. Antimicrob Agents Chemother. 1992:36:2523–5.
57. Shadomy S, Wang H, Shadomy HJ. Further in vitro studies with oxiconazole nitrate. Diagn Microbiol Infect Dis. 1988;9:231–7.
58. Evans EG. A comparison of terbinafine (Lamisil) 1% cream given for one week with clotrimazole (Canesten) 1% cream given for four weeks, in the treatment of tinea pedis. Br J Dermatol. 1994;130(suppl. 43):12–14.
59. Bergstresser PR, Elewski B, Hanifin J, et al. Topical terbinafine and clotrimazole in interdigital tinea pedis: a multicenter comparison of cure and relapse rates with 1- and 4-week treatment regimens. J Am Acad Dermatol. 1993;28:648–51.
60. Ablon G, Rosen T, Spedale J. Comparative efficacy of naftifine, oxiconazole, and terbinafine in short-term treatment of tinea pedis. Int J Dermatol. 1996;35:591–3.
61. Smith EB, Breneman DL, Griffith RF, et al. Double-blind comparison of naftifine cream and clotrimazole/betamethasone dipropionate cream in the treatment of tinea pedis. J Am Acad Dermatol. 1992;26:125–7.
62. Elewski B, Bergstresser P, Hanifin J, et al. Long-term outcome of patients with interdigital tinea pedis treated with terbinafine or clotrimazole. J Am Acad Dermatol. 1995;32:290–2.
63. Lesher JL Jr, Babel DE, Stewart DM, et al. Butenafine 1% cream in the treatment of tinea cruris: a multicenter, vehicle-controlled, double-blind trial. J Am Acad Dermatol. 1997;36:S20–4.
64. Brennan B, Leyden JJ. Overview of topical therapy for common superficial fungal infections and the role of new topical agents. J Am Acad Dermatol. 1997;36:S3–8.
65. Lesher JL Jr, Smith JG Jr. Antifungal agents in dermatology. J Am Acad Dermatol. 1987;17:383–94.
66. Lynch PJ, Minkin W, Smith EB. Ecology of *Candida albicans* in candidiasis of the groin. Arch Dermatol. 1969;99:154–60.
67. Friedlander SF, Suarez S. Pediatric antifungal therapy. Dermatol Clin. 1998;16:527–37.
68. De Backer M, De Vroey C, Lesaffre E, et al. Twelve weeks of continuous oral therapy for toenail onychomycosis caused by dermatophytes: double-blind comparative trial of terbinafine 250 mg/day versus itraconazole 200 mg/day. J Am Acad Dermatol. 1998;38:S57–63.
69. Jandourek A, Brown P, Vazquez JA. Community-acquired fungemia due to a multiple-azole-resistant strain of *Candida tropicalis*. Clin Infect Dis. 1999;29:1583–4.
70. Elewski BE. Tinea capitis: a current perspective. J Am Acad Dermatol. 2000;42:1–20.
71. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med. 2007;356:348–59.
72. Vazquez JA, Sobel JD. Anidulafungin: a novel Echinocandin. Clin Infect Dis. 2006;43:215–22.
73. Katz HI. Systemic antifungal agents used to treat onychomycosis. J Am Acad Dermatol. 1998;38:S48–52.
74. Gupta AK. Systemic antifungal agents. In: Wolverton SE (ed). Comprehensive Dermatologic Drug Therapy, 2nd edn. Philadelphia: Saunders, 2007:101–12.
75. Brooke R, Coulson IH, al-Dawoud A. Terbinafine-induced subacute cutaneous lupus erythematosus. Br J Dermatol. 1998;139:1132–3.

76. Holmes S, Kemmett D. Exacerbation of systemic lupus erythematosus induced by terbinafine. Br J Dermatol. 1998;139:1133.
77. Murphy M, Barnes L. Terbinafine-induced lupus erythematosus. Br J Dermatol. 1998;138:708–9.
78. Bonsmann G, Schiller M, Luger TA, Stander S. Terbinafine-induced subacute cutaneous lupus erythematosus. J Am Acad Dermatol. 2001;44:925–31.
79. Cowen DW, Nguyen JC, Miller DD, et al. Chronic phototoxicity and aggressive squamous cell carcinoma of the skin in children and adults during treatment with voriconazole. J Am Acad Dermatol. 2010;62:31–7.
80. Miller DD, Cowen EW, Nguyen JC, et al. Melanoma associated with long-term voriconazole therapy: a new manifestation of chronic photosensitivity. Arch Dermatol. 2010;126:300–4.
81. Smith EB. The treatment of dermatophytosis: safety considerations. J Am Acad Dermatol. 2000;43:S113–19.
82. Spruance SL, Rea TL, Thoming C, et al. Penciclovir cream for the treatment of herpes simplex labialis. JAMA. 1997;277:1374–9.
83. Vere Hodge RA. Review: antiviral portraits series, number 3. Famciclovir and penciclovir: the mode of action of famciclovir including its conversion to penciclovir. Antiviral Chem Chemother. 1993; 4: 67–84.
84. Bacon TH, Howard BA, Spender LC, Boyd MR. Activity of penciclovir in antiviral assays against herpes simplex virus. J Antimicrob Chemother. 1996;37:303–13.
85. Pope LE, Marcelletti JF, Katz LR, et al. The anti-herpes simplex virus activity of n-docosanol includes inhibition of the viral entry process. Antiviral Res. 1998;40:85–94.
86. Corey L, Nahmias AJ, Guinan ME, et al. A trial of topical acyclovir in genital herpes simplex virus infections. N Engl J Med. 1982;306:1313–19.
87. Fiddian AP, Kinghorn GR, Goldmeier D, et al. Topical acyclovir in the treatment of genital herpes: a comparison with systemic therapy. J Antimicrob Chemother. 1983;12:67–77.
88. Evans TY, Tyring SK. Advances in antiviral therapy in dermatology. Dermatol Clin. 1998;16:409–20.
89. Loveless M, Sacks SL, Harris JRW. Famciclovir in the management of first-episode genital herpes. Infect Dis Clin Pract. 1997;6:S12–16.
90. Tyring S, Barbarash RA, Nahlik JE, et al. Famciclovir for the treatment of acute herpes zoster: effects on acute disease and postherpetic neuralgia. A randomized, double-blind, placebo-controlled trial. Collaborative Famciclovir Herpes Zoster Study Group. Ann Intern Med. 1995;123:89–96.
91. Herne K, Cirelli R, Lee P, Tyring SK. Antiviral therapy of acute herpes zoster in older patients. Drugs Aging. 1996;8:97–112.
92. Chang YC, Madkan ZK, Sra K, Carrasco PA, Lee PC, Tyring SK. Systemic antiviral agents. In: Wolverton SE (ed). Comprehensive Dermatologic Drug Therapy, 2nd edn. Philadelphia: Saunders, 2007:101–12.
93. Fleming DT, McQuillan GM, Johnson RE, et al. Herpes simplex virus type 2 in the United States, 1976 to 1994. N Engl J Med. 1997;337:1105–11.
94. Centers for Disease Control and Protection (CDC). Seroprevalence of herpes simplex virus type 2 among persons aged 14–49 years – United States, 2005–2008. MMWR Morb Mortal Wkly Rep. 2010;59:456–9.
95. Wald A, Zeh J, Barnum G, et al. Suppression of subclinical shedding of herpes simplex virus type 2 with acyclovir. Ann Intern Med. 1996;124: 8–15.
96. Reitano M, Tyring S, Lang W, et al. Valacyclovir for the suppression of recurrent genital herpes simplex virus infection: a large-scale dose range-finding study. J Infect Dis. 1998;178:603–10.
97. Corey L, Wald A, Patel R, et al. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. N Engl J Med. 2004;350:11–20.
98. Englund JA, Arvin AM, Balfour HH Jr. Acyclovir treatment for varicella does not lower gpl and IE-62 (p170) antibody responses to varicella-zoster virus in normal children. J Clin Microbiol. 1990;28:2327–30.
99. Chapel KL, Rasmussen JE. Pediatric dermatology: advances in therapy. J Am Acad Dermatol. 1997;36:513–26.
100. Valtrex® product information. Research Triangle Park, NC: Glaxo Wellcome Inc., October 2000.
101. Hayden FG. Antiviral drugs (other than antiretrovirals). In: Mandell GL, Bennett JE, Dolin R (eds). Mandell, Douglas, and Bennett's Principles and Practice of Infectious Disease, 5th edn. Phildadelphia: Churchill Livingstone, 2000:460–90.
102. Zovirax® product information. Research Triangle Park, NC: Glaxo Wellcome Inc., March 2000.
103. Mutalik S, Gupte A, Gupte S. Oral acyclovir therapy for varicella in pregnancy. Int J Dermatol. 1997;36:49–51.
104. Sasadeusz JJ, Sacks SL. Systemic antivirals in herpesvirus infections. Dermatol Clin. 1993;11:171–85.
105. Leung DT, Sacks SL. Current recommendations for the treatment of genital herpes. Drugs. 2000;60:1329–52.
106. Calista D. Topical cidofovir for severe cutaneous human papillomavirus and molluscum contagiosum infections in patients with HIV/AIDS. A pilot study. J Eur Acad Dermatol Venereol. 2000;14:484–8.
107. Zabawski EJ Jr, Cockerell CJ. Topical and intralesional cidofovir: a review of pharmacology and therapeutic effects. J Am Acad Dermatol. 1998;39:741–5.
108. Crumpacker CS, Schaffer PA. New anti-HSV therapeutics target helicase-primase complex. Nat Med. 2002;8:327–8.
109. Crutte JJ, Grygon CA, Hargrave KD. Herpes simplex virus helicase-primase inhibitors are active in animal models of human disease. Nat Med. 2002;8:386–91.
110. Kleymann G, Fischer R, Betz UAK, et al. New helicase-primase inhibitors as drug candidates for the treatment of herpes simplex disease. Nat Med. 2002;8:392–8.

This page intentionally left blank

Immunomodulators 128

J Mark Jackson and Jeffrey P Callen

Chapter Contents

Interferons 2131
Imiquimod 2134
Granulocyte–macrophage and granulocyte colony-stimulating factors (GM-CSF and G-CSF) 2136
Topical calcineurin inhibitors 2136
Targeted immune modulators 2138
Alefacept 2138
Efalizumab 2140
TNF-α inhibitors – general information 2141
Ustekinumab 2145
Anakinra 2146
Rituximab 2146
Omalizumab 2147
Intravenous immune globulin (IVIg) 2147

INTERFERONS

Key features

- Human cells produce three antigenically distinct forms of interferon (IFN), originally described as leukocyte (α), fibroblast (β) and immune (γ)
- Recombinant DNA technology can produce large quantities of highly purified human IFN
- IFNs have antiviral, antiproliferative and immunoregulatory properties
- Dermatologic FDA-approved indications for IFNs include condyloma acuminata (IFN-α-2b), melanoma (IFN-α-2b) and AIDS-associated Kaposi sarcoma (IFN-α-2a and IFN-α-2b)
- Side effects include flu-like symptoms, leukopenia, nausea, vomiting and hepatitis

INTRODUCTION

Interferons (IFNs) are a family of secretory glycoproteins produced by most eukaryotic cells in response to a variety of viral and non-viral inducers. All IFNs display antiviral activity, and they also modulate other cellular functions. IFN does not inactivate viruses directly but rather renders cells resistant to viruses.

There are three antigenically distinct IFNs, originally described as leukocyte (α), fibroblast (β) and immune (γ)[1] (Table 128.1). Utilization of recombinant DNA technology has led to the production of large quantities of highly purified human IFN by *Escherichia coli*. This chapter will focus primarily on IFN-α-2a and IFN-α-2b, which are the most frequently used IFNs for patients with dermatologic diseases.

PHARMACOLOGY AND MECHANISM OF ACTION

There are over 30 subtypes of IFN-α, each composed of 165–172 amino acids with very similar sequences. For example, IFN-α-2a and IFN-α-2b differ in just a single amino acid. IFN-β has 29% structural homology to IFN-α, but IFN-γ has no significant structural homology to either IFN-α or IFN-β[2].

IFNs must be injected intralesionally or be given parenterally. Systemic absorption via the intramuscular or subcutaneous route is >80% for IFN-α, with a peak effect 3–12 hours after injection and becoming undetectable after 24 hours[1]. Pegylated forms of IFN-α have attachment of polyethylene glycol (PEG) side chains, which prolongs the therapeutic effect; as a result, the drug can be administered less frequently (see Table 128.1). IFNs undergo renal catabolism.

IFN activity is dependent upon its ability to bind to specific receptors on the surface of target cells. IFN-α and IFN-β (referred to as type I IFNs) share the same IFN-α/β receptor, whereas IFN-γ (a type II IFN) binds to a separate receptor; both receptors signal via Janus kinase (JAK)-STAT-mediated pathways. Underlying mechanisms of antiviral, antiproliferative and immunoregulatory activity of are listed in Table 128.2.

INDICATIONS AND DOSAGES (Table 128.3)

Genital and Perianal Warts (Condylomata Acuminata)

Intralesional IFN-α-2b has been found to be safe and effective in the treatment of condylomata acuminata on the external surfaces of genital and perianal areas[3]. The regimen that is typically used is 1 million IU per wart three times weekly for 3 weeks, with a maximal dose of 5 million IU per session. In a recent meta-analysis of randomized controlled trials of IFN for the treatment of condylomata, the overall complete response rate for local/intralesional administration was 44% (compared to 16% for placebo), whereas systemic administration was no better than placebo[4]. In general, IFN treatment is reserved for highly motivated patients who have failed simpler and less costly modes of therapy for condylomata.

Common Warts (Verruca Vulgaris)

In the early 1980s, Nimura[5] reported a "good response" in 81% of common warts treated with intralesional IFN-β, compared to a rate of 17% in controls. Berman et al.[6] then reported a mean reduction of 86% in the lesional area of common warts treated with 0.1 million IU IFN-α-2b, compared to 38% in the placebo-injected group.

Cutaneous T-Cell Lymphoma

The use of IFN for cutaneous T-cell lymphoma dates back to the early 1980s. IFN-α-2a is the most frequently utilized type. Although IFN may be used as a monotherapy, its administration in combination with other agents (e.g. psoralen plus ultraviolet A [PUVA], total skin electron beam, oral retinoids) results in higher response rates (e.g. as high as 70–80% for IFN-α-2a plus PUVA)[7] (see Ch. 120).

Infantile Hemangiomas

IFN-α-2a has been used to treat severe, life- or function-threatening, corticosteroid-unresponsive infantile hemangiomas[8] (see Ch. 103). However, this therapy has been associated with spastic diplegia and other neurologic dysfunction; consequently, its administration for hemangiomas has become extremely uncommon[9].

AIDS-Associated Kaposi Sarcoma

Both IFN-α-2a and IFN-α-2b are used to treat Kaposi sarcoma associated with AIDS (see Ch. 78). The overall response rates with IFN-α-2a

INTERFERONS					
Generic name	**Trade name®**	**Manufacturer**	**Route**	**Half-life**	**Peak effect**
Interferon-α-2a	Roferon-A	Roche	sc	5.1 h	3.8–7.3 h
Interferon-α-2a	Pegasys	Roche	sc	160 h	72–96 h
Interferon-α-2b	Intron A Rebetron when combined with ribavirin	Schering	iv, il, im, sc	2–3 h	30 min (iv) 3–12 h (im, sc)
Interferon-α-2b	Peg-Intron	Schering/Plough	sc	40 h	15–44 h
Interferon-α-N3	Alferon N	Hemispherx	il	2–3 h	3–12 h
Interferon-β-1a	Avonex Rebif	Biogen-Idec Serono	im sc	10 h 69 h	3–15 h 16 h
Interferon-β-1b	Betaseron	Berlex	sc	4.3 h	1–8 h
Interferon-γ-1b	Actimmune	Intermune	sc	5.9	4.7
Interferon alphacon-1	Infergen	Valeant	sc	–	24–36 h

Table 128.1 Interferons. il, intralesional; im, intramuscular; iv, intravenous; sc, subcutaneous.

MECHANISMS OF ACTION FOR INTERFERONS	
Cellular mechanism	**Clinical effect**
Induction of 2′–5′oligoadenylate synthetase Induction of ribonuclease Induction of protein kinase P1	Antiviral
Induction of 2′–5′oligoadenylate synthetase Inhibition of various growth factors Enhanced *p53* tumor suppressor gene expression Downregulation of *MYC, FOX* and certain *RAS* oncogenes	Antiproliferative
Induction of class I & II MHC antigens Increased number of natural killer (NK) cells Inhibit production of Th2 cytokines such as IL-4 and IL-5	Immunoregulatory

Table 128.2 Mechanisms of action for interferons. IL, interleukin; MHC, major histocompatibilty complex. *Courtesy, Brian Berman, MD, Tami De Araujo, MD, and Mark Lebwohl, MD.*

DERMATOLOGIC DISEASES TREATED WITH INTERFERONS
FDA-APPROVED INDICATIONS
Condyloma acuminata (α)
AIDS-associated Kaposi sarcoma (α)
Melanoma (adjuvant) (α)
Chronic granulomatous disease (γ)
SOME OFF-LABEL DERMATOLOGIC USES
Neoplasms
Basal cell carcinoma (α)
Actinic keratoses (α)
Squamous cell carcinoma (α)
Giant condyloma of Buschke-Lowenstein (α)
Cutaneous T-cell lymphoma (α, β, γ)
Granulomatous slack skin (α, γ)
Infantile hemangioma (α)
Tufted angioma (α)
Infections
Verruca vulgaris (α, β, γ)
Epidermodysplasia verruciformis (α)
Herpes zoster (α)
Herpes simplex (α)
Necrolytic acral erythema (with hepatitis C) (α)
Leishmaniasis (γ)
Leprosy (γ)
Mycobacterium avium complex infections (γ)
Inflammatory/other
Atopic dermatitis (γ)
Keloids (α, γ)
Behçet's disease (α)
Progressive systemic sclerosis (γ)
Scleromyxedema (α)

Table 128.3 Dermatologic diseases treated with interferons. *Adapted from Wolverton SE, Comprehensive Dermatologic Drug Therapy, 2nd edition. Philadelphia: WB Saunders, 2007.*

and IFN-α-2b have equaled or surpassed those achieved with conventional cytotoxic chemotherapy. The recommended dosages of IFN-α-2a and IFN-α-2b are 36 and 30 million IU, respectively, administered subcutaneously daily. Monotherapy with high-dose IFN-α-2a has been reported to achieve response rates of 7%, 27% and 45% for patients with <200, 200–400 and >400 $CD4^+$ cells/mm^3, respectively[10]. In many patients who respond, the tumors recur within 6 months, and the response to the second course of treatment is not reliable. This has led to a recommendation for maintenance therapy for as long as adverse effects are tolerated[10]. Unlike antiretroviral therapy (see Ch. 78), IFN does not reverse the underlying immunodeficiency. In addition to its immune-enhancing and antiproliferative effects, the response of Kaposi sarcoma to IFN could be explained by an antiviral effect on human herpesvirus-8 (see Ch. 80).

Basal Cell Carcinoma

Intralesional injection of IFN-α-2b into a nodular or superficial basal cell carcinoma (BCC) is occasionally used as an alternative treatment in highly selected patients (e.g. if surgery is not an option)[11]. The highest cure rates are approximately 85%, which is far below what would be expected for traditional surgical approaches.

Squamous Cell Carcinoma and Keratoacanthoma

As with BCC, IFN-α-2b therapy can be considered for patients with actinically induced or human papillomavirus (HPV)-associated squamous cell carcinoma (SCC) or keratoacanthoma who are not candidates for surgical excision[12,13].

Melanoma

The results of several trials of adjuvant interferon therapy for cutaneous melanoma are outlined in Table 113.14.

Keloids

In 1989, Berman and Duncan[14] reported a 41% reduction in the area of a keloid following intralesional injections of 1.5 million IU of IFN-α-2b twice over 4 days (the effect was seen by day 9 after the injection, when a biopsy specimen of the keloid was obtained). Lee et al.[15] compared the efficacy of intralesional therapy for keloids with IFN-α-2b plus triamcinolone acetonide to that of triamcinolone alone and found that the combination was superior.

Granstein et al.[16] performed a placebo-controlled, double-blind trial of intralesional IFN-γ for the treatment of keloids in 10 patients. Eight of the patients completed the course of treatment with injections of either diluent or IFN-γ (0.1 or 0.01 mg) three times per week for 3 weeks. The average percentage reduction in keloidal height 22 days after the initial injection was 30% for the IFN-γ-treated keloids and

only 1% for the diluent-treated keloids ($P<0.002$). No statistically significant difference was found between the effects of the lower versus the higher dose of IFN-γ. In another study of 10 scars, interferon-γ at doses of 0.5 mg (intralesionally) once weekly for 10 weeks decreased the linear dimensions by at least 50% in 5 of 10 scars, with minimal adverse effects[17].

In the postoperative setting, Berman and Flores[18] demonstrated that intralesional IFN-α-2b was superior to triamcinolone acetonide injections in preventing recurrences of excised keloids. However, Davison et al.[19] found that triamcinolone was significantly more effective than IFN-α-2b, with recurrence rates of 15% and 54%, respectively. Based on the data currently available, IFN is not considered as a first-line modality for the prevention of keloid recurrences.

Atopic Dermatitis

Evidence of reduced production of IFN-γ *in vitro* by mononuclear cells of patients with atopic dermatitis and the suppression of interleukin (IL)-4-mediated IgE stimulation by IFN-γ prompted evaluation of IFN treatment for atopic dermatitis. A randomized, placebo-controlled, double-blind, multicenter trial studied the effects of daily subcutaneous injection (50 microg/m^2) of IFN-γ versus placebo for 12 weeks in 78 patients. Altogether, 45% of the IFN-γ-treated group and 21% of the placebo-treated patients achieved a significant response (>50% improvement) by physicians' evaluations[20]. The results of additional studies using other doses and regimens have ranged from 57% clinical improvement (open trial of 14 patients)[20] to no differences compared with controls[21].

Therapy with IFN-α has also been investigated in patients with atopic dermatitis, again with varied and contradictory results. Torrelo et al.[22] reported a satisfactory response (investigator and patient global assessment) in 5 of 13 patients treated with IFN-α-2a (3 million IU subcutaneously three times weekly for 4 weeks). However, Mackie[23] reported no benefit from the same regimen administered for a total duration of 12–14 weeks. Further clinical trials are necessary in order to determine the clinical effectiveness of this expensive treatment.

Behçet's Disease

Fourteen patients with Behçet's disease who had oral ulcers, genital ulcers, pustular vasculitis, erythema nodosum and/or thrombophlebitis were treated with IFN-α-2a (3 million IU subcutaneously three times per week, escalating to 12 million IU, for a 2-month period). All patients were symptom-free at 2 months and had fewer recurrences in the post-treatment period compared with the pretreatment period[24]. Similar response rates with IFN-γ injected subcutaneously have been reported[25]. Maintenance doses once or twice weekly, however, were required to prevent early relapses.

Systemic Sclerosis

The *in vitro* ability of IFN-α, -β and -γ to inhibit collagen production and other functions of activated dermal fibroblasts derived from the involved skin of patients with scleroderma, morphea or keloids (see above) has been demonstrated[26]. IFN-γ has also been shown to temporarily inhibit the proliferation of scleroderma fibroblasts[26]. Kahan et al.[27] reported benefit of IFN-γ therapy in a small group of patients with systemic sclerosis.

CONTRAINDICATIONS

Absolute contraindications are hypersensitivity to components of the formulations. The relative contraindications are cardiac arrhythmias, depression or other psychiatric disorders, leukopenia, coagulopathies and previous organ transplantation.

MAJOR SIDE EFFECTS

The adverse effects of IFN are dose-dependent and generally improve or remit during continued therapy or following dose reduction. In addition, the adverse effects are usually rapidly reversible upon cessation of treatment.

Cutaneous Reactions

Approximately 5% of patients treated with IFN-β-1b for multiple sclerosis develop skin necrosis at the site of injection secondary to a localized vasculopathy[28] (Fig. 128.1). Plaques of psoriasis can also develop at the sites of injection of IFN, as can flares of psoriasis in patients receiving IFN (Fig. 128.2). Other occasional cutaneous side effects include alopecia, xerosis and vitiligo.

Flu-like Symptoms

The most common adverse effects are flu-like symptoms of fever, chills, fatigue, myalgias, headache and arthralgias. Generally, in healthy individuals, subcutaneous administration of IFN-α in doses of ≤3 million IU every other day induces nominal and tolerable flu-like symptoms, or no adverse effects at all. Prophylactic (1–2 hours prior to injection) administration of acetaminophen (650 mg), aspirin (650 mg) or nonsteroidal anti-inflammatory drugs (e.g. ibuprofen 400 mg) helps to prevent these effects.

Fig. 128.1 Postinflammatory hyperpigmentation and ulceration at sites of interferon-β-1b injection in a woman with multiple sclerosis. *Courtesy, Jean L Bolognia, MD.*

Fig. 128.2 Interferon-induced flare of psoriasis.

Neurologic and Psychiatric Effects

Spastic diplegia was reported in 5 of 26 patients with hemangiomas treated with 1.0–3.6 million IU/day of IFN-α-2a[9]; postulated explanations included the immaturity of the infant's central nervous system and preservatives (e.g. benzyl and phenol alcohol) in the preparations used. Depression and suicidal ideation/behavior have been reported in association with IFN-α therapy[29].

Cardiovascular Effects

Significant hypotension, arrhythmias or tachycardia (heart rate ≥150 beats/minute) can occur in association with IFN therapy[30]. Although these side effects are usually managed by modifying the dosages of IFN or discontinuing treatment, they may require specific additional therapy. Patients with a history of a myocardial infarction or arrhythmias require close monitoring.

Rhabdomyolysis

Rhabdomyolysis is occasionally seen and has proved fatal in at least one patient treated with high-dose IFN-α-2b (20 million IU intravenously twice daily for 5 days)[31]. Elevated serum creatine kinase levels should lead to a reduction in dose or cessation of therapy, depending on the severity of the elevation.

Gastrointestinal Effects and Bone Marrow Suppression

Gastrointestinal disturbances such as nausea, vomiting and diarrhea can occur, as can anorexia and hepatitis. Fatal cases of hepatitis have been reported in patients receiving high-dose IFN. Bone marrow suppression is another side effect of IFN, and it is a particular problem in patients receiving high-dose therapy or who have other reasons for bone marrow suppression (e.g. concomitant medications). Serial evaluation of liver function tests and complete blood counts is recommended.

Other Adverse Effects

Neutralizing antibodies can develop in patients receiving IFN-α-2a or IFN-α-2b, and they appear to be specific to recombinant (rather than natural) IFN[32,33]. Thyroiditis and/or hypothyroidism occurs in up to 40% of hepatitis C patients treated with IFN-α[34].

INTERACTIONS

IFN-α-2a may reduce the clearance of aminophylline, probably due to inhibition of the cytochrome P450 enzyme system[35]. Caution must be used when IFN is administered in conjunction with other potentially myelosuppressive (including zidovudine) or neurotoxic (e.g. vinca alkaloids) drugs. The concomitant use of IFN and IL-2 may increase the risk of renal failure.

USE IN PREGNANCY

IFNs are rated as pregnancy category C, although they do not appear to cross the placenta. While it is unknown whether IFN is excreted into human milk, it is excreted into mouse milk.

IMIQUIMOD

Key features

- Commercially available as a 3.75% and 5% cream
- Initially used for anogenital warts, it is now also FDA-approved for actinic keratoses on the face/scalp and superficial BCCs
- Off-label uses include common warts, molluscum contagiosum, keloids, lentigo maligna, SCC *in situ* and extramammary Paget's disease
- Stimulates an innate immune response via induction of IFN-α and TNF-α; also stimulates cell-mediated immunity

INTRODUCTION

Imiquimod (1-[2 methylpropyl]-1 H-imidazo [4, 5c] quinolin-4 amine) is an immune response modifier that stimulates innate and adaptive immune pathways, resulting in antiviral, antitumor and immunoregulatory properties.

MECHANISM OF ACTION

Imiquimod's stimulation of the innate immune response results in increased production of cytokines such as IFN-α, IL-6 and tumor necrosis factor-α (TNF-α)[36]; enhanced natural killer (NK) cell activity; and secretion of nitric oxide from macrophages[37]. Its effects on the cell-mediated arm of the adaptive immune system include augmented production of the Th1 cytokine IFN-γ (Fig. 128.3). Imiquimod also activates and enhances the migration of Langerhans cells to the regional lymph nodes, resulting in antigen presentation to T cells[38].

One important mechanism for imiquimod's effects is activation of Toll-like receptor 7 (TLR7) (see Fig. 4.1). Following binding of imiquimod to TLR7 on antigen-presenting cells (APCs), nuclear factor-κB activation stimulates production of IFN-α, IL-12 and IL-18 (see Fig. 128.3), which induce $CD4^+$ T cells to produce the IL-12 β_2 receptor (via IFN-α) and IFN-γ. This leads to enhancement of cell-mediated immunity.

After topical application of imiquimod to hairless mice, increased levels of IFN-α and TNF-α were found in treated (but not untreated) mouse skin[36]. Imiquimod's antiviral and antitumor activity in animal models is explained at least in part by the actions of IFN-α (see Table 128.2). In addition, IFN-γ stimulates cytotoxic T lymphocytes, which kill virally infected cells as well as tumors and provide the immune memory needed for future protection. In a murine tumor model, mice became free of tumor after 30 days of imiquimod treatment and remained resistant to challenge with the same tumor cells 8 months later. This demonstrated imiquimod's effects on the adaptive as well as innate arm of the immune system.

Metabolism

Percutaneous absorption of imiquimod 5% cream is minimal, with less than 0.9% of a radiolabeled 5 mg dose being recovered in the urine and feces. The site of potential metabolism is unknown, as is the degree of protein binding, if any.

INDICATIONS

Human Papillomavirus Infection

The importance of treating HPV infection is highlighted by the association of the oncogenic anogenital subtypes with SCC as well as the discomfort and psychological effects of anogenital and cutaneous warts.

External genital and perianal warts[39]

In randomized vehicle-controlled clinical trials, the topical application of imiquimod 5% cream three times a week for up to 16 weeks completely cleared lesions in approximately 50% of patients and was well tolerated. Women tend to have higher clearance rates than men, which is thought to be due to the lower degree of keratinization of the vulva compared with the shaft of the penis, the most common locations of warts. Topical imiquimod is considered to be among the first-line topical therapies for anogenital warts.

Common warts

The efficacy of topical imiquimod in the treatment of common warts, periungual warts and plantar warts is substantially lower than its efficacy for anogenital warts. However, combination therapy with sequential application of salicylic acid preparations and imiquimod can enhance its penetration and effectiveness. Several case studies have reported the successful treatment of common warts in immunocompromised patients[40]. There are also reports of the resolution of recalcitrant facial flat warts after treatment with imiquimod 5% cream.

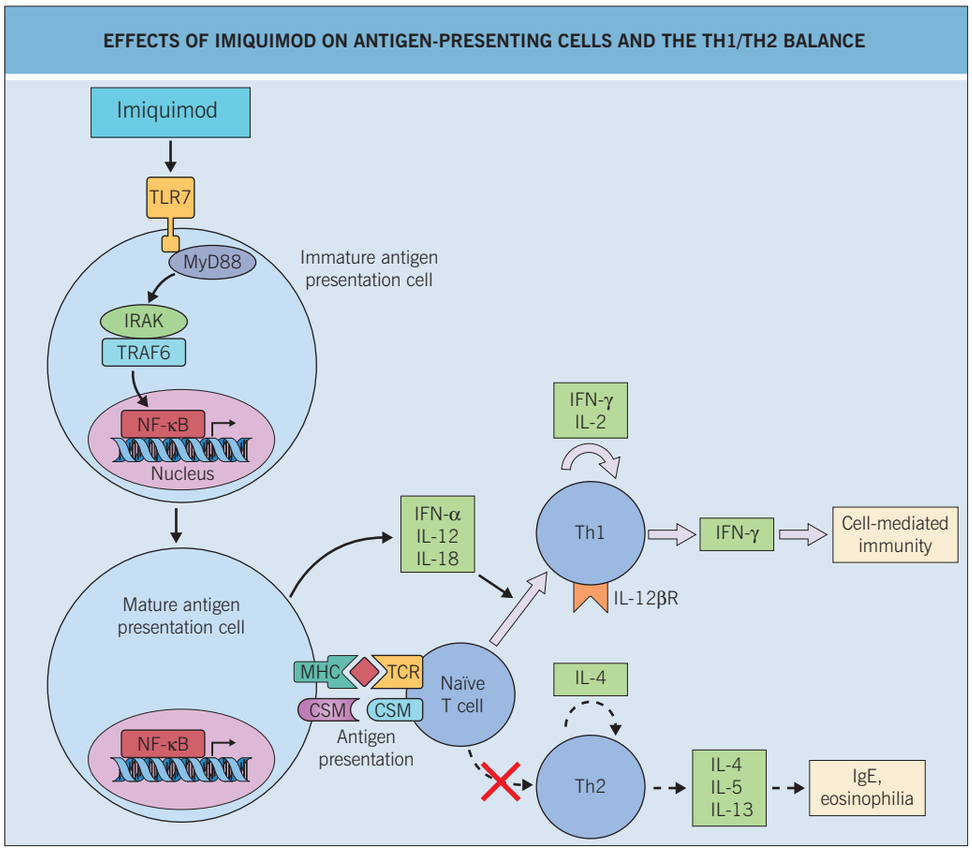


Fig. 128.3 Effects of imiquimod on antigen-presenting cells and the Th1/Th2 balance. Binding of imiquimod to Toll-like receptor 7 (TLR7) on antigen-presenting cells (e.g. Langerhans cells, other dendritic cells, macrophages) leads to interaction of the cytoplasmic portion of the receptor with MyD88. This facilitates association of MyD88 with IL-1 receptor-associated kinase (IRAK), which in turn activates TNF receptor-activated 6 (TRAF6) and ultimately results in stimulation of nuclear factor-κB-mediated signaling. Imiquimod thereby promotes antigen-presenting cell maturation and secretion of IL-12 and other cytokines, which induce IFN-γ production by naive T cells and result in a Th1-type immune response. CSM, costimulatory molecule; MHC, major histocompatibility complex; TCR, T-cell receptor.

Molluscum Contagiosum

Molluscum contagiosum, a cutaneous infection by a virus in the Poxviridae family, has been successfully treated with imiquimod 5% cream. Molluscum contagiosum tends to occur in young children, sexually active adults, and HIV-infected patients (up to 20% of the latter group). Open-label trials and some case reports have suggested that imiquimod might be effective in the treatment of molluscum contagiosum. One double-blind, placebo-controlled trial involving 23 children found a significant decrease in the number of molluscum lesions within 12 weeks of treatment with imiquimod applied three times per week compared to placebo[41]. In a randomized, observer-blinded study, treatment of molluscum contagiosum in children with imiquimod 5% cream five days per week had similar efficacy but less pain and a better cosmetic outcome than cryotherapy weekly. As with warts, sequential application of a keratolytic and imiquimod may lead to additional benefit.

Keloids

A pilot study was undertaken to evaluate the recurrence rate of keloids following surgical excision and subsequent topical application of imiquimod 5% cream[42]. Thirteen keloids (12 earlobe, 1 mid-back) in 12 patients were surgically excised and closed primarily. Nightly application of imiquimod 5% cream directly to the suture line and to the surrounding area was initiated on the day of surgery and continued for a total of 8 weeks. None of the 11 keloids recurred in the 10 patients who completed both the treatment period and at least 6 months of postoperative follow-up[42]. However, subsequent studies have had mixed results, with most failing to demonstrate benefit of imiquimod in preventing recurrence following surgical excision of keloids[43,44].

Basal Cell Carcinoma[45]

Imiquimod is FDA-approved for the treatment of superficial BCCs. Studies of both superficial and nodular BCCs have been performed using imiquimod 5% cream. Application 5–7 days per week for 6–12 weeks results in clearance rates (clinical and histologic) of roughly 70–75%. Although highly statistically significant compared to placebo, these rates are substantially lower than those for destructive and surgical methods. There are also anecdotal reports of successful use of imiquimod to treat BCCs in the setting of nevoid BCC syndrome[46].

Actinic Keratoses

Imiquimod is also FDA-approved for treatment of actinic keratoses (AKs) on the face and scalp. The results of a meta-analysis showed that application of imiquimod 5% cream three times per week for 12–16 weeks resulted in complete clearance of AKs in 50% of patients, compared to 5% for placebo[47]. In a more recent study, treatment with imiquimod 3.75% cream daily for two 2-week cycles (separated by a 2-week interval without treatment) led to complete clearance of AKs on the face and scalp in 35% of patients, compared to 6% for placebo[48]. An inflammatory reaction is often seen during therapy, especially in skin with substantial photodamage (Fig. 128.4). Various other treatment schedules have been suggested, but their efficacy has not been demonstrated with the same rigor as the "labeled" regimens. Treatment of AKs on the dorsal aspect of the hands and forearms with imiquimod appears to be less effective and to result in more inflammation[49].

Bowen's Disease (Cutaneous SCC *in situ*)

Imiquimod has been studied in a double-blind, placebo-controlled trial in patients with Bowen's disease[50]. This relatively small study demonstrated a highly significant level of efficacy compared to placebo (73% vs 0%). Follow-up periods averaging 9 months failed to demonstrate any recurrence among the complete responders. Successful use of imiquimod to treat Bowen's disease in solid organ transplant recipients and SCC *in situ* in the anogenital area (including lesions in HIV-infected patients) has also been described in case reports[51,52].

Other Dermatologic Diseases[53,54]

Imiquimod 5% cream has been reported in non-controlled case reports and series to be effective in the treatment of cutaneous T-cell lymphoma[55], extramammary Paget's disease[56], lentigo maligna[57], cutaneous melanoma metastases[58] and cutaneous leishmaniasis[59]. However, caution should be exercised when utilizing imiquimod for these

Fig. 128.4 Reaction to topical imiquimod. A Inflammation and erosions developed after application of imiquimod to an actinic keratosis and actinically damaged skin. **B** Following discontinuation of imiquimod, the inflammation subsided and the actinic keratosis had cleared. Note the residual hypopigmentation.

disorders, because in many instances failures have also been reported, including non-response of lentigo maligna melanoma[60,60a].

DOSAGES

Imiquimod 5% cream is approved in the US for the treatment of external genital and perianal warts, actinic keratoses on the face and scalp, and superficial BCCs. The recommended regimen is application three times weekly for up to 16 weeks for wart therapy, twice weekly for up to 16 weeks for actinic keratoses, and up to five times per week for up to 6 weeks for BCCs. Imiquimod 3.75% cream is approved for daily use for external genital/perianal warts (for up to 8 weeks) and actinic keratoses on the face or scalp (in two 2-week treatment cycles as described above). The frequency of application for "off-label" indications varies, and the optimal frequency and duration of therapy are still being determined in most instances.

CONTRAINDICATIONS

None are known.

MAJOR SIDE EFFECTS

The most common adverse reactions to imiquimod cream are restricted to the site of application and include erythema (Fig. 128.5; see also Fig. 128.4A), edema, scaling and ulceration. These reactions tend to be more intense and frequent in patients with actinic keratoses and BCC, and reactions with histologic findings mimicking those of lupus erythematosus have been described[60b]. Development of erosive pustular dermatosis of the scalp has been associated with the use of imiquimod for actinic keratoses of the scalp[61]. Possible systemic adverse effects include flu-like symptoms (e.g. fatigue, fever, headache, diarrhea and myalgias), which occur in approximately 1–2% of patients. Thus far, there are no reports of systemic immune alteration, an important consideration when treating patients with solid organ transplants who are on immunosuppressive therapies.

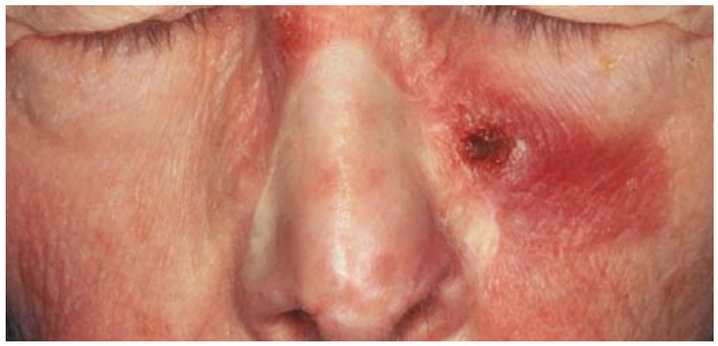


Fig. 128.5 Inflammation at the site of application of imiquimod to an amelanotic lentigo maligna. The patient had residual disease despite multiple surgical procedures including skin graft placement. The inflammation did not occur until the tenth month of application. Three years later, the lesion recurred, but only within the graft. *Courtesy, Jean L Bolognia, MD.*

INTERACTIONS

There are no known drug interactions with imiquimod cream.

USE IN PREGNANCY

Imiquimod cream is classified as pregnancy category C. It is not known whether topically applied imiquimod cream is excreted in breast milk.

GRANULOCYTE–MACROPHAGE AND GRANULOCYTE COLONY-STIMULATING FACTORS (GM-CSF AND G-CSF)

The indications and side effects of granulocyte–macrophage and granulocyte colony-stimulating factors (GM-CSF and G-CSF) are outlined in Table 128.4.

TOPICAL CALCINEURIN INHIBITORS

Key features

- Topical calcineurin inhibitors are anti-inflammatory agents that allow treatment of inflammatory dermatoses without the side effects of topical corticosteroids
- Topical tacrolimus and pimecrolimus are approved for the treatment of "moderate to severe" and "mild to moderate" atopic dermatitis, respectively; they are also effective in treating a number of other corticosteroid-responsive dermatoses

INTRODUCTION

Topical corticosteroids have been the mainstay of therapy for eczematous dermatoses and other inflammatory disorders since their introduction 60 years ago. Unfortunately, these agents may result in local side effects such as cutaneous atrophy, telangiectasias, striae, perioral

GRANULOCYTE–MACROPHAGE AND GRANULOCYTE COLONY-STIMULATING FACTORS (GM-CSF & G-CSF)
PROPERTIES
These glycoproteins regulate the survival, proliferation, differentiation and functional activation of hematopoietic cells
INDICATIONS
• Treatment of neutropenia in settings of myelosuppressive chemotherapy and hematopoietic stem cell transplantation • Other forms of neutropenia (e.g. AIDS-related, associated with dyskeratosis congenita) • Mobilization of peripheral blood progenitor cells • In dermatology, both have been studied as promoters of wound healing, and GM-CSF has been investigated as a component of melanoma therapy
SIDE EFFECTS
GM-CSF • ***Systemic:*** fever, myalgias, bone pain; occasionally flares of autoimmune disease • *Cutaneous:* morbilliform eruption (within 24–48 hours of administration; mixed infiltrate with granulocytes/macrophages); pustular or urticarial injection site reactions (Fig. 128.6); Sweet's syndrome, small vessel vasculitis, urticarial plaques with tense bullae, epidermolysis bullosa acquisita
G-CSF • ***Systemic:*** bone pain (transient, mild "dull ache"; 20% of recipients); occasionally, elevated serum uric acid, LDH or alkaline phosphatase • *Cutaneous:* Sweet's syndrome (within 1–2 weeks of administration); injection site reactions, pyoderma gangrenosum, small vessel vasculitis, folliculitis; histologically, the infiltrate is composed of neutrophils, eosinophils and large histiocytes with cytologic atypia and many mitotic figures
INTERACTIONS
Additive effects with other drugs that cause neutrophilia, e.g. corticosteroids and lithium
PREGNANCY AND LACTATION
Category C; unknown if excreted in breast milk

Table 128.4 Granulocyte–macrophage and granulocyte colony stimulating factors (GM-CSF & G-CSF). LDH, lactate dehydrogenase.

Fig. 128.6 Urticarial plaque at the site of GM-CSF injection.

dermatitis (when used on the face), and cataracts or glaucoma (when used around the eyes). Systemic absorption can also occur.

Tacrolimus ointment (0.1% and 0.03%) and pimecrolimus cream (1%) are approved for the treatment of atopic dermatitis, and they have been used for other eczematous and "steroid-responsive" dermatoses.

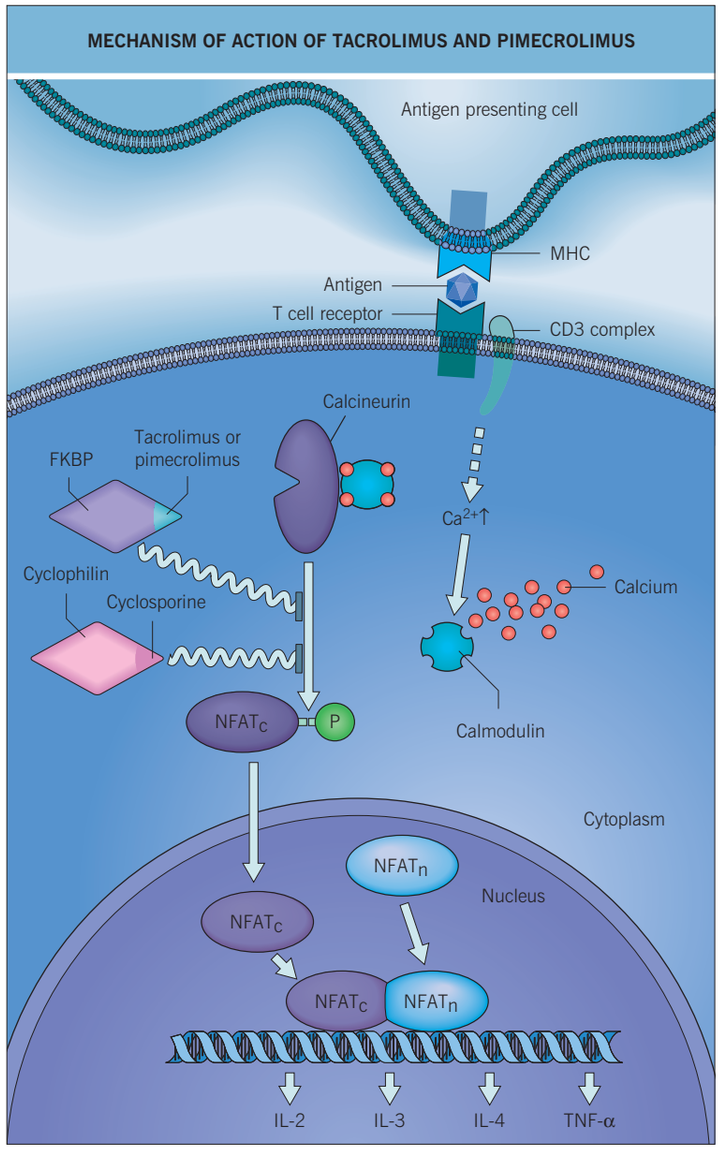


Fig. 128.7 Mechanism of action of tacrolimus and pimecrolimus. FKBP, FK506-binding protein. NFAT, nuclear factor of activated T cells.
From Nghiem P, Pearson G, Langley RG. Tacrolimus and pimecrolimus: from clever prokaryotes to inhibiting calcineurin and treating atopic dermatitis. J Am Acad Dermatol. 2002;46:228–41.

MECHANISM OF ACTION

Tacrolimus and pimecrolimus are inhibitors of the phosphatase calcineurin[62]. T-lymphocyte activation begins when costimulatory ligands on APCs interact with T-cell receptors. This increases the levels of free calcium within the cell; the calcium binds to calmodulin, which in turn activates calcineurin (Fig. 128.7). Calcineurin dephosphorylates the cytoplasmic subunit of the nuclear factor of activated T cells (NFAT). The dephosphorylated subunit is then able to translocate to the nucleus, where it forms a complex that assists in transcription of numerous cytokines. Tacrolimus and pimecrolimus bind to the FK506-binding protein, forming complexes that inhibit calcineurin, thus preventing the dephosphorylation activity of this important phosphatase and blocking cytokine-driven inflammation.

INDICATIONS

Tacrolimus ointment 0.1% and 0.03% are indicated for the treatment of "moderate to severe" atopic dermatitis in adults and in persons ≥2 years of age, respectively. Pimecrolimus cream is indicated for the treatment of "mild to moderate" atopic dermatitis in individuals ≥2 years

of age. There are numerous anecdotal reports and case series describing the use of these agents to treat other inflammatory dermatoses, including eczematous dermatitis of the eyelids, intertriginous sites and hands as well as lichen planus (oral and genital), psoriasis (facial and intertriginous), seborrheic dermatitis, vitiligo (especially facial), pyoderma gangrenosum, perioral dermatitis, granulomatous rosacea, cutaneous Crohn's disease, cutaneous lesions of dermatomyositis, cutaneous lupus erythematosus, lichen sclerosus and chronic graft-versus-host disease (GVHD)[63].

DOSAGES

Topical tacrolimus is commercially available in 0.1% and 0.03% concentrations. The 0.1% formulation is somewhat more effective than the 0.03% formulation, but only the 0.03% formulation is FDA-approved for use in children. Pimecrolimus cream is available in a 1% concentration.

CONTRAINDICATIONS

The package inserts recommend that the benefits and risks of tacrolimus ointment and pimecrolimus cream be evaluated when prescribing them in the presence of varicella or active herpes simplex virus infection (including eczema herpeticum). In addition, both labels were revised in 2006 to include warnings stating that the long-term safety has not been established regarding the theoretical potential for future malignancy. However, systematic reviews have failed to find indications of an increased level of risk from the use of these agents in humans[64], and there has been no short-term or intermediate-term (>10 years) evidence of systemic immunosuppression or an increased risk for malignancy in clinical studies or post-marketing surveillance of either medication.

Because tacrolimus and pimecrolimus shorten the time to skin tumor formation in animal photocarcinogenicity studies, the package inserts recommend that patients minimize or avoid natural or artificial sunlight exposure. Due to increased absorption of tacrolimus ointment in patients with Netherton syndrome, its use in this condition is not recommended[65]; pimecrolimus should also be used with caution in Netherton syndrome patients, but there is evidence that absorption of this agent is not as substantially elevated[66]. Systemic absorption (generally at low levels) has also been identified following application of tacrolimus to eroded mucosal surfaces or ulcers[67,68].

MAJOR SIDE EFFECTS

Application site reactions (e.g. burning, stinging, a sensation of warmth) are the most common side effects of tacrolimus ointment and pimecrolimus cream. There are scattered reports of allergic contact dermatitis and a rosacea-like granulomatous reaction on the face due to tacrolimus. Regarding skin infections, *Staphylococcus aureus* colonization is actually reduced in the skin of atopic dermatitis patients treated with tacrolimus ointment.

INTERACTIONS

Formal clinical studies have not been conducted using tacrolimus ointment together with other topical or systemic medications, but anecdotal use of tacrolimus in conjunction with topical corticosteroids suggests that the combination reduces burning and enhances efficacy. Compatibility studies of tacrolimus ointment applied in combination with desoximetasone ointment or clobetasol ointment indicate that both agents remain stable in the setting of concomitant use.

USE IN PREGNANCY

Because there are no adequate studies of topically administered tacrolimus or pimecrolimus in pregnant women, both are rated as category C. Animal studies with systemically administered tacrolimus indicate harmful fetal effects only at doses that are toxic to the mother.

TARGETED IMMUNE MODULATORS

Key features

- Agents that interfere with T-cell activation (e.g. alefacept) can be effective in the treatment of psoriasis
- Agents that block TNF-α (e.g. etanercept, infliximab, adalimumab) can also be effective as treatments for psoriasis, as well as for other dermatoses in which TNF-α signaling has a pathogenic role
- Ustekinumab, an agent that blocks IL-12 and IL-23 signaling (important for the Th17 immune response) by binding to the p40 receptor subunit shared by these cytokines, is approved for the treatment of psoriasis
- IL-1 antagonists (e.g. anakinra), which are used to treat rheumatoid arthritis, also have benefits for a few rare cutaneous diseases
- Rituximab, an agent that blocks CD20 on B cells, is approved for the treatment of B-cell lymphoma and rheumatoid arthritis but is also useful in B-cell-mediated skin diseases
- Multiple other targeted immune modulators are being developed and may have therapeutic applications for dermatologic diseases and/or cutaneous adverse reactions

INTRODUCTION

Advances in molecular technology have allowed the creation of bioengineered molecules that target specific proteins involved in the pathogenesis of immune-mediated disorders, including psoriasis (and psoriatic arthritis), pemphigus and B-cell lymphomas as well as extracutaneous conditions such as Crohn's disease, asthma, juvenile idiopathic arthritis (JIA), rheumatoid arthritis and ankylosing spondylitis. These drugs (referred to as "biologic" agents) work by mechanisms that include altering T-cell activation and differentiation (e.g. affecting the development of Th1 or Th17 cells), blocking cytokines and eliminating pathogenic B cells.

ALEFACEPT

Introduction

Alefacept (Amevive®) is a fusion protein in which the extracellular domain of lymphocyte function-associated antigen (LFA)-3 is connected to the Fc portion of human IgG1[69].

Mechanism of Action

Two signals must be delivered between APCs and T cells for activation to occur (see Fig. 4.9). The first signal occurs when the major histocompatibility complex on an APC (bound to a specific peptide antigen) interacts with the T-cell receptor. The second costimulatory signal can be one of a number of interactions between APCs and T cells, as shown in Figure 128.8A. Alefacept binds to CD2 on T cells, preventing its interaction with LFA-3 on APCs and the resultant T-cell activation (Fig. 128.8B). CD2 is maximally expressed in activated $CD45RO^+$ T cells. In addition to the interaction between the LFA-3 portion of alefacept and CD2 on $CD45RO^+$ T cells, the Fc portion of alefacept binds to receptors on the surface of natural killer cells, which leads to a reduction in the number of $CD45RO^+$ cells in the circulation.

Indications

In 2003, alefacept became the first targeted immune modulator approved by the FDA for the treatment of moderate to severe plaque-type psoriasis. Studies demonstrated that alefacept was significantly more effective than placebo in achieving a 75% reduction in the Psoriasis Area and Severity Index (PASI) score (see Ch. 8). However, only a minority of patients (~10–20%) achieve this level of improvement[70]. Some reports demonstrate greater efficacy with a 16-week rather than 12-week course[71] or additional improvement with successive courses[72].

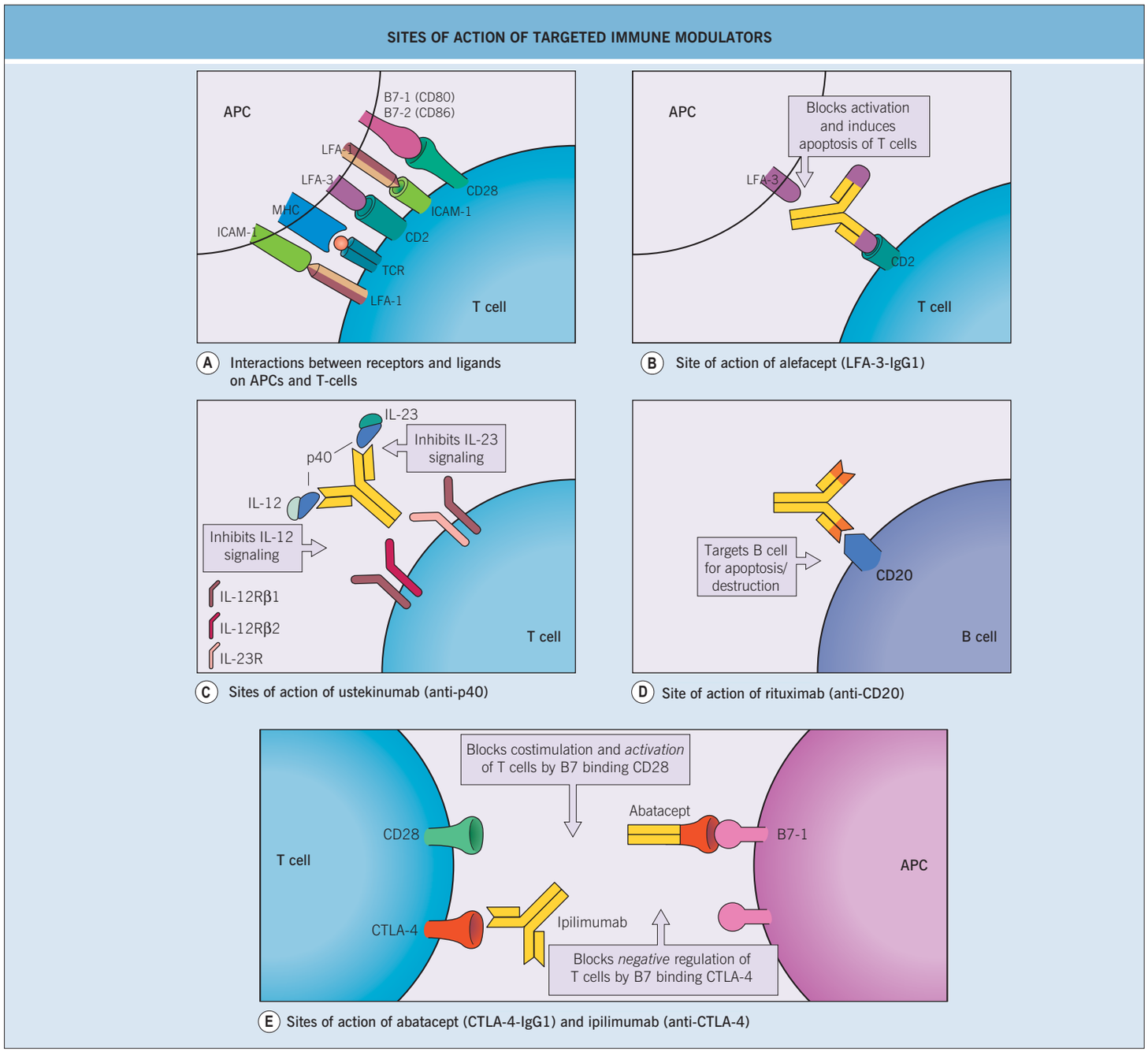


Fig. 128.8 Sites of action of targeted immune modulators. A Activation of T cells requires two signals. The first occurs when the major histocompatibility complex antigen interacts with the T-cell receptor. A second costimulatory signal is required for T-cell activation to occur. **B** Site of action of alefacept. **C** Sites of action of ustekinumab. **D** Site of action of rituximab. **E** Sites of action of abatacept and ipilimumab. APC, antigen-presenting cell; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; IL-12, interleukin-12; IL-12Rβ1, interleukin-12 receptor β1; LFA, lymphocyte function antigen.

Alefacept may also have a role in the treatment of other T-cell-dependent diseases such as lichen planus[73], cutaneous lupus erythematosus[74] and chronic GVHD[75]. Although previous reports suggested that alefacept might have utility in the treatment of alopecia areata[76], a recent randomized placebo-controlled trial failed to demonstrate a significant benefit[77]. In a pilot study, alefacept showed some efficacy in the treatment of pyoderma gangrenosum[78].

Dosages

Although both intravenous and intramuscular forms of alefacept were studied, the intravenous preparation was withdrawn from the market shortly after its approval. The dosing for intramuscular administration is 15 mg weekly. The approved regimens are a 12-week course or two 12-week courses separated by a 12-week period without treatment. Additional courses given to responsive patients can result in similar (or perhaps better) responses with the potential for more prolonged remissions.

Contraindications

Alefacept should not be administered to patients with a CD4 count <250 cells/mcl, HIV infection, other active infections or malignancies.

Major Side Effects

The most frequent side effect is a local injection site reaction. Although the label suggests that malignancy risk is increased (Table 128.5), there have not been excessive numbers of malignancies noted during or following therapy with alefacept. Primary and secondary immune responses are unaffected by treatment with alefacept, as demonstrated by normal responses to new antigens (e.g. bacteriophage phi xl74) and

FDA WARNINGS AND PRECAUTIONS FOR TARGETED IMMUNE MODULATORS WITH DERMATOLOGIC INDICATIONS
ALEFACEPT
• Induces dose-dependent decreases in $CD4^+$ (and $CD8^+$) T-cell counts • Should not be given to HIV-infected patients • Has the potential to increase the risk of infections or reactivation of latent infections • Could potentially increase the risk of malignancies • Hypersensitivity reactions (e.g. urticaria, angioedema) may occur • Hepatotoxicity has been observed (rare)
TUMOR NECROSIS FACTOR-α (TNF-α) INHIBITORS (E.G. ADALIMUMAB, CERTOLIZUMAB, ETANERCEPT, GOLIMUMAB, INFLIXIMAB)
• Increased risk of serious infections, including tuberculosis, bacterial sepsis, systemic fungal infections (e.g. histoplasmosis) and infections due to opportunistic pathogens • Risk of hepatitis B virus reactivation • Malignancies (especially lymphomas) have been reported in patients receiving these agents, including children and adolescents – For *infliximab*, lymphomas are seen more often than in the general population and fatal hepatosplenic T-cell lymphomas have developed in patients with inflammatory bowel disease who were also receiving azathioprine or 6-mercaptopurine – An increased risk of non-melanoma skin cancer and melanoma has been observed in patients with rheumatoid arthritis treated with TNF-α inhibitors • Congestive heart failure (exacerbation or new onset) has been observed • Demyelinating disease (exacerbation or new onset) has been observed • Anaphylaxis or severe allergic reactions may occur (including serum sickness-like reactions to *infliximab*) • Other potential adverse events include autoimmune hepatitis, cytopenias and a lupus-like syndrome
USTEKINUMAB
• Serious infections have been observed; has the potential to increase the risk of infection and reactivation of latent infections – Patients genetically deficient in IL-12/IL-23 have an increased risk of severe infections with mycobacteria and *Salmonella* • Possibly associated with an increased risk of major adverse cardiovascular events • Could potentially increase the risk of malignancies • Hypersensitivity reactions (e.g. angioedema, anaphylaxis) may occur • Reversible posterior leukoencephalopathy syndrome has been reported (one patient to date)
RITUXIMAB
• Severe infusion reactions can occur – 80% of fatal reactions occur with the first infusion • Tumor lysis syndrome can develop in lymphoma patients, especially those with a high tumor burden, and lead to acute renal failure • Progressive multifocal leukoencephalopathy has been reported • Serious infections (bacterial, fungal or viral; up to 1 year after completing therapy) or reactivation of viral infections may occur, especially hepatitis B virus reactivation with fulminant hepatitis • Cardiac arrhythmias and angina can occur and may be life-threatening. • Bowel obstruction and perforation have been described • Stevens–Johnson syndrome/toxic epidermal necrolysis and onset of paraneoplastic pemphigus have been described

Table 128.5 US Food and Drug Administration (FDA) warnings and precautions for targeted immune modulators with dermatologic indications.

recall antigens (e.g. tetanus and diphtheria toxoids). Although a significant decrease in circulating T-cell counts can occur, there does not appear to be an increase in the risk of infections in patients treated with this agent[79]. Recommended laboratory tests are outlined in Table 128.6.

Interactions

Alefacept has been tested in combination with other psoriasis treatments in a limited number of patients. It appears to be safe to administer alefacept together with UV light therapies, retinoids and perhaps methotrexate[80,81]. Adverse interactions with topical treatments are not likely. The combination of alefacept with other targeted immune modulators (either sequentially or simultaneously), which could potentially result in potentiation of immunosuppressive effects, has not been studied.

RECOMMENDED LABORATORY EVALUATION FOR PATIENTS RECEIVING TARGETED IMMUNE MODULATORS FOR PSORIASIS AND OTHER DERMATOLOGIC DISORDERS		
Drug	**Prior to treatment**	**During treatment**
TNF-α inhibitors (adalimumab, etanercept, golimumab, infliximab)	PPD*/interferon-γ release assay† and/or (e.g. if immunosuppression or history of tuberculosis) chest X-ray CBC, CMP Hepatitis B and C virus serologic profiles Consider HIV testing	Annual PPD*/interferon-γ release assay† and/or chest X-ray CBC & CMP every 3–12 months (or as clinically indicated)
Alefacept	$CD4^+$ T-cell count‡ CBC, CMP Hepatitis B and C virus serologic profiles HIV testing Consider PPD*/interferon-γ release assay† and/or (e.g. if immunosuppression or history of tuberculosis) chest X-ray	$CD4^+$ T-cell count every other week: • If <250 cells/mcl, withhold medication and monitor weekly • Discontinue medication if remains <250 cells/mcl for 1 month CBC & CMP every 3–12 months (or as clinically indicated) Consider annual PPD*/interferon-γ release assay† and/or chest X-ray
Ustekinumab	PPD*/interferon-γ release assay† and/or (e.g. if immunosuppression or history of tuberculosis) chest X-ray CBC, CMP Hepatitis B and C virus serologic profiles Consider HIV testing	Annual PPD*/interferon-γ release assay† and/or chest X-ray CBC & CMP every 3–12 months (or as clinically indicated)

*≥5 mm of induration should be considered as positive.
†e.g. QuantiFERON® TB Gold or T-SPOT®.TB.
‡Initial or subsequent courses of treatment should only be started if the $CD4^+$ T-cell count is within the normal range (i.e. >500 cells/mcl).

Table 128.6 Recommended laboratory evaluation for patients receiving targeted immune modulators for psoriasis and other dermatologic disorders. A complete medical history and physical examination should also be performed, with particular attention to history/risk/symptoms/signs of tuberculosis, other chronic infections, malignancy, neurologic disorders, and cardiovascular disease (especially congestive heart failure in patients receiving TNF-α inhibitors and atherosclerosis in patients receiving ustekinumab). CBC, complete blood count with differential, CMP, comprehensive metabolic panel (includes liver function tests); PPD, purified protein derivative skin test; TNF-α, tumor necrosis factor-α.

Use in Pregnancy

Alefacept is classified as pregnancy category B. Its use in pregnancy or during lactation has not been studied.

EFALIZUMAB

Efalizumab (Raptiva®) is a humanized monoclonal antibody that binds to CD11a on T cells[82–85] (Table 128.7). Although it was approved by the FDA in 2003 for the treatment of moderate to severe plaque-type psoriasis, efalizumab was voluntarily withdrawn from the market by its manufacturer in 2009 because of an increasing number of reports of progressive multifocal leukoencephalopathy in patients receiving long-term therapy[86]. We have included a brief discussion of this agent for historical purposes.

CD11a is a component of LFA-1 on the surface of T cells. LFA-1 interacts with intercellular adhesion molecule-1 (ICAM-1) that is located on: (1) *APCs*, delivering a costimulatory signal for T-cell activation (see Fig. 128.8A); and (2) *endothelial cells*, allowing T-cell migration into the skin. As a result, efalizumab can block both the activation and migration of T cells.

Approximately 25–40% of psoriasis patients treated with efalizumab achieved a 75% improvement in their PASI score. In some patients,

NOMENCLATURE FOR MONOCLONAL ANTIBODIES AND FUSION PROTEINS						
Prefix	**Sub-stem A: *target* system [previous nomenclature system]**		**Sub-stem B: *source* system**		**Suffix**	
Variable "Peg-" can be used if pegylated (or can add pegol as a second word)	-anibi- -b(a)- [-ba(c)-] -f(u)- [-fung-] -k(i)- [-ki(n)-] -l(i)- [-li(m)-] -n(e)- [-ne(u)(r)-] -tox(a)- -t(u)- -v(i)-	Angiogenesis Bacterial Fungal Interleukin Immunomodulating Nervous system Toxin* Tumor Viral	-a- -e- -i- -o- -u- -xi- -zu-	Rat Hamster Primate Mouse Human Chimeric† Humanized‡	-mab -cept -nib	Immunoglobulin variable domain Receptor (takes the place of a variable domain) Tyrosine kinase inhibitor

*If conjugated to (rather than directed at) a toxin, the suffix –tox can be used in a second word.
†Contains contiguous foreign-derived amino acids comprising the entire variable region (both heavy and light chains), linked to a constant region of human origin.
‡Has segments of foreign-derived amino acids interspersed with human-derived amino acids in the variable region, linked to a constant region of human origin.

Table 128.7 Nomenclature for monoclonal antibodies and fusion proteins. For example, ada-lim-u-mab, inf-li-xi-mab and certo-li-zu-mab pegol are immunomodulating immunoglobulins that are human, chimeric and humanized, respectively.

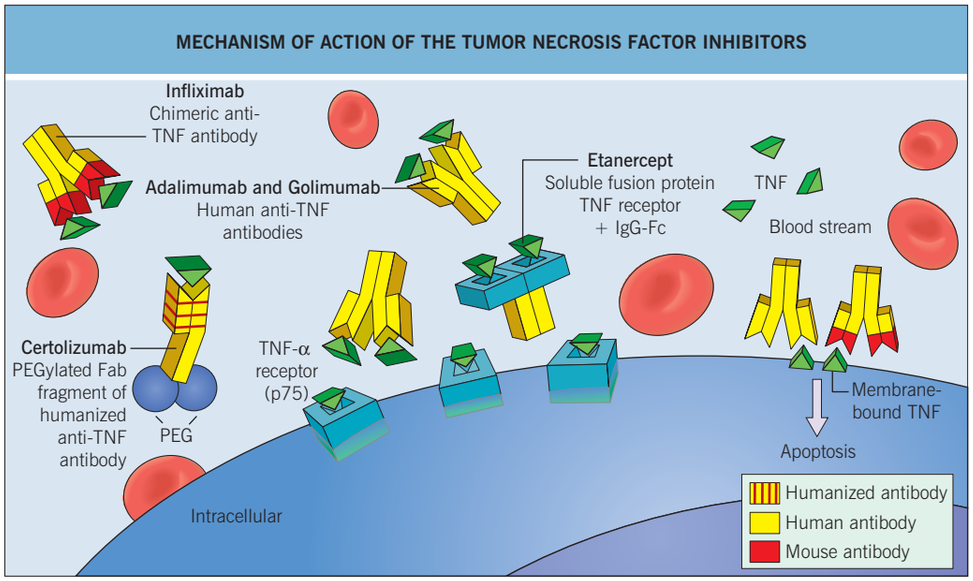


Fig. 128.9 Mechanism of action of the tumor necrosis factor (TNF) inhibitors.

tapering or cessation of therapy was associated with an acute "rebound" flare of psoriasis, which was pustular or intertriginous in a subset of these individuals. Psoriatic arthritis occasionally appeared or worsened during treatment, and other adverse effects included flu-like symptoms, thrombocytopenia and hemolytic anemia. In addition to psoriasis, there were reports of successful efalizumab therapy of several other skin conditions, including generalized granuloma annulare, cutaneous lupus erythematosus, cutaneous dermatomyositis, atopic dermatitis and alopecia areata[85,87].

TNF-α INHIBITORS – GENERAL INFORMATION

To date, five TNF-α inhibitors have been approved by the FDA: etanercept (Enbrel®), infliximab (Remicade®), adalimumab (Humira®), golimumab (Simponi®) and certolizumab pegol (Cimzia®). The mechanism of action and major side effects of these agents as well as contraindications to their use are discussed in this section, and information specific to the individual drugs (e.g. indications, dosages, interactions and pregnancy categories) is presented below.

Mechanism of Action

Four TNF-α inhibitors are monoclonal antibodies (infliximab, adalimumab, golimumab, certolizumab pegol), and one (etanercept) is a dimeric fusion protein composed of the extracellular portions of two p75 TNF-α receptors linked to the Fc portion of IgG1 (Fig. 128.9). Although all four monoclonal antibodies target human TNF-α, infliximab is chimeric (human–mouse) IgG1, adalimumab and golimumab are "fully" human recombinant IgG1, and certolizumab pegol is a humanized pegylated Fab fragment (see Table 128.7).

All of the TNF-α inhibitors can bind to soluble TNF-α and block its ability to activate TNF-α receptors (see Fig. 128.9). By interacting with membrane-bound TNF-α, the IgG1 monoclonal antibodies can also activate complement-dependent cytotoxicity and induce cellular apoptosis[88]. This capacity to destroy TNF-α-producing cells may explain the greater efficacy of these monoclonal antibodies (compared to etanercept) in the treatment of granulomatous conditions as well as the higher risk of infections associated with their use. In addition to the anti-inflammatory effects of TNF-α inhibitors, blocking TNF signaling may have an impact on the neuroendocrine system[89].

Contraindications

Each TNF-α inhibitor is contraindicated in patients with known hypersensitivity to that particular medication, and infliximab is contraindicated in those with an allergy to murine proteins. These agents should be avoided in patients with a significant active infection, malignancy, congestive heart failure (especially if unstable) or multiple sclerosis[90,91].

Major Side Effects (see Table 128.5)

Infections

Disseminated and/or opportunistic infections such as histoplasmosis, coccidioidomycosis, listeriosis and *Pneumocystis jiroveci* (*carinii*) pneumonia may occur in patients treated with TNF-α inhibitors[92]. An

Fig. 128.10 Atypical mycobacterial infection complicating adalimumab therapy. This patient was being treated for Crohn's disease.

increased risk of developing symptomatic mycobacterial infections (Fig. 128.10), including reactivation of latent tuberculosis, has also been observed in patients treated with these agents. However, most of the studies evaluating the risk of infection associated with use of TNF-α inhibitors have been in patients with rheumatoid arthritis or inflammatory bowel disease, who were often concomitantly receiving additional immunosuppressive agents. A recent meta-analysis of 20 randomized controlled trials (total n=6810) of TNF-α inhibitor therapy for psoriasis or psoriatic arthritis (over periods of 12–30 weeks) found no association between the use of these agents and the risk of infection (overall or serious) when adjusted for different follow-up times in treatment and control groups[93].

Recommended monitoring for dermatologic patients receiving TNF-α inhibitors is outlined in Table 128.6. A purified protein derivative (PPD) skin test, IFN-γ release assay (e.g. QuantiFERON® TB Gold, T-SPOT®.TB) and/or (e.g. if immunosuppression or history of tuberculosis) chest X-ray is required at baseline and (typically) repeated annually during therapy. Patients with untreated latent tuberculosis should receive antituberculous therapy (for at least 1–2 months; preferably a full 9-month course) prior to beginning treatment with a TNF-α inhibitor. Reactivation of hepatitis B virus has also been observed in patients who are chronic hepatitis B carriers (i.e. hepatitis B surface antigen positive) while receiving a TNF-α inhibitor, so patients should be evaluated for hepatitis B virus infection prior to therapy. TNF-α inhibitors do not appear to have an adverse effect on viral load or hepatitis activity in psoriasis patients with chronic hepatitis C virus infection[94].

Risk of malignancy

The potential of TNF-α inhibitors to increase the risk of malignancy is a controversial issue and may be dependent upon the disease that is being treated. TNF-α inhibitor therapy in patients with rheumatoid arthritis has been associated with an approximately threefold increase in the risk of lymphoma and malignancy in general[95,96], but this patient group is known to have a heightened susceptibility to lymphoma and often receives additional immunosuppressive agents. Most studies have not demonstrated an increase in the risk of other internal malignancies in patients treated with TNF-α inhibitors[97]. However, in one study there appeared to be an increased risk of solid malignancies associated with etanercept therapy for Wegener's granulomatosis[98]. In addition, non-melanoma skin cancers and melanoma may be more frequent in patients with rheumatoid arthritis who are treated with TNF-α inhibitors than those who do not receive these agents[98a]. A recent meta-analysis of 20 randomized controlled trials (total n=6810) of TNF-α inhibitor therapy for psoriasis or psoriatic arthritis (over periods of 12–30 weeks) found no significant association between the use of these agents and the development of malignancy in this patient population[93].

Fig. 128.11 Excellent clinical response to etanercept. Subacute cutaneous lupus erythematosus, before (**A**) and after (**B**) administration of etanercept.

Adolescents and young adults with inflammatory bowel disease who receive infliximab and concomitant azathioprine or 6-mercaptopurine appear to have an increased risk of a rare, aggressive hepatosplenic T-cell lymphoma[99]. In a recent analysis of 48 malignancies in children and adolescents treated with TNF-α inhibitors that were reported to the FDA[100], it was noted that half were lymphomas, almost two-thirds were in patients taking infliximab, and 88% of the patients were concomitantly receiving another immunosuppressive agent. Although the incidence of malignancy was higher than the background rate in the general pediatric population, the potential role of other medications as well as the underlying disorders (primarily inflammatory bowel disease and JIA) precluded establishing a causal relationship with TNF-α inhibitor therapy.

Autoimmunity

Treatment with TNF-α inhibitors is associated with an increased likelihood of developing antinuclear and anti-dsDNA antibodies. Signs and symptoms of systemic lupus erythematosus (SLE) occasionally arise in patients receiving TNF-α inhibitors, but in general this lupus-like condition resolves upon cessation of treatment[101–103]. Conversely, there are several small case series in which the use of etanercept was associated with marked improvement in subacute cutaneous lupus erythematosus[104,105] (Fig. 128.11). It is not necessary to evaluate patients for autoantibodies before or during therapy with TNF-α inhibitors. However, the development of antinuclear antibodies may be linked to loss of TNF-α inhibitor efficacy[106].

CUTANEOUS SIDE EFFECTS OF TARGETED IMMUNE MODULATORS
INJECTABLE AGENTS
• Injection site reactions (e.g. erythema/edema, occasionally small vessel vasculitis; "recall" reactions at previous sites)
TUMOR NECROSIS FACTOR-α INHIBITORS
• New-onset psoriasis, especially palmoplantar pustulosis • Interstitial granulomatous dermatitis and other granulomatous eruptions • Cutaneous small vessel vasculitis • Eczematous eruptions • Lichenoid dermatitis
EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITORS
• Papulopustular (acneiform) eruption (see Ch. 36) • Paronychia, ingrown nails, acral desquamation • Xerosis, fissures • Telangiectasias, hyperpigmentation • Increased severity of radiation dermatitis • Trichomegaly, facial hair growth, frontal alopecia, curly brittle hair
OTHER KINASE INHIBITORS AND BLOCKING ANTIBODIES – SEE TABLE 21.14
• "Hand–foot reaction" (often eventuating in hyperkeratosis) > intertriginous erythema/erosions (variant of toxic erythema of chemotherapy) • Facial swelling (especially periorbital) and erythema • Exanthematous eruptions (truncal or generalized) • "Erythema marginatum hemorrhagicum", erythema multiforme-like eruptions, small vessel vasculitis (may have an annular configuration) • Xerosis, spiny follicular keratoses • Rapid development of verrucous papules, actinic keratoses, keratoacanthomas or squamous cell carcinomas; eruptive melanocytic nevi • Ultraviolet recall dermatitis, inflammation of actinic keratoses • Leukoderma, yellowish discoloration of the skin • Subungual splinter hemorrhages • Hair de-/repigmentation, alopecia, curly brittle hair, scalp dysesthesia

Table 128.8 Cutaneous side effects of targeted immune modulators. Allergic reactions manifesting with urticaria and angioedema can also occur with most agents.

Fig. 128.12 Psoriasiform reactions to tumor necrosis factor-α inhibitors. **A** Palmoplantar pustulosis that developed as a complication of infliximab. **B** Eruption of plaque-type psoriasis in a patient receiving infliximab therapy. The patient had received infliximab for GVHD of the gastrointestinal tract.

Demyelinating diseases

Although etanercept was originally used as a therapy for multiple sclerosis, several patients treated with etanercept and other TNF-α inhibitors have developed multiple sclerosis[90]. Others with multiple sclerosis have had exacerbations of their disease when treated with these agents. In some patients, the symptoms of multiple sclerosis have abated despite continued therapy. It seems reasonable to avoid using TNF-α inhibitors in patients with a history of multiple sclerosis or other demyelinating diseases.

Congestive heart failure

There have been reports of congestive heart failure worsening or developing in patients receiving TNF-α inhibitors. As a result, it is recommended that therapy with TNF-α inhibitors be avoided in patients with unstable cardiac disease.

Cutaneous reactions

A variety of skin findings have been described as adverse reactions to TNF-α inhibitors (Table 128.8). There are reports of new-onset psoriasis in patients with no previous history of psoriasis, often manifesting as palmoplantar pustulosis (Fig. 128.12)[107]. The exact mechanism for this reaction is not known, and the possibility exists that a subset of such patients with presumed rheumatoid arthritis actually had psoriatic arthritis. Cutaneous small vessel vasculitis can complicate therapy with TNF-α inhibitors[108], but a large portion of these patients have rheumatoid arthritis, a disease known to be associated with vasculitis. In addition, interstitial granulomatous dermatitis (IGD) has been reported in patients receiving TNF-α inhibitors (sometimes in individuals with rheumatoid arthritis, which can itself be associated with IGD)[109]. Other cutaneous reactions that have been described in patients taking TNF-α inhibitors include eczematous eruptions, lichenoid dermatitis, and other granulomatous conditions[110].

VACCINES THAT CONTAIN LIVE ATTENUATED VIRUSES OR BACTERIA
Bacillus Calmette-Guérin (BCG)
Herpes zoster
Influenza (including H1N1), *intranasal form*
Measles, mumps, and rubella
Rotavirus
Polio, *oral form*
Typhoid, *oral form*
Vaccinia (smallpox vaccine)
Varicella
Yellow fever

Table 128.9 Vaccines that contain live attenuated viruses or bacteria.

Vaccination

Live vaccines are contraindicated in patients receiving TNF-α inhibitors (Table 128.9). The effectiveness of vaccines in patients receiving these agents is unknown, but an immune response to influenza and pneumococcal vaccines has been documented[111]. It is recommended that patients (especially children) be brought up-to-date with all immunizations prior to initiating treatment with TNF-α inhibitors.

ETANERCEPT

Introduction

Etanercept (Enbrel®) is a fusion protein consisting of the extracellular domain of the TNF-α receptor fused with the Fc portion of human IgG1[112].

Indications

Etanercept has been approved for the treatment of moderate to severe plaque-type psoriasis in adults since 2004. Depending on the regimen (see below), approximately 30–60% of patients achieve a 75% improvement in their PASI score; significant decreases in fatigue and depression have also been described[70,113]. The efficacy and safety of etanercept for pediatric psoriasis has been demonstrated in a randomized controlled trial including more than 200 children (4–17 years of age)[114]; however, it has not been FDA-approved for treatment of psoriasis in this age group. Other FDA-approved indications for etanercept include rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and JIA (the latter in children 2 to 17 years of age).

In addition, etanercept has been used to treat a variety of mucocutaneous disorders, including dermatomyositis, neutrophilic dermatoses, cutaneous lupus erythematosus, autoimmune bullous diseases, lichen planus, pyoderma gangrenosum, hidradenitis suppurativa, multicentric reticulohistiocytosis, relapsing polychondritis and GVHD[104,115,116]. Although successful treatment of sarcoidosis has been described in case reports and small series, etanercept therapy failed to improve several systemic manifestations of sarcoidosis in randomized controlled trials[117]. Presumably, all of the disorders for which etanercept might be effective are characterized by elevated levels of TNF-α (in the circulation, tissue or both).

Dosages

For most of its indications, etanercept was initially approved to be administered subcutaneously at a dose of 25 mg twice weekly in adults. Shortly after its approval for psoriatic arthritis, it was demonstrated that 50 mg weekly gave equivalent results to 25 mg twice weekly. The approved dose for moderate to severe plaque psoriasis is 50 mg twice weekly for the first 3 months, followed by 50 mg weekly. Some physicians choose to initiate therapy at a dose of 50 mg weekly and only escalate the dose if the patient fails to respond after 6 to 12 months. Etanercept is available in 25 and 50 mg prefilled syringes, 50 mg autoinjectors, and 25 mg multiple-use vials. The recommended dose for pediatric psoriasis is 0.8 mg/kg (maximum 50 mg) weekly.

Specific Side Effects

Side effects shared with other TNF-α inhibitors (including the potential increased risk of malignancy associated with these agents) are discussed above and summarized in Tables 128.5 and 128.8. Injection site reactions are the most common side effect of etanercept (Fig. 128.13), but in general they are mild to moderate and diminish in frequency after the first month of treatment. Erythema, pruritus, pain and swelling have been described, and "recall" reactions at sites of previous injections have been reported.

Fig. 128.13 Etanercept injection site reaction. Similar reactions occur with nearly all subcutaneously injected biologic therapies.

Interactions

The concomitant use of etanercept and methotrexate is approved for the treatment of rheumatoid arthritis and psoriatic arthritis. Due to the potential for increased immunosuppression, combination of etanercept with other targeted immune modulators should be avoided until well-designed studies demonstrate efficacy and safety. For example, a study of anakinra plus etanercept for patients with rheumatoid arthritis found no increase in efficacy but a substantial increase in the frequency of infection[118]. The use of etanercept together with narrowband UVB without an increase in adverse events (and with added therapeutic benefit) has been documented[119,120].

Use in Pregnancy

Etanercept is pregnancy category B, with no evidence of harm to the fetus in animal studies. Studies in pregnant women have not been conducted. It has been suggested that etanercept and other TNF-α inhibitors be avoided after the first trimester[121]. It is not known whether etanercept is secreted in breast milk; however, in general, this drug is not absorbed via an oral route.

INFLIXIMAB

Introduction

Infliximab (Remicade®) is a chimeric (human–mouse) monoclonal IgG_1 antibody, and its target is human TNF-α[122].

Indications

Infliximab is approved for the treatment of adults with chronic severe plaque-type psoriasis. Compared with the other TNF-α antagonists, its onset of action tends to be faster and a higher proportion of patients (~75–85%) achieve a 75% reduction in the PASI score[70]. Infliximab is also FDA-approved for the treatment of adults with psoriatic arthritis, Crohn's disease (including associated fistulas), ulcerative colitis, rheumatoid arthritis and ankylosing spondylitis, as well as for the treatment of Crohn's disease in children ≥6 years of age. Infliximab appears to be useful for pyoderma gangrenosum, whether or not it is associated with inflammatory bowel disease[123]. It has been effective as a treatment for sarcoidosis, granulomatous cheilitis, Behçet's disease, various vasculitides, pityriasis rubra pilaris, reactive arthritis (formerly Reiter's disease), subcorneal pustular dermatosis, GVHD, Sjögren's syndrome, multicentric reticulohistiocytosis, and hidradenitis suppurativa[124].

Dosages

In patients with plaque psoriasis, the typical infliximab regimen is 5 mg/kg administered by slow intravenous infusion at 0, 2 and 6 weeks, then every 8 weeks. However, doses ranging from 3 to 10 mg/kg have been used, and the frequency of administration as well as the dose can be adjusted when the response is less than adequate. For Crohn's disease, rheumatoid arthritis and psoriatic arthritis, it is approved for concomitant administration with methotrexate, azathioprine or low-dose prednisone. Loss of efficacy over time may be related to the development of neutralizing anti-chimeric antibodies[125,126] and has been associated with the presence of antinuclear antibodies[106]; the concurrent administration of low-dose weekly methotrexate may help to prevent the formation of anti-chimeric antibodies that lessen the effectiveness of the agent.

Specific Side Effects

Side effects shared with other TNF-α inhibitors are discussed above and summarized in Tables 128.5 and 128.8. Infusion-related reactions are the most commonly reported side effect of infliximab, occurring in 16% of patients. The incidence of severe reactions, including anaphylaxis, is approximately 1%. Symptoms consist of fever, chills, pruritus, urticaria, chest pain, hypotension, hypertension and shortness of breath. Infusion reaction risk has also been linked to the presence of human anti-chimeric antibodies. This risk may be lessened by concomitant use of methotrexate, azathioprine or corticosteroids[125].

Interactions

The concomitant use of infliximab and methotrexate is approved for the treatment of rheumatoid arthritis and psoriatic arthritis. Infliximab should not be administered together with other targeted immune modulators due to the potential for additive immunosuppression; concomitant use with anakinra or abatacept has been associated with the development of severe infections.

Use in Pregnancy

Infliximab is rated pregnancy category B. Its use in pregnancy should probably be avoided until long-term studies demonstrate a lack of adverse effect. It is not known whether infliximab is secreted in breast milk, and its administration to nursing mothers is not recommended.

ADALIMUMAB

Introduction

Adalimumab (Humira®) is a "fully" human recombinant IgG1 monoclonal antibody with specificity for human TNF-α[127].

Indications

Adalimumab is approved for the treatment of moderate to severe plaque-type psoriasis in adults, and approximately 50–80% of patients achieve a 75% improvement in their PASI score[70]. It is also approved for the treatment of psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis and Crohn's disease in adults, and JIA in children ≥4 years of age. There have been reports of successful adalimumab therapy for hidradenitis suppurativa[128], pustular psoriasis[129], sarcoidosis, pyoderma gangrenosum, Behçet's disease, other neutrophilic dermatoses and dermatomyositis.

Dosages

Adalimumab is supplied in a 40 mg prefilled syringe or autoinjector and administered subcutaneously. An initial loading dose of 80 mg is typically given, followed by 40 mg on day 8 and then 40 mg every other week. Weekly doses are occasionally utilized (e.g. for hidradenitis suppurativa). The pediatric dose approved for JIA is 20 mg every other week for children who weigh <30 kg and 40 mg every other week if ≥30 kg. Loss of efficacy of adalimumab over time related to the production of anti-adalimumab antibodies can occur and may be prevented by the concurrent administration of low-dose weekly methotrexate; loss of efficacy has also been associated with the development of antinuclear antibodies[106].

Side Effects

Side effects shared with other TNF-α inhibitors, including risk of infection with mycobacteria (see Fig. 128.10) and fungi, are discussed above and summarized in Tables 128.5 and 128.8.

Interactions

The concomitant use of adalimumab and methotrexate is approved for the treatment of rheumatoid arthritis and JIA. The concomitant administration of other targeted immune modulators with adalimumab may increase the risk of infection and should be avoided.

Use in Pregnancy

Adalimumab is classified as pregnancy category B. Its safety during lactation is unknown.

GOLIMUMAB

Golimumab (Simponi®) is a "fully" human recombinant IgG1 monoclonal antibody with specificity for human TNF-α[127]. It is approved for the treatment of psoriatic arthritis, rheumatoid arthritis and ankylosing spondylitis, and it can be administered along with methotrexate. Golimumab may also be useful in the treatment of other conditions that respond to TNF-α inhibitors. It is supplied in a 50 mg prefilled syringe or autoinjector that is administered subcutaneously monthly.

CERTOLIZUMAB

Certolizumab pegol (Cimzia®) is a pegylated Fab fragment of a humanized monoclonal antibody with specificity for human TNF-α. It is approved for the treatment of rheumatoid arthritis and Crohn's disease. Certolizumab may also be useful in the treatment of other conditions that respond to TNF-α inhibitors. It is supplied in a 200 mg prefilled syringe and administered subcutaneously; 400 mg is given at weeks 0, 2 and 4, followed by 200 mg every 2 weeks or 400 mg monthly for maintenance.

USTEKINUMAB

Introduction

Ustekinumab (Stelera®) is a monoclonal antibody that targets IL-12 and IL-23.

Mechanism of Action

Ustekinumab is a "fully" human IgG1 monoclonal antibody that binds with high affinity and specificity to the p40 subunit that is shared by the heterodimeric IL-12 and IL-23 cytokines (see Fig. 128.8C). IL-12 has a critical role in the development of Th1 cells and NK cell activation, whereas IL-23 is necessary for the generation of Th17 cells (see Fig. 4.10).

Indications

Ustekinumab is approved for the treatment of adults with moderate to severe plaque-type psoriasis, and approximately 65–80% of patients achieve a 75% improvement in their PASI score[130,131].

Dosages

Ustekinumab is administered as a 45 mg (if weight is ≤100 kg) or 90 mg (if weight is >100 kg) subcutaneous injection at weeks 0 and 4, then every 12 weeks.

Contraindications

Ustekinumab is contraindicated in patients with known sensitivity to the drug. It should be avoided in patients with serious active infections or malignancies.

Major Side Effects

There is a theoretical risk of severe and disseminated infections with mycobacteria and *Salmonella* based on the predisposition to these infections that is seen in patients with genetic deficiencies in IL-12/IL-23. A PPD skin test, IFN-γ release assay (e.g. QuantiFERON® TB Gold) and/or (e.g. if immunosuppression or history of tuberculosis) chest X-ray is required at baseline and (typically) repeated annually during therapy (see Table 128.6). Patients with untreated latent tuberculosis should receive antituberculous therapy for at least 1 month prior to beginning treatment.

A possible excess of major adverse cardiovascular events (MACEs; e.g. myocardial infarction, stroke) has been noted in patients who received anti-IL-12/23 therapy in clinical trials, but a recent meta-analysis did not find a significant increase in the risk of MACEs associated with the use of these agents[131a]. The effects of IL-12/23 inhibitors on vascular inflammation and thrombosis (especially early in the course of therapy) remain to be determined, and cardiovascular risk factors should be assessed prior to initiating treatment. Additional potentially severe side effects of ustekinumab are listed in Table 128.5. Injection site reactions can also occur, and retiform purpura progressing to cutaneous necrosis on the lower leg has been reported[131b].

Interactions

Live vaccines should be avoided (see Table 128.9). The response to vaccines may be muted. Other targeted immune modulators should not be administered together with ustekinumab. The concomitant administration of other immunosuppressive agents might increase the risk of infection.

Use in Pregnancy

Ustekinumab is pregnancy category B. Its safety during lactation is unknown.

ANAKINRA

Introduction

Anakinra (Kineret®) is an IL-1 antagonist[132].

Mechanism of Action

Anakinra is a recombinant, non-glycosylated form of the human IL-1 receptor antagonist. The drug binds to IL-1 type 1 receptors and thereby acts as a competitive inhibitor of IL-1, downregulating its inflammatory effects.

Indications

Anakinra is approved for the treatment of rheumatoid arthritis[132]. It is also an effective therapy for the cryopyrin-associated periodic syndrome, which includes neonatal-onset multisystem inflammatory disease (NOMID; also known as chronic infantile neurologic cutaneous articular [CINCA] syndrome), Muckle–Wells syndrome and the familial cold autoinflammatory syndrome[133] (see Table 45.2). This spectrum of autosomal dominant disorders is caused by gain-of-function mutations in the gene that encodes cryopyrin, a protein that functions in an "inflammasome" complex that produces IL-1β (see Ch. 45); additional treatments include rilonacept (a dimeric fusion protein composed of the extracellular portion of the IL-1 receptor and the Fc portion of IgG1) and canakinumab (a human monoclonal antibody against IL-1β). In addition, anakinra has been demonstrated to aid in the control of urticarial lesions associated with Schnitzler's syndrome[134] and the pustular eruptions and bone lesions (e.g. osteomyelitis) of the autosomal recessive *d*eficiency of the *I*L-1 *r*eceptor *a*ntagonist (DIRA).

Dosages

Anakinra is administered at a dose of 100 mg (2 mg/kg in children) daily via a subcutaneous injection.

Contraindications

Anakinra should not be given to patients with active infections, severe renal impairment or hypersensitivity to the drug.

Major Side Effects

Infection, neutropenia and thrombocytopenia are potentially serious reactions that can develop. Monitoring patients with complete blood counts is indicated. Injection site reactions are usually mild and tend to abate with continued therapy. Flu-like symptoms may also occur.

Interactions

Other immunosuppressive agents, particularly TNF-α inhibitors, should be avoided in patients taking anakinra[118]. Live vaccines should also be avoided, and it is unknown whether vaccines have a full effect.

Use in Pregnancy

Anakinra is pregnancy category B. Its safety during lactation is unknown.

RITUXIMAB

Introduction

Rituximab (Rituxan®) is a chimeric monoclonal antibody directed against the CD20 antigen present on the surface of mature B cells[135].

Mechanism of Action

Rituximab binds to CD20 on the surface of mature B cells and causes apoptosis of these cells (see Fig. 128.8D). It targets and selectively depletes $CD20^+$ B cells without affecting stem cells or existing plasma cells. Possible mechanisms of cell lysis include complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity. In patients with pemphigus vulgaris, downregulation of desmoglein-3-specific $CD4^+$ T cells (as well as depletion of B cells and decreased anti-desmoglein-3 antibody levels) has been observed[136]. Radioactive anti-CD20 antibodies (e.g. ibritumomab tiuxetan conjugated to yttrium-90 or indium-111; tositumomab conjugated to iodine-131) have also been approved for the treatment of non-Hodgkin B-cell lymphomas.

Indications

Rituximab is approved for the treatment of non-Hodgkin B-cell lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, Wegener's granulomatosis and microscopic polyangiitis[137]. It has been successfully used to treat cutaneous B-cell lymphoma[138]. In addition to its approved indications, rituximab has efficacy in the treatment of autoimmune bullous dermatoses (including pemphigus vulgaris[139], bullous pemphigoid and para-neoplastic pemphigus), SLE, cutaneous lupus erythematosus[140], chronic GVHD[141] small vessel vasculitis[142] and dermatomyositis[143]. Its use in pemphigus vulgaris has been associated with prolonged responses in some patients.

Dosages

For lymphomas, rituximab 375 mg/m^2 is given intravenously weekly for 4–8 weeks. For rheumatoid arthritis, rituximab is administered in "courses" consisting of a 1000 mg infusion on each of two consecutive weeks, which can be repeated at 16–24-week intervals. Methylprednisolone 100 mg intravenously is typically given 30 minutes prior to each infusion. It is approved for concomitant use with methotrexate in patients with rheumatoid arthritis, and with chemotherapy in patients with B-cell lymphoma. The optimal dosing and frequency for patients with pemphigus vulgaris are not known, but 375 mg/m^2 weekly for 3–4 weeks (sometimes followed by monthly doses) has been utilized[144]. The efficacy of rituximab might be reduced in patients who develop anti-rituximab antibodies[145].

Contraindications

Rituximab is contraindicated in patients allergic to the drug or its components, hepatitis B carriers, and patients with cardiac arrhythmias, angina pectoris, a high tumor burden or active infections.

Major Side Effects

Deaths within 24 hours of rituximab infusion have been reported. These fatalities followed infusion reactions that included hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation and cardiogenic shock. Approximately 80% of the deaths occurred in association with the first infusion. Acute renal failure requiring dialysis (with instances of fatal outcome) has also been reported in the setting of tumor lysis syndrome following treatment with rituximab. Severe mucocutaneous reactions, including Stevens–Johnson syndrome/toxic epidermal necrolysis, have occasionally been noted in patients given rituximab. Rarely patients have had the onset of paraneoplastic pemphigus during treatment, but it is not clear whether this phenomenon is drug-related or disease-related. Progressive multifocal leukoencephalopathy and hepatitis B virus activation (potentially leading to fulminant hepatitis) have been associated with the use of rituximab.

The safety profile of rituximab has been established primarily in patients with lymphoproliferative diseases and includes >730 000 patient exposures over a period of 8 years. In general, the adverse events observed in patients with rheumatoid arthritis were similar to those seen in patients with non-Hodgkin lymphoma. The most common adverse events observed in clinical trials were infusion reactions and infections. No significant change in average immunoglobulin levels was observed in treated patients within clinical trials.

Interactions

Live vaccines are contraindicated and the response to vaccines may be muted. Combination with other targeted immune modulators, particularly natalizumab, may increase the risk of infection. Combination with cisplatin increases the risk of nephrotoxicity.

SOME TARGETED IMMUNE MODULATORS THAT ARE UNDER DEVELOPMENT FOR PSORIASIS				
Name	**Company**	**Delivery mechanism**	**Mechanism of action**	**Phase**
Briakinumab (ABT874)*	Abbott	Injectable	IL-12/IL-23 inhibitor	III
Secukinumab (AIN-457), AMG827, LY2439821	Novartis, Amgen, Lilly	Injectable	IL-17 blockers	II
SCH-900222	Merck	Injectable	IL-23 blocker	II
BT-061	Biotest	Injectable	Regulatory T cell activator	II
Apremilast (CC-10004)	Celgene	Oral	Phosphodiesterase-4 inhibitor	III
Tofacitinib (CP-690,550), ASP015K	Pfizer, Genzyme	Oral	JAK3 inhibitors	III, II
AEB071	Novartis	Oral	Protein kinase C blocker	II
BMS-582949	Bristol-Myers Squibb	Oral	p38 MAP kinase inhibitor	II
*No longer being developed by Abbott.				

Table 128.10 Some targeted immune modulators that are under development for psoriasis. In addition, topical psoriasis therapies that are under development include Janus kinase 1 & 2 (JAK1/2) inhibitors and a pan-selectin inhibitor (bimosiamose). IL, interleukin; JAK, Janus kinase; LFA, lymphocyte function-associated antigen. *Adapted from the National Psoriasis Foundation website (www.psoriasis.org), updated August 2011.*

Use in Pregnancy

Rituximab is pregnancy category C, and it may be unsafe during lactation.

OMALIZUMAB

Introduction

Omalizimab (Xolair®) is a recombinant humanized monoclonal antibody that targets IgE.

Mechanism of Action

Omalizumab is a humanized monoclonal antibody (IgG1) that selectively binds to and decreases serum levels of free human IgE. It also downregulates the number of high-affinity IgE receptors on mast cells, basophils and dendritic cells[146,147]. These two mechanisms limit the release of inflammatory mediators and (via effects on dendritic cells) decrease antigen presentation to T cells.

Indications

Omalizumab is FDA-approved for the treatment of adults and adolescents (ages ≥12 years) with asthma. A recent randomized controlled trial found omalizumab to be effective in the treatment of chronic urticaria[147a], and it may have utility in the treatment of atopic dermatitis[148].

Dosages

Omalizumab is administered as a 150 to 375 mg subcutaneous injection every 2–4 weeks. Doses are determined by the baseline serum total IgE level and body weight.

Contraindications

There are no contraindications other than previous hypersensitivity to omalizumab.

Major Side Effects

The most common serious adverse events seen in clinical trials with omalizumab were anaphylaxis (0.1%; 3 of 3507 patients) and malignancy (0.5% vs 0.2% in placebo patients). Injection site reactions occurred in 12% of patients treated with omalizumab, compared to 9% of those who received placebo.

Interactions

No specific interactions with other medications have been noted.

Use in Pregnancy

Omalizumab is pregnancy category B. It is excreted into the breast milk of monkeys, and caution is advised when administering it to nursing women.

TARGETED IMMUNE MODULATORS UNDER INVESTIGATION

Development of other targeted immune modulators for use in dermatology continues. Table 128.10 is a partial listing of the drugs that are currently under investigation for psoriasis. Additional drugs that are being developed for non-cutaneous inflammatory diseases might be effective for skin disorders or associated with adverse cutaneous effects.

INTRAVENOUS IMMUNE GLOBULIN (IVIg)

Key features

- IVIg is useful for inflammatory disorders, including some cutaneous diseases
- Doses for inflammatory disorders are empiric, but have generally been 2 g/kg/month for chronic diseases, and 3 g/kg total for acute conditions
- There are only a few skin disorders for which there is a high level of evidence indicating effectiveness of IVIg

INTRODUCTION

IVIg is a sterile solution of globulins extracted from pooled plasma donated by 100 000–200 000 individuals per production cycle. Processing results in a product that is predominantly IgG, having eliminated all but trace amounts of IgA and other soluble immunologically active particles. It has a half-life of 3 to 5 weeks.

IVIg is currently used in the treatment of immunodeficiency syndromes, inflammatory disorders and infectious diseases[149]. It is occasionally administered as prophylaxis to susceptible individuals exposed to particular infectious agents (e.g. non-immune, immunocompromised patients exposed to varicella zoster virus). Clinical studies, most of which were uncontrolled, and anecdotal reports suggest that IVIg is useful for some cutaneous conditions (Table 128.11), but randomized clinical trials, barring those for dermatomyositis, are lacking. IVIg offers hope for the treatment of many severe dermatologic conditions, including toxic epidermal necrolysis/Stevens–Johnson syndrome[150], dermatomyositis[151] and chronic autoimmune blistering diseases[152].

MECHANISM OF ACTION

The immunomodulatory effects of IVIg may be exerted through one or more of the following mechanisms: 1) functional blockade of Fc receptors; 2) inhibition of complement-mediated damage; 3) alteration of cytokine and cytokine antagonist profiles; 4) reduction of circulating antibodies via anti-idiotype antibodies; and 5) neutralization of toxins that trigger autoantibody production[149,153]. In toxic epidermal

USES OF IVIg IN DERMATOLOGY			
Indication	**Summary of evidence**	**Dosing**	**Comments**
Dermatomyositis	Benefit established	2 g/kg (over 2 days) Initially given every month, maintenance schedule individualized	Beneficial in patients intolerant of prednisone or immunosuppressives
Kawasaki disease	Benefit established	2 g/kg (over 6–12 hours)	
Toxic epidermal necrolysis	Case series, anecdotal evidence	1 g/kg/day for 3 days	
Pemphigus variants	Case series, anecdotal evidence	2 g/kg (over 2–3 days) Initially given every month, maintenance schedule individualized	Adjunctive or second-line therapy
Bullous pemphigoid	Case series, anecdotal evidence	2 g/kg (over 2–3 days) Initially given every month, maintenance schedule individualized	Adjunctive or second-line therapy
Mucous membrane (cicatricial) pemphigoid	Case series, anecdotal evidence	2–3 g/kg (over 3 days) Initially given every 2–6 weeks, maintenance schedule individualized	Adjunctive or second-line therapy
Epidermolysis bullosa acquisita	Anecdotal evidence	2 g/kg (over 2–3 days) Initially given every month, maintenance schedule individualized	Adjunctive or second-line therapy
Necrotizing fasciitis	Uncertain benefit	2 g/kg (over 6–12 hours); repeat 1–2 g/kg in 2–5 days if disease progresses	Adjunctive for progressive disease
Pyoderma gangrenosum	Uncertain benefit	2 g/kg (over 2 days) Initially given every month, maintenance schedule individualized	May be considered
Atopic dermatitis	Uncertain benefit (inconsistent results in controlled studies)	2 g/kg (over 1–2 days) Monthly	

Table 128.11 Uses of IVIg in dermatology. *Adapted from Mydlarski PR, Mittman N, Shear NH: Intravenous immunoglobulin: use in dermatology. Skin Therapy Lett. 2004;9:1–6.*

SOME PREPARATIONS OF IVIg THAT ARE AVAILABLE IN THE US				
	Gammagard S/D	**Privigen**	**Gamunex**	**Carimune NF**
Manufacturer	Baxter	CSL Behring	Talecris	CSL Behring
Form	Lyophilized	Liquid	Liquid	Lyophilized
Concentration	5% (also 10%)	10%	10%	3–12%
Maximum infusion rate	4.0 ml/kg/h	4.8 ml/kg/h	4.8 ml/kg/h	2.5 ml/kg/h
Time to infuse 70 g	5.3 h	2 h	2 h	6.6 h
pH	6.8	4.8	4.25	6.4–6.8
Osmolarity (mOsm/l)	636	320	260	192–1074
Sugar content	2% glucose	None	None	1.67 g sucrose/g of protein
Sodium content	0.85%	Trace	Trace	<20 mg/g of protein
IgA (mcg/ml)	<2.2	<25	46	720

Table 128.12 Some preparations of IVIg that are available in the US.

necrolysis, IVIg is believed to block Fas (CD95)-mediated keratinocyte death by inhibiting Fas–Fas ligand interactions (see Ch. 20).

INDICATIONS

IVIg is approved for treatment of primary and secondary immunodeficiency diseases. Table 128.11 lists dermatologic disorders for which IVIg represents a therapeutic option.

DOSAGES

At least nine different preparations of IVIg are available in the US[154]. The products differ in their sugar content, sodium content, osmolarity, pH and IgA levels (Table 128.12). The doses recommended vary depending upon the disease state being treated (see Table 128.11).

CONTRAINDICATIONS

Preparations containing IgA are contraindicated in patients with a history of hypersensitivity to IVIg, the presence of anti-IgA antibodies or a profound IgA deficiency (which may be associated with the development of anti-IgA antibodies and a risk of anaphylaxis).

MAJOR SIDE EFFECTS

Major toxicity includes the potential for anaphylaxis, aseptic meningitis, renal failure (particularly with sucrose-containing products, which can lead to "osmotic nephrosis"), thromboembolic events, hyperviscosity syndromes, dyshidrotic eczema (pompholyx), cardiac collapse and pulmonary edema. These risks vary with the preparation selected and the patient being treated. Pretreatment with acetaminophen and diphenhydramine may lessen infusion reactions, and decreasing the rapidity of the infusion lessens the risk of thromboembolic events, aseptic meningitis, and renal and cardiovascular events.

INTERACTIONS

Individuals receiving IVIg may have a suboptimal response to vaccination with live viruses.

USE IN PREGNANCY

IVIg is in pregnancy category C. There does not appear to be an excessive risk in pregnancy or lactation associated with the use of IVIg.

OTHER TARGETED ("BIOLOGIC") AGENTS CURRENTLY USED IN MEDICINE		
Drug (Trade name®)	**Target**	**FDA-approved indications/non-approved dermatologically relevant uses**
Abatacept (Orencia)	B7–1 (CD80)	Rheumatoid arthritis/psoriasis (historical) (see Fig. 128.8E)
Abciximab (ReoPro)	Glycoprotein IIb/IIIa	Cardiovascular disease
Alemtuzumab (Campath)	CD52	B-cell CLL/mycosis fungoides, ATLL
Basiliximab (Simulect)	IL2Rα (CD25)	Solid organ transplantation/GVHD
Belimumab (Benlysta)	B-lymphocyte stimulator	Systemic lupus erythematosus
Bevacizumab (Avastin)	VEGF	Colorectal cancer
Brentuximab vedotin (Adcetris)	CD30	Anaplastic large cell and Hodgkin lymphomas
Canakinumab (Ilaris)	Interleukin-1β	Cryopyrin-associated periodic syndrome
Cetuximab (Erbitux; IgG1)*,†	EGFR	Head and neck SCC, colorectal cancer
Daclizumab (Zenapax)	IL2Rα (CD25)	Solid organ transplantation/GVHD
Denileukin diftitox (Ontak)	Interleukin-2 receptor	Cutaneous T-cell lymphoma
Denosumab (Prolia, Xgeva)	RANK ligand	Osteoporosis, bone metastases
Eculizumab (Sorilis)	Complement component 5	Paroxysmal nocturnal hemoglobinuria/dermatomyositis
Gemtuzumab (Mylotarg)‡	CD33	AML
Ibritumomab tiuxetan (Zevalin)§	CD20	Non-Hodgkin lymphoma
Ipilimumab (Yervoy)	CTLA-4 (CD152)	Unresectable or metastatic melanoma (Fig. 128.8E)
Muromonab (Orthoclone OKT3)	CD3	Acute allograft rejection (renal, cardiac, hepatic)
Natalizumab (Tysabri; previously Antegren)	α-4 integrin	Multiple sclerosis, Crohn's disease
Ofatumumab (Arzerra)	CD20	B-cell CLL
Palivizumab (Synagis)	Respiratory syncytial virus (RSV)	RSV infections
Panitumumab (Vectibix; IgG2)*,†	EGFR	Metastatic colorectal cancer
Ranibizumab (Lucentis; intravitreal agent)	VEGF	Age-related macular degeneration
Rilonacept (Arcalyst)	Interleukin-1	Cryopyrin-associated periodic syndrome
Tocilizumab (atlizumab; Actemra)	Interleukin-6 receptor	Rheumatoid arthritis
Tositumonomab (Bexxar)§	CD20	Non-Hodgkin lymphoma
Trastuzumab (Herceptin)	HER2/neu	Breast cancer
TYROSINE KINASE INHIBITORS*		
Crizotinib (Xalkori)	ALK	ALK+ non-small cell lung cancer
Dasatinib (Sprycel)	c-KIT, c-Abl	CML, Philadelphia chromosome-positive ALL
Erlotinib (Tarceva)†	EGFR	Non-small cell lung and pancreatic cancer
Gefitinib (Iressa)†	EGFR	Non-small cell lung cancer
Imatinib (Gleevec, Glivec)	c-KIT, c-Abl, PDGFR	CML, GIST, DFSP (see Ch. 116), systemic mastocytosis (see Ch. 118), hypereosinophilic syndrome (see Fig. 25.8), sclerodermatous conditions (e.g. morphea, chronic GVHD)
Lapatinib (Tykerb, Tycerb)†	EGFR, HER2/neu	Metastatic breast cancer
Nilotinib (Tasigna)	c-KIT, c-Abl, PDGFR	CML
Pazopanib (Votrient)	VEGFR1,2&3, PDGFR, c-KIT	Renal cell carcinoma
Ruxolitinib (Jakafi)	Janus kinases 1&2 (JAK1/2)	Myelofibrosis
Sorafenib (Nexavar)	VEGFR1&2, PDGFR, BRAF	Renal cell carcinoma/melanoma
Sunitinib (Sutent)	VEGFR1&2, PDGFR, c-KIT, FLT3	Renal cell carcinoma, GIST
Vandetanib (Caprelsa)†	VEGFR, EGFR, RET	Metastatic medullary thyroid cancer
Vemurafenib (Zelboraf)	BRAF (a serine/threonine kinase) with the V600E mutation	Unresectable or metastatic melanoma with the $BRAF^{V600E}$ mutation
HEDGEHOG PATHWAY INHIBITOR		
Vismodegib (Erivedge)	Smoothened receptor	Unresectable or metastatic basal cell carcinoma

*See Table 21.14.
†See Chapter 36.
‡Withdrawn from the market.
§Radioactive forms are used, with ibritumomab tiuxetan conjugated to yttrium-90 or indium-111 and tositumomab conjugated to iodine-131.

Table 128.13 Other targeted ("biologic") agents currently used in medicine. Additional agents with cutaneous applications that are not yet FDA-approved include epratuzumab (anti-CD20; B-cell lymphomas, systemic lupus erythematosus) and mepolizumab (anti-interleukin-5; hypereosinophilic syndrome). ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; ATLL, adult T-cell leukemia-lymphoma; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; CTLA-4, cytotoxic T-lymphocyte antigen-4; DFSP, dermatofibrosarcoma protuberans; EGFR, epidermal growth factor receptor; FLT3, FMS-like tyrosine kinase 3; GIST, gastrointestinal stromal tumors; GVHD, graft-versus-host disease; IL2Rα, interleukin-2 receptor α; PDGFR, platelet-derived growth factor receptor; RANK, receptor activator of nuclear factor κB; SCC, squamous cell carcinoma; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

OTHER AGENTS

Many other targeted immune modulators are used in other areas of medicine (Table 128.13). There are frequent cutaneous adverse reactions with some of these agents (e.g. the epidermal growth factor inhibitors used to treat solid tumors) (see Tables 21.14 and 128.8). Additionally, some of these agents might have benefit for dermatologic conditions (e.g. ipilimumab and vemurafenib for melanoma; imatinib for fibrosing conditions including scleroderma, mastocytosis and dermatofibrosarcoma protuberans)[155].

REFERENCES

1. Havell EA, Berman B, Ogburn CA, et al. Two antigenically distinct species of human interferon. Proc Natl Acad Sci USA. 1975;72:2185–7.
2. Wills RJ. Clinical pharmacokinetics of interferons. Clin Pharmacokinet. 1990;19:390–9.
3. Vance JC, Bart BJ, Hansen RC, et al. Intralesional recombinant alpha-2 interferon for the treatment of patients with condyloma acuminatum or verruca plantaris. Arch Dermatol. 1986;122:272–7.
4. Yang J, Pu YG, Zeng ZM, et al. Interferon for the treatment of genital warts: a systematic review. BMC Infect Dis. 2009;9:156.
5. Nimura M. Intralesional human fibroblast interferon in common warts. J Dermatol. 1983;10:217–20.
6. Berman B, Davis-Reed L, Silverstein L, et al. Treatment of verruca vulgaris with α-2 interferon. J Infect Dis. 1986;154:328–30.
7. Knobler E. Current management strategies for cutaneous T-cell lymphoma. Clin Dermatol. 2004;22:197–208.
8. Ezekowitz RA, Mulliken JB, Folkman J. Interferon-alfa-2a therapy for life-threatening hemangiomas of infancy. N Engl J Med. 1992;326:1456–63.
9. Barlow CF, Priebe CJ, Mulliken JB, et al. Spastic diplegia as a complication of interferon alfa-2a treatment of hemangiomas of infancy. J Pediatr. 1998;132:527–30.
10. Krown SE. Interferon and other biological agents for the treatment of Kaposi's sarcoma. Hematol Oncol Clin North Am. 1991;5:311–22.
11. Cornell RC, Greenway HT, Tucker SB, et al. Intralesional interferon therapy for basal cell carcinoma. J Am Acad Dermatol. 1990;23:694–700.
12. Edwards L, Berman B, Rapini RP, et al. Treatment of cutaneous squamous cell carcinoma by intralesional interferon alfa-2b therapy. Arch Dermatol. 1992;128:1486–9.
13. Grob JJ, Suzini F, Richard A, et al. Large keratoacanthomas treated with intralesional interferon alfa-2a. J Am Acad Dermatol. 1993;29:237–41.
14. Berman B, Duncan MR. Short-term keloid treatment in vivo with human interferon-α2b results in a selective and persistent normalization of keloidal fibroblast collagen, glycosaminoglycan and collagenase production in vitro. J Am Acad Dermatol. 1989;21:694–702.
15. Lee JH, Kim SE, Lee AY. Effects of interferon-alpha2b on keloid treatment with triamcinolone acetonide intralesional injection. Int J Dermatol. 2008;47:183–6.
16. Granstein RD, Rook A, Flotte TJ, et al. A controlled trial of intralesional recombinant interferon-γ in the treatment of keloidal scarring. Arch Dermatol. 1990;126:1295–302.
17. Larrabee WF Jr, East CA, Jaffe HS, et al. Intralesional interferon gamma treatment for keloids and hypertrophic scars. Arch Otolaryngol Head Neck Surg. 1990;116:1159–62.
18. Berman B, Flores F. Recurrence rates of excised keloids treated with postoperative triamcinolone acetonide injections or interferon-α2b injections. J Am Acad Dermatol. 1997;37:755–7.
19. Davison SP, Mess S, Kauffman LC, Al-Attar A. Ineffective treatment of keloids with interferon alpha-2b. Plast Reconstr Surg. 2006;117:247–52.
20. Hanifin SM, Schneider LC, Leung DY, et al. Recombinant interferon gamma therapy for atopic dermatitis. J Am Acad Dermatol. 1993;28:189–97.
21. Nishioka K, Matsunaga T, Katayama I. Gamma-interferon therapy for severe cases of atopic dermatitis of the adult type. J Dermatol. 1995;22:181–85.
22. Torrelo A, Harto A, Sendagorta E, et al. Interferon-α therapy in atopic dermatitis. Acta Derm Venereol. 1992;72:370–2.
23. Mackie RM. Interferon-α for atopic dermatitis. Lancet. 1990;335:1282–3.
24. Alpsoy E, Yilmaz E, Basaran E. Interferon therapy for Behçet's disease. J Am Acad Dermatol. 1994;31:617–9.
25. Mahrle G, Schulze HJ. Recombinant interferon-gamma (rIFN-gamma) in dermatology. J Invest Dermatol. 1990;95:132S–7S.
26. Rosenbloom J, Feldman G, Freundlich B, Jimenez SA. Inhibition of excessive scleroderma fibroblast collagen synthesis by recombinant gamma interferon. Arthritis Rheum. 1966;29:851–6.
27. Kahan A, Amor B, Menkes CJ, Strauch G. Recombinant interferon-γ in the treatment of systemic sclerosis. Am J Med. 1989;87:273–7.
28. Elgart GW, Sheremata W, Ahn YS. Cutaneous reactions to recombinant human interferon beta-1b: the clinical and histologic spectrum. J Am Acad Dermatol. 1997;37:553–8.
29. Interferon-β_{1a}, -β_{1b}, α_{2a}, α_{2b}, α n3. In: Physicians' Desk Reference, 52nd edn. Montvale: Medical Economics Company, 1998:305–7, 1290–2, 2489–4, 2637–44.
30. Deyton LR, Walker RE, Kovac JA, et al. Reversible cardiac dysfunction associated with interferon-alfa therapy in AIDS patients with Kaposi's sarcoma. N Engl J Med. 1989;321:1246–9.
31. Reinhold U, Hartl C, Hering R, et al. Fatal rhabdomyolysis and multiple organ failure associated with adjuvant high dose interferon alfa in malignant melanoma. Lancet. 1997;349:540–1.
32. Steis RG, Smith JW, Urba WJ, et al. Resistance to recombinant interferon-alfa2a in hairy-cell leukemia associated with neutralizing anti-interferon antibodies. N Engl J Med. 1988;318:1409–13.
33. Rajan GP, Seifert B, Prummer O, et al. Incidence and in-vivo relevance of anti-interferon antibodies during treatment of low-grade cutaneous T-cell lymphomas with interferon alpha-2a combined with acitretin or PUVA. Arch Dermatol Res. 1996;288:543–8.
34. Tomer Y, Menconi F. Interferon induced thyroiditis. Best Pract Res Clin Endocrinol Metab. 2009;23:703–12.
35. Williams SJ, Baird-Lambert JA, Farrell GC. Inhibition of theophylline metabolism by interferon. Lancet. 1987;2:939–41.
36. Imbertson LM, Bearurline JM, Couture AM, et al. Cytokine induction in hairless mouse and rat skin after topical application on the immune response modification. J Invest Dermatol. 1998;110:734–9.
37. Miller RL, Gerster JF, Owens ML, et al. Imiquimod applied topically: a novel immune response modifier and new class of drug. Int J Immunopharmacol. 1999;21:1–14.
38. Suzuki H, Wang B, Shivji GM, et al. Imiquimod, a topical immune response modifier, induces migration of Langerhans cells. J Invest Dermatol. 2000;114:135–41.
39. Workowski KA, Berman SM; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2006. MMWR Recomm Rep. 2006;55:1–94.
40. Weisshaar E, Gollnick H. Potentiating effect of imiquimod in the treatment of verrucae vulgares in immunocompromised patients. Acta Derm Venereol. 2000;80:306–7.
41. Theos AM, Cummings R, Silverberg NB, Paller AS. Effectiveness of imiquimod cream 5% for treating childhood molluscum contagiosum in a double-blind, randomized pilot trial. Cutis. 2004;74:141–2.
42. Berman B, Kaufman J. Pilot study of the effect of postoperative imiquimod 5% cream on the recurrence rate of excised keloids. J Am Acad Dermatol. 2002;47(suppl.):S209–11.
43. Cação FM, Tanaka V, Messina MC. Failure of imiquimod 5% cream to prevent recurrence of surgically excised trunk keloids. Dermatol Surg. 2009;35:629–33.
44. Berman B, Harrison-Balestra C, Perez OA, et al. Treatment of keloid scars post-shave excision with imiquimod 5% cream: a prospective, double-blind, placebo-controlled pilot study. J Drugs Dermatol. 2009;8:455–8.
45. Ceilley RI, Del Rosso JQ. Current modalities and new advances in the treatment of basal cell carcinoma. Int J Dermatol. 2006;45:489–98.
46. Kagy MK, Amonette R. The use of imiquimod 5% cream for the treatment of superficial basal cell carcinomas in a basal cell nevus syndrome patient. Dermatol Surg. 2000;26:577–9.
47. Hadley G, Derry S, Moore RA. Imiquimod for actinic keratosis: systematic review and meta-analysis. J Invest Dermatol. 2006;126:1251–5.
48. Swanson N, Abramovits W, Berman B, et al. Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: results of two placebo-controlled studies of daily application to the face and balding scalp for two 2-week cycles. J Am Acad Dermatol. 2010;62:582–90.
49. Gebauer K, Shumack S, Cowen PS. Effect of dosing frequency on the safety and efficacy of imiquimod 5% cream for treatment of actinic keratosis on the forearms and hands: a phase II, randomized placebo-controlled trial. Br J Dermatol. 2009;161:897–903.
50. Patel GK, Goodwin R, Chawla M, et al. Imiquimod 5% cream monotherapy for cutaneous squamous cell carcinoma in situ (Bowen's disease): a randomized, double-blind, placebo-controlled trial. J Am Acad Dermatol. 2006;54:1025–32.
51. Pehoushek J, Smith KJ. Imiquimod and 5% fluorouracil therapy for anal and perianal squamous cell carcinoma in situ in an HIV-1-positive man. Arch Dermatol. 2001;137:14–7.
52. Orengo I, Rosen T, Guill CK. Treatment of squamous cell carcinoma in situ of the penis with 5% imiquimod cream. J Am Acad Dermatol. 2002;47(suppl.):S225–8.
53. Berman B, Poochareon VN, Villa AM. Novel dermatologic uses of the immune response modifier imiquimod 5% cream. Skin Therapy Lett. 2002;7:1–6.
54. Berman B, Perez OA, Zell D. Immunological strategies to fight skin cancer. Skin Therapy Lett. 2006;11:1–7.
55. Suchin KR, Junkins-Hopkins JM, Rook AH. Treatment of stage IA cutaneous T-cell lymphoma with topical application of the immune response modifier imiquimod. Arch Dermatol. 2002;138:1137–9.
56. Cohen PR, Schulze KE, Tschen JA, et al. Treatment of extramammary Paget disease with topical imiquimod cream: case report and literature review. South Med J. 2006;99:396–402.
57. Ahmed I, Berth-Jones J. Imiquimod: a novel treatment for lentigo maligna. Br J Dermatol. 2000;143:843–5.
58. Wolf IH, Smolle J, Binder B, et al. Topical imiquimod in the treatment of metastatic melanoma to skin. Arch Dermatol. 2003;139:273–6.
59. Arevalo I, Tulliano G, Quispe A, et al. Role of imiquimod and parenteral meglumine antimoniate in the initial treatment of cutaneous leishmaniasis. Clin Infect Dis. 2007;44:1549–54.
60. Woodmansee CS, McCall MW. Recurrence of lentigo maligna and development of invasive melanoma after treatment of lentigo maligna with imiquimod. Dermatol Surg. 2009;35:1286–9.
60a. Ly L, Kelly JW, O'Keefe R, et al. Efficacy of imiquimod cream 5% for lentigo maligna after complete excision: a study of 43 patients. Arch Dermatol. 2011;147:1191–5.
60b. Chan MD, Zimarowski MJ. Lupus erythematosus-like reaction in imiquimod-treated skin: a report of 2 cases. Am J Dermatopathol. 2011;23:523–7.
61. Vaccaro M, Barbuzza O, Guarneri B. Erosive pustular dermatosis of the scalp following treatment with topical imiquimod for actinic keratosis. Arch Dermatol. 2009;145:1340–1.
62. Stuetz A, Baumann K, Grassberger M, et al. Discovery of topical calcineurin inhibitors and pharmacological profile of pimecrolimus. Int Arch Allergy Immunol. 2006;141:199–212.
63. Carroll CL, Fleischer AB Jr. Tacrolimus ointment: treatment of atopic dermatitis and other inflammatory cutaneous disease. Expert Opin Pharmacother. 2004;5:2127–37.
64. Callen JP, Chamlin S, Eichenfield LF, et al. A systematic review of the safety of topical therapies for atopic dermatitis. Br J Dermatol. 2007;156:203–21.

65. Allen A, Siegfried E, Silverman R, et al. Significant absorption of topical tacrolimus in 3 patients with Netherton syndrome. Arch Dermatol. 2001;137:747–50.
66. Yan AC, Honig PJ, Ming ME, et al. The safety and efficacy of pimecrolimus, 1%, cream for the treatment of Netherton syndrome: results from an exploratory study. Arch Dermatol. 2010;146:57–62.
67. Thomson MA, Hamburger J, Steward DG, Lewis HM. Treatment of erosive oral lichen planus with topical tacrolimus. J Dermatolog Treat. 2004;15:308–14.
68. Remitz A, Reitamo S. Long-term safety of tacrolimus ointment in atopic dermatitis. Expert Opin Drug Saf. 2009;8:501–6.
69. Ellis CN, Krueger GG. Treatment of chronic plaque psoriasis by selective targeting of memory effector T lymphocytes. N Engl J Med. 2001;345:248–55.
70. Brimhall AK, King LN, Licciardone JC, et al. Safety and efficacy of alefacept, efalizumab, etanercept and infliximab in treating moderate to severe plaque psoriasis: a meta-analysis of randomized controlled trials. Br J Dermatol. 2008;159:274–85.
71. Gribetz CH, Blum R, Brady C, et al. An extended 16 week course of alefacept in the treatment of chronic plaque psoriasis. J Am Acad Dermatol. 2005:53:73–5.
72. Menter A, Cather JC, Baker D, et al. The efficacy of multiple courses of alefacept in patients with moderate to severe chronic plaque psoriasis. J Am Acad Dermatol. 2006;55:916–7.
73. Fivenson DP, Mathes B. Treatment of generalized lichen planus with alefacept. Arch Dermatol. 2006;142:151–2.
74. Berthelot C, Nash J, Duvic M. Coexistent psoriasis and lupus erythematosus treated with alefacept. Am J Clin Dermatol. 2007;8:47–50.
75. Shapira MY, Resnick IB, Bitan M, et al. Rapid response to alefacept given to patients with steroid resistant or steroid dependent acute graft-versus-host disease: a preliminary report. Bone Marrow Transplant. 2005;36:1097–101.
76. Heffrenan M, Hurley MY, Martin KS, et al. Alefacept for alopecia areata. Arch Dermatol. 2005;141:1513–6.
77. Strober BE, Menon K, McMichael A, et al. Alefacept for severe alopecia areata: a randomized, double-blind, placebo-controlled study. Arch Dermatol. 2009;145:1262–6.
78. Foss CE, Clark AR, Inabinet R, et al. An open-label pilot study of alefacept for the treatment of pyoderma gangrenosum. J Eur Acad Dermatol Venereol. 2008;22:943–9.
79. Goffe B, Papp K, Gratton D, et al. An integrated analysis of thirteen trials summarizing the long-term safety of alefacept in psoriasis patients who have received up to nine courses of therapy. Clin Ther. 2005;27:1912–21.
80. Mease PJ, Gladman DD, Keystone EC; Alefacept in Psoriatic Arthritis Study Group. Alefacept in combination with methotrexate for the treatment of psoriatic arthritis: results of a randomized, double-blind, placebo-controlled study. Arthritis Rheum. 2006;54:1638–45.
81. Ortonne JP, Khemis A, Koo JY, Choi J. An open-label study of alefacept plus ultraviolet B light as combination therapy for chronic plaque psoriasis. J Eur Acad Dermatol Venereol. 2005;19:556–63.
82. Gottlieb AB, Krueger JG, Wittkowski K, et al. Psoriasis as a model for T-cell mediated disease: immunobiologic and clinical effects of treatment with multiple doses of efalizumab and anti-CDIIa antibody. Arch Dermatol. 2002;138:591–60.
83. Gordon KB, Papp KA, Hamilton TK, et al. Efalizumab for patients with moderate to severe plaque psoriasis: a randomized controlled trial. JAMA. 2003;290:3073–80.
84. Lebwohl M, Tyring SK, Hamilton TK, et al. A novel targeted T-cell modulator, efalizumab, for plaque psoriasis. N Engl J Med. 2003;349:2004–13.
85. Wellington K, Perry CM. Efalizumab. Am J Clin Dermatol. 2005;6:113–8.
86. Korman BD, Tyler KL, Korman NJ. Progressive multifocal leukoencephalopathy, efalizumab, and immunosuppression: a cautionary tale for dermatologists. Arch Dermatol. 2009;145:937–42.
87. Usmani N, Goodfield M. Efalizumab in the treatment of discoid lupus erythematosus. Arch Dermatol. 2007;143:873–7.
88. Mitoma H, Horiuchi T, Tsukamoto H, et al. Mechanisms for cytotoxic effects of anti-tumor necrosis factor agents on transmembrane tumor necrosis factor alpha-expressing cells: comparison among infliximab, etanercept, and adalimumab. Arthritis Rheum. 2008;58:1248–57.
89. Straub RH, Härle P, Sarzi-Puttini P, Cutolo M. Tumor necrosis factor-neutralizing therapies improve altered hormone axes. An alternative mode of anti-inflammatory action. Arthritis Rheum. 2006;54: 2039–46.
90. Mohan N, Edwards ET, Cupps TR, et al. Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides. Arthritis Rheum. 2001;44:2862–9.
91. Behnam SM, Behnam SE, Koo JY. TNF-alpha inhibitors and congestive heart failure. Skinmed. 2005;4:363–8.
92. Bergstrom L, Yocum DE, Ampel NM, et al. Increased risk of coccidioidomycosis in patients treated with tumor necrosis factor alpha antagonists. Arthritis Rheum. 2004;50:1959–66.
93. Dommasch ED, Abuabara K, Shin DB, et al. The risk of infection and malignancy with tumor necrosis factor antagonists in adults with psoriatic disease: a systematic review and meta-analysis of randomized controlled trials. J Am Acad Dermatol. 2011;64:1035–50.
94. Peterson JR, Hsu FC, Simkin PA, Wener MH. Effect of tumour necrosis factor alpha antagonists on serum transaminases and viraemia in patients with rheumatoid arthritis and chronic hepatitis C infection. Ann Rheum Dis. 2003;62:1078–82.
95. Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. Arthritis Rheum. 2004;50:1740–51.
96. Bongartz T, Sutton AJ, Sweeting MJ, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006;295:2275–85.
97. Lebwohl M, Blum R, Berkowitz E, et al. No evidence for increased risk of cutaneous squamous cell carcinoma in patients with rheumatoid arthritis receiving etanercept for up to 5 years. Arch Dermatol. 2005;141:861–4.
98. Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. N Engl J Med. 2005;352:351–61.
98a. Mariette X, Matucci-Cerinic M, Pavelka K, et al. Malignancies associated with tumour necrosis factor inhibitors in registries and prospective observational studies: a systematic review and meta-analysis. Ann Rheum Dis. 2011 [epub ahead of print]
99. Thayu M, Markowitz JE, Mamula P, et al. Hepatosplenic T-cell lymphoma in an adolescent patient after immunomodulator and biologic therapy for Crohn disease. J Pediatr Gastroenterol Nutr. 2005;40: 220–2.
100. Diak P, Siegel J, La Grenade L, et al. Tumor necrosis factor alpha blockers and malignancy in children: forty-eight cases reported to the Food and Drug Administration. Arthritis Rheum. 2010;62:2517–24.
101. Shakoor N, Michalska M, Harris CA, Block JA. Drug-induced systemic lupus erythematosus associated with etanercept. Lancet. 2002;359:579–80.
102. Wetter DA, Davis MD. Lupus-like syndrome attributable to anti-tumor necrosis factor alpha therapy in 14 patients during an 8-year period at Mayo Clinic. Mayo Clin Proc. 2009;84:979–84.
103. Comby E, Tanaff P, Mariotte D, et al. Evolution of antinuclear antibodies and clinical patterns in patients with active rheumatoid arthritis with longterm infliximab therapy. J Rheumatol. 2006;33:24–30.
104. Norman R, Greenberg RG, Jackson JM. Case reports of etanercept in inflammatory dermatoses. J Am Acad Dermatol. 2006;54(suppl. 2):S139–42.
105. Fautrel B, Foltz B, Frances C, et al. Regression of subacute cutaneous lupus erythematosus in a patient with rheumatoid arthritis treated with a biologic tumor necrosis factor alpha-blocking agent: comment on the article by Pisetsky and the letter from Aringer et al. Arthritis Rheum. 2002;46:1408–9.
106. Pink AE, Fonia A, Allen MH, et al. Antinuclear antibodies associate with loss of response to anti-TNF alpha therapy in psoriasis – a retrospective, observational study. Br J Dermatol. 2010;162:780–5.
107. Kary S, Worm M, Audring H, et al. New onset or exacerbation of psoriatic skin lesions in patients with definite rheumatoid arthritis receiving tumour necrosis factor alpha antagonists. Ann Rheum Dis. 2006;65:405–7.
108. Mohan N, Edwards ET, Cupps TR, et al. Leukocytoclastic vasculitis associated with tumor necrosis factor-alpha blocking agents. J Rheumatol. 2004;31:1955–8.
109. Deng A, Harvey V, Sina B, et al. Interstitial granulomatous dermatitis associated with the use of tumor necrosis factor alpha inhibitors. Arch Dermatol. 2006;142:198–202.
110. Aikaterini-Evaggelia M, Athina M, Dessinioti C, et al. Cutaneous side effects of anti-tumor necrosis factor biologic therapy: a clinical review. J Am Acad Dermatol. 2009;61:486–504.
111. Fomin I, Caspi D, Levy V, et al. Vaccination against influenza in rheumatoid arthritis: the effect of disease modifying drugs, including TNF alpha blockers. Ann Rheum Dis. 2006;65:191–4.
112. Mease PJ, Goffe BS, Metz J, et al. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomized trial. Lancet. 2000;356:385–390.
113. Tyring S, Gottlieb A, Papp K, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomized phase III trial. Lancet. 2006;367:29–35.
114. Paller AS, Siegfried EC, Langley RG, et al. Etanercept treatment for children and adolescents with plaque psoriasis. N Engl J Med. 2008;358:241–251.
115. Alexis AF, Strober BE. Off-label dermatologic uses of anti-TNF-α therapies. J Cutan Med Surg. 2005;9:296–302.
116. Keystone EC, Thorne C, Haraoui B. The utility of biologics in orphan diseases. New Developments in Rheumatic Diseases. 2005;3:9–28.
117. Baughman RP, Lower EE, Bradley DA, et al. Etanercept for refractory ocular sarcoidosis: results of a double-blind randomized trial. Chest. 2005;128:1062–7.
118. Genovese MC, Cohen S, Moreland L, et al. Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated successfully with methotrexate. Arthritis Rheum. 2004;50:412–9.
119. Kircik L, Bagel J, Korman N, et al. Utilization of narrow-band ultraviolet light B therapy and etanercept for the treatment of psoriasis (UNITE): efficacy, safety and patient reported outcomes J Drugs Dermatol. 2008;7:245–53.
120. Gambichler T, Tigges C, Scola N, et al. Etanercept plus narrowband ultraviolet B phototherapy of psoriasis is more effective than etanercept monotherapy at 6 weeks. Br J Dermatol. 2011;164:1383–6.
121. Salmon JE, Alpert D. Are we coming to terms with tumor necrosis factor inhibition in pregnancy? Arthritis Rheum. 2006;54:2353–5.
122. Chaudhari U, Romano P, Mulcahy LD, et al. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomized trial. Lancet. 2001;357:1842–6.
123. Brooklyn TN, Dunnill MG, Shetty A, et al. Infliximab for the treatment of pyoderma gangrenosum: a randomized, double-blind, placebo controlled trial. Gut. 2006;55:505–9.
124. Scheinfeld N. Off-label uses and side effects of infliximab. J Drugs Dermatol. 2004;3:273–84.
125. Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. N Engl J Med. 2003;348:601–8.
126. Miele E, Markowitz JE, Mamula P, Baldassano RN. Human antichimeric antibody in children and young adults with inflammatory bowel disease receiving infliximab. J Pediatr Gastroenterol Nutr. 2004;38:502–8.
127. Mease PJ. Adalimumab: an anti-TNF agent for the treatment of psoriatic arthritis. Expert Opin Biol Ther. 2005;5:1491–504.
128. Miller I, Lynggaard CD, Lophaven S, et al. A double blind placebo controlled randomised trial of adalimumab in the treatment of hidradenitis suppurativa. Br J Dermatol. 2011;165:391–8.
129. Callen JP, Jackson JH. Adalimumab effectively controlled recalcitrant generalized pustular psoriasis in an adolescent. J Dermatolog Treat. 2005;16:350–2.
130. Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet. 2008;371:1675–84.
131. Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet. 2008;371:1665–74.
131a. Ryan C, Leonardi CL, Krueger JG, et al. Association between biologic therapies for chronic plaque psoriasis and cardiovascular events: a meta-analysis of randomized controlled trials. JAMA. 2011;306:864–71.

131b. Lipsker D, Lutz D. Cutaneous infarction under IL12/23 p40 inhibition: a cautionary tale. Arch Dermatol. 2011;147:1344.
132. Furst DE. Anakinra: review of recombinant human interleukin-1-receptor antagonist in the treatment of rheumatoid arthritis. Clin Ther. 2004;26: 1960–75.
133. Goldbach-Mansky R, Dailey NJ, Canna SW, et al. Neonatal-onset multisystem inflammatory disease responsive to interleukin-1beta inhibition. N Engl J Med. 2006;355:581–92.
134. Crouch R, Akhras V, Sarkany R. Schnitzler's syndrome: successful treatment with anakinra. Australas J Dermatol. 2007;48:178–81.
135. Scheinfeld N. A review of rituximab in cutaneous medicine. Dermatol Online J. 2006;12:3.
136. Zambruno G, Borradori L. Rituximab immunotherapy in pemphigus: therapeutic effects beyond B-cell depletion. J Invest Dermatol. 2008;128:2745–7.
137. [Anonymous]. Rituximab (Rituxan) for rheumatoid arthritis. Med Lett Drugs Ther. 2006;48:34–5.
138. Bonnekoh B, Schulz M, Franke I, Gollnick H. Complete remission of primary cutaneous B-cell lymphoma of the lower leg by first-line monotherapy with the CD20-antibody rituximab. J Cancer Res Clin Oncol. 2002;128:161–6.
139. Joly P, Mouquet H, Roujeau JC, et al. A single cycle of rituximab for the treatment of severe pemphigus. N Engl J Med. 2007;357:545–52.
140. Anolik JH, Aringer M. New treatments for SLE: cell-depleting and anti-cytokine therapies. Best Pract Res Clin Rheumatol. 2005;19:859–78.
141. Cutler C, Miklos D, Haesook T, et al. Rituximab for steroid-refractory chronic graft-versus-host disease. Blood. 2006;108:756–62.
142. Chung L, Funke AA, Chakravarty EF, et al. Successful use of rituximab for cutaneous vasculitis. Arch Dermatol. 2006;142:1407–10.
143. Levine TD. Rituximab in the treatment of dermatomyositis: an open-label pilot study. Arthritis Rheum. 2005;52:601–7.
144. Kim JH, Kim YH, Kim MR, Kim SC. Clinical efficacy of different doses of rituximab in the treatment of pemphigus: a retrospective study of 27 patients. Br J Dermatol. 2011;165:646–51.
145. Schmidt E, Hennig K, Mengede C, et al. Immunogenicity of rituximab in patients with severe pemphigus. Clin Immunol. 2009;132:334–41.
146. Holgate S, Casale T, Wenzel S, et al. The anti-inflammatory effects of omalizumab confirm the central role of IgE in allergic inflammation. J Allergy Clin Immunol. 2005;115:459–65.
147. Beck LA, Saini S. Wanted: a study with omalizumab to determine the role of IgE-mediated pathways in atopic dermatitis. J Am Acad Dermatol. 2006;55:540–1.
147a. Saini S, et al. A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H1-antihistamine–refractory chronic idiopathic urticaria. J Allergy Clin Immunol. 2011;128:567–73.
148. Kaplan AP, Joseph K, Maykut RJ, et al. Treatment of chronic autoimmune urticaria with omalizumab. J Allergy Clin Immunol. 2008;122:569–73.
149. Mydlarski PR, Mittman N, Shear NH. Intravenous immunoglobulin: use in dermatology. Skin Therapy Lett. 2004;9:1–6.
150. French LT, Trent JT, Kerdel FA. Use of intravenous immunoglobulin in toxic epidermal necrolysis and Stevens-Johnson syndrome: our current understanding. Int Immunopharmacol. 2006;6: 543–9.
151. Dalakas MC. The role of high-dose immune globulin in the treatment of dermatomyositis. Int Immunopharmacol. 2006;6:550–6.
152. Ahmed AR. Use of intravenous immunoglobulin therapy in autoimmune blistering diseases. Int Immunopharmacol. 2006;6:557–78.
153. Bayary J, Dasgupta S, Misra N, et al. Intravenous immunoglobulin in autoimmune disorders: an insight into the immunoregulatory mechanisms. Int Immunopharmacol. 2006;6:528–34.
154. Siegel J. Safety considerations in IGIV utilization. Int Immunopharmacol. 2006;6:523–7.
155. Distler JH, Jungel A, Huber LC, et al. Imatinib mesylate reduces production of extracellular matrix and prevents development of experimental dermal fibrosis. Arthritis Rheum. 2007;56:311–22.

Other Topical Medications 129

Matthew Fox, Yolanda Helfrich and Sewon Kang

Chapter Contents

General principles of topical therapy 2153
Anesthetics 2156
Antipruritic agents 2156
Keratolytic agents 2157
Skin-lightening agents 2158
Agents that affect hair growth 2159
Chemotherapeutic agents 2159
Vitamin D analogues 2160
Miscellaneous agents 2161

Key features

- Absorption of topical medications depends upon several factors, including cutaneous barrier function, the anatomic site, the active agent, and characteristics of the vehicle
- In neonates, there is a greater risk of systemic toxicity with use of topical medications
- Combination or rotational therapy using topical agents may result in increased efficacy and decreased risk of side effects

INTRODUCTION

Topical medications are fundamental in the armamentarium of dermatologic therapeutics, offering the ability to deliver treatment directly to the skin while limiting systemic side effects. However, topical therapy can be time-consuming and messy, and it may not be practical for generalized skin disorders or effective for conditions with deeper involvement. Choosing an appropriate topical regimen requires consideration of the disease process and involved site(s) as well as the vehicle, application strategy and duration of use of the selected agent. This chapter reviews general principles of topical therapy and topical medications not discussed elsewhere in the textbook. Table 129.1 lists topical medications covered in other chapters.

GENERAL PRINCIPLES OF TOPICAL THERAPY

Topical formulations consist of an active ingredient in a non-active base (vehicle). To be effective, topical medications must gain entry into the skin and reach the desired target site (e.g. the epidermis below the stratum corneum or the dermis) in adequate concentrations. Successful topical therapy therefore requires percutaneous absorption, which depends upon factors related to the skin being treated as well as the agent and its vehicle (Table 129.2). The role of the stratum corneum in skin barrier function, including percutaneous absorption of medications, is discussed in Chapter 124.

Quantity of Application

In general, topical medications should be applied to the skin as a layer measuring approximately 0.05 to 0.1 mm in thickness (or sometimes less). A thicker layer of medication does not result in enhanced penetration or additional therapeutic benefit. It is estimated that 1 g of cream covers a 10 cm × 10 cm area of skin; 1 g of ointment spreads approximately 10% further than the same amount of cream.

A practical guide to quantifying the amount of ointment necessary to treat different areas of the body was developed by Long and Finlay[1]. They defined the "fingertip unit" (FTU) as the amount of ointment (dispensed from a 5 mm-diameter nozzle) that stretches from the distal

TOPICAL MEDICATIONS DISCUSSED IN OTHER CHAPTERS	
Topical medications	**Chapter(s)**
CHAPTERS ON MEDICAL THERAPY OR COSMETICS	
Glucocorticoids	125
Retinoids	126
Antimicrobials (antibacterials, antifungals, antivirals)	127
Immunomodulators (e.g. calcineurin inhibitors, imiquimod)	128
Sunscreens	132
Cosmeceuticals	153
Chemical peel agents	154
OTHER CHAPTERS	
Aluminum chloride for hyperhidrosis	40
Topical immunotherapy for alopecia areata (with squaric acid dibutyl ester or diphencyprone)	69
Antiparasitic agents (including treatments for infestations)	83, 84
Insect repellents	85
Wound healing agents	105, 141
Hemostatic agents	151

Table 129.1 Topical medications discussed in other chapters.

FACTORS THAT AFFECT PERCUTANEOUS ABSORPTION
CHARACTERISTICS OF THE PATIENT/SKIN
• Patient age – Suboptimal skin barrier function in neonates, especially if premature (see Table 129.7)
• Diseases, physical injuries or chemical exposures that disrupt skin barrier function (e.g. Netherton syndrome)
• A thicker stratum corneum decreases absorption
• Skin hydration and/or occlusion increase absorption (e.g. in a skin fold)
• Anatomic location (approximate ratio of absorption compared to the forearm) – *Higher absorption:* scrotum (40), face (10), axilla (4), scalp (3) – *Intermediate absorption*: trunk (1.5), arm (1) – *Lower absorption*: palm (0.8), ankle (0.4), sole (0.1)
PROPERTIES OF THE MEDICATION/ITS APPLICATION
• Drug/prodrug properties that increase absorption – Smaller molecular size and/or lower frictional coefficient – Increased lipophilicity – Increased concentration and/or solubility
• Vehicle composition
• Application under occlusion increases absorption (e.g. ointment, occlusive dressing)

Table 129.2 Factors that affect percutaneous absorption.

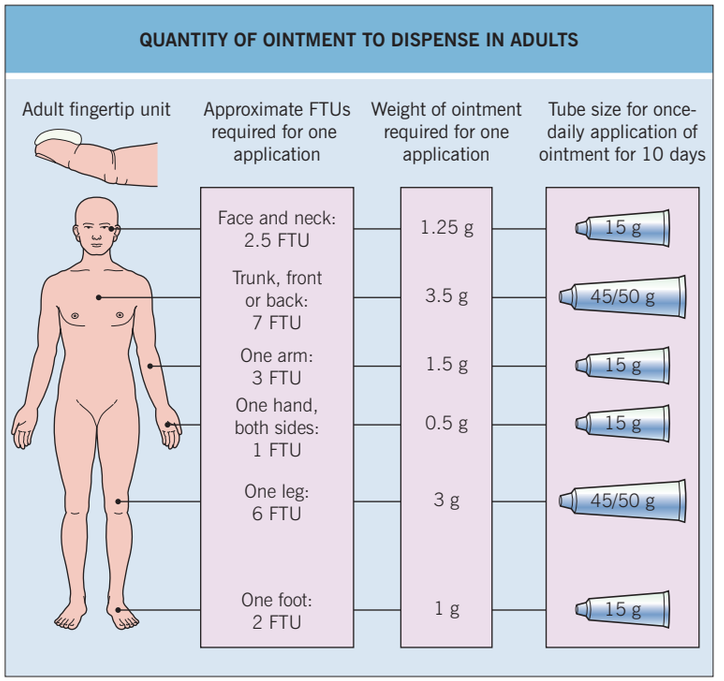
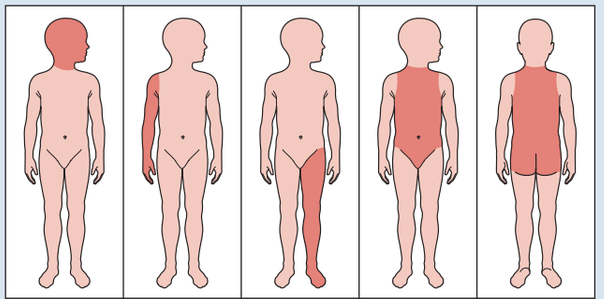


Fig. 129.1 Quantity of ointment to dispense in adults. FTU, fingertip unit.
Redrawn from Long CC, Finlay AY. The finger-tip unit – a new practical measure. Clin Exp Dermatol. 1991;16:444–7.

QUANTITY OF OINTMENT TO DISPENSE IN CHILDREN ACCORDING TO AGE



Age	Face & Neck	Arm & Hand	Leg & Foot	Trunk (Front)	Trunk (Back) inc. Buttocks
	Number of FTUs				
3–11 mos	1	1	1½	1	1½
1–2 y	1½	1½	2	2	3
3–5 y	1½	2	3	3	3½
6–10 y	2	2½	4½	3½	5

Fig. 129.2 Quantity of ointment to dispense in children, according to age. FTU, fingertip unit (in an adult). *Redrawn from Long CC, Mills CM, Finlay AY. A practical guide to topical therapy in children. Br J Dermatol. 1998; 138:293–6.*

crease to the tip of the index finger in an adult. One FTU is equal to approximately 0.5 g. The numbers of FTUs/grams that are needed to treat various areas of the body in adults and children are presented in Figures 129.1 and 129.2. Approximately 20 g are necessary to treat the entire body of an adult man, requiring ~250 g per week if applied twice daily. Approximately 0.5 FTU (0.25 g) is utilized for the area of one side of an extended ("flat") hand, and estimating the number of "flat hand areas" of affected skin can help to determine the amount of medication needed (e.g. four "flat hand areas" would require 1 g per application and ~15 g per week if applied twice daily).

CLASSIFICATION OF EXTERNAL PREPARATIONS
LIQUID
• Monophasic solutions – Pure aqueous: lotions, gels – Alcoholic, alcoholic-aqueous: paints – Oily: oils • Emulsions – Oil in water (O/W; can be washed off with water) – Water in oil (W/O; cannot be washed off with water) • Suspensions • Aerosols (solutions with pressurized gaseous propellants) – Foam – Spray
SEMISOLID
• Water-free: ointments • Water-containing – Monophasic: hydrogels – Multiphasic: emulsions, creams (O/W or W/O) • Highly concentrated suspensions: pastes
SOLID
• Powders (e.g. zinc oxide, titanium dioxide, talc)

Table 129.3 Classification of external preparations. Vehicles can also contain preservatives, emulsifiers, absorption promoters, and fragrances.

FACTORS IN THE CHOICE OF FORMULATION AND VEHICLE FOR TOPICAL MEDICATIONS
NATURE OF THE DERMATOSIS
• Wet dermatoses (e.g. oozing) – water-based formulations, drying pastes • Dry dermatoses (e.g. scaling) – ointments and other oil-based formulations • Highly inflamed or crusted dermatoses – ointment or cream following or combined with wet compresses (e.g. open wet dressings, wet wraps) or soaks • Fissured or eroded skin – avoid formulations containing alcohol or salicylates, which can lead to stinging and burning
LOCATION OF THE DERMATOSIS
• Glabrous skin – ointment, cream or emulsion • Skin folds – lotion or O/W cream; avoid occlusive ointments and W/O formulations • Hairy areas – lotion, gel, foam or oil

Table 129.4 Factors in the choice of formulation and vehicle for topical medications. O/W, oil in water; W/O, water in oil.

Formulations and Vehicles

A classification of topical formulations is provided in Table 129.3, and clinical guidelines for vehicle selection are presented in Table 129.4. A discussion of how vehicles affect drug delivery is found in Chapter 124.

Topical Therapy During Pregnancy and Lactation

When treating a woman of childbearing age, it is important to be aware of recommendations regarding the use of specific drugs during pregnancy and lactation. The decision to use topical medications during pregnancy should be based on the potential risk of the medication and the extent to which the condition affects the health of the woman. For example, use of the following topical medications during pregnancy (not a comprehensive list) is generally contraindicated: podophyllin, anthralin, lindane, chemotherapeutics (e.g. carmustine, mechlorethamine hydrochloride [nitrogen mustard], 5-fluorouracil), tazarotene, and peels with phenol or salicylic acid. Table 129.5 presents the US Food and Drug Administration (FDA) classification system of pharmaceutical pregnancy categories. Table 129.6 provides lists of topical medications with minimal risk during pregnancy and lactation.

Topical Therapy in Neonates

In full-term newborns, the stratum corneum (which represents the main barrier to percutaneous absorption) is fully developed and similar

FDA CLASSIFICATION SYSTEM OF PHARMACEUTICAL PREGNANCY CATEGORIES	
Category	**Description**
A	Controlled studies show no risk. Adequate well-controlled studies in pregnant women have failed to demonstrate risk to the fetus.
B	No evidence of risk in humans. Either animal studies show risk, but human studies do not; or, if no adequate human studies have been done, animal findings are negative.
C	Risk cannot be ruled out. Human studies are lacking, and animal studies are either positive for fetal risk or lacking as well. However, potential benefits may justify the potential risk.
D	Positive evidence for risk. Human studies, or investigational or post-marketing data, show risk to fetus. Nevertheless, potential benefits may outweigh potential risk.
X	Contraindicated in pregnancy. Studies in animals or humans, or investigational or post-marketing reports, have shown fetal risk, which clearly outweighs any possible benefit to the patient.

Table 129.5 FDA classification system of pharmaceutical pregnancy categories. FDA, Food and Drug Administration.

TOPICAL MEDICATIONS WITH MINIMAL RISK DURING PREGNANCY AND LACTATION		
Pregnancy	**FDA category (see Table 129.5)**	**Lactation**
Azelaic acid	B	Acyclovir
Ciclopirox	B	Bacitracin
Clindamycin	B	Benzoyl peroxide
Clotrimazole	B	Butoconazole
Erythromycin	B	Calcipotriene
Metronidazole*	B	Ciclopirox
Mupirocin	B	Clotrimazole
Naftifine	B	Erythromycin
Nystatin†	A (pastilles)	Hydroquinone
Oxiconazole	B	Ketoconazole
Permethrin	B	Metronidazole
Retapamulin	B	Mupirocin
Terbinafine	B	Nystatin
		Oxiconazole
		Terbinafine
		Tretinoin

*Avoidance of oral metronidazole during the first trimester is often recommended.
†Intravaginal topical application not advised close to term because of risk of contamination if membranes have ruptured.

Table 129.6 Topical medications with minimal risk during pregnancy and lactation. Minimal risk defined here as FDA pregnancy category B.

FACTORS THAT INCREASE THE RISK OF SYSTEMIC TOXICITY FROM TOPICAL MEDICATIONS IN NEONATES
Increased ratio of surface area to body weight (fourfold greater than in adults)
Suboptimal epidermal barrier function due to the higher pH of neonatal stratum corneum (neutral instead of acidic)
Decreased hepatic metabolism of drugs
Decreased renal excretion of drugs
Increased distribution of drug, including the CNS due to a more permeable blood–brain barrier
Decreased plasma protein binding

Table 129.7 Factors that increase the risk of systemic toxicity from topical medications in neonates.

POTENTIAL SYSTEMIC SIDE EFFECTS OF TOPICAL MEDICATIONS	
Medication	**Systemic side effect**
Androgens	Virilization in women and male fetuses
Boric acid	Generalized erythema, fever, vomiting, mental status change
Calcipotriene (calcipotriol)	Hypercalcemia, hypercalciuria
Carmustine (BCNU)	Bone marrow suppression
Chlorhexidine	Nausea, signs of ethanol intoxication
Clindamycin	Diarrhea, pseudomembranous colitis (controversial)
Corticosteroids	Iatrogenic Cushing's syndrome, inhibition of hypothalamic–pituitary axis
Dimethylsulfoxide	Nausea, abdominal pain
Epinephrine (adrenaline)	Tachycardia
Estrogens	Pseudoprecocious puberty, gynecomastia, hypogonadism in men
Gentamicin	Ototoxicity
Hexachlorophene	Neurotoxicity, coma, death
Iodine	Hypothyroidism
Lidocaine and other topical anesthetics	With overdose (>5 mg/kg of lidocaine absorbed): *early/lower levels* – paresthesias (e.g. perioral tingling), tinnitus, dysgeusia (e.g. metallic taste), lightheadedness, tremors; *late/higher levels* – seizures, hypotension, arrhythmias, cardiopulmonary arrest (see Ch. 143)
Lindane	CNS toxicity
Malathion	CNS toxicity, hyperglycemia
Mechlorethamine (nitrogen mustard)	Myelosuppression
Mercury	CNS and renal toxicity, acrodynia
Minoxidil	Cardiac toxicity, death
Neomycin	Ototoxicity, nephrotoxicity
Phenol	Cardiac arrhythmia, death
Podophyllin	Gastrointestinal (nausea, vomiting), neurologic (mental status changes, peripheral polyneuropathy) and hematologic (thrombocytopenia, leukopenia) effects
Prilocaine–lidocaine (EMLA®)	Methemoglobinemia (perioral/acral cyanosis, vascular "mottling") related to prilocaine; see lidocaine above
Propylene glycol	Hyperosmolality, with or without lactic acidosis
Salicylic acid	Tinnitus (early sign), gastrointestinal symptoms (e.g. nausea, vomiting), CNS toxicity (e.g. confusion, delirium, seizures), metabolic acidosis with respiratory compensation (i.e. tachypnea), hypoglycemia, coma, death
Silver (silver nitrate, silver sulfadiazine)	Leukopenia, argyria

Table 129.8 Potential systemic side effects of topical medications. For most, the risk of these side effects is either theoretical or exists only in instances where the medication is applied to neonates or in quantities greatly exceeding normal exposure. CNS, central nervous system.

in thickness to that of adults (see Ch. 2). However, several factors result in an increased risk of systemic toxicity from topically applied medications during the neonatal period (defined as the first 30 days of life) (Table 129.7). Systemic toxicity (Table 129.8) has been reported in neonates exposed to topical corticosteroids, salicylic acid, lindane, hexachlorophene, chlorhexidine and propylene glycol.

Combination and Rotational Topical Therapy

The advantages of using a single topical agent include improved compliance and (in most instances) lower cost. However, combination or rotational therapy is sometimes employed to provide additive/synergistic effects (via using medications with different mechanisms of action) or to decrease potential side effects by reducing exposure to one or both

agents (especially if they have different adverse-effect profiles). Examples of this strategy for topical therapy include various combinations of benzoyl peroxide, retinoids and antibiotics to treat acne; use of a corticosteroid together with a vitamin D analogue or tazarotene to treat psoriasis; and rotating use of a corticosteroid and calcineurin inhibitor to treat atopic dermatitis.

ANESTHETICS

Indications and general principles

Topical agents can provide a moderate degree of local anesthesia without the anxiety and discomfort associated with injections. Products containing several different anesthetics or combinations of anesthetics are available for use on intact skin (see Ch. 143). These agents can be utilized prior to a wide range of dermatologic procedures, including laser therapy, curettage (e.g. of molluscum contagiosum), cryotherapy and soft tissue augmentation, as well as preceding injection of anesthesia for skin biopsies and excisions. Topical anesthetics may also be administered for postherpetic neuralgia and painful ulcers. Treatment sites should be cleansed before application of topical anesthetics, as skin contaminants and other topical medications can alter absorption and effectiveness[2].

APPLICATION OF TOPICAL ANESTHETICS TO INTACT SKIN IN CHILDREN				
Age	**Body weight (kg)**	**Maximum dose (g)**	**Maximum application area (cm²)**	**Maximum application time (hours)**
EMLA® CREAM				
<3 months	<5	1	10	1
3–12 months	5–10	2	20	4
1–6 years	10–20	10	100	4
7–12 years	>20	20	200	4
LIDOCAINE 4% LIPOSOMAL CREAM				
<12 months	<10	NA	100	1
1–6 years	10–20	NA	200	2
7–12 years	>20	NA	600	2

Table 129.9 Application of topical anesthetics to intact skin in children. Topical lidocaine is absorbed at rates of 0.045 mg/cm²/h for 2.5% cream and 0.072 mg/cm²/h for 4% liposomal cream when applied to intact skin; the maximum recommended absorbed lidocaine dose is 5 mg/kg. EMLA, eutectic mixture of lidocaine (2.5%) and prilocaine (2.5%); NA, information not available.

EMLA® (Eutectic Mixture of Lidocaine and Prilocaine)

Introduction and mechanism of action

EMLA® is a eutectic mixture of lidocaine (2.5%) and prilocaine (2.5%), both sodium channel-blocking amide anesthetics (see Ch. 143).

Dosages and application

EMLA® is available as an oil-in-water emulsion cream and a disc (which itself provides occlusion). It is typically applied under occlusion 1 to 1.5 hours prior to a procedure; dermal anesthesia is achieved after application under occlusion for 2 to 3 hours[3]. The effectiveness and application time required vary depending on the location of treatment. On the palms and soles (with a thick stratum corneum), anesthesia is difficult to achieve even with prolonged application[4], while on mucosal surfaces (with no stratum corneum), analgesia develops in as little as 5 to 15 minutes[5]. The duration of anesthesia is approximately 1 hour.

Side effects

Application of EMLA® commonly causes transient blanching (vasoconstriction) or erythema at the application site; burning and irritation occasionally occur, and chemical injury to the eye has been described[4]. An uncommon petechial or purpuric reaction is thought to result from an idiosyncratic toxic effect on blood vessels[6]. Contact urticaria or allergic contact dermatitis, most often due to the prilocaine component, have also been reported. There is substantial systemic absorption when EMLA® is applied to mucosal surfaces[4]. Methemoglobinemia represents a potential complication of systemic exposure to prilocaine, and the surface area of application should be limited, especially in infants and children (Table 129.9). Symptoms of systemic toxicity (including methemoglobinemia) are listed in Table 129.8.

Contraindications

EMLA® should not be used in patients at increased risk for methemoglobinemia. This includes premature neonates with a gestational age <37 weeks (due to their immature reductase pathways) and individuals with pre-existing methemoglobinemia or glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Interactions

EMLA® should not be used in young children (especially those <1 year of age) receiving medications that may increase the risk of methemoglobinemia (e.g. acetaminophen, antimalarials, dapsone, nitrofurantoin, nitroglycerin, phenobarbital, phenytoin, sulfonamides)[4]. Caution is also advised for older children and adults receiving these medications.

Lidocaine

Several other lidocaine-containing topical anesthetic formulations are available (see Ch. 143), including a lidocaine–tetracaine patch that is applied for 10–20 minutes (e.g. Synera®) and needle-free powder or jet-injection lidocaine delivery systems (e.g. Zingo®, J-tip®). Lidocaine 4% or 5% in a liposomal cream (e.g. LMX®) is often used for cutaneous anesthesia, with application times of 30 to 60 minutes; occlusion is not required (but may be utilized). Prospective studies have shown that LMX® and EMLA® are equally effective in reducing needle-insertion pain. The amount of lidocaine that is systemically absorbed following topical application is directly related to the surface area to which it is applied and the duration of application; care should be taken when applying to large surface areas, and guidelines for pediatric patients are presented in Table 129.9. Signs and symptoms of systemic lidocaine toxicity (see Table 129.8) are uncommon and usually remit quickly upon removal of the medication from the skin[7].

Benzocaine

Topical benzocaine is an ester anesthetic that is found in a variety of over-the-counter topical preparations used for temporary amelioration of pain on the skin and mucous membranes. It is a potent contact sensitizer, and a recent analysis of patch testing data from the North American Contact Dermatitis Group demonstrated that half of all positive patch test reactions to local anesthetics were due to benzocaine[8].

ANTIPRURITIC AGENTS

Pruritus involves multiple components of the nervous system, including skin surface receptors, peripheral (especially unmyelinated C fibers) and central nerves, and specific brain regions (see Ch. 5). Treatment of the underlying dermatologic (e.g. with application of topical corticosteroids to inflamed skin and lubrication of dry skin) or systemic condition remains the most effective method of alleviating the sensation of itch. Topical antipruritic agents may help to reduce the urge to scratch, potentially improving the efficacy of skin disease-specific therapies. Mechanisms of topical antipruritics include substituting a different sensation for itching, anesthetizing cutaneous nerve endings and blocking molecular mediators of pruritus[9]. Unfortunately, a relative lack of comparative studies has made antipruritics difficult to evaluate. Commonly used agents are outlined in Table 129.10 (also see Table 5.5).

TOPICAL AGENTS USED TO ALLEVIATE PRURITUS			
Agent	**Classification/ derivation**	**Mechanism of action**	**Uses and side effects**
Pramoxine 1% (gel; in combination with 0.5–2.5% hydrocortisone in lotion, cream, ointment or foam)	Ester anesthetic	Blocks transmission of sensory nerve impulses; hypoalgesic effect on cold pain, but not warmth or heat pain[10]; duration of effect is 2–4 hours	• Beneficial for uremic pruritus[11] and histamine-induced itch; uses include pruritus ani, notalgia paresthetica and nonspecific mild pruritus • Allergic contact dermatitis is extremely uncommon
Menthol (up to 16% in a variety of lotions, creams, ointments and gels)	Cyclic terpene alcohol derived from plants in the *Mentha* genus	Activates TRPM8 cation channels, which also respond to cold thermal stimuli[12,13]; possible central itch modulation via Aδ fiber and/or κ-opioid receptor activation[14]	• Provides a cooling sensation • Inconsistent antipruritic results in controlled studies • Irritation, especially of inflamed or eroded skin; rare allergic contact dermatitis
Phenol	Originally a distillation product of coal tar	Thought to act directly on cold receptors	• Cooling and antipruritic effects; found in throat sprays and lozenges • Should not be used in pregnant women or infants <6 months of age • Irritation, especially of inflamed or eroded skin
Camphor (0.25–0.5%; various preparations)	Ketone originally derived from the camphor laurel tree (*Cinnamomum camphora*)	Local anesthetic effect	• Cooling sensation may relieve mild pruritus • Irritation, especially of inflamed or eroded skin
Capsaicin (0.025–0.075% cream, lotion, gel or stick; 8% patch)	Natural alkaloid; derived from Solanaceae family members, including hot chili peppers of the *Capsicum* genus	Activates the TRPV1 vanilloid receptor, which also responds to temperatures >43°C (109°F); repeated release of substance P from C neurons eventually leads to depletion of this neuropeptide (and reduced transmission of heat, pain and itch)[15]	• Applied three to five times daily or via a single 1-hour patch application • Initially evokes a sensation of warmth/ burning[16], with onset of the therapeutic effect ~1 week after initiation • Transdermal patch is FDA-approved for treatment of postherpetic neuralgia • Uses include notalgia paresthetica, brachioradial pruritus, renal pruritus, prurigo nodularis, psoriatic pruritus, and itch associated with a burning sensation • Burning, stinging and/or erythema at the application site occur in >50% of patients[17] • Hand washing after application helps to prevent contact with (and irritation of) other skin, the eyes and mucosal surfaces • Pregnancy category C
Doxepin 5% cream	Tricyclic compound	Potent histamine antagonist (H_1 and H_2); sedation via anticholinergic properties	• Applied four times daily for up to 7 days • Shown to relieve pruritus in patients with atopic dermatitis, lichen simplex chronicus and nummular eczema[18,19] • Drowsiness due to systemic absorption in ~25% of patients[20] • Occasionally irritant or (less often) allergic contact dermatitis; systemic contact dermatitis with subsequent administration of oral doxepin has been described • Contraindicated in patients with untreated narrow angle glaucoma or urinary retention and those receiving MAO inhibitors • Pregnancy category B; use during lactation is not recommended
Diphenhydramine (2% cream, lotion, gel or spray)	Antihistamine	H_1 histamine antagonist; localized anesthetic effect via blockage of sodium channels	• Use is *not recommended* due to lack of efficacy as an antipruritic agent and potency as topical sensitizer, which can lead to allergic contact dermatitis

Table 129.10 Topical agents used to alleviate pruritus. Calamine lotion is listed in Table 129.14. FDA, US Food and Drug Administration; MAO, monoamine oxidase; TRPM8, transient receptor potential melastatin 8; TRPV1, transient receptor potential vanilloid 1.

KERATOLYTIC AGENTS

Keratolytic agents reduce the thickness of the stratum corneum via elimination of squames. This can be beneficial in diseases characterized by reduced desquamation or accelerated epidermal proliferation. Use of these agents in cosmeceutical products and chemical peels is discussed in Chapters 153 and 154.

Urea

Introduction, dosages and indications

Topical urea, first synthesized in 1828 by the German chemist Frederich Wohler, has several applications in dermatology, including use as a humectant and mild keratolytic at low concentrations (10–25%) and as a hygroscopic keratolytic at higher (40–50%) concentrations. It

is occasionally employed to improve the penetration of other topical medications or for chemical nail avulsion[21]. Topical urea is available in a variety of formulations, including over-the-counter and prescription creams, lotions, gels, solutions and foams.

Mechanism of action

Urea enhances the water-binding capacity of protein. When applied topically, it incorporates itself into the stratum corneum and absorbs water from the atmosphere, which enhances barrier function by decreasing transepidermal water loss, increasing skin hydration and decreasing sensitizing effects of topical irritants[22]. The keratolytic mechanism of urea is thought to be related to its hygroscopic character, with absorption of water leading to physical alteration of the epidermis and desquamation of corneocytes[23].

Side effects

Although it is generally well tolerated, urea can cause irritation and/or burning at sites of application, especially on inflamed or eroded/fissured skin.

Use in pregnancy

Urea is pregnancy category B.

Salicylic Acid

Introduction, dosages and indications

Derived from the bark of the willow tree *Salix alba*, this β-hydroxy acid is used in the treatment of a variety of dermatologic diseases. Topical formulations containing salicylic acid include creams, lotions, ointments, gels, foams, solutions, shampoos, cleansers, pads and plasters, many of which can be obtained without a prescription. Lower concentrations (1–6%) are utilized for hyperkeratotic dermatoses, while higher concentrations (10–40%) are applied to corns, calluses, warts and focal hyperkeratosis. Low concentrations (0.5–2%) are also used for comedolytic effects in patients with acne.

Mechanism of action

Salicylic acid alters corneocyte adhesion[24], possibly by disrupting or extracting desmosomal proteins[25]. This can result in increased penetration of other topical agents. Salicylic acid may also have antimicrobial and mild anti-inflammatory effects.

Side effects

Depending upon the site and concentration, topical application of salicylic acid can result in irritation, peeling or even erosions; allergic contact dermatitis is uncommon but has been described[24]. Systemic absorption may result from extensive application, especially in neonates and infants; this can lead to salicylism, with gastrointestinal and neurologic toxicity[21,24] (see Table 129.8).

Use in pregnancy

Salicylic acid is pregnancy category C, and premature closure of the ductus arteriosus in the fetus (with subsequent pulmonary hypertension in the neonatal period) has been reported with extensive use in late pregnancy.

Alpha-hydroxy Acids

Introduction, dosages and indications

Alpha-hydroxy acids (AHAs) include glycolic, lactic, mandelic, tartaric, malic and citric acids (see Ch. 153). Lactic and glycolic acids are most commonly used in dermatologic therapy and are found at various concentrations and pH levels in a myriad of formulations, including cleansers, shampoos, lotions, creams, gels, masks and peeling agents. AHAs were first noted to have effects on corneocyte adhesion when their therapeutic role in the management of ichthyoses was described in 1974[26]. Other dermatologic conditions for which AHAs are utilized include xerosis, acne vulgaris, rosacea and photoaging.

Mechanism of action

AHAs diminish the strength of intercellular bonding, thereby weakening corneocyte cohesion and leading to exfoliation[27]. Unlike other "true" keratolytics, which cause disaggregation of corneocytes high in the stratum corneum, AHAs tend to influence corneocyte cohesion at lower, newly forming levels of the cornified layer[27]. Higher concentrations of AHAs may have dermal (e.g. increased thickness) as well as epidermal effects[28].

Side effects

Topical AHAs are generally well tolerated but can cause irritation and/or burning at sites of application (especially on inflamed or eroded/fissured skin).

Propylene Glycol

Propylene glycol is a sweet, viscous fluid that is soluble in water. It is used as a keratolytic agent at a concentration of 10–20%. Irritation is marked at higher concentrations. Propylene glycol is also employed as a preservative and a penetration enhancer.

SKIN-LIGHTENING AGENTS

Hydroquinone

Introduction, dosages and indications

Hydroquinone (1,4-dihydroxybenzene) is used for treatment for melasma and other disorders of hyperpigmentation[29] (see Ch. 67). In the US, 2% formulations are available over-the-counter, while 3% solution and 4% cream or gel require a prescription. Twice-daily application to affected areas is commonly recommended. Other products contain hydroquinone in combination with a sunscreen or with tretinoin (0.05–0.1%) and a class 5–7 corticosteroid[30].

Mechanism of action

Hydroquinone works as a bleaching agent by competing with tyrosine as a substrate for tyrosinase (the initial enzyme in melanin biosynthesis; see Ch. 65) and via selective damage to melanosomes and melanocytes by production of highly reactive oxygen radicals[29].

Side effects

Irritant or (less often) allergic contact dermatitis can develop. Exogenous ochronosis occasionally occurs with prolonged use of higher concentrations of hydroquinone. A variety of neoplasms have been noted to develop in rodents that received large systemic doses of the medication, but the relevance to topical therapy in humans has not been determined[29]. Concern regarding potential adverse effects related to misuse of hydroquinone led to its removal from Japanese and European markets.

Use in pregnancy

Hydroquinone is pregnancy category C.

Monobenzyl Ether of Hydroquinone

Monobenzyl ether of hydroquinone (MBEH) is infrequently used to depigment remaining normal skin in patients with extensive vitiligo in order to achieve a uniform appearance (see Ch. 66). MBEH was shown in 1951 to have an inhibitory effect on the tyrosine–tyrosinase reaction, thereby preventing melanin formation[31]. It is thought to act via competitive inhibition of tyrosinase and free-radical-mediated damage of melanocytes. Depigmentation is typically long-lasting, but repigmentation (especially in a perifollicular distribution) can reappear following intense sun exposure. Irritant and allergic contact dermatitis represent possible side effects[32].

Mequinol

Mequinol (4-hydroxyanisole) is a skin-lightening agent; a solution composed of mequinol 2% and tretinoin 0.01% is FDA-approved for the treatment of solar lentigines. Mequinol is a substrate of tyrosinase

and may serve as a competitive inhibitor of melanin biosynthesis[29]. The mequinol–tretinoin combination product is pregnancy category X.

AGENTS THAT AFFECT HAIR GROWTH

Both unwanted excessive hair and hair loss are common dermatologic complaints, and the underlying disorders may respond to topical therapy. Minoxidil and eflornithine are reviewed here, and a protocol for topical immunotherapy with diphencyprone (DPCP) or squaric acid dibutyl ester (SADBE) for alopecia areata is presented in Table 69.5.

Minoxidil

Introduction, dosages and indications

Originally developed as an antihypertensive agent, minoxidil has been known for decades to promote hair growth. Available in 2% and 5% solutions and a 5% foam, topical minoxidil is FDA-approved for the treatment of androgenetic alopecia in both men and women (see Ch. 69). It is also used for other forms of hair loss, including alopecia areata. Minoxidil is typically applied twice daily to the scalp[33].

Mechanism of action

Minoxidil causes premature termination of the telogen phase, lengthens the anagen phase and can increase follicle size (particularly of miniaturized follicles)[33,34]. Stimulation of vascular endothelial growth factor and prostaglandin synthesis may also play a role[34]. Although oral minoxidil relaxes vascular smooth muscle by opening ATP-dependent potassium channels, this mechanism has not been definitively linked to stimulation of hair growth[34].

Side effects

While generally well-tolerated, minoxidil can cause dryness, irritation and (uncommonly) allergic contact dermatitis. It may also result in unwanted hair growth at sites inadvertently exposed to the medication (e.g. the face or ears). Systemic side effects such as headache and peripheral edema are occasionally observed.

Use in pregnancy

Minoxidil is pregnancy category C.

Eflornithine

Eflornithine 13.9% cream is a prescription treatment for excessive and unwanted facial hair in women. It irreversibly inhibits ornithine decarboxylase in the skin, leading to decreased polyamine synthesis and arrest of follicular matrix cell proliferation[35]. Twice-daily application for 24 weeks has been shown to significantly decrease facial hair[35], and use of eflornithine together with laser hair removal may result in more rapid and complete reduction in facial hair than laser treatment alone[36]. Eflornithine is usually well tolerated, with occasional burning or acneiform eruptions at sites of application[35]; it is pregnancy category C.

CHEMOTHERAPEUTIC AGENTS

5-Fluorouracil

Mechanism of action

5-Fluorouracil (5-FU) is a pyrimidine analogue that interferes with DNA synthesis by irreversibly inhibiting thymidylate synthetase, which prevents cellular proliferation and results in cell death (preferentially affecting rapidly dividing cells)[37]. It is also incorporated into DNA and RNA, leading to DNA breakage and decreased protein synthesis, and it disrupts the exosome complex that degrades RNA.

Indications and dosages

The primary dermatologic use of topical 5-FU is the treatment of actinic keratoses (AKs; see Ch. 108)[38]. 5-FU is particularly helpful in treating numerous AKs and sites of severe actinic damage without clinically evident lesions. It is less effective for hypertrophic AKs owing to decreased percutaneous absorption through the thickened stratum corneum. Additional dermatologic applications of topical 5-FU include the treatment of actinic cheilitis, squamous cell carcinoma *in situ* (Bowen's disease), superficial basal cell carcinoma, cutaneous and genital warts, porokeratoses, nail psoriasis and extramammary Paget's disease[38]. It can also improve the appearance of photoaged skin via epidermal injury and subsequent dermal remodeling (similar to that seen following laser therapy)[39].

5-FU is available in both cream (0.5%, 1% and 5%) and solution (2% and 5%) formulations. Regimens vary depending on the concentration and vehicle as well as the indication and anatomic location (requiring a longer duration on the extremities than the face). 5-FU is typically applied once or twice daily for 2 to 6 weeks. Pretreatment with a topical retinoid for 2 weeks can increase efficacy on the extremities and trunk.

Side effects

During treatment of AKs, the skin progresses through stages of erythema (sometimes painful and associated with edema), crusted erosions and re-epithelialization. The principal side effects are related to this localized inflammatory response (Fig. 129.3), which is occasionally

Fig. 129.3 Reactions to topical 5-fluorouracil. A Inflammation with erythema and crusting at site of actinic keratoses on the forehead. **B** Large red–purple patches at sites of application on the upper chest in a patient with severe photodamage. **C** Erythema and crusting of photodamaged skin on the dorsal forearm. *B, C, Courtesy, Jean L Bolognia, MD.*

followed by residual pigmentary changes. A mid-potency topical corticosteroid can be applied for symptomatic relief once peak inflammation has been attained. Systemic adverse events are extremely rare, and absorption studies show that systemic levels of 5-FU after topical application are very low[38].

Contraindications and use in pregnancy

Use of 5-FU is contraindicated in patients with a history of hypersensitivity to this agent and those with dihydropyrimidine dehydrogenase deficiency. 5-FU is potentially teratogenic and is classified as pregnancy category X; use during pregnancy and lactation is contraindicated.

Mechlorethamine Hydrochloride

Introduction, dosages and indications

Mechlorethamine hydrochloride (HCl) (a form of nitrogen mustard) was introduced in 1959 and is used in the treatment of limited or generalized patch/plaque-stage mycosis fungoides (MF). Concentrations ranging from 10 to 40 mg/dl (0.01–0.04% w/w) are compounded in an ointment or (less often) aqueous solution. This is typically applied daily to affected areas or the entire body (sparingly to the skin folds and excluding genitalia) until clearance is achieved, which typically takes 6–12 months with ointment and 1–4 months with aqueous solution. A complete response occurs in approximately 65–75% of patients with patch/plaque-stage MF[40].

Mechanism of action

Mechlorethamine HCl is an alkylating agent (i.e. donates alkyl groups to DNA), with cytotoxicity that preferentially affects rapidly dividing cells. Immunostimulatory effects have also been postulated to have a role in the treatment of patients with MF[40].

Side effects

Irritant and/or allergic contact dermatitis occurs in approximately half of patients and may result in interruption of treatment. However, irritant reactions often improve with continued use, and patients can be desensitized if necessary. Other potential side effects include pruritus, xerosis, hyperpigmentation, urticaria, anaphylaxis and (with prolonged use) development of squamous cell carcinoma[40].

Use in pregnancy

Mechlorethamine HCl is pregnancy category D; use during pregnancy or lactation is contraindicated.

Carmustine

Introduction, dosages and indications

Topical nitrosoureas have been utilized in the treatment of MF since 1972[41]. Carmustine (1,3-bis [2-chloroethyl]-1-nitrosourea; BCNU) currently represents a second- or third-line therapeutic option for MF, due to the potential for hematologic complications secondary to systemic absorption. Like mechlorethamine HCl, it is available in an aqueous solution and ointment. Carmustine is applied once or twice daily until clearance of the treated areas occurs, which typically requires 1 to 4 months when the aqueous solution is used and 6 to 12 months with the ointment. A complete response is achieved in 85% of patients with limited patch/plaque-type disease (T1) and nearly 50% of those with generalized patch/plaque-type disease (T2)[40,42].

Mechanism of action

Carmustine is a nitrosourea alkylating agent that produces alkylation and subsequent cross-linking of DNA, thereby disrupting DNA synthesis and resulting in cytotoxicity that preferentially affects dividing cells[40].

Side effects

Erythema, tenderness, bullae and persistent telangiectasias can develop at application sites[40]. Allergic contact dermatitis occurs less frequently than with mechlorethamine HCl. However, higher levels of systemic absorption (5–30% of the administered dose) can lead to side effects such as mild to moderate myelosuppression[43].

Use in pregnancy

Carmustine is pregnancy category D; use during pregnancy or lactation is contraindicated.

VITAMIN D ANALOGUES

Mechanism of action

The skin serves as both a site of vitamin D biosynthesis (see Fig. 51.10) and a target organ for its ultimate activity. The cutaneous effects of 1,25-dihydroxyvitamin D_3 (calcitriol, the active form of vitamin D; Fig. 129.4) include inhibiting proliferation and promoting differentiation of keratinocytes as well as immunomodulatory actions such as decreasing production of inflammatory mediators (e.g. interleukin [IL]-2, IL-6, IL-8, interferon-γ and chemokines)[44]. Vitamin D exerts its regulatory functions by binding to vitamin D receptors (VDRs) on keratinocytes, melanocytes, Langerhans cells, macrophages, T cells and fibroblasts.

Topical agents and their indications

Several vitamin D analogues are available for clinical use: calcipotriene (calcipotriol) (Fig. 129.5), calcitriol, tacalcitol and maxacalcitol; their formulations and dosing are presented in Table 129.11. The primary indication for these agents is the treatment of psoriasis[45–49], and they are occasionally used for other skin conditions such as vitiligo, morphea, ichthyoses and Hailey–Hailey disease. Application of a vitamin D analogue in combination with a high-potency or superpotent topical corticosteroid in patients with psoriasis can have greater efficacy and a more rapid onset of action than either agent alone, as well as less irritation than the vitamin D analogue alone[46]. Additive benefits can also occur when vitamin D analogues are used together with acitretin, cyclosporine or phototherapy (narrowband or broadband UVB, psoralen plus UVA; applied after phototherapy

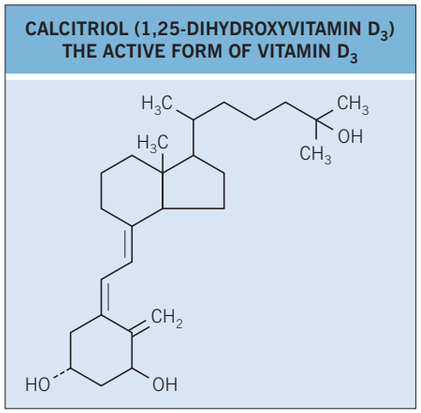


Fig. 129.4 Calcitriol (1,25-dihydroxyvitamin D_3), the active form of vitamin D_3.

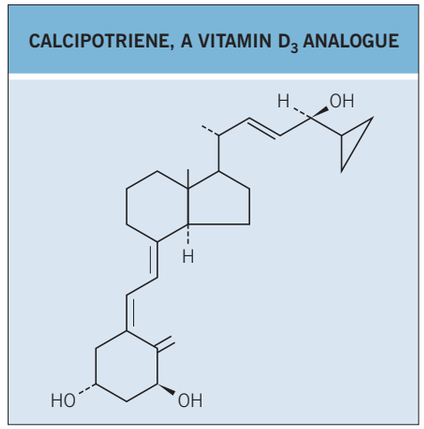


Fig. 129.5 Calcipotriene (calcipotriol), a vitamin D_3 analogue.

TOPICAL VITAMIN D_3 AND ITS ANALOGUES		
Agent	**Available formulations**	**Maximum weekly dose**
Calcipotriene (calcipotriol) 0.005% (50 microg/g)	Cream, ointment, solution; combined with betamethasone dipropionate 0.064% in an ointment and suspension	100 g
Calcitriol [1,25$(OH)_2D_3$] 3 microg/g	Ointment	200 g
Tacalcitol [1,24$(OH)_2D_3$] 4 microg/g*	Ointment, lotion	70 g
Maxacalcitol 25 microg/g*	Ointment, lotion	70 g
*Not available in the US.		

Table 129.11 Topical vitamin D_3 and its analogues. These agents are typically applied twice daily. In general, treatment of >30% of the body surface area is not recommended. Calcipotriene is the US Adopted Name (USAN) and calcipotriol is the International Nonproprietary Name (INN).

SAMPLE PROTOCOL FOR SHORT-CONTACT ANTHRALIN THERAPY FOR ALOPECIA AREATA
• Anthralin 0.5% cream is applied sparingly to affected areas of the scalp daily, followed by washing with shampoo/soap and water • An initial application time of 10 minutes is increased in 10-minute increments every 4–5 days until slight irritation (e.g. erythema, scaling, pruritus) occurs • If excessive irritation develops, treatment is withheld for several days and resumed at the last tolerated application time • If there is no irritation with a 60-minute contact time, 1% anthralin is applied for 10 minutes and application times increased as above • If there is no irritation with 1% anthralin applied for 60 minutes, overnight application is considered • Initial responses are typically seen within 12 weeks; cosmetically acceptable responses require a mean of 24 weeks
ADDITIONAL INFORMATION
• Brownish staining of treated areas of the scalp and hair is expected • To prevent staining of clothing, bedding and furniture, patients should wash their hands thoroughly after applying anthralin and avoid touching fabrics with their scalp until it has been washed off • Avoid getting anthralin into the eyes; do not apply to eyelids or eyelashes • Special care should be taken in sensitive areas (areas of scalp near the ears, eyebrows)

Table 129.12 Sample protocol for short-contact anthralin therapy for alopecia areata. *Courtesy, Julie V Schaffer, MD, and Jean L Bolognia, MD.*

sessions to avoid degradation by UV light) in the treatment of psoriasis and (for phototherapy) vitiligo.

Side effects

The most common side effect is irritation, burning and stinging at the application site, which limits the use of vitamin D analogues on the face and in intertriginous areas. Allergic contact dermatitis has been described with calcipotriene. The systemic effects of vitamin D and its analogues include releasing calcium from the bone, increasing renal tubular reabsorption and intestinal absorption of calcium, and decreasing parathyroid hormone release. Use of excessive amounts (see Table 129.11) of topical vitamin D analogues can lead to hypercalcemia and hypercalciuria. Parathyroid hormone levels should be monitored if use of these medications exceeds the recommended amounts. Patients with renal disease and those receiving medications that can increase the serum calcium level (e.g. thiazide diuretics, high doses of oral vitamin D) may be at increased risk of developing hypercalcemia.

Use in pregnancy

Calcipotriene and calcitriol are pregnancy category C.

MISCELLANEOUS AGENTS

Tar

Introduction and indications

Topical tar has served as a skin-directed therapy for over 2000 years, since the Greek physician Dioscorides applied "asphalt" to manage several cutaneous diseases[50]. Among the various types of tar (e.g. wood, bituminous [shale], petroleum, coal), coal tar is most often used as a dermatologic treatment. Currently, tar is utilized primarily in the management of psoriasis and several forms of dermatitis (e.g. seborrheic, nummular, atopic), most commonly in conjunction with other therapeutic modalities. For example, the classic Goeckerman regimen employs topical tar in combination with UVB radiation for the treatment of psoriasis[51].

Dosages

Coal tar in concentrations of 0.5% to 10% is available (or can be compounded) in a broad array of vehicles, including ointment, lotion, gel, foam, solution, oil, shampoo and soap. Liquor carbonis detergens is a distillate of crude car tar that is typically used in concentrations of 3% to 10%.

Mechanism of action

Coal tar is thought to suppress DNA synthesis, which may lead to normalization of epidermal differentiation in conditions such as psoriasis[50]. It appears to have anti-inflammatory, antimicrobial and antipruritic effects. In animal studies, tar has been found to decrease sebum secretion. Coal tar (but not other forms of tar) also has a photosensitizing effect in the 330–550 nm range of the UVA and visible light spectra[50].

Side effects

The unpleasant odor, messiness and staining potential of topical tar limit its use. Acneiform eruptions, folliculitis and irritant contact dermatitis (including pustules within plaques of psoriasis) may occur at application sites, and "tar smarts" can develop following exposure to UVA radiation. Ever since Sir Percival Pott described an increased risk of scrotal cancer in chimney sweepers in 1775, tar has been implicated as a potential carcinogen[50]. However, the evidence that topical tar formulations used in the treatment of skin disease result in an increased risk of skin cancer is inconclusive.

Use in pregnancy

Coal tar is pregnancy category C.

Anthralin

Introduction, dosages and indications

Anthralin, the synthetic form of chrysarobin (a substance found in the bark of the South American araroba tree), has been used in the treatment of dermatologic conditions for more than 80 years[52]. It is currently available in 0.5% and 1% creams. Although no longer commonly used for psoriasis, short-contact anthralin therapy (with gradual increases in the application time ± concentration) continues to be employed to treat alopecia areata via induction of an irritant effect (Table 129.12)[52].

Mechanism of action

Anthralin induces a brisk inflammatory response at sites of application, which may result from the generation of extracellular oxygen free radicals[52]. Inhibition of mitochondrial respiration and cell growth are thought to reduce keratinocyte proliferation and lead to antipsoriatic effects.

Side effects

Use of anthralin is limited by irritation at application sites (which depends on the concentration and contact time) and staining of skin, clothing, and household items (e.g. bed sheets, furniture). Staining and irritation can be ameliorated by the application of triethanolamine 10% cream to treatment sites after removal of the anthralin-containing product.

Use in pregnancy

Anthralin is pregnancy category C.

Podophyllin and Podophyllotoxin

Introduction, dosages and indications

Podophyllin resin is a crude extract from the May apple plant (*Podophyllum peltatum* or *Podophyllum emodi*) that has been employed for decades to treat condyloma acuminata. However, the concentration of its most active ingredient is not standardized in the 10–25% solutions that are applied in the physician's office weekly and washed off 1 to 4 hours later[53]. In contrast, podophyllotoxin is available in a stable and standardized 0.5% solution and gel as well as a 0.15% cream. These compounds lack the mutagens that are found in podophyllin and can be applied by the patient, usually twice daily for three consecutive days each week for 4 to 6 weeks. Reported clearance rates for condyloma acuminata range from 30% to 60% with podophyllin and from 45% to 75% with podophyllotoxin[53].

Mechanism of action

Podophyllin and podophyllotoxin act by arresting mitosis through reversible binding to tubulin.

Side effects

Common adverse effects associated with both podophyllin and podophyllotoxin include burning, erythema and skin breakdown at application sites. The extent of irritation may be reduced by application of petrolatum to the unaffected skin surrounding the warts that are treated. Because of its percutaneous absorption, application of large amounts of podophyllin can result in systemic toxicity (see Table 129.8).

Use in pregnancy

Use of podophyllin during pregnancy is contraindicated due to its teratogenic effects. However, podophyllotoxin is pregnancy category C.

SAMPLE PROTOCOL FOR TOPICAL IMMUNOTHERAPY WITH SQUARIC ACID DIBUTYL ESTER FOR CUTANEOUS WARTS
• Sensitize with a 2% SADBE solution in acetone applied to a small (e.g. 2 cm × 2 cm) area on the inner aspect of the upper arm; cover with a dressing and do not wash for 24 hours • After 1 week (2 weeks if the initial reaction was severe), apply 0.2% SADBE solution to non-facial warts; cover with a light dressing and wash after 12–24 hours • Apply approximately twice weekly to warts; can increase or decrease the length of time between treatments depending on the duration of the reaction (e.g. repeat application once the erythematous/eczematous reaction has subsided) • If there is no inflammation or response of the warts after 2–4 weeks, increase the concentration to 0.5% (and subsequently to 1% and 2% as needed); decrease concentration (e.g. from 0.2% to 0.1%) and/or amount applied if excessive inflammation (e.g. more than mild erythema and pruritus) • Responses are usually seen within 3 months, with complete clearance in 60–80% of patients after a mean of 6–8 weeks
ADDITIONAL INFORMATION
• The acetone solution should be applied using a cotton-tip applicator • SADBE should be refrigerated and protected from light • Side effects include severe or widespread eczematous reactions (which can be treated with topical or, if required, systemic corticosteroids), lymphadenopathy and postinflammatory pigment alterations (especially in patients with darkly pigmented skin)

Table 129.13 Sample protocol for topical immunotherapy with squaric acid dibutyl ester (SADBE) for cutaneous warts. This is not an FDA-approved medication.

Cantharidin

Introduction, dosages and indications

Cantharidin is a vesicant derived from "blister beetles" in the Coleoptera order and Meloidae family. It has been used since the 1950s for the treatment of warts and molluscum contagiosum. Although cantharidin met the safety requirements outlined by the Food, Drug and Cosmetic Act of 1938, it lost its FDA approval in 1962 when its manufacturers failed to submit required efficacy data[54]. A 0.7% concentration of cantharidin is currently available in a film-forming collodion vehicle; another formulation (primarily used for warts) combines 1% cantharidin with 2% podophyllin and 30% salicylic acid.

A thin film of cantharidin is typically applied to lesions in the office. After drying, occlusion may be used. The residual film is washed off

TRADITIONAL TOPICAL MEDICATIONS		
Agent	**Components**	**Classic uses**
1-2-3 paste	Burow's solution, petrolatum, zinc oxide	Hand eczema, erosions, ulcerations
Aqueous silver nitrate 10% solution*	Silver nitrate	Small recalcitrant ulcerations
Black cat*	Acetone, collodion, crude coal tar	Psoriasis, lichen simplex chronicus, nummular eczema, hypertrophic lichen planus
Burow's solution	Aluminum acetate	Weeping, macerated and/or (super)infected skin conditions, especially in intertriginous and acral sites (e.g. tinea pedis/cruris, candidiasis)
Calamine lotion	Zinc oxide, ferric oxide, glycerin, bentonite magma, calcium hydroxide solution (lime water)	Acute and subacute pruritic dermatoses
Castellani's paint (carbol fuchsin)	Phenol, resorcinol, basic fuchsin (without the latter in colorless version)	Cutaneous candidiasis, tinea pedis/cruris, pustular dermatoses of the hands and feet
Chrysarobin*	Chrysarobin, chloroform	Chronic paronychia
Fluffy tannic acid powder*	Fluffy tannic acid, bentonite, kaolin	Hyperhidrosis, contact dermatitis of the hands/feet
Gentian violet solution	Gentian violet	Candidiasis, tinea pedis/cruris
P&S® liquid	Mineral oil, glycerin, phenol	Psoriasis/sebopsoriasis with excessive hyperkeratosis (especially of the scalp)
Potassium permanganate	$KMnO_4$	Weeping, macerated and/or (super)infected skin conditions, especially in intertriginous and acral sites (e.g. tinea cruris/pedis, candidiasis)
Schamberg's lotion*	Menthol, phenol, zinc oxide, calcium hydroxide solution, olive oil	Acute and subacute pruritic dermatoses
Whitfield's ointment	Benzoic acid (6%), salicylic acid (3%)	Tinea pedis

*Primarily of historical interest.

Table 129.14 Traditional topical medications.

NEWER PRESCRIPTION BARRIER-REPAIR/MOISTURIZING AGENTS	
Agent	**Active ingredients**
Atopiclair®/Pruclair™ cream	Glycyrrhetinic acid (licorice root), *Vitis vinifera* (grape vine) extract, *Butyrospermum parkii* (shea butter), hyaluronic acid, telmesteine
Eletone® cream	70% oil (mineral oil, white petrolatum) dispersed in 30% water
EpiCeram emulsion	3:1:1 molar ratio of ceramide, cholesterol and free fatty acids (e.g. capric, linoleic, palmitic acids)
Hylatopic® (Plus) emollient foam	*Theobroma grandiflorum* seed butter, hyaluronic acid, ceramide (latter in "Plus" version)
MimyX®/PruMyx™ cream	Palmitamide monoethanolamine, palm glycerides, hydrogenated lecithin, squalane, olive oil
Neosalus™ foam	Dimethicone, stearic acid
Promiseb™ cream	Glycyrrhetinic acid, *Vitis vinifera* extract, *Butyrospermum parkii*, piroctone olamine, hydrogenated castor oil, telmesteine
Tetrix™ cream	Aluminum magnesium hydroxide stearate, cyclomethicone, dimethicone, hexyl laurate

Table 129.15 Newer prescription barrier-repair/moisturizing agents. These agents are FDA-approved as "medical devices" and available by prescription. Over-the-counter barrier-repair moisturizers containing ceramides (e.g. CeraVe® cream or lotion) or "pseudoceramides" and filaggrin breakdown products (Cetaphil®, Restoraderm® moisturizer) are also available.

thoroughly with soap and water or rubbing alcohol by the patient (or a parent) 2 to 6 hours after application. Blisters typically form during the next 24 hours, followed by superficial erosions; healing of treated areas (with temporary residual erythema) occurs over a period of 4 to 7 days[54]. Benefits of cantharidin use include painless application (particularly advantageous in young children) and a lack of scarring.

Mechanism of action

Cantharidin acts via release of neutral serine proteases that cause desmosomal plaque degeneration, leading to detachment of desmosomes from tonofilaments; resultant acantholysis is intraepidermal and therefore non-scarring[54].

Side effects

The blisters and erosions that form after cantharidin treatment can be painful or pruritic, and postinflammatory hypopigmentation may take several months to resolve. Use of cantharidin to treat warts occasionally results in a "doughnut wart" due to clearance in the center but not at the periphery of the lesion. Cantharidin poisoning has been described following ingestion, with potential sequelae including blistering and erosions in the mouth and gastrointestinal tract as well as dysuria, hematuria and renal failure. Standard in-office application of cantharidin, however, does not generally cause systemic effects.

Sulfur

Introduction

Sulfur, a yellow non-metallic element, has long been employed as a treatment for dermatologic conditions such as seborrheic dermatitis, rosacea, acne, pityriasis versicolor and scabies. Sulfur is typically used in concentrations ranging from 2% to 10%, often in combination with a second agent, e.g. 2% sulfur plus 2% salicylic acid in shampoos (used for seborrheic dermatitis) or 5% sulfur plus 10% sodium sulfacetamide in a cream, suspension or gel (used for rosacea, acne and seborrheic dermatitis; see Ch. 127).

Mechanism of action

Sulfur has antibacterial, antifungal and keratolytic properties.

Side effects

An offensive odor similar to that of rotten eggs (due to elaboration of H_2S) limits the use of sulfur in the absence of masking fragrances. Side effects are generally mild and include dryness and pruritus.

Contraindications

Topical sulfur is contraindicated in patients with a sensitivity to sulfur.

Use in pregnancy

Topical sulfur (5–10%) has been used to treat scabies in pregnant and lactating women, but precise safety data are lacking.

Azelaic Acid

Introduction and indications

Azelaic acid, a naturally occurring dicarboxylic acid, is used in the treatment of rosacea, acne vulgaris, melasma and postinflammatory hyperpigmentation.

Mechanism of action

Azelaic acid inhibits the production of free radical oxygen by neutrophils. This reduces oxidative tissue injury at sites of inflammation and decreases melanin production. Studies have also demonstrated selective cytotoxic and antiproliferative effects on hyperactive and abnormally proliferating melanocytes, with little effect on normal melanocytes. In addition, azelaic acid has antimicrobial activity against *Propionibacterium acnes* and *Staphylococcus epidermidis* as well as moderate anti-comedogenic properties via modification of epidermal keratinization.

Dosages

Azelaic acid, available in a 20% cream and 15% gel, is applied twice daily.

Side effects

Azelaic acid may cause mild to moderate irritant contact dermatitis (e.g. dryness, peeling, erythema), which often subsides after 2 to 4 weeks of treatment.

Use in pregnancy

Azelaic acid is pregnancy category B.

Diclofenac Sodium

Diclofenac sodium 3% in a gel vehicle containing hyaluronic acid is FDA-approved for the treatment of AKs. This nonsteroidal anti-inflammatory drug (NSAID) inhibits cyclooxygenase (COX)-2 and (to a lesser degree) COX-1. Its mechanism of action against AKs is thought to involve induction of apoptosis, alteration of cellular proliferation and inhibition of angiogenesis. Twice-daily application for 60 to 90 days results in AK clearance rates of up to 30–50%, with potential side effects including irritant, allergic and photoallergic contact dermatitis. Diclofenac is pregnancy category B.

Topical Immunotherapy

A sample protocol for topical immunotherapy with squaric acid dibutyl ester (SADBE) for cutaneous warts is outlined in Table 129.13, and a protocol for SADBE or diphencyprone for alopecia areata is presented in Table 69.6.

The Old and the New

Topical agents of historical interest are presented in Table 129.14. Many newer barrier-repair creams and moisturizers have purported benefit in the management of various dermatoses, such as atopic dermatitis and irritant contact dermatitis; these agents and their active ingredients are listed in Table 129.15.

REFERENCES

1. Long CC, Finlay AY. The finger-tip unit – a new practical measure. Clin Exp Dermatol. 1991;16:444–7.
2. Railan D, Alster TS. Use of topical lidocaine for cosmetic dermatologic procedures. J Drugs Dermatol. 2007;6:1104–8.
3. Gupta AK, Sibbald RG. Eutectic lidocaine/prilocaine 5% cream and patch may provide satisfactory analgesia for excisional biopsy or curettage with electrosurgery of cutaneous lesions. J Am Acad Dermatol. 1996;35(3 Pt 1):419–23.
4. Friedman P, Mafong E, Friedman E, Geronemus R. Topical anesthetics update: EMLA and beyond. Dermatol Surg. 2001;27:1019–26.
5. Rylander E, Sjoberg I, Lillieborg S, Stockman O. Local anesthesia of the genital mucosa with a lidocaine/prilocaine cream (EMLA) for laser treatment of condylomata acuminata: a placebo-controlled study. Obstet Gynecol. 1990;75:302–6.
6. Neri I, Savoia F, Guareschi E, et al. Purpura after application of EMLA cream in two children. Pediatr Dermatol. 2005;22:566–8.
7. Huether MJ, Brodland DG. Local anesthetics. In: Wolverton SE (ed). Comprehensive Dermatologic Drug Therapy, 2nd edn. Philadelphia: Saunders, 2007.
8. Warshaw EM, Schram SE, Belsito DV, et al. Patch-test reactions to topical anesthetics: retrospective analysis of cross sectional data, 2001–2004. Dermatitis. 2008;19:81–5.
9. Hercogova J. Topical anti-itch therapy. Dermatol Ther. 2005;18:341–3.
10. Yosipovitch G, Maibach HI. Effect of topical pramoxine on experimentally induced pruritus in humans. J Am Acad Dermatol. 1997;37(2 Pt 1):278–80.
11. Young TA, Patel TS, Camacho F, et al. A pramoxine-based anti-itch lotion is more effective than a control lotion for the treatment of uremic pruritus in adult hemodialysis patients. J Dermatolog Treat. 2009;20:76–81.
12. McKemy DD, Neuhausser WM, Julius D. Identification of a cold receptor reveals a general role for TRP channels in thermosensation. Nature. 2002;416:52–8.
13. Peier AM, Moqrich A, Hergarden AC, et al. A TRP channel that senses cold stimuli and menthol. Cell. 2002;108:705–15.
14. Patel T, Ishiuji Y, Yosipovitch G. Menthol: a refreshing look at this ancient compound. J Am Acad Dermatol. 2007;57:873–8.
15. Lynn B. Capsaicin: actions on nociceptive C-fibres and therapeutic potential. Pain. 1990;41:61–9.
16. Caterina MJ, Schumacher MA, Tominaga M, et al. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature. 1997;389:816–24.
17. Mason L, Moore RA, Derry S, et al. Systematic review of topical capsaicin for the treatment of chronic pain. BMJ. 2004;328:991.
18. Drake LA, Millikan LE. The antipruritic effect of 5% doxepin cream in patients with eczematous dermatitis. Doxepin Study Group. Arch Dermatol. 1995;131:1403–8.
19. Drake LA, Fallon JD, Sober A. Relief of pruritus in patients with atopic dermatitis after treatment with topical doxepin cream. The Doxepin Study Group. J Am Acad Dermatol. 1994;31:613–16.
20. Taylor JS, Praditsuwan P, Handel D, Kuffner G. Allergic contact dermatitis from doxepin cream. One-year patch test clinic experience. Arch Dermatol. 1996;132:515–18.
21. Hessel AB, Cruz-Ramon JC. Agents Used for treatment of hyperkeratosis. In: Wolverton SE (ed). Comprehensive Dermatologic Drug Therapy, 2nd edn. Philadelphia: Saunders, 2007.
22. Loden M. Urea-containing moisturizers influence barrier properties of normal skin. Arch Dermatol Res. 1996;288:103–7.
23. Hellgren L, Larsson K. On the effect of urea on human epidermis. Dermatologica. 1974;149:289–93.
24. Lin AN, Nakatsui T. Salicylic acid revisited. Int J Dermatol. 1998;37:335–42.
25. Imayama S, Ueda S, Isoda M. Histologic changes in the skin of hairless mice following peeling with salicylic acid. Arch Dermatol. 2000;136:1390–5.
26. Van Scott EJ, Yu RJ. Control of keratinization with alpha-hydroxy acids and related compounds. I. Topical treatment of ichthyotic disorders. Arch Dermatol. 1974;110:586–90.
27. Van Scott EJ, Yu RJ. Hyperkeratinization, corneocyte cohesion, and alpha hydroxy acids. J Am Acad Dermatol. 1984;11(5 Pt 1):867–79.
28. Smith WP. Epidermal and dermal effects of topical lactic acid. J Am Acad Dermatol. 1996;35(3 Pt 1):388–91.
29. Draelos ZD. Skin lightening preparations and the hydroquinone controversy. Dermatol Ther. 2007;20:308–13.
30. Torok HM, Jones T, Rich P, et al. Hydroquinone 4%, tretinoin 0.05%, fluocinolone acetonide 0.01%: a safe and efficacious 12-month treatment for melasma. Cutis. 2005;75:57–62.
31. Lea AJ. Effect of hydroquinone monobenzyl ether on melanin formation in vitro. Nature. 1951;167:906.
32. Dorsey CS. Dermatitic and pigmentary reactions to monobenzyl ether of hydroquinone: report of two cases. Arch Dermatol. 1960;81:245–8.
33. Price VH. Treatment of hair loss. N Engl J Med. 1999;341:964–73.
34. Messenger AG, Rundegren J. Minoxidil: mechanisms of action on hair growth. Br J Dermatol. 2004;150:186–94
35. Wolf JE Jr, Shander D, Huber F, et al.; Eflornithine HCl Study Group. Randomized, double-blind clinical evaluation of the efficacy and safety of topical eflornithine HCl 13.9% cream in the treatment of women with facial hair. Int J Dermatol. 2007;46:94–8.
36. Hamzavi I, Tan E, Shapiro J, Lui H. A randomized bilateral vehicle-controlled study of eflornithine cream combined with laser treatment versus laser treatment alone for facial hirsutism in women. J Am Acad Dermatol. 2007;57:54–9.
37. Longley DB, Harkin DP, Johnston PG. 5-fluorouracil: mechanisms of action and clinical strategies. Nat Rev Cancer. 2003;3:330–8.
38. Tsai EY, Zackheim HS, Kim YH. Topical and intralesional chemotherapeutic agents. In: Wolverton SE (ed). Comprehensive Dermatologic Drug Therapy, 2nd edn. Philadelphia: Saunders, 2007.
39. Sachs DL, Kang S, Hammerberg C, et al. Topical fluorouracil for actinic keratoses and photoaging: a clinical and molecular analysis. Arch Dermatol. 2009;145:659–66.
40. Berthelot C, Rivera A, Duvic M. Skin directed therapy for mycosis fungoides: a review. J Drugs Dermatol. 2008;7:655–66.
41. Zackheim HS. Treatment of mycosis fungoides with topical nitrosourea compounds. Arch Dermatol. 1972;106:177–82.
42. Zackheim HS, Epstein EH Jr, Crain WR. Topical carmustine (BCNU) for cutaneous T cell lymphoma: a 15-year experience in 143 patients. J Am Acad Dermatol. 1990;22(5 Pt 1):802–10.
43. Zackheim HS, Feldmann RJ, Lindsay C, et al. Percutaneous absorption of 1,3-bis (2-chlroethyl)-l-nitrosourea (BCNU, carmustine) in mycosis fungoides. Br J Dermatol. 1977;97:65–7.
44. Helfrich YR, Sachs DL, Kang S. Topical vitamin D3. In: Wolverton SE (ed). Comprehensive Dermatologic Drug Therapy, 2nd edn.. Philadelphia: Saunders, 2007.
45. Ashcroft DM, Po AL, Williams HC, Griffiths CE. Systematic review of comparative efficacy and tolerability of calcipotriol in treating chronic plaque psoriasis. BMJ. 2000;320:963–7.
46. Lebwohl M, Siskin SB, Epinette W, et al. A multicenter trial of calcipotriene ointment and halobetasol ointment compared with either agent alone for the treatment of psoriasis. J Am Acad Dermatol. 1996;35(2 Pt 1):268–9.
47. Kircik L. Efficacy and safety of topical calcitriol 3 µg/g ointment, a new topical therapy for chronic plaque psoriasis. J Drugs Dermatol. 2009;8(8 Suppl):s9–16.
48. Lebwohl M, Menter A, Weiss J, et al. Calcitriol 3 microg/g ointment in the management of mild to moderate plaque type psoriasis: results from 2 placebo-controlled, multicenter, randomized double-blind, clinical studies. J Drugs Dermatol. 2007;6:L48–35.
49. Veien NK, Bjerke JR, Rossmann-Ringdahl I, et al. Once daily treatment of psoriasis with tacalcitol compared with twice daily treatment with calcipotriol: a double blind trial. Br J Dermatol. 1997;137:581–6.
50. Paghdal KV, Schwartz RA. Topical tar: back to the future. J Am Acad Dermatol. 2009;61:294–302.
51. Goeckerman WH. Treatment of psoriasis. Continued observations on the use of crude coal tar and ultraviolet light. Arch Dermatol Syphilol. 1931;30:446–50.
52. Harris DR. Old wine in new bottles: the revival of anthralin. Cutis. 1998;62:201–3.
53. Rivera A, Tyring SK. Therapy of cutaneous human papillomavirus infections. Dermatol Ther. 2004;17:441–8.
54. Moed L, Shwayder TA, Chang MW. Cantharidin revisited: a blistering defense of an ancient medicine. Arch Dermatol. 2001;137:1357–60.

Systemic Drugs 130

Julia R Nunley and Stephen E Wolverton

Chapter Contents

Antimalarials 2165
Azathioprine 2169
Bleomycin 2172
Clofazimine 2172
Colchicine 2172
Cyclophosphamide 2172
Cyclosporine 2173
Dapsone 2174
Gold 2175
Hydroxyurea 2175
Leukotriene inhibitors 2176
Methotrexate 2176
Mycophenolate mofetil 2178
Saturated solution of potassium iodide (SSKI) 2179
Tacrolimus 2179
Thalidomide 2179

INTRODUCTION

This chapter is designed to be a broad overview of a variety of systemic therapies for dermatologic diseases. It provides an historical perspective for each drug, a discussion of its mechanism of action and side effects, and then touches briefly on indications and clinical use. This information should serve as a starting point, allowing the reader to readily compare and contrast various treatment options. It is not a substitute for the in-depth knowledge and experience necessary to implement these systemic therapies, nor is it a complete library of systemic drugs used in dermatology. A number of systemic medications have been reviewed in other chapters (Table 130.1) and therefore will not be discussed here.

Systemic drugs used in dermatology may be subdivided into broad categories, such as immunosuppressive, cytotoxic and antiproliferative (Table 130.2). Drugs in a single category act in a relatively similar fashion and generally have similar important side effects. For example, immunosuppressive drugs suppress the body's ability to recognize or eliminate infections and neoplastic cells. Patients may be at increased risk for opportunistic infections and selected lymphoproliferative malignancies as well as squamous cell carcinomas. Given this increased risk for opportunistic infections, patients with either an active infection or one that may reactivate (such as tuberculosis) should be given these drugs with caution.

Among the drugs discussed are several older drugs which have been reformulated either into a prodrug that is more tolerable from a side-effect standpoint (e.g. mycophenolate mofetil) or into a more readily absorbed formulation such as Neoral® and Gengraf® (cyclosporine). Others represent older drugs that have found new uses in dermatology. Most lack Food and Drug Administration (FDA) approval for the diseases for which dermatologists use them. This is not an incrimination of the practice, but is rather due to a lack of pharmaceutical company enthusiasm for putting drugs through lengthy, expensive approval processes for diseases that are relatively uncommon. When choosing therapy for an individual patient, certain broad general principles always apply. First, the physician should be aware of all the common therapeutic modalities available and become very familiar with the drugs most frequently used and most likely to yield optimal results. Certain systemic medications will not be utilized frequently enough for a given clinician to become comfortable with their use; therefore, patients requiring more specialized drugs should be referred to colleagues more experienced with their use. Patients should be advised of all the reasonable therapeutic choices as well as the risk–benefit profile of each modality. Non-compliance is a relative contraindication for all of the medications discussed in this chapter.

Part of every initial prescription should be a complete history and physical examination, with specific emphasis on the organ systems that may be affected by the particular drug. Tuberculin skin testing and/or QuantiFERON-TB Gold test should be performed prior to using some of the immunosuppressive medications, specifically corticosteroids (particularly when a prolonged course is anticipated) and tumor necrosis factor (TNF) inhibitors (FDA-required). Consultation with appropriate generalists or specialists in selected situations may be required prior to initiating therapy as well as for periodic screening for complications of therapy. Table 130.3 outlines suggested monitoring guidelines for the systemic medications discussed in this chapter. These tests may need to be performed more frequently in high-risk patients or in patients with abnormal results. Additionally, each outpatient visit should include an appropriate review of systems and physical examination.

The use of each drug during pregnancy and lactation is reviewed. Wherever possible, this has been referenced with the eighth edition of *Drugs in Pregnancy and Lactation* by Briggs and colleagues. In general, one should be very circumspect in prescribing systemic medications to women of childbearing potential. It is not adequate to merely ask the patient if she is utilizing birth control before prescribing most of the medications discussed in this chapter; the patient must be made acutely aware of the risks associated with using the medication during pregnancy and the risks of continuing therapy if pregnancy does occur. The prescribing physician also needs to be aware that birth defects have sometimes been ascribed to systemic medications despite the lack of scientific evidence. Family planning consultation and communication with the patient's obstetrician or primary care physician can prove particularly helpful.

Several drugs discussed herein have parenteral formulations. Clinicians who administer parenteral medications in the office setting should be current in their Advanced Cardiac Life Support (ACLS) training and keep emergency resuscitation supplies readily available.

ANTIMALARIALS

Quinine and its derivatives have been used since the 1600s for the treatment of malaria. Quinine is derived from the bark of the cinchona tree in South America and was first used in dermatology by Payne in 1894 to treat discoid lesions in patients with lupus erythematosus (LE). The most common antimalarials are hydroxychloroquine (Plaquenil®), chloroquine (Aralen®) and quinacrine; the latter, which can lead to yellow discoloration of the skin, is only available in the US via compounding pharmacies and it will not be covered in detail here.

The antimalarials are absorbed extensively into tissues and slowly released, leading to a half-life of 40–50 days. A steady state is achieved slowly and it may take 3–4 months to see an adequate clinical effect. Hydroxychloroquine is catabolized into two metabolites, desethylhydroxychloroquine and desethylchloroquine. Chloroquine is metabolized only into the latter. The initial metabolites then undergo further

SYSTEMIC MEDICATIONS COVERED IN OTHER CHAPTERS	
Antihistamines	Ch. 18
Antimicrobials	Ch. 127
Bioengineered immunomodulators • Alefacept • Anakinra • Rituximab • TNF-α inhibitors, e.g. adalimumab, etanercept, infliximab • Ustekinumab	Ch. 128
Cytokines • G-CSF and GM-CSF • Interferons	Ch. 128
Glucocorticosteroids	Ch. 125
Ivermectin	Ch. 84
Intravenous immunoglobulin (IVIg)	Ch. 128
Psoralens	Ch. 134
Psychotropic agents • Pimozide • Atypical antipsychotic agents	Ch. 7
Retinoids • Acitretin • Bexarotene • Isotretinoin	 Chs 8 & 126 Ch. 126 Chs 36 & 126
Spironolactone	Ch. 36

Table 130.1 Systemic medications covered in other chapters.

CATEGORIES OF SYSTEMIC DRUGS USED IN DERMATOLOGY BASED UPON MECHANISM OF ACTION			
Immunosuppressive/ Anti-inflammatory	**Cytotoxic**	**Antiproliferative**	**Miscellaneous**
Azathioprine Mycophenolate mofetil Cyclosporine Tacrolimus (FK506) Thalidomide	Cyclophosphamide Bleomycin	Methotrexate Hydroxyurea	Dapsone Antimalarials Saturated solution of potassium iodide (SSKI)

Table 130.2 Categories of systemic drugs used in dermatology based upon mechanism of action.

change into the primary amine form. Overall, 50% of each drug undergoes renal excretion[1].

Mechanism of Action

The mechanisms of action of the antimalarials are complex and incompletely understood. Known endpoints include the following: stabilization of lysosomes within injured cells; inhibition of antigen presentation, cell-mediated immunity and the synthesis of proinflammatory cytokines; and antithrombotic/antiplatelet effects[2]. The photoprotective effect attributed to the antimalarials may result from their anti-inflammatory properties[2].

Dosages

Most conditions will respond to dosages between 200 and 400 mg per day of hydroxychloroquine or 250 mg per day of chloroquine, with a maximum safe dose (from an ocular standpoint) being 6.5 mg/kg/day and 4.0 mg/kg/day, respectively. After a suitable therapeutic response has been achieved, the response may be maintained with hydroxychloroquine 100–200 mg daily. If available, quinacrine (100 mg/day) can be added to 200 mg twice daily of hydroxychloroquine, to maximize the clinical benefit without an increased risk of ocular toxicity. Lower doses of chloroquine (125 mg twice weekly) or hydroxychloroquine (100 mg three times weekly) must be used in patients with porphyria cutanea tarda, in order to minimize the risk of a toxic reaction (e.g. hepatotoxicity) in addition to a marked increase in urinary uroporphyrin output.

If no response is noted after 3–4 months, the specific antimalarial has failed and should be discontinued; however, a different antimalarial can be tried. In patients with porphyria cutanea tarda, the antimalarial can slowly be increased to daily dosing if necessary and if laboratory monitoring of transaminases allows.

Monitoring guidelines are outlined in Table 130.3. Because of the risk of dose-related ocular toxicity, a referral to an ophthalmologist is necessary for examination at baseline and then every 6 to 12 months[1].

Major Side Effects

Antimalarials are highly concentrated in the iris and choroid, reaching levels 480 000 times that of plasma[3]. Irreversible retinopathy may rarely occur and patients must be monitored by an ophthalmologist experienced with the ocular effects of antimalarials (see Table 130.4). Of note, the risk of retinopathy is much less with hydroxychloroquine as compared with chloroquine.

Up to one-third of patients who receive antimalarials for over 4 months will develop a blue–gray to black hyperpigmentation on their shins (Fig. 130.1), face, palate and/or nail beds. The discoloration fades after cessation of therapy, but may take months to resolve completely. Reversible bleaching of the hair roots (achromotrichia) occurs in up to 10% of patients, presumably due to interference with melanosomal function. Another 10–20% may develop an exanthem, ranging from urticaria to lichenoid reactions (Fig. 130.2) to exfoliative erythroderma. Of interest, morbilliform and urticarial exanthems have been observed with greater frequency in individuals with dermatomyositis as compared to in those with LE.

Antimalarials have been reported to worsen psoriasis in some patients, even though in the past they were commonly used to treat psoriatic arthritis. Psoriatic patients traveling to malaria-endemic areas may take these drugs prophylactically.

Laboratory abnormalities do not commonly occur, but it is the practice of the authors to monitor patients as outlined in Table 130.3. An overdose of antimalarials can be fatal, and although pediatric usage is safe and effective, patients should be warned to keep the drug out of the reach of small children.

Indications

The most common dermatologic use of antimalarials is as second-line therapy for cutaneous LE, after topical or intralesional corticosteroids. Antimalarials are especially useful in patients with widespread discoid lesions and in those with the annular or papulosquamous lesions of subacute cutaneous LE (SCLE). Antimalarial use has also been credited with fewer thromboembolic events in patients with systemic LE (SLE)[2]. In addition to the diseases listed in Table 130.5, other cutaneous disorders that may respond to antimalarial therapy include dermatomyositis and lichen planus[4].

Contraindications

The only true contraindication is hypersensitivity to the drug. Caution should be used in patients with severe blood dyscrasias or hepatic disorders, because hepatitis and bone marrow suppression can occasionally occur. Ophthalmologic changes of pre-maculopathy call for discontinuation of the drug. Ocular changes at this stage are potentially reversible, but could progress if the drug were continued.

Use in Pregnancy and Lactation

Chloroquine is thought to be safe for treatment and prophylaxis of malaria during pregnancy; however, there have been anecdotal reports of an increase in birth defects in pregnant women being treated for SLE. Hydroxychloroquine is thought to be safer during pregnancy, even with its much longer half-life.

Although excreted into breast milk, standard doses of either drug are not harmful to breastfed infants and are approved by the American Academy of Pediatrics for use during lactation[5].

Drug Interactions

Cimetidine may increase circulating levels of antimalarials, and antimalarials may increase digoxin levels. Kaolin and magnesium trisilicate, over-the-counter gastrointestinal drugs, decrease absorption of antimalarials. The most significant potential interaction is the additive

MONITORING GUIDELINES FOR SYSTEMIC MEDICATIONS			
Drug	**Initial screening**	**Follow-up monitoring**	**Special considerations**
Antimalarials	Ocular: Slit lamp and fundoscopic examination: assessment of visual acuity and visual field testing Laboratory: CBC CMP G6PD (selected cases)	Ocular: Repeat testing every 6 months for 1 year and then yearly Laboratory: CBC monthly for 3 months, then every 4–6 months CMP after 1 and 3 months, then every 4–6 months	G6PD testing before antimalarial therapy is controversial and is probably most important with the use of primaquine Urine or serum porphyrins should be measured when porphyria is clinically suspected Retinopathy risk is greatest for those on treatment for at least 5 years (especially with chloroquine) and if maximum daily safe dose has been exceeded
Azathioprine	CBC with PLT count CMP UA Consider pregnancy test for women of childbearing potential TPMT level, if available Tuberculin skin testing (should be considered depending on clinical situation)	CBC with PLT count every 2 weeks for 2 months, then every 2–3 months if stable AST/ALT every 2 weeks for 2 months, then every 2–3 months if stable	25% dose reduction is necessary if GFR 10–50 ml/min; 50% dose reduction if GFR <10 ml/min Frequency of laboratory studies is based on baseline TPMT determination (see Table 130.6); if TPMT is not known, hematologic parameters should be more closely monitored Discontinue therapy if WBC declines to <4000–4500 cells/mm^3 or if hemoglobin <10 g/dl Yearly skin examination and age-appropriate cancer screening, including yearly gynecologic examination in women
Cyclophosphamide	CBC with PLT count CMP UA Pregnancy test for women of childbearing potential	CBC with PLT count every week for 2–3 months, then every 2 weeks if stable. After 3–6 months, may decrease to every 3 months if stable UA every week for 2–3 months, then every 2 weeks if stable. After 3–6 months may decrease to every 3 months if stable CMP monthly for 3–6 months, then every 3 months if stable	Discontinue or lower dose if WBC declines to <4000–4500 cells/mm^3 or PLT count to <100 000 cells/mm^3 Stop treatment if red blood cells appear in urine; refer to urologist if hematuria persists Urine cytology after a cumulative dose of 50 g or after an episode of hemorrhagic cystitis; consider repeating yearly and/or after each 50 g Yearly physical examination and CBC as well as age-appropriate cancer screening
Cyclosporine	At least 2 baseline blood pressure readings At least 2 baseline serum creatinine levels CMP (must include BUN, magnesium, potassium and uric acid) CBC with PLT count UA with microscopic examination Fasting lipid profile (TG, cholesterol, HDL)	CBC with PLT count at 1 month, then every 2–4 months CMP (must include BUN, creatinine, uric acid, potassium, magnesium) every 2 weeks for 1–2 months, then monthly UA with microscopic examination every month if abnormal; otherwise yearly Fasting lipid panel every 2–4 weeks for 1–2 months, then monthly	Blood pressure must be monitored every 2 weeks for first 3 months and then monthly if stable Lower dose by 25–50% if serum creatinine remains elevated (over 2 weeks) by >25% of baseline Lower dose by 25–50%, or discontinue, if at any time serum creatinine is elevated by ≥50% of baseline Consider creatinine clearance if >6 months of therapy Skin examination at least yearly and age-appropriate cancer screening Consider trough whole drug cyclosporine level if non-compliance, poor absorption or drug interactions are suspected
Dapsone	CBC with PLT count CMP UA G6PD level	CBC with PLT count every week for 1 month, then every 2 weeks for 2 months, then every 3–4 months Reticulocyte count if anemia develops CMP every 3–4 months UA every 3–4 months	Each visit should include an assessment of peripheral motor function and an assessment for the signs and symptoms of methemoglobinemia and peripheral neuropathy (e.g. paresthesias, motor strength, reflexes) Methemoglobin level if clinically indicated Increase monitoring frequency when dose is increased

Table 130.3 Monitoring guidelines for systemic medications, as recommended by the authors (i.e. not necessarily standards of care). Before using any of these medications, the risk–benefit profiles and adverse effects should be thoroughly discussed with each patient. More frequent monitoring is needed in high-risk patients, when results are abnormal or when increasing doses. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood count with differential; CMP, comprehensive metabolic panel (includes liver function tests); G6PD, glucose-6-phosphate dehydrogenase; GFR, glomerular filtration rate; HDL, high-density lipoproteins; IM, intramuscular; PLT, platelet; TG, triglycerides; TPMT, thiopurine methyltransferase; TSH, thyroid-stimulating hormone; UA, urinalysis; WBC, white blood count.

Continued

MONITORING GUIDELINES FOR SYSTEMIC MEDICATIONS			
Drug	**Initial screening**	**Follow-up monitoring**	**Special considerations**
Hydroxyurea	CBC with PLT count CMP UA Pregnancy test for women of childbearing potential	CBC with PLT count weekly for at least 1 month until stable, then monthly CMP and UA monthly until stable, then every 3–6 months	A drop in hemoglobin of 1–2 g should be expected. Discontinue or decrease dose if the hemoglobin declines by more than 3 g or the WBC to <4000–4500 cells/mm^3 or the PLT count to <100 000/mm^3
Methotrexate	CBC with PLT count CMP Pregnancy test for women of childbearing potential Serologic tests for hepatitis A, B, C HIV testing if indicated	CBC with PLT and AST/ALT after initial 5–10 mg test dose CBC with PLT and AST/ALT every week for 2–4 weeks and after each dose escalation, then monthly for 2–4 months, and then every 3–4 months, if stable BUN and serum creatinine every 6–12 months	Per recent psoriasis treatment guidelines (2009)*, for patients without risk factors for hepatic fibrosis, liver biopsies may not be indicated or the frequency of liver biopsies may be markedly reduced (as compared to previous recommendations for liver biopsies baseline and then after every 1.5–2 g in low-risk patients). For high-risk patients, liver biopsies are done baseline and then after every 1 g, and in those with grade IIIA liver biopsy changes, every 6 months or as recommended by hepatologist Consider creatinine clearance, especially in elderly patients
Mycophenolate mofetil	CBC with PLT count CMP Pregnancy test for women of childbearing potential	CBC with PLT count every 2 weeks for 2–3 months, then monthly for first year CMP after 1 month and then every 3–4 months	Discontinue or decrease dose if WBC declines to <3500–4000 cells/mm^3
Saturated solution of potassium iodide (SSKI)	Thyroid function testing, including TSH, T_4 Pregnancy test for women of childbearing potential	TSH after 1 month of therapy	Consider antithyroglobulin and antimicrosomal antibodies in those with a history of thyroid disease
Tacrolimus	At least 2 baseline blood pressure readings At least 2 baseline serum creatinine levels CMP (must include BUN, magnesium, potassium and uric acid) CBC with PLT count UA with microscopic examination Fasting lipid profile (TG, cholesterol, HDL)	CBC with PLT count at 1 month, then every 2–4 months CMP (must include BUN, creatinine, uric acid, potassium, magnesium) every 2 weeks for 1–2 months, then monthly UA with microscopic examination every month if abnormal; otherwise yearly Fasting lipid panel every 2–4 weeks for 1–2 months, then monthly	The risk of diabetes mellitus post-transplant is higher with tacrolimus than with cyclosporine Blood pressure must be monitored every visit Lower dose or discontinue treatment if serum creatinine rises by >30% of baseline Consider creatinine clearance if >6 months of therapy Skin examination at least yearly and age-appropriate cancer screening Consider trough whole drug tacrolimus level if response is inadequate or if drug interactions are suspected
Thalidomide	CBC with PLT count CMP Pregnancy test in women of childbearing potential Subjective review of sensory and motor neurologic function and neurologic examination	Consider CBC with PLT count and AST/ALT every 2–3 months Pregnancy test every week for 4 weeks, then monthly for women of childbearing potential with regular menses, or every 2 weeks for those with irregular menses and as clinically indicated Neurologic examination monthly for 3 months, then every 1–6 months	Measurements of sensory nerve action potential amplitudes (SNAP), if indicated by history prior to therapy Consider SNAP measurements every 6 months, or as indicated

*Kalb RE, Strober V, Weinstein G, Lebwohl M. Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference. J Am Acad Dermatol. 2009;60:824–37.

Table 130.3 Monitoring guidelines for systemic medications, as recommended by the authors (i.e. not necessarily standards of care) (cont'd). Before using any of these medications, the risk–benefit profiles and adverse effects should be thoroughly discussed with each patient. More frequent monitoring is needed in high-risk patients, when results are abnormal or when increasing doses. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood count with differential; CMP, comprehensive metabolic panel (includes liver function tests); G6PD, glucose-6-phosphate dehydrogenase; GFR, glomerular filtration rate; HDL, high-density lipoproteins; IM, intramuscular; PLT, platelet; TG, triglycerides; TPMT, thiopurine methyltransferase; TSH, thyroid-stimulating hormone; UA, urinalysis; WBC, white blood count.

SIDE EFFECTS OF SYSTEMIC DRUGS USED IN DERMATOLOGY			
Drug	**Common**	**Uncommon**	**Rare**
Antimalarials	***Derm***: blue–gray to black discoloration; yellowing from quinacrine	***Derm***: bleaching of hair roots, exanthem (e.g. urticarial, lichenoid) ***GI***: nausea, vomiting, elevated liver enzymes ***Neuro***: irritability, nervousness	***Heme***: pancytopenia, hemolysis (G6PD-deficient, primarily with non-dermatologic antimalarials) ***Ophtho***: reversible (early) and irreversible retinopathy, vision changes
Azathioprine	***Derm***: non-melanoma skin cancers ***Heme***: leukopenia, thrombocytopenia, immunosuppression	***GI***: nausea, vomiting ***ID***: opportunistic infections	***Heme***: pancytopenia ***GI***: pancreatitis, hepatitis ***Malignancy***: lymphoma, cutaneous and gynecologic SCC Hypersensitivity syndrome
Cyclophosphamide	***GI***: nausea, vomiting ***GU***: sterility (higher doses or long-term administration) ***Heme***: leukopenia	***Derm***: diffuse hyperpigmentation, alopecia ***GU***: dysuria, hemorrhagic cystitis, amenorrhea, azoospermia, sterility (with lower doses) ***Heme***: anemia, thrombocytopenia ***ID***: opportunistic infections	***GI***: hemorrhagic colitis, hepatotoxicity ***Heme***: aplastic anemia ***Malignancy***: bladder (esp. chronic oral), lymphoma, acute leukemia ***Pulmonary***: pneumonitis, interstitial fibrosis Anaphylaxis
Cyclosporine	***Cardiac***: hypertension ***Derm***: non-melanoma skin cancers (NMSC) ***GU***: renal dysfunction* ***Metabolic***: hyperlipidemia ***Neuro***: headache, tremor	***Derm***: hypertrichosis, gingival hyperplasia, sebaceous hyperplasia ***GI***: nausea, diarrhea ***Neuro***: paresthesia, hyperesthesia ***Metabolic***: hyperkalemia†, hypomagnesemia, hyperuricemia	***Derm***: trichodysplasia spinulosa ***ID***: infections (unless combined with other immunosuppressives) ***Musculoskeletal***: myalgias, myositis ***GI***: hepatotoxicity ***Malignancy***: lymphoma ***Pulmonary***: dyspnea, bronchospasm
Dapsone	***Heme***: hemolysis, methemoglobinemia	***GI***: dyspepsia, anorexia	***Heme***: agranulocytosis ***Neuro***: peripheral neuropathy Sulfone syndrome
Hydroxyurea	***Heme***: anemia, megaloblastic changes	***Derm***: leg ulcers, alopecia ***Heme***: leukopenia	***Derm***: hyperpigmentation, dermatomyositis-like lesions, NMSC ***GI***: hepatitis ***GU***: renal dysfunction ***Heme***: thrombocytopenia ***Malignancies***: acute leukemia
Methotrexate	***Heme***: leukopenia	***Derm***: photosensitivity, alopecia, oral ulcers ***GI***: elevated liver enzymes, nausea, vomiting, anorexia, cirrhosis ***Heme***: thrombocytopenia	***Derm***: necrosis of psoriatic plaques, accelerated rheumatoid (cutaneous) nodulosis ***Heme***: pancytopenia, lymphoproliferative disorder (primarily in patients with RA) ***ID***: infections ***Pulmonary***: pneumonitis, fibrosis
Mycophenolate mofetil	***GI***: diarrhea, cramps, nausea, vomiting	***Heme***: anemia, leukopenia, thrombocytopenia ***ID***: opportunistic infections	***GU***: dysuria, sterile pyuria ***Neuro***: insomnia, dizziness, tinnitus
Saturated solution of potassium iodide (SSKI)	***Derm***: acneiform eruption ***GI***: nausea, vomiting, diarrhea, abdominal pain ***Metabolic***: reversible hypothyroidism	***Derm***: iododerma ***Metabolic***: hyperkalemia	***Cardiac***: CHF, pulmonary edema ***Derm***: flare of dermatitis herpetiformis ***GI***: salivary gland enlargement ***Metabolic***: hyperthyroidism, goiter, "iodism" (see text) Hypersensitivity reactions (see Ch. 100)
Tacrolimus	***Cardiac***: hypertension ***Derm***: non-melanoma skin cancers ***GU***: renal dysfunction* ***Neuro***: paresthesias	***ID***: infections ***Metabolic***: hyperkalemia†, hypomagnesemia	***Metabolic***: diabetes mellitus, hyperuricemia ***Malignancy***: lymphoma
Thalidomide	***Derm***: xerosis, pruritus ***GI***: constipation ***Neuro***: peripheral neuropathy, sedation ***Ob/Gyn***: fetal abnormalities, amenorrhea	***Cardiac***: peripheral edema ***GI***: xerostomia, increased appetite ***Gyn***: primary ovarian failure ***Heme***: thromboses ***Psych***: headache, mood changes	***Derm***: exfoliative erythroderma, TEN ***Heme***: leukopenia Hypersensitivity reaction (in HIV+)

*Not permanent during short-term treatment if guidelines are followed.
†Especially when used in conjunction with ACE inhibitors.

Table 130.4 Side effects of systemic drugs used in dermatology. CHF, congestive heart failure; Derm, dermatologic; G6PD, glucose-6-phosphate dehydrogenase; GI, gastrointestinal; GU, genitourinary; Gyn, gynecologic; Heme, hematologic; ID, infectious diseases; Neuro, neurologic; Ob/Gyn, obstetrical/gynecologic; Ophtho, ophthalmologic; Psych, psychiatric; RA, rheumatoid arthritis; SCC, squamous cell carcinoma; TEN, toxic epidermal necrolysis.

risk of retinal toxicity when chloroquine and hydroxychloroquine are used concomitantly. Combined therapy consisting of chloroquine or hydroxychloroquine plus quinacrine is acceptable.

In patients with LE, cigarette smoking has been associated with decreased efficacy of antimalarials. Whether this represents a "drug–drug" interaction or decreased compliance (as a manifestation of high-risk behavior) is not known.

AZATHIOPRINE

Azathioprine was developed in 1959 from its parent drug 6-mercaptopurine (6-MP). After its anti-inflammatory and immunosuppressive effects were noted, dermatologists began to utilize azathioprine for the treatment of inflammatory diseases. With its moderately potent immunosuppressive and anti-inflammatory effects,

azathioprine has a reasonable risk–benefit profile. However, it should be reserved for more serious, life-threatening or recalcitrant dermatoses after other therapies have failed.

Azathioprine (Imuran®, Azasan®, Azamun™) has an 88% bioavailability. Immediately after absorption, it is converted to 6-MP and subsequently processed through three different and competing pathways (Fig. 130.3). When 6-MP is catabolized via two of these metabolic pathways, by either xanthine oxidase or thiopurine methyltransferase (TPMT), inactive metabolites result. Active metabolites, such as the purine analogue thioguanine monophosphate and others, are produced from the third and only anabolic pathway via hypoxanthine-guanine phosphoribosyl transferase (HGPRT)[6]. Should either the xanthine oxidase or TPMT catabolic pathway be blocked, more 6-MP will be shunted through the anabolic HGPRT pathway, leading to more active metabolites; excessive immunosuppression and pancytopenia may result[6].

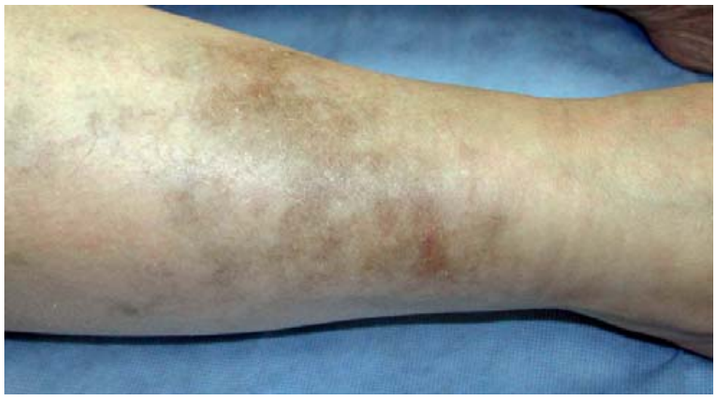


Fig. 130.1 Areas of blue–gray discoloration due to chloroquine.

Fig. 130.2 Generalized lichenoid drug eruption due to hydroxychloroquine. There is significant postinflammatory hyperpigmentation.

The TPMT pathway is interesting because the enzyme can have variable activity based upon genetic polymorphisms. Three distinct phenotypes exist and ethnicity may be a factor in the frequency of certain alleles. Encoded at the 6p22.3 locus, the TPMT activity trait is inherited in an autosomal co-dominant manner. Overall, 89% of Caucasians are homozygous for the high-activity allele and have relatively elevated levels, 11% are heterozygotes and have moderate activity, and 1/300 is homozygous for one of the seven low-activity alleles and has low TPMT activity. Red blood cell (RBC) TPMT activity mirrors systemic activity and a test for RBC TPMT activity has been developed. Although TPMT activity may vary somewhat between different laboratories and within different batches of the same test kit, knowledge of the baseline TPMT activity is clinically useful in the majority of patients who will receive azathioprine. However, vigilance in monitoring for pancytopenia will also identify those with low TMPT activity who will require dose reduction. Likewise, patients with high TMPT activity may need higher doses.

Decreased xanthine oxidase activity is rarely genetic in nature, but this enzyme is inhibited by allopurinol (see Fig. 130.3). Azathioprine dosage should be decreased by 75% in patients receiving allopurinol.

Mechanism of Action

6–Thioguanine, the active metabolite of azathioprine, is a purine analogue similar in structure to both adenine and guanine. Instead of an amino or hydroxyl group, it contains a thiol moiety. Incorporation of 6-thioguanine into DNA and RNA inhibits purine metabolism and cell division. 6–Thioguanine has other activities which are not well understood, such as suppression of T-cell function and B-cell antibody production[7]. It also decreases the number of Langerhans cells in the skin and inhibits their ability to present antigens[8].

Dosages

Available in 25, 50, 75 and 100 mg tablets, *empiric* dosing is generally started at 50 mg/day and increased to a maximum of 2.5 mg/kg/day according to clinical efficacy and careful monitoring. Maximum doses based on baseline TPMT determination are outlined in Table 130.6. In either case, doses must be reduced in the setting of renal insufficiency (see Table 130.3). Baseline evaluation should include a complete

CUTANEOUS DISORDERS THAT CAN BE TREATED WITH SPECIFIC SYSTEMIC DRUGS

Antimalarials	Azathioprine	Cyclophosphamide	Cyclosporine	Dapsone	Methotrexate	Mycophenolate mofetil	SSKI	Thalidomide
• Discoid lupus erythematosus* • GVHD (chronic) • Polymorphous light eruption • Porphyria cutanea tarda • Sarcoidosis • Subacute cutaneous lupus erythematosus	• Atopic dermatitis • Chronic actinic dermatitis • Behçet's disease • Bullous pemphigoid • Cicatricial pemphigoid • Dermatomyositis • Oral lichen planus • Pemphigus	• Mucous membrane pemphigoid • Cutaneous T-cell lymphoma* • Pemphigus • Systemic sclerosis • Wegener's granulomatosis	• Atopic dermatitis • Behçet's disease • Chronic actinic dermatitis • GVHD (acute) • Psoriasis* • Urticaria	• Behçet's disease • Mucous membrane (cicatricial) pemphigoid • Dermatitis herpetiformis* • Leprosy	• Cutaneous T-cell lymphoma • Dermatomyositis • Langerhans cell histiocytosis • Lymphomatoid papulosis • Palmoplantar pustulosis • Psoriasis* • Systemic sclerosis	• GVHD (acute and chronic) • Oral lichen planus • Pemphigus • Psoriasis • Systemic sclerosis	• Erythema nodosum	• Actinic prurigo • Aphthous stomatitis • Behçet's disease • Erythema multiforme • Erythema nodosum leprosum* • GVHD (chronic) • Uremic pruritus • Subacute cutaneous lupus erythematosus

*FDA-approved dermatologic conditions.

Table 130.5 Cutaneous disorders that can be treated with specific systemic drugs. Their use is based on double-blind controlled trials or large clinical series. SSKI, saturated solution of potassium iodide.

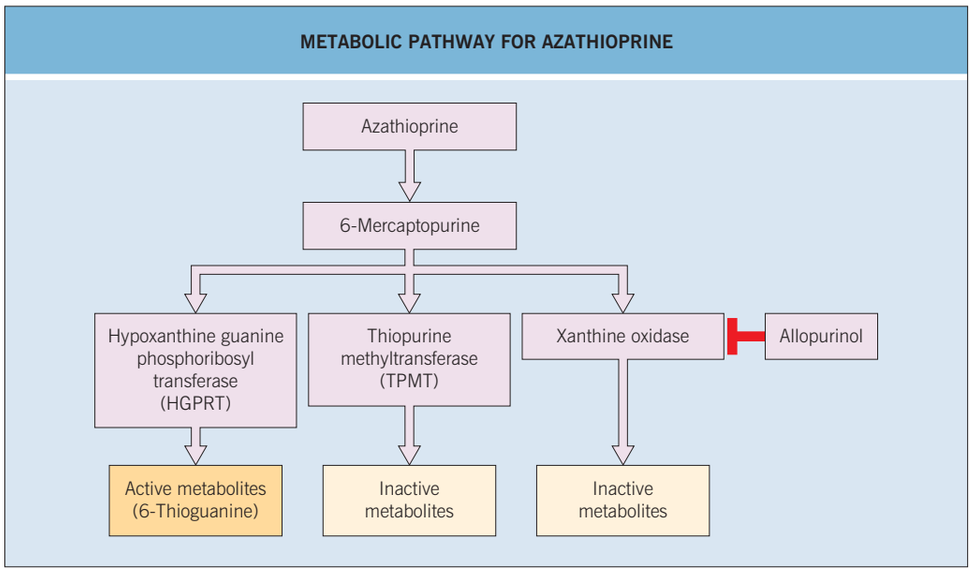


Fig. 130.3 Metabolic pathway for azathioprine. Either decreased activity of TPMT or inhibition of xanthine oxidase by allopurinol can lead to shunting of 6-mercaptopurine to the HGPRT pathway. As a result of this shunting, there is an increase in active metabolites and an increased risk of toxicity. Febuxostat also inhibits xanthine oxidase. *Adapted from Wolverton SE. Comprehensive Dermatologic Drug Therapy, 2nd edn. Philadelphia: Saunders, 2007.*

MAXIMUM DOSE OF AZATHIOPRINE AS DETERMINED BY BASELINE TPMT ACTIVITY

TPMT level	Maximum dose of AZA
<5 U	AZA contraindicated
5–13.7 U	Up to 0.5 mg/kg/day
13.7–19 U	Up to 1.5 mg/kg/day
>19 U	Up to 2.5 mg/kg/day

Table 130.6 Maximum dose of azathioprine as determined by baseline TPMT activity. AZA, azathioprine; TPMT, thiopurine methyltransferase; U, units.

medication history because of adverse effects when azathioprine is used concomitantly with allopurinol, febuxostat, captopril or warfarin (see below). Monitoring guidelines are outlined in Table 130.3.

Major Side Effects

Major side effects are related to the immunosuppressive effects of azathioprine (see Table 130.4). Pancytopenia occurs rarely, particularly when doses are based on TPMT activity. Patients may be at increased risk for malignancies, especially lymphoproliferative disorders and squamous cell carcinomas of the skin and female genitourinary tract, and patients should be monitored accordingly. Factors influencing a patient's malignancy risk include degree and duration of immunosuppression, ethnicity, and existing comorbidities.

Azathioprine may rarely cause a life-threatening hypersensitivity reaction, which most commonly develops during the first month of therapy and when the drug is used in combination with cyclosporine or methotrexate. The cutaneous eruption is typically morbilliform with areas of confluence (Fig. 130.4). Other components of the syndrome include fever, respiratory and gastrointestinal distress, hepatotoxicity and the possibility of cardiovascular collapse.

Indications

Although azathioprine has FDA approval for non-dermatologic uses only, dermatologists have been using this drug for over 35 years to treat severe dermatologic conditions, most often as a corticosteroid-sparing agent in the treatment of immunobullous diseases and various subtypes of cutaneous vasculitis (Table 130.5)[7,9]. It is inexpensive and has moderate immunosuppressive and anti-inflammatory effects. Clinical benefit of the drug may not be apparent until it has been administered for at least 4 to 6 weeks.

Fig. 130.4 Azathioprine hypersensitivity reaction. Pink to red macules, papules and areas of confluence are seen. *Courtesy, Kalman Watsky, MD.*

Contraindications

Absolute contraindications to azathioprine therapy include the history of a hypersensitivity reaction, as re-challenge may prove fatal. Active serious infection and pregnancy are relative contraindications. Concomitant use of allopurinol or febuxostat requires dose reduction of azathioprine (see above).

Use in Pregnancy and Lactation

Azathioprine is pregnancy prescribing category D. Even though it is considered relatively safe for use in transplant patients who become pregnant, for dermatologic purposes it should not be prescribed during pregnancy[5]. No information is available regarding the risk to breastfed infants.

Drug Interactions

Allopurinol or febuxostat inhibition of xanthine oxidase (see Fig. 130.3) increases the risk of pancytopenia in azathioprine-treated patients. Captopril may increase the risk of leukopenia. Azathioprine can decrease the effectiveness of warfarin and pancuronium, necessitating larger doses of these drugs. Since azathioprine may decrease the effectiveness of intrauterine contraceptive devices, alternative birth control methods should be employed.

BLEOMYCIN

The dosage, uses and side effects are outlined in Table 130.7.

CLOFAZIMINE

The dosage, uses and side effects are outlined in Table 130.8.

COLCHICINE

The dosage, uses and side effects are outlined in Table 130.9.

CYCLOPHOSPHAMIDE

Cyclophosphamide (Cytoxan®) was derived from nitrogen mustard in 1958; the latter was combined with phosphoric acid in an effort to make an inert drug capable of entering and releasing active nitrogen mustard within target cells[10]. It has approximately 75% oral bioavailability, peaks in the plasma at about 1 hour, and crosses the blood–brain barrier. Cyclophosphamide itself is inactive, but it is metabolized by cytochrome P450 (CYP) enzymes into the active metabolite 4-hydroxycyclophosphamide (nornitrogen mustard, $t_{1/2}$ 3.3 hours), which may then be converted into the other active metabolite phosphoramide mustard ($t_{1/2}$ 9 hours). Metabolites are excreted primarily via the kidney (50%). The inactive metabolite acrolein is believed to cause hemorrhagic cystitis and associated transitional cell carcinoma of the bladder[11].

BLEOMYCIN
Source: *Streptomyces verticillus* **Mechanism of action**: inhibits DNA synthesis in infected keratinocytes, but no direct effect on the human papillomavirus **Dermatologic use**: intralesional treatment of therapy-resistant verrucae vulgaris; 65–80% of lesions clear after 1 to 2 injections **Dosage**: 0.1 to 0.3 ml of 1 U/ml (of saline) injected into targeted lesions, with maximum total dose per treatment = 2 ml; repeated every 3 to 6 weeks until resolution; given its rapid degradation and expense, newly constituted solution should be divided into glass vials and stored at 20°C **Side effects**: injection is extremely painful (local or regional anesthesia may be required); pain and burning postinjection for 2–3 days; Raynaud's phenomenon occasionally; nail dystrophy; no systemic toxicity with recommended total dose **Contraindications**: pregnancy, immunosuppression, vascular compromise **Pregnancy and lactation**: not recommended; pregnancy prescribing category D

Table 130.7 Bleomycin.

CLOFAZIMINE
Drug properties: riminophenazine dye (red color) **Mechanism of action**: disrupts cell membranes (activation of phospholipase A_2 leads to generation of membrane-destabilizing lysophospholipids); enhances superoxide production; inhibits neutrophil motility and lymphocyte proliferation **Dermatologic use**: treatment of multibacillary leprosy, other infections (mycobacterial, malacoplakia, rhinoscleroma) and inflammatory skin diseases including neutrophilic dermatoses (pyoderma gangrenosum, Sweet's syndrome), granuloma faciale, orofacial granulomatosis, erythema dyschromicum perstans and discoid LE **Dosage**: 50–400 mg orally daily*; avoid long-term administration of >200 mg daily; see Table 75.4 for leprosy regimens **Side effects**: discoloration of skin† (red to red–brown diffusely, bluish to violet–brown in lesional sites), cornea/conjunctiva and body fluids (urine, sweat, tears); xerosis/ichthyosis; gastrointestinal symptoms (abdominal pain, nausea, vomiting, diarrhea); ocular irritation; elevated hepatic enzymes; crystal deposition-related enteropathy (rarely); cardiac arrhythmias (rarely; associated with electrolyte disturbances) **Contraindications**: prior hypersensitivity reaction **Pregnancy and lactation**: for dermatologic disorders, should be avoided during pregnancy (category C) and lactation (concentrated in breast milk)
*Larger doses are usually divided into two to four times daily. †Due to deposits of drug within fat and macrophages.

Table 130.8 Clofazimine. LE, lupus erythematosus.

Mechanism of Action

Cyclophosphamide is an alkylating agent that functions in a cell cycle-independent fashion. Although its major effect is suppression of B-cell function, it also suppresses that of T cells (especially regulatory T cells). Clearly, the T-cell effects are greatest if the drug is given prior to antigen presentation. Cyclophosphamide crosses the nuclear membrane, covalently binds with DNA, and inhibits the synthesis of guanine, cytosine and adenine. Cytotoxicity occurs by several mechanisms: (1) DNA cross-linking with various proteins or other DNA strands; (2) G-C → A-T substitution; and (3) depurination resulting in chain scission. These mechanisms can overwhelm the DNA repair mechanisms, inducing cell death[10].

Dosages

Cyclophosphamide is available in 25 and 50 mg tablets. Doses range from 1 to 3 mg/kg/day, either as a single morning dose or in equally divided doses. Dermatologic diseases seldom require more than 2 to 2.5 mg/kg/day of cyclophosphamide. Dose reduction is necessary in patients with hepatic or renal dysfunction. Because of the risk of hemorrhagic cystitis, patients should be advised to consume plenty of fluids on a daily basis. A monthly intravenous infusion (pulse) of 500 to 1000 mg has been used to treat a number of rheumatologic disorders, including severe SLE.

Prior to prescribing cyclophosphamide, patients should have documentation of a white blood count (WBC) of >4500/mm^3 and a granulocyte count of >1500/mm^3. Laboratory monitoring guidelines are outlined in Table 130.3. Of note, it is not necessary to induce significant myelosuppression in order to achieve immunosuppression[11].

Major Side Effects

The most common side effects from cyclophosphamide treatment are hematologic and gastrointestinal (see Table 130.4). Dermatologic side effects include anagen effluvium (5–30%, which is typically reversible), pigmented bands of the teeth (irreversible), diffuse hyperpigmentation, transverse ridging of nails, acral erythema, and, rarely, Stevens–Johnson syndrome. Up to 40% of patients have hemorrhagic cystitis, presumably from the acrolein metabolite, which is associated with a 10-fold increase in the risk for transitional cell carcinoma of the bladder. This risk is greater in patients who receive chronic "low-dose" cyclophosphamide (as given for dermatologic diseases) than in those exposed to brief courses of high-dose pulse therapy (as given for systemic lymphomas and SLE). Immunosuppression is significant, especially in patients concomitantly receiving systemic corticosteroid therapy. Infection and malignancy risks are real, and appropriate monitoring is suggested.

COLCHICINE
Source: alkaloid from *Colchicum autumnale* (autumn crocus) **Mechanism of action**: prevents microtubule assembly, resulting in mitotic arrest at metaphase and inhibiting cellular motility; decreases neutrophil chemotaxis, adhesion and degranulation **Dermatologic use**: treatment of neutrophilic dermatoses (Behçet's disease, Sweet's syndrome), small vessel vasculitis, neutrophil-rich autoimmune bullous diseases (EBA, linear IgA bullous dermatosis) and aphthous stomatitis **Dosage**: 0.5 or 0.6 mg orally two to three times daily; drug must be shielded from light (degraded by UVR) **Side effects**: commonly, gastrointestinal symptoms (diarrhea, abdominal pain, nausea, vomiting; dose-related); occasionally, alopecia, peripheral neuropathy, myopathy and bone marrow suppression (with prolonged therapy*); multiorgan failure with acute overdose† **Contraindications**: prior hypersensitivity reaction; severe renal, hepatic, gastrointestinal or cardiac disease; blood dyscrasias **Pregnancy and lactation**: for dermatologic disorders, should be avoided during pregnancy (category C); excreted in breast milk, but use during lactation allowed per AAP recommendations
*Particularly in patients with renal insufficiency. †A toxic epidermal necrolysis-like reaction has been described.

Table 130.9 Colchicine. In patients with renal or hepatic impairment on colchicine, P-glycoprotein and strong CYP3A4 inhibitors should be avoided. AAP, American Academy of Pediatrics; EBA, epidermolysis bullosa acquisita; UVR, ultraviolet radiation.

Long-term or high-dose therapy may be associated with infertility in either sex[7].

Indications

Although cyclophosphamide is only FDA-approved for use in advanced mycosis fungoides and hematopoietic malignancies, it can be extremely useful in treating a number of severe cutaneous diseases. Cyclophosphamide is a major component of treatment regimens for systemic vasculitides, especially Wegener's granulomatosis and Churg–Strauss syndrome[11]. It can also be used as a steroid-sparing agent in a variety of cutaneous diseases or as monotherapy after corticosteroids are discontinued.

Contraindications

Absolute contraindications are pregnancy, lactation, depressed bone marrow function, and hypersensitivity to the drug. Cyclophosphamide-allergic patients may have cross-reactions with chlorambucil or mechlorethamine (nitrogen mustard). Relative contraindications include active infections and significantly impaired hepatic or renal function.

Use in Pregnancy and Lactation

Cyclophosphamide is a first-trimester teratogen and is immunosuppressive in breastfed infants. It is pregnancy prescribing category D and should not be used during pregnancy or lactation[5].

Drug Interactions

Allopurinol, cimetidine and chloramphenicol may elevate cyclophosphamide drug levels and produce toxicity (via CYP450 interactions), whereas barbiturates may enhance conversion to inactive metabolites. Digoxin absorption may be decreased. Cyclophosphamide may enhance the effect of succinylcholine, increase the cardiotoxicity of doxorubicin, and cause additive immunosuppressive and carcinogenic effects with other immunosuppressive drugs. Unpredictable effects can be seen when used with the inhalation anesthetics halothane and nitrous oxide.

CYCLOSPORINE

Cyclosporine, a cyclic peptide of 11 amino acids, was isolated from the soil fungus *Tolypocladium inflatum* in 1970 and was found to have clinical immunosuppressive effects in 1976. In 1979, during a rheumatoid arthritis trial, it was discovered that cyclosporine improved cutaneous psoriasis in patients with psoriatic arthritis. Two forms are available, the original preparation (Sandimmune®) and a predigested microemulsion (Neoral®) that is more completely and consistently absorbed. The latter is available as capsules (25 mg, 100 mg) or as an oral solution (100 mg/ml)[1,2]. The solution can be mixed in orange juice or apple juice, but grapefruit juice should be avoided because it alters cyclosporine's metabolism (see Ch. 131).

Bioavailability of the microemulsion is not known, but it yields 40–106% higher peak blood levels than the original formulation. Cyclosporine is metabolized by the CYP3A4 pathway, and primary excretion is via bile and feces. Only 6% of cyclosporine is excreted unchanged in the urine. Monitoring blood levels of cyclosporine is not routinely necessary since levels correlate poorly with efficacy or toxicity; determination of drug levels (11-hour trough) is primarily of value when drug–drug interactions or non-compliance are a concern.

Mechanism of Action

T-cell receptor activation causes release of intracellular calcium that in turn binds to calmodulin and activates calcineurin (see Ch. 128). This calcineurin complex dephosphorylates the nuclear factor of activated T cells ($NFAT_c$) which is present within the cytoplasm, allowing it to migrate into the nucleus and bind with its intranuclear counterpart $NFAT_n$. This complex is a transcription factor for inflammatory cytokines such as interleukin (IL)-2. IL-2 receptors are also upregulated as a result of this process.

Cyclosporine binds to cyclophilin, a member of the family of intracytoplasmic proteins called immunophilins. This complex blocks the dephosphorylation of $NFAT_c$ and the subsequent upregulation of IL-2 and IL-2 receptors, resulting in a decrease in the number of $CD4^+$ and $CD8^+$ (cytotoxic) T cells in the epidermis[7,12].

Dosages

Cyclosporine is best used on a short-term basis (<6–12 months) to control flares of psoriasis and to provide an alternative to the patient's current regimen (see Ch. 8). However, safety has been documented in psoriasis patients receiving therapy for up to 2 years[13]. It is reasonable to use cyclosporine as sequential therapy with acitretin, methotrexate, or other systemic therapies such as TNF-α inhibitors. After psoriasis clearance has been initiated by cyclosporine, the alternative medicine may be started and advanced to the therapeutic dose. At the same time, cyclosporine may be weaned by 1 mg/kg/day each month until the patient is receiving acitretin or methotrexate alone. Historically, the maximum dermatologic dose for cyclosporine is 5 mg/kg/day, although a maximum dose of 4 mg/kg/day of the microemulsion formulation should be considered, given the greater bioavailability of this formulation. The dose for obese patients is based on ideal body weight.

For psoriasis patients with a severe flare or recalcitrant disease, cyclosporine may be initiated at the maximum dosage until significant disease resolution occurs. The dose is then tapered by 1 mg/kg/day every 2 weeks until the minimum effective maintenance dose is determined. For most patients with more moderate disease, therapy should be initiated at 2.5 mg/kg/day and increased by 0.5 to 1 mg/kg/day every other week until clinical improvement is seen or the maximum dose of 4–5 mg/kg/day (depending upon the formulation) is reached. If no improvement is observed after 3 months at the maximum dose, therapy has failed and should be discontinued[14].

Patients must be adequately monitored for the development of hypertension and laboratory abnormalities as outlined in Table 130.3. If the serum creatinine rises by >25% over baseline, the value should be rechecked within 2 weeks. If it returns to <25% over baseline, therapy can be continued at the current dose. However, if the elevation persists at that level, the dose should be decreased by 25–50% for 1 month and then the serum creatinine rechecked. If it is still >25% above baseline, therapy should be discontinued until the serum creatinine is within 10% of the baseline value. At that time, restarting therapy may be considered, but at a lower dose.

Major Side Effects

Cyclosporine is associated with a wide variety of adverse effects, including hypertension, renal dysfunction, hyperlipidemia, hyperkalemia, hypertrichosis and gingival hyperplasia (see Table 130.4). Most of the side effects associated with short-term therapy are reversible upon discontinuation of the drug. A quarter of all psoriasis patients on cyclosporine will develop hypertension, which is usually mild and manageable. A direct vasoconstrictive effect of cyclosporine on the kidney vasculature is responsible for the development of hypertension short-term[15]. Hypertension due to cyclosporine is both time- and dose-related.

Modern, conservative dosing guidelines have prevented significant kidney damage in the vast majority of patients on short-term therapy. However, renal interstitial fibrosis has been demonstrated histologically even in the absence of abnormal laboratory tests in patients on appropriate dosing and monitoring regimens. Renal biopsy specimens from patients on long-term treatment demonstrate irreversible changes including renal tubular atrophy, arteriolar hyalinosis, glomerular obsolescence and interstitial fibrosis[16,17]. In fact, all patients on cyclosporine for >2 years were shown to have some of these abnormalities.

Although transplant recipients on high doses and prolonged courses of cyclosporine have an increased risk of certain malignancies (e.g. cutaneous squamous cell carcinoma and lymphomas), patients with skin diseases on cyclosporine for less than 2 years and on lower "dermatologic" doses have not been observed to have a similar risk.

Indications

Cyclosporine can be beneficial for patients with psoriasis who have failed or cannot tolerate other therapies and for those with widespread, inflammatory disease (see Ch. 8). In fact, cyclosporine has FDA approval for three "types" of psoriasis: (1) severe; (2) recalcitrant; and (3) disabling. Patients with plaque-type psoriasis may also benefit from cyclosporine in rotating or sequential regimens with other modalities.

The use of cyclosporine in atopic dermatitis has been examined and a high percentage of patients improve with therapy; unfortunately, most relapse within 4 weeks of its discontinuation. Cyclosporine efficacy has been established in patients with severe pyoderma gangrenosum; however, some clinicians prefer cyclosporine for idiopathic pyoderma gangrenosum only, arguing that when there is a known underlying cause, therapy is best aimed at the latter (e.g. inflammatory bowel disease, myelodysplasia). Most other uses of cyclosporine are based upon anecdotal evidence[18].

Contraindications

Absolute contraindications include significant renal impairment, uncontrolled hypertension, and hypersensitivity to cyclosporine. Relative contraindications include age <18 years or >64 years, controlled hypertension, and medication usage that may interfere with cyclosporine metabolism or worsen renal function. Significant caution is necessary if used in patients with significant infections, recent live-virus vaccinations (see Table 128.9), or immunodeficiency syndromes, or in combination with methotrexate, phototherapy or other immunosuppressive drugs.

Use in Pregnancy and Lactation

Cyclosporine is not teratogenic, and it is classified as a pregnancy prescribing category C drug. Use during pregnancy should be considered only in exceptional patients for whom the potential benefits of cyclosporine therapy dramatically outweigh the risks. Cyclosporine is excreted into breast milk and should not be used during lactation, due to risks of immunosuppression and possible carcinogenesis in the breastfed infant[5].

Drug Interactions

Drugs that interact with cyclosporine are discussed in Chapter 131. The clinician should review the patient's medication list for potential interactions using the following guidelines. In general, drugs that inhibit the CYP3A4 pathway will increase cyclosporine levels, while inducers of the 3A4 pathway will decrease the effectiveness of cyclosporine, due to lower serum levels. Some drugs will potentiate renal toxicity, such as nonsteroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, amphotericin B and miscellaneous antibiotics (vancomycin, trimethoprim–sulfamethoxazole). Cyclosporine will reduce the renal clearance of digoxin, lovastatin and prednisolone. Increased risk of hyperkalemia occurs with concurrent use of angiotensin-converting enzyme (ACE) inhibitors, potassium supplements and potassium-sparing diuretics.

DAPSONE

Dapsone is a sulfone drug, and sulfones are related to the sulfonamide family (see Ch. 21). Sulfonamides were initially derived from coal tar in the early 1900s for use as fabric dyes. Medically, they were first demonstrated to be effective against streptococcal infections. Synthesized in 1908, dapsone was shown to be effective against tuberculosis and leprosy. During the first half of the twentieth century, the related drugs sulfapyridine and sulfoxone were used to treat dermatitis herpetiformis (DH). However, since 1953, dapsone (the parent compound of sulfoxone) has been the mainstay of treatment for DH. Due to its activity in neutrophil-mediated dermatoses, dapsone has also proven useful in the treatment of several forms of autoimmune bullous diseases and vasculitis syndromes.

Dapsone is 80% orally bioavailable, peaks in the serum between 2 and 6 hours post-administration, and has a half-life of 24–30 hours. Being highly lipophilic, it has excellent cell penetration. Dapsone and its major metabolite monoacetyldapsone are strongly protein-bound and undergo enterohepatic recirculation. Thus, dapsone may be found in the bloodstream up to 1 month following a single dose[19].

Dapsone is metabolized by *N*-acetylation and *N*-hydroxylation in the liver[19,20]. Acetylation yields monoacetyldapsone, which is then de-acetylated to dapsone, yielding an equilibrium between dapsone and monoacetyldapsone. Hydroxylation via CYP enzymes produces *N*-hydroxy-dapsone, the metabolite which is believed to be responsible for the majority of dapsone side effects. Both dapsone and *N*-hydroxy-dapsone undergo glucuronidation in the liver, which results in more water-soluble compounds that are rapidly excreted in the urine[19].

Mechanism of Action

Dapsone is clinically most useful in the treatment of dermatologic diseases involving neutrophilic infiltrates. Researchers have demonstrated that dapsone inhibits neutrophil myeloperoxidase, thus reducing damage from the neutrophil respiratory burst mediated by this enzyme. Furthermore, dapsone has been shown to inhibit neutrophil chemotaxis to *N*-formyl-methionyl-leucyl-phenylalanine and to interfere with the CD11b/CD18-mediated neutrophil binding that induces chemoattractant signal transduction. IgA adherence is also inhibited. It is of clinical interest that dapsone also inhibits eosinophil myeloperoxidase activity, and thus may be efficacious in diseases in which eosinophils have a central role in pathogenesis, such as eosinophilic cellulitis[20].

Dosages

Dapsone is available in 25 mg and 100 mg tablets. The initial dose is often 50 mg/day in a single dose. Most conditions require 50–200 mg/day for adequate control of symptoms; rarely are dosages up to 300 mg/day required. In those with DH who respond to dapsone, rapid resolution of symptoms (within 48 hours) is usually noted; conversely, symptoms flare relatively rapidly after discontinuing therapy. Patients must be strictly warned against self-adjustment of the dosage, due to the various side effects that are dose-dependent.

Because of potential adverse effects, any cardiopulmonary or neurologic symptoms should be assessed prior to therapy. Documentation of peripheral motor nerve function may occasionally be necessary before or during therapy. Table 130.3 outlines monitoring guidelines for therapy. The clinician must be aware of all signs and symptoms associated with methemoglobinemia and peripheral neuropathy to ensure proper monitoring.

Major Side Effects

Serious systemic side effects of dapsone may be idiosyncratic or pharmacologic. The pharmacologic and dose-dependent adverse effects include methemoglobinemia and hemolytic anemia (see Table 130.4). Agranulocytosis, peripheral neuropathy and dapsone hypersensitivity are idiosyncratic reactions; however, patients on higher daily doses or long-term therapy may be more likely to develop a peripheral neuropathy. Although rare, dapsone hypersensitivity syndrome may be fatal. Patients present with fever, hepatitis and a generalized cutaneous eruption. Cutaneous reactions range from a exanthematous eruption to toxic epidermal necrolysis (TEN). Liver failure has occurred in patients with the dapsone hypersensitivity syndrome[21], and hypothyroidism may develop following resolution of the acute eruption.

Indications

Dapsone works well in a number of neutrophilic dermatoses and immunobullous diseases. Although only FDA-approved for DH, dapsone is very useful in linear IgA bullous dermatosis, bullous eruption of SLE, and erythema elevatum diutinum[19,20]. It is also a key component of combination therapy for leprosy.

Contraindications

The absolute contraindication to dapsone therapy is prior hypersensitivity to dapsone. Relative contraindications include a low glucose-6-phosphate dehydrogenase (G6PD) level, significant cardiopulmonary disease, and an allergy to sulfonamide antibiotics (because of the possibility of cross-reactivity). Patients with low G6PD levels are at an increased risk of the oxidative stress of the dapsone metabolites on RBCs. Those with significant cardiopulmonary disease may not tolerate the methemoglobinemia and hemolysis induced by dapsone.

Use in Pregnancy and Lactation

Dapsone does not appear to present a major risk to the fetus; however, it remains a pregnancy prescribing category C drug and should only be used during pregnancy if the benefits clearly outweigh the risks. There have been published papers reporting its use in pregnant patients with

Fig. 130.5 Postinflammatory hyperpigmentation secondary to gold eruption. There were features of both a lichenoid drug eruption and a pityriasis rosea-like drug eruption.

leprosy. Dapsone is found in breast milk and can cause hemolytic anemia in breastfed infants; however, it is approved by the American Academy of Pediatrics for use during lactation when required, as in patients with leprosy[5].

Drug Interactions

Drugs that may increase dapsone levels (and side effects) are probenecid (via decreased renal clearance), trimethoprim and other folate antagonists. Sulfonamides and hydroxychloroquine increase the oxidative stress on RBCs and may worsen hemolysis. Dapsone levels may be reduced by activated charcoal, para-aminobenzoic acid (PABA) and rifampin. Although cimetidine can increase absolute levels of dapsone, the former leads to a reduction in the more toxic hydroxylamine metabolite and thus the end result is a lower level of methemoglobin.

GOLD

The dosage, uses and side effects (Fig. 130.5) are outlined in Table 130.10.

GOLD THERAPY (CHRYSOTHERAPY)
Formulations: *Parenteral (IM)*: aurothioglucose (Solganal®); aurothiomalate (Myochrysine®, Myocrisin®) with 70% renal excretion and half-life of 6 days *Oral*: auranofin (Ridaura®) with primarily hepatobiliary elimination, 25% bioavailability, and half-life of 21 days **Mechanism of action**: inhibits chemotactic and phagocytic responses of neutrophils and macrophages *in vitro*; inhibits lysosomal enzymes and interferes with prostaglandin synthesis **Dermatologic use**: treatment of autoimmune bullous diseases (pemphigus vulgaris, mucous membrane [cicatricial] pemphigoid, EBA) and connective tissue diseases (discoid LE, systemic LE) **Dosage**: *IM*: 10 mg, followed in 1 week by 25 mg, then 50 mg biweekly in adults*; for maintenance, taper dose or increase interval *Oral*: 3 mg two to three times daily with maintenance dose of 3 mg daily; because of delayed onset, should be continued for up to 6 months **Side effects**: • Mucocutaneous (40% IM; 30% oral) – lichenoid and pityriasis rosea-like eruptions (Fig. 130.5), erythroderma, cheilitis, stomatitis; may persist for weeks after discontinuing drug • Diarrhea (35–40%) • Hematologic (1–2%) – leukopenia†, thrombocytopenia, eosinophilia [follow CBC with PLT count] • Proteinuria (2–10%) [follow creatinine & urinalysis] • Nitritoid reaction (IM) – dizziness, metallic taste, hypotension, syncope • Pulmonary fibrosis (rarely) • Anaphylaxis **Contraindications**: prior significant reactions to gold (e.g. anaphylaxis, erythroderma, severe hematologic abnormalities, necrotizing enterocolitis, pulmonary fibrosis) **Pregnancy and lactation**: for dermatologic disorders, should be avoided during pregnancy (category C); experts disagree regarding lactation (excreted in breast milk) but allowed per AAP recommendations
*In children, eventual dose is 1 mg/kg/week. †Rarely, aplastic anemia with auranofin.

Table 130.10 Gold therapy (chrysotherapy). AAP, American Academy of Pediatrics; CBC, complete blood count; EBA, epidermolysis bullosa acquisita; IM, intramuscular; LE, lupus erythematosus; PLT, platelet count.

HYDROXYUREA

Although hydroxyurea (Hydrea®) was first synthesized in 1869, its beneficial effect in psoriasis was not discovered until 100 years later. Being 100% bioavailable, hydroxyurea is very well absorbed. Peak levels are seen in 2 hours, its half-life is 5.5 hours, and 80% is excreted via the kidneys. Hydroxyurea is not highly protein-bound and can cross the blood–brain barrier. Metabolic mechanisms are poorly understood, but hydroxyurea is noted to accumulate in greater concentrations in leukocytes than in erythrocytes. With about 60% of patients noticing no side effects, hydroxyurea is typically well tolerated[22]. The macrocytic anemia that commonly occurs is the primary factor limiting hydroxyurea therapy.

Mechanism of Action

Hydroxyurea inhibits the M_2 subunit of ribonucleotide reductase, thus blocking DNA synthesis. Accumulation of DNA precursors may lead to DNA damage and strand scission. Cells are arrested in the G_2 phase and thus are unable to repair UV and ionizing radiation-induced damage. Hydroxyurea also causes hypomethylation of genes, inducing differentiation and normalization of psoriatic skin. Resistance may arise via increased levels of ribonucleotide reductase or by alteration of the enzyme leading to decreased susceptibility[11].

Dosages

The usual dosage is 20–30 mg/kg/day in divided doses, with a maximum of 2 g/day. Doses ranging from 1 to 2 g/day are commonly used[11]. Hydroxyurea is available in 200, 250, 300, 400 and 500 mg tablets. Monitoring guidelines are outlined in Table 130.3. A decrease in dosage (or discontinuation of therapy) is warranted if evidence develops of any type of significant cytopenia, concomitant infection, or other organ system involvement (see Table 130.4).

Major Side Effects

All patients on hydroxyurea develop megaloblastosis; however, only 10–35% develop anemia (see Table 130.4). Leukopenia is seen in 7% and thrombocytopenia in 2–3%. These changes may occur as soon as 48 hours after initiation of therapy, but typically resolve promptly with discontinuation of the drug. Transient, reversible hepatitis occurs occasionally and is associated with an acute "flu-like" syndrome. Sporadic elevations of blood urea nitrogen (BUN) and serum creatinine have been reported, but frank renal failure is rare.

Rare cutaneous side effects include diffuse hyperpigmentation (including the buccal mucosa and tongue) and leg and foot ulcers that resolve on discontinuation of the drug (Fig. 130.6). A characteristic dermatomyositis-like eruption on the dorsum of the hands has been reported. A wide variety of relatively minor side effects are well documented in the package insert.

Indications

Hydroxyurea is typically ineffective as monotherapy for clearing psoriasis, but it is quite effective as maintenance therapy following control of the disease by another modality, either phototherapy or another systemic medication. More commonly used throughout the 1970s, it

Fig. 130.6 Hydroxyurea-induced lower extremity ulcers.

is rarely prescribed in the current era of immunomodulating agents. Hydroxyurea is ineffective in psoriatic arthritis. Other uses include lymphocytic hypereosinophilic syndrome unresponsive to corticosteroids, chronic myeloproliferative disorders, and prophylaxis against sickle cell anemia crises.

Contraindications

Absolute contraindications include pregnancy, lactation, and hypersensitivity to hydroxyurea. Relative contraindications include concomitant use of cytarabine, blood dyscrasias, infection, cardiac, renal or pulmonary disease, and unstable or fulminant psoriasis.

Use in Pregnancy and Lactation

Hydroxyurea is a teratogen and should not be used in pregnancy or lactation. It is pregnancy prescribing category D[5].

Drug Interactions

Hydroxyurea has no significant drug interactions.

LEUKOTRIENE INHIBITORS

Leukotrienes, initially identified as the slow-reacting substance of anaphylaxis, play a key role in systemic and cutaneous inflammatory reactions[23]. Originating from arachidonic acid, leukotriene A_4 (LTA_4) is metabolized by divergent pathways to either LTB_4 or to the cysteinyl leukotrienes LTC_4, LTD_4 and LTE_4 (Fig. 130.7). LTB_4 mediates its effect through the BLT receptor(s), triggering chemotaxis of neutrophils, eosinophils and monocytes. By binding with cysteinyl leukotriene receptors, LTC_4, LTD_4 and LTE_4 cause bronchoconstriction, increased vascular permeability, smooth muscle contraction, mucus secretion and edema[23]. Leukotrienes and leukotriene receptors are widely distributed throughout the body, but their concentration and relative importance are organ- and cell type-specific. Leukotriene inhibitors abrogate the biologic effects of these mediators (Table 130.11).

METHOTREXATE

The effectiveness of the folic acid analogue methotrexate (MTX) in psoriasis was noted in the early 1950s, but remained without FDA approval until the 1960s. MTX is not difficult to use and oral administration achieves reliable blood levels unaffected by food intake. MTX is widely distributed throughout the body, but penetrates the blood–brain barrier poorly.

Within 1 hour of ingestion, distribution and active cellular uptake is complete. Plasma MTX is 50% protein-bound, and irreversibly bound to dihydrofolate reductase, the enzyme it inhibits. By 4 hours, the kidneys have excreted the plasma portion of the drug[24]. Over the next 10–27 hours, the drug is slowly released from body tissues.

Mechanism of Action

Dihydrofolate reductase (DHFR) converts dihydrofolate to tetrahydrofolate (fully reduced folic acid; see Ch. 127), which is a necessary cofactor in the synthesis of thymidylate and purine nucleotides, which, in turn, are required for DNA/RNA synthesis. MTX competitively inhibits DHFR, although this inhibition can be at least partially reduced by concomitant folic acid administration. MTX also exerts partially reversible inhibition downstream on thymidylate synthetase, inhibiting cell division in the S phase[7].

Although originally believed to suppress keratinocyte proliferation, it is more likely that MTX inhibits DNA synthesis in immunologically active cells. MTX decreases inflammation through other mechanisms as well. By inhibiting aminoimidocarboxyamido-ribonucleotide transformylase, MTX increases local tissue concentrations of the potent anti-inflammatory mediator adenosine. By inhibiting methionine synthase, MTX reduces production of the proinflammatory mediator S-adenyl methionine[25] .

Dosages

MTX is administered as a once-weekly dose of up to 30 mg for dermatologic and rheumatologic diseases. Oncologists may prescribe 20–40 mg/m^2 every 1 to 4 weeks with folinic acid rescue. Historically, MTX was administered in three doses over 24 hours (8 a.m. and 8 p.m. day 1, and 8 a.m. day 2). There were theoretical advantages for the divided dosing regimen from a cell cycle kinetics standpoint. However, since the clinical result is the same, a single dose, which is easier and less confusing (for the patient and the pharmacist), is currently recommended. The patient should be admonished to adhere to the dosing schedule religiously, as more frequent dosing invariably causes major hematologic complications and potentially an increased risk of liver fibrosis. Parenteral administration (intramuscular or subcutaneous) is available for patients who cannot tolerate oral MTX and has also been advocated by some clinicians for use in erythrodermic patients who may have decreased gastrointestinal absorption or when compliance is an issue.

Available in 2.5 mg tablets, therapy should begin with a test dose of 2.5–7.5 mg followed 5–6 days later with a complete blood count with differential (CBC), platelet count and hepatic profile. The dose may be gradually increased by 2.5 to 5 mg every 2–4 weeks until satisfactory results are obtained with minimal toxicity. Once disease control has been attained for at least 1–2 months, the MTX can be tapered by 2.5 mg every 1–2 weeks to the lowest dose that still maintains disease control. The usual weekly dose for psoriasis is 10–15 mg, although doses up to 25 mg per week are not uncommonly used, except in patients with renal insufficiency. In the past, rheumatologic and dermatologic monitoring regimens differed significantly, in that liver biopsies were not routinely recommended by rheumatologists. However, per recent psoriasis treatment guidelines (2009), for patients without risk factors for hepatic fibrosis, liver biopsies may not be indicated, or the frequency of liver biopsies may be markedly reduced, as compared to previous recommendations (see Table 130.3)[26]. In general, dosing and duration of therapy may be higher and longer for psoriasis patients than for those with rheumatologic diseases.

Major Side Effects

The most important side effects of MTX include pancytopenia and hepatotoxicity (see Table 130.4). Pancytopenia typically develops early, compared to hepatic fibrosis and cirrhosis, which take years to develop. There is considerable debate over the risk of hepatotoxicity in psoriasis patients on long-term MTX. Suffice it to say that the higher the cumulative dose of MTX, the greater the risk of significant liver damage (Table 130.12). Compounding risk factors for hepatic impairment include: previous or current excessive alcohol intake, persistent abnormal liver chemistries, a history of liver disease (including hepatitis B and C viral infections), family history of inheritable liver disease, diabetes mellitus, obesity, and a history of significant exposure to hepatotoxic drugs or chemicals. References discussing this issue in detail[24] should be consulted before prescribing MTX and referral to a hepatologist can be considered.

Elevated levels of procollagen III aminopeptide have been observed to be a serologic marker of fibrosis, and, in the future, this (or a similar) assay may help to determine which patients should be sent for liver

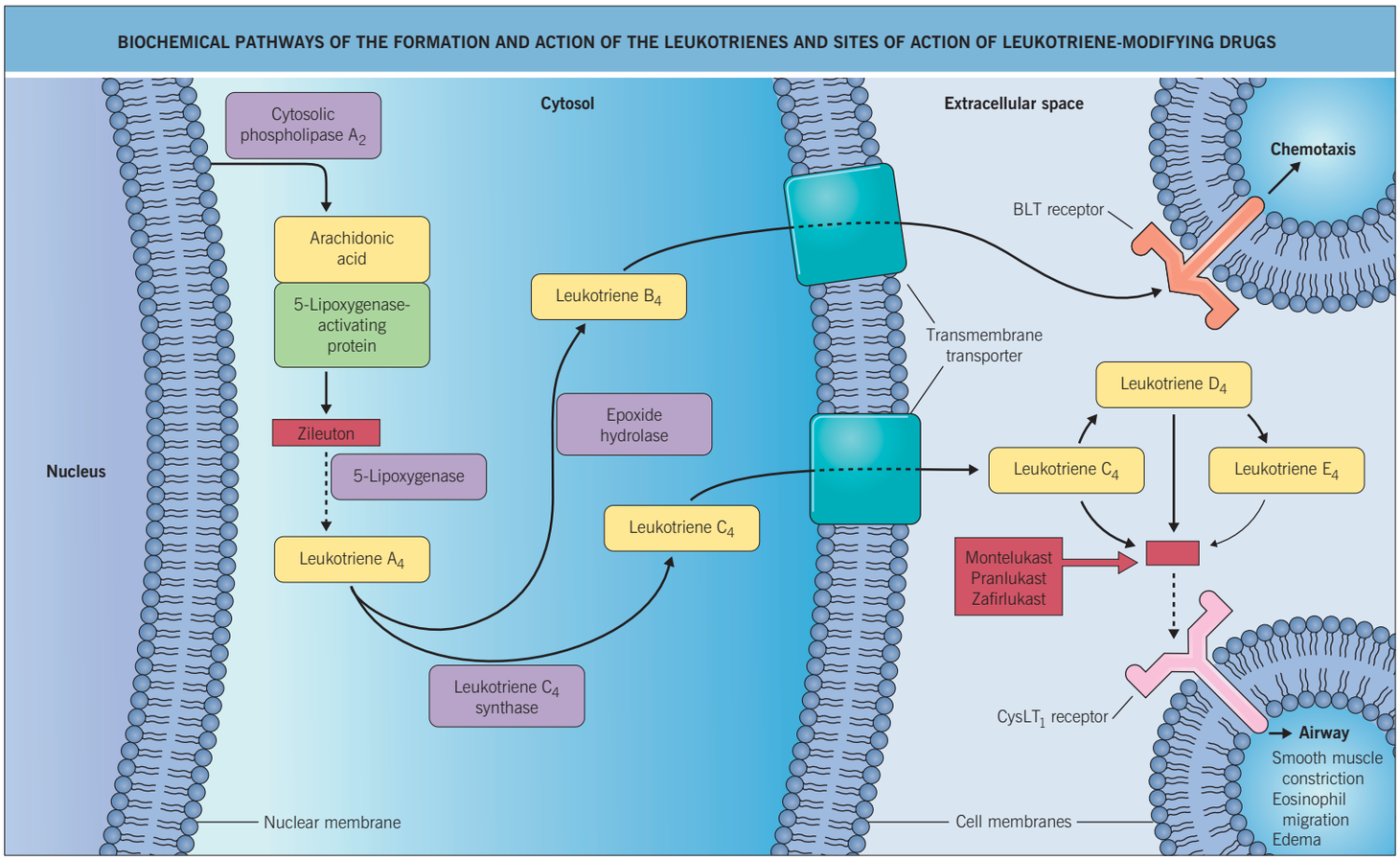


Fig 130.7 Biochemical pathways of the formation and action of the leukotrienes and sites of action of leukotriene-modifying drugs. Enzymes are shown in purple, products in yellow, essential cofactor in green, and drugs in red. Although the synthesis of leukotrienes B_4 and C_4 probably takes place in close proximity to the nuclear membrane, for clarity they are shown throughout the cytosol. An individual cell may produce the cysteinyl leukotrienes, leukotriene B_4, or, in rare cases, both. BLT, B leukotriene receptor. *From Drazen JM, Israel E, O'Byrne PM. Treatment of asthma with drugs modifying the leukotriene pathway. N Engl J Med. 1999;340:197–206.*

LEUKOTRIENE INHIBITORS

Mechanisms of action: antagonists of cysteinyl leukotriene receptors (block LTC_4, LTD_4 & LTE_4 binding) – montelukast (Singulair®), zafirlukast (Accolate®), pranlukast; inhibitor of 5-lipoxygenase – zileuton (Zyflo CR®); see Fig. 130.7
Dermatologic uses: limited evidence for atopic dermatitis, autoimmune bullous diseases, urticaria, Sjögren-Larsson syndrome; primary use is asthma
Dosages*: montelukast – 10 mg [adults], 5 mg [children 6–16 years]; zafirlukast 20 mg BID [adults & adolescents], 10 mg BID [5–11 years] on empty stomach; zileuton 1200 mg BID [adults & adolescents] with meals
Side effects: indigestion, nausea, myalgias, headaches, hepatitis; montelukast and zafirlukast have been associated with the development of eosinophilia and Churg–Strauss syndrome, usually in the setting of a taper of corticosteroids
Contraindications: prior hypersensitivity reaction to drug; significant liver disease
Pregnancy and lactation: montelukast and zafirlukast (pregnancy category B); zileuton (pregnancy category C); limited data
Drug interactions: zileuton may increase circulating levels of propranolol, theophylline, terfenadine or warfarin; zafirlukast may increase circulating levels of warfarin; aspirin or erythromycin may decrease plasma level of zafirlukast; phenobarbital may reduce levels of montelukast

*Oral.

Table 130.11 Leukotriene inhibitors.

CLASSIFICATION OF HISTOLOGIC FINDINGS IN LIVER BIOPSIES

Grade	Histologic findings	Methotrexate
I	Essentially normal liver	Continue
II	Moderate to severe fatty infiltration, nuclear variability, portal tract expansion, portal tract inflammation and necrosis	Continue; repeat biopsy after additional 1.5 g, or as recommended by hepatologist
IIIA	Mild fibrosis; fibrotic septae which extend into the lobules	Repeat biopsy in 6 months or as recommended by hepatologist
IIIB	Moderate to severe fibrosis	Discontinue
IV	Cirrhosis	

Table 130.12 Classification of histologic findings in liver biopsies. *Adapted from Roenigk H, Auerbach R, Maibach HI, et al. Methotrexate in psoriasis: revised guidelines. J Am Acad Dermatol. 1988;19:145–56.*

biopsy. In addition, based upon studies of patients with chronic hepatitis C viral infection, an index that incorporates circulating levels of a2-macroglobulin, tissue inhibitor of metalloproteinase-1 (TIMP-1), and hyaluronic acid has been developed. This index (e.g. FIBROSpect II) is commercially available and provides estimated risks of various degrees of hepatic fibrosis.

Photosensitivity may occur and patients should take appropriate sun precautions (see Ch. 21)[7]. Gastrointestinal intolerance is often abated with concomitant folic acid therapy (1–5 mg orally daily, based on symptoms). Other MTX-induced side effects include accelerated rheumatoid (cutaneous) nodulosis and reversible lymphoproliferative disorders. When used in very high doses, MTX may cause reversible oligospermia[24]. Family counseling is outlined in Table 130.13.

Drug Indications

MTX has FDA approval for use in psoriasis (see Ch. 8); however, it is used for those individuals with severe, debilitating or recalcitrant disease. In a recent randomized trial comparing methotrexate and adalimumab, 40 of 103 patients assigned to MTX (and who completed the study) had PASI 50 responses at 8 weeks at a dose of 15 mg weekly (dosage reached at week 4 from a baseline of 7.5 mg weekly). Of the

METHOTREXATE – COUNSELING FOR PATIENTS OF CHILDBEARING POTENTIAL
WOMEN
• Should not become pregnant while receiving MTX • MTX can cause birth defects and abortions • Must use highly effective means of contraception (e.g. OCPs; IUD; condom + spermicide) • After discontinuing MTX, wait at least one ovulatory cycle before attempting to become pregnant
MEN
• May lead to low sperm counts • Drug is present in semen • Must use highly effective means of contraception (e.g. OCPs; IUD [female partner]; condom + spermicide) • After discontinuing MTX, wait 3 months before attempting to have partner become pregnant

Table 130.13 Methotrexate – counseling for patients of childbearing potential. This drug is pregnancy category X. IUD, intrauterine device; MTX, methotrexate; OCPs, oral contraceptive pills.

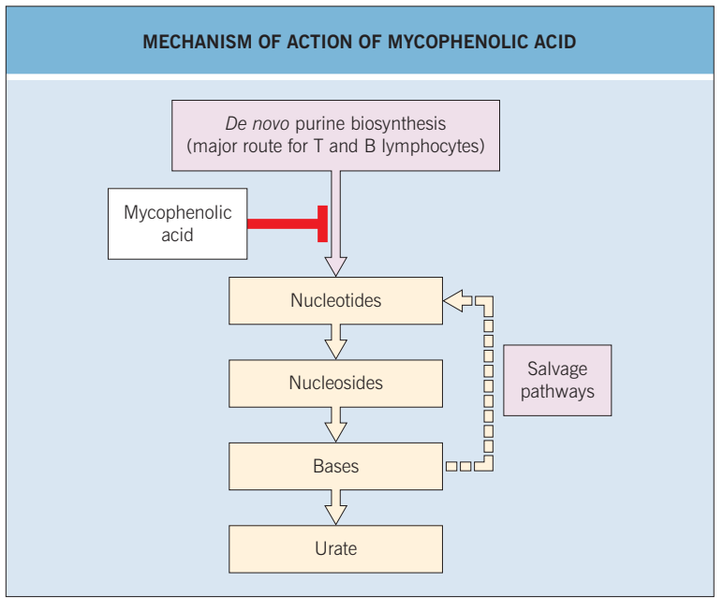


Fig. 130.8 Mechanism of action of mycophenolic acid. While most nucleated cells utilize salvage pathways, T and B lymphocytes must rely primarily on the *de novo* pathway for purine biosynthesis. Mycophenolic acid, the active drug form of the prodrug mycophenolate mofetil, inhibits inosine monophosphate dehydrogenase, an enzyme in the *de novo* pathway of purine biosynthesis.
Adapted from Wolverton SE. Comprehensive Dermatologic Drug Therapy, 2nd edn. Philadelphia: Saunders, 2007.

additional 63 patients, 22 achieved PASI 50 responses by week 12 after an increase to 20 mg weekly (at 8 weeks)[27]. This compares to PASI 75 rates of 60% at 16 weeks in patients treated with 15 mg weekly of MTX from the outset[28].

Other disorders (e.g. dermatomyositis) that respond to MTX are listed in Table 130.5. Of note, pityriasis rubra pilaris commonly requires up to twice the typical psoriasis dose, whereas PLEVA often responds to small MTX doses (2.5–5 mg/week). Methotrexate can also be used as a steroid-sparing agent, and in the elderly, monotherapy with weekly MTX is an option for the treatment of bullous pemphigoid.

Contraindications

Absolute contraindications to MTX use are pregnancy and lactation. Relative contraindications include significant liver disease or elevated liver enzymes and excessive alcohol intake. The presence of active infection or immunodeficiency, and the desire for imminent pregnancy are relative contraindications to MTX therapy (see Table 130.13). Caution is indicated and a dose reduction necessary if used in the setting of decreased renal function. In the elderly, serum creatinine levels may be deceptively low and may not reflect true renal function.

Use in Pregnancy and Lactation

MTX is an abortifacient and teratogen and should not be used during pregnancy. The American Academy of Pediatrics considers MTX to be contraindicated in breastfeeding owing to concerns of immune suppression, growth retardation and carcinogenesis[5].

Drug Interactions

Drugs that elevate MTX blood levels include NSAIDs, salicylates, sulfonamides, chloramphenicol, phenothiazines, phenytoin and tetracyclines. Dipyridamole and probenecid increase intracellular accumulation of MTX. Trimethoprim, sulfonamides and dapsone also inhibit the folate metabolic pathway (see Ch. 127) and markedly increase the risk for pancytopenia with concomitant use. Systemic retinoids and alcohol may cause synergistic liver damage in combination with MTX.

MYCOPHENOLATE MOFETIL

Mycophenolic acid (MPA) has been used in various forms for the treatment of psoriasis since the 1970s. Its use declined until the early 1990s, when a more bioavailable and safer formulation, mycophenolate mofetil (Cellcept®), became commercially available. Initially inactivated during first-pass glucuronidation in the liver (into the phenolic glucuronide of MPA, MPAG), MPA is then reactivated in the epidermis and gastrointestinal tract by β-glucuronidase (see Fig. 131.1). Mycophenolate mofetil has greater bioavailability than MPA, undergoes complete presystemic conversion to MPA after ingestion, and then follows the same inactivation/activation cycle[29]. Mycophenolate mofetil is 94% bioavailable. MPA is 97% and MPAG 82% albumin-bound. Over 90% of the drug is excreted in the urine, mainly as MPAG. Renal insufficiency can increase plasma concentrations up to sixfold[11].

Mechanism of Action

MPA selectively and non-competitively inhibits the enzyme inosine monophosphate dehydrogenase (IMPDH), preventing conversion of inosine- and xanthine-5-phosphate to guanosine-5-phosphate. This blocks *de novo* synthesis of guanine nucleotides and their subsequent incorporation into DNA (Fig. 130.8). DNA synthesis in T and B lymphocytes is preferentially inhibited because these cells lack the purine salvage pathway and are dependent on *de novo* purine synthesis. MPA decreases immunoglobulin levels and delayed-type hypersensitivity responses by inhibiting proliferative responses to mitogenic and allospecific stimulation; MPA also suppresses antibody formation by B lymphocytes.

Dosages

Mycophenolate mofetil is available in 250 mg capsules and 500 mg tablets. For dermatologic diseases, the best results are obtained with doses of 2000 mg daily. Selected patients may require doses carefully titrated up to 3000 mg daily.

Major Side Effects

The most common side effects of mycophenolate mofetil are gastrointestinal and include nausea, vomiting, diarrhea, abdominal cramps and tenderness (see Table 130.4). Significant hematologic and hepatic toxicity occur uncommonly. In 2008, the FDA released a safety report regarding a potential association (in transplant patients) between mycophenolate mofetil and the development of progressive multifocal leukoencephalopathy. Although a rare event, and cause-and-effect remains speculative, patients should be monitored accordingly[30]. Monitoring guidelines are outlined in Table 130.3. The dosage should be reduced or therapy discontinued for a WBC <3500–4000 cells/mm^3.

Indications

Mycophenolate mofetil is currently FDA-approved for renal allograft rejection only. However, it is quite useful in the treatment of autoimmune bullous diseases, severe forms of atopic dermatitis or cutaneous lupus, and refractory pyoderma gangrenosum. Mycophenolate

mofetil is generally used in conjunction with other immunosuppressive drugs, most commonly as a steroid-sparing agent.

Contraindications

Absolute contraindications to mycophenolate mofetil use are pregnancy and allergy to MPA. Relative contraindications include lactation, as MPA is partially excreted in breast milk. Peptic ulcer disease and hepatic, renal or cardiopulmonary disease are also relative contraindications. As noted previously, renal insufficiency can increase plasma concentrations up to sixfold[11].

Use in Pregnancy and Lactation

Mycophenolate mofetil is currently rated as a pregnancy prescribing category D medication[5]. Recent human data suggest that mycophenolate mofetil may cause birth defects, with a characteristic phenotype consisting of cleft lip and palate, microtia with atresia of the external auditory canal, micrognathia and hypertelorism[31]. Additional data suggest that defect severity may be dependent on the dose and duration of therapy as well as timing during pregnancy[32]. Mycophenolate mofetil is contraindicated during lactation, due to potential immunosuppression.

Drug Interactions

Drugs that alter the enterohepatic recirculation or gastrointestinal absorption of mycophenolate mofetil, such as cholestyramine, iron or aluminum and magnesium hydroxides, may decrease the effectiveness of mycophenolate mofetil (see Ch. 131). Plasma levels of acyclovir and mycophenolate mofetil are both elevated when used concomitantly.

SATURATED SOLUTION OF POTASSIUM IODIDE (SSKI)

Mechanism of Action

First discovered in seaweed in the 1800s, iodine was soon used medically for a variety of conditions, such as thyroid disease, syphilis, psoriasis and atopic dermatitis[33]. To this day, it remains an important tool in the treatment of sporotrichosis and a variety of inflammatory conditions, especially panniculitis. Most conveniently administered as a saturated solution of potassium iodide (SSKI), it is rapidly absorbed, widely distributed into the thyroid and salivary glands, choroid plexus and placenta, and then excreted primarily through the kidneys. Although its mechanism of action with regard to inflammatory diseases is speculative, it is thought to exert its effects via immune modulation. Similar to dapsone, SSKI appears to be effective in suppressing neutrophil migration and toxicity. The mechanism through which it eradicates sporotrichosis is unknown[33].

Dosages

SSKI is most commonly available in a solution with a concentration of 1000 mg/ml (see Ch. 100). The accompanying dropper has markings at 0.3 ml (300 mg) and 0.6 ml (600 mg); when lower doses are prescribed, drops (gt) are counted. The initial dose to treat inflammatory skin conditions is generally 150–300 mg three times daily, increased weekly as tolerated[34]. Improvement is generally seen within days to weeks. The dose for sporotrichosis is usually higher, beginning at 600 mg three times daily, with a maximum dose of 6 g, if tolerated[33]. The course of treatment for sporotrichosis is approximately 6–10 weeks.

Major Side Effects

Gastrointestinal side effects are common (see Table 130.4) and may be ameliorated by slow dose escalation. Long-term use can be associated with the development of "iodism", manifested by a burning mouth, a metallic taste, soreness of the teeth and gums, and a severe headache. Acneiform eruptions and iododerma can also occur, especially at higher dosages. Fortunately, symptoms abate quickly with cessation of therapy. SSKI may also alter thyroid metabolism, resulting in either hypo- or hyperthyroidism, with reversible hypothyroidism being relatively common. While hyperkalemia can occur, other side effects are rare.

Indications

Although SSKI is not FDA-approved for any cutaneous disease, it is a highly effective treatment for cutaneous and lymphocutaneous sporotrichosis. However, for systemic sporotrichosis, other drugs should be prescribed (see Ch. 77). SSKI has also been used successfully for a variety of neutrophilic disorders and granulomatous diseases as well as several types of panniculitis.

Contraindications

The only absolute contraindication is a hypersensitivity reaction to iodides. Relative contraindications include thyroid or cardiac disease, renal insufficiency and Addison's disease[35]. The latter are due to the risk of hyperkalemia.

Use in Pregnancy and Lactation

Iodide crosses the placenta and is considered pregnancy prescribing category D; fetal goiter and hypothyroidism have been described. Although it is present in breast milk, the American Academy of Pediatrics considers its use to be compatible with breastfeeding[5].

Drug Interactions

Concurrent use with other medications such as ACE inhibitors, potassium-sparing diuretics and potassium-containing medications may result in significant hyperkalemia. Hypothyroidism may result when used in combination with amiodarone, lithium, phenazone, and, possibly, sulfones[33].

TACROLIMUS

The dosage, uses and side effects are outlined in Table 130.14.

THALIDOMIDE

Few drugs have garnered such notoriety as has thalidomide. Originally introduced in Europe during the 1950s as a sedative/hypnotic, it was commonly used to control morning sickness during pregnancy. Thus, it was prescribed to thousands of pregnant women, with tragic results. By 1961, thalidomide was withdrawn from the market worldwide after being linked to thousands of babies born with phocomelia (severe underdevelopment of the extremities)[36]. At the time of worldwide withdrawal, thalidomide had never received FDA approval for use in the US. Renewed interest in the drug ensued in the mid-1960s with reports that thalidomide provided significant relief from the symptoms of erythema nodosum leprosum (ENL). Thalidomide received FDA approval for treatment of ENL in 1997.

In the US, both the prescribing physician and the dispensing pharmacist must be enrolled in the *S*ystem for *T*halidomide *E*ducation and *P*rescribing *S*afety (STEPS) program administered by the FDA and the Celgene Corporation (1–888–4–CELGEN[E] to enroll). Standardized

TACROLIMUS
Drug properties: macrolide lactone **Mechanism of action**: calcineurin inhibitor (see Ch. 128); inhibits production of cytokines such as IL-8 **Dermatologic use**: GVHD – prophylaxis, acute and chronic; pyoderma gangrenosum; recalcitrant psoriasis **Dosage**: 1–2 mg orally twice daily (blood level 5–10 ng/ml) **Side effects**: immunosuppression, renal dysfunction, hypertension, hyperkalemia (esp. in conjunction with ACE inhibitors), diabetes mellitus **Contraindications**: uncontrolled hypertension, significant renal impairment, prior hypersensitivity reaction to drug or, for parenteral administration, allergy to HCO-60 (polyoxyl 60 hydrogenated castor oil that is used as a surfactant); see contraindications for cyclosporine **Pregnancy and lactation**: for dermatologic disorders, should be avoided during pregnancy (category C) and lactation (concentrated in breast milk) **Drug interactions**: Other renal-toxic drugs; drugs that inhibit or induce CYP3A4 (see Ch. 131)

Table 130.14 Tacrolimus (Prograf®). Also known as FK506. There is significantly less hypertrichosis as compared to cyclosporine.

informed consent forms, patient education packets, and monitoring requirements are included in the program.

Thalidomide (Thalomid®) is a lipophilic, non-polar piperidine-dione that is poorly absorbed and highly protein-bound. Peak plasma levels are attained 2–6 hours after ingestion and absorption is not affected by food intake. The half-life of thalidomide is 9 hours. Although the major degradative pathway is non-enzymatic hydrolysis, the drug is also metabolized by the CYP enzymes. The precise method of excretion is not known, but it is non-renal[35].

Mechanism of Action

The precise mechanisms of action of thalidomide are unknown. However, its anti-inflammatory and immunomodulatory effects on dermatologic diseases are thought to be largely through inhibition of TNF-α release and activity.

Dosages

A major emphasis of the STEPS program is pregnancy prevention. Prior to therapy, women of childbearing potential must be on birth control for 1 month and have a negative serum pregnancy test within 24 hours of the first dose. If the initial history or physical examination indicates peripheral nervous system disease, neurologic consultation should be sought. Monitoring guidelines are listed in Table 130.3. Thalidomide is available in 50, 100, 150 and 200 mg capsules. Dosing regimens will vary according to the particular disease and its severity. Used in combination with anti-leprosy chemotherapy, the dose for ENL ranges from 100 to 400 mg per day (see package insert for details). Dosages for HIV-associated oral aphthae and neutrophilic dermatoses are generally 100 mg per day. The most common dose-limiting side effect is sedation.

Patients with recalcitrant discoid or SCLE lesions (Fig. 130.9) have 75–90% clearance rates with thalidomide. The initial dose of 50–100 mg/day is subsequently tapered to 25–50 mg/day after a clinical effect is seen, usually within 2 weeks. Acute cutaneous lesions of SLE have up to a 90% resolution rate, but require higher doses and a longer treatment period before results are noted. For some patients, intermittent courses of thalidomide (for 2–3 months) can be used to clear lesions, with antimalarials given concomitantly and as maintenance therapy.

Major Side Effects

A single dose of thalidomide during the first 21–36 days of gestation yields a 100% incidence of birth defects (see Table 130.4). Sedation is by far the most common adverse side effect and may necessitate nighttime dosing and a gradual titration of the thalidomide dose. Constipation is also relatively common. Permanent nerve damage (primarily sensory neuropathy) can develop and is more common with long-term therapy. Measurements of sensory nerve action potential amplitudes (SNAP) may be indicated before and/or during therapy. Amenorrhea and primary ovarian failure may occur.

Severe leukopenia, exfoliative erythroderma and TEN are rare, but severe, consequences of thalidomide treatment. A hypersensitivity reaction specific to HIV-positive patients has been described. Common dermatologic side effects include brittle fingernails, xerosis, pruritus and red palms. Peripheral edema can develop occasionally. Vascular thromboses are unusual unless the patient is receiving concomitant corticosteroids.

Indications

Thalidomide is FDA-approved and 99% effective for ENL (type II leprosy reaction). It has no effect on type I leprosy reactions. A variety of off-label uses of thalidomide have emerged over the years (Table 130.5)[37]. Although HIV-associated mucosal ulceration, as well as aphthae associated with neutrophilic dermatoses (including Behçet's disease), respond rapidly to thalidomide, ulcerations relapse quickly when the drug is discontinued. Curiously, the highest rate of peripheral neuropathy has been observed in prurigo nodularis patients[37].

Contraindications

Absolute contraindications to thalidomide therapy include sensitivity to thalidomide, pregnancy and a pre-existing peripheral neuropathy.

Fig. 130.9 Effect of thalidomide on subacute cutaneous lupus erythematosus. **A** The patient's disease was not controlled despite prednisone (60 mg/day), hydroxychloroquine (600 mg/day) and isotretinoin (60 mg/day), all for at least 2 months. **B** Thalidomide (50–100 mg/day) was begun and the lesions resolved over 6 to 8 weeks. *Courtesy, Jean L Bolognia, MD.*

Women of childbearing potential must agree to use highly effective methods of birth control (e.g. two reliable forms of contraception simultaneously). Men taking thalidomide who have female partners of childbearing potential must wear condoms (even if they have had a vasectomy) while their partners use an additional form of birth control (either oral or barrier). Relative contraindications include significant hepatic or renal disease, a history of neurologic disease, congestive heart failure, hypertension, constipation and hypothyroidism. In patients with a predisposing condition (e.g. antiphospholipid antibodies, myeloma), there can be an increased risk of thromboses. Individuals receiving antimalarials should continue to do so, because these drugs have been reported to inhibit platelet aggregation and adhesion.

Use in Pregnancy and Lactation

Thalidomide is pregnancy prescribing category X and should not be used in pregnant women[5]. It is wise to avoid thalidomide in nursing mothers.

Drug Interactions

Thalidomide may amplify the sedative effects of alcohol, barbiturates, chlorpromazine and reserpine. Any drug that significantly induces the CYP3A4 enzymes may decrease the effectiveness of hormonal contraception, increasing the potential of pregnancy and, thus, teratogenicity.

REFERENCES

1. Callen JP, Camisa C. Antimalarial agents. In: Wolverton SE (ed). Comprehensive Dermatologic Drug Therapy, 2nd edn. Philadelphia: WB Saunders, 2007:259–73.
2. Wozniacka A, Carter A, McCauliffe DP. Antimalarials in cutaneous lupus erythematosus: mechanisms of therapeutic benefit. Lupus. 2002;11:71–81.
3. Weiss JS. Antimalarial medications in dermatology. Dermatol Clin. 1991;9:377–85.
4. Kali S, Dutz JP. New concepts in antimalarial use and mode of action in dermatology. Dermatol Ther. 2007;160–74.
5. Briggs GG, Freeman RK, Yaffe SJ. Drugs in Pregnancy and Lactation, 8th edn. Baltimore: Lippincott Williams & Wilkins, 2008.
6. Badalamenti S, Kerdel FA. Azathioprine. In: Wolverton SE (ed.). Comprehensive Dermatologic Drug Therapy, 2nd edn. Philadelphia: WB Saunders, 2007:183–95.
7. Stern DK, Tripp JM, Ho VC, Lebwohl M. The use of systemic immune moderators in dermatology: an update. Dermatol Clin. 2005;23:259–300.
8. Liu H, Wong C. In vitro immunosuppressive effects of methotrexate and azathioprine on Langerhans cells. Arch Dermatol. 1997;289:94–7.
9. Wise M, Callen JP. Azathioprine: a guide for the management of dermatology patients. Dermatol Ther. 2007;20:206–15.
10. Ahmed AR, Hombal SM. Cyclophosphamide, a review on relevant pharmacology and clinical uses. J Am Acad Dermatol. 1984;11:1115–26.
11. Perlis C, Pan TD, McDonald CJ. Cytotoxic agents. In: Wolverton SE (ed.). Comprehensive Dermatologic Drug Therapy, 2nd edn. Philadelphia: WB Saunders, 2007:198–217.
12. Lee CS, Koo JYM. Cyclosporine. In: Wolverton SE (ed.). Comprehensive Dermatologic Drug Therapy, 2nd edn. Philadelphia: WB Saunders, 2007:220–37.
13. Dutz JP, Ho VC. Immunosuppressive agents in dermatology, an update. Dermatol Ther. 1998;16:235–51.
14. Koo J, Lee J. Cyclosporine, what clinicians need to know. Psoriasis. 1995;13:897–907.
15. Grossman RM, Chevret S, Abi-Rached J, et al. Long-term safety of cyclosporin in the treatment of psoriasis. Arch Dermatol. 1996;132:623–9.
16. Zachariae H. Renal toxicity of long-term cyclosporin. Scand J Rheumatol. 1999;28;65–8.
17. Luke RG. Mechanism of cyclosporine-induced hypertension. Am J Hypertension. 1991;4:468–71.
18. Madan V, Griffiths CEM. Systemic ciclosporin and tacrolimus in dermatology, Dermatol Ther. 2007;20:239–50.
19. Wolf R, Tuzun B, Tuzun Y. Dapsone: Unapproved uses or indications. Clin Dermatol. 2000;18:37–53.
20. Hall RP, Mickle CP. Dapsone. In: Wolverton SE (ed.). Comprehensive Dermatologic Drug Therapy, 2nd edn. Philadelphia: WB Saunders, 2007:239–57.
21. Coleman MD. Dapsone: modes of action, toxicity and possible strategies for increasing patient tolerance. Br J Dermatol. 1993;129:507–13.
22. Boyd AS, Neldner KH. Hydroxyurea therapy. J Am Acad Dermatol. 1991;25:518–24.
23. Wedi B, Kapp A. Pathophysiological role of leukotrienes in dermatologic diseases: potential therapeutic implications. BioDrugs. 2001;15:729–43.
24. Bangert CA, Costner MI. Methotrexate in dermatology. Dermatol Ther. 2007;20:216–28.
25. Olsen EA. The mechanism of action of methotrexate. Rheum Dis Clin North Am. 1997;23:739–55.
26. Kalb RE, Strober V, Weinstein G, Lebwohl M. Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference. J Am Acad Dermatol. 2009;60:824–37.
27. Saurat J-H, Stingl G, Dubertret LE, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). Br J Dermatol. 2008;158:558–66.
28. Heydendael VM, Spuls PI, Opmeer BC, et al. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. N Engl J Med. 2003;349:658–65.
29. Orvis AK, Wesson SK, Breza Jr TS, et al. Mycophenolate mofetil in dermatology. J Am Acad Dermatol. 2009;60:183–99.
30. Neff RT, Hurst FP, Falta EM, et al. Progressive multifocal leukoencephalopathy and use of mycophenolate mofetil after kidney transplantation. Transplantation. 2008;86:1474–8.
31. Perez-Aytes A, Ledo A, Boso V, et al. In utero exposure to mycophenolate mofetile: a characteristic phenotpye? Am J Med Genet A. 2008;146A:1–7.
32. Ang GS, Simpson SA, Reddy AR. Mycophenolate mofetil embryopathy may be dose and timing dependent. Am J Med Genet A. 2008;146A:1963–6.
33. Sterling JB, Heymann WR. Potassium iodide in dermatology: a 19th century drug for the 21st century – uses, pharmacology, adverse effects, and contraindications. J Am Acad Dermatol. 2000;43:691–7.
34. Horio T, Danno K, Okamoto H, et al. Potassium iodide in erythema nodosum and other erythematous dermatoses. J Am Acad Dermatol. 1983;9:77–91.
35. Knable AL, Davis LS. Miscellaneous systemic drugs. In: Wolverton SE (ed.). Comprehensive Dermatologic Drug Therapy, 2nd edn. Philadelphia: WB Saunders, 2007:471–500.
36. Powell RJ, Gardner-Medwin JMM. Guideline for the clinical use and dispensing of thalidomide. Postgrad Med J. 1994;70:901–4.
37. Faver IR, Guerra SG, Su WP, el-Azhary R. Thalidomide for dermatology: a review of clinical uses and adverse effects. Int J Dermatol. 2005;44:61–7.

This page intentionally left blank

Drug Interactions 131

Lori E Shapiro, Sandra R Knowles and Neil H Shear

Chapter Contents

Putting interactions into perspective 2183
Assessment of risk in the clinical outcome of drug interactions 2183
Levels of evidence 2184
Absorption 2184
Distribution 2186
Drug biotransformation 2186
The confusing world of drug interactions 2188
How to minimize the risk of drug–drug interactions 2189

INTRODUCTION

There are two concerns in drug safety: drug reactions and drug interactions. When multiple medications are prescribed, drug interactions become an important safety and efficacy consideration for patients and physicians alike[1]. Non-prescription drugs, as well as herbal or alternative medicines and foods (such as grapefruit juice), may also be implicated in interactions with drug therapy.

It is difficult to obtain precise rates of incidence and prevalence, as specific diagnostic codes for drug interactions are lacking[2]. Drug interactions are known to be responsible for up to 2.8% of hospital admissions[3,4]. It has been estimated that adverse drug outcomes occur about once every 100 patient days[3,5]. Although it is impossible to remember all potential drug interactions, knowledge of the interactive properties of drugs can help reduce the risk of serious adverse outcomes. Moreover, it is the responsibility of physicians to counsel patients regarding drug interactions[6]. Unfortunately, even when serious new drug interactions are recognized and reported, physicians, pharmacists and patients are often unaware that there is a risk[7].

PUTTING INTERACTIONS INTO PERSPECTIVE

Prescribing drugs with the potential for a deleterious interaction increases the risk of, but need not lead to, an adverse outcome. Many drug–drug interactions are susceptible to control by dose adjustment. Some interactions can even be exploited for a therapeutic advantage, e.g. coadministration of erythromycin to increase cyclosporine levels as a means of reducing costs associated with the latter.

While most drugs are associated with interactions, many do not produce significant outcomes[8]. In fact, not all listed or reported drug interactions are actually clinically significant. Whereas some have little clinical relevance, others are clearly defined as contraindications on the basis of substantiation of risk, potential severity and frequency of occurrence. Still others can be successfully managed by dosage adjustment and monitoring. In one study that examined the occurrence of drug interactions, based upon adverse events reported during large clinical trials[9], the authors concluded that serious adverse drug reactions (ADRs) secondary to drug–drug interactions were infrequent; however, drug–drug interactions that involved selected drugs with a narrow therapeutic index (which elicited life-threatening undesired effects) did occur. Serious ADRs secondary to drug–drug interactions were most frequently observed in elderly patients, with polypharmacy in the psychiatric patient population, and in the presence of inappropriate prescriptions or multiple prescribers. Thus, for most drug interactions, it is necessary to assess each patient situation individually.

ASSESSMENT OF RISK IN THE CLINICAL OUTCOME OF DRUG INTERACTIONS

The clinical importance of specific drug interactions is often either over- or underestimated, as these assessments are largely based on clinical experience in using a particular drug combination[10]. The clinical outcome of most drug interactions is highly situational, as most patients who receive drugs with the potential for interactions do not develop adverse effects. Emphasis should be placed on those factors that increase or decrease the risk to a given patient.

In order to prevent or detect drug interactions, the physician needs to identify risk factors in each individual patient. That said, some patient groups are more likely than others to develop adverse events caused by drug interactions. Identified risk factors are listed in Table 131.1 and are grouped by category[12].

The elderly frequently experience drug interactions because of the physiologic changes that accompany the aging process and the types of drugs that older patients tend to receive[11]. Polypharmacy, which is common in the elderly, makes them particularly susceptible. In addition, medications may impair pathways of drug elimination by interfering with drug metabolism, thereby increasing the likelihood of adverse drug reactions. Alterations due to advanced age, including changes in drug–protein binding and drug distribution within tissue, may also promote drug interactions. Of note, most adverse metabolic drug interactions occur when an inhibitor or inducer is begun in a patient who previously had stable levels of a substrate drug.

Patients with AIDS also have a high rate of adverse drug reactions[13]. In some instances, this may relate to phenotypic changes in drug metabolism, which can vary with progression of the underlying HIV infection[14]. The latter can alter enzyme function, with resultant changes in drug metabolism and a higher rate of adverse reactions in these patients.

A major source of interindividual differences in drug metabolism is genetic polymorphisms, which are inherited and can result in significant variations in the activity of drug-metabolizing enzymes. For example, the genes encoding cytochrome P450 (CYP) isoforms are highly polymorphic (see Table 131.13). In some cases, it is actually possible to determine an individual's genotype[15]. Further details on genetic polymorphisms are discussed later in the chapter.

Interactions with other drugs can predispose a patient to the development of certain types of ADR. For example, coadministration of valproic acid increases the risk of severe cutaneous adverse reactions to lamotrigine[16], and allopurinol increases the risk of exanthematous eruptions to antibiotics such as amoxicillin. A disease state itself may directly affect the likelihood of an ADR. For example, active infection with Epstein–Barr virus or cytomegalovirus also increases the risk of exanthematous eruptions to amoxicillin. The basis of these interactions is unknown but may represent a combination of factors, including alterations in drug metabolism, drug detoxification, antioxidant defenses and immune reactivity[17]. The disease state may also dictate the way in which a drug is prescribed, and this will subsequently affect the outcome. When a drug has more than one therapeutic action, an interacting drug may affect the action of the first drug when it is used to treat one disease but not when it is used to treat the first disease. This is known as pharmacologic selectivity.

An example of intrinsic effects of disease states would be when epinephrine (adrenaline) is given to patients receiving non-cardioselective

PATIENT RISK FACTORS FOR DRUG INTERACTIONS
• Multiple medications – polypharmacy
• Demographic risk factors
– Female gender
– Extremes of age (very young and elderly)
• Major organ dysfunction (especially when multiple medical problems)
– Liver dysfunction
– Renal insufficiency*
– Congestive heart failure
• Metabolic and endocrine risk factors
– Obesity
– Hypothyroidism
– Hypoproteinemia
• Pharmacogenetic risk factors
– Slow acetylator phenotype
– Reduced thiopurine methyltransferase (TPMT) activity
– Other genetic polymorphisms (see text and Table 131.13)
• Other medical issues
– Hypothermia
– Hypotension
– Dehydration
*May be underestimated in elderly patients.

Table 131.1 Patient risk factors for drug interactions[11].

β-adrenergic blockers (but who do not have anaphylaxis) and this results in hypertension. In contrast, the same β-blockers inhibit the pressor response to epinephrine[18] when the latter is given to patients with anaphylaxis.

An example of a dose-dependent drug interaction is the concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) and methotrexate. Available evidence indicates that the risk of this combination is considerably greater in patients receiving high-dose methotrexate for cancer than it is in patients receiving lower weekly dosages for psoriasis[19]. This is because the distribution of the drug is not very important mechanistically in determining drug interactions, but changes in drug elimination are. When larger doses of methotrexate (as used in cancer therapy) are given in combination with an NSAID, reduced drug elimination becomes an important issue, increasing the risk of methotrexate toxicity.

Gender-related differences in pharmacokinetics may cause variations in drug absorption, gastric emptying and distribution based on percentage of adipose tissue[20]. Gender-related differences in receptor density and sensitivity, enzyme activity (CYP2D6) and underlying disease activities also contribute to pharmacokinetic variation. The effect of obesity on metabolism is cytochrome-specific. For example, obesity decreases the activity of CYP3A4 and increases the activity of CYP2E1.

Certain medications are clearly more likely to be involved in drug interactions. More specifically, clinically significant interactions occur more frequently with drugs that have a narrow margin of safety, i.e. a narrow therapeutic window. Drugs with the potential for such serious interactions include warfarin and cyclosporine. When prescribing a new medication that could potentially interact with warfarin, it is prudent to have the patient's international normalized ratio (INR) measured within 2–3 days of administration of the new drug.

Medication-related factors that contribute to clinical risk include the dose, route of administration and duration of administration of the *precipitant drug* (the drug that causes the interaction) as well as the sequence of administration of the interacting drugs. Most metabolic drug interactions are dose-related. That is, as the dose of the precipitant drug is increased, the magnitude of its effect on the *object drug* tends to increase. Thus, the dose of the precipitant drug is often an important determinant of risk. However, the dose of the object drug may also affect the risk of an adverse drug interaction. For example, a patient who takes small doses of an object drug with serum concentrations at the lower end of the target range is at a lesser risk when an enzyme-inhibiting precipitant drug is added than would be a patient taking large doses of the same object drug. Lastly, the bioavailability of either drug may have an impact.

The route of administration is an important risk factor for some non-metabolic drug interactions, such as when one drug binds to another in the gastrointestinal (GI) tract. However, the route of administration can also be important for metabolic drug interactions, especially when the drug undergoes extensive first-pass metabolism in the gut wall and liver by CYP3A4 or P-glycoprotein. Most drug interactions also have a typical time course over which the effects develop. For example, giving rifampin, a typical inducer of CYP3A4, for only a few days is unlikely to have much effect on substrates of CYP3A4, as induction of an enzyme takes weeks to occur.

In summary, there is pharmacodynamic and pharmacokinetic variability between people, as well as host variability in terms of disease state. Overall, this variability contributes to confusion, as tables and lists that outline potentially interacting medications vary amongst different sources. One reason is that various levels of evidence exist for many of these drugs in terms of their ability to contribute to/cause drug interactions. This is outlined in more detail in the next section.

LEVELS OF EVIDENCE

Drug interaction literature is often confusing due to poorly substantiated claims[21]. This confusion occurs as a result of inaccurate or cursory evaluations of published cases or inappropriate extrapolations from the literature. Metabolic drug interactions are a major source of potential clinical problems, but their investigation during drug development is often incomplete. *In vitro* studies give very accurate data on the interactions of drugs with selective CYP isozymes, but their interpretation in the clinical context is difficult. Although *in vitro* systems have been developed to test the effects of certain drugs on the metabolism of other drugs, these systems may not accurately predict the effect in patients receiving drugs with complex metabolism. Also, problems with the detection of adverse events after a drug has been released arise mainly because such events are rare. It takes a surveillance system with a high degree of sensitivity to detect such problems[22].

Furthermore, most *in vivo* and *in vitro* studies of drug interactions evaluate two-drug regimens, and the results may not apply to the multidrug regimens used clinically. This is especially true for a regimen consisting of three or more drugs with opposing effects on CYP3A4 metabolism. The lack of studies of multiple drug interactions provides little assistance to the prescribing physician, who is left to rely on adverse events or treatment failure to demonstrate whether an interaction has occurred. In addition, the design of *in vivo* studies is sometimes poor (choice of prototype substrate, doses, schedule of administration, number of volunteers), with the risk of minimizing the real potential for interaction. To link *in vitro* and *in vivo* studies, several authors have suggested using extrapolation techniques, based on the comparison of *in vitro* inhibition data with the active *in vivo* concentrations of the inhibitor. However, the lack of knowledge with regard to one or several important parameters, such as the role of metabolites and intrahepatocyte accumulation, often limits the ability to make safe and accurate predictions.

The uncertainty and inaccuracy of predicting the extent and duration of *in vivo* drug interactions currently stems from a lack of definitive models by which to assess likely substrate and inhibitor concentrations at the active site of metabolism. Additional issues contributing to the uncertainty of predicting drug interactions include assumptions of the contribution of presystemic drug extraction and the effect of inhibitors on the processes involved. As a consequence, these methods are useful for complementing *in vivo* studies and helping to design clinically relevant *in vivo* studies, but in the foreseeable future they will not totally replace *in vivo* investigations.

ABSORPTION

Interactions that alter the absorption of drugs often lead to dramatic changes in plasma drug concentrations. Drug interactions within the GI tract can result in decreased absorption. This reduces the bioavailability or the amount of drug available to the systemic circulation and results in subtherapeutic serum concentrations. The underlying mechanisms of most drug interactions that alter GI absorption involve: (1) the formation of drug complexes that reduce absorption; (2) alterations in gastric pH; and/or (3) changes in GI motility that alter transit time[23].

Common drugs that form complexes with other drugs include antacids, sucralfate, and bile acid-binding resins used to lower cholesterol

levels (e.g. cholestyramine) (Table 131.2). A significant interaction occurs between multivalent cations – such as calcium, aluminum, iron and magnesium – and tetracyclines or fluoroquinolone antibiotics. For example, there is an 85% reduction in the absorption of ciprofloxacin when ingested 5–10 minutes after a dose of an aluminum hydroxide/magnesium hydroxide antacid[24]. These interactions can be easily avoided by administering the fluoroquinolone at least 2 hours before or 6 hours after the antacid. Alendronate, as well as other bisphosphonates prescribed for the prevention and treatment of osteoporosis, forms complexes with cations and several other drugs, thereby further decreasing their already low oral absorption. Once-weekly dosing reduces the opportunity for bisphosphonate-related interactions. When mycophenolate mofetil and iron preparations were administered concomitantly, a significant decrease in mycophenolate mofetil absorption was observed (Fig. 131.1)[25].

Drugs that increase gastric pH, such as proton pump inhibitors, antacids and H_2 antihistamines, may reduce the absorption of drugs such as ketoconazole and itraconazole, which are best absorbed in an acidic environment[26]. Although itraconazole is best absorbed when the gastric pH is low, its administration with food is more important for achieving high plasma concentrations[27]. The absorption of fluconazole is unaffected by variations in gastric pH. Drugs that affect GI motility, such as anticholinergic agents, may decrease the rate of absorption but not the extent of absorption. An overall reduction in drug absorption has more clinical significance[28].

Some drugs may interfere with the enterohepatic recirculation of a substrate drug. When the substrate is excreted into the GI tract, a second drug can bind to it and prevent its reabsorption back into the systemic circulation. The bound substrate drug is excreted in the feces, thereby effectively shortening its half-life. An example of this is the concurrent administration of warfarin and cholestyramine, in which the half-life of warfarin is shortened by oral cholestyramine.

DRUG INTERACTIONS THAT REDUCE THE EFFICACY OF SUBSTRATES

Mechanism	Substrate/ parent drug	Concomitant drugs	Time course
Reduced GI absorption	Itraconazole Ketoconazole	Antacids* Didanosine H_2 antihistamines Proton pump inhibitors Sucralfate	Rapid
	Fluoroquinolones	Antacids* Iron Sucralfate	
	Tetracycline	Divalent cations Calcium Magnesium Iron	
	Dapsone Mycophenolate mofetil	Didanosine Iron	
Induction of CYP3A4†	Calcineurin inhibitors Cyclosporine Tacrolimus Oral contraceptives Prednisone Warfarin	Anticonvulsants Carbamazepine Phenytoin Phenobarbital Antituberculous agents Isoniazid Rifampin Dexamethasone Griseofulvin	1–2 weeks
Antagonistic effects	Epinephrine Cyproheptadine	β-Blockers SSRI antidepressants Fluoxetine Paroxetine	

*Often contain aluminum hydroxide, magnesium hydroxide and/or calcium carbonate.
†Also A5, A7.

Table 131.2 Drug interactions that reduce the efficacy of substrates. In addition, bile acid-binding resins (e.g. cholestyramine, colestipol) dramatically reduce GI absorption of furosemide and thiazide diuretics and absorption of bisphosphonates is reduced by divalent cations. GI, gastrointestinal; SSRI, selective serotonin reuptake inhibitors.

P-glycoprotein (PGP)

Membrane-bound transport systems may also determine drug disposition[29]. PGP is an ATP-dependent plasma membrane glycoprotein (Fig. 131.2) belonging to the superfamily of ATP-binding cassette transporters[30]. In humans, the multidrug resistance (MDR) genes, including *MDR1*, encode membrane glycoproteins that function as drug transporters and hence affect both drug absorption and elimination. High levels of PGP are found in superficial columnar epithelial cells of the small intestine, the apical surface of epithelial cells in the proximal tubules of the kidney, and in the biliary canalicular membrane of hepatocytes. PGP is also detected in high concentrations in the endothelial cells of the capillaries of the blood–brain barrier, testes, uterus and placenta. An understanding of the physiologic regulation of these transporter proteins is key to designing strategies for improving the therapeutic efficacy of drugs that serve as their substrates (Table 131.3).

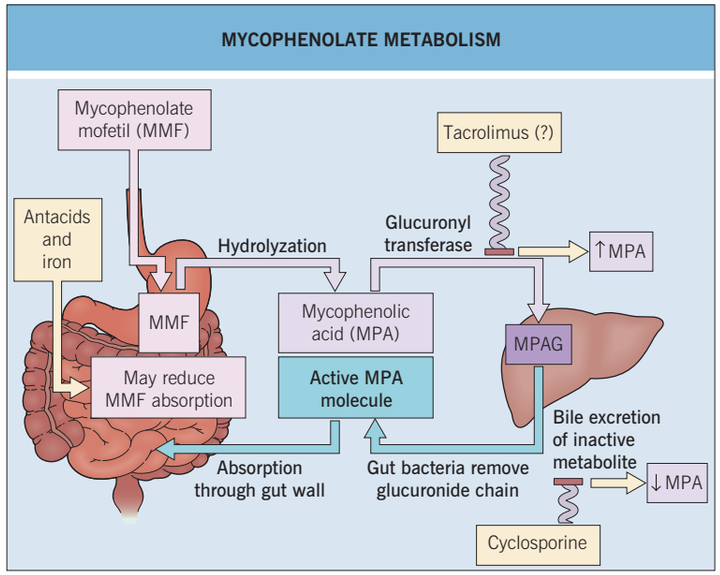


Fig. 131.1 Mycophenolate metabolism. Mycophenolate is hydrolyzed to mycophenolic acid (MPA). Following glucuronidation in the liver, inactive MPA glucuronide (MPAG) is excreted into the gut via bile acid secretion. In the gut, bacteria remove the glucuronide chain to produce MPA, the active molecule, which is then reabsorbed through the gut wall. Cyclosporine impairs MPA enterohepatic recirculation by inhibiting biliary excretion of MPAG (thereby *decreasing* MPA levels), whereas tacrolimus may inhibit UDP-glucuronyl transferase (thereby *increasing* MPA levels).

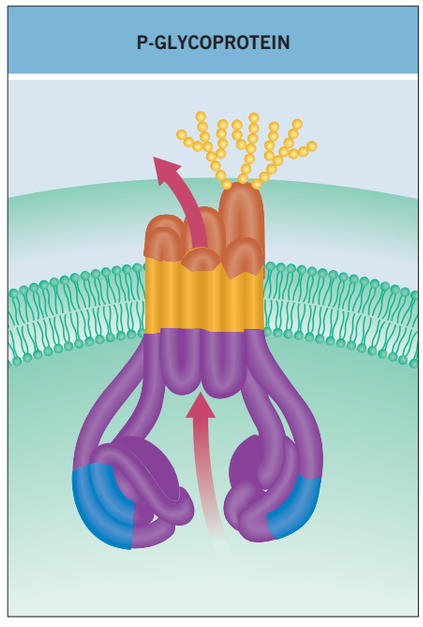


Fig. 131.2 P-Glycoprotein. This is an ATP-dependent plasma membrane glycoprotein that functions as a drug transporter and hence affects both drug absorption and elimination. *Adapted from Kartner N, Ling V. Scientific American 1989;260:44–51.*

P-GLYCOPROTEIN SUBSTRATES		
ANTIMICROBIALS	**HIV PROTEASE INHIBITORS**	**CARDIAC AGENTS**
Ciprofloxacin	Indinavir	Amiodarone
Erythromycin	Nelfinavir	Atorvastatin
Ivermectin	Ritonavir	Digoxin
Other quinolones	Saquinavir	Diltiazem
Rifampin		Lovastatin
	ANTIEMETICS	Nadolol
ANTICANCER AGENTS	Domperidone	Pravastatin
Actinomycin D	Ondansetron	Propranolol
Daunorubicin		Quinidine
Docetaxel	**RHEUMATOLOGIC AGENTS**	Timolol
Doxorubicin	Colchicine	Verapamil
Etoposide	Methotrexate	
Mitomycin C	Quinine	**MISCELLANEOUS**
Paclitaxel		Cimetidine
Vinblastine	**IMMUNOSUPPRESSIVES**	Lidocaine
Vincristine	Cyclosporine	Loperamide
	Tacrolimus	Terfenadine*

*Historical.

Table 131.3 P-Glycoprotein substrates.

INHIBITORS OF P-GLYCOPROTEIN		
ANTIMICROBIALS	**PSYCHOTROPIC AGENTS**	**CARDIAC AGENTS**
Clarithromycin	Amitriptyline	Amiodarone
Erythromycin	Chlorpromazine	Carvedilol
Itraconazole	Desipramine	Diltiazem
Ivermectin	Disulfiram	Dipyridamole
Ketoconazole	Doxepin	Felodipine
Mefloquine	Fluphenazine	Nicardipine
Ofloxacin	Haloperidol	Nifedipine
Rifampin	Imipramine	Propranolol
Voriconazole		Propafenone
	STEROID HORMONES	Verapamil
IMMUNOSUPPRESSIVES	Progesterone	
Cyclosporine	Testosterone	**MISCELLANEOUS**
Tacrolimus		Grapefruit juice
		Orange juice isoflavones
		Ritonavir
		Tamoxifen

Table 131.4 Inhibitors of P-glycoprotein.

These membrane-bound transport systems appear to have developed as a mechanism for protecting the body from harmful substances. It appears that PGP acts as a pump whereby the efflux of drugs from the cell membrane or cytoplasm is powered by the energy from ATP hydrolysis. For example, the aminoglycoside antibiotics amikacin and tobramycin are not effectively delivered orally, perhaps because of active efflux from the brush border cells of the small intestine by the PGP pump. The most remarkable property of PGP is its ability to transport a diverse array of compounds that do not appear to share obvious structural characteristics. The range of substrates, inhibitors and inducers of PGP is vast and expanding (Tables 131.3 & 131.4).

Because PGP blocks absorption in the gut, these glycoproteins should be considered part of the "first-pass effect". In fact, PGP can "set up" or act as "gatekeepers" for later cytochrome P450 actions. Although the inhibition and induction of intestinal CYP3A enzymes from metabolic processes result in direct changes in drug absorption, the inhibition and induction of PGP primarily affects the rate of drug absorption[31]. If one drug is a substrate of both PGP and CYP3A4 (which are found in close proximity in the intestinal wall), and a second drug is added that is an inhibitor of both PGP and CYP3A4 (e.g. ketoconazole, erythromycin), then a greater amount of the first drug will be absorbed. Because CYP3A4 is inhibited, higher levels of *unmetabolized* drug will enter the blood. The effect of PGP blockade is to "open the gates" so that the later actions of CYP3A4 inhibition will be increased.

PGP is an important component of the blood–brain barrier and an active PGP will prevent drugs from entering the brain. It has been suggested that the reason newer antihistamines do not cause sedation is that PGP activity acts as a barrier to CNS penetration. This would suggest that PGP inhibitors (see Table 131.4) could interact with and allow increased cerebral concentrations of these antihistamines, with an attendant increase in sedation[32].

Evidence also suggests that intestinal PGP plays a significant role in the first-pass elimination of cyclosporine, probably by being a rate-limiting step in absorption. Intestinal CYP3A4 is thought to play a lesser role[33]. However, the overlap of tissue distribution and substrate specificity of CYP3A4 and PGP in the intestinal wall makes it difficult to define the precise mechanisms of some drug interactions and to predict the plasma concentrations of certain drug combinations. Moreover, the involvement of CYP3A4 and PGP in drug interactions is not always complementary.

DISTRIBUTION

Drugs that are highly protein bound (>90%) may cause interactions based on alterations in distribution. When one drug displaces another from plasma protein-binding sites, the free serum concentration of the displaced drug is increased and its pharmacologic effect increases. However, the unbound fraction of the drug is not only more available to sites of action but is also more readily eliminated. Any enhanced pharmacologic effect occurs only transiently because of a compensatory increase in elimination, and the *effect of displacement interactions is then negligible*. Therefore, interactions involving drug displacement from binding proteins tend to be self-limiting[34]. Typically, the pharmacologic activity of the displaced drug is increased for a few days. This is followed by a return of the pharmacologic response back to the previous unbound serum concentration, even if the concomitant therapy is continued. Therefore, it is safe to say that if a patient does not manifest an adverse event from the combination therapy in the first week or so of administration, an adverse event probably will not occur.

In practice, protein-binding displacement interactions do not produce clinically important changes in drug response unless the drug also has a limited distribution in the body, is slowly eliminated, or has a low therapeutic index[28]. For this reason, protein-binding displacement interactions may assume greater importance when the displacing drug also reduces the elimination of the substrate drug. A good example of this principle involves interactions between NSAIDs and methotrexate (Table 131.5).

Medications that are most susceptible to interactions based on changes in drug distribution involving displacement from binding proteins include warfarin, sulfonamides and phenytoin[11].

DRUG BIOTRANSFORMATION

Cytochrome P450 Enzymes

After their administration, drugs are metabolized through a series of reactions to enhance their hydrophilicity and to facilitate excretion. These drug biotransformation reactions are broadly grouped into two phases, I and II. Phase I reactions involve intramolecular changes such as oxidation, reduction and hydrolysis that make the drug more polar and therefore more readily eliminated. Phase II reactions are conjugation reactions in which an endogenous substance combines with the functional group derived from phase I reactions to produce a highly polar drug conjugate that can be even more readily eliminated. These reactions involve glucuronidation and sulfation.

The cytochrome P450 (CYP) enzymes are the major drug-metabolizing enzymes (Fig. 131.3). They are present in the endoplasmic reticulum of many cells but the their highest concentrations are found in hepatocytes[35]. CYP enzymes are also present in the crypt cells of the GI tract, with the highest concentrations found in the enterocytes at the tips of the villi; their presence accounts for the first-pass metabolism of many drugs. These heme-containing proteins are encoded by a gene superfamily, with the encoded isoforms exhibiting distinct but overlapping substrate specificities and isoform-specific regulatory and pharmacogenetic properties[36]. The nomenclature employs a three-tier classification consisting of the family (40% homology in amino acid

DRUG INTERACTIONS THAT INCREASE RISK OF SUBSTRATE DRUG TOXICITY			
Mechanism	**Substrate**	**Interactive drugs**	**Time course**
Competitive inhibition of CYP3A4*	Cyclosporine Dapsone H_1 antihistamines Macrolides Erythromycin Phenytoin Warfarin Lovastatin Simvastatin	Antidepressants Fluoxetine Nefazodone Azole antifungals Ketoconazole Itraconazole Fluconazole Grapefruit juice HIV-1 protease inhibitors Indinavir Ritonavir Macrolides Clarithromycin Erythromycin Quinine Diltiazem Cimetidine	Rapid
Reduced metabolic clearance	Azathioprine Methotrexate	Allopurinol Febuxostat Salicylates	Rapid
Displacement from plasma proteins	Methotrexate	NSAIDs Salicylates Sulfonamides	Rapid
Reduced renal elimination	Methotrexate	NSAIDs Penicillins Probenecid Salicylates Sulfonamides	Rapid
Synergy	Methotrexate Retinoids Acitretin Serotonin reuptake inhibitors	Retinoids Sulfonamides Tetracyclines Alcohol Monoamine oxidase inhibitors	Variable Variable Variable

*Also A5 and A7.

Table 131.5 Drug interactions that increase risk of substrate drug toxicity[2,3]. Sulfonamides are inhibitors of anionic tubular secretion of methotrexate. NSAIDs, nonsteroidal anti-inflammatory drugs.

sequence), the subfamily (77% homology) and the individual protein (e.g. CYP2D6).

An increased understanding of CYP drug metabolism has solved much of the mystery behind drug interactions. While there are approximately 60 genes that encode CYP isoforms, over 90% of drug oxidation can be attributed to six main cytochromes: CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4[37]. The metabolism of a drug by a specific isoenzyme indicates that it is a substrate for that enzyme. *Whether enzyme inhibition or induction occurs is an entirely separate issue*. Many drugs serve only as substrates and produce no significant enzyme inhibition or induction. It is entirely possible for a drug to be a substrate for one enzyme and inhibit or induce another enzyme that is not involved with its own metabolism. Therefore, drug interactions are more aptly termed drug–protein–drug (food) interactions. These are affected by genetics (polymorphic genes cause particular enzymes to be less effective, 2D6 being an example), drugs (a drug may inhibit or induce a cytochrome, or interfere in the chemical pathway of another drug, e.g. ketoconazole reduces cyclosporine metabolism by inhibiting CYP3A4), chemicals (dioxin is an inducer of CYP3A4 while a food such as grapefruit juice is an inhibitor of CYP3A4) and the environment (cigarette smoke is an inducer of CYP1A2). Deciding what is clinically relevant is a challenging, relatively new field of investigation.

Drug metabolism is investigated even before human exposure. With recombinant human CYP enzymes, it is possible to determine the metabolic pathways, potential genetic polymorphisms, ability to induce or inhibit drug metabolism, and possible drug interactions. Although there are limitations to the information gleaned from *in vitro* studies, nonetheless this information can be used to guide more expensive *in vivo* studies.

However, using *in vitro* tests that focus on cytochrome enzymes alone to predict clinical interactions may not always be reliable for a variety of reasons. First, it is not always possible to know the therapeutic concentration of a new drug and its primary metabolites in specific tissues[29]. Second, there are a large number of pathways and interactions, and it is impossible to test them all even in an *in vitro* system. Third, the demonstration of an *in vitro* effect does not tell physicians whether that effect is likely to occur in clinical practice, i.e. the clinical significance of an *in vitro* interaction is unknown. Fourth, the underlying disease state may contribute to the development of a drug interaction and this would be unaccounted for by *in vitro* studies alone. Until clinical data demonstrate the presence or absence of a clinically significant interaction, dosage adjustments are premature[38].

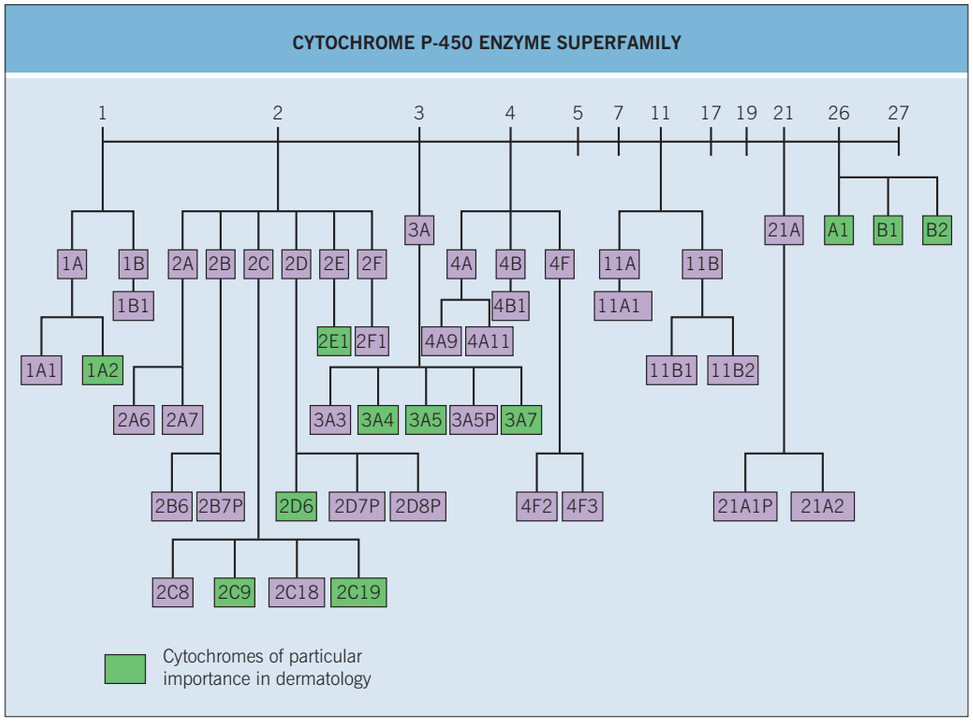


Fig. 131.3 Cytochrome P450 enzyme superfamily.

THE CONFUSING WORLD OF DRUG INTERACTIONS

Why does it take so long to learn about interactions? Some drugs come to market and their various interactions are not realized for several years. One reason is that drugs are prescribed on the basis of indications that may have their own adverse effects on patient outcome. Also, studies in healthy volunteers are not sufficient to determine the contribution of underlying diseases to the development of interactions. The latter are affected by genetics, drugs, chemicals, the underlying health status of the patient, the therapeutic index of the drug affected by the interaction, dose-related factors, the duration of coadministration, the time course of the interaction, whether active metabolites are involved, and the environment (Table 131.6). In addition, the multiple metabolic pathways of some drugs can make it difficult to predict the outcome of drug interactions.

Metabolism

The most clinically relevant drug interactions are those caused by alterations in drug metabolism, and CYP isoenzymes are the key players in drug metabolism. Members of the CYP3A subfamily are the most abundant of the human hepatic cytochromes and account for up to 70% of GI cytochromes. This subfamily contains the major metabolizing isoforms for many of the drugs prescribed by dermatologists (Tables 131.2, 131.5, 131.7 & 131.8; Fig. 131.4). CYP3A4 in particular has a pivotal role in xenobiotic metabolism and has been estimated to be involved in the metabolism of approximately 50% of the drugs in clinical use[1]. Although the most important isoform is 3A4, there is close structural homology to 3A5 and 3A7 and so these three isoforms are grouped together. Of note, CYP3A4 is also located in the placenta, uterus, kidney, lung and fetus.

INFLUENCES ON CYTOCHROME P450 ACTIVITY

	Cytochrome P450 activity				
	1A2	2C	2D6	2E1	3A4
Nutrition	↑			↑ (obesity ↑)	↓ (obesity ↓)
Smoking	↑				
Alcohol				↑	
Drugs	↑ or ↓	↑ or ↓	↑ or ↓		↑ or ↓
Environmental factors	↑			↑	↑
Genetics		↑ or ↓	+		

Table 131.6 Influences on cytochrome P450 activity.

There is significant interindividual variability in the metabolic activity of CYP3A4. The extent of variability may be as much as 20-fold and the individual level of CYP3A4 activity probably has clinical relevance. Obesity also plays a role in drug metabolism in an enzyme-specific way[39] as it decreases isoform 3A4 metabolism (see Table 131.6), and 33% of Americans are obese.

The successful application of information regarding CYP to prevent drug interactions and improve the therapeutic risk:benefit ratio can occur only if we know which enzyme is responsible for the metabolism of a particular drug. Drug interactions are also made more predictable by determining which compounds induce and inhibit which specific P450 enzymes. While knowing all of the major enzyme substrates, inhibitors and inducers is a formidable task, Tables 131.7 to 131.10 are intended to summarize large amounts of this information.

Cytochrome induction

Many enzymes involved in drug biotransformation, including CYPs, are able to increase in amount and activity in response to substances known as inducers. The onset and offset of enzyme induction is *gradual* because the induction phase depends on the accumulation of the particular inducing agent and the subsequent synthesis of new enzyme. The offset depends on elimination of the inducer and decay of the increased enzyme levels.

Inducers may enhance parent drug metabolism, so that therapeutic efficacy is actually reduced if the parent drug is the active moiety (Fig. 131.5). Alternatively, inducers may enhance the metabolism of a substrate to active metabolites, with the potential for exaggerated toxicity. For example, the alkylating agent cyclophosphamide is a prodrug that requires metabolic activation to phosphoramide mustards for its therapeutic effect. Unfortunately, metabolic activation also leads to the formation of acrolein, which causes the bladder toxicity seen with this medication[42].

Cytochrome inhibition

Inhibition of drug metabolism is the most important mechanism for drug interactions because it can lead to an increase in plasma drug concentration, enhanced drug response, and toxicity. In contrast to the time course seen with enzyme induction, inhibition of drug metabolism begins within the first one or two doses of the inhibitor and is maximal when a steady-state concentration of the inhibitor is achieved. Therefore, the time course for inhibitory actions is usually in terms of *days* not weeks.

Inhibitory interactions can be either competitive or non-competitive. An example of *competitive* inhibition involves the tight binding of inhibitors such as ketoconazole, cimetidine and macrolides to the heme moiety of the cytochrome P450 isozyme. As long as the inhibitor occupies this specific site of the CYP, the substrate cannot be biotransformed[43]. As the concentration of the inhibiting drug increases, the degree of saturation of the isoenzyme increases. When the enzyme

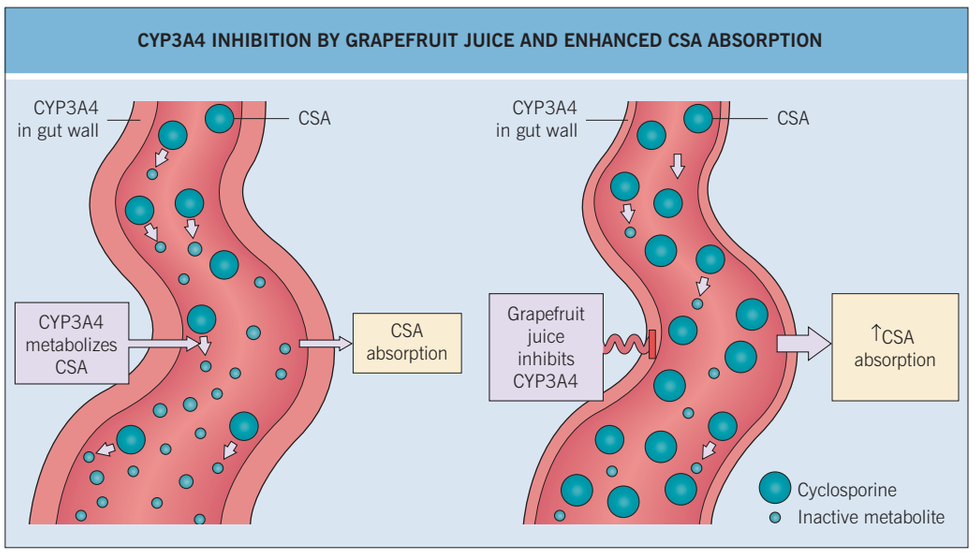


Fig. 131.4 CYP3A4 inhibition by grapefruit juice and enhanced cyclosporine absorption. CSA, cyclosporine.

SUBSTRATES OF CYP3A4,5,7		
ANTIARRHYTHMICS	**CANCER CHEMOTHERAPY**	**PROTEASE INHIBITORS**
Amiodarone	Busulfan	Indinavir
Digoxin	Cyclophosphamide	Nelfinavir
Lidocaine	Docetaxel	Ritonavir
Propafenone	Doxorubicin	Saquinavir
Quinidine	Etoposide	
	Ifosfamide	**MISCELLANEOUS**
ANTICONVULSANTS	Paclitaxel	Acetaminophen
Carbamazepine	Tamoxifen	Cisparide*
Ethosuximide	Vinblastine	Clarithromycin
Phenytoin	Vincristine	Codeine
		Colchicine
ANTIDEPRESSANTS	**HMG-COA REDUCTASE INHIBITORS**	Enalapril
Amitriptyline	Atorvastatin	Erythromycin
Doxepin	Cerivastatin	Estrogens
Imipramine	Lovastatin	Flutamide
Sertraline	Simvastatin	Losartan
		Montelukast
ANTIHISTAMINES		Omeprazole
Fexofenadine	**IMMUNOSUPPRESSIVE DRUGS**	Oral contraceptives
Loratadine	Corticosteroids	Pimozide
	Cyclophosphamide	Retinoic acid
BENZODIAZEPINES	Cyclosporine	Rifabutin
Alprazolam	Dapsone	Rifampin
Diazepam	Sirolimus	Sildenafil
Midazolam	Tacrolimus	Terazosin
Triazolam		Theophylline
		Warfarin
CALCIUM CHANNEL BLOCKERS		Zileuton
Amlodipine		
Diltiazem		
Felodipine		
Isradipine		
Nifedipine		
Verapamil		

*Historical.

Table 131.7 Substrates of CYP3A4,5,7[40].

CYP3A4 INHIBITORS AND INDUCERS	
Inhibitors	**Inducers**
ANTIBIOTICS	**ANTICONVULSANTS**
Ciprofloxacin	Carbamazepine
Clarithromycin	Ethosuximide
Erythromycin	Phenobarbital
Metronidazole	Phenytoin
Norfloxacin	Primidone
Troleandomycin	
	ANTIRETROVIRALS
ANTIFUNGALS (AZOLES)	Efavirenz
Fluconazole	Nevirapine
Itraconazole	Ritonavir
Ketoconazole	
Voriconazole	**ANTITUBERCULOUS AGENTS**
	Isoniazid
ANTIRETROVIRALS	Rifabutin
Amprenavir	Rifampin
Delavirdine	
Indinavir	**MISCELLANEOUS**
Nelfinavir	Bexarotene
Ritonavir	Dexamethasone
Saquinavir	Griseofulvin
	St John's wort
CALCIUM CHANNEL BLOCKERS	Ticlopidine
Diltiazem	Troglitazone
Nifedipine	
Verapamil	
SSRIS	
Fluoxetine	
Fluvoxamine	
Nefazodone	
Paroxetine	
Sertraline	
OTHERS	
Amiodarone	
Antiprogestins	
Cannabinoids	
Cimetidine	
Grapefruit juice	
Interferon-gamma	
Quinine	
Tacrolimus	
Tamoxifen	
Zafirlukast	

Table 131.8 CYP3A4 inhibitors and inducers[40]. Drugs in bold italics are particularly potent inhibitors. SSRI, selective serotonin reuptake inhibitors.

system is saturated, further metabolic activity by that enzyme system is limited. At that point, a patient becomes the equivalent of a poor metabolizer and concentrations of co-prescribed medications begin to rise. The extent of inhibition of one drug by another depends on the affinity each compound has for the CYP isoform. In addition to the concentration of substrate required to saturate the system and the half-life of the inhibitor drug, competitive inhibition clearly depends on the affinity of the substrate for the enzyme being inhibited. The onset and offset of enzyme inhibition are dependent on the half-life and time to steady state of the inhibitor.

The significance of an elevated plasma level of a particular drug is determined largely by the therapeutic margin of the drug. Therefore, when considering the potential clinical relevance of an interaction, one must exercise more caution with drugs that have a narrow therapeutic range. Non-competitive inhibition is less common and occurs when the enzyme is destroyed, inactivated, or changed by the inhibitor such that it can no longer metabolize the original substrate.

HOW TO MINIMIZE THE RISK OF DRUG–DRUG INTERACTIONS

One commonly perpetuated myth is that all drugs in a given class are equally susceptible or contributory to drug interactions. Understanding the differences between drugs in a particular class with regard to potential for drug interactions is clinically relevant. Specific drugs, from a given class of drugs associated with interactions, may have little or no clinical potential for drug interactions and are therefore safer choices (Table 131.11).

Various drug classes commonly encountered by dermatologists will be discussed, with emphasis on important interactions and ways to minimize risks by appropriate drug choices within a given drug class.

Allylamine Antifungals

Terbinafine is an orally active allylamine antifungal used in the treatment of dermatophytoses. Reports suggest some degree of significant inhibition of CYP2D6 and CYP1A2 by terbinafine[44]. There are three principal levels of activity of CYP2D6 in the general population: poor metabolizers (PM), extensive metabolizers (EM) and ultrarapid metabolizers. The EM status is by far the most common and is considered "normal". Approximately 7.5% of Caucasians and <2% of Asians and African-Americans are poor metabolizers. Inhibition of CYP2D6 by terbinafine would make individuals who have active enzyme (extensive metabolizers) into poor metabolizers, and this effect could possibly last for weeks after discontinuing terbinafine. This can cause two problems: there may be an accumulation of the parent drug (substrate), and this can result in dose-dependent drug toxicity, or there can be reduced formation of active metabolites, and this can result in loss of efficacy (see Fig. 131.5)[45].

For now, terbinafine appears to be a potent inhibitor of CYP2D6, and so clinicians should be aware of potential interactions (see Table 131.10). The area of greatest concern, because of possible severity and common use, would be bradycardia from excess *β-blockade* (e.g. propranolol) or from the accumulation of *donepezil* (used to treat Alzheimer's disease)[46]. Codeine could lose its analgesic effect, as the active metabolite, morphine, is not formed when CYP2D6 activity is low[47].

DRUG-METABOLIZING ENZYMES CYP1A2, 2C9 AND 2C19: SELECTED SUBSTRATES, INHIBITORS AND INDUCERS			
Isozyme	**Substrate**	**Inhibitors**	**Inducers**
CYP1A2	Amitriptyline Caffeine Clomipramine Clozapine Desipramine Fluvoxamine Haloperidol Imipramine Propranolol Tacrine Theophylline Warfarin Zileuton Zolmitriptan	***Cimetidine*** ***Ciprofloxacin*** Clarithromycin ***Erythromycin*** ***Fluvoxamine*** Ketoconazole ***Norfloxacin*** ***Paroxetine*** Terbinafine Ticlopidine	Barbiturates Brussels sprouts Cabbage Carbamazepine Charbroiled foods Cigarette smoking Omeprazole Phenobarbital Phenytoin Rifampin Ritonavir
CYP2C9	Diclofenac Fluoxetine Fluvastatin Ibuprofen Losartan Montelukast Phenytoin Piroxicam Sulfonamides Tricyclic antidepressants Valproic acid Warfarin Zafirlukast	***Amiodarone*** ***Cimetidine*** Clopidogrel Fluconazole Fluvoxamine Ketoconazole Leflunomide Omeprazole Ritonavir Sulfonamides Trimethoprim Voriconazole Zafirlukast	Barbiturates Carbamazepine Ethanol Griseofulvin Rifampin
CYP2C19	Citalopram Cyclophosphamide Diazepam Hexobarbital Imipramine Indomethacin Lansoprazole Nelfinavir Nilutamide Omeprazole Pantoprazole Progesterone Proguanil Teniposide Warfarin	Cimetidine Felbamate Fluconazole Fluoxetine Fluvoxamine Indomethacin Ketoconazole Lansoprazole Modafinil Omeprazole Paroxetine Ticlopidine Topiramate Voriconazole	Norethindrone Prednisone Rifampin

Table 131.9 Drug-metabolizing enzymes CYP1A2, 2C9 and 2C19: selected substrates, inhibitors and inducers[40,41]. Drugs in bold italics are particularly potent inhibitors.

SUBSTRATES AND INHIBITORS OF CYP2D6		
Substrates of CYP2D6		**Inhibitors of CYP2D6**
ANTIARRHYTHMICS Amiodarone Encainide Flecainide Mexiletine Propafenone **ANTIPSYCHOTICS** Aripiprazole Clozapine Haloperidol Perphenazine Remoxipride Risperidone Thioridazine Zuclopenthixol **β-BLOCKERS** Alprenolol Bufuralol Metoprolol Propranolol Timolol	**ANTIDEPRESSANTS** Amitriptyline Clomipramine *N*-desmethylclomipramine Desipramine Fluoxetine Imipramine Maprotiline Mianserin Norfluoxetine Nortriptyline Paroxetine Trazodone* Trimipramine Venlafaxine **MISCELLANEOUS** Captopril Codeine Dextromethorphan Diphenhydramine Domperidone Donepezil Ethylmorphine 4-hydroamphetamine Oxycodone Phenformin	***Amiodarone*** Amitriptyline Celecoxib Chlorpheniramine Cimetidine Clomipramine Desipramine Donepezil Doxepin ***Fluoxetine*** Fluphenazine Haloperidol Hydroxychloroquine Imipramine Indinavir Moclobemide Nortriptyline ***Paroxetine*** Pimozide Propafenone ***Quinidine*** Ranitidine ***Ritonavir*** Sertraline (weak) Terbinafine Thioridazine Ticlopidine Venlafaxine (weak)
*Applies to metabolite rather than the parent drug.		

Table 131.10 Substrates and inhibitors of CYP2D6[40,41]. Drugs in bold italics are particularly potent inhibitors.

Azole Antifungals

The imidazole ketoconazole and the triazole itraconazole require an acid milieu for absorption; therefore, concomitant *antacids, H_2 blockers, proton pump inhibitors, sucralfate* and *didanosine* significantly reduce absorption (see Table 131.2). The administration of these agents with carbonated cola beverages will acidify (pH <3) the stomach, thereby improving absorption of the antifungal drug. Fluconazole and voriconazole are alternatives for patients in whom drugs that reduce gastric acidity are required, as these antifungal medications do not rely on an acid milieu for absorption.

Among the systemic azole antifungals, ketoconazole has been shown *in vitro* to be the strongest inhibitor of CYP3A4. Many substrates are metabolized via these enzymes (see Tables 131.2, 131.5, 131.7), and moderate to severe drug interactions have been observed with several substrates, including *cyclosporine*, *warfarin* and *phenytoin*. Itraconazole is contraindicated when the patient is also receiving the following CYP3A substrate drugs: *triazolam*, *oral midazolam*, *lovastatin*, *simvastatin*, *quinidine*, *pimozide* or astemizole (historical). Caution has been suggested with *warfarin, cyclosporine, digoxin* and atorvastatin. Significant effects on the metabolism of fluvastatin or pravastatin by itraconazole do not appear to occur[48] (see Table 131.11). Fluconazole inhibition of CYP3A4 is dose-related: 100 mg/day usually has little effect on CYP3A4, but inhibition can occur at daily doses of 200–400 mg (or more), depending upon the substrate.

When the azole antifungals are administered with cyclosporine, the concentrations of the latter are increased, requiring careful monitoring of cyclosporine levels. Similarly, frequent monitoring of the INR is required for patients on warfarin who require therapy with an azole antifungal. The azole antifungals reportedly increase the anticoagulant effects of warfarin by two- to threefold. In one study, *phenytoin* concentrations were significantly increased 48 hours after fluconazole administration (400 mg daily), owing to a 33% decrease in the clearance of phenytoin[49].

Azole antifungals also interfere with the metabolism of benzodiazepines such as triazolam and midazolam, leading to increased levels and sedation. There is also decreased metabolism of some of the HMG-CoA reductase inhibitors, e.g. lovastatin and simvastatin, leading to increased levels, as well as to rhabdomyolysis. Additional drugs whose metabolism is decreased by azoles include *tacrolimus, indinavir* and *calcium channel blockers*. Peripheral edema due to an interaction between nifedipine and itraconazole has been reported. It was suspected that itraconazole inhibited the metabolism of this calcium channel blocker, resulting in an increased serum nifedipine concentration and leg edema. This hypothesis was confirmed by obtaining serum levels of nifedipine, itraconazole and hydroxyitraconazole (the active metabolite of itraconazole) before and after the administration of itraconazole[50]. The authors recommended that patients receiving both azole or triazole antifungals and calcium channel blockers be monitored for side effects such as leg edema and, more importantly, hypotension, because of the increased serum concentration of the calcium channel blocker.

Fluconazole, but not itraconazole, interacts with *losartan*, an angiotensin II receptor antagonist antihypertensive. Fluconazole inhibits losartan's metabolism to the active metabolite E-3174[51]. The clinical significance of this interaction remains unclear, but the possibility of a reduced therapeutic effect of losartan should be borne in mind. Phenytoin is also a CYP2C9 substrate, and concurrent fluconazole use at bedtime has resulted in several cases of phenytoin toxicity[52].

In contrast to the azole antifungals, terbinafine is an allylamine that does not inhibit CYP3A4[53]. This antifungal may be a viable therapeutic option in patients on concomitant therapy with a high likelihood of drug interactions with the azoles.

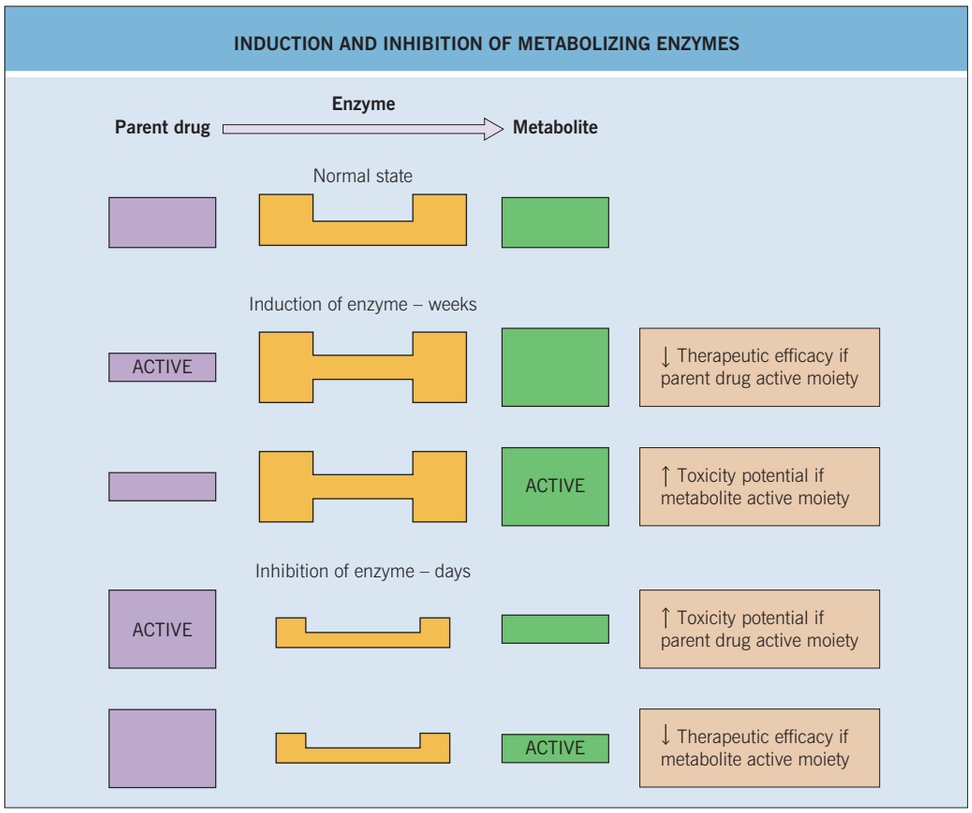


Fig. 131.5 Induction and inhibition of metabolizing enzymes.

DRUGS AND FOODS WITH DIFFERING POTENTIAL FOR DRUG–DRUG INTERACTIONS BASED ON METABOLISM

Drug/food class	More potential for interaction	Less potential for interaction
ACE inhibitors and angiotensin II receptor blockers (ARBs)	NSAIDs	Acetaminophen Celecoxib
Antifungals	Azoles and triazoles (CYP3A4 inhibition)	Terbinafine
Calcium channel blockers	Diltiazem Nicardipine Verapamil	Amlodipine Nifedipine
Macrolides	Clarithromycin Erythromycin	Azithromycin
Quinolones	Ciprofloxacin Enoxacin	Levofloxacin Lomefloxacin Ofloxacin
H_2 blockers	Cimetidine	Famotidine Nizatidine Ranitidine
Protease inhibitors	Ritonavir (most potent) Indinavir	Saquinavir Nelfinavir
HMG-CoA reductase inhibitors	Simvastatin Lovastatin Cerivastatin	Pravastatin Fluvastatin Rosuvastatin
Citrus fruit juice	Grapefruit juice	Orange juice

Table 131.11 Drugs and foods with differing potential for drug–drug interactions based on metabolism. ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs.

Azathioprine

Azathioprine is metabolized to 6-mercaptopurine (6-MP) and there are three subsequent pathways for the metabolism of 6-MP. Both thiopurine methyltransferase (TPMT) and xanthine oxidase metabolize 6-MP to inactive metabolites, whereas hypoxanthine-guanine phosphoribosyltransferase (HGPRT) metabolizes 6-MP to active purine analogues, in particular 6-thioguanine (see Fig. 130.3). *Allopurinol* and *febuxostat* inhibit the metabolism of 6-MP via xanthine oxidase; this leads to increased levels of 6-MP (plus active purine analogues via HGPRT) and, as a result, increased antimetabolite effects and associated toxicity. Combining either azathioprine or 6-MP with allopurinol or febuxostat should be avoided. If the latter must be used, an alternate immunosuppressant should be selected.

Colchicine

Colchicine is a substrate of PGP and concurrent use of PGP inhibitors has resulted in severe colchicine toxicity. It is also a substrate for CYP3A4, so inhibitors of this enzyme may result in increased plasma concentrations of colchicine. Given the possibility of fatal colchicine toxicity, few situations would warrant the concomitant use of colchicine with a *CYP3A4 or PGP inhibitor*. However, if this combination must be prescribed, careful monitoring for colchicine toxicity (diarrhea, abdominal pain, fever, muscle pain or weakness, paresthesias) should be performed. If toxicity is suspected, both drugs must be discontinued immediately. Of note, grapefruit juice is an inhibitor of both PGP and CYP3A4 and colchicine toxicity has been reported with the intake of large amounts of grapefruit juice.

Cyclosporine/Sirolimus/Tacrolimus

Numerous drug interactions with cyclosporine have surfaced that are associated with its metabolism and presystemic metabolism (both by the CYP3A4 enzyme and by PGP), in the liver and intestine, respectively. It is thought that this GI tract metabolism may explain its erratic absorption. In fact, potent 3A4 inhibitors have been administered intentionally to improve cyclosporine's bioavailability, thereby reducing dosing requirements and lowering overall drug costs. *Ketoconazole* (200–400 mg/day) can decrease the required daily dose of cyclosporine by 60–80%[54].

Diltiazem can decrease cyclosporine dosing by as much as 30%[55], while effects with *grapefruit juice* have been variable. Other drugs that alter cyclosporine concentrations via cytochrome 3A4 inhibition include other calcium channel inhibitors (*verapamil*, *nifedipine*), triazoles and imidazoles (*fluconazole*, *itraconazole*, *ketoconazole*), macrolides (*erythromycin*, *clarithromycin*) and *tacrolimus*. Conversely, isoform 3A4 inducers, such as *rifampin*, *phenytoin*, *carbamazepine* and *phenobarbital*, decrease cyclosporine concentrations. More recently, decreased

cyclosporine levels have been observed with coadministration of *troglitazone* or *ticlopidine*[56]. Cyclosporine trough levels, as well as signs of toxicity versus adequate immunosuppressive response, should be monitored when any of these drugs are combined with cyclosporine.

Grapefruit Juice

Grapefruit juice interactions are of potential clinical relevance for a wide range of drugs. The mechanisms of grapefruit juice interactions are exclusively pharmacokinetic in nature. The effect is mediated mainly by the suppression of CYP3A4 and PGP in the small intestinal wall by either fresh or frozen grapefruit juice[57] (see Fig. 131.4). This results in a diminished first-pass metabolism, with higher bioavailability and increased maximal plasma concentrations of substrates of this transporter and/or enzyme. The effect is most pronounced in drugs with high first-pass degradation, such as *felodipine*, *nifedipine*, *saquinavir*, *cyclosporine*, *midazolam*, *triazolam*, *terazosin*, *ethinylestradiol*, *17β-estradiol*, *prednisone*, and the HMG-CoA reductase inhibitors *lovastatin* and *simvastatin*[58,59].

It is not yet clear which component in grapefruit juice is to blame. Psoralen, mainly a bergamottin compound, is thought to be the major inhibitor, with a minor role attributable to flavonoids such as naringenin and quercetin[60]. Even a change in the brand or batch of grapefruit juice may influence the grapefruit juice/drug interaction to an unpredictable degree, as grapefruit juice is a natural product that is not standardized in composition. Similar interactions have not been seen with other citrus fruit juices, such as orange juice. Lack of 6,7-dihydroxybergamottin in orange juice probably accounts for the absence of inhibitory effects[61]. However, isoflavones in orange juice may mediate this food's inhibitory effect on PGP.

The idea of using grapefruit juice as a cost-cutting measure has been used in patients on concomitant cyclosporine therapy[62]. It was thought that because grapefruit juice can inhibit the metabolism of cyclosporine, combining the two would lower the required daily dose of cyclosporine, thereby reducing drug costs. However, the difficulty is that grapefruit juice is not a standardized product. More recent studies have also demonstrated that grapefruit juice increases the bioavailability of saquinavir without affecting its clearance, suggesting that inhibition of intestinal CYP3A4 may represent a way to enhance effectiveness without increasing the dose[63].

However, in general, it is recommended that patients refrain from ingesting grapefruit juice when taking a drug that is extensively metabolized, unless a lack of interaction has been documented. Many hospital cafeterias now place warnings of the potential for drug interactions in areas where grapefruit juice is sold. Orange juice is a good alternative (see Table 131.11).

Herbal Remedies

Herbal medicines (see Ch. 133) have become a popular form of therapy. They are perceived to be "natural" by the public and thus harmless. Although many current therapeutic agents (including digitalis, atropine, vincristine and narcotic derivatives) have been derived from plants, little is known about the relative safety of current herbal therapies compared with prescription drugs, and even less is known when the two are co-consumed. Because of under-reporting, our present knowledge represents the tip of the iceberg. It is estimated that 80% of the world's population relies primarily on traditional medicines utilizing plant extracts or their active ingredients.

The interactions of phytomedicines with prescription medications are under-researched[64]. Because herbs are not sold as drugs, no proof of efficacy or warnings about side effects are required. When a drug is prescribed, the dosage and quality of the substance are assured. No such standardization or quality control exists for herbal preparations. Contamination, mislabeling and misidentification of herbs are also problems. Some patients do not know what they are taking, as they may purchase a product whose ingredients are listed in a foreign language only.

A study in 12 healthy volunteers examined the effect of the ingestion of *St John's wort* on cytochrome activity[65]. Short-term administration (less than 2 weeks) of St John's wort had no effect on CYP activity, whereas long-term St John's wort administration resulted in a significant and selective induction of CYP3A activity in the intestinal wall. St John's wort did not alter the activity of CYP2C9, CYP1A2 or CYP2D6. Reduced therapeutic efficacy of drugs metabolized by CYP3A should be anticipated during long-term administration of St John's wort.

When taking a history regarding medications, it is important to ask specifically about prescription, non-prescription and herbal therapies. Patients should tell their physician if they are using herbal remedies, in order to improve monitoring of side effects and potential interactions. See Table 131.12 for some important drug interactions between herbal medicines and dermatologic therapies.

HMG-CoA Reductase Inhibitors

Although dermatologists may not prescribe these lipid-lowering agents, their use by family physicians and specialists is so widespread that it is fairly common to encounter patients who are taking this class of drugs. To date, all reports of significantly increased rates of myalgias from combination therapy with a "statin" plus certain other drugs involve simvastatin or lovastatin. Notably, these are the statins with the highest known metabolic dependency on the CYP3A4 pathway for elimination[68]. Fluvastatin is metabolized via CYP2C9 and therefore is not expected to interact with CYP3A4 inhibitors, but may interact with 2C9 inhibitors. Pravastatin is not metabolized by CYP3A4, nor is it cleared by PGP to a clinically significant degree[69].

Macrolide Antibiotics

When a macrolide is required in a patient who is receiving systemic tacrolimus, azithromycin should be used (rather than erythromycin or clarithromycin) because this does not produce significant inhibition of CYP3A4[70]. When erythromycin is prescribed to a patient on long-term *warfarin*, there is a risk of increased plasma warfarin levels, with increased anticoagulation and hemorrhage. This occurs because *tacrolimus* and warfarin are CYP3A4 substrates and erythromycin is a

HERBAL REMEDIES/PRESCRIPTION DRUG INTERACTIONS

Herbal remedy	Side effects	Drug interaction
Zemaphyte (Chinese herbal therapy)	Diarrhea, transaminitis, reversible dilated cardiomyopathy, reversible acute hepatitis, fatal hepatic necrosis, worsening of atopic dermatitis, acute urticaria	Methotrexate
Coenzyme Q10[3]	Reduced efficacy of warfarin	Warfarin
Ginseng[66]	Can reduce the anticoagulant response of warfarin	Warfarin
Kava	CNS depressant	Alcohol, barbiturates, benzodiazepines, opiates
Licorice (*Glycyrrhiza glabra* or *uralensis*)	Contraindicated if hypertension, diabetes mellitus, hypokalemia, hepatic or renal disease	Cyclosporine, digoxin, prednisone, thiazides
Purple coneflower (*Echinacea angustifolia* or *purpurea*)	Recurrent erythema nodosum Caution in patients with HIV, autoimmune CTD, TB, MS, or ragweed/sunflower allergies	Immunomodulators and cyclosporine, methotrexate, corticosteroids
Ginkgo (*Ginkgo biloba*), garlic, ginger[67]	Can cause spontaneous bleeding	Can potentiate aspirin, digoxin, NSAIDs, warfarin, heparin
St. John's wort[3] (oral) (inducer of CYP2C19, CYP3A4 & P-glycoprotein)	Photosensitivity Erectile dysfunction	Cyclosporine, digoxin, nevirapine, oral contraceptives, erlotinib, imatinib, voriconazole

Table 131.12 Herbal remedies/prescription drug interactions. CNS, central nervous system; CTD, connective tissue disease; MS, multiple sclerosis; TB, tuberculosis.

potent inhibitor. As with azole antifungals, historically the coadministration of erythromycin and astemizole or terfenadine was associated with a risk of cardiotoxicity (prolongation of the QT interval, torsades de pointes).

Erythromycin also inhibits the metabolism of *sildenafil*, resulting in a significant increase in serum levels of sildenafil[71]. If concurrent administration is unavoidable, reduced doses of sildenafil and tadalafil are recommended. In addition, an interaction between erythromycin and *carbamazepine* has been well established[72]. Erythromycin significantly inhibits hepatic metabolism of carbamazepine; the interaction is highly predictable, develops with rapid onset, and may also occur with clarithromycin or troleandomycin[72]. Concurrent use should therefore be avoided.

Quinolone Antibiotics

In the GI tract, all fluoroquinolones interact with multivalent cation-containing products, and the bioavailability of the quinolone can be reduced by up to 50% when coadministered with *iron* compounds (ciprofloxacin and moxifloxacin are more affected than levofloxacin or gemifloxacin). There is also a significant decrease in the bioavailability of quinolones when given with *sucralfate*[72], and antibiotic treatment failure has been documented. If sucralfate cannot be discontinued, the quinolone should be taken 2–6 hours before the sucralfate. Similar decreases in bioavailability occur when a quinolone is given concurrently with an *antacid*[72]. The antacid should therefore be taken 6 hours prior to or 2 hours after the antibiotic.

Sparfloxacin is associated with cardiac manifestations in the form of QTc prolongation and has a high phototoxicity potential. While moxifloxacin can prolong the QT interval, it does not alter the QT dispersion (QT dispersion is thought to be a more sensitive predictor of the risk of torsades de pointes). As such, the increased risk of torsades de pointes attributable to moxifloxacin is questionable[73]. Levofloxacin has no QT prolongation and a very low phototoxic potential, making it one of the safest fluoroquinolones[74]. An enhanced anticoagulant effect of *warfarin* has been reported after coadministration with norfloxacin, ciprofloxacin, ofloxacin or enoxacin[56].

Pimozide

Pimozide is a neuroleptic that may be used for psychogenic dermatologic problems such as delusions of parasitosis. While newer drugs may replace pimozide (see Ch. 7), as long as it is still being prescribed, dermatologists must be aware of its drug–drug interactions. Case reports suggest that pimozide prolongs the cardiac QT interval and may lead to arrhythmias. Pimozide is oxidized by two CYP isoforms, CYP3A4 and CYP1A2, with the former being the responsible isoform at therapeutically relevant pimozide concentrations[75]. Pimozide is also an inhibitor of CYP2D6 without being a substrate of this isoform. Therefore, a greater risk of adverse effects is expected when pimozide is co-prescribed with metabolic inhibitors.

The risk of concomitant administration of CYP3A inhibitors with pimozide is highlighted by a report of fatal cardiac arrhythmias in patients taking pimozide plus clarithromycin[76]. To examine the latter interaction, investigators gave a single oral dose of pimozide with and without clarithromycin to 12 healthy subjects who were documented as either extensive or poor metabolizers with regard to CYP2D6[77]. Pimozide itself was capable of prolonging QT intervals, and pimozide concentrations were increased in the presence of clarithromycin; the average QT prolongation was longer when both drugs were taken. CYP2D6 activity, however, was not a factor.

In summary, patients who are at risk of ventricular arrhythmias because of prolonged QT intervals or electrolyte disturbances, or who take other drugs that affect QT intervals, should use pimozide with caution. Adding a CYP3A4 inhibitor such as *clarithromycin*, *erythromycin* or an *azole antifungal* may increase the risk of toxicity. A baseline assessment of the QT interval and reassessment 6 hours after a pimozide dose may be helpful in patients at risk who require pimozide.

Pharmacogenetics – Role of Polymorphisms

Cytochrome P450 enzymes

The genes encoding the CYP isoenzymes are highly polymorphic, and, as a result, the individuals within a general population have different levels of enzyme activity due to the presence of variant alleles. People with genetically determined low levels of activity are referred to as poor metabolizers. Those who have a functional enzyme are known as extensive metabolizers. There are yet others who have more than the usual complement of functional genes and more than the usual amounts of certain enzymes, and they are referred to as ultrarapid metabolizers. Still others have partially functional enzymes and are slower metabolizers than normal. Poor metabolizers may have a larger response and be at greater risk of toxicity than extensive metabolizers for drugs that are highly dependent on clearance to an inactive metabolite by the particular isoform[78]. On the other hand, ultrarapid metabolizers might not reach therapeutically active plasma concentrations of certain drugs, thereby not achieving the anticipated desired effect.

CYP enzymes that exhibit genetic polymorphisms include CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP2E1 (Table 131.13). However, provocation tests are not routinely employed in clinical practice and unfortunately there are no clinical parameters that are useful in predicting the metabolizing status of a given individual. Molecular analysis of the genes that encode the key CYP isoenzymes can be performed, i.e. testing is commercially available, but this is also not routinely done.

Other drug-metabolizing enzymes

Pharmacogenetic variation can also occur in other drug-metabolizing enzymes. Pertinent to dermatologists, the enzyme thiopurine methyltransferase (TPMT) is important in the metabolism of azathioprine and 6-mercaptopurine to non-toxic metabolites. There is a 0.3% rate of homozygous deficiency of this enzyme, putting these patients at great risk for toxicity, especially myelosuppression[79]. Conversely, 88% of the population is homozygous for the active TPMT enzyme and may therefore require doses greater than the recommended daily dose of azathioprine (1–2 mg/kg/day) to achieve therapeutic success. Determination of the patient's TPMT level provides *a priori* information that allows the individualization of azathioprine dosing, thereby minimizing toxicity and maximizing efficacy.

Drug–Cytokine Interactions

Cytochrome P450 drug metabolism can be altered by certain proinflammatory cytokines, such as interleukin (IL)-6, IL-1 and tumor necrosis factor (TNF)-α[80]. These cytokines can cause a reduction in CYP3A function and they are released during periods of stress, trauma or infection, as well as administered as immunomodulators, in particular IL-2[81].

Drug–HIV Interactions

A recent review presents current information regarding drug interactions in patients with HIV infection[14]. For example, the coadministration of pimozide with most of the protease inhibitors or

PHARMACOGENETICS – IMPACT OF POLYMORPHISMS ON DRUG METABOLISM

Cytochrome P450 (CYP) isoenzyme	Frequency of poor metabolizers	Examples of drugs affected
CYP2C9	6–8%	Glyburide, warfarin, phenytoin
CYP2C19	3–5% of Caucasians 12–23% of Asians	Diazepam, omeprazole, pantoprazole
CYP2D6	6–10% of Caucasians 3–6% of Mexican-Americans 2–5% of African-Americans 1% of Asians	Codeine, imipramine, propafenone, metoprolol
CYP3A4	Under study	Numerous (probably 50% of drugs are metabolized by CYP3A4/5)

Table 131.13 Pharmacogenetics – impact of polymorphisms on drug metabolism.

delavirdine is contraindicated because of the risk of inducing ventricular arrhythmias. In addition, there are reports of adrenal suppression and iatrogenic Cushing's syndrome when patients on ritonavir-based antiretroviral therapy received inhaled, intra-articular and even topical corticosteroids[81a].

CONCLUSION

Dealing with drug interactions is a challenge in clinical practice. Although no one can be expected to know all drug interactions, good resources are available. One of the best pocket reference guides is *The Top 100 Drug Interactions* by Hansten and Horn (www.hanstenandhorn.com)[82]. This handbook is concise, up-to-date and, unlike most desk references, it is not limited by class-related statements that may falsely and unnecessarily restrict therapeutic options.

More research during the early stages of drug development is required to identify new interactions, define mechanisms of older interactions, and examine the safety of new drugs from classes that are known to cause interactions. We also need more sensitive post-marketing surveillance tools to identify important drug interactions that become evident over time in diseased hosts and that were not seen in pre-marketing studies of healthy volunteers. Physicians need better tools, but, in the meantime, understanding the nuances of the cytochrome P450s will help take the fright out of prescribing.

Because the best evidence for clinically relevant drug interactions comes from case reports, prescribing physicians can have a major impact. Observations of drug interactions should be confirmed, if possible, by serum drug concentrations. Then they should be reported to regulatory bodies and submitted to journals. By understanding the mechanisms behind drug interactions and staying alert for toxicities, we can help make drug therapy safer and reduce the fear of drug interactions.

REFERENCES

1. Shapiro LE, Shear NH. Drug-drug interactions – how scared should we be? CMAJ. 1999;161:1266–1267.
2. Weideman RA, McKinney WP, Bernstein IH. Predictors of potential drug interactions. Hosp Pharm. 1998;33:835–840.
3. Hansten P, Horn J. The Top 100 Drug Interactions: A Guide to Patient Management. Edmonds, WA: H&H Publications, 2010;1–195.
4. Schneitman-McIntire O, Farnen TA, Gordon N, et al. Medication misadventures resulting in emergency department visits at an HMO medical center. Am J Health Syst Pharm. 1996;53:1416–1422.
5. Hamilton RA, Briceland LL, Andritz MH. Frequency of hospitalization after exposure to known drug-drug interactions in a Medicaid population. Pharmacotherapy. 1998;18:1112–1120.
6. Hoey J. Drug interactions: who warns the patients? [editorial]. CMAJ. 1999;161:117.
7. Smalley W, Shatin D, Wysowski DK, et al. Contraindicated use of cisapride: impact of Food and Drug Administration regulatory action. JAMA. 2000;284: 3036–3039.
8. Shapiro LE, Shear NH. Drug interactions/P450. Curr Probl Dermatol. 2001;13:141–152.
9. du Souich P. In human therapy, is the drug-drug interaction or the adverse drug reaction the issue? Can J Clin Pharmacol. 2001;8:153–161.
10. Hansten PD, Horn JR. Drug Interactions Analysis and Management. St Louis, MO: Facts & Comparisons (Wolters Kluwer Health), 2007.
11. Montamat SC, Cusack BJ, Vestal RE. Management of drug therapy in the elderly. N Engl J Med. 1989;321: 303–309.
12. Andersen W, Feingold D. Adverse drug interactions clinically important for the dermatologist. Arch Dermatol. 1995;131:468–473.
13. Piscitelli S, Gallicano K. Interactions among drugs for HIV and opportunistic infections. N Engl J Med. 2001;344: 984–996.
14. www.hiv-druginteractions.org; University of Liverpool.
15. Brly F, Marez D, Sabbagh N, et al. An efficient strategy for detection of known and new mutations of the CYP 2D6 gene using single stand conformation polymorphism analysis. Pharmacogenetics. 1995;5:373–384.
16. Sullivan JR, Watson A. Lamotrigine-induced toxic epidermal necrolysis treated with intravenous cyclosporine: a discussion of pathogenesis and immunosuppressive management. Australas J Dermatol. 1996;37:208–212.
17. Sullivan JR, Shear NH. The drug hypersensitivity syndrome: what is the pathogenesis? Arch Dermatol. 2001;137:357–364.
18. Toogood J. Beta blocker therapy and the risk of anaphylaxis. CMAJ. 1987;136:929–933.
19. Tugwell P, Bennett K, Bell M, Gent M. Methotrexate in rheumatoid arthritis: indications, contraindications, efficacy and safety. Ann Intern Med. 1987;107:358–366.
20. Thurmann PA, Hompesch BC. Influence of gender on the pharmacokinetics and pharmacodynamics of drugs. Int J Clin Pharmacol Ther. 1998;36:586–590.
21. Del Rosso JQ. Clinically significant drug interactions: recognition and understanding of common mechanisms. Curr Pract Med. 1998;1:62–64.
22. Hoey J. Postmarketing drug surveillance: what it would take to make it work. CMAJ. 2001;165:1293.
23. Anastasio G, Cornell K, Menscer D. Drug interactions: keeping it straight. Am Fam Phys. 1997;56:883–894.
24. Marchbanks C. Drug-drug interactions with fluoroquinolones. Pharmacotherapy. 1993;13:23–25.
25. Morii M, Ueno K, Ogawa A, et al. Impairment of mycophenolate mofetil absorption by iron ion. Clin Pharmacol Ther. 2000;68:613–616.
26. Bodey GP. Azole antifungal drugs. Clin Infect Dis. 1992;14:5161–5169.
27. Zimmermann T, Yeates RA, Laufen H, et al. Influence of concomitant food intake on the oral absorption of two triazole antifungal agents, itraconazole and fluconazole. Eur J Clin Pharmacol. 1994;46:147–150.
28. Hansten PD. Drug interactions. Drug Interactions Newsletter. 1996:893–906.
29. [Anonymous]. Drug interactions. Med Lett Drugs Ther. 1999;41:61–62.
30. Preiss R. P-glycoprotein and related transporters. Int J Clin Pharmacol Ther. 1998;36:3–8.
31. Benet LZ, Izumi T, Zhang Y, et al. Intestinal MDR transport proteins and P-450 enzymes as barriers to oral delivery. J Control Release. 1999;62:25–31.
32. Chishty M, Reichel A, Siva J, et al. Affinity for the P-glycoprotein efflux pump at the blood-brain barrier may explain the lack of CNS side-effects of modern antihistamines. J Drug Target. 2001;9:223–228.
33. Lown KS, Mao RR, Leichtman AB, et al. Role of intestinal p-glycoprotein (mdr1) in interpatient variation in the oral bioavailability of cyclosporine. Clin Pharmacol Ther. 1997;62:248–260.
34. Shapiro LE, Singer MI, Shear NH. Pharmacokinetic mechanisms of drug-drug and drug-food interactions in dermatology. Curr Opin Dermatol. 1997;4:25–31.
35. Watkins PB. Drug metabolism by cytochromes P450 in the liver and small bowel. Gastroenterol Clin North Am. 1992;21:511–526.
36. Birkett DJ, Mackenqie PI, Veronese ME, et al. In vitro approaches can predict human drug metabolism. Trends Pharmacol Sci. 1993;14:292–294.
37. Pelkonen, O, Turpeinen, M, Hakkola J, et al. Inhibition and induction of human cytochrome P450 enzymes: current status. Arch Toxicol. 2008;82:667–715.
38. Ford N, Sonnichsen D. Clinically significant cytochrome P-450 drug interactions – a comment. Pharmacotherapy. 1998;18:890–891.
39. Kotlyar M, Carson SW. Effects of obesity on the cytochrome P450 enzyme system. Int J Clin Pharmacol Ther. 1999;39:8–19.
40. Michalets E. Update: Clinically significant cytochrome P450 drug interactions. Pharmacotherapy. 1998;18:84–112.
41. Rendic S, Di Carlo FJ. Human cytochrome P450 enzymes. Drug Metab Rev. 1997;29:413–580.
42. Park BK, Pirmohamed M, Kitteringham N. The role of cytochrome P450 enzymes in hepatic and extrahepatic human drug toxicity. Pharmacol Ther. 1995;68:385–424.
43. Virani A, Mailis A, Shapiro LE, Shear NH. Drug interactions in human neuropathic pain pharmacotherapy. Pain. 1997;73:3–13.
44. Abdel Rahman SM, Gotschall RR, Kaufmann RE, et al. Investigation of terbinafine as a CP2D6 inhibitor *in vivo*. Clin Pharmacol Ther. 1999;65:465–472.
45. Wormhoudt LW, Commandeur JN, Vermeulen NP. Genetic polymorphism of human *N*-acetyltransferase, cytochrome P450, glutathione-S-transferase, and epoxide hydrolase enzymes: relevance to xenobiotic metabolism and toxicity. Crit Rev Toxicol. 1999;29: 59–124.
46. Barner EL, Gray SL. Donepezil use in Alzheimer disease. Ann Pharmacother. 1999;32:70–77.
47. Tseng CY, Wang SL, Lai MD, et al. Formation of morphine from codeine in Chinese subjects of different CYP2D6 genotypes. Clin Pharmacol Ther. 1996;60:177–182.
48. Neuvonen PJ, Kantola T, Kivisto KT. Simvastatin but not pravastatin is very susceptible to interaction with the CYP3A4 inhibitor itraconazole. Clin Pharmacol Ther. 1998;64:332–341.
49. Touchette MA, Chandrasekar PH, Milad MA, Edwards DJ. Contrasting effects of fluconazole and ketoconazole on phenytoin and testosterone disposition in man. Br J Clin Pharmacol. 1992;34:75–78.
50. Tailor S, Gupta A, Walder S, Shear N. Peripheral edema due to nifedipine-itraconazole interaction: a case report. Arch Dermatol. 1996;132:350–352.
51. Kaukonen KM, Olkkola KT, Neuvonen PJ. Fluconazole but not itraconazole decreased the metabolism of losartan to E-3174. Eur J Clin Pharmacol. 1998;53:445–449.
52. Cadle RM, Zenon GJ III, Rodriguez-Bvarradas MC, et al. Fluconazole induced symptomatic phenytoin toxicity. Ann Pharmacother. 1994;28:292–295.
53. Gupta AK, Katz HI, Shear NH. Drug interactions with itraconazole, fluconazole and terbinafine and their management. J Am Acad Dermatol. 1999;41:237–248.
54. Gomez D, Wacher VJ, Tomlanovich SJ, et al. The effects of ketoconazole on the intestinal metabolism and bioavailability of cyclosporine. Clin Pharmacol Ther. 1995;58:15–19.
55. Shennib H, Auger JL. Diltiazem improves cyclosporine dosage in cystic fibrosis lung transplant recipients. J Heart Lung Transplant. 1994;10:292–296.
56. Tatro DS (ed.). Drug Interaction Facts (with quarterly updates). St Louis: Facts & Comparisons, 1999:xxi–xxvii, 39–40, 720a–b, 2406–2442.
57. Fuhr U. Drug interactions with grapefruit juice. Drug Safety. 1998;18:251–272.
58. Roller L. Drugs and grapefruit juice [letter]. Clin Pharmacol Ther. 1998;63:87–88.
59. Kantola T, Kivisto KT, Neuvonen PJ. Grapefruit juice greatly increases serum concentrations of lovastatin and lovastatin acid. Clin Pharmacol Ther. 1998;63: 397–402.
60. Schmiedlin-Ren P, Edwards DJ, Fitzsimmons ME, et al. Mechanisms of enhanced oral availability of CYP3A4 substrates by grapefruit juice constituents. Decreased enterocyte CYP3A4 concentration and mechanism-based inactivation by furanocoumarins. Drug Metab Dispos. 1997;25:1228–1233.
61. Edwards DJ, Bellevue FH, Woster PM. Identification of 6,7-dihydroxybergamottin, a cytochrome P450 inhibitor, in grapefruit juice. Drug Metab Dispos. 1996;24: 1287–1290.
62. Hollander AA, van der Woude FJ, Cohen AF. Effect of grapefruit juice on blood cyclosporin concentration [letter]. Lancet. 1995;346:123.
63. Kupferchmidt HH, Fattinger KE, Ha HR, et al. Grapefruit juice enhances the bioavailability of the HIV protease

inhibitor saquinavir in man. Br J Clin Pharmacol. 1998;45:355–359.
64. Ernst E. Harmless herbs? A review of the recent literature. Am J Med. 1998;104:170–178.
65. Wang Z, Gorski JC, Hamman MA, et al. The effects of St John's wort (*Hypericum perforatum*) on human cytochrome P450 activity. Clin Pharmacol Ther. 2001;70:317–326.
66. Yuan CS, Wei G, Dey L, et al. Brief communication: American ginseng reduces warfarin's effect in healthy patients. A randomized controlled trial. Ann Intern Med. 2004;141:23–27.
67. Matthews MK Jr. Association of ginkgo biloba with intracerebral hemorrhage. Neurology. 1998;50:1933–1934.
68. Bottorf MB. Distinct drug-interaction profiles for statins. Am J Health Syst Pharm. 1999;56: 1019–1020.
69. Ford NE, Sonnichsen DS. Clinically significant cytochrome P450 drug interactions – a comment. Pharmacotherapy. 1998;18:890–891.
70. McKindley D, Dufresne R. Current knowledge of the cytochrome p-450 isozyme system: can we predict clinically important drug interactions? Med Health. 1998;81:38–442.
71. Hansten PD, Horn JR. Drug Interactions: Hansten and Horn's Guide to Patient Management. ebook: www.hanstenandhorn.com.
72. Tatro DS (ed.). Drug Interaction Facts (with quarterly updates). St Louis: Facts & Comparisons, 1998:91–92, 609a–10, 685d–g, 714a–b.
73. Tsikouris JP, Peeters MJ, Cox CD, et al. Effects of three fluoroquinolones on QT analysis after standard treatment courses. Ann Noninvasive Electrocardiol. 2006;11:52–56.
74. Lode H. Evidence of different profiles of side effects and drug-drug interactions among the quinolones – the pharmacokinetic standpoint. Chemotherapy. 2001;47(suppl. 3):24–31, 44–8.
75. Desta Z, Kerbusch T, Soukhova N, et al. Identification and characterization of human cytochrome P450 isoforms interacting with pimozide. J Pharmacol Exp Ther. 1998;285:428–437.
76. Flockhart DA, Richard E, Woosley RL, et al. Metabolic interaction between clarithromycin and pimozide may result in cardiac toxicity. Clin Pharmacol Ther. 1996;59:189A.
77. Desta Z, Kerbusch T, Flockhart DA. Effect of clarithromycin on the pharmacokinetics and pharmacodynamics of pimozide in healthy poor and extensive metabolizers of cytochrome P450 2D6 (CYP2D6). Clin Pharmacol Ther. 1999;65:10–20.
78. Daly AK. Molecular basis of polymorphic drug metabolism. J Mol Med. 1995;73:539–553.
79. Snow J, Gibson L. A pharmacogenetic basis for the safe and effective use of azathioprine and other thiopurine drugs in dermatologic patients. J Am Acad Dermatol. 1995;32:114–116.
80. Prandota J. Important role of proinflammatory cytokines/other endogenous substances in drug-induced hepatotoxicity: depression of drug metabolism during infections/inflammation states, and genetic polymorphisms of drug-metabolizing enzymes/ cytokines may markedly contribute to this pathology. Am J Ther. 2005;12:254–261.
81. Schwartz DH, Merigan TC. Interleukin-2 in the treatment of HIV disease. Biotherapy. 1990;2:119–136.
82. Hansten P, Horn J. The Top 100 Drug Interactions: A Guide to Patient Management, 2010 Edition. Freeland, WA: H & H Publications LLP.
81a. Tseng A, Foisy M. Important drug-drug interactions in HIV-infected persons on antiretroviral therapy: An update on new interactions between HIV and non-HIV drugs. Curr Infect Dis Rep. 2011; DOI: 10.1007/ s11908-011-0229-1.

This page intentionally left blank

132 Sunscreens

Vincent A DeLeo

Chapter Contents

Sunscreen regulation 2197
Mechanisms of sunscreen action 2199
Active ingredients in sunscreens 2199
Sunscreen efficacy 2201
Sunscreen safety 2203
Sunscreen recommendations 2203

Key features

- Modern sunscreens were first developed during the 1940s with the primary aim of preventing sunburn: today, sunscreens are also used to prevent other aspects of photodamage, including carcinogenesis and photoaging
- The active ingredients in sunscreens include inorganic agents (i.e. physical blockers) and organic compounds (i.e. chemical absorbers). The latter are further classified as UVB and/or UVA absorbers
- The ability of sunscreens to prevent cutaneous squamous cell carcinoma has been demonstrated in human studies. Their ability to prevent basal cell carcinoma and cutaneous melanoma remains controversial, although evidence supports efficacy in this regard
- Side effects from sunscreens include irritation (which is common) and allergy (which is rare)
- Sunscreen usage and sun avoidance may lead to a decrease in vitamin D levels in some individuals; optimum vitamin D levels can be achieved with a healthy diet and supplements

INTRODUCTION AND HISTORY

Sun Exposure

Evidence exists that even ancient civilizations sought protection from the damaging effects of the sun. The concept of excessive sun exposure as unhealthy or at least cosmetically unacceptable eventually spread to Northern Europe, especially among the aristocracy, and continued into the nineteenth century, until the period of the Industrial Revolution. In 1890, Palm noted that children in urban slums of England had rickets whereas those in similar housing conditions in sunny India did not, and linked the lack of sun to the development of rickets[1]. Physicians then began to treat such children with artificial UV radiation. At the same time, Finsen began to treat a number of other diseases, including tuberculosis and, interestingly, lupus erythematosus, with artificial light. He was awarded the Nobel Prize for his work in 1903. At the turn of the twentieth century, the image of tanned skin as aesthetically pleasing began to emerge. The French fashion designer Coco Chanel is often credited with developing the concept of tanned skin as beautiful that still persists today. However, the twentieth century also saw the recognition of sunburn as an effect of UVB, the discovery of UVC- and UVB-induced DNA mutations, and establishment of UVB as a complete carcinogen.

During the 1990s, dermatologists and other healthcare professionals made serious efforts to educate consumers regarding the damaging effects of excessive sun exposure as well as exposure to artificial tanning devices. Despite these efforts, recent studies show that while understanding of the adverse effects of exposure has increased, there has been very little positive change in behavior. This is especially true for adolescents, who continue to suffer sunburns and who continue to seek a tan through natural and artificial exposure. Over 20 million Americans go to tanning salons every year and sunscreen usage has actually been declining in some studies[2–4]. Achieving better compliance with sun protection will depend on a better understanding of behavior modification and techniques of disseminating the right message to consumers in an effective manner.

Sunscreens

Sunscreens are pharmaceutical preparations that attenuate UV wavelengths that would otherwise interact with molecules in the skin (chromophores) to generate photochemical reactions, leading to photobiologic change. These preparations are usually combinations of active agents or ingredients which absorb or scatter incident radiation, and they are dispersed in a variety of bases. The active ingredients are not absorbed in any large quantity into the living epidermis and dermis or the general circulation.

The first modern sunscreen was a product containing benzyl salicylate and benzyl cinnamate, which was introduced in the US in 1928. However, widespread use of sunscreens did not occur until World War II, when the US Military provided preparations containing red petrolatum to prevent sunburn in troops stationed in sunny areas. After the war, there was an increased interest in UV-absorbing chemicals, and para-aminobenzoic acid (PABA), patented in 1943, was the first of these to gain widespread usage. It was not until the mid-1970s that sunscreens gained a degree of consumer acceptance.

The initial sunscreens were produced primarily to prevent sunburn and therefore contained primarily UVB-absorbing agents. As scientific evidence grew documenting the deleterious effects of longer-wavelength UVA radiation and as manufacturers strove to develop higher levels of protection against burning, agents with absorption in the longer wavelengths (e.g. benzophenones) were combined with UVB absorbers. The physical blocking sunscreens (e.g. titanium dioxide) were used from the early days of sunscreen manufacturing, but, because of large particle size, were not cosmetically acceptable in high concentrations. Newer technology allowed for micronization of such particles, with an increase in transparency and therefore greater cosmetic acceptability. More recently, chemical agents with greater UVA absorption have been introduced (see below) and are gaining in popularity.

In addition to sunscreens for "beach" use, manufacturers also began to develop various cosmetics for daily use which contained sunscreen agents. Today, a wide array of sunscreen-containing preparations, including foundations, moisturizers and lipsticks, are commercially available. Another improvement in sunscreen products has been the development of agents with increased substantivity. Such agents, usually marketed as "sports" products, have bases which persist on the stratum corneum for longer than do the usual bases, allowing for vigorous outdoor activity and even swimming with retained photoprotection.

SUNSCREEN REGULATION

Since sunscreens alter the structure or function of skin, they are considered over-the-counter drugs in the US and are regulated by the Food and Drug Administration (FDA). Regulations include the maximum concentration of active ingredients, safety labeling, and the method for determining the sun protection factor (SPF).

Sun Protection Factor

The measure of efficacy of sunscreens is designated the sun protection factor (SPF), and the SPF is determined as outlined in Table 132.1. If

DETERMINATION OF THE SUN PROTECTION FACTOR (SPF)
• 10 human subjects • Skin type I or II • Instrumentation: light source which mimics solar spectrum • Procedure: determine minimal erythema dose (MED) in protected* and unprotected skin • $SPF = \frac{MED\ protected}{MED\ unprotected}$ • To test substantivity – *after application and before MED testing*: Water resistant (40): 2 × 20-min water immersions (whirlpool bath)† Water resistant (80): 4 × 20-min water immersions (whirlpool bath)†
*Sunscreen product applied at 2 mg/cm^2. †Air drying in between immersions.

Table 132.1 Determination of the sun protection factor (SPF).

RELATIONSHIP OF THE SUN PROTECTION FACTOR (SPF) TO BLOCKAGE OF ERYTHEMAL RADIATION	
SPF	**Blockage of erythemal radiation (%)**
10	90
15	92.5
20	95
40	97.5

Table 132.2 Relationship of the sun protection factor (SPF) to blockage of erythemal radiation.

LABELING OF SUNSCREENS – ULTRAVIOLET B (UVB) AND ULTRAVIOLET A (UVA) PROTECTION (2011)
ULTRAVIOLET B (UVB) PROTECTION
• Sun protection factor (SPF): up to 50+
ULTRAVIOLET A (UVA) PROTECTION
• Either no label or BROAD SPECTRUM • BROAD SPECTRUM can be used if the critical wavelength is ≥ 370 nm
SUBSTANTIVITY
• WATER RESISTANT (40 minutes) or WATER RESISTANT (80 minutes) • No use of the following designations: "WATERPROOF", "SUNBLOCK", "ALL DAY PROTECTION", or "SWEAT PROOF"
ADDITIONAL LABELING
• If a sunscreen has an SPF ≥ 15 *and* is BROAD SPECTRUM, then can state that the product can help to reduce the risk of skin cancer and the risk of early skin aging, when used regularly and as directed in combination with other sun protection measures • If the SPF of the sunscreen is < 15 *or* it is not BROAD SPECTRUM, then it must have the following Skin Cancer/Skin Aging Alert: "Spending time in the sun increases your risk of skin cancer and early skin aging. This product has been shown only to help prevent sunburn, not skin cancer or early skin aging."

Table 132.3 Labeling of sunscreens – ultraviolet B (UVB) and ultraviolet A (UVA) protection (2011). Based upon the 2011 FDA Final Rule for "Labeling and Effectiveness Testing; Sunscreen Drug Products for Over-the-Counter Human Use". For an explanation of critical wavelength, see text. SPF is also referred to as sunburn protection factor.

properly tested and applied, a product with an SPF of 10 would allow 10 times as much time in the sun with the same resultant level of erythema as without the product in a given individual. An SPF 20 similarly would allow 20 times as much exposure with the same result. As shown in Table 132.2, this does not mean that the SPF 20 product absorbs twice as much radiation as the SPF 10 product.

Testing for UVA Protection

Since scientists became aware of the damage that can be caused by photons of wavelengths longer than 320 nm, many attempts have been made to develop a standard method of testing for protection against long-wave or UVA radiation. Because there is no easily reproducible and biologically relevant endpoint for UVA radiation (as erythema is for the UVB range), investigators have suggested a number of assays, including both *in vitro* and *in vivo* methodology (see below). Some researchers have suggested that erythema produced by UVA sources could be utilized, but the irradiation times for such wavelengths are too long to make such an assay practical. Others have utilized psoralen-sensitized human skin plus UVA, with delayed erythema as the endpoint. Such an assay, however, has the shortcoming of measuring protection from only the photons responsible for psoralen photosensitivity.

The most commonly utilized human-skin-based assays include immediate pigment darkening and persistent (delayed) pigment darkening, both with endpoints that measure the skin's overall tanning response to UVA radiation. The former, as discussed in Chapter 86, is dependent upon radiation-induced darkening of pre-formed melanin, while the latter is a more complex response which includes increased production and transfer of melanin as well as proliferation of melanocytes. Both endpoints can be produced with relatively small amounts of UVA radiation, making them reasonable for human assays. In Japan, the assay for persistent pigment darkening is favored[5].

The most commonly accepted *in vitro* method for assaying UVA protection is the critical wavelength determination, which is utilized in some countries in the European Union and in Australia. This is a relatively simple assay in which the sunscreen is dissolved in solvent and the absorption spectrum is determined in a spectrophotometer. The critical wavelength for the product is determined as the wavelength at which 90% of solar-simulated radiation above 320 nm is absorbed[6].

In 1999, the FDA regulations regarding sunscreens were published. They included a labeling cap of 30+ for the SPF and the term *waterproof* was changed to *very water resistant*. However, methods for testing and labeling for long-wave range protection were not addressed and manufacturers had to limit claims of efficacy (in labeling or marketing) to protection from sunburn. In response to the 1999 regulations, a consensus conference was held[7]. One recommendation was that there be no cap on the SPF; it was thought that such a cap would discourage manufacturers from producing more protective sunscreens, since without labeling there would be no way for clinicians and consumers to identify such products. A second recommendation was to standardize testing and labeling for long-wave range protection; both critical wavelength determination (see above) and an *in vivo* human assay such as persistent pigment darkening could be utilized and the level of UVA protection of a product should be included on the label (along with the standard SPF value). A third recommendation was for the UVA protection afforded by a product be proportional to its level of UVB protection, so that products that were highly protective in the UVB range would have comparable protection in the UVA range. Lastly, assessments of sunscreen efficacy should go beyond protection against sunburn, since additional benefits would increase consumer awareness of other harmful effects of sun exposure and hopefully lead to greater usage of sunscreens.

In August 2007, the FDA released proposed regulations for sunscreen labeling (The Final Rule) that included several changes (Table 132.3): (1) the SPF claim could be increased from 30+ to 50+; (2) the SPF would still be measured in the same manner but would be renamed the *sunburn* protection factor; (3) a descriptor of the level of UVB protection would be required on the label (in addition to the SPF number); (4) a rating system for UVA protection would consist of 1 to 4 stars (low, medium, high, highest); and (5) the UVA protection rating would be based upon an *in vivo* (persistent pigment darkening) and an *in vitro* assay and would consist of the lower of the two results. The *in vitro* assay for assessing UVA protection would be based upon the breadth of reduction of UVA penetrance and results expressed as a ratio of UVA1 absorption to total UV absorption.

After considering the many responses received regarding this very complex testing and labeling system, the FDA published its Final Rule for "Labeling and Effectiveness Testing; Sunscreen Drug Products for Over-the-Counter Human Use" in June 2011. The latter represents a much simpler system. The major label on each product consists of the SPF number and, if efficacy in the UVA range is deemed sufficient, the term "Broad Spectrum". Testing is limited to an *in vitro* critical wavelength (CW) determination (see above), with a CW ≥ 370 nm meriting the Broad Spectrum claim. Substantivity ratings are limited to "Water Resistant (40)" and "Water Resistant (80)". The SPF is capped at 50+,

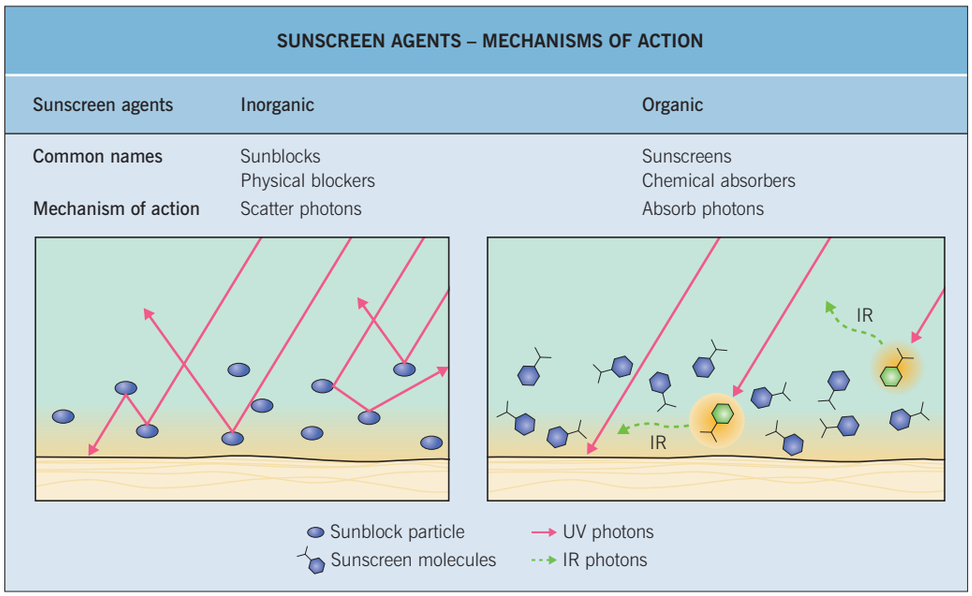


Fig. 132.1 Sunscreen agents – mechanisms of action. IR, infrared. *Courtesy, Mark Naylor, MD.*

although the FDA has stated that it will consider higher ratings if the data support sufficient increased efficacy of such products.

MECHANISMS OF SUNSCREEN ACTION

Sunscreens, when applied properly, form a film or coating on the surface of the stratum corneum and attenuate radiation that would otherwise reach the living epidermis and dermis. The active agents in sunscreen products do this by either absorbing or scattering the photons reaching the skin (Fig. 132.1). Agents that scatter radiation are opaque particles of inorganic materials and are referred to as physical agents or sunblockers. Agents that absorb radiation are organic compounds, referred to as chemical agents or sunscreens. Scattering of radiation by inorganics is based on particle size, while chemical absorption is related to chemical structure. The photons scattered by the inorganic screens are reflected back out of the skin, whereas the energy absorbed by the organic agents is converted to non-damaging energy and dissipated primarily as heat. Many sunscreen products today contain combinations of both types of agents.

Because of the large particle size of the original preparations of inorganic agents, they were not deemed cosmetically acceptable, owing to their opaque appearance on the skin. Nowadays, these agents are formulated as micronized particles, resulting in products that are more cosmetically acceptable. However, such micronized inorganics actually act more like organic sunscreens, scattering as well as absorbing radiation to some extent.

Currently, most sunscreens contain a combination of two or more agents created to offer high levels of protection against both UVB and longer-wavelength radiation.

ACTIVE INGREDIENTS IN SUNSCREENS

Figure 132.2 lists, according to type of activity and spectrum of protection, the active agents currently used in sunscreens[8].

Organic Screens

Para-aminobenzoic acid and derivatives

Padimate O (or octyl dimethyl PABA) is a PABA ester and one of the most common UVB absorbers found in sunscreens today. Both padimate O and its parent compound, PABA, are highly effective UVB absorbers. However, the latter causes staining of clothing and today is utilized infrequently.

Cinnamates

Octyl methoxycinnamate is a good UVB absorber but is not as potent as PABA and its esters. Presently, it is the most common sunscreen ingredient in the US. Although an approved agent, cinoxate is currently not used in any sunscreens in the US.

Salicylates

The salicylates are relatively weak UVB absorbers but do have the ability to stabilize other agents, thereby preventing photodegradation. Consequently, they are used in combination with other organics. This group includes octisalate, homosalate and trolamine salicylate.

Benzophenones

Benzophenones are good UVA absorbers, although their effectiveness is primarily in the UVA2 range. Oxybenzone is the most commonly used agent in this group and actually affords both UVB and UVA protection. Sulisobenzone and dioxybenzone have similar protective spectra but are infrequently utilized.

Other organic screens

Octocrylene is a commonly used UVB filter which is primarily employed to stabilize photolabile agents. Ensulizole is likewise a photostable UVB absorber. Avobenzone is an excellent UVA filter with absorption well into the UVA1 range, but is very photolabile. It is combined with other agents which assist in stabilizing its protective ability. Menthyl anthranilate is a UVA filter with a maximum absorption in the UVA2 range, but its efficacy is relatively weak.

Agents recently approved by the FDA (i.e. added to the Monograph) or awaiting FDA approval include ecamsule (UVA absorption; maximum absorption 345 nm), drometrizole trisiloxane (UVB and UVA; 344 nm), bisoctrizole (UVB and UVA; 358 nm) and bemotrizinol (UVA; see Fig. 132.2).

A process for approval of new sunscreens agents, termed the Time and Extent Application (TEA), is now available to manufacturers interested in utilizing newer agents, and studies of efficacy and safety generated outside of the US are accepted in the applications. Additional agents awaiting approval under this process include enzacamene (4-methyl-benzylidene camphor [4-MBC], Neo Heliopan® MBC, Eusolex 6300; UVB), ethylhexyl triazone (Uvinul® T 150; UVB), diethylamino hydroxybenzoyl hexyl benzoate (Uvinul® A Plus; UVA), bisdisulizole (Neo Heliopan® AP; UVA), and iscotrizinol (Uvasorb® HEB; UVB and UVA) (see Fig. 132.2).

Inorganic Screens

The two major inorganic screens are titanium dioxide and zinc oxide. There are a few so-called "chemical-free" products that contain only inorganics, but usually these agents are combined with organic screens. The activity of the inorganic agents depends upon particle size. Agents with large particle size like those on the market in the 1970s offered protection well into the UVA1 and even visible ranges, but because of

SUNSCREEN AGENTS

		Absorption			
		UVB	UVA2	UVA1	Visible
		290–320	320–340	340–400	400–800
Organic or 'chemical absorbers'					
	PABA derivates				
	PABA (para-aminobenzoic acid)	■			
	Padimate O (octyl dimethyl PABA)	■			
	Cinnamates				
	Ooctyl methoxycinnamate (Octinoxate, Parsol MCX)	■			
	Cinoxate	■			
	Salicylates				
	Octisalate (octyl salicylate)	■			
	Homosalate (homomethyl salicylate)	■			
	Trolamine salicylate	■			
	Benzophenones				
	Oxybenzone (benzophenone-3)	■	■		
	Sulisobenzone (benzophenone-4)		■	■	
	Dioxybenzone (benzophenone-8)	■	■		
	Others				
	Octocrylene	■			
	Ensulizole (phenylbenzimidazole sulfonic acid)	■			
	Enzacamene (4-methyl-benzylidene camphor [4-MBC], Eusolex 6300, Neo Heliopan® MBC)*	■			
	Ethylhexyl triazone (Uvinal® T 150)*	■			
	Avobenzone (butyl methoxydibenzoyl methane, Parsol 1789)		■	■	
	Menthyl anthranilate (meradimate)		■		
	Ecamsule (Mexoryl™ SX, terephthalylidene dicamphor sulfonic acid)		■	■	
	Drometrizole trisiloxane (Mexoryl™ XL)*	■	■	■	
	Bisoctrizole (Tinosorb® M, methylene-bis-benzotriazolyl tetramethylbutylphenol)*	■	■	■	
	Bemotrizinol (Tinosorb® S, bis-ethylhexyloxyphenol methoxyphenyl triazine)*		■	■	
	Diethyamino hydroxybenzoyl hexyl benzoate (Uvinul® A Plus)*		■	■	
	Bisdisulizole (Neo Heliopan® AP)*		■	■	
	Iscotrizinol (Uvasorb® HEB)*	■	■		
Inorganic or 'physical blockers'**					
	Titanium dioxide	■	■	■	■
	Zinc oxide	■	■	■	■
Other agents (not considered active screens)					
	Dihydroxyacetone	■	■	■	■
	Iron oxide	■	■	■	■

Fig. 132.2 Sunscreen agents. *Currently not FDA-approved or may be marketed under a new drug application. **Depending on particle size. Lighter colored bars represent variable efficacy.

their opaque appearance they were not acceptable to many consumers. More cosmetically acceptable agents were developed with smaller particle size (i.e. micronized), but at the expense of shifting the protection toward the shorter UVA2 range. Micronized zinc oxide appears to have better activity in the UVA1 range than does titanium dioxide at comparable concentrations[9]. With the advent of nanotechnology, smaller particles of inorganic agents can be incorporated into sunscreen products.

Other Agents

Dihydroxyacetone is the compound most commonly used in sunless tanners. This agent, which when applied is colorless, binds to the stratum corneum and colors the skin to produce a tanned appearance. Although it has a very low SPF, it does offer protection from long-wave radiation (even into the visible range). Iron oxide offers protection across the UV spectrum and into the visible range, and is used as a colorant in some products[10].

Other "active" ingredients have been added to sunscreens, with claims of increasing efficacy of the finished products[8]. The most popular of these are antioxidants, including vitamins E and C and green tea polyphenols, some of which have decreased UV-induced damage in *in vitro* and *in vivo* assays. However, factors including chemical structure, concentration and stability in a finished product cannot be determined from package labels, so at this point it is impossible for the clinician and the consumer to judge efficacy.

In addition, sunscreen manufacturers are beginning to incorporate "boosters" into their products. Although these agents are not UV filters, they serve to increase the protective nature of sunscreens by boosting the SPF and UVA protection (but without the addition of or increased concentrations of active agents). Examples include tiny spheres that scatter incoming radiation and agents that increase the spread of the sunscreen on the skin, leading to greater protection.

SUNSCREEN EFFICACY

A good modern sunscreen should protect against sunburn, carcinogenesis, photoaging, photoimmune suppression and photosensitivity. Efficacy of a given sunscreen product is usually assumed if the combined absorption spectra of the agents in a product match the action spectrum of a given adverse event.

The action spectra for the adverse effects of sun exposure are listed in Table 132.4. There is abundant evidence that sunburn, nonmelanoma skin cancer induction, photoimmune suppression and photoaging are all most efficiently produced by UVB radiation. However, studies have shown that for some of these events, UVA also plays a greater or lesser role. For example, UVB is about 1000 times as effective at inducing erythema in human skin as is UVA. On the other hand, photoaging was originally thought to be primarily due to UVB radiation, but UVA penetrates more deeply into the dermis and is likely to have an important role in this process. Similarly, although most studies (in a number of model systems) show that the maximal effective radiation for producing photoimmune suppression is in the UVB range, sunscreens with only UVB protective agents are not totally effective in blocking this effect[11].

With regard to cutaneous squamous cell carcinoma (SCC), epidemiologic and animal studies, combined with the identification of UVB and UVA "signature" mutations in human SCCs, strongly support causation primarily by UVB, but UVA may also play a role[12]. Most evidence also supports the role of UVB in basal cell carcinoma (BCC) induction, but a great deal of controversy exists as to the action spectrum for melanoma. Still, UVB seems the most likely culprit. For example, in transgenic mice in which melanocytes are aberrantly located in the epidermis, a single erythemal (burning) dose to neonatal mice greatly enhanced melanoma formation[13]. Additional models for melanoma are currently under investigation and may provide further insights.

It must also be remembered that even though UVA may be less effective at inducing a given event in the skin when compared to UVB, there is 10 to 20 times as much UVA as UVB in sunlight (Fig. 132.3). This ratio is even higher in the skin of an individual wearing a UVB-protective sunscreen (especially if the SPF is ≥8), which might allow him or her to stay in the sun longer and obtain larger amounts of UVA radiation[14]. Therefore, the use of broad-spectrum sunscreens should be a goal of any photoprotection strategy.

Although the effectiveness of the protection of a given product might be predicted from a comparison of the action spectrum (see Table 132.4) versus the absorption spectrum (see Fig. 132.2), the most valid measures of efficacy are prospective studies in human subjects. However, in the case of skin cancer and photoaging, these studies are difficult to conduct because the photobiologic processes have such a long latency period. Animal models can be utilized, and this has often been done for photoaging and SCC induction, but has been quite limited for BCC (e.g. mice with only one normal allele for *Ptch*) and melanoma (e.g. opossums). Another approach has been to employ assays that measure the effect of sunscreens on biologic endpoints known to be important precursors in a pathologic process (but before the development of a recognizable lesion). Examples would be studying the effects of sunscreens on the development of actinic keratoses or assaying for DNA damage or mutated genes in human skin[14]

Much of the information on sunscreen efficacy is based on retrospective case-controlled studies. Because of the lower level of validity of such studies and because of variability of study design and especially the inherent recall bias, many such studies arrive at conflicting results. In addition, prospective trials are limited by the ability to blind subjects (to control vehicle vs active ingredients) in the setting of sun exposure.

ACTION SPECTRA FOR PHOTODAMAGE

Effect	Spectrum of light			Type of evidence
	UVB	UVA	Visible	
Sunburn	++++	+		1
Photoaging	++++	++	?	3,4
Squamous cell carcinoma	++++	+		2,3,4
Basal cell carcinoma	+++	?		2,4
Cutaneous melanoma	++	+		3,4
Photoimmune suppression	++++	++		1,3,4
Photosensitivity	+	+++	+	1 (varies with disease)

Table 132.4 Action spectra for photodamage (relative values). 1, human studies; 2, epidemiologic studies; 3, animal studies; 4, *in vitro* studies of associated biologic endpoints.

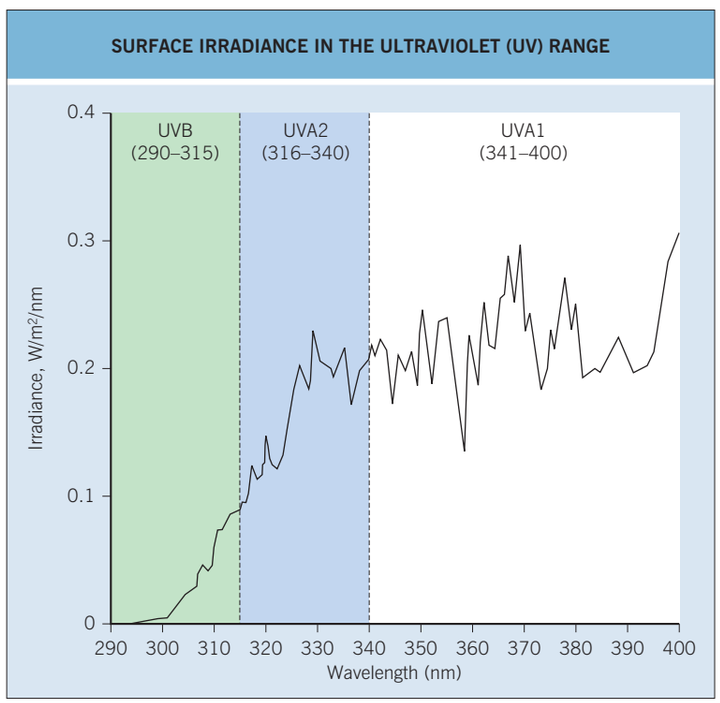


Fig. 132.3 Surface irradiance in the UV range. *Courtesy, Mark Naylor, MD.*

Fig. 132.4 Lack of sunburn in areas of sunscreen application. Peripheral edge represents outline of fingers. *Courtesy, Kalman Watsky, MD.*

Sunburn

Tens of thousands of unpublished SPF studies performed in the premarketing testing of sunscreens attest to their ability to prevent sunburn. Controlled human studies in "real world" settings have found, however, that sunscreen usage does not always prevent sunburn[15]. The major reason for this dichotomy is that individuals do not apply sunscreens at the same concentrations as are utilized in controlled SPF testing – that is, 2 mg/cm^2. Some studies have shown that most sunscreen users apply only 25–75% of that quantity[16]. This means that the SPF is similarly reduced, i.e. applying only one-half of the standard amount of an SPF 15 product will result in protection comparable to a product with an SPF of 7.5. The proper quantity of sunscreen to cover the skin of an adult is approximately 30 ml or two tablespoons. Strategies to improve compliance include applying the product twice to gain the proper concentration, which also reduces the occurrence of "skip" areas (Fig. 132.4), or to use a product with twice the SPF as desired[17,18].

Photoaging

There are numerous animal studies demonstrating that sunscreen usage prevents clinical and histologic changes of photoaging and such usage can actually help reduce some of the damage that has already occurred. In addition, Boyd et al.[19] noted a significant reduction in dermal elastosis with daily sunscreen use over a 2-year period during an actinic keratosis study. A shorter-term study found that sunscreens with broad spectral coverage (extending significantly into the UVA spectrum) prevented many biochemical measures of sun damage (from solar-simulated radiation) in human volunteers[20].

Photoimmune Suppression

Immune suppression by UV radiation was first reported in animal studies that showed that mice could no longer reject UV-induced skin tumors if they had been irradiated with non-tumorigenic doses of UV before transplantation of the tumors. This immunosuppressive effect of UV has been shown to affect delayed-type hypersensitivity and contact sensitivity as well as tumor rejection and has been shown to be active in humans as well as animals[21,22]. While the responsible action spectrum has been shown to be predominantly in the UVB range, in experimental studies UVB sunscreens have not always afforded protection against immune suppression[23]. In an elegantly designed study in a large number of human volunteers, Kelly and colleagues[24] reported that sunscreen did offer some protection against immune suppression but the level of protection was not as great as its protection against sunburn. The researchers utilized a measure of photoprotection against suppression, designated the immune protective factor (IPF), and compared it with the erythema protection factor (EPF), a measure similar to SPF. In their study, the IPF was only 4.9, while the EPF was 14.2. The authors postulated that this difference was due to UVA radiation not blocked by the applied sunscreen[24]. Some investigators concerned about the effect of photoimmune suppression on various aspects of human health have suggested that sunscreens should be tested and labeled for IPF as well as SPF.

Non-melanoma Skin Cancer

Because of the long latency period for the development of SCC and BCC, the first two prospective studies in humans examining the effect of sunscreen on cancer prevention used actinic keratoses, precursors of SCC, as surrogates for SCC development. Naylor et al.[25] studied the daily application of an SPF 29 sunscreen applied over a 2-year period in a group of 53 individuals with a previous history of actinic keratoses. The sunscreen-treated group had significantly fewer actinic keratoses over the 2-year period compared with the placebo group. The difference between the two groups with regard to skin cancers was not significant, probably due to the relatively short duration of the trial.

Thompson et al.[26] studied the effects of an SPF 17 sunscreen applied daily in 588 individuals (>40 years of age) during a single Australian summer. This study also found a significant reduction in the number of actinic keratoses in the sunscreen-treated group.

Later, Green et al.[27] undertook a prospective study of the daily use of an SPF 17 sunscreen in Australians. This study compared an active intervention group, in which sunscreen was supplied and its use encouraged, against the background rate of sunscreen use in the general population. The number of SCCs was found to be significantly less in the sunscreen-treated group, but there was no difference in the number of BCCs between the two groups. From clinical observations regarding anatomic distribution, the relationship between UV radiation and BCC is known to be more complex than with SCC.

In a prospective trial involving 120 solid organ transplant recipients (all of whom received education regarding sun protection), 60 individuals were given free broad-spectrum sunscreen to apply daily to the head and neck, forearms and hands[28]. Over a period of 24 months in which an average of 5.6 applications per week was recorded, significantly fewer new actinic keratoses and SCCs developed in the sunscreen group as compared to the control group. While the baseline actinic keratosis count was equal in the two groups, there was an overall reduction in the number of actinic keratoses in the sunscreen group.

Cutaneous Melanoma

Developing sunscreen efficacy studies for decreasing the risk of melanoma is difficult and some might not consider them to be ethical. As with SCC and actinic keratoses, a number of researchers have used the development of melanocytic nevi in children as a marker for melanoma risk. The number of nevi has been related to sun exposure in children and the former has also been linked to risk for melanoma[29]. In several retrospective epidemiologic studies, researchers have actually reported that children who used sunscreens had an increased number of nevi[30]. However, in the only prospective controlled study published to date, Gallagher et al.[31] demonstrated that sunscreens could suppress the development of nevi. The study was conducted over a 3-year period with an SPF 30 sunscreen in a total of 485 schoolchildren 6 to 9 years of age.

Retrospective case-controlled studies of melanoma patients have produced conflicting results with regard to sunscreen usage and the risk of developing melanoma. Some of these studies showed a decreased risk, while others actually showed an increased risk. Meta-analyses of the published studies by two different groups concluded that sunscreen usage did not increase the risk of developing melanoma, but the analyses could not confirm a protective effect from using sunscreen[32,33].

This dichotomy of results has led to a significant controversy concerning the use of sunscreens. The controversy is based on two different but related lines of reasoning. The first relates to the action spectrum for induction of melanoma. If in fact the action spectrum for melanoma is in the UVA range (as suggested by studies in fish), then wearing sunscreens with UVB protection will allow individuals to stay in the sun longer and receive larger doses of UVA, thereby increasing their risk of developing melanoma. However, several animal models suggest that the action spectrum is probably predominantly in the UVB range (see above). The second theory is based on the concept that sunscreen usage decreases vitamin D levels in humans. Because vitamin D has

CLASSIFICATION AND ACTION SPECTRA OF PHOTOSENSITIVE SKIN DISEASES			
Disease	**Spectrum of light**		
	UVB	**UVA**	**Visible**
Polymorphic light eruption	+	++	
Hydroa vacciniforme	+	++	
Solar urticaria	+	++	++
Chronic actinic dermatitis	+++	++	+
Actinic prurigo	++	++	
Photoallergic contact dermatitis		+++	
Photoirritant contact dermatitis		+++	
Photodrug reactions	+	+++	+
Porphyria			+++
Cutaneous lupus erythematosus	+++	++	

Table 132.5 Classification and action spectra of photosensitive skin diseases (relative values).

been shown to reduce proliferation and increase differentiation of various normal and tumor cells, low vitamin D levels might increase the risk of developing some cancers, including melanoma[34].

However, in a recently reported study, 1621 Australians (ages 25–75 years) were randomly assigned to daily or discretionary sunscreen application to the head and arms (in combination with 30 mg β-carotene or placebo supplements) for a period of 4 years[35]. They were then followed for another 10 years, and over that time period, 11 new primary cutaneous melanomas were identified in the daily sunscreen group and 22 in the discretionary group. This represented a reduction in the observed rate in the former group (hazard ratio [HR], 0.50; 95% CI, 0.24 to 1.02; p = 0.05); the reduction in invasive melanomas was more substantial (3 in the daily group versus 11 in the discretionary group).

Photosensitivity Disorders (see Ch. 87)

The action spectra of the more common photosensitivity disorders are listed in Table 132.5. Some of these reactions are caused by UVB radiation, but the majority of affected individuals react to UVA and/or visible light. Therefore they require photoprotection with agents that absorb or reflect longer wavelengths; a small number of studies have confirmed the efficacy of such agents[34]. Currently, the most protective formulations appear to be avobenzone- and ecamsule-containing products[36]. Other useful agents include inorganic titanium and zinc oxides and benzophenones. The self-tanners containing dihydroxyacetone in combination with regular sunscreen usage may offer some benefit and iron oxide-containing products can also be helpful.

SUNSCREEN SAFETY

Sunscreens have been utilized for decades with an excellent safety record. While studies appear from time to time suggesting that some sunscreen agents are mutagenic or carcinogenic or have adverse hormonal effects in various *in vitro* and animal studies, there is no convincing evidence that such studies have relevance for humans[37].

The major adverse effects of sunscreens are minor skin irritation, which is common, and allergic contact dermatitis, which is rare. These reactions are usually due to ingredients in the base of the product, such as fragrance or preservatives. Presently, the organic compounds most often responsible for the rare instances of allergy or photoallergy are oxybenzone and padimate O, and, less commonly, avobenzone[38].

As noted previously, some researchers believe that sunscreens may actually be deleterious to health by blocking the production of vitamin D. The first step in the production of this important nutrient is the conversion within the epidermis of 7-dehydroxycholesterol to pro-vitamin D_3 by UVB radiation (see Ch. 51). Sunscreens that are effective at blocking UVB photons would therefore be expected to decrease levels of vitamin D, and studies have shown that this does in fact occur. However, the majority of human studies that measured serum vitamin D levels in sunscreen users (as compared to non-users) found that the levels, though reduced, were within the normal range[39]. In addition, studies have shown that dark-skinned individuals, women, and, during the wintertime, individuals who live in northerly climes all have reduced levels[40].

Recently, scientists in the fields of nutrition and bone metabolism have presented data suggesting that individuals who have serum vitamin D levels in the low normal range may actually have insufficient vitamin D for optimum health. Some of these studies suggest that not only do these low normal or "insufficient" levels of vitamin D adversely affect good musculoskeletal health, but that they may also increase the risk of other adverse events like cancer and decreased immune function[41]. One publication linked lower levels of sun exposure to decreased survival in melanoma patients and suggested that this was related to insufficient vitamin D[41,42].

Controversy has arisen because scientists cannot agree on what constitutes the "normal" range for serum 25-OH vitamin D levels and similarly cannot agree on the minimum suggested daily intake for the vitamin. Although vitamin D can be obtained from foods such as fish oils, in developed countries the more common sources are vitamin D-fortified milk and milk products, as well as vitamin supplements. In 2010, the Institute of Medicine issued a consensus statement regarding the recommended dietary allowance for vitamin D – 600 IU per day, except for those over 70 years of age in whom 800 IU per day was recommended (www.iom.edu). Unfortunately, the tanning salon industry has "fanned the flames" by suggesting that UV light exposure and tanning represent the optimum way to assure healthy vitamin D metabolism[43].

This area of medicine is evolving, and, as specialists in skin health and disease, we should not simply deny any merit to the controversy. We should continue to evaluate studies from our colleagues in other fields. Notably, it does not mean that we should change our message about sun avoidance and sunscreen usage; we simply have to suggest that all individuals maintain adequate vitamin D intake via diet and supplements.

SUNSCREEN RECOMMENDATIONS

There is ever-increasing evidence that although the public is aware of the damaging effects of sun exposure, there does not seem to be a significant degree of alteration in behavior. In an effort to re-energize the medical community's need to try to change behavior, the American Academy of Dermatology has reformulated its message concerning protection (www.aad.org). While the importance of sunscreen is stressed, the recommendations are broader and more positive, and hopefully this and other improvements in consumer education will eventually lead to a decrease in photodamage in the world's population.

REFERENCES

1. Giacomoni PU. Sunprotection: historical perspective. In: Shaath NA (ed). Sunscreens: Regulations and Commercial Development, 3rd edn. Boca Raton, FL: Taylor & Francis, 2005:71–81.
2. Geller AC, Colditz G, Oliveria S, et al. Use of sunscreen, sunburning rates, and tanning bed use among more than 10,000 US school children and adolescents. Pediatrics. 2002;109:1009–14.
3. Davis KJ, Cokkinides VE, Weinstock MA, et al. Summer sunburn and sun exposure among US youths ages 11–18: national prevalence and associated factors. Pediatrics. 2002;110:27–35.
4. El Sayed F, Ammoury A, Nakhle F, et al. Photoprotection in teenagers. Photodermatol Photoimmunol Photomed. 2006;22:18–21.
5. Moyal D, Chardon A, Kollias N. UVA protection efficacy of sunscreens can be determined by the persistent pigment darkening (PPD) method (part 1): calibration of the method. Photodermatol Photoimmunol Photomed. 2000;16:245–9.
6. Diffey BL, Tanner PR, Matts PJ, et al. In vitro assessment of the broad spectrum ultraviolet protection of sunscreen products. J Am Acad Dermatol. 2000;43:1024–35.
7. Lim HW, Naylor M, Honigsmann H, et al. American Academy of Dermatology consensus conference on UVA protection of sunscreens: summary and recommendations. Washington, DC: Feb 4, 2000. J Am Acad Dermatol. 2001;44:505–8.
8. Kullavanijaya P, Lim HW. Photoprotection. J Am Acad Dermatol. 2005;52;938–58.
9. Pinnell SR, Fairhurst D, Gillies R, et al. Microfine zinc oxide is a superior sunscreen ingredient to microfine titanium dioxide. Dermatol Surg. 2000;26:309–14.
10. Murphy GM. Sunblocks: mechanism of action. Photodermatol Photoimmunol Photomed. 1999;15:34–6.

11. Young AR. Are broad-spectrum sunscreens necessary for immunoprotection? J Invest Dermatol. 2003;121:ix–x.
12. Agar NS, Halliday GM, Barnetson, RS, et al. The basal layer in human squamous tumors harbors more UVA than UVB fingerprint mutations: a role for UVA in human skin carcinogenesis. Proc Natl Acad Sci USA. 2004;101:4954–9.
13. Zaidi MR, Day C-P, Merlino G. From UVs to metastases: modeling melanoma initiation and progression in the mouse. J Invest Dermatol. 2008;128:2381–91.
14. Fourtanier A. Mexoryl SX protects against solar-simulated photocarcinogenesis in mice. Photodermatol Photoimmunol Photomed. 1996;64:688–93.
15. Wright MW, Wright ST, Wagner RF. Mechanisms of sunscreen failure. J Am Acad Dermatol. 2001;44:781–4.
16. Azuridia RM, Pagliaro JA, Diffey BL, et al. Sunscreen application by photosensitive patients is inadequate for protection. Br J Dermatol. 1999;140:255–8.
17. Diffey BL. When should sunscreens be reapplied? J Am Acad Dermatol. 2001;45:882–5.
18. Pruim B, Green A. Photobiological aspects of sunscreen re-application. Australas J Dermatol. 1999;40:14–8.
19. Boyd AS, Naylor M, Cameron GS, et al. The effects of chronic sunscreen use on the histologic changes of dermatoheliosis. J Am Acad Dermatol. 1995;33:941–6.
20. Stenberg C, Larko O. Sunscreen application and its importance for the sun protection factor. Arch Dermatol. 1985;121:1400–2.
21. Ullrich SE. Photoimmune suppression and photocarcinogenesis. Front Biosci. 2002;17:d684–703.
22. Hanneman KK, Cooper KD, Baron ED. Ultraviolet immunosuppression: mechanisms and consequences. Dermatol Clin. 2006;24:19–25.
23. Baron ED, Fourtanier A, Compan D, et al. High ultraviolet A protection affords greater immune protection confirming that ultraviolet A contributes to photoimmunosuppression in humans. J Invest Dermatol. 2003;121:869–75.
24. Kelly DA, Seed PT, Young AR, et al. A commercial sunscreen's protection against ultraviolet radiation-induced immunosuppression is more than 50% lower than protection against sunburn in humans. J Invest Dermatol. 2003;120:65–71.
25. Naylor MF, Boyd A, Smith DW, et al. High sun protection factor (SPF) sunscreens in the suppression of actinic neoplasia. Arch Dermatol. 1995;131:170–5.
26. Thompson SC, Jolley D, Marks R. Reduction of solar keratoses by regular sunscreen use. N Engl J Med. 1993;329:1147–51.
27. Green A, Williams G, Neale R, et al. Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. Lancet. 1999;354:723–9.
28. Ulrich C, Jurgensen JS, Degen A, et al. Prevention of non-melanoma skin cancer in organ transplant patients by regular use of a sunscreen: a 24 months, prospective, case-control study. Br J Dermatol. 2009;161(Suppl 3):78–84.
29. Azizi E, Iscovich J, Pavlotsky F, et al. Use of sunscreen is linked with elevated naevi counts in Israeli school children and adolescents. Melanoma Res. 2000;10:491–8.
30. Autier P, Dor JF, Severi G. More about sunscreen use, wearing clothes, and number of nevi in 6 to 7 year old European children. J Natl Cancer Inst. 1999;91:1165–6.
31. Gallagher RP, Rivers JK, Lee TK, et al. Broad-spectrum sunscreen use and the development of new nevi in white children: a randomized controlled trial. JAMA. 2000;283:2955–60.
32. Bastuji-Garin S, Diepgen TL. Cutaneous malignant melanoma, sun exposure, and sunscreen use: epidemiological evidence. Br J Dermatol. 2002; 146(Suppl. 61):24–30.
33. Huncharek M, Kupelnick B. Use of topical sunscreens and the risk of malignant melanoma: a meta-analysis of 9067 patients from 11 case control studies. Am J Public Health. 2003;93:11–2.
34. Eide MJ, Weinstock MA. Public health challenges in sun protection. Dermatol Clin. 2006;24:119–24.
35. Green AC, Williams GM, Logan V, Strutton GM. Reduced melanoma after regular sunscreen use: randomized trial follow-up. J Clin Oncol. 2011;29:257–63.
36. DeLeo V. Sunscreen use in photodermatoses. Dermatol Clin. 2006;24:27–33.
37. Gasparro FP, Mitchnick M, Nash JF. A review of sunscreen safety and efficacy. Photochem Photobiol. 1998;68:243–56.
38. DeLeo VA. Photocontact dermatitis. Dermatol Ther. 2004; 17:279–88.
39. Sollitto RB, Kraemer KH, DiGiovanna JJ. Normal vitamin D levels can be maintained despite rigorous photoprotection: six years' experience with xeroderma pigmentosum. J Am Acad Dermatol. 1997;37:942–7.
40. Nesby-O'Dell S, Scanlon KS, Cogswell ME, et al. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988–1994. Am J Clin Nutr. 2002;76;187–92.
41. Egan KM, Sosman JA, Blot WJ. Sunlight and reduced risk of cancer: is the real story vitamin D? J Natl Cancer Inst. 2005;97:161–3.
42. Berwick M, Armstrong BK, Ben-Porat L, et al. Sun exposure and mortality from melanoma. J Natl Cancer Inst. 2005;97:195–8.
43. Lim, HW, Gilchrest BA, Cooper KD, et al. Sunlight, tanning booths, and vitamin D. J Am Acad Dermatol. 2005;52:868–76.

Complementary and Alternative Medicine 133

Amy Geng and Raymond G Dufresne Jr

Chapter Contents

Botanicals, dietary supplements, and other biologically based practices 2205
Traditional Chinese medicine 2211
Homeopathy 2214
Aromatherapy 2215
Mind–body medicine 2216

Key features

- Globally, complementary and alternative medicine (CAM) is commonly utilized, and it is rising in popularity
- CAM encompasses a diverse group of therapies
- Among dermatology patients, the most popular forms of CAM include herbals, dietary supplements, homeopathy and acupuncture
- Scientific research regarding CAM has expanded significantly

INTRODUCTION

Complementary and alternative medicine (CAM) represents a diverse set of healthcare systems, practices and treatment modalities that are grouped together because they are not considered part of conventional medicine. Various classifications of CAM have been suggested, including one summarized in Table 133.1[1]. Integrative medicine combines the most efficacious CAM with conventional therapies.

An estimated 80% of the world's population uses CAM as their initial and perhaps only type of medical care[2]. The prevalence of CAM usage is higher in low-income countries, but is rising in high-income countries. In 2007, ~40% of adults and ~12% of children in the US used CAM[3]. Fifty percent of the US population takes dietary supplements, and ~20% of all prescription users take herbals or high-dose vitamins (megavitamins)[1]. CAM usage is also significant in Europe (10–50%), Australia (70%) and Japan (75%).

In the US, CAM usage tends to be more prevalent in women, adults 30 to 69 years of age, those with higher levels of education, and former smokers[3]. It is also associated with the number of health conditions, number of doctor visits over the past year, and hospitalization within the past year. Children whose parents used CAM were five times more likely to use CAM. When worry about cost delayed receipt of conventional care, both adults and children were more likely to use CAM. The overwhelming majority of CAM users in high-income countries, including those with dermatologic conditions, use CAM to complement conventional medicine rather than as a complete alternative[3].

Patients who report having skin "problems" are more likely to use CAM (UK: 39% vs 20% [general population]; US: 49% vs. 38% [general population]), and some use CAM specifically for dermatologic conditions (UK, 45%; US, 6%). An estimated 35% to 70% of dermatology patients use CAM during their lifetimes, most frequently herbals, dietary supplements, homeopathy and acupuncture[4].

BOTANICALS, DIETARY SUPPLEMENTS, AND OTHER BIOLOGICALLY BASED PRACTICES

Biologically based practices include herbs/botanicals, dietary supplements (e.g. animal-derived products, vitamins, minerals, fatty acids, amino acids, proteins, prebiotics/probiotics), diet-based therapies, chelation therapy and megavitamins (see Table 133.1).

Modern medicine has its roots in natural substances; however, biologically based practices and conventional medicine differ fundamentally. Conventional medicine takes a reductionist view of the body's functions, emphasizing a belief in science's ability to isolate the active molecules needed to treat specific diseases. In contrast, biologically based practices ideally take a holistic approach to health and emphasize disease prevention and health promotion by strengthening the body's own healing mechanisms.

Dermatologic Applications

Conventional dermatology uses many products of herbal origin, including podophyllin, psoralens, oatmeal and pyrethrins. Such accepted treatments are discussed elsewhere in this textbook; this chapter limits its discussion to herbals that are less well known but are commonly used. Examples are discussed below and are listed in Table 133.2.

Aloe vera

The gel from *Aloe vera* leaves is often used topically on wounds and burns. Aloe reduces burning, itching and scarring from radiation dermatitis, and it can be used for ulcers, postsurgical wounds, frostbite, pruritus and stasis dermatitis as well as for minor cutaneous infections (bacterial, fungal, herpes simplex). Double-blind, placebo-controlled studies of aloe have shown statistically significant improvement of psoriasis (83% vs 7%), seborrheic dermatitis (62% vs 25%), and irritant contact dermatitis.

Active components of aloe include: (1) salicylic acid, which decreases vasoconstriction and platelet aggregation and improves dermal perfusion via a decrease in thromboxane A_2, thromboxane B_2 and prostaglandin 2α; (2) carboxypeptidase, which inactivates bradykinin and decreases pain; (3) polysaccharides such as acemannan, which have anti-inflammatory, antimicrobial (bactericidal, viricidal, antifungal), and immune-stimulating actions; and (4) aloesin, which inhibits tyrosinase and suppresses UV-induced tanning by a third. Aloe also increases collagen biosynthesis and degradation within granulation tissue and it can cause allergic contact dermatitis[6]. If ingested, aloe can lead to hypoglycemia in diabetics on oral hypoglycemic drugs.

Honey

Randomized, controlled trials have shown that honey enhances healing of first-degree and superficial second-degree burns. The evidence is inconclusive with regard to acute wounds, postoperative wounds and pressure ulcers, and it is not effective for venous ulcers. One study suggested that honey may be more effective than topical acyclovir in the treatment of recurrent labial and genital herpes simplex[7].

Honey contains sugars, amino acids, vitamins, minerals and enzymes (e.g. catalase), which are thought to encourage debridement, promote granulation and epithelialization, and reduce edema. Antibacterial properties are related to peroxide activity and osmolarity. For example, manuka honey has antibacterial activity equivalent to that of phenolic acid. Contact dermatitis has rarely been reported[8].

Marigold

Marigold (*Calendula officinalis*) is an antiseptic and is commonly used for diaper dermatitis. *Calendula* is also used for wounds, ulcers, burns, furuncles, herpes zoster, varicose veins, eczema, and mouth and throat inflammation. There is evidence that marigold may be useful as prophylaxis for acute radiation dermatitis[9].

Marigold contains flavonoids, triterpene saponins and carotenoids. It has anti-inflammatory, antimicrobial and immunomodulating properties. Animal studies have demonstrated increased glycoproteins and

CLASSIFICATION OF COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM)		
Biologically based practices	Chelation therapy	
	Folk medicine	
	Herbs/botanicals	Non-vitamin, non-mineral, natural products
	Dietary supplements	Animal-derived extracts Vitamins Minerals Fatty acids Amino acids Proteins Prebiotics, probiotics
	Diet-based therapies	Vegetarian Macrobiotic Atkins Pritikin Ornish Zone South Beach
	Megavitamin therapy	
Alternative medical systems	Acupuncture/traditional Chinese medicine Ayurveda Homeopathic medicine Naturopathy	
	Other traditional healers	Curandero, Espiritista, Hierbero/Yerbera, Shaman, Botanica, Native American, Sobrador
Mind–body therapies	Biofeedback Meditation Guided imagery Progressive relaxation Deep breathing exercises Hypnosis Yoga Tai chi Qi gong Cognitive behavioral therapy Patient support groups Autogenic training Spirituality Prayer Mental healing	
	Therapies that use creative outlets	Music therapy Art therapy Dance therapy
Manipulative and body-based practices	Chiropractic manipulation Osteopathic manipulation Massage	
	Movement therapies	Feldenkrais method Alexander technique Pilates Trager psychophysical integration
	Bowen technique Craniosacral therapy Reflexology Rolfing	
Energy medicine	**Energy types**	**Energy therapies**
	Veritable energy:	
	Mechanical vibrations	Sound therapy
	Electromagnetic energy (light, magnetic fields, laser beams, infrared, direct and alternating current)	Light therapy Magnetic therapy Millimeter wave therapy Infrared therapy
	Putative energy:	
	Qi (Chinese)	Traditional Chinese medicine (acupuncture, qi gong)
	Ki (Japanese)	Reiki Johrei
	Dosha	Ayurvedic medicine
	Prana	Yoga
	Homeopathic resonance	Homeopathy
	Other energy types:	
	Ether (Greek) Fohat (Tibetian) Mana (Polynesian) Orgone, Odic force (European)	Therapeutic touch Vortex healing Polarity therapy Distant healing Intercessory prayer

Table 133.1 Classification of complementary and alternative medicine (CAM). Based upon classifications from the National Center for Complementary and Alternative Medicine (NIH) and the National Center for Health Statistics (CDC)[1].

collagen at wound sites treated with marigold. There are rare reports of contact dermatitis to *Calendula*[6].

Capsaicin

Capsaicin is found in hot peppers (*Capsicum*), and it is a mixture of vanillyl amides of isodecenoic acid. Topical capsaicin is used for post-herpetic neuralgia, notalgia paresthetica, diabetic neuropathy, reflex sympathetic dystrophy, and hemodialysis-related pruritus. By binding to the capsaicin vanilloid receptor-1 on pain fibers, capsaicin stimulates the release and eventually depletion of the neurotransmitter substance P. Prolonged exposure leads to death of these neurons, although they can regenerate over time.

Capsaicin also has antimicrobial properties and has been used for verrucae. It decreases scaling, thickness, erythema and pruritus in patients with psoriasis. A common side effect is temporary burning, both locally and at sites of unintended application, which may limit its use.

Arnica

Arnica (*Arnica montana*) is approved by the German Commission E for its anti-inflammatory effects[6]. It is used for treating myalgia, arthralgia, bruises, insect bites, furuncles, acne, gingivitis, hemorrhoids, seborrheic dermatitis and psoriasis. Active components include sesquiterpene lactones, which reduce inflammation by inhibiting the transcription factor NF-κB, an important regulator of inflammatory mediators. Arnica is toxic when ingested, unless given in homeopathic doses, and should only be used topically on intact skin. As a member of the Compositae (Asteraceae) family, contact dermatitis is a possible adverse effect. A single case report of Sweet's syndrome with pathergy to arnica occurred in a patient with leukemia.

Chamomile

Chamomile (*Matricaria recutita*, *Chamomilla recutita*) is used to treat inflammation of the skin and mucous membranes and to promote wound healing. It is traditionally used for dermatitis and may be ingested as a tea or applied topically. Studies have demonstrated that the anti-inflammatory effects of topical chamomile are 60% to 100% that of topical hydrocortisone 0.25%. One double-blind trial showed decreased wound surface area and healing time with chamomile. *In vitro*, chamomile has antimicrobial and antioxidant effects, while animal studies have demonstrated anti-inflammatory and antispasmodic effects.

Active components include α-bisabolol, bisabolol oxides A and B, levomenol, matricin, chamazulene, farnesene, and the flavonoids apigenin, luteolin, patuletin and quercetin. These substances inhibit cyclooxygenase and lipoxygenase, inhibit histamine release, and promote granulation tissue formation. Chamomile contains coumarins, and theoretically could increase the risk of bleeding.

BOTANICALS AND OTHER BIOLOGICALLY ACTIVE SUBSTANCES USED FOR DERMATOLOGIC CONDITIONS				
Common name	**Latin name and/or sources**	**Active components**	**Uses/properties**	**Known side effects**
PREVENTION OF BRUISING				
(Arnica is discussed in the text)				
Comfrey	*Symphytum officinale* L.	Allantoin, triterpene saponins, tannins	• Bruises, wounds, ulcers, burns, dermatitis, psoriasis • Arthritis, myalgia, acute back pain • Anti-inflammatory	• For *topical* use only; if ingested, hepatotoxic, mutagenic
Pineapple extract	*Ananas comosus*	Bromelain (a protease)	• Hematoma resorption, wound healing • Ingestion 1–2 h prior to meals enhances uptake by WBCs	• Hypersensitivity reaction, anaphylaxis
ANTIOXIDANTS USED FOR PREVENTING SKIN CANCER AND/OR PHOTOAGING				
Anapsos/calaguala/ kalawalla/golden serpent fern	*Polypodium leucotomos*	Flavonoids, alkaloids, lipids (including calaguline)	• Photoprotection, including against PUVA-induced phototoxicity, PMLE, vitiligo, psoriasis, atopic dermatitis • Commercially, may be combined with β-carotene and green tea extract • Antioxidant, immunomodulator, anti-inflammatory	• No known side effects, but a related fern, *P. vulgare*, causes hypotension, tachycardia, drowsiness
β-carotene	Sweet potatoes, carrots, kale, spinach, turnip greens, winter squash, collard greens	NA	• Photoprotection – EPP, PMLE, UV-induced erythema • Cataracts, chemotherapy-associated toxicities, COPD, immune enhancement • Antioxidant	• May increase risk of lung and prostate cancer, intracerebral hemorrhage, death from cardiovascular disease • Carotenoderma
Coffee berry	*Coffea arabica*	Polyphenols, including chlorogenic acid, quinic acid, ferulic acid, condensed proanthocyanidins	• Preventing photocarcinogenesis, photoaging • Antioxidant	• Caffeine-related: restlessness, insomnia, GI symptoms
Gingko biloba	*Gingko biloba*	Flavonoid glycosides, terpenoids (ginkgolides, bilobalides), urushiol (seed coat; see Ch. 17)	• Photoaging (*topically*), vitiligo, dementia, cardiovascular disease, multiple sclerosis • Blocks platelet-activating factor • Antioxidant	• Interactions: decreases clearance of MAO inhibitors and SSRIs • Increased risk of bleeding, GI upset, vomiting, headaches, dizziness, palpitations, restlessness
Ginseng	*Panax ginseng*, *P. quinquefolius*	Ginsenosides (triterpenoid saponin), fatty alcohols (falcarinol, panaxacol, panaxydol), polysaccharides	• Anti-aging (*topically*), immune enhancement, type II diabetes, hypertension, erectile dysfunction • Antioxidant, antineoplastic, antimicrobial	• Headache, insomnia, GI upset, hypoglycemia
Grape seed extract	*Vitis vinifera*, *V. coignetiae*	Proanthocyanidins including epicatechin and catechins, vitamin E, resveratrol	• Hyperpigmentation, reduction of photocarcinogenesis, varicose veins, chronic venous insufficiency, hypercholesterolemia, hypertension • Antioxidant, anti-inflammatory	• Interactions: inhibits hepatic clearance of some drugs • Mild stomach discomfort, nausea, headache, dizziness
Lycopene (a carotenoid)	Tomatoes, especially cooked tomato products	NA	• Photoprotection – SPF = 1.3 (oral) • Carcinoma (prostate, colon, breast, endometrial), macular degeneration • Antioxidant (*topical* and oral)	• Carotenoderma
Pine tree bark extract, from Mediterranean maritime pine tree	*Pinus pinaster* *P. pinaster* ssp. *atlantica* (French maritime pine tree)*	Pycnogenol®, proanthocyanidins including catechin, epicatechin, taxifolin	• Chronic venous insufficiency, hyperpigmentation, anti-aging (*topically*), diabetes • Binds and stabilizes collagen and elastin; increases endothelial nitric oxide • Antioxidant, anti-inflammatory	• Interactions: inhibits hepatic clearance of some drugs • Mild stomach discomfort, nausea, headache, dizziness • Possible allergen
Pomegranate	*Punica granatum* L.	Alkaloids, polyphenols, ellagic acid	• Photoaging, photoprotection, rheumatoid arthritis • Oral ellagic acid 5% increases sunscreen SPF by 25%; topical ellagic acid inhibits UVA-mediated activation of cellular pathways in keratinocytes • Antioxidant, antiviral, photoprotectant	
Resveratrol-containing plants	Grapes (skin and seeds), many berries (e.g. cranberries, blueberries, bilberries), fruits, and nuts (e.g. peanuts)	Resveratrol (polyphenol)	• Coronary artery disease, diabetes • *Topically*, decreases UVB-induced damage and carcinogen-induced skin cancers in mice • Anti-inflammatory, antineoplastic, antioxidant	• Interactions: inhibits cytochrome P450 3A4 • Phytoestrogen-like effects, slows wound healing (antiangiogenic), inhibits platelet aggregation
*Source of Pycnogenol®[5].				

Table 133.2 Botanicals and other biologically active substances used for dermatologic conditions. COPD, chronic obstructive pulmonary disease; EPP, erythropoietic protoporphyria; GI, gastrointestinal; h, hours; MAO, monoamine oxidase; NA, not applicable; PMLE, polymorphic light eruption; SPF, sun protection factor; WBCs, white blood cells.

Continued

BOTANICALS AND OTHER BIOLOGICALLY ACTIVE SUBSTANCES USED FOR DERMATOLOGIC CONDITIONS				
Common name	**Latin name and/or sources**	**Active components**	**Uses/properties**	**Known side effects**
Shiitake mushroom	*Lentinula* (*Lentinus*) *edodes*	Eritadenine, L-ergothioneine, active hexose correlated compound (AHCC), lentinan, vitamin D†	• Anti-aging, carcinomas (esp. gastric, colorectal) • Immunostimulant, antibacterial, antiviral	• Flagellate hyperpigmentation (if eaten raw or partially cooked)
Silymarin (milk thistle)	*Silybum marianum*	Silibinin (silybin), a flavonoid	• Anti-aging (*topically*), liver disease (e.g. hepatitis, cirrhosis), carcinomas (e.g. breast), type II diabetes, hypercholesterolemia • Antioxidant, hepatoprotectant, antineoplastic	• Interactions: inhibits cytochrome P450 • GI upset, diarrhea • Allergenic (Compositae [Asteraceae] family)
Soy	*Glycine max* L. Merr	Phospholipids (phosphatidylcholine), essential fatty acids (omega-3), vitamin E, isoflavones‡ (genistein, daidzein, glycitein), soybean trypsin inhibitor, Bowman Birk inhibitor	• Hyperpigmentation (*topically*), photoprotection (*topically*), photodamage (*topically*), reducing unwanted body hair (*topically*), hypercholesterolemia, osteoporosis prevention, cancer prevention • *Topically*, estrogenic effects (theoretical); soybean trypsin inhibitor is thought to inhibit activation of PAR-2 on keratinocytes, thereby reducing melanosome transfer • Antioxidant, anti-inflammatory, antineoplastic (esp. genistein), estrogenic and anti-estrogenic properties	• Mild indigestion • Potential food allergen • Conflicting data regarding breast cancer
Vitamin C (L-ascorbic acid)	Broccoli, bell peppers, kale, cauliflower, strawberries, lemons, mustard, turnip greens§	NA	• Photoprotection, photoaging, melasma, solar lentigines, acne, acne scarring • Promotes collagen synthesis, decreases collagen degradation • Antioxidant, anti-inflammatory	• Diarrhea, nausea, vomiting, flushing, insomnia (very large systemic doses) • *Topical* – mild ICD
Vitamin E (tocopherol)	Nuts, seeds, spinach, mustard greens, peppers, olive oil	NA	• Atopic dermatitis; prevention of age-related macular degeneration, cataracts and cognitive decline • Antioxidant	• Increased risk of cardiovascular disease, hemorrhagic stroke, possibly prostate cancer • *Topical*: rarely dermatitis
SUPPLEMENTS CONTAINING ANTI-INFLAMMATORY FREE FATTY ACIDS				
Acai berry	*Euterpe oleracea*	Oleic acid (omega-9; 60%), linoleic acid (omega-6; 12%), phytosterols, anthocyanins (flavonoid)	• Antioxidant	• Major food source for indigenous populations in Brazil
Black currant seed oil	*Ribes nigrum*	γ-linolenic acid (13%), α-linolenic acid (17%)	• Atopic dermatitis, rheumatoid arthritis, cardiovascular disease, premenstrual symptoms, • Reduces inflammatory cytokines IL-1 and TNF-α	• Few data available
Borage seed oil	*Borago officinalis*	γ-linolenic acid (GLA; 23%)	• Atopic dermatitis, infantile seborrheic dermatitis, rheumatoid arthritis • Richest plant-based source of GLA	• GI upset, nausea, headache
Evening primrose oil	*Oenothera biennis*	Linolenic acid (72%), γ-linolenic acid (10%)	• Atopic dermatitis, especially pruritus (oral and *topical*), hypercholesterolemia • Anti-inflammatory, antineoplastic	• Nausea, diarrhea, headache, thrombosis, immunosuppression with prolonged use (>1 year)
Fish oil (algae sources)	Tuna, salmon, sardines, herring, oysters, crab	Omega-3 fatty acids (eicosapentaenoic acid, docosahexaenoic acid)	• Psoriasis (conflicting data), cardiovascular disease, hypertriglyceridemia, rheumatoid arthritis, cell-protective during chemotherapy	• Diarrhea, anticoagulation, risk of methylmercury contamination (fish sources)
See also: olive oil (discussed in text)				
SUPPLEMENTS USED FOR PIGMENTARY DISORDERS				
Bearberry	*Arctostaphylos uva-ursi*	Arbutin, a glycosylated hydroquinone	• *Topical*: melasma, postinflammatory hyperpigmentation; suppresses UV-induced tanning, alone (43%) or with aloesin (63%) • Systemic: urinary tract infections, nephrolithiasis • Inhibits tyrosinase *in vitro*	• Systemic: nausea, vomiting, green urine, tinnitus
Chitin (insect and crustacean shell component)	Many	N-acetylglucosamine	• *Topical*: Hyperpigmentation • Inhibits tyrosinase activation	• Limited data

†Vitamin D activity is greater in dried shiitake mushrooms.
‡A class of phytoestrogens.
§Also Brussels sprouts, papaya, chard, cabbage, spinach, kiwis, snowpeas, cantaloupe, oranges, grapefruit, limes, tomatoes.

Table 133.2 Botanicals and other biologically active substances used for dermatologic conditions (cont'd). GI, gastrointestinal; ICD, irritant contact dermatitis; IL, interleukin; NA, not applicable; PAR-2, protease-activated receptor-2; TNF, tumornecrosis factor.

Continued

BOTANICALS AND OTHER BIOLOGICALLY ACTIVE SUBSTANCES USED FOR DERMATOLOGIC CONDITIONS				
Common name	**Latin name and/or sources**	**Active components**	**Uses/properties**	**Known side effects**
Paper mulberry	*Broussonetia papyrifera* L.	Root extract contains prenylated, polyhydroxylated mono- and bis-phenyl derivatives	• *Topical*: Melasma • Root extract (0.4%) inhibits tyrosinase by 50% (equivalent to hydroquinone 5.5% and kojic acid 10%)	• Limited data
Supplements that contain free fatty acids: nuts, seeds, vegetable oils (see previous section)	Many diverse plants and animals	α-linolenic, linoleic acid, γ-linolenic acid	• *Topical*: reduces UVB-induced hyperpigmentation, especially α-linolenic acid	• Variable, depending on particular supplement
Zengse pill	Proprietary Traditional Chinese medicine formula	Unknown	• Vitiligo • Immunomodulator: increases $CD4^+$ and decreases $CD8^+$ T cells	• Limited data
See also: soy, pine bark extract, grape seed extract, anapsos, persimmon leaf (listed in this table); licorice root (discussed in text), vitamins B_3 and C (Ch. 51).				
ASTRINGENTS USED TOPICALLY FOR TREATING ACNE				
English walnut leaf	*Juglans regia*	Tannins¶	• Acne, type I diabetes (very controversial)	• Unknown; limited data
St. John's wort	*Hypericum perforatum*	Naphthodianthrones (hypericin, pseudohypericin), tannins¶, flavonoids, phenolic acids, phloroglucinols, sesquiterpenes	• Acne, wounds, burns, insect bites • Most commonly used for depression, anxiety, insomnia	• Interactions: induces cytochrome P450 and P-glycoprotein • Systemic: photosensitivity, anxiety, sexual dysfunction
White oak bark	*Quercus alba*	Tannins¶	• Acne	
Witch hazel	*Hamamelis virginiana*	Tannins¶, gallic acid, catechins, proanthocyanins, flavonoids, polyphenols	• Acne, eczema, oral ulcers, bruises, edema, varicose veins, hemorrhoids • Vasoconstrictor, hemostatic, antioxidant	• Systemic: nausea, vomiting, hepatotoxic, nephrotoxic
Additional astringents that contain tannins¶ (with potential side effects) include: agrimony (urticaria), Labrador tea (muscle cramps, paralysis), goldenrod (contact dermatitis), Lady's mantle, rhubarb (nephrotoxicity due to oxalic acid), and yellowdock (diarrhea, metabolic diarrhea); lavender (*Lavendula* spp.) is also an astringent				
TREATMENT OF INFESTATIONS				
Anise seeds	*Pimpinella anisum*	Terpenoid anethole, phytoestrogens	• Infestations	• Contraindicated during pregnancy and breastfeeding
Chrysanthemums	Asteraceae (Compositae) family	Pyrethrins	• Scabies	• Allergic contact dermatitis, photosensitivity
Neem	*Azadirachta indica*	Nimbidin	• Infestations, psoriasis (better than placebo)	• Contraindicated during pregnancy and breastfeeding and in children
TREATMENT OF CHRONIC VENOUS INSUFFICIENCY				
(Horse chestnut seed extract is discussed in the text)				
Buckwheat	*Fagopyrum esculentum*	Rutin, D-chiro-inositol	• Chronic venous insufficiency, including decreasing leg edema, type 2 diabetes, PCOS	• Increased risk of bleeding
Butcher's broom	*Ruscus aculeatus*	Polyphenols, steroidal saponins	• Chronic venous insufficiency, hemorrhoids • Vasoconstrictor, diuretic, diaphoretic	• Nausea
Sweet clover (yellow)	*Melilotus officinalis*	Polyphenols, coumarins	• Chronic venous insufficiency, hypertension, insomnia, improvement of lymphatic drainage	• Increased risk of bleeding
TREATMENT OF CONDYLOMATA ACUMINATA AND VERRUCAE				
Bittersweet nightshade	*Solanum dulcamara*	Solanine (toxin)	• Condylomata, verrucae	• Contraindicated during pregnancy and breastfeeding
Calotropis	*Calotropis procera*	Calotropin (toxin)	• Condylomata, verrucae	• Contraindicated during pregnancy and breastfeeding
Greater celandine	*Chelidonium majus*	Coptisine, and other isoquinoline alkaloids (toxins)	• Condylomata, verrucae	• Contraindicated during pregnancy and breastfeeding
Wild oats (straw)	*Avena sativa*	Straw contains silica	• Condylomata, verrucae	• Few data
OTHER SUPPLEMENTS USED FOR DERMATOLOGIC CONDITIONS				
(Aloe vera, arnica, capsaicin, chamomile, fumaric acid esters, honey, horse chestnut seed extract, licorice root, marigold, olive oil/olive leaf extract, teas and tumeric are discussed in the text; see Ch. 153 for fruit acids; see Ch. 51 for vitamins B_3, B_6 and B_{12}, zinc, and selenium)				
Chaparral	*Larrea tridentate*	Nordihydroguaiaretic acid	• Native American remedy for actinic keratoses • Antioxidant, antibiotic	• Contact dermatitis • Renal and liver toxicity
¶Tannins coagulate cell surface proteins to form a protective barrier.				

Table 133.2 Botanicals and other biologically active substances used for dermatologic conditions (cont'd). BCC, basal cell carcinoma; PCOS, polycystic ovary syndrome.

Continued

BOTANICALS AND OTHER BIOLOGICALLY ACTIVE SUBSTANCES USED FOR DERMATOLOGIC CONDITIONS				
Common name	**Latin name and/or sources**	**Active components**	**Uses/properties**	**Known side effects**
Echinacea	*Echinacea purpurea*, *E. angustifolia*, *E. pallida*	Inulin	• Eczema, burns, herpes simplex, wound healing • Stimulates neutrophils & macrophages, antimicrobial, antihyaluronidase	• Hypersensitivity reaction; contraindicated in autoimmune diseases
False hellebore, corn lily	*Veratrum californicum* Durand	Cyclopamine	• Burns (roots), possibly BCC, psoriasis • Cyclopamine inhibits sonic hedgehog signaling pathway	• Contraindicated during pregnancy, breastfeeding
Feverfew	*Tanacetum (Chrysanthemum) parthenium*	Parthenolides vs parthenolide-free extract (PFE), melatonin	• Fevers – oral parthenolide • Anti-inflammatory – *topical* feverfew PFE (topical parthenolide produces ICD)	• GI upset, mouth ulcers, inhibits platelet aggregation; if withdrawal, headache, irritability, insomnia • Contraindicated during pregnancy
Garlic	*Allium sativum*	Allicin, allyl sulfides, ajoene, vinyldithiins	• Atherosclerosis, hypercholesterolemia, hypertriglyceridemia, occasionally verrucae, tinea pedis • Antibacterial, antiviral, antifungal	• Enhances anticoagulation by inhibiting platelet aggregation and increasing fibrinolysis • *Topically*, contact dermatitis
Gotu kola, luei gong gen	*Centella asiatica*	Triterpenoids	• Burns, scars, varicose veins, psoriatic arthritis, scleroderma • Stimulates collagen & fibronectin production; inhibits keratinocyte proliferation	• Absolute contraindication during pregnancy and breastfeeding
Jewelweed	*Impatiens biflora, I. capensis*	Tannins	• *Toxicodendron* dermatitis (conflicting data)	• Nausea, vomiting, diarrhea
Oregon grape root, barberry	*Mahonia aquifolium* (syn. *Berberis aquifolium*)	Berberine	• Psoriasis, chronic pustular eruptions • Antimicrobial, anti-inflammatory, antihistamine, antineoplastic; inhibits sebaceous gland lipogenesis	• Jaundice in infants; caution during pregnancy and breastfeeding
Pansy flower	Viola tricolor	Salicylic acid, saponins, mucilage	• Seborrheic dermatitis in infants	• Salicylate toxicity a *theoretical* risk
Persimmon leaf	*Diospyros kaki* folium	Polyphenols, catechins, vitamins C, B_1, K, β-carotene, flavonoids, tannins	• Eczema, acne • Antioxidant; inhibits tyrosinase, collagenase & elastase	
Propolis	Resinous substance collected by bees, esp. poplars & conifers	Flavonoids, phenolic acids, clerodane diterpenoid	• Aphthous ulcers, herpes simplex (comparable to topical antivirals) • Antimicrobial, anti-inflammatory, antioxidant, antitumorigenic	• Hypersensitivity reactions (see Fig 133.1); contraindicated if allergy to honey, bee products, conifers, poplars
Rosemary	*Rosmarinus officinalis*	Cineole, rosmarinic acid, carnosol	• Antibacterial, antioxidant, antineoplastic	• Contraindicated during pregnancy
Sarsaparilla	*Smilax* spp.	Saponins, sarsaponin, β-sitosterol	• Psoriasis, eczema, scleroderma; anti-inflammatory	• GI symptoms, renal dysfunction
Vitex	*Vitex agnus-castus*	Flavonoids, iridoid glycosides, terpenoids	• Acne related to menstrual cycle • Decreases stress-induced secretion of prolactin via dopaminergic effects; thought to decrease progesterone and increase estrogen levels	• Contraindicated during pregnancy, breastfeeding

Table 133.2 Botanicals and other biologically active substances used for dermatologic conditions (cont'd). GI, gastrointestinal; ICD, irritant contact dermatitis.

Allergic reactions to chamomile, a member of the Compositae (Asteraceae) family, include contact dermatitis and anaphylaxis[6,10].

Horse chestnut seed extract

Horse chestnut seed extract (HCSE) (*Aesculus hippocastanum* L.) is a remedy for chronic venous insufficiency. *Topical* HCSE can be used for varicose veins, phlebitis and hemorrhoids, while *oral* HCSE is effective for chronic venous insufficiency. Controlled studies have shown a decrease in leg volume, calf and ankle circumferences, and pain, with efficacy equivalent to that of grade II compression stockings.

HCSE contains escin (a triterpene saponin), which inhibits the release of elastase and hyaluronidase from leukocytes, thus preventing proteoglycan degradation and vascular leakage. Release of enzymes from activated leukocytes is considered one component of the pathophysiology of chronic venous insufficiency.

Natural horse chestnut seeds are poisonous and need to be processed to remove esculin, a toxic component. Side effects of esculin include hepatotoxicity, renal toxicity, anaphylaxis and possible potentiation of anticoagulation. There has been one case report of drug-induced lupus from a German HCSE-containing oral medication. Irritant contact dermatitis has also been reported[11]. Of note, drug interactions may limit the use of oral HCSE in patients receiving oral hypoglycemics, insulin, anticoagulants, aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), or other supplements that affect serum glucose levels.

Tea (white, green, oolong, black)

Tea (*Camellia sinensis*) has antioxidant, anti-inflammatory, anticarcinogenic, wound-healing, anti-aging and antimicrobial effects. Tea contains flavonoids, caffeine and fluoride. Flavonoid compounds are polyphenolic structures which serve as scavengers for reactive oxygen species[12]. Green tea polyphenols, especially (-)-epigallocatechin gallate (EGCG), also modulate gene transcription and signaling pathways. Although their antioxidant effects are commonly known, it is now thought that tea flavonoids act as anticarcinogens primarily via modulation of cell-signaling pathways.

Both topical and oral green tea can protect against inflammation, UVR-induced photodamage, chemical carcinogenesis and photocarcinogenesis. Green tea appears to have antitumor effects that include melanoma, basal cell carcinoma and squamous cell carcinoma. Because black tea is oxidized (oolong tea to a lesser extent) and this process destroys polyphenols (converting them into theaflavins and thearubigins), white and green teas have higher amounts of polyphenols than do black and oolong teas. Nonetheless, black tea has been shown to decrease UVB-induced damage and inhibit tumor proliferation.

Caffeine, present in teas, appears to have an independent protective effect against photocarcinogenesis[13].

A topical formulation of green tea, sinecatechins ointment 15% (Veregen®), is FDA-approved for treating condylomata acuminata. In addition, patients with atopic dermatitis experienced improvement when they drank oolong tea.

Tea is generally safe for adults; common side effects are caffeine-related (gastrointestinal symptoms, restlessness, insomnia). Liver damage has been reported with concentrated green tea extracts, and two cases of hypokalemia occurred in elderly individuals with extreme tea consumption (3–14 liters/day).

Licorice root

Licorice root (*Glycyrrhiza inflata*, *G. uralensis*, *G. glabra*) is used for its anti-inflammatory properties by both European and Chinese herbalists. It can be used, both topically and orally, for rosacea and eczematous dermatitis. Licorice contains flavonoids, chalcones (antioxidants), glycyrrhizin and liquiritin. Liquiritin cream has been used to treat melasma, with enhanced efficacy compared to placebo (70% vs 20%). Glycyrrhizin confers anticarcinogenic and antiviral effects, but it also inhibits 11β-hydroxysteroid dehydrogenase and can have mineralocorticoid-like effects. Excessive use of licorice root may lead to hypertension, edema, congestive heart failure and hypokalemia (i.e. syndrome of apparent mineralocorticoid excess)[6].

Fumaric acid esters

Fumarates represent breakdown products of the urea cycle, which then enter the Krebs cycle and produce energy. Good evidence exists for the use of an oral fumarate for severe psoriasis[14]; this is widely accepted in Europe. Fumaric acid esters inhibit epidermal cell turnover, lymphocyte proliferation and intercellular adhesion molecule expression, and they alter the cytokine profile in psoriatic plaques. Side effects are common and include gastrointestinal upset, cramping, diarrhea, skin flushing, lymphopenia and eosinophilia.

Olive oil and olive leaf extract

Olive oil and olive leaf extract (*Olea europaea*) can be used for hydration, for wound healing, and to stimulate blood flow[15]. The oil is used for scars, cleansing, calluses, brittle nails, onychomycosis, hair conditioning, sunburn and diaper dermatitis. Extra-virgin grade is preferred, produced by physical means only (without heat or chemicals for extraction). Both olive oil and olive leaf extract contain oleic and palmitic acids as well as a number of antioxidants, primarily secoiridoids (oleuropein), lignans, flavonoids, phenolic acids and alcohols.

Topical olive oil applied after UVB exposure decreases DNA damage (in the form of 8-hydroxy-2′-deoxyguanosine) and it protects against photocarcinogenesis in mice; this effect is not seen if the oil is applied *prior* to UVB exposure, implying photolability of the active component. Olive leaf extract administered orally decreased UVB-induced tumors in mice, presumably by inhibiting the expression of matrix metalloproteinases, VEGF and cyclooxygenase-2.

Turmeric

Turmeric (*Curcuma longa*) contains curcumin, which consists of tumerone, curcuminoids and heptanoids[15]. It is used both orally and topically to treat wounds, ulcers, dermatitis and pruritus. In general, turmeric is administered orally for radiation dermatitis and psoriasis. Curcumin has anti-inflammatory, antioxidant, anticarcinogenic and antimicrobial properties. It inhibits lipoxygenase and cyclooxygenase, thereby reducing levels of leukotrienes, thromboxanes and prostaglandins. Turmeric also reduces expression of interleukin-12, NF-κB and TNF-α as well as impairing induction of a Th-1 immune response. In addition, curcumin inhibits collagenase, elastase and hyaluronidase. The most common side effect is gastrointestinal upset; curcumin is contraindicated in patients with gallbladder disease.

Escharotics

Escharotics include zinc chloride, bloodroot (*Sanguinaria canadensis*) and goldenseal (*Hydrastis canadensis*)[16]. These agents are caustic and can produce necrotic crusts, pain and even scarring. In the past, escharotics were used topically to treat skin cancers, but they have since been replaced by more efficacious methods. Nowadays, patients may erroneously use them for this purpose.

Prebiotics and probiotics

Prebiotics are non-digestible sugars that encourage the growth of certain "good" types of bacteria within the intestine. Probiotics are live microorganisms that are ingested in an attempt to alter the gastrointestinal flora into a beneficial mix. Probiotics can be in tablets or food, especially yogurt, fermented and unfermented milk, miso, tempeh and soy beverages. The most commonly used probiotics are *Lactobacillus*, *Bifidobacterium* and *Saccharomyces boulardii*.

Patients with eczema have been shown to have different gastrointestinal flora (e.g. a reduced proportion of *Bifidobacteria* spp. in the feces of infants with eczema) and are thought to have more inflammation and permeability of their intestines. Probiotics decrease intestinal inflammation and permeability, and perhaps this may alter antigen presentation in a way that is beneficial for eczema. However, in trials, probiotics have led to a modest, if any, improvement in eczema, but additional subspecies have yet to be studied. Side effects usually consist of mild gastrointestinal symptoms, but there have been case reports of probiotic sepsis[17].

Diet-based therapies

Dietary modifications have been used to treat atopic dermatitis. Certain foods, thought to be allergenic, are excluded from the diet. Most commonly, the diet involves elimination of common allergens such as cow's milk and/or eggs, or elimination of a food associated with a proven food allergy. More extreme diets include the "few foods diet", in which only a few foods are permitted, and the "elemental diet", which is an all-liquid diet containing vitamins, minerals, amino acids, carbohydrates and fat (e.g. triglycerides); these diets can cause nutritional deficiencies. Kwashiorkor has even been observed in infants on the rice milk diet. Although several randomized, controlled trials support the use of an egg-free diet to treat atopic dermatitis in infants with IgE antibodies to eggs, there does not seem to be any benefit in restricting foods for patients without a known food allergy[18]. Exacerbation of acne by high glycemic load diets has been reported by several groups, and increased dairy ingestion appears to be weakly associated with acne.

Side Effects

Herbs are composed of organic and inorganic components that are biologically active, and as with any medication, may have serious side effects[19] and/or interact with other medications. Multiple herbal and dietary supplements can affect coagulation, as both procoagulants and anticoagulants (Table 133.3). Because patients often do not report use of CAM (up to 70%), it is recommended that preoperative assessments include specific questioning regarding dietary supplements (see Ch. 151).

A common misperception exists that herbs are "natural" and "safer" than prescription medications. Hematologic, nephrotoxic, cardiotoxic and hepatotoxic effects have been observed, as well as contact allergy (Fig. 133.1), phototoxicity (Fig. 133.2) and hypersensitivity reactions, including anaphylaxis, Stevens–Johnson syndrome and toxic epidermal necrolysis. Additionally, in most countries, herbal medicine is not subject to the same regulation as prescription medications. Some herbal supplements have been found to be contaminated with metals, prescription drugs (e.g. corticosteroids, NSAIDs), microorganisms and other substances.

Several challenges stem from the use of plants as therapeutics. These considerations include differences in: climate and soil; cultivars and species; growing, harvesting and storage conditions; methods of extraction; chemical standardization of products; and bioavailability of formulations[1].

TRADITIONAL CHINESE MEDICINE

Traditional Chinese medicine (TCM) is a system of healing that originated in China prior to 2000 BC. Unique versions then developed in Japan, Korea and other countries. TCM encompasses a myriad of treatment modalities, including herbal medicine, acupuncture, massage, exercise, and dietary and lifestyle modifications (Table 133.4). Herbal medicine represents approximately two-thirds of the TCM armamentarium, and acupuncture one-third.

TCM takes a holistic attitude towards health. For health to occur, balance and harmony must be achieved between two opposing and complementary forces, Yin and Yang. Central to Yin–Yang theory is the

DIETARY SUPPLEMENTS AND EFFECTS ON COAGULATION		
MOST COMMONLY USED DIETARY SUPPLEMENTS (US)		
Name	**Common uses**	**Effects on coagulation**
Fish oil, omega-3 fatty acids (eicosapentaenoic acid, docosahexaenoic acid)	Cardiovascular disease, hypertriglyceridemia, see Table 133.2	Inhibits platelet aggregation
Glucosamine sulfate	Osteoarthritis, chronic venous insufficiency	Increases INR, potentiates warfarin
Flaxseed, flaxseed oil	Constipation, menopausal symptoms (seed), arthritis, hypercholesterolemia	Theoretically, may potentiate anticoagulation
Ginseng	Mental and physical performance, see Table 133.2	Inhibits platelet aggregation, contains coumarins, decreases anticoagulant effect of warfarin (by inducing P450)
Ginkgo biloba	Dementia, cardiovascular disease, see Table 133.2	Inhibits platelet aggregation (blocks platelet-activating factor), decreases plasma viscosity
Chondroitin sulfate	Osteoarthritis	Antithrombotic
Garlic	Hypercholesterolemia, atherosclerosis, hypertension	Increases clotting time, inhibits platelet aggregation, increases fibrinolysis, decreases plasma viscosity
Coenzyme Q10	Hypertension, age-related macular degeneration, atherosclerosis, cardiomyopathy; slowing the progression of Parkinson's disease, dementia	Possible competitive inhibitor of vitamin K-dependent clotting factors; paradoxically, decreases the anticoagulant effect of warfarin
Fiber or psyllium	Constipation, diarrhea, irritable bowel syndrome, diverticulosis, hypercholesterolemia, colorectal carcinoma prevention	Psyllium may reduce absorption of warfarin
Green tea	Prevention of cardiovascular disease, cancer, kidney stones, see Table 133.2	Inhibits platelet aggregation, but contains vitamin K and decreases warfarin efficacy in large quantities
Cranberry (pills, gelcaps)	Urinary tract infections, *Helicobacter pylori* infection	May increase INR in patients taking warfarin
Saw palmetto	Benign prostatic hypertrophy	May increase effects of anticoagulants, antiplatelet medications, and NSAIDs
Soy or other isoflavones	Hypercholesterolemia, cancer prevention	May decrease efficacy of warfarin slightly
Melatonin	Jet lag, insomnia	Probably minimal; may increase efficacy of warfarin
Vitamin C	Prevention of URIs, urinary tract infections, cancer	Increases effects of aspirin, but conversely, very high doses may lower prothrombin time
Vitamin E	Antioxidant	Inhibits platelet adhesion and aggregation
Magnesium	Hypertension, cardiovascular disease, diabetes	Inhibits platelet adhesion and aggregation
ADDITIONAL SUPPLEMENTS		
Name	**Medicinal (other) uses**	**Effects on coagulation**
Alfalfa	Atherosclerosis, diabetes, hypercholesterolemia	Contains coumarins and vitamin K
Bilberry	Diabetes, retinopathy, diarrhea	Contains coumarins
Capsaicin	Dyspepsia, arthritis, postherpetic neuralgia	Contains coumarins, inhibits platelet aggregation
Celery	Arthritis, urinary tract infections	Contains coumarins
Chamomile	Dyspepsia, anxiety, dermatitis	Contains coumarins, inhibits P450
Dan shen	Cardiovascular disease, thrombosis	Inhibits platelet aggregation, antithrombin III-like activity
Dang gui (dong quai)	Menopausal symptoms, menstrual disorders	Contains coumarins
Fenugreek	Dyspepsia, diabetes, stimulation of breastmilk production (cooking)	None known, but contains coumarins
Feverfew	Migraines, arthritis, fever	Inhibits platelet aggregation
Ginger	Nausea, osteoarthritis, rheumatoid arthritis (cooking)	Inhibits platelet function, decreases platelet thromboxane production, vitamin K antagonist
Goldenseal	URIs, inflammation	Contains coumarins and berberine, a heparin antagonist
Horse chestnut seed extract	Chronic venous insufficiency, hemorrhoids	If raw or not processed well, contains esculin, a coumarin
Horseradish	Infection, inflammation	Contains coumarins
Huang qi	Immune system stimulant	Inhibits platelet aggregation and increases fibrinolysis (*in vitro*)
Kava kava	Anxiety, stress	Decreases platelet aggregation, can cause severe hepatotoxicity
Licorice	Cough, inflammation	Contains coumarins
Passion flower	Anxiety, insomnia	Contains coumarins
Red clover	Respiratory "problems", menopausal symptoms, psoriasis	Contains coumarins
St. John's wort	Depression	Induces hepatic cytochrome P450 and increases metabolism of warfarin

Table 133.3 Dietary supplements and effects on coagulation. List of most commonly used dietary supplements based upon data from the National Center for Health Statistics. Most commonly used supplements for which no effects on coagulation have been reported to date include echinacea, silymarin and lutein; minimal data are available for grape seed extract and methysulfonylmethane. **Sweet clover and buckwheat are reviewed in Table 133.2.** INR, international normalized ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; URIs, upper respiratory tract infections. *Adapted with permission from Collins SC, Dufresne RG. Dietary supplements in the setting of Mohs surgery. Dermatol Surg. 2002;28:447–52.*

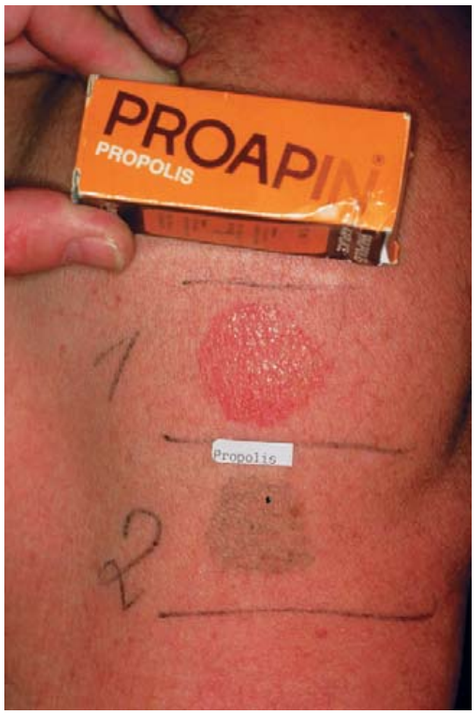


Fig. 133.1 Contact allergy to propolis. This is a frequently used topical agent in central Europe. *Courtesy, Josef Smolle, MD.*

TRADITIONAL CHINESE MEDICINE (TCM) TREATMENT MODALITIES	
Modality	**Delivery methods/related modalities**
Herbal medicine	Decoctions – water is used to simmer herbs, then the decanted fluid is taken in divided doses
	Topical poultices
	Essential oils
	Lotions, creams, ointments
	Tablets, capsules
Acupuncture	Needles – stainless steel (most common), gold, silver
	Moxibustion
	Cupping, coining, rubbing
	Acupressure
	Electroacupuncture
	Auricular acupuncture
	Laser acupuncture
	Medicamentous acupuncture
	Magnet therapy
Therapeutic exercise	Tai ji (tai chi), qi gong (chi gong)
Massage therapy	Tui na, acupressure
Dietary modification	
Meditation	

Table 133.4 Traditional Chinese medicine (TCM) treatment modalities.

Fig. 133.2 Phototoxic reaction due to herbal tea. *Courtesy, Josef Smolle, MD.*

concept that no single part can be understood except in relation to the whole. Yin–Yang theory takes a dialectical view of health, which differs fundamentally from conventional medicine's reductionist view of disease. Normal flow patterns of Qi, or life-force (which is Yang), and Blood (which is Yin) are essential for health, and disruptions of flow cause pain and disease. Regulation of flow is the goal of therapy, and acupuncture, moxibustion and massage are thought to correct Qi/Blood flow and thus health.

TCM has been employed for most dermatologic conditions. While a complete discussion is beyond the scope of this chapter, the next section focuses on TCM treatments for atopic dermatitis and psoriasis.

TCM – Herbal Medicine

Atopic dermatitis

A Cochrane systematic review analyzed a number of studies involving the use of Chinese herbal preparations for atopic dermatitis, including three double-blind, randomized, controlled, crossover trials, all investigating a standardized mixture of 10 raw herbs (see below)[20]. In two of these trials, greater improvement was observed with the herb decoction (extraction of water-soluble components via boiling) than with placebo. For both adults and children, the 10-herb decoction led to greater reductions in erythema, surface area of involvement, and pruritus, as well as improved sleep quality. A third trial failed to demonstrate any difference between the 10-herb decoction and placebo. Hematologic cell counts, renal function, and liver function studies were performed in all three studies, and no changes were observed.

One-year follow-up observational studies were performed with both adult and pediatric patients who chose to continue the herbal decoction. There was a significant benefit as compared with patients who chose not to continue. During this 1-year study, two of 37 children experienced asymptomatic elevations in serum levels of aspartate aminotransferase which normalized after discontinuing the herbs; no adult patient experienced laboratory abnormalities.

By focusing on the 10 herbs present in the decoction (*Ledebouriella seseloides*, *Potentilla chinensis*, *Anebia clematidis*, *Rehmannia glutinosa*, *Paeonia lactiflora*, *Lophatherum gracile*, *Dictamnus dasycarpus*, *Tribulus terrestris*, *Glycyrrhiza uralensis* and *Schizonepeta tenuifolia*), multiple studies have sought to characterize possible mechanisms of action. For example, CD23, a low-affinity IgE receptor found on monocytes/macrophages in the peripheral blood and skin, is overexpressed in patients with atopic dermatitis, and these herbs can lead to a dose-dependent reduction in CD23 expression, and they may also reduce HLA-DR expression. Additionally, these herbs have antioxidant properties.

For pruritus associated with atopic dermatitis, two Japanese remedies (Sho-seiryu-to, Moku-boi-to) have antihistamine effects equal to that of diphenhydramine.

Psoriasis

TCM herbs with anti-inflammatory and immunosuppressive effects are used to treat psoriasis, including *Indigo naturalis*, *Tripterygium wilfordii* Hook, *Tripterygium hypoglaucum* Hutch and *Camptotheca acuminata*

Decne. A randomized, placebo-controlled trial of *Tripterygium wilfordii* Hook for rheumatoid arthritis showed a significant dose-dependent immunosuppressive response[21], and when compared to sulfasalazine, the herb extract was superior[22]. Side effects include gastrointestinal symptoms, myelosuppression and elevated liver enzymes.

In a study of 801 psoriatic patients, over half responded to a decoction of five herbs (*Rhizoma sparganii*, *Rhizoma zedoariae*, *Herba serissae*, *Resnia boswelliae* and *Myrrha*)[23]. Herbs that contain furocoumarins, such as *Radix angelicae dahuricae* and *Radix angelicae pubescentis*, can be used in conjunction with UVA phototherapy for a psoralen-like effect. Psoriasis clearance rates were similar for *Radix angelicae dahuricae* plus UVA versus PUVA (with 8-MOP), with fewer side effects.

Side effects

As with other botanicals, TCM herbs have biologically active components, and may have serious side effects. TCM should be administered under the supervision of a licensed practitioner.

TCM – Acupuncture

Acupuncture is considered less useful than herbal medicine for dermatologic conditions. There are case reports of using acupuncture for atopic dermatitis, neurodermatitis, lichen planus, psoriasis, alopecia areata, verrucae, herpes viral infection, postherpetic neuralgia, and urticaria[24]. One controlled trial of acupuncture for psoriasis failed to demonstrate any efficacy over placebo. More support exists for the use of acupuncture for symptoms associated with dermatologic conditions, e.g. pain, pruritus, stress, anxiety and depression.

Mechanism of action

Proposed mechanisms of action for acupuncture analgesia include: gate control, diffuse noxious inhibitory control, and stimulating release of neuroactive substances including endorphins and enkephalins[25]. By altering the release of neurotransmitters, acupuncture may exert anti-inflammatory and immunomodulatory effects. In addition, it has the potential for balancing the sympathetic (Yang) and parasympathetic (Yin) nervous systems. Acupuncture has also been shown to increase adrenal production of corticosterone and cortisol as well as production of β-endorphin and corticotropin by the pituitary.

The proposed mechanism of action of acupuncture for depression and anxiety incorporates the monoamine hypothesis for affective disorders. Both cerebral serotonin release and intracephalic blood flow are increased by specific acupuncture points.

Side effects

Fatigue is the most common side effect associated with acupuncture (<10% of patients), with a small minority of patients (<1%) experiencing cutaneous side effects such as pruritus, petechiae, ecchymoses, or subcutaneous hematomas. Infection and pneumothorax have also been reported. Infectious risks are minimized by using single-use needles, and the risk of pneumothorax is minimized by using traditional angles of insertion. Localized argyria (rare) can result from using subcutaneous permanent needles made of silver instead of stainless steel.

TCM – Moxibustion, Cupping and Other Treatment Modalities

Moxibustion is the practice of burning dried moxa (*Artemisia vulgaris*), placed in small cone-shaped piles, over acupuncture points. Moxibustion may be either direct, in which the moxa-cones are allowed to burn completely down to the skin surface, or indirect, in which the cones are removed prior to the burning fibers touching the skin. Side effects include first- and second-degree burns.

Cupping is another method used to stimulate acupuncture points. It is accomplished by igniting alcohol-soaked cotton, placing the burning cotton in a jar, and placing the jar on the skin. A vacuum is created, and circular areas of erythema and ecchymosis may result (Fig. 133.3).

Skin scraping, also known as coining or spooning, is commonly practiced in Southeast Asia to improve circulation. A tool is used to rub skin that has been treated with oil; symmetric, linear ecchymoses may result (Fig. 133.4).

Fig. 133.3 Cupping. Well-demarcated circular areas that are pink-purple and yellow in color and contain petechiae. *Courtesy, Donald J Baker, MD.*

Fig. 133.4 Linear ecchymoses on the back due to coining.

Any Asian patient with cutaneous lesions in patterns suggestive of external causes should be asked about traditional medicine before accusations of abuse arise. Ethiopians have similar practices of moxibustion and cupping.

HOMEOPATHY

Homeopathy is a system of healing founded by Samuel Hahnemann (1755–1843), a German physician. He hypothesized that one can select treatments based on the "principle of similars", which states that symptoms may be cured by giving a therapy that induces the same symptoms. A homeopathic therapy provides the additional stimulus needed for the body to recognize and fight an illness. Hahnemann studied remedies by giving repeated doses to healthy volunteers and then observing their physical symptoms, emotions and mental states[26].

Homeopathic remedies are given in dilutions; a second assumption of homeopathy, the "principle of infinitesimals", hypothesizes that the higher the dilution, the greater the effect. Some remedies are so highly diluted (one part in 10^{24} or higher) that not a single molecule of the substance remains, according to the laws of chemistry and Avogadro's number (6.023×10^{23}). In homeopathy, however, it is believed that the dilutant, usually alcohol and water, or sugar pellets, carries an "essence" of the original substance, which can be used to treat disease. This "essence" is thought to be an imprint of the electromagnetic frequency of the original substance, which then acts as an "energetic vaccine" to stimulate the body to heal itself.

Dermatologic Applications

Skin disease is one of the most common reasons why patients seek homeopathic treatment. At a British homeopathic hospital, eczema and psoriasis accounted for 13% of referrals[27]. Homeopathy is also used to treat seborrheic dermatitis, urticaria, acne, rosacea, alopecia areata, radiation-induced pruritus, verrucae and other infections. Unlike herbal remedies, the manufacture and sale of homeopathic remedies are regulated by the FDA, although the FDA does not endorse the use of homeopathy.

Mechanism of Action and Clinical Evidence

In general, evidence to support the use of homeopathy for dermatologic conditions is limited to anecdotal case reports. A few studies have tried to demonstrate the "essence" of water dilutant. A study published in *Nature* demonstrated degranulation of human basophils using very dilute antiserum against IgE[28], but this has not been replicated.

Meta-analyses of the literature have found conflicting evidence regarding the efficacy of homeopathy. Randomized, controlled trials of homeopathic treatment of warts have not found any efficacy beyond that of placebo[26].

Side Effects

Because homeopathic remedies are usually highly diluted, side effects, e.g. headache, fatigue, myalgia, arthralgia, diarrhea, are rare. Contact dermatitis has been reported[27]. Homeopathy should be used under the supervision of a licensed practitioner.

AROMATHERAPY

Aromatherapy is the therapeutic use of aromatic essential oils. Considered a subset of botanical medicine, aromatherapy may use any plant part, including leaves, stems, flowers, fruits, roots and wood resins. Essential oils are obtained via solvent extraction, steam distillation, cold-pressing or other methods.

The term "aromathérapie" was coined in 1927 by René-Maurice Gattefossé, a French chemist, whose interest began after a personal incident. After burning his hand in the laboratory, Gattefossé dipped it into a nearby vat of lavender oil. His hand healed rapidly, and he subsequently studied essential oils at military hospitals during World War I. Today, France is a leader in aromatherapy research.

Aromatherapy is used to treat a wide range of physical, mental and emotional states. Oils may be used externally or internally. External methods are more common and include inhalation, massage, compresses, gels/creams/pastes, sprays and baths. Internal routes include oral, otic, intrarectal and intravaginal[29].

Dermatologic Applications

Aromatherapy may be used directly to treat dermatologic conditions, or indirectly to treat the anxiety or other psychiatric symptoms associated with psychocutaneous disorders (Table 133.5). Indications for aromatherapy include: wound healing (burns, ulcers), acne, alopecia areata, pruritus, xerosis, psoriasis, contact dermatitis, radiation dermatitis, herpes viral infections, scarring and analgesia. Treatments often employ multiple oils, e.g. for psoriasis, lemon balm is used for associated xerosis and pruritus, chamomile for stress reduction, and lavender to promote relaxation[29].

Mechanism of Action and Clinical Evidence

Essential oils are mixtures of organic compounds including acids, alcohols, aldehydes, coumarins, esters, ethers, ketones, lactones, oxides, phenols and terpenes. Oils high in ketones are used for wound healing, while acids, aldehydes and alcohols have antimicrobial and immunostimulatory properties. Phenols, ethers and terpenes are antimicrobial, with terpenes also having antihistamine and cortisone-like effects. Of note, essential oils that are inhaled or applied topically have been shown to enter the bloodstream.

Because of its antimicrobial properties, tea tree oil (*Melaleuca alternifolia*) is one of the most commonly used aromatherapies for skin disorders. A single-blind trial in acne patients found similar efficacies for tea tree oil 5% gel and benzoyl peroxide 5% lotion; tea tree oil had a slower onset of action but fewer side effects. The efficacy profile of tea tree oil 100% for onychomycosis is similar to that of clotrimazole 1% solution. For tinea pedis, tea tree oil 10% cream helps ameliorate symptoms, but is no more effective than placebo in achieving mycologic cure. As tea tree oil contains terpinenes, it can cause allergic contact dermatitis[29].

In a randomized, controlled, double-blind trial in alopecia areata, aromatherapy (thyme, rosemary, lavender, cedarwood) led to significantly greater improvement than did the placebo (44% vs 15%)[30].

AROMATHERAPY: ESSENTIAL OILS USEFUL IN DERMATOLOGICAL CONDITIONS

Latin name	Common name	Actions/Indications
Boswellia carterii	Frankincense	Immunostimulant; wound healing
Citrus aurantium var. *amara*	Petitgrain	Infected acne
Citrus bergamia	Bergamot	Pruritus, psoriasis, HSV-1 infection, wound disinfection
Citrus sinensis	Sweet orange	Wound disinfection
Cymbopogon citratus	Lemongrass	Anti-inflammatory
Eucalyptus citriodora	Eucalyptus (lemon scented)	Anti-inflammatory, analgesic; herpes zoster, candidiasis
Eucalyptus radiata	Australian eucalyptus	Acne
Jasminum officinalis	Jasmine	Antiseptic, anti-inflammatory
Juniperus communis	Juniper berry	Anti-inflammatory, analgesic; skin "problems"
Juniperus communis	Juniper twig	Acne
Lavandula angustifolia	True lavender	Burns, wound healing, analgesic
Lavandula latifolia	Spike lavender (French)	First-degree burns, neuralgia
Lavandula stoechas	Stoechas lavender	Dermatitis
Melaleuca alternifolia	Tea tree	Antifungal, antiviral, antibacterial; acne, verrucae, radiation burn prevention
Melaleuca leucadendra	Cajeput	Genital herpes viral infection, radiation burn prevention
Melaleuca quinquenervia/ viridiflora	Nialouli	Dermatitis
Melissa officinalis	Lemon balm	Viral skin infections
Mentha x piperita	Peppermint	Dermatitis, herpes viral infections
Ocimum basilicum	Basil	Dermatitis
Pelargonium x asperum	Geranium	Acne, impetiginized dermatitis
Pinus sylvestrus	Scots pine	Allergy, inflammation
Piper nigrum	Black pepper	Analgesic
Pogostemon cablin	Patchouli	Anti-inflammatory, antiseptic, antimicrobial; acne, seborrhea, dermatitis (including weeping forms), scars, tinea pedis
Ravensara aromatica	Ravensara	Herpes zoster
Rosa damascena	Rose	Dermatitis
Rosmarinus officinalis	Rosemary (verbenone) CT verbenone	Antispasmodic
Satureja montana	Winter savory	Oil used for its antibacterial, antiparasitic, antiviral and antifungal properties; psoriasis, analgesia
Styrax benzoe	Benzoin	Skin infections, acne, dermatitis, psoriasis, ulcers

Table 133.5 Aromatherapy: essential oils useful in dermatological conditions. HSV, herpes simplex virus. *Reproduced with permission from Stevenson CJ. Aromatherapy in dermatology. Clin Dermatol. 1998;16:689–94.*

Lemon balm (*Melissa officinalis*) may be used for herpes labialis; it resulted in a decrease in lesion size and healing time in a double-blind, randomized, controlled trial. The active components are tannins, polyphenols, terpenes and sesquiterpenes, including citronella, citral-A and citral-B. Lastly, a number of essential oils, including lavender, have anxiolytic and sedative properties and may be useful for dermatologic disorders worsened by stress[31].

Additional potential uses of essential oils in dermatology include as antitumor agents, enhancers of transdermal drug delivery, and promoters of cutaneous blood flow.

Side Effects

Essential oils have biologically active components and may be toxic. For example, ketones can have neurotoxic effects, especially in patients with seizure disorders, pregnant women and children. Some compounds are potentially carcinogenic, including safrole in sassafras oil and β-asarone in calamus oil[29]. Cutaneous side effects include contact dermatitis and phytophotodermatitis.

MIND–BODY MEDICINE

Mind–body medicine encompasses a wide range of therapeutic interventions which emphasize the complex interactions involving the brain, mind, behavior, spirit and body. Mind–body interventions include meditation, relaxation, hypnosis, imagery, yoga, tai chi, qi gong, biofeedback, cognitive behavioral therapies, group therapy, breathing techniques, autogenic training, dance therapy, music therapy, spirituality and prayer (see Table 133.1). Excluding prayer, approximately 30% of the US population has used mind–body therapy, most commonly meditation, guided imagery and yoga. Prayer was used by more than 50%[1].

Western medicine acknowledges mind–body relationships such as the placebo effect, which accounts for 35% of the therapeutic response to any treatment[1]. However, the mental and spiritual aspects of health are challenging to study, and scientific and technologic advances have led to an emphasis on the physical aspects of medicine and a separation from the less tangible facets of healing.

Dermatologic Applications

Patients with psychocutaneous disorders are good candidates for mind–body interventions, including those with skin manifestations of primary psychiatric diagnoses (e.g. obsessive–compulsive disorder, body dysmorphic disorder); dual psychiatric/dermatologic diagnoses (e.g. neurotic excoriations, trichotillomania); and dermatologic conditions that can be worsened by emotional factors (e.g. acne, psoriasis, atopic dermatitis) (Table 133.6)[32].

Good evidence exists for the use of hypnosis for atopic dermatitis, alopecia areata, verrucae and psoriasis, as well as for relaxation during procedures. Patients who have higher levels of hypnotic susceptibility seem to benefit more. There are scattered case reports of its use in urticaria, hyperhidrosis, acne excoriée and vitiligo. For verrucae, hypnosis has response rates of 27% to 55%, and children respond better than adults[33]. In a study of 21 patients with severe alopecia areata refractory to standard therapy (nine with totalis or universalis), 12 (57%) showed hair regrowth of 75% to 100% after three to eight sessions of hypnotherapy; five patients had subsequent relapse.

There is preliminary evidence supporting the use of group therapy, biofeedback, psychotherapy and massage therapy for atopic dermatitis[34]. Controlled trials using cognitive behavioral therapy, meditation, hypnosis and/or stress-reduction audiotapes have shown promising results for psoriasis[35]. One study of trichotillomania found cognitive behavioral therapy to be better than fluoxetine, while a controlled trial of massage therapy for children with atopic dermatitis (as an adjunct following medication application) observed a greater decrease in redness, lichenification, excoriation, pruritus and anxiety levels in the massage therapy group (compared to medication alone). There are case reports of using biofeedback (e.g. for rosacea, acne, urticaria, Raynaud's phenomenon), guided imagery/relaxation therapy (e.g. acne excoriée, psoriasis, hyperhidrosis, neurotic excoriations), and cognitive behavioral therapy (e.g. acne excoriée, prurigo nodularis, onychotillomania, trichotillomania, body dysmorphic disorder)[36].

Mind–body interventions have been found to be useful in treating problems indirectly associated with dermatologic conditions. Nociception is readily altered by meditation and behavioral techniques, and in dermatologic surgery, there is the potential for improved wound healing and pain reduction.

DERMATOLOGICAL CONDITIONS ASSOCIATED WITH PSYCHO-EMOTIONAL FACTORS

DERMATOLOGICAL CONDITIONS WITH PSYCO-EMOTIONAL COMPONENT	
• Hyperhidrosis	• Telogen effluvium
• Dyshidrotic eczema	• Alopecia areata
• Pruritus sine materia	• Median nail dystrophy
• Urticaria	• Acne vulgaris
• Lichen simplex chronicus	• Rosacea
• Atopic dermatitis	• Perioral dermatitis
• Nummular dermatitis	• Warts
• Psoriasis	• Herpes simplex
• Seborrheic dermatitis	• Vitiligo
• Lichen planus	• Contact dermatitis
PSYCHOCUTANEOUS DISORDERS	
• Dermatitis artefacta	• Dermatologic phobias
• Neurotic excoriations	Venereophobia
• Trichotillomania	Oncophobia
• Onychotillomania	Dysmorphophobia (dermatologic non-disease)
• Delusions of parasitosis (Ekbom's syndrome)	Bromidrosiphobia
• Body dysmorphic syndrome	• Glossodynia/glossopyrosis*
• Hypochondriasis	• Vulvodynia/vulvopyrosis*

*Following exclusion of underlying medical etiologies.

Table 133.6 Dermatological conditions associated with psycho-emotional factors. *Adapted with permission from Panconesi E, Gallassi F, Sarti MG, Bellini MA. Biofeedback, cognitive-behavioral methods, hypnosis: 'alternative psychotherapy'? Clin Dermatol. 1998;15:709–10.*

Mechanism of Action and Clinical Evidence

Mind–body medicine is an active area of research. The hypothalamic–pituitary–adrenal (HPA) axis and autonomic nervous system (ANS) affect immunity and endocrine function via their regulation of glucocorticoid and catecholamine production, respectively. Therefore, psychological and behavioral interventions that affect the HPA and ANS activity have the potential to treat disease. Stress or different mood changes can slow wound healing, in part by altering the expression of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) and by activating the HPA axis[1].

The skin itself produces enough hormones, neurotransmitters, neuropeptides and functional receptors to form complete, cutaneous neuroendocrine axes. These include cutaneous equivalents of: (1) the HPA axis; (2) the cholinergic system; (3) the catecholaminergic system; (4) the serotoninergic/melatoninergic system; (5) steroidogenic pathways; and (6) pituitary–thyroid axis elements. These local neuroendocrine systems are used by the skin to preserve homeostasis[37]. However, most of the research has focused on interactions just within the skin, rather than on interactions between the skin, central nervous system, and body.

One model is the "neuro-immuno-cutaneous-endocrine (NICE)" network, in which four physiologic systems interact via a complex amalgamation of neurotrophic substances, cytokines, hormones including glucocorticoids, and other molecules. For example, physical stimulation of the skin induces the release of neuropeptides, which can influence the CNS as well as having local effects. In particular, α-melanocyte stimulating hormone (α-MSH), which is produced by the skin and the pituitary gland, may play a key role. α-MSH inhibits experimentally induced cutaneous inflammation[38]. In addition, fibroblasts and melanocytes, but not keratinocytes, respond to corticotropin-releasing hormone in a manner analogous to the HPA axis, by releasing corticosterone (fibroblasts and melanocytes) and cortisol (melanocytes). Through this network, the mind can exert a myriad of physiologic effects on nociception, wound healing, immunity and other aspects of health.

Side Effects

Mind–body interventions have minimal side effects because physical agents are not used. Potential side effects include autonomic responses such as lightheadedness, nausea, vomiting or syncope.

CONCLUSION

Globally, CAM is increasing in popularity for all diseases, including many dermatologic disorders. It is important for dermatologists to recognize and acknowledge the use of CAM in their patients, both to better empathize with their patients as well as to recognize potential side effects. There are a few studies supporting the role of CAM modalities in dermatology, including herbal medicine, traditional Chinese medicine, homeopathy, aromatherapy and mind–body medicine. However, many of these studies are case series, or animal or *in vitro* studies, and there is a need for additional and better-designed studies.

REFERENCES

1. National Center for Complementary and Alternative Medicine. www.nccam.nih.gov. 2008.
2. The World Health Organization. www.who.int. 2008.
3. Barnes PM, Bloom B, Nahin R. Complementary and alternative medicine use among adults and children: United States, 2007. CDC National Health Statistics Report. 2008:12.
4. Smith N, Shin DB, Brauer JA, et al. Use of complementary and alternative medicine among adults with skin disease: results from a national survey. J Am Acad Dermatol. 2009;60:419–25.
5. Rohdewald P. A review of the French maritime pine bark extract (Pycnogenol), a herbal medication with a diverse clinical pharmacology. Int J Clin Pharmacol Ther. 2002; 40:158–68.
6. Bedi MK, Shenefelt PD. Herbal therapy in dermatology. Arch Dermatol. 2002;138:232–42.
7. Al-Waili NS. Topical honey application vs. acyclovir for the treatment of recurrent herpes simplex lesions. Med Sci Monit. 2004;10:MT94–8.
8. Jull AB, Rodgers A, Walker N. Honey as topical treatment for wounds. Cochrane Database Syst Rev. 2008;(4): CD005083.
9. Kassab S, Cummings M, Berkovitz S, et al. Homeopathic medicines for adverse effects of cancer treatments. Cochrane Database Syst Rev. 2009;(2):CD004845.
10. Brown DJ, Dattner AM. Phytotherapeutic approaches to common dermatologic conditions. Arch Dermatol. 2002; 134:1401–4.
11. Pittler MH, Ernst E. Horse chestnut seed extract for chronic venous insufficiency. Cochrane Database Syst Rev. 2006;(1):CD003230.
12. Hsu S. Green tea and the skin. J Am Acad Dermatol. 2005;52:1049–59.
13. Koo SW, Hirakawa S, Fujii S, et al. Protection from photodamage by topical application of caffeine after ultraviolet irradiation. Br J Dermatol. 2007;156: 957–64.
14. Griffiths CEM, Clark CM, Chalmers RJG, et al. A systematic review of treatments for severe psoriasis. Health Technol Assess. 2000;4:1–125.
15. Baumann L, Woolery-Lloyd H, Friedman A. "Natural" ingredients in cosmetic dermatology. J Drugs Dermatol. 2009;8(6 Suppl):S5–9.
16. Jellinek N, Maloney ME. Escharotic and other botanical agents for the treatment of skin cancer: review. J Am Acad Dermatol. 2005;53:487–95.
17. Boyle RJ, Bath-Hextall FJ, Leonardi-Bee J, et al. Probiotics for treating eczema. Cochrane Database Syst Rev. 2008; (4):CD006135.
18. Bath-Hextall FJ, Delamere FM, Williams HC. Dietary exclusions for established atopic eczema. Cochrane Database Syst Rev. 2008;(1):CD005203.
19. Lim A, Cranswick N, South M. Adverse events associated with the use of complementary and alternative medicine in children. Arch Dis Child. 2011;96:297–300.
20. Zhang W, Leonard T, Bath-Hextall F, et al. Chinese herbal medicine for atopic eczema. Cochrane Database Syst Rev. 2004;(4):CD002291.
21. Tao X, Younger J, Fan FZ, et al. Benefit of an extract of *Tripterygium wilfordii* Hook F in patients with rheumatoid arthritis: a double-blind, placebo-controlled study. Arthritis Rheum. 2002;46:1735–43.
22. Goldback-Mansky R, Wilson M, Fleischmann R, et al. Comparison of *Tripterygium wilfordii* Hook F versus sulfasalazine in the treatment of rheumatoid arthritis. A randomized trial. Ann Intern Med. 2009;151:229–40.
23. Koo J, Desai R. Traditional Chinese medicine in dermatology. Dermatol Ther. 2003;16:98–105.
24. Chen CJ, Yu HS. Acupuncture, electrostimulation, and reflex therapy in dermatology. Dermatol Ther. 2003;16: 87–92.
25. Geng A, Geng J. Acupuncture Primer. http://www.geocities.com/koaika. 2006.
26. Smolle J. Homeopathy in dermatology. Dermatol Ther. 2003;16:93–7.
27. Thompson E, Barron S, Spence D. A preliminary audit investigating remedy reactions including adverse events in routine homeopathic practice. Homeopathy. 2004;93:203–9.
28. Davenas E, Beauvais F, Amara J, et al. Human basophil degranulation triggered by very dilute antiserum against IgE. Nature. 1988;333: 816–18.
29. Stevensen CJ. Aromatherapy in dermatology. Clin Dermatol. 1998;16:689–94.
30. Hay IC, Jamieson M, Ormerod AD. Randomized trial of aromatherapy: successful treatment for alopecia areata. Arch Dermatol. 1998;134: 1349–52.
31. Perry N, Perry E. Aromatherapy in the management of psychiatric disorders. CNS Drugs. 2006;20: 257–80.
32. Fried RG, Hussain SH. Nonpharmacologic management of common skin and psychocutaneous disorders. Dermatol Ther. 2008;21:60–8.
33. Bellini MA. Hypnosis in dermatology. Clin Dermatol. 1998;16:725–6.
34. Hanifin JM, Cooper KD, Ho VC, et al. Guidelines of care for atopic dermatitis. J Am Acad Dermatol. 2004;50: 391–404.
35. Smith N, Weymann A, Tausk FA, et al. Complementary and alternative medicine for psoriasis: a qualitative review of the clinical trial literature. J Am Acad Dermatol. 2009;61:841–56.
36. Shenefelt PD. Complementary pyschocutaneous therapies in dermatology. Dermatol Clin. 2005;23: 723–34.
37. Slominski A. Neuroendocrine system of the skin. Dermatology. 2005;211:199–208.
38. Brazzini B, Ghersetich I, Hercogova J, Lotti T. The neuro-immuno-cutaneous-endocrine network: relationship between mind and skin. Dermatol Ther. 2003;16:123–31.

This page intentionally left blank

Ultraviolet Therapy 134

Herbert Hönigsmann and Thomas Schwarz

Chapter Contents

Phototherapy with UVB 2219
Phototherapy with the 308 nm excimer laser 2223
Phototherapy with UVA1 2223
Phototherapy with psoralens (PUVA) 2224
Extracorporeal photochemotherapy (photophoresis) 2233

Key features

- Phototherapy denotes the use of ultraviolet (UV) light in the treatment of skin disease
- Currently, phototherapy encompasses irradiations with broadband UVB (290–320 nm), narrowband UVB (311–313 nm), 308 nm excimer laser, UVA1 (340–400 nm), UVA plus psoralens (PUVA), and extracorporeal photochemotherapy (photopheresis)
- Therapeutic success depends upon proper selection of the phototherapy modality for a given disease
- Proper dosimetry is required to avoid acute side effects such as a sunburn reaction, blistering, and burning sensations
- The risk of skin carcinogenesis represents the major long-term side effect of phototherapy. Except for PUVA, the magnitude of this risk is not yet clearly delineated

INTRODUCTION

Over the past 40 years, phototherapy has greatly influenced treatment concepts in dermatology. Studies focusing on the effects of electromagnetic radiation (Fig. 134.1) on the skin have induced fruitful collaborations between basic scientists and clinicians.

Although ultraviolet (UV) radiation had been used for decades in the management of common skin diseases such as psoriasis and atopic dermatitis, the introduction of PUVA in the mid-1970s sparked a whole new series of discoveries, including high-intensity UV sources and selective spectra in the UVB and UVA range, e.g. narrowband UVB (311–313 nm) and UVA1 (340–400 nm).

PHOTOTHERAPY WITH UVB

Historical Aspects

Phototherapy using artificial light sources has a tradition dating back more than 80 years. The combination of topical crude coal tar and subsequent UV irradiation for the treatment of psoriasis was introduced by Goeckerman in 1925 and became a standard therapy for psoriasis for half a century, particularly in the US. In the 1970s, it was observed that broadband UVB radiation alone, if given in doses that produce a slight erythema, could clear the milder forms of psoriasis, particularly the seborrheic and guttate types. A major advance was the development of fluorescent bulbs that emitted narrowband UVB radiation at 311–313 nm in the mid-1980s. This narrow spectrum is superior in clearing psoriasis and thus represents the most effective and most frequently used UVB phototherapy for psoriasis; it is also beneficial for a variety of other dermatoses that were previously treated with PUVA (see below).

Principles and Mechanisms

UVB phototherapy refers to the use of artificial UVB radiation without the addition of exogenous photosensitizers. The radiation is absorbed by endogenous chromophores, and photochemical reactions involving these UV-absorbing biomolecules mediate a variety of biologic effects, ultimately leading to the therapeutic effects. The most important chromophore for UVB is nuclear DNA. Absorption of UV by nucleotides causes the formation of DNA photoproducts, primarily pyrimidine dimers (see Ch. 86)[1].

UVB exposure reduces DNA synthesis and thus is used to suppress the accelerated DNA synthesis found in psoriatic epidermal cells. UVB also induces the expression of the tumor suppressor gene *p53*, and this can lead to either cell cycle arrest (allowing time for DNA repair) or apoptosis of keratinocytes ("sunburn cells") if the DNA damage is too severe to be repaired. Through these mechanisms, *p53* prevents photocarcinogenesis.

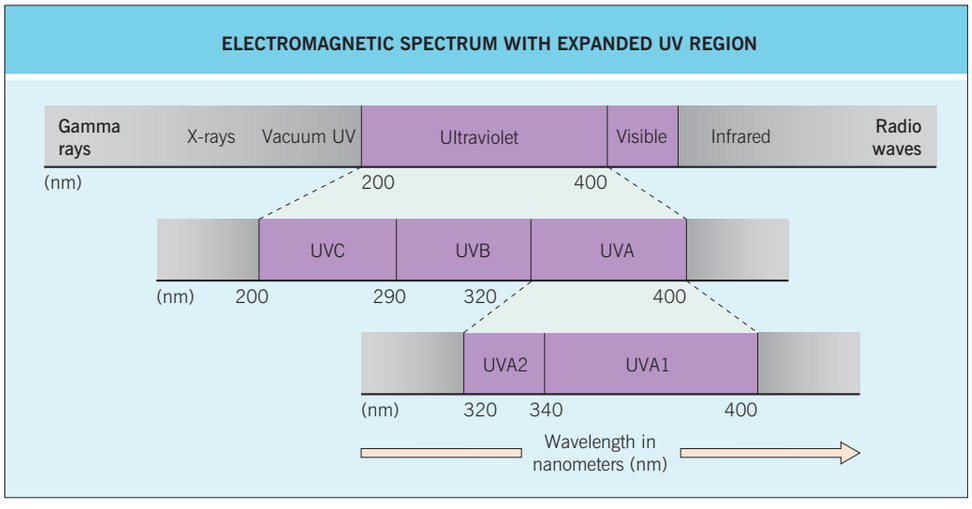


Fig. 134.1 Electromagnetic spectrum with expanded UV region.

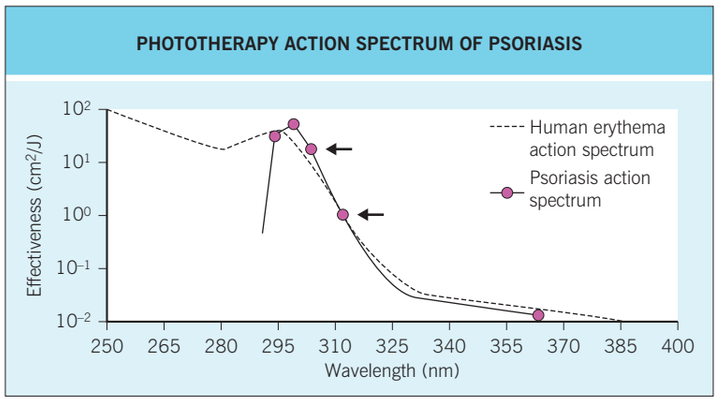


Fig. 134.2 Phototherapy action spectrum of psoriasis. The phototherapy action spectrum of psoriasis is plotted as the reciprocal of the lowest effective daily dose to clearing versus wavelength. The dashed line shows the human erythema action spectrum. The solid line is the action spectrum of psoriasis. Circles represent the reciprocal of the lowest effective daily dose for wavelengths that cleared psoriasis (295, 300, 304, 313, 365 nm); the arrows point to the wavelengths that were optimally effective (304, 313 nm). Presently, narrowband UVB sources that emit wavelengths between 311 and 313 nm are available. *Adapted from Parrish JA, Jaenicke KF. Action spectrum for phototherapy of psoriasis. J Invest Dermatol. 1981;76:359–62.*

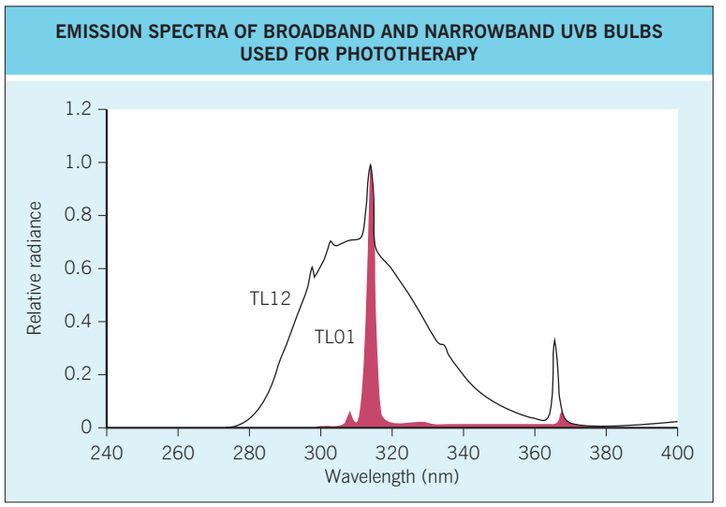


Fig. 134.3 Emission spectra of broadband and narrowband UVB bulbs used for phototherapy. Philips TL12, broadband UVB bulb; Philips TL01, narrowband UVB bulb.

In addition to its effect on the cell cycle, UV induces the release of prostaglandins and cytokines. Interleukin (IL)-6 and IL-1, for example, seem to play important roles in producing the systemic symptoms of UV phototoxicity (sunburn) and immune suppression, respectively[1]. These responses may, however, prove to be equally important for therapeutic effectiveness.

There is also increasing evidence that UV radiation can affect, in addition to DNA, extranuclear molecular targets located in the cytoplasm and cell membrane. These targets include cell surface receptors, kinases, phosphatases and transcription factors. It was has been shown that nuclear and cytoplasmic/membrane effects are not mutually exclusive, rather they independently contribute to the various biologic effects of UVB.

Many of the therapeutic effects of UVB may be due to its immunosuppressive properties which have been linked to the formation of pyrimidine dimers. UV radiation suppresses contact allergy, delayed-type hypersensitivity and immune surveillance against UV-induced non-melanoma skin cancers in mice. Of note, Langerhans cells are very sensitive to UVB, which alters their antigen-presenting function. Keratinocytes also secrete soluble mediators such as IL-1 and IL-6, prostaglandin E_2 and TNF-α in response to UVB, which by themselves can alter the immune response. Therapeutic UVB suppresses the type 1 (proinflammatory) axis as defined by IL-12, interferon-γ and IL-8, and can selectively reduce proinflammatory cytokine production by individual T cells[1].

The interplay of the various photobiological pathways is far from being completely understood. In psoriasis, both epidermal keratinocytes and cutaneous lymphocytes may be targeted by UVB. Immune suppression, alteration of cytokine expression, and cell cycle arrest may all contribute to the suppression of disease activity in psoriatic plaques[2]. In addition, a subset of T cells, Th17 cells, which seem to play a central role in the immunopathogenesis of psoriasis, are also down-regulated by UVB[3]. Recently, evidence was presented that keratinocyte apoptosis may be a key mechanism in the clearance of psoriatic plaques[3a].

EXPOSURE DOSES FOR MED ASSESSMENT WITH BROADBAND AND NARROWBAND UVB SOURCES (mJ/cm²)						
Broadband UVB	20	40	60	80	100	120
Narrowband UVB	200	400	600	800	1000	1200

*1 joule (J) of energy/second = one watt (W); irradiation (dose) is measured in J/cm² (UVA) or mJ/cm² (UVB).

Table 134.1 Exposure doses for minimal erythema dose (MED) assessment with broadband and narrowband UVB sources (mJ/cm²)*. Physical doses as measured with an integrated UV meter (Waldmann, Schwenningen, Germany).

Action Spectrum and Radiation Sources

Parrish and Jaenicke[4] demonstrated that for antipsoriatic activity, 304 and 313 nm were the optimally effective wavelengths (Fig. 134.2), even at suberythemogenic doses. Erythemogenic UVA doses are also therapeutically effective, but 1000 times higher fluences are needed (as compared with UVB), and, on a practical level, this is not feasible. The addition of UVA also does not enhance the therapeutic efficacy of UVB in psoriasis (unlike atopic dermatitis). The Philips TL01 fluorescent lamp that emits narrowband UVB (311–313 nm) was introduced to optimally meet the requirements for antipsoriatic activity (Fig. 134.3).

Treatment Protocols

Before starting phototherapy, determination of the patient's UV sensitivity via phototesting is recommended, since skin typing alone does not always reflect the actual sensitivity of a particular individual. However, phototesting is not mandatory for the experienced therapist and, for practical reasons, is often not done. Testing is performed by exposing four to six small template areas (e.g. 1 cm diameter circles) of usually non-sun-exposed skin (lower back, buttocks) to an incremental series of UVB irradiations. Increases are made by fixed values (e.g. 10 or 20 mJ/cm²) or by a fraction of the last dose (e.g. 40%). An example is given in Table 134.1. Note that these doses strongly depend on the photometer used. Narrowband UVB is much less erythemogenic with regard to physical units (mJ/cm²) than broadband UVB.

The minimal erythema dose (MED) is defined as the lowest dose that causes a minimally perceptible erythema reaction at 24 hours after irradiation. Sunbathing or exposure to "sunlamps" should be avoided before phototesting. It is crucial to document the type of lamp used for the MED determination, since the values obtained with broadband and narrowband sources differ tremendously (see Table 134.1).

Despite continued discussion as to whether visual assessment of the MED is the optimal method for establishing a reference value for dosimetry, it is an easily performed procedure that does not require any specialized equipment. An initial therapeutic UVB dose equal to 70% of the MED is recommended. Treatments are given two to five times weekly. Since UVB erythema peaks within 24 hours after exposure, doses may be increased with each successive treatment. However, if treatments are given five times weekly, the doses should be increased every other treatment. The rate of increase depends on treatment frequency and the outcome of the preceding UVB exposure. The objective of the dose increments is to achieve a minimally perceptible erythema

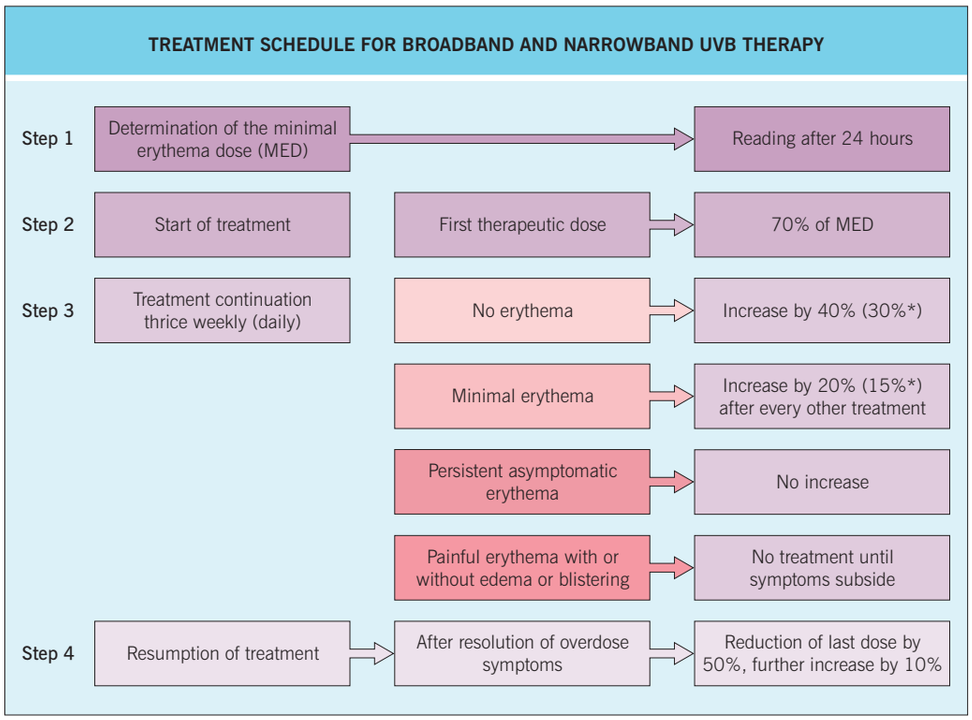


Fig. 134.4 Treatment schedule for broadband and narrowband UVB therapy. *If treatments are given five times per week or daily.

as a clinical indicator of optimal dosimetry. For example, with thrice-weekly exposures, doses are increased by 40% if no erythema appears, and by 20% upon development of slight erythema. If mild erythema persists, the dose should be maintained. With daily exposures, these rates are no more than 30%, 15% and 0%, respectively. If more intensive or painful erythema develops, irradiations are stopped until the symptoms disappear. Treatment is then continued until complete remission is achieved or no further improvement can be obtained with continued phototherapy (Fig. 134.4).

Whether maintenance treatment leads to a more prolonged remission time is still a matter of debate, since minimal precise data are available. In cutaneous T-cell lymphoma (CTCL), most therapists perform maintenance treatment for several months to a year. For psoriasis, some centers use a 2-month maintenance phase with twice-weekly exposures for 1 month and once-weekly exposures for another month. The last effective UVB dose is given throughout the maintenance phase. If relapses occur during the maintenance phase, treatment frequency and UVB dose are increased again until clearing. Of note, there was some evidence in a recent study that maintenance narrowband UVB may lead to longer remission times in plaque-type psoriasis[5].

Excellent guidelines for use of narrowband UVB have been prepared by the British Photodermatology Group. They present evidence-based guidance for treatment of patients with a variety of dermatoses and photodermatoses, with identification of the strength of evidence available at the time of preparation[6].

Phototherapy for Psoriasis

Guttate and seborrheic (minimally elevated) forms of psoriasis respond most favorably and rapidly to broadband UVB, while chronic, plaque-type psoriasis is more resistant. Despite its proven efficacy, broadband UVB is certainly inferior to PUVA, both in terms of clearing efficiency and duration of remission.

However, narrowband UVB phototherapy is superior to conventional broadband UVB with respect to both clearing and remission times. In many countries, narrowband UVB has mostly replaced conventional UVB phototherapy. Based on our own studies and other publications, we regard narrowband UVB phototherapy to be less effective than PUVA[7].

In addition to the treatment protocols mentioned above, other regimens may be used. Some schedules utilize skin type-dependent starting doses and fixed increments regardless of skin reaction. Sometimes, the patient's extremities (in particular the lower extremities) are exposed to higher doses than the trunk.

Adjunctive topical agents and combination therapies are often tried in order to improve efficacy and to reduce the cumulative UVB dose, with the ultimate aim of minimizing the risk of long-term side effects. Narrowband UVB has been successfully combined with therapies such as anthralin and calcipotriol. The use of bland emollients before UVB treatment is laborious and time-consuming. In our experience, it does not dramatically increase treatment efficacy. The concurrent use of topical corticosteroids may reduce remission times and thus is discouraged[8].

Systemic drugs such as retinoids increase efficacy, particularly in patients with chronic plaque-type psoriasis[9]. In addition, retinoids may reduce the carcinogenic potential of UVB phototherapy. There have been open-label studies and small comparison studies regarding the efficacy of combining UVB phototherapy and biologic agents[10,10a]. To date, there have been no large-scale studies, and long-term data, including remission times, are unavailable.

Phototherapy for Cutaneous T-Cell Lymphoma, in particular Mycosis Fungoides

For early stages (IA, IB and IIA) of mycosis fungoides (MF), conventional treatment strategies include topical corticosteroids, UV radiation, and topical cytotoxic agents such as nitrogen mustard (mechlorethamine). More advanced stages are treated with total body electron beam radiation therapy (see Ch. 139), X-irradiation, systemic retinoids, systemic chemotherapy and biologic therapies (e.g. IFN), but none of these regimens has been demonstrated to induce permanent remission.

Lesions of MF frequently occur in non-sun-exposed areas of the body, and patients with early stage MF often benefit from exposure to natural sunlight. In one study with long-term follow-up, 74% of patients treated with broadband UVB remained in complete remission after a median treatment period of 5 months[11]. Response to phototherapy was related to the type (i.e. patch stage MF did better than the plaque type) but not the extent of skin involvement. In a more recent study, prolonged maintenance therapy (up to 30 months) resulted in a relapse-free period of 26 ± 10 months[12].

The proposed mechanisms for UVB phototherapy of MF include impairment of epidermal Langerhans cell function and alterations in cytokine production and adhesion molecule expression by keratinocytes[13]. Moreover, it was noted that narrowband UVB induces apoptosis of T lymphocytes, which may contribute particularly to the beneficial effect of this light source[14].

UVB phototherapy is clearly less efficient than PUVA, and the duration of treatment in the clearing and maintenance phases is longer and thus requires higher patient compliance. Whether patients would benefit from adding UVA, as is sometimes recommended, remains questionable. Likewise, narrowband UVB and broadband UVB therapy have not been compared in MF. It is possible that combining a systemic retinoid (e.g. bexarotene) with narrowband UVB may increase efficacy. Lastly, a pilot study documented the efficacy of medium- to high-dose UVA1 therapy (see below) in patients with stage IA and IB MF. However, there is no evidence that UVA1 is superior to PUVA and no long-term follow-up is available.

Phototherapy for Vitiligo

Many patients observe follicular repigmentation in areas of vitiligo following sun exposure. Because of seasonal and weather-dependent variations in sunlight intensity in moderate climates, exposure to natural sunlight is often not a practical option for inducing complete repigmentation. In the past, PUVA was most frequently used for the treatment of vitiligo, but exposure to artificial UVB irradiation, in particular narrowband UVB, can also provide an acceptable therapeutic effect, if given for a sufficiently long period. Although the action spectrum for phototherapy of vitiligo is not known, narrowband UVB has clearly become quite popular in recent years. In comparison studies of narrowband UVB with PUVA, narrowband UVB was as effective as PUVA but had fewer side effects (Fig. 134.5). Also, in a recent randomized double-blind trial of non-segmental vitiligo, narrowband UVB therapy was superior to oral PUVA therapy and the color match of repigmented skin was considered to be better in the patients treated with narrowband UVB[15]. UVA alone is of limited benefit.

Since intense erythema may induce the Koebner phenomenon and worsening of the disease, it is necessary to stay within a dose range that induces minimally perceptible erythema. Therefore, initial assessment of the MED in a vitiliginous area that is normally not sun-exposed (e.g. buttocks, lower back or abdomen) is recommended. The UVB doses have to be increased more carefully than in other disorders, because of the increased photosensitivity.

The initial exposure is 70% of the MED in *lesional* skin, and subsequent doses are chosen according to the response in vitiligo areas, i.e. the goal is to induce a barely perceptible erythema. This minimal erythema is the only useful parameter for determining dosage increments. The dose should not be increased more than once weekly by 10–20% of the preceding dose. Despite the lack of pigment, vitiliginous skin does develop some tolerance, probably as a result of epidermal hyperplasia and thickening of the stratum corneum. Usually, a maximum dose will be reached during the first couple of months which is used throughout the entire treatment period. Most commonly, two to three treatments per week are given. However, too few controlled studies are available for any particular phototherapy regimen to be preferred over another.

Fig. 134.5 Narrowband phototherapy for vitiligo. A Before treatment. **B** After 10 months of treatment (twice weekly). Note the persistence of depigmentation of the areolae, an area which is particularly resistant to treatment.

Phototherapy for Atopic Dermatitis

Broadband UVB phototherapy

Based on the empirical experience that sun exposure was beneficial for patients with atopic dermatitis, broadband UVB has been used to treat atopic dermatitis since the end of the 1970s.

UVA/UVB phototherapy

More recent studies suggest that a combination of UVA plus UVB irradiation (UVA/UVB therapy) is superior to conventional broadband UVB, conventional UVA, or low-dose UVA1 therapy in the management of chronic, moderate atopic dermatitis. A paired-comparison study demonstrated statistically significant differences in favor of UVA/UVB therapy, compared with broadband UVB therapy[16].

Narrowband UVB phototherapy

George et al.[17] first used an air-conditioned narrowband UVB irradiation unit to treat atopic dermatitis. It not only improved the total clinical score, but also substantially reduced the need for potent topical corticosteroids. These beneficial effects were still present in the majority of patients 6 months after cessation of phototherapy. A randomized controlled trial has shown similar results[18]. Narrowband UVB therapy has been used successfully in conjunction with UVA1 therapy.

Phototherapy for Graft-versus-Host Disease

Experience with UVB therapy of GVHD is very limited, since it has been used only in selected patients. It is still unclear whether irradiation of the skin shortly after transplantation is of benefit in the prevention of human cutaneous GVHD[19]. Currently, PUVA represents the mainstay for phototherapy of GVHD.

Phototherapy for Pityriasis Lichenoides and Lymphomatoid Papulosis

Both pityriasis lichenoides acuta and chronica can have a prolonged course and be rather resistant to therapy. As sunlight may lead to some improvement, UVB phototherapy has also been associated with some success. However, PUVA seems to be more effective (see below), especially in the acute form of the disease (perhaps because of the deeper extension of the dermal inflammatory infiltrate). Although Honig et al.[20] have recommended PUVA as the treatment of choice for the acute form, PUVA may be reserved for cases of pityriasis lichenoides chronica that are UVB-resistant.

Phototherapy for Seborrheic Dermatitis

Seborrheic dermatitis generally improves during the summer and "sunny" vacations. Accordingly, UV radiation also seems to have a beneficial effect on this condition. However, flares of dermatitis may occasionally occur. In an open prospective study, narrowband UVB was found to be an effective treatment in severe cases[21].

Phototherapy for Pruritus

Both narrowband and broadband UVB therapy can be beneficial in various forms of pruritus, particularly those associated with diabetes

Fig. 134.6 Target-like appearance of psoriatic lesions secondary to phototoxicity due to UVB. Annular erythema is separated from the psoriatic plaques by Woronoff's ring.

and hepatic disorders or those that are idiopathic in nature. Remissions in hepatic disease, however, are relatively short-lived. In a case series, narrowband UVB led to improvement of uremic pruritus[22].

Side Effects of Phototherapy with UVB

Short-term side effects include erythema (Fig. 134.6), xerosis accompanied by pruritus, occasional blistering, and an increased frequency of recurrent herpes simplex viral infections. Painful erythema resulting from overexposure is treated with topical corticosteroids. Systemic nonsteroidal anti-inflammatory drugs and corticosteroids can prove useful in severe cases, if administered early.

Long-term side effects include photoaging and carcinogenesis. Although UVB is a known carcinogen, its carcinogenic potential seems to be lower than that of PUVA. A 16-center study conducted by Stern and Laird[23] did not detect a relationship between UVB phototherapy and non-melanoma skin cancer. In a recent British study comprised of 3867 patients treated with narrowband UVB, no significant association between narrowband UVB treatment and basal cell carcinoma (BCC), squamous cell carcinoma (SCC) or melanoma was found[24]. There was a small increase in BCCs amongst those patients who also had been previously treated with PUVA. To determine the true carcinogenic risk of narrowband UVB phototherapy, additional longitudinal studies are essential.

Because narrowband UVB has been in use for just over two decades, its long-term side effects are not yet known. Compared with broadband UVB, up to 10-fold higher physical doses of narrowband UVB are required to produce erythema, edema and sunburn cell formation. Using single-cell gel electrophoresis (the comet assay), therapeutically equivalent doses from these two radiation sources produced minimal differences in the amount of DNA damage[25]. As narrowband UVB is clinically more effective than broadband UVB, the former requires less MED-equivalents to achieve a therapeutic response, implying that narrowband UVB will be less carcinogenic than broadband UVB[26].

PHOTOTHERAPY WITH THE 308 NM EXCIMER LASER

The use of the 308 nm excimer laser represents an enhancement of narrowband UVB delivery. The clinical use of this laser for plaque-type psoriasis was first reported in 1997[27]. Subsequent reports[28] showed that in some patients, high multiples of the MED, such as 4 and 6 MEDs, could induce a longer duration of remission than achieved with conventional narrowband therapy. Other advantages of the use of the excimer laser for psoriasis are the lower number of treatments that may be necessary to induce clearing and the ability to treat exclusively the affected skin and with a reduced cumulative dose, thus perhaps reducing the long-term risk of carcinogenicity[29]. However, widespread psoriasis generally cannot be treated with this modality because the spot size is less than 2 cm^2. Clearly, the excimer laser will be most suitable for patients with stubborn plaques unresponsive to other treatments and/or those with difficult-to-treat localized areas such as the palms, soles, knees and elbows. The excimer laser is now approved by the Food and Drug Administration (FDA) for the treatment of psoriasis. Whether it really represents a therapeutic advancement still remains to be determined by larger and longer-term studies, particularly in view of the high costs of the laser treatment. However, the newer excimer *lamps* are less expensive and appear to be similarly effective[29].

Based upon case series, targeted phototherapy with the excimer laser may also serve as a new treatment modality for the management of stable vitiligo[30] and for a variety of chronic inflammatory localized dermatoses such as granuloma annulare, lichen planus, lichen simplex chronicus and alopecia areata[31].

PHOTOTHERAPY WITH UVA1

The UVA spectrum (320–400 nm) has been arbitrarily subdivided into two parts: UVA1 (340–400 nm) and UVA2 (320–340 nm) (see Fig. 134.1). The main reason for this subdivision was the observation that UVA2 resembled UVB in its ability to cause erythema as well as immunomodulation and photocarcinogenesis. Because of its longer mean wavelength, UVA1 radiation penetrates more deeply into the skin than UVA2 (see Ch. 86), and thus affects not only epidermal structures, but also mid and deep dermal components, especially blood vessels. Since the skin is a large organ, exposure of circulating immune cells to UVA1 irradiation may have significant systemic ramifications. In particular, its ability to induce T-lymphocyte apoptosis is likely to be relevant in the treatment of atopic dermatitis and possibly of MF. It may reduce the number of Langerhans cells and mast cells in the dermis in atopic dermatitis, and in cutaneous mastocytosis. In addition, it has been shown that increased collagenase expression in treated lesions of localized scleroderma accompanies improvement with UVA1 irradiation. Perhaps the efficacy of UVA1 in localized scleroderma, and in other sclerosing conditions, is in part due to this action.

UVA1 phototherapy is currently being investigated as a safer alternative to PUVA for treating chronic conditions. To date, most of the UVA1 studies have been performed in Europe, where efficient sources of UVA1 radiation are more widely available (Fig. 134.7).

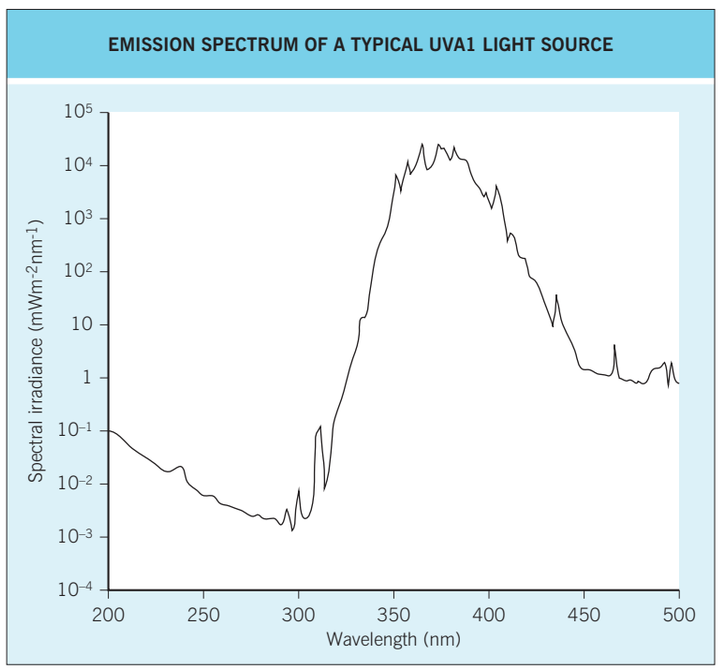


Fig. 134.7 Emission spectrum of a typical UVA1 light source (filtered metal halide lamp).

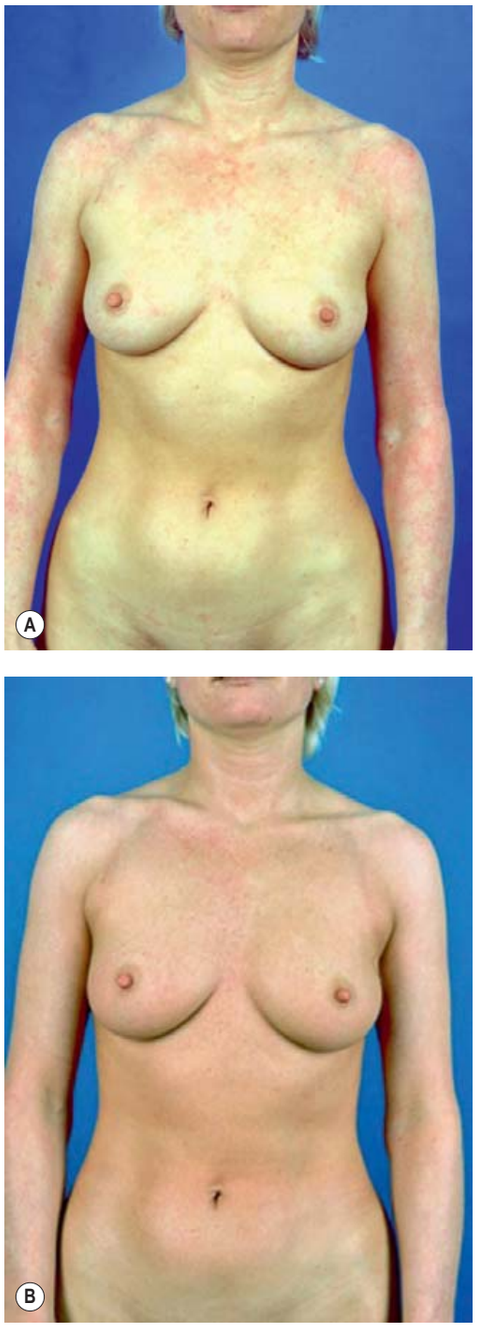


Fig. 134.8 UVA1 phototherapy of atopic dermatitis (split-body comparison). A Before treatment. **B** After treatment (15 exposures) with high-dose (130 J/cm^2, left side) *versus* medium-dose (65 J/cm^2, right side) UVA1 phototherapy. Note that there is no difference in the therapeutic result.

UVA1 can have a therapeutic effect on atopic dermatitis[32,33] (Fig. 134.8). It seems to be more effective than UVA/UVB therapy, at least for severe exacerbations of atopic dermatitis. If used as a monotherapy, medium and high daily doses are better than low doses. When UVA1 and narrowband UVB were compared for the treatment of atopic dermatitis, they seemed to be equally effective[34].

UVA1 therapy has been reported to be beneficial in several other dermatoses[35], including localized scleroderma[36], acute and chronic sclerodermoid GVHD[37,38], urticaria pigmentosa[35] and MF[39]. However, the latter indication in particular requires confirmation in larger patient series. Clearly, this area of phototherapy is still under evaluation.

Side Effects of Phototherapy with UVA1

The adverse effects of UVA1 are less severe than those of UVB and UVA2. Until more is known about UVA1 therapy, its use (especially with high doses such as 130 J/cm^2) should be limited to treating diseases with periods of severe, acute exacerbations, and, in general, one treatment cycle should not exceed 10–15 successively administered exposures and should not be repeated more than once a year. A European prospective longitudinal study has been initiated to monitor patients treated with UVA1 phototherapy for the development of skin cancer and photoaging. An increased expression of *p53* and a slight increase in Bcl-2 protein expression in keratinocytes were found in human skin after UVA1 irradiation (even with suberythemogenic doses), suggesting that UVA1 may cause DNA damage[40]. In addition, UVA1 induced promutagenic cyclobutane pyrimidine dimers and oxidative DNA damage (at both the genomic and nucleotide resolution level) in normal human skin fibroblasts[41]. Of note, in the years since the widespread use of UVA1 phototherapy in Europe began in 1992, no serious negative side effects in humans have been reported.

PHOTOCHEMOTHERAPY WITH PSORALENS (PUVA)

Psoralen photochemotherapy (PUVA) combines the use of psoralens (P) and long-wave UV radiation (UVA). This combination results in a therapeutically beneficial phototoxic effect, which is not produced by either of the components alone. Psoralens can be administered orally or applied topically in the form of solutions, creams or baths, with subsequent UVA exposure.

Historical Aspects

Topical exposure to extracts, seeds or parts of plants (e.g. *Ammi majus*, *Psoralea corylifolia*) that contain natural psoralens, followed by exposure to sunlight, was used as a remedy for vitiligo for thousands of years in ancient Egypt and India[42]. In 1974, it was shown that the oral ingestion of 8-methoxypsoralen (8-MOP) and subsequent exposure to a new, high-intensity, artificial UVA radiation source was highly effective for the treatment of psoriasis[43]. This was followed by a recognition of its therapeutic effect for multiple skin disorders (Table 134.2)[17].

Psoralens

Psoralens are naturally occurring linear furocoumarins that are found in a large number of plants, and there are several synthetic psoralen compounds. For oral and topical (bath, cream) PUVA, 8-MOP (methoxsalen) is used primarily; it is of plant origin but also available as a

PUVA-RESPONSIVE DISEASES	
Therapy of disease	**Prevention of disease**
Psoriasis	Polymorphic light eruption†
Palmoplantar pustulosis	Solar urticaria†
Atopic dermatitis	Chronic actinic dermatitis*,†
Mycosis fungoides (stages IA, IB, IIA)	Hydroa vacciniforme*,†
Vitiligo	Erythropoietic protoporphyria*,†
Generalized lichen planus	
Urticaria pigmentosa	
Cutaneous GVHD	
Generalized granuloma annulare	
Prurigo nodularis	
Pityriasis lichenoides (acute and chronic)*	
Lymphomatoid papulosis*	
Pityriasis rubra pilaris*,†	
Purpura pigmentosa chronica*	
Langerhans cell histiocytosis*	
Localized scleroderma*	

*Experience is limited to a small number of patients.
†These diseases may flare prior to therapeutic response.

Table 134.2 PUVA-responsive diseases. GVHD, graft-versus-host disease.

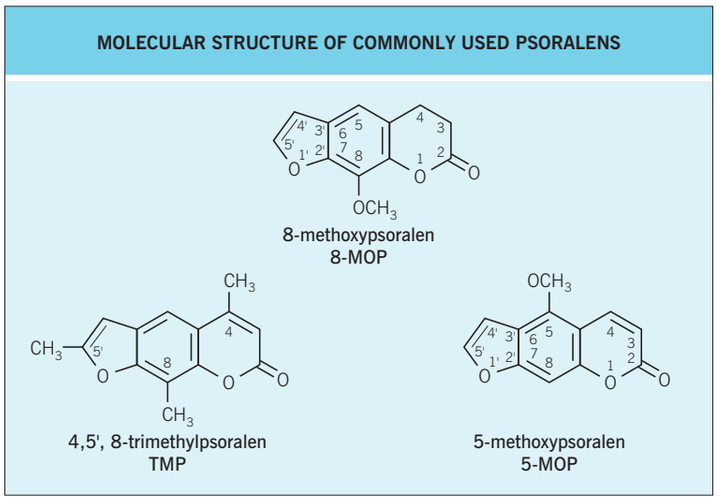


Fig. 134.9 Molecular structure of commonly used psoralens.

synthetic drug. The synthetic compound, 4,5′,8-trimethylpsoralen (TMP, trioxsalen), is less phototoxic than 8-MOP after oral administration, but more phototoxic when bath-water-delivered. TMP is used primarily in Scandinavia for bath PUVA. 5-Methoxypsoralen (5-MOP, bergapten) is also therapeutically effective when given orally; it is less erythemogenic and is not associated with gastrointestinal intolerance (Fig. 134.9). In Europe (where available) it is now used for routine PUVA. Oral preparations of 8-MOP and 5-MOP contain either crystals, micronized crystals or solubilized psoralens in a gel matrix. The liquid preparation induces earlier, higher and more reproducible peak plasma levels than the crystalline preparations.

The steps between the ingestion of a psoralen and its arrival in the skin include disintegration and dissolution of the drug, absorption, first-pass effect, blood transportation, and tissue distribution. The absorption rate of a psoralen from the gut depends on the physicochemical properties of the molecule, the rate of dissolution, the galenic characteristics of the preparation, and the fat content of concomitantly ingested food. 5-MOP is less water-soluble than 8-MOP and its absorption rate is approximately 25% of that of 8-MOP. Like 8-MOP, liquid preparations of 5-MOP give higher and earlier peak serum levels than do crystalline formulations. In addition, peak serum levels are achieved by liquid preparations after a relatively reproducible time interval, whereas wide time variability occurs with crystalline formulations. Before reaching the skin via the circulation, psoralens are metabolized during their passage through the liver. Plasma levels of 8-MOP administered orally at different doses show a strong non-linearity, indicating a saturable first-pass effect. Thus, small differences in the ingested doses and absorption rates of psoralens lead to large differences in plasma levels. As a practical consequence, small amounts of the drug are almost completely metabolized by the liver during the first pass and therefore may be therapeutically inactive.

8-MOP and 5-MOP serum levels show a wide range of inter-individual differences. Even on different occasions in the same patient, serum levels may differ; however, the levels are usually sufficiently constant to provide for relatively reproducible therapeutic results. This unpredictable pharmacokinetic behavior is probably due to inter- and intra-individual variations in intestinal absorption, first-pass effect, blood distribution in the body, and metabolism and elimination of the drug.

In a particular individual, serum levels of 8-MOP correspond fairly well with skin reactivity, with the peak of skin phototoxicity coinciding with peak serum levels. A correlation between 8-MOP and 5-MOP serum levels and epidermal concentrations does exist. Whether there is a significant correlation between maximum psoralen blood concentrations and the minimal phototoxicity dose (MPD) remains equivocal.

The pharmacokinetics of topical 8-MOP depend on the mode of application. 8-MOP administered topically as a 0.15% emulsion or solution has been shown to result in plasma levels comparable to those obtained by oral delivery, when large areas of the body are treated. In contrast, due to the much lower concentrations that are used, plasma levels following bath-PUVA treatment of almost the entire body surface are very low. Bath-water-delivered psoralens are readily absorbed into the skin, but are promptly eliminated without cutaneous accumulation[2].

Psoralen photochemistry

Psoralens react with DNA in three steps. First, in the absence of UV radiation, the psoralen intercalates into the DNA double strand. Absorption of photons in the UVA range results in the formation of a 3,4- or 4′,5′-cyclobutane monoadduct with pyrimidine bases of native DNA. The 4′,5′ monoadducts can absorb a second photon and this reaction leads to the formation of an interstrand cross-link of the double helix with the 5,6 double bond of the pyrimidine base of the opposite strand (Fig. 134.10).

Excited psoralens can also react with molecular oxygen. The reactive oxygen species formed by this reaction cause cell membrane damage by lipid peroxidation and may activate the cyclooxygenase and arachidonic acid metabolic pathways.

The cross-linking of psoralens with epidermal DNA inhibits DNA replication and causes cell cycle arrest. Although not proven, it is generally assumed that this effect may be the therapeutic mechanism in psoriasis. Psoralen photosensitization also causes an alteration in the expression of cytokines and cytokine receptors. However, DNA cross-linking does not appear to be a prerequisite for all the therapeutic effects of PUVA, and the successful treatment of other skin diseases is unlikely to be due directly to this molecular reaction. Psoralens also interact with RNA, proteins and other cellular components and indirectly modify proteins and lipids via singlet oxygen-mediated reactions or by generating free radicals[44,45].

PUVA can reverse the pathologically altered patterns of keratinocyte differentiation markers and reduce the number of proliferating epidermal cells. Infiltrating lymphocytes are strongly suppressed by PUVA, with variable effects on different T-cell subsets. PUVA is far more potent in inducing apoptosis in lymphocytes than in keratinocytes[1], which may explain its efficacy in CTCL as well as in inflammatory skin diseases. Although much is known about pathways and mechanisms in psoralen photosensitization, the interactions and relative contributions to the clearing of a specific disease are not well understood.

Psoralens also stimulate melanogenesis. This involves the photoconjugation of psoralens to DNA in melanocytes, followed by mitosis and subsequent proliferation of melanocytes, increased formation and melanization of melanosomes, enhanced transfer of melanosomes to keratinocytes, and increased synthesis of tyrosinase via stimulation of cAMP activity.

Action Spectrum and Light Sources

The action spectrum for 8-MOP-induced delayed erythema has its maximum activity in the 330–335 nm range and the antipsoriatic activity of 8-MOP (plus UVA) appears to parallel its erythema action spectrum[46]. Conventional therapeutic UVA fluorescent tubes and broad-spectrum metal halide lamps, which are filtered in the UVB and UVC range, cover well the psoralen action spectrum. The typical fluorescent UVA lamp used for PUVA therapy peaks at 352 nm and emits approximately 0.5% in the UVB range (Fig. 134.11). Major advantages of mercury halide units are the stability of output and their high irradiance, enabling short treatment times.

UVA doses are given in J/cm^2, instead of mJ/cm^2 used for UVB, and usually measured with a photometer with a maximum sensitivity at 350–360 nm. Within the treatment system, the irradiance must be relatively uniform so that the dose does not vary at different anatomic sites. UVB emission should be kept low enough to avoid erythemogenic UVB doses before sufficient UVA is absorbed to produce the psoralen photosensitivity reaction.

Photosensitivity Effects of PUVA

PUVA treatment produces an inflammatory response that manifests as delayed phototoxic erythema. The reaction depends on the dose of drug,

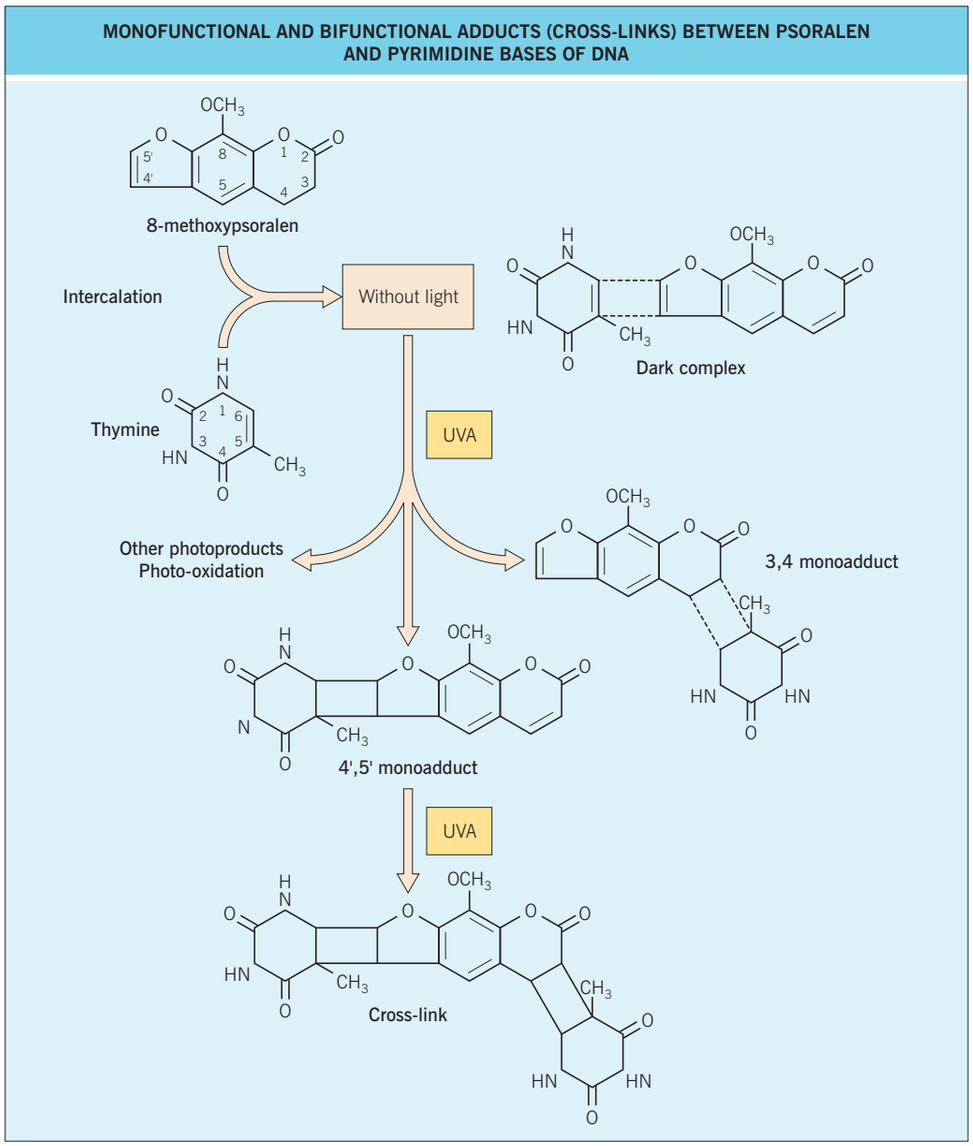


Fig. 134.10 Monofunctional and bifunctional adducts (cross-links) between psoralen and pyrimidine bases of DNA.

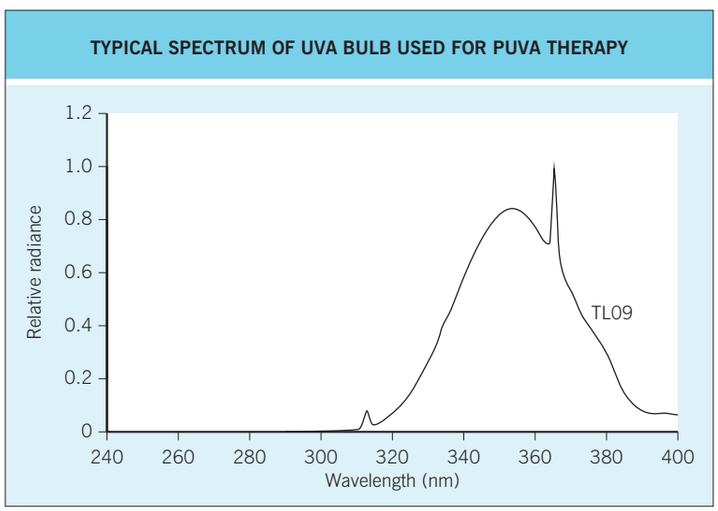


Fig. 134.11 Typical spectrum of a UVA bulb (Philips TL09) used for PUVA therapy.

the dose of UVA, and the individual's sensitivity (skin type). Recently, it was shown that changes in 8-MOP dose had no detectable effect on the maximum slope of the PUVA erythema dose–response curve. Thus, 8-MOP dose changes within individuals, over a narrow but clinically relevant range, appear to significantly alter the threshold response to PUVA erythema but not the rate of increase in erythema with increasing UVA dose[47].

PUVA erythema differs remarkably from the sunburn or UVB erythema that appears after 4–6 hours and peaks 12–24 hours after exposure to UVB. PUVA erythema does not occur before 24–36 hours and it peaks at 72–96 hours or even later after exposure. It has a shallower dose–response curve than UVB erythema (by a factor of approximately 2) and this difference is maintained even at the time of maximum erythema[48]. PUVA erythema persists for longer periods of time (lasting up to more than 1 week) and it consists of a deeper red, even a violaceous, hue. Severe reactions may lead to blistering and to superficial skin necrosis. Overdoses of PUVA are frequently followed by edema, intense pruritus and sometimes by a peculiar stinging sensation in the affected skin area. At present, erythema is the only available parameter that allows an assessment of the magnitude of the PUVA reaction and thus represents an important factor for determining UVA dose adjustments[2].

Pigmentation, the second important effect of PUVA, may develop without clinically evident erythema, especially when oral 5-MOP or TMP is used; this is of particular importance in the treatment of vitiligo and for the preventive treatment of some photodermatoses. In normal skin, PUVA pigmentation peaks about 7 days after exposure and may last from several weeks to months. As with sun-induced tanning, the individual's ability to tan is genetically determined, but the dose–response curve is much steeper. A few PUVA exposures result in a much deeper tan than that produced by multiple exposures to solar radiation. One goal of phototherapy of inflammatory and neoplastic disorders

SKIN PHOTOTYPES AND INITIAL DOSE OF UVA FOR PUVA THERAPY		
Skin phototype*	**Skin reaction**	**Recommended initial dose (J/cm²)**
I†	Always burns, never tans	0.5
II	Always burns, but sometimes tans	1.0
III	Sometimes burns, but always tans	1.5
IV	Never burns, always tans	2.0
V‡	Moderately pigmented skin	2.5
VI	Darkly pigmented skin	3.0

*Types I–IV are determined by history; types V and VI by physical examination (racial descent).
†Patients with erythrodermic psoriasis are to be classified as skin phototype I for determination of UVA dosage.
‡Patients with this phototype should be classified into a lower skin phototype category if the sunburning history so indicates.

Table 134.3 Skin phototypes and initial dose of UVA for PUVA therapy. These irradiation doses are based upon an oral 8-MOP dose of 0.6–0.8 mg/kg.

is to produce a clinical response prior to the induction of significant pigmentation.

Treatment Protocols

Oral PUVA

The general principle of oral PUVA is to keep the dose of psoralen, as well as the interval between drug intake and UVA exposure, constant, and to vary the UVA dose according to the patient's sensitivity. A dosage of 8-MOP of 0.6 to 0.8 mg/kg is administered orally 1–3 hours before exposure, depending on the absorption characteristics of the particular drug brand. For example, liquid drug preparations are absorbed faster and yield higher and more reproducible serum levels than do microcrystalline forms. For 5-MOP, the usual dosage is 1.2–1.8 mg/kg.

The initial UVA doses are selected either by skin typing[9,49] or by determining the minimal phototoxicity dose (MPD)[50]. In the US, skin reactivity to solar radiation is evaluated and patients are classified based on a skin phototype scheme according to their sunburn history. Therapeutic doses of UVA are then given according to an empirical scheme based on this classification[9,47] (Table 134.3). In Europe, the most widely used approach consists of MPD determination analogous to MED determination. The MPD is defined as the minimal dose of UVA (following psoralen ingestion) that produces a barely perceptible, but well-defined, erythema. The doses range from 0.5 to 5 J/cm² if 8-MOP is used and 1 to 10 J/cm² if 5-MOP is used. Erythema readings are performed 72 (not later than 96) hours after irradiation, when the phototoxicity reaction usually peaks. As with the MED, the MPD should be determined on previously non-sun-exposed skin (lower back or buttocks). This will yield lower values than on previously exposed skin and thus contributes to a safer initial dosimetry. Although performing an MPD is more time-consuming than phototyping, it should be done whenever possible, since it allows for far more accurate and higher UVA doses during the initial treatment phase. As with UVB therapy, some experienced therapists do not consider phototesting to be mandatory.

Oral PUVA should not be used in patients with hepatitis, because slower metabolization of psoralens may prolong photosensitivity. Also, impaired renal function may slow down psoralen excretion.

Bath PUVA

Bath-water delivery of psoralens is becoming increasingly popular because it provides a uniform drug distribution over the skin surface, very low psoralen plasma levels, and a quick elimination of free psoralens from the skin, thereby reducing the period of photosensitivity. Due to the absence of systemic photosensitization, bath-water delivery of 8-MOP circumvents gastrointestinal side effects and potential ocular effects. Skin psoralen levels are highly reproducible and photosensitivity lasts no more than 2 hours. The higher incidence of unwanted phototoxicity can be prevented by a lower starting dose (30% of the initial MPD) and more cautious dosimetry during the initial treatment phase.

Originally, bath PUVA was performed with TMP, but 8-MOP and 5-MOP are now being used as well. Bath PUVA consists of 15–20 minutes of whole body (or hand and foot) immersion in solutions of 0.5–5.0 mg of 8-MOP per liter of bath water. Irradiation has to be performed immediately thereafter, as photosensitivity decreases rather rapidly. TMP is more phototoxic after topical application and thus is used at lower concentrations than 8-MOP. MPD testing for bath PUVA must take into account that, unlike with oral PUVA, the phototoxic threshold declines during the early treatment phase. In our experience, when the MPD is determined on a consecutive daily basis, the fourth MPD is approximately 50% of the first MPD (this may be due to persistent psoralen adducts)[2].

Topical PUVA

Application of 8-MOP (0.1–0.01%) in creams, ointments or lotions, followed by UVA irradiation, is effective but has several disadvantages. The non-uniform distribution on the skin surface may produce unpredictable phototoxic erythema reactions, and inadvertent application to surrounding uninvolved skin can lead to cosmetically unacceptable hyperpigmentation; this is a particular problem in patients with vitiligo. Furthermore, if numerous lesions are present, the application is laborious and time-consuming, and the treatment does not prevent the development of new active lesions in previously unaffected, untreated areas. Finally, extensive application ("paint" PUVA) of a 0.15% 8-MOP emulsion was found to cause plasma levels comparable to those detected with oral ingestion. Therefore, topical PUVA utilizing psoralen creams, ointments or lotions is now reserved primarily for psoriasis of the palms and soles and limited stable vitiligo.

Guidelines for bath, local immersion and other forms of topical PUVA have been published by the British Photodermatology Group. These recommendations are based, where possible, on the results of controlled studies; otherwise they represent a consensus view on current practice[51].

Initial Treatment (Clearing) Phase

The initial treatment phase is defined as the treatment period until clearing of the disease is achieved; repeated exposures are required, with gradual dose increments as pigmentation develops. Doses that are too low frequently result in failure of treatment, except in those diseases in which induction of pigmentation is the desired objective. In most dermatoses amenable to PUVA, the frequency of treatments should be reduced after satisfactory control of the disease.

Treatment should not be started until the end of the 72-hour period after MPD testing. A safe initial therapeutic dose for oral PUVA is 70% of the MPD (recent studies have shown that 50% is often sufficient for the effective treatment of psoriasis). For bath PUVA, it is advisable to start at only 30% of the MPD, because photosensitivity is up to 10 times higher than with oral PUVA (Fig. 134.12).

Irradiations are given two to four times weekly. Dose increments are performed no more often than twice a week (at least 72 hours apart) and never during the first week of treatment (if initial dose is based on MPD), in order to avoid accumulation of delayed cutaneous phototoxicity. Although not necessary for therapeutic success, a minimally perceptible erythema is considered a clinical indicator of adequate dosimetry. There exists no rigid scheme for dose increments; the major parameter for dose adjustments should be the clinical response of the disease. It is essential to note that with bath PUVA, the MPD can even decrease during the first days after initiation of treatment by up to 50%, but then increases at later stages. This may be due to persistent psoralen adducts which are converted into cross-links upon subsequent exposures.

In the absence of erythema, the UVA dose can be increased safely by 30% in both oral PUVA and bath PUVA (see Fig. 134.12). However, some patients will not need dose adjustments over prolonged periods of time, because of erythema formation (e.g. vitiligo) and/or adequate treatment response.

Maintenance Phase

The purpose of maintenance therapy is to achieve a longer remission. In the European regimen, maintenance therapy consists of one month of twice-weekly treatments utilizing the final UVA dose administered during the clearing phase, followed by another month of once-weekly

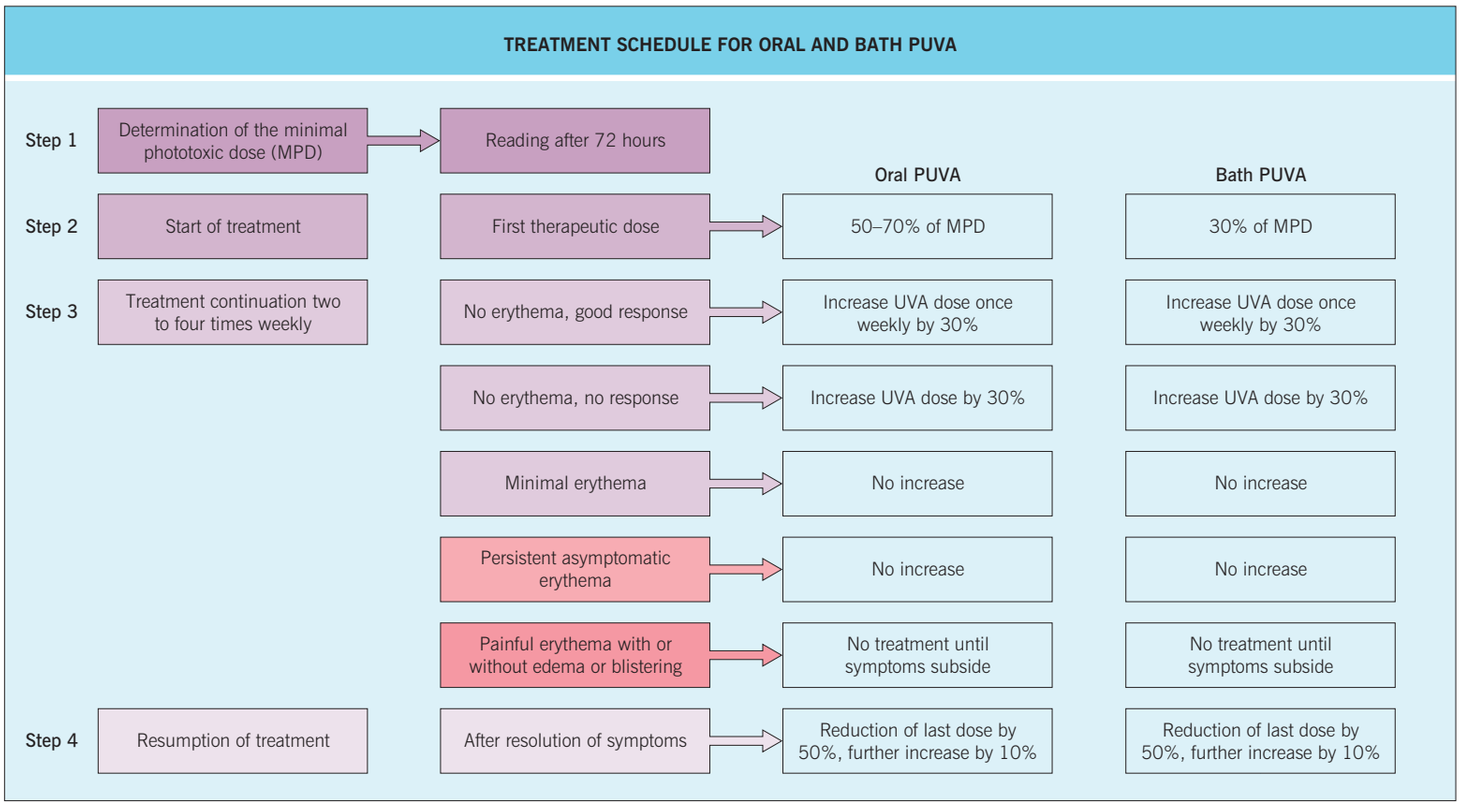


Fig. 134.12 Treatment schedule for oral and bath PUVA.

exposures. However, results of a recent study indicated that short-term maintenance therapy was not effective in preventing early relapses of psoriasis[52]. For MF, many institutions recommend some form of permanent maintenance therapy. However, due to the lack of prospective studies, no valid recommendation can be given. Perhaps a once-monthly treatment would be a feasible compromise.

Mild relapses during the maintenance phase are handled by temporarily increasing the frequency of treatments; in the case of a severe relapse, the original clearing phase schedule must be resumed until clearing is once again achieved. A disadvantage of maintenance therapy for patients in remission is the potential to overtreat the patient and to increase the potential for long-term toxicity that is related to the total cumulative dose of the PUVA.

PUVA for Psoriasis

Basically, all types of psoriasis respond to PUVA, although the management of erythrodermic or generalized pustular psoriasis is more difficult[2]. Both the US and the European regimens have proven to be highly efficient and therefore have remained in use, although with the advent of bioengineered immunomodulators (see Ch. 128), phototherapy of all types has lessened. Table 134.4 lists the differences between these two methods of administering oral 8-MOP PUVA[49,50].

Three studies have compared bath-water delivery of 8-MOP with oral administration[53–55]. In two reports, initial doses were determined by skin typing and treatments were given two to three times weekly. Dosage increments were done with every treatment in the first study[53], whereas smaller increments were performed every third treatment in the second[54]. Patients in the third study were treated according to the guidelines of the standard European regimen for oral PUVA; this group had the lowest incidence of treatment failures and overdose episodes[55]. Relative to the results obtained with oral PUVA, bath PUVA showed equal clearing rates with lower numbers of exposures. The greater therapeutic efficacy could be due to a higher penetration of psoralens through the abnormal stratum corneum overlying psoriatic plaques as compared with healthy perilesional skin where phototoxicity is monitored during the therapy. The incidence of erythema and pruritus was similar or lower with bath PUVA as compared to oral therapy. In all the investigations, episodes of systemic intolerance such as nausea and vomiting were recorded only with oral PUVA[2].

DIFFERENCES BETWEEN THE US AND EUROPEAN PROTOCOLS FOR PUVA THERAPY

	US	Europe
UVA dosimetry	Predetermined dose according to skin phototype	Individualized dose according to MPD determination
Frequency of treatment	Two to three times per week	Four times per week
Dose increments	Predetermined	Individualized
Principle of approach	Rigid, cautious	Flexible, aggressive
Goal	To clear without ponderous testing and acute side effects	To clear rapidly before maximum pigmentation develops

Table 134.4 Differences between the US and European protocols for PUVA therapy. MPD, minimal phototoxicity dose.

Oral 5-MOP PUVA represents another alternative to 8-MOP PUVA. Psoriatic lesions clear with a comparable number of exposures, but 5-MOP requires significantly higher cumulative UVA doses (Fig. 134.13). This is due to the lower phototoxic potential of 5-MOP and to its greater tanning activity. Nevertheless, 5-MOP PUVA therapy seems particularly valuable because of the absence of nausea and vomiting, and the lower incidence of pruritus and severe phototoxic skin reactions.

PUVA alone can produce a definite remission in many cases of psoriasis, but a considerable number of patients require combination therapy (see below).

Combination Treatments

Topical combination

As with UVB phototherapy, PUVA can be combined with other treatment modalities to improve efficacy and to reduce potential side effects[2]. Topical adjuvant therapies include corticosteroids, anthralin and tar, and, more recently, calcipotriol and tazarotene (see Chs 125, 126 &

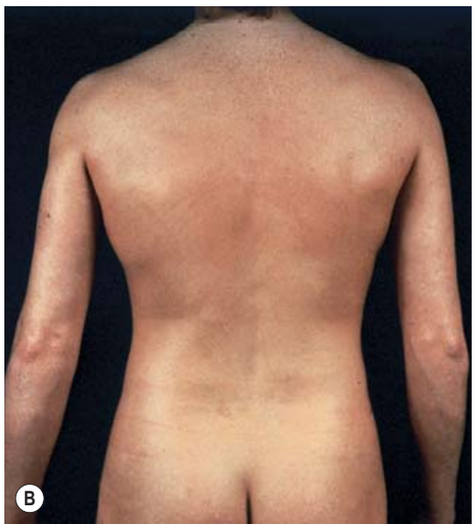


Fig. 134.13 PUVA treatment for psoriasis (5-MOP; four times weekly). A Before treatment. **B** After 6 weeks of treatment.

129). However, some patients are reluctant to "retry" topical agents that previously proved unsuccessful when used alone.

Methotrexate, cyclosporine, bioengineered immunomodulators

The combination of PUVA and methotrexate (MTX) during the clearing phase reduces the duration of treatment, number of exposures, and cumulative UVA dose, and is also effective in clearing patients unresponsive to PUVA or UVB alone[56]. If used for long-term treatment, this combination might be potentially hazardous because PUVA and MTX could act synergistically in the development of skin cancers[23]. However, to date, no increased risk of non-melanoma skin cancer has been reported for this combination. In contrast, cyclosporine plus PUVA has been clearly shown to dramatically enhance skin carcinogenesis. Thus, this combination should be categorically discouraged[57], including the use of cyclosporine subsequent to PUVA therapy. Presently, there are no studies evaluating the safety and efficacy of the combination of any bioengineered immunomodulators ("biologics") with PUVA.

Retinoids

The combination of PUVA with systemic retinoids (RePUVA) is one of the most potent therapeutic regimens for psoriasis. The therapeutic efficacy of PUVA therapy is significantly enhanced upon daily combination with oral retinoids (acitretin, isotretinoin) (0.75–1 mg/kg for etretinate and isotretinoin, 0.5–0.75 mg/kg for acitretin) administered for 5–10 days before PUVA is started, with the combination continued throughout the clearing phase. RePUVA reportedly can reduce the number of exposures by one-third and the total cumulative UVA dose by more than one-half. RePUVA can also clear "poor PUVA responders"[2].

The underlying mechanism of the synergistic action of retinoids plus PUVA may be a reduction in the inflammatory infiltrate and an accelerated desquamation of the psoriatic plaques, thereby optimizing the optical properties of the skin. In theory, retinoids may also reduce the long-term carcinogenic risk of PUVA by reducing the number of exposures and providing chemoprevention against skin cancers. Some evidence for this was presented in a study where patients with psoriasis treated with PUVA in combination with systemic retinoids showed a reduced risk of SCC but not a significantly altered incidence of BCC[58].

Short-term side effects of retinoids are completely reversible upon discontinuation, and long-term toxicity is not relevant because of the limited duration of their use (until clear). The potential teratogenicity of retinoids represents a serious concern. For women of childbearing age, the use of isotretinoin is an option, because contraception is only necessary for 1–2 months after discontinuation of therapy, as opposed to acitretin, which requires at least 2 years of contraception[2].

PUVA for Cutaneous T-Cell Lymphoma, in particular Mycosis Fungoides

Based on the empirical beneficial effect of natural sunlight on early stage MF, Gilchrest et al.[59] first reported the successful use of PUVA for MF. Patients with unsatisfactory responses to other therapies and histologically confirmed plaque or tumor stage MF or the erythrodermic form of CTCL were subjected to PUVA. Complete clearing was observed, except in those areas that were shielded from UVA exposures, thus excluding the possibility of spontaneous remission. This also indicated that the therapeutic effect of PUVA was local rather than systemic.

Numerous studies followed which addressed the rates of initial response and average duration of remission in relation to the stage of MF, the efficacy of PUVA compared with other established treatment options, the efficacy of combination treatments, the mechanisms responsible for the therapeutic effects, and the risk of short- and long-term side effects[2].

Treatment schedules and dosimetry in the photochemotherapy of MF are essentially the same as for psoriasis, consisting of three phases – clearing, maintenance and follow-up. Some authors suggest that remission should be confirmed by histologic examination of previously involved areas. In some institutions, maintenance therapy includes two exposures per week for one month and one exposure per week for another month. If still in remission, therapy is discontinued and the patient is monitored monthly and then bimonthly. If a relapse occurs, the patient is again treated with three or four PUVA exposures per week until complete clearing. However, some investigators advocate permanent maintenance treatment consisting of treatments once monthly or every other month, as it appears that PUVA treatment is not curative. Since the course of MF varies considerably from patient to patient, the final answer remains to be determined. Clinical experience indicates that patients benefit most from individualized schedules.

Several studies involving large patient cohorts have provided information on the initial response rates of PUVA treatment in relation to disease stage. Overall, the best initial complete response rates were obtained for stages IA (~90%), IB (~76%) and IIA (~78%), as compared to stages IIB and III (~60%). There was some heterogeneity in results and the use of different treatment protocols, psoralen preparations and light sources may have contributed to this finding. Only a few patients with stage IV disease have been treated with PUVA monotherapy, because, in this stage, PUVA is generally considered to be only a palliative or adjunctive therapy.

The long-term outcome is strictly dependent on the relapse rates and the mean disease-free intervals. In the first follow-up study of 44 PUVA-treated patients, 56% (5/9) with stage IA disease and 39% (10/26) with stage IB disease remained in remission during a mean follow-up period of 44 months[60]. Patients who experienced relapses had mean disease-free intervals of 20 months for stage IA and 17 months for stage IB. All patients (7/7) with stage IIB disease had multiple recurrences[60]. In a second study of 82 patients with a median follow-up period of 43 months, 53% in stage IA, 37% in stage IB, 50% in stage IIA, and the only one in stage IVA did not develop recurrences after complete

Fig. 134.14 PUVA treatment for cutaneous T-cell lymphoma (mycosis fungoides) (8-MOP; four times weekly). A Before treatment. **B** After 12 weeks of treatment.

clearing. One stage IIB patient and two of six stage III patients initially cleared, but they all eventually relapsed[61].

Relapses usually respond to PUVA in the same manner as the initial response. Clinical remissions appear to be directly related to phototoxic destruction of the malignant infiltrate. Thus, complete clearing may be induced when the cells are confined to the epidermis and the superficial dermis and do not exceed the depth of UVA penetration into the skin. Patients with tumor stage MF exhibit a high rate of early recurrences, which require permanent maintenance treatment; often only the combination of PUVA with local radiotherapy and/or systemic chemo-immunotherapy can result in complete tumor resolution[60].

In summary, the data thus far indicate that PUVA is an excellent treatment option for early stage (IA–IIA) CTCL (Fig. 134.14). High rates of complete clearing can be achieved and a substantial percentage of patients remain free of disease for many years. In advanced stages (IIB–IVB), PUVA is not sufficient as monotherapy, but as adjunctive treatment it can reduce the tumor burden in the skin and can improve the quality of life for patients. Presently, no therapeutic regimen is known to arrest eventual progression of advanced stages of MF to tumor formation, dissemination and fatal outcome. Prolonged remissions have been observed with combinations of PUVA with first- or second-generation retinoids, bexarotene[62] or interferon-α-2a[63,64]. Possible long-term side effects related to frequent PUVA treatments are probably less meaningful for patients with CTCL compared with patients with benign conditions.

While PUVA therapy is very effective in inducing remission as long as the lymphoma is confined to the skin, the impact of this therapy on the natural course of CTCL and on patient survival is not yet determined. However, data from Sweden have shown a significant drop in the death rates of CTCL patients since the introduction of PUVA[65].

PUVA for Vitiligo

As mentioned above, vitiligo was the first disease treated with an ancient form of psoralen photochemotherapy in India and Egypt. PUVA in its modern form stimulates melanogenesis, melanocyte proliferation and migration, and reconstitutes the normal skin color in more than 50% of vitiligo patients.

Treatment protocols and results

Oral 8-MOP and TMP are the photosensitizers most frequently used, followed by exposure to sunlight or artificial UVA radiation. A large, controlled clinical trial by the Harvard group provided detailed information regarding different treatment schedules. Also, 5-MOP was used in a large trial in India and is used in Europe, where available, with good success[2]. To induce repigmentation, patients need constant long-term therapy. It is crucial that the patient understands that PUVA, like other vitiligo therapies, may require months or even years to achieve a satisfactory result. All too optimistic prognoses regarding therapeutic efficacy and length of time to produce adequate repigmentation should be avoided. The patients must also be aware that the treatments stimulate the pigmentation of normal skin, which will intensify the contrast between normal and vitiliginous skin.

Because of weaker phototoxicity, oral TMP is preferred to 8-MOP for treatment with sunlight as the radiation source. Treatments should be given at least twice a week, but not more than three times, with at least one day between treatments. If there is no response after 4–5 months or approximately 30–40 treatments, PUVA should be terminated. Responsiveness is defined as development of multiple perifollicular macules of repigmentation, or, in the case of small (<2 cm) lesions, contraction in size. If treatment is discontinued, reversal of acquired repigmentation may occur unless the lesion has completely repigmented. Completely repigmented areas can be stable for a decade or more without relapse[66].

Another photochemotherapeutic regimen for vitiligo consists of khellin (a furanochromone) as the photosensitizer and UVA irradiation (KUVA). Khellin is not phototoxic and exhibits substantially lower mutagenic activity than psoralens. Its efficacy and failure rate in vitiligo are comparable with PUVA[67]. The major advantage of khellin is that, given its lack of phototoxicity, it can be considered safe for home treatment or treatment with natural sunlight. The treatment schedule is the same as for PUVA; khellin is administered orally at a dose of 100 mg 2 hours before treatment or applied topically as a 5% cream. Khellin is not available in the US. With oral khellin, approximately 30% of vitiligo patients develop reversible increases in liver transaminases that remain to be explained[67]. Under special circumstances, KUVA may be considered an alternative to conventional photochemotherapy. However, the efficacy of topical KUVA in comparison with oral PUVA or other therapeutic modalities has not been established.

Photochemotherapy with topical 8-MOP can be used in patients with small lesions (less than 5% total body surface area) or in children in whom one may hesitate to use systemic PUVA. The therapy must be done in an office setting, since home treatment involves a high risk of severe phototoxic side effects. Topical 8-MOP preparations (0.01% or 0.1% 8-MOP in a cream or ointment base) are applied evenly on the treatment area 30 minutes prior to irradiation. Exposure times (beginning at ≤0.25 J/cm^2) are increased weekly in increments of 0.25 J/cm^2 unless marked erythema occurs. Once- to twice-weekly treatments are recommended. TMP and 5-MOP can also be used for topical PUVA but

are more phototoxic than 8-MOP. For topical application, the vehicle plays a major role in delivery and resulting cutaneous psoralen levels. Solutions should be avoided as they can "run", producing hyperpigmented streaks. Application of sunscreen to the surrounding uninvolved skin prior to application of the topical psoralen can reduce hyperpigmented rims.

Patient selection appears to be critically important in vitiligo treatment. For oral PUVA, the patients should be ages 10–12 years or older, and for all forms, they must be available for 12–24 months of continuous therapy. Lips, distal dorsal hands, fingers and toes, palms, soles and nipples are very refractory to treatment, as are large areas with only white hairs. Patients need to be made aware of this fact.

Stable disease, e.g. segmental vitiligo present for at least a year, is usually easier to treat. On average, a complete treatment course consists of at least 150 exposures. However, because of the different response rates in different body areas, total repigmentation is only rarely achieved, and approximately 30% of patients do not respond at all, despite months of therapy. As mentioned above, in a recent trial of non-segmental vitiligo, narrowband UVB therapy resulted in a better color match as compared to oral PUVA[15].

The mechanisms by which PUVA induces repigmentation in vitiligo remain mostly speculative. Bearing in mind the immunomodulating effect of UV radiation, one might postulate a hypothetical suppressor cell population generated by PUVA that suppresses the stimulus for melanocyte destruction.

PUVA for Atopic Dermatitis (see Ch. 12)

Many patients with moderate, severe and even erythrodermic forms of atopic eczema can benefit from PUVA therapy[56]. The treatment guidelines are essentially the same as for psoriasis. However, as compared to psoriasis, atopic dermatitis is more difficult to treat; quite often, a higher number of treatments is required. Although atopic eczema may be cleared by PUVA, recurrence rates are high and rapid, requiring frequent maintenance exposures. Due to the average patient's young age, however, long-term maintenance therapy should be avoided. A combination of PUVA with topical corticosteroids appears to be superior to PUVA alone in maintaining remissions, and in a recent study involving patients with severe atopic dermatitis, PUVA provided better short- and long-term responses than did medium-dose UVA1[68]. The mechanism of action of photochemotherapy in atopic dermatitis is unclear; current concepts support an alteration of lymphocyte function in the dermal infiltrate.

PUVA for Lichen Planus (see Ch. 11)

The beneficial effect of PUVA in lichen planus was first reported shortly after its introduction. In generalized lichen planus, PUVA can provide an effective alternative to systemic corticosteroids. Later studies pointed to an overall response rate between 50% and 90%, suggesting that lichen planus was less responsive than psoriasis to PUVA. In addition, more treatment sessions and higher cumulative UVA doses were generally necessary for complete remission and not all patients responded satisfactorily. Marked postinflammatory hyperpigmentation may impair the final cosmetic result. An exacerbation during PUVA treatment has been reported in a few patients. Bath PUVA also works in lichen planus. A combined RePUVA regimen (as is used for psoriasis) may accelerate clearing in disseminated and particularly keratotic forms of lichen planus. Compared to narrowband UVB, oral PUVA led to a better initial clinical response rate, but both were effective treatments and produced similar long-term outcomes[69]. Thus, overall, PUVA is an effective therapeutic option for extensive lichen planus; however, this disease is usually more resistant than psoriasis.

PUVA for Graft-versus-Host Disease

An indication of increasing importance may be acute and chronic cutaneous GVHD. Due to clinical and histologic similarities between idiopathic lichen planus and lichenoid GVHD, PUVA treatment was evaluated for the latter[70]. Beneficial effects were observed in patients who had not responded to conventional immunosuppressive therapy alone. PUVA can also improve acute GVHD[71]. Results of PUVA therapy for scleroderma-like variants of cutaneous GVHD are controversial. In our experience, the more localized and circumscribed morpheaform lesions appear to respond to PUVA fairly rapidly, concomitantly with softening of the associated sclerosis. However, the more advanced and widespread sclerodermoid form hardly responds to PUVA.

As opposed to other conditions, PUVA may exert not only local, but also systemic, effects, since improvement of mucosal erosions was observed during treatment of chronic lichenoid GVHD with PUVA, but this could also be mere coincidence. Apparently, there is no improvement of GVHD of other organs, e.g. liver and gut. Of note, deterioration of liver GVHD has not been reported thus far. This is important, since psoralens are metabolized by the liver.

The therapeutic regimen used for the treatment of chronic GVHD is basically the same as for psoriasis. UVA doses should not be increased too aggressively, in order to avoid erythema and possible (re)activation of GVHD. The UVA dosage is increased by no more than 0.5 J/cm^2 every second to fourth exposure, and patients are treated three to four times weekly. After clearing of skin lesions, exposures are reduced according to the maintenance schedule outlined for psoriasis.

There may be a slight overall increased risk of cutaneous malignancies in all hematopoietic stem cell recipients, but much less than in solid organ transplant patients who receive long-term immunosuppression. If patients are receiving long-term prophylactic treatment with voriconazole, switching to posaconazole should be considered in order to reduce possible enhancement of SCC formation. Serial cutaneous examinations are recommended, especially in those who have received PUVA and are of fair complexion.

PUVA for Urticaria Pigmentosa (see Ch. 118)

PUVA causes a temporary involution of cutaneous mastocytosis[72,73]. The treatment results in loss of Darier's sign, relief of itching, and flattening and sometimes even complete disappearance of cutaneous macules and papules. Surprisingly, even systemic symptoms such as histamine-induced migraines and flushing fade gradually as treatment is continued[72]. In most patients, the manifestations of the disease recur several months after discontinuation of PUVA. The recurrences respond as well as the original lesions, and complete clearing of signs and symptoms can again be achieved. In children, PUVA is also often helpful, and appears to be justified in widespread, disabling mastocytosis. To avoid sudden mediator release from mast cells, a PUVA regimen of gradually increasing doses, especially during the initial phase, seems advisable, although the therapy should otherwise be undertaken according to the usual guidelines.

PUVA for Miscellaneous Dermatoses

Both acute and chronic *pityriasis lichenoides*[20] respond to photochemotherapy and favorable results have been reported for *lymphomatoid papulosis*[20,74]. Nevertheless, the experience with these conditions is limited to a few anecdotal cases. In *pityriasis rubra pilaris*, the results are quite inconsistent. Some patients seem to respond well[20], while others may flare and some require combination treatment with retinoids or methotrexate. Generalized *granuloma annulare* has been reported to clear completely, but long-term maintenance treatment was required to maintain remissions[75]. Regrowth of hair was described in *alopecia areata* (with either topical or systemic PUVA) in which exposures were localized to the alopecia areas. There was a great variation in the number of treatments required for regrowth, and circumscribed lesions responded better than did total alopecia. However, follow-up studies of larger patient groups concluded that PUVA is generally not effective in alopecia areata[76,77], which is in accordance with our own experience. *Localized scleroderma* and *pansclerotic morphea* have been successfully treated with bath PUVA and oral PUVA[78,79].

PUVA for Photodermatoses

Tolerance to sunlight can be induced in several photodermatoses with PUVA[80]. In *polymorphic light eruption* (PMLE), the most common photodermatosis, PUVA is a very effective preventive treatment (via hardening)[81]. In approximately 70% of patients with this condition, a 3- to 4-week course of PUVA suffices to suppress the disease upon subsequent exposure to sunlight. The initial exposure and dose increments should be performed according to the guidelines outlined for psoriasis. PUVA induces pigmentation rapidly and intensively at relatively low (suberythemogenic) UVA doses that usually remain well below the threshold doses for eliciting the PMLE. About 10% of the patients develop typical lesions during the initial phase of PUVA.

Interruption of treatment or reduction in the UVA dose is rarely required in such cases. Usually, brief symptomatic treatment with topical corticosteroids suffices.

PUVA hardening is indicated in selected patients with severe PMLE whose disease cannot be prevented with the use of sunscreens or UVB phototherapy. Treatment is given three times weekly over a period of 4 weeks in the early spring. Both 8-MOP and 5-MOP can be used as photosensitizers; however, 5-MOP is preferable because of better tolerability and higher pigment potential. The PUVA therapy protects only temporarily, and regularly repeated sun exposures are subsequently required to maintain protection. However, a considerable number of patients remain protected for 2 to 3 months, even after pigmentation has faded.

The mechanisms by which phototherapy induces tolerance to sunlight are not clear. Hyperpigmentation and thickening of the stratum corneum may be important factors for this protective effect. However, other mechanisms may also be involved, since PMLE does occur in darkly pigmented individuals and even patients with skin type I who do not tan profit from hardening. Modulation of cutaneous immune functions is a possible explanation.

The therapeutic value of preventive photochemotherapy for PMLE has to be balanced against its potential long-term side effects. Given the fact that very few treatments and low cumulative UVA doses (ranging from 15 to 40 J/cm^2 per treatment course, depending on skin type and photosensitizer) are required for photoprotection and that PMLE can severely impair patients in their outdoor activities, PUVA treatment of PMLE is justified when other preventive measures (e.g. antimalarials) fail[81].

There is also some experience with PUVA prophylaxis of other photodermatoses. In *solar urticaria*, PUVA therapy appears to be the most effective preventive treatment available and it is certainly better than antihistamines[82]. Tolerance to sunlight can be increased 10-fold or more after a single treatment course. The suppressive effect may last throughout the summer, depending on regularly repeated sunlight exposures. Problems may occur during the first several PUVA exposures, since in some patients the urticaria threshold dose appears to be lower than their MPD. In these cases, stepwise UVA irradiation of single quadrants of the body a few hours before each PUVA treatment has proven useful[82]. PUVA is then administered during the refractory period.

Successful photochemotherapy has also been reported in occasional patients with *chronic actinic dermatitis*[83] and *hydroa vacciniforme*[84]. Limited experience in patients with *erythropoietic protoporphyria* indicates that, with a very cautious approach and in combination with β-carotene, PUVA may increase light tolerance considerably[85].

Side Effects and Long-Term Hazards of PUVA

As discussed above, oral 8-MOP has a high incidence of nausea (30% of patients) and vomiting (10% of patients), and this may occasionally require discontinuation of the treatment. These side effects are more common with liquid than with crystalline preparations, probably because of higher psoralen serum levels. With 5-MOP, nausea is nearly absent, even with doses up to 1.8 mg/kg, and this is the major reason for increased usage of this compound.

The short-term side effects of the combined action of psoralens plus UVA radiation consist of redness, swelling, and occasionally blister formation as can be seen with excessive sunburns. Generalized pruritus or tingling sensations may herald phototoxic side effects. When large areas of skin are affected, systemic symptoms of excess phototoxicity such as fever and general malaise may occur. Nonsteroidal anti-inflammatory drugs and topical and systemic corticosteroids may be required to alleviate the symptoms, but have to be given early. Such overdosage phenomena are more common after topical psoralen application, because of high epidermal psoralen concentrations. Accumulation of phototoxic effects after several consecutive UVA exposures is also more common with topical PUVA.

Some patients experience persistent pruritus during PUVA treatment, particularly after slight UVA overdosage, and, in rare cases, a stinging pain may develop in circumscribed areas. PUVA-induced skin pain unrelated to actual phototoxic burns occurs rarely, but it may necessitate discontinuation of treatment. The mechanism is unknown and the symptoms are unresponsive to antihistamines. Usually, these complaints subside slowly upon continuation of treatment.

Ophthalmologic effects

Eye protection is mandatory during UVA exposure, and UVA-opaque glasses are required for ambient exposure until the evening of the treatment day. UVA penetrates into the ocular lens and potentially could induce cataracts by forming psoralen-protein photoproducts. The higher permeability of the ocular lens at a younger age led to the relative contraindication of oral PUVA in children younger than 12 years of age. Despite the experimental data indicating a risk of premature cataract formation, clinical evaluation has shown no increase in lens opacities even in patients who neglected careful eye protection[86]. Obviously, there is no risk with topical or bath PUVA.

Laboratory data

Because psoralens can cause liver damage in laboratory animals when given in excessive doses, concern was expressed in the past regarding possible hepatotoxic effects in humans. Several large-scale studies demonstrated no significant abnormal laboratory findings in patients receiving PUVA over prolonged periods of time[49,50,87]. In particular, serial laboratory examinations performed over a period of several years have not revealed any substantial evidence for an impairment of hepatic function. Liver biopsies after 1 year of therapy did not show signs of hepatotoxicity. Anecdotal case reports of hepatitis during PUVA treatment were most likely unrelated to therapy. Several large-scale studies have negated a possible relationship between PUVA therapy and the occurrence of antinuclear antibodies[88].

Potential long-term risks of PUVA

Repeated phototoxic injury to the skin can be expected to result in cumulative actinic damage regardless of whether it is induced by sunlight, artificial UV radiation or PUVA. Although the precise action spectrum of actinic damage has not been determined, epidermal changes are attributed to UVB and dermal changes more to UVA, because the latter penetrates more deeply into the skin. Thus, chronic exposure to PUVA may produce changes in the skin that generally resemble those known as dermatoheliosis and may add to the injury induced by sunlight. High cumulative doses of whole body UVB or PUVA result in pigmentary changes, xerosis, loss of elasticity, wrinkle formation and actinic keratoses. Additionally, PUVA may induce profuse formation of dark stellate lentigines (Fig. 134.15), termed PUVA lentiginosis[50]. These lentigines result from repeated and prolonged treatment and are commonly associated with high cumulative doses of UVA and a high number of treatments. So far, no increased risk of cutaneous melanoma associated with these lentigines has been recorded, but the cosmetic effect may be quite disturbing.

The major concern with prolonged and repeated phototherapeutic regimens is photocarcinogenesis. Therefore, from the onset, PUVA-treated patients were carefully monitored for the development of precursors and malignant skin tumors. Almost all data were obtained from psoriatics, since they represent the largest group of patients receiving PUVA.

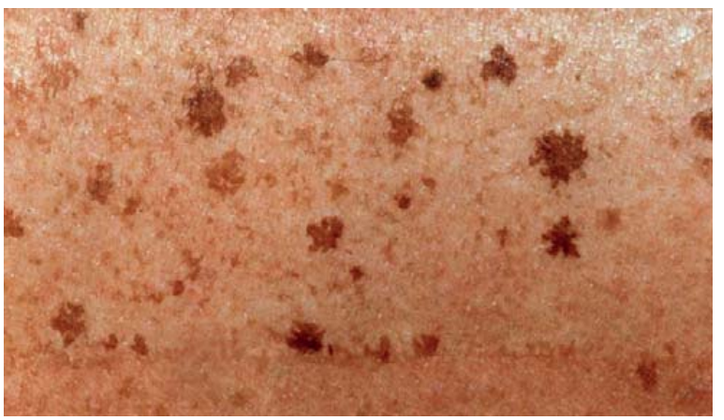


Fig. 134.15 PUVA lentigines. These develop after repeated PUVA treatments over several years.

The risk is certainly related to DNA damage, but PUVA-induced immunosuppression may play a role as well. In PUVA patients, the risk of SCC, but not of BCC, is significantly increased in comparison with matched controls, and the magnitude of the increase appears to be dose-dependent[23,89]. However, there is uncertainty regarding PUVA being the sole factor; many of the affected patients had previous exposure to excessive sunlight and to treatments with carcinogenic potential, including arsenic, UVB and antimetabolite therapy[90]. Particularly, high levels of UVB exposure appear to increase the risk of non-melanoma skin cancer in PUVA-treated patients[91]. In non-Caucasians who received long-term oral PUVA therapy, an increased risk of skin cancers was not observed[92].

According to a single study, the genitalia of male patients previously treated with tar and UVB appeared to be particularly susceptible to the carcinogenic stimuli of PUVA[93], but the risk seemed not to be increased if only PUVA were used[94]. In a retrospective study from France comprised of 5400 patients treated between 1978 and 1998, no case of genital skin cancer was found, despite the fact that the genital area had not been protected during UVA exposure, and this raises the question whether genital shielding is absolutely necessary[95]. Interestingly, no increased risk of skin carcinoma has so far been reported for patients treated with PUVA for vitiligo.

The carcinogenicity of 5-MOP PUVA is unknown, but in *in vitro* photomutagenicity and photocarcinogenicity studies in mice, the activity of 5-MOP was similar to that of 8-MOP.

Only a few anecdotal cases of cutaneous melanoma have been described in long-term PUVA-treated psoriatics, and, to date, with one exception, no increased risk of melanoma has been observed in any reported large-scale study. However, Stern et al.[96] reported on the cohort of 1380 patients enrolled in the PUVA Follow-up Study (16-center study), and, since 1975, 23 patients had developed 26 invasive or *in situ* cutaneous melanomas. Beginning 15 years after the initial exposure to PUVA, an increased risk of melanoma was observed in their cohort of PUVA-treated patients. However, the lead author concluded that perhaps PUVA has been treated unfairly. Its long-term risks have been subject to much greater scrutiny than the risks of other therapies utilized for severe psoriasis, such as methotrexate and particularly immunosuppressive therapies such as cyclosporine (CSA). Of note, several other US studies, as well as European studies, have not observed an increased risk of melanoma in patients treated with PUVA[97,98].

An increased risk of cutaneous SCC has been observed in patients with solid organ transplants who have received long-term CSA and in patients who have received CSA subsequent to PUVA therapy[57]. UVA-sparing, aggressive regimens without prolonged maintenance therapy may be safer than continuous non-aggressive regimens[99] (see Table 134.4).

In a study of 944 Swedish and Finnish patients[100], bath PUVA with TMP appeared to have no relevant risk of carcinogenesis. In addition, no association between cutaneous carcinoma and 8-MOP bath PUVA was found in 158 Finnish psoriatic patients[101]. Perhaps related to lower cumulative UVA doses, these data on the long-term safety of bath PUVA are encouraging, but no premature conclusions should be drawn. The risk/benefit ratio still seems very favorable for PUVA[102], and, so far, no single therapy, except perhaps narrowband UVB, has been accepted as equally safe and efficient.

UVB and PUVA in HIV-Infected Patients

Treatment of psoriasis with oral PUVA has not induced progression of HIV disease nor was there an increase in side effects. The conclusion is that PUVA may be safe for HIV-infected patients with psoriasis. Theoretical modeling of UVB- and PUVA-induced HIV promoter activation in human skin indicated that UVB was more likely than PUVA to activate viral transcription *in vivo*. Although further studies will be needed to unequivocally establish the safety of both UVB and PUVA phototherapy in HIV-associated psoriasis, the benefits are considerable, particularly in those with severe psoriasis[103].

EXTRACORPOREAL PHOTOCHEMOTHERAPY (PHOTOPHERESIS)

Extracorporeal photochemotherapy (photopheresis, ECP) was introduced in the early 1980s for the palliative treatment of erythrodermic CTCL[104]. Efficacy was observed in several uncontrolled clinical trials, and it was FDA-approved as a device in 1988 for the treatment of this disease. In 1994, at the International Consensus Conference on Staging and Treatment Recommendations for CTCL, ECP was recommended as the first line of treatment for patients with erythrodermic CTCL[105]. However, not all authorities agree (see Ch. 120).

Attempts to better characterize those CTCL patients who are more likely to respond to ECP revealed the following:

- There seems to be a significant linear association between response and CD4:CD8 ratio. Patients with a ratio <10 are more likely to respond than are patients with a ratio >10.
- There is a marginally significant linear association between response and LDH level. Patients whose LDH is not elevated at the start of treatment tend to have a better response to ECP compared to patients with an elevated LDH[106].

ECP has also been advocated for the treatment of chronic cutaneous GVHD as well as acute GVHD[107], in addition to acute allograft rejection in solid organ transplant recipients[108].

Treatment Protocols

The ECP procedure involves the oral administration of 8-MOP followed by passage of blood fractions from one arm vein through a photopheresis machine and then back. A discontinuous flow cell separator harvests mononuclear cells (PBMC) within a buffy coat collection. The red cell fraction is returned to the patient without further treatment. 8-MOP can also be administered directly into the collection of the PBMC, thereby avoiding 8-MOP-induced nausea. The collection of PBMC is then exposed to 2 J/cm^2 of UVA and reinfused into the patient. This treatment is typically repeated on two successive days with 2- to 4-week intervals.

Mechanism of Action

Despite the fact that ECP has been in use for almost 20 years, the mode of action still remains enigmatic. It was postulated that the response of CTCL to ECP is due to the induction of an immune response against the malignant cells. Recent experimental results suggest that infusion of autologous haptenated cells, in which apoptosis was induced by 8-MOP/UVA, induces immunologic tolerance. The nature of this tolerance is due primarily to regulatory T cells, because transfer in an animal model conferred similar protection. The demonstration of the induction of regulatory T cells may explain why, in humans, ECP exerts a beneficial effect in a wide variety of diseases which would be amenable to such activity. The generation of antigen-specific regulatory T cells may explain why generalized immunosuppression has not been noted with ECP[109,110]. Monocyte-derived immature dendritic cells may play a role.

Side Effects

Side effects of ECP are uncommon and consist of transient nausea after oral ingestion of 8-MOP and episodes of hypotension and vasovagal reflex due to volume shifts during treatments; the latter usually do not interfere with the treatment.

Other Indications

A number of studies have been performed in order to evaluate the efficacy of ECP in inflammatory diseases other than CTCL and chronic GVHD where autoreactive T cells play a key role. Uncontrolled clinical trials have revealed variable success in selected entities such as atopic dermatitis, systemic sclerosis, pemphigus vulgaris, and systemic lupus erythematosus[111,112].

REFERENCES

1. Weichenthal M, Schwarz T. Phototherapy. How does UV work? Photodermatol Photoimmunol Photomed. 2005; 21:260–6.
2. Hönigsmann H. Phototherapy for psoriasis. Clin Exp Dermatol. 2001;6:343–50.
3. Nickoloff BJ. Cracking the cytokine code in psoriasis. Nat Med. 2007;13:242–4.

3a. Weatherhead SC, Farr PM, Jamieson D, et al. Keratinocyte apoptosis in epidermal remodeling and clearance of psoriasis induced by UV radiation. J Invest Dermatol. 2011;131:1916–26.

4. Parrish JA, Jaenicke KF. Action spectrum for phototherapy of psoriasis. J Invest Dermatol. 1981;76:359–62.
5. Boztepe G, Karaduman A, Sahin S, et al. The effect of maintenance narrow-band ultraviolet B therapy on the duration of remission for psoriasis: a prospective randomized clinical trial. Int J Dermatol. 2006;45: 245–50.
6. Ibbotson SH, Bilsland D, Cox NH, et al. An update and guidance on narrowband ultraviolet B phototherapy: a British Photodermatology Group Workshop Report. Br J Dermatol. 2004;151: 283–97.
7. Tanew A, Radakovic-Fijan S, Schemper M, Hönigsmann H. Narrow band UV-B phototherapy vs photochemotherapy in the treatment of chronic plaque-type psoriasis: a paired comparison study. Arch Dermatol. 1999;135:519–24.
8. Meola T Jr, Soter NA, Lim HW. Are topical corticosteroids useful adjunctive therapy for the treatment of psoriasis with ultraviolet radiation? A review of the literature. Arch Dermatol. 1991;127:1708–13.
9. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 5. Guidelines of care for the treatment of psoriasis with phototherapy and photochemotherapy. J Am Acad Dermatol. 2010;62:114–35.
10. Wolf P, Hofer A, Legat FJ, et al. Treatment with 311-nm ultraviolet B accelerates and improves the clearance of psoriatic lesions in patients treated with etanercept. Br J Dermatol. 2009;160:186–9.

10a. Gambichler T, Tigges C, Scola N, et al. Etanercept plus narrowband ultraviolet B phototherapy of psoriasis is more effective than etanercept monotherapy at 6 weeks. Br J Dermatol. 2011;164:1383–6.

11. Resnik KS, Vonderheid EC. Home UV phototherapy of early mycosis fungoides: long-term follow-up observations in thirty-one patients. J Am Acad Dermatol. 1993;29:73–7.
12. Boztepe G, Sahin S, Ayhan M, et al. Narrowband ultraviolet B phototherapy to clear and maintain clearance in patients with mycosis fungoides. J Am Acad Dermatol. 2005;53:242–6.
13. Volc-Platzer B, Hönigsmann H. Photoimmunology of PUVA and UVB therapy. In: Krutmann J, Elmets CA (eds). Photoimmunology. Oxford: Blackwell Science, 1995:265–73.
14. Ozawa M, Ferenczi K, Kikuchi T, et al. 312-nanometer ultraviolet B light (narrow-band UVB) induces apoptosis of T cells within psoriatic lesions. J Exp Med. 1999;189: 711–18.
15. Yones SS, Palmer RA, Garibaldinos TM, Hawk JLM. Randomized double-blind trial of treatment of vitiligo. Arch Dermatol. 2007;143:578–84.
16. Jekler J, Larkö O. Phototherapy for atopic dermatitis with ultraviolet A (UVA), low-dose UVB and combined UVA and UVB: two paired comparison studies. Photodermatol Photoimmunol Photomed. 1991;8:151–6.
17. George SA, Bilsland DJ, Johnson BE, Ferguson J. Narrow-band (TL-01) UVB air-conditioned phototherapy for chronic severe adult atopic dermatitis. Br J Dermatol. 1993;128:49–56.
18. Reynolds NJ, Franklin V, Gray JC, et al. Narrow-band ultraviolet B and broad-band ultraviolet A phototherapy in adult atopic eczema: a randomised controlled trial. Lancet. 2001;357:2012–16.
19. Torinuki W, Mauduit G, Guyotat D, et al. Effect of UVB radiation on the skin after allogeneic bone-marrow transplantation in man. Arch Dermatol Res. 1987;279: 424–6.
20. Honig B, Morison WL, Karp D. Photochemotherapy beyond psoriasis. J Am Acad Dermatol. 1994;31:775–90.
21. Pirkhammer D, Seeber A, Hönigsmann H, Tanew A. Narrow-band ultraviolet B (TL-01) phototherapy is an effective and safe treatment option for patients with severe seborrhoeic dermatitis. Br J Dermatol. 2000; 143:964–8.
22. Ada S, Seçkin D, Budakoğlu I, Ozdemir FN. Treatment of uremic pruritus with narrowband ultraviolet B phototherapy: an open pilot study. J Am Acad Dermatol. 2005;53:149–51.
23. Stern RS, Laird N. The carcinogenic risk of treatments for severe psoriasis. Cancer. 1994;73:2759–64.
24. Hearn RM, Kerr AC, Rahim KF, et al. Incidence of skin cancers in 3867 patients treated with narrow-band ultraviolet B phototherapy. Br J Dermatol. 2008;159: 931–5.
25. Tzung TY, Rünger TM. Assessment of DNA damage induced by broadband and narrowband UVB in cultured lymphoblasts and keratinocytes using the comet assay. Photochem Photobiol. 1998;67:647–50.
26. Young AR. Carcinogenicity of UVB phototherapy assessed. Lancet. 1995;345:1431–2.
27. Bónis B, Kemeny L, Dobozy A, et al. 308-nm UVB excimer laser for psoriasis. Lancet. 1997;350:1522.
28. Asawanonda P, Anderson RR, Chang Y, Taylor CR. 308 nm excimer laser for the treatment of psoriasis: a dose-response study. Arch Dermatol. 2000;136:619–24.
29. Köllner K, Wimmershoff MB, Hintz C, et al. Comparison of the 308-nm excimer laser and a 308-nm excimer lamp with 311-nm narrowband ultraviolet B in the treatment of psoriasis. Br J Dermatol. 2005;152:750–4.
30. Nicolaidou E, Antoniou C, Stratigos A, Katsambas AD. Narrowband ultraviolet B phototherapy and 308-nm excimer laser in the treatment of vitiligo: a review. J Am Acad Dermatol. 2009;60:470–7.
31. Aubin F, Vigan M, Puzenat E, et al. Evaluation of a novel 308-nm monochromatic excimer light delivery system in dermatology: a pilot study in different chronic localized dermatoses. Br J Dermatol. 2005;152:99–103.
32. Krutmann J, Diepgen TL, Luger TA, et al. High-dose UVA1 therapy for atopic dermatitis: results of a multicenter trial. J Am Acad Dermatol. 1998;38:589–93.
33. Tzaneva S, Seeber A, Schwaiger M, et al. High-dose versus medium-dose UVA1 phototherapy for patients with severe, generalized atopic dermatitis. J Am Acad Dermatol. 2001;45:503–7.
34. Majoie IM, Oldhoff JM, van Weelden H, et al. Narrowband ultraviolet B and medium-dose ultraviolet A1 are equally effective in the treatment of moderate to severe atopic dermatitis. J Am Acad Dermatol. 2009;60: 77–84.
35. Tuchinda C, Kerr HA, Taylor CR, et al. UVA1 phototherapy for cutaneous diseases: an experience of 92 cases in the United States. Photodermatol Photoimmunol Photomed. 2006;22:247–53.
36. Andres C, Kollmar A, Mempel M, et al. Successful ultraviolet A1 phototherapy in the treatment of localized scleroderma: a retrospective and prospective study. Br J Dermatol. 2010;162:445–7.
37. Ständer H, Schiller M, Schwarz T. UVA1-therapy for treatment of sclerodermic graft-versus-host-disease of the skin. J Am Acad Dermatol. 2002;46:799–800.
38. Wetzig T, Sticherling M, Simon JC, et al. Medium dose long-wavelength ultraviolet A (UVA1) phototherapy for the treatment of acute and chronic graft-versus-host disease of the skin. Bone Marrow Transplant. 2005;35:515–19.
39. Zane C, Leali C, Airo P, et al. 'High-dose' UVA1 therapy of widespread plaque-type, nodular, and erythrodermic mycosis fungoides. J Am Acad Dermatol. 2001;44: 629–33.
40. Edström DW, Porwit A, Ros A-M. Effects on human skin of repetitive ultraviolet-A1 (UVA1) irradiation and visible light. Photodermatol Photoimmunol Photomed. 2001; 17:66–70.
41. Besaratinia A, Synold TW, Chen HH, et al. DNA lesions induced by UV A1 and B radiation in human cells: comparative analyses in the overall genome and in the *p53* tumor suppressor gene. Proc Natl Acad Sci USA. 2005;102:10058–63.
42. Pathak MA, Fitzpatrick TB. The evolution of photochemotherapy with psoralens and UVA (PUVA): 2000 BC to 1992 AD. J Photochem Photobiol B. 1992; 14:3–22.
43. Parrish JA, Fitzpatrick TB, Tanenbaum L, Pathak MA. Photochemotherapy of psoriasis with oral methoxsalen and long wave ultraviolet light. N Engl J Med. 1974;291: 1207–11.
44. Caffieri S, Zarebska Z, Dall'Acqua F. Psoralen photosensitization: damages to nucleic acid and membrane lipid components. Acta Biochim Pol. 1996;43: 241–6.
45. Averbeck D. Recent advances in psoralen phototoxicity mechanism. Photochem Photobiol. 1989;50:859–82.
46. Brücke J, Tanew A, Ortel B, Hönigsmann H. Relative efficacy of 335 and 365 nm radiation in photochemotherapy of psoriasis. Br J Dermatol. 1991; 124:372–4.
47. Ibbotson SH, Dawe RS, Farr PM. The effect of methoxsalen dose on ultraviolet-A-induced erythema. J Invest Dermatol. 2001;116:813–15.
48. Ibbotson SH, Farr PM. The time-course of psoralen ultraviolet A (PUVA) erythema. J Invest Dermatol. 1999; 113:346–50.
49. Melski JW, Tanenbaum L, Parrish JA, et al. Oral methoxsalen photochemotherapy for the treatment of psoriasis: a cooperative clinical trial. J Invest Dermatol. 1977;68:328–35.
50. Henseler T, Wolff K, Hönigsmann H, et al. Oral 8-methoxypsoralen photochemotherapy of psoriasis. The European PUVA study: a cooperative study among 18 European centres. Lancet. 1981;i:853–7.
51. Halpern SM, Anstey AV, Dawe RS, et al. Guidelines for topical PUVA: a report of a workshop of the British photodermatology group. Br J Dermatol. 2000;142: 22–31.
52. Radakovic S, Seeber A, Hönigsmann H, Tanew A. Failure of short-term psoralen and ultraviolet A light maintenance treatment to prevent early relapse in patients with chronic recurring plaque-type psoriasis. Photodermatol Photoimmunol Photomed. 2009;25: 90–3.
53. Lowe NJ, Weingarten D, Bourget T, et al. PUVA therapy for psoriasis: comparison of oral and bath-water delivery of 8-methoxypsoralen. J Am Acad Dermatol. 1986;14: 754–60.
54. Collins P, Rogers S. Bath-water compared with oral delivery of 8-methoxypsoralen PUVA therapy for chronic plaque psoriasis. Br J Dermatol. 1992;127:392–5.
55. Calzavara-Pinton PG, Ortel B, Hönigsmann H, et al. Safety and effectiveness of an aggressive and individualized bath-PUVA regimen in the treatment of psoriasis. Dermatology. 1994;189:256–9.
56. Morison WL. Phototherapy and photochemotherapy. Adv Dermatol. 1992;7:255–70.
57. Marcil I, Stern RS. Squamous-cell cancer of the skin in patients given PUVA and ciclosporin: nested cohort crossover study. Lancet. 2001;358:1042–5.
58. Nijsten TEC, Stern RS. Oral retinoid use reduces cutaneous squamous cell carcinoma risk in patients with psoriasis treated with psoralen-UVA: a nested cohort study. J Am Acad Dermatol. 2003;49: 644–50.
59. Gilchrest BA, Parrish JA, Tanenbaum L, et al. Oral methoxsalen photochemotherapy of mycosis fungoides. Cancer. 1976;38:683–9.
60. Tanew A, Hönigsmann H. Ultraviolet B and psoralen plus UVA phototherapy for cutaneous T-cell lymphoma. Dermatol Ther. 1997;4:38–46.
61. Herrmann JJ, Roenigk HH Jr, Hurria A, et al. Treatment of mycosis fungoides with photochemotherapy (PUVA): long-term follow-up. J Am Acad Dermatol. 1995;33:234–42.
62. Zhang C, Duvic M. Treatment of cutaneous T-cell lymphoma with retinoids. Dermatol Ther. 2006;19: 264–71.
63. Stadler R. Optimal combination with PUVA: rationale and clinical trial update. Oncology. 2007;21(Suppl 1): 29–32.
64. Stadler R, Otte HG, Luger T, et al. Prospective randomized multicenter clinical trial on the use of interferon-α-2a plus acitretin versus interferon-α-2a plus PUVA in patients with cutaneous T-cell lymphoma stages I and II. Blood. 1998;92:3578–81.
65. Swanbeck G, Roupe G, Sandström MH. Indications of a considerable decrease in the death rate in mycosis fungoides by PUVA treatment. Acta Derm Venereol. 1994;74:465–6.
66. Ortel B, Tanew A, Hönigsmann H. Vitiligo treatment. Curr Probl Dermatol. 1986;15:265–71.
67. Ortel B, Tanew A, Hönigsmann H. Treatment of vitiligo with khellin and ultraviolet A. J Am Acad Dermatol. 1988;18:693–701.
68. Tzaneva S, Kittler H, Holzer G, et al. 5-Methoxypsoralen plus ultraviolet (UV) A is superior to medium-dose UVA1 in the treatment of severe atopic dermatitis: a randomized crossover trial. Br J Dermatol. 2010;162: 655–60.
69. Wackernagel A, Legat FJ, Hofer A, et al. Psoralen plus UVA vs. UVB-311 nm for the treatment of lichen planus. Photodermatol Photoimmunol Photomed. 2007;23: 15–9.
70. Volc-Platzer B, Hönigsmann H, Hinterberger W, Wolff K. Photochemotherapy improves chronic cutaneous

graft-versus-host disease. J Am Acad Dermatol. 1990;23: 220–8.
71. Kunz M, Wilhelm S, Freund M, et al. Treatment of severe erythrodermic acute graft-versus-host disease with photochemotherapy. Br J Dermatol. 2001;144:901–2.
72. Christophers E, Hönigsmann H, Wolff K, Langner A. PUVA-treatment of urticaria pigmentosa. Br J Dermatol. 1978;98:701–2.
73. Kolde G, Frosch PJ, Czarnetzki BM. Response of cutaneous mast cells to PUVA in patients with urticaria pigmentosa: histomorphometric, ultrastructural, and biochemical investigations. J Invest Dermatol. 1984;83: 175–8.
74. Christensen HK, Thomsen K, Vejlsgaard GL. Lymphomatoid papulosis: a follow-up study of 41 patients. Semin Dermatol. 1994;13:197–201.
75. Kerker BJ, Huang CP, Morison WL. Photochemotherapy of generalized granuloma annulare. Arch Dermatol. 1990;126:359–61.
76. Healy E, Rogers S. PUVA treatment for alopecia areata - does it work? A retrospective review of 102 cases. Br J Dermatol. 1993;129:42–4.
77. Taylor CR, Hawk JLM. PUVA treatment of alopecia areata partialis, totalis and universalis: audit of 10 years' experience at St. John's Institute of Dermatology. Br J Dermatol. 1995;133:914–18.
78. Kerscher M, Volkenandt M, Meurer M, et al. Treatment of localised scleroderma with PUVA bath photochemotherapy. Lancet. 1994;343:1233.
79. Scharfetter-Kochanek K, Goldermann R, Lehmann P, et al. PUVA therapy in disabling pansclerotic morphoea of children. Br J Dermatol. 1995;132:830–1.
80. Hönigsmann H. Mechanisms of phototherapy and photochemotherapy for photodermatoses. Dermatol Ther. 2003;16:23–7.
81. Hönigsmann H. Polymorphous light eruption. Photodermatol Photoimmunol Photomed. 2008;24: 155–61.
82. Roelandts R. Diagnosis and treatment of solar urticaria. Dermatol Ther. 2003;16:52–6.
83. Hindson C, Spiro J, Downey A. PUVA therapy of chronic actinic dermatitis. Br J Dermatol. 1985;113:157–60.
84. Jaschke E, Hönigsmann H. Hydroa vacciniforme-action spectrum. UV-tolerance following photochemotherapy. Hautarzt. 1981;32:350–3.
85. Roelandts R. Photo(chemo)therapy and general management of erythropoietic protoporphyria. Dermatology. 1995;190:330–1.
86. Malanos D, Stern RS. Psoralen plus ultraviolet A does not increase the risk of cataracts: a 25-year prospective study. J Am Acad Dermatol. 2007;57:231–7.
87. Hönigsmann H. Psoralen photochemotherapy - mechanisms, drugs, toxicity. Curr Probl Dermatol. 1986; 15:52–66.
88. Calzavara-Pinton PG, Franceschini F, Rastrelli M, et al. Antinuclear antibodies are not induced by PUVA treatment with uncomplicated psoriasis. J Am Acad Dermatol. 1994;30:955–8.
89. Henseler T, Christophers E, Hönigsmann H, Wolff K. Skin tumors in the European PUVA study. Eight year follow-up of 1643 patients treated with PUVA for psoriasis. J Am Acad Dermatol. 1987;16:108–16.
90. Stern RS, Liebman EJ, Vakeva L. Oral psoralen and ultraviolet-A light (PUVA) treatment of psoriasis and persistent risk of nonmelanoma skin cancer. PUVA Follow-up Study. J Natl Cancer Inst. 1998;90:1278–84.
91. Lim JL, Stern RS. High levels of ultraviolet B exposure increase the risk of non-melanoma skin cancer in psoralen and ultraviolet A-treated patients. J Invest Dermatol. 2005;124:505–13.
92. Murase JE, Lee EE, Koo J. Effect of ethnicity on the risk of developing nonmelanoma skin cancer following long-term PUVA therapy. Int J Dermatol. 2005;44: 1016–21.
93. Stern RS. Genital tumors among men with psoriasis exposed to psoralens and ultraviolet A radiation (PUVA) and ultraviolet B radiation. N Engl Med J. 1990;322: 1093–7.
94. Wolff K, Hönigsmann H. Genital carcinomas in psoriasis patients treated with photochemotherapy. Lancet. 1991; 337:439.
95. Aubin F, Puzenat E, Arveux P, et al. Genital squamous cell carcinoma in men treated by photochemotherapy. A cancer registry-based study from 1978 to 1998. Br J Dermatol. 2001;144:1204–6.
96. Stern RS. PUVA Follow up Study. The risk of melanoma in association with long-term exposure to PUVA. J Am Acad Dermatol. 2001;44:755–61.
97. Forman AB, Roenigk HH Jr, Caro WA, Magid ML. Long-term follow-up of skin cancer in the PUVA-48 cooperative study. Arch Dermatol. 1989;125:515–19.
98. Chuang TY, Heinrich LA, Schultz MD, et al. PUVA and skin cancer: a historical cohort study on 492 patients, J Am Acad Dermatol. 1992;26:173–7.
99. Young AR. Photochemotherapy and skin carcinogenesis: a critical review. In: Hönigsmann H, Jori G, Young AR (eds). The Fundamental Bases of Phototherapy, Milan: OEMF, 1996:77–87.
100. Hannuksela-Svahn A, Sigurgeirsson B, Pukkala E, et al. Trioxsalen bath PUVA did not increase the risk of squamous cell skin carcinoma and cutaneous malignant melanoma in a joint analysis of 944 Swedish and Finnish patients with psoriasis. Br J Dermatol. 1999;141: 497–501.
101. Hannuksela-Svahn A, Pukkala E, Koulu L, et al. Cancer incidence among Finnish psoriasis patients treated with 8-methoxypsoralen bath PUVA. J Am Acad Dermatol. 1999;40:694–6.
102. Morison WL, Baughman RD, Day RM, et al. Consensus workshop on the toxic effects of long-term PUVA therapy. Arch Dermatol. 1998;134:595–8.
103. Menon K, Van Voorhees AS, Bebo BF Jr, et al. Psoriasis in patients with HIV infection: from the Medical Board of the National Psoriasis Foundation. J Am Acad Dermatol. 2010;62:291–9.
104. Edelson R, Berger C, Gasparro F, et al. Treatment of cutaneous T-cell lymphoma by extracorporeal photochemotherapy. Preliminary results. N Engl J Med. 1987;316:297–303.
105. Trautinger F, Knobler R, Willemze R, et al. EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome. Eur J Cancer. 2006;42:1014–30.
106. Knobler E, Warmuth I, Cocco C, et al. Extracorporeal photochemotherapy - the Columbia Presbyterian experience. Photodermatol Photoimmunol Photomed. 2002;18:232–7.
107. Greinix HT, Volc-Platzer B, Rabitsch W, et al. Successful use of extracorporeal photochemotherapy in the treatment of severe acute and chronic graft-versus-host disease. Blood. 1998;92:3098–104.
108. Kumlien G, Genberg H, Shanwell A, Tyden G. Photopheresis for the treatment of refractory renal graft rejection. Transplantation. 2005;79:123–5.
109. Maeda A, Schwarz A, Kernebeck K, et al. Intravenous infusion of syngeneic apoptotic cells by photopheresis induces antigen-specific regulatory T cells. J Immunol. 2005;174: 5968–76.
110. Maeda A, Schwarz A, Bullinger A, et al. Experimental extracorporeal photopheresis inhibits the sensitization and effector phases of contact hypersensitivity via two mechanisms: generation of IL-10 and induction of regulatory T cells. J Immunol. 2008;181: 5956–62.
111. Knobler R, Barr ML, Couriel DR, et al. Extracorporeal photopheresis: past, present, and future. J Am Acad Dermatol. 2009;61:652–65.
112. McKenna KE, Whittaker S, Rhodes LE, et al. Evidence-based practice of photopheresis 1987-2001: a report of a workshop of the British Photodermatology Group and the U.K. Skin Lymphoma Group. Br J Dermatol. 2006; 154:7–20.

This page intentionally left blank

Photodynamic Therapy 135

Harvey Lui and Rolf-Markus Szeimies

Chapter Contents

History and development 2237
Photodynamic therapy (PDT) – photochemistry, photobiology and mechanism of action 2238
Components of PDT 2241
Indications 2243
Adverse effects and complications 2248
Practice and techniques 2249
Future directions 2249

Synonym: ■ Photoradiation therapy

Key features

- Over the past two decades, photodynamic therapy (PDT) has evolved into a practical and effective therapeutic option, especially for actinic keratoses and superficial non-melanoma skin cancer, with an expanding range of applications including acne, photoaging, cutaneous infections, and vascular anomalies
- The photodynamic effect is due to a photochemical reaction which requires the presence of a photosensitizing molecule, photoactivating wavelengths of light, and tissue oxygen to generate singlet oxygen
- Singlet oxygen is highly reactive and initiates a series of reactions that culminate in necrosis, apoptosis and antimicrobial death
- Target cells may undergo either apoptosis due to photosensitizer-induced membrane damage or ischemic necrosis due to vascular injury from photosensitizers concentrated within endothelial cells, or both; host immunologic responses may also contribute to the overall clinical effect
- Photosensitizers may be applied topically as pro-photosensitizers (e.g. aminolevulinic acid) that are metabolized *in situ* to photoactive porphyrins or administered systemically as intact porphyrins (e.g. verteporfin)
- An incubation period is required after drug administration to allow photosensitizer production as well as its partitioning into targeted tissue and cellular compartments
- Red or blue light is typically used to illuminate the skin and energize the photosensitizer

INTRODUCTION

Photodynamic therapy (PDT) involves the administration of a photosensitizing agent followed by its photoactivation by light which then generates singlet oxygen within biologic tissues (Fig. 135.1). Singlet oxygen is a highly reactive form of oxygen that can induce necrosis and/or apoptosis and modulates a variety of other biologic processes. During the latter part of the twentieth century, PDT was synonymous with the use of *systemic* photosensitizers in combination with red *laser* light in order to treat cancers. Although there are a number of clinical variations, nowadays for dermatologists PDT consists primarily of applying a topical photosensitizer precursor to the skin and then illuminating the treatment site with blue or red light.

HISTORY AND DEVELOPMENT

The photodynamic effect was originally studied in the early 1900s by a German medical student, Oscar Raab, who noted that cultures of *Paramecium* would die only if exposed to both an organic dye (acridine) and visible light. His professor, Dr Von Tappeiner, discovered the oxygen-dependence of this effect and coined the term "photodynamic action" to describe the phenomenon. In humans, hematoporphyrin was shown by Meyer Betz to induce profound and persistent generalized photosensitivity, beginning with when he self-injected this agent. By capitalizing on its fluorescent properties when illuminated with a Wood's lamp (365 nm), hematoporphyrin was shown in animals to localize to neoplastic tissue. Hematoporphyrin was also noted to induce tumor involution when exposed to visible light. *Hematoporphyrin derivative* was subsequently developed by Schwartz in an attempt to improve upon the tumor-localizing properties of hematoporphyrin, and then utilized by his colleague Lipson in animal models[1].

The mid 1970s marked the beginning of the modern era of clinical PDT when Dougherty and colleagues combined systemically administered hematoporphyrin derivative with visible light to treat cutaneous and subcutaneous malignancies in humans; they also confirmed the role of singlet oxygen[2,3]. With the advent of lasers and fiberoptic-equipped endoscopes, the use of PDT was extended to carcinomas of the lung, bladder and esophagus. PDT finally gained regulatory approval by the US Food and Drug Administration (FDA) in 1995, but not for skin. Although the skin is obviously relatively easy to illuminate with light, there were two major limitations in using hematoporphyrin derivative or its more purified, commercially available form (porfimer sodium [Photofrin®]) for cutaneous malignancies. Firstly, both of these photosensitizers require intravenous administration, and secondly, they induce marked generalized cutaneous photosensitivity that lasts 6–8 weeks, necessitating strict avoidance of outdoor light.

Because they are relatively large molecules, the percutaneous absorption of porphyrins is rather poor. The breakthrough in developing PDT as a practical treatment option in dermatology can be attributed to the Canadian team of Kennedy and Pottier, who noted in the 1980s that a naturally occurring porphyrin precursor, 5-aminolevulinic acid (ALA), could photosensitize the skin by inducing *local intracutaneous* production of protoporphyrin IX (PpIX; see Fig. 135.1). Their successful treatment of non-melanoma skin cancers with topical ALA plus broadband red light abrogated the two major disadvantages associated with systemic photosensitizers (see above)[4]. The elegance of using topical ALA for PDT consists of how it takes advantage of the endogenous porphyrin biosynthetic pathway (which is present in all nucleated cells) in order to generate PpIX from ALA. The simplicity of this approach greatly facilitated clinical research, with the bulk of clinical studies and experience emanating, to date, from Europe. Although almost a century passed from when Raab and Von Tappeiner conducted their seminal studies to the initial regulatory approval of porfimer sodium, the use of topical ALA (Levulan®) plus blue fluorescent light (Blu-U®) for the treatment of actinic keratoses was approved by the US FDA in 1999, just one decade after the first original publication by Kennedy and colleagues[4]. More recently, topical methyl aminolevulinate (mALA; Metvixia®), an esterified congener of ALA, in combination with red LED (light-emitting diode) light (Aktilite®), has been approved in a number of countries for dermatologic PDT.

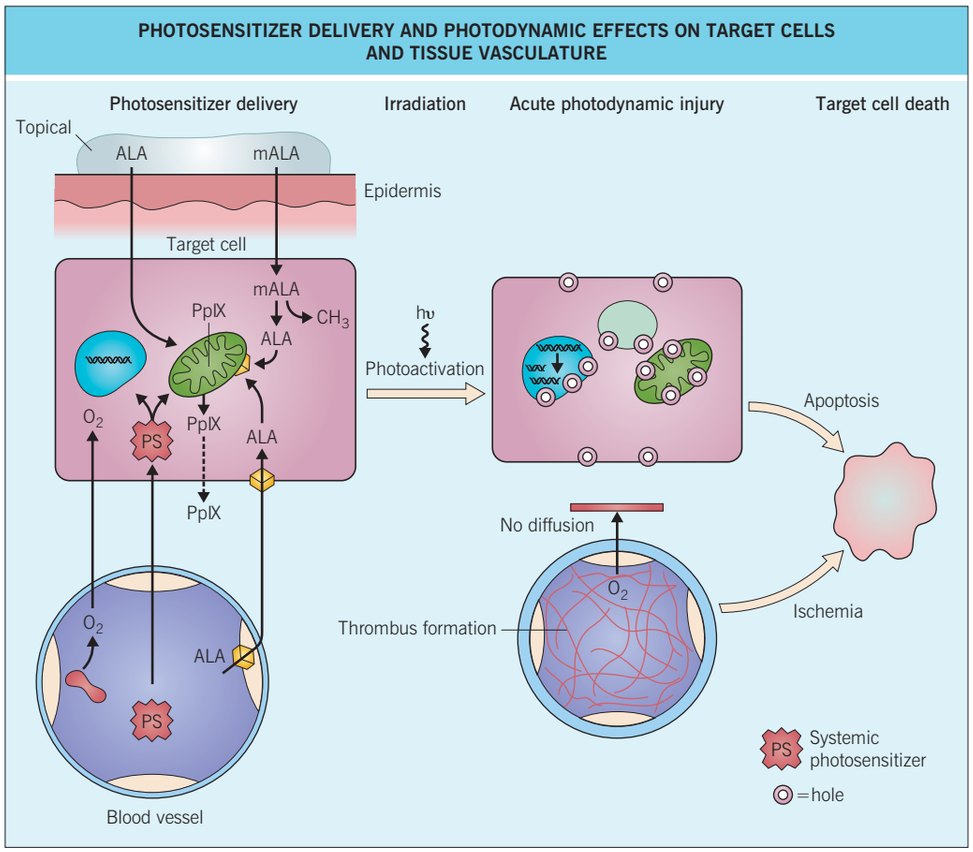


Fig. 135.1 Photosensitizer delivery and photodynamic effects on target cells and tissue vasculature. Topical photosensitizers 5-aminolevulinic acid (ALA) and methyl aminolevulinate (methyl-esterified ALA; mALA) diffuse through the stratum corneum into target epithelial cells. Systemic photosensitizers arrive through the bloodstream. Oxygen is delivered via erythrocyte circulation. ALA derived from any source is converted to protoporphyrin IX (PpIX) within mitochondria. PpIX then leaks from the mitochondria to other cellular structures. Systemically delivered photosensitizers concentrate within endothelial cells and diffuse through the interstitium to target cells. After there has been sufficient time for photosensitizer partitioning to subcellular structures, target tissue is irradiated with photoactivating light. During acute photodynamic injury, plasma and nuclear membranes lose integrity. Acute injury in endothelial cells leads to thrombus formation and vascular collapse. Target cell and tissue oxygen delivery cease. Both apoptosis and ischemic necrosis contribute to irreversible target cell injury and death.

PDT – PHOTOCHEMISTRY, PHOTOBIOLOGY AND MECHANISM OF ACTION

PDT is superficially analogous to PUVA (psoralen plus UVA light) therapy to the extent that both of these treatment modalities involve the administration of photosensitizers followed by exposure to specific wavelengths of light. Mechanistically, both involve exogenous chromophores that transfer photon energy from light to drive specific photochemical reactions within the skin. Nevertheless, there are important differences between PDT and PUVA (Table 135.1), the most fundamental of which is the fact that, by definition, PDT generates singlet oxygen.

PDT Photochemistry

The transfer of energy from light to tissue can be illustrated diagrammatically by considering the resting and excited states of the molecules involved in photochemical reactions (Fig. 135.2). The photosensitizer is delivered to or generated within the target tissue in its ground, lower-energy resting state. Its efficiency as a chromophore for absorbing light energy is governed by its absorption spectrum (Fig. 135.3). If light of an appropriate wavelength is used to irradiate the photosensitizer within tissue, photon absorption occurs and the photosensitizer is excited to a higher-energy "singlet" state. The excited singlet is short-lived, lasting nanoseconds, and then undergoes intersystem crossing to a more stable "triplet" state which has a lifetime on the order of microseconds. The "triplet" photosensitizer species can transfer its energy to molecular oxygen, yielding singlet oxygen ($^1O_2$), and as a result, returns to its resting ground state. Photochemical reactions that are mediated by oxygen are referred to as type II photochemical or photosensitized reactions. The singlet oxygen thus generated reacts with a variety of cellular components, including lipids, proteins and nucleic acids. The efficiency by which a given photosensitizer generates singlet oxygen from light can be expressed as its quantum yield; photosensitizers with a high quantum yield are better suited for clinical PDT.

Singlet oxygen is by no means the only active intermediate generated by the triplet photosensitizer. A variety of other reactive oxygen species, including peroxides (H_2O_2), superoxide anion (O_2^-) and hydroxyl radicals (.OH), are generated from molecular oxygen and undoubtedly contribute to the overall biologic effect. Singlet oxygen and other reactive oxygen species can also interact chemically with the photosensitizer itself, leading to its inactivation by a process known as photobleaching. In this way, the PDT process can in part shut itself off automatically.

Light within the visible spectrum is typically used for PDT. This is because ultraviolet light has limited tissue penetration and infrared radiation (>850 nm) does not possess sufficient photon energy to trigger the transformation of molecular oxygen into singlet oxygen via an excited photosensitizer intermediary.

When PDT photosensitizers are excited to their singlet states, they can alternatively return to their ground state via the emission of a

PHOTODYNAMIC THERAPY VERSUS PUVA THERAPY	
SIMILARITIES	
• Chromophore is an exogenous drug • Photosensitizer can be topical or systemic • Specific wavelengths of light are used to activate photosensitizer within tissue • Broad range of potential dermatologic applications	
DIFFERENCES	
PDT	**PUVA**
• Topical photosensitization based on ALA and its derivatives relies on the endogenous metabolism of prodrugs	• Topical psoralen is active in its native form as administered
• Systemic PDT photosensitizers are administered parenterally	• Systemic psoralens are administered orally
• Visible light used for photosensitizer activation	• UVA light activates psoralens
• Type II photochemical reactions convert molecular oxygen to singlet oxygen	• Type I photochemical reactions generate covalent adducts between psoralens and DNA
• Can be used to treat non-melanoma skin cancer	• Carcinogenic

Table 135.1 Photodynamic therapy (PDT) versus PUVA (psoralens plus UVA light) therapy.

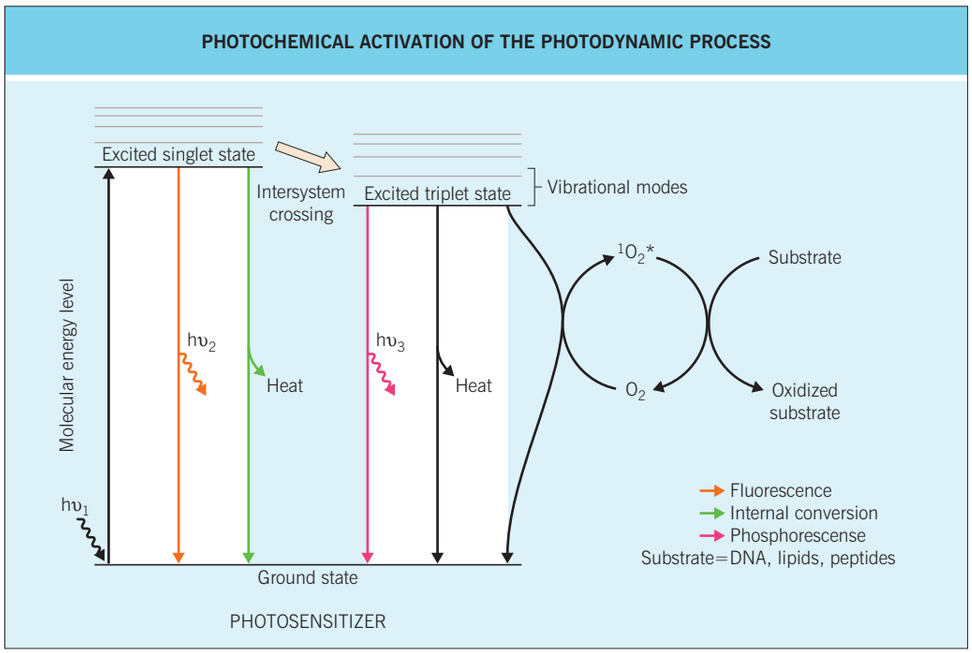


Fig. 135.2 Photochemical activation of the photodynamic process and the generation of reactive singlet oxygen: the Jablonski energy state diagram. The photosensitizer is delivered to or generated within the target tissue in its ground, lower-energy resting state. If light of an appropriate wavelength is used to irradiate the photosensitizer within tissue, photon absorption occurs and the photosensitizer is excited to a higher-energy "singlet" state. The excited singlet is short-lived, lasting nanoseconds, and then undergoes intersystem crossing to a more stable "triplet" state which has a lifetime on the order of microseconds. The "triplet" photosensitizer species can transfer its energy to molecular oxygen, yielding singlet oxygen ($^1O_2$), and as a result, returns to its resting ground state. See PDT Photochemistry section for additional details. *Excited state.

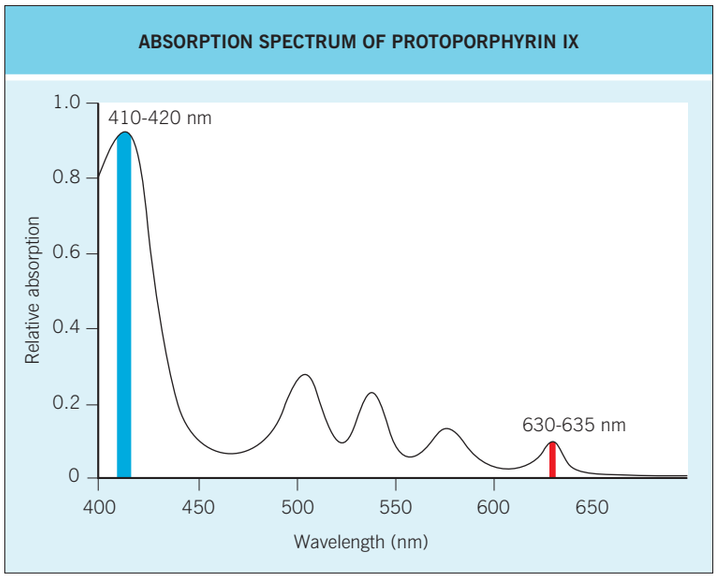


Fig. 135.3 Absorption spectrum of protoporphyrin IX (PpIX). The absorption spectrum depicts the efficiency of absorption of light as a function of wavelength. It reveals the major absorption (photoactivation) peaks of PpIX. The blue (410–420 nm) and red (630 nm) wavelengths are typically used to activate PpIX in photodynamic therapy.

photon. This emission of light by the photosensitizer is termed fluorescence and the latter property permits, with Wood's lamp illumination (365 nm), direct visualization of photosensitizer accumulation or photobleaching within tissue. Because of minor energy dissipation during the singlet state, the actual energy of the emitted fluorescence photon is typically slightly lower than that of the initially absorbed photon; therefore, the fluorescence signal is of a higher wavelength (red- or "Stokes"-shifted) than the ultraviolet-A (UVA) light emitted by a Wood's lamp. Another pathway whereby an excited singlet can return to the ground state is non-radiative decay in which heat is released. This latter photothermal pathway is the primary mechanism of action for lasers and intense pulsed light (IPL) sources.

By way of comparison to PUVA, UVA absorption by a psoralen molecule elevates it to an excited state. The latter then reacts directly with biomolecules such as DNA without any requirement for oxygen as an intermediary. These non-oxygen-dependent processes are customarily termed type I photochemical or photosensitized reactions.

Photobiologic Mechanisms of Action

As previously noted, type II photochemical (photosensitized) reactions require oxygen in order to generate reactive oxygen species, with singlet oxygen being the most important reactive oxygen species in PDT. The net biologic effects of singlet oxygen are presumably dependent upon the extent and location of its production. Although the exact and most relevant molecular sequence of reactions initiated by singlet oxygen has not been determined, oxidative damage (including to cellular membranes) is known to trigger cellular injury and apoptosis. For a given PDT clinical effect or indication, the specific mechanism of action depends on the target tissue, the photosensitizer and its mode of delivery, subcellular photosensitizer localization, and the overall drug–light dose delivered. For example, systemic photosensitizers are known to preferentially localize to the vascular bed of tumors. Light activation then leads to vascular collapse and ischemic tumor necrosis (see Fig 135.1)[5]. In contrast, when topical ALA is applied to an epidermal carcinoma such as Bowen's disease, PpIX accumulates within the actual tumor cells, with direct cytotoxicity upon light activation.

At a high drug–light dose, greater levels of singlet oxygen are presumably generated during PDT, leading to necrotic tissue damage. With lower levels of drug and/or light, damage is more limited, with apoptotic changes in a fraction of the cells. Because PDT is oxygen-dependent, target tissues that are hypoxic may prove relatively resistant to the desired therapeutic effect.

Tissues exposed to PDT can become inflamed as a result of normal host responses to injury as well as activation of specific immunologic reactions. As with the underlying mechanism of action, the type of immunologic reaction varies depending upon the target and mode of PDT delivery. In animal models of contact hypersensitivity, PDT suppresses local and systemic immune responses in addition to reducing epidermal Langerhans cells[6]. There is also evidence that the photosensitizers used in PDT can target activated T cells[7,8], providing one rationale for using PDT to treat inflammatory disorders such as psoriasis. Microbes, including viruses, bacteria, fungi and parasites, may be susceptible to singlet oxygen, and there is a growing number of clinical studies attesting to the potential utility of PDT in the treatment of skin infections.

PDT Selectivity

PDT was initially conceived and developed as a method for achieving selective tumor destruction. Several factors lead to this selectivity (Table 135.2). In neoplasms, where cellular metabolism is higher than normal, local factors such as enhanced perfusion, vascular and lymphatic hyperpermeability, pH and lipoprotein receptors on target cells may lead to preferential accumulation and retention of photosensitizers within the

MECHANISMS FOR ACHIEVING SELECTIVITY DURING PHOTODYNAMIC THERAPY	
Photosensitizer effects	**Light effects**
• Selective photosensitizer retention • Selective photosensitizer biodistribution and uptake • Ability to limit surface area of photosensitizer application (non-systemic drugs) • Variation of the time between drug administration and light exposure	• Spatial confinement of irradiation to the target • Wavelength dependence for light penetration into skin • Photobleaching of photosensitizer • Interstitial delivery of light via fiberoptic probes

Table 135.2 Mechanisms for achieving selectivity during photodynamic therapy.

tumor. With topical PDT, the surface area of drug application can be confined, thus limiting the zone of photosensitization. There are also inherent differences in the permeability barrier of skin lesions such as basal cell carcinomas, actinic keratoses, and psoriasis that facilitate the uptake of ALA-like prodrugs into the epidermis and dermis. In addition, the temporal differences in how photosensitizers are partitioned between diseased versus normal tissue can be exploited to enhance selectivity; by varying the time delay (that is typically required between drug administration and light exposure), a more advantageous photosensitizer ratio between diseased and normal skin can be achieved. Determining the optimal time for this delay or incubation period is usually a matter of systematic empiric testing.

Selectivity is also achieved by manipulation of the light component of PDT (see Table 135.2). At the simplest level, this entails restricting the area of light exposure on the skin, usually with the lesion in the center plus a limited margin of adjacent normal-appearing skin. Most clinical photosensitizers exhibit multiple absorption maxima across the visible spectrum (see Fig. 135.3). Because light propagation within tissue is wavelength-dependent, the use of shorter wavelengths, i.e. blue light, will confine the PDT effect to primarily the epidermis, while red light will exert a deeper effect. For deeper targets within the skin, fiberoptic probes can be implanted interstitially in the dermis or subcutaneous tissue to deliver light.

Photobleaching is another mechanism by which PDT can exert selectivity. A certain threshold "drug–light PDT dose" exists for effects such as tissue necrosis. If the level of photosensitizer within *normal* tissue is below this threshold, light exposure will induce predominantly photobleaching rather than generating sufficient singlet oxygen to damage tissue. On the other hand, within the adjacent target site where the photosensitizer concentration is presumably above the required threshold, singlet oxygen generation will prevail.

Photosensitizer selectivity can readily be demonstrated given that PDT molecules usually have high fluorescence quantum yields that can actually be visualized (Fig. 135.4). Via fluorescence examination with a Wood's lamp, the margins of skin tumors can be delineated and this technique has been proposed as a diagnostic approach to non-melanoma skin cancers irrespective of any PDT intervention[9]. More accurate tumor delineation can be very helpful in planning treatment approaches to non-melanoma skin cancer. However, the fluorescence intensity, as assessed visually or by instrumentation, does not necessarily correlate with the ensuing PDT reaction or ultimate clinical outcome. Immediately, at the conclusion of the light exposure stage, the phenomenon of photobleaching can be confirmed visually by the absence or marked reduction of fluorescence.

Fig. 135.4 Fluorescence of intratumor protoporphyrin IX (PpIX) when illuminated by a Wood's lamp (365 nm). A Superficial basal cell carcinoma (BCC). **B** Following application of topical methyl aminolevulinate (mALA) for 3 hours under occlusion, the BCC demonstrates red fluorescence due to accumulation of PpIX.

Advantages and Limitations of PDT

Advantages of PDT include its relative conceptual simplicity as well as the accessibility of the skin to direct application of photosensitizing drugs and activating light. PDT photosensitizers typically have minimal dark toxicity (i.e. toxicity in the absence of light) and are therefore relatively safe. PDT can also be used in patients with a variety of comorbidities, including those who are anticoagulated, and general anesthesia is rarely required or even used for cutaneous PDT. There is a broad range of potential clinical applications and an ability to fine-tune and modulate the therapeutic effect by altering any one of several different treatment parameters, including drug dose, incubation time, light fluence, exposure time or field size. When used to treat actinic keratoses and superficial non-melanoma skin cancer, PDT has been shown to lead to better cosmesis than conventional approaches such as cryotherapy and surgery; perhaps this is due to its selective properties.

Nonetheless, PDT is far from being a perfect therapeutic modality as it has inherent limitations. The generation of singlet oxygen within the target site is critically dependent on the ability to deliver both photosensitizer and light to this site in the presence of oxygen. Systemic administration results in more widespread distribution of photosensitizer, which is advantageous when treating extensive areas of involvement or for delivering drug to thicker lesions such as invasive carcinomas. However, systemic drug delivery is via the intravenous route, and as a consequence, there is generalized cutaneous photosensitivity. Topical photosensitization is limited by drug penetration into the epidermis and dermis, while light delivery by surface illumination is limited by the depth of penetration of visible light. Although wavelengths such as infrared are more penetrating, they do not have

sufficient photon energy to generate singlet oxygen. Thus, PDT is useful primarily for superficial cutaneous tumors and diseases.

The fact that there are multiple treatment parameters can also be a disadvantage in that the multiplicity of combinations and permutations makes it complicated to determine the conditions necessary for optimal clinical outcomes. Moreover, the literature is replete with an array of different reported parameters, making it difficult to standardize treatment regimens and evaluate clinical evidence of efficacy, even for the same indication. The commercially recommended treatment parameters are based on strict clinical trial protocols and do not afford much flexibility in terms of dosing. From the patient perspective, intraoperative local pain at the site of light exposure can be intense and even intolerable, and for many patients this represents a significant disincentive for repeat treatments. Finally, commercially available PDT systems (i.e. photosensitizers and light sources) incur significant cost, thereby posing a practical barrier to accessing a treatment that is fundamentally based on a naturally occurring compound combined with visible light.

COMPONENTS OF PDT

In PDT, the physician provides two of the three essential components – the photosensitizing drug and light. A wide range of photosensitizers (Fig. 135.5) have been developed and evaluated along with a multiplicity of different light sources and delivery systems. Of these, only two commercial systems are currently approved for use by the US FDA: ALA plus blue light and mALA plus red light.

Photosensitizers

Topical photosensitizers

Although topical photosensitizers based on the porphyrin backbone have been developed and evaluated, none to date have become practical, on a clinical or commercial level, for dermatologic use. For practical purposes, topical PDT relies primarily on the ALA prodrug approach.

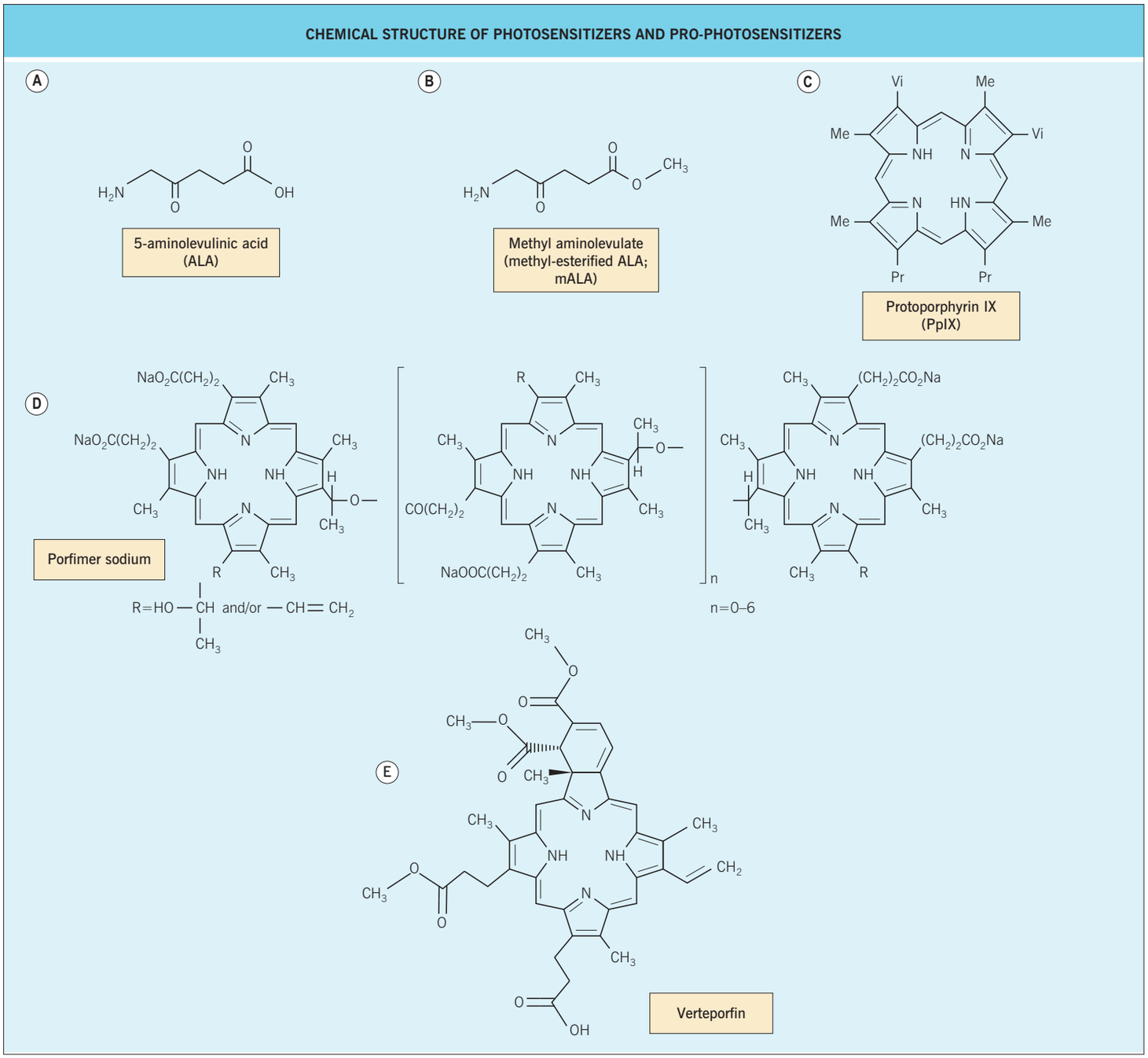


Fig. 135.5 Chemical structures of photosensitizers and pro-photosensitizers. A 5-aminolevulinic acid (ALA). **B** Methyl aminolevulinate (methyl-esterified ALA; mALA). **C** Protoporphyrin IX (PpIX). **D** Porfimer sodium. **E** Verteporfin. Me, methyl; Pr, propionic acid; Vi, vinyl.

TOPICAL PHOTOSENSITIZER PRODRUGS USED FOR DERMATOLOGIC PHOTODYNAMIC THERAPY		
Drug – generic name	5-aminolevulinic acid HCl (ALA)	Methyl aminolevulinate (methyl-esterified ALA; mALA)
Drug – trade name® and formulation	Levulan, 20% hydroalcoholic solution	Metvixia, 16.8% cream
Photosensitizer produced	PpIX	PpIX
Treatment λ (nm)	417, 630	630
Time period between administration and irradiation (incubation time)	14–18 h, but often reduced to 1–4 h with retention of efficacy and less phototoxicity	3–4 h under occlusion
Light source	Blue fluorescent lamp* Various other sources also used	Red LED (light emitting diode) lamp* Various other light sources also used
Cutaneous FDA-approved indications†	AKs	AKs
Common off-label uses	BCC, Bowen's disease, mycosis fungoides, photoaging, acne	BCC, Bowen's disease, mycosis fungoides, photoaging, acne

*FDA-approved light source.
†At the time of writing.

Table 135.3 Topical photosensitizer prodrugs used for dermatologic photodynamic therapy. AKs, actinic keratoses; BCC, basal cell carcinoma; FDA, Food and Drug Administration; PpIX, protoporphyrin IX.

Aminolevulinic acid (ALA) and methyl aminolevulinate (mALA) prodrugs

Aminolevulinic acid (ALA) and methyl aminolevulinate (mALA) represent prodrugs that are converted within the skin into PpIX (Table 135.3). A familiarity with porphyrinogenesis in mammalians aids in understanding the pharmacology of ALA and its congeners. ALA (5-aminolevulinic acid, δ-aminolevulinic acid) is synthesized in all nucleated cells, and it is an intermediate compound in the heme biosynthetic pathway (see Fig. 49.1); ALA synthase catalyzes the formation of ALA from succinyl-CoA and glycine. The latter reaction represents the rate-limiting step in this pathway and is inhibited by heme.

When pharmacologic quantities of ALA are supplied to cells as in PDT, this regulatory step is bypassed, leading to an intracellular accumulation of PpIX, which is photodynamically active. The formation of PpIX is the penultimate step in the *de novo* synthesis of heme, with the formation of heme requiring the addition of Fe^{2+} to PpIX via ferrochelatase. The effect of topical ALA can be enhanced by using an iron chelator to decrease heme formation, thereby allowing unfettered ALA synthase activity (due to a lack of feedback inhibition). The net result is a greater concentration of PpIX and an enhanced PDT effect[10]. Of note, PpIX is synthesized within mitochondria (see Fig. 135.1) and then diffuses to cellular membrane systems such as the endoplasmic reticulum and the plasma membrane.

ALA can be administered via topical, oral or parenteral routes, and for cutaneous indications, the topical approach is preferred due to its simplicity. Unlike fully formed porphyrin molecules that are relatively large, ALA is small and simple and crosses the surface permeability barrier readily via active transport mechanisms. Within the skin, the absorbed ALA induces porphyrinogenesis, thereby inducing a porphyric state at the cellular level. Since the skin's barrier function is often impaired in diseased states, there can be selective PpIX generation due to enhanced ALA absorption. In some PDT applications, the skin is first prepared by gentle curettage of excess surface scale and crust, and this may also promote topical drug absorption. Within the skin, PpIX accumulates in the epidermis and sebaceous glands due to its lipophilicity[11].

The carboxyl moiety of ALA can be esterified by a variety of alkyl groups, the simplest of which results in methyl aminolevulinate (mALA). Substituted ALA congeners are absorbed into the skin by passive and active mechanisms different from those of ALA, and upon their uptake into cells, these substituents are hydrolyzed to yield free ALA (see Fig. 135.1). Esters other than mALA are currently investigational agents only, with the exception of hexyl-aminolevulinate which is used for bladder carcinoma in Europe. Both ALA and mALA are considered prodrugs or pro-photosensitizers since the skin actually generates the active photosensitizer from these exogenous compounds. The relative merits of ALA versus mALA as a topical photosensitizer have been actively debated on various theoretical grounds, but there are no clear results from clinical studies to settle this issue.

ALA has been compounded in a variety of different vehicles for topical application, and in North America it is commercially available in a 20% preparation marketed as Levulan®. The latter is a topical hydroalcoholic solution that is freshly prepared immediately prior to application. Its labeled use is for treating actinic keratoses, although multiple off-label applications have been explored and described (see Table 135.3). Time is required to allow ALA to be absorbed and converted to PpIX, with a recommended incubation period of 14–18 hours without occlusion prior to exposure to blue fluorescent light. Many clinicians typically use a shorter incubation period of 1–4 hours, instead of the recommended 14–18 hours which was based primarily on controlled clinical trials.

Mechanistically, mALA is similar in principle to ALA; it is available in a 16.8% cream formulation (Metvixia®) that must be stored in a refrigerator. mALA is applied for 3–4 hours under occlusion prior to exposure to red light from an LED. mALA has also been used for multiple different applications but its labeled use is only for actinic keratoses and superficial non-melanoma skin cancers in various countries (see Table 135.3).

Photochemically, PpIX has an absorption spectrum similar to that of other porphryins (see Fig. 135.3). There is a prominent, broad blue Soret absorption band along with four smaller "Q" bands between 500 and 635 nm. PpIX will be converted to its singlet and triplet states more efficiently if pumped by light at one or more of these absorption maxima.

Systemic photosensitizers

Hematoporphyrin derivative and porfimer sodium are considered first-generation PDT photosensitizers. Both are preferentially retained by neoplastic tissue and thus provide some degree of treatment selectivity. Hematoporphyrin derivative and porfimer sodium are complex mixtures of covalently linked esters and ethers of dimeric and oligomeric hematoporphyrin subunits that have a relative absorption maximum near 630–635 nm (see Fig. 135.5). Unfortunately, these first-generation agents also persist in the skin for several weeks, resulting in marked photosensitivity to ordinary outdoor light.

Second-generation porphyrin photosensitizers were developed with pharmacokinetic profiles that favored more rapid elimination from the skin, resulting in shorter periods of generalized photosensitivity, e.g. 1–3 days in the case of verteporfin[12]. Systemic second-generation photosensitizers are pure substances that have a defined composition and are based on the tetrapyrrole porphyrin backbone. They exhibit absorption maxima that are at longer wavelengths (660–700 nm) than those of the first-generation agents, thus allowing a more penetrating light to be used for drug activation. Second-generation photosensitizers have been explored in limited studies for non-melanoma skin cancer, psoriasis and port-wine stains, but the only FDA-approved second-generation agent is verteporfin and its indication is for PDT of age-related macular degeneration. Although systemic porphyrins are not used to any great extent for treating skin disease, dermatologists should nonetheless be familiar with their medical use given their propensity to cause phototoxic cutaneous drug reactions.

Light Sources

Choosing a light source for PDT depends fundamentally on three considerations. First, the spectral output of the light should include a waveband that corresponds to one or more of the peaks in the absorption spectrum of the photosensitizer. Next, the desired depth of effect determines which photosensitizer absorption peak should be chosen. For PpIX, red light activation will provide a deeper clinical effect as compared to blue light. The surface area to be treated must also be taken into account. For example, while lasers can provide precise

LIGHT SOURCES FOR PHOTODYNAMIC THERAPY (PDT)			
Light source	**Spectral output**	**Commercial name**	**Properties and comments**
Sunlight	Broadband	–	• Universally accessible, although highly variable • Difficult to standardize light dose • Significant risk of excess phototoxicity
Incandescent	Broadband	–	• Optical filters used to produce specific wavebands • Slide projector is an example
Arc lamp	Broadband	–	• Optical filters used to produce specific wavebands
Metal halide lamp	Broadband	–	• Optical filters used to produce specific wavebands
Fluorescent lamp	Broadband	Blu U®	• Blue output to match the Soret band • Recommended fluence of 10 J/cm^2 • FDA-approved for use with ALA to treat actinic keratoses
Light-emitting diodes (LED)	Narrowband	Aktilite®	• Red output • Recommended fluence of 37 J/cm^2 • FDA-approved for use with mALA to treat actinic keratoses; also approved in other countries for treating superficial BCC and Bowen's disease
Lasers	Monochromatic	Various	• Relatively expensive • May generate photothermal effects in addition to PDT • Small exposure field • Output can be continuous or pulsed
Intense pulsed light (IPL)	Broadband	Various	• Relatively expensive • May generate photothermal effects in addition to PDT

Table 135.4 Light sources for photodynamic therapy (PDT). ALA, 5-aminolevulinic acid; BCC, basal cell carcinoma; FDA, Food and Drug Administration; mALA, methyl aminolevulinate.

irradiation, they may be impractical for treating broad or extensive surfaces.

Several different types of light sources have been used for PDT (Table 135.4), but only two of these are approved by the FDA. These commercial devices are relatively simple to use and can be powered by standard electrical outlets. Although lasers are essential for endoscopic PDT applications in which fiberoptic probes are required, they are optional when treating the skin. For PDT, continuous wave lasers are usually configured as argon- or KTP-pumped dye lasers emitting red light; pulsed dye lasers have been used primarily for the treatment of actinic keratoses with ALA. Of note, non-monochromatic sources are simpler, cheaper and more efficient than lasers for PDT. In theory, natural sunlight can also be used for drug activation in PDT since it contains all of the appropriate wavelengths, and pilot clinical studies have demonstrated its potential efficacy[13]. The main drawback to sunlight is the inability to accurately control the light dose delivered to the skin and the increased risk of excessive phototoxicity. Therefore, at present, it is not routinely recommended outside of a research setting.

Regardless of the specific light source, in PDT the light dose is measured and delivered in a manner analogous to conventional phototherapy. The ***irradiance*** of the lamp is specified in units of W/cm^2, and this represents the power density over a surface area unit. Irradiance (or power density) depends on the light source itself, and irradiance can vary based on the lamp's age, overall operating conditions, and the distance from the lamp to the skin target. The absolute light dose used to activate the photosensitizer is also known as the ***fluence*** and is measured in J/cm^2. The ***exposure time*** in seconds required to deliver a specified fluence can be determined from the formula:

$$\text{exposure time} = \frac{\text{fluence (J/cm}^2\text{)}}{\text{irradiance (W/cm}^2\text{)}}$$

PDT Dosimetry

Although PDT is deceptively simple in concept, there is a multitude of considerations in determining the appropriate doses of photosensitizer and light. Current clinical PDT dosing guidelines have been determined by systematic as well as semi-empiric clinical investigations; nevertheless, they are based on several basic concepts unique to PDT. The net production of singlet oxygen depends on both the amount of photosensitizer and the fluence of light delivered to the target. A certain degree of reciprocity exists between these two components, in that a high photosensitizer level combined with a low fluence can in theory produce the same amount of singlet oxygen as a low concentration of photosensitizer activated by a high fluence. The overall "PDT dose" can thus be viewed mathematically as a "drug × light dose" product so that an equivalent clinical effect can be achieved using different combinations of drug and light. However, for topical PDT, there are upper limits as to the amount of photosensitizer that can actually be delivered to the skin, due to absorption issues.

Another important limit to the principle of drug–light dose reciprocity relates to the irradiance of the activating light. At very high irradiances, there is significant heat production due to both non-radiative photosensitizer absorption/relaxation and nonspecific light absorption by other tissue chromophores. This leads to photothermal effects superimposed on the PDT process itself. For example, utilization of a yellow pulsed dye laser to activate PpIX within actinic keratoses will induce a combination of PDT plus photothermal reactions since each laser pulse has a very high peak irradiance[14]. In some instances, these added photothermal effects may possibly be desirable, but to date this approach has not been systematically studied for cutaneous PDT. At lower irradiances, on the other hand, there is evidence that the pain associated with PDT might be reduced[15].

Other factors that can influence the PDT effect include the waiting period between drug administration and light exposure and the mode by which the light is delivered. There must be a sufficient "incubation" time for the photosensitizer to specifically accumulate within the target sites prior to activation. A longer incubation time for topical ALA or mALA may achieve a higher level of photosensitization without the need for a higher prodrug concentration. An interesting and potentially useful variation in light delivery is to fractionate the total light dose into a series of two or more separate exposures, each punctuated by defined intervals. The potential net effect of fractionating the light dose is achieving a greater overall PDT effect even without applying more drug[16]. Mechanistically, there are several reasons why this can happen. During PDT, molecular oxygen is consumed, and a pause in light exposure allows oxygen to be replenished via vascular reperfusion and diffusion. Likewise, this pause may also allow more photosensitizer to be either: (1) synthesized *de novo* from the residual ALA that may still be present within viable skin cells (following topical application); or (2) delivered via the bloodstream (systemic photosensitizers).

INDICATIONS

The applications of PDT in dermatology have extended far beyond its initial use for eradicating skin cancers. Although the ever-expanding use of PDT has been partly random and empiric, certain pharmacologic properties provide a rational basis for many of these proposed and accepted indications. PDT agents can photosensitize neoplastic, inflamed and vascular tissues, modulate immunologic processes, localize to the pilosebaceous unit, and cause lethal damage to microbes. Historically, the field has evolved from myriad scattered case reports to larger controlled trials. To date, good-quality clinical evidence outside of cutaneous oncology is limited; for the most part,

PROSPECTIVE CONTROLLED STUDIES OF TOPICAL PHOTODYNAMIC THERAPY OF ACTINIC KERATOSES						
Comparator and design (ref.)	**No. of patients**	**Topical photosensitizer & concentration**	**Incubation time**	**Light source**	**Response rate**	**Comments**
Paired comparison to topical 5-FU[19]	14 (hand AKs)	ALA 20% under occlusion	4 h	Red light (580–740 nm) at 150 J/cm^2 and mean irradiance of 86 mW/cm^2	Total surface area of AKs reduced by 70% (73% for 5-FU)	• 5% 5-FU cream was applied twice daily for 3 weeks • Assessed over 6 months • Pain and erythema similar in two groups*
Comparison with cryotherapy[20]	193 (95 cryotherapy controls)	mALA 16% under occlusion	3 h	Red light (570–670 nm) at 75 J/cm^2	69% (75% for cryotherapy)	• Prior to PDT or cryotherapy, superficial curettage was performed • Two cycles of cryotherapy • Excellent or good cosmetic outcome: PDT, 98%; cryotherapy, 91%
Comparison to cryotherapy or vehicle[21]	204	mALA 16% under occlusion	3 h	Red light (570–670 nm) at 75 J/cm^2	91% at 3 months (68% for cryotherapy and 30% for vehicle alone)	• Two cycles of PDT • Single freeze–thaw cryotherapy • Superior cosmesis with PDT versus cryotherapy
Comparison to vehicle[22]	80	mALA 16% under occlusion	3 h	Red light (570–670 nm) at 75 J/cm^2	89% at 3 months (38% for vehicle alone)	• Two cycles
Vehicle-controlled[23]	243	ALA 20%	14–18 h	Blue fluorescent lamp at 10 J/cm^2	89% at 12 weeks (13% for vehicle alone)	• Two sessions of PDT allowed
Vehicle-controlled in organ transplant recipients[24]	17	mALA 16% under occlusion	3 h	Red light (600–730 nm) at 75 J/cm^2	90% at 16 weeks (0% for vehicle alone)	• Two sessions of PDT
Comparison to cryotherapy; right–left intra-individual design[17]	119	mALA 16% under occlusion	3 h	Red LED light (near 630 nm) at 37 J/cm^2	89% at 24 weeks (86% for cryotherapy)	• PDT retreatment at 12 weeks allowed • Double freeze–thaw cryotherapy • Superior cosmesis with PDT
Vehicle-controlled[25]	49	mALA 16% under occlusion	3 h	Red LED light (near 630 nm) at 37 J/cm^2	86% at 3 months (52% for vehicle alone)	• Two sessions of PDT
Comparison to topical imiquimod on extremities[26]	30	ALA 20% under occlusion	4 h	Red light (570–670 nm) at 75 J/cm^2	65% at 6 months (56% for imiquimod)	• Two sessions of PDT • Imiquimod three times per week for 4 weeks; second 4-week course of imiquimod allowed 4 weeks after end of first course
*Pain and erythema was maximal at the start of therapy for PDT and at the end of therapy for 5-FU.						

Table 135.5 Prospective controlled studies of topical photodynamic therapy (PDT) of actinic keratoses (AKs). Unless noted otherwise, each patient received a single PDT session. ALA, 5-aminolevulinic acid; 5-FU, 5-fluorouracil; h, hours; LED, light-emitting diode; mALA, methyl aminolevulinate (methyl-esterified ALA).

non-oncologic uses of PDT are off-label or investigational in virtually all jurisdictions. The overwhelming majority of indications in dermatology involve photosensitization via the topical route with an ALA-type prodrug, as no systemic photosensitizers are currently approved for dermatologic use.

Oncologic

PDT is an accepted and approved treatment for actinic keratoses (AKs). For superficial carcinomas such as superficial basal cell carcinoma (BCC) and Bowen's disease (*in situ* squamous cell carcinoma), there are controlled trials on the use of topical PDT and licensed approvals vary according to country. PDT is not used for treating melanoma because of the competition between melanin and photosensitizer for light absorption.

Based on biophysical considerations alone, AKs can be treated with blue or red light, whereas only red light should be used for non-melanoma skin cancer. Multiple studies have documented that cosmesis following PDT can be superior to that following conventional therapies[17,18]. One of the ideal aspects of PDT is that it seems to be particularly practical and well suited for patients with multiple synchronous AKs or cutaneous carcinomas or evidence of field cancerization. In patients with an extensive burden of many superficial, disseminated tumors, the availability of a systemic photosensitizer would be advantageous.

Actinic keratoses (AKs)

Being superficial, AKs would not be expected to pose any major obstacles to efficacy, and clinical trials have demonstrated that up to 90% of AKs can be cleared with topical PDT[17,19–26] (Table 135.5, Fig. 135.6). Hypertrophic AKs may prove more difficult to eradicate due to drug and light penetration issues; so, prior to PDT, curettage debridement of scale is often recommended. For hypertrophic AKs, multiple treatment sessions may be required to achieve a satisfactory overall result.

AKs can be treated on a lesion-by-lesion basis, or by applying photosensitizer to a broad area of photodamaged skin harboring active lesions. A more brisk and extensive reaction may occur when applying topical ALA or mALA to a broad field and it may be reasonable to consider a shorter incubation period. The latter approach allows for concomitant treatment of subclinical AKs[27]. Actinic cheilitis represents an excellent potential PDT application since alternative treatment approaches such as surgical vermilionectomy or laser vaporization are more complicated and morbid[28].

Basal cell carcinoma (BCC)

Superficial BCCs respond well to PDT, with an expected primary clearance rate of 87% with a follow-up of 3–36 months[29] (Table 135.6, Fig. 135.7). Nodular BCCs do not appear to be as well suited to PDT as a

Fig. 135.6 Photodynamic therapy (PDT) of facial actinic keratoses. A Pre-treatment. **B** Three months following PDT utilizing topical methyl aminolevulinate (mALA; 3 hours under occlusion) plus irradiation with red light from an LED (light-emitting diode), resulting in clearing of lesions.

PROSPECTIVE CONTROLLED TRIALS OF TOPICAL PHOTODYNAMIC THERAPY OF BASAL CELL CARCINOMA						
Comparator and design (ref.)	**No. of patients or lesions**	**Topical photosensitizer (concentration)**	**Incubation time**	**Light source**	**Response rate**	**Comments**
SUPERFICIAL BCC						
Comparison with cryosurgery[30]	36 lesions (21 PDT; 15 cryotherapy)	ALA (20%) under occlusion	6 h	635 nm laser at 60 J/cm^2 and 60–100 mW/cm^2	61% for PDT at 1 year (93% for cryosurgery)	• Response rate based on histologic evaluation at 1 year • Prior to PDT, crusts, stratum corneum and lipids removed • Cryosurgery consisted of two 25–30-sec freeze–thaw cycles with a 2–4-min interval
Comparison with cryotherapy[31]	118 patients	mALA (160 mg/g) under occlusion	3 h	Red light (570–670 nm) at 75 J/cm^2	5-year recurrence rate 22% (20% recurrence rate for cryotherapy)	• Up to two additional PDT sessions if incomplete response at 3 months • Cryotherapy performed with two freeze–thaw cycles • Better cosmesis with PDT
Comparison with surgery[32]	196 patients	mALA (160 mg/g) under occlusion	3 h	Red LED light at 37 J/cm^2	12-month recurrence rate 9.3% (0% for surgery)	• PDT: two sessions 7 days apart; two sessions repeated in 3 months if incomplete response • Better cosmesis with PDT
NODULAR BCC						
Comparison to excisional surgery with ≥5 mm margins[18]	101 patients	mALA (160 mg/g) under occlusion	3 h	Red light (570–670 nm) at 75 J/cm^2	83% at 1 year (96% for surgical excision)	• PDT: two sessions 7 days apart • If incomplete response at 3 months, second course (two sessions) of PDT given • Prior to PDT, superficial curettage was performed • Better cosmesis with PDT

Table 135.6 Prospective controlled trials of topical photodynamic therapy (PDT) of basal cell carcinoma (BCC). Unless noted otherwise, each patient received a single PDT session. ALA, 5-aminolevulinic acid; h, hours; LED, light-emitting diode; mALA, methyl aminolevulinate; min, minutes; sec, seconds.

lower response rate of 53–71% has been observed[29]. More than one session of PDT may be required to treat a given BCC. Multiple BCCs arising in the context of cancer-prone genodermatoses such as nevoid basal cell carcinoma syndrome are probably a good application for PDT since multiple lesions can be treated during one session[33]. Difficult-to-treat BCCs (e.g. recurrent, sclerosing type, large volume) are probably best dealt with by Mohs micrographic surgery or radiotherapy because of the importance of achieving deep margin control.

Bowen's disease

Bowen's disease (BD) is confined, by definition, to the epidermal compartment and is thus eminently within the therapeutic range of PDT (Table 135.7). Many PDT experts consider BD to be an ideal indication since PDT can be used to treat multiple lesions as well as large, extensive plaques[37]. Tumors that behave clinically like BD but with microinvasive histology also seem to respond to PDT[38]. Invasive squamous cell carcinomas are ill-suited to PDT and clinical experience confirms this statement. BD of the genital region and extramammary Paget's disease can be appropriate targets for PDT.

Mycosis fungoides

Activated and malignant T cells can be selectively sensitized by exogenous ALA, and this is why PDT has been used to treat the mycosis fungoides form of cutaneous T-cell lymphoma. Interestingly, these lymphocytes express high levels of transferrin and have a corresponding low intracellular level of iron, conditions that favor PpIX accumulation

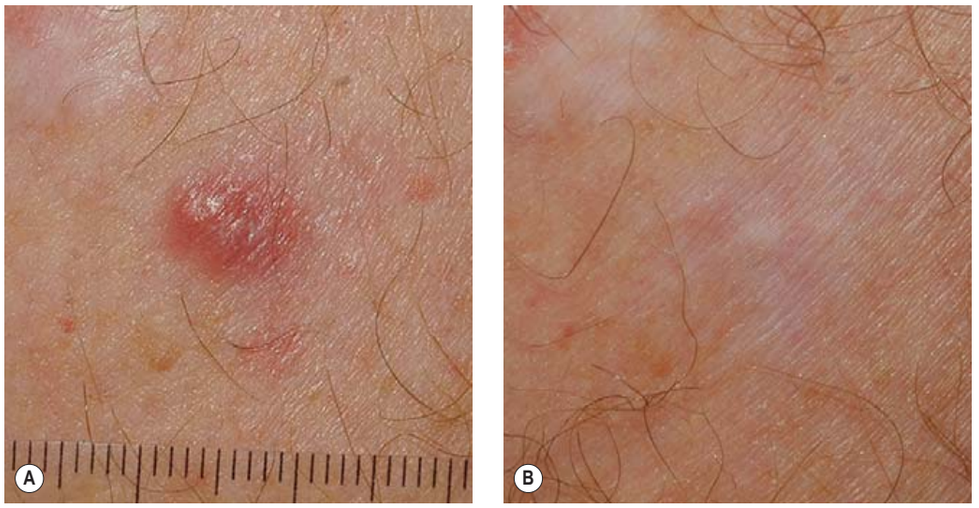


Fig. 135.7 Photodynamic therapy (PDT) of a superficial basal cell carcinoma (BCC). **A** Superficial BCC prior to treatment. **B** Two years following PDT utilizing topical methyl aminolevulinate (mALA; 3 hours under occlusion) plus irradiation with red light from an LED (light-emitting diode; 37 J/cm^2), with complete clinical resolution.

PROSPECTIVE CONTROLLED TRIALS OF TOPICAL PHOTODYNAMIC THERAPY OF BOWEN'S DISEASE (*IN SITU* SQUAMOUS CELL CARCINOMA)

Comparator and design (ref.)	No. of patients or lesions	Topical photosensitizer (concentration)	Incubation time	Light source	Response rate	Comments
Comparison with cryotherapy[34]	40 lesions (<2 cm)	ALA (20%)	4 h	Red light (615–645 nm) at 125 J/cm^2 and 70 mW/cm^2	75% [15/20 at 1 year] (50% [10/20] for cryotherapy)	• Cryotherapy (cryo) was a 20-second freeze–thaw cycle • PDT: one session • For complete clearance of non-responding tumors, cryo-treated group required 2–3 more cryo treatments (2 recurrences at 1 year) and PDT-treated group required 1 more PDT treatment (0 recurrences)
Comparison with 5-FU[35]	40 patients	ALA (20%)	4 h	Red light (615–645 nm) at 100 J/cm^2	82% at 1 year (48% for 5-FU)	• 5-FU daily for 1 week followed by twice daily for 3 additional weeks • PDT repeated after 6 weeks if necessary
Comparison with 5-FU and cryotherapy[36]	225 patients	mALA (160 mg/g) under occlusion	3 h	Red light (570–670 nm) at 75 J/cm^2	80% at 1 year (69% for 5-FU and 67% for cryotherapy)	• PDT repeated in 1 week; if necessary, additional PDT (1 cycle [2 sessions]) in 3 months • 5-FU applied for 4 weeks • Single freeze–thaw cycle for cryotherapy

Table 135.7 Prospective controlled trials of topical photodynamic therapy (PDT) of Bowen's disease (*in situ* squamous cell carcinoma). Unless noted otherwise, each patient received a single PDT session. ALA, 5-aminolevulinic acid; BD, Bowen's disease; 5-FU, 5-fluorouracil; h, hours; mALA, methyl aminolevulinate.

(see above)[7]. Because sufficient topical ALA can reach the target T cells within the epidermis and dermis, an appreciable clinical effect can be observed. Comparative studies are lacking, although some case series are quite encouraging[39].

Cutaneous metastases

PDT's historical roots in dermatology lie in its initial use during the 1970s to treat intracutaneous metastases[2]. Such treatment is palliative, and, depending on the thickness of the nodule, systemic rather than topical photosensitization may be preferable. In the past, PDT was often employed to treat advanced cancers, but it is now widely accepted that PDT is far more appropriate for treating superficial carcinomas.

Non-oncologic PDT Applications

Acne

Not only did early studies demonstrate that exogenous ALA could induce PpIX formation within the skin, they also noted the preferential accumulation of active photosensitizer and selective phototoxicity within the pilosebaceous unit[11]. In addition, singlet oxygen exerts antibacterial and anti-inflammatory effects. These effects, plus the increasing practical impediments to using oral isotretinoin, have provided a powerful impetus to developing PDT regimens for acne. The initial systematic study was published in 2000, where sustained improvement for 20 weeks following treatment with ALA and red light was observed[40]. The therapeutic effect correlated histologically with sebocytopenia, suggesting that sebaceous gland involution was a desirable and achievable endpoint. Since then, a variety of different treatment regimens have been described, but to date there have been no comparative trials with conventional acne therapies. Published clinical studies have focused primarily on high-dose or low-dose treatment regimens with reports of varying results and putative mechanisms[41]. High-dose PDT is associated with more durable responses but at the expense of increased pain and local reactions (Fig. 135.8), whereas with low-dose PDT, improvement is more modest and transient. There remains no consensus as to the optimum treatment parameters for achieving either type of anti-acne effect.

Parenthetically, it should be noted that *Propionibacterium acnes* produces cutaneous porphyrins, which can be readily demonstrated by Wood's light examination of any sebaceous-dense area, including normal skin. Exposure to high-intensity blue light alone, in the absence of any exogenous PDT drug, can lead to clinical improvement of up to two-thirds of inflammatory acne lesions after eight treatment sessions[42].

Photoaging

When used to treat non-melanoma skin cancer and AKs, subjectively PDT is thought to produce cosmetically favorable results, including improvement of sun-damaged skin (Table 135.8). Well-designed trials directly comparing PDT to non-PDT treatments in which photoaging

Fig. 135.8 Use of photodynamic therapy (PDT) for moderate but recalcitrant acne vulgaris. This patient declined the use of oral isotretinoin and had failed therapy with topical agents and oral antibiotics. **A** Baseline. **B** Three days after PDT utilizing topical 20% 5-aminolevulinic acid (ALA; 3 hours incubation) followed by irradiation with red light from an LED (light-emitting diode; 630 nm; 37 J/cm^2; 70 mW/cm^2); intense inflammation and pustulation is limited to treated sites. **C** Two months after single treatment session. *Courtesy, Sunil Kalia, MD.*

is the primary focus are sparse relative to the extent that this treatment approach is advocated in clinical practice. Nonetheless, two separate studies of ALA-based PDT combined with IPL showed superiority for IPL alone in a side-by-side design involving 20 patients and 16 patients, respectively[44,45]. At the molecular level, PDT appears to stimulate the production of dermal collagen[46], while another study demonstrated expression of matrix metalloproteinases in photodamaged skin after PDT[47].

Psoriasis

In theory and practice, psoriatic plaques can be readily photosensitized by topical agents used in PDT. Lesional clearing has been observed with various light sources, including UVA and red light. High levels of PpIX within treated plaques correlated with significant and often dramatic pain upon light exposure. Pain, combined with the need for multiple treatments and a controlled trial demonstrating results inferior to narrowband UVB phototherapy[48], have made PDT a much less attractive option for psoriasis when compared to existing therapies, including targeted molecular therapies (biologics).

Cutaneous infections

There are several mechanisms by which PDT can treat infectious diseases. Singlet oxygen may destroy the microbes directly or it may activate host immunologic reactions against the microorganisms. In addition, PDT can induce necrosis of infected tissue, for example, in the treatment of verrucae or condylomata. Conditions that have been shown in controlled trials to improve with PDT include verruca vulgaris[49], condyloma acuminata[50,51], and leishmaniasis[52]. The emergence of drug-resistant bacteria has also motivated investigations into the treatment of bacterial skin infections with PDT[53].

Vascular anomalies

Systemic photosensitizers are biodistributed via the peripheral circulation and it stands to reason that intravascular drug activation with light would be useful in inducing the involution of abnormal vascular

SELECTED STUDIES OF TOPICAL PHOTODYNAMIC THERAPY FOR THE TREATMENT OF PHOTOAGING

Type of study (ref.)	No. of patients	Topical photosensitizer (concentration)	Incubation time	Light source	Response	Comments
Prospective, randomized, varying incubation times[27]	18	ALA (20%) solution	1, 2 or 3 h	Blue light (417 nm) at 10 J/cm^2	Improvement in skin quality, fine wrinkling and sallowness of facial skin	• 90% of treated hypertrophic AKs also responded
Case series, varying incubation times and light doses[43]	3 (phototypes I–III)	ALA (20%)	30 or 60 min	IPL (28 J/cm^2 or 26 J/cm^2 for skin types I/II and III, respectively)	Possible synergistic photo-rejuvenation due to potentiation of PDT by concomitant hyperthermia, but there were no PDT-alone or radiofrequency-alone controls	• IPL-based PDT was combined with radiofrequency (20 J/cm^2) • Erythema seen with 60-min incubation times but not with 30-min incubation times
Prospective, randomized, split-face, with comparison to IPL alone[44]	20	ALA (20%) solution applied twice after an acetone scrub	30–60 min	IPL (515–1200 nm) at 23–28 J/cm^2 (single pass; 2.4 ms pulse/15 ms delay/4 ms pulse)	Four weeks after the last treatment, in the ALA/IPL-based PDT group, global photodamage and mottled pigmentation were improved*; fine lines and pigmentation were successfully treated†	• Three treatments at 3-week intervals • All patients received two additional full-face IPL treatments • Contact cooling was used • Blinded observer • ALA/IPL-based PDT vs IPL – similar effects on tactile roughness and sallowness
Prospective, split-face, with comparison to IPL alone[45]	16	ALA (20%)	30–60 min	IPL (550/570–1200 nm) at 34 J/cm^2, double pulsing	Three months after final treatment, greater improvement with PDT: 55% vs 29.5% for IPL (crow's feet), 60% vs 37% for mottled pigmentation, 85% vs 54% for telangiectasia; greater clearance of AKs with PDT: 78% vs 54%	• Three treatments at monthly intervals

*Improved defined as a decrease in score by 1 point (5-point scale).
†Successful treatment defined as a decrease in score to 0 or 1.

Table 135.8 Selected studies of topical photodynamic therapy (PDT) for the treatment of photoaging. ALA, 5-aminolevulinic acid; AKs, actinic keratoses; h, hours; IPL, intense pulsed light; min, minutes; ms, milliseconds.

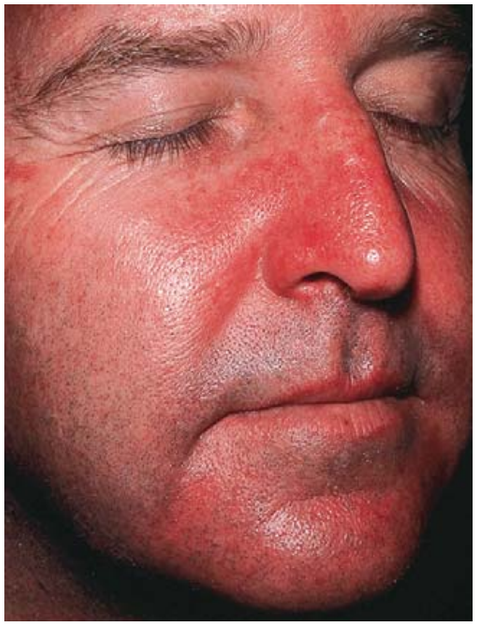


Fig. 135.9 Photosensitivity after oral 5-aminolevulinic acid (ALA). This patient sustained a phototoxic reaction 24 hours earlier by walking in bright sunlight several hours after oral ALA administration. The reaction resolved several days later. *Courtesy, Whitney Tope, MD.*

structures. Nowadays, this effect is clearly operative in two clinical situations: (1) vascular bed damage and ischemic necrosis following systemic photosensitization of carcinomas; and (2) destruction of hyperproliferative retinal blood vessels in age-related macular degeneration with systemic verteporfin-based PDT. Vascular malformations such as port-wine stains have been shown to respond to systemic PDT with results that appear to be at least equivalent to those achieved with conventional pulsed laser therapy[54]. Experience with this technique is largely from China, where hematoporphyrin-type preparations are used systemically.

ADVERSE EFFECTS AND COMPLICATIONS

PDT agents (prodrugs or photosensitizers) and visible light ordinarily possess minimal inherent toxicity, and the adverse effects related to PDT are largely an extension of the photochemical and photobiologic reactions that involve the generation of reactive oxygen moieties, especially singlet oxygen. Interestingly, erythropoietic protoporphyria could be considered a possible toxicity model for ALA and its congeners, since both clinical scenarios result in the overproduction of PpIX. The primary difference is that with erythropoietic protoporphyria, PpIX excess is constitutive, whereas with ALA-based PDT, the effect is transient.

Photosensitivity

Depending on the drug delivery method, cutaneous photosensitivity is generalized or localized. Systemic photosensitizers carry a greater risk of photosensitization and the risk depends on the particular agent and its dose. Photosensitivity manifests as varying degrees of erythema (Fig. 135.9), edema and/or blistering of any exposed site, with subjective symptoms of pain, a burning sensation, lightheadedness and photophobia. Patients receiving systemic PDT photosensitizers must be instructed to strictly avoid outdoor light as well as bright indoor light. Appropriate opaque clothing must be worn. Conventional chemical sunscreens, even those with a high sun protection factor, are not useful in managing at-risk patients since the action spectrum extends throughout the visible spectrum, which is not blocked by sunscreens. Complete avoidance of all light is unnecessary, since regular indoor light exposure provides a safe means by which low-level photobleaching can hasten the clearance of photoactive agents from the skin. In the case of topical PDT, applying an opaque covering to the treatment site during the incubation period will prevent inadvertent activation.

STEPS IN ADMINISTERING TOPICAL PHOTODYNAMIC THERAPY AND PRACTICAL CONSIDERATIONS
PREOPERATIVE PHASE
• Confirm that the patient is a good candidate for PDT: appropriate indication, assess comorbidities; consider PDT especially in the setting of: – Field cancerization – Multiple synchronous or metachronous superficial tumors – Skin cancer-prone genodermatosis – Organ transplant recipient • Select treatment site(s) and confirm diagnosis by histologic examination if necessary • Exclude contraindications: porphyria, photosensitivity disorder, pregnancy, photosensitizer hypersensitivity • Provide patient with counseling and education in terms of expectations and precautions • Determine the photosensitizer, light and treatment parameters that will be employed • Determine the number of PDT sessions to be given and the time interval; for non-melanoma skin cancer, two separate PDT sessions one week apart are recommended
INTRAOPERATIVE PHASE
Topical drug application
• Confirm treatment site(s) • Consider degreasing the treatment surface with topical acetone or by microdermabrasion • Prepare treatment site(s); gently curette excess stratum corneum or scale-crust if appropriate • Apply topical photosensitizer to the target treatment site(s) (i.e. ALA solution or mALA cream); occlusion and coverage by opaque material are optional • Incubate the photosensitizer for 1–4 hours (or up to 18 hours), depending on the indication and specific prodrug • Remove the medication; confirm the presence of PpIX fluorescence by Wood's lamp illumination (optional)
Light administration/drug activation
• Provide protective eyewear to patient and staff • Position patient and lamp(s) for uniform exposure and patient comfort; if necessary, consider covering certain skin sites with opaque material to limit light exposure to the target of interest • Confirm light dose to be given, and then initiate light exposure (Blu-U®: 10 J/cm^2 of blue light, ~ 16 minutes; Aktilite®: 37 J/cm^2 of red LED light, ~ 7–9 minutes); a healthcare professional should ideally remain with the patient for the duration of the light exposure • At the completion of the light exposure, confirm the photobleaching of PpIX by Wood's lamp illumination (optional)
Pain management during light exposure
• Assemble tools and devices for pain control; consider premedication with analgesics or sedatives • The physical presence of a healthcare professional is very important for providing reassurance and monitoring; constant verbal reassurance and distraction are essential • Reinforce to the patient that the sensation of pain indicates that the appropriate PDT reactions are occurring • Additional specific strategies for managing pain include: – Applying an ice cube or ice pack near the treatment site – Spraying cold water over the treatment site – Applying a fan that can be held by the patient – Directing forced cold air towards the treatment site – Interrupting the light exposure temporarily – Infiltration or nerve block anesthesia
POSTOPERATIVE PHASE
• Apply wound dressing if there is an acute exudate • Reduce swelling by using ice packs • Prescribe oral analgesics to be taken if necessary • If patient has been given a systemic photosensitizer, provide detailed photoprotection instructions • Arrange follow-up, including next PDT session if appropriate; for non-melanoma skin cancer, a repeat course/cycle of PDT may be appropriate 3 months after the first course/cycle if there is clinical evidence of residual disease

Table 135.9 Steps in administering topical photodynamic therapy (PDT) and practical considerations. ALA, 5-aminolevulinic acid; LED, light-emitting diode; mALA, methyl aminolevulinate; PpIX, protoporphyrin IX.

Pain

The incubation period, which follows application of the topical photosensitizer, is generally uneventful, but within seconds to minutes of illumination of the skin with light, patients will often experience a range and series of unpleasant sensations at the site of light exposure. A variety of terms are used by patients to describe these sensations, including pain, warmth, burning, stinging, smarting and stabbing. The intensity will usually build with time and there can be spread of the discomfort beyond the actual treatment field. This pain does not necessarily correlate with the intensity of visible fluorescence present at the end of the incubation period and prior to light exposure. The rate of light delivery can sometimes influence the degree of pain, with lower irradiances being more tolerable[15]. Sometimes, temporary interruption of the light exposure will allow the pain to dissipate temporarily. A variety of practical strategies have been designed to manage the pain of PDT (Table 135.9). For some patients, the pain can be so intense that they will not be willing to undergo more than one treatment session.

Inflammation

At the end of the light exposure, the treated site will exhibit an immediate wheal and flare reaction. Over the next 24–48 hours, there may be edema, induration, purpura and blistering, along with exudation and crusting. Depending on the indication and the PDT drug–light dose, frank tissue necrosis may supervene accompanied by erosions and ulceration. Local reactions evolve over the ensuing 1–6 weeks and any wounds will heal by second intention.

Other Local Reactions

As with any physical modality, PDT can induce scarring and postinflammatory hyper- and hypopigmentation. Development of these complications depends primarily on the extent of the iatrogenic injury and the patient's constitutive injury and wound healing propensity.

Photosensitizer Allergy

Multiple case reports have documented contact hypersensitivity to mALA. In a controlled trial, contact sensitization to mALA was observed in as many as 35% of patients who had *previously* undergone five or more mALA-based PDT sessions; only 1.7% of the control subjects who had not previously undergone PDT demonstrated sensitization[55].

PRACTICE AND TECHNIQUES

The practical administration of PDT requires attention to a number of details during the preoperative, intraoperative and postoperative stages (see Table 135.9). Although the commercial PDT systems for dermatology come with officially recommended and approved protocols, the practice of PDT is not uncommonly off-label, both in terms of indications and specific procedural steps guided by the individual practitioner's experience and empiric preferences. One round of drug plus light administration can be considered a single PDT session, and a "course" or "cycle" of PDT may involve one or more PDT sessions separated by a set time interval. What should not be underestimated is the time and staffing necessary to provide appropriate patient counseling and education as well as intraoperative support during the light exposure phase.

FUTURE DIRECTIONS

Although PDT predates the discovery of antibiotics, corticosteroids, Mohs micrographic surgery and lasers by many years, only during the past decade did it become an accepted therapeutic modality in dermatology. Previous limitations to exploiting light-generated singlet oxygen were solved by the development of the topical ALA prodrug methodology, thereby fulfilling the promise of PDT as a simple and practical treatment. Controlled trials and cumulative clinical experience have defined the current spectrum of applications. Ongoing challenges include managing intraoperative pain, increasing the effective depth, and further simplifying the therapy in order to make it more accessible and practical.

On the horizon are novel ways of delivering ALA, including new formulations and a topical ALA-impregnated patch, which has shown efficacy in the treatment of actinic keratoses[56]. Adhesive, wearable, light-emitting patches have also been considered for PDT[57]. Since the latter operate at low irradiances, there may be less pain associated with these devices. In terms of innovative applications, it appears that PDT can be effective for managing field cancerization beyond just clearing visible and subclinical actinic keratoses. There is direct evidence that skin sites treated with topical PDT will develop new lesions at a slower rate, raising the possibility of PDT for photochemoprevention[58,59]. The fortunate irony is that light can now be used to effectively treat and even prevent the neoplasia that were induced by light in the first place.

REFERENCES

1. Lipson RL, Baldes EJ. The photodynamic properties of a particular hematoporphyrin derivative. Arch Dermatol. 1960;82:508–516.
2. Dougherty TJ, Kaufman JE, Goldfarb A, et al. Photoradiation therapy for the treatment of malignant tumors. Cancer Res. 1978;38:2628–2635.
3. Weishaupt KR, Gomer CJ, Dougherty TJ. Identification of singlet oxygen as the cytotoxic agent in photoinactivation of a murine tumor. Cancer Res. 1976;36:2326–2329.
4. Kennedy JC, Pottier RH, Pross DC. Photodynamic therapy with endogenous protoporphyrin IX: basic principles and present clinical experience. J Photochem Photobiol B. 1990;6:143–148.
5. Henderson BW, Waldow SM, Mang TS, et al. Tumor destruction and kinetics of tumor cell death in two experimental mouse tumors following photodynamic therapy. Cancer Res. 1985;45:572–576.
6. Hayami J, Okamoto H, Sugihara A, Horio T. Immunosuppressive effects of photodynamic therapy by topical aminolevulinic acid. J Dermatol. 2007;34:320–327.
7. Rittenhouse-Diakun K, Van Leengoed H, Morgan J, et al. The role of transferrin receptor (CD71) in photodynamic therapy of activated and malignant lymphocytes using the heme precursor delta-aminolevulinic acid (ALA). Photochem Photobiol. 1995;61:523–528.
8. Bissonnette R, Tremblay JF, Juzenas P, et al. Systemic photodynamic therapy with aminolevulinic acid induces apoptosis in lesional T lymphocytes of psoriatic plaques. J Invest Dermatol. 2002;119:77–83.
9. Redondo P, Marquina M, Pretel M, et al. Methyl-ALA-induced fluorescence in photodynamic diagnosis of basal cell carcinoma prior to Mohs micrographic surgery. Arch Dermatol. 2008;144:115–117.
10. Campbell SM, Morton CA, Alyahya R, et al. Clinical investigation of the novel iron-chelating agent, CP94, to enhance topical photodynamic therapy of nodular basal cell carcinoma. Br J Dermatol. 2008;159:387–393.
11. Divaris DX, Kennedy JC, Pottier RH. Phototoxic damage to sebaceous glands and hair follicles of mice after systemic administration of 5-aminolevulinic acid correlates with localized protoporphyrin IX fluorescence. Am J Pathol. 1990;136:891–897.
12. Lui H, Hobbs L, Tope WD, et al. Photodynamic therapy of multiple nonmelanoma skin cancers with verteporfin and red light-emitting diodes: two-year results evaluating tumor response and cosmetic outcomes. Arch Dermatol. 2004;140:26–32.
13. Wiegell SR, Haedersdal M, Eriksen P, Wulf HC. Photodynamic therapy of actinic keratoses with 8% and 16% methyl aminolaevulinate and home-based daylight exposure: a double-blinded randomized clinical trial. Br J Dermatol. 2009;160:1308–1314.
14. Alexiades-Armenakas MR, Geronemus RG. Laser-mediated photodynamic therapy of actinic keratoses. Arch Dermatol. 2003;139:1313–1320.
15. Cottrell WJ, Paquette AD, Keymel KR, et al. Irradiance-dependent photobleaching and pain in delta-aminolevulinic acid-photodynamic therapy of superficial basal cell carcinomas. Clin Cancer Res. 2008;14:4475–4483.
16. de Haas ER, Kruijt B, Sterenborg HJ, et al. Fractionated illumination significantly improves the response of superficial basal cell carcinoma to aminolevulinic acid photodynamic therapy. J Invest Dermatol. 2006;126:2679–2686.
17. Morton C, Campbell S, Gupta G, et al. Intraindividual, right-left comparison of topical methyl aminolaevulinate-photodynamic therapy and cryotherapy in subjects with actinic keratoses: a multicentre, randomized controlled study. Br J Dermatol. 2006;155:1029–1036.
18. Rhodes LE, de Rie M, Enstrom Y, et al. Photodynamic therapy using topical methyl aminolevulinate vs surgery for nodular basal cell carcinoma: results of a multicenter randomized prospective trial. Arch Dermatol. 2004;140:17–23.
19. Kurwa HA, Yong-Gee SA, Seed PT, et al. A randomized paired comparison of photodynamic therapy and topical 5-fluorouracil in the treatment of actinic keratoses. J Am Acad Dermatol. 1999;41:414–418.
20. Szeimies RM, Karrer S, Radakovic-Fijan S, et al. Photodynamic therapy using topical methyl 5-aminolevulinate compared with cryotherapy for actinic keratosis: a prospective, randomized study. J Am Acad Dermatol. 2002;47:258–262.
21. Freeman M, Vinciullo C, Francis D, et al. A comparison of photodynamic therapy using topical methyl aminolevulinate (Metvix) with single cycle cryotherapy in patients with actinic keratosis: a prospective, randomized study. J Dermatolog Treat. 2003;14:99–106.

22. Pariser DM, Lowe NJ, Stewart DM, Jarratt MT, Lucky AW, Pariser RJ, et al. Photodynamic therapy with topical methyl aminolevulinate for actinic keratosis: results of a prospective randomized multicenter trial. J Am Acad Dermatol. 2003;48:227–232.
23. Piacquadio DJ, Chen DM, Farber HF, et al. Photodynamic therapy with aminolevulinic acid topical solution and visible blue light in the treatment of multiple actinic keratoses of the face and scalp: investigator-blinded, phase 3, multicenter trials. Arch Dermatol. 2004;140:41–46.
24. Dragieva G, Prinz BM, Hafner J, et al. A randomized controlled clinical trial of topical photodynamic therapy with methyl aminolaevulinate in the treatment of actinic keratoses in transplant recipients. Br J Dermatol. 2004;151:196–200.
25. Pariser D, Loss R, Jarratt M, et al. Topical methyl-aminolevulinate photodynamic therapy using red light-emitting diode light for treatment of multiple actinic keratoses: a randomized, double-blind, placebo-controlled study. J Am Acad Dermatol. 2008;59:569–576.
26. Sotiriou E, Apalla Z, Maliamani F, et al. Intraindividual, right-left comparison of topical 5-aminolevulinic acid photodynamic therapy vs. 5% imiquimod cream for actinic keratoses on the upper extremities. J Eur Acad Dermatol Venereol. 2009;23:1061–1065.
27. Touma D, Yaar M, Whitehead S, et al. A trial of short incubation, broad-area photodynamic therapy for facial actinic keratoses and diffuse photodamage. Arch Dermatol. 2004;140:33–40.
28. Berking C, Herzinger T, Flaig MJ, et al. The efficacy of photodynamic therapy in actinic cheilitis of the lower lip: a prospective study of 15 patients. Dermatol Surg. 2007;33:825–830.
29. Babilas P, Schreml S, Landthaler M, Szeimies RM. Photodynamic therapy in dermatology: state-of-the-art. Photodermatol Photoimmunol Photomed. 2010;26:118–132.
30. Wang I, Bendsoe N, Klinteberg CA, et al. Photodynamic therapy vs. cryosurgery of basal cell carcinomas: results of a phase III clinical trial. Br J Dermatol. 2001;144:832–840.
31. Basset-Seguin N, Ibbotson SH, Emtestam L, et al. Topical methyl aminolaevulinate photodynamic therapy versus cryotherapy for superficial basal cell carcinoma: a 5 year randomized trial. Eur J Dermatol. 2008;18:547–553.
32. Szeimies RM, Ibbotson S, Murrell DF, et al. A clinical study comparing methyl aminolevulinate photodynamic therapy and surgery in small superficial basal cell carcinoma (8-20 mm), with a 12-month follow-up. J Eur Acad Dermatol Venereol. 2008;22:1302–1311.
33. Oseroff AR, Shieh S, Frawley NP, et al. Treatment of diffuse basal cell carcinomas and basaloid follicular hamartomas in nevoid basal cell carcinoma syndrome by wide-area 5-aminolevulinic acid photodynamic therapy. Arch Dermatol. 2005;141:60–67.
34. Morton CA, Whitehurst C, Moseley H, et al. Comparison of photodynamic therapy with cryotherapy in the treatment of Bowen's disease. Br J Dermatol. 1996;135:766–771.
35. Salim A, Leman JA, McColl JH, et al. Randomized comparison of photodynamic therapy with topical 5-fluorouracil in Bowen's disease. Br J Dermatol. 2003;148:539–543.
36. Morton C, Horn M, Leman J, et al. Comparison of topical methyl aminolevulinate photodynamic therapy with cryotherapy or fluorouracil for treatment of squamous cell carcinoma in situ: results of a multicenter randomized trial. Arch Dermatol. 2006;142:729–735.
37. Morton CA, Whitehurst C, McColl JH, et al. Photodynamic therapy for large or multiple patches of Bowen disease and basal cell carcinoma. Arch Dermatol. 2001;137:319–324.
38. Calzavara-Pinton PG, Venturini M, Sala R, et al. Methylaminolaevulinate-based photodynamic therapy of Bowen's disease and squamous cell carcinoma. Br J Dermatol. 2008;159:137–144.
39. Recio ED, Zambrano B, Alonso ML, et al. Topical 5-aminolevulinic acid photodynamic therapy for the treatment of unilesional mycosis fungoides: a report of two cases and review of the literature. Int J Dermatol. 2008;47:410–413.
40. Hongcharu W, Taylor CR, Chang Y, et al. Topical ALA-photodynamic therapy for the treatment of acne vulgaris. J Invest Dermatol. 2000;115:183–192.
41. Sakamoto FH, Torezan L, Anderson RR. Photodynamic therapy for acne vulgaris: a critical review from basics to clinical practice. Part II. Understanding parameters for acne treatment with photodynamic therapy. J Am Acad Dermatol. 2010;63:195–211.
42. Elman M, Slatkine M, Harth Y. The effective treatment of acne vulgaris by a high-intensity, narrow band 405-420 nm light source. J Cosmet Laser Ther. 2003;5:111–117.
43. Hall JA, Keller PJ, Keller GS. Dose response of combination photorejuvenation using intense pulsed light-activated photodynamic therapy and radiofrequency energy. Arch Facial Plast Surg. 2004;6:374–378.
44. Dover JS, Bhatia AC, Stewart B, Arndt KA. Topical 5-aminolevulinic acid combined with intense pulsed light in the treatment of photoaging. Arch Dermatol. 2005;141:1247–1252.
45. Gold MH, Bradshaw VL, Boring MM, et al. Split-face comparison of photodynamic therapy with 5-aminolevulinic acid and intense pulsed light versus intense pulsed light alone for photodamage. Dermatol Surg. 2006;32:795–801.
46. Orringer JS, Hammerberg C, Hamilton T, et al. Molecular effects of photodynamic therapy for photoaging. Arch Dermatol. 2008;144:1296–1302.
47. Almeida Issa MC, Pineiro-Maceira J, Farias RE, et al. Immunohistochemical expression of matrix metalloproteinases in photodamaged skin by photodynamic therapy. Br J Dermatol. 2009;161:647–653.
48. Beattie PE, Dawe RS, Ferguson J, Ibbotson SH. Lack of efficacy and tolerability of topical PDT for psoriasis in comparison with narrowband UVB phototherapy. Clin Exp Dermatol. 2004;29:560–562.
49. Stender IM, Na R, Fogh H, et al. Photodynamic therapy with 5-aminolaevulinic acid or placebo for recalcitrant foot and hand warts: randomised double-blind trial. Lancet. 2000;355:963–966.
50. Chen K, Chang BZ, Ju M, et al. Comparative study of photodynamic therapy vs CO2 laser vaporization in treatment of condylomata acuminata: a randomized clinical trial. Br J Dermatol. 2007;156:516–520.
51. Liang J, Lu XN, Tang H, et al. Evaluation of photodynamic therapy using topical aminolevulinic acid hydrochloride in the treatment of condylomata acuminata: a comparative, randomized clinical trial. Photodermatol Photoimmunol Photomed. 2009;25:293–297.
52. Asilian A, Davami M. Comparison between the efficacy of photodynamic therapy and topical paromomycin in the treatment of Old World cutaneous leishmaniasis: a placebo-controlled, randomized clinical trial. Clin Exp Dermatol. 2006;31:634–637.
53. Dai T, Huang YY, Hamblin MR. Photodynamic therapy for localized infections – state of the art. Photodiagnosis & Photodynamic Therapy 2009 Sep–Dec;6(3–4):170–188.
54. Yuan KH, Li Q, Yu WL, Huang Z. Photodynamic therapy in treatment of port wine stain birthmarks–recent progress. Photodiagnosis Photodyn Ther. 2009;6:189–194.
55. Korshoj S, Solvsten H, Erlandsen M, Sommerlund M. Frequency of sensitization to methyl aminolaevulinate after photodynamic therapy. Contact Dermatitis. 2009;60:320–324.
56. Szeimies RM, Stockfleth E, Popp G, et al. Long-term follow-up of photodynamic therapy with a self-adhesive 5-aminolaevulinic acid patch: 12 months data. Br J Dermatol. 2010;162:410–414.
57. Attili SK, Lesar A, McNeill A, et al. An open pilot study of ambulatory photodynamic therapy using a wearable low-irradiance organic light-emitting diode light source in the treatment of nonmelanoma skin cancer. Br J Dermatol. 2009;161:170–173.
58. Apalla Z, Sotiriou E, Chovarda E, et al. Skin cancer: preventive photodynamic therapy in patients with face and scalp cancerization. A randomized placebo-controlled study. Br J Dermatol. 2010;162:171–175.
59. Willey A, Mehta S, Lee PK. Reduction in the incidence of squamous cell carcinoma in solid organ transplant recipients treated with cyclic photodynamic therapy. Dermatol Surg. 2010;36:652–658.

Lasers and Other Energy Technologies – Principles & Skin Interactions

136

Fernanda H Sakamoto, Mathew M Avram and R Rox Anderson

Chapter Contents

Lasers 2251
Skin optics 2252
Thermal interactions 2252
Selective photothermolysis 2253
Photomechanical effects 2253
Skin cooling 2254
Applications of laser principles 2254
Principles of laser safety 2257
Non-laser energy sources 2257

Synonym: ■ LASER – light amplification by stimulated emission of radiation

Key features

- Laser surgery works by precise tissue heating when optical energy is absorbed within the skin
- Heat is created exactly where light is absorbed by molecules called chromophores
- The major chromophores for visible and near-infrared light are melanin and hemoglobins. Water is the major far-infrared chromophore
- Red and near-infrared wavelengths are deeply penetrating.
- Wavelength(s) of lasers or intense pulsed light (IPL) sources are often matched for absorption by chromophores in skin targets such as blood vessels, hair follicles, melanin-containing cells, tattoo ink or tissue layers
- Selective heating and damage of targets can occur when a pulse of selectively absorbed light is delivered faster than the targets can cool by heat conduction
- The time for a tissue target to cool is its thermal relaxation time, equal in seconds to approximately the square of the target size in millimeters
- Very short (nanosecond) laser pulses, produced by Q-switched lasers, can precisely damage small targets such as individual melanocytes
- Millisecond lasers and IPLs selectively affect multicellular targets such as blood vessels, hair follicles and tissue layers
- Fractional laser treatments create an array of microscopic thermal injury zones
- Radiofrequency electrical current, traditionally used for skin surgery, has been re-configured for aesthetic applications
- High-intensity, focused ultrasound can heat a precise focus within or below the skin
- Laser microscopy of live, intact skin is an emerging diagnostic tool for dermatology

INTRODUCTION

Modern dermatology is inextricably linked to photomedicine, which includes all diagnostic and therapeutic uses of light. The last century took us from Einstein's insight into the quantum nature of light, to the invention of the ruby laser in 1960, to the wide spectrum of lasers available today. In particular, the principle of selective photothermolysis guided the development of pulsed lasers that target specific skin structures such as blood vessels, melanosomes and hair follicles. Laser dermatology is a dynamic field and a steady source of therapeutic innovation.

LASERS

LASER is an acronym for *l*ight *a*mplification by *s*timulated *e*mission of *r*adiation, and this describes the physical process by which, in accordance with Einstein's principles of electromagnetic radiation[1], lasers produce light[2]. Electromagnetic radiation is a basic form of energy that exhibits both wave and particle properties. The quantum of electromagnetic energy is called a photon, and a photon can stimulate an excited atom to emit another photon with the same energy, wavelength and phase. The idea of lasers was envisioned by Charles Townes, followed in 1960 by the actual demonstration of a laser utilizing a flashlamp-excited ruby crystal[3]. Soon thereafter, Dr Leon Goldman initiated dermatologic application of laser technology.

All laser systems are composed of four essential components (Fig. 136.1), including: (1) a gas, liquid or solid medium (Table 136.1) that can be excited to generate light; (2) a source of pump energy to excite the medium; (3) mirrors at the ends of the laser, forming an optical cavity that favors the amplification process; and (4) a delivery system.

Stimulated emission occurs when more than half of the atoms within the laser medium are excited by the pump energy source; this ensures that photons traveling in the laser medium are more likely to encounter an excited atom (leading to stimulated emission) than a resting atom that can simply absorb the light. Light is amplified as it travels back and forth between the laser's mirrors, and a very high intensity can be achieved.

Laser light has several properties that are different from other light sources[4]. *Monochromicity* refers to emission of a well-defined wavelength, rather than a band of wavelengths. *Coherence* describes light waves that travel in phase, both in time and space, similar to a column of soldiers marching in step. *Collimation* refers to a very parallel beam of light. Coherence and collimation allow lasers to be focused to very small spot sizes (see Fig. 136.1).

Lasers may emit a continuous beam or pulses of light. Continuous lasers usually have limited power, whereas extremely high peak power can be emitted during a short laser pulse[5]. Q-switched lasers produce short pulses at very high peak power. "Q" refers to a quality factor for light traveling across the laser cavity, which can be changed suddenly to produce a short, intense burst of light. Dermatologic Q-switched lasers are designed to produce pulses of 10–100 nanoseconds, with fluence (energy density) typically in the 2–10 J/cm^2 range. These short, high-power pulses are particularly useful for selective removal of tattoos and pigmented lesions[6].The repetition rate for pulsed lasers is expressed in hertz (Hz). Of note, some lasers emit a rapid train of low-energy pulses that behave surgically like continuous-wave lasers and are called quasicontinuous.

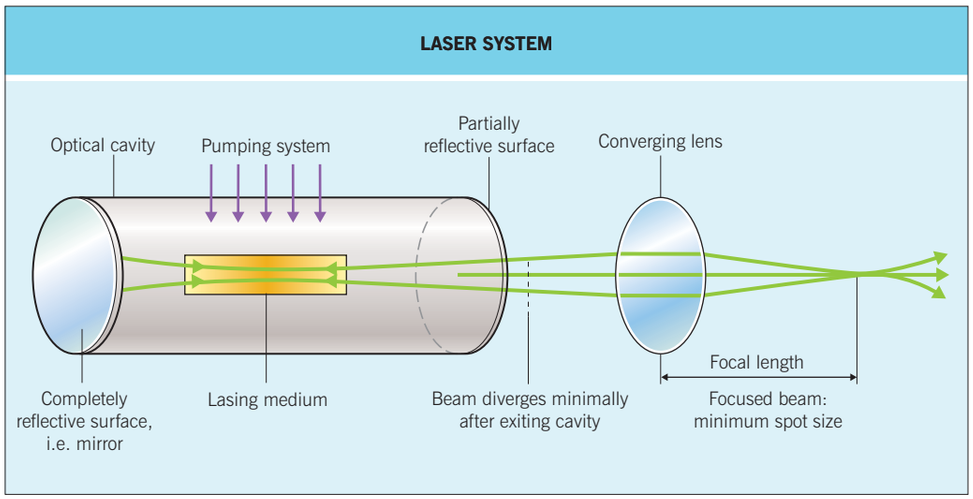


Fig. 136.1 Laser system. The pumping system stimulates the lasing medium to emit photons. The mirrors at the ends of the cavity reflect this light back and forth along one axis, leading to amplification of the stimulated emission process; one of the mirrors is only partially reflective, allowing the laser light to exit. Lasers produce beams of light with low divergence (spread) that are close to being collimated (i.e. parallel light waves). This then allows the beam to be tightly focused by a converging lens or mirror as focusing is required to produce a specific spot size.

TYPES OF LASER MEDIA

Gas	Liquid	Solid
Argon Carbon dioxide Copper vapor Helium–neon Krypton Xenon chloride*	Rhodamine dye dissolved in organic solvent†	Crystal • Alexandrite • Erbium-doped yttrium aluminum garnet (YAG) • Holmium-doped YAG • Neodymium-doped YAG • Potassium titanyl phosphate • Ruby Semiconductor • Diode (e.g. aluminum gallium arsenide)

*In excimer lasers.
†In pulsed dye lasers.

Table 136.1 Types of laser media. Lasers are often named for the medium contained within their optical cavity.

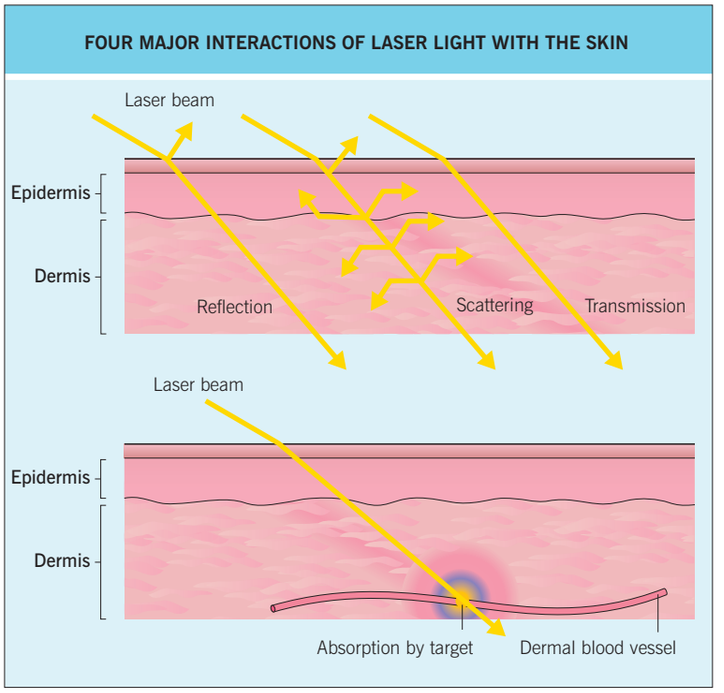


Fig. 136.2 Four major interactions of laser light with the skin. These are reflection, scattering, transmission and absorption.

SKIN OPTICS

At the skin surface, 4–7% of light is typically reflected because of the difference in the refractive index between air (n = 0) and stratum corneum (n = 1.45)[7]. This is termed the Fresnel reflectance because it follows Fresnel's equations relating reflectance to the angle of incidence, plane of polarization, and refractive index[8]. The remaining 93–96% of incident light enters the skin, where it is primarily scattered and/or absorbed (Fig. 136.2). Scattering occurs when photons "bounce" off particles and fibers within the skin, leading to diffusion of the incoming beam of light and limiting its depth of penetration. Tissue effects occur only when light is absorbed.

The *absorption coefficient* is defined as the probability per unit path length that a photon at a particular wavelength will be absorbed, and it depends on the concentration of chromophores (absorbing molecules) present. When absorption occurs, the photon surrenders its energy to a chromophore. Once absorbed, the photon ceases to exist and the chromophore becomes excited.

Three primary skin chromophores are water, hemoglobin and melanin (Fig. 136.3). Chromophores exhibit characteristic bands of absorption at certain wavelengths. It is this fact that allows for the delineation of specific targets for laser activity. While melanin absorbs broadly across the visible and ultraviolet (UV) spectrum, the oxyhemoglobin and reduced hemoglobin in blood exhibit strong bands in the UV, blue, green and yellow regions. Water has strong absorption in the infrared (IR) region (Fig. 136.4).

Optical properties of the epidermis and dermis are different. In pigmented epidermis, melanin absorption is usually the dominant process over the majority of the optical spectrum (200–1000 nm) (see Fig. 136.3). In the dermis, there is strong, wavelength-dependent scattering by collagen fibers, which attenuates penetration of light. This scattering varies inversely with wavelength. In general, between 280 and 1300 nm, the depth of penetration increases with wavelength (see Fig. 136.5). Above 1300 nm, penetration decreases due to the absorption of light by water. The most deeply penetrating wavelengths are 650–1200 nm, while the least penetrating wavelengths are within the far-UV and far-IR regions.

THERMAL INTERACTIONS

Most laser interactions involve heat. As temperature is raised, many essential molecules within cells are denatured, including proteins, DNA, RNA and cell membranes. This results in loss of function via unfolding and coagulation of macromolecules. Thermal coagulation yields cell necrosis and, if widespread, a burn. Laser skin surgery requires precise control over the placement and amount of heat-induced injury.

Most human cells can easily withstand temperatures of up to 40°C. Whether a given cell population can survive higher temperatures is dependent upon both exposure time and temperature. This is because the rate of thermal denaturation depends upon temperature: heat increases the rate at which molecules denature. In most organisms, exposure to sub-lethal heat induces a cellular reaction termed the heat shock response. Normal protein synthesis is replaced by synthesis of proteins called heat shock proteins, which confer some resistance to thermal injury[9]. Laser-induced thermal injury is well described by an Arrhenius model[10] – the rate of denaturation is exponentially related to temperature. Thus, accumulation of denatured material rises exponentially with temperature and proportionally with time[11]. Near a critical temperature (which is different for different tissues), rapid coagulation occurs; this is what accounts for the well-defined histologic boundaries of dermal coagulation in laser and other burn injuries. In the dermis, type I collagen plays a primary role in thermal coagulation, whereas elastin is extremely thermally stable and can survive boiling without apparent injury. Fibrillar type I collagen has a sharp melting transition at 60–70°C. At or above this temperature range, scarring becomes likely. Selective photothermolysis permits selected heating of targets within the dermis, such as blood vessels or hair follicles, with preservation of dermis between targets. However, even with selective photothermolysis, there is an absolute need to keep the bulk skin temperature below ~60–70°C.

When laser light, intense pulsed light (IPL), radiofrequency (RF) waves or other form of energy is absorbed by tissue, most of the absorbed energy is converted to heat; the latter then begins to diffuse into the surrounding tissue. Heat diffusion via conduction is also called thermal relaxation. *Thermal relaxation time* (TRT) is defined, for a given tissue structure, as the time required for the heated tissue to cool halfway towards its initial temperature. The key to clean ablation of tissue is to ablate it quickly, before much heat is conducted into surrounding tissue[12].

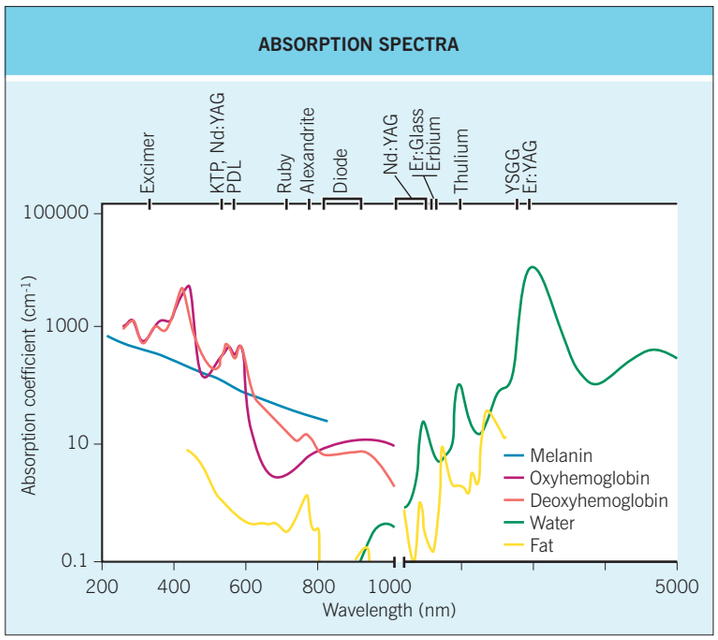


Fig. 136.3 Absorption spectra. The heterogeneous absorption spectra of chromophores allow selective photothermolysis to work. Er, erbium; KTP, potassium titanyl phosphate; Nd:YAG, neodymium-doped yttrium aluminum garnet; PDL, pulsed dye laser; YSGG, yttrium scandium gallium garnet.

SELECTIVE PHOTOTHERMOLYSIS

The concept of selective photothermolysis[13] first arose to guide the design of a laser for treating pediatric port-wine stains. Selective, localized heating (with focal destruction of "target" structures) is achieved by a combination of selective light absorption and a pulse duration shorter than or approximately equal to the TRT of the targets. Choice of wavelength(s) must correspond to absorption by chromophores within the skin targets. The wavelength must also penetrate to the anatomic depth of the skin targets.

The TRT of a target is proportional to the square of its size (Table 136.2). Thus, for a given material and shape, an object half the size will cool in one-quarter of the time. For most tissue structures, TRT (in seconds) is approximately equal to the square of the target dimension (in millimeters). Shape also affects TRT, and for a given thickness, spheres cool faster than cylinders, which cool faster than planes.

In general, the optimal pulse duration for *selective photothermolysis* is approximately equal to the TRT. Selective photothermolysis typically utilizes pulsed (rather than continuous) sources[14]. Blood vessels encompass a wide range of TRTs, including capillaries (tens of microseconds), large venules of adult port-wine stains (up to tens of milliseconds) and leg veins (hundreds of milliseconds). Small pigmented targets (e.g. melanosomes within pigmented melanocytes in a nevus of Ota) are best treated with short (sub-microsecond) pulses, while larger pigmented targets (e.g. hair follicles) have longer TRTs and are best treated with longer (millisecond) pulses[15].

PHOTOMECHANICAL EFFECTS

Pulsed lasers can also cause mechanical effects[16]. Sudden heating induces thermal expansion with consequent acoustic and/or shock waves. These waves can rupture or increase permeability of cell membranes. Cavitation, the violent formation and collapse of steam bubbles, may also occur. The latter is the dominant mechanism of vessel rupture by pulsed dye lasers emitting pulses less than ~20 milliseconds[17].

A number of parameters control laser–tissue effects, including wavelength, fluence, irradiance, spot size, and pulse duration (Table 136.3). With smaller spot sizes, scattering leads to a more rapid loss of photons from the beam as it penetrates the skin, whereas a large spot size allows more photons to remain within a beam's diameter. The greatest effec-

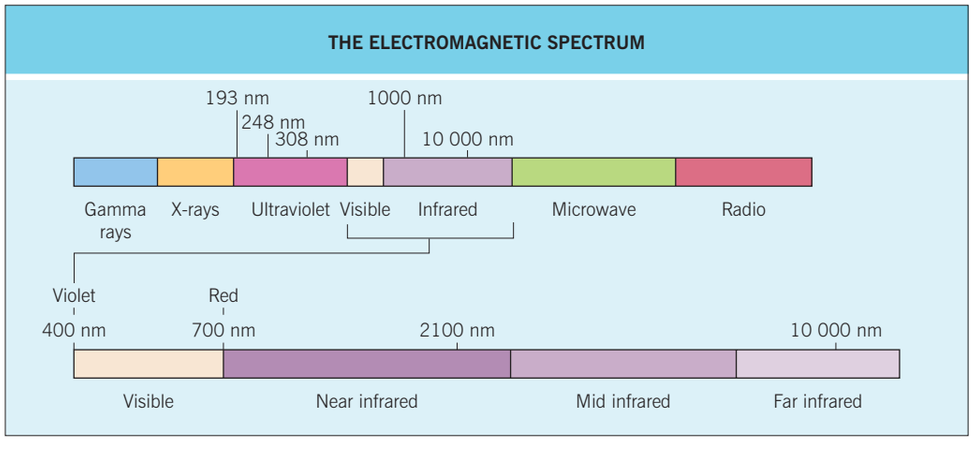


Fig. 136.4 The electromagnetic spectrum. The visible portion is only a small range of the spectrum.

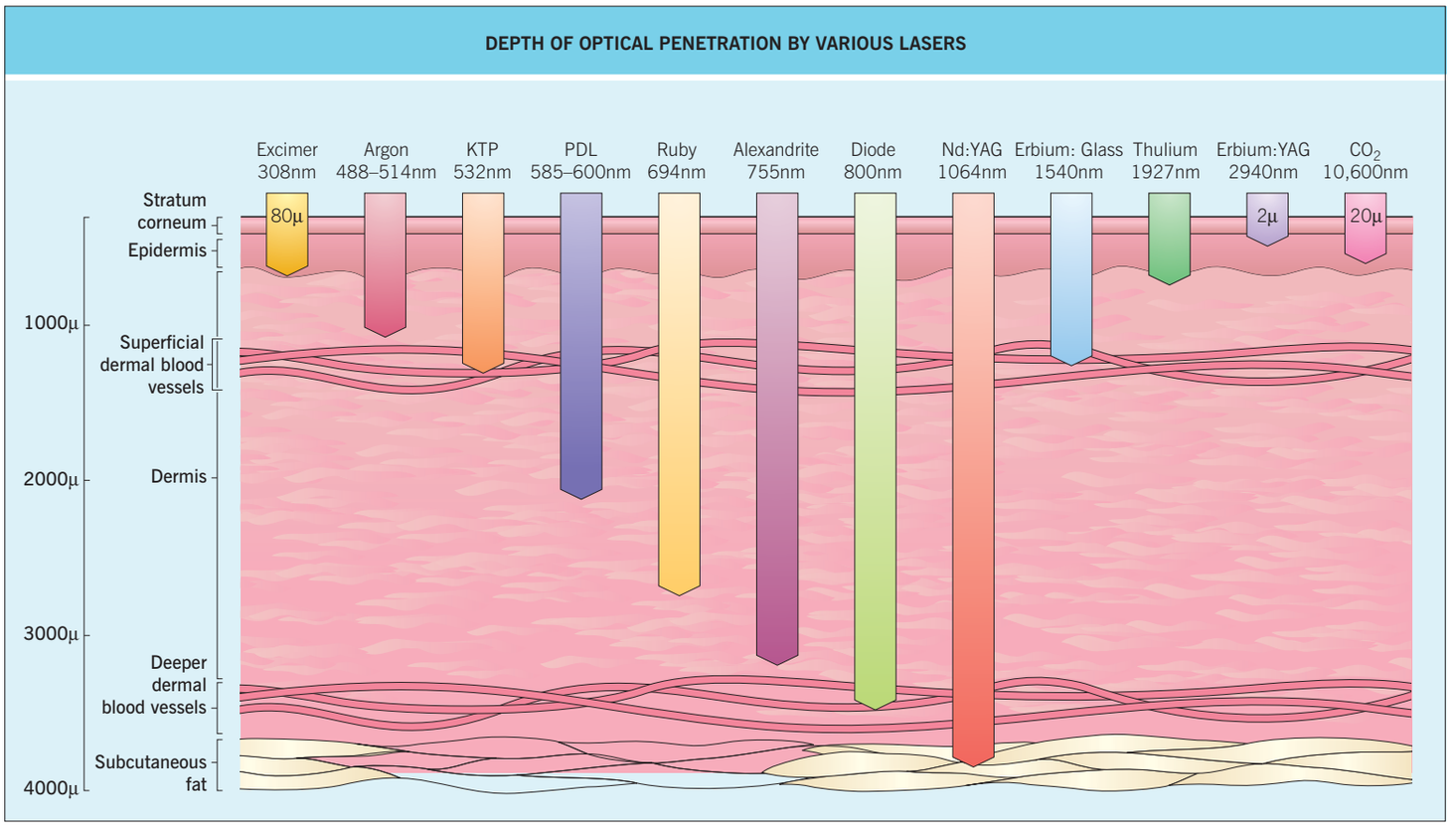


Fig. 136.5 Depth of optical penetration by various lasers. It should be noted that the treatment depth can greatly exceed the optical penetration depth for ablative lasers. On the face, the fat can be present at depth of 2–3 mm. For example, the depth of optical penetration for CO_2 lasers is only ~20 microns, but fractional CO_2 lasers can vaporize nearly full-thickness microchannels through the dermis. KTP, potassium titanyl phosphate; Nd, neodymium; PDL, pulsed dye laser; YAG, yttrium aluminum garnet.

PULSE DURATIONS AND TARGETS OF SELECTIVE PHOTOTHERMOLYSIS

Chromophore	Diameter	TRT	Typical laser pulse duration
Tattoo ink particle	0.1 micron	10 ns	10 ns
Melanosome	0.5 micron	250 ns	10–100 ns
PWS vessels	30–100 microns	1–10 ms	0.4–20 ms
Terminal hair follicle	300 microns	100 ms	3–100 ms
Leg vein	1 mm	1 s	0.1 s

Table 136.2 Pulse durations and targets of selective photothermolysis. m, milli; n, nano; s, second; PWS, port-wine stain; TRT, thermal relaxation time.

LASER AND LASER DERMATOLOGY TERMS

Term	Definition	Unit
Energy	Fundamental unit of work	Joules (J)
Power	Rate at which energy is delivered	Watts (W)
Fluence	Amount of energy delivered per unit area	J/cm^2
Irradiance	Power delivered per unit area	W/cm^2
Pulse duration (pulse width)	Laser exposure duration	Seconds (s)
Spot size	Diameter of the laser beam on the skin surface	mm
Chromophore	Medium that absorbs light	
Thermal relaxation time	Time required for heated tissue to lose 50% of its heat through diffusion	Seconds (s)

Table 136.3 Laser and laser dermatology terms.

tive penetration depth into skin occurs with a combination of a penetrating wavelength (600–1300 nm; Fig. 136.5) and a large spot size.

SKIN COOLING

Epidermal melanin is an undesired chromophore when treating dermal targets. Epidermal damage can be minimized through the use of skin cooling, and this is especially important with darkly pigmented skin. All cooling methods extract heat at the skin surface via a cooling agent (gas, liquid or solid). For spray cooling, a cold *liquid* is used, e.g. liquid fluorocarbon is sprayed on the skin. *Solid* contact cooling often consists of a cold sapphire window held against the skin, through which laser or IPL energy is delivered. *Cold air* or *cold gels* can also be applied for passive skin cooling.

There are three basic types of skin cooling: precooling, parallel cooling and post-cooling, which correspond to extracting heat from the skin before, during and after the laser exposure, respectively[18]. For pulse durations shorter than ~5 milliseconds (e.g. many pulsed dye and all Q-switched lasers), there is not enough time for parallel cooling to extract much heat, but precooling provides some protection. For short pulsed lasers, cryogen spray cooling represents the most aggressive and effective form of precooling.

Parallel cooling is effective for pulses longer than ~5 milliseconds. Solid contact cooling with a cold sapphire window pressed against the skin just before and during a long laser pulse allows safer delivery of high fluences, even in darkly pigmented skin[19]. Bulk skin cooling before and after laser treatments (e.g. with ice or cold air) is useful for minimizing pain, erythema and edema[15].

APPLICATIONS OF LASER PRINCIPLES

Currently available medical lasers are outlined in Table 136.4 and their applications are discussed in Chapter 137.

LASERS IN MEDICINE							
Laser	**Wavelength (nm)**	**Mode**	**Average power (W)**	**Average energy per pulse (J)**	**Pulse duration (sec)**	**Pulse rep. rate (Hz)**	**Target chromophore**
Excimer (ArF)	193	Pulsed	10	0.1	10^{-8}	100	Proteins
Excimer (XeCl)	308	Pulsed	10	0.1	10^{-7}	100	Proteins
Argon	488, 514	CW	1–10				Hemoglobins, melanin
Copper vapor	511, 578	Quasi-CW	1–10	10^{-3}	10^{-8}	2×10^{3}	Hemoglobins, melanin
KTP	532	Quasi-CW	1–10	10^{-4}	10^{-8}	104	Hemoglobins, melanin
Q-switched, frequency-doubled Nd:YAG	532	Pulsed (ns)	1–3	0.2^{-1}	10^{-8}	5–10	Melanin, red tattoos
Pulsed dye	585–600	Pulsed	10	5	$(0.45–40) \times 10^{-3}$	2	Hemoglobins
Argon dye	630	CW	0.5–2				Photosensitizing drugs
Ruby	694	Pulsed	30	30	10^{-3}	1	Melanin
Q-switched ruby	694	Pulsed (ns)	2	2	3×10^{-8}	1	Melanin, black and green tattoos
Alexandrite	755	Pulsed	30	30	10^{-3}	1	Melanin, deoxyhemoglobin
Q-switched alexandrite	755	Pulsed	5	0.5–5	10^{-7}	1–10	Melanin, black and green tattoos
Diode (AlGaAs)	~800	CW/pulsed	5–3000	5–100	$(5–400) \times 10^{-3}$	1–2	Melanin, hemoglobins
Nd:YAG	1064	CW	10–100				Hemoglobins
Q-switched Nd:YAG	1064	Pulsed (ns)	5–10	1	10^{-8}	5–10	Black tattoos
Long-pulsed Nd:YAG	1064	Pulsed	1–50	1–50	$(1–200) \times 10^{-3}$	0–10	Hemoglobins, melanin
Long-pulsed Nd:YAG	1320	Pulsed	1–50	1–50	$(1–200) \times 10^{-3}$	0–10	Water
Diode	1450	Pulsed	10–15	10–15	0.15–0.25	1	Water
Erbium:glass	1540	Pulsed	10	5	1×10^{-3}	2	Water
Holmium:YAG	2000	Pulsed	5–100	0.2–5	10^{-3}	10–20	Water
Erbium:YAG	2940	Pulsed	10–20	0.1–3	$(3–100) \times 10^{-4}$	5–100	Water
Carbon dioxide	10 600	CW/pulsed	1–500	0.05–0.5	10^{-5}–10^{-3}	10^{2}–10^{4}	Water

Table 136.4 Lasers in medicine. AlGaAs, aluminum gallium arsenide; ArF, argon fluoride; CW, continuous wave; KTP, potassium titanyl phosphate; Nd, neodymium; ns, nanosecond; XeCl, xenon chloride; YAG, yttrium aluminum garnet.

Ablative (Vaporizing) Skin Resurfacing

The ablative lasers are far-IR CO_2 (10 600 nm) or erbium:yttrium aluminum garnet (Er:YAG; 2940 nm) devices which emit wavelengths strongly absorbed by water. Pulsed and/or scanned focused beams are used to precisely vaporize superficial tissue, causing a "plume" of material leaving the skin. Most of the heat is removed during vaporization, but a thin layer of residual thermal damage remains that is useful for hemostasis. Laser resurfacing is very useful for treating photoaging, scars, and lesions such as epidermal nevi and seborrheic keratoses. Resurfacing removes the old epidermis and stimulates contraction and remodeling of the dermis for many months after treatment. Being a controlled partial-thickness burn, meticulous technique and wound care are important in order to avoid infection and other complications. Scarring, transient hyperpigmentation, delayed-onset permanent hypopigmentation, prolonged erythema, and bacterial, viral and fungal infections have been reported after laser resurfacing[20].

Interactions During Treatment of Vascular Lesions

A peak of absorption by oxyhemoglobin occurs at 577 nm within the yellow spectrum (see Fig. 136.3). Flashlamp-pumped *pulsed dye lasers* (PDLs) are frequently used to treat microvascular lesions and they emit 585–600 nm light (i.e. within this absorption band), with pulse durations ranging from 0.45 to 40 milliseconds. Because of the range of target vessel sizes and associated TRTs (see above), variable pulse duration PDLs are now widely employed. Despite this and other improvements (e.g. skin cooling), the majority of port-wine stains require six or more treatments in order to achieve stable improvement, and only a minority can be fully removed. Resistance appears to be primarily attributable to vessels deeper than 1.5 mm (see Fig. 136.5).

For the treatment of deeper vessels, high-fluence, millisecond-domain, *pulsed neodymium:YAG* (Nd:YAG) lasers (1064 nm) may offer an improvement when compared to PDLs, but the former has a variable and narrow range of safe and effective fluence. *Alexandrite* lasers (755 nm, ~3 millisecond pulse duration) are also effective for treating hypertrophic and/or PDL-resistant vascular lesions, with a better range of safe and effective fluence. This difference may be due to preferential absorption by oxyhemoglobin at 1064 nm, in contrast to preferential absorption by deoxyhemoglobin at 755 nm. Other lasers with wavelengths in the near-IR range (e.g. 980 nm and 810 nm diode lasers) have been utilized to target larger, deeper vessels (e.g. leg veins).

Currently, the 585–600 nm flashlamp PDL is a standard treatment for cutaneous microvascular lesions, including port-wine stains, telangiectasias, erythematous scars, and, when indicated, hemangiomas. The treatment fluence is decreased for more deeply pigmented skin, and the principal side effect is purpura, which is dependent on pulse duration, fluence and spot size[21]. Purpura is the result of microvascular hemorrhage, subsequent thrombosis and delayed appearance of vasculitis. When the pulse duration (or dwell time) exceeds ~20 milliseconds, there is little or no immediate purpura because cavitation and vessel rupture are avoided. It should be noted, however, that delayed purpura can still occur due to a phase of vasculitis several days after treatment, even when no immediate post-treatment purpura is observed.

Continuous- and quasicontinuous-wave green or yellow lasers as well as various IPL devices have less vascular specificity than PDLs, but they offer the advantage of markedly less post-treatment purpura because of longer pulse duration or dwell time. *Copper vapor* or *copper bromide* lasers emit either green light at 511 nm or yellow light at 578 nm. With their high pulse repetition rates, tissue effects are comparable to those of continuous-wave lasers. Minimal swelling and crusting can occur, with resolution within 1 week[22].

Potassium titanyl phosphate (KTP) lasers, at a wavelength of 532 nm (with variable pulse durations in the millisecond domain), have also been introduced for treating telangiectasias, again with less resultant purpura than with PDLs. In combination with parallel skin cooling windows, these lasers are versatile for vascular lesion treatment.

IPLs are filtered xenon flashlamps which emit a wide range of wavelengths. Compared with most vascular lasers, IPLs are less selective and less powerful but still useful for selective photothermolysis of telangiectasias and poikiloderma.

Interactions During Treatment of Pigmented Lesions and Tattoos

Melanosomes are melanin-containing organelles that range from ~0.5 to 1.0 micron in size, and they can act as a primary target for selective photothermolysis of pigmented lesions[23]. Melanin has a broad absorption spectrum (see Fig. 136.3), which lends itself to possible targeting by a wide variety of lasers[24]. Choice of treatment wavelength is based on avoiding absorption by other chromophores and on matching depth of penetration to the depth of the lesion. In general, red and near-IR lasers are the most selective and penetrating devices for pigment cell targeting. The TRT of melanosomes is about 70–250 nanoseconds[13], and therefore Q-switched lasers are excellent for targeting melanosomes. When the fluence threshold for melanosome disruption is reached, the pigmented cell dies. Q-switched lasers selectively attack individual pigmented cells, so when the goal is to also remove adjacent, non-pigmented cells (e.g. during hair removal), millisecond pulses are used in order to allow heat transfer from pigmented to adjacent non-pigmented cells.

Treatment of tattoos with Q-switched lasers fragments the ink particles and selectively kills pigment-containing cells, with resultant ink particle release. Subsequent removal of tattoo ink particles can occur via an epidermal crust and/or lymphatic transport, and some particles are re-phagocytosed by dermal cells[25]. Of note, different laser wavelengths are needed for different ink colors (see Table 136.4).

Q-switched ruby and *alexandrite* lasers are very useful for epidermal and dermal pigmented lesions (e.g. lentigines, nevus of Ota) as well as for black and green tattoos (see Ch. 137). Café-au-lait macules and melanocytic nevi may respond to treatment with Q-switched ruby lasers (or, for nevi, long-pulsed ruby lasers that target nests of melanocytes), but recurrences are common and residual dermal melanocytes remain in laser-treated nevi[26,27]. Laser treatment of congenital melanocytic nevi is usually considered when surgical options are limited. However, laser removal of acquired melanocytic nevi is quite controversial given the potential risk for partial removal of a subtle early melanoma. Of note, postinflammatory hyperpigmentation and melasma respond poorly to laser treatment[28].

The *Q-switched Nd:YAG* laser emits at 1064 nm, with typical pulse durations of 10 nanoseconds. Its primary use is in the treatment of black tattoos and dermal melanocytoses such as nevus of Ota in darkly pigmented skin. Frequency-doubling to produce 532 nm visible green light is generally available in the same device, which can effectively remove epidermal melanin pigment as well as red tattoos.

Interactions During Hair Removal

Hair removal is the most popular laser procedure, and it probably requires damage to follicular stem cells in the bulge region of the outer root sheath and/or the dermal papilla at the base of the hair follicle. These are non-pigmented targets, located away from the pigmented hair shaft. High-energy, millisecond-domain pulses of wavelengths in the red to near-IR region of the spectrum (i.e. deeply penetrating) are used, from *ruby*, *alexandrite*, *diode* and *Nd:YAG* lasers. None of these sources works well for blond or white hair due to the paucity of melanin.

Since light must first travel through the pigmented epidermis to reach hair follicles, skin cooling is essential for safe permanent removal of hair in individuals with darkly pigmented skin. The primary mechanism for *temporary* hair loss is induction of catagen, which can occur at very low fluences; an 810 nm diode laser source intended for home use has been reported to reliably induce temporary reduction of pigmented terminal hair[29]. However, *permanent* loss of terminal hair typically requires either miniaturization to produce vellus-like hairs or complete degeneration with local fibrosis. For unknown reasons, an unwanted stimulation of a vellus-to-terminal hair transition can occur after laser or IPL treatments, particularly on the face in Mediterranean women.

Fig. 136.6 Histologic findings following ablative fractional photothermolysis. A microthermal zone (MTZ) of injury (arrow) is apparent after use of a CO_2 laser (10 600 nm) at 100 mJ/pulse. E, epidermis; D, dermis. *Courtesy, Wellman Center for Photomedicine.*

Interactions During Non-ablative Skin Rejuvenation

Non-ablative facial rejuvenation for the treatment of fine lines and non-dynamic rhytides uses mid-IR lasers (e.g. 1320 nm Nd:YAG, 1450 nm diode and 1540 nm erbium:glass lasers) and IPL sources (see below). These work by subtle thermal effects on the dermis, presumably stimulating a wound healing response. Responses to non-ablative rejuvenation are usually gradual and subtle, and well-controlled studies are lacking.

Fractional Photothermolysis

Fractional photothermolysis (FP) represents a treatment strategy in which many thousands of nearly invisible, microscopic zones of thermal injury are created (Fig. 136.6), stimulating turnover and remodeling of both the epidermis and dermis[29]. *Non-ablative* FP uses focused mid-IR laser microbeams to create a pixilated pattern of small columns of thermal damage, called microthermal treatment zones (MTZs). Typically, up to 1 million MTZs are placed per full-face treatment. Pattern density and depth of thermal damage are separately controlled. Density affects coverage whereas energy per MTZ is used to control depth of treatment (up to about 1.5 mm). In general, the depth of treatment should correlate with the depth of skin pathology being treated.

Tissue spared around each MTZ initiates rapid repair and stimulates remodeling. Desquamation of the epidermal portion of each MTZ removes some basal layer pigment and a small amount of papillary dermal debris. Non-ablative FP has been reported to improve

several skin conditions, including scars, fine rhytides, telangiectasias, dermatoheliosis and poikiloderma. There are a myriad of commercially available non-ablative FP devices (see Ch. 137).

Ablative FP uses carbon dioxide or erbium (Er:YAG) lasers to vaporize a similar pattern of small vertical channels that can extend deeply into the skin. Because remodeling is provided by tissue between the columns of ablation, the depth of ablation can be far deeper than with traditional ablative resurfacing procedures. However, care must be taken to avoid scarring, particularly in the infraorbital and neck regions where thin skin overlies a muscle (platysma). In theory, ablative FP may also be an effective mechanism for topical drug delivery, by providing many channels directly into the dermis.

Laser-Based Diagnostics

Laser technology has been instrumental in the development of biological microscopy and tissue imaging. Optical coherence tomography (OCT) uses near-IR, low-coherence light for high-resolution cross-sectional imaging of body tissues. OCT is a standard procedure in ophthalmology, is emerging as a means of rapidly imaging coronary arteries[30], and may have applications in dermatology[31]. For example, a Doppler version has been shown to be capable of imaging blood flow before and after laser treatment of vascular lesions[32].

Laser confocal microscopy captures light scattered or emitted from a thin plane "section" inside skin. Reflectance confocal microscopy is able to view the skin *in vivo* with histology-like resolution down to a depth of approximately 0.3 mm. Because histochemical stains are not used, confocal microscopy of skin tumors reveals diagnostic features that are different from those of conventional histology. For example, microvascular blood flow and trafficking of lymphocytes can be observed. In a preliminary study, the sensitivity and specificity of *in vivo* confocal microscopy for differentiating melanocytic nevi and seborrheic keratoses from cutaneous melanoma and basal cell carcinoma were 94% and 98%, respectively[33].

PRINCIPLES OF LASER SAFETY

The principles of laser safety are outlined in Table 136.5[34].

PRINCIPLES OF LASER SAFETY
POTENTIAL EYE INJURIES (PATIENTS AND DERMATOLOGISTS)
Blindness occurs rapidly and painlessly
• Blindness can occur even if only 1% of the beam is reflected into the eye from shiny metal, glass or plastic surfaces • Highest risk of eye injury and blindness with near-infrared Q-switched lasers • Lasers and IPL sources used for hair removal can target the retina and uveal tract • Anterior eye injury from lasers or IPL sources usually occurs with treatment of the lower eyebrow or vascular lesions near the eye (without an eye shield properly in place) • An opaque laser eye shield covering the patient's cornea will not prevent damage if the laser or IPL directly impacts exposed sclera • Long-pulse near-infrared laser light can penetrate through the eyelid to damage the eye
PREVENTION OF EYE INJURIES
Proper use of laser-protective eyewear (including eye shields)
• Wrap-around glasses and goggles are rated by optical density (OD) at specific wavelengths (corresponding to various lasers): OD = log (1/T), where T is transmittance of light through the eyewear; OD = 6 implies transmittance through the goggles is 10^{-6} • After determining wavelength of laser, check goggles for required OD and wavelength ranges of protection (printed directly on eyewear) • For dermatological lasers, proper protection is an OD ≥4 at the wavelength of the laser being used • Color of the goggles is not an indication of protection
FIRE HAZARDS
• Drapes, clothing, dry hair and plastic materials, including endotracheal tubes, can be ignited, especially when oxygen is in use • Greatest risk is with the CO_2 and erbium:YAG lasers used for skin resurfacing and ablative fractional treatments
PREVENTION OF FIRES
• Remember to place the laser in STANDBY mode when not actually treating the patient • Avoid inadvertently activating the laser foot-switch • Moisten any hair near the treatment field; remove mascara and eye makeup when working around eyelids • Alcohol, acetone or other flammable skin-cleaning solutions must be allowed to completely dry before laser use • Reduce intraoperative oxygen concentration to <40% • A fire extinguisher and water should be readily available
POSSIBLE CUTANEOUS BURNS
• Can occur with essentially all dermatological laser, IPL, RF or therapeutic ultrasound devices • Primarily due to improper device, dosimetry and/or treatment technique
PREVENTION OF CUTANEOUS BURNS
• Knowledge and careful observation of specific clinical endpoint responses for a particular laser–lesion combination
INHALATION OF LASER-GENERATED "PLUME" MATERIALS
• Particularly with resurfacing or vaporization of hair during its removal; latter can release irritating sulfur and other oxides
PREVENTION OF LASER "PLUME" BIOHAZARDS
• Smoke evacuator and good ventilation are most effective measures • Sub-micrometer surgical filter masks provide some protection when worn properly • Q-switched lasers capture particulate material in plastic cones

Table 136.5 Principles of laser safety. IPL, intense pulsed light; RF, radiofrequency.

NON-LASER ENERGY SOURCES

Flashlamps

Filtered xenon flashlamps, also referred to as intense pulsed light (IPL) sources, are also used for non-ablative skin rejuvenation, hair removal, and the treatment of vascular and pigmented lesions. By utilizing filters, different wavelength bands can be chosen, which are delivered in millisecond-domain pulses. Compared with lasers, IPLs are generally less target-selective, as they are unable to deliver the very short pulses needed for selective photothermolysis of very small targets such as the pigmented cells of tattoos or nevus of Ota. Attempts to remove tattoos with an IPL are inappropriate (despite advertising or FDA approvals to the contrary), as this often leads to burns and/or scarring. In a side-by-side comparative study, IPL was inferior to PDL for the treatment of port-wine stains.

Radiofrequency

Radiofrequency (RF) is a rapidly alternating electric current that locally heats tissue, based on both local current density and electrical resistance of the tissue. The energy deposited at a certain site is proportional to the local tissue impedance multiplied by the square of the local current density. As the name implies, RF generators operate at frequencies similar to AM and FM radio bands. The current is delivered from one or more electrodes held in contact or close proximity to the skin. The number of treatment electrodes defines an RF device as monopolar, bipolar or multipolar. In monopolar RF devices, one pole is located on the treatment handpiece, while the other (if present at all) is a large "passive" electrode placed remotely on the patient's body (Fig. 136.7A). Bipolar RF devices have two active electrodes held in contact with the tissue, and current flows between them (Fig. 136.7B). Because electrode size and spacing have a strong influence, the pattern and depth of heating can be adjusted to some extent.

Unlike most lasers and IPLs, there is little or no intrinsic selectivity to the deposition of energy from an RF source. The single relevant exception is lipid-rich tissue such as subcutaneous fat, which has substantially higher electrical impedance due to lower water content. As with lasers, skin cooling is useful with RF devices, in order to minimize the risk of burns near the delivery electrode.

While many monopolar and bipolar RF devices have been described for skin "tightening" and removal of cellulite or fat, the quality of clinical study-based evidence is generally poor. Because improper electrode

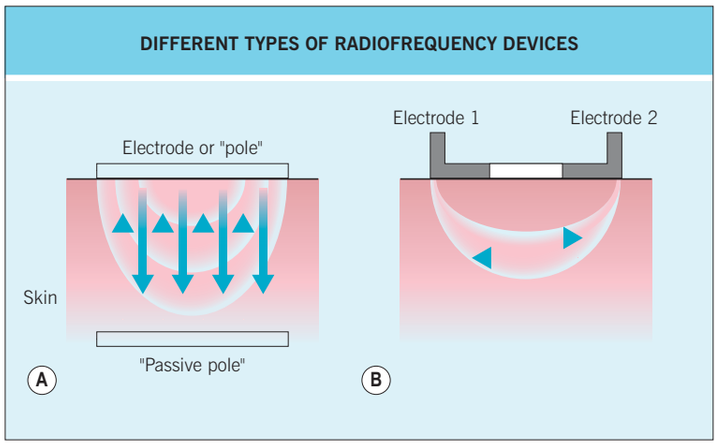


Fig. 136.7 Different types of radiofrequency (RF) devices. A A monopolar RF device has one pole located on the treatment handpiece, while the other (if present at all) is a larger "passive" electrode placed remotely on the patient's body. **B** A bipolar RF device has both poles located within the treatment handpiece and current flows between the electrodes, often in a banana-shaped pattern.

contact with skin is a common cause of injury (e.g. burns), some devices have sensors that monitor proper electrode–skin contact and/or integral skin cooling systems. The RF devices intended for "tightening" are designed to produce partial denaturation of type I collagen, which occurs at temperatures above ~60°C and leads to some immediate tissue contraction and subsequent new collagen synthesis[35].

At high frequencies, RF waves can also be transmitted across a dielectric (insulating) material, similar to radio transmissions through air. RF transmission to the skin from an emitting electrode is called capacitive coupling, and capacitive coupling electrodes have recently been described as "unipolar" RF. At the high frequencies utilized with capacitive coupling, a combination of induced current and rotational oscillations in water molecules produces tissue heating[36].

Fat lobules have higher electrical impedance than skin, fibrous septae or muscle. Thus, the lobules of fat can act as an electrical insulator. A large RF electrode configured to deliver a current path through subcutaneous fat could, in theory, preferentially heat fibrous septae, because these septae must carry a higher current density than the lobules which surround them. Cellulite improvement has been described by different authors following large-electrode, monopolar or bipolar RF. However, the apparent improvement in the appearance of cellulite does not correspond to fat destruction[36,37].

Ultrasound

High-frequency acoustic waves are routinely used for diagnostic medical imaging, at frequencies from ~20 kHz to 10 MHz. Ultrasound is an oscillating pressure (stress) wave that propagates at the speed of sound[38,39], with minimal scattering in soft tissues. The minimal scattering implies that ultrasound waves can be focused deeply in most tissues. Intensity is concentrated near the focal point, to the extent that tissue damage can occur by one or more of three mechanisms – heating, cavitation or shock waves. Heating is favored at high ultrasound frequencies while cavitation (a rapidly expanding gas bubble) is favored at low ultrasound frequencies; shock waves are high pressure, supersonic pressure waves that can be very destructive. Therapeutically, focused ultrasound can be used to destroy targets (e.g. kidney stones by shock waves, tumors by heating, thrombus by cavitation), and it can also promote tissue remodeling or membrane translocations (used in gene therapy)[40–42]. The attenuation (absorption) of ultrasound is greater at higher frequencies, and different materials have different attenuation coefficients[39].

Invasive ultrasonic liposuction probes were introduced over a decade ago to mechanically and thermally assist removal of fat, but with an additional risk of tissue burns (see Ch. 156)[43,44]. Non-invasive, unfocused ultrasound devices are also available, which operate at moderate power levels and are used for physical therapy of the skin (via warming and mechanical stimulation). A focused, pulsed ultrasound device capable of locally destroying subcutaneous abdominal fat was introduced and widely used in Europe, but results were inconsistent.

A non-invasive, focused ultrasound device, operating at megahertz (MHz) frequencies, was recently cleared in the US for the indication of brow lift. However, limited data regarding safety and efficacy are currently available. This device focuses millisecond-domain pulses at the level of the deep dermis and/or superficial fascia, up to a depth of ~4.5 mm. A small focal zone of thermal damage is produced with each pulse, sufficient to achieve tissue contraction at the focus. The treatment transducer is also used for imaging, in order to verify positioning and treatment at a proper tissue plane. This is the first combined diagnostic and therapeutic ultrasound device intended for dermatology.

Low Level Light Therapy (LLLT)

Over the past 50 years, lasers and light-emitting diode (LED) sources have been used for medical "biostimulation", mainly outside the US. Moderate irradiances of light, at certain visible and near-IR wavebands, have long been reported to modulate metabolism in mammals. The FDA mandate to balance risks and benefits is such that devices that pose no known risk are sometimes cleared for sale, with little or no evidence of efficacy. Most sources sold for LLLT do not have specifically approved indications.

That said, the FDA has cleared low power red lasers (continuous, milliwatt power, 630–800 nm wavelength) for treatment of carpal tunnel syndrome and for stimulating hair growth in male pattern alopecia, based on evidence from clinical trials. Moreover, scientific and clinical evidence is mounting in support of LLLT having bona-fide photobiologic effects. Stimulation of mitochondrial activity via light absorption is thought to occur. Mitochondrial signaling pathways affected by light include those that are redox-sensitive, ATP- and cyclic AMP-dependent, and regulated by nitric oxide[45,46].

LLLT may be appropriate as adjunctive therapy in the setting of ischemia, hypoxia or oxidative stress. These conditions exist in many primary cutaneous disorders, as well as after surgery and various laser treatments. The levels of light emitted by available LLLT devices are considered safe during exposure of unprotected skin and eyes.

REFERENCES

1. Einstein A. Zur Quantentheorie der Strahlung. Physiol Z. 1917;18:121–8.
2. Goldman L, Blaney DJ, Kindel DJ, Frank EK. Effect of the laser beam on the skin: preliminary report. J Invest Dermatol. 1963;40:121–2.
3. Maiman TH. Stimulated optical radiation in ruby. Nature. 1960;187:493–4.
4. Carroll L, Humphreys TR. LASER-tissue interactions. Clin Dermatol. 2006;24:2–7.
5. Herd RM, Dover JS, Arndt KA. Basic laser principles. Dermatol Clin. 1997;15:355–72.
6. Raulin C, Schonermark MP, Greve B, Werner S. Q-switched ruby laser treatment of tattoos and benign pigmented skin lesions: a critical review. Ann Plast Surg. 1998;41:555–65.
7. Anderson RR, Parrish JA. The optics of human skin. J Invest Dermatol. 1981;77:13–9.
8. Anderson RR. Polarized light examination and photography of the skin. Arch Dermatol. 1991;127:1000–5.
9. Polla BS, Anderson RR. Thermal injury by laser pulses: protection by heat shock despite failure to induce heat-shock response. Lasers Surg Med. 1987; 7:398–404.
10. Henriques FC. Studies of thermal injury. Arch Pathol. 1947;43:489–502.
11. Welch AJ. The thermal response to laser irradiated tissue. IEEE J Quant Electron. 1984;20:1471.
12. Hruza GJ, Geronemus RG, Dover JS, Arndt KA. Lasers in dermatology – 1993. Arch Dermatol. 1993;129: 1026–35.
13. Anderson RR, Parrish JA. Selective photothermolysis: precise microsurgery by selective absorption of pulsed radiation. Science. 1983;220:524–7.
14. Anderson RR. Laser-tissue interactions. In: Goldman MP, Fitzpatrick RE (eds). Cutaneous Laser Surgery. St Louis: Mosby, 1994:1–17.
15. Anderson RR. Lasers in dermatology – a critical update. J Dermatol. 2000;27:700–5.
16. Watanabe S, Flotte TJ, McAuliffe DJ, Jacques SL. Putative photoacoustic damage in skin induced by pulsed ArF excimer laser. J Invest Dermatol. 1988;90:761–6.
17. Garden JM, Tan OT, Kerschmann R, et al. Effect of dye laser pulse duration on selective cutaneous vascular injury. J Invest Dermatol. 1986;87:653–7.
18. Zenzie HH, Altshuler GB, Smirnov MZ, Anderson RR. Evaluation of cooling methods for laser dermatology. Lasers Surg Med. 2000;26:130–44.
19. Battle EF, Suthamjariya K, Alora MB, et al. Very long-pulsed (20-200 ms) diode laser for hair removal on all skin types. Lasers Surg Med. 2000;12(suppl):85.

20. Nanni CA, Alster TS. Complications of carbon dioxide laser resurfacing. An evaluation of 500 patients. Dermatol Surg. 1998;24:315–20.
21. Lanigan SW. Patient-reported morbidity following flashlamp-pumped pulsed tunable dye laser treatment of port wine stains. Br J Dermatol. 1995;133:423–5.
22. Waner M, Dinehart SM, Wilson MB, Flock ST. A comparison of copper vapor and flashlamp pumped dye lasers in the treatment of facial telangiectasia. J Dermatol Surg Oncol. 1993;19:992–8.
23. Polla LL, Margolis RJ, Dover JS, et al. Melanosomes are a primary target of Q-switched ruby laser irradiation in guinea pig skin. J Invest Dermatol. 1987;89:281–6.
24. Murphy GF, Shepard RS, Paul BS, et al. Organelle-specific injury to melanin-containing cells in human skin by pulsed laser irradiation. Lab Invest. 1983;49:680–5.
25. Taylor CR, Anderson RR, Gange RW, et al. Light and electron microscopic analysis of tattoos treated by Q-switched ruby laser. J Invest Dermatol. 1991;97:131–6.
26. Goldberg DJ. Benign pigmented lesions of the skin. Treatment with the Q-switched ruby laser. J Dermatol Surg Oncol. 1993;19:376–9.
27. Grossman MC, Anderson RR, Farinelli W, et al. Treatment of cafe au lait macules with lasers. A clinicopathologic correlation. Arch Dermatol. 1995;131:1416–20.
28. Taylor CR, Anderson RR. Ineffective treatment of refractory melasma and postinflammatory hyperpigmentation by Q-switched ruby laser. J Dermatol Surg Oncol. 1994;20:592–7.
29. Wheeland RG. Simulated consumer use of a battery-powered, hand-held, portable diode laser (810 nm) for hair removal: a safety, efficacy and ease-of-use study. Lasers Surg Med. 2007;39:476–93.
30. Tearney GJ, Jang IK, Kang DH, et al. Porcine coronary imaging in vivo by optical coherence tomography. Acta Cardiol. 2000;55:233–7.
31. Gambichler T, Moussa G, Sand M, et al. Applications of optical coherence tomography in dermatology. J Dermatol Sci. 2005;40:85–94.
32. Nelson JS, Kelly KM, Zhao Y, Chen Z. Imaging blood flow in human port-wine stain in situ and in real time using optical Doppler tomography. Arch Dermatol. 2001;137:741–4.
33. Gerger A, Koller S, Weger W, et al. Sensitivity and specificity of confocal laser-scanning microscopy for in vivo diagnosis of malignant skin tumors. Cancer. 2006;107:193–200.
34. Hammes S, Augustin A, Raulin C, et al. Pupil damage after periorbital laser treatment of a port-wine stain. Arch Dermatol. 2007;143:392–4.
35. Arnoczky SP, Aksan A. Thermal modification of connective tissues: basic science considerations and clinical implications. J Am Acad Orthop Surg. 2000;8:305–13.
36. Goldberg DJ, Fazeli A, Berlin AL. Clinical, laboratory, and MRI analysis of cellulite treatment with a unipolar radiofrequency device. Dermatol Surg. 2008;34:204–9.
37. Emilia del Pino M, Rosado RH, Azuela A, et al. Effect of controlled volumetric tissue heating with radiofrequency on cellulite and the subcutaneous tissue of the buttocks and thighs. J Drugs Dermatol. 2006;5:714–22.
38. Carstensen EL, Miller MW, Linke CA. Biological effects of ultrasound. J Biol Physics. 1974;2:173–92.
39. Ziskin MC. Fundamental physics of ultrasound and its propagation in tissue. Radiographics. 1993;13:705–9.
40. Madersbacher S, Marberger M. High-energy shockwaves and extracorporeal high-intensity focused ultrasound. J Endourol. 2003;17:667–72.
41. Miller DL, Pislaru SV, Greenleaf JE. Sonoporation: mechanical DNA delivery by ultrasonic cavitation. Somat Cell Mol Genet. 2002;27:115–34.
42. Miller DL, Thomas RM. The role of cavitation in the induction of cellular DNA damage by ultrasound and lithotripter shock waves in vitro. Ultrasound Med Biol. 1996;22:681–7.
43. Zocchi M. Ultrasonic liposculpturing. Aesthetic Plast Surg. 1992;16:287–98.
44. Palmieri B, Gozzi G, Perrone V. [Ultrasonic liquid medium for lipo-emulsification. An experimental study]. Minerva Chir. 1994;49:199–201.
45. Huang Y-Y, Chen AC-H, Hamblin MR. Advances in low-intensity laser and phototherapy. In: Tuchin VV (ed.). Handbook of Photonics for Biomedical Science. Boca Raton, FL: Taylor and Francis, 2009:687–716.
46. Borutaite V, Budriunaite A, Brown GC. Reversal of nitric oxide-, peroxynitrite- and S-nitrosothiol-induced inhibition of mitochondrial respiration or complex I activity by light and thiols. Biochim Biophys Acta. 2000;1459:405–12.

This page intentionally left blank

137 Laser Therapy

Christopher B Zachary and Rana Rofagha

Chapter Contents

Types of lasers and intense pulsed light 2261
Treatment of vascular lesions 2263
Treatment of tattoos 2267
Treatment of melanin-containing lesions 2268
Treatment of striae distensae 2271
Ablative lasers: carbon dioxide and Er:YAG 2271
Fractionated lasers 2272
Plasmakinetic resurfacing 2277
Other photorejuvenation devices 2277
Radiofrequency (RF) 2277
Hair removal 2278
Treatment of psoriasis and vitiligo 2279

The advancements in laser and light therapies over the past three decades are built upon the foundation of Albert Einstein's *The Quantum Theory of Light*. In these prescient 1917 writings, he proposed, amongst other concepts, that light consists of quanta of energy, and he hinted at the notion of amplification. In 1958, Townes and Schalow described Microwave Amplification by Stimulated Emission of Radiation (MASER). This was further refined by Thomas Maiman as Light Amplification by Stimulated Emission of Radiation (LASER)[1]. Early laser devices, however, were functionally limited by their lack of selectivity. Anderson and Parrish developed the concept of selective photothermolysis whereby laser energy could be used for targeted destruction of skin components (see Ch. 136). Their 1983 treatise continues to support our understanding of laser–tissue interactions and still drives new therapeutic applications of lasers in dermatology.

This chapter will consider laser and light applications for both medical and aesthetic purposes as related to the skin. Given the multiplicity of lasers available, the laser surgeon must understand the capabilities and limitations of each device so that the appropriate system can be selected and the parameters tailored to treat the intended target (Fig. 137.1). Safe and effective laser therapy is achieved when the operator understands the nature of the target, its location in the skin, and the potential collateral damage.

TYPES OF LASERS AND INTENSE PULSED LIGHT

The earliest lasers used by dermatologists were applied to vascular lesions and consisted of continuous or quasi-continuous wave lasers which emitted a constant beam of light. These included argon (488, 514 nm), argon pumped tunable dye (488–638 nm), copper vapor and copper bromide (511 nm, 578 nm), potassium titanyl phosphate (KTP, 532 nm), and krypton (568 nm) lasers. Although these lasers had wavelengths that corresponded to the hemoglobin absorption spectrum, the nature of their continuous beams generally induced nonspecific thermal damage to surrounding structures, leading to scarring and dyschromia. The root of the problem, a mismatch between the laser pulse duration and the thermal relaxation time of the target tissue (see Ch. 136), was effectively resolved once it was understood that laser pulse duration should approximately match the thermal relaxation time of the targeted tissue.

Pulsed Dye Laser

The pulsed dye laser (PDL) is considered to be the laser of choice for the treatment of many cutaneous vascular lesions, especially port-wine stains (PWS), superficial hemangiomas, poikiloderma of Civatte, facial telangiectasias and rosacea[2]. Hypertrophic and keloidal scars, psoriasis and warts are also amenable to treatment with PDL. While the initial PDL systems emitted 577 nm yellow light, slightly longer wavelength PDL devices (585 or 595 nm) were subsequently adopted to allow deeper tissue penetration of up to 1.2 mm.

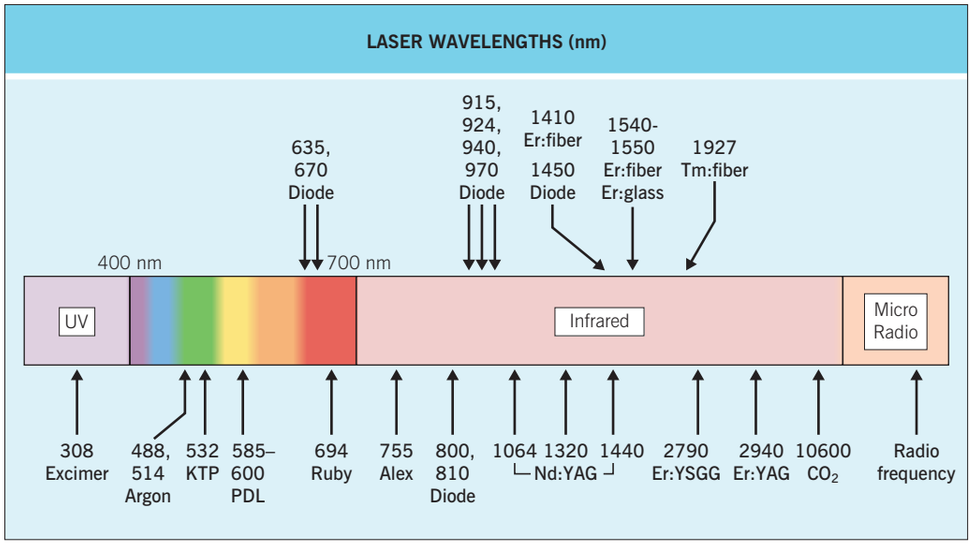


Fig. 137.1 Laser wavelengths (nm). Laser wavelengths lie predominantly within the ultraviolet, visible and infrared portions of the electromagnetic spectrum. Alex, alexandrite; Er, erbium; KTP, potassium titanyl phosphate; Micro, microwaves; Nd, neodymium; PDL, pulsed dye laser; Radio, radio waves; Tm, thulium; UV, ultraviolet; YAG, yttrium-aluminum-garnet; YSGG, yttrium-scandium-gallium-garnet.

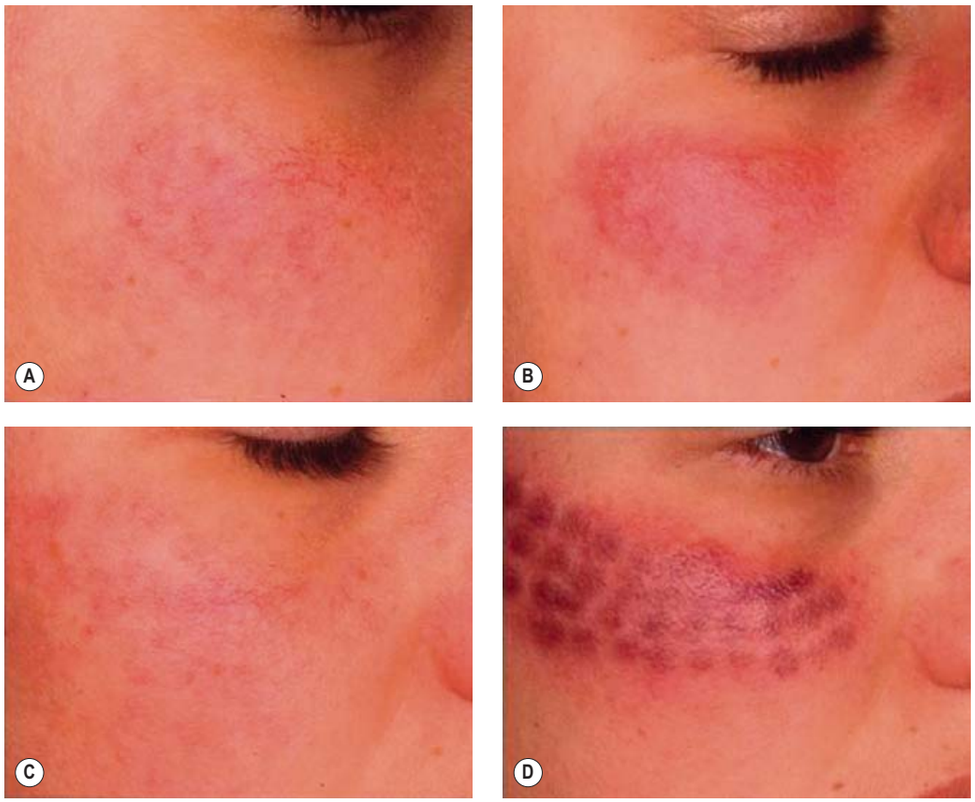


Fig. 137.2 Treatment of facial telangiectasias – potassium titanyl phosphate (KTP) laser versus pulsed dye laser (PDL). A, **C** Pretreatment. Mild erythema follows KTP therapy (**B**) compared to circles of purpura after PDL (**D**).

The choice of appropriate PDL parameters affects tissue response, in terms of both efficacy and appearance. Short pulse durations (0.45–3 millisecond [ms]) cause a purpuric reaction related to intravascular coagulation (Fig. 137.2). While very effective for telangiectasias, the bruised appearance is not cosmetically acceptable to many patients. Although slightly less effective, longer pulse durations (6–10 ms) with "pulse stacking" (application of a rapid succession of pulses to a particular location with cooling to achieve "purpura-free" treatments) is quite effective and less noticeable. The latest generations of PDL modulate this approach by dividing each pulse into eight micro-pulses. This is said to be more selective, to provide uniform vascular heating with a reduction in purpura, and to be more comfortable[3].

Epidermal protection during laser treatments, including those with PDL, is critical. Cooling helps to reduce blistering, crusting, and subsequent dyspigmentation (i.e. hypo- and hyperpigmentation). The most common cooling strategies are contact cooling, forced cold air, and cryogen spray. The Candela PDL systems incorporate cryogen spray cooling (Dynamic Cooling Device™) which is deployed immediately before the light pulse, while Cynosure systems use forced cold air. In addition to protecting the epidermis from non-selective thermal damage, cooling allows for the use of higher fluences, with improved efficacy.

KTP Laser (Frequency-Doubled Nd:YAG Laser)

KTP 532 nm laser light is produced by passing 1064 nm light from an Nd:YAG (neodymium-yttrium-aluminum-garnet) laser through a potassium titanyl phosphate (KTP) crystal, which effectively halves the wavelength and doubles the frequency. Since this wavelength closely corresponds to the first absorption peak of hemoglobin at 542 nm, the KTP laser can be used to effectively treat some vascular lesions (e.g. telangiectasias) in a purpura-free manner (see Fig. 137.2). In addition, this laser is a popular device for the removal of lentigines and other epidermal pigmented lesions. While this laser is best employed in patients with skin phototypes I–III, it can used in darker skin types (IV–VI) for unique applications, such as dermatosis papulosis nigra.

Nd:YAG Laser

The deeply penetrating Nd:YAG 1064 nm laser has significantly less hemoglobin absorption than the wavelengths of the PDL or KTP laser. However, its absorption by melanin is also very limited. The latter property enhances the safety profile of the 1064 nm laser in patients with darker phototypes. Also, this laser can be used to treat deeper vascular lesions and spider veins up to 3 mm in size[4]. Because of its poor coefficient of absorption by hemoglobin, much higher fluences are required to produce transmural heating of blood vessels. As a consequence of the higher fluences and longer pulse widths, this wavelength has a narrow window of safety, with the potential for volumetric heating and collateral damage; in addition, it tends to be quite painful. Cooling is critical for epidermal protection and pain control, as well as to reduce the risk of scarring from nonspecific thermal injury.

Intense Pulsed Light

Intense pulsed light (IPL) systems emit filtered polychromatic light with wavelengths ranging from visible to near infrared (500–1200 nm). Sophisticated filtering and pulsing systems prevent unwanted wavelengths from damaging the skin, and they have made this device more specific and quite versatile. Handpiece cooling is a useful feature present in some devices, and it can be employed to provide epidermal protection, while at the same time allowing greater fluences to reach deeper targets. IPL systems can be used to treat a number of conditions, including rosacea, PWS, hemangiomas, poikiloderma of Civatte and lentigines, as well as provide overall photorejuvenation. The new IPL devices are fast, reliable, and durable.

Cold ultrasound gel or aloe vera gel should be applied as a supplementary technique in order to diffuse surface heat and to act as a "heat sink" away from the epidermis. The gel also reduces the refractive index between air and skin, thus allowing better penetration and absorption of light. In addition, it enhances gliding of the handpiece from one location to the next.

In spite of these measures, thermal injury to the epidermis can still occur, leading to blistering, scarring and permanent pigmentary alterations. This is generally operator-dependent, with a greater risk when treating patients with a tan or darker skin phototypes (Fig. 137.3). IPL is most commonly used for patients with phototypes I–III with chronic photodamage or for hair removal. For treatment of more darkly pigmented patients, longer wavelength filters or lower fluences plus longer pulse widths can be used (Fig. 137.4).

The authors' preferred technique is to deliver multiple passes to a particular treatment area, with each subsequent pass oriented at

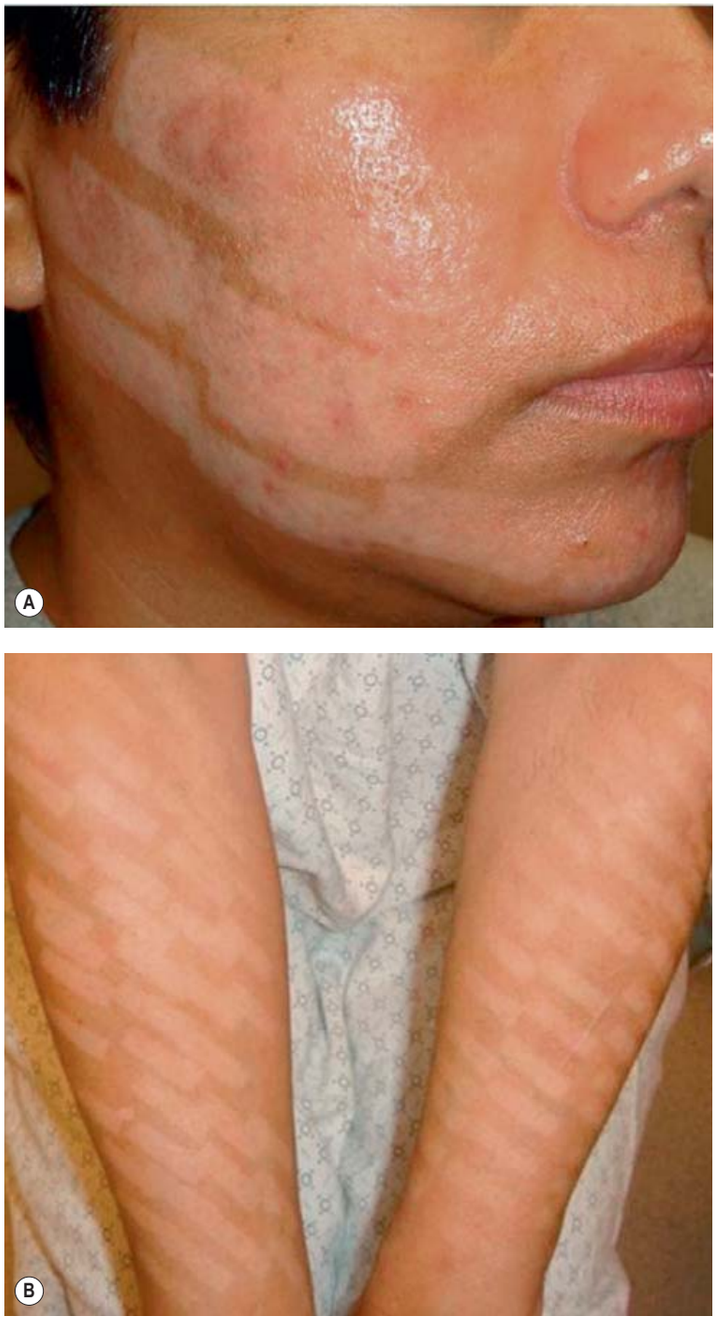


Fig. 137.3 Dyspigmentation and potential scarring due to inappropriate intense pulsed light (IPL) treatments in two patients with darker skin phototypes.

a different angle. This allows for uniform, consistent coverage and prevents zebra-like pigmentary irregularities and skip areas. If double or triple pulses are utilized in any one area, adequate time for epidermal cooling should be allowed between passes. The observable endpoints of IPL treatment are darkening of lentigines (see Fig. 137.4C) and either a disappearance or a darker blue appearance of telangiectasias.

As with any of these devices, the initial pulses should be assessed in terms of the tissue response. Potential problems that should be avoided are excessive blanching, bruising, and production of the Nikolsky sign or other signs of excessive non-selective heating. If cooling is being used, it should be assessed for efficacy. Additionally, care must be taken to avoid inadvertent photoepilation of eyebrows, and, for men, bearded skin.

TREATMENT OF VASCULAR LESIONS

Although patients most commonly present with telangiectasias and rosacea, one should also be familiar with the latest techniques available for the treatment of PWS and hemangiomas. The target chromophore in vascular lesions is oxyhemoglobin[5], with absorption peaks at 418, 542 and 577 nm (see Fig. 136.3). While the primary target is hemoglobin, the structurally dynamic nature of the skin does not allow for simplistic "targeting". Factors such as blood vessel depth, thickness, and skin phototype are also highly relevant considerations when treating vascular lesions.

Equally important considerations are the structures that the laser surgeon wishes to avoid, such as normal epidermal melanocytes, hair follicles, and the epidermis as a whole. Therefore, while the above wavelengths allow for maximal absorption, longer wavelengths are associated with less melanin absorption and deeper penetration. The most commonly used devices for the treatment of vascular lesions include IPL and the 532 nm KTP, 595 nm PDL, and 1064 nm Nd:YAG lasers. Other systems such as the 755 nm alexandrite and the 940 nm diode lasers also play an important role in the treatment of vascular lesions (Table 137.1).

Clinical improvement is best achieved by photothermal vascular damage[6]. As the pulse width approximates or exceeds the thermal relaxation time of the target vessel (approximately 1.5 ms), photothermal damage results. This induces *intravascular* thrombosis and subsequent collagenous fibrosis of the blood vessel wall and adjacent tissues[6]. These changes result in an immediate purpuric reaction (see Fig. 137.2D). Given the unwanted cosmetic appearance of the latter, which can last for 2 weeks, longer pulse widths (>6 ms) are often used, as they produce more gentle heating of the target vessel and avoid bruising altogether. However, some degree of intravascular thrombosis may be a prerequisite for clinical improvement and resolution of vascular lesions, as is the case in PWS.

Port-Wine Stains (PWS)

One of the first clinical applications of laser therapy was treatment of congenital vascular lesions, namely port-wine stains (PWS). PWS are capillary malformations that involve primarily the mid to superficial dermis; they occur in up to 0.5% of newborns and initially present as faint, light pink patches. These vascular anomalies are cosmetically and psychologically problematical as they are frequently located on the face. Approximately 5–10% of patients with unilateral PWS involving V1 have Sturge–Weber syndrome, with associated ocular and neurologic involvement. When located on the extremities, patients may develop Klippel–Trenaunay syndrome with soft tissue hypertrophy, especially when there is a sharply demarcated geographic stain (see Ch. 104).

Prior to laser therapy, PWS were treated via destructive modalities such as cryosurgery, dermabrasion, and X-ray radiation. These therapies often resulted in disfiguring scars. An early and relatively successful treatment of PWS utilized the continuous wave argon laser (488 and 514 nm). Despite the wavelength's relative specificity for its vascular target, this laser caused marked scarring in up to a third of patients[7]. The latter was caused by nonspecific thermal injury due to the exposure time of the beam (~ 200 ms) being in dramatic excess of the thermal relaxation time of the PWS vessels (~ 1–10 ms)[8].

A therapeutic paradigm shift evolved with the concept of selective photothermolysis and the development of the PDL, which was specifically designed to treat PWS. The first study, conducted by Tan et al.[9], demonstrated significant fading in all 35 patients (ages 3 months to 14 years) after an initial treatment and complete clearance after an average of 6.5 treatments. Most remarkably, the sequelae were minor, with some patients experiencing short-term hyperpigmentation and only two patients developing shallow depressed scarring. Although subsequent studies found significantly lower clearance rates, this initial study demonstrated a pattern of safety and efficacy of PDL for treatment of PWS.

While the early PDLs emitted a 577 nm wavelength, the current PDL systems deliver 585 and 595 nm, allowing targeted delivery of laser energy deeper into the skin with increased efficacy. These longer wavelengths are less well absorbed by hemoglobin, but they penetrate deeper into the vascular malformation, inducing a more even heating of the PWS[10]. Addition of the Dynamic Cooling Device™ (DCD) has allowed for the use of much higher fluences. Commonly used settings range from fluences of 4 to 15 J/cm^2 with pulse widths of 1.5–10 ms with a 7–12 mm spot size[11]. Larger spot sizes are associated with deeper energy penetration, but the fluence should be moderated with increasing beam diameter in order to avoid thermal damage related to the

Fig. 137.4 Intense pulsed light (IPL) treatment of lentigines in a patient with Fitzpatrick phototype IV skin. Because of the more darkly pigmented skin, lower energy and a longer pulse duration were carefully employed. **A** Preoperative. **B** Lentigines are appropriately slightly darker immediately following IPL. **C** Dry crusting of the skin 3 days postoperatively. **D** Excellent improvement of facial lentigines at 10 days.

Gaussian distribution of energy (i.e. the beam is hotter in the center than laterally, see Ch. 136).

For both technical and psychological reasons, early treatment of PWS is recommended. As compared to infantile hemangiomas, the dilated and ectatic vessels of PWS are not proliferative nor do they self-involute. Their surface area becomes proportionately larger as the child grows and many become thicker (with soft tissue hypertrophy), darker in color and deeper. As such, their treatment becomes clinically more challenging and often requires use of lasers with longer wavelengths, along with higher fluences and longer pulse durations to effectively treat the deeper and thicker vessels. Studies support this notion and have demonstrated that the extent of clearance is dependent on lesion size and depth[12]. From the psychological standpoint, PWS have been shown to impact childhood social and cognitive development and can have lasting repercussions on adult social relationships[13,14]. In addition, early treatment permits shorter treatment sessions (as the lesions are smaller), fewer sessions, and may allow resolution of the vascular anomaly prior to the child developing memory of the treatment and its associated stressors. Lastly, laser treatment in children younger than 6 months of age has been demonstrated to be safe and effective[15].

While 70% of PWS will have good or very good improvement (Fig. 137.5), a minority (<10%) will have very modest or no improvement. The degree of PWS clearance is dependent on the size of the lesion and its anatomic location[16]. For example, centrally located facial lesions (i.e. medial cheeks, upper lip and nose) require multiple sessions for improvement and tend to be more treatment-resistant as compared to lesions located in the periorbital region or on the forehead, lateral cheeks, or chin. Classically, treatment-resistant areas of PWS, which may correspond to more deeply situated vessels, are distributed within the second branch of the trigeminal nerve (V2). Likewise, PWS on distal extremities are more treatment-resistant and require a more aggressive approach. Although remarkable responses can be obtained after one laser treatment, treatment of PWS typically requires multiple sessions.

Given that PWS are composed of various-sized blood vessels, each with their own required treatment parameters, the PDL may prove inadequate in eliminating the entire capillary malformation. Poor responses may be related to poor laser penetration, a mismatch of parameters to vessel size, inadequate vascular heating, or scarce or poor chromophore uptake[17]. Given the limitations of the PDL, resistant

LASERS AND OTHER DEVICES USED FOR THE TREATMENT OF VASCULAR LESIONS					
Laser/device	**Wavelength (nm)**	**Fluence (J/cm²)**	**Pulse duration (ms)**	**Target structure**	**Applications**
SKIN-SURFACE APPLICATION					
Variable-pulsed KTP laser	532	Up to 240	1–100	Telangiectasia, venulectasia	Facial telangiectasias, erythematotelangiectatic rosacea, leg telangiectasias, venous malformations, cherry angiomas
Pulsed dye laser	585, 590, 595, 600	Up to 40	0.45–40	Telangiectasia	Port-wine stains, erythematotelangiectatic rosacea, facial and leg telangiectasias, infantile hemangiomas, hypertrophic scars, striae rubra, verrucae, cherry angiomas, spider angiomas, venous lakes
Long-pulsed alexandrite laser	755	Up to 100	3–100	Venulectasia, telangiectasia	Leg telangiectasias ("spider veins"), venous malformations
Diode laser	800	10–100	5–400	Venulectasia, telangiectasia	Leg venulectasias and telangiectasias ("spider veins"), blue reticular veins, venous malformations
Long-pulsed Nd:YAG laser	1064	5–900	0.25–500	Venulectasia, telangiectasia	Leg venulectasias and telangiectasias ("spider veins"), blue reticular veins, facial telangiectasias, venous lakes
Intense pulsed light	400–1200	10–80	2–200	Telangiectasia, venulectasia	Erythematotelangiectatic rosacea, leg telangiectasias ("spider veins")
ENDOVASCULAR APPLICATION					
Diode lasers	810, 940			Varicose veins	Saphenous vein insufficiency
Nd:YAG laser	1320			Varicose veins	Saphenous vein insufficiency
Radiofrequency energy source	Radiofrequency			Varicose veins	Saphenous vein insufficiency

Table 137.1 Lasers and other devices used for the treatment of vascular lesions. For details on endovascular applications, see Chapter 155. ms, millisecond.

Fig. 137.5 Treatment of a port-wine stain with the pulsed dye laser (PDL). A Before treatment. **B** Purpuric response immediately after treatment with the PDL (585 nm, 450 ms). **C** Six weeks after the fourth treatment. *Courtesy, Jeffrey Dover, MD, and Kenneth Arndt, MD.*

components of PWS may also be treated with the alexandrite and Nd:YAG lasers or IPL.

Infantile Hemangiomas

Representing the most common tumor of infancy, hemangiomas have a predilection for the head and neck region (60%), followed by the trunk and the extremities. They are present in 1–2% of neonates and there is a higher incidence in premature infants. These tumors are classically absent or very small at birth, but then appear and/or grow rapidly within the first few weeks of life. Infantile hemangiomas may have both superficial and deep components, with the superficial portions appearing red and the deeper components appearing blue. They can be categorized as segmental or focal (see Ch. 103)[17]. Their natural maturation involves a proliferative phase, a static phase, and an involutional phase. According to the classic teaching, 50% regress by age 5 years, 70% by age 7, and >90% by adolescence. Although hemangiomas can regress leaving the affected skin with normal texture and color, many heal with hyper- or hypopigmentation and atrophy or fibrofatty change (see Fig. 103.11).

Treatment of infantile hemangiomas, if any, should be tailored to the specific lesion, with consideration of its location, size, proliferative rate, and whether it is likely to produce a functional or anatomic deficit. Complicated infantile hemangiomas require a multidisciplinary approach, involving dermatology, pediatrics, interventional radiology, otolaryngology, plastic surgery, and ophthalmology. Common therapeutic options include monitoring, intralesional corticosteroids, systemic corticosteroids, surgical excision, and laser therapy. However, multiple recent studies have demonstrated the efficacy of propanolol in producing regression[18]. To date, the use of β-blockers appears to be relatively safe and propranolol is becoming a mainstay of treatment regimens for large or functionally significant hemangiomas.

Although the role of laser therapy in the treatment of infantile hemangiomas is controversial, PDL can be used and it may decrease the risk of ulceration and scarring. A retrospective study demonstrated a distinct improvement in 50% of infants with painful, ulcerated infantile hemangiomas (18% had no response and 5% were made worse) following therapy[19]. While some authors maintain that treatment with PDL can moderate the proliferative phase of infantile hemangiomas, this issue is contentious and debatable[20]. In the largest study of hemangiomas in children, abruption in growth was demonstrated in 96.6% of 692 lesions after PDL[21]. While these results seem extremely optimistic,

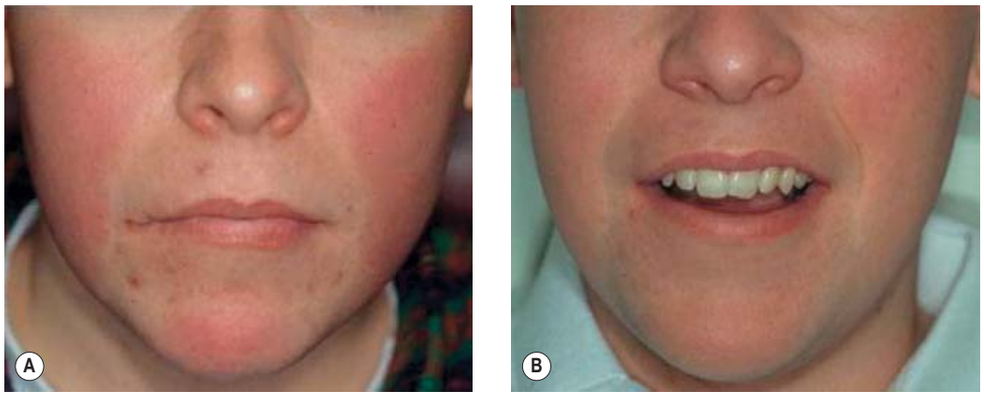


Fig. 137.6 Erythematotelangiectactic rosacea. Improvement of facial erythema and flushing 2 months following pulsed dye laser (PDL) therapy.

they do balance the opposing view that the PDL has limited benefit in children with hemangiomas. Other options that may be beneficial for these hemangiomas are IPL and, for deeper hemangiomas, the Nd:YAG (1064 nm) laser, although the latter can induce significant scarring.

Epidermal protection is critical in the treatment of infantile hemangiomas. Among the most significant side effects of laser therapy are scarring and pigmentary changes, both of which can be minimized by appropriate epidermal cooling mechanisms (e.g. contact cooling, cryogen spray cooling, forced cold air). These not only protect the epidermis, but also allow the use of higher fluences.

Telangiectasias

Patients frequently present with facial telangiectasias. These are most commonly associated with rosacea and chronic photodamage, but are also seen in the setting of liver disease, autoimmune connective tissue disorders, surgical scars, and misuse of topical corticosteroids. They are typically located on the nose, cheeks and chin and measure 0.1–1.0 mm in diameter. Facial lesions of this caliber are commonly treated with the KTP laser, IPL and PDL systems. When the PDL is used with short pulse durations, significant clearance can be achieved, albeit with significant bruising (see Fig. 137.2D). Clearance of facial vessels can be achieved with *non-purpuric fluences* or treatments that employ fluences ranging from 6.5 to 8.5 J/cm^2 with longer pulse durations (10–16 ms) using 10–12 mm spot sizes. At these settings, multiple passes and/or pulse-stacking techniques are typically employed to improve efficacy. Additionally, multiple treatment sessions may be required[22,23]. These techniques can be particularly beneficial for patients with recurring flushing and central facial erythema (Fig. 137.6).

Treatment of telangiectasias with the KTP laser with a small (0.2 to 2 mm) beam diameter induces few side effects, with little or no bruising and less swelling, pain and redness than is seen with the PDL (see Fig. 137.2). Larger-caliber, darker, deeper facial vessels can be effectively treated with the Nd:YAG laser, particularly in dark-skinned patients. However, to compensate for the diminished absorption of 1064 nm light by hemoglobin (nearly 10-fold less compared with 595 nm light), an increased fluence is required, making vigorous cooling necessary both for epidermal protection and to reduce patient discomfort. Finally, IPL is commonly used for purpura-free treatment of facial telangiectasias utilizing a 550 or 560 nm cut-off filter. The treatment endpoint for telangiectasias is vessel spasm or the change of the vessel color to a more dusky appearance.

Poikiloderma of Civatte

Poikiloderma of Civatte is a hallmark reflection of photodamage and involves the lateral aspects of the cheeks, neck and upper chest. While a prominent component is telangiectasias, there is also epidermal atrophy and actinic dyspigmentation. Comprehensive treatment requires consideration of each component. Options include IPL, PDL and KTP laser; new devices such as the fractionated ablative and nonablative lasers can also be used. When there is insufficient overlap of adjacent PDL pulses, a persistent "honeycomb-like" appearance may occur, with circles of improvement in color, texture and tone surrounded by a network of relatively untreated skin (Fig. 137.7). This

Fig. 137.7 "Footprinting" on the cheek of a young girl following pulsed dye laser (PDL) therapy of a port-wine stain. There is a honeycomb-like appearance due to circles of improvement surrounded by a network of relatively untreated skin.

mottled look can require multiple treatments to eradicate, and it is due to the Gaussian distribution of the light beam in which the center of the beam produces greater clearance than the edges.

Since IPL can favorably improve both dyspigmentation and telangiectasias, this system is perhaps more ideally suited to treat poikiloderma of Civatte. Several studies have reported 50–75% improvement in both the vascular component and the actinic dyspigmentation, with a low side-effect profile[24]. The pertinent short-term side effects are transient erythema and intentional darkening of lentigines, which all disappear in about a week. Although "footprinting" is possible with IPL, it is far less common than with PDL, given the larger size of the crystal IPL handpiece. Additionally, use of a multiple-pass technique applied in different orientations tends to minimize this unintended "footprint" consequence.

Telangiectasias and Venulectasias of the Leg ("Spider" Leg Veins)

"Spider veins" of the legs affect approximately 80% of men and women in the US[25]. These telangiectasias and venulectasias are red and blue in color, measure 0.2 to 2 mm in diameter, and develop in dependent areas, predominantly the legs. While a number of spider veins appear independently of deeper vascular disorders, a surprisingly high percentage can be improved by treating deeper underlying venous disease. While the superficial venous plexus is located in the skin, subcutaneous tissue and superficial fascia, the deep venous plexus is located within underlying muscle, with the two plexuses interconnected by perforating veins[26]. Whether as a consequence of age, hormonal or genetic factors, or trauma to the vessel wall, venous valvular incompetence produces increased hydrostatic pressure and ultimately vessel dilation (see Ch. 155).

Whereas facial telangiectasias are generally superficial, small in caliber, and have normal hydrostatic pressures, leg veins are larger in diameter, thicker in caliber, and are situated more deeply in the skin[27]. Additionally, as in any treatment site, there is heterogeneity in the size,

color and caliber of ectasias. These properties make treatment of leg veins even more challenging. While sclerotherapy is still the first-line therapy for spider veins (see Ch. 155), laser treatment is a viable option in a minority of patients (see Table 137.1). The latter include those with needle phobias, telangiectatic matting, ankle veins, and lack of a favorable response to sclerotherapy[27]. Also, laser therapy may be advisable in patients with a previous history of adverse reactions to sclerosing agents. The PDL and KTP laser can be used to treat small-caliber pink and red vessels which are too fine to cannulate with sclerotherapy needles, e.g. the telangiectatic matting that can be a consequence of prior sclerotherapy.

The target chromophore for leg veins is hemoglobin. While the 532 nm KTP laser, 585–595 nm PDL, and IPL are well absorbed by this target, the more limited depth of penetration does not allow for consistent treatment of vessels >1 mm in width located at depths >1.0 mm[28]. The results with IPL devices are inconsistent, unpredictable and vary depending on the selected parameters. Furthermore, these devices have more unfavorable side effects compared to sclerotherapy. Hyperpigmentation following PDL occurs in 20–40% of patients and can persist for 3 months or longer. This side effect may be related both to red cell extravasation and to epidermal cryogen spray injury. Many laser surgeons (including the authors) have used the long-pulsed Nd:YAG laser for the treatment of larger, deeper leg veins. While there is no doubt that some leg veins can be cleared, the pain, postinflammatory hyperpigmentation, and potential for scarring have many clinicians avoiding this device for this indication.

Given that leg veins are heterogeneous in their color, size, caliber and depth, and that many result from venous valvular incompetence, ultrasound investigation can assist in determining the most appropriate treatment strategy. Combination therapy using endovenous lasers, ambulatory phlebectomy, and sclerotherapy may represent the best approach for long-term, successful treatment of lower extremity ectasias. Synergistic improvement has been demonstrated when these treatments were used in combination (see Ch. 155)[4].

Verrucae

Verruca vulgaris is caused by the human papillomavirus, which induces epidermal hyperplasia and neovascularization in affected skin. The use of lasers is said to be based on the principle of targeting their vascular component which is evident histologically as dilated blood vessels in the dermal papillae. Early on, successful treatment was reported with the copper vapor laser, presumably by its inducing vascular coagulation of these reactive vessels[29]. Use of the PDL has been shown to induce intravascular thrombosis and vessel wall necrosis in patients with verrucae[30]. However, the nonspecific heat effect from lasers is likely the main mechanism for wart clearance with laser therapy. "Laserthermia" of warts, particularly with the Nd:YAG laser, has produced clearance in 75% of patients[31]. The mechanism may involve coagulation of epidermal proteins and blood vessels, with stimulation of a reactive inflammatory response. Although a similar tissue response is likely caused by carbon dioxide ablation of verrucae, response rates have been more variable, ranging from 30% to 80%[32]. Most notably, scarring and onychodystrophy can result from treatment of periungual verrucae with such ablative laser therapies[33,34].

Currently, the PDL is the most commonly used laser for the treatment of recalcitrant verrucae. A notable lack of bleeding and scarring makes this laser a favorable choice. Given the limited penetration of the PDL, hyperkeratotic portions of the wart are first pared down without inciting bleeding. Then, the lesions are treated until a dusky gray color is seen. However, rather high fluences are used, making this treatment quite painful, especially on the fingers. Depending upon the pain tolerance of the patient, digital nerve blocks may be needed. This procedure is repeated every 2 weeks until clinical resolution.

Clearance rates vary from 20% to 95%, and this range has been attributed to the variability (between studies) in the number and frequency of treatments as well as applied fluences. Despite these data, absolute benefit of the PDL over "conventional therapy" (consisting of cryotherapy and cantharidin) was not established in a prospective randomized trial. In fact, the two arms of the trial were similar in the percentage of patients with complete verruca clearance and the number of treatments needed for complete responses[33]. While laser therapy for verrucae is not exclusively beneficial, it does supplement the dermatologist's armamentarium in the treatment of these recalcitrant lesions.

Pyogenic Granulomas

Pyogenic granulomas (PG) are idiopathic, abruptly presenting, vascular neoplasms that tend to grow rapidly and bleed easily. Over 50% of these lesions recur after electrocoagulation, presumably because such desiccative treatments fail to ablate the deeper vascular components[35]. Both the argon and CO_2 lasers have been used to treat these neoplasms. More specific targeting of the vascular nature of PG has been attempted with the PDL, whether used directly on the lesion or in combination with glass slide diascopy to blanch out superficial components. Greater success may be achieved with antecedent removal of the papular component (by shave or electrodesiccation techniques) prior to PDL of the more deeply situated vessels. While shave removal followed by desiccation is still the first-line treatment for most patients, less scarring is noted with the PDL, when used either with modest fluences (1.5 ms pulses) *without cooling* or multiple stacked pulses (5–10 ms) *with cooling*.

Venous Lakes

Venous lakes are commonly seen on the lips or ears as gray–blue to purple compressible papulonodules and represent dilated venules in the superficial dermis. While innocent biologically, these lesions are brought to the attention of dermatologists because of cosmetic concerns or a history of periodic bleeding. Traditionally, electrocoagulation has been used, but scarring and recurrence are common sequelae. IPL, the argon laser, PDL, Nd:YAG laser and infrared coagulator have all been used successfully. It is likely that the alexandrite laser would also be effective.

Pain Considerations

PDL treatment can be associated with significant discomfort and has been typically described as a "hot rubber band" snapping on the skin. Whereas this procedure is generally well tolerated by adults, children typically require topical anesthesia for localized lesions. More diffuse vascular processes in children may require local or general anesthesia. KTP laser therapy is associated with fleeting stinging on the skin as the laser is applied onto the skin. IPL treatments can be performed with or without topical anesthesia. Forced cold air or ice chilling is an effective method for reducing discomfort and protecting the epidermis at the same time. Vibration distraction (gate theory) can also be effective. Nerve blocks are simple and effective for digital procedures.

TREATMENT OF TATTOOS

A tattoo is the deposition of an exogenous pigmented material into the skin. Although the most common purpose for tattooing is artistic and cosmetic, it has also been utilized in the medical field, in particular as radiation port markers. Additionally, tattoo pigment composed of lead, asphalt, gunpowder or coal can be induced explosively or traumatically. Once embedded, the exogenous pigment is taken up into lysosomes within dermal fibroblasts, macrophages and mast cells. These pigment granules measure 2–400 nm, but generally average about 40 nm in diameter. Regardless of the inciting cause or initial motivation, removal of such pigment is a common patient demand. Prior to advancements in laser technology, the removal of tattoos was frequently associated with disfiguring scarring. Methods utilized were excision, dermabrasion, salabrasion, laser ablation and electrodesiccation. With the evolution of the Q-switched laser, pigment eradication can be more safely achieved, with less scarring and/or pigmentary changes.

Q-switched lasers are characterized by having extremely short, nanosecond pulses of energy. The latter induce photomechanical and photoacoustic laser–tissue interactions. The exceptionally short pulse duration limits the thermal damage to just the lysosome. The rapid pulse induces an exponential increase in temperature to 200–300°C within nanoseconds, causing dramatic expansion within the organelle, followed by an equally catastrophic contraction/collapse of the same compartment, leading to *cavitation* of the lysosome. Clinically, the laser tissue reaction is seen as immediate epidermal whitening, which is essentially water vapor within the epidermis (Fig. 137.8). Mechanical damage results in cell membrane rupture and the release of exogenous

Fig. 137.8 Immediate tissue whitening following treatment of a tattoo with the Q-switched alexandrite laser. *Courtesy, Roy Grekin, MD.*

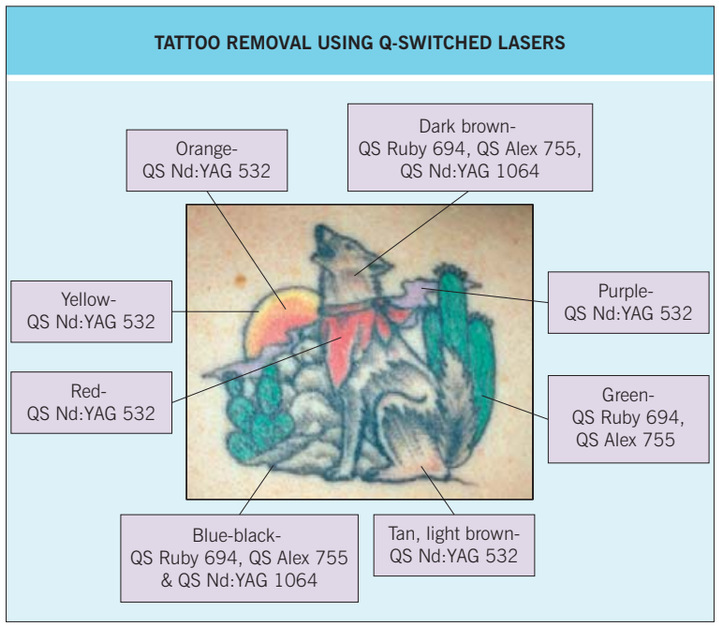


Fig. 137.9 Tattoo removal using Q-switched lasers. The Q-switched (QS) Nd:YAG (532 nm) laser can be used to try to remove red, orange, yellow, purple and tan/light brown pigments. The QS alexandrite (Alex; 755 nm) and QS ruby (694 nm) lasers can be employed to remove green tattoo ink, while the QS Alex, QS ruby and QS Nd:YAG (1064 nm) lasers can remove blue–black and dark brown tattoo ink. See Table 137.2 for details. *Courtesy, Jean L Bolognia, MD.*

pigment into the extracellular space. The pigment is then removed predominantly via lymphatic drainage, or it is simply re-phagocytosed.

Selection of the appropriate Q-switched laser is determined by the colors of tattoo pigment to be targeted (Fig. 137.9). Based on "complementary matching" of tattoo pigment, green tattoo pigment is most effectively removed by a red laser (694 nm), and red tattoo pigment is best removed with a green laser (532 nm). Blue and black pigments are removed with all three Q-switched lasers – ruby, alexandrite and Nd:YAG. More difficult to remove are yellow and orange pigments, as these are not well absorbed by currently commercially available laser light.

Although the advancements in laser technology and the refinement of Q-switched lasers have made pigment removal more safe and effective than before, absolute eradication of the pigment can be quite difficult (Table 137.2). Whether the tattoo was placed by an amateur or a professional tattoo artist is an important factor in how completely the tattoo can be removed. Amateur tattoos often incorporate blue–black pigments that are carbon-based, such as India ink. Given that these tattoos have only a few colors, and coupled with the observation that they may be placed more superficially in the skin, amateur tattoos are relatively easy to remove. Professional tattoo artists incorporate a wider spectrum of colors and deposit the pigments within the deep papillary and superficial reticular dermis. Hence, removal of these more complex professional tattoos can be problematic, even with the best devices.

Complications of tattoo removal include both hyper- and hypopigmentation. While hypopigmentation is observed with the ruby and alexandrite lasers, hyperpigmentation is common in more darkly pigmented patients. It has often been said that the Q-switched lasers removed tattoo pigment without scarring. While this is often true, there can be significant textural changes after multiple treatments with high-fluence devices. Additionally, inflammatory reactions to tattoo ink have been reported, including eczematous, granulomatous and lichenoid reactions. When systemic reactions occur after laser treatment, they are the consequence of mobilized antigens.

Paradoxical darkening of skin-colored tattoo ink is a common phenomenon following treatment with any of the Q-switched lasers. This unfortunate event happens immediately after a single laser pulse and is caused by a shift from an oxidized state to a reduced state in the tattoo pigment. This was classically reported as darkening of red "lip liner" to dark brown or black pigment as the ferric oxide tattoo was reduced to ferrous oxide (Fig. 137.10). Similar color changes can be seen in tattoos with titanium dioxide, a common agent used to lighten tattoo pigments; when a Q-switched laser is applied to titanium, it can change from white to blue–black. Although this problematic side effect can be improved via continued treatment with any of the Q-switched lasers, a test spot is wise with such tattoos, particularly on the face.

Fig. 137.10 Paradoxical tattoo darkening reaction following Q-switched laser removal of pink tattoo at the lip margin.

TREATMENT OF MELANIN-CONTAINING LESIONS

Ephelides and Lentigines

Since melanin has a broad absorption spectrum (see Fig. 136.3), many lasers can be used to treat melanin-containing lesions. At the lower end of the therapeutic window, the penetration of green lasers is limited to

TATTOO PIGMENTS, LASERS USED FOR THEIR REMOVAL, AND POTENTIAL COMPLICATIONS			
Color/ etiology	**Pigment**	**Lasers**	**Complications**
Traumatic	Lead, dirt, gunpowder, other	QS ruby, QS alexandrite, QS Nd:YAG (1064)	Hypopigmentation, micro-explosions (gunpowder)
Amateur black	India ink, carbon	QS ruby, QS alexandrite, QS Nd:YAG (1064)	Hypopigmentation
Professional black	Carbon, iron oxide, logwood extract	QS ruby, QS alexandrite, QS Nd:YAG (1064)	Hypopigmentation
Blue	Cobalt aluminate (azure blue)	QS ruby, QS alexandrite, QS Nd:YAG (1064)	Hypopigmentation
Green	Chromium oxide (casalis green), hydrated chromium sesquioxide (guignet green), malachite green, lead chromate, ferro-ferric cyanide, curcumin green, phthalocyanine dyes (copper salts with yellow coal tar dyes)	QS ruby, QS alexandrite	Hypopigmentation, allergic reactions (chromium)
Red	Mercury sulfide (cinnabar), cadmium selenide (cadmium red), sienna (red ochre; ferric hydrate and ferric sulfate), azo dyes	QS Nd:YAG (532)	Hypopigmentation, tattoo ink darkening, allergic reactions (mercury sulfide, cadmium, azo dyes)
Yellow	Cadmium sulfide (cadmium yellow), ochre, curcumin yellow	QS Nd:YAG (532)	Hypopigmentation, tattoo ink darkening, allergic reactions (cadmium)
Brown	Ochre	Tan/light brown: QS Nd:YAG (532) Dark brown: QS ruby, QS alexandrite, QS Nd:YAG (1064)	Hypopigmentation, tattoo ink darkening
Violet	Manganese violet	QS Nd:YAG (532)	Hypopigmentation, tattoo ink darkening
White	Titanium dioxide, zinc oxide	QS Nd:YAG (532)	Hypopigmentation, tattoo ink darkening
Skin colored	Iron oxides	QS Nd:YAG (532)	Hypopigmentation, tattoo ink darkening

Table 137.2 Tattoo pigments, lasers used for their removal, and potential complications. Hyperpigmentation and textural changes also occasionally occur as complications. Hypo- and hyperpigmentation are more common in individuals with darkly pigmented skin, and they are best treated with the Q-switched (QS) Nd:YAG (1064) laser to reduce this risk.

the superficial papillary dermis. These lasers are best utilized for epidermal pigmented lesions. Thus, the frequency-doubled Nd:YAG (532 nm), either Q-switched or normal mode, effectively treats lentigines and ephelides in most skin types with limited recurrence[36]. Additional lasers, e.g. the 800 nm diode, as well as IPL can also be used to treat epidermal pigmented lesions (Table 137.3). While the PDL is most commonly used for vascular lesions, 595 nm light is also well absorbed by melanin and can be used to treat pigmented lesions. By incorporating compression, the vascular component of the skin is blanched out and melanin-containing lesions can be targeted. Newer PDL systems have incorporated such a "compression handpiece".

In general, the Q-switched ruby and alexandrite lasers are more effective for treatment of more deeply situated pigmented lesions (e.g. nevus of Ota), as these wavelengths have an increased depth of penetration. Q-switched ruby (694 nm) laser light is better absorbed by melanin than is alexandrite (755 nm) laser light, which might be an advantage in lighter-skinned individuals, but problematic in darker-skinned patients, given the increased likelihood of nonspecific heating of normal epidermal melanin. Nd:YAG laser light is much less well absorbed by melanin, but reaches deeply into the skin; therefore, it is primarily used to treat dermal pigmented lesions. For the treatment of lentigines, ephelides, and café-au-lait macules as well as nevus of Ota, understanding these profiles allows one to choose the optimal device. The clinical response of pigmented lesions to Q-switched lasers is determined by where the pigment is localized (epidermal, dermal or mixed), whether it is intracellular or extracellular, and what the pigment is composed of (usually melanin)[37].

Benign Melanocytic Nevi

Laser removal of acquired and congenital nevi is controversial since no specimen is submitted for tissue diagnosis and margin assessment. Furthermore, the future biologic behavior of laser-resistant cells and the effect (if any) of laser thermal injury on these cells is unknown. Since the clinical standard of care is excision for any atypical pigmented lesion, laser treatment of melanocytic lesions should only be considered for clinically banal lesions in patients with no personal or family history of melanoma.

Both acquired and congenital melanocytic nevi have been treated with Q-switched ruby, alexandrite and Nd:YAG lasers[38]. The 694 and 755 nm devices can improve the appearance of acquired junctional melanocytic nevi without scarring[39]. In general, smaller and thinner lesions are typically more treatment-sensitive. While congenital lesions can be lightened, complete eradication is much more difficult and recurrence is common. Laser therapy decreases the number of the pigmented nevomelanocytic cells in the papillary dermis, but is unlikely to treat deeper seated non-pigmented cells that are closely associated with adnexal structures. This has been demonstrated histologically as persistent nevomelanocytic nests in the mid papillary and deeper dermis at depths of 0.16–0.44 mm. Deeper components of these nevi located in muscle or under fascia will remain unaffected by laser surgery.

The normal mode (non-Q-switched) long-pulsed ruby and alexandrite lasers have also been used to treat acquired nevi. Some of the clinical lightening observed has been attributed to fibroplasia of the dermis overlying the residual nevomelanocytes. Although fibroplasia may be cosmetically useful, this change potentially hides early signs of malignant transformation and might cause a delay in diagnosis. Therefore, patients who have any melanocytic nevi treated with lasers should understand that they need to report subsequent changes in color, shape or size. As long-pulse lasers deposit a lot of energy into the tissue, the potential for nonspecific thermal injury increases, with an associated increased risk of scarring. Lastly, the clinician must remember that early cutaneous melanoma can have a subtle clinical appearance.

Café-au-Lait Macules and Nevus Spilus

Café-au-lait macules (CALM) are tan–brown patches which histologically correspond to hypermelanosis of the basal melanocytes and

LASERS AND OTHER LIGHT-BASED DEVICES USED FOR THE TREATMENT OF PIGMENTED LESIONS				
Laser/device	**Wavelength (nm)**	**Fluence (J/cm²)**	**Pulse duration**	**Applications**
Q-SWITCHED LASERS (HIGHLY PIGMENT-SPECIFIC)				
Q-switched Nd:YAG, frequency-doubled	532	0.4–6	5–10 ns	Lentigines
Q-switched ruby	694	3–12	20–40 ns	Lentigines, nevi*
Q-switched alexandrite	755	1–12	50–100 ns	Lentigines, nevi*
Q-switched Nd:YAG	1064	3–12	5–10 ns	Nevi*
IPL, LONG-PULSED LASERS AND PDL WITH COMPRESSION (LESS PIGMENT-SPECIFIC)				
Intense pulsed light (IPL)	500–1200	Up to 30	5–10 ms	Lentigines, nevi*
Long-pulsed ruby†	694	5–30	Up to 4 ms	Nevi*
Diode	800	5–50	5–100 ms	Lentigines, nevi*
Nd:YAG	1064	Up to 300	1–100 ms	Nevi*
PDL with compression	595	3–5	0.45–1.5 ms	Lentigines
Long-pulsed alexandrite	755	25–50	0.5–300 ms	Lentigines, nevi*

*Treatment of pigmented melanocytic nevi (especially acquired lesions) is controversial.
†No longer being manufactured.

Table 137.3 Lasers and other light-based devices used for the treatment of pigmented lesions. Q-switched lasers are most effective for treating pigmented lesions due to their very short pulse durations, which effectively target the melanosome. In addition to the lasers listed above, pigment non-selective ablative lasers, such as CO_2 (10 600 nm) and erbium:YAG (Er:YAG; 2940 nm), can remove superficial pigmented lesions via nonspecific destruction. Parameters are dependent upon skin phototype, skin cooling technology and morphologic features; a test site is recommended.

keratinocytes. While these lesions can be seen in genodermatoses such as neurofibromatosis and McCune-Albright syndrome (see Chs 61 & 112), they are typically isolated benign lesions. Cosmetic improvement can be achieved with the Q-switched ruby, alexandrite and KTP lasers[40]. However, CALM can be resistant to laser therapy, and they are prone to a high rate of recurrence. Use of the long-pulsed alexandrite laser for the treatment of CALM has been reported to have a lower incidence of recurrence[41].

Nevus spilus consists of multiple melanocytic nevi superimposed on a background CALM. Although the treatment of these lesions is very similar to that of CALM, these are typically more resistant and require multiple sessions. They may respond to normal-mode laser wavelengths or IPL. Rarely, malignant transformation has been described in nevus spilus, and thus cautious laser or light therapy is advised[42].

Nevus of Ota and Nevus of Ito

Clinically, nevus of Ota and nevus of Ito are seen as gray–blue patches which correspond histologically to spindled pigment-producing melanocytes in the papillary dermis. These entities differ only in their anatomic location. Nevus of Ota involves the face (primarily V1/V2 distribution), while nevus of Ito corresponds to the distribution of the posterior supraclavicular and lateral brachial nerves. Both have been successfully treated with Q-switched ruby, alexandrite and Nd:YAG lasers[43]. Generally, high fluences are required, with multiple treatments spaced at least 6 weeks apart. A drawback of the Q-switched ruby laser is the tendency for hypopigmentation, which is a consequence of increased absorption by normal epidermal melanin. Hypopigmentation is observed less often with Q-switched alexandrite lasers (755 nm), which also achieve deeper penetration into the dermis[44].

Near-infrared lasers, namely the Q-switched Nd:YAG (1064 nm), have even deeper penetration into the skin but are less well absorbed by melanin. Although these characteristics appear to negate each other, they allow for safer use in patients with darker skin and also allow for clearance of more deeply seated pigment.

Blue nevi share some histologic features with nevi of Ota and Ito but are well-circumscribed gray-blue to blue-black papules (common) and plaques (cellular). As such, laser treatment of these lesions is similar to that of nevi of Ota and Ito[45]. While blue nevi are clinically benign, rare malignant transformation has been reported in cellular blue nevi.

Melasma

Melasma is a complex and therapeutically challenging disorder with both intrinsic (e.g. genetic, hormonal) and extrinsic (e.g. ultraviolet light) factors (see Ch. 67). It most commonly involves the face and presents as tan to dark brown patches with sparing of photoprotected sites. The majority of those affected are women and hormonal stimuli, including pregnancy and oral contraceptive use, tend to aggravate the condition. Medical and procedural therapeutic strategies include topical retinoids, hydroquinone, chemical peels and laser therapy. While treatment regimens boast varying degrees of improvement, recurrence is the norm despite precautionary measures such as strict sun protection.

Clinically, melasma is often categorized by distribution pattern and location of excess melanin. In epidermal melasma, melanin is localized to the basal and suprabasal epidermal layers, and in dermal melasma melanin is deposited within melanophages. The mixed variant includes features of both epidermal and dermal types. These subtypes are said to be distinguishable by Wood's lamp illumination, which accentuates epidermal pigmentation, but histologic and confocal microscopy studies have shown an admixture of both types within a single lesion. Of note, dermal deposits of melanin respond poorly to commonly prescribed topical therapeutic agents.

Since melasma is a disorder of hyperpigmentation due to increased melanin within epidermal melanocytes and dermal melanophages, it may seem intuitive that melasma should respond favorably to Q-switched lasers. However, this assumption has been demonstrated to be less than accurate. Although the melanophages present in dermal melasma can be selectively damaged by Q-switched lasers, the subsequent epidermal response frequently induces an inflammatory process and perpetuates or aggravates the problem[46]. Attempts at improving melasma by superficial laser resurfacing with Er:YAG may lead to temporary improvement, only to be followed by problematic postinflammatory hyperpigmentation[47].

Non-ablative, fractionated laser systems (see below) were initially touted to be a breakthrough therapy for melasma, with predictable and reproducible improvements. A preliminary case report described significant clinical improvement of treatment-resistant facial melasma after two treatments[48], with a subsequent study demonstrating that 60% of patients with skin phototypes III–V achieved 75–100% improvement[49]. The clinical improvements seemed to be paired with appropriate histologic findings of melanin extrusion in the dermal and epidermal necrotic debris[50]. Although the precise explanation for how the photothermal energy improves melasma is not clear, the clinical improvements may be the direct consequence of increased hydroquinone absorption into the epidermis and dermis (to affect dermal melanophages) via the microscopic tunnels. Despite this novel application of these fractionated lasers, melasma tends to recur and well-established regimens of topical retinoids, bleaching agents, and diligent sun protection remain the mainstay of therapy.

Becker's Nevus (Melanosis)

Becker's nevi are hamartomas that typically present during childhood or early adolescence as light to dark-brown patches or plaques on the shoulder, upper back or lateral arm (see Ch. 112). They are associated with variable amounts of hypertrichosis as well as smooth muscle hamartomas. Because melanin is located in both the epidermis and the dermal follicular matrix, treatment of Becker's nevus may require targeting of both these components. The basal layer melanin component requires nanosecond range pulse durations, and successful lightening has been accomplished with Q-switched ruby and alexandrite lasers[51]. In contrast, the follicular melanin responds more favorably to the millisecond pulse durations that characterize photoepilation systems. While these simplistic distinctions allow for methodical treatment, Becker's nevi are typically somewhat resistant to therapy. Often,

cosmetic improvement is more reasonably and realistically approached with the objective of photoepilation alone, as opposed to comprehensive eradication of the hamartoma

Postinflammatory or Drug-Induced Hyperpigmentation and Post-Sclerotherapy Discoloration

Postinflammatory hyperpigmentation (PIH) is a common side effect of many dermatologic procedures, both medical or cosmetic. For patients with darker skin phototypes, PIH should be anticipated and a treatment plan promptly initiated. Common topical therapies include corticosteroids, retinoids and bleaching creams. A newer treatment strategy is the use of fractionated photothermolysis with a low density and low energy. The fine, deep columns (referred to as microthermal or microablative zones; see below) serve as a drug delivery system and increase the penetration of these topical agents into the skin. For treatment-resistant patients, Q-switched ruby, alexandrite and Nd:YAG lasers have been used to expedite resolution of PIH. However, since PIH can be caused by these devices, circumspection is appropriate.

As opposed to PIH, which is due to excess melanin, discoloration that results from sclerotherapy is a consequence of vessel destruction, erythrocyte extravasation, and interstitial hemosiderin deposition. The Q-switched ruby laser has been used successfully to treat this common sequela from sclerotherapy, with a reported 92% improvement rate[52], but the success rate is quite variable.

Drug-induced hyperpigmentation or discoloration represents deposition of drug metabolites, hemosiderin, melanin, or a combination of these components in the dermis and/or epidermis (see Ch. 67). The resultant color depends on the initiating medication and can range from blue-gray or brown to yellow or red. Use of Q-switched ruby, alexandrite, and 1064 nm Nd:YAG lasers has led to improvement of minocycline-, amiodarone-, and imipramine-induced hyperpigmentation or discoloration[39].

TREATMENT OF STRIAE DISTENSAE

Striae distensae are common after pregnancy, growth spurts in adolescence, or rapid weight gain. Histologically, there is thinning of the epidermis and atrophy of the dermis. In their early inflammatory stages, they appear pink to purple in color and are called striae rubra. The latter mature and take on a more pallid color and then are termed striae alba (see Ch. 99).

Although treatment of striae is not medically necessary, many patients seek cosmetic improvement. PDL, pulsed CO_2, 308 nm excimer, and non-ablative 1450 nm lasers as well as IPL have been used with varying degrees of success with regard to the color and texture of striae[53–56]. More targeted studies have correlated clinical improvement with increased elastin remodeling or formation. Specifically, low-fluence 585 nm PDL (3 J/cm^2) has been demonstrated to dramatically stimulate elastin production[57]. Recently, fractionated photothermolysis was shown to improve atrophic scars[58]. Specifically, a pilot study of striae in patients with skin phototypes IV–VI demonstrated epidermal thickening and remodeling of collagen and elastin fibers after 1550 nm fractionated photothermolysis[59]. In spite of these reports, in clinical practice, the results of striae treatment with lasers have been quite disappointing.

ABLATIVE LASERS: CARBON DIOXIDE AND Er:YAG

Both the CO_2 and Er:YAG lasers have wavelengths in the infrared portion of the electromagnetic spectrum (see Fig. 137.1), and thus the chromophore is predominantly water. Selective photothermolysis of the epidermis and dermis is accomplished as nearly 80% of the skin is composed of water.

For CO_2 lasers, the depth of tissue ablation is very superficial, in the range of 20 microns. Based upon the heat vaporization of water and the energy absorbed per volumetric unit, the minimum fluence necessary to produce tissue ablation has been calculated to be 5 J/cm^2. Below this fluence, tissue is not vaporized, rather it is coagulated. However, both vaporization and coagulation are useful in the treatment of skin disease, and these wavelengths can be manipulated so as to achieve an appropriate balance of the two. When using the short-pulse or scan-type resurfacing CO_2 lasers, the coagulative or photothermal effect extends the depth of injury to 100–150 microns.[60], and this is responsible for the hemostasis, collagen rejuvenation, skin tightening, and, by extension, many of the complications such as scarring, seen with CO_2 lasers[61].

To achieve selective photothermolysis with the CO_2 laser, it has been suggested that the ideal pulse duration is ≤1 ms. The development of high-powered, short-pulsed CO_2 lasers (as compared to their continuous wave predecessors) has allowed for more selective control of tissue vaporization and thermal injury. The first pass of the high-energy, short-pulsed CO_2 laser induces localized tissue vaporization with surrounding coagulation/desiccation. Since this residual carbonized tissue acts as a heat sink, subsequent CO_2 laser pulses tend to vaporize less and heat more, causing non-selective damage. Thus, second and subsequent passes should only be applied after removal of the desiccated "charred" material at the surface of the skin[61].

The Er:YAG laser emits light at 2940 nm, with the water affinity being nearly 15 times greater than that of the CO_2 laser. This allows the Er:YAG laser to vaporize tissue more efficiently, leaving only a small residue of coagulated tissue. As a consequence of the limited photothermal effects, hemostasis and collagen contraction are significantly reduced with Er:YAG lasers. Coagulation settings, achieved by lengthening the laser pulse duration, have been incorporated into newer modulated Er:YAG laser systems (e.g. Sciton), inducing more hemostasis and resulting in better tissue contraction. While pure Er:YAG lasers demonstrated only modest tissue tightening as compared to CO_2 lasers, modulated Er:YAG systems have produced comparable resurfacing results, e.g. with settings on the Sciton laser of 50% overlap, 25–100 microns of ablation (depending on the regional thickness of the treated skin) and 50–100 microns of coagulation[62].

Use of the Er:YAG laser requires more skill and technical finesse than does use of the CO_2 laser as the clinical endpoints allowing the laser surgeon to gauge depth when resurfacing with the CO_2 laser are not seen with Er:YAG laser ablation. With the CO_2 laser, a chamois color is seen with ablation of the papillary dermis and further penetration into the reticular dermis produces a "water-logged cotton thread" appearance. These typical visual markers are lacking with Er:YAG laser resurfacing. Furthermore, the plateau response of diminishing ablation characteristic of the CO_2 laser is not seen with the Er:YAG[61]. There is significant energy absorption of 2940 nm light by residual desiccated tissue and the less skilled laser surgeon can unintentionally drill deep wounds into the skin. Therefore, it is critical that the operator constantly be aware of the depth of vaporization. Additionally, in contrast to the CO_2 laser, the desiccated tissue need not be wiped off. This barrier allows for faster healing and decreased risk of postoperative pigmentary changes.

The CO_2 laser remains the gold standard for photorejuvenation, wrinkle reduction and skin tightening. To date, nothing can beat the results obtained by an experienced laser surgeon using one of the high-energy short-pulsed CO_2 lasers. Specifically, even deep, coarse and fixed perioral and periorbital rhytides can be significantly diminished or eliminated (Fig. 137.11)[63]. Redundant skin is tightened by thermal coagulation as well as wound healing with associated fibroplasia, which can cause collagen contraction. However, this dramatic improvement comes at the expense of slow healing, prolonged erythema, permanent and patchy loss of pigmentation, and other complications. A split-face study of Er:YAG and CO_2 laser resurfacing demonstrated this duality; the side treated with the CO_2 laser had 63% improvement with 7.7 days of crusting, compared to the Er:YAG laser-treated side which had 48% improvement with an average of 3.4 days of crusting[64].

In general, more significant clinical improvement has gone hand in hand with more thermal damage, leading to more discomfort, more extensive wound care, and longer healing times. Additional side effects include persistent erythema for 3+ months, risk of scarring, a 20% chance of delayed-onset permanent hypopigmentation, and a line of demarcation between treated and untreated areas. All patients with actinic bronzing will note an improvement or lightening of their skin pigmentation in the treated areas. To avoid any demarcation lines in these regions, it is prudent to treat entire anatomic areas. This is particularly true for skin phototypes I and II. Skin phototypes IV–VI tend

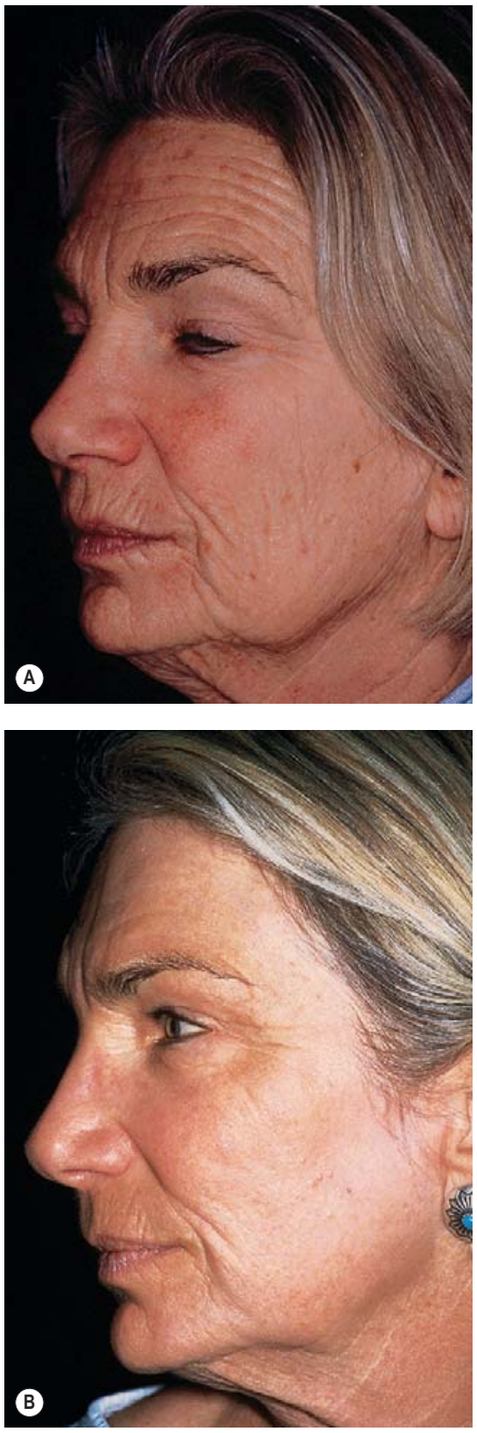


Fig. 137.11 Ablative CO_2 laser resurfacing. **A** Before treatment. **B** One year after resurfacing. *Courtesy, Jeffrey Dover, MD, and Kenneth Arndt, MD*

not to have actinic bronzing and hence focal or geographic areas can be treated.

Treatment of acne scarring is a common indication for ablative lasers. In general, more improvement of acne scarring is seen after CO_2 laser resurfacing than with the traditional Er:YAG laser. However, the dual mode or "hot" Er:YAG laser is equivalent to the CO_2 laser in many respects, and is preferred by many laser surgeons. Elevated or distensible acne scars are most amenable to resurfacing, compared to ice-pick and non-distensible scars, which are often resistant[65]. Focal ablation has been effectively used for resurfacing elevated, irregular epidermal lesions such as seborrheic keratoses, epidermal nevi, and verrucae; actinic keratoses and actinic cheilitis can also be significantly improved[66]. Additionally, benign hyperplasias or neoplasms with an elevated component can be "debulked", e.g. hypertrophic scars, rhinophyma, lymphangioma, adnexal tumors (including syringomas and angiofibromas), and xanthomas. Based upon more limited experience and case reports, effective treatment of balanitis xerotica obliterans, lichen sclerosus, porokeratosis, keratoderma, chondrodermatitis nodularis helicis, and Hailey–Hailey disease has been observed. Other possible indications for both the CO_2 and Er:YAG lasers include treatment of hidroadenomas, colloid milia, eruptive hair cysts, and onychodystrophy[61].

Among the most significant risks with ablative resurfacing is infection, whether by bacteria, viruses or fungi. Specifically, and especially if the treated region involves perioral skin or adjacent areas, antiviral medications (e.g. valacyclovir, famciclovir) should be initiated prophylactically (even in the absence of prior herpetic infection) to prevent the possibility of a generalized herpetic infection in the denuded skin. Antibiotic coverage, especially against staphylococci, may be prudent but is much debated. Desiccated, proteinaceous skin debris that results from resurfacing is a favorable culture medium for pathogens. Antiviral prophylaxis should be commenced the day prior to or at least the morning of the procedure and continued for 15 days. Antifungal prophylaxis with fluconazole (a single-dose 200 mg tablet) given during the early postoperative period has been demonstrated to prevent candidal infection, and may promote re-epithelialization[67].

FRACTIONATED LASERS

Traditional laser resurfacing yielded impressive facial photorejuvenation and significant tissue tightening. However, these outcomes were often at the cost of delayed healing, persistent redness and swelling, infection, unpredictable pigmentary changes (hypo- or hyperpigmentation) and scarring. In 2004, fractionated photothermolysis (FP) was introduced (Table 137.4) The development of fractionated lasers has changed the way laser surgeons practice. One can be aggressive in terms of depth and density, and yet relatively safe in terms of patient downtime, postoperative recovery, and complications. In contrast to traditional lasers where the spot size of the device defined the smallest treatment unit on the skin, hundreds of controlled microscopic zones of coagulative or ablative injury are delivered to the skin with each scan or stamp of the fractional device[68]. These areas of microscopic thermal injury are defined as microscopic treatment zones (MTZs; also referred to as microthermal zones). While MTZs appear to be minute dots on the skin, they actually represent exact columns or cylinders of epidermal and dermal thermal damage (see Fig. 136.6)[50]. MTZs are deliberate and calibrated such that the resultant depth, width and density are defined. Each microdot or cylinder of damage is surrounded by normal, unaffected skin, which acts as a reservoir for healing and enables these microwounds to resolve quickly, with minimal discomfort (Fig. 137.12). These healing wounds appear histologically as microscopic epidermal necrotic debris (MENDs); they are composed of fragmented and damaged skin components, including epidermis, dermis, melanin and elastin[69]. The skin surface heals within 7 days with extrusion of the MENDs.

Non-ablative Fractional Photothermolysis

The first system to be approved for clinical use was the Fraxel® SR750 (Reliant Technologies), which is a 1550 nm erbium-doped fiber fractionated laser that targets water as its chromophore. The laser handpiece employs a scanning system (Intelligent Optical Tracking System [IOTS]), allowing for uniform deposition of MTZs. The second-generation system (Fraxel re:store®) allows for adjustment of the MTZ energies up to 70 mJ with a depth of injury down to 1500 microns and treatment densities of 5–50%. The depth of these MTZs is an operator-dependent parameter and can be adjusted to match the thickness of skin or entity being treated.

Collagen remodeling is induced with this fractionated heating of the skin. The very nature of FP allows for the safe application of incredibly high fluences to narrow tissue columns, which if applied to confluent areas would certainly cause delayed healing and tissue scarring.

As the technology of fractionated systems is enhanced, a unique "telescoping mechanism" has been developed such that minor changes in beam diameter make a major impact on epidermal injury and depth of thermally altered tissue. More specifically, this device provides wider beam diameters the higher the energy. There is a "sweet spot" in terms of beam diameter at which epidermal disruption is minimized and

TYPES OF FRACTIONATED LASER DEVICES				
Laser type	**Wavelength (nm)**	**Laser name™,® (examples)**	**Energy of MTZ or macrofluence**	**MTZ depth (microns)**
		ABLATIVE		
Rolling scanner				
CO_2	10 600	Fraxel re:pair	5–70 mJ/MTZ	200–1500
Stamping scanner				
CO_2	10 600	Deep FX	2.5–50 mJ/MTZ	50–1500
YSGG	2790	Pearl Fractional	60–320 mJ/MTZ	1000
Er:YAG	2940	Lux 2940	<15 mJ/MTZ	50–300
Er:YAG	2940	Pixel	14–27 mJ/MTZ	30–70
Er:YAG	2940	Pro-Fractional	<400 J/cm^2	1000
		NON-ABLATIVE		
Rolling scanner				
Erbium fiber	1550	Fraxel re:store	4–70 mJ/MTZ	500–1400
Erbium/thulium fiber	1550/1927	Fraxel Dual	4–70 mJ/MTZ	500–1400/200
Erbium fiber	1410	Fraxel re:fine	5–20 mJ/MTZ	650
Stamping scanner				
Diode/bipolar RF	915 and bipolar RF	Matrix IR	<70 J/cm^2	500
Nd:YAG	1440 ± 1320	Affirm	8–12 mJ/MTZ	200–300
Er:Glass	1540	Fractional 1540	15–50 mJ/MTZ	125–850
Er:Glass	1540	Mosaic	5–40 mJ/MTZ	1000
Er:Glass	1540	Matisse	<250 J/cm^2	30–150

Table 137.4 Types of fractionated laser devices. CO_2, carbon dioxide; Er, erbium; Er:YAG, erbium-doped yttrium-aluminum-garnet; J, joule; mJ, millijoule; MTZ, microthermal zone or microscopic treatment zone; Nd, neodymium; RF, radiofrequency; YSGG, yttrium-scandium-gallium-garnet.

depth of dermal coagulation is maximized. Many laser companies are now producing fractionated non-ablative devices (see Table 137.4), and the prospective buyer should take the time to review in detail the various options, including power, speed, reliability and science in addition to the cost of the device and its consumables.

New indications and applications for this novel technology are evolving rapidly and include patients with chronic photodamage, skin laxity, rhytides, and multiple types of scarring, including acne scars, hypopigmented scars, and traumatic and surgical scars (Fig. 137.13). One of the first clinical applications of FP was treatment of facial melasma. While initial studies were promising with near-complete clearance of melasma after a few treatments, this early exuberance has been tempered by a more considered and lengthy assessment of response, with the tendency of melasma to recur.

Ablative Fractional Photothermolysis

Following the success of fractionated *non-ablative* rejuvenation came the development of fractionated *ablative* rejuvenation. The first commercially available system was Fraxel re:pair® (Reliant Technologies). This was a scanning fractionated CO_2 laser with the ability to place 2000 microablative MTZs per second. At the present time, no other scanning device can match this rate, though there are other devices that can provide the same clinical outcomes. Indeed, many other companies have produced their own fractionated ablative devices using

Fig. 137.12 Photodamage treated with fractionated ablative CO_2 laser. **A** Preoperative. **B** Characteristic pin-point bleeding from microscopic treatment zones (MTZ; also referred to as microthermal zones) immediately following laser therapy. **C** Improvement of lentigines, solar elastosis and fine static rhytides 3 months postoperatively.

Fig. 137.13 Non-ablative fractionated laser therapy for scar remodeling. **A** Patient at presentation with traumatic hypertrophic and fibrotic scarring. **B** After three treatments with Fraxel re:store®. **C** Marked improvement of scarring after five treatments performed over 6 months.

CO_2, Er:YAG and YSGG (2970 nm) wavelengths (see Table 137.4). For example, the re:pair® system creates MTZs approximately 120–150 microns wide and 200–1500 microns in depth (depending on the operator's selected parameters). The speed of delivery corresponds to the speed at which the operator moves the handpiece over the skin. The fluence of each laser microbeam can be adjusted up to 70 mJ/MTZ by the operator and the density ranges from 10% to 70% of the skin surface. A very equivalent system, the Lumenis DeepFX™ creates a pattern of MTZs 110 microns wide and 50–1500 microns deep (depending on parameters) with a galvanic scanner that creates a square template of MTZs[70]. The operator then advances the scanner onto adjacent untreated skin and repeats the process. This device can create identical tissue effects to the re:pair® system but is significantly slower.

Er:YAG- and YSGG-based fractionated ablative systems can also provide significant improvements in texture, tone, wrinkling and scars. Because of space limitations, a more detailed description of all of these systems is not possible, but references 71 and 72 provide additional information.

The fractional devices, both ablative and non-ablative, have made inroads into the traditional indications for laser resurfacing such as improvement of rhytides, scar revision and acne scarring (Fig. 137.14). Initial studies utilizing re:store® for the treatment of periorbital rhytides showed mild improvement in 12% of patients, noticeable improvement in 30%, and moderate to significant improvement in 54% after one to four treatments[68]. Settings of pulse energy and treatment density should be tailored for the individual patient, for the specific problem being addressed, and considering the anatomic site. However, in general, fractional treatments using a higher treatment density appear to impart greater improvement in texture, tone and dyspigmentation, while increased pulse energies lead to more significant improvements in rhytides and scarring. Collective experience has also shown that fine to moderate rhytides respond more favorably than deeper rhytides, and that less dramatic improvement should be expected compared to fully ablative resurfacing[73].

When used for acne scarring, fractional deep dermal ablation (FDDA™) treatment has demonstrated significant efficacy. In a study of 30 patients with moderate to severe acne scarring who underwent one to three treatments[74], mild to moderate overall improvement was noted with energies ranging from 20 to 100 mJ and densities of 600–1600 MTZ/cm^2. With further experience, it is clear that for a given beam diameter, very high energy (70 mJ) associated with very high density (70%) will be more efficacious than low energy and low density

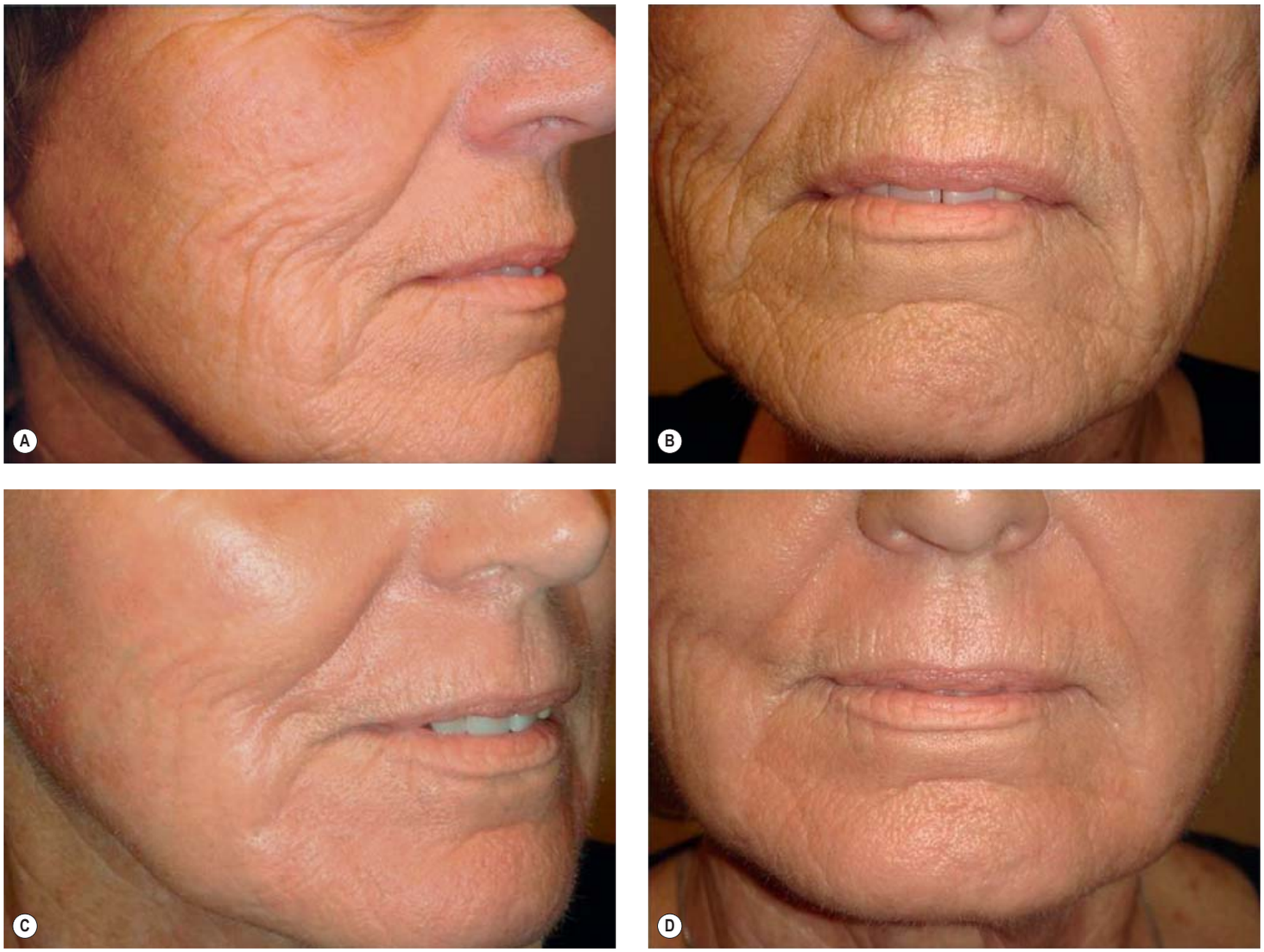


Fig. 137.14 Fractionated CO_2 laser (Fraxel re:pair®). A, B Coarse rhytides and solar elastosis. **C, D** Significant improvement in color, texture, tone and wrinkling following one treatment. Mild residual erythema and edema persist at 1 month.

when treating skin laxity and acne scarring. Although some patients may initially view multiple treatments as inconvenient, the benefits of rapid skin healing (generally within 7 days) and remarkably little discomfort compared to traditional laser resurfacing are distinct advantages (Fig. 137.15). Furthermore, sequential FDDA™ therapy may produce amplified benefit as collagen remodeling and skin contraction are enhanced with subsequent treatments.

Ablative FP offers the opportunity for relatively safe treatment of anatomic regions that were notoriously difficult to rejuvenate with conventional ablative resurfacing. Areas such as the neck and upper chest can now be more easily treated, albeit at reduced energy and density. Another advantage of fractionated systems is the ability to safely treat all skin types, including very darkly pigmented patients.

Evidence that fractionated laser therapies induce neocollagenesis is supported histologically. Increased expression of collagen remodeling markers such as heat shock proteins (47, 70 and 72), collagen III, proliferating cell nuclear antigen, and α-smooth muscle actin have been demonstrated within treatment areas[75,76]. More specifically, expression of heat shock proteins 47 and 72, which is required for collagen remodeling and maturation, has been detected within 1 week of an FP treatment and has persisted for nearly 3 months[76]. In addition to inducing neocollagenesis, ablative fractionated systems induce *volumetric tissue reduction* dermal plumping[76,77]. Taken collectively, the vaporization volume of millions of tiny-diameter cylinders of skin adds up. A standard aggressive fractionated CO_2 laser treatment can remove 5–7 cm^3 from the skin of the face[78]. As such, regular or intermittent treatments will improve skin laxity and could possibly prevent or delay the need for future facelift procedures.

Preoperative Considerations

Prior to any laser procedure (especially ablative), an appropriate medical history should be obtained, including allergies and medications. Physicians should specifically elicit any history of cosmetic procedures. Patients with a history of autoimmune connective tissue disease, diabetes, or drug, alcohol or tobacco abuse should be treated cautiously, as wound healing may be impaired. Those who have used isotretinoin during the past 6 months or those with a history of keloids may be at increased risk for scarring.

During the consultation, the patient and laser surgeon must mutually identify the problem(s) to be treated and establish reasonable expectations for improvement. Whereas one ablative fractionated procedure may achieve marked improvement in rhytides and acne scarring, three to six treatments may be required with a non-ablative system if little "downtime" is required. Potential risks of laser therapy are reviewed, which may include scarring, blistering, infection, hyper- or hypopigmentation, and milia/acne formation. If an ablative fractional laser treatment is planned, then there is a thorough discussion of postoperative wound care (see below).

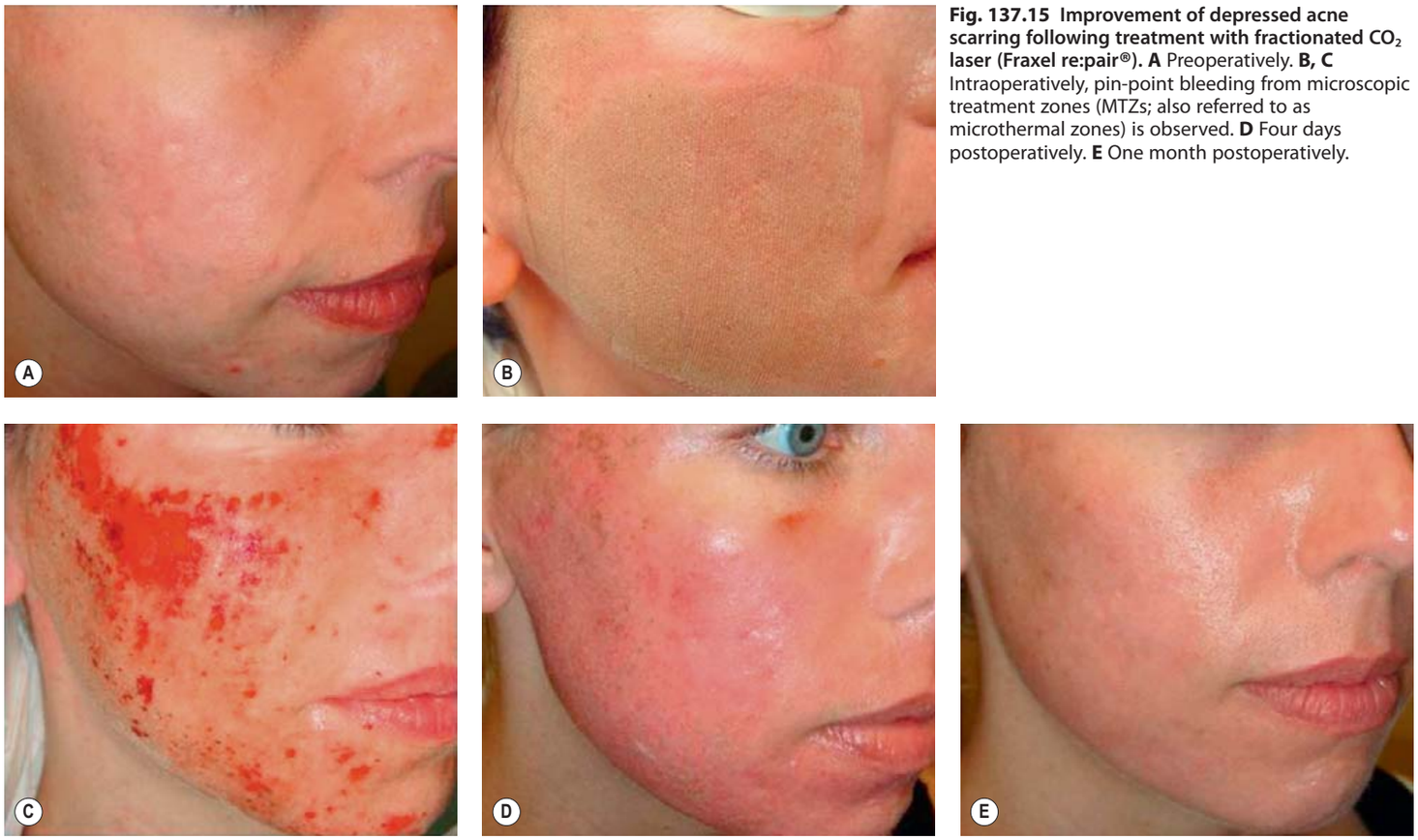


Fig. 137.15 Improvement of depressed acne scarring following treatment with fractionated CO_2 laser (Fraxel re:pair®). A Preoperatively. **B, C** Intraoperatively, pin-point bleeding from microscopic treatment zones (MTZs; also referred to as microthermal zones) is observed. **D** Four days postoperatively. **E** One month postoperatively.

Anesthesia

Both ablative and non-ablative fractional resurfacing can be quite painful without appropriate anesthesia, particularly when using high energies with a high density. Application of topical anesthetics in a lipophilic ointment base or under occlusion for approximately 1 hour after thorough skin cleansing is a simple and effective method for increasing patient comfort. Cooling strategies such as forced cold air or contact cooling can enhance patient tolerance. For more aggressive ablative procedures, supplementary anesthesia with nerve blocks, tumescent anesthesia, systemic narcotics, or anxiolytics is often used.

Post-therapy Considerations, Side Effects and Complications

Following ablative fractional resurfacing, punctate bleeding and serosanguineous drainage are normal side effects (see Figs 137.12 & 137.15), which dry into a thin keratinous crust within 24–48 hours. Patients are encouraged to minimize this crusting and aid in its exfoliation by applying dilute vinegar–water soaks to the treated sites every couple of hours. This is followed by a thin coat of white petrolatum ointment or generous amounts of a bland moisturizing cream until re-epithelization is completed.

Significant edema and erythema of treated skin is observed with both ablative and non-ablative fractionated therapies, though the latter is quite limited[79]. Topical application of a potent corticosteroid (e.g. fluocinonide ointment) immediately following the procedure can reduce these side effects. By using the MTZs as a drug delivery mechanism, very high local cutaneous concentrations of the corticosteroid can be achieved and the risks of systemic corticosteroid administration can be avoided (R Rox Anderson, personal communication, 2009). Non-ablative FP typically requires little or no "downtime" for healing, and the edema and erythema resolve within 24–48 hours. For ablative FP, the erythema dramatically improves within 1 week, but mild erythema and edema can persist for 3–6 weeks (see Fig. 137.15). Most patients are able to return to their normal activities, including work, and to apply makeup around 7 days following ablative FP, depending on the depth and density of treatment. Well-documented side effects of generalized and persistent erythema or delayed hypopigmentation that are seen with traditional resurfacing have not been reported to date with fractionated lasers. The exceptions here are some incidents of angulated erythema and infection related to poor technique leading to bulk heating and slow healing. Additionally, lines of demarcation are easily avoided by feathering the transitional skin between treated and untreated regions with near-minimal fluence and density settings.

Because only minute areas of damage are induced and the skin heals rapidly, fractionated ablative systems offer an unparalleled safety margin as compared to traditional ablative lasers. However, infection is still the most significant complication and it can lead to permanent scarring. It is essential that all patients begin oral antiviral therapy from at least the morning of the procedure and early on have frequent postoperative skin evaluations. Use of oral antibiotics and antifungal agents can be decided on a case-by-case basis.

Although scarring is an infrequent event, recent case reports have alerted laser surgeons to be cautious in "underpriviledged" areas such as the neck and chest[80]. Whereas skin on the cheek with its thicker dermis and abundant adnexal structures can tolerate high energies and up to 70% ablation for certain indications, more modest energy and significantly less ablation density should be employed on thinner, finer, and less privileged areas. As such, the laser surgeon must possess comprehensive knowledge of skin thickness at various locations on the face and also appreciate the composition of the skin structures in those locations.

Another noteworthy consideration for minimizing the risk of scarring is avoidance of immediate and direct overlap of treatment areas. Use of a non-overlapping technique allows the treated skin sufficient time to cool before the application of the subsequent pass. This prevents bulk heating, a likely cause of scarring in fractional laser therapy. While ancillary cooling is not necessary, forced cold air is recommended as it facilitates heat dissipation and further minimizes the potential for non-selective heat injury. Cooling also enhances patient comfort.

Postinflammatory hyperpigmentation is a near certain side effect when treating darker skin phototypes. This predictable event can be mitigated with early application of 4% hydroquinone cream twice a day

starting immediately post-therapy for non-ablative procedures. For those who have undergone ablative FP, this topical treatment can be started once the serosanguineous discharge of the immediate postoperative period has ceased. Patients with a prior history of melasma or other pigmentary disorders might be pretreated with hydroquinone prior to the procedure.

PLASMAKINETIC RESURFACING

Plasmakinetic resurfacing is another approach to skin rejuvenation. This technology converts nitrogen gas into a highly energized state (called *plasma*). Specifically, nitrogen gas is ionized as electrons are excited and plasma is created. The energy contained in the plasma is released from the device and aimed at the skin surface, but no direct contact is made between the skin and the device. The plasma energy can be adjusted (ranging from 1.0 to 4.0 J) by the operator. The spot diameter is 10 mm. Plasmakinetic energy heats the skin directly and there is no target chromophore as with lasers. Therefore, there is uniform heating of the skin surface without ablation. Although this indirect heating produces epidermal necrosis, the epidermis remains in place for several days and serves as a biologic dressing. By adjusting the energies, differential depths (from superficial to deep dermal heating) can be achieved for targeted therapies.

Several studies have been performed to compare plasmakinetic resurfacing with traditional ablative laser resurfacing clinically and histologically, and they have found comparable results. However, plasmakinetic resurfacing has the advantage of a favorable side-effect profile and more rapid recovery[81]. The FDA approved this technology (Portrait, Rhytec, Inc.) for the treatment of facial rhytides, acne scarring, and superficial lesions (e.g. actinic and seborrheic keratoses). Despite clinical success, the company producing the device has gone out of business.

OTHER PHOTOREJUVENATION DEVICES

While the ablative lasers can produce dramatic improvement in skin laxity and photodamage, their short-term side effects of discomfort, extended healing times, persistent erythema, postinflammatory hyperpigmentation, and the potential risks of scarring and permanent dyspigmentation have led to a shift toward non-ablative laser therapies. Photorejuvenation by "subsurface remodeling" is designed to induce dermal remodeling and volume restoration via selective dermal injury alone. Early incidental findings of modest rhytide improvement in patients undergoing PDL for facial telangiectasias suggested that selective photothermolysis of dermal vasculature stimulated collagen remodeling. Although the precise mechanism of this process is unclear, the photothermal energy emitted by non-ablative systems has been shown to stimulate a cascade of wound healing responses, including the release of collagenase and platelet-derived growth factor which promotes fibroblast activity and type I collagen formation[82]. These molecular changes offered early evidence to substantiate the use of non-ablative lasers for photorejuvenation and scar amelioration.

Photorejuvenation of the skin entails improvement of actinic telangiectasias, lentigines, solar elastosis and wrinkling. To a broader extent, it involves enhancing the color, tone and texture of the skin. The laser surgeon must appreciate the science and physics behind the energy delivery, rather than base his or her assumptions on a manufacturer's often exaggerated claims. Complete photorejuvenation often requires targeting hemoglobin, melanin and water, and no one laser or wavelength meets all of these objectives on its own. Given that laser and IPL applications for telangiectasias and pigmented lesions were previously reviewed, the use of PDL, Nd:YAG and KTP lasers or IPL for photorejuvenation will only be briefly discussed here. Instead, there will be a more detailed review of devices that improve skin texture and tone; such lasers emit infrared light, which is absorbed primarily by water and leads to collagen remodeling. The devices most frequently used within this group are the 1320, 1450 and 1540 nm lasers and, more recently, the fractionated 1550 nm laser.

Visible light lasers are effectively used to treat the telangiectasias and dyspigmentation associated with photodamaged skin. In addition to specifically improving pigmentation, KTP and Nd:YAG lasers have also been shown to cause a 20–40% improvement in texture and 20–30% improvement in rhytides[83]. The long-pulsed PDL can be used with a multiple-pass technique for photorejuvenation. It is worthy to note that both the 585 and 595 nm PDLs have received FDA clearance for treatment of periocular wrinkling. While collagen remodeling has been demonstrated histologically, clinical improvement of wrinkles is variable and modest.

Likewise, IPL is frequently used to improve photoaging. Its broad range of wavelengths allows the telangiectatic and pigmentary aspects of photoaging to be addressed simultaneously. In a study of 135 patients with poikiloderma of Civatte, IPL treatment of the neck and/or upper chest led to >75% clearance of telangiectasias and hyperpigmentation after a mean of three treatments[24]. While the emitted light is broad, IPL filters allow for more targeted treatments. It has been postulated that the shorter wavelengths are responsible for the improvement in pigmentation and telangiectasias, while the longer wavelengths are responsible for collagen remodeling via thermal effects on tissue water[83].

Infrared lasers whose wavelengths are absorbed almost exclusively by water are the 1320 nm Nd:YAG, 1450 nm diode, and 1540 nm erbium glass lasers. Of these, the 1320 nm Nd:YAG laser has the least affinity for water, and, consequently, the absorbed energy is scattered throughout the dermis. This characteristic permits penetration to at least 500 microns, and potentially up to 2 mm into the skin[84]. The 1320 nm laser has an incorporated cryogen spray (CoolTouch3) which can be set for pre-cooling, mid-pulse cooling, and post-laser pulse cooling. These options, like other cooling strategies with non-ablative lasers, provide epidermal protection and reduce epidermal injury.

Both the 1320 nm Nd:YAG laser and the 1450 nm diode laser, which decrease the activity of sebaceous glands, have received FDA clearance for the treatment of acne. Furthermore, the 1450 nm laser has been reported to be useful for the treatment of sebaceous hyperplasia. When used for the treatment of wrinkles, the 1450 nm diode laser produced only modest improvement and the improvement was not as clearly appreciated by study patients.

RADIOFREQUENCY (RF)

A huge amount of research and development went into constructing a radiofrequency-based skin tightening device. Monopolar RF energy generates heat in a manner which is directly related to tissue impedance. The first commercially available monopolar RF device was ThermaCool TC™ (Thermage) which delivered high-frequency RF energy to the skin via a thin coupling electrode handpiece with active cooling. *In vivo* studies demonstrated that RF energy produced collagen contraction after disrupting hydrogen bonds of the collagen triple-helix structure[85].

After RF tissue tightening received FDA approval for periorbital rhytide reduction in 2002, it was more widely used on the face and neck for improvement of skin laxity. A split-face study demonstrated average brow elevation of 2–4 mm, superior palpebral crease elevation of 1.9 mm, and reduction of jowl surface area by 22%[80]. Although other early studies reported similar conclusions, results in clinical practice were far more variable and unpredictable, and the treatments were associated with significant patient discomfort[86]. Aside from transient erythema and edema, irregular depressions ("mattress-top" irregularities) were seen, which were attributed to excessive treatment (outside the recommended parameters) causing localized fat atrophy. New algorithms were developed, which increased both the reproducibility of the results and patient comfort. They included the use of lower energies over a larger tip in a multiple-pass technique[70]. The most recent development is the CPT (Comfort Pulse Technology) Thermage device. It has been designed to reduce discomfort and increase the efficacy of tissue tightening. The CPT device provides a transcutaneous electrical nerve stimulation (TENS)-like interruption of RF energy interspersed with hot/cold skin stimulation, as well as vibration (acting on the gate theory of pain), a modulated RF profile, and a more distributive electrode.

Bipolar RF devices create localized heat by conducting current between the two electrodes on the skin surface (see Fig. 136.7). Studies purport to have shown a 25–50% improvement in wrinkles, skin smoothness and texture[87]. Recently, RF technologies combined with light have been introduced into the marketplace (e.g. Polaris™, ReFirme™). The objective of these combined light and bipolar RF devices is to create more

efficient tissue heating. The synergistic effects may increase the efficacy of each, but no studies have been performed to substantiate a benefit beyond RF alone. There are reasons to believe that the bipolar devices are not as efficient as monopolar devices in their ability to tighten tissue.

HAIR REMOVAL

Hair removal remains as popular as ever. According to the American Society for Aesthetic Plastic Surgery (ASAPS), laser hair removal was only second to botulinum toxin A injections as one of the most requested cosmetic procedures in 2008. While the distribution, density and color of hair is related to gender and genetic background, the acceptability and desirability of hair are often related to societal and cultural norms. Markedly excessive hair can be a marker for an underlying endocrinopathy or a medication side effect, and a possible etiology should be investigated prior to photoepilation (see Ch. 70). While most patients who undergo photoepilation have the cosmetic objective of decreasing unwanted hair, there are several medical applications of laser hair removal, such as treatment of pseudofolliculitis barbae.

Although the patient's ultimate desire may be to achieve total hairlessness in an anatomic region, complete eradication of hair is often an unattainable objective. In this regard, permanent hair removal, as defined by the FDA in 1998, is "…the long-term, stable reduction in the number of hairs re-growing after a treatment regime…and does not necessarily imply the elimination of all hairs in the treatment area"[88]. Realistic expectations are key and the laser surgeon should clearly and specifically communicate these objectives to the patient. For some patients with particularly coarse, dense unwanted hair, a successful outcome might be a transition to finer, lighter hair. Potential side effects should be reviewed, including pigmentary changes (hyper- or hypopigmentation), erythema, edema, discomfort, and very rarely scarring.

Photoepilation is based on selectively delivering energy to the hair follicle, specifically to the bulge region where follicle stem cells reside, causing their destruction while minimizing non-selective injury to the surrounding tissues. Additional melanin targets are located in the follicular hair shaft, the outer root sheath of the infundibulum, and the hair bulb matrix (see Ch. 68)[89]. Three mechanisms have been proposed to explain hair follicle destruction. These include photothermal injury to the follicle via direct heating of the follicle, photomechanical injury by induction of shock waves and violent cavitation, and photochemical injury by production of toxic intermediaries such as singlet oxygen or free radicals[90]. The ultimate objective of laser or IPL hair removal is seen after heat-induced change of the follicular structures and immediate surrounding tissues. These follicular changes are described as either transient growth arrest or permanent hair removal[91]. Whereas transient hair arrest occurs by induction of catagen, long-term removal is achieved as terminal hairs undergo either follicular fibrosis or miniaturization into vellus hairs.

Although the absorption of melanin corresponds to wavelengths from 400 to 1200 nm, the best lasers for photoepilation have wavelengths between 600 and 1100 nm, a range where there is more selective absorption by melanin and the light penetrates relatively deeply into the skin. Given this relatively broad therapeutic spectrum, many laser systems have been utilized, including the ruby (694 nm), alexandrite (755 nm), diode (800–810 nm) and Nd:YAG (1064 nm) lasers in addition to a variety of IPL systems with different cut-off filters. The optimal wavelength is probably in the ruby laser range (694 nm), but longer pulsing beyond 3 to 4 milliseconds is problematic, which has led to the utilization of alternative wavelengths. However, the safety and efficacy of laser hair removal is dependent on the operator's sophisticated knowledge regarding the practical application of laser–tissue interactions and the principles of selective photothermolysis. From a practical perspective, this entails accurate selection of: the laser system, the optimal pulse duration, and the appropriate fluence to achieve hair removal while protecting the epidermis and minimizing non-selective dermal heat injury. Inappropriate selection can result in permanent scarring and dyspigmentation.

Selection of the appropriate pulse duration is critical for effective photoepilation. As the thermal relaxation time of a hair follicle is 10–50 ms, the pulse duration should be adjusted to match these parameters[92]. However, extension of the pulse duration beyond the thermal relaxation time of the follicular unit could promote delivery of thermal damage to the surrounding non-pigmented stem cells and might induce more consistent follicular destruction[89]. This notion is illustrated by the relative ineffectiveness of Q-switched lasers for hair reduction; although their nanosecond pulse durations can deliver energy to individual pigmented cells, the pulse duration of Q-switched lasers is insufficient to permanently affect the follicular unit as an entity. In general, the ideal pulse duration would be between the thermal relaxation time of the epidermis (1 ms) and the hair follicle. Coarser, thicker and darker hairs may have relatively longer thermal relaxation times compared to thinner, finer hairs[90]. The ideal patient for hair removal is one with lighter skin (phototypes I–III) and dark brown to black hair (Fig. 137.16).

In general, higher fluences achieve greater hair reduction. However, since overzealous fluence might induce excessive collateral heat, a conservative selection of parameters is recommended. Typical danger zones are the chin and lip (where there is a greater density of hair follicles) as well as pigmented genital or inguinal skin. Fluence should be titrated up, if necessary, with each treatment. As a final note of caution, parameters are not interchangeable between devices, even those with the same laser or IPL wavelength. It is incumbent on the operator to know how to operate each system that he or she uses.

Laser hair removal in patients with darker skin can be more problematic as epidermal melanin competes with the follicular target. For patients with skin phototypes IV–VI, the long-pulsed Nd:YAG laser is

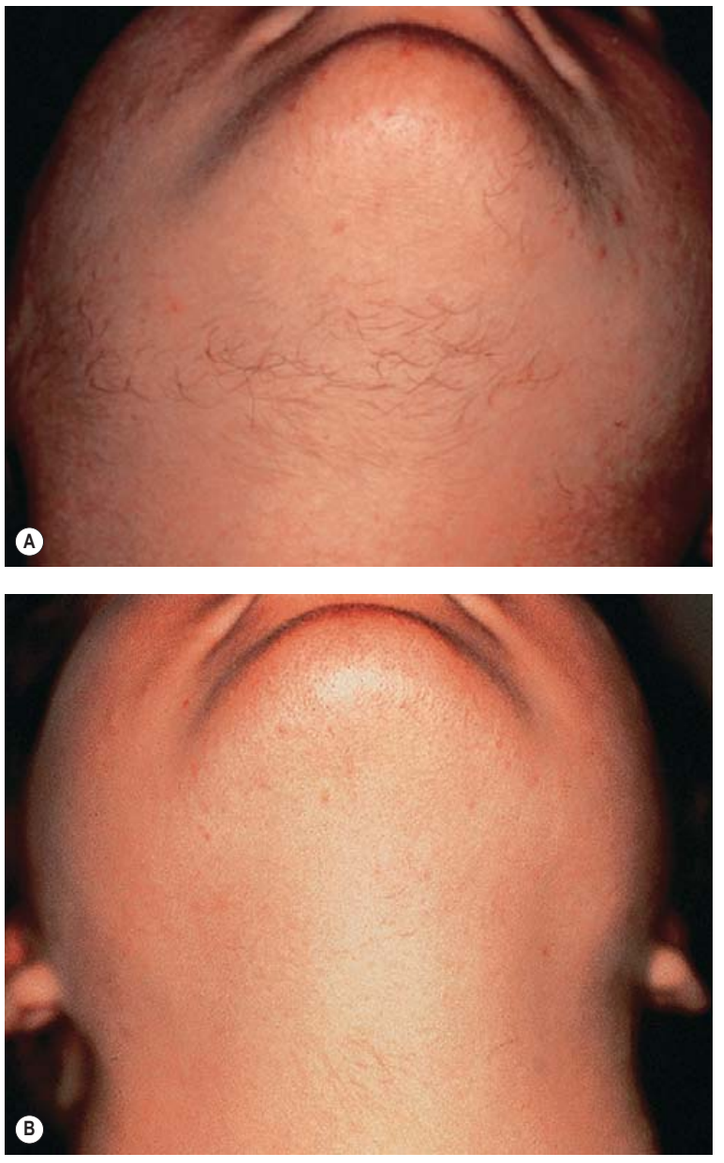


Fig. 137.16 Laser hair removal. A Before treatment. **B** Two years after three long-pulsed diode laser treatments; there is almost complete and long-term hair growth reduction. *Courtesy, Jeffrey Dover, MD, and Kenneth Arndt, MD.*

generally regarded as the safest system. However, the most common criticism of the long-pulsed Nd:YAG laser is the associated pain and relative lack of overall efficacy.

While IPL was initially designed for the treatment of vascular lesions, it has also been modified specifically for laser hair removal. With appropriate use of longer wavelength cut-off filters, short wavelengths can be eliminated and (relatively) more melanin-selective treatments can be delivered. Additionally, use of multiple synchronized pulses allows for heat retention within the hair shaft to produce selective thermal damage. This notion has been termed thermokinetic selectivity[93].

Appropriate cooling of the epidermis is critical with these hair removal devices. Cooling can be applied immediately prior to (pre-cooling), during (parallel cooling), or after laser pulsing (post-cooling). Aside from protecting the epidermis from excessive heat, contact cooling handpieces allow compression of the skin and facilitate delivery of more laser energy to the targeted hair follicles.

Although commercial laser and IPL companies might argue otherwise, no system is inherently superior for photoepilation. However, given a certain hair color, or skin type, there are differential decisions to be made regarding which system to purchase. In general, lighter skin phototypes (I–III) respond better to treatment with the 755 nm alexandrite or the 800 nm diode laser, while darker skin phototypes (IV–VI) respond better to treatment with the 1064 nm Nd:YAG laser. Most studies have shown comparable efficacy rates when sufficient fluence is used and multiple treatments are performed. Regardless of the laser or IPL system utilized, serial treatments are required for significant, long-term hair reduction. Typically, three to eight treatments spaced at 6–10-week intervals are recommended. Response rates of 70–90% hair reduction at a 6-month follow-up have been reported[94]. As stated previously, the "ideal" patient for photoepilation is one who has light skin and dark hair. Long-term efficacy of laser hair removal correlates with higher concentrations of eumelanin[95]. Recent attempts have been made to treat non-pigmented, gray or white hair, but so far there is little evidence of benefit.

Paradoxical hypertrichosis following the use of hair removal devices is a common and well documented side-effect of photoepilation. This has generally been described in patients with Mediterranean, Hispanic or Asian backgrounds and phototypes III or IV and dark lanugo hair. Of note, it can occur with any of the laser or IPL hair removal systems. Initial reports suggested that affected patients should be evaluated for hyperandrogenemia[96]. However, the largest retrospective analysis to date of 750 patients found that the overall incidence of paradoxical hypertrichosis was 4.5%, and it occurred most often on the face and neck of patients with skin phototypes III and IV. These authors postulated that the hair induction occurred at the borders of the treated areas, perhaps because of sub-therapeutic fluences during laser therapy and local inflammatory responses following photoepilation[97]. In the authors' experience, paradoxical hypertrichosis can be reversed using a photomechanical approach with a Q-switched Nd:YAG laser at high fluence.

Proper pre-treatment preparation of the skin prior to photoepilation allows for optimal treatment results. Failure to recognize the need to avoid treating suntanned skin has resulted in numerous burns, scarring, and permanent pigmentary changes. In sunny climates, patients should be advised to apply broad-spectrum sunscreens for weeks prior to laser therapy and to avoid tanning both before and after photoepilation, in order to prevent postinflammatory hyperpigmentation. Secondly, patients should avoid plucking, waxing, threading, and electrolysis prior to laser treatment as these will remove the target chromophore. Patients can be advised that shaving or depilatory creams are acceptable. Shaved hair (or at least hair cut flush with the skin surface) also minimizes inadvertent heat transfer to the epidermis during laser therapy. Finally, given that photoepilation is often associated with some degree of discomfort, topical anesthetics can be applied prior to treatment. While increasing patient comfort during the procedure is an important objective, several deaths have been reported with misuse of strong topical anesthetics in unsupervised situations.

During the procedure, the laser surgeon should constantly assess the skin's reaction to this or any other laser energy, and adjust parameters if necessary. The operator should expect to observe appropriate follicular reactions (such as perifollicular erythema and focal edema) indicating proper parameter selection, and should be critically inspecting the skin frequently for evidence of whiteness, blistering or crusting. A most ominous finding is a grey or white epidermal discoloration. This reflects dermal heat injury and is a marker of an inappropriately high fluence. Blister formation and epidermal necrosis may ensue, and in severe cases, may result in dermal necrosis and marked scarring.

While office-based laser photoepilation currently predominates, home-based systems have reached the marketplace. These systems offer a low-cost treatment alternative, abundant privacy, and convenience to the patient. Concerns have been raised by physicians about the safety of home systems and the ability of the lay operator to use them correctly. Although little peer-reviewed literature is available, one small office-based study demonstrated that nearly all of the patients were able to correctly administer their own treatments. Additionally, the observed side effects of hyper- and hypopigmentation, crusting and blistering were transient and had resolved by the conclusion of the study[98]. Use of these devices on inappropriate skin phototypes and tanned skin is clearly contraindicated. The patients need to assume a high degree of responsibility with these devices. There will be complications, but we should not underestimate the ability of the public to use (or abuse) these devices, just as with any other device such as a hair curler, which is arguably a significantly more dangerous piece of equipment.

TREATMENT OF PSORIASIS AND VITILIGO

Psoriasis affects nearly 2% of the US population and often commits patients to a lifetime of treatment. The range of therapies includes topical corticosteroids and vitamin D_3 analogues, systemic retinoids, methotrexate, phototherapy, and newer targeted immunomodulators ("biologic agents"; see Ch. 8). Despite the variety of treatment options available, some psoriatic plaques are recalcitrant. Application of laser therapy may represent a new approach to resistant lesions, particularly those in "problem areas" such as the scalp and intertriginous zones. The most commonly used laser for psoriasis is the 308 nm XeCl excimer laser. As a localized narrowband UVB therapy, the excimer laser has been demonstrated to clear psoriatic plaques by impeding epidermal cell proliferation and perhaps inducing localized immunosuppression. Compared to conventional UVB phototherapy, treatment with the excimer laser cleared psoriatic plaques two times faster and with lower cumulative UVB doses[99]. Additionally, PDL has been used to treat psoriasis by targeting the underlying abnormal vasculature. While both systems are beneficial, the excimer laser has been demonstrated to yield more favorable improvement[100]. The excimer laser has also been shown to produce impressive improvement of vitiliginous skin when used as adjuvant therapy, especially when combined with topical tacrolimus[101]. In the authors' opinion, the excimer device plays an important role in the photobiology section of the dermatologist's practice. Lastly, the excimer laser has been used to repigment some of the patients who developed delayed-onset permanent hypopigmentation following standard CO_2 or Er:YAG laser resurfacing procedures.

CONCLUSIONS

Increasingly, we are asking the question, "Lasers: what's the truth"? This reality check is necessary so that we start to ask the right questions and are critically aware of the answers. Laser engineers are very insightful, and they can provide us with semi-intelligent laser, light and other energy systems that can more precisely target the correct structures, and induce the correct healing responses. We should celebrate the enormous energy that goes into newer and more sophisticated devices, just as we should criticize and reject devices which under perform and over promise. Those of us who are involved in new technology development know that, just around the corner, advances are going to bring us smarter, cheaper, more durable, more tunable devices. Total internal reflection of spontaneous emission of radiation (TRASER) devices, which are neither lasers nor IPL, are more efficient than lasers and are tunable. New wavelengths are becoming available, targeting structures important in the control of acne or for body contouring. Our hope is that as this new technology comes online, there will be a continued attempt to answer the ongoing tough questions pertaining to both surgical and medical dermatology. In this regard, lasers and IPL should just be considered as "drugs", i.e. something that can be manipulated to ease the burden of those suffering from skin diseases.

REFERENCES

1. Anderson RR, Parrish JA. Selective photothermolysis: precise microsurgery by selective absorption of pulsed radiation. Science. 1983;220:524–527.
2. Alexiades-Armenakas MR, Dover JS, Arndt KA. The spectrum of laser skin resurfacing: nonablative, fractional, and ablative laser resurfacing. J Am Acad Dermatol. 2008;58:719–737.
3. Ross EV, Uebelhoer NS, Domankevitz Y. Use of a novel pulse dye laser for rapid single-pass purpura-free treatment of telangiectases. Dermatol Surg. 2007;33:1466–1469.
4. Levy JL, Elbahr C, Jouve E, Mordon S. Comparison and sequential study of long pulsed Nd:YAG 1,064 nm laser and sclerotherapy in leg telangiectasias treatment. Lasers Surg Med. 2004;34:273–276.
5. Anderson RR, Parrish JA. Microvasculature can be selectively damaged using dye lasers: a basic theory and experimental evidence in human skin. Lasers Surg Med. 1981;1:263–276.
6. Garden JM, Tan OT, Kerschmann R, et al. Effect of dye laser pulse duration on selective cutaneous vascular injury. J Invest Dermatol. 1986;87:653–657.
7. Dixon JA, Huether S, Rotering R. Hypertrophic scarring in argon laser treatment of port-wine stains. Plast Reconstr Surg. 1984;73:771–779.
8. Dierickx C, Goldman MP, Fitzpatrick RE. Laser treatment of erythematous/hypertrophic and pigmented scars in 26 patients. Plast Reconstr Surg. 1995;95:84–90.
9. Tan OT, Sherwood K, Gilchrest BA. Treatment of children with port-wine stains using the flashlamp-pulsed tunable dye laser. N Engl J Med. 1989;320:416–421.
10. Tan OT, Morrison P, Kurban AK. 585 nm for the treatment of port-wine stains. Plast Reconstr Surg. 1990;86: 1112–1117.
11. Galeckas KJ. Update on lasers and light devices for the treatment of vascular lesions. Semin Cutan Med Surg. 2008;27:276–284.
12. van der Horst CM, Koster PH, de Borgie CA, et al. Effect of the timing of treatment of port-wine stains with the flash-lamp-pumped pulsed-dye laser. N Engl J Med. 1998;338:1028–1033.
13. Lanigan SW, Cotterill JA. Psychological disabilities amongst patients with port wine stains. Br J Dermatol. 1989;121:209–215.
14. Tan E, Vinciullo C. Pulsed dye laser treatment of port-wine stains. A patient questionnaire. Dermatol Surg. 1996;22:119–122.
15. Chapas AM, Eickhorst K, Geronemus RG. Efficacy of early treatment of facial port wine stains in newborns: a review of 49 cases. Lasers Surg Med. 2007;39:563–568.
16. Renfro L, Geronemus RG. Anatomical differences of port-wine stains in response to treatment with the pulsed dye laser. Arch Dermatol. 1993;129:182–188.
17. Waner M, Suen JY. A classification of congenital vascular lesions. In: Waner M, Suen JY (eds). Hemangiomas and Vascular Malformations of the Head and Neck. New York: Wiley-Liss, 1999.
18. Leaute-Labreze C, Dumas de la Roque E, Hubiche T, et al. Propranolol for severe hemangiomas of infancy. N Engl J Med. 2008;358:2649–2651.
19. Kim HJ, Colombo M, Frieden IJ. Ulcerated hemangiomas: clinical characteristics and response to therapy. J Am Acad Dermatol. 2001;44:962–972.
20. Garden JM, Bakus AD, Paller AS. Treatment of cutaneous hemangiomas by the flashlamp-pumped pulsed dye laser: prospective analysis. J Pediatr. 1992;120:555–560.
21. Hohenleutner S, Badur-Ganter E, Landthaler M, Hohenleutner U. Long-term results in the treatment of childhood hemangioma with the flashlamp-pumped pulsed dye laser: an evaluation of 617 cases. Lasers Surg Med. 2001;28:273–277.
22. Tanghetti EA, Sherr EA, Alvarado SL. Multipass treatment of photodamage using the pulse dye laser. Dermatol Surg. 2003;29:686–690.
23. Rohrer TE, Chatrath V, Iyengar V. Does pulse stacking improve the results of treatment with variable-pulse pulsed-dye lasers? Dermatol Surg. 2004;30: 163–167.
24. Goldman MP, Weiss RA. Treatment of poikiloderma of Civatte on the neck with an intense pulsed light source. Plast Reconstr Surg. 2001;107:1376–1381.
25. Kunishige JH, Goldberg LH, Friedman PM. Laser therapy for leg veins. Clin Dermatol. 2007;25:454–461.
26. Hsu J. Leg vein management. In: Kaminer MS, Arndt KA, Dover JS, et al. (eds). Atlas of Cosmetic Surgery, 2nd edn. Philadelphia: Elsevier, 2009:456.
27. Kauvar AN, Khrom T. Laser treatment of leg veins. Semin Cutan Med Surg. 2005;24:184–192.
28. Reichert D. Evaluation of the long-pulse dye laser for the treatment of leg telangiectasias. Dermatol Surg. 1998;24:737–740.
29. Nemeth AJ, Reyes BA. Copper vapor laser treatment of genital and body warts. Lasers Surg Med. 1990;10:52–53.
30. Tan OT, Hurwitz RM, Stafford TJ. Pulsed dye laser treatment of recalcitrant verrucae: a preliminary report. Lasers Surg Med. 1993;13:127–137.
31. Pfau A, Abd-el-Raheem TA, Baumler W, et al. Nd:YAG laser hyperthermia in the treatment of recalcitrant verrucae vulgares (Regensburg's technique). Acta Derm Venereol. 1994;74:212–214.
32. Street ML, Roenigk RK. Recalcitrant periungual verrucae: the role of carbon dioxide laser vaporization. J Am Acad Dermatol. 1990;23:115–120.
33. Robson KJ, Cunningham NM, Kruzan KL, et al. Pulsed-dye laser versus conventional therapy in the treatment of warts: a prospective randomized trial. J Am Acad Dermatol. 2000;43:275–280.
34. Logan RA, Zachary CB. Outcome of carbon dioxide laser therapy for persistent cutaneous viral warts. Br J Dermatol. 1989;121:99–105.
35. Patrice SJ, Wiss K, Mulliken JB. Pyogenic granuloma (lobular capillary hemangioma): a clinicopathologic study of 178 cases. Pediatr Dermatol. 1991;8:267–276.
36. Rashid T, Hussain I, Haider M, Haroon TS. Laser therapy of freckles and lentigines with quasi-continuous, frequency-doubled, Nd:YAG (532 nm) laser in Fitzpatrick skin type IV: a 24-month follow-up. J Cosmet Laser Ther. 2002;4:81–85.
37. Dierickx CC. Lasers in pigmentary disorders. Pigment Cell Res. 2003;16:590.
38. Grevelink JM, van Leeuwen RL, Anderson RR, Byers HR. Clinical and histological responses of congenital melanocytic nevi after single treatment with Q-switched lasers. Arch Dermatol. 1997;133:349–353.
39. Westerhof W, Gamei M. Treatment of acquired junctional melanocytic naevi by Q-switched and normal mode ruby laser. Br J Dermatol. 2003;148:80–85.
40. Carpo BG, Grevelink JM, Grevelink SV. Laser treatment of pigmented lesions in children. Semin Cutan Med Surg. 1999;18:233–243.
41. Railan D, Kilmer S. Laser treatment of benign pigmented cutaneous lesions. In: Goldman MP (ed.). Cutaneous and Cosmetic Laser Surgery. Philadelphia: Mosby; 2006:98.
42. Rhodes AR, Mihm MC Jr. Origin of cutaneous melanoma in a congenital dysplastic nevus spilus. Arch Dermatol. 1990;126:500–505.
43. Chan HH, Leung RS, Ying SY, et al. A retrospective analysis of complications in the treatment of nevus of Ota with the Q-switched alexandrite and Q-switched Nd:YAG lasers. Dermatol Surg. 2000;26:1000–1006.
44. Alster TS, Williams CM. Treatment of nevus of Ota by the Q-switched alexandrite laser. Dermatol Surg. 1995; 21:592–596.
45. Milgraum SS, Cohen ME, Auletta MJ. Treatment of blue nevi with the Q-switched ruby laser. J Am Acad Dermatol. 1995;32:307–310.
46. Taylor CR, Anderson RR. Ineffective treatment of refractory melasma and postinflammatory hyperpigmentation by Q-switched ruby laser. J Dermatol Surg Oncol. 1994;20:592–597.
47. Manaloto RM, Alster T. Erbium:YAG laser resurfacing for refractory melasma. Dermatol Surg. 1999;25:121–123.
48. Tannous ZS, Astner S. Utilizing fractional resurfacing in the treatment of therapy-resistant melasma. J Cosmet Laser Ther. 2005;7:39–43.
49. Rokhsar CK, Fitzpatrick RE. The treatment of melasma with fractional photothermolysis: a pilot study. Dermatol Surg. 2005;31:1645–1650.
50. Laubach HJ, Tannous Z, Anderson RR, Manstein D. Skin responses to fractional photothermolysis. Lasers Surg Med. 2006;38:142–149.
51. Raulin C, Schonermark MP, Greve B, Werner S. Q-switched ruby laser treatment of tattoos and benign pigmented skin lesions: a critical review. Ann Plast Surg. 1998;41:555–565.
52. Tafazzoli A, Rostan EF, Goldman MP. Q-switched ruby laser treatment for postsclerotherapy hyperpigmentation. Dermatol Surg. 2000;26:653–656.
53. Nouri K, Romagosa R, Chartier T, et al. Comparison of the 585 nm pulse dye laser and the short pulsed CO2 laser in the treatment of striae distensae in skin types IV and VI. Dermatol Surg. 1999;25:368–370.
54. Tay YK, Kwok C, Tan E. Non-ablative 1,450-nm diode laser treatment of striae distensae. Lasers Surg Med. 2006;38:196–199.
55. Goldberg DJ, Sarradet D, Hussain M. 308-nm Excimer laser treatment of mature hypopigmented striae. Dermatol Surg. 2003;29:596–598.
56. Hernandez-Perez E, Colombo-Charrier E, Valencia-Ibiett E. Intense pulsed light in the treatment of striae distensae. Dermatol Surg. 2002;28:1124–1130.
57. Jimenez GP, Flores F, Berman B, Gunja-Smith Z. Treatment of striae rubra and striae alba with the 585-nm pulsed-dye laser. Dermatol Surg. 2003;29:362–365.
58. Alster TS, Tanzi EL, Lazarus M. The use of fractional laser photothermolysis for the treatment of atrophic scars. Dermatol Surg. 2007;33:295–299.
59. Kim BJ, Lee DH, Kim MN, et al. Fractional photothermolysis for the treatment of striae distensae in Asian skin. Am J Clin Dermatol. 2008;9:33–37.
60. Walsh JT Jr, Flotte TJ, Anderson RR, Deutsch TF. Pulsed CO2 laser tissue ablation: effect of tissue type and pulse duration on thermal damage. Lasers Surg Med. 1988;8:108–118.
61. Willard RJ, Moody BR, Hruza GJ. Carbon dioxide and erbium:YAG ablation. In: Goldman MP (ed.). Cutaneous and Cosmetic Laser Surgery. Philadelphia: Mosby; 2006:158–159.
62. Zachary CB. Modulating the Er:YAG laser. Lasers Surg Med. 2000;26:223–226.
63. Alster TS, Garg S. Treatment of facial rhytides with a high-energy pulsed carbon dioxide laser. Plast Reconstr Surg. 1996;98:791–794.
64. Newman JB, Lord JL, Ash K, McDaniel DH. Variable pulse erbium:YAG laser skin resurfacing of perioral rhytides and side-by-side comparison with carbon dioxide laser. Lasers Surg Med. 2000;26:208–214.
65. Jacob CI, Dover JS, Kaminer MS. Acne scarring: a classification system and review of treatment options. J Am Acad Dermatol. 2001;45:109–117.
66. Johnson TM, Sebastien TS, Lowe L, Nelson BR. Carbon dioxide laser treatment of actinic cheilitis. Clinicohistopathologic correlation to determine the optimal depth of destruction. J Am Acad Dermatol. 1992;27:737–740.
67. Conn H, Nanda VS. Prophylactic fluconazole promotes reepithelialization in full-face carbon dioxide laser skin resurfacing. Lasers Surg Med. 2000;26:201–207.
68. Manstein D, Herron GS, Sink RK, et al. Fractional photothermolysis: a new concept for cutaneous remodeling using microscopic patterns of thermal injury. Lasers Surg Med. 2004;34:426–438.
69. Hantash BM, Bedi VP, Sudireddy V, et al. Laser-induced transepidermal elimination of dermal content by fractional photothermolysis. J Biomed Opt. 2006;11:041115.
70. Ross EV. Nonablative laser rejuvenation in men. Dermatol Ther. 2007;20:414–429.
71. Ross EV, Swann M, Soon S, et al. Full-face treatments with the 2790-nm erbium:YSGG laser system. J Drugs Dermatol. 2009;8:248–252.
72. Dierickx CC, Khatri KA, Tannous ZS, et al. Micro-fractional ablative skin resurfacing with two novel erbium laser systems. Lasers Surg Med. 2008;40:113–123.
73. Geronemus RG. Fractional photothermolysis: current and future applications. Lasers Surg Med. 2006;38:169–176.
74. Walgrave SE, Ortiz AE, MacFalls HT, et al. Evaluation of a novel fractional resurfacing device for treatment of acne scarring. Lasers Surg Med. 2009;41:122–127.
75. Jih MH, Kimyai-Asadi A. Fractional photothermolysis: a review and update. Semin Cutan Med Surg. 2008; 27:63–71.
76. Hantash BM, Bedi VP, Kapadia B, et al. In vivo histological evaluation of a novel ablative fractional resurfacing device. Lasers Surg Med. 2007;39: 96–107.
77. Hantash BM, Bedi VP, Chan KF, Zachary CB. Ex vivo histological characterization of a novel ablative fractional resurfacing device. Lasers Surg Med. 2007;39:87–95.
78. Rahman Z, MacFalls H, Jiang K, et al. Fractional deep dermal ablation induces tissue tightening. Lasers Surg Med. 2009;41:78–86.

79. Fisher GH, Geronemus RG. Short-term side effects of fractional photothermolysis. Dermatol Surg. 2005;31:1245–1249.
80. Fife DJ, Fitzpatrick RE, Zachary CB. Complications of fractional CO2 laser resurfacing: four cases. Lasers Surg Med. 2009;41:179–184.
81. Groff WF, Fitzpatrick RE, Uebelhoer NS. Fractional carbon dioxide laser and plasmakinetic skin resurfacing. Semin Cutan Med Surg. 2008;27:239–251.
82. Zelickson BD, Kist D. Pulsed dye laser and photoderm treatment stimulates production of type 1 collagen and collagenase transcripts in the papillary dermis fibroblasts. Laser Surg Med. 2001;28(Suppl 13):33.
83. Hardaway CA, Ross EV. Nonablative laser skin remodeling. Dermatol Clin. 2002;20:97–111, ix.
84. Hardaway CA, Ross EV, Paithankar DY. Non-ablative cutaneous remodeling with a 1.45 microm mid-infrared diode laser: phase II. J Cosmet Laser Ther. 2002;4:9–14.
85. Zelickson BD, Kist D, Bernstein E, et al. Histological and ultrastructural evaluation of the effects of a radiofrequency-based nonablative dermal remodeling device: a pilot study. Arch Dermatol. 2004;140:204–209.
86. Jacobson LG, Alexiades-Armenakas M, Bernstein L, Geronemus RG. Treatment of nasolabial folds and jowls with a noninvasive radiofrequency device. Arch Dermatol. 2003;139:1371–1372.
87. Sadick NS, Trelles MA. Nonablative wrinkle treatment of the face and neck using a combined diode laser and radiofrequency technology. Dermatol Surg. 2005;31:1695–1699.
88. US Food and Drug Administration. Hair removal. 2009. http://www.fda.gov/cdrh/consumer/laserfacts.html. Accessed 11/04/2009.
89. Dierickx CC. Hair removal by lasers and intense pulsed light sources. Dermatol Clin. 2002;20:135–146.
90. Dierickx C. Laser-assisted hair removal: state of the art. Dermatol Ther. 2000;13:80–89.
91. Dierickx CC, Grossman MC, Farinelli WA, Anderson RR. Permanent hair removal by normal-mode ruby laser. Arch Dermatol. 1998;134:837–842.
92. van Gemert MJ, Welch AJ. Time constants in thermal laser medicine. Lasers Surg Med. 1989;9:405–421.
93. Raulin C, Greve B, Grema H. IPL technology: a review. Lasers Surg Med. 2003;32:78–87.
94. Lepselter J, Elman M. Biological and clinical aspects in laser hair removal. J Dermatolog Treat. 2004;15:72–83.
95. Liew SH, Ladhani K, Grobbelaar AO, et al. Ruby laser-assisted hair removal success in relation to anatomic factors and melanin content of hair follicles. Plast Reconstr Surg. 1999;103:1736–1743.
96. Moreno-Arias G, Castelo-Branco C, Ferrando J. Paradoxical effect after IPL photoepilation. Dermatol Surg. 2002;28:1013–1016.
97. Kontoes P, Vlachos S, Konstantinos M, et al. Hair induction after laser-assisted hair removal and its treatment. J Am Acad Dermatol. 2006;54:64–67.
98. Rohrer TE, Chatrath V, Yamauchi P, Lask G. Can patients treat themselves with a small novel light based hair removal system? Lasers Surg Med. 2003;33: 25–29.
99. Bonis B, Kemeny L, Dobozy A, et al. 308 nm UVB excimer laser for psoriasis. Lancet. 1997;350:1522.
100. Taibjee SM, Cheung ST, Laube S, Lanigan SW. Controlled study of excimer and pulsed dye lasers in the treatment of psoriasis. Br J Dermatol. 2005;153:960–966.
101. Passeron T, Ostovari N, Zakaria W, et al. Topical tacrolimus and the 308-nm excimer laser: a synergistic combination for the treatment of vitiligo. Arch Dermatol. 2004;140:1065–1069.

This page intentionally left blank

138 Cryosurgery

Emanuel G Kuflik and Julianne H Kuflik

Chapter Contents

Indications and contraindications 2283
Preoperative history and considerations 2284
Treatment factors 2284
Description of techniques 2285
Treatment 2285
Variations and unusual situations 2288
Postoperative care 2288
Complications 2288

Synonyms: ■ Cryotherapy ■ Contact therapy ■ Freezing

Key features

- Versatile modality for benign, premalignant and malignant lesions on all areas of the body
- Entails fast freezing and slow thawing, with a single freeze–thaw cycle for benign lesions and a double freeze–thaw cycle for malignant ones
- A tissue temperature of –50°C to –60°C is needed for destruction of malignant lesions, while lesser degrees of freezing are needed for benign lesions
- Because of its lower boiling point (–196°C), liquid nitrogen is preferred as the cryogen over nitrous oxide, carbon dioxide and fluorinated hydrocarbons
- Depth dose is determined by observation, palpation, freeze time, thaw time, lateral spread of freeze, and measurement of the tissue temperature. Cancer depth dose is achieved when these factors have reached the desired endpoint
- The tissue reactions are predictable, including crust or bulla formation after treatment of a benign lesion, and exudation, edema and sloughing after treatment of a malignant one
- Melanocytes are more sensitive to freezing than are keratinocytes, thus cryosurgery can lead to depigmentation

INTRODUCTION AND BACKGROUND

Cryosurgery is a treatment modality that is used frequently, to one degree or another, by all dermatologists. It is useful either as a primary or as an alternate form of treatment (Table 138.1). The word cryotherapy is often used interchangeably with cryosurgery, although the latter is a more accurate description of the destruction that is attainable with this modality.

The objective of cryosurgery is to cause selective necrosis of tissue, the extent of which depends on the type of lesion and the volume of freezing required. Tissue alterations are caused by reduction of the skin temperature with consequent freezing of cells[1]. The rate of heat transfer is a function of the temperature difference between the skin and the heat sink, or liquid nitrogen. Because the difference between the skin temperature and the temperature of liquid nitrogen is great, rapid heat transfer away from the skin results.

The tissue response ranges from an inflammatory reaction, as in the treatment of acne, to mild destruction for a benign lentigo, or even more destruction as for actinic keratoses. A greater amount of necrosis is needed for eradication of malignant lesions[2,3]. The mechanisms of injury in cryosurgery can be attributed to the direct effects of freezing tissue and to vascular stasis. Freezing tissue results in intracellular and extracellular ice crystal formation, disruption of cell membrane integrity, pH changes, impairment of multiple homeostatic functions, and thermal shock. This damage is enhanced during subsequent thawing of the tissue by the development of vascular stasis, which leads to failure of the local microcirculation. Slow cooling produces extracellular ice, but this is not as damaging as rapid cooling, which produces intracellular ice. Therefore, rapid cooling of the target tissue is desirable. On the other hand, the rate of rewarming, or thawing, should proceed slowly. With repeated freeze–thaw cycles, maximum destructive effects are produced. The tissue reactions that ensue after either light or deep freezing are predictable, and the underlying stroma provides a structural framework for wound repair.

Liquid nitrogen is the coldest medical cryogenic agent (–196°C boiling point) with the greatest freezing capability. It can be used for cutaneous malignancies as well as for small benign lesions. Although other cryogenic agents are available, including nitrous oxide, carbon dioxide and fluorinated hydrocarbons (latter phased out due to hydrochlorocarbon ban for ozone protection), they are not recommended for skin cancer but rather for lesions that require lesser degrees of freezing. Modern cryosurgery uses an apparatus that employs liquid nitrogen in a closed system that permits continuous and rapid extraction of heat from tissue. The dominant apparatus for dermatologic use is a hand-held unit that can be used either with a spray-tip accessory or with a closed cryoprobe (also known as contact therapy). Although the same equipment is used for a wide variety of conditions, the volume of liquid nitrogen, the technique of treatment, the duration of cooling and the amount of tissue being destroyed varies. Other techniques still in use include a cotton-tipped applicator and crushed carbon dioxide. Home freezing products that contain dimethyl ether and propane are occasionally effective for warts (although this may represent the natural history), but are inadequate for treating skin cancer.

INDICATIONS AND CONTRAINDICATIONS

Cryosurgery is a versatile modality that is used for many benign, premalignant and malignant lesions. The indications are related to the nature of the lesion and to the type of patient.

More than 50 benign conditions are amenable to cryosurgical management (Table 138.2). This is in addition to premalignant lesions and *in situ* malignancies including actinic keratoses, actinic cheilitis, lentigo maligna, Bowen's disease and erythroplasia of Queyrat.

Various sizes and subtypes of basal and squamous cell carcinomas can be treated, including papulonodular, cystic, superficial, ulcerative, keratotic and exophytic tumors[4,5]. The general indications for cryosurgery of tumors are outlined in Table 138.3. While not the usual initial therapeutic approach, cryosurgery has been used for selected recurrent tumors and ones that are fixed to cartilage or bone. However, many dermatologists feel that cryosurgery is not a good choice for treating most recurrent tumors.

Contraindications for cryosurgery include patients who have cold urticaria, cold intolerance, cryofibrinogenemia or cryoglobulinemia. Tumors with indistinct or ill-defined borders (e.g. morpheaform or infiltrative histologic subtypes), as well as deeply penetrating and very aggressive lesions, are best treated by other modalities. Cryosurgery is not considered to be a standard treatment for invasive melanoma.

ADVANTAGES OF CRYOSURGERY
• Versatility – treatment of diverse conditions
• Treatment of any area of the body
• Safe and relatively simple procedure
• Low cost
• Excellent cosmetic results
• Suitable for office, nursing home, or outpatient facility; operative suite not required
• No general anesthesia; local anesthesia optional
• Usually no restriction of work or sports
• Safe during pregnancy
• For patients who are fearful of undergoing surgery
• For poor-surgical-risk patients
• No age limitations – excellent for the very elderly
• Suitable for wheelchair and stretcher patients
• When other methods are impractical or undesirable

Table 138.1 Advantages of cryosurgery.

BENIGN CONDITIONS AMENABLE TO CRYOSURGERY	
• Acne cysts	• Lichen sclerosus (of vulva)
• Acne keloidalis nuchae	• Lymphangioma
• Acne vulgaris	• Cutaneous lymphoid hyperplasia (lymphocytoma cutis)
• Acquired perforating disorder	• Molluscum contagiosum
• Angiofibroma	• Mucocele
• Angiokeratomas, including of Fordyce	• Myxoid cyst
• Cherry angioma	• Nevoid hyperkeratosis of the nipple
• Chondrodermatitis nodularis helicis	• Orf
• Chromoblastomycosis	• Pearly penile papules
• Clear cell acanthoma	• Porokeratosis
• Condyloma acuminatum	• Prurigo nodularis
• Dermatofibroma	• Pyogenic granuloma
• Discoid lupus erythematosus	• Rhinophyma
• Eccrine poroma	• Rosacea
• Elastosis perforans serpiginosa	• Sarcoidosis
• Epidermal nevus	• Sebaceous hyperplasia
• Erosive adenomatosis of the nipple	• Seborrheic keratosis
• Folliculitis keloidalis	• Syringocystadenoma papilliferum
• Granuloma annulare	• Syringoma
• Granuloma faciale	• Trichiasis
• Hemangioma	• Trichoepithelioma
• Herpes simplex	• Venous lake
• Keloid	• Verruca vulgaris
• Leishmaniasis	• Xanthoma
• Lentigo	

Table 138.2 Benign conditions amenable to cryosurgery.

GENERAL INDICATIONS FOR CRYOSURGERY OF TUMORS
• Lesions with well-delineated borders
• Any anatomical site, including the eyelids
• Tumors difficult to treat by other methods
• Patients are elderly, debilitated, or have limited mobility
• Patients with pacemakers, defibrillators, and/or coagulopathies
• Inoperable tumors or for palliation

Table 138.3 General indications for cryosurgery of tumors.

Caution should be observed when confronted with patients who have darkly pigmented skin, since freezing of skin can result in hypopigmentation. Also, cryosurgery of facial lesions in patients with telangiectasias and facial erythema due to photodamage and/or rosacea can lead to obvious treatment sites. While overfreezing should be avoided in the case of benign and premalignant lesions, undertreatment of malignancies can lead to inadequate destruction or recurrence. Also, lesions that overlie superficial nerves, such as on the fingers or ulnar fossa, should

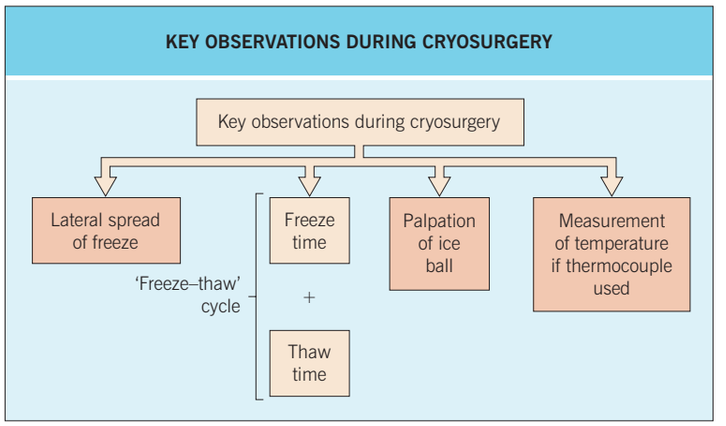


Fig. 138.1 Key observations during cryosurgery.

be carefully treated. Some anatomic areas where cryosurgery should be undertaken cautiously include the corners of the mouth, the vermilion margin of the lips, eyebrows, inner canthi, the free margin of the ala nasi, and the auditory canal, since scarring or retraction of the tissue can occur. Lesions in which treatment might lead to functional compromise or an unsightly cosmetic appearance are best treated by other means. Patients may also opt for another form of treatment when faced with the prospect of a long healing period.

PREOPERATIVE HISTORY AND CONSIDERATIONS

In planning treatment, consideration should be given to the characteristics of the lesion, which technique of cryosurgery to employ, and the expected results. An explanation of the procedure and the anticipated response of the tissue to freezing, including exudation, crusting, re-epithelialization and healing time, should be discussed with the patient.

TREATMENT FACTORS

When tissue is frozen, the surface freezing and extension of the ice ball is visible, yet the depth of freeze cannot be seen. Therefore, the amount of freezing and the temperature reached beneath and surrounding the lesion must be determined by the surgeon. This is referred to as the depth of freeze (depth dose) and consists of measuring certain clinical factors, including observation, palpation, freeze time, thaw time and lateral spread of freeze, as well as the tissue temperature (Fig. 138.1). The proper depth dose estimation is achieved when clinical observations and the tissue temperature, if measured, have reached the desired endpoint[6].

Freeze Time

The freeze time refers to the duration of cooling. It is shorter for a benign lesion than it is for a malignancy, e.g. about 5–7 seconds of freeze time with the open-spray technique will eliminate an actinic keratosis, whereas a freeze time of 45 seconds *and* a double freeze–thaw cycle may be required for a small basal cell carcinoma. The freeze time can be altered by the thickness of the lesion and by the amount of liquid nitrogen being emitted from the spray tip. Spray tips are available with varying aperture diameters and selection is influenced by the freeze time required. When the cryoprobe technique is used, the freeze time is approximately two to three times longer than with the open-spray technique. After freezing with either technique, the tissue is permitted to thaw spontaneously. The thaw time is usually two to three times longer than the freeze time.

Lateral Spread of Freeze

The lateral spread of freeze refers to the freezing of the tissue beyond the margins of the lesion. For some benign lesions, such as verrucae or dermatofibromas, it should reach 2 to 3 mm for the treatment to be successful. For basal cell and squamous cell carcinomas, the lateral spread of freeze should extend at least 3 to 5 mm or more beyond the tumor.

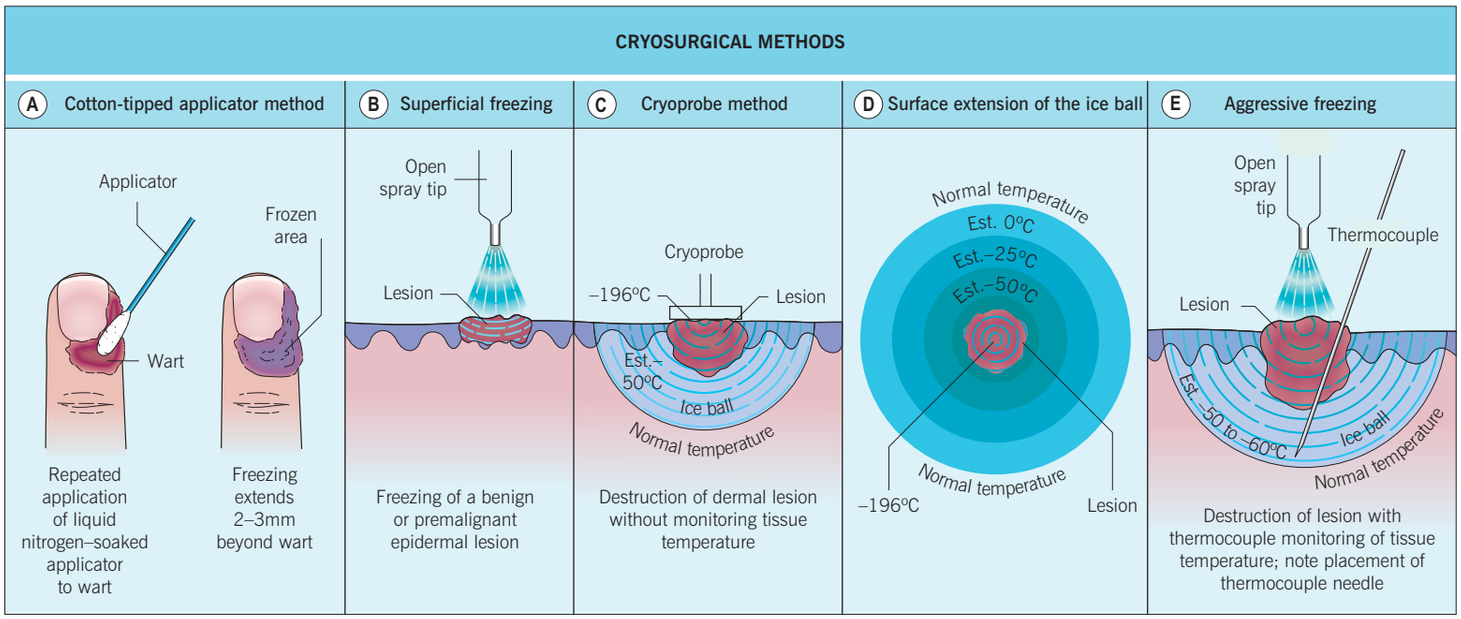


Fig. 138.2 Cryosurgical methods. A The cotton-tipped applicator method used in the treatment of verrucae vulgares, including periungual warts. **B** Superficial freezing used for treating benign lesions and actinic keratoses. **C** Cryoprobe method which is useful for round lesions and those on flat surfaces. **D** Surface extension of the ice ball: note the diminution of the temperature as the ice ball progresses outwards; this can be determined with palpation. **E** Aggressive freezing is deeper and employs thermocouple monitoring of tissue temperature.

Freeze–Thaw Cycle

A freeze–thaw cycle refers to the actual freezing and thawing of the lesion. A single cycle is usually sufficient for benign and premalignant conditions, while a double cycle is recommended for malignant lesions to ensure greater lethality to cancerous cells.

Temperature at the Base of the Tissue

To supplement the clinical estimation, one can measure the temperature at the base of a malignancy with the use of a thermocouple that is mounted in the tip of a 25- to 30-gauge needle. It is inserted into the skin at a 25° to 30° angle, from a point lateral to the lesion, with the tip coming to lie beneath the lesion (Fig. 138.2). This is useful for those lesions that lie more than 3 mm below the skin surface and for medicolegal reasons. Since the temperature recorded is very localized, more than one thermocouple may need to be inserted for a large lesion. The recommended temperature that should be achieved at the base of a malignancy is between –50°C and –60°C (see below).

DESCRIPTION OF TECHNIQUES

There are six techniques of cryosurgical treatment, and the choice of which is employed depends on the lesion and operator preference.

Dipstick Technique

The dipstick technique is the oldest method that employs liquid nitrogen. It consists of application of a saturated, cotton-tipped applicator onto the lesion (Fig. 138.2A). It is a method preferred by the authors for verrucae.

Solidified Carbon Dioxide

A less commonly performed method is crushed solidified carbon dioxide, contained in a disposable towel, and secured around a pestle. It is dipped in acetone and applied lightly onto the skin for mild freezing and exfoliation. This is known as slush therapy and can be used for acne vulgaris, acne cysts, rosacea and flat warts.

Open Spray

The open-spray method is the most frequently used technique, employing liquid nitrogen within a cryosurgical unit that has spray-tip attachments (Fig. 138.2B&E). It is suitable for diverse conditions, including seborrheic keratoses, acne cysts, lentigines, verrucae, dermatofibromas, condyloma acuminatum, actinic keratoses, actinic cheilitis, keratoacanthoma, lentigo maligna, basal cell carcinoma and squamous cell carcinoma. A fine spray of liquid nitrogen is directed at the lesion from a distance of approximately 1 to 2 cm. It is particularly useful for superficial, irregular, or multiple lesions and for those on a curved surface. An intermittent spray of liquid nitrogen of 60 seconds or more is used for malignant lesions, to allow for a deeper freeze.

Cryoprobe

The cryoprobe technique, also known as contact therapy, employs a cryosurgical unit and consists of application of a flat, pre-cooled metal tip that is placed firmly onto the lesion. It is useful for round lesions and those on flat surfaces (Fig. 138.2C). Venous lakes[7], hemangiomas, dermatofibromas, myxoid cysts, sebaceous hyperplasia, xanthelasma, condylomata acuminata, and basal cell and squamous cell carcinomas are examples of lesions that can be managed with this technique. The freeze time can range between 15 and 20 seconds for the benign lesions and up to several minutes for malignancies.

Confined Spray

The confined-spray technique is a variation of the open-spray in which the liquid nitrogen spray is confined within a cone that is held against the skin. Both plastic otoscope cones and specifically designed polycarbonate cones can be used to precisely localize the spray. The freeze time is the same as for the open-spray technique.

Closed Cone

The closed-cone technique also confines the spray, but the freeze time is half that of the open-spray since there is concentration of the liquid nitrogen to a very focal area of skin. This accessory is attached directly to the cryosurgical unit at one end, allowing the nitrogen to enter the cone. It is held against the skin, enabling it to rapidly freeze the lesion.

TREATMENT

Benign Lesions

Freezing is carried out after determination of the type of lesion and selection of the technique of treatment. For benign lesions, one may choose between the cotton-tipped applicator method, a spray technique or the cryoprobe.

For verrucae vulgares and periungual warts, the dipstick or open-spray techniques can be used[8]. The authors prefer the former because of greater control and exactness of the freeze, as well as for its predictability. The cotton-tipped applicator is repeatedly dipped into a cup of liquid nitrogen and applied directly onto the wart until a 2 to 3 mm halo forms around it (see Fig. 138.2A). Large lesions that encircle the nail are also treatable. The freeze time ranges between 20 and 60 seconds. A local anesthetic can be used to alleviate the stinging associated with this type of treatment. A bulla develops after several hours that should extend beyond the wart for treatment to be successful. The blister is caused by separation at the dermal–epidermal junction. The authors recommend sterile puncture of the bulla (approximately 12 hours following freezing) and washing of the site. Healing occurs within 3 weeks, without scarring or damage to the nail plate, and the cosmetic results are excellent. If a lesion recurs, it can be retreated in a similar manner.

Filiform warts are easily eradicated with this technique. They need only freezing of the lesion itself, with no halo, since vesicle formation is not necessary.

Acne comedones, closed or inflamed, can be diminished and improved by short freezing times using an acne spray tip. Small and large acne cysts can be reduced by spraying them between 5 and 15 seconds.

Keloids can be treated with the open-spray technique, alone or in combination with intralesional corticosteroid injections.[9] Deep freezing of the keloid leads to necrosis, crusting, and eventually diminution of the lesion, but multiple treatments may be required. When combined with intralesional corticosteroids, cryotherapy (freeze time of ~20–60 seconds) is performed 1–2 minutes prior to the injection. This prevents freezing of the triamcinolone acetonide suspension and the resulting edema "softens" the keloid, facilitating the injection. Caution is advised when treating keloids in patients with darkly pigmented skin, as depigmentation can occur.

Myxoid cysts are treated by deroofing and freezing for 15 to 20 seconds. One author (EK) reported a cure rate of 76.7% for these cysts, with excellent cosmetic results, using either the open-spray or cryoprobe technique[10].

Lentigines can be eradicated with a very brief freezing of 3 to 4 seconds. Overfreezing should be avoided to prevent hypopigmentation. Studies have shown that judicious use of liquid nitrogen cryotherapy can be as safe and effective as laser treatment for lentigines.

Cryosurgery is effective for eradication of dermatofibromas following shave removal of the surface of the lesion. The freeze time is approximately 15 seconds and either the open-spray or cryoprobe technique can be used.

Premalignant Lesions

Premalignant lesions are treated with one of the spray techniques or a cryoprobe. A local anesthetic and dressings are optional. The prototype lesion for the open-spray technique is an actinic keratosis (see Fig. 138.2B). A shallow crust forms and falls off within 2 weeks (Fig. 138.3). Multiple lesions can be easily treated at one visit[11]. The freeze time for actinic cheilitis ranges between 10 and 20 seconds. Bowen's disease can be treated with a single freeze–thaw cycle and a freeze time of approximately 20 seconds for a small lesion.

Malignant Lesions

In the treatment of malignant lesions, the same volume of tissue must be destroyed by freezing that would have been removed by conservative local excision if that had been the chosen procedure. Complete destruction is possible with cryosurgery. Lesions are treated aggressively using one of the spray techniques or the cryoprobe. Several preoperative biopsy specimens can be obtained to delineate the margins of a tumor. The target site is cleansed and a local anesthetic can be injected. Thermocouple needles can be implanted at this time. The entire tumor is generally frozen in one session using a double freeze–thaw cycle. Through palpation one can ascertain the extent of the ice ball (Fig. 138.2D). The recommended temperature is between –50°C and –60°C at the base of the tumor, and the freeze time is approximately 45 seconds for a 1 cm lesion. During the past two decades, there has been an increased use of colder temperatures, greater use of debulking techniques, and a trend toward more aggressive treatment for basal and invasive squamous cell carcinomas. At the conclusion of treatment, a dry gauze dressing is applied and instructions given to the patient for postoperative care.

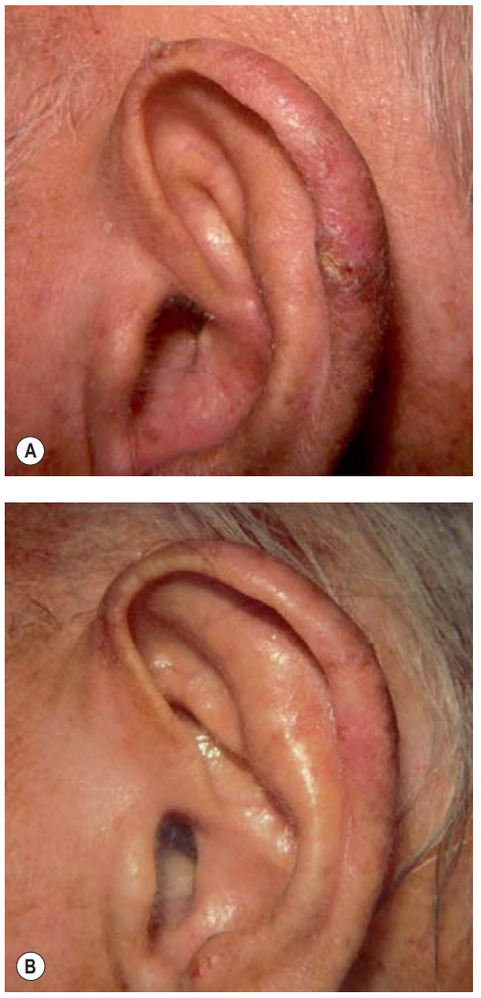


Fig.138.3 Actinic keratoses treated with cryosurgery (open-spray technique). A Prior to treatment. **B** Two to three weeks later.

One author (EK) reported a 5-year cure rate of 99% for 522 primary non-melanoma skin cancers[12]. The overall 30-year cure rate was 98.6% for 4406 basal cell, squamous cell and basosquamous cell carcinomas. Other investigators have obtained similar results[13–15]. Graham[16] had a combined cure rate of 98% for 3593 primary basal cell carcinomas using mostly the open-spray technique. Zacarian[17] reported an 18-year cure rate of 97.4% in the treatment of 4228 carcinomas. A 5-year follow-up study by Nordin et al.[18] of 50 patients with large primary basal cell carcinomas on the nose reported only one recurrence.

Cryosurgery is useful as an alternative modality for lentigo maligna (Fig. 138.4). Aggressive treatment using the open-spray technique is recommended, including freezing to –40°C to –50°C and a 1 cm lateral spread of freeze. With this technique, a recurrence rate of 6.6% was observed[19].

After treatment of a malignancy, the tissue responds in a predictable manner that leads to healing of the wound by second intention. The reactions that ensue after freezing include erythema, vesiculation, edema, exudation and sloughing (Fig. 138.5). Benign and premalignant lesions usually heal within 2 to 4 weeks. Malignant lesions on the face, eyelids, nose, ears and neck generally require 4 to 6 weeks to heal. Large tumors and those on the trunk and extremities take longer to heal, sometimes up to 14 weeks. The cosmetic results after cryosurgery are often equal or superior to those achieved by other modalities. Wounds reproduce natural skin contours and keloid formation typically does not occur. Cryosurgery is advantageous for tumors on the ears and nose because cartilage is relatively resistant to freezing damage and the architecture of the structure is preserved. Lesions on the eyelids and in the vicinity of the lacrimal duct are good candidates for cryosurgery, as the likelihood of ectropion is small and damage to the lacrimal outflow system is rare (Fig. 138.6)[20,21].

Fig. 138.4 A lentigo maligna on the forehead of a 72-year-old man. A The lesion measures 3.1 × 2.5 cm. **B** Cryosurgery to the entire lesion. Note the wide lateral spread of freeze. **C** The healed cryosurgical site 5 months after treatment.

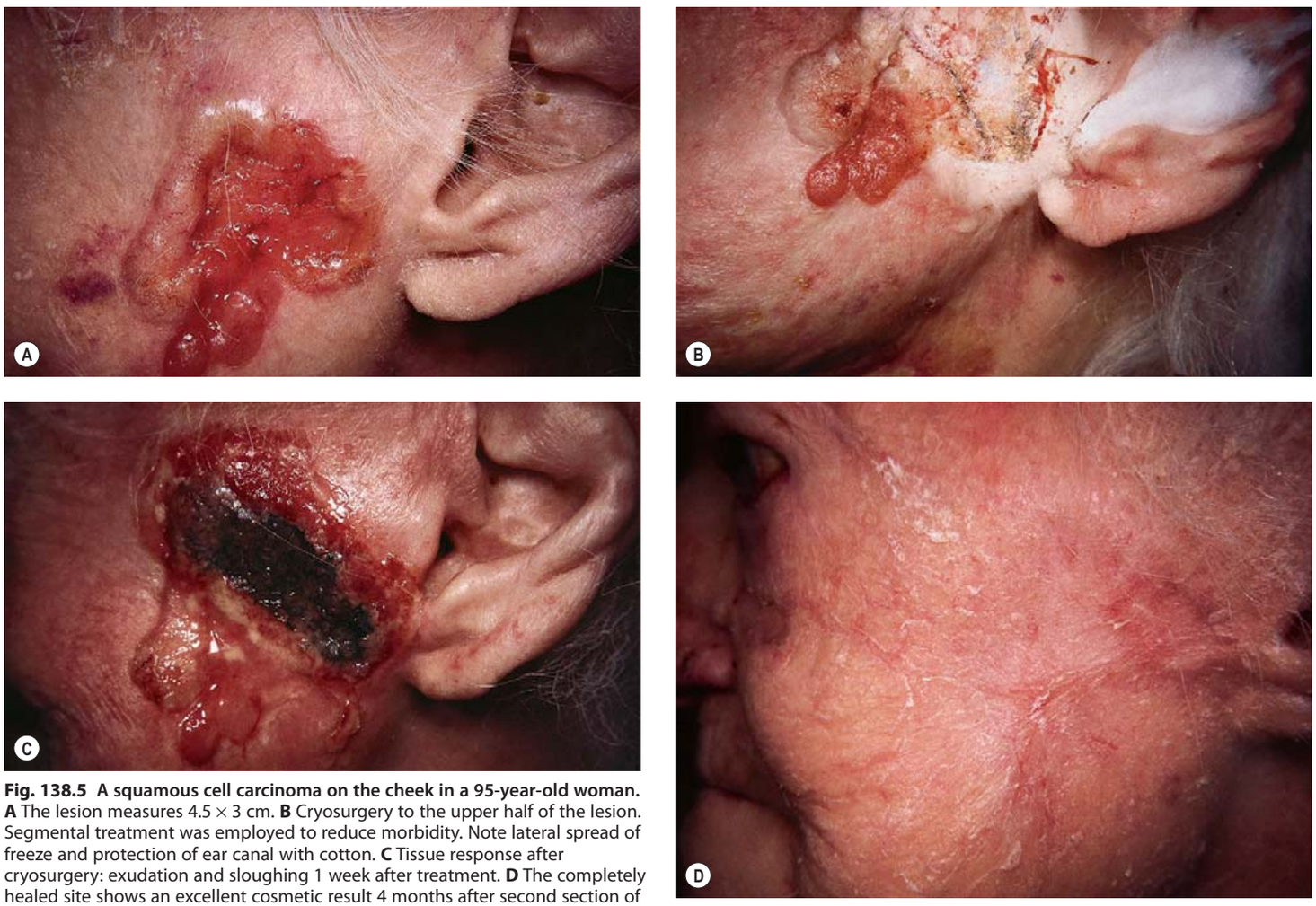


Fig. 138.5 A squamous cell carcinoma on the cheek in a 95-year-old woman. A The lesion measures 4.5 × 3 cm. **B** Cryosurgery to the upper half of the lesion. Segmental treatment was employed to reduce morbidity. Note lateral spread of freeze and protection of ear canal with cotton. **C** Tissue response after cryosurgery: exudation and sloughing 1 week after treatment. **D** The completely healed site shows an excellent cosmetic result 4 months after second section of tumor was treated.

Fig 138.6 Basal cell carcinoma on the right lower eyelid margin. A Papular lesion with telangiectasias on the eyelid margin of an 82-year-old woman. **B** Cryosurgery to lesion: note placement of thermocouple needle and protection of eye. **C** The healed cryosurgical site 6 months after treatment. Excellent cosmetic result; note loss of cilia.

VARIATIONS AND UNUSUAL SITUATIONS

If a lesion is thick or bulky, it is beneficial to reduce it to a shallow one by debulking with a curette, scissors or electrosurgery. This is done because the mass is detrimental to proper treatment, either by hindering the advancement of the ice ball, misjudging the placement of thermocouple needles or by prevention of proper assessment of the lateral margins and base of the lesion. After debulking, hemostasis must be obtained before proceeding with cryosurgery.

It is sometimes beneficial to inject lidocaine under a lesion for the purpose of lifting it away from underlying tissue or superficial nerves. Examples include the treatment of warts or actinic keratoses on the fingers and hands, and malignancies on the head, neck and scalp.

Selected large basal or squamous cell carcinomas are amenable to cryosurgery using segmental treatment (see Fig. 138.5). A lesion is treated in stages after being divided into sections and can be treated either on the same day or at subsequent visits. Each section is treated according to its characteristics and depth. Wound healing is not hindered by overlapping treatment at the margins.

POSTOPERATIVE CARE

Postoperative care varies according to the lesion, location and depth of freeze. Most benign lesions require little or no aftercare except for ordinary washing. A shallow eschar develops that falls off spontaneously. In some instances, a watery exudate may develop beneath an eschar or excessive granulation tissue may develop. This can be treated by debridement with a curette or simply cleansed with soap and water. An antibiotic ointment can be applied.

In the case of cutaneous malignancies, extensive exudation begins within 24 hours and diminishes in an orderly manner as the wound heals and re-epithelializes. The authors recommend washing with soap and water four times daily in the exudative stage and less often during the granulating period. A dry gauze dressing is initially applied, and, as the wound begins to heal, an antibiotic ointment is used. In some instances, oral antibiotics are beneficial, such as for lesions on the legs and ears, or where otherwise indicated. Bullae may form at the periphery of a large lesion and this is not a complication. The bullae are drained and healing is not affected.

COMPLICATIONS

The incidence of complications after cryosurgery is low. It is important to distinguish between expected sequelae and untoward results. A complication may arise in several ways: (1) as an unexpected event (e.g. infection); (2) as an unsatisfactory cosmetic result (e.g. hypertrophic scarring); and (3) as a more pronounced response of the tissue to freezing than had been anticipated (e.g. residual hypopigmentation).

Temporary complications may develop during the healing stage or after completion of treatment and generally resolve spontaneously. Commonly described examples include edema of the eyelids or ears and hypertrophic scarring. Edema, particularly periorbital, can be minimized or ameliorated with open wet compresses, corticosteroid cream or a short course of systemic corticosteroids. One author (EK) reported using an intramuscular injection of 4 mg betamethasone sodium phosphate 30 minutes before treatment, followed by an adult dose of oral prednisone (20 mg/day for 3 days)[22]. Occasionally, hypertrophic scarring may develop, particularly after treatment of a large lesion, but this always improves and resolves with time, usually within months. Intralesional corticosteroid injections can hasten resolution. Uncommon reactions include delayed bleeding, headache, paresthesia, neuropathy, secondary infection, syncope, nitrogen gas insufflation (gas bubbles in skin), milia, hyperpigmentation and pyogenic granuloma.

Permanent complications include tissue retraction (e.g. lips, eyebrows, ala nasi), tissue defect, depigmentation, notching, ectropion, alopecia and contour defects. Improvement sometimes occurs, especially in elderly patients with skin laxity.

FUTURE TRENDS

Cryosurgery is an old technique that will remain very popular for the treatment of actinic keratoses and warts. The technique has remained relatively unchanged for several decades. It is far less commonly performed than excision and Mohs surgery for cutaneous malignancies, and the expert use of cryoprobes has become an art performed by a limited number of dermatologists. The authors feel that new instrumentation and techniques may be forthcoming, e.g. "fractional" cryosurgery, the ability to measure the skin surface temperature during cryotherapy.

REFERENCES

1. Kuflik EG, Gage AA. Cryobiology. In: Cryosurgical Treatment for Skin Cancer. New York: Igaku-Shoin, 1990:35–51.
2. Kuflik EG. Cryosurgery updated. J Am Acad Dermatol. 1994;31:925–44.
3. Yamada S, Tsubouchi S. Rapid cell death and cell population recovery in mouse skin epidermis after freezing. Cryobiology. 1976;13:317–27.
4. Gabbi T, de Lacerda D, Maruta C, et al. Giant superficial basal cell carcinoma treated with cryosurgery. Dermatol Surg. 2008;34:1441–2.
5. Jaramillo-Ayerbe F. Cryosurgery in difficult to treat basal cell carcinoma. Int J Dermatol. 2000;39:223–9.
6. Torre D. Depth dose in cryosurgery. J Dermatol Surg Oncol. 1983;9:219–25.
7. Suhonen R, Kuflik EG. Venous lakes treated by liquid nitrogen cryosurgery. Br J Dermatol. 1997;137:1018–19.
8. Kuflik EG. Cryosurgical treatment of periungual warts. J Dermatol Surg Oncol. 1984;10:673–6.
9. Fikrle T, Pizinger K. Cryosurgery in the treatment of earlobe keloids: report of seven cases. Dermatol Surg. 2005;31:1728–31.
10. Kuflik EG. Specific indications for cryosurgery of the nail unit. Myxoid cysts and periungual verrucae. J Dermatol Surg Oncol. 1992;18:702–6.
11. Lubritz RR, Smolewski SA. Cryosurgery cure rate of actinic keratoses. J Am Acad Dermatol. 1982;7: 631–2.
12. Kuflik EG. Cryosurgery for skin cancer: 30-year experience and cures rates. Dermatol Surg. 2004;24: 297–300.
13. Bernardeau K, Derancourt C, Cambie M, et al. Cryosurgery of basal cell carcinoma: a study of 358 patients. Ann Dermatol Venereol. 2000;127:175–9.
14. Kokoszka A, Scheinfeld N. Evidence-based review of the use of cryosurgery in treatment of basal cell carcinoma. Dermatol Surg. 2003;29:566–71.
15. Nordin P, Stenquist B. Five-year results of curettage-cryosurgery for 100 consecutive auricular non-melanoma skin cancers. J Laryngol Otol. 2002;116: 893–8.
16. Graham GF. Cryosurgery. Clin Plast Surg. 1993;20: 131–47.
17. Zacarian SA. Cryosurgery of cutaneous carcinomas: an 18-year study of 3022 patients with 4228 carcinomas. J Am Acad Dermatol. 1983;9:947–56.
18. Nordin P, Larko O, Stenquist B. Five-year results of curettage-cryosurgery of selected large basal cell carcinomas on the nose: an alternative treatment in a geographical area underserved by Mohs' surgery. Br J Dermatol. 1997;136:180–3.
19. Kuflik EG, Gage AA. Cryosurgery for lentigo maligna. J Am Acad Dermatol. 1994;31:75–8.
20. Kuflik EG. Cryosurgery for carcinomas of the eyelids: a 12-year experience. J Dermatol Surg Oncol. 1985;11:243–6.
21. Tuppurainen K. Cryotherapy for eyelid and periocular basal cell carcinomas: outcome in 166 cases over an 8-year period. Graefes Arch Clin Exp Ophthalmol. 1995;233:205–8.
22. Kuflik EG, Webb W. Effects of systemic corticosteroids on post-cryosurgical edema and other manifestations of the inflammatory response. J Dermatol Surg Oncol. 1985;11:464–8.

This page intentionally left blank

139 Radiotherapy

Michael Veness and Shawn W Richards

Chapter Contents

Radiotherapy of benign skin disorders *2293*
Radiotherapy of *in situ* cutaneous malignancies *2294*
Palliation *2298*

Synonyms: ■ Radiation treatment ■ Radiation therapy ■ X-ray therapy

Key features

- Radiotherapy is an important modality in the treatment of patients with skin malignancies
- Radiotherapy may reduce morbidity (as compared to surgery), decrease the risk of recurrent disease, and even be life-saving
- Although most patients with skin cancer are adequately treated by modalities other than radiotherapy, there are factors that may favor its recommendation (e.g. comorbidities, location)
- Modern radiotherapy has an established role as a definitive, adjuvant or palliative treatment
- Treating benign skin disease with radiotherapy must always be carefully considered in light of the risk of radiation-induced malignancy, especially in younger patients

BASICS OF RADIOTHERAPY

Indications

In dermatology, the primary role of radiotherapy is to treat basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (SCC; see Ch. 108)[1]. It is also used to treat less common, but potentially aggressive, cutaneous malignancies and, occasionally, benign diseases. The former include Merkel cell carcinoma, Kaposi sarcoma (AIDS- and non-AIDS-related), angiosarcoma, adnexal carcinoma, lymphoma and melanoma (especially lentigo maligna).

While the majority of skin cancers are amenable to excision or other treatment modalities (e.g. electrodessication and curettage) which are often more cost-effective, there are clinical settings where radiotherapy is favored. For example, *definitive* radiotherapy is often recommended when the outcome (functional and/or cosmetic) is likely to be better with radiotherapy than with surgery, especially in the situation where the clinician is constrained by the site or size of the tumor. Likewise, elderly patients with advanced lesions for whom complex surgery is best avoided are also excellent candidates for radiotherapy. The aim of *adjuvant* radiotherapy is to reduce the risk of recurrence, whereas *palliative* radiotherapy plays an important role in patients with advanced and/or incurable disease.

Mechanism of action

X-rays are a powerful form of ionizing electromagnetic radiation and the lethal damage they produce within double-stranded DNA represents the basis for radiation therapy[2]. When X-rays (often referred to as photons) are absorbed by biological matter, an electron may be ejected from an atom with the local release of large amounts of energy. The result is that replicating, i.e. more rapidly dividing, malignant cells undergo a mitotic death. Although normal adjacent tissues maintain mechanisms for repair following sublethal damage, there are limitations as to the dose of ionizing radiation normal tissue can tolerate, beyond which late reactions arise (see below). Enhancement of the difference in the response of malignant cells versus normal tissue is accomplished via delivery of the radiation in small divided doses (referred to as fractions).

Treatment machines

In the modern era of radiation oncology, high-energy megavoltage (mV) photons (6–25 mV) are generated by a linear accelerator (LINAC) located within a heavily shielded concrete bunker. One of the advantages of megavoltage radiotherapy is its ability to treat deep-seated internal malignancies with relative skin sparing. However, when treating cutaneous lesions, deep beam penetration and skin sparing are usually not desirable. The delivery of *low-energy* kilovoltage (kV) photons (50–300 kVp) by a *superficial/orthovoltage* machine is preferable, as it avoids both skin sparing and the irradiation of deeper tissues. With low-energy photons, tissue penetration is measured in millimeters to centimeters. Shielding is achieved by applying 3–4 mm of lead either directly onto the skin or by using an internal (e.g. eye or mouth) shield.

Terminology

The International Unit of radiotherapy is a Gray (Gy)[3]. One Gy is equivalent to 100 cGy or 100 rads (in the older terminology). A fraction of radiotherapy refers to the dose delivered in one treatment. A typical course of radiotherapy for a cutaneous malignancy in an otherwise healthy patient is 50 Gy delivered in 20 daily (Monday through Friday) fractions (2.5 Gy/fraction). Historically, patients were often administered only two or three fractions per week. At the very least, this latter schedule simply protracted the overall treatment period, but in some cases may have resulted in decreased local control. The daily outpatient irradiations are only minutes in duration and treatment regimens usually consist of 10 to 30 weekday visits.

Radiotherapy doses

Hypofractionation refers to the delivery of larger doses per fraction (4–7 Gy). However, when the dose per fraction is increased, the total dose delivered is then decreased. For example, commonly prescribed dose fractionation schedules are 45 Gy in 15 (3 Gy) fractions, 40 Gy in 10 (4 Gy) fractions, and 35 Gy in 5 (7 Gy) fractions. Using a 2 Gy per fraction equivalent, this variation in the total dose results when the biological effective dose (BED) needed for eradicating a tumor is calculated[4]. Despite this, the data suggest that, at least for small (≤2 cm) SCCs and BCCs, there is not a marked dose–response, and local control is similar whether a patient receives 40 Gy in 10 fractions (47 Gy BED) or 50 Gy in 20 fractions (52 Gy BED). However, when the tumors are larger or more infiltrative, better local control is achieved with a BED of around 60 Gy. Of note, late effects increase as the total dose and dose per fraction increase and it is these late effects that will impact on cosmesis and late tissue damage (necrosis).

Radiation physics

The qualities and "hardness" of a superficial/orthovoltage photon beam are determined by the placement of filters within the radiation beam[5]. In radiation physics, a standard term is the "half value layer" (HVL) which refers to the thickness of a material (often copper [Cu] or aluminum [Al]) that is required to reduce the beam intensity by 50%. The

filter serves to remove the softer photon component and improve the penetration quality of the beam. A second concept is half value depth (D½) and here filters are used to achieve radiation with a D½ that corresponds to tumor depth. For each superficial and orthovoltage beam, at least one to two filters should be available.

Low-energy photons (superficial/orthovoltage) and common cutaneous protocols

A typical 100 kVp superficial photon beam with an HVL of 7 mm of aluminum will deliver 100% of prescribed dose to the surface, 85% at 5 mm, and 70% at 10 mm. A 250 kVp orthovoltage beam with an HVL of 2.5 mm of copper will deliver 95% of prescribed dose at 5 mm and 90% at 10 mm. Most superficial lesions (<5 mm depth) will be adequately treated by a 100 kVp beam with an HVL of 6–8 mm aluminum (or similar). Deeper, more invasive lesions (5–10 mm in depth) are adequately encompassed by a 250 kVp orthovoltage beam with an HVL of 2–4 mm copper.

Some clinicians estimate tumor thickness and then choose an appropriate beam energy and HVL that will achieve 90–95% of the prescribed dose at the depth of the tumor. However, this latter approach requires an accurate estimate of tumor thickness.

The photoelectric effect is a phenomenon whereby underlying bone or cartilage receives a higher dose of radiation when low-energy photons are used. This is not the case with electrons (see below) and is used by some clinicians as a justification for the use of electrons when treating lesions in close proximity to bone or cartilage. However, there are no convincing data that the late effects in these tissues are markedly increased when low-energy photons are used instead of electrons[6].

Grenz ray treatment

Grenz rays are very-low-energy (5–15 kVp) photons that penetrate only superficially (0.5–1 mm)[7]. Nowadays, the use of this modality is very limited, but, in the past, several inflammatory dermatoses (e.g. chronic hand dermatitis) were treated with grenz rays. The latter are reported to be relatively safe in lifetime doses of up to 50 Gy to treated areas. Nevertheless, grenz rays should *never* be viewed as first-line therapy. Worldwide, the machines used to generate these very soft X-rays are rare and are not utilized in modern departments of radiation oncology.

Electrons

A linear accelerator can also generate electrons and they are utilized in a variety of treatment settings. Unlike X-rays, electrons are a particulate radiation that carries a negative charge. Low-energy electrons (6–8 MeV [million electron volts]) offer an alternative to low-energy photons when treating cutaneous tumors, but the former do have some disadvantages[8]. For example, electron beams are relatively skin-sparing (Fig. 139.1), and, as a result, a tissue equivalent bolus needs to be placed on the skin surface (Fig. 139.2). Also, utilizing electron beams for small treatment fields (<4 cm^2) may result in tumor underdosing at the deepest extent of the tumor.

Electrons offer the advantage of a rapid linear decline in dose beyond a well-defined tissue depth that is a function of the selected beam energy (see Fig. 139.1). For example, a 6 MeV electron beam provides some of its dose (~87%) at the surface, but deposits 100% of the specified dose at a depth of approximately 1 cm. Using a higher-energy beam will result in deposition of a higher percentage of the dose at the skin surface, but with a higher dose to subcutaneous tissues. On the other hand, if a tissue equivalent bolus of 1 cm is applied in conjunction with a 6 MeV beam, close to 100% of the desired dose will be obtained at the skin surface (see Fig. 139.2). All of the deposition of dose will be brought 1 cm closer to the skin surface, further minimizing the dose to underlying structures.

In addition, tumors treated with electrons require 10–20 mm margins as a consequence of a wider penumbra (dose drop-off at the field edge). Electrons also have a lower relative biological effectiveness (RBE) in comparison to photons, leading some clinicians to recommend a 10–15% increase in total dose to compensate.

In summary, there are data to suggest that local control of skin tumors may not be as good with electrons when compared to low-energy photons. However, this may reflect an under-appreciation by some clinicians of the intricacies of using small field electrons to treat skin cancers.

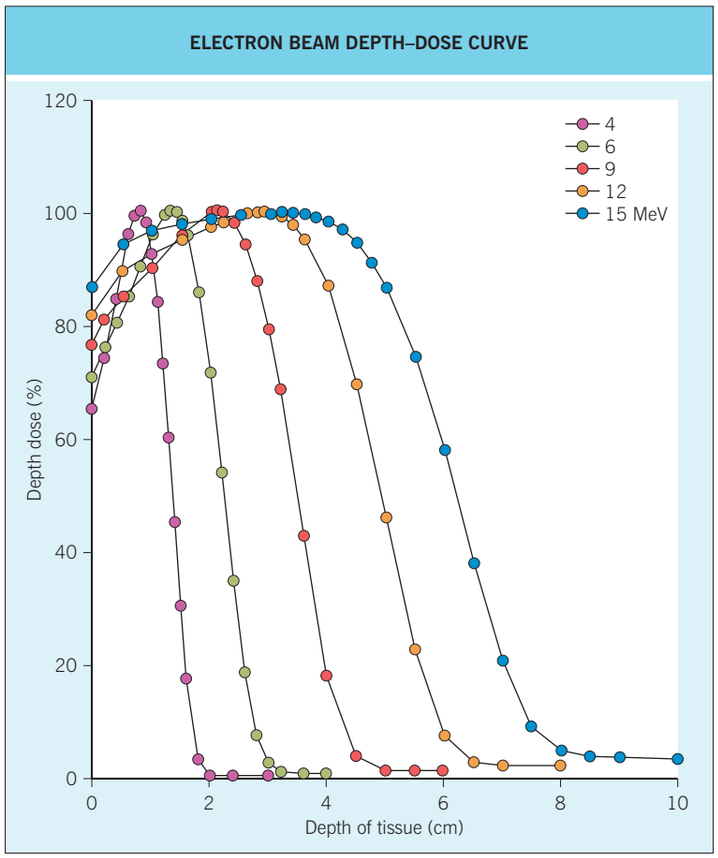


Fig. 139.1 Electron beam depth-dose curve. Electrons offer the advantage of a rapid linear decline in dose beyond a well-defined tissue depth that is a function of the selected beam energy. *Courtesy, Lynn Wilson, MD.*

Brachytherapy

Brachytherapy is a type of radiotherapy that is delivered by the direct application of a radioactive source to involved tissues. In the vast majority of clinical settings, radioactive molds and implants offer little advantage over the range of energies of external beam photons and electrons currently available. As a result, they are rarely used nowadays to treat BCCs and SCCs. Nonetheless, some clinicians have advocated using radioactive molds for areas with poor vascularity and slow rates of healing (e.g. the anterior lower limb or dorsum of the hand)[9]. However, suitable lesions need to be superficial (<3–4 mm in depth) and there are radiation safety issues if this approach is utilized.

Office-based radiotherapy

Office-based superficial radiotherapy was once the standard modality by which dermatologists treated skin cancer[10]. Typical machines delivered photons of 70–100 kVp with a depth dose suitable for most patients with cutaneous malignancies. However, in the past two decades, the rising cost of radiotherapy machines combined with increased enthusiasm and training in dermatologic surgery have led to a significant decline in office-based radiotherapy. Nowadays, radiotherapy for skin cancer is performed almost exclusively by radiation oncologists. However, this does not diminish the need for dermatologists to understand the role of radiotherapy and to become familiar with its indications and treatment regimens, since dermatologists frequently diagnose skin cancer and outline therapeutic options.

Advantages of radiotherapy

Radiotherapy offers the advantage of a non-surgical approach, thereby avoiding surgical morbidity, scarring and the need for reconstruction. In situations where reconstruction with grafts or flaps is required, improved cosmesis may result from radiotherapy[11]. Radiotherapy fields

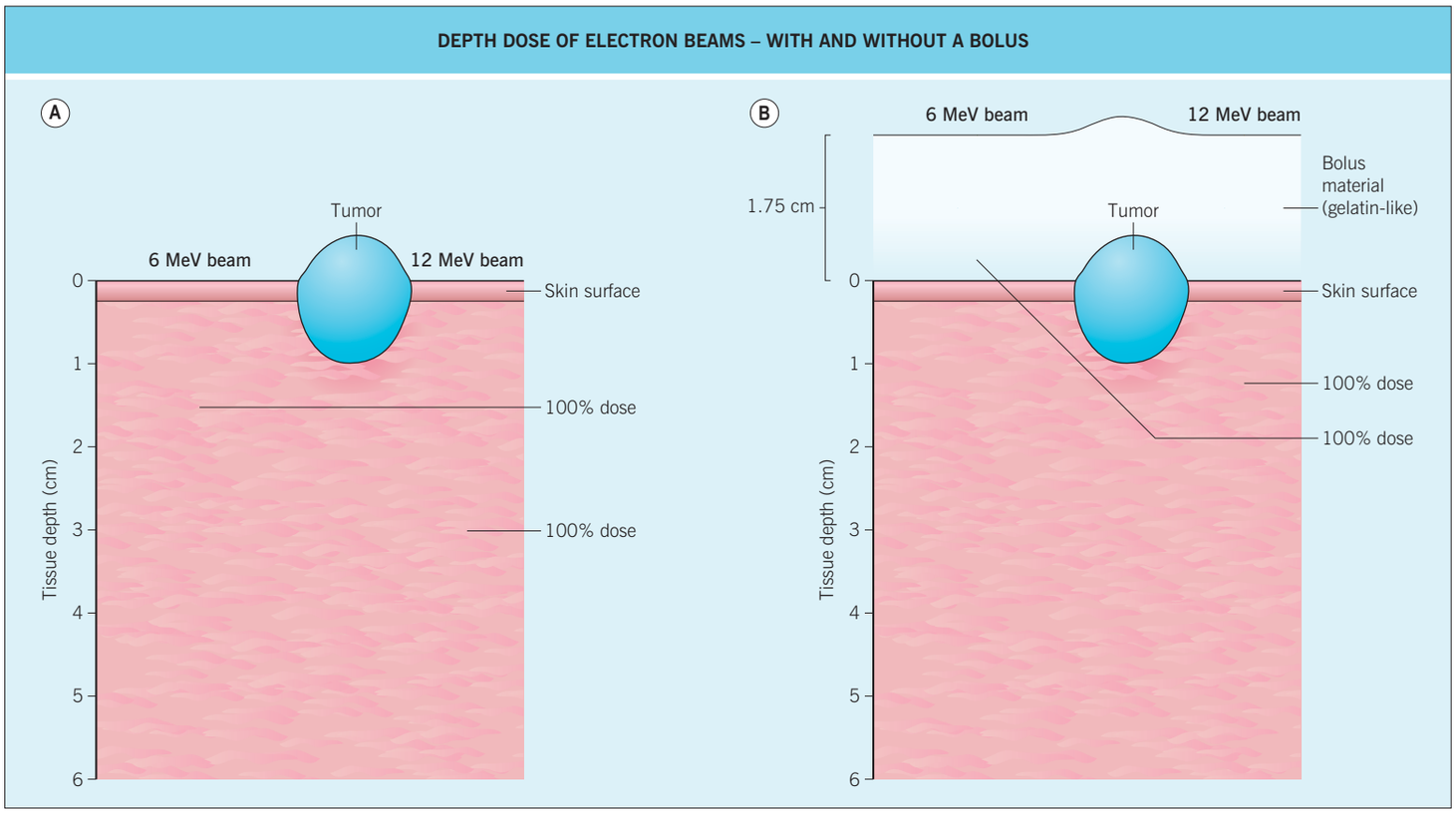


Fig. 139.2 Depth dose of electron beams – with and without a bolus. A Beams with a dose of 6 MeV and 12 MeV. **B** Demonstration of the bolus effect whereby a more appropriate dose of radiation is obtained at the skin surface. *Courtesy, Lynn Wilson, MD.*

can also be tailored with generous margins in order to encompass "at-risk" areas (e.g. possible sites of clinically inapparent tumor extensions) that, if surgically approached, would require involved and complex surgery. In addition, standard oncologic excision margins in certain sites are often difficult to achieve without causing surgical morbidity; such sites include the midface triangle, i.e. the periorbital region (especially the medial canthus), the lower eyelid, nose (especially the ala nasi and nasal tip), nasolabial fold, lip and chin.

Disadvantages of radiotherapy

Radiotherapy does have its disadvantages; in particular, most patients require a protracted course of treatment compared to what is often a simple outpatient excision. Patients should also be informed that because of the risk of serious late effects such as soft tissue and cartilage necrosis, a second course of definitive radiotherapy cannot be delivered to the same site. In addition, the reduced "quality" of irradiated skin makes subsequent surgery difficult if the tumor recurs or persists following radiation therapy. Lastly, individuals with xeroderma pigmentosum or nevoid basal cell carcinoma syndrome should not be irradiated owing to their marked predisposition for developing multiple and recurrent skin cancers, often at a young age.

Lesions that have deeply invaded cartilage or bone often do better with a combination of excision plus adjuvant radiotherapy, although definitive radiotherapy still remains an option (local control 60–70%). Radiotherapy of lesions located on the foot, anterior lower leg or dorsum of the hand, although not contraindicated, should be avoided if possible; lesions in such sites are best treated with excision. Unfortunately, radiotherapy to poorly vascularized, edematous tissues is often associated with poor healing. Skin cancers arising in sites of chronic ulceration, trauma or thermal burns should not be irradiated if at all possible. These sites often have poor vascularity and consequently poor healing. Patients with scleroderma and other causes of cutaneous fibrosis are also best treated by surgical means, as radiotherapy may enhance the fibrosis and lead to poor healing.

Radiotherapy has a very small (~1 in 1000) risk of causing a radiation-induced in-field malignancy (often soft tissue/bone sarcoma) 10–15 or more years after exposure[12]. However, these data were obtained from studies involving many different malignancies treated by various techniques and dosing schedules. It is likely that with modern radiotherapeutic techniques as well as the smaller volumes being irradiated when treating skin cancers, a figure of 1 in 1000 represents an overestimate of the real risk, which is actually rare. Despite this, in younger patients (<50 years of age), this is an important issue and patients must be informed of the risk.

RADIOTHERAPY OF BENIGN SKIN DISORDERS

Background

The role of radiotherapy in treating benign disorders has markedly diminished over the past several decades. It is no longer ethically acceptable to offer radiotherapy as a treatment for acne, warts, hirsutism or tinea capitis. The role of radiotherapy in treating inflammatory skin conditions (e.g. dermatitis, psoriasis, lichen planus) is primarily historical due to efficacious alternative treatments (e.g. corticosteroids, phototherapy) and the risk of exposing patients to ionizing radiation. Previous studies suggested that low-dose (8–12 Gy) soft X-rays often resulted in satisfactory resolution of symptoms, especially in eczematous conditions, but clinicians must carefully weigh the risks versus the benefits before recommending radiotherapy. Specific guidelines have been published regarding the risk/benefit ratio and obtaining informed consent when radiotherapy for benign disorders is being considered[13].

Keloids

Recurrent keloids, often refractory to re-excision and intralesional corticosteroid injections, can have significant cosmetic and psychologic sequelae for patients, many of whom are young women. The addition of low-dose (12–16 Gy) adjuvant radiotherapy delivered in three to four fractions, beginning within 24–48 hours following surgery, can markedly and safely reduce the incidence of recurrence[14]. A common site is the earlobe and patients can be treated with low-energy photons plus lead shielding of surrounding tissues. Young patients with keloids of the lower anterior neck (in close proximity to the thyroid gland) should not be irradiated.

Pseudolymphomas

Cutaneous pseudolymphoma (cutaneous lymphoid hyperplasia) often arises on the face (see Ch. 121). When lesions fail to respond to intralesional corticosteroids, low-dose fractionated radiotherapy (10–15 Gy in five fractions) utilizing low-energy photons is an efficacious treatment option with minimal, if any, side effects.

Scleredema

There are a few case reports of the use of electron beam therapy for patients with scleredema. Obviously, it would be reserved for those with recalcitrant disease and functional impairment.

RADIOTHERAPY OF *IN SITU* CUTANEOUS MALIGNANCIES

Squamous cell carcinoma *in situ* (Bowen's disease)

Radiotherapy can be used, albeit infrequently, to treat SCC *in situ*. The malignancy is limited to the epidermis and its appendages, arises more commonly in sun-exposed sites, and usually presents as a slowly growing scaly erythematous plaque. A biopsy is important to exclude the possibility of eczema or psoriasis. Only a small minority (<5%) become invasive SCCs, although this may be higher (10–30%) in genital lesions such as erythroplasia of Queyrat. Patients are treated with 40–50 Gy in 10–20 fractions using superficial low-energy photons (110–150 kVp), with reported local control rates of 98–100%[15].

Patients with widespread actinic keratoses have been treated with radiotherapy under special circumstances. Given that other very effective therapies are readily available (see Ch. 108), radiotherapy should not be considered a first-line treatment modality.

Lentigo maligna

Lentigo maligna (melanoma *in situ* arising within photodamaged skin) often presents as a longstanding and large-sized hyperpigmented patch on the face of elderly patients (see Ch. 113). The size and location often preclude simple excision, and radiotherapy remains a well-established option with excellent control rates (Fig. 139.3)[16]. Reported doses range from 35 to 100 Gy administered in 5–10 fractions, i.e. large doses per fraction. However, dose fractionation schedules of 40–50 Gy in 10–20 fractions would also be efficacious[17].

Fig. 139.3 Lentigo maligna (melanoma *in situ*). A An 82-year-old man with a lentigo maligna on his right cheek. **B** Three months after superficial radiotherapy (45 Gy in 15 daily fractions, 120 kVp, HVL 4.2 mm Al).

RADIOTHERAPY OF INVASIVE CARCINOMAS, SARCOMAS AND LYMPHOMAS

Basal Cell Carcinoma

Definitive radiotherapy

BCCs – in particular, primary tumors <2 cm in diameter – can be treated with a number of therapeutic modalities. However, there is a paucity of randomized controlled trials comparing these different modalities. In a recent Cochrane Review, the authors analyzed the published results of seven different treatment categories[18]. Although they suggested the need for further research, surgery and radiotherapy appeared to be the two most efficacious modalities, with surgery probably leading to the lowest recurrence rates[18]. Of note, Mohs micrographic surgery is said to result in some of the highest cure rates.

While local control rates (90–95%) for either excision or radiotherapy are probably similar, management decisions are often based on other factors (Table 139.1). For example, radiotherapy would be favored in an elderly patient with a BCC located on the nasal tip or nasal alae (Fig. 139.4). In the locations outlined in Table 139.1, excision followed by primary closure is often difficult to accomplish and grafts or flaps are frequently required if surgical excision is chosen (Fig. 139.5). In addition, achieving negative deep margins via excision may be difficult in these locations. Although larger lesions (>20 mm) can still be eradicated via definitive radiotherapy (see below), with increasing size and depth of invasion, local control rates decrease. Therefore, surgery combined with adjuvant radiotherapy is often recommended in order to try to achieve better local control.

Superficial BCCs that involve large areas are also treated with radiotherapy (Fig. 139.6), although alternatives such as photodynamic therapy, curettage and topical imiquimod are reasonable options. It is important to note that tumors can take many weeks to completely regress after radiotherapy and, therefore, early re-biopsy is not recommended. Dose fractionation schedules vary and are determined by patient and tumor factors (see below).

PATIENT FACTORS AND TUMOR CHARACTERISTICS THAT FAVOR RADIOTHERAPY	
Patient factors	Older age (>70 years)
	Patient preference (avoidance of surgery)
	Receiving medications that affect coagulation and platelet function
	Significant medical comorbidities
Tumor characteristics	Site: Ala nasi, nasal tip, nasal bridge, lower eyelid, medial canthus, helix
	Size/depth: Extensive and superficial
	Stage: Locally advanced requiring complex surgery

Table 139.1 Patient factors and tumor characteristics that favor radiotherapy. Many of these indications are relative.

Fig. 139.4 Superficial pigmented basal cell carcinoma. A 77-year-old woman with a 1 cm superficial pigmented basal cell carcinoma (BCC) on the nasal tip, a location where excision followed by primary closure can be difficult. The BCC was treated with superficial energy photons (45 Gy in 15 daily fractions, 100 kVp, HVL 7 mm Al).

Fig. 139.5 Nodular basal cell carcinoma. A A 56-year-old woman with a 1.5 cm nodular basal cell carcinoma of the right medial canthus. The patient received 55 Gy in 25 daily fractions using orthovoltage energy photons (250 kVp, HVL 2.5 mm Cu) following pre-treatment insertion of an internal eye shield. **B** A 10 mm radiotherapy field margin has been placed around the patient's tumor in order to encompass both macroscopic disease and possible surrounding microscopic (subclinical) spread. **C** At completion of radiotherapy, the tumor has regressed markedly. Note the confluent erythema demarcating the treatment field.

Fig. 139.6 Extensive basal cell carcinoma. A An elderly woman with a large basal cell carcinoma occupying much of the left temple region. **B** Three months after 40 Gy in 10 daily fractions using superficial energy photons (100 kVp, HVL 7 mm Al).

Adjuvant (postoperative) radiotherapy

A recommendation for radiotherapy is often made in the setting of incomplete excision of a BCC. A positive deep margin is always a concern, especially when a local flap has been used for reconstruction, because deep recurrences can be difficult to detect. In particular, undetected deep recurrences of tumors located within the midface and periorbital region may be associated with significant local morbidity. It is accepted that at least 20–30% of incompletely excised BCCs will recur[19] and re-excision is often recommended in order to achieve a negative margin[20]. In one study, for example, residual BCC was found in 45% of the re-excised specimens[19]. However, in some circumstances, the involved margin precludes simple re-excision (e.g. the periosteum of the nose). In these situations, radiotherapy is an option. The aim of adjuvant radiotherapy is to reduce the incidence of local recurrence by eradicating residual microscopic BCC. One study of 33 patients with a medial canthus BCC (and positive excisional margins) reported a 100% local control rate with adjuvant radiotherapy[20]. In a Canadian trial, the addition of adjuvant radiotherapy improved the 5-year local control rate from 61% to 91%[21]. Not surprisingly, the 10-year local control rates were similar (92% vs 90%), as the majority of recurrences were successfully salvaged via surgery.

Squamous Cell Carcinoma

Definitive radiotherapy

The approach to treating patients with cutaneous SCC is influenced by the small risk (<5%[22] to <1%) of metastatic spread to regional lymph nodes and the need to achieve local control. Of note, some patients can be considered as having high-risk SCC when certain unfavorable features are present; these include thickness >2 mm and especially >6 mm, diameter >2 cm, recurrent tumor, high-grade (i.e. poorly differentiated) histology, neurotropism, location on or around the ear or lower lip, and immunosuppressed host. These SCCs have a greater risk of developing recurrences and metastatic nodal disease[23,24].

In general, high-risk patients should have lesions excised with wider margins (see below) and be followed closely for at least 5 years[25]. However, depending upon the circumstances (see Table 139.1), some patients are treated with definitive (or adjuvant) radiotherapy. To date, there is no consensus as to which high-risk patients should be offered elective treatment (e.g. surgical, radiotherapy) of regional lymph nodes, but future sentinel lymph node biopsy studies may help resolve this issue. Patient stratification, based upon depth of invasion, may also influence recommendations. In a recent study of 615 patients with SCC followed for an average of 43 months, no metastases were seen with tumors ≤2 mm in depth, while metastases developed in 16% of those patients with tumors >6 mm in depth[26].

The aim in excising any SCC is to achieve adequate margins, taking into consideration cosmesis and function. Surgical excision of SCC is often more extensive than for BCC, with wider margins (>5 mm) usually recommended[27], and it may entail the Mohs micrographic surgical technique or wide local excision under general anesthesia with flap/graft reconstruction. In a study of cutaneous SCCs <2 cm in diameter, the investigators reported that with a 4 mm excision margin, 95% of the tumors were removed with negative margins. For SCCs >2 cm, a 6 mm excision margin led to negative margins in 95% of the cases[28]. Of note, the local control rate for SCCs is, on average, 10–15% lower than for equivalent-sized BCCs[1,4,29].

It is generally not appropriate to merely observe an incompletely excised SCC. Recurrent SCC is associated with a higher incidence of regional metastases (compared to the initial presentation), with rates of up to 25–45%, depending on the tumor location[22]. Both recurrent BCC and recurrent SCC are associated with a control rate that is lower by at least 10% (compared to untreated lesions of equivalent size), again emphasizing the need to reduce the risk of local relapse[4,28].

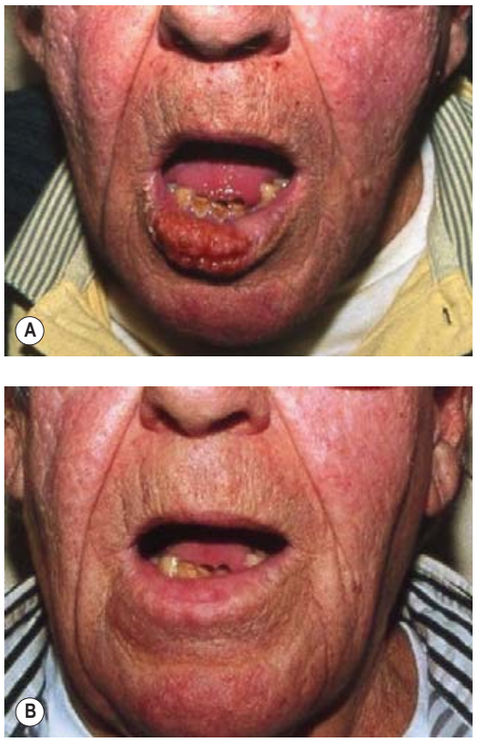


Fig. 139.7 Squamous cell carcinoma. A A 67-year-old man with a squamous cell carcinoma occupying much of the lower lip. The patient received 50 Gy in 20 daily fractions using orthovoltage energy photons (250 kVp, HVL 2.5 mm Cu) and oral cavity lead shielding to protect the teeth and mandible. **B** An excellent cosmetic and functional outcome has been achieved.

Definitive radiotherapy of cutaneous SCC is an excellent treatment option, especially in the clinical settings outlined in Table 139.1. For example, multiple medical comorbidities may preclude patients from having extensive surgery. In addition, in sites such as the lower lip, radiotherapy can result in excellent maintenance of function (even with more extensive tumors; Fig. 139.7) as well as cure rates comparable to surgery (see section on lip SCC)[30].

Keratoacanthomas

A keratoacanthoma (KA) typically presents as a rapidly enlarging papulonodule with a central keratin plug. Difficulty often arises in distinguishing these tumors histologically from well-differentiated SCCs, and many authorities consider most KAs to be a well-differentiated variant of SCC. Although KAs often regress spontaneously, a significant number become large and unsightly. Radiotherapy is an efficacious treatment option if excision is not contemplated. Regimens consisting of 25 Gy in five fractions have been reported to lead to a durable regression. Despite this, if the diagnosis of KA versus well-differentiated SCC is uncertain, a dose fractionation schedule appropriate for a SCC should be prescribed (40–50 Gy in 10–20 fractions; see section below on dose fractionation schedules).

Adjuvant (postoperative) radiotherapy

Adjuvant radiotherapy is an option when excision of an SCC is incomplete and re-excision is not considered possible. It is imperative that every pathology report documents and quantifies margin status, and a patient with an incompletely excised SCC, i.e. positive or close margin, remains at risk of local recurrence. While there is no consensus with regard to the most appropriate surgical margin for cutaneous SCCs, published recommendations range from 3 to 10 mm[31], often depending upon size (see above). In one series of patients with SCC of the lip, a 37% local recurrence rate was observed in patients who underwent excision alone (27% close/positive margins) versus a 6% local recurrence rate in patients treated with surgery plus adjuvant radiotherapy (94% close/positive margins)[32].

Special clinical situations

SCC of the lip

In regions of the world that have a high incidence of non-melanoma skin cancer (e.g. Australia), SCC of the lip is considered a skin cancer, not an oral cancer[30]. Compared to oral SCC, there is a lower propensity for spread to regional nodes. Nearly all lesions arise on the lower lip, usually as a consequence of chronic sun exposure.

As with small to moderate-sized SCCs of the skin, the outcome with surgery versus radiotherapy is similar. The laxity of the lip means that wedge excision (± vermilionectomy) is the procedure of choice, with primary closure often possible. When >30–50% of the lip is involved, excision with appropriate margins is usually not achievable without risking function (e.g. oral competency). Complex reconstruction is an option, but insensate tissue may be needed for reconstruction, again with an impact on function. Radiotherapy is therefore an excellent treatment option for SCC of the lip. The lower lip lends itself very well to treatment with orthovoltage photons following insertion of a 3 mm intraoral lead shield to protect the mandible and teeth (see Fig. 139.7). Doses are similar to those for any other equivalent-sized SCC, with a recommended total dose of 50–55 Gy in 20–25 fractions[32].

Lymph node metastases of SCC

Patients with metastatic SCC involving regional lymph nodes (usually of the head and neck) are best referred to a multidisciplinary cancer service[33]. Metastases within the cervical lymph nodes can be due to an occult SCC of the oropharynx or a previously treated cutaneous SCC. Parotid lymph nodes represent a common site for metastases from a previously treated scalp, forehead or ear SCC; in such cases, surgery (parotidectomy ± neck dissection) is required.

Adjuvant radiotherapy is nearly always recommended in patients with nodal metastases in order to improve locoregional control, as the risk of nodal relapse remains high despite surgery[34]. Even patients with multiple unfavorable features (e.g. involvement of multiple nodes, extranodal spread, close margins) can still expect a 5-year disease-free survival of 70–75% with the combination of surgery and adjuvant radiotherapy[34].

Perineural invasion of SCC and BCC

Perineural invasion is an uncommon but serious consequence of SCC and, to a lesser extent, BCC[35]. Up to 2% and 5% of excised BCCs and SCCs, respectively, are noted to have incidental perineural invasion, and a minority (30–40%) of these will present with, or eventually develop, neurologic signs (e.g. motor deficit) or symptoms. Formication (sensation of ants crawling) may herald the diagnosis of perineural invasion, but dysesthesias, paresthesias, numbness and pain are all suggestive symptoms. The diagnosis is frequently delayed because perineural invasion is often not suspected.

A consensus is lacking regarding the most appropriate treatment following the diagnosis of perineural invasion. Patients with limited disease usually undergo surgery plus adjuvant radiotherapy, while radiotherapy alone is often recommended for those with advanced disease extending into the cranial cavity. Prognosis is poor once signs (e.g. craniopathies) or symptoms develop, with 5-year survival rates reported to be around 50%. When periorbital SCCs, especially those in the supraorbital area, are associated with perineural invasion, further treatment should definitely be considered[36]. Retrograde spread of SCC along the first division of the trigeminal nerve towards the orbital apex can occur. In addition, both the second division of this nerve and the facial nerve are potential conduits for spread back to the CNS.

In some circumstances, additional surgery, often extensive, may be undertaken to explore and dissect out potentially involved nerves. Alternatively, radiotherapy, often requiring multi-field megavoltage photons to treat neural pathways to the brainstem as well as first echelon lymph nodes, can be recommended[35–37]. While radiotherapy has the advantage of avoiding surgery, there is some risk of late radiation damage to orbital and CNS structures. Doses of 50–70 Gy (2 Gy/fraction) are often utilized, although late complications can occur (10–35% of patients). Hyperfractionated radiotherapy (i.e. delivery of smaller-than-usual doses per fraction) and concomitant chemotherapy may improve outcome and decrease late reactions[37].

Immunosuppressed hosts

Immunosuppression in the setting of solid organ transplantation (usually renal or cardiac) may be associated with significant morbidity due to the development of malignancies, especially lymphomas and skin cancers. In some transplant populations, the risk of developing a cutaneous SCC exceeds 50%, and there is a greater risk of metastatic spread (compared to the general population). An interesting phenomenon is

the higher incidence of SCCs compared to BCCs. Transplant patients also have an increased incidence of cutaneous melanoma, Merkel cell carcinoma and Kaposi sarcoma. Additional patients at increased risk for developing aggressive cutaneous SCCs are individuals infected with HIV and those with chronic lymphocytic leukemia, especially when undergoing therapy (e.g. fludarabine, alemtuzumab). A subset of the SCCs that arise in immunosuppressed patients are clearly aggressive, with rapid growth and the development of regional and distant metastases[38]. There is some evidence that reducing the level of immunosuppression may be beneficial, although this potentially puts the patient at risk of organ rejection. The role of chemoprophylaxis (retinoids) in reducing the future development of skin cancers is unclear, although there is recent evidence to suggest a possible benefit. However, tolerability of dose-related side effects remains an issue.

The basic tenets of obtaining adequate surgical margins and examining for perineural invasion are of particular importance in this group of patients. Whilst prophylactic treatment to regional lymph nodes cannot be recommended, adjuvant radiotherapy to incompletely excised tumors or those with perineural invasion should be strongly considered. Transplant patients usually tolerate radiotherapy quite well, with no greater degree of acute toxicity[39].

Dose fractionation schedules and fields

An appropriate dose fractionation schedule depends upon both patient and tumor factors. However, decisions should not be based on age alone, as the presence or absence of relevant comorbidities must also be considered. As a generalization, smaller lesions (2–3 cm) in older patients (>70 years of age) are adequately treated by using 40–45 Gy in 10–15 daily fractions, resulting in acceptable local control and cosmesis (Table 139.2). Elderly or infirm patients may be best served by prescribing single large fractions (see palliation below) or even three to five fractions of 6–7 Gy. For larger invasive lesions (>3–4 cm) and/or younger patients, a lower fraction size (2–2.5 Gy) and a "hotter" total dose of 50–60 Gy are recommended in order to optimize local control and produce acceptable late effects. Some clinicians administer a higher dose for cutaneous SCCs than for equivalent-sized BCCs. However, the data to support this practice are conflicting, and, in the opinion of the authors, this is not required. Also, the dose for different subtypes or grades of BCC or SCC does not need to vary nor does the dose prescribed in the adjuvant setting.

A field margin of 5–10 mm beyond macroscopic disease or a surgical site is usually adequate (see Fig. 139.5B). For a small, well-defined BCC, a 5 mm field margin is adequate if superficial photons are used. For SCCs and infiltrative BCCs, a wider margin of 10–15 mm is required in order to encompass surrounding subclinical spread. Ideally, adjuvant treatment should start within 6–7 weeks of excision. Whilst some clinicians are reluctant to administer radiotherapy to a grafted site, it is uncommon for a healed skin graft to be lost because of radiotherapy[40]. Occasionally, poorly vascularized or infected grafts, especially on the scalp, do not tolerate radiotherapy.

SUGGESTED DOSE FRACTIONATION SCHEDULES FOR BASAL CELL CARCINOMAS AND SQUAMOUS CELL CARCINOMAS

Dose fractionation schedule	Indication	Biological effective dose*
Single 12–20 Gy fraction	Elderly, infirm (palliation)	
35 Gy in 7 fractions of 5 Gy	Elderly, medical comorbidity	44 Gy
40 Gy in 10 fractions of 4 Gy	Older, otherwise well	47 Gy
45 Gy in 15 fractions of 3 Gy	Older, otherwise well	49 Gy
50 Gy in 20 fractions of 2.5 Gy	Younger and/or lesion <2–3 cm	52 Gy
60 Gy in 30 fractions of 2 Gy	Younger and/or large lesion	60 Gy

*Calculated by converting to 2 Gy/fraction using the linear quadratic equation.

Table 139.2 Suggested dose fractionation schedules for basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs).

Merkel Cell Carcinoma

Merkel cell carcinoma is a primary cutaneous neuroendocrine (small cell) carcinoma that most often arises in the head and neck region (see Ch. 115)[41]. These tumors often lack diagnostic clinical features but usually have grown rapidly. Merkel cell carcinomas are aggressive, having a high propensity for locoregional relapse and distant spread, and patients need to be appropriately evaluated prior to instituting therapy. Merkel cell carcinoma is both a radio- and chemo-responsive carcinoma. Currently, wide local excision of the primary lesion with margins of at least 10–20 mm or Mohs micrographic surgery is recommended. Some clinicians also advocate sentinel lymph node biopsy, and treatment of the regional lymph nodes must always be considered (see below). When adjuvant locoregional radiotherapy is administered, there is evidence that extensive local surgery may not necessarily lead to a better outcome[42]. In patients considered medically or technically inoperable, radiotherapy alone (50–55 Gy in 20–25 fractions) can result in excellent in-field control in most patients, with death usually from distant relapse[43].

Although there are proponents of surgery alone for selected cases of Merkel cell carcinoma, adjuvant locoregional radiotherapy should nearly always be considered and represents "best practice" in the opinion of the authors[44–46]. Treatment should include the excision site, in-transit tissue (because of the risk of in-transit metastases), and regional lymph nodes. In an attempt to reduce the risk of locoregional relapse (which occurs in 40–50% of patients treated with surgery alone), a typical dose fractionation schedule would be 50 Gy in 20–25 daily fractions, usually requiring megavoltage photons or moderate-energy (9–12 MeV) electrons plus bolus[47]. Because of insufficient data, the role of adjuvant chemotherapy (cisplatin or carboplatin ± etoposide) is currently unresolved. In advanced or metastatic disease, both palliative radiotherapy and chemotherapy can offer effective symptom improvement.

Angiosarcoma

Most angiosarcomas present as violaceous plaques on the scalp and face of older adults (see Ch. 114). These tumors often extend well beyond the clinically evident/apparent margins[48] and locally extensive disease is usually present at the time of diagnosis. Unfortunately, excision alone is usually followed by local recurrences because of the multicentric and insidious nature of this tumor. Relapses can occur at the periphery of treated sites as well as regionally.

Angiosarcomas tend to be radio-responsive and therefore can be treated with radiotherapy. Patients with limited and operable disease may undergo excision followed by *adjuvant* radiotherapy. Alternatively, *definitive* radiotherapy is also an option, with a reasonable likelihood of obtaining in-field control[49]. In the case of scalp involvement, a technique can be used that encompasses the entire scalp and combines matching photon and electron fields[48]. Other options include multiple static electron fields or electron arcs. Lastly, single-agent chemotherapy with paclitaxel may be helpful in patients with recurrent disease.

Kaposi Sarcoma

Kaposi sarcoma (KS) is a type of spindle cell malignancy that arises from the vascular endothelium, usually presenting as violaceous papules and plaques (see Ch. 114). Classic KS favors the legs of elderly men of Mediterranean or Jewish origin[50], whereas AIDS-associated KS has a more widespread distribution pattern, including the oral cavity (see Ch. 78).

While the role of radiotherapy for AIDS-related KS has markedly diminished with the advent of antiretroviral therapy (ART; formerly referred to as highly active antiretroviral therapy [HAART]), it is a radio-responsive tumor and various dose fractionation schedules have been used to effectively treat cutaneous lesions. Regimens range from a single 8 Gy irradiation to 30–40 Gy in 10–20 daily fractions[51]. Because patients often develop acute painful reactions from radiotherapy to the oral cavity and the plantar surface, they should undergo radiotherapy to only one foot at a time.

Classic KS usually has a long and indolent clinical course. Patients with localized resectable tumors that are symptomatic may undergo excision, but the multifocal nature of the disease must be kept in mind.

Fig. 139.8 Kaposi sarcoma. A A 53-year-old man with a localized plaque of Kaposi sarcoma on the lateral aspect of the distal lower leg. **B** Two months after 50 Gy in 25 daily fractions using megavoltage photons plus a tissue equivalent bolus. There is erythema within the radiation field and residual brown discoloration.

Radiotherapy is also an effective modality for palliating areas of symptomatic disease. Single small doses of 8–12 Gy are reported to result in symptom relief and tumor reduction in most patients; however, in some circumstances, higher, more-fractionated doses may be considered to sites of limited disease (Fig. 139.8). Occasionally, there is a sense of chasing the disease, as lesions gradually appear at the periphery of irradiated sites. For patients with widespread disease, total skin electron beam therapy (see below) has been utilized.

Cutaneous Lymphomas

Cutaneous lymphomas are exquisitely radio-sensitive. However, with the exception of primary cutaneous B-cell lymphoma (see Ch. 119) and selected patients with cutaneous T-cell lymphoma (CTCL; see Ch. 120), the role of radiotherapy is essentially palliative. Patients with sites of symptomatic local disease (lymph nodes, dermal nodules and plaques, ulcers) can be palliated with doses of 20–30 Gy, often requiring orthovoltage or megavoltage energy photons. In primary cutaneous B-cell lymphoma, a form of indolent extranodal non-Hodgkin lymphoma, local radiotherapy with doses of 36–40 Gy may be curative[52].

Total skin electron beam therapy

Selected patients with mycosis fungoides and Sézary syndrome may be treated with total skin electron beam therapy (TSEBT) to a dose of 36 Gy over 9 weeks[53]. This treatment, which is complex and usually delivered by specialized centers of radiation oncology, has particular advantages:

- comprehensive coverage of the entire skin surface
- can be repeated should other modalities fail to control the CTCL
- an acceptable toxicity profile when given over a 6–9-week period.

While TSEBT can be offered to patients with all stages of disease, it is usually reserved for more advanced stages (IIB, III, IV) and/or disease that has failed to respond to less aggressive therapies (e.g. phototherapy, topical alkylating agents).

Treatment consists of a 4–6 MeV beam (see Fig 139.1), with patients often treated in the standing position at a distance of 7 m from the linear accelerator. Irradiation is administered 4 days per week for 9 weeks (i.e. 36 fractions). To some degree, X-ray contamination is always a feature of electron beam therapy. Typically, if using a 4–6 MeV electron beam, X-ray contamination is less than 2% of the dose. Each week, the entire skin surface receives two cycles of treatment and a total of 2 Gy is given to the entire skin surface each cycle. The perineum, plantar surface and scalp receive supplemental "boosts", as these areas are not adequately treated with the patient in the standing position. Lead contact lenses are used to shield the eyes during the initial 18 fractions of TSEBT, and external shielding of the eyelids is done during the second portion of the treatment; hands and feet are also shielded 50% of the time during TSEBT. Patients with tumor stage disease often receive supplemental boosts via orthovoltage or electrons at the completion of the TSEBT.

As there is no significant dose of radiation to the bone marrow or viscera[54], patients receiving TSEBT should not have systemic sequelae (e.g. cytopenias, nausea, vomiting, diarrhea). However, alopecia, dyspigmentation and hypohidrosis often occur and in many patients are permanent side effects. A repeat course of TSEBT may be given months to years later for those who develop recurrent treatment-resistant disease. The most suitable candidates for repeat TSEBT are individuals with longer intervals between courses (>6 months) and those who had a longer disease-free interval following the first course.

Adnexal Carcinomas

Adnexal (appendageal) carcinomas, such as microcystic adnexal carcinomas and sebaceous, eccrine or apocrine carcinomas, are rare and therefore any treatment approach needs to be individualized (Ch. 111). Many of these tumors are aggressive in nature, with a propensity to develop regional and distant metastases. While patients with operable cancers should have them excised with appropriate margins, inoperable lesions may respond to radiotherapy[55]. Adjuvant radiotherapy may also be recommended in the setting of incomplete excision. Doses similar to those for equivalent non-melanoma skin cancers should be administered (see Table 139.2).

PALLIATION

Locally Advanced Tumors

Occasionally, elderly, debilitated or mentally ill patients present with advanced and neglected skin cancers, which, though not curable, can be palliated. Such tumors are often painful, bleeding and infected, causing problems for both the patient and the caregiver. With the addition of a bolus (see Fig. 139.2), single large fractions of 12–20 Gy can be given quickly (within minutes) using megavoltage photons. Uncooperative patients may require mild sedation prior to treatment. These large single fractions are well tolerated with minimal toxicity. Alternative regimens include multiple medium-sized fractions given once or twice a week (e.g. 8 Gy × 3). In elderly patients who are otherwise well, higher total dose fractionation schedules such as 35 Gy in 5–7 fractions or 40 Gy in 10 fractions (Fig. 139.9) may be more appropriate and can be considered more radical in intent. These are often given as two or three fractions per week.

Metastases

Dermal-based metastases occur most frequently in patients with lung and breast cancer, and, in general, are associated with a poor prognosis (see Ch. 122). Both in-transit metastases and distant dermal metastases can develop in patients with cutaneous SCC, Merkel cell carcinoma, and melanoma. Cutaneous metastases may also present as rapidly enlarging subcutaneous masses with intact overlying skin.

Ulceration and bleeding are complications of cutaneous metastases that do respond to palliative radiotherapy. Orthovoltage photons or megavoltage photons (with a bolus) administered as a single 8 Gy fraction or as 20 Gy in five fractions are effective regimens. Metastatic

Fig. 139.9 Metastatic squamous cell carcinoma involving the parotid lymph nodes. A An 85-year-old man with advanced and inoperable SCC of his right parotid lymph nodes. **B** Following a 2-week course of palliative radiotherapy (40 Gy in 10 daily fractions using 12 MeV electrons plus a tissue equivalent bolus), he experienced a complete clinical response.

deposits elsewhere (e.g. skeletal) are also palliated with a similar dose fractionation schedule.

REACTIONS AND COMPLICATIONS

Acute Reactions

Acute morbidity from skin-directed radiotherapy is usually minimal (in-field cutaneous erythema and desquamation) and limited to a small area (Table 139.3). Systemic side effects such as fatigue, nausea and vomiting do not occur. The daily application of a bland emollient, aloe vera or vitamin E cream is recommended while receiving radiotherapy. Most patients can expect to have local discomfort and moist desquamation by the conclusion of the radiation therapy (Fig. 139.10), which then lasts for a few weeks. Hemorrhagic crusting can also develop and re-epithelization usually occurs by week 3 or 4 following completion of radiotherapy. During the healing phase, patients are advised to keep the irradiated tissue clean and dry (after washing). Delayed healing (beyond 6–8 weeks) is uncommon, as is associated soft tissue infection.

Late Reactions

The late effects of radiotherapy (e.g. telangiectasia, epidermal atrophy, dyspigmentation; see Table 139.3 & Fig. 139.10) often appear months to years later. They are more likely to appear with continued unprotected sun exposure, when a large dose per fraction (>3–4 Gy) was delivered, if the total dose was >55 Gy, and when large fields were irradiated. Chronic non-healing, radiation-induced ulcers represent poorly vascularized tissue that requires the importation of well-vascularized tissue to enable healing. The latter usually consists of local skin flaps or sometimes staged skin–muscle or axial pedicle flaps of non-irradiated tissue; grafts do not take well on irradiated tissue due to the poor vascular bed.

In a review of over 400 patients treated with radiotherapy, 92% were considered to have a good or excellent cosmetic result[1]. However, 36% of those receiving >60 Gy in ≤2 Gy fractions had only a fair (16%) or poor (20%) cosmetic result. Smaller treatment fields (2–3 cm) tolerate hypofractionation better than do larger areas, but, even so, if cosmesis is an important consideration, larger fractions should be avoided. Patients should also be warned of the small risk (<5%) of late soft tissue and cartilage necrosis, which are related to larger tumor size and larger doses per fraction.

RADIOTHERAPY REACTIONS AND COMPLICATIONS	
	Reaction or complication
Acute	Dry desquamation, moderate erythema Moist desquamation and mild bleeding
Late*	Hypo- or hyperpigmentation† Telangiectasia† Epidermal atrophy† and fragility Permanent epilation/alopecia, sweat gland atrophy Necrosis of soft tissue, cartilage and/or bone Subdermal fibrosis Radiation-induced malignancy‡ – SCC, BCC, angiosarcoma; malignant fibrous histiocytoma

*Many late effects are uncommon.
†Components of poikiloderma; a *TP53* haplotype containing two variant alleles was associated with almost a twofold increase in risk for telangiectasia. Variants in the *TP53* gene may therefore modify the risk of late skin toxicity after radiotherapy.
‡Many reports have been in patients whose dose fractionation schedules and techniques are now historical in nature.

Table 139.3 Radiotherapy reactions and complications. BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

DISEASES INDUCED BY RADIATION THERAPY
DISEASE NOT CONFINED TO THE SITES OF IRRADIATION
• Erythema multiforme • Bullous pemphigoid • Pemphigus foliaceus, pemphigus vulgaris • Brunsting–Perry mucous membrane (cicatricial) pemphigoid • Paraneoplastic pemphigus • Herpes zoster
DISEASE LIMITED TO SITES OF IRRADIATION
• Bullous pemphigoid • Erythema multiforme • Comedonal acne, folliculitis • Graft-versus-host disease • Lichen planus • Lichen sclerosus • Morphea (localized scleroderma) • Pseudosclerodermatous panniculitis • Urticaria pigmentosa • Digitate keratoses (also referred to as postirradiation minute digitate hyperkeratosis)
LESIONS THAT SPARE IRRADIATION SITES
• Exanthematous drug eruption

Table 139.4 Diseases induced by radiation therapy. Neoplasms are listed in Table 139.3.

Younger Patients

When irradiating younger patients, better long-term cosmetic results are more likely if a low dose per fraction (2 Gy/fraction) is administered. A typical dose for a small BCC would be 50–54 Gy delivered in 25–27 daily fractions[56]. However, even with this dose fractionation schedule, patients can still expect some degree of in-field hypopigmentation and telangiectasia; the latter can be addressed via pulsed dye laser treatment. Other options, therefore, should be considered prior to recommending radiotherapy to younger patients. The risk of a radiotherapy-induced in-field malignancy arising decades after high-dose therapeutic skin-directed radiotherapy is rare and poorly documented in the literature (see Table 139.3).

Cutaneous Diseases Induced by Radiation Therapy

Table 139.4 outlines the cutaneous disorders that are induced by radiotherapy, with some occurring outside the field of radiation[57] and others limited to the site of irradiation.

Fig. 139.10 Acute and chronic cutaneous side effects of radiation therapy. A Confluent moist desquamation and marked edema in a patient near completion of radiation therapy for a squamous cell carcinoma with neurotropism. **B** Stevens–Johnson syndrome localized to multiple radiation ports in a patient receiving phenobarbital. **C** Dry desquamation and erythema of the neck 10 days following radiation therapy for a pharyngeal Hodgkin lymphoma. **D** In-field telangiectasias; note the square distribution pattern. **E** In-field hypo- and hyperpigmentation 10 years after radiotherapy for a basal cell carcinoma. **F** In-field poikiloderma, fibrosis and ulceration; nowadays, this is seen much less often. **G** Spindle cell carcinoma within a radiation port. Note the background poikiloderma. *A, D, Courtesy, Jean L Bolognia, MD. B, Reprinted with permission from Duncan KO, Tigelaar RE, Bolognia JL. J Am Acad Dermatol. 1999;40:493–6. C, Courtesy, Louis A Fragola, Jr, MD. G, Courtesy, Robert Hartman, MD.*

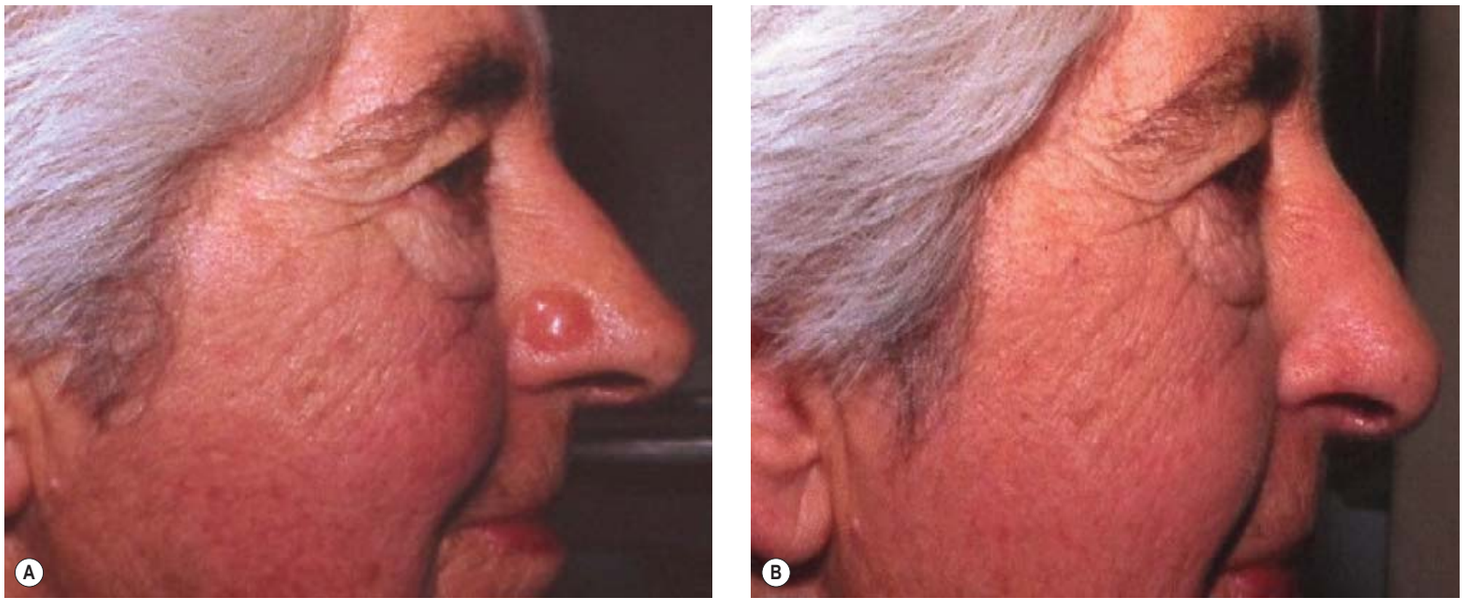
FUTURE TRENDS

Modern radiotherapy has entered a new and exciting era. Accurate conformal radiotherapy is being delivered via sophisticated three-dimensional CT-based planning and treatment systems. Intensity-modulated radiotherapy (IMRT) is allowing tumor doses to escalate and normal tissue doses to decrease. The integration of MRI and functional imaging such as positron emission tomography (PET) into planning systems will further enhance the accurate delivery of radiotherapy.

REFERENCES

1. Locke J, Karimpour S, Young G, et al. Radiotherapy for epithelial skin cancers. Int J Radiat Oncol Biol Phys. 2001;51:748–55.
2. Withers HR. Biological basis of radiation therapy for cancer. Lancet. 1992;339:156–63.
3. Goldschmidt H, Breneman JC, Breneman DL. Ionizing radiation therapy in dermatology. J Am Acad Dermatol. 1994;30:157–82.
4. Silva JJ, Tsang RW, Panzarella T, et al. Results of radiotherapy for epithelial skin cancer of the pinna: the Princess Margaret Hospital experience, 1982–1993. Int J Radiat Oncol Biol Phys. 2000; 47:451–9.
5. Khan FM. Quality of x-ray beams. In: Khan FM (ed.). The Physics of Radiation Therapy, 1st edn. Baltimore: Williams & Wilkins, 1984:110–20.
6. Tsao MN, Tsang RW, Liu FF, et al. Radiotherapy management for squamous cell carcinoma of the nasal skin: the Princess Margaret Hospital experience. Int J Radiat Oncol Biol Phys. 2002;52:973–9.
7. Goldschmidt H. FDA recommendations on radiotherapy of benign diseases. J Dermatol Surg Oncol. 1978;4:619–20.
8. Miller RA, Spittle MF. Electron beam therapy for difficult cutaneous basal and squamous cell carcinoma. Br J Dermatol. 1982;106:429–30.
9. Svoboda VHJ, Kovarik J, Morris F. High dose-rate microselection molds in the treatment of skin tumors. Int J Radiat Oncol Biol Phys. 1995;31:967–72.
10. de Launey JW, MacKenzie-Wood AR. Office radiotherapy in dermatology: a contemporary perspective. Australas J Dermatol. 1996;37:71–9.
11. Veness MJ. The important role of radiotherapy in patients with non-melanoma skin cancer and other cutaneous entities. J Med Imaging Radiat Oncol. 2008;52:278–86.
12. Feigen M. Should cancer survivors fear radiation induced sarcomas? Sarcoma. 1997;1:5–15.
13. Order SE, Donaldson SS. Radiation Therapy of Benign Diseases: A Clinical Guide, 2nd edn. New York: Springer, 1998:7.
14. Huang Q, Veness M, Richards S. The role of adjuvant radiotherapy in recurrent keloids. Austral J Dermatol. 2004;45:162–6.
15. Dupree MT, Kitely RA, Weismantle K, et al. Radiation therapy for Bowen's disease: lessons for lesions of the lower extremity. J Am Acad Dermatol. 2001;45: 401–4.

16. Schmid-Wendtner MH, Brunner B, Konz B, et al. Fractionated radiotherapy of lentigo maligna and lentigo maligna melanoma in 64 patients. J Am Acad Dermatol. 2000;43:477–82.
17. Huynh NT, Veness MJ. Radiotherapy for lentigo maligna. Arch Dermatol. 2002;138:981–2.
18. Bath FJ, Bong J, Perkins W, Williams HC. Interventions for basal cell carcinoma of the skin (Cochrane Review). In: The Cochrane Library, Issue 2, Chichester, UK: John Wiley & Sons, 2004.
19. Wilson AW, Howsam G, Santhanam V, et al. Surgical management of incompletely excised basal cell carcinomas of the head and neck. Br J Oral Maxillofac Surg. 2004;42:311–14.
20. Swanson EL, Amdur RJ, Mendenhall WM, et al. Radiotherapy for basal cell carcinoma of the medial canthus. Laryngoscope. 2009;119:2366–8.
21. Liu FF, Maki E, Warde P, et al. A management approach to incompletely excised basal cell carcinomas of the skin. Int J Radiat Oncol Biol Phys. 1991;20:423–8.
22. Rowe DE, Carroll RJ, Day CD. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear and lip. J Am Acad Dermatol. 1992;26:976–90.
23. Veness MJ. Treatment recommendations for patients diagnosed with high-risk cutaneous SCC. Australas Radiol. 2005;49:365–76.
24. Veness MJ, Palme CE, Morgan GJ. High-risk cutaneous squamous cell carcinoma of the head and neck: results from 266 patients treated with metastatic nodal disease. Cancer. 2006;106:2389–96.
25. Motley R, Kersey P, Lawrence C. Multiprofessional guidelines for the management of the patient with primary cutaneous squamous cell carcinoma. Br J Dermatol. 2002;146:18–25.
26. Brantsch KD, Meisner C, Schönfisch B, et al. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. Lancet Oncol. 2008;9:713–20.
27. Griffiths RW, Feeley K, Suvarna SK. Audit of clinical and histological prognostic factors in primary invasive squamous cell carcinoma of the skin: assessment in a minimum 5 year follow-up study after conventional excisional surgery. Br J Plast Surg. 2002;55:287–92.
28. Brodland DG, Zitelli JA. Surgical margins for excision of primary cutaneous squamous cell carcinoma. J Am Acad Dermatol. 1992;27:241–8.
29. Kwan W, Wilson D, Moravan V. Radiotherapy for locally advanced basal cell and squamous cell carcinomas of the skin. Int J Radiat Oncol Biol Phys. 2004;60: 406–11.
30. Veness MJ, Ong C, Cakir B, Morgan G. Squamous cell carcinoma of the lip. Patterns of relapse and outcome: reporting the Westmead Hospital experience, 1980–1997. Australas Radiol. 2001;45:195–9.
31. de Visscher JG, Gooris PJJ, Vermey A, Roodenburg JLN. Surgical margins for resection of squamous cell carcinoma of the lower lip. Int J Oral Maxillofac Surg. 2002;31:154–7.
32. Babington S, Veness MJ, Cakir B, et al. Squamous cell carcinoma of the lip: is there a role for adjuvant radiotherapy in improving local control following incomplete or inadequate excision? ANZ J Surg. 2003;73:621–5.
33. Veness MJ, Porceddu S, Palme CE, Morgan GJ. Cutaneous head and neck squamous cell carcinoma metastatic to parotid and cervical lymph nodes. Head Neck. 2007;29:621–31.
34. Veness MJ, Morgan GJ, Palme CE, Gebski V. Surgery and adjuvant radiotherapy in patients with cutaneous head and neck squamous cell carcinoma metastatic to lymph nodes: combined treatment should be considered best practice. Laryngoscope. 2005;115: 870–5.
35. Garcia-Serra A, Hinerman RW, Mendenhall WM, et al. Carcinoma of the skin with perineural invasion. Head Neck. 2003;25:1027–33.
36. Geist DE, Garcia-Moliner M, Fitzek MM. Perineural invasion of cutaneous squamous cell carcinoma and basal cell carcinoma: raising awareness and optimizing treatment. Dermatol Surg. 2008;34:1642–51.
37. Galloway TJ, Morris CG, Mancuso AA, et al. Impact of radiographic findings on prognosis for skin carcinoma with clinical perineural invasion. Cancer. 2005;103:1254–7.
38. Veness MJ, Quinn DI, Ong CS, et al. Aggressive cutaneous malignancies following cardiothoracic transplantation: the Australian experience. Cancer. 1999;85:1758–64.
39. Veness MJ, Harris D. Role of radiotherapy in the management of organ transplant recipients diagnosed with non-melanoma skin cancers. Australas Radiol. 2006;51:12–20.
40. Bui DT, Chunilal A, Mehrara BJ, et al. Outcome of split-thickness skin grafts after external beam radiotherapy. Ann Plast Surg. 2004;52:551–7.
41. Veness MJ, Palme CE, Morgan GJ. Merkel cell carcinoma: a review of management. Curr Opin Otololaryngol Head Neck Surg. 2008;16:170–4.
42. Poulsen M, Harvey J. Is there a diminishing role for surgery for Merkel cell carcinoma of the skin? A review of current management. ANZ J Surg. 2002;72:142–6.
43. Veness M, Foote M, Gebski V, Poulsen M. The role of radiotherapy alone in patients with Merkel cell carcinoma: reporting the Australian experience of 43 patients. Int J Radiat Oncol Biol Phys. 2010;78:703–9.
44. Veness MJ, Perera L, McCourt J, et al. Merkel cell carcinoma: improved outcome with adjuvant radiotherapy. ANZ J Surg. 2005;75:275–81.
45. Clark JC, Veness MJ, Gilbert R, et al. Merkel cell carcinoma of the head and neck: is adjuvant radiotherapy necessary? Head Neck. 2007;29:249–57.
46. NCCN Clinical Practice Guidelines in Oncology. Merkel cell carcinoma. V.I.2009. www.nccn.org.
47. Foote M, Harvey J, Porceddu S, et al. Effect of radiotherapy dose and volume on relapse in Merkel cell cancer of the skin. Int J Radiat Oncol Biol Phys. 2010;77:677–84.
48. Veness M, Cooper S. Treatment of cutaneous angiosarcomas of the head and neck. Australas Radiol. 1995;39:277–81.
49. Sasaki R, Soejima T, Kishi K, et al. Angiosarcoma treated with radiotherapy: impact of tumor type and size on outcome. Int J Radiat Oncol Biol Phys. 2002;52:1032–40.
50. Caccialanza M, Marca S, Piccinno R, Eulisse G. Radiotherapy of classic and human immunodeficiency virus-related Kaposi's sarcoma: results in 1482 lesions. J Eur Acad Dermatol Venereol. 2008;22:297–302.
51. Lukawska J, Cottrill C, Bower M. The changing role of radiotherapy in AIDS-related malignancies. Clin Oncol. 2003;15:2–6.
52. Smith BD, Glusac EJ, McNiff JM, et al. Primary cutaneous B-cell lymphoma treated with radiotherapy: a comparison of the European Organization for Research and Treatment of Cancer and the WHO classification systems. J Clin Oncol. 2004;22:634–9.
53. Jones GW, Kacinski BM, Wilson LD, et al. Total skin electron radiation in the management of mycosis fungoides: consensus of the European Organization for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Project Group. J Am Acad Dermatol. 2002;47:364–70.
54. Wilson LD. Delivery and sequelae of total skin electron beam therapy. Arch Dermatol. 2003;139:812–13.
55. Dowd M, Kumar RJ, Sharma R, Mural R. Diagnosis and management of sebaceous carcinoma: an Australian experience. ANZ J Surg. 2008;78:158–63.
56. Huynh NT, Veness MJ. Basal cell carcinoma of the lip treated with radiotherapy. Australas J Dermatol. 2002;43:15–19.
57. Veness MJ, Dwyer P. Erythema multiforme-like reaction associated with radiotherapy. Australas Radiol. 1996;40:334–7.



Nodular basal cell carcinoma. A A 72-year-old woman with a 1 cm nodular basal cell carcinoma on the right ala nasi. **B** Four months after superficial radiotherapy (45 Gy in 15 daily fractions, 100 kVp, HVL 7 mm Al).

This page intentionally left blank

140 Electrosurgery

Sheldon V Pollack

Chapter Contents

Indications/contraindications 2305
Preoperative history and considerations 2305
Description of techniques 2306
Variations/unusual situations 2308
Postoperative care 2309
Complications 2309
Electroepilation 2310
Iontophoresis 2310

Synonym ■ Radiosurgery

Key features

- Electrosurgery encompasses a group of procedures by which tissue is removed or destroyed through the application of electrical energy
- True electrocautery uses direct current to create a red-hot tip, which can be safer for patients with pacemakers and implantable cardioverter-defibrillators
- In modern electrosurgery, high-frequency alternating current is converted to heat within the treated tissues as a result of resistance to its passage
- Electrodesiccation is superficial ablation by touching the tissue with a monoterminal device
- Electrofulguration is superficial ablation by use of a monoterminal device whose electrode is held at a slight distance from the tissue, allowing a spark to jump to the tissue
- Electrocoagulation uses a biterminal device for deeper coagulation
- Electrosection uses a biterminal device to cut while achieving hemostasis by mild lateral heat spread
- In order to minimize adverse sequelae, lateral heat spread should be kept to a minimum by using the appropriate waveform, power setting and electrode size

INTRODUCTION AND BACKGROUND

Definition

Modern electrosurgery is a group of techniques by which high-frequency alternating electrical current is applied to living tissues in order to achieve superficial coagulation, deep coagulation, or cutting of the skin. Since living tissue is a poor conductor of electricity, the flow of electrical current is hampered and builds up at the site of application. This resistance to the flow of electricity results in its conversion to heat. The use of different varieties of electrosurgical current, each characterized by a distinctive waveform, results in unique biologic outcomes, including desiccation, coagulation or section of treated skin.

Electrocautery

The forerunner of modern electrosurgery was electrocautery (from Greek *kauterion*, branding iron)[1]. In electrocautery, invented in 1875, a metal wire is heated by resistance to the flow of direct current electricity, as in an electric toaster. Hemostasis (even in a wet field) can be obtained with electrocautery, but the resulting third-degree burn may result in prolonged healing times and may cause inferior cosmetic outcomes.

Of note, electrocautery, with its hot element (Fig. 140.1), is different from modern electrosurgery, in which high-frequency alternating current is applied via an unheated electrode. Electrocautery units are of value for providing hemostasis for surgical patients with pacemakers and implantable cardioverter-defibrillators (ICDs), because external electromagnetic fields may compromise the function of these devices. A number of electrocautery units are currently produced; among them is the Thermal Cautery Unit (Geiger Medical Technologies Inc.).

Historical Aspects

Although used by most dermatologists on a daily basis, high-frequency electrosurgery (often referred to as "radiosurgery") could not have been developed if several major advances in the knowledge of electricity had not occurred. In order for alternating current electricity to be utilized for medical purposes, it was necessary for high-frequency currents to be produced. A generator that could provide such current was developed in 1889 by Thompson, who noted heat in his wrists when current was passed through his hands when immersed in saline solution[2]. Experiments conducted by Jacques Arsene d'Arsonval in 1891 established that the application, in human subjects, of electric currents with frequencies greater than 10 000 cycles per second (10 KHz) failed to cause neuromuscular stimulation and the associated tetanic response[3,4]. Also in the 1890s, Oudin, following some modifications to d'Arsonval's equipment, was able to generate a spray of sparks that caused superficial tissue destruction.

At the turn of the twentieth century, Rivière conceived the notion of using very small treatment electrodes in order to concentrate the current density. This would enable one to treat a skin lesion with an electric spark[5]. Walter de Keating-Hart and Pozzi[6] in 1907 introduced the term "fulguration" (from Latin *fulgur*, lightning), referring to the superficial carbonization that resulted when the spark from the Oudin coil was used to treat skin. They claimed that this modality was ideal for treating skin cancer and that the spark could selectively destroy tumor cells by interfering with their source of nutrition.

In 1909, Doyen[7] introduced the term "electrocoagulation" (from Latin *coagulare*, to curdle) to describe a different form of electrosurgery in which tissue was touched directly with the treatment electrode and an indifferent electrode was added to the circuit. The indifferent electrode allowed for direct removal of the electricity entering the patient and caused the latter to flow back into the electrosurgical device. By removing this static energy build-up, shocks were avoided in surgeons and other bystanders. The amperage was effectively increased while the "recycling" of electrical current allowed for lower voltages to be utilized. The current produced with this biterminal arrangement penetrated more deeply than fulguration and directly coagulated tissues rather than causing only surface carbonization. Doyen claimed that this more deeply penetrating current was more likely to be effective in the destruction of tumor cells.

William Clark, in 1911, reported on the use of an electrosurgical output that caused dehydration of tissue without carbonization at the surface[8]. He substituted a multiple spark gap for the usual single one in a monoterminal Oudin current generator. This provided a smoother current that resulted in the production of fine sparks as opposed to the

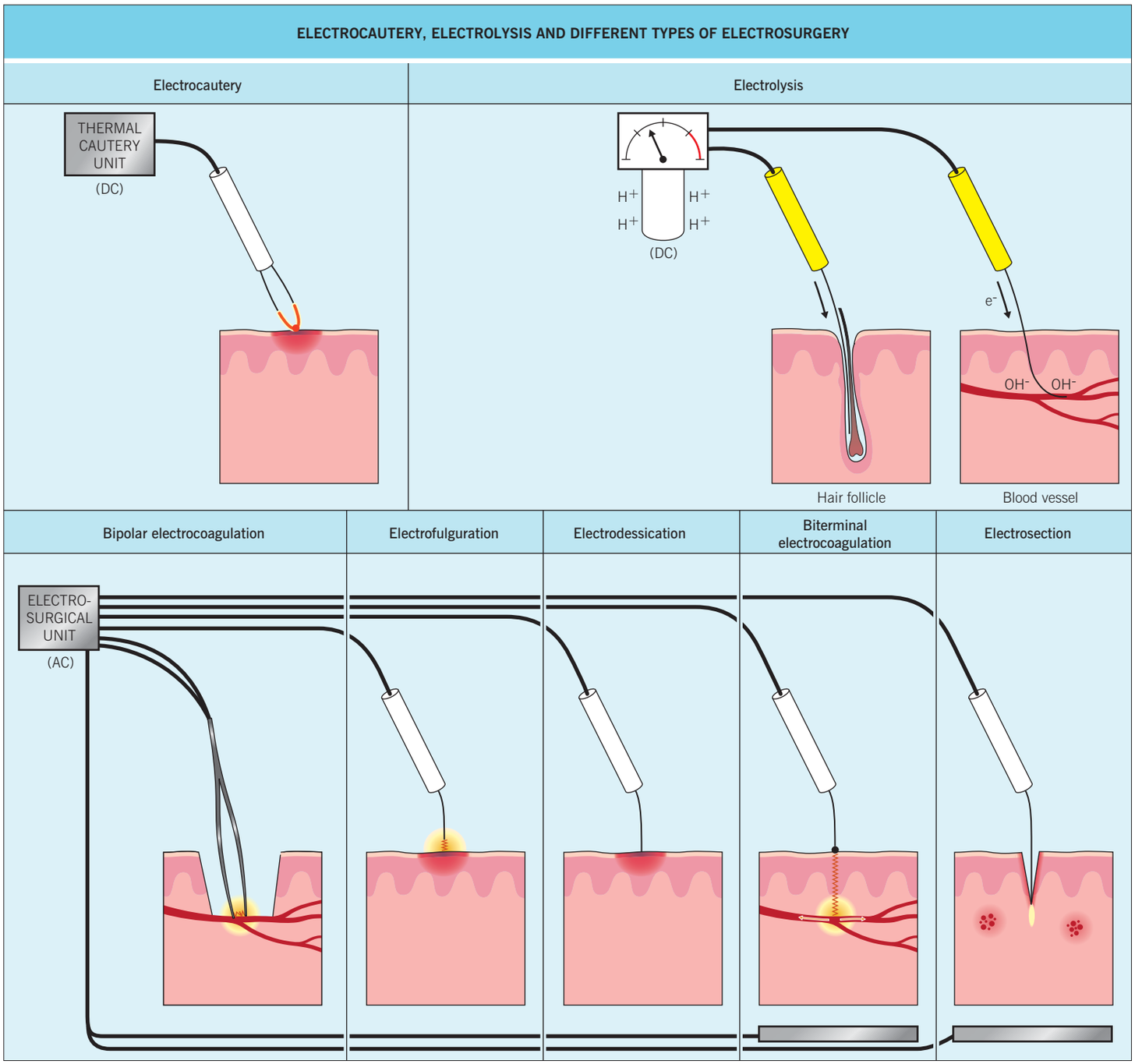


Fig. 140.1 Electrocautery, electrolysis and different types of electrosurgery. AC, alternating current; DC, direct current; e^-, electron; H^+, proton; OH^-, hydroxide ion.

long, thick sparks seen with electrofulguration. Clark used the term "desiccation" (from Latin *desiccare*, to dry out) to describe this action.

The next major event in the development of electrosurgery came in 1923 when Dr George A Wyeth, a noted tumor surgeon, used electrosurgery for cutting tissues[9]. His apparatus, which he termed an "endotherm knife" (Greek *endo*, within; *thermē*, heat), used a thermionic vacuum tube instead of a spark gap[10]. Wyeth called the technique "electrothermic endothermy". He believed that the technique was particularly applicable to tumor surgery since it sealed off not only the smaller blood vessels but also the lymphatics that might otherwise provide for dissemination of metastatic disease.

A Harvard physicist, William Bovie PhD, probably made the most important contribution to the development of electrosurgery. With financial assistance from the Liebel-Flarsheim Company of Cincinnati, he built an operating room electrosurgical device that offered both coagulation and cutting currents[11]. Dr Harvey Cushing, a distinguished neurosurgeon, became quite interested in these techniques and, with Bovie at the controls, began using electrosurgery for controlling bleeding and cutting through tissues during surgical procedures at Peter Bent Brigham Hospital in 1926. Dr Cushing's favorable impressions of electrosurgery assured acceptance of this technique by the surgical world. The subsequent impact of Bovie's machine upon medicine was so great that the word "bovie" is still often used generically as a noun to refer to an electrosurgical apparatus or even as a verb to describe the act of performing electrosurgery[12].

Electrosurgical Devices and Outputs

The circuitries of all electrosurgical instruments share certain design features necessary for production of suitable electrical outputs for electrosurgery. Standard household current first passes through a transformer which alters the voltage, providing the levels and characteristics required for the instrument's various circuit functions. The current

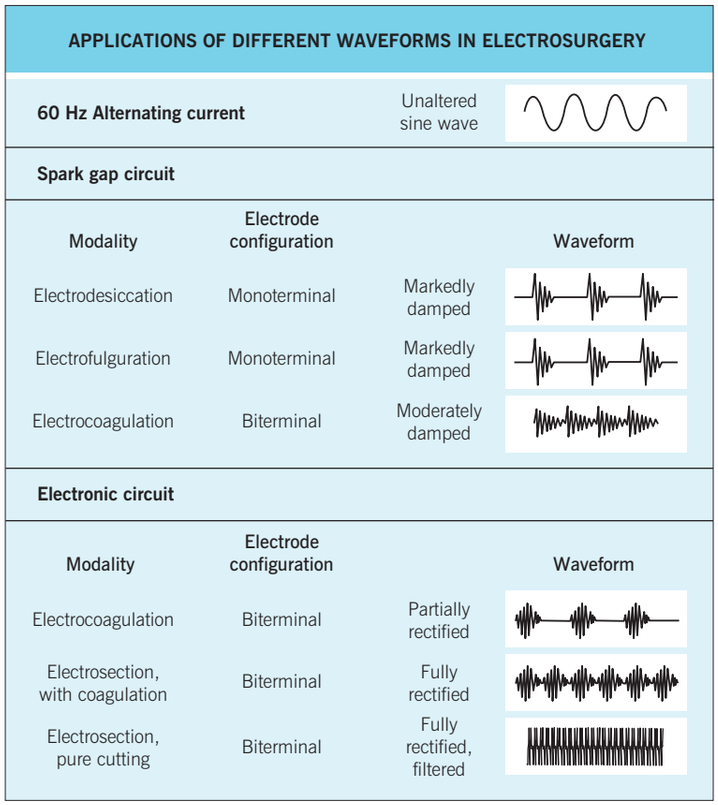


Fig. 140.2 Applications of different waveforms in electrosurgery.

next travels through an oscillating circuit that may employ a spark gap, a thermionic vacuum tube, or solid state transistors to increase electrical frequency. Finally, this altered electrical energy is delivered to the treatment electrode.

Each electrosurgical current produces its own unique wavy pattern of current flow, or *waveform*. The latter may be either *damped* or *undamped*, depending on the type of oscillating circuit used. In general, damped waveforms provide electrodesiccation and electrofulguration, whereas the application of moderately damped and undamped currents results in electrocoagulation and cutting currents, respectively (Fig. 140.2). The spark gap generator produces a damped wave, consisting of bursts of energy in which successive wave amplitudes gradually return to zero. This occurs due to the resistance to energy flow presented by the gap.

Use of a thermionic tube results in a more uniform output. The valve tube circuit is able to neutralize the internal resistance responsible for the damping effect seen in the spark gap circuit, and the amplitude of output therefore remains unchanged. Depending on the circuitry used, the output can be moderately damped (partially rectified) or slightly damped (fully rectified). A filtered, fully rectified output is essentially continuous and uniform, similar to an undamped wave. The different types of waveforms each result in different biologic outcomes and are, therefore, used for different electrosurgical procedures.

Terminology: Monopolar, Bipolar, Monoterminal and Biterminal

The terms *monopolar* and *bipolar* denote the number of tissue contacting tips at the end of the surgical electrode. When the surgical electrode has only one tip projecting from its end, it is a monopolar electrode. If it has two tips, it is a bipolar electrode. Therefore, an electrosurgical forceps (that plugs into two ports on the electrosurgical device) is considered to be bipolar, as opposed to a pointed electrode, which is monopolar (and plugs into one port on the device).

Monoterminal refers to the use of a treatment electrode without an indifferent or dispersive electrode ("ground plate"). *Biterminal* denotes that both treatment and indifferent electrodes are used (see Fig. 140.1). Such is the case with electrocoagulation and electrosection, in which use of the indifferent plate, although not *technically* necessary for the machine to work, will definitely enhance the efficiency of the electrosurgical apparatus. In biterminal electrosurgical applications, there is "recycling" of the energy that comes out of the treatment electrode, passes through the patient and is then removed from the patient via the indifferent electrode. Electrodesiccation and its variant, electrofulguration, are monoterminal procedures in which the indifferent electrode serves no purpose and, in most instances, is not even connected to the patient.

A simple way to visualize this is to think of the wires coming out of the machine as terminals. If only one wire (the handpiece for the electrode) is attached to the machine, then the application is monoterminal in nature. If, in addition, a "ground plate" is used, requiring a second wire to be attached to the machine, then the procedure is biterminal (see Fig. 140.6).

When a ball electrode is used to electrocoagulate a bleeding vessel, one is using biterminal, monopolar electrosurgery. In the case of bipolar forceps in which the electrode is connected to both the active and the dispersive electrode termini, we are using a biterminal, bipolar modality.

INDICATIONS/CONTRAINDICATIONS

The simplest way to think of electrosurgical applications in the clinical setting is to consider the three major capabilities of electrosurgery units. These include superficial tissue destruction (electrodesiccation), deep tissue destruction (electrocoagulation) and cutting (electrosection)[13,14]. Destruction or excision of skin lesions by electrosurgery should be accomplished with the smallest possible amount of damage to normal tissues. Whether electrosurgery, cryosurgery or CO_2 laser surgery is used, the greater the penetration of the destructive modality into the skin, the greater the likelihood that unacceptable scarring will result. Because the destructive effects of electrocoagulation extend more deeply than those of electrodesiccation, the clinician must consider the histologic characteristics of the lesion to be treated when selecting the appropriate current. A partial list of dermatologic conditions that are commonly treated by each electrosurgical modality is found in Table 140.1.

There are no absolute contraindications to the use of electrosurgery, but precautions should be taken during the treatment of patients with pacemakers or ICDs (see Variations/unusual situations, below).

PREOPERATIVE HISTORY AND CONSIDERATIONS

The preoperative assessment of patients undergoing electrosurgery should concentrate on potential hazards to either the patient or the treatment team. A patient history of previous allergic reactions to skin cleansers, anesthetics, or postoperative topicals and dressings should be sought. Electrosurgery should be used with care in patients with cardiac pacemakers and ICDs.

Smoke evacuation equipment should always be available to safely remove the smoke plume when extensive electrosurgery, particularly electrosection, is performed. In such procedures, the operator and assistants should wear masks and use eye protection to prevent exposure to smoke-borne microbes. Gloves should always be worn when electrosurgical procedures are performed.

Preparatory to electrosurgery, the lesion and surrounding skin should be cleansed with a non-alcoholic skin cleanser such as chlorhexidine or povidone iodine. There is a potential for alcohol to ignite with electrosurgery, so it should be avoided or allowed to thoroughly dry prior to therapy.

Local anesthesia, usually via 1% lidocaine with epinephrine (adrenaline), is almost always used when performing electrosurgery. The usual exception is in the treatment of small facial telangiectasias, in which anesthesia is omitted. Local infiltration is most often used for anesthetizing localized surface lesions, whereas field blocks and/or nerve blocks should be considered when performing larger electrosurgical procedures such as rhinophyma repair. When a local anesthetic is used prior to treatment of a dome-shaped lesion, such as a large angioma, it is helpful to massage the swollen anesthetized treatment site prior to electrosurgery, in order to flatten it. This prevents the development of a depressed scar subsequent to the procedure.

Prior to activating the electrosurgery unit, the operator should determine that the appropriate current and power settings for the particular

COMMON DERMATOLOGIC INDICATIONS FOR ELECTROSURGERY
ELECTROFULGURATION/ELECTRODESICCATION (SUPERFICIAL SKIN ABLATION)
Acrochordon
Actinic keratosis
Angioma (small)
Epidermal nevus
Hemostasis (capillary bleeding)
Lentigo
Seborrheic keratosis
Verruca plana
ELECTROCOAGULATION (DEEP SKIN ABLATION)
Angiofibroma
Angioma (large)
Basal cell carcinoma
Bowen's disease
Hemostasis (arterial bleeding)
Hirsutism (electroepilation)
Ingrown toenail matrixectomy
Banal melanocytic nevi
Sebaceous hyperplasia
Squamous cell carcinoma
Syringoma
Telangiectasia
Trichoepithelioma
Verruca vulgaris (all locations)
ELECTROSECTION (SKIN INCISION/EXCISION)
Acne keloidalis nuchae
Blepharoplasty incision
Debulking procedures
Hair transplant strip harvesting
Rhinophyma repair
Rhytidectomy incisions and undermining
Scar revision
Shave removal of benign skin lesions (fibromas, nevi, etc.)
Skin flap incisions and undermining
Skin resurfacing
Surgical excision of malignant or benign skin lesions

Table 140.1 Common dermatologic indications for electrosurgery.

procedure have been selected, that the dispersive electrode has been properly placed and that the correct treatment electrode has been chosen. Sterile sleeves that slip over the handle of the wand and disposable electrode tips are often utilized. It is unacceptable to use the same electrode tip on multiple patients without sterilization, erroneously assuming that heat will destroy pathogens.

DESCRIPTION OF TECHNIQUES

Electrodesiccation and Electrofulguration

For very superficial lesions, such as those involving only the epidermis, electrosurgical destruction by *electrodesiccation* can be achieved with little, if any, scarring. The markedly damped, high-voltage current generated by spark gap electrosurgical units causes superficial tissue damage by dehydration of the treatment site. It is delivered in a monoterminal (concentrative) fashion (see Fig. 140.1). If the electrode is held at a slight distance from the tissue, a spark is formed between the electrode and the tissue. This technique, termed *electrofulguration*, achieves very superficial destruction because the surface carbonization it produces insulates the underlying tissues from thermal heat spread.

Dermatologists who employ a Hyfrecator® or similar device often utilize this type of waveform. As the surface becomes charred by sparking at the surface, it is common for blood to appear in droplets that penetrate through the surface char. This is because the electrical current does not penetrate deeply enough to seal nearby blood vessels. Therefore, when surgical excision is undertaken, electrocoagulation is a better current to employ in order to provide hemostasis (see below). However, for treatment of very superficial epidermal lesions, electrofulguration should be considered the waveform of choice.

Electrodesiccation is the method of choice when the most superficial type of tissue destruction is desired. For example, it is ideal for treatment of epidermal lesions such as seborrheic or actinic keratoses (Fig. 140.3), acrochordons, verrucae planae or small epidermal nevi. Hemostasis of mild capillary bleeding can also be achieved by use of electrodesiccation. A standard technique for treating keratoses by this method is to move the electrode slowly across the surface of the lesion (for small lesions) or to insert it directly into the lesion (for larger lesions), while applying current at a low power setting. After a few seconds, the lesion bubbles as the epidermis separates from the underlying dermis. It can then be easily removed with a curette or simply by rubbing a piece of gauze across the treatment site. The clinical endpoint in treating epidermal lesions is punctate bleeding, which is controlled with pressure, by spot electrocoagulation, or by topical hemostatic agents such as aluminum chloride. More profuse bleeding indicates probable damage to the dermis, with a greater likelihood of subsequent scarring. Extremely small superficial lesions can be treated by electrofulguration, which causes the least amount of damage to adjacent tissues.

Electrocoagulation

In electrocoagulation, a moderately damped current is applied in a *biterminal* manner (both concentrative and dispersive electrodes are used). This current is of higher amperage and lower voltage than that utilized for electrodesiccation. Because this type of current penetrates more deeply, it has the potential for greater tissue destruction.

Electrocoagulation is particularly useful for deep tissue destruction and surgical hemostasis. It is our preferred modality for treating small and uncomplicated primary basal cell and squamous cell carcinomas, as well as other lesions such as trichoepitheliomas, which extend into the dermis. Much of the literature refers to "curettage and electrodesiccation (C&E)" or "electrodessication and curettage (ED&C)", but, in fact, electrocoagulation may be the preferred electrosurgical waveform for all but the most superficial tissue destruction.

When performed properly, electrosurgery plus curettage yields cure rates of 90–95% for uncomplicated basal cell carcinomas and superficial squamous cell carcinomas, making it an efficient, cost-effective treatment. Thorough curettage is likely the key element affecting success. Initially, a large curette (4–6 mm) is used to debulk the tumor, followed by a smaller curette (2 mm). The curette should be scraped across the surface of the treatment site in every direction, from superior to inferior, inferior to superior, left to right and right to left, using fairly firm downward pressure. In this way, all tumor extensions are eradicated.

After thorough curettage, the electrode is brought into direct contact with the tissue to be treated and is moved slowly around the periphery and across the curetted portion of the lesion, which eventually becomes charred. A curette may then be used to gently remove the charred tissue. For treatment of skin cancers, this procedure is repeated two or more times in an attempt to remove any small tumor extensions (Fig. 140.4). During the last curettage, a very small curette (1 mm) may be used to remove the final tiny "roots" of the tumor. Scarring must be expected with this procedure, and wounds following curettage and electrosurgery are allowed to heal by second intention.

Electrocoagulation is also effective for treatment of superficial telangiectasias (Fig. 140.5), unwanted hair (electroepilation) and ingrown toenails (electrosurgical matrixectomy). Hemostasis using electrocoagulation can be achieved by either monopolar or bipolar means. Because the electrosurgical energy may be transmitted for several millimeters along the vessel wall, it is important to use the minimum effective exposure time and power setting in order to prevent delayed bleeding from damaged vessels. We often use monopolar electrocoagulation, in which the electrode is touched directly to the bleeding vessel. Coagulation can also be achieved by touching the electrode to a hemostat that has been clamped on the severed vessel. In bipolar electrocoagulation (Fig. 140.6), a bipolar forceps is used to provide more directed pinpoint hemostasis. Electrocoagulation current delivered in this manner causes less adjacent tissue damage but requires a dry operative field to be effective.

Electrosection (cutting)

Electrosection involves the biterminal application of a slightly damped current. The current, of low voltage and high amperage, causes minimal lateral heat spread and tissue damage, and has the additional advantage

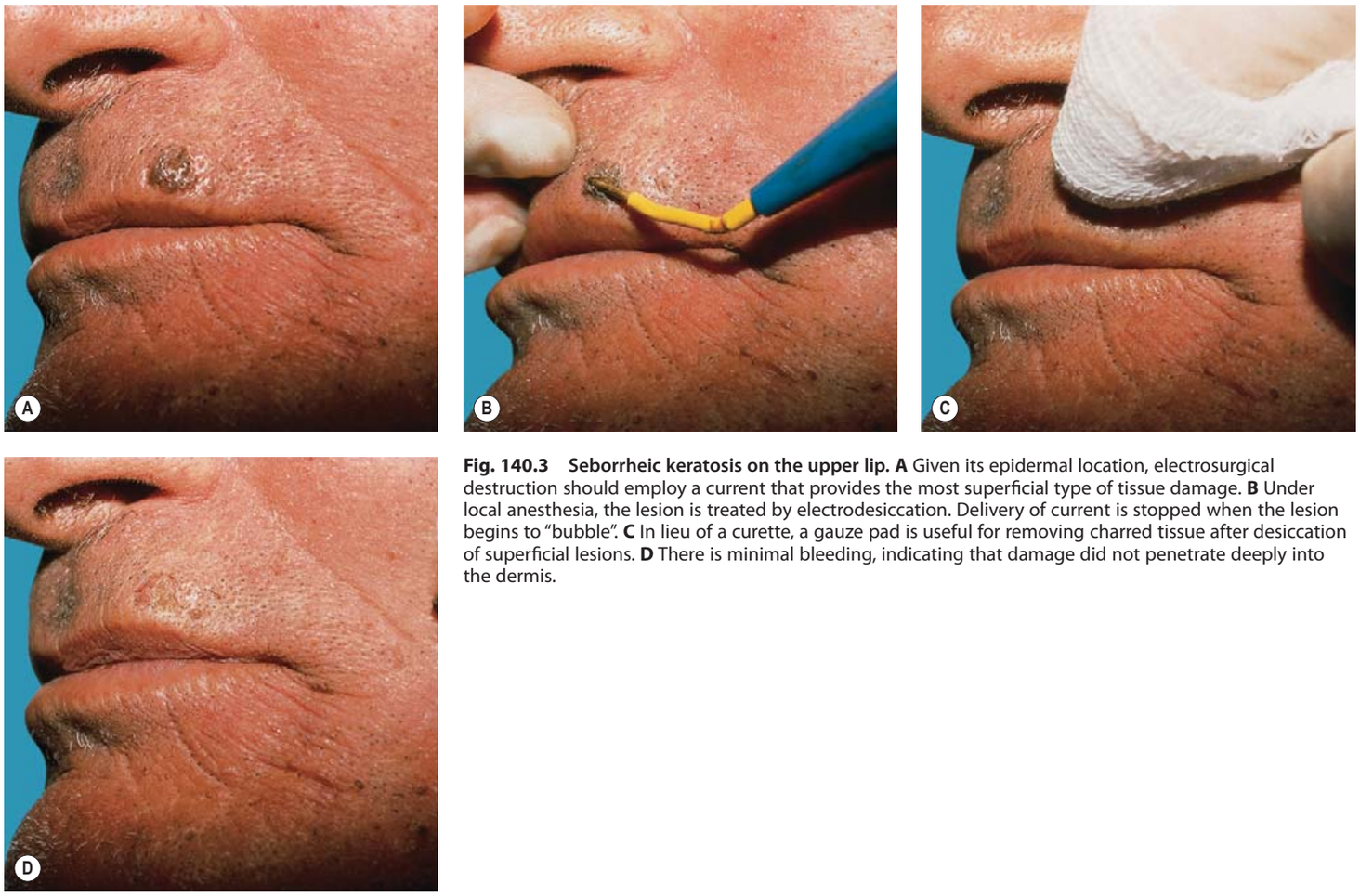


Fig. 140.3 Seborrheic keratosis on the upper lip. A Given its epidermal location, electrosurgical destruction should employ a current that provides the most superficial type of tissue damage. **B** Under local anesthesia, the lesion is treated by electrodesiccation. Delivery of current is stopped when the lesion begins to "bubble". **C** In lieu of a curette, a gauze pad is useful for removing charred tissue after desiccation of superficial lesions. **D** There is minimal bleeding, indicating that damage did not penetrate deeply into the dermis.

Fig. 140.4 Basal cell carcinoma on the right deltoid area, treated by curettage and electrosurgery. A Nodular basal cell carcinoma preoperatively after injection of local anesthesia. **B** The tumor is curetted to debulk all friable tissue. **C** Further curettage, often with a smaller-diameter curette, should proceed in all directions to remove small extensions of tumor. **D** Following thorough curettage, the surface and periphery of the wound are treated by electrocoagulation current to stop bleeding and potentially remove further tumor. **E** Final wound – curettage and electrosurgery have been repeated twice more, until all friable tissue has been removed. Healing occurs over 4–6 weeks, depending upon the site.

Fig. 140.5 Telangiectasias on nose and upper lip being treated by fine-needle electrocoagulation. A Preoperative photograph shows linear telangiectasias on the nose and upper lip. **B** The electrode consists of a hub adapter with a 30-gauge metal-hubbed needle attached. The machine is energized at a low power setting and the electrode momentarily touches the skin surface, along the length of the vessel being treated, at 3 to 4 mm intervals. The patient experiences some discomfort during the procedure, but this is usually tolerable. **C** The same patient immediately after treatment. This technique is usually performed quickly without anesthesia.

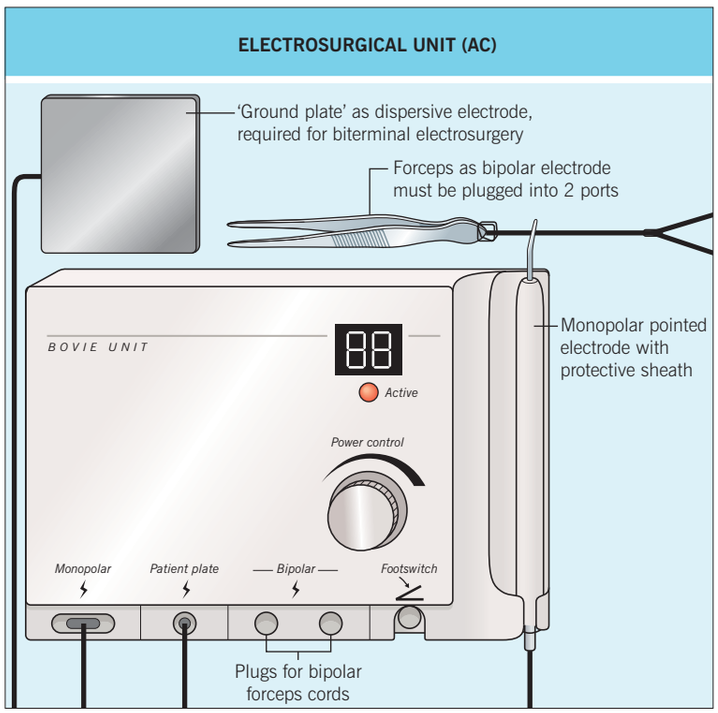


Fig. 140.6 Electrosurgical unit (AC) with attached electrosurgery pencil. The monopolar pencil is used for electrodesiccation and electrofulguration. When used with the grounding plate, it is utilized in a biterminal mode for electrocoagulation. Alternatively, the unit can be used with the bipolar forceps to provide pinpoint electrocoagulation for hemostasis. Bipolar electrocoagulation is also recommended for use in patients with cardiac pacemakers.

of simultaneously achieving hemostasis and cutting. "Pure" cutting can be obtained using a true undamped tube current, which provides the least amount of lateral heat spread and causes vaporization of tissue without hemostasis. Such current has been suggested by Chiarello[15] to be useful in debulking large skin cancers, contouring surrounding skin following shave excisions, scar revision following skin flaps and grafts, and rhinophyma repair. When electrosection is performed using a filtered, fully rectified current, subsequent spot electrocoagulation can be achieved by changing to the electrocoagulation current.

Electrosection can be used to perform rapid and effortless excisions or incisions. Virtually no manual pressure by the operator is required. Electrodes configured as loops, triangles or diamonds can be used for quick removal of skin tags, papillomas, intradermal nevi and other exophytic skin lesions. A straight, narrow electrode is most often used to incise the skin and is applied to the tissue in brisk, continuous paintbrush-like strokes. The difference between electrosection and scalpel excision is immediately apparent to the first-time user of electrosection. At the appropriate power setting, the electrode passes smoothly through the tissue like a "hot knife through butter". If perceptible sparking occurs during incision, the power setting is too high; if the electrode "drags", the power setting is too low.

Slightly damped currents cause some charring at the margins of the excised tissue. Therefore, when a specimen suitable for histopathologic analysis is required, the filtered current (see Fig. 140.2) should be used because it does not create significant electrosurgical artifact. It is recommended that the new initiate to electrosection develop technical skills and concepts by practicing on beefsteak before utilizing these techniques in the clinical arena.

The major advantage of electrosection over scalpel surgery is that when a blended cutting and coagulating current is utilized, hemostasis is achieved immediately as the incision is made. However, larger blood vessels (>2 mm) require additional spot electrocoagulation at the completion of the excision. Another drawback is that vaporization of the tissue generates a smoke plume, which can be unpleasant for both the patient and the operator and may contain potentially infectious viral particles (see below). Consequently, effective smoke evacuation equipment should be available during such procedures.

Electrosection is extremely useful for achieving relatively bloodless excision of large, bulky lesions, such as acne keloidalis nuchae and rhinophyma (Fig. 140.7), in which the surgical defect is allowed to heal by second intention. Electrosurgical excision followed by primary closure can also be undertaken with no impairment of wound healing, as compared with conventional scalpel surgery. This modality has been used, without complication, to create skin flaps and perform cosmetic facial surgery, including blepharoplasty and rhytidectomy, with excellent outcomes.

VARIATIONS/UNUSUAL SITUATIONS

Cardiac Pacemakers and ICDs

The use of electrosurgery in patients with cardiac pacemakers or ICDs raises the question of whether the flow of electrical energy during electrosurgery might interfere with the function of these devices[16]. Although modern pacemakers and ICDs have improved shielding technology to guard them from the influence of external electromagnetic currents, prudence requires that a modicum of precaution be taken. If used indiscriminately in these patients, electrosurgery can occasionally

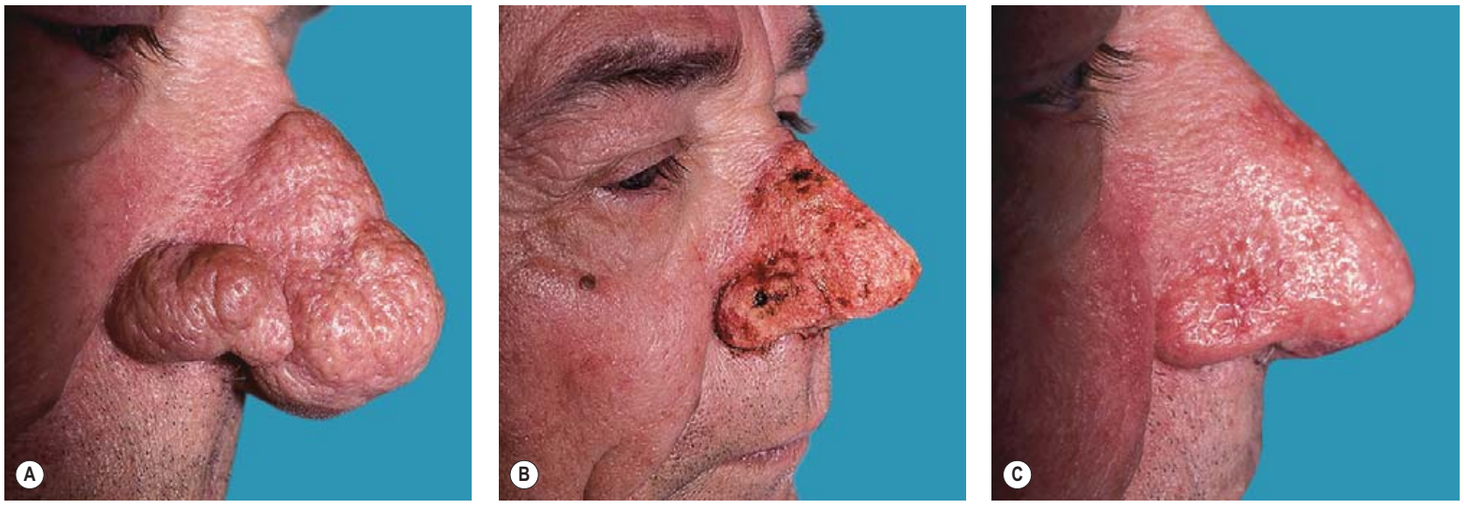


Fig. 140.7 Rhinophyma. A Moderately severe rhinophyma in a middle-aged man. **B** Immediately after electrosurgical planing of excess sebaceous glands. Care is taken to perform subtotal removal as very aggressive therapy can result in significant scarring and possible deformity caused by scar contracture. **C** Four weeks later, healing with good cosmetic outcome is noted. During healing, the wound is kept moist with an antibiotic ointment and semi-occlusive dressings.

trigger skipped beats, reprogramming of a pacemaker, firing of an ICD, asystole or bradycardia.

Routine precautions recommended when using electrosurgery in patients with pacemakers and ICDs include: (1) utilize short bursts of energy that are less than 5 seconds in duration; (2) keep power settings as low as possible; (3) avoid the use of cutting current; and (4) avoid use on the skin around the pacemaker or ICD. Although recommended in the literature, most dermatologists do not follow specific precautions such as intraoperative monitoring, preoperative cardiology consultation, or postoperative evaluation of the cardiac device by a cardiologist. This may be due to the fact that to date there have been no reported cases of interference with a pacemaker or ICD in a dermatologic setting. Also, at least one article suggests that practical experience of complications due to electrosurgical interference is rare among dermatologic surgeons[17].

There is less risk of potential side effects when the electrosurgical current is confined to a very small area, as is the case when bipolar forceps are used as electrodes. A way to virtually eliminate such risk in very unstable cardiac patients or those with ICDs is to use true electrocautery, rather than other forms of electrosurgery[18]. Although the use of this modality may cause more of a burn injury than does true electrosurgery, there is no flow of current to cause electrical interference. In a survey of Mohs surgeons, 34% used electrocautery and 19% used bipolar forceps in patients with pacemakers or ICDs. Among this group, there was only one reported case of interference in one of the electrocautery patients. However, since there is no current flow in true electrocautery, this was likely an error in reporting.

It is the author's belief that the use of either electrocautery or bipolar forceps as electrodes in pacemaker and ICD patients will eliminate the need for intraoperative monitoring, preoperative cardiology consultation or postoperative evaluation by a cardiologist in the majority of patients.

POSTOPERATIVE CARE

Standard postoperative wound management, incorporating antibiotic ointments and/or semi-occlusive dressings, is followed. For superficial skin ablations, such as those following electrodesiccation or electrofulguration, twice-daily application of an antibiotic ointment or petrolatum is generally all that is required. An adhesive plaster may be used if the area is prone to rubbing. An eschar forms within a few days and separates in about 10 days. For deeper wounds, in which healing can take 2–4 weeks (or longer on the lower extremities), once- or twice-daily application of an antibiotic ointment followed by an adhesive plaster is recommended. For larger wounds, such as those following rhinophyma repair, Telfa™ sheets are cut to size to cover the defect and kept in place with semi-occlusive paper tape (e.g. Micropore®, 3M Corporation, MN).

COMPLICATIONS

Patients should be warned of the possibility of delayed bleeding and should be reassured that it can, in the vast majority of cases, be controlled by 20–30 minutes of constant direct pressure over the wound. Trips to the local emergency room to stop postoperative bleeding are unusual but can occur. Patients should also be advised that for ablative procedures, scarring, in the form of a hypopigmented area, may occur.

Other potential hazards of electrosurgery are briefly discussed below.

Fire

There is a risk of fire or explosion if electrosurgical procedures are conducted in the presence of alcohol, oxygen or bowel gases (methane). Care should be taken to be certain that the operative site is free of alcohol residue. Oxygen is usually not a problem except in the operating room setting. Bowel gases are highly flammable! Use care in the perianal region.

Thermoelectric Burns

Although modern generators are isolated from earth, and are often equipped with sophisticated monitoring systems, current can still be diverted away from the return electrode and cause an accidental burn at the point at which it leaves the patient's body. Alternative pathways occur when the current is diverted from the return electrode and finds an alternative path to return to the generator. When the point of contact between the patient and the grounded object is small, even a relatively low-power current can generate sufficient current density to cause a burn. Grounded objects may include metal parts of the operating table, table accessories, or ECG electrodes. This problem is reduced, but not eliminated, by the use of isolated electrosurgical units, which have little or no connection to the ground.

Microorganism Transmission

The potential exists for transmission of microorganisms either via the electrode[19,20] or via smoke plume inhalation. Neither possibility has been investigated in sufficient depth to yield conclusive results. Practitioners should minimize the risk of possible electrode transmission by using disposable or sterilized electrodes. Adapters are available that allow disposable metal hypodermic needles to be used as electrodes.

Surgical Smoke

During surgical procedures using a laser or electrosurgical unit, the thermal destruction of tissue creates a smoke by-product. Research studies have confirmed that this smoke plume can contain toxic gases and vapors such as benzene, hydrogen cyanide and formaldehyde, bioaerosols, dead and live cellular material (including blood fragments)[21],

and viruses[22]. At high concentrations, the smoke causes ocular and upper respiratory tract irritation in healthcare personnel and creates visual problems for the surgeon. The smoke has unpleasant odors and has been shown to have mutagenic potential[23].

Research by the National Institute for Occupational Safety and Health (NIOSH) has shown that airborne contaminants generated by these surgical devices can be effectively controlled by appropriate ventilation using a portable smoke evacuation system. Smoke evacuators contain a suction unit (vacuum pump), filter, hose, and an inlet nozzle. The smoke evacuator should have high efficiency in airborne particle reduction and should be used in accordance with the manufacturer's recommendations to achieve maximum efficiency. A capture velocity of approximately 100–150 feet per minute at the inlet nozzle is generally recommended. It is also important to choose a filter that is effective in collecting the contaminants. A high-efficiency particulate air (HEPA) filter or equivalent is recommended for trapping particulates. Various filtering and cleaning processes also exist which remove or inactivate airborne gases and vapors. The different filters and absorbers used in smoke evacuators require monitoring and replacement on a regular basis and are considered a possible biohazard requiring proper disposal.

The smoke evacuator hose inlet nozzle must be kept within 2 inches of the surgical site to effectively capture airborne contaminants generated by these surgical devices. The smoke evacuator should be activated at all times when airborne particles are produced during an electrosurgical procedure that generates a significant smoke plume. After each procedure, all tubing distal to the filter must be considered infectious waste and be disposed of appropriately. The filters themselves may be used for the cumulative time specified by the manufacturer, before replacement.

ELECTROEPILATION

Electroepilation is the use of electricity for the permanent removal of hair[24]. It predated the development of laser hair removal and is still used, in a variety of forms, by aestheticians and electrologists. The word *electrolysis,* which is used by most people as a generic term to mean the electrical destruction of hair, is technically the use of direct (galvanic) current for hair removal. Hair destruction with an alternating current occurs as a result of the accumulation of heat in the vicinity of the hair bulb and is designated *thermolysis*.

Electrolysis vs Thermolysis

Electrolysis uses direct current to create a destructive chemical reaction at the hair root. The negative electrode (anode) is inserted into the hair follicle (see Fig. 140.1). The positive electrode (cathode) is a moistened pad held in the patient's hand. When direct current is applied, a chemical reaction at the tip of the anode causes the production of sodium hydroxide. The latter acts as a caustic and destroys the hair root. This process may take from 30 to 60 seconds to occur, so pure "galvanic electrolysis" is a tedious procedure to perform. Of note, electrolysis can also be used to treat small telangiectasis (see Fig. 140.1).

Thermolysis relies on heat to cause hair destruction. A high-frequency (13.56 MHz) alternating current is used. As the current passes through tissue, it encounters resistance, causing the current to stall and convert to heat. Current can be applied by the "slow" (manual) technique or the "flash" technique. Lower heat is used over 3–10 seconds in the slow technique. Gentle traction of the hair allows the operator to determine when destruction is complete. The flash technique uses higher heat, delivered by a preset mechanical timer (<1 second). Several such pulses may be required to cause hair root destruction. Theoretically, the flash technique is less painful.

The technique for needle insertion is the same as for electrolysis. A patient hand-held electrode is not required since the patient is not included in the electrical circuit. The speed of thermolysis allows for treatment of much larger areas over a shorter time period. For this reason, it has replaced galvanic electrolysis as the preferred manner of electroepilation. The *blend* is a form of electroepilation that takes advantage of attributes of both electrolysis and thermolysis, by blending the two types of current in one machine. The blend is slower than thermolysis, but may offer some advantages in rate of hair root destruction, particularly for coarser hairs.

Side Effects

Thermolysis and the blend are more painful than classic galvanic electrolysis and the risk of scarring and hair regrowth may be higher. However, highly motivated patients generally tolerate the pain and are treated with 30–60-minute sessions once or twice weekly. The use of topical anesthetics under occlusion for 1–2 hours pretreatment decreases the pain in some patients. Scarring is a real risk and is operator-dependent. Generally, when this occurs, it presents as punctate or ice-pick-like depressed lesions. In some patients, small hypertrophic papules may be present.

Hair regrowth has been reported in the range of 15% to 50%, and this is also technique-dependent. Regrowth may be related, in part, to the hair cycle. Hairs treated while in telogen phase may not experience root destruction. Some electrologists recommend shaving 2 days prior to treatment so that only actively growing hairs will be apparent.

Varying degrees of erythema and edema may be present shortly after the procedure. Postinflammatory hypo- and hyperpigmentation have been reported. The theoretical risk of infections, both local and systemic, exists, but proper skin cleansing helps prevent this problem. Some patients have a higher propensity for developing post-treatment folliculitis and it is recommended that they cleanse with an antibacterial cleanser (e.g. chlorhexidine), before and after treatment. Disposable needles are the norm in the practice of permanent hair removal.

IONTOPHORESIS

In some patients, tap or deionized water iontophoresis can be used successfully to treat localized hyperhidrosis of the palms, soles or axillae. In this technique, direct electrical current is passed through the treatment site while the patient is in contact with an aqueous ionic solution. The electric current introduces ions from the solution into the patient's skin and appears to inhibit sweating by occluding the eccrine ducts at the level of the stratum corneum[25].

A battery-powered unit for home use (Drionic®) is available. It is more effective for treatment of palmoplantar hyperhidrosis than for axillary hyperhidrosis. Cessation of sweating usually requires treatment of each palm or sole with 20 mA of current for 30 minutes daily. The recent use of botulinum toxin type A injections for hyperhidrosis has provided many hyperhidrosis sufferers with a more efficient and lasting treatment modality, albeit at greater expense.

FUTURE TRENDS

Interest and innovation in electrosurgery have actually increased over the past two decades, since continuous wave CO_2 laser systems were introduced. Practitioners came to realize that superficial ablation, deep ablation, and tissue incision with immediate hemostasis were available through electrosurgery without the need for expensive laser systems. As examples, specially adapted electrosurgery equipment that utilizes electricity to remove the epidermis and upper dermis for facial skin resurfacing has been introduced[26] as has the use of electrosurgical cutting current (Ellman Surgitron®) to resurface surgical scars. The latest electrosurgical development is use of a standard radiosurgery device (Surgitron® Dual Frequency RF) for non-ablative tightening of skin laxity[27]. Radiofrequency current produces heat because of resistance in the dermis and subcutaneous tissue. When heated, collagen fibrils will denature and contract, presumably leading to the observed tissue tightening.

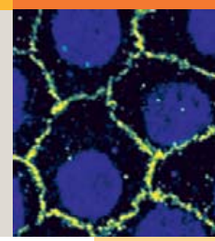
REFERENCES

1. Blankenship ML. Physical modalities. Electrosurgery, electrocautery and electrolysis. Int J Dermatol. 1979;18:443–52.
2. Mitchell JP, Lumb GN. Principles of surgical diathermy and its limitations. Br J Surg. 1962;50:314–20.
3. d'Arsonval A. Action physiologique des courants alternatifs. Soc Biol. 1891;43:283–6.
4. d'Arsonval A. Action physiologique des courants alternatifs à grande fréquence. Arch Physiol Norm Path. 1893;5:401–8.
5. Rivière AJ. Action des courants de haute fréquence et des effleuves du résonateur Oudin sur certaines tumeurs malignes. J Méd Intern. 1900;4:776–7.
6. Pozzi M. Remarques sur la fulguration. Bull Assoc Franc Cancer. 1909;2:64–9.

7. Doyen D. Sur la destruction des tumeurs cancéreuses accessibles par la méthode de la voltaisation bipolaire et de l'électro-coagulation thermique. Arch Elec Med Exp Clin. 1909;17:791–5.
8. Clark WL. Oscillatory desiccation in the treatment of accessible malignant growths and minor surgical conditions: a new electrical effect. J Adv Therap. 1911;29:169–83.
9. Wyeth GA. Endothermy, surgical adjunct in accessible malignancy and precancerous conditions. Surg Gynec Obstet. 1923;36:711–14.
10. Wyeth GA. The endotherm. Am J Electrotherapeut Radiol. 1924;42:186–7.
11. Cushing H. Electro-surgery as an aid to the removal of intracranial tumors, with a preliminary note on a new surgical-current generator by WT Bovie, PhD. Surg Gynec Obstet. 1928;47:751–2.
12. Goldwyn RM. Bovie: the man and the machine. Ann Plast Surg. 1979;2:135–53.
13. Pollack SV. Electrosurgery of the Skin. New York: Churchill Livingstone, 1991.
14. Sebben JE. Cutaneous Electrosurgery. Chicago: Year Book Medical Publishers, 1989.
15. Chiarello S. Controlled vaporization of tumor tissue utilizing radio frequency cutting current through a blunt hockey stick scalpel or radio frequency knife. Dermatol Surg. 1998;24:158–60.
16. Riordan AT, Gamache C, Fosko SW. Electrosurgery and cardiac devices. J Am Acad Dermatol. 1997;37:250–5.
17. El-Gamal HM, Dufresne RG Jr, Saddler K. Electrosurgery, pacemakers and ICDs: a survey of precautions and complications experienced by cutaneous surgeons. Dermatol Surg. 2001;27:385–90.
18. Wilson JH, Lattner S, Jacob R, Stewart R. Electrocautery does not interfere with the function of the automatic implantable cardioverter defibrillator. Ann Thorac Surg. 1991;51:225–6.
19. Sherertz EF, Davis GL, Rice RW, et al. Transfer of hepatitis B virus by contaminated reusable needle electrodes after electrodesiccation in simulated use. J Am Acad Dermatol. 1986;15:1242–6.
20. Bennett RG, Kraffert CA. Bacterial transference during electrodesiccation and electrocoagulation. Arch Dermatol. 1990;126:751–5.
21. Berberian BJ, Burnett JW. The potential role of common dermatologic practice techniques in transmitting disease. J Am Acad Dermatol. 1986;15:1057–8.
22. Sawchuck WS, Weber PJ, Lowy DR, et al. Infectious papillomavirus in the vapor of warts treated with carbon dioxide laser or electrocoagulation: detection and protection. J Am Acad Dermatol. 1989;21:41–9.
23. Tomita Y, Mihashi S, Nagata K, et al. Mutagenicity of smoke condensates induced by CO_2-laser irradiation and electrocauterization. Mutat Res. 1981;89:145–9.
24. Pollack SV, Grekin RC. Electrosurgery and Electroepilation. In: Roenigk RK, Roenigk HH (eds). Dermatologic Surgery: Principles and Practice, 2nd edn. New York: Marcel Dekker, 1996:219–31.
25. Sato K, Timm DE, Sato F, et al. Generation and. transit pathway of H^+ is critical for inhibition of palmar sweating by iontophoresis in water. J Appl Physiol. 1993;75:2258–64.
26. Grekin RC, Tope WD, Yarborough JM Jr, et al. Electrosurgical facial resurfacing: a prospective multicenter study of efficacy and safety. Arch Dermatol. 2000;136:1309–16.
27. Rusciani A, Curinga G, Menichini G, et al. Nonsurgical tightening of skin laxity: a new radiofrequency approach. J Drugs Dermatol. 2007;6:381–6.

This page intentionally left blank

Biology of Wound Healing



Sabine A Eming

Chapter Contents

Wound repair and regeneration in different species 2313
Impact of wound depth on wound healing 2314
Skin repair – cellular and molecular aspects 2315
Abnormal wound healing 2322
Therapeutic options for chronic wounds 2323
Future directions 2323

Key features

- Wound healing is a complex and dynamic biologic process, consisting of three consecutive phases: inflammation, tissue formation and tissue remodeling
- Effective wound healing requires synchronization of cell–cell and cell–matrix interactions as well as an interplay of cytokines
- Extracellular matrix proteins are multifunctional molecules that bind directly to cell surface receptors (e.g. integrins) and influence the effects of growth factors on cells (e.g. TGF-β)
- In children and adults, the cutaneous wound healing response represents a *reparative* process that can lead to fibrosis (scar), whereas injured fetal tissue can heal completely without fibrosis, in a process resembling *regeneration*
- A number of systemic diseases (e.g. diabetes mellitus, atherosclerosis) as well as more local factors (e.g. pressure, infection) are associated with chronic non-healing wounds

INTRODUCTION

Restoration of skin integrity and homeostasis following injury is a fundamental process that ensures survival. The primary goal of the wound healing response is to re-establish a functional skin barrier as quickly as possible. Ideally, the wound healing response would lead to complete regeneration of skin tissue and its adnexal structures, with complete restoration of original skin function and morphology. Unfortunately, this is often not the final result of wound repair and the quality of newly formed skin tissue varies considerably.

Regeneration Versus Repair

In children and adults, the wound healing response characteristically leads to fibrosis, i.e. scar formation. In addition, adnexal structures (e.g. hair follicles, sweat and sebaceous glands) as well as components of the dermal extracellular matrix may fail to regenerate, resulting in a loss of normal skin function and impaired morphology. Because it is less than ideal, this type of wound healing is sometimes referred to as a *reparative process*.

In contrast, during embryogenesis, injured fetal skin can heal completely without fibrosis. Thus, the process resembles *regeneration*. Fibromodulin (FMOD), a small leucine-rich proteoglycan, is thought to mediate scarless fetal skin wound repair, at least in part, via transforming growth factor-β (TGF-β) modulation[1]. Compared to wild-type mice, *fmod*$^{-/-}$ mice were found to have delayed wound closure and a significant increase in scar size, and this was partially rescued by exogenous FMOD administration[1].

Of note, there are vertebrates such as amphibians and fish that retain the capability to regenerate tissues throughout adult life (see below). Obviously, insights gained into this process, as well as from fetal skin wound repair, could provide methods for transforming repair into regeneration and novel therapies for wound healing.

Effect of Immune Response on Wound Healing

The immune system, including neutrophils and macrophages, plays a critical role in wound healing (see Fig. 141.3). By influencing the repair process, inflammation has an impact on the quality of the wound and the extent of scarring[2]. In a number of models, there appears to be an inverse correlation between the strength of the inflammatory immune response and the ability to undergo regeneration, with inappropriate immune reactions leading to tissue damage and impairment of tissue repair (Fig. 141.1). On the other hand, there is evidence that appropriate immune responses may actually promote repair and protect local tissues.

WOUND REPAIR AND REGENERATION IN DIFFERENT SPECIES

Amphibians

Among the vertebrates, amphibians and fish are exceptional in their capacity to regenerate anatomically complete and fully functional tissues and organs during adulthood. In particular, urodele amphibians (newts and salamanders) can regenerate a range of organs and tissues[3], with cellular and molecular studies focusing on limb regeneration. Regeneration in urodele amphibians involves dedifferentiation of cells at the site of amputation injury, followed by their proliferation to produce a blastema that finally reforms the missing tissue. The excellent capacity for regeneration in these species may be related to the fact that the regenerative response induces only minimal inflammation, but further investigations are required.

Zebrafish

Zebrafish also represent a valuable model for the study of regeneration because even as adults, they are able to regenerate their entire caudal fin following its amputation[5]; this includes the original pigment and color structures. Early on, there is an infiltration of myeloid inflammatory cells, with complete regeneration occurring in the presence of this inflammation. Of note, loss of the gene responsible for myeloid cell lineage development (PU.1) can fully abrogate the inflammatory response, but this has no effect on fin regeneration[6]. In other words, fin regeneration in zebrafish is independent of the inflammatory response.

Mammals

The effects of inflammation on regeneration and repair have also been studied in mammals, primarily in mice, but also in humans. Postnatally, the repair response leads to scar formation whereas injured fetal

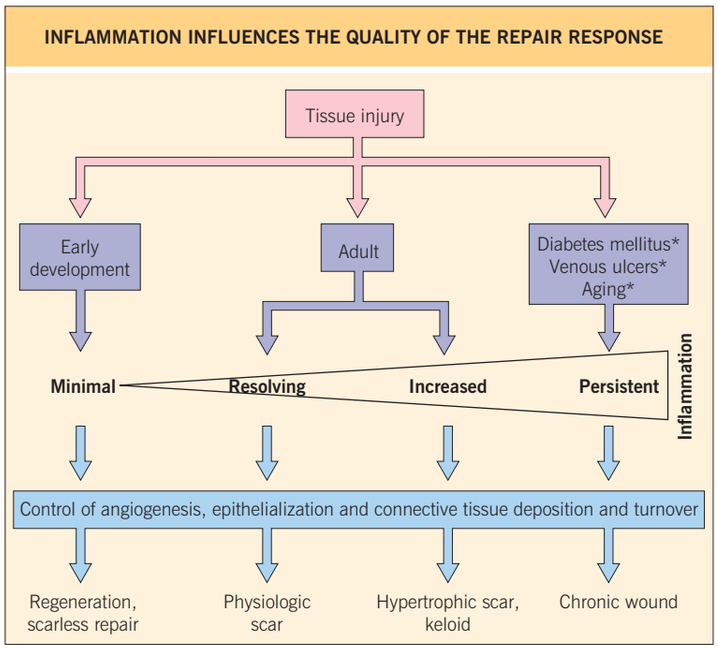


Fig. 141.1 Inflammation influences the quality of the repair response. Modulation of the local immune response at the site of injury can influence repair mechanisms and the quality of tissue restoration. *The underlying etiology of chronic, non-healing ulcers is multifactorial and it includes hypoxia due to vascular disease or sustained pressure and infection, as well as persistent inflammation (see Ch. 105).

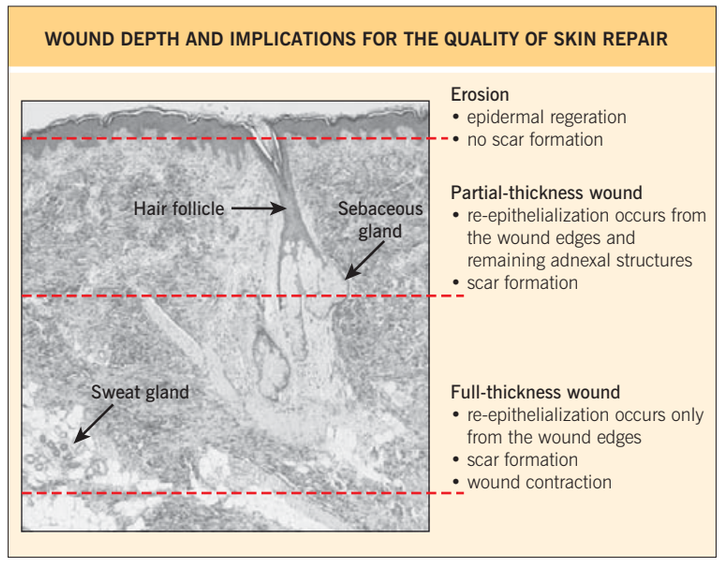


Fig. 141.2 Wound depth and implications for the quality of skin repair. The depth of skin injury determines the ability of the skin to repair versus regenerate. The red dashed lines indicate the levels of injury: injury limited to the epidermis has the capability for regeneration, while injuries to the dermis heal with scar formation. If adnexal structures are present, they contribute to re-epithelialization and wound closure is faster (see Fig. 141.3). If these structures are lost, epithelia can only migrate from the wound edges and complete restoration of the epidermis will require a longer time period.

skin can completely regenerate in a scarless manner (see above)[7]. One major difference between these two clinical settings is the lack of significant inflammation in fetal skin post injury. Other factors that may possibly play a role include differences in the extracellular matrix, cellular mediators, gene expression profiles, and as revealed by transplantation experiments, yet unknown factors intrinsic to fetal skin[7a].

One remarkable example of tissue regeneration in the presence of a functional immune system is the phenomenon of post-amputation fingertip regeneration in higher vertebrates, including rodents and humans. In neonate and adult rodents, regeneration of the digital tip can occur, including the terminal phalangeal bone[8], via the formation of a blastema-like structure containing proliferating undifferentiated cells (similar to limb regeneration in amphibians). These cells express bone morphogenetic protein-4 (BMP-4), the protein product of a gene known to be expressed during the embryonic development of digits[9]. Even in children, but not adult humans, conservatively managed amputation injuries can be followed by restoration of the contour, fingerprints, and normal sensation and function of the digit, with minimal scarring[10]. In humans, the molecular mechanisms underlying this phenomenon are not known.

More recently, transgenic mouse models have provided insights into wound healing[11]. For example, *delayed* wound healing has been observed in mice lacking nidogen 1 (a basement membrane component) or TGF-β, in mice with a fibroblast-specific deletion of integrin β1 (which binds extracellular matrix proteins), in mice that lack superoxide dismutase (an important antioxidative enzyme) or interleukin (IL)-6, and in mice that lack Toll-like receptor 3 and have defective recruitment of neutrophils and macrophages. In contrast, *accelerated* wound healing has been observed in mice that lack matrix metalloproteinases (MMPs) (e.g. ADAM-9) which degrade extracellular matrix proteins and in mice deficient in NK/T cells. Obviously, wound healing is a very complex process and over the next decade, a more precise understanding should emerge.

Clinical Implications

The underlying etiology of chronic, non-healing ulcers is multifactorial (see Ch. 105). It includes hypoxia due to vascular disease or sustained pressure, infection and persistent inflammation[12]. How the latter impairs the healing response is still not well understood, but increased protease activity (e.g. MMPs) and generation of reactive oxygen species are thought to play a role. Additional studies to unravel the underlying molecular pathophysiology of chronic wounds in humans are required, as the search for novel therapies continues.

IMPACT OF WOUND DEPTH ON WOUND HEALING

Skin wounds are often categorized according to their depth (Fig. 141.2). Defects that affect only the epidermis (or a portion of the epidermis) are referred to as *erosions*. When the wound extends into the dermis, it is termed an *ulceration*. In "partial-thickness" wounds, the epidermis and a portion of the dermis are missing, with the ulcer extending into the mid dermis, but the adnexal structures remain. Full-thickness wounds, on the other hand, involve the entire dermis and extend into the subcutaneous fat. As a result, adnexal structures are lost as a source of keratinocytes for re-epithelialization.

The depth of a skin injury clearly affects the capacity of the skin to repair or regenerate. When erosions heal, there is regeneration of the entire epidermis, without scarring (see Fig. 141.2). Ulcerations, however, heal via a reparative process and are associated with scar formation. In partial-thickness wounds, the preserved adnexal structures serve as a source of epithelial cells to repopulate the epidermis (Fig. 141.3). Epithelia from these structures, as well as from the wound edge, migrate across the wound surface to provide coverage. In contrast, because adnexal structures are lost in full-thickness wounds (see above), re-epithelialization can only occur from the wound edges.

Healing of full-thickness wounds includes, to some extent, contraction. While there is minimal contraction in partial-thickness wounds, the reason for this difference is not clear. Contraction may be mediated by mechanical or biologic factors, e.g. the differentiation of fibroblasts into myofibroblasts. During contraction, the wound area decreases via centripetal movement of *pre-existing* tissue, not the formation of new tissue. Unfortunately, contraction of wounds may result in cosmetically disfiguring contractures. However, the contraction of wounds occurs in predictable directions (in relation to "skin tension lines"; see Fig. 142.7) and surgical incisions should be placed, if possible, parallel to these

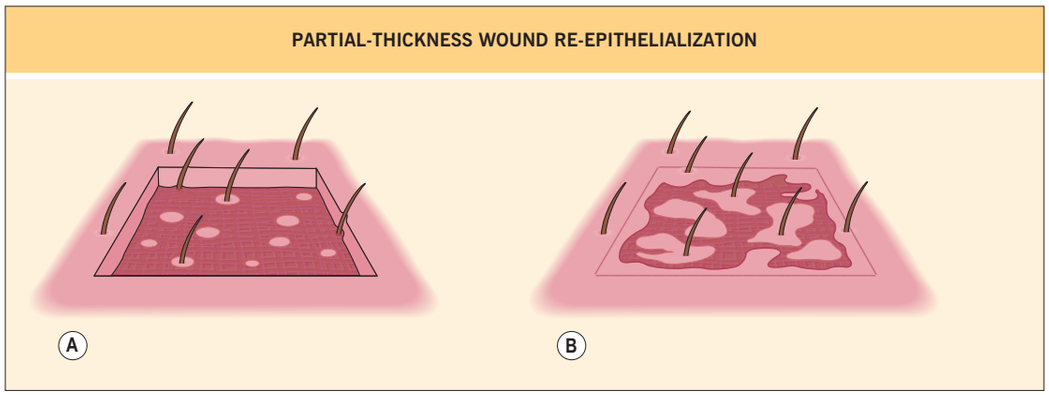


Fig. 141.3 Partial-thickness wound re-epithelialization. A The red area is the wound bed and the pink areas within the wound bed represent remaining adnexal structures; the latter serve as a source of keratinocytes. **B** Over a period of several days after wounding, cells migrate from both the wound edges and the adnexal structures, eventually leading to re-epithelialization. *Courtesy, Robert S Kirsner, MD.*

skin tension lines in order to direct the contracture. Also, an argument in favor of the use of full-thickness skin grafts is to prevent wound contraction and subsequent contracture (see Ch. 148).

Primary versus Second Intention Healing

When an acute wound, such as one resulting from a surgical excision, is allowed to heal on its own, this is termed second (secondary) intention healing (see Ch. 146). In primary intention healing, closure of the wound is accomplished by approximating the wound edges; the latter includes side-to-side closures, flaps and grafts. Both primary and second intention forms of wound healing proceed through the three phases of healing.

In secondary intention healing, the time interval until complete re-epithelialization depends upon several factors. These include wound depth, anatomic location (e.g. facial wounds heal faster than acral wounds), any secondary infection, vascular supply, and geometric shape (for a given area, a more narrow diameter will heal faster). For smaller wounds, especially those that are partial-thickness, primary and second intention healing can produce similar cosmetic results. Once wounds have a diameter >8 mm, primary intention healing leads to better cosmetic results. Tertiary intention healing refers to wounds that are closed with the goal of primary intention healing, but dehiscence occurs and the wound is then allowed to heal by second intention (Fig. 141.4).

The decision to choose primary versus second intention wound healing depends on a number of variables, including a patient's overall medical status and cosmetic concerns, as well as the anatomic location, depth and size of the wound and whether it is located on a convex or concave surface. In addition to comorbidities such as atherosclerosis, venous hypertension and diabetes mellitus, the risk of infection (which may be increased in open wounds) and the patient's preference also influence the decision.

Fig. 141.4 Tertiary intention healing. A Dehiscence of a surgical excision that was closed primarily. **B** Same wound 1 month later, following second intention healing. *Courtesy, Robert S Kirsner, MD.*

SKIN REPAIR – CELLULAR AND MOLECULAR ASPECTS

In most mammalian organ systems, the repair response involves a complex and dynamic interplay of numerous cell types, including cells that reside within the tissue (e.g. keratinocytes, endothelial cells, fibroblasts) and hematopoietic cells recruited to the site of tissue damage. Three sequential phases of wound repair have been delineated – inflammatory, proliferative and remodeling (maturation)[13] and this section discusses the associated cellular and molecular events.

Three Phases of Wound Healing

Tissue injury causes leakage of blood constituents into the wound site and release of vasoactive factors (Table 141.1), resulting in the activation of the clotting cascade. Clotted blood provides a matrix that allows for cell adhesion and migration. Not only do platelets trapped within the clot play an important role in hemostasis, but they also represent a rich source of growth factors (e.g. PDGF) and proinflammatory cytokines that mediate the recruitment of inflammatory cells and fibroblasts into the wound site (Fig. 141.5). The early *inflammatory phase* of repair is characterized by local activation of innate immune

CHEMICAL MEDIATORS OF INFLAMMATION THAT PLAY A ROLE IN WOUND HEALING

Chemical mediator	Action
Histamine	Increased vascular permeability
Serotonin	Stimulation of fibroblast proliferation Cross-linking of collagen molecules
Kinins	Increased vascular permeability
Prostaglandins	Increased vascular permeability Sensitize pain receptors Increased synthesis of GAGs
Complement	Increased vascular permeability Increased phagocytosis Enhanced bacterial lysis Mast cell and basophil activation

Table 141.1 Chemical mediators of inflammation that play a role in wound healing. GAGs, glycosaminoglycans.

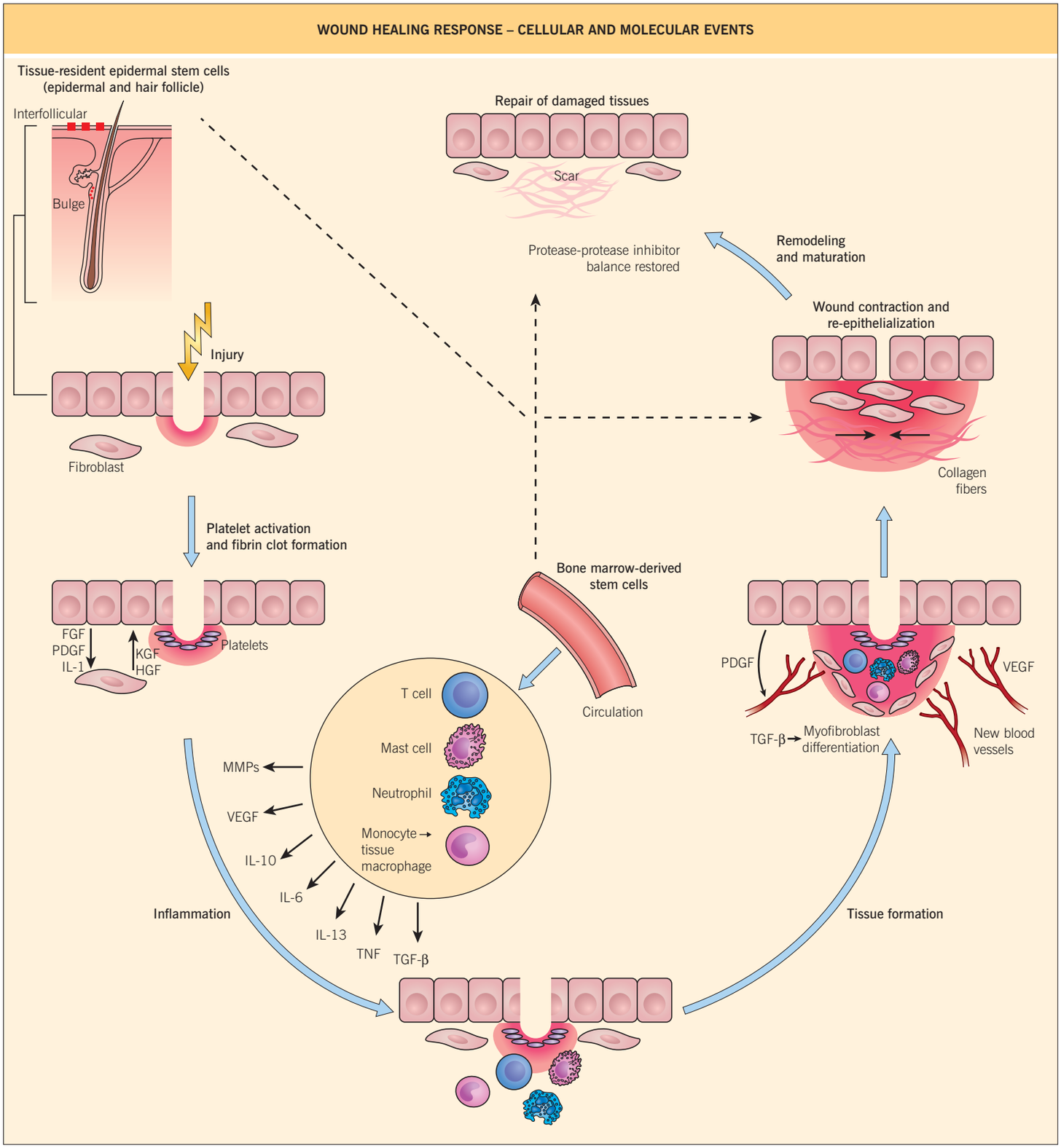


Fig. 141.5 Wound healing response – cellular and molecular events. Leakage of blood constituents and vasoactive factors into the wound site leads to hemostasis. The fibrin clot consists of platelets as well as extracellular matrix molecules (e.g. fibronectin, vitronectin) which facilitate the infiltration and migration of cells. Influx of different subsets of leukocytes characterizes the *inflammatory phase* of repair. These cells release angiogenic growth factors and proinflammatory cytokines, which then induce the recruitment of additional inflammatory cells, fibroblasts and endothelial cells into the wound site. During the *proliferative phase* in which there is formation of granulation tissue, activated macrophages, endothelial cells and fibroblasts form a functional unit essential for efficient blood vessel growth. Transformation of granulation tissue and provisional wound matrix into scar tissue occurs during the *remodeling phase* and this is characterized by a decrease in inflammation and regression of vascular structures. Lastly, stem cells that are intrinsic to the skin (e.g. epidermal stem cells) as well as circulating stem cells contribute to the repair response. FGF, fibroblast growth factor; HGF, hepatocyte growth factor; IL, interleukin; KGF, keratinocyte growth factor; MMPs, matrix metalloproteinases; PDGF, platelet-derived growth factor; TGF, transforming growth factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.
Adapted from Wynn TA. Common and unique mechanisms regulate fibrosis in various fibroproliferative diseases. J Clin Invest. 2007;117:524–9.

GROWTH FACTORS INVOLVED IN WOUND HEALING			
Growth factor	**Abbreviation**	**Source**	**Functions**
Platelet-derived growth factor	PDGF	Platelets, keratinocytes, fibroblasts, endothelial cells, perivascular cells	Fibroblast proliferation, chemotaxis & collagen metabolism; angiogenesis
Transforming growth factor-β	TGF-β	Platelets, keratinocytes, fibroblasts, endothelial cells, macrophages	Fibroblast proliferation, chemotaxis & collagen metabolism; angiogenesis; immunomodulation
Transforming growth factor-α	TGF-α	Platelets, keratinocytes	Keratinocyte proliferation & migration
Epidermal growth factor	EGF	Platelets	Keratinocyte proliferation & migration
Interleukins	IL-1, IL-10	Leukocytes, keratinocytes	Fibroblast proliferation; promotes inflammation
Tumor necrosis factor-α	TNF-α	Leukocytes, keratinocytes	Promotes inflammation
Connective tissue growth factor	CTGF	Fibroblasts, endothelial cells	Fibroblast proliferation, chemotaxis & collagen metabolism
Fibroblast growth factor	FGF	Keratinocytes, macrophages	Fibroblast and epithelial cell proliferation; matrix deposition, wound contraction; angiogenesis
Keratinocyte growth factor	KGF	Fibroblasts	Keratinocyte proliferation
Insulin-like growth factor 1	IGF-1	Fibroblasts	Keratinocyte proliferation & differentiation
Hepatocyte growth factor	HGF	Fibroblasts, macrophages	Keratinocyte proliferation
Vascular endothelial growth factor	VEGF	Platelets, keratinocytes, macrophages, neutrophils	Angiogenesis; vascular permeability; macrophage chemotaxis

Table 141.2 Growth factors involved in wound healing.

functions and chemoattraction, both of which lead to an early influx of polymorphonuclear leukocytes (PMNs; neutrophils). This is followed by invasion of blood monocytes, which differentiate into tissue macrophages[14].

While one function of the inflammatory infiltrate is to combat invading microbes, another equally important function is the release of cytokines and growth factors (e.g. IL-1, IL-6, vascular endothelial growth factor [VEGF] tumor necrosis factor [TNF], TGF-β; Table 141.2), which are critical for the initiation of the second *proliferative phase* of skin repair (see Fig. 141.5). During this phase of tissue formation, newly formed granulation tissue, consisting primarily of invading macrophages and fibroblasts as well as endothelial cells (as vessel precursors), covers and fills the wound area. Fibrin, fibronectin, vitronectin, collagen III and tenascin are components of the provisional extracellular wound matrix which facilitate cell adhesion, migration and proliferation. At the wound edge, epidermal–mesenchymal interactions stimulate keratinocyte proliferation and migration, leading to re-epithelialization[15].

Upon completion of epithelialization, cell proliferation and neovascularization cease, scar tissue forms and the wound enters the *remodeling* (*maturation*) *phase,* which lasts for several months. This last phase is characterized by a balance between the synthesis of new components of the scar matrix and their degradation by proteases. This balance determines whether there is normal versus abnormal scar formation (e.g. atrophic scars, hypertrophic scars, keloids). The mechanisms underlying granulation tissue regression and its transformation into scar tissue during this phase are largely unknown. Typically, there is also regression of vascular structures, transformation of fibroblasts into myofibroblasts, substitution of provisional extracellular matrix (ECM) with a permanent collagenous matrix (see Fig. 141.10), and a final resolution of the inflammatory response. Potential explanations for the latter are increased production of anti-inflammatory mediators, active suppression of proinflammatory factors, normalization of microvascular permeability, and induction of apoptosis of inflammatory cells and their efflux from the tissue.

Cellular Components

Keratinocytes

Within hours after injury, keratinocytes at the wound edge are activated and undergo marked phenotypic and functional alterations, a fundamental change required for re-epithelialization of the wound bed (Fig. 141.6). In order to initiate migration, keratinocytes need to undergo significant alteration of their junctions and adhesion molecules; this includes detachment of hemidesmosomes and replacement of their collagen-binding receptors with new integrins that allow the keratinocytes to adhere to the newly formed provisional wound matrix. In addition, these keratinocytes begin to proliferate as they reduce the production of proteins normally expressed by differentiated stratified epidermis, in particular specific keratins (see Ch. 56). During wound healing, one classic marker of activated keratinocytes is the expression of keratins associated with proliferation, keratins 6 (K6) and K16.

It has been proposed that the cytoskeletal changes associated with activation, including the expression of these particular keratin filaments, provide plasticity and flexibility, while still maintaining resilience of the intracellular scaffold that is important for migration[16]. Many of the growth factors active during wound healing, such as keratinocyte growth factor (KGF) and hepatocyte growth factor (HGF), are potential regulators of these processes. These growth factors can be synthesized either by activated keratinocytes (and act in an autocrine loop) or by cells present in the dermis, in particular fibroblasts, and then act in an paracrine fashion[16a].

As the stratified epithelium consists of keratinocytes committed to multiple stages of differentiation, it is important to know which keratinocytes can be activated for regeneration. Experimental data from mice expressing a transgene within defined keratinocyte subpopulations revealed that interfollicular epidermal stem cells, transient amplifying cells and early differentiated cells have the ability to form a fully differentiated epidermis[17]. These data suggest that primarily skin stem cells and transient amplifying cells contribute to wound healing and that keratinocytes become irreversibly committed to the differentiation process fairly rapidly and then respond poorly to activating signals. Once keratinocytes process profilaggrin into filaggrin, they undergo specific changes that mark late terminal differentiation, which seemingly demarcates the final "line of regenerative potency" within the differentiating keratinocyte population (see Fig. 141.6)[17a].

Although epidermal regeneration via cell division within the basal layer of the interfollicular epidermis is well characterized, there appears to be a second type of resident epidermal stem cell that has attracted intensive research in recent years – the stem cells in the bulge region of the outer follicular root sheath (see Fig. 141.5). These cells, the hair follicle stem cells (HFSCs), are multipotent stem cells[18]. Originally, HFSCs were thought to be responsible for just the regeneration of hair follicles and sebaceous glands. Later studies suggested that they are also responsible for long-term replenishment of the interfollicular epidermis, and, more recently, repopulation of the epidermis following injury[19]. Based upon studies in mice, it appears that for re-epithelialization following mechanical injury, both interfollicular stem cells and stem cells in the bulge region contribute to the newly

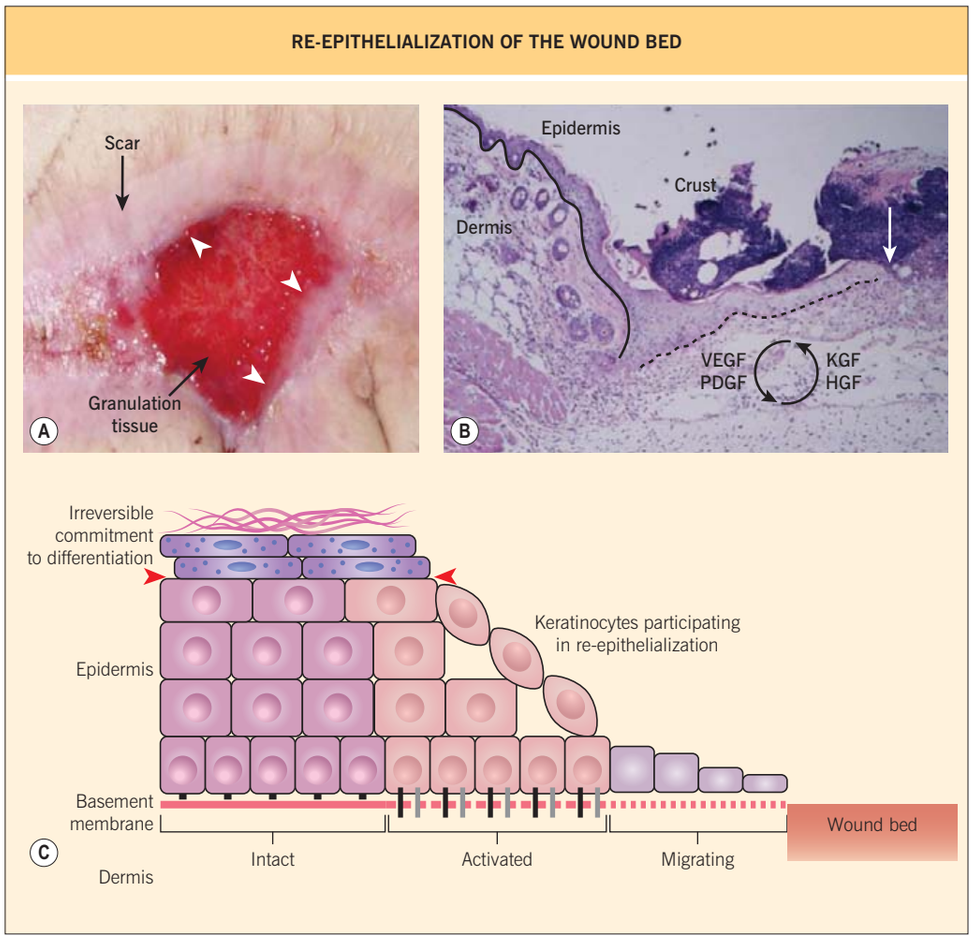


Fig. 141.6 Re-epithelialization of the wound bed. **A** Clinical appearance of a re-epithelializing wound; arrowheads indicate the epithelial wound edge. **B** Photomicrograph of the wound edge demonstrating the migration of keratinocytes over the wound bed; this process is in part regulated by growth factors synthesized by fibroblasts such as keratinocyte growth factor (KGF) and hepatocyte growth factor (HGF). The white arrow indicates the tip of the epithelial tongue, the black dashed line indicates activated and migrating epithelium, and the black solid line indicates intact epithelium. **C** Epithelial cells present at the wound edge undergo marked morphologic and functional alterations. They lose their contacts with neighboring cells and the underlying extracellular matrix, then proliferate and migrate toward the center of the wound. The red arrowheads demarcate the terminally differentiated cells that are irreversibly committed.

generated epidermis. These findings help to explain how depth of injury affects the capability of a wound to repair and to re-epithelialize.

Endothelial cells

Activated and proliferating endothelial cells that form blood vessels normally express the $\alpha_v\beta_3$ integrin and make a significant contribution to angiogenesis, which is a vital component of normal wound healing (Fig. 141.7)[20]. New blood vessels ensure delivery of nutrients to meet the increased metabolic requirements of wound tissue and they help to reverse the hypoxic and acidotic milieu. Several features characterize neoangiogenesis within wounds: firstly, there is increasing evidence that this process occurs via both *angiogenesis* (sprouting of capillaries from existing blood vessels) and *vasculogenesis* (mobilization of bone marrow-derived endothelial progenitor cells; see Ch. 102). Secondly, the process is highly complex and requires a dynamic, temporally and spatially regulated, interaction amongst endothelial cells, soluble angiogenic growth factors and ECM molecules. Thirdly, wound angiogenesis is induced, at least in part, by the activation of the innate immune response. Immediately after injury, different subsets of leukocytes are attracted to the wound site and they release multiple pro-angiogenic mediators (e.g. IL-6, IL-8, TNF) that trigger and sustain the angiogenic response. Importantly, as shown for TNF, the time of action and the concentration of a given cytokine determine whether it activates, terminates or inhibits angiogenesis.

Several additional mediators have been identified that are crucial for vessel formation and play a role in controlling vascular remodeling and angiogenesis. Genetically engineered mice, in particular, have provided substantial evidence that wound angiogenesis requires a dynamic interaction amongst endothelial cells, pro- and anti-angiogenic growth factors, and the ECM environment. Of the cytokines involved in angiogenesis (and there is significant functional redundancy), basic fibroblast growth factor (bFGF) and platelet-derived growth factor (PDGF) are two with key functions. In addition to these more classic cytokines, the family of VEGF proteins and their receptors has emerged as key mediators in embryonic vascular development, as well as physiologic and pathologic angiogenesis in adults[21].

As with many physiologic and pathologic processes of tissue remodeling, ECM molecules play a pivotal role in the repair response and wound angiogenesis. For example, basement membrane proteins provide essential information for the organization and orientation of endothelial cells; the latter are anchored to this dense polymeric sheet that is crucial for the proper function of blood vessels. The essential nature of the basement membrane has been demonstrated in that removal of its major components leads to leakiness of blood vessels. Such major constituents of this polymer structure include laminins, nidogens, collagens III and IV, and heparin sulfate proteoglycans (e.g. perlecan). A vital role for these components is reflected in genetic disorders such as the vascular form of Ehlers–Danlos syndrome in which reduced or abnormal type III collagen fibers are associated with marked vascular fragility.

During neoangiogenesis, new vessels sprout from existing vessels and grow along a growth factor gradient, determined primarily by VEGF. Degradation of the surrounding ECM also has to occur via MMPs (see below) as well as serine and cysteine proteases[22]. Both the ECM (often via integrins) and growth factor concentrations provide signals that lead to a balance between the formation of new blood vessels and the prevention of aberrant angiogenesis.

There is a growing appreciation of how interactions between endothelial cells and vascular mural cells (pericytes) play a role in the regulation of vascular formation, stabilization, remodeling and function. For example, pericytes have been shown to play a role in large, well-vascularized tumors, and in such tumors, pharmacologic anti-angiogenic targeting of only the endothelial cells (and not the pericytes) often proves ineffective. A role for pericytes in dermal wound healing was predicted several decades ago, but so far their precise functional relevance is largely unknown.

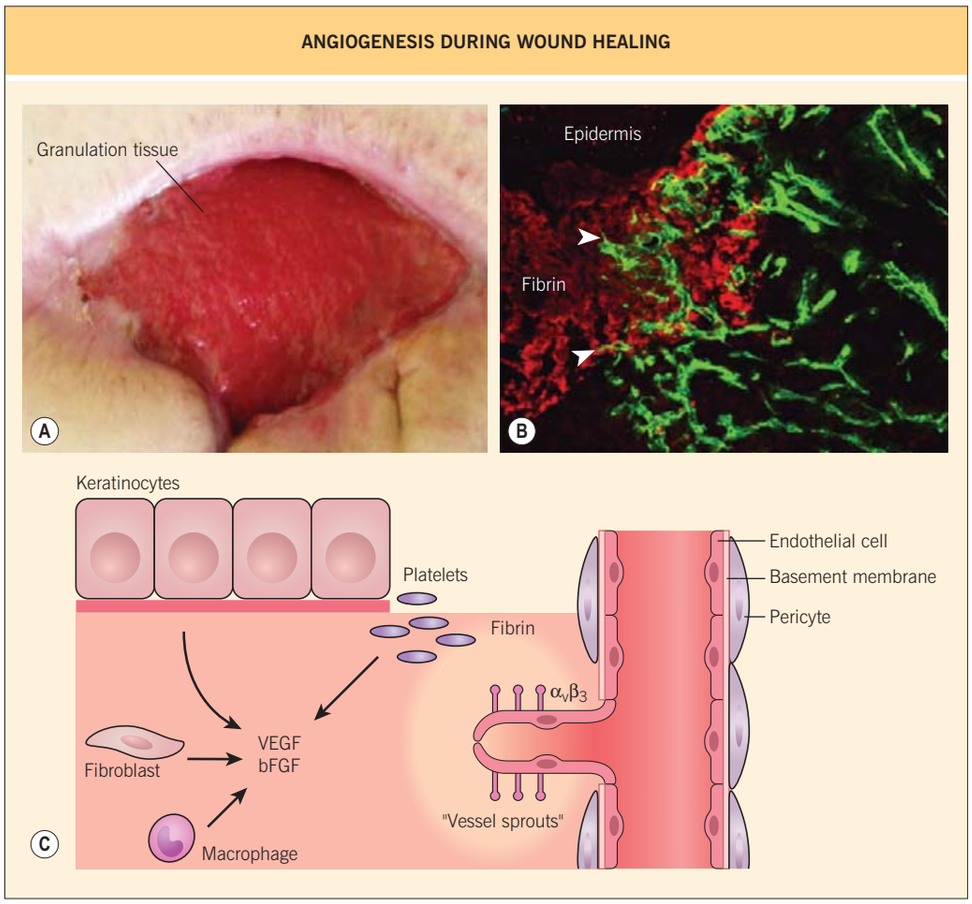


Fig. 141.7 Angiogenesis during wound healing. **A** Clinical appearance of a highly vascularized wound bed. **B** Immunohistochemical staining demonstrating endothelial invasion ($CD31^+$ [green]) into a fibrin matrix (red); white arrowheads indicate sprouting capillaries. **C** Capillary sprouts invade the fibrin/fibronectin-rich provisional wound matrix and within a few days they organize into a microvascular network throughout the granulation tissue. The process is regulated by a dynamic interaction among endothelial cells, growth factors (e.g. VEGF, bFGF) and the extracellular matrix. In particular, the $\alpha_v\beta_3$ integrin appears to be required for endothelial cell attachment and wound angiogenesis. bFGF, basic fibroblast growth factor; VEGF, vascular endothelial growth factor.

Leukocytes and platelets

The inflammatory response in normal wound healing is characterized by spatially and temporally changing patterns of various leukocyte subsets. The well-defined chronology of these events seems essential for optimal repair.

Polymorphonuclear leukocytes and platelets

Immediately after injury, extravasated blood constituents form a hemostatic blood clot (Fig. 141.8). Platelets then aggregate within the clot and release a wide spectrum of factors that amplify the aggregation response, trigger the coagulation cascade, or act as chemoattractants for cells involved in the inflammatory phase. Within a few hours following the injury, polymorphonuclear leukocytes (PMNs; neutrophils) transmigrate across the endothelial cell wall of capillaries. Upon activation, the neutrophils produce and release proinflammatory cytokines including IL-8 and TNF, in addition to growth-related oncogene-α (GRO-α) and monocyte chemoattractant protein-1 (MCP-1)[23]. This leads to expression of various classes of adhesion molecules (selectins, ICAM, VCAM) essential for leukocyte adhesion and diapedesis (see Fig. 141.8 and Ch. 102)[24]. Neutrophils can further amplify their own recruitment via IL-8 and GRO-α.

Recruited neutrophils play a major role in the debridement of devitalized tissue and in controlling infectious agents. To perform this task, they release a large variety of highly active antimicrobial substances (reactive oxygen species [ROS], cationic peptides, eicosanoids) and proteases (elastase, cathepsin G, proteinase 3 [PR-3], urokinase-type plasminogen activator [uPA]). Uncontrolled release of these factors can cause severe damage to the tissues of the host[25]. Of note, bacterial products such as lipopolysaccharides and formyl-methionyl peptides, which accumulate within infected wounds, can accelerate directed neutrophil locomotion. The important role of neutrophils in phagocytosis and debridement is underlined by the observation that patients with defined deficiencies in PMN function, such as the leukocyte-adhesion deficiency syndrome 1 (LAD1)[26] or attenuated PMN actin polymerization[27], in which neutrophil locomotion is impaired, also display impaired wound healing.

Blood monocytes and tissue macrophages

Attraction of monocytes to the wound site occurs via chemotactic factors, including growth factors, proinflammatory cytokines, and chemokines. The latter include macrophage inflammatory protein 1α (MIP-1α), MCP-1, RANTES and fraktalkine. Within the wound, major sources of these chemoattractants include platelets trapped in the fibrin clot, hyperproliferative keratinocytes at the wound edges, fibroblasts and various subsets of leukocytes, including macrophages. As monocytes extravasate from the blood vessel, they become activated and differentiate into mature tissue macrophages.

Macrophages display a variety of functions during wound healing[14]. While their role as antigen-presenting cells may be less important in this setting (e.g. RAG 1 knockout mice which lack mature T cells have normal wound healing)[27a], they are important phagocytes. Macrophages are also a major source of growth factors, such as TGF-β, TNF, PDGF, bFGF and VEGF. These factors critically regulate angiogenesis, keratinocyte motility, the recruitment and activation of immune cells, and the synthesis of ECM molecules.

Over 30 years ago, a crucial role for macrophages in wound repair was established. Macrophage depletion in rats, using antisera, resulted in a significant delay of wound healing[28]. More recent studies have supported and extended these observations[12]. For example, in transgenic mice in which the accumulation of macrophages (but not monocytes or neutrophils) within wounds has been ablated, there is delayed re-epithelialization, reduced collagen deposition and impaired angiogenesis[29]. In addition, P- and E-selectin-double-deficient mice, mice deficient in β-1,4-galactosyltransferase (which glycosylates P- and E-selectins), and ICAM-1-deficient mice all have a profound delay in wound closure (see Fig. 141.8); this delay is associated with a significantly reduced infiltration of macrophages. These studies demonstrate the importance of cell adhesion molecules in the regulation of blood monocyte recruitment and infiltration into the wound site.

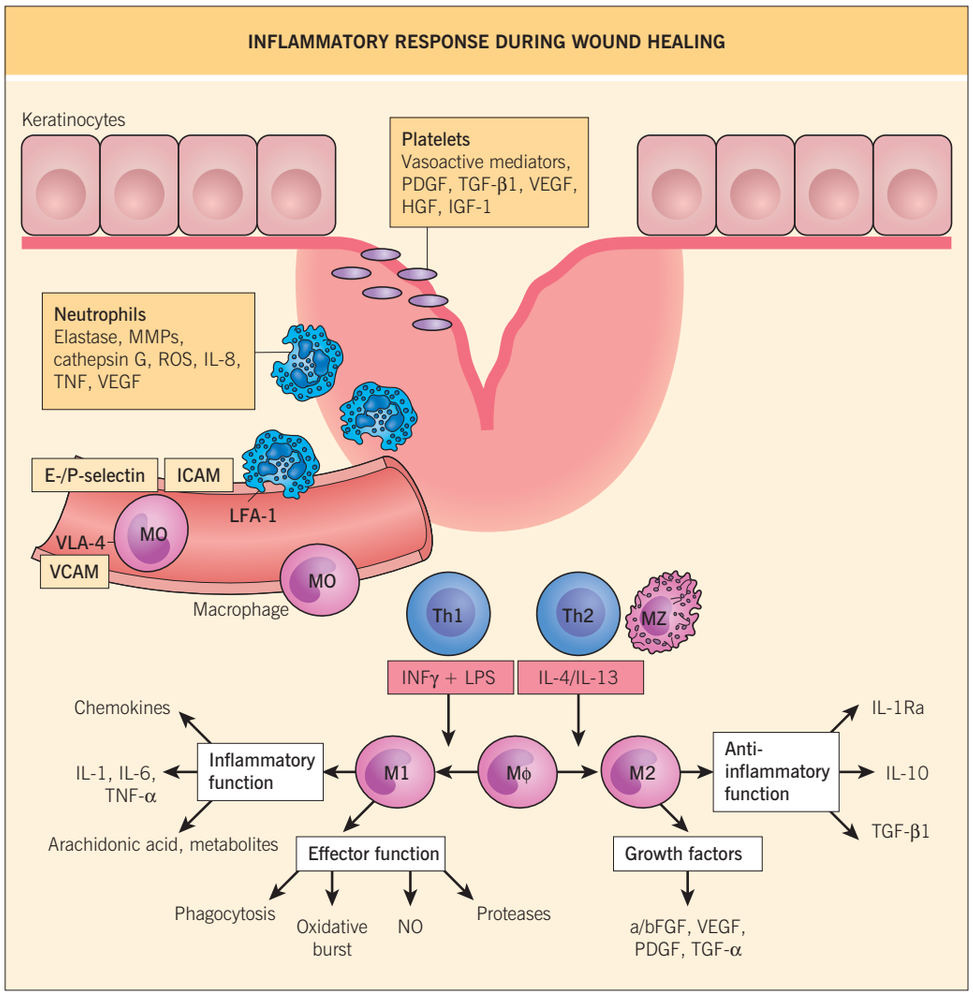


Fig. 141.8 Inflammatory response during wound healing. During normal wound healing, the inflammatory response is characterized by spatially and temporally changing patterns of leukocyte subsets. A well-defined chronology and interplay is essential for optimal repair. Within a few hours after injury, neutrophils transmigrate across the endothelial cell wall of blood capillaries; recruited neutrophils begin to debride devitalized tissue and attack infectious agents by releasing a number of antimicrobial molecules, proteases and cytokines. Shortly after the neutrophils appear, monocytes migrate from the blood vessels into the dermis, become activated within the wound environment and transform into tissue macrophages. In addition to functioning as antigen-presenting cells and phagocytes, macrophages are thought to play an integral role in wound healing due to their release of numerous growth factors. Their morphologic and functional heterogeneity is a reflection of factors released by other cells, e.g. T cells or mast cells, present in the wound environment. FGF, fibroblast growth factor; ICAM, intercellular adhesion molecule; IFN, interferon; IL, interleukin; IL-1Ra, interleukin-1 receptor antagonist; LFA-1, lymphocyte function-associated antigen 1; LPS, lipopolysaccharide; M1, classically activated macrophages; M2, alternatively activated macrophages; MMPs, matrix metalloproteinases; MO, monocyte; Mϕ, macrophage; MZ, mast cell; NO, nitric oxide; PDGF, platelet-derived growth factor; ROS, reactive oxygen species; TGF, transforming growth factor; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor; VLA-4, very late antigen-4.

Activation and differentiation of monocytes into mature tissue macrophages involves changes in gene expression and cellular function. This activation is directed by mediators present in the microenvironment, and it is thought to be crucial for the proper adaptation of macrophage functions to the specific requirements of the wound site[30]. Macrophages sense their microenvironment via numerous cell surface receptors, including Toll-like receptors, complement receptors, Fc receptors and cytokine receptors[31].

One current model of tissue macrophage activation is based on the observation that macrophages may acquire distinct activation states, in particular macrophages that are "classically activated" (also called M1) versus "alternatively activated" macrophages (also called M2; see Fig. 141.8). M1 macrophages exhibit proinflammatory activities, including production of IL-1 and nitric oxide (NO), eradication of invading microorganisms and promotion of type I immune responses. On the other hand, M2 macrophages produce IL-10 (but minimal NO), are hyporesponsive to proinflammatory stimuli and are involved in debris scavenging, angiogenesis and tissue remodeling[30]. These latter cells play a role in the resolution of inflammation and are thought to promote repair.

Classical macrophage activation is mediated by priming of macrophages by cytokines, in particular interferon-γ (IFN-γ), followed by Toll-like receptor (TLR)-mediated triggers such as lipopolysaccharide signaling via TLR4. Key mediators of *alternative macrophage activation* are IL-4 and IL-13, acting through a common receptor chain IL-4Rα. Manipulation of macrophage polarization might represent a potential avenue for future therapeutic approaches to wound healing.

T cells

During the phase of tissue remodeling (maturation), when wound closure is complete and local infections have been overcome, cells of the *adaptive* immune response, in particular T cells, are the most frequent leukocyte subset in human skin wounds[32]. Definitive understanding of T-cell functions during repair requires further investigation in that wound healing appears to be unaffected in T-cell-deficient mice (e.g. RAG-1 knockout mice). Similar to macrophages, $CD4^+$ T cells can differentiate into different subsets, e.g. Th1 and Th2 cells (see Ch. 4), and thereby influence the wound microenvironment by secreting distinct cytokine profiles (see Fig. 141.8)[33]. Th1 cells are a primary source of IFN-γ while Th2 cells are the major source of IL-4 and IL-13. As noted previously, these cytokines have a major effect on the state of macrophage differentiation. Thus, even though they are not mandatory for wound healing, $CD4^+$ T-cell cytokines critically influence two important components of wound healing: macrophage function and angiogenesis.

Mast cells

Mast cells are a hematopoietic cell population that normally resides in skin and mucous membranes. They are an important source of a number of mediators such as prostaglandins and biogenic amines as well as pro- and anti-inflammatory cytokines (e.g. TNF, IL-8) that strongly influence inflammation, tissue modulation and vascular modeling. Even though they influence both innate and adaptive tissue inflammation and can affect angiogenesis and the risk of wound infection, an essential role for mast cells in normal wound healing has not been determined. It is most likely that mast cells represent redundant "players" in wound healing, i.e., they are not required for normal wound healing but can modify its course[34].

Fibroblasts

Connective tissues, including the dermis, typically have large amounts of ECM in which a small number of relatively quiescent fibroblasts are

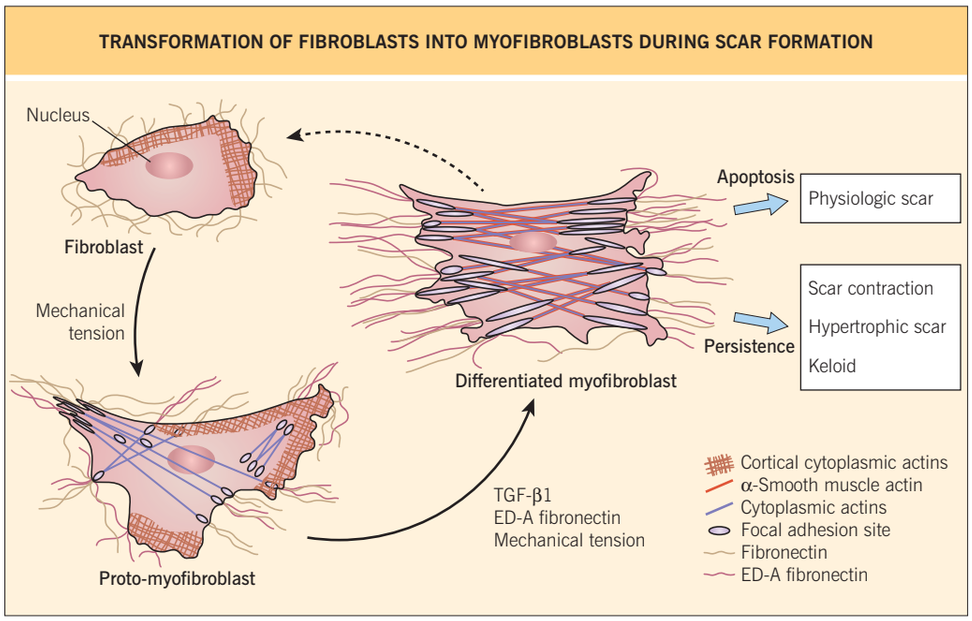


Fig. 141.9 Transformation of fibroblasts into myofibroblasts during scar formation. Fibroblasts undergo a series of phenotypic and functional changes during granulation tissue formation and then scar formation. Under mechanical stress, fibroblasts differentiate into proto-myofibroblasts which are characterized by the expression of a fibronectin variant ED-A; the latter, in combination with TGF-β1, promotes the differentiation of proto-myofibroblasts into myofibroblasts. Typically, myofibroblasts express α-smooth muscle actin (SMA) and can generate potent contractile forces. The persistence of myofibroblasts within the scar may lead to disabling scar contraction. *From Tomasek JJ, Gabbiani G, Hinz B, et al. Myofibroblasts and mechano-regulation of connective tissue remodelling. Nat Rev Mol Cell Biol. 2002;3:349–63.*

embedded. During development, fibroblasts establish a "resting" tension by actively synthesizing and cross-linking fibrillar ECM proteins such as collagen and elastin (see Ch. 95), thereby establishing the shape of the skin and ensuring that the skin retains its shape in response to mechanical stress[35].

During tissue repair, fibroblasts next to the site of injury become activated and reconstitute new ECM and restore proper matrix tension. To achieve these goals, fibroblasts acquire smooth muscle cell-like features, including contractile stress fibers and *de novo* expression of α-smooth muscle actin (α-SMA), thus differentiating into myofibroblasts (Fig. 141.9)[36]. The transition of a fibroblast into a myofibroblast depends on the concerted action of cytokines, in particular TGF-β1, and specific ECM proteins, especially the cellular fibronectin splice variant ED-A. Acquisition and maintenance of the myofibroblast phenotype also depends on mechanical tension, which is regulated by the continuous interaction between the rigidity of the ECM and the contractile activity of its cells.

Following closure of the wound, apoptosis of myofibroblasts or their reverse differentiation into fibroblasts normally occurs. However, abnormal persistence of myofibroblasts has been observed in hypertrophic scars and keloids (see Fig. 141.9). Determining how perception of mechanical signals translates into myofibroblast differentiation may lead to therapeutic strategies for exaggerated scarring[37].

Stem cells

Stem cells are defined as cells that have clonogenic and self-renewing capabilities and can differentiate into multiple cell lineages (see Ch. 2). Whereas *embryonic stem cells* are derived from mammalian embryos in the blastocyst stage and have the ability to generate any terminally differentiated cell in the body, *adult stem cells* are postnatal tissue-specific cells that are primarily committed to differentiate into the cells of the tissue in which they reside. During cutaneous wound healing, tissue-resident stem cells (e.g. epidermal stem cells, hair follicle stem cells, mesenchymal stem cells)[18,19,38] and/or stem cells recruited from the bloodstream into the wound can participate in the repair process (see Fig. 141.5)[39].

Currently, the best-studied model of adult stem cells is the hematopoietic system, in which long-term self-renewal is achieved only by specific and rare hematopoietic stem cells (HSC). These cells reside within the bone marrow niche and retain their ability to both self-renew and give rise to all blood cell lineages. In addition to hematopoietic progenitors, other cells with stem cell-like qualities such as mesenchymal stem cells (MSC) and multipotent adult progenitor cells (MAPC) have been cultured from human and murine bone marrow[40].

MSC were first isolated from bone marrow and later from different tissues, including adipose, pancreas, skeletal muscle, nervous tissue, and skin. Upon appropriate stimulation *in vitro*, these cells differentiate into mature, committed cells. In animal studies, they migrated from their bone marrow niche to sites of injury and differentiated appropriately, e.g. into endothelial, nervous or cardiac tissues. Differentiation into fibroblasts, endothelial cells and keratinocytes has been observed in injured murine skin[41].

Based on studies in mice, the percentage of MSCs recruited into small cutaneous wounds appears to be low[42]. Nonetheless, there is significant therapeutic interest in the delivery of stem or progenitor cells to skin wounds to promote repair or to optimize the quality of the repair response (see below)[40].

Cytokines and their Receptors

In addition to cell–matrix interactions (see below), all stages of the repair process are influenced by a complex network of soluble peptide growth factors, chemokines and hormones as well as their receptors (see Figs 141.5, 141.7 & 141.8)[43]. Major growth factor families have been identified that contribute significantly to the wound healing process, such as PDGF, FGF, VEGF and TGF-β (see Table 141.2).

Growth factors were initially discovered by their ability to stimulate continuous mitosis of quiescent cells in a complete culture medium that lacked serum. This is in contrast to essential elements, cofactors and nutrients, which are required for metabolic processes but are not sufficient to initiate cell division. Growth factors are synthesized and secreted by various cell types involved in the wound healing process, including keratinocytes, fibroblasts, vascular endothelial cells, platelets and inflammatory cells. Growth factors may act on the producer cell (autocrine stimulation), an adjacent cell (paracrine stimulation), or distant cells (endocrine stimulation)[43]. Following binding of growth factors to their respective receptors, complex signaling cascades (e.g. β-catenin) result in cellular functions crucial for wound healing, including cellular proliferation and migration[44].

Extracellular Matrix

Although the ECM was long viewed as an inert scaffold upon which cells were arranged, it has been redefined as a dynamic, mobile and flexible entity that plays a key role in regulating cellular behavior. Genetically modified mice have greatly accelerated the understanding of the multifunctionality of the ECM in developmental and regenerative processes[45].

Within the wound site, the components of the ECM vary continuously as the healing process evolves, and they support fundamental, wound phase-specific repair mechanisms. During the inflammatory phase, the initial wound matrix (consisting primarily of blood constituents such as fibrin and fibronectin) provides a substrate for the

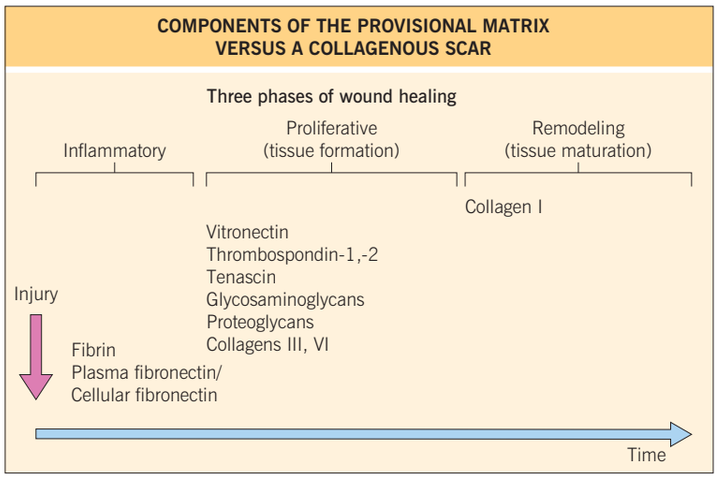


Fig. 141.10 Components of the provisional matrix versus a collagenous scar. The first extracellular matrix to be deposited within the wound space and surrounding tissue is the fibrin clot. Leukocytes, fibroblasts and endothelial cells invade the fibrin clot, which is then lysed. These cells begin to deposit a network of ECM components, including fibronectin, vitronectin, tenascin and type III collagen. Following complete re-epithelialization, fibroblasts start to deposit a stable matrix composed of type I collagen. Thus the wound evolves from an initial plasma-derived provisional matrix to an *in situ* cell-derived provisional matrix and finally to a mechanically stable collagen matrix. Examples of glycosaminoglycans are hyaluronic acid, chondroitin-4-sulfate and dermatan sulfate, while examples of proteoglycans are decorin, biglycan, versican and syndecan (see Ch. 95).

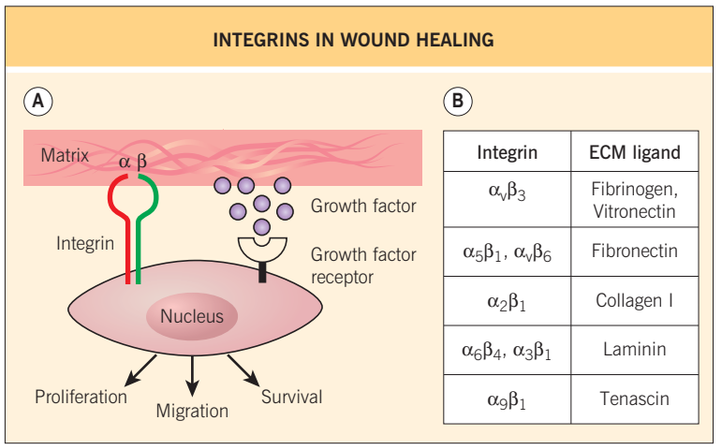


Fig. 141.11 Integrins that play a role in wound healing. A Integrins are transmembrane receptors that recognize and bind to extracellular matrix (ECM) proteins. They are heterodimers composed of one α-subunit and one β-subunit. Integrins allow cells to attach to the ECM and they interact with growth factor receptors, ultimately controlling cellular functions essential for wound healing. **B** The composition of integrins expressed by a cell determines the ECM components to which that cell can bind. Examples of the integrins and their ECM ligands that are important for wound healing are listed.

migration and in-growth of various cell types, including macrophages and fibroblasts (Fig. 141.10). During the formation of granulation tissue (the proliferative phase of wound healing), components of the provisional matrix, such as vitronectin and tenascin, facilitate cell adhesion, migration and proliferation (see Fig. 141.5). As the provisional matrix matures over the ensuing weeks, it is replaced by type I collagen during the remodeling phase, thus increasing wound tensile strength.

Matrix molecules can regulate cellular functions via interaction with specific cell surface transmembrane receptors (integrins) that transduce signals into the nucleus (see below). In addition, they can bind growth factors, e.g. TGF-β, and act as a reservoir (see Fig. 95.7).

Integrins

Integrins are cell surface transmembrane receptors that can recognize and bind to ECM proteins. They are heterodimers composed of α-subunits and β-subunits. Eighteen α-subunits and eight β-subunits can assemble in 24 different combinations, with overlapping substrate specificity and cell type-specific expression patterns[46]. For example, integrins containing β1 or β3 chains are ECM receptors, whereas those containing β2 chains are leukocyte cell–cell receptors. The composition of integrins expressed by a particular cell determines to which ECM components that cell can bind. For example, $\alpha_9\beta_1$ binds to tenascin and $\alpha_v\beta_6$ binds to fibronectin (Fig. 141.11).

Upon binding of an integrin to its ligand, the integrin may change its configuration and transform into an activated state[47]. This can trigger a signaling cascade within the cell that leads to an alteration in gene expression, as well as a change in the integrin's binding characteristics. Integrin-mediated signaling is also influenced by the binding of growth factors and cytokines to their respective receptors, along with various levels of cross-talk (see Fig. 141.11). For example, $\alpha_v\beta_3$ binding in conjunction with VEGF-A binding to its receptor leads to synergistic downstream effects regulating endothelial cell function. Thus, today it is very clear that integrins are more than just simple receptors mediating physical attachment of cells to their environment.

Proteases (Proteinases)

Proteases are enzymes that cleave peptide bonds at specific sites along polypeptides, and they can be classified into distinct groups based upon the biochemical mechanisms responsible for their catalytic activities[48].

Proteases are crucial for tissue remodeling, which is a fundamental process during all stages of wound repair, including inflammation, angiogenesis and re-epithelialization. Those most crucial for skin repair are serine proteases and metalloproteinases. In addition to matrix degradation, these proteases are crucial for growth factor activation, and they exert antimicrobial activities. To protect tissues from excessive and uncontrolled proteolytic degradation, protease activity has to be tightly regulated by protease inhibitors. An imbalance, with high levels of proteases and low levels of protease inhibitors, is considered a major contributor to chronic, non-healing skin ulcers[12,49,50].

Serine proteases have a catalytically essential serine residue in their active site. Neutrophils and macrophages are an important source of this group of proteases which includes neutrophil elastase, cathepsin G and proteinase 3. Furthermore, plasmin and its activators, tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA), are serine proteases that are fundamental for wound repair. In addition to dissolving the fibrin clot, the plasmin-related proteases are involved in the activation of matrix metalloproteinases (MMPs) and numerous growth factors.

The major *ser*ine *p*rotease *in*hibitors (SERPINs; e.g. α_1-antichymotrypsin) as well as α_2-macroglobulins are synthesized by hepatocytes and are released into the plasma. In contrast, *s*ecretory *l*eukocyte *p*rotease *i*nhibitor (SLPI) and elafin are synthesized locally by keratinocytes. Plasminogen activator inhibitors (PAIs) are the major inhibitors of uPA and are produced by endothelial cells.

The family of MMPs shares a common domain structure, and collectively they are capable of degrading all the components of the ECM. To date, at least 28 members of the human MMP family have been identified and they are differentially expressed by diverse cell types[51]. MMPs can be subdivided into several groups based upon substrate specificity (Table 141.3). Tissue inhibitors of metalloproteinases (TIMPs), which are synthesized by connective tissue cells and leukocytes, specifically inhibit MMPs.

ABNORMAL WOUND HEALING

The complex network of cell–cell and cell–matrix interactions leading to wound healing can be disturbed. This may result in either a delayed healing response and ultimately a chronic wound, or excessive scarring as in hypertrophic scars or keloids. Dysfunctional wound healing represents a major clinical and socioeconomic problem and the development of effective therapies is essential.

Impaired healing can be classified according to whether it results from systemic factors or from the local microenvironment (see Ch. 105)[12]. A chronic wound is a symptom of an underlying disease, rather

DIFFERENT TYPES OF MATRIX METALLOPROTEINASES INVOLVED IN WOUND REPAIR	
Enzyme	**MMP number**
Collagenase-1	MMP-1
Collagenase-2	MMP-8
Collagenase-3	MMP-13
Collagenase-4	MMP-18
Stromelysin-1	MMP-3
Stromelysin-2	MMP-10
Stromelysin-3	MMP-11
Gelatinase-A	MMP-2
Gelatinase-B	MMP-9
Matrilysin	MMP-7
Macrophage metalloproteinase (elastase)	MMP-12
MT1-MMP	MMP-14

Table 141.3 Different types of matrix metalloproteinases (MMPs) involved in wound repair. MT1, membrane-type 1.

than a disease entity. The most common systemic factors influencing wound repair are venous insufficiency, advanced age, ischemia and diabetes mellitus-associated microangiopathy (see Fig. 105.1), and, less often, vasculitis, hypercoagulability, malnutrition, and concomitant therapies (e.g. hydroxyurea, immunosuppressives). Local factors include inadequate blood supply, necrotic tissue, increased proteolytic activity, mechanical irritation, pressure, bacterial components, local toxins, and growth factor deficiency. Each of these factors has to be critically considered when assessing factors responsible for impaired healing and when outlining a treatment regimen for a non-healing wound.

Wound Healing and Aging

The prevalence of chronic wounds in the population increases with age[52,53], as does the prevalence of venous hypertension, peripheral artery disease and diabetes mellitus. Aging can be regarded as an accumulation of molecular changes that leads to functional failure in different tissues, including impaired wound healing.

Human aging may be triggered by two principal mechanisms: telomere shortening (see Fig. 67.21) and DNA damage. Telomere shortening or dysfunction leads to instability of chromosomes, and a functional link between age-dependent telomere shortening and impaired wound healing has been demonstrated in telomerase-deficient mice (telomerase is an enzyme that prevents telomere shortening)[54]. How telomere shortening translates into impaired cell function during the healing response is not understood. Furthermore, mice with increased activation of the transcription factor p53 within the epidermis develop an early aging phenotype of their skin with impaired wound healing[54a].

THERAPEUTIC OPTIONS FOR CHRONIC WOUNDS

Wound Dressings

A large variety of wound dressings is currently available, with recommendations for particular dressings based upon characteristics of the wound (see Ch. 145). Clinical experience, rather than controlled trials, forms the basis of many of these recommendations. There is still no consensus on the mechanisms of action, but most dressings are thought to support wound healing by acting as a barrier between the wound and the environment, by preventing drying of the tissue[55–57], or by allowing autolytic debridement. Only a few dressings appear capable of interfering with cellular and molecular mechanisms of the wound microenvironment or to counteract mechanisms that are considered hostile for repair. Of note, controlled trials have shown the benefit of compression therapy in the case of venous ulcers.

Growth Factors

As outlined previously, growth factors are essential regulators of cell function during repair. Experimental studies have shown that the topical application of certain growth factors can modify and probably even accelerate wound repair[43,44]. Based on these observations, clinical studies to determine whether tissues with inherently poor or pathologically altered healing potential could profit from therapeutic growth factor interventions have been conducted. PDGF-BB was the first, and to date the only, recombinant growth factor to be approved for the topical treatment of diabetic foot ulcers (see Ch. 105). The efficacy of perilesional injections of granulocyte–macrophage colony-stimulating factor (GM-CSF) awaits further studies, but in transgenic mice where an antagonist of GM-CSF was overexpressed in the epidermis, delayed wound healing was observed, suggesting a role for this growth factor.

The limited success of clinical trials with peptide growth factors underscores an important aspect of the growth factor/tissue repair paradigm: the effective delivery of these polypeptides to the wound site. The latter is biologically and biochemically complex, and in situations such as a chronic or infected wound, the environment is hostile to repair. Current drug delivery strategies suffer from the inherent loss of drug activity due to the combined effects of physical inhibition and proteolytic degradation. While this may account for some of the limited success of clinical studies, a key factor is a poor blood supply. A combined molecular and genetic approach, where genetically modified cells synthesize and deliver the desired growth factor in a time-regulated and locally restricted manner to the wound site, may overcome some of the limitations inherent to the local application of recombinant growth factors.

Cell-Based Therapies

When skin defects are too large to heal by second intention, skin grafts and cell-based treatments may be used to cover the wound and to replace the defect. Split-thickness skin grafts are most commonly used for the treatment of acute surgical or chronic wounds (see Ch. 148), as are "pinch" grafts. The latter are 2–5 mm superficial skin biopsies, often obtained from the anterolateral thigh, that are placed dermis-down in a clean wound bed.

Numerous efforts have been directed toward the development of skin substitutes with qualities similar to native skin in order to aid in the healing of acute surgical or chronic wounds as well as extensive thermal burns[58]. Both autologous and allogeneic components have been incorporated into bioengineered human skin equivalents (see Ch. 145), and several clinical studies have demonstrated a beneficial effect on chronic wounds refractory to conventional therapy. However, these skin substitutes tend to be expensive and grafted cells are eventually lost.

FUTURE DIRECTIONS

Current limitations in the treatment of chronic wounds are due to the incomplete understanding of the molecular mechanisms hindering repair. Therefore, the success of novel therapies depends upon a comprehensive knowledge of the underlying pathomechanisms and correction of pathogenic factors. Advances in molecular and cellular biology, as well as in material sciences, have broadened research and it is expected that those findings, together with a better understanding of the molecular aspects of tissue repair, will lead to the development of enhanced therapeutic modalities.

Gene Therapy

Effective local treatment of chronic wounds requires an adequate delivery of drugs or proteins that promote healing of the injured tissue. A critical issue is optimizing this delivery. A molecular genetic approach in which genetically modified cells synthesize and deliver the desired peptide factor (e.g. growth factor) in a time-regulated manner may overcome the limitations associated with simple topical application.

In various animal models, different gene delivery technologies (*ex vivo* and *in vivo*) have been investigated and successfully applied to tissue repair[59]. Despite the fact that *ex vivo* techniques (i.e. *in vitro* gene transfer and subsequent cell transplantation; see Ch. 3) have been shown to be safe and successful in various experimental models of

tissue repair, to date only direct *in vivo* gene transfer approaches have been tested for wound repair in humans.

Recently, a phase I/II clinical trial evaluating the safety and potential clinical utility of topical applications of a gene that encodes PDGF-B and is contained within an adenoviral vector formulated in a bovine collagen matrix (gene-activated matrix) was published[60]. This treatment regimen did not appear to have any toxicity at doses that showed biologic activity and is promising as treatment for non-healing diabetic foot ulcers. Furthermore, there is a phase II clinical trial investigating the overall safety and clinical outcome of a gene therapy approach for peripheral artery disease based on a hepatocyte growth factor (HGF) plasmid vector. Evaluation includes reduction of amputation and mortality rates, speed of wound healing, rest-pain reduction, and improvement in subject's ability to function without adverse consequences on quality of life (www.clinicaltrials.gov).

Stem Cells

Recent advances in stem cell biology may provide novel treatment strategies for acute and chronic wounds (Fig. 141.12)[40]. There is great interest in the delivery of stem or progenitor cells (see above), either applied topically or via stimulation of their recruitment from the circulation into the wound site. Preliminary work suggests that topically applied autologous bone marrow-derived cells promote the healing of treatment-resistant chronic wounds[61]. Furthermore, recruitment of $CD34^+$ cells from the circulation has shown promise in ischemic limbs[61a]. However, stem cell therapy still poses many questions regarding timing of stem cell application, stem cell survival and differentiation within the hostile "chronic wound" environment, and potential side effects.

Molecular Modeling of Growth Factors

Advances in the field of biomaterial science and protein engineering are expected to contribute to the development of novel therapies for tissue repair. For example, the development of protease-resistant growth factors might circumvent the imbalance in proteolytic activity that is characteristic of chronic wounds[62]. Moreover, growth factors engineered for enhanced binding to ECM molecules had an augmentation of their biologic properties with regard to tissue repair[63]. This approach not only utilizes the ECM as a carrier, but it also mimics the natural interactions between growth factors and the ECM, which appears to be crucial for the physiologic actions of growth factors.

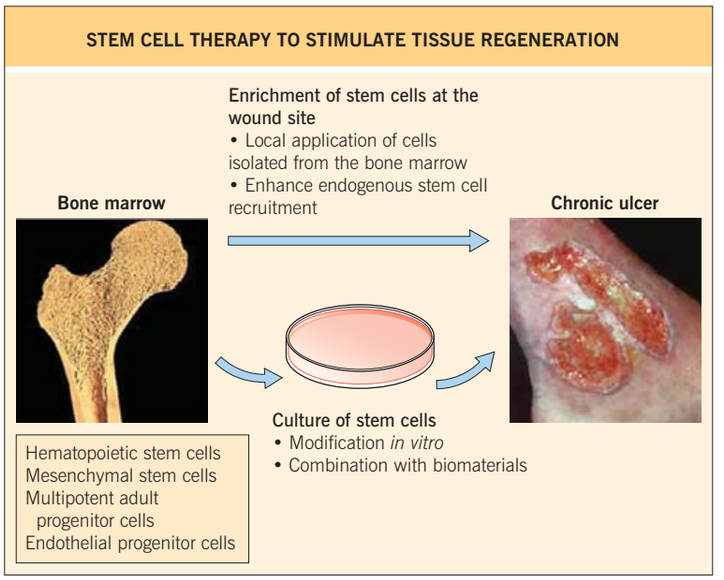


Fig. 141.12 Stem cell therapy to stimulate tissue regeneration. Wounding stimulates the engraftment of bone marrow-derived stem/progenitor cells to the skin and induces bone marrow-derived cells to incorporate into skin structures. Therefore, bone marrow might provide a valuable source of stem cells for skin repair.

REFERENCES

1. Zheng Z, Nguyen C, Zhang X, et al. Delayed wound closure in fibromodulin-deficient mice is associated with increased TGF-beta3 signaling. J Invest Dermatol. 2011; 131:769–78.
2. Eming SA, Hammerschmidt M, Krieg T, Roers A. Interrelation of immunity and tissue repair or regeneration. Semin Cell Dev Biol. 2009;20:517–27.
3. Brockes JP, Kumar A. Comparative aspects of animal regeneration. Annu Rev Cell Dev Biol. 2008;24:525–49.
4. Gardiner DM, Endo T, Bryant SV. The molecular basis of amphibian limb regeneration: integrating the old with the new. Semin Cell Dev Biol. 2002;13:345–52.
5. Poss KD, Keating MT, Nechiporuk A. Tales of regeneration in zebrafish. Dev Dyn. 2003;226:202–10.
6. Mathew LK, Sengupta S, Kawakami A, et al. Unraveling tissue regeneration pathways using chemical genetics. J Biol Chem. 2007;282:35202–10.
7. Reed MJ, Cooper L, Wood W, et al. Wound healing and inflammation: embryos reveal the way to perfect repair. Phil Trans R Soc Lond. 2004;359:777–84.

7a. Larson BJ, Longaker MT, Lorenz HP. Scarless fetal wound healing: a basic science review. Plast Reconstr Surg. 2010;126:1172–80.

8. Neufeld DA, Zhao W. Bone regrowth after digit tip amputation in mice is equivalent in adults and neonates. Wound Repair Regen. 1995;3:461–6.
9. Han M, Yang X, Lee J, et al. Development and regeneration of the neonatal digit tip in mice. Dev Biol. 2008;315:125–35.
10. Lee LP, Lau PY, Chan CW. A simple and efficient treatment for fingertip injuries. J Hand Surg 1995;20: 63–71.
11. Grose R, Werner S. Wound-healing studies in transgenic and knockout mice. Mol Biotechnol. 2004;28:147–66.
12. Eming SA, Krieg T, Davidson D. Inflammation on wound repair: molecular and cellular mechanisms. J Invest Dermatol. 2007;127:514–25.
13. Gurtner GC, Werner S, Barrandon Y, Longaker MT. Wound repair and regeneration. Nature. 2008;453:314–21.
14. Martin P, Leibovich SJ. Inflammatory cells during wound repair: the good, the bad and the ugly. Trends Cell Biol. 2005;15:599–607.
15. Werner S, Krieg T, Smola H. Keratinocyte-fibroblast interactions in wound healing. J Invest Dermatol. 2007;127:998–1008.
16. Coulombe PA. Wound epithelialization: accelerating the pace of discovery. J Invest Dermatol. 2003; 121:219–30.

16a. Szabowski A, Maas-Szabowski N, Andrecht S, et al. c-Jun and JunB antagonistically control cytokine-regulated mesenchymal-epidermal interaction in skin. Cell. 2000;103:745–55.

17. Li A, Pouliot N, Redvers R, Kaur P. Extensive tissue-regenerative capacity of neonatal human keratinocyte stem cells and their progeny. J Clin Invest. 2004;113:390–400.

17a. Morasso MI, Tomic-Canic M.Epidermal stem cells: the cradle of epidermal determination, differentiation and wound healing. Biol Cell. 2005;97:173–83.

18. Cotsarelis G, Sun TT, Lavker RM. Label-retaining cells reside in the bulge area of pilosebaceous unit: implications for follicular stem cells, hair cycle, and skin carcinogenesis. Cell. 1990;61:1329–37.
19. Ito M, Liu Y, Yang Z, et al. Stem cells in the hair follicle bulge contribute to wound repair but not to homeostasis of the epidermis. Nat Med. 2005;11: 1351–4.
20. Eming SA, Brachvogel B, Odorisio T, Koch M. Regulation of angiogenesis: wound healing as a model. Prog Histochem Cytochem. 2007;42:115–70.
21. Olsson AK, Dimberg A, Kreuger J, Claesson-Welsh L. VEGF receptor signalling – in control of vascular function. Nat Rev Mol Cell Biol. 2006;7:359–71.
22. Roy R, Zhang B, Moses MA. Making the cut: protease-mediated regulation of angiogenesis. Exp Cell Res. 2006;312:608–22.
23. Gillitzer R, Goebeler M. Chemokines in cutaneous wound healing. J Leukoc Biol 2001;69:513–21.
24. Nathan C. Neutrophils and immunity: challenges and opportunities. Nat Rev Immunol. 2006;6:173–82.
25. Henson PM, Vandivier RW. The matrix degrades, neutrophils invade. Nat Med. 2006;12:280–1.
26. Kuijpers TW, Van Lier RA, Hamann D, et al. LAD1/variant. A novel immunodeficiency syndrome characterized by dysfunctional beta2 integrins. J Clin Invest. 1997;100:1725–33.
27. Roos D, Kuijpers TW, Mascart-Lemone F, et al. A novel syndrome of severe neutrophil dysfunction: unresponsiveness confined to chemotaxis-induced functions. Blood. 1993;81:2735–43.

27a. Pull SL, Doherty JM, Mills JC, et al. Activated macrophages are an adaptive element of the colonic epithelial progenitor niche necessary for regenerative responses to injury. PNAS. 2005;102:99–104.

28. Leibovich SJ, Ross R. The role of the macrophage in wound repair. Am J Pathol. 1975;78:71–100.
29. Mirza R, DiPietro LA, Koh TJ. Selective and specific macrophage ablation is detrimental to wound healing in mice. Am J Pathol. 2009;175:2454–62.
30. Gordon S. Alternative activation of macrophages. Nature. 2003;3:23–35.
31. Karin M, Lawrence T, Nizet V. Innate immunity gone awry: linking microbial infections to chronic inflammation and cancer. Cell. 2006;124:823–35.
32. Fishel RS, Barbul A, Beschorner WE, et al. Lymphocyte participation in wound healing: morphologic assessment using monoclonal antibodies. Ann Surg. 1987;206:25–9.
33. Park JE, Barbul A. Understanding of the role of immune regulation in wound healing. Am J Surg. 2004;187(Suppl):11S–6S.
34. Kneilling M, Röcken M. Mast cells: novel clinical perspectives from recent insights. Exp Dermatol. 2009;18:488–96.
35. Hinz B. Formation and function of the myofibroblast during tissue repair. J Invest Dermatol. 2007;127: 526–37.
36. Tomasek JJ, Gabbiani G, Hinz B, et al. Myofibroblasts and mechano-regulation of connective tissue remodelling. Nat Rev Mol Cell Biol. 2002;3:349–63.
37. Bayat A, McGrouther DA, Ferguson MW. Skin scarring. BMJ. 2003;11;326:88–92.
38. Blanpain C, Fuchs E. Epidermal stem cells of the skin. Annu Rev Cell Dev Biol. 2006;22:339–73.
39. Cha J, Falanga V. Stem cells in cutaneous wound healing. Clin Dermatol. 2007;25:73–8.

40. Kørbling M, Estrov Z. Adult stem cells for tissue repair – a new therapeutic concept? N Engl J Med. 2003;349: 570–82.
41. Krause DS, Theise ND, Collector MI, et al. Multi-organ, multi-lineage engraftment by a single bone marrow-derived stem cell. Cell. 2001;105:369–77.
42. Badiavas EV, Abedi M, Butmarc J, et al. Participation of bone marrow derived cells in cutaneous wound healing. J Cell Physiol. 2003;196:245–50.
43. Werner S, Grose R. Regulation of wound healing by growth factors and cytokines. Physiol Rev. 2003;83: 835–70.
44. Schäfer M, Werner S. Transcriptional control of wound repair. Annu Rev Cell Dev Biol. 2007;23:69–92.
45. Aszódi A, Legate KR, Nakchbandi I, Fässler R. What mouse mutants teach us about extracellular matrix function. Annu Rev Cell Dev Biol. 2006;22:591–621.
46. Hynes RO. Integrins: bidirectional, allosteric signaling machines. Cell. 2002;110:673–87.
47. Legate KR, Wickström SA, Fässler R. Genetic and cell biological analysis of integrin outside-in signaling. Genes Dev. 2009;23:397–418.
48. Barrick B, Campbell EJ, Owen CA. Leukocyte proteinases in wound healing: roles in physiologic and pathologic processes. Wound Repair Regen. 1999;7: 410–22.
49. Weiss SJ. Tissue destruction by neutrophils. N Engl J Med. 1989;320:365–76.
50. Fu X, Parks WC, Heinecke JW. Activation and silencing of matrix metalloproteinases. Semin Cell Dev Biol. 2008;19: 2–13.
51. Chen P, Parks WC. Role of matrix metalloproteinases in epithelial migration. J Cell Biochem. 2009;108: 1233–43.
52. Sen CK, Gordillo GM, Roy S, et al. Human skin wounds: a major and snowballing threat to public health and the economy. Wound Repair Regen. 2009;17: 763–71.
53. Partridge L, Gems D. Mechanisms of ageing: public or private? Nat Rev Genet. 2002;3:165–75.
54. Rudolph KL, Chang S, Lee HW, et al. Longevity, stress response, and cancer in aging telomerase-deficient mice. Cell. 1999;96:701–12.
54a. Gannon HS, Donehower LA, Lyle S, Jones SN. Mdm2-p53 signaling regulates epidermal stem cell senescence and premature aging phenotypes in mouse skin. Dev Biol. 2011;353:1–9.
55. Fonder MA, Lazarus GS, Cowan DA, et al. Treating the chronic wound: a practical approach to the care of nonhealing wounds and wound care dressings. J Am Acad Dermatol. 2008;58:185–206.
56. Singer AJ, Dagum AB. Current management of acute cutaneous wounds. N Engl J Med. 2008;359:1037–46.
57. O'Donnell TF Jr, Lau J. A systematic review of randomized controlled trials of wound dressings for chronic venous ulcer. J Vasc Surg. 2006;44:1118–25.
58. Landsman A, Taft D, Riemer K. The role of collagen bioscaffolds, foamed collagen, and living skin equivalents in wound healing. Clin Podiatr Med Surg. 2009;26:525–33.
59. Eming SA, Krieg T, Davidson JM. Gene therapy and wound healing. Clin Dermatol. 2007; 25:79–92
60. Mulder G, Tallis AJ, Marshall VT, et al. Treatment of nonhealing diabetic foot ulcers with a platelet-derived growth factor gene-activated matrix (GAM501): results of a phase 1/2 trial. Wound Repair Regen. 2009;17:772–9.
61. Badiavas EV, Falanga V. Treatment of chronic wounds with bone marrow-derived cells. Arch Dermatol. 2003;139:510–16.
61a. Kawamura A, Horie T, Tsuda I, et al. Clinical study of therapeutic angiogenesis by autologous peripheral blood stem cell (PBSC) transplantation in 92 patients with critically ischemic limbs. J Artif Organs. 2006;9:226–33.
62. Roth D, Piekarek M, Paulsson M, et al. Plasmin modulates vascular endothelial growth factor-A-mediated angiogenesis during wound repair. Am J Pathol. 2006;168:670–84.
63. Martino MM, Tortelli F, Mochizuki M, et al. Engineering the growth factor microenvironment with fibronectin domains to promote wound and bone tissue healing. Sci Transl Med. 2011;3:100ra89.

This page intentionally left blank

Surgical Anatomy of the Head and Neck

142

Franklin P Flowers and Thomas S Breza Jr

Chapter Contents

Topographic anatomy of the head and neck 2327
The superficial musculoaponeurotic system 2329
Skin tension lines 2330
Cosmetic subunits 2332
Free margins 2334
Muscles of facial expression 2334
Vascular anatomy 2335
The facial nerve 2336
Sensory innervation of the head and neck 2338
Lymphatic drainage of the head and neck 2340

Key features

- The muscles of facial expression all arise from the second branchial arch, are concentrated in the central facial region, and receive their motor innervation from the facial (7th cranial) nerve
- The superficial musculoaponeurotic system (SMAS) is a fibromuscular layer that ensheathes and connects the facial muscles and plays an intricate role in coordinating facial expressions
- The SMAS can be utilized as a guide to dissection, tissue mobilization and closure, minimizing trauma to neurovascular tissues
- The three branches of the trigeminal (5th cranial) nerve provide sensory innervation to the face, while various branches of the cervical plexus provide sensory innervation to the neck, parts of the ear, and posterior scalp
- Familiarity with the muscular and neurovascular structures of the head and neck region allows the surgeon to properly approach the "danger zones", e.g. Erb's point in the neck, the temporal nerve as it crosses the zygomatic arch, and the marginal mandibular nerve at the jawline just anterior to the masseter muscle
- The rich and anastomosing vascular supply of the face and scalp, derived from both the external and internal carotid arteries, explains the excellent healing potential and viability of local flaps and grafts in this region
- Cosmetic subunits and the junction lines separating them should be considered when planning excisions, repairs and cosmetic procedures of the head and neck

The dermatologic surgeon must have a comprehensive knowledge of regional anatomy in order to obtain acceptable operative results. Tissue movement on the face and neck must be considered in order to obtain closure under minimal tension without cosmetic distortion or functional loss of vital structures. Preservation of tissue viability, sensory and motor innervation, and prevention of postoperative morbidity can be achieved with a fundamental appreciation for the macromechanics of the head and neck[1,2]. The fascial planes, vascular supply, innervation, and aesthetic subunits of the face must be considered when planning a surgical or cosmetic procedure. In order to accurately and thoroughly counsel patients regarding procedural risks and benefits, the surgeon must have a thorough appreciation of head and neck anatomy.

TOPOGRAPHIC ANATOMY OF THE HEAD AND NECK

It is possible to pinpoint underlying anatomic structures of the head and neck by observing surface anatomy. The bony structure of the face serves as a simple anatomic framework (Fig. 142.1). The supraorbital ridges are formed by the frontal bone and are more prominent in men. The supraorbital foramen transmits the sensory supraorbital nerve (from the ophthalmic division of the trigeminal nerve), artery and vein. It is palpable on the bony supraorbital ridge at the vertical midpupillary line. This line lies approximately one finger-breadth lateral to the lateral nasal root or 2.5 cm lateral of the midline on the face (Fig. 142.2). Other important foramina lie in this midpupillary line and transmit important neurovascular bundles. The infraorbital foramen is located 1 cm below the infraorbital rim in the midpupillary line. It transmits the sensory infraorbital nerve (from the maxillary division of the trigeminal nerve) and its associated artery and vein. The mental foramen lies in the same vertical line in the midportion of the mandible. The mental neurovascular bundle emerges here as a terminal sensory branch of the mandibular division of the trigeminal nerve.

The anterior border of the temporalis muscle can be palpated in the temporal fossa above the zygomatic bone. The latter bone forms the malar eminence of the cheek. The buccal fat pad provides fullness to the cheek; elderly or cachectic patients often have very prominent zygomatic arches. These arches form the widest points on the face and serve as the point of attachment for several muscles of facial expression and for a muscle of mastication called the masseter. The masseter muscle spans the zygomatic arch and mandibular ramus, serving as a muscle of mastication innervated by a motor branch of the trigeminal nerve (see below). This muscle is easily palpated by clenching the jaw.

The parotid gland lies beneath the subcutaneous fat of the lateral cheek and is invested by parotid fascia. The superficial lobe of the parotid covers the posterior half of the masseter muscle and extends from the preauricular sulcus to the angle of the mandible. The deep lobe lies on the medial side of the ramus of the mandible and is connected to the superficial lobe by an isthmus. The superficial temporal artery and vein, as well as branches of the facial nerve (which provides motor innervation to the muscles of facial expression), course through the parotid gland in channels between glandular tissue[3]. The duct of the parotid gland (Stensen's duct) travels across the anterior surface of the masseter muscle (Fig. 142.3). After crossing the muscle surface, the duct penetrates deeper to pierce the buccinator muscle and eventually drains into the mouth at the level of the second upper molar. It can be palpated as a "cord" crossing a clenched masseter muscle. If the duct is transected, a chronic draining fistula will form, requiring corrective surgical intervention. Stensen's duct can be identified topographically by drawing a line between the tragus and the midportion of the cutaneous upper lip. The duct traverses the masseter muscle at the middle one-third of this line (see Fig. 142.3).

Several structures of importance can be located by observing the surface anatomy of the neck. The sternocleidomastoid muscle comprises two heads originating from the sternum and the medial one-third of the clavicle. It inserts onto the outer surface of the mastoid process and nuchal ridge, dividing the neck into anterior and posterior triangles. A dermatologic surgeon should be familiar with the anatomic structures that lie within each of these topographic triangles (Fig. 142.4). Although the sternocleidomastoid muscle covers and protects most of the major anatomic structures in the neck, the external jugular vein traverses its surface with many cutaneous sensory nerves of the cervical plexus. In addition, the posterior triangle of the neck contains trunks of the brachial and cervical plexus as well as the spinal accessory nerve

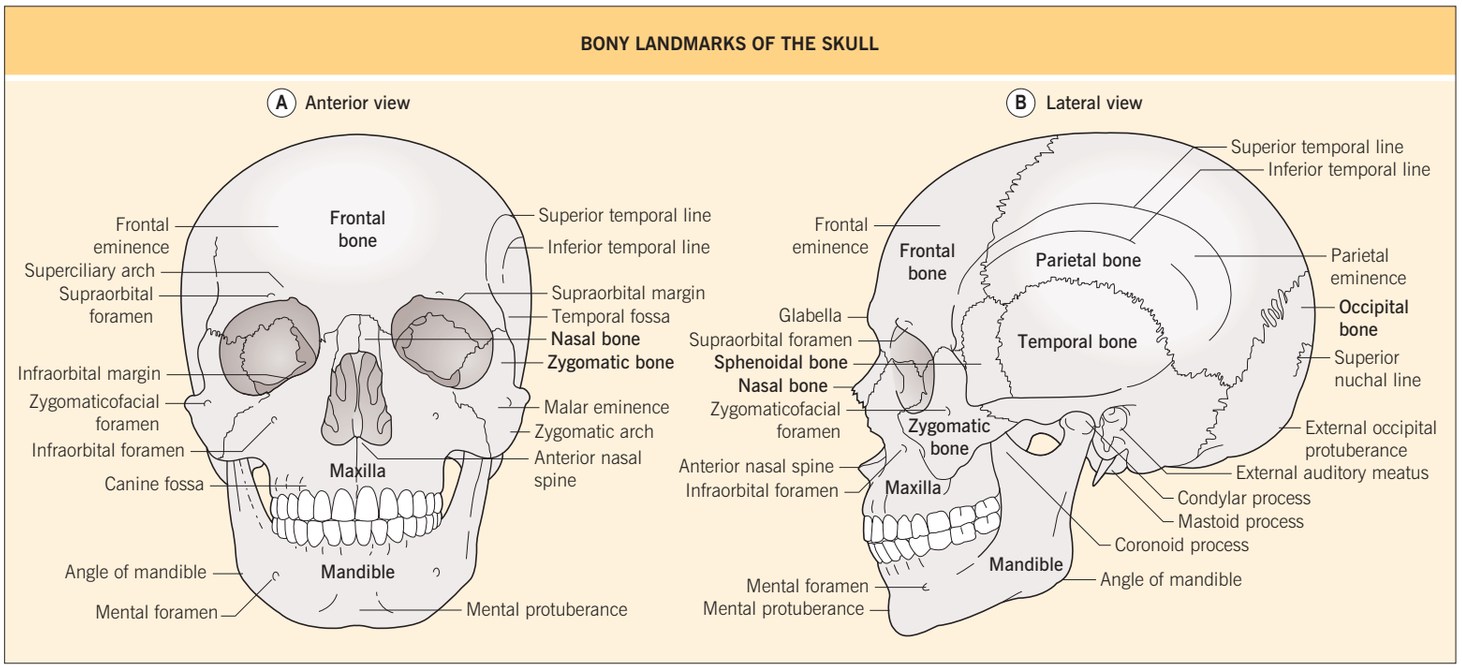


Fig. 142.1 Bony landmarks of the skull. A Anterior view. **B** Lateral view.

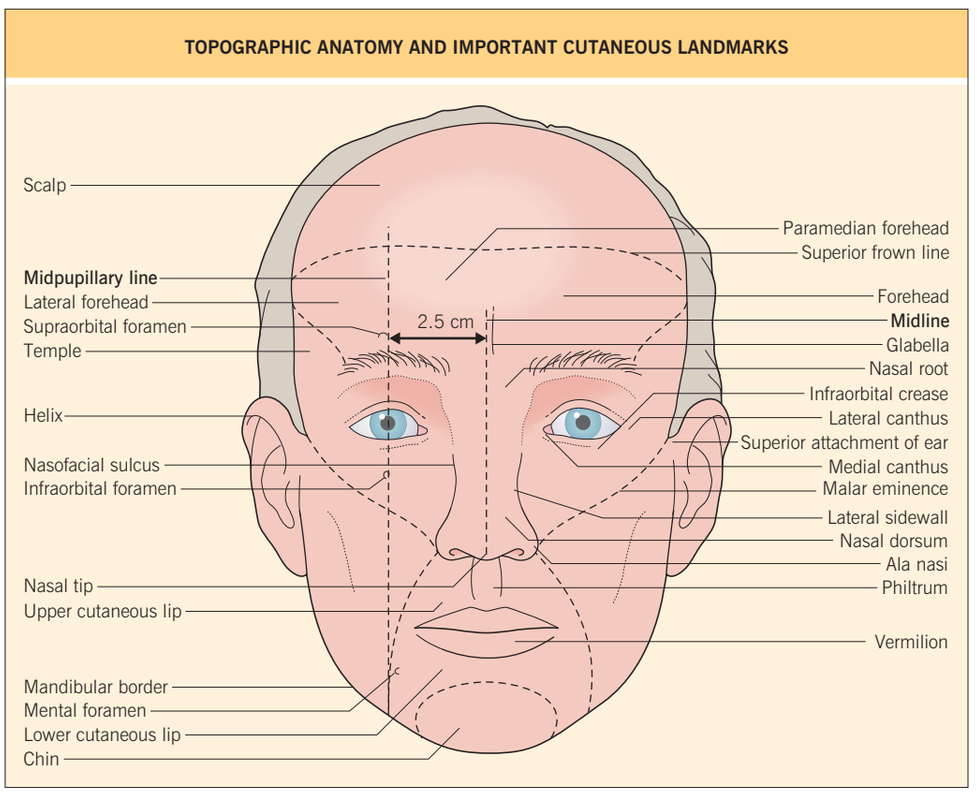


Fig. 142.2 Topographic anatomy and important cutaneous landmarks.

(cranial nerve XI). Cranial nerve XI innervates the trapezius muscle of the back. It may be damaged when operating in this posterior triangle. This may result in chronic shoulder and neck pain, shoulder drop and trapezius atrophy, arm paresthesias, and the inability to abduct the arm greater than 80°.

Erb's point designates the area where the cervical plexus emerges from the posterior margin of the sternocleidomastoid muscle (see Figs 142.4 & 151.6). The spinal accessory nerve courses through this area on its way to the trapezius muscle. This surgical danger zone can be visualized by drawing a line connecting the angle of the jaw to the mastoid process. In an adult, a perpendicular line dropped 6 cm from the midpoint of this connector will intersect the posterior border of the sternocleidomastoid where the spinal accessory nerve and cervical plexus emerge[4]. Extreme caution is warranted when dissecting around these anatomic structures, in order to avoid loss of innervation to the trapezius muscle.

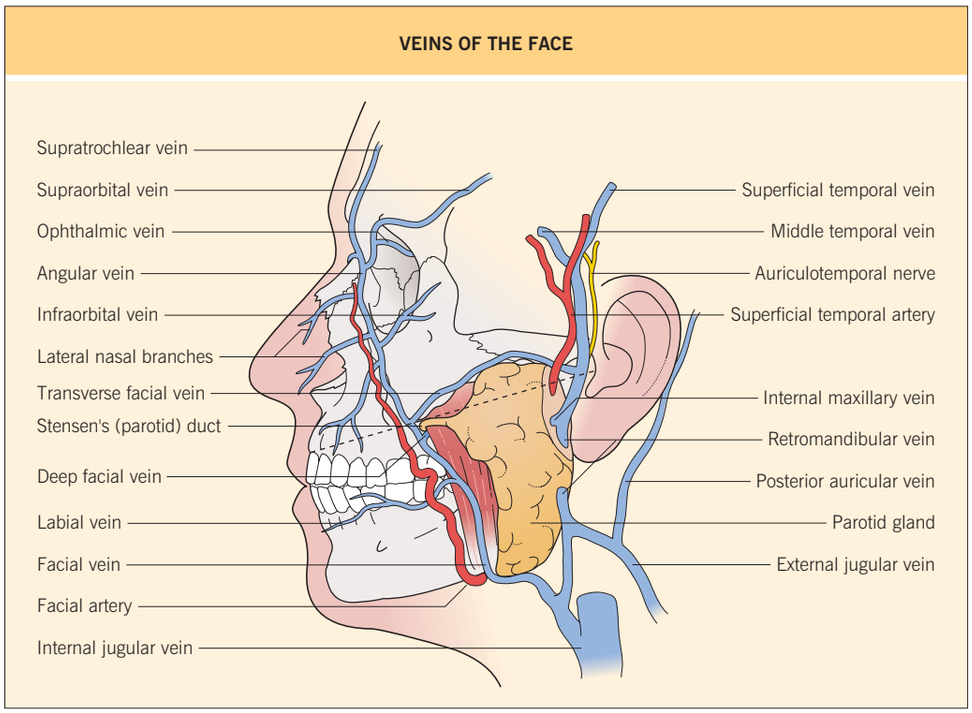


Fig. 142.3 Veins of the face. Stensen's duct can be identified topographically by drawing a line between the tragus and mid portion of the cutaneous upper lip (dotted line). It can be palpated as a cord at the middle third of this line.

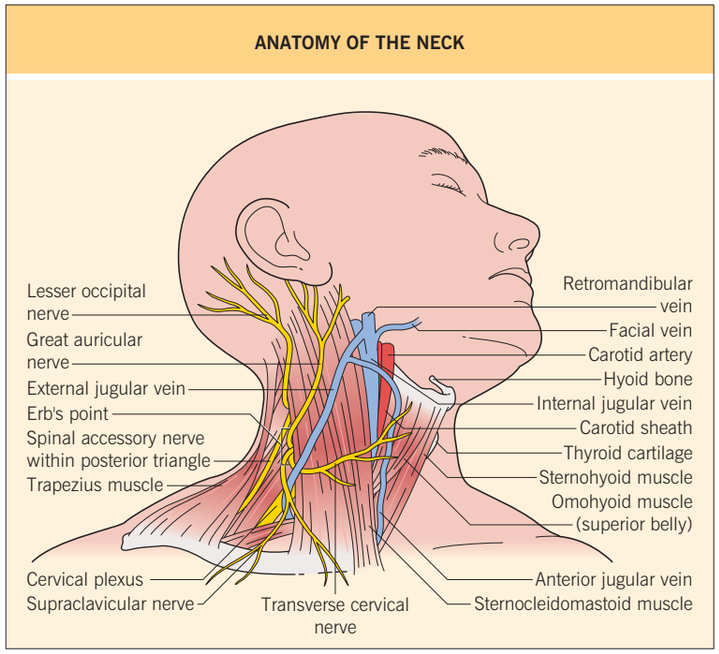


Fig. 142.4 Anatomy of the neck.

THE SUPERFICIAL MUSCULOAPONEUROTIC SYSTEM

The superficial musculoaponeurotic system (SMAS) or superficial fascia of the head and neck region plays an intricate role in coordinating and exaggerating facial expressions. It is a fibromuscular layer that ensheathes and connects the facial muscles. When the regional muscles contract, their impulse is distributed by the SMAS via fibrous connections to the skin and other muscle groups. This contributes to organized movements, symmetry in facial expression, and the appearance of skin tension lines. In certain areas where facial musculature is absent, the SMAS layers form a thick, inelastic membrane. These regions are clinically identifiable as the galea aponeurotica of the scalp and the superficial temporalis fascia. Major anatomic structures predictably course in and around the superficial fascia. The dermatologic surgeon can maximize this relatively avascular dissection plane and minimize trauma to important neurovascular structures by using the SMAS as a guide to dissection, tissue mobilization, and closure. Rejuvenation procedures such as facelifts rely on the redistribution and manipulation or plication of the head and neck SMAS.

The deep fascia of the face covers bone, cartilage, muscles of mastication, and visceral structures. It is a continuous sheath, forming periosteum, perichondrium, temporalis muscle fascia, and the parotid-masseteric fascia[1]. This fascia is resistant to stretch and particularly impedes tissue movement on the scalp. Plication or suspension sutures are often used to "tack" overlying structures to the deeper fascia in order to secure tissue and redirect tension vectors.

The SMAS of the cheek is located between the skin and the deeper muscles of mastication. By mobilizing the preauricular SMAS plane, the anterolateral neck and lower cheek below the zygomatic arch can be repositioned as a whole. The SMAS of the cheek is continuous with the orbicularis oculi muscle of the lower eyelid and has several bony attachments in the periocular region[5]. Note that the SMAS of the upper face is discontinuous with the SMAS below the zygoma. Different embryologic development patterns of the upper and lower facial muscle groups account for this separation. The galea aponeurotica of the scalp and the fascia of the superficial temporalis muscle split to envelop the frontalis muscle of the forehead and the occipitalis muscle of the posterior scalp. This superior SMAS terminates 1 cm below the zygomatic arch.

The parotid gland, Stensen's duct, and emerging branches of the facial nerve lie on the deep masseteric fascia. They are covered by thin fibrotic platysma remnants called the parotid fascia, which is covered by the SMAS. The aponeurotic investiture of the central face is thin and often indistinct. The intrinsic nasal muscles and lip elevators and depressors are essentially devoid of superficial fascial interconnections. This makes dissection in this area challenging, because the planes are often difficult to establish and many important anatomic structures are under threat of compromise.

Large sensory nerves and axial blood vessels that supply the face ascend to lie within the SMAS or between the SMAS and subcutaneous fat (Fig. 142.5). Motor nerves run deep to the SMAS and penetrate the muscles of facial expression from their undersurface. Knowledge of these anatomic relationships assists the surgeon in establishing a relatively avascular and safe plane of dissection. Blunt dissection of the scalp SMAS separates the galea aponeurotica from the skull periosteum, the superficial temporalis fascia from the deep temporalis fascia, and the subfrontalis SMAS from the forehead periosteum. This is called

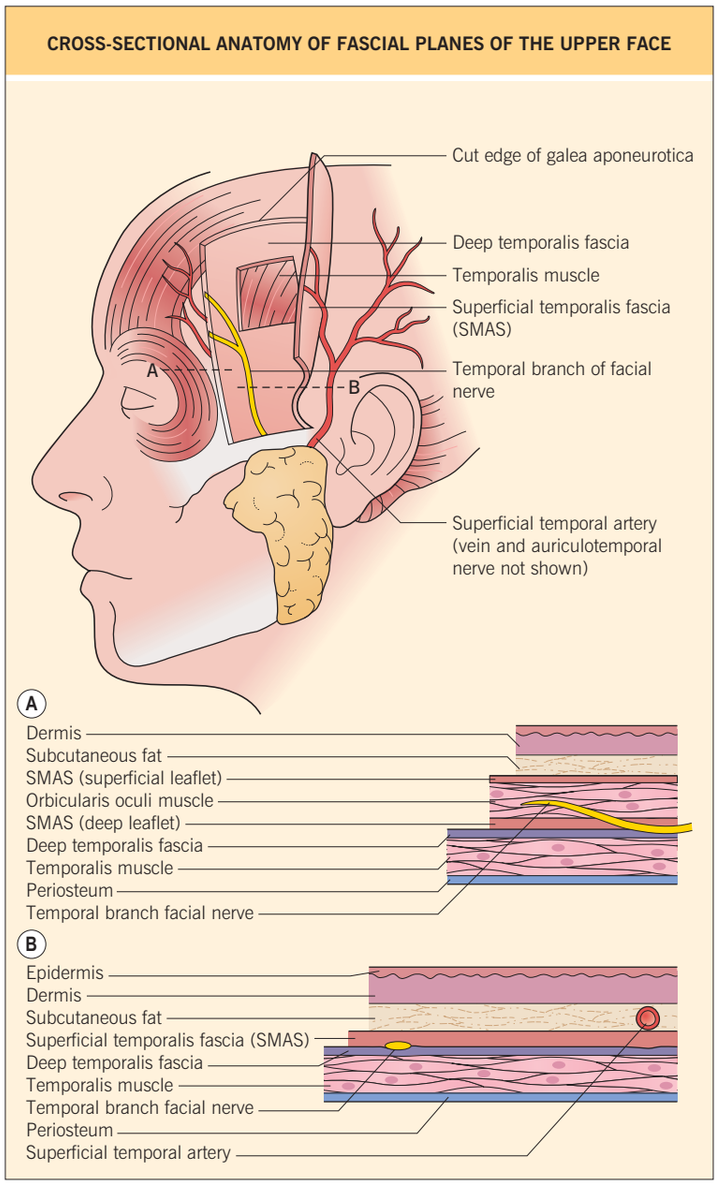


Fig. 142.5 Cross-sectional anatomy of fascial planes of the upper face. SMAS, superficial musculoaponeurotic system.

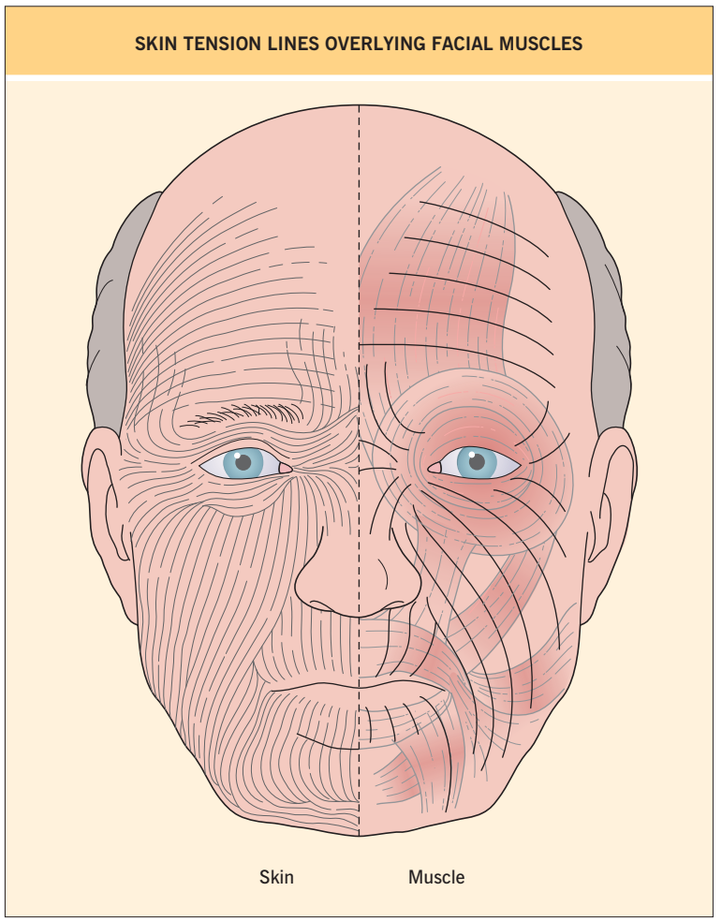


Fig. 142.6 Skin tension lines overlying facial muscles. Note that wrinkles are often directed perpendicularly to the underlying muscle fibers of facial expression.

the subgaleal plane, and it is the ideal avascular dissection plane for scalp surgery. Beware of the supraorbital/supratrochlear neurovascular bundles above the eyebrows when dissecting to the deep galea, as these can be damaged as they exit the inferior frontalis muscle origin. In the SMAS-parotid fascial plane of the cheek, the buccal and zygomatic branches of the facial nerve are endangered due to thin protective aponeurotic tissue in this area. The superficial temporal vessels and auriculotemporal nerve course within the superficial temporalis fascia above the zygomatic arch, then assume a superficial plane in the subcutaneous fat.

Surgical undermining and dissection should maximize the horizontal planes provided by the superficial fascial network of the head and neck. Undermining in the subcutaneous fat of the face below the subdermal plexus minimizes the risk to motor nerves, but remember that sensory branches and blood vessels do course through this area. There is sparse subcutaneous fat on the dorsal nose, forehead, upper lip, and eyelid. The ideal dissection plane in these regions lies just superficial to the thin investing fascia (SMAS) covering the regional muscles of facial expression[6].

In short, the SMAS acts as a unifying infrastructure to the head and neck that creates an anatomic plane for identification and protection of key structures. Knowledge of neurovascular anatomy with respect to the superficial investing fascia will promote effective surgical dissection and closures that minimize functional compromise and maximize cosmesis.

SKIN TENSION LINES

Collagen and elastin afford flexibility and extensibility to the skin, and derangements of their architecture or abundance contribute to the aging process. Wrinkles (rhytides) develop over time in predictable areas on the face. The fine wrinkles seen on an aged face may be referred to as the skin tension lines (Fig. 142.6); on the body, skin tension lines (Fig. 142.7) are an important consideration when designing surgical excisions (see Ch. 146). Many environmental and intrinsic factors, such as ultraviolet exposure, smoking, underlying facial muscles, etc., contribute to the appearance of the expressive human face. A thorough understanding of the derivation and implications of skin tension lines is essential to successful dermatologic surgery.

Continuous tension is exerted on the skin of the head and neck by the muscles of facial expression. A complicated network composed of muscles, fibrous septae of collagen, elastin and fascial planes contributes to this stress, which eventually results in sagging, wrinkling and redundant skin. Collagen is flexible but much less extensible than elastic fibers. The resistance to tensile forces by collagen promotes a "youthful" appearance. Over time, the prolonged tension exerted on the skin from many factors forces collagen fibrils to accommodate by way of elongation. Eventually, aged skin manifests the consequences of persistent skin tension. The collagenous tissue becomes increasingly intertwined, diminished in volume, and permanently elongated. This causes the accentuation of skin tension lines[4].

Elastic fibers promote extensibility (i.e. the ability of skin to stretch) and elasticity (i.e. the skin's capacity to restore its original shape after physical stress). They contribute to the skin tension lines by promoting vector distribution of tension along fascial planes. The elastic properties

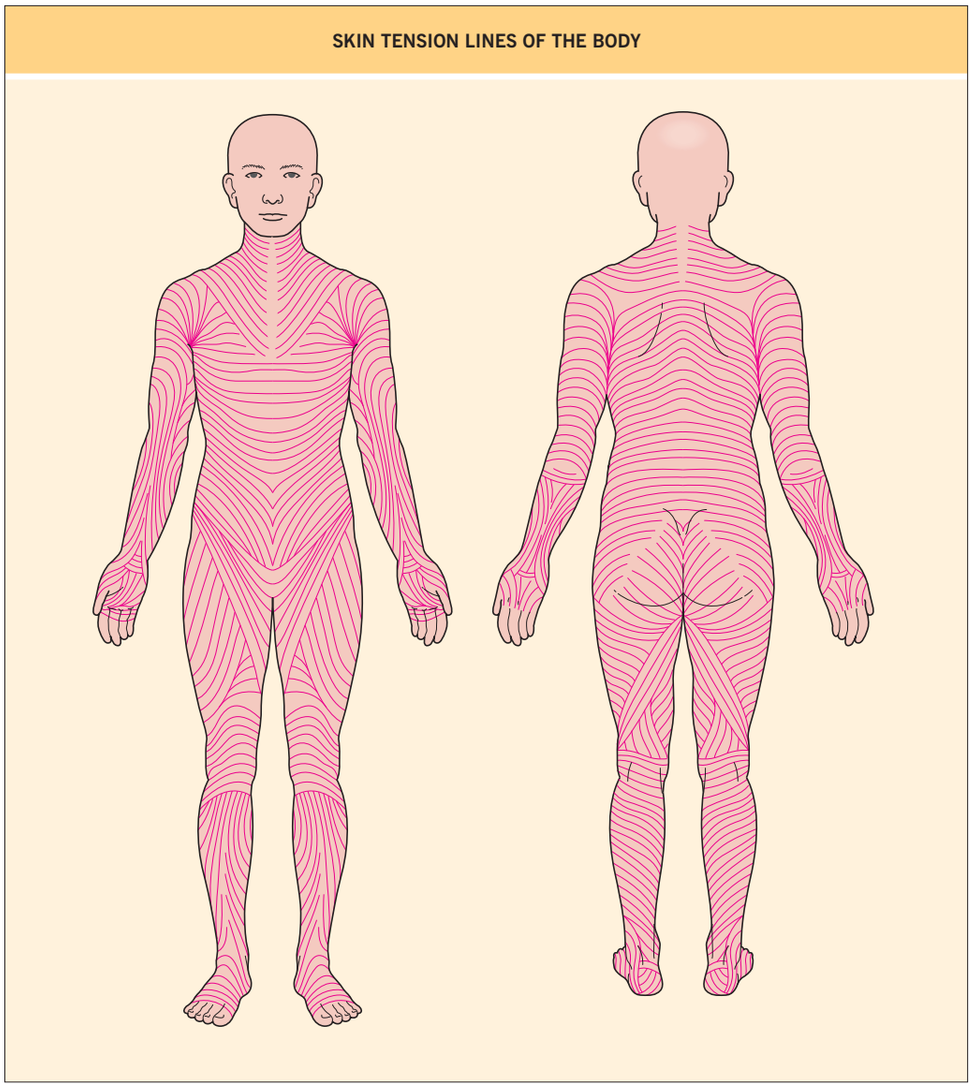


Fig. 142.7 Skin tension lines of the body.

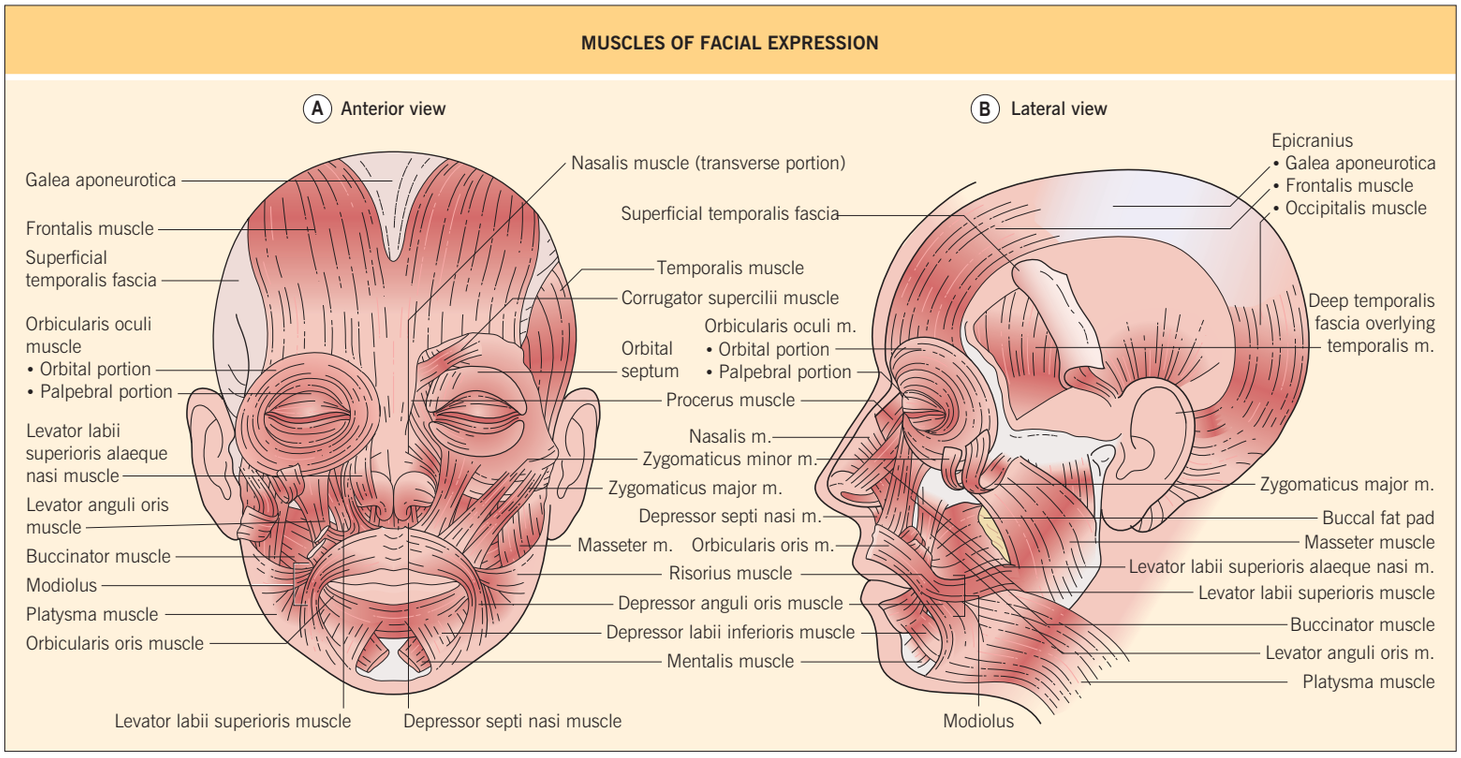


Fig. 142.8 Muscles of facial expression. A Anterior view. **B** Lateral view. The transverse portion of the nasalis muscle is identified. m, muscle.

of the skin explain the phenomenon whereby round surgical wounds relax into an axis parallel to the patient's wrinkles. Tension vectors are increased parallel to the skin tension lines and are diminished perpendicular to them; therefore, the linear appearance of wrinkles is often directed perpendicularly to the underlying muscle fibers of facial expression (see Fig. 142.6). The continuous tension exerted on the overlying skin by these muscles challenges the competency of elastic tissue and collagen. They induce this geometric linearity via fibrous connections to the dermis via the SMAS. For example, the forehead undergoes transverse wrinkling due to contractions of the frontalis muscle, whose fibers run in a cephalocaudad direction. Periocular rhytides are often radially oriented due to underlying contraction of the orbicularis oculi. Similarly, perioral wrinkling occurs under the influence of the concentric orbicularis oris muscle, which induces a radial arrangement of skin tension lines as well. The procerus muscle causes transverse nasal root lines, and vertical glabellar lines are determined by the corrugator supercilii muscles (Fig. 142.8).

Knowledge of these functional anatomic principles is necessary in surgical and cosmetic dermatology. For example, the successful use of botulinum toxin for the diminution of rhytides requires an understanding of the anatomic relationships between various muscle groups and their influence on the skin tension lines. Proper surgical technique entails placement of incision lines parallel to the skin tension lines in order to achieve excellent cosmesis. It is helpful to determine and even sketch the patient's skin tension lines with a gentian violet pen. This will help orient the axis of incision and guide the closure parallel to and preferably "buried" within individual lines of tension.

There is often a significant amount of recruitable or "redundant" skin within the skin tension lines. In addition, "extra" skin may also be found in the preauricular folds, glabella, nasolabial folds, and the "jowls" or lower cheeks[7]. These tissue reservoirs can be used as donor sites for flaps (see Ch. 147) and grafts (see Ch. 148) in order to achieve surgical closure under minimal tension.

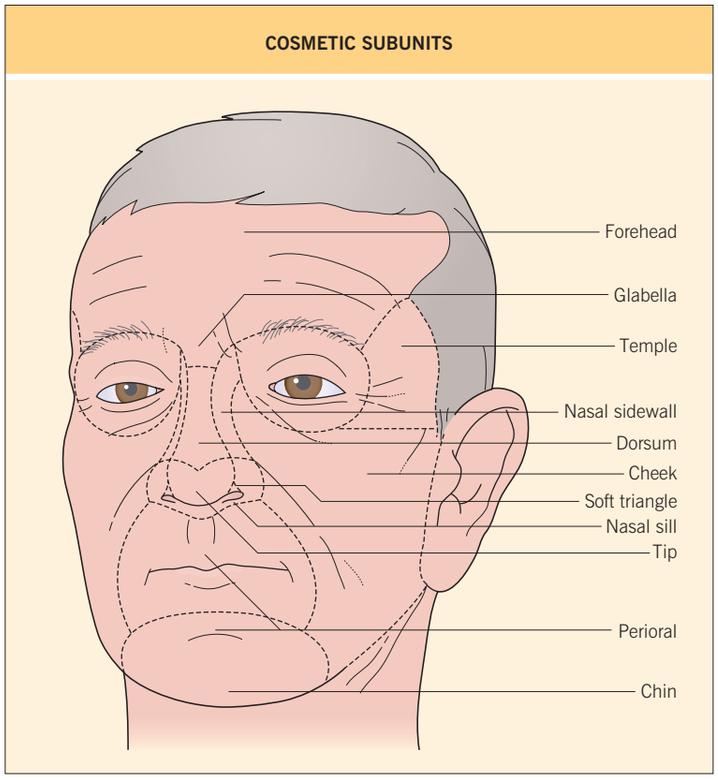


Fig. 142.9 Cosmetic subunits.

COSMETIC SUBUNITS

Cosmetic units (i.e. aesthetic, topographic or regional units) represent the major structural areas of the face that are separated by contour or junctional lines or boundaries (Fig. 142.9). Units are designated based upon their similarity in topographic anatomy, texture and color, solar exposure, hair density, and sebaceous features. The forehead, temples, eyelids, nose, cheeks, upper and lower lips, chin, and ears represent the major cosmetic subunits of the face. Within each division, smaller units are designated that further guide surgical closures. The junctional or contour lines between cosmetic units serve as excellent locations to place incisions and hide surgical scars. They include the hairline, alar and nasolabial creases, eyebrows, the philtrum, the labiomental crease,

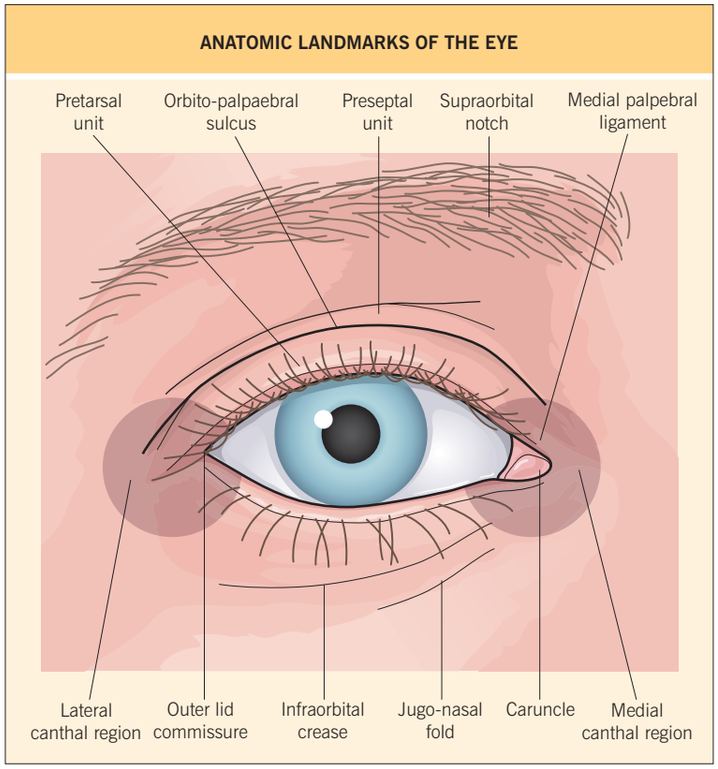


Fig. 142.10 Anatomic landmarks of the eye.

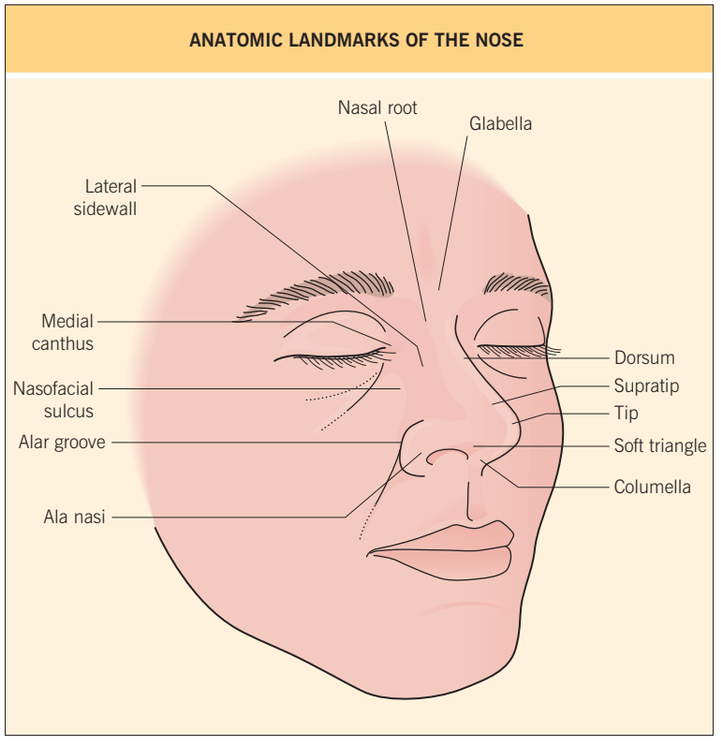


Fig. 142.11 Anatomic landmarks of the nose.

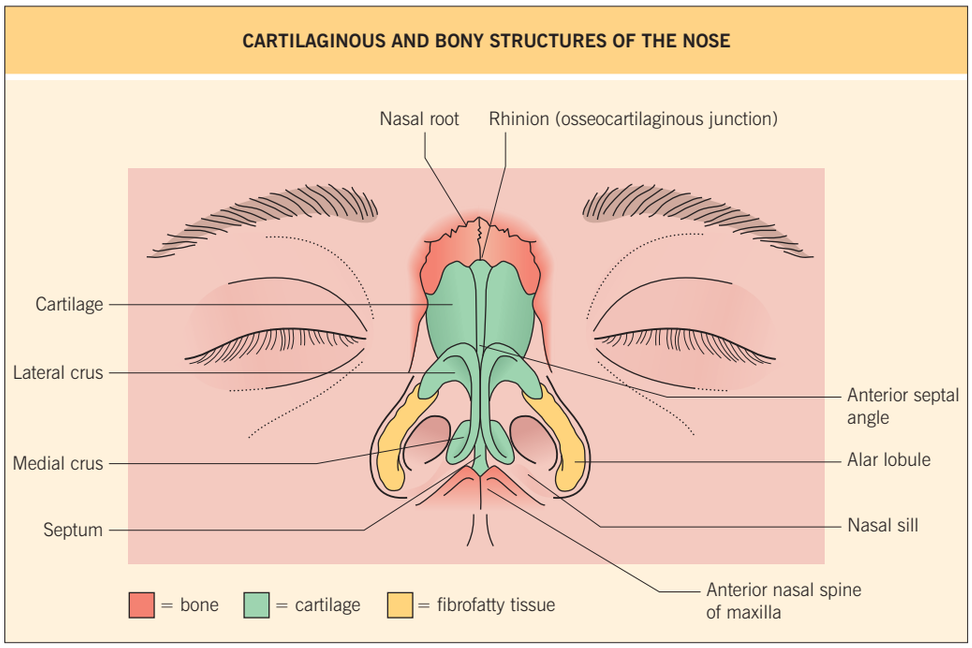


Fig. 142.12 Cartilaginous and bony structures of the nose.

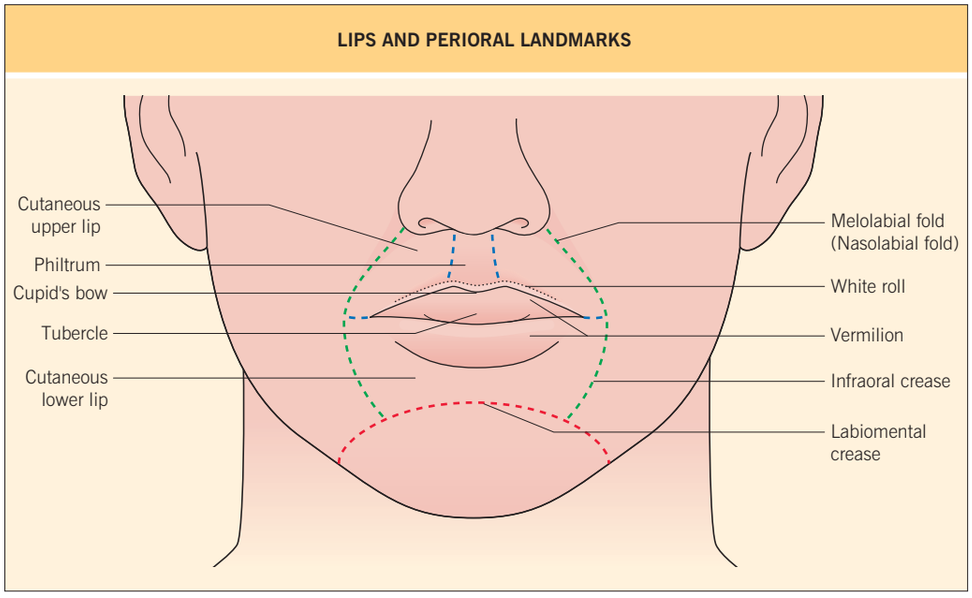


Fig. 142.13 Lips and perioral landmarks.

and the upper and lower vermilion–cutaneous interfaces (see Figs 142.2 & 142.13).

In general, defects should be repaired with tissue from within the same cosmetic unit in order to preserve topographic consistency and to match skin color and texture. If this cannot be achieved, it is reasonable to utilize tissue from an adjacent aesthetic unit, which will most closely match the skin of the recipient cosmetic unit. The goal is to optimize the match in skin texture, color, actinic damage and thickness. Scars that cross aesthetic units and boundary lines are obvious and often cosmetically unacceptable. A primary goal of cutaneous surgery is to "respect" the cosmetic subunits.

An appreciation for cosmetic units and contour lines also helps the surgeon determine areas of "recruitable" tissue for closures. Redundant or freely mobile skin can be mobilized from the preauricular folds, neck, nasolabial folds, temple, glabella, the lower and lateral cheeks, and the "jowls". The potential for such tissue recruitment depends on the patient's age, degree of actinic damage and skin elasticity, which varies from patient to patient. Areas of redundancy or high elasticity may serve as excellent donor sites within or adjacent to the cosmetic subunit which contains a given surgical defect. For example, cheek advancement flaps and temple to lateral forehead advancement and rotation flaps are frequently used for defect repairs.

The forehead unit can be divided into the glabella, temple and supraeyebrow aesthetic subunits. The transverse creases of this region serve as excellent sites to place cosmetically acceptable incisional scars. The eyelids represent a major cosmetic subunit of the face whose subdivisions correspond to portions of the orbicularis oculi muscles[8] (Fig. 142.10). The inferior pretarsal portion of the upper eyelid is relatively fixed, while the preseptal unit becomes increasingly redundant with age. Over time, progressive laxity of the preseptal unit can cause functional visual impairment in some patients. It is the preseptal unit of the palpebral portion of the lid that is reduced in blepharoplasties. The infraorbital crease lies between the lower eyelid and the upper cheek.

Nasal cosmetic subunits include the alar groove (which defines the ala nasi) and the columella, which extends from the nasal tip to the junction with the upper cutaneous lip. The dorsum, lateral sidewalls, soft triangles, root and nasal tip are important landmarks that pose a significant challenge in dermatologic surgery (Fig. 142.11). The nasal tip unit forms the shape of a chevron or heart due to the anatomy of the nasal cartilage (Fig. 142.12). When possible, surgical defects should

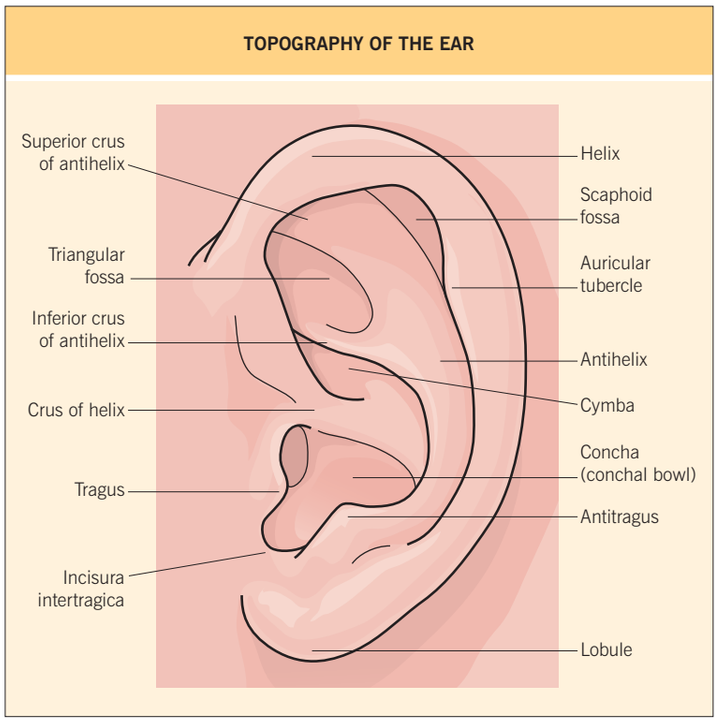


Fig. 142.14 Topography of the ear.

be contained within the boundaries of a given nasal subunit in order to effect acceptable cosmesis[9].

The philtrum is located above the upper vermilion lip and extends superiorly to the columella of the nose (Fig. 142.13). Because it is a midline structure, even minimal anatomic distortion results in a poor cosmetic outcome. The vermilion lip extends from the vermilion lip–cutaneous junction to the mucous membrane junction. It is a modified epithelium that usually does not contain adnexal structures or salivary glands. Approximation of the vermilion borders is crucial to maintaining facial symmetry. The melolabial or nasolabial crease serves as a useful landmark that separates the cheek from the mouth and chin aesthetic units. It is an ideal place to hide suture lines and often serves as a generous donor site for repairs.

The external ear (auricle or pinna) consists of a single cartilaginous plate that results in the complex curves and folds of the ear (Fig. 142.14). The skin is loose on the posterior portion but tightly adherent on the anterior surface.

FREE MARGINS

Free margins of the face are anatomic structures that are in some way discontinuous with adjacent skin. They include the lips, helices, eyelids and nostrils. These areas deserve special attention from the dermatologic surgeon because they do not have evenly distributed tension vectors. This characteristic makes the free margins especially vulnerable to any iatrogenic directional pull. Surgical closures, wound healing and scar contraction can cause these free margins to lose their cosmetic or functional integrity. Ectropion (eyelid eversion) or eclabium (lip eversion) may ensue. Primary elliptical closures that are strictly parallel to a free margin and second intention healing are not frequently used in these areas.

The opposing force inflicted upon a free margin depends on closure axis orientation, flap or graft design, and the tensile strength and elasticity of the skin. Aged skin is often less able to resist directional vectors. The lower eyelid often becomes especially lax with cumulative actinic damage and age. The "pinch" or "snap" test can be used in free margin evaluation by gently pulling the lower lid away from the eye. Upon release, a competent lower lid should assume its original shape against the globe, while a lax lid will regain its configuration slowly[4]. Instruct the patient to open his or her mouth and gaze upwards while simulating closure options under the eye. This generates the maximum intraoperative tension on the lower eyelid and can help to estimate the risk for distortion of this free margin. No more than 2 mm of inferior pull or "drag" on the lower eyelid can generally be tolerated during cutaneous surgical repairs. Any additional inferior tension puts the patient at high risk for ectropion[10].

Maintenance of cosmesis and function of the lip vermilion is of utmost importance. Elliptical closures often create drag on these free margins, but careful redirection of tension vectors may allow simple closures here as well. Flaps that can be performed in this area are reviewed in Chapter 147. Although the helical rims are free margins, they are far more "forgiving" than the aforementioned sites. Second intention healing and axial elliptical closures can achieve excellent results on the ear. The tissue is easily dissected and the posterior auricular skin provides excellent mobility. Most patients have some ear asymmetry at baseline, thus making this free margin less cosmetically sensitive.

The nasal tip, alae and adjacent lateral sidewall require special consideration due to their classification as "free margins" and the underlying cartilage framework that prevents significant tissue mobility. Elevation and distortion of the nasal rim may occur if second intention healing or simple primary closure is attempted. Full-thickness skin grafts and transposition or rotation flaps from adjacent areas are particularly appealing repairs in this cosmetically sensitive area[11].

MUSCLES OF FACIAL EXPRESSION

The muscles of facial expression arise from the second branchial arch, are innervated by the facial nerve (cranial nerve VII), and are concentrated in the central facial region. They insert into overlying skin and other local muscle groups and contribute to the relaxed skin tension lines of this region. Fluidity of facial movements is orchestrated by their interaction with the SMAS. A surgeon must have detailed knowledge of these muscles and the potential consequences of disrupting their innervation.

The epicranius or occipitofrontalis muscle of the scalp has an anterior and posterior region connected by the galea aponeurotica (see Fig. 142.8). Contraction of these muscles allows the skin to slide over the scalp. Humans no longer have voluntary control of the posterior muscle group, which is innervated by the posterior auricular branch of the facial nerve. The frontalis muscle is a member of the epicranius complex that begins at the anterior hairline and inserts into the forehead and eyebrow skin. It also connects with the procerus, orbicularis oculi and corrugator supercilii muscles. Midline vertical forehead skin tension lines occur due to variation in distance between the left and right frontalis bellies. Horizontal skin tension lines occur perpendicular to the frontalis contractile orientation (see Fig. 142.6). Loss of frontalis function results in flattening of forehead skin tension lines and a drooping eyebrow. This occurs when the temporal branch of the facial nerve is disrupted. Patients with compromised frontalis function may be unable to open their eyes widely, due to the synergistic effect this muscle has with the orbicularis oculi muscle.

The small periauricular muscles or the temporoparietalis group arise from the superficial temporalis SMAS and the lateral galea. They help draw back the temporal skin and are innervated by the posterior ramus of the temporal branch of the facial nerve. The orbicularis oculi muscle complex is the major group that acts on the eyelid and periorbital skin. It inserts into the medial and lateral canthal tendons and encircles the eye region. Its palpebral portion has a preseptal component overlying the orbital septum and a pretarsal portion overlying the tarsal plate of the eyelid. The palpebral orbicularis oculi muscle aids in tear excretion. Upper pretarsal and preseptal muscles depress the upper lid. The orbital component of this muscle group allows voluntary tight closure of the eye. The palpebral portion allows gentle eye closure and blinking. The orbicularis oculi is intertwined with the procerus, corrugator supercilii, and frontalis muscles and attaches to the superficial temporal fascia at its lateral border.

The corrugator supercilii muscle is located over the medial upper orbital rim. It contributes to a "scowling" facial expression by drawing the eyebrows medially and downward. It interdigitates with and is covered by the frontalis and orbicularis oculi muscles. The vertical and oblique skin tension lines of the glabella are caused by contraction of

INNERVATION OF THE MUSCLES OF FACIAL EXPRESSION VIA CRANIAL NERVE VII (THE FACIAL NERVE)
TEMPORAL BRANCH
• Frontalis muscle (m.) • Corrugator supercilii m. • Orbicularis oculi m. (upper portion) • Auricular m. (anterior and superior; also known as the temporoparietalis m.)
POSTERIOR AURICULAR BRANCH
• Occipitalis m. • Auricular m. (posterior)
ZYGOMATIC BRANCH

• Orbicularis oculi m. (lower portion)
• Nasalis m. (alar portion)
• Procerus m.
• Upper lip muscles
  • Levator anguli oris m.
  • Zygomaticus major m.

BUCCAL BRANCH

• Buccinator m. (muscle of mastication)
• Depressor septi nasi m.
• Nasalis m. (transverse portion)
• Upper lip muscles
  • Zygomaticus major and minor m.
  • Levator labii superioris m.
  • Orbicularis oris m.
  • Levator anguli oris m.
• Lower lip muscles (orbicularis oris m.)

MARGINAL MANDIBULAR BRANCH

• Lower lip muscles
  • Orbicularis oris m.
  • Depressor anguli oris m.
  • Depressor labii inferioris m.
  • Mentalis m.
• Risorius m.
• Platysma m. (upper portion)

CERVICAL BRANCH
• Platysma m.

Table 142.1 Innervation of the muscles of facial expression via cranial nerve VII (the facial nerve)[4,12].

this muscle, which is innervated by the temporal branch of the facial nerve (Table 142.1).

The procerus muscle overlies the nasal bone and attaches to the nasal root skin. It causes foreshortening of the nose and "bunny lines" (i.e. skin tension lines exaggerated by wrinkling up the nose). The nasalis muscle courses across the nasal dorsum and facilitates alar "flaring" and compression. These muscles are innervated by the zygomatic and buccal branches of the facial nerve. The depressor septi nasi muscle lies deep to the orbicularis oris and can form a transverse skin tension line across the philtrum. It plays a minor role in facial expression by pulling the columella down toward the lip.

An intricate network of interdigitating agonist and antagonist muscle groups contributes to lip movements and oral expression. Lip elevators, depressors and retractors assist the sphincteric orbicularis oris muscle in lip movement. The orbicularis oris muscle allows pursing and puckering of the lips, apposition of the corners of the mouth, and pulling of the lips up against the teeth and gingivae. It has no bony or cartilaginous attachment and is innervated by the buccal or marginal mandibular branches of the facial nerve. This circumferential muscle is necessary for correct speech and allows enunciation of the letters M, V, F, P and O[4].

The facial arteries and veins are covered and protected from damage by the lip elevator muscles. The quadratus labii superioris muscle group comprises several lip elevators. The levator anguli oris and risorius muscles are mouth angle retractors and elevators. The zygomaticus major muscle travels from the zygoma downward and diagonally to the upper corner of the mouth, where it contributes to the nasolabial fold. Zygomaticus major and minor muscles are the main contributors to smile formation. The risorius muscle also contributes to a smiling facial expression by drawing back the corners of the mouth. The modiolus platform is formed by the convergence of fibers from the orbicularis oris and lip elevators and depressors. It is located 1 cm lateral to the mouth angle and accounts for cheek "dimples" in some patients. It works in synergy with the perioral muscles to facilitate speech enunciation.

The buccinator muscle constitutes a large area of the cheek as it courses from the posterior maxillary area to the upper medial surface of the mandible, where it interdigitates with the orbicularis oris. The facial vascular bundle crosses its surface. The parotid duct and transverse facial artery run parallel to each other as the duct pierces the buccinator to enter the mouth at the second maxillary molar. The buccinator is innervated by the buccal branch of the facial nerve and contracts synergistically with the orbicularis oris muscle. Together, these muscles allow pursing of the lips as in whistling. The buccinator also keeps the cheek flat against the teeth, which prevents food accumulation during chewing. It also prevents overextension of the cheek when high intraoral pressures are generated.

The depressor anguli oris (triangularis), depressor labii inferioris (quadratus) and the mentalis muscles are lip depressors and retractors that antagonize the superior perioral muscle groups. They are innervated by the marginal mandibular branch of the facial nerve. The deep mentalis muscle permits chin elevation and depression and protrusion of the lower lip. The bellies of the mentalis muscles have variable proximities to each other. A patient with a chin "dimple" or "cleft chin" has a larger distance between mentalis muscles. This is a normal anatomic variant.

The platysma muscle runs from the superficial fascia of the chest across the anterior and lateral neck over the mandible to intercalate with the lower lip depressors and retractors. It is innervated by the cervical branch of the facial nerve and is continuous with the superficial fascia or SMAS of the lower face. It provides only a thin protective cover to the anterior facial vascular bundle and mandibular branch of the trigeminal nerve.

VASCULAR ANATOMY

The internal carotid artery supplies the eyelids, upper nose and nasal dorsum, forehead and scalp via sub-branches of its ophthalmic branch. The ophthalmic artery arises behind the eye and branches into the orbital and ocular group. The orbital group includes the supraorbital, dorsal nasal and the anterior ethmoidal artery (Fig. 142.15). The supraorbital artery exits the orbit through the supraorbital foramen alongside the supraorbital nerve and perforates the frontalis muscle to ultimately course in the subcutaneous tissue of the forehead and scalp. The supratrochlear artery exits the medial orbit and courses medial to the supraorbital artery to supply the nasal root and the low midline forehead. This artery serves as the axial blood supply for the midline forehead flap often used to repair nasal defects. The success of this flap depends upon isolation and preservation of the supratrochlear artery. The anterior ethmoidal artery exits the nasal passage at the interface of the nasal bone and nasal cartilage to provide arterial supply to the nasal dorsum. The dorsal nasal artery crosses the midline over the nasal root and anastomoses with the angular artery, which originates from the external carotid artery.

While the internal carotid artery contributes to some areas of the scalp and upper face, the external carotid artery supplies most of the face. The facial artery branches off from the external carotid artery and courses deep to the mandible up through or behind the submandibular salivary gland. It passes over the mandibular ridge onto the face anterior to the masseter muscle, where it can be palpated. Its tortuous course maintains a diagonal and superior direction passing alongside the nose and terminating at the medial canthus. The platysma and risorius muscles protect the facial artery near the mandible. As the vessel traverses up the face, it becomes covered by the zygomaticus muscles of the midface and the orbicularis oculi as it nears the medial canthus.

The facial artery gives rise to the inferior and superior labial arteries that course horizontally below and above the lips, respectively. These arteries are found deep to the lip mucosa, but can course more superficially into the submucosa of the lip in elderly patients. After forming the superior labial branch, it becomes known as the angular artery. At its endpoint near the medial canthus tendon, the angular (or facial) artery anastomoses with the dorsal nasal branch of the ophthalmic

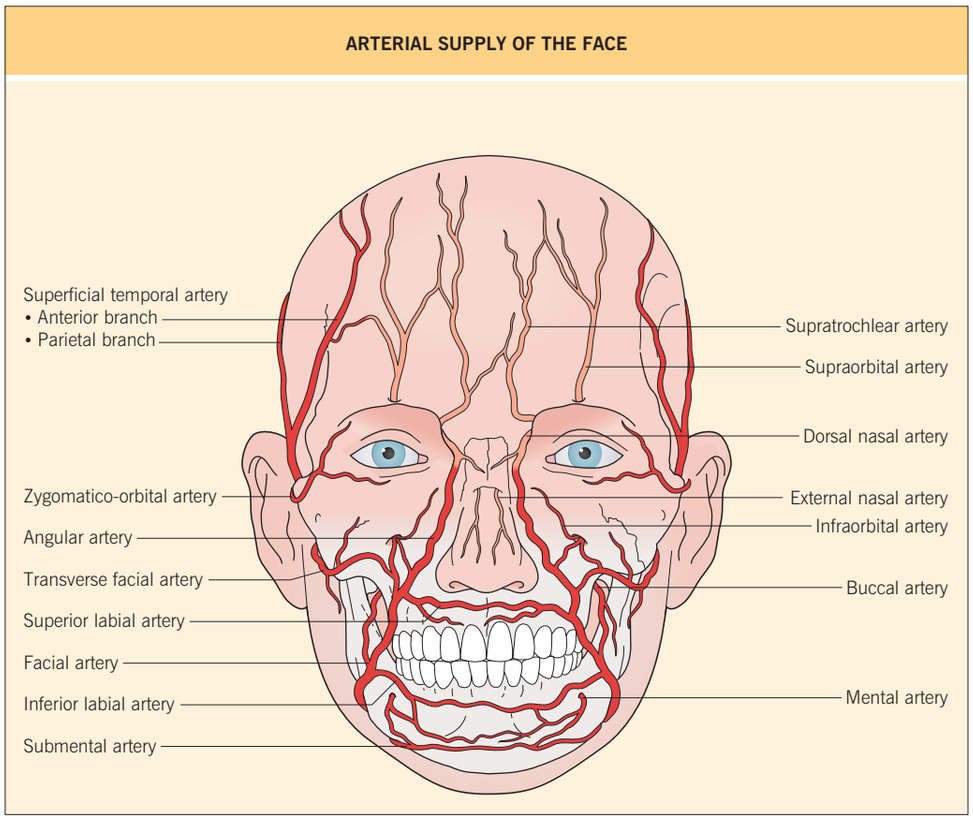


Fig. 142.15 Arterial supply of the face. Light pink designates arteries derived from the internal carotid artery; dark pink, from the external carotid artery.

artery. Since the ophthalmic artery is a branch of the internal carotid system, this anastomosis joins the internal and external carotid arterial systems. During most of their course, the facial artery and vein are covered by the superficial muscles of facial expression. The facial artery also anastomoses with branches of the internal maxillary (the infraorbital branch) and superficial temporal (transverse facial) arterial tree. This allows excellent blood supply to the facial skin even if distal arterial branches are cut or tied during surgery. The high density of arterial supply to the head and neck accounts for its excellent healing potential and viability of local flaps and grafts.

The lateral face, scalp and forehead are primarily supplied by the superficial temporal artery and its branches. This artery arises in the superficial lobe of the parotid gland as the terminal branch of the external carotid artery. It courses superficially to the main facial nerve trunks, then gives off the transverse facial artery before exiting the parotid gland superficially. The latter transverse artery runs parallel to and 2 cm below the zygomatic arch[4]. The superficial temporal artery exits the parotid and enters the subcutaneous fat in the preauricular crease, where it assumes an ascending vertical course over the zygomatic arch. It can be easily palpated just medial to the upper tragus of the ear. It runs alongside and superficial to the auriculotemporal nerve within, then above the SMAS layer of the temple and lateral forehead. The most superficial portion of the superficial temporal artery is often visible in aged patients within the subdermal fat above the galea aponeurotica as it courses cephalad above and anterior to the ear. Here it forms the parietal and frontal (anterior) arterial branches that originate just above the uppermost attached portion of the ear. The forehead, eyebrows and lateral scalp receive their arterial supply from these branches of the superficial temporal artery. There are many anastomoses on the scalp between the bilateral superficial temporal arteries. Because of this rich supply chain, the entire scalp tissue remains viable even if one of these arteries is occluded. This rich anastomotic network also explains why scalp surgery can be a very bloody process. Surgical dissection at the level of the galea aponeurotica may serve to avoid transection of the copious subdermal vascular supply.

Most of the arteries of the face run anterior to and parallel with their corresponding veins (see Fig. 142.3). The veins lack valves and therefore permit two-way flow of venous blood. The facial vein connects to the deep facial vein as it drains the cheek. The latter vein parallels the internal maxillary artery and anastomoses with the pterygoid venous plexus medial to the upper mandibular ramus. The facial vein crosses over the submandibular glands, while its corresponding artery passes beneath them. It then drains into the internal jugular vein, which connects with the external jugular vein via the retromandibular vein. The facial vein can communicate with the cavernous sinus of the brain via the ophthalmic vein or the pterygoid plexus. The paranasal area and upper lip are the regions drained by this network. This interface may permit skin or wound infections to gain access to the cavernous sinus of the brain from the draining facial or ophthalmic veins, with potentially devastating consequences.

Arterial blood supply to the face is delivered by a rich subdermal plexus that is fed by larger perforating arteries. Wound healing and flap success depend on maximal blood supply to the area. Axial flaps, such as the paramedian forehead flap, incorporate a known subcutaneous artery (e.g. the supratrochlear artery) into their design. Random pattern flaps are maintained by the subdermal arterial plexus and do not rely on a single feeder artery to maintain blood flow. The anastomotic vascular network permits facial arteries to be clamped or tied off during surgery without compromising tissue viability. Nearby ipsilateral or contralateral anastomotic arterial branches can often compensate for any loss in local blood supply.

THE FACIAL NERVE

The muscles of facial expression are innervated by the facial nerve, or cranial nerve VII. The facial nerve courses between the SMAS and the deep fascia before its branches penetrate the lateral underside of the facial muscles. There is significant variability in the course and arborization of this nerve from patient to patient. Cranial nerve VII has two major roots, the smaller of which, via the chorda tympani branch, provides taste sensation to the anterior two-thirds of the tongue; the chorda tympani nerve travels with the lingual nerve (cranial nerve V_3) to the tongue. Sensory innervation to a portion of the external auditory meatus, soft palate, and pharynx is also derived from this small facial nerve root. The submaxillary, submandibular and lacrimal glands contain parasympathetic fibers of the facial nerve that have secretory effects. In addition to the muscles of facial expression (see Table 142.1), the buccinator, stapedius, posterior belly of the digastric, stylohyoid and platysma muscles are all innervated by branches of the facial nerve.

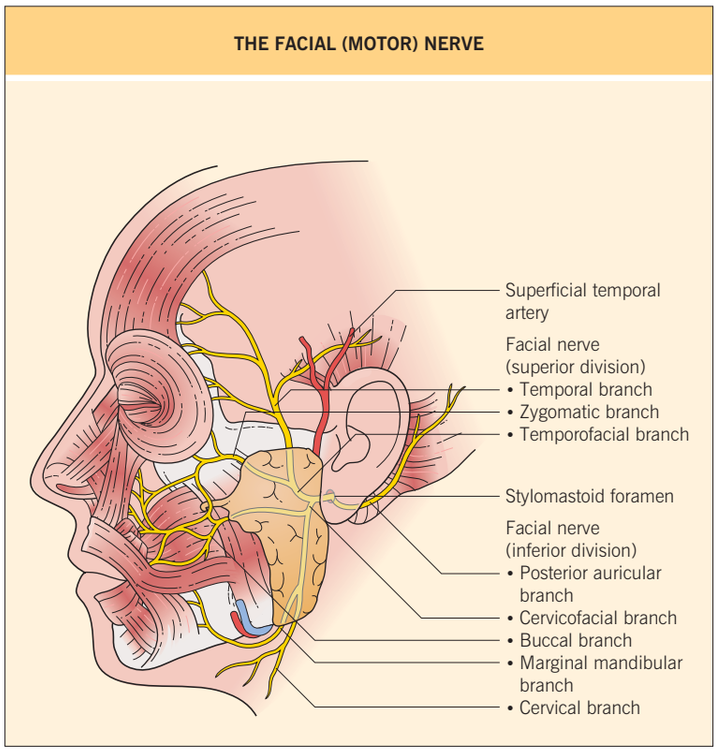


Fig. 142.16 The facial (motor) nerve.

Upon exiting the skull at the stylomastoid foramen near the level of the earlobe, the facial nerve immediately gives off the posterior auricular branch, which provides motor innervation to the occipitalis and posterior auricular muscles (Fig. 142.16). The remainder of the nerve trunk enters the parotid gland and bifurcates into the horizontally oriented temporofacial branch and lower cervicofacial branch. If a line is drawn from the superior border of the tragus to the angle of the mandible, the entrance site of the facial nerve trunk into the parotid gland lies at the midpoint. The temporal, zygomatic, buccal, marginal mandibular, and cervical branches arise from the two major rami of the facial nerve. It courses in between the glandular parotid tissue and becomes more superficial as it follows an upward curvilinear pathway on its way to the ventral surfaces of the muscles of facial expression.

While the facial nerve trunk is well protected in adults at its exit from the skull by the mastoid process, the surgeon must beware when performing procedures in this anatomic region in children. Because the mastoid process is not fully developed until age five, the main facial nerve trunk lies in a superficial subcutaneous plane behind the earlobe and may be damaged in superficial cutaneous procedures. The major facial nerve branches on the cheek are protected only by a small amount of parotid tissue, parotid fascia and subcutaneous fat. If a surgical procedure requires violation of the parotid fascia, meticulous dissection is necessary to avoid major facial nerve damage and subsequent functional disability. The motor nerves of the face course deeper than the sensory nerves or axial vasculature.

The temporal branch of the facial nerve provides motor innervation to the frontalis, upper orbicularis oculi, and corrugator supercilii muscles. It usually has four rami that originate over the middle third of the zygomatic arch for a combined approximately 2.5 cm "danger" zone in this area (see Fig 151.6). The most posterior ramus of the temporal branch can be topographically located on the temple 1 cm anterior to a vertical line drawn from the anterior insertion of the ear to the scalp. This posterior ramus runs anterior to the superficial temporal artery and vein. The most significant "danger zone" for the temporal branch of the facial nerve lies between a line drawn from the earlobe to the lateral edge of the eyebrow and a line drawn from the tragus to just above and lateral to the highest forehead crease. Within this zone, the temporal branch is at highest risk as it crosses the midzygomatic arch, where it lies most superficially over this bony prominence.

The temporal branch of the facial nerve courses between the superficial and deep temporalis fascia, penetrating the underside of the frontalis muscle from its lateral edges. The superficial temporal artery and vein as well as the auriculotemporal sensory nerve run posterior to but more superficial than the temporal nerve branch (compare Fig. 142.3 with Fig. 142.16). This neurovascular bundle lies in the subcutaneous fat overlying the SMAS of the temple and lateral forehead region. Remember that once the temporal nerve reaches the lateral underbelly of its ipsilateral target muscles, it is most protected. In order to avoid damaging this facial nerve branch, the surgeon should either remain superficial to the SMAS (i.e. the superficial temporalis fascia) or dissect in the subgaleal plane from the medial to lateral forehead. Similar to the other facial nerve divisions, the greatest potential for nerve damage lies in the lateral regions of the face. The central face has many nerve arborizations and protective muscles that usually afford a minimal risk for facial motor nerve damage.

Damage to a ramus of the temporal branch of the facial nerve can result in notable cosmetic and functional loss. The temporal branch consists of long, usually singular and often superficially coursing rami that have few arborizations or cross-innervations. These characteristics make nerve damage and permanent sequelae more likely when cutaneous procedures are performed in the lateral forehead and temporal regions. Even though the upper orbicularis oculi and corrugator supercilii muscles are innervated by the temporal branch, minimal functional or cosmetic compromise occurs, due to cross-innervation by other motor nerves. However, only 15% of patients will have any cross-innervation to the frontalis muscle by the more inferior zygomatic branch of the facial nerve. Such arborization permits retention of some functional mobility of the frontalis should the temporal branch be sacrificed. For the other 85% of patients, violation of the temporal nerve results in motor denervation and the inability to raise a now lowered or "droopy" eyebrow[4] (see Fig 151.7). Flattening of the forehead with diminished visibility of wrinkles and skin tension lines on the ipsilateral side is easily noted. The functional loss of the frontalis muscle significantly hampers a patient's ability to communicate non-verbally via facial expression and may have devastating psychosocial consequences. Over time, the inability to raise one's eyebrow can lead to eyebrow and eyelid ptosis and upper visual field compromise as muscular disuse atrophy progresses. Brow lifts and blepharoplasty may be necessary if the temporal nerve branch is permanently damaged.

The zygomatic branch of the facial nerve provides motor innervation to the lower orbicularis oculi, procerus, mouth elevators and nasal muscles. Its fibers overlie the parotid (Stensen's) duct and course horizontally and upwards after emerging from the parotid gland as the second division of the facial nerve. There is marked variability in the innervation it provides to these muscles; thereby, damage to this nerve branch can have unpredictable outcomes. Generally, injury to the zygomatic branch results in decreased orbicularis oculi function and a diminished ability to close the ipsilateral eyelid tightly. The orbicularis oculi is also innervated in its supraorbital aspect by the temporal branch of the facial nerve. Therefore, complete loss of circumferential periocular motor function is highly unlikely. Other effects may include dysfunction of nasal muscles and lip elevators.

The buccal branch is the third division of the facial nerve, and it courses inferiorly to the zygomatic branch in a downward direction on the cheek. It innervates the orbicularis oris muscle, the zygomaticus muscles, the lip elevators, the buccinator muscle and nasal muscles to a variable extent. Damage to this nerve causes buccinator dysfunction that results in accumulation of food between the teeth and the buccal mucosa with chewing. Approximately 80% of patients have anastomoses between the fibers of the zygomatic and buccal branches[13]. Each branch has two points of arborization, with the first occurring 2 cm anterior to the anterior edge of the parotid gland and the second usually occurring under the modiolus 1 cm lateral to the oral commissure at the anterior aspect of the buccal fat pad. Here the nerves may be damaged due to their superficial anatomy, protected only by the thin fascia of the SMAS, an often underdeveloped risorius muscle, and the subcutaneous fat. At the first branching site near the parotid, the zygomatic and buccal nerves lie between the masseter muscle and the posterior side of the buccal fat pad.

Although damage to the zygomatic or buccal branches of the facial nerve may occur during surgical procedures, subsequent motor dysfunction is often temporary and far less debilitating than a similar injury to the temporal nerve. The high degree of anastomoses between the zygomatic and buccal branches minimizes functional damage and promotes nerve recovery after trauma. Partial paralysis of the perioral muscles may occur, causing variable symptomatic defects in facial

expression, including a diminished ability or unilateral defect in forming a smile or pucker, lip pursing and lip seal formation. Drooling, food accumulation between the cheeks and gingivae, and muffled speech may occur secondary to buccal or zygomatic nerve damage. Orbicularis oculi defects have already been discussed and include lower eyelid droop, which can lead to chronic conjunctivitis, sicca symptoms, and ectropion. Difficulty wrinkling up the nose and inability to flare the nostrils may also occur with zygomatic or buccal branch trauma. Fortunately, most of these symptoms resolve within 6 months due to the extensive ramification and cross-innervation of these branches of the facial nerve.

The orbicularis oris, mentalis, and lip depressor muscles are innervated by the marginal mandibular branch of the facial nerve. The nerve courses along the angle of the mandible below the parotid gland and continues up over the mandibular body anterior to the facial artery, which can be palpated easily as it courses over the medial mandible. The nerve is very susceptible to damage, due to its superficial location over the bony edge of the jaw (i.e. just inferior and lateral to the lateral oral commissure), where it is covered only by fascia and an often unpredictably thin or poorly developed platysma muscle. This facial nerve branch is often composed of only one ramus. The marginal mandibular nerve "communicates" with the buccal branch of the facial nerve in only 10% of patients; therefore, damage to the former branch can lead to permanent disfiguring and functional defects in facial expression[4]. Normal symmetric facial expression and function of the mouth depends upon the equal and opposite effects exerted by the lip depressors and elevators in conjunction with the orbicularis oris muscle. Characteristically, a patient with marginal mandibular nerve damage cannot form a symmetric smile. There is inability to pull the ipsilateral lower lip downward and laterally or evert the corresponding vermilion border. The end result is a "crooked" smile. The defect is appreciated upon smiling, but is not as apparent when the patient is at rest.

The cervical branch of the facial nerve innervates the platysma muscle. This muscle receives nerve fibers from the marginal mandibular nerve as well. Damage incurred to the cervical branch rarely causes functional or cosmetic defects.

SENSORY INNERVATION OF THE HEAD AND NECK

The trigeminal nerve, or cranial nerve V, provides the primary sensory innervation to the face, while the upper cervical nerves (C2, C3) provide sensory supply to the neck, part of the ear, and posterior scalp (Fig. 142.17; Table 142.2). The facial, glossopharyngeal and vagus nerves provide a small portion of sensory innervation to the ear[14] (Fig. 142.18). The trigeminal nerve is the largest cranial nerve. It has motor (to the muscles of mastication), sensory and parasympathetic functions, supplying secretory fibers (originating from the facial and glossopharyngeal nerves) to the lacrimal and parotid glands. The sensory branches of the trigeminal nerve course more superficially than the trunk of the facial nerve, and are thereby readily subject to damage during surgical procedures. Fortunately, most resulting sensory dysfunction is not debilitating or permanent. Transmedian re-innervation after unilateral trigeminal root transection has been demonstrated. This is due to collateral sprouting of sensory nerves from the contralateral trigeminal nerve root[15]. The sensory nerves exist in the superficial plane between the subcutaneous fat and the SMAS and often run together with arteries and veins in neurovascular bundles. Knowledge of the sites where the major branches of sensory nerves emerge from the skull assists the surgeon in performing regional nerve blocks that facilitate facial surgery and improve patient comfort.

The trigeminal nerve is divided into three main branches: the ophthalmic (V_1), maxillary (V_2) and mandibular (V_3) (see Fig. 142.17). The smallest, uppermost sensory branch is the ophthalmic division, which gives off three branches (nasociliary, frontal and lacrimal nerves) before exiting the orbit (Fig. 142.19). Sensory fibers to the sinuses and upper nasal septal mucosa, as well as secretory parasympathetic fibers (that originate from the facial nerve) to the lacrimal gland, are also provided by the ophthalmic branch of the trigeminal nerve. The nasociliary branch gives rise to the infratrochlear nerve and the external branch of the anterior ethmoidal nerve. Sensory innervation to the root of the nose and part of the medial canthus is supplied by the infratrochlear nerve. The nasal dorsum, tip, supratip and columella derive cutaneous innervation from the external nasal branch of the anterior ethmoidal nerve, which emerges between the upper nasal cartilage and nasal bones. Nerve blocks for the nose rely on knowledge of these anatomic relationships among the sensory nerves. The nasociliary branch also supplies the corneal surface via

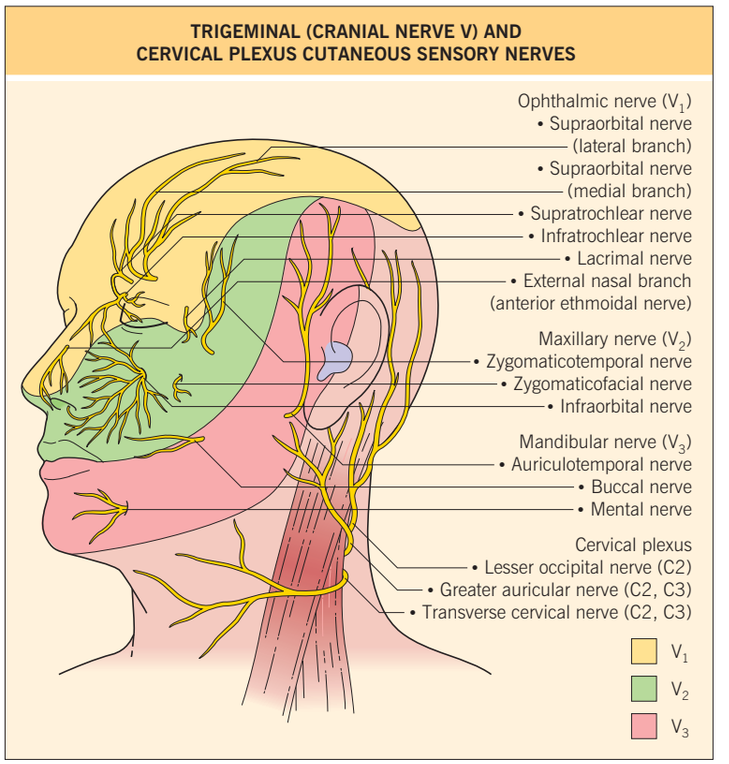


Fig. 142.17 Trigeminal (cranial nerve V) and cervical plexus cutaneous sensory nerves. The concha and external auditory canal are variably innervated by branches of the vagus, glossopharyngeal and facial nerves (see Fig. 142.18).

SENSORY INNERVATION OF THE HEAD AND NECK

- **Trigeminal nerve**
  - Ophthalmic branch (V_1)
    - Nasociliary
      - Infratrochlear – root of nose, medial canthus
      - Anterior ethmoidal (external nasal branch) – nasal dorsum, tip, supratip, columella
      - Ciliary – corneal surface
    - Frontal
      - Supratrochlear – medial upper eyelid, medial forehead, frontal scalp
      - Supraorbital – forehead, scalp, upper eyelid
    - Lacrimal – lateral eyelid
  - Maxillary branch (V_2)
    - Infraorbital – medial cheek, upper lip, nasal sidewall and ala, lower eyelid
    - Zygomaticofacial – malar eminence
    - Zygomaticotemporal – temple, supratemporal scalp
    - Superior alveolar and palatine – upper teeth, palate, nasal mucosa, gingiva
  - Mandibular branch (V_3)
    - Auriculotemporal – external anterior ear and auditory canal, temple, temporoparietal scalp, temporomandibular joint, tympanic membrane
    - Buccal – cheek, buccal mucosa, gingiva
    - Inferior alveolar – mandibular teeth; chin and lower lip (mental nerve)
    - Lingual – anterior two-thirds of tongue, floor of mouth, lower gingivae
- **Greater auricular nerve** (C2, C3) – lateral neck, angle of the jaw, posterior and inferior ear, portions of the helical rim, postauricular scalp
- **Lesser occipital nerve** (C2) – neck, postauricular scalp
- **Transverse cervical nerve** (C2, C3) – anterior neck
- **Supraclavicular nerve** (C3, C4) – anterior chest, shoulder

Table 142.2 Sensory innervation of the head and neck.

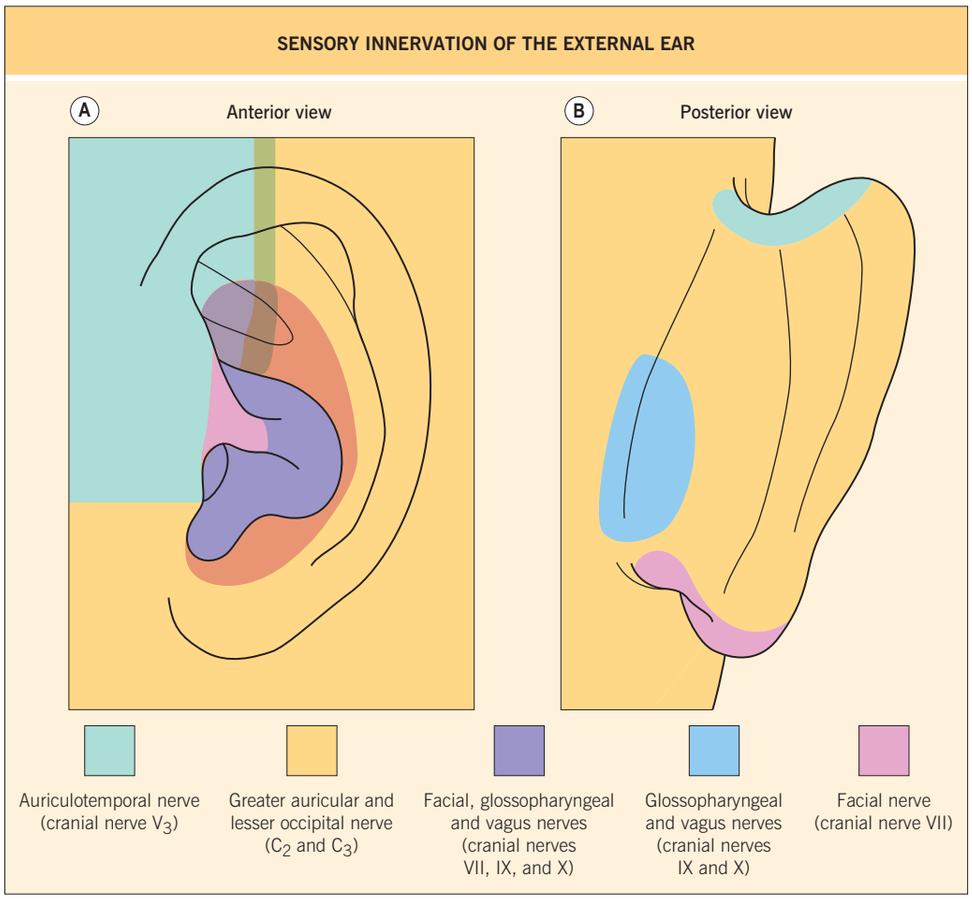


Fig. 142.18 Sensory innervation of the external ear. A Anterolateral view. **B** Posterior view.

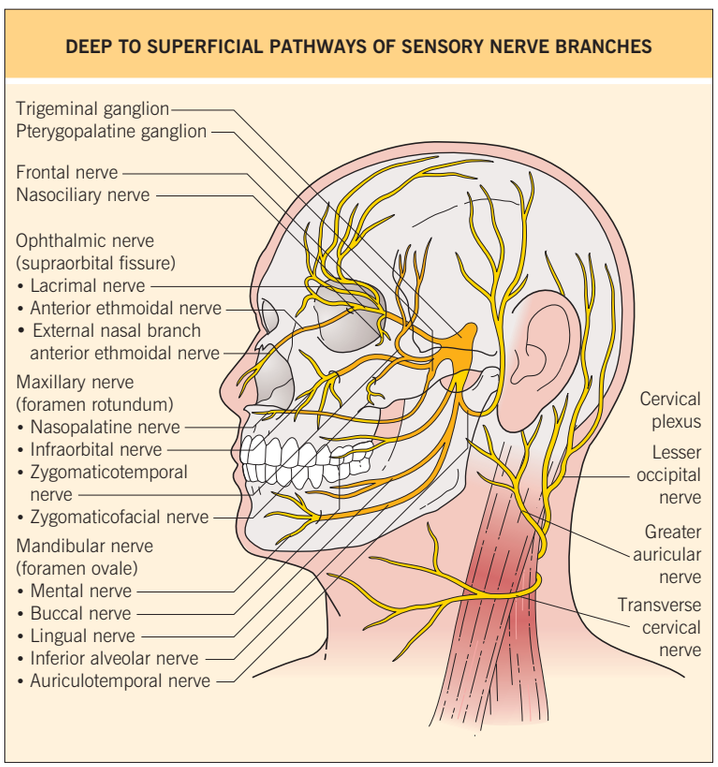


Fig. 142.19 Deep to superficial pathways of sensory nerve branches.

the ciliary nerve. If an episode of zoster (varicella zoster virus) involves the nasal tip, then close ophthalmologic follow-up is warranted due to presumed corneal involvement.

The frontal nerve branch of the ophthalmic division forms the supratrochlear and supraorbital nerves. The exit route (supratrochlear ridge) of the supratrochlear nerve lies 1 cm lateral to the midline on the supraorbital ridge. This branch of the frontal nerve provides sensory innervation to the medial upper eyelid, medial forehead, and frontal scalp. The supraorbital foramen (through which emerges the supraorbital neurovascular bundle) lies 2.5 cm lateral to the midline on the supraorbital ridge (see Fig. 142.2). After penetrating the frontalis muscle to emerge above the frontalis SMAS, the supraorbital nerve provides cutaneous sensation to the forehead, scalp and upper eyelid. A small lacrimal nerve branch of the ophthalmic division of cranial nerve V innervates the lateral eyelid skin and lies near the upper lateral orbital rim. Frontal nerve blocks, and specifically the supratrochlear and supraorbital block, offer quick and effective anesthesia for surgical procedures of the forehead.

The maxillary branch (V_2) of the trigeminal nerve forms the infraorbital, zygomaticofacial and zygomaticotemporal cutaneous sensory branches (see Fig. 142.17). The infraorbital foramen lies 2.5 cm lateral to midline and 1 cm inferior to the infraorbital rim, in the same vertical line as the supraorbital and mental foramina. The infraorbital neurovascular bundle emerges here to provide significant sensory innervation to the medial cheek, upper lip, nasal sidewall and ala, and the lower eyelid. Infraorbital nerve blocks offer simple and effective anesthesia for much of the cheek, lower eyelid, and nose. Lateral to the infraorbital foramen, the zygomaticofacial nerve emerges to innervate the skin of the malar eminence. Cutaneous innervation of the temple and supratemporal scalp region is provided by a third branch of the maxillary division, the zygomaticotemporal nerve. It emerges from the lateral orbital margin at the zygomatic bone. The superior alveolar and palatine nerves are deeper branches of V_2 that provide sensory innervation to the upper teeth, palate, nasal mucosa, and gingiva.

The mandibular branch (V_3) is the largest division of the trigeminal nerve and the only one to carry both cutaneous sensory and motor fibers. It supplies cutaneous sensory innervation to the face as well as motor innervation to the muscles of mastication. The auriculotemporal, buccal and inferior alveolar nerves represent the three main cutaneous branches of V_3 (see Fig. 142.19). The auriculotemporal nerve emerges from behind the neck of the mandible to course just deep to the superficial temporal artery from the superior margin of the parotid gland in the

preauricular sulcus up towards the lateral scalp. It provides sensory innervation to the external ear and auditory canal, temple, temporoparietal scalp, temporomandibular joint and tympanic membrane. It also carries parasympathetic secretory fibers to the parotid gland.

The buccal nerve supplies sensory innervation to the cheek, buccal mucosa, and gingiva. It runs deep to the parotid over the pterygoid muscle to the upper surface of the buccinator, which it pierces to reach the overlying skin. Because the terminal branches of the buccal nerve are small and numerous, regional buccal nerve block techniques are not feasible anesthetic options. The inferior alveolar branch of V_3 innervates the mandibular teeth as it courses through the mandibular sulcus. Its terminal branch forms the mental nerve, which emerges from the mental foramen in the same topographic line as the supraorbital and infraorbital neurovascular bundles (i.e. 2.5 cm lateral to the midline). The mental vein, artery and nerve emerge from the mental foramen below the lower second premolar. The lingual nerve supplies sensory innervation to the anterior two-thirds of the tongue, the floor of the mouth, and the lower gingivae. It arises from V_3 and courses parallel and superior to the inferior alveolar nerve.

The cervical plexus is a network of arborizing and anastomosing nerve branches of the ventral rami of the four most superior cervical nerves. It emerges from the mid-posterior margin of the sternocleidomastoid (SCM) muscle at Erb's point to give off three branches, designated as C2, C3 and C4. C2 and C3 compose the greater auricular nerve, which runs from the posterior edge of the SCM towards the earlobe in the same plane and path as the external jugular vein (see Fig. 142.17). It innervates the skin of the lateral neck, angle of the jaw, and part of the auricular and postauricular skin (see Fig. 142.18).

The lesser occipital nerve (C2) emerges from the same point at the SCM and assumes a course parallel to the SCM upward to innervate the skin of the neck and postauricular scalp. The transverse cervical nerve (C2 and C3) likewise emerges from behind the SCM and arcs anteriorly around and across the SCM in a transverse direction. Its many terminal branches supply the skin of the anterior neck. The supraclavicular nerve (C3 and C4) emerges from the same point at the SCM posterior margin, then courses inferiorly until it reaches the supraclavicular region, where it terminates, and provides sensory innervation to the anterior chest and shoulder skin (see Fig. 142.4).

Perineural invasion of cutaneous tumors such as basal cell carcinomas, neurotropic melanomas and squamous cell carcinomas may be encountered by the clinician. Patients are often asymptomatic from dermal nerve twig infiltration by tumor cells, with the diagnosis made only by histopathologic tissue examination. Some patients may experience sensory abnormalities and, rarely, motor dysfunction. Most of these scenarios occur in the setting of squamous malignancies (incidence rates range from 3% to 14%), with less than 1% of basal cell carcinomas showing any histologic evidence of perineural spread[13]. Knowledge of the neuroanatomy of the head and neck assists the surgeon in planning adjuvant therapy, such as radiation, for patients with nerve involvement.

LYMPHATIC DRAINAGE OF THE HEAD AND NECK

Squamous cell carcinomas, melanomas, Merkel cell carcinomas and other cutaneous neoplasms may spread via lymphatics to regional lymph nodes and subsequently metastasize to other organs. It is important for the clinician to have a thorough understanding of the lymphatic drainage of the head and neck (Fig. 142.20), as well as the remainder of the body, in order to appropriately stage and manage patients. Before any surgical endeavor is undertaken for a malignancy, palpation of regional lymph nodes and basins should be performed. Head and neck cancers usually spread to adjacent lymph nodes in a diagonal direction from cephalad to caudad (see Fig. 142.20). There is a large degree of variability in drainage pathways, but the anatomic location of individual lymph nodes is more consistent from patient to patient. Cutaneous neoplasms that breach the papillary dermis may spread from small lymph capillaries to progressively larger and deeper lymphatic trunks in the area. Lymph channels often course along the same directional pathway as the head and neck veins. They are more numerous and often more superficial than the corresponding veins and lie predominantly between the superficial and deep fascial layers.

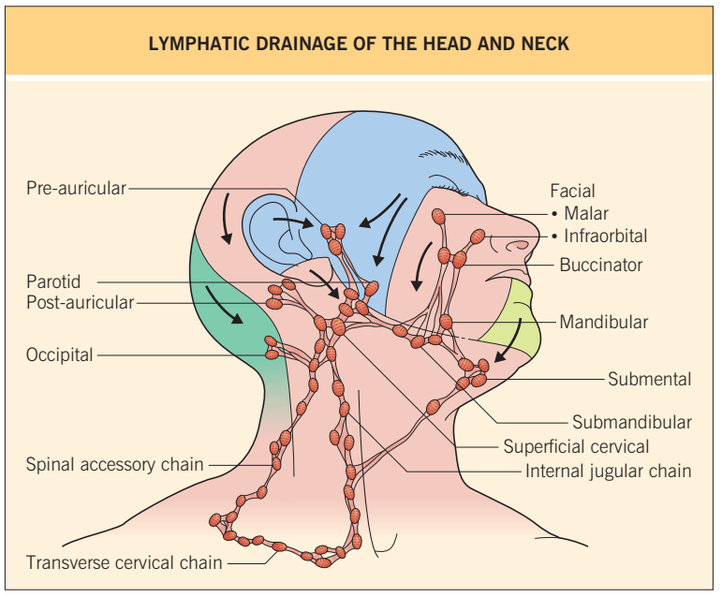


Fig. 142.20 Lymphatic drainage of the head and neck.

Important primary lymphatic drainage patterns of the head and neck region include the following: parotid nodes often collect from the forehead and eyelids (upper lateral face); submandibular nodes from the lower and medial face or from the submental nodes; and submental nodes from the central lower lip and chin. Lateral cervical nodes are the common subsequent lymph collection site from these areas. Parotid nodes may be extraglandular or intraglandular. The extraglandular channels are invested within the parotid sheath. Two-thirds of all people will also have one to three pretragal and infra-auricular lymph nodes that are considered part of the parotid node basin[4]. These pre- and infra-auricular nodes drain the ear, the lateral lower cheek, the frontolateral scalp and the forehead, as well as the nasal root. Drainage of the parotid unit may then follow the external or internal jugular vein in the jugular lymph node chain; therefore, palpation for nodes from the site of the cutaneous lesion to the supraclavicular and even axillary nodal basins is recommended.

Submandibular nodes should be examined as the patient relaxes the neck muscles and tilts the chin down. This nodal group drains the gingival and mucous membranes, lower eyelids, anterior two-thirds of the tongue, lips, nose and medial cheeks. The submental nodes (up to eight) of the neck lie beneath the platysma and drain the anterior third of the tongue and floor of the mouth, in addition to the lower middle lip, chin and medial lower cheeks. They are best examined by elevating the chin and asking the patient to engage the platysma. Submental nodes frequently drain bilaterally or contralaterally and empty into the submandibular basin or directly into the internal jugular lymphatic chain. Note that up to one-quarter of healthy people have small (less than 1 cm) non-fixed palpable submental nodes[4].

The superficial lateral cervical nodes are adjacent to the infra-auricular parotid nodes and lie near the high external jugular vein. Use the sternocleidomastoid muscle as a landmark to palpate these nodes (up to four) over its cephalad portion. Deeper lateral cervical nodes include the spinal accessory, internal jugular and transverse cervical chains, which form a triangle on the neck. The internal jugular chain is the main lymphatic collection trunk of the head and neck and may contain up to 25 lymph nodes in each patient. The internal jugular chain on the right often drains into the subclavian vein, whereas the left-sided lymphatic chain empties into the thoracic duct. These nodes can be palpated by rolling two fingers over the area of the carotid triangle.

Acute or chronic lymphedema may ensue after transection of larger lymphatic channels or nodes, or even after disruption of smaller channels in areas (e.g. infraorbital) with limited or vulnerable lymphatic drainage. Adequate drainage can be achieved by orienting flaps in the same direction as lymphatic patterns. The surgeon must be mindful of the variability in drainage patterns and sites and the fact that malignancies do not respect the midline. Since cross-communication between lymphatics may result in contralateral drainage, bilateral examination for lymphadenopathy should be undertaken before a neoplasm is excised.

REFERENCES

1. Dzubow LM. Tissue movement – a macrobiomechanical approach. J Dermatol Surg Oncol. 1989;15:389–99.
2. Dzubow LM. Facial Flaps: Biomechanics and Regional Application. Norwalk: Appleton & Lange, 1990.
3. Robinson JK, Sengelmann RD, Hanke CW, Siegel DM. Surgery of the Skin: Procedural Dermatology. St Louis: Mosby, 2005.
4. Salasche SJ, Bernstein G, Senkarik M. Surgical Anatomy of the Skin. Norwalk: Appleton & Lange, 1988.
5. Gosain AK, Yousif NJ, Madiedo G, et al. Surgical anatomy of the SMAS: a reinvestigation. Plast Reconstr Surg. 1993;92:1254–65.
6. Burger GC, Menick FJ. Aesthetic reconstruction of the nose. St Louis: Mosby, 1994.
7. Summers BK, Siegle RJ. Facial cutaneous reconstructive surgery: general aesthetic principles. J Am Acad Dermatol. 1993;29:669–81.
8. Zide BM, Jelks GW. Surgical Anatomy of the Orbit. New York: Raven Press, 1985.
9. Stegman SJ, Tromovitch TA, Glogau RG. Cosmetic Dermatologic Surgery, 2nd edn. St Louis: Mosby, 1990.
10. Larrabee WF, Makielski KH. Surgical Anatomy of the Face. New York: Raven Press, 1993.
11. Tromovitch TA, Stegman SJ, Glogau RG. Flaps and Grafts in Dermatologic Surgery. Chicago: Year Book, 1989.
12. Bennett RG. Fundamentals of Cutaneous Surgery. St Louis: Mosby, 1988.
13. Carlson KC, Roenigk RK. Know your anatomy: perineural involvement of basal and squamous cell carcinoma on the face. J Dermatol Surg Oncol. 1990;16:827–33.
14. Drake RL. Gray's Atlas of Anatomy. Churchill Livingstone, 2007.
15. Robinson PP. Recession of sensory loss from the midline following trigeminal sensory root section: collateral sprouting from the normal side? Brain Res. 1983;259:177–80.

This page intentionally left blank

143 Anesthesia

George J Hruza

Key features

- Local anesthetics are classified into two groups – amides and esters, depending upon the linkage in their intermediate chain
- "Anesthetic allergies" vary from palpitations secondary to epinephrine and vasovagal reactions, to urticaria and anaphylaxis from preservatives or the local anesthetic (especially esters)
- Additives to the local anesthetic include epinephrine, sodium bicarbonate and hyaluronidase
- Nerve blocks are particularly helpful when performing procedures on the face, digits and palmoplantar surfaces

INTRODUCTION

Effective anesthesia is an essential component of dermatologic surgery. Almost all dermatologic surgical procedures can be performed under local anesthesia. Local anesthetics have been in use since the 1880s with the introduction of cocaine hydrochloride, which was extracted from the leaves of the South American bush *Erythroxylon coca*[1]. This was followed by procaine in 1904, tetracaine in 1930, and the first amide local anesthetic, lidocaine, was introduced in 1943[1]. The introduction of lidocaine was a major breakthrough because lidocaine is far less likely to cause an allergic reaction than the ester-type anesthetics that preceded it.

Local anesthesia has several advantages over general anesthesia, including reduced morbidity (especially in patients who are poor anesthesia risks), reduced cost, reduced procedure time and faster recovery. The main disadvantages are some limitation on the extent of a procedure and the possibility of greater patient discomfort from the injections. Knowledge of the physiology, dosage, side effects, and proper "painless" local anesthesia technique are essential for performing dermatologic surgery and to keep patients safe and satisfied.

DISCUSSION

Physiology and Structure

Local anesthetics act by blocking sodium channels in the axon cell membrane, and this prevents sodium from entering the nerve cell. The nerve cell is not depolarized and consequently the action potential is blocked. The cationic form of the anesthetic appears to bind to the inner pore of voltage-gated sodium channels, possibly leading to both narrowing of the pore lumen (steric block) and creation of an electrostatic barrier to permeation[2]. Smaller unmyelinated C-type nerve fibers that conduct pain sensation are blocked more quickly and easily than intermediate fibers that carry sensations of heat and cold. The myelinated A-type fibers that carry pressure sensation and motor fibers are blocked last. Clinically, this is evident when an area seems fully anesthetized for scalpel surgery, but the patient still feels the pressure of the surgeon's fingers at the surgical site.

All local anesthetics consist of three parts (Fig. 143.1):

- a secondary or tertiary amine end
- an aromatic end
- an intermediate connecting chain that contains an ester or amide.

The aromatic portion is hydrophobic and lipophilic. This is essential to allow the anesthetic to diffuse through nerve cell membranes. The amine portion is hydrophilic and is responsible for the anesthetic's water solubility, which is important for preparing, storing and administering the anesthetic[2].

Local anesthetics are weak organic bases, which, to be water-soluble and injectable, require the addition of a hydrochloride salt. In aqueous solution, the salt equilibrates between the ionized and non-ionized form. The ionized form is water-soluble, allowing injection into and diffusion through tissue. However, it is the non-ionized, lipid-soluble base that can diffuse into the nerve cell membrane. Within the sodium channel's inner pore, it is the ionized cation that is responsible for blocking nerve conduction (see above)[2].

The dissociation constant (pKa) of each anesthetic determines the proportion of the anesthetic base and its cation at a given pH. The pKa of all local anesthetics is higher than physiologic pH. For most local anesthetics at a pH of 7.4, 80% or more is in the cationic ionized form. Alkalinization of the anesthetic solution, as is done with the addition of sodium bicarbonate, will speed its onset of action as more of the anesthetic will be in the non-ionized form. However, if the pH is raised too much, the anesthetic may precipitate out of solution. Anesthetic sensitivity to pH also helps explain why infected tissue is difficult to effectively anesthetize[3]. The inflammatory response surrounding the infection acidifies the site (reduces the pH), which reduces the proportion of the anesthetic in the non-ionized, lipid-soluble form.

Pharmacology

Local anesthetics are classified into two groups, depending on the linkage in the intermediate chain (Table 143.1). Amide anesthetics have an amide linkage and ester anesthetics have an ester linkage (see Fig. 143.1). They differ in how they are metabolized and in the risk of sensitization. Ester anesthetics are hydrolyzed by plasma pseudocholinesterase, and the metabolites are excreted by the kidneys. Patients with a deficiency of functional pseudocholinesterase, who are often diagnosed after prolonged paralysis following administration of standard doses of succinylcholine, are at an increased risk of ester anesthetic toxicity. The metabolite para-aminobenzoic acid (PABA) is responsible for the allergic reactions seen with ester anesthetics. Amide anesthetics are metabolized by the hepatic microsomal cytochrome P450 enzyme system, and the metabolites are excreted by the kidneys. Patients with severe liver disease may be at increased risk of amide anesthetic toxicity.

Local anesthetics differ in the speed of onset, duration of action, and potency, depending on each compound's intrinsic chemical characteristics (Table 143.1). A low pKa leads to rapid onset of anesthesia, as more of the anesthetic will be in the non-ionized form. Greater lipid solubility is associated with higher anesthetic potency, as the compound penetrates the nerve cell membrane more easily. Duration of action is determined by the strength of anesthetic binding to the sodium channel pore.

Occasionally, pregnant women need to undergo skin surgery. The local anesthetic of choice in pregnancy is lidocaine. It is classified as pregnancy category B, which means that, in animal studies, no teratogenic effects have been documented. Studies in pregnant women who received lidocaine during the first trimester of pregnancy have shown no increase in anatomic abnormalities in the newborns. However, it is recommended that lidocaine, as with all other pharmacologic agents, be used cautiously during the first 4 months of pregnancy, when maximum organogenesis takes place. Lidocaine crosses the placenta into the fetus. Lidocaine can be safely used in nursing mothers with the realization that some of the anesthetic may be excreted in the mother's milk.

Lidocaine can be safely used in children, but the maximum recommended dosage should be adjusted downward based on the child's

LOCAL ANESTHETICS FOR INFILTRATIVE AND NERVE BLOCK ANESTHESIA					
Generic name	**Trade name®**	**Onset (min)**	**Duration plain (h)**	**Maximum dose plain (mg for 70 kg man)**	**Maximum dose with epinephrine (mg for 70 kg man)**
AMIDES					
Articaine	Septocaine	2–4	0.5–2	350	500
Bupivacaine hydrochloride	Marcaine	5–8	2–4	175	225
Etidocaine	Duranest	3–5	3–5	300	400
Levobupivacaine hydrochloride	Chirocaine	2–10	2–4	150	Not available
Lidocaine	Xylocaine	Rapid	0.5–2	350	500 (3500 dilute)
Mepivacaine	Carbocaine	3–20	0.5–2	300	500
Prilocaine hydrochloride	Citanest	5–6	0.5–2	400	600
Ropivacaine*	Naropin	1–15	2–6	200	Not available
ESTERS					
Chloroprocaine hydrochloride	Nesacaine	5–6	0.5–2	800	1000
Procaine	Novocaine	5	1–1.5	500	600
Tetracaine	Pontocaine	7	2–3	100	Not available

*Addition of epinephrine has no effect on onset or duration of action of ropivacaine.

Table 143.1 Local anesthetics for infiltrative and nerve block anesthesia. In clinical practice, the duration of anesthesia appears to be less than stated, especially for head and neck areas. Addition of epinephrine prolongs anesthesia by a factor of two.

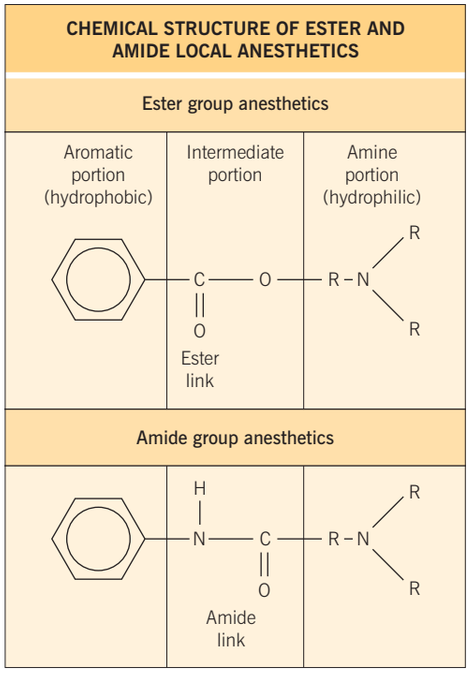


Fig. 143.1 Chemical structure of the ester and amide group local anesthetics. The aromatic (hydrophobic and lipophilic) end is joined to the amine (hydrophilic) end with an ester or amide linkage.

weight and age. Care must be taken in premature infants due to cardiovascular effects. Parabens, used as preservatives, are bound to albumin. In a jaundiced newborn, they could displace bilirubin from the albumin, worsening the hyperbilirubinemia[4]. For this reason, only paraben-free anesthetics should be used in newborns.

Additions to Local Anesthetics

Epinephrine

All local anesthetics, except for cocaine hydrochloride, relax vascular smooth muscle, which results in vasodilation. This causes increased bleeding at the operative site and reduced duration of anesthetic action as the anesthetic is rapidly removed from the surgical site via the dilated blood vessels. The addition of epinephrine (adrenaline) has the beneficial effect of constricting blood vessels, which prolongs the duration of anesthesia 100% to 200% by slowing removal of the anesthetic from the surgical site. Also, there is reduced intraoperative bleeding due to the vasoconstriction. The addition of epinephrine provides more effective anesthesia by decreasing the volume of anesthetic needed. The reduced absorption rate decreases anesthetic toxicity and allows larger doses to be used safely. The vasoconstrictive effect of epinephrine, manifested by skin blanching, takes about 15 minutes to fully develop. While they usually coincide, blanching does not always denote the anesthetized area.

Epinephrine is premixed with local anesthetics at a concentration of 1:100 000 or 1:200 000. However, concentrations as low as 1:1 000 000 achieve effective vasoconstriction, while concentrations greater than 1:100 000 are associated with greater risk of side effects. The concentration used in a given patient should be individualized. Patients who have relative contraindications to epinephrine should receive lower concentrations, while highly vascular areas such as the scalp should receive higher concentrations. The maximum dosage used at a concentration of 1:100 000 is determined by the anesthetic with which the epinephrine is premixed (Table 143.1).

Epinephrine is a strong β- and α-agonist and, as such, it must be used cautiously in patients with altered β- and α-receptors. Absolute contraindications to the use of epinephrine include hyperthyroidism and pheochromocytoma. Patients taking β-blockers, monoamine oxidase inhibitors, tricyclic antidepressants, and phenothiazines are more sensitive to epinephrine. Therefore, epinephrine should be used with caution, with the dose and concentration reduced accordingly. Severe hypertension developing after epinephrine-containing anesthetic injection in patients taking β-blockers has been reported[5]. This is probably due to unopposed α-adrenergic activity with its associated vasoconstriction. Fortunately, this reaction seems to be quite rare[6], and mainly occurs when higher doses are used. Patients with severe hypertension or with severe cardiovascular disease (especially coronary artery disease) may have their underlying disease exacerbated if large amounts of epinephrine are administered with the local anesthetic. High doses of epinephrine can induce labor. However, the low doses of epinephrine used in cutaneous surgery can be safely used during pregnancy. Epinephrine use in the periorbital area in patients with narrow angle glaucoma should be avoided, as it may aggravate the patient's glaucoma.

DIFFERENTIAL DIAGNOSIS OF LOCAL ANESTHETIC SYSTEMIC REACTIONS				
Diagnosis	**Pulse rate**	**Blood pressure**	**Signs and symptoms**	**Emergency management**
Vasovagal reaction	Low	Low	Excess parasympathetic tone; diaphoresis, hyperventilation, nausea	Trendelenburg, cold compress, reassurance
Epinephrine reaction	High	High	Excess α- and β-adrenergic receptor stimulation; palpitations	Reassurance (usually resolves within minutes), phentolamine, propranolol
Anaphylactic reaction	High	Low	Peripheral vasodilation with reactive tachycardia; stridor, bronchospasm, urticaria, angioedema	Epinephrine 1:1000 0.3 ml subcutaneous, antihistamines, corticosteroids, fluids, oxygen, airway maintenance
Lidocaine overdose				
1–6 mcg/ml	Normal	Normal	Circumoral and digital paresthesias, restlessness, drowsiness, euphoria, lightheadedness	Observation
6–9 mcg/ml	Normal	Normal	Nausea, vomiting, muscle twitching, tremors, blurred vision, tinnitus, confusion, excitement, psychosis	Diazepam, airway maintenance
9–12 mcg/ml	Low	Low	Seizures, cardiopulmonary depression	Respiratory support
>12 mcg/ml	None	None	Coma, cardiopulmonary arrest	Cardiopulmonary resuscitation and life support

Table 143.2 Differential diagnosis of local anesthetic systemic reactions. In case of systemic reactions during or after local anesthetic injections, hemodynamic signs are helpful in determining the cause of the reaction.

The use of epinephrine on digits has been controversial. Historically, epinephrine was not used on digits for fear of causing vasoconstriction that might result in digital necrosis. More recent studies have not demonstrated any increased risk from epinephrine in digital anesthesia. It appears that most cases of digital necrosis occurred due to vessel compression from too much anesthetic volume being injected (tamponade), constricting circumferential dressings, tourniquets, postoperative hot soaks, infection, use of vasoconstrictive anesthetics such as cocaine hydrochloride, or non-standard mixing of lidocaine with epinephrine[7]. There is no evidence of digital necrosis due solely to commercially available lidocaine with epinephrine[7]. However, epinephrine is clearly contraindicated for digital anesthesia in patients with peripheral vascular disease. I have found that combining lidocaine with dilute epinephrine (1:500 000) and small volumes provides safe digital anesthesia. Ring blocks of the digit should be avoided.

Self-limited systemic side effects of epinephrine include palpitations, anxiety, fear, diaphoresis, headache, tremor, weakness, tachycardia and elevated blood pressure. These signs and symptoms can be seen on occasion even with normal doses used for skin surgery, but they usually resolve within a few minutes (Table 143.2). They are more commonly seen when injecting highly vascular areas, especially the face and scalp. Skin necrosis from vasoconstriction is an extremely rare complication of epinephrine injection and would be an issue only in patients with severe vascular compromise at the injection site.

Serious side effects of epinephrine injection include arrhythmias, ventricular tachycardia, ventricular fibrillation, cardiac arrest and cerebral hemorrhage. None of these should be expected to occur at the doses used for skin surgery. However, it is prudent to limit the total dose injected in patients with severe cardiac disease.

Epinephrine is stable only in an acidic environment. Therefore, when epinephrine is premixed with local anesthetics, the pH is lowered into the 3.5 to 5.5 range with the addition of acidic preservatives such as sodium metabisulfite to stabilize the epinephrine. This acidic solution not only is more painful at the time of injection[8], but also slows the onset of anesthetic action, as less anesthetic is in the non-ionized form. By preparing the mixture fresh daily and using it by the end of the day, the mixture has a higher pH, which is less painful. Adding 0.5 ml epinephrine (1:1000) to 50 ml plain lidocaine will give a final concentration of 1:100 000 epinephrine. Alternatively, the lidocaine with epinephrine can be neutralized with sodium bicarbonate (see below).

Sodium bicarbonate

Injecting the standard lidocaine with epinephrine mixture at a pH of 3.5 to 5.5 is quite painful, with significant stinging due to the acidic pH. The pH can be neutralized with the addition of sodium bicarbonate. Adding one part of 8.4% sodium bicarbonate to ten parts lidocaine with epinephrine will bring the pH into a more physiologic 7 to 8 range. This mixture significantly reduces the pain of anesthetic injection[8,9]. Both components can be drawn up into the syringe, immediately before injection. Alternatively, 5 ml sodium bicarbonate (8.4%) can be added to a 50 ml bottle of lidocaine with epinephrine. As the epinephrine activity is lost at a rate of 25% per week in an alkaline or neutral environment, the mixture should be labeled with the date prepared, kept refrigerated, and used within about 1 week.

Hyaluronidase

Hyaluronidase (derived from bovine testicular hyaluronidase) depolymerizes hyaluronic acid, which breaks up ground substance, allowing anesthetics to diffuse further away from the injection point. In addition, there is less distortion of the injected structures[10]. The greater diffusion of anesthetic may decrease its duration of action. Hyaluronidase is most useful for periorbital surgery and to increase the rate of successful nerve blocks. It is prepared by adding 150 units to 30 ml of local anesthetic. Allergic reactions to hyaluronidase are rare, but they can occur. Some surgeons recommend an intradermal skin test before using hyaluronidase. In addition, the preparation may contain thimerosal preservative, which can cause contact dermatitis.

Anesthetic Mixtures

In an attempt to take advantage of different anesthetic properties, some surgeons combine two local anesthetics in one syringe. For example, a combination of lidocaine, for its rapid onset of action, with bupivacaine hydrochloride, for its longer duration of action, is often used. However, a study looking at such combinations has found that these mixtures do not live up to their promise. The mixture seems to take on the properties of one of the components to the exclusion of the other[11]. Therefore, most surgeons will inject the rapid-onset anesthetic first and the longer-acting anesthetic later, to minimize the pain of injection and maximize the duration of action.

Side Effects

Vasovagal reactions

By far the most common side effect of local anesthetic injection is a vasovagal reaction, in which the vagus nerve discharges due to patient anxiety, resulting in an increase in parasympathetic tone (Table 143.2). Vasovagal reactions are manifested by dizziness, diaphoresis, syncope, bradycardia and hypotension. Placing the patient in the Trendelenburg position will rapidly relieve the patient's symptoms. A cold towel on the forehead can also be helpful. Oxygen, fluids or epinephrine are usually not necessary. To avoid significant vasovagal reactions, all patients should have local anesthetic infiltrated in the recumbent position.

Allergic reactions

The most important side effect of local anesthetics is the development of allergic reactions. The allergy is usually a type I IgE-mediated reaction manifested by urticaria, angioedema, bronchospasm, and, on rare occasions, anaphylaxis with associated hypotension and tachycardia (Table 143.2). Most true local anesthetic allergies have been reported with ester anesthetics; amide anesthetics are implicated only very rarely. Preservatives added to multidose vials, especially methylparaben and sodium metabisulfite, have frequently been shown to be the cause of "local anesthetic" allergy[12].

There is some allergy cross-reactivity within the various ester anesthetics and within the amide anesthetics, but there is no cross-reactivity between the ester and amide anesthetic classes. It is PABA (the metabolite of ester anesthetics) that is thought to be responsible for the ester anesthetic allergic reactions. Ester anesthetics can also cause type IV delayed hypersensitivity reactions and cross-react with several contact sensitizers, including PABA, para-amino salicylic acid and para-phenylenediamine.

Patients who present with a history of "local anesthetic" allergy need to be questioned in detail about the "allergy" with a review of relevant medical records whenever possible. Often, the "allergy" is a result of a vasovagal reaction or epinephrine sensitivity. If the reaction seems to represent a true allergic reaction and the offending anesthetic is known (usually an ester), using an anesthetic from the other class (usually an amide) in a preservative-free solution is a reasonable option. Skin testing, by an allergist, may be warranted if the offending agent is not certain[13]. The testing should include pinprick followed by intradermal tests of an ester anesthetic, an amide anesthetic, methylparaben and sodium metabisulfite. Alternatively, for small procedures, adequate anesthesia can be obtained with intradermal injection of 1% diphenhydramine solution. Epinephrine may be added to counteract vasodilation caused by diphenhydramine, to enhance the anesthetic effect, and to reduce systemic antihistamine symptoms[14]. Intradermal normal saline with benzyl alcohol preservative will achieve very brief anesthesia through pressure effects on cutaneous nerve endings and the anesthetic properties of the benzyl alcohol preservative. It can be used for very short procedures such as a shave biopsy[15].

Limited allergic reactions can be managed with oral antihistamines and prednisone. However, patients developing bronchospasm, angioedema, or hemodynamic compromise require immediate emergency management including epinephrine, bronchodilators, parenteral antihistamines, corticosteroids, intravenous fluids, and oxygen (Table 143.2).

Local side effects

Bruising and edema are frequently seen after local anesthetic infiltration, especially in the periorbital area. Periorbital edema will often develop after surgery on the forehead and frontal scalp. Transient motor nerve paralysis is sometimes seen. This may be delayed for some time after the sensory nerves have become anesthetized, because of the large myelinated nerve fibers involved. The paralysis may persist for several hours after the sensory nerves have returned to normal. Informing the patient when a motor nerve has been affected by the anesthetic will eliminate distressed patient telephone calls later in the day. Prolonged sensory nerve paresthesia may develop if a sensory nerve is injured through intraneural injection. This is most commonly seen after nerve blocks. It can be minimized by avoiding intraneural injection and by using small gauge needles for injection.

Overdosage

If the local anesthetic dosage administered is kept within the recommended maxima, clinical symptoms of local anesthetic overdose are unlikely to be encountered. Maximum recommended dosages of *lidocaine* are 5 mg/kg plain (i.e. with no epinephrine), 7 mg/kg if with epinephrine and at standard (1–2%) concentrations, and 35–50 mg/kg for tumescent lidocaine anesthesia with dilute lidocaine (0.05–0.1%) as well as epinephrine concentrations (Table 143.1)[16–18].

The symptoms of local anesthetic overdose are directly related to the serum blood level, and include increasing CNS and cardiovascular signs and symptoms (Table 143.2). CNS symptoms start with circumoral and digital numbness and tingling, followed by lightheadedness, tinnitus, visual disturbances, slurred speech, muscle twitching, and, finally, seizures and coma. Cardiovascular and pulmonary symptoms develop at significantly higher doses than do early CNS symptoms and include hypotension, arrhythmias, respiratory arrest and cardiac arrest.

When lidocaine is administered, there are over 150 potential drug–drug interactions. Most are minor or only relevant when large doses of lidocaine are used. Patients receiving medications that inhibit the liver's cytochrome P450 system (e.g. erythromycin, ketoconazole, itraconazole; see Ch. 131), and therefore inhibit lidocaine metabolism, can exhibit signs of lidocaine overdose at lower doses. With large doses of lidocaine, patients taking class I and III antiarrhythmic drugs are at increased risk of cardiac arrhythmias and those taking CNS depressants (e.g. opiates) are at increased risk of CNS toxicity.

Bupivacaine hydrochloride has a greater risk of cardiac toxicity than lidocaine. *Prilocaine hydrochloride* metabolizes to ortho-toluidine, which is an oxidizing agent capable of converting hemoglobin to methemoglobin. This can become significant with large doses of more than 500 mg. *Benzocaine* has also been implicated in causing methemoglobinemia when used on mucosal surfaces[19]. The treatment of methemoglobinemia is methylene blue infusion.

Topical Anesthetics

Skin

Historically, the only anesthetic used for topical anesthesia of keratinized skin was benzocaine, which is an ester anesthetic. Anesthesia was generally effective only when applied to traumatized skin. Little, if any, anesthesia was achieved in intact normal skin. Of greater concern was the high rate of allergic contact dermatitis seen with benzocaine.

More recently, there have been several topical anesthetics introduced that seem to achieve moderate topical anesthesia of intact skin (Table 143.3). EMLA® cream is a eutectic mixture of 2.5% lidocaine and 2.5% prilocaine hydrochloride. It is able to achieve superficial anesthesia, with the degree of anesthesia related to the amount and duration of application before surgery. EMLA® is applied as a thick layer under occlusion at least 1 hour before the procedure. It is especially useful for reducing the pain of non-ablative laser procedures and to reduce the pain of local anesthetic or other injections. There are reports of more extensive procedures, such as split-thickness skin graft harvesting, being done with EMLA® alone. However, I have found the degree of anesthesia to be too unpredictable to rely on EMLA® alone for most surgical procedures. Some dermatologists who perform CO_2 laser ablative resurfacing solely under EMLA® anesthesia prepare the skin with vigorous degreasing followed by two applications of EMLA® 1 hour apart under occlusion. Additional EMLA® is applied to the skin after the first pass with the laser has removed the epidermis.

EMLA® appears to be safe, but some caution is advised when using large amounts on skin with a damaged skin barrier and in infants who might be susceptible to methemoglobinemia from too much prilocaine hydrochloride absorption. For recommended applications in children, see Table 143.4. EMLA® often blanches the skin after application, followed by vasodilation 30–60 minutes after its removal. Even though this initial blanching has no effect on treatment efficacy, when treating vascular lesions, relatively light-colored lesions may become difficult to identify. I have patients mark out the outline of the vascular lesion before applying EMLA®. The vasodilation is usually of no clinical significance, but a few case reports of purpura developing at the site of EMLA® application have been reported in children.

Other preparations that have been optimized for epidermal penetration and have been shown to achieve moderate superficial skin anesthesia include: Betacaine-LA®, consisting of a proprietary mixture of lidocaine and prilocaine hydrochloride; LMX®, containing 4% or 5% lidocaine (Table 143.5); Topicaine®, containing 4% lidocaine; 4% tetracaine gel; 30–40% lidocaine in acid mantle cream; and various other compounded mixtures of lidocaine, benzocaine and tetracaine (Table 143.3). In a comparison study, EMLA® and LMX® 4% were found to achieve superior anesthesia to tetracaine 4% gel, which was superior to Betacaine-LA®, which was superior to control[20]. According to the manufacturers, Betacaine-LA® and LMX® do not require occlusion to be effective. A comparison of EMLA® under occlusion and LMX® unoccluded found that LMX® achieved equivalent anesthesia to EMLA® after less than one-third of application time[21]. None of the topical anesthetics have any significant effectiveness for palmar or plantar surfaces.

TOPICAL ANESTHETICS FOR MUCOUS MEMBRANE AND INTACT SKIN ANESTHESIA				
Generic name	**Trade name®**	**Concentration (%)**	**Type**	**Primary use**
Benzocaine	Americaine otic	20	Ester	Tympanic membrane
Benzocaine	Hurricaine	20	Ester	Mucous membranes
Benzocaine/tetracaine/butamben (butyl aminobenzoate)	Cetacaine, Exactacain		Ester	Mucous membranes
Benzocaine/lidocaine/ tetracaine	compounded	Various	Ester/amide	Intact skin
Cocaine hydrochloride		2–10	Ester	Nasal mucosa
Dibucaine (cinchocaine)	Nupercaine	1	Amide	Mucous membranes
Lidocaine	LMX	4–5	Amide	Intact skin (4%); anorectal (5%)
Lidocaine	Topicaine	4	Amide	Intact skin
Lidocaine	Xylocaine	2–5	Amide	Mucous membranes
Lidocaine in acid mantle cream	compounded	30–40	Amide	Intact skin
Prilocaine/lidocaine	EMLA	2.5/2.5	Amide	Intact skin
Proparacaine (proxymetacaine)	Alcaine	0.5	Ester	Conjunctiva
Prilocaine/lidocaine mix	Betacaine LA	Proprietary	Amide	Intact skin
Tetracaine gel	Tetracaine gel	4	Ester	Intact skin
Tetracaine	Pontocaine	0.5	Ester	Conjunctiva

Table 143.3 Topical anesthetics for mucous membrane and intact skin anesthesia. Anesthetics for topical skin anesthesia require application 0.5–2 hours prior to surgery under occlusion for maximal effect.

MAXIMUM RECOMMENDED EMLA® APPLICATION IN CHILDREN				
Age	**Weight**	**Maximum total dose of cream**	**Maximum area**	**Maximum time**
<3 months	<5 kg	1 g	10 cm^2	1 hour
3–12 months	5–10 kg	2 g	20 cm^2	4 hours
1–6 years	10–20 kg	10 g	100 cm^2	4 hours
7–12 years	>20 kg	20 g	200 cm^2	4 hours

Table 143.4 Maximum recommended EMLA® application in children.

MAXIMUM RECOMMENDED LIDOCAINE 4% LIPOSOMAL CREAM (LMX4®) APPLICATION IN CHILDREN			
Age	**Weight**	**Maximum area**	**Maximum time**
<12 months	<10 kg	100 cm^2 (4 × 4 in)	1 hour
1–6 years	10–20 kg	200 cm^2 (5.5 × 5.5 in)	2 hours
7–12 years	>20 kg	600 cm^2 (9 × 9 in)	2 hours*
*0.072 mg 4% lido absorption/cm^2/h × 600 cm^2 × 2 h = 86 mg (≤4 mg/kg).			

Table 143.5 Maximum recommended lidocaine 4% liposomal cream (LMX4®) application in children. Cream should be applied to intact skin, with or without occlusion. Currently not approved for children less than 2 years of age so its application in that age group represents an off-label use. *Courtesy, Julie V Schaffer, MD.*

Iontophoresis of 1–4% lidocaine with epinephrine can enhance the depth and effectiveness of topical anesthesia. It is practical only for rather small areas, but anesthesia can be achieved within a few minutes with a 1 mA current. The main drawback is the additional equipment and supplies needed. Ultrasound or warm steaming of the skin also enhances the effect of topical anesthetics, probably by enhancing anesthetic penetration.

Topical skin anesthetics are useful primarily for non-invasive laser and intense pulsed light treatments, including laser hair removal, laser acne treatment, tattoo fading, pigmented lesion destruction, vascular lesion photocoagulation and non-ablative photorejuvenation. They are very useful in reducing the pain of needle insertion as well as some of the pain of injection when injecting local anesthetics, botulinum toxin or filler materials such as the various hyaluronic acid-based filler materials that, due to their acidity, sting on injection. Anesthesia is too unpredictable to be able to use topical skin anesthetics even for minor surgical procedures such as skin biopsies, curettage or electrodesiccation.

The various preparations have different recommendations regarding times of application and whether or not occlusion is necessary. However, for maximal effectiveness, the anesthetic should be applied as a thick layer under occlusion to the proposed treatment area for at least 1 hour. Caution should be exercised when large areas are to be anesthetized, especially when using compounded mixtures with high lidocaine concentrations, as several deaths have been reported in patients applying compounded topical anesthetics under occlusion to their entire legs and thighs.

Mucous membranes

Topical anesthetics for mucous membranes are far more effective than skin anesthetics, as the stratum corneum barrier is absent (Table 143.3). One to two drops of 0.5% tetracaine into each eye achieves complete conjunctival anesthesia after a few seconds of stinging. This allows for insertion of eye shields or painless injection through the conjunctiva. Proparacaine (proxymetacaine) hydrochloride is an equally effective alternative conjunctival anesthetic.

A 2–10% solution of cocaine hydrochloride is the topical anesthetic of choice for intranasal anesthesia because of its excellent vasoconstrictive and hemostatic properties. However, onerous record-keeping requirements make it relatively impractical for in-office use. Due to its significant cardiac stimulatory effects, cocaine hydrochloride should be used with caution in patients with significant heart disease.

Oral and anal mucosa can be effectively anesthetized within a couple of minutes with 2–4% lidocaine jelly or viscous lidocaine as well as various benzocaine-containing preparations. Topical intraoral anesthesia is especially helpful in reducing the pain of nerve block injections done through the intraoral route.

Cryoanesthesia

Rapid cooling of the skin surface is used routinely for many non-ablative laser procedures. The anesthesia is achieved with one of the following: a short burst of cryogen sprayed onto the skin surface (Dynamic Cooling Device™); a cold glass window placed directly onto the site being treated (contact cooling); an iced gel placed on the surface being treated (passive cooling); or −5°C refrigerated air blown onto the

skin surface with a coupling gel in place (Cryo 5™). All of these methods cool the skin to reduce pain of laser treatment and to protect the epidermis from laser-induced heat injury.

Cryoanesthesia can also be helpful in skin surgery. Dermabrasion can be done entirely under cryoanesthesia by freezing the skin with a cryogen spray before dermabrading. Unfortunately, the most effective and safe cryogen sprays (Frigiderm®, Fluro-Ethyl®) contain chlorofluorocarbons that are harmful to the ozone layer, and their manufacture has been discontinued. They are still available in limited quantities at ever-escalating prices. Ethyl chloride spray can, through evaporative cooling, achieve brief anesthesia to reduce the pain of needle insertion. An ice cube or –5°C forced air cooling (see above) will likewise numb the skin just long enough to reduce the pain of needle insertion. I have found forced air cooling helpful in reducing the pain of palmar and finger injections of botulinum toxin A for hyperhidrosis. However, if the cold air is directed directly onto the needle, the liquid within the needle may freeze momentarily, making it seem that the needle is clogged. Moving the cold air blower away from the needle for 5 to 10 seconds will permit the contents of the needle to thaw out, allowing injection to continue.

Anesthetic Injection Techniques

Local infiltration

The great majority of dermatologic surgical procedures are done under anesthesia achieved with local infiltration. Every attempt should be made to minimize the pain of injecting the anesthetic. There are several maneuvers that can significantly reduce pain of injection[22]. The pain of needle insertion is reduced by reassurance, verbal distraction, and mechanical distraction such as a pinch at the site of injection. An explanation for how mechanical distraction works is the gate theory of pain. The pinching stimulates cutaneous nerves, making them somewhat refractory to the immediately following pinprick sensation from needle insertion. A very useful adjunct, which also takes advantage of the gate theory of pain, is the use of vibration at or immediately proximal to the injection site. This is very useful when injecting anesthetic in very anxious or young patients and has made it feasible for us to eliminate the need for nerve block anesthesia when injecting botulinum toxin A into the palms and soles in many patients. Care must be taken when applying a vibrator to the injection site, as the needle may move unpredictably across the skin surface due to the vibration before being inserted into the skin. Small 30-gauge needles that are inserted quickly further reduce pain. Slow, timid needle insertion is felt more by the patient than a quick needle insertion. Topical anesthesia, as noted above, can almost completely eliminate the pain of needle insertion.

The actual injection of the anesthetic causes a significant stinging sensation that is usually far more painful than the needle insertion. Buffering the anesthetic to a physiologic pH and using anesthetic that has been warmed to body temperature will reduce the stinging sensation[8,9,23]. Injecting the anesthetic as slowly as practical will reduce the pain from tissue distention by the anesthetic fluid, and this also allows the injection of additional anesthetic to be done through an already numb area. Additional sticks should be through an already numb area, and the injection should start on the side that the sensory innervation is coming from and proceed distally. Using the smallest practical syringe size, usually 1 or 3 ml, will allow for low pressures of injection, which are less painful. Subcutaneous anesthetic injection is less painful than intradermal injection, but the onset of anesthesia is slower and of shorter duration. I usually start by creating a small intradermal wheal, followed by subcutaneous injection, and finish with intradermal injection at the incision line to enhance anesthesia and hemostasis.

Field block anesthesia

Field block anesthesia involves injecting a ring of anesthetic around the proposed surgical site. It is useful for anesthetizing large areas while conserving the amount of anesthetic used and minimizing distortion of the surgical site. Injecting a ring of anesthesia around a cyst will avoid puncturing the cyst. Ring block anesthesia is practical only in areas where innervation arrives horizontally through the skin, such as is seen on the scalp, rather than vertically from deeper tissues, as is seen on the eyelid. A ring block may achieve anesthesia, but there will be no hemostasis at the incision site. Therefore, the addition of intradermal anesthetic with epinephrine at the proposed incision site is recommended. The most frequent use of ring block anesthesia is on the scalp, nose (for rhinophyma repair), ear pinna, and on the trunk and extremities (where the injection is started as a ring block but often finished with infiltration inside the ring block).

TUMESCENT ANESTHESIA FORMULA	
Ingredient	**Quantity (ml)**
Lidocaine 1%	50–100
Epinephrine (1:1000)	1
Sodium bicarbonate 8.4%	10
Hyaluronidase 150 U/ml	6 (optional)
Triamcinolone acetonide 40 mg/ml	0.25 (optional)
Normal saline 0.9%	900–950

Table 143.6 Tumescent anesthesia formula. For tumescent anesthesia, a final concentration of 0.05% to 0.1% lidocaine with 1:1 000 000 epinephrine is prepared. Hyaluronidase may be added to enhance diffusion and corticosteroids may be added to reduce inflammation, edema and possibly fibrosis.

Tumescent anesthesia

Tumescent anesthesia involves the subcutaneous infiltration of large amounts of dilute 0.05–0.1% lidocaine with 1:1 000 000 epinephrine (Table 143.6). It has been used most extensively for liposuction under local anesthesia (see Ch. 156), ambulatory phlebectomy, hair transplantation, and dermabrasion. The anesthetic is infiltrated with the help of a pump, with the injection carried out through long 18–20-gauge 3.5 inch (8.9 cm) spinal needles or specially designed multiport cannulas. The infiltration is started slowly with small needles and then gradually speeded up utilizing spinal needles and finally infiltration cannulas. Infiltration of the deep subcutaneous plane is done first, followed by the superficial fat compartment. The solution is injected until firm tumescence of the tissue has been achieved. Anesthesia and epinephrine-induced hemostasis develop within about 20 minutes and last for several hours, which is significantly longer than the duration of anesthesia achieved with conventional concentrations of lidocaine with epinephrine. In the subcutaneous fat, dilute lidocaine is absorbed at a much slower rate than standard lidocaine concentrations. Doses as high as 35–50 mg/kg lidocaine have been found to be safe when used in tumescent anesthesia[16–18].

Nerve Block Techniques

Nerve blocks are an effective and efficient way to anesthetize large areas using the least amount of anesthetic, minimizing both patient discomfort and distortion of the operative site. When injecting in the region of a nerve, care must be taken not to inject the accompanying blood vessels. Using larger, 25–27-gauge needles allows one to draw back to make sure that the needle is not intravascular. To reduce pain of injection, an intradermal wheal using a 30-gauge needle should be placed first. The aim of nerve block injections is to deposit the anesthetic near, but not into, the nerve, as intraneural injection may cause nerve injury and subsequent dysesthesia. Insertion of the needle into a nerve is usually felt by the patient as a sharp pain radiating along the nerve. If this happens, the needle should be pulled back and repositioned slightly. Intra-foramina injections should also be avoided to minimize the risk of nerve injury. With proper placement, most nerves can be blocked with a 1–2 ml injection. The addition of hyaluronidase will enhance diffusion of the anesthetic and increase the rate of nerve block "take".

For most nerve blocks, 1% lidocaine with epinephrine and sodium bicarbonate is used. If prolonged anesthesia is desired, 0.25% bupivacaine hydrochloride with epinephrine can be added. As the sensory nerves are large and myelinated, anesthetic effect may take 10 to 20 minutes to develop[24]. Using 2% lidocaine may increase success of the nerve block. Articaine 4% with or without epinephrine supplied in dental carpules seems to be especially effective for relatively painless facial nerve blocks, with very small volumes (often less than 0.2 ml/injection site) of anesthetic needed for effective anesthesia. This seems

to be due to its more effective diffusion from the site of injection compared to lidocaine. Some surgeons omit epinephrine from the nerve block anesthetic as it is not needed for vasoconstriction at the site of the nerve. I use it as part of my anesthetic mix to prolong the duration of the nerve block. Once a nerve has been effectively blocked, local infiltration of lidocaine with epinephrine along the proposed incision line to achieve local vasoconstriction may be helpful in reducing bleeding.

Facial nerve blocks

The forehead and frontal scalp above the eyebrows are innervated by the *supraorbital nerve* (Fig. 143.2), which exits the skull through the supraorbital foramen at or immediately above the orbital rim in the midpupillary line (Fig. 143.3). The notch can often be palpated on the patient. Approximately 1 ml of anesthetic is infiltrated through a 0.5 inch (1.3 cm) needle inserted perpendicularly into the skin immediately superficial to the periosteum at the orbital rim in the midpupillary line (Fig. 143.4). The *supratrochlear nerve* innervates the midforehead, glabella and frontal scalp (Fig. 143.2). It exits the skull at the upper medial portion of the orbit (Fig. 143.3). Injecting 1 ml of anesthetic immediately superficial to the periosteum at the superomedial orbital rim at the junction of the glabella and eyebrow will block the supratrochlear nerve (Fig 143.4). To achieve complete forehead and frontal scalp anesthesia requires extending a line of anesthetic injected in the subcutaneous plane laterally from the supraorbital nerve to the region immediately superior and posterior to the attachment of the ear pinna. This will block the auriculotemporal nerve and greater auricular nerve branches that innervate the forehead, temple and frontal scalp.

The *infraorbital nerve* exits the skull through the infraorbital foramen (Fig. 143.3) and innervates the medial cheek, upper lip and nasal ala (Fig. 143.2). With a 1 inch (2.5 cm) needle inserted perpendicularly to the skin, 2 ml of anesthetic is injected approximately 1 cm inferior to the orbital rim in the midpupillary line, immediately superficial to the maxillary bone periosteum (Fig. 143.4). A less painful and more reliable alternative is to block the infraorbital nerve through the intraoral approach. The needle is inserted between the first and second premolars (bicuspids), moving cephalad along the periosteum until bone is reached (Fig. 143.5). The needle is pulled slightly back and the anesthetic is injected. The pain of needle insertion can be lessened by applying a topical anesthetic to the mucosa a couple of minutes prior to injection. The *infratrochlear nerve*, which innervates the lateral and dorsal nose (Fig. 143.2), can be blocked by injecting anesthetic superficial to the periosteum at the inferomedial orbital rim at the superior end of the nose-cheek concavity (Fig. 143.4). The nasal tip receives innervation from the external nasal branch of the *anterior ethmoidal nerve* (Fig. 143.2), which emerges at the nasal cartilage and bone junction slightly lateral from the midline (Fig. 143.3). Perichondrial infiltration of anesthetic at this spot will anesthetize the nasal tip (Fig. 143.4). To complete nasal anesthesia, a few drops of anesthetic at the base of the columella may be needed as well.

The lower lip and portions of the chin are innervated by the *mental nerve* (Fig. 143.2), which exits the mandible through the mental

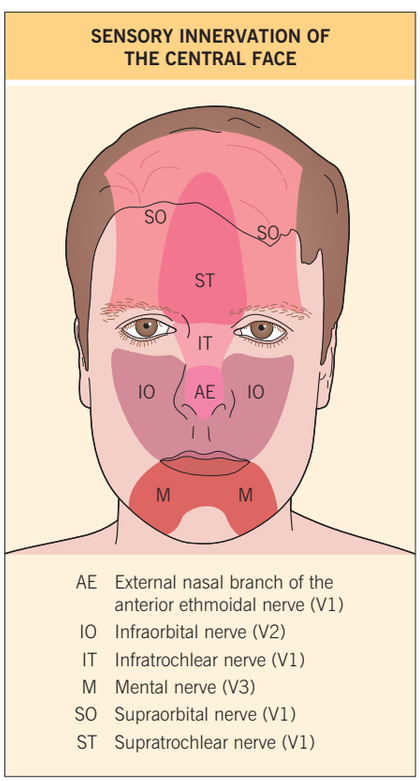


Fig. 143.2 Sensory innervation of the central face.

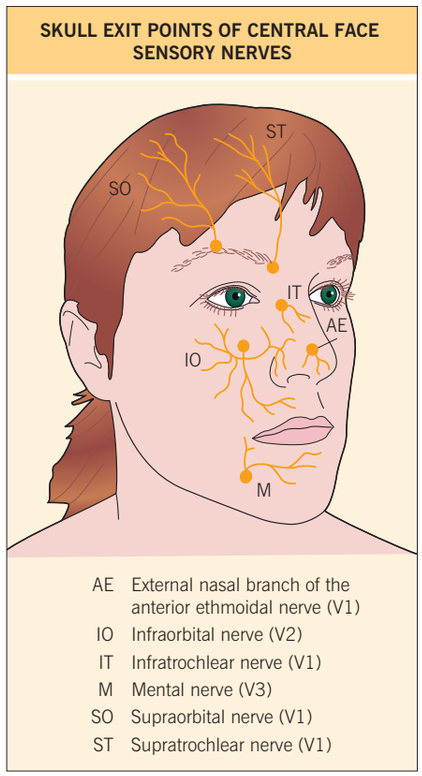


Fig. 143.3 Skull exit points of central face sensory nerves.

Fig. 143.4 Locations of needle insertions for central face nerve blocks. From superior to inferior, the supraorbital, infraorbital and mental nerves are marked with an "x" and the supratrochlear, infratrochlear and external nasal nerves are marked with a rectangle.

Fig. 143.5 Intraoral route for infraorbital nerve block. The needle is inserted cephalad between the premolar (bicuspid) teeth in the midpupillary line.

Fig. 143.6 Intraoral route for mental nerve block. The needle is inserted caudally between the premolar (bicuspid) teeth in the midpupillary line.

foramen in the midpupillary line (Fig. 143.3). A 0.5 inch (1.3 cm) needle is inserted perpendicular to the skin to the level of the periosteum in the midpupillary line halfway cephalad along the mandible, and 1 ml of anesthetic is injected to block the mental nerve (Fig. 143.4). The intraoral route is less painful and more reliable. The needle is inserted between the first and second premolars (bicuspids) caudally along the periosteum to a halfway point down the mandible (Fig. 143.6).

Digital nerve blocks

Nerve blocks for the fingers and toes are technically very similar. There are two options to anesthetize a digit. The technique most commonly used by dermatologists blocks the sensory nerves coursing laterally along the digit. A 0.5 inch (1.3 cm) needle is inserted perpendicular to the digit near its base in the horizontal plane until the bone is touched. At this point, the needle is withdrawn slightly, positioned dorsally and anesthetic is injected. Next, the needle is positioned ventrally and additional anesthetic is injected. This process is repeated on the other side of the digit. This block should be done without epinephrine, and small volumes (usually less than 1.5 ml) should be injected to minimize the risk of ischemic injury from mechanical circumferential compression of the blood supply to the digit.

Alternatively, the digit can be blocked at the level of the metacarpal or metatarsal bone. A 1.5 inch (3.8 cm) needle is inserted dorsally between the metacarpal/metatarsal bones, and anesthetic is infiltrated as the needle is advanced ventrally, with most of the anesthetic injected just dorsal to the palmar/plantar skin. This injection will block the metacarpal/ metatarsal nerve, which travels immediately superficial to the flexor retinaculum. The process is repeated on the other side of the metacarpal/metatarsal bone of the digit being anesthetized. The advantage of this block is that there is less risk of compression injury than can occur with the more commonly performed digital block.

Penile nerve block

The dorsal nerve of the penis is a branch of the pudendal nerve. It divides into major anterior (dorsal) and minor posterior (ventral) branches at the base of the penis. By injecting a ring of anesthesia without epinephrine in the subcutaneous plane around the base of the penis, most of the penis will be anesthetized. The only areas that may require additional anesthetic infiltration will be the periurethral region of the glans and, sometimes, the ventral glans and frenulum.

Hand nerve block

With the popularity of botulinum toxin A for palmar and plantar hyperhidrosis, a method to anesthetize the palmar surface is necessary. Topical anesthetics are ineffective on palmoplantar skin, and local anesthetic injections are too painful in the palms or soles. Nerve block of the median nerve will anesthetize the palmar surface of the first three and a half fingers plus two-thirds of the palmar surface (Fig. 143.7). Block of the ulnar nerve will anesthetize the rest of the fingers and palm (Fig. 143.7). The median nerve lies in the carpal tunnel, deep to the palmaris longus tendon and between the flexor digitorum superficialis and flexor carpi radialis tendons. By apposing the thumb and fifth finger with the wrist slightly flexed, the palmaris longus tendon will become apparent. A 0.5–1 inch (1.3–2.5 cm) needle is inserted at the first (proximal) wrist crease, immediately medial (ulnar) to the palmaris longus tendon (Fig. 143.8). It is then advanced deep into the carpal tunnel and a few milliliters of anesthetic are injected. A slight "popping" or reduction in resistance can be felt as the needle enters the carpal tunnel.

The ulnar nerve is most easily blocked at the elbow where it travels between the olecranon process and the epicondyle of the humerus. The

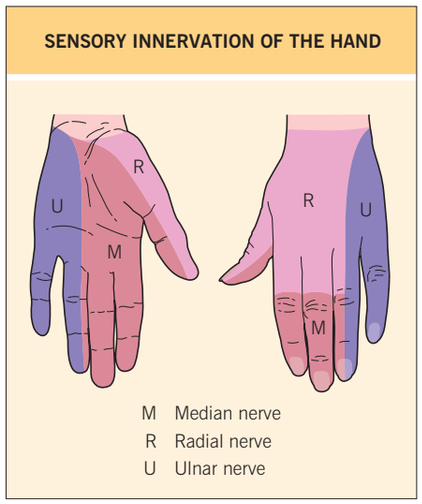


Fig. 143.7 Sensory innervation of the palmar surface and dorsal surface of the right hand.

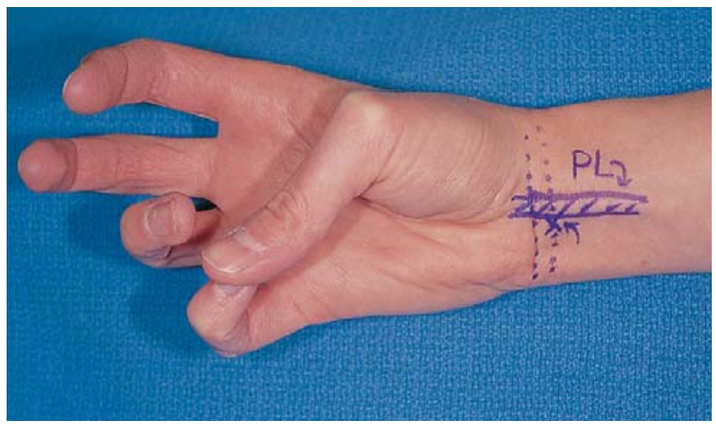


Fig. 143.8 Cutaneous markers for the median nerve location at the wrist. Note thumb and little finger apposition and wrist flexion to visualize the palmaris longus (PL) tendon. X, needle entry point.

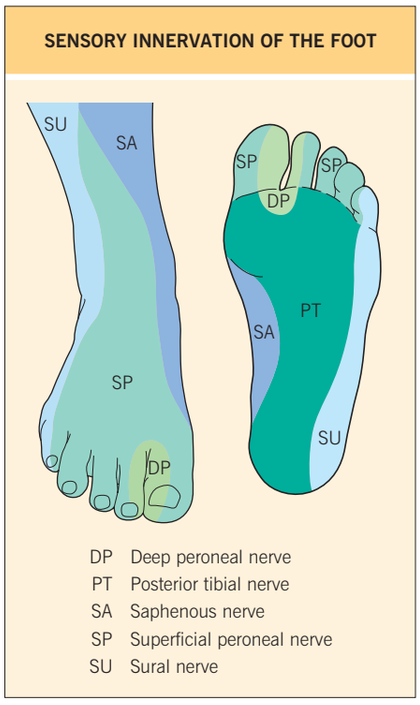


Fig. 143.9 Sensory innervation of the dorsal surface and plantar surface of the right foot.

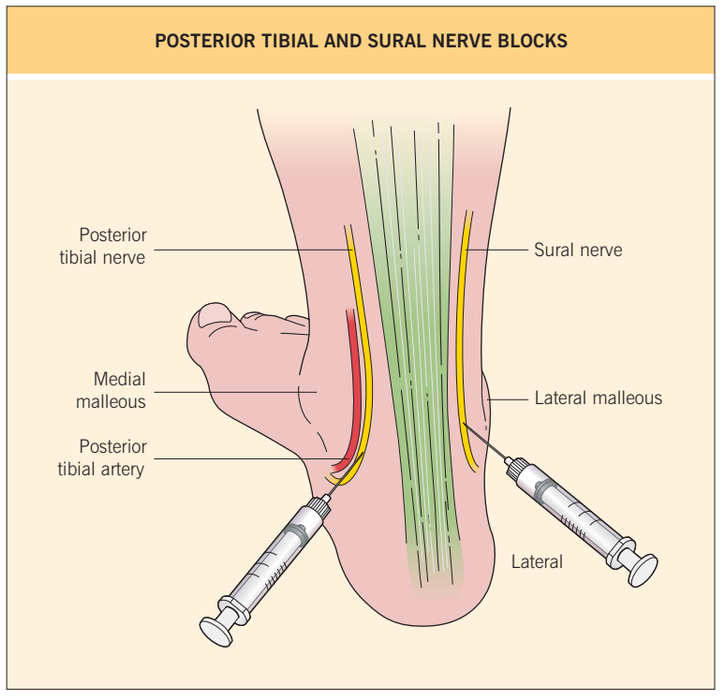


Fig. 143.10 Posterior tibial and sural nerve blocks.

ulnar nerve is the "funny bone". The patient's arm is flexed, and the needle is inserted between the bones with several milliliters of anesthetic injected.

An alternative is to have an anesthesiologist perform a Bier block, in which the blood is pushed out of the arm with a compressive bandage, a tourniquet is applied, and dilute lidocaine is injected intravenously. Anesthesia of the hand will develop in 5 to 10 minutes and last for about 1 hour. Once the procedure is complete, the tourniquet is gradually released and the anesthetic is released into the general circulation. Therefore, the dose administered should be monitored to keep it at a safe level.

Foot nerve block

Anesthesia of the plantar surface requires nerve blocks of the posterior tibial nerve, which innervates the heel and middle of the sole of the foot; the sural nerve, which innervates the fifth toe and the lateral side of the sole of the foot; the superficial peroneal nerve, which innervates the skin of the toes; the saphenous nerve, which innervates the instep; and the deep peroneal nerve, which innervates the skin between the first and second toes (Fig. 143.9). Before starting injections around the ankle, the area should be thoroughly prepared with antiseptic to minimize the risk of infection.

The patient is placed in the prone position. The posterior tibial artery is palpated using a Doppler ultrasound probe if needed, and a 1.5 inch (3.8 cm) needle is directed anteriorly and laterally, immediately lateral to the arterial pulse, until the bone is touched. The needle is pulled back slightly, and several milliliters of anesthetic are injected in the groove between the medial malleolus and the Achilles tendon (Fig. 143.10). The sural nerve is blocked by injecting anesthetic in the groove between the lateral malleolus and Achilles tendon in an identical fashion to the tibial nerve injection (Fig. 143.10).

The patient is placed in the supine position. The saphenous and superficial peroneal nerves are blocked by infiltrating anesthetic subcutaneously from malleolus to malleolus on the dorsal surface of the foot (Fig. 143.11). The deep peroneal nerve is blocked by inserting a 1.5 inch (3.8 cm) needle lateral (toward the middle of the foot) to the extensor hallucis longus tendon down to the bone (Fig. 143.11). Next, the needle is pulled back slightly, and several milliliters of anesthetic are injected. The tendon is identified by having the patient dorsiflex his or her great toe against resistance. Alternatively, local anesthetic infiltration between the first and second toes may be easier and more expeditious.

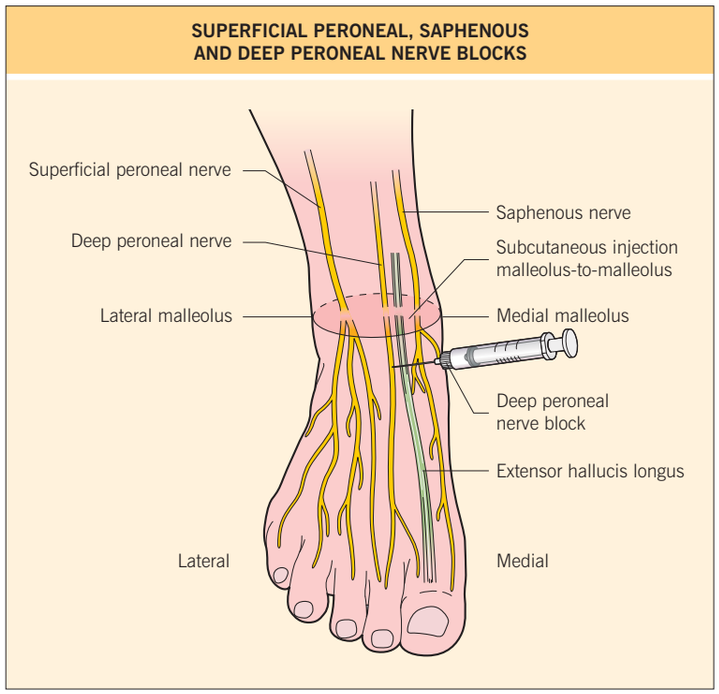


Fig. 143.11 Superficial peroneal, saphenous, and deep peroneal nerve blocks. Great toe dorsiflexion aids in visualizing the extensor hallucis longus tendon.

Higher Levels of Anesthesia

In anxious patients, or when relatively large areas are to be anesthetized, oral or sublingual anxiolytics such as triazolam (Halcion®) 0.25–0.5 mg or zolpidem tartrate (Ambien®) 5–10 mg will reduce anxiety and may even generate a certain degree of amnesia for the procedure. The addition of a narcotic analgesic such as oxycodone (10 mg)/acetaminophen (650 mg) orally (Percocet®) or meperidine hydrochloride (Demerol®) 50 mg intramuscularly, will act synergistically with the anxiolytics to achieve a greater degree of sedation as well as reducing the pain of local

anesthetic infiltration. I find these useful for procedures done under tumescent anesthesia. Of course, patients given any sedating medications should have someone else take them home after the procedure.

Credentialing for higher levels of anesthesia may be regulated by local medical licensure authorities and hospitals, and the physician must be in full compliance with the rules in his or her particular locale. Most of the regulations require procedures done under general anesthesia or with intravenous sedation to be done in an ambulatory surgery center or hospital with a supervising anesthesiologist. Higher levels of anesthesia involving the use of intravenous medications such as midazolam hydrochloride (Versed®) and fentanyl should be done in a monitored environment with appropriate resuscitative equipment readily available. Nitrous oxide administration is a useful form of moderate analgesia, with the degree depending on the concentration administered. At a 20% concentration, the analgesia is equivalent to giving a narcotic analgesic. At an 80% concentration, most patients will become unconscious. The advantage of nitrous oxide is the rapid reversal of anesthetic effect as soon as the gas is turned off. With proper training, nitrous oxide can be safely administered in the office, as it has been done for many years in many dental offices. General inhalation anesthesia or deep intravenous sedation with propofol should generally be performed by anesthesiologists.

REFERENCES

1. Wildsmith JAW, Strichartz GR. Local anaesthetic drugs-an historical perspective. Br J Anaesth. 1984;56:937–9.
2. McNulty MM, Edgerton GB, Shah RD, et al. Charge at the lidocaine binding site residue Phe-1759 affects permeation in human cardiac voltage-gated sodium channels. J Physiol. 2007;581:741–55.
3. Bieter RN. Applied pharmacology of local anesthetics. Am J Surg. 1936;34:500–10.
4. Rasmussen LF, Ahlfors CE, Wennberg RP. The effect of paraben preservatives on albumin binding of bilirubin. J Pediatr. 1976;89:475–8.
5. Foster CA, Aston SJ. Propranolol-epinephrine interaction: a potential disaster. Plast Reconstr Surg. 1983;72:74–8.
6. Dzubow LM. The interaction between propranolol and epinephrine as observed in patients undergoing Mohs surgery. J Am Acad Dermatol. 1986;15:71–5.
7. Krunic AL, Wang LC, Soltani K, et al. Digital anesthesia with epinephrine: an old myth revisited. J Am Acad Dermatol. 2004;51:755–9.
8. Stewart JH, Chinn SE, Cole GW, Klein JA. Neutralized lidocaine with epinephrine for local anesthesia – II. J Dermatol Surg Oncol. 1990;16:842–5.
9. Stewart JH, Cole GW, Klein JA. Neutralized lidocaine with epinephrine for local anesthesia. J Dermatol Surg Oncol. 1989;15:1081–3.
10. Lewis-Smith PA. Adjunctive use of hyaluronidase in local anaesthesia. Br J Plast Surg. 1986;39:554–8.
11. Galindo A, Witcher T. Mixtures of local anesthetics: bupivacaine-chloroprocaine. Anesth Analg. 1980;59:683–5.
12. Nagel JE, Fuscaldo JT, Fireman P. Paraben allergy. JAMA. 1977;237:1594–5.
13. Glinert RJ, Zachary CB. Local anesthetic allergy. Its recognition and avoidance. J Dermatol Surg Oncol. 1991;17:491–6.
14. Roberts EW, Loveless H. The utilization of diphenhydramine for production of local anesthesia: report of a case. Texas Dent J. 1979;97:13–15.
15. Wiener SG. Injectable sodium chloride as a local anesthetic for skin surgery. Cutis. 1979 23:342–3.
16. Lillis PJ. Liposuction surgery under local anesthesia: limited blood loss and minimal lidocaine absorption. J Dermatol Surg Oncol. 1988;14:1145–8.
17. Klein JA. Tumescent technique for regional anesthesia permits lidocaine doses of 35 mg/kg for liposuction. J Dermatol Surg Oncol. 1990;16:248–63.
18. Klein JA. Improved technique for local anesthesia: improved safety in large volume liposuction. J Plast Reconstr Surg. 1993;92:1085–98.
19. Kane GC, Hoehn SM, Behrenbeck TR, Mulvagh SL. Benzocaine-induced methemoglobinemia based on the Mayo Clinic experience from 28 478 transesophageal echocardiograms: incidence, outcomes, and predisposing factors. Arch Intern Med. 2007;167:1977–82.
20. Friedman PM, Fogelman JP, Nouri K, et al. Comparative study of the efficacy of four topical anesthetics. Dermatol Surg. 1999;25:950–4.
21. Altman DA, Gildenberg SR. High-energy pulsed light source hair removal device used to evaluate the onset of action of a new topical anesthetic. Dermatol Surg. 1999;25:816–18.
22. Arndt KA, Burton C, Noe JM. Minimizing the pain of local anesthesia. Plast Reconstr Surg. 1983;72:676–9.
23. Bainbridge LC. Comparison of room temperature and body temperature local anaesthetic solutions. Br J Plast Surg. 1991;44:147–8.
24. Grekin RC, Auletta MJ. Local anesthesia in dermatologic surgery. J Am Acad Dermatol. 1988;19:599–614.

Wound Closure Materials and Instruments

144

Christie Travelute Ammirati and Glenn Goldman

Key features

- The characteristics ascribed to a suture include:
  - capillarity
  - physical configurations
  - USP size
  - elasticity
  - coefficient of friction
  - memory
  - plasticity
  - pliability
  - tensile strength
  - tissue reactivity
- Sutures used to approximate the dermis and deeper tissue layers are generally absorbable, while cutaneous sutures are usually non-absorbable and require removal
- The most commonly employed needle in dermatologic surgery is a 3/8 circle that is triangular in shape, with a reverse cutting surface
- Needle holders with small smooth jaws accommodate finer needles and those with large serrated jaws are best for larger needles
- The major types of scissors used in dermatologic surgery are Gradle, tissue, undermining, suture-cutting, and bandage-cutting

INTRODUCTION

As dermatologic surgery continues to expand as a specialty, so does the variety of materials and instruments that are available to facilitate the greater complexity of tissue excisions and repairs. A thorough working knowledge of these tools is essential and allows the physician to optimize the cosmetic and functional outcome of a given procedure. For example, the suture material and surgical instruments chosen for a melanoma excision on the back will vary greatly from those for a blepharoplasty. This chapter will carefully review the wound closure materials and surgical instruments of greatest value to the dermatologic surgeon. Helpful hints and model surgical tray setups are included to assist in the preparation for surgery in specific anatomic locations.

DISCUSSION

Sutures

Although it has been thought that humans have been using various materials to sew skin wounds since prehistoric times, the first known reference appears in the Edwin Smith Papyrus (c. 1600 BC)[1]. The precise suture material was not described, but based upon artifacts from that time period, it was most likely linen. Hippocrates (400 BC) has been credited with being the first to use the term "suture" in reference to sewing human tissue.

In the history of medicine, there are many accounts of the quest by surgeons for the ideal suture material. Their ingenuity is reflected in the vast array of materials that have been tried over time, including cotton, leather, flax, insect mandibles, horse hair and even human hair[2–8]. Ancient Roman physicians would braid the hair of gladiators tightly when closing their scalp wounds, having realized that "sutures" can provide immediate hemostasis as well as wound edge approximation.

The ideal suture would handle easily, hold a secure knot, and have high tensile strength. It would neither cause inflammation nor promote infection, and it would gradually dissolve, thereby obviating the need for suture removal. Unfortunately, the perfect suture material does not exist. However, the ever-widening array of choices available to the dermatologic surgeon and a knowledge of each suture's individual characteristics increases the likelihood of choosing the best possible materials for each surgical situation.

Suture materials are subdivided into absorbable and non-absorbable. Studies of wound healing have shown that during the first 1–2 weeks following surgery, the intrinsic tensile strength of the wound is approximately 7–10% of native bursting pressure[9]. At 5 weeks, the intrinsic tensile strength is approximately 60%, and dehiscence is unlikely with normal activity. During this time period, absorbable buried dermal sutures are utilized to alleviate tension and maintain wound edge approximation. Epidermal, non-absorbable sutures are non-tension-bearing, but allow for fine adjustments of the epidermal edges and thus provide for an improved cosmetic result.

The characteristic attributes ascribed to a suture are defined and standardized by the United States Pharmacopeia (USP) as follows:

- **Capillarity** is defined as the ability of a suture to absorb and transfer fluid. Multifilament (braided or twisted) sutures have greater capillarity than monofilament (single-stranded) sutures.
- Two **physical configurations** exist: monofilament and multifilament. Multifilament suture may be spun, twisted or braided. Braiding serves to increase pliability, strength, knot security and handling[10], but it can lead to abrading or shearing of tissue. In addition, braiding potentially increases the risk of infection by allowing bacteria to become entrapped between filament strands[11]. Therefore, rather than a braided suture, a monofilament suture may be more appropriate for closing a contaminated wound[10,12–15]. Monofilament sutures have a low coefficient of friction and, as such, slide easily through tissue (see below)[15]. Their drawback is that they are traditionally stiffer than braided sutures and may have decreased knot security, requiring additional throws to ensure that the knot is secure. Until recently, monofilament sutures were used primarily for exterior suturing, and most buried sutures were braided. With the introduction of poliglecaprone 25 (Monocryl®), monofilament absorbable suture is now regularly employed for deep sutures.
- The **USP size** of a suture is determined by the diameter of the suture material needed to achieve a given tensile strength and is expressed in multiples of zeros; the smaller the cross-sectional diameter of the suture, the more zeros. For example, 7–0 polyglactin 910 (Vicryl®) is a much finer suture than 3–0 Vicryl®. The actual diameter of a given USP size varies depending upon the composition of the suture; for example, 4–0 surgical gut is a larger-diameter suture than 4–0 polypropylene (Prolene®) because polypropylene is innately stronger for a given diameter. In general, the smallest suture that will provide adequate tensile strength for the indicated repair should be utilized.
- **Elasticity** refers to the ability of a suture to regain its original length after being stretched. An elastic suture, such as polybutester (Novafil®), allows for tissue swelling, and then maintains tension on the wound edges after the edema has resolved.
- The **coefficient of friction** determines the ease with which a suture will pull through tissue. A suture with a low friction coefficient, such as polypropylene (Prolene®), slides easily through tissue (Fig. 144.1). For this reason, polypropylene is the material most commonly used for the running subcuticular suture (see Ch. 146). Knot strength is directly proportional to the friction coefficient of the suture material. The more slippery the suture material, the more likely it is that the resulting knot will unravel. Hence, when suturing with polypropylene, it may be useful to place several additional throws for each knot.

- **Memory** is defined as a suture's tendency to retain its natural configuration and is determined by the elasticity and plasticity of the suture material. Memory is a useful property for maintaining closure during the postoperative period, and high-memory sutures such as nylon are widely used for surface approximation. Drawbacks of high-memory sutures are that they do not handle very easily and they have a relatively low knot strength. As with sutures that have a low coefficient of friction, the surgeon may find that it is helpful to place a few extra throws in order to ensure a secure knot. Suture material with low memory, such as silk, is easy to handle and rarely becomes untied.
- **Plasticity** is the ability of the suture to be molded or to retain its new length and form as well as tensile strength after it has been stretched. This is an important characteristic for a suture material that is to be used in situations with tissue edema. Sutures with plasticity, such as polypropylene, will stretch to accommodate edema and not cut into tissue[16].
- **Pliability** refers to how easily the suture can be bent. Braided suture materials, such as silk, are the most pliable, and they are capable of readily being tied into a knot. Polyglactin (Vicryl®) is a buried, absorbable braided suture that is also easily tied.
- The **tensile strength** of a suture is determined by the force (in pounds) required to snap it divided by the cross-sectional diameter of the suture. In general, synthetic materials are stronger than natural materials. A suture that has been knotted has approximately one-third of the tensile strength of the same material unknotted[17].
- **Tissue reactivity** is the degree of foreign body inflammatory response evoked by a suture when placed into a wound. In general, natural materials (e.g. surgical gut, silk) cause much more of an inflammatory response than synthetic materials (e.g. nylon, polypropylene, polyester)[13,18].

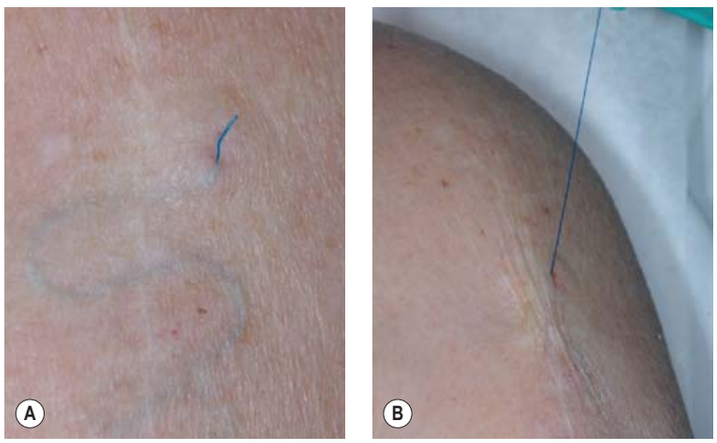


Fig. 144.1 Polypropylene suture – demonstration of its low coefficient of friction. A The blue color of the polypropylene suture is visible under the skin 1 year after its placement as a running subcuticular closure; the patient had neglected to return for suture removal. **B** The ease of removal, despite having been in the skin for 1 year, demonstrates its very low coefficient of friction and minimal tissue adherence.

Types of Suture Material

Sutures are characterized as absorbable or non-absorbable, based upon their ability to be enzymatically digested or hydrolyzed. Most *absorbable* sutures lose the majority of their tensile strength long before they are fully absorbed. In general, absorbable sutures are used to close the dermis and deeper subcutaneous layers and are not removed. *Non-absorbable* sutures are resistant to hydrolysis and enzymatic degradation. Non-absorbable sutures such as nylon and polypropylene are usually used as surface sutures, and they are routinely removed 5–10 days after surgery (earlier on the face and later on the trunk and extremities).

Absorbable Sutures

The most commonly employed absorbable sutures are outlined in Table 144.1[19].

Surgical gut

Surgical gut (catgut), one of the first sutures ever mass-produced, is derived from bovine or sheep intestine. It is a natural tan fiber that is packaged wet in alcohol and dries quickly when exposed to air. Plain

COMMONLY USED ABSORBABLE SUTURES

Suture	Configuration	Tensile strength	Ease of handling	Knot security*	Tissue reactivity	Uses
Surgical gut (plain)	Virtually monofilament	Poor at 7–10 days	Fair	Poor	Moderate	Rarely used today in skin
Surgical gut (chromic)	Virtually monofilament	Poor at 21–28 days	Poor	Poor	Less than plain	Skin grafts; surface sutures for mucosae
Surgical gut (fast-absorbing)	Virtually monofilament	50% at 3–5 days	Fair	Poor	Low	Skin grafts, surface sutures
Polyglycolic acid (Dexon®)	Braided†	20% at 21 days	Good	Good	Low	Subcutaneous closure, vessel ligature
Polyglactin 910 (Vicryl®, Polysorb®)	Braided†	75% at 14 days; 50% at 21 days	Good	Fair	Low	Subcutaneous closure, vessel ligature
Polydioxanone (PDS II®)	Monofilament	70% at 14 days; 50% at 30 days; 25% at 42 days	Poor	Poor	Low	Subcutaneous closure (high-tension areas)
Polyglyconate, a copolymer of glycolic acid and trimethylene carbonate (Maxon®)	Monofilament	81% at 14 days; 59% at 28 days	Fair	Good	Low	Subcutaneous closure (high-tension areas)
Poliglecaprone 25, a copolymer of glycolide and ε-caprolactone (Monocryl®)	Monofilament	50–60% at 7 days	Good	Good	Minimal	Subcutaneous closure when minimal tissue reactivity is essential
Glycomer 631 (Biosyn®)	Monofilament	75% at 14 days; 40% at 21 days	Good	Poor	Minimal	Subcutaneous closure (high-tension areas)

*Directly proportional to the friction coefficient and indirectly proportional to memory.
†Multifilament.

Table 144.1 Commonly used absorbable sutures. Adapted from ref. 19.

surgical gut is rarely used today because of its poor tensile strength and high tissue reactivity. When used as a buried suture, plain gut loses its tensile strength in 7 to 10 days and is completely digested in 60 to 70 days[20].

Chromic gut is plain gut that has been processed with chromium salts to increase its resistance to enzymatic degradation and to decrease its tissue reactivity. The tensile strength of chromic gut typically lasts for 10 to 14 days. Chromic gut is still widely used for surface suturing of mucosal surfaces, where it lasts long enough to maintain wound edge apposition but breaks down reasonably fast.

Fast-absorbing gut is plain gut that has been heated to begin breakdown of the collagen within the suture prior to use. This suture maintains its tensile strength for 3 to 5 days[21]. Fast-absorbing gut has experienced renewed popularity over the past 10 years for suturing skin grafts and for placing surface sutures in wounds that are well approximated by buried sutures. No increase in wound infections has been reported and it is convenient for both the surgeon and patient because suture removal is not necessary[21,22]. However, wound edge dehiscence is a possible risk due to the short duration of tensile strength.

Polyglycolic acid

Polyglycolic acid (Dexon®), introduced in 1970, was the first synthetic absorbable suture and its low tissue reactivity and predictable absorption profile represented a vast improvement over surgical gut[23]. It is a braided glycolic acid polymer with easy handling qualities, and it maintains 20% of its tensile strength at 3 weeks. Dexon® produces minimal inflammation, because it is absorbed primarily by hydrolysis, unlike surgical gut, which is degraded by proteolytic enzymes[23,24]. Poloxamer 188-coated and uncoated Dexon® are available. The lubricant coating makes the suture easier to tie and allows it to pass more easily through tissue.

Polyglactin 910

Polyglactin 910 (Vicryl®, Polysorb®), a synthetic, braided copolymer of glycolide and L-lactide, was first introduced in 1974 and supplanted Dexon® as the most popular buried suture in cutaneous surgery[25]. Similar to Dexon®, the absorption of Vicryl® occurs primarily via hydrolysis. The water-repelling properties of lactide delay penetration of water, and thus delay the loss of tensile strength. Polyglactin 910 (Vicryl®) maintains 75% of its tensile strength at 2 weeks and 50% at 3 weeks. Although stronger than polyglycolic acid, polyglactin 910 absorption is usually complete by 90 days, whereas polyglycolic acid is usually still being absorbed at 120 days[24].

Vicryl® is available either undyed or dyed violet. The violet form may be visible when embedded in the skin, and for cutaneous surgery, it should be avoided[26]. Vicryl® is available with a lubricant coating of polyglactin 370 and calcium stearate that allows for easier suture passage through tissue. Vicryl® is immensely popular due to its easy handling characteristics. It also holds knots well and does not tear tissue.

Although polyglactin 910 is traditionally used as an absorbable dermal suture, it may safely be used for wound edge approximation as a running suture and then removed at 5–14 days[27]. This method still requires suture removal, but the use of a single suture for both the dermal and epidermal wound closure results in a 50% saving of suture cost per reconstruction. Based upon the authors' experience, it is also an excellent choice for the vermilion lip as it causes much less inflammation than silk and still does not irritate the opposing mucosal surface.

Polyglactin 910 is also available in a partially hydrolyzed form (Vicryl Rapide®), which is particularly useful as a percutaneous suture that does not need to be removed because it spontaneously dislodges within 7–14 days. Similar to fast-absorbing gut, it is indicated for wound edge approximation where only 1–2 weeks of support will be needed and suture removal may be painful or is not convenient.

Polydioxanone

Polydioxanone (PDS II®) is a monofilament polymer made from the polyester poly (*p*-dioxanone). Introduced in 1980, the primary advantage of PDS® over polyglycolic acid (Dexon®) and polyglactin 910 (Vicryl®) is prolonged tensile strength[28]. It maintains approximately 70% of its tensile strength at 2 weeks and 50% at 4 weeks. Traces of buried polydioxanone are present in 6-month histologic preparations[15]. PDS® is employed in high-tension areas, such as the proximal extremities and trunk.

Similar to Dexon® and Vicryl®, PDS® has minimal tissue reactivity[28]. As a monofilament suture, it retains packaging memory[15], and can be relatively stiff and difficult to tie[29]. However, polydioxanone demonstrates an optimal capacity to glide through tissue[15], and the monofilament configuration allows it to be used safely in contaminated wounds. When compared with polypropylene, nylon and polyglycolic acid as a subcuticular closure, polydiaxanone was associated with a lower incidence of hypertrophic scar formation[30].

Polyglyconate

Polyglyconate, a copolymer of glycolic acid and trimethylene carbonate, is used to create a monofilament suture (Maxon®). It combines the prolonged tensile strength of PDS® with supple handling and smooth knot formation[29]. This suture maintains 81% of its tensile strength at 2 weeks and 59% at 4 weeks[31], with complete absorption occurring via hydrolysis within ~180 days. Despite this prolonged absorption, there is minimal tissue reactivity. Maxon® may be most useful for large surgical procedures on the trunk or extremities that are under substantial tension and which require prolonged, suture-based approximation during healing.

Poliglecaprone 25

Poliglecaprone 25 (Monocryl®) is an absorbable monofilament suture consisting of a copolymer of glycolide and ε-caprolactone. At 7 days, it maintains approximately 50–60% of its tensile strength, and complete absorption by hydrolysis occurs at ~90 days[15]. Similar to Maxon®, Monocryl® offers supple handling and minimal tissue reactivity, which led to a lower incidence of hypertrophic scarring in a breast reduction scar model[32]. Furthermore, poliglecaprone 25 demonstrates better knot tying and security than other commonly used absorbable monofilament suture materials[15]. Because poliglecaprone 25 leads to less inflammation than polyglactin 910 and glides easily through tissue, it has become the absorbable suture-of-choice for many dermatologic surgeons when performing closures in the head and neck region.

Glycomer 631

Glycomer 631 (Biosyn®) is an absorbable monofilament suture material with physical characteristics similar to poliglecaprone 25 (Monocryl®). Complete absorption occurs at approximately 6 months, with low tissue reactivity[15]. Because of its relative permanence, Biosyn® (like Maxon®) is used to suture large truncal wounds.

Non-absorbable Sutures

The most commonly employed non-absorbable sutures are outlined in Table 144.2[19].

Silk

Silk is a braided, natural suture. It represents the gold standard with regard to ease of handling, knot formation and knot stability, by which newer synthetic sutures are measured. Also, braided silk is very soft and pliable, and, therefore, it is commonly used on mucosal surfaces and in intertriginous regions. Despite these advantages, there are major drawbacks to its use in cutaneous surgery. Silk has a low tensile strength, its braided configuration produces a high coefficient of friction, and the high capillarity increases the risk of infection. In one study, for example, the presence of one braided silk suture increased the risk for a staphylococcal infection by 10 000-fold[33]. As an organic, foreign protein (fibroin) made by the silkworm, silk has greater tissue reactivity than any other suture except surgical gut.

Nylon

Nylon (Ethilon®, Dermalon®), a monofilament, polymerized polyamide introduced in 1940, was the first synthetic non-absorbable suture to become commercially available. Nylon quickly became very popular, and because it has high tensile strength and low tissue reactivity and is inexpensive, it is the most commonly used non-absorbable suture in dermatologic surgery[34,35]. Monofilament nylon is available in clear, black or green colors, and the green suture can be particularly helpful

COMMONLY USED NON-ABSORBABLE SUTURES						
Suture	**Configuration**	**Tensile strength**	**Ease of handling**	**Knot security***	**Tissue reactivity**	**Uses**
Silk	Braided†	None in 365 days	Gold standard	Good	Moderate	Mucosal surfaces
Nylon:						
Ethilon®	Monofilament	Decreases 20% per year	Good to fair	Poor	Low	Skin surface closure
Dermalon®	Monofilament	Good	Good to fair	Poor		
Surgilon®	Braided†	Good	Good	Fair		
Nurolon®	Braided†	Good	Good	Fair		
Polypropylene (Prolene®, Surgilene®, Surgipro®)	Monofilament	Extended	Good to fair	Poor	Minimal	Skin surface closure, running subcuticular suture
Polyester (Dacron®, Mersilene®, Ethibond®)	Braided†	Indefinitely	Very good	Good (coating decreases)	Minimal	Mucosal surfaces
Polybutester (Novafil®)	Monofilament	Extended	Good to fair	Poor	Low	Skin closure when significant edema is anticipated (elastic suture)

*Directly proportional to the friction coefficient and indirectly proportional to memory.
†Multifilament.

Table 144.2 Commonly used non-absorbable sutures. Adapted from ref. 19.

when performing closures in dark hair-bearing areas. Nylon is also available as a braided suture (Surgilon®, Nurolon®), which handles more easily but is more expensive.

Nylon's elasticity allows it to expand and contract with transient wound edema but its stiffness and memory lead to decreased knot security[35]. In practice, this can be easily counteracted by firmly setting knots and increasing the number of knot throws. Traditionally, nylon is placed as a cutaneous suture but clear nylon may be used as a permanent, tension-bearing, dermal suture that is not removed. This can be very useful when approximating the orbicularis oris muscle in a lip wedge repair or when tacking tissue to the periosteum, i.e. situations where prolonged wound strength is desired. In addition, when compared to polyglycolic acid, subcuticular nylon sutures were found to decrease the risk for scar spread[36].

Polypropylene

Polypropylene (Prolene®, Surgilene®, Surgipro®) is a monofilament polymer of propylene[37]. An inert plastic, it has minimal tissue reactivity. The major advantage of this suture is its low coefficient of friction, which allows for a gentle, smooth pull through tissue[37]. Even after extended periods of time, it can be withdrawn easily without disrupting the wound (see Fig. 144.1). This characteristic makes it the suture of choice for the running subcuticular suture. Polypropylene also has high plasticity and stretches with tissue swelling, thus reducing the likelihood of postoperative track marks[16,35] (see Ch. 151). Disadvantages of this suture are its memory (which compromises knot security) and increased cost compared to nylon. It is available in clear and blue colors. Similar to nylon, clear polypropylene may be used as a dermal suture in areas of high tension in order to provide prolonged support.

Polyester

Polyester sutures (Dacron®, Mersilene®, Ethibond®) are braided, multifilament sutures with high tensile strength, very good handling, and low tissue reactivity. These sutures last indefinitely in the body. Ethibond® comes coated with polybutilate, which decreases its drag through tissue (decreased friction coefficient). Similar to Vicryl®, polyester sutures are of great assistance for approximation of mucosal tissues, particularly the vermilion lip. They combine the soft feel of silk with a lack of tissue reactivity.

Polybutester

Polybutester (Novafil®) is a monofilament suture of polyglycol terephthalate and polybutylene terephthalates. Its major advantages are excellent handling, low coefficient of friction, high elasticity, and low tissue reactivity[38].

COMMONLY UTILIZED SUTURES BY SITE			
Site	**Deep suture**	**Surface suture**	**Other suture**
Face	4–0 or 5–0 polyglactin 910 or poliglecaprone 25	5–0 or 6–0 nylon or polypropylene	
Neck and distal extremities	4–0 polyglactin 910 or poliglecaprone 25	4–0 or 5–0 nylon or polypropylene	
Trunk and proximal extremities	3–0 or 4–0 polyglactin 910 or polyglyconate	3–0 or 4–0 nylon or polypropylene	
Mucosa	None	5–0 silk or polyester	
Vascular ligature			4–0 or 5–0 polyglactin 910

Table 144.3 Commonly utilized sutures by site. Note that there is considerable variation, depending upon the preference of the surgeon.

Suture Selection

In general, a surgeon should select the smallest suture that will provide adequate strength for a given closure (Table 144.3). For facial repairs, 4–0 or 5–0 polyglactin 910 (Vicryl®) are common absorbable sutures, and 5–0 or 6–0 nylon or polypropylene are typical surface sutures. Poliglecaprone 25 (Monocryl®) is popular as a dermal suture due to its relatively fast absorption and lack of tissue reactivity; it is useful in areas where minimal tissue reactivity is essential. Prolene® is the suture of choice for the running subcuticular suture given its low coefficient of friction.

For larger truncal defects, 3–0 or 4–0 Vicryl® or Monocryl® for buried sutures and 3–0 or 4–0 nylon for epidermal closure are good choices. PDS® is used mainly for dermal and subcutaneous suturing of large truncal defects, because it assures prolonged support. Maxon® can also be used when very-long-term wound support is essential. Skin staples offer a quick, strong alternative for epidermal closure of large scalp and truncal defects[39].

Fast-absorbing gut (6–0 or 5–0) is a convenient suture for small full-thickness skin grafts and for linear repairs that are well approximated with buried sutures. Recent studies have confirmed the safety, convenience and economy of using absorbable sutures (e.g. Vicryl®, Monocryl®, surgical gut) for epidermal skin closures in certain clinical situations, but they still require removal, similar to a non-absorbable suture[22,27,40].

Octylcyanoacrylate tissue adhesive (Dermabond®) is a practical, but expensive, alternative method of epidermal closure in wounds with minimal to no tension[41,42]. Wound closure tapes offer a non-traumatic alternative to epidermal sutures, and they are useful when applied to healing wounds following suture or staple removal. Additionally, they can be used over a running subcuticular suture at the time of surgery, relieving tension from the wound edges and providing a cosmetic, convenient alternative to a daily dressing change[43]. The optimal application of wound closure tapes is in a parallel, non-overlapping pattern (perpendicular to wound tension), following complete coating of the skin surface with Mastisol® adhesive[44].

Complications

Suture-related complications are generally due to placement technique, i.e. the sutures are tied too tightly and strangulate tissue or they are tied too loosely and not do not adequately approximate the wound edges. However, suture materials can also create complications due to their inherent properties. For example, sutures such as surgical gut and silk frequently induce inflammatory tissue reactions. Absorbable sutures (e.g. Vicryl®, Monocryl®) generally lead to little or no tissue reaction, but occasionally they may cause a granulomatous foreign body reaction (see Fig. 151.18). The latter can be seen with both braided and monofilament sutures.

Patients can develop a sterile pustule or suture abscess with associated inflammation ranging from mild to marked (Fig. 144.2A,B). These reactions can be distressing, especially if the patient has not been warned of the possibility they may occur. In patients receiving anticoagulants, the reaction may be hemorrhagic rather than purulent (Fig. 144.2C,D). Rarely, they may become secondarily infected (Fig. 144.2E). Sutures may also extrude or "spit" and create a sinus track within the skin (Fig. 144.2F).

Removal of the offending suture is the basic treatment for both a suture abscess and an extruding or "spitting" suture. If it is readily accessible, the suture should be grasped with a smooth forceps and snipped. A comedone extractor may help to express a suture that is slightly embedded; otherwise, the intact skin overlying the suture may need to be nicked with a #11 blade. Unless there is a secondary infection, antibiotics are not necessary. Removing the foreign suture material is usually sufficient to resolve the reaction.

Needles

The ideal needle is sharp and strong, and closely matches the suture diameter. The needle should be strong enough to hold its shape and retain its sharpness, pass after pass. In addition, the size and shape of the needle should be selected to correspond to the thickness and toughness of the tissue to be sutured.

There are several major brands of suture materials and each manufacturer uses a different needle nomenclature (Fig. 144.3). Most manufacturers, however, provide needle comparison reference guides. In general, the needle is the most expensive component of the needle/suture unit.

A needle is composed of three parts: the shank, the body and the point (Fig. 144.4)[45]. In dermatologic surgery, most needles have a swaged (eyeless) shank with a hollow proximal end into which the suture is inserted and then crimped. The suture track is determined by

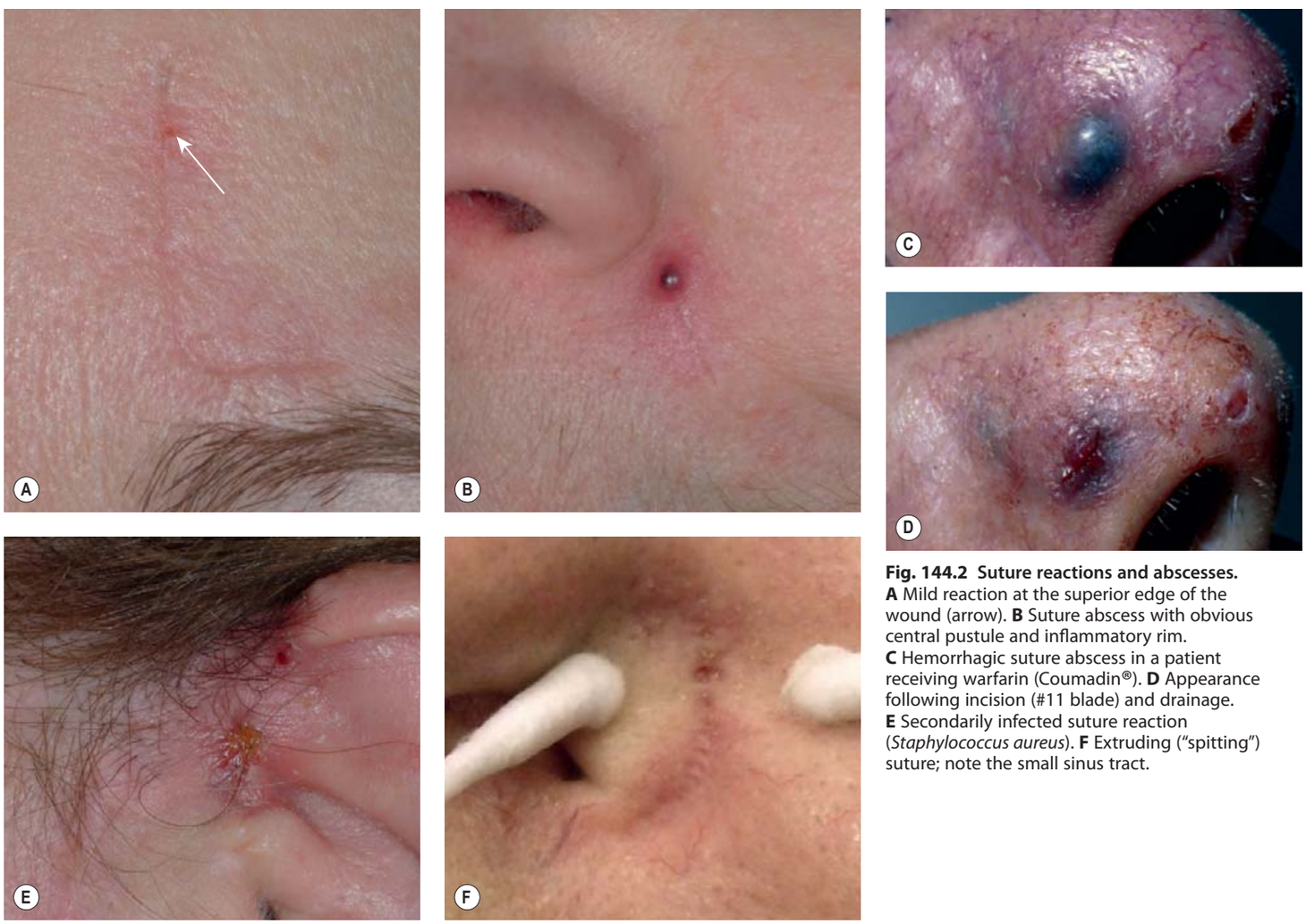


Fig. 144.2 Suture reactions and abscesses. **A** Mild reaction at the superior edge of the wound (arrow). **B** Suture abscess with obvious central pustule and inflammatory rim. **C** Hemorrhagic suture abscess in a patient receiving warfarin (Coumadin®). **D** Appearance following incision (#11 blade) and drainage. **E** Secondarily infected suture reaction (*Staphylococcus aureus*). **F** Extruding ("spitting") suture; note the small sinus tract.

the size of the needle shank, not the suture size. The body of the needle can be straight, 1/4 circle, 3/8 circle, 1/2 circle, or 5/8 circle (Fig. 144.5). The most common shape used in skin surgery is the 3/8 circle. Flattened needle bodies allow for firm grasping with needle holders to limit "twisting" during suture placement.

The most common needle-point used in cutaneous surgery is triangular in shape (see Fig. 144.4). Triangular-shaped "cutting" needles are preferred because they are easier to pass through tissues than are round needles. The conventional cutting needle has a triangular tip and is flat along the outer arc, with a sharp edge on the inside arc of the needle.

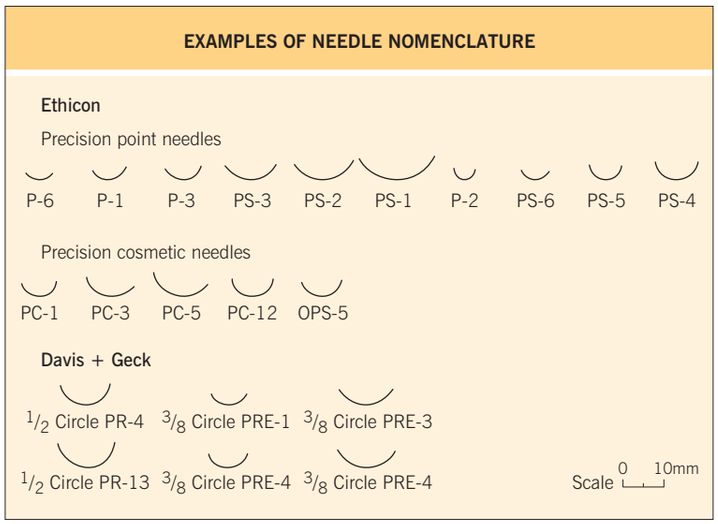


Fig. 144.3 Needle nomenclature by two representative manufacturers.

The reverse cutting tip has a flat edge facing the inside arc of the needle, and a sharp edge facing the outer arc. Reverse cutting needles have the advantage of minimizing the risk of tearing through the wound edge during suture placement. The more the needle-point is honed, the sharper the needle is and the greater the cost of the suture unit.

For the majority of wound closures on the face, the Ethicon P ("plastic") and PS ("plastic skin") or an equivalent series are adequate and economical. The P-3 and PS-3 needles are particularly suited to dermatologic surgery. They are hand-honed and reverse cutting. The PC ("precision cosmetic") series represents Ethicon's superior skin surgery needle, and it can be used for fine, delicate work. These are the sharpest, most expensive needles, and they have flattened bodies for better grasping and conventional cutting points. The PC-1 needle is a very fine sharp needle ideal for repair of delicate facial areas such as the eyelid.

The FS ("for skin") and equivalent series of needles are not finely honed, and they are less sharp and less expensive. These needles are certainly adequate for skin surgery on the trunk or extremities, although some dermatologic surgeons usually use PS needles even for these sites.

The number after the series designation denotes the needle size. Most needles are drawn to size on the package (Fig. 144.6). The smallest needle/suture unit that will provide adequate tensile strength for a given repair should be utilized. In areas with thick dermis (e.g. the back), larger needles are much easier to pass through the tissue and do not bend. A PS-2 reverse cutting needle is very useful for this indication.

Instruments

Proper instruments are essential for effective execution of cutaneous surgery. Instruments should be selected to allow the greatest precision and speed for a given procedure. There is a wide variation in the cost and quality of surgical instruments, and it is clear that "you get what you pay for". A high-quality instrument will more than make up for

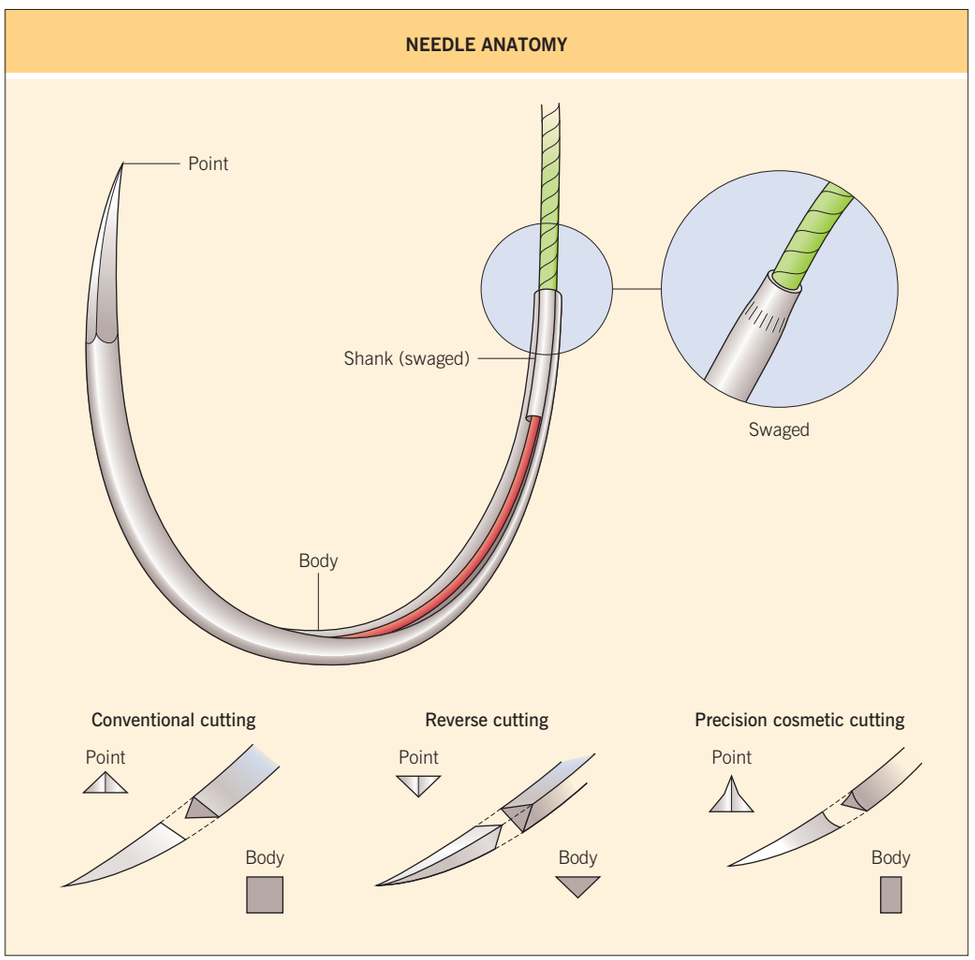


Fig. 144.4 Needle anatomy. The shank body and point are shown, and specific needle points for different types of cutting.

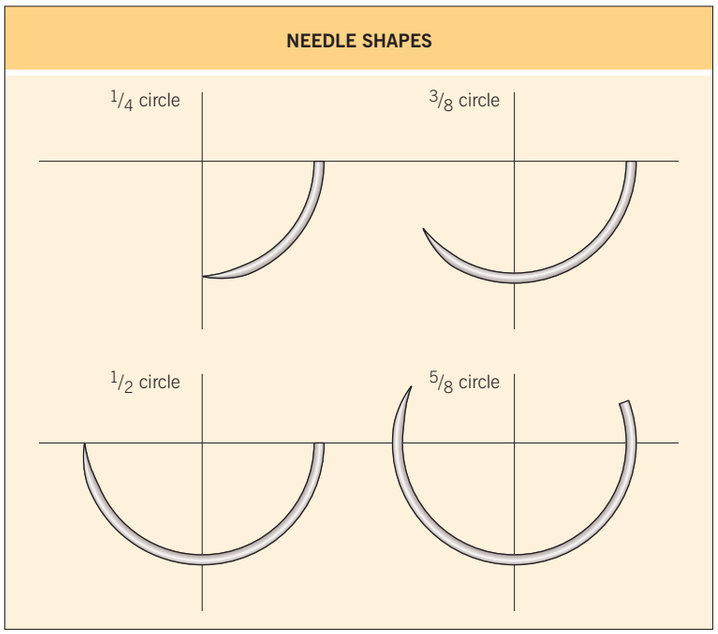


Fig. 144.5 Needle shapes. The most common shape used in skin surgery is the 3/8 circle.

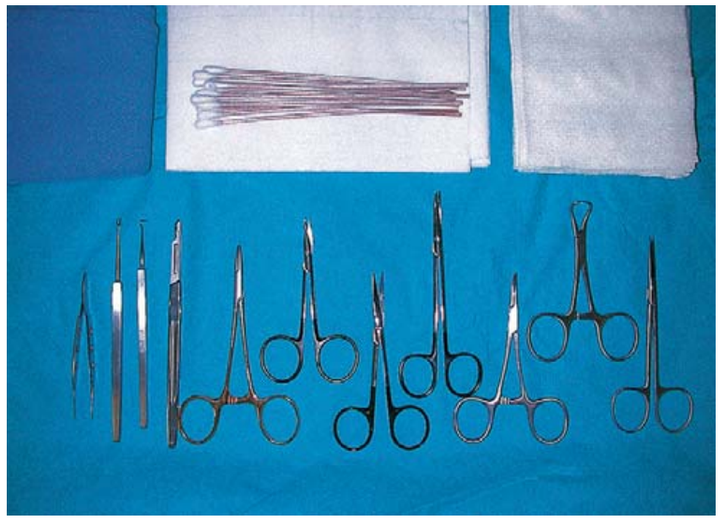


Fig. 144.7 Facial surgery tray or repair tray. Tray setup for facial surgery/repair includes (from left to right) Bishop–Harmon forceps, delicate standard skin hooks, #7 handle with #15 blade, delicate Webster needle holder, Supercut® Gradle scissors, Supercut® curved iris scissors, delicate Supercut® Shea undermining scissors, small hemostat, towel clamp, and suture scissors. *Instruments courtesy of George Tiemann & Company, Hauppauge, NY, USA.*

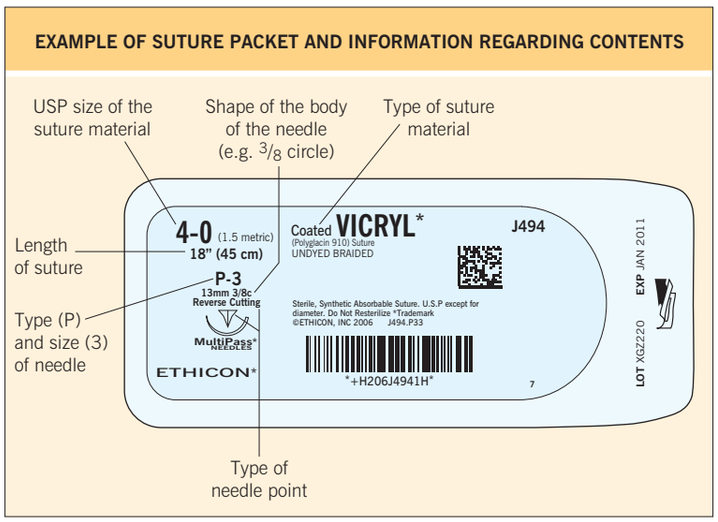


Fig. 144.6 Example of suture packet and information regarding contents.

Fig. 144.8 Trunk or extremity surgery tray. Tray setup for truncal or extremity surgery includes (from left to right) Petri dish, skin hooks, #7 handle with #10 blade, larger Halsey needle holder, Supercut® curved iris scissors, Supercut® baby Metzenbaum undermining scissors, small hemostat, towel clamp, Adson forceps, and suture scissors. *Instruments courtesy of George Tiemann & Company, Hauppauge, NY, USA.*

its cost by performing well day after day in countless procedures. Modern instruments are a blend of surgical stainless steel with carbon alloy, chromium, nickel and tungsten carbide. Tungsten carbide is a very hard alloy that enhances function and durability of blades of scissors and jaws of needle holders. Quality instruments are usually covered by a warranty which will range from 1 to 5 years, depending on the instrument type and cost. The surgeon should work closely with a reputable dealer to collect a set of instruments that best fulfills his or her special needs. It is important to keep instruments in good condition by caring for them properly and keeping them sharp.

Some of the authors' instruments and trays of choice for given procedures are listed and shown in Figures 144.7–144.9.

Biopsy blades

Shave biopsies can be performed using a #15 blade on a disposable handle. However, an economical alternative that allows great precision is a Gillette® blade. The disadvantage of this blade is that two back-to-back blades must be separated and sterilized by office staff. In addition, the blades may snap and present a sharp hazard. A similar, more convenient (but more expensive) alternative is the DermaBlade®, which comes prepackaged and sterilized. The DermaBlade® offers a plastic holder that adds a margin of safety for the operator.

Curettes

The first dermatologic instruments were curettes. Developed in the late 1800s, the dermal curette has been used to treat a wide variety of cutaneous neoplasms, both benign and malignant, and they have changed relatively little over the years. Common curettes have a round head (Fox) or an oval head (Cannon), and they are labeled by size (much like sutures), depending upon the aperture of the head of the curette. For standard curettage and electrodesiccation, a set of curettes ranging from 4.0 or 5.0 down to 1.0 or 2.0 is employed. Curettes must be sharpened periodically. They are used for tumor removal and debulking, and they may allow a surgeon to better define tumor margins prior to excision[46]. Disposable curettes tend to be very sharp and may cut into tissue, and the surgeon must be aware of this potential drawback.

Fig. 144.9 Eyelid tray. Tray setup for eyelid surgery includes (from right to left) topical anesthetic, Teflon® eye shield, Beaver blade setup, Westcott (or Castroviejo) scissors, Bishop–Harmon forceps, and ophthalmic ointment. *Instruments courtesy of George Tiemann & Company, Hauppauge, NY, USA.*

Fig. 144.10 Standard scalpel handles. From top to bottom: Beaver blade handle, #7 handle, and #3 handle. *Instruments courtesy of George Tiemann & Company, Hauppauge, NY, USA.*

Scalpels

The choice of scalpel handle and blade is based on the surgical site and personal preference of the surgeon (Fig. 144.10). Available blade handles are flat, round, or long and thin in shape. The flat, standard #3 handle is the most frequently used handle in dermatologic surgery, and it comes with or without an imprinted ruler. This is a durable, inexpensive handle that is adequate for most cutaneous procedures. Many plastic surgeons prefer the rounded, textured #7 handle and feel that it gives better control and comfort because the cutting angle of the blade may be changed by rolling the handle with the fingers rather than having to use the wrist to accomplish the same task with a flat #3 handle. For small procedures, such as those on the eyelid and/or ear, some surgeons prefer small hexagonal or round knurled blade handles.

The most commonly used blades in dermatologic surgery are #15, #10 and #11. The #15 blade is the most popular blade. It is gently curved and is appropriate for the majority of skin surgery. The #10 blade is a wide blade, similar in shape to the #15 blade, and it is used primarily for larger excisional procedures on sites such as the back. Of note, the sharpest area of a curved blade is the belly, not the tip. The #11 blade is tapered to a sharp point; it is used for stab incisions in incision and drainage procedures, removal of milia, and for "through and through" excision. For small specialty procedures, disposable mini-blades are available for use in conjunction with small hexagonal or round knurled blade handles. Scalpel blades are made of either stainless steel or the sharper, more expensive carbon steel. Disposable scalpels are available, but they are not weighted and are usually less sharp. For operator protection, blade extractors are available.

Fig. 144.11 Standard delicate Webster and Halsey needle holders. *Instruments courtesy of George Tiemann & Company, Hauppauge, NY, USA.*

Needle holders

Needle holders for facial and hand surgery are small and light with narrow, fine jaws, while larger needle holders with wide sturdy jaws are designed for work on the trunk and proximal extremities. The jaws of needle holders are either smooth or serrated. As a general rule, smaller, smooth jaws can accommodate finer needles and suture materials, and larger, serrated jaws accommodate larger needles and sutures. Serrations prevent "twisting" of larger needles (e.g. Ethicon PS-2 and FS-2) during suturing. Smooth jaws are less damaging to fine-caliber needles (e.g. Ethicon P-3) and will not tear smaller sutures (6–0), but suture needles may slip if not grasped carefully. There are now some small needle holders that have delicate serrated jaws. These allow for a good grip on fine needles without damaging the needle. Large needles should not be used with fine needle holders as this may lead to damage to the inserts of these delicate instruments, i.e. a fine needle driver used a single time to suture a large wound on the back may never again function properly.

Because of constant metal-to-metal contact, needle holders must be strong and durable. Alloy inserts of tungsten carbide are used to increase the strength and hardness of the jaws and prolong the life of the needle holder. Carbide inserts are more expensive, but they are typically guaranteed for 5 years. Instruments with tungsten carbide have gold finger handles.

Popular models such as the Webster and Halsey needle holders (Fig. 144.11), which have smooth or delicately serrated jaws and tapered tips, are ideal for small needles and fine suture materials. Use of these instruments for procedures on the trunk will lead to their demise. The Crile–Wood needle holder has a gently tapered blunt tip and is designed to hold larger needles. Baumgartner and Mayo–Hegar holders are durable, strong drivers with serrated jaws, which will stand up to repeated use on the back. The Olsen–Hegar needle holder has suture-cutting scissors behind the jaws and is convenient to use when working alone.

Fig. 144.12 Standard scissors. From left to right: Supercut® Gradle scissors, Supercut® iris scissors, and Supercut® baby Metzenbaum scissors. *Instruments courtesy of George Tiemann & Company, Hauppauge, NY, USA.*

Fig. 144.13 Suture-removal scissors (with groove to grab suture) and forceps. *Instruments courtesy of George Tiemann & Company, Hauppauge, NY, USA.*

Scissors

Surgical scissors are used for cutting skin, undermining, cutting sutures, and removing wound dressings (Fig. 144.12). Scissors may have long or short handles, and the blades are straight or curved and serrated or smooth. The tips may be sharp or blunt. Scissors used in cutaneous surgery can be either completely stainless steel (most popular, least expensive) or have tungsten carbide inserts to strengthen the blades.

Gradle scissors are small, delicate, sharp-tipped, and tapered to a very fine point with a gentle curve[47]. Due to their sharpness and precision, Supercut® Gradle scissors are ideal for removing thin stages during Mohs surgery and for removing skin tags. Gradle scissors must be used with care, and they should never be used to cut sutures. With improper use, they are quickly dulled and the tips are easily malpositioned.

Tissue scissors have relatively short handles and sharp tips. They are available in straight or curved models, with or without the serrations that prevent tissue motion during cutting. Of the various models available, the authors prefer curved Supercut® iris scissors to cut tissue and for sharp dissection. Supercut® iris scissors have the sharpest edge and are easily recognized by their black handles. They are available with smooth edges or one serrated edge. The "razor-like" edge of these scissors makes it possible to cut tissue with a smooth, easy cutting motion.

Westcott and Castroviejo scissors are delicate, spring-loaded tissue scissors with very sharp tips (see Fig. 144.9). The configuration of their handle and spring-loaded action make them ideal for manipulation in small delicate sites, specifically the eyelid. For this reason, they are popular with oculoplastic surgeons. They should only be used for eyelid surgery or they will quickly dull.

Large, less expensive scissors are sufficient for cutting sutures. Tissue scissors should never be used to cut suture material. Specially designed suture-removal scissors with a half-moon hook on the lower blade are available and the small hooked tip easily grasps the loop and prevents accidental sticks (Fig. 144.13). The O'Brien scissors have a short-angled blade that allows for suture cutting with the very tip of the blade so as to avoid digging into the skin.

Undermining scissors are usually blunt-tipped (for safety) and have longer handles (for comfort). They are available in different sizes to accommodate the various anatomic regions in which skin surgery is performed. Baby Metzenbaum scissors have a high handle-to-blade length ratio (see Fig. 144.12), and, with the resultant small blade arc, they have become the most widely used scissor for sharp or blunt undermining. Larger Metzenbaum scissors are ideal for undermining in fascial planes on the scalp, trunk and extremities. Steven's tenotomy scissors and Supercut® Shea undermining scissors are ideal for more superficial, delicate undermining. The tips of these scissors allow for sharp, less traumatic undermining.

The most popular bandage cutting scissors are the 5.5-inch Lister scissors, which have angled blades and large blunt tips that easily slide under a dressing without damaging the underlying skin. The Universal scissor is another popular choice. The serrated edges and larger rings provide greater cutting power.

Forceps

Proper forceps are essential for delicate, safe handling of tissue and suture needles during skin surgery. The most useful forceps in skin surgery are lightweight and have fine tips. The tips may be either toothed (tissue forceps) or serrated (thumb forceps). Serrated forceps can exert excessive pressure on tissues, resulting in crush injury. Toothed forceps have opposing teeth and allow for gentle handling of tissue. The most popular tissue forceps have 1×2 teeth; however, 2×3 and multi-toothed patterns are available. Some forceps have both distal teeth for handling of tissue and a more proximal raised platform for firmly grasping suture needles, allowing the surgeon to avoid manual handling of sharp needles.

Forceps are available with delicate (≤0.6 mm), regular (1–1.5 mm) or heavy (≥1.6 mm) tips. Adson forceps are the standard large forceps used for excisional surgery on the trunk and proximal extremities (see Fig. 144.8). Both the Bishop–Harmon and Foerster forceps are very lightweight, fine-tipped, and ideal for delicate work on the face and hand, where they are our forceps of choice (see Figs 144.7 & 144.9). Because Bishop–Harmon forceps are easily bent and "offset", they must be handled with care, and they should not be used for manipulating the thicker skin of the trunk or proximal extremities.

Both epilating and jewelers' forceps have a fine, sharp point and are useful for suture removal. Splinter forceps have fine, extra-fine or super-fine delicate pointed tips; they are used in hair transplants, for splinter removal, for removing embedded sutures, and for grasping bleeding vessels prior to cautery or electrodesiccation.

Hemostats

Hemostats are used to grasp bleeding vessels prior to ligation. The most popular hemostat is the Halstead Mosquito model, which is available in 3.5-inch and 5-inch lengths, either curved or straight, and either delicate- or regular-tipped.

Skin hooks

Skin hooks enable the surgeon to handle tissue with minimal trauma, and they are particularly useful for elevating flaps and reflecting skin edges during undermining[48]. Many surgeons also use skin hooks to visualize bleeding vessels for hemostasis and for placement of dermal sutures. Since the rise in HIV and hepatitis C viral infections, some

STERILIZATION METHODS		
Method	**Advantages**	**Disadvantages**
Steam autoclave	Most popular in office; easiest; safest	Must use 20–30 min at 2 atm pressure and 121°C; corrosive; may dull sharp instruments
Chemiclave	Lower humidity than steam; less dulling of sharp instruments; instruments are drier	Special chemical needed (mixture of formaldehyde, methyl ethyl ketone, acetone and alcohols)
Dry heat (oven)	Inexpensive; no corrosion or dulling	High temperature, longer time (1 h at 171°C; 6 h at 121°C); cannot use cloth, paper or plastic
Gas sterilization	Good for large volumes (mostly used in hospitals)	Expensive equipment; prolonged times (1 day for paper, 7 days for polyvinyl chloride); toxic and mutagenic gas
Cold sterilization (alcohol, detergent, quaternary ammonium, or more effective glutaraldehyde solutions)	Simple; inexpensive	Irritating to skin; not recommended as only method; not always effective against bacterial spores or hepatitis B virus

Table 144.4 Sterilization methods.

surgeons have abandoned the use of the skin hook in exchange for a fine forceps, hoping to decrease the risk of an accidental stick. With caution, however, skin hooks can be valuable when elevating flaps.

Skin hooks are available in single-, double- or multiple-pronged patterns. The multiple-pronged instruments are referred to as skin rakes; they are used mainly for rhytidectomies and larger truncal procedures in which large flaps or margins of tissue are being elevated and/or undermined. Single-pronged hooks are used most frequently in cutaneous surgery for flap elevation and undermining delicate skin (see Fig. 144.7). The single shepherd hook – which has a more circular shape – holds tissue better than does the single standard hook, but it does not release as easily.

Special Instruments

For delicate work near the eye, the dermatologic surgeon needs fine instruments that allow for precise cutting and carefully controlled tissue manipulation. The Beaver handle (see Fig. 144.10), which comes in a variety of sizes, can be rolled with one's fingertips, providing greater precision and control. Beaver handles are fitted with specialized smaller, sharper blades. The #64 blade has a rounded shape with a blunt tip that one may prefer for work around the eye. The #67 blade is smaller but similar in shape to the standard #15 blade, and the #65 blade is a miniature version of the #11 blade for stab incisions. Beaver blades dull more rapidly than do the standard #15 blades. Angled Beaver blades are useful for taking Mohs stages or biopsies in the external ear canal.

The Castroviejo needle holder is ideal for suturing the delicate skin near the eye or for use by a surgeon with small hands and for whom the rings in the standard needle driver prove cumbersome. This needle holder has spring handles and an optional self-locking device. Castroviejo and Westcott scissors provide precise meticulous control when cutting eyelid skin. Lightweight forceps, such as Bishop–Harmon or Foerster forceps, aid in achieving the delicate handling of tissues necessary in this region. Plastic, Teflon® and metal eye shields can be used when the lid margin will be breached and when cautery will be performed near the eye. Metal eye shields conduct heat and electricity while smooth ones reflect laser beams, which may be a disadvantage. Chalazion clamps are commonly used for immobilizing earlobes, lips, eyelids and tongues during procedures on these areas.

Nail nippers, splitters and elevators are necessary for nail surgery (see Ch. 149). The double-action nail nipper is extremely strong, and it will cut the thickest nails. Nail splitters have a perpendicular, flat second blade that will not damage the nail bed.

Sterilization

A summary of sterilization methods is presented in Table 144.4[49].

REFERENCES

1. Artandi C. A revolution in sutures. Surg Gynecol Obstet. 1980;150:235–6.
2. Snyder CC. On the history of the suture. Plast Reconstr Surg. 1976;58:401–6.
3. Goldenberg I. Catgut, silk and silver. Surgery. 1959;46:908–12.
4. Wangensteen OH, Wangensteen SD, Klinger CF. Wound management of Ambroise Pare and Dominique Larrey, great French military surgeons of the 16th and 19th centuries. Bull Hist Med. 1972;46:207–34.
5. Toledo-Pereyra LH. Galen's contribution to surgery. J Hist Med Allied Sci. 1973;28:357–75.
6. Melle GJ. The history of the ligature. S Afr Med J. 1934;8;290–2.
7. Gudger EW. Stitching wounds with the mandibles of ants and beetles. JAMA. 1925;84:1861–4.
8. Ahmad A, O'Leary JP. Observations on early suture materials: The first stitch in time. Am Surg. 1997; 63:1027–8.
9. Levenson S, Geever EF, Crowley LV, et al. The healing of rat skin wounds. Ann Surg. 1965;161:293–308.
10. Usher FC, Allen JE, Crosthwait RW, Cogan JE. Polypropylene monofilament: a new biologically inert suture for closing contaminated wounds. JAMA. 1962;179:780–2.
11. Bucknall T. Factors influencing wound complications: a clinical and experimental study. Ann R Coll Surg. 1983;65:71–7.
12. Sharp WV, Belden TA, King PH, et al. Suture resistance to infection. Surgery. 1982;91:61–3.
13. Postlethwait RW, Willigan DA, Ulin AW. Human tissue reaction to sutures. Ann Surg. 1975;181:144–50.
14. Alexander JW, Kaplan JZ, Altemeier WA. Role of suture materials in the development of wound infection. Ann Surg. 1967;165:192–9.
15. Molea G, Schonauer F, Bifulco G, et al. Comparative study on biocompatibility and absorption times of three absorbable monofilament suture materials (Polydioxanone, Poliglecaprone 25, Glycomer 631). Br J Plast Surg. 2000;53:137–41.
16. Holmlund DE. Physical properties of surgical suture materials: stress-strain relationship, stress-relaxation and irreversible elongation. Ann Surg. 1976;184:189–93.
17. Herrmann JB. Tensile strength and knot security of surgical suture materials. Am Surg. 1971;37: 209–17.
18. Bennett RG. Selection of wound closure materials. J Am Acad Dermatol. 1988;18:619–37.
19. Garrett AB. Wound closure materials. In: Wheeland R (ed). Cutaneous Surgery. Philadelphia: WB Saunders, 1994:199–205.
20. Jenkins HP, Hrdina LS, Owen FM, et al. Absorption of surgical gut (catgut). III. Duration in the tissue after loss of tensile strength. Arch Surg. 1942;45:74–102.
21. Webster RC, McCollough EG, Giandello PR, et al. Skin wound approximation with new absorbable suture material. Arch Otolaryngol. 1985;111:517–19.
22. Guyuron B, Vaughan C. A comparison of absorbable and non-absorbable suture materials for skin repair. Plast Reconstr Surg. 1991;89:234–6.
23. Postlethwait R. Polyglycolic acid surgical suture. Arch Surg. 1970;101:489–94.
24. Craig PH, Williams JA, Davis KW, et al. A biologic comparison of polyglactin 910 and polyglycolic acid synthetic absorbable sutures. Surg Gynecol Obstet. 1975;141:1–10.
25. Conn J Jr, Oyasu R, Welsh M, et al. Vicryl (polyglactin 910) synthetic absorbable sutures. Am J Surg. 1974;128:19–23.
26. Aston SJ, Rees TD. Vicryl sutures. Aesthetic Plast Surg. 1977;1:289–93.
27. Fosko SW, Heap D. Surgical pearl: an economical means of skin closure with absorbable suture. J Am Acad Dermatol. 1998;39:248–50.
28. Lerwick E. Studies on the efficacy and safety of polydioxanone monofilament absorbable suture. Surg Gynecol Obstet. 1983;156:51–5.
29. Rodeheaver GT, Powell TA, Thacker JG, et al. Mechanical performance of monofilament synthetic absorbable sutures. Am J Surg. 1987;154:544–7.
30. Chantarasak ND, Milner RH. A comparison of scar quality in wounds closed under tension with PGA [Dexon] and polydioxanone [PDS]. Br J Plast Surg. 1989;42:687–91.
31. Katz AR, Mukherjee DP, Kaganov AL, et al. A new synthetic monofilament absorbable suture made from

polytrimethylene carbonate. Surg Gynecol Obstet. 1985;161:213–22.
32. Niessen FB, Spauwen PHM, Kon M. The role of suture material in hypertrophic scar formation: Monocryl vs. Vicryl-rapide. Ann Plast Surg. 1997;39:254–60.
33. Elek SO, Conen PE. The virulence of *Staphylococcus pyogenes* for man. Br J Exp Pathol. 1957;38:573–86.
34. Nilsson T. Mechanical properties of Prolene and Ethilon sutures after three weeks *in vivo*. Scand J Plast Reconstr Surg. 1982;16:11–5.
35. Nilsson T. Mechanical properties of Prolene, Ethilon and surgical steel loops. Scand J Plast Reconstr Surg. 1981;15:111–15.
36. Hartman LA. Intradermal sutures in facial lacerations. Comparative study of clear monofilament nylon and polyglycolic acid. Arch Otolayngol. 1977;103: 542–3.
37. Miller JM, Kimmel LE Jr. Clinical evaluation of monofilament polypropylene suture. Am Surg. 1967;33:666–70.
38. Bang RL, Mustafa MD. Comparative study of skin wound closure with polybutester (Novafil) and polypropylene. J R Coll Surg (Edinb). 1989;34:205–7.
39. Campbell JP, Swanson NA. The use of staples in dermatologic surgery. J Dermatol Surg Oncol. 1982;8:680–90.
40. Rosenzweig LB, Abdelmalek M, Ho J, Hruza GJ. Equal outcomes with 5-0 poliglecaprone-25 versus 6-0 polypropylene for superficial closures. Dermatol Surg. 2010;36:1309–11.
41. Maw JL, Quinn JV, Wells GA, et al. A prospective comparison of octylcyanoacrylate tissue adhesive and suture for the closure of head and neck incisions. J Otolaryngol. 1997;26:26–30.
42. Quinn J, Wells G, Sutcliffe T, et al. A randomized trial comparing octylcyanoacrylate tissue adhesive and sutures in the management of lacerations. JAMA. 1997;277:1527–30.
43. Taube M, Porter RJ, Lord PH. A combination of subcuticular suture and sterile Micropore tape compared with conventional interrupted sutures for skin closure. A controlled trial. Ann R Coll Surg Engl. 1983;65:164–7.
44. Katz KH, Desciak EB, Maloney ME. The optimal application of surgical adhesive tape strips. Dermatol Surg. 1999;25:686–8.
45. Bernstein G. Needle basics. J Dermatol Surg Oncol. 1985;11:1177–8.
46. Johnson TM, Tromovitch TA, Swanson NA. Combined curettage and excision: a treatment method for primary basal cell carcinoma. J Am Acad Dermatol. 1991;24:613–17.
47. Gibbs RC. A love affair with a Gradle scissors. J Dermatol Surg Oncol. 1981;7:771.
48. Boyer JD, Zitelli JA, Brodland DG. Undermining in cutaneous surgery. Dermatol Surg. 2001;27: 75–8.
49. Sebben JE. Sterilization and care of surgical instruments and supplies. J Am Acad Dermatol. 1984;11: 381–92.

This page intentionally left blank

145 Dressings

Gregg M Menaker, Stephanie L Mehlis and Sarah Kasprowicz

Chapter Contents

The history of dressings ... 2365
The functions of a wound dressing ... 2365
Moist healing environment ... 2365
The role of oxygen ... 2366
Traditional wound dressings ... 2366
First and second intention healing ... 2367
Dressings that contain antimicrobial agents ... 2368
Absorptive and paste dressings ... 2368
Occlusive dressings ... 2369
Wound therapy – supplemental treatments ... 2373
Tissue-engineered skin equivalents ... 2374

Key features

- Dressings should provide the optimum environment for rapid healing by protecting the wound from further trauma or bacterial invasion
- Dressings that provide a moist environment and prevent eschar formation allow wounds to re-epithelialize and heal faster than if left uncovered
- Semipermeable or occlusive dressings provide a moist environment, retain wound fluid that contains growth factors conducive to healing, and promote a low tissue oxygen tension that stimulates angiogenesis and deposition of collagen
- A traditional layered dressing consists of a non-adherent contact layer, an absorbent contouring layer and a securing layer
- Advanced technology dressings include the following types: hydrogels, alginates, foams, films and hydrocolloids
- More recently, tissue-engineered composite skin equivalents have been developed, combining living keratinocytes and fibroblasts from human foreskins with bovine collagen

INTRODUCTION

The variety of cutaneous surgical procedures performed by dermatologists, as well as the types of wounds they manage clinically, require dressing materials and techniques that address the specific needs of the injury. In addition to the care of surgical incision sites such as those created by any surgeon, the dermatologist's armamentarium often extends into the care of poorly healing and chronic wounds. The choice of treatment modalities is indeed substantial and ever-expanding, giving dermatologists flexibility in wound care strategy.

THE HISTORY OF DRESSINGS

The practice of using dressings dates back thousands of years. The use of fabrics such as linen on wounds continued for at least 4000 years until woven absorbent cotton gauze was introduced in 1871. The Edwin Smith Surgical Papyrus, which is one of the earliest medical treatises (dating back to 1615 BC), describes the use of linen strips and plaster to dress wounds, stating that closed wounds would heal more quickly than open wounds[1]. Ancient documents disclose how lint was used to pack and fill open wounds and how bandages were used to re-approximate wounds in order to facilitate healing. Linen strips were sometimes coated with grease or oil to prevent adherence to wounds or with honey to create a semi-occlusive and adherent dressing[2].

Lister connected the presence of pus with infections. However, this association became linked such that it was held that one is always indicative of the other, which is not always true. It is this link that interfered with the acceptance of occlusive dressings, as well as with progress in the study of their value. Although the work of Pasteur, Koch and Lister in the late 1800s on the cause of bacterial infections spurred the investigation of specific therapies for wound management, it was not until the mid-1900s that the understanding of wound healing completely changed. Until that time, it was firmly believed that wounds healed more quickly if they were kept dry and uncovered.

In 1948, Oscar Gilje described a "moist chamber effect" for healing ulcers[3]. Two years later, Schilling and colleagues published a study in which the treatment of common minor wounds with highly occlusive or semi-occlusive nylon films was evaluated. They found semi-occlusive dressings to be more effective for healing than open treatment. The fact that the semi-occlusive dressing proved to be more effective than the highly occlusive dressing is said to have set back this area of study. In 1962, George Winter conducted what is considered to be the landmark study on moist wound healing, demonstrating a 30% greater benefit of occlusive dressings versus air drying of wounds[4]. Many studies conducted since Winter's work have contributed to the concept of the benefits of moist wound healing by occlusive dressings.

THE FUNCTIONS OF A WOUND DRESSING

A wound dressing is a substitute for native epithelium lost as a result of injury. The process of wound repair occurs in stages (see Ch. 141), each of which may require different dressings. An ideal wound dressing would have many features (Table 145.1). However, the main function of a dressing is to provide the optimal environment for rapid healing by protecting the wound from further trauma, bacterial invasion or exposure to caustic substances, which is especially important during the early acute, inflammatory stage. The composition of the dressing is also an important consideration. It should be composed of inert material that does not shed fibers or compounds into the wound that could lead to a foreign body reaction or an irritant or allergic reaction[5]. The "ideal" dressing that meets all these requirements for every wound type does not yet exist (Table 145.2). However, in the vast array of dressings available, it is quite possible to select or fashion one for achieving one's goal.

MOIST HEALING ENVIRONMENT

A wound dressing's capacity to maintain a moist environment is of prime importance in healing (Fig. 145.1). There are several mechanisms by which moisture assists the reparative process, the most basic of which is the suppression of tissue desiccation and crust formation. A "scab" or eschar forms as a result of the drying of a wound, particularly of the superficial dermis which itself becomes integrated into the scab. The studies of Winter and Scales illustrated that uncovered, air-dried wounds developed thicker scabs and re-epithelialized at a slower rate. This slower rate has been attributed to the requirement of the regenerating epidermis to migrate deeper below the dry fibrous tissue to a region of moisture where live cells survive. It is only in such an

environment that epidermal cells can move toward bridging the defect of the wound; therefore, the thicker the scab, the deeper the migration. This, along with the continuing loss of dermis and collagen and a reduction in adnexal structures, contributes to the depth of the scars and a worse cosmetic outcome[1].

Many endogenous factors that are critical to wound healing (e.g. fibrin degradation products, platelet-derived growth factor) are found in fluid from occluded (or dressed) acute cutaneous wounds and may be more available in a moist environment (see Ch. 141). Another possible value of a moist wound environment may be its ability to confer an electrical gradient between the wound and normal skin. That is, upon injury of skin, an internal battery and a current flow are created until drying of the wound occurs. It is thought that in maintaining moisture, this electrical gradient may promote epidermal cell migration between the wound and surrounding skin[6].

THE ROLE OF OXYGEN

For many years, it was believed that oxygen availability was of primary importance in the rate of healing. However, subsequent studies have shown that the oxygen requirement is initially low during the early wound repair stages. After acute injury, wounds experience a temporary but extreme hypoxia due to disruption of blood flow from clotting that prevents exsanguination. This distress is the signal for migration of keratinocytes and fibroblasts as well as the initiation of angiogenesis. Hypoxia has been shown to upregulate proliferation and production of transforming growth factor (TGF)-β by dermal fibroblasts; TGF-β is known to stimulate production of extracellular matrix molecules. Under hypoxic conditions, keratinocytes migrate better along collagen and fibronectin, and low oxygen levels also promote angiogenesis in the acute wound[7]. The use of a semipermeable dressing can provide the appropriate oxygen tension for wound repair to proceed quickly.

In summary, *acute* wounds that heal under occlusion have demonstrated accelerated healing, greater resistance to breaking open, and better cosmetic outcomes than those that heal open to the air. Also, as a result of occlusion, *chronic* wounds are often less painful (particularly upon wound debridement) and they have better formation of granulation tissue.

TRADITIONAL WOUND DRESSINGS

Wound dressings can be categorized either by the composition and structure of the dressing or by the dressing technique and how the dressing is utilized relative to the wound. Traditional or conventional dressings have commonly been made of natural, synthetic or partially synthetic materials[1]. Readily available and inexpensive traditional wound dressings include Band-Aids® and Telfa® pads, while multilayered Exu-dry® dressings are more costly.

Naturally occurring materials such as cotton, silk, linen or cellulose-based substances have a long history of use and have been produced in various combinations for maximal clinical usefulness. Bleached cotton is processed into balls or fibers which are woven into gauze pads, packing strips, wrapping strips, knitted tubes and compressed felt.

The basic cotton gauze dressing in use today is frequently composed of cotton plus cellulose acetate (added for increased absorbency) and is

FEATURES OF AN IDEAL WOUND DRESSING
Protects the wound from further trauma
Protects the wound from bacterial invasion or exposure to caustic substances
Conforms to the shape of the wound
Absorbs wound fluid without increasing bacterial proliferation or causing excessive desiccation
Provides pressure for hemostasis
Prevents leakage from the bandage
Supports the wound and surrounding tissues
Eliminates pain
Promotes re-epithelialization during the reparative phase
Can be easily applied and removed with minimal injury to the wound
Composed of an inert material

Table 145.1 Features of an ideal wound dressing.

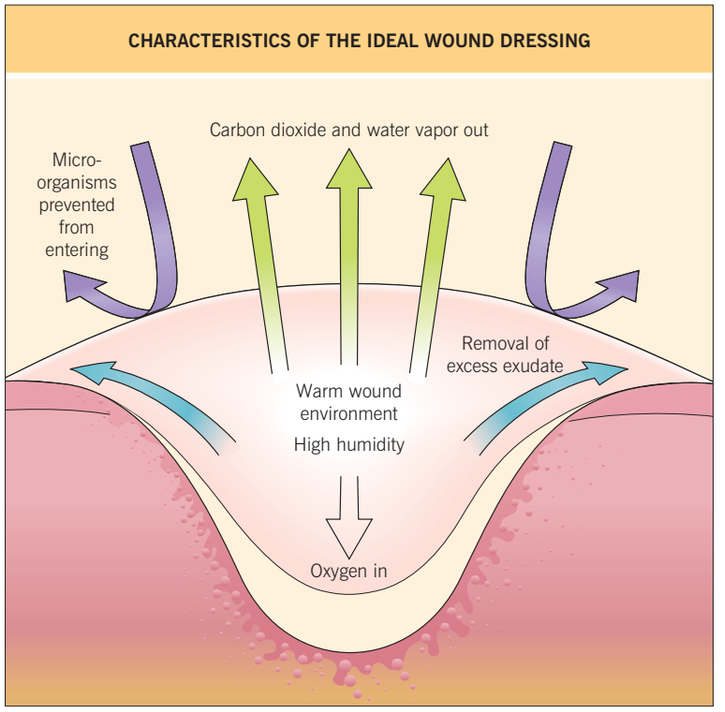


Fig. 145.1 Characteristics of the ideal wound dressing.

COMPARISON OF THE IDEAL DRESSING VERSUS OCCLUSIVE DRESSINGS AND SKIN SUBSTITUTES										
	Characteristics of an ideal dressing									
	Conforms	Absorbs wound fluid	Decreases bacterial proliferation	Provides pressure	Supports surrounding tissue	Eliminates pain	Promotes re-epithelialization	Easily reapplied	Inert material	Does not shed fibers or compounds into the wound
Films						+	+		+	+
Foams	+	++		+		+	+	+	+	
Hydrogels	++	+				++	+	+	+	+
Alginates	++	++	+				+	+		
Hydrocolloids	+	++		+		+	+	+	+	
Epidermal grafts						+	++			+
Dermal grafts					+	+	++	+		+
Composite grafts					+	+	++			+

Table 145.2 Comparison of the ideal dressing versus occlusive dressings and skin substitutes (i.e. ideal dressing versus reality).

manufactured with or without various substances incorporated into the fabric. White petrolatum and other ointments such as soft paraffin wax (e.g. Vaseline™ gauze, Aquaphor® gauze, Adaptic®), with or without antibacterials such as povidone-iodine (Betadine®), sulfadiazine, bismuth tribromophenate (Xeroform®), framycetin and chlorhexidine, are examples of impregnated substances. Balsam of Peru is found in the tulle gras used predominantly in Western Europe. These medicated dressings are often composites of rayon, nylon or gauze, and are used for malodorous wounds such as chronic ulcers. Activated charcoal cloth (with or without antibacterial silver salt) is also used for exudate absorption plus odor control.

These types of dressings are placed directly against the wound bed and have the advantage of having less chance of adhering to the wound as well as the ability to mold into the depression of deeper wounds for the purpose of filling dead space and providing absorption. The disadvantage of this type of dressing is the potential for maceration of the wound and surrounding skin should the dressing remain in place for an extended period of time. Other pros and cons of traditional dressings are that although relatively inexpensive and readily available, they do require frequent replacement, which is time-consuming for the medical staff and the patient and is potentially costly in healthcare personnel time[8].

The technique used for most conventional dressings is that of the "layered dressing" and it is either a "pressure" or "non-pressure" dressing. A layered dressing is usually constructed in three parts (Fig. 145.2): (1) the contact or interface layer, which is usually a non-adherent, fluid-permeable material that makes direct contact with the wound; (2) the absorbent layer, usually a cotton pad, gauze or other such material, which is placed on top of the contact layer to "wick in" and retain wound exudate and help the dressing mold to the shape of the wound; and (3) the outer layer or wrap, often tape or other banding material for retention of the underlying layers. Of note, each layer should be placed in close approximation to the one before it, with no gaps or air pockets, and should increase in size and degree of overlap, from wound bed to outermost layer.

A "pressure" dressing has more bulk added to the absorbent layer and is arranged so as to create hemostasis at the wound site. Usually applied immediately after surgery and changed to a lighter dressing within 24 hours, the body sites for this type of dressing are most often digits, extremities and the scalp. In addition to limiting bleeding, the pressure dressing also minimizes edema and lends support to the surrounding tissue. It is important to be aware of the amount of pressure exerted upon the wound bed so as not to create localized ischemia, potentially resulting in tissue necrosis[9].

FIRST AND SECOND INTENTION HEALING

Postsurgical skin wound defects healing by first intention are those that are clean, free of debris and sutured by aseptic technique. Placing sutures postsurgically provides hemostasis, reduces the possibility of wound infection (which may potentiate a delay in healing and chance of dehiscence), and usually improves the ultimate cosmetic result (see Fig 145.2A). After suture removal, the use of external splinting tape (such as Steri-Strips™) supports the tissues, enabling favorable collagen remodeling that may limit scar formation and hypertrophy.

Second intention healing is often employed following many cutaneous surgical techniques such as punch biopsy, cryosurgery, laser surgery, excision (Fig. 145.3) and curettage. In such cases, moisture at the wound bed is the key to optimal spontaneous healing. A semi-occlusive dressing is the treatment of choice, with the topical application of ointment directly on the wound. Monitoring of the wound, as it progresses

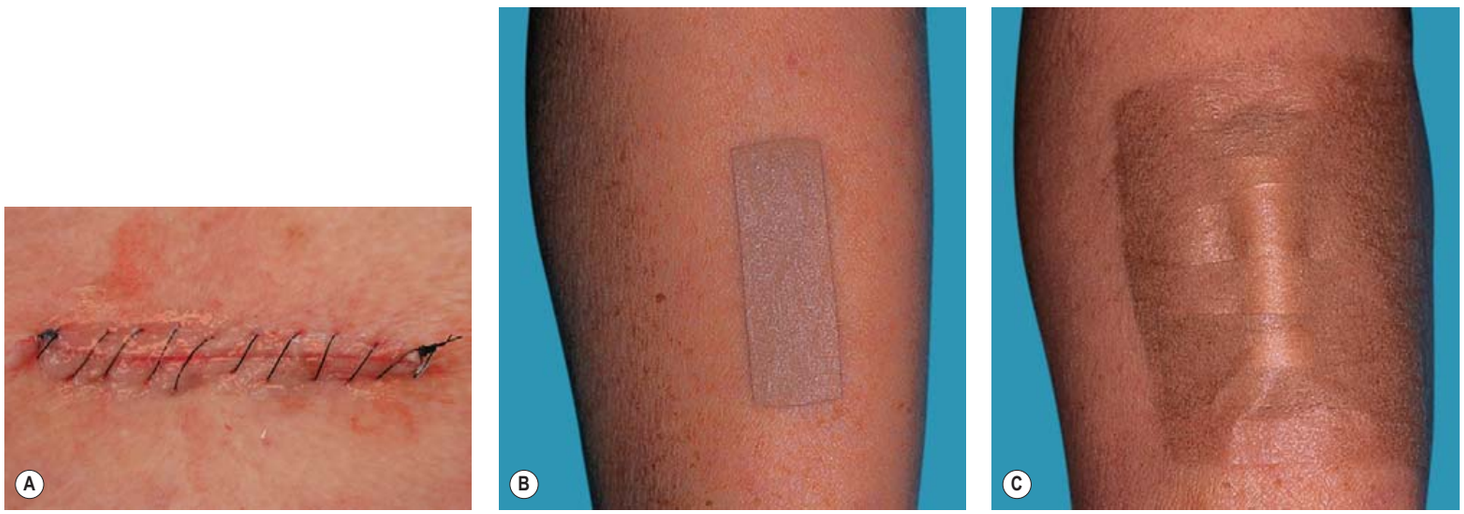


Fig. 145.2 Pressure dressing. A Antibiotic ointment applied over sutures helps to prevent infection and prevents the contact layer from adhering directly to the wound. **B** Three layers of paper tape comprise the contact layer. **C** Rolled gauze or a cotton dental roll can be used to: (i) provide pressure for hemostasis; (ii) aid in conforming the dressing to the wound; and (iii) absorb excess exudate. The entire dressing is secured with additional layers of tape.

Fig. 145.3 Second intention healing. A Surgical wound immediately following Mohs micrographic surgery; a semi-occlusive dressing will be used. **B** Wound healing by second intention 3 weeks following surgery. Note abundance of pink granulation tissue. **C** Fully re-epithelialized wound 6 weeks following surgery.

through stages of healing, for signs of infection and prevention of drying of the wound bed until re-epithelialization has occurred is usually sufficient in the management of this type of surgical wound[10].

DRESSINGS THAT CONTAIN ANTIMICROBIAL AGENTS

The usefulness of topical antimicrobial agents for cutaneous wounds is a matter of debate. It is thought by some that a clean wound created with good aseptic technique does not require a topical antimicrobial, as long as the wound is well cared for in the postsurgical period. Also, while it is well known that infection prolongs wound healing, a distinction must be made between bacterial colonization of the wound and true infection that leads to tissue compromise. Lastly, chronic wounds treated with the most commonly used topical antibiotic preparations often require repeated, sometimes painful, dressing changes.

There are, however, more sophisticated methods of providing bacterial control of wounds. For example, a number of dressings include compounds such as silver and iodine that attempt to control infection (Table 145.3). Silver is an ion that has been used for decades for treating wound infections owing to its strong antimicrobial activity. Silver ions kill microorganisms by inhibiting bacterial-specific enzymes important in bacterial cell wall synthesis and gene transcription. Studies have shown that silver-containing dressings can significantly reduce burn wound-associated sepsis and bacteremia as well as shorten hospitalization time. In addition, silver ions appear to decrease the levels of matrix metalloproteinases that are upregulated in non-healing, chronic wounds.

In older silver-containing dressings, the silver ions were present in the form of silver nitrate ($AgNO_3$) and silver sulfadiazine. However, newer formulations consist of high-density polyethylene mesh impregnated with nanocrystalline silver. Examples of nanocrystalline silver dressings include Acticoat™, Actisorb® Silver (Fig. 145.4), Contreet® Foam, Contreet® Hydrocolloid and Silverlon®. They offer broad-spectrum antibiotic activity against both Gram-positive (including methicillin-resistant *Staphylococcus aureus* [MRSA]) and Gram-negative pathogens[11]. These dressings can release antibacterial levels of silver for 3 to 7 days. A recent meta-analysis found that silver-impregnated dressings may improve the short-term healing of wounds and ulcers, but how these agents affect long-term wound care is still unclear[12].

For over 150 years, iodines have been used to aid wound healing[13]. However, povidone-iodine, a commonly used antiseptic, can actually inhibit wound healing. In contrast, newer formulations – such as cadexomer-iodine polymer, which slowly releases iodine from dextran beads – have not demonstrated toxic effects on keratinocytes. The level of iodine that is slowly released from the beads is sufficiently low so as to confer antimicrobial activity, but with little or no cytotoxic effects; the gel that results from the process then works to absorb exudate. Bacteria and cellular debris become trapped in the spaces between the beads and are removed with irrigation at the time of dressing changes. Recommended for exudative wounds such as leg ulcers, a layer of beads is applied to the wound and covered with a pad or other suitable secondary dressing. The frequency of dressing changes is determined by the nature of the wound, perhaps requiring daily changes (if the beads are saturated) reducing to three times per week as the healing progresses[7]. Studies have shown a significant decrease in ulcer size with cadexomer-iodine when compared to hydrocolloid and paraffin gauze dressings[14].

Cadexomer-iodine is also found in multiple types of occlusive dressings (see next section), including hydrogels (e.g. Iodoflex®). Because the iodine is absorbed, caution must be taken when using these dressings in patients with a history of thyroid disease. They should not be used in young children, pregnant or lactating women, or patients with a known or suspected iodine sensitivity.

Fig. 145.4 Activated charcoal cloth impregnated with silver (Actisorb® Silver 220). The envelope is spun bonded nylon.

ABSORPTIVE AND PASTE DRESSINGS

Medicated paste bandages can be used alone or underneath graduated compression dressings, especially on the lower extremities. In addition, they are used to treat the chronic dermatitis associated with leg ulcers, by creating an absorptive, protective, contact layer against the wound surface and surrounding skin. These open-weave, cotton bandages are impregnated with zinc paste, calamine or ichthammol, all of which have a soothing action on irritated skin; coal tar, which has an

DRESSINGS THAT CONTAIN ANTIMICROBIAL AGENTS

Antimicrobial agent	Examples of dressings	Coverage spectrum	Advantages	Disadvantages
Silver	Acticoat™ (A or N), Actisorb® Silver 220, Algicell® (alginate), Aquacel® Ag, Contreet® Foam, Contreet® Hydrocolloid, Silvercel®, SilvaSorb®, Silverlon®	Broad-spectrum antibacterial, including MRSA and VRE	Release antibacterial levels of silver for 3–7 days Appear to decrease the levels of matrix metalloproteinases that are up-regulated in non-healing, chronic wounds Microbial resistance is rare Variety of products available for different wound situations Infrequent application required	Levels of silver absorption are not well-defined Silver may stain tissues Relatively expensive
Iodine				
• Povidone-iodine	Inadine®; Betadine® cream applied to gauze	Broad-spectrum antimicrobial – bacteria, fungi, viruses	Less irritating to skin than iodine alone	May cause stinging and local irritation May inhibit wound healing
• Cadexomer-iodine	Iodosorb®, Iodoflex®	Broad-spectrum (see above)	Less irritating to skin than iodine alone	May cause stinging and local irritation

*Not to be used in young children, pregnant or lactating women, or individuals with a known iodine sensitivity; to be used cautiously in patients with thyroid disorders.

Table 145.3 Dressings that contain antimicrobial agents. MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci.

anti-inflammatory effect; or clioquinol, which has deodorizing and antibacterial actions (plus some type of preservative). There are also commercially available preservative-free zinc oxide formulas as well as combinations of zinc oxide with each of the above components and calamine–clioquinol combinations.

Examples

Calaband® (ZnO, calamine); Ichthaband® (zinc paste, ichthammol); Quinaband® (ZnO, clioquinol, calamine); Steripaste® (ZnO; preservative-free); Tarband® (ZnO, coal tar); Viscopaste™ PB7 (ZnO); and Zincaband® (ZnO).

OCCLUSIVE DRESSINGS

Occlusive dressings are a separate category of dressings, commonly divided into five major groups: films, foams, hydrogels, alginates and hydrocolloids (Table 145.4 & Fig. 145.5).

Polymer Films

Polymer films are thin, elastic, transparent sheets of polyurethane or other synthetic semipermeable, self-adhesive, polymer dressing (Fig. 145.6). This dressing is gas-permeable, allowing for the exchange of oxygen, carbon dioxide and water vapor, but impermeable to larger molecule efflux, due to its pore size. Therefore, bacteria and the proteins and water of wound fluids are prevented from moving across the dressing. Its permeability to water vapor allows for the release of insensible water and for sweat from the skin to vaporize. This provides the potential advantage of preventing maceration of the wound and its surrounding skin. The semi-occlusive nature of this dressing allows for passage of oxygen to the wound, which had been considered to be an important feature when these dressings were initially introduced. There has been evidence since then, however, that low pO_2 levels (similar to those that actually exist under the dressings) facilitate healing.

Uses

Although polymer film dressings may theoretically be used on any uncontaminated wound, they are most commonly used to cover intravenous catheter sites and sites of partial-thickness wounds such as skin tears, superficial decubitus ulcers, split-thickness graft donor sites, burns, laser wounds, dermabrasion, and Mohs surgery defects[15]. They are also useful for holding pinch grafts in place for venous ulcer treatment. As the dressing allows for the visual monitoring of the wound, it may be used to keep a graft in place until engraftment. A film dressing can also be used as a "splint" to hold a thin split-thickness graft stiff as it is being harvested from the donor site. The harvested skin graft is prevented from folding or wrinkling by the attached film as it is sutured into place at the recipient site. An additional piece of film may be used to secure the graft instead of using sutures[16].

Examples

Bioclusive™ (Johnson & Johnson); Mefilm® (Mölnlycke); Opsite™ (Smith & Nephew); Polyskin® II (Kendall); ProCyte Transparent Film Dressing (Bard Medical); Silon-TSR® (Bio Med Sciences); and Tegaderm™ Transparent Film Dressing (3M).

Advantages/disadvantages

The advantages of this type of dressing are: its translucency, thereby allowing direct visualization of the wound without removal of the

OCCLUSIVE DRESSINGS

Dressing type	Composition	Permeability	Indicated uses	Advantages	Disadvantages
Films	Thin polyurethane sheet	Semipermeable	Intravenous sites Skin tears Split-thickness graft donor sites Laser resurfacing Mohs surgery defects	Translucent Permeable to water vapor Tends to reduce postoperative pain Creates bacterial barrier	Difficult to position properly May adhere to wound as it dries Possible exudate accumulation Non-absorbent
Foams	Bilaminate polyurethane or silicone	Semipermeable	Chronic wounds Dermabrasion Burns Mohs surgery defects Laser resurfacing	Absorbent Permeable to water vapor Conforms to wound shape Thermally insulates Comfortable	Opaque Cannot be used on dry wounds Possible undesirable drying effect on inadequately exudative wounds
Hydrogels	Hydrophilic polymer sheets, gel and impregnated dressings	Semipermeable with outer membrane in place	Ulcers Dermabrasion Laser resurfacing Superficial thermal burns Chemical peels Graft donor sites	Semitransparent Donates fluid to necrotic tissue Soothing, cushioning and cooling effect, reduction of postoperative pain Available in sheets, powdered or pre-mixed amorphous gels Low trauma at dressing changes Reportedly helpful for pruritus	No spontaneous sucking ability Absorption is slow Requires secondary dressing Caution in infected wounds
Alginates	Seaweed-based complex polysaccharide	Semipermeable	Chronic highly exudative wounds Full-thickness burns Surgical wounds Split-thickness graft donor sites Mohs surgery defects	Highly absorbent with spontaneous sucking ability Hemostatic properties Non-adherent Conforms to wound shape Soluble for low trauma dressing changes with normal saline No reports of toxicity Useful in infected wounds	Requires a secondary dressing to prevent desiccation Gel has unpleasant appearance and odor Mild burning sometimes reported upon application
Hydrocolloids	Starch or plastic woven polymer, dextran, polyethylene glycol, water	Semipermeable	Chronic ulcers Burns Trauma wounds Surgery wounds Dermabrasion Bullous disorders Inflammatory disorders (e.g. lichen simplex chronicus)	Capillary action facilitates debris removal Conforms to wound shape Directly adheres to wound site and is easy to use Increased patient comfort Thermal insulation	Risk of maceration of surrounding skin Possible wound trauma with dressing change Gel has unpleasant appearance and odor Opaque Caution in infected wounds

Table 145.4 Occlusive dressings.

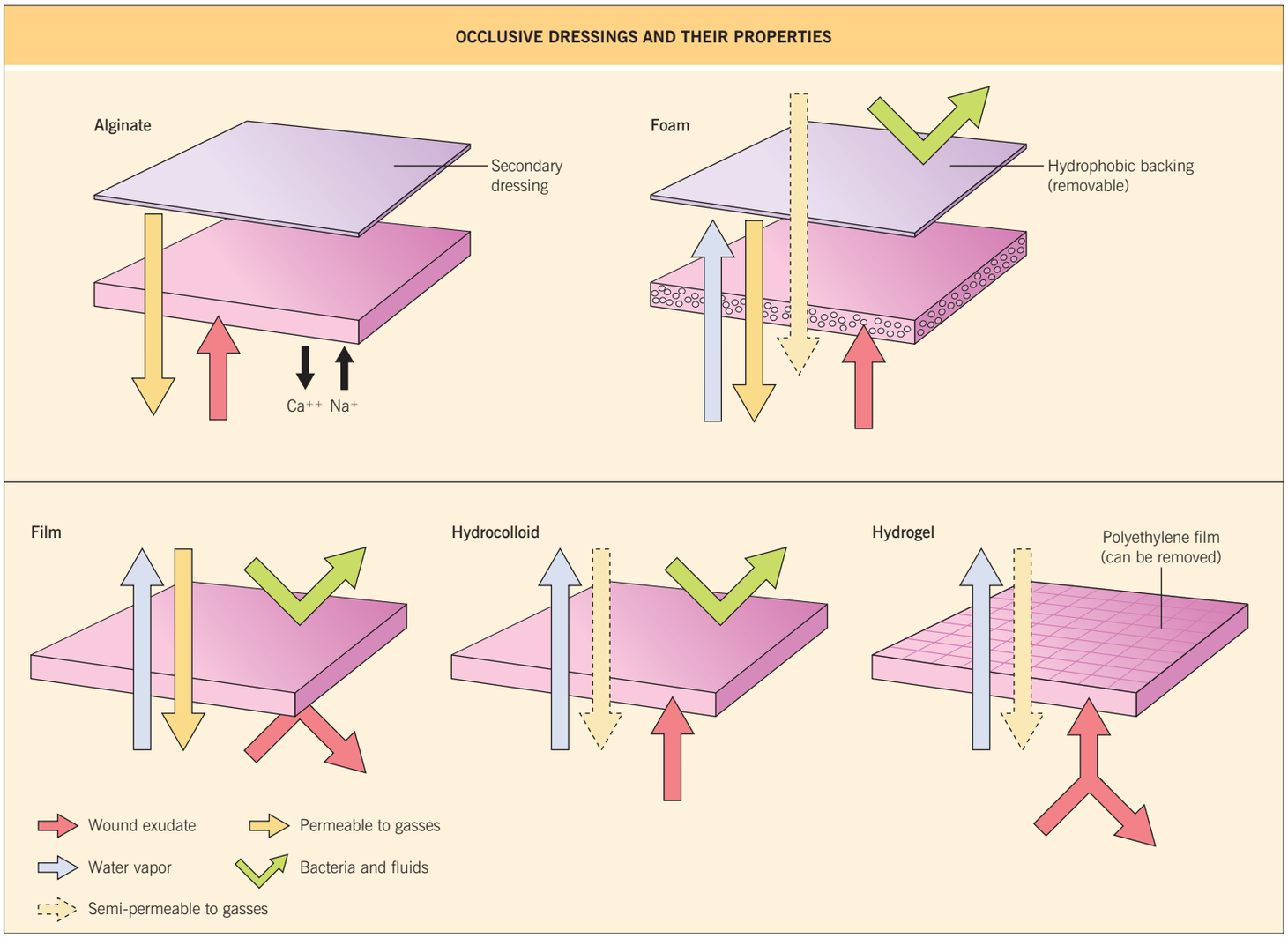


Fig. 145.5 Occlusive dressings and their properties. The five major dressings are polymer films, polymer foams, hydrogels, alginates and hydrocolloids.

Fig. 145.6 A polymer film is used to occlude a wound that has been covered by cotton gauze.

dressing; its permeability to water vapor; and its tendency to reduce postoperative pain. It is also thought to enhance re-epithelialization of graft donor sites, with a reported increase in healing rates of 25–45%[17]. One disadvantage of film dressings is that they are difficult to place properly, requiring uniform tension on the film to prevent wrinkling and its adhering to itself. As the film usually only adheres to intact skin, a 1–2 cm application margin is recommended. Films may also adhere to the wound as drying progresses, thereby risking disruption or stripping of the newly formed epithelium which is not yet tightly bound to the underlying dermal layer. It is possible also to traumatize newly grafted skin tissue during dressing changes. For these reasons, it is advised to allow the film dressing to remain in place until it spontaneously falls off, which can occur after 1–2 weeks.

There are several film dressings, however, that have no adhesive at all or have an adhesive-free zone. Examples of such dressings are Blister Film® (which is composed of polyester rather than polyurethane) and Omniderm®. A dressing with no adhesive maintains contact with the wound via the surface tension created by the fluid layer of the wound. This type of product has been reported to promote wound healing without toxic effects to the underlying tissue[18]. However, any wrinkling of the film during placement can create a conduit for bacterial penetration and for leakage of wound exudative fluid. It is therefore recommended that the film be placed over the wound with a complete 2–3 cm adhesion margin to prevent this leakage.

Another disadvantage of film dressings is that they are non-absorbent; therefore, wound fluid can accumulate under the dressing layer, especially with highly exudative wounds. This is often the case during the first 7–10 days after the creation of a wound. Exudate accumulation does not adversely affect wound healing; in fact, in a study by Buchan et al.[19] it was shown to have significant bactericidal activity. This aside, fluid can leak out, necessitating frequent changing of the dressing for comfort and appearance sake. Because the adherent characteristic of film dressings makes frequent changing undesirable (especially for

certain types of wounds), a 27- or 30-gauge needle can be used to puncture the film for the purpose of aspirating the exudate. This is followed by placement of another piece of the same film to reseal the wound site. Another method employs the placement of butterfly tubing as a drain under the film dressing, with the needle inserted into a Vacutainer® for aspiration.

Numerous studies regarding the proliferation of bacteria under occlusive dressings have documented significant increases in bacterial growth. In such studies, significant increases in bacterial populations, with a shift toward Gram-negative organisms, have been noted and documented[20]. The elevated bacterial counts, however, have not correlated with an increased rate of infection.

Polymer Foams

Polymer foam dressings are semi-occlusive, bilaminate, and polyurethane- or silicone-based. They consist of a hydrophilic foam with a hydrophobic backing, which can prevent leakage, provide a barrier against bacterial penetration, and provide the moist environment afforded by films but with the addition of some absorbency (Fig. 145.7). The inner layer is composed of an absorbent, gas-permeable polyurethane foam mesh, which lies adjacent to the wound. The outer layer is a semipermeable, non-absorbent membrane composed of polyurethane, polyester, silicone or Gore-Tex®, surrounded by a polyoxyethylene glycol foam. This layer protects against outside bacterial contamination to some extent and against the drying out of the underlying layers.

Foam dressings are typically non-adherent, thereby requiring secondary dressing layers to ensure secure placement with a good seal. The quality of the seal is important to prevent leakage, desiccation and problems with adherence. There are, however, some foams available with an adhesive surface, usually surrounding a central absorptive core. Ideally, once a foam dressing has absorbed some amount of exudate, it should be able to retain that fluid, even if exposed to pressure. Some brands are described as having that quality.

Uses

They have been used for: wounds from Mohs surgery, surgical incisions, dermabrasion and burns; chronic wounds such as diabetic ulcers, venous ulcers and pressure ulcers (stages I, II and III); and deep cavity wounds refractory to other methods[21]. They have also gained popularity for use after laser resurfacing, as they greatly reduce postprocedure discomfort and simplify wound care.

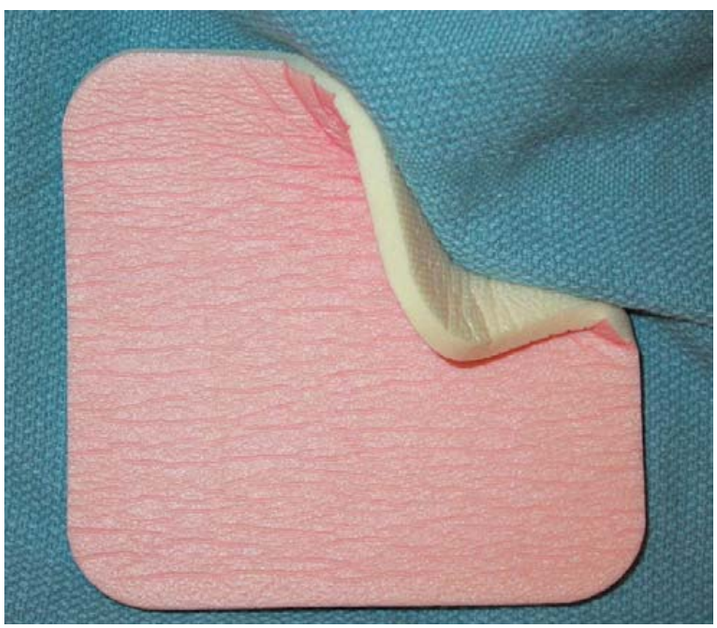


Fig. 145.7 Example of a polymer foam. It consists of a hydrophilic foam with a hydrophobic backing.

Examples

Adherent and non-adherent: Allevyn™ (Smith & Nephew); Biatain™ (Coloplast); Curafoam™ and Hydrosorb® (Kendall); Flexzan® (Bertek); Lyofoam® (Convatec); Mepilex® (Mölnlycke); Optifoam® (Medline); Reston™ (3M); and Sof-Foam™ (Johnson & Johnson).

Advantages/disadvantages

Although very absorbent, there is a limit to the amount of wound exudate this type of dressing can absorb. Therefore, it should be changed every 1–3 days. The permeability of foams to both gas and water vapor makes them suitable for mild to moderately exudative wounds, although there are brands designed for heavily exudative wounds.

Silicone-based rubber foams, known as silastic foams, are composed of a silicone mixture to which a stannous octoate catalyst has been added. This type molds and contours to the shape of the wound and therefore can be used for packing cavities or deep ulcers such as pilonidal sinuses. The additional advantages are absorbency, non-adherence, increased comfort for the patient, a tendency to be less expensive, and dressing changes that do not generally require skilled nursing care[22].

The disadvantages of foam dressings are the inability to use them with dry wounds, their opacity, which prevents visual monitoring of the wound, and the need for frequent changing, perhaps as often as every day. Infrequent changing could risk incorporation of the dressing material into the wound itself. There is also the possibility of an undesirable drying effect of the wound if drainage is insufficient to maintain a moist environment.

Hydrogels

As their name implies, hydrogels are composed primarily of water – up to 96% of the content. This dressing type consists of a cross-linked hydrophilic polymer network composed of polyvinyl alcohol, polyacrylamides, polyethylene oxide or polyvinyl pyrrolidone; it is produced as sheets (Fig. 145.8), amorphous gels (pre-mixed or dry), or as impregnated dressings. Hydrogels are semitransparent (allowing visual inspection of the wound), have a high absorptive capacity (between 100% and 200% of their volume), and are able to maintain a moist wound environment. However, this absorptive action is delayed in its onset and increases slowly as it provides for continuous, long-term absorption. Hydrogels are described as semi-adherent or completely non-adherent, depending upon the subtype, and therefore require a secondary dressing to hold them in place[23]. The latter is necessary as hydrogels are poor bacterial barriers and selectively permit Gram-negative organisms to proliferate. For this reason, antibiotic ointment is often applied prior to the application of the dressing[24]. Hydrogels are soothing and actually lower the temperature of cutaneous wounds, a cooling effect that can be augmented by refrigerating the dressing prior to application.

In general, the sheet form of a hydrogel dressing is constructed by sandwiching the hydrophilic polymer between two removable thin sheets of polyethylene film, with some types containing a supportive inner gel mesh. For application to the wound, the film on the contact side is removed, leaving the outer film in place. With this mode of application, the dressing is semipermeable to gases (including oxygen) and water vapor. If the outer film is also removed, then the dressing

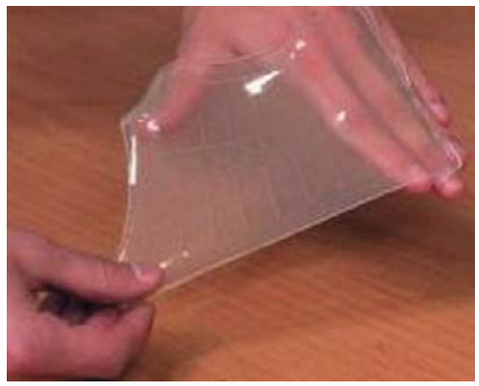


Fig. 145.8 Example of a hydrogel sheet.

becomes permeable to fluid as well; as a result, exudate can pass to a secondary gauze dressing. The polymer sheets can be removed easily without trauma to the wound bed. The amorphous type of hydrogel is composed of a cornstarch-derived, polymerized compound that forms a gel upon hydration at the time of its use. It is available commercially in a powdered or pre-mixed form, is applied wet to the wound defect, requires a secondary outer dressing and requires water application to the surface for removal.

Uses

Hydrogels are particularly useful with dermabrasion, laser resurfacing, chemical peels, superficial thermal burns, ulcers, surgical wounds such as graft donor sites, and partial-thickness wounds in which an interval of light-to-moderate exudate production is likely. They are also quite helpful in the prevention of pressure ulcers.

Examples

Hydrogel sheets: Aquaflo™ (Kendall); Aquasite™ Hydrogel Sheet (Derma); CarraDres™ Clear Hydrogel Sheet, CarraSorb™ M Freeze Dried Gel (Carrington Labs); Lamin-2™ (Procyte Corporation); Nu-Gel™ (Johnson & Johnson); and Vigilon® (Bard Medical).

Amorphous gels: Biolex® Wound Gel (Bard); CarraSyn™ Hydrogel, CarraSorb™ M Freeze Dried Gel (Carrington); GRX® Wound Gel (Geritrex Corp.); Intrasite™ Gel (Smith & Nephew); and Tegagel™ Hydrogel Wound Filler (3M).

Impregnated dressings: Aquagauze™ (Deroyal); DermaGauze™ (DermaRite); and Tegagel™ Hydrogel Wound Filler with gauze (3M).

Advantages/disadvantages

One significant advantage to hydrogel dressings is a reduction in postoperative pain and inflammation. Another is that hydrogels have been shown to accelerate the rate of wound healing when compared to traditional Telfa® and gauze dressings. For example, Geronemus and Robins[25] found, on average, a 25–45% faster rate of re-epithelialization of split-thickness wounds in pig skin. They reported that 100% of hydrogel-treated wounds were healed by postoperative day 4 compared with 32% of open-air (control) wounds. Hydrogels have also been credited with faster healing rates in studies of dermabrasion and hair transplant donor and recipient sites, when compared to standard Telfa® and Adaptic™ dressings[26].

One potential disadvantage is that hydrogels allow bacterial growth at the wound site. However, as with other types of occlusive dressings, studies have not shown an increase in infection rate. The semi- or non-adherent nature of hydrogels often results in more frequent dressing changes than is seen with other occlusive dressings.

Alginates

Alginate dressings are made from a natural, complex polysaccharide derived from various types of algae or kelp (seaweed). An extraction process produces a sodium salt form of alginic acid, and, during a second step, sodium ions are exchanged for calcium, zinc and magnesium. The end result is an alginate fiber, and non-woven mats or twists of this fiber are then made into a dressing (Fig. 145.9). Upon application of the dressing, a reverse ion exchange occurs between the calcium within the alginate fibers and the sodium from blood or the wound exudate. This results in the formation of a soluble sodium alginate gel that fills and completely covers the wound in a non-adherent manner, providing a moist wound healing environment. The extent and rate of gel formation depends on the amount of wound exudate. Alginate dressing materials have hemostatic properties, believed to be the result of the release of free calcium by the fibers during the ion exchange. This release of calcium augments the clotting cascade, producing the hemostatic advantage.

Alginate gel dressings are highly absorbent, which allows them to remain in place at the wound site for several days at a time, thereby minimizing dressing changes. To secure an alginate dressing, a secondary dressing is required. A dressing change is indicated when the dressing has been in place for several days or when exudate soaks through to the secondary dressing[27]. Removal of the dressing in a dried state can re-injure the wound.

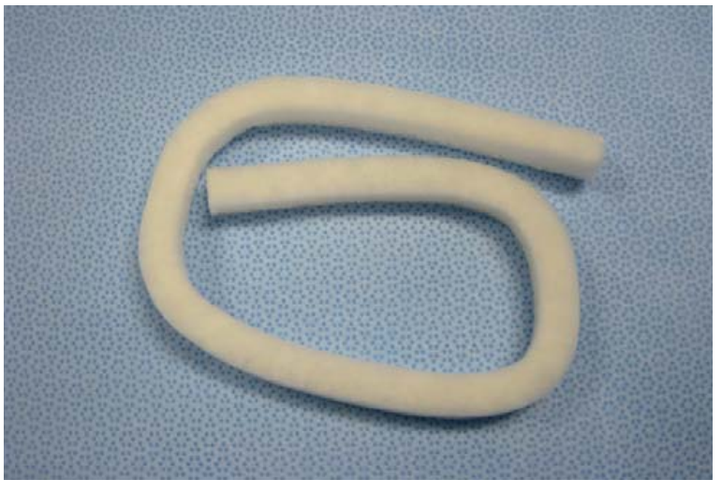


Fig. 145.9 Example of a collagen–alginate complex dressing. The rope form can be used to pack deep wounds.

Uses

As alginates are transformed into a gel matrix by wound fluid, they are best employed for highly exudative wounds. Full-thickness burns and surgical wounds, split-thickness graft donor sites, Mohs surgery defects, and refractory decubitus and chronic ulcers may benefit from alginate dressing application. Alginates can reportedly be used on dry wounds as well, but moistening with saline pre-application is necessary, and the dressing should be changed on a daily basis to limit desiccation.

Examples

Algicell® (Derma Sciences); Algiderm® (Bard Medical); AlgiSite™, Algosteril® (Smith & Nephew); Fibracol® Plus, a collagen–alginate complex dressing (Johnson & Johnson); Kalginate® (DeRoyal); Kaltostat® (ConvaTec); Maxorb® (Medline); and Sorbsan® (Bertek).

Advantages/disadvantages

Alginate dressings are soluble and can be removed by saline irrigation, which allows for less painful dressing changes. They have been shown to encourage wound healing and are metabolized by the body, should residual material remain at the wound. Despite concerns about the potential toxicity of alginates, they have been used for over 50 years without any commonly reported complications. One disadvantage of alginates is that the gel has a yellow–brown appearance, which can be confused with purulent discharge. Therefore, careful wound monitoring for signs of infection is indicated. Similar to hydrocolloids, alginate gel may have an unpleasant odor associated with its normal use, so patients should be made aware of this feature. Additionally, removal of the secondary outer dressing is necessary to visually inspect the wound and to monitor for desiccation.

Hydrocolloids

Colloid is a Greek term for a two-phase system comprised of a uniform dispersion of one phase of matter (unfilterable small particles) into another phase of matter or matrix. Mutually attractive charges exist between the particles, which contributes to the diffusible properties of colloids. Colloids are characterized by the strength of attraction of the particles to the continuous medium and to the proportion of water within that medium. This property accounts for the absorptive and expansive capacity of colloid gels, which function as a semipermeable membrane. Gel swelling occurs because the particle concentration of the gel is usually higher than that of the surrounding medium, thereby drawing water from the surroundings into the gel.

Since cells and tissues throughout the body are comprised of colloids, it seems reasonable that the creation of an environment similar to that found on cell surfaces would aid in the healing process. Colloid dressings are available in more than one usable form, and they were first used as ostomy products. Chronic ulcers and fissures around ostomy

sites were found to heal rapidly when they were bandaged with hydrocolloid products, so these materials were quickly adapted for use as wound dressings.

The most commonly used hydrocolloid dressings (e.g. DuoDERM®) are available as sheets with an inner adhesive layer consisting of a hydrophilic colloid base that is a mixture of pectin, karaya, guar or carboxymethyl cellulose and an adhesive containing polyisobutylene, styrene isoprene or ethylene vinyl acetate (Fig. 145.10). The outer layer is composed of a thin semipermeable material such as polyurethane. A gel is formed in the presence of wound exudate, and as a unit, the dressing is semipermeable to water vapor and gases[28].

Another type of hydrocolloid dressing is a synthetic, non-adherent, high-density plastic woven polymer (e.g. N-Terface®). Fluid is able to flow through this matrix to be absorbed by an overlying dressing without adherence to the new epithelial surface.

Uses

Hydrocolloids are used for the treatment of burns, partial-thickness and dermabrasion wounds, traumatic wounds such as lacerations and abrasions, surgical wounds such as donor graft sites and excisions, chronic ulcers, bullous disorders such as epidermolysis bullosa, and refractory inflammatory diseases such as lichen simplex chronicus and psoriasis.

Examples

Allevyn™ (formerly Cutinova™; Smith and Nephew), RepliCare™ (Smith and Nephew); DuoDERM® (Convatec); Exuderm® (Medline); N-Terface® (Winfield Labs); Primacol® (Derma Sciences); Tielle™ (Johnson &Johnson); Sorbex® (Bard); and Tegasorb™ (3M).

Advantages/disadvantages

When in sheet form, these dressings can be cut and conformed to the shape of the wound. They are waterproof and adhere directly; as a result, they do not require a secondary dressing. In addition, these dressings have a cushioning or pressure-relieving effect (especially at bony sites), which increases as the dressing absorbs exudate. The resulting colloidal gel that forms prevents the dressing from adhering to the wound base. Accumulation of the exudate itself in a moist, semipermeable environment becomes a source of phagocytic cells and endogenous enzymes. This feature, along with the gel, results in autolytic debridement that can be washed away with saline irrigation of the wound bed[29].

Due to their semipermeable outer barrier, hydrocolloids have also been shown to stimulate angiogenesis and increase the rate of healing by as much as 40% when compared to open-air controls. A comparison of hydrocolloids versus wet-to-dry saline gauze dressings in the treatment of decubitus ulcers found that hydrocolloids do not require as many dressing changes as traditional wound dressings. Although the cost of individual hydrocolloid dressings is greater than gauze dressings and the healing rates were the same, the savings were in the cost of nursing time. In addition, the dressing changes tend to be simple and painless for the patient[30].

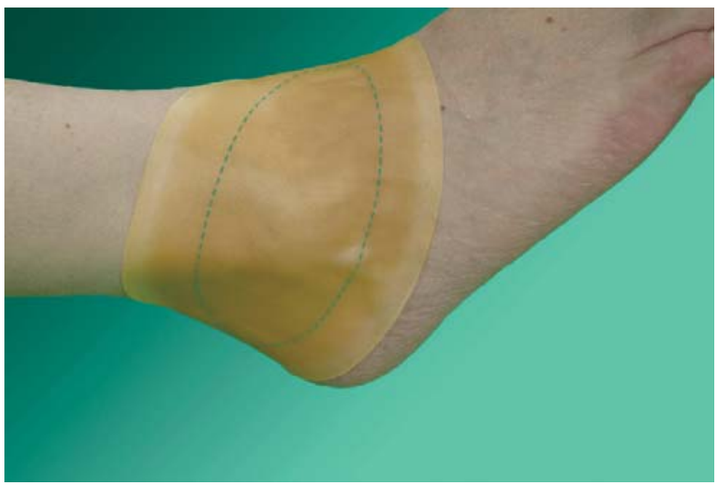


Fig. 145.10 Hydrocolloid wound dressing (DuoDERM®) placed over a healing wound on the ankle. *Courtesy of ConvaTec, Skillman, NJ.*

One disadvantage of hydrocolloids is that as an occlusive dressing, maceration of the skin surrounding the wound is possible. Leakage of excessive tissue exudate can also occur, resulting in soiling of outer garments and bedding. In addition, there is the possibility of the growth of excessive granulation tissue, the extension of which into a woven matrix (as is found in N-Terface®) could result in trauma to the wound upon attempted removal of the dressing. Similar to alginate dressings, the end product of hydrocolloids is a yellow–brown, thick, foul-smelling gel resembling purulent discharge. As with other occlusive dressings, hydrocolloids are subject to similar bacterial proliferation and colonization within the moist environment underneath the dressing, but they have not shown increased rates of infection as a result. Some investigators, in fact, have reported a decrease in the growth of *Pseudomonas* spp.[20].

Composites

The designs of occlusive dressings are constantly changing, with the goal of improved and simplified care for a greater range of wounds. Several new types of composite dressings, which combine two or more types of semi-occlusive dressings into one product, are commercially available. They have three components: (1) a semi- or non-adherent layer that contacts the wound (like a hydrogel, hydrocolloid, foam or alginate); (2) an absorptive layer; and (3) an outer layer (like a film with an adhesive border). This maximizes the efficiency and comfort of the dressing by expanding absorbency as well as lessening the chance of maceration[31]. Other features include the lack of need for secondary retention dressings and better waterproof coverings, which enable the patient to shower or bathe.

Examples

Alldress® (Mölnlycke); Covaderm Plus® (DeRoyal); Stratasorb® (Medline); Telfa XTRA® (Kendall); and Tegaderm™ +Pad (3M).

WOUND THERAPY – SUPPLEMENTAL TREATMENTS

Debridement

With the possible exception of ulcers due to pyoderma gangrenosum, the practice of wound debridement is commonly accepted as the standard of care for leg ulcers. Although there is no solid scientific evidence for the benefit of this procedure, it is thought to permit the adequate development of granulation tissue and epithelialization. Debridement can be accomplished by the following mechanisms: surgically; mechanically via irrigation, wet-to-dry dressings or the use of dextranomers; autolytically via compression bandaging and the use of occlusive dressings such as hydrocolloids and alginates (see above); chemically via proteolytic enzymes; and biosurgically via leeches and maggots[32].

A moist wound environment promotes the lytic activity of enzymes that clear residual debris during early wound healing. Topical application of the commercially available enzymatic agents – collagenase, papain and trypsin, can be used to supplement this autolytic activity. Collagenase (Santyl® ointment) is reported to be effective in the removal of devitalized tissue and to contribute to the formation of granulation tissue and ulcer epithelialization, without attacking healthy or new granulation tissue. Papain (e.g. Accuzyme® ointment, Panafil® ointment or spray) is harmless to viable tissue, while functioning as a potent digestive agent to non-viable tissue. Its action, however, requires the presence of an activator such as urea with which it is processed (usually at a concentration of 10%), since papain alone is relatively ineffective; some formulations also contain chlorophyllin copper complex sodium, which adds to the healing action. Trypsin (e.g. Granulex®, Balsa-Derm®) is processed with balsam of Peru, an effective capillary bed stimulant and mild bactericide, and castor oil, which is used to reduce premature epithelial desiccation and cornification as well as pain.

Fly larvae (order Diptera) have been used for centuries to biosurgically debride chronic ulcers. Today, the most commonly used maggots are

those of the green bottle fly *Lucilia sericata*. These maggots digest necrotic tissue, leaving healthy tissue exposed. This digestion is accomplished though collagenases and trypsin-like enzymes. They also have antimicrobial effects via secretion of antibacterial compounds (e.g. phenylacetic acid, phenylacetaldehyde) and the ingestion and subsequent killing of Gram-positive bacteria (including MRSA) and, to a lesser extent, Gram-negative bacteria. In a small clinical trial, larval therapy was superior to hydrogel therapy with regard to cost-effectiveness and superior wound healing ability[33].

Topical Growth Factors

It is known that exudate from acute cutaneous wounds contains many endogenous factors that are critical to the wound healing process, including growth factors such as platelet-derived growth factor (PDGF) and epidermal growth factor (EGF). As a result, retaining this fluid over wounds, as is accomplished by the use of occlusive dressings, has been shown to augment wound healing. The potential therapeutic use of exogenous growth factors to enhance healing is reviewed in Chapter 141.

Examples

Regranex® 0.01% gel (recombinant human PDGF [rPDGF-BB]; Ortho-McNeil); Procuren® (Cytomedix).

Topical Emulsions

A water-based, trolamine-containing topical emulsion (Biafine®) has been approved for the treatment of minor abrasions, superficial and full-thickness wounds, dermal ulcers (including pressure-induced), donor graft sites, first- and second-degree burns, and radiation dermatitis. This emulsion is thought to promote wound healing by recruiting macrophages to the wound site, with an associated increase in the IL-1/IL-6 ratio enhancing granulation tissue formation. In addition, its occlusive properties impart protection from external contaminants and hydration of the wound aids in healing[34]. However, in a porcine partial-thickness burn model, similar rates of re-epithelialization were observed when silver sulfadiazine 1% cream, Biafine® topical emulsion, and saline-soaked gauze were compared[35].

Heat

The use of infrared energy[36] and radiant heat[37] bandages has been effective in the laboratory and in small trials involving healing leg ulcers that were refractory to other methods as well as ulcers of different etiologies. The practical value of these therapies has yet to be determined.

TISSUE-ENGINEERED SKIN EQUIVALENTS

Advances in tissue culture techniques for keratinocytes and fibroblasts, as well as new methods that allow the generation of large quantities of these cells, are rapidly being incorporated into a new group of wound dressings that blur the distinction between wound dressing and tissue-engineered skin (Table 145.5). For chronic ulcers that are resistant to healing, skin equivalents can be used. One advantage is that painful, often slow-to-heal donor sites do not have to be created. These previously unresponsive wounds undergo an "edge effect", where the skin equivalents promote epithelialization from the edge of the ulcer toward its center, likely due to a release of cytokines by the donor cells that stimulates healing[38]. There are three types of skin substitutes: epidermal grafts, dermal replacements, and composite grafts (with both an epidermal and dermal component).

Epidermal Grafts

The first epidermal autografts were successfully cultivated in 1975 by Rheinwald and Green. They have been used successfully in a variety of clinical situations, including burns, chronic ulcers, vitiligo and post-surgical wounds. Only one product is currently commercially available in the US: Epicel® (Genzyme Biosurgery). A skin biopsy is first obtained from the patient and then the autologous keratinocytes are co-cultured with irradiated murine fibroblasts that serve as a feeder layer. A sheet of keratinocytes two to eight cells thick forms and is attached to petroleum gauze. The graft must be sutured into place and the gauze backing is removed after 1 week, when the keratinocytes have attached to the wound. Biopsies of skin obtained 6 months to 1 year post-grafting show anchoring fibrils and neovascularization. This epidermal autograft is approved for use in partial- and full-thickness burns.

There are several studies demonstrating the efficacy of cultured epidermal autografts. For example, in a review of 30 patients with burns averaging 78% of the body surface area, 69% of the grafts had permanently adhered to the patients[39]. The advantages of this type of graft are the use of autologous keratinocytes and the ability to minimize the amount of tissue harvesting. Epidermal grafts must be placed onto clean wound beds, and the primary disadvantages are the short shelf-life, the expense, and the 3-week interval required for the culture of the keratinocytes.

There are additional epidermal grafts available outside of the US, such as Laserskin® and Celaderm™. Laserskin® (Anika Therapeutics) is another cultured autologous keratinocyte sheet requiring an initial small skin biopsy, but the sheet is attached onto a hyaluronic membrane with laser-drilled microperforations to allow keratinocytes to migrate onto the wound bed[40]. This hyaluronic membrane is a biodegradable biopolymer of esterified hyaluronic acid (referred to as HYAFF™) and is also available without keratinocytes (Hyalofill®, Hyalomatrix®) for use as a primary dressing for wounds such as ulcers[41].

Celaderm™ (Advanced BioHealing) is composed of allogenic keratinocytes cultured from neonatal foreskins. It has a much longer shelf-life, but, as an allogenic rather than autologous graft, it is not permanent. The graft is placed on the wound every other week until it heals; pain relief occurs and stimulation of epithelialization is observed. Although clinical trials of both Laserskin® and Celaderm™ are limited, improved healing of diabetic foot ulcers and venous stasis ulcers was noted when compared to saline gauze[42]. They are also used for partial- and full-thickness burns.

Dermal Replacements

There are two types of dermal replacements: allogenic and xenogenic (see Table 145.5). Neither of these is permanent: DNA analysis of wounds after the application of non-autologous skin substitutes shows complete disappearance of grafted cells after 2 months[43]. The goal of these dermal grafts is to provide a temporary biologic dressing in order to stimulate the healing process. They are placed over the wound, extending slightly onto normal skin, and then bolstered into place. Secondary dressings must be applied. The major component of dermal replacements is collagen, and occasionally there are additions such as extracellular matrix (including glycosaminoglycans), fibroblasts, and basement membrane material.

Xenogenic

Details of the xenogenic dermal replacements are outlined in Table 145.6. The advantages of these products are their ability to effect hemostasis and to provide immediate closure as well as cosmetically acceptable scars with second intention healing, safety from potential human pathogen transmission due to their animal origin, and an adequate shelf-life, facilitating off-the-shelf access. Biobrane® has significant elasticity, enabling a full range of motion to the covered body part, and it has no requirement for dressing changes once it has adhered to the wound bed.

The drawbacks are that these dressings need to remain dry and a pressure dressing is often needed to keep the graft in place. They are all ineffective over exposed bone, and because healing time is slower compared to sutured repairs, there is the potential for infection if not cared for adequately. Bovine allergy is also a possibility. Biobrane® may adhere to the wound so tightly that it could damage newly developed epithelium and inhibit wound contraction[49]. Because Integra™ has a complicated application procedure, the Food and Drug Administration (FDA) requires that all physicians complete a company-sponsored training program.

Allogenic

Details of the allogenic dermal replacements are outlined in Table 145.6. The advantages of these products are their ability to provide immediate closure, cosmetically acceptable scars with second intention healing, and adequate shelf-life, facilitating off-the-shelf access.

TISSUE-ENGINEERED SKIN EQUIVALENTS			
Name and description	**Possible uses**	**Advantages**	**Disadvantages**
EPIDERMAL–AUTOLOGOUS			
Epicel® – sheet of cultured keratinocytes (derived from a skin biopsy) attached to petrolatum gauze Laserskin® – esterified hyaluronic acid (laser-perforated) and seeded with keratinocytes	Partial- and full-thickness burns Congenital melanocytic nevus excision sites Pyoderma gangrenosum (non-inflammatory; see Ch. 26) Epidermolysis bullosa Chronic ulcers	Capable of self-repair Single application is often sufficient Permanent and cosmetically acceptable Good adherence Covers a large surface area from a small skin biopsy	Very expensive Minimal shelf-life; must be used soon after delivery from manufacturer Needs biopsy of normal skin Available 3 weeks after biopsy Technically difficult to apply Susceptible to infection
DERMAL			
Xenogenic (see Table 145.6)			
Biobrane®, E-Z Derm™ – acellular porcine collagen type I Oasis® – porcine intestinal collagen type I and extracellular matrix (Fig. 145.11) Integra™ – bovine tendon collagen and shark chondroitin	Burns Split-thickness graft donor sites Post-laser resurfacing Chronic ulcers	Translucent Elastic Minimal exudate accumulation Reduces pain of some wounds Long shelf-life Non-human origin avoids human pathogen transmission Immediately available	May adhere to wound strongly enough to damage new epithelium May have higher infection rate Expensive Possible bovine allergy Usually needs multiple applications
Allogenic (see Table 145.6)			
Alloderm® – cadaveric decellularized dermis Transcyte™ – neonatal foreskin fibroblasts grown on Biobrane® (see above)§ Dermagraft™ – neonatal foreskin fibroblasts grown on a biodegradable mesh	Burns and split-thickness skin graft sites Chronic ulcers Epidermolysis bullosa, in particular recessive dystrophic	Decreased pain Immediate availability Immunologically inert Easy to remove	Theoretical risk of transmission of human pathogens Usually needs multiple applications
COMPOSITE			
Xenogenic & allogenic			
Apligraf®, OrCel™ – neonatal foreskin keratinocytes and fibroblasts plus bovine collagen type I; bilayered§	Chronic ulcers, e.g. venous, diabetic Wounds resistant to healing Burns Epidermolysis bullosa, in particular recessive dystrophic	Capable of self-repair Single application is often sufficient Immediately available	Very expensive Minimal shelf-life (Apligraft®); must be used soon after delivery from manufacturer
Allogeneic			
StrataGraft® – NIKS cells form a fully stratified squamous epithelium in organotypic culture plus a dermal equivalent	Deep partial- and full-thickness burns Chronic, non-healing ulcers	Promotes self-repair Single application may be sufficient Immediately available Long shelf-life (can be cryopreserved) Pathogen-free human cell source	Expensive Currently in clinical trials as a regulated biologic (not a device)

*NIKS cells, spontaneously immortalized human keratinocyte cell line.
§At the time of writing, Transcyte™ and OrCel™ are not commercially available.

Table 145.5 Tissue-engineered skin equivalents.

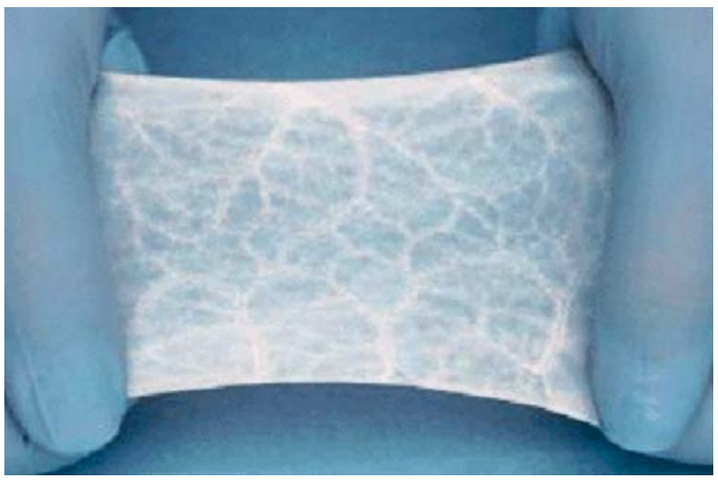


Fig. 145.11 Example of a xenogenic wound matrix derived from porcine small intestine submucosa (Oasis®).

Composite Grafts

Apligraf® (Organogenesis) is a bilayered human skin equivalent derived from human neonatal foreskins (Fig. 145.12). It contains living human keratinocytes within an epidermal layer and a dermal layer equivalent consisting of bovine collagen type I gel seeded with fibroblasts. This composite graft produces its own matrix proteins and growth factors, and, if wounded, it can repair itself. Apligraf® has been used to treat both acute and chronic wounds that fail to heal by standard means. Whereas several applications of the material may be required to completely heal chronic wounds, a single application may be sufficient to initiate a satisfactory healing response. Chronic venous ulcers that were randomized to receive compression plus Apligraf® healed in a shorter time period compared to compression alone, especially in the case of larger defects[50]. It is currently approved by the FDA for venous and diabetic ulcers, but has also been shown to be useful in epidermolysis bullosa, pyoderma gangrenosum, burns and surgical excisions.

OrCel™ (Forticell Bioscience) is a similar bilayered skin equivalent. It is composed of neonatal foreskin-derived keratinocytes grown on the non-porous side of a cross-linked bovine collagen I sponge. On the other, porous side of this sponge are human dermal fibroblasts that

DERMAL REPLACEMENT GRAFTS		
	Description	**Comments**
	XENOGENIC	
Biobrane® (Dow Hickam/Bertek)	Bilayer dressing: inner nylon mesh fabric coated with porcine type I collagen ("dermis") bonded to a semipermeable silicone film membrane ("epidermis")	Tissue ingrowth into the nylon fabric following binding of collagen to fibrin[44] Two versions: (1) trilaminar nylon (better for clean, partial-thickness burn wounds or donor sites); and (2) monofilament nylon (better for meshed autografts) Approved for burns
E-Z Derm™ (Brennen Medical)	Porcine-derived type I collagen attached to a gauze liner	Gauze liner is discarded upon placement[45] Approved for partial-thickness skin loss injuries
Oasis® (Healthpoint)	Derived from porcine small intestine submucosa (mucosa and muscle removed) Porcine type I collagen, extracellular matrix (e.g. hyaluronic acid, fibronectin) and growth factors (FGF, TGF-β)	In study of 120 patients with venous leg ulcers, after 12 weeks of treatment, 55% of Oasis® + compression group healed vs 34% in compression alone group; at 6 months, 100% and 70% remained healed, respectively[46] Approved for venous, diabetic and pressure ulcers, second-degree burns, graft donor sites, and full-thickness skin injuries
Integra™ (Integra LifeSciences)	Bilayer dressing: bovine tendon collagen admixed with shark-derived, modified GAGs ("dermis") plus an outer silicone membrane	Debridement required prior to graft placement with sutures or staples Outer silicone cover removed after several weeks; in large wounds, replaced by ultrathin autograft (two-step process) In a controlled trial of matched-pair thermal injuries, as efficacious as other xenografts and synthetic skin substitutes[47] Approved for life-threatening third-degree burns
	ALLOGENIC	
Alloderm® (LifeCell)	Human cadaveric skin, chemically treated and purified to remove epidermis, all cellular components and pathogens Cryopreserved (shelf-life of 6 months)	Repopulation of host fibroblasts and endothelial cells seen within 10 days of grafting Approved for repair or replacement of damaged or inadequate integumental tissue, e.g. breast reconstruction
Transcyte™ (Advanced BioHealing; Smith & Nephew)	Biobrane® (see above) plus neonatal foreskin fibroblasts	Approx. 2 weeks for graft take Fibroblasts initially secrete extracellular matrix (including collagen) and growth factors that stimulate granulation tissue and epithelialization but then die In a controlled trial of excised burns, easier to use and similar outcomes when compared to human cadaveric skin Approved for partial- and full-thickness burns
Dermagraft™ (Advanced BioHealing)	Neonatal foreskin fibroblasts are seeded onto a 3-D scaffold of biodegradable polyglactin mesh	Similar time to graft take and similar fibroblast function as Transcyte™ (see above) In 235 patients with diabetic ulcers, improved but not a significant difference in healing time compared to conventional therapy Approved for full-thickness diabetic foot ulcers and chronic ulcers that are deep but do not involve tendons, muscle or bone; previously HDE for ulcers in epidermolysis bullosa[48]

*At the time of writing, not commercially available.

Table 145.6 Dermal replacement grafts. 3-D, three-dimensional; FGF, fibroblast growth factor; GAGs, glycosaminoglycans; HDE, Humanitarian Device Exemption; TGF-β, transforming growth factor-β.

Fig. 145.12 Example of a composite (xenogenic and allogenic) graft sutured into place (Apligraf®).

also produce multiple matrix proteins and growth factors. As with all of the allogenic and xenogenic grafts, this is not a permanent skin replacement, and DNA from the cultured cells is not detectable 2 weeks post-grafting. It is FDA-approved for the treatment of full- and partial-thickness donor sites as well as burns[43].

Each of these products is extremely expensive, at approximately US $1000 per graft. However, they have the advantage of mimicking the structure and function of normal human skin. Apligraf® has great safety data based upon its use in over 200 000 patients. OrCel™ has the advantage of a 9-month shelf-life because it is cryopreserved, whereas Apligraf® has a shelf-life of only 5 days. Another disadvantage is the potential for disease transmission. Nevertheless, these composite grafts may be justified in certain situations when adequate skin grafts cannot be obtained from the patient. Of note, at the time of writing, OrCel™ is not commercially available.

SPECIAL CONSIDERATIONS

Leg Ulcers

The predominant types of skin ulcers that affect the lower extremity are venous, arterial and neuropathic; less commonly, they are due to inflammation, infection, trauma or malignancy (see Ch. 105). Venous disease is by far the most common etiology, causing up to 80% of leg ulcers. Moisture retention at the ulcer site is often best accomplished

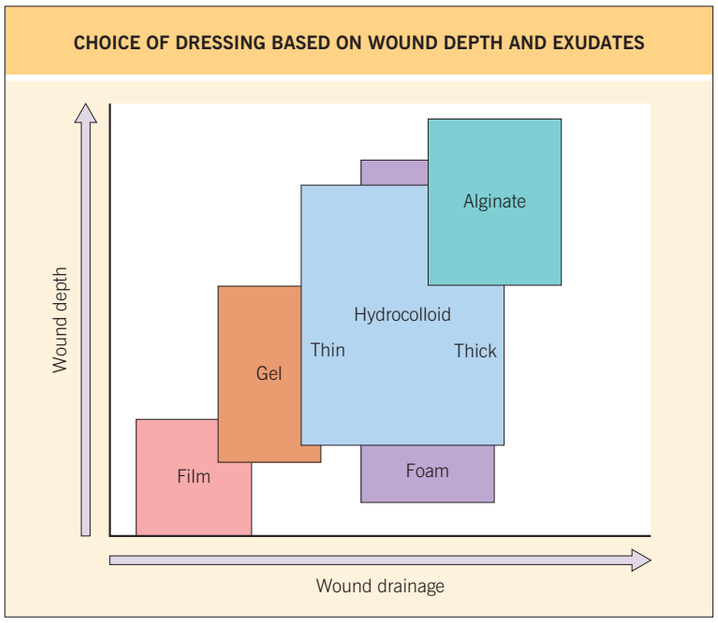


Fig. 145.13 Choice of dressing based on wound depth and exudates.

Fig 145.14 Unna boot. It confers semi-rigid compression and should be changed once-weekly unless heavy drainage from the wound necessitates more frequent replacement.

with occlusive dressings (see Fig. 145.5), and choice of a particular dressing type is influenced by ulcer depth and drainage (Fig. 145.13). However, only a few comparative studies of dressings have been conducted, and no particular category has been proven conclusively to enhance rates of healing of acute surgical wounds or chronic ulcers[22,51]. Therefore, the choice of a moisture-retaining dressing is often determined by the preference of the physician and patient.

Compression is considered to be of utmost importance in the care of venous ulcers. It alleviates edema by increasing hydrostatic pressure and decreasing the pressure of surface veins, thereby decreasing macromolecule and fluid extravasation. Compression is also said to promote fibrinolysis and ultimately improve cutaneous blood flow once edema has been mechanically reduced. Studies by Fletcher et al.[52] concluded not only that compression increased healing rates, but that high compression was better than low, and that compression without a moist dressing yielded better results than did a moist dressing without compression.

Types of compression

Compression can be accomplished by dressings that range from adhesive, relatively non-absorbent types to those which are moderately compressive and absorbent. Traditionally, compression or "pressure dressings" are composed of a non-adherent contact layer, followed by an absorbent layer, and then an outer layer. The efficacy and benefit of the dressing depends upon the role of each of these layers. Although the definitive optimal pressure required to prevent the capillary leakage that occurs with venous hypertension has not been delineated, the general recommendation for leg ulcers is to achieve an ankle pressure of 30–40 mmHg (see Ch. 105)[53].

Compression stockings

With graduated compression stockings, the patient is afforded some independence in the application of the device, if he or she is physically capable. However, for arthritic and/or elderly patients, application can be difficult. Some stockings are fashioned with silk inner linings or zippers for easier use.

Examples

Relief, Vairox, UlcerCARE (Jobst); Futuro™ Energizing, Futuro™ Restoring (3M); Varin Dynamic, Silver Soft (Juzo); Assure, Forte (Mediven); Support Therapy, EverSheer (Sigvaris).

Compression bandages

The Unna boot has existed for over 100 years. Created by Paul Gerson Unna during the 1880s for the treatment of venous stasis ulcers and selected eczematous dermatoses, it was originally a cotton bandage impregnated with zinc oxide, gelatin and glycerin paste. It is frequently the preferred dressing for this type of wound[54]. Applied in a semi-rigid state, the Unna boot confers (semi-rigid) compression, along with the advantages of a moisture-retaining occlusive dressing (Fig. 145.14). It should be applied by a qualified medical professional and changed once a week unless heavy drainage from the wound necessitates more frequent replacement. Correct application of the Unna boot prevents excessive or abnormal pressure to the limb, compromised circulation, skin breakdown, additional ulcer formation or further limb deterioration[55]. In one study, healing time for ulcers treated with Unna boots alone was less than half the time required to heal ulcers treated with only support stockings[56]. Combining compression with occlusive dressings also increased the healing rate of venous ulcers[57].

The use of a flexible compression bandage has the advantage of increased absorbency and compression maintenance as compared to the rigidity of the Unna boot. There is a wide selection of elasticity gradations and brands, and they are categorized as elastic or inelastic, single- or multilayer, long- or short-stretch compression, and cohesive wrap. The greatest difficulty in using elastic compression is determining the proper amount of tension needed to safely and effectively achieve the desired goal. One manufacturer's attempt to help resolve this problem involved marking the bandage with a drawing that changed as the bandage was stretched to the proper tension during application. In general, it is thought that multilayered compression bandaging is superior to single-layered techniques.

Multilayer compression bandages

The components of this system often include four distinct layers, the first of which is an orthopedic wool layer applied loosely in a spiral fashion. It absorbs exudate as well as redistributes pressure around the ankle. The second layer is a crepe bandage, used to smooth the wool layer and to increase absorbency. The third layer is a light elastic compression bandage, followed by the fourth and last layer, which is the outer, elastic, cohesive bandage used to secure all the layers in place. The four-layered system can remain in place for up to 1 week and has the advantage of providing absorption as well as evenly distributed pressure throughout the leg. Multilayered compression systems are available commercially in complete kits[58].

Examples

Unna boot: Gelocast® Unna's Boot (Beiersdorf-Jobst); Primer Modified Unna Boot (Glenwood); Tenderwrap Unna Boot Bandage (Kendall); and UNNA-FLEX® Elastic Unna Boot (ConvaTec).

Single layer: CircAid Ready-Fit™ 2000 (CircAid Medical); SurePress® High Compression Bandage (ConvaTec).

Multilayer: DYNA-FLEX™ Multi-Layer Compression System (Johnson & Johnson Medical); Profore™ (Smith & Nephew).

Cohesive wrap: FLEX-WRAP™ Self Adherent Wrap (Kendall); 3M™ Coban™ Self Adherent Wrap (3M Health Care).

Laser Resurfacing

Laser skin resurfacing has emerged as a useful modality for conditions such as actinic skin damage, acne scarring and rhytides (see Ch. 137), although it does require a prolonged and often painful recovery period for the patient. The primary goal after laser resurfacing is total and uniform re-epithelialization. In the absence of infection and with the use of occlusive dressings, this is possible within 5–7 days. Delay of re-epithelialization has been attributed to crust formation, to which the wound is most prone during the first 2–3 postoperative days.

Occlusive dressings may be classified as open or closed. An open dressing is defined as the application of an ointment or cream directly to the skin wound without an overlying textile dressing. The choice of this more labor-intensive method requires the commitment of the patient to maintain adequate coverage of the wound by frequent, scheduled ointment reapplications and to be able to tolerate the soiling of bedding and garments during the healing period. However, an open dressing does result in less bacterial colonization than closed dressings and it allows for easy wound monitoring; an open dressing is also less expensive than the closed wound care technique. Examples of products used for open dressings are: petrolatum, Aquaphor® (Beiersdorf-Jobst), Neova® Complex CU_3™ lotion (Procyte), and Elta® Crème (Swiss-America Products). Antibiotic ointment applied to facial wounds less than 48 hours old has been reported to significantly increase the rate of contact dermatitis and is therefore not recommended.

Closed dressings representing four of the major occlusive dressing categories (all but alginates) have been specifically designed for post-laser skin resurfacing care. Weinstein et al.[59] examined the most commonly used post-laser resurfacing dressings in order to compare their clinical advantages and disadvantages. Samples from each of the following categories were evaluated: composite foams (Flexzan®), hydrogels (2nd Skin®), polymer films (Silon-TSR®), and hydrocolloids (N-Terface®, Mepitel®).

Among their conclusions were that when compared with open dressing techniques, closed dressings overall resulted in faster re-epithelialization with improved patient comfort. In following their postoperative care protocol, they found that regular wound inspection within the first postoperative week was necessary in order to monitor for signs of infection, healing progress, and patient adherence to care instructions, regardless of the choice of occlusive dressing. The immediate placement of a closed dressing after surgery was followed by return of the patient on postoperative days 1 and 2, at which point the wound was cleaned and the entire dressing was changed. There was no perceptible delay or interference in re-epithelialization by changing the dressing at this point. The replacement dressing remained in place until postoperative day 5, at which time the closed dressing was removed and the patient was converted to only an open dressing[59].

Desirable characteristics of a closed dressing for laser resurfacing include absorbency without saturation, placement stability, ease of use, patient comfort, and minimal adherence to the newly developing epithelium. Flexzan® is an open cell (porous) polyurethane foam with an adhesive coating that is applied in strips and does not need an absorptive secondary dressing. Patients appreciated the light maintenance it required. Because this foam is opaque, careful removal with sufficient moistening is necessary for inspection of the wound.

The hydrogel 2nd Skin® was reported to decrease pain and pruritus, but maintaining the dressing in place was challenging. There was a preference for the use of this dressing in areas of prolonged re-epithelialization. Silon-TSR® and N-Terface® are thin, transparent polymer films that have slits or are meshed in order to allow passage of exudate into an overlying absorptive secondary dressing. They conform well to facial contours and do not adhere to new epithelium, but they do have the problem of slippage. Mepitel® is a silicone polymer, with large pores to allow escape of exudate, that is self-adhesive only to dry areas. It has several benefits, including passage of exudate into a secondary dressing without crust formation, stability without slipping from the original placement site, and easy removal from the moist wound. This dressing is reported to leave behind an imprint of its mesh pattern on the healing skin, a side effect that fades within a few weeks of converting to an open dressing[59].

Oxygen mist therapy following CO_2 laser resurfacing has also been examined. In one study, a semipermeable polyurethane foam dressing was applied as the postoperative dressing on one half of the face and oxygen mist therapy was applied to the other half. Mist therapy consists of oxygen (93% at 15 liters/minute) and a nutrient mist (Aminoplex®) consisting of sterile water, sodium, chloride, potassium, lactate, acetate, glucose, urea, choline, amino acids, and nucleic acid derivatives. The two methods demonstrated comparable healing rates, with no significant differences in the occurrence of erythema, scarring and acne. Patients did, however, express a preference for the oxygen mist therapy over the foam dressing because of decreased pain and less of a sense of confinement. The additional benefit of oxygen mist therapy was that as an "open" dressing, it allowed for wound monitoring. Therefore, oxygen mist therapy may represent another option following laser resurfacing[60].

FUTURE DIRECTIONS

The past 100 years have brought great advances in wound dressing technology. Research into the mechanisms of wound healing has led to our ability to heal wounds in nearly half the time using occlusive dressings. With recent advances in both polymer and tissue-engineering technology, it is likely that the field will continue to change at an even faster pace. While topical synthetic growth factors will likely speed the healing of all types of wounds, their cost is still a concern. Complex bioengineered skin replacements will likely continue to proliferate (e.g. skin grafts that express angiogenesis growth factors or antimicrobials such as cathelicidins [ExpressGraft™]), as will mechanical skin equivalents; for example, an electronic skin that can sense touch was recently described in which a matrix of nanowires and nano-scale transistors on a polyimide film was overlaid with flexible, pressure-sensitive rubber.

REFERENCES

1. Bennett RG. Dressings and miscellaneous surgical materials. In: Fundamentals of Cutaneous Surgery. St Louis: Mosby, 1987:xii, 823.
2. Cho CY, Lo JS. Dressing the part. Dermatol Clin. 1998;16:25–47.
3. Gilje O. On taping (adhesive tape treatment) of leg ulcers. Acta Derm Venereol. 1948;28:454–67.
4. Winter GD. Formation of the scab and the rate of epithelization of superficial wounds in the skin of the young domestic pig. Nature. 1962;193:293–4.
5. Cunningham BB, Bernstein L, Woodley DT. Wound dressings. In: Roenigk RK, Roenigk HH (eds). Dermatologic Surgery: Principles and Practice, 2nd edn. New York: Marcel Dekker, 1996:131.
6. Eaglstein WH, Davis SC, Mehle AL, Mertz PM. Optimal use of an occlusive dressing to enhance healing. Effect of delayed application and early removal on wound healing. Arch Dermatol. 1988;124:392–5.
7. Li W, Dasgeb B, Phillips T, et al. Wound-healing perspectives. Dermatol Clin. 2005;23:181–92.
8. Matthews DN. Dressing of open wounds and burns with tulle gras. Lancet. 1941;1:43.
9. Ersek RA. Ischemic necrosis and elastic net bandages. Tex Med. 1982;78:47–9.
10. Zitelli JA. Wound healing by first and second intention. In: Roenigk RK, Roenigk HH (eds). Dermatologic Surgery: Principles and Practice, 2nd edn. New York: Marcel Dekker, 1996:101–30.
11. Strohal R, Schelling M, Takacs M, et al. Nanocrystalline silver dressings as an efficient anti-MRSA barrier: a new solution to an increasing problem. J Hosp Infect. 2005;60:226–30.
12. Carter MJ, Tingley-Kelley K, Warriner RA 3rd. Silver treatments and silver-impregnated dressings for the healing of leg wounds and ulcers: a systematic review and meta-analysis. J Am Acad Dermatol. 2010;63:668–79.
13. Cooper RA. Iodine revisited. Int Wound J. 2007;4:124–37.
14. Hansson C. The effects of cadexomer iodine paste in the treatment of venous leg ulcers compared with hydrocolloid dressing and paraffin gauze dressing. Cadexomer Iodine Study Group. Int J Dermatol. 1998;37:390–6.
15. Rubio PA. Use of semiocclusive, transparent film dressings for surgical wound protection: experience in 3637 cases. Int Surg. 1991;76:253–4.
16. Gilmore WA, Wheeland RG. Treatment of ulcers on legs by pinch grafts and a supportive dressing of polyurethane. J Dermatol Surg Oncol. 1982;8:177–83.
17. Hien NT, Prawer SE, Katz HI. Facilitated wound healing using transparent film dressing following Mohs micrographic surgery. Arch Dermatol. 1988;124:903–6.
18. Rosdy M, Clauss LC. Cytotoxicity testing of wound dressings using normal human keratinocytes in culture. J Biomed Mater Res. 1990;24:363–77.
19. Buchan IA, Andrews JK, Land SM. Clinical and laboratory investigation of the composition and properties of human skin wound exudate under semipermeable dressings. Burns. 1980;7:326–34.
20. Gilchrist B, Reed C. The bacteriology of chronic venous ulcers treated with occlusive hydrocolloid dressings. Br J Dermatol. 1989;121:337–44.
21. Viamontes L, Temple D, Wytall D, Walker A. An evaluation of an adhesive hydrocellular foam dressing and a self-adherent soft silicone foam dressing in a

nursing home setting. Ostomy Wound Manage. 2003;49:48–52, 54–6, 58.
22. Vermeulen H, Ubbink DT, Goossens A, et al. Systematic review of dressings and topical agents for surgical wounds healing by secondary intention. Br J Surg. 2005;92:665–72.
23. Eisenbud D, Hunter H, Kessler L, Zulkowski K. Hydrogel wound dressings: where do we stand in 2003? Ostomy Wound Manage. 2003;49:52–7.
24. Mertz PM, Marshall DA, Eaglstein WH. Occlusive wound dressings to prevent bacterial invasion and wound infection. J Am Acad Dermatol. 1985;12:662–8.
25. Geronemus RG, Robins P. The effect of two new dressings on epidermal wound healing. J Dermatol Surg Oncol. 1982;8:850–2.
26. Mandy SH. A new primary wound dressing made of polyethylene oxide gel. J Dermatol Surg Oncol. 1983;9:153–5.
27. Thomas S. Alginate dressings in surgery and wound management – Part 1. J Wound Care. 2000;9:56–60.
28. Cassidy C, St Peter SD, Lacey S, et al. Biobrane versus Duoderm for the treatment of intermediate thickness burns in children: a prospective, randomized trial. Burns. 2005;31:890–3.
29. Bolton LL, Johnson CL, Van Rijswijk L. Occlusive dressings: therapeutic agents and effects on drug delivery. Clin Dermatol. 1991;9:573–83.
30. Xakellis GC, Chrischilles EA. Hydrocolloid versus saline-gauze dressings in treating pressure ulcers: a cost-effectiveness analysis. Arch Phys Med Rehabil. 1992;73:463–9.
31. Hansbrough JF, Franco ES. Skin replacements. Clin Plast Surg. 1998;25:407–23.
32. Phillips TJ. Successful methods of treating leg ulcers. The tried and true, plus the novel and new. Postgrad Med. 1999;105:159–61, 165–6, 173–4 passim.
33. Beasley WD, Hirst G. Making a meal of MRSA – the role of biosurgery in hospital-acquired infection. J Hosp Infect. 2004;56:6–9.
34. Coulomb B, Friteau L, Dubertret L. Biafine applied on human epidermal wounds is chemotactic for macrophages and increases the IL-1/IL-6 ratio. Skin Pharmacol. 1997;10:281–7.
35. Glesinger R, Cohen AD, Bogdanov-Berezovsky A, et al. A randomized controlled trial of silver sulfadiazine, Biafine, and saline-soaked gauze in the treatment of superficial partial-thickness burn wounds in pigs. Acad Emerg Med. 2004;11:339–42.
36. Posten W, Wrone DA, Dover JS, et al. Low-level laser therapy for wound healing: mechanism and efficacy. Dermatol Surg. 2005;31:334–40.
37. Thomas DR, Diebold MR, Eggemeyer LM. A controlled, randomized, comparative study of a radiant heat bandage on the healing of stage 3–4 pressure ulcers: A pilot study. J Am Med Dir Assoc. 2005;6:46–9.
38. Kirsner RS, Falanga V, Kerdel FA, et al. Skin grafts as pharmacological agents: pre-wounding of the donor site. Br J Dermatol. 1996;135:292–6.
39. Carsin H, Ainaud P, Le Bever H, et al. Cultured epithelial autografts in extensive burn coverage of severely traumatized patients: a five year single-center experience with 30 patients. Burns. 2000;26:379–87.
40. Lobmann R, Pittasch D, Muhlen I, Lehnert H. Autologous human keratinocytes cultured on membranes composed of benzyl ester of hyaluronic acid for grafting in nonhealing diabetic foot lesions: a pilot study. J Diabetes Complications. 2003;17:199–204.
41. Campoccia D, Hunt JA, Doherty PJ, et al. Quantitative assessment of the tissue response to films of hyaluronan derivatives. Biomaterials. 1996;17:963–75.
42. Khachemoune A, Bello YM, Phillips TJ. Factors that influence healing in chronic venous ulcers treated with cryopreserved human epidermal cultures. Dermatol Surg. 2002;28:274–80.
43. Bello YM, Falabella AF. Use of skin substitutes in dermatology. Dermatol Clin. 2001;19:555–61.
44. Smith DJ. Use of Biobrane in wound management. J Burn Care Rehabil. 1995;16(3 Pt 1):317–20.
45. Davis DA, Arpey CJ. Porcine heterografts in dermatologic surgery and reconstruction. Dermatol Surg. 2000;26:76–80.
46. Mostow EN, Haraway GD, Dalsing M, et al; OASIS Venus Ulcer Study Group. Effectiveness of an extracellular matrix graft (OASIS Wound Matrix) in the treatment of chronic leg ulcers: a randomized clinical trial. J Vasc Surg. 2005;41:837–43.
47. Heimbach D, Luterman A, Burke J, et al. Artificial dermis for major burns. A multi-center randomized clinical trial. Ann Surg. 1988;208:313–20.
48. Eisenbud D, Huang NF, Luke S, Silberklang M. Skin substitutes and wound healing: current status and challenges (part 1 of 2). Wounds. 2004;16:2–17.
49. Yang JY, Tsai YC, Noordhoff MS. Clinical comparison of commercially available Biobrane preparations. Burns. 1989;15:197–203.
50. Falanga V, Margolis D, Alvarez O, et al. Rapid healing of venous ulcers and lack of clinical rejection with an allogeneic cultured human skin equivalent. Human Skin Equivalent Investigators Group. Arch Dermatol. 1998;134:293–300.
51. Consensus Development Conference on Diabetic Foot Wound Care: 7–8 April 1999, Boston, Massachusetts. American Diabetes Association. Diabetes Care. 1999;22:1354–60.
52. Fletcher A, Cullum N, Sheldon TA. A systematic review of compression treatment for venous leg ulcers. Br Med J. 1997;315:576–80.
53. Stemmer R, Marescaux J, Furderer C. [Compression therapy of the lower extremities particularly with compression stockings]. Hautarzt. 1980;31:355–65.
54. Kikta MJ, Schuler JJ, Meyer JP, et al. A prospective, randomized trial of Unna's boots versus hydroactive dressing in the treatment of venous stasis ulcers. J Vasc Surg. 1988;7:478–83.
55. Callam MJ, Ruckley CV, Dale JJ, Harper DR. Hazards of compression treatment of the leg: an estimate from Scottish surgeons. Br Med J (Clin Res Ed). 1987;295:1382.
56. Hendricks WM, Swallow RT. Management of stasis leg ulcers with Unna's boots versus elastic support stockings. J Am Acad Dermatol. 1985;12(1 Pt 1):90–8.
57. Cordts PR, Hanrahan LM, Rodriguez AA, et al. A prospective, randomized trial of Unna's boot versus Duoderm CGF hydroactive dressing plus compression in the management of venous leg ulcers. J Vasc Surg. 1992;15:480–6.
58. Cullum N, Nelson EA, Fletcher AW, Sheldon TA. Compression bandages and stockings for venous leg ulcers. Cochrane Database Syst Rev. 2000;(2):CD000265.
59. Weinstein C, Ramirez O, Pozner J. Postoperative care following carbon dioxide laser resurfacing. Avoiding pitfalls. Dermatol Surg. 1998;24:51–6.
60. Onouye T, Menaker G, Christian M, Moy R. Occlusive dressing versus oxygen mist therapy following CO_2 laser resurfacing. Dermatol Surg. 2000;26:572–6.

This page intentionally left blank

Biopsy Techniques and Basic Excisions

146

Suzanne Olbricht

Chapter Contents

Key concepts ... 2381
Indications/contraindications ... 2387
Preoperative history and considerations ... 2387
Techniques ... 2388
Variations/unusual situations ... 2395
Postoperative care ... 2396
Complications ... 2396

Key features

- Choice of a particular biopsy technique is based upon the anatomic site, type of skin lesion, desired histologic information and patient preference
- Wound closure is accomplished via suturing (primary intention) or second intention
- Choice of a specific suturing technique depends upon the needs of the wound, e.g. eversion of the edges, with the goal being an optimal functional and aesthetic result
- Excision *in toto* with repair is a common surgical procedure for dermatologists and it is accomplished through a series of well-defined steps
- Postoperative care and instructions minimize the risk of complications

INTRODUCTION

The cornerstone of dermatologic diagnosis is the correlation of clinical and histologic findings. A biopsy procedure is required in order to obtain tissue for pathologic examination, and fortunately the skin is more accessible than most other tissues. Modern instruments and techniques allow cutaneous biopsies to be performed efficiently with minimal tissue distortion. In some situations, a biopsy procedure is also curative, either coincidentally or intentionally. Knowledge of basic excisional surgical techniques can minimize cosmetic and functional impairment. Performance of a timely skin biopsy may also circumvent the need for more invasive procedures, and even critically ill patients can undergo a skin biopsy with minimal risk.

KEY CONCEPTS

Site Selection

Performance of a biopsy that will yield accurate and relevant histologic information depends upon the selection of an appropriate lesion or site within a lesion (Table 146.1).

The anticipated depth of the lesion to be biopsied must also be considered. In the case of a superficial lesion, e.g. an actinic keratosis versus Bowen's disease, it can be assessed via a more "superficial" biopsy that extends to the papillary dermis. On the other hand, accurate diagnosis of a subcutaneous nodule, e.g. panniculitis versus polyarteritis nodosa, requires a biopsy that includes subcutaneous tissue. Occasionally, fascia must be obtained, e.g. morphea profunda versus eosinophilic fasciitis. Disorders that primarily affect the collagen and elastic fibers within the dermis may have subtle histologic findings (e.g. atrophoderma of Pasini and Pierini) and longitudinally sectioned wedge biopsies that include both the affected area as well as adjacent normal-appearing skin prove most helpful.

Biopsy Technique Selection

Seven major methods are employed to biopsy skin: curettage, snip or scissors biopsy, shave biopsy, saucerization biopsy, punch biopsy, incisional biopsy, and excision *in toto* (Table 146.2). Depending upon the type of lesion and its size, several of these procedures are also curative, especially excision *in toto*. However, these methods do differ with regard to the quality and quantity of skin obtained. Lesional characteristics and operator experience are factors that influence the choice of a particular procedure.

Although *curettage* is frequently used to remove clinically benign epidermal lesions (e.g. verrucae, seborrheic keratoses) as well as actinic keratoses (e.g. in patients with vascular rosacea in whom hypopigmentation from liquid nitrogen application can be problematic), there are situations where histologic confirmation of the presumed diagnosis is desirable. For example, curettings are used to confirm the clinical diagnosis of basal cell carcinoma (BCC) just prior to definitive treatment by curettage and electrodesiccation. However, because the tissue specimen is often fragmented, pathologic orientation is difficult, and this may hinder histologic interpretation. *Snip or scissors biopsy* is an efficient technique for assessing pedunculated lesions as well as removing benign growths (e.g. acrochordons, filiform warts).

The *shave biopsy* usually provides a specimen consisting of epidermis, papillary dermis and, sometimes, reticular dermis (particularly in elevated lesions). It is a popular biopsy technique for "planing" papular, clinically benign lesions (e.g. irritated or unwanted compound and dermal melanocytic nevi, fibrous papules of the nose) where histologic confirmation is desired. Shave biopsy is also a useful procedure for diagnosing superficial carcinomas, e.g. nodular and superficial BCCs, squamous cell carcinoma (SCC) *in situ*, lentigo maligna.

Some authors distinguish a shave biopsy from a *saucerization procedure* in which the depth of the biopsy specimen is intentionally deeper due to the angulation of the blade. This latter technique is often used to biopsy melanocytic nevi with atypical features, especially on the trunk, as well as minimally invasive SCCs or keratoacanthomas. Its advantage is that it allows histologic examination of the entire lesion, which increases diagnostic accuracy, especially in the case of larger lesions (as compared to partial punch biopsy).

BIOPSY SITE SELECTION

Lesion/disorder	Appropriate site
Tumor	Thickest portion; avoid necrotic tissue
Blister	Edge of lesion, including perilesional skin (see Fig. 0.11)
Ulcerated/necrotic lesion	Edge of ulcer or necrosis plus adjacent skin
Generalized polymorphous eruption	Characteristic lesion of recent onset (± more developed lesion)
Small vessel vasculitis	Characteristic lesion of recent onset

Table 146.1 Biopsy site selection.

SELECTION OF TYPE OF BIOPSY TECHNIQUE				
Method	**Indication**	**Type of specimen obtained**	**Anesthetic technique (see Fig. 146.1)**	**Closure**
Curettage	• Lesions involving the epidermis (e.g. SKs, AKs, verrucae) • Confirm clinical diagnosis of BCC prior to definitive treatment	Epidermal sheet or fragmented	Wheal	Secondary
Scissors biopsy	• Pedunculated lesion	Tissue above connection to the epidermis	None or wheal	Secondary
Shave biopsy	• Lesions involving the epidermis ± superficial dermis • Elevated lesion	Epidermis, papillary dermis and, occasionally, reticular dermis (elevated lesions)	Wheal	Secondary
Saucerization biopsy	• Lesions involving the epidermis and dermis	Similar to a shave biopsy, but specimen is thicker (i.e. contains reticular dermis)	Wheal	Secondary
Punch biopsy	• Process (e.g. tumor, inflammation) involves the dermis • Depressed lesion	Epidermis, dermis and, sometimes, subcutaneous fat	Wheal or deep	Primary; simple suture
Incisional biopsy	• Process (e.g. tumor, inflammation) involves the subcutaneous fat or fascia • Large-sized tumors • Subtle disorders of dermal connective tissue	Epidermis, dermis and subcutaneous fat	Deep	Primary; layered closure
Excision *in toto*	• Biopsy intended to be definitive treatment • Strong clinical suspicion of cutaneous malignancy (e.g. invasive melanoma)	Epidermis, dermis and subcutaneous fat	Deep	Primary; layered closure

Table 146.2 Selection of type of biopsy technique. AKs, actinic keratoses; BCC, basal cell carcinoma; SKs, seborrheic keratoses.

SPECIMEN HANDLING		
Proposed laboratory test	**Carrier medium**	**Comments**
Routine microscopy, immunohistochemistry, PCR	10% neutral buffered formalin	Fixation process begins immediately
Direct immunofluorescence	Michel's medium or fresh*	Depends on laboratory preference or availability
Flow cytometry	Fresh*	Lymphoma cutis
Culture for bacteria, mycobacteria or fungi	Fresh* or minced in sterile culture/carrier medium appropriate for organism (usually performed by laboratory)	
Culture for viruses	Viral transport medium (e.g. M4RT)	
Electron microscopy	Glutaraldehyde	

*Laboratory must be in close proximity and specimen placed on saline-moistened gauze, but need to avoid bacteriostatic saline solution when culturing for microbes.

Table 146.3 Specimen handling. PCR, polymerase chain reaction.

The *punch biopsy* supplies a cylindrical to conically shaped specimen consisting of epidermis, dermis and, sometimes, subcutaneous fat. The volume of tissue sampled correlates with the size of the punch biopsy instrument. In general, the diameter of the metal "barrel" varies from 2 to 6 mm, and the wider the diameter, the greater the likelihood of obtaining subcutaneous fat. However, the thickness of the dermis and the amount of subcutaneous fat required to establish the diagnosis must be kept in mind. Punch biopsies are particularly helpful for examining processes within the dermis, e.g. tumors, inflammation (see Table 146.2). In the case of tumors, sampling a majority of the lesion is desirable, but for large-sized tumors, multiple punch biopsies may be required.

The *incisional* biopsy removes a wedge of tissue from the center or edge of a lesion (see Site selection) and is the best option for obtaining deep subcutaneous fat or fascia for histologic examination. It is also used to sample a significant portion of large-sized tumors. Excision *in toto* removes the entire lesion and includes epidermis, dermis and subcutaneous fat. For these reasons, it is often the biopsy of choice for a presumed invasive cutaneous melanoma[1].

Specimen Handling

Transportation of the biopsy specimen to the laboratory differs according to the processing and type of examination required. Most specimens are placed in formalin, but, occasionally, special carrier media are necessary (Table 146.3). Fresh tissue specimens are sent on saline-moistened gauze and either promptly delivered to the laboratory or packed in ice; the laboratory must be in reasonable proximity and have the capability of processing the tissue immediately. When handling small or thin biopsy specimens, it is important to confirm that they are clearly within the formalin solution and not adhering to the upper portions of the container or lid; this prevents desiccation artifact.

A protocol must be established within the clinician's practice to ensure that specimens and results are appropriately tracked and assigned to the correct patient. Immediately after the biopsy specimen has been obtained, it should be placed in a container previously labeled with the patient's name and other identifying information. If multiple biopsies are to be performed, prelabeling the containers alphabetically and with the respective sites avoids confusion. The specimen and its accompanying requisition form are then taken to a designated site, where the appropriate information is first logged into a pathology specimen book (paper or electronic), and then the specimen is set aside for delivery to the pathology laboratory.

When the report is received, a notation is made in the pathology book, cross-checking the patient-identifying information. It is also useful to have the pathology book identify the plan for the patient and whether the plan has been accomplished. For instance, the book may document that the patient already has an appointment for suture removal. When the suture removal has taken place and the patient has been informed of the results of the biopsy, this information is also logged into the book. Some patients prefer a call regarding any anxiety-provoking biopsy results such as skin cancer, but most patients appreciate a written letter detailing the diagnosis and recommended treatment plan. Regardless, if a biopsy has been performed, it is the physician's responsibility to track the specimen and follow through to notification of the results to the patient and disposition of recommended care.

Patient Preparation

A discussion of the reason(s) to do the biopsy, the site to be biopsied and the technique to be used can be brief and to the point. Informed consent requires a discussion of the major risks, which include bleeding, discomfort, infection and scarring (see Ch. 151). Bleeding can often be controlled by firm pressure at the site of the wound, but may require more aggressive forms of hemostasis. Discomfort is usually minimal, although some sites such as the forehead, fingers and feet may throb.

Infection is unusual. Except when the area to be biopsied is already infected or the site is mucosal, the skin can be prepared by application of an antiseptic agent and the procedure is then considered to be a *clean* procedure. For clean procedures of non-mucosal sites, preoperative prophylactic antibiotics are currently not recommended, even in patients with artificial valves or joints (with the possible exception of sites at high risk of infection, e.g. groin, during the first 2 years after joint placement)[2–4]. Tables 151.2 and 151.3 review the guidelines for antibiotic prophylaxis as well as regimens for both oral and non-oral sites. Preoperative antibiotics are administered within a 2-hour window before the incision; there is debate as to whether or not a second dose is administered 6 hours later and under which circumstances antibiotics should be continued for 48–72 hours[5]. When pretreated with a 5-day regimen of intranasal mupirocin ointment (twice daily) and a total body wash with chlorhexidine soap (daily), nasal carriers of *Staphylococcus aureus* were observed to have fewer postoperative infections[6].

Most patients are primarily interested in discussing whether or not there will be visible scarring. This is best predicted by the type of biopsy to be performed and the anatomic site. Generally, patients can be reassured that small biopsies may be done without grossly noticeable permanent "marks".

Many patients are anxious about the needle sticks required for administration of the local anesthesia and the pain of the procedure. The patient's cooperation is easily obtained in an organized and peaceful environment with a calm and reassuring staff. A well-informed, comfortable patient in a supine position will tolerate the procedure without difficulty.

Site Preparation and Anesthesia

Effective site preparation is most efficient if a standard clinical protocol has been established (Table 146.4). Marking and photographing the site[7], cleansing the skin (Table 146.5)[8], and draping are important procedures prior to the instillation of local anesthesia. Local anesthesia is adequate for all skin biopsies and is reviewed in detail in Chapter 143.

When the local anesthetic agent is instilled in a deep compartment (i.e. subcutaneous fat; Fig 146.1A), 5 to 10 minutes is required for anesthesia to develop on the surface of the skin. Gentle massage of the site may assist in spreading the agent subepidermally and achieving

SITE PREPARATION PROTOCOL

Sequential steps	Comments
Mark site with surgical pen or ink	Local anesthesia may obscure site, especially when the erythematous color is due to vasodilation or when there is a minimally elevated dermal tumor
Time out for patient and site identification	JCAHO universal protocol for patient safety
Photograph site or record landmarks	Up to ~15% of biopsy sites may be later incorrectly identified by the patient and ~5% by the surgeon[7]
Clip hair as needed	Shaving hair increases incidence of infection
Cleanse skin surface	Antiseptic agents listed in Table 146.5
Drape	Gauze (small biopsies) or sterile cloths
Anesthetize	Local instillation of anesthetic agent

Table 146.4 Site preparation protocol. JCAHO, Joint Commission on Accreditation of Healthcare Organizations.

ANTISEPTIC AGENTS

Agent	Advantages	Disadvantages
Povidone-iodine (Betadine®)	Broad antimicrobial spectrum, including fungi	Skin irritant; contact dermatitis; residual color; may cross-react with radiopaque iodine and iodides in medications
Chlorhexidine (Hibiclens®)	Broad antimicrobial coverage; no absorption; non-toxic; prolonged suppression of bacterial growth	Irritating to eyes (keratitis) and middle ear (otitis)
Isopropyl alcohol	Inexpensive; denatures protein, including bacterial cell walls; immediate (but not prolonged) effect	Weak antimicrobial activity; flammable in the setting of cautery; skin irritant; skin must remain wet for 2 minutes for maximum effect
Chlorhexidine–isopropyl alcohol combination (ChloraPrep®)	Combination provides both short-term and long-term effects; evidence it is more effective than povidone-iodine[8]	Those of either agent alone (see above)
Hexachlorophene (pHisoHex®)	Strong effect against Gram-positive cocci	Little effect on Gram-negative organisms or fungi; teratogen; absorbed through skin with potential neurotoxicity in infants
Soap and water	Traditional preoperative handwashing regimen; disinfects hands as well as alcohol-based rubs[9]; better against *Clostridium difficile* and Norwalk virus	At operative site, cumbersome and messy; no prolonged antisepsis
Hydrogen peroxide		No significant antiseptic properties; cytotoxic to keratinocytes in culture

Table 146.5 Antiseptic agents.

LOCAL ANESTHESIA INJECTION

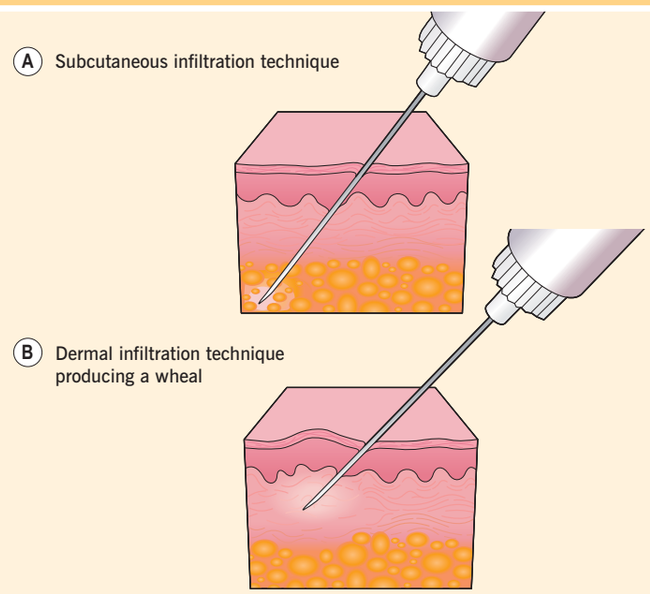


Fig. 146.1 Local anesthesia injection. A Deep infiltration. **B** Superficial infiltration.

METHODS OF HEMOSTASIS	
Method	**Comments**
Compression	• Appropriate for small-diameter, superficial wounds • Folded dry sponge with tightly applied bandage
Styptics: aluminum chloride hexahydrate (Drysol™, Xerac AC™) or ferric subsulfate (Monsel's solution)*	• Apply pressure to diminish active bleeding • Then apply styptic with cotton-tipped swab and pressure to wound bed for 30 sec - 2 min
Absorbable hemostatic sponge: Gelfoam®, Instat®	• Apply pressure to diminish active bleeding • Then place sponge in wound and bandage in place with pressure • Warn patient of presence of "foreign body"
Electrocoagulation and heat cautery	• Reviewed in Chapter 140
Sutures	• When used for wound closure, generally creates sufficient hemostasis in the sidewalls of the wound • Figure-of-eight stitch, utilizing an absorbable suture (see Fig. 146.2), may be required for a large-caliber vessel
*Ferric subsulfate (Monsel's solution) can result in a tattoo.	

Table 146.6 Methods of hemostasis.

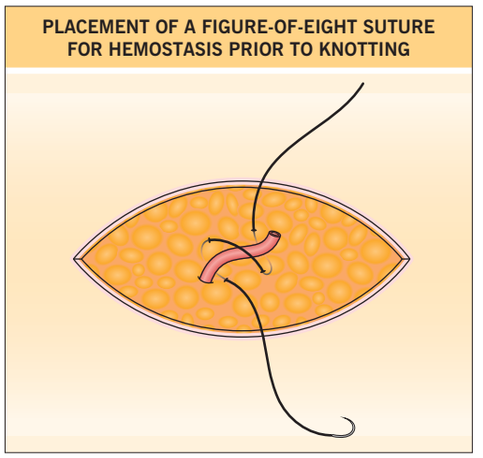


Fig. 146.2 Placement of a figure-of-eight suture for hemostasis prior to knotting.

SECOND INTENTION HEALING – INDICATIONS, DISADVANTAGES AND CONTRAINDICATIONS
INDICATIONS
• Shallow wounds • In combination with a primary closure in which the deepest portion is closed primarily • Concave sites (e.g. medial canthus, conchal bowl, alar crease, temple) • Mucosal sites (e.g. conjunctivae, lip, genitalia) • Infected, necrotic or easily infected sites • Sites under significant tension because of physical exercise or size of the wound • Preferred by patient (simple, no sutures, normal activities)
DISADVANTAGES
• Sometimes prolonged healing time • Scarring which may be depressed and angulated or circular (especially if not in concave site)
CONTRAINDICATIONS
• Relative: wound into muscle or fascia • Absolute: inability to stop bleeding without a suture

Table 146.7 Second intention healing – indications, disadvantages and contraindications.

good anesthesia. Injection of the agent superficially, creating an edematous wheal, has immediate efficacy but is more painful (Fig. 146.1B). Since a punch or shave biopsy requires very little agent and therefore a very short injection time, superficial instillation is the technique often used. In addition, a wheal is helpful prior to a shave biopsy as the lesion is further elevated from the plane of the surrounding skin. Of note, since epinephrine (adrenaline) requires up to 15 minutes to produce maximal vasoconstriction and thereby minimize bleeding[10], lidocaine without epinephrine is sufficient for an immediate biopsy. Regardless of other considerations, it is critical to have the local anesthesia in the compartment that is to be biopsied, i.e. a superficial wheal may be entirely adequate as anesthesia for a shave biopsy but will not suffice for an incisional wedge biopsy that extends into the subcutaneous fat.

Hemostasis

All biopsy procedures require attention to hemostasis of the wound bed (Table 146.6; see Table 151.4). While styptics and absorbable hemostatic sponges are used for those wounds healing by second intention, punch biopsy sites are usually closed primarily, with the suturing itself providing sufficient hemostasis. Wounds created during incisional biopsy or excision *in toto* may require electrocoagulation for hemostasis before closure (see Ch. 140). The endpoint is no active bleeding in the wound bed. Bleeding within the dermis in the sides of the wound can be controlled by suturing and does not need cautery. At times, to produce hemostasis, a large actively bleeding vessel may need to be identified, grasped with a hemostat, and tied off with an absorbable suture and a figure-of-eight stitch (Fig. 146.2).

Wound Closure

Closure of wounds created by a biopsy procedure may occur by either secondary or primary intention healing. Second intention healing repairs wounds by the processes of granulation tissue formation, epidermal cell migration, and contraction (see Ch. 141). These processes occur simultaneously, beginning within the first few days after surgery and continuing until the wound has completely re-epithelialized. For the remainder of the patient's life, maturation of the scar occurs, with gradual improvement in color, texture and contour. Indications, disadvantages and contraindications for second intention healing are outlined in Table 146.7.

Closure of the wound via suturing is regarded as primary intention healing. The same processes of granulation tissue formation, epithelial migration, and contraction occur; however, they are significantly reduced, because the sides of the wound are already opposed. Processes related to fibroblast activity and collagen deposition play a more important role in primary intention healing, allowing adequate tensile strength to develop in order to keep the wound closed[11]. These scars also undergo maturation throughout the remainder of the patient's life. Both secondary and primary intention healing are promoted by appropriate wound care and dressings.

For primary intention healing, wounds may be closed either by placement of a simple full-thickness suture or by a layered closure. In a layered closure, subepidermal buried sutures oppose subcutaneous and dermal tissue, provide alignment of the wound edges, set up the wound edges for eversion, and assist with hemostasis by occluding any vessels bleeding within the edge of the wound. In addition, the subepidermal sutures supply strength to handle tension within the closure. Although subepidermal sutures are generally absorbable, they remain intact within the tissue for 8 to 12 weeks, the period during which the scar is slowly acquiring tensile strength. As a result, they prevent dehiscence and spread of the scar. Epidermal or skin sutures oppose the epidermal edges and complete eversion. They can also correct minor degrees of misalignment in the closure. Satisfying these objectives via conscious placement of sutures improves the function and appearance of the scar[12].

Knotting is the means for stabilizing the placement of the suture, usually produced with an instrument tie (Fig. 146.3). The first throw of the knot is started by pulling the long end of the suture tight with the fingers of the non-dominant hand and looping it around the needle holder once or twice. The needle holder then grasps the short end and pulls it through the loops. The loops are pulled across the wound so that they lie flat. These steps are then repeated to produce the second throw of the knot, but this time with the loop in the opposite direction around the needle holder. When this second loop is pulled across the wound, a square knot is created. Depending on the memory and thickness of the suture material (see Ch. 144), three to six throws may be required to properly secure the knot. Care is taken to ensure that the knot lies flat without significant tension or tightness[13]. Sometimes, a loose loop is left in the second throw, to allow the suture to adjust to any wound swelling that may develop.

Sutures commonly used for subepidermal placement are composed of synthetic absorbable materials, e.g. braided polyglactin (Vicryl®) and monofilament polydioxanone (PDS®). The *interrupted buried dermal stitch* (Fig. 146.4A) is designed such that the stitch is in the dermis and fat and the knot is inverted (buried). The needle enters the undermined deep surface of the wound (not the sidewall) and passes up into the dermis. After crossing the wound, it enters the opposite side of the wound at the same level in the dermis and then exits the deep surface. The knot is then tied and the ends of the suture cut. When the suture material is released, the knot settles within the deep portion of the wound, minimizing tissue reaction to the suture and extrusion through the wound. Enough buried dermal sutures are placed such that tension is eliminated and the deep tissues are completely opposed. In order to facilitate eversion, this basic stitch may be modified, creating a *buried vertical mattress stitch*[14]. In this stitch, the suture is nearest to the skin surface (within the superficial dermis) at a point 3–4 mm lateral to the wound edge, and then it exits the wound deeper in the dermis (Fig. 146.4B). A very subtle dimple may be appreciated above the suture where it lies superficially in the dermis.

On occasion, a *running dermal stitch* is used to close the deep component. This stitch is begun similarly to the interrupted buried dermal stitch, but, after tying, only the short end of the suture is cut. The needle then draws the suture through the subcutaneous fat and dermis on one side, passing to the other side, and then continuing along the length of the wound. At each step, the suture is pulled tightly to oppose the edges. At the end of the wound, the knot is achieved by tying the loose end to the last loop. This stitch is only used when there is little tension in the wound, as rupture of the suture material anywhere along the suture line would release the suture for the entire length of the wound, allowing dehiscence or spread of the scar.

Monofilament nylon (Ethilon®) or polypropylene (Prolene®) are commonly used epidermal sutures. The *simple interrupted epidermal stitch* is placed by passing the needle through the epidermis into the superficial dermis in a plane just superior to the buried suture, across the wound, into the dermis on the opposite side and then up through the epidermis (Fig. 146.4C). Eversion is assisted by placing the suture closer to the wound edge but relatively deeper in the wound so the epidermal surface does not roll. Using the curve of the needle to create the path for the suture also facilitates eversion. If there are no buried sutures, the stitch opposes the edges for the full depth of the wound (e.g. for closure of punch biopsies).

The *vertical mattress stitch* (Fig. 146.4D) is sometimes used for wounds in thicker skin where eversion may be difficult and when a single suture opposing the deep and superficial edges is desired. This stitch has four points of entry into the skin. It is started by passing the needle through the epidermis 5–8 mm lateral to the wound edge, exiting from the deep portion of the wound. It re-enters the opposite side of the wound in the same deep position, and exits from the epidermis equidistant from the wound edge as the entry point. The needle is reversed and the epidermis is re-entered *closer* to the wound edge; it is then drawn through the upper dermis before crossing the wound, entering the dermis and finally exiting close to the wound edge. Once tied, the knot is positioned on one side of the wound, not over the line of closure.

A *horizontal mattress stitch* can be used in thinner skin such as the neck or the dorsum of the hand, and it also has four points of entry into the skin. The first two points of entry are the same as in the vertical mattress stitch (Fig. 146.4E), but closer to the wound edge (i.e. 3–5 mm). However, after the needle is reversed, the third point of entry into the epidermis is *lateral* to the exit point (i.e. on the same side of the wound edge) and at the same distance from the wound edge. The suture is then drawn through the deep portion of the wound again, crosses the wound, enters the opposite sidewall in the same deep position and finally exits at the same distance from the wound edge, lateral to the first entry point. This knot, when tied, is also positioned on one side of the wound, not over the line of closure.

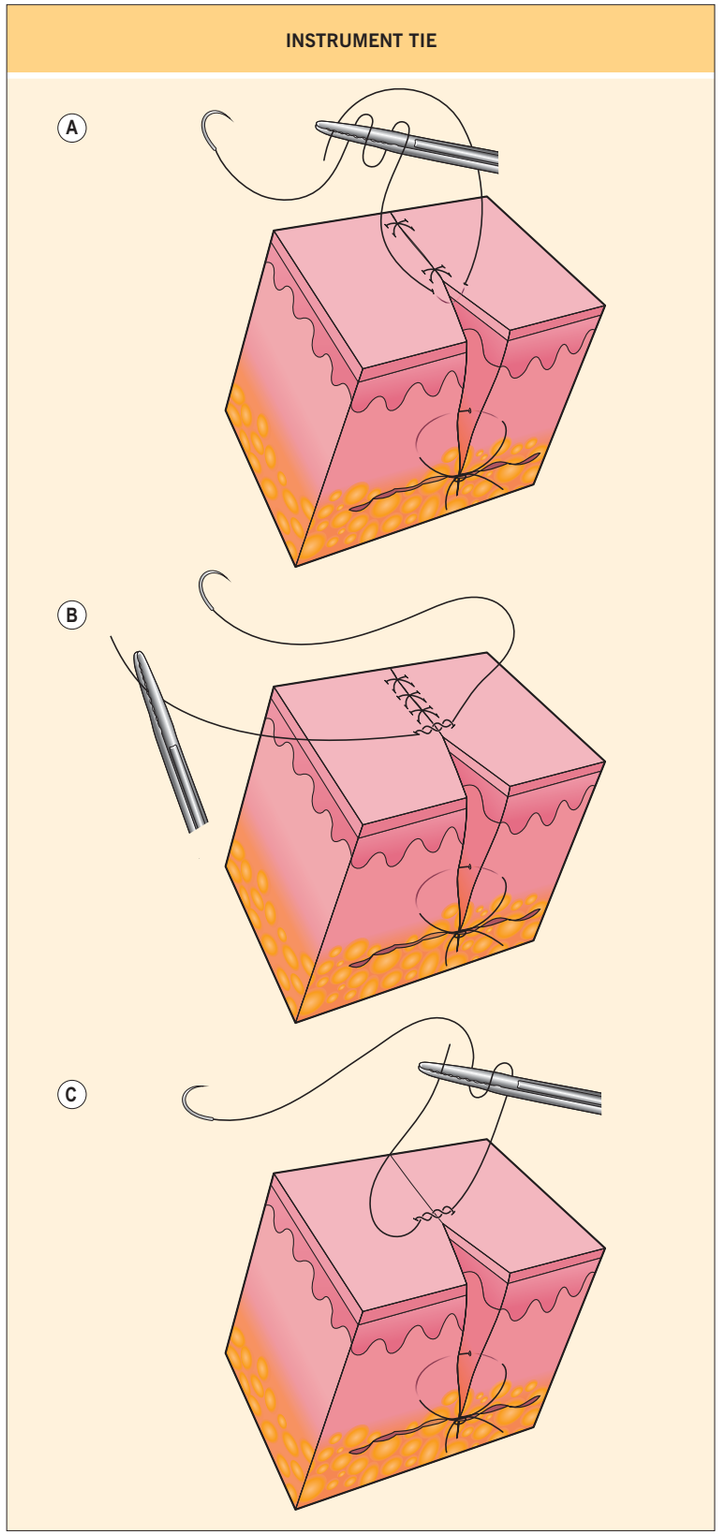


Fig. 146.3 Instrument tie. A The suture is looped around the needle holder, then the needle holder grasps the short end and pulls it through the loops to create a knot. **B** The suture is drawn over the wound so that the knot lies flat across the wound. **C** A loop is made around the needle holder in the opposite direction. The needle holder then grabs the short end and pulls it through so that the knot lies flat on the skin surface.

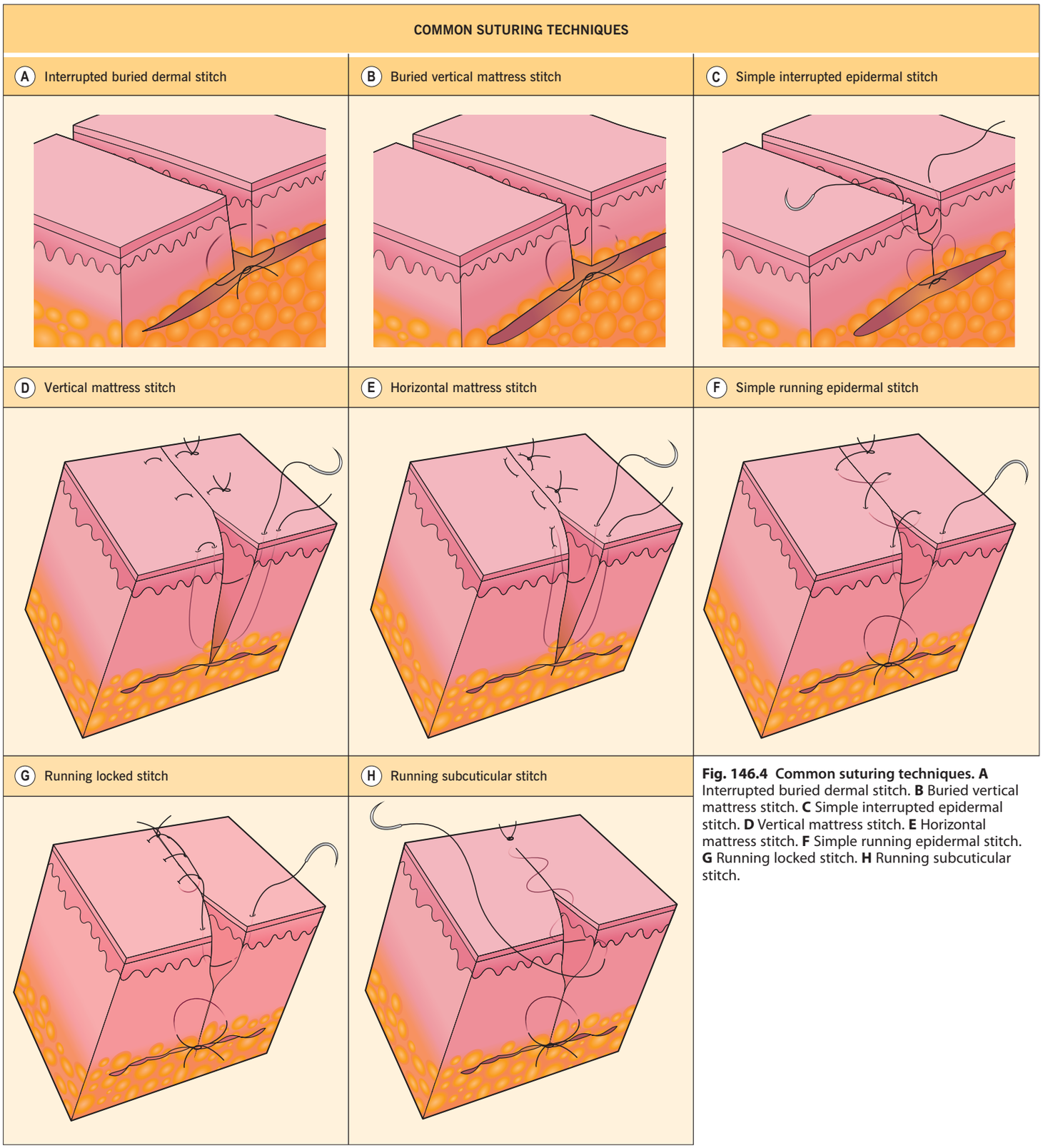


Fig. 146.4 Common suturing techniques. A Interrupted buried dermal stitch. **B** Buried vertical mattress stitch. **C** Simple interrupted epidermal stitch. **D** Vertical mattress stitch. **E** Horizontal mattress stitch. **F** Simple running epidermal stitch. **G** Running locked stitch. **H** Running subcuticular stitch.

Since sutures of both the vertical mattress and horizontal mattress stitches must be removed within 1–2 weeks (depending upon the site), they are not good stitches to use as the sole means of closure in a wound with tension. Of note, a variant, the running combined simple and vertical mattress stitch, also everts well and saves surgical time[15].

In the presence of buried sutures, a *simple running epidermal stitch* may be placed for opposition of the epidermal edges. This running stitch may be passed via the dermis and the epidermis in a fashion similar to the simple interrupted epidermal stitch (Fig. 146.4F). In addition, the needle may be passed under the superficial loop of the previous stitch, thus creating the *running locked stitch* (Fig. 146.4G). This stitch can assist with hemostasis and will not completely unravel if the suture breaks under wound tension. Alternatively, the stitch may be placed within the upper dermis, referred to as a *running subcuticular*

WOUND CLOSURE – ALTERNATIVES TO SUTURING	
Adhesive tapes (Steri-Strips™)	• For perfectly opposed lacerations or wound edges under little tension • Often used with a liquid adhesive, e.g. Mastisol®
Staples*	• Highest tensile strength • Good for wounds under tension
Tissue glues (e.g. 2-octyl cyanoacrylate [Dermabond™], fibrinogen [Tisseel™], hydrogel [Duraseal™])	• Can be considered for epidermal closure of wounds under little tension • Less effective than suturing for minimizing dehiscence
Laser welding (Nd:YAG, CO_2, argon lasers)	• Experimental and used infrequently in the clinical setting
Photochemical welding (Rose Bengal plus green light)	• Experimental
*Also requires skin stapler and staple remover.	

Table 146.8 Wound closure – alternatives to suturing.

stitch (Fig. 146.4H). This stitch is placed with the needle passing in and out of the upper dermis in a plane horizontal to the surface. Two knots are tied, one on each end of the wound, and they are the only visible portion of the suture. Running stitches are frequently used to save time, but they can accentuate minor misalignments of the wound edges[16]. They also do not necessarily prevent track marks, which occur because of tension, inadequate undermining, ineffective buried dermal sutures, and poor placement of the epidermal suture.

Non-absorbable sutures that pass through to the surface of the skin are removed. If they remain in place, they cause tissue inflammation and create a less than optimal functional and cosmetic result. To remove a suture, the thread is severed near the knot with either fine-tipped scissors or a #11 blade. The knot is then pulled over the line of closure so that the wound edges are not pulled apart. Sutures on the face are generally removed after 5–7 days, and sutures elsewhere, at 10–14 days. If buried dermal sutures are used, the epidermal sutures may be removed at the earlier times. Sometimes, absorbable suture material is used for superficial closures, especially in the simple running epidermal stitch, precluding the need for suture removal. Sterile adhesive tapes such as Steri-Strips™ or tissue glue (Dermabond™) are also occasionally used instead of epidermal sutures to avoid the need for suture removal, but they are ineffective in producing eversion and in dealing with tension. They may, however, reduce the amount of scar spreading if they are placed after suture removal and left in position for several weeks[17]. Table 146.8 outlines alternatives to sutures for wound closure[18–20].

INDICATIONS/CONTRAINDICATIONS

A biopsy is indicated at any time in which the clinical diagnosis of a cutaneous disorder is unclear or must be substantiated before a course of treatment is undertaken. Inflammatory disorders are often biopsied to assist in the differentiation of multiple processes that may have a similar clinical appearance. Infectious processes are biopsied so as to observe the causative organism in tissue sections and/or to obtain tissue for culture. Lesions suspicious for malignancy are biopsied in order to develop a surgical plan appropriate for the tumor type. Biopsies of normal skin may also be performed, to obtain tissue for metabolic or genetic studies[21,22]. Nowadays, skin biopsies are even performed prenatally.

Most patients can safely undergo a skin biopsy, so contraindications are not absolute. A skin biopsy may save the patient from a more invasive procedure if the disease process can be determined via histologic examination of the skin. Patients who are immunosuppressed because of medications (e.g. cyclosporine, prednisone, chemotherapy) or underlying diseases (e.g. HIV infection, lymphoma, leukemia) often require biopsies because of the complicated interplay between the underlying disorders and the side effects of therapy (e.g. infections, drug reactions).

In addition, there are no cutaneous or mucosal sites where a biopsy is contraindicated. Diagnostically, it is more useful to biopsy a lesion from the hand or the face that provides accurate information than it is to biopsy a late-stage, nonspecific lesion on the arm. Biopsies can be done on the legs of patients with diabetes mellitus as well as the digits of patients with vascular compromise, although greater attention to postoperative care may be necessary. For patients with coagulation or platelet disorders (due to either underlying diseases or medications), it may be preferable to biopsy a site that can be compressed to produce hemostasis. For example, if an arm or leg were biopsied, postoperative bleeding can be controlled by pressure applied by an elastic circumferential bandage.

In certain anatomic sites, it may be necessary to exercise caution to avoid injuring a vital structure (see Chs 142 & 151). The temporal nerve lies in a superficial location, just beneath thin dermis and subcutaneous fat, midway between the eyebrow and the temporal hairline. The spinal accessory nerve also courses superficially at the posterior edge of the sternocleidomastoid muscle at a point one-third of the distance between the mastoid process and the inferior attachments of the muscle. Severing these nerves leads to motor dysfunction; thus, these sites are best biopsied in a superficial manner. The temporal and thyroid arteries are also relatively superficial. Cutting them leads to temporary difficulty with hemostasis but has no long-term adverse effect.

Some lesions require special consideration before performing a biopsy. A mass that is pulsatile may indicate large arterial vessel involvement, a situation requiring additional clinical evaluation prior to biopsy and special surgical arrangements in case of bleeding. A post-traumatic cephalic mass or cystic midline lesion may need preoperative radiologic examination to determine any possible connection to the intracranial or intraspinal space[23]. Biopsy of a lesion on the upper trunk or shoulders of a patient who tends to form keloids must be carefully discussed, weighing the possibility of keloid formation against the utility of the information that will be obtained. Hypertrophic scars, on the other hand, are common and resolve with time and/or pressure as well as corticosteroid injections, and need not interfere with the performance of a biopsy.

PREOPERATIVE HISTORY AND CONSIDERATIONS

While there are no absolute contraindications to performing a biopsy, a clinician will want to be aware of certain features of a patient's medical and surgical history in order to formulate an adequate surgical plan and to predict the need to manage possible complications. Table 146.9 summarizes information pertinent to the issues previously discussed. In particular, patients who are taking medications or have underlying disorders that lead to abnormalities in coagulation or platelet function should be identified in advance. Almost all procedures can be done despite a patient receiving warfarin, heparin, clopidogrel or aspirin if the site of the biopsy is planned carefully and the options for hemostasis are readily available. The bleeding time may also be affected by alcohol ingestion, oral vitamin E, and nonsteroidal anti-inflammatory drugs, in addition to a number of alternative therapies,

PREOPERATIVE HISTORY
Allergies
Medications, including nutritional supplements and over-the-counter preparations (see Ch. 133)
Past reactions to local anesthesia
Difficulties with hemostasis during previous procedures
Past problems with wound healing, including infection, keloid formation
Pacemaker or implantable cardioverter-defibrillator (ICD)
Disease or past replacement of the cardiac valves
Past orthopedic surgery with joint replacement
Hypertension
Diabetes mellitus
Immunosuppression
Infection or vascular compromise at the biopsy site
Possible pregnancy

Table 146.9 Preoperative history.

including garlic, gingko, ginger, ginseng, feverfew, fish oil and green tea[24] (see Table 133.3). While biopsies may be done safely during pregnancy[25], the emotional turmoil surrounding a coincidental miscarriage or pregnancy mishap is great enough to defer elective procedures (e.g. shave biopsy of an unwanted intradermal nevus) to the postpartum period, whereas biopsies of atypical pigmented lesions in which the differential diagnosis includes cutaneous melanoma are not deferred. As long as they can cooperate, biopsies and excisions can also be done safely in children under local anesthesia.

TECHNIQUES

Curettage

Local anesthesia is achieved by wheal formation (see Fig. 146.1). Depending upon the size and thickness of the lesion, a curette 3–5 mm in diameter is held like a pencil and drawn with pressure under the lesion (if epidermal) or through the lesion (e.g. presumed BCC). With one smooth movement and moderate pressure (as well as traction by the non-dominant hand), an epidermal sheet or ball of tissue may be obtained (Fig. 146.5). In the case of incomplete removal, further fragments may be obtained by repeated curettage. This type of biopsy assumes that healing will be by second intention. Hemostasis may be obtained by a styptic, electrodesiccation, absorbable hemostatic sponge, or pressure. The resulting scar is usually minimal in the case of epidermal lesions or of no significant concern in the case of a BCC, as it is definitive treatment of the latter that produces the final scar.

Snip or Scissors Biopsy

Pedunculated lesions can be biopsied via a snip or scissors biopsy (Fig. 146.6). Local anesthesia is obtained by wheal formation in the upper dermis just under the narrow attachment of the lesion to the skin surface. For tumors with a very narrow neck, this type of biopsy can be done quickly without anesthesia. Scissors, usually fine iris scissors or sharp Gradle scissors, are used to separate the lesion from its base at the level of the skin surface. A toothed forceps is often used to handle the tissue. Healing is by second intention, and a styptic, electrodesiccation, absorbable hemostatic sponge, or pressure may be required for hemostasis. Scarring produced by this type of biopsy procedure is a small, often hypopigmented macule and may be very difficult to see.

Shave Biopsy and Saucerization Biopsy

Shave biopsy is the most commonly used technique for obtaining a skin specimen for histologic examination (Fig. 146.7). A local anesthetic is used to produce a wheal under the lesion so that it is elevated above the plane of the surrounding skin. A #15 blade on a blade handle is used (almost parallel to the skin surface) to cut the specimen from its bed. Alternatively, only the blade without the blade handle is used. Cutaneous surgeons generally hold the blade or the blade handle like a pencil, to facilitate control of small movements. It is helpful to begin on one edge by holding the blade vertically and incising only through the epidermis. The blade is then turned to a horizontal position and a smooth sawing motion is used to complete the removal of the specimen. A good specimen may also be obtained by a single-edged razor blade held in a semi-curved shape[26].

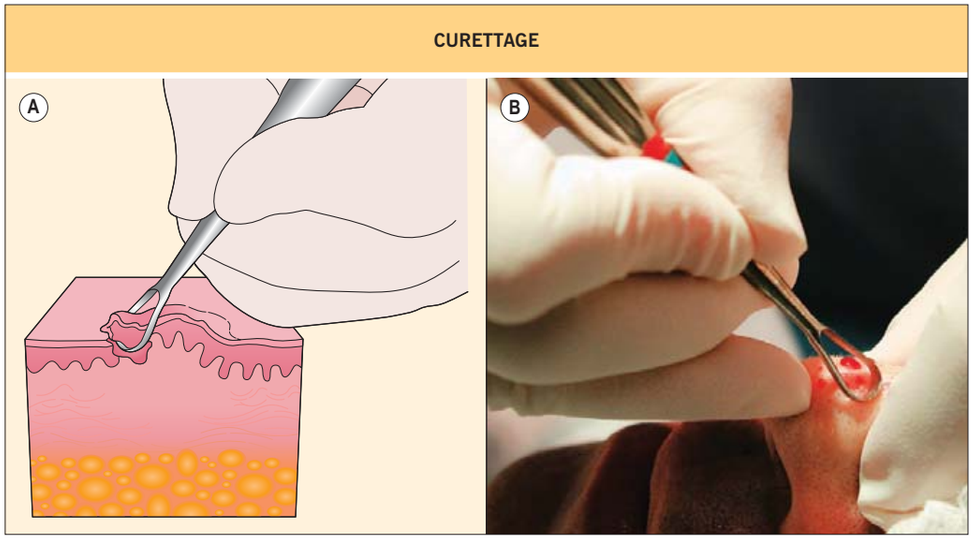


Fig. 146.5 Curettage. A Diagram. **B** Demonstration of technique.

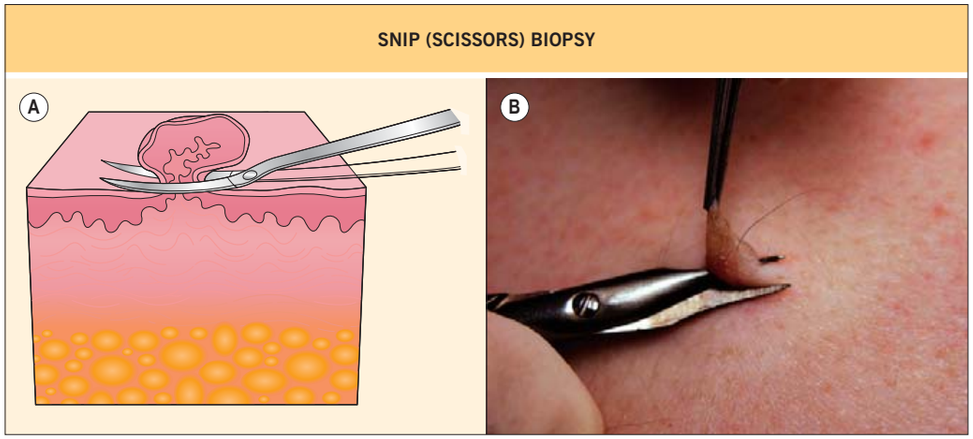


Fig. 146.6 Snip (scissors) biopsy. A Diagram. **B** Demonstration of technique.

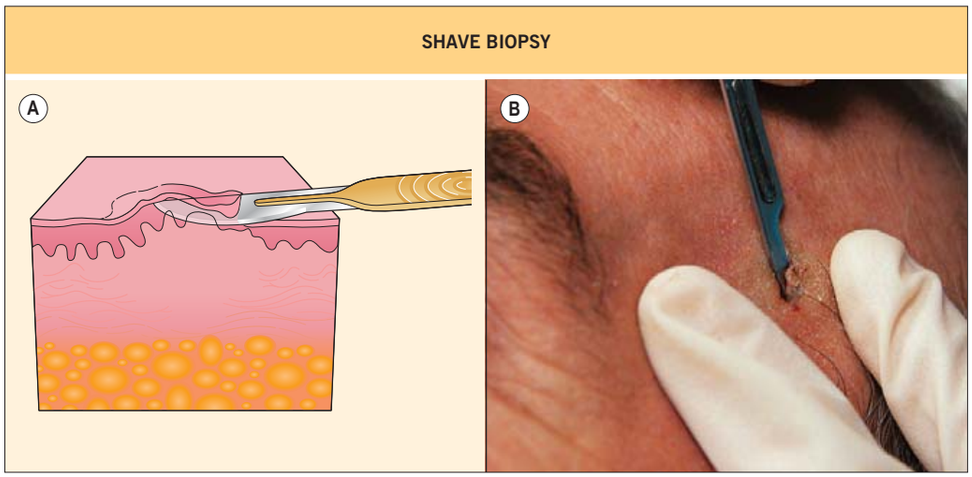


Fig. 146.7 Shave biopsy. A Diagram. **B** Demonstration of technique.

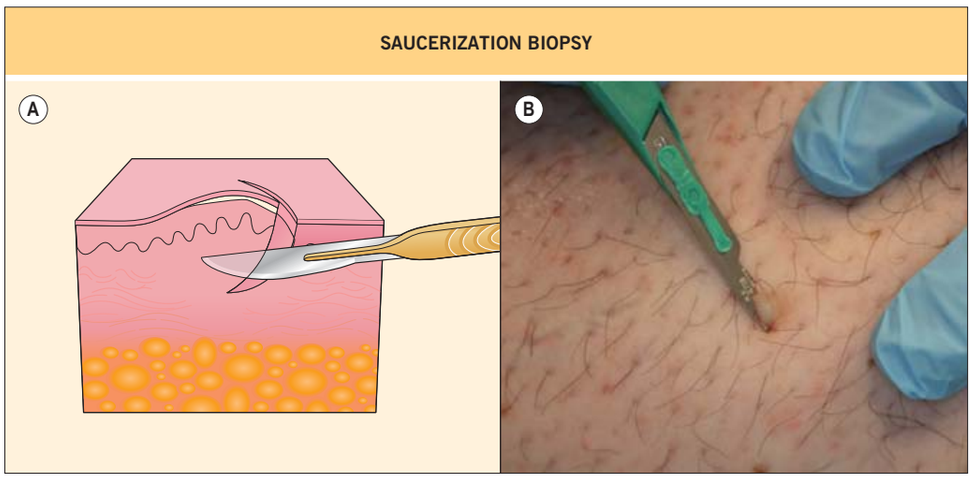


Fig. 146.8 Saucerization biopsy. A Diagram. **B** Demonstration of technique.

The goal is a shallow, saucer-shaped defect and a single piece of unfragmented tissue; edges should be smooth. Forceps may be used to hold the specimen while *in situ* in order to supply traction against the movement of the blade and then to remove the entire specimen and place it in the appropriate container. However, the tissue must be handled gently so that crush artifact does not confuse the microscopic appearance. Toothed, as opposed to smooth or ridged, forceps minimize crushing of the tissue. The specimen should include full-thickness epidermis and superficial dermis. The most common error when first performing shave biopsies is to remove only keratotic debris or the upper portion of the epidermis. The latter is especially true in areas with thick stratum corneum (e.g. palms, soles). Therefore, the dermatologist needs to appreciate the angulation of the blade that is required in order to obtain the full thickness of the epidermis for histologic examination. Observation of the wound bed and review of the tissue sections will help refine the skills needed to perform this procedure.

In a saucerization procedure, the depth of the biopsy specimen is intentionally deeper due to the angulation of the blade (Fig. 146.8). Both saucerization and shave biopsy sites heal by second intention. As with curettage and snip biopsy, hemostasis is easily obtained with a styptic, electrodesiccation, absorbable hemostatic sponge, and/or pressure. With practice and skill, as well as choosing the appropriate lesion to biopsy in this manner, the resulting mature scar is flat or slightly depressed with slight hypopigmentation.

Punch Biopsy

Punch biopsy is used to sample processes within the dermis or the occasional depressed lesion. As discussed above, the volume of tissue obtained varies depending upon the diameter of the metal "barrel". For example, the specimen obtained with a 2 mm punch biopsy is very small and may not yield sufficient pathologic findings for an accurate diagnosis. In one study, however, where 2 mm punch biopsy specimens (examined by a dermatopathologist) were compared to excisional specimens, an accurate diagnosis was made in 79 of 84 cases[27]. For most punch biopsies, an instrument with a 3 to 4 mm diameter is adequate. Occasionally, a 6 mm punch biopsy is performed to increase the likelihood of obtaining subcutaneous fat. However, as stated previously, the thickness of the dermis and the amount of subcutaneous fat required to establish the diagnosis must be kept in mind.

Disposable punch biopsy instruments are generally used. Reusable stainless steel instruments are available but must be sterilized following each procedure and sharpened frequently. Toothed forceps, scissors, needle holder, and suture material are also required. Local anesthesia is achieved with either superficial or deep instillation of the agent.

An optimal aesthetic result is obtained when the round punch biopsy instrument is used to produce an oval-shaped defect that can be closed without standing cone (dog-ear) formation when sutured into a straight line parallel to the other skin lines in the region. While traction is applied by stretching or spreading the skin with the index finger and thumb of one hand in the direction perpendicular to the relaxed skin tension lines (see Figs 142.6 & 142.7), the instrument is pushed into the skin and rotated in one direction with the other hand (Fig. 146.9). Back-and-forth twisting is not recommended as epidermis may be sheared off. Generally, the instrument is pushed and rotated until the subcutaneous plane is reached, as indicated by loss of the resistance encountered while cutting through the dermis. At times, the punch biopsy is utilized to just incise the skin superficially as when the skin is very thin (e.g. on the ear). The punch biopsy instrument is then

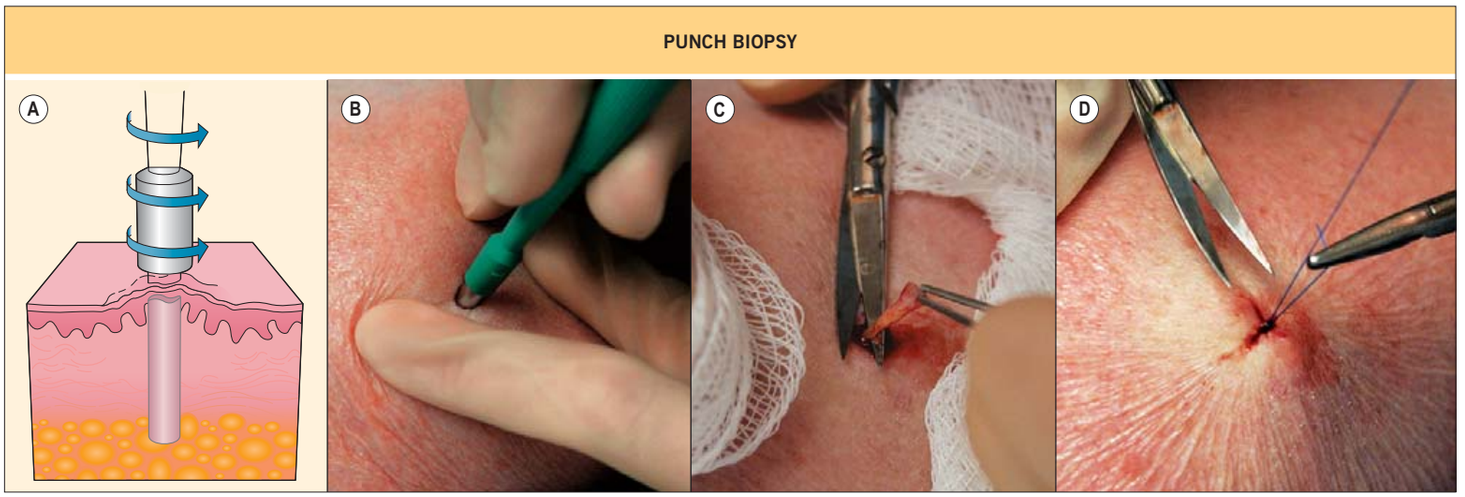


Fig. 146.9 Punch biopsy. A Diagram. **B** Punch biopsy instrument rotated into the skin. **C** Cutting the base of the specimen. **D** Closure of the biopsy wound with a simple epidermal stitch.

SPECIAL CONSIDERATIONS FOR A PUNCH BIOPSY ON THE FACE

- Position patient in a supine position with draping or gauze to protect the eyes from light or inadvertent damage by suture or instrument
- Use a 3 mm punch biopsy instrument (if possible); a 4 mm punch biopsy wound can produce standing cones when closed
- Choose a site with low visibility (if possible), e.g. in the shadows of the face, at cosmetic unit boundaries, or off/beyond the center of the face
- Protect underlying tissue with an anesthetic wheal
- Tailor depth of excision to depth of pathology rather than rotating and pushing the punch biopsy instrument to its hub
- Control bleeding with suture(s) – simple interrupted stitches of monofilament 5–0 or 6–0 nylon or polypropylene
- Protect with bandage and remove sutures at 5–7 days

Table 146.10 Special considerations for a punch biopsy on the face.

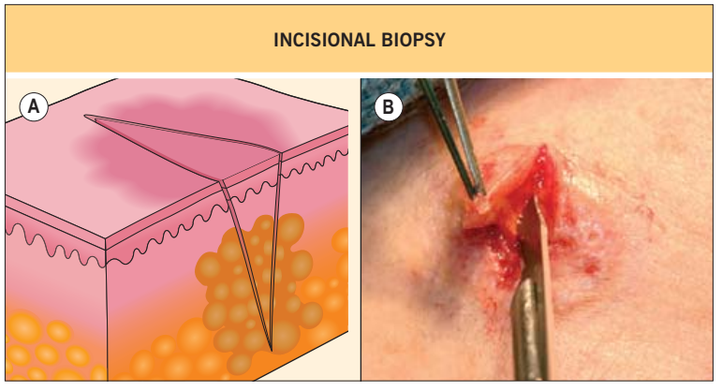


Fig. 146.10 Incisional biopsy. A Diagram. **B** Demonstration of the procedure.

removed and forceps are used (peripherally at one superficial edge) to gently extricate the specimen from the wound. Scissors may be needed to detach the base of the specimen, which can then be transferred to the appropriate container. In the case of fibrotic tumors or disorders, pressure may need to be applied to the surrounding skin to elevate the biopsy specimen.

Although a punch biopsy wound can be left to heal by second intention after achieving hemostasis, the resulting scar is often depressed and takes several weeks to heal. Usually this wound is closed primarily, and the resulting scar is generally white or hypopigmented and has a linear or cruciate configuration. On the trunk or extremities, one or two simple interrupted epidermal stitches of 4–0 nylon or polypropylene monofilament suture achieve closure and hemostasis. On the face, neck or hands, the resulting scar may be less apparent if 5–0 or 6–0 simple interrupted sutures are utilized. Some physicians use fast-absorbing gut for patients who are unable to return for suture removal. However, it is also reasonable to have the patient return for a face-to-face discussion of the biopsy results, since the biopsy is being done to establish a diagnosis and determine a treatment plan. Sutures on the face are removed at 5–7 days, and on the trunk or extremities, at 10–14 days. A pathology report is usually available within 7 days.

Table 146.10 highlights special considerations when performing a punch biopsy on the face.

Incisional Biopsy

Large lesions in which the characteristic pathology is within the dermis or subcutis are often biopsied via an incisional or wedge biopsy (Fig. 146.10). The specimen may be entirely lesional or may contain an edge of clinically normal skin, which allows comparison of involved versus uninvolved skin as well as examination for any microscopically apparent early changes at the edge of the lesion. The goal is to obtain a wedge of tissue 3–4 mm wide and as deep as necessary. The tissue should be in one piece for accurate orientation of the specimen during preparation; depending upon the possible diagnoses, longitudinal sectioning may be requested. The length of the wedge varies, but should be long enough to avoid cutaneous cone formation in the final closure.

Local anesthesia is obtained by deep and slow infiltration of the agent. It is advisable to wait 10 to 15 minutes after instillation to allow for complete anesthesia and to obtain the maximal vasoconstrictive effect of epinephrine. With a #15 blade (mounted on a blade handle) held perpendicular to the skin surface, a superficial incision into the epidermis scores one long side of the wedge using a light touch and one long motion, facilitated by traction by the non-dominant hand or an assistant. The second long side is then scored similarly. These lines are then redrawn with the blade held in the same manner but with firm pressure, incising into deep tissue, first one side, then the other. The incision is continued until the desired depth has been reached, usually in one or two more cutting movements. The incision is angled toward the center axis so that deep within the tissue, the two incisions meet and complete the separation of the tissue. A forceps is used to lift the tissue out of the wound. If the tissue is still connected at its base, the blade or tissue scissors may be used to complete the detachment.

Hemostasis is best achieved by point electrocoagulation. Large arterioles may require tying off with absorbable suture. An incisional biopsy wound is generally closed with suturing. In some circumstances, such as a site compromised by necrosis or infection, second intention healing may be the best option, even if it is slow and prolonged (see Table 146.7). Deep interrupted stitches of absorbable suture material, 4–0 or 5–0 in caliber, with the knot inverted are utilized to close the subcutis and the dermis (see Fig. 146.4). The epidermis is then closed with

EXCISION OF COMMON BENIGN CUTANEOUS LESIONS	
Lesion	**Comments**
Epidermoid inclusion cyst	Dissection facilitated by injection of liberal amount of local anesthesia into surrounding tissue; allows surgeon to work in plane between resulting edema and cyst wall[29] Fusiform excision should include any poral opening or scarring attaching the cyst to the surface Fusiform excision may be smaller than the area deformed by the cyst, but enough of the redundant expanded tissue should be excised so that the scar lies flat
Pilar cyst	See epidermoid inclusion cyst; dissection usually easier
Lipoma	The extent can be appreciated by palpation, then marked with surgical marking pen. A linear incision is made in the middle of the skin covering the lipoma. The tumor is more firm and dense than the surrounding normal subcutaneous fat
Dermatofibroma	Patient needs to be warned that scar may be more noticeable than original lesion, especially on the lower extremities
Melanocytic nevi	See text

Table 146.11 Excision of common benign cutaneous lesions.

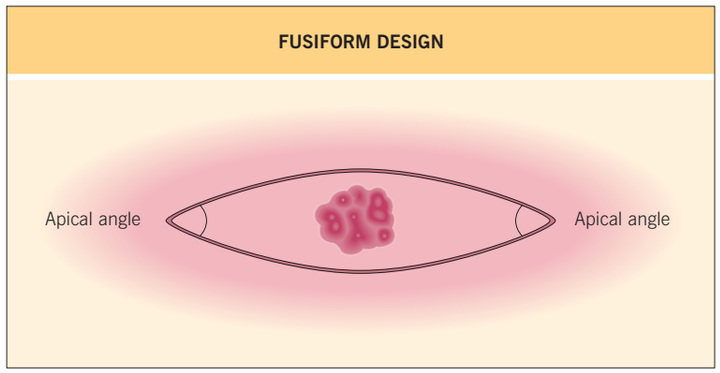


Fig. 146.11 Fusiform design.

simple interrupted sutures of nylon or polypropylene monofilament. The size of the epidermal suture varies depending upon the site; the face is generally closed with 6–0 suture and other sites by 4–0 or 5–0 suture.

Excisional Biopsy (Excision *in toto*)

Excision represents the workhorse of dermatologic surgery[28]. The procedure is designed to remove entire lesions for histopathologic examination as well as for surgical cure. Lesions such as a clinically typical BCC or an unsightly or troublesome subepidermal lesion presumed to be benign are commonly biopsied (or excised) in this fashion (Table 146.11). Atypical pigmented lesions highly suspicious for invasive melanoma are typically excised *in toto* as a biopsy procedure because the degree of atypia and depth of invasion may not be uniform; the excision allows the pathologist to examine the entire lesion and decreases the likelihood of sampling error. In addition, excision is frequently the treatment of choice after the diagnosis of a cutaneous malignancy has been established by a previous biopsy. The excision specimen is again submitted for histologic examination in order to confirm the diagnosis and for comment as to whether the margins of the specimen are clear of tumor. Although the basic concepts discussed above with regard to an incisional biopsy also pertain to this procedure, an excision *in toto* is more complicated because it is intended to be the final definitive procedure. Therefore, margins required for cure, as well as cosmetic and functional challenges with respect to the final scar, must be carefully considered in advance.

Recommended margins for removal of an entire lesion depend on the clinical diagnosis. Most benign lesions can be removed completely by including a 1–2 mm margin of normal-appearing skin around the circumference of the tumor. A clinically well-demarcated, small BCC or SCC is generally, though not always, cured with 4–5 mm margins[30,31]. Atypical nevi are frequently excised with 3–4 mm margins. While 4 mm may not be required for complete removal of the lesion, it may save some patients from a second procedure, since it is standard practice to re-excise a nevus with severe atypia that is still present at the margins microscopically. The suggested margin for melanoma *in situ* (with the possible exception of lentigo maligna, where wider margins may be required) is 5 mm. For invasive melanoma, the recommended margin depends on the Breslow depth, e.g. 1 cm margins for tumors ≤1.0 mm in depth (see Ch. 113). The depth of the defect to be created must also be planned in advance[32]. Primary closure is facilitated when the base of the surgical wound lies within subcutaneous fat. In the case of melanomas, the excision should include full-thickness skin and subcutis, with fascia at the base of the wound.

Although an excision is often referred to as an ellipse, the actual shape is fusiform (Fig. 146.11). The optimal geometry of the wound varies depending on the contour of the site and the elasticity and thickness of the skin[33]. The angle at each end of the excision varies from 30 to 75 degrees[34]. In order to minimize standing cone formation, each side of the fusiform shape is three to four times as long as it is wide. The central axis becomes the line of closure and dictates where the surface scar will be visible. The mature scar should appear as a thin line, although some spreading may be seen on the upper trunk and shoulders. From a cosmetic standpoint, an optimal scar results when the line of closure is placed within major skin folds, skin lines with minimal tension, wrinkles, or boundaries between distinct cosmetic units (see Ch. 142). Movement of underlying muscles may distort the line of closure, but this can be predicted in advance and the excision plan adjusted. For hair-bearing areas, the line of closure should follow the normal patterns of hair growth.

The process of excision and repair can be divided into a series of steps (Fig. 146.12). Local anesthesia is best obtained by injection into the subcutaneous tissue. The planned excision, which can be delineated with surgical marking dye *prior* to injection, is ringed by the anesthetic agent, with the needle pointed outward to include the area needed for undermining. After ensuring that anesthesia has developed, the site is cleansed and draped with sterile cloths. The excision is begun by stabilizing the site either with the non-dominant hand or by an assistant. As with an incisional biopsy (see above), the epidermis is scored on both sides by drawing lightly with a #15 blade (mounted on a blade handle) along the lines chosen to create the fusiform shape. With continued traction, the incision is completed to the base of the wound by drawing the blade with increased pressure. Unlike with the incisional biopsy, the blade is held vertically throughout the procedure so that the edges of the wound are perpendicular to the skin surface, not angled inward to create a wedge. Completing the incision in one to two strokes after scoring minimizes ragged edges. Care is taken at both apical angles to completely incise to the same depth as that reached at the center of the wound. When the fusiform incision is complete, to either the level of the subcutaneous fat or the fascial plane, the specimen sits up from its base like an island. The specimen is then dissected from the base of the wound using scissors or a blade and the specimen is transferred to the appropriate container. The end result of the excision is a fusiform-shaped wound with vertical sides and a flat even base consisting of subcutaneous fat or fascia. Hemostasis is achieved by electrocoagulation.

The remainder of the procedure deals with the creation of a cosmetically acceptable and functional closure. In order to free tissue for movement into the wound, undermining is performed at the edges of the wound with either scissors or a scalpel. A favorite technique is to use scissors with rounded tips for insertion and then spreading of the tissue to produce blunt dissection in the plane of undermining, a procedure advocated because of the belief that it is less likely to cut arteries or nerves. Using the same scissors, but with a snipping or cutting motion to sharply dissect, is also safe and more effective in generating a smooth, less ragged unit of skin[35]. Sometimes, the two techniques are combined, with spreading followed by snipping of the intervening tethering strands. Undermining is done in a controlled fashion, and

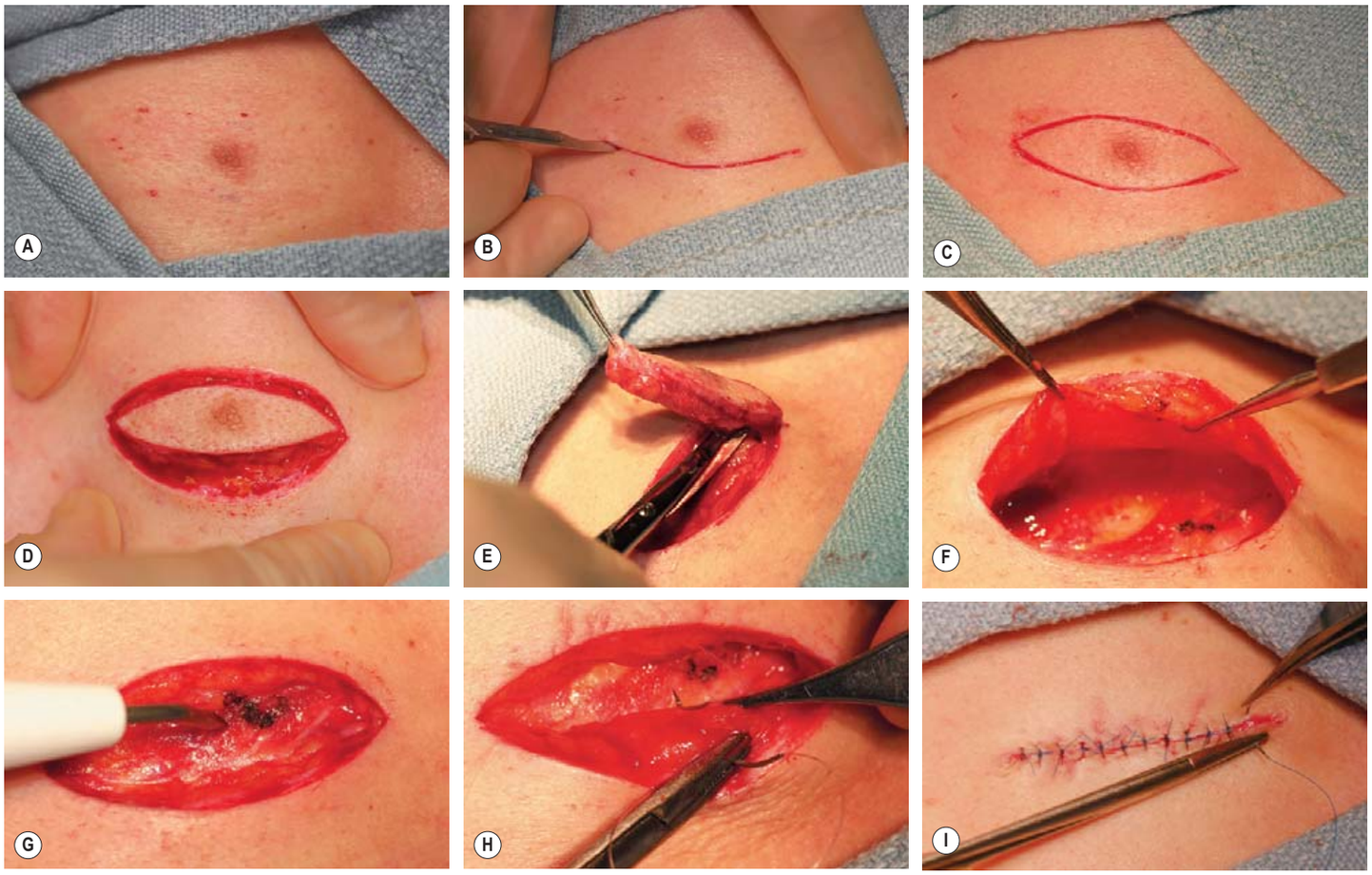


Fig. 146.12 Fusiform excision of an atypical melanocytic nevus. A After the margins are marked, the site is anesthetized, prepared with an antiseptic agent, and draped with sterile cloths. **B** Stabilizing the site with traction, the epidermis on one side of the fusiform design is scored using a #15 blade. **C** The epidermis on the opposite side is then scored. **D** The incision is completed into the appropriate plane in the subcutaneous tissue and the specimen then sits up in the middle of the wound like an island. **E** The base of the specimen is dissected with scissors or a blade. **F** The wound edges are then undermined in the same plane as the base of the wound. **G** Electrodesiccation or electrocoagulation is used to address small actively bleeding vessels to achieve hemostasis. **H** The subepidermal space is closed with buried stitches. **I** The epidermal edges are opposed by simple interrupted stitches.

good exposure and visualization is achieved by maintaining adequate hemostasis as the dissection proceeds. Tactile confirmation of the position of the tips of the scissors is also helpful.

In order to fill the defect with skin that matches with regard to thickness, the level of undermining is almost always at the same depth as the base of the wound, i.e. within the subcutaneous fat or at the fascial plane. Rarely, when there are superficially located arteries and nerves to be avoided, the plane of undermining is more superficial than the base of the wound. The use of curved scissors with the tips pointed upwards may facilitate staying in the appropriate plane.

The goals of undermining are to mobilize a unit of skin to be moved into the defect[36] in order to reduce wound closure tension[37], to allow proper wound edge eversion[38], and to provide a wide area for distribution of redundant tissue over the base of the wound. Undermining around the entire wound to a distance that is at least the diameter of the wound may be required to meet these goals. When little undermining is done, opposed wound edges are pulled inward and redundant tissue bunches up in the wound bed. This redundant tissue has a force and mass that may apply pressure to the healing wound, producing a situation that allows for maturing scars to spread out (Fig. 146.13). During closure, wide undermining disperses the redundant tissue over a large area of wound bed. It may also serve to create a plate-like horizontal scar that distributes the forces of contraction and stabilizes the final result. Undermining must include the apical angles, where it facilitates the rotation that occurs as the two sides of the fusiform shape are brought together. The adequacy of the width of undermining can be tested either by picking up both wound edges with toothed forceps or skin hooks and opposing them or by placing a large temporary suture. The temporary suture may also supply some intraoperative tissue expansion that will facilitate closure. Braided polyester (e.g. Ethibond®) suture is commonly used for this purpose since it is soft and will not cut through tissue. If, with these tests, the wound edges cannot be draped easily for closure, undermining can be extended.

Once undermining is adequate and after again ensuring that the wound is dry, subcutaneous and epidermal sutures are placed to complete the closure. As with the incisional biopsy, deep interrupted stitches of absorbable suture material (4–0 or 5–0 in caliber, with the knot inverted) close the subcutis and the dermis. If the wound is thick or under tension, optimal closure may entail two layers of subcutaneous stitches (i.e. a complex layered closure). The epidermis is then closed with simple interrupted or running sutures with a smaller caliber. For a fusiform excision *in toto*, the end result of the procedure is a straight or curved line of closure that has the wound edges completely opposed and everted. The line of closure sits above the surrounding skin, sometimes described as having the appearance of the ridge line of a tent or a mountain range. The healing of a tensionless everted wound edge results in a flat, hairline scar.

Cutaneous cone (dog-ear) Repair

Closure of a fusiform excision may create cutaneous cones, i.e. tissue redundancies that distort the normal contour of the skin at the apical angles[39]. These cutaneous cones are also referred to as dog-ears and may consist of standing cones, lying cones, inverted cones or protruding cones. Inverted cones can be the most difficult to diagnose, as the appearance is that of a subtle dimple rather than a protrusion.

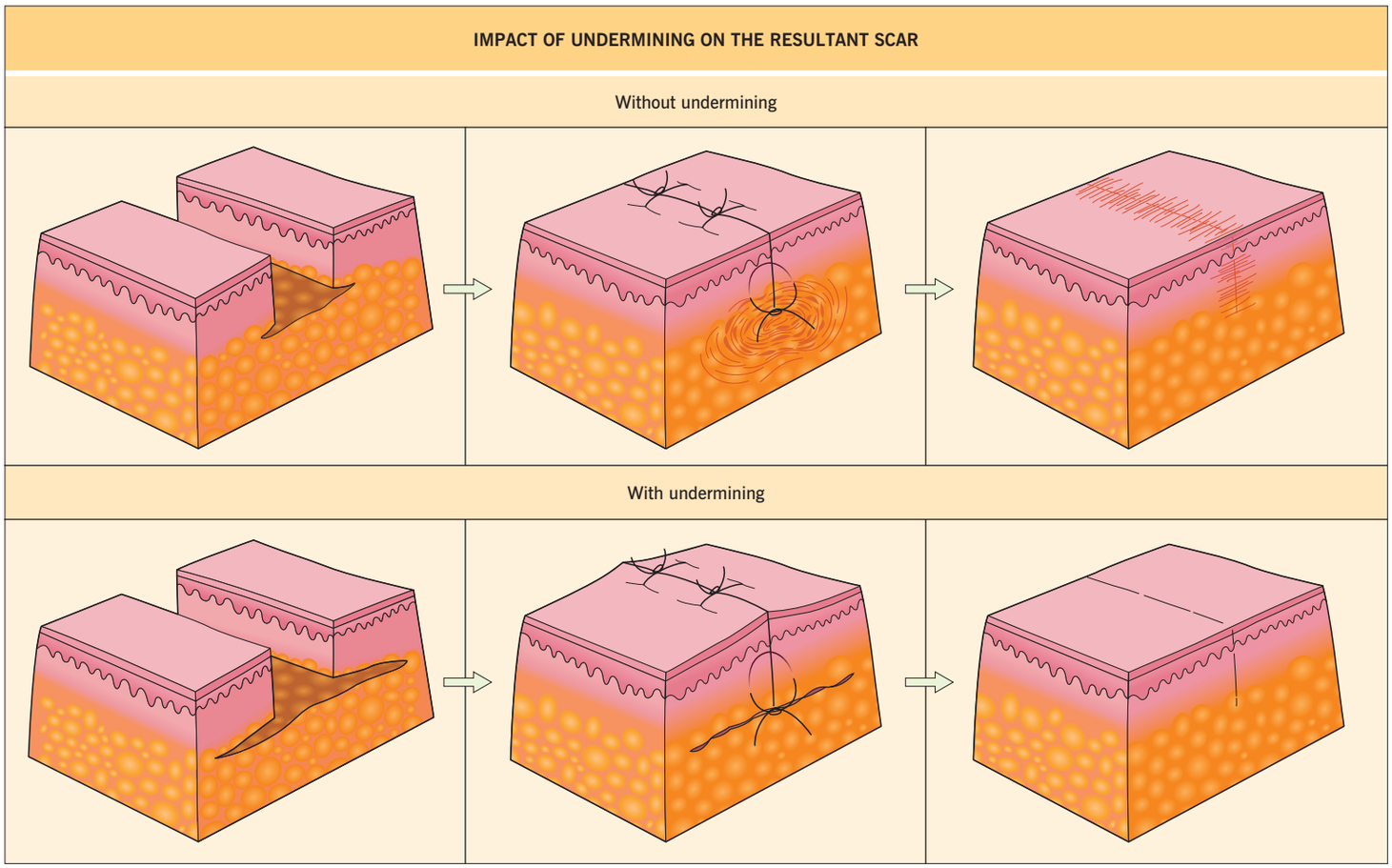


Fig. 146.13 Impact of undermining on the resultant scar. Without undermining, there is tension on the wound and eversion of the wound edges does not occur. Another consequence is spreading of the scar.

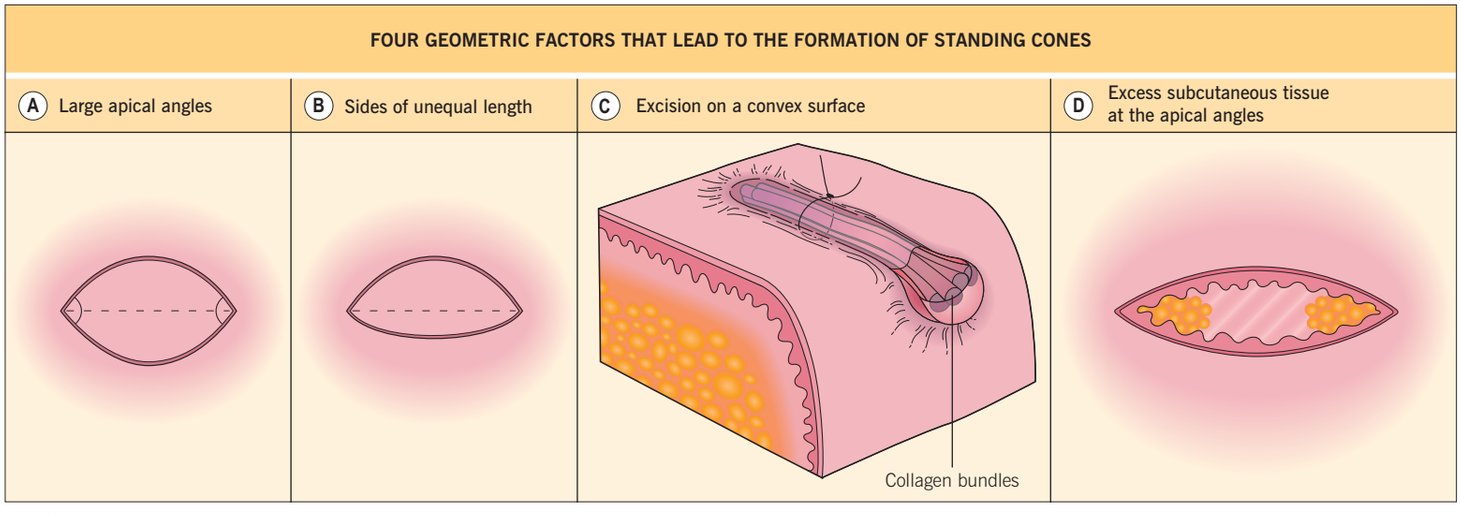


Fig. 146.14 Four geometric factors that lead to the formation of standing cones.

Regardless of their subtle nature, these redundancies will distort the final scar unless they are repaired. Cutaneous cones are also produced by tissue movement during flap closures.

Standing cones primarily result from geometric factors (Fig. 146.14). They may appear in closures of fusiform excisions (with sides of equal length) when the sides are of insufficient length compared to the width of the excision. The resulting apical angles are too wide to rotate in and maintain a flat contour to the skin surface. For this reason, linear closure of a circle, an oval or an ellipse will always create standing cones. Also, cutaneous cones always form during closure of fusiform shapes that have sides of unequal length; redundant tissue becomes apparent on the longer side. Notably, when an excision is performed on a convex surface, standing cones may occur despite seemingly small apical angles. With suture placement, collagen bundles are pulled together and act as rigid rods that will not lie flat on a curved surface.

In addition to geometric forces, protrusions are produced when there is excessive subcutaneous tissue in the base of the wound at the apices (as compared to the center of the wound). A lack of adequate undermining at the apices will then magnify these protrusions. This process is usually called "boating" or "pseudo dog-ear" formation. It is

important to distinguish boating from true standing cone formation because repair of the former requires removal of the excess subcutaneous tissue and appropriate undermining as opposed to the techniques described below.

Many standing cones are small and can be repaired via a closure that employs the rule of halves (Fig. 146.15). The midpoint of each side is opposed with a suture, bisecting the wound. Each unclosed half is then bisected again and the closure is continued until all tissue has been opposed. For a fusiform shape with unequal sides, repair of standing cones in this manner produces a curved line of closure. The curvature is directly proportional to the size of the dog-ear. If the wound is in a site such as the forehead, which lacks loose tissue to free up and mobilize, the line of closure may remain straight; however, there will be noticeable gathering on one side of the line and a depressed contour on the opposite side of the line where the skin thinned as it was stretched to fit.

Simple straight, curvilinear or angled excisions of standing cones will also restore the desired contour of the site, even though they lengthen the scar (Fig. 146.16). The first step is to close the center portion of the wound with subcutaneous sutures. It is helpful to continue to oppose subcutaneous tissue from the center of the wound outward until the standing cones become visible. Epidermal sutures may also need to be placed since any gaping at the center of the wound will underestimate the size of the dog-ears. After undermining, one limb of the standing cone is cut through to the base of the wound along the line that is desired for final closure. Undermining is repeated until the excess tissue can be draped over the cut edge. The new apical angle will lie flat if the limb has been adequately cut and if undermining has been sufficient. The second limb of the standing cone is then addressed by cutting from the wound to the new apical angle. The excess tissue that is removed will be in the shape of a triangle that is referred to as a Burow's triangle[40]. An alternative method, helpful for novices wanting to create a straight closure, is bisection of the standing cone, laying each half out along the skin surface and then cutting the two triangles of excess tissue. Closure is then completed with subcutaneous and epidermal sutures.

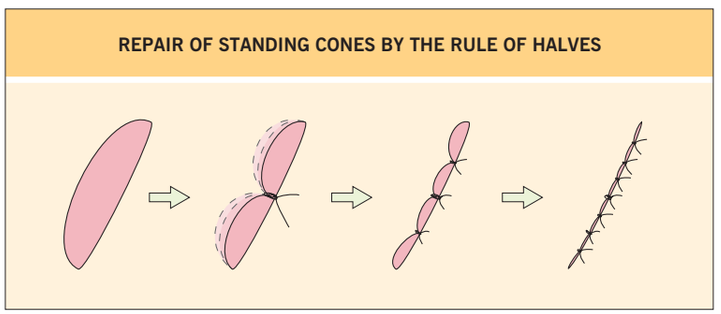


Fig. 146.15 Repair of standing cones by the rule of halves.

An M-plasty is a dog-ear repair that shortens the total scar length (Fig. 146.17). Depending upon the site, M-plasty scars may also fit within prominent lines and folds more accurately. This procedure is particularly helpful in sites that are not flat. The first step, as above, is to close the center portion of the wound and adequately undermine the apical angle. *Both* lateral limbs are cut at an obtuse angle from the end of the wound to about halfway toward the apex of the redundancy. The excess tissue is then draped over the cut edge and an M is now apparent. Cutting from the central tip to the two new apical angles removes two pieces of tissue that are also triangular in shape. The area of these two triangles is equal to the area of the single triangle that would have been removed had a simple excision of the standing cone been performed. If the central tip lies in a good position, then a standard closure is performed. If the tip needs to be advanced to approximate the wound edges and fill the defect, a *half-buried horizontal mattress stitch* (also called a *tip stitch* or *three-corner stitch*) is used (see Fig. 146.17E). Care must be taken with the three-corner stitch, as necrosis of the tip can occur with too much tension.

A dog-ear may also be displaced to a distant site. After closure of the central portion of the wound, an incision is made perpendicular to the dog-ear to an appropriate site where there is enough redundant tissue such that it can be removed as a triangle (Fig. 146.18). Undermining is required over a wide area so that tissue can be moved without tension. This procedure is also referred to as a Burow's advancement flap (see Ch. 147). It is commonly used to avoid dog-ear repair in a free margin or in a cosmetically or functionally sensitive area.

Finessing closure of fusiform excisions may require changing the axis of the line of closure so that the scar blends better with the prominent lines and folds of the site. Changing the axis will produce dog-ears that can be repaired by any of these methods.

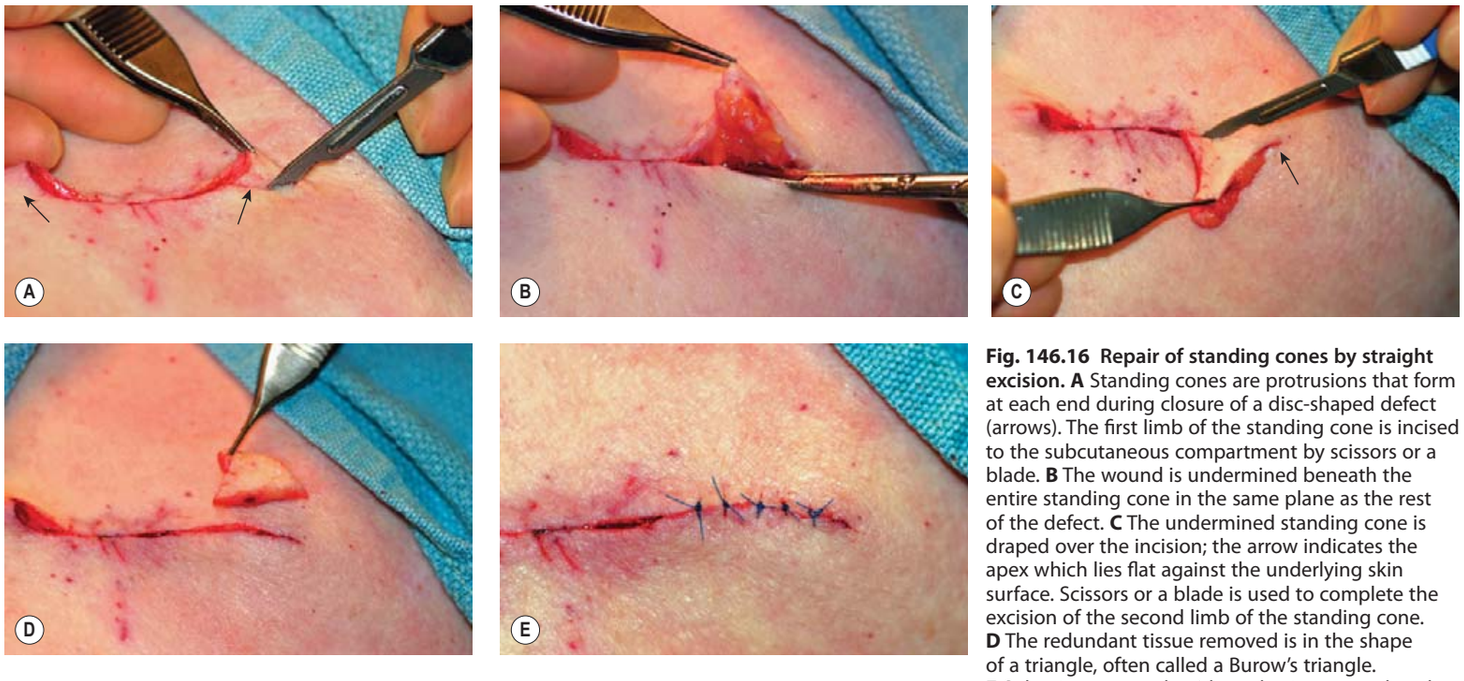


Fig. 146.16 Repair of standing cones by straight excision. A Standing cones are protrusions that form at each end during closure of a disc-shaped defect (arrows). The first limb of the standing cone is incised to the subcutaneous compartment by scissors or a blade. **B** The wound is undermined beneath the entire standing cone in the same plane as the rest of the defect. **C** The undermined standing cone is draped over the incision; the arrow indicates the apex which lies flat against the underlying skin surface. Scissors or a blade is used to complete the excision of the second limb of the standing cone. **D** The redundant tissue removed is in the shape of a triangle, often called a Burow's triangle. **E** Subcutaneous and epidermal sutures are placed to complete the closure.

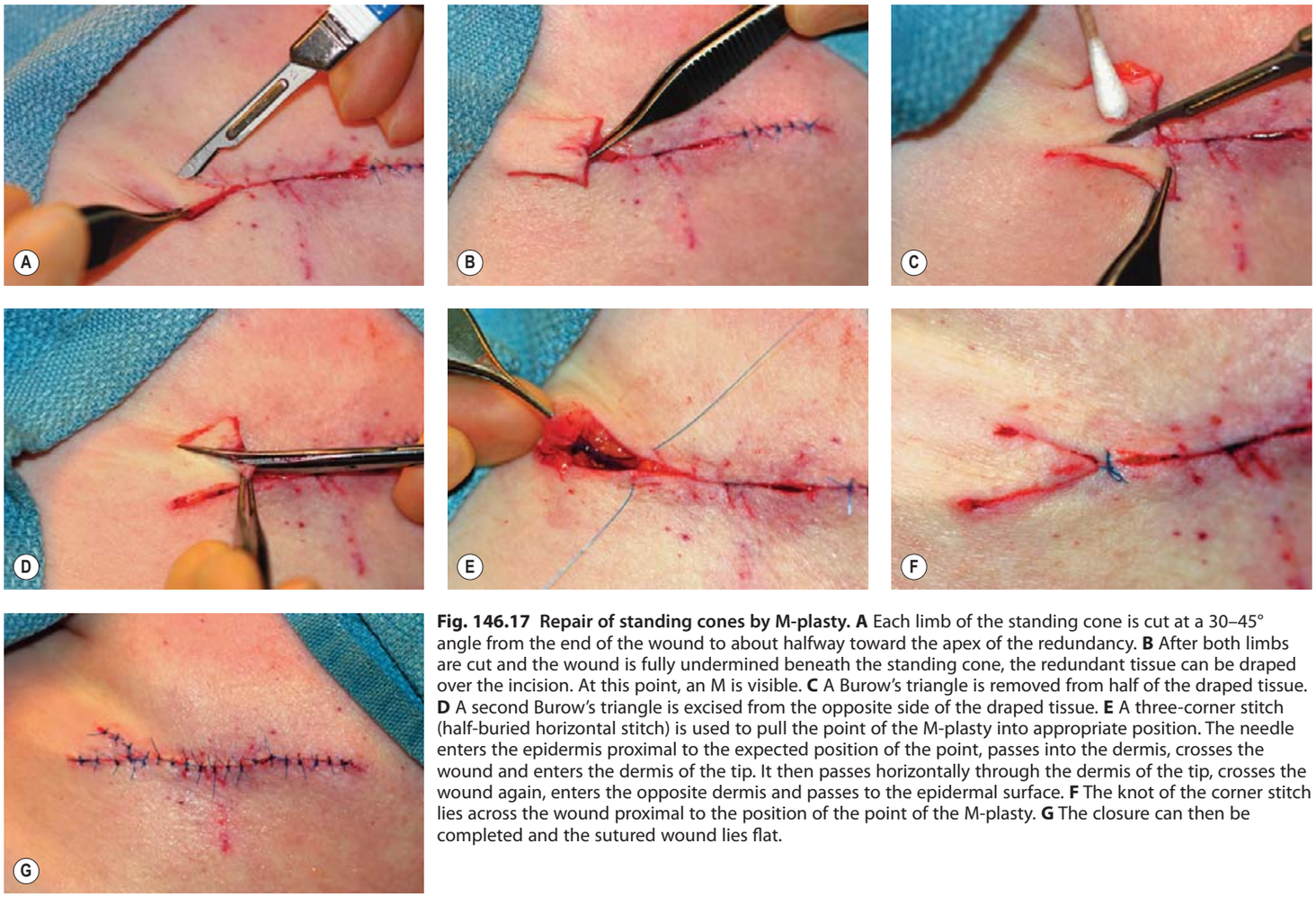


Fig. 146.17 Repair of standing cones by M-plasty. A Each limb of the standing cone is cut at a 30–45° angle from the end of the wound to about halfway toward the apex of the redundancy. **B** After both limbs are cut and the wound is fully undermined beneath the standing cone, the redundant tissue can be draped over the incision. At this point, an M is visible. **C** A Burow's triangle is removed from half of the draped tissue. **D** A second Burow's triangle is excised from the opposite side of the draped tissue. **E** A three-corner stitch (half-buried horizontal stitch) is used to pull the point of the M-plasty into appropriate position. The needle enters the epidermis proximal to the expected position of the point, passes into the dermis, crosses the wound and enters the dermis of the tip. It then passes horizontally through the dermis of the tip, crosses the wound again, enters the opposite dermis and passes to the epidermal surface. **F** The knot of the corner stitch lies across the wound proximal to the position of the point of the M-plasty. **G** The closure can then be completed and the sutured wound lies flat.

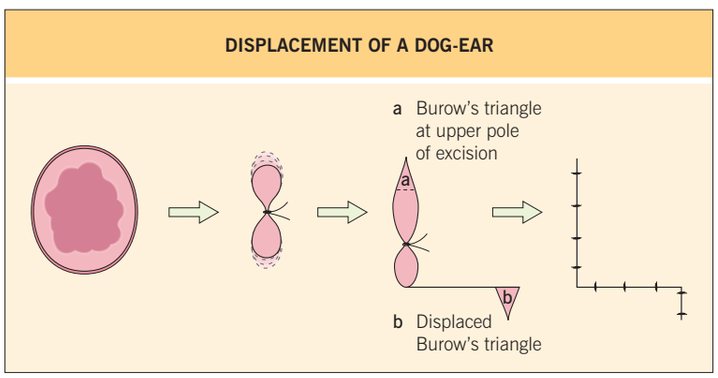


Fig. 146.18 Displacement of a dog-ear.

VARIATIONS/UNUSUAL SITUATIONS

A disc excision (with straight or angled edges) may be performed either for biopsy purposes or for biopsy and definitive treatment. This option is chosen when healing by second intention is preferred[41] or when it is desirable to remove the tumor first and then repair the dog-ears during the closure. Second intention healing may be advantageous when the risk of adverse reactions with primary closure is high. For example, excisions of even small tumors on the anterior lower leg that are closed primarily can produce wounds with tension and wounds that are more likely than those at other sites to dehisce, become infected or be painful. This is especially true if undermining is inadequate and weight-bearing is not minimized for the first 5–7 postoperative days (including, at times, the use of crutches).

Another option for wounds with too much tension on the anterior lower leg is the placement of a skin graft, but postoperative care requires leg elevation and the absolute avoidance of weight-bearing. Alternatively, the wound can be closed, either partially or completely, with a pursestring suture[42,43]. The latter is a running suture that is placed around the entire perimeter of the disc. After its placement, tension is applied to the ends of the suture until maximum constriction is obtained and then the ends are knotted. Advantages of the pursestring suture are speed, distribution of tension circumferentially, and amelioration of the need for the removal of excess normal skin in order to complete a fusiform excision. Since the time for complete re-epithelialization of a wound undergoing second intention healing is related to the diameter of the largest circle that can be drawn within the wound, even closure of a wound by 30% can result in a significant reduction in healing time. This smaller wound can also be grafted if desired.

When wounds heal by second intention, postoperative care is less burdensome, as the patient may resume normal activities almost immediately while dressing and bandaging the wound daily. However, compared to a linear excision, re-epithelialization requires a significantly longer period of time; the latter varies directly with the size of the wound and can range from 2 weeks to at least 2 months on the distal lower extremities. The patient also needs to consider the resultant scar, i.e. a depressed circular scar versus a graft versus a linear scar.

Removal of melanocytic nevi on the upper trunk and shoulders via disc excision or saucerization (angled edges) results in a smaller, often more cosmetically acceptable scar than does a fusiform excision. Also, the excision of tumors in sites such as the ear may be amenable to disc excision followed by second intention healing.

Performing a disc excision and then repairing the dog-ears during the closure allows the surgeon to pay particular attention to the issue of appropriate curative margins without dealing simultaneously with the cosmetic and functional issues of the closure. Once the tumor has been removed and the area widely undermined, the line of closure can be determined, that is, the closure with the least amount of tension that fits into the dominant lines of the site[44,45]. The central portion of the wound is opposed by subcutaneous and epidermal sutures or by a large simple interrupted temporary suture and then the dog-ears are repaired. Since the cosmetic and functional issues are addressed after excision of the tumor and undermining, the resulting scar can be optimized.

The shape of the excision can also be modified via a procedure known as an S-plasty[46]. Most useful on convex surfaces, this variation increases the total length of the scar while keeping the linear distance between the two apices constant. In a simple fusiform excision, the tension is located primarily in the center of the wound and is exerted along a single vector that is perpendicular to the axis of the wound. On the other hand, an S-plasty redirects and redistributes tension into multiple vectors along the wound, thereby minimizing tension in the center of the wound; in addition, the central tension vector is perpendicular to the primary tension vectors at the apices of the wound. Because much of the tension is displaced from the area of maximal convexity, the likelihood of a central depression or dehiscence is reduced.

POSTOPERATIVE CARE

Wound care and bandaging both play an important role in minimizing the risk of complications and in obtaining optimal cosmetic and functional results. Wound care removes surface debris and promotes re-epithelialization. A good bandage supports and stabilizes the wound in the closed position, wicks away excessive blood or tissue fluid, supplies pressure to the wound for hemostasis, and protects the wound from the dryness and bacterial contamination of the external environment.

A small shallow wound that is to heal by second intention is cared for by daily cleansing of the site with mild soap and water, application of petrolatum and coverage with an adhesive bandage such as a Band-Aid® (with a central non-adherent area). A liquid adhesive bandage has also been reported to be effective, and, in a trial on minor cuts and abrasions, proved easy to use[47]. A large shallow wound that is to close by second intention may need a bandage fashioned specifically for that site, usually consisting of layers of petrolatum, Telfa®, gauze or cotton, and tape or other means of adhering the bandage at the site.

A layered bandage is also required for a sutured wound. A liquid adhesive (e.g. Mastisol®) is applied to the skin surface surrounding the sutures. Petrolatum is applied in a thin line onto the wound edge. Sterile tapes such as Steri-Strips™ are placed perpendicular to the line of closure. The final layer is rolled gauze or cotton, which is then taped in place with paper tape or Hy-Tape® ("pink" tape). Elastic dressing (e.g. Coban®) can be used for compression, but should be released and reapplied if it is used circumferentially, so that vascular compromise distally does not occur.

Patients need oral and written instructions regarding the care the wound will require at home. Most simple wounds are cleansed daily with soap and water and redressed until the sutures are removed or the wound has completely re-epithelialized. Patients should understand that they need to remove any crusting or debris from the wound as they cleanse it and they may prefer to use cotton-tipped swabs or gauze. Instructions regarding bandages should likewise be clear. Leaving the wound open to the air or allowing it to become dry retards re-epithelialization and may compromise the final appearance or the scar[48].

Bandages that minimize the need for wound care are preferred by many patients. In addition, the stability and protection afforded by a bandage that stays in place for a week or more may further optimize the results, especially for wounds closed primarily. These bandages may be constructed in layers as discussed above and should be kept dry to prevent maceration of the covered skin. On the trunk and extremities, a bandage can be made of a polyurethane foam dressing (e.g. Cutinova Hydro®) covered by a water repellent film (e.g. Bioclusive®), precluding the need for any care and allowing ease of movement and a normal regimen for bathing.

Once the sutures have been removed and the wound cleaned, the use of liquid adhesive and sterile tapes for another week or two further stabilizes the wound. Many specialized bandaging systems are available for complicated wounds (see Ch. 145).

COMPLICATIONS

Short-term complications of biopsies and excisions are few in number and generally engender limited morbidity (Table 146.12)[49]. In addition, the smaller the procedure, the fewer the complications, which explains why shave biopsies and snip biopsies are quite safe. Hemorrhage may occur, from the time of the procedure to afterwards when the patient has returned home, and it usually occurs within the first 24 hours. Although many patients take aspirin, warfarin or other agents that affect coagulation or platelet function, hemostasis can be achieved during the procedure, resulting in few adverse bleeding events[50].

Infection occurs rarely, in less than 1% of most procedures[51]. Some patients have difficulty with either irritant or allergic reactions to topical antibiotics[52] or to tapes and bandages. These often pruritic eruptions are managed with a change in the wound care regimen but do not usually require topical corticosteroid creams. Biopsies performed on the lower limbs, limbs affected by lymphedema, intertriginous areas, and ears are most susceptible to infections. If an infection develops, oral antibiotics may be required.

Pain is generally minimal. When it occurs 3–5 days after the procedure, infection is the most likely cause, even in the absence of erythema, tenderness and purulence. Very rarely, paresthesias may result and can persist for several months, especially on the forehead. Wounds that are closed primarily may dehisce because of tension, hematoma formation, poor wound healing or infection. These wounds are thereafter managed for second intention healing and a delayed reconstruction can be undertaken, if needed, when the attendant inflammation has resolved.

Long-term complications (see Table 146.12) generally consist of functionally or cosmetically adverse scarring[53]. Depressed scars may occur if not enough subcutaneous tissue is brought into the line of closure. Atrophic and widened scars occur in areas where there is intermittent stretching of the scar as it overlies major muscle groups. Careful surgical technique that includes adequate undermining, minimization of tension at the line of closure and the use of multiple subcutaneous sutures can reduce the likelihood of this complication.

Scars may pursue a prolonged course of healing with erythematous thickening at the line of closure. These hypertrophic scars do resolve with time. To speed their resolution, practitioners often advise massage

SHORT-TERM AND LONG-TERM COMPLICATIONS OF BIOPSY PROCEDURES AND EXCISIONS
SHORT-TERM COMPLICATIONS
• Irritant or allergic reactions to topical antibiotics and/or tapes and bandages • Hemorrhage • Poor wound healing; dehiscence of closed wounds • Pain • Infection • Pruritus, paresthesias
LONG-TERM COMPLICATIONS
• Atrophic scars (thin, depressed, spread) • Hypertrophic scars (red, thickened) • Keloids • Distortion of normal structures (e.g. ectropion, elevated nasal ala, notching of the lip or helix of the ear) • Hypoesthesia, anesthesia • Paralysis (e.g. due to injury to facial nerve branches)

Table 146.12 Short-term and long-term complications of biopsy procedures and excisions.

or inject triamcinolone (10–40 mg/ml) into the scars. Silicone dressings are also recommended, but they are probably no more effective than non-silicone gel dressings[54]. In addition, scars may have a fragile surface (due to reduced dermal–epidermal attachments), pruritus or paresthesias, most of which resolve with time.

A true keloidal scar is one that grows beyond the boundaries of the original surgical injury and appears as a thickened erythematous or hyperpigmented nodule or plaque (see Ch. 98). It occurs in predisposed individuals who may have a history of previous keloid formation. Keloidal scarring is most commonly observed when procedures are performed on the upper trunk and shoulders and may be very difficult to treat.

FUTURE TRENDS

For the foreseeable future, histologic examination of tissue specimens will be the mainstay of dermatologic diagnostic testing. Excisions likewise will be frequently utilized, both to remove a specimen for diagnosis as well as to clear pathologic tissue completely. Future near-term advances will include improved means of anesthesia[55] and improved wound care with the development of agents to speed healing and minimize scarring. It is possible that advances in confocal laser microscopy may visualize *in situ* microscopic tissue architecture and cellular detail, but it is unlikely that this process will replace standard biopsy techniques.

REFERENCES

1. Ng JC, Swain S, Dowling JP, et al. The impact of partial biopsy on histopathologic diagnosis of cutaneous melanoma. Arch Dermatol. 2010;146:234–9.
2. Messingham MJ, Arpey CJ. Update on the use of antibiotics in cutaneous surgery. Dermatol Surg. 2005;31:1068–78.
3. Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association. Circulation. 2007;116:1736–54.
4. Meyer GW, Artis AL. Antibiotic prophylaxis for orthopedic prostheses and GI procedures: report of a survey. Am J Gastroenterol. 1997;92:989–91.
5. Classen DC, Evans RS, Pestotnik SL, et al. The timing of prophylactic administration of antibiotics and the risk of surgical wound infection. N Engl J Med. 1992;326: 281–6.
6. Bode LGM, Kluytmans AJW, Wertheim HFL, et al. Preventing surgical-site infections in nasal carriers of Staphylococcus aureus. N Engl J Med. 2010;362:9–17.
7. McGuinness JL, Goldstein G. The value of preoperative biopsy site photography for identifying cutaneous lesions. Dermatool Surg. 2010;36:194–7.
8. Darouiche RA, Wall MJ, Itani KMF, et al. Chlorhexidine-alcohol versus povidone-iodine for surgical site antisepsis. N Engl J Med. 2010;362:18–26.
9. Nthumba PM, Stepita-Poenaru E, Poenaru D, et al. Cluster-randomized, crossover trial of the efficacy of plain soap and water versus alcohol-based rub for surgical hand preparation in a rural hospital in Kenya. Br J Surg. 2010; 97:1621–8.
10. Lui S, Carpenter RL, Chiu AA, et al. Epinephrine prolongs duration of subcutaneous infiltration of local anesthesia in a dose related manner. Reg Anesth. 1995;20:378–84.
11. Baum CL, Arpey CJ. Normal cutaneous wound healing: clinical correlation with cellular and molecular events. Dermatol Surg. 2005;31:674–86.
12. Perry AW, McShane RH. Fine tuning of the skin edges in the closure of surgical wounds: controlling inversion and eversion with the path of the needle. J Dermatol Surg Oncol. 1981;7:471–6.
13. Annunziata CC, Drake DB, Woods JA, et al. Technical considerations in knot construction. J Emerg Med. 1997;15:351–6.
14. Zitelli JA, Moy RL. Buried vertical mattress suture. J Dermatol Surg Oncol. 1989;15:17–19.
15. Krunic AL, Weitzul S, Taylor RS. Running combined simple and vertical mattress suture: a rapid skin-everting stitch. Dermatol Surg. 2005;31:325–9.
16. Wong NL. Review of continuous sutures in dermatology surgery. J Dermatol Surg Oncol. 1993;19:923–31.
17. Hodges JM. Management of facial lacerations. South Med J. 1976;69:1413–18.
18. Kamegaya Y, Farinelli WA, Vila Echague AV, et al. Evaluation of photochemical tissue bonding for closure of skin incisions and excisions. Lasers Surg Med. 2005;37:264–70.
19. Biancari F, Tiozzo V. Staples versus sutures for closing leg wounds after vein graft harvesting for coronary artery bypass surgery. Cochrane Database Syst Rev. 2010;(5):CD008057.
20. Coulthard P, Esposito M, Worthington HV, et al. Tissue adhesives for closure of surgical incisions. Cochrane Database Syst Rev. 2010;(5):CD004287.
21. Niyama T, Higuchi I, Sakoda S, et al. Diagnosis of dystrophinopathy by skin biopsy. Muscle Nerve. 2002;25:398–401.
22. Prasa A, Kaye EM, Alroy J. Electron microscopic examination of skin biopsy as a cost-effective tool in the diagnosis of lysosomal storage diseases. J Child Neurol. 1996;11:301–8.
23. Baldwin HE, Berck CM, Lynfield YL. Subcutaneous nodules of the scalp: preoperative management. J Am Acad Dermatol. 1991;25:819–30.
24. Chang LK, Whitaker DC. The impact of herbal medicines on dermatologic surgery. Dermatol Surg. 2001;27:759–63.
25. Richards KA, Stasko T. Dermatology surgery and the pregnant patient. Dermatol Surg. 2002;28:248–56.
26. Harvey DT, Fenske NA. The razor blade biopsy technique. Dermatol Surg. 1995;21:345–7.
27. Todd P, Garioch JJ, Humphreys S, et al. Evaluation of the 2-mm punch biopsy in dermatological diagnosis. Clin Exp Dermatol. 1996;21:11–13.
28. Dunlavey E, Leshin B. The simple excision. Dermatol Clin. 1998;16:49–64.
29. Salasche SJ, Giancola JM, Trookman NS. Surgical pearl: hydroexpansion with local anesthesia. J Am Acad Dermatol. 1995;33:510–12.
30. Wolf DJ, Zitelli JA. Surgical margins for basal cell carcinoma. Arch Dermatol. 1987;123:340–4.
31. Brodland DG, Zitelli JA. Surgical margins for excision of primary cutaneous squamous cell carcinoma. J Am Acad Dermatol. 1992;27:241–8.
32. Takenouchi T, Nomoto S, Ito M. Factors influencing the linear depth of invasion of primary basal cell carcinoma. Dermatol Surg. 2001;27:393–6.
33. Chretien-Marquet B, Caillou V, Brasnu DN, et al. Description of cutaneous excision and suture using a mathematical model. Plast Reconstr Surg. 1999;103:145–50.
34. Moody BR, McCarthy JE, Sengelmann RD. The apical angle: a mathematical analysis of the ellipse. Dermatol Surg. 2001;27:61–3.
35. Boyer JD, Zitelli JA, Brodland DG. Undermining in cutaneous surgery. Dermatol Surg. 2001;27:75–8.
36. Mackay DR, Saggers GC, Kotwal N, et al. Stretching skin: undermining is more important than intraoperative tissue expansion. Plast Reconstr Surg. 1990;86:722–30.
37. McGuire MF. Studies of the excisional wound: I. Biomechanical effects of undermining and wound orientation on closing tension and work. Plast Reconstr Surg. 1980;66:419–27.
38. Zitelli JA. Tips for a better ellipse. J Am Acad Dermatol. 1990;22:101–3.
39. Gormley DE. The dog-ear: causes, prevention, and correction. J Dermatol Surg Oncol. 1977;3:194–8.
40. Gormley DE. A brief analysis of the Burow's wedge/triangle principle. J Dermatol Surg Oncol. 1985;11:121–3.
41. Zitelli JA. Wound healing by secondary intention. A cosmetic appraisal. J Am Acad Dermatol. 1983;9:407–15.
42. Harrington AC, Montemarano A, Welch M, et al. Variations of the pursestring suture in skin cancer reconstruction. Dermatol Surg. 1999;25:277–81.
43. Romiti R, Randle HW. Complete closure by purse-string suture. Dermatol Surg. 2002;28:1070–2.
44. Davis TS. The circular excision. Ann Plast Surg. 1980;4:21–5.
45. Spicer TE. Techniques of facial lesion excision and closure. J Dermatol Surg Oncol. 1982;8:551–6.
46. Paolo B, Stefania R, Massimiliano C, et al. Modified S-plasty: an alternative to the elliptical excision to reduce the length of suture. Dermatol Surg. 2003;29:394–8.
47. Eaglstein WH, Sullivan TP, Giordano PA, et al. A liquid adhesive bandage for the treatment of minor cuts and abrasions. Dermatol Surg. 2002;28:263–7.
48. Eaglstein WH. Moist wound healing with occlusive dressings: a clinical focus. Dermatol Surg. 2001;27:175–81.
49. Salasche SJ. Acute surgical complications: cause, prevention and treatment. J Am Acad Dermatol. 1986;15:1163–85.
50. Otley C, Olbricht SM, Frank EW, et al. Risks of perioperative anticoagulation in dermatologic surgery. Arch Dermatol. 1996;132:161–5.
51. Futoryan T, Grande D. Postoperative wound infection rates in dermatology surgery. Dermatol Surg. 1995;21:509–14.
52. Gette MT, Marks JC, Maloney ME. Frequency of postoperative allergic contact dermatitis to topical antibiotics. Arch Dermatol. 1992;128:365–7.
53. Hayes CM, Whitaker DC. Complications of cutaneous surgery. Adv Dermatol. 1994;9:161–77.
54. De Oliveira GV, Nunes TA, Magna LA, et al. Silicone versus nonsilicone gel dressings: a controlled trial. Dermatol Surg. 2001;27:721–6.
55. Greenbaum SS. Iontophoresis as a tool for anesthesia in dermatologic surgery: an overview. Dermatol Surg. 2001;27:1027–30.

This page intentionally left blank

147 Flaps

David G Brodland and David B Pharis

Key features

- A cookbook approach to flap reconstruction is not realistic
- The mnemonic STARTS lists basic reconstruction options: simple side-to-side closures, transposition flaps, advancement flaps, rotation flaps, tissue importation flaps, and skin grafts
- Understanding the dynamics of a flap optimizes its execution
- For reconstruction, the simplest approach that achieves the desired result is often best
- Extensive undermining, everted wound edges, meticulous hemostasis without excessive electrocoagulation, and technical precision are important in achieving an outstanding result

INTRODUCTION

Cutaneous reconstruction has played an important role in the establishment of dermatologic surgery as a vital discipline within dermatology. An in-depth understanding of reconstructive options, combined with a dermatologist's intimate familiarity with skin, enables optimal aesthetic and functional results. Equally important is an intimate understanding of the tissue dynamics of flaps, why they work, what problems each flap type can address, and their limitations. A cookbook approach to flap reconstruction is not realistic because of the many variables relating to the characteristics of the defect, the donor skin, the patient and the surgeon. It is better to attempt to provide a foundation of basic concepts from which the individual can build his or her skills and, hopefully, his or her unique style in reconstruction. Therefore, this chapter will emphasize the fundamentals of the various types of flaps and their execution. Clinical examples will be used to illustrate these key points.

BACKGROUND

At the patient's side, it is always helpful to have an on-demand recall of the flap options that are available. With experience, this is automatic, but those with less experience may find the mnemonic STARTS helpful (Table 147.1). The basic options for reconstruction include: simple side-to-side closures, transposition flaps, advancement flaps, rotation flaps, tissue importation flaps, and skin grafts. It is incumbent upon the surgeon to synthesize the many factors that may affect the choice of the most appropriate flap for a defect. The characteristics of the wound, qualities of the adjacent skin, the functional aspects of the affected anatomic site, the pertinent aesthetic considerations, the anatomic borders in proximity to the defect, and the age and expectations of the patient all contribute to the decision regarding the most appropriate reconstructive approach.

STARTS MNEMONIC
Simple side-to-side closure
Transposition flaps
Advancement flaps
Rotation flaps
Tissue importation flaps
Skin grafts

Table 147.1 STARTS mnemonic.

The most important goal in reconstruction is functional aesthetics. This means that the reconstruction should first and foremost maintain all vital functions and accomplish this with an aesthetic result. It should be remembered that not all aesthetic reconstructions are functional, but all functional reconstructions can be aesthetic.

Fundamentals of Flap Design and Suturing Technique

Technical precision, including suturing technique, may be the most important variable in achieving an outstanding result. The first important step is to prepare the wound edges of both the defect and the flap. All incisions should be made at a 90° angle to the skin surface such that the wall of the defect and the skin edge of the flap are square. Secondly, the wound base should be made a uniform depth. Whether reconstructing with an elliptical side-to-side closure or with any of the more intricate flaps, the contour of the wound base will persist and may affect the long-term appearance of the wound. Likewise, the thickness of the flap should be uniform. While the thickness of the flap relative to the depth of the defect merits some consideration, care should be taken when considering the use of a flap with a thick subcutaneous tissue component, since these flaps are much more prone to postoperative edema and "pincushioning". Nevertheless, all components of the flap should be fashioned with uniformity in mind.

Widespread undermining of the subcutaneous tissue adjacent to both the defect and the donor site defect is important for creating a broad "plate-like scar". This results in the distribution of scar contraction over a greater area and diffuses the effects of contraction such that the latter is not focused on the flap itself or the incision lines of the flap (Fig. 147.1). Undermining should be uniform and complete, including the areas of low tissue tension such as the tips of an ellipse or the pivot points of flaps.

Next, meticulous pinpoint hemostasis with complete visualization of all undermined skin with the help of an assistant is critical. Excessive postoperative bleeding within a sutured wound often results in an inferior outcome. It should be emphasized, however, that extensive tissue injury caused by electrosurgical hemostasis should be avoided as fervently as postoperative bleeding, since this can contribute equally to unwanted results. With a well-prepared wound and flap that are characterized by uniformity in thickness, sharply squared edges, well-loosened tissue margins and excellent hemostasis, the wound is ready for suturing.

Whether it is a side-to-side closure or a flap, eversion of the skin edges (along with undermining) is also essential (Fig. 147.2). Given their longer period of effectiveness, as compared to epidermal sutures, the authors prefer the use of subcutaneous ("buried") vertical mattress sutures to achieve eversion (see Ch. 146).

Flap Movement Characteristics

It is helpful to broadly characterize flap types according to their mechanism of skin rearrangement. By understanding the dynamics of each flap, it is easier to select one that will provide functionally aesthetic results. Upon consideration of the unique characteristics of the defect, the donor skin, and the functional and aesthetic issues of reconstruction in the context of the mechanics of flap tissue movement, a rational decision regarding the method of closure can be made. The components flaps share include the flap body, the pedicle or vascular base, primary and secondary defects, and, as an integral part of flap dynamics, the primary and secondary movements (Table 147.2, Fig. 147.3).

Most tissue movement results in some degree of tension. This tension creates vectors of force that tend to return moving skin to its original position. Therefore, the primary movement of a flap creates a

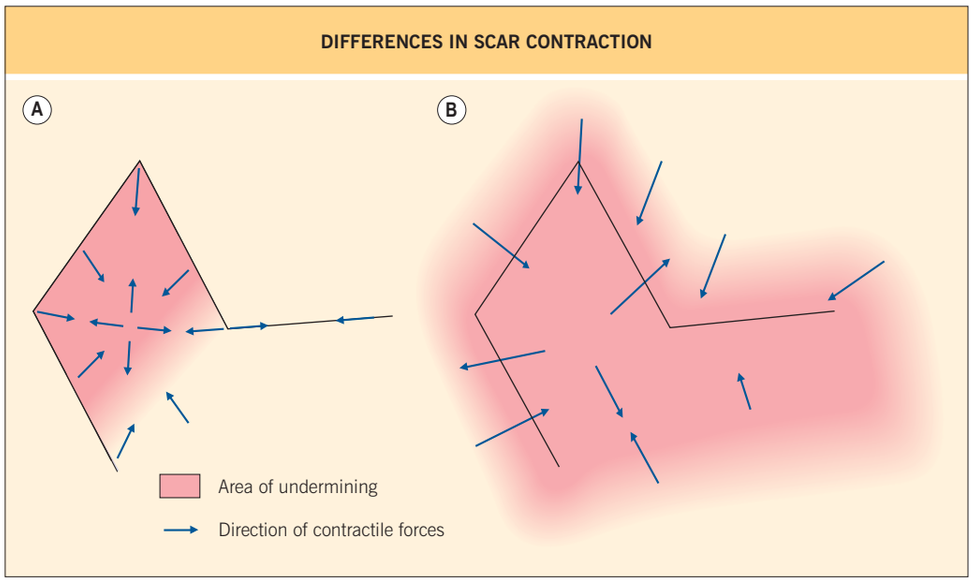


Fig. 147.1 Differences in scar contraction. Depiction of differences between wounds that are undermined and those that are not undermined prior to suture placement. **A** The contraction forces are focused on the margins of the flap in a wound that was not widely undermined. **B** Broad diffusion of contractile forces that are not concentrated at the flap margins, making "pincushioning" less likely in the widely undermined flap.

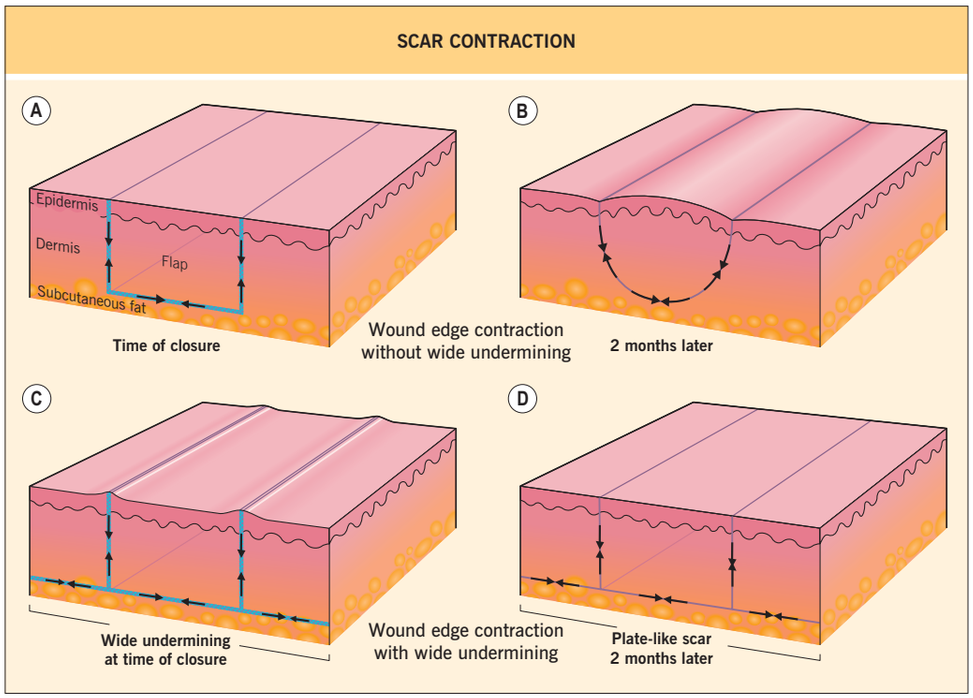


Fig. 147.2 Scar contraction. A Sutured wound without wound edge eversion and without undermining of the surrounding tissue. **B** The results of scar contraction, leading to inversion of the scars and "pincushioning" of the flap. **C** A wound sutured with eversion and wide undermining. **D** The canceling effect of scar contraction and wound eversion as well as the diffusion of scar contraction in the deep, undermined wound plane.

DEFINITIONS OF FLAP COMPONENTS	
Body	The skin being advanced, transposed, rotated, interpolated or imported into the primary defect
Pedicle	Also known as the vascular base of the flap, it is the conduit of the vascular supply that will remain intact and maintain the vascularization of the body of the flap intraoperatively and for the early postoperative period
Primary defect	The area deficient in skin that will be reconstructed by the movement of the body of the flap
Secondary defect (donor site defect)	The area devoid of skin created by the movement of the body of the flap
Primary flap movement	The movement of the flap body into the defect
Secondary flap movement	The tissue movement necessary to close the void or donor site defect created by the movement of the body of the flap
Primary tension vector	The direction of the force tending to counteract the movement of the body of the flap
Secondary tension vector	The direction of the force created by the closure of the donor site defect

Table 147.2 Definitions of flap components.

primary tension vector, while the secondary movement (during closure of the donor site defect) creates a secondary tension vector. Consideration of these forces and the effects of these forces on adjacent tissue and even the blood supply of the flap is the primary factor in selecting one flap over another. The most perfectly executed flap that via tension vectors results in the distortion of a free margin (e.g. a lip or eyelid) is of little value to the patient or the goal of aesthetic restoration. Therefore, the initial and most important skill required for the proper execution of flaps is the ability to anticipate the direction and amount of tension created by particular flaps and to predict what effects this tension will have on adjacent structures.

There are four broad categories of flaps based upon how the tissue is rearranged in order to achieve closure (Table 147.3). The first category of flaps essentially displaces one or both Burow's triangles that would be removed if the wound were closed by a simple side-to-side closure. The second category includes the flaps that reconfigure defects, while the third includes flaps that reorient tissue from adjacent pools of laxity into the defect. Finally, there is a category of flaps that enables defect closure by tissue importation.

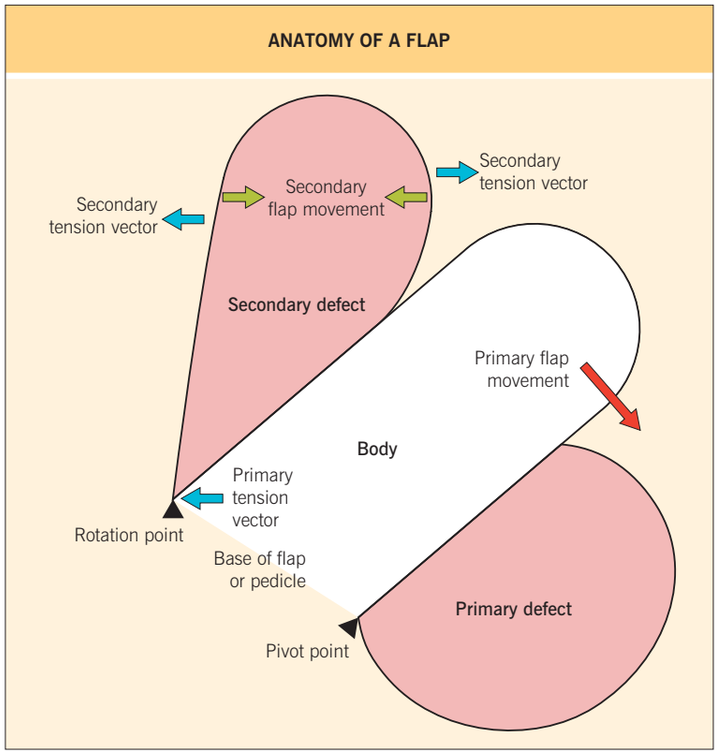


Fig. 147.3 Anatomy of a flap. Definitions of the components of a flap are outlined in Table 147.2.

Burow's triangle displacement flaps

Flaps that displace Burow's triangles to a convenient location distant from the defect include the single tangent advancement flap (Burow's flap), the bilateral single tangent advancement flap (A-to-T flap), the double tangent advancement flap (U-flap), the bilateral double tangent advancement flap (H-flap), and rotation flaps (including the glabellar or Rigor flap, Mustarde flap and the helical advancement flap) (Fig. 147.4). For the most part, these flaps displace Burow's triangles along straight or curved incision(s) tangential to the wound.

The key features of these flaps are: (1) they displace Burow's triangles to a distant site; (2) there is limited reorientation of tissue; and (3) their movement is dependent upon the intrinsic elasticity of the skin. Just as a simple side-to-side closure performed in stiff, inelastic skin would result in a tense closure, so would a Burow's triangle displacement-type flap. When the surrounding skin is elastic and "loose", the wound edges can be closed under minimal tension in both a side-to-side closure and with these flaps. Thus, the only advantage that these flaps confer over a side-to-side closure in tight skin is that a larger area of skin is typically undermined, which releases the latter from the tethering effect of the subcutaneous tissue. This allows for a modest decrease in wound closure tension. The most obvious utility of these flaps is in defects where, for functional or aesthetic reasons, it is inconvenient to remove a Burow's triangle immediately adjacent to the defect. An example of

CLASSIFICATION OF FLAPS BASED ON DESIGN CHARACTERISTICS

Flap category	Flap variations	Synonyms	Mechanism of tissue movement	Advantages	Disadvantages
Burow's triangle displacement flaps	Single tangent adv flap Bilateral single tangent adv flap Double tangent adv flap Bilateral double tangent adv flap Curvilinear tangent adv flap	Burow's flap A-to-T flap, O-to-T flap U-flap H-flap Rotation flap, Karpandzic flap, Mustarde flap	Tissue advancement: dependent upon intrinsic tissue elasticity	• Enables closures adjacent to vital structures through displacement of Burow's triangles • Single tangent flaps have excellent blood supply	• Depends on intrinsic skin laxity of the flap skin • Requires extensive undermining • Double tangent flaps have a more limited blood supply
Defect reconfiguration flaps	Island pedicle flap	Kite flap, myocutaneous pedicle flap	Tissue advancement: dependent upon intrinsic elasticity of subcutaneous pedicle Tissue movement results in reconfiguration of the defect	• Tissue-conservative due to reconfiguration of the defect without removal of Burow's triangle	• Blood supply is limited to the subcutaneous pedicle • Use limited to locations with spongy, elastic subcutaneous tissue
Tissue reorientation flaps	Rhombic transposition flap Bilobed transposition flap Nasolabial transposition flap Nasolabial flap with a twist (Spear's flap)	Limberg flap, Dufourmentel flap, Webster's 30° flap Melolabial fold flap	Reorientation of adjacent tissue laxity	• Effective for tight closures • Directional tissue gain can be achieved in direction of tissue deficit	• Depends on laxity adjacent to the defect • Multidirectional incisions; difficult to place all in RSTL
Tissue importation flaps	Paramedian forehead flap Nasolabial interpolation flap Retroauricular pedicled flap Modified Hughes flap Abbe cross-lip flap	Indian flap Pin back flap	Importation of tissue from a distant site	• Coverage of large wounds • Can provide vascularity for coverage of avascular grafts such as cartilage grafts	• Two-stage flap • Vascular supply limited to narrow pedicle

Table 147.3 Classification of flaps based on design characteristics. adv, advancement; RSTL, relaxed skin tension lines.

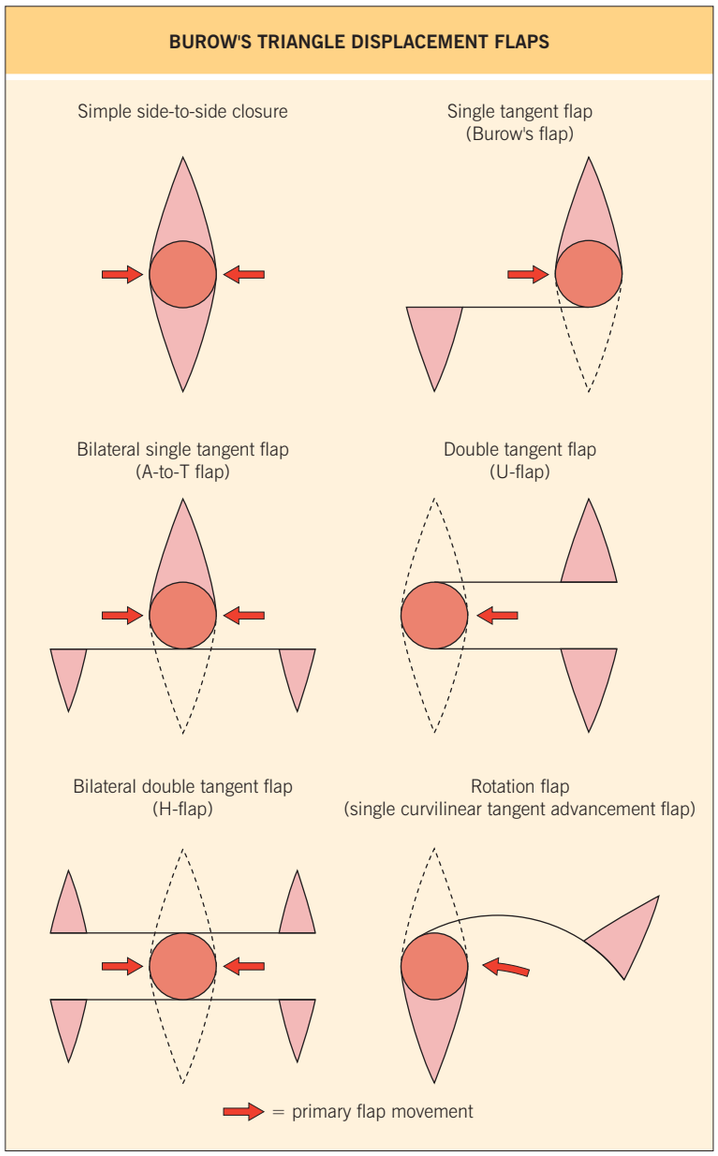


Fig. 147.4 Burow's triangle displacement flaps.

this is a defect above or below the eye in which displacement of the Burow's triangle is useful in order to avoid removing a triangle from the eyebrow or eyelid skin (Fig. 147.5).

Defect reconfiguration flaps

The island pedicle advancement flap is unique in that it is an advancement of tissue oriented in a plane perpendicular to the skin and at 90° to the more traditional advancement or rotation flaps. In this case, the tissue redundancy created at the pivot point of the flap is buried in the subcutaneous plane at the advancing edge of the flap (see below).

Tissue reorientation flaps

The tissue reorientation flaps are characterized by the lifting of skin from an adjacent donor site and reorienting it through the transposition of the flap over a peninsula of skin between the donor site and the defect. There is a pivot point at the base of this flap (see Fig. 147.3). The tissue movement depends on the presence of laxity in adjacent tissue. Although intrinsic elasticity of the flap skin may facilitate the ease of execution, without ample laxity in the flap donor site, the transposition can not be performed. Some of the flaps that fall into this category include the rhombic transposition flap, the bilobed transposition flap, and the nasolabial transposition flap (see Table 147.3).

To better understand the reorientation of tissue that occurs in these flaps, a review of the most basic tissue reorientation flap, the Z-plasty, is helpful. Z-plasties transpose two angular flaps, placing them in a complementary fashion into the defects of the other flap (Fig. 147.6). This reorientation of tissue ultimately results in the lengthening of the skin in the direction of the middle arm of the Z-plasty (Fig. 147.7). There is a complementary decrease in the length of skin perpendicular to this same arm. The amount of lengthening is proportional to the angles of the flap(s). Put another way, tissue gain in the direction of the middle arm is directly proportional to the width of the base of the flaps. This is effectively the mechanism of tissue reorientation in transposition flaps. Upon careful examination, Z-plasties can be found within the design of transposition flaps (Fig. 147.8). Therefore, just as with Z-plasties, transposition flaps work because the reorientation of the tissue results in lengthening of tissue in the direction of the skin deficit at the expense of the laxity in the donor site.

It is helpful to understand the utility of these principles of reorientation. An example of the utilization of these principles is in the case of a defect on the nasal tip (Fig. 147.9). The skin is typically very tight in this area, making simple side-to-side closure in the vertical direction difficult. Side-to-side closure in the horizontal direction is impractical because of the distortion that would occur to the free margin of the ala. When one looks for donor sites, there is typically a substantial amount of laxity on the mid nasal dorsum and nasal sidewall. A bilobed flap allows utilization of this laxity through tissue reorientation using two lobes. The underlying mechanism of tissue reorientation is a series of Z-plasties inherent in this flap. Since tissue gain in Z-plasties is in the direction of the middle arm of the Z-plasty, a substantial reorientation and lengthening of tissue in the desirable direction for repair of the defect occurs without distortion. In contrast to the Burow's triangle displacement flap, this flap does not rely upon intrinsic elasticity of the flap skin. This is key to avoiding distortion of the alar rim.

Tissue importation flaps

Large defects, or defects in areas where tissue laxity is lacking, may be reconstructed by importing vascularized tissue from a site that is not adjacent to the defect (see Table 147.3). Tissue importation flaps are typically derived from a distant donor site with ample tissue laxity and, most importantly, an excellent blood supply. This blood supply may be based on a particular artery (e.g. paramedian forehead flap based on the supratrochlear artery) or by a rich, random-patterned blood supply (e.g. the retroauricular pedicled flap).

These flaps are typically two-staged flaps requiring a period of vascular ingrowth from the wound bed of the defect. This time period ranges from 2 to 6 weeks, with 3 weeks being the most commonly reported time point for transection of the pedicle. In the head and neck region, defect sites where tissue importation flaps are commonly employed include the nose, ear, eyelid and lip. The appropriate selection and execution of these four broad flap categories are discussed in more detail below.

DESCRIPTION OF TECHNIQUE

Burow's Triangle Displacement Flaps

The group of flaps that comprise the Burow's triangle displacement flaps has the common feature of the displacement of Burow's triangle(s) along an incision made tangential to the defect (see Fig. 147.4). In each case, the basic method of closure is side-to-side advancement of tissue with the removal of Burow's triangles in the direction perpendicular to the side-to-side tissue movement. The greatest utility of these flaps is in situations where the normal adjacent location of one or both of the Burow's triangles would impinge upon a vital functional or cosmetic structure (see Fig. 147.5). These flaps allow for displacement or relocation of the triangle(s) to a more convenient location. As discussed earlier, one drawback is that the area of the flap is relatively large and the resulting tissue undermining is increased dramatically with only a modest increase in lax tissue recruitment.

Single tangent advancement flaps (STAF) and rotation flaps

There are several variants of Burow's triangle displacement flaps that are differentiated by the number of Burow's triangle displacements, or the configuration of the tangential line extending to the displaced

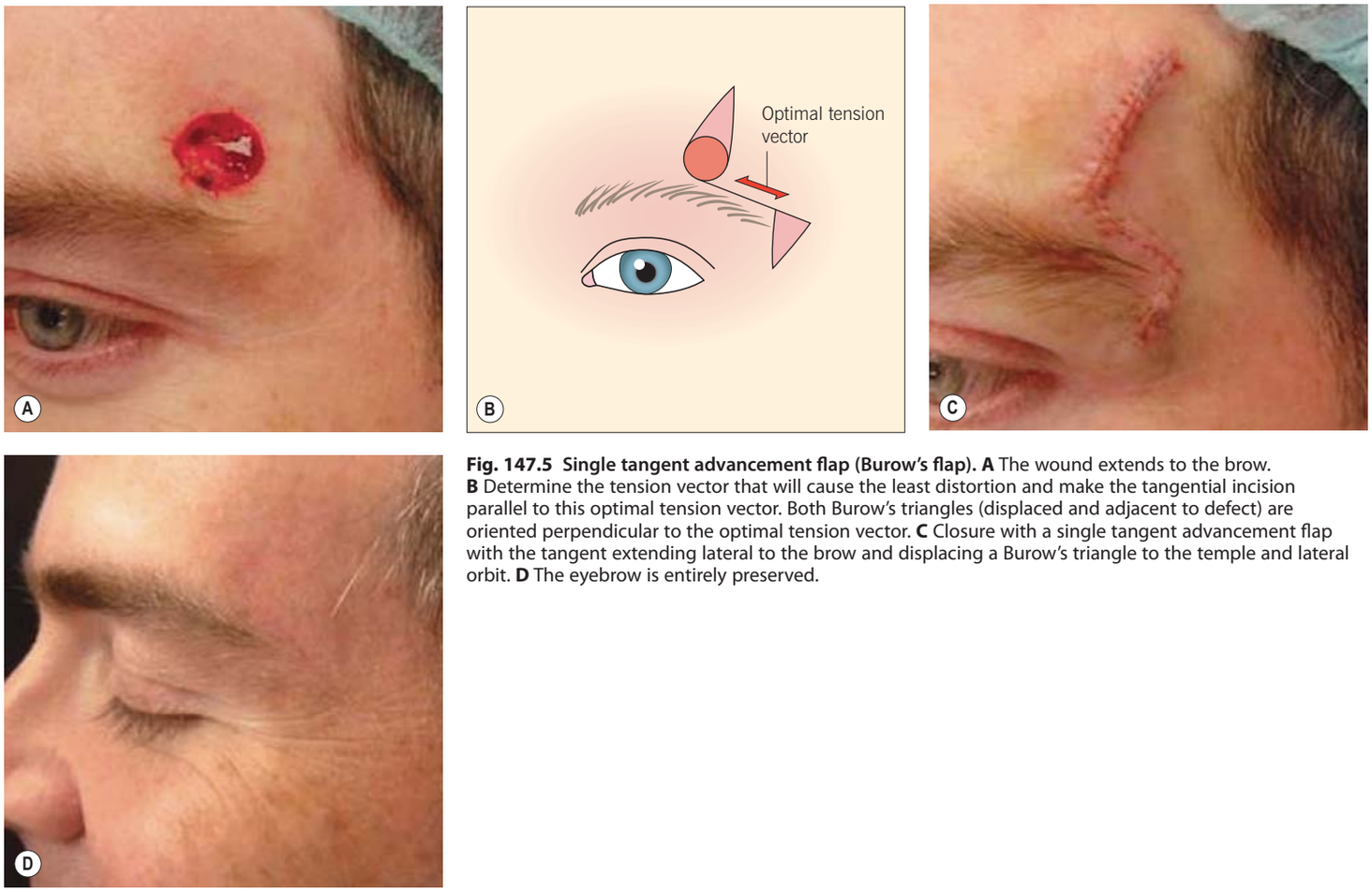


Fig. 147.5 Single tangent advancement flap (Burow's flap). A The wound extends to the brow. **B** Determine the tension vector that will cause the least distortion and make the tangential incision parallel to this optimal tension vector. Both Burow's triangles (displaced and adjacent to defect) are oriented perpendicular to the optimal tension vector. **C** Closure with a single tangent advancement flap with the tangent extending lateral to the brow and displacing a Burow's triangle to the temple and lateral orbit. **D** The eyebrow is entirely preserved.

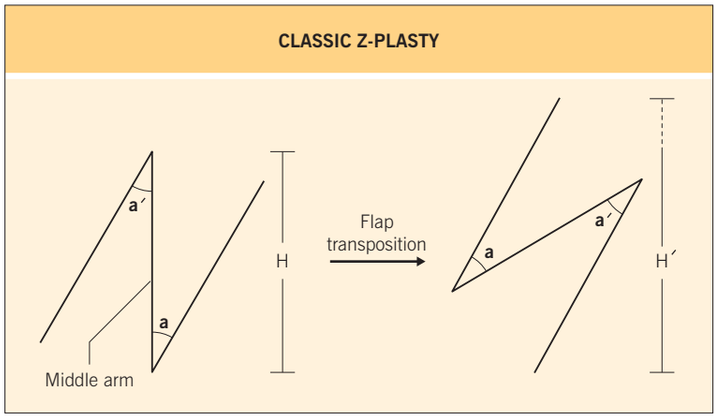


Fig. 147.6 Classic Z-plasty. The directional tissue gain (dotted line) is depicted (H to H') after flap transposition in the direction of the middle arm of the Z-plasty.

triangle (see Fig. 147.4). Ideally, the design of these flaps should, when possible, incorporate the concept of placing surgical scars at cosmetic subunit borders and within relaxed skin tension lines. Therefore, when a defect is located near an arcing junction of a cosmetic subunit or if the relaxed skin tension lines are curved, the Burow's triangle displacement flap, classically known as the rotation flap, may be an excellent option. An example of this would be the cheek rotation flap for a defect on the mid to medial upper cheek (Fig. 147.10). On the other hand, when the cosmetic subunit junctions or relaxed skin tension lines are relatively straight, the single tangent advancement flap, traditionally known as the Burow's advancement flap, may be optimal. A variation, the crescentic advancement flap, can be employed when the anatomic structures are naturally curved (Fig. 147.11).

Once the need to displace a Burow's triangle in order to avoid a vital structure is established, the incision lines should be planned in the optimal location. The incision, whether straight or arced, should be made perpendicular to the skin and should extend to the point of preferred displacement of the triangle. The triangle should then be excised to a depth commensurate with the depth of the defect being repaired and the thickness of the flap. The flap should be elevated by dissection in the subcutaneous plane and all other wound edges should be widely undermined at a similar depth. The optimal thickness of a flap will depend upon the location of the flap. Creating a flap that is too thin with dissection at the dermal–subcutaneous junction may compromise the flap's blood supply and may lead to a less natural-looking flap. Conversely, if the flap is in a site with very thick subcutaneous tissue and an excessively thick flap is created, flap mobility may be decreased, the flap edges may be more difficult to evert, and the underlying neurovascular structures or facial muscles can be unintentionally damaged. Therefore, the optimal plane of dissection of a flap is normally somewhere between the upper mid subcutaneous tissue and the deep subcutaneous tissue. Flaps involving the movement of hair-bearing skin, cartilage or other special anatomic structures may specifically dictate the thickness of the flap.

Once the flap has been raised and the surrounding skin undermined, the flap is ready to be sutured into place. If the flap is large and heavy and would result in distortion of adjacent structures (e.g. eyelids), it may be necessary to use a flap suspension suture. This is typically achieved by placing a suture in a fixed or rigid structure that underlies the flap. Periosteal placement is often the most effective way of anchoring a suspension suture. The suture is then placed into the flap's undersurface through the subcutaneous tissue, into the deep dermis. Placement within the flap should correspond topographically to its

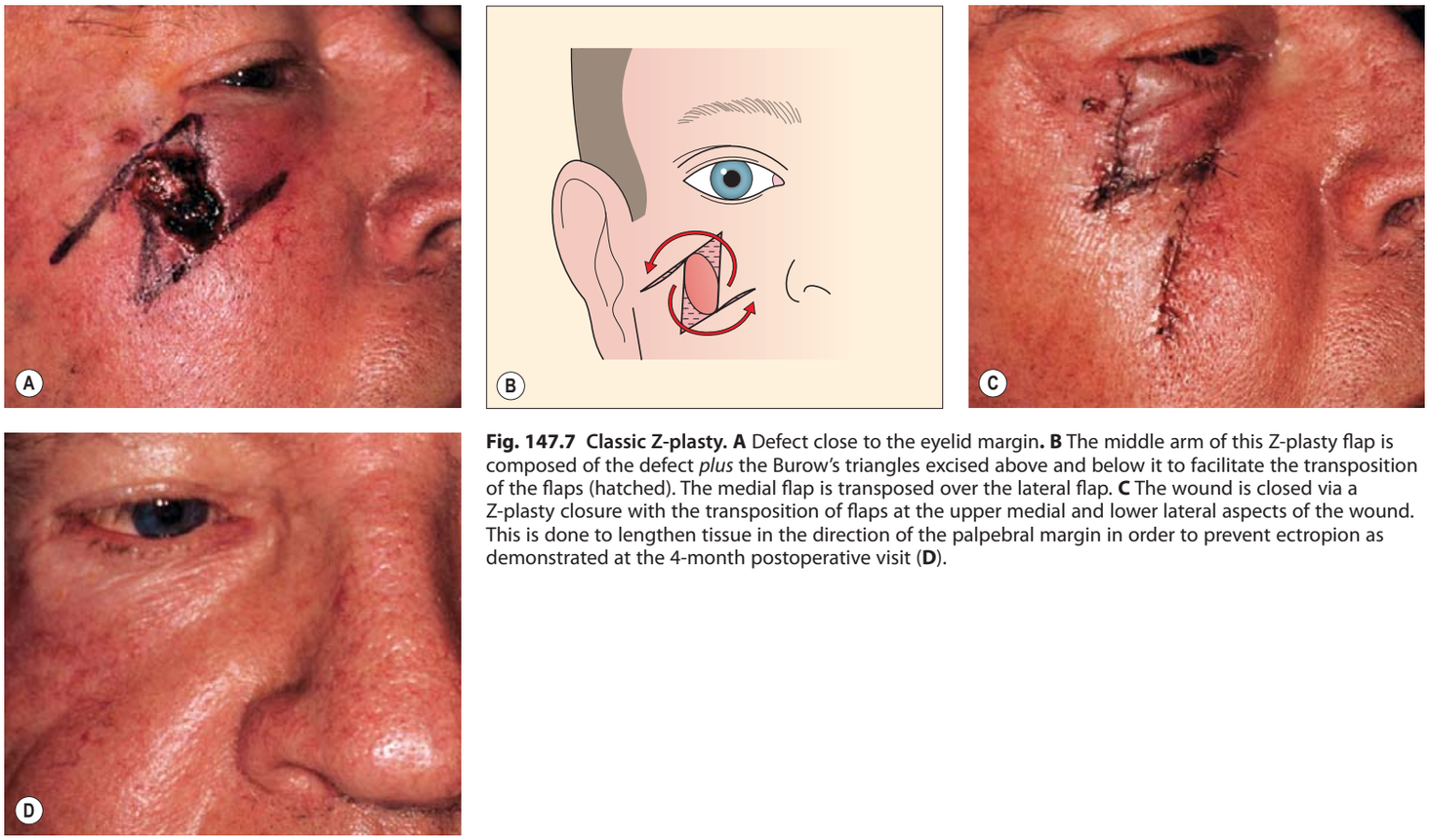


Fig. 147.7 Classic Z-plasty. A Defect close to the eyelid margin**. B** The middle arm of this Z-plasty flap is composed of the defect *plus* the Burow's triangles excised above and below it to facilitate the transposition of the flaps (hatched). The medial flap is transposed over the lateral flap. **C** The wound is closed via a Z-plasty closure with the transposition of flaps at the upper medial and lower lateral aspects of the wound. This is done to lengthen tissue in the direction of the palpebral margin in order to prevent ectropion as demonstrated at the 4-month postoperative visit (**D**).

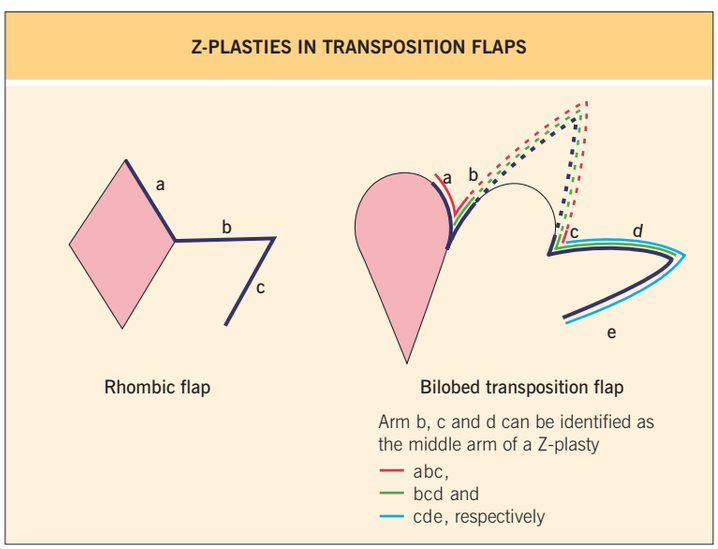


Fig. 147.8 Z-plasties in transposition flaps. Z-plasties are highlighted within the designs of both the rhombic and the bilobed transposition flap. Note in the rhombic flap the middle arm of the Z-plasty is line B and is the direction of anticipated tissue lengthening. In the bilobed transposition flap diagram, there is a series of three Z-plasties all contributing to tissue gain in the desired direction of the defect.

desired location relative to the periosteal suture. This can be repeated as necessary, with care to avoid interruption of vascular supply.

The next step of the closure is to suture the skin edges of the two Burow's triangles, evenly distributing them. The remainder of the flap can now be completely sutured into the defect with even distribution of the wound edges of the flap and opposing skin.

Double tangent advancement flaps (DTAF)

Double tangent advancement flaps displace both Burow's triangles along parallel tangents (see Fig. 147.4). Therefore, these flaps are typically peninsular in configuration with an isolated vascular base at the distal ends of the tangents. The execution of this flap is very similar to that of single tangent advancement flaps, except that one must be mindful of the more limited vascular supply (Fig. 147.12). This isolated vascular supply necessitates limiting the length of the flap to three to four times the width. The thickness of the flap should be commensurate with the thickness of the defect, with the typical plane of dissection between the upper mid subcutaneous tissue and the deep subcutaneous tissue. When suspension sutures are necessary, extreme caution is necessary in order to avoid compromise of the vascular supply to the leading edge of the flap. Again, the first closure points are at the site of the displaced Burow's triangles. Suturing the advancing flap with even distribution of the flap along the recipient tissue margins completes the execution of this flap.

Site-Specific Variations of Burow's Triangle Displacement Flaps

Helical advancement flaps

Helical advancement flaps are often discussed as a unique entity, but they are merely variants of Burow's triangle displacement flaps. As the name indicates, they are specific for the helix of the ear. The characteristics of the helix are unique owing to its highly distortable free margin that is curved in nearly every dimension and its limited pool of adjacent tissue laxity. The most typical form of the helical advancement flap is directly analogous to the double tangent advancement flap in that parallel tangents are incised from the helical defect along the anterior rim of the helix and the posterior helix. A less commonly described variant of the helical advancement flap is the single tangent advancement flap in which a single incision is made along the anterior helical rim while a non-displaced Burow's triangle is excised directly posterior to the defect on the posterior ear. Both the double tangent advancement flap and the single tangent advancement flap variant can

Fig. 147.9 Bilobed flap. A Defect on the nasal tip adjacent to the free margin of the ala. Bilobed flap reconstruction with minimal distortion of the alar rim (**B**) and long-term result (**C**).

Fig. 147.10 Rotation flap. Large defect (**A**) on the medial cheek and lower eyelid reconstructed with a rotation flap (Mustarde flap) with displacement of the superior Burow's triangle laterally along the curvilinear tangent which follows the relaxed skin tension lines (**B**). **C** Final results with no distortion of the eyelid and incision lines nicely camouflaged along cosmetic subunit borders and relaxed skin tension lines.

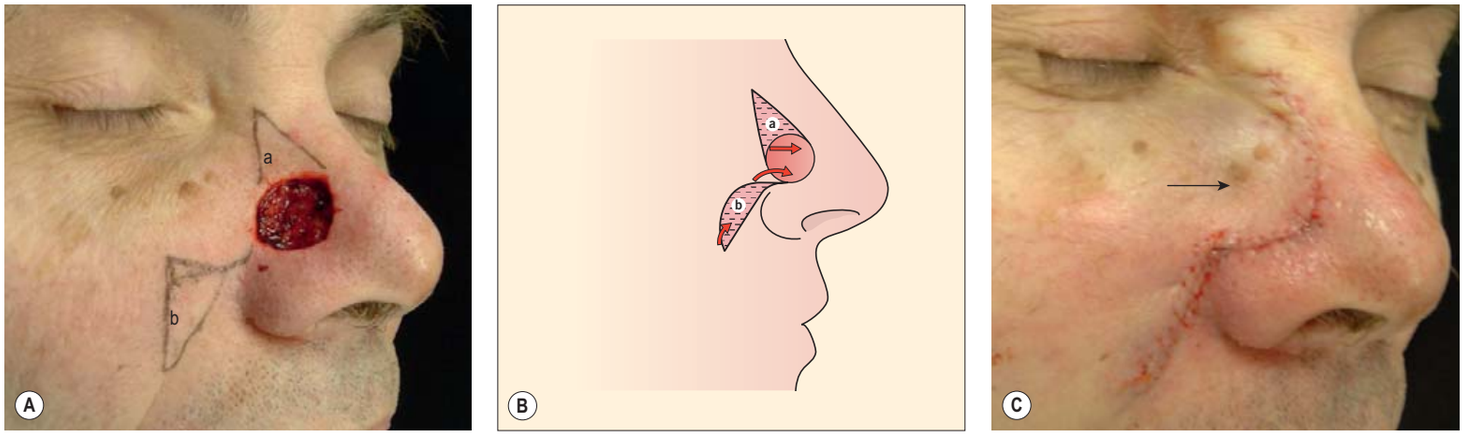


Fig. 147.11 Crescentic advancement flap. A Medium-sized defect on the right inferior nasal sidewall. A single tangent advancement flap (Burow's flap) is planned with a crescent-shaped Burow's triangle on the medial cheek. **B** The crescent (b) fits nicely with the naturally curved anatomic configuration of the alar crease and creates a "wound edges of unequal length" situation which further contributes to the advancement of skin onto the nose. **C** Flap sutured in place; note the subtle indentation (arrow) that corresponds to a periosteal suture placed at the nasofacial sulcus in order to prevent tenting and to recreate the sulcus. **D** Four-month postoperative appearance.

Fig. 147.12 Double tangent advancement flap. This technique was used to reconstruct and preserve the continuity of the eyebrow in this patient.

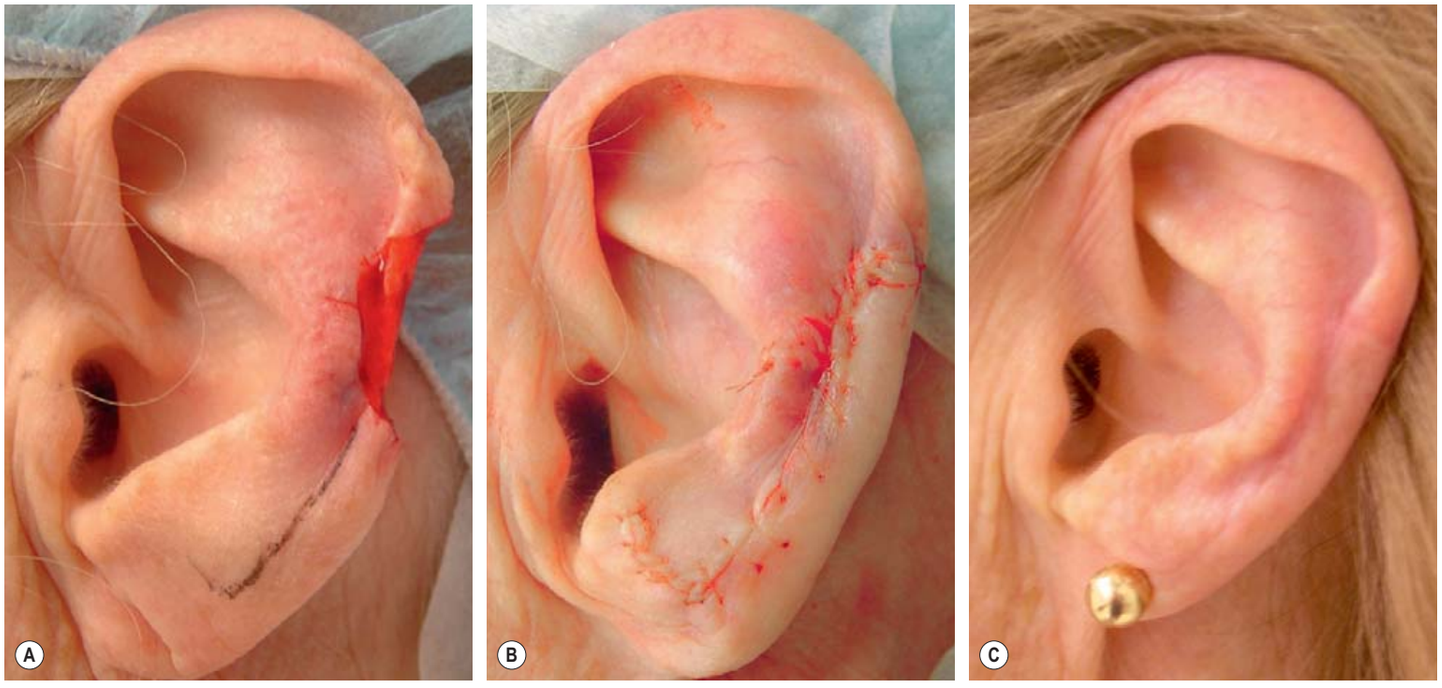


Fig. 147.13 Helical advancement flap. A Defect of the mid helix involving a small amount of cartilage. A single tangential incision is planned inferiorly within the helical groove to the earlobe. A Burow's triangle excision is planned directly behind the defect on the posterior ear. The flap will be raised by dissection of the skin from the posterior ear above the perichondrium. The displaced Burow's triangle will be removed from the earlobe and the skin of the flap will be redraped through upward advancement into the defect. **B** The flap is sutured after a very small wedge of cartilage has been removed to reconstitute the helical rim of cartilage. **C** Three-month postoperative appearance.

be either a single flap (derived superior or inferior to the defect) or two flaps (derived both above and below the defect). As with all Burow's triangle displacement flaps, the helical advancement flap is a technique devised to displace the Burow's triangle to a more convenient location distant from the defect. The majority of the defects on the helix derive donor pool skin from the inferior direction. The donor pool from the superior helix is typically less abundant but is very beneficial in large mid-helical defects (when two flaps are used) and in defects of the superior helix.

A common use of the helical advancement flap is for a small- to medium-sized defect on the mid helix not involving the cartilage (Fig. 147.13). While a wedge closure of the ear could be considered, displacing the anterior triangle by utilizing the lax skin of the lower helix and earlobe obviates the need to do a wedge resection of the auricular cartilage. Burow's triangles can easily be displaced to the earlobe, which facilitates the advancement of the helical skin into the defect. Despite the resultant decrease in the size of the earlobe, the aesthetic impact tends to be minimal as long as the anterior profile of the ear is maintained. Since the earlobe is most visible on the lateral view and because the opposite earlobe is not simultaneously visible, subtle changes in size often go unnoticed.

With a more superiorly located defect, the donor pool is at the anterior aspect of the helical rim. Although the extent of tissue movement from the anterior helix is often less than can be expected on the inferior helix, this varies greatly and must be determined for each case.

In the "classic" helical advancement flap, which is a double tangent flap or "U-flap", the parallel lines are well hidden in the helical groove or on the helical rim and posteriorly on the ear. A possible disadvantage is the very narrow flap base through which all blood flow must pass. However, the helical rim has a rich vascular supply and is more forgiving even when tension on the wound edges is considerable. Nevertheless, there is a risk of distal necrosis of a "classic" helical advancement flap that is under tension.

The lesser known variant (see above), which is analogous to a Burow's flap, does not have the same narrow base. Rather than a parallel incision being made on the posterior surface of the ear, a Burow's triangle is excised directly posterior to the defect. The same anterior incision is made along the helical rim (see Fig. 147.13), but the base of the flap now becomes the entire posterior ear. The flap can be dissected from the cartilage on the posterior ear and redraped with advancement over the defect. Equally excellent cosmetic results can be obtained with this variant, with very little downside.

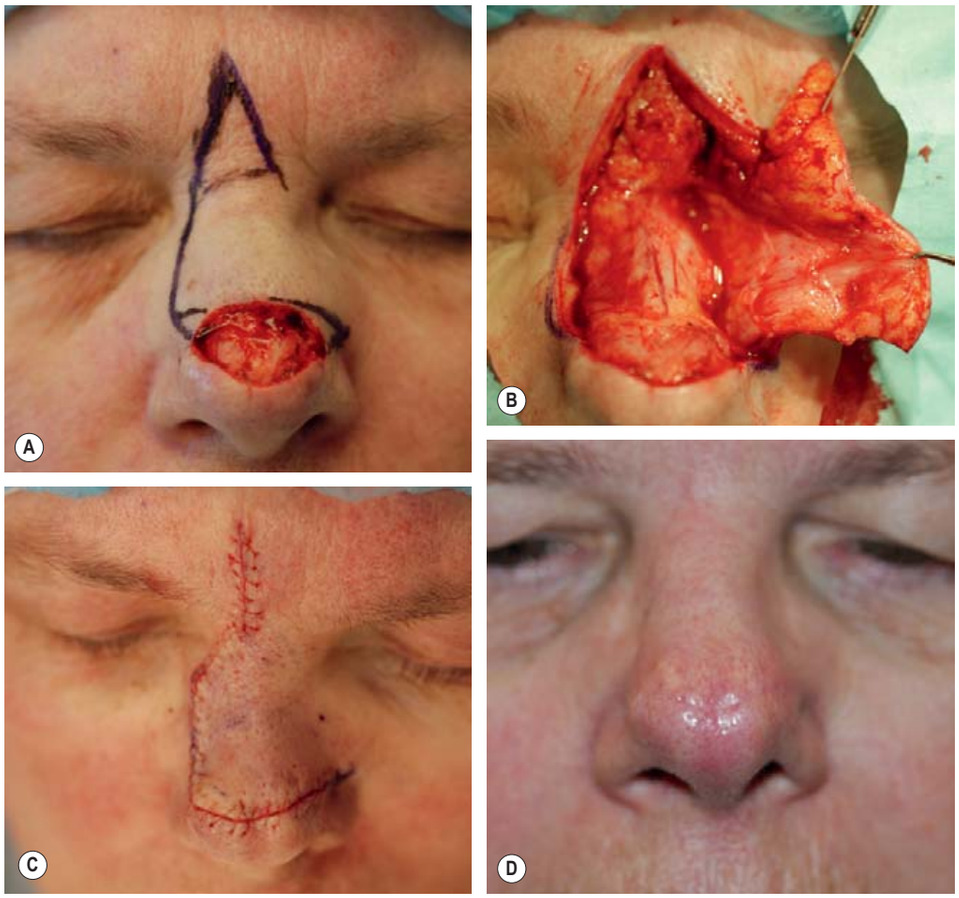


Fig. 147.14 Dorsal nasal flap. A Moderate-sized defect of the nasal tip. **B** The flap is incised and reflected demonstrating the deep plane of dissection just above the nasal periosteum. The flap will be redraped over the tip of the nose with primary closure of the displaced Burow's triangle on the glabella. **C** Flap sutured into place. **D** Result four months postoperatively.

Dorsal nasal flap

The dorsal nasal flap is a specialized, site-specific variant of the Burow's triangle displacement flap that is useful for reconstructing moderately sized distal nasal defects. The basic design of this flap is predicated upon the fact that it is often inconvenient or unfeasible to remove a Burow's triangle on the nasal tip. Therefore, the design of this flap displaces a Burow's triangle from the nasal tip to the glabella along an incisional arc that extends from the more inferior aspect of the defect (above the alar crease) to along the nasofacial sulcus and finally onto the glabella (Fig. 147.14). However, this flap involves a large area of skin in order to accomplish the closure of a relatively small defect.

The dorsal nasal flap relies on the rich blood supply of the medial canthal plexus that is largely supplied by the angular artery. Classically, in a dorsal nasal flap, there is a back cut in the glabellar skin; this skin is then trimmed after rotation of the flap and is equivalent to the removal of the displaced Burow's triangle. The back-cut technique narrows the base of the rotation flap, thereby reducing the overall pivotal restraint on the flap. Because of its excellent vascular supply, the dorsal nasal flap is ideally suited for this technique. The reduction in the pivotal restraint decreases the secondary tension on the nasal tip defect, which helps to avoid distortion of its free margins.

The most important aspect in the execution of the dorsal nasal flap is creation of a broad-enough arc by extending to the nasofacial sulcus, but skirting the medial canthal skin en route to the glabella. The second key element is the plane of dissection when elevating the flap. While the portions of the flap that will be covering the nasal defect can be trimmed and thinned to match the native skin and defect, the body of the flap must be dissected at the level of the perichondrium and periosteum. This assures incorporation of the perforator arteries from the canthal plexus and subsequent survival of the flap. When these principles are observed, this flap is robust and can reconstruct moderately large-sized nasal tip defects without distortion and with an excellent tissue match.

While the surgeon must be aware of important variables that can substantially affect the successful use of any flap, this is especially true in the case of the dorsal nasal flap. The ideal situation is a patient with very non-sebaceous and elastic or "loose" skin of the nasal dorsum. Characteristics that raise concern about whether this flap can be successfully executed include thick, inflexible and highly sebaceous skin. Also, prior surgeries on the nose or the medial canthus should be viewed as a potential source of compromised vascular supply. Distortion of the distal nose structures may occur if there is severe structural compromise of the free margin or the cartilage of the nasal tip and consideration should be given to other reconstructive options (e.g. a tissue importation flap). The dorsal nasal flap should be reserved for defects that are too large to be reconstructed with a small local flap such as the bilobed flap yet smaller than a defect for which a tissue importation flap would be more ideally suited. The most difficult aspect of successfully executing a dorsal nasal flap is anticipating and dealing with the secondary motion inherent in this flap.

Wedge closure of the lip

Wedge closure of the lip is a special form of the simple elliptical closure that deserves mention here. It is used in small- to moderate-sized defects of the lip that involve the vermilion or the vermilion border. It is traditionally taught as a full-thickness excision of skin, mucosa, submucosa and musculature. However, when tissue-conserving excisions (e.g. Mohs micrographic surgery) are employed and much of the orbicularis oris muscle is preserved, a subtotal wedge excision of the muscle is preferred due to its simplicity, the decreased chance of lip dysfunction and the smaller chance of complications.

For an excellent cosmetic result, careful realignment of the vermilion border is essential. Prior to excision of the tumor, hash marks are made with a scalpel along the vermilion border as reference points. This is done because after injection of anesthesia and excision, the precise location of the vermilion border can often become indistinct. The hash marks ensure precise realignment of the vermilion border (Fig. 147.15).

In assessing how much muscle needs to be removed in a subtotal wedge excision, the surgeon surveys the amount of redundant soft tissue that forms when the wound edges are approximated. Usually,

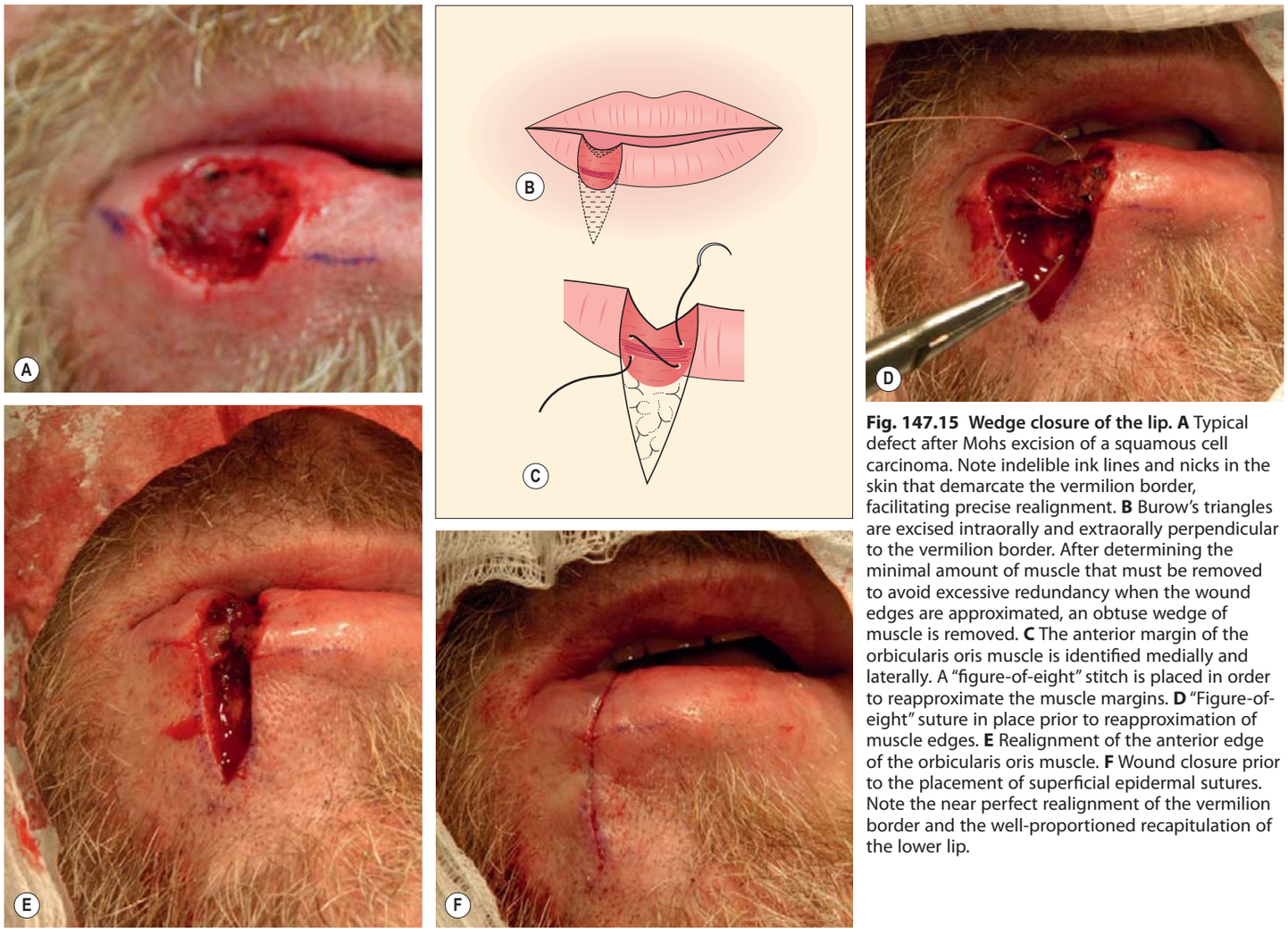


Fig. 147.15 Wedge closure of the lip. A Typical defect after Mohs excision of a squamous cell carcinoma. Note indelible ink lines and nicks in the skin that demarcate the vermilion border, facilitating precise realignment. **B** Burow's triangles are excised intraorally and extraorally perpendicular to the vermilion border. After determining the minimal amount of muscle that must be removed to avoid excessive redundancy when the wound edges are approximated, an obtuse wedge of muscle is removed. **C** The anterior margin of the orbicularis oris muscle is identified medially and laterally. A "figure-of-eight" stitch is placed in order to reapproximate the muscle margins. **D** "Figure-of-eight" suture in place prior to reapproximation of muscle edges. **E** Realignment of the anterior edge of the orbicularis oris muscle. **F** Wound closure prior to the placement of superficial epidermal sutures. Note the near perfect realignment of the vermilion border and the well-proportioned recapitulation of the lower lip.

the apex of the wedge (after removal of redundant muscle) is obtuse, creating a very slight trough in the lip in an anterior-to-posterior direction. In our experience, the less muscle that is removed, the less likely a noticeable notch or dip in the vermilion lip will form and the function of the lip is beautifully maintained. After excision of Burow's triangles on the external lip and the internal lip (see Fig. 147.15B), and after undermining the cutaneous portion of the defect, the key suture is the one that reapproximates the medial and lateral muscle edges. This is best done by the placement of a "figure-of-eight" suture, which is similar to a horizontal mattress suture and snares the bellies of the anterior edge of the orbicularis oris muscle and precisely approximates them (see Fig. 147.15C–E). Upon healing, the ridge created by this approximation becomes a functional and aesthetic component of the lip and recreates the appropriate muscular bulge at the vermilion border.

Adjustment of the wound edges to perfectly realign the previously placed hash marks with epidermal sutures will ensure a perfectly realigned vermilion border.

Defect Reconfiguration (Island Pedicle) Flaps

The island pedicle flap is a unique advancement flap in that the creation of an island of epidermis and dermis eliminates any blood supply from the rich vascular plexus within the deep dermis and superficial subcutaneous skin. In effect, the vascular supply is isolated to the subcutaneous tissue. The two variations in pedicle design hinge upon whether the pedicle is created immediately beneath the island or from the subcutaneous tissue lateral to the island (Fig. 147.16). The variant with the vascular pedicle immediately beneath the island of skin is created by dissecting away surrounding superficial subcutaneous tissue and eliminating the tethering effects of the tissue adjacent to the pedicle. The island pedicle flap with laterally based pedicles is created by tunneling immediately beneath the island while carefully maintaining vascularized sheets of subcutaneous tissue, either bilaterally or unilaterally to the side of the island (Fig. 147.17). The authors' preference has been to develop a pedicle immediately under the island because of the more durable and reliable vascular supply. However, there are clearly some anatomic sites where the lateral pedicles provide adequate blood supply and better flap mobility.

In general, it is appropriate to think of the island pedicle flap as an advancement of what would be one of the Burow's triangles in a simple side-to-side closure. It must be located in areas with very elastic and spongy subcutaneous tissue with a rich blood supply. The island pedicle flap is an extremely tissue-efficient flap in which little or no tissue is discarded and yet it often provides outstanding clinical results. The mechanism for tissue conservation involves a reconfiguration of the defect into an angular shape via the use of what would be a Burow's triangle (Fig. 147.18). The original shape of the defect is reconfigured behind the advancing island to a defect of equal area but very angular in shape that can be closed without tissue redundancy, obviating removal of a Burow's triangle.

It is useful from the standpoint of flap execution to recognize conceptually that an island pedicle flap (especially those with the pedicle based immediately beneath the island) is essentially a rotation flap turned perpendicular to the surface of the skin (Fig. 147.19). Whereas, in a rotation flap, the vascular source lies parallel with the skin, the analogous vascular supply of the island pedicle flap runs perpendicular to the skin. While the plane of tissue movement in the traditional rotation flap is parallel with the skin, it is perpendicular to the skin in an island pedicle flap. Once this analogy between a rotation flap and

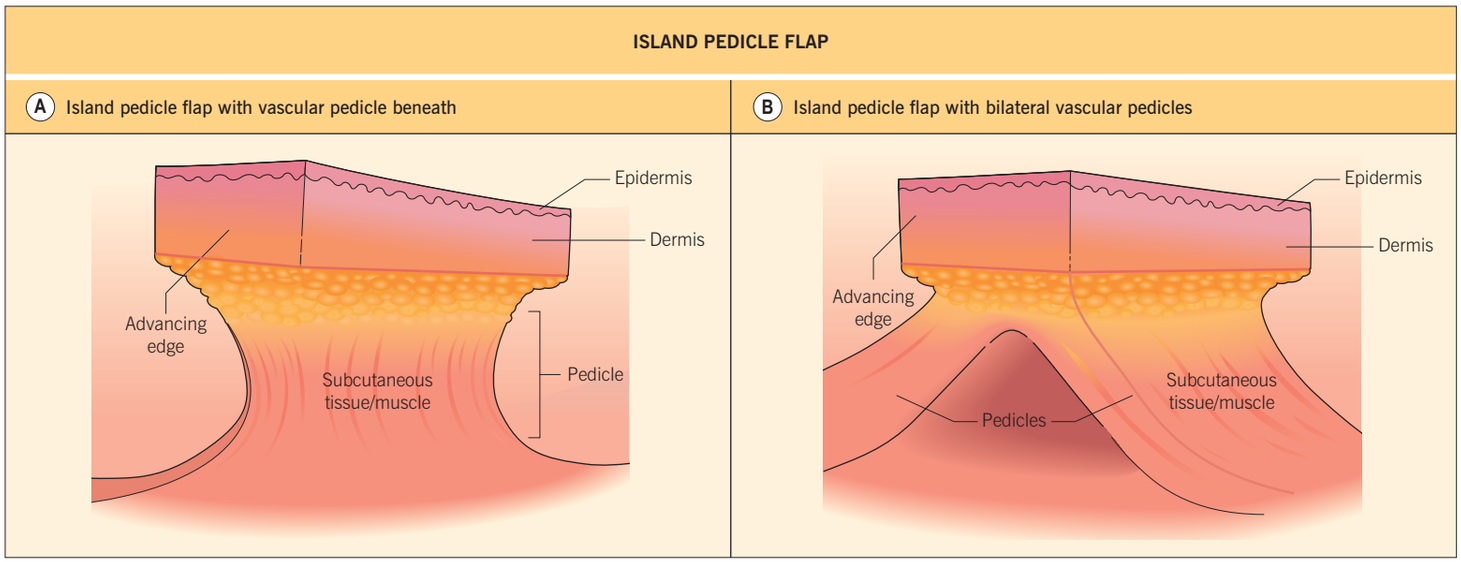


Fig. 147.16 Island pedicle flap. A Vascular pedicle derived immediately beneath the island of skin. **B** Vascular pedicles derived from tissue lateral to the island flap.

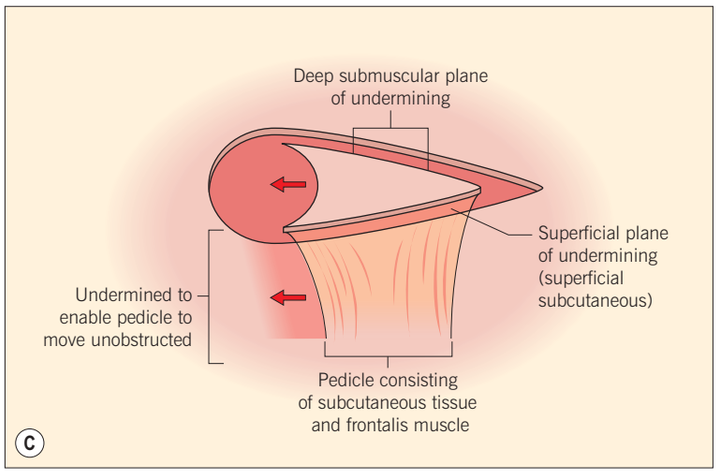


Fig. 147.17 Island pedicle flap. A Large mid-upper forehead defect. **B** Intraoperatively, an island pedicle flap is designed with a single inferior muscular pedicle based on the rich blood supply of the supratrochlear and supraorbital arteries. **C** The frontalis muscle serves as the inferiorly based pedicle for the flap. This muscular pedicle is constructed via undermining in the subcutis beginning at the lower edge of the flap (superficial plane) and undermining in the submuscular plane which is begun at the superior edge of the flap (deep plane). The skin medial to the pedicle must also be undermined to facilitate its advancement in the direction of the defect. **D** The defect is now comprised of acute angles which are more easily closed primarily.

an island pedicle flap is understood, it is easy to see that movement of the island pedicle flap is facilitated by the same factors that facilitate movement of a rotation flap. For example, excision of the Burow's triangle facilitates the rotation and advancement of the rotation flap. Likewise, the advancement of an island pedicle flap is facilitated by the removal of the tissue analogous to the Burow's triangle, i.e. any subcutaneous tissue at the base of the defect (see Fig. 147.19B). Without its removal, the subcutaneous tissue left in the base of the wound serves as a physical impedance to the advancing island pedicle flap.

Another technique for enhancing rotation flap mobility, the back cut, is also applicable to the island pedicle flap. A back cut for a rotation flap releases some of the restraining tension of the flap and is helpful in its mobilization. The equivalent of a back cut can also improve the mobility of an island pedicle flap. This is done by incising the subcutaneous pedicle at the trailing edge of the flap in a direction beveled slightly into the pedicle (see Fig 147.19B).

In order to enable eversion of the skin edges of the island pedicle flap, the island is very slightly undermined at the dermal–subcutaneous junction to facilitate its eversion. Extreme care must be taken to avoid compromise of the vascular supply. The skin surrounding the island pedicle flap is widely undermined in the superficial subcutaneous tissue. Once adequate mobility of the flap is obtained, it is advanced into the defect, with closure of the donor site behind the flap and closure of all skin edges.

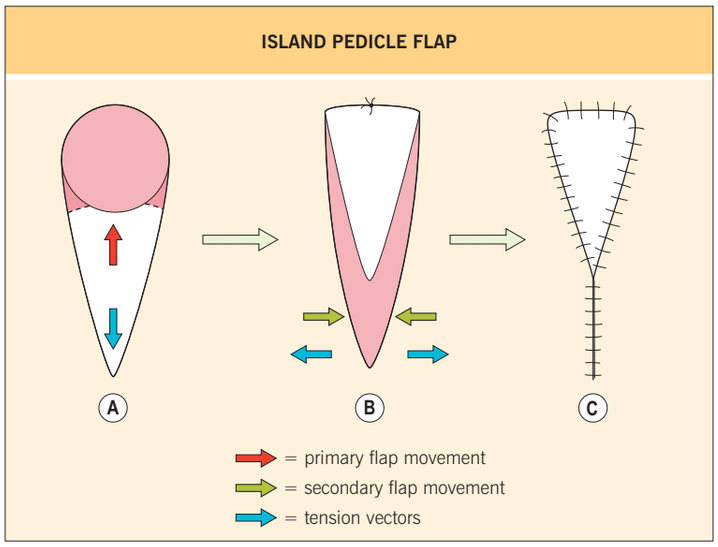


Fig. 147.18 Island pedicle flap. Reconfiguration of the defect (shaded area) in **A** to the defect in **B.** The shaded secondary defect in **B** is comprised entirely of acute angles which are easily closed primarily (**C**).

Subcutaneous tunneling island pedicle flap

The subcutaneous tunneling island pedicle flap is not a traditional island pedicle flap and technically is not a defect reconfiguration flap. Rather, it is a type of tissue importation flap. However, this flap is based upon a pedicle that, like the traditional island pedicle flap but unlike other tissue importation flaps, is composed entirely of subcutaneous and muscular tissues. The flap skin and its pedicle are then passed through a tunnel beneath intervening skin to the defect (Fig. 147.20). As a result, it is a higher-risk flap than most island pedicle flaps and tissue importation flaps. Finding suitably vascular locations for these flaps is the initial key step.

First, the donor skin is identified in an area with a suitably vascular pedicle (see Fig. 147.20A). Careful measurements of both the defect and the length of the subcutaneous pedicle are necessary so that the latter reaches the defect under minimal tension. Next, the island is incised and a pedicle deep to the island is developed (see Fig. 147.20B). It is helpful to elevate the skin overlying the prospective pedicle in order to visualize its construction. Once an adequate pedicle is developed, the skin between the base of the pedicle and the defect is undermined, creating a tunnel. The tunnel must be large enough for the tissue to pass and not be compressed; cautious defatting of the tunnel walls is often helpful to ensure ample room. This defatting also decreases the degree of fullness of the intervening skin created by the bulk of the pedicle. We recommend limiting the length of the pedicle to three to four times its diameter unless it is an axial flap based directly on and incorporating a known axial vessel.

The best locations for these types of flaps are the melolabial and paranasal areas as well as the glabellar region. Of note, it prudent to anticipate a 10–20% "shortening" of the pedicle as it is rotated and stretched through the tunnel into the defect. Careful preoperative planning improves the success of this flap.

Tissue Reorientation Flaps

Transposition flaps as a whole are some of the most useful flaps because of their ability to tap into adjacent tissue reservoirs in order to repair defects in anatomic locations with minimal inherent laxity. These flaps allow for repair of even large defects with minimal or no skin tension and without distortion of important surrounding anatomic structures. The classic transposition flap is the rhombic flap, with other useful transposition flap variants being the bilobed flap and the single-staged nasolabial transposition flap.

Rhombic transposition flap

The classic rhombic flap, originally described by Limberg in 1963, was based on the concept of placing the tension vector of the secondary defect nearly perpendicular to that of the primary defect (Fig. 147.21A). After closure of the donor site, the Limberg flap allowed for repair of the primary defect with essentially no wound edge tension. Dufourmentel added important modifications that made the closure of the donor site easier by placing the secondary defect at an acute angle (60°) to the primary defect. Thus, the flap must pass through a shorter arc in order to be positioned within the primary defect (Fig. 147.21B). Webster modified the rhombic flap further by making the angle of the secondary defect even more acute (30°) to further facilitate closure of the secondary defect (Fig. 147.21C). The smaller flap size of the Webster variant allows the surgeon to position the flap in almost any position relative to the primary defect in order to tap into the most lax skin available. However, as the angle of the secondary defect becomes more acute, more of the wound tension is transferred from the donor site to the primary defect. Care must be taken to ensure that the tension on the flap does not compromise vascular supply and flap viability. Another important concept to bear in mind is that as more tension is transferred to the primary defect, important nearby anatomic structures will be more prone to distortion.

Careful planning is required prior to incising the rhombic transposition flap in order to ensure that the donor site comes from the area

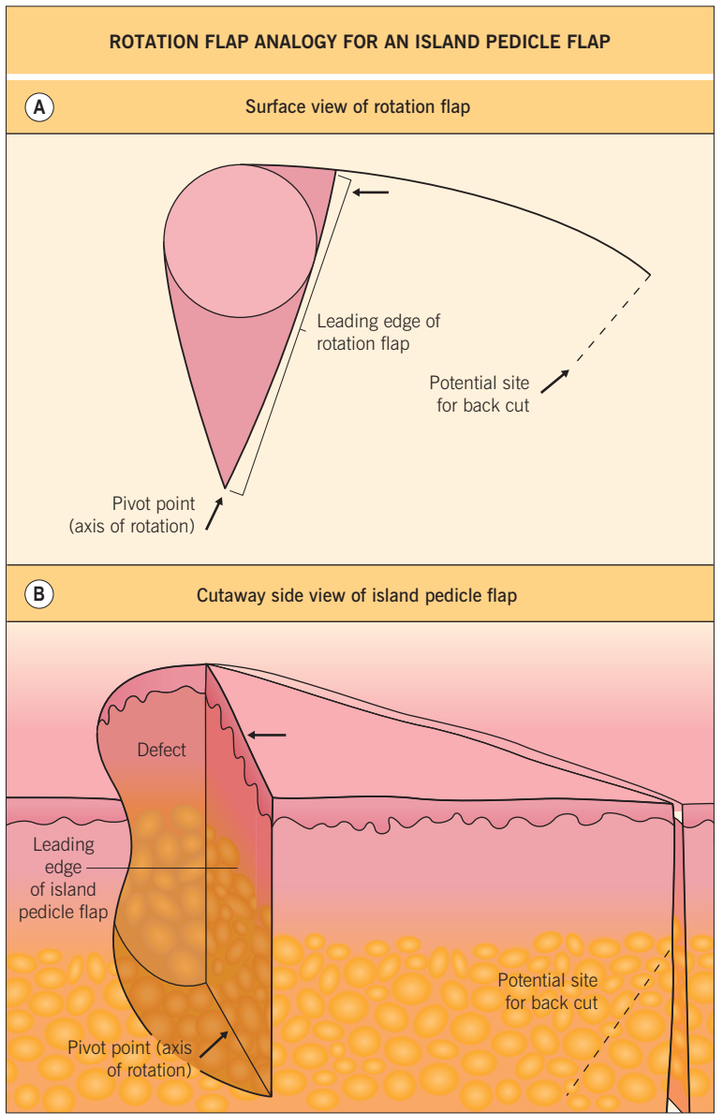


Fig. 147.19 Rotation flap analogy for an island pedicle flap. A A rotation flap with standard removal of a Burow's triangle adjacent to the defect and the site of a potential back cut which would facilitate flap movement. **B** Side view of a defect and an island pedicle flap. The plane of rotation is perpendicular to the skin surface. The shaded area is where the equivalent of a Burow's triangle has been removed to facilitate flap movement. The dotted line is analogous to the back cut of a rotation flap. Note the similarities between a rotation flap and an island pedicle flap.

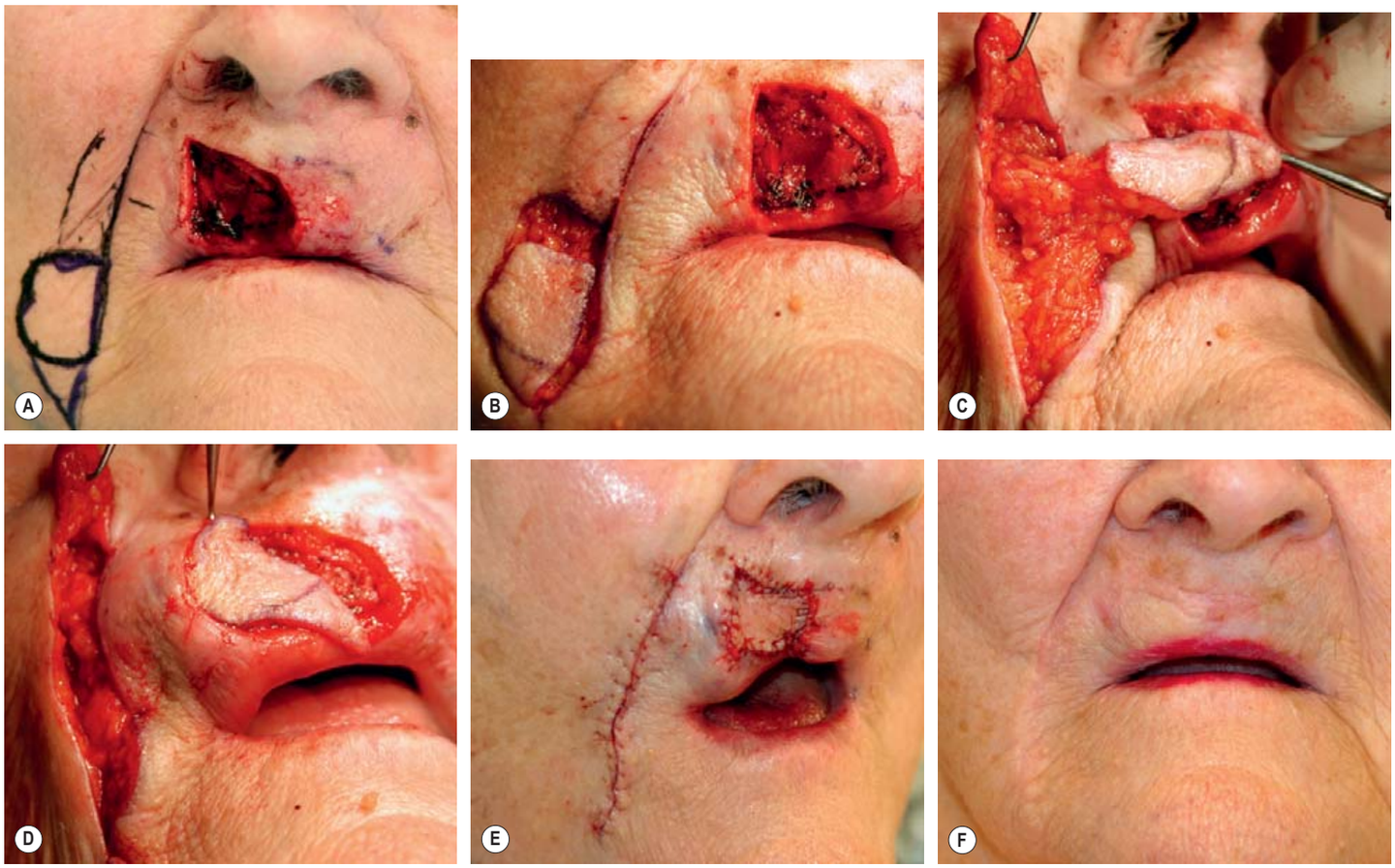


Fig. 147.20 Subcutaneous tunneling island pedicle flap (IPF). A Large upper lip defect with donor skin identified for a tunneling IPF. **B** Incision of the island and development of the pedicle. **C** Adequate length of the pedicle is assured. **D** The IPF is passed through the tunnel. Cautious defatting of the tunnel lessens the bulk effect of the pedicle plus the overlying skin. **E** Flap sewn in place with the donor site closed primarily. **F** Appearance at 1 year.

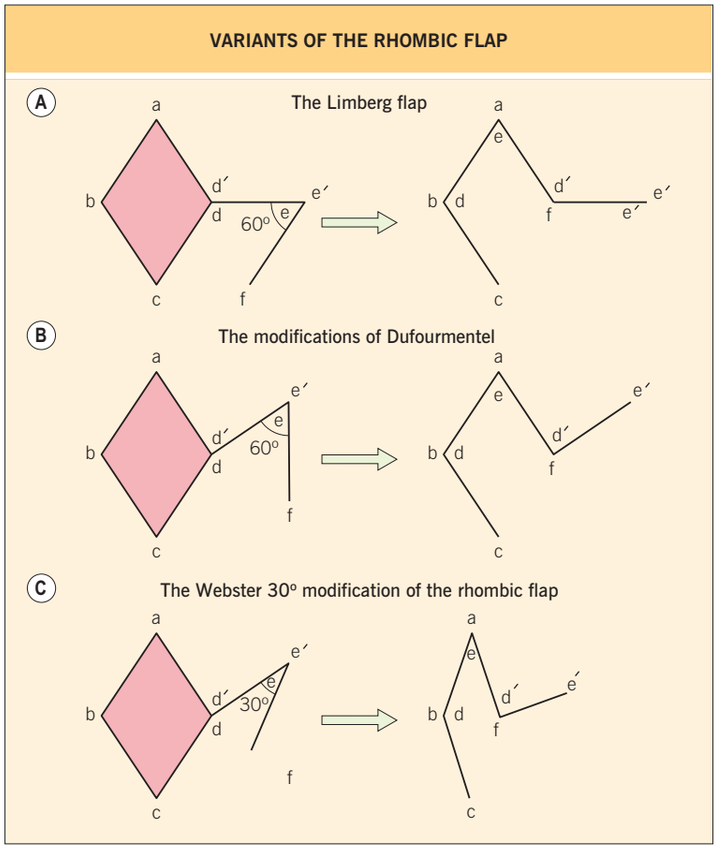


Fig. 147.21 Variants of the rhombic flap. A The Limberg flap is the standard rhombic flap. **B** The modifications of Dufourmentel. **C** The Webster 30° modification of the rhombic flap.

adjacent to the defect with the most abundant tissue laxity. This donor site, most commonly, parallels the relaxed skin tension lines. We prefer to remove the Burow's triangle at the pivot point prior to insetting of the flap. This ensures more accurate incision lines and allows more precise suture placement in order to distribute the flap tension evenly. The flap and the skin surrounding the defect and the donor site are undermined to ensure all are of the same thickness. Following careful hemostasis, the secondary defect is closed in a layered fashion. Next, the flap is inset into the defect, trimmed to fit and sutured in place.

Although extremely versatile, there are specific areas where the rhombic transposition flap provides reliable and reproducible results. The lateral, upper two-thirds of the nose and the lateral forehead are ideally suited for the rhombic flap because of the frequent difficulty in closing defects in these areas primarily (Fig. 147.22). The adjacent tissue laxity available on the nasal sidewall and the lateral cheek provide ample reservoirs of donor tissue. Large defects of the central cheek may occasionally be closed by the rhombic flap when simpler options are not possible because of the size of the defect. In other anatomic sites on the face, the rhombic flap may be a second or third option for repair, but other options are usually chosen first because of the difficulty in concealing the geometric shape of the incision lines of the rhombic flap.

Bilobed transposition flap

The bilobed flap is essentially two transposition flaps in series, and it is one of the most useful flaps for repair of defects of the lower one-third of the nose. The bilobed flap was first described by Esser in 1918 and important modifications to the flap were described by Zitelli in 1989. Zitelli modified the classic flap to decrease the pivot angle of the flap from 180° to close to 90–100° (Fig. 147.23). This simple modification helps to minimize two of the most common problems associated with the bilobed flap – the problem of pincushioning of the primary lobe and the tendency for standing cones to form at the pivot point of the flap.

Careful planning is required for the bilobed flap in order to ensure minimal distortion of surrounding structures. Figure 147.23B depicts

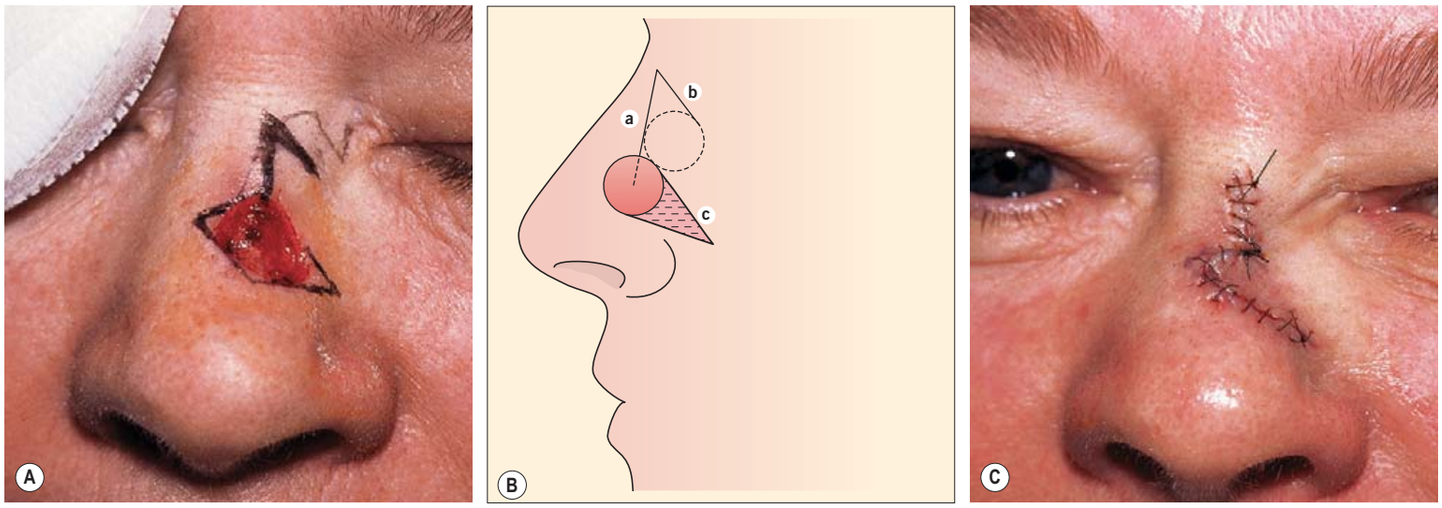


Fig. 147.22 Rhombic transposition flap on the upper lateral nose. A,B Key to the correct design of this flap is identification of the center point of the defect. The first incision for the flap is made in a line (**a**) along a vector radiating from the central point into the donor skin. The second incision (**b**) is made at an angle between 45° and 60° to this radiating incision, keeping in mind that the width of the flap must equal the width of the defect. Next, a 30° Burow's triangle is excised such that the flap side of the incision (**c**) is parallel to the lateral edge of the rhombic flap (**b**). **C** The tip of the flap is trimmed to fit the defect and the wound edges are sutured.

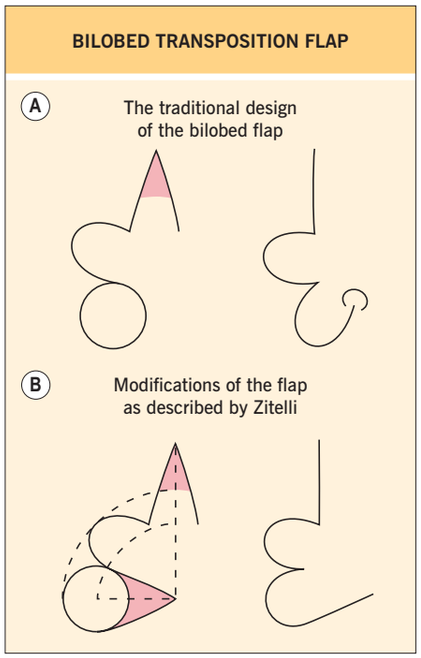


Fig. 147.23 Bilobed transposition flap. A The traditional design of the bilobed flap results in tissue protrusion at the pivot point. **B** Modifications of the bilobed flap as described by Zitelli.

a reliable method for planning the incisions of the bilobed flap. Drawing with a sterile marker on the patient (prior to incising the flap) ensures that the incision lines are placed in such a way as to maximize both functional and aesthetic results. For nasal defects, the flap should be designed so that the tertiary defect is closed in a fashion that is perpendicular to the line of the alar rim. This ensures that the contralateral ala is not lifted during closure of the tertiary defect. We remove the Burow's triangle when incising the bilobed flap, in order to provide the most accurate placement. Wide undermining of both the donor and recipient sites in a submuscular plane allows for good tissue mobility while providing excellent blood supply. On the side of the flap where the pivot point is located, we carry the plane of undermining to the nasofacial groove in order to facilitate proper placement of the flap, with no distortion of surrounding anatomic structures. Careful hemostasis is followed by closure of the tertiary site, followed by careful insetting and suturing of the flap into the primary defect. The secondary flap is then trimmed to match the circular secondary defect and sutured in place (Fig. 147.24).

Defects of the lower one-third of the nose measuring between 0.5 and 1.5 cm are the ideal size for the use of the bilobed flap. Smaller defects can often be closed in a primary fashion and larger defects may need either a skin graft or a two-staged tissue importation flap. Although the bilobed flap is the most common flap chosen for the distal third of the nose, it is rarely used in other anatomic sites because simpler options are usually available for those locations.

Nasolabial transposition flap

The single-staged nasolabial (melolabial) flap is a variation of a transposition flap that can be used to reconstruct defects of the nasal sidewall or large alar defects. Traditional designs of the nasolabial flap resulted in significant blunting of the nasofacial groove and frequent flap pincushioning, often requiring one or more postoperative revisions. This is perhaps why this flap has been underutilized in reconstruction of the nose. In 1990, Zitelli described several modifications of the traditional design that helped to minimize the need for surgical revisions. These modifications are outlined below.

The flap should be designed to include the preplanned excision of the Burow's triangle along the lateral nasal sidewall (Fig. 147.25). The donor site should parallel the nasolabial fold and, once incised and elevated, should be widely undermined in a subcutaneous plane across the cheek. The recipient site should be undermined in a submuscular plane on the nose and then the surgeon should transition to the more superficial subcutaneous plane at the nasofacial sulcus. After careful hemostasis has been obtained, a periosteal suture is placed in the undersurface of the flap corresponding to the new location of the nasofacial groove. This is secured to the periosteum of the nasal sidewall and, once tied, recreates this important cosmetic structure while at the same time essentially eliminates any tension on the flap. The periosteal sutures also minimize secondary flap movement that might pull the ala laterally postoperatively. The flap should then be thinned of subcutaneous fat and sutured in place. We frequently utilize tacking sutures on the undersurface of the flap in an attempt to recreate the alar crease and to prevent collapse of the internal nasal valve. The tip of the flap is finally trimmed to match the distal aspect of the defect and sutured in place with minimal tension in order to limit flap ischemia.

Tissue Importation Flaps

Tissue importation flaps are a loosely associated group of flaps that employ the concept of transferring tissue from a distant reservoir into a defect when other adjacent repair options are unsatisfactory. The flap itself is supported by either: (1) a single vessel as in the paramedian forehead flap (an axial flap); or (2) a rich collection of subcutaneous perforating vessels that enter the flap pedicle through underlying muscle

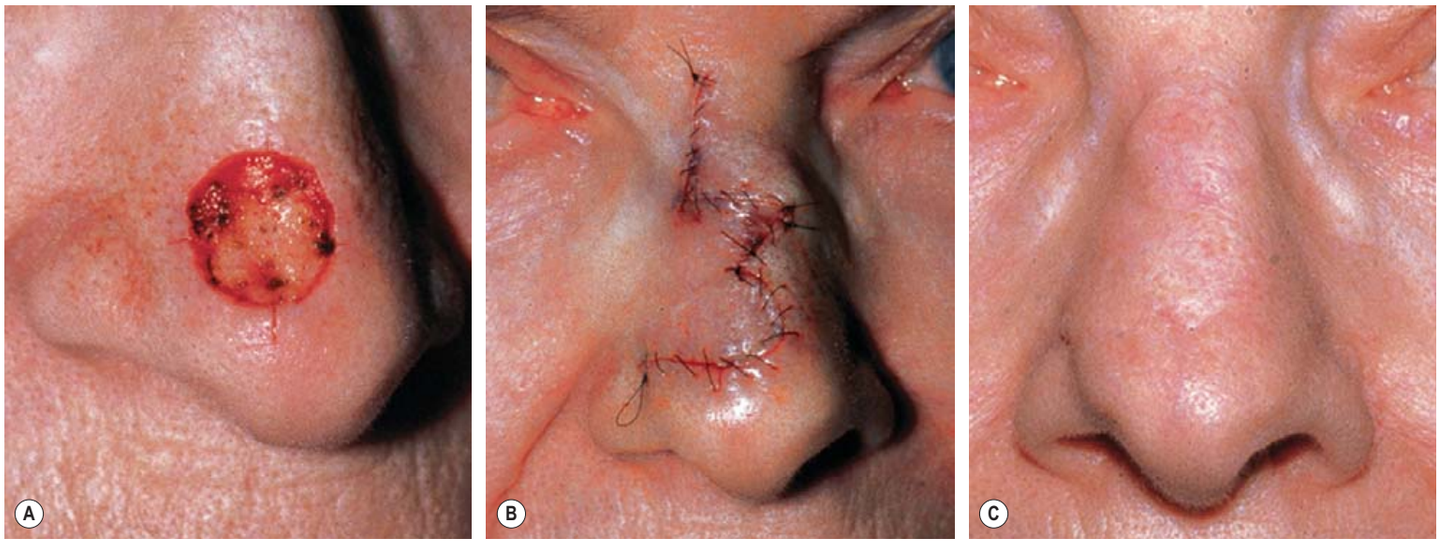


Fig. 147.24 Bilobed flap. A Distal nose defect. **B** Defect reconstructed with a modified bilobed transposition flap. **C** Cosmetic result at 1 year postoperatively.

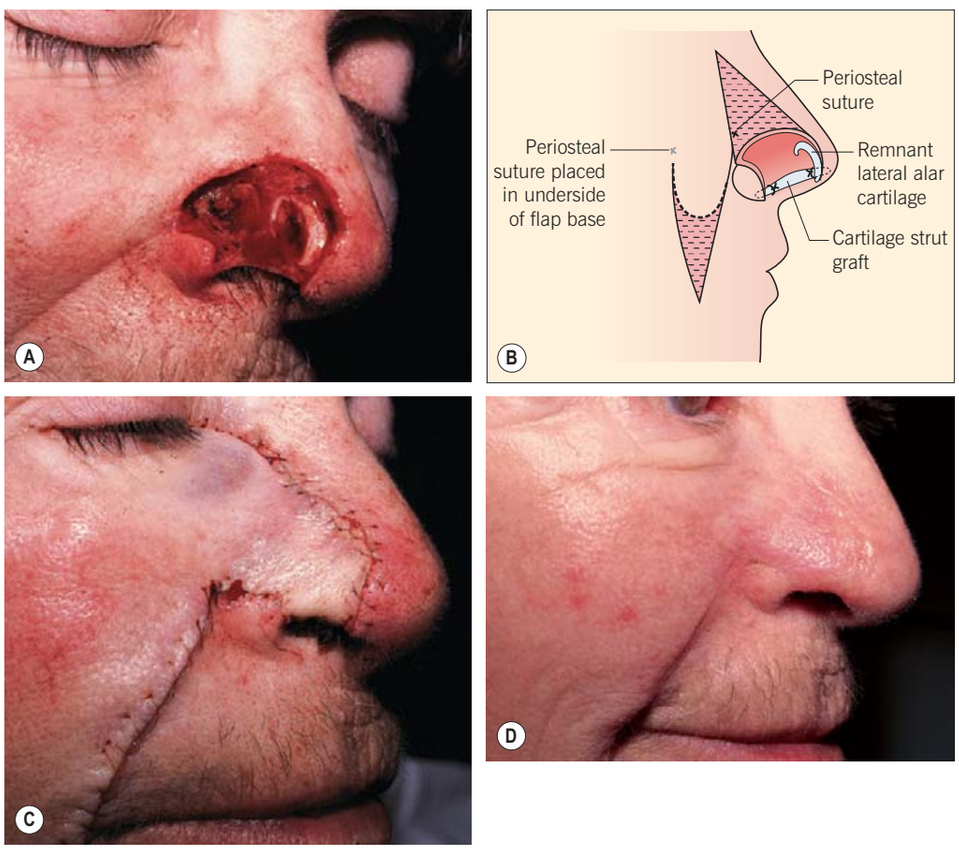


Fig. 147.25 Nasolabial transposition flap. A Large nasal defect involving loss of cartilage and extending to the intranasal skin. **B** Excision of a Burow's triangle on the nasal sidewall is oriented towards the medial canthal tendon. The lateral incision of the flap should extend no higher than the apex of alar skin over which the flap is to be transposed. In this case, an auricular cartilage strut graft is placed along the alar rim and inserted into medial and lateral dermal pockets and anchored with deep sutures into the wound base. The points of placement of the periosteal sutures into the undersurface of the advancing flap are indicated with an X. The distal flap is aggressively defatted. **C** The flap is trimmed to fit the defect, wrapped around the alar rim and folded onto itself, reforming the rim. **D** Cosmetic result at 6 months postoperatively.

(random pattern flap). Tissue importation flaps are ordinarily two-stage procedures. The first stage includes the initial planning and implementation of the flap. The vascular pedicle is left in place after the first stage in order to ensure adequate blood supply. The second stage involves the separation of the pedicle and the insetting of the proximal flap. Tissue importation flaps are most useful for reconstruction of large defects and are especially valuable when cartilage grafting is required to rebuild normal anatomic substructure and preserve proper function. The most common tissue importation flaps used in dermatologic surgery include the paramedian forehead flap, the nasolabial interpolation flap, the retroauricular flap, and the turnover nasolabial or Spear's flap.

Paramedian forehead flap

The paramedian forehead flap, an axial flap based on the supratrochlear artery, is the most useful flap for reconstruction of subtotal and total nasal defects. The excellent vascular supply supports both the flap as well as any cartilage grafts that are used to rebuild the cartilage framework of the nose. The paramedian forehead flap also provides the best color and texture match of any of the tissue importation flaps used to reconstruct large defects of the nose and far exceeds the cosmetic results of a skin graft (Fig. 147.26).

An important concept in flap design includes the enlargement of the nasal defect to encompass the entire cosmetic unit when possible. This makes the junction of the flap and the remaining nasal skin less

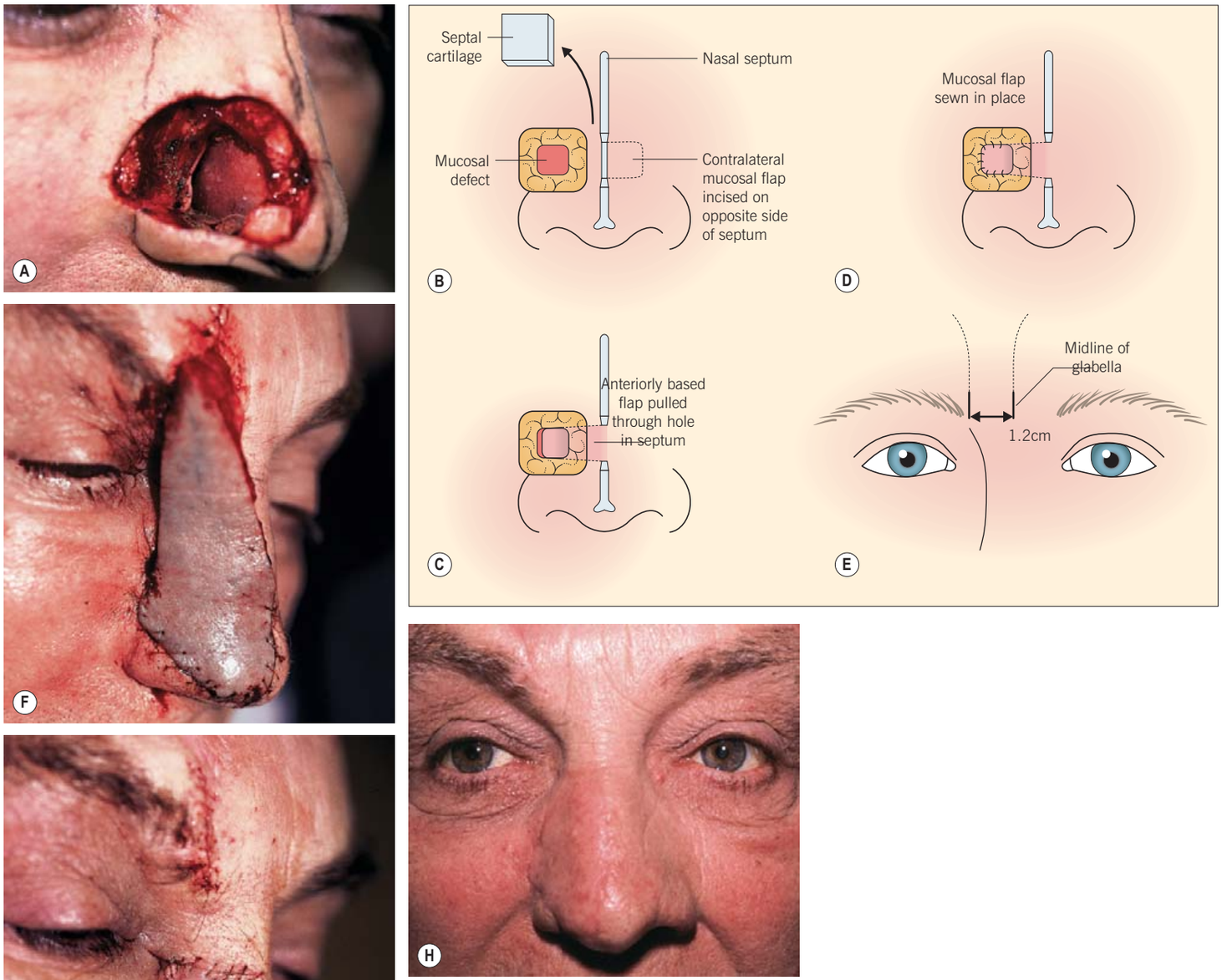


Fig. 147.26 Paramedian forehead flap. A Large full-thickness defect of the right half of the distal nose. **B** The mucosal defect is reconstructed with a contralateral septal mucosal pull-through flap. A U-shaped incision is made in the contralateral septal mucosa, based anteriorly and correctly sized to cover the defect. In addition, a 15 mm^2 cartilage graft is harvested from the nasal septum and used to reconstitute the structural integrity of the nasal sidewall. (Note that the remainder of the nasal sidewall cosmetic subunit and the right nasal tip subunit will be excised prior to reconstruction with the forehead flap.) **C** The mucosal flap is delivered through the septal defect into the right nasal vestibule. **D** The mucosal flap is sutured into place. **E** The design of the pedicle uses the midline of the glabella as the medial incision point; the lateral incision is made 1.2 cm lateral to the midline. Using a template, the forehead flap is then incised and raised on this 1.2 cm-wide pedicle. **F** Immediately postoperatively. **G** Immediately after takedown of flap 3 weeks later. **H** Early cosmetic results with no revision 2 months postoperatively.

conspicuous and is more likely to result in an excellent cosmetic outcome. If necessary, proper mucosal lining is ensured by using a nasal mucosal flap or split-thickness skin graft. If cartilage support is required, conchal or nasal septal cartilage is used to rebuild the normal subcutaneous cartilage framework. Next, a foil template of the defect is constructed and then transferred to the forehead. Using a length of 4-inch × 4-inch gauze to simulate the length of the pedicle, the surgeon ensures that the flap is long enough to be inset without tension on the tip. The base of the pedicle, fed by the supratrochlear artery, can be located with the use of a Doppler device, but this artery is consistently located 10 mm lateral to the midline of the glabella. When planning the forehead flap, keep in mind that the base of the flap must be thin enough to allow adequate twisting of the base in order to reach the defect. However, too small a pedicle base may risk vascular compromise that would result in disastrous consequences. We find a pedicle width between 8 and 15 mm to be adequate for both flap mobility and vascular supply.

Flap procurement is begun by incising the distal flap (on the upper forehead) in the subcutaneous plane and, as work progresses proximally (toward the inferior forehead), dissecting to a gradually deeper plane. The distal one-third of the flap should be dissected in the superficial subcutaneous plane, the middle one-third in the deep subcutaneous plane, and the proximal one-third (just above the brow) in the sub-muscular plane. The surgeon must carefully dissect the remaining pedicle above the periosteum, being sure to not sever the supraorbital artery as it exits the supraorbital foramen. Bilaterally,

the forehead is undermined in a subgaleal plane and then closed in a layered fashion. The widest part of the forehead defect may not close, but heals well by secondary intention. Finally, the distal end of the flap is thinned to match the thickness of the remaining nasal skin before it is inset.

The second stage of the forehead flap is performed 3 weeks later. The pedicle is severed near the brow and the edges of both the brow and the pedicle stump are freshened so that an upside-down V is formed by both the pedicle stump and the brow defect. The stump is then trimmed of all fat and inset in a layered fashion, being sure to reposition the medial brow to match the contralateral side. After carefully trimming and thinning of the proximal edge of the remaining flap, it is inset into the remaining nasal defect.

Nasolabial interpolation flap

The nasolabial (melolabial) interpolation flap, a random pattern pedicle flap, has traditionally been utilized primarily for defects of the nasal ala. This flap is especially useful for large defects and complex defects involving the alar rim. In certain circumstances, the nasolabial interpolation flap may be utilized for the repair of nasal tip defects when the latter are moderate in size and a paramedian forehead flap is less optimal.

When utilizing the nasolabial interpolation flap for the repair of alar defects, we recommend excising the remainder of the cosmetic unit of the ala in order to ensure a better aesthetic and functional result (Fig. 147.27). After providing any necessary cartilage support, a foil template is made of the contralateral ala and then it is turned over and placed on the ipsilateral nasolabial skin. A length of 4-inch × 4-inch gauze can be utilized to ensure proper flap length prior to outlining the flap on the cheek skin. The flap on the cheek is incised and dissected to a well-vascularized pedicle deep in the subcutis. The cheek and the defect are widely undermined in the superficial subcutaneous plane; the flap is then turned on its pedicle, trimmed, and sutured into place in a layered fashion. The donor defect is closed up to the base of the pedicle.

Three weeks later, the patient returns for separation of the pedicle. The surgeon amputates, trims and sutures the flap and the cheek in a layered fashion to ensure recreation of the normal complex anatomic features of this aesthetically important area. We find that fusiform excision of the pedicle stump provides for the most aesthetically pleasing repair of the cheek donor site.

Retroauricular flap

The two-staged retroauricular flap is useful for large defects of the helical rim that involve loss of cartilaginous support (Fig. 147.28). The retroauricular flap is a random pattern flap without a single vascular pedicle. Nonetheless, because of the rich blood supply of the scalp skin, this is one of the most well-vascularized random pattern tissue importation flaps.

After providing cartilage support (if needed), a foil template of the defect is fashioned and then placed on the skin of the postauricular scalp. The necessary size of the flap is marked and then the flap is incised from the retroauricular sulcus back to the hairline. The flap is dissected in a subcutaneous plane and the tip judiciously thinned to match the thickness of the skin at the defect. The flap is sutured into place in a layered fashion, being sure to minimize tension as the flap curls around the anterior helical rim. We find the use of bolster sutures to be very helpful in recreating the curve of the antihelix. Three weeks later, the pedicle is severed near the scalp and the posterior aspect of the flap is sutured into place. The donor site can either be closed with a skin graft or left to heal by second intention.

Spear's flap

The reverse nasolabial (melolabial) pedicle flap, described by Spear, is useful for reconstruction of full-thickness defects of the ala that involve the attachment point of the lateral ala to the cheek (Fig. 147.29).

The design of the Spear's flap is planned in a manner similar to that of the single-staged nasolabial interpolation flap, with the use of a foil template made from the contralateral ala. This template is placed upside down on the skin of the cheek lateral to the nasolabial fold and the flap is incised to a point just lateral to the edge of the defect. The flap is then dissected to a well-vascularized pedicle deep in the subcutis adjacent to the defect. Next, the flap is twisted on its pedicle and the edge of the mucosal defect adjacent to the nasal tip is sutured to the under-turned skin of the medial edge of the flap; we use a 5–0 chromic gut suture for this portion of the flap. The lateral portion of the under-turned flap is then sutured to the lateral mucosal defect. By folding the flap on itself, the alar rim and the surface of the ala are recreated, and the tip of the flap is carefully trimmed to match the contralateral ala. The surface of the flap is closed in a layered fashion. As with the other nasolabial flaps, the donor site is closed after widely undermining the

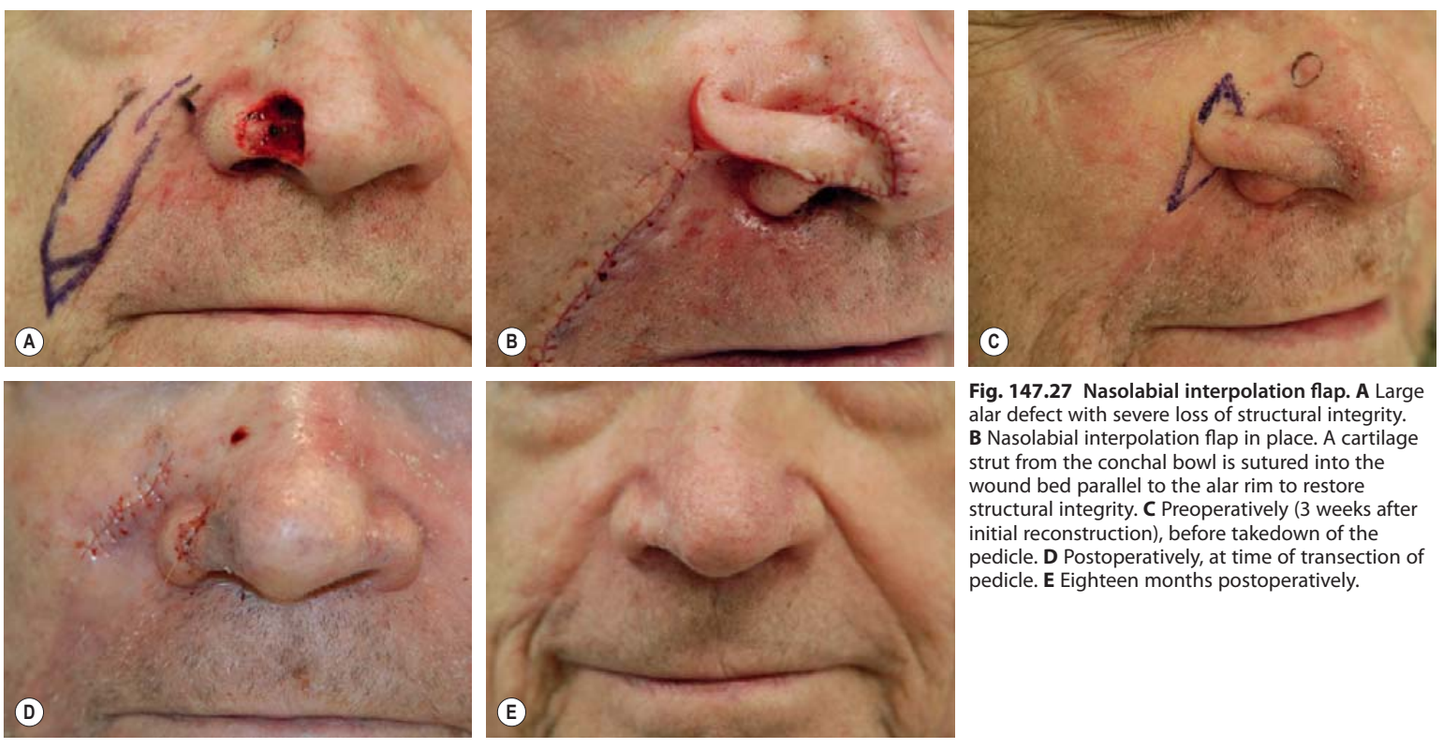


Fig. 147.27 Nasolabial interpolation flap. A Large alar defect with severe loss of structural integrity. **B** Nasolabial interpolation flap in place. A cartilage strut from the conchal bowl is sutured into the wound bed parallel to the alar rim to restore structural integrity. **C** Preoperatively (3 weeks after initial reconstruction), before takedown of the pedicle. **D** Postoperatively, at time of transection of pedicle. **E** Eighteen months postoperatively.

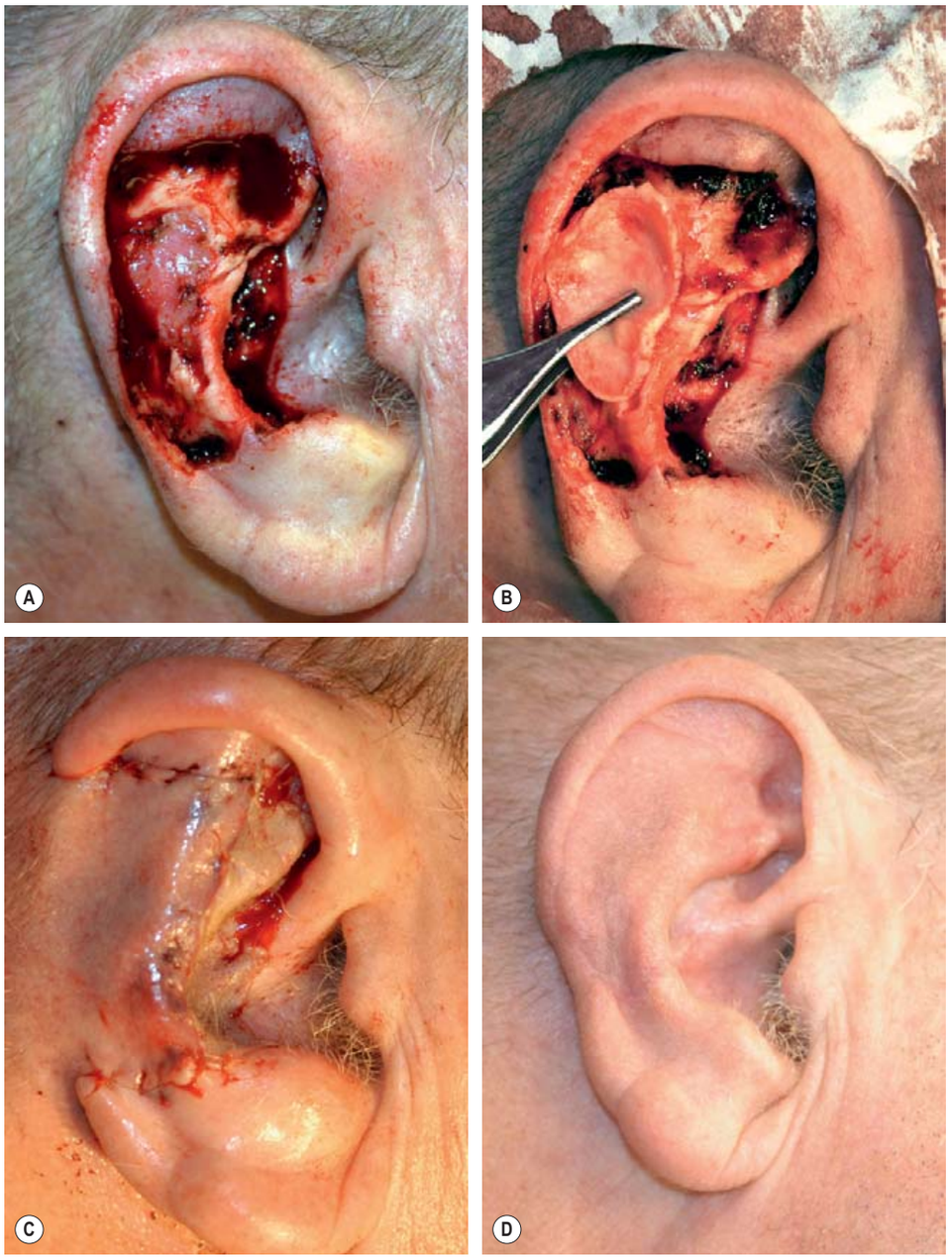


Fig. 147.28 Retroauricular flap. A Large defect of the anterior ear including substantial loss of cartilage of the mid antihelix and helical rim. **B** A cartilage graft harvested from the contralateral conchal bowl is used to restore structural integrity of the infrastructure of the auricle. **C** Closure of the retroauricular flap with resurfacing of the helix and antihelix. A split-thickness skin graft is used to resurface the crus of the antihelix and a portion of the conchal bowl. The pedicle from the retroauricular skin will be divided at 3 weeks. **D** Reconstructive results at 4 months.

skin of the cheek. Occasionally, a standing cone is created superolaterally to the new ala and it needs to be excised and sutured to complete the repair. Usually, a second stage to reposition the new, lateral aspect of the ala is necessary by folding the flap on itself. Typically, the newly formed ala is positioned too far laterally and is shifted up to 1 cm medially to correspond with the position of the contralateral ala.

Combination Flaps

Not all defects can be conveniently closed with a single flap. There are times when a combination of closure techniques is employed, either because the defect is too large or because the defect involves more than one cosmetic subunit. These types of wounds are better closed using a combination of flaps or flaps plus grafts. Combination closures for very large defects are usually employed when a flap is able to close a significant portion, but not all, of the defect. In that situation, a full-thickness graft may be used to supplement a flap and complete the coverage of a defect (Fig. 147.30). Grafts can be harvested from any of the common donor sites, depending on ideal tissue match and the adequacy of donor skin. When reconstructing a wound after Mohs surgery (i.e. a high degree of certainty of cancer-free margins exists), tissue adjacent to the wound can be safely used as "Burow's grafts". The Burow's triangle(s) of a flap can be defatted and trimmed to fit the remaining defect rather than being discarded.

Sometimes, flap and graft combinations are used to reconstruct defects that involve more than one cosmetic subunit. In such a wound, a flap is used to reconstruct one cosmetic subunit while a full-thickness skin graft is used to reconstruct the other, maintaining the "separateness" of each cosmetic subunit. The principle of maintaining the boundaries between cosmetic subunits is very useful in achieving a much less noticeable cosmetic result. If flaps or grafts are applied across the cosmetic subunits, the aesthetic disruption that occurs becomes more visible.

There are also defects that involve multiple cosmetic subunits that are best repaired individually with different flaps (Fig. 147.31). The same principle applies in that maintaining the integrity of individual cosmetic subunits is an important consideration in achieving a more natural and less noticeable result. These types of closures require crea-

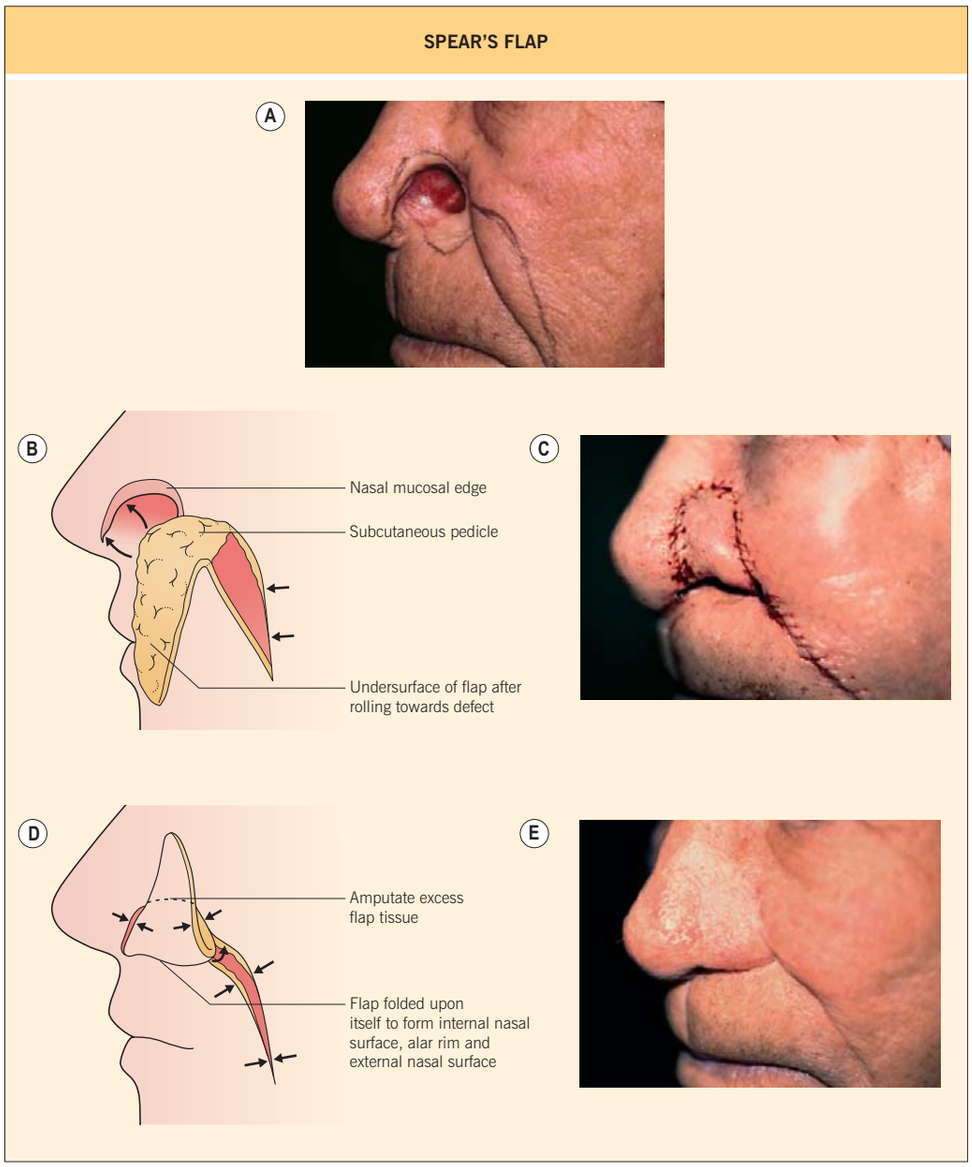


Fig. 147.29 Spear's flap. A Nasal defect involving the entire nasal ala and a portion of the nasal sidewall with the plans marked for a nasolabial transposition flap with a twist as described by Spear. **B** Corresponding schematic. **C** Flap in place having been twisted on a subcutaneous pedicle sutured into the mucosal side of the defect and folded upon itself followed by suturing of the cutaneous side of the defect. **D** Corresponding schematic demonstrating placement of the flap and amputation of the distal portion. **E** Early results after second revision.

tivity and sometimes ingenious methods in order to accomplish complete closure.

Table 147.4 summarizes the flaps discussed above and lists the areas of the face where the specific flaps are most useful for providing excellent functional and aesthetic results.

POSTOPERATIVE CARE

Postoperative care after flap surgery varies from practice to practice. Some surgeons have the patient change the bandage once or several times a day, cleansing the wound at each bandage change. Others apply a bandage for a day or two and leave the sutured wounds open to air thereafter. Still others apply a single bandage at the time of the surgery and leave it undisturbed for up to a week. Regardless of how the postoperative care is accomplished, there are common goals to achieve during the postoperative period.

One of these common goals is to prevent postoperative bleeding. The first 48 hours is the time period during which bleeding from the wounds and the formation of hematomas most commonly occur. Efforts to reduce these complications include meticulous intraoperative hemostasis and the application of pressure to the wounds. Pressure can be applied by using taping techniques, pressure wraps or specialized pressure garments. Normally, pressure becomes less important after 24 to 48 hours. In the patient at higher risk for bleeding, it may be necessary to maintain pressure for a more prolonged period of time. In some patients with a very high risk of postoperative bleeding, it may be helpful to use a tie-over bolster dressing directly over the wound to ensure constant firm pressure throughout the postoperative period.

Another common goal in the postoperative care of flaps is to reduce the risk of infection. All forms of infection can complicate the postoperative course and affect the cosmetic and functional results. Prevention of postoperative infections is covered elsewhere (Ch. 151). However, good surgical technique and observance of sterile technique during reconstruction is paramount. One novel approach, particularly well suited for cutaneous reconstructions, is the direct infiltration of the unclosed wound preoperatively with local anesthesia containing antibiotics. The benefit of intralesional nafcillin and clindamycin has been studied and this procedure is used routinely in some practices prior to reconstruction.

An additional important goal in the postoperative care of flap reconstructions is protection of the flap tissue from all environmental insults, including contamination, physical injury, temperature extremes, excessive movement and stretching of the sutured skin during the early postoperative period, and UV radiation. This is best accomplished by occlusive bandaging techniques and thorough education of the patient.

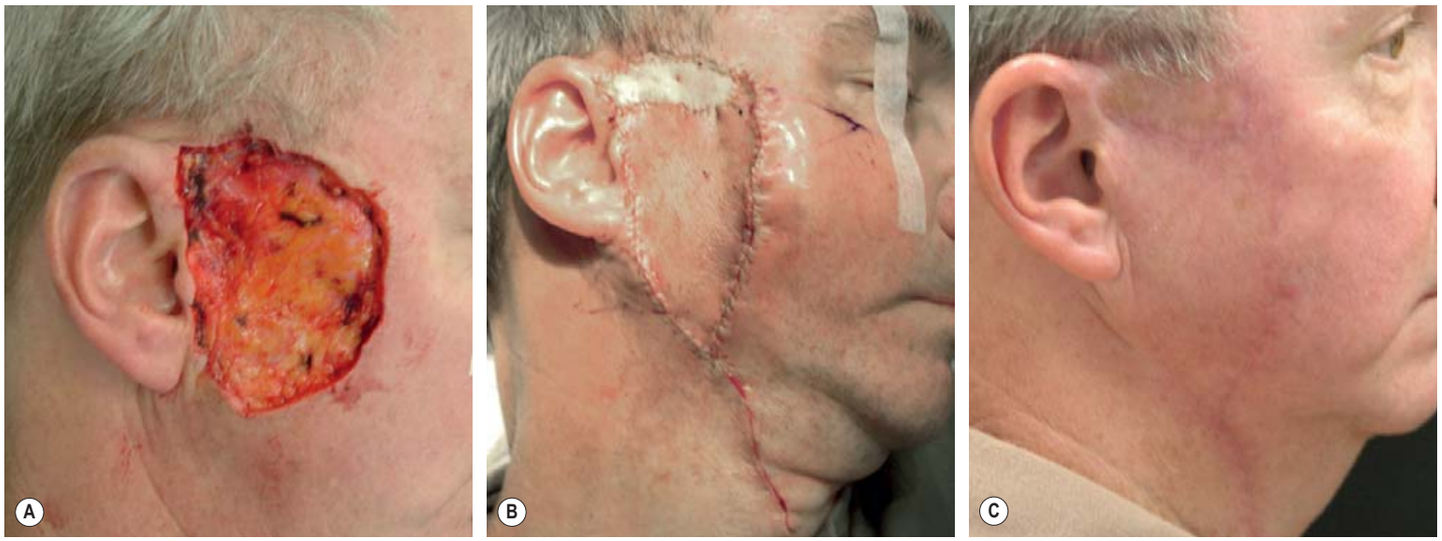


Fig. 147.30 Combination flap and graft. A Large defect of the preauricular cheek. **B** Partial closure of the lower 75% of the defect with an island pedicle flap. The remaining defect is closed with a full-thickness skin graft derived from an extension of the wound inferior to the donor site of the flap on the anterior neck. **C** Reconstructive results 3 months postoperatively.

Fig. 147.31 Combination flap closure of multiple cosmetic subunits. A Deep defect involving the upper cutaneous lip and the lateral ala, including the alar rim. **B** Combination of an island pedicle flap to reconstruct the cutaneous lip plus a nasolabial interpolation flap to reconstruct the lateral alar rim. **C** Division and debulking of the interpolation flap pedicle at 2.5 months with contouring of the ala and the alar crease. **D** Immediately postoperative. **E** Six months postoperatively.

Presented here are the details of postoperative flap care as routinely implemented in one surgical practice. After the completion of the flap reconstruction, a light bandage is applied over a very thin coat of antibiotic ointment which is placed directly over the incision lines. The light bandage consists of non-stick gauze that is affixed with hypoallergenic paper tape. The tape completely covers the non-stick gauze, resulting in complete occlusion of the sutured skin. A "bulky" secondary bandage is then applied on top of this thin primary bandage. The bulky bandage consists of rolled or fluffed absorbent gauze, which is affixed again with paper tape, using a technique of taping which applies downward pressure to the bulky gauze. This is accomplished by the placement of one end of the tape on the skin of one side of the wound and stretching it over the top of the bulky gauze and then attaching the other end to the opposite side of the flap under tension. This is repeated numerous times with thin, 1-cm-wide strips of tape until the bulky gauze is entirely covered and firmly affixed by the tape. The patient is instructed not to allow the bandage to become wet for 1 week. He or she is instructed to remove the bulky secondary bandage 24 to 48 hours

COMMON LOCATIONS FOR FLAP TYPES
BUROW'S TRIANGLE DISPLACEMENT FLAPS
Burow's flap (single tangent advancement flap) and bilateral single tangent advancement flap (A-to-T flap)
– Distal, lateral nasal sidewall – Upper lateral lip – Infranasal upper lip – Eyebrow and suprabrow forehead – Mid helix
Unilateral or bilateral double tangent advancement flap (U- or H-flap)
– Forehead – Helix – Large defect of upper lip
Rotation flap(s)
– Upper cheek – Medial chin – Nasal dorsum (Rigor flap) – Lower eyelid
DEFECT RECONFIGURATION FLAPS
Island pedicle flap
– Upper lateral and mid upper cutaneous lip – Mucosal lip – Lateral chin and lower lip – Distal nasal sidewall – Preauricular cheek – Eyebrow
TISSUE REORIENTATION FLAPS
Rhombic transposition flap
– Nasal sidewall – Temples and lateral forehead – Lateral canthus and lateral lower lid – Lateral chin and lower lip – Superior and anterior helix
Bilobed transposition flap
– Nasal tip and supratip – Lower lateral lip
Nasolabial transposition flap
– Alar defects, especially those involving the lateral portion of the ala – Lateral alar crease and distal nasal sidewall
TISSUE IMPORTATION FLAPS
Paramedian forehead flap
– Large nasal defects – Moderate-size nasal tip defect – Nasal defects with loss of cartilage and/or nasal lining – Large medial canthus defects
Nasolabial (melolabial) interpolation flap
– Nasal ala and alar rim – Nasal tip – Mid upper lip
Melolabial flap with a twist (Spear's flap)
– Full-thickness alar defects involving the junction of the lateral ala and the cheek/upper lip
Retroauricular flap
– Large defects of the anterior ear or helix – Full-thickness defects requiring cartilage graft reconstruction

Table 147.4 Common locations for flap types.

after the surgery, leaving the thin, primary bandage in place. This bandage is left undisturbed and kept dry for the remainder of the week.

The patient returns to the office after 1 week for bandage removal, suture removal and evaluation of the wound. Any evidence of hematoma, infection or other complication is addressed at that time. The skin is cleansed and another thin bandage with topical antibiotic ointment, non-stick gauze and hypoallergenic paper tape is applied for one more week. The patient is instructed again to keep this bandage dry and to remove it in 1 week (i.e. 2 weeks after the surgery). The patient is encouraged to contact the physician in the postoperative period if there are any problems and to return in 3 months for a final evaluation of the wound healing process. Minor revisions may be made at that time to optimize the aesthetic and functional results.

COMPLICATIONS

In the immediate postoperative period, the potentially serious sequelae are primarily postoperative bleeding and infection. Both adverse events are rare if meticulous surgical technique is used. Nonetheless, failure to recognize either complication and intervene appropriately can lead to disastrous postoperative results. Postoperative bleeding that results in a hematoma requires immediate attention. The most effective intervention is an immediate return to the operating suite to remove the sutures, evacuate the hematoma, locate and ligate the bleeding vessel, and re-suture the wound. Failure to do so likely risks flap necrosis. If a postoperative infection is present, immediate oral antibiotics and drainage of any trapped purulent material are required.

In the mid-postoperative period, the most common complication requiring intervention is the development of a hypertrophic scar or trapdoor deformity. This usually becomes evident about 4 to 8 weeks after surgery and occasionally develops despite wide undermining, appropriate flap thinning, and meticulous suturing technique at the time of surgery. Often, the patient is advised to aggressively massage the site many times per day. Massage and tincture of time often promote adequate remodeling of the healing wound. Occasionally, active intervention is necessary. We use a varying concentration of intralesional triamcinolone acetonide injections (5–40 mg/ml), depending upon the location and thickness of the flap.

Late postoperative complications include persistent pincushioning, surface irregularities, blunting or ablation of the junction between cosmetic units, and surface telangiectasias. Persistent pincushioning and minor surface irregularities can be addressed as early as 6 to 12 weeks postoperatively with the use of a scalpel to plane the surface and dermabrasion or dermasanding to blend the planed surface. In order to redefine the junction between cosmetic units that may have been ablated by the placement of a flap (e.g. the alar crease in a nasolabial transposition flap), incising the area, thinning the subcutis and re-suturing the skin edges to recreate the natural fold is usually all that is required. Laser ablation of telangiectasias that not infrequently develop around the incision lines of large nasal flaps can be done at any time. We find that these tend to develop gradually over time and that ablation may need to be repeated at future visits.

Sometimes, regardless of proper patient selection, flap planning and suturing technique, some amount of postoperative refinements may be necessary. These may vary from simple procedures to correct surface irregularities to more complicated interventions requiring further scalpel surgery. The key to a successful outcome from a postoperative intervention is recognizing the circumstances where an intervention would be helpful and then choosing the appropriate intervention. Understanding the normal sequence of healing after a surgical procedure helps the surgeon to decide when and by what means to intervene in this process.

FURTHER READING

Borges AF. The rhombic flap. Plast Reconst Surg. 1981;67:458–66.

Boyer JD, Zitelli JA, Brodland DG. Undermining in cutaneous surgery. Dermatol Surg. 2001;27:65–8.

Brodland DG. Fundamentals of flap and graft wound closure in cutaneous surgery. Cutis. 1994;53:192–200.

Brodland DG. Advancement flaps. In: Roenigk RK, Roenigk HH Jr (eds). Dermatologic Surgery: Principles and Practice, 2nd edn. New York: Marcel Dekker, 1996.

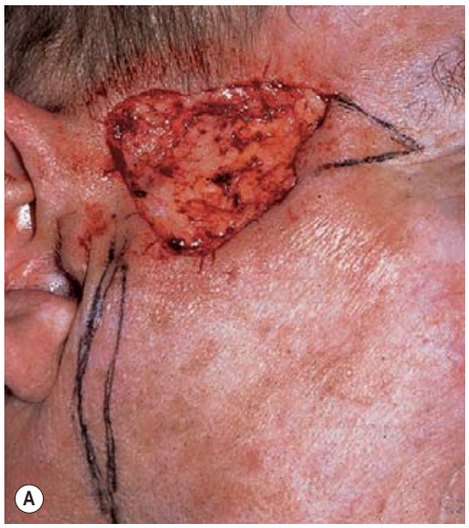
Brodland DG. Complex cutaneous closures. In: Ratz JL (ed.). Textbook of Dermatologic Surgery. Philadelphia: Lippincott-Raven, 1998.

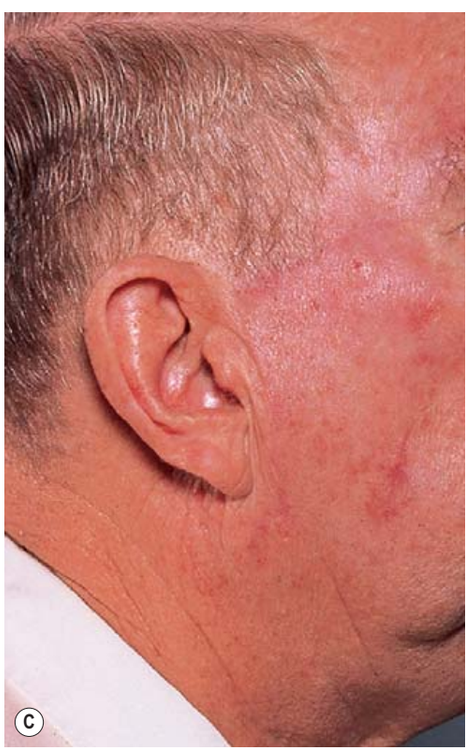
Brodland DG. Paramedian forehead flap reconstruction for nasal defects. Dermatol Surg. 2005;31:1046–52.

Brodland DG. Auricular reconstruction. Dermatol Clin. 2005;23:23–41.

Burget GC, Menick FJ. Aesthetic Reconstruction of the Nose. St. Louis: CV Mosby, 1994.

Dzubow LM. Subcutaneous island pedicle flaps. J Dermatol Surg Oncol. 1986;12:591–6.
Dzubow LM. Flap dynamics. J Dermatol Surg Oncol. 1991;17:116–30.
Fazio MJ, Zitelli JA. Principles of reconstruction following excision of nonmelanoma skin cancer. Clin Dermatol. 1995;13:601–16.
Futoryan T, Grande D. Postoperative wound infection rates in dermatologic surgery. Dermatol Surg. 1995;21:509–14.
Goldman GD. Rotation flaps. Dermatol Surg. 2005;31:1006–13.
Griego RD, Zitelli JA. Intra-incisional prophylactic antibiotics for dermatologic surgery. Arch Dermatol. 1998;134:688–92.
Pharis DB, Papadapoulos DJ. Superiorly based nasolabial interpolation flap for repair of nasal tip defects. Dermatol Surg. 2000;26:19–24.
Spear SL, Kroll SS, Romm S. A new twist to the nasolabial flap for reconstruction of lateral alar defects. Plast Reconstr Surg. 1987;79:915–20.
Zitelli JA. Tips for wound closure: pearls for minimizing dog-ears and applications of periosteal sutures. Dermatol Clin. 1989;7:123–28.
Zitelli JA. The bilobed flap for nasal reconstruction. Arch Dermatol. 1989;125:957–59.
Zitelli JA. The nasolabial flap as a single-staged procedure. Arch Dermatol. 1990;126:1445–8.
Zitelli JA. Tips for a better ellipse. J Am Acad Dermatol. 1990;22:101–3.
Zitelli JA, Brodland DG. A regional approach to reconstruction of the upper lip. J Dermatol Surg Oncol. 1991;17:143–8.
Zitelli JA, Fazio MJ. Reconstruction of the nose with local flaps. J Dermatol Surg Oncol. 1991;17:184–9.
Zitelli JA, Moy RL. Buried vertical mattress suture. J Dermatol Surg Oncol. 1989;15:17–9.





Single tangent advancement flap. **A** Large defect situated between the ear and the eye. **B** A single tangent advancement flap (Burow's flap) reconstructs the defect by displacing a Burow's triangle inferiorly to just below the earlobe. **C** One month after reconstruction.

Island pedicle flap. Reconstruction of a nasal defect **(A)** with an island pedicle flap whose pedicle is derived deep to the island along the alar crease **(B)**. Island pedicle flap. **C** Cosmetic result at one year.

Grafts 148

Désirée Ratner

Chapter Contents

Wound healing considerations 2421
Full-thickness skin grafts 2422
Split-thickness skin grafts 2427
Composite grafts 2429
Free cartilage grafts 2431

Key features

- Free skin grafts are pieces of skin that have been severed from their local blood supply and transferred to another location
- Grafts for soft tissue reconstruction can be divided into four types: full-thickness skin grafts, split-thickness skin grafts, composite grafts, and free cartilage grafts
- In dermatologic surgery, grafts are most commonly used to repair defects created after removal of skin cancers; grafts also provide coverage and more rapid healing of leg ulcers
- The clinical situation determines the type of graft to be placed
- A working knowledge of the indications, techniques, donor site considerations, postoperative care, and postoperative complications of all types of skin grafting is essential for optimal soft tissue reconstruction

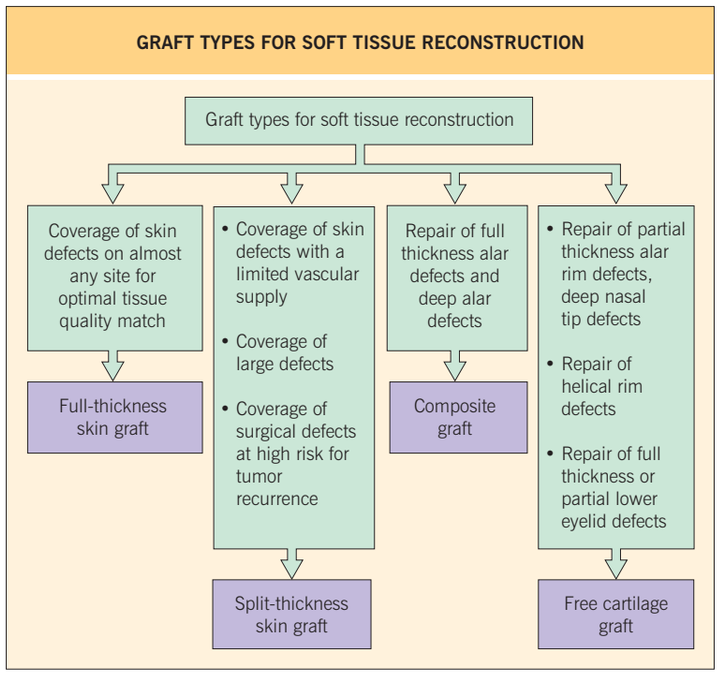


Fig. 148.1 Graft types for soft tissue reconstruction.

INTRODUCTION AND BACKGROUND

Skin grafting procedures originated approximately 2500 to 3000 years ago, when surgeons of the Hindu Tilemaker caste replaced noses amputated as punishment for theft and adultery with skin grafts harvested from the gluteal region[1]. It was not until the nineteenth century, however, that skin grafting was reintroduced. In 1869, Reverdin's account of pinch grafting for leg ulcers was published; in subsequent decades, Ollier and Thiersch's accounts of thin split-thickness skin grafting, and Wolfe and Krause's accounts of full-thickness skin grafting, appeared in the literature. While these and other nineteenth-century surgeons used skin grafts to address only the most difficult problems of surgical management, skin grafting has since evolved into a reconstructive option that is routinely, and sometimes preferentially, used for the surgical repair of skin defects.

Free skin grafts are pieces of skin that have been severed from their blood supply and transferred to another location. They can be divided into four types: full-thickness skin grafts (FTSGs), split-thickness skin grafts (STSGs), composite grafts, and free cartilage grafts (Fig. 148.1; Tables 148.1 & 148.2)[2,3]. FTSGs are composed of the entire epidermis and the full thickness of dermis, including adnexal structures such as hair follicles and sweat glands. STSGs are composed of the full thickness of the epidermis and partial thickness of dermis. These can be subdivided into thin, medium and thick grafts, depending on the amount of dermis included in the graft. Composite grafts are composed of at least two different tissue types, usually skin and cartilage. Free cartilage grafts consist of cartilage with its overlying perichondrium.

WOUND HEALING CONSIDERATIONS

Wound healing after skin grafting proceeds through a unique series of events[2,4]. The first 24-hour period following graft placement is termed the stage of plasmatic imbibition, during which fibrin glue attaches the graft to its recipient bed, allowing it to take up the underlying wound exudate and to become edematous, gaining up to 40% in weight. The graft thereby remains hydrated and obtains a supply of nutrients, which maintains graft vessel patency until revascularization begins. The fibrin beneath the graft is subsequently replaced by granulation tissue, which attaches the graft permanently to its bed.

With proper apposition of the graft to its bed, revascularization may proceed. Anastomoses begin to form within 48–72 hours of grafting, between the recipient bed and pre-existing vessels in the dermis of the graft, a process known as inosculation. Vascular proliferation occurs next, with sprouting and budding of vessels in the graft and its bed. Even relatively avascular tissue may be grafted, as long as the avascular area is small and surrounded by a rich vascular supply. Through a process known as the bridging phenomenon, vascular connections arising from the recipient bed allow blood flow to occur through pre-existing graft vasculature, so that nutrients reach the part of the graft overlying the avascular area. Full circulation is restored to the graft within 4–7 days.

Restoration of the lymphatic circulation parallels restoration of the blood supply over the first week. Epidermal proliferation occurs between the 4th and 8th day post-transplant and persists for several weeks. Degeneration of sebaceous and eccrine glands may occur initially, but subsequent glandular regeneration may allow partial function to be maintained. Graft reinnervation and return of sensory nerve function may begin as early as 2–4 weeks after grafting, although patients do not usually regain full sensation for many months.

COMPARISON OF GRAFT TYPES USED IN SOFT TISSUE RECONSTRUCTION								
Graft type	**Tissue match**	**Nutritional requirements**	**Requirement for recipient bed vascularity**	**Infection risk**	**Graft contraction risk**	**Durability**	**Sensation**	**Adnexal functions**
FTSG	Good to excellent	High	High	Low	Low	Good to excellent	Good	Excellent
STSG	Poor to fair	Low	Low	Low	High	Fair to good	Fair	Poor
Composite	Good	High	Very high	Moderate	Low	Fair	Fair	Good
Free cartilage	NA	Moderate	High	Moderate	Migration or deformation possible, with subsequent resorption	Good	NA	NA

Table 148.1 Comparison of graft types used in soft tissue reconstruction. FTSG, full-thickness skin graft; STSG, split-thickness skin graft.

INDICATIONS, CONTRAINDICATIONS, ADVANTAGES AND DISADVANTAGES OF GRAFT TYPES USED IN SOFT TISSUE RECONSTRUCTION				
Graft type	**Indications**	**Contraindications**	**Advantages**	**Disadvantages**
Full-thickness skin graft (FTSG)	Coverage of skin defects, usually located on the face or scalp, requiring an optimal tissue quality match	Avascular graft bed	Excellent color and texture match Minimal graft contraction	Time consuming Donor site requires closure Requires meticulous technique
Split-thickness skin graft	Coverage of large defects, defects with a limited vascular supply, or at sites at high risk for tumor recurrence	Defects near free margins Facial defects in cosmetically sensitive areas	Increased chance of survival Ease of application Ability to cover large defects Able to act as a "window" to detect recurrence of high-risk tumors	Suboptimal cosmetic appearance Decreased durability Presence of granulating donor site wound Greater graft contraction Special equipment required to harvest larger grafts
Perichondrial cutaneous graft	Repair of deep nasal tip and alar defects, especially those with exposed cartilage	Avascular graft bed	Thicker than FTSG Contract less than FTSG Increased chance of survival under conditions of vascular compromise (compared to FTSG)	
Composite	Repair of full-thickness alar defects or nasal tip defects (<2 cm in diameter) with cartilage loss	Defects >2 cm in diameter	Single-stage procedure May yield good functional and aesthetic results when used to repair appropriately sized defects	Greater risk of graft failure under conditions of vascular compromise Graft size limitations (<2 cm) Limited donor tissue available Donor site may require flap or complex closure Increased risk of infection and graft displacement
Free cartilage	Repair of defects of nasal ala, tip or sidewall, ear or eyelid requiring restoration of structural support or preservation of contour of free margins	None	Provide structural support for selected facial and ear defects	Donor site may be painful Increased risk of postoperative infection Increased risk of graft displacement

Table 148.2 Indications, contraindications, advantages and disadvantages of graft types used in soft tissue reconstruction.

If extension of the ischemic period occurs, decreased graft survival may result (Table 148.3). Hematoma or seroma formation, infection, or mechanical shear forces may disrupt the fragile vascular connections between the graft and its recipient bed. These complications tend to affect FTSGs (which have a greater volume to nourish and revitalize) more than STSGs.

Even after the ischemic period is past, other factors may combine to decrease the vascular supply nourishing the undersurface of the graft[2,3,5]. The most important of these factors is cigarette smoking[5], but diabetes mellitus, protein deprivation, and severe trace element or vitamin deficiencies may also increase the risk of graft failure. Certain systemic medications, such as corticosteroids, chemotherapeutic agents, other immunosuppressive drugs and anticoagulants, may interfere with wound healing as well.

Other causes of graft failure include: insufficient vascularity due to necrotic debris within the recipient bed, hematoma, seroma, an avascular wound bed, previous radiotherapy, infection, excessive graft tension, mechanical shearing forces, and improper postoperative care (see Table 148.3)[2,3]. The most common infectious agents associated with graft failure include coagulase-positive staphylococci, β-hemolytic streptococci and *Pseudomonas* spp. Pseudomonal infections are particularly common in auricular grafts. For all of these reasons, a thorough preoperative evaluation, meticulous intraoperative technique, and good postoperative care are essential to maximize graft survival.

FULL-THICKNESS SKIN GRAFTS

Indications/Contraindications

FTSGs are most commonly used to repair facial defects resulting from the removal of skin cancers. They may be used to repair defects at virtually any site, as long as the recipient bed has both a sufficiently rich vascular supply to promote capillary regrowth and fibroblasts to supply collagen for graft adherence. Small avascular areas may be grafted due to the bridging phenomenon. Larger areas of avascular tissue, including patches of exposed bone, cartilage, tendon or nerve

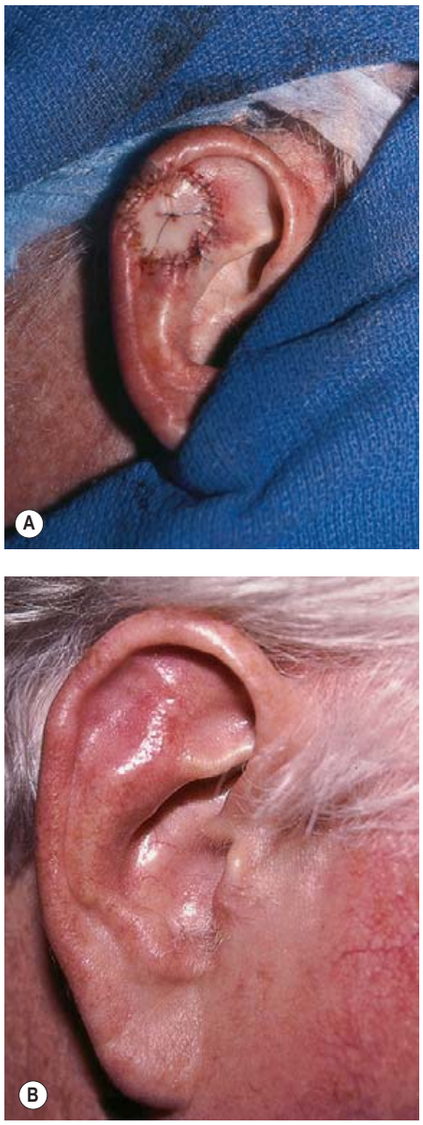


Fig. 148.2 Full-thickness skin graft. A Full-thickness skin graft taken from the preauricular region was used to repair this defect of the right upper anterior ear. **B** Eight-week postoperative result.

devoid of periosteum, perichondrium, peritenon or perineurium, respectively, are unable to support FTSGs. For this reason, FTSGs should not be placed over such avascular tissue.

Under the proper circumstances, FTSGs can provide excellent color, texture and thickness matches for facial defects because they include the full thickness of epidermis and dermis. Wound contraction is minimized since the full thickness of dermis is present, and dermal adnexal structures remain intact[6]. FTSGs may be especially useful for the cosmetically and functionally acceptable repair of defects of the nasal tip, dorsum, ala and lateral sidewall, as well as the lower eyelid and ear (Fig. 148.2)[7].

Preoperative History and Donor Site Considerations

A thorough preoperative evaluation that includes questions regarding bleeding tendencies, alcohol use, use of anticoagulant medications (including aspirin and nonsteroidal anti-inflammatory drugs) and a history of hypertension can help assess the risk of excessive bleeding and clot formation beneath the graft postoperatively[2,3]. Diabetes mellitus, nutritional deficiencies, cigarette smoking or the use of other nicotine-containing products may increase the risk of graft failure, and any history of these should be identified preoperatively.

Selection of a donor site for full-thickness skin grafting depends upon the color, texture, thickness, and sebaceous qualities of the skin surrounding the defect (Tables 148.4 & 148.5). Most FTSGs are taken from sun-exposed areas above the shoulders whose color, vascular pattern, texture, and distribution of adnexal structures best match the skin surrounding facial defects. The thinnest grafts are usually harvested from the upper eyelid or the postauricular sulcus. Medium-thickness grafts are often harvested from the preauricular and cervical regions, while thicker grafts may be taken from the supraclavicular or clavicular region, conchal bowl or nasolabial fold. Donor skin thickness, irrespective of site, will vary from one patient to another. It is

CAUSES OF GRAFT FAILURE	
Poor graft–bed contact	Hematoma Seroma Shearing forces due to excessive postoperative activity Shearing forces due to inadequate immobilization of graft
Poor recipient bed vascularity	Inadequate vascular bed (e.g. previous radiotherapy) Exposed cartilage, bone, tendon Nicotine-induced vasoconstriction
Infection	Coagulase-positive *Staphylococcus* spp. Beta-hemolytic *Streptococcus* spp. *Pseudomonas* spp.
Host factors	Diabetes mellitus Immunosuppression Poor general health Nutritional deficiencies Systemic conditions with vascular compromise
Technique	Rough handling of tissue Excessive devitalized tissue in recipient bed due to cautery Increased tension on graft due to inadequate size Inadequate hemostasis Inadequate trimming of adipose layer Placement of upside-down graft (more common with STSG) Inadequate anchoring (composite and free cartilage grafts)

Table 148.3 Causes of graft failure. STSG, split-thickness skin graft.

DONOR SITE CONSIDERATIONS FOR FULL-THICKNESS SKIN GRAFTS
• Pattern of sun exposure • Color • Vascular pattern • Texture • Sebaceous quality • Skin thickness • Skin consistency • Sufficient tissue available for harvesting • Ability to camouflage donor site scar

Table 148.4 Donor site considerations for full-thickness skin grafts.

SUMMARY OF POSSIBLE FULL-THICKNESS DONOR SITES FOR DEFECTS IN DIFFERENT LOCATIONS	
Defect sites	**Donor sites**
Nasal dorsum, sidewalls, tip	Preauricular region, supraclavicular region or lateral neck (if large)
Nasal tip, ala	Preauricular region, conchal bowl, nasolabial fold
Junction of nasal dorsum/tip	Burow's graft
Ear	Postauricular sulcus, preauricular
Lower eyelid/medial canthus	Upper eyelid, postauricular sulcus
Scalp	Supraclavicular region, lateral neck, inner upper arm
Forehead	Burow's graft, supraclavicular region, lateral neck, inner upper arm (if large)

Table 148.5 Summary of possible full-thickness donor sites for defects in different locations.

therefore important to examine all sites carefully to find the best possible tissue match. This approach will ensure optimal donor site selection for each individual patient and surgical defect.

A regional approach may at times be used to obtain the best possible match for a given defect. Grafts taken from redundant upper eyelid skin may be used to repair lower eyelid defects, providing a good color and texture match in addition to a well-camouflaged donor site scar. Grafts used for lower eyelid defects should be oversized by 100–200% to allow for contraction and to avoid ectropion. Due to its relatively large size and inconspicuous location, postauricular skin may also be useful as a donor site for eyelid and auricular defects. Because postauricular skin is relatively non-sun-exposed, grafts harvested from this region may not provide a good color or texture match for other facial defects.

Preauricular skin is more versatile and can be used to repair most nasal defects, since the thickness and degree of sun exposure of these areas tend to be comparable. Donor site scars in this region can be easily camouflaged, as in facelift surgery, to provide a cosmetically desirable result. Even bearded individuals have a 1–2 cm hairless zone in the preauricular region. Care must be taken not to harvest hair-bearing skin in grafts taken from this area. Accidentally including mature follicular units may produce undesirable hair growth within the graft. Hair-bearing skin from the temporoparietal region may be used to repair eyebrow defects, where survival of the follicular units after transplantation may help to produce a superior cosmetic result. Skin from the nasolabial fold or the conchal bowl can sometimes be used to graft small nasal tip defects[8]. At times, sufficient skin laxity may be present, particularly on the nose or forehead, to allow for partial defect closure by utilizing the adjacent Burow's triangle as a FTSG, providing an excellent tissue match[9–11].

For larger defects requiring FTSGs of sun-damaged skin, such as the forehead and scalp vertex, the supraclavicular region or lateral neck can be used as a donor site. Again, care must be taken not to harvest unwanted hair along with the graft. These donor sites are often more difficult to camouflage, and must be carefully placed, especially in areas that might not always be covered by clothing. Although the color and texture match may be suboptimal, areas below the neck with thin, redundant skin, such as the upper inner arms, forearms and inguinal area, can be used.

Description of Technique

Varying techniques for harvesting and placing FTSGs have been described[2,3,9–11]. To perform a FTSG, a template of the defect is first made, using any flexible material, such as gauze, Telfa™ or aluminum foil, which can be bent to conform to the defect. After marking the periphery of the recipient site with a marking pen, the template material is pressed against the defect, and the resulting outline of the inked margin serves as a guide to cut a perfect template (Fig. 148.3A,B). The template is applied to the donor site, and inking material applied around it (Fig. 148.3C). The graft should be 3–5% larger in size than the true template to allow for the natural contraction and shrinkage of the graft after it has been harvested. Often, just cutting around the outside of the inked margin accounts for this extra "safety" skin. For eyelid defects, grafts should be oversized significantly, to minimize the risk of ectropion. Marking the donor site prior to local anesthesia prevents incorrect sizing due to tissue stretch from lidocaine infiltration. It is important to note that a donor site ellipse with a 3:1 ratio may not always be required, allowing for smaller donor site defects[12].

After the donor site is marked, local anesthesia may be injected into the donor and recipient sites. Epinephrine (adrenaline) may be used without compromising graft survival. If waterproof ink is not available for template marking, the outline of the template may be scored on the donor site with a needle. The donor site and recipient beds are then scrubbed with an antibacterial preparation such as chlorhexidine, rinsed with saline, and draped with sterile towels.

The donor site is excised with a scalpel to the level of the subcutaneous fat. The graft is placed in a sterile bowl or Petri dish containing normal saline, where it may remain for up to 1–2 hours. Grafts may be utilized up to 24 hours after harvesting if refrigerated or kept on ice. Before suturing the graft into place, defatting should occur (Fig. 148.3D). This is an essential step, since direct contact between the graft and its bed allows for connections between existing vessels as well as new vessel growth and nutritional support from the base of the defect. Adipose tissue adherent to the graft is poorly vascularized and is therefore not a good medium for new vessel growth between the graft and its bed.

When defatting is performed, the graft is placed dermal-side-up on the fingers or in the palm. All fat is trimmed from the underside using sharp scissors. Fat is adequately removed when all of the yellow globular material is gone, leaving a white glistening dermal surface. If indicated, part of the dermis can also be trimmed to allow for differences in recipient site depth, although adnexal structures may be removed in the process, potentially altering the cosmetic result. The graft is then placed dermis-down in its bed, and rotated and trimmed if necessary, to achieve a perfect fit (see Fig. 148.3F). While one surgeon is trimming the graft, another may close the donor site, usually in a linear layered fashion with bilateral removal of standing cones (Fig. 148.3E). If the conchal bowl is the donor site, a 2 or 3 mm punch biopsy instrument may be used to remove full-thickness discs of cartilage from its central aspect, thereby facilitating second intention healing from the underlying dermis.

Contouring of donor skin in FTSGs may be challenging, particularly when repairing defects on the nasal tip, ala, lateral nasal sidewall, helical rim of the ear, and eyelid[13]. Graft contouring often requires multiple trial placements within the recipient bed, as well as multiple trimmings, to obtain an optimal result (Fig. 148.3F). Removal of cartilage not needed for structural support may increase the chance of graft survival, particularly for auricular defects, without compromising the aesthetic appearance of the repair[14,15].

Securing the Graft

Perimeter sutures, basting sutures, support dressings, or a combination of any or all of these can be used to anchor the FTSG. Depending upon the graft's size, four to eight interrupted 5-0 or 6-0 absorbable or non-absorbable sutures may be placed at opposite edges of the graft periphery (e.g. at 3, 6, 9 and 12 o'clock) to tack down its four quadrants. A simple running suture, such as 6-0 fast-absorbing chromic gut suture (Fig. 148.3G), may then be placed around the graft's perimeter. Great care is taken to achieve perfect epidermal wound approximation. The running suture is placed in almost epicuticular fashion, passing the needle first through the graft and then through the surrounding skin. Placing the suture slightly higher in the dermis on the graft side and slightly deeper in the dermis of the surrounding skin makes suture placement easier, prevents tenting of the graft edges, and maximizes graft–recipient bed contact.

The use of tissue adhesives in full-thickness skin grafting has been investigated. In an initial pilot study, it was found that using cyanoacrylate tissue adhesive to secure FTSGs to their recipient bed wound edges produced cosmetic results essentially identical to those achieved with suturing[16]. Because these adhesives set virtually instantaneously, the graft must be perfectly trimmed and aligned before adhesive application, since fine adjustments in positioning the edges of the graft are not easily made. Tissue adhesives may represent a useful time-saving alternative for securing the periphery of certain grafts, particularly those in relatively immobile areas such as the temple, forehead and distal nose.

Basting sutures, usually simple interrupted 6-0 fast-absorbing gut sutures, can occasionally be placed to secure the central portion of the graft. They can be useful in securing large grafts to provide extra support against movement, as well as grafts placed on a concave surface where tenting could possibly occur. All sutures should be snug, but not strangulating, so as to not compromise graft survival.

Immobilization of the graft over its bed can be maximized with pressure dressings. Classically, tie-over bolster dressings have been employed to immobilize grafts, using anchoring stents to ensure direct contact between the graft and its bed[2,3]. These stents may consist of various materials such as Xeroform™ gauze (bismuth tribromophenate-petrolatum-impregnated gauze, Kendall), cotton balls, foam rubber, sponges, plastic beads or disks. Although sutures or skin staples are usually employed to anchor the stent, adhesive wound closure tapes or Steri-Strips™ can also be applied to exert even pressure on the bolster[17]. Adherence of the dressing to the graft, which tends to pull the graft from its bed at the time of dressing removal, is minimized by first applying antibiotic ointment, a non-adherent contact dressing, or Xeroform™ gauze to the graft site. Pressure or tie-over dressings help to immobilize the newly placed graft during the critical period

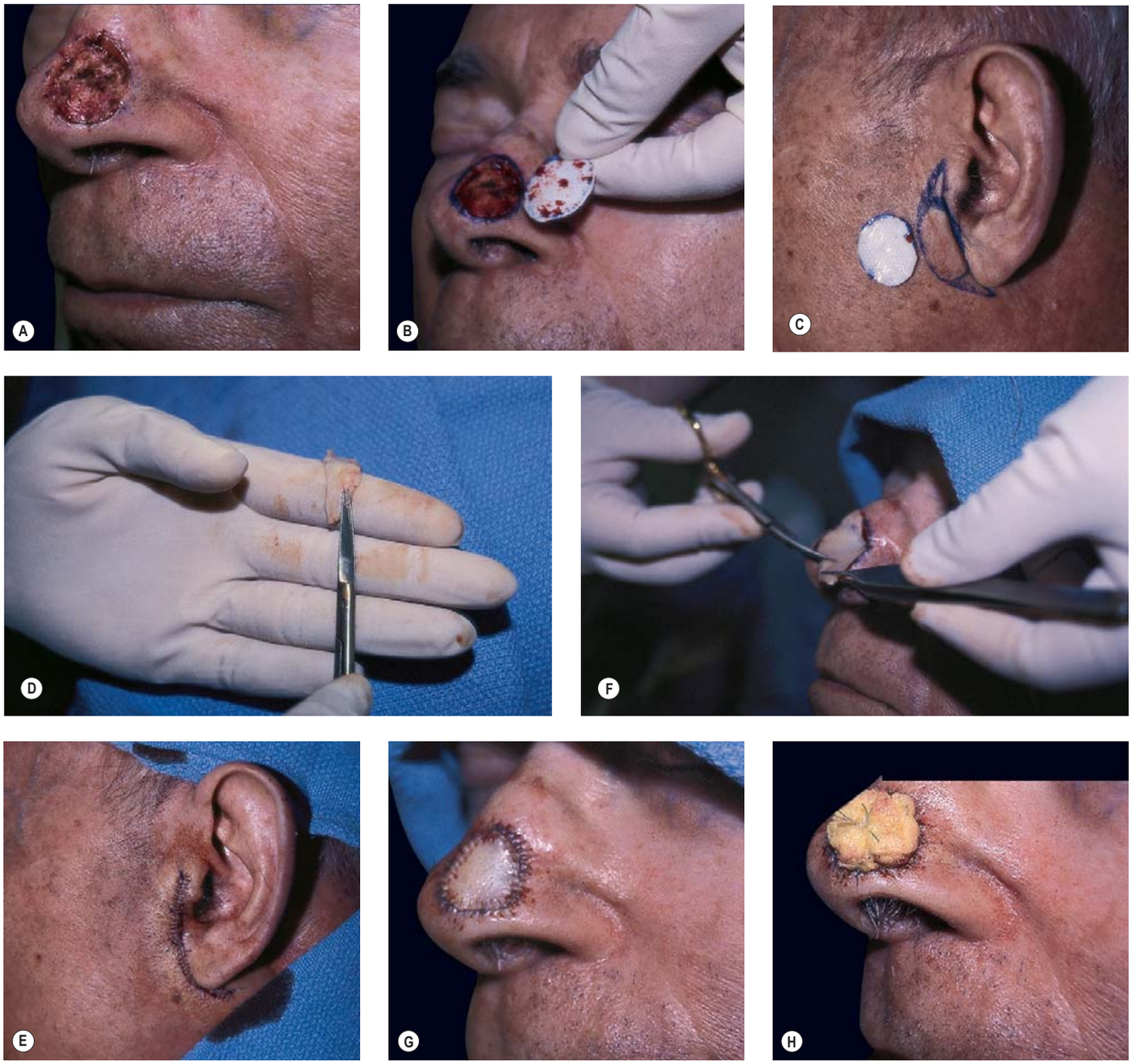


Fig. 148.3 Placement of a full-thickness skin graft. A A 1.7 × 2.0 cm defect of the nasal tip is present after removal of recurrent basal cell carcinoma with Mohs surgery. A preauricular donor site provides the best match in this case for color, sebaceous quality, degree of photodamage, and thickness. **B** After marking the periphery of the recipient site with a marking pen, the template material is pressed against the defect. The resulting outline of the inked margin serves as a guide to cut a perfect template, seen here adjacent to the nasal defect. **C** The template has been applied to the preauricular donor site, and inking material applied around it. Burow's triangles are outlined on either side of the template to close the site primarily. Marking the donor site prior to local anesthesia prevents incorrect sizing due to tissue stretch from lidocaine infiltration. **D** The graft is carefully defatted with curved iris scissors so that only the white, glistening surface of the dermis remains. **E** The preauricular donor site is closed primarily. **F** The full-thickness skin graft is trimmed with curved iris scissors to ensure a perfect fit. **G** Full-thickness skin graft sewn into place with 6-0 fast-absorbing chromic gut sutures. **H** Xeroform™ bolster sewn into place over full-thickness skin graft with 5-0 polypropylene tie-over sutures.

of revascularization, and they help to prevent hematoma or seroma formation. Some authors postulate that such dressings may not be necessary to secure very small FTSGs[18].

The simplest bolster consists of Xeroform™ gauze alone, which is molded and placed to apply pressure to the graft. One end of each of the peripheral non-absorbable sutures is cut long, to a length of approximately 3–6 cm, and its opposing suture is left uncut. The suture ends can then be tied over the dressing two at a time (i.e. 12 o'clock to 6 o'clock and 3 o'clock to 9 o'clock) to secure the bolster (Fig. 148.3H). A running bolster suture has also been described[19]. A light dressing consisting of Telfa™ and Hypafix® (Smith & Nephew) may be placed over the graft. The donor site is dressed with a pressure dressing for 24 hours.

Postoperative Care

After the pressure dressings are removed, careful wound care should be performed once to twice daily. One method is to gently clean the donor site and area immediately surrounding the bolster with hydrogen peroxide to remove all crusts, followed by application of antibiotic or

petrolatum ointment (Vaseline®). The bolster is not disturbed until dressing removal at 1 week, at which point the bolster and all tie-over sutures are removed. Steri-Strips™ may be applied to the donor site as needed after suture removal.

The ideal graft is light pink when the bolster is removed. Its color may range, however, from pink or red to darker blue or purple, depending on the extent of graft revascularization. Patients should be cautioned about these color changes beforehand. A bluish tinge may be a sign of ecchymosis rather than graft failure. At this 1-week time point, a white graft is a sign that the graft has not revascularized and will fail, requiring the underlying wound to heal by second intention. A black graft signals necrosis and is undesirable. It is possible that the entire epidermal surface may become black and necrotic, and then slough without adversely affecting the dermal portion of the graft, as re-epithelialization can occur from adnexal structures and the epithelial edges, with an acceptable cosmetic result. Therefore, eschars should not be debrided, since they can serve as natural dressings under which healing will progress. Patients should be counseled that the vascular supply of the graft remains fragile for weeks. For this reason, trauma, including direct shower water to the area, and excessive activity should be avoided for an additional 1 to 2 weeks.

Variations/Unusual Situations

Purse-string suture

The purse-string suture is a subcuticular stitch placed around the periphery of a circular or oval surgical defect[20]. This type of suture allows partial defect closure by advancing skin from the entire periphery of the wound, and it may help to cover areas of exposed cartilage or bone at the wound edges that could inhibit graft take. In addition, the graft required to cover the remainder of the defect is greatly reduced in size due to an approximately 50% decrease in the defect area. Because of this reduced defect size, the graft needed to complete the repair may be harvested from traditional preauricular, postauricular or supraclavicular donor sites, which provide the best color, texture and thickness match for most sun-exposed areas. Furthermore, FTSG placement decreases the risk of significant wound contraction, resulting in better cosmetic and functional results than would be produced by split-thickness skin grafting or second intention healing.

Large scalp defects extending to bone can present a significant management challenge, which can be handled by placing a purse-string suture followed by a galeal hinge flap[21]. After purse-string placement, the galea aponeurotica adjacent to the scalp defect is scored with a scalpel, and a partial-thickness galeal flap of sufficient size to cover all or a portion of the exposed periosteum or bone may be dissected free and transposed into place, using the same motion as turning a page of a book. This hinged galeal tissue serves to recreate the vascular bed required for successful graft placement, and it permits repair of deep and often difficult scalp defects in a single operative session.

Burow's grafts

Defects of the nasal sidewall and dorsum, and sometimes of the forehead, lateral neck or other areas, may be repaired with Burow's grafts[9–11,22]. Because Burow's grafts utilize skin adjacent to the defect, they tend to provide a cosmetically superior match compared to grafts harvested from distant locations. These grafts are harvested from the skin superior to the defect if on the nose, and medial or lateral to the defect if on the forehead. The Burow's triangle is excised (see Ch. 146) and the resulting donor defect is closed primarily, thereby partially decreasing the original defect size. The triangle is defatted, trimmed, and sutured into the defect. Operating time is decreased because a separate donor site is not required. Burow's grafts tend to be limited in size. When insufficient laxity is present for partial donor site closure, or if the Burow's triangle does not appear to be sufficiently large to cover the remaining defect, alternative donor sites should be sought.

Deep nasal defects

Deep postsurgical defects on the nose may at times pose a challenge for repair. Delaying FTSG placement for 12 to 14 days may increase the likelihood of graft survival over defects of the nasal tip and ala with denuded cartilage[23]. Also, when tissue loss is deep in these areas, delaying skin grafting for 7 to 14 days may allow granulation tissue to fill in the defect such that a better contour may ultimately be achieved[23]. Because the early granulating wound produces an excellent vascular bed, delayed grafting may be considered in patients with reduced wound bed vascularity, e.g. those who smoke or have had previous radiotherapy. At the time of delayed graft placement, the wound bed is debrided by rubbing with dry gauze and the edges are refreshed by scraping the wound edges with a scalpel held perpendicular to the edge. Prophylactic antibiotics are often prescribed when placing delayed grafts.

If a depressed defect is anticipated, but immediate reconstruction is preferred, dermal grafts can be used as a tissue filler prior to FTSG placement[24]. Dermal grafts can effectively fill the defect, with little risk of resorption, and eliminate the need for a more complicated repair choice. The "drumhead" graft repair of deep nasal alar defects involves application of an overlying rigid plastic suspension coupled with an undersized graft, thereby preventing graft depression and nasal valve collapse; a cut portion of the periphery of the sterile plastic packaging from a suture packet can serve as the plastic suspension[25].

Perichondrial cutaneous grafts (PCCGs) are actually composite grafts composed of full-thickness skin and subjacent perichondrium, and may be used as a substitute for FTSGs when reconstructing deep nasal tip and alar defects, particularly those with exposed cartilage[26,27]. PCCGs are harvested from the conchal bowl, utilizing the subperichondrial plane as the plane of dissection. The cartilage is not removed, making this graft more analogous to a FTSG than a cartilage-containing composite graft. The advantages of PCCGs over FTSGs include the following: PCCGs are thicker, have a greater chance of survival under conditions of vascular compromise, contract less than FTSGs, and may achieve better skin texture match on the distal nose due to the sebaceous nature of conchal bowl skin.

Postoperative Complications

The complications of full-thickness grafting can be divided into short-term problems of graft failure and long-term functional and cosmetic problems[2,3]. Short-term problems include infection, hematoma, seroma, and shearing of the graft over its bed. These problems are significant when they occur, but can usually be avoided. Infection after grafting of facial defects, in particular, is not often encountered, and oral antibiotics are not routinely given postoperatively. Nevertheless, it is important to be gentle while handling tissue intraoperatively and to minimize devitalized tissue created by electrocoagulation in order to minimize the risk of infection. Prophylactic oral antibiotics covering *Staphylococcus* and *Streptococcus* spp. may be helpful in selected patients, especially those with diabetes mellitus, immunosuppression, or a prolonged intraoperative time. Grafts on the ears, fingers and legs may benefit from prophylactic antibiotics, as these sites seem more prone to postoperative wound infections.

Hematoma and seroma formation can be avoided by meticulous hemostasis intraoperatively, pressure dressings, and postoperative caution. After consultation with the patient's internist, cardiologist or primary care physician, patients may be instructed to avoid aspirin for 10 days before surgery, nonsteroidal anti-inflammatory drugs for 5 days before surgery, and alcohol for 2 days before and 2 days after surgery. Warfarin can often be discontinued 2 days before surgery and resumed the day after, based on the recommendations of the patient's internist or cardiologist. Patients are also advised not to engage in vigorous activity, heavy lifting or bending for at least 2 weeks postoperatively. The latter measures help to inhibit graft movement and supplement the bolster's effectiveness in minimizing shearing of the graft over its bed.

Long-term complications of FTSGs consist of cosmetic and functional problems. It is imperative to stress to the patient prior to graft placement that FTSGs usually take months to look natural. Preoperative counseling may help to alleviate fears concerning the graft's appearance during the first weeks after bolster removal. Make-up can usually be applied 3–4 weeks after graft placement. It is important to note that FTSGs are often depressed during their first 2–4 weeks. This depression will usually correct itself within 4–6 weeks.

Although careful donor site selection will minimize the color, texture and contour deformities that can occur, patient and physician satisfaction with the cosmetic result may not be complete after healing has finished. Spot dermabrasion or laser resurfacing may be performed after 6 weeks to 6 months to correct differences in elevation between the graft and its surrounding skin, as well as to improve color and texture

mismatch[28]. Resurfacing of the entire cosmetic unit may be helpful in optimizing the cosmetic result. Graft hyperpigmentation can be treated with a brief course of topical hydroquinone and/or tretinoin. The use of tretinoin pre- and postoperatively has not been shown to alter the healing of FTSGs[29].

Functional complications of FTSGs occur primarily as a result of wound contraction. Grafts contract secondary to the centripetal movement of unopposed elastic fibers. A variable amount of shrinkage can therefore be expected, depending upon donor site thickness and elasticity[6,30,31]. In one study, it was found that the area of FTSGs contracted by a mean of 38% by 16 weeks after placement, with grafts applied to the periorbital area and nose contracting more than those on the scalp and temples[30]. Graft contraction usually increases as graft thickness decreases, and is thought to occur in the fibrous layer under the graft, either in the bed itself or in the layer of scar tissue wedged between the graft and its bed[6]. Complications due to graft contraction are usually minimal in FTSGs. If wound contraction does produce functional or cosmetic abnormalities, secondary revisional surgery may be needed.

Future Directions

For patients with an inadequate vascular bed, full-thickness skin grafting may not be possible, necessitating repair with a less cosmetically elegant STSG. High-density porous polyethylene implants have therefore been designed which permit ingrowth of fibroneovascular tissue without changing the size or shape of the implant[32]. When these prefabricated implants were placed in rabbits, it was found that they developed sufficient vascularity to sustain FTSGs. This technology holds promise for patients with deep nasal and ear defects, in whom an anatomically correct structure could be implanted, after which, time could be allowed for fibrovascular tissue ingrowth, and full-thickness skin grafting performed later for a superior cosmetic result. Progress is also being made on incorporating complex blood vessels into bioengineered skin equivalents.

SPLIT-THICKNESS SKIN GRAFTS

Split-thickness skin grafts (STSGs) consist of epidermis and a portion of the dermis. These grafts vary in thickness from approximately 0.005 to 0.030 inches (0.13–0.78 mm), and are classified as thin, medium or thick, depending upon the amount of dermis included in the graft (Table 148.6).

Indications/Contraindications

STSGs have less tissue requiring revascularization than FTSGs, and are therefore more likely to survive when placed on almost any recipient bed, including those with a limited vascular supply. As a result, these grafts may be placed over periosteum, perichondrium, peritenon and perineurium. STSGs are also used to cover large defects, particularly those that cannot be covered by a flap or would heal too slowly by second intention, as well as refractory venous leg ulcers[2,3]. STSGs may be useful for covering surgical defects in sites at high risk for tumor recurrence, since recurrent tumor is usually visible when growing through split-thickness skin. If the tumor has not recurred after 1–2 years, the graft can be removed and a definitive reconstruction performed.

Advantages of STSGs over FTSGs include their improved chance of survival under conditions of vascular compromise, their ease of application, their ability to cover large defects, and their ability to act as a "window" for recurrence of high-risk lesions. The principal disadvantages of STSGs include their suboptimal cosmetic appearance, the presence of a granulating donor site wound requiring postoperative care, greater graft contraction, and the special equipment required to harvest larger grafts. Furthermore, because of their relative thinness, STSGs may be less durable than FTSGs, necessitating regrafting or partial healing by second intention.

While thicker STSGs tend to be cosmetically superior to thinner ones, poor color and texture match with the surrounding skin often occurs after STSG placement. STSGs tend to be pale or white in color, hairless, and smooth in texture, with impaired sweating due to the fact that adnexal structures are not removed in their entirety with the graft and do not survive. The contrast between the STSG and its surrounding skin can therefore produce a "tire-patch" appearance (Fig. 148.4), which is more pronounced than seen with FTSGs.

CLASSIFICATION OF SPLIT-THICKNESS SKIN GRAFTS	
Thin	0.005–0.012 in/0.13–0.31 mm
Medium	0.012–0.018 in/0.31–0.47 mm
Thick	0.018–0.030 in/0.47–0.78 mm

Table 148.6 Classification of split-thickness skin grafts.

Preoperative History and Donor Site Considerations

Cosmesis of the donor site scar should be taken into consideration when selecting a split-thickness donor site. The ease of postoperative donor site care and the type of instrument used to harvest the graft may also help to dictate donor site choice. Ideally, STSGs should be harvested from a site where a broad area of skin can be removed while still being concealed beneath clothing. The most common donor sites include the anterior, medial and lateral portions of the upper thigh, the inner and outer aspects of the upper arm, and the inner aspect of the forearm. Lower back and abdominal skin can also be harvested. The anteromedial thigh is most frequently used as the donor site for STSGs, as harvesting and wound care are convenient, and wounds in this location do not interfere with ambulation. Donor site wounds on the buttocks tend to require assisted postoperative care, although their scars are ideally placed from a cosmetic standpoint. Power-driven dermatomes and large freehand knives require large flat donor surfaces, which may limit donor sites to the thighs, abdomen and buttocks, while smaller grafts can be harvested freehand or with a power-driven dermatome.

Description of Grafting Techniques

A wide variety of techniques for harvesting and placing STSGs have been described[2,3,33]. The instruments used to harvest STSGs can be classified into freehand and electric dermatomes. Freehand dermatomes include scalpel blades, double-edged razor blades, and knives such as the Weck blade. Although acceptable grafts can be obtained using these freehand devices, considerable technical expertise is required to harvest them.

A standard #15, #15c or #10 blade can be an effective tool for harvesting small STSGs of medium thickness. After a template of the

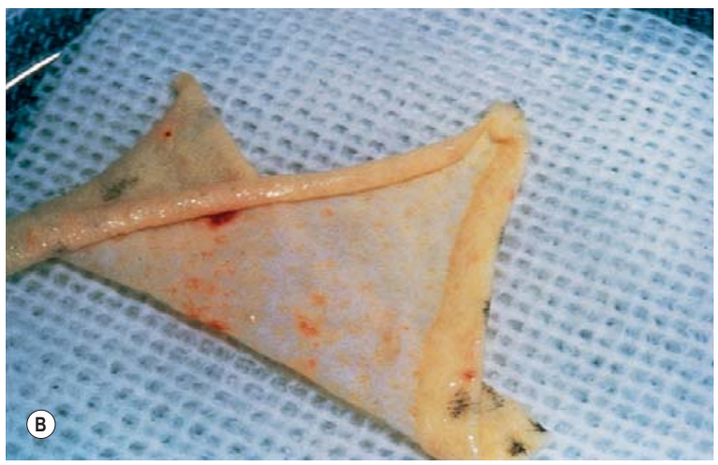
Fig. 148.4 Appearance of a split-thickness skin graft (STSG) on the forehead and scalp placed several years prior, following excision of a cutaneous melanoma. Note the relative hypopigmentation, altered texture and obvious depression of the STSG as compared to the normal surrounding skin. *Courtesy, Jean L Bolognia, MD.*

defect is made, the donor site is marked, anesthetized, and scored lightly with the blade. The graft is then harvested by orienting the blade parallel to the skin and gently sweeping it just below the level of the epidermis, so that the blade is visible beneath the skin (Fig. 148.5). It is helpful to have an assistant apply traction to the donor site while the graft is harvested. Several blades may be required for harvesting, as blade sharpness diminishes quickly with multiple passes. This technique may be especially useful in harvesting small medium-thickness STSGs to repair auricular and postauricular defects.

Fig. 148.5 Freehand harvesting of a small split-thickness skin graft from the upper outer arm. The blade is oriented parallel to the skin, and gently swept just below the level of the epidermis, so that it is just visible through the graft. An assistant applies traction to the donor site to facilitate harvesting.

Power-driven dermatomes became the standard method of harvesting larger STSGs after Brown developed the first such instrument in the 1940s. Electric dermatomes designed to harvest STSGs of varying thicknesses and widths, from several centimeters up to nearly 15 cm, are now commonly employed, and lithium ion battery-powered units are also available. Although STSGs can be obtained easily and reliably with any of these devices when properly used, the quality of the graft is technique-dependent, and substantial irregularity in graft thickness and width may at times occur. The Zimmer dermatome, which was originally powered by compressed water-pumped nitrogen and subsequently modified into an electrically powered version, tends to harvest uniform grafts of predetermined width and thickness such that consistent graft quality tends to be less dependent on the operator's technique. Multipurpose motor systems now exist which include a control box, foot switch and autoclavable motor that can be used not only with dermatomes, but also with diamond fraises for dermabrasion, adjustable skin graft meshers, and other types of surgical handpieces, allowing a wide array of procedures to be performed using a single unit.

After the dermatome is prepared, the donor and recipient sites are anesthetized, prepped and draped in the usual sterile fashion. If chlorhexidine surgical scrub is used, a saline wash is employed to remove any excess scrub. The donor site is lubricated in advance with sterile mineral oil or another lubricant to ease travel of the dermatome over the skin. The handpiece is held on the donor site at an angle of 30–45°. A throttle control is pressed to start the cut, and the unit is guided forward using light downward pressure to ensure that the cutting edge remains in continuous contact with the donor site. An assistant applies tension by pulling the skin away from the donor area to create a flat, even surface. As the dermatome glides over the donor skin, the graft emerges from the pocket area of the dermatome, and is lifted away from the machine with tissue forceps or hemostats (Fig. 148.6A). Once a sufficiently large graft has been harvested, the dermatome is pulled away from the skin and the graft is placed in sterile saline or on sterile saline-soaked gauze (Fig. 148.6B).



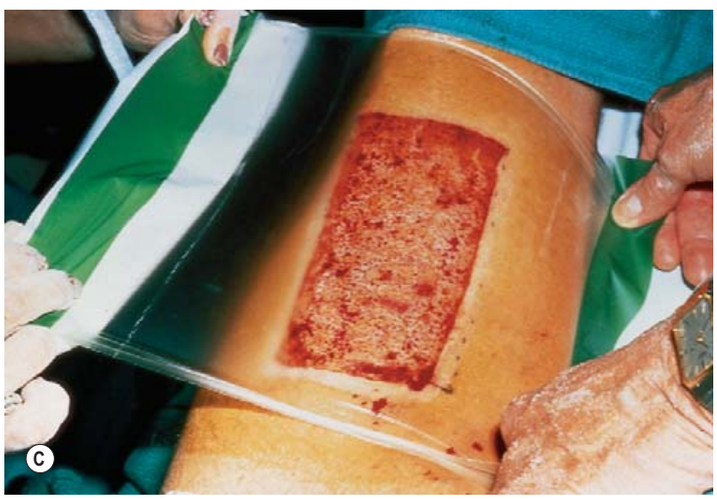


Fig. 148.6 Harvesting of a large split-thickness skin graft with an electric dermatome. A As the Zimmer dermatome glides over the donor skin, the graft emerges from the pocket area of the dermatome, and is lifted away from the machine with sterile hemostats. **B** Split-thickness skin graft placed on sterile saline-soaked gauze. Note that the edges curl inward toward the dermal surface of the graft. **C** An Opsite® dressing is placed over the donor site on the anterior thigh immediately after harvesting.

Securing the Graft

As in the case of FTSGs, STSGs should be secured so that infection, hematoma or seroma formation, and mechanical shearing forces can be prevented. Both the perimeter and the central portion of the graft must be secured for adequate nutritional support and to ensure graft survival. The edges of STSGs need not be as closely approximated to the surrounding wound edge as those of FTSGs, since overlapping skin will slough without affecting the ultimate cosmetic result. After the graft has been placed such that the dermal side is adherent to the recipient bed, the perimeter of the graft may be secured with sutures or staples. Centrally placed basting sutures may also be helpful in ensuring good apposition of the graft to its bed. Once the graft has been secured and its bolster sewn into place, a non-adhesive dressing or pressure dressing may be applied as an additional precaution. Sutures or staples are removed after 7–10 days.

Donor Site Care

Harvesting STSGs creates a second wound, the donor defect, which often causes more postoperative discomfort than the grafted area itself. This partial-thickness wound heals by second intention. While STSG donor sites were once treated with bulky occlusive dressings left in place for 10–14 days, the advent of transparent, vapor-permeable dressings such as Opsite® (Smith & Nephew) has made the postoperative period easier in terms of comfort and ease of care (Fig. 148.6C)[34]. These dressings are advantageous because they allow the serosanguineous drainage that inevitably accumulates at the donor site to collect, keeping the wound moist and thereby shortening healing time. Because these dressings are transparent, the wound can easily be observed for complications during the healing process. In one review, these dressings were found to be associated with the fastest healing rates, a low infection rate, the least amount of pain, and lower cost when compared with other dressings[35].

After the skin around the donor site area is cleaned and dried, a thin coat of an adhesive such as Mastisol® (Ferndale Laboratories) is applied around the wound and allowed to dry. An Opsite® dressing is then placed over the wound. Paper tape is placed around the perimeter of the Opsite®, followed by a gauze dressing and an Ace® wrap (Becton-Dickinson).

Variations/Unusual Situations

Meshing the graft with scalpel slits may be performed to allow drainage of accumulated blood or serosanguineous material that could otherwise inhibit graft–bed contact. This technique may also be used to expand the surface area of STSGs. A graft meshing machine may be utilized to expand the surface area of the graft further by ratios ranging from 3:1 to 9:1. Meshing can help to provide coverage of a large recipient area with smaller donor grafts. Expanded meshed grafts placed experimentally on contaminated recipient beds have been found to exhibit increased take as compared with non-meshed donor skin[36].

Postoperative Care

During the first 24 hours after grafting, a large amount of serosanguineous fluid may accumulate beneath the donor site dressing. Patients need to be forewarned of this so that they do not become alarmed. If this occurs, the fluid can be drained with a needle and syringe, and an Opsite® patch applied. Alternatively, a new Opsite® dressing can be placed. The dressing can then be left in place until healing is complete. Depending on the thickness of the STSG, the donor site should fully re-epithelialize in 7–21 days. The scar usually evolves in color from pink to white over a period of months.

Complications

The complications of split-thickness skin grafting can be divided into early complications, which stem from failure of engraftment, and late complications[2,3]. Failure of engraftment may result from hematoma or seroma formation, infection, or shearing forces. Late complications can be divided into cosmetic and functional problems (Fig. 148.7).

Color and texture mismatch of STSGs with the surrounding skin is predictable and expected. Grafts often remain erythematous for months to years after placement. More importantly, they may exhibit significant postoperative hyperpigmentation or hypopigmentation. Darker-skinned patients are especially prone to graft hyperpigmentation, despite observance of preventive measures. Patients should minimize graft exposure to the sun without sunscreens for 6 months, and wear sunscreens consistently thereafter. The absence of adnexal structures can predispose to xerosis and a build-up of keratinous debris. The resultant scaling, pruritus and dryness can be minimized with liberal use of emollients.

Functional considerations are of paramount concern, since STSGs contract more than FTSGs and can create forces powerful enough to produce joint contraction if placed over or near joints. Contraction of facial grafts, especially near the nasal ala, the eyelid, the helical rim and the free margins of the vermilion border, may produce significant cosmetic deformities, including alar retraction, ectropion, helical rim distortion and vermilion border distortion. Hypertrophic scarring of the graft and donor sites may also occur, and can be treated with corticosteroid-impregnated tape, intralesional corticosteroids, or pulsed dye laser. Graft fragility and breakdown can occur in areas of trauma, particularly in sites such as the lower leg, or in areas with little underlying soft tissue support, such as those directly overlying perichondrium or periosteum. These complications are not always avoidable, but forewarning patients may reduce unnecessary trauma to the area. Lastly, bullae can occur within graft sites, presumably related to decreased anchoring properties of the basement membrane zone (see Ch. 33).

Future Directions

In recent years, biosynthetic and tissue-engineered living skin replacements have been the focus of research in skin transplantation[37–39]. Cultured human keratinocytes have been seeded onto type I collagen membranes to reconstitute the epidermis, enabling transfer of actively proliferating keratinocytes onto partial-thickness wounds. Human epidermal tissues mimicking the biochemical and morphologic properties of human skin have been established *in vitro* by growing human keratinocytes on a dermal fibroblast-containing collagen gel. Such skin-equivalent cultures may hold promise in reconstituting the epidermis in patients with full-thickness burn wounds and chronic ulcers (see Ch. 145).

Artificial dermis is now routinely used prior to full-thickness grafting, and an acellular allograft dermal matrix has been shown to provide a good bed for STSGs in patients with full- and partial-thickness burns. A tissue-engineered human skin equivalent, i.e. a bilayered product containing living human fibroblasts, keratinocytes and bovine collagen, is commercially available for the repair of surgical defects and coverage of lower leg ulcers that would previously have been repaired with STSGs. Dermal–epidermal composites using autologous keratinocytes and human allodermis may in the future be used for grafting full-thickness wounds in patients with burns, leg ulcers or surgical wounds.

COMPOSITE GRAFTS

Indications/Contraindications

Composite grafts are modified FTSGs, consisting of two or more tissue layers. In dermatologic surgery, these grafts are usually composed of skin and cartilage, although they may be composed of skin and fat or skin and perichondrium[3,26,40–47]. Composite grafts are especially useful for repairing full-thickness alar rim defects, as well as nasal tip defects with cartilage loss[45,46]. Full-thickness nasal mucosal defects can be repaired using composite grafts to provide mucosal lining and structural support, with a nasolabial or forehead flap placed thereafter to reconstruct the overlying soft tissue defect. As discussed earlier, conchal bowl composite grafts or PCCGs, consisting of skin and perichondrium, may be used (with or without an underlying cartilage graft) for deeper nasal defects requiring skin coverage, especially defects with exposed cartilage[47].

Preoperative History and Considerations

Composite grafts require rapid revascularization to survive. Early re-establishment of circulation occurs via direct vessel anastomoses between the subdermal plexus of the graft and the subdermal plexus of the wound edge. Since composite grafts are dependent upon this

Fig. 148.7 Late complications of skin grafts. A Hyperpigmentation of an entire STSG placed following excision of an *in situ* ungual melanoma; the sites of suture placement also developed hyperpigmentation. Increased scaling compared to the surrounding skin is commonly observed. **B** Hypertrophic scarring of a STSG placed following partial excision of a large congenital melanocytic nevus on the arm 1 year prior; the skin overlying the elbow was not excised, in an attempt to prevent joint contraction. **C** Mismatch of color, texture and hair density in a skin graft of abdominal skin placed on the face following excision of a congenital melanocytic nevus. **D** Growth of hair within a graft placed on the inner aspect of the foot following excision of a cutaneous melanoma. *Courtesy, Jean L Bolognia, MD.*

bridging phenomenon for their survival, they are of necessity limited in size, with no point being more than 1 cm from a vascular source, as the risk of central necrosis increases significantly at graft diameters greater than 2 cm[3,46]. Composite grafts for nasal alar and ear reconstruction are possible because of the rich vascular supply of the nose and ear, and because of the small surface areas generally involved. Composite grafts, like FTSGs, are threatened by excessive shearing forces on the graft over its bed, which prevent revascularization.

During the healing process, composite grafts pass through four stages[3,46]. After graft placement, the tissue blanches completely. By 6 hours, the graft becomes pale pink, signifying anastomosis of the graft vessels with those of the recipient site. At 12–24 hours, the graft appears dusky blue, reflecting venous congestion, and by 3–7 days, it should be pink, indicating graft survival.

Donor Site Considerations for Composite Grafts

The complexity of nasal alar anatomy makes reconstruction of full-thickness defects involving this area difficult. There may be insufficient nasal skin to develop adequate local flaps, and nasolabial flaps, which provide reasonable defect coverage, generate other cosmetic deformities. The loss of alar tissue support also creates a functional deficit, as the alar skin is liable literally to "blow in the breeze" on inspiration and expiration. Composite grafts provide an excellent cosmetic and functional alternative for repair of full-thickness alar rim defects less than 2 cm in diameter[46]. Grafts taken from the earlobe have been used successfully for this type of repair, although grafts taken from the cartilaginous portion of the ear are more frequently used[41,44,45].

Donor sites for harvesting auricular composite grafts include the helical crus, helical rim and conchal bowl (see Ch. 142)[44–47]. Small alar defects involving loss of cartilage can be elegantly repaired using the helical crus as donor site, while more substantial defects may require repair using the helical rim or conchal bowl, since the crus may not provide sufficient inner lining for the graft. Donor defects involving the helical crus can be repaired with minimal scar formation, while wedge excisions are usually necessary to repair helical rim donor sites. Conchal bowl donor sites heal by second intention.

The advantages of auricular composite grafts in repairing full-thickness alar rim defects relate mainly to the presence of cartilage, which provides structural support and stability, with prevention of alar distortion during inspiration and at rest[45,47]. Disadvantages include a higher risk of graft failure with an increased number of tissue layers, substantial graft size limitations, and limited donor tissue availability. Nevertheless, these grafts, when properly applied, can yield outstanding results.

Composite grafts used for full-thickness nasal mucosal repair are usually obtained from the triangular fossa, scapha, conchal cavum, cymba or helical crus (see Fig. 142.14). The appropriate donor site is that which best matches the contour of the surgical defect. These donor sites are usually allowed to heal by second intention, with good aesthetic outcomes.

Description of Technique

Composite grafts used for alar repair are performed as follows (Fig. 148.8)[40,45,47]. The donor and recipient sites are anesthetized using local anesthesia, and prepped with an antiseptic solution. If the alar tissue is scarred and retracted, the area must be vigorously debrided to assure the best possible blood supply for the graft. The defect is then measured and a template made as described previously. The donor site is marked and anesthetized, and the graft is harvested. The tissue is handled very gently and placed in sterile saline until ready for placement.

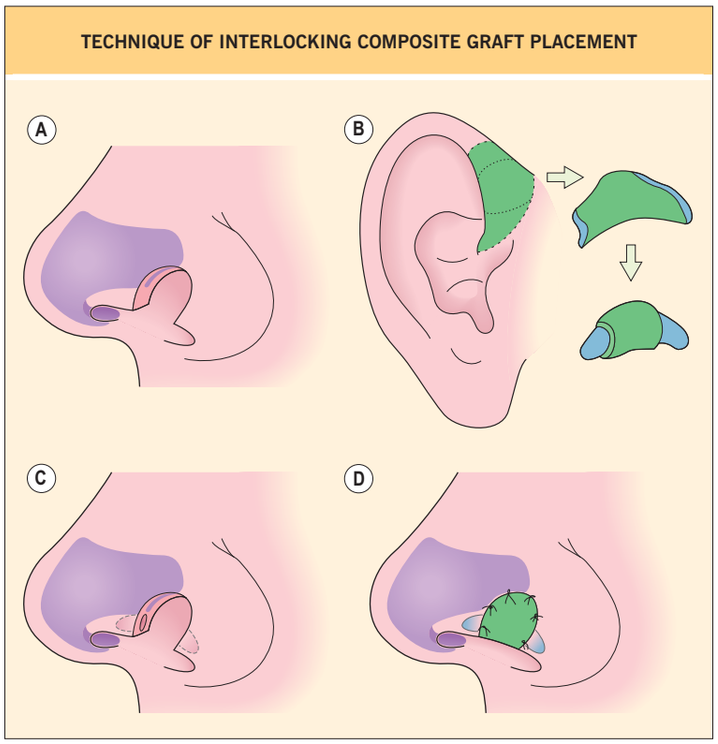


Fig. 148.8 Technique of interlocking composite graft placement. A A full-thickness nasal alar defect extending through both skin and cartilage requires repair. **B** Donor site at the crus of the helix. An area of skin approximately 5–10% greater in area than the actual defect is marked out, with cartilaginous wings marked out on either side. After the graft is harvested, the skin is removed on both sides to expose the cartilaginous portion of the graft, such that two cartilaginous pegs with their overlying perichondrium frame the lateral aspects of the graft. **C** A pocket is undermined on either side of the recipient site, into which the cartilaginous pegs will be placed. **D** The cartilaginous pegs are inserted into the holes prepared within the alar tissue on either side of the defect. The graft is then sutured into place.

Due to the fragility of composite grafts, a tongue-in-groove technique is recommended to maximize graft stability and increase graft survival[45,47]. Two cartilaginous wings are marked out and anesthetized on either side of the donor site prior to graft harvesting. After the graft is harvested, the skin overlying these two cartilaginous wings is removed, leaving the cartilage with its overlying perichondrium (Fig. 148.8B). These wings are then inserted into pockets prepared within the alar tissue of both sides of the defect (Fig. 148.8C) such that the graft interlocks with its recipient bed (Fig. 148.8D). Interlocking the graft with its bed may help to minimize shearing forces and provide a larger surface area for revascularization.

The graft is sutured into place in two layers. The undersurface of the graft, which replaces the inner lining of the nose, can be secured first using a 6-0 absorbable suture. The skin is then closed with a 6-0 nonabsorbable suture, taking very small tissue bites to minimize vessel strangulation and to maximize the number of potential vessels available for reanastomosis. The needle should pass through the mucosal portion of the graft first, then through the outer epithelial edge of the graft, so that the knots are tied externally, and are not buried between the graft and its recipient bed. The cartilage does not need to be sutured, as it will heal on its own. A Vaseline® gauze or Xeroform™ dressing can then be placed in the nasal vestibule for support, and antibiotic ointment applied to the external suture line. A non-stick dressing is then applied to protect the graft from external injury.

Conchal bowl composite grafts used for reconstruction of deep alar defects are harvested in essentially the same way as composite grafts taken from the helical crus[47]. Potential advantages of the conchal bowl technique include increased bulk, which may be superior in filling deep partial-thickness alar defects, and an excellent cosmetic match for the missing sebaceous skin of the nose.

Donor Site Closure[48]

Helical crus defects can often be closed in a side-to-side fashion. A simple advancement, rotation or transposition flap may also be utilized to take advantage of loose preauricular skin. Helical rim defects are usually closed with an ear wedge resection. Auricular grafts obtained from the triangular fossa, scapha, conchal bowl or cymba heal well by second intention. Conchal bowl defects may heal more rapidly if a 2 mm punch biopsy instrument is used to remove small plugs of conchal cartilage, which allows healing by second intention from the soft tissue on the opposite side.

Variations/Unusual Situations

When securing composite grafts onto the nasal ala, delayed intranasal knot tying has been recommended by some authors to facilitate wound closure by improving visualization, allowing gentler manipulation of tissue, and enabling precise suture placement in a confined space[49]. When placing the intranasal sutures, the needle of the 6-0 fast-absorbing chromic gut suture is first passed through the nasal mucosa, and then through the corresponding location on the "mucosal" side of the graft. Sutures are placed at 1–2 mm intervals along the defect and graft, and their free ends are held separately by hemostats to prevent tangling. After all intranasal sutures are placed, the composite graft may be placed into the alar defect and the cartilaginous wings inserted. The most internal intranasal sutures are then tied first, followed by the more accessible external sutures.

Postoperative Care

To minimize graft edema, ice packs should be applied to the grafted area as often as possible for up to several days postoperatively to minimize graft edema. Oral antibiotics are generally advisable because of the high bacterial colonization around the nares and the higher risk of failure with composite grafts. Sutures are removed after 1 week.

Complications

As with other types of grafts, there is a risk of necrosis in the early stages of healing, and contraction, textural changes, atrophy and contour irregularities thereafter. If the graft survives but the cosmetic result is suboptimal, dermabrasion or laser resurfacing may be performed 6 weeks to 6 months postoperatively to correct textural differences between the graft and the surrounding skin, and to improve the color match between them. Resurfacing of the entire cosmetic unit may provide superior cosmetic results. In the event of composite graft failure, a two-stage revision with placement of a cheek interpolation flap may be performed or, alternatively, a second composite grafting procedure may be undertaken.

Conchal bowl donor sites are at somewhat greater risk of postoperative bleeding than other areas if left to heal by second intention. Application of pressure dressings over the front and back of the ear to "sandwich" the conchal cartilage with placement of hemostatic foam over the donor site itself may decrease this risk. Other types of complications at auricular donor sites are rare[48].

The ear is also prone to infection with *Pseudomonas* spp., which reside in the external auditory meatus. Cleaning the ear with a dilute vinegar solution, applying topical gentamicin ointment, and oral quinolone antibiotics are all helpful prophylactic measures which should be considered after harvesting auricular cartilage. If infection is suspected, oral quinolone antibiotics should be started immediately, and therapy guided thereafter by the results of cultures and sensitivities. If the infection does not resolve with appropriate antibiotics, the presence of a fungal infection, most often secondary to *Candida*, should be excluded.

FREE CARTILAGE GRAFTS

Indications/Contraindications

Free cartilage grafts are used most commonly in dermatologic surgery to reconstruct the nasal ala, tip and sidewall, the ear, and the eyelid[40,42,49–51]. These grafts may be used to restore the architecture of an anatomic site that has undergone significant cartilage loss. Free cartilage grafts

are also useful in maintaining the position and contour of free margins against the forces of contraction during wound healing.

Nasal Ala

Partial-thickness alar defects extending into deep soft tissue or approaching the alar rim often lead to alar rim collapse, producing a functional as well as a cosmetic deficit. Placement of free cartilage grafts, consisting of cartilage with its overlying perichondrium, can be used to avert this potential problem[50–53]. The grafted cartilage provides a rigid but flexible cartilaginous framework that braces the alar rim against collapse during inspiration and expiration. Cartilage grafts may be used in conjunction with flaps and FTSGs to maintain airway patency and to minimize the risk of alar retraction during wound healing[42,49–51].

The major usefulness of the free cartilage graft lies in its ability to prevent alar retraction. It is possible that long-term survival of the cartilage itself may not ultimately be important, as the mere presence of the rigid framework of the graft in the initial stages of wound healing seems to be sufficient to inhibit alar retraction.

Nasal Sidewall and Tip

Deep defects of the nasal sidewall may, at times, involve loss of the upper lateral nasal cartilage. Nasal valve obstruction may result, which becomes noticeable with inspiration and resolves on expiration. Delayed nasal valve obstruction can also occur if unresisted scar contracture collapses the remaining cartilaginous structure of the nasal sidewall. Replacement of lost cartilage at the time of reconstruction can avert these potential problems. Similarly, loss of cartilage at the distal nasal tip necessitates replacement of structural support for optimal function and cosmesis.

Ear

Auricular defects involving loss of cartilage are generally repaired for cosmetic, rather than functional, reasons. Cartilage grafts may be used as braces along the helical rim to minimize the risk of contracture, and may also be used in the conchal bowl to assist in hearing-aid placement[40].

Preoperative History and Donor Site Considerations

Potential donor sites for free cartilage grafts include the conchal bowl, the auricular helix, the antihelix, nasal septum, and ribs[40]. The conchal bowl is the donor site most frequently used by dermatologic surgeons[42,46,51]. Conchal cartilage is elastic, has a high degree of memory, and has varied contours that can be matched to the desired alar contour. Although an anterior approach to the conchal bowl may be used, the posterior approach results in better camouflage of the donor site scar and preservation of the shape of the ear. If the antihelix is used as a donor site, it is recommended that subtotal resection of the antihelical cartilage be performed, leaving a complete rim of intact cartilage to prevent distortion.

Description of Technique

Nasal ala

The techniques for alar batten cartilage grafting have been well described[40,42,46,49]. The alar batten provides a rigid but flexible cartilaginous framework to brace the alar rim against collapse. The length of the cartilage graft is determined by measuring the distance between the lateral and medial borders of the defect at the alar rim, and adding to that measurement an extra 4–5 mm. The conchal bowl donor site is incised anteriorly or posteriorly. The skin overlying the cartilage is then undermined with blunt-scissor dissection to expose the perichondrial surface. The desired length of cartilage is incised with a scalpel (Fig. 148.9A), and a second incision is made exactly parallel to the first, creating a cartilaginous strip that may be 3–6 mm in width, depending upon the desired width of the graft. Alternatively, a larger disk or oblong-shaped piece may be harvested to match the base of the defect. The cartilage is easily separated from the anterior skin with sharp-scissor dissection. The graft is placed in sterile saline while the donor site is reapproximated with non-absorbable sutures.

The cartilaginous strip graft is secured by undermining the soft tissue of the recipient bed medially and laterally with a hemostat or blunt-scissor dissection, and the ends of the graft are inserted into the undermined pockets such that the graft interlocks with its bed (Fig. 148.9B). The graft is anchored to its bed with one or two 5-0 absorbable sutures for additional security. A disk- or oblong-shaped cartilage graft also requires suturing for secure placement.

After the graft has been anchored, a nasolabial transposition flap or FTSG is sutured into place to complete the closure (Fig. 148.9C,D). A standard tie-over bolster is placed over the FTSG and secured with 5-0 non-absorbable sutures. Sutures are removed at 1 week.

Nasal sidewall and tip

Free cartilage grafts used for nasal sidewall and tip reconstruction are harvested in much the same way as free cartilage grafts for alar reconstruction[40]. Nasal sidewall grafts tend to be wider and broader than alar grafts, since they must brace a broader surface area against the forces of inspiration. Alternatively, multiple cartilaginous strips can be placed perpendicular to the lateral nasal sidewall, and then secured with absorbable or non-absorbable sutures to brace the side of the nose against collapse. After the cartilaginous structure is in place, a flap or FTSG may be performed to cover the remaining cutaneous defect.

Nasal tip grafts for distal nasal reconstruction are organized to provide both proximal and distal structural support, thus optimizing the aesthetic and functional result[40,49,50]. The proximal grafts consist of bilateral batten grafts secured to the lateral cartilages with 5-0 or 6-0 non-absorbable sutures. On top of these may be sewn a dorsal nasal cartilage graft. A columellar strut of cartilage often provides distal support, on top of which may be sewn an additional tip graft. Alar batten grafts secured to the columellar strut and lateral alar soft tissue provide alar rim support. A paramedian forehead flap or melolabial interpolation flap may be placed thereafter to provide coverage of the cutaneous defect.

Ear

If conchal cartilage is used to repair a large helical defect, the cartilage graft should match the defect as closely as possible in size and shape[40]. Harvesting and placing a narrow strip of cartilage matching the helical defect alone will result in helical rim collapse under the forces of wound contraction. If necessary, a partial wedge closure of the defect may be performed to decrease the portion of the defect requiring replacement of structural support. The cartilage graft is secured by sewing it to the intact cartilaginous framework with 6-0 absorbable or non-absorbable sutures. The graft is then generally covered with a pedicled retroauricular advancement flap.

Eyelid

Partial-thickness lower eyelid defects with loss of the tarsal plate, as well as full-thickness lower eyelid defects, may be repaired with cartilage grafts. Stabilization of the eyelid with free cartilage grafts provides structural support, minimizing the risk of ectropion and preventing corneal desiccation. The technique for performing free cartilage grafts to repair full-thickness and partial-thickness lower eyelid defects is beyond the scope of this chapter, but is well described by Otley and Sherris[40].

Postoperative Care

Regardless of the site of free cartilage grafting, care must be taken postoperatively to minimize movement of the graft. Routine wound care is performed to the flap or graft overlying the free cartilage graft. Trauma to the area should be minimized.

Complications

Postoperative complications following cartilage grafting are rare. There is a risk of postoperative infection at the conchal bowl donor site, particularly with Gram-negative bacilli, which reside within the external auditory meatus. Appropriate bacterial and fungal cultures of any tissue

Fig. 148.9 Harvesting and placement of a free cartilage graft. A The posterior conchal bowl donor site has been incised to the level of the perichondrium. The desired length of cartilage was incised with the scalpel, and a second incision made parallel to the first to isolate a cartilaginous strip with its overlying perichondrium. **B** The ends of the cartilaginous strip with its overlying perichondrium have been inserted into pockets undermined on either side of the recipient bed, such that the graft interlocks with its recipient bed on the left nasal ala. The graft is sutured to the underlying dermis with one 5-0 absorbable suture for additional security. **C** A full-thickness skin graft has been sutured into place over the free cartilage graft. **D.** Eight-week postoperative view of the full-thickness skin graft and underlying free cartilage graft on the left nasal ala. The alar rim remains in perfect alignment.

exudate should be obtained if infection is suspected. Empiric therapy with quinolone antibiotics should be initiated, and modified as sensitivities dictate. When prophylactic antibiotics and appropriate operative technique are used, the risk of suppurative chondritis is extremely low[52].

Postoperative tenderness, swelling and erythema may herald inflammatory chondritis or perichondritis, which should be treated with cool compresses and nonsteroidal anti-inflammatory drugs for several weeks or even months postoperatively.

Later complications may include graft resorption, displacement or deformation after placement, and extrusion. Surgical revision may be required if these complications occur. Auricular and nasal recipient sites are subject to trauma and are therefore at increased risk of graft displacement and resorption. Every effort should therefore be made intraoperatively to utilize grafts of sufficient thickness and stiffness to resist the forces of trauma and wound contracture, and to anchor these grafts so as to maximize their stability.

Future Trends

While autologous cartilage is considered to be the optimal grafting material due to its pliability, accessibility, and ease of harvesting under local anesthesia, its supply may be limited, and harvesting may entail additional morbidity for the patient. Other implantable materials for nasal reconstruction have been investigated, including porous, high-density polyethylene implants[53]. Such implants have shown the ability to heal by second intention and support skin grafts when used to reconstruct auricular cartilage in rabbits[53]. They were also well tolerated as replacements for native cartilage in patients requiring rhinoplasty or nasal reconstruction[54].

Tissue engineering has been used to generate autologous cartilage implants to fill defects of the nose or outer ear[55]. Chondrocytes can be stimulated with growth factors to increase their proliferative rate and extracellular matrix production. Such chondrocytes, when implanted on a resorbable synthetic scaffold, can thereby be induced to produce three-dimensional aggregates of cartilage. In a recent study, collagen lattices containing cultured chondrocytes implanted into rabbit auricular cartilage generated new cartilage within 5 weeks[56]. *In vitro* engineering of human cartilage could be the ideal replacement method, without the risk of infection and with the possibility of reconstructing large defects with different configurations[55]. These and newer implantable materials will, over time, become increasingly available, and will certainly be useful to dermatologic surgeons who perform nasal reconstruction.

CONCLUSIONS

A working knowledge of the indications, techniques, donor site considerations, and postoperative complications of all types of skin grafts is necessary for soft tissue reconstruction. As the incidence of skin cancer continues to rise, increasing numbers of patients are likely to require reconstructive procedures to repair their defects. Furthermore, split-thickness skin grafting for lower extremity ulcers is an effective, reasonable treatment for patients with refractory leg ulcers. With proper defect assessment, reconstructive planning, and attention to detail preoperatively, intraoperatively and postoperatively, optimal cosmetic and functional results using grafting techniques can be achieved. A thorough understanding of skin grafting is invaluable for all physicians performing reconstructive surgery.

REFERENCES

1. Hauben DJ, Baruchin A, Mahler A. On the history of the free skin graft. Ann Plast Surg. 1982;9:242–5.
2. Ratner D. Skin grafting. Semin Cutan Med Surg. 2003;22:295–305.
3. Adams DC, Ramsey ML. Grafts in dermatologic surgery: review and update on full- and split-thickness grafts, free cartilage grafts and composite grafts. Dermatol Surg. 2005;31:1055–67.
4. Smahel J. The healing of skin grafts. Clin Plast Surg. 1977;4:409–24.
5. Goldminz D, Bennett RG. Cigarette smoking and flap and full-thickness graft necrosis. Arch Dermatol. 1991;127:1012–15.
6. Walden JL, Garcia H, Hawkins H, et al. Both dermal matrix and epidermis contribute to an inhibition of wound contraction. Ann Plast Surg. 2000;45:162–6.
7. Gloster HM Jr. The use of full-thickness skin grafts to repair nonperforating nasal defects. J Am Acad Dermatol. 2000;42:1041–50.
8. Rohrer TE, Dzubow LM. Conchal bowl skin grafting in nasal tip reconstruction: clinical and histologic evaluation. J Am Acad Dermatol. 1995;33:476–81.
9. Zitelli JA. Burow's grafts. J Am Acad Dermatol. 1987;17:271–9.
10. Krishnan R, Hwang L, Orengo I. Dog-ear graft technique. Dermatol Surg. 2001;27:312–14.
11. Kaufman AJ. Adjacent-tissue skin grafts for reconstruction. Dermatol Surg. 2004;30:1349–53.
12. Wang Q, Cai M, Wu YL, Zhang GC. Mathematical guide to minimize donor site in full-thickness skin grafting. Dermatol Surg. 2009;35:1364–7.
13. Hill TG. Contouring of donor skin in full-thickness skin grafting. J Dermatol Surg Oncol. 1987;13:883–8.
14. Mellette JR Jr, Swinehart JM. Cartilage removal prior to skin grafting in the triangular fossa, antihelix, and concha of the ear. J Dermatol Surg Oncol. 1990;16:1102–5.
15. Larson PO, Ragi G, Mohs FE, Snow SN. Excision of exposed cartilage for management of Mohs surgery defects of the ear. J Dermatol Surg Oncol. 1991;17:749–52.
16. Craven NM, Telfer NR. An open study of tissue adhesive in full-thickness skin grafting. J Am Acad Dermatol. 1999;40:607–11.
17. Orengo I, Lee MW. Surgical pearl: the "unsuture" technique for skin grafts. J Am Acad Dermatol. 1998;38:758–9.
18. Langtry JA, Kirkham P, Martin IC, Fordyce A. Tie-over bolster dressings may not be necessary to secure small full thickness skin grafts. Dermatol Surg. 1998;24: 1350–3.
19. Adams DC, Ramsey ML, Marks VJ. The running bolster suture for full-thickness skin grafts. Dermatol Surg. 2004;30:92–4.
20. Brady JG, Grande DJ, Katz AE. The purse-string suture in facial reconstruction. J Dermatol Surg Oncol. 1992;18:812–16.
21. Halpern ME, Adams C, Ratner D. Galeal hinge flaps: a useful technique for immediate repair of scalp defects extending to periosteum. Dermatol Surg. 2009;35:1127–30.
22. Silapunt S, Peterson SR, Alam M, Goldberg LH. Clinical appearance of full-thickness skin grafts of the nose. Dermatol Surg. 2005;31:177–83.
23. Robinson JK, Dillig G. The advantages of delayed nasal full-thickness skin grafting after Mohs micrographic surgery. Dermatol Surg. 2002;28:845–51.
24. Meyers S, Rohrer T, Grande D. Use of dermal grafts in reconstructing deep nasal defects and shaping the ala nasi. Dermatol Surg. 2001;27:300–5.
25. Draper BL, Wentzell JM. The "drumhead" graft repair of deep nasal alar defects. Dermatol Surg. 2007;33:17–22.
26. Gloster HM Jr, Brodland DG. The use of perichondrial cutaneous grafts to repair defects of the lower third of the nose. Br J Dermatol. 1997;136:43–6.
27. Thibault MJ, Bennett RG. Success of delayed full-thickness skin grafts after Mohs micrographic surgery. J Am Acad Dermatol. 1995;32:1004–9.
28. Nehal KS, Levine VJ, Ross B, Ashinoff R. Comparison of high-energy pulsed carbon dioxide laser resurfacing and dermabrasion in the revision of surgical scars. Dermatol Surg. 1998;24:647–50.
29. Otley CC, Gaynor SM, Ahmed I, et al. Preoperative and postoperative topical tretinoin on high-tension excisional wounds and full-thickness skin grafts in a porcine model: a pilot study. Dermatol Surg. 1999;25:716–21.
30. Stephenson AJ, Griffiths RW, La Hausse-Brown TP. Patterns of contraction in human full thickness skin grafts. Br J Plast Surg. 2000;53:397–402.
31. Harrison A, MacNeil S. The mechanism of skin graft contraction: an update on current research and potential future therapies. Burns. 2008;34:153–63.
32. Can Z, Ercocen AR, Apaydin I, et al. Tissue engineering of high density porous polyethylene implant for three-dimensional reconstruction: an experimental study. Scand J Plast Reconstr Surg Hand Surg. 2000;34:9–14.
33. Glogau RG, Stegman SJ, Tromovitch TA. Refinements in split-thickness skin grafting technique. J Dermatol Surg Oncol. 1987;13:853–8.
34. James JH, Watson AC. The use of Opsite, a vapour permeable dressing, on skin graft donor sites. Br J Plast Surg. 1975;28:107–10.
35. Rakel BA, Bermel MA, Abbott LI, et al. Split-thickness skin graft donor site care: a quantitative synthesis of the research. Appl Nurs Res. 1998;11:174–82.
36. Nappi JF, Falcone RE, Ruberg RL. Meshed skin grafts versus sheet skin grafts on a contaminated bed. J Dermatol Surg Oncol. 1984;10:380–1.
37. Horch RE, Debus M, Wagner G, Stark GB. Cultured human keratinocytes on type I collagen membranes to reconstitute the epidermis. Tissue Eng. 2000;6: 53–67.
38. Suzuki S, Shin-ya K Kawai K, Nishimura Y. Application of artificial dermis prior to full-thickness skin grafting for resurfacing the nose. Ann Plast Surg. 1999;43: 439–42.
39. Metcalfe AD, Ferguson MW. Bioengineering skin using mechanisms of regeneration and repair. Biomaterials. 2007;28:5100–3.
40. Otley CC, Sherris DA. Spectrum of cartilage grafting in cutaneous reconstructive surgery. J Am Acad Dermatol. 1998;39:982–92.
41. Haas AF, Glogau RG. A variation of composite grafting for reconstruction of full-thickness nasal alar defects. Arch Dermatol. 1994;130:978–80.
42. Adams C, Ratner D. Composite and free cartilage grafting. Dermatol Clin. 2005;23:129–40, vii.
43. Geyer AS, Pasternack F, Adams C, Ratner D. Use of a skin-fat composite graft to prevent alar notching: an alternative to the delayed postoperative repair. Dermatol Surg. 2005;31:602–7.
44. Field LM. Nasal alar rim reconstruction utilizing the crus of the helix, with several alternatives for donor site closure. J Dermatol Surg Oncol. 1986;12:253–8.
45. Ratner D, Katz A, Grande DJ. An interlocking auricular composite graft. Dermatol Surg. 1995;21:789–92.
46. Weisberg NK, Becker DS. Repair of nasal ala defects with conchal bowl composite grafts. Dermatol Surg. 2000;26:1047–51.
47. Haug MD, Rieger UM, Gubisch W. Managing the ear as a donor site for composite graft in nasal reconstruction: update on technical refinements and donor site management in 110 cases. Ann Plast Surg. 2009;63:171–5.
48. Albertini JG, Ramsey ML. Surgical pearl: delayed intranasal knot tying for composite grafts of the ala. J Am Acad Dermatol. 1998;39:787–8.
49. Otley CC. Alar batten cartilage grafting. Dermatol Surg. 2000;26:969–72.
50. Byrd DR, Otley CC, Nguyen TH. Alar batten cartilage grafting in nasal reconstruction: functional and cosmetic results. J Am Acad Dermatol. 2000;43:833–6.
51. Boccieri A, Marano A. The conchal cartilage graft in nasal reconstruction. J Plast Reconstr Aesthet Surg. 2007;60:188–94.
52. Kaplan AL, Cook JL. The incidences of chondritis and perichondritis associated with the surgical manipulation of auricular cartilage. Dermatol Surg. 2004;30:58–62; discussion 62.
53. Williams JD, Romo T III, Sclafani AP, Cho H. Porous high-density polyethylene implants in auricular reconstruction. Arch Otolaryngol Head Neck Surg. 1997;123:578–83.
54. Naumann A, Rotter N, Bujia J, Aigner J. Tissue engineering of autologous cartilage transplants for rhinology. Am J Rhinol. 1998;12:59–63.
55. Sterodimas A, DeFaria J, Correa WE, Pitangiy I. Tissue engineering in plastic surgery: an up-to-date review of the current literature. Ann Plast Surg. 2009;62:97–103.
56. Sanz E, Penas L, Lequerica JL. Formation of cartilage in vivo with immobilized autologous rabbit auricular cultured chondrocytes in collagen matrices. Plast Reconstr Surg. 2007;119:1707–13.

149 Nail Surgery

Phoebe Rich

Chapter Contents

Surgical anatomy of the nail unit 2435
Patient preparation and preoperative evaluation 2436
Instruments for nail surgery 2437
Nail avulsion and nail matrix exploration 2437
Nail excisions and biopsies 2438
Dressings and postoperative care following nail surgery 2441
Special situations in nail surgery 2441
Complications of nail surgery 2444

Key features

- A thorough understanding of the anatomy and physiology of the nail unit is crucial to performing successful nail surgery
- The nail matrix forms the nail plate; damage to the nail matrix (including from surgical procedures) can cause permanent nail dystrophy
- There is no subcutaneous tissue in the nail unit, so the dermis of the nail bed sits on the periosteum of the distal digit
- Preoperative evaluation prior to nail surgery is essential and should include a radiograph of the digit when a subungual tumor is suspected

INTRODUCTION

Nail surgery allows the dermatologist to diagnose clinically ambiguous nail lesions or dystrophies, remove nail tumors, and alleviate pain caused by ingrown or traumatized nails. The major goal of nail surgery is to achieve the desired diagnosis or outcome by performing the procedure safely with minimal pain and scarring[1]. Because dermatologists are the physicians who understand and manage nail disorders, they are well suited to perform nail surgery. A solid grasp of the anatomy and physiology of the nail unit is a prerequisite for successful nail surgery. Other necessities for an optimal outcome include a well-prepared patient, adequate anesthesia and hemostasis, and proper technique (Table 149.1).

SURGICAL ANATOMY OF THE NAIL UNIT

The structures that comprise the nail unit are the nail matrix, the proximal and lateral nail folds, the hyponychium and the nail bed (Fig. 149.1). The nail matrix is the most vital component of the nail unit, because it is the germinative epithelium from which the nail plate is generated via differentiation of matrix keratinocytes. The distal third of the nail matrix is sometimes visible through the proximal nail plate as the white half-moon-shaped structure called the lunula. Whereas the proximal nail matrix forms the superficial (dorsal) surface of the nail plate, the distal nail matrix forms the inferior (ventral) portion of the nail plate (Fig. 149.2). This observation is key to understanding the clinical presentations of certain pathologic processes and nail tumors and it provides a rationale for basic nail surgery principles and techniques. For example, given that damage to the matrix can cause permanent nail dystrophy, distal matrix surgery is preferable to proximal matrix surgery, since a defect due to the former would be less obvious on the undersurface of the nail plate[2,3].

The nail bed, sometimes referred to as the sterile matrix, extends from the distal lunula to the hyponychium. Its rich vascular supply results in the pink color of the nail bed that is seen through the translucent nail plate. The nail bed is composed of longitudinal ridges and grooves, which explains clinical phenomena such as the longitudinal orientation of splinter hemorrhages. While the bulk of the nail plate is formed by the nail matrix, the nail bed probably contributes a few epithelial cells to the undersurface of the nail plate, which helps to explain the tight adhesion of the nail plate to the nail bed. Surgery of the nail bed rarely leads to permanent dystrophy of the nail apparatus, but it may result in mild onycholysis. An important feature of the nail bed is that there is no subcutaneous tissue beneath it. The dermis of the nail bed sits directly on the periosteum of the distal digit. The lack of subcutaneous tissue in the nail unit explains why nail surgical specimens extend to the level of the periosteum.

The proximal and lateral nail folds support and protect the nail plate. The end product of the proximal nail fold is the cuticle, which adheres tightly to the proximal nail plate and seals and protects the nail unit from environmental pathogens and irritants. The insertion of the extensor tendon of the digit is approximately 12 mm proximal to the cuticle, and is usually proximal to the surgical field in all but the most extensive nail surgery. The proximal and lateral nail folds are collectively called the paronychium. The perionychium consists of the paronychium plus the hyponychium and nail bed[4].

The hyponychium is located under the free edge of the nail plate. It begins at the most distal part of the nail bed (in the region just proximal to the distal groove) and then becomes contiguous with the volar skin of the digit. Like the cuticle, the hyponychium also functions to seal and protect the nail unit from environmental factors. Disruption of the hyponychium by trauma or disease can result in onycholysis with subsequent bacterial and fungal infections.

Sensory Nerves and Anesthesia of the Nail Unit

For patient acceptance of nail surgery, complete anesthesia and a resultant pain-free procedure are mandatory. The sensory nerves to the nail course along the lateral sides of the digit in close approximation to the digital arteries. Anesthesia can be administered as a digital block and/or a wing block. In a digital block, 2–3 ml of 1% or 2% plain lidocaine (without epinephrine [adrenaline]) is injected superficially into the base of the digit on both lateral sides with a 30-gauge needle (Fig. 149.3). To prevent vasospasm and tamponade of the vessels, the volume of local anesthetic should be less than 1.0–1.5 ml on each side of the digit.

An adjunctive or alternative anesthetic approach is a paronychial or wing block in which plain lidocaine is injected into the proximal and lateral nail folds. A small volume of anesthetic is injected, which blanches the skin of the nail fold and may help somewhat with hemostasis. The wing block has several advantages over the digital ring block: (1) the onset of action is more rapid; (2) less volume is required; (3) the injection is more comfortable; and (4) if using epinephrine, there is minimal risk of intra-arterial injection, due to the much smaller diameter of the distal vessels. It is sometimes useful to inject a long-acting anesthetic (e.g. bupivacaine, ropivacaine) around the nail unit at the end of the procedure to provide more prolonged anesthesia, sometimes lasting up to 12 hours.

Although the dogma in nail surgery has been to avoid the use of epinephrine in digital blocks, several recent comprehensive reviews describe the safe use of lidocaine with epinephrine in the digits of

PREREQUISITES FOR SUCCESSFUL NAIL SURGERY OR NAIL BIOPSY
1. Understanding of nail anatomy and physiology
2. Proper patient selection and preparation
3. Adequate anesthesia
4. Hemostasis
5. A nail condition that has eluded diagnosis by routine clinical inspection, history, diagnostic (radiologic) imaging and/or microbiologic evaluation
6. A dermatopathologist who is familiar with the histopathologic idiosyncrasies of the nail unit

Table 149.1 Prerequisites for successful nail surgery or nail biopsy.

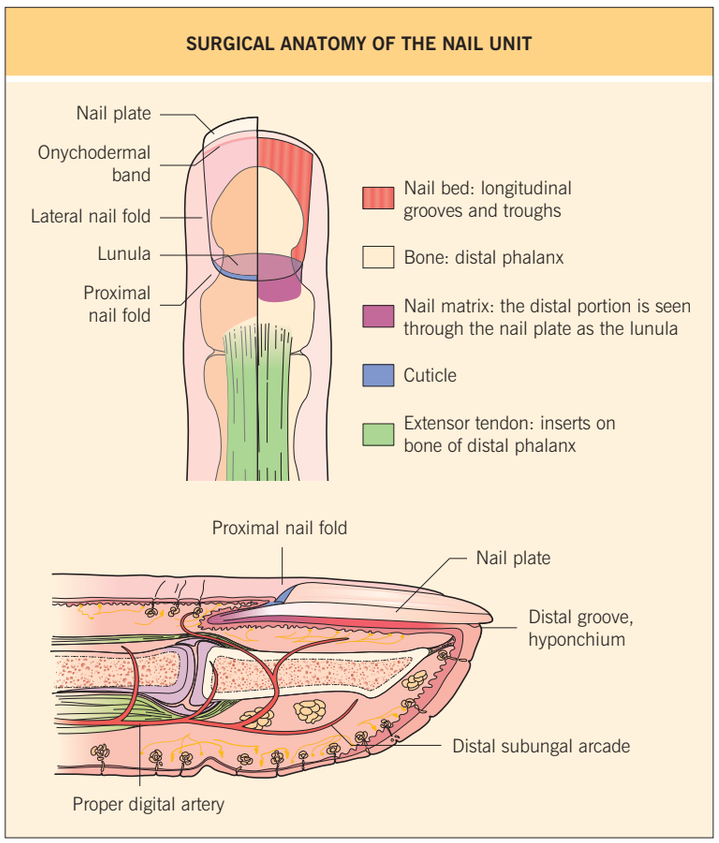


Fig. 149.1 Surgical anatomy of the nail unit.

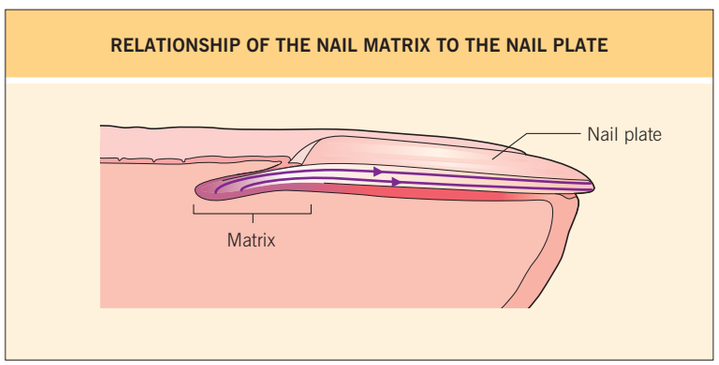


Fig. 149.2 Relationship of the nail matrix to the nail plate. The proximal part of the nail matrix forms the superficial (dorsal) nail surface; the distal portion of the matrix forms the inferior (ventral) portion of the nail plate. Hence, surgery to the distal matrix is preferable to surgery of the proximal matrix, because, if there is scarring, that associated with the former will be on the undersurface of the nail plate and therefore less obvious.

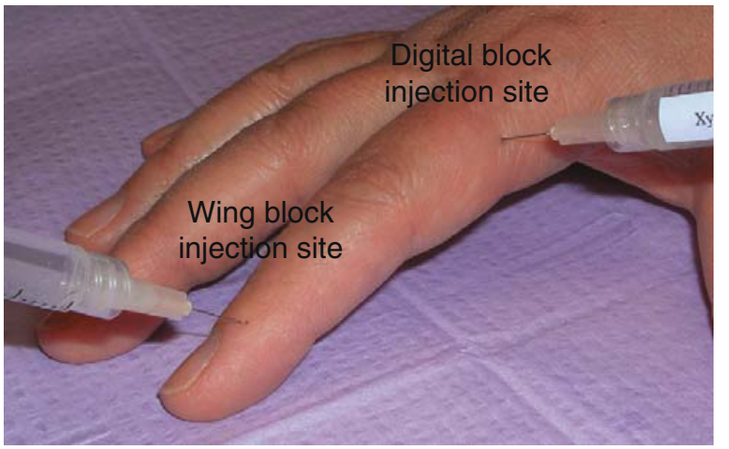


Fig. 149.3 The location of lidocaine injections for a wing block and a digital block.

patients with no history of vascular disease[5]. The author has safely performed over 200 nail procedures using a wing block and a low concentration of epinephrine (1 : 200 000), obtained by mixing lidocaine with 1 : 100 000 epinephrine and lidocaine without epinephrine in a 1 : 1 ratio. Within 15 minutes there is excellent anesthesia and usually no need for a tourniquet for hemostasis. Some nail surgeons use a 1 : 4 ratio (final concentration of epinephrine 1 : 500 000), but then there is less hemostasis and a tourniquet may be required.

Vascular Supply of the Nail Unit and Hemostasis

The proper and lateral digital arteries course along the lateral sides of the digit and represent the main blood supply to the nail unit. The proper digital arteries give rise to branches that form the superficial arcade supplying the nail fold and matrix, as well as a second arcade that feeds the bone, distal nail bed, and hyponychial area (see Fig. 149.1).

Hemostasis is necessary to adequately visualize the surgical field. Although a tourniquet is often not necessary for nail surgery, when one is used, it should be a flat Penrose drain so as not to be too constrictive. Rubber bands should not be used as tourniquets because of the potential for lateral digital nerve damage, and any tourniquet should not be left in place for more than 15 minutes. An assistant applying pressure to the sides of the digit during the procedure usually achieves hemostasis without resorting to a tourniquet. A sterile glove on the patient's hand is sometimes used to impart a sterile field while also providing hemostasis. The tip of the glove finger is removed, and the remainder is rolled back past the affected nail to the base of the finger to act as a gentle tourniquet and to provide a sterile field for the nail surgery (Fig. 149.4).

PATIENT PREPARATION AND PREOPERATIVE EVALUATION

A well-prepared patient facilitates a successful surgical procedure (see Ch. 151). A complete history and appropriate clinical examination of the nail unit are paramount. The history should include prescribed medications (especially anticoagulants and antiplatelet agents) and supplements (see Ch. 133) in addition to a review of systems, with particular attention to the presence or absence of diabetes mellitus, autoimmune connective tissue diseases, peripheral vascular disease, cutaneous conditions with nail manifestations, and prosthetic valves and joints (Table 149.2). Physical examination should include inspection of all 20 nails as well as palpation of peripheral pulses. Appropriate laboratory tests for bacteria, fungi and/or viruses should be obtained when there is a possibility of infection. Radiographic studies to define space-occupying lesions and underlying bony defects are often necessary prior to nail surgery. A full "procedure, alternatives and risks" (PAR) discussion should include the possibility of permanent nail dystrophy, bleeding, pain and infection. While not mandatory, clinical photographs of the preoperative nail are usually worthwhile. The digit is then washed with alcohol or a surgical soap such as chlorhexidine (e.g. Hibiclens®) or

Fig. 149.4 Sterile glove used as a tourniquet and sterile field. The tip of the glove finger is removed, then the remainder is rolled back to the base of the finger.

Fig. 149.5 Instruments used in nail surgery. Freer septum elevator, English nail splitter, and double-action nail clipper (left to right).

PATIENT EVALUATION PRIOR TO NAIL SURGERY
HISTORY

• Medical history
  • Diabetes mellitus
  • Peripheral vascular disease
  • Autoimmune connective tissue disease
  • Raynaud's phenomenon
  • Arthritis
  • Prosthetic joints or heart valves
  • Bleeding diathesis
• Drug history
  • Allergies
  • Use of anticoagulants, antiplatelet agents (salicylates, clopidogrel, NSAIDs)
  • Use of herbal medicine
• Cutaneous history
  • History of the nail condition (duration, progression, exposures, trauma)
  • Psoriasis, lichen planus or other cutaneous disorders with nail manifestations
  • Previous malignancies
  • Previous fungal, bacterial and/or viral cultures or diagnostic tests
  • Occupation and hobbies

EXAMINATION
• All 20 nails, good lighting and magnification • Mucous membranes, hair and scalp • Pertinent cutaneous examination • Peripheral pulses, especially in toenail surgery
LABORATORY TESTS
• Radiography, diagnostic imaging studies (e.g. MRI) • Mycology, microbiology or virology studies
"PROCEDURE, ALTERNATIVES AND RISKS" DISCUSSION (SEE TABLE 149.6)
• Possibility of permanent dystrophy • Possibility of no diagnosis • Length of time for nail to regrow • Bleeding, infection and pain, as with any surgery

Table 149.2 Patient evaluation prior to nail surgery.

povidone-iodine (e.g. Betadine®) and sterilely draped. A sterile glove on the patient's hand can also provide a sterile field (see Fig. 149.4)[6].

INSTRUMENTS FOR NAIL SURGERY

Most of the instruments used in nail surgery are standard instruments used in cutaneous surgery. However, there are several special instruments that can make nail surgery easier (Fig. 149.5). The Freer septum elevator is an instrument with thin curved blades that facilitates atraumatic nail avulsion. An English nail splitter has a cutting blade opposed to a flat anvil-like surface that facilitates partial longitudinal nail avulsion. A double-action nail clipper is an indispensable instrument that easily cuts thickened nail plates.

NAIL AVULSION AND NAIL MATRIX EXPLORATION

Nail avulsion is the most basic procedure in nail surgery and is a prelude to additional surgical procedures that may need to be performed. Avulsion can be partial or total, and it involves removal of the nail by separating the nail plate from its attachments to the nail bed, matrix and nail folds. Avulsion of the nail plate facilitates examination of the nail bed and matrix area for tumors, and thus provides good exposure for subsequent excision or biopsy (Fig. 149.6). Partial

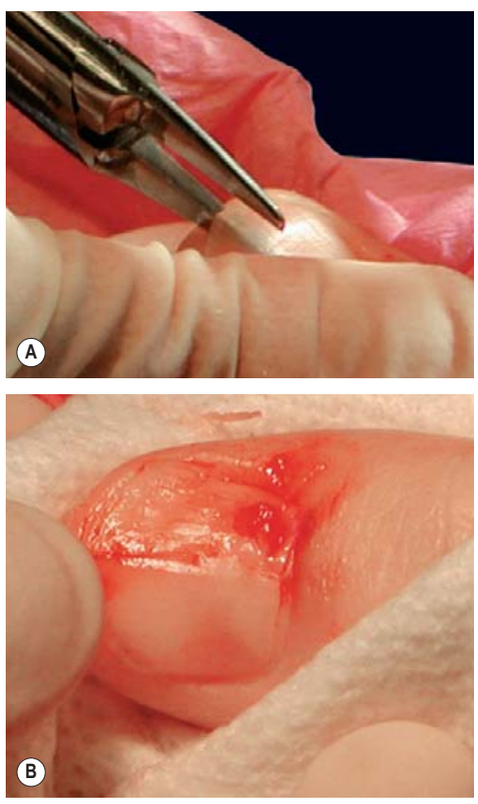


Fig. 149.6 An English nail splitter is used to divide the nail plate prior to partial longitudinal nail avulsion. A Note the flat, anvil-like blade of the English nail splitter that is inserted under the nail plate. **B** After partial nail avulsion, a glomus tumor is identified prior to excision.

Fig. 149.7 Distal nail plate avulsion. A The Freer septum elevator is inserted under the nail plate (from the hyponychium) in several parallel passes. **B** The loosened nail plate is grabbed with a hemostat and removed.

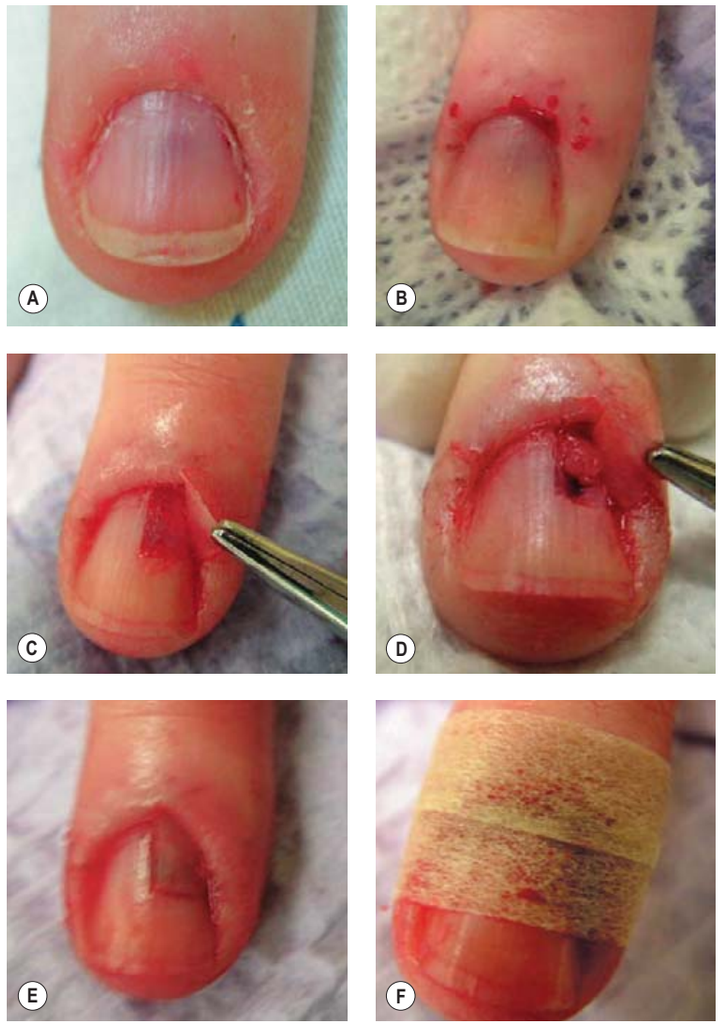


Fig. 149.8 Focal nail surgery with partial removal and then replacement of loosened nail plate. A Preoperatively, a glomus tumor is present beneath the proximal nail plate. **B** The nail unit after wing block anesthesia. **C** A cut in the nail plate allows a flap of nail to be reflected (with a hemostat), thereby exposing the subungual area. **D** The glomus tumor is removed, leaving a small defect. The flap of nail is replaced (**E**) and secured with Steri-Strips™ (**F**).

longitudinal avulsion is useful in the management of ingrown nails when surgical or chemical (phenol) matricectomy is performed (see below). In an acute bacterial infection of the nail unit, distal and/or lateral partial nail avulsion allows drainage of the subungual purulent material.

The basic principle in nail avulsion is to loosen the nail plate from its attachments to the underlying nail bed, matrix, and proximal and lateral nail folds. There are two approaches to nail avulsion: distal and proximal, although the latter is rarely used.

When performing a *distal nail plate avulsion*, after anesthesia, an instrument such as a Freer elevator or dental spatula is inserted under the free edge of the nail plate in a distal to proximal direction (Fig. 149.7A). As the instrument reaches the area of the matrix where the attachment of the nail plate is looser, the decrease in resistance is felt. One must anticipate that change, so that the instrument is not inadvertently jammed into the proximal groove and cul-de-sac with such force as to traumatize that area. It is preferable to insert the instrument from the hyponychium several times rather than to try to slide the instrument back and forth across the nail bed to loosen the nail plate. The attachment of the proximal and lateral nail folds to the nail plate is weak, so those areas are easily separated. Once the attachments to the nail plate are severed, the nail plate can be grasped by a hemostat on one lateral edge and rotated or pulled off the nail bed (Fig. 149.7B).

Partial nail plate avulsion is useful when the precise location of the lesion under the nail is known (see Fig. 149.6). In some cases it is possible to cut a portion of the overlying nail plate and reflect the partially loosened nail plate to expose the lesion so it can be excised (Fig. 149.8)[7]. The nail plate can then be repositioned to cover and protect the wound during the early stages of the healing process. While the piece of replaced nail plate does not reattach and will eventually be shed, it does provide protection and minimizes discomfort for the patient during the immediate postoperative period. The replaced nail plate can be secured with a suture or Steri-Strips™. Partial nail avulsion is also useful in the surgical approach to pigmented lesions within the nail matrix – the distal portion of the nail plate containing the pigmented band is left in place, serving as a marker for the appropriate location for the matrix biopsy (see Fig. 149.17).

The second fundamental nail surgical procedure is *nail matrix exploration*, which allows the clinician to examine the nail matrix and ventral surface of the nail fold for tumors and other pathology. Releasing incisions, about 5 mm in length, are made in the proximal nail fold beginning at the junction of the proximal and lateral nail folds and angling laterally and proximally (Fig. 149.9A). This allows the nail fold to be reflected so that the matrix can be inspected. Skin hooks or sutures, placed through the nail fold and retracted proximally, allow for exposure of the matrix for visual inspection as well as for subsequent biopsy or excision (Fig. 149.9B). At the end of the procedure, the fold is reflected back into place and secured with simple interrupted sutures or Steri-Strips™ (Fig. 149.9C).

NAIL EXCISIONS AND BIOPSIES

The techniques used for nail excision and/or biopsy depend upon the location of the pathology within the nail unit, the type of lesion, and the objective of the procedure. Useful nail surgery techniques are the punch biopsy (with or without prior nail avulsion), the tangential and elliptical excision in the nail bed or matrix, the lateral longitudinal combined biopsy/excision, and the chemical matricectomy. Surgical procedures should be oriented properly so that the nail unit heals in a manner that minimizes scarring and has the best functional and cosmetic outcome. In the nail bed, an excision is usually oriented along the longitudinal axis, whereas in the matrix the orientation of the excision is horizontal (Fig. 149.10). For biopsies of the nail bed, the size of the surgical specimen is determined by the type of lesion; as a general guideline, excisions of 3 mm or less are preferable and defects should be sutured when possible. Nail punch biopsy, elliptical excision and matricectomy will be discussed separately, based on location within the nail unit.

Fig. 149.9 Nail matrix exploration. A After nail plate avulsion, releasing incisions in the proximal nail fold (PNF) are made. **B** The PNF is retracted with skin hooks or sutures to allow visualization of the nail matrix. **C** The PNF is replaced and sutured or approximated with Steri-Strips™.

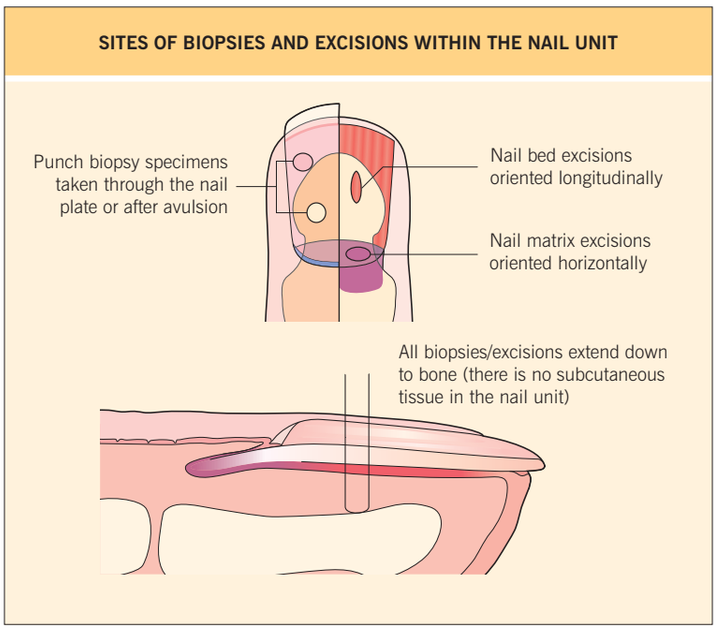


Fig. 149.10 Sites and orientations of biopsies and excisions within the nail unit.

Fig. 149.11 Nail fold biopsy of a space-occupying lesion. A Freer elevator is inserted beneath the proximal nail fold and a crescent of nail fold is removed.

Surgery of the Proximal Nail Fold

The epidermis of the nail folds is similar to that of other cutaneous sites, with two exceptions: the nail matrix lies beneath the proximal nail fold and should be protected, and the nail fold produces the cuticle that attaches to the nail plate. A space-occupying lesion in the proximal nail fold, such as a fibroma or cutaneous myxoid cyst, often presses on the underlying nail matrix and causes a characteristic longitudinal depressed defect in the nail plate immediately distal to its site (see Ch. 71). Lesions of the nail fold can be biopsied via shave, punch or incisional techniques or excised *en bloc*[8]. It is useful to insert a Freer elevator beneath the proximal nail fold in order to shield the matrix from inadvertent damage from the scalpel (Fig. 149.11). The majority of the time, the nail is not avulsed prior to nail fold surgery. A punch or shave biopsy of the nail fold is performed as for other cutaneous sites. Also, a crescent of nail fold can be removed and allowed to heal by second intention; this provides an aesthetically acceptable cosmetic result, with more of the nail plate and lunula visible. For best results with this latter technique (e.g. when excising a myxoid cyst), it is better to remove the entire width of the proximal fold in a symmetric manner to prevent distorted healing.

In the surgical approach to digital mucous cysts (cutaneous myxoid cysts), two more recently described techniques may be of value. Methylene blue can be injected into the cyst to help identify its communication with the joint space. In addition, a rotation flap elevation between the joint and the mucous cyst can disrupt the connection between the cyst and the joint space via the creation of a plate of subdermal scar tissue. Both appear to achieve long-term cure rates of approximately 90%.

Biopsy or Surgery of the Nail Bed

In pathologic conditions, the nail bed has a limited number of responses, including hyperkeratosis, onycholysis, erosion, dyschromia or a space-occupying mass. The similarity of clinical findings due to dissimilar nail conditions makes nail biopsy a useful diagnostic tool. Nail bed biopsy is a simple and safe technique that facilitates the diagnosis and even treatment of a variety of nail bed disorders (Table 149.3). The nail plate is usually avulsed prior to the nail bed biopsy; however, occasionally the biopsy is performed through the nail plate. When a punch biopsy is performed through the nail plate, a "double punch" technique is employed, with a trephine of a greater diameter used to make a larger hole in the nail plate, then a trephine with a smaller diameter used to remove the specimen. This facilitates non-traumatic retrieval of the specimen. When an elliptical excision of a nail bed lesion such as a glomus tumor is performed, the nail bed excision is oriented longitudinally (see Fig. 149.10). The area can be undermined at the level of the periosteum and absorbable polyglactin (e.g. Vicryl®) sutures placed to approximate the nail bed wound edges (Fig. 149.12). The nail bed usually heals with minimal scarring, although occasionally there may be onycholysis.

Nail Matrix Biopsy

Nail matrix biopsy has multiple indications, the most important of which is to exclude the diagnosis of subungual melanoma in a patient

CLINICAL FEATURES OF NAIL BED DISORDERS IN WHICH A BIOPSY MAY FACILITATE DIAGNOSIS AND SUBSEQUENT TREATMENT	
Diagnosis	**Clinical features**
MALIGNANT TUMORS OF THE NAIL BED	
Squamous cell carcinoma, Bowen's disease	Hyperkeratosis, dyschromia, onycholysis, destruction of the nail plate
Keratoacanthoma	Multiple or solitary, nail plate destruction, mass, erosion, granulation tissue, ± pain
Melanoma	Pigmentation of the nail bed, erosion, destruction of the nail plate; 25% are amelanotic
Metastatic carcinomas	Mass, pseudo-clubbing, nail dystrophy, dusky red color, ± pain
Kaposi sarcoma	Pigmentation, elevation, destruction of the nail plate
Basal cell carcinoma	Rare, variable clinical appearance
BENIGN TUMORS OF THE NAIL BED	
Pyogenic granuloma	Exuberant friable mass, needs to be distinguished from amelanotic melanoma
Glomus tumor	Spontaneous pain, blue–red mass
Epidermoid cyst	Mass, nail plate deformity
Fibroma	Mass, elevation, distortion of the nail (if presses on matrix, distal groove; if underneath nail plate, elevation of plate)
Exostosis	Mass, elevation of the nail plate, tenderness, secondary infection can occur
Osteochondroma	Enlargement of digit, elevation or destruction of the nail plate
Enchondroma	Mass, alteration of the nail plate, pain
INFECTIOUS CONDITIONS OF THE NAIL BED	
Onychomycosis	Hyperkeratosis, dyschromia, nail dystrophy, onycholysis
Warts	Verrucous mass, sometimes painful, nail plate deformity or destruction, must distinguish from verrucous or squamous cell carcinoma
Subungual scabies	Hyperkeratosis of hyponychium
INFLAMMATORY DERMATOSES INVOLVING THE NAIL BED	
Psoriasis	Onycholysis, hyperkeratosis, splinter hemorrhages, oil drop discoloration
Lichen planus	Violaceous discoloration, atrophy of nail bed; if nail matrix is involved, trachyonychia, hapalonychia (soft nails), dorsal pterygium
OTHER NAIL BED CONDITIONS	
Hemorrhage, trauma	Red–violet to black discoloration under nail plate; persistent or non-migrating discoloration needs to be distinguished from melanoma

Table 149.3 Clinical features of nail bed disorders in which a biopsy may facilitate diagnosis and subsequent treatment. *Adapted from Rich P. Nail biopsy: indications and methods. J Dermatol Surg Oncol. 1992;18:673–82.*

Fig. 149.12 Nail bed excision of a glomus tumor. A Elliptical excision is oriented longitudinally. **B** Absorbable sutures approximate the wound edges.

with abnormal pigmentation of the nail plate (see Ch. 71). A biopsy of a pigmented band (longitudinal melanonychia) must be taken from the nail matrix where the pigment is generated (see below). Of all the locations within the nail unit where a biopsy can be performed, it is the nail matrix that carries the greatest risk in terms of scarring. However, a nail matrix biopsy is a relatively safe and simple procedure when the principles of nail surgery are followed. With regard to nail anatomy and physiology, it is important to remember that the distal matrix forms the inferior (ventral) surface of the nail plate, and the proximal matrix forms its superficial (dorsal) surface (see Fig. 149.2). When there is a choice, the distal matrix is the preferred site for a matrix biopsy because any resultant split or defect will be hidden in the undersurface (ventral aspect) of the nail plate. Split nails that involve the dorsal surface are unsightly and easily traumatized as they catch on items such as clothing.

Prior to nail matrix biopsy, the nail plate is usually avulsed and the matrix exploration facilitated by releasing incisions that allow the proximal nail fold to be retracted (see Fig. 149.9). The nail plate avulsion can be total or partial. When an elliptical excision is performed within the nail matrix, the preferred orientation is horizontal (Fig. 149.13), and after undermining at the periosteal level, absorbable polyglactin (e.g. Vicryl®) interrupted sutures should be used to approximate the wound edges for the best cosmetic result. Of note, a punch biopsy that is 3 mm or smaller in the mid or distal matrix does not need to be sutured. Nail matrix excision and repair does result in a thinner nail plate because the thickness of the nail plate is to a large extent related to the length of the matrix.

For superficial lesions within the nail matrix, including the origin of broad pigmented bands, a tangential excision can be employed (Fig. 149.14)[9]. This technique, which is analogous to saucerization of a junctional melanocytic nevus elsewhere, allows a conservative margin yet minimizes the risk of scarring and subsequent permanent nail dystrophy. If an invasive process is suspected clinically, then an elliptical excision which extends to the level of the periosteum is more appropriate.

Great care must be exercised when handling the small fragile tissue specimen that is obtained from the nail biopsy. The tissue must be oriented and marked so that it is received by the pathologist in a state that allows for appropriate histologic evaluation. It is best to use surgical markers for the biopsy specimen so as to allow the examining pathologist to orient the epidermal surface properly. Undercutting the specimen avoids the crush artifact often caused by forceps[10].

Fig. 149.13 Nail dystrophy following biopsy of the nail matrix. The excision is oriented in a horizontal axis within the matrix and then sutured.

Fig. 149.14 Tangential excision (saucerization) of nail matrix for assessment of longitudinal melanonychia. This is performed when the pathologic process is thought to be superficial, as elsewhere on the body.

Lateral Longitudinal Nail Biopsy and Excision

Lateral longitudinal nail biopsy is a useful procedure where a length of the lateral nail unit is removed, including the nail matrix, nail fold, nail bed, nail plate and hyponychium. This procedure allows all these parts of the nail unit to be histologically examined simultaneously. It is useful for longitudinal pigmented bands of the lateral one-third of the nail and for inflammatory conditions in which the nail bed, nail matrix, nail plate, nail folds and hyponychium are involved concurrently. In this technique, the lateral one-third of the nail plate with its surrounding and supporting structures is removed *en bloc*. This is performed by incising through the nail plate and the matrix into the proximal nail fold and then laterally through the lateral nail fold up to and including the hyponychium (Fig. 149.15). The scalpel cuts through the nail unit down to the periosteum and the specimen is removed intact by loosening it from the underlying bone. The resultant defect is undermined and sutured or allowed to heal by second intention. The lateral groove heals with a narrower but cosmetically acceptable nail. However, retention of the lateral horn of the nail matrix can lead to a nail spicule which may become tender (Fig. 149.16).

Fig. 149.15 Lateral longitudinal nail biopsy and excision. The lateral portions of the nail unit are excised *en bloc* including the hyponychium, nail plate, nail bed, nail matrix and proximal nail fold.

Fig. 149.16 Complication of a lateral longitudinal biopsy and excision. This nail spicule (arrow) is due to incomplete lateral nail matrix resection. It can become tender. *Courtesy, Jean L Bolognia, MD.*

DRESSINGS AND POSTOPERATIVE CARE FOLLOWING NAIL SURGERY

Proper dressings can reduce postoperative pain and throbbing and minimize postoperative complications. A layer of antibiotic ointment is applied to the surgical site and covered with a non-stick dressing such as Vaseline™ gauze or Telfa®. A bulky gauze dressing is used for its absorptive and protective functions. Tube gauze such as Xspan® secures the dressing, and tape anchors the dressing to the skin. Given the likelihood of postoperative edema, the dressing should not be too tight and the tape should be non-constrictive. Patients should be instructed to keep the dressing dry. Preoperative nonsteroidal anti-inflammatory drugs (NSAIDs) are helpful in controlling mild discomfort and inflammation; narcotic analgesics are sometimes prescribed. Keeping the digit elevated higher than the heart will minimize painful throbbing. Bleeding into the dressing can result in the bandage sticking to the surgical site, in which case discomfort can be minimized by soaking the bandage to loosen it prior to removal.

SPECIAL SITUATIONS IN NAIL SURGERY

Nail Tumors

There are several nail unit tumors that are difficult to diagnose by clinical appearance alone (e.g. pyogenic granuloma, squamous cell carcinoma) and there are others where a preoperative radiograph points to the correct diagnosis (e.g. osteochondroma). These tumors are discussed in Chapter 71 and their treatment is outlined in Table 149.4.

Management of Malignant Neoplasms of the Nail Unit

Melanoma

Approximately 1–3% of all melanomas in Caucasians and 20% of melanomas in African-Americans occur within the nail unit[18]. Due to delays in diagnosis, subungual melanoma often has a poor prognosis.

NAIL UNIT TUMORS: RADIOGRAPHIC FINDINGS AND SURGICAL TREATMENTS

Tumor	Radiographic findings	Surgical treatment
Subungual exostosis	Radiopaque bone growth that is well circumscribed	Nail plate avulsion followed by surgical removal (can use bone rongeur)[11]
Keratoacanthoma	Cup-shaped radiolucent defect (early)	Surgical excision[12]
Enchondroma	Central round radiolucent defect	Surgical excision*
Squamous cell carcinoma	Radiolucent defect (late)	Microscopically controlled (Mohs) surgery[13–15]
Glomus tumor	Occasional radiolucent defect	Surgical excision (nail bed – longitudinal axis; nail matrix – horizontal axis)[16]
Myxoid cyst	Osteoarthritis	Cryosurgery, surgical excision (can use Freer elevator to protect matrix)[17]

*Performed primarily by other surgical subspecialists.

Table 149.4 Nail unit tumors: radiographic findings and surgical treatments.
Adapted from Rich P. Curr Prob Dermatol. 1999;11:161–208.

In many patients, melanoma of the nail unit is treated as a chronic paronychia, verruca, onychomycosis or an ingrown nail prior to biopsy and the correct diagnosis being established. A study by Glat et al.[19] reported a delay of nearly 2 years in the diagnosis of 22 subungual melanomas, resulting in 10- and 5-year survival rates of 13% and 30%, respectively[20].

The most reliable way to diagnose ungual melanoma is by histologic examination of the appropriate part of the nail matrix (or, rarely, the nail bed)[21]. Certain clinical features should raise one's suspicion of the possibility of melanoma. These clinical features are outlined in the mnemonic ABCDEF: *age* of the patient (older); *brown*/black and *breadth* greater than 3 mm; *change* in the band; *digit* involved (thumb, great toe); *extension* of pigment onto the nail fold(s) (Hutchinson's sign); and *family* history of melanoma[22]. Algorithms based on patient age, single or multiple bands, presence of Hutchinson's sign (see below), and ethnic background suggest a logical approach for diagnosis, but the bottom line is that in a Caucasian, a new, unexplained pigmented band in the nail should usually be biopsied, and the biopsy specimen should be taken from the nail matrix at the origin of the pigmented band (Fig. 149.17).

Dermoscopy may be helpful in evaluating pigmented lesions in the nail plate in two ways: (1) end-on dermoscopy of the distal nail plate to determine whether the pigment is dorsal versus ventral as a means of predicting the location of the pigment-producing cells (proximal and/or distal matrix; see Fig. 149.2); and (2) dermoscopic evaluation of the pigmented band itself. While dermoscopic features of pigmentation within the nail plate are not diagnostic[23], they may aid in guiding the decision to biopsy the nail matrix. Some authors believe that the most useful dermatoscopic feature is variability in the color, width and thickness of the lines that compose the pigmented band[24,25].

The clinical diagnosis of nail apparatus melanoma is difficult because there are many benign causes of longitudinal melanonychia (melanonychia striata), including trauma and drugs (see Ch. 71). Inactive

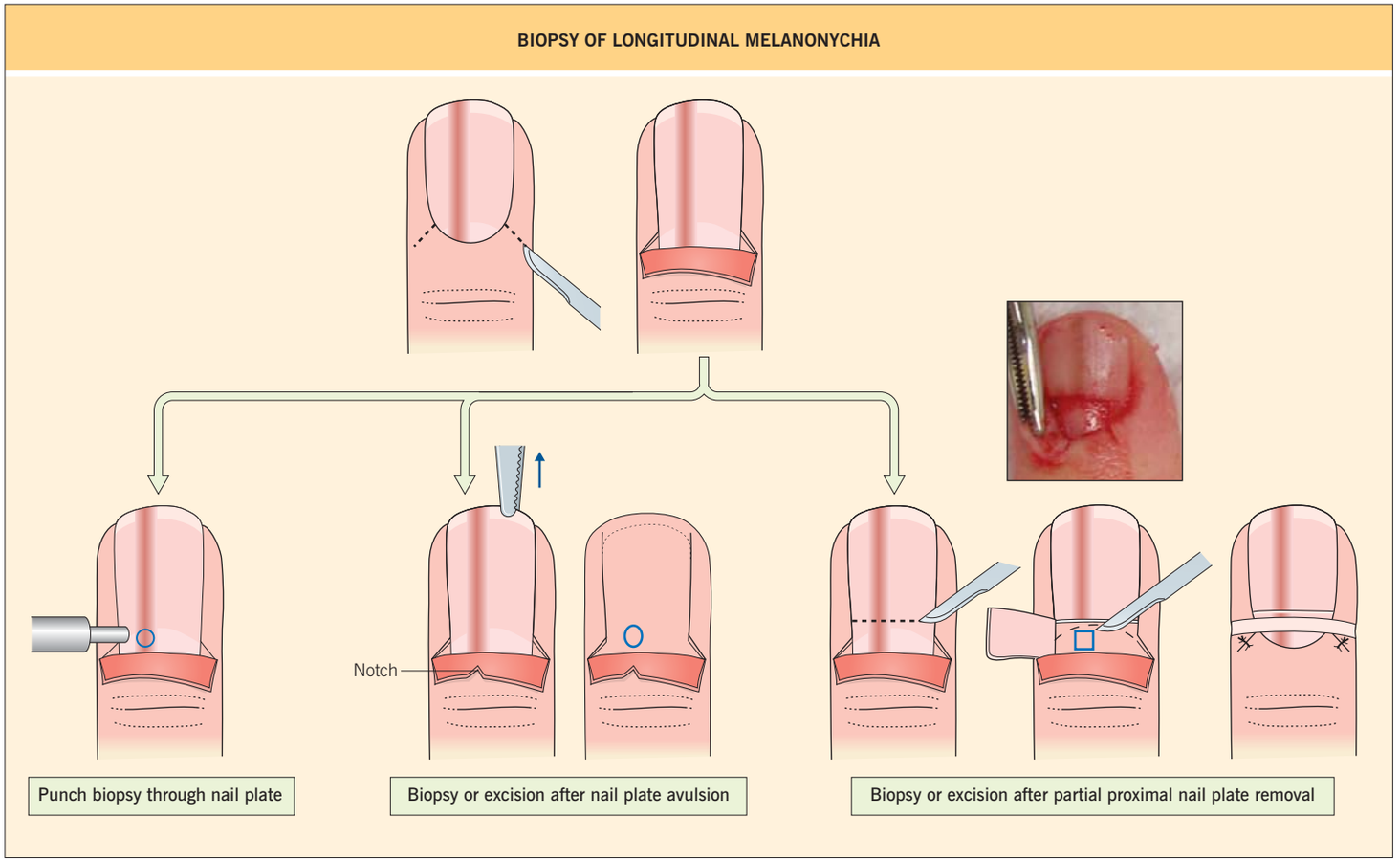


Fig. 149.17 Biopsy of longitudinal melanonychia. Histologic examination of the nail matrix can be achieved via three different initial approaches. A biopsy can be performed without removing the nail plate, following a complete nail plate avulsion or after removal of the proximal nail plate. Depending upon the lesion, a punch biopsy, an excision to the periosteum or a tangential excision (saucerization; see Fig. 149.14) can be performed.

melanocytes are present in the nail matrix and nail bed of Caucasians. When they are stimulated to proliferate or produce melanin, the pigment is incorporated into the nail plate and appears as a longitudinal brown or black band. Histologically, melanocyte activation is seen much more commonly than nevi; additional causes are listed in Table 71.2.

An additional consideration is that darkly pigmented individuals frequently have benign pigmented bands of the nail. In fact, over 90% of African-Americans have one or more longitudinal pigmented bands by the age of 50 years. Longitudinal melanonychia occurs in over 10–20% of Asians and the incidence is much higher in Hispanics and Middle Eastern populations[18]. Because the precise etiology of longitudinal melanonychia often cannot be ascertained from clinical inspection and history alone, subungual melanoma should always be included in the differential diagnosis and a biopsy of any suspicious lesion is mandatory[21].

The management of longitudinal melanonychia in children (<12 years of age) presents a particularly challenging problem. This is because nail unit melanomas are very rare in children, with reported cases primarily *in situ* and in children with more darkly pigmented skin[26]. As a result, there is controversy regarding whether all pigmented bands in children need to be biopsied, with some authors suggesting that it may be safe to observe some of these lesions[27]. Hopefully, additional studies examining the impact of color, width, change and dermoscopic features will provide guidance in the future.

Much discussion has centered around the presence or absence of Hutchinson's sign, which is the leaching of pigment into the perionychium in association with a melanoma. While at times helpful in confirming the clinical diagnosis of melanoma of the nail unit, it is an inconsistent feature and sometimes not particularly helpful. Melanoma can occur without Hutchinson's sign, and pseudo-Hutchinson's sign can occur in the absence of melanoma. Pseudo-Hutchinson's sign represents the presence or illusion of pigment in the perionychium and can be associated with a variety of disorders (Table 149.5).

ETIOLOGIES OF A PSEUDO-HUTCHINSON'S SIGN
PIGMENT PRESENT IN PARONYCHIUM
• Normal variant for Fitzpatrick skin phototypes IV, V and VI
• Laugier–Hunziker syndrome, Peutz–Jeghers syndrome
• Radiation exposure
• Malnutrition
• Minocycline, zidovudine (AZT)
• Postinflammatory
• Benign melanocytic nevi
• Regressing nevoid melanosis in childhood
• Subungual hematoma
PIGMENT VISIBLE THROUGH PARONYCHIUM
• Neoplasms (benign nevi, squamous cell carcinoma, basal cell carcinoma)
• Subungual hematoma

Table 149.5 Etiologies of a pseudo-Hutchinson's sign. *Adapted from Baran R. Hutchinson's sign: a reappraisal. J Am Acad Dermatol. 1996;34:87–90.*

Squamous cell carcinoma

Squamous cell carcinoma (SCC) is the most common malignancy of the nail unit. However, the associated clinical features can be nonspecific and tumors may mimic verrucae as well as dermatitis of the paronychium, or appear as onycholysis, painful erosions or nail dystrophy. The clinical presentation depends in part on the location, duration and extent of the SCC. Because nail unit SCC can imitate a variety of other nail disorders, a high index of suspicion is required. In a review of 35 histologically proven nail SCCs, the most common clinical diagnoses were verrucae, onychomycosis and longitudinal melanonychia, with only 25% of the tumors correctly diagnosed as SCC prior to biopsy[28]. Undiagnosed nail lesions or those that remain unresponsive to therapy for an extended period of time, including hyperkeratosis of the lateral groove or onycholysis with oozing, deserve a biopsy to exclude SCC. Predisposing factors are radiation exposure and infection with high-risk human papillomavirus (HPV) types 16 and 18[29]. While Mohs surgery is the treatment of choice for SCC of the nail apparatus[14,15], well-circumscribed SCC *in situ* of the nail bed can be treated via wide excision. Bony involvement, however, requires amputation. Lastly, even though SCC is the most common malignant tumor of the nail unit and there is often a long delay in diagnosis, it rarely metastasizes.

Management of Ingrown Toenails

An ingrown toenail occurs when a portion of the nail plate grows into the skin of the lateral nail groove. This sharp nail spicule acts as a foreign body, and secondary infection and formation of granulation tissue often ensue. Heredity, poorly fitting shoes and improper nail grooming can contribute to the development of ingrown toenails. Any associated infection should be treated and conservative measures tried first, such as placing lamb's wool between the nail plate and the lateral nail groove and growing longer toenails. Surgical management involves partial or total nail plate avulsion followed by chemical or surgical destruction of the lateral portion of the nail matrix.

Phenol matricectomy is used more commonly than surgical matricectomy, because it is easier to perform and causes less postoperative discomfort. The principle of phenol matricectomy is chemical destruction of the portion of the nail matrix associated with the ingrowing part of the nail. After anesthetizing the digit, the nail is partially or completely avulsed. Full-strength phenol (88%) is applied to the lateral part of the nail matrix with a small cotton swab fashioned from small wisps of cotton wound around a small wooden stick or toothpick. The swab is dipped into the phenol and the excess is drained off, and it is then carefully inserted under the nail fold in the desired area (Fig. 149.18). The swab is rotated over the surface of the matrix for 30 seconds and this is then repeated. A bloodless field is important for this part of the procedure.

Phenol is caustic and causes a chemical destruction of the matrix cells by denaturing proteins and preventing further nail growth in the treated area. The nail folds and nail bed should be protected from the phenol by applying a thin layer of petrolatum, and the phenol is neutralized with isopropyl alcohol or saline following the second pass. The digit is dressed with a bulky dressing which is changed the next day and the nail is soaked daily during the healing phase. There is generally

Fig. 149.18 Phenol matricectomy for ingrown toenails. A portion or all of the nail plate is avulsed (**A, B**) and full-strength phenol on a small cotton wisp on a small wooden stick is inserted under the nail fold and applied to the nail matrix (**C**).

Fig. 149.19 Long-term clinical appearance following total phenol matricectomy. Successful complete destruction of the toenail matrix. *Courtesy, Jean L Bolognia, MD.*

POSSIBLE COMPLICATIONS OF NAIL SURGERY
SHORT-TERM (WITHIN 14 DAYS OF SURGERY)
• Bleeding, pain, infection (including septic arthritis, osteomyelitis), pyogenic granuloma*
LONG-TERM (3 MONTHS OR LONGER AFTER SURGERY)
• Neurologic: paresthesias, reflex sympathetic dystrophy (very rare) • Scarring of the: matrix – nail plate dystrophy (splits, ridges, grooves, thinning†) proximal matrix – pterygium nail bed – permanent onycholysis nail fold – notch in the cuticle • Failure to remove the lesion of concern: recurrence of tumor (e.g. glomus, fibroma, onychomatricoma), confusing clinical picture (e.g. recurrent longitudinal melanonychia) • Retention of matrix (usually lateral horns): spicules of nail plate (inset) • Postinflammatory hyperpigmentation: more common in darkly pigmented individuals
*More common with toenails. †May lead to erythronychia.

Table 149.6 Possible complications of nail surgery. These are in addition to false-negative biopsies, i.e. the pathologic findings are not found within the biopsy specimen.

minimal postoperative pain with this simple, yet effective treatment. The recurrence rate is low, but occasionally nail spicules can be seen in an incomplete phenol matricectomy. Pincer nails, which are characterized by hypercurvature of both sides of the nail, can be managed with bilateral phenol matricectomy[30,31]. Onychogryphosis is sometimes treated with total phenol matricectomy (Fig. 149.19).

Surgical excision of the lateral nail matrix is sometimes performed for the treatment of ingrown toenails and pincer nails. This procedure involves reflecting the proximal nail fold and scalpel excision of the lateral portion of the nail matrix, including the lateral horn[32]. This technique is more complicated and has greater postoperative discomfort than phenol matricectomy and therefore is less frequently performed for simple ingrown nails.

COMPLICATIONS OF NAIL SURGERY

Nail surgery is safe and effective. However, as with all cutaneous surgical procedures, there are occasionally complications. A number of the complications are similar to those associated with other surgical procedures, e.g. bleeding, infection, pain and deformity. In addition, nail surgery can lead to pyogenic granuloma formation, reflex sympathetic dystrophy, and deep infections such as osteomyelitis and septic arthritis (Table 149.6). The most characteristic complication of nail surgery is nail plate deformity, which results from nail matrix damage. When care is taken and the principles of nail surgery are strictly followed, significant complications are rare.

REFERENCES

1. Rich P. Nail biopsy: indications and methods. Dermatol Surg. 2001;27:229–34.
2. Rich P, Scher RK. An Atlas of Diseases of the Nail. New York: Parthenon Publishing Group, 2003.
3. Fleckman P, Allan C. Surgical anatomy of the nail unit. Dermatol Surg. 2001;27;257–60.
4. Haneke E. Surgical anatomy of the nail apparatus. Dermatol Clin. 2006;24:291–6.
5. Denkler K. A comprehensive review of epinephrine in the finger: to do or not to do. Plast Reconstr Surg. 2001;108:114–24.
6. McGinness JL, Parlette HL 3rd. Versatile sterile field for nail surgery using a sterile glove. Dermatol Online J. 2005;11:10.
7. Collins SC, Cordova K, Jellinek NJ. Alternatives to complete nail plate avulsion. J Am Acad Dermatol. 2008;59:619–26.
8. Grover C, Bansal S, Nanda S, et al. En bloc excision of proximal nail fold for treatment of chronic paronychia. Dermatol Surg. 2006;32:393–8.
9. Jellinek N. Nail matrix biopsy of longitudinal melanonychia: diagnostic algorithm including the matrix shave biopsy. J Am Acad Dermatol. 2007:56:803–10.
10. Scher RK, Daniel CR (eds). Nails: Diagnosis, Therapy, Surgery, 3rd edn. Philadelphia: WB Saunders, 2005.
11. Carrol RE, Chance JT, Inan Y. Subungual exostosis of the hand. J Hand Surg Br. 1992;17:569–74.
12. Baran R, Gottman S. Distal digital keratoacanthoma: a report of 12 cases and review of the literature. Br J Dermatol. 1998;139:512–15.
13. Jellinek NJ. Primary malignant tumors of the nail unit. Adv Dermatol. 2005;21:33–64.
14. de Berker DA, Dahl MG, Malcolm AJ, Lawrence CM. Micrographic surgery for subungual squamous cell carcinoma. Br J Plast Surg. 1996;49:414–19.
15. Goldminz D, Bennett RG. Mohs micrographic surgery of the nail unit. J Dermatol Surg Oncol. 1992;18: 721–6.
16. Baran R, Dawber RPR, de Berker D, et al (eds). Diseases of the Nails and their Management, 3rd edn. London: Blackwell, 2001.
17. Salasche SJ. Myxoid cysts of the proximal nail fold: a surgical approach. J Dermatol Surg Oncol. 1984;10:35–9.
18. Baran R, Kechijian P. Longitudinal melanonychia (melanonychia striata): diagnosis and management. J Am Acad Dermatol. 1989;21:1165–75.
19. Glat PM, Spector JA, Roses DF, et al. The management of pigmented lesions of the nail bed. Ann Plast Surg. 1996;37:125–34.
20. Klausner JM, Inbar M, Gutman M, et al. Nail-bed melanoma. J Surg Oncol. 1987;34:208–10.
21. Daniel CR. Longitudinal melanonychia and melanoma: an unusual presentation. Dermatol Surg. 2001;27:294–5.
22. Levit EK, Kagen MH, Scher RK, et al. The ABC rule for clinical detection of subungual melanoma. J Am Acad Dermatol. 2000;42:269–74.
23. Di Chiacchio N, Hirata SH, Enokihara MY, et al. Dermatologists' accuracy in early diagnosis of melanoma of the nail matrix. Arch Dermatol. 2010;146:382–7.
24. Hirata SH, Yamada S, Almeida FA, et al: Dermoscopic examination of the nail bed and matrix. Int J Dermatol. 2006;45:28–30.
25. Tosti A, Piraccini BM, de Farias DC. Dealing with melanonychia. Semin Cutan Med Surg. 2009;28:49–54.
26. Iorizzo M, Tosti A, Di Chiacchio N, et al. Nail melanoma in children: differential diagnosis and management. Dermatol Surg. 2008;34:974–8.
27. Goettmann-Bonvallot S, André J, Belaich S. Longitudinal melanonychia in children: a clinical and histopathologic study of 40 cases. J Am Acad Dermatol. 1999;41:17–22.
28. Dalle S, Depape L, Phan A, et al. Squamous cell carcinoma of the nail apparatus: clinicopathological study of 35 cases. Br J Dermatol. 2007;156:871–4.
29. Guitart A, Bergfeld WF, Tuthill RJ, et al. Squamous cell carcinoma of the nail bed: a clinicopathological study of 12 cases. Br J Dermatol. 1990;123:215–22.
30. Haneke E. Surgical treatment of ingrowing toenails. Cutis. 1986;37:251–6.
31. Byrne DS, Caldwell D. Phenol cauterization for ingrowing toenails: a review of five years experience. Br J Surg. 1989;76:598–9.
32. Haneke E, Baran R. Nail ablation and matrixectomy. In: Krull EA, Zook EG, Baran R, Haneke E (eds). Nail Surgery: A Text and Atlas. Philadelphia: Lippincott Williams & Wilkins, 2001:83–8.

Proximal nail plate avulsion. The Freer elevator is inserted under the proximal portion of the nail plate **(A)** and rotated to lift the thickened nail plate from the nail bed **(B)**. This procedure is being done less frequently than in the past.

Mohs Surgery 150

Stephen N Snow and Juliet Gunkel

Chapter Contents

History ... 2445
Training in Mohs surgery ... 2446
Indications ... 2446
Contraindications ... 2450
Preoperative history and considerations ... 2451
Description of technique ... 2451
Variations/refinements/special situations ... 2451
Challenges and pitfalls of frozen sections ... 2455
Postoperative care ... 2455
Complications ... 2455

Synonyms: ■ Mohs micrographic surgery ■ Chemosurgery ■ Mohs chemosurgery (fresh tissue technique and fixed tissue technique)

Key features

- 100% microscopic tissue margin examination
- Highest evidence-based cure rate for cutaneous malignancies
- Precise excision of cancerous tissue
- Preservation of the maximum amount of non-cancerous tissue
- Total tissue control and precise mapping
- Same physician serves as both surgeon and pathologist
- Immediate re-excision of residual cancerous tissue as indicated
- Least complicated reconstruction possible, due to preservation of non-cancerous tissue

INTRODUCTION

Mohs micrographic surgery is a specialized method for the removal of skin cancer that combines surgery with pathology. It has an evidenced-based, 5-year cure rate of 99% for basal cell carcinoma (BCC)[1,2] and 94% for cutaneous squamous cell carcinoma (SCC)[3,4]. There are four major components: surgical excision, histopathologic examination, precise mapping and wound management.

The *surgical* component consists of removing a disc of tissue with a beveled surgical margin (see Fig. 150.6). The disc of tissue, or "layer", ensures that the entire 360° of tumor margin is circumferentially removed and examined. A beveled plane of excision allows the tissue specimen sides and bottom to be flattened completely into a single plane. The *histopathologic* component involves removing several thin sections from the bottom of the flattened cryopreserved tissue specimen and mounting them onto glass slides, followed by staining and microscopic examination for residual tumor. Precise *mapping* entails marking any residual tumor on the map or "graph" of the excision with the remaining positive area of tumor re-excised as indicated. This three-step process is then repeated until there is no residual tumor identified microscopically. During this procedure, the Mohs surgeon has complete control of the excised tissue, including laboratory processing and interpretation of the tissue sections, as well as precise mapping. In the fourth step, *wound management*, the tumor-free defect is surgically closed or allowed to heal by second intention.

Cost-effective Care and Indications

In addition to offering the highest cure rates for BCCs and SCCs, only cancerous tissue is removed during Mohs surgery, thereby preserving the maximum amount of normal tissue from a functional, aesthetic and reconstructive perspective. This is of particular importance for skin cancers near the orbit, nose, lips and ears. Mohs surgery is the preferred method of treatment for skin cancers that are clinically poorly defined, recurrent and/or have a higher risk of recurrence because of histologic features or anatomic location (e.g. ear, lips) (Table 150.1). In addition to the face, preservation of tissue also plays an important role in the anogenital region and digits.

The escalating cost of medical care has led to a paradigm shift away from evidence-based treatment (e.g. Mohs surgery) to cost-effective care (e.g. surgical excision). However, typically, the excised specimen is submitted to a pathology service for tissue processing and professional interpretation of histologic sections obtained via "bread-loafing" (Fig. 150.1). When the advantage of a higher cure rate and the costs of pathologic interpretation are considered, the cost differential becomes minimal. Concern has been raised regarding the overutilization of Mohs surgery, e.g. for small primary nodular BCCs or Bowen's disease of the trunk, but adherence to the indications listed in Table 150.1 should lead to its appropriate use.

HISTORY

Mohs surgery was developed by Dr Frederic E Mohs, whose pioneering work was performed at the University of Wisconsin-Madison in the 1930s and first published in 1941[5]. Dr. Mohs described his technique as chemosurgery. In his initial experiments, he observed that intralesional injection of 20% zinc chloride solution produced tumor necrosis with preservation of histology. His original clinical technique involved the application of a zinc chloride paste to cancerous tissue 24 hours prior to surgical removal of the tumor. The paste essentially fixed and isolated the tumor *in vivo*. Subsequently, the tumor was excised, sectioned into multiple pieces, and marked with colored dyes for orientation. A precise and detailed map of the excised tumor was created, including orientation relative to remaining tissue and anatomic landmarks. The specimen was flattened with physical pressure so that the histologic sections would encompass all lateral and deep margins. Serial tissue sections were cut on a freezing microtome, arranged on glass slides, and then stained. The precise location of any residual tumor seen on histologic examination was noted on the map. In cases with residual tumor at the margins, zinc chloride paste was re-applied to cancerous margins for 24 hours; then further tissue resection, processing and analysis were performed until complete tumor clearance was obtained.

With the original fixed tissue technique, the zinc chloride caused tissue necrosis, rendering wounds unacceptable for surgical reconstruction. From this limitation, Dr Mohs' second major innovation emerged – an objective analysis of second intention wound healing. Until that time, surgical dogma held that allowing wounds to heal by second intention (without closure) produced inferior cosmetic results compared to reconstruction, the surgeon's "first intention for healing". The acceptable, and, at times, superior, cosmetic outcome associated with second intention healing, particularly on concave surfaces, was documented by Dr Mohs, affording second intention healing its rightful place among valid reconstructive techniques.

INDICATIONS FOR MOHS SURGERY FOR NON-MELANOMA SKIN CANCER
TUMOR CHARACTERISTICS
• Recurrent • High-risk* anatomic location (periorbital, perinasal, periauricular, perioral, hair-bearing scalp) • Other anatomic sites where tissue preservation is imperative (digits, genitals) • Aggressive histologic subtype: – Morpheaform (sclerosing), micronodular or infiltrating BCC – High-grade, poorly differentiated and/or deeply penetrating SCC – Infiltrating, spindle cell SCC • Perineural invasion • Large size (>2 cm diameter) • Poorly defined clinical borders (lateral and/or deep) • Rapid growth
CHARACTERISTICS OF BACKGROUND SKIN
• Prior exposure to ionizing radiation • Chronic scar (Marjolin's ulcer) • Site of positive margins on prior excision
PATIENT CHARACTERISTICS
• Immunocompromised • Underlying genetic syndrome, e.g. xeroderma pigmentosum, nevoid BCC (Gorlin) syndrome, or Bazex–Dupré–Christol syndrome
*High risk for recurrence.

Table 150.1 Indications for Mohs surgery for non-melanoma skin cancer. BCC, basal cell carcinoma; SCC, squamous cell carcinoma. *Courtesy, Clark C Otley, MD.*

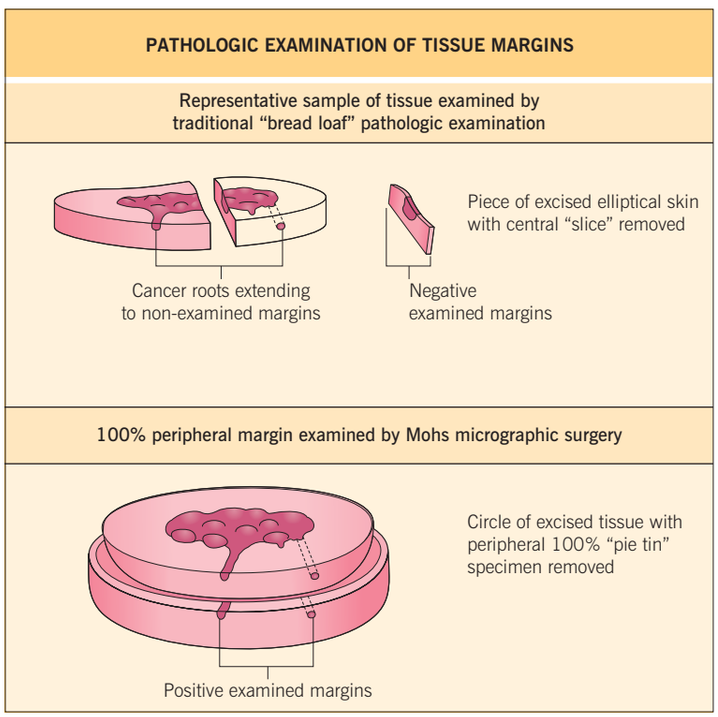


Fig. 150.1 Pathologic examination of tissue margins. Comparison of traditional "bread loaf" sections (0.01% of total margin examined) versus Mohs micrographic surgery (100% of total margins examined). *Courtesy, Clark C Otley, MD.*

Over 30 years ago, the tissue-processing procedure for Mohs surgery evolved from a zinc chloride-based, fixed tissue technique to a fresh-frozen tissue technique, an innovation initially performed by Dr Mohs in 1953 for eyelid cancers. In 1974, the fresh-frozen tissue technique was described in detail and popularized by Tromovitch and Stegman[6]. The fresh-frozen section technique eliminated the need for the escharotic zinc chloride paste, and it allowed complete tumor clearance with multiple resections in 1 day. Furthermore, without a zinc chloride-induced necrotic base, immediate surgical reconstruction could be performed when appropriate. The fresh tissue technique has become the standard of care for modern Mohs surgery.

TRAINING IN MOHS SURGERY

Training in Mohs surgery involves all aspects of tumor resection, tissue preparation and histologic interpretation. Additionally, the surgeon must have an excellent grasp of cutaneous and soft tissue anatomy, particularly of the face, both for excision of tumor and subsequent reconstruction. Knowledge of vascular, muscular and neural anatomy is essential, especially in "danger zones" of the face (see Ch. 142). The substantial clinical, surgical and pathologic training received in a dermatology residency provides the background for specialized training in Mohs surgery. Therefore, the technique has been primarily performed by dermatologists rather than surgeons who lack a background in pathology and other aspects of cutaneous oncology. In addition to the Mohs surgeon's involvement in all aspects of tissue handling, one of the unique advantages of Mohs surgical training is the degree of expertise in clinicopathologic correlation, which derives from dual training in both clinical and pathologic tumor assessment. After the tumor has been excised, the dermatologic surgeon must also have a mastery of soft tissue and cutaneous reconstruction, with an emphasis on both function and aesthetic restoration. While international training programs are of varying lengths, those in the US are one year in duration.

INDICATIONS

Most skin cancers are locally invasive, growing in a relentless and unpredictable manner. On the face, they can invade vital structures such as the eye, nose, lips and ears, leading to significant destruction. With time and neglect, metastasis (SCC and melanoma) may develop. That said, the majority of non-melanoma skin cancers are treated with superficial ablative techniques (e.g. electrodesiccation and curettage) because they are low-risk tumors and these techniques produce reasonable cure rates and are cost-efficient. In contrast, Mohs surgery is ideally suited for skin cancers at high risk of recurrence.

The definition of "high risk" for skin cancer depends on multiple factors, including the clinical and histologic characteristics of the tumor (see Ch. 108), the anatomic site, and history of prior treatments (see Table 150.1). Although these indications are not considered absolute, Mohs surgery is often preferred because of its high cure rate. A thorough review of indications for Mohs surgery can be found in *Guidelines of care for Mohs micrographic surgery*, issued by the American Academy of Dermatology[7].

Because of the diligent and complete histologic examination of the surgical margins, Mohs surgery can be utilized to track unpredictable superficial or deep projections of tumor. In addition, Mohs surgery is extremely useful for tracking tumors that involve embryonic fusion planes, the periorbital region, nerves and bone. These deep and irregular tumor extensions are responsible for the higher recurrence rates with other techniques. We will review the use of Mohs surgery for each of the more commonly managed tumors (Table 150.2).

Basal Cell Carcinoma

For primary BCCs, cure rates of 87% to 95% can be obtained with superficial ablative therapies and excision, especially on the trunk and extremities. Theoretically, the optimal cure rates associated with Mohs surgery could be applied to all BCCs, but from a practical perspective, the majority of BCCs are well managed with the former modalities. Therefore, Mohs surgery is usually limited to BCCs that meet the indications listed in Table 150.1.

For high-risk BCCs (Fig. 150.2), Mohs surgery provides superior cure rates. In the meta-analysis by Rowe et al.[1], the 5-year cure rate for *primary* BCC treated with Mohs surgery was 99%, as compared to 90% to 92% using standard treatments (Table 150.3). The 5-year cure rate for *recurrent* BCC treated with Mohs surgery was 94.4%, as compared to 80% for standard treatments (surgical excision, radiotherapy, cryotherapy, curettage and electrodesiccation)[2].

Mohs surgery is also well suited for the treatment of large BCCs (>2 cm), as size has been directly related to recurrence rate. In general,

CUTANEOUS TUMORS TREATED WITH MOHS SURGERY AND REPORTED CURE RATES	
Cutaneous tumors	**Cure rates (5-year)**
Basal cell carcinoma	99% (primary tumors)[1] 90–93% (recurrent tumors)[2]
Squamous cell carcinoma	92–99% (primary tumors)[3] 90% (locally recurrent tumors)[4]
Erythroplasia of Queyrat	90%[8]
Keratoacanthoma	97.5%[9,*]
Cutaneous melanoma *in situ*, including lentigo maligna	98%[10]
Atypical fibroxanthoma	93–100%[11]
Dermatofibrosarcoma protuberans	98–100%[12–14]
Merkel cell carcinoma	84%[15]
Microcystic adnexal carcinoma	90%[16–18]
Sebaceous carcinoma	89%[19]
Extramammary Paget's disease	92%[20]
Leiomyosarcoma (superficial)	87%[21]
*Only 2-year cure rate.	

Table 150.2 Cutaneous tumors treated with Mohs surgery and reported cure rates. For eccrine porocarcinoma, angiosarcoma and lymphoepithelioma-like carcinoma, efficacy based only upon case reports. For mucinous eccrine carcinoma, increased efficacy relative to wide excision not established. Some surgeons also use Mohs surgery for invasive cutaneous melanoma.

FIVE-YEAR CURE RATES FOR PRIMARY BCC AND SCC		
Treatment modality	**5-year cure rate**	
	BCC (%)	**SCC (%)**
Surgical excision	90	92
Electrodesiccation & curettage	92	96
Radiation	91	90
Cryotherapy	92	N/A
All non-Mohs modalities	91	92
Mohs surgery	99	97

Table 150.3 Five-year cure rates for primary basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) by treatment modality. Based upon refs 1 and 4. There is some inherent bias in these data as the studies quoted in this table did not all use the same patient selection criteria. For example, techniques such as electrodesiccation and curettage appear to have higher cure rates for SCC than excision to adipose, but it is likely that patients who had curettage selected as a definitive treatment had superficial tumors. N/A, not available.

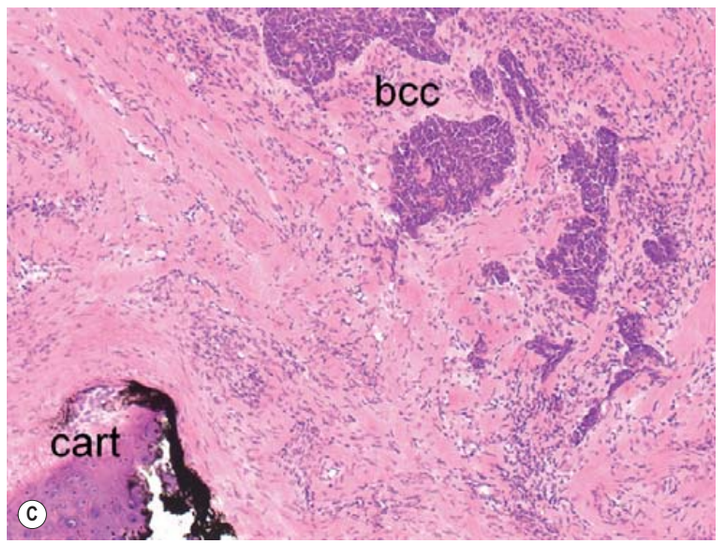


Fig. 150.2 Recurrent biopsy-proven basal cell carcinoma (BCC) of the cymba of the left ear. A Prior to Mohs surgery. **B** Tumor extirpation required 8 Mohs stages as there was unpredictable extension of the BCC. **C** In a frozen section, BCC (infiltrative subtype) invading the dermis (bcc) and adjacent to auricular cartilage (cart). *Reproduced with permission from Stephen Snow, Atlas of Mohs Surgery Wound Management: Flaps, Grafts and Wound Care, Scope Publishing: Madison, WI, 2010.*

tumors >2 cm that have been present for a prolonged period of time have a greater likelihood of recurring if treated by standard methods. When large lesions are present in cosmetically important areas, the sparing of normal tissue is also a critical advantage of Mohs surgery. In addition to aggressive histologic subtypes (see Table 150.1), perineural invasion is an indication for Mohs surgery (Fig. 150.3). Lastly, baso-squamous cell carcinoma, a hybrid between basal and squamous cell carcinoma, has a high risk of local recurrence and is also well managed with Mohs surgery[22].

Squamous Cell Carcinoma

When compared with other treatments, Mohs surgery offers the highest cure rates for patients with high-risk primary or recurrent SCCs. The local recurrence rates, based on a retrospective review of Mohs surgery versus non-Mohs surgery modalities for primary SCC, are outlined in Table 150.3[4].

As with BCC, Mohs surgery is indicated for management of SCCs with one or more risk factors for recurrence or metastasis (see Table 150.1). These indications include large SCCs (>2 cm), recurrent tumors, incompletely excised SCCs, and tumors with ill-defined clinical margins, rapid growth, an aggressive histologic subtype or perineural

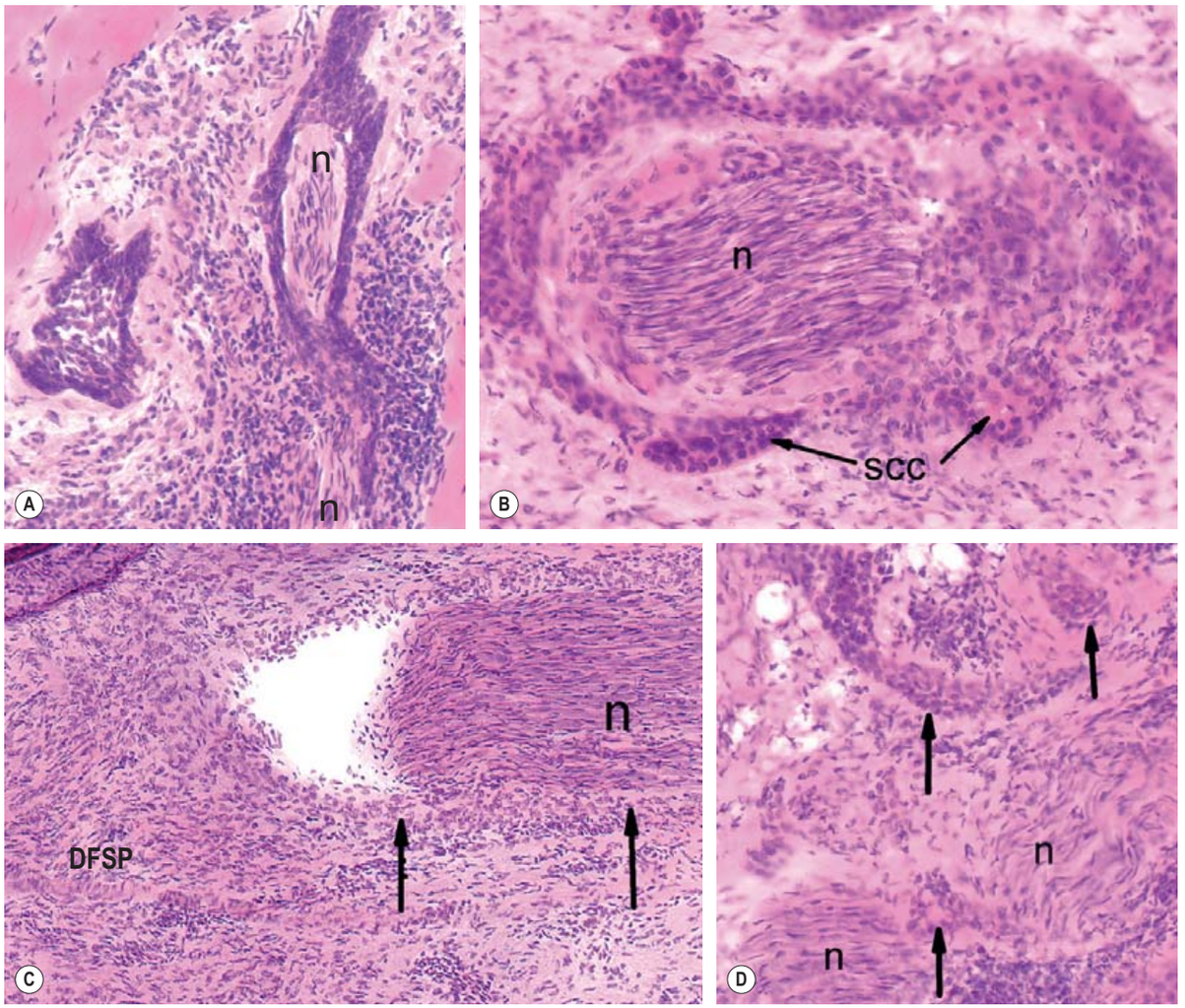


Fig. 150.3 Perineural involvement by various cutaneous tumors (frozen sections). A Basal cell carcinoma with a halo of basal cells enveloping a cutaneous nerve (n). **B** Squamous cell carcinoma (SCC) surrounding nerve fiber (n). **C** Spindle cells of dermatofibrosarcoma protuberans (DFSP) invading a cutaneous nerve (n; arrows); the clear area represents retraction artifact. **D** Microcystic adnexal carcinoma with perineural invasion by dominant pilar structures (arrows) in the deep subcutaneous portion of the tumor excised from the patient depicted in Fig. 150.4. n, nerve.
Reproduced with permission from Stephen Snow, Atlas of Mohs Surgery Frozen Sections, Scope Publishing: Madison, WI, 2010.

invasion (see Fig. 150.3), as well as SCCs arising in chronic scar tissue[23]. The latter, termed Marjolin's ulcers, can behave aggressively, and a multidisciplinary approach to regional node assessment and reconstruction may be necessary in these patients. Numerous, rapidly arising SCCs may affect immunosuppressed solid organ transplant recipients or individuals with chronic lymphocytic leukemia receiving fludarabine, and Mohs surgery is well suited for the management of these neoplasms.

SCC arising in high-risk anatomic sites may also be managed with Mohs surgery. For example, tumors of the lip have a high propensity for recurrence and metastasis, and cure rates as high as 92% have been obtained with Mohs surgery[24]. Mohs surgery is also well suited for SCCs occurring in anogenital areas and on the digits, where tissue conservation is important. When compared with conventional methods, Mohs surgery for the treatment of penile SCC offers comparable survival rates. Prior to Mohs surgery, most cases of SCCs involving the nail unit were treated with amputation, electrocoagulation or radiation. Mohs surgery provides an excellent choice for treatment of periungual and subungual SCC without osseous involvement, with cure rates of up to 96%[25].

Erythroplasia of Queyrat

Erythroplasia of Queyrat (EQ) is a term for SCC *in situ* confined to mucosal epithelium. In men, an erythematous thin plaque is typically seen on the inner surface of the foreskin, glans penis and/or coronal sulcus (see Chs 73 & 108). Of note, EQ is seen primarily in uncircumcised men. In women, mucosal SCC *in situ* favors the labia minora and the vestibule. Oncogenic human papillomaviruses often play an etiologic role and immunosuppressed individuals (e.g. HIV-infected) are at greater risk for developing anogenital SCC *in situ*.

Mohs surgery is an effective treatment for EQ, with a 5-year cure rate of 90%[8]. When excising EQ of the glans penis, Mohs layers should be very thin in order to minimize entry into and resection of the corpus spongiosum and cavernosum. If either is entered, achieving hemostasis can be challenging. EQ can often extend into the urethra and here differentiation of SCC *in situ* from transitional epithelium is often difficult on frozen sections. With deep extension along the urethra, collaboration with a urologist and completion of the surgery under general anesthesia are recommended.

Keratoacanthoma

Keratoacanthoma (KA) may be considered a well-differentiated SCC with specific histologic features. KAs classically grow quickly and then spontaneously involute; however, there are exceptions and metastasis has been reported, implying that the tumor was actually an SCC. Also, microscopically, some KAs may be difficult to distinguish from an SCC. As a result, nowadays, most KAs are considered to be well-differentiated SCCs and are managed with excisional or Mohs surgery. Mohs surgery may be particularly beneficial for large lesions, as well as those occurring in anatomically sensitive areas. In 1987, Larson[9] reported a 97.5% 2-year cure rate for KAs treated via Mohs surgery (see Table 150.2).

SPECIAL AND IMMUNOHISTOCHEMICAL STAINS USED IN MOHS SURGERY						
	Squamous cell carcinoma (perineural & spindle cell/ infiltrating)	**Basal cell carcinoma**	**Dermato-fibrosarcoma protuberans**	**Extramammary Paget's disease**	**Sebaceous carcinoma**	**Melanoma *in situ* (lentigo maligna)**
Special stains	–	Toluidine blue	–	PAS	Oil red O	–
Immunohistochemical stains	Pancytokeratin (AE1/AE3)	–	CD34	Cytokeratin 7	–	Melan-A/MART-1 (Fig. 150.5), MITF, Mel-5

Table 150.4. Special and immunohistochemical stains used in Mohs surgery. Additional special stains and immunohistochemical stains are reviewed in Table 0.11. MITF, microphthalmic transcription factor; PAS, periodic acid-Schiff.

Verrucous Carcinoma

Verrucous carcinoma is considered a variant of SCC, and it can be triggered by the human papillomavirus. It occurs most commonly in the oral cavity, on the plantar surface of the foot, or on the penis (see Ch. 108). While generally considered a low-grade carcinoma, there are reports of metastasis. Because the tumors are usually localized, Mohs surgery is an excellent treatment option. Sometimes, the histopathologic interpretation of frozen sections can be challenging because the tumor cells are very well differentiated and lack nuclear atypia, making distinction from epithelial hyperplasia, verruca vulgaris or condyloma acuminatum difficult.

Lentigo Maligna

Since lentigo maligna (melanoma *in situ* of sun-damaged skin) may be a clinically and histologically ill-defined tumor, it has a high local recurrence rate with standard wide-excisional surgery. Although frozen section histology of lentigo maligna can be challenging, Mohs surgery offers the possibility of complete margin examination and tissue sparing. Lentigo maligna that is at risk of recurrence or in an anatomically sensitive site may be managed with wide excision Mohs surgery (see below) followed by tangential permanent histologic confirmation, with immunostains as needed[26,27]. This dual method ("slow" Mohs technique) employs the advantages of both Mohs surgery and permanent histology, albeit with the disadvantage of delayed closure for complex cases. Another approach is the geometric staged excision (see Variations). Some groups also use frozen section immunostains to enhance diagnostic accuracy (see below)[26].

Melanoma Other Than Lentigo Maligna

The role of Mohs surgery for the treatment of cutaneous melanoma in which only frozen sections are utilized continues to be controversial. As with lentigo maligna, this is due to disagreements regarding the reliability of detecting atypical melanocytes in frozen sections. The use of special stains, such as HMB45, Mel-5, Melan-A/MART-1 and S100, may increase histologic sensitivity during Mohs surgery for melanocytic lesions (Table 150.4)[26]. Even so, some dermatologic surgeons advocate the examination of formalin-fixed tissue margins to confirm that the final Mohs surgery margin is negative[27].

Another controversial aspect of Mohs surgery for melanoma involves the advisability of margins that are narrower than published guidelines for a tumor that has a higher capacity to metastasize than BCC or SCC. Although uncontrolled, the extensive experience of Zitelli and colleagues in the management of melanoma with Mohs surgery provides reassurance that outcomes are equivalent to standard margins[28,29]. While many clinicians do not find significant benefits to Mohs surgery for routine management of melanoma (e.g. most tumors, with the exception of lentigo maligna, are well defined), specific clinical scenarios appear especially appropriate. These include: locally recurrent melanoma; tumors with a large diameter; ill-defined or amelanotic melanoma; and melanoma near critical anatomic structures such as the genitals, digits, eyelids, nose and ears. Of note, many dermatologic surgeons remove a clinically tumor-free margin of at least 5 mm when managing melanoma, a technique termed "wide excision Mohs surgery" (see below). Mapped serial sections and the "square method" (also referred to as geometric staged excision; see below) are modifications based upon similar histologic principles that attempt to achieve complete margin control with paraffin-embedded pathology only[30,31].

Atypical Fibroxanthoma

Atypical fibroxanthoma (AFX) typically presents as an ulcerated nodule in the head and neck region of an elderly person with sun-damaged skin. In general, it grows in a contiguous fashion. Histologically, AFX is composed of spindle cells mixed with bizarre, multinucleated giant cells, making the tumor relatively easy to identify on Mohs surgery frozen sections. Mohs surgery has demonstrated utility in the management of AFX, especially in areas of cosmetic importance[11]. By immunohistochemistry, the tumor is positive for CD10 and CD68.

Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans (DFSP) is an uncommon, slow-growing, locally aggressive soft tissue sarcoma that most often arises on the trunk of young to middle-aged adults. DFSP typically invades beyond the clinically visible tumor margins with unpredictable and irregular extensions. Recurrence rates after standard excision range from 11% to 53%. Mohs surgery is ideally suited to track the irregular tumor extensions of DFSP and offers cure rates from 98% to 100%[12–14]. Removal of DFSP with Mohs surgery can be quite time consuming due to the frequently large size of these tumors. Some physicians have proposed a modified "slow" Mohs technique in which paraffin-embedded sections ("rush" permanent sections) are utilized for tumors such as DFSP that may be difficult to interpret on frozen sections. Alternatively, CD34 staining can be employed to better define the tumor cells.

Merkel Cell Carcinoma

Merkel cell carcinoma (MCC) is an uncommon, but very aggressive, skin cancer, usually arising in elderly patients (see Ch. 115)[32]. There is usually a history of significant cumulative sun exposure or immunosuppression. Clinically, the tumor presents as a pearly to red–blue papulonodule and is often in the head and neck region. Microscopically, the tumor cells are uniformly deep blue, polygonal in shape and aggregate in large sheets, allowing them to be easily identified in frozen sections. By immunohistochemistry, MCC is positive for CK20 and synaptophysin. Treatment consists of complete surgical removal of the primary tumor via either Mohs surgery or wide excision, followed by radiotherapy to the primary site and regional lymph nodes (unless the lesion is low risk; see Fig. 115.20).

Microcystic Adnexal Carcinoma

Microcystic adnexal carcinoma (MAC) is an uncommon, locally aggressive tumor that typically involves the face of older adults (Fig. 150.4). Histologically, the cells demonstrate eccrine and pilar differentiation and often have an infiltrative growth pattern with frequent perineural invasion (see Fig. 150.3). In the literature, the overall recurrence rate for MAC approaches 40%. To date, Mohs surgery appears to offer the highest cure rate while permitting tissue sparing (see Table 150.2)[17]. A study by Chiller et al.[18] demonstrated that defects following Mohs surgery were four times larger than clinical estimates. They concluded that preoperative estimation of margins is generally unreliable, and complete histologic verification of clear margins is advisable.

Sebaceous Carcinoma

The use of Mohs surgery for management of sebaceous carcinoma has also been debated, primarily due to reports of discontiguous growth.

Fig. 150.4 Basal cell carcinoma (BCC) with microcystic adnexal carcinoma (MAC). A An elderly man who was referred for a biopsy-proven BCC of the left lateral cheek (small circle, upper); the tumor was treated three times as a BCC over the previous 15 years. Six months ago he developed a lump in the cheek (large circle, lower). **B** Defect after 4 Mohs stages confirmed a tumor-free margin; the buccal branch of the facial nerve was transected during tumor removal. Review of the frozen sections showed cells that were suspicious for MAC, so the specimen was thawed and submitted for routine histopathologic examination. **C** Because paraffin-embedded sections also suggested MAC, immunohistochemical stains were performed, demonstrating ductal structures that were CEA-positive (arrows), supporting the diagnosis of MAC. *Reproduced with permission from Stephen Snow, Atlas of Mohs Surgery Wound Management: Flaps, Grafts and Wound Care, Scope Publishing: Madison, WI, 2010.*

However, discontiguous growth will thwart any method of histologic margin evaluation. The desire for tissue conservation on the eyelid (the most common site of sebaceous carcinoma) makes Mohs surgery a logical approach. The removal of an extra safety margin of tissue for permanent sections may be a reasonable strategy with this type of tumor. The advantages of Mohs surgery for sebaceous cell carcinoma of the eyelid have been documented in a study showing an 11% recurrence rate with Mohs surgery, as compared to 30% with standard excision[19].

Other Adnexal Carcinomas

This group consists of the uncommon tumors that have sweat gland (eccrine, apocrine), sebaceous gland, or follicular differentiation. In addition to microcystic adnexal carcinoma (MAC) and sebaceous carcinoma, it includes mucinous eccrine carcinoma, eccrine porocarcinoma, adenoid cystic carcinoma, papillary eccrine carcinoma, and extramammary Paget's disease (EMPD). Except for EMPD of the groin or sebaceous carcinoma of the eyelid, the clinical features are rarely diagnostic[20]. As a group, the tumors are locally destructive with extensive unpredictable local tissue invasion, have a high rate of local recurrence when treated by wide excision, and metastasize late in the course of the disease.

Routine histology of paraffin-embedded sections plus immunohistochemistry are often necessary to confirm the initial diagnosis of these tumors. In addition, perineural spread (e.g. MAC) and epidermotropism (e.g. EMPD, sebaceous carcinoma) can be seen. Because their microscopic features are readily recognizable in frozen sections, they are amenable to treatment by Mohs surgery. EMPD may sometimes be the exception and PAS staining can help delineate the tumor cells within the epidermis.

Other Tumors and Applications

Mohs surgery has been used to treat a number of other malignant neoplasms, including angiosarcoma, lymphoepithelioma-like carcinoma, and leiomyosarcoma[21,33], as well as benign tumors that tend to recur, such as infantile digital fibroma and granular cell tumor. Experience with these rare neoplasms is limited, but the complete margin examination of Mohs surgery may provide enhanced tumor clearance. Mohs surgery has also been used to extirpate difficult-to-treat cutaneous fungal infections.

CONTRAINDICATIONS

Discontiguous tumors can create problems with false-negative margins, but this problem also occurs with all other methods of evaluating surgical margins histologically. Therefore, it is not an absolute contraindication. If a tumor cannot reliably be identified histologically, especially on frozen sections, this can also be a relative contraindication. For example, some cases of lentigo maligna can be difficult to identify as compared to the proliferation of atypical melanocytes found in adjacent

sun-damaged skin uninvolved by malignancy (Fig. 150.5). Also, spindle cell neoplasms can be difficult to distinguish from fibrosis. If patients are unwilling or unable to undergo surgery, then a non-surgical approach such as radiotherapy may be a better option. However, for some patients with serious medical problems, Mohs surgery done under local anesthesia may be safer than more extensive anesthesia and surgery in a hospital operating room facility.

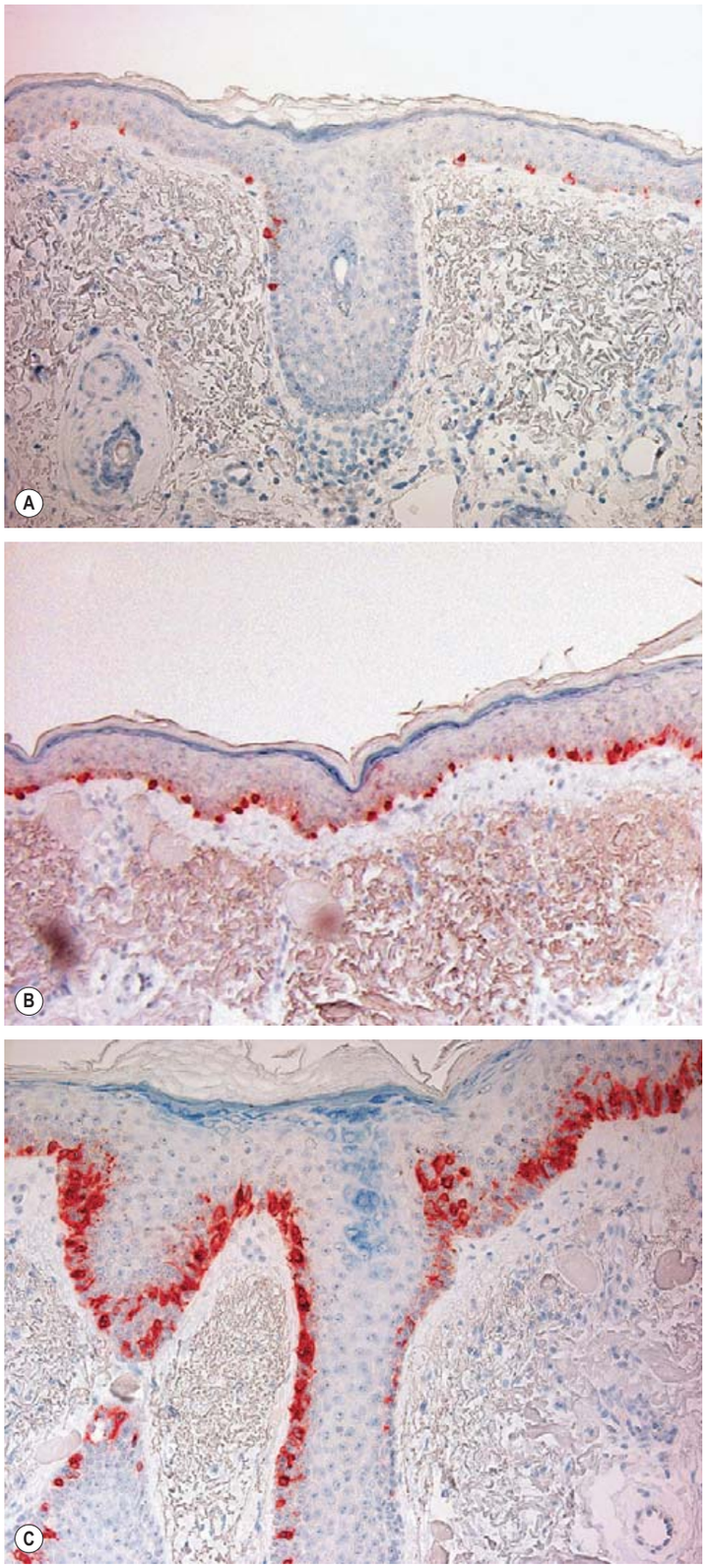


Fig. 150.5 Immunostaining with Melan-A/MART-1. A Normal density of melanocytes. **B** Melanocytic hyperplasia with scattered atypical melanocytes in sun-damaged skin. **C** Lentigo maligna with atypical melanocytic proliferation, some pagetoid spread, and adnexal extension. *Courtesy, Clark C Otley, MD and Randall K Roenigk, MD.*

PREOPERATIVE HISTORY AND CONSIDERATIONS

A history and focused skin examination should be performed at the time of consultation. The pathology report should be reviewed and if the diagnosis appears problematic, the histologic sections should be re-examined. Indications for antibiotic prophylaxis should be evaluated and then reviewed with the patient's primary physician if necessary[34]. Similarly, the management of any implanted cardiac pacemakers and defibrillators should be considered, with cardiology consultation if needed. Finally, the management of "blood thinners", including warfarin, aspirin, clopidogrel and nonsteroidal anti-inflammatory drugs (NSAIDs), should be discussed (see Ch. 151).

Upon completion of the medical evaluation, the Mohs surgeon should explain the nature of the tumor and the therapeutic options, and then obtain informed consent. The repair options should be briefly described. The patient should be encouraged to continue regular medications and eat a light meal on the morning of surgery, unless conscious sedation is planned. It is recommended that patients bring a friend or relative on the day of surgery.

Patients with extremely large or deeply invasive tumors may require preoperative evaluation with a CT scan, MRI or PET scan. Very complex cases requiring a multidisciplinary approach should be evaluated preoperatively by other subspecialties (e.g. neurosurgery) as needed. Following removal of the tumor by or with the assistance of the Mohs surgeon, the repair is performed by the most appropriate specialist. The team approach is especially useful in areas such as the periorbital area and external auditory canal. Mohs surgery is most commonly performed under local anesthesia. Conscious sedation may be an option for managing patients with multiple tumors who wish to be treated in one session.

DESCRIPTION OF TECHNIQUE

Table 150.5 provides a flow sheet for performing Mohs surgery and Figure 150.6 depicts the procedure.

VARIATIONS/REFINEMENTS/SPECIAL SITUATIONS

Over the past several decades, there have been several refinements made to the Mohs technique. The goals of these innovations are to improve the speed of tissue processing, the efficiency of tumor removal and the recognition of individual tumor cells in order to improve cure rates. Surgical improvements include: (1) the single section method; (2) geometric staged excision; (3) non-beveled 90° incisions; and (4) wide excision. Improvements to better recognize tumor cells include: (1) immunostains for frozen sections (see Table 150.4); and (2) submission of tissue specimens for routine histology ("rush" permanent sections) and immunohistochemistry (see Ch. 0). For example, the latter is done in the "slow" Mohs surgery method and in geometric staged excision.

Single Section Method

The single section (specimen) method for tissue processing of smaller tumors was described by Randle et al.[35]. The single section involves a highly beveled specimen processed with relaxing incisions on the superior, tumor-bearing portion of the specimen that allow all peripheral edges to fold outward into a single plane. The single section method is particularly useful for tumors in which a shallow Mohs layer can be taken, with the goal of allowing the resulting wound to heal by second intention. Additionally, the single section method allows unaltered examination of the complete deep margin, with no possibility of areas being missed by tissue subdivision.

Geometric Staged Excision

Geometric staged excision (GSE) is a process by which facial lentigo maligna is excised with perpendicular skin margins. Some surgeons use two closely spaced, parallel blades to create a square-shaped defect (thin

MOHS SURGERY FLOW SHEET
PREOPERATIVE ASSESSMENT
• Upon arrival, the patient's demographic information is confirmed, allergies, pertinent medications and vital signs are recorded, and the preoperative biopsy is reviewed • Any prophylactic antibiotic, anti-anxiety drug or cardiac device is either administered or managed as needed • The tumor is closely examined (Fig. 150.6A) and the clinical margin is marked (e.g. with gentian violet) • Reference to diagrams, landmarks and photographs is made to ensure correct site identification and every patient is asked to confirm the tumor location with a mirror • The planned procedure and possible reconstruction are reviewed and consent obtained
PREPARATION OF THE SITE AND FIRST MOHS SURGERY LAYER
• The site is then wiped with alcohol, local anesthetic (see Ch. 143) is infiltrated and the site is prepped with chlorhexidine or povidone-iodine • The central portion of the tumor is de-bulked with a curette to further define subclinical tumor extension (Fig. 150.6B) • The first Mohs surgery layer includes all clinically evident tumor plus a small margin of normal-appearing tissue (Fig. 150.6C) – Depending on the histologic subtype and likelihood of subclinical tumor extensions, the margin of normal skin may range from 1 to 10 mm (with narrower margins taken in areas where tissue sparing is essential) – For shallow tumors or those at sites favorable for second intention healing, the first Mohs layer is planned as a shallow excision – For deep tumors or at sites where second intention healing is not a good option, a full-thickness excision to subcutaneous fat is performed • For recurrent tumors, the most thorough approach is to resect all tissue involved by the previous treatments, including the primary site and reconstruction scar; if the recurrence is clearly isolated to only one site and/or complete resection would cause difficulties, then a localized resection of the clinically recurrent area can be considered • When excising the Mohs layer, the scalpel is held at a 30–60° angle to the skin surface to create a beveled incision (Fig. 150.6C) • Before the layer is completely removed, both the layer and the adjacent surrounding tissue are marked with one or more shallow scalpel cuts or notches to help orient the specimen to the defect (Fig. 150.6D) • The layer is removed with either a scalpel or iris scissors and placed on a transfer card or marked gauze while maintaining correct orientation relative to the defect (Fig. 150.6E) • Hemostasis is then obtained using electrocoagulation or thermocautery as indicated • A sterile pressure dressing is placed on the wound and the patient is discharged to a waiting room for 1–2 hours while the tissue is being processed
HANDLING OF THE TISSUE SPECIMEN
• A map of the specimen is drawn that is relative to anatomic landmarks and includes the skin notches (Fig. 150.6H) • The specimen is cut precisely into sections of sufficient size so that they can fit on the cryostat chuck and microscope slide (Fig. 150.6F) • Particular attention must be paid to maintain proper numbering, inking and mapping of specimens • All cut margins, except the epidermal edge, are inked systematically with different colored dyes and recorded on the specimen map (Fig. 150.6G, H) • The technician prepares the tissue pieces for freezing by flattening them so that the epidermis lies in the same plane as the dermis and deep margins, using one of several available techniques; if any edge or portion of the specimen curves upward, relaxing cuts are placed on the top surface of the specimen • The histotechnician embeds the tissue piece (deep surface upward) on a chuck with embedding medium and freezes it in the cryostat • Frozen sections are then cut, mounted on slides and stained with H&E – Some Mohs surgeons prefer the toluidine blue stain because it is rapid and the purplish metachromatic stromal staining helps to distinguish BCCs from adnexal structures
HISTOPATHOLOGIC ASSESSMENT AND ADDITIONAL LAYERS
• The surgeon examines the frozen sections and marks any residual tumor foci on the specimen map (Fig. 150.6J) • In patients requiring further resection, the surgeon precisely removes additional tissue only in the area of residual tumor, using the map and skin notches present on the patient for orientation (Fig. 150.6K) • This process is repeated until all tissue margins are microscopically free of tumor • Once the tumor is completely removed, the final defect is measured and photographed and wound management options are discussed and implemented

Table 150.5 Mohs surgery flow sheet. Figure 150.6 depicts the procedure. BCCs, basal cell carcinomas.

and frame-like) with the tumor and presumed adequate margins left intact. If the excised peripheral tissue is found to contain no tumor cells, then the central square is removed surgically. Others have found it easier to excise the entire specimen in a geometric pattern, ink the margins and then cut off strips along the margins; the latter are then oriented, inked, processed and cut *en face* while the central portion is cut vertically to determine the thickness of the tumor. These variations of GSE differ from the "slow" Mohs surgery method that uses beveled skin edges and creates an oval outline of excision. Whether the skin margin is vertical or beveled, "rush" paraffin-embedded sections are read the next day. If there are residual tumor cells, another peripheral thin square is removed until a negative (tumor-free) margin is achieved. The disadvantage of GSE is that there are a few extra millimeters of skin that are sacrificed in order to provide the straight lengths of tissue. For small tumors, i.e. when one to two layers are required to complete treatment, this difference is marginal. However, GSE loses its advantage when several layers are required and/or the tumor is irregularly shaped, because reconstruction becomes more complex. GSE is requested by dermatopathologists who prefer to read non-ovoid nuclei created by tangential sections and who find it easier to process the tissue so as to see the entire perpendicular epidermal margin.

Non-Beveled 90° Incisions

Some dermatologic surgeons perform non-beveled 90° incisions for most Mohs surgical procedures on the extremities. An advantage of this technique is that the vertical edges created are ideal for reconstruction. A disadvantage is that it requires excision of more tissue. Although a traditional beveled edge can be trimmed in preparation for reconstruction, a true, sharp, straight 90° angle is more difficult to obtain after resection of tissue. The 90° Mohs incisions do necessitate more extensive manipulation during tissue preparation, principally by creation of relaxing incisions in the upper portion of the specimen, in order to induce the tissue to flatten into a single plane.

Wide Excision Mohs Surgery

Wide excision Mohs surgery ("wide Mohs") is a modification of traditional Mohs surgery in which a larger, clinically tumor-free margin is taken either before or after Mohs histologic margin evaluation. This is performed on tumors that have a high propensity for recurrence or metastases (including satellite metastases), in particular melanoma, Merkel cell carcinoma and cutaneous sarcomas[8]. In utilizing wide Mohs margins, the surgeon is actively deciding to prioritize tissue processing speed over tissue sparing for high-risk tumors. Wide Mohs margins of 5–20 mm can be taken with high-risk tumors, while maintaining the advantages of 100% margin examination, in cases where tissue sparing is a lower priority.

Supplementation with Permanent Sections and Immunostains

During the removal of skin cancers, it is not uncommon for the surgeon to encounter a second neoplasm or to acquire evidence that the type of tumor being removed and the preoperative diagnosis differ (see Fig. 150.4). Reassessment and review of permanent sections can provide clarification. If the tumor is a spindle cell neoplasm, submission for routine histology (permanent sections) and immunohistochemistry is also reasonable (Fig. 150.7).

When confronted with tumors where histologic features in frozen sections may be challenging, e.g. lentigo maligna and DFSP, some Mohs surgeons elect to supplement the usual frozen sections with additional immunostained frozen sections, especially for high-risk tumors[26]. Alternating tissue sections are stained with H&E versus rapid immunostains; the latter are outlined in Table 150.4.

Tumors that Invade Bone

Invasion of bone by skin cancer occurs as a result of previous treatment, anatomic site, cancer type and biologic behavior, and patient comorbidities. For example, previous irradiation can damage the bone while direct invasion of bone favors sites where the overlying skin is thin (e.g. scalp, sinuses, sternum, distal phalanx). Bone involvement is also seen with difficult cancers in strategic sites such as a

desmoplastic SCC of the scalp, an invasive DFSP of the anterior chest or a metatypical BCC over the maxillary sinus. In addition, an SCC or BCC with perineural invasion can gain access to the bony canal through which the nerves pass.

Although skin cancer invades bone infrequently, when it does the following strategies are used to control its growth and potentially effect a cure: (1) establish the diagnosis and mode of invasion of the tumor histologically; (2) obtain an X-ray, CT scan and/or MRI to determine the macroscopic extent of bone involvement and status of the regional lymph nodes; and (3) refer to a related subspecialist for wide excision as indicated. In difficult or tumors with perineural invasion, additional Mohs layers should be taken to assure a tumor-free plane. Small foci of sinus, nasal or scalp bone may be excised locally with a bone rongeur or a chisel and mallet. Even when bone is exposed during tumor surgery, healing by second intention is possible. If sufficient granulation tissue can be stimulated to cover the exposed facial or scalp bone quickly, cellulitis and osteomyelitis are rarely problems[36]. Other options include coverage with an acellular dermal matrix or a split-thickness skin graft. These three methods of wound management are preferred over more complex flaps that may hide and bury residual tumor. Of course, patients who are immunosuppressed by age, illness or drugs will require close surveillance.

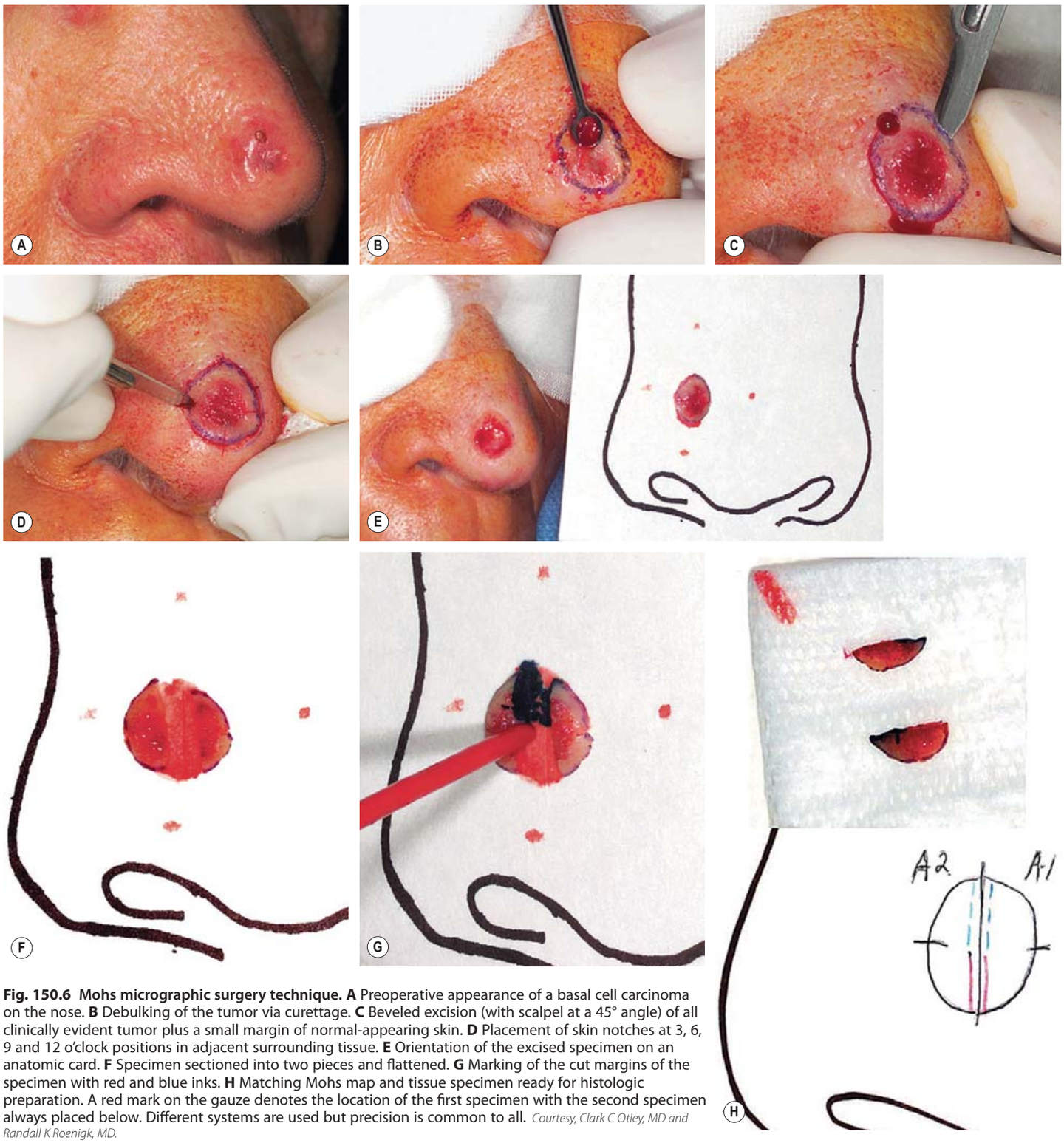


Fig. 150.6 Mohs micrographic surgery technique. A Preoperative appearance of a basal cell carcinoma on the nose. **B** Debulking of the tumor via curettage. **C** Beveled excision (with scalpel at a 45° angle) of all clinically evident tumor plus a small margin of normal-appearing skin. **D** Placement of skin notches at 3, 6, 9 and 12 o'clock positions in adjacent surrounding tissue. **E** Orientation of the excised specimen on an anatomic card. **F** Specimen sectioned into two pieces and flattened. **G** Marking of the cut margins of the specimen with red and blue inks. **H** Matching Mohs map and tissue specimen ready for histologic preparation. A red mark on the gauze denotes the location of the first specimen with the second specimen always placed below. Different systems are used but precision is common to all. *Courtesy, Clark C Otley, MD and Randall K Roenigk, MD.*

Continued

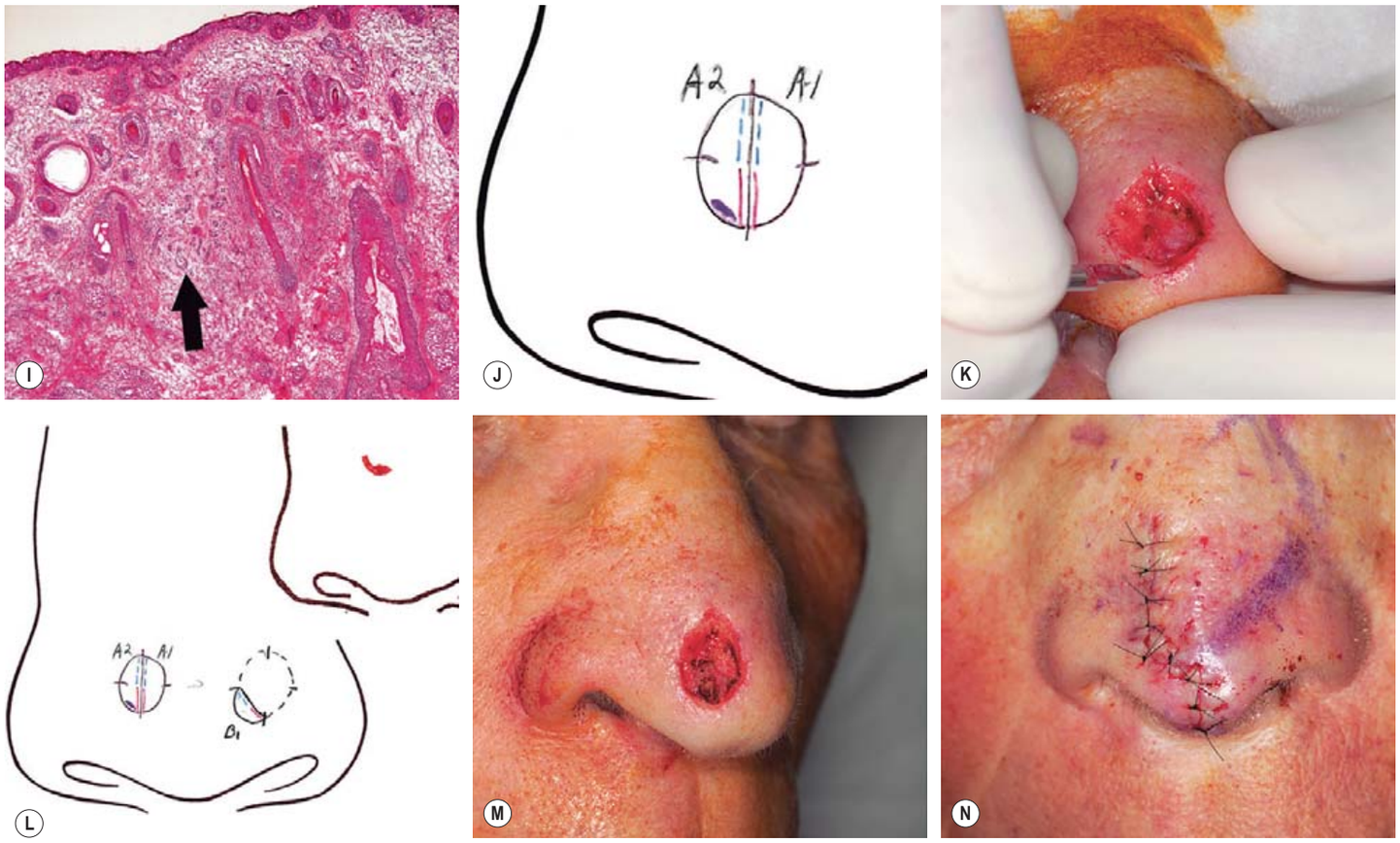


Fig. 150.6 Mohs micrographic surgery technique (cont'd). **I** Histopathologic section with positive tumor denoted by the arrow. **J** Mohs map marked with purple at the site of cancer at the margin. **K** Re-excision of the area of residual basal cell carcinoma. **L** Mohs map from the second layer with corresponding tissue. **M, N** Postoperative tumor-free defect and repair. *Courtesy, Clark C Otley, MD and Randall K Roenigk, MD.*

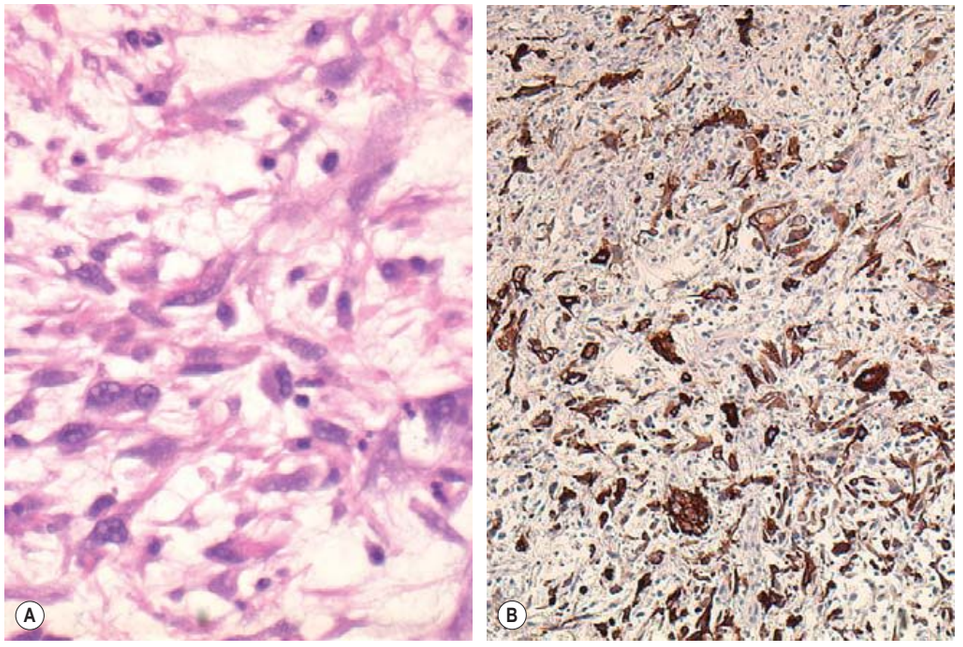


Fig. 150.7 Spindle cell squamous cell carcinoma (SCC). **A** Poorly differentiated SCC with spindle cell morphology in a bone marrow transplant recipient. **B** Positive immunohistochemical stain for high-molecular-weight cytokeratin (paraffin-embedded sections).

CHALLENGES AND PITFALLS OF FROZEN SECTIONS

The challenges and pitfalls encountered with frozen sections fall into four broad categories: (1) excisional factors; (2) physician factors; (3) laboratory processing; and (4) pathologic interpretation (Table 150.6).

MOHS SURGERY – CHALLENGES AND PITFALLS
EXCISIONAL FACTORS
• Includes patient skin characteristics such as thickness, contour and texture • Severely sun-damaged skin is more fragile and will tear and fragment, resulting in an incomplete Mohs layer and/or more pieces of skin to process • Some sites have complex tissue components such as muscle, cartilage and bone (must be decalcified before sectioning) • Each tissue component must be flattened and frozen to a single plane • Fatty tissue requires intense freezing, which can lead to an increase in epidermal freeze artifacts, tissue fractures and specimen chipping
PHYSICIAN FACTORS
• Includes proper numbering, inking and mapping • Excessive electrocautery can cause elongation of the nuclei and cytoplasm of epidermal keratinocytes as well as basement membrane retraction artifact, thus resembling BCC histologically – If the surgeon leaves excess epidermal tissue centrally within the layer, when the layer is divided and flattened, these cells may be pushed to the surface and be misinterpreted as residual tumor – "Persistence" of epidermal cells may lead to removal of an unnecessary Mohs layer
LABORATORY PROCESSING
• Include microsection preparation, cutting, staining and mounting • Improper cutting techniques lead to specimens that are too thick, too thin, folded or fractured • Dull knife blades result in fragmented or incomplete sections and "chatter" marks • Poor-quality staining with H&E and/or dehydration can compromise cancer cell recognition • Problems with mounting include inappropriate amounts of media, air trapping and dry slides
PATHOLOGIC INTERPRETATION (Fig. 150.8)
• Includes inability to recognize minute cancer foci that are hidden by inflammation or tissue camouflage • For some tumors, paraffin-embedded ("rush" permanent) sections may be easier to interpret as compared to frozen sections (e.g. lentigo maligna) • In cancers like DFSP, EMPD, and/or tumors that demonstrate perineural extension, frozen sections may be used to achieve a preliminary tumor-free margin and then an additional final layer may be removed and submitted for routine histology (i.e. permanent sections) and immunohistochemistry[37]

Table 150.6 Mohs surgery – challenges and pitfalls. BCC, basal cell carcinoma; DFSP, dermatofibrosarcoma protuberans; EMPD, extramammary Paget's disease.

POSTOPERATIVE CARE

Multiple options exist for management of tissue defects after tumor clearance with Mohs surgery. The management strategy will take into account anatomic location, patient comorbidities, likelihood of surgery in the future, severity of the tumor, and the aesthetic needs of the patient. With guidance from the Mohs surgeon, patients are able to select the best options for reconstruction.

Allowing surgical defects to heal by second intention may result in excellent cosmetic results in areas that are concave, as demonstrated by the experience of Dr Mohs and others. Second intention healing can also be used for recurrent tumors in which flaps or grafts might hinder surveillance of the treatment site. Patients must be willing to meticulously cleanse the area over a 2- to 8-week healing period. Typically, wound care regimens involve cleansing the wound daily with a saline solution or soapy water, applying a layer of ointment, and then covering with a non-adherent dressing. Wound care after cutaneous reconstruction is similar to second intention wound care, although limited to 1–2 weeks. A discussion of cutaneous reconstruction can be found in Chapters 146–148.

Antibiotics may be given postoperatively for wound infection prophylaxis if surgery is extensive[34]. Additionally, surgical reconstruction on highly sebaceous noses and other sites with significantly high bacterial colonization may require prophylactic antibiotics. Pain control is assessed on a case-by-case basis. Substantial pain following Mohs surgery is uncommon, and, usually, acetaminophen is sufficient for postoperative discomfort. If warranted, oral narcotic analgesics may be prescribed for patients with low pain thresholds, large tumors, complex reconstruction, or wounds in anatomic locations of high tension.

Ongoing surveillance at least annually for new primary and recurrent cancer is recommended for all patients, given that 50% of patients with non-melanoma skin cancer will experience another skin cancer during the subsequent 5 years.

COMPLICATIONS

Fortunately, complications from Mohs surgery are uncommon. Intraoperative considerations include anxiety, pain (with local anesthesia injection), bleeding, nerve damage and allergic reactions. If warranted, oral midazolam can be given in the range of 5–15 mg for healthy adults. Hemorrhage is a potential risk during surgery, which is minimized with meticulous hemostasis and pressure bandaging. Epinephrine (adrenaline) included in the local anesthetic temporarily augments hemostasis. To date, there is no evidence that patients taking aspirin or warfarin for serious medical problems experience increased risks of serious hemorrhage or bleeding complications. In addition, while there is a significantly increased risk of bleeding complications in patients on thienopyridines (e.g. clopidogrel, ticlopidine) undergoing dermatologic surgery, these medications are typically continued due to the possible risk of internal thrombotic complications[37a,37b]. The most common site for major arterial transection is the superficial temporal artery, which usually requires suture ligation.

Injury to cutaneous sensory nerves occurs during all cutaneous surgery. Transection of significant motor nerves is occasionally necessary for removal of deeply invasive tumors, especially in the temporal region. Whenever possible, the surgeon should inform the patient before surgery of any possible loss of function or sensation. Before beginning surgery, the patient should be thoroughly questioned regarding allergies. Considerations include past reactions to local anesthetics, antibiotics, iodine, latex, and tape products. Fortunately, lidocaine allergy is rare, but the surgeon should be prepared for an emergency response if necessary.

Postoperative complications include bleeding, hematoma/seroma formation, infection, necrosis, dehiscence and scarring (see Ch. 151). The infection rate after Mohs surgery is very low (0.7%)[38]. Antibiotics should be considered for reconstructed sites on sebaceous noses and distal lower extremities (below the knee) as well as those near the nares and mouth. Antibiotics should also be considered when multiple Mohs layers were required for tumor clearance and for any debilitated patient when proper wound care is a concern.

Potential pitfalls result from lack of attention to detail, incorrect interpretation of histopathology (Fig. 150.8), and lack of appreciation of aggressive tumor characteristics[39].

FUTURE TRENDS

The history of Mohs surgery is one of continuous innovation and improvement. Given increases in the incidence of skin cancer, the demand for Mohs surgery services will continue to rise. Preoperative tumor definition with confocal scanning laser microscopy is being explored to assist in efficient removal of tumors[40]. Digital technology has been applied to Mohs surgery, enabling telepathology confirmation. The use of newer immunostains for either frozen or microwave-processed paraffin-embedded tissue continues to enhance the diagnostic sensitivity and specificity of pathologic examination. Finally, these and other innovations that are beyond the scope of this chapter promise to bolster the status of Mohs surgery as the gold standard for removal of cutaneous tumors[41–44], as will evidence gathered from computerized databases.

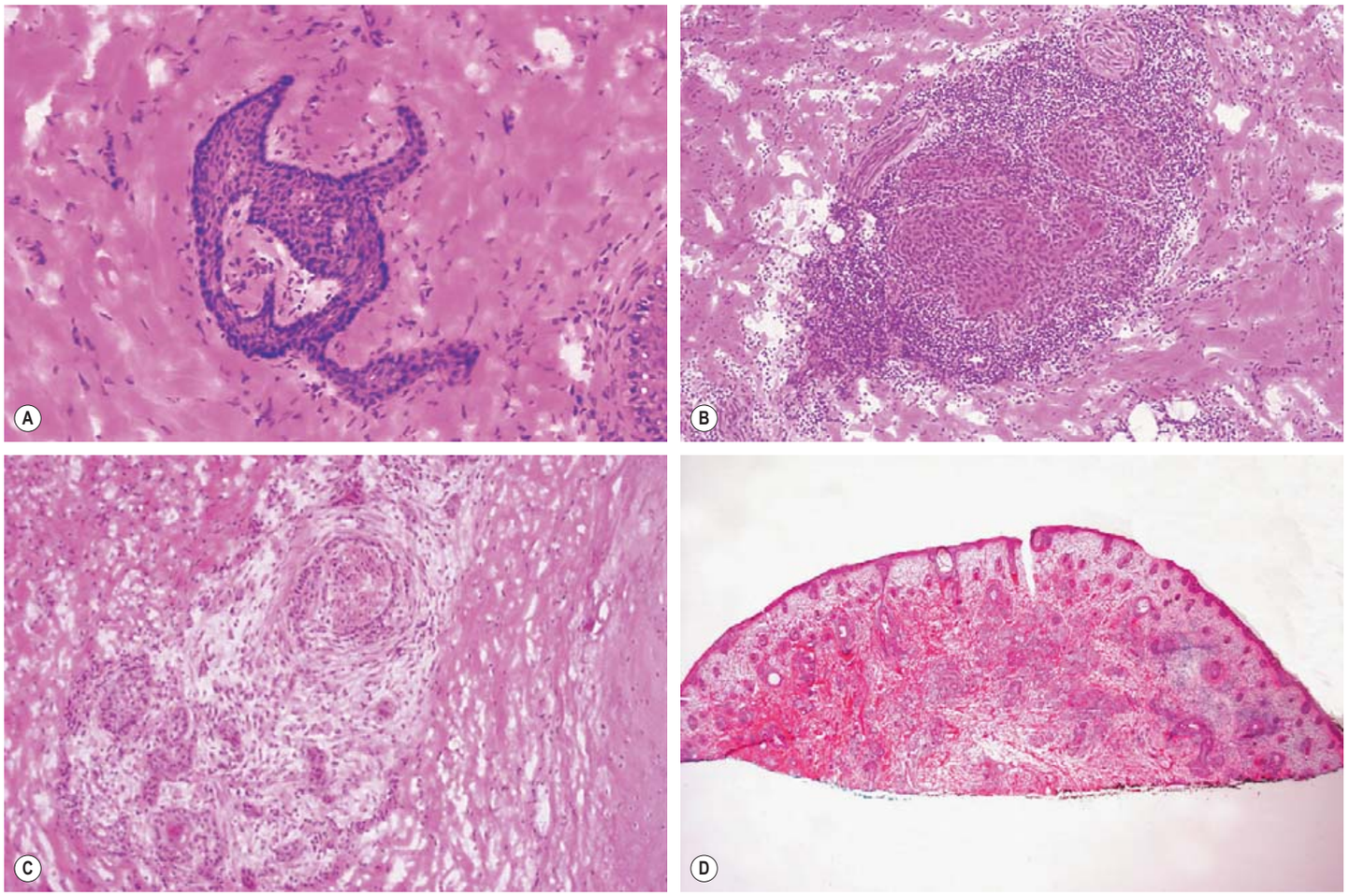


Fig. 150.8 Histologic challenges in Mohs surgery. A Folliculocentric basaloid hyperplasia may mimic basal cell carcinoma; however, the lack of clefting adjacent to the cells, apoptosis or mitotic figures as well as the presence of a fibrous sheath permits distinction. **B** Dense inflammation can obscure tumor cells, as seen here with a squamous cell carcinoma in a patient with chronic lymphocytic leukemia. **C** Careful evaluation is required to identify subtle foci of perineural squamous cell carcinoma. **D** Incomplete histologic margins (e.g. due to a small portion of missing epidermis) can lead to false-negative readings. *Courtesy, Clark C Otley, MD and Randall K Roenigk, MD.*

REFERENCES

1. Rowe DE, Carroll RJ, Day LC. Long-term recurrence rates in previously untreated (primary) basal cell carcinoma – implications for patient follow-up. J Dermatol Surg Oncol. 1989;15:315–28.
2. Rowe DE, Carroll RJ, Day CL. Mohs surgery is the treatment of choice for recurrent (previously treated) basal cell carcinoma. J Dermatol Surg Oncol. 1989;15:424–31.
3. Roenigk RK, Roenigk HH. Current surgical management of skin cancer in dermatology. J Dermatol Surg Oncol. 1990;16:135–51.
4. Rowe DE, Carroll RJ, Day CL Jr. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip: implications for treatment modality selection. J Am Acad Dermatol. 1992;26:976–90.
5. Mohs FE. Chemosurgery: a microscopically controlled method of cancer excision. Arch Surg. 1941;42:279–95.
6. Tromovitch TA, Stegman SJ. Microscopically controlled excision of skin tumors: chemosurgery (Mohs) fresh tissue technique. Arch Dermatol. 1974;110:231–2.
7. Drake LA, Dinehart SM, Goltz RW, et al. Guidelines for care for Mohs micrographic surgery. J Am Acad Dermatol. 1995;33:271–8.
8. Mikhail GR. Cancers, precancers, and pseudocancers of the male genitalia. J Dermatol Surg Oncol. 1980;6:1027–35.
9. Larson PO. Keratoacanthomas treated with Mohs' micrographic surgery (chemosurgery). A review of forty-three cases. J Am Acad Dermatol. 1987;16:1040–4.
10. Bene NI, Healy C, Coldiron BM. Mohs micrographic surgery is accurate 95.1% of the time for melanoma in situ: a prospective study of 167 cases. Dermatol Surg. 2008;34:660–4.
11. Davis JL, Randle JW, Zalla MJ, et al. A comparison of Mohs micrographic surgery with wide excision for the treatment of atypical fibroxanthoma. Dermatol Surg. 1997;23:105–10.
12. Ratner D, Thomas CO, Johnson TM, et al. Mohs micrographic surgery for the treatment of dermatofibrosarcoma protuberans: results of a multi-institutional series with an analysis of the extent of microscopic spread. J Am Acad Dermatol. 1997;37:600–13.
13. Gloster HM, Harris KR, Roenigk RK. A comparison between Mohs micrographic surgery and wide surgical excision for the treatment of dermatofibrosarcoma protuberans. J Am Acad Dermatol. 1996;35:82–7.
14. Snow SN, Gordon EM, Larson PO, et al. Dermatofibrosarcoma protuberans: a report on 29 patients treated with Mohs micrographic surgery with long-term follow-up and review of the literature. Cancer. 2004;101:28–38.
15. Boyer JD, Zitelli JA, Brodland DG, D'Angelo G. Local control of primary Merkel cell carcinoma: review of 45 cases treated with Mohs micrographic surgery with and without adjuvant radiation. Dermatol Surg. 2002;47:885–92.
16. Snow S, Madjar D, Hardy S, et al. Microcystic adnexal carcinoma: report of 13 cases and review of the literature. Dermatol Surg. 2001;27:401–8.
17. Leibovitch I, Huilgol SC, Selva D, et al. Microcystic adnexal carcinoma: treatment with Mohs micrographic surgery. J Am Acad Dermatol. 2005;52:295–300.
18. Chiller K, Passaro D, Scheuller M, et al. Microcystic adnexal carcinoma: forty-eight cases, their treatment and their outcome. Arch Dermatol. 2000;136:1355–59.
19. Spencer JM, Nossa R, Tse DT, et al. Sebaceous carcinoma of the eyelid treated with Mohs micrographic surgery. J Am Acad Dermatol. 2001;44:1004–9.
20. O'Connor WJ, Lim KK, Zalla MJ, et al. Comparison of Mohs micrographic surgery and wide excision for extramammary Paget's disease. Dermatol Surg. 2003;29:723–7.
21. Humphreys TR, Finkelstein DH, Lee JB. Superficial leiomyosarcoma treated with Mohs micrographic surgery. Dermatol Surg. 2004;30:108–12.
22. Leibovitch I, Huilgol SC, Selva D, et al. Basosquamous carcinoma: treatment with Mohs micrographic surgery. Cancer. 2005;104:170–5.
23. Leibovitch I, Huilgol SC, Selva D, et al. Cutaneous squamous cell carcinoma treated with Mohs micrographic surgery in Australia I. Experience over 10 years. J Am Acad Dermatol. 2005;53:253–60.
24. Holmkvist KA, Roenigk RK. Squamous cell carcinoma of the lip treated with Mohs micrographic surgery: outcome at 5 years. J Am Acad Dermatol. 1998;38:960–6.
25. Zaiac MN, Weiss E. Mohs micrographic surgery of the nail unit and squamous cell carcinoma. Dermatol Surg. 2001;27:246–51.
26. Zalla MJ, Lim KK, DiCaudo DJ, et al. Mohs micrographic excision of melanoma using immunostains. Dermatol Surg. 2000;26:771–84.
27. Cohen LM, McCall MW, Zax RH. Mohs micrographic surgery for lentigo maligna melanoma: a follow-up study. Dermatol Surg. 1998;24:673–7.

28. Zitelli JA, Brown C, Hanusa BH, et al. Mohs micrographic surgery for the treatment of primary cutaneous melanoma. J. Am Acad Dermatol. 1997;37:236–45.
29. Bricca GM, Brodland DG, Ren D, Zitelli JA. Cutaneous head and neck melanoma treated with Mohs micrographic surgery. J Am Acad Dermatol. 2005;52:92–100.
30. Huilgol SC, Selva D, Chen C, et al. Surgical margins for lentigo maligna melanoma: the technique of mapped serial excision. Arch Dermatol. 2004;140:1087–92.
31. Johnson TM, Headington JT, Baker SR, et al. Usefulness of staged excision for lentigo maligna melanoma: the 'square' procedure. J Am Acad Dermatol. 1997;37:758–64.
32. O'Connor WJ, Roenigk RK, Brodland DG. Merkel cell carcinoma: comparison of Mohs micrographic surgery and wide excision in eighty-six patients. Dermatol Surg. 1997;23:929–33.
33. Bernstein SC, Roenigk RK. Leiomyosarcoma of the skin: treatment of 34 cases. Dermatol Surg. 1996;22:631–35.
34. Maragh SL, Otley CC, Roenigk RK, Phillips PK. Antibiotic prophylaxis in dermatologic surgery: updated guidelines. Dermatol Surg. 2005;31:83–93.
35. Randle HW, Zitelli J, Brodland DG, et al. Histologic preparation for Mohs micrographic surgery: the single section method. J Dermatol Surg Oncol. 1993;19: 522–24.
36. Snow SN, Stiff MA, Bullen R, et al. Second intention healing of exposed facial-scalp bone after Mohs surgery for skin cancer. Review of 91 cases. J Am Acad Dermatol. 1994;31:450–4.
37. Maloney ME, Torres A, Hoffmann TJ, Helm KF (eds). Surgical Dermatopathology. Malden, MA: Blackwell Science, 1999.
37a. Cook-Norris RH, Michaels JD, Weaver AL, et al. Complications of cutaneous surgery in patients taking clopidogrel-containing anticoagulation. J Am Acad Dermatol. 2011;65:584–91.
37b. Bordeux JS, Martires KJ, Goldberg D, et al. Prospective evaluation of dermatologic surgery complications including patients on multiple antiplatelet and anticoagulant medications. J Am Acad Dermatol. 2011;65:576–83.
38. Whitaker DC, Grande DJ, Johnson SS. Wound infection rate in dermatologic surgery. J Dermatol Surg. 1988;14:525–8.
39. Mehrany K, Weenig RH, Pittelkow MR, et al. High recurrence rates of squamous cell carcinoma in patients with chronic lymphocytic leukemia. Dermatol Surg. 2005;31:38–42.
40. Busam KJ, Hester K, Carlos C, et al. Detection of clinically amelanotic malignant melanoma and assessment of its margins by in vivo confocal scanning laser microscopy. Arch Dermatol. 2001;137:923–9.
41. Phillips PK, Roenigk RK. Statistics. In: Snow SN, Mikhail GR (eds). Mohs Micrographic Surgery, 2nd edn. Madison: University of Wisconsin Press, 2004:414–20.
42. Gross KG, Steinman HK, Rapini RP. Mohs Surgery: Fundamentals and Techniques. St. Louis: Mosby, 1999.
43. Snow, SN. Mohs surgery wound management: flaps, grafts and wound care. Madison, WI: Scope Publishing, 2010.
44. Mohs FE, Snow SN, Kivett WF, et al. Anatomic rubber stamps of the face and body to document procedures in dermatologic surgery: One picture is worth a thousand words. J Dermatol Surg Oncol. 1990;16:280–91.

This page intentionally left blank

Surgical Complications and Optimizing Outcomes

151

Anna S Clayton and Thomas Stasko

Key features

- A thorough preoperative assessment of the patient is required to increase the chances for a successful outcome for any surgical procedure
- Attention to detail, selection of the simplest procedures that will produce the desired result, and meticulous intraoperative technique will prevent many complications
- Anticipation of avoidable complications and careful management of unavoidable ones optimize the results
- Clear communication between patient and surgeon must begin before the start of the procedure and continue through every stage, including the recovery and healing phases
- Many complications do not manifest until several days to months postoperatively; the patient must be monitored periodically to ensure that all parties are satisfied with the final outcome

INTRODUCTION

The verb "to complicate" means to make or become intricate and/or difficult. Surgical complications are deviations from the original planned outcome, which usually occur as the result of a series of multiple interrelated events (Fig. 151.1)[1]. Because of the nature of cutaneous surgery, the unexpected can and does happen; however, with careful planning and meticulous attention to technique and detail, many potential complications can be avoided or minimized.

Complications can threaten the patient's life, the ability to heal, and the cosmetic appearance of the scar. Life-threatening emergencies in cutaneous surgery are rare, but the surgeon must be prepared to deal with such problems as cardiac arrhythmias and anaphylaxis. Proper, well-maintained resuscitation equipment must be readily available, and the staff should be trained in Basic Life Support. Physicians in offices where extensive cutaneous surgery is performed should also have training in Advanced Cardiac Life Support. A full discussion of this topic is beyond the scope of this chapter, but it is well covered in other sources[2,3].

The surgeon should conduct a thorough preoperative assessment of the patient, including history and directed physical examination, to identify pre-existing conditions that may affect the patient's ability to heal. Informed consent obtained at this time and again just prior to the procedure ensures that the patient is well educated about what to expect. This education may minimize future misunderstandings. An outcome that the patient perceives as unexpected may in reality be an expected outcome for the given procedure. A discussion of the possible risks prior to the procedure may avoid this confusion.

Prevention of an unsatisfactory outcome starts in the planning stage of the procedure, then continues with good intraoperative surgical technique and careful postoperative care. Anticipation of avoidable complications and management of unavoidable ones optimize the results. Throughout the process, it is essential to involve the patient in his or her own care.

DISCUSSION

Preoperative Assessment

A thorough preoperative assessment is an invaluable tool for identifying conditions that could lead to surgical complications. A simple one-page preoperative questionnaire can be completed by the patient – with help from the nurse, technician or physician, as needed – at the time of the initial evaluation. "Yes" or "no" answers to specific questions can indicate a need for further evaluation or for a change in operative procedure or plan (Fig. 151.2).

Potential for bleeding

Although some bleeding is an expected part of any surgical procedure, excessive bleeding is a common complication. The discovery of a bleeding disorder prior to surgery allows for an attempt to correct the condition if it is reversible, or postponing or changing plans for surgery if it is not. The bleeding disorder may be due to abnormalities in the *coagulation cascade* (inherited deficiencies in coagulation factors, as in hemophilia) or with the *platelets*, or a combination of the two[4]. Platelet problems can be subdivided into problems with *production* (leukemia, use of myelosuppressive drugs), problems with *survival* (disseminated intravascular coagulation, idiopathic thrombocytopenic purpura), or problems with *function* (drugs, Hermansky–Pudlak syndrome).

If there is no history indicative of a bleeding disorder, and the patient is otherwise well, laboratory testing is usually unnecessary; however, appropriate screening laboratory tests should be checked if there is a suspicion of a hereditary or acquired bleeding disorder. A platelet count as part of the CBC (complete blood count) identifies only a quantitative problem. The bleeding-time test measures platelet function, but it can be difficult to perform and interpret as the results are very much operator-dependent. An *in vitro* bleeding-time assay, the platelet function analyzer 100 (PFA-100), provides an easy method for rapidly assessing platelet function. Unlike the bleeding time, the PFA-100 can be performed on a collected blood specimen. It is useful in detecting platelet defects, most cases of von Willebrand disease, and the effects of aspirin and other antiplatelet agents[5,6]. Additional standard screening tests include a PT (prothrombin time) test, which can determine a defect in the extrinsic clotting pathway and an aPTT (activated partial thromboplastin time) test, which can determine a defect in the intrinsic pathway[7].

A review of medications and nutritional supplements should be a part of the preoperative assessment. *Aspirin* and aspirin-containing products are well-documented sources of bleeding problems. Platelet aggregation is irreversibly affected when the aspirin acetylates cyclooxygenase. One aspirin affects a platelet throughout its lifespan of 6–10 days. Medically indicated aspirin should not be stopped. However, if the patient can safely discontinue aspirin without a high risk for stroke or myocardial infarction, it should be withheld for 10 days before surgery and then 5–7 days after surgery. Nonsteroidal anti-inflammatory drugs affect the same enzyme, though the block is not as severe or irreversible[8]. If possible, the patient should stop these medications 1–4 days prior to surgery, depending on the half-life of the drug. *Thienopyridines* (e.g. clopidogrel, ticlopidine) irreversibly inhibit platelet aggregation via inhibition of an ADP receptor on platelets. Normal platelet function usually returns 5–7 days after discontinuing these medications. In patients who take a thienopyridine for cardiac or neurologic indications, it is typically not advisable to stop the drug. Although there is a slightly increased risk of complications associated with dermatologic surgery in patients receiving thienopyridines, these medications can typically be continued without significant issues[9,9a].

Warfarin is a commonly used anticoagulant. Several studies have been published in the vascular, oral and dermatologic surgery literature that support the viewpoint that surgery can be performed without stopping warfarin as long as the international normalization ratio (INR) equals 2 to 3 or less[9–11]. The surgeon should minimize unnecessary undermining and ensure that intraoperative control of bleeding is meticulous. An INR should be checked just before surgery. The oral direct thrombin inhibitor, *dabigatran*, is increasingly been used as an

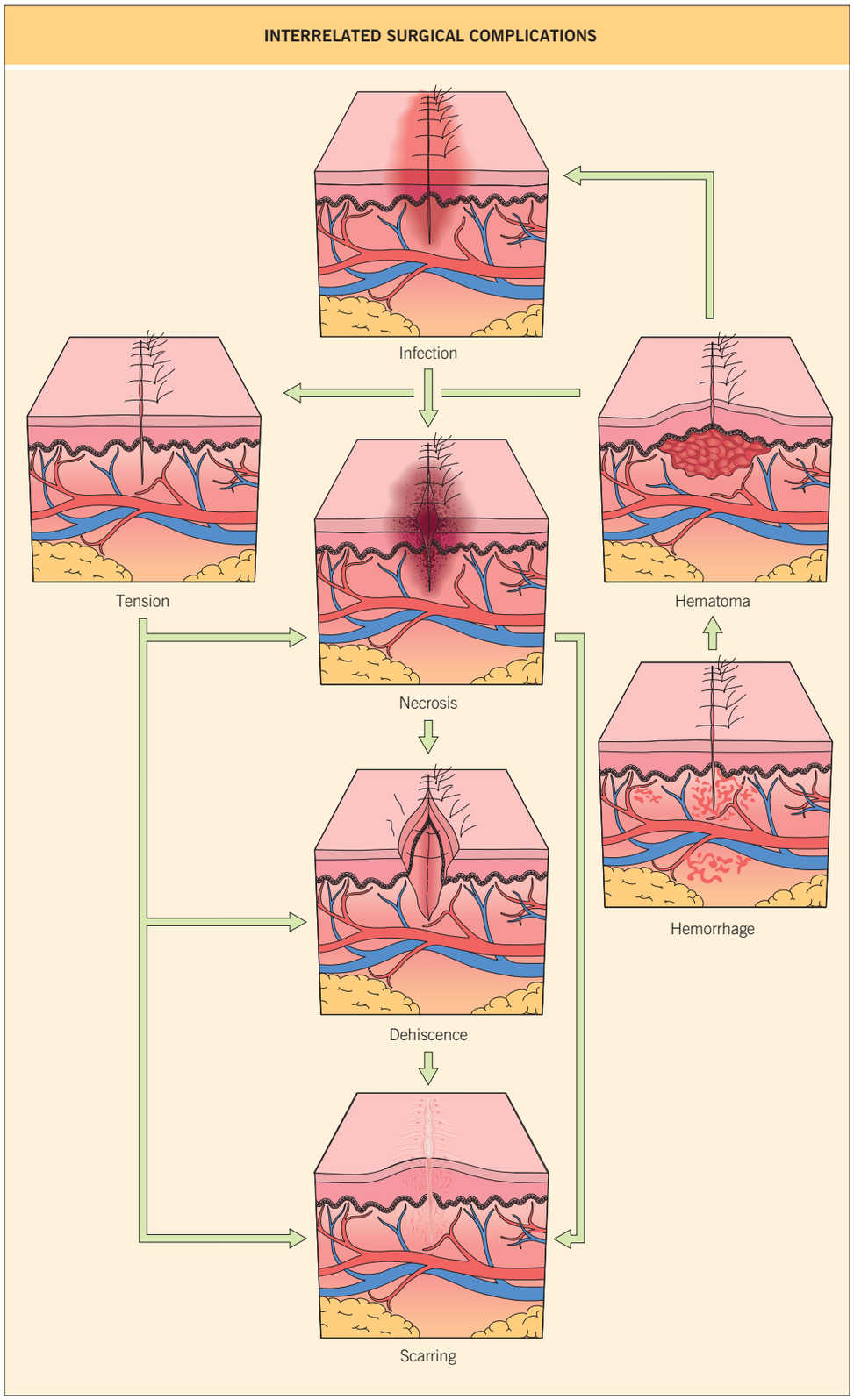


Fig. 151.1 Interrelated surgical complications.

alternative to warfarin[12a]. Literature is not yet available regarding the use of dabigatran in patients undergoing dermatologic surgery, but the authors would take similar intraoperative precautions as were mentioned above for patients on warfarin.

Heparin is given parenterally and acts as an antithrombin factor. When administered intravenously, heparin has a short half-life of approximately 1 hour and can be rapidly reversed by intravenous protamine sulfate. Heparin can be used to bridge patients who need an operative procedure that the surgeon feels should not be attempted in the presence of warfarin, but who cannot go without anticoagulation for prolonged periods of time. In a controlled setting, either subcutaneous low-molecular-weight heparin or intravenous unfractionated heparin is substituted for warfarin. Immediately before the surgery, heparin is discontinued or reversed with protamine sulfate. The heparin is then restarted post-procedure, again in a controlled setting[13].

Studies have shown that *vitamin E* in doses of 200–400 IU per day reduces platelet adhesion. Patients with abnormal platelets, such as diabetics and renal dialysis patients, treated with vitamin E have

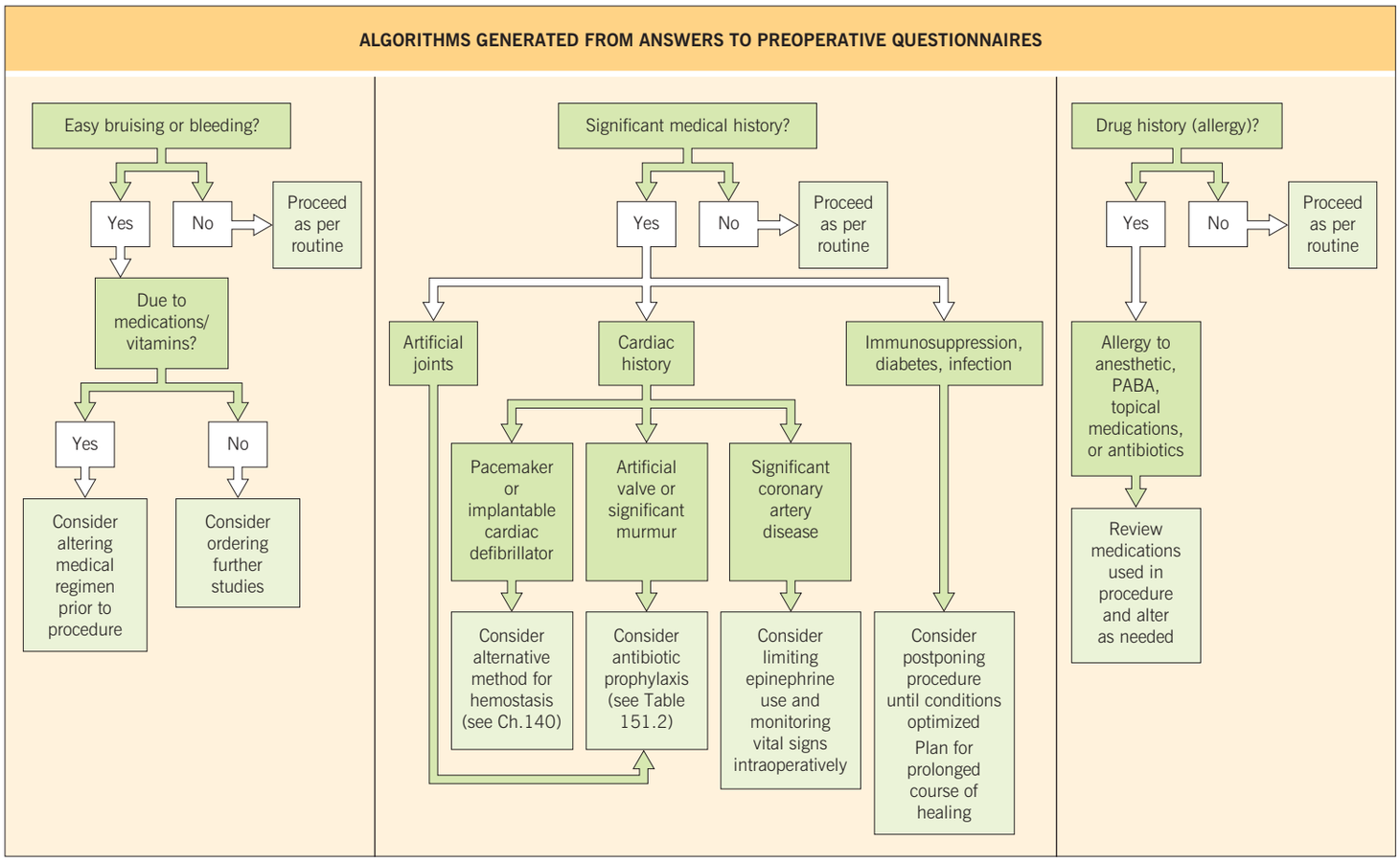


Fig. 151.2 Algorithms generated from answers to preoperative questionnaires. PABA, para-aminobenzoic acid.

decreased platelet aggregation. The effect is synergistic when vitamin E is taken with other antiplatelet agents such as aspirin and garlic. *Garlic* decreases platelet aggregation, and it significantly increases fibrinolytic activity at a dose of 900 mg/day. *Eicosapentaenoic acid* (fish oil) decreases platelet aggregation and adhesion and increases bleeding time. Many *other dietary supplements* such as dong quai, licorice, devil's claw and danshen have the same effect (see Table 133.3)[14]. Patients should be advised to discontinue supplements containing these substances in preparation for a surgical procedure.

Ethanol is a potent vasodilator. It may cause bleeding by inhibiting platelet aggregation and platelet granule release. It may also accentuate the increase in bleeding time caused by aspirin[15]. In addition, excessive alcohol consumption may decrease the patient's attention to optimal wound protection. Patients should be advised to avoid alcohol consumption during the immediate perioperative period.

Wound healing

The principles of wound healing are covered in detail in Chapter 141. To forestall complications due to poor wound healing, close attention should be paid to pre-existing medical conditions and medications that may affect wound healing. If the patient is a brittle diabetic, is suffering acutely from congestive heart failure, or has uncontrolled hypertension or a myriad of other severe conditions, it may be best to postpone the procedure until the patient's medical problems are under better control. If the procedure cannot be postponed, the patient should be forewarned that there might be a prolonged postoperative healing phase. In addition, any chronic debilitating illness may predispose patients to developing secondary infections.

Medications such as corticosteroids may also delay healing and predispose the patient to secondary infections and a prolonged postoperative course. Patients on other immunosuppressive medications such as cyclosporine may also be prone to infections and prolonged healing.

Cigarette smoking interferes with wound healing, and areas repaired by flaps or grafts are particularly susceptible. There is a dose-dependent decrease in the ability to heal after dermatologic surgery, with heavier smokers having an increased risk of post-operative necrosis as compared to lighter- and non-smokers[16]. In the authors' opinion, if the patient refuses to stop smoking, he or she should be strongly encouraged to decrease consumption to less than half a pack per day for 1 week preoperatively and for 3–4 weeks postoperatively, to attempt to maximize wound healing.

There is literature to support delaying procedures on patients who are on, or have recently completed, isotretinoin therapy, because of poor wound healing and the formation of excessive granulation tissue. In keloid fibroblast cultures, retinoids have been shown to modulate connective tissue metabolism. Most reported problems have been individual case reports involving resurfacing procedures after courses of isotretinoin for acne therapy. It may be prudent to postpone cosmetic procedures in such patients for up to 1 year after the cessation of isotretinoin therapy[17–19]. However, more recent data suggest that in select patients, acne scars can be treated with dermabrasion while taking isotretinion without side effects[19a].

Reactivation of a herpes simplex virus (HSV) infection can dramatically interfere with the postoperative course. Patients with a history of herpes labialis or other facial herpetic infections should receive prophylactic antiviral therapy prior to dermabrasion, laser resurfacing or chemical peels. Antiviral therapy, such as oral acyclovir at a dose of 200 mg five times a day, should start 2–5 days prior to the procedure and continue for 5 days postoperatively or until the skin has re-epithelialized[20]. Similar regimens consisting of oral famciclovir 250 mg three times daily or oral valacyclovir 1 g twice daily can also be utilized as they have more convenient dosing which can increase compliance.

The shoulders, central chest, upper arms and upper back are more prone to the development of hypertrophic scars, keloids and spread scars. The patient should be counseled before surgery about the increased risk of scarring in these areas.

Prophylactic antibiotics

Antibiotic prophylaxis is administered to prevent surgical site wound infection, the development of bacterial endocarditis, or infection in

WOUND CLASSIFICATION		
Class	**Attributes**	**% that develop infections**
Clean	Technique immaculate Non-inflammatory	1–4
Clean-contaminated	Small breaks in technique Gastrointestinal, respiratory or genitourinary tracts entered without gross contamination	5–15
Contaminated	Major breaks in technique Gross contamination from gastrointestinal, genitourinary or respiratory tracts	6–25
Dirty and/or infected	Wound with acute bacterial infection ± pus	>25

Table 151.1 Wound classification[1]. Technique in the table refers to sterile surgical technique.

implanted prosthetic devices. The risk and consequences of infection must be weighed against the risk and cost of administration of the antibiotic.

Wounds are placed into four general categories (Table 151.1). The majority of dermatologic surgical procedures fall into the clean or clean-contaminated categories and do not need prophylaxis. However, prophylactic antibiotics may be helpful in certain clean-contaminated wounds. Patients undergoing procedures involving the oronasal mucosa or genitourinary, axillary and gastrointestinal tissues should be considered for prophylactic antibiotics. In addition, procedures that approach the ear canal may be at higher risk for infection with Gram-negative organisms. Long procedures are also more likely to develop wound infections: the infection rate almost doubles with each hour of operation. Prophylactic antibiotics should be considered for procedures involving the lower extremities as well as more complicated procedures such as wedge excisions of the lip or ear, flaps on the nose and all grafts[21]. Antibiotics are therapeutic, not prophylactic, for contaminated or dirty and infected wounds; in such cases, a bacterial culture is helpful to best guide the antibiotic regimen.

When considering antibiotic prophylaxis, two special categories of patients should be addressed: (1) those at risk for infective endocarditis; and (2) those at risk for bloodborne infection of total joint replacements (Table 151.2)[21]. In the case of patients with total joint replacements (but not cardiac disease), prophylactic antibiotics are also recommended for surgery in non-infected sites at high risk of surgical site infection. However, if the surgical procedure and uncomplicated repair is to be performed in a non-infected, low-risk site, no antibiotic prophylaxis is indicated. Table 151.3 summarizes suggestions for antibiotic prophylaxis regimens. If any question arises, consultation with the patient's cardiologist, internist or orthopedic surgeon may prove quite helpful in determining the need for prophylaxis and the regimen to be used.

Defibrillators and pacemakers

The electrosurgical instruments often used in cutaneous procedures have the potential to interfere with the function of pacemakers and implantable cardioverter-defibrillators (ICD; see Ch. 140). If the patient's preoperative history reveals the presence of such devices, caution should be exercised to avoid inducing arrhythmias. Alternatives to electrosurgery may be considered. Battery-operated and AC-powered thermal cautery units have been used successfully in dermatologic surgery. They do not produce high-frequency electromagnetic interference or electrical currents traversing the body. Bipolar instruments concentrate the current across the tips, minimizing the chance of interference with implanted devices. If conventional electrosurgery must be used, the active tip should not be applied to an area within 15 cm of the implanted device whenever possible. Electrocoagulation should also be kept at as low a setting as possible, and it should be delivered in bursts lasting <5 seconds in order to minimize the chance of prolonged inhibition[22].

In consultation with the patient's cardiologist, the ICD can be deactivated for the duration of the procedure. The pacemaker can also be

ANTIBIOTIC PROPHYLAXIS FOR DERMATOLOGIC SURGERY – PATIENT GROUPS AT RISK FOR INFECTIVE ENDOCARDITIS AND INFECTION OF TOTAL JOINT REPLACEMENTS
HIGH-RISK CARDIAC CONDITIONS (INFECTED SKIN OR BREACH OF ORAL MUCOSA)
• Prosthetic heart valve • History of infective endocarditis • Unrepaired cyanotic congenital heart disease (includes palliative shunts) • Completely repaired congenital heart defects with prosthetic materials or devices* • Repaired congenital heart disease with residual defects at or adjacent to site of prosthetic patch or device • Cardiac transplant recipients who develop cardiac valvulopathy
TOTAL JOINT REPLACEMENTS (INFECTED SKIN, BREACH OF ORAL MUCOSA, OR NON-INFECTED SITE AT HIGH RISK OF SURGICAL SITE INFECTION)
• First 2 years after joint placement • Previous prosthetic joint infections • Type 1 diabetes mellitus • Immunosuppression (HIV infection, medications, underlying malignancy) • Malnourishment • Hemophilia
*First 6 months after procedure.

Table 151.2 Antibiotic prophylaxis for dermatologic surgery – patient groups at risk for infective endocarditis and infection of total joint replacements. Adapted from the American Heart Association, the American Dental Association, and the American Academy of Orthopedic Surgeons[21].

RECOMMENDATIONS FOR ANTIBIOTIC PROPHYLAXIS IN PATIENTS AT RISK FOR INFECTIVE ENDOCARDITIS AND INFECTION OF TOTAL JOINT REPLACEMENTS			
Surgical site/procedure	**Allergy**	**Antibiotic**	**Dose**
Non-oral – wedge excisions of lip or ear, nasal flaps, all grafts	None	Cephalexin* or dicloxacillin* *– or –* cefazolin/ceftriaxone*	2 g PO† 1 g IM/IV
Non-oral – wedge excisions of lip or ear, nasal flaps, all grafts	Penicillin	Clindamycin or azithromycin/ clarithromycin* *– or –* clindamycin	600 mg PO 500 mg PO 600 mg IM/IV
Oral mucosa breached	None	Amoxicillin *– or –* cefazolin/ceftriaxone or ampicillin	2 g PO 1 g IV/IM 2 g IV/IM
Oral mucosa breached	Penicillin	Clindamycin or azithromycin/ clarithromycin *– or –* clindamycin	600 mg PO 500 mg PO 600 mg IM/IV
Lesions in the groin or on the legs	None	Cephalexin* or TMP-SMX DS *– or –* ceftriaxone*	2 g PO 1 tablet PO 1–2 g IV
Lesions in the groin or on the legs	Penicillin	TMP-SMX DS or levofloxacin* *– or –* clindamycin and gentamicin	1 tablet PO 500 mg PO 600 mg and 2 mg/kg IV
*In communities with increased risk for methicillin-resistant *Staphyloccoccus aureus*, consider prophylaxis with TMP-SMX DS (1 tab PO) or clindamycin (600 mg PO). †Give PO single dose 30–60 minutes before procedure.			

Table 151.3 Recommendations for antibiotic prophylaxis in patients at risk for infective endocarditis and infection of total joint replacements (Mayo Clinic)[21]. IM, intramuscular; IV, intravenous; PO, by mouth; TMP-SMX DS, trimethoprim–sulfamethoxazole double-strength.

placed in a fixed rate mode, rather than the sensing mode, to minimize the possibility of interference. During the procedure, if conventional electrosurgery is to be used, continuous cardiac monitoring with an ECG and possibly a pulse oximeter should be strongly considered. A contingency plan should be in place to deal with an arrhythmia should it occur and an automated external defibrillator (AED) should be immediately available. If the device is deactivated or its function altered for the procedure, it is the surgeon's responsibility to ensure that the patient returns to his or her cardiologist within a reasonable time, for readjustment and evaluation post-procedure. Electrical equipment should be properly grounded during the procedure. If bipolar forceps or true electrocautery is used instead of electrosurgery, intraoperative monitoring, cardiology consultation and postoperative evaluation may be unnecessary for most stable patients[23].

Allergies

True allergic reactions to local anesthetics may be type I (immediate) or type IV (delayed-type hypersensitivity) (see Ch. 143). Patients who have a type IV sensitivity to one major group of local anesthetics (ester or amide) are usually not allergic to members of the other group. However, patients with a history of para-aminobenzoic acid (PABA) allergy can cross-react with anesthetics in the ester group (e.g. procaine). Type I reactions are more commonly associated with the ester anesthetics and their PABA metabolite. Although the lack of cross-reactivity between ester and amide anesthetics is true for type IV sensitivity, it has not been adequately studied for anaphylaxis. If there is a possibility of a type I amide allergy by history, or if the surgeon is reluctant to substitute an amide in an ester-allergic patient, referral to an allergist for a progressive challenge protocol can be considered to identify a suitable amide anesthetic[24]. It is also important to consider the possibility that the allergic reaction is due to the preservative (e.g. methylparaben, metabisulfite) and the use of preservative-free anesthetics can resolve this problem.

Epinephrine (adrenaline) is a vasoconstrictive agent commonly added to local anesthetics because it lessens bleeding and prolongs the duration of anesthesia. Patients will occasionally report a history of an "allergy" to local anesthetic, describing their symptoms of palpitations, headache, tachycardia, tachypnea or tremor (see Ch. 143). These reports may, in truth, be reactions to epinephrine given in high dosages or inadvertently injected intravascularly. Since the half-life of epinephrine in serum is short, when these reactions do develop, specific therapy is usually not necessary. In order to avoid them, the lowest dosage and concentration of epinephrine (less than 1 : 200 000) should be used and injection of significant amounts intravascularly should be avoided using proper infiltration technique[25].

Another very commonly encountered systemic side effect often mistaken by the patient as an allergic reaction is the vasovagal reaction. The patient recalls becoming pale, sweaty and lightheaded, perhaps even fainting. In contrast to a true toxic or allergic reaction, the pulse remains slow and regular and the blood pressure and respiratory rate are normal (see Table 143.3). No loss of bowel or bladder control or prolonged tonic-clonic movement occurs unless the patient has a seizure secondary to brain hypoxia during the vasovagal reaction. Treatment consists of keeping the patient supine or in the Trendelenburg position and giving reassurance until the patient recovers sufficiently to be allowed to gradually sit up and ambulate[26].

Chlorhexidine gluconate is a frequently utilized surgical skin preparation. It is a broad-spectrum antibacterial of the halogenated phenol class. Though it has a very weak sensitizing potential, it has been reported to cause allergic contact dermatitis[27]. Similar reactions have also occurred with the iodophor povidone-iodine (Betadine®)[28]. Both compounds can also be skin irritants, especially when occluded. Care must be taken to ensure that all traces of skin cleanser are removed prior to application of the dressing.

Topical antibiotics can cause allergic contact dermatitis. Neomycin is the most common sensitizer, though bacitracin can also cause sensitization. Co-reactivity against both neomycin and bacitracin is common. Cross-sensitivity between neomycin and gentamicin, kanamycin, streptomycin and tobramycin can also occur. Mupirocin or erythromycin ointment are alternatives if the patient is allergic to both neomycin and bacitracin. As there is no convincing evidence that topical antibiotic ointment prevents infection, plain petrolatum (paraffin) ointment may be the best agent for wound dressing.

Informed consent

The lines of communication should be open between the surgeon and the patient before the procedure begins. The physician should make the patient aware of his or her condition, how it affects overall health, if treatment is imperative, and what different treatment options might be available. Pros and cons of surgery as well as alternative therapies should be discussed in a language that the patient can easily understand. To assess how much the patient understands, it helps to ask the patient to describe the procedure in his or her own words. The patient should also be informed about the risks of the procedure and the results to be reasonably expected. Common complications (like bleeding, infection, allergic reactions, scarring) should be addressed and strategies for dealing with them discussed. In turn, the patient must accept responsibility for preoperative preparation and postoperative wound care.

It is the surgeon's responsibility to provide oral and written, clear, detailed information delineating the indications for the procedure and describing the procedure, the risks involved, and the postoperative care necessary to ensure the best outcome possible. Should complications arise, as they inevitably will in some cases, the surgeon should be honest with the patient about treatment options and outcome.

Intraoperative Considerations

Contamination

Although good statistics are lacking, the risk of infection in cutaneous surgery is very low. It is certainly less than 5%, and most probably is in the range of 1–2%. The indications for prophylactic antibiotics were discussed previously. Although wound infections usually do not become evident until 4–8 days postoperatively, in most cases the infection truly begins at the time of surgery. The surgical team should prepare the skin and the surgical field, prepare the instruments, and wear the correct protective equipment in order to help reduce the incidence of infection and protect both the patient and caregivers.

The skin cannot be sterilized, but it is possible to remove the majority of the resident flora and pathogenic bacteria by using mechanical cleansing and antiseptic agents. The extent of skin preparation varies with the invasiveness and complexity of the proposed surgical procedure. A 2-second wipe with 70% isopropyl alcohol or a 10-second cleansing with an iodophor swab may be adequate for most shave and superficial biopsies[29]. Chlorhexidine produces rapid bacterial destruction, is effective against a wide range of Gram-positive and Gram-negative bacteria, and binds with the protein of the stratum corneum, providing residual action. These properties make it the most frequently used preoperative preparation for skin surgery. It is, however, irritating to the conjunctiva, and it may be toxic to the cornea or tympanic membrane and middle ear, so caution must be exercised in these areas. Iodophors are another excellent antiseptic; one advantage is that the area that has been prepared is readily apparent because of the brownish-orange color. They are effective against Gram-positive and Gram-negative bacteria and some fungal spores, but they have a slower and shorter duration of action than chlorhexidine. Also, as noted earlier, they can cause skin irritation, and there are patients who may develop an allergic contact dermatitis to this cleanser.

The preparation and sterilization of surgical instruments is covered in Chapter 144. Use of the surgical mask may help protect the patient from surgical personnel with active upper respiratory tract infections. The mask protects the surgical team from contamination by saliva droplets or blood from the patient. It is also essential to protect the eyes from accidental splashes of body fluid. Appropriate surgical attire and glove use is advocated in all surgical situations as part of universal precautions. In cases where sterility is not essential, such as superficial shave biopsies and electrodesiccation and curettage, non-sterile examination gloves can be used. Some dermatologic surgeons perform Mohs surgery in a sterile fashion while others use a clean technique. Recent data suggest that Mohs surgery can be performed as a clean procedure with low infection rates[29a].

Bleeding and hemostasis

Hemostasis can be approached based on the amount of bleeding encountered (Fig. 151.3). Bleeding that occurs during shave biopsies, i.e. superficial dermal oozing, can be controlled through the use of mechanical pressure or topical hemostatic agents such as aluminum

chloride[30] or electrodesiccation. Bleeding which occurs during more extensive procedures such as excisions or Mohs procedures, i.e. vascular bleeding or muscle oozing, may require suturing, use of other hemostatic agents (Table 151.4), electrocoagulation, or a combination of techniques.

Intraoperative bleeding can obscure the surgical site. It can be upsetting to both the surgeon and the patient. If it continues after closure, it can cause a hematoma that can lead to infection, increased tension on wound edges, and dehiscence (see Fig. 151.1). A careful history should have helped to identify patients prone to bleeding, and

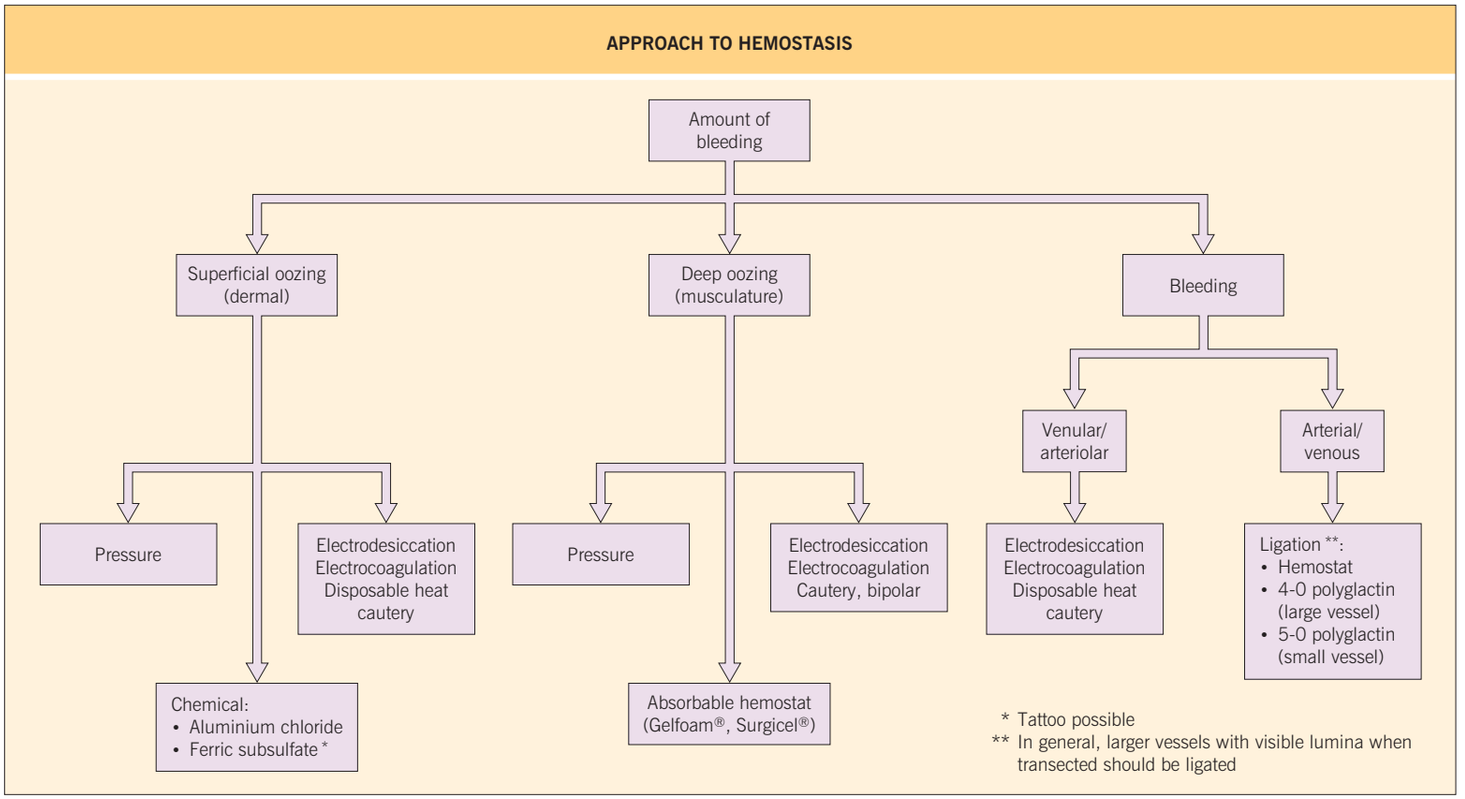


Fig. 151.3 Approach to hemostasis. *Courtesy, Glenn Goldman, MD.*

HEMOSTATIC AGENTS

Generic name	Trade name®,™	Advantages	Disadvantages
Bone wax	Bone wax	Effectively controls bony surface bleeding (skull)	Impedes bacterial clearance; nidus for infection
Gelatin foams	Gelfoam, Gelfilm, Surgifoam	Non-antigenic; absorbed within 4–6 weeks; controls small vessel and bony bleeding	Significant swelling occurs
Oxidized cellulose	Surgicel, Oxycel	Low pH has antimicrobial effect; dissolves in 2–6 weeks	May cause foreign body reaction; can not combine with thrombin
Microfibrillar collagen	Avitene, Helistat, Instat, Collastat	Swelling not significant; absorbed in <8 weeks	Less effective in thrombocytopenic patients
Thrombin	Thrombin-JMI, Evithrom, Recothrom	Fast, controls minor capillary and small venule bleeding	Do not use in individuals who react to human blood products
Thrombin with gelatin	Floseal	Controls moderate arterial bleeding	Can swell up to 20%; needs contact with blood which serves as fibrinogen source
Fibrin sealants	Tisseel, Evicel	Controls venous oozing from raw surfaces	Can be denatured by antiseptics containing alcohol, iodine or heavy metal ions
Ferric subsulfate (20% solution)	Monsel's solution	Inexpensive; low pH resists bacterial contamination	Can cause tattoo/discoloration; for superficial oozing
Silver nitrate (applicator sticks)		Easily stored; some bacteriostatic properties	Tattoo risk; for superficial oozing
Aluminum chloride (20–40% solution)	Drysol, Xerac AC, Certain Dri	Inexpensive	Some formulations flammable; may delay wound healing; for superficial oozing
Powders composed of hydrophilic polymers with potassium salts	QR powder	Fast, inexpensive	Can only be used on wounds healing by second intention
Powders composed of microporous polysaccharide hemospheres	Bleed-X	Absorbed by body so can be used on wounds that will be closed	

Table 151.4 Hemostatic agents.

it may have allowed for changes in medical management or medications preoperatively, to reduce intraoperative bleeding. When not contraindicated (e.g. procedures on toes or fingers in patients with peripheral vascular disease), use of epinephrine with the anesthetic is helpful (see Ch. 143). Suction can also maintain good visualization in an otherwise bloody field. An assistant can provide traction across the wound surface or pressure at the periphery of the site. Frequent blotting with sponges or cotton-tipped applicators also helps to keep the field clear.

Bleeding should be controlled as soon as is practical; individual small vessels should be isolated and precisely cauterized (to avoid excessive char) or ligated. It may be prudent to ligate visible vessels lying proximal to the wound bed, since they might be nicked or partially cut during the procedure. Large vessels noted in the surgical wound should be tied off or cauterized at both visualized ends as long as the surgeon is sure there is adequate collateral circulation to the area. Tying off visible vessel ends using a figure-of-eight technique with an absorbable suture provides reliable hemostasis (see Fig. 146.2). Of note, bleeding, which may not be apparent at the time of the closure, may develop once the effect of epinephrine diminishes. The surgeon must ensure that the surgical field is as dry as possible prior to closure. Particular attention should be paid to apices or cut muscle that can steadily ooze.

If, at the beginning of the procedure, bleeding is more than usual, undermining should be minimized and consideration should be given to a linear closure rather than a flap or graft. Blood easily accumulates unnoticed in non-visualized "dead space". Placement of a drain should be considered for larger flaps or complex multilayered linear closures, to allow egress of small amounts of continued bleeding and to avoid hematoma formation. Drains can be classified into open and closed systems. An example of an open system, which lacks an enclosed network or collecting system, is a Penrose drain. It is a passive drain, allowing fluids to flow passively by gravity into gauze. For dermatologic surgery, a simple fenestrated small Penrose drain can often suffice (Fig. 151.4). It should be removed 24–48 hours later, once bleeding has lessened and the chance for hematoma formation has diminished. Closed systems are sealed, with a draining tube connected to a container with the potential for generating active suction to draw the fluid from the tissue cavity into the container. Examples of closed systems include the vacuum mini-flap drain[31] and the Jackson–Pratt drain.

In open wounds that continue to bleed in spite of adequate attempts at hemostasis, hemostatic agents[32,32a] such as gelatin foams (Gelfoam®), oxidized cellulose (Oxycel®, Surgicel®), microfibrillar collagen (Avitene®, Collastat®) or topical thrombin can be applied to the wound to provide a matrix to speed coagulation (see Table 151.4). Caution should be exercised when using oxidized cellulose, because the use of excessive amounts can result in foreign body reactions[33].

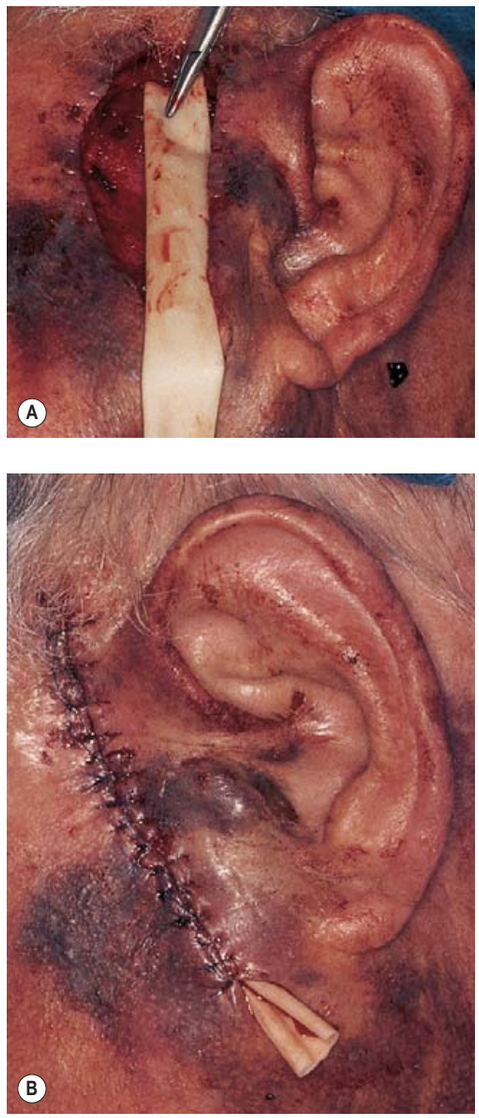


Fig. 151.4 Placement of Penrose drain because of excessive bleeding.

Tissue injury

Because of the nature of invasive procedures, some tissue injury is unavoidable. Gentle handling of the wound edges during the procedure minimizes trauma and allows the viable tissue to heal more rapidly. Skin hooks or single-toothed forceps should be used carefully to grasp tissue without crushing it. When using electrocautery or electrocoagulation to control bleeding, avoid indiscriminate and excessive burning. Large areas of charred and necrotic tissue left in the wound increase the risk of inflammation and infection.

Tension

Excessive tension at the closure site can cause tissue necrosis and dehiscence (see Fig. 151.1). Postoperatively, tension can be a source of increased discomfort for the patient once the local anesthesia has dissipated. There is a tendency for the surgeon to tighten surface sutures when wounds gape open. Such action can lead to "train track" scars. At the time of surgery, the operative site should be thoroughly evaluated and the closure planned to minimize wound tension. Adequate undermining should be accomplished. Buried absorbable sutures should bear the burden of the tension, minimizing the need for tight surface sutures. The closure should be oriented to take advantage of maximal tissue movement. Instead of a linear closure, using a flap or graft to close the defect can minimize tension in appropriate circumstances. Relaxing incisions can also be performed 2–3 cm from the wound edge, parallel to the incision site, to share tension over a larger area. If the defect cannot be completely closed due to excessive tension, partial closure can be accomplished and the remainder of the wound allowed to heal secondarily. If the site is chosen well (usually in concave areas), this method yields an excellent cosmetic result. Intraoperative or preoperative tissue expansion may also allow for the safe closure of large defects[34]. If a wound appears too tight at the time of closure, it probably is, making complications more likely (Fig. 151.5).

Necrosis

Necrosis is usually the result of a hematoma, an infection, or wound tension compromising blood flow to the skin edge, resulting in necrotic tissue (see Fig. 151.1). Although pale, poorly perfused tissue at a flap or wound edge may be a warning of future problems with perfusion, actual necrosis will not become evident until the postoperative time period. The factors leading to necrosis begin preoperatively and continue into the perioperative period. The hazards of smoking have been discussed earlier, but they cannot be overemphasized. Smoking decreases perfusion and increases the risk of necrosis. Patients should be counseled repeatedly to stop, or at the very least decrease, their exposure to tobacco or other nicotine-containing products.

The blood supply to the skin arises primarily from the subdermal plexus. Extensive superficial undermining may damage this plexus and the segmental arteries supplying it. Hematoma formation may compromise blood flow to and from the area through pressure on this plexus. Even normal postoperative edema may compromise blood flow. Sutures tied too tightly may also decrease perfusion, leading to necrosis. The use of a loop stitch, leaving space between the first and second

Fig. 151.5 Postoperative appearance of wound closed under tension with resulting necrosis.

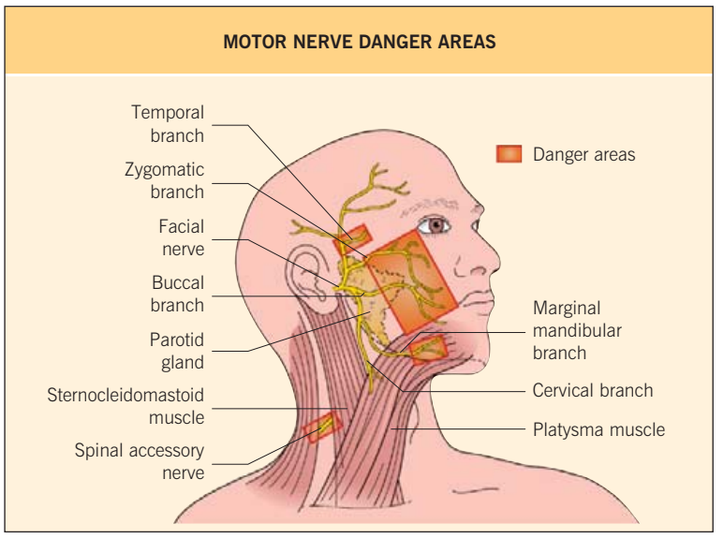


Fig. 151.6 Motor nerve danger areas.

loops of the surgeon's knot, may allow for tissue expansion from post-surgical edema, decreasing the risk of tissue necrosis.

The vasoconstrictive properties of epinephrine that make it ideal in most locations may be extremely detrimental in areas with limited collateral circulation such as the digits. In such cases, it would be prudent to use smaller amounts of an anesthetic that contains epinephrine, a more dilute epinephrine concentration (e.g. 1 : 500 000 instead of 1 : 100 000), or a local anesthetic without epinephrine.

Flap tips may become necrotic because of an inadequate blood supply. If the 3 : 1 length-to-base ratio is exceeded, circulation to the distal tip may be poor. When correcting redundancies caused by rotation at the base of a flap, the surgeon must ensure that the pedicle is not narrowed. Correction of the redundancy may need to be delayed in order to protect the vascular supply to the flap.

Grafts may become necrotic if an adequate blood supply from the wound bed is not established. In general, full-thickness skin grafts require more nutrients than split-thickness grafts (see Ch. 148). Areas with a poor or absent vascular supply, such as exposed bone, exposed cartilage or sites of previous therapeutic radiation, often cannot support full-thickness grafts and may not fully support even split-thickness grafts. In particular, sites with greater than 1 cm^2 of exposed bone or cartilage have a greater incidence of graft failure. Delaying graft placement for about 10 days after the initial surgery may improve graft take.

The graft must also be well apposed to the wound bed. Strict hemostasis is required to prevent blood from accumulating in the space between the graft and the wound. However, excessive electrocoagulation should also be avoided because of the resulting necrotic debris created. Absorbable hemostatic agents may also interfere with the engrafting of the new tissue. The placement of basting sutures and tie-down bolsters may help ensure adequate contact between the graft and the wound bed (see Ch. 148).

Nerve deficits

The preoperative evaluation should include a quick survey of neurologic function in the areas that could be affected by the proposed procedure. During cutaneous surgery, sensory and motor nerves may be injured or cut (see Ch. 142). It is essential to document – and, more importantly, make the patient aware of – pre-existing deficits prior to infiltrating the anesthetic (see Ch. 143). Local anesthesia or nerve blocks can lead to temporary nerve deficits lasting 6–12 hours. Full evaluation of the extent of the injury may have to wait until a day to several weeks after surgery.

Skin surgery will result in the transection of cutaneous nerves. Patients frequently note sensory deficits at the site of primary closures or flaps. Almost all will experience hypoesthesia in skin grafts. Most areas have diverse sensory innervation, and, unless a major nerve is injured, there are very few significant permanent deficits. Sensory nerves often do regenerate, though this process may take a number of months. The patient should be aware preoperatively that there may be paresthesias in the area as it heals. Occasionally, completely normal sensation never returns. The areas most prone to sensory nerve injury leading to noticeable sensory defects are the digits, the forehead and the scalp.

Injury to motor nerves can be more alarming, since this can result in paralysis of the denervated muscles. The closer to the nerve root that the injury takes place, the more severe the consequence. Thankfully, most of the larger branches of the facial nerve are deep to the muscle fascia and well protected. As a result, injuries to the main trunk of the facial nerve (or its zygomatic and buccal branches) rarely occur in dermatologic surgery, because these nerves lie relatively deep and are somewhat protected. Injuries to these nerves do, however, result in significant sequelae, including an inability to close the eyelids, loss of sphincter control around the mouth leading to drooling, and a distorted face.

The area of highest consequence on the cheek lies lateral to a line drawn from the lateral canthus of the eye to the angle of the mouth and medial to where the nerve divides into five major branches near the surface of the parotid gland (Fig. 151.6). Medial to this area, innervation is usually diverse enough to render the results of transection of a single nerve mild. Lateral to this area, the main trunk lies deep within the parotid gland and is relatively well protected by it[35]. Unless the procedure is a deep excision of an infiltrative skin cancer, the majority of cutaneous surgeons are unlikely to cause significant motor nerve injury except in the following important danger zones:

- The *temporal branch of the facial nerve* courses very superficially as it crosses the zygomatic arch and traverses the temple where it is covered only by the superficial temporalis fascia, with very little subcutaneous fat. The nerve lies deep to the superficial temporal artery. Paralysis of the frontalis muscle results from transection of the nerve in this location. The ability to elevate the forehead on the affected side is lost (Fig. 151.7A). This loss is often of only cosmetic concern; however, if there is pre-existing brow ptosis, the paralysis may result in a severe ptosis that interferes with vision and requires surgical correction with a brow pexy.
- The *zygomatic branch of the facial nerve*. Damage to this nerve, although less common than damage to the temporal branch, can lead to an inability to completely appose the upper and lower eyelids and subsequent corneal desiccation. This is due to its innervation of the obicularis oculi muscles.
- The *mandibular branch of the facial nerve* is subject to injury as it crosses the mandible, near the facial artery and vein. It is covered at this point only by skin and thin platysma muscle. This nerve innervates the lip depressors, and injury can cause asymmetry visible when the patient smiles or attempts other facial expressions using these muscles. In addition, mouth function may be compromised, resulting in drooling.
- The *spinal accessory nerve* can be damaged as it exits from behind the sternocleidomastoid muscle at Erb's point in the posterior

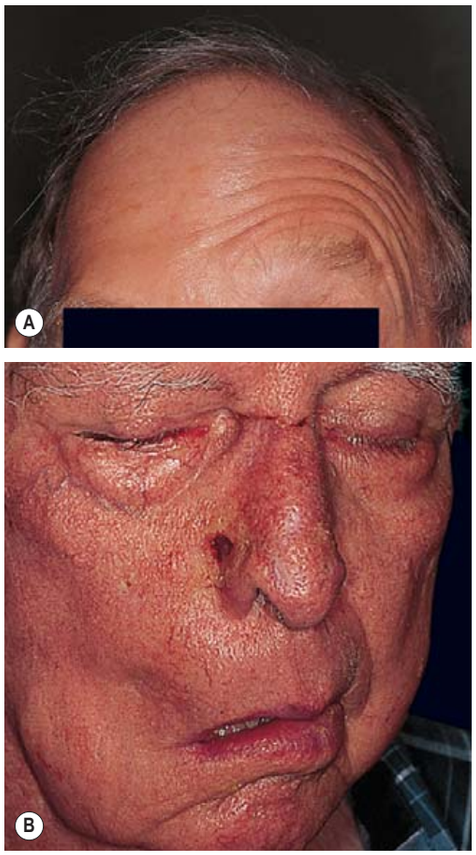


Fig. 151.7 Damage to the facial nerve. A Loss of the ability to elevate the forehead due to transection of the temporal branch. **B** Loss of function of the main branch of the facial nerve. The ability to close the right eye has been restored by the placement of a gold weight in the eyelid.

Fig. 151.8 "Trapdoor" or "pincushion" appearance of a flap reconstruction.

triangle of the neck. Damage leads to winging of the scapula and difficulty abducting the arm, because of paralysis of the trapezius muscle. Pain is a frequent accompaniment of injury to the spinal accessory nerve.

The surgeon must be aware of these danger zones and be on the lookout for these nerves (see Fig. 151.6). Injury is sometimes unavoidable even with the most careful dissection, especially if a neoplasm involves the nerve. Early consultation, even preoperatively, with the appropriate specialties (neurology, neurosurgery, radiation oncology) may allow for optimal management of the problems. Regeneration of motor nerves is possible, but unpredictable. When major motor branches are cut, surgical reapproximation or nerve grafts may be necessary. Muscle stimulation may prevent atrophy while awaiting return of function. At times it may be practical to simply address the functional problems created, such as placing gold weights to allow eye closure (Fig. 151.7B).

Unsatisfactory scarring

Although scars do not acquire their final appearance until months postoperatively, operative techniques can greatly affect the appearance. Spread scars were discussed earlier. Though they may be unavoidable in certain anatomic areas, the surgeon may choose to use longer-lasting absorbable or non-absorbable sutures in the deeper layers of the closure, in order to reduce the risk of early spread scars[36].

A trapdoor or pincushion-like appearance may develop in the area of transposition flaps (Fig. 151.8). Wide undermining at the time of repair and squaring off the corners, rather than trimming more circular wound edges, may reduce the incidence of this complication[37]. Removing excess subcutaneous tissue underneath the flap and trimming the flap so that it just covers the defect without any redundancy may also help.

Postoperative Considerations

After the procedure is complete and the patient has left the office, complications may still occur. Before the patient leaves, detailed wound care instructions should be reviewed with the patient and whomever else may be helping to care for the wound site. The surgeon must also ensure that the patient has been provided with easy-to-understand, written postoperative wound care instructions. These instructions should include answers to the most commonly asked questions, for example, "How do I know if it is infected?" "How much bleeding is too much bleeding?" "When can I take a shower/bath?" "When can I play golf/ tennis?" The patient should also have a direct method of contacting the physician or a suitable representative if there are questions or concerns not answered by the handout provided. A little foresight and education can greatly reduce the number of midnight calls or quickly bring to the attention of the physician a complication best addressed earlier rather than later. It is imperative that the contact physician be available and responsive. It is helpful for the physician or designee to call the patient postoperatively to check on his or her progress and answer questions.

Bleeding/hematoma/ecchymosis

Some cases of postoperative bleeding will occur despite exhaustive preoperative evaluation, preparation, and careful intraoperative hemostasis. Most bleeding occurs within the first 24 hours, with the majority occurring within 6 hours. During this period, clots are still fragile and movement can easily dislodge them. As the epinephrine dissipates, small vessel bleeding may increase. A pressure dressing applied immediately after the procedure helps to prevent this problem. The patient should be instructed to leave the dressing in place for at least 24 hours. If the surgical procedure was more involved than a superficial shave or punch biopsy, the dressing should consist of multiple layers: ointment, then an initial non-adherent contact layer (e.g. Telfa®, Release®), followed by a bulky absorbent layer consisting of gauze, cotton, sponges or eye pads. An outer layer of tape or stretchable gauze (e.g. Ace Wrap®, Coban®) then covers all of these. The bandage should provide pressure but not cause ischemia.

A small amount of bleeding is normal; however, the patient should be told that bleeding which soaks the dressing needs attention. The patient should be instructed to remove the old dressing, as saturated dressings no longer provide any meaningful pressure, and apply firm pressure without release to the site for 15–20 minutes as timed *by the clock*. If pressure stops the bleeding, then the dressing should be reinforced with additional gauze and tape. If bleeding persists, then the patient needs to be evaluated by the surgeon.

The surgeon can once again attempt direct pressure, but, if this fails, the wound should be exposed, and the area reanesthetized and explored. If a single bleeding vessel is identified, then it can be electrocoagulated or ligated. Frequently, a single source is not identified. Bleeding can occur in multiple areas and each must be addressed. A drain may be helpful if a very dry surgical field cannot be achieved. If possible, surgical procedures should be scheduled early in the day to prevent having to bring the patient in during the wee hours of the morning to accomplish this.

If blood collects in the open space of a wound instead of seeping out through the wound edge, a hematoma forms. The presenting symptom

may be an acute, throbbing pain if the hematoma is a large, expanding one. Smaller hematomas cause more of a pressure sensation. Early, expanding hematomas should be evacuated. Hematomas can lead to dehiscence or necrosis due to pressure, and they may act as a nidus for infection. Hematomas consist of gelatin-like clots that are usually too firm to evacuate without removing sutures (anesthetize the area first!). After evacuation (Fig. 151.9), the site should be irrigated and any residual bleeding controlled. The wound may be re-closed, with particular attention paid to closing any dead space. Placing a drain is often appropriate. Many surgeons advocate empirical antibiotics after hematoma evacuation, because of an increased risk of infection.

If the hematoma goes unnoticed and untreated for several days after surgery, the clot becomes organized (Fig. 151.10). It is then thick, fibrous, and adherent to the surrounding tissue. If large or actively expanding, it should still be evacuated. In most circumstances, the resulting wound should be allowed to heal by second intention with possible delayed closure, instead of primary closure (Fig. 151.11).

Small, organized hematomas can be allowed to reabsorb without evacuation. If at around 1–2 weeks postoperatively there is significant liquefaction leading to a fluctuant mass, the fluid can be aspirated with a large bore (16–18-gauge) needle. Warm compresses applied for 30- to 60-minute intervals several times daily, can speed resolution.

Bromelain (bromelin), found in the pineapple plant, has been used as a medicinal throughout the ages. One placebo-controlled study found that bromelain decreased the time required for resorption of surgery-associated hematoma. The recommended dose was 500 mg immediately postoperatively and then three to four times a day on an empty stomach until the hematoma resolved. Patients not allergic to pineapple reported no side effects[14].

Ecchymoses occur when there is leakage of a small amount of blood into the interstitial space. A bruised appearance is common following surgical procedures involving areas with loose distensible tissue, such as the periorbital area or the upper chest in the elderly. It can be alarming to the patient who is not counseled to expect this possibility. The involved area changes in color from deep purple, black and blue, to green, and then to yellow as the hemoglobin is degraded to bilirubin.

Fig. 151.9 Hematoma. **A** Postoperative hematoma formation. **B** Evacuation of gelatin-like clot.

Fig. 151.10 Organized hematoma of the upper back.

Fig. 151.11 Evacuation of an organized hematoma. Prior to (**A**) and immediately after (**B**) evacuation of the clot. **C** After 2 weeks of healing by second intention.

The ecchymosis can extend widely, usually migrating to dependent areas. The concern is mainly cosmetic and temporary, because most resolve with time and leave no sequelae.

Infection

Although most cases of infection begin at the time of surgery, postoperative contamination is possible if good wound care does not occur. Blood-soaked dressings are excellent breeding grounds for bacteria. The patient or caregiver should be instructed to wash their hands carefully prior to changing any dressings or cleaning the wound site. Excessive exposure or manipulation of the wound site during the first 24–48 hours after the procedure should be avoided.

Infection usually does not become evident until 4–8 days after surgery. The patient may note increasing erythema (Fig. 151.12). Instead of dissipating with time, pain and tenderness may increase. Ascending red streaks (lymphangitis), swelling, and a purulent discharge may develop. Systemic symptoms of fever and chills indicate spread of the infection.

The area should be placed at rest, elevated, and heat applied. If the infection seems more than just mild, sutures should be removed and the defect left open. If an abscess is present, it should be drained. Deep cavities should be packed lightly with iodoform gauze. Packing needs to be changed daily until drainage stops. Discharge or exudate should be sent for Gram stain and culture. Antibiotics should be initiated based on the most likely causative organism(s) and a Gram stain if available. The choice of antibiotic should be adjusted as necessary once the culture results are available. *Staphylococcus aureus* is the most frequent culprit in the skin. A first-generation cephalosporin, a β-lactamase-resistant penicillin or a penicillin/β-lactamase inhibitor combination would be an appropriate choice (see Ch. 127). If *Pseudomonas aeruginosa* is suspected, as in postoperative chondritis of the external ear, a fluoroquinolone would be appropriate. If there is rapid spread, systemic symptoms, or extensive lymphangitis, the patient may need parenteral antibiotics, more aggressive wound care, and possible hospitalization.

The rise in the incidence of methicillin-resistant *S. aureus* (MRSA) is concerning. It would be wise for the surgeon to familiarize him- or herself with the rates of MRSA in the local community. Although the incidence of MRSA surgical site infections in dermatologic surgery is unknown, it is important to consider this as a possibility. After culture of the site, if there is a high index of suspicion for MRSA infection, consider the use of oral trimethoprim–sulfamethoxazole or clindamycin while awaiting culture results[21].

Contact dermatitis, or candidal or dermatophyte infections, may mimic bacterial infection. Contact dermatitis due to topical antibiotics frequently presents with pruritus rather than pain and with erythema corresponding to all areas of ointment application rather than being confined to limited portions of the wound (Fig. 151.13). Contact dermatitis from bandage adhesives will usually be strikingly limited to the area of adhesive contact. Inflammatory suture reactions may occur without infection (Fig. 151.14).

Necrosis

The earliest sign of necrosis may be pallor. There may also be cyanosis at the periphery of the flap or graft. Early intervention could include judicious suture removal or replacement to reduce tension, elevation to reduce edema, thereby improving blood flow, and gentle heat applied to the area to improve circulation. Treatment with hyperbaric oxygen may be appropriate in the face of early necrosis of a large or vital reconstruction[38].

Once necrosis is established, very minimal cleaning and debridement should be undertaken until the full extent of necrosis is clearly demarcated. More vigorous debridement may extend the process further. An eschar eventually forms and will separate from the wound base as it heals by second intention (Fig. 151.15). If infection is present, it should be treated appropriately. Delayed scar revision is an option if the site does not heal with an acceptable appearance.

Dehiscence

Wound edges can separate because of excessive tension, infection and necrosis (see Fig. 151.1). Dehiscence most often occurs at the time of suture removal, though it can certainly happen before or after. Scar tensile strength never exceeds 80% of the strength of uncut skin and maximum tensile strength is not achieved until months after the procedure. At 2 weeks after surgery, tensile strength is less than 10% of normal (Fig. 151.16)[1]. Patient education must emphasize and re-emphasize this lack of tensile strength. Patients should be told specifically in which activities they may or may not engage (i.e. no lifting more than "x" pounds, no running, no jogging, no sit-ups, etc.).

Fig. 151.12 Wound infection and necrosis at full-thickness skin graft site.

Fig. 151.13 Contact dermatitis to antibiotic ointment.

Fig. 151.14 Inflammatory suture reaction.

Fig. 151.15 Necrosis of a full-thickness skin graft. Two weeks after placement.

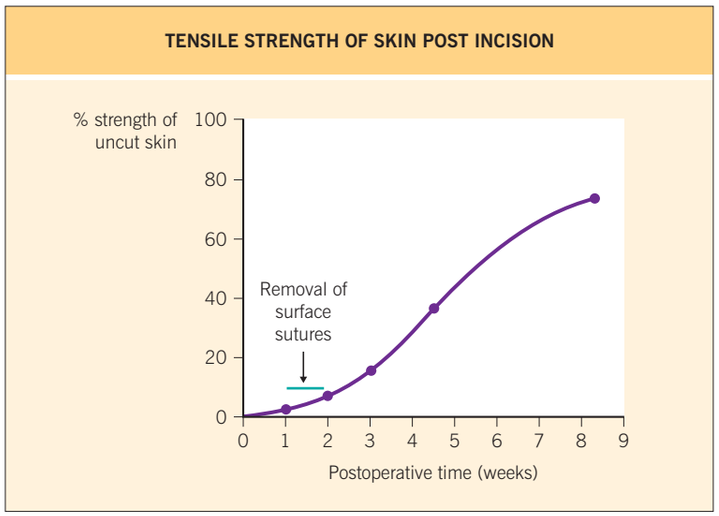


Fig. 151.16 Tensile strength of skin post-incision.

Fig. 151.17 Wound dehiscence after suture removal.

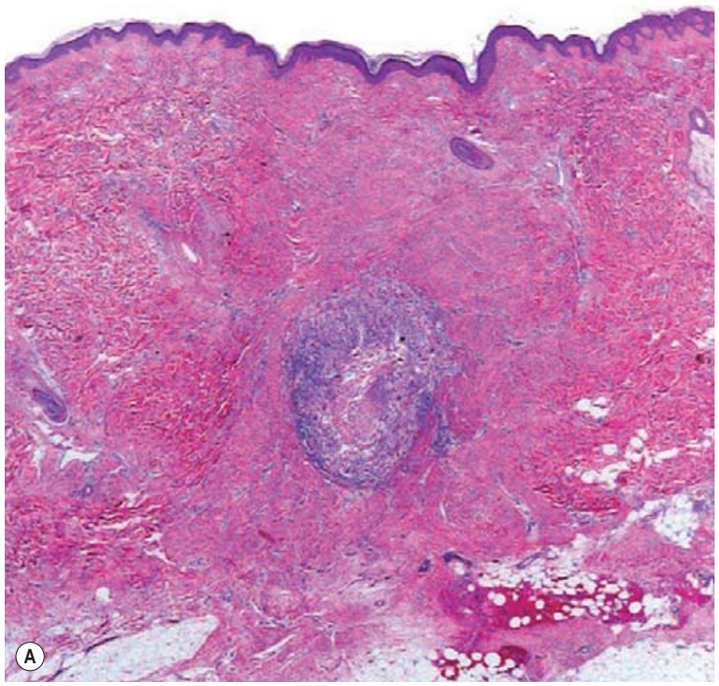
If prolonged support is needed, sutures may be removed in stages. Adhesive strips can provide some short-lived support for 1–2 days after suture removal. If the wound opens at suture removal because of excessive tension or too much activity (Fig. 151.17), the surgeon can consider resuturing if there is no infection, hematoma or necrosis. If dehiscence is due to another underlying complication, such as infection or hematoma, that condition should be treated first.

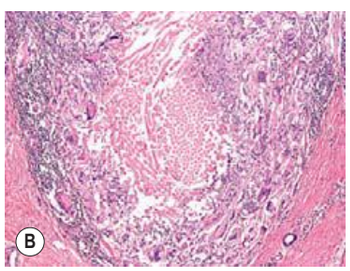
Wound appearance

Postoperative wound appearance may be a source of anxiety for both patient and surgeon. Problems may range from the simple (e.g. a spitting subcutaneous suture) to the more complex (e.g. a trapdoor deformity or spread scar). A key to dealing with most of these problems is continued and open communication between patient and surgeon. The patient who does not feel free to express concern or dissatisfaction in the office may all too readily do so in other places where the surgeon may not hear about it and cannot act to correct what can be corrected.

Buried sutures should be absorbed uneventfully by the body within the period of time specified by the manufacturer. Unfortunately, nature does not always adhere to package inserts. As digestion of the suture takes place, sterile abscesses may form as pustules along the suture track as well as granulomatous reactions (Figs 151.18 & 151.19). In addition, sutures may extrude or be "spit" from the skin intact (Fig. 151.20); while some authors believe this is more likely to occur if the sutures are placed too superficially within the dermis, even deeply placed sutures can be extruded in some patients. These events may occur anywhere from 1 to 4 months postoperatively, most commonly at about 6 weeks. The pustules can be opened with a sterile needle and the remaining suture gently removed. Sometimes, the papules are deeper. If the appearance is consistent with a suture reaction, reassure the patient that it is not a recurrence of the excised malignancy, then instruct the patient to gently massage the site. Perform a biopsy if warranted. If the suture is protruding, it can be carefully removed. The ultimate appearance of the scar is usually unaffected by this process.

Fig. 151.18 Sterile pustule and granulomatous reaction to suture placement.





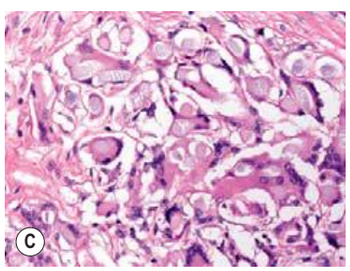


Fig. 151.19 Histologic features of a granulomatous reaction to braided suture material. A, B The suture material present within the dermis is cut both en face and longitudinally; on higher power, histiocytes and multinucleated giant cells surround the suture (**B**) and the giant cells have engulfed the suture material (**C**). *Courtesy, Lorenzo Cerroni, MD.*

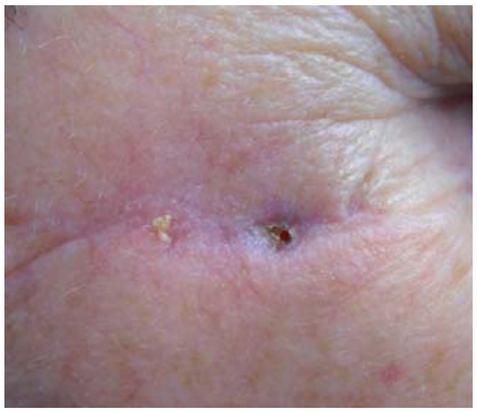


Fig. 151.20 Spitting suture within the incision line.

Fig. 151.21 Suture "tracks" in a spread scar.

Fig. 151.22 Hypertrophic scar. One month after excisional surgery.

Suture tracks or railroad tracking is caused by tight sutures left in place too long (Fig. 151.21). The best way to avoid this appearance is to minimize wound tension and to allow for early suture removal. Proper placement of buried sutures can help relieve wound edge tension.

Some anatomic sites are more prone to the development of keloids and hypertrophic scars (Fig. 151.22), and some individuals may have a genetic predisposition to keloid development. Keloids differ from hypertrophic scars by growing beyond the margins of the original wound (see Ch. 98). Intervention at the early stages of a hypertrophic scar can yield a more acceptable result. High-potency topical corticosteroids or intralesional corticosteroids may decrease the thickness of the scar and the accompanying symptoms of pain and pruritus. However, there is a risk of telangiectasias, atrophy or widening of the scar. Smaller hypertrophic scars may respond to simple massage. Silicone gel sheeting applied to the scars and worn for 12–24 hours per day for at least 2 months has been shown to improve the appearance of hypertrophic scars and keloids[39]. Simple occlusion and hydration may be just as effective without silicone[40]. One study using topical onion extract found that it was ineffective in improving erythema or pruritus of postsurgical scars, while petrolatum-based ointment alone did improve appearance[41].

Scar appearance can also be improved by dermabrasion or ablative laser resurfacing. When performed during the 4–8-week interval following the initial injury, it superimposes the mechanisms of second intention wound healing on the remodeling phase of the primary scar. This in turn appears to re-establish a normal-appearing epidermis across initial scar boundaries[42]. Lasers such as the pulsed carbon dioxide (CO_2) laser, fractionated ablative and non-ablative lasers, and the 585 nm pulsed dye laser, or a combination of these lasers, are also used in the treatment of hypertrophic scars and keloids[43,44].

Keloids tend to develop more frequently on the earlobes, neck and trunk. In predisposed individuals, especially those with a personal or family history of keloid formation, even superficial shave biopsies can result in keloid formation. Patients at risk should be counseled about this prior to the procedure. There are several treatment modalities used for keloids, with varying degrees of success (see Ch. 98).

Even well-approximated wound edges can produce spread scars. Like hypertrophic scars and keloids, they are more prevalent in certain anatomic areas such as the back, chest and shoulders. Patients who need excisions in these areas should be counseled preoperatively about the possibility that what may initially appear as a thin scar may widen over time. Most of this process occurs within 6 months after the surgery.

If a trapdoor deformity forms in the area of a flap, corticosteroid injections can improve the appearance. The patient should also be instructed to massage the area. Revision can be considered if these interventions do not produce an acceptable cosmetic result. Multiple small Z-plasties along the scar as well as peripheral undermining can also improve the appearance[45]. However, patience often produces the best results.

Any time the epidermis is injured, hyper- or hypopigmentation can result. This is more pronounced in dark-skinned individuals. Again, patients should be warned about this possibility pre- and postoperatively. The wound site should be strictly protected from UV exposure. Early epidermal hyperpigmentation can be improved with the use of topical hydroquinones, though this is ineffective unless combined with UV protection.

CONCLUSIONS

Avoiding complications requires planning and careful evaluation at each stage of the procedure: preoperative, intraoperative and postoperative. Despite the best of intentions, careful planning, and the most expert of hands, complications still occur. The surgeon must learn from experience, and the experience of others, to improve patient care. Finally, the surgeon must always remember to treat the patient, not just the condition. The patient's expectations and concerns must be addressed, not simply the surgeon's. Like beauty, complications are in the eye of the beholder. The patient who feels abandoned by his or her physician may not be happy with any outcome, no matter how technically perfect.

REFERENCES

1. Stasko T. Complications of cutaneous procedures. In: Roenigk RK, Roenigk HH Jr (eds). Dermatologic Surgery Principles and Practice, 2nd edn. New York: Marcel Dekker, 1996;149–75.
2. Fader DJ, Johnson TM. Medical issues and emergencies in the dermatology office. J Am Acad Dermatol. 1997; 36:1–16.
3. Bennett RG. Fundamentals of Cutaneous Surgery. St Louis: Mosby, 1988:553–90.
4. Peterson SR, Joseph AK. Inherited bleeding disorders in dermatologic surgery. Dermatol Surg. 2001;27:885–9.
5. Harrison P. Progress in the assessment of platelet function. Br J Haematol. 2000;111:733–44.
6. Vora A, Makris M. An approach to investigation of easy bruising. Arch Dis Child. 2001;84:488–91.
7. Maloney ME. Management of surgical complications and suboptimal results. In: Wheeland RG (ed). Cutaneous Surgery. Philadelphia: WB Saunders, 1994: 921–34.
8. Salasche SJ. Acute surgical complications: cause, prevention, and treatment. J Am Acad Dermatol. 1986; 15:1163–85.
9. Cook-Norris RH, Michaels JD, Weaver AL, et al. Complications of cutaneous surgery in patients taking clopidogrel-containing anticoagulation. J Am Acad Dermatol. 2011;65:584–91.

9a. Bordeux JS, Martires KJ, Goldberg D, et al. Prospective evaluation of dermatologic surgery complications including patients on multiple antiplatelet and anticoagulant medications. J Am Acad Dermatol. 2011; 65:576–83.

10. Alcalay J, Alkalay R. Controversies in perioperative management of blood thinners in dermatologic surgery: continue or discontinue? Dermatol Surg. 2004;30:1091–4.
11. Caliendo FJ, Halpern VJ, Marini CP, et al. Warfarin anticoagulation in the perioperative period: is it safe? Ann Vasc Surg. 1999;13:11–16.
12. Campbell JH, Alvarado F, Murray RA. Anticoagulation and minor oral surgery: should the anticoagulation regimen be altered? J Oral Maxillofacial Surg. 2000;58: 131–5.

12a. Tran A, Cheng-Lai A. Dabigatran etexilate: The first oral anticoagulant available in the United States since warfarin. Cardiol Rev. 2011;19:154–61.

13. Bithell TC. Blood coagulation. In: Lee RG (ed). Wintrobe's Clinical Haematology. Philadelphia: Lea & Febiger, 1993:566–615.
14. Dinehart SM, Henry L. Dietary supplements: altered coagulation and effects on bruising. Dermatol Surg. 2005;31:819–26.
15. Deykin D, Janson P, McMahon L. Ethanol potentiation of aspirin-induced prolongation of the bleeding time. N Engl J Med. 1982;306:852.
16. Smith JB, Fenske NA. Cutaneous manifestations and consequences of smoking. J Am Acad Dermatol. 1996; 34:733–4.
17. Rubenstein R, Roenigk HH Jr, Stegman SJ, Hanke CW. Atypical keloids after dermabrasion of patients taking isotretinoin. J Am Acad Dermatol. 1986;15:280–5.
18. Zacharieae H. Delayed wound healing and keloid formation following argon laser treatment or dermabrasion during isotretinoin treatment. Br J Dermatol. 1988;118:703–6.
19. Bernestein LJ, Geronemus RG. Keloid formation with the 585-nm pulsed dye laser during isotretinoin treatment. Arch Dermatol. 1997;133:111–13.

19a. Bagatin E, Ramos dos Santos Guadanhim L, Yarak S, et al. Dermabrasion for acne scars during treatment with oral isotretinoin. Dermatol Surg. 2010;36:483–9.

20. Roenigk RK. Chemical peel with trichloroacetic acid. In: Roenigk RK, Roenigk HH Jr (eds). Dermatologic Surgery Principles and Practice, 2nd edn. New York: Marcel Dekker, 1996:1121–35.
21. Wright TI, Baddour LM, Berbari EF, et al. Antibiotic prophylaxis in dermatologic surgery: advisory statement 2008. J Am Acad Dermatol. 2008;59:464–73.
22. LeVasseur JG, Kennard CD, Finley EM, Muse RK. Dermatologic electrosurgery in patients with implantable cardioverter-defibrillators and pacemakers. Dermatol Surg. 1998;24:233–40.
23. El-Gamal HM, Dufresne RG, Saddler KS. Electrosurgery, pacemakers and ICDs: a survey of precautions and complications experienced by cutaneous surgeons. Dermatol Surg. 2001;27:385–90.
24. Skidmore RA, Patterson JD, Tomsick RS. Local anesthetics. Dermatol Surg. 1996;22:511–22.
25. Thomas RM, Amonette RA. Emergencies in skin surgery. In: Roenigk RK, Roenigk HH Jr (eds). Dermatologic Surgery Principles and Practice, 2nd edn. New York: Marcel Dekker, 1996:77–89.
26. Vance JW. Anesthesia. In: Roenigk RK, Roenigk HH Jr (eds). Dermatologic Surgery Principles and Practice, 2nd edn. New York: Marcel Dekker, 1996:31–9.
27. Ljunggren B, Moller H. Eczematous contact allergy to chlorhexidine. Acta Dermatol. 1972;52:308–10.
28. Marks JG. Allergic contact dermatitis due to povidone-iodine. J Am Acad Dermatol. 1982;6:473.
29. Takegami KT, Siegle RJ, Ayers LW. Microbiologic counts during outpatient office-based cutaneous surgery. J Am Acad Dermatol. 1990;23:1149.

29a. Rogers HD, Desciak EB, Marcus RP, et al. Prospective study of wound infections in Mohs micrographic surgery using clean surgical technique in the absence of prophylactic antibiotics. J Am Acad Dermatol. 2010;63:842–51.

30. Palm MD, Altman JS. Topical hemostatic agents: a review. Dermatol Surg. 2008;34:431–45.
31. Nasser NA. The use of the mini-flap wound suction drain in maxillofacial surgery. Ann R Coll Surg Engl. 1986;68:151–3.
32. Achneck HE, Sileshi B, Jamiolkowski RM, et al. A comprehensive review of topical hemostatic agents. Ann Surg. 2010;251:217–28.

32a. Ho J, Hruza G. Hydrophilic polymers with potassium salt and microporous polysaccharides for use as hemostatic agents. Dermatol Surg. 2007;33:1430–3.

33. Billingsley EM, Maloney ME. Considerations in achieving hemostasis. In: Robinson JK, Arndt KA, Leboit PE, Wintroub BU (eds). Atlas of Cutaneous Surgery. Philadelphia: WB Saunders, 1996:67–73.
34. Greenbaum SS, Greenbaum CH. Intraoperative tissue expansion using a Foley catheter following excision of a basal cell carcinoma. J Dermatol Surg Oncol. 1990;16:45–8.
35. Salasche SJ, Bernstein G, Senkarik M. Surgical Anatomy of the Skin. Norwalk: Appleton & Lange, 1988:100–25.
36. McDonald M, Stasko T. Prevention of unsatisfactory scarring. In: Harahap M (ed). Surgical Techniques for Cutaneous Scar Revision. New York: Marcel Dekker, 2000:53–80.
37. Kaufman AJ, Kene KL, Moy RL. Role of tissue undermining in the trapdoor effect of transposition flaps. J Dermatol Surg Oncol. 1993;19:128–32.
38. Pellitteri PK, Kennedy TL, Youn BA. The influence of intensive hyperbaric oxygen therapy on skin flap survival in a swine model. Arch Otolaryngol. 1992;118:1050–4.
39. Berman B, Flores F. Comparison of a silicone gel-filled cushion and silicone gel sheeting treatment of hypertrophic or keloid scars. Dermatol Surg. 1999;24:484–6.
40. Ricketts CH, Martin L, Faria DT, et al. Cytokine mRNA changes during the treatment of hypertrophic scans with silicone and nonsilicone gel dressings. Dermatol Surg. 1996;22:955–9.
41. Jackson BA, Shelton AJ. Pilot study evaluating topical onion extract as treatment for post surgical scars. Dermatol Surg. 1999;25:267–90.
42. Harmon CB, Yarborough JM. Scar revision by dermabrasion. In: Roenigk RK, Roenigk HH Jr (eds). Dermatologic Surgery Principles and Practice, 2nd edn. New York: Marcel Dekker, 1996:911–21.
43. Alster TS, Lewis AB, Rosenbach A. Laser scar revision: comparison of CO_2 laser vaporization with simultaneous pulsed dye laser treatment. Dermatol Surg. 1998;24:1299–302.
44. Alster TS, Handrick C. Laser treatment of hypertrophic scars, keloids, and striae. Semin Cutan Med Surg. 2000;19:287–92.
45. Koranda FC, Webster RC. Trapdoor effect in nasolabial flaps. Causes and corrections. Arch Otolaryngol. 1985;111:421–4.

Evaluation of Beauty and the Aging Face 152

Thomas E Rohrer, Naissan O Wesley, Richard Glogau and Jeffrey S Dover

Chapter Contents

Evaluation of beauty 2473
Anatomic basis for the aging appearance 2474
Photoaging 2474
Pigmentary system 2476
Volume changes – the loss of subcutaneous fat 2476
Changes in facial musculature 2476
Changes in underlying cartilage and bone 2477
Inherent loss of elasticity 2477
Gender differences 2478
Ethnic differences 2478
Combination therapies 2478

INTRODUCTION

"It is amazing how complete is the delusion that beauty is goodness."

~Leo Tolstoy

Nancy Etcoff, in *Survival of the Prettiest: the Science of Beauty*, explains that beauty is a universal component of the human experience which promotes pleasure, rivets attention, and impels action that helps ensure survival of our genes[1].

Striving to be more beautiful is not a new phenomenon. Human preoccupation with beauty and a youthful appearance dates back as far as recorded history. Anthropologists have determined that over 40 000 years ago, red ochre paints were used in southern Africa for facial and body ornamentation[2]. In 5 BC, the Roman author Ovid wrote *The Art of Beauty*, the first known book on beauty and cosmetics, detailing the use of black eye shadow made from wood ash and golden eye shadow made from saffron.

Few human traits are as ingrained as beauty. It is thought to be hardwired into our brains and can even be detected in infants. Studies have shown that by the age of 3 months, babies stare longer at attractive faces than those judged to be less attractive. Also, 1-year-old toddlers will play longer with attractive dolls than more plain dolls[3]. In functional magnetic resonance imaging studies where subjects were shown photographs of attractive men and women, viewing beautiful faces activated reward circuitry within the brain and dopamine pathways[4].

If examined from an evolutionary standpoint, this innate attraction to beauty certainly makes sense. Those who are attracted to the opposite sex and likewise are found to be attractive are more likely to mate and pass on their genes. Attraction to beauty also makes sense from a disease perspective. It is said that "beauty is a burden that only the healthy can carry." In other words, the sickly are by nature not attractive. Those with an ideal physique and youthful proportions are much more likely to be healthy and be able to reproduce. Again, by choosing an attractive mate, one is increasing the odds that his or her genes will be passed on.

In one study, 20 subjects were asked to grade graduates from a 1920s high school yearbook on their attractiveness. When the actual lifespans of these graduates were determined, facial attractiveness correlated with increased lifespan. Correlations between beauty and health help to explain why, from an evolutionary standpoint, the concept of beauty may become an innate concept within a species[5].

Besides being considered a more ideal mate, attractiveness may also have a number of other benefits. Nancy Etcoff has stated that people tend to respond positively to good-looking people without expectation of reward, and, further, that good-looking people tend to be less penalized for everything from shoplifting to cheating at exams[1]. In the same workplace, attractive people were found to earn up to 12% higher wages as compared to co-workers who were considered average-looking[2]. Also, pharmaceutical representatives have been shown to have a 1.9% increase in sales for every unit increase in the Likert Scale for attractiveness. While the average height of a man in the US is 5′ 7″ (170.2 cm), the average height of Fortune 500 CEOs is 6′ 1″ (185.4 cm). Statistically, US Presidents have also been found to be significantly taller than their constituents. Lastly, even West Point graduates who had higher scores on an attractiveness scale rose to higher military ranks.

EVALUATION OF BEAUTY

Recognizing beauty and understanding its significance may be far easier than actually defining it[6]. Anthropometry represents the quantitative

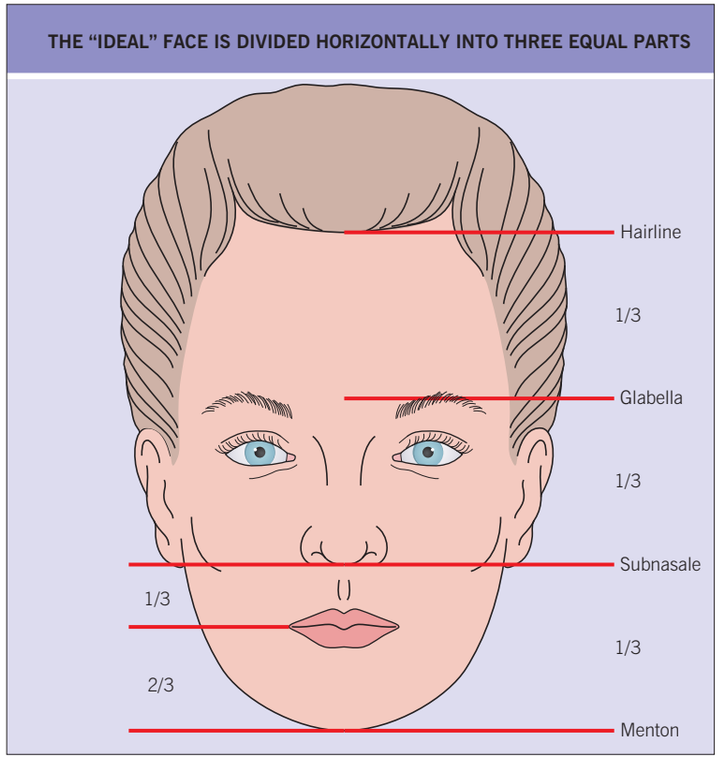


Fig. 152.1 The "ideal" face is divided horizontally into three equal parts. These three parts are composed of the distances between: (1) the frontal hairline and the top of the brow; (2) the brow and the base of the nose; and (3) the base of the nose and the inferior aspect of the chin. The divisions were originally proposed by Leonardo DaVinci.

FACIAL ANALYSIS OF WOMEN OF DIFFERENT ETHNIC GROUPS						
	Caucasian	African-American	Latino-American			Southern Chinese
			Caribbean	Central	South	
Horizontal proportions*	1:1:1	1:1.2:1.3 or 1:1.2:1.2				
Nasofrontal angle	125°–135°	127.6° or 136.8°–137.4°	110°	137°	136°	137.9° (119–166)
Nasofacial angle	36°–40°	33.4° or 38.9°	41°	44°	46°	36.4° (20–46)
Alar width: intercanthal distance	1:1	1.2:1	1.2:1	1:1	1.1:1	>1:1
Columella:lobule	2:1	1.3:1 or 1:1.2 or 1:1.3	1.5:1	1.1:1	1.5:1	1.2:1
Nasolabial angle	90°–120°	73.9° or 85.6°–90.3°	110°	99°	100°	87.8° (55–108)
*Horizontal proportions derived from relationship of: trichion to glabella, glabella to subnasale, subnasale to gnathion ratio.						

Table 152.1 Facial analysis of women of different ethnic groups. *Adapted from Powell N, Humphreys B. Proportions of the Aesthetic Face. Thieme-Stratton: New York, 1984.*

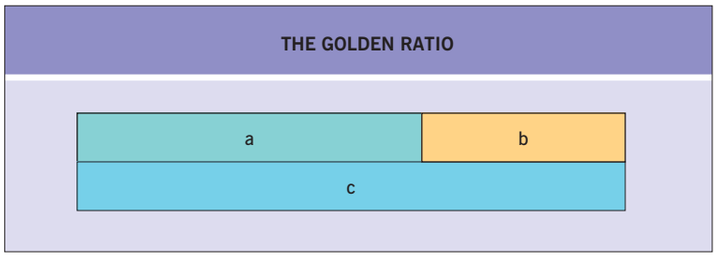


Fig. 152. 2 The golden ratio based upon Phi. Phi is the unique point on a line that divides the line into two lines in such a manner that the ratio of the smaller portion (b) to the larger portion (a) is the same as the ratio of the larger portion (a) to the whole line (c). In other words, b is to a as a is to c. This ratio is a repeating number that is rounded off to 1:1.618. A triangle composed of lines with lengths in the Phi ratio is referred to as a golden triangle.

measurement of facial features and an assessment of resultant ratios. It is based on proportional relationships of the face that are known as the neoclassical canons, which have been studied and revised for centuries. As originally proposed by Leonardo DaVinci, the ideal face can be divided horizontally into three equal parts; these parts are composed of the distances between: (1) the frontal hairline and the top of the brow; (2) the brow and the base of the nose; and (3) the base of the nose and the inferior aspect of the chin (Fig. 152.1). In general, mathematically idealized facial proportions translate into a symmetric, oval- or heart-shaped face, with prominent cheekbones, tapered jaw line, narrow nasal base and thin lips. These proportions, however, are largely based on facial features in Caucasian women. Ethnic variations of these "ideal" proportions may exist and are outlined in Table 152.1.

Another method for calculating beauty via mathematical proportions is the concept of "Phi", or the golden ratio. A ratio of 1:1.618 was described by ancient Greeks as a mathematical method for calculation of the optimal proportions for all structures in nature. In fact, some authorities believe that the neoclassical canons (see above) are modifications of Phi. Phi represents the unique point on a line that divides the line into two lines in such a manner that the ratio of the smaller portion to the larger portion is the same as the ratio of the larger portion to the whole line (Fig. 152.2). This ratio is a repeating number that is rounded off to 1:1.618. Of note, there are innumerable examples of the use of the Phi ratio in nature and art, including the Parthenon, the sculpture Venus de Milo, the shell of a nautilus and the petals of a sunflower.

A triangle composed of lines with lengths in the Phi ratio is referred to as a golden triangle. When expanded, one can even create golden pentagons and golden decagons. Stephen Marquardt trademarked the "Phi mask", a facial mask composed of proportions that incorporate the 1:1.618 ratio, to describe the mathematically ideal attractive face (Fig. 152.3). Although the Phi mask has been applied to persons of all races and ethnicities, Marquardt recognized that ethnic variations may exist and has incorporated modifications for three different ethnic groups – Caucasian, Asian, and African.

ANATOMIC BASIS FOR THE AGING APPEARANCE

Knowledge of facial anatomy and anatomic changes that occur with aging is essential for properly evaluating and treating the aesthetic patient. With aging, both the golden ratio (Phi) and the neoclassical canons start to shift. The upper one-third of the face *elongates* due to recession of the frontal hairline and brow ptosis, while proportionately the middle third remains relatively stable (but may elongate with nasal tip ptosis). However, mid-face volume loss can occur as a result of fat redistribution and skeletal changes. The lower third of the face becomes *shortened* with perioral fat redistribution and significant resorption of the bony mandible.

The appearance of the aging face is multifactorial and does not appear to simply be a matter of sagging from the effect of years of gravitational forces pulling the face downwards. Rather, a complex ongoing alteration in proportions occurs as one ages. Notably, recent studies by Rohrich and Pessa[7] have shown that there is not one large confluent layer of subcutaneous fat in the face but rather multiple distinct compartments that act independently from one another (see below). For example, the malar fat pad in the mid cheek is composed of three separate compartments; as these compartments change in size, the ligaments separating the compartments become more evident and a smooth, rounded, youthful appearance transforms into the multi-contoured aged face.

After examining numerous photographs of patients as they aged, Lambros[8] concluded that there is actually very little positional change in the midface region. Despite the common perception that the face drops inferiorly with age, he noted that the eyelid–cheek margin did not change with advancing years, nor did facial nevi of the midface descend with age. Just as individual water molecules simply move up and down rather than actually traveling with waves at sea, the wave of downward motion "seen" in an aging face may simply represent shifts in subcutaneous tissue.

Rhytides also play a key role in producing an aged appearance. The underlying causes of rhytides are multiple and include ultraviolet radiation-induced damage, loss of skin elasticity, repetitive movement of underlying facial musculature, changes in volume from fat redistribution, and bone as well as cartilage resorption (Fig. 152.4).

PHOTOAGING

Cumulative exposure to sunlight is a major factor in aging skin. Clinical signs of cutaneous photoaging include: rhytides, lentigines, keratoses, telangiectasias, loss of translucency, loss of elasticity, and a sallow color[9,10]. The Fitzpatrick Skin Phototype System (see Table 0.5) serves as a good indicator of the potential for developing signs of photoaging as well as developing dyschromia following epidermal/papillary dermal injury from trauma or cosmetic procedures.

A simple systematic classification of patient photoaging types (types I through IV) was developed by Dr. Richard Glogau (Table 152.2; Fig. 152.5)[11]. However, the generalizations outlined in Table 152.2, and explained below, usually apply at a later age and to different degrees in

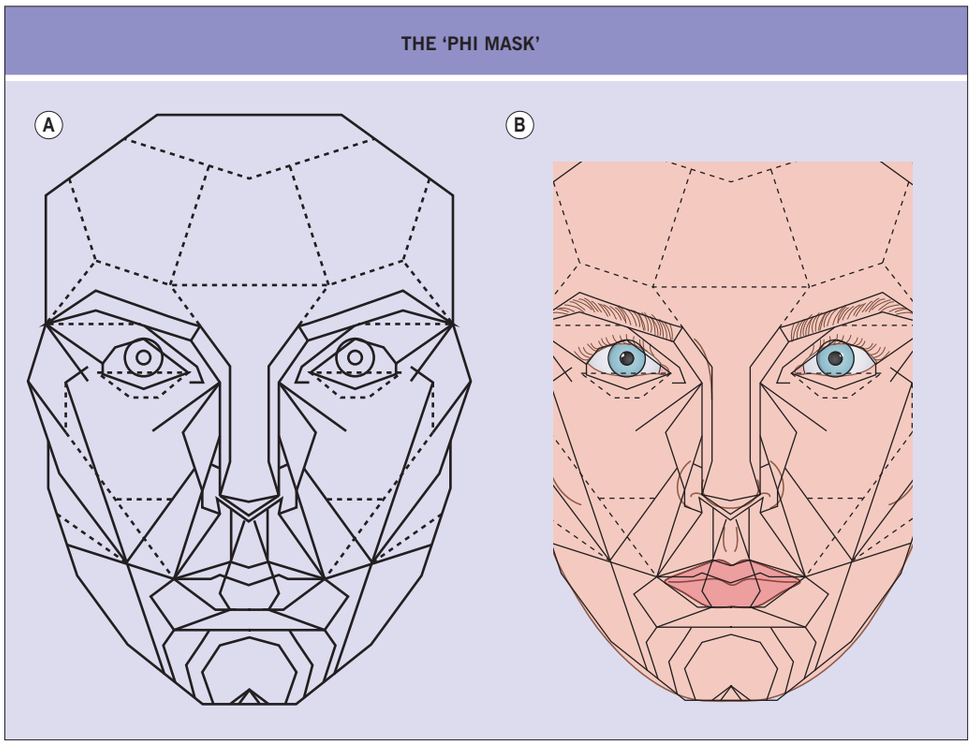


Fig. 152.3 The "Phi mask". A By incorporating the 1:1.618 ratio into numerous golden triangles and hexagons, the Phi mask reflects the mathematically ideal face. **B** The Phi mask superimposed on the human face.

Fig. 152.4 Rhytides of the aging face. Rhytides form as a result of UV radiation-induced damage, loss of skin elasticity, repetitive movement of underlying facial musculature, changes in volume from fat redistribution, and bone as well as cartilage resorption.

GLOGAU PHOTOAGING CLASSIFICATION – WRINKLE SCALE
TYPE I – "NO WRINKLES"
• Early photoaging – Mild pigmentary changes – No keratoses – Minimal wrinkles • Patient age (yrs) – 20's or 30's • Minimal or no makeup
TYPE II – "WRINKLES IN MOTION"
• Early to moderate photoaging – Early senile lentigines visible – Keratoses palpable but not visible – Parallel smile lines beginning to appear • Patient age (yrs) – late 30's or 40's • Usually wears some foundation
TYPE III – "WRINKLES AT REST"
• Advanced photoaging – Obvious dyschromia, telangiectasias – Visible keratoses – Wrinkles even when not moving facial muscles • Patient age (yrs) – 50's or older • Wears heavy foundation
TYPE IV – "ONLY WRINKLES"
• Severe photoaging – Yellow–gray color of skin – Prior skin malignancies – Wrinkled throughout with no normal skin • Patient age (yrs) – 60's to 70's • Can't wear makeup – "cakes and cracks"

Table 152.2 Glogau photoaging classification – wrinkle scale. yrs, years

more darkly pigmented skin, partially depending upon the degree of sun exposure. Type I refers to younger patients with no rhytides, even when the face is animated by talking or expression. Type II refers to patients with "wrinkles in motion", who demonstrate the influence the underlying musculature has on the skin.

As the photoaging process advances, there is greater damage to collagen and elastic fibers. Of note, collagen production is maintained by dynamic mechanical tension placed on fibroblasts by intact collagen fibers. With age and particularly sun-related damage, type I collagen (most prevalent form with a half-life of 15 years) becomes more and more fragmented. As more collagen becomes fragmented, there is less stretching tension placed on fibroblasts and they respond by making more metalloproteases and less collagen. This creates a vicious cycle of increasing collagen loss and subsequent thinning of the skin[12]. Eventually, with substantial breakdown of collagen and elastic fibers, the wrinkles produced by dynamic movement of the face persist, even when the face is at rest.

Generally, by the sixth or later decade of life, there are visible parallel lines lateral to the eye ("crow's feet"), at the corners of the mouth, and

Fig. 152.5 The Glogau wrinkle scale. A Type I ("no wrinkles"): skin is uniform in color. There is an absence of lines even at the corners of the eyes and mouth. **B** Type II ("wrinkles in motion"): when the face is at rest, the patient appears similar to type I. But when the face is animated by expression, there are many parallel lines which appear, first at the corners of the mouth, then parallel to the melolabial folds, then at the corners of the eyes, and finally over the malar cheeks. **C** Type III ("wrinkles at rest"): this patient clearly shows the parallel lines seen with animation in type II, except they are now present with the face at complete rest. **D** Type IV ("only wrinkles"): the perioral skin in particular is likely to demonstrate the total replacement of normal skin with minute, rhomboid and geometric rhytides, clearly seen in this patient. The entire face shows similar rhytides on close inspection.

radiating down from the lower eyelids onto the malar cheeks, as well as around the upper lip and lower lip. These patients appear lined, even when their face is at rest, and are classified as type III, "wrinkles at rest". The repetitive effect of underlying muscular expression is now permanently "ingrained" into the skin i.e. lines are readily visible, even without active muscular contraction.

With continued photoaging, the wrinkles gradually spread to cover the majority of the facial skin, while the dermis becomes totally engorged with accumulations of poorly staining ground substance, giving a thickened, coarse quality to the skin. This is classified as photoaging type IV, "only wrinkles".

PIGMENTARY SYSTEM

Patients should also be categorized according to their Fitzpatrick Sun-Reactive Skin Type[13]. This classification scheme (see Table 0.5) is based upon the skin's response to erythema-producing doses of UV light. Patients differ in their reactivity to sunlight, and the skin type serves as a very good indicator of the potential for developing dyschromia following epidermal/papillary dermal injury. The scale also reflects the likelihood of developing postinflammatory hyperpigmentation during the near-term postoperative period, and the potential for permanent leukoderma resulting from destruction of melanocytes.

VOLUME CHANGES – THE LOSS OF SUBCUTANEOUS FAT

A major component of aesthetic disharmony in the aging face is the loss or redistribution of subcutaneous fat. Detailed studies by Rohrich and Pessa[7], utilizing cadaver dissections, have demonstrated that facial fat (unlike fat elsewhere in the body) is partitioned into discrete compartments which may age independently of one another (Fig. 152.6). Redistribution and loss of these fat pads contribute to formation of the nasojugal fold, malar crease, nasolabial fold, pre-jowl sulcus and marionette lines as well as wasting of the temples, superior brow and buccal fat (Fig. 152.7).

While in some areas (e.g. the submental region), unwanted subcutaneous fat may lend itself to removal via liposuction, in general there is

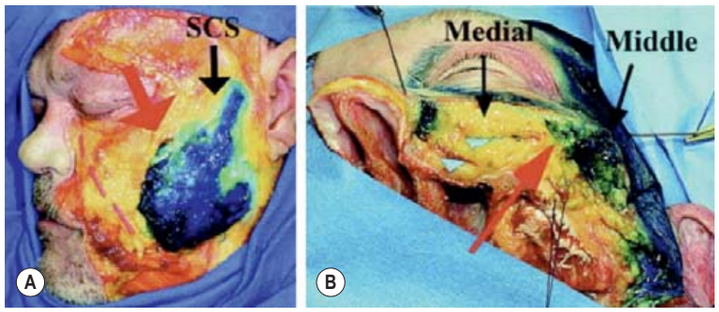


Fig. 152.6 Multiple distinct subcutaneous fat compartments of the face. A The middle cheek (blue) fat compartment lies between the medial (yellow) and lateral temporal-cheek (yellow) fat compartments. The superior border is defined by the superior cheek septum (SCS; green). A zone of fixation (red arrow) is noted where this compartment adjoins the middle compartment and inferior orbital (yellow) compartment. **B** Cross-sectional anatomy illustrates the anatomic principle that fusion planes exist between adjacent fat compartments. A dense fascial system (red arrow) exists where the medial and middle fat compartments meet. The red zygomaticus major muscle is noted deep to this fusion plane. From ref. 7.

a modern appreciation that removal of fat should be done with caution due to the flattening or hollowing of contours that could result and possibly lead to a more aged appearance. Due to a loss of subcutaneous fat, the older face has a flattened quality to the cheekbones, a sunken appearance to the lips, a bulging of the inferior fat pads of the eye, and, in general, a loss of the fullness and roundness of youth. Experienced aesthetic surgeons have recognized this, and are moving away from excessive fat removal to fat repositioning or augmentation. Dr Steven Hoefflin has written, "In the aging face it is not the tightness of the SMAS (platysma aponeurosis) or skin that makes the difference, but the quantity and position of subcutaneous fat"[14].

As an example, the routine removal of the infraorbital fat as a part of blepharoplasty, which often accentuated the deep grooves between the lower eyelid and the cheek, has become outdated. Now surgeons prefer to utilize an arcus marginalis release and mobilize the fat medially and anteriorly to fill in the groove and return a more youthful appearance to the lower eyelids through restoration of lower lid convexity. Similarly, repositioning of the premalar fat has become an important part of routine facelifting, reversing the aged appearance that comes from flattening of the cheekbone contours.

Restoration of volume loss can also be readily achieved less invasively with the use of injectable fillers (see Ch. 158).[15]

CHANGES IN FACIAL MUSCULATURE

Perhaps nothing has driven home the impact of facial musculature on facial aging like the introduction of botulinum toxins for selective chemical denervation of muscles of the face. Paralysis or partial weakening of the glabellar corrugator/procerus complex, the forehead frontalis muscle, and the lateral orbicularis muscles has revolutionized the management of the upper third of the aging face. In addition, judicious use and careful placement of neuromodulators into the orbicularis oris, depressor anguli oris, and platysmal neck bands can aid in managing creases, wrinkling and banding of the lower face and neck.

Brow position is closely associated with emotional states, and the medial and lateral portions of the brow function independently in this regard. Surgeons must be conscious of the strong impact that brow shape and position can have on appearance and even interpersonal relationships. For example, people tend to treat you better if you do not have a glabellar scowl, if your eyebrows arch properly (if you are female), and if the relationship between the lateral and medial brow is flattering.

In young women, the arch of the brow has been found to be most attractive when located above the lateral limbus (Fig. 152.8). Photographs of patients following botulinum exotoxin A injection were rated by 40 subjects to be 40% less angry, 49% less fearful, 10% less sad, and 71% more happy than photographs of the same patients prior to their injections[16]. In a small series of 10 patients suffering from depression,

Fig. 152.7 Laser resurfacing. This patient has undergone laser resurfacing to her full face. She looks "better" but not "younger", because no attention has been paid to volume changes.

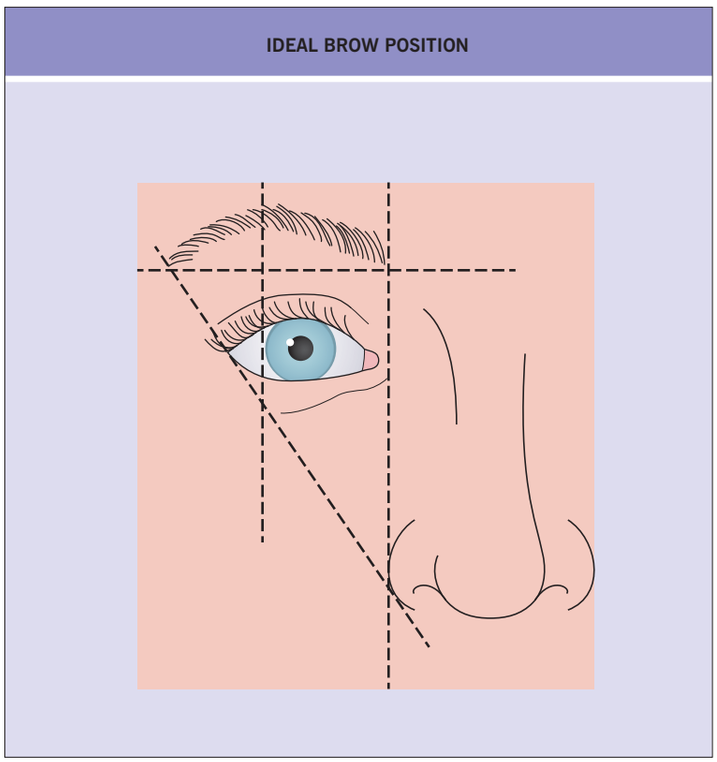


Fig. 152.8 Ideal brow position. In young women, the arch of the brow has been found to be most attractive when it peaks above the lateral limbus.

nine reported significant improvement in their symptoms to the point of no longer feeling depressed 2 months following botulinum toxin injection[17]. It may be that when people feel that they are more attractive, they become more confident and have more positive interactions with others. Alam et al.[18] postulate that muscular manipulations which result in more positive facial expressions may lead to more positive emotional states. Likewise, reducing external signs of anger, fear and sadness may reduce internal negative emotions.

CHANGES IN UNDERLYING CARTILAGE AND BONE

Due to changes in the underlying cartilage, the aging nose elongates and the tip droops. The aging mouth is affected by bony resorption and remodeling of the maxilla, while the chin sharpens and protrudes. The ears appear to lengthen as the lobes droop. The tarsal plate softens and no longer holds the lower lid margin in its proper position or curve. Various surgical procedures address these problems, including tip rhinoplasty, tarsal lid tightening, canthoplasty and chin implants. Newer dental implant procedures and maxillofacial surgery can also address intrinsic changes affecting the lower face. In addition, some of the newer soft tissue fillers can be used to correct the aging changes associated with bony resorption and may result in a more natural appearance and feel than an implant. For example, these fillers may be placed in the nasal dorsum, jawline, marionette lines, ear lobes, tear troughs, and mid-face.

The diagnostic eye of the cosmetic surgeon should not overlook the contribution of the underlying hard structures of the face, particularly when assessing for the presence (or, more commonly, absence) of facial symmetry. Patients often present with requests for the treatment of facial problems without appreciating the contribution of underlying structures to their facial asymmetry. Recognizing, photographing and discussing pre-existing facial asymmetry due to underlying bony or cartilaginous structural differences is an important component of setting realistic patient expectations.

INHERENT LOSS OF ELASTICITY

As the facial soft tissue ages, both the skin and the underlying supporting structures, while sagging under the effects of gravity, also lose their inherent resiliency or ability to resist stretching. Skin laxity occurs as a result of a decreased underlying framework, a thinned and damaged dermis, and a breakdown in elastic and collagen fibers[12].

In the lower third of the face, a facelift procedure is often essential for a successful aesthetic outcome. Redraping, repositioning and judicious removal of skin and soft tissue that has lost its elasticity can lead to the restoration of a youthful appearance that cannot be achieved with resurfacing, fillers, fat transfer or botulinum toxin.

GENDER DIFFERENCES IN CHARACTERISTICS OF ATTRACTIVE HUMAN FACES	
Idealized female facial features	**Idealized male facial features**
A larger, smooth forehead with a smaller nose	An overhanging, horizontal brow with minimal arch
Eyebrows that have an arch or gull-wing shape	Deeper set eyes that look closer together
Eyes that are set wider apart, creating a bigger look	A somewhat larger nose
Prominent cheekbones	A wider mouth
A heart-shaped taper to the lower face, with a smaller lower : upper face ratio	A squared lower face with a more equal ratio of lower : upper face
Full vermilion lips	A beard or coarser texture to the lower facial skin

Table 152.3 Gender differences in characteristics of attractive human faces. These characteristics are cross-culturally persistent.

OBJECTIVE DIFFERENCES IN SKIN STRUCTURE AND PHYSIOLOGY BASED ON RACE		
Evidence supports:	**Insufficient evidence* for:**	**Inconclusive:**
• Increased melanin content and melanosomal dispersion in persons of color • Multinucleated and larger fibroblasts in black persons compared with white persons • pH black skin < pH white skin • Larger mast cell granules, increased PLS, and increased tryptase localized to PLS in black compared to white skin • Variable blood vessel reactivity	Racial differences in: • Skin elastic recovery/ extensibility • Skin microflora • Facial pore size†	Racial differences in: • Transepidermal water loss • Water content • Corneocyte desquamation • Lipid content
*Categorized under this heading because only two studies or fewer examined these variables. †Sugiyama-Nakagiri Y, Sugata K, Hachiya A, et al. Ethnic differences in the structural properties of facial skin. J Dermatol Sci. 2009;53:135-9.		

Table 152.4 Objective differences in skin structure and physiology based on race. PLS, parallel-linear striations (seen within mast cells by electron microscopy). *Adapted from Wesley NO, Maibach HI. Racial (ethnic) differences in skin properties: the objective data. Am J Clin Dermatol. 2003;4:843–60.*

GENDER DIFFERENCES

The idealized female face tends to exhibit several characteristics that are reproducible from culture to culture and across the ages. On the other hand, the attractive masculine face tends to have a very different set of characteristics (Table 152.3), although they have not been studied as extensively as those for women.

ETHNIC DIFFERENCES

According to the American Society of Plastic Surgery, since 2001 there has been an increase in cosmetic procedures performed on ethnic minorities in the US. Based upon US Census Bureau projections, by the year 2056, >50% of the US population will be of non-Caucasian descent. While mathematical anthropometric measurements of the ideal facial structure have been determined, most of these measurements were based on the Caucasian face. Future anthropometric facial analyses need to take into account not only ethnocentric variations in facial structure and the effects of aging, but also ethnically diverse perceptions of beauty. Ethnic patients do not necessarily desire a Westernized look, as what constitutes beauty is influenced by racial, cultural and environmental factors. Descriptions of ethnocentric variability in these ideals have begun to appear in the dermatologic literature[19].

The cosmetic concerns of ethnic patients also vary due to inherent differences in skin structure and physiology (Table 152.4), mechanisms of aging, and facial anatomy (see Table 152.1). While lentigines and facial rhytides can occur decades later in darkly pigmented individuals (as compared to age-matched fair-skinned individuals) due to the protective effects of melanin, dyschromia can be a significant cosmetic concern in the former group.

COMBINATION THERAPIES

Optimal improvement in appearance can more often be obtained by combining procedures. At one end of the therapeutic spectrum, topical agents such as tretinoin, α-hydroxy acids, hydroquinone and 5-fluorouracil can inhibit or reverse UV radiation-associated changes in aging skin. At the other end of the therapeutic spectrum, rhytidectomy, blepharoplasty, brow lift, and suction-assisted lipectomy often provide dramatic results in facial rejuvenation. The choice of specific therapies rests on the ability of the surgeon to look at the face, analyze the anatomic components of the aging appearance, and then prioritize them, matching the risk : benefit ratios of various procedures to each element. Is the predominant problem photodamage, dynamic rhytides, sagging, or the loss or shift of facial volume? Often there are also overriding constraints, e.g. the "down time", surgical risk, cost, likelihood of benefit, that all weigh in on the selection of the appropriate therapy. However, underlying all of these choices must be a rational analysis of the various elements that comprise the aging face. The more an aesthetic surgeon is able to specifically tailor treatments to the individual patient, the more likely the outcome will be aesthetically optimal and be associated with a higher degree of patient satisfaction.

REFERENCES

1. Etcoff N. Survival of the Prettiest: the Science of Beauty. New York: Doubleday, 1999.
2. Luftman D, Ritvo E. The Beauty Prescription: The Complete Formula For Looking and Feeling Beautiful. McGraw-Hill, 2008:8.
3. Langlois JH, Roggman LA, Casey RJ, et al. Infant preferences for attractive faces: rudiments of a stereotype. Dev Psychol. 1987;23:363–9.
4. Aharon I, Etcoff N, Ariely D, et al. Beautiful faces have variable reward value: fMRI and behavioral evidence. Neuron. 2001;32:537–51.
5 Henderson JJA. Facial attractiveness predicts longevity. Evol Hum Behav. 2003;24:351–6.
6. Alam M. Dover JS. On beauty: evolution, psychosocial considerations, and surgical enhancement. Arch Dermatol. 2001;137:795–807.
7. Rohrich R, Pessa J. The fat compartments of the face: anatomy and clinical implications for cosmetic surgery. J Plast Reconstr Surg. 2007;119:2219–27.
8. Lambros V. Observations on periorbital and midface aging. Plast Reconstr Surg. 2007;120:1367–76.
9. Balin A, Pratt L. Physiological consequences of human skin aging. Cutis. 1989;43:431–6.
10. Montagna W, Carlisle K, Kirchner S. Epidermal and Dermal Histological Markers of Photodamaged Human Facial Skin. Shelton, CT: Richardson-Vicks, 1988.
11. Glogau RG. Chemical peeling and aging skin. J Geriatr Dermatol. 1994;2:30–5.
12. Fisher GJ, Varani J, Voorhees JJ. Looking older: fibroblast collapse and therapeutic implications. Arch Dermatol. 2008;144:666–72.
13. Fitzpatrick T. The validity and practicality of sun-reactive skin types I through VI. Arch Dermatol. 1988;124:869–71.
14. Hoefflin SM. The youthful face: tight is not right, repositioning is right. Plast Reconstr Surg. 1998;101:1417.
15. Glogau RG, Tan SR. Filler esthetics. In: Carruthers J, Carruthers A (eds). Soft Tissue Augmentation. In: Dover JS, Alam M (series eds). Procedures in Cosmetic Dermatology. Edinburgh: Elsevier Saunders, 2005:11–18.
16. Heckmann M, Teichmann B, Schröder U, et al. Pharmacologic denervation of frown muscles enhances baseline expression of happiness and decreases baseline expression of anger, sadness, and fear. J Am Acad Dermatol. 2003;49:213–16.
17. Finzi E, Wasserman E. Treatment of depression with botulinum toxin A: a case series. Dermatol Surg. 2006;32:645–9.
18. Alam M, Barrett KC, Hodapp RM, Arndt KA. Botulinum toxin and the facial feedback hypothesis: can looking better make you feel happier? J Am Acad Dermatol. 2008;58:1061–72.
19. Talakoub L, Wesley NO. Differences in perceptions of beauty and cosmetic procedures performed in ethnic patients. Semin Cutan Med Surg. 2009;28:115–29.

Cosmetics and Cosmeceuticals 153

Zoe Diana Draelos

Synonyms: ■ Cosmetics ■ Skin care products ■ Cosmeceuticals ■ Bioactive cosmetics ■ Nail products ■ Hair care products ■ Exfoliants ■ Moisturizers ■ Cleansers

Key features

- Colored cosmetics and skin care products have an important role in the prevention of dermatologic disease and the maintenance of skin health
- Hair is a non-living structure whose appearance and behavior can be improved via the use of shampoos and conditioners
- Nail cosmetics primarily adorn the nails, but improper use can lead to nail disease
- Cosmeceuticals are non-prescription products designed to improve the functioning of the skin, primarily through a reversal of the aging process
- Skin, hair and nail care products have a profound impact on these structures, and they should be part of the knowledge base of the dermatologist

INTRODUCTION

Cosmetics and skin care products are assuming an increasingly important role in dermatology as the sophistication of raw materials and the resulting formulations provide for the development of products that impact the functioning of the skin. It was traditionally thought that the stratum corneum was a non-living, biologically inert layer of skin upon which skin care products and cosmetics impinge. It was also thought that the stratum corneum was a complete barrier unaffected by the application of non-prescription topical agents. An improved understanding of stratum corneum function, primarily obtained through the use of non-invasive bioengineering techniques, has demonstrated that the stratum corneum can be dramatically influenced by non-prescription topical agents, and that these agents can indeed penetrate the stratum corneum and influence skin function.

This new understanding of the biologic importance of the stratum corneum to skin health led to the development of a new category of skin care product, known as the cosmeceutical[1]. A cosmeceutical is a scientifically designed, useful product intended for external application to the human body that has desirable aesthetic effects and meets rigid chemical, physical and medical standards[2]. Even though many cosmeceuticals currently exist for use on the skin, hair and nails, there is no regulatory description that acknowledges the current scientific sophistication of these formulations. Rather, a cosmetic is defined by the US Federal Food, Drug and Cosmetic Act, written in 1938, as "articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance", without affecting structure or function[3].

Cosmeceuticals are now a reality due to the expanding dermatologic knowledge-base, which has rendered obsolete the prior outdated clear distinction between cosmetics and drugs[4]. It is somewhat bewildering to realize that water is a cosmeceutical. Water profoundly influences the structure and function of the viable epidermis. Many substances can function as cosmeceuticals if entry into and through the stratum corneum is facilitated via the use of penetration enhancers, such as propylene glycol, isopropyl myristate, and pyrrolidone derivatives. Propylene glycol profoundly alters the barrier characteristics of the stratum corneum, while isopropyl myristate is capable of penetrating into the lipid bilayer of cell membranes. Pyrrolidone derivatives interact with both keratin and stratum corneum lipids to drive substances into the skin. These substances are commonly found in cosmetic formulations; however, new understanding of skin physiology allows recognition of their profound effects on the skin, which were previously unknown.

DISCUSSION

Skin Care Products

The three basic categories of skin care products are cleansers, astringents and moisturizers. Cleansers are designed to remove sebum, desquamating corneocytes, bacteria, fungi and environmental dirt from the face and body, while leaving the intercellular lipid barrier intact. Astringents are actually a subset of cleansers designed to supplement the failure of the cleanser to perform its intended function. Moisturizers are designed to minimize the barrier damage induced by cleansing. Thus, these three skin care products work together to balance the hygiene needs of the skin with the important task of preserving barrier function.

Cleansers

The development of soaps designed to cleanse the skin has been the single most important advance in decreasing disease worldwide. Even though soap is ubiquitous in the developed world, one of the main goals of world health organizations is to introduce the concept of cleansing with soap to areas of the globe where contagious diseases run rampant. In basic chemical terms, soap is a fatty acid salt resulting from a reaction between a fat and an alkali[5]. The soap solubilizes sebum and environmental dirt, such that it can be rinsed away with water. The mechanics of rubbing the soap over the skin with the hand or a bathing implement results in the physical removal of skin scale, bacteria and fungi from the skin surface. In high-income countries, where bathing has become a daily ritual, excessive use of soap has resulted in dermatologic conditions such as xerotic eczema. This has led to the development of cleansers with skin conditioning benefits that are chemically not true soaps, and they are referred to as detergents.

Cleansers, whether formulated as bars or liquids, can be divided into three basic types: soaps, syndets and combars (Table 153.1). True soaps, discussed previously, are composed of long-chain fatty acid alkali salts with a pH of between 9 and 10. This alkaline pH raises the pH of the skin following cleansing, resulting in stratum corneum barrier disruption and the resultant feeling of tightness following bathing. Alkalinization of the skin disrupts the natural acid mantle, which may be significant in dermatitic skin. Recognition of the need to preserve skin pH at 5.4 led to the development of *syn*thetic *det*ergents, known as syndets, such as sodium cocoyl isethionate. Syndet cleansers, also known as beauty cleansers, contain less than 10% soap, and are designed with a pH of 5.5–7.0 in order to minimize cutaneous alkalinization[6]. The third type of cleanser, known as a combar, is composed of an alkaline soap to which surface active agents with a pH of 9–10 have been added. Combars are milder cleansers than true soaps, but induce more thorough cleansing than syndets. For example, true soap is a good cleansing choice for excessively oily or dirty skin, while a combar is a good cleanser for normal skin with a moderate amount of environmental dirt. Syndets would be the least damaging to the cutaneous barrier in persons with dry skin or any form of dermatitis.

CATEGORIES OF CLEANSING PRODUCTS		
Product type	**Composition**	**Product examples®,™**
Bar soap	True soap in bar form; pH 9–10	Ivory Bar Soap (Procter & Gamble) Cashmere Bouquet (Colgate-Palmolive)
Syndet bar cleanser	Synthetic detergents (no soap), in bar form; pH 5.5–7	Cetaphil Bar (Galderma) Dove Bar (Unilever) Olay Quench Moisturizing Bar (Procter & Gamble)
Syndet liquid	Synthetic detergents, in liquid form; pH 5.5–7	Dove Liquid (Unilever) Oil of Olay Foaming Face Wash (Procter & Gamble)
Combar soap	Combination of true soap and synthetic detergent; pH 9–10	Dial (Dial Corporation) Irish Spring (Colgate-Palmolive)
Body wash	Emulsion system applied with a puff, allowing synthetic detergent cleansing combined with enhanced skin moisturization and emolliency	Aveeno Body Wash (Johnson & Johnson) Dove Body Wash (Unilever) Oil of Olay Daily Renewal Body Wash (Procter & Gamble)
Lipid-free cleanser	Cleans without fats; may contain glycerin, cetyl alcohol, stearyl alcohol, sodium lauryl sulfate and, occasionally, propylene glycol	Aquanil (Person & Covey) CeraVe Cleanser (Coria) Cetaphil (Galderma)
Cleansing cream	Waxes and mineral oil with detergent action from borax	Noxema (Noxell Corporation) Pond's Cold Cream
Astringent/toner	Alcohol-based product that may contain witch hazel, salicylic acid or glycolic acid	Clarifying Lotion 2, 3, 4 (Clinique)
Moisturizing astringent/toner	Glycerin-based humectant moisturizer	Clarifying Lotion 1 (Clinique)
Exfoliant cleanser	Glycolic or salicylic acid-containing cleanser	Oil-free Acne Face Wash (Neutrogena)
Abrasive cleanser	Polyethylene beads or other small particles within the syndet cleanser	Clinique 7 Day Scrub Cream Olay Age Defying Daily Renewal Cleanser (Procter & Gamble)

Table 153.1 Categories of cleansing products.

SPECIALTY SOAP FORMULATIONS	
Type of soap	**Unique ingredients**
Superfatted soap	Increased oil and fat and fat ratio up to 10%
Castile soap	Olive oil used as main fat
Deodorant soap	Antibacterial agents
French milled soap	Additives to reduce alkalinity
Floating soap	Extra air trapped during mixing process
Oatmeal soap	Ground oatmeal added (coarsely ground to produce abrasive soap; finely ground for gentle cleanser)
Acne soap	Sulfur, resorcinol, benzoyl peroxide or salicylic acid added
Facial soap	Smaller bar size, no special ingredients
Bath soap	Larger bar size, no special ingredients
Aloe vera soap	Aloe vera added to soap, no special skin benefit
Vitamin E soap	Vitamin E added, no special skin benefit
Cocoa butter soap	Cocoa butter used as major fat
Nut or fruit oil soap	Nut or fruit oils used as major fat
Transparent soap	Glycerin and sucrose added
Abrasive soap	Pumice, coarse oatmeal, maize meal, ground nut kernels, dried herbs or flowers added
High impact soap	Strong, high-concentration fragrance added to scent skin after cleansing
Soap-free soap	Contains synthetic detergents (syndet bar)

Table 153.2 Specialty soap formulations.

The many brands of cleansers currently on the market fall into one of the three aforementioned groups, yet there must be something unique, for marketing purposes, about each cleanser. The unique aspects of each cleanser are created through the addition of specialty additives (Table 153.2). Common cleanser additives include various fragrances and foaming agents designed to alter the aesthetics of the lather, but the most dermatologically relevant additives are antibacterial agents. The most widely used antibacterial in both bar and liquid cleansers is triclosan[7]. Triclosan works by blocking lipid synthesis in the bacterial cell wall, thus decreasing the skin biofilm bacteria count and reducing odor.

Another important dermatologic need with regard to skin cleansing is minimization of skin barrier dysfunction. Unfortunately, surfactants cannot distinguish between unwanted sebum and oil-soluble dirt and the intercellular lipids. Thus, increases in transepidermal water loss are typically noted in direct proportion to the cleansing ability of the cleanser. An attempt to provide cleansing and barrier restoration in the same product has led to the development of body washes. Since body washes are liquids, incorporating both hydrophilic and lipophilic ingredients emulsified into a single phase, it is possible to cleanse and moisturize simultaneously while allowing for rinsing away of the surfactants. Body washes must be used with a puff to induce both water and air into the cleanser emulsion in sufficient quantity to allow cleansing and moisturization to occur. The syndet detergent, primarily ammonium laureth sulfate, solubilizes oil-soluble dirt into the rinse water for removal during the cleansing phase when the body wash concentration is high and the water concentration low, while occlusive moisturizing substances (e.g. petrolatum) and emollients (e.g. soybean oil) are left behind to retard transepidermal water loss and improve skin smoothness during the rinse phase when the body wash concentration is low and the water concentration is high.

Other cleanser variants for persons with dry, dermatitic skin include lipid-free, non-foaming cleansers and cold creams. These products are excellent at removing cosmetics and low levels of environmental dirt. Lipid-free cleansers are non-foaming, soap-free liquid products applied to dry or moistened skin, rubbed to produce minimal lather, and rinsed or wiped away. They possess low surfactant capabilities, and they can only remove bacteria through mechanical means, yet they are important in persons with barrier disruption[8]. The classic cleanser for dry, dermatitic skin is cold cream, which combines the effect of a lipid solvent, such as wax or mineral oil, with detergent action from borax[9].

Occasionally, a dermatologic need arises for specialty cleansers designed to offer a skin benefit beyond pure removal of sebum and environmental dirt. For example, it may be desirable to induce corneocyte disadhesion in older patients requiring an exfoliant cleanser. This can be accomplished through the addition of chemical exfoliants, such as salicylic acid or glycolic acid, to the cleanser formulations discussed previously. Exfoliant cleansers containing benzoyl peroxide or salicylic acid are sometimes used as an adjunct in topical acne treatment. Exfoliation can also be induced mechanically through the incorporation of fine abrasive particles (such as polyethylene beads, aluminum oxide, ground fruit pits, or sodium tetraborate decahydrate granules) in a liquid syndet cleanser to remove skin scale. Lastly, mechanical exfoliation can be encouraged through the use of specially woven face cloths, designed to remove skin scale without inducing epidermal damage.

The development of novel detergents and cleansing specialty additives has created a confusing plethora of consumer products, yet the goal remains the same: to allow adequate skin hygiene without barrier damage. Our next concern is the discussion of moisturizers, designed to replace skin sebum in instances where the stratum corneum barrier has been damaged from exuberant cleansing.

Moisturizers

The term "moisturizer" is somewhat misleading to the consumer, who assumes that the cream or lotion actually puts moisture or water back into the skin[10]. Moisturizers do not put water back into the skin externally, nor do they get incorporated into the intracellular lipids. Moisturizers simply attempt to retard transepidermal water loss and create an optimal environment for restoration of the stratum corneum barrier[11]. The optimal water content for the stratum corneum is between 10% and 30%, depending on the measurement technique employed, and moisturizers can function to raise the cutaneous water content through occlusion or humectancy with a variety of active agents (Table 153.3)[12].

Occlusive moisturizers prevent evaporative water loss to the environment by placing an oily substance on the skin surface through which water cannot penetrate, thus replenishing the stratum corneum moisture by water movement from the lower viable epidermal and dermal layers[13]. There are many different classes of chemicals that can function as occlusive moisturizers[14], for example, hydrocarbon oils and waxes (petrolatum, mineral oil, paraffin, squalene), silicone (cyclomethicone, dimethicone), vegetable oils (castor oil, corn oil, grape seed oil, soybean oil), animal oils (mink oil, emu oil), fatty acids (lanolin acid, stearic acid), fatty alcohol (lanolin alcohol, cetyl alcohol), polyhydric alcohols (propylene glycol), wax esters (lanolin, beeswax, stearyl stearate), vegetable waxes (carnauba wax, candelilla wax), phospholipids (lecithin) and sterols (cholesterol, ceramides)[15].

The most effective occlusive moisturizer is petrolatum, since it reduces transepidermal water loss by 99%[16]. Total occlusion of the stratum corneum is undesirable, since transepidermal water loss is the cellular signal that initiates barrier repair and the resulting synthesis of intercellular lipids[17,18]. Complete cessation of transepidermal water loss results in no barrier repair, allowing water loss to return to its normal pretreatment level once the complete occlusion has been removed[17–19]. Petrolatum allows barrier repair while permeating throughout the interstices of the stratum corneum[20].

Another technique for rehydrating the stratum corneum is the use of humectants. Humectants are substances that attract moisture; they include glycerin, honey, sodium lactate, urea, propylene glycol, sorbitol, pyrrolidone carboxylic acid, gelatin, hyaluronic acid, and some vitamins and proteins[14,21]. The body utilizes hyaluronic acid and other glycosaminoglycans in the dermis as biologic humectants to prevent desiccation of the skin. Humectants can only hydrate the skin from the environment when the ambient humidity exceeds 70%. Consequently, rehydration of the stratum corneum generally occurs by water that is attracted from the deeper epidermal and dermal tissues. Most moisturizers combine both occlusive and humectant moisturizing ingredients, since water drawn by a humectant to a damaged stratum corneum barrier will be lost to the atmosphere unless trapped by an occlusive[22,23]. Humectants also help to improve the smoothness of xerotic skin by inducing corneocyte swelling and minimizing voids between the desquamating corneocytes[24].

In summary, remoisturization of the skin must occur in four steps:

- initiation of barrier repair (see Ch. 124)[25]
- alteration of surface cutaneous moisture partition coefficient
- onset of dermal–epidermal moisture diffusion
- synthesis of intercellular lipids[26].

Moisturizers attempt to increase stratum corneum water content through the principles of occlusion and humectancy. The discovery of aquaporin 3 channels in the skin and their modulation by glycerin and urea has increased research into osmotic cell balance as another mechanism for moisturization.

Astringents

Occasionally, patients use skin care products that either correct the deficiencies of the cleanser or supplement the effects of the moisturizer. These products are known as astringents or toners (see Table 153.1). They are used after cleansing but before moisturizing, and they are left on the face following use. Astringents are usually liquids wiped over the face with a cotton ball. Originally, astringents were intended to remove soap scum left behind on the face from the use of lye-based soaps and hard water. If left behind, this soap scum could cause irritant contact dermatitis. The original astringents were fragranced isopropyl alcohol or propylene glycol solutions designed to remove oil-soluble residue. The development of synthetic detergents and treated water has made this original intent obsolete, yet astringents remain popular.

Currently, astringents are used to remove the oily residue left behind after cleansing of the face with lipid-free cleansers or cleansing creams, discussed previously. Oily complexion astringents are formulated to remove any remaining sebum from the face following synthetic detergent cleansing or to deliver keratolytics, such as salicylic acid, glycolic acid or witch hazel. Some astringents designed for dry skin contain a humectant liquid moisturizer, such as propylene glycol or glycerin, and skin soothing agents, such as allantoin, guaiazulene or quaternium-19[27]. A complete cosmetic-counter facial treatment routine involves a cleanser followed by an astringent and then a moisturizer. Once the skin has been prepared in this manner, colored cosmetics are applied.

Colored Facial Cosmetics

Colored facial cosmetics are intended to adorn the eyes, lips and cheeks with color for the purposes of creating a fashionable appearance, highlighting certain desirable features, and camouflaging facial flaws. Colored cosmetics are of importance to the dermatologist for their role in maintaining skin health, inducing dermatitis, and camouflaging surgical defects.

Facial foundations

Formulation

Facial foundations are the first cosmetic applied to the face following the use of a moisturizer and, therefore, represent the colored facial cosmetic with the greatest impact on the integrity of the skin. Facial foundations are basically pigmented moisturizers worn for 8 hours or longer before removal. Consequently, this class of color cosmetics, more than any other, has an impact on the integrity of the skin. Facial foundations are available for every complexion type and skin color, fulfilling the needs listed in Table 153.4.

There are four basic facial foundation formulations: oil-based, water-based, oil-free, and water-free or anhydrous forms[28]. Oil-based products are designed for dry skin, while water-based products can be adapted

DIFFERENT TYPES OF MOISTURIZERS

Moisturizer type	Composition	Product examples®,™
Oil only	Petrolatum	Vaseline petroleum jelly (Chesebrough Ponds)
Oil-in-water emulsion	Water, petrolatum	Eucerin cream (Biersdorf)
Polymer-based	Water, polyglycerylmethacrylate, petrolatum	Cetaphil cream (Galderma)
Vegetable oil and wax	Castor oil, corn oil, ozokerite, beeswax, paraffin, carnauba wax	Lip moisture (Neutrogena)
Glycerin-rich	Water, glycerin, petrolatum	Norwegian formula hand cream (Neutrogena) Curel lotion (Andrew Jergens)
Dimethicone and ceramides	Water, petrolatum, dimethicone, ceramides	CeraVe (Coria) EpiCeram (Ceragenix)

Table 153.3 Different types of moisturizers. Additional prescription moisturizers are based upon glycyrrhetinic acid and shea butter (Atopiclair®), palmitoylethanolamide (MimyX®), paraffin (Biafine®), and sodium hyaluronate (Hylira™, Hylatopic™).

FUNCTIONS OF FACIAL FOUNDATION
Add facial color
Blend facial color
Camouflage pigmentation irregularities
Normalize facial skin
Provide sun protection
Act as a treatment product

Table 153.4 Functions of facial foundation.

for all skin types. Oil-free formulations are used in oily skin foundations, while anhydrous forms are extremely long-wearing and used for camouflage or theatrical purposes.

Oil-based foundations are water-in-oil emulsions containing pigments suspended in oil (e.g. mineral oil) or lanolin alcohol. Vegetable oils (grape seed, coconut, sesame, safflower) and synthetic esters (isopropyl myristate, octyl palmitate, isopropyl palmitate) may also be incorporated. The water evaporates from the foundation following application, leaving the pigment in oil on the face. This creates a moist skin feeling, especially desirable in dry complected patients. Oil-based foundations do not shift color as they mix with sebum, since the color is fully developed in the oily phase of the formulation. These foundations are easy to apply, since the pigment can be spread over the face for up to 5 minutes, prior to setting.

Water-based facial foundations are oil-in-water emulsions containing a small amount of oil, in which the pigment is emulsified, and a relatively large quantity of water. The primary emulsifier is usually a soap, such as triethanolamine, or a non-ionic surfactant. The secondary emulsifier, present in smaller quantity, is usually glyceryl stearate or propylene glycol stearate. These popular foundations are appropriate for minimally dry to normal skin. Since the pigment is already developed in oil, this foundation type is also not subject to color drift. The amount of time the product can be moved over the face, known in the industry as playtime, is shorter than with oil-based foundations.

Oil-free facial foundations contain no animal, vegetable or mineral oils. They contain other oily substances, such as dimethicone or cyclomethicone. These foundations are usually designed for oily complected individuals, since they leave the skin with a dry feeling. Dimethicone is non-comedogenic, non-acnegenic and hypoallergenic, accounting for the tremendous popularity of this type of facial foundation formulation. Both water-based and oil-free foundations are usually packaged in a bottle.

Water-free, or anhydrous, foundations are waterproof. Vegetable oil, mineral oil, lanolin alcohol and synthetic esters form the oil phase, which may be mixed with waxes to form a cream. High concentrations of pigment can be incorporated into the formulation, yielding an opaque facial foundation. The coloring agents are based on titanium dioxide with iron oxides, occasionally in combination with ultramarine blue. Titanium dioxide acts both as a facial concealing agent and sunscreen. These products can be dipped from a jar, squeezed from a tube, wiped from a compact, or stroked from a stick. Water-free foundations are well suited for use in people who require facial camouflaging. They can be combined with a high-coverage powder foundation to increase the opacity of the cosmetic.

Application and cutaneous effects

Facial foundations must be evenly applied to create the optimal cosmetic appearance and achieve the secondary benefit of sun protection. The iron oxide pigment and other covering agents, for example, titanium dioxide, zinc oxide and kaolin, are physical particulates that block both UVA and UVB radiation (see Ch. 132). A facial foundation *without* any added organic sunscreen ingredients, such as ecamsule, octyl methoxycinnamate, oxybenzone or avobenzone, usually has a sunburn protection factor (SPF) of at least 4. Facial foundations that have greater coverage in order to camouflage underlying pigmentation defects usually possess an SPF of at least 8. The inclusion of additional sunscreen agents to the facial foundation can raise the SPF to 15. Thus, facial foundation is an excellent, cosmetically elegant facial photoprotectant.

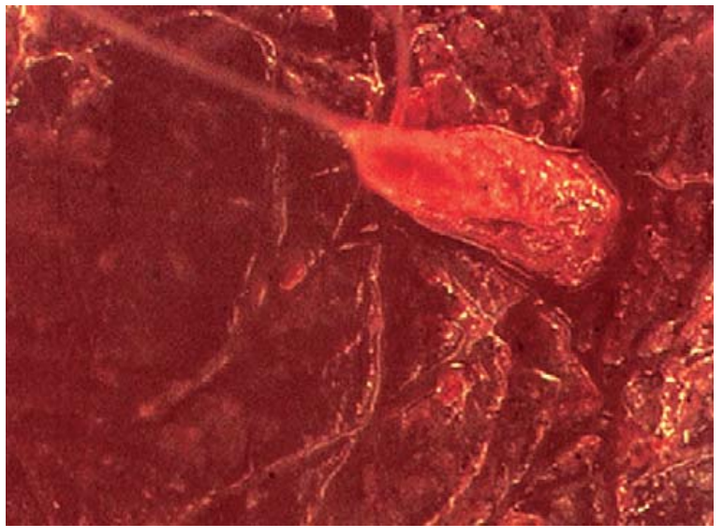


Fig. 153.1 Migration of iron oxide particles in facial foundation to follicular ostia. As seen by video microscopy (400×), this migration tends to occur as sebum and eccrine secretions mix with the cosmetic film.

An even, cosmetically acceptable application of facial foundation begins with a proper color match to the skin at the jawline and application with the fingertips. A dab of foundation should be placed on the forehead, nose, cheeks and chin, and blended with a light circular motion until it is evenly spread over the entire face, including the lips. Finally, a puff or sponge should be used, stroking in a downward direction, to remove any streaks and to flatten vellus facial hair. Special care should be taken to rub the foundation into the hairline, over the tragus, and beneath the chin. Foundation should also be blended around the eyes, and it may even be applied to the entire upper eyelid if desired. The foundation should be allowed to set or dry until it can no longer be removed with light touch. If additional coverage is desired, a second layer of foundation can be applied.

The most common adverse dermatologic effect related to the use of facial foundation is a condition patients describe as "breakouts". Patients typically note small perifollicular papules 48 hours after using a new facial foundation. The appearance is that of acne; however, the 48-hour time course is inconsistent with a diagnosis of acne. This condition may represent a perifollicular irritant contact dermatitis, since facial foundations tend to migrate to the follicular ostia as they mix with eccrine secretions and sebum, which break down the cosmetic film (Fig. 153.1). This observation may explain why facial foundations that have been found on clinical testing to be non-comedogenic and non-acnegenic cause acneiform eruptions in individuals with self-diagnosed sensitive skin. Overall, however, facial foundations are an infrequent cause of dermatologic problems.

Powders

One of the ways of preventing migration of facial foundation, improving its sun protective capabilities, and increasing oil absorption, is to apply powder over the foundation. Facial powders contain predominantly talc (hydrated magnesium silicate) and increased amounts of covering pigments. The covering pigments used in face powder are listed in order of increasing opaqueness in Table 153.5. It is generally accepted that the optimum opacity is achieved with a particle size of 0.25 μm. Black dermographism from earrings can result when face powders contain ingredients, e.g. zinc oxide, that are harder than platinum, silver or gold.

Facial powders usually also contain magnesium carbonate and/or kaolin (hydrated aluminum silicate) to absorb oil and perspiration. Full-coverage face powders with increased pigments and light reflective particles are usually packaged as a cake in a compact and applied to the face with a puff, loose in a jar and dusted over the face with a brush, or stroked over the face from an automatic brush dispenser. These face powders with increased pigments can be used as a facial foundation

COVERING ABILITY OF FACE POWDER INGREDIENTS
1. Titanium dioxide
2. Kaolin (hydrated aluminum silicate)
3. Magnesium carbonate
4. Magnesium stearate
5. Zinc stearate
6. Prepared chalk
7. Zinc oxide
8. Rice starch
9. Precipitated chalk
10. Talc (hydrated magnesium silicate)

Table 153.5 Covering ability of face powder ingredients. Listed in order of increasing opacity.

PIGMENTS ALLOWED BY THE US FDA IN EYE SHADOW COSMETICS
Iron oxides
Titanium dioxide (alone, or combined with mica)
Copper, aluminum and silver powder
Ultramarine blue, violet and pink
Manganese violet
Carmine
Chrome oxide and hydrate
Iron blue
Bismuth oxychloride (alone, or on mica or talc)
Mica

Table 153.6 Pigments allowed by the US Food and Drug Administration (FDA) in eye shadow cosmetics.

and are known as mineral make-ups. They are recommended for persons with sensitive skin and rosacea as they contain no liquids, fewer preservatives, and fewer ingredients. As a result, there is decreased potential for allergic and irritant contact dermatitis. Specially pigmented powders are used to redden the cheeks, known as blushes, and to color the eyelids, known as eye shadows.

Facial blushes

Facial blushes are typically powders designed to simulate rosy cheeks, occasionally an unwanted finding in rosacea patients. Blushes have the same basic formulation as face powders, except for the presence of different surface characteristics that can vary from a matte dull finish, to a frosted shine, to a metallic glow, depending on current fashion trends[29]. Some of the rough-edged particles designed to produce light reflection can cause irritation in people with sensitive skin. Powder blush can be used to absorb facial oil, blend the facial erythema of rosacea across the cheeks, and add color to a sallow face, by dusting on the central chin, cheeks, nasal tip and forehead.

Eye shadows

Eye shadows are similar to powder blushes in formulation and surface characteristics, except that the color variation is broader, but limited in the US by the Food and Drug Administration (FDA) to the purified natural colors or inorganic pigments listed in Table 153.6[30]. Eye shadow can be used to camouflage misshapen eyes, provide sun protection to the upper eyelid, and minimize the appearance of unwanted periorbital pigmentation. Eye shadows are a common concern to dermatologists, since they may be responsible for eyelid dermatitis. They may contain the same light-reflective particles as blushes and cause pruritus of the eyelids due to irritant contact dermatitis until discontinued (Fig. 153.2).

The North American Contact Dermatitis Group has determined that 12% of cosmetic reactions occur on the eyelid, but only 4% could be linked to eye make-up use[31]. Unfortunately, it can be difficult to determine the etiology of allergic contact eyelid dermatitis with routine patch testing[32], since many substances can be transferred to the eye area by the hands, complicating the dermatologic evaluation[33]. However, eye shadows are a rare cause of eye infections, since the dry powder cake does not support bacterial growth.

Fig. 153.2 Upper eyelid dermatitis. Upper eyelid dermatitis may be exacerbated by the use of heavily pigmented, light-reflective eye shadows.

Mascaras

Mascaras are eyelash cosmetics, as opposed to eye shadows, which are eyelid cosmetics. Mascaras are designed to color, camouflage, elongate and thicken the eyelashes, which are the frame to the eyes. They must be carefully formulated to allow easy and even application without smudging, irritancy or toxicity. Some of the coloring agents employed include iron oxide to produce black, ultramarine blue to create navy, and umber, burnt sienna or synthetic brown oxide to create brown[34].

Most modern mascaras are formulated as liquids, then stored in a tube with a multitufted applicator brush or comb. The applicator is inserted into the tube between uses, providing numerous opportunities to inoculate bacteria into the cosmetic. The most dangerous bacterial infection is a *Pseudomonas aeruginosa* corneal infection, which can permanently diminish visual acuity[35,36]. *Staphylococcus epidermidis, S. aureus* and fungal organisms may also proliferate in contaminated mascaras[37,38]. Infections are more common if the globe is traumatized with the infected mascara wand. Even though mascaras contain antibacterials, it is still wise to discard all mascara tubes after 3 months and not allow multiple persons to use the same mascara tube[39].

DIFFERENT TYPES OF MASCARA FORMULATIONS		
Mascara formulation	**Composition**	**Advantages/Disadvantages**
Water-based	Waxes, pigments, resins	Easy to remove with water; runs with tearing; supports bacterial growth
Solvent-based waterproof	Petroleum distillates, pigments, waxes	Must be removed with solvent; waterproof; does not support bacterial growth
Water-resistant water/solvent hybrid	Oil-in-water emulsion, pigments	Removal with water and cleanser; resists running with tearing; less likely to support bacterial growth
Compressed cake	Pigments, talc	Removal with water; runs with tearing; least allergenic; does not support bacterial growth

Table 153.7 Different types of mascara formulations.

There are several mascara formulations that are less likely to support bacterial and fungal growth (Table 153.7). Mascaras are available as water-based, solvent-based, and a water/solvent hybrid. Water-based mascaras are easily removed with water and less likely to cause eye area irritation, but the presence of water provides welcome media for bacterial growth. Solvent-based mascaras are manufactured without water, must be removed with a special cleanser, and are more irritating; however, they are less likely to support bacterial growth, and they are the formulation of choice for individuals who are carriers of *Staphylococcus* or *Streptococcus* spp[40]. The water/solvent hybrid mascaras are

an attempt to provide a water-resistant cosmetic with the benefits of both.

Another dermatologic side effect of the use of mascara is conjunctival pigmentation, resulting from the washing of mascara into the conjunctival sac by lacrimal fluid[41]. This colored particulate matter can be observed on the upper margin of the tarsal conjunctiva. Histologically, the pigment is seen within macrophages and extracellularly in association with a variable lymphocytic infiltrate. Electron microscopy suggests that ferritin, carbon and iron oxides are present within the tissues[42]. Unfortunately, there is no treatment for the condition, which is usually asymptomatic.

Specialty mascaras are available for curling and elongating the eyelashes. These mascaras contain pigmented polymers that polymerize on the lash as they dry. The polymer then shrinks, curling the eyelash and placing a thin, long-wearing, pigmented film around the hair which thickens and elongates the lash. In addition, a prescription cosmeceutical containing bimatoprost 0.03% (Latisse®; originally indicated for the treatment of glaucoma) is available to elongate eyelashes via prostaglandin modulation (see Ch. 70)[43]. Side effects include iris and eyelid pigmentation, which may be permanent.

Lipsticks

Lipstick is a lip cosmetic designed to frame the teeth. Traditional lipsticks are mixtures of waxes, oils and pigments in various concentrations to yield the characteristics of the final product. For example, a lipstick designed to remain on the lips for a prolonged period of time is composed of high wax, low oil and high pigment concentrations, whereas a product designed for a smooth creamy feel on the lips is composed of low wax and high oil concentrations[44]. The waxes commonly incorporated into lipstick formulations are white beeswax, candelilla wax, carnauba wax, ozokerite wax, lanolin wax, ceresin wax and other synthetic waxes. Usually, lipsticks contain a combination of these waxes carefully selected and blended to achieve the desired melting point. Oils for pigment dispersion are then selected, such as castor oil, white mineral oil, lanolin oil, hydrogenated vegetable oils or oleyl alcohol, to form a film suitable for application to the lips[45,46].

Newer lipstick formulations contain long-wearing polymers that create a waterproof film over the lips that remains in place indefinitely until worn away with speech or eating. These long-wearing lip products can cause cheilitis, due to their non-moisturizing formulations. In addition, lip products are marketed that claim to plump the lips. These products contain irritants, such as capsaicin, that create a mild irritant contact dermatitis resulting in short-lived lip edema.

Certain common lipstick ingredients can cause difficulty in the sensitized patient[47]. Castor oil, found in almost all lipsticks due to its excellent ability to dissolve bromo acid dyes, can cause allergic contact dermatitis[48–50]. Even the bromo acid dyes, such as eosin (D & C Red No. 21), found in indelible lipsticks can cause allergic contact dermatitis[51]. Other lipstick ingredients reported to cause allergic contact dermatitis include: ricinoleic acid[52], benzoic acid[53], lithol rubine BCA (Pigment Red 57–1)[54], microcrystalline wax[55], oxybenzone[56], propyl gallate[57] and C18 aliphatic compounds[58].

Facial cosmetics for camouflaging

All of the colored cosmetics previously discussed are used together for facial camouflaging purposes to minimize facial defects while accentuating attractive facial features. Camouflage cosmetics are used by paramedical aestheticians, dermatologists, plastic surgeons, and cosmetic consultants[59]. Their successful use requires a well-formulated, quality product applied with the skill of a stage make-up technician and the artistic abilities of a painter[60]. Facial defects requiring camouflaging are defects of pigmentation, contour, or a combination of both[61].

Pigmentation defects represent abnormalities limited to the color of the skin, whereas contour defects are defined as areas where the facial skin is hypertrophic or atrophic, with textural changes due to the absence of appendageal structures. Table 153.8 lists examples of pigmentary abnormalities frequently encountered by dermatologists that arise from inflammatory disorders, systemic diseases or extrinsic effects (e.g. sun exposure). Pigmentation defects can be camouflaged either by applying an opaque cosmetic that allows none of the abnormal underlying skin tones to be appreciated or by applying foundations of complementary colors. For example, red discoloration can be camouflaged by applying a green foundation, since green is the complementary color to red. The blending of the red skin with the green foundation yields a brown tone, which can be readily covered by a more conventional facial foundation. Furthermore, yellow skin tones can be blended with a complementary-colored purple foundation to also yield brown tones.

CAMOUFLAGE FOR ABNORMALITIES OF FACIAL PIGMENTATION		
Facial color	**Disease process**	**Undercover foundation color**
Red	Psoriasis, lupus erythematosus, rosacea	Green
Yellow	Solar elastosis, chemotherapy, dialysis	Purple
Brown hyperpigmentation	Melasma, lentigines, nevi	White
Hypopigmentation and depigmentation	Postinflammatory, congenital, vitiligo	Brown

Table 153.8 Camouflage for abnormalities of facial pigmentation.

The camouflaging of facial contour abnormalities is based on the principle that dark colors make protuberances appear to recede while light colors make surface depressions appear more shallow. Creating an even-appearing surface on a scarred face is achieved through artistic shading. Powdered blush-type products are best suited for this purpose. Areas of the face that need to be lightened should be brushed with a light pink or peach pearled blush or buffer. Areas of the face that need to be darkened should be brushed with a deep plum or bronze matte-finish blush or highlighter.

There are special cosmetics manufactured for these camouflaging purposes. A reference list of the websites of the recommended camouflaging cosmetic companies is given in the Appendix.

Hair Care Products

Some of the material discussed above is applicable to hair care products, since shampoos can be likened to skin cleansers, while conditioners are similar to skin moisturizers.

Hair shampoos

Shampoos are simply designed to cleanse the hair; however, this is a complicated task considering that the average woman has 4–8 m^2 of hair surface area to clean[62]. Shampoos are intended to remove sebum, sweat components, desquamated stratum corneum, styling products and environmental dirt from the hair and scalp[63]. They contain detergents, foaming agents, conditioners, thickeners, opacifiers, softeners, sequestering agents, fragrances, preservatives and specialty additives[64]. Synthetic detergents remove sebum and dirt; however, excessive removal of sebum leaves the hair dull, susceptible to static electricity, and difficult to comb, creating the need for hair conditioners[65]. Shampoo detergents can be chemically classified as anionics, cationics, nonionics, amphoterics and natural surfactants (Table 153.9)[66]. The basic difference between bar soap and shampoo is the addition of a higher concentration of sequestering agents to chelate magnesium and calcium ions, preventing the formation of other salts or insoluble soaps known as soap scum. Without sequestering agents, shampoos would leave the hair dull and contribute to scalp pruritus. There are many different types of shampoo, designed to meet various hair cleansing needs (Table 153.10).

Hair conditioners

The need for hair conditioners arises from the inability of shampoos to remove just enough sebum to leave the hair clean, without removing too much sebum and creating dry, unmanageable, dull hair[67]. Conditioners are also required because permanent waving, permanent coloring and other chemical hair treatments damage the cuticle, making the hair harsh, brittle and difficult to disentangle (Table 153.11; Fig. 153.3)[68]. Hair conditioners are designed to reverse this hair damage by improving sheen, decreasing brittleness, decreasing porosity, increasing strength, and repairing degradation in hair protein[69,70].

SHAMPOO DETERGENTS		
Surfactant type	**Chemical class**	**Characteristics**
Anionics	Lauryl sulfates, laureth sulfates, sarcosines, sulfosuccinates	Deep cleansing; may leave hair harsh
Cationics	Long-chain amino esters, ammonio esters	Poor cleansing; poor lather; impart softness and manageability
Non-ionics	Polyoxyethylene fatty alcohols, polyoxyethylene sorbitol esters, alkanolamides	Mildest cleansing; impart manageability
Amphoterics	Betaines, sultaines, imidazolinium derivatives	Non-irritating to eyes; mild cleansing; impart manageability
Natural surfactants	Sarsaparilla, soapwort, soap bark, ivy, agave	Poor cleansing; excellent lather

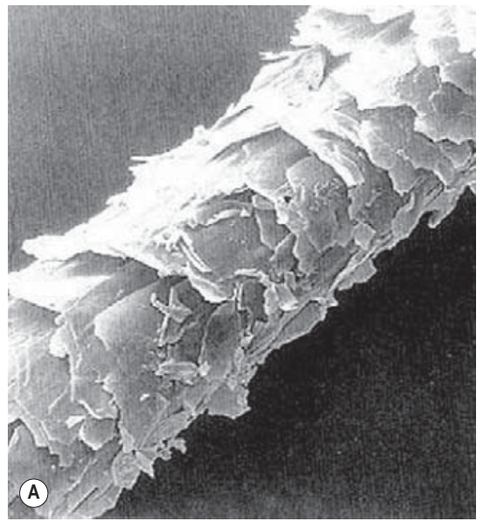
Table 153.9 Shampoo detergents.

SPECIALTY SHAMPOOS		
Shampoo type	**Function**	**Unique ingredients**
Oily hair	Provide excellent cleansing to remove sebum with minimal conditioning	Strong surfactants such as sodium lauryl sulfate or the sulfosuccinates
Dry hair	Provide mild cleansing and excellent conditioning	Milder surfactants such as sodium laureth sulfate
Conditioning	Contain added conditioners to enhance shine and minimize static electricity	Hydrolyzed proteins designed to penetrate the hair shaft
Baby	Utilize mild detergents that anesthetize the conjunctiva to prevent stinging, burning and irritation	Detergents from the amphoteric group such as the betaines
Medicated	Designed to treat dandruff and seborrheic dermatitis through the use of keratolytics as well as antiproliferative and anti-inflammatory agents	Tar, salicylic acid, sulfur, selenium disulfide, ketoconazole, and zinc pyrithione
Professional	Designed for use following hair coloring to reduce hair shaft swelling	Cationic acidic shampoos to neutralize residual hair shaft alkalinity following permanent hair coloring

Table 153.10 Specialty shampoos.

Hair conditioners improve manageability by decreasing static electricity. Following combing or brushing, the hair shafts become negatively charged, causing the hairs to repel one another. Conditioners deposit positively charged ions on the hair shaft, neutralizing the electrical charge. They also improve manageability by reducing hair shaft combing friction by as much as 50%, leading to enhanced disentangling, and conditioners smoothe the cuticular scale to increase hair shine (Fig. 153.4)[71,72]. Maximum hair shine is produced by large-diameter, elliptical hair shafts with a sizable medulla and intact, overlapping cuticular scales[73]. Hair that lacks shine is missing its cuticle (Fig. 153.5).

Special hair conditioner formulations attempt to repair split-ends by temporarily reapproximating the frayed remnants of remaining medulla and cortex. This is accomplished through the use of hydrolyzed animal proteins that can minimally penetrate the hair shaft, enhancing hair tensile strength by 5% until the hair is next shampooed. There are several types of conditioners formulated for a variety of needs (Table 153.12). Leave-in conditioners are specially designed for Afro-textured hair in order to maintain hair water content despite the unavoidable loss that occurs following hair straightening.



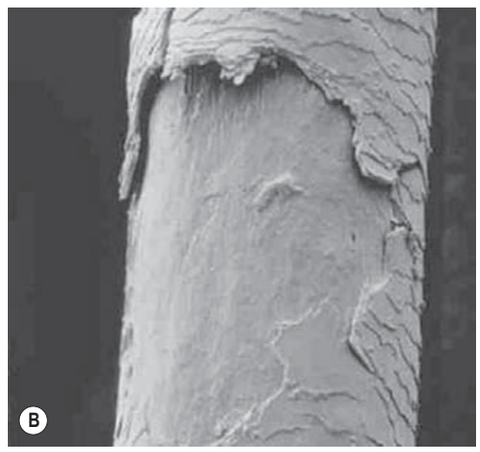
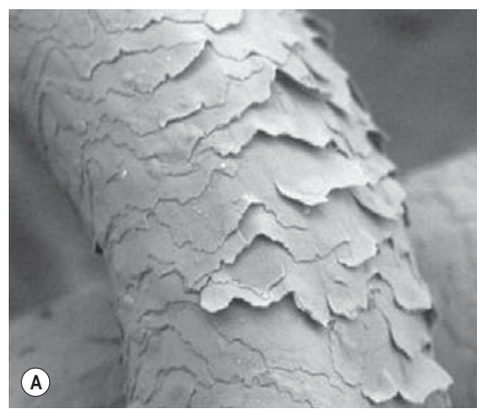


Fig. 153.3 Electron photomicrographs of chemically damaged hair shafts. A Loose cuticle, compared to the tightly overlapping cuticle of normal hairs (see Fig. 153.5). **B** Missing cuticle with exposed cortex.



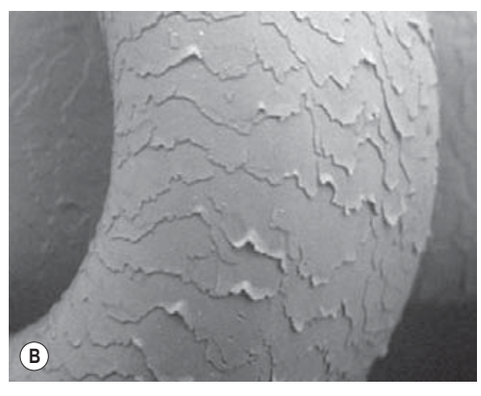


Fig. 153.4 Electron photomicrographs demonstrating the effect of hair conditioners. A Unconditioned hair shaft with uplifted cuticle. **B** Conditioned hair shaft with tightly adherent cuticle.

CHEMICAL HAIR TREATMENTS: COLORING, PERMANENT WAVING AND RELAXING				
Treatment	**Definition**	**Chemicals used**	**Process**	**Adverse effects**
Permanent coloring	Color persists indefinitely (until new growth appears)	• H_2O_2 (referred to as the developer or oxidizing agent) • Ammonia • Dye (e.g. *p*-phenylenediamine, aminophenols)	• H_2O_2 lightens ("lifts") the previous color by oxidizing melanin, and it causes the dye to "develop" and deposit color • Alkaline pH leads to swelling and disruption of the cuticle, allowing the dye to penetrate into the cortex • To dye dark hair to a light blonde color, the hair must first be bleached (e.g. with a mixture of ammonium persulfate and H_2O_2)	• Dull, brittle hair (especially with permanent color) • Allergic contact dermatitis • Staining of the skin
Demi-permanent coloring	Color lasts 2–3 months (12–24 shampoos)	• Low concentration of H_2O_2 • Non-ammonia alkali (e.g. monoethanolamine) • Dye (e.g. *p*-phenylenediamine, aminophenols)	• Similar to permanent color (but to a lesser degree)	
Semi-permanent coloring	Color lasts 4–6 weeks (6–12 shampoos)	• No H_2O_2 • Mild non-ammonia alkali • Azo dyes, henna, polymerized dyes, aminophenols ± *p*-phenylenediamine	• Small dye particles both coat the cuticle and penetrate into the cortex, or dye polymers coat the cuticle • The hair is not lightened	
Gradual coloring	Color slowly builds up over time	• Metallic dyes (e.g. salts of lead, bismuth or silver)	• Dye particles slowly accumulate in the cuticle, darkening the hair within a limited (brown–black) range	
Temporary coloring	Color is removed with 1–2 shampoos	• Azo and other FD&C dyes	• Dye coats the cuticle of the hair shaft (particles are too large to penetrate the cuticle)	
Permanent waving ("perm")*	Chemical treatments "permanently" curl hair (until new growth appears)	• Ammonium or sodium thioglycolate (pH 9–10; "alkaline perm") *– or –* • Glycerol monothioglycolate (pH 6.5–8; "acid perm"; requires application of heat) *– or –* • Bisulfites or mercaptamine (low/neutral pH, "thioglycolate-free perms")	• The hair is wrapped around rods and the chemical solution is applied to break disulfide bonds between keratin polypeptide chains • Neutralizing solution is then used to reform the disulfide bridges, and the hair takes the shape of the rod	• Dull, brittle hair (especially with alkaline perms) • Irritant contact dermatitis • Allergic contact dermatitis • Glycerol monothioglycolate may be retained in hair for up to 3 months
Chemical relaxing (lanthionizing)*	Chemical treatments "permanently" straighten hair (until new growth appears)	• Sodium hydroxide (lye) *– or –* • Guanidine hydroxide (calcium hydroxide cream + guanidine carbonate activator solution; "no-lye" relaxers) *– or –* • Ammonium thioglycolate ("thio" relaxers)	• Disulfide bonds between keratin polypeptide chains are broken and reformed in a similar manner to permanent waving • Relaxer cream is brushed onto the hair, which is mechanically smoothened section by section; this is followed by use of a neutralizing shampoo	• Dull, brittle hair (breakage may be substantial, especially with sodium hydroxide) • Irritant contact dermatitis/chemical burns • Allergic contact dermatitis

*Permanent waving or relaxing should be performed before coloring hair, since the former procedures can produce irreversible color loss; to minimize damage to the cuticle, it is best to wait 2–4 weeks before color is applied.

Table 153.11 Chemical hair treatments: coloring, permanent waving and relaxing. Brazilian keratin straightening is a semi-permanent method in which a keratin-containing solution is applied to the hair prior to the use of a straightening iron; concerns have been raised regarding the inhalation (as fumes) of formaldehyde present in some of the keratin solutions. FD&C, Federal Food, Drug and Cosmetic Act; H_2O_2, hydrogen peroxide.

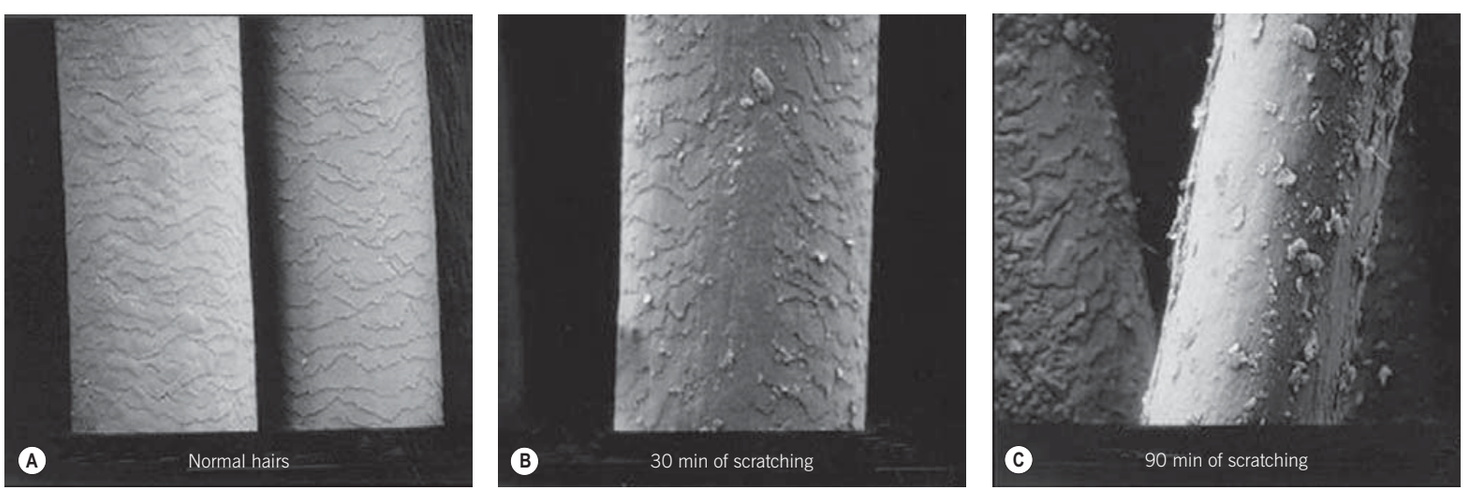


Fig. 153.5 Electron photomicrographs demonstrating the progressive removal of the hair cuticle as a result of scratching. The most common cause of cuticle removal is scratching and this leads to dull fragile hair. Note that the normal hairs have a tightly overlapping cuticle.

HAIR CONDITIONERS		
Type	**Use**	**Indication**
Instant	Apply following shampoo; rinse	Minimally damaged hair; aids wet combing
Deep	Apply for 20–30 minutes; shampoo; rinse	Chemically damaged hair
Leave-in	Apply to towel-dried hair; style	Prevents hair-dryer or hair-straightening damage; aids in combing and styling
Rinse	Apply following shampoo; rinse	Aids in disentangling if creamy rinse; removes soap residue if clear rinse

Table 153.12 Hair conditioners.

NAIL COSMETICS			
Nail cosmetic	**Main ingredients**	**Function**	**Adverse reactions**
Nail polish	Nitrocellulose, tosylamide formaldehyde resin*, plasticizers, solvents, colorants	Add color and shine to nail plates	Allergic contact dermatitis to tosylamide formaldehyde resin; nail plate staining
Nail hardener	Formaldehyde, acetates, acrylics or other resins	Increase nail strength and prevent breakage	Allergic contact dermatitis to formaldehyde
Nail enamel remover	Acetone, alcohol, ethyl acetate or butyl acetate	Remove nail polish	Irritant contact dermatitis
Cuticle remover	Sodium or potassium hydroxide	Destroy keratin that forms excess cuticular tissue on nail plate	Irritant contact dermatitis Paronychia
Nail white	White pigments	Whiten free nail edge	Practically none
Nail bleach	Hydrogen peroxide	Remove nail plate stains	Irritant contact dermatitis
Nail polish drier	Vegetable oils, alcohols or silicone derivatives	Speed drying time of nail polish	Practically none
Nail buffing cream	Pumice, talc or kaolin	Smooth ridges in nails	Practically none
Nail moisturizer	Occlusives, humectants, lactic acid	Increase water content of nails	Practically none

*Also referred to as toluene sulfonamide-formaldehyde resin.

Table 153.13 Nail cosmetics.

Nail Care Products

There are a variety of nail care products (Table 153.13). The focus of this section is on nail polish and the use of nail sculptures, since these are of most concern to the dermatologist. Nail changes associated with a manicure or a pedicure are outlined in Table 71.10.

Nail polish

Nail polish is a cosmetic designed to temporarily place a pigmented layer over the natural nail plate, and it consists of pigments suspended in a volatile solvent to which film-forming agents have been added[74]. Nitrocellulose is the most commonly employed primary film-forming agent in nail lacquer. It produces a shiny, tough film that adheres well to the nail plate. The film is somewhat oxygen-permeable, thus allowing gas exchange between the atmosphere and the nail plate, which is required to maintain nail strength. It also decreases nail water vapor loss from 1.6 to 0.4 mg/cm^2/h, preventing nail plate dehydration[75].

Fig. 153.6 Yellow nail staining due to wearing deeply pigmented red and orange nail polishes. This type of staining is common and reversible.

A resin, such as tosylamide formaldehyde (also referred to as toluene sulfonamide-formaldehyde resin), must be added to the nitrocellulose to decrease hardness, but some individuals are sensitive to this substance, which is found on the standard dermatology patch test tray. This resin has been eliminated in hypoallergenic nail enamels, which instead contain a polyester resin or cellulose acetate butyrate, but allergic contact dermatitis is still possible and the enamel is less durable[76].

A professional nail enamel application requires three layers of polish: a base coat, a pigmented nail enamel, and a top coat. The base coat ensures good adhesion to the nail plate and prevents polish chipping. The second layer is the actual pigmented nail enamel, while the third layer or top coat provides gloss and resistance to chipping.

Problems associated with nail enamels include nail plate discoloration and allergic contact dermatitis. Nail staining is most commonly seen following the use of deep red nail polishes containing D & C Reds No. 6, 7, 34, or 5 Lake[77]. The nail plate will be stained yellow after 7 days of continuous nail polish wear and will fade without treatment in approximately 14 days, once the enamel has been removed (Fig. 153.6)[78]. Allergic contact dermatitis is seen in persons sensitive to tosylamide formaldehyde, who may develop proximal nail fold erythema and edema, fingertip tenderness and swelling, and/or eyelid dermatitis[79]. The North American Contact Dermatitis Group determined that 4% of positive patch tests were due to tosylamide formaldehyde resin allergy[32].

Nail sculptures

Nail polish is designed to color the nail plate, and it may make the nail somewhat stronger due to the presence of the resin layer, but it cannot elongate fingernails. Since long fingernails are considered attractive by some women, this has led to the development of a new industry dedicated to the application of nail prostheses. These nail prostheses, known as nail sculptures, are applied over the natural fingernails and toenails (Table 153.14).

Nail sculptures are formed by mixing liquid ethyl or isobutyl methacrylate monomers with powdered polymethyl methacrylate polymer. The mixture is allowed to polymerize in the presence of a benzoyl peroxide accelerator and a formable acrylic is made, which hardens in 7–9 minutes[80]. Usually, hydroquinone, monomethyl ether of hydroquinone, or pyrogallol is added to slow down polymerization[81].

Many patients are not aware that the finished nail sculptures require more care than natural fingernails. With continued wear of the sculpture, the acrylic loosens from the natural nail, especially around the edges. These loose edges must be clipped and new acrylic applied approximately every 3 weeks to prevent infection and onycholysis[82,83]. However, damage to the natural nail plate is inevitable with the use of nail sculptures (Fig. 153.7). After 2 to 4 months of wear, the natural nail plate becomes yellowed, dry, thin and bendable. This is due to interference with the nail's normal vapor exchange, nail plate trauma during the removal process, and damage to the underlying nail bed[84]. For this reason, it is not advisable to wear sculptured nails for more

NAIL SCULPTURE APPLICATION
Nail sculpture application is an involved process requiring approximately 2 hours to sculpt 10 fingernails. The basic process is as follows: 1. All nail polish and oils are removed from the nail. 2. The nail is roughened with a coarse emery board, pumice stone or grinding drill to create an optimal surface for sculpted nail adhesion. 3. An antifungal, antibacterial liquid, such as decolorized iodine, is applied to the entire nail plate to minimize onychomycosis and paronychia. 4. The loose edges of the cuticle are trimmed, removed or pushed back, depending on the operator. 5. A flexible template is fitted beneath the natural nail plate, upon which the elongated sculpted nail will be built. Or, a preformed nail tip is used for this purpose. 6. The acrylic is mixed and applied with a brush to cover the entire natural nail plate and extended onto the template or preformed nail tip to obtain the desired nail length. 7. The final sculpture is sanded to a high shine. 8. Nail polish, jewels, decals, decorative metal strips or airbrushed designs may be added.

Table 153.14 Nail sculpture application.

Fig. 153.7 Onychodystrophy of the central nail due to wearing a nail prosthesis. The nail prosthesis grows out with the nail plate and new polymer must be applied to the proximal nail fold. The polymer has damaged the cells of the central nail matrix.

Fig. 153.8 Continuous use of a nail prosthesis can result in dramatic nail plate damage.

than 3 months consecutively, allowing 1 month between applications (Fig. 153.8).

Allergic contact dermatitis is an important dermatologic issue, since isobutyl, ethyl and tetrahydrofurfuryl methacrylate are strong sensitizers[85,86]. However, the polymerized, cured acrylic is not sensitizing, only the liquid monomer[87]. Therefore, a careful operator who avoids skin contact with the uncured acrylic can avoid sensitizing the patient. Patch testing should be performed in suspected sensitized individuals with methyl methacrylate monomer (10% in olive oil) and methacrylate acid esters (1% and 5% in olive oil and petrolatum)[88].

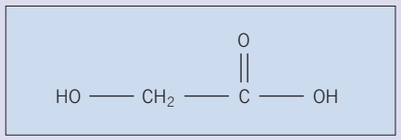
CHEMICAL STRUCTURE OF GLYCOLIC ACID


Fig. 153.9 The chemical structure of glycolic acid, accounting for its hydrophilic properties.

Hydroxy Acid Cosmeceuticals

The discussion so far has focused on products intended to function purely in a cosmetic realm, yet there are cosmeceuticals in the current marketplace known as hydroxy acids. These hydroxy acids address the scaliness and roughness of aged skin that is not due to an inherently lower stratum corneum water content[89]. The roughness associated with mature skin may be due to an abnormal desquamation associated with a possible failure in intercellular communication[90]. This observation has led to the enormous popularity of α- and β-hydroxy acids.

Alpha-hydroxy acids

This group of organic carboxylic acids is distinguished by a substituted hydroxy group covalently bonded to the α-carbon of a carboxylic acid. The linear, aliphatic nature of the α-hydroxy acid (AHA) structure accounts for its water-soluble or hydrophilic properties (Fig. 153.9). The three subcategories of AHA consist of: (1) monocarboxylic acids – glycolic (2-hydroxyethanoic acid), lactic (2-hydroxy-propanoic acid) and mandelic acid (2-hydroxy-2-phenylethanoic acid); (2) dicarboxylic acids – malic (2-hydroxy-1,4-butanedioic acid) and tartaric acid (2,3-dihydroxy-1,4-butanedioic acid); and (3) tricarboxylic acids – citric acid (2-hydroxy-1,2,3-propanetricarboylic acid). The intricacies of the formulation are more important than the nature of the AHA, since the exfoliative effect is similar[91].

AHAs induce immediate epidermal effects through corneocyte disadhesion, which is thought to require disruption of ionic bonding[92,93]. The corneocyte disadhesion occurs initially in the stratum corneum at the level of the stratum granulosum; once the cutaneous barrier has been disrupted, this is followed by dermal penetration[94]. The epidermal effects of AHAs are a thinned stratum corneum with acanthosis and decreased melanogenesis. The dermal effects of AHAs are delayed and include increased synthesis of glycosaminoglycans, prevention of topical corticosteroid atrophy, and increased dermal thickness, possibly due to enhanced production of collagen via fibroblast proliferation, in a dose-dependent manner[95,96].

Disruption of corneocyte adhesion is ultimately valuable in a large variety of dermatologic conditions (Table 153.15)[97]. For example, AHAs can be incorporated into an acne treatment regimen, given their ability to induce epidermolysis and dislodge comedones; however, AHAs cannot enter the milieu of the pore[98]. Benefit has also been shown by Briden and Rendon-Pellerano[99] in the treatment of rosacea with monthly glycolic acid peels. Sloughing of corneocytes and smoothing of seborrheic keratoses, verrucae and calluses can also be achieved[100,101]. Glycolic acid preparations, either formulated as topicals or short-contact peels, appear to be appropriate for both lightly and darkly pigmented skin[102]. Lastly, AHAs have been purported to function as anti-inflammatory agents and antioxidants by alleviating the erythema associated with cutaneous UV exposure[103]. Glycolic acid appears to confer an SPF of 2.4 to the skin[104].

Beta-hydroxy acid

The previously discussed α-hydroxy acids form only one component of the hydroxy acid family, which has been demonstrated to enhance cutaneous functioning. A similar, but chemically different, hydroxy acid is salicylic acid (ortho-hydrobenzoic acid), the only so-called β-hydroxy acid (BHA). Salicylic acid is an organic aromatic carboxylic acid with a hydroxy group in the beta position (Fig. 153.10). This

DERMATOLOGIC USES OF HYDROXY ACIDS AS TOPICAL PREPARATIONS AND PEELS
SKIN CONDITIONS
Photodamaged skin
Ichthyosis
Xerotic eczema
Acne
Acne rosacea
Seborrheic keratoses (improves appearance)
Actinic keratoses
Lentigines (improves appearance)
Verrucae
CUTANEOUS EFFECTS
Moisturizing exfoliant
Skin peeling agent
Penetration enhancer
Preventative for corticosteroid-induced skin atrophy

Table 153.15 Dermatologic uses of hydroxy acids as topical preparations and peels.

CHEMICAL STRUCTURE OF SALICYLIC ACID

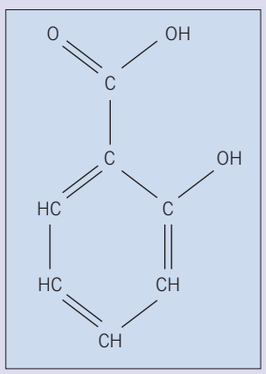


Fig. 153.10 The chemical structure of salicylic acid, accounting for its lipophilic properties.

Fig. 153.11 Lightening of facial lentigines. **A** Numerous facial lentigines due to photodamage. **B** Lightening of lentigines after treatment with a formulation containing kojic acid, emblica extract and glycolic acid.

phenolic, hydrophobic, lipophilic compound is a white crystalline powder chemically unrelated to the α-hydroxy acids. Perhaps even labeling it as a hydroxy acid is somewhat of a marketing misnomer.

Salicylic acid is unique among the hydroxy acids, since it can enter the milieu of the sebaceous unit, inducing exfoliation in the oily areas of the face[105]. For this reason, it has been used for years by dermatologists as a comedolytic in over-the-counter (OTC) preparations designed to improve comedonal acne[106,107]. Salicylic acid is approved for the treatment of acne as an OTC drug, monographed by the FDA at a level of 2% or less. It is also an excellent keratolytic, inducing exfoliation of calluses, corns and warts[108]. Salicylic acid is incorporated into many shampoos designed to remove undesquamated corneocytes from the scalp of patients with seborrheic dermatitis and psoriasis[109].

Salicylic acid is thought to function through solubilization of intercellular cement, thereby reducing corneocyte adhesion. It appears to eliminate the stratum corneum layer by layer from the outermost level downward[110]. This is in contrast to the α-hydroxy acids, which appear to diminish cellular cohesion between the corneocytes at the lowest levels of the stratum corneum. This difference is probably due in part to the water-soluble characteristics of the α-hydroxy acids, which readily penetrate into the stratum corneum, and the oil-soluble characteristics of salicylic acid, which remains on the stratum corneum. Differences in penetration also explain the decreased stinging and burning experienced with topical salicylic acid compared with glycolic acid, since the salicylic acid does not readily penetrate to the dermis.

Topical application of salicylic acid can also take the form of short-contact cutaneous peels. Salicylic acid can be used alone in concentrations of 10–50% or combined with the α-hydroxy acid lactic acid in Jessner's solution. Salicylic acid will remain in solution at concentrations of ≤20% in 95% ethyl alcohol; however, at concentrations of 30% and above, it precipitates, necessitating shaking of the solution prior to its use. In contrast to glycolic acid peels, salicylic acid is a self-neutralizing peel that ends with the formation of white salicylic acid crystals on the skin[111]. The crystals are easily rinsed from the skin surface with water, but they remain in the follicular ostia, providing a prolonged keratolytic effect. Thus, salicylic acid peels are useful for general exfoliation in patients with photoaging, comedolysis in acne patients, and patients with sensitive skin, such as rosacea patients, where dermal penetration should be minimized.

In addition to α- and β-hydroxy acids, there are water-soluble polyhydroxy acids (e.g. gluconolactone, lactobionic acid) which can act as exfoliants but have less dermal penetration.

Additional Cosmeceuticals

As a group, cosmeceuticals can offer other skin benefits in addition to those previously described for the hydroxy acids (Table 153.16; Fig. 153.11).

POPULAR INGREDIENTS IN COSMECEUTICAL FORMULATIONS		
Cosmeceutical category	**Ingredient**	**Comments**
Antioxidant carotenoids	Retinol	Oxidized to retinaldehyde and then retinoic acid for activity
	Astaxanthin	Found in high concentration in salmon
	Lutein	Extensive conjugated double bonds in polyene side chain
Antioxidant flavonoids	Soy	Contains genestein and diadzein which function as phytoestrogens and protect against lipid peroxidation
	Curcumin	Active ingredient is tetrahydrocurcumin – quenches oxygen radicals and inhibits NFκB
	Silymarin	Milk thistle plant extract; contains antioxidants silybin, silydianin, silychristin
	Pycnogenol®	French marine bark extract; contains antioxidants taxifolin, catechin, procyanidins
Antioxidant polyphenols	Green tea	Contains antioxidant polyphenols: epicatechin, epicatechin-3-gallate, epigallocatechin, epigallocatechin-3-gallate
	Pomegranate	Extract contains pantothenic acid, polyphenols
Endogenous antioxidants	Vitamin E	Primary antioxidant in skin
	Vitamin C	Secondary antioxidant in skin
	Ubiquinone (coenzyme Q10)	Tertiary antioxidant in skin
Anti-inflammatory	Aloe vera	Mucilage contains choline, choline salicylate
	Gingko	Contains bilobalides, ginkgolides, ginkgolic acid
Pigment lighteners	Vitamin C	May interrupt melanogenesis by interacting with copper ions
	Licorice extract	Contains liquiritin and isoliquertin, which disperse melanin, and glabridin, which inhibits tyrosinase
	Kojic acid	A hydrophilic fungal derivative; inhibits tyrosinase activity *in vitro*
	Aleosin	Naturally occurring hydroxymethylchromone; inhibits tyrosinase by competitive inhibition
	Arbutin	A naturally occurring gluconopyranoside; decreases tyrosinase activity and may inhibit melanosomal maturation
Peptides		Peptides (e.g. lysine, threonine), attached to palmitic acid (penetration enhancer), mimic proteins such as collagens 1 and 3

Table 153.16 Popular ingredients in cosmeceutical formulations. These are in addition to the hydroxy acids. NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells. Adapted from refs 112–116.

FUTURE DIRECTIONS

Improved understanding of the physiology of the stratum corneum is leading to new dermatologic developments within the realm of cosmetics and skin care products. This has spurred the growth in cosmeceuticals that promise to improve cutaneous function and enhance appearance. In addition, technology that was originally developed for skin keratin can be directly transferred to hair and nail keratin. Future research will undoubtedly explore methods of preventing cutaneous inflammation, which represents a common thread between dermatologic disease and potential adverse effects of cosmetics.

APPENDIX

CAMOUFLAGE COSMETIC MANUFACTURERS

Atelier Esthetique, Veil *www.veilcovercream.com*	Fashion Fair Cosmetics, Cover Tone *www.fashionfair.com*
Ben Nye Company, Inc., Coverette *www.bennyemakeup.com*	Innoxa Ltd., Keromask Cover Cream *www.beautycafe.com*
Cosmetic Specialty Labs *www.aloe-vera.com*	Il Makiage Cosmetics, Cream Makiage *www.il-makiage.com*
Dermablend Corrective Cosmetics *www.dermablend.com*	Joe Blasco Cosmetics, Dermaceal *www.joeblasco.com*
Dermacolor *www.dermacolor-camouflage.com*	Lydia O'Leary, Covermark *www.cm-beauty.com*

REFERENCES

1. Vermeer BJ, Gilchrest BA. Cosmeceuticals. Arch Dermatol. 1996;132:337–40.
2. Epstein H. Factors in formulating cosmeceutical vehicles. Cosmet Toilet. 1997;112:91–9.
3. Federal Food, Drug, and Cosmetic Act (sections [21 USC 301–392]).
4. Lavrijsen APM, Vermeer BJ. Cosmetics and drugs: is there a need for a third group: cosmeceutics. Br J Dermatol. 1991;124:503–4.
5. Willcox MJ, Crichton WP. The soap market. Cosmet Toilet. 1989;104:61–3.
6. Wortzman MS, Scott RA, Wong PS, et al. Soap and detergent bar rinsability. J Soc Cosmet Chem. 1986;37:89–97.
7. Schreiber J. Antiperspirants. In: Barel AO, Paye M, Maibach HI (eds). Handbook of Cosmetic Science and Technology. New York, NY: Marcel Dekker, 2001:689–701.
8. Mills OH, Berger RS, Baker MD. A controlled comparison of skin cleansers in photoaged skin. J Geriatric Dermatol. 1993;1:173–9.
9. Jass HE. Cold creams. In: deNaarre MG (ed). The Chemistry and Manufacture of Cosmetics, Vol III, 2nd edn. Wheaton, IL: Allured Publishing, 1975:237–49.
10. Baker CG. Moisturization: new methods to support time proven ingredients. Cosmet Toilet. 1987;102:99–102.
11. Lynde CW. Moisturizers: what they are and how they work. Skin Therapy Lett. 2001;6:3–5.
12. Ghali FE. Improved clinical outcomes with moisturization in dermatologic disease. Cutis. 2005;76(6 Suppl):13–18.
13. Wilhelm KP, Cua AB, Maibach HI. Skin aging. Effect on transepidermal water loss, stratum corneum hydration, skin surface pH, and casual sebum content. Arch Dermatol. 1991;127:1806–9.
14. Lodén M. Role of topical emollients and moisturizers in the treatment of dry skin barrier disorders. Am J Clin Dermatol. 2003;4:771–88.
15. de Jager MW, Gooris GS, Ponec M, Bouwstra JA. Lipid mixtures prepared with well-defined synthetic ceramides closely mimic the unique stratum corneum lipid phase behavior. J Lipid Res. 2005;46:2649–56.
16. Friberg SE, Ma Z. Stratum corneum lipids, petrolatum and white oils. Cosmet Toilet. 1993; 107:55–9.
17. Jass HE, Elias PM. The living stratum corneum: implications for cosmetic formulation. Cosmet Toilet. 1991;106:47–53.
18. Holleran W, Feingold K, Man MQ, et al. Regulation of epidermal sphingolipid synthesis by permeability barrier function. J Lipid Res. 1991;32:1151–8.
19. Buraczewska I, Berne B, Lindberg M, et al. Changes in skin barrier function following long-term treatment with moisturizers, a randomized controlled trial. Br J Dermatol. 2007;156:492–8.
20. Ghadially R, Halkier-Sorensen L, Elias PM. Effects of petrolatum on stratum corneum structure and function. J Am Acad Dermatol. 1992;26:387–96.
21. Spencer TS. Dry skin and skin moisturizers. Clin Dermatol. 1988;6:24–8.
22. Rieger MM, Deem DE. Skin moisturizers II. The effects of cosmetic ingredients on human stratum corneum. J Soc Cosmet Chem. 1974;25:253–62.

23. Idson B. Dry skin: moisturizing and emolliency. Cosmet Toilet. 1992;107:69–78.
24. Robbins CR, Fernee KM. Some observations on the swelling of human epidermal membrane. JSCC. 1983;37:21–34.
25. Bouwstra J, Pilgram G, Gooris G, et al. New aspects of the skin barrier organization. Skin Pharmacol Appl Skin Physiol. 2001;14(Suppl 1):52–62.
26. Jackson EM. Moisturizers: What's in them? How do they work? Am J Contact Dermatitis. 1992;3:162–8.
27. Wilkinson JB, Moore RJ. Astringents and skin toners. In: Harry's Cosmeticology, 7th edn. New York: Chemical Publishing, 1982:74–81.
28. Draelos ZK. Cosmetics in Dermatology. Edinburgh: Churchill Livingstone, 1995:1–14.
29. Schlossman ML, Feldman AJ. Fluid foundation and blush make-up. In: deNavarre MG (ed). The Chemistry and Manufacture of Cosmetics. Wheaton, IL: Allured Publishing, 1988:748–51.
30. Lanzet M. Modern formulations of coloring agents: facial and eye. In: Frost P, Horowitz SN (eds). Principles of Cosmetics for the Dermatologist. St Louis: Mosby, 1982:138–9.
31. Adams RM, Maibach HI. A five-year study of cosmetic reactions. J Am Acad Dermatol. 1985;13:1062–9.
32. Wolf R, Perluk H. Failure of routine patch test results to detect eyelid dermatitis. Cutis. 1992;49:133–4.
33. Nethercott JR, Nield G, Linn Holness D. A review of 79 cases of eyelid dermatitis. J Am Acad Dermatol. 1989;21:223–30.
34. Wilkinson JB, Moore RJ. Coloured make-up preparations. In: Harry's Cosmeticology, 7th edn. New York: Chemical Publishing, 1982:341–7.
35. Wilson LA, Ahearn DG. Pseudomonas-induced corneal ulcer associated with contaminated eye mascaras. Am J Ophthalmol. 1977;84:112–19.
36. MMWR Reports. Pseudomonas aeruginosa corneal infection related to mascara applicator trauma. Arch Dermatol. 1990;126:734.
37. Ahearn DG, Wilson LA. Microflora of the outer eye and eye area cosmetics. Develop Ind Microbiol. 1976;17:23–8.
38. Kuehne JW, Ahearn DG. Incidence and characterization of fungi in eye cosmetics. Develop Ind Microbiol. 1971;12:1973–7.
39. Bhadauria B, Ahearn DG. Loss of effectiveness of preservative systems of mascaras with age. Appl Environ Microbiol. 1980;39:665–7.
40. Ahern DG, Wilson LA, Julian AJ, et al. Microbial growth in eye cosmetics: contamination during use. Develop Ind Microbiol. 1974;15:211–16.
41. Jervey JH. Mascara pigmentation of the conjunctiva. Arch Opthalmol. 1969;81:124–5.
42. Platia EV, Michels RG, Green WR. Eye-cosmetic-induced conjunctival pigmentation. Ann Ophthalmol. 1978;10: 501–4.
43. Tosti A, Pazzaglia M, Voudouris S, Tosti G. Hypertrichosis of the eyelashes caused by bimatoprost. J Am Acad Dermatol. 2004;51(5 Suppl):S149–50.
44. Cunningham J. Color cosmetics. In: Williams DF, Schmitt WH (eds). Chemistry and Technology of the Cosmetics and Toiletries Industry. London: Blackie, 1992:143–9.
45. deNavarre MG. Lipstick. In: deNavarre MG (ed). The Chemistry and Manufacture of Cosmetics, 2nd edn. Wheaton, IL: Allured Publishing, 1975:778.
46. Boelcke U. Requirements for lipstick colors. J Soc Cosmet Chem. 1961;12:468.
47. Sulzberger MD, Boodman J, Byrne LA, Mallozzi ED. Acquired specific hypersensitivity to simple chemicals. Cheilitis with special reference to sensitivity to lipsticks. Arch Dermatol. 1938;37:597–615.
48. Sai S. Lipstick dermatitis caused by castor oil. Contact Dermatitis. 1983;9:75.
49. Brandle I, Boujnah-Khouadja A, Foussereau J. Allergy to castor oil. Contact Dermatitis. 1983;9:424–5.
50. Andersen KE, Neilsen R. Lipstick dermatitis related to castor oil. Contact Dermatitis. 1984;11:253–4.
51. Calnan CD. Allergic sensitivity to eosin. Acta Allergol. 1959;13:493–9.
52. Sai S. Lipstick dermatitis caused by ricinoleic acid. Contact Dermatitis. 1983;9:524.
53. Calnan CD. Amyldimethylamino benzoic acid causing lipstick dermatitis. Contact Dermatitis. 1980;6:233.
54. Hayakawa R, Fujimoto Y, Kaniwa M. Allergic pigmented lip dermatitis from lithol rubine BCA. Am J Contact Dermatitis. 1994;5:34–7.
55. Darko E, Osmundsen PE. Allergic contact dermatitis to Lipcare lipstick. Contact Dermatitis. 1984;11:46.
56. Aguirre A, Izu R, Gardeazabal J, et al. Allergic contact cheilitis from a lipstick containing oxybenzone. Contact Dermatitis. 1992;27:267–8.
57. Cronin E. Lipstick dermatitis due to propyl gallate. Contact Dermatitis. 1980;6:213–14.
58. Hayakawa R, Matsunaga K, Suzuki M, et al. Lipstick dermatitis due to C18 aliphatic compounds. Contact Dermatitis. 1987;16:215–19.
59. Rayner V. Clinical Cosmetology: A Medical Approach to Esthetics Procedures. Albany, NY: Milady Publishing, 1993:116–22.
60. Buchman H. Stage Makeup. New York: Watson-Guptill, 1979:15–18.
61. Draelos ZK. Cosmetic camouflaging techniques. Cutis. 1993;52:362–4.
62. Bouillon C. Shampoos and hair conditioners. Clin Dermatol. 1988;6:83–92.
63. Robbins CR. Interaction of shampoo and creme rinse ingredients with human hair. In: Chemical and Physical Behavior of Human Hair, 2nd edn. New York: Springer-Verlag, 1988:122–67.
64. Fox C. An introduction to the formulation of shampoos. Cosmet Toilet. 1988;103:25–58.
65. Zviak C, Vanlerberghe G. Scalp and hair hygiene. In: Zviak C (ed). The Science of Hair Care. New York: Marcel Dekker, 1986:49–86.
66. Rieger M. Surfactants in shampoos. Cosmet Toilet. 1988;103:59–72.
67. Garcia ML, Epps JA, Yare RS, Hunter LD. Normal cuticle-wear patterns in human hair. J Soc Cosmet Chem. 1978;29:155–75.
68. Corbett JF. Hair conditioning. Cutis. 1979;23:405–13.
69. Zviak C, Bouillon C. Hair treatment and hair care products. In: Zviak C (ed). The Science of Hair Care. New York: Marcel Dekker, 1986:115–16.
70. Rook A. The clinical importance of 'weathering' in human hair. Br J Dermatol. 1976;95:111–12.
71. Price VH. The role of hair care products. In: Orfanos CE, Montagna W, Stuttgen G (eds). Hair Research. Berlin: Springer-Verlag, 1981:501–6.
72. Robinson VNE. A study of damaged hair. J Soc Cosmet Chem. 1976;27:155–61.
73. Zviak C, Bouillon C. Hair treatment and hair care products. In: Zviak C. (ed.). The Science of Hair Care. New York: Marcel Dekker, 1986:134–7.
74. Wing HJ. Nail preparations. In: deNavarre MG (ed). The Chemistry and Manufacture of Cosmetics. Wheaton, IL: Allured Publishing, 1988:983–1005.
75. Mast R. Nail products. In: Whittam JH (ed). Cosmetic Safety: A Primer for Cosmetic Scientists. New York: Marcel Dekker, 1987:265–313.
76. Schlossman ML. Nail-enamel resins. Cosmetic Technol. 1979;1:53.
77. Samman PD. Nail disorders caused by external influences. J Soc Cosmet Chem. 1977;28:351.
78. Daniel DR, Osmet LS. Nail pigmentation abnormalities. Cutis. 1980;25:595–607.
79. Scher RK. Cosmetics and ancillary preparations for the care of the nails. J Am Acad Dermatol. 1982;6:523–8.
80. Barnett JM, Scher RK, Taylor SC. Nail cosmetics. Dermatol Clin. 1991;9:9–17.
81. Viola LJ. Fingernail elongators and accessory nail preparations. In: Balsam MS, Sagarin E (eds). Cosmetics, Science and Technology, 2nd edn. New York: Wiley-Interscience, 1972:543–52.
82. Goodwin P. Onycholysis due to acrylic nail applications. J Exp Dermatol. 1976;1:191–2.
83. Lane CW, Kost LB. Sensitivity to artificial nails. Arch Dermatol. 1956;74:671–2.
84. Baden H. Cosmetics and the nail. In: Diseases of the Hair and Nails. Chicago: Yearbook Publishers, 1987: 99–102.
85. Marks JG, Bishop ME, Willis WF. Allergic contact dermatitis to sculptured nails. Arch Dermatol. 1979;115:100.
86. Fisher AA. Cross reactions between methyl methacrylate monomer and acrylic monomers presently used in acrylic nail preparations. Contact Dermatitis. 1980;6:345–7.
87. Fisher AA, Franks A, Glick H. Allergic sensitization of the skin and nails to acrylic plastic nails. J Allergy. 1957;28:84.
88. Baran R, Dawber RPR. The nail and cosmetics. In: Samman PD, Fenton DA (eds). The Nails in Disease, 4th edn. Chicago: Yearbook Publishers, 1986:129.
89. Potts RO, Buras EM, Chrisman DA. Changes with age in the moisture content of human skin. J Invest Dermatol. 1984;82:97–100.
90. Wepierre J, Marty JP. Percutaneous absorption and lipids in elderly skin. J Appl Cosmetol. 1988;6:79–92.
91. Stiller MJ, Bartolone J, Stern R, et al. Topical 8% glycolic acid and 8% l-lactic acid creams for the treatment of photodamaged skin. Arch Dermatol. 1996;132:631–6.
92. Dietre CM, Griffin TD, Murphy, GF, et al. Effects of alpha-hydroxy acids on photoaged skin. J Am Acad Dermatol. 1996;34:187–95.
93. Berardesca E, Maibach H. AHA mechanism of action. Cosmet Toilet. 1995;110:30–1.
94. Van Scott EJ, Yu RJ. Hyperkeratinization, corneocyte cohesion and alpha hydroxy acids. J Am Acad Dermatol. 1984;11:867–79.
95. Bernstein EF, Uitto J. Connective tissue alterations in photoaged skin and the effects of alpha hydroxy acids. J Geriatric Dermatol. 1995;3(suppl.):7A–18A.
96. Lavker RM, Kaidbey K, Leyden JJ. Effects of topical ammonium lactate on cutaneous atrophy from a potent topical corticosteroid. J Am Acad Dermatol. 1992;26:535–44.
97. Van Scott EJ, Yu RJ. Alpha hydroxy acids: procedures for use in clinical practice. Cutis. 1989;43:222–8.
98. Van Scott EJ, Yu RJ. Alpha hydroxy acids: therapeutic potentials. Can J Dermatol. 1989;1:108–12.
99. Briden ME, Rendon-Pellerano MI. Treatment of rosacea with glycolic acid. J Geriatric Dermatol. 1996;4(suppl.):17B–21B.
100. Klaus MV. Evaluation of ammonium lactate in the treatment of seborrheic keratoses. J Am Acad Dermatol. 1977;22:199–203.
101. Siskin SB. The effects of ammonium lactate 12% lotion versus no therapy in the treatment of dry skin of the heels. Int J Dermatol. 1993;32:905–7.
102. Kakita LS, Petratos MA. The use of glycolic acid in Asian and darker skin types. J Geriatric Dermatol 1996;4(suppl.):8B–11B.
103. Perricone NV. An alpha hydroxy acid acts as an antioxidant. J Geriatric Dermatol. 1993;1:101–4.
104. Perricone NV, DiNardo JC. Photoprotective and antiinflammatory effects of topical glycolic acid. Dermatol Surg. 1996;22:435–7.
105. Davies M, Marks R. Studies on the effect of salicylic acid on the normal stratum corneum. Br J Dermatol. 1980;103:191–6.
106. DiNardo JC. A comparison of salicylic acid, salicylic acid with glycolic acid and benzoyl peroxide in the treatment of acne. Cosmet Dermatol. 1995;8:12.
107. Kligman A, Kligman AM. Salicylic acid as a peeling agent for the treatment of acne. Cosmet Dermatol. 1997;10:44–7.
108. Huber C, Christopher E. Keratolytic effect of salicylic acid. Arch Dermatol Res. 1977;257:293–7.
109. Draelos ZD. Salicylic acid in the dermatologic armamentarium. Cosmet Dermatol. 1997;10(suppl. 4):7–8.
110. Roberts DL, Marshall R, Marks R. Detection of the action of salicylic acid on the normal stratum corneum. Br J Dermatol. 1980;103:191–6.
111. Kligman D, Kligman AM. Salicylic acid peels for the treatment of photoaging. Dermatol Surg. 1998;24: 325–8.
112. Singh M, Griffiths CE. The use of retinoids in the treatment of photoaging. Dermatol Ther. 2006;19: 297–305.
113. Serri R, Iorizzo M. Cosmeceuticals: focus on topical retinoids in photoaging. Clin Dermatol. 2008;26(6): 633–5.
114. Mehta RC, Fitzpatrick RE. Endogenous growth factors as cosmeceuticals. Dermatol Ther. 2007;20:350–9.
115. Leonard SS, Cutler D, Ding M, et al. Antioxidant properties of fruit and vegetable juices: more to the story than ascorbic acid. Ann Clin Lab Sci. 2002;32(2):193–200.
116. Ortonne JP, Passeron T. Melanin pigmentary disorders: treatment update. Dermatol Clin. 2005;23:209–26.

This page intentionally left blank

Chemical and Mechanical Skin Resurfacing

154

Gary D Monheit and Mark A Chastain

Chapter Contents

Preoperative history and considerations *2494*
Chemical resurfacing procedures *2496*
Mechanical resurfacing procedures *2502*
Postoperative care *2505*
Complications *2506*

Synonyms: ■ Chemical resurfacing: chemical peeling, chemexfoliation ■ Mechanical resurfacing: dermabrasion (includes dermasanding) ■ Cosmeceutical: topical agent possessing pharmacologic and physiologic effects but promoted to a variable degree as a cosmetic ■ Jessner's peel: Combes' peel ■ Baker–Gordon peel: deep phenol peel

Key features

- Chemical peeling, dermabrasion and laser ablation are the three main methods of skin resurfacing
- Chemical and mechanical resurfacing procedures have a long history of safety and efficacy in ameliorating various skin conditions
- Resurfacing procedures represent one part of a comprehensive skin care program that should include photoprotective measures and topical medical and/or cosmeceutical agents
- Each resurfacing procedure injures the skin to a specific depth in order to promote the regrowth of new skin with improved surface characteristics
- The degree of clinical improvement, the length of the recovery period, and the risk of complications are all proportionate to the depth of tissue injury
- Selection of suitable patients and proper choice of resurfacing procedure are critical to success
- Both dermabrasion and the "TCA Cross" technique are methods for treating acne scars
- Prolonged erythema, pigmentary or textural irregularities, infection, delayed healing and scarring are potential complications of resurfacing
- Resurfacing procedures are a rewarding part of dermatologic practice, both for the patient and for the physician

INTRODUCTION

Resurfacing procedures to improve the health and appearance of the skin have been utilized by humans for thousands of years. The ancient Egyptians applied various chemicals to the skin and may have even used sandpaper in order to obtain a smoother skin surface[1,2]. Resurfacing methods within the practice of dermatology were initially described over 100 years ago, but their role has expanded dramatically over the last several decades. Our society's increasing emphasis on a youthful image and aesthetic appearance has resulted in an explosion in public demand for commercial skin care products, professional assistance from physicians and non-physicians to assure proper medical and cosmeceutical skin therapy, and procedural intervention by physicians.

All ablative resurfacing procedures injure the skin, in a controlled fashion, to a specific depth and thereby promote the growth of new skin with improved surface characteristics. The three fundamental methods used to create the controlled injury are chemical resurfacing (chemical peeling), mechanical resurfacing (motorized dermabrasion or manual dermasanding) and laser resurfacing (see Ch. 137). Chemical resurfacing entails the application of irritating chemical substances, mechanical resurfacing involves skin contact with an abrasive surface, and laser resurfacing is accomplished by irradiating the skin with a laser beam. In general, skin resurfacing procedures can be classified as superficial, medium-depth or deep, according to their level of injury (Table 154.1). Skin resurfacing is usually performed only on the head and neck, in part because of the critical aesthetic value of this area. Caution must be exercised in treating the neck, due to its propensity for complications; only superficial procedures should be performed on the lower one-third of the neck. Resurfacing of other areas, including the hands and arms, has yielded less predictable and less impressive results.

CLASSIFICATION OF ABLATIVE SKIN RESURFACING METHODS
SUPERFICIAL – VERY LIGHT
• Low-potency formulations of glycolic acid or other α-hydroxy acids • 10–20% TCA (weight-to-volume formulation) • Tretinoin • 20% salicylic acid • Jessner's solution
• Microdermabrasion
SUPERFICIAL – LIGHT
• 50–70% glycolic acid • Jessner's solution (see Table 154.4) • 25–30% TCA • Solid CO_2 slush • 30% salicylic acid
• Microdermabrasion
MEDIUM-DEPTH
• Jessner's–35% TCA (the most popular combination) • 70% glycolic acid–35% TCA • Solid CO_2–35% TCA (most potent combination) • 40% TCA (not recommended) • 88% phenol (rarely used)
• Conservative manual dermasanding • Erbium:YAG laser resurfacing • Conservative CO_2 laser resurfacing • Ablative fractional erbium:YAG laser resurfacing
DEEP
• Unoccluded or occluded Baker–Gordon phenol peel (see Table 154.5) • TCA in concentrations > 50% (not recommended)
• Wire-brush or diamond-fraise dermabrasion • Aggressive manual dermasanding • Manual dermasanding or motorized dermabrasion after a medium-depth peel • Aggressive erbium:YAG laser resurfacing • CO_2 laser resurfacing • Combination erbium:YAG/CO_2 laser resurfacing • Ablative fractional CO_2 laser resurfacing

Table 154.1 Classification of ablative skin resurfacing methods. Although this classification represents an oversimplification because the depth of injury actually varies somewhat along a continuum for each different type of resurfacing procedure, it is helpful when discussing the various options with a patient. The lighter shade represents chemical methods and the darker shade mechanical methods. TCA, trichloroacetic acid.

MAJOR INDICATIONS FOR CHEMICAL AND MECHANICAL SKIN RESURFACING
• Actinically damaged skin and rhytides
• Scarring
• Pre-neoplastic or neoplastic lesions (e.g. actinic keratoses)
• Underlying skin diseases such as acne
• Pigmentary dyschromias (including tattoos)
• Demarcation lines secondary to other resurfacing procedures

Table 154.2 Major indications for chemical and mechanical skin resurfacing.

CONTRAINDICATIONS TO CHEMICAL AND MECHANICAL SKIN RESURFACING
ABSOLUTE
• Poor physician–patient relationship
• Lack of psychological stability and mental preparedness
• Unrealistic expectations
• Poor general health and nutritional status
• Isotretinoin therapy within the last 6 months*
• Complete absence of intact pilosebaceous units on the face
• Active infection or open wounds (such as herpes simplex, excoriations or open acne cysts)
RELATIVE
• Medium-depth or deep resurfacing procedure within the last 3–12 months*
• Recent facial surgery involving extensive undermining, such as a rhytidectomy*
• History of abnormal scar formation or delayed wound healing
• History of therapeutic radiation exposure
• History of certain skin diseases (such as rosacea, seborrheic dermatitis, atopic dermatitis, psoriasis and vitiligo) or active retinoid dermatitis
• Fitzpatrick skin types IV, V and VI*
*These contraindications apply only to medium-depth and deep resurfacing procedures.

Table 154.3 Contraindications to chemical and mechanical skin resurfacing.

In comparison to the other resurfacing modalities available for skin rejuvenation, chemical resurfacing probably has the longest and most well-documented history[1]. Experimentation with various peeling compounds in the late nineteenth and early twentieth centuries led to sporadic reports describing their use in the medical literature. The initial reports were met with skepticism, but further investigation by both dermatologists and plastic surgeons verified their effectiveness in facial skin rejuvenation. Over the past several decades, chemical peeling has experienced a tremendous growth in popularity and has become an important part of our armamentarium in the management of various cosmetic as well as non-cosmetic skin problems.

Since Kromayer's original report of motorized dermabrasion in 1905, there has been considerable growth not only in chemical resurfacing procedures, but also in other forms of mechanical resurfacing. Mechanical resurfacing is most often known as dermabrasion but it refers to any procedure that involves surgical planing of the skin using an abrasive surface. The use of dermabrasion was originally limited to the treatment of scars, but its role expanded during the latter half of the twentieth century to include a multitude of indications[2]. Recent adaptations of the traditional techniques of dermabrasion have led to the development of a less invasive procedure, known as microdermabrasion[3]. Dermasanding, which is a manual technique for dermabrasion utilizing abrasive paper, has been in use since the early days, but has experienced a recent resurgence in interest[4,5]. Although overshadowed by ablative laser resurfacing, mechanical resurfacing procedures remain a popular option for both patients and physicians.

Over the past two decades, the practice of skin rejuvenation has been revolutionized by the development of resurfacing lasers. Carbon dioxide (CO_2), erbium and fractional laser resurfacing is invaluable in treating cutaneous photoaging because it can consistently deliver impressive results. However, the deep wounds and extensive recovery time seen with CO_2 laser resurfacing have led to the development of less invasive modalities, such as erbium:YAG laser resurfacing, non-ablative laser treatments, and fractional laser ablation. Despite the capabilities of lasers in facial rejuvenation, their use is limited by the considerable monetary cost to either rent the equipment or purchase and maintain it. Furthermore, while nearly all the complications associated with chemical peeling and dermabrasion can occur with laser resurfacing, the use of lasers carries additional risks, such as exposure to infectious agents in the smoke plume, fire hazards and ocular injury by the laser beam. There may also be an increased risk of anesthesia-related problems, as well as higher financial costs of surgery, because of the greater level of sedation often required. The following discussion will focus on chemical peeling and dermabrasion, as laser therapy is covered in Chapter 137.

PREOPERATIVE HISTORY AND CONSIDERATIONS

Indications

The preoperative consultation is important in identifying at-risk patients who are best avoided or who require an extra-cautious approach, as well as in selecting patients who are ideal candidates for intervention. The dermatologist must evaluate the prospective patient and his or her skin condition carefully, in order to determine if a chemical or mechanical resurfacing procedure is indicated. When resurfacing is deemed appropriate, selection of the proper procedure for each patient is critical to assure that the desired results are achieved in a safe and effective manner. In general, the degree of skin surface irregularities is proportional to the depth of the injury that must be created by resurfacing in order to achieve significant improvement. There are six major indications for resurfacing (Table 154.2).

Pre-neoplastic or neoplastic skin lesions can certainly be improved with resurfacing procedures. Those originating in the epidermis, such as actinic keratoses or lentigines, are more amenable to treatment than those with a dermal origin. Although some dermatologic conditions may be aggravated by resurfacing, acne and pigmentary dyschromias such as melasma respond favorably to superficial chemical peeling or microdermabrasion. Another indication for chemical and mechanical skin resurfacing is to blend the effects of other procedures by preventing or eliminating lines of demarcation.

Photoaging is probably the single condition for which skin resurfacing procedures are most often performed. For patients with photoaging and acne scarring, the Glogau system (see Ch. 152) is helpful in deciding upon the most appropriate skin rejuvenation program. It classifies patients into one of four groups based on degree of severity. Patients in category I are often young with minimal to mild photoaging and are best managed with superficial chemical peels or microdermabrasion in conjunction with medical or cosmeceutical therapy (e.g. topical retinoids, glycolic acids, active cosmeceutical preparations). Patients in category II would likely benefit from a medium-depth chemical peel as well as long-term medical therapy to include a retinoid and/or an α-hydroxy acid (AHA). Individuals in category III typically need prolonged medical treatment in conjunction with one of the following: a medium-depth chemical peel (with or without dermasanding), a deep chemical peel, dermabrasion or laser resurfacing. A medium-depth or deep chemical peel, dermabrasion or laser resurfacing as well as adjunctive medical therapy would certainly be indicated in patients with category IV photoaging. However, an invasive surgical operation such as a rhytidectomy, blepharoplasty or scar revision is often required in addition to resurfacing in order to achieve the desired results.

Contraindications and Patient Selection

When evaluating a patient for chemical or mechanical resurfacing, a careful history and physical examination are important to assess the skin problems which prompted his or her presentation and to identify any factors that may contribute to intraoperative or postoperative difficulties (Table 154.3) The patient should be asked about prior resurfacing procedures, rhytidectomy (facelift) or oral isotretinoin therapy within the last 6 months, as these can increase the risk of complications following medium-depth and deep resurfacing[6,7]. Any history of abnormal scar formation or therapeutic radiation exposure warrants extreme caution when considering a patient for skin resurfacing. Individuals with prior radiation exposure should be examined closely for the presence of intact facial hair in order to ensure that there are enough pilosebaceous units to promote re-epithelialization[8]. Another important element of the patient's history is the presence or absence of a prior herpes simplex infection. Recurrence of oral herpes simplex can

be triggered by a resurfacing procedure, especially in the perioral and periorbital regions. Risk factors for HIV infection or viral hepatitis should be identified, and routine laboratory screening is recommended in individuals undergoing dermabrasion with a powered engine. The general health and nutritional status of the patient is also an important consideration, especially for medium-depth and deep resurfacing procedures, to ensure timely and complete healing.

Patients with certain cutaneous disorders, such as rosacea, seborrheic dermatitis, atopic dermatitis, psoriasis or vitiligo, may be at increased risk for postoperative complications, including disease exacerbation, prolonged erythema, contact dermatitis or even delayed healing. In particular, individuals with rosacea have vasomotor instability and may develop an exaggerated inflammatory response to the resurfacing procedure. Caution should also be exercised for patients with autoimmune connective tissue diseases (e.g. cutaneous lupus, scleroderma) as the trauma of chemical peeling may activate the disease. Evaluation of the patient's Fitzpatrick skin type (see Ch. 134) is helpful in predicting the chance of postoperative pigmentary dyschromias. Individuals with Fitzpatrick skin types I or II are at low risk for hyperpigmentation or hypopigmentation after medium-depth or deep resurfacing, whereas those with types III through VI are at greater risk for these complications[9].

The patient should understand that chemical and mechanical resurfacing procedures cannot reliably reduce pore size and their ability to improve lax skin or deeper wrinkles and scars is limited, depending on the type of intervention being performed. While dermabrasion may sometimes eliminate telangiectasias, chemical peels cannot accomplish this and can even unmask them by removing the pigmentary irregularities. The patient must fully understand the potential benefits, limitations and risks of the procedure, and an informed consent must be signed. A test spot (e.g. along the lateral hair line) may be useful in some patients to assess their suitability for resurfacing and may be particularly helpful when there is a great deal of concern about the chances of postoperative pigmentary dyschromias[10]; test spots are definitely recommended for individuals with skin types III–VI. Although a favorable test spot result does not guarantee a positive outcome following full-face resurfacing, an unfavorable test spot result is useful in identifying high-risk patients. If the dermatologist feels any uncertainty about the patient's suitability or the likelihood of a favorable result, the procedure should not be performed.

Preoperative and Intraoperative Preparations

Another purpose of the preoperative consultation is to ensure that the patient is adequately prepared for the procedure. Almost every patient desiring facial rejuvenation for cutaneous photoaging would benefit from botulinum toxin injections to alleviate dynamic wrinkles (see Ch. 159). These injections appear to enhance the results of deeper resurfacing procedures by immobilizing the muscles implicated in the development of dynamic rhytides during the critical time of postoperative collagen remodeling. It is recommended that botulinum toxin injections be administered as an adjunctive therapy preoperatively in patients with photoaging undergoing medium-depth or deep chemical peels, dermabrasion or laser resurfacing.

Due to the significant morbidity associated with herpetic infections during the healing period, patients who undergo medium-depth or deep resurfacing (see Table 154.1) should be treated prophylactically with an antiviral agent, regardless of whether there is a history of herpes simplex infection[11]. These drugs are not routinely given to patients having a superficial chemical peel or microdermabrasion, because the injury is generally not sufficient to activate the virus. However, therapy may be considered in conjunction with superficial resurfacing in patients with a strong personal history of recurrent herpes simplex. Recommended prophylaxis consists of acyclovir 400 mg three times daily, valacyclovir 500 mg twice daily or famciclovir 250 mg twice daily, beginning on the day of the procedure. It is advisable to administer the drug for at least 10 to 14 days[12]. The reason for such a long duration of therapy is that viral replication is possible only in intact epidermal cells, making clinical infection unlikely during the first few days postoperatively. The risk of an eruption increases dramatically with the onset of re-epithelialization and remains high until this process is complete.

It is important that the patient adhere to a strict skin care regimen during the immediate preoperative and postoperative periods in order to achieve optimal results. The authors treat patients with topical tretinoin on a nightly basis prior to the procedure. Retinoids increase epidermal proliferation and presumably lead to more rapid re-epithelialization after the chemical peel. Because of the tendency for retinoids to cause irritation within 1 to 2 weeks of starting therapy (i.e. retinoid dermatitis), a weaker, more gentle tretinoin formulation should be used in patients with sensitive skin. In patients with active retinoid dermatitis, resurfacing should be delayed, because this condition may lead to a prolongation in postoperative erythema. Decreasing the frequency of application or switching to a less irritating retinoid will allow the inflammation to subside, so that the procedure can be performed[13].

All-*trans*-retinoic acid, or tretinoin, has been classified as a superficial chemical peeling agent, but it is best considered as an integral component of a complete skin rejuvenation program. With chronic use, this drug has been shown to improve actinically damaged skin both clinically and histologically[14]. The use of tretinoin prior to chemical peeling, dermabrasion or laser resurfacing speeds epidermal healing and enhances the effects of the procedure[13,14]. Tretinoin increases the depth of a chemical peel by decreasing the thickness of the stratum corneum. Its use is restricted, however, during the postoperative healing period, until there is complete re-epithelialization and diminished inflammatory erythema.

Hydroquinone blocks the enzyme tyrosinase and can reduce the production of epidermal melanin during the healing phase. Patients with skin type III or higher may benefit from twice-daily application of a 4% to 8% topical hydroquinone in the preoperative and postoperative (post-healing) periods – even if there is no history of pigmentary abnormalities[9]. It is also necessary to use hydroquinone when peeling for the treatment of pigmentary dyschromias, such as melasma, in patients of any skin type[9]. While a Wood's lamp was used in the past to localize melanin pigment to either the epidermis or dermis (i.e. epidermal versus dermal melasma), histopathologic studies and confocal microscopy have shown that there is often a mixture of the two forms in an individual patient. Nonetheless, in both melasma and postinflammatory hyperpigmentation, increased melanin within the epidermis responds better to superficial peels than does dermal pigment. The use of non-inflammatory peeling agents such as salicylic acid are preferred for disorders such as melasma as there is less tendency for postinflammatory hyperpigmentation (Fig. 154.1).

All patients undergoing any type of skin resurfacing procedure must adhere to strict photoprotective measures during the postoperative period. This issue is critical in patients whose Fitzpatrick skin type is III or higher, in patients with pigmentary disturbances, in patients taking exogenous estrogens, as well as in all patients having medium-depth or deep resurfacing. Specific methods to minimize sun exposure and proper use of sun blocks should be discussed. Patients are also counseled to avoid tobacco use, as smoking in the postoperative period may limit the effectiveness of the resurfacing and increase the risk of poor wound healing.

The need for intraoperative sedation and analgesia is also discussed with the patient preoperatively, so that plans are made accordingly. Superficial resurfacing procedures usually require only "talkesthesia", a

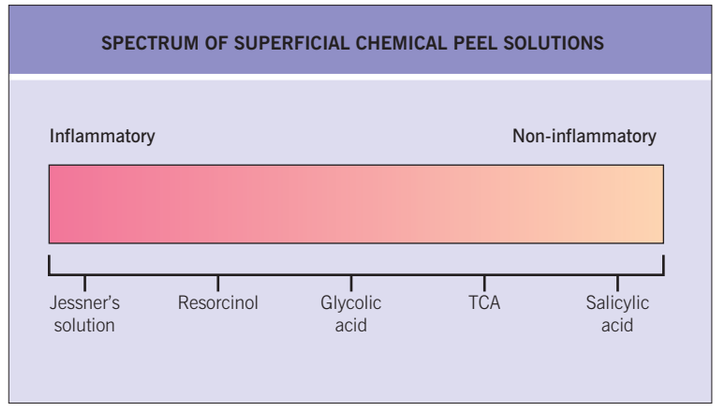


Fig. 154.1 Spectrum of superficial chemical peel solutions. Inflammatory chemical peel solutions are used primarily for photoaging, while non-inflammatory chemical peel solutions are best for Fitzpatrick skin types III–VI, melasma and postinflammatory hyperpigmentation. TCA, trichloroacetic acid.

technique that is extremely helpful in awake patients undergoing a procedure (talking calmly to the patient with encouragement during the procedure). Medium-depth chemical or mechanical resurfacing usually requires a limited degree of perioperative sedation and analgesia, which may include the application of topical amide anesthetics, regional blocks of the supraorbital, infraorbital and mental nerves (see Ch. 143), as well as oral diazepam, intramuscular meperidine hydrochloride and/or intramuscular hydroxyzine hydrochloride. Although deep resurfacing procedures can be accomplished entirely with nerve blockade, local injections of lidocaine and mild sedatives, some patients require intravenous or general (endotracheal tube) anesthesia. Application of the tumescent technique (see Ch. 156) to resurfacing has allowed many patients to undergo deep resurfacing procedures without the additional risks of intravenous or general anesthesia[15]. The patient's inherent pain tolerance, level of anxiety, concomitant medical conditions, and willingness to pay the extra costs of heavier sedation are important topics in the preoperative consultation that are used to plan for appropriate anesthesia.

The patient must be given specific instructions to follow on the day of the procedure. Upon awakening, the patient washes his or her face with a gentle cleanser and preferably avoids the application of any cosmetics. Individuals undergoing procedures requiring minimal or no sedation are encouraged to eat a light breakfast, but patients receiving deeper anesthesia should have nothing by mouth except their usual medications. Particularly for the medium-depth and deep resurfacing procedures, the dermatologist should meet with the patient and his or her family preoperatively to re-establish rapport, answer last-minute questions, discuss perioperative and postoperative expectations and instructions, and assure compliance with antimicrobial prophylaxis as needed.

CHEMICAL RESURFACING PROCEDURES

Although there is currently a wide variety of resurfacing procedures available for facial rejuvenation, chemical peeling remains a popular choice for both patient and physician. In comparison to some of the newer options, chemical peels have a longstanding safety and efficacy record, are performed with ease, are low in cost, and have a predictable and relatively quick recovery time. Various acidic and basic compounds are used to produce a controlled skin injury and are classified as superficial, medium-depth and deep peeling agents, according to their level of penetration, destruction and inflammation (see Table 154.1). In general, superficial peels cause epidermal injury and occasionally extend into the papillary dermis, medium-depth peels cause injury through the papillary dermis to the upper reticular dermis, and deep peels cause injury to the mid-reticular dermis.

Prior to the application of peeling solutions, the skin surface must be vigorously cleansed to remove residual oils, debris and excess stratum corneum. The authors use gauze pads containing 0.25% triclosan (an ingredient found in some deodorant soaps), followed by rinsing with water and drying. Because of the defatting and degreasing properties of acetone, gauze pads moistened with an acetone preparation are then used to cleanse the skin even further. Finally, the cleansed skin is palpated immediately prior to peeling, in order to check for the presence of residual oil, and if any is felt, the process is repeated. The importance of cleansing prior to the peeling procedure cannot be overemphasized. A thorough and evenly distributed cleansing and degreasing of the face assures uniform penetration of the peeling solution and leads to an even result without skipping areas (Fig. 154.2).

The effect of a chemical peel is dependent upon the agent used, its concentration, and the techniques employed before and during its application. Each wounding agent used in peels has unique chemical properties and causes a specific pattern of injury to the skin[15–20]. It is important for the physician using these solutions to be familiar with their cutaneous effects and proper methods of application, to assure correct depth of injury. The marketplace has been flooded with numerous proprietary formulations of these peeling agents, with each product claiming unique advantages. These products are often expensive and have not been shown to be safer or more effective than the conventional solutions. Their advantage rests in the prepackaging of materials and ease for the physician. The following discussion on superficial, medium-depth and deep peeling will therefore focus on the specific chemical agents that are actively responsible for producing the various patterns of injury.

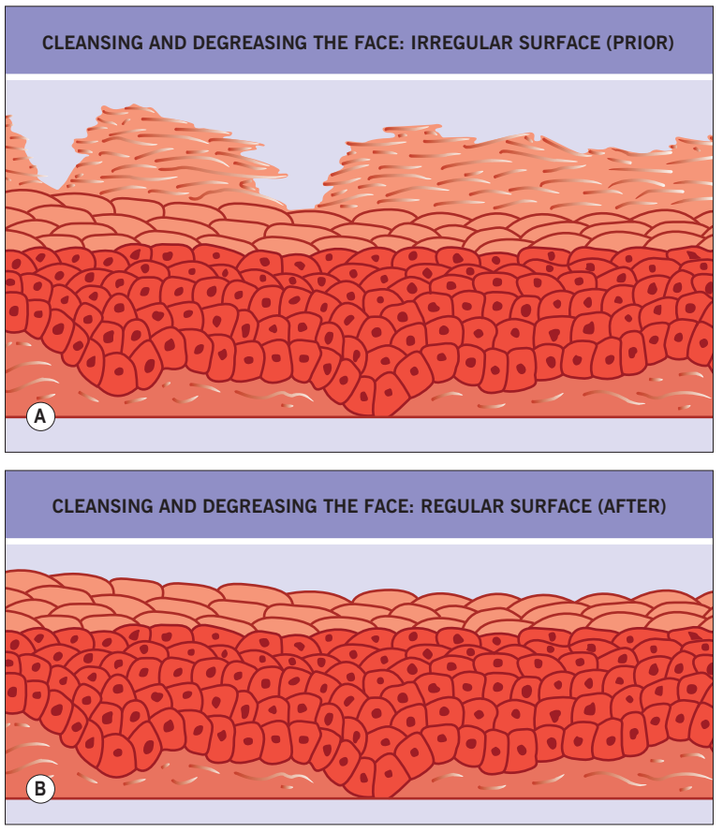


Fig. 154.2 Cleansing and degreasing the face. A Irregular surface (prior). **B** Clean, regular surface (after).

Superficial chemical peeling

Superficial chemical peels are indicated in the management of acne and its postinflammatory erythema, mild photoaging (Glogau I and II), epidermal lesions such as lentigines and keratoses, as well as melasma and other pigmentary dyschromias. Multiple peels on a repeated basis are usually necessary to obtain optimal results. The frequency of peels and degree of exposure to the peeling agent may be increased gradually as necessary. Results are enhanced by medical or cosmeceutical therapy, including a retinoid and, if necessary, a bleaching agent. All superficial chemical peels share the advantages of only mild stinging and burning during application as well as minimal time (a few days) needed for recovery.

Superficial chemical peels are divided into two varieties – very light and light (see Table 154.1). With *very light* peels, the injury is usually limited to the stratum corneum and only creates exfoliation; however, the injury may extend into the stratum granulosum. The agents used for these peels include low-potency formulations of glycolic acid, 10–20% trichloroacetic acid (TCA), tretinoin, 20% salicylic acid and Jessner's solution (Table 154.4)[21–23]. *Light* peels injure the entire epidermis down to the basal layer, stimulating the regeneration of a fresh new epithelium. Agents used for light peels include 50–70% glycolic acid, 25–30% TCA, Jessner's solution, 30% salicylic acid and solid CO_2 slush[21,22]. During the application of superficial peeling agents, there may be mild stinging followed by a level I frosting, defined as the appearance of erythema and streaky whitening on the surface (Fig. 154.3).

Alpha-hydroxy acids (AHAs) are naturally found in foods and have been used widely in skin rejuvenation programs since the early 1990s. The depth of injury is determined by the specific AHA used, its pH, the concentration of free acid, the volume applied to the skin, and the duration of contact. In low concentrations, AHAs have been shown to decrease the cohesion of corneocytes at the junction of the stratum corneum and the stratum granulosum[24]. Higher concentrations are associated with complete epidermolysis. With chronic use of AHA-containing products on a daily basis, there is an increase in skin

JESSNER'S SOLUTION (COMBES' FORMULA)	
Resorcinol	14 g
Salicylic acid	14 g
85% lactic acid	14 g
95% ethanol (q.s.ad)	100 ml

Table 154.4 Jessner's solution (Combes' formula). q.s.ad, a sufficient quantity up to.

Fig. 154.3 Levels of frosting. A Level I frosting as found with light chemical peeling: erythema with streaky frosting. **B** Level II frosting: erythema with diffuse white frosting. **C** Level III frosting: solid white enamel frosting.

thickness, acid mucopolysaccharides, and the density of collagen, as well as an improvement in elastic fiber quality[19]. The most popular of the AHAs, glycolic acid, is available in a variety of over-the-counter preparations and can be purchased by physicians in buffered as well as unbuffered concentrations as high as 70% for chemical peels. Weekly or biweekly applications of 40–70% glycolic acid (with cotton swabs, a sable brush, or 2-inch × 2-inch gauze pads) have been used most often for acne, mild photoaging and melasma[25]. The time of application is critical for glycolic acid, as it must be rinsed off with water or neutralized with 5% sodium bicarbonate after 2 to 4 minutes. It is the only peeling agent requiring neutralization to end its action.

Application of 10–20% TCA with either a saturated gauze pad or sable brush produces erythema and a very light frost within 15 to 45 seconds. The depth of penetration of the peeling solution is related to the number of coats applied. Protein precipitation results and leads to exfoliation without vesiculation. Concentrations of TCA up to 25% can also be used alone as a superficial peeling agent, but may create an injury that extends partially into the upper dermis. Jessner's solution is a combination of keratolytic ingredients that has been used for over 100 years in the treatment of inflammatory and comedonal acne as well as hyperkeratotic skin disorders (see Table 154.4). Jessner's solution has intense keratolytic activity, initially causing loss of corneocyte cohesion within the stratum corneum and subsequently creating intercellular and intracellular edema within the upper epidermis if application is continued[26]. The mode of application for the Jessner's peel is similar to that of the 10–20% TCA peel. The clinical endpoint of treatment is erythema and blotchy frosting.

Salicylic acid, also referred to as a β-hydroxy acid, is one of the ingredients in Jessner's solution. It can be used alone for superficial chemical peeling and is a preferred therapy for comedonal acne and inflammatory rosacea as it is lipophilic and concentrates within the pilosebaceous apparatus (Fig. 154.4)[23]. Salicylic acid is quite effective as an adjunctive therapy for both open and closed comedones and for resolving postacne erythema. As noted previously, salicylic acid produces less inflammation than other superficial peeling agents (see Fig 154.1) and therefore is associated with a lower risk of postinflammatory hyperpigmentation. As a result, it is preferred for the removal of excess cutaneous pigmentation.

Prior to the initial treatment, the patient must understand that the net effect of repetitive superficial chemical peels never approaches the beneficial effect obtained with a single medium-depth or deep peel. The improvements in cutaneous photoaging following superficial peels are usually subtle because there is little to no effect on the dermis. These peels thus cannot produce an appreciable effect on textural changes such as deep wrinkles and furrows which originate within the

Fig. 154.4 Salicylic acid peels. These peels are effective for the treatment of acne, including comedones. Repetitive peels over 6 weeks combined with medical acne treatment will hasten resolution of the condition. Note the perifollicular frosting seen with salicylic acid, a lipophilic chemical.

Fig. 154.5 Medium-depth chemical peel used to treat moderate photoaging of the skin. A Preoperative, demonstrating actinic keratoses plus aging textural changes. **B** Application of 35% trichloroacetic acid (TCA) directly after Jessner's solution. **C** White enamel frosting (level III) from 35% TCA. **D** Desquamation and inflammation 4 days after peel. **E** Final results 6 months later.

dermis. Nevertheless, their ease of use and minimal downtime makes these "lunchtime" peels rewarding for patients with realistic expectations and are a favorite of busy patients. Superficial peels can also be used in combination with cosmeceutical agents and other minimal to no downtime procedures such as botulinum toxin A injections and intense pulsed light treatments.

Medium-depth chemical peeling

Medium-depth chemical peels consist of controlled damage through the epidermis and papillary dermis, with variable extension to the upper reticular dermis. Both medium-depth and deep chemical peeling produce epidermal necrosis, papillary dermal edema and homogenization, and a sparse lymphocytic infiltrate within the first several days[15]. Postoperatively, over a period of 3 months, there is increased collagen production with expansion of the papillary dermis and the development of a mid-dermal band of thick fibers. These changes correlate with continued clinical improvement during this time.

For many years, 40–50% TCA was the prototypical medium-depth peeling agent because of its ability to ameliorate fine wrinkles, actinic changes and "pre-neoplasias". TCA as a single agent for medium-depth peeling has fallen out of favor because of the high risk of complications, especially scarring and pigmentary alterations, when used in strengths approaching 50% and higher[27]. Today, most medium-depth chemical peels are performed utilizing 35% TCA in combination with Jessner's solution, 70% glycolic acid or solid CO_2 as the "priming" agent. These combination peels have been found to be as effective as 50% TCA alone, but with fewer risks. The level of penetration is better controlled with these combination peels, thereby preventing the "hot spots" seen with higher concentrations of TCA that can produce dyschromia and scarring.

Brody and Hailey[28] developed the use of solid CO_2 to freeze the skin prior to the application of 35% TCA. This causes epidermal necrosis and significant dermal edema, thereby allowing deeper penetration of the TCA in selected areas. This technique is particularly useful for effacing the edges of mild acne scars and destroying thicker epidermal growths. Monheit[26] then described a combination medium-depth peel in which Jessner's solution is first applied, followed by 35% TCA. Similarly, Coleman and Futrell[29] have demonstrated the usefulness of 70% glycolic acid prior to the application of 35% TCA for medium-depth peeling. The Jessner's solution and glycolic acid both appear to effectively weaken the epidermal barrier and allow deeper, more uniform and more controlled penetration of the 35% TCA.

Current indications for medium-depth chemical peeling include Glogau group II photoaging, epidermal lesions such as actinic keratoses, pigmentary dyschromias and mild acne scarring, as well as blending of the effects of deeper resurfacing procedures. The most popular of the medium-depth peels for facial rejuvenation is the Jessner's–35% TCA peel, with other combination peels being utilized less frequently. This peel has been widely accepted because of its broad range of uses, the large number of individuals in whom it is indicated, its ease of modification according to the situation, and its excellent safety profile.

The Jessner's–35% TCA peel is particularly useful for the improvement of mild to moderate photoaging (Fig. 154.5). It freshens sallow, atrophic skin and softens fine rhytides, with minimal risk of textural or

Fig. 154.6 Combination of medium-depth peel of the face plus CO_2 laser ablative resurfacing of the periorbital region. A before, **B** after treatment.

pigmentary complications. Collagen remodeling occurs for as long as 3 to 4 months postoperatively, during which time there is continued improvement in texture and rhytides. Deep furrows, however, are not eliminated with this peel and there is no significant skin retraction as is seen with ablative fractional laser resurfacing. When used in conjunction with a retinoid, bleaching agent and sunscreens, a single Jessner's–35% TCA peel lessens pigmentary dyschromias and lentigines more effectively than repetitive superficial peels. Epidermal growths such as actinic keratoses also respond well to this peel. In fact, the Jessner's–35% TCA peel has been found as effective as topical 5-fluorouracil chemotherapy in removing both grossly visible and clinically undetectable actinic keratoses, but has the added advantages of lower morbidity and greater improvement in associated photoaging[30,31].

Another indication for the Jessner's–35% TCA peel is to blend the effects of other resurfacing procedures with the surrounding skin[31a]. Patients who undergo CO_2 or ablative fractional laser resurfacing, deep chemical peeling or dermabrasion to a localized area such as the periorbital or perioral region often develop a sharp line of demarcation between the treated and untreated skin. The treated skin may appear hypopigmented (also known as pseudohypopigmentation) in comparison to the untreated skin. These irregularities are often conspicuous and are troubling to the patient. A Jessner's–35% TCA peel performed on the adjacent untreated skin helps to blend the treated area into its surroundings. For example, a patient with advanced photoaging in the periorbital region and moderate photoaging on the remaining face may desire CO_2 laser resurfacing only around the eyes. In this patient, medium-depth chemical peeling of the areas not treated with the laser would improve the photoaging in these regions and avoid a line of demarcation[32] (Fig. 154.6). Similarly, a patient having spot dermabrasion or ablative fractional laser resurfacing to a localized scar would benefit from a Jessner's–35% TCA peel to the remainder of that cosmetic unit or to the rest of the face. It is important to note that when used in combination with other resurfacing procedures such as laser ablation or dermabrasion, the peel should be performed first, in order to avoid accidental application of the peeling agent onto previously abraded areas of skin which may lead to scarring (Fig. 154.7).

Using either cotton-tipped applicators or gauze pads, a single, even coat of Jessner's solution is applied first to the forehead, then the cheeks, nose and chin, and, lastly, the eyelids. Proper application of Jessner's solution causes minimal discomfort and creates a faint frost within a background of mild erythema (level I; Fig. 154.8A)[32a]. After waiting 1 to 2 minutes for the Jessner's solution to completely dry, 35% TCA is applied evenly with one to four cotton-tipped applicators (Fig. 154.8B). The ultimate effectiveness of this peel is directly dependent upon the depth of penetration of the peeling solutions, and this depth is a function of the adequacy of degreasing and the amount of both solutions applied. The use of cotton swabs, particularly for the application of TCA, is advantageous because is allows the surgeon to quantitatively vary the amount of solution applied according to the patient's specific needs. The amount of TCA delivered to the skin surface is determined by the number of applicators used, their degree of saturation, the amount of pressure applied to the skin surface, and the duration of their contact with the skin. Four moist cotton-tipped applicators are applied in broad strokes over the forehead and on the medial cheeks. Two mildly soaked cotton-tipped applicators can be used across the lips and chin, and one damp cotton-tipped applicator on the eyelids (Fig. 154.8C).

When applying TCA, anatomic areas of the face are peeled sequentially from the forehead to the temple to the cheeks and finally to the lips and eyelids. Careful feathering of the solution into the hairline and around the rim of the jaw and brow conceals the demarcation line between peeled and non-peeled skin. Areas of wrinkled skin are stretched taut with the help of an assistant, to allow even application of the solution into the folds and troughs. This technique is particularly helpful on the skin of the upper and lower lips. For perioral rhytides, TCA is applied with the wooden portion of a cotton-tipped applicator and extended onto the vermilion border (Fig. 154.8D).

Eyelid skin must be treated delicately and carefully to avoid overapplication to this thinner skin and to prevent exposure of the eyes to the TCA solution. The patient should be positioned with the head elevated at 30°. Excess peel solution on the cotton tip should be squeezed out so that the applicator is semi-dry. With the eyes closed, a single applicator is rolled gently from the periorbital skin onto the upper eyelid skin without going beyond the superior aspect of the supratarsal plate. Another semi-dry applicator is then rolled onto the lower eyelid skin within 2 to 3 mm of the lid margin while the patient is looking superiorly. Excess peel solution should never be left on the lids, because it can roll into the eyes. Any tears should be immediately dried with a cotton-tipped applicator because they may pull the solution into the eye by capillary action (see Fig. 154.8C). Tears can also travel down the cheek and carry TCA onto the neck, resulting in a linear streak.

The white frost from the TCA application appears on the treated area within 30 seconds to 2 minutes. This response is representative of keratocoagulation and indicates that the TCA's physiologic reaction is complete. The Jessner's–35% TCA combination takes longer to frost than phenol preparations, but a shorter period of time than the superficial peeling agents. The desired endpoint for medium-depth peeling is level II to level III frosting. Level II frosting is defined as a white-coated frosting with a background of erythema (see Fig 154.3B). Level III frosting, which is associated with penetration to the reticular dermis, is a solid white enamel frosting with no background of erythema (see Fig. 154.3C). A deeper level III frosting should be restricted only to areas of thick skin and heavy actinic damage. Most medium-depth chemical peels achieve a level II frosting and this is especially important over the eyelids and areas of sensitive skin. Areas with a greater tendency to form scars, such as the zygomatic arch and the bony prominences of the jawline and chin, should receive no greater than level II frosting.

Before re-treating an area, the surgeon should wait at least 3 to 4 minutes after the application of TCA, to ensure that frosting has reached its peak. Each cosmetic unit is then assessed, and areas of incomplete or uneven frosting are carefully re-treated with a thin

Fig. 154.7 Combination procedure utilizing perioral–periorbital CO_2 laser resurfacing with Jessner's–35% trichloroacetic acid peel to the remainder of the face. The peel will blend the color and texture of the laser-treated areas. **A** Preoperative: the eyelids and lips need deeper resurfacing than do the cheeks, which require only medium-depth injury. **B** Four days postoperative: note difference in the rate of healing between laser- and peel-treated areas. **C** One year postoperative.

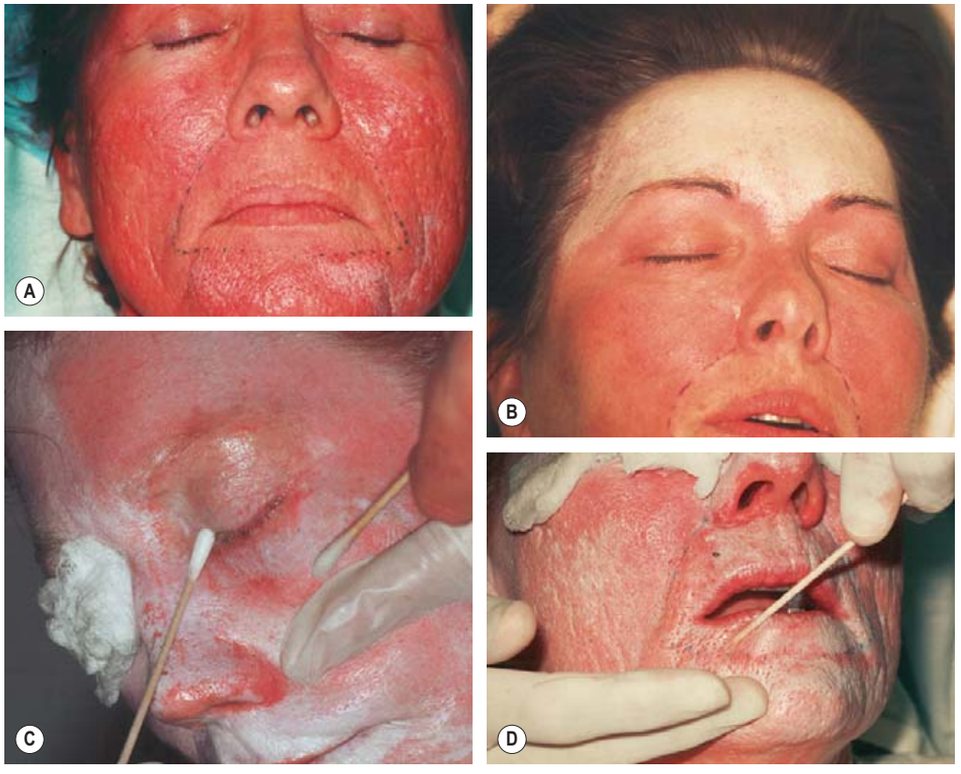


Fig. 154.8 Technical aspects of the Jessner's–35% trichloroacetic acid (TCA) peel. A Appearance of level I frosting after application of Jessner's solution – erythema with blotchy frosting. **B** 35% TCA applied, after Jessner's solution dries, with an even application using cotton-tipped applicators (one to four). A level III or white enamel frosting is obtained. **C** Eyelids are treated with one cotton-tipped applicator moistened with 35% TCA. A dry applicator is used to absorb tears during eyelid peeling. **D** Lip rhytides are peeled with saturated cotton-tipped applicators. The wooden shaft is used to rub peel solution further into the lip rhytides.

application of TCA. Additional applications of TCA increase the depth of penetration as well as the risk of complications, so one should apply more solution only to the underfrosted areas. In other words, do not apply 35% TCA to fully frosted areas. Thicker keratoses do not frost as well as the surrounding skin, so vigorous rubbing of the lesion may be needed for adequate TCA penetration. If necessary, thicker epidermal lesions may be treated with liquid nitrogen cryotherapy for several seconds prior to the application of TCA. As will be discussed later, mechanical abrasion can also be performed in selected areas at the completion of the Jessner's–35% TCA chemical peel, to enhance the results.

Although there is an immediate burning sensation as the peel solution is applied, the discomfort begins to subside as frosting occurs and resolves fully by the time of discharge. If necessary, a topical amide anesthetic can be applied under occlusion prior to a medium-depth peel, for pain relief[33]. Cool saline compresses offer symptomatic relief at the conclusion of the peel. Unlike the compresses utilized in glycolic acid peels, the saline following a TCA peel simply provides relief and does not "neutralize" the acid.

TCA Cross

The "TCA Cross" technique is a newer innovative approach to deep ice-pick and fibrotic acne scars (Fig. 154.9A). Rather than a peel or method of exfoliation, it is the use of 90% TCA as a full-thickness destructive tool. When applied to an ice-pick scar, it destroys the epidermis and deep dermal tunnel, creating a full-thickness skin wound which will heal with the formation of new collagen, thus filling the depressed scar. This method offers a new, simpler approach to these full-thickness depressions in which the alternatives are surgical: punch grafts, excision and scar revision. The procedure is performed independently of other resurfacing procedures such as peeling, laser resurfacing or dermabrasion.

After the face is cleansed and degreased with acetone (see above), the ice-pick and depressed fibrotic scars to be treated are outlined with a

Fig. 154.9 "TCA Cross" technique used as a destructive method for ice-pick scars. **A** Preoperative with ice-pick scars of the nose and cheek. **B** Frosting limited to just the ice-pick scars. **C** Postoperative.

THE BAKER–GORDON FORMULA	
88% liquid phenol, USP	3 ml
Tap water	2 ml
Septisol® liquid soap	8 drops
Croton oil	3 drops

Table 154.5 The Baker–Gordon formula. Septisol®, 0.25% hexachlorophene.

skin marker and photographed. This serves as a guide for further treatment sessions. The 90% TCA is applied to the interior of the ice-pick scar with a toothpick, being careful not to drip the acid onto normal skin. Of note, this is a full-thickness destruction of skin and not a peel, so the TCA should be applied *only* to the scar itself[33a]. Each of the scars is treated until a brilliant white frosting appears (Fig. 154.9B). A topical antibiotic is then placed on each treated site. The procedure is performed with no anesthesia or sedation, as it only produces a brief stinging equivalent to the sensation of cryosurgery.

Healing occurs over the next 2 to 3 weeks, with granulation tissue, fibroplasia and remodeling of new collagen, which will elevate and soften the depressed scars (Fig. 154.9C). The procedure is then repeated during two to six sessions at 6-week intervals until substantial elevation is achieved. Then, a more superficial resurfacing procedure such as medium-depth peeling, laser resurfacing or dermabrasion can be performed to smooth the more superficial scars and blend them with other treated areas.

The clinician must warn the patient about potential dyschromia, especially in Fitzpatrick skin types III through VI, as skin destruction of this depth can depigment the treated areas. The multiple procedures may not be able to raise all the scars to the surface but they will surely provide improvement. The TCA Cross technique does add another simple therapeutic option for treating scars and for facial resurfacing.

Deep chemical peeling

Patients in Glogau groups III and IV may require deep chemical peeling, motorized dermabrasion or laser resurfacing to improve their greater degree of skin damage. Deep chemical peeling leads to production of new collagen and ground substance down to a level in proportion to the depth of the peel. Deep chemical peels create an injury through the papillary dermis and into the superficial reticular dermis, which may extend into the mid-reticular dermis. For deep peeling, either TCA in concentrations above 50% or a phenol-containing preparation is used. Because of the risk of scarring and other complications with such potent concentrations of TCA, this agent is not recommended for deep chemical peeling. Therefore, solutions containing phenol remain the preferred formulation for deep chemical peels.

The application of pure, undiluted, 88% phenol to the skin causes rapid and complete coagulation of epidermal keratin proteins and is thought to block itself from further penetration. Classified as a medium-depth peeling agent, pure phenol is rarely used for chemical peeling because its limited depth of penetration results in a lesser degree of effectiveness. In contrast, the Baker–Gordon peel utilizes phenol in a formulation that permits deeper penetration into the dermis than is achieved with full-strength phenol[34] (Table 154.5). First described in 1961[35], the Baker–Gordon peel has been used successfully for over 50 years. The Baker–Gordon formula consists of Septisol® (hexachlorophene 0.25%; Vestal Laboratories), croton oil and tap water added to a solution of phenol, reducing its concentration to 50% or 55%. The mixture of ingredients is freshly prepared and must be stirred vigorously prior to application due to its poor miscibility. The liquid soap, Septisol®, is a surfactant that reduces skin tension, allowing a more even penetration. Croton oil is a vesicant and epidermolytic agent that enhances phenol absorption. More recent investigations into the effects of this peel, using varying concentrations of both phenol and croton oil, have suggested that the procedure's efficacy is more related to the amount of croton oil than it is to that of phenol[34,36]. Modifications of the original Baker–Gordon formula, in order to improve the risk-to-benefit ratio of deep peeling, are currently being investigated[37].

There are two major variations of deep chemical peeling with the Baker–Gordon phenol formula – occluded and unoccluded. Occlusion of the peeling solution with tape is thought to increase its penetration and extend the injury into the mid-reticular dermis. This technique is particularly helpful for deeply lined, "weather-beaten" faces, but should be utilized only by experienced surgeons because of the higher risk of complications[38]. The latter include hypopigmentation and a "plastic" or alabaster appearance with an effacement of normal skin texture. The unoccluded technique as modified by McCollough involves more cleansing of the skin and the application of more peel solution. This may enhance the efficacy of the solution but without its penetrating as deeply as in an occluded peel. In the hands of a skilled and knowledgeable surgeon, both methods are safe and reliable in rejuvenating severely photoaged skin. Deep chemical peeling can significantly improve or even eliminate deep furrows as well as other textural and pigmentary irregularities associated with advanced photoaging (Fig. 154.10). When performed properly on carefully selected patients, a remarkable degree of improvement is the expected result from deep chemical peeling.

Patients must be made aware of potential complications, including scarring, textural changes such as "alabaster skin", and pigmentary

Fig. 154.10 Advanced photoaging in the form of perioral rhytides treated with a Baker–Gordon phenol peel. **A** Preoperative, demonstrating perioral rhagades, textural and pigmentary changes, and epidermal lesions. **B** Postoperative: 2 years later. Note the phenol peel maintains correction for many years.

Fig. 154.11 Complications from a Baker–Gordon phenol peel. There was prolonged non-healing, resulting in hypopigmentation and marbled scarring.

disturbances (Fig. 154.11). Patients often experience postoperative erythema that may require many months to resolve and can be followed by variable hypopigmentation. Male patients and patients with darker complexions are less favorable candidates for deep chemical peeling, since the hypopigmentation is more difficult to camouflage. Because phenol is cardiotoxic and undergoes hepatic and renal elimination, preoperative evaluation includes a complete blood count, serum levels of liver enzymes, blood urea nitrogen, creatinine and electrolytes, and a baseline electrocardiogram. Any patient who has a history of cardiac arrhythmias or who is taking a medication known to precipitate arrhythmias should not undergo a full-face Baker–Gordon phenol peel. Patients with a history of hepatic or renal disease are also poor candidates.

Compared to medium-depth and superficial peeling, the Baker–Gordon phenol peel is a time-consuming procedure that must only be performed in a properly equipped facility. The required waiting period after the treatment of each cosmetic unit limits the rate of cutaneous absorption, thereby preventing the serum levels of phenol from reaching a dangerous peak during the procedure[39]. Intravenous hydration with a liter of lactated Ringer's solution before the procedure and another liter during the peel also promotes phenol excretion and prevents toxicity. Continuous electrocardiography, pulse oximetry and blood pressure monitoring are mandatory during the entire perioperative period. Any abnormalities, such as a premature ventricular contraction (PVC) or premature atrial contraction (PAC), necessitate abrupt discontinuation of the procedure and careful evaluation for toxicity[40]. Oxygen is supplemented throughout the procedure, as some physicians feel that it has a protective effect against cardiac arrhythmias.

On the morning of the procedure, the patient shaves and cleanses the face and does not eat breakfast or apply cosmetics. Before the administration of anesthesia (general or deep sedation), the patient is examined while he or she is in a seated position and appropriate landmarks are noted. After thorough cleansing and degreasing of the skin, the chemical agent is applied sequentially to six aesthetic units: forehead, perioral region, right cheek, left cheek, nose and periorbital region. There is a 15-minute time interval between the treatment of each cosmetic area, allowing 60 to 90 minutes for the entire procedure. Cotton-tipped applicators are used with a similar technique as discussed for the medium-depth Jessner's–35% TCA peel. However, less solution is used because frosting occurs very rapidly. Occlusion of the peel can be accomplished with strips of waterproof zinc oxide tape applied to each cosmetic unit just after the phenol has been applied and then removed on postoperative day 1 (see below). Care is exercised to extend the peel slightly beyond the mandibular rim to conceal the demarcation between treated and untreated skin.

The last aesthetic unit, the periorbital skin, is treated cautiously and conservatively to avoid overpenetration, which can lead to ectropion or scarring. It is important to remember that diluting a phenol compound with water may increase its penetration, so mineral oil rather than water should be used to flush the eyes if contact occurs. As noted previously, the croton oil may be an important factor in determining the depth of penetration of the phenol peel[34]. Using one or two drops of croton oil, rather than the three in the Baker–Gordon formula, can limit the risk of phenol complications such as textural effacement or hypopigmentation.

Application of the peeling agent creates an immediate burning sensation which lasts for 15 to 20 seconds, subsides for 20 minutes, and then returns for the next 6 to 8 hours. Ice packs may be applied as necessary for patient comfort. Narcotics are usually prescribed upon discharge for adequate pain control. Systemic corticosteroids are also administered by some surgeons to lessen the inflammatory response. For untaped (unoccluded) peels, petrolatum is applied and a biosynthetic dressing can be used for the first 24 hours.

MECHANICAL RESURFACING PROCEDURES

For over 50 years, dermabrasion utilizing a rotating abrasive surface attached to a power-driven hand engine has been considered the premier skin resurfacing procedure for facial scars. It has generally been regarded as a deep resurfacing modality based on its depth of injury and its prolonged healing time. The original descriptions of modern dermabrasion involved the use of a wire brush (which remains in use today), but there has been a slow movement towards more superficial methods of mechanical resurfacing. In 1957, the diamond fraise was introduced and became the preferred instrument for dermabrasion by some surgeons because it is less aggressive and more forgiving than the wire brush[41]. There has also been a resurgence of interest in manual dermasanding, which allows for more deliberate and controlled skin planing[4,5]. Microdermabrasion, the mechanical resurfacing procedure developed most recently, is the most conservative of all forms of mechanical resurfacing[3].

Microdermabrasion

Because microdermabrasion removes the stratum corneum and superficial spinous layer and the injury rarely extends past the basal layer, this modality is considered superficial in depth. Whether it is classified as very light or light in comparison to other superficial resurfacing procedures depends upon the techniques and aggressiveness of the operator. The microdermabrasion unit's handpiece is a closed system which propels aluminum oxide crystals at the skin at high speeds and simultaneously removes them with suction (Fig. 154.12). These units were developed commercially in the mid-1990s and are currently in widespread use in both physicians' offices and non-medical aesthetic spas.

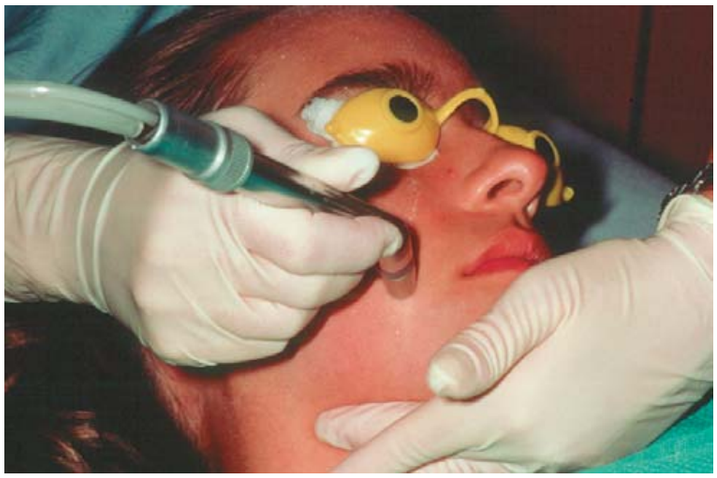


Fig. 154.12 Microdermabrasion. Aluminum oxide crystals are propelled at high speeds within a closed system and removed with suction.

ADVANTAGES OF MANUAL DERMASANDING OVER MOTORIZED DERMABRASION
• Greater control over depth of injury, particularly on the lips and orbital rims
• Blending of abraded areas into adjacent unabraded areas accomplished more easily and with better results
• Lower cost and greater simplicity of instrumentation and set-up
• Risk of aerosolizing infectious particles is far less
• Possibly lower incidence of postinflammatory hypopigmentation

Table 154.6 Advantages of manual dermasanding over motorized dermabrasion.

Fig. 154.13 Dermasanding. Manual dermasanding utilizing #320 grit silicon carbide sandpaper to blend CO_2 laser resurfacing into the eyebrow area.

Microdermabrasion may be indicated for acneiform conditions, pigmentary dyschromias, and as a "lunchtime" procedure for facial rejuvenation in all skin types[42], but in general it is not considered effective for improving the appearance of rhytides[43,44]. Its use in improving the appearance of scars is controversial, but it has been explored with favorable results[3]. Both the patient and physician must understand that the degree of objective improvement with microdermabrasion may be limited. Ideal candidates for microdermabrasion typically desire facial rejuvenation without "downtime". Appropriately selected patients have a subjective perception of improvement usually exceeding the objective signs depicted with photographs. Patients often report that their skin has a smoother texture and that cosmetics are easier to apply and blend in with their skin more easily. Microdermabrasion has also been successfully combined with intense pulsed light (IPL) therapy in order to enhance penetration of the light.

Although the role of microdermabrasion in facial rejuvenation grew dramatically after these units were initially developed, the scientific data to justify their use were lacking until more recently. An increase in epidermal and dermal thickness, flattening of the rete pegs, vascular ectasia with perivascular inflammation, papillary dermal hyalinization, and newly deposited collagen and elastic fibers have all been observed[45]. Following microdermabrasion, there also appears to be a significant alteration in epidermal barrier function[46]. Investigators have also observed an elevation of transcription factors, cytokines and matrix metalloproteinases following microdermabrasion[47].

Manual dermasanding

Manual dermasanding involves abrading the skin by hand using silicon carbide sandpaper or wallscreen that is commercially available at any hardware store. It is gaining in popularity for skin resurfacing because it has several advantages over power-driven dermabrasion (Table 154.6). Its classification as a wounding agent is entirely dependent upon the type of paper used, the force applied by the surgeon, and the duration of contact with the skin. Although manual dermasanding can be used to produce a wound as deep as with wire-brush dermabrasion or several passes with a pulsed CO_2 laser, it is probably most commonly used as a medium-depth or "minimally deep" resurfacing modality.

Manual dermasanding can be used to resurface an entire face, but because it is so labor-intensive it is most often utilized for resurfacing localized regions to minimize the appearance of a scar[48] or to blend or enhance the effects of a medium-depth chemical peel or a combination procedure[49]. It can be used following CO_2 laser resurfacing to feather the transition into hair-bearing areas that are inaccessible to the laser. Manual dermasanding of the eyebrows and hairline and gently abrading the upper neck at the inferior aspect of the laser-irradiated zone are all effective at minimizing lines of demarcation between treated and untreated skin (Fig. 154.13). It can also be useful immediately after laser resurfacing for stubborn rhytides, particularly in the perioral region; manual dermasanding can improve the outcome by producing a slightly greater depth of injury in a controlled fashion where further thermal injury would be risky. It will also remove adherent necrotic debris and thermal damage, thus enhancing the healing process. Similarly, a medium-depth chemical peel can be immediately followed by manual dermasanding of the more troublesome areas to enhance the results and also along the borders of the peeled skin to blend the effects.

Our clinical experience suggests that dermasanding after a Jessner's –35% TCA peel may yield impressive postoperative results that approach those seen with either motorized dermabrasion or CO_2 laser resurfacing in patients with cutaneous photoaging (Fig. 154.14). This combination is particularly helpful in patients who may not tolerate the greater degree of sedation often necessary with CO_2 laser resurfacing or who cannot afford the additional fees to cover anesthesia services.

The necessary materials for manual dermasanding include silicon carbide sandpaper or wallscreen. Both may be purchased in a variety of grades: fine grade (#400), medium grade (#220–320) and coarse grade (#180). The sandpaper is easier to use because of its flexibility and it is also more easily cut into smaller pieces which can be steam autoclaved. A 1.5-inch (4 cm) × 3-inch (8 cm) piece of sterilized sandpaper is wrapped around either the barrel of a 3 ml syringe or a rolled-up gauze pad and moistened with saline or a soap-free cleanser for lubrication. A 1% solution of lidocaine with epinephrine (adrenaline) may be used if additional anesthesia is necessary. The skin is stretched and both back-and-forth and circular motions are used to gradually abrade the skin, layer by layer, until the hills and valleys are softened or adjacent areas are blended to the desired degree. Coarse grades may be used initially for "debulking", followed by finer grades later in the procedure. The fine grade is used to blend delicate areas of skin such as around the eyelids. At the completion of the procedure, the dark-colored silicon carbide particles remaining on the skin surface should be rinsed off because there is a risk of their becoming implanted, creating a pigmented tattoo.

Fig. 154.14 Medium-depth chemical peel plus manual dermasanding. Jessner's–35% trichloroacetic acid was applied to the face followed immediately by manual dermasanding of the cutaneous lips and chin. **A** Preoperative with obvious perioral rhytides. **B** Postoperative with significant improvement.

Fig. 154.15 Mechanical dermabrasion. This technique is performed with a diamond fraise over rigid skin cooled with a topical refrigerant spray.

Motorized dermabrasion

Although various abrasive materials have long been used for mechanical resurfacing, the development of a power-driven unit to facilitate the procedure was revolutionary. Some of the units most commonly used today are the Bell hand engine (Bell International), the AEV-12 hand engine (Ellis International), and the Osada surgical handpiece (Osada, Inc.). A topical refrigerant spray is used to produce anesthesia and to harden the skin as it is abraded (Fig. 154.15). The spray immobilizes the topographic features so that there is no distortion by the pressure of the abrasive instrument. Concerns regarding potential harm to the environment from cryogenic sprays has limited the availability of topical refrigerant sprays in several countries, including the US. Utilizing liquid nitrogen or agents that cryopreserve tissue specimens is *not* recommended because they create a colder temperature that can lead to hypopigmentation and/or scarring. Options include tumescent anesthesia as a means of firming the tissue or use of the diamond fraise without a cryogen.

The two abrasive instruments most often employed with these units are the wire brush and the diamond fraise. The wire brush has numerous small-caliber, stainless steel wires that project circumferentially from the curved side of a cylindrical hub. A diamond fraise consists of a stainless-steel cylinder to which industrial-grade diamonds are bonded to create the abrasive surface. Compared with wire-brush instruments, diamond fraises are manufactured with a greater variety in their shape, width of abrasive surface, wheel diameter, and coarseness of grit. While there continues to be considerable controversy regarding which one of these instruments is superior[41], surgeons generally agree that the wire brush is more aggressive. The wire brush cuts more quickly and more deeply into the skin with each stroke, thereby posing a greater risk for injury and requiring more skill to operate. Although the diamond fraise is generally safer and more forgiving, it may not yield the degree of improvement possible with the wire brush, especially for more stubborn conditions such as acne scarring.

Because dermabrasion with either instrument is highly technique-dependent and the learning curve is steep, there may be considerable variability in the clinical results obtained by different operators. It is very important for beginner dermabraders to receive hands-on instruction from an experienced operator in order to be adequately trained. The proper techniques for motorized dermabrasion have also been the subject of comprehensive reviews in the literature[41]. Careful evaluation of the depth of injury throughout the procedure is critical in order to assure a sufficient depth for optimal results without penetrating beyond the desired level and risking scar formation. Because of the potential for aerosolization of infectious particles during dermabrasion, appropriate precautions are mandatory to protect the operating room staff (see Ch. 136).

All of the conditions amenable to treatment with manual dermasanding can also be managed with motorized dermabrasion. Although manual dermasanding is very well suited to combination resurfacing procedures for enhancement and blending, this concept was originally popularized with the use of the motorized dermabrasion[50]. The latter motor-driven technique may still be preferable to manual dermasanding for full-face resurfacing because less time and energy are expended. It also continues to be widely utilized for resurfacing localized areas, a procedure known as spot dermabrasion. This procedure, which can also be performed with the manual technique, is most useful for improving the appearance of surgical or traumatic scars[51]. Spot dermabrasion yields the greatest amount of improvement when performed about 6 weeks after the initial injury. A medium-depth peel can be performed on the remainder of the cosmetic unit or on the rest of the face to assure that the adjacent areas are blended.

The resurgence of manual dermasanding and the development of laser technology have led to a decline in the number of motorized dermabrasion procedures. Although all of the major indications for skin resurfacing that were mentioned earlier also apply to dermabrasion, many dermatologic surgeons only use this modality for selected conditions in which dermabrasion can consistently achieve superior results. A list of these conditions, as compiled by the authors according to their experience, is found in Table 154.7. It should be noted that any such list must be viewed with some degree of hesitation because very few controlled studies have been performed to evaluate the safety and efficacy of power-driven dermabrasion in comparison with either CO_2 laser resurfacing or manual dermasanding[52–56].

Moderate to severe acne scarring is the most notable of these conditions, for which laser resurfacing has yielded variable results and

CONDITIONS FOR WHICH MOTORIZED DERMABRASION MAY BE THE PREFERRED RESURFACING MODALITY
• Acne scarring
• Surgical or traumatic scars
• Benign neoplasms (multiple trichoepitheliomas, syringomas, angiofibromas)
• Malignant and pre-malignant neoplasms (skin cancer treatment and prevention in nevoid basal cell carcinoma syndrome and xeroderma pigmentosum, as well as management of extensive carcinoma *in situ*)
• Extensive epidermal lesions such as epidermal nevi
• Decorative or traumatic tattoos unresponsive to the pigmented lesion lasers
• Rhinophyma

Table 154.7 Conditions for which motorized dermabrasion may be the preferred resurfacing modality.

chemical peeling is generally disappointing. Dermabrasion selectively planes off the "hilltops" that surround the atrophic "valleys", whereas chemical peeling and laser irradiation may produce an injury of equivalent depth in both areas (Fig. 154.16). Effacing the edges of atrophic scars can be accomplished with the CO_2 laser or the solid CO_2–35% TCA peel[28], but these methods may be more difficult and their results less predictable as compared with dermabrasion. It is our opinion that conventional motorized dermabrasion remains the gold standard in resurfacing procedures for this condition. That said, the recently developed fractional CO_2 resurfacing laser has the advantage of creating greater skin contraction (due to deeper penetration of the microthermal zones) and can produce significant improvement in acne scars, in some cases equal to dermabrasion.

The physician must choose the scars most amenable to dermabrasion alone. These include shallow fibrotic scars, hypertrophic scars and undulating, rolling scars. The deeper fibrotic scars, ice-pick scars and scars with significant tissue loss may require a lifting or filling procedure prior to dermabrasion. In these patients, the results are significantly enhanced with one or more of the following adjunctive procedures 4 to 6 weeks preoperatively: punch or scalpel excision, TCA Cross technique, punch grafting, dermal grafting, fat grafting, or scar undermining (subcision)[57].

POSTOPERATIVE CARE

Because superficial resurfacing procedures generally do not extend beyond the epidermis, the dermal wound healing mechanisms are not activated. In contrast, medium-depth and deep resurfacing procedures stimulate the following four stages of dermal wound healing (see Ch. 141): (1) inflammation and coagulation; (2) re-epithelialization; (3) fibroplasia and matrix formation; and (4) collagen remodeling.

Because the pronounced edema following medium-depth and deep resurfacing procedures may minimize the appearance of scars, rhytides and other irregularities, the patient's initial perception of his or her improvement may be exaggerated. As swelling subsides postoperatively, patients should be reassured and advised that collagen remodeling continues for several months and leads to further clinical improvement. At some point in the postoperative course, patients often want to know when another resurfacing procedure can be performed if it is necessary. The presence of persistent postoperative erythema may indicate continued collagen remodeling and may serve as a warning that a similar resurfacing procedure performed prematurely could produce scarring. To assure their safety, patients undergoing medium-depth resurfacing should not undergo another medium-depth or deep procedure for the next 3 to 9 months. An individual having a deep resurfacing procedure should avoid another one for at least 12 months postoperatively. Touch-up procedures for revision of a prior suboptimal outcome are also best avoided during these time periods, so repeated efforts to counsel and reassure the patient are necessary.

The length of the healing time is generally proportional to the depth of the resurfacing procedure. Superficial resurfacing procedures cause minimal downtime and necessitate little postoperative care. They usually produce mild erythema and desquamation that lasts from 1 to

Fig. 154.16 Full-face dermabrasion performed for acne scars. A Preoperative: shallow and atrophic scars that are most amenable to dermabrasion. **B** Postoperative: dermabrasion prior to biosynthetic dressing. **C** Three months postoperative.

4 days depending on the wounding agent and the techniques used. Regular washing with a mild cleanser and the use of routine moisturizers and sunscreens are generally sufficient during the healing period.

Following medium-depth resurfacing procedures, there is a considerably longer healing time and more intensive postoperative care is necessary. Follow-up visits are scheduled regularly in order to monitor the patient's postoperative course. After a medium-depth chemical peel, occlusive dressings are not necessary because the epidermis, which is not removed intraoperatively, functions as a biologic dressing until peeling occurs. Because areas of medium-depth peeling which have been enhanced by manual dermasanding do not possess residual epidermis, occlusive dressings may be used on these areas during the first 3 days postoperatively.

The patient is instructed to soak the areas four times daily with warm compresses and to apply an emollient after each soak and during the intervening periods as necessary. A solution of 0.25% acetic acid (one tablespoon of white vinegar added to one pint of warm water) is preferred for the soaks because the mild acidity is physiologic for healing granulation tissue. It is also a mild debridant and has antibacterial effects, especially against *Pseudomonas* spp. and other Gram-negative organisms. Occlusive emollients, such as petrolatum, Aquaphor® or Eucerin® Creme, speed the process of re-epithelialization and lessen the tendency for delayed healing[58]. These emollients are also helpful in wound debridement and in the prevention of crust formation and infection.

Following medium-depth resurfacing, edema begins to appear almost immediately and progressively worsens during the first 48 hours. It can even be severe enough to close the eyelids and impair the patient's visual fields. If tolerated, aspirin or others nonsteroidal anti-inflammatory drugs (NSAIDs) can be administered, preoperatively and during the first 24 hours postoperatively to alleviate discomfort and reduce swelling. After a medium-depth chemical peel such as the Jessner's–35% TCA peel, there is initially a brawny, dusky erythema which is followed by the formation of a brownish crust that begins to separate from the skin surface between days 4 and 8 postoperatively. The underlying, newly formed epithelium is brightly erythematous but fades to a pink color that resembles a sunburn (see Fig. 154.5D). By postoperative day 7 to 10, re-epithelialization has occurred and the erythema can be camouflaged with cosmetics. Within 2 to 4 weeks after the procedure, the erythema usually resolves fully and retinoids and sunscreens can be restarted as tolerated.

Deep resurfacing procedures, such as the Baker–Gordon phenol peel or dermabrasion, require a follow-up visit the next day, several visits during the first week, and very close monitoring thereafter. At each visit, instructions for wound care are reviewed with the patient and any questions are answered. The immediate postoperative course after deep resurfacing is similar to that following medium-depth procedures, except that edema and erythema may be even more severe and persistent. NSAIDs can provide some relief, but an intramuscular corticosteroid injection is often administered on the day of surgery, even though its effects on wound healing are not completely understood. Pruritus may occur during the healing phase following a resurfacing procedure of any depth, but is particularly prevalent after deeper resurfacing. This problem can be alleviated by the use of emollients, ice packs, NSAIDs and antihistamines until the pruritus spontaneously resolves. Milia formation, which commonly occurs 3 to 4 weeks after deep chemical peeling or mechanical resurfacing, is easily managed with needle extraction.

Patients undergoing deep mechanical resurfacing with either motorized dermabrasion or manual dermasanding can have an occlusive biosynthetic dressing applied immediately after the procedure. In patients undergoing a Baker–Gordon phenol peel, occlusive tape or a biosynthetic dressing is usually utilized postoperatively. Occlusive tape dressings must be removed on the first postoperative day and this procedure may require analgesia and sedation. For this reason, the authors prefer untaped phenol peels with application of ointment or bio-occlusive dressings. Whenever a biosynthetic dressing is used, it must be removed daily and replaced with a new one for the first 2 or 3 days postoperatively so that the face can be gently debrided with saline soaks and moistened cotton tips. The patient should be instructed to regularly apply an occlusive ointment to areas around the mouth, eyelids and hairline that are not adequately covered by the dressing. Occlusive biosynthetic dressings have been shown to enhance collagen synthesis and hasten re-epithelialization in superficial wounds. They also minimize the amount of discomfort and obviate the need for repeated soaks by the patient during the first few days after the procedure.

By the third day following deep mechanical or chemical resurfacing, the patient begins open wound care with 0.25% acetic acid soaks four to six times daily and regular applications of an occlusive ointment. By the 7th to the 14th day postoperatively, re-epithelialization is usually complete and the ointment is replaced by a heavy moisturizer. The marked edema and erythema typically seen after dermabrasion or dermasanding generally resolve after several weeks. The erythema resulting from deep peeling may be more persistent, but is rarely present beyond 2 to 4 months. Strict sun avoidance is critical for 3 to 6 months after dermabrasion or deep chemical peeling. The patient typically restarts sunscreens and retinoid therapy within a couple weeks of re-epithelialization, as tolerated.

COMPLICATIONS

Complications may occur following any method of skin resurfacing involving injury to any depth, but are more common after medium-depth and deep procedures. It is far simpler to prevent the development of a complication than to manage it once it has occurred. Complications may be prevented by proper selection of suitable patients and appropriate resurfacing modalities, precise intraoperative technique, and proper patient management before and after the procedure (see Table 154.3). The dissatisfied patient represents a complication even when the cosmetic result is favorable. Improper wound care, trauma to healing areas resulting from overzealous debridement, compulsive picking or scratching, and premature use of irritating substances such as depilatories or wax for the removal of hair can each cause the depth of injury to extend beyond the threshold of safety. As discussed below, the development of infection in the postoperative period can also extend the depth of injury and increase the risk of permanent sequelae.

With specific regard to chemical peeling, excessive injury to the skin can result from poor technique during application or problems with the chemical agents utilized. The degree of frosting is monitored closely to assure that the agent has been applied evenly and that the injury extends to the proper depth (Table 154.8). Although it does not always correlate completely with the depth of injury, the level of frosting is a very valuable guide for determining the appropriate endpoint of treatment (see Fig. 154.3). Injuring the skin too deeply during a chemical peel, as suggested by an excessive degree of frosting, may result not only from over-application but also from the use of excessively concentrated peeling solutions. The latter error can be caused by the surgeon's choice of an improper peeling agent, such as 50% TCA, or it can be related to unexpected disturbances in a solution's pharmacologic mixture. For Baker–Gordon peels, a new batch should be mixed by the surgeon prior to each procedure in order to be certain that the preparation is made correctly. The other peeling solutions are available in various formulations and strengths for purchase directly from medical supply dealers. Reputable dealers mix and label these solutions properly according to the standard weight-to-volume formula. Storage of peeling solutions in proper containers away from sunlight and immediate replacement of expired solutions are important measures to ensure chemical stability of the agents being used[59]. Immediately prior to peeling, an ample volume of the solution should be poured from the primary storage container into a smaller, secondary cup. The peeling agent is applied directly to the skin surface from this cup and the excess subsequently discarded in order to avoid contamination of the storage container and to avoid the accidental transfer of concentrated crystals from the neck of the storage container to the patient's skin.

CLINICAL SIGNS THAT REFLECT DEPTH OF WOUNDING
• Level of frosting (see Fig. 154.3)
• Time for frosting to appear
• Time for frosting to disappear
• Skin turgor
• Epidermal slide*
*Sliding of the epidermis off the dermis due to separation of the two tissues.

Table 154.8 Clinical signs that reflect depth of wounding.

Errors during mechanical resurfacing procedures may also lead to an injury of excessive depth and a higher risk of adverse sequelae. This problem can result from poor technique in the handling of the instruments or from failure to recognize the appropriate treatment endpoint. The beginner should first start by conservatively dermasanding small areas to get a comfortable feel for the skin's response to this type of injury. As knowledge and experience is gained, one can then progress on to diamond fraise dermabrasion and later to the use of the wire brush. Observation of experienced surgeons and hands-on training are invaluable. The beginner should always err on the side of conservatism, while still yielding favorable results, in order to avoid excessively deep tissue injury that could produce long-term complications.

During chemical peeling or mechanical resurfacing, intraoperative exposure of vital structures to the resurfacing agent may occur and can have serious adverse consequences. Extreme care must be exercised when dermabrading with a power-driven, rotating instrument, assuring that the dominant hand maintains complete control continuously and free skin edges (e.g. eyelid, lip) are not caught up in the wire brush or diamond fraise, as the latter may result in tearing of the skin. During chemical peeling, the moistened applicator should never be passed over the central face, in order to avoid inadvertent exposure of a vulnerable surface such as the eye to the solution. There should always be appropriate fluids readily available to rinse the area in case such an exposure does occur. In particular, saline is used to dilute TCA, mineral oil is used to dilute Baker–Gordon phenol solutions, and sodium bicarbonate is used to neutralize glycolic acid.

Adverse systemic effects related to a resurfacing procedure are very uncommon but can usually be traced to an identifiable causative factor in the perioperative period. Peeling with phenol solutions has been associated with systemic toxicities, so these procedures must be performed slowly and only on properly selected, healthy patients in an appropriate clinical setting. The use of Jessner's solution poses a theoretical risk of systemic salicylate or resorcinol toxicity, but this is probably not clinically significant when application is limited to the face and neck. Undoubtedly, the most common cause of systemic problems related to resurfacing procedures is an adverse allergic or physiologic reaction to a medication used for anesthesia. It is imperative that the surgeon knows all the physiologic effects and the potential adverse consequences of each drug administered systemically, unless there is an attending anesthesiologist who assumes this responsibility. Fortunately, the chemical and mechanical resurfacing procedures utilized most often can be performed with little or no sedation.

It is important to make a distinction between a true complication and an expected side effect of a resurfacing procedure. With medium-depth and deep resurfacing, transient erythema, flushing, increased skin temperature, pruritus, edema, milia formation and mild alterations in mood are typical occurrences, so they should not be classified as true complications. Patient reassurance may be all that is necessary, since these problems usually resolve spontaneously. True complications that may develop within a treated area include infection, delayed wound healing, persistent erythema, scarring, and pigmentary or textural abnormalities[60,61]. Any of these true complications can occur despite proper patient and procedure selection, perfect surgical technique, and appropriate management before and after the operation.

Infection is an uncommon complication that develops during the postoperative period and may be caused by bacterial, viral or fungal organisms. An important preventive measure is the continuous use of soaks for adequate wound debridement. Frequent postoperative visits are helpful to assure early recognition and treatment of any infection so that scarring does not result. An infection may present with delayed wound healing, ulcerations, excessive necrotic material and crusting, purulent drainage or odor. An acneiform eruption or pustular folliculitis can even be a manifestation of infection and should initially be treated as such. Infection with streptococcal and staphylococcal organisms can occur under biosynthetic membranes or thick, occlusive ointments, so these are best avoided, except in the immediate postoperative period. Other organisms, such as *Escherichia coli* or *Pseudomonas* spp., may even infect the area if there is improper wound care. *Candida* infections can also occur and are sometimes related to the use of prophylactic antibiotics or occlusive wound care. Clinical suspicion of a wound infection necessitates immediate institution of empiric antimicrobial therapy, laboratory culture for identification of the organism(s), and wound debridement as necessary[62].

Herpes simplex infection can occur during the healing period following medium-depth or deep resurfacing and has the potential for devastating sequelae. An outbreak can even occur in patients on the recommended 10–14-day prophylactic antiviral regimen. The keys to avoiding scar formation are rapid recognition and aggressive therapy begun early in the course of the infection. The dosage of antiviral drug should be increased to the recommended maximum in cases of active herpetic infection.

Persistent erythema beyond 2 months after a medium-depth procedure may be precipitated by the use of topical or systemic retinoid therapy, contact with various allergens or irritants, an underlying skin condition or genetic susceptibility, or the presence of active infection[60,63]. Persistent erythema may indicate the impending development of scar formation. Especially when indurated, it should be treated promptly and aggressively. Management includes massage therapy, topical, intralesional or even systemic corticosteroids, silicone gel sheeting, and pulsed dye laser therapy. In most cases, scarring can be prevented. Mild scarring may even fade away spontaneously. Rarely, ectropion can occur when aggressive resurfacing creates scarring or excessive tightening of periorbital skin in a susceptible patient.

Textural abnormalities, skin atrophy and dyspigmentation are additional complications that may occur with medium-depth and deep resurfacing procedures. The return of normal pigmentation in patients whose Fitzpatrick skin type is IV or higher is less predictable, so an extra measure of caution is necessary. Postoperative hyperpigmentation may be prevented and/or treated with a topical retinoid, a 4–8% hydroquinone preparation and strict photoprotection, but the hypopigmentation that can follow deeper resurfacing is typically permanent. Another potential pigmentary problem following deeper resurfacing procedures is a conspicuous demarcation line separating the untreated and treated areas. Although this problem can usually be avoided with adequate planning and proper technique, the approach to its management should focus on lightening the pigment in the adjacent untreated areas.

CONCLUSIONS AND FUTURE TRENDS

The sheer number of patients demanding medical therapy or procedural intervention to rejuvenate their skin mandates that dermatologists be well versed in this area. The field of resurfacing is constantly changing, with the development of new techniques and procedures as well as fluctuations in patient demands and expectations. In all areas of cosmetic surgery, there has been a recent trend in favor of less invasive procedures. Dermatologists often choose to learn and implement only a handful of resurfacing procedures that best fulfill the needs of their practice and meet the demands of their patient population.

REFERENCES

1. Brody HJ, Monheit GD, Resnik SS, Alt TH. A history of chemical peeling. Dermatol Surg. 2000;26:405–9.
2. Lawrence N, Mandy S, Yarborough J, Alt T. History of dermabrasion. Dermatol Surg. 2000;26:95–101.
3. Tsai RY, Wang CN, Chan HL. Aluminum oxide crystal microdermabrasion. A new technique for treating facial scarring. Dermatol Surg. 1995;21:539–42.
4. Harris DR, Noodleman FR. Combining manual dermasanding with low strength trichloroacetic acid to improve actinically injured skin. J Dermatol Surg Oncol. 1994;20:436–42.
5. Chiarello SE. Tumescent dermasanding with cryospraying. A new wrinkle on the treatment of rhytids. Dermatol Surg. 1996;22:601–10.
6. Dingman DL, Hartog J, Siemionow M. Simultaneous deep-plane face lift and trichloroacetic acid peel. Plast Reconstr Surg. 1994;93:86–93; discussion 4–5.
7. Rubenstein R, Roenigk HH, Stegman SJ, Hanke CW. Atypical keloids after dermabrasion of patients taking isotretinoin. J Am Acad Dermatol. 1986;15:280–5.
8. Wolfe SA. Chemical face peeling following therapeutic irradiation. Plast Reconstr Surg. 1982;69:859–62.
9. Monheit GD. Chemical peeling for pigmentary dyschromias. Cosmet Dermatol. 1995;8:10–15.
10. Swinehart JM. Test spots in dermabrasion and chemical peeling. J Dermatol Surg Oncol. 1990;16:557–63.
11. Gilbert S, McBurney E. Use of valacyclovir for herpes simplex virus-1 (HSV-1) prophylaxis after facial resurfacing: a randomized clinical trial of dosing regimens. Dermatol Surg. 2000;26:50–4.
12. Monheit GD. Facial resurfacing may trigger the herpes simplex virus. Cosmet Dermatol. 1995;8:9–16.

13. Monheit GD. Skin preparation: an essential step before chemical peeling or laser resurfacing. Cosmet Dermatol. 1996;9:13–14.
14. Yamamoto O, Bhawan J, Hara M, Gilchrest BA. Keratinocyte degeneration in human facial skin: documentation of new ultrastructural markers for photodamage and their improvement during topical tretinoin therapy. Exp Dermatol. 1995;4:9–19.
15. Goodman G. Dermabrasion using tumescent anesthesia. J Dermatol Surg Oncol. 1994;20:802–7.
16. Stegman SJ. A comparative histologic study of the effects of three peeling agents and dermabrasion on normal and sun-damaged skin. Aesthetic Plast Surg. 1982;6:123–5.
17. Stegman SJ. A study of dermabrasion and chemical peels in an animal model. J Dermatol Surg Oncol. 1980;6:490–7.
18. Nelson BR, Fader DJ, Gillard M, et al. Pilot histologic and ultrastructural study of the effects of medium-depth chemical facial peels on dermal collagen in patients with actinically damaged skin. J Am Acad Dermatol. 1995;32:472–8.
19. Ditre CM, Griffin TD, Murphy GF, et al. Effects of alpha-hydroxy acids on photoaged skin: a pilot clinical, histologic, and ultrastructural study. J Am Acad Dermatol. 1996;34:187–95.
20. Fitzpatrick RE, Tope WD, Goldman MP, Satur NM. Pulsed carbon dioxide laser, trichloroacetic acid, Baker-Gordon phenol, and dermabrasion: a comparative clinical and histologic study of cutaneous resurfacing in a porcine model. Arch Dermatol. 1996;132:469–71.
21. Rubin M. Chemical Peels. Philadelphia: Saunders, 2005.
22. Clark CP. Office-based skin care and superficial peels: the scientific rationale. Plast Reconstr Surg. 1999;104:854–64; discussion 65–6.
23. Kligman D, Kligman AM. Salicylic acid peels for the treatment of photoaging. Dermatol Surg. 1998;24:325–8.
24. Van Scott EJ, Yu RJ. Hyperkeratinization, corneocyte cohesion, and alpha hydroxy acids. J Am Acad Dermatol. 1984;11:867–79.
25. Slavin JW. Considerations in alpha hydroxy acid peels. Clin Plast Surg. 1998;25:45–52.
26. Monheit GD. The Jessner's + TCA peel: a medium depth chemical peel. J Dermatol Surg Oncol. 1989;15:945–50.
27. Brody HJ. Trichloroacetic acid application in chemical peeling, operative techniques. Plast Reconstr Surg. 1995;2:127–8.
28. Brody HJ, Hailey CW. Medium-depth chemical peeling of the skin: a variation of superficial chemosurgery. J Dermatol Surg Oncol. 1986;12:1268–75.
29. Coleman WP, Futrell JM. The glycolic acid trichloroacetic acid peel. J Dermatol Surg Oncol. 1994;20:76–80.
30. Witheiler DD, Lawrence N, Cox SE, et al. Long-term efficacy and safety of Jessner's solution and 35% trichloroacetic acid vs 5% fluorouracil in the treatment of widespread facial actinic keratoses. Dermatol Surg. 1997;23:191–6.
31. Spira M, Freeman R, Arfai P, et al. Clinical comparison of chemical peeling dermabrasion, and 5-fu for senile keratoses. Plast Reconstr Surg. 1970;46:61–6.
31a. Monheit GD. Combinations of therapy. In: Tung R, Rubin M (eds). Chemical Peels, 2nd edn. Philadelphia: Elsevier, 2011:133–50.
32. Monheit GD, Zeitouni NC. Skin resurfacing for photoaging: laser resurfacing versus chemical peeling. Cosmet Dermatol. 1997;10:11–22.
32a. Monheit GD, Prather CL. Chemical peels for precancerous skin lesions. In: Macfarlane D (ed). Skin Cancer Management: A Practical Approach. New York: Springer, 2010:27–39.
33. Koppel RA, Coleman KM, Coleman WP. The efficacy of EMLA versus ELA-Max for pain relief in medium-depth chemical peeling: a clinical and histopathologic evaluation. Dermatol Surg. 2000;26:61–4.
33a. Lee JB, Chung WG, Kwahck H, Lee KH. Focal treatment of acne scars with trichloroacetic acid: Chemical reconstruction of skin scars method. Dermatol Surg. 2002;28:1017–21.
34. Hetter GP. An examination of the phenol-croton oil peel: Part I. Dissecting the formula. Plast Reconstr Surg. 2000;105:227–39; discussion 49–51.
35. Baker TJ, Gordon HL. The ablation of rhytides by chemical means: a preliminary report. J Fla Med Assoc. 1961;48:451–4.
36. Hetter GP. An examination of the phenol-croton oil peel: Part IV. Face peel results with different concentrations of phenol and croton oil. Plast Reconstr Surg. 2000;105:1061–83; discussion 84–7.
37. Stone PA. The use of modified phenol for chemical face peeling. Clin Plast Surg. 1998;25:21–44.
38. Alt T. Occluded Baker/Gordon chemical peel. Review and update. J Dermatol Surg Oncol. 1989;15:980–93.
39. Wexler MR, Halon DA, Teitelbaum A, et al. The prevention of cardiac arrhythmias produced in an animal model by the topical application of a phenol preparation in common use for face peeling. Plast Reconstr Surg. 1984;73:595–8.
40. Beeson WH. The importance of cardiac monitoring in superficial and deep chemical peeling. J Dermatol Surg Oncol. 1987;13:949–50.
41. Alt TH. Facial dermabrasion: advantages of the diamond fraise technique. J Dermatol Surg Oncol. 1987;13:618–24.
42. Bernard RW, Beran SJ, Rusin L. Microdermabrasion in clinical practice. Clin Plast Surg. 2000;27:571–7.
43. Shim EK, Barnette D, Hughes K, Greenway HT. Microdermabrasion: a clinical and histopathologic study. J Dermatol Surg. 2001;27:524–30.
44. Coimbra M, Rohrich RJ, Chao J, Brown SA. A prospective controlled assessment of microdermabrasion for damaged skin and fine rhytides. Plast Reconstr Surg. 2004;113:1438–43; discussion 1444.
45. Freedman BM, Rueda-Pedraza E, Waddell SP. The epidermal and dermal changes associated with microdermabrasion. J Dermatol Surg. 2001;27:1031–3; discussion 1033–4.
46. Rajan P, Grimes PE. Skin barrier changes induced by aluminum oxide and sodium chloride microdermabrasion. J Dermatol Surg. 2002;28: 390–3.
47. Karimipour DJ, Kang S, Johnson TM, et al. Microdermabrasion: a molecular analysis following a single treatment. J Am Acad Dermatol. 2005;52:215–23.
48. Zisser M, Kaplan B, Moy RL. Surgical pearl: manual dermabrasion. J Am Acad Dermatol. 1995;33:105–6.
49. Lusthaus S, Benmeir P, Neuman A, et al. The use of sandpaper in chemical peeling combined with dermabrasion of the face. Ann Plast Surg. 1993;31:281–2.
50. Ayhan S, Baran CN, Yavuzer R, et al. Combined chemical peeling and dermabrasion for deep acne and posttraumatic scars as well as aging face. Plast Reconstr Surg. 1998;102:1238–46.
51. Katz BE, Oca AG. A controlled study of the effectiveness of spot dermabrasion ("scarabrasion") on the appearance of surgical scars. J Am Acad Dermatol. 1991;24:462–6.
52. Nehal KS, Levine VJ, Ross B, Ashinoff R. Comparison of high-energy pulsed carbon dioxide laser resurfacing and dermabrasion in the revision of surgical scars. Dermatol Surg. 1998;24:647–50.
53. Kitzmiller WJ, Visscher M, Page DA, et al. A controlled evaluation of dermabrasion versus CO_2 laser resurfacing for the treatment of perioral wrinkles. Plast Reconstr Surg. 2000;106:1366–72; discussion 73–4.
54. Holmkvist KA, Rogers GS. Treatment of perioral rhytides: a comparison of dermabrasion and superpulsed carbon dioxide laser. Arch Dermatol. 2000;136:725–31.
55. Gin I, Chew J, Rau KA, et al. Treatment of upper lip wrinkles: a comparison of the 950 microsec dwell time carbon dioxide laser to manual tumescent dermabrasion. Dermatol Surg. 1999;25:468–73; discussion 73–4.
56. Chew J, Gin I, Rau KA, et al. Treatment of upper lip wrinkles: a comparison of 950 microsec dwell time carbon dioxide laser with unoccluded Baker's phenol chemical peel. Dermatol Surg. 1999;25:262–6.
57. Goodman GJ. Postacne scarring: a review of its pathophysiology and treatment. Dermatol Surg. 2000;26:857–71.
58. Collawn SS, Boissy RE, Gamboa M, Vasconez LO. Ultrastructural study of the skin after facial chemical peels and the effect of moisturization on wound healing. Plast Reconstr Surg. 1998;101:1374–9; discussion 80.
59. Spinowitz AL, Rumsfield J. Stability-time profile of trichloroacetic acid at various concentrations and storage conditions. J Dermatol Surg Oncol. 1989;15:974–5.
60. Brody HJ. Complications of chemical peeling. J Dermatol Surg Oncol. 1989;15:1010–19.
61. Demas PN, Bridenstine JB. Diagnosis and treatment of postoperative complications after skin resurfacing. J Oral Maxillofac Surg. 1999;57:837–41.
62. Giandoni MB, Grabski WJ. Cutaneous candidiasis as a cause of delayed surgical wound healing. J Am Acad Dermatol. 1994;30:981–4.
63. Maloney BP, Millman B, Monheit G, McCollough EG. The etiology of prolonged erythema after chemical peel. Dermatol Surg. 1998;24:337–41.

Phlebology and Treatment of Leg Veins 155

Mitchel P Goldman and Robert A Weiss

Chapter Contents

Venous anatomy, physiology and pathophysiology 2509
Physical examination of the phlebology patient 2510
Laboratory evaluation of the superficial venous system 2512
Compression in sclerotherapy and venous disease 2512
Sclerosing solutions 2513
Techniques for treating telangiectasias and reticular veins 2515
Larger varicose veins 2517
Postsclerotherapy compression 2518
Complications 2518
Ambulatory phlebectomy 2520
Endovenous laser and radiofrequency ablation 2522

Key features

- Superficial telangiectasias, reticular veins and varicose veins of the lower extremities are interconnected and develop after impairment of venous return
- Poor venous return results from venous valvular incompetence or primary muscle pump failure
- A pretreatment physical examination to assess the extent and cause of the venous abnormalities should be performed with the patient in a standing position
- The physical examination should be supplemented by Doppler or duplex ultrasonography
- Both preoperative and postoperative compression are important in the management of venous insufficiency
- Sclerosing agents should destroy the entire vascular wall, producing permanent fibrosis of the vessel
- The minimal concentration and volume of sclerosing agent should be used to achieve the desired results
- All of the affected portions of the superficial venous system should be treated, starting with the most proximal
- Large veins should be treated before smaller veins, and veins should be treated from proximal to distal
- FDA-approved sclerosing agents are sodium tetradecyl sulfate, polidocanol and sodium morrhuate; hypertonic saline (11.7–23.4%) and glycerin (72% mixed 2:1 with 1% lidocaine, with or without epinephrine) are not approved for vein sclerosis and represent off-label usage
- The most common local side effects following injection of sclerosing agents are hyperpigmentation, telangiectatic matting, and cutaneous ulcers
- Patients generally require one to three sclerosant injection treatment sessions spaced at 6- to 8-week intervals

INTRODUCTION

Varicose and telangiectatic leg veins increase in extent and severity with increasing age. The evolution of safe and effective treatment options has made sclerotherapy, ambulatory phlebectomy, and endovenous radiofrequency (RF) and laser ablation (LA) an expanding area of the dermatologic surgeon's practice. The utilization of improved diagnostic modalities, more efficient sclerosing agents and simplified surgical techniques have made the treatment of venous disease safe, efficient and highly satisfying for both physician and patient. This chapter presents the most recent advances in sclerotherapy, ambulatory phlebectomy, and endovenous RF and LA as they relate to the management of telangiectasias, reticular veins and varicose veins, both non-saphenous and saphenous.

VENOUS ANATOMY, PHYSIOLOGY AND PATHOPHYSIOLOGY

The peripheral venous system functions both as a reservoir to hold extra blood (e.g. during pregnancy) and as a conduit to return blood from the periphery to the heart and lungs. The correct function of the venous system depends on a complex series of pumps and valves that are individually frail, yet the system as a whole performs well under extremely adverse conditions[1] (Fig. 155.1). Superficial veins carry less than 5% of venous blood, while the deep venous system carries 95% of the blood.

The superficial venous system is a complicated variable network of interconnecting veins, most of which are unnamed[2]. A few larger

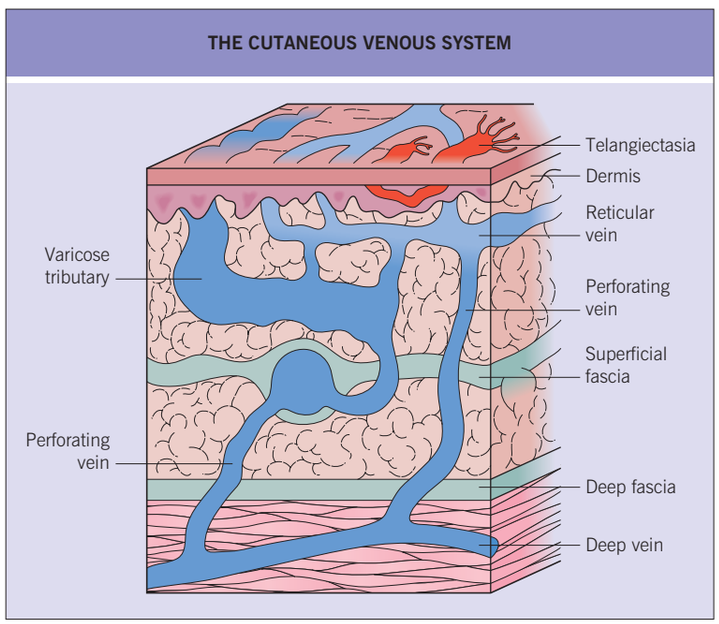


Fig. 155.1 The cutaneous venous system. The deep venous system drains the superficial venous system, which, in turn, is fed from the skin surface by telangiectasias in the dermis. The latter drain via reticular veins into the larger venous channels located in the reticular dermis and subcutaneous compartments. *Redrawn from: Somjen GM, Ziegenbein R, Johnston AH, Royle JP: Anatomical examination of leg telangiectases with duplex scanning. J Dermatol Surg Oncol. 1993;19:940.*

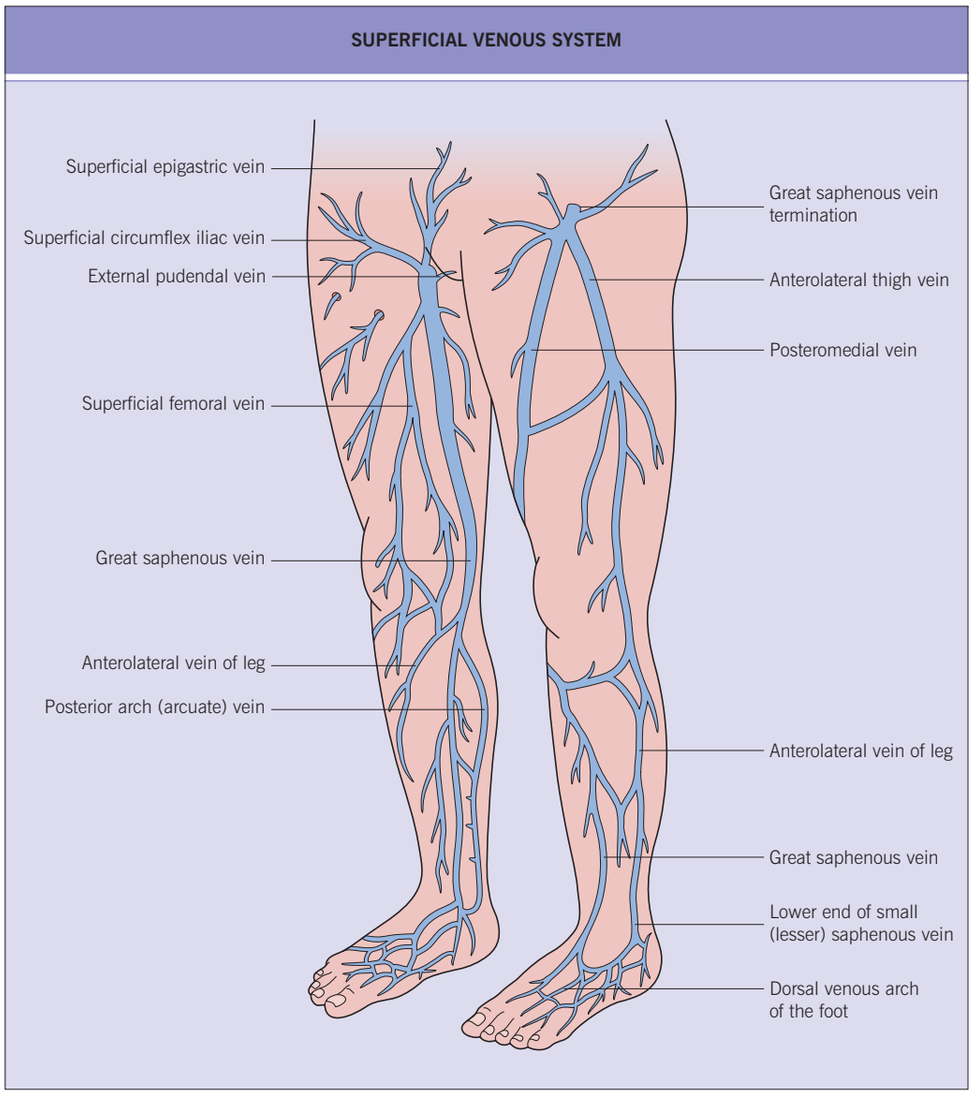


Fig. 155.2 Superficial venous system. Lateral and medial views of the distribution of the major axial trunks of the superficial venous system, the great and small saphenous veins, and associated tributaries. The anterolateral thigh vein was previously referred to as the lateral circumflex vein.

truncal superficial veins are fairly constant in location. These truncal superficial veins serve as a conduit to pass blood centrally into the deep venous system. The principal named superficial veins are the small saphenous vein (SSV), which runs from the ankle to the knee, and the great saphenous vein (GSV), which runs from the ankle to the groin[3] (Fig. 155.2).

An interconnecting system of perforating veins that pass through the deep fascia connects the superficial veins to the deep veins of the calf or thigh (Figs 155.1 & 155.3). All venous blood eventually is received by the deep venous system on its way back to the right atrium of the heart.

Blood is propelled back to the heart via the pumping action of the foot and calf muscles, which squeeze blood out of a venous segment through one-way valves when muscle contractions increase the pressure within the fascial muscle compartment (Fig. 155.4). Venous pathology can result from primary muscle pump failure due to venous obstruction (thrombotic or non-thrombotic) or from venous valvular incompetence[4].

A genetic predisposition for the development of varicose veins has been observed, and both dominant and recessive patterns of inheritance have been described. Approximately 70% of patients can identify superficial venous disease as a familial trait. Hormonal influences from pregnancy or estrogen and progesterone supplementation are believed to be additional predisposing factors[5].

In summary, telangiectasias, reticular veins and varicose veins are derived from a hereditary substrate that is influenced by hormones as well as static gravitational pressures and dynamic muscular forces transmitted through failed venous valves. The hereditary substrate cannot be altered, but the influence of hemodynamic forces and hydrostatic pressure can be modified, both by sclerotherapy and by surgical techniques.

PHYSICAL EXAMINATION OF THE PHLEBOLOGY PATIENT

The purpose of the clinical examination is to survey the main venous trunks in order to determine where the primary or highest points of reflux are located. During the examination, the patient should be standing, preferably on a platform. It is important to determine the grade of venous insufficiency[6]. The recommended CEAP classification system is based on clinical manifestations (C), etiologic factors (E), anatomic distribution of disease (A), and the underlying pathophysiologic findings (P)[7]. The venous severity scoring (VSS) system is based on three elements: the number of anatomic segments affected, grading of symptoms and signs, and disability. The consensus statement on this approach to clinical assessment was published in 25 journals and books in eight languages, truly a worldwide distribution.

For the practicing physician, CEAP is an instrument for establishing the correct diagnosis, guiding treatment and assessing prognosis. It is important to stress that CEAP is a descriptive classification, while VSS and quality-of-life (QoL) scores represent instruments for longitudinal research in order to assess outcomes. In modern phlebologic practice, the vast majority of patients will have a duplex scan of the venous system of the leg, which will provide data on E, A and P. In basic CEAP, the single highest descriptor should be used for clinical class, e.g. a patient with varicose veins, swelling and lipodermatosclerosis will be C4b (Table 155.1). However, use of just the C-classification provides no advantage

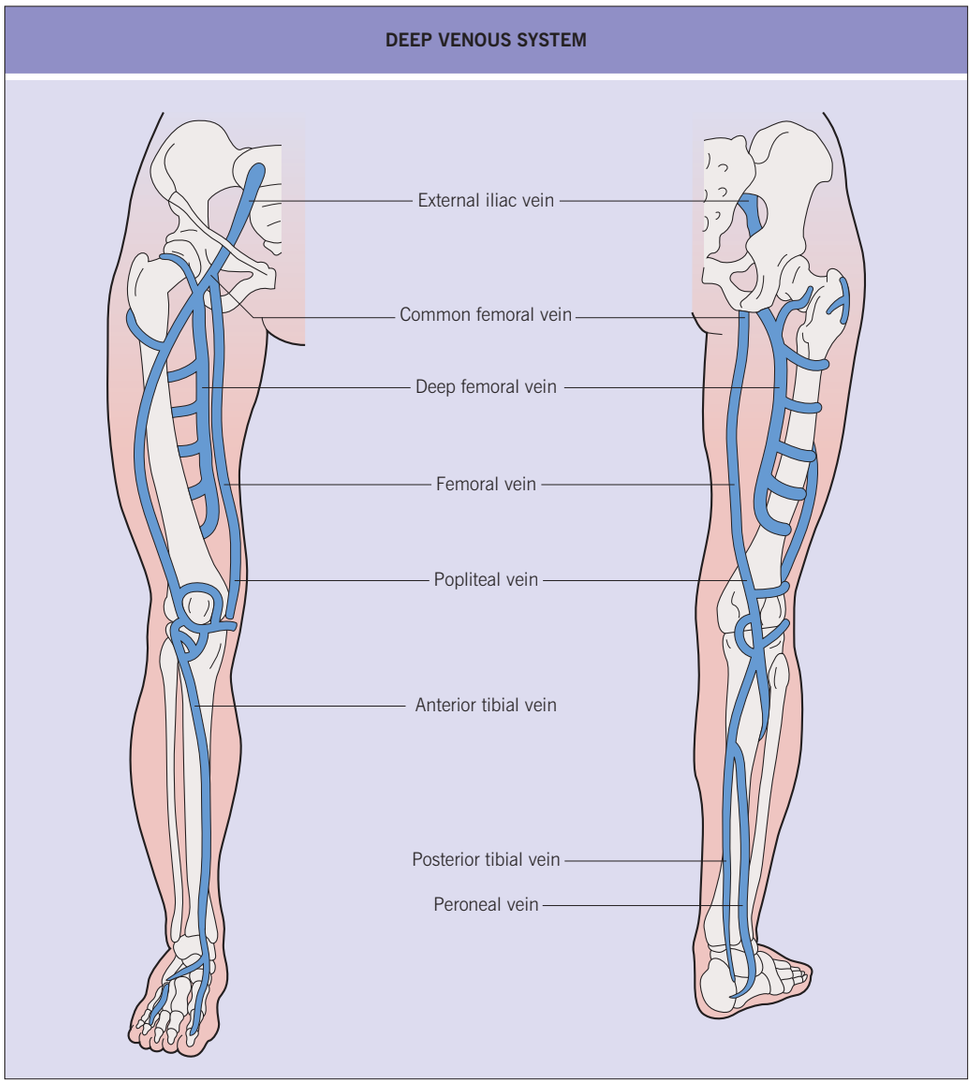


Fig. 155.3 Deep venous system. The major drainage vessel below the knee is the popliteal vein, while the femoral vein is the major portal of drainage in the inguinal area of the groin (great saphenous distribution).

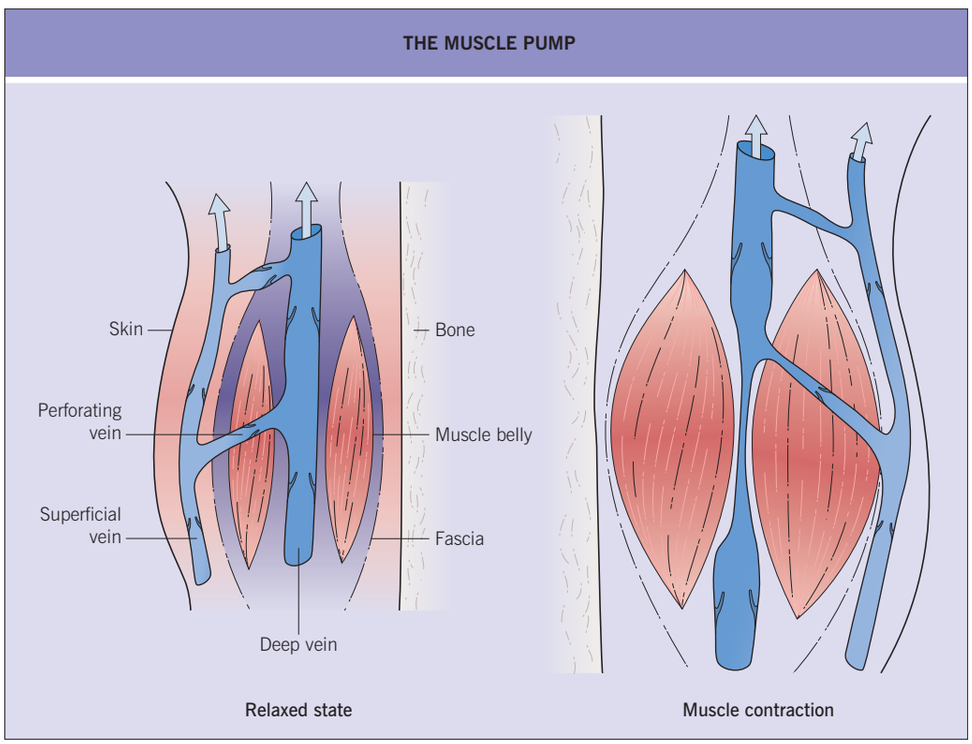


Fig. 155.4 The muscle pump, or "peripheral heart". This is located primarily in the calves. During muscle contraction, compression of veins transports blood to the heart by means of the deep venous system.
Adapted from Goldman MP, et al. Sclerotherapy, 5th edn. London: Mosby, 2011.

CEAP CLASSIFICATION OF CHRONIC VENOUS DISORDERS
CLINICAL CLASSIFICATION (C)
C0: no visible or palpable signs of venous disease
C1: telangiectasias or reticular veins
C2: varicose veins
C3: edema
C4a: hemosiderin pigmentation, eczematous dermatitis (stasis dermatitis)
C4b: lipodermatosclerosis, atrophie blanche (livedoid vasculopathy)
C5: healed venous ulcer
C6: active venous ulcer
S: symptoms including aches, pains, tightness, skin irritation, heaviness, muscle cramps, and other complaints attributable to venous dysfunction
A: asymptomatic
ETIOLOGIC CLASSIFICATION (E)
Ec: congenital
Ep: primary
Es: secondary (post-thrombotic)
En: no venous etiology identified
ANATOMIC CLASSIFICATION (A)
As: superficial veins
Ap: perforator veins
Ad: deep veins
An: no venous location identified
PATHOPHYSIOLOGIC CLASSIFICATION (P)
Pr: reflux
Po: obstruction
Pr,o: reflux and obstruction
Pn: no venous pathophysiology identified

Table 155.1 CEAP (Clinical, Etiologic, Anatomic, Pathophysiologic) classification of chronic venous disorders.

over previous classification schemes that were based solely on clinical appearance. Even in basic CEAP, where a duplex scan is performed, classification of E, A and P with multiple descriptors is recommended. For A (anatomic classification), the simple s, p and d descriptors should be used, e.g. a patient with primary disease of the superficial and deep veins could be classified as C4aS; Ep; As,d; Pr. While venous disease is complex, it can be described using this system, and clinicians are encouraged to use all four components of CEAP (see Table 155.1).

A disposable sclerotherapy garment is an excellent means for preserving patient modesty while gaining full access to the entire lower extremity. A two-step examination stool also aids in the clinical assessment. The medial plantar and ankle regions are examined for the presence of specific skin changes, including clusters of telangiectatic veins (referred to as "corona phlebectasia"), hemosiderin deposition, atrophie blanche (livedoid vasculopathy), lipodermatosclerosis, and/or active or healed ulceration (see Ch. 105). These findings suggest a chronic state of venous insufficiency, located in either the saphenous veins or the deep venous systems. The lateral posterior malleolar region is similarly examined. Skin changes in this area most often indicate small saphenous vein insufficiency.

There are three branch veins that are important for evaluating the saphenofemoral junction (SFJ)[8]. Attention is first directed toward the anterior abdominal wall. The presence of varices in this area ("caput medusae") indicates insufficiency of the superficial epigastric vein (see Fig. 155.2); this is always abnormal and should alert the phlebologist to underlying deep venous obstruction, usually in the iliofemoral segment (see Fig. 155.3). The posteromedial thigh vein and the anterolateral thigh vein are often also insufficient in patients with GSV insufficiency and this usually presents as dilated reticular veins and telangiectasias within the involved anatomic zones[7].

LABORATORY EVALUATION OF THE SUPERFICIAL VENOUS SYSTEM

Vascular testing is indicated for symptomatic patients in whom the source of reflux is unclear by physical examination and in other clinical situations as outlined in Table 155.2. A key instrument is a Doppler device which detects increased or decreased frequency shifts from

INDICATIONS FOR VASCULAR TESTING
1. Any varicosity greater than 2 mm in diameter extending the length of the calf or thigh
2. Presence of a "starburst" cluster of telangiectasias over sites of perforating veins (medial distal calf, mid-posterior calf, medial knee, medial midthigh)
3. Evidence of incompetent perforating veins (connect the superficial and deep venous systems)
4. Varicose veins, either truncal or saphenous
5. Clinical signs of venous insufficiency
6. Symptomatic veins of any diameter
7. History of deep venous thrombosis and/or thrombophlebitis
8. History of previous venous surgery or sclerotherapy with poor results or recurrence of varicosities

Table 155.2 Indications for vascular testing.

ultrasound waves that are reflected from blood cells coming toward or going away from the Doppler ultrasound probe, respectively[9]. A bidirectional Doppler can produce a hard copy, while a unidirectional Doppler cannot (the former may be useful for insurance purposes). Bidirectional Doppler devices have 4 MHz probes that are deeper penetrating (up to 8 cm) and 8 MHz probes that penetrate more superficially (0.5–2 cm).

When utilizing a Doppler device, the examiner places the probe over the vein in question, and then compresses distal to the probe to create a flux sound (Fig. 155.5)[10]. Because the veins have one-way valves, if a vein is normal there will be no reflux or reversal of flow upon release of the distal compression. If a reflux sound is heard after release of the distal compression, this is abnormal and diagnostic of venous valvular insufficiency. It is best to hold the probe at a 30° to 45° angle[11]. Reversal of blood flow, as the patient increases abdominal pressure with the Valsalva maneuver, indicates incompetent valves from the SFJ to the distal-most site of the probe. When placed on the medial superior thigh over the GSV a few centimeters distal to the SFJ, reversal of blood flow for >0.5 seconds indicates an incompetent SFJ. These patients require endovenous RF or laser closure of the GSV before any treatment is given to the distal varicose, reticular and/or telangiectatic leg veins.

Duplex ultrasonography is a highly accurate, non-invasive technique that can provide both anatomic and physiologic information regarding the venous system[12] (Table 155.3). For this reason, it is rapidly becoming the modality of choice, not only for pretreatment assessment of varicose veins, but also for guidance during endovenous RF and laser procedures and for performance of follow-up studies. Duplex examination of normal veins involves the use of a ≥7.5 MHz high-resolution β-mode scanner and a 5 MHz Doppler probe. While the β-mode scanner provides real-time anatomic images, the Doppler probe supplies physiologic information in the form of blood flow data (Fig. 155.6). Incorporation of the real-time image allows reproducible positioning of the Doppler probe at a known anatomic site. Using this method, the physician can obtain longitudinal and transverse images of veins and arteries that are up to 8 cm below the skin surface. For deeper assessment, a <7.5 MHz scanner may be needed.

COMPRESSION IN SCLEROTHERAPY AND VENOUS DISEASE

Graduated compression has many benefits in patients with venous disease. It reduces the diameter of the veins, thereby increasing flow velocity and decreasing the chance of thrombus formation. Following sclerotherapy (which is essentially a *controlled* thrombophlebitic reaction), compression reduces the diameter of the resulting thrombosis of the treated vein, which minimizes the inflammatory reaction, thereby decreasing the extent and incidence of post-treatment hyperpigmentation, recanalization of the vein, and telangiectatic matting. Compression also increases the contact between the sclerosant and the endothelial lining of the vessel wall, potentiating pan-vessel obliteration. There are three main types of graduated compression: graduated elastic compression stockings or bandages, inelastic compression garments or bandages, and pneumatic compression pumps[13]. Compression bandages are not recommended, as they are difficult to apply in a graduated manner and hold their compression for only a few hours after application.

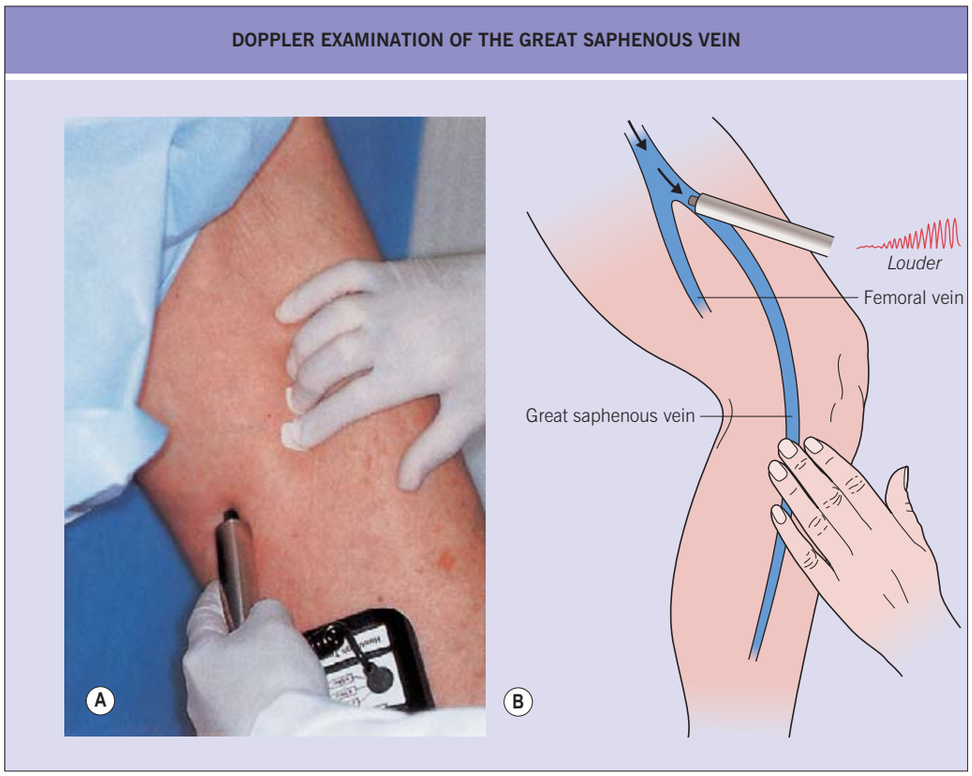


Fig. 155.5 Doppler examination of the great saphenous vein. A Doppler probe held at a 30° to 45° angle. **B** Doppler examination of the great saphenous vein; a reflux found after the release of distal compression denotes venous valvular insufficiency. *Courtesy, Neil Sadick, MD*

COMPARISON OF DOPPLER ULTRASOUND AND DUPLEX SCANNING FOR PRESCLEROTHERAPY EVALUATION

	Doppler	Duplex
Portability	Yes	Yes
Easy to use	Yes	Yes
Cost (2012) (approximate in US dollars)	Unidirectional: $500–$750	Color: $25 000–50 000
Information obtained	1. Patency, competence of venous valves 2. Detection of deep venous thrombosis in thigh	1. Patency, competence of venous valves 2. Detection of deep venous thrombosis with greater accuracy (thigh > calf) 3. Velocity of reflux 4. Anatomy and anomalies of venous system (number of great saphenous veins) 5. Termination of small saphenous vein 6. Thrombosis versus sclerosis
Reliability	Less reliable because of blind, non-timed pulsed sound beam	More reliable because of actual visualization of venous anatomy

Table 155.3 Comparison of Doppler ultrasound and duplex scanning for presclerotherapy evaluation.

Fig. 155.6 Duplex ultrasonography. In the duplex image (**A**) reverse flow (shown in blue) is seen coming from a branch of the great saphenous vein (GSV); the branch is superior to the GSV. **B** The Doppler signal shows reverse flow.

Graduated elastic compression stockings are most commonly employed following sclerotherapy. They come in four classes, based upon the pressure generated by the stocking at the level of the ankle, that range from 20–30 mmHg (class I) to 50–60 mmHg (class IV) (see Ch. 105)[14]. Most sclerotherapy patients wear thigh-high or panty-hose stockings. In addition, most manufacturers now offer so-called "fashion hose" which approximate 18 mmHg pressure and are sheer, leading to greater patient compliance. In a multicenter study performed by Weiss et al[15], 20–30 mmHg graduated compression stockings were shown to increase sclerotherapeutic efficacy and diminish post-treatment hyperpigmentation. At least 3 days of compression were necessary to produce this positive effect and 3 weeks of daytime wear was found to be the optimal time required for the maximal effect[15].

We recommend that all patients wear graduated compression stockings for 1 week ("24/7") after the procedure. It is important for the patient to wear the stockings 24 hours a day, even while in the shower and when sleeping. If one removes the stockings in the shower, the veins dilate. If one removes the stockings at night, the superficial system also dilates. For this reason, it is recommended that all patients wear the thigh-high stockings, as these are more hygienic and easier to use than panty-hose, which extend higher up to the waist.

SCLEROSING SOLUTIONS

The optimal sclerosing agent is one that induces pan-endothelial destruction or removal[16]. Thrombosis alone will not obliterate vessels because intact endothelium contains tissue plasminogen activator that can dissolve thrombi, leading to recanalization. The ideal sclerosing

A GUIDE FOR THE SELECTION OF SCLEROSING SOLUTION CONCENTRATION AND VOLUME BY VESSEL TYPE		
Vessel	**Solution concentration**	**Volume (per region)**
Telangiectatic matting (after previous treatment)	Glycerin, 72%, diluted 2:1 with 1% lidocaine with epinephrine	0.1–0.2 ml
Telangiectasias (up to 1 mm)	Glycerin, 72%, diluted 2:1 with 1% lidocaine with epinephrine Sodium tetradecyl sulfate, 0.1–0.25% Polidocanol, 0.25–0.5% Hypertonic saline, 11.7% Hypertonic saline, 10% and dextrose, 25% Polyiodide iodide, 0.1%	0.1–0.3 ml
Venulectasias (1–2 mm)	Sodium tetradecyl sulfate, 0.25–0.5% Glycerin, 72% Polidocanol, 0.5–0.75% Hypertonic saline, 11.7–23.4% Hypertonic saline, 10% and dextrose, 25%	0.2–0.5 ml
Reticular veins (2–4 mm subcutaneous blue veins)	Sodium tetradecyl sulfate, 0.1–0.25%, *foam* Polidocanol, 0.25–0.5%, *foam* Polyiodide iodide, 0.3–1.0%	0.5 ml (may increase to 1–3 ml if filling of reticular vein by foam is observed)
Non-saphenous varicose veins (3–8 mm)	Sodium tetradecyl sulfate, 0.5–1.0%, *foam* Polidocanol, 1.0–3.0%, *foam* Polyiodide iodide, 1.0–2.0%	0.5 ml for liquids, 3 ml of foam per injection site in a large-capacity vein
Saphenous varicose trunks (usually >5 mm)	Sodium tetradecyl sulfate, 1.0–3.0%, *foam* Polidocanol, 3.0–5.0%, *foam* Polyiodide iodide, 2.0–6.0% (rarely to 12%)	0.5 ml for liquids (low-volume injection critical at high concentrations), 3 ml with foam

Table 155.4 A guide for the selection of sclerosing solution concentration and volume by vessel type. The sclerosing agents are listed in order of preference.

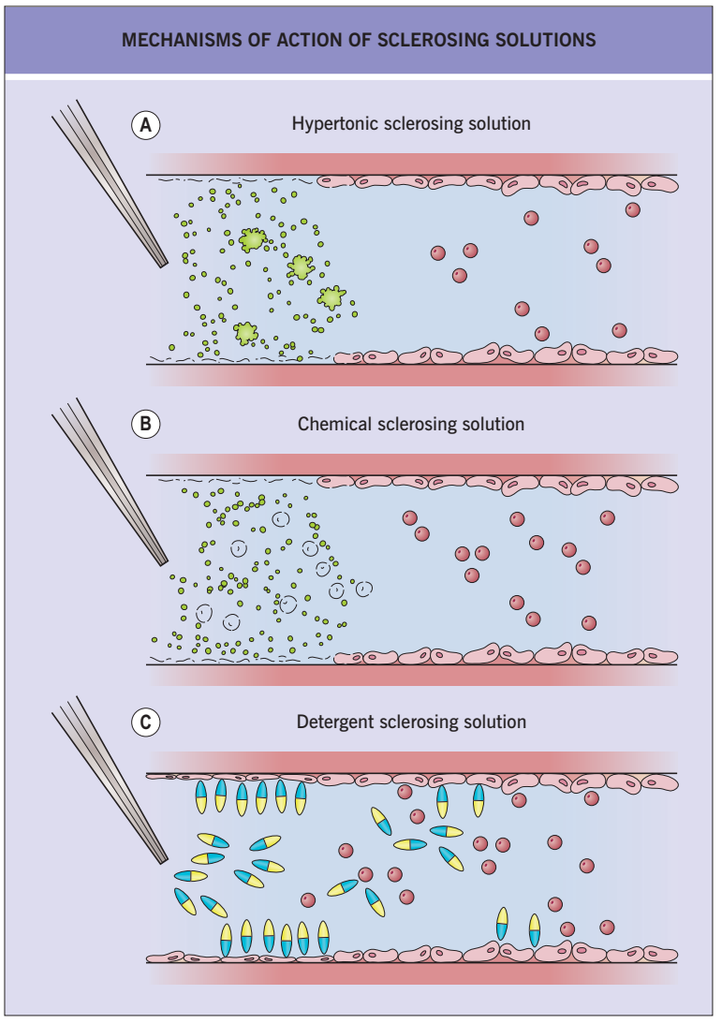


Fig. 155.7 Mechanisms of action of sclerosing solutions. A Hypertonic, which induces endothelial damage via a gradient dehydration effect. **B** Chemical, which injures cells by acting as a corrosive. **C** Detergent, where the hydrophobic portion of the detergent molecule (blue) attaches to the endothelial cell wall while the hydrophilic portion (yellow) draws water into the cell, leading to an overhydrated maceration effect. *Adapted from Goldman MP, et al. Sclerotherapy, 5th edn. London: Mosby, 2011.*

agent should possess no systemic toxicity and produce local endothelial destruction that fully extends to the adventitia with minimal thrombus formation[17]. The resultant vascular destruction induces an inflammatory reaction which leads to fibrosis and eventually obliteration of the vessel.

There are several important points to remember when choosing a particular sclerosing solution and determining the appropriate sclerosant concentration (Table 155.4)[18]:

1. If the sclerosant is too weak, insufficient endothelial damage will occur, leading to thrombosis secondary to varicose vessel wall damage. However, there will be no fibrosis and recanalization of the vessel occurs.
2. Too strong a solution may lead to uncontrolled destruction of vascular endothelium and other layers, which may eventuate in hyperpigmentation, neoangiogenesis (telangiectatic matting) and ulceration secondary to sclerosant extravasation.
3. Choose the minimal sclerosant concentration (MSC) that will cause irreversible damage to the cellular wall of the abnormal vessel.

Sclerosing agents are classified into three groups based upon the mechanism whereby they cause injury to the endothelium (Table 155.5):

1. Hyperosmotic agents – the osmotic agents include hypertonic saline and hypertonic saline–dextrose. Their primary mechanism of action involves endothelial cell damage via dehydration (Fig. 155.7A).
2. Chemical irritants – the chemical irritants include chromated or non-chromated glycerin and polyiodide iodide. They injure cells by acting as corrosives; their cauterizing effect is thought to be due to the associated heavy metal (Fig. 155.7B).
3. Detergent sclerosants – the detergent sclerosants include sodium tetradecyl sulfate, polidocanol and sodium morrhuate. This group of agents causes vascular injury by altering the surface tension around endothelial cells (Fig. 155.7C).

The only agents that are Food and Drug Administration (FDA)-approved for sclerotherapy in the US are sodium tetradecyl sulfate, sodium morrhuate (fatty acids in cod liver oil) and polidocanol[19]; hypertonic saline is approved as an abortifacient rather than for the treatment of varicose veins. Glycerin is approved as a hyperosmotic agent for the treatment of acute intracerebral edema and acute angle glaucoma. Polyiodide iodide, a chemical irritant, lacks FDA approval for any indication. Glycerin, hypertonic saline (11.7–23.4%), polidocanol (0.25–5%), and sodium tetradecyl sulfate (0.1–3%) are the current sclerosants of choice in the US.

Determining the minimal volume and minimal concentration of the most appropriate sclerosing agent is a key factor in producing effective sclerotherapy results. This concept, termed the minimal sclerosant concentration (MSC), will enable the sclerotherapist to achieve maximal results while minimizing the complication profile[20,21]. A guide to suggested sclerosing agents and initial choices of sclerosant concentrations and volumes for instillation as related to vessel type and diameter is presented in Table 155.4.

It is also important to have a working knowledge of the complication profile of each sclerosing solution (see Table 155.5). The osmotic sclerosants such as hypertonic saline are associated with burning and cramping on injection and an increased incidence of ulcerative necrosis secondary to extravasation.

IMPORTANT CHARACTERISTICS OF SCLEROSING SOLUTIONS					
Sclerosing solution (Brand name)	**Class**	**Allergenicity**	**Risks**	**FDA approval**	**Dose limitation**
Hypertonic saline [11.7–23.4%]	Hyperosmotic	None	Pain* and cramping Necrosis of skin Hyperpigmentation	Yes, as abortifacient [18–30%]	6–10 ml
Hypertonic saline [10%] and dextrose [25%] (Sclerodex®)	Hyperosmotic	Low (due only to added phenethyl alcohol)	Pain* (much less than with hypertonic saline alone)	No (sold in Canada)	10 ml of undiluted solution
Sodium tetradecyl sulfate (Sotradecol® [USA], Fibrovein®, Thromboject®)	Detergent	Very rare anaphylaxis	Pain* with perivascular injection Necrosis of skin (with higher concentrations) Hyperpigmentation	Yes	10 ml of 3%
Polidocanol (Asclera® [USA], Asklerol®, Aethoxysklerol®, Aetoxisclerol®, Sclerovein®)	Detergent	Very rare anaphylaxis	Lowest risk of pain Necrosis usually from arteriole injection Hyperpigmentation (with higher concentrations) Disulfiram-like reaction	Yes	5 ml of 3% (depends on body weight, see ref. 5)
Sodium morrhuate (Scleromate®)	Detergent	Anaphylaxis, highest risk	Pain* Necrosis of skin Hyperpigmentation	Yes	10 ml
Ethanolamine oleate	Detergent	Urticaria, anaphylaxis	Pain* Necrosis of skin Hyperpigmentation Viscous, difficult to inject Acute renal failure Hemolytic reactions	Yes (used primarily for esophageal varices)	10 ml
Polyiodide iodide (Varigloban®, Variglobin®, Sclerodine®)	Chemical irritant	Anaphylaxis Iodine hypersensitivity reactions	Pain* Necrosis of skin Dark brown color makes intravascular placement more difficult to confirm	No	5 ml of 3%
Glycerin [72%] with chromium potassium alum [8%] (Chromex®, Scleremo®); glycerin [72%] diluted 2:1 with 1% lidocaine, with or without epinephrine)	Chemical irritant (plain glycerin may be an osmotic agent as well)	Very rare anaphylaxis (none for glycerin alone)	Pain* and cramping Low risk of hyperpigmentation Viscous, difficult to inject Hematuria with injections >10 ml	Yes (for treatment of acute intracerebral edema and acute angle glaucoma)	10 ml

*Includes burning.

Table 155.5 Important characteristics of sclerosing solutions. Sclerosing agents are classified into three groups: hyperosmotic agents, detergents and chemical irritants.

Sodium tetradecyl sulfate and polidocanol have been associated with a low incidence of allergic reactions, ranging from urticaria to anaphylaxis (<0.01%)[5]. However, with increasing usage, it is now thought that the risk of type I (i.e. immediate hypersensitivity) reactions is extremely low. In fact, after over 25 years of use in over 25 000 patients, the authors have never seen an allergic reaction except for one case of urticaria. Hyperpigmentation has been reported in 5–30% of patients treated with all sclerosing solutions except glycerin, which has a <1% incidence of pigmentation. In the authors' experience, the incidence of hyperpigmentation is related more to the concentration of the sclerosing agent as well as host skin type, vessel type and other vascular fragility factors[22–24].

Creating foaming detergent solutions by mixing them with air or CO_2 (typically in a mixture of 1 ml of solution with 4 ml of air or CO_2) has been found to increase the potency of the sclerosing solution twofold while decreasing its adverse effect profile fourfold. Foam displaces blood and remains for an extended time in the target vessel. This makes the sclerosing solution more efficient, so that it may be utilized at lower concentrations. The use of CO_2 rather than room air allows the gas–sclerosant bubbles to breakdown more quickly, minimizing the possibility of gas embolization into the arterial circulation via a patent foramen ovale.

TECHNIQUES FOR TREATING TELANGIECTASIAS AND RETICULAR VEINS

The treatment of telangiectasias and reticular veins is most commonly performed for cosmetic improvement, but up to 50% of these patients also report a variety of symptoms, from dull aching legs to throbbing pain over the telangiectasia[25]. Telangiectasias are best defined as flat, red to blue vessels 0.1–1 mm in diameter (Table 155.6). Venulectasias are blue- to violet-colored vessels, sometimes distended above the skin surface and most often 1–2 mm in diameter. Reticular veins have a cyanotic blue to blue–green hue and are visually 2–4 mm in diameter. When a complex of reticular veins is located on the lateral thigh, it is felt to be a vestige of embryonal development known as the lateral subdermal plexus[26,27].

The treatment of telangiectasias and reticular veins is undertaken only after all sources of reflux have been addressed, as it is important to treat proximal sites of reflux first and to treat larger vessels before smaller veins. Alone or in combination with laser or intense pulsed light technology, sclerotherapy of small-diameter vessels is the most common challenge faced by the dermatologic surgeon who performs sclerotherapy. Preoperative photographic documentation and full informed consent outlining all possible risks and complications as well as treatment expectations should be obtained prior to therapy[28–30].

Materials employed in the treatment of telangiectasias and reticular veins are relatively simple. They may include:

- cotton balls soaked with 70% isopropyl alcohol
- protective gloves
- 3 and 5 ml disposable syringes
- 30-gauge disposable ½-inch transparent hub needles
- magnifying lens (2–3×)
- nitroglycerin paste for prolonged blanching
- bronchodilator inhaler in case of bronchospasm
- epinephrine (adrenaline) in case of anaphylaxis.

CLASSIFICATION OF VEINS AND CLINICAL APPROACH TO TREATMENT OF VENOUS PATHOLOGY

Type	Description	Diameter (mm)	Color	Treatment
I	Telangiectasias (spider veins) Telangiectatic matting	0.1–1	Usually red network	• Microsclerotherapy • Intense pulsed light • Laser (e.g. pulsed dye, 1064 nm Nd:YAG)
II	Venulectasias	1–2	Violaceous	• Sclerotherapy • Laser (e.g. 1064 nm Nd:YAG)
III	Reticular varicosities	2–4	Cyanotic blue to blue–green	• Sclerotherapy • Ambulatory phlebectomy • Laser (e.g. 1064 nm Nd:YAG)
IV	Varicosities (secondary saphenous branch or perforator-related)	3–8	Blue to blue–green	• Ambulatory phlebectomy • Sclerotherapy
V	Saphenous varicosities (truncal or axial varicosities including main saphenous trunks and first-generation branch varicosities)	≥5	Blue to blue–green May be palpable and not visible	• Ambulatory phlebectomy • Endovenous radiofrequency closure • Sclerotherapy • Endovenous laser ablation (EVLA)

Table 155.6 Classification of veins and clinical approach to treatment of venous pathology. ND:YAG, neodymium-doped yttrium aluminum garnet. *Photographs, Courtesy, Jean L Bolognia, MD.*

Flow sheets with segmental numerical division of the legs are helpful in documenting areas that are treated at each session. Because successful sclerotherapy that results in pan-luminal endofibrosis can take up to 6 weeks, it is recommended that treatment sessions should not be repeated for at least this interval of time.

There are four variable components that may be employed in the treatment of telangiectatic and reticular veins[30–32]. They include:

1. ***Aspiration.*** Aspiration of a small amount of blood into the needle hub may ensure that the dermatologic surgeon has adequately cannulated the vein. Of note, the vein may collapse if aspiration is too strong.
2. ***Direct puncture without aspiration.*** This technique relies on the feeling associated with perforating the vein wall. Although it is slightly more precarious for beginners, this technique can be mastered with time.
3. ***Air bolus variant*** (Fig. 155.8)**.** Injection of <0.5 ml of air prior to introduction of the sclerosant will displace blood in the vein. Once intravascular access is confirmed, the sclerosant can be safely injected. Air inadvertently introduced into the tissues is not as damaging as the sclerosant might be. Too strong of a push may lead to truncal distention and rupture. The small air bolus technique is ideal for hypertonic saline, as even slight extravasation of solution will cause epidermal ulceration.
4. ***Empty vein variant.*** In an attempt to remove as much blood as possible, the leg is elevated and kneading with gentle pressure is performed before the sclerosant is injected. The persistence of varicose veins after treatment is usually due to recanalization of the intramural thrombus that develops, and the empty vein technique may reduce the amount of thrombus. This concept is more important when treating larger veins. Other advantages of this technique are that an empty vein has minimal volume and therefore the endothelium is exposed to a concentration of sclerosant similar to that injected. Also, a smaller volume of sclerosant is necessary to ensure contact with the endothelial surface and lower concentrations of sclerosant may be employed since there is less blood in the vein to dilute the solution[33]. Foamed sclerosing agents, discussed later, displace blood from veins, thereby automatically resulting in the empty vein technique with an enhanced efficacy.

Injection Technique

Injection is carried out utilizing one or more of the previously described techniques. The needle may be bent at an angle of 30°. Hand traction is used by either the dermatologic surgeon or an assistant to keep the skin taut. Large vessels are injected before smaller vessels, i.e. injection of the reticular veins feeding smaller telangiectasias or venules may

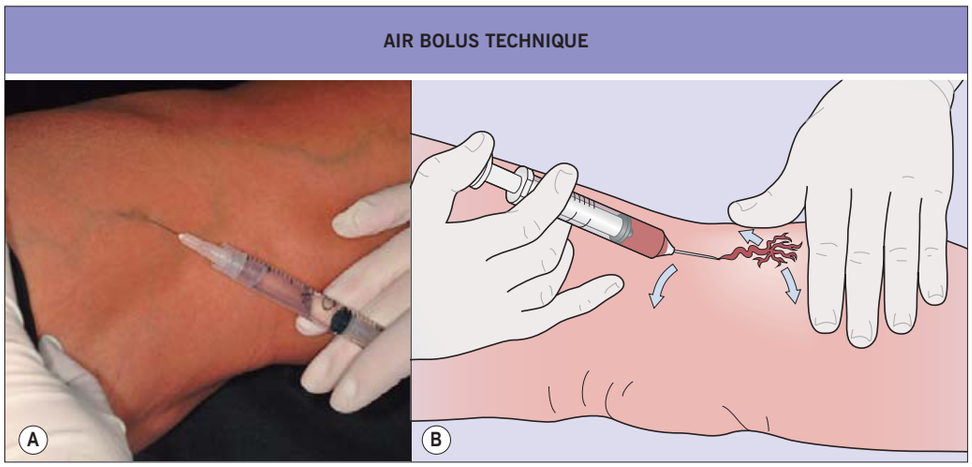


Fig. 155.8 Air bolus technique. A Injection of an air bolus (<0.5 ml) prior to injection of sclerosant can displace blood in the vein and ensure intravascular needle location. Air inadvertently introduced into the tissues is not as damaging as the sclerosant might be. **B** Three-point stretching of the skin allows for more accurate cannulation of the vessel. *B, Redrawn from Goldman MP, et al. Sclerotherapy, 5th edn. London: Mosby, 2011.*

eradicate the latter, minimizing side effects such as hyperpigmentation. Areas of vascular arborization (Fig. 155.9) should be treated before single discrete linear vessels are cannulated[34].

The utilization of alcohol in swabbing the skin prior to injection will decrease the index of refraction of light and thus make the vessels more visible at the skin surface. Brisk cannulation of veins causes minimal vascular trauma, less vasoconstriction, and less chance of extravasation of blood. Injection pressure is kept to a minimum by performing the injection slowly in order to prevent vascular distention, and to allow adequate time for the sclerosing agent to interact with the endothelium. A small amount of sclerosant is used at each injection site (0.1–0.4 ml) in order to minimize side effects such as telangiectatic matting, post-sclerosis pigmentation, and ulcerative necrosis due to extravasation. The sclerosing injection is stopped when the solution has filled the targeted veins. Injections are carried out at approximately 3–6 cm intervals until the entire vessel has been treated.

Foamed Detergent Solutions

A detergent solution such as sodium tetradecyl sulfate and polidocanol can be foamed to a thick consistency by rapidly agitating it with air or CO_2 in a ratio of solution to gas of 1 : 4 (see above). There are numerous advantages of using foam when treating larger varicosities. For instance, an increased quantity of solution can be injected over longer segments of veins. Also, a foamed sclerosing solution retains more of its potency, as the full concentration of the sclerosant is present on each microbubble, residing on the outer micelle. Due to persistence and increased potency, foamed agents reduce the number of necessary treatments and allow treatment of larger vessels. In contrast, for smaller vessels, non-foamable glycerin and hypertonic saline are rapidly diluted and they act only within their concentration gradients, thus limiting the extent and intensity of sclerosing action. It is not practical to treat large veins with glycerin or hypertonic saline, as more frequent injections would be necessary and the potency rapidly diminishes due to the concentration being rapidly diluted by blood within the treated vein.

Treatment sessions are carried out at 6- to 8-week intervals in order to allow enough time for full endosclerosis to occur and for post-treatment inflammation to resolve, and to evaluate the results of the previous treatment session. Most patients will require one to three treatment sessions in order to clear their legs of unwanted telangiectatic and reticular vessels. If a poor response is seen at the end of this treatment schedule, the dermatologic surgeon may:

- increase the concentration of sclerosant
- switch to another sclerosant
- re-examine the patient to find a possible source of reflux previously missed.

Lasers and Intense Pulsed Light Sources for Treatment of Telangiectasias

Laser and intense pulsed light (IPL) therapy of lower extremity vessels may have a synergistic effect when used in combination with sclerotherapy (see Ch. 137).

Fig. 155.9 Treatment of arborizing feeder veins. This therapeutic approach (arrow) diminishes the number of injections required in a given sclerotherapy treatment session, thus minimizing potential side effects. *Courtesy, Jean L Bolognia, MD.*

LARGER VARICOSE VEINS

The treatment of large-diameter blood vessels requires greater and more precise attention to details regarding anatomy and points of reflux[35]. Contraindications to treatment of large-diameter veins include pregnancy, lactation, allergy to the sclerosing agent, thrombophilia or a hypercoagulable state (see Table 105.9), non-ambulation, and non-compliance[36]. A foamed detergent is currently recommended as the sclerosing agent, with the concentration determined by the size of the vein to be injected (see Table 155.4).

Factors of importance in the treatment of large-diameter veins include:

1. An understanding of the precise anatomy of the varicosity under consideration for treatment.
2. Adherence to a rational treatment plan in which injections begin at the highest point of reflux, with progression to the next highest point in a proximal-to-distal direction.
3. Determination of the most significant reflux point[37,38].

The dermatologic surgeon must determine whether reflux originates in the deep venous system, GSV or SSV, or a perforator (see Figs 155.2 & 155.3). The veins which represent the primary source of reflux must be treated before secondary sources of reflux are treated. Duplex ultrasound guidance (see Table 155.3) is often helpful in the therapeutic approach to larger-diameter vessels, particularly those cases where the anatomy is so intricate that the point of reflux would otherwise be difficult to detect.

Several slightly modified techniques and/or positions for large-vein sclerotherapy have been described. Three positions for treating

large-diameter vessels are: (1) the standing supine elevation direct cannulation technique; (2) the multiple precannulation sites (MPS) technique; and (3) the supine cannulation (SC) technique[5,38,39].

In the *standing supine elevation direct cannulation* technique, the patient stands at first, causing the varices to bulge and become more visible (Fig. 155.10)[27]. Injection points are marked at primary sites of reflux into the superficial venous system and approximately every 3–4 cm along the vein to be treated. The patient is then placed in a supine or prone position, the vein is emptied to maximize sclerosant–endothelial contact, and a small volume of sclerosant is injected at each of the marked points along the vein to be treated. A 27- to 30-gauge needle on a 3 ml syringe is often employed for this technique. The needle is advanced while aspirating into the syringe until aspiration of dark venous blood indicates penetration of the lumen. Concentrated sclerosant (0.5–1.5 ml) is injected at each site, followed by massage, again to ensure maximum sclerosant–endothelial contact. The vein will appear visually contracted at the end of the treatment. Leg elevation for a minute following the injection of foam allows the larger veins to contract. This may result in further spread and better contact of the sclerosant with the endothelium, improving the clinical results.

In the *multiple precannulation sites* (MPS) variation, the patient initially stands, in order to induce the varices to bulge and become more visible. Injection points are marked at proximal as well as distal sites along the distended vein. The veins are subsequently cannulated with either a 23-gauge butterfly needle and tubing or a plastic intravenous cannula and extension tubing at *both* the proximal and distal sites[40].

The butterfly needles or cannulas must be firmly secured, as the patient then moves to the treatment table and elevates the extremity undergoing treatment. After an intravascular position has been verified, 2–3 ml of sclerosant is infused into the cannula and subsequently into the vein while the surrounding area is observed for swelling or other evidence of extravasation. In the majority of cases, a single proximal and a single distal injection point are sufficient to sclerose a large tortuous vessel[41].

The authors routinely use the *supine cannulation* (SC) position, as it is faster and has less risk of a vasovagal reaction when compared to the upright position. Just prior to injection, the detergent sclerosing solution is foamed by mixing one part sclerosing solution with four parts air or CO_2[42]. Larger veins are treated proximally to distally with an appropriate concentration of sclerosing solution (see Table 155.4).

In addition to delineating vascular anatomy, duplex ultrasonography (see Fig. 155.6) can be used to assess the vascular response to sclerotherapy, including that of large non-junctional varicose veins. Incomplete endosclerosis has a pattern of intravascular thrombosis (multiple echoes), with the vein lumen remaining partially patent. When sclerotherapy has been successful, the vein wall is thickened and non-compressible (non-echogenic)[35,43]. Duplex ultrasonography can also provide guidance during sclerotherapy with *foamed* sclerosing agents. The distribution of foamed sclerosant as it flows into the targeted vein is easily visible as a sparkling. This also decreases the chance for inadvertent arterial injection. Nowadays, Doppler guidance is no longer recommended.

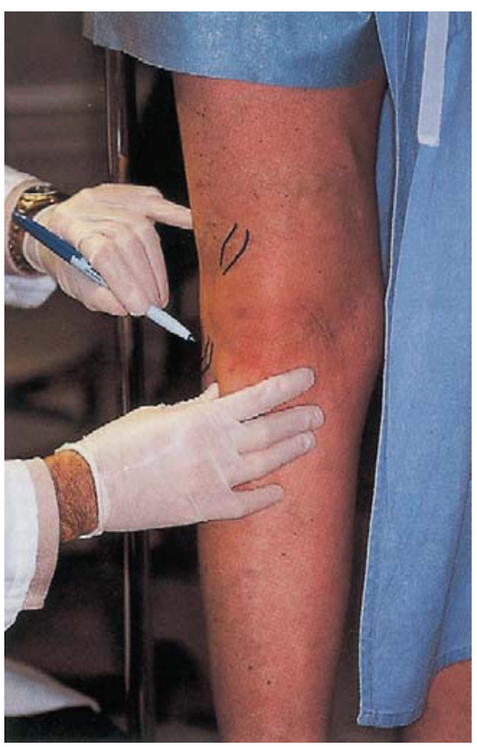


Fig. 155.10 Initial step prior to large-vein sclerotherapy. Marking of treatment sites in a standing position by indelible marker is performed. *Courtesy, Neil Sadick, MD*

POSTSCLEROTHERAPY COMPRESSION

Cotton-roll pads or foam pads may be applied along the entire course of the treated vessels and they are held in place by a compression garment. Graduated compression stockings that are class I (20–30 mmHg) or preferably class II (30–40 mmHg) are suggested for all patients following sclerotherapy of telangiectasias and reticular veins[15]. Patients should be instructed to walk 30 minutes after each treatment session, in order to minimize thromboembolic events as well as decrease the diameter of the superficial veins. The optimal duration of compression was shown in a recent study to be a minimum of 3 weeks of daytime wear, although 3 days of compression led to better results than no compression[15]. After large-vein sclerotherapy, we recommend 7 days of uninterrupted compression (24/7), during which the patient may bathe or shower by either placing a large plastic bag over the compression bandage or stocking or just allowing the stocking to get wet and then drying it with a hairdryer. After the first 7 days, the compression pads or cotton rolls are discarded and patients are permitted to remove the stocking, as needed, for bathing and sleeping. Ambulation is begun immediately post-treatment.

COMPLICATIONS

There are three major considerations when anticipating and managing complications of sclerotherapy (Table 155.7). The first is that fastidious technique will minimize the incidence of side effects. Second is an appropriate understanding of maneuvers that may be instituted if something is felt to go wrong. Finally, an appreciation of the management options available for adverse sequelae can minimize the intensity of complications when they occur[44].

Postsclerotherapy Pigmentation

The incidence of postsclerotherapy hyperpigmentation (Fig. 155.11) varies from 5% to 30%[24,42,45,46]. The purple–brown pigmentation has been shown to be due to extravascular deposits of hemosiderin[47]. Hypercoagulability syndromes such as antithrombin III, protein C or protein S deficiencies, use of nonsteroidal anti-inflammatory drugs

SCLEROTHERAPY COMPLICATIONS	
Cutaneous complications	**Extracutaneous complications**
EARLY	**EARLY**
• Localized urticaria • Bruising • Edema • Ischemia/necrosis (e.g. due to arterial injection, vasospasm, extravasation)	• Systemic allergic reactions (e.g. anaphylaxis) • Scotomata (with foam sclerosants) • Vasovagal syncope
DELAYED	**DELAYED**
• Superficial thrombophlebitis • Ulceration (secondary to ischemia/necrosis) • Hyperpigmentation • Telangiectatic matting (neoangiogenesis) • Hypertrichosis • Compression-related problems (folliculitis, irritant contact dermatitis)	• Deep venous thrombosis/pulmonary embolus • Nerve damage

Table 155.7 Sclerotherapy complications.

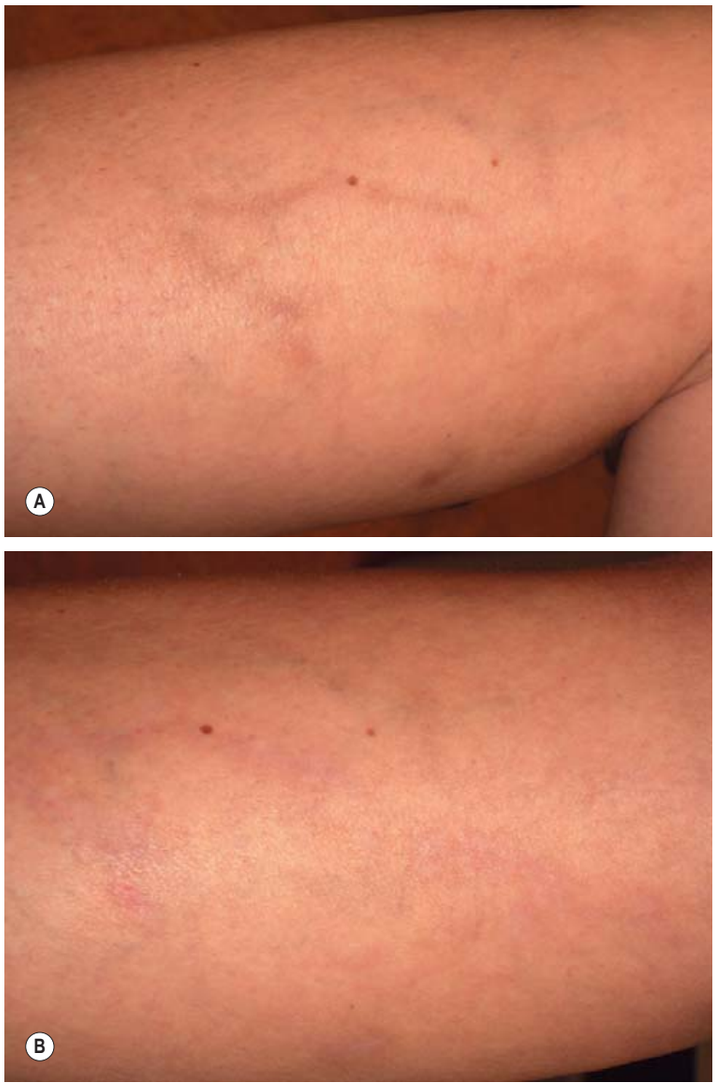


Fig. 155.11 Sclerotherapy-induced hyperpigmentation. A Development of hyperpigmentation along the course of a 3–4 mm diameter reticular vein 3 months after treatment with sodium tetradecyl sulfate 0.5% foam. **B** Six months after treatment with the Q-switched ruby laser at 6 J/cm^2, 5 mm diameter spot. Note complete resolution of hyperpigmentation.

(NSAIDs), high total body iron stores, use of minocycline, or the vessel fragility commonly noted in the elderly may predispose to this adverse sequela[48]. Methods to minimize the incidence of postsclerotherapy pigmentation are outlined in Table 155.8. Although various treatment modalities have been tried for this complication, only the utilization of the Q-switched ruby laser has shown any degree of reproducible success[49–51]. Pigmentation usually lasts for 6–12 months. If it persists, the dermatologic surgeon should search for a vessel with persistent reflux into the area or an underlying predisposition.

Telangiectatic Matting

Blushes or nets composed of very fine telangiectasias may occur around sites of previously injected veins or sites of previous surgical interruption, e.g. ligation or ambulatory phlebectomy (Fig. 155.12). They may occur from days to months after treatment and are seen in 5–15% of patients[24,42,52]. Sites of predilection include the thighs, medial malleolus, and medial and lateral calves. Risk factors include obesity, use of estrogen-containing medications, pregnancy and a family history of telangiectatic veins. Excessive postsclerotherapy inflammation may also predispose individuals to this complication, due to inadequate compression or exceeding the minimal sclerosant concentration (MSC) of the sclerosing solution.

Generally, telangiectatic matting resolves within 3–12 months without specific treatment. Persistence should lead the dermatologic surgeon to attempt to locate a source of reflux in the area (usually a feeding reticular vein), although matting may be a sign of underlying saphenous insufficiency. Low injection pressure utilizing the MSC is the most effective way to minimize this complication. Additional measures include the use of no more than 1 ml of sclerosant per injection site, limiting the injection blanch to 1–2 cm, encouraging normalization of weight, and discontinuation of oral contraceptives for 1 month prior and 2 months following sclerotherapy. Short-wavelength lasers (595–600 nm) and intense pulsed light sources as well as reinjection of vessels utilizing a glycerin solution are the most effective ways of managing this problem (see Table 155.4)[53].

Fig. 155.12 Telangiectatic matting (neoangiogenesis). This developed after vein surgery at the site of the scar.

METHODS TO MINIMIZE POSTSCLEROTHERAPY HYPERPIGMENTATION
PRETREATMENT PLANNING
• Evaluate for a hypercoagulable state in patients with a history of venous thrombosis (see Table 105.9) • Avoid treating patients with known defects in iron transport (e.g. hemochromatosis) • Avoid concomitant use of minocycline, aspirin or NSAIDs
TREATMENT TECHNIQUE
• Eliminate high-pressure reflux before treating smaller vessels • Select a sclerosant with the least inflammatory effects • Use a sclerosant concentration appropriate for the vessel size (see Table 155.4) • Minimize intravascular pressure by elevating the leg during treatment • Direct treatment at the deepest site in a telangiectatic cluster • Minimize risk of vessel rupture (e.g. by slow injection) • Avoid excessive syringe pressure
POST-TREATMENT CARE
• Apply compression immediately after treatment • Remove postsclerotherapy thrombi as early as possible

Table 155.8 Methods to minimize postsclerotherapy hyperpigmentation. NSAIDs, nonsteroidal anti-inflammatory drugs.

Ulceration

Cutaneous necrosis may occur with any sclerosing agent (although the authors have never seen this with glycerin). It may be the result of extravasation of a sclerosing agent into the perivascular tissues, which is especially common with the use of hypertonic saline and non-foamed sodium tetradecyl sulfate that is >1% in concentration (Fig. 155.13); injection into a dermal arteriole or an arteriovenous anastomosis; reactive vasospasm of such a vessel; or excessive cutaneous pressure created by compression techniques[54]. If there is extravasation of hypertonic saline into the perivascular tissue, infiltration of the area with normal saline may dilute the sclerosant. A hemorrhagic bulla may form over the area within 12–24 hours and later progress to an ulcer. If a porcelain-white area appears within the skin immediately after injection, this indicates arteriole injection or spasm. To reduce the likelihood of ulceration, the physician may rub a small amount of 2% nitroglycerin ointment into the area until a reactive hyperemia is seen. Since most ulcerations are less than 4 mm in diameter, second intention healing usually results in an acceptable scar. Larger ulcerations may be excised (as early as possible) and closed for faster healing and a smaller scar. Application of topical antibiotic ointments (e.g. mupirocin) and hydrocolloid or hydrophilic dressings may reduce the pain associated with the ulcer and speed the rate of healing[55].

Fig. 155.13 Postsclerotherapy necrotic ulceration due to extravasation of hypertonic saline. *Courtesy, Neil Sadick, MD*

Systemic Allergic Reaction

True allergic reactions following sclerotherapy treatments are extremely rare. Delayed hypersensitivity reactions, which may be urticarial or morbilliform in nature, can occur from 8 to 16 hours after treatment. Type I immediate reactions varying from urticaria to bronchospasm to anaphylaxis eventuating in cardiovascular collapse have been rarely reported. Intrinsically, only hypertonic saline has no potential to act as an allergen. However, the presence of additives such as benzoate or lidocaine may lead to the development of hypersensitivity reactions.

Sodium tetradecyl sulfate has a surprisingly low allergic potential (< 0.01%). The most commonly reported hypersensitivity reactions are morbilliform eruptions developing 30–90 minutes after injection[56]. Reactions to polidocanol are similarly rare (<0.01%). Both urticarial and morbilliform reactions have been reported, as well as a rare anaphylaxis-related fatality[56].

Antihistamines and oral corticosteroids (e.g. prednisone 40–60 mg/day for 7–10 days) can be used for the milder reactions, whereas intravenous corticosteroids and subcutaneous epinephrine are often required for more serious reactions.

Arterial Injection

The most feared complication in sclerotherapy is inadvertent injection into an artery. Arterial injection of a sclerosing agent produces a sludge embolus that obstructs small arteries as well as the microcirculation. The most common location for an arterial injection to occur is the popliteal fossa, when attempting to inject the small saphenous vein. After an intra-arterial injection, the patient usually notes immediate pain, but not always. A dusky cyanotic hue and pallor in the distribution of the injected artery usually occurs within a few minutes to several hours. Arterial pulsations in the posterior tibial or dorsalis pedis are not usually affected. Sloughing of superficial tissues may result in significant scarring or may even require amputation[57].

Arterial injection is a true sclerotherapy emergency. Immediate intervention has been advocated, but has never been proven to affect outcome. Procaine (1%), administered via periarterial infiltration, forms a complex with sodium tetradecyl sulfate, rendering it inactive; however, procaine is not effective for polidocanol. Cooling of the limb to minimize tissue anoxia, followed by immediate heparinization for 7–10 days and administration of intravenous dextran (10%, 500 mg daily) for 3 days is recommended. Thrombolysis and the utilization of long-term vasodilator therapy (e.g. calcium channel blockers) should be considered.

Miscellaneous Complications

Localized urticaria following injection is common and most likely related to mast cell degranulation and cytokine release. No treatment is indicated, although pretreatment with an H_1 antihistamine or immediate application of a class I ultra-potent topical corticosteroid may ameliorate the erythema, if bothersome to the patient. Compression-related problems such as ulcers, pressure bullae, contact dermatitis and folliculitis may be minimized by adherence to appropriate compression guidelines[44].

Nerve damage may occur secondary to direct injection of sclerosant or as a result of perivascular inflammation around nerve sheaths. The saphenous and sural veins of the inner leg and foot are high-risk locations and special care should be taken when injecting these locations. The utilization of NSAIDs may shorten the duration of symptoms[58].

Superficial thrombophlebitis develops 1–3 weeks after injection, presenting as tender erythematous induration of the injected vein. This complication is observed less often if compression is maintained for an adequate period of time following sclerotherapy. When superficial thrombophlebitis occurs, the thrombus should be evacuated and adequate compression, frequent ambulation, and aspirin or an NSAID instituted. The concomitant presence of deep vein thrombosis (DVT) must be considered[44], and a search for underlying causes for thrombophlebitis other than the sclerotherapy procedure may be warranted.

AMBULATORY PHLEBECTOMY

Ambulatory phlebectomy is an in-office surgical procedure designed for the complete removal of diseased venous segments by means of hook avulsion of the targeted vessel, developed in the 1950s by the Swiss dermatologist Robert Mueller[59]. All superficial veins, with the exception of the groin termination of the GSV, may be easily avulsed utilizing this technique. Large veins – in particular, well-demarcated branches of the GSV, SSV or perforators – can be avulsed through microstab incisions[59,60].

Preoperative Considerations

Doppler and duplex ultrasound evaluations are necessary in order to confirm the competence of the saphenofemoral and saphenopopliteal junctions, as well as that of the deep venous system[61]. The varicose veins to be removed are outlined with an indelible pen with the patient in a standing position. Marking of appropriate venous segments is the most important aspect of this procedure because it allows rapid isolation of desired venous segments to be removed. Because of potential shift of the vein up to 3 to 4 cm when moving from an upright vertical to a transverse horizontal position, the patient is then asked to lie in the operative position and confirmation of venous position by either Doppler or transepidermal illumination (Vein-Lite® or Venoscope®) with separate marking over the veins is performed. This double-marking technique has been found to be helpful in determining positional shift[62,63] (Fig. 155.14).

Anesthesia and Intraoperative Materials for Ambulatory Phlebectomy

Tumescent anesthesia has several advantages when performing ambulatory phlebectomy. These include: rapid anesthesia of an extensive segment of diseased vein; compression of the vein, allowing it to be removed through a 2–3 mm incision; and easier location of the vein owing to the temporary swelling and firmness of the soft tissues which press the vein against the skin. In addition, tumescent anesthesia reduces blood loss, diminishes bruising, eliminates multiple needle

Fig. 155.14 Double-marking technique for ambulatory phlebectomy. Outlining of the varicose veins while the patient is standing (black ink) and then while the patient is lying down in the operative position (green ink) utilizing transillumination.

sticks, and produces greater postoperative comfort. Most commonly, tumescent anesthesia comprised of 0.05% lidocaine with 1 : 1 000 000 epinephrine is employed (see Table 156.2)[64,65].

Instrumentation for the ambulatory phlebectomy procedure involves the use of a number of varied hook devices, which come in small, medium and large diameters (sizes 2 to 4) from various manufacturers. The ideal hook should have a comfortable grip to prevent fatigue and a sharp harpoon to catch the adventitia of the vein[59,66] (Fig.155.15).

Ambulatory Phlebectomy Technique

Microincisions measuring from 1 to 3 mm in length and parallel to the long axis of the extremity are made with an 18- or 16-gauge hypodermic needle or a #11 blade. The microincisions are made vertically and should follow the relaxed skin tension lines. The interval between incisions varies between 3 and 5 cm according to the patient and type of vein being removed. Separation of the vein from the surrounding adventitia may be accomplished by utilizing an iris scissor or blunt probe and should follow the tension lines of Langer[63].

The vein is then exteriorized utilizing the phlebectomy hook. Next, the exteriorized vein is clamped proximally and distally and pushed or pulled, depending on operator preference, from each end until the vein is avulsed (Fig. 155.16). A gentle rotation or rolling motion of the clamp in the same and/or opposite direction pulls and frees the vein from its secondary connective tissue sheath. The process is repeated at 3–5 cm intervals along the entire length of the marked vein, until the entire diseased vein has been removed or adequate interruption has been made[67,68].

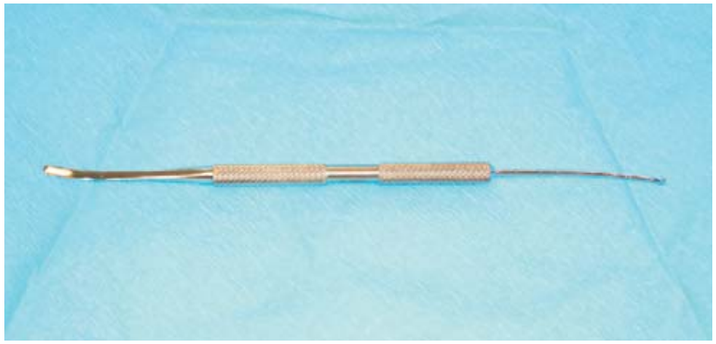


Fig. 155.15 Phlebectomy hook. A classic Mueller type of hook at one end and a Varaday dissector at the other end ("Goldman hook").

Special care is required in difficult anatomic zones such as the knees, ankles and feet. The "hooking" should be gentle and slow. Once the vein is hooked, it should come out easily. If it is difficult and if removal of the vein requires a lot of traction, it is possible that a fascial strand structure has been hooked. The hook should be removed, reintroduced, and another attempt should be made. Ambitious "hooking" in the ankle and foot region should be avoided in order to eliminate complications such as swelling, hematomas and nerve damage. Phlebectomy in the pretibial area should also be performed very carefully because many lymphatic vessels are normally located in this area. Aggressive damage to lymphatic vessels can result in a lymphocele. Phlebectomy in the popliteal area should be particularly gentle since the skin of the back of the knee is very soft and microincisions are very easily enlarged by overzealous "hooking".

Postoperative Considerations for Ambulatory Phlebectomy

Postoperatively, the area is cleansed and antibiotic ointment applied to the puncture sites. The leg is then wrapped, first with cotton gauze and then with an elastic compression dressing extending from the dorsum of the foot to the groin. This dressing helps to promote hemostasis, reduces swelling of the foot and leg, and speeds wound healing. The bandage is removed in 24 hours and a class II (30–40 mmHg) graduated compression stocking is then worn continuously for 1 week (24/7) and after that during working hours for 2–4 weeks.

Walking while the patient is still in the office is encouraged, to help mold the pressure wrap and uncover any persistent bleeding. This allows the patient to quickly return to a normal gait, thus generating normal function of the calf muscle pump, minimizing potential thromboembolic complications.

Complications of Ambulatory Phlebectomy

Ambulatory phlebectomy satisfactorily removes varicosities of different sizes, and it results in a series of micro-scars that are cosmetically pleasing to the patient and dermatologic surgeon. The entire procedure can be performed under local anesthesia on an ambulatory basis in all but the most severe and complicated cases[69,70]. Complications may be divided according to the system that has been affected (Table 155.9). The most common complication is the development of a lymphocele, which presents as a firm subcutaneous nodule. Simple aspiration with a 22-gauge needle of yellow–clear lymphatic fluid should be performed every few days, with immediate compression over the drained area. Resolution typically occurs after two to three drainage sessions.

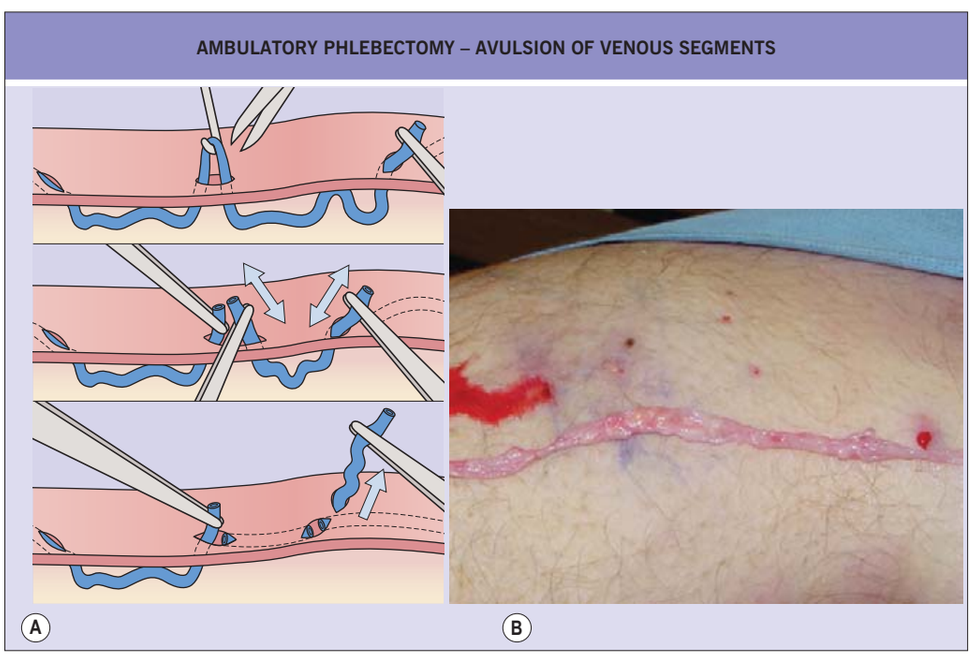


Fig. 155.16 Ambulatory phlebectomy – avulsion of venous segments. A After pinpoint incisions, the dilated vein is hooked at several sites and incised; the venous segments are clamped both proximally and distally and then pulled and rolled to free them from their attachments to the surrounding adventitia. **B** Avulsed segment of the varicose vein next to pinpoint incisions. *A, Redrawn from Ricci S, Georgiev M, Goldman MP. Ambulatory Phlebectomy: A Practical Guide to Stab Avulsion Variectomey, 2nd edn. London: Taylor & Francis, 2005.*

COMPLICATIONS OF AMBULATORY PHLEBECTOMY
ANESTHETIC COMPLICATIONS
Allergic reaction
VASCULAR COMPLICATIONS
Bleeding, seroma Superficial thrombophlebitis Deep venous thrombosis/pulmonary embolus Telangiectatic matting Lymphocele Persistent edema
NEUROLOGIC COMPLICATIONS
Nerve damage around the ankle Hypesthesia (temporary) Dysesthesia (temporary or permanent) Traumatic neuroma
CUTANEOUS COMPLICATIONS (OTHER THAN VASCULAR SEQUELAE)
Skin necrosis (blistering, ulceration) related to the procedure or compression bandage Postoperative infection (e.g. cellulitis) Hypo- or hyperpigmentation of the microincision Dimpling Tattooing with marking pen ink Talc granuloma

Table 155.9 Complications of ambulatory phlebectomy.

Fig. 155.17 Endovenous laser ablation. Insertion of the diode laser fiber (815 nm) into the great saphenous vein under duplex ultrasonography guidance. *Courtesy, Neil Sadick, MD.*

ENDOVENOUS LASER AND RADIOFREQUENCY ABLATION

Endovenous technologies, which incorporate either laser- or RF-induced thermal damage, have replaced saphenofemoral/saphenopopliteal ligation and stripping procedures. Lasers can be used by placing an optic fiber endoluminally and utilizing various lasers (810, 940, 980, 1064, 1320, 1440, 1500 nm). Typically, the laser fiber or the catheter containing the insulated electrode is inserted into the GSV either under duplex guidance (Fig. 155.17) or through exteriorization of the GSV via a variation of ambulatory phlebectomy.

Mechanism of Action

With the 810–1064 nm lasers, the heat energy created by heating of blood causes thermal destruction and contraction of the vein wall[71–75]. The 1320, 1440 and 1500 nm lasers operate by targeting water, not blood, so that the vein wall absorbs most of the energy and results in a more controlled, uniform heating. Also, because tissue water is the target of these lasers (1320, 1440, 1500 nm), the presence of red blood cells (and hemoglobin) within the vessels is not required as it is for the other lasers with shorter wavelengths.

In endovenous RF closure (ablation), a catheter containing an insulated electrode delivers RF energy-generated heat directly to the vein wall, resulting in endothelial denudation, collagen fibril shortening and thickening, and contraction of the vein, with subsequent vein occlusion.

Comparative Clinical Results

In a comparison of GSVs treated endovenously with the 810 nm diode laser (n = 36), the 1320 nm Nd:YAG laser (n = 42), or RF closure (n = 174), a 95% success rate and no adverse effects were observed with the latter two modalities[76]. Treatment with the 810 nm diode laser led to an 86% success rate and adverse effects in 53% of patients. The most common adverse effects were significant pain with ambulation for 2–3 days and significant bruising. The 1320 nm Nd:YAG laser was also associated with fewer side effects when compared to the 940 nm diode laser for endovenous treatment of the GSV[77]; treatment-related pain and the use of analgesics were significantly less.

In a group of 24 patients treated with the 1320 nm Nd:YAG laser, and then observed for 6 to 12 months, 100% efficacy was reported without evidence of vessel perforation[78]. With over 10 years of clinical follow-up, one author (MG) has observed a 10% recurrence rate of GSV incompetence, while the other author (RW) has not observed any recurrences.

Surgical Technique

The patient is evaluated clinically in both a standing and a supine position and double-marked, as with ambulatory phlebectomy (see above). Tumescent anesthesia is then delivered along the course of the vein to be treated.

Endovenous laser ablation (EVLA)

A laser fiber with a 600 micron diameter is inserted into the vein. When the laser is on, a helium–neon (He:Ne) aiming beam is continuously illuminated, helping to ensure that the laser fiber is in the superficial venous system. Correct placement of the laser fiber tip 20 cm distal to the SFJ is confirmed via direct visualization with duplex ultrasonography and secondarily by laser fiber measurement and viewing of the He:Ne aiming beam through the skin. Utilization of an automated catheter drawback system, set at 1 mm/second, provides uniform heating of the vessel.

Endovenous laser treatment is stopped when the distal tip of the fiber reaches a point 1 to 3 cm from the vein entry site. This can also be confirmed with direct visualization of the aiming beam through the skin or more typically by duplex ultrasonography. Total laser application time is then recorded. Repeat duplex ultrasonography of the saphenous vein is performed to confirm successful treatment. If unsuccessful, it is typically difficult to retreat the vein at this point and a subsequent session may be required. After the terminal portion of the vein (immediately adjacent to the point of entry) has been treated, the catheter/sheath and fiber are withdrawn and manual pressure is applied to the puncture site. If clinically indicated, ambulatory phlebectomy and/or sclerotherapy of tributaries are then performed (see below).

Endovenous radiofrequency (RF) closure (ablation)

Heat generated by RF energy is also used to occlude veins. An endovenous catheter-based approach is employed in which a specially designed insulated electrode that is 7 cm in length delivers the RF energy-induced heat directly to the vein wall (VNUS Closure™ procedure). The vein is treated in fixed 7 cm segments.

In the most recent design modification (VNUS ClosureFAST™ catheter; Fig 155.18), the endovenous catheter is held in place while energy heats it to the specified temperature of 120°C. Because the temperature increase remains localized to a narrow rim around the active electrode, this process is believed to be relatively safe. Proper use of the RF device does require close, stable contact between the active electrode and the vessel wall and it requires tumescent anesthesia to allow contact of the vein wall with the central 7 cm metal core. By strictly controlling the temperature, boiling, vaporization and carbonization of the tissue

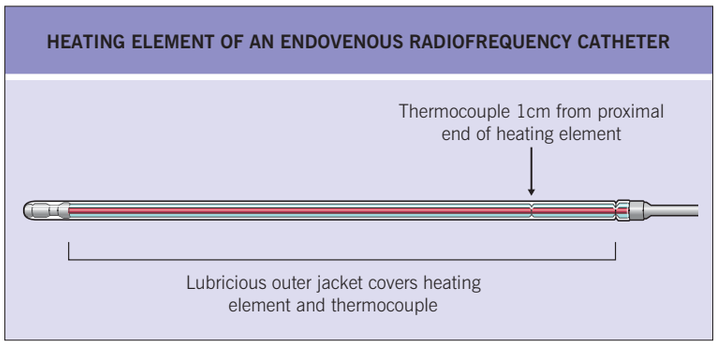


Fig. 155.18 Heating element of an endovenous radiofrequency catheter (VNUS ClosureFAST™ catheter). After heating to 120°C, 7 cm segments of the varicose vein are treated.

is avoided. Ten years of clinical experience suggest that the RF endovenous procedure is highly effective at occluding saphenous veins and abolishing reflux. Of note, it is associated with a rapid reduction in lower extremity pain, fatigue, aching and CEAP clinical class.

General anesthesia is the most significant risk factor for developing DVT and the failure to use tumescent local anesthesia is the major risk factor for developing skin burns. In our clinical practices, tumescent anesthesia is always used in non-sedated patients and no skin injuries or thrombi have been observed to date. Some bruising from the tumescent anesthesia can occur and anesthesia of the treated portion of the leg may persist for 8 to 24 hours. It is advisable to limit endovenous RF treatment to the GSV segment above the knee in order to minimize the risk of paresthesias due to injury to the saphenous nerve. Collectively, two of our patients have developed focal numbness (4 cm in diameter) on the lower medial leg, which resolved within 6 months.

Combination with Ambulatory Phlebectomy

Based upon our experience in over 500 patients, the combination of endovenous ablation techniques with ambulatory phlebectomy can be very effective in eliminating saphenous reflux along with varicose tributaries. As outlined above, following the double-marking of varicose veins, the area surrounding the GSV and distal tributaries to be treated is infiltrated with tumescent anesthesia. Usually 20 cm inferior to the SFJ (mid medial thigh), the GSV can be accessed through a 2–3 mm incision. The GSV is then treated with the endovenous ablation technique (RF or laser) and the varicose tributaries are removed via standard ambulatory phlebectomy technique. A ligature is placed on the exposed portion of the GSV.

At the conclusion of the surgery, the entire leg is wrapped in a short stretch compression bandage over copious padding that has been placed on the sites where the varicose veins were removed via phlebectomy. The tiny incisions are not sutured as these open 2 mm incisions allow for drainage of the anesthetic solution over the next 24 hours. This helps to minimize swelling and bruising. The patient is seen the next day, the compression bandage is removed, and the leg is examined for hematoma formation or other adverse sequelae. All incisions are covered with antibacterial ointment and a Band-Aid® and a class II (30–40 mmHg) graduated stocking is applied. The latter is left on 24 hours a day for 1 week (as compared to 3 days if only RF ablation is performed).

The major complications of endovenous laser or RF treatment plus ambulatory phlebectomy are temporary pigmentation over the treated vein, temporary nerve damage, hematoma, localized superficial thrombophlebitis, and temporary lymphocele. All other adverse effects are extremely rare. For a complete discussion, see reference 79.

CONCLUSIONS

Sclerotherapy, ambulatory phlebectomy, and endovenous vein ablation techniques are excellent techniques for both cosmetic and symptomatic venous disease[80]. Although they all require some additional training and knowledge of superficial venous anatomy and physiology, remarkable medical and cosmetic improvements in the sensation and appearance of legs can be achieved. Thus, the dermatologic surgeon now has the ability to treat all forms of varicose and telangiectatic leg veins from the largest to the smallest.

REFERENCES

1. Boisseau MR. Venous valves in the legs: hemodynamic and biological problems and relationship to physiopathology. J Mal Vasc. 1997;22:122–7.
2. Griton P, Vanet P, Cloarec M. Anatomic and functional features of venous valves. J Mal Vasc. 1997;22:97–100.
3. Labropoulos N, Giannoukas AD, Nicolaides AN, et al. The role of venous reflux and calf muscle pump function in nonthrombotic chronic venous insufficiency. Correlation with severity of signs and symptoms. Arch Surg. 1996;131:403–6.
4. Labropoulos N, Delis K, Mansour MA, et al. Prevalence and clinical significance of posterolateral thigh perforator vein incompetence. J Vasc Surg. 1997;26:743–8.
5. Goldman M, Bergan J, Guex J-J. Sclerotherapy. St Louis: Mosby, 2006.
6. Butie A. Clinical examination of varicose veins. Dermatol Surg. 1995;21:52–6.
7. Kistner RL, Elkof B, Masuda EM. Diagnosis of chronic venous disease of the lower extremities: the 'CEAP' classification. Mayo Clin Proc. 1996;71:338–45.
8. Furderer CR. Les crosses sapheniennes. anatomie et concepts therapeutiques. Phlebologie. 1986;39: 3–14.
9. Weiss RA. Evaluation of the venous system by Doppler ultrasound and photophlethysmography or light reflection rheography before sclerotherapy. Semin Dermatol. 1993;12:78–87.
10. Weiss RA. Vascular studies of the legs for venous or arterial disease. Dermatol Clin. 1994;12:175–90.
11. Weiss RA, Weiss MA. Continuous wave venous Doppler examination for pretreatment diagnosis of varicose and telangiectatic veins. Dermatol Surg. 1995;21:58–62.
12. Thibault PK. Duplex examination. Dermatol Surg. 1995;21:77–82.
13. Veraart JCJM, Neumann HAM. Interface pressure measurements underneath elastic and non-elastic bandages. Phlebologie. 1996;1(suppl,):56–9.
14. Veraart JCJM, Koster D, Neumann HAM. Compression therapy and the pressure in the deep venous system. Phlebologie. 1996;1(suppl.):68–73.
15. Weiss RA, Sadick NS, Goldman MP, Weiss MA. Post-sclerotherapy compression: controlled comparative study of duration and its effect on clinical outcome. Dermatol Surg. 1999;25:105–8.
16. Carlin MC, Ratz JL. Treatment of telangiectasia: comparison of sclerosing agents. J Dermatol Surg Oncol. 1987;13:1181–4.
17. Sadick NS. Advances in sclerosing solutions. Cosmet Dermatol. 1996;20:313–16.
18. Sadick NS. Hyperosmolar versus detergent sclerosing agents in sclerotherapy. Effect on distal vessel obliteration. J Dermatol Surg Oncol. 1994;20: 313–16.
19. Goldman MP. A comparison of sclerosing agents. Clinical and histologic effects of intravascular sodium morrhuate, ethanolamine oleate, hypertonic saline (11.7%) and sclerodex in the dorsal rabbit ear vein. J Dermatol Surg Oncol. 1991;17:354–62.
20. Sadick NS. Sclerotherapy of varicose and telangiectatic leg veins. Minimal sclerosant concentration of hypertonic saline and its relationship to vessel diameter. J Dermatol Surg Oncol. 1991;20:65–70.
21. Weiss RA, Goldman MP. Advances in sclerotherapy. Dermatol Clin. 1995;13:431–45.
22. Sadick NS. Treatment of varicose and telangiectatic leg veins with hypertonic saline: a comparative study of heparin and saline. J Dermatol Surg Oncol. 1995;16:24–8.
23. Sadick NS, Farber B. A microbiologic study of diluted sclerotherapy solutions. J Dermatol Surg Oncol. 1993;19:450–4.
24. Leach BC, Goldman MP. Comparative trial between sodium tetradecyl sulfate and glycerin in the treatment of telangiectatic leg veins. Dermatol Surg. 2003;29: 612–15.
25. Weiss MA, Weiss RA, Goldman MP. Sclerotherapy: how minor varicosities cause leg pain. Contemp Ob Gyn. 1991;36:113–25.
26. Weiss MA, Weiss RA. Sclerotherapy. Curr Opin Dermatol. 1997;4:167–74.
27. Goldman MP, Weiss RA, Bergan JJ. Diagnosis and treatment of varicose veins: a review. J Am Acad Dermatol. 1994;31:393–413.
28. Goldman MP, Bennett RG. Treatment of telangiectasia: a review. J Am Acad Dermatol. 1987;17:167–82.
29. Baccaglini H, Spreafico G, Castro C, Sorrentino P. Consensus conference on sclerotherapy of varicose veins of the lower limbs. Phlebologie. 1997;12:2–16.
30. Guex J-J. Microsclerotherapy. Semin Dermatol. 1993;12:129–34.
31. Duffy DM. Sclerotherapy. Clin Dermatol. 1992;10:373–80.
32. Bodian EL. Techniques for sclerotherapy for sunburst venous blemishes. J Dermatol Surg Oncol. 1985;11:696–704.
33. Duffy DM. Small vessel sclerotherapy: an overview. Adv Dermatol. 1988;13:221–42.
34. Goldman MP. Advances in sclerotherapy treatment of varicose and telangiectatic leg vein. Am J Cosmet Surg. 1992;9:235–40.
35. Zummo M, Forrestal M. Sclerotherapy of the long saphenous vein – a prospective Duplex controlled comparative study. Phlebologie. 1995;(Suppl. 1):571–3.
36. Baccaglini B, Spreafico G, Costoro C, Sorrentino P. Sclerotherapy of varicose veins of the lower limbs. Consensus paper. Dermatol Surg. 1996;22:883–9.
37. Cornu-Thenard A, de Cottreau H, Weiss RA. Sclerotherapy. Continuous wave Doppler-guided injections. Dermatol Surg. 1995;21:867–70.
38. de Groot WP. Practical phlebology. Sclerotherapy of large veins. J Dermatol Surg Oncol. 1991;17:589–95.
39. Gallagher PL. Varicose veins – primary treatment with sclerotherapy. A personal appraisal. J Dermatol Surg Oncol. 1992;18:39–42.

40. Marley WM, Marley NF. Sclerotherapy treatment of varicose veins. Semin Dermatol. 1993;12:98–101.
41. Orbach EJ. Sclerotherapy of varicose veins. Utilization of intravenous air-block technique. Am J Surg. 1944;66:362–6.
42. Barrett JM, Allen B, Ockelford A, Goldman MD. Microfoam ultrasound guided sclerotherapy of varicose veins in 100 legs. Dermatol Surg. 2004;30:6–12.
43. Raymond-Martimbeau P. Advanced sclerotherapy treatment of varicose veins with duplex ultrasonographic guidance. Semin Dermatol. 1993;12:123–8.
44. Leibaschoff G, Brizzio E, Ferreira J, Banf J. Prevention of iatrogenic complications in the treatment of varicosities. Am J Cosmet Surg. 1994;11:51–3.
45. Georgiev M. Postsclerotherapy hyperpigmentations: a one-year follow-up. J Dermatol Surg Oncol. 1990;16:608–10.
46. Georgiev M. Postsclerotherapy hyperpigmentations. Chromated glycerin as a screen for patients at risk (a retrospective study). J Dermatol Surg Oncol. 1993;19:649–52.
47. Thibault P, Wlodarczyk J. Postsclerotherapy hyperpigmentation. The role of serum ferritin levels and the effectiveness of treatment with the copper vapor laser. J Dermatol Surg Oncol. 1992;18:47–52.
48. Goldman MP. Post-sclerotherapy hyperpigmentation: treatment with a flashlamp-excited pulsed dye laser. J Dermatol Surg Oncol. 1992;18:417–22.
49. Goldman MP, Kaplan RP, Duffy DM. Postsclerotherapy hyperpigmentation: a histologic evaluation. J Dermatol Surg Oncol. 1987;13:547–50.
50. Scott C, Seiger E. Postsclerotherapy pigmentation. Is serum ferritin level an accurate indicator? Dermatol Surg. 1997;23:281–3.
51. Tafazzoli A, Rostan E, Goldman MP. Q-switched ruby laser treatment for postsclerotherapy hyperpigmentation. Dermatol Surg. 2000;26:653–6.
52. Goldman MP, Sadick NS, Weiss RA. Cutaneous necrosis, telangiectatic matting, and hyperpigmentation following sclerotherapy. Etiology, prevention and treatment. Dermatol Surg. 1995;21:19–29.
53. Davis LT, Duffy DM. Determination of incidence and risk factors for post-sclerotherapy telangiectatic matting of the lower extremity: a retrospective analysis. J Dermatol Surg Oncol. 1990;16:327–30.
54. Zimmet SE. The prevention of cutaneous necrosis following extravasation of hypertonic saline and sodium tetradecyl sulfate. J Dermatol Surg Oncol. 1993;19:641–6.
55. Zimmet SE. Hyaluronidase in the prevention of sclerotherapy-induced extravasation necrosis. A dose-response study. Dermatol Surg. 1996;22:73–6.
56. Weiss RA, Weiss MA. Incidence of side effects in the treatment of telangiectasias by compression sclerotherapy: hypertonic saline vs. polidocanol. J Dermatol Surg Oncol. 1990;16:800–4.
57. Biegeleisen K, Neilson RD, O'Shaughnessy A. Inadvertent intra-arterial injection complicating ordinary and ultrasound-guided sclerotherapy. J Dermatol Surg Oncol. 1993;19:953–8.
58. Thibault PK, Wlodarczyk J. Correlation of serum ferritin levels and postsclerotherapy pigmentation. A prospective study. J Dermatol Surg Oncol. 1994;20:684–6.
59. Goldman MP, Geogiev M, Ricci S. Ambulatory Phlebectomy: A Practical Guide for Treating Varicose Veins, 2nd edn. New York: Taylor Francis, 2005.
60. Garde C. Cryosurgery of varicose veins. J Dermatol Surg Oncol. 1994;20:56–8.
61. Georgiev M, Ricci S, Carbone D, et al. Stab avulsion of the short saphenous vein. Technique and duplex evaluation. J Dermatol Surg Oncol. 1993;19:456–64.
62. Neumann HAM. Ambulatory minisurgical phlebectomy. J Dermatol Surg Oncol. 1992;18:53–4.
63. Weiss RA, Goldman MP. Transillumination mapping prior to ambulatory phlebectomy. Dermatol Surg. 1998;24:447–50.
64. Olivencia JA. Maneuver to facilitate ambulatory phlebectomy. Dermatol Surg. 1996;22:654–5.
65. Smith SR, Goldman MP. Tumescent anesthesia in ambulatory phlebectomy. Dermatol Surg. 1988;24:453–6.
66. Ramelet AA. Muller phlebectomy. A new phlebectomy hook. J Dermatol Surg Oncol. 1991;17:814–16.
67. Sadick NS, Schanzer H. Combined high ligation and stab avulsion for varicose veins in an outpatient setting. Dermatol Surg. 1998;24:475–9.
68. Sadick NS. Multi-focal pull-through endovascular cannulation technique of ambulatory phlebectomy. Dermatol Surg. 2002;28:32–7.
69. Ramelet AA. Complications of ambulatory phlebectomy. Dermatol Surg. 1997;23: 947–54.
70. Olivencia JA. Complications of ambulatory phlebectomy. Review of 1000 consecutive cases. Dermatol Surg. 1997;23:51–4.
71. Proebstle TM, Sandhofer MD, Kargl A, et al. Thermal damage of the inner vein wall during endovenous laser treatment: key role of energy absorption by intravascular blood. Dermatol Surg. 2001;28:596–600.
72. Weiss RA. Comparison of endovascular radiofrequency versus 810 nm diode laser occlusion of large veins in an optimal model. Dermatol Surg. 2002;28:56–61.
73. Novarro L, Min RJ, Bone C. Endovenous laser: a new minimally invasive method of treatment for varicose veins: preliminary observations using an 810 nm diode laser. Dermatol Surg. 2001;27:117–22.
74. Goldman MP. Intravascular lasers in the treatment of varicose veins. J Cosmet Dermatol. 2004;3:162–6.
75. Goldman MP, Mauricio M, Rao J. Intravascular 1320nm laser closure of the great saphenous vein: a 6–12 month follow-up study. Dermatol Surg. 2004;30:1380–5.
76. Weiss RA, Munavalli G, Bellew SG, Beasley K. Comparison of endovenous saphenous vein obliteration techniques: 810 nm versus 1320 nm versus radiofrequency. Lasers Surg Med. 2005;S17:34.
77. Proebstle TM, Moehler T, Gul D, Herdemann S. Endovenous treatment of the great saphenous vein using a 1,320 nm Nd:YAG laser causes fewer side effects than using a 940 nm diode laser. Dermatol Surg. 2005;31;1678–83.
78. Goldman MP, Mauricio M, Rao J. Intravascular 1320-nm laser closure of the great saphenous vein: a 6- to 12-month follow-up study. Dermatol Surg. 2004;30:1380–5.
79. Goldman MP, Weiss RA. Ambulatory phlebectomy and endolumenal closure of varicose veins. In: Robinson JK, Hanke CW, Sengelmann RD, Siegel DM (eds). Surgery of the Skin: Procedural Dermatology, 2nd edn. Philadelphia: Elsevier Mosby, 2010:589–600.
80. Alam M, Nguyen T (eds). Treatment of Leg Veins (Procedures in Cosmetic Dermatology). Philadelphia: Saunders, 2006.

Liposuction 156

William P Coleman III, Timothy C Flynn and Kyle M Coleman

Chapter Contents

Description of techniques 2528
Instrumentation 2529
Postoperative care 2532
Complications 2533

Synonyms: ■ Liposculpture ■ Tumescent liposuction ■ Lipoplasty ■ Fat suction

Key features

- Liposuction is indicated for spot reduction of localized adiposities
- Liposuction is ideally suited for healthy patients who are near their ideal body weight
- The tumescent local anesthetic technique is the safest approach to anesthesia for liposuction
- Liposuction consists of destruction and aspiration of lipocytes through criss-crossing tunnels in the subcutaneous tissue
- Non-cosmetic uses for liposuction include treatment of hyperhidrosis and lipomas as well as breast reduction

INTRODUCTION AND BACKGROUND

Liposuction is an effective method for surgically improving localized areas of excess subcutaneous fat. Modern liposuction is performed using dilute local anesthesia via the tumescent technique, together with small cannulas connected to a vacuum aspirator. Liposuction can be safely performed in an office setting, and conservative techniques ensure few complications. Substantial amounts of fat can be aspirated with minimal blood loss and excellent aesthetic results.

The history of modern liposuction traces its roots back to 1975, when Drs Arpad and Giorgio Fischer developed hollow cannulas attached to a suction source which, when placed subcutaneously, were capable of aspirating subcutaneous fat[1]. In Paris, Illouz developed updated equipment for performing liposuction. He also promoted the concept of a "wet technique" in which saline was injected into the fat before suctioning[2]. Pierre Fournier further refined the techniques of liposuction, teaching many physicians around the world. He popularized the idea of postoperative compression to help support the suctioned tissue following surgery[3].

American dermatologic surgeons including Lawrence Field, Rhoda Narins, Samuel Stegman, William Coleman and Bruce Chrisman learned the technique early on and advanced the field[4]. Jeffrey Klein developed the tumescent technique in 1985, which allowed liposuction under local anesthesia with minimal blood loss, vastly increasing the safety of the procedure[5–8]. The American Academy of Dermatology and the American Society for Dermatologic Surgery promoted education in liposuction in the Core Surgical Curriculum in Dermatology as early as 1987[9]. Importantly, the American Academy of Dermatology was the first specialty organization to approve and publish clinical guidelines of care for liposuction in 1991, which have been subsequently updated[10].

Liposuction is currently among the most common cosmetic procedures performed in the US. A conservative estimate is that there are now between 300 000 and 400 000 procedures performed in the US annually[11].

INDICATIONS AND CONTRAINDICATIONS

Tumescent liposuction is indicated for improving localized adiposities. Certain areas of subcutaneous fat are often not fully responsive to diet and exercise alone[12], and excessive dieting or caloric expenditure as a means of improving body shape can have serious health consequences.

Most liposuction patients complain that the troublesome areas of fat excess "run in the family". Furthermore, these areas of excess subcutaneous fat can be resistant to caloric restriction or exercise. Tumescent liposuction is a procedure that is able to specifically target these localized areas of excess subcutaneous fat. Thus, it is a complement to, not a replacement for, diet and exercise.

Liposuction can be used to treat localized areas of adiposities from the face to the ankles. Common areas improved by liposuction include the abdomen (Fig. 156.1) and inner and outer thighs on women (Fig. 156.2). Other sites include the neck and jowls (Fig. 156.3), male and female breasts, back, flanks (Fig. 156.4), hips (see Fig. 156.2), buttocks, upper arms, knees (Fig. 156.5), calves and ankles. Genetic predisposition determines the location of excess fat storage in each individual.

Non-cosmetic indications for liposuction include aspiration of lipomas[13–15] (Table 156.1). Liposuction is an effective technique for debulking these benign tumors, and, often, large lipomas can be successfully treated, leaving only minimal scars. Liposuction is also an excellent alternative for treating axillary hyperhidrosis by destroying eccrine and apocrine glands (Fig 156.6)[15].

Contraindications are outlined in Table 156.2.

PREOPERATIVE HISTORY AND CONSIDERATIONS

As with any other medical or surgical consultation, a pertinent review of the past medical history, medications and allergies is essential. The review of systems should be comprehensive enough to exclude any underlying abnormalities which would preclude or modify surgery. Social and psychiatric histories may reveal details which would make the patient an inappropriate candidate for cosmetic surgery.

The physical examination for liposuction should be performed with patients completely unclothed in the body areas of concern to them. Tight-fitting undergarments can distort fatty bulges and mask contours. The patient should be examined standing up so that the full effects of gravity are apparent. Physical examination consists of both observation and palpation. Grasping the skin and fatty tissues using a "pinch test" technique will reveal the thickness of areas of adiposity as well as the firmness of underlying fat. The surgeon should look for asymmetries, scars, hernias, musculoskeletal abnormalities, signs of previous liposuction, dimples, skin laxity, and overlying cutaneous lesions. During this examination, it is useful to describe any abnormalities detected to the patient. This will add to the patient's understanding and can show him or her what may or may not be able to be achieved through liposuction. It is important to accurately describe individual body parts in words that the patient will understand, pointing them out as reinforcement. Colloquialisms may lead to confusion about which anatomic part is being discussed. A diagram of typical anatomic sites for liposuction may prove helpful (Fig. 156.7). Also, it is important to remember that the patient has a different vantage point looking down at the areas of adiposity; photography may be helpful during this

consultation period to be sure that the physician and patient are in agreement.

The presence of obesity and/or poor muscle tone are warning signs that the patient may not be an appropriate candidate for liposuction. A small minority of physicians perform liposuction on obese patients. These large-volume extractions are intrinsically more dangerous, especially when performed on patients who are poor-risk candidates for anesthesia due to their obesity. The notion that atherosclerotic heart disease and diabetes mellitus can be improved with liposuction is still unproven[15].

Some patients are relatively slender except for the abdominal area. Upon physical examination, it is obvious that most of their fat is stored around the viscera. Palpation of the abdominal tissues reveals a firm underlying musculature with very little fat on the pinch test. These patients not only are poor candidates for liposuction but also are at increased risk for cardiovascular disease. This physical finding is most common in men but can be seen in women as well. The surgeon should have a frank discussion with these patients about the implications of the genetic tendency to store fat around the viscera and recommend consultation with an internist and appropriate nutritional experts.

In general, operating on over 10% of the body increases liposuction risks. Guidelines of care published by dermatologic organizations recommend fat extractions of less than 4500–5000 ml[16,17]. This volume should be considered as an uppermost limit; beyond this, profound fluid shifts may occur, resulting in cardiovascular compromise. Many experienced liposuction surgeons rarely, if ever, remove anywhere near 5000 ml in a single session. Larger extractions also necessitate larger infiltrations of local anesthetics. When the tumescent technique is employed, guidelines of care recommend not exceeding a lidocaine dose of 55 mg/kg[10,17,18]. In slender patients, this should probably be adjusted down to 45 mg/kg. These dose limits also restrict the number of areas that can be treated during a single liposuction procedure.

If, in the physician's judgment, it is risky to treat all of the areas that concern the patient, serial liposuction should be recommended. These separate surgeries can be spaced days or months apart, according to the patient's preference.

If there are any questions about the patient's medical status, consultation with the appropriate specialist should be planned well ahead of the anticipated date of liposuction to be certain that the patient is healthy enough to undergo surgery. In some cases, psychiatric evaluation or consultation with the patient's current psychiatrist may be needed to help the surgeon determine if the patient is an appropriate candidate.

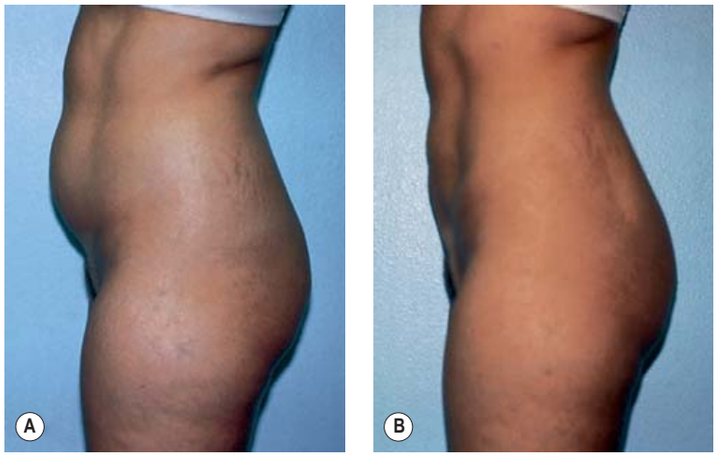


Fig. 156.1 Liposuction of the upper and lower abdomen. A Preoperative. **B** Postoperative, showing improved contours. *Courtesy, WP Coleman III, MD.*

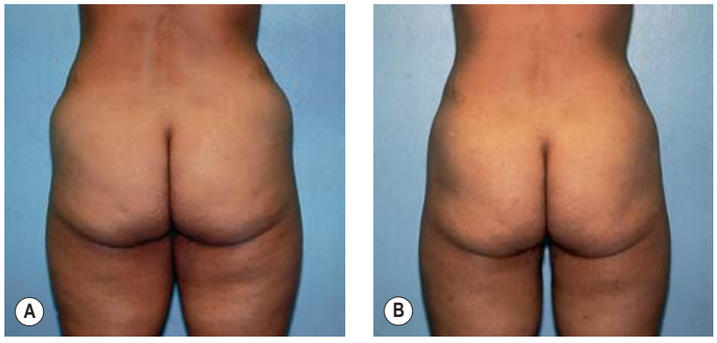


Fig. 156.2 Liposuction of the inner and outer thighs and hips. A Preoperative. **B** Postoperative, showing improved contours. *Courtesy, WP Coleman III, MD.*

Fig. 156.3 Liposuction of the neck and jowls. A Preoperative. **B** Postoperative, showing improved appearance. *Courtesy, WP Coleman III, MD.*

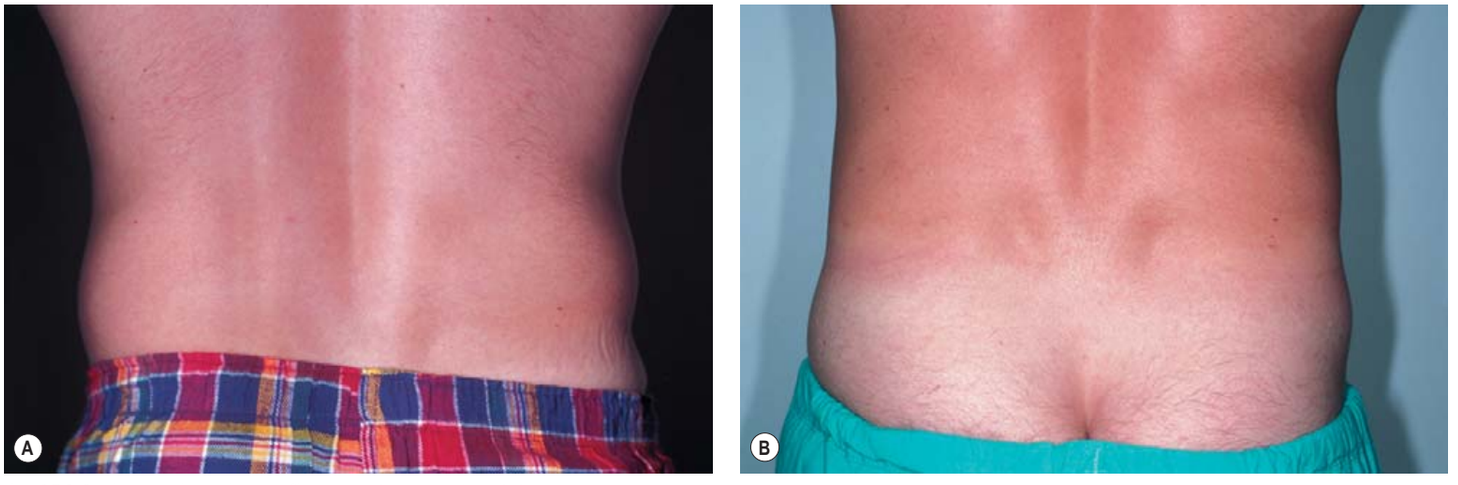


Fig. 156.4 Liposuction of male flanks. A Preoperative. **B** Postoperative, showing the improvement. *Courtesy, TC Flynn, MD.*

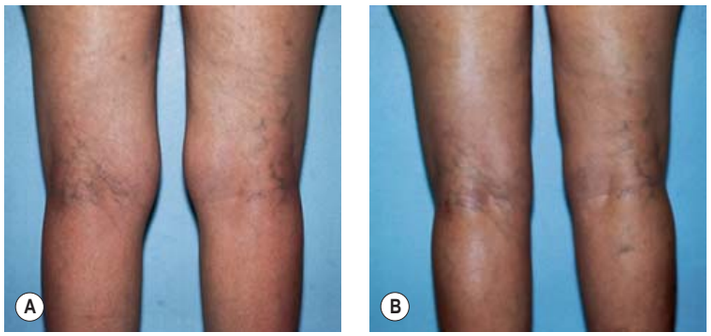


Fig. 156.5 Liposuction of the medial knees. A Preoperative. **B** Postoperative, showing more even contours. *Courtesy, WP Coleman III, MD.*

Fig. 156.6 Superficial liposuction of the axilla is performed for improvement of hyperhidrosis. *Courtesy, WP Coleman III, MD.*

NON-COSMETIC INDICATIONS FOR LIPOSUCTION
Lipomas
Familial multiple lipomatosis
Adiposis dolorosa (Dercum disease)
Gynecomastia
Pseudogynecomastia
Insulin-induced lipohypertrophy
"Buffalo hump" due to Cushing's syndrome
HIV/ART-associated lipodystrophy
Axillary bromhidrosis
Axillary hyperhidrosis (Fig. 156.6)
Undermining flaps
Aspirating hematomas
Lymphedema following axillary lymphadenectomy

Table 156.1 Non-cosmetic indications for liposuction. ART, antiretroviral therapy.

CONTRAINDICATIONS TO TUMESCENT LIPOSUCTION
ABSOLUTE
Severe obesity
Individuals seeking liposuction as a weight-loss procedure
Body dysmorphic syndrome
Untreated psychiatric illness
Excessive scarring in the areas to be improved
RELATIVE
Moderate obesity
Poor wound healing (including Ehlers–Danlos syndrome)
Hypertrophic or keloidal scarring
Coagulation or bleeding disorders
Allergy to lidocaine
Adverse reaction to epinephrine (e.g. tachycardia)
Significant medical illnesses
Unstable psychiatric illnesses

Table 156.2 Contraindications to tumescent liposuction.

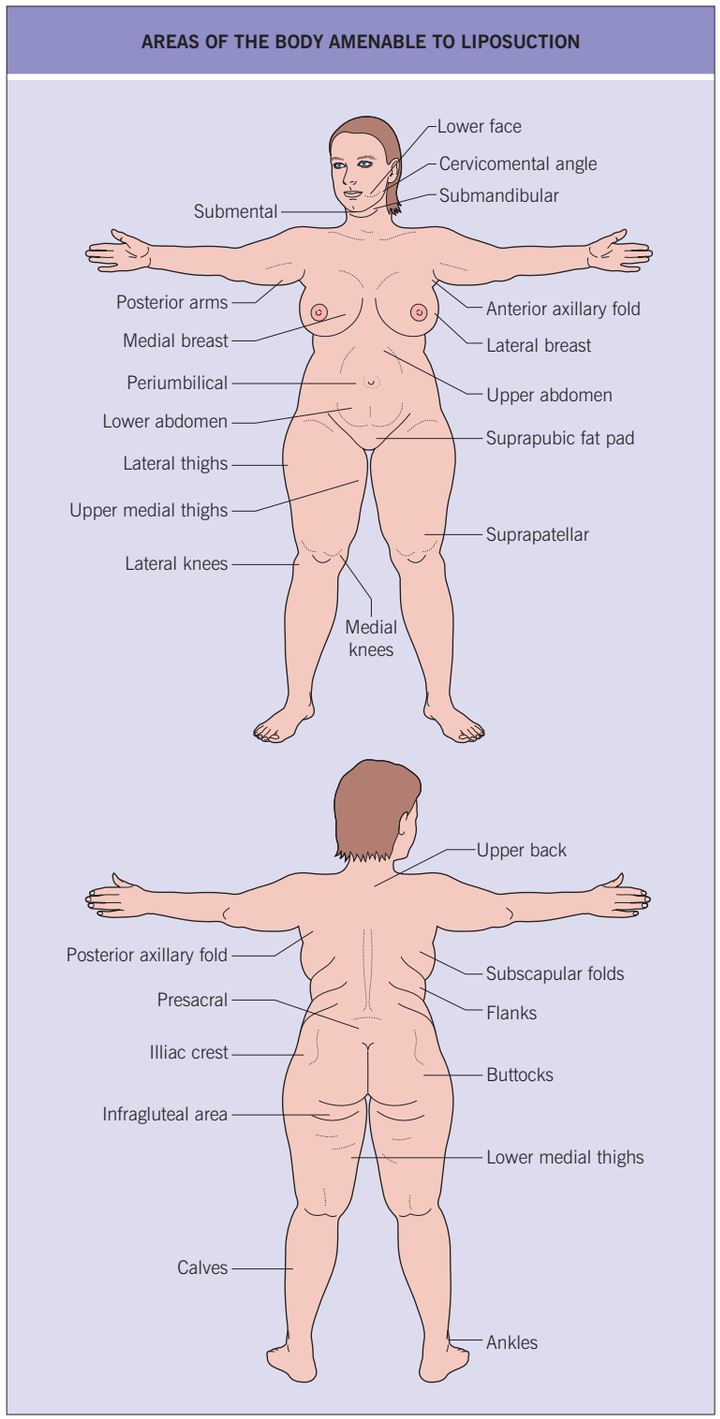


Fig. 156.7 Areas of the body amenable to liposuction.

THE PREOPERATIVE VISIT

A carefully planned preoperative visit, usually scheduled two or more weeks prior to the actual date of the surgery, is an important component of risk management for liposuction surgery. Generally, a complete blood count, a prothrombin time, a partial thromboplastin time, and a general chemistry panel are obtained. Some physicians also perform a urinalysis and tests for infectious diseases such as viral hepatitis and HIV. One reason for scheduling the preoperative visit 2 weeks or so before the surgery is to allow time for the laboratory evaluation to be completed so that the physician can detect any abnormalities. Also, occasionally laboratory tests are incorrectly performed and must be repeated.

Detailed pre- and postoperative instructions should be provided to the patient during this visit. Preoperative instructions should include a list of over-the-counter medications that should be avoided. Aspirin,

nonsteroidal anti-inflammatory drugs (e.g. ibuprofen), vitamin E, fish oil and alcohol are common anticoagulants that patients should carefully avoid preoperatively. Herbal remedies may also have anticoagulant activity (see Table 133.3). It is wise to discontinue all herbal remedies for 2 weeks preoperatively to be certain. Drugs that affect the hepatic cytochrome P450 system should be discontinued if possible (see later). Patients should also be counseled about proper nutrition. Trying to lose weight rapidly or eating excessively should both be discouraged. Many patients benefit from nutritional counseling on a pre- and postoperative basis.

DESCRIPTION OF TECHNIQUES

Tumescent Anesthesia

The technique of using tumescent local anesthesia for liposuction was developed by the dermatologist Dr Jeffrey Klein. In 1987, Klein published his technique for the infiltration of a dilute solution of lidocaine with epinephrine (adrenaline) into fat[5]. The technique allowed for liposuction to be performed totally by local anesthesia as well as significantly reducing bleeding. The previous common complications of seroma formation and hematomas became uncommon[7]. Bruising was also minimized. The procedure has been proven to be remarkably safe.

Klein demonstrated that dilute concentrations of lidocaine with epinephrine are not absorbed to the same degree as commercially available solutions of lidocaine, even when the total dose is equal. He confirmed that tumescent liposuction performed using only dilute solutions of lidocaine with epinephrine safely allowed dosages of up to 35 mg of lidocaine per kilogram of body weight[6]. This advance allowed larger amounts of fat to be removed with only local anesthesia.

A typical tumescent anesthetic formulation is shown in Table 156.3. Dilute solutions of lidocaine with epinephrine provide safe local anesthesia with excellent vasoconstriction. Sodium bicarbonate is added to adjust the solution to a more physiologic pH closer to the pKa of lidocaine[8]. The combination of dilute solutions of lidocaine with the vasoconstrictive effects of epinephrine ensures minimal systemic absorption of lidocaine[19].

The tumescent technique provides a number of advantages (Table 156.4). There is complete regional anesthesia without the need for nerve blocks. Local anesthesia persists for up to 24 hours after tumescent liposuction, reducing the needs for postoperative analgesia[8]. There is minimal blood loss, and the extensive vasoconstriction produced by the dilute epinephrine reduces the volume of whole blood for each liter of pure fat removed by liposuction to less than 12 ml[7,8]. Because there is little blood loss, there is minimal postoperative bruising and risk of hematoma formation. Patients can thus return to their normal lives quickly, with a rapid postoperative recovery. Improved aesthetic results are also seen with tumescent liposuction because smaller cannulas can be used, reducing irregularities of the skin[20].

An important advantage is the decrease in anesthetic risk observed with tumescent anesthesia for liposuction, as compared to intravenous or general anesthesia[11,21–23]. Systemic anesthesia is associated with a significant risk of serious complications[24] and converting liposuction to a procedure performed with local anesthesia increases safety. More recent research has indicated that the maximum safe dosage of lidocaine, when used with the tumescent technique for liposuction, is 55 mg/kg[17,18]. Klein recommends an upper limit of 45 mg/kg for thinner individuals[20].

Fresh tumescent anesthetic solution must be correctly and carefully prepared prior to each procedure by a trained healthcare professional. Personnel must be familiar with the importance of careful records and drug preparation. All individuals who prepare tumescent anesthesia must be familiar with sterile technique. Normal saline should be used as the vehicle for the dilute solutions of lidocaine with epinephrine. Standardization is important in preparing tumescent anesthesia, i.e. by using the same commercial solutions of lidocaine as well as individual 1 ml ampules of 1 : 1000 epinephrine. This minimizes confusion and limits risk.

The concentrations of lidocaine and epinephrine can be varied depending on the anatomic site. The standard formula of 0.05% lidocaine with 1 : 1 000 000 epinephrine plus sodium bicarbonate works well for most areas of the body (see Table 156.3). Occasionally, individual "hot spots" such as the periumbilical area or breast require increased concentrations of lidocaine, up to 0.1%, in the tumescent anesthetic solution.

Proper infiltration of tumescent anesthesia is important. The skin is initially cleansed with an antimicrobial scrub to reduce bacterial contamination. Insertion sites for the infiltration needles are anesthetized with small wheals of 1% lidocaine with epinephrine. While waiting for the intradermal anesthetic to provide cutaneous anesthesia, the prepared tumescent anesthetic bags are suspended from an intravenous pole. Commercially available infiltration tubing is connected to the bag containing the tumescent anesthesia, and the tubing is connected to a peristaltic pump. Air is removed from the infiltration tubing and a small-gauge, blunt-tipped infiltrating cannula or spinal needle is connected to the tubing. Warming the anesthetic solution to body temperature prior to infiltration may reduce the pain of infiltration.

The anesthesia may initially be infiltrated into the subcutaneous fat using 20-gauge spinal needles. More extensive infiltration is then performed using a blunt-tipped side-port 16–18-gauge infiltrating cannula (Fig. 156.8). These small-diameter infiltration cannulas can be passed through slit incisions created in the skin with a #15c or #11 blade; other authors recommend using 1–2 mm punch biopsy instruments to create openings for cannula insertion. A peristaltic pump (Fig. 156.9) facilitates infiltration of the anesthetic fluid into subcutaneous fat. The cannula must be repositioned from site to site to ensure an even distribution of the tumescent anesthetic. Moving the needle while infiltrating is associated with increased pain; consequently, a gentle, slow infiltration technique is preferred. In certain areas where the patient

TYPICAL TUMESCENT ANESTHETIC FORMULATION (LIDOCAINE 0.05%, EPINEPHRINE 1 : 1 000 000)
50 ml 1% plain lidocaine (500 mg)
1 ml 1 : 1000 epinephrine from ampule (1 mg)
10 ml sodium bicarbonate (of an 8.4% $NaHCO_3$ solution)
1 liter normal saline (0.9% NaCl solution)

Table 156.3 Typical tumescent anesthetic formulation (lidocaine 0.05%, epinephrine 1 : 1 000 000).

ADVANTAGES OF TUMESCENT LIPOSUCTION
Complete regional anesthesia without the need for nerve blocks
Local anesthesia persists for up to 24 hours, reducing the need for postoperative analgesia
Minimizes blood loss
Minimal postoperative bruising
Rapid postoperative recovery
Smaller cannulas can be used, reducing irregularities of the skin
Decreased anesthetic risk compared to intravenous or general anesthesia

Table 156.4 Advantages of tumescent liposuction.

Fig. 156.8 Infiltration of tumescent anesthetic into the previously marked patient. Concentric circles denote areas of increased fat. Sterile towels are positioned to absorb leaking fluids. *Courtesy, WP Coleman III, MD.*

Fig. 156.9 Peristaltic pump for infiltration of tumescent anesthetic mixtures. *Courtesy, HK Surgical, San Clemente, CA.*

EXAMPLES OF POSSIBLE DRUG INTERACTIONS WITH LIDOCAINE	
Drug	**Comments**
Anesthetics	
• Bupivacaine	Lidocaine is displaced from plasma binding proteins by bupivacaine
• Halothane plus nitrous oxide	Increase in lidocaine plasma concentration (lowers maximum safe dose)
Amiodarone	Sinus bradycardia, seizures; competes with lidocaine for binding to CYP3A4
Beta-blockers	Decrease in systemic clearance (including hepatic); propranolol and lidocaine both metabolized by CYP2D isoenzymes
Cocaine	Increased risk of seizures and death
Phenytoin	Additive cardiac depressant effects
Benzodiazepines, e.g. alprazolam, diazepam, flurazepam, midazolam	Inhibit lidocaine metabolism
Azole and triazole anti-fungals, e.g. ketoconazole, itraconazole, fluconazole	Inhibit lidocaine metabolism

Table 156.5 Examples of possible drug interactions with lidocaine. *Adapted from Klein JA. Lidocaine toxicity and drug interactions. In: Tumescent Technique. Tumescent Anesthesia and Microcannular Liposuction. St. Louis: Mosby, 2000.*

has more sensitivity, infiltration must be done more slowly than in others. Sensitive areas include the inner thighs, breasts, upper abdomen, and periumbilical area. An infiltration speed of 100 ml/min is usually tolerated quite well.

Once sufficient tumescent anesthesia has been infiltrated, the surgeon should wait at least 15 minutes to allow for maximal vasoconstrictive effect of the epinephrine before beginning surgery. An overlying blanching of the skin which is cool to the touch will gradually appear. The patient is then properly "tumesced" and ready for aspiration of adipose tissue. Allowing even up to an hour between conclusion of infiltration and the onset of suctioning may result in fat removal with less infranate.

Drug interactions must be considered when using any form of anesthesia[25]. Caution must be exercised with patients on β-blockers, especially those that are non-selective. Although rapid absorption of epinephrine may result in hypertension and bradycardia in these patients, when the epinephrine is absorbed slowly, as in the case of tumescent anesthesia, there is minimal risk[20]. In other words, while tumescent liposuction performed in the setting of β-blockade has not led to any evidence of hypertension, one must still be cautious in these patients[20]. Of note, patients on propranolol may also experience chest pain following subcutaneous injection of concentrated epinephrine.

Tumescent anesthesia and certain sedatives may have significant interactions[25]. Some sedatives (such as diazepam and flurazepam) can reduce the rate of lidocaine metabolism after liposuction. Lidocaine is rapidly eliminated by hepatic metabolism, but a number of drugs can inhibit lidocaine metabolism, and there is a long list of medications associated with an increase in lidocaine toxicity[20]. Examples of such drugs are provided in Table 156.5. These medications should be avoided or discontinued prior to liposuction, or the total dose of lidocaine should be reduced.

Bupivacaine should not be substituted for lidocaine, as the former is contraindicated for tumescent liposuction[26]. Bupivacaine cardiac toxicity can be subtle and is not preceded by convulsions. Lidocaine usually gives warning signs of CNS toxicity long before the onset of dangerous cardiotoxic effects. Furthermore, the cardiotoxicity of bupivacaine is often unresponsive to resuscitation efforts. Prilocaine has been used in Europe for tumescent anesthesia instead of lidocaine[27]. However, rigorous comparative studies have not been performed, and, in the US, prilocaine does not have Food and Drug Administration (FDA) approval to be marketed for local anesthesia for dermatologic surgical procedures. Prilocaine can also produce methemoglobinemia (see Ch. 143)[27]. Ropivacaine is a new long-acting amide local anesthetic that resembles bupivacaine[28]. Insufficient data are available at this time to compare dilute tumescent solutions of ropivacaine and dilute solutions of lidocaine in terms of safety and efficacy.

Surgical Technique

The patient is taken to the preparative area, where he or she changes into a surgical gown. Vital signs are taken, including blood pressure and heart rate. Photographs should then be taken if they have not been done preoperatively. These should include multiple views of the sites of surgery with the areas completely unclothed so as not to distort the areas to be treated.

Next, the surgeon marks the patient, who is standing to allow for the effects of gravity. Marking can be done according to the custom of the surgeon, but should be devised so that the subsequent distortion by local anesthetic infiltration will not obscure the various thicknesses of the adiposity. One way to mark is to use concentric circles, as in a topographic map (see Fig. 156.8). Pluses or minuses can be drawn on the patient to indicate areas where more or less fat should be removed. Existing dimples and dents should also be outlined for later identification during surgery so that they can be avoided.

The previously marked patient is then positioned on the surgical table. If significant sedation is to be employed, intravenous lines and monitoring devices such as pulse oximeters and cardiac monitors can be utilized. While patients undergoing the tumescent technique usually require very little ancillary sedation, most patients do appreciate presedation with mild oral sedatives such as lorazepam. Those who are pain-sensitive, or afraid they will be so, can receive minor additional sedation such as 25 mg of meperidine intramuscularly, a dose which does not impair protective reflexes.

Once the patient is relaxed, tumescent infiltration can begin (see Fig. 156.8). Slow infiltration is much less painful than rapid infiltration. Peristaltic pumps can be regulated for a comfortable rate of infiltration, e.g. 100 ml/min (see Fig 156.9). Of note, physicians who use rapid infiltration techniques also typically employ more aggressive forms of systemic anesthesia. Furthermore, rapid infiltration is associated with an increased potential for abdominal perforation. This is compounded by the fact that deeply sedated patients are not awake enough to complain of discomfort associated with muscular penetration. Another disadvantage of moderate and deep sedation is that because of concerns about total anesthesia time, there is usually little or no delay between infiltration of the tumescent fluid and the beginning of the procedure. Significant vasoconstriction from the infiltration of the tumescent fluid does not occur for at least 10–15 minutes after infiltration.

INSTRUMENTATION

The basic instruments required for liposuction are suction cannulas, tubing and an aspirator[29]. Each surgeon must make individual decisions about instrumentation based on personal style and experience. However, liposuction can be performed using many different types of cannulas and aspirators. The number of holes arranged along the shaft of the

Fig. 156.10 A variety of small-diameter liposuction cannulas. The presence of two or more holes increases the flow of fat through the instrument, and while longer cannulas allow the surgeon to work from fewer skin insertion sites, shorter cannulas are easier to control. *Courtesy, WP Coleman III, MD.*

Fig. 156.11 Reciprocating powered cannula. This reciprocating powered cannula has a 3 mm to-and-fro motion. *From Coleman WP III, Katz B, Bruck M, et al. The efficacy of powered liposuction. Dermatol Surg. 2001;27:735–8.*

cannula is probably unimportant, although two or more holes increase the flow of fat through the instrument. The most important parameter for choosing cannulas is size: the smallest possible cannula should be employed. Smaller-diameter cannulas (≤3 mm) create smaller tunnels through the fat and achieve smoother results (Fig. 156.10). Also smaller-diameter cannulas penetrate the fat more easily and create less tissue trauma. Longer cannulas allow the surgeon to work from fewer skin insertion sites, leaving fewer scars. However, depending on the shape and location of the adiposity, better access often requires multiple incision sites. Shorter cannulas are easier to control as they pass through subcutaneous tissue. The tiny incisions required for insertion of 3 mm cannulas leave nearly invisible scars in most patients, but can be an issue if the patient has a tendency towards keloids or hyperpigmentation.

Over the years, a number of instruments have been developed with the goal of making liposuction easier for the surgeon to perform. For example, ultrasound was introduced in the 1990s, but has largely been abandoned by most dermatologic surgeons. *External* ultrasound involves preoperative use of an ultrasonic probe over the areas to be suctioned, in an attempt to liquefy or loosen the fat. However, double-blind studies found no benefit to this approach[30]. *Internal* ultrasonic liposuction employs a probe or cannula with an ultrasonic vibration at the tip. These instruments have been shown to liquefy fat prior to suction. Although this makes subsequent liposuction easier, studies have shown increased potential for seromas and burns[31]. Ultrasonic probes pass through the tissue like a "hot knife through butter" and do not provide the usual tactile feedback from tissue resistance that manual cannulas do. This makes it difficult for the surgeon to determine in exactly what level of the fat the cannula is located and increases the possibility of intra-abdominal perforation or "end hits" to the opposing dermis.

Another innovation in liposuction technology has been powered liposuction. These instruments feature a motorized cannula, which moves in a "to-and-fro" motion, from 800 to 10 000 repetitions per minute (Fig. 156.11). The short motorized strokes vary from 2 to 12 mm, according to the instrument, and allow the surgeon to precisely sculpt

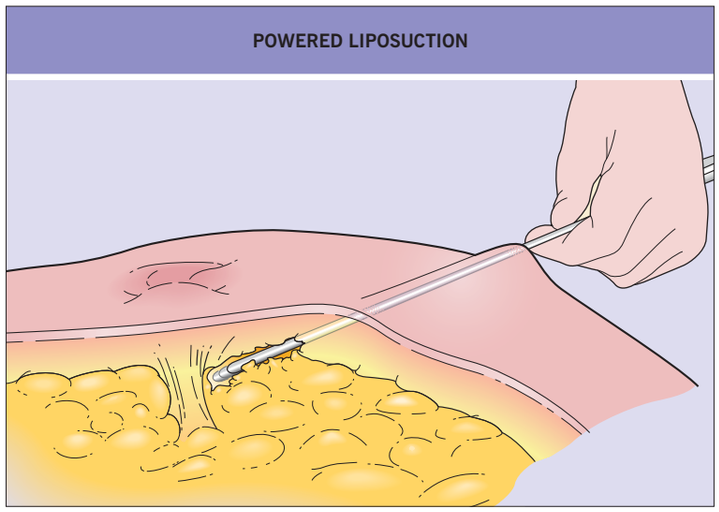


Fig. 156.12 Powered liposuction. Using powered liposuction to more precisely sculpt small areas of fat around the umbilicus.

small areas of excess fat (Fig. 156.12). Powered liposuction instruments also allow easier penetration of fat, when compared to manual cannulas, but retain the feel of tissue resistance[32]. The key to properly using this technology is to move the cannula slowly and allow the motorized motion to work efficiently. Studies have shown that powered liposuction increases the fat aspirated (per minute) by 30% or more[32]. There have been no significant complications reported with the use of this approach, although some early users described increased problems with seromas. This was probably due to the incidental radial movement of these instruments which enlarges the subcutaneous tissue tunnel. Thus, a 4 mm cannula might have the effect of a 5 or 6 mm cannula in the tissue. Therefore, 2 or 3 mm powered liposuction cannulas are preferable and usually avoid problems with seromas.

"Laser-assisted liposuction" is the latest "buzz word" in liposuction technology. These devices are designed to be placed subcutaneously during liposuction in order to generate heat. However, to date, there are no good studies confirming their efficacy. In fact, one study demonstrated no difference in clinical results between laser liposuction and manual liposuction[33]. Representatives from laser companies claim increased skin tightening, but this has not been validated. Diode and Nd:YAG laser liposuction devices are available from several manufacturers in a variety of wavelengths. As of this writing, there is no consensus as to what is the ideal wavelength for laser liposuction. Internal radiofrequency devices for liposuction are being researched as well. The major risk of both lasers and radiofrequency devices for liposuction is dermal burns and dents in the superficial fat. Laser liposuction also takes more time to perform and increases costs. With many devices, manual liposuction must also be performed after use of the laser device. It is unclear at the current time if this technology will overcome these drawbacks.

Water jets have been used for years in general surgery to remove tissue, and liposuction devices based on this technology have been available for the last few years. Powerful streams of concentrated water are directed into the fat layer to create tunnels. Proponents of this approach claim that this reduces the volume of tumescent fluid required. This makes very little sense since the anesthetic effects of the fluid take several minutes to take effect, long after the tunnel is already bored by the water jet.

All of these alternative instruments for liposuction claim less physical force is needed and bleeding is reduced. In fact, manual liposuction requires very little physical strength and bleeding is minimal, so the benefits are suspect. Some companies tend to exaggerate the advantages of their liposuction instruments, and the costs of many of these are staggering, especially when one takes into account the required disposables. Each surgeon needs to determine which instrument he or she is most comfortable with and stick with the approach that is most successful. Each instrument has a steep learning curve. Excellent liposuction results can be achieved with any of these devices, but only if the surgeon is experienced and well trained.

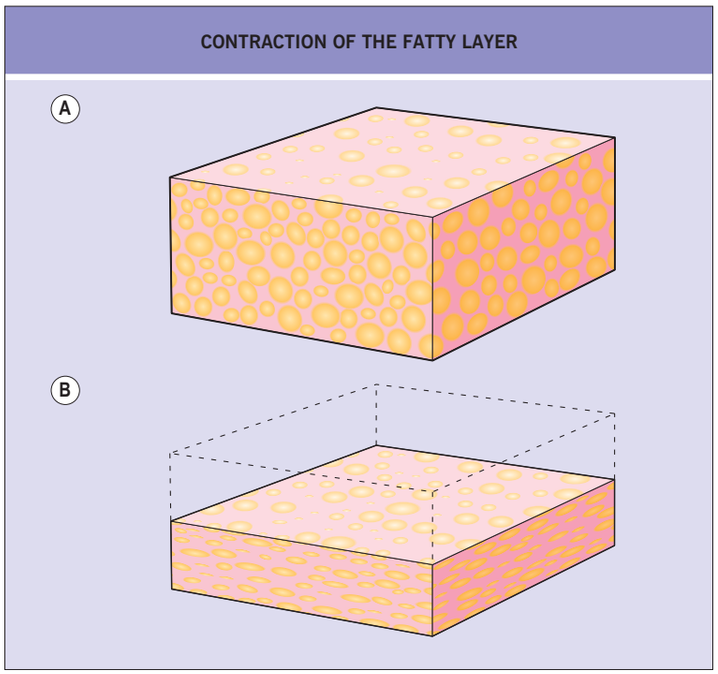


Fig. 156.13 Contraction of the fatty layer. A Immediately after liposuction, the fatty layer resembles a wet sponge. With subsequent subtraction of the fat cells, the thickness of the subcutaneous tissue decreases. **B** Much like a dry sponge, the subcutaneous tissue has compacted.

Fig. 156.14 Bloodless liposuction aspirate. Typical, nearly bloodless liposuction aspirate using the tumescent technique. *Courtesy, WP Coleman III, MD.*

Liposuction is based on the technique of criss-crossing tunnels (from multiple insertion sites) through the subcutaneous tissue. Each area to be suctioned should be tunneled from at least two different directions, but often three or four are more effective. For instance, in the lower abdomen, suctioning can be performed from multiple pubic and flank incisions. Multiple small tunnels ultimately provide the smoothest contraction of the overlying skin and the most thorough removal of fat. Subsequent contraction of the fatty layer occurs much like a wet sponge contracting into a dry one (Fig. 156.13).

The liposuction aspirate should be yellow or slightly blood-tinged (Fig. 156.14). A red aspirate in the suction tubing indicates excessive bleeding and the surgeon should immediately move on to a different tunnel. The surgeon's dominant hand acts as the piston moving the instrument in and out of the tissue, while the non-dominant hand pulls, presses and squeezes the skin to facilitate penetration of the cannula and provides important tactile information about the thickness of the underlying fat. The final surgical endpoint should be a skin thickness in the suctioned areas which is similar to that of the surrounding non-treated skin.

Surgeons may safely aspirate several liters of fat during one operative session. The guidelines of care published by the American Academy of Dermatology recommend a maximum fat removal of 4500 ml[10]. However, it is in fact very unusual to extract 4500 ml of fat in a patient who is healthy and near their ideal body weight. Larger fat extractions imply an obese patient. In these cases, consideration should be given to proper dieting and exercise before the procedure. In larger patients, serial liposuction may be performed at different times to avoid exceeding the recommended volume extraction.

Cannula insertion sites are routinely left open rather than being sutured closed. Experience has shown that closing insertion sites with sutures leads to a greater increase in postoperative edema as well as greater bruising. Closing cannula insertion sites also decreases tissue drainage out of the subcutaneous space. Klein[20] has advocated the use of small adits: 1–2 mm openings made with a common punch biopsy instrument. These are more likely to stay open during the initial postoperative period than are "stab"-type incisions with a #11 or #15c blade, but may leave worse scars.

VARIATIONS/UNUSUAL SITUATIONS

Guidelines of care published by dermatologic organizations recommend that liposuction be performed as a solo procedure and not combined with other techniques[10,16]. However, there are cases in which liposuction is employed as a fundamental part of a combined surgical technique. For instance, in face lifting, liposuction of the neck and pre-tunneling of the cheeks are often performed prior to flap dissection and advancement. In patients in whom the neck alone is to be treated, liposuction may be combined with submental resection and platysmal plication, with each surgical component contributing to the final result. Cook[34] has also described a technique of CO_2 laser desiccation of fat over the platysma and subdermally, as an added component to improve neck tightening. External light-based and radiofrequency devices may also be combined with neck liposuction to improve skin contraction.

In other anatomic sites, skin excision may be combined with liposuction. Where there is a significant abdominal panniculus, a suprapubic incision may be used to remove excess skin in conjunction with liposuction of the rest of the abdomen. In most patients, however, even with a large panniculus, this is unnecessary because of the significant skin retraction that occurs after liposuction of the lower abdomen. Experience shows that most patients who consult for abdominoplasty achieve excellent results with liposuction alone. Abdominoplasty is a much more aggressive procedure, with significantly increased morbidity and mortality. The final scar is significant and often unattractive as well.

Liposuction is an excellent option for improvement of pseudogynecomastia in men. In these patients, the breast enlargement results primarily from excess fat rather than the excess glandular tissue present in true gynecomastia. Multiple insertion sites are used, usually one in the anterior axilla, one submammary and one presternal. Aggressive liposuction is required to remove what is usually thicker and more fibrotic fat. Powered or ultrasonic liposuction is sometimes useful in tunneling through this more fibrous fat. In patients with true gynecomastia, the glandular tissue must also be removed, usually through a submammary or periareolar incision, to obtain sufficient flattening of the breast. Liposuction can also be used for moderate breast reduction in females. The best results are seen in women with soft breasts. Very firm glandular breasts of younger patients do not respond well to liposuction, nor do ptotic breasts, which may sag more after the procedure. These patients are better served with excisional breast reduction.

Liposuction of the arms can provide excellent recontouring, particularly in women. Excessive fatty accumulations over the triceps make the arms unattractively large. Liposuction here is typically performed through incisions in the axilla and superior to the elbow. Relatively aggressive liposuction is usually indicated in order to achieve sufficient tightening of the overlying skin. In rare cases, a Z-plasty skin excision on the posterior surface of the arm is required to further tighten up loose skin. Liposuction should not be carried over to the ventral surface of the arms by anyone other than the most experienced surgeon, as this is an area prone to irregularities.

NON-COSMETIC LIPOSUCTION

Liposuction may also be used for non-cosmetic indications (see Table 156.1). The chief among these is hyperhidrosis[13]. Patients with excessive eccrine and apocrine axillary sweating are often miserable, with constantly wet armpits which can ruin clothing. When prescription antiperspirants and iontophoresis are ineffective, the three major options comprise botulinum toxin injections, sympathectomy and liposuction. Botulinum toxin injections are efficient and require no recovery, but must be repeated every 6–12 months. Since 100 units or more of botulinum A are typically required, this treatment is quite expensive and therefore not economically feasible for many individuals. Sympathectomy is also expensive and has the potential for associated morbidity. Liposuction of the axilla is a permanent option preferred by many patients and physicians. For axillary hyperhidrosis, subdermal liposuction is used aggressively to remove as much of the subdermal fat in the axilla as possible (see Fig. 156.6). Since many of the eccrine and apocrine sweat glands reside in the upper fat, sweating is diminished postoperatively. The goal is to make the patient sweat normally, but not to become anhidrotic. Preoperatively, a starch iodine test identifies the areas of greatest sweating (see Ch. 39). The axilla is most efficiently approached from inferior and superior insertion sites. The liposuction should be aggressive enough to create some subdermal fibrosis, in an attempt to eliminate as many dermal eccrine and apocrine structures as possible. Patients are usually comfortable within 24 hours and able to resume normal activities within 2–3 days. Often, there is immediate diminished sweating with a rebound 2–3 weeks postoperatively, followed by a gradual decrease in sweating as fibrosis develops in the subdermal region.

Larger lipomas can also be removed efficiently using liposuction. The goal here is to flatten out the lipoma but not necessarily remove the entire lesion. A portion of it should be submitted for pathologic examination. The advantage of liposuction over standard excisional surgery is that a much smaller scar results. As with any adiposity, the lipoma is tunneled in a criss-cross direction until flat. Subsequent healing and fibrosis usually flattens the remaining lipoma further, resulting in a normal contour. It is difficult to suction smaller lipomas and these are best removed through direct puncture excision. However, lipomas the size of a golf ball or larger are excellent candidates for liposuction. Since the entire lesion is not surgically removed, lipomas treated in this fashion may be more likely to recur; the patient should be made aware of this possibility. Liposuction should be reserved for lesions that are in cosmetically sensitive areas or those of a size which would necessitate a larger incision.

POSTOPERATIVE CARE

Following liposuction, patients are usually quite comfortable during the initial postoperative period. It is important to remind patients, well before the procedure takes place, that they are going to have significant drainage for the first day following liposuction surgery. Barrier protection is recommended for car seats, furniture and bed linens. Large plastic trash bags or plastic-lined absorbent drapes (such as Chux blue pads) may be used for this function.

The patient's insertion sites may be coated with petrolatum or antibiotic ointment prior to application of absorbent materials. Modern absorbent pads are capable of absorbing significant amounts of drainage from the insertion sites. Alternatively, diapers or sanitary napkins may be used to absorb the drainage.

Following the application of sufficient amounts and layers of absorbent pads (held in place with tape), a compression garment or a compression bandage is fitted. Numerous styles of postoperative liposuction compression garments are available (Fig. 156.15). Postoperative compression minimizes bruising and aids in drainage. Gravitational drainage minimizes postoperative edema. It is important to use firm compression immediately following tumescent liposuction[35]. Mild compression is sufficient after 3 or 4 days. Mild compression assists patients in feeling more secure and decreases pain by restricting movement of the treated tissue. Many patients actually enjoy the comfort and feel of a compression garment due to the soreness sometimes associated with movement in the immediate postoperative period.

Fig. 156.15 Examples of liposuction compression garments. *Courtesy, Miller Medical, Tuscon, AZ.*

Infections have occasionally been reported with liposuction and oral antibiotics may provide prophylaxis against more serious infections. Of note, lidocaine is bactericidal[36]. This may explain, in part, the relatively few infections seen with tumescent liposuction. Careful local wound care and cleanliness are essential in producing a good liposuction outcome.

Patients are asked to change the absorptive pads and bandages the morning after their liposuction. Most individuals will experience continued drainage for 24–48 hours following liposuction. Patients are advised to take their first shower with the absorbent bandages and the tape in place, as the shower assists in the removal of the tape. Patients then follow the shower by reapplying antibiotic ointment, absorbent pads where needed, and their compression garment on top of the pads.

Most patients can return to work within 48 hours following their liposuction. It is important to ask the patients to ambulate regularly beginning the day after surgery. This movement encourages further drainage as well as remodeling of the subcutaneous tissue. Movement has the additional benefit of increasing lymphatic drainage through intermittent pumping action of skeletal muscles. Light exercise may begin 24 hours after surgery, but patients should be advised to start at 30–50% of their normal routine. Exercise keeps the patient from losing lean body mass during the postoperative period.

All patients are given a set of written postoperative liposuction instructions including important phone numbers should the patient need to contact the doctor. These postoperative instructions remind the patient that swelling and firmness beneath the skin and a reduced sensation in the skin are common. This will usually resolve over the first 3 to 4 weeks after the surgery. The postoperative instructions also remind patients that the final results are not seen until 6–12 months following the liposuction.

Patients return for their first postoperative appointment 1 day following liposuction. This visit is important to check for problems and reassure the patient. The next visit usually occurs at 3 weeks. The areas that have been treated are examined and palpated by the liposuction surgeon and the patient's progress is assessed. It is often necessary to remind patients that improvement from liposuction is a gradual process. This postoperative visit is a good opportunity for encouraging patients to exercise, maintain an active and healthy lifestyle, and eat a reasonable diet. Many liposuction surgeons recognize that liposuction may be used to "jump-start" a patient's conversion to a healthy lifestyle and an improved dietary pattern. Patients are seen for 3-month and 6-month follow-up visits. If touch-ups are required, it is wise to wait 1 year before proceeding, to be certain that the final results have been achieved. Secondary liposuctions that are performed too early in the postoperative period may lead to skin irregularities.

POSSIBLE COMPLICATIONS OF LIPOSUCTION
Infection (e.g. bacterial, atypical mycobacterial)
Hematomas
Seromas
Skin indentations
Erosions, ulcerations
Thrombophlebitis (non-septic, septic)
Pulmonary embolism
Abdominal perforation

Table 156.6 Possible complications of liposuction.

COMPLICATIONS

Complications of liposuction (Table 156.6) must be differentiated from common sequelae. After liposuction, it is common to have prolonged swelling, areas of numbness, bruising, and red incisions. Infections, hematomas and seromas are uncommon complications that require medical attention, but can usually be resolved rapidly.

Serious complications of liposuction are closely linked to the type of sedation employed. There have been a number of deaths from liposuction in patients who had moderate or deep sedation[11,21,37]. The authors are not aware of any deaths from liposuction in patients who underwent the procedure with true tumescent local anesthesia[38].

Thrombophlebitis and pulmonary embolism postoperatively are surgical complications associated with non-ambulatory patients and prolonged procedures under general anesthesia. This is also true for liposuction. An advantage of the tumescent local anesthetic technique is that patients are ambulatory immediately after surgery, thus minimizing the risks of this potential problem. Patients who are obese and inactive are more at risk for the development of this complication; this should be taken into consideration during the preoperative evaluation.

Abdominal perforation is one of the leading causes of liposuction deaths[39]. This is exclusively a complication of liposuction under general anesthesia[22]. Deeply sedated patients have decreased muscle tone and are unable to alert the physician to the pain of penetration of the liposuction cannula. Occult abdominal hernias may contribute to this complication. The treating physician should be aware of any abdominal scars and palpate for hernias during the preoperative visit.

General anesthesia also increases risks of respiratory failure and cardiac death[24]. Besides the direct effect of the systemic anesthesia, fluid overload may contribute to these problems. Anesthesiologists or anesthetists who are not accustomed to working with patients who have been infiltrated with tumescent anesthetic fluids may inadvertently overhydrate the patient with additional intravenous fluids. A significant amount of the saline infused subcutaneously is absorbed systemically, automatically correcting for surgical fluid losses. No additional intravenous fluids are usually required. Compounding this problem is the recent discovery that intravenous fluid bags are typically overfilled by at least 10%, leading to further errors in calculating fluid replacement in liposuction[40].

The keys to avoiding complications in liposuction lie in proper patient selection, appropriate patient evaluation, monitoring according to the degree of sedation, good surgical technique, avoidance of excessive fat removal or overzealous additional simultaneous procedures, and adequate postoperative care.

ALTERNATIVE TRENDS

Liposuction is now a mature procedure and most patients obtain predictable results[41,42]. However, as with all cosmetic procedures, there is a general trend toward trying to accomplish similar results with less invasive techniques. Several *external* modalities are currently under investigation for the treatment of localized subcutaneous fat. Some of these treatments, such as mesotherapy, have been in existence for many years, but recently have garnered more interest; other technologies, such as external ultrasonic devices, external cryolipolysis, and low-level laser treatments, are relative newcomers to the field.

Mesotherapy, which was originally developed in the 1950s, has re-emerged as a treatment for localized adiposities. Most commonly, this technique involves the subcutaneous injection of a formulation containing phosphatidylcholine plus a detergent solvent that leads to the dissolution of fat cells[43]. Recent work has shown that the detergent solvent, usually deoxycholic acid, is more likely the active ingredient in this solution[44]. The injections are followed by a 1–2-month period of panniculitis which is associated with significant edema and discomfort. Unfortunately, the injections produce varying and unpredictable results. There is also a general lack of standardization of the injectable material as well as the technique of injection. Mesotherapy has led to complications such as scarring, ulcerations and mycobacterial infections[45]. Currently, in the US, mesotherapy does not have FDA clearance, and it is banned in Brazil and the UK due to concerns about its safety.

Several *external* light- and energy-based therapies are in use for the treatment of the appearance of subcutaneous fat and cellulite. For example, there is an external 635 nm diode laser (Zerona™; Erchonia) that theoretically reduces the size of subcutaneous fat by induction of a photochemical reaction which creates small pores in the adipocyte cell membrane; it is FDA-approved for external laser-assisted liposuction[46]. Patients must undergo at least six treatments (no greater than 72 hours apart) to achieve results. Patients are also asked to decrease their caloric intake and to drink extra water. There is no downtime from the procedure and no pain associated with treatments. However, results of these treatments have been variable and were not comparable to those achieved with liposuction surgery. The long-term results are also still in question. In addition, there is a device which combines intense pulsed light, suction and radiofrequency that is FDA-approved for the reduction of the appearance of cellulite (VelaSmooth™; VelaShape). Unfortunately, the results appear to be only transient and not very impressive.

As of the writing of this chapter, there are two *external* ultrasound devices that are being evaluated for localized fat reduction. One is a high-frequency ultrasound device (LipoSonix™; Medicis) that relies upon ultrasound-induced thermal destruction of adipocytes. This device is based on technology currently employed in the treatment of malignant tumors, in particular prostate cancer. The other is a non-thermal, external ultrasound device (Contour I™; UltraShape) that produces targeted cavitation of fat cells without producing significant heating; this allows the device to achieve lipolysis without destruction of blood vessels and nerves[47–49]. Although early reports seem promising, the results are clearly not comparable to liposuction.

Another interesting technology is cryolipolysis. This technology involves the targeted production of adipocyte apoptosis via thermal energy extraction (without damage to the epidermis). Porcine models have shown significant reduction in subcutaneous fat, but there is still a question regarding the possibility of sensory nerve injury[50–52]. In early clinical trials, modest, localized fat reduction has been achieved without significant complications.

Technology is constantly providing physicians with new ways to minimize localized adiposities. As we gain more experience with each new treatment and device, we can determine if it provides any benefit over existing technology. Regardless of what instrumentation is used, it is likely that liposuction will remain one of the most popular and predictable cosmetic procedures in the future.

REFERENCES

1. Fischer A, Fischer G. First surgical treatment for molding body's cellulite with three 5 mm incisions. Bull Int Acad Cosmet Surg. 1976;3:35.
2. Illouz YG. Body contouring by lipolysis: a 5-year experience with over 3000 cases. Plast Reconstr Surg. 1983;72:591–7.
3. Fournier PF, Otteni FM. Lipodissection in body sculpturing: the dry procedure. Plast Reconstr Surg. 1983;72:598–609.
4. Field LM. The dermatologist and liposuction – a history. J Dermatol Surg Oncol. 1987;13:1040–1.
5. Klein JA. Tumescent technique for liposuction surgery. Am J Cosmet Surg. 1987;4:263–7.
6. Klein JA. Tumescent technique for regional anesthesia permits lidocaine doses of 35 mg/kg for liposuction. J Dermatol Surg Oncol. 1990;16:248–63.

7. Lillis PJ. Liposuction surgery under local anesthesia: limited blood loss and minimal lidocaine absorption. J Dermatol Surg Oncol. 1988;14:1145–8.
8. Klein JA. Tumescent technique for local anesthesia improves safety in large-volume liposuction. Plast Reconstr Surg. 1993;92:1085–98; discussion 99–100.
9. Flynn TC, Coleman WP III, Field LM, et al. History of liposuction. Dermatol Surg. 2000;26:515–20.
10. Coleman WP III, Glogau RG, Klein JA, et al. Guidelines of care of liposuction. J Am Acad Dermatol. 2001;45;438–47.
11. Coleman WP III, Hanke CW, Glogau RG. Does the specialty of the physician affect fatality rates in liposuction? A comparison of specialty specific data. Dermatol Surg. 2000;26:611–15.
12. Flynn TC, Narins RS. Preoperative evaluation of the liposuction patient. Dermatol Clin. 1999;17:729–34.
13. Coleman WP III. Noncosmetic applications of liposuction. J Dermatol Surg Oncol. 1988;14:1085–90.
14. Chastain MA, Chastain JB, Coleman WP III. HIV lipodystrophy: review of the syndrome and report of a case treated with liposuction. Dermatol Surg. 2001;27:497–500.
15. Coleman WP III, Letessier S, Hanke CW. Liposuction. In: Coleman WP III, Hanke CW, Alt TH, Asken S (eds). Cosmetic Surgery of the Skin. St Louis: Mosby, 1997: 178–205.
16. Lawrence N, Clark RE, Flynn TC, Coleman WP III. American Society for Dermatologic Surgery Guidelines of Care for Liposuction. Dermatol Surg. 2000;26:265–9.
17. Ostad A, Kageyama N, Moy RL. Tumescent anesthesia with a lidocaine dose of 55 mg/kg is safe for liposuction. Dermatol Surg. 1996;22:921–7.
18. Coleman WP III. Tumescent anesthesia with a lidocaine dose of 55 mg/kg is safe for liposuction (editorial). Dermatol Surg. 1996;22:919.
19. Klein JA. Anesthetic formulation of tumescent solutions. Dermatol Clin. 1999;17:751–9.
20. Klein JA. Tumescent Technique. Tumescent Anesthesia and Microcannular Liposuction. St Louis: Mosby, 2000.
21. Rao RB, Ely SF, Hoffman RS. Deaths related to liposuction. N Engl J Med. 1999;30:1471–5.
22. Coleman WP III, Hanke CW, Lillis P, et al. Does the location of the surgery or the specialty of the physician affect malpractice claims in liposuction? Dermatol Surg. 1999;25:343–7.
23. Hanke CW, Bernstein G, Bullock S. Safety of tumescent liposuction in 15,336 patients. National survey results. Dermatol Surg. 1995;21:459–62.
24. Forrest JB, Rehder K, Cahalan MK, Goldsmith CH. Multicenter study of general anesthesia. III. Predictors of severe perioperative adverse outcomes. Anesthesiology. 1992;76:3–15.
25. Klein JA, Kassarjdian N. Lidocaine toxicity with tumescent liposuction. A case report of probable drug interactions. Dermatol Surg. 1997;23:1169–74.
26. Klein JA. Intravenous fluids and bupivacaine are contraindicated in tumescent liposuction. Plast Reconstr Surg. 1998;102:2516–19.
27. Breuninger H, Wehner-Caroli J. Subcutaneous infusion anesthesia with prilocaine diluted with Ringer's lactate. Hautarzt. 1998;49:709–13.
28. Breuninger H, Hobbach PS, Schimek F. Ropivacaine: an important anesthetic agent for slow infusion and other forms of tumescent anesthesia. Dermatol Surg. 1999; 25:799–802.
29. Bernstein G. Instrumentation for liposuction. Dermatol Clin. 1999;17:735–49.
30. Lawrence N, Coleman WP III. Ultrasonic-assisted liposuction. Internal and external. Dermatol Clin. 1999;17:761–71.
31. Lawrence N, Coleman WP III. The biologic basis of ultrasonic liposuction. Dermatol Surg. 1997;23: 1197–200.
32. Coleman WP III, Katz B, Bruck M, et al. The efficacy of powered liposuction. Dermatol Surg. 2001;27:735–8.
33. Prado A, Andrades P, Danilla S, et al. A prospective, randomized, double-blind, controlled clinical trial comparing laser-assisted lipoplasty with suction-assisted lipoplasty. Plast Reconstr Surg. 2006;118: 1032–45.
34. Cook W. Laser neck and jowl liposculpture including platysma laser resurfacing, dermal laser resurfacing and vaporization of subcutaneous fat. Dermatol Surg. 1997;23:1143–8.
35. Klein JA. Post-tumescent liposuction care. Open drainage and bimodal compression. Dermatol Clin. 1999;17:881–9.
36. Klein JA. Antibacterial effects of tumescent lidocaine. Plast Reconstr Surg. 1999;104:1934–6.
37. Grazer FM, de Jong RH. Fatal outcomes from liposuction: census survey of cosmetic surgeons. Plast Reconstr Surg. 2000;105:436–46; discussion 447–8.
38. Hanke W, Cox SE, Kuznets N, Coleman WP 3rd. Tumescent liposuction report performance measurement initiative: national survey results. Dermatol Surg. 2004;7:967–77.
39. Talmor M, Hoffman LA, Lieberman M. Intestinal perforation after suction lipoplasty: a case report and review of the literature. Ann Plast Surg. 1997;38: 169–72.
40. Coleman WP IV, Flynn TC, Coleman KL. When one liter does not equal 1000 milliliters: implications for the tumescent technique. Dermatol Surg. 2000;26:1024–8.
41. Yoho RA, Romaine JJ, O'Neil D. Review of the liposuction, abdominoplasty, and face-lift mortality and morbidity risk literature. Dermatol Surg. 2005;31:733–43.
42. Shiffman MA, Di Giuseppe A. Liposuction: Principles and Practice. Berlin: Springer-Verlag, 2006.
43. Rotunda AM, Kolodney MS. Mesotherapy and phosphatidylcholine injections: historical clarification and review. Dermatol Surg. 2006;32:465–80.
44. Rotunda AM, Weiss SR, Rivkin LS. Randomized double-blind clinical trial of subcutaneously injected deoxycholate versus a phosphatidylcholine-deoxycholate combination for the reduction of submental fat. Dermatol Surg. 2009;35:792–803.
45. Sañudo A, Vallejo F, Sierra M, et al. Nontuberculous mycobacteria infection after mesotherapy: preliminary report of 15 cases. Int J Dermatol. 2007;46:649–53.
46. Neira R, Arroyave J, Ramirez H, et al. Fat liquefaction: effect of low-level laser energy on adipose tissue. Plast Reconstr Surg. 2002;110:912–22.
47. Brown SA, Greenbaum L, Shtukmaster S, et al. Characterization of nonthermal focused ultrasound for noninvasive selective fat cell disruption (lysis): technical and preclinical assessment. Plast Reconstr Surg. 2009; 124:92–101.
48. Teitelbaum SA, Burns JL, Kubota J, et al. Noninvasive body contouring by focused ultrasound: safety and efficacy of the Contour I device in a multicenter, controlled, clinical study. Plast Reconstr Surg. 2007; 120:779–89.
49. Moreno-Moraga J, Valero-Altés T, Riquelme AM, et al. Body contouring by non-invasive transdermal focused ultrasound. Lasers Surg Med. 2007;39:315–23.
50. Manstein D, Laubach H, Watanabe K, et al. Selective cryolysis: a novel method of non-invasive fat removal. Lasers Surg Med. 2008;40:595–604.
51. Zelickson B, Egbert BM, Preciado J, et al. Cryolipolysis for noninvasive fat cell destruction: initial results from a pig model. Dermatol Surg. 2009;35:1462–70.
52. Coleman SR, Sachdeva K, Egbert BM, et al. Clinical efficacy of noninvasive cryolipolysis and its effects on peripheral nerves. Aesthetic Plast Surg. 2009;33:482–8.

Hair Restoration 157

Marc R Avram, Sharon A Keene, Dowling B Stough and Nicole E Rogers

INTRODUCTION

Hair frames our face and its length, color and style reflect our personality and how we perceive ourselves. The framing preserves a youthful facial appearance by shortening the face and returning the viewer's focus to the center of the face. While hair is one of the few physical characteristics we can easily control, the inability to correct hair loss can lead to concerns regarding appearance and psychological stress. In the case of androgenetic alopecia, some individuals accept the hair thinning as an unavoidable aging phenomenon whereas others actively seek medical and/or surgical treatment options.

HISTORICAL PERSPECTIVE

The first hair transplantation procedure for male pattern hair loss was successfully performed in the 1950s, using large punch autografts. Alternative techniques such as hair-bearing flaps and scalp reductions were also performed in an effort to redistribute hair or reduce the size of bald scalp. However, because of unsightly large "plugs", obvious scars due to continued hair loss and an unnatural orientation of hair, these techniques were largely abandoned in favor of follicular unit grafts. The latter are placed into small "recipient" sites (0.5–1 mm in diameter) produced by a blade or needle. Utilizing CO_2 lasers to create recipient sites was briefly investigated, but the associated thermal injury to surrounding skin led to poor wound healing and necrosis.

MALE AND FEMALE PATTERN HAIR LOSS (ANDROGENETIC ALOPECIA)

Pathogenesis

Miniaturization of terminal pigmented anagen hairs to fine hypopigmented vellus hairs is the hallmark of androgenetic alopecia (AGA; Fig. 157.1). Androgens, in particular testosterone and dihydrotestosterone (DHT), are required for the progressive reduction in hair follicle size with each cycle. The enzyme 5α-reductase, which is inhibited by drugs such as finasteride (see Fig. 69.6), converts testosterone to DHT. Multiple androgen-metabolizing enzymes actually reside within the hair follicle itself, providing an explanation for "end-organ" sensitivity (see Fig. 69.2).

Stem cells, which reside in the hair follicle bulge, are responsible for hair follicle cycling and when these cells are destroyed, there is loss of the follicle. In mice, combining bulge cells with neonatal dermal cells can give rise to a hair follicle as well as the sebaceous gland and epidermis[1]. Within the hair follicle, stem cells give rise to secondary germ cells with each hair cycle; the latter cells represent a progenitor population that is responsible for the production of the hair shaft during anagen (but undergoes apoptosis at the end of anagen)[2]. In a recent study comparing bald scalp with hair-bearing scalp in men, the stem cell population was maintained in the bald scalp but there was a marked reduction in progenitor cells, suggesting that study of this second population of cells could provide further insight into male pattern hair loss[3].

Population studies have pointed to a polygenic inheritance pattern, with both maternal and paternal genetic influences. Of the associated genes identified to date, the androgen receptor (AR) gene, present on the long arm of the X chromosome (Xq11–12), has been identified as a major determinant of hair loss in men[4–6]. Within exon 1 of the AR gene is the AR-CAG polymorphism, which refers to the number of repeat sequences of cytosine–adenine–guanine (CAG) present, with the normal range of CAG repeats being 13–40. The number of CAG repeats appears to *inversely* correlate with the degree of androgen sensitivity. Men with fewer CAG repeats have an increased risk of developing AGA and a higher cellular sensitivity to androgens; they also demonstrate a greater response to finasteride treatment[7]. In contrast, men with >40 repeats appear to be protected and have androgen insensitivity[8]. Variants in the AR gene may influence hair loss in women as well[8a].

The AR gene also has single nucleotide polymorphisms (rs6152; see Ch. 54) and Caucasian men with the A (adenine) allele have a low likelihood of developing AGA[9] while those with the G (guanine) allele have a 70% lifetime risk of developing AGA, which increases to >80% if there is a positive paternal family history. Other implicated genes include *EDA2R*, which encodes the ectodysplasin A2 receptor and is also found on the X chromosome (see Ch. 63)[10], as well as genes located at 20p11[11] and 3q26[12]. As more insight is gained into the interplay of these genes, it may be possible to diagnose androgenetic alopecia at an early age and predict who may benefit from therapy. Of note, it is important for patients to realize that while a family history of androgenetic alopecia provides useful information, it does not predict the rate and extent of hair loss in a particular individual.

Clinical Features

The diagnosis of androgenetic alopecia is usually straightforward, especially in men. This is based upon the characteristic pattern, the miniaturization of hairs and the lack of clinical inflammation (see Ch. 69). Occasionally, an unusual presentation requires clinicopathologic correlation. In women, the patterned alopecia may first become clinically apparent as a result of a superimposed telogen effluvium, perhaps following a febrile illness or birth of a child. These patients require an evaluation for telogen effluvium as outlined in Table 69.2 and possible hyperandrogenemia (e.g. serum free testosterone, DHEA-S), especially in the setting of hirsutism and/or recalcitrant acne vulgaris or any signs of virilization. Female pattern hair loss has to be distinguished from other causes of alopecia, including central centrifugal cicatricial alopecia, early lichen planopilaris or frontal fibrosing alopecia and diffuse alopecia areata; as a result, histologic evaluation may be required.

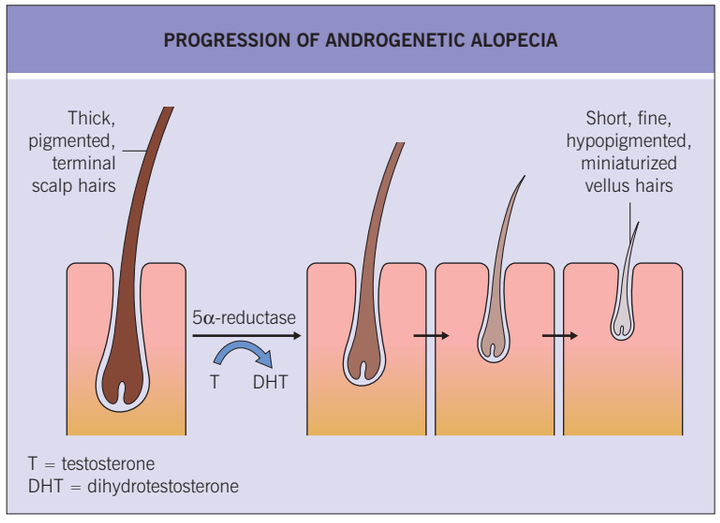


Fig. 157.1 Progression of androgenetic alopecia. Testosterone is metabolized into dihydrotestosterone (DHT) by the enzyme 5α-reductase and this conversion can occur within the hair follicle.

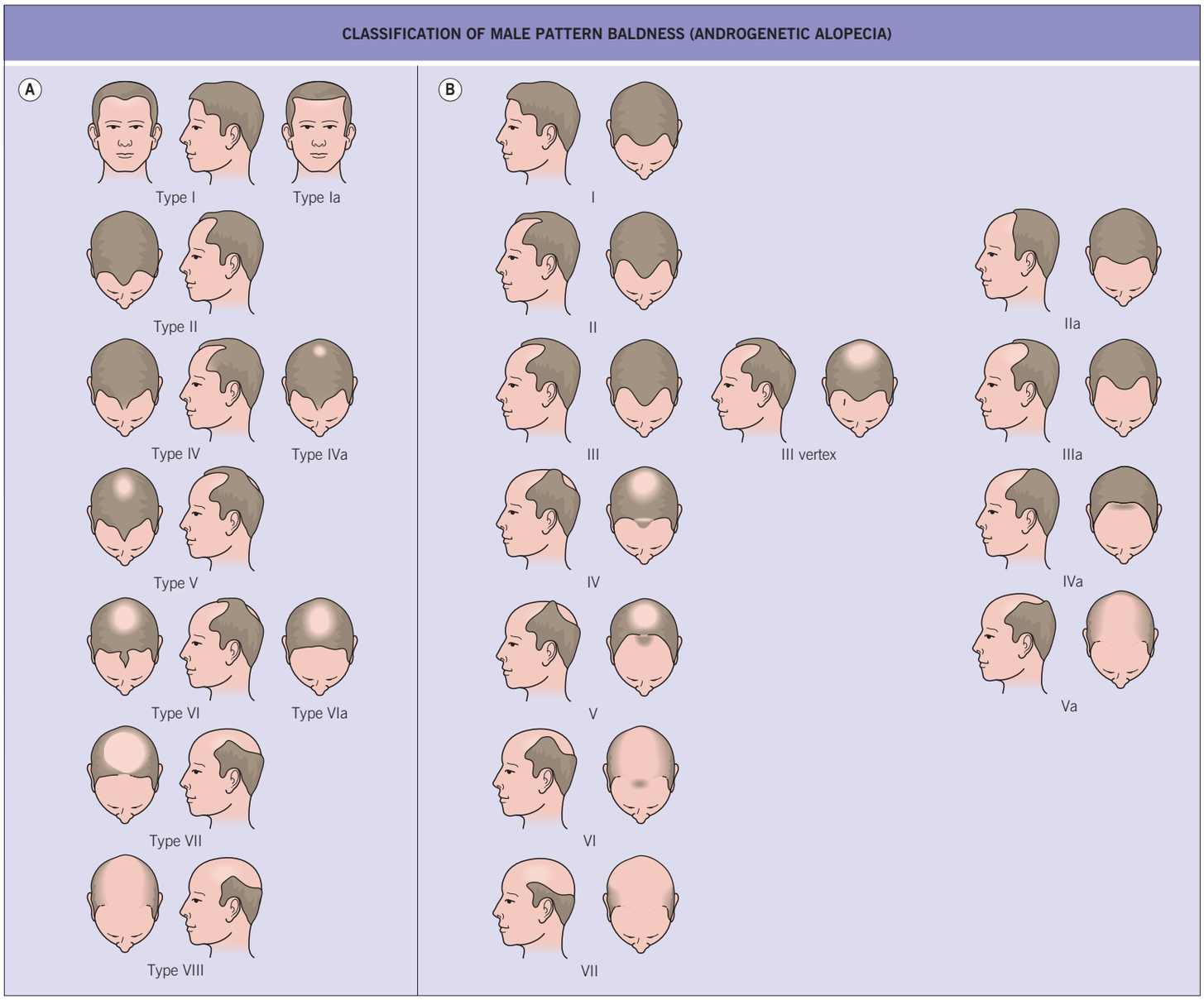


Fig. 157.2 Classification of male pattern baldness (androgenetic alopecia). A Hamilton grading scale. **B** Norwood grading scale.

There are grading systems for androgenetic alopecia that allow assessment of severity, progression and response to therapy. In men, the Norwood classification (Fig. 157.2) is used more often than the Hamilton classification system. Patterned hair loss in women is classically given a Ludwig grade (I, II or III; Fig. 157.3), even though the hair loss often has a Christmas tree pattern. Occasionally, the classification scheme for men is used.

Treatment (Other Than Transplant Surgery)

Medical therapies

Topical minoxidil (5% solution or foam) is FDA-approved for men[13] and the 2% solution is approved for both women and men. In general, the therapeutic effects are modest, but it can prove helpful as an adjunct to hair transplantation[14]. Although there is ongoing debate as to minoxidil's exact mechanism of action, it is thought to be related to its vasodilatory or angiogenic properties and perhaps its effect on potassium channels[15]. Increased proliferation of dermal papilla cells[16], an increase in hair caliber, and more time spent in the anagen phase have all been observed[17].

A possible explanation for the variability in therapeutic responses amongst individuals is differing levels of sulfotransferase activity (which catalyzes minoxidil sulfate) in their hair follicles[18]. Side effects of topical minoxidil include unwanted hypertrichosis of the cheeks or forearms, headache, ankle edema, and allergic or irritant contact dermatitis. With regard to the latter, propylene glycol in the vehicle is often the culprit and it has been removed from the 5% foam product (Rogaine®). Fetal hypertrichosis has also been reported and so use of topical minoxidil is discouraged in pregnant or breastfeeding women.

Finasteride inhibits 5α-reductase, which converts testosterone to DHT (see Fig. 69.6) and is present in hair follicles. Oral finasteride (1 mg daily) is FDA-approved for men with AGA. In a randomized trial of 1553 men given either finasteride 1 mg or placebo for 1 year (with a blinded extension for a second year), significantly greater hair counts in the balding vertex were observed in those receiving finasteride[19]. Five-year results from the same study demonstrated that hair growth peaked at 1–2 years, but hair counts remained well above baseline for 90% of patients[20]. Its use in combination with hair transplantation has yielded statistically greater hair counts 48 weeks after surgery in comparison to the control/placebo group[21]. Recent evidence suggests that finasteride may work better in men with higher levels of DHT (such as those in their mid-twenties)[22].

Patients are advised to allow at least 6 months before expecting to see a therapeutic effect. If they discontinue the finasteride, the AGA will return to its pre-treatment appearance. Because finasteride is metabolized extensively in the liver, it should be used with caution in

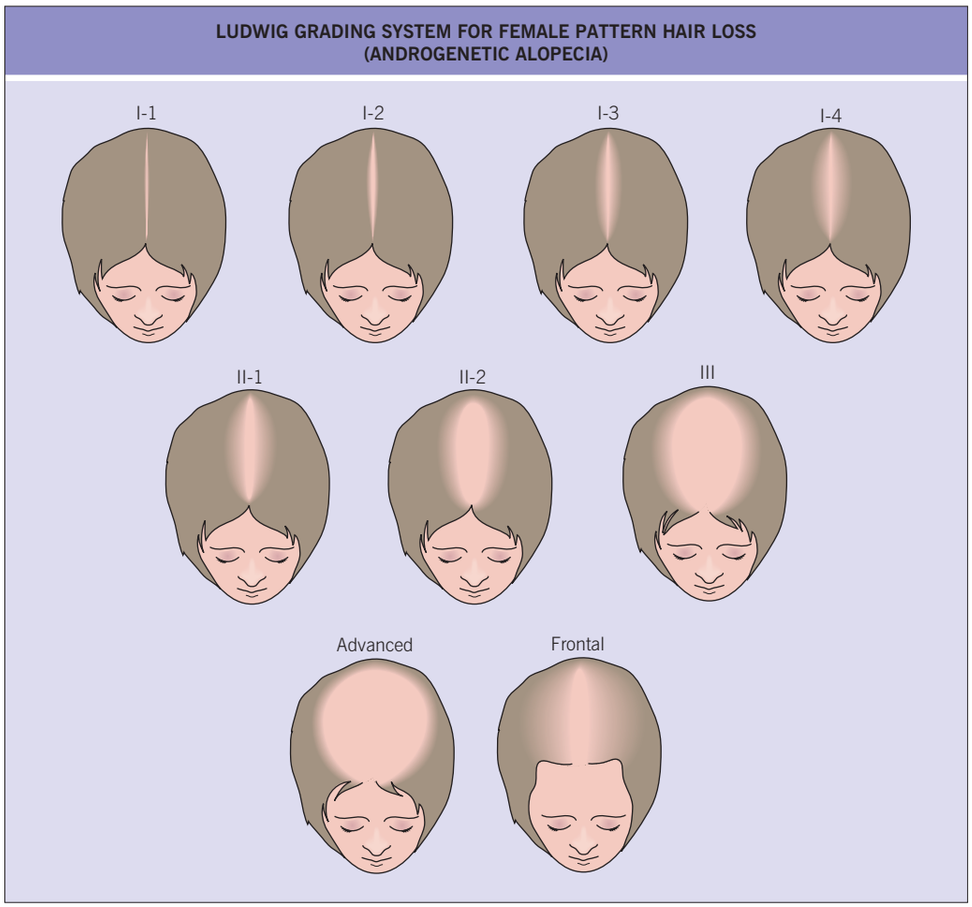


Fig. 157.3 Ludwig grading scale for female pattern hair loss (androgenetic alopecia).

patients who have known liver disease[23]. Finasteride also artificially lowers the serum prostate-specific antigen (PSA) level by approximately 50%[24]. Therefore, both the primary care physician and the patient need to be made aware of this effect. Although early data from prostate cancer trials suggested that finasteride might increase the histologic grade (i.e. severity) of prostate cancer[25], subsequent analyses suggested a detection bias[26].

Overall, the drug is well tolerated. Side effects that occur in less than 2% of men taking finasteride include decreased libido, erectile dysfunction and ejaculation disorder, compared with their occurrence in 1% of the placebo group. Rarer side effects include gynecomastia, breast tenderness and depression[27]. In a double-blind, placebo-controlled, multicenter trial in young men, no changes in spermatogenesis or semen production were observed[28]. However, there have been two reports of severe azoospermia leading to impaired fertility[29]. While the authors feel comfortable prescribing finasteride for men who are planning to have children, it should be discontinued if there are fertility issues, before embarking upon more invasive infertility treatments.

We encourage surgical candidates to stabilize their hair loss by taking finasteride for 6 to 12 months prior to hair transplantation. As stated previously, most men benefit from combination therapy (Fig. 157.4). Patients who report sexual dysfunction side effects should discontinue the medication and, after an interval of 1–2 weeks, try every second- or third-day dosing.

Finasteride is not FDA-approved for women with AGA, and at a dosage of 1 mg daily, no improvement was observed in clinical trials[30]. Of note, finasteride can cause feminization of the male fetus. In uncontrolled series of normoandrogenic women, higher doses of 2.5 mg and 5 mg daily led to improvement in hair density in 62% and 81% of patients, respectively[31,32]. If a decision is made to try higher-dose finasteride in a women with female pattern hair loss, counseling regarding fetal risk and its off-label use is essential.

Dutasteride differs slightly from finasteride in that it blocks both the type I and type II 5α-reductase isoenzymes (see Fig. 69.1). It has been used off-label at a dosage of 0.5 mg daily for AGA in men who did not respond to finasteride, and increased hair counts were observed in a randomized, placebo-controlled trial[33]. However, the drug's half-life is 5 weeks, compared with 6–8 hours for finasteride. Thus, side effects are longer-lasting (several months) and more difficult to reverse. In a double-blind, placebo-controlled trial, men who received oral dutasteride (0.5 mg daily) versus placebo for 1 year had significant decreases from baseline in sperm count: by 28.6% at 26 weeks, 25% at 52 weeks, and 23% at 24 weeks after the trial ended[34]. Sperm motility was also reduced at the latter time point. This potentially irreversible drop in sperm count and motility is an issue for men who still desire to have children.

Low-level light therapy

There has been emerging interest in the use of low-level light therapy (LLLT) for photo-biostimulation of hair growth. This was initially based upon the observation that laser hair removal can sometimes trigger paradoxical hair growth in the surrounding skin[35]. Based upon their approval by the FDA as a medical device (rather than a drug), multiple LLLT products are commercially available. The patient combs light (650–700 nm) through the hair two to three times per week with the expectation of hair growth. To date, there have been only two published studies examining the effects of LLLT on hair growth[36,37]. Although skepticism regarding the therapeutic effects of LLLT still exists, it may be an option for patients who cannot tolerate medical therapy or are not yet candidates for hair transplantation.

HAIR TRANSPLANTATION

Hair transplantation is a procedure performed in an outpatient setting under local anesthesia. It is based on the theory of donor dominance, i.e. terminal hair from the unaffected posterior scalp will continue its growth pattern even when transplanted to the balding frontal scalp[38]. Unfortunately, until the 1990s, hair transplants often had an unnatural appearance due to unsightly and obvious "plugs", sometimes likened to a "Barbie-doll" appearance. Over the past two decades, there has been a revolutionary movement away from 3–4 mm grafts containing 15–30

Fig. 157.4 Combination of hair transplantation and oral finasteride (1 mg daily). A 38-year-old man with male pattern hair loss (baseline). **B** Appearance following 1 year of finasteride plus hair transplantation (500 grafts).

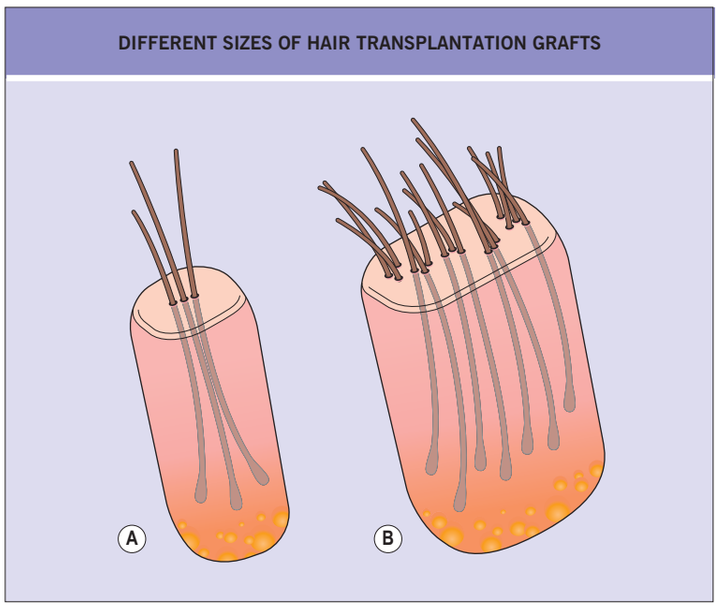


Fig. 157.5 Different sizes of hair transplantation grafts. A The newer technique uses 1- to 4-hair follicular unit grafts. **B** The older technique uses larger 10- to 15-hair grafts.

Fig. 157.6 Hair transplantation for male pattern hair loss. A Norwood IV pattern (baseline). **B** Appearance following transplantation of 900 hair grafts, each with one to three hairs.

hair follicles to grafts containing groupings of one to four hair follicles, referred to as individual follicular units (Fig. 157.5). This has resulted in the transplanted hair having a more natural appearance (Figs 157.6 & 157.7).

The net perceived density from a hair transplant is equal to the number of follicles transplanted minus ongoing hair loss. In order to maximize long-term results, all patients undergoing this surgical procedure are encouraged to continue topical minoxidil and/or oral finasteride (see above). Halting or at least slowing the miniaturization process allows for the perception of greater hair density.

Candidate Selection

As with all surgical procedures, the preoperative consultation is key to the success of the procedure. The consultation establishes whether the patient is an appropriate or inappropriate candidate for hair transplantation, both from a medical and a psychological perspective. In addition, it allows for an assessment of areas of greatest concern and whether the patient has realistic expectations of what a hair transplant can achieve.

A complete medical, surgical and hair loss history is obtained, including previous hair transplants and scalp surgeries as well as scar formation. The etiology of the hair loss is determined, primarily via physical

Fig. 157.7 Hair transplantation for female pattern hair loss. A Ludwig II pattern (baseline). **B** Appearance following transplantation of 750 hair grafts, each with one to three hairs.

examination of the scalp. Occasionally, additional sites need to be examined and/or clinicopathologic correlation is required. The stage of patterned hair loss also needs to be established (see Figs 157.2 & 157.3). All medications, prescription, over-the-counter and herbal, are reviewed with regard to their effects on hair growth and hemostasis.

The basic criteria for assessing the appropriateness of a candidate for hair transplantation are outlined in Table 157.1. In particular, the density of donor hair in the occipital scalp and the caliber of the hair need to be appraised, as both have an impact on the perceived density of the transplant (Table 157.2). Obviously, greater donor density and more grafts to transplant as well as thicker hairs lead to a fuller-appearing transplant.

FIVE BASIC CRITERIA FOR ASSESSING CANDIDATES FOR HAIR TRANSPLANTATION	
Age	Patients over the age of 25 years are preferable. While patients younger than 25 years of age often seek consultation, there is a hesitancy to operate. The predictive value of future hair loss is much lower for individuals between 15 and 25 years of age. Even with the theoretical safety net of finasteride, physicians should carefully choose candidates under 25 years of age. This subgroup also tends to desire a return to a full head of hair as opposed to a mature pattern of restoration that is routinely performed in older age groups
Hair shaft caliber	The caliber of the hair shaft is crucial. Those with large-caliber hair shafts (greater than 70 microns) obtain much denser coverage than individuals with corn silk quality hair. This can be demonstrated mathematically in that very small volume increases in hair shaft diameter result in exponential increases in surface area coverage
Donor hair	A variety of instruments are available to measure donor hair density. Measuring a 0.25 cm^2 field and multiplying by four is the preferred method. Patients seeking hair transplantation who have >80 follicular units/cm^2 are excellent candidates. Those with donor hair density <40 follicular units/cm^2 are considered poor candidates
Degree of baldness	The degree of baldness is perhaps the most important criterion in candidate selection. Those with complete baldness of the frontal scalp as opposed to baldness limited to the vertex are excellent candidates. When frontal baldness is corrected, this creates the most dramatic positive change in appearance
Hair color	Follicular unit grafting has made hair color less of an issue than when punch grafts were employed. Color contrast between hair and skin can make grafts apparent if not transplanted with great care. Individuals with "salt-and-pepper" hair, red hair or blonde hair are preferential to those with jet-black hair. Black-haired individuals are not exempt as hair transplant candidates, but should receive only one-hair follicular units in the frontal hairline for the most natural result. Proper technique eliminates most problems with dark-haired candidates

Table 157.1 Five basic criteria for assessing candidates for hair transplantation.

HAIR TRANSPLANTATION – CLINICAL FINDINGS AND REALISTIC EXPECTATIONS		
Clinical findings	**Realistic expectations**	**Comment**
• High donor density • Large-caliber (thick) hair • Stabilized hair loss via topical minoxidil and/or oral finasteride	1000–1500 graft sessions will create the perception of increased hair density	Need to plan the procedure *assuming* the patient may stop the medication(s) and the hair loss will resume
• Poor donor density • Thin-caliber hair • Ongoing hair loss	1000–1500 graft sessions may create little increase in *perceived* density	Although the transplant will result in more hair, this may not be apparent due to ongoing hair loss and thin-caliber hair

Table 157.2 Hair transplantation – clinical findings and realistic expectations. The net density from a transplant = number of follicles transplanted minus ongoing hair loss.

Key Concepts

Both men and women should be made aware that AGA represents an ongoing process, i.e. it will progress despite undergoing hair transplantation. Medications (e.g. oral finasteride) can help to maximize hair density from a transplant by minimizing ongoing hair loss. However, in planning for the transplant procedure, the surgeon should always assume that in the future these medications may be discontinued (see Table 157.2). Also, the progressive nature of AGA means that additional hair transplants may be required, perhaps in another 5 or 10 years. The physician should therefore emphasize *before* the procedure how ongoing hair loss will affect the density and cosmetic appearance of the transplant as well as how this influences the placement of the grafts so as to assure a long-term natural appearance.

The number of expected procedures to accomplish both short- and long-term goals should be reviewed, as well as the limits on available donor hairs. Reasons for preferring to transplant the frontal scalp as opposed to the vertex need to be explained – the vertex can consume donor grafts, it exhibits a continued 360° progression of hair loss which can lead to a peripheral rim of bald scalp, and this area of the scalp remains visible due to a central gravity pull. Concentrating the transplants in the frontal scalp will allow maximum long-term density with minimal long-term cosmetic risk.

Patients have to realize that elliptical donor harvesting will lead to a permanent scar of the posterior scalp (Fig. 157.8). The scar is of no practical concern unless the patient has his or her hair closely cut. If the patient expresses an interest in having closely cropped hair, follicular unit extraction should be considered (see below). Lastly, the patient must appreciate the need for a conservative approach to placement of the anterior hairline so that it will have a natural appearance over a lifetime.

Fig. 157.8 Occipital scalp scar secondary to elliptical donor harvesting.

Staff Training

Contemporary hair transplantation is a team procedure, and an efficient, high-quality transplant requires a well-trained surgical team. Assistant technicians should be motivated and interested in learning and mastering the procedure. In addition, they need to be able to do repetitive tasks without tiring, losing concentration or become frustrated. Technicians are utilized primarily for cutting and planting. The first task involves sectioning of the donor strip into slivers, followed by further meticulous sectioning into follicular units and prompt placement into chilled saline (Fig. 157.9). The second task requires creation of recipient sites and proper insertion of follicular unit grafts. Even with highly trained and efficient staff, it will take twice as long to place grafts into pre-made recipient sites at a density of 35–40 follicular units/cm^2 as it does to place the same number of grafts loosely (i.e. 20–25 follicular units/cm^2).

During the procedure, the physician closely monitors the quality of graft creation and placement. It is recommended that physicians learning the procedure have a staff member train at the same time. In order to avoid repetitive strain syndrome, technicians should position their elbows or forearms on a firm, supportive surface while using wrist and

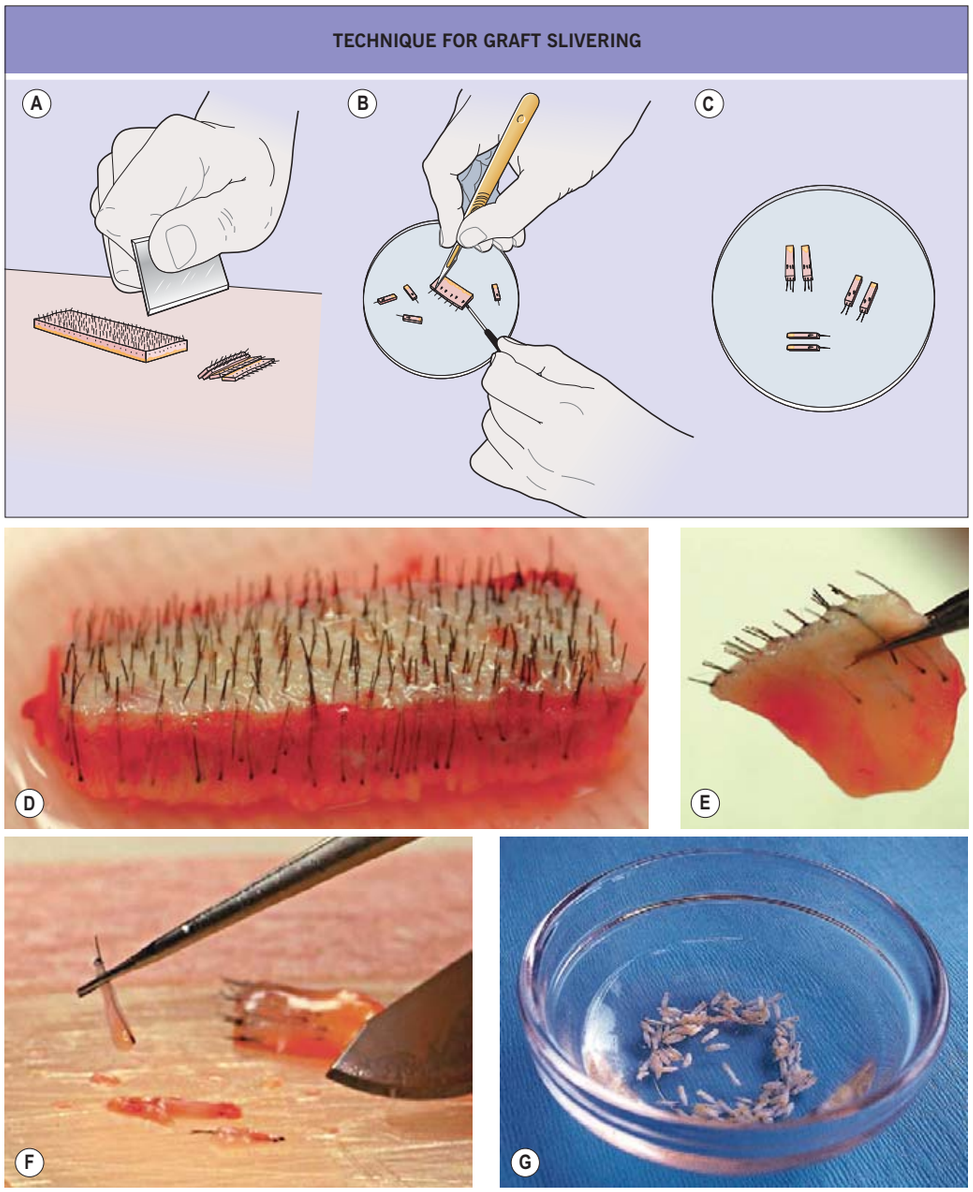


Fig. 157.9 Technique for graft slivering. A Donor slivering producing slivers 2 mm wide by 10 mm long. **B** Slivers being sectioned into follicular units. **C** Follicular unit grafts are placed into dish with saline and separated into one-, two- and three-haired follicular units. **D** A portion of donor strip prior to slivering. **E** Appearance of a sliver. **F** A single follicular unit produced by microscopic dissection of a sliver. **G** Follicular unit grafts are stored in isotonic saline to maintain their viability.

COMPARISON OF ELLIPTICAL DONOR HARVESTING VERSUS FOLLICULAR UNIT EXTRACTION		
	Elliptical donor harvesting	**Follicular unit extraction**
Visible scar if short hair cut	Yes	No
Transection of hair follicles	Minimal	Variable
Time required to perform harvest	10–20 minutes	30–90 minutes
Need to create grafts	Yes	No
Quality of resulting transplant	Excellent	Excellent

Table 157.3 Comparison of elliptical donor harvesting versus follicular unit extraction.

finger movements to plant grafts. Rotation of duties can also prove helpful.

Donor Region

The amount of available donor hair is the primary limiting factor in hair transplantation. In general, there are 65–85 follicular groupings/cm^2 in the occipital donor scalp[39]. If there are <40 follicular units/cm^2, the patient is considered a poor candidate (see Table 157.1). The mid occipital scalp between the upper and lower occipital protuberances is the recommended donor site, given its density of hair and the ability to camouflage the donor scar given the lack of involvement by AGA. Of note, the donor density does not correlate with the extent of current or future hair loss in the frontal scalp or vertex.

Harvesting of donor hair is performed via two different techniques: elliptical donor harvesting and follicular unit extraction (Table 157.3).

Elliptical donor harvesting

In the vast majority of patients, elliptical donor harvesting is performed because it allows for the safe and rapid removal of large numbers of hair follicles, with minimal transection of hairs[40]. The width of the donor ellipse ranges from 7 mm to 1.2 cm, while the length should be less than 30 cm. The number of follicular groupings required determines the dimensions of the donor ellipse. For example, if 1000 follicular groupings are needed for the frontal scalp and a patient has an average donor density of 75 follicular units/cm^2, a 13.5 cm by 1 cm strip should contain approximately 1000 follicular grafts. It is important to remember that increasing the width of a donor ellipse creates more wound tension which may lead to a hypertrophic or wide scar.

The ellipse is removed under local anesthesia. Ideal anesthesia is obtained by infiltrating 0.5–1% lidocaine with epinephrine (adrenaline) superficially in the dermis. Once anesthesia is obtained, 20 ml of normal saline can be injected to provide further anesthesia, hemostasis and dermal turgor; the latter helps to reduce the transection of hair follicles. Initial scoring of the excision may be done with a single or double #15 blade scalpel. The blade should be oriented parallel to the exiting follicles, again to avoid transection of hair follicles. The incision should be into the subcutaneous fat and not deeper, in order to avoid transecting the occipital arteries and nerves (Fig. 157.10). Lateral retraction using fine skin hooks exerts tension away from the excision and creates good visibility for the surgeon harvesting the ellipse[41] (Fig. 157.11). The ellipse can be removed by scissors or a scalpel, being careful to avoid damage to any follicles in the subcutaneous tissue.

If the incision does not go any deeper than the subcutaneous fat, the ellipse can be removed without the use of electrocoagulation or thermal coagulation. The donor ellipse can often be primarily repaired with no undermining if it is <1 cm in width. Some surgeons utilize a two-layer closure while others perform a single-layer closure. Staples or sutures can placed and then removed 7–10 days later. Absorbable sutures may be used for those patients who live a long distance away from the physician's office.

Follicular unit extraction

Follicular unit extraction (FUE) represents the removal of individual follicular groupings from the posterior scalp via an approximately 0.75–1.2 mm punch device[42,43]. The incisions are so small that they leave no visible scar after they heal. For patients who like to have closely cropped hair and do not want a visible scar, FUE is an excellent alternative technique for harvesting donor hair. It is also an option for those patients with extensive scarring from previous transplant procedures. However, FUE requires more time than elliptical donor harvesting, fewer follicular groupings are obtained from each procedure, and there is a higher rate of transection of the follicular groupings. In the future, refined instruments and robotics will hopefully lead to more rapid and precise harvesting of individual follicular groupings.

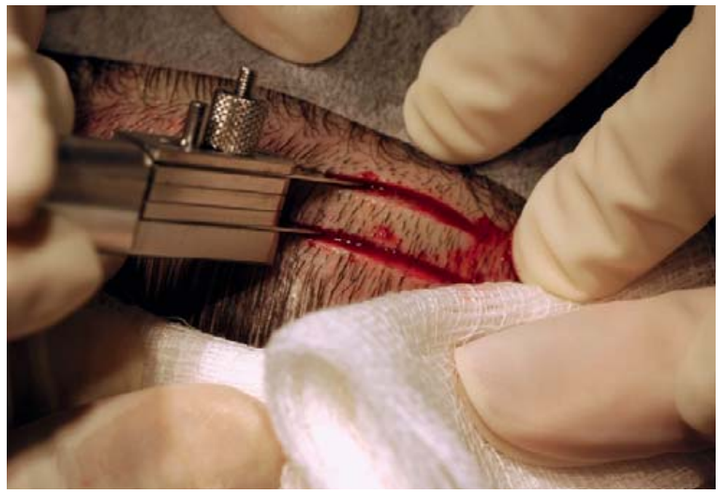


Fig. 157.10 Elliptical donor harvesting. To avoid transection of the hair follicles, the double blades should be oriented parallel to the exiting follicles. The incision should extend into the subcutaneous fat but not deeper (~5 mm into the scalp). Some surgeons prefer a single blade for performing the ellipse.

Fig. 157.11 Elliptical donor harvesting. Lateral retraction using fine skin hooks exerts tension away from the excision and creates good visibility. The ellipse can be removed by scissors or a scalpel, being careful to avoid damage to any follicles in the subcutaneous tissue.

Follicular Grafts

Hair naturally grows in bundles of one to four hair follicles, referred to as a follicular unit (see Fig. 157.5)[44]. Earlier punch grafts that measured 3–4 mm in diameter were often oriented in a perpendicular fashion and contained multiple follicular units, leading to an unnatural appearance. Nowadays, each graft contains just one follicular grouping and is oriented at an acute, 30–45° angle toward the front and slightly toward the midline (see below). Thus, these grafts mimic the natural grouping and orientation of scalp hairs.

Over several hours, surgical teams can carefully separate 500–2000 follicular units from the donor strip (see Fig. 157.9). Cutting instruments include #11 and #15 blades as well as #10 prep blades. Good lighting, comfortable chairs and well-designed instruments are prerequisites for producing follicular units with minimal transection.

Fig. 157.12 Use of magnification to separate follicular units from the donor strip.

Fig. 157.13 Immediate postoperative appearance with graft placement and hairline design.

Some surgeons believe microscopic dissection or magnification reduces transection of follicles during the separation process (Fig. 157.12)[45]. However, the data are still inconclusive. What is not debated is the need to create intact, minimally traumatized follicular units and place the transplanted hair into the recipient sites as efficiently and quickly as possible. As soon as the follicular unit grafts are separated from the donor ellipse, they must be put into chilled saline or an equivalent medium until they are placed into the recipient sites. If grafts desiccate for even a few minutes they will die and not grow.

The number of follicular units required for each surgery depends on the extent of hair loss, available donor hair and density of pre-existing terminal hair follicles in the recipient area. This can vary from 100 to 2500 follicular groupings per procedure.

Hairline Design and Recipient Site Creation

In men, the hairline defines the cosmetic success of a hair transplant. Because women have stable frontal, temporal and posterior hairlines, recreating a hairline in them is usually not necessary. As with hair graft creation, hairline design should mimic as closely as possible what occurs in nature. Unfortunately, patients and physicians often try to recreate the hairline a patient had before the hair loss began. Even if all the available follicular units are utilized, this approach often leads to cosmetic failure. The explanation is the slow steady recession of the temporal and posterior hairlines as well as the frontal hairline.

The design of the frontal hairline should be such that it will remain balanced with the temporal and posterior hairlines. This requires re-creating a frontal hairline which is higher and more receded than the one which was present before the process began. Initially, some patients will resist this idea, but explaining and demonstrating with a mirror how recession of their temporal and posterior hairlines precludes such a low frontal hairline will hopefully convince them of the wisdom of this recommendation.

Rather than viewing the hairline as a fixed boundary, it should be considered a natural transition zone of gradually increasing density from skin to terminal hair-bearing skin. This ill-defined "feathering zone" is re-created by randomly placing, in an irregular pattern, follicular unit grafts along the newly created hairline (Fig. 157.13)[46]. Dense packing of grafts should not be performed because this will lead to a hairline with an unnatural appearance. The level at which the hairline is placed varies from individual to individual and it is important to first examine each patient in a global, 360° manner.

While male pattern hair loss is progressive, transplanted hair will have long-term growth. Therefore, when evaluating patients, the surgeon must assume that all patients will progress to the highest grade of involvement (see Fig. 157.2) with only transplanted hair remaining. This assumption allows transplanted hair to look equally natural 1 year and 20 years after surgery. As noted previously, for several reasons, transplanting into the vertex is ill-advised (see above).

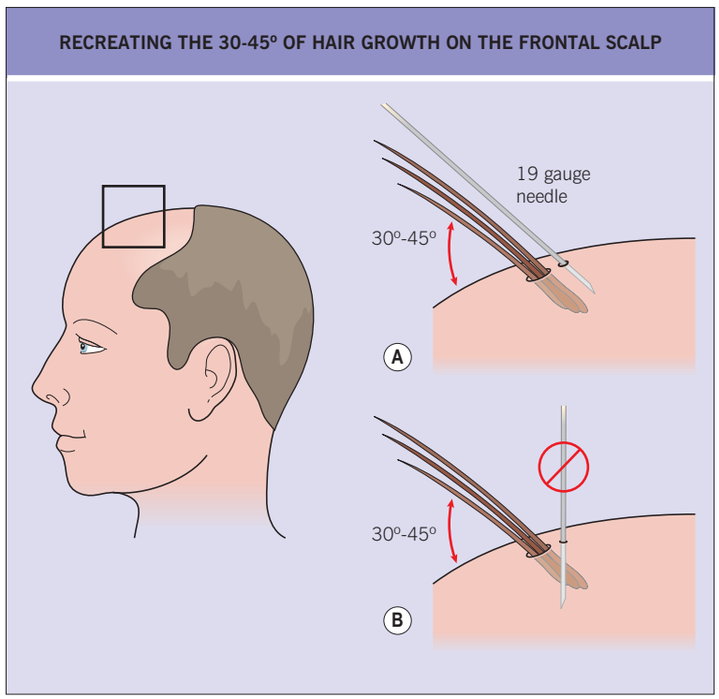


Fig. 157.14 Recreating the 30–45° of hair growth on the frontal scalp. Correct **(A)** versus incorrect technique **(B).** Grafts should not be oriented perpendicular to the scalp surface.

Anesthesia and Recipient Site Creation

While the hair grafts are being harvested from the donor ellipse, the physician anesthetizes the recipient zone. A combination of supraorbital/supratrochlear nerve blocks, field blocks and local infiltration with 1% lidocaine with epinephrine can be performed. Hemostasis is essential for good visibility when creating recipient sites and for graft placement. The epinephrine in the local anesthetic (placed into the dermis and not the subcutaneous space) creates excellent hemostasis.

Recipient sites should mimic the natural 30–45° angle of hair growth on the scalp (Fig. 157.14). There are a variety of needles, including 19- and 20-gauge needles, that are used to make sites large enough to place individual follicular units. When making recipient sites, surgeons must be careful not to transect existing hair follicles. Some advocate using magnification to create recipient sites, in order to limit the loss of existing hair during surgery[47]. The key to success is to create recipient sites in a random, highly irregular pattern with 10–30 follicular units/cm^2, depending on the density of existing hair on the scalp. Sometimes multiple sessions are required when lower densities are utilized.

Graft Placement and Postoperative Course

Two to three surgical assistants place the grafts with microvascular forceps. These forceps are used to gently grasp the follicular units by their perifollicular tissue, avoiding trauma to the hair follicles. Regular surgical forceps are not recommended. Placement of the grafts into recipient sites is often the most challenging component of the hair transplant procedure, both for novice and experienced hair transplant teams. The major challenges include hemostasis and "popping" of grafts from recipient sites after they are placed. With the use of smaller-caliber needles to create recipient sites, hemostasis has become less of a problem. However, it is difficult to predict which patient will have "popping" grafts. This phenomenon is overcome by applying light pressure over a placed graft for 5–15 seconds with a saline-soaked cotton swab (e.g. Q-tip®) before placing the next graft.

After the procedure, an overnight dressing to protect the grafts is placed. The entire dressing should be non-adherent and removed by the patient the next morning (Table 157.4). Staples or sutures are removed during a postoperative visit 7–10 days after surgery. The transplanted hair begins to appear 3–6 months after the procedure and is fully grown by 9–14 months. Patients must be warned of the possibility of post-transplant telogen effluvium.

HAIR TRANSPLANTATION – POSTOPERATIVE INSTRUCTIONS	
Day of the procedure	• Apply non-adherent dressing overnight • Oral acetaminophen (paracetamol) 300 mg/codeine 30 mg [Tylenol #3®] every 4–6 hours as needed with food* • Oral prednisone 40 mg daily for 3 days to reduce frontal scalp edema • Resume regular activities, but no heavy lifting or strenuous exercise until staples/sutures removed • Sleep with head elevated
Postoperative days 1–3	• Day 1 – remove dressing • Shower each day and allow water to run over grafts • Comb hair without allowing comb's teeth to hit perifollicular crusts • Do not pick or scratch at perifollicular crusts • Apply emollient to the donor site(s) daily • Days 1, 2 – continue prednisone (see above)
Postoperative days 4–7	• Resume light exercise • Follow instructions outlined above for showering, combing and emollient application
Postoperative days 7–10	• Staples/sutures removed • Resume regular exercise regimen • Perifollicular crusts gradually disappear
*In general, only required the day of surgery.	

Table 157.4 Hair transplantation – postoperative instructions. Patients should not wear a hairpiece for at least 2 weeks after the procedure.

Complications

Medical and surgical complications from a hair transplant procedure are unusual. The extensive vascular supply to the scalp results in rapid wound healing and a low risk of infection. In addition to reactions to medications and vasovagal episodes, complications include excessive swelling (~5%), postoperative bleeding (<0.5%), folliculitis, a temporary headache, and temporary pruritus or numbness of the scalp. Persistent problems include permanent numbness in the donor or recipient sites, abnormal scarring around the grafts, hypertrophic scarring of the donor site, and poor growth of hair grafts. The latter can be minimized by keeping the grafts constantly moist.

Corrective Hair Transplant Surgery

When patients present for corrective surgery due to previous transplantation of 3–4 mm punch grafts that have led to unnatural large "plugs", i.e. a "pluggy" transplant, three major options exist: (1) add a large number of follicular unit grafts containing one to four hairs between the larger plugs to soften their appearance; (2) surgically remove the large grafts; and/or (3) perform laser-assisted hair removal. Which option is best suited for an individual patient is determined during the consultation.

Adding follicular unit grafts

Transplantation of a large number of follicular unit grafts containing one to four hair follicles – in front of, in between and behind large grafts – will soften the "pluggy" appearance (Fig. 157.15). This option is appealing for many patients because it allows for both cosmetic improvement and increased density (Fig. 157.16). Unfortunately, some patients with an unnatural hairline have a depleted donor supply from previous transplant procedures while others are reluctant to have another surgery following the emotional trauma from the initial transplant.

Surgical removal of grafts

Some hairlines are so cosmetically inappropriate that there is no worthwhile corrective option other than surgically removing the grafts. This option is also indicated for large grafts with perifollicular white scar tissue. The grafts can be removed by either a 2–4 mm punch instrument or an elliptical excision. Another option is to perform follicular unit extractions from larger grafts via 1 mm punch instruments. The latter procedure reduces the "pluggy" appearance of the larger grafts while allowing a more natural appearing graft to remain.

In general, scars on the scalp heal well with minimal evidence of the surgical procedure. However, all patients should be warned that cosmetically evident scars develop in a small minority of cases. If unacceptable scars do arise, pulsed dye, ablative, non-ablative, or fractional ablative laser treatments can be used to help improve the cosmetic appearance.

Laser-assisted removal of large grafts

As with other parts of the body, lasers only remove pigmented terminal hair follicles[48]. Typically 5–10 treatments are needed to permanently

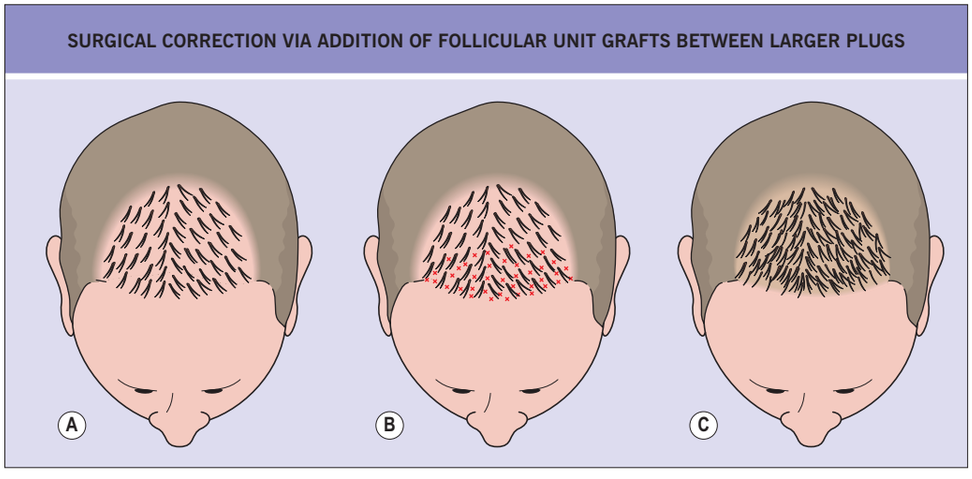


Fig. 157.15 Surgical correction via addition of follicular unit grafts between larger plugs. **A** Previous transplantation of 3–4 mm punch grafts can lead to unnatural large "plugs" of hair. **B**, **C** Addition of follicular unit grafts between and in front of the larger grafts softens the hairline and the overall appearance.

Fig. 157.16 Corrective hair transplant surgery. A Widely scattered large plugs with significant contrast between the lightly pigmented scalp and the black hairs. **B** Softened and improved appearance after the transplantation of 1000 follicular unit grafts containing one to three hairs.

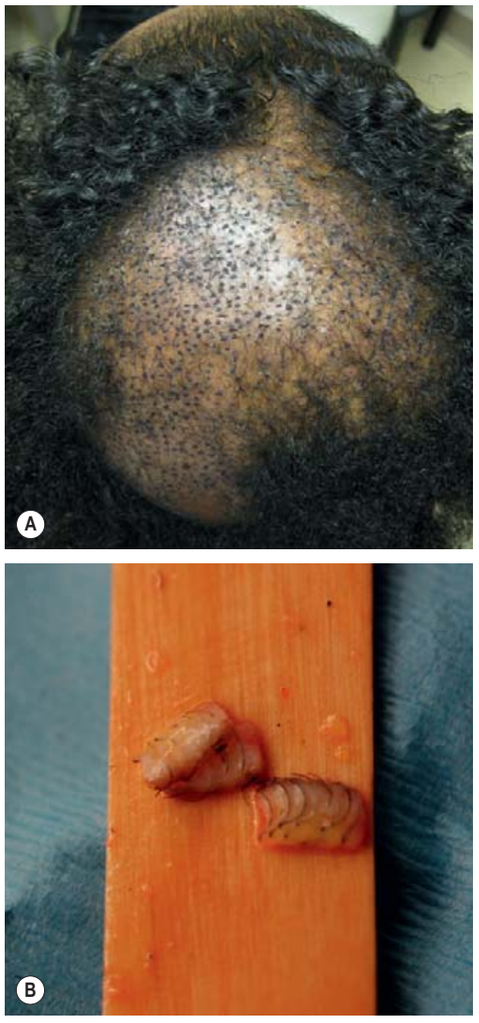


Fig. 157.17 Hair transplantation for central centrifugal cicatricial alopecia. A Appearance 1 week following transplantation of 1200 follicular unit grafts in an African-American woman. **B** Cross-section of African-American hair follicles demonstrating their characteristic C-shaped curve.

remove the majority of follicles. Similar to follicular unit extraction of larger grafts, laser-assisted removal eliminates the majority, but not all, of the hairs, thus providing a substantial cosmetic improvement of the unnatural plugs while retaining some of the transplanted hair for a more natural appearance. Laser therapy is an excellent option for patients who want to improve their cosmetic appearance in a safe, non-invasive manner.

Hypertrophic or broad scars in the donor region

All patients have a permanent scar from elliptical donor harvesting, but the majority of scars are 1–2 mm wide and are of no practical concern (see Fig. 157.8). That said, patients should be made aware of this permanent donor scar *before* they have a transplant. If the patient expresses a possible interest in having their hair cut short, follicular unit extraction should be considered (see above).

When wide donor scars occur, they can be a major cosmetic problem without an easy solution for repair. Scar revision leads to variable improvement. Pulsed dye, non-ablative or fractional ablative lasers may be used to help reduce the thickness and erythema of hypertrophic scars. The best method for minimizing the risk of a wide scar is to keep the width of the donor strip to ≤1 cm. While this does not guarantee a fine, thin scar, it does reduce the risk of a wide scar. Another option is to transplant a large number of follicular groupings into the scar in an attempt to provide camouflage.

Hair Transplantation in Scarring Alopecias

Hair transplantation can be successfully performed in scarred skin. However, it is important that any inflammation, whether from a primary scalp dermatosis, infection or surgery, be resolved completely before hair is transplanted. In the case of inflammatory scalp dermatoses, patients should have no evidence of inflammation for 6 months off therapy before the transplant procedure is performed. If there is any concern regarding active inflammation, a biopsy specimen should be obtained. When there is any active inflammation, the transplanted hair may not grow. All patients should also be told *before* their first transplant that any future flare of scalp inflammation will likely affect the growth of the transplanted hair. Compared to sites without scarring, the yield is less when hair is transplanted into scar tissue. How large the difference will be varies from patient to patient. In general, more transplant sessions are needed in patients with scarring alopecia. Although more surgeries are required to create equal or less density, patient satisfaction is high.

Hair Transplantation in African-Americans

In addition to pattern hair loss in men and women of African ancestry, traction alopecia and central centrifugal cicatricial alopecia (CCCA) are also commonly seen in women (see Ch. 69)[49]. For CCCA, as stated previously, there should be no evidence of inflammation for 6 months (off therapy) before the transplant procedure is performed. While patients can wear wigs or hair pieces, hair transplantation is the only way to permanently fill in the areas of alopecia (Fig. 157.17A).

When transplanting Afrocentric hair, it important to note that the curl of the follicles and the C-shaped curve of the hairs make separation of the follicles slightly more difficult (Fig. 157.17B). Rather than using a straight blade, the blade must be bent in order to not transect the

hair follicles. Also, there is an increased risk of keloid formation, more often in the donor region than in the recipient sites.

FUTURE TRENDS

Regeneration and cloning of hair follicles represents the next step in revolutionizing hair transplantation. With an unlimited supply of hairs, there will no longer be constraints based upon the density of hairs in the donor region. In recent studies, keratinocyte tubulogenesis has been induced by cultured dermal papilla cells[50]; bone marrow- and umbilical cord-derived mesenchymal stem cells were shown to be a reservoir for follicle regeneration[51]; and epidermal wounding, with upregulation of Wnt proteins, led to hair follicle regeneration in adult mouse skin[52]. In addition, erythropoietin has been found to promote the growth of dermal papilla cells as well as to prolong the anagen phase of cultured human hair follicles[53]. Lastly, ongoing research utilizing a mouse model for androgenetic alopecia should provide insights into mechanisms of disease and therapies[54].

REFERENCES

1. Blanpain C, Lowry WE, Geoghegan A, et al. Self-renewal, multipotency, and the existence of two cell populations within an epithelial stem cell niche. Cell. 2004;118: 635–48.
2. Ito M, Kizawa K, Hamada K, Cotsarelis G. Hair follicle stem cells in the lower bulge form the secondary germ, a biochemically distinct but functionally equivalent progenitor cell population, at the termination of catagen. Differentiation. 2004;72:548–57.
3. Garza LA, Yang C-C, Zhao T, et al. Bald scalp in men with androgenetic alopecia retains hair follicle stem cells but lacks CD200-rich and CD34-positive hair follicle progenitor cells. J Clin Invest. 2011;121:613–22.
4. Ellis J, Stebbing M, Harrap S. Polymorphism of the androgen receptor gene is associated with male pattern baldness. J Invest Dermatol. 2001;116:452–5.
5. Hillmer A, Hanneken S, Tirzmann S, et al. Genetic variation in the human androgen gene is the major determinant of common early onset androgenetic alopecia. Am J Hum Genet. 2005;77:140–8.
6. Levy-Nissenbaum E, Bar-Natan M, Frydman M, Pras E. Confirmation of the association between male pattern baldness and the androgen receptor gene. Eur J Dermatol. 2005;15:339–40.
7. Wakisaka N, Taira Y, Ishikawa M, et al. Effectiveness of finasteride on patients with male pattern baldness who have different androgen receptor gene polymorphisms. J Investig Dermatol Symp Proc. 2005;10:293–4.
8. Sinclair R, Greenland KJ, Egmond S, et al. Men with Kennedy disease have a reduced risk of androgenetic alopecia. Br J Dermatol. 2007;157:290–4.

8a. Sawaya ME, Shalita AR. Androgen receptor polymorphisms (CAG repeat lengths) in androgenetic alopecia, hirsutism and acne. J Cutan Med Surg. 1998;3:9–15.

9. Hayes V, Severi G, Eggleton S, et al. The E211 G>A androgen receptor polymorphism is associated with a decreased risk of metastatic prostate cancer and androgenetic alopecia. Cancer Epidemiol Biomarkers Prev. 2005;14:993–6.
10. Prodi DA, Pirastu N, Maninchedda G, et al. EDA2R is associated with androgenetic alopecia. J Invest Dermatol. 2008;128:2268–70.
11. Hillmer AM, Brockschmidt FF, Hanneken S, et al. Susceptibility variants for male-pattern baldness on chromosome 20p11. Nat Genet. 2008;40:1279–81.
12. Hillmer AM, Flaquer A, Hanneken S, et al. Genome-wide scan and fine-mapping linkage study of androgenetic alopecia reveals a locus on chromosome 3q26. Am J Hum Genet. 2008;82:737–43.
13. Olsen EA, Whiting D, Bergfeld W, et al. A multicenter, randomized, placebo-controlled double-blind clinical trial of a novel formulation of 5% topical minoxidil topical foam vs. placebo in the treatment of androgenetic alopecia in men. J Am Acad Dermatol. 2007;57:767–74.
14. Avram MR, Cole JP, Gandelman M, et al. The potential role of minoxidil in the hair transplantation setting. Dermatol Surg. 2002;28:894–900.
15. Messenger AG, Rundegren J. Minoxidil: mechanisms of action on hair growth. Br J Dermatol. 2004;150:186–94.
16. Han JH, Kwon OS, Chung JH, et al. Effect of minoxidil on proliferation and apoptosis in dermal papilla cells of human hair follicle. J Dermatol Sci. 2004;34:91–8.
17. Abell E. Histologic response to topically applied minoxidil. Curr Ther Res. 1984;36:1098–106.
18. Buhl AE, Baker CA, Cietz AJ. Minoxidil sulphotransferase activity influences the efficacy of Rogaine topical solution (TS): enzyme studies using scalp and platelets. J Invest Dermatol. 1994;102:534.
19. Leyden J, Dunlap F, Miller B, et al. Finasteride in the treatment of men with frontal male pattern hair loss. J Am Acad Dermatol. 1999;40:930–7.
20. Finasteride Male Pattern Hair Loss Study Group. Long-term (5-year) multinational experience with finasteride 1 mg in the treatment of men with androgenetic alopecia. Eur J Dermatol. 2002;12:38–49.
21. Leavitt M, Perez-Meza D, Rao NA, et al. Effects of finasteride (1 mg) on hair transplant. J Dermatol Surg. 2005:31:1268–76.
22. Camacho FM, Garcia-Hernandez MJ, Fernandez-Crehuet JL. Value of hormonal levels in patients with male androgenetic alopecia treated with finasteride: better response in patients under 26 years old. Br J Dermatol. 2008;158:1121–4.
23. McClellan KJ, Markham A. Finasteride: a review of its use in male pattern hair loss. Drugs. 1999;57:111–26.
24. D'Amico AV, Roehrborn CH. Effect of 1 mg/day finasteride on concentrations of serum prostate-specific antigen in men with androgenetic alopecia: a randomized controlled trial. Lancet Oncol. 2007; 8:21–5.
25. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. N Engl J Med. 2003;349:215–24.
26. Cohen YC, Liu KS, Heyden NL, et al. Detection bias due to the effect of finasteride on prostate volume: a modeling approach for analysis of the Prostate Cancer Prevention Trial. J Natl Cancer Inst. 2007;99:1366–74.
27. Propecia (package insert). Whitehouse Station, NJ: Merck & Co: 2004.
28. Overstreet JS, Fug VL, Gould J, et al. Chronic treatment with finasteride daily does not affect spermatogenesis or semen production in young men. J Urol. 1999;162: 1295–300.
29. Liu KE, Binsaleh S, Lo KC, Jarvi K. Propecia-induced spermatogenic failure: a report of two cases. Fertil Steril. 2008;90:849.
30. Price VH, Roberts JL, Hordinsky M, et al. Lack of efficacy of finasteride in postmenopausal women with androgenetic alopecia. J Am Acad Dermatol. 2000;43: 768–76.
31. Iorizzo M, Vincenzi C, Voudouris S, et al. Finasteride treatment of female pattern hair loss. Arch Dermatol. 2006;142:298–302.
32. Yo JH, Jung JY, Choi JW, et al. 5 mg/day finasteride treatment for normoandrogenic Asian women with female pattern hair loss. J Eur Acad Dermatol Venereol. 2011;25:211–14.
33. Eun HC, Kwon OS, Yeon JH, et al. Efficacy, safety, and tolerability of dutasteride 0.5mg once daily in male patients with male pattern hair loss: a randomized, double-blind, placebo-controlled phase III study. J Am Acad Dermatol. 2010;63:252–8.
34. Amory JK, Wang C, Swerdloff RS, et al. The effect of 5-alpha-reductase on semen parameters and serum hormones in healthy men. J Clin Endocrinol Metab. 2007;92:1659–65.
35. Desai S, Mahmoud BH, Bhatia AC, Hamzavi IH. Paradoxical hypertrichosis after laser therapy: a review. Dermatol Surg. 2010;36:291–8.
36. Avram MR, Rogers NE. The use of low-level light for hair growth: part I. J Cosmet Laser Ther. 2009;11:110–17.
37. Leavitt M, Charles G, Heyman E, Michaels D. HairMax LaserComb laser phototherapy device in the treatment of male androgenetic alopecia: a randomized, double-blind, sham device-controlled, multicentre trial. Clin Drug Invest. 2009;29:283–92.
38. Orentreich N. Autografts in alopecias and other selected dermatological conditions. Ann N Y Acad Sci. 1959;83: 463–79.
39. Jimenez F, Ruifernández JM. Distribution of human hair in follicular units. A mathematical model for estimating the donor size in follicular unit transplantation. Dermatol Surg. 1999;25:294–8.
40. Avram M, Rogers N. Contemporary hair transplantation. Dermatol Surg. 2009;35:1705–19.
41. Pathomvanich D. Donor harvesting: a new approach to minimize transection of hair follicles. Dermatol Surg. 2000;26:345–8.
42. Harris JA. Follicular unit extraction. Facial Plast Surg. 2008;24:404–13.
43. Onda M, Igawa HH, Inoue K, Tanino R. Novel technique of follicular unit extraction with a powered punching device. Dermatol Surg. 2008;34:1683–8.
44. Sinclair R, Jolley D, Mallari R, Magee J. The reliability of horizontally sectioned scalp biopsies in the diagnosis of chronic diffuse telogen hair loss in women. J Am Acad Dermatol. 2004;51:189–99.
45. Limmer BL. Elliptical donor stereoscopically assisted micrografting as an approach to further refinement in hair transplantation. J Dermatol Surg Oncol. 1994;20: 789–93.
46. Stough DB, Schell BJ, Weyrich R. The role of facial proportion in hair restoration surgery. Ann Plast Surg. 1997;38:129–36.
47. Avram MR. Polarized light-emitting diode magnification for optimal recipient site creation during hair transplant. Dermatol Surg. 2005;31:1124–7.
48. Grossman MC, Dierickx C, Farinelli W, et al. Damage to hair follicles by normal mode ruby laser pulses. J Am Acad Dermatol. 1996;35:889–94.
49. Callender VD, McMichael AJ, Cohen GF. Medical and surgical therapies for alopecias in black women. Dermatol Ther. 2004;17:164–76.
50. Chermnykh ES, Vorotelyak EA, Gnedeva KY, et al. Dermal papilla cells induce keratinocyte tubulogenesis in culture. Histochem Cell Biol. 2010;133:567–76.
51. Yoo BY, Shin YH, Yoon HH, et al. Application of mesenchymal stem cells derived from bone marrow and umbilical cord in human hair transplantation. J Dermatol Sci. 2010;60:74–83.
52. Ito M, Yang Z, Andl T, et al. Wnt-dependent de novo hair follicle regeneration in adult mouse skin after wounding. Nature. 2007;447:316–20.
53. Kang BM, Shin SH, Kwack MH, et al. Erythropoietin promotes hair shaft growth in cultured human hair follicles and modulates hair growth in mice. J Dermatol Sci. 2010;59:86–90.
54. Crabtree JS, Kilbourne EJ, Peano BJ, et al. A mouse model of androgenetic alopecia. Endocrinology. 2010;151:2373–80.

This page intentionally left blank

Soft Tissue Augmentation 158

Nazanin Saedi, Adam M Rotunda, Derek H Jones, Rhoda S Narins, Seth L Matarasso and Neil S Sadick

Chapter Contents

Filler materials and general injection technique 2548
Temporary fillers 2550
Semi-permanent fillers 2554
Permanent fillers 2555

Key features

- Fillers are used to soften the appearance of superficial wrinkles and to recontour and smooth the deep folds of the face
- Other indications include reducing the appearance of atrophic, traumatic and acne scars; lip augmentation; and volumizing the face in areas of lipoatrophy or senescence-associated fat loss
- Agents include autologous fat grafts, hyaluronic acid derivatives, bovine collagen and synthetic materials
- Selection of an agent depends on the size, depth and location of the volume deficiency
- Agents are injected into the dermis or subcutaneous fat by various techniques, such as serial puncture, linear threading, fanning, cross-hatching or depot injection
- Fillers can be used as monotherapy or as an adjunct to other rejuvenating injectable techniques or surgical procedures in order to maximize longevity and aesthetic correction
- Complications are technique-dependent or material-related, and include hypersensitivity reactions, granuloma formation, bacterial biofilms, contour irregularities and vascular occlusion

Interventions for the aging face can be broadly categorized into the four "R's" of facial rejuvenation: **R**esurfacing (chemical peels, dermabrasion, and ablative and non-ablative lasers); **R**edraping (the various pulling and lifting facial surgical procedures); **R**elaxing (chemodenervation with paralytic agents); and **R**eplacement/Recontouring (the use of filling agents for superficial and deep soft tissue augmentation). This fourth "R" has recently witnessed remarkable growth, and as patient demand for safe and effective minimally invasive aesthetic techniques has increased, the menu of available dermal fillers and agents for soft tissue augmentation has expanded exponentially. More recently, there has been a shift from filling wrinkles and lines to volumization of atrophied fat and bone[1].

Patients often do not adequately appreciate the degree and significance of their volume defect, and must first be educated about the underlying anatomy of what is producing their "wrinkle". In addition to explaining the significance of volume deficits adjacent to the areas of primary concern, a distinction must be made between dynamic versus static lines as well as cutaneous changes due to photodamage versus those due to chronologic aging (senescence) and gravity (Table 158.1). Although these defects often appear in combination, they must be assessed individually. Patients should be made aware of newer, commercially available injectable products so that the physician is able to personalize their treatment and cater to subtle nuances of their faces. Many of the newer products have unique characteristics and indications that make them more suitable for some patients. Although once a physician becomes enamored with a particular product, it may become the "workhorse" filler in his or her clinical practice.

While the type of defect is clearly important, so are its size, depth and location, as well as the appearance and integrity of the adjacent tissue (Table 158.2). A discussion regarding therapeutic options should include alternatives such as surgery (e.g. rhytidectomy, excision, punch grafting), resurfacing (see Ch. 137) and chemodenervation agents (see Ch. 159), as well as no intervention at all. Patients should understand the indications, technique, advantages, disadvantages and inherent risks of each procedure, with an estimation of the financial cost and recuperation time ("downtime"). As with any treatment, the degree of overall success is largely proportional to the creation (and achievement) of realistic and appropriate goals and expectations by both the physician and the patient. Patients undergoing elective rhytid effacement with soft tissue augmentation must realize that replacing lost or atrophic subcutaneous tissue is often temporary (Table 158.3). Monotherapy with one agent may not be adequate and multiple agents may be required. All wrinkles are not created equal; they come in many shapes and sizes, and, as such, there is no one filler agent that is suitable for all defects. The choice of an appropriate dermal or subcutaneous implant whether temporary, semi-permanent or permanent – requires knowledge of the available options and their characteristics.

CAUSES OF CUTANEOUS DEFECTS
CHRONOLOGIC AGING
• Loss of subcutaneous fat • Gravity
PHOTODAMAGE
• Degradation of collagen, elastin, hyaluronic acid and other components of the extracellular matrix • Neoplastic changes
TRAUMA
• Disease • Inflammation • Surgery

Table 158.1 Causes of cutaneous defects.

SOFT TISSUE AUGMENTATION: PREINJECTION CONSIDERATIONS	
Defect parameters and medical background	**Patient goals**
Medications (anticoagulants) History of hypersensitivity reaction History of herpes simplex viral infections of the face Volume required Location Alternative/simultaneous treatments Medical history (e.g. autoimmune connective tissue disease) Prior procedures (e.g. facelifts, reconstruction, implants and/or injections) Pregnancy/lactation	What defect is of concern to the patient? Expectations regarding degree of correction (facilitated by standardized photoscales) Expectations regarding product longevity Morbidity ("downtime") patient is willing to tolerate and sustain Risk/benefit ratio

Table 158.2 Soft tissue augmentation: preinjection considerations.

SOFT TISSUE AUGMENTATION INDICATIONS
• Non-dynamic rhytides – nasojugal and nasolabial folds, jowls and marionette lines
• Volume deficits – lipoatrophy (associated with antiretrovirals, senescence), sunken temples, tear trough deformity, atrophic dorsal hands
• Building up volume – malar prominence, chin, eyebrow elevation
• Distensible scar
– Acne scar
– Traumatic/surgical scars
• Perioral – vermilion, vertical "bar code" lines, oral commissure
• Combination therapy
– Multiple fillers
– Paralytic agents (botulinum A toxin)

Table 158.3 Soft tissue augmentation indications.

PARTIAL LIST OF CHARACTERISTICS OF THE IDEAL FILLER SUBSTANCE	
Material	**Administration**
Non-allergenic (minimal risk of hypersensitivity)	Basic instrumentation
FDA-approved	Painless
Non-carcinogenic/non-teratogenic	Outpatient
No migration	Minimal recuperation
Minimal inflammation	User-friendly product (e.g. easy flow, ergonomic syringe)
No overt cutaneous change (undetectable)	Versatile syringe volumes (i.e. touch up syringes)
Reproducible	Easy storage (no need for refrigeration)
Durable	Long shelf-life
Minimal adverse sequelae (infection, ecchymosis)	
Stable (inert)	
Affordable	
Malleable post-injection	
Correctable post-injection (e.g. with hyaluronidase, collagenase)	

Table 158.4 Partial list of characteristics of the ideal filler substance. FDA, Food and Drug Administration.

HISTORICAL PERSPECTIVE

Dating back to 1893, Neuber used blocks of autologous fat harvested from the arms for tissue augmentation of depressed facial defects. In 1899, Gersvny injected paraffin into the scrotum as a testicular prosthesis for a patient with advanced tuberculosis. Twelve years later, Brunings first described using the syringe technique to transfer free fat. Then, in 1953, Baronders published a review of permanent soft tissue augmentation with liquid silicone. Finally, in 1981, bovine collagen (Zyderm® I) became the first US Food and Drug Administration (FDA)-approved xenogenic agent for soft tissue augmentation, followed by Zyderm® II and Zyplast®.

It was not until 20 years later that the FDA rapidly began to approve new fillers for temporary soft tissue augmentation. The CosmoDerm® family of injectable collagens, derived from a single human fibroblast source, was soon followed by the fast-track release of an entirely new class of agents – the hyaluronans. Restylane®, a non-animal stabilized hyaluronic acid (NASHA), was shortly followed by hyaluronans derived from rooster combs (Hylaform® and then Hylaform Plus®). A survey by the American Society for Aesthetic Plastic Surgery in 2004 revealed that the hyaluronans had become the most popular filling agents and this trend has continued to the present. The release, popularity and safety of these new agents prompted further investigation and this was shortly followed by the availability of the longer-lasting synthetic products – calcium hydroxylapatite (Radiesse®) and poly-L-lactic acid (Sculptra®) – and a renewed interest in permanent fillers such as silicone oil and polymethylmethacrylate microspheres[2].

FILLER MATERIALS AND GENERAL INJECTION TECHNIQUE

There is an ever-expanding array of materials and devices for soft tissue augmentation (Tables 158.4 & 158.5). They can be subdivided, based on site of cutaneous placement (subcutaneous space or dermis), derivation (autologous, xenograft, allograft, synthetic or semi-synthetic) or, most commonly, duration of effect. In this chapter, the soft tissue fillers are categorized as *temporary* (effect <6 months), *long-lasting* (6 months to 2 years), *semi-permanent* (2 to 5 years), and *permanent*

COMPARISON OF FILLERS CURRENTLY EMPLOYED IN THE US								
Filler trade name (®,™)	**Source**	**Material**	**Duration of effect**	**Advantages**	**Disadvantages**	**Use in lips**	**Approved by the FDA**	**Volume filler**
Zyderm*, Zyplast*	Bovine	Collagen	2–4 months	Natural appearance, little swelling, less painful to inject	Bovine, requires two skin tests, short-lived	Yes	Yes	No
Cosmoderm*, Cosmoplast*	Human	Collagen	2–4 months	Natural appearance, little swelling, less painful to inject, no skin test	Short-lived	Yes	Yes	No
Restylane Fine Lines	Bacteria-derived	Hyaluronic acid (smaller particle size)	4–6 months	No skin testing, effective for vertical lip lines	Short-lived	Yes	No	Yes
Restylane/ Restylane-L*	Bacteria-derived	Hyaluronic acid	6–12 months	No skin testing, relatively long-lasting, versatile	Lip swelling, painful to inject without lidocaine	Yes	Yes	No
Perlane/Perlane-L*	Bacteria-derived	Hyaluronic acid	6–12 months	No skin testing, relatively long-lasting	Lip swelling, painful to inject without lidocaine	Yes	Yes	Yes
Hylaform	Rooster comb	Hyaluronic acid	3–4 months	No skin testing, less lip swelling, versatile	Short-lived, painful to inject†	Yes	Yes	No
Hylaform Plus	Rooster comb	Hyaluronic acid (larger particle size)	4 months	No skin testing, less swelling	Short-lived, painful to inject†	Yes	Yes	Yes
Belotero Balance	Bacteria-derived	Hyaluronic acid	6 months	No skin testing, excellent for treating fine and superficial rhytides	Cannot treat deep rhytides, painful to inject†	No	Yes	No
Juvéderm/ Juvéderm XC*	Bacteria-derived	Hyaluronic acid	6–12 months	No skin testing	Painful to inject if without lidocaine	Yes	Yes	Yes

*Contains lidocaine.
†Pain of injection reduced by addition of lidocaine.

Table 158.5 Comparison of fillers currently employed in the US. FDA, Food and Drug Administration. *Adapted from Wesley N, Dover J. The filler revolution: a six year retrospective. Drugs Dermatol. 2009;8:903–7.*

Continued

COMPARISON OF FILLERS CURRENTLY EMPLOYED IN THE US								
Filler trade name (®,™)	**Source**	**Material**	**Duration of effect**	**Advantages**	**Disadvantages**	**Use in lips**	**Approved by the FDA**	**Volume filler**
Juvéderm Ultra/ Juvéderm Ultra XC*	Bacteria-derived	Hyaluronic acid	6–12 months	No skin testing, less lip swelling, versatile	Painful to inject if without lidocaine	Yes	Yes	Yes
Juvéderm Ultra Plus/Juvéderm Ultra Plus XC*	Bacteria-derived	Hyaluronic acid (double cross-linked)	6–12 months	No skin testing, less lip swelling, versatile	Painful to inject if without lidocaine	Yes	Yes	Yes
Prevelle Silk*	Bacteria-derived	Hyaluronic acid	4–8 months	No skin testing	Short-lived, less painful to inject	Yes	Yes	No
Artefill	Synthetic	Bovine collagen and polymethyl-methacrylate beads (PMMA)	Permanent	Long-lasting, permanent	Skin testing (contains collagen), problematic injecting lips, permanent, including side effects (e.g. formation of nodules and granulomas)	No	Yes	Yes
Sculptra	Synthetic	Poly-L-Lactic acid	>1 year	Long-lasting, good volume filler	Tricky to inject, suspension preparation requires hours to days, multiple sessions required for correction, occasionally formation of long-lasting palpable, but not visible, papules‡	No	Yes	Yes
Radiesse	Synthetic	Calcium hydroxylapatite	>1 year	Long-lasting, good volume filler, equivalent volume appears to produce greater correction than the same volume of hyaluronic acid	Problematic injecting lips, painful to inject unless premixed with lidocaine	No	Yes	Yes
Silicone	Synthetic	Polydimethylsiloxane	Permanent	Versatile, permanent	Permanent, difficult injection technique (microdroplets), need for multiple sessions for correction, formation of permanent nodules	Yes	Yes (but not for aesthetic indication)	Yes
SoftForm	Synthetic	Expanded polytetrafluoroethylene	Permanent	Permanent	Permanent, not widely used, difficult to place	Yes	Yes	Yes
Gore-Tex Subcutaneous Augmentation Material	Synthetic	Expanded polytetrafluoroethylene	Permanent	Permanent	Permanent, not widely used, difficult to place	Yes	Yes	Yes
Autologous fat	Human	Fat	Permanent (in some patients)	Good for large areas of volume loss, permanent (in some patients)	Less predictable effects, permanence technique-dependent, requires more instrumentation	Yes	Not applicable to autologous tissue	Yes
Fascian	Human (allograft)	Fascia	Months to years	Duration	Not widely used, difficult to place	Yes	Yes	Yes

*Contains lidocaine.
†Pain of injection reduced by addition of lidocaine.
‡Reduced to 1–2% by using larger volumes for dilution

Table 158.5 Comparison of fillers currently employed in the US (cont'd). FDA, Food and Drug Administration. *Adapted from Wesley N, Dover J. The filler revolution: a six year retrospective. Drugs Dermatol. 2009;8:903–7.*

(>5 years). While it is true that a filler is either "permanent" or not, these terms were originally introduced as marketing terms to differentiate those fillers that are relatively rapidly absorbed (months) from those that last for years or longer.

To reduce ecchymosis, patients should be instructed to abstain from medications that would inhibit platelet aggregation for at least 10 days prior to injection. In order to fully appreciate the depth and scope of the defect, patients should be placed in a gravity-dependent or seated position, and there should be adequate lighting and, if necessary, magnification. Lighting at an acute angle to the skin surface can help to accentuate surface irregularities and deficits. Prior to the procedure, written consent should be obtained and cosmetic makeup and cutaneous debris removed.

Percutaneous injections of fillers can be painful, especially in the central face and perioral areas. Surface anesthesia can be achieved by using a topical preparation or ice approximately 15 minutes prior to administration. Some injectable products may require nerve blocks and/or regional anesthesia. Although fillers can be extemporaneously combined with lidocaine (by the physician) in order to reduce the pain of injection, a number of commercial products now contain a combination of lidocaine plus filler (see Table 158.5).

Proper placement of the filler material is crucial. Injection techniques that are commonly used include serial puncture, linear threading, fanning, cross-hatching and depot injection[3]. In the *serial puncture technique*, small amounts of filler are sequentially deposited along the wrinkle or fold. The injections are placed close to one another so that

the filler can blend in a continuous fashion; postinjection massage can also help to blend the filler so that it is evenly distributed. Using the *linear threading technique*, the full length of the needle is inserted into the proper dermal or subcutaneous plane and the filler is injected in a retrograde manner as the needle is withdrawn. Conversely, the material can be injected as the needle is advanced (anterograde), creating blunt dissection within the tissue space. The latter version may be particularly useful when an anesthetic is combined with the product.

The *fanning technique* involves multiple passes in different, but evenly spaced, directions without withdrawing the needle from the skin. A relatively recent trend is to use this technique to treat the nasolabial fold. The *cross-hatching* or *radial injection technique* involves linear injections in a grid-like pattern, and the pattern of lines needs to be evenly spaced. This technique is used for filling large areas and for the oral commissures[4]. Finally, *depot injections* are useful when placing volumizing fillers within the subcutaneous fat or along the periosteum near the malar eminence. Occasionally, small depot aliquots are also placed along the infraorbital ridge. Depot placement of filler is immediately followed by massage by the injector in order to blend the product into the natural contour of the region.

TEMPORARY FILLERS

Bovine Collagen

Bovine collagen is an injectable filler with a long safety track record of use in more than a million patients[5]. However, its use has declined markedly with the introduction of other fillers, in particular hyaluronic acid. The three forms (Zyderm® collagen I, Zyderm® collagen II and Zyplast®) are all derived from a closed US cattle herd that is carefully monitored to prevent transmission of bovine spongiform encephalitis, a prion-mediated disease. The products consist primarily of a sterile, purified fibrillar suspension that contains 98% type I dermal bovine collagen, with the remainder consisting of type III collagen, suspended in phosphate-buffered physiologic saline containing 0.3% lidocaine[2].

Zyderm® I, the original implant (1981), has a concentration of 35 mg/ml, and Zyderm® II (1983) has a concentration of 65 mg/ml. Zyplast®, the third form (1985), is cross-linked by the addition of glutaraldehyde. The latter characteristic decreases digestion by collagenase and makes it less immunogenic and longer-lasting than the 3 months anticipated for the Zyderm® products[6].

All three products are supplied in boxes of preloaded syringes, each containing 0.5–1.5 ml of product that should be kept refrigerated (4°C) to assure homogenicity and fluidity of the fibrils. A 30-gauge, 0.5-inch needle is usually used, but the company also supplies an adjustable depth gauge (ADG) needle to manually adjust the length of the needle.

Hypersensitivity to all three formulations can be reduced with double skin testing. The skin test is available in 1.0 ml tuberculin syringes that contain 0.3 ml of Zyderm® I, which screens for allergy to all three forms of bovine collagen. Approximately 0.1 ml of the contents is injected subcutaneously in an inconspicuous area, such as the volar aspect of the forearm or in postauricular skin. Localized hypersensitivity is found in 3% of patients and is manifested as swelling, induration, tenderness or erythema that persists or occurs 6 or more hours following implantation. Despite a negative preliminary test, an additional 1–2% of people will subsequently develop an allergic reaction to the products. Therefore, performance of a second skin test 2 weeks after the initial skin test is recommended. This test, using a similar volume, can be injected into the contralateral arm or the periphery of the face (pretragal area, anterior hairline), and should be monitored for an additional 2 weeks. A positive reaction occurring with either test is a contraindication and should preclude further therapy with bovine collagen. Conversely, negative double skin testing allows the patient to proceed with treatment 4 weeks after the initial test or 2 weeks after the second test. For patients who have not had collagen injected for a year or longer, a single re-test with a 2-week observation period is suggested, prior to initiating further treatment.

Zyderm® I is implanted into the superficial dermis by introducing the needle at a 20–30° angle to the plane of the skin. Proper placement should be apparent with a flat, yellow blanching of the skin. Because a significant portion of Zyderm® I is water, overcorrection is commonly utilized to maximize the aesthetic result. It is primarily suited to smooth out and fill superficial wrinkles such as perioral and periocular rhytides. Zyderm® I is the most forgiving and versatile of the three collagen preparations. Zyderm® II is more viscous than Zyderm® I; it is suitable for shallow scars and can be used synergistically with botulinum toxin in the glabellar region. When injected too superficially, persistent whiteness can be appreciated.

Zyplast® is injected with the needle at more of an angle (45–90°) to the defect and it is placed into the mid dermis. If placed properly, it does not cause immediate blanching, but a more subtle and somewhat delayed blanch. Deep nasolabial folds, marionette grooves and lip augmentation respond best to Zyplast®. Lip enhancement is the most common use of bovine collagen; it is indicated only for the vermilion border and is not FDA-approved for the mucosa. The different types of collagen may be used simultaneously, particularly when the cosmetic defect has multiple depths or is quite deep. This is well illustrated in the perioral area, where Zyplast® can be injected in a continuous flow along the vermilion border and Zyderm® into the radiating vertical lines. Similarly, a deep nasolabial fold can be softened by first injecting Zyplast® into the deep dermis, then layering Zyderm® above it in the superficial papillary dermis.

In addition to a delay in initiating treatment, a common source of frustration for patients receiving bovine collagen injections is the short-lived correction. In general, patients can anticipate 3 to 6 months of improvement, with gradual diminution of results; however, patients can receive additional treatment or maintenance therapy at any time. Adverse treatment responses to injectable collagen can be divided into non-hypersensitive and hypersensitive reaction patterns (Fig. 158.1) and are outlined in Table 158.6[7,8]. Of note, Koken Atelocollagen® and Resoplast® are non-fibrillar forms of implantable bovine collagen that are not approved for use in the US.

Porcine Collagen

A novel form of injectable collagen was Evolence®, a type I collagen extracted from porcine tendons and cross-linked with the sugar ribose. It came in a 35 mg/ml concentration and was approved in 2008 for the correction of moderate to deep facial wrinkles, such as the nasolabial folds. Benefits, as compared to bovine collagen, included the rarity of hypersensitivity reactions (so skin testing was not required) and a possibly longer duration of correction (up to 1 year)[9]. It was recommended that Evolence® not be injected into the lips because of the risk of nodule formation following lip augmentation[10]. In November 2009, the manufacturing of Evolence® was discontinued.

Fig. 158.1 Bovine collagen – "hypersensitivity" reaction. Formation of granulomas at the site of injection. This reaction can be seen in ~1% of patients who have had two negative skin tests.

COMPLICATIONS FROM SOFT TISSUE FILLERS		
Complication		**Methods to reduce complication**
GENERAL		
Ecchymoses		• Avoid aspirin and vitamin E for 10–14 days prior to procedure • Use blunt-tipped needle
Beading		• Inject smoothly and not superficially
Painful blanching or necrosis due to vascular injury or occlusion		• Exercise caution in the glabellar region* • For blanching, warm compresses and topical nitroglycerin • For necrosis, appropriate wound care • Frequent visits and emotional support • If due to HA, can inject hyaluronidase during the blanched phase
Foreign body granulomas (see Ch. 93)		• NSAIDs • Intralesional triamcinolone • Topical tacrolimus • Occasionally, oral immunosuppressants • If due to HA, inject hyaluronidase
Sterile abscesses		• Incision and drainage • Intralesional triamcinolone • If due to HA, inject hyaluronidase
Bacterial biofilms		• While waiting for culture results, oral broad-spectrum antibiotics, e.g. chlarithromycin, minocycline • If due to HA, inject hyaluronidase to reduce biofilm
Vision loss		• Exercise caution in the glabellar region* • Avoid intravascular injection by pulling back plunger prior to injection • Do not use a lot of pressure when injecting • Use fillers that can be injected intradermally
Reactivation of facial herpes simplex viral (HSV) infection		• Treat prophylactically with oral acyclovir if history of previous post-procedure reactivation • Review signs and symptoms with patient and state if they occur to alert the physician • Treat suspected HSV infections with oral acyclovir, famciclovir or valacyclovir
SPECIFIC		
Persistent papules	Artefill®, Sculptra®, silicone	• For Artefill®, inject smoothly • For Sculptra®, greater volume dilution • For silicone, use microdroplet technique
Delayed granulomas	Artefill®, silicone	• Oral antibiotics, e.g. clarithromycin, minocycline • Intralesional corticosteroids (may require 10–40 mg/ml)
Papulonodules	Hyaluronic acid	• Incision and drainage • Inject hyaluronidase • Oral antibiotics (see bacterial biofilms)
*Zyplast® is contraindicated in this location.		

Table 158.6 Complications from soft tissue fillers. HA, hyaluronic acid; NSAIDs, nonsteroidal anti-inflammatory drugs.

Human Collagen – Cadaveric

In the late 1980s, research began on extracting intact collagen fibers and acellular dermal matrix from human cadavers for soft tissue augmentation. Dermalogen® and Cymetra® are examples of products derived from human cadavers and they were available as preloaded syringes and implantable grafts. However, as with bovine collagen, their use has declined with the introduction of newer fillers.

Dermalogen® was an injectable allograft material of human tissue origin composed predominantly of intact collagen and elastin fibers as well as glycosaminoglycans harvested from the dermal layer of human cadaveric skin. The indications were similar to those for bovine collagen: facial rhytides, atrophic scars and lip enhancement. Compared to bovine collagen, correction may have been longer-lasting[8] and no skin testing was required.

Cymetra® consisted primarily of micronized human collagen fibers and the indications were the same as for Dermalogen®. To date, there have been no reports of hypersensitivity reactions. One distinction of Cymetra® is that it was a powder, prolonging its shelf-life. It was rehydrated prior to injection with 1.0 ml of 1% lidocaine. Once completely saturated, the product changed from a white powder to a cream color with a paste-like consistency.

Human Collagen – Bioengineered

The risk of hypersensitivity to bovine collagen led to the development of human collagen as a dermal filler. The CosmoDerm® family of dermal fillers has a reassuring safety profile based historically on the extensive use of this synthetic human collagen in burns and wounds. All three formulations – CosmoDerm® 1, CosmoDerm® 2 and CosmoPlast® – closely resemble the bovine-sourced products. They have the same consistency, concentration (dispersed in phosphate-buffered saline with 0.3% lidocaine) and injection technique as their Zyderm®/Zyplast® counterparts. The primary distinction is that they are grown from a single human fibroblast cell culture and, unlike other human-derived products, are not cadaveric in nature. They are the result of tissue-engineering technology and have undergone extensive pathology screening for viral and bacterial contamination to avoid the possibility of disease transmission. As these products are non-animal-based, they do not require an initial skin test for hypersensitivity. Therefore, they can be injected on the same day as the initial consultation.

Similar to its bovine analogue Zyderm® I, CosmoDerm® 1 has a concentration of 35 mg/ml and is placed into the superficial papillary dermis with a comparable degree of blanching and overcorrection, and it is also primarily indicated for superficial lines and defects. CosmoDerm® 2 has a concentration of 65 mg/ml human-based collagen and has similar indications as Zyderm® II. CosmoPlast®, like Zyplast®, contains 35 mg/ml of human-derived collagen cross-linked with glutaraldehyde, which makes it less immunogenic and increases its durability. It is a deeper implant, to a depth of approximately 2.0 mm, and *does not* require overcorrection to improve deep folds and wrinkles.

All three CosmoDerm® products are packaged similarly to the three bovine products and are prepackaged as an opaque white material in preloaded syringes with adhesive labels and 30-gauge, 0.5-inch and adjustable depth gauge (ADG) needles. The cost of the CosmoDerm® group is slightly higher than that of the Zyderm® group, even though the initial screening process with skin tests is eliminated. The cosmetic result and duration of correction appear to be comparable[7]. Anecdotally, some physicians have noted that human-derived products have better flow characteristics and are easier to inject than bovine-derived collagens.

Human Fascia – Cadaveric

Fascia lata has long been utilized in surgery, first as suture material and later for repair of hernias and eyelid ptosis as well as for reconstructive purposes in orthopedic surgery and otolaryngology[11]. Preserved particulate fascia, harvested primarily from cadaveric fascia lata, became FDA-approved in 1999 (Fascian®) and is registered as a tissue product designed to replace areas of lost fascia or collagen. It is supplied in 3 ml syringes and, as it is in powder form, can be stored at room temperature. Prior to injection, it is hydrated with 1.5 to 3.0 ml of 0.5% lidocaine with 1 : 100 000 epinephrine (adrenaline) or with normal saline. A Luer-to-Luer lock syringe connector is used to emulsify the powder. Syringes containing five different particle sizes (0.1, 0.25, 0.5, 1.0 and 2.0 mm) are available, all with 80 mg of the product. The larger-sized particles give a greater volumetric correction, but they are also more likely to clog in the syringe upon injection. Obstructions can be released by aspirating an additional 0.5 ml of saline or replacing the needle. Skin testing is not required[12].

Using a 16- to 18-gauge needle, the reconstituted Fascian® is injected above the superficial subcutaneous fat. Pretunneling (subcision) with the needle prior to injection will create a pocket for the deposition of Fascian®. Overcorrection is recommended, to anticipate reabsorption of the diluent. Perhaps due to relatively limited use, few adverse reactions have been reported; however, postinjection edema can be

significant and should be addressed with cool compresses and, if necessary, systemic corticosteroids.

Unlike other fillers, Fascian® is not marketed as a "device" in the US, but rather is supplied under the criteria of the Tissue Reference Group (TRG) and comes with no prescribed indications. The grafts are, in theory, applicable to any body defect that would be amenable to other forms of soft tissue augmentation. Fascian® is advantageous not only because of its ease of storage, availability in multiple sizes, and lack of need for skin testing, but also because of the potential for large volumetric correction and applicability to deep subdermal defects. It is, however, limited by the need for preparation and the use of large-bore needles for administration, as well as the lack of controlled studies documenting its longevity.

Autologous Fibroblasts and Collagen

Several of the initial products that were based upon the concept of utilizing autologous fibroblasts are no longer commercially available in the US (e.g. Autologen®, Fibrel®, Isolagen®). Basically, a punch biopsy of skin is obtained from the patient and shipped to the manufacturer, where fibroblasts are isolated and expanded *in vitro*. After a period of months, the cells are then sent back to the clinician for injection. Shortcomings have included the limited yield of product (1–2 ml), the need for shipments, the wait time, and concern regarding the extent to which the fibroblasts continue to produce collagen and lead to soft tissue correction. Recently, azfibrocel-T (laViv®) was FDA-approved for treating rhytides on the basis of 57% of patients noting an improvement compared to 30% who received the placebo.

Hyaluronic Acid Derivatives

The hyaluronic acid derivatives have become the most widely used soft tissue fillers and have spawned an entire new industry, complete with competing products and brand loyalty. Presently, there are at least three manufacturers, with well over a dozen hyaluronic acid-based injectable agents; all are remarkably similar (see Table 158.5). Hyaluronic acid is named for its glassy appearance and is derived from the Greek word for glass, *hyalos*. Hyaluronic acid is an acid mucopolysaccharide (glycosaminoglycan) that resides within the cutaneous dermal ground substance and fills the extracellular spaces between collagen fibers. It is a ubiquitous component of connective tissue and is identical in chemical and molecular form in all tissues and all mammals, making it species-nonspecific.

The hyaluronic acid molecule has a simple chemical structure consisting of a high-molecular-weight, long-chain polysaccharide that is composed of repeating disaccharide units of N-acetylglucosamine and D-glucuronic acid (see Ch. 95). The intertwining coils are polar in nature and have an enormous ability (up to 1000 times their weight) to attract water (hydrophilic) and impart skin turgor. Within connective tissue, hyaluronic acid's major biologic function is to create volume and lubricate extracellular structures by forming a gelatinous matrix in which collagen and elastin fibers are held together in proper alignment. It also regulates cell movement and function, and is particularly important in development and remodeling of tissues. A direct correlation exists among the amount of hyaluronic acid in dermal tissue, the dermal water content, and the viscoelastic properties of the extracellular matrix. The concentration of naturally occurring hyaluronic acid in the skin decreases with age, resulting in decreased ability to hold water (hydration), which renders the dermis less voluminous and increases its propensity to wrinkle.

A dual mechanism of action accounts for the correction of facial wrinkles: hyaluronic acid integrates into dermal tissue, then attracts and binds water molecules to sustain augmentation. In its natural unmodified state, implanted exogenous hyaluronic acid is rapidly degraded by hyaluronidase and has a half-life of only 12 to 24 hours. It was not until the hyaluronic acid molecule was "stabilized" via chemical cross-linking that its enzymatic breakdown was slowed and its viability and *in situ* residency was increased; it could then be used as an acceptable, durable filler.

Its viscoelastic properties, lack of hypersensitivity and migration, and relative insolubility make it an appropriate agent for soft tissue augmentation. After implantation into tissues, injectable hyaluronic acid is metabolized into carbon dioxide and water and eliminated by the liver[13–15] (Table 158.7).

There are two broad categories of injectable cross-linked hyaluronic acids. One category, the Hylaform® group, is animal-derived (rooster combs), stabilized hyaluronic acid. The second is non-animal stabilized hyaluronic acid (NASHA). The NASHA group, Restylane®, Belotero® and Juvéderm®, is generated from bacterial (*Streptococcus*) fermentation. The two categories share many characteristics: they are clear, non-particulate, colorless, thick gels that contain no lidocaine. Without the addition of an anesthetic, they are fairly painful to administer and therefore require some type of topical or regional nerve block anesthesia prior to injection, especially in the perioral region.

All are similarly packaged and are available in preloaded single-use syringes that are accompanied by 30-gauge, 0.5-inch needles as well as labels with lot numbers that can be removed and affixed to the patient's record. The products do not require skin testing and can be stored at room temperature. Placement should be in the mid to deep dermis to the point of correction but without overcorrecting the defect. These products are more viscous than many other injectables, especially the collagen products. Therefore, they have different flow characteristics (rheology), requiring greater pressure to the plunger of the syringe for injection. However, they are more malleable and contour irregularities are responsive to postinjection, manual massage. Augmentation lasts approximately 6–9 months, which is longer than with most other temporary fillers (Table 158.8)[16]. They are approved for "correction of moderate to severe facial wrinkles and folds, such as the nasolabial

BENEFITS OF HYALURONIC ACID DERIVATIVES
• Identical in all species and all tissue types
• No skin test required
• Room temperature storage
• Biodegradable
• Long-lasting/stable
• High degree of safety (biocompatible, resorbable, reversible)

Table 158.7 Benefits of hyaluronic acid derivatives.

COMPARISON OF COLLAGEN AND HYALURONANS		
	Collagen (Cosmoderm® and Zyderm® series)	**Hyaluronans**
Compatibility	Species- and tissue-specific	Identical in all species and tissues
Duration	3–4 months	4–10+ months (longer with subsequent injections)
Origin	Bovine or human	Animal (avian) or bacterial (streptococcal fermentation)
Augmentation	Filler replacement	Water absorption
Pattern of loss	Steady volume loss	Isovolemic degradation*
Viscosity	Constant	Dynamic
Anesthesia	0.3% lidocaine	May require topical/block, though newer formulations contain 0.3% lidocaine
Discomfort	Minimal	Minimal with lidocaine, moderate without lidocaine
Correction	50–100% overcorrection	No overcorrection
Preinjection skin test	Double skin test	Not required
Allergy prevalence (hypersensitivity)	~3% of population	~0.4% of population
Shipping & storage	Refrigerated	Room temperature

*It would seem that isovolemic degradation implies a cliff-drop loss of correction once most of the material has been absorbed, i.e. constant correction with rapid drop-off at the end of the life of the correction.

Table 158.8 Comparison of collagen and hyaluronans.

folds" but are routinely used off-label for other facial indications, including lip augmentation. Perhaps due to the durability or malleability of the product, the non-traditional use of injectable hyaluronic acids has greatly expanded. They are used on the face in the suprabrow area to assist in elevating the brow, in the infraocular sulcus, and even in the periauricular area to rejuvenate the appearance of the senescent/atrophic ear. Additionally, on the extremities, using hyaluronic acid instead of autologous fat in the dorsum of the hand provides volume and camouflages the vasculature and tendons that appear with increasing age.

More recently, there have been studies evaluating the safety of NASHA dermal fillers in patients with more darkly pigmented skin, i.e. Fitzpatrick skin phototypes IV, V and VI. They were shown to be safe for the correction of moderate to severe facial folds and there were no reports of immunogenicity or keloid formation (to date). Only mild to moderate local adverse effects at the injection sites were observed[17]. When non-Caucasian patients were compared to Caucasian patients, there was no increase in the incidence of hyperpigmentation or hypopigmentation[18].

Adverse reactions reportedly occur in fewer than 2% of patients. One of the major advantages of hyaluronic acid gels over bovine collagen is the decreased incidence of delayed hypersensitivity reactions (see Table 158.8). Since it should be nearly impossible to react to pure hyaluronic acid, as it is identical in all species and tissue types, any such reactions are thought to be due to impurities in hyaluronan production: residual avian proteins (Hylaform®) or by-products of bacterial fermentation (Restylane®; Fig. 158.2)[19]. Similar to all injectables, other adverse reactions include ecchymosis, acneiform eruptions and reactivation of herpes simplex[20,21]. Injection discomfort and postinjection ache, erythema and edema are expected sequelae.

With most fillers, if the placement is too superficial, a contour irregularity results and resolution occurs only with time. However, with the hyaluronic acids, a "lump" can often be redistributed into the desired location by physician massage. If the lump persists, the irregularity can be treated via one of two methods. The easiest is to express the material by simple incision and drainage. With manual pressure, the clear intact hyaluronan is readily extruded. If the administration has been too deep and the localized bump is not readily accessible to drainage, local injection of small amounts of hyaluronidase (Vitrase®) can reduce its size (Fig. 158.3).

When the hyaluronic acid is placed too superficially, it causes the formation of a cutaneous bead that is blue–gray in color due to the Tyndall effect. The scatter of different wavelengths of light depends on the size of the substance they encounter; in the skin, long red wavelengths penetrate deeper into the tissue while the shorter blue wavelengths are scattered and reflected[22]. The Tyndall effect also explains the blue–green color of cutaneous veins. Fortunately, this filler "complication" responds to the intralesional injection of hyaluronidase[23]. A rare complication is skin necrosis, with the glabella being the most commonly reported site. Prompt recognition of skin blanching followed by injection of hyaluronidase may prevent or reduce the area of necrosis (see Table 158.6).

Animal-derived hyaluronic acid

The avian-derived form of hyaluronic acid (extracted from rooster combs) is distributed as Hylaform® in three concentrations: Hylaform Fine Lines® for superficial lines and wrinkles, Hylaform® for moderate rhytides, and Hylaform Plus® for deep folds. At the time of publication, only the last two agents have received FDA approval. They all have a high molecular weight but low concentration of hyaluronic acid (5.5 mg/ml).

Non-animal stabilized hyaluronic acid (NASHA)

There are currently three major injectable hyaluronic acids produced by streptococcal fermentation (non-animal stabilized hyaluronic acid [NASHA]). In the Restylane® family, three forms are available: Restylane Fine Line®, Restylane® and Perlane®; however, only Restylane® and Perlane® are currently FDA-approved and available in the US. Each has a concentration of 20 mg/ml of hyaluronic acid; the difference is the size of the gel particles. Restylane Fine Line® is injected into the

Fig. 158.2 Pustular and granulomatous reaction to injections of hyaluronic acid (Restylane®). *Courtesy, Julie V Schaffer, MD.*

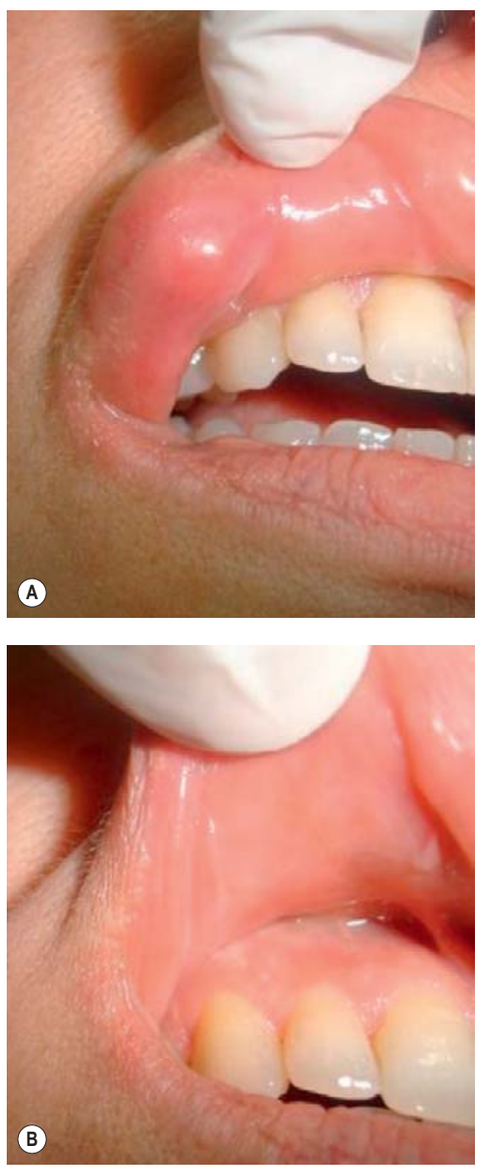


Fig. 158.3 Hyaluronic acid – foreign body reaction. A Nodule due to granulomatous inflammation arose 6 weeks after injection. **B** Resolution following intralesional hyaluronidase and triamcinolone. *Courtesy, Mahmoud Abdallah, MD.*

upper dermis for superficial lines and contains 500 000 gel particles per ml. Restylane®, for mid-dermal applications, has 100 000 gel particles per ml, and it is FDA-approved for deep wrinkle correction, lip augmentation, nasolabial fold correction, and for glabellar creases (Fig. 158.4). Restylane® has also been used with success for the treatment of tear trough deformities[24]. Perlane®, with 8000 gel particles per ml, is appropriate for deep dermal augmentation and more profound facial folds. Postinjection swelling, erythema and bruising are not atypical and may be more prolonged than with other hyaluronic acid fillers. When small particle gels are compared to large particle gels, they demonstrate similar efficacy, durability and safety. In one study, the incidence of adverse reactions was higher when the fanning technique was used and when a faster rate of injection was employed[25].

Juvéderm® is similar to Restylane® in that it is based on non-animal, cross-linked technology. There are three forms: Juvéderm® with a concentration of 18 mg/ml of hyaluronic acid, designed for the superficial dermis; Juvéderm® Ultra with 24 mg/ml of hyaluronic acid for deeper mid-dermal defects; and Juvéderm® Ultra Plus, which contains 30 mg/ml of hyaluronic acid for correction of the deepest contour irregularities (Figs 158.5 & 158.6)[21]. The two thicker forms, Juvéderm® Ultra and Juvéderm® Ultra Plus, were granted FDA approval in January 2007. The most recently approved NASHA (2011) is Belotero Balance® which contains 22.5 mg/ml of hyaluronic acid (see Table 158.5).

Captique® was a re-formulation of Hylaform® with 5.5 mg/ml of hyaluronic acid, but, as opposed to being of avian derivation, it was non-animal stabilized hyaluronic acid (NASHA). This product had FDA approval for mid-dermal defects, but is no longer commercially available. Although it did not have the erythema and reactivity of other NASHA products, its low hyaluronic acid concentration did not sustain long augmentation.

Fig. 158.4 Hyaluronic acid – lip and perioral augmentation. A Prior to injection of Restylane® into the perioral area. **B** Three months postinjection with correction maintained. *Courtesy, Seth L Matarasso, MD.*

Elevess® was also a bacteria-derived hyaluronic acid. It was produced by fermentation of *S. equi* and then suspended in a buffered solution of 0.3% lidocaine hydrochloric acid. Elevess® was the first FDA-approved soft tissue filler that contained both hyaluronic acid and lidocaine, but it is no longer commercially available[3]. Prevelle® Silk was then the next hyaluronic acid plus lidocaine to be FDA-approved[26]. It is supplied in preloaded single-use syringes (0.9 ml) with 30-gauge needles. Although the injections are less painful, the duration of correction is shorter-lived at 3 to 6 months.

Formulations of the Juvéderm® family, Restylane® and Perlane® that contain lidocaine have been FDA-approved; members of the first group are labeled with "XC" and the latter two with "-L" (see Table 158.5).

SEMI-PERMANENT FILLERS

Poly-L-Lactic Acid

Polymerized poly-L-lactic acid (Sculptra®) can also serve as a soft tissue filler as it stimulates the production of collagen. In 2004, it was FDA-approved for the correction of shape and contour deficiencies secondary to the lipoatrophy associated with antiretroviral therapy for HIV infection[27]. Five years later, the FDA approved Sculptra® for the correction of shallow to deep nasolabial fold contour deficiencies and other facial wrinkles. It can also be used for re-volumizing the face of healthy individuals (Fig. 158.7) and for hand rejuvenation.

Sculptra® is powdered lyophilized suture material (Vicryl® [polyglactin 910]) and therefore the freeze-dried preparations of poly-L-lactic acid can be stored at room temperature. Prior to injection, each vial is reconstituted with a total of 5 ml of liquid: 4 ml of sterile water and 1 ml of lidocaine. The result is a thick 5 ml suspension of 4.45% poly-L-lactic acid. To adequately saturate the powder and obtain a uniform suspension and homogeneous deposition of material, it is recommended that the diluent be added approximately 2 to 4 hours prior to use; however, it is often added 24 hours in advance to ensure a more uniform suspension. In addition, higher dilutions (up to 9 to 11 ml) are used by some physicians to try to reduce the risk of papule formation.

Immediately prior to injection, the mixture is vigorously agitated. A 26-gauge needle is used to place the filler high in the subcutaneous plane without overcorrection. Frequent needle changes may be necessary, as the material has a tendency to form clumps. There may be the appearance of some immediate augmentation due to edema, but in order to achieve desired dermal thickness and prolonged neocollagenesis, the recommended protocol is a series of three or more injections at 3- to 6-week intervals. Persistence of augmentation has varied, but some improvement can be seen at 1.5 to 2 years.

Palpable, but not visible, papulonodules develop in some patients and a granulomatous reaction at sites of injection can also arise. All of these complications tend to persist for a year or more. To try to minimize papule formation, the following can be done: greater dilution, increasing the time interval between reconstitution and injection, deeper injections, injecting smaller aliquots per site, and vigorous massage of the injected areas to eliminate any lumpiness.

Calcium Hydroxylapatite

Initially approved for laryngoplasty (vocal cords) and stress-related bladder sphincter incompetence, Radiesse® has found a niche in the filler market because its duration is estimated to be up to 1 to 2 years, with reports that it may last 2 to 5 years[28]. It is a milky white suspension comprised of two components: (1) an aqueous gel carrier containing glycerin, sodium carboxymethylcellulose and water; and (2) the matrix particle. As the gel carrier correction gradually dissipates via dissolution, longer-term correction from new collagen formation (stimulated by the 25–125 μm microspheres of calcium hydroxylapatite) replaces it. Calcium hydroxylapatite is a non-allergenic (inert) bioceramic that is identical to the primary mineral constituents found in bone and teeth. This biocompatible product contains no human, bacterial or animal products and therefore does not pose a risk of hypersensitivity. The material is individually packaged in 1.0 ml syringes and requires the use of a larger-bore needle (25- to 27-gauge). Utilization of the product was initially limited due to the significant discomfort and throbbing after injection, but the FDA has cleared the practice of

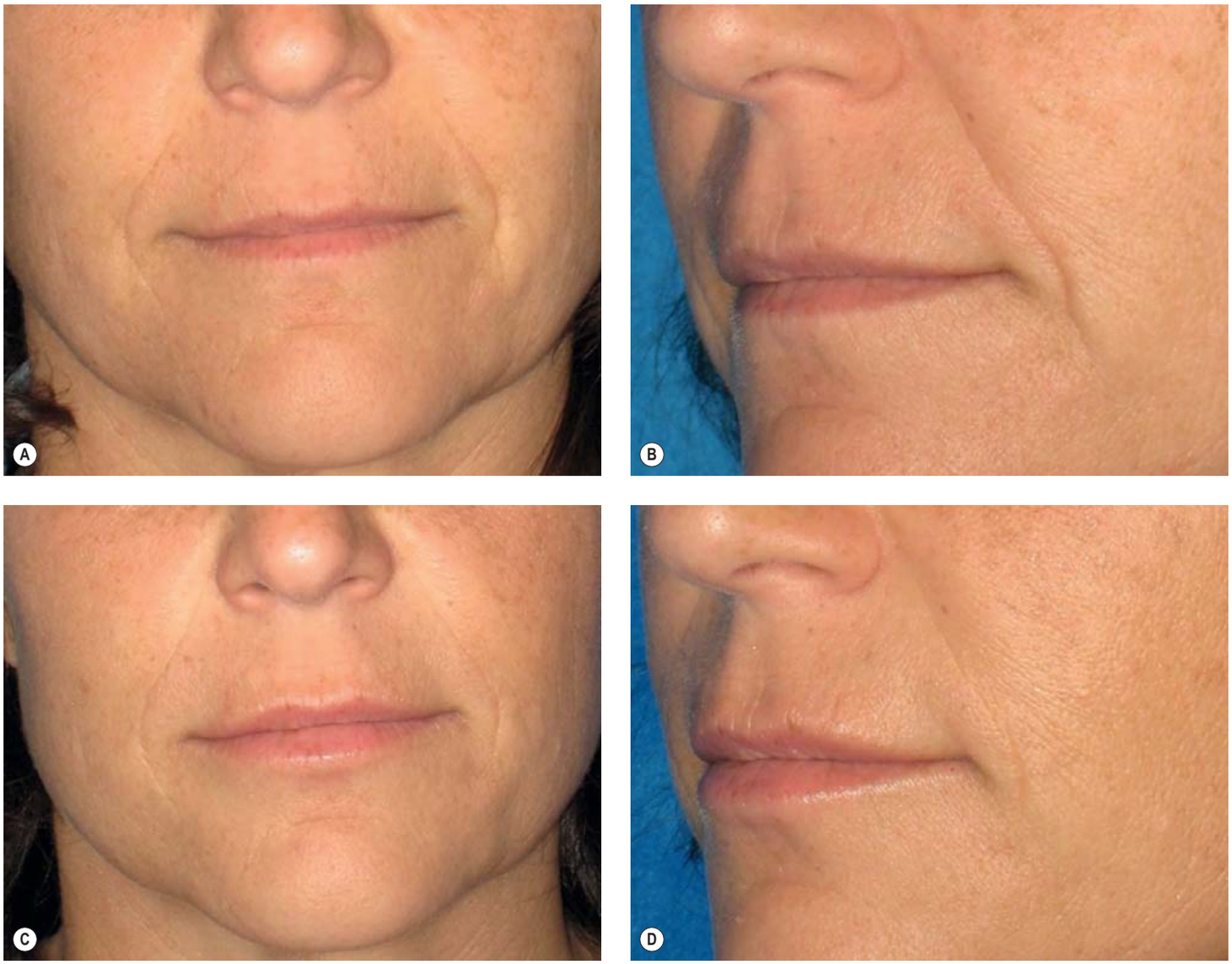


Fig. 158.5 Hyaluronic acid – augmentation of nasolabial folds, lips and oral commissures. A,B Pre-treatment. **C,D** Following injection of Juvéderm Ultra®.

pre-mixing Radiesse® with 1% or 2% lidocaine immediately prior to injection. The material is deposited deeply at the dermal–subcutaneous junction. Injection provides immediate results, and no overcorrection or undercorrection is required[1].

Like Sculptra®, this product stimulates neocollagenesis around the injected microspheres, and the latter are eventually degraded over several years. This product was approved in 2006 for the correction of facial wrinkles and folds and also for antiretroviral-associated facial lipoatrophy. It is particularly suited for patients who have had prior experience with fillers but request a longer duration (Fig. 158.8). Lip augmentation is contraindicated, as mucosal granulomas may form and the constant motion of the lip and compression from contraction of the orbicularis oris may cause migration and clumping of the filler (Fig. 158.9)[29,30]. Off-label uses of this product include correction of volume loss in the infraorbital region[1], re-volumizing the face of healthy individuals (Fig. 158.10), and hand rejuvenation.

Since the Radiesse® implant is radio-opaque, the patient should be informed that it may be visible on dental radiographs as well as CT scans. The safety of calcium hydroxylapatite in patients with Fitzpatrick skin phototypes IV to VI has been studied. When used to treat nasolabial folds, individuals with darkly pigmented skin did not form keloids or hypertrophic scars nor did they develop hyper- or hypopigmentation[31].

PERMANENT FILLERS

Expanded Polytetrafluoroethylene

Expanded polytetrafluoroethylene (ePTFE) is a synthetic solid material that is soft, pliable and clinically inert, with minimal tissue reactivity and high tensile strength. These characteristics have made it useful as a vascular graft in cardiac, urogynecologic, ophthalmologic, and plastic and reconstructive surgery since 1975. In 1993, it received FDA approval for soft tissue augmentation, and currently there are two major products with aesthetic indications. Gore-Tex® Subcutaneous Augmentation Material comes in two forms, single- and multi-stranded, which are both 15 cm in length. In addition, SoftForm® is available as hollow tubes of three lengths (50, 70 and 90 mm) with varying external diameters (2.4, 3.2 and 4.0 mm). They are useful, either as solitary filling agents or in conjunction with other fillers, for addressing deep nasolabial folds, atrophic lips, and lipoatrophy associated with antiretrovirals. Following a combination of nerve blocks and local anesthesia, entry and exit incisions are made and the ePFTE is implanted.

A straight Keith needle with a suture (0-silk) attached to the Gore-Tex® implant is used to perpendicularly enter and exit the skin. The Gore-Tex® is pulled through the subcutaneous tissue by pulling the attached suture. There will be some resistance and steady constant

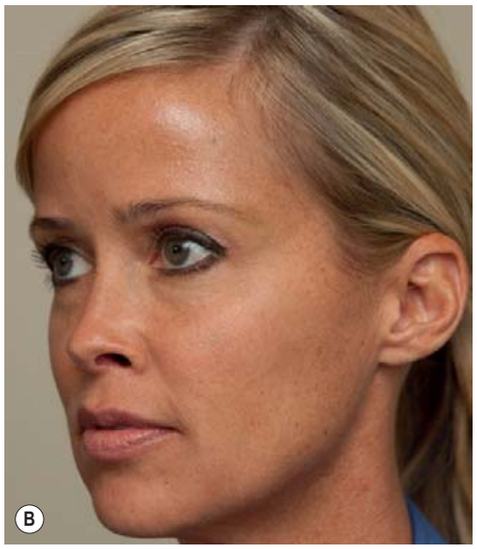


Fig. 158.6 Hyaluronic acid – volumization in a patient with lean body mass. A Pre-treatment. **B** Following injection of large volumes of Juvéderm Ultra Plus® to the cheeks and Juvéderm Ultra® to the brow area, nasolabial folds and oral commissures. *Courtesy, Derek H Jones, MD.*

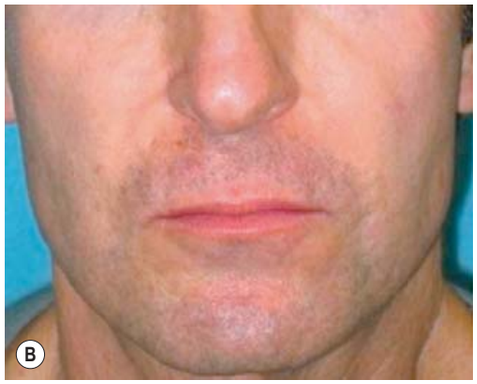


Fig. 158.7 Poly-L-lactic acid – correction of facial fat loss. A Pre-treatment in a patient with facial fat loss related to aging and lean body mass. **B** Eight months post-treatment of the cheeks (and temples) with 10 vials of Sculptra® (five treatments, two vials per treatment) over 4 months.

pressure will be required. With the implant in place, the sutures are cut free and the tips of the implant are buried in the deep dermis. Closure of the incision sites may not be necessary. The porosity of the implant leads to fibrous in-growth, improving the degree of augmentation and anchoring the implant via decreased movement[32].

SoftForm® is inserted via a preloaded trochar delivery system. Once the thick delivery apparatus is removed, the implant ends are tapered and buried subdermally; the incision sites need to be sutured. The hollow-tube configuration of SoftForm® is designed to promote ingrowth of fibroblasts with subsequent neocollagenesis. Placement of both ePTFE products is unforgiving and should be directly beneath and parallel to the overlying defect, high in the subcutaneous fat, just underneath the deep reticular dermis[6].

The primary advantages of ePTFE are that it is not degraded, it remains intact, and it is essentially permanent. However, the disadvantages include: the potential for small incisional scars; the risk of infection, extrusion and migration; and the fact that, even under the best of circumstances, patients can palpate it. In addition, a solid implant placed in a mobile area may intrinsically be counterintuitive and, in fact, may create a new defect. Fortunately, should an adverse event occur, the ePTFE can be removed in a similar fashion to the original insertion. However, the longer the implants remain in place, the more fibrosis there is, and it becomes increasingly difficult to remove them. Compared to other agents, these fillers are technically more difficult to place, and their use seems to have decreased significantly[33].

Fig. 158.8 Calcium hydroxylapatite – perioral augmentation. A Prior to injection of 1 ml of Radiesse®. **B** Follow-up: softening of nasolabial fold and elevation of lateral oral commissure. *Courtesy, Seth L Matarasso, MD.*

Fig. 158.9 Calcium hydroxylapatite – labial mucosal nodule. Radiesse® was placed too superficially. *Courtesy, Seth L Matarasso, MD.*

Fig. 158.10 Calcium hydroxylapatite – correction of facial fat loss. **A** Pre-treatment in a patient with facial fat loss related to aging and lean body mass. **B** Following injection of Radiesse® into the midface.

Lipotransfer

Historically, autologous fat has always been considered one of the safest fillers, with estimates of success as high as 50%, but two concerns have remained. The original *en bloc* technique required excision of the donor tissue and a resultant second defect; essentially, patients traded one defect for another. Furthermore, the non-particulate solid nature of the tissue required implantation, with the potential for incisional scars. The arrival of liposuction in the 1980s solved many of these existing problems. A by-product of liposuction, the suctioned fat was easily accessible and could be reinjected through small cannulas and needles. Consequently, there has been a renaissance of autologous fat transplantation.

For many, autologous fat is considered to be the optimal filler. The advantages remain the biocompatibility and avoidance of allergy, the relative abundance of graft supply, the ability to address three-dimensional volume correction, and the possibility of permanent correction. Theoretical disadvantages include the inability to place material into the dermis to address fine lines and wrinkles or small scars, the cumbersome aspects of harvesting the fat and determining the optimal donor site, the inability to predict the percentage of graft survival, and the debate over viability of stored fat. Perhaps the major drawback is that it requires two procedures: harvesting and insertion of the fat[34,35].

Fat may be harvested from any site where there is excess adiposity. Ironically, those patients who most often request this procedure have limited donor subcutaneous supply. Definitive studies have not yet determined if one area is preferable to others; however, areas with easy access, with limited postoperative morbidity, and which appear to be relatively insensitive to dietary fluctuation include the abdomen, medial knee, and upper outer buttock areas[36].

The donor and recipient sites are photographed and prepared, and the patients are provided with an oral anxiolytic. The subcutaneous space of the donor site is infiltrated with tumescent anesthesia (see Ch. 143)[37]. Through a percutaneous stab incision made with a #11 blade, the donor fat can be aspirated using a 12- to 14-gauge single-holed microcannula (1.5–4.0 inches [3.8–10.2 cm]) that has a beveled edge. The needle is mounted on a conventional hypodermic (10–20 ml) Luer-Lok® syringe. Similar to standard liposuction, the non-dominant hand grasps the subcutaneous adipose tissue and, with the dominant hand holding the syringe under negative pressure, the needle/microcannula is placed in the subcutaneous fat. Moving up and down in a vertical motion perpendicular to the skin, a mixture of yellow fat, some anesthetic solution and, as the procedure progresses and the fat store is depleted, some blood will appear in the syringe. The filled syringes are placed upright in a dependent position, allowing gravity to separate the supernatant fat from the infranatant blood and anesthetic fluid, which can be discarded.

The relatively pure supernatant fat is injected using a large-bore (16- or 18-gauge) needle. After a small bleb of local anesthesia is introduced, the needle is inserted almost parallel to the skin and is advanced to the farthest point of interest. The plunger is then drawn back to aspirate, to ensure that intravascular placement does not occur. The fat is threaded as the needle is withdrawn; frequently, it dissects along the subcutaneous plane without assistance. Although there is some discomfort associated with the injection, it relates primarily to the sudden stretch and expansion of the subcutaneous space and is generally well tolerated by most patients. Molding is undertaken by firm massage to encourage proper subcutaneous fat distribution and a uniform contour. There remains a great deal of variability in technique. Some physicians prefer multiple passes with an intricate layering of small fat droplets, while others have recently found success with intramuscular placement[38,39].

Sterile pressure dressings are applied to the donor site and ice compresses to both the donor and recipient sites. The patient is instructed in postoperative care, including systemic antibiotics, and pain management without aspirin-containing products. Any remaining fat can be meticulously labeled and frozen. When properly stored, it has been suggested that frozen fat can be utilized for up to 12–18 months[40].

Areas amenable to autologous fat transfer on the aging face include the nasolabial folds, cheeks (Fig. 158.11), infraorbital area, marionette lines, lips, scars from acne, and stable disease processes associated with idiopathic facial subcutaneous atrophy (e.g. linear morphea [including coup de sabre], Parry–Romberg syndrome)[41,42]. The dorsum of the hand often shares all of the signs of aging found in sun-exposed areas, but the advances available for facial rejuvenation often compound the disparity between the aging face and hand. Replacing fat in the dorsal hand masks the appearance of protruding tendons and vessels (Fig. 158.12). This imparts a more youthful appearance that is compatible with a rejuvenated face. Adipose transfer has also been shown to be effective in treating partial lipodystrophies associated with antiretrovirals.

Despite the expanding use of transplanted adipose tissue, the literature has few objective studies documenting persistence of grafted material and rate of resorption[43]. Results seem to depend on repeated injections with smaller amounts over time, rather than single injections of larger amounts, which seem to be subject to lower survival rates and higher volume resorption. Presumably because large volumes cannot be sustained by passive diffusion of the recipient bed, overcorrection is discouraged, with the transplanted area corrected to 100%.

Fig. 158.11 Lipotransfer and subcision to correct scarring due to previous surgical excision of a cyst. A Pre-treatment. **B** Post-treatment.

Fig. 158.12 Lipotransfer. Before (**A**) and after (**B**) injection of approximately 10 ml of autologous fat into the dorsum of each hand. *Courtesy, Seth L Matarasso, MD.*

There are still many unanswered questions with regard to lipotransfer technique, viability and persistence of the transplant, and storage[44,45].

Silicone

Silicone (polydimethylsiloxane) consists of repeating units of dimethylsiloxane terminated with trimethylsiloxane. Centistoke (cs) refers to the viscosity of silicone oil and is directly related to the chain length of the repeating units. A 1 cs product is equivalent in consistency to water, 350 cs products are oils similar in consistency to mineral oils, and a 1000 cs product is similar in texture to honey. Although useful when injected by an experienced physician, silicone has had a tumultuous history and continues to be controversial. Pure injectable-grade (350 cs) liquid silicone was never approved by the FDA and remains prohibited in the US. However, injectable intraocular silicone (AdatoSil® 5000 centistoke) was approved in 1994 for tamponade to treat complicated retinal detachment. Silikon 1000® was approved for intraocular use in 1997. Under the US FDA Modernization Act, which afforded physicians the right to use medical devices under the same off-label provisions applicable to drugs, physicians could legally use standardized silicone oils for soft tissue augmentation. Since this off-label ruling, there has been an increase in interest and use of silicone for permanent soft tissue augmentation. In 2001, the FDA approved a clinical study of SilSkin®, a highly purified 1000 cs oil, for the treatment of nasolabial folds, marionette lines, and mid-malar depressions. In 2003, the FDA also approved SilSkin® for investigational treatment of antiretroviral-associated lipoatrophy[46,47].

The only form of injectable liquid silicone currently available for soft tissue augmentation is Silikon® 1000 (an off-label use; see above). As the placement of the product results in permanent augmentation, there is very little margin for error, and meticulous technique is essential. Many practitioners prefer to use a glass syringe attached to a 30-gauge needle. The silicone is deposited using a microdroplet serial puncture technique, using 0.005–0.01 ml aliquots placed at 2 mm to 5 mm intervals within the dermis without overcorrection. The average treatment should not exceed 0.25–0.75 ml of silicone and the intervals between sessions are usually monthly until the collagen response and cumulative fibroplasia achieve the desired result (Fig. 158.13). As the endpoint of treatment approaches, the volume injected per visit diminishes and the time interval between treatments lengthens. Patients can expect slow and gradual, but permanent, improvement of 30–90%.

Common post-treatment events include erythema, edema and ecchymosis. The incidence of overcorrection with superficial beading, granulomatous and inflammatory reactions, and movement of the product to a distant site (drift) have improved with purer (unadulterated) silicone oil and strict adherence to indications and protocol[48,49]. Nonetheless, delayed granuloma formation can occur and management options include intralesional injections of triamcinolone.

Polymethylmethacrylate (PMMA) Microspheres

Known as Artecoll® outside of the US and designated by the manufacturer as Artefill® for FDA approval, the product contains polymethylmethacrylate (PMMA) microspheres suspended in a solution of 3.5% bovine collagen and 0.3% lidocaine. The collagen serves as a carrier, and by 1–3 months following injection, it is degraded. The remaining intact, inert, non-biodegradable 30–40 μm PMMA beads, commonly known as Lucite™ or Plexiglas™, are large enough to avoid phagocytosis but small enough to promote permanent augmentation. Once the host's collagen has encapsulated the microspheres, the augmentation has been purported to be permanent.

Prepackaged in a 1.0 ml syringe, Artefill® is injected with a 27-gauge needle and by subdermal tunneling, with placement at the dermal-subcutaneous junction. However, as with bovine collagen alone (see above), it is prudent to perform a skin test prior to augmentation to screen for a hypersensitivity reaction. In an inconspicuous site, a small aliquot (0.05 ml) can be injected at the junction of the dermis and subcutaneous tissue. In addition to hypersensitivity reactions, there is also a risk of delayed granuloma formation.

It is likely that a history of reformulations, name changes and varied manufacturers has led to significant confusion regarding the safety of Artefill® among clinicians already leery of permanent fillers. Primarily

Fig. 158.13 Silicone – correction of HIV lipoatrophy. A Pre-treatment. **B** Following soft tissue augmentation with injectable liquid silicone.

due to reports of granuloma formation, questions have been raised about PMMA manufactured outside the US. Positive outcomes from a large, long-term, prospective study beginning in 2008 that examined the safety and efficacy of Artefill® and involved 1000 patients has renewed interest in the product. As of 2009, Artefill® has been manufactured in the US.

CONCLUSION

The vast array of available filler products, and those that are on the horizon, are only one means to improve tissue loss associated with aging and trauma. The optimal result may be best achieved by combining fillers of different depth, origin and durability with other aesthetic procedures[29,50]. The science of soft tissue augmentation is clearly evolving. Keeping abreast of advances and perfecting a few techniques will be most advantageous for patients; it is not only what is injected, but how it is injected, that determines the degree of success. Finally, regardless of the treatment chosen, it is the combination of clinical judgment, realistic expectations, meticulous preparation, and surgical skill that provides optimal results.

REFERENCES

1. Hevia O. A retrospective review of calcium hydroxylapatite for correction of volume loss in the infraorbital region. Derm Surg. 2009;35:1–8.
2. Aschinoff R. Overview: soft tissue augmentation. Clin Plast Surg. 2000;274:479–87.
3. Rohrich RJ, Nguyen AT, Kenkel JM. Lexicon for soft tissue implants. Dermatol Surg. 2009;35:1605–11.
4. Rohrich RJ, Ghavami A, Crosby MA. The role of hyaluronic acid fillers (Restylane) in facial cosmetic surgery: review and technical considerations. Plast Reconstr Surg. 2007;120:41S–54S.
5. Drake L, Dinehart SM, Farmer ER, et al. Guidelines of care for soft tissue augmentation. J Am Acad Dermatol. 1996;34:695–7.
6. Kaminer MS, Krauss MC. Filler substances in the treatment of facial aging. Med Surg Dermatol. 1998;5:215–21.
7. Baumann L, Kerdel F. The treatment of bovine collagen allergy with cyclosporin. Dermatol Surg. 1999;25:247–9.
8. Moody BR, Sengelmann RD. Topical tacrolimus in the treatment of bovine hypersensitivity. Dermatol Surg. 2001;27:789–91.
9. Narins RS, Brandt FS, Lorenc ZP, et al. Twelve-month persistency of a novel ribose-cross-linked collagen dermal filler. Dermatol Surg. 2008;34(Suppl 1):S31–9.
10. Braun M, Braun S. Nodule formation following lip augmentation using porcine collagen-derived filler. J Drugs Dermatol. 2008;7:579–81.
11. Burres S. Preserved particulate fascia lata for injection: a new alternative. Dermatol Surg. 1999;25:790–4.
12. Burres S. Soft tissue augmentation with Fascian. Clin Plast Surg. 2001;28:101–9.
13. Piacquadio S, Jarcho M, Goltz R. Evaluation of Hylan B gel as soft tissue augmentation implant material. J Am Acad Dermatol. 1997;35:544–9.
14. Frank T, Gendler E. Hyaluronic acid for soft tissue augmentation. Clin Plast Surg. 2001;28:121–7.
15. Matarasso SL. Hyaluronic acids: a review and update of available filling agents. Aesthetic Surg J. 2004;24:1–4.
16. Narins RS, Brandt F, Leyden J, et al. A randomized, double blind, multicenter comparison of the efficacy and tolerability of Restylane versus Zyplast for the correction of nasolabial folds. Derrnatol Surg. 2003;29:588–95.
17. Taylor SC, Burgess CM, Callender VD. Safety of nonanimal stabilized hyaluronic acid dermal fillers in patients with skin of color: a randomized evaluator-blinded comparative trial. Dermatol Surg. 2009;35(Suppl 2):1653–60.
18. Grimes PE, Thomas JA, Murphy DK. Safety and effectiveness of hyaluronic acid fillers in skin of color. J Cosmet Dermatol. 2009;8:162–8.
19. Matarasso SL, Herwick R. Hypersensitivity reaction to injectable non-animal stabilized hyaluronic acid. J Am Acad Dermatol. 2006;55:128–31.
20. Friedman PM, Mafong EA, Kauver AN, Geronemus RG. Safety data of injectable nonanimal stabilized hyaluronic acid gel for soft tissue augmentation. Dermatol Surg. 2002;28:491–4.
21. Lowe NJ, Maxwell A, Lowe P, et al. Hyaluronic acid fillers: adverse reactions and skin testing. J Am Acad Dermatol. 2001;45:930–3.
22. Hirsh R, Stier M, Complications of soft tissue augmentation. J Drugs Dermatol. 2008;7:841–5.
23. Brody HJ. The use of hyaluronidase in the treatment of granulomatous hyaluronic acid reactions or unwanted hyaluronic acid misplacement. Dermatol Surg. 2005:31;893–7.
24. Gold MH. Use of hyaluronic acid fillers for the treatment of the aging face. Clin Interv Aging. 2007;2:369–76.
25. Dover JS, Rubin MG, Bhatia AC. Review of the efficacy, durability, and safety data of two nonanimal stabilized hyaluronic acid fillers from a prospective, randomized, comparative, multicenter study. Dermatol Surg. 2009;35:322–31.
26. Wesley N, Dover J. The filler revolution: a six year retrospective. J Drugs Dermatol. 2009;8:903–7.
27. Day JN, Raabe A, Shiner AM, et al. Intradermal polylactic acid (NewFill) for treatment of severe HIV-associated facial lipoatrophy. HIV Med. 2002;3:162.
28. Flaharty P. Radiance. Facial Plast Surgery. 2004; 20:165–9.
29. Hoffman C, Schuller-Petrovic S, Soyer HP, et al. Adverse reactions after cosmetic lip augmentation with permanent biological inert materials. J Am Acad Dermatol. 1999;40:100–2.
30. Tzikas TL. Evaluation of the Radiance FN soft tissue filler for facial soft tissue augmentation. Arch Facial Plast Surg. 2004;6:234–9.
31. Marmur ES, Taylor SC, Grimes PE et al. Six-month safety results of calcium hydroxyapatite for treatment of nasolabial folds in Fitzpatrick skin types IV to VI. Dermatol Surg. 2009;35(Suppl 2):1641–5.
32. Lawrence N. Goretex. In: Narins RS (ed). Cosmetic Surgery: An Interdisciplinary Approach. New York: Marcel Dekker, 2001:289–311.
33. Cox SE. Who is still using ePTFE (Gortex/Softform)? Dermatol Surg. 2005;31:163–5.
34. Glogau RG, Matarasso SL, Markey AC. Microlipoinjection: autologous fat grafting. In: Moy R, Lask G (eds). The Principles and Techniques of Cutaneous Surgery. New York: McGraw-Hill, 1996:437–44.
35. Tzikas TL. Autologous fat grafting for midface rejuvenation. Facial Plast Surg Clin North Am. 2006;14:229–40.
36. Pinski KS, Roenigk HH. Autologous fat transplantation: long-term follow-up. J Dermatol Surg Oncol. 1992;18:179–84.
37. Klein JA. The tumescent technique for liposuction surgery. Am J Cosmet Surg. 1987;4:263–7.

38. Coleman SR. Long-term survival of fat transplants: controlled demonstrations. Aesthetic Plast Surg. 1995;19:421–5.
39. Coleman SR. The techniques of periorbital lipoinfiltration. Oper Tech Plast Reconstr Surg. 1994;1:120–6.
40. Takasu K, Takasu S. Long-term frozen fat for tissue augmentation. J Aesthetic Dermatol Cosmet Surg. 1999;1:173–8.
41. Matarasso A, Matarasso SL. Autologous fat transplantation: a long-term following. Plast Reconstr Surg. 1995;5:988.
42. Chajchir A, Benzaquen I. Liposuction fat grafts in face wrinkles and hemifacial atrophy. Aesthetic Plast Surg. 1986;10:115–17.
43. Carpaneda CA, Ribeiro MT. Percentage of graft viability versus injected volume in adipose autotransplants. Aesthetic Plast Surg. 1994;18:17–9.
44. Sadick NS. Fatty acid analysis of transplanted adipose tissue. Arch Dermatol. 2001;37:723–9.
45. Drake L, Dinehart S, Farmer E, et al. Guidelines of care for soft tissue augmentation with fat transplantation. J Am Acad Dermatol. 1996;34:690–4.
46. Orentreich DS, Orentreich NO. Injectable fluid silicone. In: Roenigk RK, Roenigk HH (eds). Dermatologic Surgery: Principles and Practice. New York: Marcel Dekker, 1989:1349–95.
47. Jones D, Carruthers A, Orentreich D, et al. Highly purified 1000-cst silicone oil for the treatment of human immunodeficiency virus-associated facial lipoatrophy: an open pilot trial. Dermatol Surg. 2004;30: 1279–86.
48. Baumann L, Halem M. Lip silicone granulomatous foreign body reaction treated with Aldara (imiquimod 5%). Dermatol Surg. 2003;29:429–32.
49. Duffy DM. The silicone conundrum: a battle of anecdotes. Dermatol Surg. 2002;28:590–4.
50. Miller TA, Klein AW, Lambros VS, Matarasso SL. Soft tissue augmentation. J Aesthetic Surg. 2001;20: 309–14.

Botulinum Toxin 159

Alastair Carruthers and Jean Carruthers

Chapter Contents

Properties of botulinum toxins 2561
Clinical use of botulinum toxin type A 2561
Description of techniques 2562
Postprocedural care 2570
Complications 2570

Synonyms: ■ Botulinum toxin type A, botulinum A exotoxin, BoNT-A; onabotulinumtoxinA – BOTOX®/BOTOX Cosmetic®; abobotulinumtoxinA – Dysport®, Azzalure®; incobotulinumtoxinA – Xeomin®/Bocouture® ■ Botulinum toxin type B, BoNT-B; rimabotulinumtoxinB – Myobloc®

Key features

- Botulinum toxin (BoNT) causes chemodenervation of muscles by blocking acetylcholine release
- Injections of botulinum toxin type A (BoNT-A) that weaken or relax muscles can smooth hyperfunctional lines and change the contour of the face and neck
- Adjunctive use of BoNT-A with laser resurfacing or soft tissue augmentation is beneficial, particularly in active regions such as the perioral and periocular areas
- The cosmetic effects of BoNT-A typically last months and may increase with subsequent injections
- In addition to its effect on musculature, BoNT-A successfully denervates sweat glands, serving as an effective alternative treatment for hyperhidrosis
- Complications (e.g. eyelid ptosis) are generally caused by diffusion of the toxin to non-targeted muscles and can be minimized by using concentrated doses and careful technique

INTRODUCTION

Botulinum exotoxin (BoNT) injections are commonly used to improve facial aesthetics by smoothing hyperdynamic rhytides in the upper face. In recent years, BoNT has been used increasingly in the mid- and lower face and neck, in part because of its demonstrated efficacy and safety for indications in the upper face, and in part because of awareness that muscular hyperactivity (in addition to volume depletion) contributes to the aesthetic appearance of the mid- and lower face and neck. Today, BoNT therapy is an integral aspect of most cosmetic practices.

PROPERTIES OF BOTULINUM TOXINS

Various strains of the bacterium *Clostridium botulinum* produce, as a group, seven distinct serotypes of BoNT that affect neural function: A, B, C1, D, E, F and G[1]. Although all serotypes produce chemodenervation and atrophy of skeletal muscles by blocking acetylcholine release from motor neurons at the neuromuscular junction (Fig. 159.1), they differ with regard to cellular mechanism of action and clinical profile.

BoNT type A (BoNT-A) was the first serotype developed for use in humans. Of the multiple formulations currently in use or undergoing clinical testing for cosmetic applications in North America (Table 159.1), three have been approved by the US Food and Drug Administration (FDA) for glabellar rhytides – onabotulinumtoxinA (BOTOX®/BOTOX Cosmetic®), abobotulinumtoxinA (Dysport®, Azzalure®), and incobotulinumtoxinA (Xeomin®/Bocouture®). AbobotulinumtoxinA differs from onabotulinumtoxinA in purification procedures, dosing, injection patterns, and adverse effects (AEs)[2]. Evidence suggests that abobotulinumtoxinA is associated with greater diffusion and migration[3,4], and early studies in a therapeutic setting found that abobotulinumtoxinA, while slightly more effective than onabotulinumtoxinA, had a higher incidence of adverse effects[5,6].

One formulation of BoNT type B (BoNT-B) is also available in North America (see Table 159.1). RimabotulinumtoxinB (Myobloc®/NeuroBloc®) was FDA-approved in 2000 for the treatment of cervical dystonia; it has been used off-label to treat facial rhytides, having been evaluated in several smaller clinical trials[7–9]. Research indicates that for the treatment of facial rhytides, there are key differences between BoNT-A and BoNT-B: BoNT-B has a more rapid onset of action but a shorter duration of effect, diffuses more widely, and is associated with greater pain and other side effects when compared to BoNT-A[10]. However, one study examining seven doses of BoNT-B found all to be safe and effective for the treatment of hyperfunctional rhytides, with a dose-related duration of effect[11].

CLINICAL USE OF BOTULINUM TOXIN TYPE A

Hyperkinetic lines result from the repeated contraction of muscles perpendicular to the rhytides. Weakening or relaxing these muscles with BoNT-A can smooth these lines, including horizontal lines on the forehead (from frontalis contraction), vertical lines in the glabellar region between the eyebrows (from corrugator contraction), horizontal creases across the bridge of the nose (from procerus contraction), "crow's feet" and lateral lines along the lower eyelid (from lateral orbicularis oculi contraction), and perioral lines (from orbicularis oris contraction). Deep grooves or folds elsewhere that are exacerbated by muscle activity are also amenable to treatment. Patients 30–50 years of age may be most responsive to BoNT-A, because their rhytides are more likely to be caused by muscle activity than by the loss of skin elasticity that occurs during aging.

The effects of BoNT-A injections are usually apparent within a day or two and are obvious for 3 or 4 months, although they may last for 6 months or longer. With repeated injections, there is a tendency for subsequent injections to provide aesthetic improvement that lasts longer. It is possible that over the course of treatment, individuals alter their habitual use of muscles that cause expression lines. Long-term remodeling of the dermis and epidermis that helps to sustain the cosmetic effects also occurs in most individuals, because the tissue is no longer subjected to the same forces of muscle contraction.

Of note, intramuscular injections of BoNT-A have also become the treatment of choice for a number of disorders characterized by muscular hyperactivity, such as strabismus[12], blepharospasm, hemifacial spasm[13] and cervical dystonia[14]. In addition, the ability of BoNT to block acetylcholine release from autonomic nerve endings innervating glandular tissue or smooth muscle has led to investigation of its use for other indications, including hyperhidrosis[15] and migraine[16] (see Table 159.1).

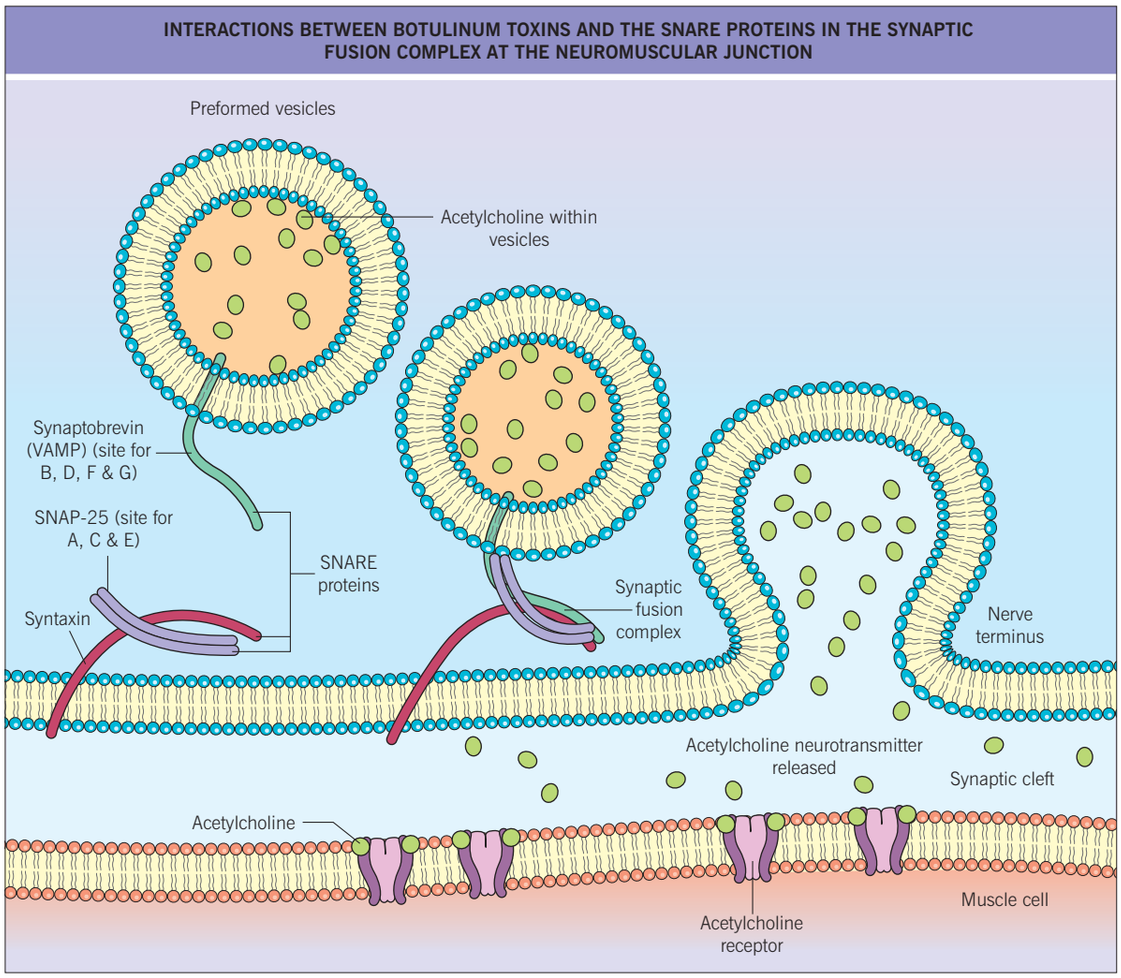


Fig. 159.1 Interactions between botulinum toxins and the SNARE proteins in the synaptic fusion complex at the neuromuscular junction. Botulinum toxins A, C and E catalyze the cleavage of the SNAP-25 protein. Botulinum toxins B, D, F and G catalyze the cleavage of synaptobrevin (or the vesicle-associated membrane protein, VAMP). *Adapted from Rohrer TE, Beer K. Background to botulinum toxin. In: Carruthers A, Carruthers J (eds). Botulinum Toxin. Philadelphia: Saunders, 2005.*

FORMULATIONS AND CLINICAL USE OF BOTULINUM TOXINS (BoNT) IN NORTH AMERICA

	Generic name [Trade name(s)®]	FDA indications or stages of development	Off-label uses
BoNT-A	OnabotulinumtoxinA [BOTOX®/BOTOX Cosmetic®/Vistabel®/Vistabex® (Allergan Inc.)]	Moderate-to-severe glabellar rhytides (approved dose = 20 U); primary axillary hyperhidrosis; blepharospasm; strabismus; cervical dystonia; chronic migraine	Dermatologic: upper, mid- and lower face rejuvenation; palmar hyperhidrosis
			Other: neck pain; back pain; bladder spasms; limb spasticity; tension headaches
	AbobotulinumtoxinA [Dysport® (Ipsen Ltd./ Medicis), Azzalure® (Galderma)]	Moderate-to-severe glabellar lines (approved dose = 50 U); cervical dystonia	Same as above
	PurTox® (Mentor Corporation)	Phase 3 testing for glabellar rhytides; various stages of development for therapeutic indications	
	IncobotulinumtoxinA [Xeomin® (Merz Pharmaceuticals)]	Glabellar rhytides	
BoNT-B	RimabotulinumtoxinB [Myobloc®/ NeuroBloc® (Solstice Neurosciences, Inc.)]	Cervical dystonia	Upper, mid- and lower face rejuvenation; limb spasticity

Table 159.1 Formulations and clinical use of botulinum toxins (BoNT) in North America.

A Note About Dosing

All preparations of BoNT differ in potency and clinical effect, and their units are not interchangeable. Clinicians are advised to consult official product inserts for more information on storage, dilution, dosing, and contraindications. Since most of the information available regarding the cosmetic uses of BoNT – both from published reports and from our personal experience – pertains to the use of onabotulinumtoxinA, the following discussion (including units and descriptions of techniques) focuses on those formulations specifically, unless otherwise stated.

DESCRIPTION OF TECHNIQUES

Injections for aesthetic indications may be given intramuscularly, subcutaneously or intradermally. We use intradermal injections, especially in the crow's feet area, to minimize bruising. All of the usual precautions prior to any injection should be followed. The area may be chilled with ice before the injections to minimize any discomfort in sensitive individuals. Alternatively, a topical anesthetic can be applied 15 to 30 minutes prior to injection to minimize discomfort, and some physicians report great benefits from vibration analgesia[17].

Electromyographic (EMG) guidance can be used to inject BoNT into the most active region of the muscle. Once a thorough understanding of the relevant facial anatomy is attained (see Fig. 142.8), injection with an EMG system provides little benefit. However, even experienced clinicians may find EMG guidance to be useful for the occasional difficult-to-treat patient.

Glabellar Frown Lines

Frown lines in the glabellar region are caused by contraction of the corrugator supercilii and orbicularis oculi muscles, which move the

brow medially, and the procerus and depressor supercilii muscles, which pull the brow inferiorly. Because the corrugator and procerus are used only to control facial expression, the goal of treatment should be to produce a significant weakening of these muscles. The treatment sites and doses should be individualized because the location, size and use of the frown muscles vary greatly between individuals. We currently use five injection sites when treating glabellar frown lines and vary the dosage depending on the individual brow (Fig. 159.2; Table 159.2). The procedure effectively smoothes the glabellar lines at rest and prevents their appearance when the patient attempts to frown, for an average of 3 to 4 months (Fig. 159.3).

Crow's Feet

Contraction of the lateral fibers of the orbicularis oculi muscle produces "crow's feet", lines that radiate from the lateral canthus. Since forceful closure of the eyelids requires orbicularis contraction, the goal of treatment is to produce weakening just in the lateral orbital area, rather than a complete paralysis of the muscle. Because the orbicularis oculi is diffusely innervated, multiple injections are required to weaken broad areas of the muscle.

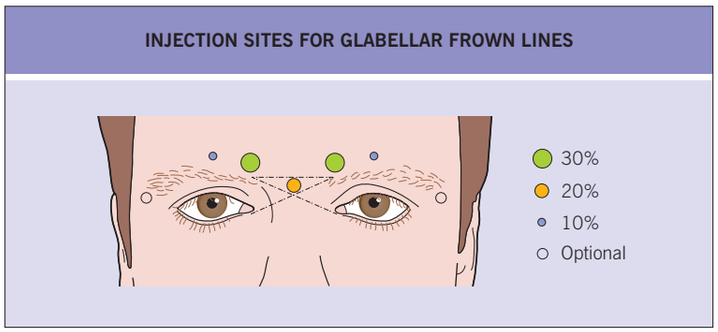


Fig. 159.2 Injection sites for glabellar frown lines. The authors currently use five injection sites when treating glabellar frown lines and vary the dosage depending on the individual brow. The injection in the midpupillary line may be omitted if eyebrow ptosis seems likely or possible. Sometimes, an injection is made above the lateral canthus or into the tail of the eyebrow.

USE OF BoNT-A [onabotulinumtoxinA] IN THE UPPER FACE: DOSING AND TECHNIQUES

Treatment area	Injection sites and tips
Glabellar rhytides	• Men: starting dose 60 U, titrate to 100 U; women: starting dose 30 U, titrate to 50 U • 7–10 U (women) or 15–20 U (men) just above the superior bony orbital rim directly above the inner canthus on each side (see Fig. 159.2) • 5–10 U into procerus muscle at midline • For horizontal brows: 4–5 U 1 cm above bony supraorbital rim in the midpupillary line* • Sometimes necessary to inject above lateral canthus or into the tail of the eyebrow to improve lateral eyebrow position
Lateral canthal rhytides (crow's feet)	• 12–15 U/side, distributed amongst 2–4 sites (see Fig. 159.4) • Inject when patient is *not* smiling to avoid affecting the ipsilateral zygomaticus complex (which can lead to upper lip ptosis) • Inject lateral to the lateral orbital rim; more medial injections can cause lower eyelid droop • Superficial injections (as few as possible) will avoid bruising • Avoid injecting superficial veins
Horizontal forehead rhytides	• 10–15 U amongst multiple sites horizontally across the midforehead, 2–3 cm above the eyebrows (see Fig. 159.7) • 5 injection sites for broad foreheads†; 4 injection sites and a slightly lower dose for narrow foreheads
Hypertrophic orbicularis oculi muscle	• Subcutaneous injections of 2–4 U in the midpupillary line, 3 mm below the ciliary margin (see Fig. 159.8) • Higher doses can result in keratoconjunctivitis sicca (dry eye)

*Injection site most likely to cause ptosis.
†More than 12 cm between the temporal fusion lines (the slight prominence at the point where the temporalis fascia joins the skull) at the midforehead level.

Table 159.2 Use of BoNT-A [onabotulinumtoxinA] in the upper face: dosing and techniques.

Fig. 159.3 Glabellar lines. In a subject at rest (**A**) and during frowning (**B**). Subject at rest (**C**) and attempting to frown (**D**) 1 week after BoNT-A treatment.

While doses and sites vary amongst clinicians, we evenly distribute the BoNT-A into two to four separate injection sites (Fig. 159.4; see Table 159.2). Results last approximately 3 months (Fig. 159.5).

Horizontal Forehead Lines

Deep horizontal creases in the forehead are produced by the repeated contraction of the frontalis muscle. This large, vertically oriented muscle is the brow elevator; it inserts superiorly into the galea aponeurotica and inferiorly into the skin of the brow. Unfortunately, weakening the frontalis muscle sufficiently to eliminate hyperkinetic forehead lines can result in undesired brow ptosis or a complete lack of expressiveness. Therefore, the goal of treatment is to only soften, rather than completely eliminate, forehead lines. Ideally, the individual will still be able to elevate the eyebrows, albeit to a lesser extent, after treatment (Fig. 159.6). We believe that the brow depressors should *always* be treated at the same time as the frontalis, and therefore we use the technique described in the next section. It is our practice to divide the BoNT-A among multiple sites distributed horizontally across the midforehead (Fig. 159.7; see Table 159.2). Effects typically last from 3 to 6 months.

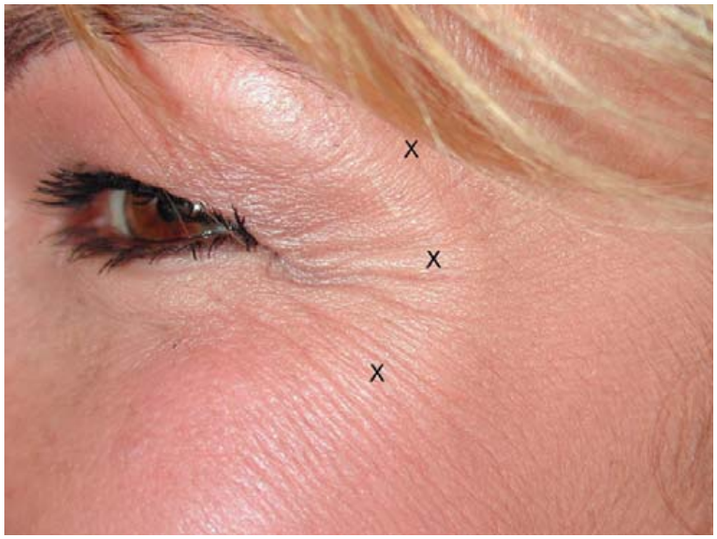


Fig. 159.4 Injection sites for crow's feet. The authors inject 12 to 15 U of BoNT-A [onabotulinumtoxinA] per side among two to four injection sites.

Brow Lift and Shaping

Brow ptosis often occurs during aging, resulting in an angry, scowling expression. Notably, the shape and height of the eyebrow are determined by the opposing activity of the frontalis muscle, which elevates the brow, and the brow depressors. The medial brow depressors are the corrugator supercilii, the procerus, and the medial portion of the orbicularis oculi; the lateral depressor is the lateral portion of the orbicularis oculi (that is lateral to the temporal fusion line). Previously, we believed that brow lifts were a result of the inactivation of the brow depressors[18–20]. However, additional analysis of a dosing study showed that central injections of 20 to 40 U of BoNT-A [onabotulinumtoxinA] into the glabella alone (with the most lateral injection at the midpupillary line) led to a dramatic lateral eyebrow elevation, followed by an entire brow lift that peaked at 12 weeks after treatment[21]. Interestingly, too little BoNT-A (10 U) led to a brief *fall* in eyebrow position. We now believe that the change in eyebrow position after glabellar injection in women is due to diffusion of BoNT-A into the lower frontalis muscle, which causes an improved resting tone in the remainder of the muscle and in eyebrow position.

Hypertrophic Orbicularis Oculi

The pretarsal portion of the orbicularis oculi muscle is involved in the blink reflex. Contraction of the pretarsal orbicularis during smiling tends to decrease the size of the palpebral aperture. Hypertrophy of this muscle can give a "jelly roll" appearance to the lower eyelid, enough that some individuals may complain that they look overweight. We have found that injection of 2 U (or occasionally 4 U) of BoNT-A [onabotulinumtoxinA] into the lower pretarsal orbicularis (Fig. 159.8) opens the palpebral aperture both at rest and during smiling (Fig. 159.9; see Table 159.2)[22,23].

Lateral orbital injections have a synergistic effect with lower eyelid injections and can be used as a safe way to enhance the lower eyelid effect without using too high a dose in the lower lid orbicularis. This procedure is used only for patients who respond well to a preinjection snap test, in which the lower eyelid is briefly pulled off the globe by

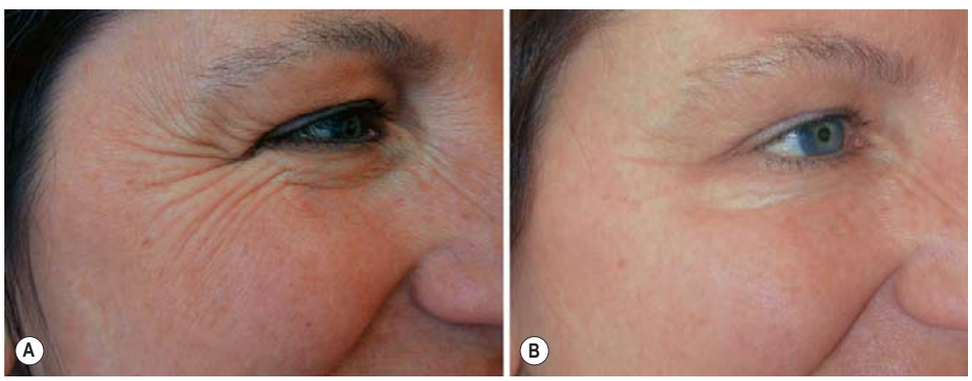


Fig. 159.5 Crow's feet. Subject with crow's feet before (**A**) and 3 weeks after BoNT-A treatment (**B**).

Fig. 159.6 Horizontal forehead lines. Produced when the subject elevated the brows before (**A**) and 1 month after BoNT-A treatment (**B**).

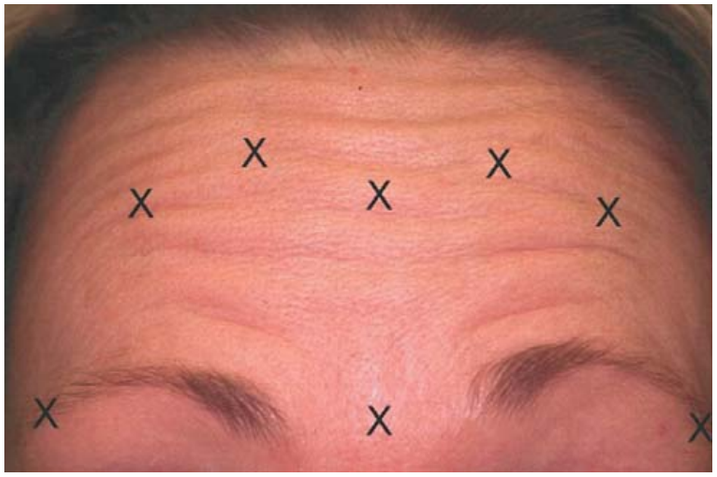


Fig. 159.7 Injection sites for horizontal forehead lines. Injection sites must be kept well above the brow. The lower X's mark the sites of injection of the brow depressors.

Fig. 159.8 Injection sites for hypertrophic orbicularis oculi muscle. 2–4 U of BoNT-A [onabotulinumtoxinA] are injected into the lower pretarsal orbicularis oculi muscle.

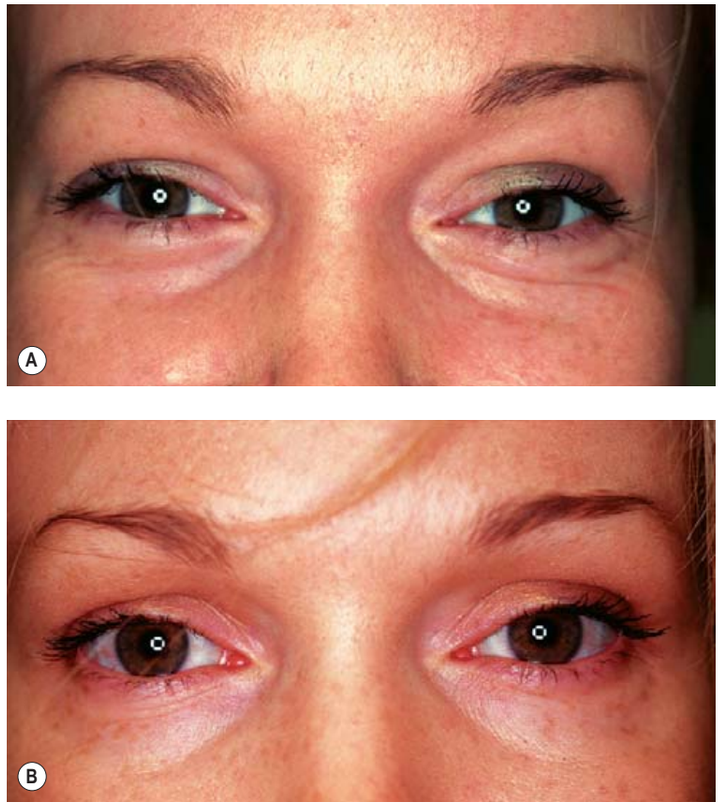


Fig. 159.9 Hypertrophic orbicularis oculi muscle. BoNT-A treatment of the lower pretarsal orbicularis opens the palebral aperture. Note the position of the lower eyelids in the subject before (**A**) and after treatment (**B**).

Fig. 159.10 Injection sites for "bunny lines". 2–4 U of BoNT-A [onabotulinumtoxinA] are injected into each belly of the upper nasalis as it traverses the lateral bony dorsum of the nose. Usually one injection per side is sufficient.

downward pressure on the lower eyelid skin, then quickly released, and the speed with which the eyelid snaps back to the globe assessed. Patients who have had previous lower eyelid ablative resurfacing or infralash blepharoplasty without a coexisting canthopexy to support the normal position of the lower eyelid are not good candidates for this procedure.

Midface Injections

Contraction of the upper nasalis muscle causes fanning rhytides ("bunny lines") at the radix (root) of the nose. BoNT-A treatment weakens the upper nasalis effectively and dramatically softens these lines. Bunny lines are typically treated in conjunction with the glabellar complex (Fig. 159.10; Table 159.3).

Some individuals repeatedly and embarrassingly dilate their nostrils in social situations. The sides of the columella/septum become visible when the nostrils are prominently flared. Contraction of the nasalis muscle accentuates the nasal flare. Small doses of BoNT-A can produce a satisfactory decrease in involuntary nostril flare in some patients for 3 to 4 months (see Table 159.3).

Nasolabial folds extend from the lateral nasal ala to a point lateral to the external angle of the mouth. Young adults have a shallow indentation, but older individuals who smile excessively or sustain photodamage can develop a permanent, deep crevice. The most common treatments for nasolabial folds have been soft tissue fillers and laser resurfacing. Although muscle contraction contributes to the appearance of the folds, injecting BoNT-A directly into the area of the fold is not the treatment of choice, because it is likely to result in an asymmetric smile, flaccid cheek and flattening of the midface, leading to incomplete or disappointing results; in addition, the cutaneous upper lip lengthens vertically, as is often seen during aging. However, for some individuals who have a naturally shorter cutaneous upper lip, very small doses of

USE OF BoNT-A [onabotulinumtoxinA] IN THE MIDFACE: DOSING AND TECHNIQUES	
Treatment area	**Injection sites and tips**
Bunny lines	• 2–4 U into the upper nasalis muscle, usually 1 injection/side (see Fig. 159.10) • Inject well above nasofacial groove* to avoid lip ptosis (due to relaxing the levator labii superioris muscle • Injection followed by gentle massage
Repeated nasal flare	• 5–10 U bilaterally into lower nasalis muscle fibers covering the lateral nasal ala • Inject the most active area of contraction
Nasolabial folds	• Select patients only, e.g. those with a naturally shorter cutaneous upper lip • 1 U into each lip elevator complex above the nasofacial groove
Nasal tip droop	• 2–3 U into depressor septi nasi muscle at the base of the columella
*Refers to groove between the nose and cheek.	

Table 159.3 Use of BoNT-A [onabotulinumtoxinA] in the midface: dosing and techniques.

BoNT-A can be beneficial for improving nasolabial folds (see Table 159.3), particularly when the injections are given concurrently with other treatment (fillers or resurfacing). Because the duration of effect of this procedure is relatively long (~6 months), it is important to be very careful in patient selection and to be clear about the potential results of the procedure.

Nasal tip droop is common during aging. Contraction of the depressor septi nasi, a small muscle located at the external base of the nasal septum, pulls the tip of the nose downward. Injection of BoNT-A slightly elevates the nasal tip (see Table 159.3). Caution should be taken with individuals who already have a long non-vermilion upper lip, because of an associated risk of lip ptosis.

Vertical Lip Rhytides (Perioral Lines)

During aging, the area of the mouth undergoes characteristic changes: the lateral portions of the lips recede to produce a "rosebud mouth"; the vertical distance between the columella and the vermilion border of the upper lip increases, and the substance of the vermilion lip rolls inside, producing the thin and disappointed lips characteristic of old age. Dense vertical perioral rhytides are often associated with the lengthening of the cutaneous upper lip during aging. These vertical lines are commonly referred to as "smokers' lines" but can have other causes, such as heredity, photodamage, or activities such as playing a musical instrument that require pursing of the lips. Radial upper lip rhytides are exaggerated by the pursestring-like action of the orbicularis oris sphincter muscle of the lip. Multiple fine rhytides of the upper lip can be effectively treated with fillers such as collagen or hyaluronic acid or with mid-depth or deeper resurfacing. However, deeper rhytides may be resistant to these treatments.

BoNT-A treatment of the lip sphincter is recommended only for deep lines. Small doses that produce localized microparesis of the orbicularis oris can dramatically reduce radial lip lines and improve the appearance of the lips (Table 159.4). To maintain competence of the mouth, it is important to be conservative with dosing, and superficial injections are recommended over deep injections (Fig. 159.11). Even with conservative dosing, however, BoNT-A treatment of perioral lines may result in lip sphincter weakening that subtly affects mouth function. This procedure may not be desirable for musicians who play wind instruments and professional singers or speakers. Some patients have difficulty with lip proprioception after treatment, but eating, drinking and singing are typically not affected. BoNT-A injections for radial lip lines may be particularly useful in combination with perioral laser or electrosurgical resurfacing or in combination with a soft tissue-augmenting agent such as hyaluronic acid.

Upper Gum Show

When some individuals smile, the upper lip is retracted too far, resulting in excessive exposure of the upper gum. The gum line, upper

USE OF BoNT-A [onabotulinumtoxinA] IN THE LOWER FACE AND NECK: DOSING AND TECHNIQUES	
Treatment area	**Injection sites and tips**
Perioral rhytides	• 4 U/lip (2 U/lip quadrant); typically 1 U/lip line (see Fig. 159.11) • Inject into area of muscle contraction adjacent to the creases at the vermilion border on either side of Cupid's bow • Avoid injecting lip corners (can lead to drooping of the lateral lip and drooling) as well as the midline (can lead to flattening of Cupid's bow)
Upper gum show	• 1–2 U into levator labii superioris alaeque nasi muscle (on each side of the bony nasal prominence) • Younger patients
Mouth frown	• 2–3 U into the posterior aspect of the depressor anguli oris (DAO) muscle on each side, close to the mandible (see Fig. 159.13) • Additional 3 U into each mentalis muscle insertion • Asking the patient to frown can aid in identifying the DAO muscle • Not recommended for singers or musicians
Marionette lines	• 2–5 U into each DAO muscle immediately above the angle of the mandible and 1 cm lateral to the lateral oral commissure; amount injected depends upon size of the muscle • Injection must be lateral and low, at the junction of the depressor and the superior margin of the mandible • An injection too medial or too high can cause ipsilateral weakness of the depressor labii inferioris muscle and flattening of the lower lip contour when the mouth attempts to form an "O"; an injection too high may compromise sphincter function and cause mouth incompetence
Mental crease	• 3–5 U/mentalis muscle band
Peau d'orange chin	• 5–10 U into mentalis muscle at the most distal point from the orbicularis oris muscle (i.e. the prominence of the chin; see Fig. 159.16)
Masseteric hypertrophy	• 20–35 U into each masseter muscle
Horizontal neck lines	• 10–20 U/treatment session (see Fig. 159.18) • 1–2 U into the deep *intradermal* plane at 2–3 cm intervals, followed by gentle massage
Platysmal bands	• 5 U into contracted platysma muscle; 3 sites at 1–1.5 cm intervals for a total of 15 U/band (see Fig. 159.19) • Single treatment typically involves 2 bands and a total dose of 30 U into the neck • Recommended only for patients who have obvious platysmal bands, good cervical skin elasticity and minimal submental fat accumulation

Table 159.4 Use of BoNT-A [onabotulinumtoxinA] in the lower face and neck: dosing and techniques.

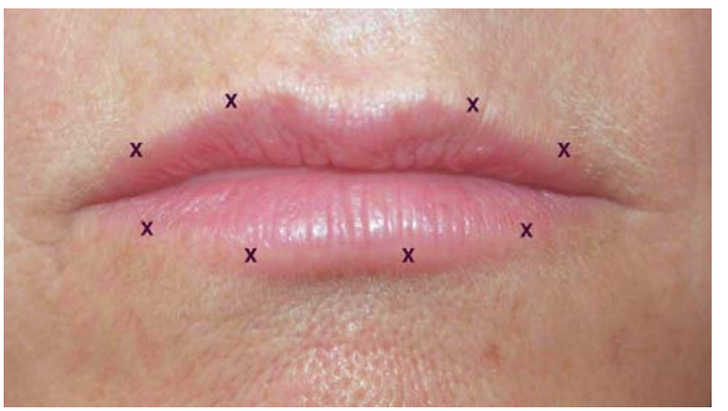


Fig. 159.11 Injection sites for perioral rhytides. The authors typically inject 1 U of BoNT-A [onabotulinumtoxinA] per lip line.

incisors and canines are fully revealed. The levator labii superioris alaeque nasi muscle retracts the upper lip; chemodenervation of the muscle with BoNT-A results in a moderate drop in the upper lip sufficient to cover the upper gum. Small concentrated doses are used (see Table 159.4), often injected with EMG guidance to accurately target the muscle. An undesired side effect of this treatment is the vertical elongation of the cutaneous upper lip. Because this effect is already an undesirable sign of aging, the procedure generally produces unsatisfactory results in patients who are middle-aged and older, and it is usually recommended only for younger patients. For most patients, the best results are obtained when this procedure is used in combination with soft tissue augmentation of the lip margins.

Facial Asymmetry: Functional Muscle Imbalance

Injections of BoNT-A can also be used to correct facial asymmetry resulting from facial nerve palsies[24], dystonias[13,25], surgery[26] or trauma[27]. In cases of hemiparesis, BoNT-A is used to decrease muscle activity on the unaffected side; for hyperkinesia, the affected muscles are treated. Physicians who are not thoroughly comfortable with facial surface anatomy are well advised to use an EMG guidance system for these injections.

Midfacial asymmetry may have bony tissue, soft tissue, innervational or muscular causes. BoNT-A treatment can be invaluable for patients with facial asymmetry caused by neuromuscular abnormalities. In hemifacial spasm, repeated clonic and tonic facial movements draw the facial midline over toward the hyperfunctional side. BoNT-A treatment of the hyperfunctional zygomaticus, risorius and masseter muscles allows the face to be centered at rest. Hypofunctional asymmetry, such as that seen in Bell's palsy due to unilateral seventh nerve dysfunction, can be relieved by small doses of BoNT-A injected into muscles on the normofunctional side. Only 1 to 2 U of BoNT-A [onabotulinumtoxinA] into the zygomaticus, risorius and orbicularis oris muscles and 5 to 10 U into the masseter muscle are needed to restore facial symmetry (Fig. 159.12).

For patients with asymmetric jaw movement, intraoral injection of 10 to 15 U of BoNT-A [onabotulinumtoxinA] into the internal pterygoid on the hyperfunctional side can relax the jaw and relieve discomfort. Unilateral surgical or traumatic injury of the orbicularis oris or the risorius muscle can cause the mouth to be pulled off-center by the unopposed actions of the partner muscles on the uninjured side. Chemodenervation of the risorius immediately lateral to the corner of the mouth on the uninjured side re-centers the mouth when the face is at rest. Similarly, facial asymmetry is evident in individuals with congenital or acquired unilateral weakness of the depressor anguli oris (DAO) muscle, who are unable to depress the corner of one side of the mouth. In these cases as well, BoNT-A treatment of the partner muscle restores aesthetic balance.

Fig. 159.12 Bell's palsy. Patient before **(A)** and after (**B**) treatment, with improvement in asymmetry**.** The authors typically inject 1–2 U of BoNT-A [onabotulinumtoxinA] into the zygomaticus, risorius and orbicularis oris muscles and 5–10 U into the masseter muscle.

Mouth Frown

The frowning expression created when the lateral corners of the mouth are permanently angled downward can create an impression of disapproval and unpleasantness. The DAO muscle pulls down the corner of the mouth in opposition to the zygomaticus major and minor muscles. BoNT-A can be used to weaken the DAO and reset muscular balance (Fig. 159.13), allowing the zygomaticus to elevate the corners of the mouth and return them to a horizontal position (Fig. 159.14; see Table 159.4) The effects of this procedure may be potentiated with repeated treatment.

Fig. 159.13 Injection sites for mouth frown. The authors typically inject 2 to 3 U of BoNT-A [onabotulinumtoxinA] into the posterior aspect of the depressor anguli oris muscle and 3 U into each insertion of the mentalis muscle.

Fig. 159.14 Mouth frown. The subject before (**A**) and after BoNT-A treatment (**B**) of the depressor anguli oris muscle.

It is always important to be cautious when injecting toxin close to the mouth. A misplaced injection could result in complications, including a flaccid cheek, incompetent mouth or asymmetric smile. This treatment is not recommended for singers or musicians, or for patients who use their perioral muscle with intensity. With this procedure, as for others in the perioral area, the most pleasing results may be obtained with BoNT-A injections in combination with laser resurfacing.

Melomental Folds (Marionette Lines)

Melomental folds ("drool grooves" or marionette lines) extending from the down-turned corner of the mouth to the lateral mentum involuntarily produce a sad expression and give the appearance of advancing age. Traditionally, soft tissue augmentation has been used; however, the effects are not long-lasting, because filling agents do not endure in this highly mobile and expressive region of the face. Because contraction of the DAO muscle exacerbates the melomental folds, BoNT-A treatment is a useful adjunct to soft tissue augmentation (see Table 159.4). Best results in this area are obtained with combined therapy as BoNT-A treatment prevents the repeated molding and contortion of the implant, enhancing and extending the duration of the soft tissue augmentation.

Mental Crease

The convexity between the lower lip and the prominence of the chin is called the mental crease. Contraction of the mentalis muscle can produce a deep groove in this region. This area is closely tethered to the bony mentum (chin), and soft tissue augmentation of the mental crease is often unsuccessful because the filling agent visibly beads. BoNT-A injections at the level of the crease may also give unsatisfactory results because the orbicularis oris is weakened, sometimes resulting in an incompetent mouth. However, injection of the mentalis muscle gives a satisfactory softening of the crease while avoiding complications from weakening of the orbicularis oris (see Table 159.4). Injections to the mentalis are especially valuable in individuals who have had previous trauma or surgery to this area (Fig. 159.15).

Peau d'Orange (Apple Dumpling) Chin

An "orange peel" appearance of the chin during aging results from the loss of dermal collagen and subcutaneous fat at the mentum. The appearance worsens when the mentalis and depressor labii inferioris muscles are used together with the orbicularis oris muscle during mastication or speech. *Peau d'orange* chin is frequently seen asymmetrically during and after recovery from unilateral facial paresis (Bell's palsy). Previous treatment options have included soft tissue augmentation to fill in the tissue gaps and ablative and non-ablative laser resurfacing. Depending upon the patient's aesthetic need for chin augmentation, BoNT-A and soft tissue augmentation can be used together, or BoNT-A can be used alone to improve the appearance of the chin (Fig. 159.16; see Table 159.4). Following treatment, the chin is massaged to facilitate diffusion of the toxin.

Masseteric Hypertrophy

A number of studies have observed a reduction of muscle thickness in Asian[28–30] and Caucasian[31] patients with masseteric hypertrophy who were treated with BoNT-A. Reductions in muscle bulk ranged from 19% to 50% and lasted from 3 to 6 months, depending upon the doses used. Effective sculpting of the jawline can be achieved (Fig. 159.17; see Table 159.4). When investigated in a Caucasian versus East Asian population, smaller doses were required for aesthetic improvement in the former versus the latter, and patients experienced a 6- to 7-month improvement in symptoms of bruxism[31], which had been reported previously[32].

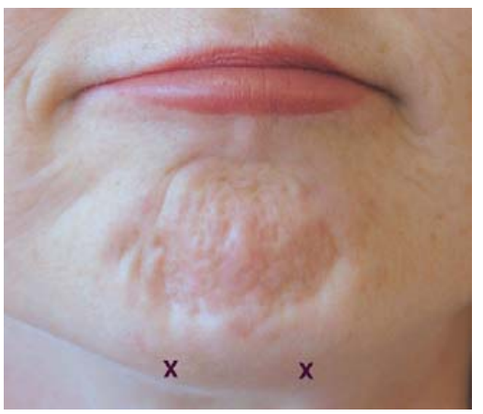


Fig. 159.16 Injection sites for *peau d'orange* chin. The authors inject 5 to 10 U of BoNT-A [onabotulinumtoxinA] into the mentalis muscle at these sites.

Fig. 159.15 Mental crease. Treatment of traumatically damaged mentalis muscle. **A,B** Subject puckers before treatment. **C,D** Two weeks after chemodenervation of the mentalis muscle with BoNT-A.

Fig. 159.17 Masseteric hypertrophy. Subject before (**A**) and after treatment (**B**). The authors inject 20 to 35 U BoNT-A [onabotulinumtoxinA] into each masseter muscle.

Fig. 159.18 Injection sites for horizontal necklace lines. Aliquots of 1 to 2 U of BoNT-A [onabotulinumtoxinA] are injected into the deep intradermal plane at 2 to 3 cm intervals.

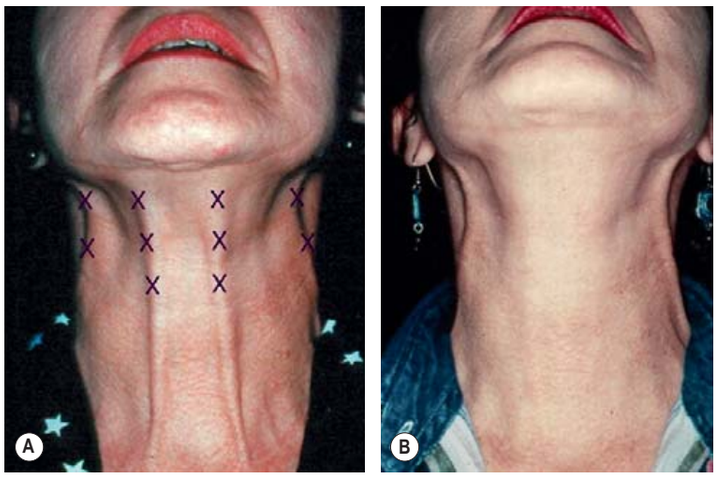


Fig. 159.19 Injection sites for platysmal bands. Before (**A**) and after treatment (**B**). Each band is injected in three sites at 1 to 1.5 cm intervals with 3–4 U of BoNT-A [onabotulinumtoxinA] per site. *Courtesy, M Carney, MD.*

Horizontal Neck Lines

Some individuals, especially those with chubbier necks, have two or three horizontal "necklace" lines of skin indentation caused by the superficial musculoaponeurotic system attachments in the neck. Our treatment approach for softening these lines is to inject small doses of BoNT-A at multiple sites along the horizontal lines (Fig. 159.18; see Table 159.4). The neck is gently massaged following the injections to avoid bruising. The physician is cautioned to use deep dermal rather than subcutaneous injections for two reasons: (1) venous perforators that are deeper in the neck, especially in the lateral neck, can bleed; and (2) the underlying muscles of deglutition are cholinergic and could potentially be affected.

Platysmal Bands

Platysmal bands are formed when the anterior fibers of the platysma separate into two discrete vertical bands. The bands often tighten and become more visible when the neck is animated, as when the patient speaks, exercises or plays a musical instrument. The emergence of platysmal bands during aging is often accompanied by other senescent changes, including loss of cervical skin elasticity and accumulation of submental fat. BoNT chemodenervation of the anterior part of the platysma muscle can soften the platysmal bands (Fig. 159.19) and produce a gentle anterior neck lift. However, in aging necks with jowl formation and bone resorption, BoNT-A treatment of the platysma may emphasize, rather than soften, the muscle cords. Thus chemodenervation of the platysma is recommended only for patients who have obvious platysmal bands, good cervical skin elasticity and minimal submental fat accumulation.

For many patients, BoNT-A may be most useful as an adjunct to traditional facelift surgery; residual muscular banding that becomes apparent in the postoperative period can be simply treated with BoNT-A rather than by a second invasive surgical procedure. BoNT-A treatment can also be used as a "rehearsal", so that individuals who are not ready to undergo traditional facelift surgery can experience immediate aesthetic enhancement without a significant period of convalescence. BoNT-A treatment might even slow the degenerative changes occurring in the neck and postpone the need for rhytidectomy.

Large doses of BoNT-A must be used cautiously in the neck. The platysma is external to the larynx and the muscles of deglutition and neck flexion. Doses from 75 to 100 U of BoNT-A can produce weakness in the neck flexors and dysphagia, and we have reported one patient treated with only 60 U in her neck who developed such profound dysphagia that she required a nasogastric tube until she could swallow again[33]. Therefore, we recommend that the physician proceed with caution and inject no more than 30–40 U of BoNT-A [onabotulinumtoxinA] spread over multiple sites per cervical treatment session (see Fig. 159.19A; see Table 159.4).

Adjunctive Use

BoNT-A is beneficial in many patients as an adjunct therapy to enhance or prolong the results of other cosmetic procedures. Prior to surgery, BoNT-A treatment to chemodenervate specific muscles can facilitate subsequent manipulation of tissues during the surgery and permit a greater surgical correction or a better concealment of the surgical incision. BoNT-A can also be used to reduce tension exerted on a wound or surgical incision by the underlying muscles, thereby promoting better healing with less scar formation.

Although BoNT-A can be used alone to create a mild brow lift, an endoscopic brow lift or facelift is often required when brow ptosis is moderate to severe and a greater elevation is desired. Preoperative relaxation of the brow depressors with BoNT-A can facilitate a greater brow elevation, and postoperative BoNT treatment can help prolong the benefits of surgery by relaxing the muscles that work to re-establish the depressed brow. With upper and lower lid blepharoplasty, BoNT-A pretreatment of the crow's feet area relaxes the orbicularis oculi muscle and permits a more accurate estimation of the amount of skin to be resected during surgery, as well as better placement of the incision so that it is concealed within the orbital margin. After lower eyelid ectropion and "roundeye" repair, dehiscence of the temporal incision can damage the results. Dehiscence can be prevented with BoNT-A treatment to temporarily weaken the lateral fibers of the orbicularis oculi, which pull on the medial side of the incision. BoNT-A injections can also be given in combination with all surgeries that correct hyperkinetic lines to delay or prevent the reappearance of rhytides, and BoNT-A treatment is often used adjunctively with traditional rhytidectomy surgery, as described above.

BoNT-A in conjunction with ablative resurfacing leads to optimal improvement of dynamic rhytides, with superior and longer-lasting outcomes[34]. Regular postoperative injections, given every 6 to 12 months, prolong the effects of resurfacing, and many clinicians now use BoNT-A injections as part of their standard laser resurfacing protocol. Of note, several studies have found that combined BoNT-A and laser resurfacing leads to longer-lasting improvement than either modality alone[35–37].

Likewise, combination treatment with BoNT-A and intense pulsed light (IPL) therapy may be a synergistic approach to the treatment of facial aging. In one study in which we compared the treatments alone and in combination, we found that patients treated with both therapies experienced a 15% greater global aesthetic improvement (reduction in crow's feet in addition to an improvement in skin tone and texture) compared to IPL alone[38]. Similarly, Khoury and colleagues found that a significantly higher proportion of patients had improvement in small rhytides and fine lines with IPL plus BoNT-A when compared to IPL alone (93% vs 29% at week 4), as well as an improvement in erythema[39].

BoNT-A is also frequently used in combination with soft tissue augmentation, where it prevents the distortion of the filler and prolongs the beneficial effects of tissue augmentation (see above). Preceding the injection of filling agents by approximately 1 week, BoNT-A may work on several levels, including reducing the dynamic component of rhytid formation in newly remodeled skin and allowing more permanent eradication of rhytides[34]. Studies have documented the synergistic effect of adjunctive BoNT-A and fillers, citing a greater aesthetic improvement of longer duration with combination therapy than with fillers alone[40–42].

Hyperhidrosis

BoNT-A has been used in the management of hyperhidrosis since early reports of its use to treat Frey's syndrome (see Ch. 39)[43]. Subsequently, a number of authors published reports demonstrating the therapeutic efficacy of BoNT-A in patients with hyperhidrosis, both palmoplantar and axillary[15,44–47].

Dramatically effective with minimal side effects, BoNT-A was approved for the treatment of axillary hyperhidrosis in Canada and the US in 2001 and 2004, respectively. Along with a decrease in perspiration lasting from 6 to 24 months[48], injections can improve quality of life and decrease body odor for up to 7 months[49,50]. In one long-term study, repeated injections over 16 months were safe and efficacious, with minimal side effects and 50% or greater reduction in sweating in 96% of patients after the first treatment[46]. Similarly, BoNT-A was well tolerated and highly effective in 322 patients with primary axillary hyperhidrosis treated over 52 weeks[51].

Typically, 50–150 U of BoNT-A per axilla are divided among 10–20 injection sites (defined by Minor's starch-iodine test, see Fig. 39.6). Because BoNT-A diffuses approximately 1 cm from its injection point, injection sites are located 1.5–2 cm apart and approximately 1 cm from the edge of the affected area. BoNT-A is injected intradermally or immediately subdermally. Injections are usually repeated at 6- to 12-month intervals, although, in the experience of the authors, most subjects are far below their preinjection degree of hyperhidrosis when they present for reinjection. Alternatively, large doses of topically applied BoNT-A (200 U), combined with a transport peptide molecule, has been shown to be safe and may prove to be an effective method for treating axillary hyperhidrosis, although further research is warranted[52].

The value of BoNT-A in the management of palmoplantar hyperhidrosis, while marked, is not as clear as in axillary hyperhidrosis. This relates to both the need for anesthesia to inject the palmar or plantar surface in the majority of individuals as well as the large surface area affected and therefore the high dose of BoNT-A required. Local anesthesia for the hand and foot is usually accomplished by using median and ulnar nerve blocks at the wrist or posterior tibial, sural, superficial peroneal, deep peroneal and saphenous nerve blocks at the ankle, respectively (see Ch. 143). Typical doses of BoNT-A for the palm or sole of the foot are 100–150 U distributed among 50–100 injection sites, including the distal wrist crease and the thenar and hypothenar eminences for the hand injection (Fig. 159.20). In a study involving 69 patients with palmar hyperhidrosis treated over a period of 44 months (using 80 to 100 U BoNT-A in each palm after regional nerve block), 27 had to be treated twice and 11 required a third treatment session[53]. At 1 month after treatment, 54% of patients reported an excellent improvement. Side effects included transitory hand weakness, wrist pain, and cramps.

Migraine

Early investigations into the use of BoNT-A for the treatment of migraine showed a decrease in the incidence and severity of headaches, as well as a decrease in the use of pain medications, for up to 4 months after a single or multiple injection sessions[16,54]. Migraine treatment typically requires 100 U of BoNT-A distributed between the brow, temples and occipital areas, with injections into any additional trigger sites.

More recently, it has become apparent that the response to treatment depends on several factors, including headache characteristics, disease duration, and the use or overuse of medications[55]. For example, trials involving patients with episodic migraine show little to no improvement after BoNT-A injections[56]. On the other hand, chronic migraine

Fig. 159.20 Injection sites for palmar hyperhidrosis. The authors inject 100 to 150 U BoNT-A [onabotulinumtoxinA] per hand (depending on size) in approximately 100 injection sites.

results are mixed: while some data suggest superiority over placebo in patients with or without medication overuse[57], others have found no statistically significant benefit as a prophylactic treatment[58,59]. Lastly, imploding or ocular migraine appears to have a greater likelihood of responding to prophylactic BoNT-A than does exploding migraine[60,61].

While some authors believe that BoNT-A treatment is probably ineffective for any migraine or chronic tension headache, regardless of type of headache or injection regimen[62], many researchers continue to consider it a promising therapeutic option for headache disorders[62]. In 2011, onabotulinumtoxinA received FDA approval for chronic migraine.

POSTPROCEDURAL CARE

Manual pressure can be applied to the injection site immediately after withdrawal of the needle to help prevent bruising. Depending upon the site of injection, the physician may massage the area after the injection to spread the toxin, but only if it is possible to do so without spreading the toxin to non-targeted muscles. To minimize undesired toxin diffusion, patients should be directed to remain upright for at least 2–4 hours after the procedure and to refrain from rubbing or manipulating the area for 24 hours. Because there is evidence suggesting that BoNT-A binds preferentially at actively stimulated muscles, patients are also asked to contract and relax the treated muscles as much as possible for 2–3 hours following the injections. Patients should be told to expect some transient redness, swelling or bruising at the injection sites, and advised that the effects of treatment will probably begin to diminish in 3–4 months.

COMPLICATIONS

BoNT-A occasionally affects non-targeted muscles or glandular tissue in the areas surrounding the injection, which can result in effects such as eyelid ptosis (Fig. 159.21), lower eyelid laxity, epiphora (excessive tearing), diplopia, brow ptosis, decreased strength of eye closure, dry eye, mouth incompetence, difficulties in speech, and the inability to whistle. Use of careful injection technique to target the toxin to the appropriate muscles and the use of concentrated low doses to limit its diffusion to non-targeted muscles or glands are recommended to try to prevent the occurrence of these adverse effects[63]. In general, a higher concentration allows for more accurate placement, greater duration of effect, and fewer side effects, since lower concentrations may encourage the spread of toxin. Of note, there is an area of denervation associated with each point of injection of about 1–1.5 cm (diameter, 2–3 cm) that is due to toxin spread.

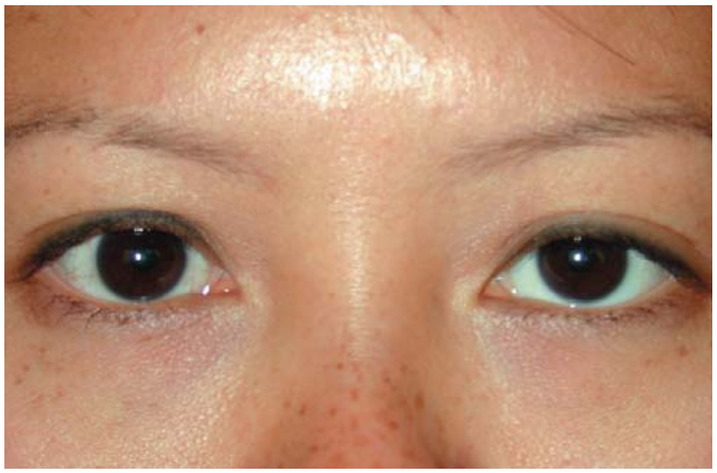


Fig. 159.21 Blepharoptosis. Diffusion of toxin to the levator of the upper eyelid resulted in eyelid ptosis (subject's left eye).

Fig. 159.22 "Cockeyed" brow. A quizzical appearance can occur when the lateral fibers of the frontalis muscle are not injected appropriately, and the untreated lateral fibers of the frontalis muscle pull upward on the brow.

A quizzical or "cockeyed" appearance can occur in the brow when the lateral fibers of the frontalis muscle have not been injected adequately and these untreated lateral fibers pull upward on the brow (Fig. 159.22). Brow ptosis may last upwards of 3 months, while upper eyelid ptosis can persist from 2 to 12 weeks. Bruising, diplopia, ectropion, a drooping lateral lower eyelid, and an asymmetric smile (caused by the spread of toxin to the zygomaticus major) are all reported complications of BoNT-A injections in the periorbital area. Transient local bruising, ptosis, dry eyes, diplopia and facial droop can occur with injections into the cheek.

Complications of the lower face involve effects on muscle function and facial expression, usually due to use of BoNT-A in large doses. Injections placed too close to the mouth, injection into the mental fold, and interaction with the orbicularis oris muscle can all result in a flaccid cheek, incompetent mouth or asymmetric smile. Large doses (>100 U) of BoNT-A [onabotulinumtoxinA] in the platysma have resulted in reports of dysphagia and weakness of the neck flexors.

Although one of the greatest concerns associated with the use of BoNT-A is the formation of neutralizing antibodies leading to non-response of subsequent injections, the overall risk is actually low (<1%) when BoNT-A is used at recommended doses for cosmetic applications. Of note, the protein content in current lots of BoNT-A is significantly lower than in previous batches and has been shown to be less antigenic than the original product. Although antibody formation has occurred with current lots of BoNT-A[64], it is usually associated with large doses and therapeutic, rather than cosmetic, use[65]. Injecting the lowest effective doses, with the longest feasible intervals between injections, minimizes the potential for immunogenicity.

Allergic reactions to BoNT-A are rare but have been described in the literature. Additional reactions include serious or non-serious cutaneous eruptions[66] as well as granulomas[67]. After large doses for therapeutic purposes, anaphylactic reactions[68,69] and severe respiratory failure have occurred.

Safety

No long-term adverse effects have been reported, and no systemic safety problems have been associated with FDA-approved uses of BoNT-A. A review of the long-term safety of BoNT-A for cosmetic purposes revealed no serious adverse events (AEs) in over 850 treatment sessions for up to 9 years[70]. An interim analysis of 768 patients enrolled in phase 3 clinical trials, who received up to six treatments of abobotulinumtoxinA, found that multiple treatments over 17 months were well tolerated[71].

However, the risk of serious complications increases with higher doses: in an analysis of 1031 AE reports submitted to the FDA, 407 occurred with higher therapeutic doses, including 28 deaths and other serious cardiovascular complications[66]. The FDA could not determine a causal relationship between the fatalities and BoNT-A injections, especially since 26 patients who died had underlying cardiovascular diseases with an elevated mortality risk. Notably, no deaths or cardiovascular complications were associated with cosmetic doses. Similarly, another investigation of 658 FDA-submitted AEs, which included 180 cases of aspiration, dysphagia and/or pneumonia and 16 deaths, involved only therapeutic doses in already compromised individuals[72]. As a result, the FDA requested safety label changes with black box warnings and a *r*isk *e*valuation and *m*itigation *s*trategy (REMS; a consumer guide outlining the risks associated with treatment) for all BoNT products[73].

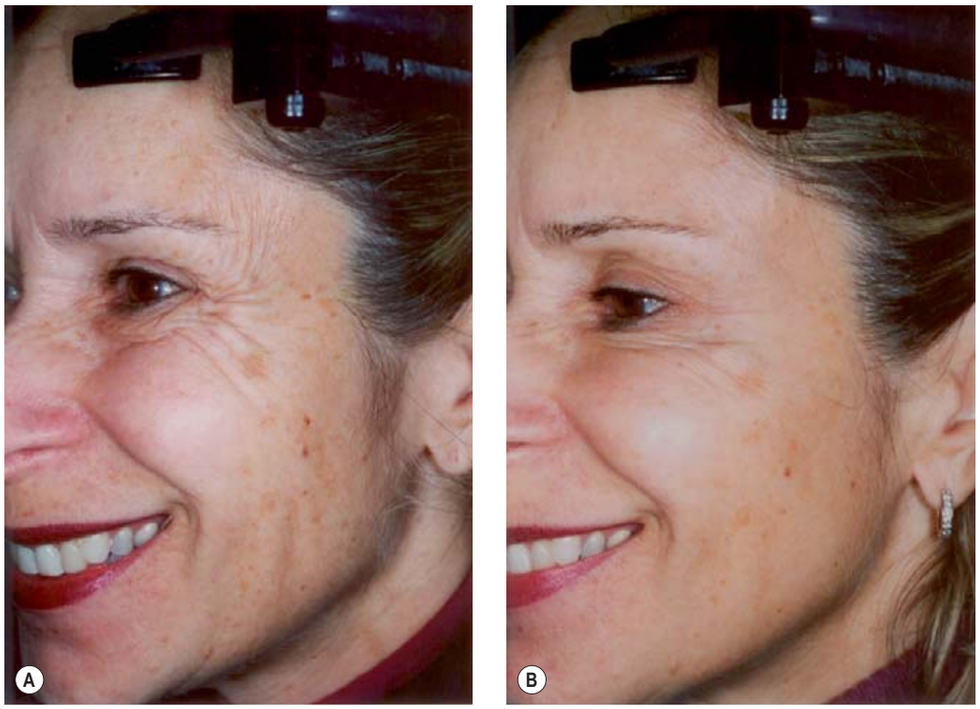
FUTURE TRENDS

BoNT-A has become the treatment of choice for smoothing hyperkinetic lines in the face and neck, creating a more pleasant and youthful appearance. Alone or in combination with surgery, soft tissue augmentation, or ablative and non-ablative laser resurfacing, BoNT-A treatment is both an art and a science, with its use in facial sculpting and enhancing, along with dermatologic correction. Moreover, the number of dermatologic indications for BoNT-A is likely to continue to grow. Easy to use, minimally invasive, very well tolerated by patients and extremely safe, injections of BoNT-A can be used alone or in combination with other cosmetic procedures and are an integral part of most cosmetic practices.

REFERENCES

1. Jankovic J, Hallett M (eds). Therapy with Botulinum Toxin. New York: Marcel Dekker, 1994.
2. Carruthers A, Carruthers J. Botulinum toxin products overview. Skin Therapy Lett. 2008;13:1–4.
3. Trindade de Almeida AR, Marques E, de Almeida J, et al. Pilot study comparing the diffusion of two formulations of botulinum toxin type A in patients with forehead hyperhidrosis. Dermatol Surg. 2007;33(1 Spec No.): S37–43.
4. Cliff SH, Judodihardjo H, Eltringham E. Different formulations of botulinum toxin type A have different migration characteristics: a double-blind, randomized study. J Cosmet Dermatol. 2008;7: 50–4.
5. Ranoux D, Gury C, Fondarai J, et al. Respective potencies of Botox and Dysport: a double blind, randomised, crossover study in cervical dystonia. J Neurol Neurosurg Psychiatry. 2002;72:459–62.
6. Simonetta Moreau M, Cauhepe C, Magues JP, Senard JM. A double-blind, randomized, comparative study of Dysport vs. Botox in primary palmar hyperhidrosis. Br J Dermatol. 2003;149:1041–5.
7. Ramirez AL, Reeck J, Maas CS. Botulinum toxin type B (Myobloc) in the management of hyperkinetic facial lines. Otolaryngol Head Neck Surg. 2002;126: 459–67.
8. Alster TS, Lupton JR. Botulinum toxin type B for dynamic glabellar rhytides refractory to botulinum toxin type A. Dermatol Surg. 2003;29:516–18.
9. Sadick NS. Prospective open-label study of botulinum toxin type B (Myobloc) at doses of 2,400 and 3,000 U for the treatment of glabellar wrinkles. Dermatol Surg. 2003;29:501–7.

10. Matarasso SL. Comparison of botulinum toxin types A and B: a bilateral and double-blind randomized evaluation in the treatment of canthal rhytides. Dermatol Surg. 2003;29:7–13.
11. Carruthers A, Carruthers J, Flynn TC, Leong MS. Dose-finding, safety, and tolerability study of botulinum toxin type B for the treatment of hyperfunctional glabellar lines. Dermatol Surg. 2007;33(1 Spec No.): S60–8.
12. Scott AB. Botulinum toxin injection into extraocular muscles as an alternative to strabismus surgery. Ophthalmology. 1980;87:1044–9.
13. Carruthers J, Stubbs HA. Botulinum toxin for benign essential blepharospasm, hemifacial spasm and age-related lower eyelid ectropion. Can J Neurol Sci. 1987;14:42–5.
14. Jankovic J, Schwartz K. Botulinum toxin injections for cervical dystonia. Neurology. 1990;40:277–80.
15. Glogau R. Botulinum A neurotoxin for axillary hyperhidrosis. No sweat Botox. Dermatol Surg. 1998;24:817–19.
16. Silberstein S, Mathew N, Saper J, et al. Botulinum toxin type A as a migraine preventive treatment. Headache. 2000;40:445–50.
17. Smith KC, Comite SL, Balasubramanian S, et al. Vibration anesthesia: a noninvasive method of reducing discomfort prior to dermatologic procedures. Dermatol Online J. 2004;10:1.
18. Ahn MS, Catten M, Maas CS. Temporal brow lift using botulinum toxin A. Plast Reconstruct Surg. 2000; 105:1129–35.
19. Huang W, Rogachefsky AS, Foster JA. Brow lift with botulinum toxin. Dermatol Surg. 2000;26:55–60.
20. Huilgol SC, Carruthers A, Carruthers JDA. Raising eyebrows with botulinum toxin. Dermatol Surg. 2000;25:373–6.
21. Carruthers A, Carruthers J. Eyebrow height after botulinum toxin type A to the glabella. Dermatol Surg. 2007;33(1 Spec No.):S26–31.
22. Carruthers J, Carruthers A. BOTOX use in the mid and lower face and neck. Semin Cutan Med Surg. 2001; 20:85–92.
23. Flynn TC, Carruthers JA, Carruthers JA. Botulinum-A toxin treatment of the lower eyelid improves infraorbital rhytides and widens the eye. Dermatol Surg. 2001;27: 703–8.
24. Armstrong MWJ, Mountain RE, Murray JAM. Treatment of facial synkinesis and facial asymmetry with botulinum toxin type A following facial nerve palsy. Clin Otolaryngol Allied Sci. 1996;21:15–20.
25. Blitzer A, Brin MF, Keen MS, Aviv JE. Botulinum toxin for the treatment of hyperfunctional lines of the face. Arch Otolaryngol Head Neck Surg. 1993;119:1018–22.
26. Borodic GE. Botulinum A toxin for (expressionistic) ptosis overcorrection after frontalis sling. Ophthal Plast Reconstr Surg. 1992;8:137–42.
27. Carruthers A, Carruthers J. Clinical indications and injection technique for the cosmetic use of botulinum A exotoxin. Dermatol Surg. 1998;24:1189–94.
28. To EW, Ahuja AT, Ho WS, et al. A prospective study of the effect of botulinum toxin A on masseteric muscle hypertrophy with ultrasonographic and electromyographic measurement. Br J Plast Surg. 2001;54:197–200.
29. von Lindern JJ, Niederhagen B, Appel T, et al. Type A botulinum toxin for the treatment of hypertrophy of the masseter and temporal muscle: an alternative treatment. Plast Reconstr Surg. 2001;107:327–32.
30. Park MY, Ahn KY, Jung DS. Application of botulinum toxin A for treatment of facial contouring in the lower face. Dermatol Surg. 2003;29:477–83.
31. Liew S, Dart A. Nonsurgical reshaping of the lower face. Aesthet Surg J. 2008;28:251–7.
32. Chikhani L, Dichamp J. Bruxisme, syndrome algodysfonctionnel des articulations temporo-mandibulaires et toxine botulique. Ann Readapt Med Phys. 2003;46:333–7.
33. Carruthers J, Carruthers A. Practical cosmetic Botox techniques. J Cutan Med Surg. 1999;3(suppl. 4):S49–52.
34. Fagien S. Botox for the treatment of dynamic and hyperkinetic facial lines and furrows: adjunctive use in facial aesthetic surgery. Plast Reconstr Surg. 2003;112; 40S–52S.
35. West TB, Alster TS. Effect of botulinum toxin type A on movement-associated rhytides following CO_2 laser resurfacing. Dermatol Surg. 1999;25:259–61.
36. Zimbler MS, Holds JB, Kokoska MS, et al. Effect of botulinum toxin pretreatment on laser resurfacing results: a prospective, randomized, blinded trial. Arch Facial Plast Surg. 2001;3:165–9.
37. Yamauchi PS, Lask G, Lowe NJ. Botulinum toxin type A gives adjunctive benefit to periorbital laser resurfacing. J Cosmet Laser Ther. 2004;6:145–8.
38. Carruthers J, Carruthers A. The effect of full-face broadband light treatments alone and in combination with bilateral crow's feet botulinum toxin type A chemodenervation. Dermatol Surg. 2004;30:355–66.
39. Khoury JG, Saluja R, Goldman MP. The effect of botulinum toxin type A on full-face intense pulsed light treatment: a randomized, double-blind, split-face study. Dermatol Surg. 2008;34:1062–9.
40. Carruthers J, Carruthers A, Maberley D. Deep resting glabellar rhytides respond to BTX-A and Hylan B. Dermatol Surg. 2003;29:539–44.
41. Carruthers J, Carruthers A. A prospective, randomized, parallel group study analyzing the effect of BTX-A (Botox) and nonanimal sourced hyaluronic acid (NASHA, Restylane) in combination compared with NASHA (Restylane) alone in severe glabellar rhytides in adult female subjects: treatment of severe glabellar rhytides with a hyaluronic acid derivative compared with the derivative BTX-A. Dermatol Surg. 2003;29:802–9.
42. Patel MP, Talmor M, Nolan WB. Botox and collagen for glabellar furrows: advantages of combination therapy. Ann Plast Surg. 2004;52:442–7.
43. Bushara KO, Jones, JW, Park DM, Schutta HS. Botulinum toxin and sweating [abstr]. Mov Disord. 1995;10:391.
44. Lowe NJ, Yamauchi PS, Lask GP, et al. Efficacy and safety of botulinum toxin type A in the treatment of palmar hyperhidrosis: a double-blind, randomized, placebo-controlled study. Dermatol Surg. 2002;28:822–7.
45. Lowe PL, Cerdan-Sanz S, Lowe NJ. Botulinum toxin type A in the treatment of bilateral primary axillary hyperhidrosis: efficacy and duration with repeated treatments. Dermatol Surg. 2003;29:545–8.
46. Naumann M, Lowe NJ, Kumar CR, Hamm H. Botulinum toxin type A is a safe and effective treatment for axillary hyperhidrosis over 16 months: a prospective study. Arch Dermatol. 2003;139:731–6.
47. Vlahovic TC, Dunn SP, Blau JC, Gauthier C. Injectable botulinum toxin as a treatment for plantar hyperhidrosis: a case study. J Am Podiatr Med Assoc. 2008;98:156–9.
48. Moffat CE, Hayes WG, Nyamekye IK. Durability of botulinum toxin treatment for axillary hyperhidrosis. Eur J Vasc Endovasc Surg. 2009;38:188–91.
49. Campanati A, Penna L, Guzzo T, et al. Quality-of-life assessment in patients with hyperhidrosis before and after treatment with botulinum toxin: results of an open-label study. Clin Ther. 2003;25:298–308.
50. Heckmann M, Teichmann B, Pause BM, Plewig G. Amelioration of body odor after intracutaneous axillary injection of botulinum toxin A. Arch Dermatol. 2003; 139:57–9.
51. Lowe NJ, Glaser DA, Eadie N, et al. Botulinum toxin type A in the treatment of primary axillary hyperhidrosis: a 52-week multicenter double-blind, randomized, placebo-controlled study of efficacy and safety. J Am Acad Dermatol. 2007;56:604–11.
52. Glogau RG. Topically applied botulinum toxin type A for the treatment of primary axillary hyperhidrosis: results of a randomized, blinded, vehicle-controlled study. Dermatol Surg. 2007;33(1 Spec No.):S76–80.
53. Pérez-Bernal AM, Avalos-Peralta P, Moreno-Ramírez D, Camacho F. Treatment of palmar hyperhidrosis with botulinum toxin type A: 44 months of experience. Cosmet Dermatol. 2005;4:163–6.
54. Binder WJ, Brin MF, Blitzer A, et al. Botulinum toxin type A (BOTOX) for treatment of migraine headaches: an open-label study. Otolaryngol Head Neck Surg. 2000; 123:669–76.
55. Ashkenazi A, Silberstein S. Is botulinum toxin useful in treating headache? Yes. Curr Treat Options Neurol. 2009;11:18–23.
56. Shuhendler AJ, Lee S, Siu M, et al. Efficacy of botulinum toxin type A for the prophylaxis of episodic migraine headaches: a meta-analysis of randomized, double-blind, placebo-controlled trials. Pharmacotherapy. 2009;29:784–91.
57. Freitag FG, Diamond S, Diamond M, Urban G. Botulinum toxin type A in the treatment of chronic migraine without medication overuse. Headache. 2008;48: 201–9.
58. Cady R, Schreiber C. Botulinum toxin type A as migraine preventive treatment in patients previously failing oral prophylactic treatment due to compliance issues. Headache. 2008;48:900–13.
59. Petri S, Tölle T, Straube A, et al. Botulinum toxin as preventive treatment for migraine: a randomized double-blind study. Eur Neurol. 2009;62:204–11.
60. Jakubowski M, McAllister PJ, Bajwa ZH, et al. Exploding vs. imploding headache in migraine prophylaxis with botulinum toxin A. Pain. 2006;125:286–95.
61. Burstein R, Dodick D, Silberstein S. Migraine prophylaxis with botulinum toxin A is associated with perception of headache. Toxicon. 2009;54:624–7.
62. Obermann M, Diener HC. Is botulinum toxin useful in treating headache? No. Curr Treat Options Neurol. 2009;11:24–31.
63. Klein AW. Complications, adverse reactions, and insights with the use of botulinum toxin. Dermatol Surg. 2003;29:549–56.
64. Lee SK. Antibody-induced failure of botulinum toxin type A therapy in a patient with masseteric hypertrophy. Dermatol Surg. 2007;33(1 Spec No.):S105–10.
65. Mejia NI, Vuong KD, Jankovic J. Long-term botulinum toxin efficacy, safety, and immunogenicity. Mov Disord. 2005;20:592–7.
66. Coté TR, Mohan AK, Polder JA, et al. Botulinum toxin type A injections: adverse events reported to the US Food and Drug Administration in therapeutic and cosmetic cases. J Am Acad Dermatol. 2005;53:407–15.
67. Ahbib S, Lachapelle JM, Marot L. Granulomes sarcoïdosiques après injections de toxine botulique A (Botox®) pour correction de rides. Ann Dermatol Venereol. 2006;133:43–5.
68. LeWitt PA, Trosch RM. Idiosyncratic adverse reactions to intramuscular botulinum toxin type A injection. Mov Disord. 1997;12:1064–7.
69. Li M, Goldberger BA, Hopkins C. Fatal case of BOTOX-related anaphylaxis? J Forensic Sci. 2005;50:169–72.
70. Carruthers J, Carruthers A. Complications of botulinum toxin type A. Facial Plast Surg Clin North Am. 2007;15: 51–4.
71. Monheit GD, Cohen JL. J Long-term safety of repeated administrations of a new formulation of botulinum toxin type A in the treatment of glabellar lines: interim analysis from an open-label extension study. J Am Acad Dermatol. 2009;61:421–5.
72. U.S. Food and Drug Administration. Early communication about an ongoing safety review Botox and Botox Cosmetic (botulinum toxin type A) and Myobloc (botulinum toxin type B). Plast Surg Nurs. 2008;28:150–1.
73. Kuehn BM. FDA requires black box warnings on labeling for botulinum toxin products. JAMA. 2009;301:2316.



Intense pulsed light plus BoNT-A injections. Subject before **(A)** and after combined therapy **(B).**

Injection sites for migraine. The authors usually inject 100 U BoNT-A [onabotulinumtoxinA] distributed between the brow, temples, and occipital areas.

Index

Page numbers followed by "f" indicate figures, "t" indicate tables, and "b" indicate boxes.
Entries under "skin," and "cutaneous" have been kept to a minimum; readers are advised to seek more specific index entries.

A-β fibers 100t
A-δ fibers 100t
A-to-T flap *see* single tangent advancement flaps
Aagenaes syndrome 1722–1723
abacavir
  adverse reactions 1299t
    erythroderma 176t
abacept, lupus erythematosus 628t
abatacept 2149t
ABCC6 transporter 1593t
ABCD syndrome 1034t
abciximab 2149t
abietic acid dermatitis 1509t
abrasive cleansers 2480t
abrasive soap 2480t
Abrikossoff's tumor *see* granular cell tumor
abscesses 1190
  and drug abuse 1515t, 1516
  Munro's microabscesses 221
  Pautrier's microabscesses 1474, 1799, 2007–2009
  periapical 1153
  suture 2357f
  sweat gland 599
Absidia 1280
absorption
  drug interactions affecting 2184–2186, 2185f, 2185t
  transdermal 2068
absorptive dressings 2368–2369
ABT874 2147t
abuse 1521–1527
  child abuse 1521–1525
  elder abuse 1525–1527
acai berry 2207t
acanthamebiasis, HIV-related 1293
Acanthamoeba castellani 1293
acantholysis 19, 465
  Darier disease 892f
  Hailey-Hailey disease 893–895
  suprabasilar 469, 469f
acantholytic dermatosis, relapsing linear 954
acantholytic dyskeratotic epidermal nevus 954, 955f
acantholytic ectodermal dysplasias 510t, 808t, 832t–833t
acanthoma
  acantholytic (dyskeratotic) 1807
  clear cell 1805–1806
  epidermolytic 1808
  fissuratum 1503–1504, 1504f
  large cell 1808–1809, 1809f
  pilar sheath 1818–1819
acanthosis nigricans 763, 1812
  and Crouzon syndrome 818t–819t
  endocrine 768t
  and lipodystrophy 1667f, 1669f
  obese patients 751t, 766f–767f
  paraneoplastic 764t–765t
  patient evaluation 767f
Acaridae 1445t
Acarus siro 1445t
accessory tragi 1006, 1006f, 1829
Accuzyme 2373
ACE inhibitors, adverse reactions
  lymphocytic infiltrate of Jessner 2037
  secondary cutaneous vasculitis 390t
  urticaria 294
acetaminophen 2191t
  adverse reactions, pruritus 120t
acetazolamide, hypertrichosis 1118t
acetic acid 252
acetylcholine, and eccrine sweating 590t
acetylsalicylic acid *see* aspirin
Acharia stimulea 1441t
Achillea millefollium see yarrow
achromatic retinal patches 935t
acid glycosaminoglycans 687
  staining 687t
acid maltase deficiency, eccrine gland changes 598t
acidic sphingomyelinase 810t–811t
acids 263
  irritant 252
  mechanisms of toxicity 250t
Acinetobacter spp. 1187t
  chronic granulomatous disease 910t
acitretin 2089, 2091–2092
  adverse reactions, erythroderma 176t
  formulations 2097t
  indications
    Darier disease 893, 2096
    ichthyosis 851, 2096
    IgA pemphigus 473
    lichen planus 195
    lupus erythematosus 2097–2098
    pityriasis rubra pilaris 165, 2097
    premalignant/malignant skin lesions 2097
    psoriasis 152t, 1137t, 2094
  pharmacologic features 2092t
  structure 2090f
  teratogenicity 2091–2092
Ackerman, A Bernard 16–17
Ackerman tumor *see* verrucous carcinoma
acne
  drug-induced 549, 550f, 550t
  glucocorticoid-induced 2086f
  infantile 550–551, 551f
  keloids 3t–4t
  neonatal 550
  occupational 269–270, 550
    clinical features 270, 270f
    epidemiology 269
    history 269
    pathogenesis 269
    pathology 270
    treatment 270
  radiation 552–553
  treatment
    photodynamic therapy 558, 2246, 2247f
    retinoids 555t–556t, 2093, 2095–2096, 2096f
  tropical 552
acne comedones, cryosurgery 2286
acne conglobata 549
acne cosmetica 270, 550
acné excoriée 132, 132f, 1050t
  des jeunes filles 549
acne fulminans 548–549, 549f
acne inversa *see* hidradenitis suppurativa
acne keloidalis 581–583, 1580
  clinical features 581–582, 581f–582f
    alopecia 1096t, 1107–1108
  differential diagnosis 582
  epidemiology 581
  history 581
  pathogenesis 581
  pathology 582, 582f
  treatment 582–583, 582t
acne keloidalis nuchae *see* acne keloidalis
acne mechanica 270, 549, 1509t
acne rosacea, sebaceous gland in 543t
acne soap 2480t
acne vermoulante 1638
acne vulgaris 545–559
  and anetoderma 1633t, 1634
  clinical features 547–553, 547f–548f
    postinflammatory hyperpigmentation 1050t
  differential diagnosis 554–555, 554t
  distribution 9
  epidemiology 545
  history 545, 555t
  pathogenesis 545, 546f
    comedo formation 545
    diet 547
    genetic factors 545
    hormonal influences 546–547
    inflammatory responses 545–546
    Propionibacterium acnes 546
    sebum production 545
  pathology 553, 553f
  post-adolescent 548
  sebaceous gland in 543t
  solid facial edema 549, 549f
  treatment 555–558, 555t–556t
    oral 556–558, 557t, 558f
    retinoids 555t–556t, 2093, 2095–2096, 2096f
    surgical 558
    topical 555–556, 2105–2107
acneiform eruptions 551–553
  Apert syndrome 551
  drug-induced 354
  epidermal growth factor receptor inhibitor-induced eruption 551–552, 552f
  idiopathic facial aseptic granuloma 553
  irritant/toxic causes 251t
  radiation acne 552–553
  transverse nasal crease 553, 553f
  tropical acne 552
acneiform nevus 954
acoustic neuroma *see* schwannoma
acquired perforating dermatosis
  clinical features 1601–1602, 1602f
  pathology 1603f
acquired progressive kinking of hair 1111–1112
acral dry gangrene, endocrine 768t
acral erythema *see* palmar-plantar erythrodysesthesia
acral fibrokeratoma 1964–1965, 1965f
acral fibromyxoma, superficial 1965, 1965f
acral ischemia, and leukemia 2042t
acral lentiginous melanoma 1893–1894, 1895f
acral nevus 1864
  clinical features 1862t, 1864, 1864t, 1869f
  pathology 1864
acral peeling skin syndrome 852t–854t
acral pseudolymphomatous angiokeratoma of children 2040
Acremonium spp.
  mycetoma 1271t
  onychomycosis 1265t
acrivastine 304t
acroangiodermatitis 1724–1725
acrobullous dermatosis, PUVA-induced 521
acrocephalosyndactyly *see* Apert syndrome
acrochordon *see* skin tags
acrocyanosis 1495t
acrodermatitis chronica atrophicans 1215, 1216f
  and anetoderma 1633t
acrodermatitis continua of Hallopeau 142, 143f, 1136–1137, 1137f, 1137t
acrodermatitis enteropathica
  differential diagnosis 212t
  genetics 810t–811t
  neonates 526t–528t
acrogeria 838t, 863–864
  clinical features 864, 864f
  differential diagnosis 864
  epidemiology 864
  genetics 832t–833t
  history 864
  pathogenesis 864
  pathology 864
  treatment 864
acrokeratoelastoidosis 883, 883f
acrokeratosis paraneoplastica *see* Bazex syndrome
acrokeratosis verruciformis 1804
  clinical features 1804
  differential diagnosis 892, 892f, 1804
  pathology 1804
  treatment 1804
acromegaly
  and cutis verticis gyrata 1626t
  fissured tongue 1150
  with hypertrichosis 1116t
acromelanosis albo-punctata 1072t–1073t
acropustulosis of infancy 531–533, 531f
  differential diagnosis 147t, 524t–525t
acrospiroma *see* poroma
acrylates 242t
acrylic acid 252, 253t–254t
ACTH-induced hyperpigmentation 1056t–1057t
Acticoat 2368, 2368f, 2368t
Actimmune 2132t
actin filaments 452, 921
actinic cheilitis 1162, 1779
  treatment
    cryosurgery 2286
    photodynamic therapy 2244
actinic elastosis, differential diagnosis 1614t
actinic folliculitis 573t
actinic granuloma *see* annular elastolytic giant cell granuloma
actinic keratosis 1773, 1777–1784
  atrophic 1779
  clinical features 1777–1779, 1778f
  hyperkeratotic 1778

lichenoid 1779
oral 1779
pathology 1783, 1783f
pigmented 1778
treatment
imiquimod 2135
photodynamic therapy 2244, 2245f
see also non-melanoma skin cancer
actinic lichen nitidus 201
actinic lichen planus 189, 1053t
actinic prurigo 1470–1471
action spectrum 2203t
clinical features 1470–1471, 1471f
differential diagnosis 1471
epidemiology 1470
history 1470
pathogenesis 1470
pathology 1471
treatment 1471
actinic (solar) purpura 358f
Actinida chinensis see kiwi
Actinobacillus spp. 1450t
Actinomadura madurae 1270–1271, 1271t
Actinomadura pelletieri 1271t
Actinomyces israelii 1217–1218, 1271t
actinomycin, adverse reactions 349t
actinomycosis 1217–1218
clinical features 1217, 1217f
diagnosis 1217–1218
epidemiology and pathogenesis 1217
pathology 1217
treatment 1218
Actisorb Silver 2368, 2368t
activated charcoal, renal pruritus 118t
activated partial thromboplastin time 361, 2459
activated protein C resistance 818t–819t
acupuncture 2214
reflex sympathetic dystrophy 122t
acute cutaneous lupus erythematosus 618f
clinical features 621f
butterfly rash 621f
dyspigmentation 620–621
toxic epidermal necrolysis-like eruption 621f
differential diagnosis 625–626, 626t
histopathology 624t
inflammatory infiltrates 618f
acute delayed irritant contact dermatitis 251
acute febrile neutrophilic dermatosis *see* Sweet's syndrome
acute generalized exanthematous pustulosis 338t, 342–343, 519t
clinical features 343f–344f
differential diagnosis 342–343
drug-induced 1518t
acute hemorrhagic edema of infancy 393–395
clinical features 394, 394f
differential diagnosis 308t–310t, 394
epidemiology 393–394
pathogenesis 394, 394t
pathology 394
treatment 394–395, 402t
acute inflammatory erythema *see* sunburn
acute intermittent porphyria 719t, 725
biochemical findings 720t
genetics 719t
treatment 725t
acute irritant contact dermatitis 251
delayed 251
acute lymphoblastic leukemia 845
acute myelogenous leukemia 1066
acute retroviral syndrome 1287
acyclovir
adverse reactions 2127t
dosage 2126t–2127t
formulations 2124t, 2126t
indications 2126t
erythema multiforme 323
herpes simplex 1329t
varicella-zoster 1329t
mechanism of action 2125f
pregnancy and lactation 2124t, 2155t
trade names 2124t
viral susceptibility to 2125t
acylceramides 2066
adalimumab 2145
adverse reactions 2145
ANA/anti-dsDNA antibody induction 608–609
dosage 2145
FDA warnings 2140t
indications 2145
psoriasis 153t
sarcoidosis 1563t
interactions 2145
laboratory evaluation 2140t
pregnancy and lactation 2145
Adams-Oliver syndrome 1001–1002, 1003t, 1718
digital anomalies 1005t
genetics 807t
ADAMTS2 1593t
ADAMTS13 autoantibodies 373
adapalene 2091
acne vulgaris 556, 2093, 2106t
formulations 2097t
pharmacologic features 2092t
structure 2090f
Adaptic dressings 2366–2367
adaptive immunity 84–96
antigen-presenting cells 84–87
AdatoSil 1581t
Addison's disease
cutaneous manifestations 770f, 771t
and dermatitis herpetiformis 493t
adducted thumbs syndrome 1116t
adenoid cystic carcinoma 1790t, 1847
adenosine deaminase deficiency 920t
adenovirus 77t
and erythema multiforme 320t
adherens junctions 464f, 833
adhesion molecules 1684f, 1685t
adhesion proteins 449t
Adie's syndrome 594
adipocytes 1663
adiponectin 1663
adiposis dolorosa (Dercum's disease) 1985
liposuction for 2527t
adnexal carcinoma 1845–1847
microcystic 1790t, 1846, 1846f
radiotherapy 2298
adnexal neoplasms 1829–1849
apocrine differentiation 1840–1847
apocrine ductular and tubular differentiation 1841–1844
apocrine lineage, undifferentiated 1844–1847
eccrine differentiation 1847–1848
follicular lineage 1829–1839
follicular and folliculosebaceous-apocrine hamartomas 1829–1834
follicular germinative differentiation 1834–1835
follicular sheath differentiation 1836–1837
matrical differentiation 1835–1836
superficial follicular differentiation 1837–1839
sebaceous differentiation 1839–1840
sebaceous adenoma, sebaceous epithelioma and sebaceoma 1839–1840
sebaceous carcinoma 1840
sebaceous hyperplasia 1839–1840
see also individual conditions
adnexal tumors 1771
adoptive cell therapy 1909–1910
adrenal hirsutism 1121t
adrenal hyperplasia 1121–1122, 1121t
congenital 551, 812–814, 1121, 1121t
adrenal insufficiency 2086
electrolytes in sweat 597t
adrenal SAHA syndrome 1121t
adrenal suppression 1124
adrenaline *see* epinephrine
adrenergic urticaria 298
adrenoleukodystrophy, eccrine gland changes 598t
ADULT syndrome
genetics 808t
adult T-cell leukemia/lymphoma 2020t, 2028
adverse drug reactions 335–356, 335t
clinical features 338–355
acneiform eruptions 354
alopecia 351
anticoagulant-induced skin necrosis 348–349, 348f
bullous eruptions 345–347
chemotherapy reactions 349t, 350–352, 350f–352f
DRESS syndrome 330, 338t, 339, 344–345, 345f, 345t
drug-induced hair loss/hair growth 350
drug-induced lupus 349–350
drug-induced psoriasis 139, 352f, 353
exanthematous drug eruptions 338–339
granulomatous reactions 348
HIV infection 352–353, 353t
localized reactions to injected medications 354f, 354t, 355
mucosal ulceration 350
neutrophilic drug eruptions 342–344
photosensitivity 341, 341f–342f
pigmentary changes 354, 354f
pseudolymphoma 347–348
SDRIFE 347, 347t
serum sickness-like eruption 348f, 349
stomatitis 351–352
urticaria, angioedema and anaphylaxis 339–341
vaccine-induced eruptions 354–355
vasculitis 342
diagnostic features 337–338, 337t–338t
epidemiology 335–336, 336t
pathogenesis 336–337, 337t
idiosyncratic 337
immunologically mediated 336
non-immunologic mechanisms 336–337
severe (SCARs) 335t
treatment 355
see also individual drugs
AEB071 2147t
Aedes aegypti, repellents 1437
Aeromonas hydrophila 375, 1450t, 1451
Aesculus hippocastanum see horse chestnut seed extract
AESOP syndrome
monoclonal gammopathy 2014t
paraneoplastic 764t–765t
Aethoxysklerol 2515t
Aetoxisclerol 2515t
African blackwood dermatitis 1509t
African tick bite fever 1244t, 1246t
African trypanosomiasis *see* trypanosomiasis
Afzelius' disease *see* erythema migrans
agammaglobulinemia
autosomal dominant 917t
autosomal recessive 917t
X-linked 900t, 915, 916f
agatoxins 1448
Agavaceae 278t
Agave americana see century plant
Agelenopsis aperta 1448
agouti protein 1019f–1020f
agouti signaling protein 795
agranulocytosis, dapsone-induced 496
Agricola, Georg 249
agrimony 2207t
Aicardi-Goutières syndrome 818t–819t
AIDS *see* HIV/AIDS
AIN-457 2147t
airbag burns 1491–1492
clinical features 1492, 1492t
differential diagnosis 1492
pathogenesis 1492
treatment 1492
airborne irritant contact dermatitis 246, 246f, 252, 287f
alatrofloxacin 2116t
albendazole 1402t–1403t, 1417, 1420
albinism 48, 49f, 1034t
oculocutaneous *see* oculocutaneous albinism
albinism-deafness syndrome 1038
Albright hereditary osteodystrophy 734
genetics 818t–819t
Alcaine *see* proparacaine
Alcian blue stain 27t–28t
alclometasone dipropionate 245t, 2079t
alcohols 255
alcohol abuse, prevalence 1512t
alcohol and psoriasis 139
aldehydes 249, 253t–254t
hyperhidrosis 594t
hypohidrosis/anhidrosis 595t
aldosteronism, electrolytes in sweat 597t
alefacept 2138–2140
contraindications 2139
dosage 2139
FDA warnings 2140t
indications 2139
lichen planus 195t, 196
psoriasis 153t
interactions 2140
laboratory evaluation 2140t
major adverse reactions 2139–2140
mechanism of action 2138, 2139f
pregnancy and lactation 2140
alemtuzumab 754–755, 1336
alendronate 1239, 2080–2081
aleosin 2490t
aleukocytosis 920t
alexandrite lasers 2251
hair removal 2256
optical penetration depth
pigmented lesions/tattoos 2256, 2268f, 2269t–2270t
Q-switched 2251
skin penetration 2254f
vascular lesions 2255, 2265t
Alezzandrini syndrome 1027
alfalfa 275t, 2212t
Alferon N 2132t
Algicell 2368t, 2372
Algiderm 2372
alginates 2369t, 2372, 2372f
leg ulcers 1735t
AlgiSite 2372
Algosteril 2372
Alibert, Jean Louis 2017
alitretinoin 2093
formulations 2097t
indications
hand eczema 2096
Kaposi's sarcoma 2094
pharmacologic features 2092t
alkalis 264
irritant 252, 264f
mechanisms of toxicity 250t
alkaptonuria 709t
genetics 810t–811t
Alldress 2373
alleles 784t
allelic heterogeneity 785, 785t, 800t–801t, 801
allergens 240–245, 241t–243t
bacitracin 241t, 244
balsam of Peru 241t, 243
cobalt 241t, 244
corticosteroids 245, 245t
formaldehyde 241t, 243–244
fragrance mix 241t, 243
gold/gold salts 244–245
methyldibromoglutaronitrile phenoxyethanol 244
neomycin sulfate 241t, 244
nickel 241–243, 241t, 242f
p-phenylenediamine 244
quaternium-15 241t, 244
thimerosal 242t, 244, 253t–254t
allergic contact dermatitis 12t, 233–248, 263, 264t
airborne 246, 246f, 252, 287f
allergens 240–245, 241t–243t
bacitracin
balsam of Peru 241t, 243
cobalt 241t, 244
corticosteroids 245, 245f, 245t
formaldehyde 241t, 243–244

fragrance mix 241t, 243
gold 244–245
methyldibromoglutaronitrile phenoxyethanol 244
neomycin sulfate 241t, 244
nickel 241–243, 241t, 242f
p-phenylenediamine 244
quaternium-15 241t, 244
thimerosal 242t, 244, 253t–254t
in amputees 1508t
clinical features 9f, 18f, 233f–236f, 235, 236t, 284–286
postinflammatory hyperpigmentation 1050t
differential diagnosis 227t, 236–239, 237t, 414t, 639t
epidemiology 234–235, 282–284
musical instrument-related 1509t
non-eczematous 264t
patch testing 236–239, 237f, 238t–239t, 239f–240f
history 234
pathogenesis 235, 284
pathology 235–236, 237f
peristomal 772t
plants causing 281–288
Alliaceae 278t, 287–288
Alstroemeriaceae 288
Anacardiaceae 282–283, 282f, 282t
clinical features 284–286, 286f
epidemiology 282–284
Liliaceae 288
Myrtaceae 288
pathogenesis 284
Peruvian lily 288, 288f
treatment 286–287
systemic 246, 246f, 246t
textile dermatitis 243, 245–246
treatment and patient education 239–240, 240t–241t, 241f
allergic contact hypersensitivity 95
elicitation of 95–96, 96f
induction of 95, 95f
allergic shiners 209t
allergic urticarial eruption 308t–310t
allergy *see* allergic contact dermatitis; atopic dermatitis
Allevyn 2371, 2373
Alliaceae 278t
allergic contact dermatitis 287–288
allicin 273t, 287–288
Allium cepa see onion
Allium sativum see garlic
Allium schoenoprasum see chives
Alloderm 2375t–2376t
Allodermanyssus (Liponyssoides) sanguineus
alloknesis 105
allopurinol
adverse reactions 338t
erythroderma 176t
fixed drug eruption 346f
lichen planus 185t
secondary cutaneous vasculitis 390t
Stevens-Johnson syndrome/toxic epidermal necrolysis 325t
indications
gout 711
perforating disease 1604t
sarcoidosis 1563t
interactions 2191
allylamine antifungals
interactions 2189
mechanism of action 2119t
aloe vera 2205, 2490t
soap 2480t
alopecia 1079t, 1593t
androgenetic 1093–1097, 2535–2537
biopsy 14t–15t
cicatricial (scarring) 1096t, 1104–1109
acne keloidalis 1107–1108
Brocq's alopecia 1096t, 1108, 1109f
"burnt-out" 1108
central centrifugal 1105–1106, 1106f
classification 1105t
discoid lupus erythematosus 1096t, 1107, 1107f
dissecting cellulitis of scalp 1108, 1108f
"folliculitis decalvans" 1109
lichen planopilaris 190–191, 191f, 1095f, 1106–1107, 1106f
traction alopecia 1109, 1109f
"tufted folliculitis" 1109, 1109f
congenital atrichia with papules 1104, 1104t
and drug abuse 1514t
drug-induced 335t, 349t, 350–351
female pattern 1094, 1094f–1095f, 1096t, 1098f
frictional 1506t
frontal fibrosing 1107, 1107f
genetics 795f
hair shaft abnormalities 841t–842t, 1109–1112
acquired progressive kinking 1111–1112
"bubble hair" 1110, 1110f
loose anagen hair syndrome 1112
monilethrix 827, 1110–1111, 1110f–1111f
Netherton syndrome 858f
pili annulati 1110f, 1112
pili bifurcati 1112
pili multigemini 1112
pili torti 841t–842t, 1110f, 1111
spun-glass hair 1110f, 1112
tiger-tail hair 841t–842t
trichonodosis 1110f
trichoptilosis 1110f
trichorrhexis invaginata 841t–842t, 1110f, 1111
trichorrhexis nodosa 841t–842t, 1110f, 1111
trichothiodystrophy 838t, 861–862, 1104t, 1110f, 1111
woolly hair 803t–804t, 1112, 1112f
irritant/toxic causes 251t
lipedematous 1103
male pattern 1093–1094, 1096t
neoplastica 2051t
non-cicatricial 1103–1104
postoperative (pressure-induced) 1096t, 1103
psoriasiform 1096t, 1103–1104
telogen effluvium 1098–1099
temporal triangular 1095f, 1103, 1103f
TNF-α-induced 1103–1104, 1593t
traction 1096t
traumatic 1522
treatment
finasteride 1097
minoxidil 1097, 2159
trichotillomania 132–133, 1099–1100
clinical features 132–133, 132f, 1099–1100, 1100t
differential diagnosis 133
epidemiology 133
management 133
pathogenesis 1099
pathology 133, 133f
treatment 1100
alopecia areata 53f, 1100–1102
clinical features 1095f, 1100, 1101f–1102f
and dermatitis herpetiformis 493t
differential diagnosis 1100
disase associations 1101t
epidemiology 1100
histologic features 1096t, 1102f
nails in 1100, 1101f, 1130f, 1138
pathogenesis 1100
treatment 1100–1102, 1103t
photodynamic therapy 1103t
phototherapy 2231
alopecia mucinosa *see* follicular mucinosis
alopecia neoplastica 2051t
α-hydroxy acids 2158, 2488
Alport syndrome 454
alprazolam 2189t
interaction with lidocaine 2529t
alprenolol 2190t
alprostadil, Raynaud's phenomenon
Alstroemeria spp. *see* Peruvian lily
Alström syndrome 750
Alternaria spp. 1251t
alternative medicine *see* complementary and alternative medicine
aluminum
dermatosis 1499t
foreign body reaction 1574t, 1579
histopathology 1576t
aluminum chloride 590, 2464t
aluminum chloride hexahydrate, hyperhidrosis 594t
aluminum salts, hypohidrosis/anhidrosis 595t
aluminum-induced panniculitis 1656t
alymphocytosis *see* severe combined immunodeficiency
amalgam tattoo 1167f
amantadine-induced livedo reticularis 1748t
Amaryllidaceae *see* daffodils
amastia *see* nipple, absent, hypoplastic or anomalous
amaurosis congenita, cone-rod type with hypertrichosis 1116t
ambenonium, eccrine sweating 590t
Amblyomma spp. 1442–1443
Amblyomma americanum 1244t, 1245f, 1442, 1443f
Amblyomma aureolatum 1244t
Amblyomma cajennense 1244t
Amblyomma hebraeum 1244t
Amblyomma maculatum 1244t
Amblyomma triste 1244t
Amblyomma variegatum 1244t
Ambras syndrome 1081, 1116t
genetics 809t
ambrisentan 651
Ambrosia spp. *see* American ragweed
ambulatory phlebectomy 2520–2521
anesthesia and intraoperative materials 2520–2521, 2520f–2521f
combination with endovenous laser/radiofrequency ablation 2523
complications 2521, 2522t
postoperative considerations 2521
preoperative preparation 2520
technique 2521, 2521f
amcinonide 245t, 2079t
amoebae, diseases caused by 1397–1399
amebiasis 1397–1398, 1398f
Balamuthia mandrillaris 1398–1399
amelanotic melanoma 37f, 1894, 1895f
ameloblastoma 1790t
amenorrhea-galactorrhea syndrome 1124
Americaine otic *see* benzocaine
American dog tick *see* dermacentor ticks
American ragweed 285t
American tick bite fever 1244t, 1246t
American trypanosomiasis *see* trypanosomiasis
AMG827 2147t
amicrobial pustulosis of folds 147t
amidoamine 242t
amikacin, tuberculosis 1234t
aminocaproic acid, vasculitis 402t
aminoglycosides 2105t
sites of action 2109t
5-aminolevulinic acid 2238f, 2241f, 2242, 2242t
aminolevulinic acid dehydratase deficiency porphyria 719t, 726
biochemical findings 720t
genetics 719t
treatment 725t
aminopenicillins
adverse reactions 338t
Stevens-Johnson syndrome/toxic epidermal necrolysis 325t
aminophylline, systemic contact dermatitis 246t
para-aminosalicylic acid, tuberculosis 1234t
amiodarone
adverse reactions
erythroderma 176t
hyperpigmentation 354f, 1056t–1057t
linear IgA bullous dermatosis 498t
pseudoporphyria 724t
interactions, lidocaine 2529t
amiphenazole-induced lichen planus 185t
amithiozone-induced toxic epidermal necrolysis 325t
amitriptyline
adverse reactions
hyperpigmentation 1056t–1057t
lichen planus 185t
and eccrine sweating 590t
amlodipine 2191t
gingival hyperplasia 1156t
Ammi majus see false bishop's weed
amniotic band syndrome 1009–1010
amoxapine, and eccrine sweating 590t
amoxicillin
borreliosis 315t
dosage 2110t
prophylactic 2462t
amoxicillin-clavulanic acid
adverse reactions, pruritus 120t
dosage 2110t
tuberculosis 1234t
amphetamines
abuse 1511
cutaneous reactions 1518t
treatment 1520t
adverse reactions, gingival hyperplasia 1156t
and eccrine sweating 590t
amphibians, wound healing 2313
amphotericin B
adverse reactions 2122
dosage 2122
formulations 2107–2108
indications 2120t
aspergillosis 1283t
blastomycosis 1277
candidiasis 1283t
coccidioidomycosis 1278
cryptococcosis 1283t
fusariosis 1283t
histoplasmosis 1274
leishmaniasis 1397t
mycetoma 1272
paracoccidioidomycosis 1262
penicilliosis 1255
zygomycosis 1283t
interactions 2127t
pregnancy and lactation 2118t, 2120t
trade names 2107–2108
ampicillin
adverse reactions 336t
cutaneous eruption 1335f
pseudoporphyria 724t
systemic contact dermatitis 246t
dosage 2110t
prophylactic 2462t
amprenavir 2186–2187
adverse reactions 1299t
amputation neuroma 1944
amputation-related dermatoses 1508, 1508t
α-amyl cinnamic aldehyde 243t
amyloidosis 699–708, 709t
amyloid characteristics 700f–701f, 700t, 701–702
classification 699t–700t, 700
differential diagnosis 650t
epidemiology 699–700
familial cutaneous *see* X-linked reticulate pigmentary disorder
Finnish-type 1617t–1618t
history 699–702
lichen 702, 702f
macular 702
monoclonal gammopathy 2014t
nodular 703, 704f
and anetoderma 1633t
oral manifestations 705, 1167–1168
paraneoplastic 764t–765t
pathogenesis 700–701
primary (localized) cutaneous 702–705, 1054
clinical features 702–703, 702f–703f
differential diagnosis 703

pathology 703
treatment 703–705, 703t
renal disease 707
secondary cutaneous 705
systemic 705–708
hemodialysis-associated 707
inherited 707–708
primary 705–707, 705f–707f
secondary 707
X-linked reticulate pigmentary disorder 708
ANA *see* antinuclear antibodies
anabolic steroids
abuse 1512
cutaneous signs 1514t
prevalence 1512t
adverse reactions
acne 550t
pruritus 120t
urticaria 305
Anacardiaceae 278t, 282–283, 282f, 282t, 285t
allergens 282t
dermatitis 284–286, 286f
Anacardium occidentale see cashew tree
anacetrapib 1554t–1555t
anaerobic cellulitis 1200, 1201t
anagen 1078, 1079t, 1083f, 1099f
duration of 1078
anagen effluvium, drug-induced 350
anagrelide, thrombocytosis 372
anakinra 294, 2146
contraindications 2146
dosage 2146
indications 2146
relapsing polychondritis 677
interactions 2146
major adverse reactions 2146
mechanism of action 2146
pregnancy and lactation 2146
anal intraepithelial neoplasia 1177
anal pain 1183
Ananas comosus see pineapple; pineapple extract
anaphylactoid purpura *see* Henoch-Schönlein purpura
anaphylatoxins 81
anaphylaxis
drug-induced 338t, 341
exercise-induced 298
food- and exercise-induced 298
local anesthetic-induced 2345t, 2346
Anaplasma phagocytophilum 1244t, 1250
anaplasmosis 1244t, 1246t, 1250
anaplastic lymphoma kinase 29t–33t
anapsos 2207t
anasarca 517t
anastrazole, dermatomyositis 639t
anatomy and physiology 43–54
attraction function of skin 51–52
barrier function of skin 47–48
communication in skin 50–51
DNA protection 45
immunologic function of skin 45
skin disease 44–45
skin as nutritive organ 49–50
skin repair mechanisms 48–49
skin structure 43–53
thermoregulatory function of skin 51
see also epidermis; skin
ANCA 611f
disorders associated with 613t
see also C-ANCA; P-ANCA
ANCA-associated vasculitides 387, 399–405
Churg-Strauss syndrome *see* Churg-Strauss syndrome
microscopic polyangiitis 399–401
natural history 399
pathogenesis 386f, 399
Wegener's granulomatosis *see* Wegener's granulomatosis
anchoring fibrils 455–456
anchoring plaques 450, 450f, 455
Ancylostoma braziliense 1406
Ancylostoma caninum 1406
Ancylostoma duodenale 1407t–1408t
ancylostomiasis 1407t–1408t
Androctonus australis 1449t
Androctonus carssicauda 1449t
androgenetic alopecia 1093–1097, 2535–2537
clinical features 1094, 1094f–1095f, 2535–2536
differential diagnosis 1097
histologic features 1096t, 1102f
pathogenesis 1093–1094, 2535, 2535f
pathology 1094
progression of 2535f
treatment 1097, 2536–2537
see also male pattern baldness
androgens
adverse reactions 2155t
synthesis 1122f
Androlaelaps spp. 1445t
Anebia clematidis 2213
anemia, cutaneous 1047
anesthesia 2343–2352
biopsy 2383–2384, 2383f, 2383t
laser therapy 2276
nail bed 2435–2436
topical 2346–2348, 2347t
cryoanesthesia 2347–2348
mucous membranes 2347
skin 2346–2347
anesthetics, topical 2156, 2156t
benzocaine 2156
EMLA cream 2156
lidocaine 123, 2156
anetoderma 1632–1635, 1632t
associated conditions 1633t
classification 1633t
clinical features 1633, 1634f
differential diagnosis 1634
epidemiology 1633
history 1632
Jadassohn-Pellizzari type 1633
pathogenesis 1633
pathology 1633–1634, 1634f
Schweninger-Buzzi type 1633
treatment 1634–1635
aneuploidy 791–792
Ang-1 59, 1681
angel kiss 1713
angelica 279t
wild 279t
Angelica archangelica see angelica
Angelica sylvestris see angelica, wild
Angelman syndrome 791f
angioblastoma of Nakagawa *see* tufted angioma
angioblasts 1681f
angiocentric lymphoma *see* natural killer cell lymphoma, extranodal
angiodysplasia 1691
angioedema 291, 292f, 296
clinical classification 295t
drug-induced 299, 340–341
episodic with eosinophilia 300
hereditary 299, 810t–811t
juvenile idiopathic arthritis
monoclonal gammopathy 2014t
paraneoplastic 764t–765t
and pseudocellulitis
vibratory 297
without wheals 299
diagnosis 301
see also urticaria
angioendotheliomatosis
monoclonal gammopathy 2014t
reactive 1916–1917
angiofibroma 935, 938, 1961–1962
clinical features 936f, 1961–1962
fibrous papules 1961, 1962f
pearly penile papules 1961, 1962f
periungual fibroma 1962
linear 955
pathology 1962, 1962f
angiogenesis 1681–1684, 1682f–1683f, 1682t, 1764
molecular control 1683f
stepwise induction 1681f, 1682t
in wound healing 2319f
angioid streaks 1614
angioimmunoblastic lymphadenopathy *see* angioimmunoblastic T-cell lymphoma
angioimmunoblastic T-cell lymphoma 2045–2046
clinical features 2046
differential diagnosis 2046
epidemiology 2046
history 2046
pathogenesis 2046
pathology 2046
treatment 2046
angiokeratoma 1919–1920
circumscriptum 1719–1720, 1920, 1920f
clinical features 1719–1720, 1919–1920
angiokeratoma corporis diffusum 1919
angiokeratoma of Mibelli 1719–1720, 1919
scrotum and vulva 1719–1720, 1919, 1919f
solitary or multiple angiokeratoma 1919, 1919f
dermoscopy 36f
differential diagnosis 1920
in Fabry's disease 1719–1720
pathology 1920
treatment 1920
angiolieomyoma 1979
angiolipoma 1985–1986, 1986f
angiolupoid sarcoidosis 1559–1560
angiolymphoid hyperplasia with eosinophilia 1920–1921
clinical features 1921, 1921f
differential diagnosis 414t, 1921
epidemiology 1921
pathogenesis 1921
pathology 1921, 1921f
treatment 1921
angioma
cavernosum 1691
cherry 1924
serpiginosum 1754, 1755f
simplex 1712
tufted 1926–1927, 1927f
angioma serpiginosum 1718
angiomyolipoma 823
(angio)myxoma 697
vs cutaneous focal mucinosis 696
angiopoietins 1682f
angiopoietin-1 1682f
angiopoietin-2 1682f
angiosarcoma 1935–1936
clinical features 1935–1936, 1935f
differential diagnosis 1936
epidemiology 1935
history 1935
pathogenesis 1935
pathology 1936, 1936f
radiotherapy 2297
treatment 1936
angiospastic macules *see* Bier spots
angiostatin 360–361
angiotensin II receptor blockers
cutaneous lymphoid hyperplasia 2039t
Raynaud's phenomenon 651
angiotensin-converting enzyme inhibitors *see* ACE inhibitors
angry back 224
anhidrosis 541, 594–595
causes 594t–595t
diagnosis 595
with insensitivity to pain 818t–819t
peripheral 595
treatment 595
anhidrotic ectodermal dysplasia *see* hypohidrotic ectodermal dysplasia
anidulafungin
indications 2120t
aspergillosis 1283t
candidiasis 1283t
cryptococcosis 1283t
penicilliosis 1283t
zygomycosis 1283t
pregnancy and lactation 2120t
animal models
bullous pemphigoid 477
pruritus 103t
anise seeds 2207t
ankle-brachial index 1739t
ankyloblepharon-ectodermal dysplasia-clefting syndrome 510t
neonates 526t–528t
annular elastolytic giant cell granuloma 1568–1570
clinical features 1558t, 1569, 1569f
differential diagnosis 308t–310t, 1569
epidemiology 1568
history 1568
pathogenesis 1568–1569
pathology 1562t, 1569, 1569f
treatment 1569–1570
annular epidermolytic ichthyosis 308t–310t
annular erythema
of infancy 308t–310t, 414t
Sjögren's syndrome 678, 761–763
annular lichen planus 189, 189f
annular lichenoid dermatitis of youth 201–202, 308t–310t
annular lupus erythematosus 308t–310t, 620f
annulus migrans 142
anogenital dermatitis 1175–1177
clinical features 1176, 1176f
differential diagnosis 1176, 1176f
pathogenesis 1175–1176
treatment 1176–1177
anogenital disease 1171–1186
benign lesions 1183, 1183t
epidermoid cysts 1183
vestibular papillomatosis 1183
dysesthetic genital pain syndromes 121–122, 122t, 1180–1183, 1182f
anal pain 1183
cyclical vulvovaginitis 1182
generalized vulvodynia/scrotodynia 1182
localized vulvodynia 1181–1182, 1182t
epithelial disorders 1175–1177
contact dermatitis 1177
dermatitis 1175, 1176f
pruritus 116–117
psoriasis 141f, 1177, 1177f
erosive 1184–1185
bullous pemphigoid 479f, 1185
causes of 1184t
cicatricial pemphigoid 485, 1185
erythema multiforme 321, 1185
fixed drug eruptions 346f, 1185
Hailey-Hailey disease 895, 1185
linear IgA bullous dermatosis 1185
pemphigus vulgaris 1185, 1185f
Stevens-Johnson syndrome 327f, 1185
infections 1183–1184
cutaneous candidiasis 1183–1184
cyclical vulvovaginitis 1184–1185
dermatophytosis 1183
erythrasma 1183
Fournier's gangrene 1183
Kawasaki disease 1183
perianal streptococcal disease 1183
recurrent candidiasis 1184
recurrent toxin-mediated perineal erythema 1183
lichen planus 189f, 1173–1175
clinical features 1174, 1174f
differential diagnosis 1174
epidemiology 1174
history 1173–1174
pathology 1174
treatment 1174–1175, 1175t
lichen sclerosus 664–666, 665f, 1175
clinical features 1171–1172, 1172f–1173f
differential diagnosis 1172–1173
epidemiology 1171
etiology 1171
history 1171
pathology 1172
treatment 1173, 1173t
premalignant and malignant lesions 1177–1180
anogenital melanoma 1179
basal cell carcinoma 1179

extramammary Paget's disease 1179–1180, 1180f–1181f
intraepithelial neoplasia 1177–1178, 1178f
squamous cell carcinoma 1178–1179, 1179f
of systemic origin 1183
Behçet's disease 433f, 1183
inflammatory bowel disease 1183
Langerhans cell histiocytosis 1183
zinc deficiency 1183
Zoon's balanitis/vulvitis 1175, 1175f
see also sexually transmitted infections
anogenital hemangioma 1697
anogenital pain syndromes 121–122, 122t
anogenital syringoma 1183t
anogenital warts *see* condylomata acuminata
Anonaceae 274t
anonychia congenita 800t–801t, 809t
anorexia nervosa 750
anosmia 841t–842t
antacids, interactions 2124t, 2190
anterior ethmoidal nerve 2349, 2349f
anthracyclines, adverse reactions
acral erythema 349t
nail changes 1141t
neutrophilic eccrine hidradenitis 349t
anthralin 2161, 2161t
alopecia areata 1103t
hair discoloration 1498t
psoriasis 149–150, 149t
anthrax 1203–1204
clinical features 1203, 1203t
diagnosis 1204
epidemiology 1203
history 1203
occupational 271t
pathogenesis 1203
pathology 1203–1204
treatment 1204
anti-α-fodrin antibodies 607t, 611t
anti-aminoacyl-tRNA synthetases 633t
anti-β2-glycoprotein I antibodies 607t, 1744t
anti-C1q antibodies 607t
anti-CADM-140 antibodies 609t, 633t
anti-calpastatin antibodies 610t
anti-centromere antibodies 610t
anti-cyclic citrullinated protein antibodies 611t
anti-DNA antibodies, systemic lupus erythematosus 627t
anti-dsDNA antibodies 607t
induction by TNF-α inhibitors 608–609
anti-EJ antibodies 609t
anti-endothelial cell antibodies 610t
anti-epilgrin cicatricial pemphigoid, paraneoplastic 456t
anti-Fer antibodies 609t
anti-fibrillarin antibodies 610t
anti-fibrillin-1 antibodies 610t
anti-histone antibodies 607t, 610t
anti-HMG antibodies 610t
anti-Jo-1 antibodies 609t, 610
anti-Ku antibodies 607t, 609t
anti-La (SS-B) antibodies 607t, 611t
anti-Mas antibodies 609t
anti-Mi-2 antibodies 609t, 610, 633t
anti-MMP1/3 antibodies 610t
anti-NAG-2 antibodies 610t
anti-OJ antibodies 609t
anti-p140 antibodies 633t
anti-p155 antibodies 609–610, 609t, 633t
anti-p200 pemphigoid 482
anti-PCNA antibodies 607t
anti-PDGRF antibodies 610t
anti-PL-7 antibodies 609t
anti-PL-12 antibodies 609t
anti-PM-Scl (PM-1) antibodies 609t–610t
anti-rheumatoid factor antibodies 607t, 610t–611t
anti-RNA polymerase antibodies 610t
anti-Ro antibodies
dermatomyositis 609t
lupus erythematosus 308t–310t, 607t
rheumatoid arthritis 611t
Sjögren's syndrome 678
anti-rRNP antibodies 607t
anti-SAE antibodies 633t
anti-Scl-70 antibodies 610t
anti-Sm antibodies
cutaneous lupus erythematosus 607t
SLE 627t
anti-SRP antibodies 609t, 633t
anti-ssDNA antibodies 607t, 609t–610t
anti-synthetase syndrome 604f
anti-TG3 antibodies 493
anti-Th/To RNP antibodies 610t
anti-TNF agents
adverse reactions, secondary cutaneous vasculitis 390t
vasculitis 402t
anti-topoisomerase I (Scl-70) antibodies 644t
anti-U1RNP antibodies 607t, 609t, 611t
anti-U2RNP antibodies 609t
antiandrogens, mechanism of action 1098f
antiangiogenesis 1688, 1688f
antiarrhythmics and cutaneous lymphoid hyperplasia 2039t
antibacterial agents 2105–2117
adverse reactions
alopecia 348t
cutaneous lymphoid hyperplasia 2039t
bactericidal 2105t
bacteriostatic 2105t
prophylaxis
Mohs surgery 2451
preoperative 2461–2462, 2462t
systemic 2109–2117
cephalosporins 2111–2112
clindamycin 2115
macrolides 2113–2114
metronidazole 2116–2117
penicillins 2110–2111
quinolones 2116
sites of action 2109f, 2109t
sulfonamides 2112–2113
tetracyclines 2114–2115
topical 2105–2109
acne vulgaris and rosacea 555t, 556, 2105–2107, 2106t
adverse reactions 2107, 2107t
contraindications 2106–2107
dosage 2106
indications 2106
interactions 2107
mechanism of action 2105–2106, 2106t
pregnancy and lactation 2107
superficial infections 2107–2108
adverse reactions 2108
contraindications 2108
dosage 2108, 2108t
indications 2107–2108
interactions 2108
mechanisms of action 2107, 2108t
pregnancy and lactation 2108, 2108t
see also individual drugs
antibiotics *see* antibacterial agents
antibodies
ANCA 611f, 613t
anti-α-fodrin 607t, 611t
anti-β2-glycoprotein I 607t
anti-C1q 607t
anti-CADM-140 609t, 633t
anti-calpastatin 610t
anti-centromere 610t
anti-cyclic citrullinated protein 611t
anti-DNA 627t
anti-dsDNA 607t, 608–609
anti-EJ 609t
anti-endomysial 494
anti-endothelial cell 610t
anti-Fer 609t
anti-fibrillarin 610t
anti-fibrillin-1 610t
anti-histone 607t, 610t
anti-HMG 610t
anti-Jo-1 609t, 610
anti-Ku 607t, 609t
anti-La (SS-B) 607t, 611t
anti-Mas 609t
anti-Mi-2 609t, 610, 633t
anti-NAG-2 610t
anti-OJ 609t
anti-p140 633t
anti-p155 609–610, 609t, 633t
anti-PCNA 607t
anti-PL-7 609t
anti-PL-12 609t
anti-PM-Scl (PM-1) 609t–610t
anti-rheumatoid factor 607t, 610t–611t
anti-RNA polymerase 610t
anti-Ro *see* anti-Ro antibodies
anti-rRNP 607t
anti-SAE 633t
anti-Scl-70 610t
anti-Sm *see* anti-Sm antibodies
anti-SRP 609t, 633t
anti-ssDNA 607t, 609t–610t
anti-TG3 493
anti-Th/To RNP 610t
anti-topoisomerase I (Scl-70) 644t
anti-U1RNP 607t, 609t, 611t
anti-U2RNP 609t
antidesmoglein 465
antiendomysial 494
antinuclear *see* antinuclear antibodies
antiphospholipid 379–380
antitopoisomerase I 643
see also autoantibodies
antibody responses 1348t
antibody-dependent cellular cytotoxicity 83
anticardiolipin antibodies 380, 607t, 1744t
anticentromere antibodies 644t
anticholinergics, interactions 2124t
anticoagulants 361, 364t–365t
adverse reactions
cutaneous lymphoid hyperplasia 2039t
skin necrosis 348–349, 348f
see also individual drugs
anticonvulsants
adverse reactions 338t
alopecia 348t
cutaneous lymphoid hyperplasia 2039t
erythema multiforme 320t
see also individual drugs
antidepressants 133–134
adverse reactions
alopecia 348t
cutaneous lymphoid hyperplasia 2039t
antidesmoglein antibodies 465
antiendomysial antibodies 494
antiepiligrin cicatricial pemphigoid *see* cicatricial pemphigoid
antifungals 2117–2124, 2118t
adverse reactions 2122–2123, 2123f, 2123t
contraindications 2122
dosage 2120–2122, 2121t–2122t
indications 2117–2119, 2120t
interactions 2123, 2124t
mechanism of action 2117–2124, 2119f, 2119t
pregnancy and lactation 2118t, 2120t, 2123–2124
sites of action 2119f
see also individual drugs
antigen presentation 86–87
to T cells 86–87
types of 86f
antigen-presenting cells 84–87
activation and migration 86
antiherpetic drugs 2124t, 2126t
antihistamines
adverse reactions, cutaneous lymphoid hyperplasia 2039t
atopic dermatitis 215
mastocytosis 2001
parapsoriasis 159t
perforating disease 1604t
pityriasis lichenoides 162t
in pregnancy 442t
pruritus 106t
urticaria 302–303
vasculitis 402t
antihypertensives
adverse reactions
alopecia 348t
cutaneous lymphoid hyperplasia 2039t
antileukoprotease 83t
antimalarials 2165–2169
adverse reactions 2166, 2169t
hyperpigmentation 2166, 2170f
nail changes 1141t
contraindications 2166
dosage 2166
indications 2166, 2170t
lichen planus 195t
lupus erythematosus 628
interactions 2166–2169
mechanism of action 2166
monitoring 2167t–2168t
pregnancy and lactation 2166
antimicrobial drugs 2105–2129
antibacterial agents *see* antibacterial agents
antifungals 2117–2124
antivirals 2124–2127
in dressings 2368, 2368f, 2368t
and erythema multiforme 320t
perforating disease 1604t
pityriasis lichenoides 162t
see also individual drugs
antimicrobial peptides 82, 83t
antimicrobial proteins 82
antimitotic agents
anthralin *see* anthralin
azelaic acid *see* azelaic acid
carmustine 2160
coal tar *see* coal tar
5-fluorouracil *see* 5-fluorouracil
mechlorethamine hydrochloride 2160
podophyllin 1316, 2162
podophyllotoxin 1314t, 1316, 2162
antimony, adverse reactions 1397t
antimony-induced dermatosis 1499t
antineutrophil cytoplasmic antibodies *see* ANCA
antinuclear antibodies
assay 604–605
'normal' vs 'abnormal' values 605
technical aspects 604–605
clinical significance 604t, 605–606
clinical utility of laboratory testing 605–606, 609t
clinical value 606
evaluation of positive ANA result 606, 610t
immunofluorescence patterns 605, 605f
induction by TNF-α inhibitors 608–609
phototherapy and ANA assay 606
"Sonthelmer's Corollary" 606
drug-induced 608
lupus erythematosus 606f, 607–609, 607t
scleroderma 644t
antioxidants
in cosmeceuticals 2490t
vitiligo 1030
antiphospholipid antibodies 379
screening for 379–380
SLE 627t
antiphospholipid antibody/lupus anticoagulant syndrome 379–380
and anetoderma 1633t
clinical features 379, 380f, 775f
criteria for 379t
cutaneous findings 379t
differential diagnosis 380
epidemiology 379
pathogenesis 379
pathology 379–380
treatment 380
antiplatelet agents in Raynaud's phenomenon 651
antiprogestins 2189t
antipruritic agents 2156, 2157t

antipsychotics
  adverse reactions 129t
  and cutaneous lymphoid hyperplasia 2039t
antiretroviral therapy 1298
  adverse reactions 1299t
    cutaneous lymphoid hyperplasia 2039t
    lipodystrophy *see* HIV/ART-related lipodystrophy
    nail changes 1141t
    Stevens-Johnson syndrome 325t
    toxic epidermal necrolysis 325t
  immune reconstitution inflammatory syndrome 1298–1300, 1298f, 1300t
  see also individual drugs
antirheumatics and cutaneous lymphoid hyperplasia 2039t
antiseptics 2383t
antisynthetase syndrome 610
antithrombin III 359–360
  deficiency 818t–819t, 1744t
antithyroid drugs
  adverse reactions
    alopecia 348t
    cutaneous lymphoid hyperplasia 2039t
antitopoisomerase I antibodies 643
α1-antitrypsin deficiency panniculitis 1646–1647
  clinical features 1647, 1647f
  differential diagnosis 1647
  epidemiology 1646
  history 1646
  pathogenesis 1646–1647
  pathology 1647
  sites of 1642f
  treatment 1647
antivenin 1447–1448
antivirals 2124–2127, 2124t–2125t
  adverse reactions 2126, 2127t
  contraindications 2126
  dosage 2125–2126, 2126t–2127t
  formulations 2126t
  indications 2124–2125
  interactions 2126, 2127t
  mechanism of action 2106–2107
  pregnancy and lactation 2126
  see also individual drugs
anxiety disorder 131t
  treatment 133
Apert syndrome
  acne in 551
  digital anomalies 1005t
  genetics 818t–819t
aphthosis *see* aphthous stomatitis
aphthous stomatitis 433
aphthous ulcers *see* recurrent aphthous stomatitis
Apiaceae 279–280, 279t, 280f
Apium graveolens see celery
apixaban 365t
aplasia cutis congenita 526t–528t, 531f, 1000–1003, 1001t
  classification 1002t
  clinical features 531f, 1001f, 1004f
  locations 1005f
  syndromes associated with 1003t
Apligraf 2375, 2375t, 2376f
apocrine adenoma 1847
apocrine chromhidrosis 542
apocrine cystadenoma of penis *see* median raphe cyst
apocrine (decapitation) secretion 542
apocrine glands 540t, 541–542
  cell types 540t
  development 60, 540t, 541
  disorders of 601
  function 540t, 542
  innervation 540t–541t
  localization 540t
  morphology 540t
  pathophysiology 539, 542
  structure 541
apocrine hidrocystoma 1075, 1823–1824
  histology 1824f
apocrine miliaria *see* Fox-Fordyce disease
apoeccrine glands 540t, 542
  cell types 540t
  development 540t, 542
  function 540t, 542
  innervation 540t
  localization 540t
  morphology 540t
  pathophysiology 539, 542
  structure 542
apolipoproteins *see* apoproteins
apoproteins 1547, 1547t
apoprotein A-I 700t, 1547t
apoprotein B-48 1547t
apoprotein B-100 1547t
  familial defective 1551–1552
apoprotein C-II 1547t
  deficiency 810t–811t
  dysfunctional 1550
apoprotein E 1547t
  deficiency 1549t
apoptosis 327f, 1762–1763, 1763f
apoptotic pan-epidermolysis 330
apple 275t
apremilast 2147t
aprepitant, pruritus 106t
apricot 275t
apudoma, cutaneous *see* Merkel cell carcinoma
Aquacel 2368t
Aquaflo 2372
Aquagauze 2372
aquagenic palmoplantar keratoderma 883
aquagenic pruritus 116, 116t
aquagenic urticaria 298
Aquamid 1581t
Aquaphor dressings 2366–2367
Aquasite 2372
Aquilegia spp. *see* columbine
Araceae *see* dumb cane; philodendron
arachidonic acid 2176, 2225
arachnids 1440–1449
  Amblyomma ticks 1442–1443, 1443f
  Dermacentor ticks 1443, 1443f
  Ixodes ticks 1444, 1444f
  Rhipicephalus ticks 1443–1444, 1444f
  tick bites 1440–1442
Araliaceae 277t
arbutin 2490t
Arcanobacterium haemolyticum 1195
Arctostaphylos uva-ursi see bearberry
ardeparin 364t
AREDYLD syndrome 1673
arenaviruses 1360t
argatroban 364t, 370
argininosuccinic aciduria 1104t
argon dye lasers 2255t
argon lasers 2255t
  penetration depth 2254f
argyria 6t–7t, 25, 1055f, 1056t–1057t
  eccrine gland changes 598t
aripiprazole
  adverse reactions 129t
  psychosis 134
armadillo proteins 833
arnica 285t, 2206
Arnica spp. 274t
Arnica montana see arnica
aromatherapy 2215–2216, 2215t
arrector pili muscle 1079t, 1093
  bulge 1079t
arrhythmogenic right ventricular dysplasia/cardiomyopathy 803t–804t, 832t–833t
arsenic
  adverse reactions
    dyschromatosis 1072t–1073t
    hyperpigmentation 1056t–1057t
    lichen planus 185t
  and NMSC 1775t, 1779
  poisoning 1498t
arsenic salts 253t–254t
arsenical dermatosis 1498–1501
  clinical features 1500, 1500f
  differential diagnosis 1501
  epidemiology 1500
  history 1498–1500
  pathogenesis 1500
  pathology 1500
  treatment 1501
arsenical keratoses 884
ART *see* antiretroviral therapy
Artecoll 2558–2559
Artefill 2548t–2549t
Artemis deficiency 920t
Artemisia vulgaris see mugwort
arterial tortuosity syndrome 1593t, 1617t–1618t
arterial ulcers 1738–1740
  clinical features 1739, 1739f
  differential diagnosis 1739–1740
  laboratory evaluation 1739
  pathogenesis 1738–1739
  treatment 1740
arteriovenous anastomoses 49
arteriovenous malformations
  Bonnet-Dechaume-Blanc syndrome 1724f, 1725
  clinical features 1724–1725, 1724f–1725f
  Cobb syndrome 1725, 1725f
  histology 1726f
  investigative tools 1714t
  Parkes Weber syndrome 1725
  pathology 1726
  treatment 1727
arteriovenous shunts, and nail growth 1090t
arthritis
  autoantigens 1596t
  enthesitis-related 672t
  juvenile idiopathic 671–672
    classification 672t
    clinical features 671–672, 673f
      exanthem 671–672
    differential diagnosis 672
    epidemiology 671
    history 671
    oligo/pauciarticular 672t
    pathogenesis 671
    pathology 672
    polyarticular 671
    treatment 672
  mutilans 1541
  psoriatic 672t
  rheumatoid *see* rheumatoid arthritis
  and systemic lupus erythematosus 627t
arthritis-dermatosis syndrome 1381, 1381f
arthrochalasia 1593t, 1609t, 1611
arthrogryposis 841t–842t
arthrogryposis-renal dysfunction-cholestasis syndrome 803t–804t, 852t–854t
arthropod bite
  differential diagnosis 414t
  pruritus in 113t
  pseudocellulitis 1196t
articaine 2344t, 2348–2349
Asboe-Hansen sign 326, 467
ascariasis 1407t–1408t
Ascaris lumbricoides 1407t–1408t
ascertainment bias 2062
Asclera 2515t
Ascoschoengastia indica
Aselli, Gasparo 1685
asenapine, adverse reactions 129t
ash leaf macules 936f
ashy dermatitis *see* erythema dyschromicum perstans
ashy dermatosis *see* erythema dyschromicum perstans
Asklerol 2515t
ASP015K 2147t
asparaginase 349t
aspergillosis 778t–779t, 1279f, 1280
  and drug abuse 1515t
Aspergillus spp.
  chronic granulomatous disease 910t
  neonates 524t–528t
  onychomycosis 1265t
  panniculitis 1658t
Aspergillus flavus 1282
Aspergillus fumigatus 375
aspirin
  adverse reactions
    erythroderma 176t
    lichen planus 185t
    and bleeding disorders 2462
    and eccrine sweating 590t
    erythromelalgia 1752–1753
    intolerance 299
    as mast cell stimulant 2001t
assassin bugs *see* triatome reduviids
astaxanthin 2490t
asteatosis 222
asteatotic dermatitis 252
asteatotic eczema 221–222
  clinical features 222, 222f
  differential diagnosis 222
  epidemiology 222
  history 222
  pathogenesis 222
  pathology 222
  treatment 222
astemizole, interactions 2124t
Asteraceae 277t, 284, 285t
  allergenic 284
  allergens 284
  dermatitis 286
  identification 284, 284f
  photosensitivity 286
asteroid bodies 1272–1273
astringents 2479, 2481
asymmetric periflexural exanthem of childhood *see* unilateral laterothoracic exanthem
ataxia 841t–842t
ataxia-telangiectasia 899–902, 900t, 1755
  clinical features 899–901, 901f, 932t–933t, 1719
  differential diagnosis 652t, 902
  epidemiology 899
  genetics 816t
  molecular genetics 1713t
  pathogenesis 899
  pathology 901
  treatment 902
atazanavir, adverse reactions 1299t
athelia *see* nipple, absent, hypoplastic or anomalous
atherosclerosis *see* hyperlipidemia
athlete's foot *see* tinea pedis
atomoxetine, and eccrine sweating 590t
atopic dermatitis (eczema) 203–217, 203f
  adult/adolescent 205, 208f
  associated features 209–211, 209t
  barrier-disrupted skin 205, 206t
  children 205, 208f
  clinical features 205–211, 208f
    course of disease 205–207
    postinflammatory depigmentation 207f
    postinflammatory hyperpigmentation 1050t
    pruritus 113–114, 114f, 205, 209–210
  complications 211
    erythroderma 173t–174t, 176
    infection 211
    ocular 211
  definition 203, 204t
  diagnostic features 204t, 211
  diagnostic guidelines 204t
  differential diagnosis 212–213, 212t, 228t, 414t, 639t
  epidemiology 203–204
  and erythroderma 173t–174t, 176
  genetics 203f, 204–205, 204t, 205f, 832t–833t
  hand eczema 208f, 209, 211f
  history 203
  immunology 206t
  immunopathology 205
  infants 205, 207f, 221
  lichenified 208f
  pathogenesis 204–205
  pathology 211, 212f
  prurigo form 209
  regional variants 207–209
  treatment 213–216, 213t, 2077t
    adjunctive agents 215
    alternative/complementary therapy 215, 2213

avoidance of trigger factors 213–214
emerging therapies 215
immune globulin 2148t
interferons 2133
patient education 215–216
phototherapy 214–215
PUVA 2231
UVA_1 2224
UVB 2222
primary prevention 216
skin care 214
systemic agents 215
targeted molecular therapy 215
topical agents 214
atopic dirty neck 1065t
atopic eruption of pregnancy 440t, 445–447
clinical features 445, 445f–446f
differential diagnosis 445
epidemiology 445
history 445
pathogenesis 445
pathology 445
treatment 447
atopic keratoconjunctivitis 211
atopic march 203, 203f
atopic stigmata 210
atopic winter feet *see* plantar dermatosis, juvenile
Atopiclair cream 2156
Atopobium vaginae 1367t
atopy 203
atorvastatin
interactions 2190, 2191t
and linear IgA bullous dermatosis 498t
ATP-binding cassette transporter defects 800t–801t, 806
ATP2A2 gene mutation 888
ATP7A 785t
atretic encephalocele 1946t
atretic meningocele 1946t
atrial myxoma 377
atrichia 579, 786–787
atrophia maculosa cutis *see* anetoderma
atrophic connective tissue panniculitis 1646t, 1670
atrophic lichen planus 189–190, 190f
atrophic maculosa varioliformis cutis 1639, 1639f
atrophic polychondritis *see* relapsing polychondritis
atrophie blanché *see* livedoid vasculopathy
atrophoderma
follicular 1637–1639
of Moulin 1064f
of Pasini and Pierini 660, 1636–1637
hyperpigmentation 1050t, 1055
reticulata symmetrica faciei 1638
vermiculatum 577, 578t, 1638, 1638f
atrophy 4t–5t
palpation 6t
atropine, hypohidrosis/anhidrosis 595t
attractiveness 51–52, 52f
atypical antipsychotics, adverse reactions 129t
atypical dysplastic melanocytic nevus 1868–1871
clinical features 1869, 1869f
differential diagnosis 1870
epidemiology 1868–1869
history 1868
melanoma risk 1868t
pathology 1869–1870, 1869f
phenotypes 1868t
treatment 1870–1871, 1871f
atypical fibroxanthoma 1973, 1973f, 2449
atypical lymphocytic lobular panniculitis 1660t
atypical nevus *see* atypical dysplastic melanocytic nevus
atypical tuberous myxedema 696
Aureobasidum pullulans, panniculitis 1658t
auriculotemporal syndrome *see* Frey's syndrome
Auspitz sign 139
Austin disease *see* multiple sulfatase deficiency
Australian eucalyptus (*Eucalyptus radiata*) 2215t
autoantibodies 603–614, 604f
ADAMTS13 373
classical ANA assay 604–605
'normal' vs 'abnormal' values 605
technical aspects 604–605
clinical approach 610f–611f
clinical significance of ANA 604t, 605–606
clinical utility of laboratory testing 605–606, 609t
clinical value 606
drug-induced ANA/SLE 608
evaluation of positive ANA result 606, 610t
immunofluorescence patterns 605, 605f
induction by TNF-α inhibitors 608–609
phototherapy and ANA assay 606
"Sonthelmer's Corollary" 606
dermatomyositis 609–610, 609t
diagnosis versus disease activity monitoring 606
historical perspective 603–604
idiopathic inflammatory dermatomyopathies 609–610, 609t
lupus erythematosus 606f, 607–609, 607t
morphea 610t, 613
pemphigus 462, 466
rheumatic diseases with cutaneous manifestations 611t, 613
scleroderma 604–605, 613, 613t, 647–649
urticaria 293
autoantigens
blistering diseases 476t
ECM components as 1596, 1596t
and lichen planus 185
autoerythrocyte sensitization *see* Gardner-Diamond syndrome
autoimmune attack 186f
autoimmune chronic active hepatitis, and dermatitis herpetiformis 493t
autoimmune connective tissue disease 729–731
ANCA associated with 613t
nail abnormalities 1140
papulonodular mucinosis associated with 695–696, 695f
see also individual diseases
autoimmune liver disease, ANCA associated with 613t
autoimmune lymphoproliferative syndrome 906t
autoimmune polyendocrinopathy syndrome type 1 1101t
autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome 903t, 1027–1028
genetics 818t–819t
autoimmune progesterone dermatitis 447–448
autoimmunity 47, 47f, 47t
in atopic dermatitis 206t
Autologen 2552
autologous fat 2548t–2549t
autologous serum skin test 301f
Automeris io 1441t
autonomic dysreflexia 591
autosensitization dermatitis *see* disseminated eczema
autosomal dominant inheritance 786, 786t
autosomal recessive chronic granulomatous disease 910t
autosomal recessive congenital ichthyosis with hypotrichosis 813t
autosomal recessive exfoliative ichthyosis 852t–854t
autosomal recessive inheritance 786–787, 786t
Avena sativa see wild oats
Avitene 2464t, 2465
avobenzone 2199, 2200f
Avonex 2132t
avotermin 1625t
axillary granular parakeratosis *see* granular parakeratosis
axillary hyperhidrosis 588
axillary/inguinal freckling 932t–933t
axon reflex (local inflammatory) sweating 591t
Azadirachta indica see neem
azathioprine 2169–2171
adverse reactions 2169t, 2171, 2171f
acne 550t
contraindications 2171
dosage 2170–2171, 2171t
indications 2170t, 2171
atopic dermatitis 213t, 215
Behçet's disease 435t
bullous pemphigoid 483t–484t
chronic actinic dermatitis 1475
dermatomyositis 639t
linear IgA bullous dermatosis 499
lupus erythematosus 628t
pemphigus vulgaris 472, 472t
pyoderma granulosum 432t
vasculitis 402t
interactions 2171, 2191
mechanism of action 2170
metabolism 2171f
monitoring 2167t–2168t
and nail growth 1090t
pregnancy and lactation 2171
AZD6244 1887t
azelaic acid 2105, 2163
adverse reactions 2107t
dosage 2106t
formulations 2106t
indications 2106
acne vulgaris 555t–556t, 556, 2106t
alopecia areata 1103t
rosacea 567t, 2106t
mechanism of action 2106t
pregnancy and lactation 2106t, 2155t
trade names 2106t
azidothymidine-induced hyperpigmentation 1056t–1057t
azithromycin 2191t
dosage 2114t
indications
acne vulgaris 556t
bacillary angiomatosis 1209t
bartonellosis 1209t
cat scratch disease 1209t
chancroid 1386t
donovanosis 1389t
rickettial disease 1245, 1249t
SAPHO syndrome 437t
syphilis 1379t
prophylactic 2462t
azole antifungals, interactions 2190
aztreonam-induced erythroderma 176t

B cells 93–95
activation 94–95, 94f
B-cell lymphoma 2003–2015
clinical features 2004–2006
differential diagnosis 2010–2013, 2010f, 2040t
diffuse intravascular type
clinical features 2005–2006
pathology 2009, 2010f
diffuse leg type
clinical features 2005, 2005f
pathology 2007–2009, 2009f
epidemiology 2003–2004
etiology and pathogenesis 2004
follicle center type
clinical features 2004, 2004f
pathology 2006–2010, 2006f–2007f
history 2003
marginal zone type (MALT lymphoma)
clinical features 2004–2005, 2005f
pathology 2007, 2008f
monoclonal gammopathy 2013–2014, 2014t
pathology 2006–2010
precursor B lymphoblastic lymphoma/leukemia
clinical features 2006, 2006f
pathology 2009–2010, 2011f
treatment 2012f, 2013
WHO-EORTC classification 2004t
B-K mole *see* atypical dysplastic melanocytic nevus
babesiosis 1250, 1442
baboon syndrome 246
bacillary angiomatosis 1208–1210
HIV-related 1291
bacillary peliosis hepatitis 1209t
Bacillus anthracis 262, 1203–1204
see also anthrax
Bacillus cereus 1204
Bacillus polymyxa 2107
Bacillus subtilis 2107
bacitracin 2105t, 2107
adverse effects 2108
hypersensitivity 241t, 244
dosage 2108t
formulations 2108t
indications 2107–2108
mechanism of action 2108t
pregnancy and lactation 2108t, 2155t
trade names 2108t
baclofen, reflex sympathetic dystrophy 122t
bacteremia 1200, 1209t
bacterial diseases 1187–1218
and drug abuse 1514–1516, 1515t
Gram-negative bacteria 1204–1214
Bartonella spp. 1207–1210
brucellosis 1210
cutaneous malacoplakia 1211
ehrlichiosis and anaplasmosis 1244t, 1246t, 1250
Francisella tularensis 1211–1212
glanders 1210–1211
Haemophilus influenzae cellulitis 1212
melioidosis 1211
Neisseria meningitidis 1204–1206
Pseudomonas aeruginosa 1206–1207
rhinoscleroma 1212
Salmonella spp. 1213
Streptobacillus moniliformis 1213
Vibrio vulnificus 1213
Yersinia pestis 1213–1214
Gram-positive bacteria 1187–1204
Bacillus anthracis 1203–1204
Bacillus cereus 1204
Corynebacterium diphtheriae corynebacterium skin infections 1200–1203
Erysipelothrix rhusiopathiae 1204
listeriosis 1204
staphylococcal/streptococcal infections 1187–1200
HIV-related 1291
bacillary angiomatosis 1291
mycobacteria 1291
Staphylococcus aureus 1291
syphilis 1291
and lichen planus 184
normal skin flora 1187
spirochetes 1214
actinomycosis 1217–1218
Borellia burgdorferi 1214–1215
leptospirosis 1217
nocardiosis 1218
non-venereal treponematoses 1216–1217
see also individual conditions
bacterial folliculitis 1188–1190
clinical features 1189
diagnosis 1190
epidemiology and pathogenesis 1188–1189
treatment 1190
bacterial pseudomycosis *see* botryomycosis
Bacteroides bivius 1516
Bad protein 1762–1763
Bairnsdale ulcer *see Mycobacterium ulcerans*
Baker-Gordon peel 2501–2502, 2502f

Baker-Gordon solution 2501t
baker's itch 1445t
Balamuthia mandrillaris 1398–1399, 1399f
balanitis
  candidal 1269t
  xerotica obliterans *see* lichen sclerosus
Balsa-Derm 341
balsam of Peru 243
  exposure information sheet 240t
  hypersensitivity 241t, 243
  systemic contact dermatitis 246t
bamboo hair 841t–842t, 1095f, 1110f, 1111
banana 275t
Band-aids 2396
band-like infiltrates 18f
Bandler syndrome 1857t
Bang's disease *see* brucellosis
Bannayan-Riley-Ruvalcaba syndrome 932t–933t, 1857t
  lipoma 1985
  genetics 816t
bar soap 2479
Barber-Say syndrome 1116t
Barber's interdigital pilonidal sinus *see* pilonidal cyst
barber's itch *see* pseudofolliculitis barbae
barbiturates
  adverse reactions 336t
    Stevens-Johnson syndrome/toxic epidermal necrolysis 325t
  cutaneous reactions in abuse 1514t, 1518t
Bardet-Biedl syndrome 750
bariatric surgery 750–751
barium dermatosis 1499t
Barmah Forest virus 1359–1361
Barraquer-Simons syndrome 818t–819t, 1665t
  clinical features 1669–1670, 1669f–1670f
  genetics 818t–819t
  pathogenesis 1666
  treatment 1673
barrier creams 106t, 258
barrier function of skin, failure of 47–48, 105
  dehydration and infection 48, 48f
  toxic chemicals 47–48, 48f
  UV radiation 48, 49f
Bart syndrome 510
Bart-Pumphrey syndrome 874t, 878, 878f
  genetics 803t–804t
Bartonella spp. 1207–1210
  bacillary angiomatosis 1208–1210
  bartonellosis 1207–1208, 1209t
  cat scratch disease 1208
Bartonella bacilliformis 1207–1208, 1209t
Bartonella henselae 1208–1210, 1209t
  secondary cutaneous vasculitis 390t
Bartonella quintana 1208–1210, 1209t
bartonellosis 1207–1208, 1209t
basal cell carcinoma 1457, 1463, 1764, 1768–1769, 1784–1788, 2202
  action spectrum 2201t
  anogenital 1179
  cancer 1768
  clinical features 1784–1788
    basosquamous 1787–1788
    fibroepithelioma of Pinkus 1787, 1787f
    micronodular 1788
    morpheaform 1786–1787, 1787f
    nodular 1785–1786, 1786f, 1787t
    pigmented 1787f
    superficial 1786, 1786f
  cryosurgery 2286, 2288f
  dermoscopy 36f–37f
  epidemiology 1774
  histologic simulators 1788, 1790t
  HIV-related 1296
  in vivo imaging 1788
  incidence 1774, 1774t
  linear 945t–946t, 955
  metastasis 1768–1769, 1769f
  nail bed 2440t
  nevoid *see* Gorlin syndrome
  pathology 1788, 1789f
  precursors 1768
  radiotherapy 2294–2295, 2294f–2295f
    adjuvant 2295
    definitive 2294
  treatment
    electrosurgery 2307f
    imiquimod 2135
    interferons 2132
    Mohs surgery 1790–1791, 2446–2447, 2447f–2448f, 2447t, 2450f
    NCCN guidelines 1788
    photodynamic therapy 2244–2245, 2245f–2246f
    radiotherapy 1791
  see also non-melanoma skin cancer
basal cell nevus syndrome *see* nevoid basal cell carcinoma syndrome
basal keratinocytes 55
basaloid cells 1638, 1788
basaloid follicular hamartoma 955, 1790t
Basan syndrome 526t–528t
basement membrane zone 449–459
  adhesion proteins in 449t
  anchoring fibrils and sublamina densa 455–456
    basement membrane remodeling 456
    microfibrils 455–456
    microthread-like fibers 456
    type VII collagen 455
  in bullous diseases 456–458, 456t
    autoimmune subepidermal blistering diseases 456–457, 456f–457f, 457t
    inherited subepidermal blistering diseases 457–458, 458t
  hemidesmosome-anchoring filament complexes/integrins 450–452
    bullous pemphigoid antigen 1 450–451
    bullous pemphigoid antigen 2 451–452
    integrins 452
    plectin 450
    tetraspan CD151 452
  lamina densa 452–454
    heparan sulfate proteoglycans 454
    laminins 452–453, 452f, 453t
    nidogen 454, 455f
    type IV collagen 453–454, 454f
  'laminated' model 450f
  molecular interactions in 451f
  origin of 450
  ultrastructure 450f
basic fibroblast growth factor 2318
basidiobolomycosis 1266
Basidiobolus ranarum 1266
basil (*Ocimum basilicum*) 2215t
basiliximab 2149t
  lichen planus 195t, 196
basophils 83, 423
bath soap 2480t
bathing suit ichthyosis 850
bathing-trunk nevus *see* congenital melanocytic nevus
battered child syndrome *see* child abuse
bax gene 1765t
BAX protein 1762–1763
Bazex syndrome 1638, 1771
  differential diagnosis 228t
  genetics 813t
  hypohidrosis in 595
  and NMSC 1776–1777
  paraneoplastic 764t–765t, 770t
Bazex-Dupré-Christol syndrome *see* Bazex syndrome
Bazin, Ernest 1648
Bazin's hydroa vacciniforme *see* hydroa vacciniforme
BCG inoculation 29t–33t, 1233, 1233f–1234f, 1234t
bcl-2 gene 1761t, 1765t
Bcl-2 protein 29t–33t
Bcl-6 protein 29t–33t
BCNU *see* carmustine
Bean syndrome *see* blue rubber bleb nevus syndrome
bearberry 2207t
beard hemangioma 1698, 1700f
Beare-Stevenson cutis gyrata syndrome 767f
  cleft lip/palate 1005t
  genetics 818t–819t
Beau's lines 1090, 1130
  drugs causing 1141t
beauty 51–52, 52f, 2473–2478
  evaluation of 2473–2474, 2473f–2474f, 2474t
  golden ratio 2474
  ideal brow position 2477f
  Phi mask 2475f
  see also facial aging
Beaver handle 2360f, 2362
becaplermin gel 1704
Becker's melanosis 1119, 1119f, 1853–1854
  clinical features 1853, 1853f
  differential diagnosis 1853–1854
  epidemiology 1853
  pathogenesis 1853
  pathology 1853
  treatment 1854
Becker's nevus syndrome 2270–2271
bedbugs 1438, 1438f
  as vectors of Chagas' disease 1438
bee stings 1577f
beeswax 2481t
Béguez César-Steinbrinck syndrome *see* Chédiak-Higashi syndrome
behavioral therapy 2216
Behçet's disease 431–434
  ANCA in 613t
  anogenital manifestations 433f, 1183
  clinical features 433, 776t–778t
    mucocutaneous 433, 433f
    oral 433f, 1159
    systemic 429f, 433, 433f, 433t
  diagnosis 434, 434t
  differential diagnosis 433
  epidemiology 432
  and erythema multiforme 320t
  and erythema nodosum 1644t
  history 432
  neonates 524t–525t, 534–536, 534f
  pathogenesis 432–433
  pathology 434
  treatment 434, 435t
    interferons 435t, 2133
  ulceration 1745t
bejel *see* syphilis, endemic
belimumab 2149t
  lupus erythematosus 628t
bemotrizinol 2199
benign acantholytic dermatosis *see* Grover's disease
benign cephalic histiocytosis 1535–1536
  antigenic markers 1533t
  clinical features 1530t–1531t, 1536, 1536f
  differential diagnosis 1536
  epidemiology 1536
  history 1535
  pathogenesis 1536
  pathology 1536
  treatment 1536
benign epidermal tumors 1795–1815
  acantholytic (dyskeratotic) acanthoma 1807
  acanthosis nigricans *see* acanthosis nigricans
  acrokeratosis verruciformis 1804
  clear cell acanthoma 1805–1806
  clear cell papulosis 1813–1814
  confluent and reticulated papillomatosis 1812–1813
  cutaneous horn 1805
  dermatosis papulosa nigra 1799–1800
  epidermal nevus 1809–1810
  epidermolytic acanthoma 1808
  Flegel disease 1803–1804
  inflammatory linear verrucous epidermal nevus 1810–1811
  inverted follicular keratosis 1806
  large cell acanthoma 1808–1809
  lichenoid keratosis 1798–1799
  nevus comedonicus 1811–1812
  porokeratosis 1801–1803
  seborrheic keratosis 1795–1798
  stucco keratosis 1800–1801
  warty dyskeratoma 1806–1807
benign fibrous histiocytoma *see* dermatofibroma
benign hypergammaglobulinemic purpura *see* Waldenström's hypergammaglobulinemic purpura
benign lichenoid keratosis *see* lichenoid keratosis
benign lymphocytic infiltration of skin *see* lymphocytic infiltrate of Jessner
benign melanocytic neoplasms 1851–1880
  atypical dysplastic melanocytic nevus 1868–1871
  Becker's melanosis 1119, 1119f, 1853–1854
  blue nevus 1860–1861
  café-au-lait macules *see* café-au-lait macules
  combined nevus 1876–1877
  common acquired melanocytic nevi 1861–1863
  congenital melanocytic nevus 1871–1874
  dermal melanocytosis 1858
  ephelides 1851
  halo nevus 1875–1876
  lentigo simplex and mucosal melanotic lesions 1855–1858
  melanocytic nevi of acral skin 1864
  melanocytic nevi of genital and flexural skin 1863–1864
  nevus of Ota 1858–1859
  nevus spilus 1874–1875
  partial unilateral lentiginosis 1856
  pigmented spindle cell nevus 1867–1868
  recurrent melanocytic nevus 1877–1878
  solar lentigenes 1854–1855
  Spitz nevus/tumor 1864–1867
benign migratory glossitis *see* geographic tongue
benign migratory stomatitis *see* geographic tongue
benign mucous membrane pemphigoid *see* cicatricial pemphigoid
benign tumors *see* benign epidermal tumors; benign melanocytic neoplasms
benoxaprofen
  adverse reactions
    hypertrichosis 1118t
    lichen planus 185t
benzalkonium chloride 242t, 251
benzathine penicillin, syphilis 1379t
benzene 253t–254t
benznidazole 1402t–1403t
benzocaine 2156, 2347t
  hypersensitivity 242t
benzocaine/lidocaine/tetracaine 2347t
benzocaine/tetracaine/butamben 2347t
benzodiazepines 133
  abuse 1511
  interactions 2124t, 2529t
benzoic acid 252, 2105
benzoin (*Styrax benzoe*) 2215t
benzophenones 2199, 2200f
benzoyl peroxide 255
  adverse reactions 2107t
  dosage 2106t
  formulations 2106t
  indications 2106
    acne vulgaris 555t–556t, 556, 2106t
    folliculitis 573t
    perforating disease 1604t
    rosacea 567t, 2106t
  mechanism of action 2106t
  pregnancy and lactation 2106t, 2155t
  trade names 2106t
benzyl alcohol, head lice 1428t, 1429
benzyl cinnamate 2197
benzyl salicylate 2197
Berardinelli-Seip syndrome 818t–819t, 1665t

anabolic syndrome 1667
clinical features 1667, 1667f, 1667t
hypertrichosis 1117t
genetics 818t–819t
metabolic disturbances 1665t
pathogenesis 1664
bergamot (*Citrus bergamia*) 2215t
bergamot orange 280
bergapten 2224–2225
Bergeyella zoohelcum 1450t
beriberi 740t–742t
Berlin syndrome 1072t–1073t
berlock dermatitis 281
berry rue 280t
beryllium 253t–254t
dermatosis 1499t
foreign body reaction 1574t, 1579
histopathology 1576t
Besnier's 'prurigo gestationis' *see* atopic eruption of pregnancy
β-blockers
adverse reactions
erythroderma 176t
nail changes 1141t
pruritus 120t
secondary cutaneous vasculitis 390t
interaction with lidocaine 2529t
β-carotene 746t
β-hydroxy acids 2488–2489, 2489f
β-lactam antibiotics
adverse reactions 338t, 343
erythroderma 176t
Betacaine LA *see* prilocaine/lidocaine
Betadine *see* povidone-iodine
betamethasone 245t, 2079t
pharmacology 2076t
betamethasone dipropionate 245t, 2079t
absorption 2069t
betamethasone valerate 245t, 2079t
Betaseron 2132t
betel leaf-induced dyschromatosis 1072t–1073t
betel nuts 1517
bevacizumab 1688, 2149t
bexarotene 2089, 2092–2093
formulations 2097t
indications
cutaneous T-cell lymphoma 2094, 2097t
parapsoriasis 159
pharmacologic features 2092t
structure 2090f
Biafine 2374
Bichet's fat pad 1667f
bicho de pie *see* tungiasis
Bier spots 1047, 1756, 1756f
Bifidobacterium spp. 2211
biglycan 1592t
bilberry 2212t
bile acid-binding resins 1554t–1555t
bile duct cancer, metastatic 2049t, 2053t
biliary cirrhosis, pruritus in 112t
bilobed transposition flap 2411–2412, 2412f–2413f
bimatoprost 1119–1120, 2484
bimoctrizole 2200f
binding injuries 1522, 1522f
Biobrane 2375t–2376t
Bioclusive 2369
biogenesis of lysosome-related organelles complex (BLOCs) 1014f
bioinformatics 72f
Biolex Wound Gel 2372
biopsy 2, 12–16, 2381–2397
complications 2396–2397, 2396t
dog-ear repair 2392–2394, 2393f–2395f, 2397
future trends
hemostasis 2384, 2384f, 2384t
indications and contraindications 2387
information obtained from 14t–15t
nail 2436t, 2438–2441
lateral longitudinal 2441, 2441f
nail bed 2439, 2440t
nail matrix 2439–2440, 2441f
patient preparation 2383
peroperative history 2387–2388, 2387t
postoperative care 2396
site preparation and anesthesia 2383–2384, 2383f, 2383t
site selection 12, 13f, 2381, 2381t
specimen handling 15–16, 2382, 2382t
techniques 12–15, 14f, 14t–15t
curettage 2381, 2382t, 2388, 2388f
excisional biopsy 2381, 2382t, 2391–2392, 2391f, 2391t, 2393f
incisional biopsy 2382, 2382t, 2390–2391, 2390f
punch biopsy 13, 2382, 2382t, 2389–2390, 2390f, 2390t
saucerization 12–15, 2381, 2382t, 2388–2389, 2389f
selection of 2381–2382, 2382t
shave biopsy 12–15, 2381, 2382t, 2388–2389
snip or scissors biopsy 2381, 2382t, 2388, 2388f
variations/unusual situations 2395–2396
wound closure 2384–2387, 2385f
biopsy blades 2359
biotin 744t–745t
deficiency 740t–742t, 749f
biotinidase deficiency
genetics 810t–811t
4,4′-bipyridyl, and NMSC 1775t
Birbeck granules 84, 84t
bird's eyes 1312
Birt-Hogg-Dubé syndrome 1831f
clinical features
pulmonary disease 778t–779t
renal disease 780t–781t
genetics 816t
birthmarks *see* infantile hemangiomas
bismuth
adverse reactions
hyperpigmentation 1056t–1057t
lichen planus 185t
dermatosis 1499t
bisoctrizole 2199, 2200f
bisphosphonates, SAPHO syndrome 437t
bites 1435–1453
centipedes and millipedes 1449
dog and cat 1450
human 1450t, 1522–1523, 1523f
insect 1435–1437
leeches 1450–1451
snakes 1449–1450
spiders 1446
ticks 1440–1442
Bitot's spots 740t–742t
bittersweet nightshade 2207t
bivalirudin 364t
Björnstad syndrome 1104t, 1111
Black cat 2162t
black currant seed oil 2207t
black hairy tongue *see* hairy tongue
black heel and palm 1501–1502
clinical features 1502, 1502f
differential diagnosis 1502
epidemiology 1502
history 1502
pathogenesis 1502
pathology 1502
sports-related 1506t
treatment 1502
black lesions 6t–7t
black mustard 278t
black pepper (*Piper nigrum*) 2215t
black piedra 1252, 1252f, 1252t
black-eyed Susan 285t
black-spot reaction 282, 285
blacklegged tick (*Ixodes scapularis*) 1244t, 1245f
bladder cancer, metastatic 2049, 2052f, 2053t
BLAISE *see* lichen striatus
Blaschkitis 956
Blaschko, Alfred 943
Blaschko's lines 8, 943, 943f–944f, 946t–947t
hyperpigmentation along 841t–842t, 1062–1064, 1063t
linear cutaneous lesions following 948f
blastic plasmacytoid dendritic neoplasm 2044–2045
clinical features 2045, 2045f
differential diagnosis 2045
history and epidemiology 2044
pathogenesis 2045
pathology 2045, 2045f
treatment 2045
Blastomyces dermatitidis 1274
panniculitis 1658t
blastomycosis 1274–1277
Brazilian *see* paracoccidioidomycosis
clinical features 1276, 1276f
pulmonary disease 778t–779t
differential diagnosis 1276
epidemiology 1274–1276
and erythema nodosum 1644t
pathogenesis 1276
pathology 1276
South American *see* paracoccidioidomycosis
treatment 1277
blastomycosis-like pyoderma 1206
Blau syndrome 807f
genetics 818t–819t
bleeding
intraoperative 2463–2465, 2464f–2465f
postoperative 2467–2469, 2467f–2468f
potential for 2459–2461
bleomycin 2172t
adverse reactions
flagellate pigmentation 1056t–1057t, 1061, 1061f
hyperpigmentation 349t
nail changes 349t, 1141t
neutrophilic eccrine hidradenitis 344
sclerodermoid syndromes 650t, 654
blepharitis 565f
blepharophyma 564t
blisters 841t–842t
coma *see* coma blisters
delayed postburn/postgraft *see* delayed postburn/postgraft blisters
edema 517t, 520–521
friction *see* friction blisters
sucking 526t–528t, 530
blister beetles 1439
Blister Film 2370
blister plant 280t
blistering distal dactylitis 1191
Bloch-Siemens syndrome *see* incontinentia pigmenti
Bloch-Sulzberger syndrome *see* incontinentia pigmenti
BLOCs *see* biogenesis of lysosome-related organelles complex
blood monocytes 2319–2320
blood vessels
markers for 1686t
occlusion 49
structure and function 1679–1681, 1679f–1680f
bloodroot 2211
Bloom syndrome 1476t–1477t, 1478–1479
clinical features 932t–933t, 1479
epidemiology 1478
genetics 816t
history 1478
pathogenesis 1478–1479
treatment 1479
blue lesions 6t–7t
blue nevus 1860–1861
cellular 1860
clinical features 1860–1861, 1860f
common 1860
differential diagnosis 1861
epidemiology 1860
epithelioid 1860
malignant 1861, 1895–1896, 1897f
pathogenesis 1860
pathology 1860f, 1861
treatment 1861
blue rubber bleb nevus syndrome 772f, 1721, 1722f
and gastric hemorrhage 773t–774t
blue vitiligo 1026
blueberry muffin baby 2038, 2041f
blunt trauma 1522
blushing 1751
BMS-582949 2147t
Bockhart's impetigo 1189
bodily fluids, sensitivity to 256
see also diaper dermatitis
body dysmorphic disorder 129–130, 130t
body lice 1430–1431
clinical features 1431, 1431f
differential diagnosis 1431
epidemiology 1431
pathogenesis 1431
pathology 1431
treatment 1431
body wash 2479
Bohn's nodules 1819
bone fragility 1593t
bone marrow suppression 2134
bone marrow transplantation 922f, 1025t, 1862t
bone morphogenetic proteins 1086, 1589–1590, 2314
bone pain, retinoid-induced 2099–2101
bone wax 2464t
Bonnet-Dechaume-Blanc syndrome 1724f, 1725
borage 277t, 2207t
Boraginaceae 277t
Borago officianalis see borage
Borellia burgdorferi 29t–33t
boric acid 2155t
boron dermatosis 1499t
Borrelia burgdorferi
acrodermatitis chronica atrophicans 1215, 1216f
B-cell lymphoma 2003–2005, 2011
borrelial lymphocytoma 1215
erythema migrans 313
idiopathic atrophoderma of Pasini and Pierini 1636
Lyme disease 1214–1215, 1215t
lymphocytic infiltrate of Jessner 2037
panniculitis 1658t
borrelial lymphocytoma 1215
bortezomib, scleromyxedema 690
bosentan 651
botanicals 2205–2211, 2207t
adverse reactions 2211
aloe vera 2205
arnica 285t, 2206
capsaicin 274t, 278t, 279, 2206
chamomile 274t, 285t, 2206–2210
English walnut leaf 2206t
escharotics 2211
honey 2205
horse chestnut seed extract 2210
insect repellents 1437t
licorice root 2211
marigold 285t, 287f, 2205–2206
olive oil/olive leaf extract 2211
propopolis 2213f
tea 2210–2211, 2213f
white oak bark 2207t
witch hazel 2207t
see also plant dermatoses
Bothriocroton hydrosauri 1244t
Botox *see* botulinum toxin
botryomycoma *see* pyogenic granuloma
botryomycosis 1199
botulinum toxin 2561–2572
applications 2562–2570
adjunctive use 2569–2570
brow lift and shaping 2564
'bunny lines' 2563f, 2565, 2565f
crow's feet 2563–2564, 2563t, 2564f
facial asymmetry 2567, 2567f
glabellar frown lines 2562–2563, 2563f, 2563t
Hailey-Hailey disease 895
horizontal forehead lines 2563t, 2564, 2564f–2565f

horizontal neck lines 2566t, 2569, 2569f
hyperhidrosis 540, 593f, 594t, 2570, 2570f
hypertrophic orbiculari oculi 2561, 2564–2565, 2565f
marionette lines 2566t, 2568
masseteric hypertrophy 2566t, 2568, 2568f
mental crease 2566t, 2568, 2568f
migraine 2570
mouth frown 2566t, 2567–2568, 2567f
nasal flare 2566t
nasal tip droop 2566t
nasolabial folds 2565–2566, 2566t
peau d'orange (apple dumpling) chin 2568, 2568f
platysmal bands 2566t, 2569, 2569f
upper gum show 2566–2567, 2566t
vertical lip rhytides 2566, 2566f, 2566t
BTX-A 2561–2562, 2562t–2563t
BTX-B 2561, 2562t
complications 2570–2571, 2571f
dosing 2562
formulations and clinical use 2562f, 2562t
future trends 2571
postprocedural care 2570
properties of 2561
safety 2571
Bourne's 'toxaemic rash of pregnancy' *see* polymorphic eruption of pregnancy
Bourneville disease *see* tuberous sclerosis
boutonneuse fever 1243, 1244t, 1246t, 1248
Bovie, William 2304
bovine collagen 1574t, 1575f, 1581t, 1582, 2550–2554, 2550f
bowel-associated dermatosis-arthritis syndrome 435–436
associated conditions 435t
clinical features 436, 436f
differential diagnosis 436
history 435
pathogenesis 435–436
pathology 436
treatment 436, 436t
bowenoid papulosis 1309, 1310f, 1779–1780, 1779f
see also Bowen's disease
Bowen's disease 1177–1178, 1769
clinical features 1178, 1178f, 1779–1780
cryosurgery 2286
dermoscopy 37f
differential diagnosis 1178
epidemiology 1177
nail bed 1146, 1146f, 2440t
paraneoplastic 764t–765t
pathogenesis 1177
pathology 1177–1178, 1783–1784, 1784f
treatment 1178
imiquimod 2135
photodynamic therapy 2245, 2246t
see also non-melanoma skin cancer
box jellyfish 1452
BP180 antigen 481f
BP230 antigen 481f
BPAG *see* bullous pemphigoid antigen
brachial cutaneous dyschromatosis, acquired 1074
brachioradial pruritus 120–121, 120f
brachyonychia 1130f, 1135
brachytherapy 2292
bradykinin 2205
in itch 119
brain-derived neurotrophic factor 104, 1084f
brain-like heterotopia *see* nasal glioma
branchial cleft
cyst 1006
sinuses/fistulae 1006
branchio-oculo-facial syndrome
cleft lip/palate 1005t
genetics 818t–819t
Brassica nigra see black mustard
Brassica oleraceae 'botrytis' see cauliflower
Brassica oleraceae 'capaitata' see cabbage
Brassicaceae 278t
Brauer lines 1003t
Braun-Falco-Marghescu syndrome 1638
Brazilian blastomycosis *see* paracoccidioidomycosis
Brazilian pemphigus *see* pemphigus
Brazilian pepper tree 282t, 283
breakfast, lunch and dinner sign 111f
breast cancer
metastatic 1790t, 2049, 2052f, 2053t
histology 2054f
and Mondor's syndrome 367
breast hemangioma 1696–1697
Brevibacterium epidermidis 1187t
briakinumab 2147t
Bridges-Good syndrome *see* chronic granulomatous disease
Brill-Zinsser disease 1243, 1244t, 1246t
brittle hair syndrome 1478
brittle nails 1130f, 1141t, 1142
broad beta disease 1549t
Brocq's alopecia 1096t, 1108, 1109f
bromelain 278t, 2468
Bromeliaceae *see* pineapple
bromhidrosis 598t
apocrine 542, 598t
eccrine 541, 598t
liposuction for 2527t
bromides, and acne 550t
2-bromo-2-nitropropane-1,3-diol 242t
bromocriptine 647t
bromoderma 344, 519t
bromphenacylbromide 2067
bronchogenic cyst 1726–1727, 1824
bronze diabetes *see* hemochromatosis
Brooke-Spiegler syndrome 813t, 955
Broussonetia papyrifera see paper mulberry
brow lift and shaping, botulinum toxin 2564
brown dog tick *see* rhipicephalus ticks
brown lesions 6t–7t
brown recluse spider 383, 1447f–1448f
Brown-Brenn stain 26, 27t–28t
Brucella spp., secondary cutaneous vasculitis 390t
Brucella abortus 271t
Brucella mellitensis 271t
Brucella suis 262
brucellosis 1210, 1211f
occupational 271t
Brugia malayi 1416
Brugia timori 1416
bruising
herbs used to prevent 2207t
physical abuse 1521, 1522f
Brunsting-Perry cicatricial pemphigoid 485
Brussels sprouts 2207t
BT-061 2147t
buba *see* yaws
"bubble hair" 1110, 1110f
bubonic plague 1214
buccal fat pad 1667f, 1669f
buccal nerve 2340
buccinator muscle 2335
buck moth caterpillar 1441t
buckle injuries 1522, 1522f
Buckley syndrome *see* hyper-IgE syndrome
buckwheat 2207t
budesonide 242t, 245t
Buerger's disease, ANCA in 613t
bulimia 750
bulla-spread phenomenon 467
bullae 3t–4t, 841t–842t
in drug abuse 1518f
bullosis diabeticorum 515, 768t
clinical features 515, 516f, 768f
differential diagnosis 515, 517t
epidemiology 515
history 515
pathogenesis 515
pathology 515
treatment 515
bullous acrokeratotic poikiloderma of Kindler and Weary *see* Kindler syndrome
bullous congenital ichthyosiform erythroderma *see* epidermolytic ichthyosis
bullous dermolysis of newborn 501, 502f
bullous drug eruptions 518, 519t
differential diagnosis 517t
bullous eruption, drug-induced 1518t
bullous erythema multiforme 519
bullous impetigo 524t–525t
genetics 832t–833t
neonates 529f
bullous insect bite reactions 518–520
clinical features 519, 519f
differential diagnosis 517t, 519
epidemiology 518
pathogenesis 518
pathology 519
treatment 519–520
bullous lichen planus 190, 190f
bullous mastocytosis 536f, 1995
bullous morphea 660–661
bullous pemphigoid 1–2, 2f, 45t, 456t, 475–490
anogenital 479f, 1185
associated diseases 478–479
autoantibodies 475–477
autoantigens 456t, 476t
blister formation 476f
in children 478, 479f
clinical features 20f, 477–478
bullous phase 477f, 478
clinical variants 478, 479t
non-bullous phase 477, 477f–479f
diagnosis 479–482
immunochemical studies 481, 481f
immunoelectron microscopy 480, 481f
immunofluorescence 480, 480f
light microscopy and electron microscopy 479–480
differential diagnosis 308t–310t, 414t, 481–482, 495t
drug-induced 347, 479
epidemiology 475
and erythroderma 172t–173t
history 475
immunoreactants in 457t
neonates 526t–528t
pathogenesis 475–477
humoral and cellular responses 475–477
prognosis 482
treatment 482, 483t–484t
immune globulin 2148t
urticarial 477f, 480f
bullous pemphigoid antigen 1 47t, 450–451, 463–464
bullous pemphigoid antigen 2 47t, 451–452
cleavage ectodomains 497f
bullous small vessel vasculitis 518
differential diagnosis 517t
bullous systemic lupus erythematosus 456t, 623f
autoantigens 456t, 476t, 1596t
differential diagnosis 489
bumetanide 479
'bunny lines', botulinum toxin 2563f, 2565, 2565f
bunyaviruses 1360t
bupivacaine 2344t
cardiac toxicity 2346
interactions, lidocaine 2529t
Burkholderia cepacia, chronic granulomatous disease 910t
Burkholderia mallei 1210–1211
Burkholderia pseudomallei 1211
burning bush 280t
burning mouth syndrome 121
burning scalp syndrome 121
burns
airbag 1491–1492
chemical 1497
and drug abuse 1517
electrical 1496–1497
fluoroscopy 1491f
MRI 1491
postburn blisters 520
postburn pruritus 117
thermal 1487–1489, 1488f, 1522–1523, 1523f
clinicopathological features 1489t
rule of nines 1489f
thermoelectrical 2309
ulceration 1745t
Burow's grafts 2426
Burow's solution 2162t
Burow's triangle displacement flaps 2401–2404, 2402f
dorsal nasal flap 2407, 2407f
double tangent advancement flaps 2404, 2405f–2406f
helical advancement flaps 2404–2406, 2406f
rotation flaps 2402–2404
single tangent advancement flaps 2402–2404, 2403f–2405f
wedge closure of lip 2407–2408, 2408f
burrowing flea *see* tungiasis
Buruli ulcer *see Mycobacterium ulcerans*
Buschke-Fischer-Brauer keratoderma *see* punctate palmoplantar keratoderma
Buschke-Löwenstein tumor 1310, 1311f–1312f, 1312
histology 1311f
pathology 1312
Buschke-Ollendorf syndrome *see* connective tissue nevus
buspirone
anxiety disorder 133
and eccrine sweating 590t
interactions 2124t
busulfan
adverse reactions
alopecia 349t
eccrine squamous syringometaplasia 349t
hyperpigmentation 349t, 1056t–1057t
mucosal hyperpigmentation 349t
pruritus 120t
butcher's broom 2207t
butcher's warts 271t, 1308
butenafine
formulations 2118t
pregnancy and lactation 2118t
trade names 2118t
Buthus occitanus tunetanus 1449t
butoconazole
formulations 2118t
mucocutaneous candidiasis 1269t
pregnancy and lactation 2118t, 2155t
trade names 2118t
butorphanol
adverse reactions, pruritus 120t
pruritus 106t
cholestatic 119t
buttercups 278t, 279
butterfly sign 112, 115f
buttonhole sign 1949–1950
p-tert-butylphenol formaldehyde resin 242t
Bywater's lesions 681, 762f

C fibers 100t, 102f–103f
itch transmission 102f–103f
C-ANCA
approach to patient 611f
disorders associated with 613t
C1 esterase inhibitor 358–359
C1 esterase inhibitor deficiency 294
treatment 305
C1 inhibitor 909t
C1q 908t–909t
C1r 908t–909t
C1s 908t–909t
C2 909t
deficiency 907–908, 909t
C2a 908t
C2b 908t

C3 81, 909t
in pemphigoid gestationis
C3 convertase 81
C3a 81, 908t
C3b 81, 908t
C3(H2O) 908t
C4 909t
C4a 81, 908t
C4b 908t
C5
deficiency 909t
dyfunction 909t
C5a 81, 83, 908t
C5a receptor 83
C5b 81, 908t
C6 81, 909t
C7 81, 909t
C8 81
C8α 909t
C8β 909t
C9 81, 909t
CA125 636t, 2053t
cabbage 275t
Cactaceae 277t
cactus spines, foreign body reaction 1574t, 1579–1580
histopathology 1576t
pathology 1579–1580
CADASIL 1713t
cadexomer-iodine polymer 2368t
cadherins
in pemphigus 463
see also individual cadherins
CADM-140 609–610
café-au-lait macules 925, 927t, 1055, 1851–1853
clinical features 927f, 1852, 1852f
diagnosis 931f
differential diagnosis 930–931, 1852–1853
disorders associated with 932t–933t
epidemiology 1852
pathogenesis 1852
pathology 1852
treatment 1853
laser therapy 2269–2270
caffeine, and eccrine sweating 590t
Caffey, John 1521
CAHMR syndrome 1116t
cajeput (*Malaleuca leucondendron*) 2215t
Calaband 2369
calaguala *see* anapsos
calamine lotion 2162t
calcaneal petechiae *see* black heel and palm
calcific arteriolopathy *see* cutaneous calciphylaxis
calcifying aponeurotic fibroma 1971, 1971f
calcifying and ossifying disorders 729–736
cutaneous ossification (osteoma cutis) 733–735, 734f–735f
dystrophic calcification 729–731
autoimmune connective tissue disease 729–730, 730f
genetic disorders 730
infections 730
neoplasms 731
panniculitis 730
iatrogenic calcification 733
idiopathic calcification 732–733
idiopathic calcified nodules of scrotum 732–733
milia-like calcinosis 733
subepidermal calcified nodule 733
tumoral calcinosis 733
laboratory evaluation 735, 736t
metastatic calcification 731–732, 732f
hypervitaminosis D 732, 733t
milk-alkali syndrome 732
renal disease 731–732, 731f–732f
secondary cutaneous ossification 735
calcineurin inhibitors
adverse reactions 2185t
indications
atopic dermatitis 213t, 214
granuloma annulare 1566t
lichen planus 195t, 1175t
lupus erythematosus 628t
morphea 667t, 668
psoriasis 150
sarcoidosis 1563t
topical *see* pimecrolimus; tacrolimus
vitiligo 1028–1029
calcinosis 635
calcinosis cutis 8, 709t, 730f
scleroderma 646, 646f
calcinosis universalis 729
calciphylaxis 8, 9f, 731, 732f, 1749f
cutaneous 383, 775f
treatment 732
calcipotriene 2160f, 2161t
adverse reactions 2155t
dosage 2161t
indications
prurigo nodularis 115
psoriasis 149t, 1137t
pregnancy and lactation 2155t
calcipotriol, psoriasis 149t
calcitonin 700t
reflex sympathetic dystrophy 122t
calcitonin gene-related paptide 84
calcitriol 2160f, 2161t
dosage 2161t
Hailey-Hailey disease 895
psoriasis 149t, 153t
calcium channel blockers
adverse reactions 338t
hypohidrosis/anhidrosis 595t
interactions 2124t, 2190, 2191t
Raynaud's phenomenon 651
calcium channel deficiency 920t
calcium, in epidermal differentiation 830–831
calcium gluconate 265
calcium hydroxyapatite 1581t, 2554–2555, 2556f–2557f
calcium oxalate 274t, 278t, 279
calcium oxide 253t–254t
calcium pump 887f
defects 800t–801t, 805–806
calcium pyrophosphate disease *see* pseudogout
caldesmon 29t–33t
calendula *see* marigold
Calendula officionalis see marigold
California disease *see* coccidioidomycosis
California glory 277t
callosity *see* corns and calluses
calnexin 87f
calotropis 2207t
Calotropis procera see calotropis
calreticulin 608
Caltha spp. *see* marsh-marigold
Calymmatobacterium (Klebsiella) granulomatis 1276t
Camellia sinensis see tea
camouflage makeup 2484, 2484t, 2490t
manufacturers 2490t
cAMP/AMP-activated protein kinase pathway defects 800t–801t
Campbell-De Morgan spot *see* cherry angioma
camphor
insect bites/stings 1436
pruritus 2157t
Camptotheca acuminata Decne 2213–2214
Campylobacter spp. 1367t
secondary cutaneous vasculitis 390t
canakinumab 294, 2149t
Canale-Smith syndrome *see* autoimmune lymphoproliferative syndrome
Cananga odorata 274t
cancer 1759
basal cell carcinoma *see* basal cell carcinoma
increased susceptibility to 841t–842t
metastatic *see* metastases, cutaneous and psoriasis 146
skin gene therapy 72–75, 76t–77t, 77f
squamous cell carcinoma see squamous cell carcinoma
see also tumors
cancer stem cells 1764
cancer vaccines 1909
Candida spp. 1251t
chronic granulomatous disease 910t
folliculitis 573t
panniculitis 1658t
tinea pedis 1261
see also candidiasis
Candida albicans 375, 1367t
superficial mycoses 1251t
Candida folliculitis 573t
Candida tropicalis 1279f
candidiasis 1279f, 1280
anogenital 1183–1184
recurrent 1184
chronic localized 903t
chronic mucocutaneous 818t–819t, 900t, 902–904, 1266
CARD9-associated 903t
familial 903t
familial chronic nail candidiasis 903t
congenital cutaneous 173t–174t
differential diagnosis 147t
and drug abuse 1515t
HIV/AIDS-related 1291, 1298f
infantile 221
late-onset 903t
mucocutaneous 818t–819t, 900t, 902–904, 1266, 1268f
neonatal 524t–525t, 529f, 530
treatment
candidiasis endocrinopathy syndrome 771t
canker sores *see* recurrent aphthous stomatitis
cannabinoids 2189t
cannabinoid receptors 104
cannabis abuse 1511
cannulas for liposuction 2530f
canstatin 454
cantharidin 1439, 2162–2163
molluscum contagiosum 1357
cantu *see* hyperkeratosis-hyperpigmentation syndrome
Cantu syndrome 1065t, 1116t
capecitabine 349t
adverse reactions, nail changes 1141t
capillaritis *see* pigmented purpuric eruptions
capillary hemangioma 1691
capillary malformations 1001t
cerebral 1713t
clinical features 1713–1720, 1714f
angiokeratoma 1719–1720
cerebral capillary malformation 1720
CLAPO syndrome 1718
CLOVES syndrome 1718
Klippel-Trenaunay syndrome 1717, 1717f
macrocephaly-capillary malformation 1718, 1718f
port-wine stain 1713–1715, 1715f
Proteus syndrome 1717, 1717f
Sturge-Weber syndrome 1715–1718, 1716f
telangiectasias 1718–1719
evaluation 1714f
histology 1726f
investigative tools 1714t
pathology 1725
treatment 1727
see also individual malformations
capillary malformation-arteriovenous malformation 1713t, 1725
capillary morphogenesis protein 2 712–713, 808t
Capnocytophaga canimorsus 1450t
capreomycin, tuberculosis 1234t
capsaicin 274t, 278t, 279, 2206, 2212t
notalgia paresthetica 121
prurigo nodularis 115
pruritus 106t, 123, 2157t
renal 118t
Capsicum annuum see hot peppers
Capsicum frutescens see capsaicin
Captique 2548t–2549t, 2554
captopril
adverse reactions
erythroderma 176t
lichen planus 185t
linear IgA bullous dermatosis 498t
pemphigus 467
pruritus 120t
caraway 275t
carba mix 242t
carbamazepine
adverse reactions
erythroderma 176t
lichen planus 185t
linear IgA bullous dermatosis 498t
Stevens-Johnson syndrome/toxic epidermal necrolysis 325t
interactions 2124t, 2191–2193
carbapenems 2105t
sites of action 2109t
carbaryl, head lice 1428t, 1429
carbimazole
and alopecia 348t
and aplasia cutis congenita 1002t
Carbocaine *see* mepivacaine
carbon dioxide lasers 2251, 2271–2272
basal cell carcinoma 1791
fibrofolliculoma 1829
granuloma annulare 1566t
morphea 667t
optical penetration depth
rosacea 567t
sarcoidosis 1563t
skin penetration 2254f
skin resurfacing 2273t
carbon dioxide, solidified 2285
carboplatin-induced erythroderma 176t
carboxymethylcellulose 1581t
carbuncles 1190
carcinoembryonic antigen 29t–33t
carcinogenesis 1759–1760, 1762f
carcinoid syndrome 776t–778t, 1751t
differential diagnosis 650t
paraneoplastic 764t–765t
carcinoma *en cuirasse* 2051t, 2052f
differential diagnosis 650t
carcinoma erysipeloides 2051t
carcinoma telangiectodes 2051t
CARD9-associated chronic mucocutaneous candidiasis 903t
cardiac disease 635
cardiofaciocutaneous syndrome 776t–778t, 932t–933t
genetics 803t–804t
Carduus spp. *see* thistle
caries *see* dental caries
Carimune NF 2148t
carisoprodol-induced pseudoporphyria 724t
carmustine 2160
adverse reactions 2155t, 2160
eccrine squamous syringometaplasia 349t
extravasation reactions 349t
hyperpigmentation 1056t–1057t
dosage 2160
indications 2160
mycosis fungoides
parapsoriasis 159t
mechanism of action 2160
pregnancy and lactation 2160
carnauba wax 2481t
Carney complex 377, 776t–778t, 1856, 1857t
genetics 818t–819t
Carnoy's fluid 709t
β-carotene 2207t
carotenemia 746f, 768t
carotenoderma 746t
carpal ankylosis 675
carpal tunnel syndrome 688–690, 705
CarraDres 2372
CarraSorb 2372
CarraSyn 2372
Carrion's disease *see* bartonellosis
carrot 275t
cartilage tumors 1991
cartilage-hair hypoplasia 904, 1104t
Carum carvi see caraway
Carvajal syndrome 776t–778t, 873t, 882
genetics 803t–804t, 832t–833t
Carybdea alata 1452

case-control studies 2058–2059, 2058t
cashew nut shell oil hypersensitivity 246t, 278t
cashew nut tree 278t, 282t, 283
caspases 1762
caspofungin 2119f
  adverse reactions 2123
  dosage 2122
  indications 1283t, 2120t
    aspergillosis 1283t
    candidiasis 1269t, 1283t
    cryptococcosis 1283t
    penicilliosis 1283t
    zygomycosis 1283t
  interactions 2122
  pregnancy and lactation 2120t
caspofungin acetate *see* caspofungin
Castellani's paint 2162t
Castile soap 2480t
Castleman's disease 1552–1553
castor oil 2481t
castor oil plant 275t
Castroviejo needle holder 2362
cat bites 1450, 1450t
cat-eye syndrome 1823
cat-scratch disease 1208, 1209t
  and erythema nodosum 1644t
catagen 1078–1080, 1079t
cataracts 841t–842t, 874t
  glucocorticoid-induced 2083, 2083f
catechols 284
caterpillar dermatitis *see* lepidopterism
cathelicidins 2378
cathepsins 101
  cathepsin G 2319, 2322
  cathepsin S 101t, 106t
cauliflower 275t
cauliflower ear *see* traumatic auricular hematoma
causal inference 2060t
cave disease *see* histoplasmosis
cavernous sinus thrombosis 1153
cavitation 2072
CBTX-A *see* botulinum toxin
CC-10004 2147t
CCR2 85
CCR3 188t
CCR6 82, 84t
CCR7+ 90
CCR7 84t, 85, 93
CD markers 2007
CD1 88
CD1a 29t–33t, 84t
CD1c 58
CD2 89t, 90
CD3 29t–33t
CD4+ lymphocytopenia 900t
CD4+/CD56+ hematodermic neoplasm 2044–2045
CD4 29t–33t, 88
CD5 29t–33t, 90
CD7 29t–33t
CD8 29t–33t, 88
CD8 deficiency 920t
CD8α+ 85
CD10 29t–33t
CD11a 93, 1685t
CD11b 84t
CD11c 84t
CD15 29t–33t
CD16 83, 94
CD19 93
CD20 29t–33t, 93
CD21 29t–33t
CD22 93
CD23 94
CD25 29t–33t
CD27 89t
CD28 89, 89t
CD30+, primary cutaneous lymphoproliferative disorders 1159
CD30 29t–33t, 89t
CD31 29t–33t, 1685t
CD32 94
CD34 29t–33t, 1686t
CD35 81
CD38 2010
CD39 92
CD40 29t–33t, 86, 89t, 94
CD43 29t–33t
CD44 86
CD44v6 86
CD45 29t–33t
  expression by Langerhans cells 84t
CD45 deficiency 920t
CD45RA 29t–33t, 90
CD45RB 2044
CD45RO 29t–33t
CD46 81
CD52 29t–33t
CD54 *see* ICAM-1
CD55 81
CD56 29t–33t
CD57 29t–33t
CD58 29t–33t, 86, 89t
CD59 81
CD62E *see* E-selectin
CD62L 93
CD64 94
CD68 29t–33t
CD69 188f
CD73 92
CD79a 29t–33t
CD80 29t–33t, 86, 89, 89t, 92
CD86 29t–33t, 89, 89t, 92
CD88 83
CD89 94
CD95 29t–33t, 91
CD95L 91
CD99 29t–33t
CD103 85
CD106 *see* VCAM-1
CD117 29t–33t
CD134 89t
CD138 29t–33t
CD151 450
CD152 29t–33t, 89, 89t
CD153 89t
CD154 29t–33t, 89t, 94
CD162 93
CD178 29t–33t
CD205 87
CD207 29t–33t
CD252 89t
CD254 89t
CD265 89t
CD273 89t
CD274 89t
CD275 89t
CD278 89t
CD279 89t
CDKN2A gene mutations 1464–1465, 1760, 1889
CDw137 89t
CDX2 29t–33t
CEDNIK syndrome 852t–854t
  genetics 803t–804t
cefaclor 2112t
  dosage 2112t
cefadroxil 2112t
  dosage 2112t
cefamandole 2112t
cefazolin 2112t
  prophylactic 2462t
cefdinir 2112t
  dosage 2112t
cefditoren 2112t
cefepime 2112t
cefixime 2112t
  dosage 2112t
  gonorrhea 1383t
cefmetazole 2112t
cefonicid 2112t
cefoperazone 2112t
cefotaxime 2112t
  borreliosis 315t
  syphilis 1383t
cefotetan 2112t
cefoxitin 2112t
cefpodoxime proxetil 2112t
  dosage 2112t
cefprozil 2112t
  dosage 2112t
ceftaroline 2112t
ceftazidime 2112t
ceftibuten 2112t
  dosage 2112t
ceftizoxime 2112t
ceftriaxone 2112t
  dosage 2112t
  indications
    borreliosis 315t
    chancroid 1386t
    gonorrhea 1383t
    impetigo 1189t
    syphilis 1369, 1379t
  prophylactic 2462t
cefuroxime axetil 2112t
  dosage 2112t
  indications
    borreliosis 315t
    impetigo 1189t
cefuroxime sodium 2112t
Celaderm 2374
celecoxib 2191t
  adverse reactions, pseudoporphyria 724t
celery 274, 274t–275t, 279t, 2212t
cell cycle 1760, 1760f
  checkpoint defects 800t–801t
cell therapy 822–823
cellist's chest/knee 1509t
cellular communication 50
  failure of 50–51
cellular neurothekeoma 1951–1952
cellulitis 1153, 1197–1198
  anaerobic 1200, 1201t
  clinical features 1197–1198, 1198f
  dependent 357
  diagnosis 1198, 1198f
  in drug abuse 1514t–1515t, 1515f
  epidemiology and pathogenesis 1197
  Haemophilus influenzae 1212
  occupational 271t
  pathology 1198
  treatment 1198
cellulose, oxidized 2464t
cement 253t–254t
  sensitivity to 264f
Centella asiatica see gotu kola
centipedes 1449
central centrifugal cicatricial alopecia 1105–1106, 1106f
central memory T cells 90
central papillary atrophy *see* median rhomboid glossitis
centrifugal lipodystrophy 1671f
centrofacial lentiginosis 1857t
centromere 784t
Centruroides exilicauda 1449t
Centruroides limpidus 1449t
Centruroides noxius 1449t
Centruroides suffusus 1449t
Centruroides vittatus 1449t
century plant 275t, 278t, 279
cephalexin 2112t
  dosage 2112t
  indications, ecthyma 1189t
  prophylactic 2462t
cephalic pustulosis, neonatal 524t–525t, 529–530, 530f
cephaloceles 996–997, 997f
cephalopod envenomation 1452
cephalosporins 2111–2112
  adverse reactions 336t, 338t, 2112
  contraindications 2111–2112
  dosage 2111, 2112t
  indications 2111
  interactions 2112
  and linear IgA bullous dermatosis 498t
  mechanism of action 2111, 2112t
  pregnancy and lactation 2112
  sites of action 2109t
  see also individual drugs
cephalothin 2112t
cephapirin 2112t
cephradine 2112t
ceramides 543, 2066, 2481t
ceramide synthase 2067f
cerebrotendinous xanthomatosis 1552
  genetics 810t–811t
cerivastatin 2191t
Certain Dri 2464t
certolizumab 2145
  FDA warnings 2140t
certolizumab pegol 2141
ceruloderma 6t–7t
cervical accessory tragi *see* congenital cartilaginous rests of neck
cervical cancer
  AIDS-related 1288t
  metastatic 2049
cervical clefts 998
cervical hypertrichosis 1118t
cervical intraepithelial neoplasia 1289
cervical plexus 2340
cesium dermatosis 1499t
Cetacaine *see* benzocaine/tetracaine
cetirizine 246t, 304t
cetuximab 2149t
  adverse reactions 353t
    hypertrichosis 1118t
    nail changes 1141t
cevimeline, and eccrine sweating 590t
Chagas' disease
  clinical features 1400–1401, 1400f–1401f
  vectors of
    bedbugs 1438
    triatome reduviids 1399
  see also trypanosomiasis
chain termination 2125f
chalazia 564
chalazion clamps 2362
Chamaemelum nobile see chamomile
chamomile 274t, 285t, 2206–2210
  effects on coagulation 2212t
Chanarin-Dorfman syndrome *see* neutral lipid storage disease with ichthyosis
chancroid 1383–1386
  clinical features 1385, 1385f
  diagnosis 1385–1386
  differential diagnosis 1386
  epidemiology 1384, 1384t
  Haemophilus ducreyi vector 1384, 1385f
  history 1384
  HIV-related 1384
  pathogenesis 1384–1385
  pathology 1385
  prevalence 1384f
  transmission 1384
  treatment 1386, 1386t
chaparral 2207t
charbroiled foods 2190t
charcoal
  activated *see* activated charcoal
  perforating disease 1604t
Charcot-Marie-Tooth disease 871, 874t
Chédiak-Higashi syndrome 900t, 904–905, 906t, 1036, 1072t–1073t
  clinical features 905
  differential diagnosis 905
  epidemiology 905
  genetics 1015t
  pathogenesis 905
  pathology 905, 905f
  treatment 905
cheek chewing/biting *see* morsicatio buccarum
cheilitis 256f
  actinic 1162
  causes 256t
  clarinetist's 1509t
  differential diagnosis 257f
  glandularis 1164, 1164f
  granulomatosa *see* orofacial granulomatosis
  Kawasaki disease
  retinoid-induced 2100f
  sicca 207
  see also contact stomatitis
cheiropompholyx *see* dyshidrotic eczema
Chelepteryx collesi 1440
Chelidonium majus see greater celandine
chemical burns 263–264
  airbags 1491–1492
  oral 1155, 1155f
chemical exposure injury 1497–1498
  arsenical/heavy metal dermatoses 1498–1501
  chemical hair discoloration 1497–1498
  NMSC 1775, 1775t

chemical hair discoloration 1497–1498
clinical features 1498
differential diagnosis 1498
epidemiology 1497
history 1497
pathogenesis 1497–1498, 1498t
pathology 1498
treatment 1498
chemical hypomelanosis 1044–1045, 1044f, 1044t
chemical irritant dermatitis 278–279
epidemiology 278, 278t
history 278
pathogenesis, clinical features and treatment 278–279
chemical irritants 250t, 252–256, 253t–254t
chemical mediators of inflammation 2315t
chemical peels 558, 2489t
chemical relaxers 2486t
chemical-induced photosensitivity 1480–1482, 1482f
chemical-induced sclerodermoid syndromes 654
chemical/mechanical skin resurfacing *see* skin resurfacing
chemiclave 2362t
chemokines 82, 411
in atopic dermatitis 204t, 206t
α-chemokines 82
β-chemokines 82
lichen planus 188t
psoriasis 137
chemokine receptors 1687
D6 1687
lichen planus 188t
chemotherapeutic agents 2159–2160
adverse reactions 349t, 350–352, 350f–352f
hyperpigmentation 349t
mucositis 349t
nail changes 1141t
toxic erythema 349t, 352f, 541f
see also individual drugs
chemotherapy recall 349t
cherry angioma 1924
clinical features 1924, 1924f
differential diagnosis 1924
epidemiology 1924
pathogenesis 1924
pathology 1924, 1924f
treatment 1924
Cheyletiella spp. 1445t, 1446, 1446f
Cheyletiella blakei 1446
Cheyletiella parasitovorax 1446
Cheyletus malaccensis 1445t
chicken pox *see* varicella-zoster virus
chicory 275t, 285t
chiggers 1446
chigoe flea *see* tungiasis
Chikungunya fever 1359
chilblains *see* pernio
chilblain lupus 621–622
clinical features 622f
differential diagnosis 1488
child abuse 1521–1525
clinical features 1521–1524
emotional deprivation 1523
physical abuse 1521–1523, 1522f–1523f
physical neglect 1523
sexual abuse 1523–1524, 1523t, 1524f–1525f, 1525t
conditions mimicking 1524t
differential diagnosis 1524
epidemiology 1521
evaluation and management 1524–1525, 1525t
history 1521
CHILD syndrome 838t, 866–867, 952, 1553
clinical features 866, 866f
differential diagnosis 866
epidemiology 866
genetics 803t–804t
history 866
neonatal 847t
pathogenesis 866
pathology 866
treatment 866–867
childhood flexural comedones 553
childhood tumor syndrome 818t–819t
children
acral pseudolymphomatous angiokeratoma 2040
allergens in 242t
atopic dermatitis (eczema) 205, 208f
bullous pemphigoid 478, 479f
condylomata acuminata 1303–1304
Gianotti-Crosti syndrome 1353–1354
linear IgA bullous dermatosis 498f
melanoma 1897
morphea in 661–662
psoriasis 141f, 155
unilateral laterothoracic exanthem 1352–1353
vitiligo 1028
vulvar pemphigoid 478
see also infants; neonates
chili burns 279
chimerism 788–789, 945t, 960
Chirocaine *see* levobupivacaine hydrochloride
Chironex fleckeri 1451
chitin 2207t
chives 275t
Chlamydia spp., secondary cutaneous vasculitis 390t
Chlamydia pneumoniae, and erythema nodosum 1644t
Chlamydia trachomatis 1367t
and erythema nodosum 1644t
genital ulcer disease 1384t
lymphogranuloma venereum 1386
perinatally acquired 1524
and urethritis 144–145
chloasma *see* melasma
chloracne 269, 550, 551f
clinical features 270, 270f
pathogenesis 269
chloral hydrate, adverse reactions 336t
chlorambucil
Behçet's disease 435t
bullous pemphigoid 484t
dermatomyositis 639t
granuloma annulare 1566t
chloramphenicol 2105t
indications
bartonellosis 1209t
rickettsial disease 1243, 1249t
sites of action 2109t
chlordiazepoxide, adverse reactions 336t
chlorhexidine 2383t, 2463
adverse reactions 2155t
chlorhexidine gluconate 2463
chlorinated hydrocarbons 253t–254t
chlorines 253t–254t
chlormezanone, adverse reactions 325t
chloroacetate esterase (Leder) stain 27t–28t
Chlorophyllin Copper Complex Sodium
chloroprocaine hydrochloride 2344t
chloroquine
adverse reactions
erythroderma 176t
hyperpigmentation 1056t–1057t, 2170f
lichen planus 185t
pruritus 104, 120t
indications
granuloma annulare 1566t
lichen sclerosus 667t
lupus erythematosus 627–628, 628t
morphea 667t
porphyria 726
sarcoidosis 1563t
vasculitis 402t
chlorothalidone 342f
chlorothiazide 342f
adverse reactions 185t
chlorotrichosis *see* chemical hair discoloration
chlorpheniramine 303, 304t
chlorpromazine
adverse reactions
erythroderma 176t
hyperpigmentation 1056t–1057t
lichen planus 185t
pruritus 120t
and eccrine sweating 590t
chlorpropamide 342f
adverse reactions 185t
chlorprothixene, and eccrine sweating 590t
chlorthalidone-induced pseudoporphyria 724t
cholestasis of pregnancy *see* intrahepatic cholestasis of pregnancy
cholestatic jaundice of pregnancy *see* intrahepatic cholestasis of pregnancy
cholestatic pruritus 118, 119t
cholesterol 2066
cholesterol clefts 851
cholesterol embolus 348, 375–377
clinical features 376, 376f
differential diagnosis 376
pathogenesis 375
pathology 376
treatment 377
cholesterol sulfate 2067–2068
cholestyramine
pruritus
cholestatic 119t
renal 118t
cholinergic urticaria 294, 298, 298f
cholinesterase inhibitors, and eccrine sweating 590t
chondrocalcinosis *see* pseudogout
chondrodermatitis nodularis helicis 1502–1503, 1503f, 1600t
chondrodysplasia punctata, rhizomelic 800t–801t, 803t–804t, 852t–854t
chondrodystrophia calcificans punctata *see* rhizomelic chondrodysplasia punctata
chondroid syringoma 1831–1834, 1833f–1834f
chondroitin sulfate 411, 2212t
chondroma, extraskeletal 1991
chorda tympani syndrome 590
Chrisman, Bruce 2525
Christ-Siemens-Touraine syndrome *see* hypohidrotic ectodermal dysplasia
Chromex 2515t
chromhidrosis 597–598
apocrine 542
eccrine 597–598
chromic acid 253t–254t
chromium
dermatitis 250t, 1509t
dermatosis 1499t
hair discoloration 1498t
chromium potassium alum 2515t
Chromobacterium violaceum, chronic granulomatous disease 910t
chromoblastomycosis 1267–1273, 1600t
clinical features 1269, 1270f
differential diagnosis 1269–1270
epidemiology and pathogenesis 1267–1269
history 1267
pathology 1269
treatment 1270
chromogranin 29t–33t
chromomycosis *see* chromoblastomycosis
chromophores 2254t
absorption 2253f
chromosomal disorders 791–792, 817–820
cutaneous manifestations 822t
chromosomal non-disjunction 945t
chromosomes 784t
chronic actinic dermatitis 1473–1475
action spectrum 2203t
clinical features 1470, 1473–1474, 1474f
differential diagnosis 1474
epidemiology 1473
and erythroderma 171, 172t–173t
history 1473
HIV-related 1295
pathogenesis 1473
pathology 1474
treatment 1475
PUVA phototherapy 2232
chronic bullous disease of childhood *see* linear IgA bullous dermatosis
chronic cutaneous lupus erythematosus 618f
chronic granulomatous disease 900t, 908–911
autosomal recessive 910t
clinical features 910, 910f, 910t–911t
differential diagnosis 911, 912t
epidemiology 908–909
genetics 818t–819t
infections in 910t
pathogenesis 909–910
pathology 910–911
treatment 911
X-linked recessive 910t
chronic localized candidiasis 903t
chronic lymphocytic leukemia 2041t, 2043f
chronic myelogenous leukemia 344
chronic plaque psoriasis 139–140, 140f
chronic superficial dermatitis *see* parapsoriasis
chronic venous insufficiency 663
see also lipodermatosclerosis
chrysanthemums 274t–275t, 285t, 287f, 2207t
chrysarobin 2162t
chrysiasis 6t–7t, 1056t–1057t
Churg-Strauss syndrome 404–405
clinical features 404–405, 405f
differential diagnosis 401t, 405, 414t
epidemiology 404
pathogenesis 404
pathology 405
pulmonary disease 778t–779t
treatment 405
chylomicronemia syndrome *see* lipoprotein lipase deficiency
chylomicrons 1547, 1547t
chymase 101
CIAS1 674t
cicatricial pemphigoid 456t, 482–487
anogenital 485, 1185
antiepiligrin 457t, 764t–765t
autoantibodies 484
autoantigens 456t, 476t
clinical features 484–485
cutaneous lesions 485
mucous membranes 484–485, 484f–486f
diagnosis 486
immunochemical studies 486
immunoelectron microscopy 486
immunofluorescence microscopy 486
light microscopy and electron microscopy 486
differential diagnosis 486
epidemiology 484
history 484
immunoreactants in 457t
ocular 484–485, 485f
pathogenesis 484
prognosis 486–487
treatment 487
immune globulin 2148t
cicatricial (scarring) alopecia 1096t, 1104–1109
acne keloidalis 1107–1108
Brocq's alopecia 1096t, 1108, 1109f
"burnt-out" 1108
central centrifugal 1105–1106
classification 1105t
discoid lupus erythematosus 1096t, 1107, 1107f
dissecting cellulitis of scalp 1108, 1108f
"folliculitis decalvans" 1109
lichen planopilaris 190–191, 191f, 1095f, 1106–1107, 1106f
traction alopecia 1109, 1109f
"tufted folliculitis" 1109, 1109f
Cichorium endiva see endive
Cichorium intybus see chicory

ciclopirox
  formulations 2118t
  indications
    mucocutaneous candidiasis 1269t
    seborrheic dermatitis 221
  mechanism of action 2119t
  pregnancy and lactation 2118t, 2155t
  trade names 2118t
cidofovir 2127
  cytomegalovirus 1326–1328
  herpes simplex 1329t
  human papillomavirus 1314t, 1317
  viral susceptibility to 2125t
cigarette burns 1517
ciliated cyst 1825, 1825f
  of vulva 1825, 1825f
cilostazol 1615t
cimetidine
  adverse reactions, erythroderma 176t
  indications
    molluscum contagiosum
    urticaria 303, 304t
  interactions 2127t, 2191t
Cimex hemipterus 1438
Cimex lectularius 1438
cinacalcet, calciphylaxis 732
CINCA syndrome 673f
  genetics 818t–819t
Cinderella dermatosis *see* erythema dyschromicum perstans
cinnamates 2199, 2200f
cinnamic aldehyde 242t
cinnamon 275t
cinnarizine-induced lichen planus 185t
cinoxate 2200f
ciprofloxacin 2116t, 2191t
  adverse reactions
    fixed drug eruption 346f
    pseudoporphyria 724t
  dosage 2116
  indications
    bartonellosis 1209t
    chancroid 1386t
    donovanosis 1373–1375
  interactions 2191t, 2193
  routes of administration 2116t
  in sweat 541
circulatory failure 49–50
circumscribed palmar/plantar hypokeratosis 884
cirrhosis
  cutaneous manifestations 774t
  familial 832t–833t
Cirsium spp. *see* thistle
cisapride, interactions 2114, 2124t
cisplatin
  adverse reactions
    erythroderma 176t
    hyperpigmentation 349t
    neutrophilic eccrine hidradenitis 349t
  interactions 2123
  site of action 350f
citalopram 2190t
  depression 133
Citanest *see* prilocaine hydrochloride
Citrobacter diversus 1516
citrullinemia 749f, 1111
Citrus aurantifolia see key lime
Citrus aurantium var. *amara* 274t
Citrus bergamia see bergamot orange
Citrus latifolia see Peruvian lime
Citrus limetta see sweet lemon
Citrus limon see lemon
Citrus paradisi see grapefruit
Citrus sinensis see orange
Civatte bodies 198–199
CK 5/6 29t–33t
CK 7 29t–33t
CK 20 29t–33t
Cladophialophora carrionii 1267
cladosporiosis *see* chromoblastomycosis
cladribine, mastocytosis 2001t
clap *see* gonorrhoea
CLAPO syndrome 1718
clarinetist's cheilitis 1509t
clarithromycin
  dosage 2114t
  indications
    bacillary peliosis hepatis 1209t
    rickettsial disease 1248
    tuberculosis 1234t
  interactions 2191–2192, 2191t
Clark, William 2303–2304
Clark's nevus *see* atypical dysplastic melanocytic nevus
Clarkson syndrome *see* systemic capillary leak syndrome
class II-associated invariant peptide (CLIP) 87
claudication 1614
clavus *see* corns and calluses
cleansers 255, 2479–2480, 2480t
cleansing cream 2479
clear cell acanthoma 1805–1806
  clinical features 1805–1806, 1806f
  differential diagnosis 1806
  epidemiology 1805
  pathogenesis 1805
  pathology 1806, 1806f
  treatment 1806
clear cell papulosis 1046f, 1813–1814
clear cell sarcoma 1895
clear/pale cell neoplasms 1845f
cleft lip/palate 1005t, 2084–2085
cleft lip/palate-ectodermal dysplasia 800t–801t
  digital anomalies 1005t
  genetics 808t
Clericuzio-type poikiloderma with neutropenia 818t–819t
climatic bubo *see* lymphogranuloma venereum
clindamycin 2105t, 2115
  adverse reactions 2107t, 2115, 2155t
  contraindications 2115
  dosage 2115
  formulations 2106t
  indications 2106, 2115
    acne vulgaris 556, 556t, 2105, 2106t
    MRSA 1191t
    rosacea 567t, 2105, 2106t
    SAPHO syndrome 437t
    toxoplasmosis 1405–1406
  interactions 2115
  mechanism of action 2106t, 2115
  pregnancy and lactation 2106t, 2115, 2155t
  prophylactic 2462t
  resistance 1191f
  sites of action 2109t
  trade names 2106t
Cline, Henry 1625
clinical trials 2060, 2060t
clioquinol
  formulations 2118t
  pregnancy and lactation 2118t
  trade names 2118t
Clitopilus passeckerianus 2107
cloacogenic carcinoma 1790t
clobetasol propionate 245t, 2079t
  absorption 2069t
  adverse reactions, hypersensitivity
  bullous pemphigoid 483t
  lichen sclerosus 668
clobetasone butyrate 245t
clocortolone pivalate 2079t
clofarabine 349t
clofazimine 2172t
  adverse reactions
    erythroderma 176t
    hyperpigmentation 1055f, 1056t–1057t
  granuloma faciale 415
  leprosy 1228t
  lupus erythematosus 628t
  pyoderma granulosum 432t
  tuberculosis 1234t
clofibrate
  adverse reactions, pruritus 120t
  xanthoma 1554t–1555t
clomipramine 2190t
clonazepam 594t
clonidine
  adverse reactions, pruritus 120t
  hyperhidrosis 594t
cloning
  functional 792
  positional 792
clopidogrel 1615t, 2190t, 2451
closed-cone cryosurgery 2285
clostridial skin infections 1200
  anaerobic cellulitis 1200, 1201t
  myconecrosis (gas gangrene) 1200, 1201t
Clostridium spp. 1515t
Clostridium botulinum
  infection in drug abuse 1514t–1515t, 1515
  see also botulinum toxin
Clostridium perfringens 1200
  anaerobic cellulitis 1200, 1201t
  gas gangrene 1200, 1201t
cloth, patch testing 264t
clotrimazole
  formulations 2118t
  mucocutaneous candidiasis 1269t
  pregnancy and lactation 2118t, 2155t
  trade names 2118t
clotting factors 364t
  see also coagulation
Clouston syndrome *see* hidrotic ectodermal dysplasia
CLOVES syndrome 1718, 1984–1985
clozapine 2190t
  adverse reactions 129t
club hair 1079, 1079t
Clutton's joints 1377t
Cneoridium dumosoum see coast spice bush
coagulation 357–361
  and inflammatory vessel disease 360–361
  tests for 361
coagulation cascade 358, 363f, 2459
coal tar 2161
  acne 270
  adverse reactions 2161
  dosage 2161
  indications 2161
    parapsoriasis 159t
    pityriasis lichenoides 162t
    psoriasis 150
  mechanism of action 2161
  and NMSC 1775t
  pregnancy and lactation 2161
coal tar derivatives 253t–254t
coal tar shampoo, hair discoloration 1498t
coast spice bush 280t
cobalt
  dermatosis 1499t
  hair discoloration 1498t
  hypersensitivity 241t, 244, 250t
cobalt salts 253t–254t
Coban elastic bandage 1704
Cobb syndrome 1000, 1725, 1725f
cocaine
  abuse 1511–1512
    cutaneous reactions 1514t, 1518, 1518t
    prevalence 1512t
    treatment 1512
  adverse reactions, pruritus 120t
  interactions, lidocaine 2529t
  mucous membranes 2347, 2347t
cocamide MEA 255
cocamidopropyl betaine 242t, 255
Coccidioides immitis 1277
  life cycle 1278f
coccidioidomycosis 1277–1278
  AIDS-related 1288t
  clinical features 1277, 1277f
  differential diagnosis 1277–1278
  epidemiology 1277
  pathogenesis 1277
  pathology 1277
  treatment 1278
coccydynia 122t
Cochliomyia hominivorax 1433
Cockayne syndrome 1462t, 1476t–1477t, 1478
  clinical features 1478
  differential diagnosis 1673
  epidemiology 1478
  genetics 818t–819t
  history 1478
  pathogenesis 1478
  treatment 1478
cocoa butter soap 2480t
cocobolo wood dermatitis 1509t
codeine
  adverse reactions
    erythroderma 176t
    pruritus 120t
Codiaeum variegatum see florist's 'croton'
coenzyme Q10 2212t
  adverse reactions 2192t
Coffea arabica see coffee
coffee 275t, 2207t
Coffin-Siris syndrome 1116t
cohort studies 2058t, 2059, 2059f
coin rubbing 1524t
coining 9, 2214, 2214f
COL6A 1596
COL7A1 458t
COL17A1 458t, 1595–1596
colchicine 2169–2171
  adverse reactions, alopecia
  indications
    Behçet's disease 435t
    complex aphthosis 1159t
    dystrophic calcification 730
    folliculitis 574
    gout 711
    IgA pemphigus 473
    primary systemic amyloidosis 707
    pyoderma granulosum 432t
    relapsing polychondritis 677
    SAPHO syndrome 437t
    Sweet's syndrome 427
    urticaria 304–305, 304t
    vasculitis 391, 402t
  interactions 2191
cold agglutinins 374
cold agglutinin disease, differential diagnosis 1495t
cold erythema 591t, 592
cold exposure injury 51, 1492–1494
  differential diagnosis 1495t
  frostbite 51, 1492–1493
  pernio 1493–1494
  ulceration 1745t
cold exposure as therapy 51
cold hemolysins 1495t
cold panniculitis 1655–1656
  clinical features 1655, 1655f
  differential diagnosis 1495t, 1659
  epidemiology 1655
  history 1655
  microscopic features 1656t
  pathogenesis 1655
  pathology 1655, 1656t
  treatment 1659
cold sore *see* herpes simplex viruses
cold sterilization 2362t
cold sweat 589
cold urticaria 297–298, 297f, 1495t
  familial 298
  primary 297
  reflex 298
  secondary 297
cold water immersion foot 1492
cold-induced sweating syndrome 818t–819t
Cole disease 872t
Coleman, William 2525
collagens 411, 1585–1589, 1586f, 1587t, 1588f
  anchoring fibril, type VII 47t, 451t, 455, 502f, 1593t
  autologous 2552
  basement membrane, type IV 453–454, 454f, 1686t
  biosynthesis 1585–1587, 1586f, 1610f
  bovine 1574t, 1575f, 1581t, 1582, 2550–2554, 2550f
  FACITs
    type IX 1587t
    type XII 1587t
    type XIV 1587t
    type XIX 1587t

type XVI 1587t
type XX 1587t
type XXI 1587t
type XXII 1587t
type XXVI 1587t
fibril-forming
type I 1587t
type II 1587t
type III 1587t, 1593t
type V 1587t, 1593t
type XI 1587t
type XXIV 1587t
type XXVII 47t, 502f, 1587t
human bioengineered 2551
human-derived cadaveric 2551
microfibrillar 1587t, 2464t, 2465
type VI 1587t, 1593t
multiplexins
type XV 1587t
type XVIII 451t, 1587t, 1686t
network-forming
type VIII 1587t
type X 1587t
novel, type XXVIII 1587t
porcine 2550, 2550f
secretion 1610f
skin 1588–1589, 1588f
transmembrane
type XIII 1587t
type XVII 1585, 1587t
type XXIII 1587t
type XXV 1587t
triple helix 1585
collagen bodies 1957
collagen defects 800t–801t
collagen dressings 1735t
collagenase 86
debridement 2373
in wound healing 2323t
collagenoma *see* connective tissue nevus
collagenome perforant verruciforme *see* verrucous perforating collagenoma
Collastat 2465
collodion baby 57, 849–850
clinical features 849, 849f
differential diagnosis 850, 850t
epidemiology 849
pathogenesis 849
pathology 849–850
self-healing 847t
treatment 850
colloid bodies 194
colloid milium 709t, 713–714, 1484
clinical features 714
differential diagnosis 714
epidemiology 714
pathogenesis 714
pathology 714
treatment 714
colloidal iron stain 26f, 27t–28t
colony-stimulating factors 82
colophony 242t, 1509t
colophony dermatitis 250t
color
of lesions 5–8, 6t–7t
variation in 5–8, 8t
colorectal cancer, metastatic 2049t, 2050f, 2053t
colored facial cosmetics 2481–2484
camouflage makeup 2484, 2484t, 2490t
eye shadows 2483, 2483f
facial blushes 2483
facial foundations 2481–2482, 2482f, 2482t
lipsticks 2484
mascaras 2483–2484, 2483t
powders 2482–2483, 2483t
columbine 278t
coma blisters 515–517
clinical features 516, 516f
differential diagnosis 517, 517t
epidemiology 516
history 516
pathogenesis 516
pathology 517, 517f
treatment 517
combar soap 2479
combination flaps 2416–2417, 2418f
combined nevus 1876–1877, 1877f
comedo
extraction 558
formation 545, 546f
comedo nevus *see* nevus comedonicus
comedonal acne 547f, 553f
radiation-induced 2299t
comedones
childhood flexural 553
cryosurgery 2286
Comèl-Netherton syndrome *see* Netherton syndrome
comfrey 2207t
common acquired melanocytic nevus 1861–1863
clinical features 1862–1863, 1862f
differential diagnosis 1863
epidemiology 1861
growth triggers 1862t
pathogenesis 1861–1862
pathology 1863, 1863f
treatment 1863
common variable immunodeficiency 900t, 915b, 917t
communication in skin 50–51
community-acquired MRSA 1191t
compensatory hyperhidrosis 591–592, 592f
complement 2315t
complement disorders 900t, 905–908, 908t–909t
clinical features 907–908
differential diagnosis 908
epidemiology 907
pathogenesis 907
pathology 908
treatment 908
complement fixation 1348t
complement receptor *see* CR
complement split products 908t
complement system 81, 907f
alternative pathway 81
classical pathway 81
lectin pathway 81
see also individual factors
complementary and alternative medicine 2205–2217
aromatherapy 2215–2216, 2215t
botanicals 2205–2211, 2207t
adverse reactions 2211
aloe vera 2205
arnica 285t, 2206
capsaicin 274t, 278t, 279, 2206
chamomile 274t, 285t, 2206–2210
English walnut leaf 2206t
escharotics 2211
honey 2205
horse chestnut seed extract 2210
licorice root 2211
marigold 285t, 287f, 2205–2206
olive oil/olive leaf extract 2211
propopolis 2213f
tea 2210–2211, 2213f
turmeric 2211
white oak bark 2207t
witch hazel 2207t
classification 2206t
diet-based therapies 2211
dietary supplements 2212t
fumaric acid esters 2211
homeopathy 2214–2215
mind-body medicine 2216, 2216t
prebiotics and probiotics 2211
traditional Chinese medicine 2211–2214, 2213t
acupuncture 2214
coining 2214f
cupping 2214, 2214f
herbal medicine 2213–2214
moxibustion 2214
see also individual conditions
complex regional pain syndrome *see* reflex sympathetic dystrophy
complex traits 795, 795f
Compositae 276–277
composite dressings 2373
composite grafts 2375–2376, 2376f, 2429–2431
complications 2431
donor site 2430
donor site closure 2431
indications/contraindications 2429
postoperative care 2431
preoperative history 2429–2430
technique 2430–2431, 2431f
variations/unusual situations 2431
compression bandages 1734, 2377, 2377f
multilayer 2377
compression garments 2532, 2532f
compression pumps 1737t
compression stockings 1736, 1736t–1737t, 2377
condylomata acuminata 1309, 1309f–1310f, 1312
in children 1303–1304
differential diagnosis 1313–1314
giant *see* Buschke-Löwenstein tumor
pathology 1313–1314
treatment 1315f
imiquimod 2134
interferons 2131
see also human papillomavirus
condylomata plana 1309
confetti ichthyosis 818t–819t, 848
configuration of skin lesions 8–9
annular 8
clustered 8
linear 8
reticulated 8
retiform 8
serpiginous 8
confined-spray cryosurgery 2285
confluent and reticulated papillomatosis 1812–1813
clinical features 1813, 1813f
differential diagnosis 1813
epidemiology 1813
of Gougerot and Carteaud 1065f, 1065t
history 1812
pathogenesis 1813
pathology 1813
treatment 1813
confounding 2058, 2059f
congenital absence of skin *see* aplasia cutis congenita
congenital adrenal hyperplasia 551, 812–814, 1121, 1121t
cryptic 1122
late-onset 1121–1122
congenital atrichia with papules 1104, 1104t
congenital auricular fistula *see* ear pit
congenital cartilaginous rests of neck 1006
congenital erosive and vesicular dermatosis 526t–528t, 534–535, 535f
congenital erythropoietic porphyria 510t, 719t, 723, 723f
biochemical findings 720t
genetics 719t, 810t–811t
treatment 725t
congenital fascial dystrophy *see* stiff skin syndrome
congenital hemidysplasia with ichthyosiform erythroderma and limb defects *see* CHILD syndrome
congenital ichthyosiform erythroderma 177–178, 838t, 851–855
clinical features 855, 855f
differential diagnosis 855
epidemiology 851–852
genetics 803t–804t
mosaic type 1052–1053
neonatal 847t
pathogenesis 852–855
pathology 855
treatment 855
congenital lip pits 1004–1010, 1005f
congenital melanocytic nevus 1001t, 1119, 1871–1874
clinical features 1872–1873, 1872f–1873f
differential diagnosis 1873
epidemiology 1871–1872
pathogenesis 1872
pathology 1873, 1874f
treatment 1868t, 1874
congenital melanosis bulbi *see* nevus of Ota
congenital reticular ichthyosiform erythroderma *see* confetti ichthyosis
congenital scars *see* aplasia cutis congenita
congenital self-healing reticulohistiocytosis *see* Hashimoto-Pritzker disease
congestion eczema *see* stasis dermatitis
Congo red stain 27t–28t
congress weed 284, 286
conidia 1266f
Conidiobolus coronatus 1266
conjunctival lesions 485
connective tissue atrophies 1631–1640
anetoderma 1632–1635, 1632t
atrophic maculosa varioliformis cutis 1639, 1639f
follicular atrophoderma 1637–1639
atrophoderma vermiculatum 1638, 1638f
Bazex-Dupré-Christol syndrome 1638
Conradi-Hünermann-Happle syndrome 1638–1639
idiopathic atrophoderma of Pasini and Pierini 1636–1637
mid-dermal elastolysis 1631–1632, 1632t
piezogenic pedal papules 1639, 1639f
striae 1635–1636
connective tissue disorders
autoimmune *see* autoimmune connective tissue disease
autoimmune, biopsy 14t–15t
hereditary 807t
heritable 1607–1620, 1608t
cutis laxa 1615–1619
Ehlers-Danlos syndrome *see* Ehlers-Danlos syndrome
pseudoxanthoma elasticum 1612–1615
connective tissue growth factor 1596
in wound healing 2317t
connective tissue nevus 937f, 938, 1001t, 1608t, 1628t, 1969, 1969f
genetics 807t
connective tissue sheath 1079t
connexins 871, 874f
connexin defects 800t–801t, 802, 874t
Conradi-Hünermann-Happle syndrome 173t–174t, 838t, 867–868, 952, 1638–1639
clinical features 867, 867f
differential diagnosis 867–868
epidemiology 867
genetics 803t–804t
history 867
neonatal 847t
pathogenesis 867
pathology 867
treatment 868
consanguinity *see* inbreeding
Consolidated Standards for Reporting Trials (CONSORT) 2063
constitutional mismatch repair deficiency syndrome 816t, 932t–933t
contact activation complex 358
contact allergens, and lichen planus 184
contact dermatitis 261–272, 263f–265f
airborne 252
allergic *see* allergic contact dermatitis
anogenital 1177
chemical burns 263–264
clinical features 262–265, 263f–265f
postinflammatory hyperpigmentation
differential diagnosis 261, 265
epidemiology 262, 262f

fiberglass dermatitis 264, 265f
history 262, 263t
irritant *see* irritant contact dermatitis
mechanical 265, 265f
pathogenesis 262
pathology 265
phototoxic eruptions 264–265
pigmented 1053t
treatment 265–266, 266t, 2077t
contact lichenoid reaction *see* contact stomatitis
contact sensitization 86
contact stomatitis 1157–1158
causes of 1157t
clinical features 1157, 1157f
epidemiology 1157
pathology 1157
treatment 1157–1158
contact urticaria 252, 298–299
causes 213t
clinical features 267–268
cross-reactions 267t
differential diagnosis 268, 268f
epidemiology 266, 266f–267f
foods 267
history 266
latex 267, 268f
low-molecular-weight chemicals 267
pathogenesis 266–267
pathology 268
protein contact dermatitis 267–268
treatment 268
contamination of surgical site 2463
contiguous gene syndromes 812–814
continual peeling skin syndrome *see* peeling skin syndrome
contrast media, adverse reactions 338t, 340t
Contreet Foam 2368, 2368t
Contreet Hydrocolloid 2368, 2368t
contusion 1506t
copper 748–750
deficiency 748, 750f, 1038
dermatosis 1499t
hair discoloration 1498t
toxicity 750
copper salts 253t–254t
copper transporter defects 800t–801t
copper vapor lasers 2255t
vascular lesions 2255
copra itch 1445t
coproporphyrin 510t, 546
see also porphyria
corals, foreign body reactions 1574t, 1580
clinical features 1580, 1580f
histopathology 1576t
pathology 1580
treatment 1580
Cordylobia anthropophaga see myiasis
corkscrew hairs 740t–742t, 743f
corn 275t
corn oil 2481t
corneal opacity 841t–842t
Cornelia de Lange syndrome, hypertrichosis 1117t
corneocytes 826
corneodesmosin 700t
corneodesmosomes 826f
cornified cell envelope 825–826, 826f
cornified lipid envelope 826
corns and calluses 1501, 1501f
musical instrument-related 1509t
sports-related 1506t
cornu cutaneum *see* horn, cutaneous
corona phlebectasia 2512
coronin 1A deficiency 920t
corps ronds 892
corrugator supercilii muscle 2334–2335
cortical hyperhidrosis 588f
causes of 588t
disorders associated with 588–589
cortical tubers 935t–936t
corticosteroids
adverse reactions 2155t
hypersensitivity 245, 245t
hypopigmentation 1044–1045, 1044f
alopecia areata 1103t
atopic dermatitis 213t, 214
Behçet's disease 435t
bullous pemphigoid 484t
dermatomyositis 639t
foreign body reaction 1574t, 1582
granuloma annulare 1566t
Hailey-Hailey disease 895
hypertrophic scars 1520
infantile hemangioma 1704–1705
injection site reactions 663
insect bites/stings 1436
interactions 2124t
juvenile idiopathic arthritis 672
lichen planus 195t
lichen sclerosus 657
lupus erythematosus 627–628, 628t
mastocytosis 2001t
morphea 667t
mycosis fungoides 2023
neurotic excoriations 131–132
parapsoriasis 159t
pemphigoid gestationis 441, 442t
pemphigus vulgaris 472
perforating disease 1604t
pityriasis lichenoides 162t
poison ivy dermatitis 287
polymorphic eruption of pregnancy 443
in pregnancy 442t
psoriasis 148–149, 149t
pyoderma granulosum 432t
reflex sympathetic dystrophy 122t
SAPHO syndrome 437t
sarcoidosis 1563t
vasculitis 391–393, 402t
vitiligo 1028
cortisone 245t
pharmacology 2076t
Corynebacterium spp.
bromhidrosis 542
chromhidrosis 542
skin infections 1200–1203
erythrasma 1200–1201, 1202f
pitted keratolysis 1201
trichomycosis axillaris 1202
Corynebacterium diphtheriae 1202–1203, 1203f
Corynebacterium jeikeium 1187t
Corynebacterium lipophilicus 1187t
Corynebacterium minutissimum 1187t
erythrasma 1200
Corynebacterium xerosis 1187t
cosmetic subunits of head and neck 2332–2334, 2332f
cosmetic surgery
botulinum toxin 2561–2572
applications 2562–2570
complications 2570–2571, 2571f
dosing 2562
formulations and clinical use 2562f, 2562t
future trends 2571
Hailey-Hailey disease 895
postprocedural care 2570
safety 2571
liposuction 2525–2534
alternative trends 2533
background 2525
complications 2533, 2533t
indications and contraindications 2525, 2526f–2527f, 2527t
instrumentation 2529–2531, 2530f–2531f
non-cosmetic 2532
postoperative care 2532
powered 2530, 2530f
preoperative history 2525–2526, 2527f
preoperative visit 2527–2528
surgical technique 2529
tumescent anesthesia 2528–2529, 2528f–2529f, 2528t
variations/unusual situations 2531
skin resurfacing 2493–2508
anesthesia 2276
chemical resurfacing 2495f, 2496–2502
classification of methods 2493t
complications 2506–2507, 2506t
contraindications and patient selection 2494–2495, 2494t
indications 2494–2496, 2494t
laser resurfacing
ablative 2255, 2271–2272, 2272f
fractional 2256–2257, 2272–2277, 2273f, 2273t
non-ablative 2256
mechanical resurfacing 2502–2505
plasmakinetic 2277
postoperative care 2505–2506
preoperative and intraoperative preparations 2493f, 2495–2496
radiofrequency 2257–2258, 2258f, 2277–2278
cosmetics/cosmeceuticals 2479–2491, 2490t
colored facial cosmetics 2481–2484
camouflage makeup 2484, 2484t, 2490t
eye shadows 2483, 2483f
facial blushes 2483
facial foundations 2481–2482, 2482f, 2482t
lipsticks 2484
mascaras 2483–2484, 2483t
powders 2482–2483, 2483t
hair care products 2484–2485
conditioners 2484–2485, 2485f, 2487t
shampoos 2484, 2485t
treatments 2486f, 2486t
hydroxy acids 2488–2489, 2489t
α-hydroxy acids 2488
β-hydroxy acids 2488–2489, 2489f
ingredients 2490t
nail care products 2483, 2487–2488
nail polish 2487, 2487f
nail sculptures 2487–2488, 2488f, 2488t
sensitivity to 250t
skin care products 2479–2489
astringents 2481
cleansers 2479–2480, 2480t
moisturizers 2481, 2481t
Cosmoderm 2548t–2549t
CosmoPlast 2548t–2549t
Costa's acrokeratoelastoidosis *see* acrokeratoelastoidosis
Costello syndrome 776t–778t, 814f, 1617t–1618t
genetics 816t
paraneoplastic
cotrimoxazole *see* sulfonamides
coumadin necrosis 362f, 389t
coumarin-induced secondary cutaneous vasculitis 390t
counfounding 2058, 2059f
Covaderm Plus 2373
cow parsley 279t
cow parsnip 279t
Cowden disease 932t–933t, 1857t
clinical features
fissured tongue 1150
gingival cobblestoning 772f
and gastric hemorrhage 773t–774t
Cowden-like syndrome 816t
cowpox 1355t–1356t
COX-1 104
COX-2 104
COX-2 inhibitors
adverse reactions, secondary cutaneous vasculitis 390t
juvenile idiopathic arthritis
Coxiella burnetii 1244t, 1250
panniculitis 1658t
coxsackievirus
and acute hemorrhagic edema of infancy 394t
and dermatomyositis 632t
and erythema multiforme 1350
and urticarial vasculitis 394t
CP-690,550 2147t
CR1 81
CR35 81
crab lice 1424–1426, 1429–1430
clinical features 1430, 1430f
differential diagnosis 1430
epidemiology 1429
history 1429
pathogenesis 1429–1430
pathology 1430
treatment 1430, 1430t
cradle cap 220
cranberry 2212t
cranial nerves 2339f
facial (VII) *see* facial nerve
ophthalmic (VI) 2338f–2339f
trigeminal (V) 2338f
cranioectodermal dysplasia 808t
craw-craw *see* onchocerciasis
creeping eruption *see* cutaneous larva migrans
creeping myiasis 1433
CREST syndrome 645, 729–730, 730f
see also scleroderma
Crimean-Congo fever virus 1360t
crocodile tears syndrome 590–591
Crohn's disease
ANCA in 613t
cutaneous 771t, 1570–1571
clinical features 1558t, 1570, 1570f
differential diagnosis 1570–1571
epidemiology 1570
history 1570
pathogenesis 1570
pathology 1562t, 1570
treatment 1571
and gastric hemorrhage 773t–774t
'metastatic' 771f
oral manifestations 1167–1168, 1168f
cromolyn sodium
mastocytosis 2001t
pyoderma granulosum 432t
Cronkhite-Canada syndrome 1857t
and gastric hemorrhage 773t–774t
Cross syndrome 1036
cross-presentation 87
cross-sectional studies 2058t, 2059–2060
Crosti's lymphoma 2013
crotamiton, scabies 1424–1426, 1426t
Crouzon syndrome 818t–819t
Crowe's sign 928
crow's feet, botulinum toxin 2563–2564, 2563t, 2564f
crusts 2, 4t–5t
cryoanesthesia 2347–2348
cryofibrinogen 374, 1495t
cryofibrinogenemia 374, 1744t
cryogelling/cryoagglutination disorders 373–374
clinical features 374, 374f
differential diagnosis 374
pathogenesis 374
pathology 374, 374f
treatment 374
cryoglobulins 370, 398t, 1495t
cryoglobulinemia 374f
differential diagnosis
mixed 398
monoclonal 398t
paraneoplastic 764t–765t
type I 1744t
cryoglobulinemic occlusive vasculopathy 2014t
cryoglobulinemic vasculitis 385t, 397–399
classification 398t
clinical features 398–399, 398f
differential diagnosis 399
epidemiology 398
pathogenesis 398
pathology 399
treatment 399, 402t
cryoprobe 2285
cryopyrin 673f
associated periodic syndromes 294, 299–300
cryosurgery 2283–2289
advantages of 2284t
complications 2288
description of techniques 2285, 2285f
closed cone 2285
confined spray 2285
cryoprobe 2285
dipstick 2285
open spray 2285
solidified carbon dioxide 2285
future trends 2288

granuloma annulare 1566t
indications and contraindications 2283–2284
postoperative care 2288
preoperative history 2284
treatment 2285–2286, 2286f–2287f
benign lesions 2284t, 2285–2286
malignant lesions 2284t, 2286
premalignant lesions 2286
treatment factors 2284–2285
freeze time 2284
freeze-thaw cycle 2285
lateral spread of freeze 2284
temperature at base of tissue
unusual situations 2288
cryotherapy
condylomata acuminata 1314t
human papillomavirus 1314–1315
hypertrophic scars/keloids 1625t
molluscum contagiosum 1357
NMSC 1791, 2286
cryptococcosis 778t–779t, 1279f
AIDS-related 1292f
Cryptococcus neoformans 1280
panniculitis 1658t
cryptorchidism 841t–842t
cryptosporidiosis, AIDS-related 1288t
crystal deposition diseases 1660t
crystal globulin hypereosinophilic syndrome
crystal globulin vasculopathy 377
crystal violet stain 27t–28t
Ctenocephalides canis 1440t
Ctenocephalides felis 1244t, 1439, 1440t
CTLA-4 blockade 1909
cucumber 275t
Cucumis melo see melon
Cucumis sativus see cucumber
cuff sign 1739f
Culex quinquefasciatus, repellents 1437
cumulative drug toxicity 337
cumulative irritant contact dermatitis 251
cupping 9, 2214, 2214f
Curafoam 2371
Curcuma longa see turmeric
curcumin 2490t
curettage 2381, 2382t, 2388, 2388f
with electrodesiccation 1787f, 1790, 2304f, 2306
Langerhans cell histiocytosis 1534
NMSC 1790
xeroderma pigmentosum 1477
curettes 2359
Curth's postulates 763, 763t
Curzio, Carlo 657
Cushing, Harvey 2304
Cushing's disease/syndrome 750, 2084
buffalo hump 770f
cutaneous manifestations 770t, 1118t, 1122–1123
electrolytes in sweat 597t
striae 770f, 1635
cutaneous B-cell lymphoma *see* B-cell lymphoma
cutaneous collagenous vasculopathy 1753, 1755f
Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) 637
cutaneous field stimulation 105–107
cutaneous focal mucinosis 696
cutaneous keratocyst 1822
cutaneous larva migrans 1406
clinical features 1406, 1409f
differential diagnosis 1406
epidemiology and pathogenesis 1406
pathology 1406
treatment 1406
cutaneous lupus erythematosus *see* lupus erythematosus, cutaneous
cutaneous lupus mucinosis *see* papulonodular mucinoses
cutaneous lymphocyte antigen 93, 325
cutaneous metaplastic synovial cyst 1828
cutaneous sinus of dental origin 1154f
cutaneous T-cell lymphoma *see* T-cell lymphoma
cutaneous venous system 2509f
cuticle remover 2487t
cuticular dystrophy 633f
cutis aplasia *see* aplasia cutis congenita
cutis hyperelastica *see* Ehlers-Danlos syndrome
cutis laxa 1593t, 1594, 1595f, 1615–1619, 1632t
acquired 1618t
clinical features 776t–778t, 1616–1618, 1619f
cardiac disease 1617t–1618t
monoclonal gammopathy 1616, 1618t
differential diagnosis 1618–1619
epidemiology 1616
genetics 1616
heritable forms 1617t–1618t
history 1616
pathogenesis 1616
pathology 1618, 1619f
treatment 1619
cutis marmorata 1747
telangiectatica congenita 1718, 1718f, 1747
see also livedo reticularis
cutis rhomboidalis nuchae 1483–1484
cutis verticis gyrata 1626, 1626f, 1626t
cyanamide-induced lichen planus 185t
cyanocobalamin *see* vitamin B12
cyanosis 8
cyclic neutropenia 818t–819t, 912t
cyclical vulvovaginitis 1182, 1184
cyclobutane dimers 1460f
cyclobutane-pyrimidine dimers 1459, 1459f
cyclooxygenase-1 *see* COX-1
cyclooxygenase-2 *see* COX-2
cyclophosphamide 2172–2173
adverse reactions 2169t, 2172–2173
acral erythema 2172–2173
alopecia 349t
eccrine squamous syringometaplasia
hyperpigmentation 349t, 1056t–1057t
mucosal hyperpigmentation 349t
mucositis 349t
nail hyperpigmentation 349t
neutrophilic eccrine hidradenitis 349t
contraindications 2173
dosage 2172
indications 2170t, 2173
B-cell lymphoma 2013
Behçet's disease 435t
bullous pemphigoid 484t
dermatomyositis 639t
pemphigus vulgaris 472, 472t
pyoderma granulosum 432t
rheumatoid vasculitis 683
vasculitis 402t
interactions 2173
mechanism of action 2172
monitoring 2167t–2168t
pregnancy and lactation 2173
in sweat 541
cycloserine, tuberculosis 1234t
cyclosporine 2173–2174
adverse reactions 2169t, 2173, 2185t
acne 550t
gingival hyperplasia 1156t
hypertrichosis 1118t
linear IgA bullous dermatosis 498t
pseudoporphyria 724t
contraindications 2174
dosage 2173
indications 2170t, 2173–2174
alopecia areata 1103t
atopic dermatitis 213t, 215
Behçet's disease 435t
chronic actinic dermatitis 1475
dermatomyositis 639t
epidermolysis bullosa 511
Hailey-Hailey disease 895
lichen planus 195t, 196
lichen sclerosus 667t
morphea 667t
pemphigoid gestationis
pemphigus vulgaris 472t
psoriasis 151, 152t, 1137t
pyoderma granulosum 432t
rosacea 567t
sarcoidosis 1563t
urticaria 305
Wells' syndrome 417–418
interactions 2124t, 2174, 2190–2192
mechanism of action 2173
monitoring 2167t–2168t
pregnancy and lactation 2174
and PUVA 2229
cylindrocarcinoma 1847
cylindroma 955, 1845, 1845f
Cymetra 2551
Cynara scolymus see globe artichoke
CYP1A2 2187
substrates, inhibitors and inducers 2188t, 2190t
CYP2C9 2187, 2193t
substrates, inhibitors and inducers 2190t
CYP2C19 2187, 2193t
substrates, inhibitors and inducers 2190t
CYP2D6 2187, 2193t
substrates and inhibitors 2188t
CYP2E1 2187, 2188t
CYP3A4 2187–2188, 2193t
substrate, inhibitors and inducers 2188t–2189t
grapefruit juice 2188f
cyproheptadine, interactions 2185t
cyproterone acetate
acne vulgaris 557, 557t
hirsutism 1124–1125
cystadenoma *see* hidrocystoma
cystatin 825–826
cystic chondromalacia *see* pseudocyst of auricle
cystic fibrosis 749f
ANCA associated with 613t
electrolytes in sweat 597t
sweat glands in 540–541
cystic hygroma 1723
cysticercosis 1419–1420
cysts 1817–1828, 1818f
branchial cleft 1006
bronchogenic 1726–1727, 1824
ciliated of vulva 1825, 1825f
cutaneous ciliated 1825, 1825f
cutaneous keratocyst 1822
cutaneous metaplastic synovial 1828
dermoid 995–996, 996f, 1822–1823
digital mucous 1826, 1827f
ear pit 1823, 1823f
epidermoid *see* epidermoid cysts
follicular hybrid 1822
ganglion 1827, 1827f
hidrocystoma 1823–1824, 1823f–1824f
median raphe 1825
milia 1819–1820
mucocele 1826, 1826f
myxoid 1144, 1145f
omphalomesenteric duct 1825–1826, 1826f
pigmented follicular 1822
pilonidal 1823
pseudocyst of auricle 1827–1828, 1827f
renal 936t, 938
steatocystoma 1822, 1822f
thyroglossal duct 1824–1825, 1825f
trichilemmal 1820
proliferating 1820–1821
vellus hair 1821–1822, 1821f
cytarabine
adverse reactions
eccrine squamous syringometaplasia
erythroderma 176t
neutrophilic eccrine hidradenitis 344
in sweat 541
cytochrome P450 enzymes 2186–2189, 2187f
factors affecting 2188t
induction 2188
inhibition 2186t, 2188–2189
pharmacogenetics 2193, 2193t
substrates 2189t–2190t
see also CYP
cytoid bodies *see* Civatte bodies
cytokeratins 830f
cytokines 50, 82, 2321
in atopic dermatitis 206t
failure of communication 50–51
interactions 2193
in psoriasis 137
cytomegalovirus 1367t
cytomegalovirus (HHV-5) 29t–33t, 1322t, 1336–1338
clinical features 1337–1338, 1337f, 1337t
diagnosis and pathology 1338, 1338f
differential diagnosis 1338
epidemiology 1337
and erythema multiforme 320t
history 1337
HIV-related 1289
pathogenesis 1337
secondary cutaneous vasculitis 390t
treatment and prevention 1338, 1338t
cytomegalovirus retinitis 1288t–1289t
cytophagic histiocytic panniculitis 1659, 1659f
cytoplasmic antineutrophil cytoplasmic antibodies *see* C-ANCA
cytosolic retinoic acid binding proteins 2089–2090
cytotoxic drug-induced reactions 336
cytotoxic T cells 90–91, 326
cytotoxic T lymphocyte-associated antigen *see* CD152
cytstatin C 700t

dabigatran 365t
Dabska-type hemangioendothelioma 1930–1931
clinical features 1930
differential diagnosis 1930–1931
epidemiology 1930
history 1930
pathology 1930, 1930f
treatment 1931
dacarbazine 1909t
daclizumab 2149t
dactinomycin-induced hyperpigmentation 1056t–1057t
dactylitis 144
blistering distal 1191
daffodils 274t, 278t, 279
dahlia 285t
Dakin's solution 253t–254t
dalteparin 364t
dan shen 2212t
danaparoid 364t, 370
danazol
and acne 550t
C1 esterase inhibitor deficiency 305
dandelion 274t, 285t
dandruff 220
dang gui 2212t
dapsone 2117, 2174–2175
adverse reactions 496t, 2107t, 2169t, 2174, 2185t
erythroderma 176t
lichen planus 185t
pseudoporphyria 724t
contraindications 2174
dosage 2106t, 2174
formulations 2106t
indications 2106, 2170t, 2174
acne vulgaris 555t–556t, 556, 2106, 2106t
Behçet's disease 435t
bullous pemphigoid 484t
complex aphthosis 1159t
dermatitis herpetiformis 493–496, 496t
dermatomyositis 639t
folliculitis 574
granuloma annulare 415
IgA pemphigus 473
leprosy 1228t
linear IgA bullous dermatosis 491
lupus erythematosus 628, 628t
pyoderma granulosum 432t

rosacea 2106, 2106t
spider bites 1448
Sweet's syndrome 427
vasculitis 391, 402t
interactions 2175
mechanism of action 2106t, 2174
monitoring 2167t–2168t
pregnancy and lactation 2106t, 2174–2175
trade names 2106t
dapsone hypersensitivity syndrome 496
daptomycin 2117t
indications, MRSA 1191t
Darier disease 47, 887–897
clinical features 888–892
course of disease 890
modifying factors 890
onset and clinical pattern 888–889, 888f–891f
symptoms 890
clinical subtypes 891–892, 892t
acral hemorrhagic 891
segmental 891–892, 891f
complications 891
infections 890, 891f
neuropsychiatric disorders 891
salivary glands 890
differential diagnosis 892–893
epidemiology 887
genetics 803t–804t, 888
history 887
linear 954, 955f
nails in 890f, 1130f, 1136, 1136f
pathogenesis 888
pathology 892, 892f
sites of 889f
treatment 893
retinoids 2096
Darier, Jean 887
Darier-Roussy disease *see* sarcoidosis
Darier-White disease *see* Darier disease
Darier's sign 1997f
Darling's disease *see* histoplasmosis
d'Arsonval, Jacques Arsene 2303
darunavir, adverse reactions 1299t
dasatinib 353t, 1887t, 2149t
Daucus carota see carrot
daunorubicin 2186t
adverse reactions
alopecia 349t
hyperpigmentation 349t
mucositis 349t
nail changes 349t
Kaposi sarcoma 1341
site of action 350f
de Barsy syndrome 1593t
de novo mutations 788
dead finger *see* vibration white finger
debridement 1734–1735, 2373–2374
DEC-205 *see* CD205
decay-accelerating factor *see* CD55
deck-chair sign 416
decorin 1592t
dectin-1 deficiency 903t
decubitus ulcers *see* pressure ulcers
deep folliculitis 579–585
acne keloidalis 581–583
follicular occlusion tetrad 583, 583f
hidradenitis suppurativa 583–585
pseudofolliculitis barbae 572f, 579–581, 827, 832t–833t, 1580
deep peroneal nerve block 2351f
deer fly fever *see* tuleremia
deer-associated parapoxvirus infection 1355t–1356t
DEET 1436, 1437t
defect reconfiguration (island pedicle) flaps 2402, 2408–2410, 2409f–2410f
subcutaneous tunneling 2410, 2411f
defibrillators 2462–2463
Degos' acanthoma *see* clear cell acanthoma
Degos disease 382, 623
clinical features 382
differential diagnosis 382
and gastric hemorrhage 773t–774t
pathogenesis 382
pathology 382
treatment 382
degreaser's flush 253t–254t
dehiscence, postoperative 2469–2470, 2470f
delavirdine
adverse reactions 1299t
interactions 1300
delayed drug toxicity 336–337
delayed postburn/postgraft blisters 520
differential diagnosis 517t
delayed pressure urticaria 297, 297f
Delleman-Oorthuys syndrome 959
delusionoid ideation 128
delusions of parasitosis 127–129, 128t
matchbox sign 128f
demeclocycline
adverse reactions, phototoxicity
dosage 2114t
Demodex spp. 562, 1445t
Demodex folliculitis 573t, 575f
Demodex folliculorum 543t
Demodicidae 1445t
demodicosis, HIV-related 1293
dendritic cells 85–86
in atopic dermatitis 206t
expression of TLRs by 81
plasmacytoid 206t, 617
in psoriasis 137
T-cell responses 546
dendritic epidermal T cells 93
Dendrolimus punctatus 1441t
Dengue fever 1361f
denileukin difitox 2149t
tumors 2025
Dennie-Morgan lines 209t, 210f
denosumab 2149t
dental caries 1153–1154, 1154f
and drug abuse 1514t, 1517f
deodorant soap 2480t
dependent cellulitis 357
depigmentation 1023
atopic dermatitis 207f
see also hypopigmentation; vitiligo
depilation 1126
depilatory creams 581, 2279
deposition diseases 709–716, 709t
colloid milium 713–714
gout 709–711
lipoid proteinosis 712–713
mucopolysaccharidoses 714–716, 715t
pseudogout 711–712
depression 131t
treatment 133–134
depressor anguli oris 2335
Dercum's disease *see* adiposis dolorosa
dermabrasion 2502–2505
manual dermasanding 2503, 2503f–2504f
microdermabrasion 2502–2503, 2503f, 2503t
motorized 2504–2505, 2504f–2505f, 2505t
Dermacentor spp. 1441, 1443, 1443f
Dermacentor andersoni 1244t, 1443
Dermacentor marginatus 1244t
Dermacentor nuttallii 1244t
Dermacentor reticularis 1244t
Dermacentor silvarum 1244t
Dermacentor taiwanensis 1244t
Dermacentor variabilis 1244t, 1245f, 1443, 1443f
DermaGauze 2372
Dermagraft 2375t–2376t
dermal dendrocyte hamartomas 1545, 1545t
dermal dendrocytoma *see* dermatofibroma
dermal hypertrophies 1621–1629
elastic tissue-related disorders 1628, 1628f, 1628t
related conditions
cutis verticis gyrata 1626
Dupuytren's contracture 1625–1626
infantile systemic hyalinosis 1626–1628
juvenile hyaline fibromatosis 1626–1628
scars and keloids 1621–1625, 2471, 2471f
clinical features 1622, 1622f–1624f, 1623t
differential diagnosis 1624
epidemiology 1621
pathogenesis 1621–1622, 1621f
pathology 1622–1624, 1623f–1624f, 1624t
treatment 1624–1625, 1625t
dermal melanocytoma *see* blue nevus
dermal melanocytosis 1858, 1858f
cleft lip/palate 1005t
dermal replacement grafts 2374, 2375f, 2376t
allogenic 2374
xenogenic 2374
dermal sinus 1001t
dermal stem cells 62t
dermal-epidermal junction 43
development of 59
in lichen sclerosus 664, 666f
in scleroderma 662–663
Dermalogen 2551
Dermanyssidae 1445t
Dermanyssus avium 1445t
Dermanyssus gallinae 1445t
dermatan sulfate 364t, 687
dermatan-4-sulfotransferase-1 1593t
dermatitic epidermal nevus *see* epidermal nevus, inflammatory linear verrucous
dermatitis 8
anogenital 1175–1177
clinical features 1176, 1176f
differential diagnosis 1176, 1176f
pathogenesis 1175–1176
treatment 1176–1177
atopic *see* atopic dermatitis (eczema)
autoimmune progesterone 447–448
chronic actinic, and erythroderma 172t–173t
diffuse 21–22, 22f
and erythroderma 176, 178
fiberglass 117, 264, 265f
fibrosing 22, 24f
flagellate mushroom 1062
infective *see* infective dermatitis
interface 16f–18f, 17–18
interstitial granulomatous 683–684
irritant *see* irritant contact dermatitis
lichenoid 201–202
nodular 21–22, 22f
perivascular 17, 17f
psoriasiform 18–19, 19f
spongiotic *see* spongiosis
vesicular 285
dermatitis artefacta 130–131
clinical features 130, 130f
differential diagnosis 130–131
epidemiology 130
management 131
pathology 130
dermatitis cenicienta 200
dermatitis herpetiformis 47t, 491–500
associated disorders and malignancies 494
clinical features 493f–494f, 494
differential diagnosis 495, 495t
epidemiology 491
history 491, 492t
paraneoplastic 764t–765t
pathogenesis 491–494, 492f
circulating antibodies 493
genetic predisposition 491
gluten-sensitive enteropathy 491–493
granular IgA deposition 493
iodide and dapsone 493–494
pathology 494–495, 494f–495f
patient support 496
treatment 495–496, 496t
and vitiligo 493t
dermatitis papillaris capillitii *see* acne keloidalis
dermatitis plantaris sicca *see* plantar dermatosis, juvenile
dermatitis repens *see* acrodermatitis continua of Hallopeau
dermato-epidemiology 2063
see also epidemiology
Dermatobia hominis see myiasis
dermatochalasia *see* cutis laxa
dermatofibroma 1790t, 1962–1964
and anetoderma 1633t
clinical features 1962–1963, 1963f
deep 1964
dermoscopy 36f
differential diagnosis 1964, 1964f
differentiating 1964f
histologic variants 1963t, 1964, 1964f
pathology 1963–1964, 1963f
treatment 1964
dermatofibrosarcoma protuberans 1973–1974
clinical features 1973–1974, 1973f
Mohs surgery 2449
pathology 1974, 1974f
treatment 1974
dermatofibrosis lenticularis disseminata *see* connective tissue nevus
dermatoglyphs, congenital anomalies 1009
dermatology, 00163c.00163
etiologic framework 1, 1f
inflammatory vs neoplastic 1
Dermatology Life Quality Index (DLQI) 2061–2062
dermatomegaly *see* cutis laxa
dermatomes, distribution of 1331f
dermatomyofibroma 1967, 1967f
dermatomyositis 184t, 631–641
antiaminoacyl-tRNA synthetase antibodies
autoantibodies 609–610, 609t
classification 632t
clinical features 632–636
cardiovascular disease 635, 776t–778t
cutaneous disease 632–634, 633f–636f, 636t
malignancy 635–636
systemic disease 634–635
clinical subtypes 632t
differential diagnosis 637–638, 637f–639f, 639t
distribution 9
epidemiology 631
evaluation 636t
history 631
mucin deposition 637
panniculitis of 640, 1646t, 1654
paraneoplastic 764t–765t
pathogenesis 631–632, 632t
pathology 637
pulmonary disease 635, 778t–779t
serum autoantibodies 633t
treatment 638–640, 639t
immune globulin 2148t
dermatomyositis sine myositis 631
Dermatomyositis Skin Severity Index (DSSI) 637
dermatopathia pigmentosa reticularis 810t, 835t, 1065t, 1069, 1069f
genetics 810t, 832t–833t
dermatopathology 1, 11–26
biopsy *see* biopsy
immunohistochemistry 26, 28f, 29t–33t
pattern analysis 16–25, 16f
stains 25–26
Dermatophagoides farinae 1445t
Dermatophagoides pteronyssinus 1445t
Dermatophilus congolensis 1201
dermatophyte folliculitis 573t, 575f
dermatophytoses 46, 46f, 1255–1266, 1255t
anogenital 1183
chronic mucocutaneous candidiasis 818t–819t, 900t, 902–904, 1266
clinical features 1256–1262
tinea barbae 271t, 1259, 1259f
tinea capitis 221, 271t, 1095f, 1260f–1261f
tinea corporis 8, 271t, 308t–310t, 1256–1257, 1257f
tinea cruris 1258f
tinea faciei 1259f
tinea manuum 1258f
tinea nigra 1252f

tinea pedis 1263f, 1263t
tinea unguium 1264f
differential diagnosis 147t, 1256t, 1263–1264, 1265f–1266f
epidemiology 1255
granuloma gluteale infantum 1266, 1270f
history 1255
HIV-related 1291
invasive 1265–1266
pathogenesis 1255–1256, 1256t
pathology 1262
treatment 1264–1265, 1267t
see also individual conditions
dermatoscopy *see* dermoscopy
dermatosis papulosa nigra 1799–1800
clinical features 1800, 1800f
differential diagnosis 1800
epidemiology 1800
history 1799
pathogenesis 1800
pathology 1800
treatment 1800
dermatosparaxis 1595f, 1609t, 1611
dermicidin 83t
dermis 43
development of 58–59
healing *see* wound healing
papillary 25
reticular 25
dermographism 296, 297f
white 209t
dermoid cyst 995–996, 996f, 1822–1823
dermolytic pemphigoid *see* epidermolysis bullosa acquisita
dermoscopy 1, 2442
basal cell carcinoma 1788
colors 33f
melanoma 34f–35f, 1897–1899, 1898f–1899f, 1900t
squamous cell carcinoma 1783
vascular structures 36f
descriptive studies 2057–2058, 2058t
desert hedgehog gene 1766
desert rheumatism *see* coccidioidomycosis
desipramine
adverse reactions, hyperpigmentation 1056t–1057t
and eccrine sweating 590t
desloratadine 304t
desmin 29t–33t
desmocollin 831f, 871
as pemphigus antigen 463
desmogleins 831f, 871
autoimmunity against 465
hair follicle 1082
as pemphigus antigens 462–464, 462t–463t
desmoglein 1 47t, 880
as pemphigus antigen 463t
desmoglein 3 47t
as pemphigus antigen 463t
desmoglein compensation theory 464–465, 465f
Desmons (Senter) syndrome 865
desmoplakins 463–464, 464f, 502f, 785t, 831f, 880
desmoplastic melanoma 1895, 1896f
desmoplastic trichoblastoma (trichopithelioma) 1790t, 1835, 1835f
desmosomes 464f, 831–833, 831f, 871
hair follicle 1081–1083
malfunction 800t–801t, 802, 832–833, 832t–833t
desogestrel, acne vulgaris 557
desonide 245t, 2079t
desoximetasone 245t, 2079t
desquamation, radiotherapy-induced 2300f
desquamative gingivitis 484–485, 484f, 1152–1153, 1153f
see also cicatricial pemphigoid
dessication dermatitis *see* asteatotic eczema
detergents 2070–2071
sensitivity to 250t, 255
shampoo 2485t
developmental anomalies 993–1010, 994f
absent, hypoplastic or anomalous nipples 1007–1008
accessory tragi 1006
amniotic band syndrome 1009–1010
aplasia cutis congenita 1000–1003
branchial cleft sinuses/fistulae 1006
congenital cartilaginous rests of neck 1006
congenital dermatoglyph malformations 1009
congenital lip pits 1004–1006
midline lesions 993–1000
head and neck 993–998, 994f, 994t
spine 998–1000, 999f
oral cavity 1149–1151
fissured tongue 1150, 1150f
Fordyce granules 1149
geographic tongue 1149–1150
hairy tongue 1150–1151
median rhomboid glossitis 1151
rudimentary supernumerary digits 1009
skin dimples 1008–1009
supernumerary nipples 1007
Devergie's disease *see* pityriasis rubra pilaris
'dew drops' *see* milaria crystallina
dew itch *see* ground itch
dexamethasone 245t, 2079t
and acne 550f
indications
prurigo nodularis
scleromyxedema 690
pharmacology 2075
dextromethorphan, and eccrine sweating 590t
diabetes insipidus 1530t–1531t, 1531
diabetes mellitus
cardiovascular disease 776t–778t
compensatory hyperhidrosis 591–592
and dermatitis herpetiformis 493t
dermatologic associations 768f–769f, 768t
pruritus in 119
diabetic bullae *see* bullosis diabeticorum
diabetic cheiroarthropathy 768t
differential diagnosis 650t
diabetic dermatopathy 768t, 769f
diabetic sensory neuropathy 769f
diabetic ulcers *see* neuropathic/diabetic ulcers
Diadema setosa 1451
dialkyl thioureas 242t
diallyldisulfide 274t
diamond skin disease *see Erysipelothrix rhusiopathiae*
diapedesis 425t
diaper dermatitis 230
clinical features 229f, 230
differential diagnosis 229f, 230
epidemiology 230
irritant 221
pathogenesis 230
treatment 230
diarrhea 841t–842t
diazepam
adverse reactions 336t
interaction with lidocaine 2529t
diazolidinyl urea 242t
diazoxide
adverse reactions
hypertrichosis 1118t
lichen planus 185t
dibenzofurans 269
dibucaine 2347t
dichlorvos 1438
diclofenac 2163
and linear IgA bullous dermatosis 498t
and pseudoporphyria 724t
dicloxacillin
dosage 2110t
indications
ecthyma 1189t
linear IgA bullous dermatosis 499
prophylactic 2462t
Dictamnus albus see burning bush
Dictamnus dasycarpus 2213
didanosine
adverse reactions 1299t
interactions 2124t, 2190
didymosis 816
Dieffenbachia picta see dumb cane
diet-based therapies 2211
dietary supplements 2212t
diethanolamine 255
diethylamino hydroxybenzoyl hexyl benzoate 2199, 2200f
diethylcarbamazine 1402t–1403t, 1417
diffuse dermal angiomatosis 1744
diffuse dermatitis 21–22
diffuse hyperpigmentation 1049–1058
diffuse non-epidermolytic palmoplantar keratoderma
with sensorineural deafeness
with woolly hair and cardiomyopathy *see* Naxos disease
diflorasone diacetate ointment 2079t
diflunisal, adverse reactions
erythroderma 176t
lichen planus 185t
pseudoporphyria 724t
difluprednate emulsion 2079t
DiGeorge syndrome 900t
digital anomalies 1008t
digital fibroma 1969–1970, 1970f
digital mucous cyst 1826, 1827f
pathology 1826, 1827f
treatment 1826
digital necrosis 342, 351f, 352
digital nerve block 2350
digitate dermatosis *see* parapsoriasis
digoxin, interactions 2124t, 2127t, 2190
7,8-dihydro-8-oxoguanosine 1460f
dihydroxyacetone 2200f, 2201
dilated pore of Winer 1818–1819
dill 275t
diloxanide, amebiasis 1398
diltiazem
adverse reactions
erythroderma 176t
gingival hyperplasia 1156t
hyperpigmentation 1056t–1057t
dystrophic calcification 730
interactions 2191–2192, 2191t
dilute Russell viper venom time 361
dimethicone 2481t
dimethindene 123
dimethylsulfoxide 2069
adverse reactions 2155t
diode lasers 2251
hair removal 2256
pigmented lesions 2270t
skin penetration 2254f
skin resurfacing 2273t
vascular lesions 2265t
Diospyros kaki see persimmon leaf
dioxin-induced hyperpigmentation 1056t–1057t
dioxybenzone 2199, 2200f
diphencyclopropenone-induced dyschromatosis 1072t–1073t
diphenhydramine 304t
pruritus 2157t
diphenylcyclopropenone, alopecia areata 1103t
diplegia 841t–842t
diploid cells 784t
dipstick cryosurgery technique 2285
Dirofilaria spp. 1407t–1408t
dirofilariasis 1407t–1408t
dirty neck disease *see* steroid sulfatase deficiency
discoid eczema *see* nummular dermatitis
discoid lupus erythematosus 8, 47t, 618–620
and anetoderma 1633t
clinical features 619f–620f, 1095f
alopecia 1096t, 1107, 1107f
hyperpigmentation 618–619
hypomelanosis 1040–1041
postinflammatory hyperpigmentation 1050t
differential diagnosis 625–626, 626t
dyspigmentation 618–619
histopathology 624f, 624t
hypertrophic 620
inflammatory infiltrates 618f
discoid rash 627t
disease genes 792–795
disinfectants, sensitivity to 255, 255f
disorganization syndrome 1009–1010
Disperse Blue 242t
dissecting cellulitis of scalp 1108, 1108f
disseminate/recurrent infundibulofolliculitis 576–577, 576f
disseminated cat scratch disease *see* bacillary angiomatosis
disseminated eczema 224–225
clinical features 225, 225f
differential diagnosis 225
epidemiology 225
history and pathogenesis 224
pathology 225
secondary dissemination 224
treatment 225
disseminated granuloma annulare 768t
disseminated intravascular coagulation 6t–7t
heat-related 1488t
meningococcemia 1205
purpura 358f
spider bites 1448
toxic shock syndrome 1195
disseminated xanthosiderohistiocytosis *see* xanthoma disseminatum
distichiasis 1118t
distribution of skin lesions 9
photodistribution 9
seborrheic 9
disulfiram 246t
dithranol *see* anthralin
DMDM hydantoin 242t
DNA
amplification by polymerase chain reaction 66f, 66t
damage
UV-induced 1459–1460
repair of 1460–1462, 1460f, 1461t, 1462f
microarrays 793
nuclear 784t
repair defects 800t–801t, 808–812, 1462t
repair genes, deficient 1461t
sequencing 66f–67f, 66t–69t, 67–70, 69f
skin protection of 45
docetaxel 2186t, 2189t
and alopecia 349t
Kaposi sarcoma 1934
docosanol 2124t
dosage 2126t
formulations 2124t
pregnancy and lactation 2124t
trade names 2124t
dog bites 1450, 1450t
dog tick (*Dermacentor variabilis*) 1244t, 1245f
dolichol kinase deficiency 803t–804t
domperidone 649t
donepezil 2189, 2190t
and eccrine sweating 590t
Donohue syndrome *see* leprechaunism
donovanosis 1387–1389
clinical features 1388, 1388f
diagnosis 1388–1389
differential diagnosis 1276t, 1389
epidemiology 1388, 1388f
history 1387–1388
pathogenesis 1388
pathology 1388
treatment 1389, 1389t
L-dopa
and alopecia 348t
and nail growth 1090t
oxidation to melanin 1017
dopamine, and eccrine sweating 590t
Doppler ultrasound, presclerotherapy evaluation 2520
Doppler-guided sclerotherapy 2520
dorsal nasal flap 2407, 2407f

dorzolamide 342f
Doss porphyria *see* aminolevulinic acid dehydratase deficiency porphyria
double tangent advancement flaps 2404, 2405f–2406f
doughnut sign 688
Dowling-Degos disease 810t, 835t, 1065t, 1070–1071
  clinical features 1070, 1070f
  differential diagnosis 1070–1071
  epidemiology 1070
  genetics 810t, 832t–833t
  pathogenesis 1070
  pathology 1070
  treatment 1071
Dowling-Meara epidermolysis bullosa simplex 507f, 511t
  genetics 832t–833t
Down syndrome 791–792
  eccrine gland changes 598t
  fissured tongue 821f, 1150
  genetics 822t
  leukemoid reaction 534
  vesiculopustular eruption 524t–525t, 534
doxazosin-induced lichen planus 185t
doxepin
  anxiety disorder 132
  depression 132–133
  and eccrine sweating 590t
  pruritus 106t, 115
  psychocutaneous diseases 132
  urticaria 303–304, 304t
doxepin cream, pruritus 2157t
doxorubicin
  adverse reactions
    alopecia 349t
    hyperpigmentation 349t, 1056t–1057t
    mucositis 349t
    nail changes 349t
  B-cell lymphoma 2013
doxycycline
  dosage 2114t
  indications
    acne vulgaris 556t
    bacillary angiomatosis 1209t
    bartonellosis 1209t
    borreliosis 315t
    cat scratch disease 1209t
    donovanosis 1389t
    lymphogranuloma venereum 1387t
    MRSA 1191t
    rickettial disease 1246–1247, 1249t
    rosacea 567t
    SAPHO syndrome 437t
    syphilis 1379t
dracunculiasis 1407t–1408t
Dracunculus medinensis 1407t–1408t
DRESS syndrome 330, 338t, 339, 344–345, 345f, 345t, 776t–778t
dressings 2323, 2365–2379
  absorptive and paste 2368–2369
  antimicrobial agents in 2368, 2368f, 2368t
  epidermolysis bullosa 511t
  first/second intention healing 2367–2368, 2367f
  functions 2365
  future directions 2378
  history 2365
  ideal characteristics 2366f, 2366t
  laser resurfacing 2378
  leg ulcers 1735, 1735t, 2376–2377
    compression 1736, 1736t–1737t, 2377, 2377f
    moisture and occlusion 1734
    skin substitutes 1736–1737
  moist healing environment 2365–2366
  nail surgery 2441
  occlusive 2366t, 2369–2373, 2369t, 2370f
    alginates 2366t, 2369t, 2372, 2372f
    composites 2369t, 2373
    hydrocolloids 2369t, 2372–2373, 2373f
    hydrogels 2366t, 2369t, 2371–2372, 2371f
    polymer films 2366t, 2369–2371, 2369t, 2370f
    polymer foams 2366t, 2369t, 2371, 2371f
  pressure 2367f
  role of oxygen 2366
  traditional 2366–2367, 2367f
driver mutations 1760–1761
drometrizole trisiloxane 2199, 2200f
dronabinol, cholestatic pruritus 119t
drospirenone 1125
drug abuse 1511–1520, 1511t
  amphetamines 1511
  anabolic steroids 1512
  benzodiazepines 1511
  cannabis 1511
  clinical features 1513–1519, 1514t
    bacterial infections 1514–1516, 1515f, 1515t
    bullous reactions 1518f
    burns 1517
    drug-induced reactions 1518, 1518t
    formication 128, 1517, 1517f
    fungal infections 1516, 1516f
    granulomas 1516, 1516f
    mucous membrane lesions 1516–1517, 1517f
    scars 1513–1514, 1513f, 1515f
    systemic complications 1519
    ulcers 1517
    vascular lesions 1518–1519
  cocaine 1511–1512
  epidemiology 1512–1513, 1512f, 1512t
  γ-hydroxybutyrate 1512
  lysergic acid diethylamide 1512
  opiates 1512
  pathophysiology of addiction 1512
  treatment 1519–1520, 1520t
drug biotransformation 2186–2187
drug eruptions
  differential diagnosis 414t
  erythroderma 176, 176t, 178
  exanthematous 12t
  lichenoid 185t, 188f, 193–194, 193f, 194t
  morbilliform 6t–7t
drug interactions 337, 2183–2195
  absorption 2184–2186, 2185f, 2186t
  distribution 2186, 2187t
  drug biotransformation 2186–2187, 2187f
  increased risk of substrate toxicity 2187t
  levels of evidence 2184
  metabolism 2188–2189, 2188t–2191t, 2191f
  perspective 2183
  reduced substrate efficacy 2185t
  retinoids 2102
  risk assessment 2183–2184, 2184t
  risk minimization 2189–2194
    allylamine antifungals 2189
    azole antifungals 2190
    colchicine 2191
    cyclosporine/sirolimus/tacrolimus 2191–2192
    drug-cytokine interactions 2193
    drug-HIV interactions 2193–2194
    grapefruit juice 2192
    herbal remedies 2192, 2192t
    HMG-CoA reductase inhibitors 2192
    macrolides 2192–2193
    pharmacogenetic variation 2193, 2193t
    pimozide 2193
    quinolone antibiotics 2193
  see also individual drugs and groups
drug overdose 336
drug reaction with eosinophilia and systemic symptoms *see* DRESS syndrome
drug-induced conditions
  acne 549, 550f, 550t
  acute generalized exanthematous pustulosis 1518t
  alopecia 348t–349t, 350–351
  angioedema 299, 340–341
  autoimmune blistering diseases 519t
  bullous pemphigoid 347, 479
  folliculitis 3t–4t, 573t
  hypertrichosis 350, 1117, 1118t
  lichen planus 185t, 188f, 193–194, 193f, 194t
  linear IgA bullous dermatosis 347, 495f
  lipoatrophy 1670, 1672
  lupus 349–350
  morbilliform eruption 1518t
  neutrophilic eccrine hidradenitis 344, 344f, 349t
  onycholysis 337, 1141t
  palmoplantar keratoderma 349t
  pemphigus 347, 467
  pseudolymphoma 347–348
  pseudoporphyria 341, 515, 724t
  psoriasis 139, 352f, 353
  pyoderma gangrenosum 344
  sclerodermoid syndromes
  SLE 350, 608
  Stevens-Johnson syndrome 325t, 338t, 347, 347f, 1518t
  stomatitis 351–352
  Sweet's syndrome 343–344
  toxic epidermal necrolysis 325t, 338t, 347, 1518t
  urticaria 294, 338t, 339–340, 340f, 340t, 349t, 1518t
  vasculitides 342, 349t
    small vessel vasculitis 390t, 1518t
drug-induced hyperpigmentation 1055, 1056t–1057t
  see also individual drugs
drug-induced hypersensitivity syndrome 338t
drug-induced nail abnormalities 1140–1141, 1141f, 1141t
drug-induced photosensitivity 341, 341f–342f, 349t, 1480–1482, 1481f
drummer's digit 1509t
drumstick fingers *see* nail clubbing
dry heat sterilization 2362t
Drysol 2464t
Duhring, Louis 491
Duhring's disease *see* dermatitis herpetiformis
duloxetine, and eccrine sweating 590t
dumb cane 273t, 278t, 287f
Duncan syndrome *see* X-linked lymphoproliferative syndrome
duodenal carcinoid 927t
DuoDERM 2373
duplex scanning, presclerotherapy evaluation 2520
Dupuytren's contracture 1625–1626
  clinical features 1625, 1625f
  differential diagnosis 1625
  epidemiology 1625
  history 1625
  pathogenesis 1625
  pathology 1625
  treatment 1626
Durand-Nicolas-Favre disease *see* lymphogranuloma venereum
Duranest *see* etidocaine
dust mites 1445t
dusulfiram, and acne 550t
dutasteride 1097, 2537
Dutcher bodies 2007
DX-9065a 364t
dyes
  patch testing 264t
  sensitivity to 255
dysbetalipoproteinemia 1551
  familial 1549t
  genetics 810t–811t
dyschromatosis symmetrica hereditaria 1071f, 1072t–1073t, 1073
  genetics 810t
dyschromatosis universalis hereditaria 810t, 1071f, 1072t–1073t, 1073–1074
dyschromic amyloidosis cutis 1071f, 1072t–1073t
dysesthesias 120–123
  anogenital pain syndromes 121–122, 122t, 1180–1183
  cyclical vulvovaginitis 1182, 1184
  penile pain and scrotodynia 1182
  vulvodynia 121–122
  brachioradial pruritus 120–121, 120f
  burning mouth syndrome 121
  burning scalp syndrome 121
  distribution 120f
  meralgia paresthetica 121, 121f
  notalgia paresthetica 121
  reflex sympathetic dystrophy 122, 122f, 122t
  treatment 123–124
  trigeminal neuralgia 122–123
  trigeminal trophic syndrome 123, 123f
  see also pruritus
dysfibrinogenemia 1744t
dyshidrosiform pemphigoid 478f, 479t
dyshidrosis *see* dyshidrotic eczema
dyshidrosis lamellosa sicca 227
dyshidrotic eczema 209, 227–228
  clinical features 227, 227f
  differential diagnosis 228
  pathogenesis 227
  pathology 227, 227f
  treatment 228
dyskeratosis 2137t
  Darier disease 892f
  focal acantholytic 163
dyskeratosis congenita 810t, 1065t, 1066–1068, 1072t–1073t
  clinical features 1065f–1067f, 1066–1067, 1068t
  differential diagnosis 1067
  epidemiology 1066
  genetics 816t
  pathogenesis 1066
  pathology 1067
  treatment 1067–1068
dyskeratosis follicularis *see* Darier disease
dyskerin 818t–819t
dyslipidemia, retinoid-induced 2101–2102
dyspigmentation 1029
  and ablative laser resurfacing 2277
  acute cutaneous lupus erythematosus 620–621
  discoid lupus erythematosus 618–619
  and intense pulsed light treatment 2263f
  lupus panniculitis 1670f
  and UV light exposure 1456f
  see also dyschromatosis
Dysport *see* botulinum toxin
dystonin 502f
dystrophic calcification
  autoimmune connective tissue disease 729
  genetic disorders 730
  infections 730
  neoplasms 731
  panniculitis 730
  treatment 730
dystrophic epidermolysis bullosa *see* epidermolysis bullosa, dystrophic

E-cadherin 84t, 86, 833
E-selectin 85, 93
E-Z Derm 2376t
ear
  accessory tragi 1006, 1006f
  cartilage grafts 2432
  eczema 207
  external, sensory innervation 2339f
  hypertrichosis 1118t
  in relapsing polychondritis 676f
  topography 2334f
  traumatic hematoma 1504–1505
  weathering nodules of 1504, 1504f
ear corn *see* chondrodermatitis nodularis helicis
ear pit 1823, 1823f
eating disorders 750
EBNA-1 protein 1334–1335
ebola hemorrhagic fever, eccrine gland changes 598t
ebola virus 1360t
ecamsule 2199, 2200f

ecchymoses
  differential diagnosis 359t
  postoperative 2467–2469, 2467f–2468f
eccrine angiomatous hamartoma 592f
eccrine bromhidrosis 541, 598t
eccrine carcinoma 1790t
eccrine glands 539–542, 540t
  acrosyringium 539
  anhidrosis 541
  cell types 540t
  development 60, 539, 540t
  diseases of 587–602
    altered sweat composition 597–598
    anhidrosis 594–595
    cytologic inclusions 598
    hyperhidrosis 587–594
    hypohidrosis 594–595
    miliaria 595–597
    sweat and skin disease 598–601
  drug-related disorders 541, 541f
  function 539–540, 540t
  hyperhidrosis 541
  hypohidrosis 541
  innervation 539, 540t
  localization 539, 540t
  morphology 540t
  pathophysiology 540–541
  structure 539, 540f
  sweat retention 541
eccrine hidrocystoma 1823–1824, 1824f
  histology 1824f
eccrine mucinosis 696
eccrine nevus 1847–1848, 1847f
eccrine spiradenoma 1921
eccrine squamous syringometaplasia 344
echinacea 2192t, 2207t
Echinacea angustifolia 2207t
Echinacea pallida 2207t
Echinacea purpurea 2207t
echinococcosis 1419–1420
ECM *see* extracellular matrix
ECM1 gene 712, 1596
econazole
  formulations 2118t
  pregnancy and lactation 2118t
  trade names 2118t
ecstasy abuse, cutaneous signs 1514t
ecthyma 1191
  clinical features 1189t, 1192f
  treatment 1189t, 1192t
  see also impetigo
ecthyma diphtheticum 1203f
ecthyma gangrenosum 375, 1207, 1207f
ectodermal dysplasia 60, 808t
  acantholytic 510t, 807t, 832t–833t
  cleft lip/palate 1005t
  digital anomalies 1005t
  genetics 808t
  hidrotic 874t, 878–879, 879f
    genetics 808t
  hypohidrotic 60
    genetics 808t
    with immunodeficiency 917t
    X-linked 60, 817f, 952
  nails in 1135
  pure hair-nail type 808t, 1104t
  see also individual conditions
ectodermal dysplasia-ectrodactyly-clefting syndrome 951
  genetics 808t
ectodermal dysplasia-neoplastic syndrome 808t
ectodermal dysplasia-syndactyly syndrome 808t
ectodermal dysplasia/skin fragility syndrome 510t
ectoparasitic infestations, HIV-related 1293
ectopic ACTH syndrome, paraneoplastic 764t–765t
ectopic sebaceous glands *see* Fordyce granules
ectothrix hair invasion 1260
eculizumab 373, 2149t
eczema
  craquelé 10t–11t
    see also asteatotic eczema
  dyshidrotic *see* dyshidrotic eczema
  herpeticum 211, 211f, 1323t, 1326f
  nails in 1138
  papular 9
  see also atopic dermatitis
eczematid-like purpura of Doucas and Kapetanakis 365t
eczematous pemphigoid 477f, 479t
edema
  acute hemorrhagic of infancy 393–395
  cutaneous 1047
  heat 1487–1492
  non-pitting, in pregnancy 447t
edema blisters 520–521
  differential diagnosis 517t
edema bullae *see* edema blisters
edrophnium, and eccrine sweating 590t
Edwards syndrome 791–792
  eccrine gland changes 598t
Edwardsiella lineata 1451
EEC syndrome 809t
  cleft lip/palate 1005t
  digital anomalies 1005t
EEM syndrome 809t
  digital anomalies 1008t
efalizumab 2140–2141, 2141t
  adverse reactions, erythroderma 176t
efavirenz
  adverse reactions 1299t
    nail abnormalities 1141t
  interactions 1300
effect modification 2059, 2059f
effectiveness 2061
effector memory T cells 90
effector T cells 90–93, 185–187
  access to epidermis 186f–187f, 187
efficacy 2061
efficiency 2061
effluvium 1079t
eflornithine 1125, 1402t–1403t, 2159
Ehlers-Danlos syndrome 59, 730, 1591–1596, 1593t, 1595f, 1607–1612
  arthrochalasia 1593t, 1609t, 1611
  cardiac disease 1593t, 1609t
  classic 1593t, 1609t
  classification 1609t
  clinical features 776t–778t, 1609–1611, 1610f
    piezogenic papules 1639
  dermatosparaxis 1609t, 1611
  differential diagnosis 1611–1612
  epidemiology 1607
  and gastric hemorrhage 773t–774t
  history 1607
  hypermobility 1593t, 1609t
  keloidal nodules/plaques 1624
  kyphoscoliosis 1593t, 1609t, 1611
  musculocontractural 1593t, 1609t
  pathogenesis 1607–1609
  pathology 1611
  periventricular nodular heterotopic variant 1593t, 1609t
  progeroid 1593t, 1609t
  spondylocheirodysplasia 1609t
  treatment 1611f, 1612
  vascular 1593t, 1609t
  vs Marfan syndrome 1612t
Ehrlich, Paul 411
Ehrlichia chaffeensis 1244t, 1442
Ehrlichia ewingii 1244t
Ehrlichia phagocytophila
ehrlichioses 1249, 1249f
  monocytotrophic 1244t, 1246t, 1250t
Ehrlichiosis ewingii 1246t
eicosapentaenoic acid 2460–2461
Eikenella corrodens 1450t, 1514t
Ekbom syndrome *see* delusions of parasitosis
elafin 825–826
elastic fibers 1589–1590, 1589f
  absence of 26f, 1632f
  neonates 58t
  premature infants 58t
elastic tissue disorders 1628, 1628f, 1628t, 1632t
  see also connective tissue atrophies
elastic wraps 1737t
elastin 1589, 1593t
elastoderma 1614t, 1628t
elastofibroma dorsi 1628f, 1628t
elastoma *see* connective tissue nevus
elastomers, sensitivity to 1581f
elastosis perforans serpiginosa 308t–310t, 1600t, 1628t
  clinical features 1600–1601, 1601f
  pathology 1603f
elaunin fibers 1589
elder abuse 1525–1527
  clinical features and assessment 1526, 1526t
  management 1526–1527, 1526t
  risk factors 1526
  types of 1526t
elecampane 285t
electrical burns 1496–1497
  clinical features 1497
  pathogenesis 1497
  pathology 1497
  treatment 1497
electrocautery 2303
  waveforms 2305f
electrocoagulation 2304f, 2306, 2308f
  indications 2306t
electrodesiccation 2304f, 2306
  with curettage 1787f, 1790, 2304f, 2306, 2307f
  indications 2306t
electroepilation 2310
electrofulguration 2304f, 2306
  indications 2306t
electrolysis 2310
electromagnetic spectrum 2219f, 2253f
electromyography 638
electrons 2292
electroporation 2070f, 2071–2072
electrosection (cutting) 2304f, 2306–2308
  indications 2306t
electrosurgery 2303–2311
  bipolar 2305
  biterminal 2305
  cardiac pacemakers and intracardiac devices 2308–2309
  complications
    fire 2309
    microorganism transmission 2309
    surgical smoke 2309–2310
    thermoelectric burns 2309
  contraindications 2305
  definition 2303
  electrocautery 2303, 2304f
  electrocoagulation 2306, 2306t
  electrodesiccation 2306, 2306t
  electrofulguration 2306, 2306t
  electrosection (cutting) 2306–2308, 2306t
  electrosurgical devices and outputs 2304–2305, 2305f
  future trends 2310
  history 2304–2305
  indications 2305, 2306t
    basal cell carcinoma 2307f
    rhinophyma 2309f
    rosacea 567t
    telangiectasia 2308f
  monopolar 2305
  monoterminal 2305
  postoperative care 2309
  preoperative history and considerations 2305–2306
Elejalde syndrome 1036
elephantiasis 49–50, 693
  compression stockings 1736t
  differential diagnosis 1415–1416
  of genitalia 1387–1388, 1387t, 1414
elephantiasis nostras verrucosa 584–585, 1738, 1738f
Eletone cream 2156
ELISA 471, 1348t
Ellis-van Creveld syndrome 808t
EMBASE 2061
embolic occlusion 49, 375–377
  cholesterol embolus 375–377, 376f
  oxalate embolus 377
embryology 55, 56f
  cutaneous stem cells 60–63, 61t–62t
  dermal-epidermal junction 59
  dermis and subcutis 58–59
  epidermis 831
    specialized cells 57–58
  prenatal diagnosis of genodermatoses 63, 822
  skin appendages 59–60
    eccrine and apocrine sweat glands 60, 539, 540t, 541
    hair follicles and sebaceous glands 59–60, 1082t
    nails 60, 1087, 1087f
  skin development in postnatal life 63
EMLA cream 2156, 2346
  adverse reactions 2156
  contraindications 2156
  dosage 2156, 2347t
  indications 1334
  interactions 2156
  mechanism of action 2156
emollients
  atopic dermatitis 214
  perforating disease 1604t
emopamil-binding protein 952
emotional deprivation 1523
emperipolesis 1543
emtricitabine, adverse reactions 1299t
emulsions, topical 2374
enalapril 2189t
  adverse reactions, lichen planus 185t
enamel hypoplasia 506
enamel paint appearance 740f
encainide 2190t
encephalocele 996–997
  atretic 998
  cleft lip/palate 1005t
encephalocraniocutanous lipomatosis 959
encephalopathy, HIV-related
enchondroma, nail bed 2440t
end-stage renal disease, pruritus in 112t, 117–118, 117f, 118t
endemic pemphigus foliaceus *see* pemphigus foliaceus
endive 275t, 285t
endocarditis 9–11, 776t–778t, 1209t
  and drug abuse 1515t, 1519
  infective 377
  marantic 377
endochondral pseudocyst *see* pseudocyst of auricle
endocrine acral dry gangrene 768t
endocrine cancer, metastatic 2049, 2053t
endocrine disease 768–769, 768f–770f, 768t–771t
endocrine pruritus 119
endogenous familial hypertriglyceridemia 1549t, 1550
endoplasmic reticulum 86–87
  overload response 888
endostatin 1587t, 1588f
endothelial cells
  in atopic dermatitis 206t
  in scleroderma 643, 644f
  in wound healing 2318
endothelin receptor antagonists 651
endothelin-1 1680–1681
endothrix hair invasion 1260
endovascular lasers *see* vascular lasers
endovascular papillary angioendothelioma *see* Dabska-type hemangioendothelioma
endovenous laser/radiofrequency ablation 2522–2523, 2522f
  clinical results 2522
  combination with ambulatory phlebectomy 2523
  mechanism of action 2522
  surgical technique 2522–2523
enfermedad de Robles *see* onchocerciasis
enfuvirtide
  adverse reactions 1299t
  injection site reactions 663
English walnut leaf 2206t
English-Wear infection *see* cat scratch disease
enoxacin 2116t
  interactions 2191t
  photoallergy 1480t

enoxaparin 364t
ensulizole 2199, 2200f
entactin *see* nidogen
Entamoeba histolytica 1367t
Enterobacter spp., chronic granulomatous disease 910t
enterobiasis 1407t–1408t
Enterobius vermicularis 1407t–1408t
Enterococcus faecalis 1516
enteroviruses 1346–1348
  clinical features and differential diagnosis 1347, 1347f
  epidemiology 1346
  pathogenesis 1347
  pathology 1347
  treatment 1347–1348
enthesitis-related arthritis 672t
Entrez 72f
envoplakin 463–464, 825–826
enzymatic panniculitis *see* pancreatic panniculus
enzyme deficiency diseases
  alkaptonuria 709t
  Fabry disease *see* Fabry disease
  fucosidosis 810t–811t
  Gaucher disease 803t–804t, 810t–811t
  Hartnup disease 810t–811t
  Niemann-Pick disease 810t–811t
  phenylketonuria *see* phenylketonuria
enzyme replacement therapy 716
  porphyria cutanea tarda 724
  SCID 921
enzyme-linked immunosorbent assay *see* ELISA
eosinophils 423
  in atopic dermatitis 206t
  biology 411–412, 412f
  granular contents 411–412
  within dermis 413f
eosinophil cationic protein 411
eosinophil peroxidase 411–412
eosinophil-derived neurotoxin 411
eosinophilia-myalgia syndrome 654
  differential diagnosis 650t
  lichen myxedematosus 692
eosinophilic angiocentric fibrosis 412
eosinophilic cationic protein 83
eosinophilic cellulitis *see* Wells' syndrome
eosinophilic dermatoses 411–421
  differential diagnosis 414t
  eosinophil biology 411–412, 412f
  evaluation 413f
  granuloma faciale 412–416
  hypereosinophilic syndrome 418–421
  papuloerythroderma of Ofuji 416, 416t
  Wells' syndrome 416–418
eosinophilic fasciitis 651–652
  clinical features 644t, 652f
  differential diagnosis 414t, 650t
  history 651
  pathology 652, 652f
  treatment 652
eosinophilic folliculitis 572–576
  AIDS-associated 574–575, 575f, 1294–1295, 1294f
eosinophilic granuloma 1530t–1531t, 1531
eosinophilic pustular folliculitis 572–574
  clinical features 572
  differential diagnosis 308t–310t, 414t, 574
  epidemiology 572
  history 572
  of infancy 531–532, 575–576
    clinical features 532f, 576
    differential diagnosis 524t–525t, 576
    epidemiology 576
    history 576
    pathogenesis 576
    pathology 576
    treatment 576
  pathogenesis 572
  pathology 572–574
  treatment 574
eosinophilic spongiosis 470t
eosinophilic ulcer of oral mucosa 414t, 1159
eosinophilic vasculitis 414t
eosinophils 83
eotaxins 411
ephelides 1484, 1854–1855
  clinical features 1852t
  laser therapy 2268–2269
  and melanoma risk 1890
ephrins 1681
Epicauta funebris 1439
Epicel 2374, 2375t
EpiCeram emulsion 2156
epicranius muscle 2334
epicutaneous sensitization 206t
epidemic louse-borne typhus 1244t, 1246t
epidemiology 2057, 2057t
  causal inference 2060t
  and cause of disease 2058–2060
  genetic 2061
  prognosis 2060t
  systematic reviews 2060–2061
  see also statistics
epidermal atrophy 624t, 637
epidermal cyst *see* epidermoid cyst
epidermal grafts 2374
epidermal growth factor 2374
  in wound healing 2317t
epidermal growth factor receptor inhibitor-induced eruption 551–552, 552f, 569
epidermal hyperplasia 1483
epidermal inclusion cyst *see* epidermoid cyst
epidermal lipid metabolism 2066–2068
  acidification 2068, 2068f
  biosynthetic activities 2066–2067, 2066f
  extracellular processing 2067–2068, 2067f
  lamellar body secretion 2066f, 2067
epidermal nevus 8, 953t, 1809–1810
  clinical features 1809, 1810f
  differential diagnosis 1810
  epidemiology 1809
  epidermolytic verrucous 953, 953f, 953t
  inflammatory linear verrucous *see* ILVEN
  pathogenesis 1809
  pathology 1810, 1810f
  treatment 1810
  unilateral palmoplantar verrucous 953, 953t
epidermal nevus syndrome 957–958, 1809
epidermal stem cells 60–61, 61f
epidermal transglutaminase 492
epidermis 43, 44f
  development 55–57, 56f–57f, 830–831
  differentiation 825f, 830–831
    regulatory pathways 830–831
  healing *see* wound healing
  palmoplantar 58
  specialized cells 57–58
  structure and function 825–827
  thickness 55
epidermodysplasia verruciformis 1303, 1308, 1309f, 1775
  genetics 813t
  histology 1312f
  and NMSC 1776
  pathology 1312
  see also human papillomavirus
epidermoid cysts 3t–4t, 1817–1823
  anogenital 1183
  clinical features 1818f
  excision biopsy 1818
  histology 1819f
  inflamed 1819f
  nail bed 2440t
  pathology 1818
  proliferating 1817t, 1818f, 1821
  see also Gardner syndrome
epidermolysin 330
epidermolysis bullosa 59, 501–513, 502f, 1595–1596
  autoantigens 456f
  blister formation 503f–504f
  cleavage planes in 502f
  clinical features 504–508
    cutaneous findings 504–506, 504f–507f
    cutaneous malignancies 507–508, 508f
    extracutaneous findings 506, 508t
  complications 511t–512t
  differential diagnosis 509–510
  dominant dystrophic 458t, 509t
    pretibial 502f, 505–506
    pruriginosa 502f
    transient bullous dermolysis of newborn 502f, 509t
  dystrophic 502t, 1117t, 1593t
    clinical features 505f
    Hallopeau-Siemens 502f, 504
    and NMSC 507, 1776
    pathogenesis 502–504
    subtypes 502f
  epidemiology 501
  history 501
  junctional 502t, 509t, 1593t, 1595f
    generalized 509t
    Herlitz 458t, 507f, 509t, 801
    non-Herlitz 458t, 501–502, 509t
    pathogenesis 501–502
    with pyloric atresia 457t, 509t
    subtypes 502f
  nails in 502f, 505, 1135
  neonates 501, 502f, 526t–528t
  pathogenesis 501–504
  pathology 508–509, 509f
  recessive dystrophic 458t, 506f, 508f, 509t
    centripetalis 502f, 505–506
    Hallopeau-Siemens 502f
    inversa 502f, 505–506
  simplex *see* epidermolysis bullosa simplex
  target proteins 502f
  treatment 510–511, 511t
  ultrastructural findings 509t
  see also Kindler syndrome
epidermolysis bullosa acquisita 47t, 455, 456t, 481, 487–489
  autoantigens 456t, 476t, 1596t
  clinical features 488, 488f
  diagnosis 488–489
    immunochemical studies 489
    immunoelectron microscopy 489
    immunofluorescence microscopy 488–489
    light microscopy and electron microscopy 488
  differential diagnosis 489
  epidemiology 487
  history 487
  immunoreactants in 457t
  monoclonal gammopathy 2014t
  pathogenesis 487–488
  treatment 489
    immune globulin 2148t
epidermolysis bullosa nevi 1863
epidermolysis bullosa simplex 458t, 504f–505f, 834, 835t, 1065t, 1593t
  autosomal recessive 509t
  differential diagnosis 509–510
  Dowling-Meara *see* Dowling-Meara epidermolysis bullosa simplex
  genetics 785t, 832t–833t
  Koebner *see* Koebner epidermolysis bullosa simplex
  lethal acantholytic 502f, 509t–510t, 832t–833t
  migratory circinate 502f, 835t
  with mottled pigmentation 505, 1072t–1073t
  with muscular dystrophy 458t, 509t
  Ogna 458t, 502f
  pathogenesis 501
  with pyloric atresia 458t
  subtypes 502f
  superficialis 509t
  suprabasal forms 510t
  target proteins 502f
  ultrastructural findings 509t
  Weber-Cockayne *see* Weber-Cockayne syndrome
epidermolytic acanthoma 1808, 1808f
epidermolytic hyperkeratosis *see* bullous congenital ichthyosiform erythroderma
epidermolytic ichthyosis 47, 510t, 803t–804t, 832t–833t, 834, 835t, 838t, 845–847
  clinical features 535f, 845, 846f
  differential diagnosis 847
  epidemiology 845
  genetics 785t, 803t–804t
  history 845
  mosaic 845
  neonatal 526t–528t, 847t
  pathogenesis 845, 846f
  pathology 846–847, 846f
  superficial *see* ichthyosis bullosa of Siemens
  treatment 847
epidermolytic nevi 845
epidermolytic palmoplantar keratoderma 832t–833t
epidermolytic verrucous epidermal nevus 953, 953f
Epidermophyton spp.
  superficial mycoses 1251t
Epidermophyton floccosum 1255t
  tinea corporis 1256t
  tinea cruris 1258t
  tinea pedis 1261, 1263t
epidermotropism 348, 416
epigenetic change 1762
epigenetics 790–791, 790f
epiloia *see* tuberous sclerosis
epinephrine
  adverse reactions 2155t, 2185t
  and digital necrosis 2344
  and eccrine sweating 590t
  in local anesthesia 2344–2345
  systemic reactions 2345t
  tumescent anesthesia 2348t
  urticaria 303, 304t
EpiPen 1437
epithelial cell adhesion molecule 84t, 85
epithelial giant cells 1136
epithelial membrane antigen 29t–33t
epithelioid angiomatosis *see* bacillary angiomatosis
epithelioid fibrous histiocytoma 1966
epithelioid hemangioendothelioma 1931–1932
  clinical features 1931
  differential diagnosis 1932
  epidemiology 1931
  history 1931
  pathogenesis 1931
  pathology 1931–1932, 1932f
  treatment 1932
epithelioid hemangioma *see* angiolymphoid hyperplasia with eosinophilia
epithelioid sarcoma 1975–1976, 1975f
epithelioma cuniculatum *see* verrucous carcinoma
epitope spreading 475
epoprostenol 651
epoxy resin 242t
Epstein-Barr virus (HHV-4) 29t–33t, 1321–1328, 1334–1336
  clinical features 1335–1336, 1335f
  diagnosis and pathology 1336, 1336t
  differential diagnosis 1336
  epidemiology 1334, 1335t
  and erythema multiforme 320t
  history 1334
  HIV-related 1289
  lymphoproliferative syndrome 906t
  pathogenesis 1334–1335
  treatment 1336
  see also infectious mononucleosis
Epstein's pearls 1819
ERBIN 450–451
erbium glass lasers 2251
  skin penetration 2254f
erbium YAG lasers 2251, 2271–2272
  skin penetration 2254f
  skin resurfacing 2273t
Erb's point 2328
Erdheim-Chester disease 1530t–1531t
erlotinib 2149t

adverse reactions 353t
hypertrichosis 1118t
nail changes 1141t
erosions 4t–5t, 2314
erosive adenomatosis 1843
erosive pustular dermatosis 1484
errors, statistical 2062, 2062f, 2062t
eruptive hemangioma *see* pyogenic granuloma
eruptive histiocytoma *see* generalized eruptive histiocytoma
eruptive pseudoangiomatosis 1347
eruptive xanthoma 768t, 769f, 1550–1551, 1550f, 1553
erysipelas 1196
clinical features 1196, 1197f
diagnosis 1196
epidemiology and pathogenesis 1196
history 1196
occupational 271t
pathology 1196
treatment 1196
erysipelas (erisipela) de la costa *see* onchocerciasis
erysipeloid 1204, 1204f
occupational 271t
of Rosenbach *see Erysipelothrix rhusiopathiae*
Erysipelothrix rhusiopathiae 271t, 1204, 1451
erythema 6t–7t, 8
erythema ab igne 8, 1065t, 1489–1491
clinical features 1490, 1490f
differential diagnosis 1491
epidemiology 1490
history 1489–1490
pathogenesis 1490, 1490t
pathology 1490–1491, 1490f
treatment 1491
erythema annulare centrifugum 307–312
clinical features 307–311, 311f
differential diagnosis 308t–310t, 311
epidemiology 307
history 307
pathogenesis 307
pathology 311
treatment 312
erythema annulare rheumaticum *see* erythema marginatum
erythema contusiformis *see* erythema nodosum
erythema dyschromicum perstans 184t, 199–201, 1050–1052
clinical features 200, 200f, 1051–1052, 1051f
postinflammatory hyperpigmentation 1050t
differential diagnosis 200, 1052, 1053t
distribution 9
epidemiology 200, 1051
history 200
pathogenesis 200, 1051
pathology 200, 1052
treatment 200–201, 1052
erythema elevatum diutinum 396–397
clinical features 396–397, 396f
differential diagnosis 397
epidemiology 396
monoclonal gammopathy 2014t
pathogenesis 396
pathology 397, 397f
treatment 397, 402t
erythema gyratum repens 163
clinical features 316, 316f
differential diagnosis 308t–310t, 316–317
epidemiology 316
history 316
paraneoplastic 763f, 764t–765t
pathogenesis 316
pathology 316
treatment 317
erythema induratum 1232, 1648–1649
clinical features 1648, 1648f
differential diagnosis 1649
epidemiology 1648
history 1648
pathogenesis 1648
pathology 1648–1649, 1648f–1649f
sites of 1642f
treatment 1649
erythema induratum of Bazin 1232
erythema infectiosum 1349–1352
clinical features and differential diagnosis 1350, 1351f
epidemiology 1350
history 1349
pathogenesis 1350
pathology 1350
treatment 1350–1352
erythema marginatum 312–313
clinical features 312, 312f–313f
differential diagnosis 308t–310t, 313
epidemiology 312
history 312
pathogenesis 312
pathology 312–313
treatment 313
erythema marginatum rheumaticum *see* erythema marginatum
erythema migrans 313–316, 1215f
clinical features 17f, 313–314, 314f, 314t
differential diagnosis 308t–310t
epidemiology 313
history 313
pathogenesis 313
pathology 314, 315f, 315t
treatment 315–316, 315t
erythema multiforme 184t, 285t, 319–323
anogenital 321, 1185
clinical features 320–322, 320t, 321f–322f
distribution of skin lesions 321
elementary skin lesions 320–321
mucosal lesions 321, 322f
natural history 322
systemic symptoms 321–322
differential diagnosis 308t–310t, 320t, 322–323, 323f, 323t
epidemiology 319
history 319
and leukemia 2042t
major 320t
minor 319
pathogenesis 319–320
pathology 322, 323f
precipitating factors 320t
radiation-induced 319
treatment 323
vs urticaria 323f, 323t
erythema nodosum 1641–1645
clinical features 1642–1643, 1643f
differential diagnosis 1644–1645
epidemiology 1642, 1644t
history 1642
pathogenesis 1642
pathology 1643, 1644f
and sarcoidosis 1560f
sites of 1642f
systemic causes 1644t
treatment 1645, 1645t
see also sarcoidosis
erythema nodosum leprosum 1225
erythema nodosum migrans *see* subacute nodular migratory panniculitis
erythema perstans *see* erythema annulare centrifugum
erythema toxicum *see* erythema toxicum neonatorum
erythema toxicum neonatorum 414t, 523, 524t–525t, 528f
erythematotelangiectactic (vascular) rosacea 562, 562f, 563t
treatment 567t
erythermalgia *see* erythromelalgia
erythma chronicum migrans *see* erythema migrans
erythralgia *see* erythromelalgia
erythrasma 1183, 1200–1201, 1202f
in athletes 1507t
erythroderma 171–181, 841t–842t
atopic 176, 178
bullous form 177–178, 178f
cardiac disease 171, 175
causes
adults 172t–173t
neonates and infants 173t–174t
clinical features 171–178, 776t–778t
cutaneous manifestations 171–175, 175f
systemic manifestations 175
congenital ichthyosiform 177–178, 838t, 851–855
cutaneous T-cell lymphoma 177–178
desquamation 175f
differential diagnosis 179
adults 179f
neonates 180f
drug-related 176, 176t, 178
epidemiology 171
history 171
idiopathic 176, 176f, 178
non-bullous form 177–178
paraneoplastic 177, 764t–765t
pathogenesis 171
pathology 178–179
psoriatic 175, 175f, 178–179
treatment 179–181, 2077t
erythrodermic pemphigoid 479t
erythrodermic psoriasis 139–142, 175, 175f, 178–179
erythrodontia 719t, 723f
erythrokeratodermas 838t, 862, 872t
diagnosis 841t–842t
hystrix-like ichthyosis-deafness syndrome 874t
keratitis-ichthyosis-deafness syndrome *see* keratitis-ichthyosis-deafness syndrome
progressive symmetric 838t, 863–864
erythrokeratodermia with ataxia 852t–854t
erythrokeratodermia progressiva Burns *see* keratitis-ichthyosis-deafness syndrome
erythrokeratodermia variabilis 838t, 862–866, 874t
clinical features 862–863, 862f–863f
hypertrichosis 1117t
differential diagnosis 308t–310t, 863
epidemiology 862
genetics 803t–804t
history 862
pathogenesis 862
pathology 863
treatment 863
erythrokeratolysis hiemalis 852t–854t
erythromelalgia 371, 1751–1753
clinical features 1752, 1752f
differential diagnosis 1752
epidemiology 1751–1752
genetics 818t–819t
history 1751
pathogenesis 1752
pathology 1752
treatment 1752–1753
erythromelanosis faciei 565, 1638
erythromelanosis follicularis faceie et colli 577, 1053t
erythromycin 2105t
adverse reactions 2107t
gingival hyperplasia 1156t
pruritus 120t
dosage 2114t
formulations 2106t
indications 2106
acne vulgaris 556, 556t, 2105, 2106t
bacillary angiomatosis 1209t
bullous pemphigoid 484t
chancroid 1386t
donovanosis 1389t
linear IgA bullous dermatosis 499
lymphogranuloma venereum 1387t
pityriasis lichenoides 157
rosacea 567t, 2105, 2106t
interactions 2191–2193, 2191t
mechanism of action 2106t
pregnancy and lactation 2106t, 2155t
trade names 2106t
erythromycin estolate
dosage 2114t
pregnancy and lactation 2114
pruritus 120t
erythromycin ethyl succinate, dosage 2114t
erythromycin stearate, dosage 2114t
erythronychia 887, 893
erythroplakia 1160–1161, 1161f
erythroplasia of Queyrat 1309, 1311f, 1780f
Mohs surgery 2448
erythropoietic protoporphyria 719t, 722, 722f
biochemical findings 720t
genetics 719t, 810t–811t
treatment 725t
PUVA phototherapy 2232
erythropoietin
adverse reactions, erythroderma 176t
renal pruritus 118t
eschar 1203f
escharotics 2211
Escherichia coli 375
chronic granulomatous disease 910t
and erythema nodosum 1644t
escitalopram 133
esophageal cancer, metastatic 2049
esophageal candidiasis 1269t
esophageal dysmotility 633
essential fatty acid deficiency 738t, 740, 749f
essential oils 2215t
essential thrombocythemia 370–371, 624t
17beta-estradiol, interactions 2192
estrogens
adverse reactions 2155t
pruritus 120t
estrogen dermatitis 447–448
etanercept 2143–2144
adverse reactions 608, 762f, 2144, 2144f
ANA/anti-dsDNA antibody induction 608
Behçet's disease 435t
dosage 2144
FDA warnings 2140t
indications 2144
dermatomyositis 639t
psoriasis 153t
injection site reactions 354t
interactions 2144
laboratory evaluation 2140t
pregnancy and lactation 2144
Etcoff, Nancy, *Survival of the Prettiest: The Science of Beauty*
ethambutol
adverse reactions, lichen planus 185t
indications, tuberculosis 1234t
ethanol 2070–2071, 2461
ethanolamine oleate 2515t
ethinylestradiol, interactions 2192
ethionamide, tuberculosis 1234t
ethnic differences
facial aging 2478, 2478t
lupus erythematosus 615
ethosuximide 663t
adverse reactions
cutaneous lymphoid hyperplasia 2039t
gingival hyperplasia 1156t
ethylene glycol 255
ethylene oxide 253t–254t
ethylenediamine dihydrochloride 242t, 246t
ethyleneurea 242t
ethylhexyl triazone 2199
etidocaine 2344t
etoposide 2297
adverse reactions 349t
etravirine, adverse reactions 1299t
etretinate 2089
adverse reactions
osteoporosis 2101
pseudoporphyria 724t
indications
pityriasis rubra pilaris 165, 2097
premalignant/malignant skin lesions 2097
psoriasis 2094–2095
pharmacologic features 2092t
structure 2090f

eucalyptus
  Australian (*Eucalyptus radiata*) 2215t
  lemon-scented (*Eucalyptus citriodora*) 2215t
eugenol 1155, 1157t
Eulaelaps spp. 1445t
eumelanin 8, 1016f
Euphorbia esula 278t
Euphorbia pulcherrina see poinsettia
Euphorbiaceae 276t, 278t, 279
Euroglyphus maynei 1445t
European Porphyria Initiative 725
EUSOL 253t–254t
Euterpe oleracea see acai berry
evening primrose oil 2207t
Evicel 2464t
Evithrom 2464t
Evolence 2550
exanthem of primary HIV infection 1287
exanthem subitum *see* human herpesvirus-6
exanthematous drug eruptions 12t, 338–339, 338t, 339f
excess ovarian androgen release syndrome 1125
excimer lasers 2255t
  alopecia areata 1103t
  lichen planus 195t
  phototherapy 2223
  skin penetration 2254f
  vitiligo 1029
excisional biopsy 2381, 2382t, 2391–2392, 2391f, 2391t, 2393f
  fusiform excision 2391f–2392f
  undermining 2393f
excited skin syndrome 224
excoriations 4t–5t, 1514t
exercise-induced anaphylaxis 298
exfoliants 2480t
exfoliative dermatitis *see* erythroderma
exfoliative erythroderma *see* erythroderma
exogen 1079t, 1081
Exophiala 1279f
exostosis, nail bed 2440t
ExpressGraft 2378
exsiccosis 222
extracellular matrix 1585–1598, 2321–2322
  animal models 1596–1597
  components as autoantigens 1596, 1596t
  functions of 1590
  potential for molecular therapy 1597
  related diseases 1591–1597, 1593t
    cutis laxa *see* cutis laxa
    Ehlers-Danlos syndrome *see* Ehlers-Danlos syndrome
    epidermolysis bullosa *see* epidermolysis bullosa
    Marfan syndrome *see* Marfan syndrome
    pseudoxanthoma elasticum *see* pseudoxanthoma elasticum
  structure and function 1585–1591, 1586f, 1586t
    collagens 1585–1589, 1586f, 1587t, 1588f
    elastin and elastic fibers 1589–1590, 1589f–1590f
    extrafibrillar matrix 1590
    laminins 1590
    microfibrils 1589–1590, 1590f
extracellular matrix protein-1 1593t
extractable nuclear antigens 400t
extrafibrillar matrix 1590
extramammary Paget's disease *see* Paget's disease, extramammary
extramedullary cutaneous plasmacytoma, monoclonal gammopathy 2014t
extramedullary hematopoiesis 2040–2041
  clinical features 2041, 2041f
  differential diagnosis 2041, 2041t
  epidemiology 2040–2041
  pathogenesis 2041
  pathology 2041
  treatment 2041
extranodal NK/T-cell lymphoma, nasal type 2033, 2033f
extraskeletal chondroma 1991
extrinsic pathway inhibitors 364t
Exu-dry dressings 2366
Exuderm 2373
eye, anatomic landmarks 2332f
eye shadows 2483, 2483f
eyebrows
  hypertrichosis 1118t
  ideal position 2477f
eyeglass frame acanthoma *see* acanthoma fissuratum
eyelashes, hypertrichosis 1118t
eyelid tray 2360f
eyelids
  cartilage grafts 2422t
  dermatitis 207, 237t
  in dermatomyositis 634f

F(ab) fragments 93
Fab fragments 93
Fabaceae 280
Fabry disease
  clinical features 1719–1720
    cardiovascular disease 776t–778t
    renal disease 780t–781t
  genetics 810t–811t
face
  arterial supply
  Blaschko's lines 943f–944f
  fascial planes 2343
  innervation 2349, 2349f
  venous supply 2329f
face lifting
  botulinum toxin *see* botulinum toxin
  liposuction 2531
facial aging 2473–2478
  anatomic basis 2474
  cartilage and bone changes 2477
  combination therapies 2478
  ethnic differences 2478, 2478t
  gender differences 2478, 2478t
  Glogau wrinkle scale 2475t, 2476f
  loss of elasticity 2477
  loss of subcutaneous fat 2476, 2477f
  musculature changes 2476–2477
  photoaging *see* photoaging
  pigmentary system 2476
  rhytides see rhytides
  see also photoaging
facial angiofibroma 823, 932t–933t
facial asymmetry, botulinum toxin 2567, 2567f
facial blushes 2483
facial expression, muscles of 2331f, 2334–2335, 2335t
  innervation 2335t
facial foundations 2481–2482, 2482f, 2482t
facial hirsutism 1124f
facial nerve 2336–2338, 2337f
  damage to 2466–2467, 2467f
  mandibular branch 2461
  temporal branch 2466
  zygomatic branch 2466
facial nerve block 2349–2350, 2349f–2350f
facial rejuvenation, non-ablative 2256
facial soap 2480t
facial surgery tray 2359f
factitial dermatitis *see* dermatitis artefacta
factitious urticaria *see* dermographism
factor D 909t
factor H 909t
factor I 909t
factor IIa *see* thrombin
factor IX 358
  excess 1744t
factor IXa 358
factor V Leiden 1744t
factor Va 358
  inhibitors 364t
factor VIIa 358
factor VIII excess 1744t
factor VIIIa 358
  inhibitors 364t
factor X 358
factor Xa 358
  inhibitors 364t
factor XI 358
  excess 1744t
factor XIa 358
factor XII 358
factor XIIIa 29t–33t
Fagopyrum esculentum see buckwheat
false bishop's weed 279t
false hellebore 2207t
famciclovir
  adverse reactions 2127t
  dosage 2126t–2127t
  formulations 2126t
  indications 2126t
    herpes simplex 1329t
    varicella-zoster 1329t
  viral susceptibility to 2125t
familial atypic mole and multiple melanoma syndrome 813t
familial benign chronic pemphigus *see* Hailey-Hailey disease
familial chilblain lupus 818t–819t
familial chronic mucocutaneous candidiasis 903t
familial chronic nail candidiasis 903t
familial chylomicronemia 810t–811t
familial cirrhosis 832t–833t
familial cold autoinflammatory syndrome 673f, 818t–819t
familial cold urticaria *see* Muckle-Wells syndrome
familial colorectal polyposis *see* Gardner syndrome
familial continual skin peeling *see* peeling skin syndrome
familial cutaneous amyloidosis *see* X-linked reticulate pigmentary disorder
familial cutaneous leiomyomatosis, renal disease 780t–781t
familial cutaneous and mucosal venous malformations 1713t, 1721
familial cylindromatosis 813t
familial defective apolipoprotein B-100 1551–1552
familial dysautonomia *see* Riley-Day syndrome
familial dysbetalipoproteinemia 1549t
familial generalized lentiginosis 818t–819t
familial hemophagocytic lymphohistiocytosis 906t
familial Hibernian fever 818t–819t
familial hirsutism 1121t
familial hypercholesterolemia 1549t, 1551–1552
  genetics 810t–811t
familial hyperchylomicronemia 1549t
familial hypertriglyceridemia 810t–811t
familial intrahepatic cholestasis, electrolytes in sweat 597t
familial lipoprotein lipase deficiency 1549t
familial mastocytosis 813t, 1994t
familial Mediterranean fever 673f, 707
  genetics 818t–819t
familial mucocutaneous candidiasis 903t
familial multiple lipomatosis 1984
  liposuction for 2527t
familial partial lipodystrophy *see* Köbberling-Dunnigan syndrome
familial polyposis of colon *see* Gardner syndrome
familial progressive hyperpigmentation 810t, 1054
familial reactive perforating collagenosis 1600t
familial/hereditary polymorphous light eruption of American Indians *see* actinic prurigo
famotidine 303, 2191t
Fanconi anemia 932t–933t, 1065t, 1068t
Farber lipogranulomatosis 810t–811t
farnesol pyrophosphate synthase 2067f
Fas (death receptor) *see* CD95
Fas ligand 326
Fas signaling pathway 326f
fascia lata, human cadaveric 2551–2552
Fascian 2548t–2549t
fasciectomy 1626, 1953
fasciitis-panniculitis syndrome 1660t
Fasciola hepatica 1407t–1408t
fascioliasis 1407t–1408t
FasL (death ligand) *see* CD95L
fat distribution 52
fat, tumors of 1984–1990
  angiolipoma 1985–1986
  hibernoma 1987–1988
  lipoblastoma/lipoblastomatosis 1988–1989
  lipoma 1984–1985
  liposarcoma/atypical lipomatous tumor 1989–1990
  nevus lipomatosus superficialis 1988
  spindle cell lipoma 1986–1987
  see also xanthoma
fatty acid synthase 2067f
faulty immunity 47
faun tail 999, 1000f, 1119
Favre-Racouchot syndrome 1458f, 1484
favus hair invasion 1260
Fc receptor 83, 2147–2148
FcεR receptors 83–84
feathering 1497
febuxostat 711
felodipine
  adverse reactions, gingival hyperplasia 1156t
  interactions 2192
Felty's syndrome 681
female pattern alopecia 1094, 1094f–1095f, 1096t, 1098f
  hair transplantation 2539f
  Ludwig grading system 2537f
  see also androgenetic alopecia
fenclofenac-induced lichen planus 185t
fennel 279t
fenofibrate 1554t–1555t
fenoterol, hypertrichosis 1118t
fentanyl 2352
  adverse reactions, pruritus 120t
  and eccrine sweating 590t
fenugreek 2212t
Ferguson-Smith multiple self-healing squamous epitheliomas 813t
Ferguson-Smith syndrome 801
  clinical features 1781
  and NMSC 1781
ferrous subsulfate 2464t
fetal alcohol syndrome 1117t
fetal hydantoin syndrome 1117t
fetus papyraceus 1001–1002, 1002t
fever
  with cutaneous eruption 13f
  and nail growth 1090t
fever blisters *see* herpes simplex viruses
feverfew 274t, 284, 285t, 2207t, 2212t
  wild 285t
fexofenadine 303, 304t
fiberglass dermatitis 117, 264, 265f
Fibracol Plus 2372
fibrillins 1589
fibrillin-1 1593t, 1594
fibrin sealants 2464t
fibrinogen 1592t
  excess 1744t
fibroblast growth factor 1681f
  in wound healing 2317t
fibroblast growth factor receptor 2 mosaicism 954
fibroblast growth factor receptor 3 mosaicism 817f, 953–954, 954f
fibroblast growth factor receptor 1761f
fibroblastic rheumatism, differential diagnosis 650t
fibroblasts 947t
  autologous 2552
  in scleroderma 644f
  in wound healing 2320–2321, 2321f
fibrodysplasia ossificans progressiva 733–734, 818t–819t
fibroepithelial polyp *see* skin tags

fibroepithelioma of Pinkus
  clinical features 1787, 1787f
  histology 1788
fibrofolliculoma 1830, 1831f
fibrokeratoma
  acral 1964–1965, 1965f
  nail bed 937f, 1144, 2440t
fibroma
  calcifying aponeurotic 1971, 1971f
  infantile digital 1969–1970, 1970f
  nail bed 937f, 1144, 2440t
  oral 1154–1155
  perifollicular 1830
  periungual 937f, 938
  pleomorphic 1966, 1966f
  of tendon sheath 1968
fibroma simplex *see* dermatofibroma
fibromatoses 1971–1972, 1972f
  linear 927t
fibromatosis hyalinica multiplex juvenilis *see* juvenile hyaline fibromatosis
fibromodulin 1592t, 2313
fibronectin 411, 834t, 1592t
  in perforating disease 1599
fibroplasia 1962f
fibrosarcoma 1975, 1975f
fibrosing dermatitis, pattern analysis 22, 24f
fibrous hamartoma of infancy 1971, 1971f
fibrous histiocytoma
  benign *see* dermatofibroma
  epithelioid 1966
fibrous papule *see* angiofibroma
Fibrovein 2515t
fibroxanthoma, atypical 1973, 1973f, 2449
fibulin-4 1593t
fibulin-5 1593t
Ficus benjamina 287f
Ficus carica see fig
fiddler's neck 549, 1509t
field block 2305, 2348
Field, Lawrence 2525
fifth disease *see* erythema infectiosum
fig 275t, 277t
figurate erythemas 307–317
  differential diagnosis 308t–310t
  erythema annulare centrifugum 307–312
  erythema gyratum repens 316–317
  erythema migrans 313–316
  erythma marginatum 312–313
filaggrin 204–205, 825–826, 2066
filaggrin disorders 834–835, 836f
filamin A 810t
filariasis 1416–1417
  clinical features 1416–1417
  diagnosis 1417, 1417f
  differential diagnosis 1417
  epidemiology 1416
  insect vectors 1416
  pathogenesis 1416
  treatment 1417
filensin 828t
filiform warts, cryosurgery 2286
filler materials 2548–2550
  autologous fibroblasts and collagen 2552
  bovine collagen 1574t, 1575f, 1581t, 1582, 2550–2554, 2550f
  calcium hydroxyapatite 1581t, 2554–2555, 2556f–2557f
  characteristics of 2548t
  complications 2551t
  expanded polytetrafluoroethylene 2555–2559
  foreign body reactions 1580–1582, 1581f, 1581t
  human bioengineered collage 2551
  human cadaveric collagen 2551
  human cadaveric fascia 2551–2552
  hyaluronic acid derivatives *see* hyaluronic acid; hyaluronic acid derivatives
  lipotransfer 2557–2558, 2558f
  poly-L-lactic acid 1581t, 2554, 2556f
  polymethylmethacrylate microspheres 1581t, 2558–2559
  porcine collagen 2550, 2550f
  silicone *see* silicone
film dressings 1735t
filoviruses 1360t
finasteride 1098f
  adverse reactions 2537
  in alopecia 1097, 2536, 2538f
  hirsutism 1124–1125
  mechanism of action 1098f
finger calluses 1509t
finger swelling 645t
fingertip unit 1087, 2153–2154
Finlay-Marks syndrome 1003t
FIP1L1-PDGFRA fusion gene 418
fipronil 1440
fire ant bites 1437–1438
  clinical features 1437–1438, 1437f
  pathogenesis 1437
  treatment 1438
fire stains *see* erythema ab igne
first intention healing 2367–2368
Fischer, Giorgio 2525
fish oils 2207t, 2212t
fish tank granuloma *see Mycobacterium marinum*
fissured tongue 1150, 1150f
fissures 4t–5t
Fite stain 26, 26f
Fite-Faraco stain 27t–28t
Fitzpatric Sun-Reactive Skin Type 2476
Fitzpatrick Scale of skin phototypes 5–8, 8t, 2474
five day fever 1209t
fixed drug eruptions 3t–4t, 184t, 188f, 338t, 345–347, 519t, 1518t
  anogenital 346f, 1185
  postinflammatory hyperpigmentation 1050t
flagellate mushroom dermatitis 1062
flagellate pigmentation from bleomycin 1061
  clinical features 1061, 1061f
  differential diagnosis 1061
  epidemiology 1061
  pathogenesis 1061
  pathology 1061
  treatment 1061
"flame figures" 416–417, 417f
flannel-plant 277t
flaps 2399–2420
  background 2399–2402, 2399t
  Burow's triangle displacement flaps 2401–2404, 2402f
  dorsal nasal flap 2407, 2407f
  double tangent advancement flaps 2404, 2405f–2406f
  helical advancement flaps 2404–2406, 2406f
  rotation flaps 2402–2404
  single tangent advancement flaps 2402–2404, 2403f–2405f
  wedge closure of lip 2407–2408, 2408f
  classification 2401t
  combination 2416–2417, 2418f
  complications 2419
  defect reconfiguration (island pedicle) flaps 2402, 2408–2410, 2409f–2410f
  subcutaneous tunneling 2410, 2411f
  design and suturing 2399, 2400f, 2401t
  locations for 2419t
  movement characteristics 2399–2402, 2400t, 2401f
  postoperative care 2417–2419
  scar contraction 2400f, 2467f
  STARTS mnemonic 2399t
  tissue importation flaps 2402, 2412–2416
  nasolabial interpolation flap 2415, 2415f
  paramedian forehead flap 2413–2415, 2414f
  retroauricular flap 2415, 2416f
  Spear's flap 2415–2416, 2417f
  tissue reorientation flaps 2402, 2410–2412
  bilobed transposition flap 2411–2412, 2412f–2413f
  nasolabial transposition flap 2412, 2413f
  rhombic transposition flap 2410–2411, 2411f–2412f
  see also grafts
flashlamps 2257
flat warts 1308f
  pathology 1308, 1312, 1312f
flautist's chin 1509t
flaxseed 2212t
flea-borne spotted fever 1246t
fleas 1439, 1440f, 1440t
flecainide 1752–1753
Flegel disease 1803–1804
  clinical features 1804, 1804f
  differential diagnosis 1804
  epidemiology 1803
  pathogenesis 1804
  pathology 1804, 1804f
  treatment 1804
"flesh-eating bacteria" syndrome *see* necrotizing fasciitis
flexural psoriasis 143, 144f
Flexzan 2371, 2378
Flinders Island spotted fever 1244t, 1246t
floating harbor syndrome 1118t
floating soap 2480t
floret giant cells
Florida holly *see* Brazilian pepper tree
florist's "croton" 278t, 287f
florists, plant dermatoses 288
Floseal 2464t
Flt-1 1681
Flt-4 1681, 1687
flucinonide 245t
fluconazole
  adverse reactions 2123t
  dosage 2121, 2121t
  indications 1283t, 2120t
  aspergillosis 1283t
  candidiasis 1283t
  cryptococcosis 1283t
  dermatophytoses 1267t
  mucocutaneous candidiasis 1269t
  mycetoma 1272
  penicilliosis 1255
  yellow nail syndrome 1139
  zygomycosis 1255
  interactions 2190–2192
  pregnancy and lactation 2120t
flucytosine
  adverse reactions 2122
  dosage 2122
  indications 2120t
  mechanism of action 2119t
  pregnancy and lactation 2120t
  site of action 2119f
fludarabine
  adverse reactions 349t
  indications, dermatomyositis 639t
fluffy tannic acid powder 2162t
fluid drainage 1685f
flukes 1412f
fluocinolone acetonide 2079t
fluocinonide 2069
  absorption 2069t
fluocortolone 245t
fluodinonide cream 2079t
fluorazepam, interaction with lidocaine 2529t
fluorescence in-situ hybridization (FISH) 419f, 791
fluorescent nucleotide analogues 67t
fluoroderma 344
fluorometholone 2079t
fluoroscopy burns 1491
5-fluorouracil 2159–2160
  adverse reactions 2159–2160, 2159f
  acral erythema 349t
  erythroderma 176t
  extravasation reactions 349t
  hyperpigmentation 349t, 1056t–1057t
  hypohidrosis/anhidrosis 595t
  mucosal hyperpigmentation 349t
  mucositis 349t
  nail changes 349t
  photosensitivity 349t, 1481
  pseudoporphyria 724t
  contraindications 2160
  dosage 2159
  indications 2159
  hypertrophic scars/keloids 1625t
  NMSC 1791
  mechanism of action 2159
  pregnancy and lactation 2160
  topical 2159–2160
fluoxetine 2189t–2190t
  adverse reactions
  acute hemorrhagic edema of infancy 394t
  alopecia 348t
  cutaneous lymphoid hyperplasia 2039t
  eccrine sweating 590t
  indications
  anxiety disorder 133
  depression 134
  drug addiction 1520t
  interactions 2185t, 2187t
fluphenazine
  and eccrine sweating 590t
  and leukoderma 1044t
flurandrenolide 2079t
flurazepam, adverse reactions 336t
flurbiprofen-induced lichen planus 185t
flushing 1750–1751
  carcinoid syndrome 1751t
  causes 1750t
  clinical features 1751
  differential diagnosis 1751
  pathogenesis 1750–1751
  treatment 1751, 1751t
flutamide
  adverse reactions, pseudoporphyria 724t
  indications
  acne vulgaris 557
  hirsutism 1124–1125
fluticasone propionate 2079t
fluvastatin 2191t
fluvoxamine 2189t–2190t
fly larvae, wound debridement 2373–2374
flying squirrel typhus 1244t, 1246t
foam cells 1547
foam dressings 2366t
  leg ulcers 1735t
foamed detergent solutions 2517
focal acral hyperkeratosis 883
focal dermal elastosis 1614t
focal dermal hypoplasia *see* Goltz syndrome
focal palmoplantar and gingival keratosis 872t
focal palmoplantar keratoderma 803t–804t
Foeniculum vulgare see dill; fennel
fogo selvagem 465f
  see also pemphigus
folate 744t–745t
  deficiency 740t–742t
  normal laboratory values
folie à deux 128
follicle pigmentary unit 1079t
follicular atrophoderma 1637–1639
  atrophoderma vermiculatum 1638
  Bazex-Dupré-Christol syndrome 1638
  Conradi-Hünermann-Happle syndrome 1638–1639
  X-linked dominant chondrodysplasia punctata
follicular degeneration syndrome *see* central centrifugal cicatricial alopecia
follicular dendritic sarcoma 1545t
follicular hybrid cyst 1822
follicular hyperkeratosis 1081, 1111
follicular inclusion tetrad 1823
follicular infundibular tumor *see* isthmicoma
follicular keratinization disorders 577–579, 578t
  erythromelanosis follicularis faceie 577

keratosis pilaris atrophicans 577–578, 578t
lichen spinulosus 578–579, 578f
phrynoderma 579
follicular mucinosis 696, 697f
clinical features 696
differential diagnosis 696
history, epidemiology and pathogenesis 696
pathology 696
treatment 696
urticaria-like 696–697
follicular occlusion tetrad 583, 583f
follicular prominence 209t
follicular/folliculosebaceous-apocrine hamartomas 1829–1834
fibrofolliculoma 1830, 1831f
hair follicle nevus 1829
mixed tumor (chondroid syringoma) 1831–1834, 1833f–1834f
nevus sebaceus 1830–1831, 1833f
perifollicular fibroma 1830
trichodiscoma 1830
trichofolliculoma 1829–1830, 1830f
folliculitis 571–586, 573t, 1445t
actinic 573t
and anetoderma 1633t
in athletes 1507t
bacterial 1188–1190
Candida 573t
deep 579–585
acne keloidalis 581–583
follicular occlusion tetrad 583, 583f
hidradenitis suppurativa 583–585
pseudofolliculitis barbae 572f, 579–581, 827, 832t–833t, 1580
Demodex 573t, 575f
dermatophyte 573t, 575f
differential diagnosis 147t
disseminate/recurrent infundibulofolliculitis 576–577, 576f
and drug abuse 1514t
drug-induced 3t–4t, 573t
eosinophilic 572–576
AIDS-associated 574–575, 575f, 1294–1295, 1294f
pustular 572–574
pustular of infancy 575–576
Gram-negative 573t
herpes simplex 573t, 575f, 1323t
hot tub 574f, 1206–1207
irritant 573t
irritant/toxic causes 251t
pattern analysis 22, 24f
perforating 1600t
Pityrosporum 573t, 1253
superficial 571–577, 571f
clinical features 571, 572f
differential diagnosis 572
pathology 571–572, 575f
treatment 572
folliculitis barbae traumatica *see* pseudofolliculitis barbae
folliculitis keloidalis *see* acne keloidalis
folliculitis keloidis nuchae *see* acne keloidalis
folliculitis spinulosa decalvans 578t
folliculitis ulerythema reticulata 1638
folliculocentric basaloid proliferation 1790t
folliculotropic mycosis fungoides 2025–2026
clinical features 2025, 2026f
definition 2025
differential diagnosis 2025–2026
epidemiology 2025
pathology 2025, 2026f
treatment 2026
fomivirsen, cytomegalovirus 1338t
fondaparinux 364t
Fong disease *see* nail-patella syndrome
Fonsecaea compacta 1267
Fonsecaea monophora 1267
Fonsecaea pedrosoi 1267
Fonseca's disease *see* chromoblastomycosis
Fontana-Masson stain 26f, 27t–28t
food contact hypersensitivity syndrome *see* oral allergy syndrome
food hypersensitivity 213–214
food- and exercise-induced anaphylaxis 298
foods
contact urticaria 267
patch testing 264t
sensitivity to 250t, 256
see also individual foods
foot nerve block 2351, 2351f
forceps 2361
Forchheimer's spots 1349
Fordyce angiokeratoma *see* angiokeratoma
Fordyce granules 1149
forefoot dermatitis *see* plantar dermatosis, juvenile
forehead, cosmetic subunits 2333
foreign body giant cells 1575f
foreign body granulomas 21
foreign body reactions 25, 1573–1583
classification 1574t
clinical features 1573–1574, 1575t–1576t
definition 1573
diagnosis 1575
granulomatous 21, 1575f
inorganic and metallic compounds
aluminum 1579
beryllium 1579
paraffin (sclerosing lipogranuloma) 1578
silica 1578–1579
silicone 1578
silver 6t–7t, 25
talc 1579
tattoo 9f, 1575–1578, 1577f
zinc 1579
zirconium 1579
organic and biologic products
cactus spines 1579–1580
Cnidaria 1580, 1580f
hyaluronic acid 1580–1582, 1581t
injectable bovine collagen 1581f, 1581t, 1582
intralesional corticosteroids 1582
keratin 1580
mesotherapy 1582
polyamide "hair" implants 1582, 1582f
starch 1579
suture granuloma 1582
pathogenesis 1573
pathology 1575f, 1576t, 1577f
routes of entry 1573, 1574t
formaldehyde hypersensitivity 241t, 243–244
formic acid 252, 253t–254t
formication 128, 1517, 1517f
formulations, topical *see* topical medications
fos 1761t, 1765t
fosamprenavir, adverse reactions 1299t
foscarnet 2127
cytomegalovirus 1338t
herpes simplex 1329t
viral susceptibility to 2125t
fotemustine 1909t
founder effect 712, 789
four-layer bandage 1737t
Fournier, Pierre 2525
Fournier's gangrene 1183
Fox-Fordyce disease 542, 601
clinical features 601
epidemiology 601
pathogenesis 601
pathology 601
treatment 601
FOXC2 1524, 1713t
foxhole foot *see* immersion foot
FOXP3 91, 92f
fragile X syndrome, and cutis verticis gyrata 1626t
fragrance mix
components 243t
hypersensitivity 241t, 243, 250t
frambösie *see* yaws
Francisella tularensis 1211–1212
frankincense (*Boswellia carterii*) 2215t
Fras1 834
Fraser syndrome 834
freckles *see* ephelides
freckles, senile *see* solar lentigines
free cartilage grafts 2431–2433
complications 2432–2433
donor site 2432
ear 2432
future trends 2433
indications/contraindications 2431–2432
nasal ala 2432
nasal sidewall and tip 2432
postoperative care 2432
preoperative history 2432
technique 2432, 2433f
free fatty acids 2066
Frem1 834
Frem2 834
Fremontodendron spp. *see* California glory
French milled soap 2480t
Fresnel reflectance 2252
Frey's syndrome 540–541, 590, 591f
friction blisters 517–518, 1506t
clinical features 518
differential diagnosis 517t, 518
epidemiology 517
pathogenesis 517
pathology 518
treatment 518
friction burns, airbags 1491–1492
frictional irritant contact dermatitis 252
frictional lichenoid eruption 209
frictional/traumatic injury 1501–1505
acanthoma fissuratum 1503–1504
black heel and palm 1501–1502
chondrodermatitis nodularis helicis 1502–1503
corns and calluses 1501
traumatic auricular hematoma 1504–1505
weathering nodules of ear 1504
Friedreich ataxia 788
frontal fibrosing alopecia 1107, 1107f
frost-nip *see* frostbite
frostbite 51, 1492–1493
clinical features 1493, 1493f
differential diagnosis 1493
epidemiology 1492
history 1492
pathogenesis 1493
pathology 1493
stages of 1493t
treatment 1493
fruit products in soap formulations 2480t
α-fucosidase deficiency 1719–1720
fucosidosis
electrolytes in sweat 597t
genetics 810t–811t
fuels, sensitivity to 253t–254t
full-thickness grafts 2422–2427, 2423f
Burow's grafts 2426
deep nasal defects 2426
donor site 2423–2424, 2423t
future directions 2427
indications/contraindications 2422–2423, 2422t, 2423f
postoperative care 2425–2426
postoperative complications 2426–2427
preoperative history 2423–2424
purse-string suture 2426
securing of graft 2424–2425
technique 2424, 2425f
fumarates
psoriasis 153t
fumarate hydratase 780t–781t, 790
fumaric acid esters 2211
functional cloning 792
fungal diseases 1251–1284, 1251t
in drug abuse 1516
HIV-related 1281f, 1291–1292
candidiasis 1291
dermatophytoses 1291
Pneumocystis jiroveci 1284, 1292, 2084
systemic fungal infections 1291–1292
specimen collection 1265f
subcutaneous mycoses 1266–1273
chromoblastomycosis 1267–1273
lobomycosis 1273
mycetoma 1270–1272
sporotrichosis 1272–1273
superficial mycoses 1251–1266
dermatophytoses 1255–1266
non-inflammatory 1251–1266
systemic mycoses 1273–1284, 1275f
opportunistic pathogens 1279–1284
true pathogens 1273–1279
funnel web spiders 1448, 1448f
furocoumarins 274t, 280
furosemide
adverse reactions 336t
lichen planus 185t
phototoxicity
pseudoporphyria 724t
secondary cutaneous vasculitis 390t
and linear IgA bullous dermatosis 498t
furrowed tongue *see* fissured tongue
furuncles 1190, 1190f
in athletes 1507t
furuncular myiasis 1433
Fusarium spp. 375
onychomycosis 1265t
panniculitis 1658t
fuscidic acid 567t
fusidic acid 2108–2109
indications, impetigo 1189t
Fusobacterium spp. 1152
fusospirochetal gingivitis *see* necrotizing ulcerative gingivitis
Futcher's lines *see* pigmentary demarcation lines

G-CSF 83, 2136, 2137t
injection site reactions 354t
and linear IgA bullous dermatosis 498t
G-protein-coupled receptor 1019f
gabapentin
pruritus 106t, 114
renal 118t
reflex sympathetic dystrophy 122t
GADD45 gene 1765t
galactosyltransferase-1 1593t
galantamine, and eccrine sweating 590t
gallbladder cancer, metastatic 2049t
Galli-Galli disease 1065t
Gallium aparine see goose-grass
γ-hydroxybutyrate abuse 1512
γ-linolenic acid, renal pruritus 118t
Gammagard 2148t
Gammel's disease *see* erythema gyratum repens
Gamunex 2148t
ganciclovir
cytomegalovirus 1338t
viral susceptibility to 2125t
ganglion 1827, 1827f
gangrene 6t–7t
endocrine acral dry 768t
Fournier's 1183
gas 1200, 1201t
perinatal of buttock 526t–528t
gap junctions 871, 874f
Gardner syndrome 1151
clinical features
lipoma 1985
and gastric hemorrhage 773t–774t
genetics 816t
Gardner-Diamond syndrome 365–367
clinical features 366
differential diagnosis and treatment 366–367
pathology 366
Gardnerella vaginalis 1367t
garlic 274t, 2207t
chemical irritant dermatitis 278t
effect on coagulation 2212t
immunologic contact urticaria 275t
and intraoperative bleeding 2460–2461
and platelet aggregation 2460–2461
garment nevus *see* congenital melanocytic nevus

Garrod's pads 1509t
gas gangrene 1200, 1201t
gas plant 280t
gas sterilization 2362t
gases 264
Gasterophilus intestinalis 1433
gastrin-releasing peptide 101
  receptor 99
gastrocutaneous syndrome 932t–933t, 1857t
gastroenterological disease 771, 771f–772f, 771t–774t
gastrointestinal malabsorption 750–751
gastropod envenomation 1452
gatifloxacin 1234t, 2116t
Gaucher disease
  genetics 803t–804t, 810t–811t
gauze dressings 1735t
GCDFP-15 29t–33t
GDC0941 1887t
gefitinib 2149t
  adverse reactions 353t
    hypertrichosis 1118t
    nail changes 1141t
gel electrophoresis 67t
gelatin foam 2464t
gelatin sponge 2465
gelatinases 412f
  in wound healing 2323t
Gelfilm 2464t
Gelfoam 2464t, 2465
gelsolin amyloidosis 700t
gemcitabine
  adverse reactions 349t
    linear IgA bullous dermatosis 498t
gemfibrozil
  adverse reactions, lichen planus 185t
  xanthoma 1554t–1555t
gemifloxacin 2116t
gemtuzumab 2149t
GenBank 72f
genes 784t
  disease-causing 792–795
  positional candidate 794
gene locus 784t
gene mapping 793
gene silencing 1762
gene therapy 822
  for cancer 72–75, 76t–77t, 77f
  targeting keratinocyte stem cells 75–77, 78f
  viral vectors 77t
  wound healing 2323–2324
general essential telangiectasia
generalized anxiety disorder 131t
generalized eczema *see* disseminated eczema
generalized elastolysis *see* cutis laxa
generalized elastorrhexis *see* cutis laxa
generalized eruptive histiocytoma 1530t–1531t, 1536–1537
  antigenic markers 1533t
  clinical features 1537, 1537f
  differential diagnosis 1537
  epidemiology 1536
  history 1536
  pathogenesis 1536–1537
  pathology 1537
  treatment 1537
generalized pustular psoriasis 140–141
  annular pattern 141, 143f
  exanthematic type 141
  "localized" pattern 143f
  von Zumbusch pattern 140–141, 142f
genetics 783–823
  basic concepts 784t
  chromosomal disorders 791–792
  complex traits 795, 795f
  contiguous gene syndromes 812–814
  disease genes 792–795
  gene therapy *see* gene therapy
  genodermatoses 785t
  genotype-phenotype correlations 801
  McKusick's Mendelian Inheritance in Man 801
  molecular classification of hereditary skin disorders 800t–801t
  mosaicism *see* mosaicism
  patterns of inheritance 786t
  preimplantation diagnosis 63, 822
  see also individual conditions
genetic diseases 783
  autosomal dominant inheritance 786, 786t
  autosomal recessive inheritance 786–787, 786t
  Mendelian 783–787, 786f
  X-linked dominant inheritance 786t, 787
  X-linked recessive inheritance 786t, 787
  Y-linked inheritance 787
  see also individual diseases
genetic epidemiology 2061
genetic heterogeneity 785, 785t, 801
genetic polymorphisms 794f
genital anatomy 1172f
genital erosions 1184–1185
  bullous pemphigoid 479f, 1185
  causes of 1184t
  cicatricial pemphigoid 485, 1185
  erythema multiforme 321, 1185
  fixed drug eruptions 346f, 1185
  Hailey-Hailey disease 895, 1185
  linear IgA bullous dermatosis 1185
  pemphigus vulgaris 1185, 1185f
  Stevens-Johnson syndrome 327f, 1185
genital herpes 1324f
  see also herpes simplex viruses
genital psoriasis 141f
genital warts *see* condylomata acuminata
genodermatoses 815f, 820–821, 831f
  ectodermal dysplasias *see* ectodermal dysplasias
  poikiloderma 632
  premature aging syndromes 818t–819t
  prenatal diagnosis 63, 822
genome-wide association studies 795, 796f
genomic imprinting 790–791, 790f–791f
genotype 794–795
genotype-phenotype correlations 801
gentamicin 2107
  adverse reactions 2155t
  dosage 2108t
  formulations 2108t
  indications 2107
  mechanism of action 2108t
  pregnancy and lactation 2108t
  prophylactic 2462t
  trade names 2108t
gentian violet solution 2162t
geographic tongue 1149–1150
  clinical features 1149, 1150f
  epidemiology 1149
  pathology 1149–1150
  treatment 1150
Geraniaceae 274t
geraniol 1437t
geranium (*Pelargonium x asperum*) 287f, 2215t
German measles *see* rubella
gerodermia osteodysplastica 1593t, 1617t–1618t
gestational pemphigoid *see* pemphigoid gestationis
gestodene 557
ghost cells 1835–1836
Gianotti-Crosti syndrome 1353–1354
  clinical features and differential diagnosis 1353–1354, 1354f
  epidemiology 1353
  etiology 1354t
  history 1353
  pathogenesis 1353
  pathology 1354
  treatment 1354
giant axonal neuropathy with curly hair 1104t
giant cells 21
giant cell astrocytoma 823
giant cell elastophagocytosis *see* annular elastolytic giant cell granuloma
giant cell fibroblastoma 1974–1975, 1975f
giant cell lichenoid dermatitis 193–194
giant cell reticulohistiocytoma *see* reticulohistiocytosis
giant cell tumor of tendon sheath 1967–1968, 1968f
giant hairy nevus *see* congenital melanocytic nevus
giant pigmented nevus *see* congenital melanocytic nevus
giant Russian hogweed 279t
giant silkworm moth 1441t
Giardia lamblia 1367t
giardiasis, and erythema nodosum 1644t
Giemsa stain 26, 27t–28t
Gilbert, Camille Melchior 165
Gilchrist's disease *see* blastomycosis
Gilje, Oscar 2365
ginger 2212t
gingival fibroma 935t, 1832f
gingival fibromatosis with hypertrichosis 1116t
gingival hyperemia/hyperplasia, in pregnancy 447t
gingival hyperplasia, drug-related 1156, 1156t
gingival hypertrophy. vitamin C deficiency
gingivitis
  desquamative 484–485, 484f, 1152–1153, 1153f
  necrotizing ulcerative 1152
gingko biloba 2490t
Ginkgo biloba 282t, 283, 283f, 2207t
  adverse reactions 2188
  effects on coagulation 2212t
ginseng 2207t
  adverse reactions 2192t, 2207t
  effects on coagulation 2205–2211
Giroux-Barbeau syndrome *see* erythrokeratoderma with ataxia
GJB3 785t
glabellar frown lines 2562–2563
  botulinum toxin 2562–2563, 2563f, 2563t
glanders 1210–1211
glandular fever *see* infectious mononucleosis
Glanzmann-Riniker syndrome *see* severe combined immunodeficiency
glass fiber, sensitivity to 251t
glatiramer acetate
  injection site reactions 354t
  lymphocytic infiltrate of Jessner 2037
glaucoma 2080t
Gleich syndrome 300
gliadin 491–492
glial fibrillary acidic protein 828t
glial hamartoma *see* nasal glioma
glimepiride 342f
glioma, nasal 994–995, 994t
glipizide 342f
globe artichoke 285t
glochids 274t, 277, 278f
Glogau wrinkle scale 2475t, 2476f
glomangioma 1937–1939, 1938f
glomangiomatosis 1713t, 1939
glomeruloid hemangioma 1917–1918
  clinical features 1918, 1918t
  differential diagnosis 1918
  pathogenesis 1918
  pathology 1918, 1919f
  treatment 1918
glomulin 945t–946t, 1713t
glomus bodies 1087
glomus tumor 928–929, 1145, 1937–1939, 2440t
  clinical features 1937–1938, 1937f–1938f
  differential diagnosis 1939
  epidemiology 1937
  pathogenesis 1937
  pathology 1938, 1938f
  treatment 1939, 2440f
glomuvenous malformations 955, 1722
  clinical features 1722, 1722f
  molecular genetics 1713t
glossitis areata migrans *see* geographic tongue
glucagonoma syndrome 767
  paraneoplastic 764t–765t
β-glucocerebrosidase 2067f
glucocorticoids 2075–2087
  adverse reactions 2077–2078, 2080–2087, 2080t
    cardiovascular effects 2084
    cataracts 2083, 2083f
    cutaneous 2085, 2085f–2086f
    gastrointestinal effects 2084
    growth retardation 2081
    HPA axis suppression 2086–2087
    hypertrichosis 1118t
    infection 2084
    metabolic effects 2083–2084
    myopathy 2082–2083, 2083t
    nervous system 2085
    obstetric and gynecologic 2084–2085
    osteonecrosis 2081, 2083f
    osteoporosis 2080–2081, 2081f–2082f
  contraindications 2079
  dosage 2086t
  dosage alterations 2087
  high risk patients 2081t
  indications 2077t
  interactions 2087
  intralesional therapy 2079
  intramuscular therapy 2078
  intravenous pulse therapy 2078
  mechanism of action 2075–2077, 2076f
    HPA axis function 2076–2077
    inflammatory cell effects 2077t
    molecular mechanisms 2077
  ophthalmic 2079t
  oral therapy 2077–2078, 2077t–2078t
  pharmacology 2075–2077, 2076t
    absorption/distribution 2075–2076
    structure/metabolism 2075, 2075f
  potency ranking 2079t
  synthesis 1122f
  topical therapy 2078–2079
glucosamine sulfate 2212t
glucose transporter protein-1
glucose transporter protein-10
glucosylceramides 2067, 2067f
glue
  patch testing 264t
  sensitivity to 250t
Gluta renghas see rengas tree
glutaraldehyde sensitivity 236f
gluten-sensitive enteropathy 491–493
glyburide
  adverse reactions, lichen planus 185t
  interactions 2127t
  and linear IgA bullous dermatosis 498t
glycerin 2515t
glycerophospholipids 2066f
glyceryl thioglycolate 242t
glycogen storage disease type I, electrolytes in sweat 597t
glycolic acid 252, 2488f
glycols 255
glycomer sutures 2354t, 2355
glycoproteins 1592t
β_2 glycoprotein I 379
glycopyrrolate
  hyperhidrosis 594t
  hypohidrosis/anhidrosis 595t
glycosaminoglycans 411, 1590, 1592f
Glycyphagidae 1445t
Glycyphagus domesticus 1445t
Glycyrrhiza glabra see licorice root
Glycyrrhiza uralensis see licorice root
GM-CSF 83, 411, 2136, 2137t
  injection site reactions 354t, 2137f
gnathophyma 564t
Goeckerman therapy 1774
Goeminne syndrome 1624
gold 761t
gold dermatosis 1499t
gold salts
  adverse reactions 2175t
    erythroderma 176t
    hyperpigmentation 1056t–1057t
    lichen planus 185t

nail changes 1141t
pruritus 120t
hypersensitivity 244–245, 2175f
golden serpent fern *see* anapsos
Goldenhar syndrome 1823
goldenrod 2207t
goldenseal 2211
effects on coagulation 2212t
Golgi apparatus 83, 87f
golimumab 2145
FDA warnings 2140t
laboratory evaluation 2140t
Goltz syndrome 59, 951
clinical features 815f, 951, 952f
cleft lip/palate 1005t
differential diagnosis 951
digital anomalies 1005t
genetics 807t, 949t, 951
neonates 526t–528t
pathogenesis 951
pathology 951
treatment 951
Goltz-Gorlin syndrome *see* Goltz syndrome
Gomori methenamine silver stain 27t–28t
gonadotropin-releasing hormone agonists 1125
gonococcemia 1381, 1381f
gonorrhea 1379–1383
clinical features 1380–1381, 1381t
disseminated gonococcal infection 1381
gonococcal ophthalmia 1381
men 1380
pharyngeal gonorrhea 1381
rectal gonorrhea 1381
women 1381
differential diagnosis 1383
epidemiology 1380
and erythema nodosum 1644t
history 1380
incidence 1380
laboratory diagnosis 1381–1383, 1382f
culture techniques 1382
non-amplified DNA hybridization 1383
non-culture techniques 1382–1383
nucleic acid amplification 1383
staining methods 1381–1382, 1383f
Neisseria gonorrhoeae vector 1380
pathogenesis 1380
pathology 1383
transmission 1380
treatment 1376f, 1383
Goodpasture syndrome 1596t
goose-grass 277t
Gore-Tex Subcutaneous Augmentation Material 2548t–2549t
Gorham-Stout disease 1724
Gorlin syndrome 1151, 1774
cleft lip/palate 1005t
clinical features 1777f
diagnosis 1777t
digital anomalies 1005t
genetics 813t
and NMSC 1776
Gorlin-Chaudry-Moss syndrome 1116t
Gorlin-Goltz syndrome *see* nevoid basal cell carcinoma syndrome
Gorlin's sign 1609
Gottron syndrome *see* acrogeria
Gottron tumor *see* human papillomavirus
Gottron's papules 610, 633, 634f–635f
gotu kola 2207t
gout 709–711, 709t, 1600t
clinical features 710–711
acute gouty arthritis 710
chronic tophaceous gout 710–711, 710f
differential diagnosis 711
epidemiology 710
pathogenesis 710
pathology 711
treatment 711
Gradle scissors 2359f
graft-versus-host disease 184t, 753–760
acute 757, 759
chronic 661, 757–760
clinical features 754f, 755t, 756f–757f, 757–758
morphea reaction 758
clinical staging 755t
differential diagnosis 650t, 759
epidemiology 753–755
histologic grading 755t
history 753
pathogenesis 755–757
pathology 758f–759f, 759
risk factors 753t
treatment 759–760
phototherapy
PUVA 2231
UVB 2222
grafts 2421–2434, 2422t
causes of failure 2423t
composite 2375–2376, 2376f, 2429–2431
free cartilage 2431–2433
indications/contraindications 2422t
split-thickness 2427–2429, 2427f–2428f, 2427t
types 2421f
wound healing considerations 2421–2422
see also flaps; and individual graft types
Graham Little-Piccardi-Lassueur syndrome 191, 191f
Gram stain 26, 27t–28t
Gram-negative bacteria 1204–1214
Bartonella spp. 1207–1210
bacillary angiomatosis 1208–1210
bartonellosis 1207–1208, 1209t
cat scratch disease 1208
brucellosis 1210
cutaneous malacoplakia 1211
ehrlichiosis and anaplasmosis 1244t, 1246t, 1250
Francisella tularensis 1211–1212
glanders 1210–1211
Haemophilus influenzae cellulitis 1212
melioidosis 1211
Neisseria meningitidis 1204–1206
Pseudomonas aeruginosa 1206–1207
blastomycosis-like pyoderma 1206
ecthyma gangrenosum 375, 1207, 1207f
green nail syndrome 1134, 1206, 1206f
hot tub folliculitis 574f, 1206–1207
otitis externa 1206
pseudomonal pyoderma 1206, 1206f
pseudomonas hot-foot syndrome 1207, 1207f
rhinoscleroma 1212
Salmonella spp. 1213
Streptobacillus moniliformis 1213
Vibrio vulnificus 1213
Yersinia pestis 1213–1214
Gram-negative folliculitis 573t
Gram-positive bacteria 1187–1204
Bacillus anthracis 1203–1204
Bacillus cereus 1204
clostridial skin infections 1200
anaerobic cellulitis 1200, 1201t
myconecrosis (gas gangrene) 1200, 1201t
Corynebacterium diphtheriae 1202–1203, 1203f
Corynebacterium skin infections 1200–1203
erythrasma 1200–1201, 1202f
pitted keratolysis 1201
trichomycosis axillaris 1202
Erysipelothrix rhusiopathiae 1204
listeriosis 1204
staphylococcal/streptococcal infections 1187–1200
abscesses 1190
bacteremia/septicemia 1200
bacterial folliculitis 1188–1190
blistering distal dactylitis 1191
botryomycosis 1199
carbuncles 1190
cellulitis 1197–1198
ecthyma 1191
erysipelas 1196
furuncles 1190
impetigo 1187–1188
MRSA 1190–1191
necrotizing fasciitis 1199–1200
pyomyositis 1198
scarlet fever 1194–1195
streptococcal intertrigo 1196–1197
streptococcal perianal disease 1197
toxic shock syndrome
staphylococcal 1193–1194
streptococcal 1195–1196
granular bacteriosis *see* botryomycosis
granular cell tumor 1952–1953, 1953f
granular parakeratosis 167–168
clinical features 168, 168f
differential diagnosis 168
epidemiology 168
history 168
pathogenesis 168
pathology 168, 168f
treatment 168
granulation tissue 2367f, 2373
Granulex 2373
Granulobacter bethesdensis, chronic granulomatous disease 910t
granulocytes 423
granulocyte apheresis 432t
granulocyte colony-stimulating factor *see* G-CSF
granulocyte-macrophage colony-stimulating factor *see* GM-CSF
granulocytotropic anaplasmosis 1244t, 1246t, 1250
granuloma
actinic 427t
in drug abuse 1516, 1516f
eosinophilic 1530t–1531t, 1531
fish tank 271t
grease gun 1641t, 1655, 1656t
irritant/toxic causes 251t
Majocchi's 575f
non-infectious 1557–1572, 1558f, 1558t
annular elastolytic giant cell granuloma 1568–1570
cutaneous Crohn's disease 1570–1571
foreign body 21, 1571
granuloma annulare 8, 1563–1566
histologic diagnosis 1562t
interstitial 21–22
necrobiosis lipoidica 1566–1568
palisaded 21–22, 23f
sarcoidal 21, 23f, 1557–1562
oil 1656f
palisading 21–22, 23f, 761t
pyogenic 1922–1923
nail bed 2440t
suppurative 22, 23f
tuberculoid 21, 23f
ulcerating sclerosing *see* donovanosis
granuloma annulare 8, 1563–1566
and anetoderma 1633t
clinical features 1558t, 1562f–1564f, 1563–1564
differential diagnosis 308t–310t, 1565
disseminated 768t, 1564f
epidemiology 1563
generalized 1563–1564
history 1563
papular 1565, 1565f
patch 1564
pathogenesis 1563
pathology 1562t, 1564–1565, 1565f
perforating 1564–1565, 1564f, 1600t
subcutaneous 1564–1565
treatment 1565–1566
phototherapy 2231
granuloma faciale 412–416
clinical features 412, 415f
differential diagnosis 413
epidemiology 412
history 412
pathogenesis 412
pathology 412–413, 415f
treatment 415–416
granuloma fissuratum *see* acanthoma fissuratum
granuloma genitoinguinale *see* donovanosis
granuloma gluteale infantum 1266, 1270f
granuloma inguinale *see* donovanosis
granuloma pyogenicum *see* pyogenic granuloma
granuloma venereum *see* donovanosis
granulomatous cheilitis *see* orofacial granulomatosis
granulomatous drug reactions 348
granulomatous rosacea 413, 2137–2138
granulomatous slack skin 2027, 2027f
granulomatous vasculitis 20
granulosis rubra nasi 599
granzymes 91
granzyme-B 29t–33t
grape seed extract 2207t
grapefruit 275t, 280t
grapefruit juice, interactions 2191–2192, 2191t
grasses 277t
Graves disease 439–440, 632t
gravitational dermatitis *see* stasis dermatitis
gravitational eczema *see* stasis dermatitis
gray lesions 6t–7t
grease gun granuloma 1641t, 1655
microscopic features 1656t
greases, sensitivity to 251t
great saphenous vein 2513f
greater celandine 2207t
green hair *see* chemical hair discoloration
green lesions 6t–7t
green nail syndrome 1134, 1206, 1206f
green tea 2210–2211, 2490t
effects on coagulation 2212t
polyphenols, in sunscreens 2201
Greenwald, Robert A 606
Greenwald's Law of Lupus 604t, 606
Greither syndrome 873t, 877
Grenz ray treatment 2292
Grenz zone 694
Grevillea spp. 277t
Griscelli syndrome 906t, 1035t
differential diagnosis
genetics 1015t
griseofulvin
adverse reactions 2122
lichen planus 185t
dosage 2121–2122, 2122t
indications 2120t
dermatophytoses 1267t
lichen planus 195–196, 195t
mechanism of action 2119t
pregnancy and lactation 2120t
grocer's itch 1445t
grocery store workers, plant dermatoses 288
Grönblad-Strandberg syndrome *see* pseudoxanthoma elasticum
groove sign 651–652
gross cystic disease fluid protein-15 1181f, 1790t
ground glass appearance 1533
group A streptococcal infection 524t–525t
group B *Streptococcus* 524t–525t
neonates 526t–528t
Grover's disease 471, 601, 1485
sites of 889f
growth factors
molecular modeling 2324
topical 2374
in wound healing 2317t, 2323
growth hormone 1666t, 1671t
growth retardation, glucocorticoid-induced 2081
GRX Wound Gel 2372
GSK690693 1887t
GSK1120212 1887t
GSK2118436 1887t
GTPase-activating proteins 926
guaifenesin, adverse reactions 336t
Guanarito virus 1360t
guitar nipple 1509t

Günther disease *see* congenital erythropoietic porphyria
guttate leukoderma 936f
  differential diagnosis 1037t
guttate morphea 660
guttate parapsoriasis *see* pityriasis lichenoides
guttate psoriasis 139–140, 142f
gynecomastia
  and drug abuse 1514t
  liposuction for 2527t
gypsy moth caterpillar dermatitis 1435, 1440

H syndrome 806f, 1117t
  differential diagnosis 652t
  genetics 810t–811t
H-ras 1761
H_2 antihistamines
  interactions 2124t, 2190, 2191t
  urticaria 303
HAART therapy *see* antiretroviral therapy
Haber syndrome 1065t, 1070–1071
Haberland syndrome 959
Haemaphysalis concinna 1244t
Haemaphysalis flava 1244t
Haemaphysalis longicornis 1244t
Haemoganasidae 1445t
Haemophilus ducreyi 1367t
  biology 1384
Haemophilus influenzae 524t–525t
  cellulitis 1212
Hageman factor XII 294, 295f
Hahnemann, Samuel 2214
Hailey-Hailey disease 893–896
  acantholysis in 893–895
  anogenital 895, 1185
  clinical features 817f, 894–895, 894f
  clinical subtypes 895
  complications 895
  differential diagnosis 471, 895
  epidemiology 893–894
  genetics 803t–804t, 893–894
  history 893
  linear 954
  malignant transformation 895
  pathogenesis 894
  pathology 895, 895f
  sites of 889f
  treatment 895–896
Haim-Munk syndrome 879
  genetics 803t–804t
hair
  biology 1075–1085, 1075f
  bleaching 1126
  in Chédiak-Higashi syndrome 905f
  club 1079, 1079t
  connective tissue sheath 1079t
  corkscrew 740t–742t, 743f
  density 1082t
  dermatophyte invasion *see* tinea capitis
  embryology 1082t
  excessive *see* hypertrichosis
  fiber structure 1081
  follicular units *see* hair follicles
  graying 1075–1085
  hereditary disorders 809t, 1104t
  in HIV 1295
  hypomelanosis 1025–1026, 1033t, 1046, 1047t
  inappropriate distribution 52
  inner root sheath 1079t
  keratins 827, 829f, 1081, 1084f
  lack of *see* alopecia; hypotrichosis
  lanugo 1079t
  miniaturization 1079t
  in Netherton syndrome 841t–842t, 1095f
  non-tylotrich pelage 1079t
  outer root sheath 1079t
  patterns of 1082t
  shedding rate 1082t
  terminal 1079t
  vellus 1079t
  woolly
    Carvajal syndrome 873t, 882
    Naxos disease 0 873t, 879
hair bulb 1079t
hair care products 2484–2485
  conditioners 2484–2485, 2485f, 2487t
  shampoos 2484, 2485t
  treatments 2486f, 2486t
hair casts 1252f
hair collar sign 995, 995f–996f, 1119
hair colorants 2486f, 2486t
hair conditioners 2484–2485, 2485f, 2487t
hair cycle 1078–1081, 1079t, 1080f
  control 1082t
  distribution 1082t
  duration 1082t
  number of 1082t
  signaling control 1084f
hair follicle 1082t
  androgen metabolizing enzymes in 1094f
  average density 1082t
  blood supply 1680f
  cycling 59, 1078–1081, 1084f
  desmosomes 1081–1083
  development 59–60, 1075–1078, 1076f–1077f
    patterning 1076–1078
    postnatal 1078
  functional anatomy 1078–1081
  immunology 1084–1085, 1085t
  infundibulum 1079t
  innervation 1078f
  isthmus 1079t
  morphogenesis 1078
  number of 1082t
  pigmentary unit 1079t
  sebaceous 543f
  stem cells 61, 62f, 1083–1084
  terminal 1090t
  tylotrich 1079t
  vellus 1082t
hair follicle nevus 1829
hair keratins 828t, 829f, 1574t
hair loss
  drug-induced 348t, 350
  see also alopecia
hair matrix 1079t
hair perforation test 1266f
hair pulling *see* trichotillomania
hair removal 2256, 2278–2279, 2278f
hair repair *see* hair transplantation
hair shaft 1081t
  components of 1093
  diameter and length 1082t
  pigmentation 1082t
  structures 1082t
hair shaft abnormalities 841t–842t, 1109–1112
  acquired progressive kinking 1111–1112
  "bubble hair" 1110, 1110f
  loose anagen hair syndrome 1112
  monilethrix 827, 1110–1111, 1110f–1111f
  Netherton syndrome 858f
  nodules 1252f
  pili annulati 1110f, 1112
  pili bifurcati 1112
  pili multigemini 1112
  pili torti 841t–842t, 1110f, 1111
  spun-glass hair 1110f, 1112
  tiger-tail hair 841t–842t
  trichonodosis 1110f
  trichoptilosis 1110f
  trichorrhexis invaginata 841t–842t, 1110f, 1111
  trichorrhexis nodosa 841t–842t, 1110f, 1111
  trichothiodystrophy 838t, 861–862, 1104t, 1110f, 1111
  woolly hair 803t–804t, 1112, 1112f
hair shampoos *see* shampoos
hair tourniquet 1524t
hair transplantation 2535–2545
  African-Americans 2544–2545, 2544f
  candidate selection 2538–2539, 2539t
  clinical findings and expectations 2539t
  complications 2543
  corrective 2543–2544
    addition of follicular unit grafts 2543, 2543f–2544f
    hypertrophic/broad scars in donor region 2540f, 2544
    laser-assisted removal of grafts 2543–2544
    surgical removal of grafts 2543
  donor region 2541
    elliptical donor harvesting 2540f–2541f, 2541, 2541t
    follicular unit extraction 2540f, 2541, 2541t, 2542f
  female pattern alopecia 2539f
  follicular grafts 2538f, 2541–2542
  graft placement and postoperative course 2542f, 2543, 2543t
  history 2535
  male pattern baldness 2536f, 2538f
  recipient site creation
    anesthesia 2542, 2542f
    hairline design 2542, 2542f
  scarring alopecias 2544
  staff training 2540–2541
HAIR-AN syndrome 551
hair-nail hypoplasia 878
hair-nail type ectodermal dysplasia 827, 832t–833t
hairless gene 1079–1080
hairy cell leukemia 1660t
hairy palms and soles 1118t
hairy tongue 1150–1151, 1151f
halcinonide 245t, 2079t
half-and-half nails 1140
half-chromatid mutation 945t
Hallopeau's acrodermatitis *see* acrodermatitis continua of Hallopeau
hallucinogen abuse, prevalence 1512t
hallux, lateral fold hypertrophy 1135
halo nevus 1028, 1042–1043, 1875–1876
  clinical features 1875–1876, 1876f
  differential diagnosis 1876
  epidemiology 1875
  pathogenesis 1875
  pathology 1876
  treatment 1876
halobetasol propionate 2079t
Haloclava producta 1451
halogen acne 270
halogenoderma 344, 344f
haloperidol
  in drug addiction 1520t
  and eccrine sweating 590t
halothane
  adverse reactions, pruritus 120t
  interactions, lidocaine 2529t
Hamamelis virginiana see witch hazel
hamartomas
  basaloid follicular 955
  eccrine angiomatous 592f
  fibrous of infancy 1971, 1971f
  follicular/folliculosebaceous-apocrine chondroid syringoma 1831–1834, 1833f–1834f
  fibrofolliculoma 1830, 1831f
  hair follicle nevus 1829
  nevus sebaceus 953t, 1600t, 1790t, 1830–1831
  perifollicular fibroma 1830
  trichodiscoma 1830
  trichofolliculoma 1829–1830, 1830f
  glial *see* nasal glioma
  retinal 937f
  smooth muscle 1983–1984
    clinical features 1983, 1983f
    differential diagnosis 1984
    epidemiology 1983
    history 1983
    pathology 1983–1984
    treatment 1984
  vellus *see* hair follicle nevus
hand eczema 208f, 209, 211f, 2096
hand nerve block 2350–2351, 2350f
hand-arm vibration syndrome *see* vibration white finger
hand-foot-and-mouth disease 1347, 1347f
  see also enterovirus infections
Hand-Schüller-Christian disease 1530t–1531t, 1531
Hansen's disease *see* leprosy
hantavirus 1360t
haploid cells 784t
haploinsufficiency 1608
haplotype analysis 794f
Happle syndrome *see* Conradi-Hünermann-Happle syndrome
Happle-Tinschert syndrome 955
haptenization 95
harlequin ichthyosis 57, 803t–804t, 838t, 855–857
  clinical features 856, 856f
  differential diagnosis 856
  epidemiology 856
  genetics 803t–804t
  history 856
  pathogenesis 856
  pathology 856
  treatment 856–857
harpist's finger 1508–1509
Hartnup disease
  genetics 810t–811t
Haserik, John 603
Hashimoto-Pritzker disease 1530t–1531t, 1531, 1533f
Hashimoto's thyroiditis, and dermatitis herpetiformis 494
Haverhill fever *see* rat-bite fever
Hawaiian tree 282t, 284
Haxthausen's disease 1641t
Hay-Wells syndrome *see* ankyloblepharon-ectodermal dysplasia-clefting syndrome
HBD *see* human β-defensin
head lice 1426–1429, 1427f
  clinical features 1427, 1428f
  differential diagnosis 1427
  epidemiology 1427
  history 1427
  nits 1252f, 1428f
  pathogenesis 1427
  pathology 1427
  treatment 1427–1429, 1428t
    benzyl alcohol 1428t, 1429
    carbaryl 1428t, 1429
    ivermectin 1428t, 1429
    lindane 1428t, 1429
    malathion 1428t, 1429
    permethrin 1428t, 1429
    pyrethrin 1428–1429, 1428t
    spinosad 1428t, 1429
head and neck 2327–2341
  congenital cartilaginous rests 1006
  cosmetic subunits 2332–2334, 2332f
  cutaneous landmarks 2332f–2334f
  dermatitis 207
  facial nerve 2336–2338, 2337f
  free margins 2334
  lymphatic drainage 2340, 2340f
  midline lesions 993–998, 994f
    cephaloceles 996–997, 997f
    cervical clefts 998
    dermoid cysts 995–996, 996f
    heterotopic brain tissue 998
    nasal gliomas 997–998, 998f
    nasal lesions 994–995, 994t
    rudimentary meningoceles 997f, 998
    scalp lesions 995, 995f–996f
    sternal clefts and supraumbilical raphae 998, 999f
  muscles of facial expression 2331f, 2334–2335, 2335t
  oral disease 1151–1152
    Gardner syndrome 1151
    multiple endocrine neoplasia syndrome type 2B 1151–1152
    nevoid basal cell carcinoma syndrome 1151
  sensory innervation 2338–2340, 2338f–2339f, 2338t
  skin tension lines 2330–2332, 2330f–2331f
  superficial musculoaponeurotic system 2329–2330, 2330f
  topographic anatomy 2327–2328, 2328f–2329f

vascular anatomy 2335–2336, 2336f
health services research 2061–2062
hearing impairment
non-syndromic 874t
sensorineural 841t–842t
see also various forms of deafness
heat
as mast cell stimulant 2001t
in wound healing 2374
heat contract urticaria 297
heat cramps 1488t
heat edema 1487–1492
heat exhaustion 1487–1492
heat exposure injury 51, 1487–1492
airbag burns 1491–1492
erythema ab igne 8, 1065t, 1489–1491
fluoroscopy burns 1491f
heat-related illness 1487–1489
MRI burns 1491
thermal burns 1487–1489, 1488f, 1522–1523, 1523f
heat rash *see* miliaria
heat shock proteins 2253
heat stroke 1487–1492
eccrine gland changes 598t
heat syncopy 1488t
heat therapy 51
heat-related illness 1487–1489, 1488t
clinical features 1488
differential diagnosis 1488–1489
epidemiology 1487
history 1487
pathogenesis 1487–1488
pathology 1488
risk factors 1488t
treatment 1489
heavy metals
dermatoses 1498–1501
hyperpigmentation 354
Heck's disease 1310
Hedera helix see ivy
hedgehog gene 1765, 1767f
Hedgehog signaling pathway 1463
heel stick wounds 531
Heerfordt's syndrome *see* sarcoidosis
Helenium autumnale see sneezeweed
Helianthus annuus see sunflower
helical advancement flaps 2404–2406, 2406f
Helicobacter cinaedi 1367t
Helicobacter fennelliae 1367t
Helicobacter pylori
and lichen planus 184
MALT lymphoma 678
and rosacea 562
heliodermatitis 561, 562f
heliotrope sign 634f
Helistat 2464t
helium-neon lasers 1029
helminths *see* worms
heloma *see* corns and calluses
heloma durum *see* corns and calluses
heloma molle *see* corns and calluses
hemagglutination inhibition 1348t
hemangioblasts 1681, 1681f
hemangioendothelioma
Dabska-type 1930–1931
epithelioid 1931–1932
kaposiform 1928–1930
retiform 1931
hemangioma
capillary 1691
epithelioid *see* angiolymphoid hyperplasia with eosinophilia
eruptive *see* pyogenic granuloma
glomeruloid 1917–1918
hobnail 1925–1926
hypertrophic *see* tufted angioma
infantile *see* infantile hemangiomas
microvenular 1920
non-involuting congenital 1693
progressive capillary *see* tufted angioma
rapidly involuting congenital 1693
sinusoidal 1721, 1924–1925
spindle cell 1921–1922
treatment
interferons 2131
laser therapy 2265–2266
hemangiomatosis
benign neonatal 1699
diffuse neonatal 1701f
hepatic 1701f
laryngeal 1698
lumbosacral 1698
hemangiosarcoma *see* angiosarcoma
hematidrosis 597–598
hematologic pruritus 119
hematological disease 763–767, 763f, 763t–765t, 766f–767f
hematoma
postoperative 2467–2469, 2467f–2468f
and retiform purpura 383
traumatic auricular 1504–1505
hematopoietic infiltrates
malignant 2041–2047
angioimmunoblastic T-cell lymphoma 2045–2046
leukemia cutis 2041–2043
lymphomatoid granulomatosis 2046–2047
non-B-cell, non-T-cell lymphoma 2043–2045
hematopoietic stem cell transplantation
dermatomyositis 639t
SCID 921
scleroderma 651
hematoporphyrin derivatives 2242
hematoxylin and eosin (H&E) 25, 26f
heme arginate 726
heme biosynthetic pathway 718f
hemidesmosome-associated integrin $\alpha_6\beta_4$ 452
hemidesmosomes 59, 450f
hemifacial atrophy
non-progressive 1670
progressive *see* Parry-Romberg syndrome
hemihyperplasia-multiple lipomatosis syndrome 1984–1985
Hemileuca maia 1441t
hemin 726
Hemiptera
bedbugs 1438, 1438f
triatome reduviids 1399, 1438–1439, 1439f
hemizygosity 791f
hemochromatosis 774t, 776t–778t
endocrine 768t
genetics 810t–811t
hemodialysis-associated amyloidosis 707
hemolytic anemia, systemic lupus erythematosus 623, 627t
hemophagocytic lymphohistiocytosis 1530t–1531t
hemorrhoids, in pregnancy
hemostasis 2464f–2465f, 2464t
hemostats 2361
Henderson-Patterson bodies 1356–1357
Hennekam lymphangiectasia-lymphedema syndrome 1713t
Henoch-Schönlein purpura 392–393
ANCA in 613t
clinical features 392, 393f
differential diagnosis 393
epidemiology 392
genetics 392t
pathogenesis 392
pathology 392
renal disease 780t–781t
treatment 393, 402t
heparan sulfate proteoglycans 454
heparin 364t, 2460
adverse reactions 336t
injection site reactions 354t
heparin necrosis 369–373
clinical features 369–370, 372f
differential diagnosis 370
pathogenesis 369
pathology 370
treatment 370
heparin-induced thrombocytopenia syndrome *see* heparin necrosis
hepatitis 1361, 1361t
and drug abuse 1515t
drug-induced, ANCA in 613t
and erythema multiforme 320t
hepatitis A 1361
hepatitis B 774t, 1361, 1367t
and erythema nodosum 1644t
hepatitis C 774t, 1361
and lichen planus 183–184
pruritus in 112t
secondary cutaneous vasculitis 390t
hepatocyte growth factor, in wound healing 2317t
hepatoerythropoietic porphyria 719t, 723, 723f
biochemical findings 720t
genetics 719t, 810t–811t
treatment 725t
hepatomegaly 841t–842t
heptad repeats 827
HER2/neu 2149t
Heracleum laciniatum see Tromso palm
Heracleum lanatum see cow parsnip
Heracleum mantegazzianum see giant Russian hogweed
Heracleum sphondylium see cow parsnip, European; hogweed
Herba serissae 2214
herbal remedies 2213–2214
adverse reactions 2214
interactions 2192, 2192t
see also botanicals
herbal teas, phototoxic reaction 2213f
hereditary coproporphyria 719t, 726
biochemical findings 720t
genetics 719t, 810t–811t
treatment 725t
hereditary gelsolin amyloidosis 700t
hereditary hemorrhagic telangiectasia 772f, 1754–1755
clinical features 1718–1719
diagnosis 1719t
and gastric hemorrhage 773t–774t
genetics 785t
with juvenile polyposis 1713t
molecular genetics 1713t, 1754
pulmonary disease 778t–779t
hereditary neuralgic amyotrophy, and cutis verticis gyrata 1626t
hereditary periodic fever syndromes 299–300, 674t
hereditary progeroid syndrome 818t–819t
hereditary progressive mucinous histiocytosis 1530t–1531t
antigenic markers 1533t
heredopathia atactica polyneuritiformis *see* Refsum disease
Hermansky-Pudlak syndrome 361, 1035–1036, 1035t, 2459
clinical features 1036
hirsutism 1118t
genetics 785t, 1015t
laboratory findings and pathology 1036
pathogenesis 1035–1036
treatment 1036
heroin abuse
cutaneous signs 1514t
prevalence 1512t
herpangina 1347
herpes encephalitis 1323t
herpes febrilis *see* herpes simplex viruses
herpes gestationis *see* pemphigoid gestationis
herpes gladiatorum 1323t, 1326f
see also herpes simplex viruses
herpes labialis *see* herpes simplex viruses
herpes progenitalis *see* herpes simplex viruses
herpes simplex viruses (HSV-1/HSV-2) 29t–33t, 1321–1328, 1322t, 1367t, 2461
in athletes 1507t
clinical features 1322–1323, 1323f–1324f, 1325t, 1326f–1327f
diagnosis and pathology 1323–1325, 1327f–1328f
differential diagnosis 1325–1326
epidemiology 1321
and erythema multiforme 320, 320t
folliculitis 573t, 575f, 1323t
genital herpes 1324f
history 1321
HIV-related 1287–1288, 1290f, 1298f
immune system interaction 1323t
in neonates 524t–528t, 534f, 1323t, 1327f
ocular infection 1323t
pathogenesis 1321–1322
treatment and prevention 1326–1328
herpes zoster 1–2, 2f, 3t–4t, 8f, 46f
clinical features 1329–1330, 1331t, 1332f–1334f
hypomelanosis 1042
in neonates 524t–525t
pruritus in 112t
treatment 1334
see also varicella-zoster virus
herpesvirus *see* human herpesviruses
herpetic sycosis 572f
herpetic whitlow 271t, 1323t, 1326f
see also herpes simplex viruses
herpetiform pemphigus 467
Hertoghe sign 209t
Herxheimer disease *see* acrodermatitis chronica atrophicans
heterochromia irides 1034, 1034f
heterodisomy 790
heteroplasmy 790
heterotopic brain tissue 998
heterotopic meningeal tissue 1957
heterotopic neuroblastic tissue 1957–1958, 1958f
heterotopic neuroglial tissue 1955–1957, 1957f
heterotopic/anomalous sebaceous glands *see* Fordyce granules
heterozygosity, loss of 789–790, 1761, 1763f
Hevea brasiliensis see rubber tree
hexachlorobenzene, hypertrichosis 1118t
hexachlorophene 2383t
adverse reactions 2155t
hexamethonium, hypohidrosis/anhidrosis 595t
hexobarbital 2114, 2190t
hibernoma 1987–1988
clinical features 1988
differential diagnosis 1988
epidemiology 1987
history 1987
pathogenesis 1987
pathology 1988, 1988f
treatment 1988
hidradenitis suppurativa 583–585
clinical features 583, 584f, 1624f
differential diagnosis 584–585
epidemiology 583–585
familial 818t–819t
history 583
pathogenesis 583, 584t
pathology 584, 584f
treatment 584t, 585
hidradenocarcinoma 1847
hidradenoma 1842–1843, 1843f
hidradenoma papilliferum 1843, 1844f
hidroacanthoma simplex 1842
hidrocystoma 1823–1824, 1823f–1824f
hidrotic ectodermal dysplasia 874t, 878–879, 879f
genetics 808t
high impact soap 2480t
high-density lipoproteins 1547, 1547t, 1549
highly active antiretroviral therapy *see* HAART therapy
Higouménakis' sign 1377t
Hippocrates 135
Hippocratic fingers *see* nail clubbing
Hippomane mancinella see Manchineel tree
Hirschsprung disease 904
hirsutism 1079t, 1120–1126
adrenal 1121–1123, 1121t
adrenal hyperplasias 1121–1122

classification 1120, 1121t
Abraham's 1124, 1125t
constitutional or dermatologic 1120
defeminization vs. virilization 1122t
degrees of 1125f
diagnosis 1124
differential diagnosis 1126f
and drug abuse 1514t
ectopic hormones 1124
epidemiology 1120
excess ovarian androgen release syndrome 1125
facial 1124f
familial 1122f
Ferriman and Gallway score 1124
HAIR-AN syndrome 1120
hyperprolactinemic SAHA syndrome 1120, 1122f
iatrogenic 1124–1125
ovarian 1121t, 1123
ovarian hyperthecosis 1123
persistent adrenarche syndrome
pituitary 1116, 1124
polycystic ovary syndrome 1121t, 1123, 1123f–1124f
treatment 1124–1126
dermato-cosmetic therapy 1126
excess ovarian androgen release syndrome 1125
iatrogenic hirsutism 1125
SAHA with hyperprolactinemia 1125
surgery 1126
systemic 1124–1125
topical 1125
tumoral adrenal 1123
tumoral ovarian 1123
see also hypertrichosis
hirudin 364t
histamine 101, 101t, 2315t
in plants 274t
histamine liberators 298–299
histiocytes 21
histiocytic necrotizing lymphadenitis *see* Kikuchi's disease
histiocytic sarcoma 1545t
histiocytoid hemangioma *see* angiolymphoid hyperplasia with eosinophilia
histiocytoma
benign fibrous *see* dermatofibroma
epithelioid fibrous 1961
generalized eruptive 1530t–1531t, 1536–1537
progressive nodular 1530t–1531t
see also dermatofibroma
histiocytoses 1529–1546
antigenic markers 1533t
clinical features 1530t–1531t
immunohistochemistry 1534f
Langerhans cell *see* Langerhans cell histiocytosis
malignant 1545, 1545t
non-Langerhans cell 1535–1545
benign cephalic histiocytosis 1535–1536
generalized eruptive histiocytoma 1536–1537
indeterminate cell histiocytosis 1537–1538
juvenile xanthogranuloma 1538–1539
necrobiotic xanthogranuloma 1539–1541
reticulohistiocytosis 1541–1542
Rosai-Dorfman disease 1542–1544
xanthoma disseminatum 1544–1545
histiocytosis X 1529
histocompatibility antigens in psoriasis 135–136
histone deacetylase inhibitors 2025
Histoplasma capsulatum 1276t
and erythema multiforme 319, 320t
panniculitis 1658t
histoplasmosis 1273–1274
clinical features 1274, 1275f
differential diagnosis 1274, 1276t
epidemiology 1273
and erythema nodosum 1644t
pathogenesis 1274
pathology 1274
treatment 1274
HIV-associated lipodystrophy 1295–1296
HIV-drug interactions 2193–2194
HIV/AIDS 46, 46f, 1285–1302, 1367t
and anetoderma 1633t
CD4+ cell count 1289t
diagnosis of cutaneous disorders 1297–1298
differential diagnosis of cutaneous disorders 1296–1297
and drug abuse 1515t
drug reactions 352–353, 353t, 1299t
epidemiology 1285, 1286f
and erythema multiforme 320t
and erythema nodosum 1644t
history 1285
infectious cutaneous disorders 1287–1293, 1288t
bacterial infections 1291
bacillary angiomatosis 1291
mycobacteria 1291
Staphylococcus aureus 1291
syphilis 1291
ectoparasitic infestations 1293
fungal infections 1291–1292
candidiasis 1291
dermatophytoses 1291
Pneumocystis jiroveci 1292
systemic 1291–1292
parasitic infections 1292–1293
leishmaniasis 1292–1293, 1395–1396
viral diseases 1287–1289
cytomegalovirus 1289
Epstein-Barr virus 1289
exanthem of primary HIV infection 1287
herpes simplex virus 1287–1288
human papillomavirus 1288–1289
poxvirus 1288
varicella-zoster virus 1288
lichen myxedematosus 691
lipoatrophy 1676
lipohypertrophy 1676
neoplastic cutaneous disorders 1296
Kaposi's sarcoma 1296
lymphomas 1296
squamous and basal cell carcinomas 1296
and NMSC 1776
non-infectious cutaneous disorders 1293–1296
hair 1295
metabolic changes 1295–1296
nails 1140, 1295
papulosquamous disorders 1293–1294
eosinophilic folliculitis 574–575, 575f, 1294–1295, 1294f
papular pruritic eruption of AIDS 1294–1295
psoriasis 139, 1294
reactive arthritis 1294
seborrheic dermatitis 219, 1293–1294
photosensitivity 1295
vasculitis 1295
occupational 271t
oral erosions 1292f, 1292t
pathogenesis 1285–1287, 1287f
pruritus in 112f, 119–120, 414t
treatment 1298–1300
adverse cutaneous drug eruptions 1300
antiretroviral therapy *see* antiretroviral drugs
drug-drug interactions 1300
viral diseases related to 1287–1289
viral load 1290f
virus replication 1287f
HIV/ART-related lipodystrophy 1665t
clinical features 1674–1676, 1675f
pathogenesis 1673–1674, 1674f, 1674t
treatment 1676
HMB45 29t–33t
HMGCoA reductase 2067f
HMGCoA reductase inhibitors
indications
cholesterol embolus
xanthoma 1554t–1555t
interactions 2124t, 2191t
HMGCoA synthase 2067f
hobnail hemangioendothelioma *see* Dabska-type hemangioendothelioma; retiform hemangioendothelioma
hobnail hemangioma 1925–1926
clinical features 1925, 1925f
differential diagnosis 1926
epidemiology 1925
pathogenesis 1925
pathology 1925, 1926f
treatment 1926
Hodgkin disease 2043–2044
clinical features 2043–2044, 2044f
pruritus 112t, 119
differential diagnosis 414t
epidemiology 2043
and erythema nodosum 1644t
history 2043
pathogenesis 2043
pathology 2044, 2044f
treatment 2044
Hodgkin, Thomas 2043
hogweed 279t, 280
hogweed tree 279t
holandric inheritance 787
holmium YAG lasers 2251
holocarboxylase synthetase deficiency genetics 810t–811t
homeopathy 2214–2215
Homer Wright rosettes 1955
homocystinuria 776t–778t, 1608t
genetics 810t–811t
homoplasmy 790
homosalate 2199, 2200f
homozygosity 790–791
honey 2205
honeycomb atrophy 1638
hookworm 1407t–1408t
Hori's nevus 1859
differential diagnosis 1053t
horizontal forehead lines, botulinum toxin 2563t, 2564, 2564f–2565f
horizontal neck lines, botulinum toxin 2566t, 2569, 2569f
hormones 50
horn, cutaneous 1805
clinical features 1805, 1805f
pathology 1805
treatment 1805
horn pearls 1785f
Horner's syndrome 590–591
horse bites 1450t
horse chestnut seed extract 2210
effect on coagulation 2212t
horseradish 2212t
Hortaea werneckii 1251, 1251t
horticulturalists, plant dermatoses 288
hot comb alopecia *see* central centrifugal cicatricial alopecia
hot flashes 1751
hot peppers 274t, 278t
hot tub folliculitis 574f, 1206–1207
in athletes 1507t
housewife's eczema *see* irritant contact dermatitis
Howel-Evans syndrome 880, 880f
genetics 816t
Hoyeraal-Hreidarsson syndrome 1067
hSPCA1 887f
huang qi 2212t
human β-defensin-1 83t
human β-defensin-2 82, 83t
human β-defensin-3 83t
human β-defensin-4 83t
human bites 1450t, 1522–1523, 1523f
Human Genome Project 2061
human herpesviruses 1321–1343, 1322t
cytomegalovirus (HHV-5) 1322t, 1336–1338
clinical features 1337–1338, 1337f, 1337t
diagnosis and pathology 1338, 1338f
differential diagnosis 1338
epidemiology 1337
history 1337
pathogenesis 1337
treatment and prevention 1338, 1338t
Epstein-Barr virus (HHV-4) 1321–1328, 1334–1336
clinical features 1335–1336, 1335f
diagnosis and pathology 1336, 1336t
differential diagnosis 1336
epidemiology 1334, 1335t
and erythema multiforme 320t
history 1334
pathogenesis 1334–1335
treatment 1336
herpes simplex viruses (HSV-1/HSV-2) 1321–1328, 1322t
clinical features 1322–1323, 1323f–1324f, 1325t, 1326f–1327f
diagnosis and pathology 1323–1325, 1327f–1328f
differential diagnosis 1325–1326
epidemiology 1321
and erythema multiforme 320, 320t
folliculitis 573t, 575f, 1323t
history 1321
HIV-related 1287–1288, 1290f, 1298f
immune system interaction 1323t
in neonates 524t–528t, 534f, 1323t, 1327f
pathogenesis 1321–1322
treatment and prevention 1324f, 1326–1328
varicella-zoster virus (HHV-3) 1–2, 2f, 3t–4t, 29t–33t, 1322t, 1328–1334
and anetoderma 1633t
clinical features 1328–1330, 1330f, 1332f–1333f
diagnosis and pathology 1330
differential diagnosis 1330, 1333t
epidemiology 1328
and erythema multiforme 320t
history 1328
in neonates 524t–528t
pathogenesis 1328
treatment and prevention 1329t, 1330–1334
viral susceptibility 2108t
human herpesvirus-6 1322t, 1338–1339
clinical features 1339, 1339f
diagnosis and pathology 1339
differential diagnosis 1339
epidemiology 1339
history 1338–1339
and lichen planus 184
pathogenesis 1339
roseola infantum 1352
treatment 1339
human herpesvirus-7 1322t, 1339–1340
and lichen planus 184
human herpesvirus-8 29t–33t, 1322t, 1340–1341
clinical features 1340–1341, 1341f
diagnosis and pathology 1341, 1341f
differential diagnosis 1341
epidemiology 1340
history 1340
pathogenesis 1340
treatment 1341
human immunodeficiency virus *see* HIV/AIDS
human papillomavirus 271t, 1303–1319, 1367t
clinical features 1307–1311, 1307t
cutaneous infections 1307–1309, 1307f–1309f
mucosal infections 1309–1311, 1309f–1311f
differential diagnosis 1312–1314
anogenital lesions 1313–1314

common warts 1313, 1313f
oral warts 1314, 1314f
doughnut of diagnoses 1304f
epidemiology 1303–1304, 1304f
history 1303
HIV-related 1288–1289
and NMCC 1775
pathogenesis 1304–1306
evolution 1304
host immune response 1306
life cycle 1305–1306, 1306f
oncogenic potential 1306
virology 1305, 1305f
pathology 1311–1312
common and deep palmoplantar warts 1311–1312, 1312f
condylomata acuminata 1312
epidermodysplasia verruciformis 1312
flat warts 1312
giant condylomata of Buschke-Löwenstein 1312, 1312f
squamous intraepithelial neoplasias 1312, 1313f
treatment 1314–1318, 1314t, 1315f
antiviral agents 1317
imiquimod 2134
immunotherapy 1316–1317
local destructive therapy 1314–1316
retinoids 1317
systemic immunomodifiers 1316
topical cytotoxic therapy 1316
topical immunomodifiers 1316
vaccines 1317–1318
human T-cell lymphotrophic virus 226, 1367t
see also infective dermatitis
human-derived cadaveric collagen 2551
human-derived cadaveric fascia 2551–2552
humectants 843, 2481
Hunan hand syndrome 279
Hunter syndrome 715t
hunting response of Lewis 1493
Huriez syndrome
differential diagnosis 652t
genetics 813t
Hurler syndrome 715t
Hurler-Scheie syndrome 715t
Hurricaine *see* benzocaine
Hutchinson-Gilford progeria syndrome
differential diagnosis 652t
genetics 818t–819t
Hutchinson's sign 1133–1134, 2442
Hutchinson's summer prurigo *see* actinic prurigo
Hutchinson's teeth 1376–1377
hyacinth 278t
Hyacinthus orientalis see hyacinth
HYAFF 2374
hyaline bodies *see* Civatte bodies
hyaline fibromatosis, juvenile 1626–1628
clinical features 1627, 1627f, 1627t
differential diagnosis 1627–1628
epidemiology 1627
history 1627
pathogenesis 1627
pathology 1627
treatment 1628
hyalinosis cutis et mucosae *see* lipoid proteinosis
Hyalofill 2374
hyalohyphomycosis 1279f, 1280
Hyalomma asiaticum 1244t
Hyalomma marginatum 1244t
hyaluronic acid 411
animal-derived 2553
foreign body reaction 1574t, 1580–1582, 1581t
injection site reactions 354t
non-animal stabilized 2553–2554
hyaluronic acid derivatives 2552–2554, 2552t, 2554f–2556f
benefits of 2552t
foreign body reactions 2553f
hyaluronidase 2345
tumescent anesthesia 2348t
hybrid cyst *see* follicular hybrid cyst
hydralazine-induced secondary cutaneous vasculitis 390t
Hydrastis canadensis see goldenseal
hydroa aestivale *see* actinic prurigo
hydroa vacciniforme 1472–1473
action spectrum 2203t
clinical features 1472, 1472f
differential diagnosis 1472–1473, 1473f
epidemiology 1472
history 1472
pathogenesis 1472
pathology 1472, 1473f
treatment 1473
PUVA phototherapy 2232
hydrochloric acid 253t–254t
hydrochlorothiazide 336t, 342f
adverse reactions
cutaneous lymphoid hyperplasia 2039t
lichen planus 185t
lichenoid drug eruption 193f
photolichenoid 341f
pseudoporphyria 724t
hydrocolloids 2369t, 2372–2373, 2373f
leg ulcers 1735t
hydrocortisone 245t, 2075
pharmacology 2076t
structure 2075f
hydrocortisone acetate 245t
hydrocortisone butyrate 245t, 2076–2077
hydrocortisone probutate 2079t
hydrocortisone valerate 245t, 2079t
hydrofiber dressings, leg ulcers
hydroflumethiazide 342f
hydrofluoric acid 253t–254t
hydrogels 2366t, 2369t, 2371–2372, 2371f
leg ulcers 1735t
hydrogen peroxide 2383t
Hydrophyllaceae 276t
hydropic degeneration 759
hydroquinone 2158
adverse reactions 2158
hyperpigmentation 1056t–1057t
hypomelanosis 1044
monobenzyl ether 1072t–1073t, 2158
pregnancy and lactation 2155t
Hydrosorb 2371
hydrostatic bullae *see* edema blisters
hydroxocobalamin *see* vitamin B12
hydroxy acids 2488–2489, 2489t
α-hydroxy acids 2488
β-hydroxy acids 2488–2489, 2489f
hydroxychloroquine
adverse reactions
erythroderma 176t
hyperpigmentation 1056t–1057t, 2170f
lichen planus 185t
indications
dermatomyositis 639t
lichen planus 195–196
lichen sclerosus 667t
lupus erythematosus 628t
morphea 667t
porphyria 726
sarcoidosis 1563t
vasculitis 402t
hydroxycitronellal 243t
12-hydroxyeicosatetraenoic acid (12-HETE) 412f
hydroxyethyl starch-induced pruritus 120t
hydroxyethylmethacrylate 1581t
21-hydroxylase deficiency 1121
hydroxyurea 2175–2176
adverse reactions 2169t, 2175, 2176f
dermatomyositis 632t
hyperpigmentation 349t, 1056t–1057t
lichen planus 185t
mucosal hyperpigmentation 349t
nail hyperpigmentation 349t
photosensitivity 349t
vascular occlusion 383
contraindications 2176
dosage 2175
indications 2175–2176
psoriasis 153t
interactions 2176
mechanism of action 2175
monitoring 2167t–2168t
pregnancy and lactation 2176
hydroxyzine 246t, 304t
Hylaform 2548t–2549t, 2552
Hylaform Plus 2550
Hylatopic (Plus) emollient foam 2156
Hylesia alinda 1441t
Hylesia metabus 1441t
hyper-IgE syndrome 533, 900t, 911–915
clinical features 913–914, 913f–914f
differential diagnosis 524t–525t, 914t
epidemiology 913
pathogenesis 913
pathology 914
treatment 915
hyper-IgM syndrome 900t, 915b, 918f
autosomal recessive 917t
X-linked 917t
hyperandrogenism 551
hyperbaric oxygen
calciphylaxis 732
M. ulcerans 1237
necrotizing fasciitis 1200
spider bites 1448
hypercoagulability 1744t
hypereosinophilia 302f
hypereosinophilic dermatitis of Nir-Westfried 414t
hypereosinophilic syndrome 377, 418–421
classification 419f
clinical features 420
differential diagnosis 420
epidemiology 418
history 418
pathogenesis 418–420
lymphocytic 418–419
myeloproliferative 419–420
pathology 420
treatment 420–421
hypergammaglobulinemia, ANCA associated with 613t
hypergranulosis 308t–310t
hyperhidrosis 50, 541, 587–594
axillary 588, 593f
axon reflex (local inflammatory) sweating 591
botulinum toxin 540, 593f, 594t, 2570, 2570f
compensatory 591–592, 592f
cortical 588f
causes of 588t
disorders associated with 588–589
diagnosis 592–593, 593f, 593t
diagnostic criteria 587t
and drug abuse 1518
drug-induced 590t
hypothalamic (thermal) 589
causes of 589t
liposuction for 2527f, 2527t, 2532
medullary (gustatory) 590–591
non-neural 591t, 592, 592f
obese patients 751t
palmar 593f
primary 587–588, 588f
secondary 588–592
spinal (cord transection) sweating 591
treatment 593–594, 594t
volar 588, 588f
hyperhomocyseinemia 1744t
hypericin-induced phototoxicity 1480t
Hypericum perforatum see St John's wort
hyperimmunoglobulinemia 227t
hyperimmunoglobulinemia D syndrome 300, 673f, 818t–819t
hyperimmunoglobulinemia E syndrome 818t–819t
hyperkeratosis
discoid lupus erythematosus 619f
epidermolytic *see* bullous congenital ichthyosiform erythroderma
focal acral 883
follicular 1081, 1111
hystrix-like 841t–842t
palmoplantar 353t, 1514t
subungual *see* subungual hyperkeratosis
hyperkeratosis lenticularis perstans *see* Flegel's disease
hyperkeratosis-hyperpigmentation syndrome 1857t
hyperkeratotic cutaneous capillary-venous malformation 1720
hyperkeratotic spicules, monoclonal gammopathy 2014t
hyperlipidemia 776t–778t, 1547
glucocorticoid-induced 2084
see also xanthomas
hyperlipoproteinemias 1549t
hypermelanosis, linear and whorled 960, 1062–1063, 1063f
hypermobility 1593t, 1609t
hypernatremic dehydration 841t–842t
hyperoxaluria 377
hyperphosphatemia 731f
hyperphosphatemic familial tumoral calcinosis 818t–819t
hyperpigmentation 1001t, 1049–1074
chemotherapy-induced 349t
chimerism 960
diffuse circumscribed 1049–1058
atrophoderma of Pasini and Pierini 660, 1050t, 1055, 1636–1637
drug-induced hyperpigmentation 1055, 1059f
erythema dyschromicum perstans *see* erythema dyschromicum perstans
lichen planus pigmentosus 1052, 1052f
mastocytosis 1054–1055
melasma 1052–1054
pigmented lesions 1055
pityriasis (tinea) versicolor 1041–1042, 1055
postinflammatory hyperpigmentation 1049–1050
primary (localized) cutaneous amyloidosis 1054
dychromatoses 1071–1074, 1072t–1073t
familial progressive 810t, 1054
irritant/toxic causes 251t
laser therapy 2271
linear 1058–1064
along Blaschko's lines 1062–1064, 1063t
flagellate mushroom dermatitis 1062
flagellate pigmentation from bleomycin 1061, 1061f
pigmentary demarcation lines 8, 1058–1059, 1058t, 1060f
postinflammatory 1059–1060, 1060f–1061f
obese patients 751t
post-inflammatory 8, 2271
postsclerotherapy 2518–2519, 2519f, 2519t
pregnancy 52, 1052–1054
reticulated 1064–1071, 1065t
dermatopathia pigmentosa reticularis 810t, 1065t, 1069, 1069f
Dowling-Degos disease 810t, 1065t, 1070–1071
dyskeratosis congenita 810t, 1065t, 1066–1068
Naegeli-Franceschetti-Jadassohn syndrome 810t, 835t, 1065t, 1068–1069
prurigo pigmentosa 1064, 1065t
reticulate acropigmentation of Kitamura 1065t, 1071
X-linked 810t, 1065t, 1069–1070, 1070f
scleroderma 646
hyperprolactinemic hirsutism 1121t
hyperprolactinemic SAHA syndrome 1121t, 1125
hyperprothrombinemia 818t–819t
hypersensitivity 50

hypersensitivity angiitis *see* small vessel vasculitis
hypersensitivity syndrome, drug-induced *see* DRESS syndrome
hypertelorism 802t, 927t
hyperthecosis 1121t
hyperthermia 175
hyperthyroidism
  and nail growth 1090t
  skin manifestations 770t
hypertonic saline 2515t
hypertrichosis 1115–1120
  Becker's nevi 1119, 1119f
  congenital melanocytic nevi and plexiform neurofibromas 1119
  drug-induced 350, 1117, 1118t
  eyebrows and eyelashes
  generalized 1115–1117, 1115f
    acquired 1116–1117
    congenital 1116
  hair collar sign 995, 995f–996f, 1119
  hepatoerythropoietic porphyria 1117t
  localized 1117–1120
    acquired 1119–1120, 1120f
    congenital 1116t, 1117–1119
    hereditary and acquired systemic diseases 1116t–1118t, 1119
  midline 1119
  nevoid 1119, 1119f
  prepubertal 1116
  spinal dysraphism 999, 1000f, 1001t, 1119
  sports-related 1506t
  treatment 1120
  X-linked 809t, 1116t
  see also hirsutism
hypertrichosis cubiti 1118f, 1118t
hypertrichosis lanuginosa 52, 1116t
  acquired 1116
  congenital 1116
  paraneoplastic 764t–765t, 1116
hypertrichosis terminalis 809t
hypertrichosis universalis congenital 809t
hypertriglyceridemia 1550
hypertrophic hemangioma *see* tufted angioma
hypertrophic orbiculari oculi, botulinum toxin 2561, 2564–2565, 2565f
hypertrophic scars 1621–1625, 2471, 2471f
  laser therapy 1625t
  mucin deposition 688t
hyperuricemia
  classification 710t
  drug-induced 2169t
  see also gout
hypervitaminosis A 746t
hypervitaminosis C 746t
hypervitaminosis D 732, 746t
hypervitaminosis E 746t
hypervitaminosis K 746t
hyphae 1266f
hypoalphalipoproteinemia 810t–811t
hypocalcemia, and psoriasis 139
hypochondriacal psychosis *see* delusions of parasitosis
hypocomplementemic urticarial vasculitis syndrome 395
Hypoderma bovis 1433
hypodermis 58t
hypodermitis sclerodermiformis *see* lipodermatosclerosis
hypodontia with nail dysgenesis *see* tooth and nails syndrome
hypofractionation 2291
hypogammaglobulinemia, transient of infancy 917t
hypogonadism 841t–842t
hypogranulosis 140f
hypohidrosis 541, 594–595
  causes 594t–595t
  central and neuropathic 594
hypohidrotic ectodermal dysplasia 60, 1104t
  genetics 808t
  with immunodeficiency 808t, 917t
  X-linked 60, 817f, 952
hypomastia *see* nipple, absent, hypoplastic or anomalous
hypomelanosis 1023
  chemical 1044–1045, 1044f–1045f, 1044t
  hair 1025–1026, 1033t, 1046, 1047t
  hereditary 1030–1038
    oculocutaneous albinism 48, 1030–1032
    piebaldism 932t–933t, 1032–1033, 1034t
    Waardenburg syndrome 1011, 1033–1035
  idiopathic guttate 1045–1046, 1045f
  infectious and parasitic 1041–1042
    herpes zoster 1042
    leprosy 1042, 1042f
    onchocerciasis 1042, 1042f
    pityriasis versicolor 1041–1042, 1041f
    post-kala-azar dermatosis 1042
    treponematoses 1042
  melanocytic 1023
  melanopenic 1023
  nutritional 1038
  phylloid 820, 821f, 822t, 1037–1038
  physical agents 1045
  postinflammatory 1038–1041, 1040f
  progressive macular 1046, 1046f
hypomelanosis of Ito 959–960, 1037–1038
  clinical features 1037–1038, 1038f
  diagnosis 1038
  digital anomalies 1005t
  pathology 1038
hypomelanotic macules 888–889
hypomyopathic dermatomyositis *see* dermatomyositis sine myositis
hyponychium 1089t, 2435
hypopigmentation 1001t, 1023
  chimerism 960
  copper deficiency 1038
  irritant/toxic causes 251t
  linear 1038t
  mycosis fungoides 1039–1040, 1041f
  progressive familial 810t
  selenium deficiency 1038
hypoplastic left heart syndrome 874t
hyposensitivity 50
hypothalamic (thermal) hyperhidrosis 589
  causes of 589t
hypothalamic-pituitary-adrenal axis 2076–2077
hypothenar hammer syndrome 271
hypothermia 175
hypothyroidism
  adult 694
  congenital 694, 1117t
  cutaneous manifestations 770t
    eccrine gland changes 598t
    hair discoloration 1498t
    hypertrichosis 1117t
    palmoplantar keratoderma 883
  juvenile 694
  retinoid-induced 2101
hypotrichosis 841t–842t
  autosomal recessive 1104t
  genetics 832t–833t
  with juvenile macular dystrophy 1104t
  Mari type 1104t
  Marie-Unna type 1104t
hypotrichosis simplex of scalp 708, 832t–833t, 1104t
hypotrichosis-lymphedema-telangiectasia syndrome 1738t
  molecular genetics 1713t
hypovitaminosis A *see* phrynoderma
hypoxia, and infantile hemangiomas 1692
hystrix-like hyperkeratoses 841t–842t
hystrix-like ichthyosis-deafness syndrome 874t

iatrogenic calcification 733
ibandronate 2080–2081, 2082f
IBIDS *see* trichothiodystrophy
ibritumomab tiuxetan 2149t
ibuprofen 2190t
  adverse reactions
    lichen planus 185t
    lichenoid drug eruptions 185t
ICAM-1 86, 93, 1685t
ICAM-2 1685t
ICAM-3 1693t
ICF syndrome 917t
Ichthaband 2369
ichthyoses 838t, 840–862
  with associated keratoderma 872t
  autosomal recessive
    exfoliative 852t–854t
    with hypotrichosis 813t
  diagnosis 841t–842t
  en confetti 803t–804t, 818t–819t, 848
  epidermolytic *see* epidermolytic ichthyosis
  and erythroderma 172t–174t
  harlequin 57, 803t–804t, 838t, 855–857
  lamellar *see* lamellar ichthyosis
  late-onset autosomal recessive congenital 803t–804t, 852t–854t
  mosaic epidermolytic 845
  with neutral lipid storage disease 838t
  paraneoplastic 764t–765t
  treatment, retinoids 2096
  trichothiodystrophy 1478
  X-linked dominant 838t, 866–868
  X-linked recessive see steroid sulfatase deficiency
  see also individual types
ichthyosis bullosa of Siemens 510t, 835t, 838t, 847–848
  clinical features 847–848, 848f
  hypertrichosis 1117t
  differential diagnosis 848
  epidemiology 847
  genetics 803t–804t, 832t–833t
  history 847
  neonatal 847t
  pathogenesis 847
  pathology 848
  treatment 848
  see also epidermolytic ichthyosis
ichthyosis congenita *see* collodion baby
ichthyosis congenita gravior *see* harlequin ichthyosis
ichthyosis exfoliativa *see* ichthyosis bullosa of Siemens
ichthyosis follicularis-atrichia-photophobia syndrome 803t–804t, 820f, 852t–854t
ichthyosis hystrix 848–849
ichthyosis hystrix Curth-Macklin 835t, 838t, 848
  clinical features 848
  differential diagnosis 848
  epidemiology 848
  genetics 803t–804t
  history 848
  pathogenesis 848
  pathology 848
  treatment 848
ichthyosis linearis circumflexa *see* Netherton syndrome
ichthyosis variegata *see* confetti ichthyosis
ichthyosis vulgaris 838t, 840–843
  in atopic dermatitis 209t
  clinical features 840–843, 843f
  differential diagnosis 843
  epidemiology 840
  genetics 803t–804t, 832t–833t
  history 840
  pathogenesis 840
  pathology 843, 843f
  treatment 843
ichthyosis-hypotrichosis syndrome 852t–854t
ichthyosis-hypotrichosis-sclerosing cholangitis syndrome 803t–804t, 852t–854t
ichthyosis-prematurity syndrome 803t–804t, 852t–854t
id reaction *see* disseminated eczema
idarubicin-induced alopecia 349t
idiopathic atrophoderma of Pasini and Pierini 1636–1637
  clinical features 1636–1637, 1637f
  differential diagnosis 1637
  epidemiology 1636
  history 1636
  pathogenesis 1636
  pathology 1637
  treatment 1637
idiopathic calcification 732–733
  idiopathic calcified nodules of scrotum 732–733
  milia-like calcinosis 733
  subepidermal calcified nodule 733
  tumoral calcinosis 733
idiopathic calcified nodules of scrotum 732–733
idiopathic deciduous skin *see* peeling skin syndrome
idiopathic facial aseptic granuloma 553
idiopathic guttate hypomelanosis 1045–1046, 1045f
idiopathic inflammatory dermatomyopathy *see* dermatomyositis
idiopathic livedo reticularis with cerebrovascular accidents *see* Sneddon syndrome
idiopathic palmoplantar hidradenitis 600–601, 601f, 1660t
idiosyncratic drug reactions 337
idraparinux 364t
ifosfamide 2189t
  adverse reactions, alopecia 349t
Ig A deficiency 915b
IgA 94
  deficiency 900t, 917t
  FcαR 94
  granular deposition 493
IgA complexes 359t
IgA pemphigus 461
  clinical features 469, 469f
  differential diagnosis 147t, 472
  pathology 470, 471f
  target antigens 463t
  treatment 473
    PUVA 473
IgA vasculitis 392
IgD 94
IgE 94
  elevated 841t–842t
  FcεRI 83, 94
  FcεRII 84, 94
  in urticaria 293–294
IgE-dependent adverse reactions 336
IgG 94
  atopic dermatitis 213t
  FcgammaRI 94
  FcgammaRII 94
  FcgammaRIII 94
  intravenous 2148t
    in linear IgA bullous dermatosis 499
    in pemphigus vulgaris 472
    in pyoderma granulosum 432t
    in toxic epidermal necrolysis 331t
    in urticaria 305
IgG autoantibodies 462–466
IgM 94
IgM complexes 359t
IgM deficiency 900t, 917t
IgM storage papules, monoclonal gammopathy 2014t
IL *see* interleukin
IL-1 receptor-associated kinase
iloperidone, adverse reactions 129t
iloprost 651
ILVEN 144, 959, 959f, 1810–1811
  clinical features 1811, 1811f
  differential diagnosis 1811
  history 1810
  pathogenesis 1811
  pathology 1811, 1811f
  treatment 1811
imatinib 2149t
  adverse reactions 353t
    hyperpigmentation 1056t–1057t
    hypomelanosis 1045
    lichen planus 185t

indications
hypereosinophilic syndrome 420
mastocytosis 2001–2002, 2001t
melanoma 1887t
neurofibromatosis 931–933
imidazole 1269t
imidazolidinyl urea 242t
imipenem 1234t
imipramine
adverse reactions
hyperpigmentation 1056t–1057t
lichen planus 185t
and eccrine sweating 590t
imiquimod 2134–2136
dosage 2136
indications 2134–2136
actinic keratoses 2135
basal cell carcinoma 2135
Bowen's disease 2135
condylomata acuminata 1314t
human papillomavirus 1314t, 1316, 2134
hypertrophic scars and keloids 1625t
keloids 2135
molluscum contagiosum 2135
NMSC 1791
major adverse reactions 2136, 2136f
mechanism of action 2134, 2135f
pregnancy and lactation 2136
immediate contact reaction *see* contact urticaria
immediate pigment darkening 1482–1483
immersion foot 1494–1496
clinical features 1496
cold water 1493t, 1495–1496
differential diagnosis 1496
epidemiology 1495
history 1495
pathogenesis 1495–1496
pathology 1496
treatment 1496
tropical 1496t
warm water 1495, 1496t
immune cells 104–105
immune complex-dependent adverse reactions 336
immune globulin 2147–2148
contraindications 2148
dosage 2148, 2148t
indications 2148, 2148t
interactions 2148
major adverse reactions 2148
mechanism of action 2147–2148
pregnancy and lactation 2148
preparations 2148t
immune reconstitution inflammatory syndrome 1298–1300, 1298f, 1300t
immune response
herpes simplex viruses 1323t
human papillomavirus 1306, 1316
ultraviolet light 1457, 1457t
and wound healing 2313, 2315f
immunity
adaptive 84–96
failure of 45–47
faulty 47
innate 81–84, 137–139
specific 81
immunoblastic lymphadenopathy *see* angioimmunoblastic lymphadenopathy
immunoblot *see* Western blot
immunocytoma, and anetoderma 1633t
immunodeficiency
with hypohidrotic ectodermal dysplasia 917t
with lymphoid proliferation 906t
immunodeficiency, myopathy and ectodermal dysplasia 808t
immunodiffusion 1348t
immunofluorescence 1348t
immunoglobulins 93–94, 1684f, 1685t
complementarity-determining regions 93
intravenous
indications
dermatomyositis 639t
Stevens-Johnson syndrome 330f
vasculitis 402t
structure 93f
see also individual Ig types
immunoglobulin deficiency disorders 915, 917t
see also individual disorders
immunoglobulin heavy chain 700t
immunoglobulin light chain 29t–33t, 700t
immunohistochemistry 26, 28f, 29t–33t
immunologic contact urticaria 274–275
causes 275f, 275t
clinical features 275
epidemiology 274
pathogenesis 275
treatment 275
see also urticaria
immunologic function of skin 45–47
failure of immunity
cancer 47, 47f
dermatophytosis 46, 46f
human immunodeficiency virus 46, 46f
infection 45–47
leprosy 46–47
faulty immunity (autoimmunity) 47, 47f, 47t
immunology 81–98
immunomodifiers 1316
immunomodulators 2131–2152
G-CSF 2136, 2137t
and linear IgA bullous dermatosis 498t
GM-CSF 2136, 2137t
imiquimod 2134–2136
immune globulin 2147–2148
interferons *see* interferons
pimecrolimus 2136–2138
and PUVA 2229
tacrolimus *see* tacrolimus
targeted 2138–2147, 2139f, 2140t, 2149t
adalimumab 2145
alefacept 2138–2140
anakinra 2146
certolizumab 2146
efalizumab 2140–2141
etanercept 2143–2144
golimumab 2146–2147
infliximab 2144–2145
omalizumab 2147
rituximab *see* rituximab
TNF-α inhibitors 2141–2143
ustekinumab 2146
immunoprecipitation 69t
immunoreceptor tyrosine-based activation motifs (ITAMs) 89
immunosuppressants
lupus erythematosus 628t
and NMSC 1775–1776
immunosuppression, UV light-induced 92
immunotherapy
allergen-specific 213
alopecia areata 1103t
human papillomavirus 1316–1317
melanoma 1908–1910
topical 2162t, 2163
Impatiens biflora see jewelweed
Impatiens capensis see jewelweed
impetiginization 211
impetigo 1187–1188, 1189t
in athletes 1507t
of Bockhart *see* superficial folliculitis
bullous 1188, 1189t
clinical features 1188f, 1189t
postinflammatory hyperpigmentation 1050t
diagnosis 1188, 1189t
differential diagnosis 147t
epidemiology 1188
non-bullous 1188, 1189t
occupational 271t
pathogenesis 1188
pathology 1188
treatment 1188, 1189t
impetigo herpetiformis 139
imprinting *see* genomic imprinting
Inadine *see* povidone-iodine
inbreeding 787, 789
incidence 2059
incisional biopsy 2382, 2382t, 2390–2391, 2390f
inclusion body fibromatosis *see* infantile digital fibroma
incomplete/reduced penetrance 787
incontinentia pigmenti 533, 949–951, 1063–1064
achromians *see* hypomelanosis, of Ito
clinical features 949–950, 950f, 950t, 1064f
differential diagnosis 414t, 524t–525t, 950–951
genetics 810t, 949, 949t, 950f
history 949
pathogenesis 949
pathology 533f, 950
treatment 951
indapamide 342f
indeterminate cell histiocytosis 1530t–1531t, 1537–1538
antigenic markers 1533t
clinical features 1530t–1531t, 1537–1538
differential diagnosis 1538
epidemiology 1537
history 1537
pathogenesis 1537
pathology 1538
treatment 1538
indian hedgehog gene 1766
Indian marking nut tree 282t, 283
Indigo naturalis 2213–2214
indinavir 2190
adverse reactions 1299t
erythroderma 176t
nail changes 1141t
interactions 2124t, 2190, 2191t
indirect Nikolsky sign 467
indium, dermatosis 1499t
indoleamine,3-dioxygenase 92
indomethacin 2190t
adverse reactions
alopecia 348t
lichen planus 185t
indications
follicular mucinosis 696
folliculitis 574
gout 711
Sweet's syndrome 454
vasculitis 402t
infantile acne 550–551, 551f
infantile acropustulosis *see* acropustulosis of infancy
infantile digital fibroma 1969–1970, 1970f
infantile eosinophilic pustular folliculitis *see* eosinophilic pustular folliculitis of infancy
infantile hemangiomas 813t, 1001t, 1691–1709, 1692t, 1712t
and anetoderma 1633t
classification 1692t
clinical features 1693–1701, 1701t
beard hemangioma 1698, 1700f
congenital 1701t
deep 1695f
lip hemangioma 1696, 1698f
nasal tip hemangioma 1696
pinna hemangioma 1696
presentation 1694f
superficial 1694f
ulcerated 1696, 1697f
complications 1696–1699
differential diagnosis 526t–528t, 1703–1704
disfigurement 1696, 1698f
epidemiology 1691
history 1691
and hypoxia 1692
involuting 1696f, 1699–1700, 1702f
Kasabach-Merritt syndrome *see* Kasabach-Merritt syndrome
lower body 1698–1699
midline lumbosacral 1698, 1701f
minimal/arrested growth 1696f
natural history 1694–1696, 1695f
pathogenesis 1691–1692, 1693f, 1693t
pathology 1702–1703, 1703f
PHACES syndrome 776t–778t, 998, 1697–1698, 1698f, 1699t
placental hypothesis 1692
precursors 1694f
radiology 1701–1702, 1703t
residua 1697f
segmental patterns 1695f
systemic involvement 1697–1699, 1698f, 1700f–1701f
treatment 1704–1707
active non-intervention 1704
corticosteroids 1704–1705
laser therapy 1706–1707
management of ulceration 1704
surgery 1706–1707
systemic therapy 1704t, 1705–1706, 1705f
see also vascular malformations
infantile hemangiopericytoma 1939
infantile kaposiform hemangioendothelioma *see* kaposiform hemangioendothelioma
infantile myofibromatosis 1970, 1970f
infantile spasms 935t
infantile systemic hyalinosis 807t, 1626–1628
clinical features 1622, 1627, 1627f
differential diagnosis 1627–1628
epidemiology 1627
history 1627
pathogenesis 1627
pathology 1627
treatment 1628
infants
acropustulosis 147t, 524t–525t, 531–533, 531f
acute hemorrhagic edema 393–395
annular erythema 308t–310t, 414t
atopic dermatitis (eczema) 205, 207f, 221
eosinophilic pustular folliculitis
erythroderma 173t–174t, 180f
lipodystrophia centrifugalis 1671f
lipodystrophia centrifugalis abdominalis 1666, 1670, 1671f, 1672
panniculitis 1660t
phenotypic diarrhea 1036
seborrheic dermatitis 220–221, 220f
transient hypogammaglobulinemia 917t
see also children; infantile; neonatal; neonates
infections
ANCA associated with 613t
anogenital 1183–1184
cutaneous candidiasis 1183–1184
cyclical vulvovaginitis 1184–1185
dermatophytosis 1183
erythrasma 1183
Fournier's gangrene 1183
Kawasaki disease 1183
perianal streptococcal disease 1183
recurrent candidiasis 1184
recurrent toxin-mediated perineal erythema 1183
bacterial *see* bacterial diseases
Darier disease 890
and dystrophic calcification 730
fungal *see* fungal diseases
and glucocorticoid therapy 2084
Hailey-Hailey disease 895
increased susceptibility to 841t–842t
nails 1141–1142
occupational 271–272, 271t
post-chemical/mechanical skin resurfacing
postoperative 2469, 2469f
and pruritus 113t
and psoriasis 139, 146
viral *see* viral diseases
infection-induced panniculitis 1658–1659, 1658f, 1658t
infectious mononucleosis *see* Epstein-Barr virus

infective dermatitis 226–227
  clinical features 226, 227t
  differential diagnosis 226
  epidemiology 226
  pathogenesis 226
  treatment 227
infective endocarditis 377
Infergen 2132t
infestations 1423–1434
  body lice 1430–1431
    clinical features 1431, 1431f
    differential diagnosis 1431
    epidemiology 1431
    pathogenesis 1431
    pathology 1431
    treatment 1431
  crab lice 1424–1426, 1429–1430
    clinical features 1430, 1430f
    differential diagnosis 1430
    epidemiology 1429
    history 1429
    pathogenesis 1429–1430
    pathology 1430
    treatment 1430, 1430t
  head lice 1426–1429, 1427f
    clinical features 1427, 1428f
    differential diagnosis 1427
    epidemiology 1427
    history 1427
    pathogenesis 1427
    pathology 1427
    treatment 1427–1429
  myiasis 1432–1433
    clinical features 1433, 1433f
    differential diagnosis 1433
    epidemiology 1432
    history 1432
    pathogenesis 1432–1433
    pathology 1433
    preventative measures 1433
    treatment 1433
  scabies 1423–1426, 1424f
    clinical features 1423–1424, 1425f
    crusted 1423, 1425f
    differential diagnosis 1424
    epidemiology 1423
    history 1423
    neonatal 524t–525t
    pathogenesis 1423
    pathology 1424, 1426f
    pruritus in 113, 1424
    subungual 1423, 1425f
    treatment 1424–1426, 1426t
  tungiasis 1431–1432
    clinical features 1431, 1432f
    differential diagnosis 1432
    epidemiology 1431
    history 1431
    pathogenesis 1431
    pathology 1432
    treatment 1432
inflammation, chemical mediators 2315t
inflammatory angiomatous nodule *see* angiolymphoid hyperplasia with eosinophilia
inflammatory arteriovenous hemangioma *see* angiolymphoid hyperplasia with eosinophilia
inflammatory bowel disease
  ANCA in 613t
  anogenital manifestations 1183
  cutaneous manifestations 771f
  and erythema multiforme 320t
  and erythema nodosum 1644t
inflammatory dendritic epidermal cells, in atopic dermatitis 206t
inflammatory myopathy *see* dermatomyositis
inflammatory phase of wound healing 2314f, 2320f
inflammatory skin disorders 1
  chemical mediators 2315t
  pattern analysis 16–25, 16f
  pruritus in 113–114, 113t
inflammatory vitiligo 1026, 1027f
infliximab 2144–2145
  adverse reactions 2144
    lichen planus 185t
  ANA/anti-dsDNA antibody induction 608
  dosage 2144
  FDA warnings 2140t
  indications 2144
    Behçet's disease 435t
    dermatomyositis 639t
    psoriasis 153t
    relapsing polychondritis 677
    sarcoidosis 1563t
  interactions 2145
  laboratory evaluation 2140t
  pregnancy and lactation 2145
influenza virus, secondary cutaneous vasculitis 390t
information bias 2062
informed consent 2463
infraorbital nerve 2349, 2349f
infraorbital nerve block 2350f
infrared lasers
  skin resurfacing 2277
  vascular lesions 2270
infratrochlear nerve 2349, 2349f
infundibular cyst *see* epidermoid cyst
infundibuloma *see* isthmicoma
ingrown toenail 1144, 2443–2444, 2443f–2444f
inhalant abuse 1511
inherited amyloidosis 707–708
injection site reactions 354f, 354t, 355
injection-induced panniculitis 1656t
ink, patch testing 264t
innate immunity 81–84, 137–139
inoculation lymphoreticulosis *see* cat scratch disease
inorganic chemicals 264
insect bites/stings 111f, 1435–1437
  arachnids 1440–1449
    Amblyomma ticks 1442–1443, 1443f
    Dermacentor ticks 1443, 1443f
    Ixodes ticks 1444, 1444f
    Rhipicephalus ticks 1443–1444, 1444f
    tick bites 1440–1442
  bedbugs 1438, 1438f
    as vectors of Chagas' disease 1438
  blister beetles 1439
  bullous reactions 517t, 518–520, 519f, 1436f
  centipedes and millipedes 1449
  Cheyletiella spp. 1445t, 1446, 1446f
  chiggers 1446
  clinical features 1435, 1436f
    postinflammatory hyperpigmentation 1050t
  differential diagnosis 1436
  fire ants 1437–1438, 1437f
  fleas 1439, 1440f, 1440t
  in HIV patients 1293
  lepidopterism 1440, 1440f, 1441t
  mites 1444–1445, 1445f, 1445t
  pathogenesis 1435
  pathology 1436
  prevention *see* insect repellents
  and pseudocellulitis 1196t
  spider bites 1446
    funnel web spiders 1448, 1448f
    Loxosceles spiders 1447–1448, 1447f
    tarantulas 1448
    widow spiders 1446–1447
  tick-borne disease
    encephalitis
    lymphadenopathy 1244t, 1246t
  treatment 1436–1437
  triatome reduviids 1438–1439, 1439f
  see also pruritus
insect repellents 1436, 1437t
Instat 2464t
instruments
  liposuction 2529–2531, 2530f–2531f
  nail surgery 2437, 2437f
  wound closure *2180* 2358–2362, 2359f–2360f
    biopsy blades 2359
    curettes 2359
    forceps 2361
    hemostats 2361
    needle holders 2360, 2360f
    scalpels 2360, 2360f
    scissors 2361, 2361f
    skin hooks 2361–2362
    special 2362
    sterilization 2362, 2362t
insulin
  adverse reactions 340t
  and eccrine sweating 590t
  injection site reactions 1666
insulin resistance 1667t, 1672
  and cutis verticis gyrata 1626t
insulin-induced lipodystrophy 1673
  liposuction for 2527t
insulin-like growth factor 1, in wound healing 2317t
Integra 2375t–2376t
integrins 452, 1685t, 2322, 2322f
  hemidesmosome-associated integrin $\alpha_6\beta_4$ 452, 502f
  plasma membrane-associated 452
integrin receptors 834t
integrin subunit β_4 451t
intense pulsed light sources 2257, 2262–2263
  dyspigmentation 2263f
  inappropriate use 2263f
  pigmented lesions 2270t
  telangiectasia removal 2517
  telangiectasias 2517
  vascular lesions 2265t
  see also lasers; laser therapy
intercellular adhesion molecules *see* ICAMs
intercellular junction defects 802
interdigitating dendritic cell sarcoma 1545t
interface dermatitis 1449
  pattern analysis 16f–18f, 17–18
interferons 81–82, 2132t
  adverse reactions
    alopecia 348t
    cutaneous necrosis 383
    secondary cutaneous vasculitis 390t
  contraindications 2133
  indications, condylomata acuminata 2131
  indications and dosage 2131–2133, 2132t
    AIDS-associated Kaposi's sarcoma 2131–2132
    atopic dermatitis 2133
    basal cell carcinoma 2132
    Behçet's disease 428, 2133
    condylomata acuminata 2131
    cutaneous T-cell lymphoma 2131
    hemangiomas 2131
    keloids 2132–2133
    melanoma 2132
    mycosis fungoides 2024
    psoriasis 152–154, 153t
    squamous cell carcinoma 2132
    systemic sclerosis 2133
    vasculitis 402t
    warts 2131
  injection site reactions 354t
  interactions 2127t, 2134
  major adverse reactions 2133–2134
    bone marrow suppression 2134
    cardiovascular effects 2134
    cutaneous reactions 2133, 2133f
    flu-like symptoms 2133
    gastrointestinal 2134
    neurologic and psychiatric effects 2134
    rhabdomyolysis 2134
  mechanism of action 2131, 2132t
  pharmacology 2131
  pregnancy and lactation 2134
interferon-α 82
  adverse reactions
    hypertrichosis 1118t
    lichen planus 185t
  hypereosinophilic syndrome 421
  infantile hemangioma 1705f
  Kaposi's sarcoma 1341
  and linear IgA bullous dermatosis 498t
  molluscum contagiosum 1359t
interferon-α-2, melanoma 1909t
interferon-α-2a 2132t
  Behçet's disease 428
interferon-α-2b 2132t
  hypertrophic scars/keloids 1625t
  mastocytosis 2001t
interferon-α-N3 2132t
interferon-αcon-1 2132t
interferon-β 82
interferon-β-1a 2132t
interferon-β-1b 2132t
interferon-γ 82
  atopic dermatitis 213t
  lichen sclerosus 667t
  and linear IgA bullous dermatosis 498t
  morphea 667t
interferon regulatory factor 3 81
interleukins 82
  in wound healing 2317t
interleukin-1 (IL-1) 81–82
interleukin-1 receptor antagonist deficiency 818t–819t
interleukin-1 receptor-associated kinase 81, 82f, 900t
interleukin-2 (IL-2) 82, 101t, 104
  injection site reactions 354t
  and linear IgA bullous dermatosis 498t
  melanoma 1908–1909, 1909t
interleukin-3 (IL-3) 411
interleukin-4 (IL-4) 82, 90–91
interleukin-5 (IL-5) 90–91, 411
interleukin-6 (IL-6) 82, 90–91, 105
  antibodies 628t
interleukin-7 receptor deficiency 920t
interleukin-8 (IL-8) 901
interleukin-10 (IL-10) 82, 90–91, 411
  antibodies 628t
interleukin-11 (IL-11) 82
interleukin-12 (IL-12) 82
interleukin-13 (IL-13) 82, 411
interleukin-17 (IL-17) 82
interleukin-18 (IL-18) 82
interleukin-19 (IL-19) 82
interleukin-20 (IL-20) 82
interleukin-22 (IL-22) 82
interleukin-23 (IL-23) 82
interleukin-24 (IL-24) 82
interleukin-26 (IL-26) 82
interleukin-27 (IL-27) 82
interleukin-31 (IL-31) 101t, 104–105
interleukin-34 (IL-34) 85
interlocking composite graft placement 2431f
intermediate-density lipoproteins 1547t
international normalization ratio 2459–2460
α-internexin 828t
interstitial granulomatous dermatitis 683–684
  causes 685t
  clinical features 683, 684f, 762f
  differential diagnosis 308t–310t, 684
  histologic features 684f
  history 683
  pathogenesis 683
  pathology 683, 1562t
  and pseudocellulitis
  treatment 684
interstitial granulomatous drug reaction 308t–310t
intertriginous granular parakeratosis *see* granular parakeratosis
intertrigo
  candidal 1269t
  obese patients 751t
  streptococcal 1196–1197
  vitamin B_6 deficiency 740t–742t
intra-oral dental sinus 1153
intracartilaginous cyst *see* pseudocyst of auricle
intraepithelial neoplasia, anogenital *see* Bowen's disease
intrahepatic cholestasis of pregnancy 443–445
  clinical features 444, 444f
  differential diagnosis 444
  epidemiology 443–444
  history 443
  pathogenesis 444

pathology 444
treatment 444–445
intraoperative complications 2463–2467
bleeding and hemostasis 2463–2465, 2464f–2465f, 2464t
contamination 2463
necrosis 2465–2466
nerve deficits 2466–2467, 2466f–2467f
tension 2465, 2466f
tissue injury 2465
unsatisfactory scarring 2467
Intrasite Gel 2372
intrauterine epidermal necrosis 526t–528t, 534
intravasation 2050t
intravascular lymphoma 382, 382f
intravenous atypical vascular proliferation *see* angiolymphoid hyperplasia with eosinophilia
intrigo 220
Intron A 2132t
Inula helenium see elecampane
inverse psoriasis 144f
inverted follicular keratosis 1806, 1807f
invisible dermatoses 25, 25t
involucrin 825–826
Io moth caterpillar 1441t
iodides
adverse reactions, lichen planus 185t
in dermatitis herpetiformis 494
iodine 253t–254t
adverse reactions 2155t
iododerma 344f, 519t
Iodoflex 2368t
iodoform gauze 2469
iodopropynyl butylcarbamate 242t
iodoquinol 2109
amebiasis 1398
formulations 2118t
pregnancy and lactation 2118t
trade names 2118t
Iodosorb 2368t
ionizing radiation, and NMSC 1774–1775
iontophoresis 2071–2072, 2310
hyperhidrosis 594t
ipecac, and eccrine sweating 590t
IPEX syndrome 818t–819t, 904, 915
ipilimumab 1887t, 2149t
IR3535 1437t
IRAK *see* IL-1 receptor-associated kinase (IRAK)
irinotecan, adverse reactions 349t
iron
dermatosis 1499t
hyperpigmentation 1056t–1057t
injection site reactions 354t
iron deficiency pruritus 118
iron oxide 2200f, 2201, 2483t
irritant chemicals 250t, 252–256, 253t–254t
irritant contact dermatitis 12t, 249–259, 263, 526t–528t
causes 250t
classification 257f
clinical features 250f, 251t, 255f, 256t
acute delayed form 251
acute form 251
airborne form 252
asteatotic dermatitis 221–222, 252
contact urticaria 252
cumulative form 251
frictional 252
irritant reaction 251
non-erythematous form 252
postinflammatory shyperpigmentation 1050t
pustular and acneiform form 252
subjective/sensory form 252
traumatic irritant form 252
differential diagnosis 228t, 256
epidemiology 249–250
history 249
irritants 250t, 252–256, 253t–254t
pathogenesis 250–251
pathology 252–256
acids 252
alcohols 255
alkalis 252
bodily fluids 256
detergents and cleansers 255, 255f
disinfectants 255, 255f
food 256
metal salts 252
plastics 255–256
solvents 252–255
water 256
peristomal 772t
prognosis 256–258
treatment 258
phototherapy 258
irritant folliculitis 573t
irritant reaction *see* irritant contact dermatitis
iscotrizinol 2199, 2200f
island pedicle flaps –6 2402, 2408–2410, 2409f–2410f
subcutaneous tunneling 2410, 2411f
isocarboxazid, and eccrine sweating 590t
isodisomy 790
isoeugenol 243t
Isolagen 2552
isomorphic Koebner phenomenon 1026
isoniazid
adverse reactions
acne 550f, 550t
erythroderma 176t
lichen planus 185t
pruritus 120t
indications, tuberculosis 1234t
interactions 2124t
isopropyl alcohol 2383t
isoproterenol, and eccrine sweating 590t
isosporiasis, AIDS-related 1288t
isotretinoin 2089, 2092
adverse reactions 558, 558f
erythroderma 176t
lichen planus 185t
pseudoporphyria 724t
xerosis 2100f
formulations 2097t
indications
acne vulgaris 555t–556t, 557–558, 2092, 2095
Darier disease 893
lupus erythematosus 2097–2098
rosacea 567t, 2097
sarcoidosis 1563t
pharmacologic features 2092t
teratogenicity 558
isradipine 2189t
isthmicoma 1837–1838
clinical features 1837
pathology 1837–1838, 1837f
treatment 1838
isthmus-catagen cyst *see* trichilemmal cyst
itch *see* pruritus
"itchy red bump disease" *see* papular dermatitis
ITGA6 458t
ITGB4 458t
Ito's lines *see* pigmentary demarcation lines
itraconazole
adverse reactions 2123t
dosage 2120, 2121t
indications 2120t
aspergillosis 1283t
blastomycosis 1277
candidiasis 1283t
coccidioidomycosis 1278
cryptococcosis 1283t
dermatophytoses 1267t
fusariosis 1283t
histoplasmosis 1274
mucocutaneous candidiasis 1269t
mycetoma 1272
paracoccidioidomycosis 1279
penicilliosis 1283t
yellow nail syndrome 1139
zygomycosis 1283t
interactions 2191–2192
and nail growth 1090t
pregnancy and lactation 2120t
Iva spp. 282t
Iveegam 2148t
ivermectin
crab lice 1430t
head lice 1428t, 1429
onchocerciasis 1416
scabies 1426, 1426t
tungiasis 1432
ivy 277t
Ixodes spp. 1441, 1444, 1444f
Ixodes holocyclus 1244t
Ixodes ovatus 1244t
Ixodes pacificus 1244t, 1444
Ixodes persulcatus 1244t, 1444
Ixodes ricinus 1244t
repellents 1437
Ixodes scapularis 1244t, 1245f, 1444, 1444f

Jablonski energy state diagram 2239f
Jacquet's erosive dermatitis 1266
Jadassohn syndrome *see* epidermal nevus syndrome
Jadassohn-Dosseker syndrome 696
Jadassohn-Pellizzari anetoderma 1633
Jadassohn-Tièche blue nevus *see* blue nevus
Jaffe-Campanacci syndrome 932t–933t
JAK3 deficiency 920t
Janeway lesions 773t–774t, 1200
Janus kinases 913
Japanese lacquer tree 282t, 283–284
Japanese spotted fever 1244t, 1246t
jasmine (*Jasminum officinalis*) 2215t
jellyfish stings 1451
foreign body reaction 1574t, 1580
clinical features 1580, 1580f
histopathology 1576t
pathology 1580
treatment 1580
Jessner-Kanof lymphocytic infiltration of skin *see* lymphocytic infiltrate of Jessner
Jessner's lymphocytic infiltration of skin *see* lymphocytic infiltrate of Jessner
Jessner's solution 2497t
Jessner's-35% TCA peel 2500f
jewelweed 2207t
jigger flea *see* tungiasis
Job syndrome *see* hyper-IgE syndrome
jock itch 1507
jogger's nipple 1506t
Johanson-Blizzard syndrome 1003t
Johnson-McMillin syndrome 932t–933t
Joubert syndrome 1009
Juglans regia see English walnut leaf
jun gene 1765t
jungle rot *see* immersion foot
Junin virus 1360t
juniper berry (*Juniperus communis*) 2215t
juniper twig (*Juniperus communis*) 2215t
Juvéderm 2548t–2549t, 2554
Juvéderm Ultra 2548t–2549t
Juvéderm Ultra Plus 2548t–2549t
Juvéderm Ultra Plus XC 2548t–2549t
Juvéderm Ultra XC 2548t–2549t
juvenile idiopathic arthritis 671–672
classification 672t
clinical features 671–672, 673f
exanthem 671–672
differential diagnosis 672
epidemiology 671
history 671
oligo/pauciarticular 672t
pathogenesis 671
pathology 672
polyarticular 671
treatment 672
juvenile myelomonocytic leukemia 764t–765t
juvenile plantar dermatosis 209
juvenile xanthogranuloma 932t–933t, 1538–1539
and anetoderma 1633t
antigenic markers 1533t
clinical features 1530t–1531t, 1538–1539, 1539f
differential diagnosis 414t, 1539
epidemiology 1538
history 1538
paraneoplastic 764t–765t
pathogenesis 1538
pathology 1539, 1539f
treatment 1539

K-ras 1761
Kabuki syndrome 1005–1006
kahili tree 282t
Kairo cancers 1490
kala-azar 1393t
hypomelanosis 1042
see also leishmaniasis
kalawalla *see* anapsos
Kalginate 2372
kallikrein 294
Kaltostat 2372
kanamycin
adverse reactions, systemic contact dermatitis 246t
tuberculosis 1234t
Kang cancers 1490
Kangri ulcers 1490
Kaposi sarcoma 1932–1935
AIDS-related 1296, 1297f
clinical features 1340–1341, 1341f, 1933, 1933f
African endemic form 1341, 1933
AIDS-related epidemic forms 1341, 1933
classic form 1340
gastric hemorrhage 773t–774t
immunosuppression-associated 1341, 1933
pulmonary disease 778t–779t
diagnosis and pathology 1341, 1341f
differential diagnosis 1341, 1934
epidemiology 1340, 1932t
history 1340, 1932
nail bed 2440t
pathogenesis 1340, 1932–1933
pathology 1933–1934, 1934f
treatment 1341, 1934–1935
interferons 2131–2132
radiotherapy 2297–2298, 2298f
kaposiform hemangioendothelioma 1928–1930
clinical features 1929, 1929f
differential diagnosis 1930
epidemiology 1928
history 1928
pathogenesis 1928–1929
pathology 1929–1930, 1929f
treatment 1930
Kaposi's sarcoma-associated herpesvirus *see* human herpesvirus-8
Kaposi's varicelliform eruption 211, 211f, 891f, 1323t, 1326f
karyotype 784t
Kasabach-Merritt syndrome
clinical features 1701, 1702f
radiologic evaluation 1703t
treatment 1707
see also infantile hemangiomas
kava kava 2192t, 2212t
Kawasaki disease 9–11
anogenital 1183
clinical features 776t–778t, 1363–1364, 1363f–1364f
differential diagnosis 330, 1363–1364
epidemiology 1362
history 1362
pathogenesis 1362–1363
pathology 1364
treatment 1364
immune globulin 2148t
keloid morphea 657, 660f
keloidal blastomycosis *see* lobomycosis
keloids 8, 49, 1621–1625, 2471, 2471f
acne-induced 3t–4t
clinical features 1622, 1622f–1624f, 1623t
cryosurgery 2286
differential diagnosis 1624
epidemiology 1621
pathogenesis 1621–1622, 1621f
pathology 1622–1624, 1623f–1624f, 1624t
radiotherapy 2293

treatment 1624–1625, 1625t
imiquimod 1625t, 2135
interferons 2132–2133
laser therapy 1625t
see also scars; wound healing
keratin 29t–33t, 449t, 700t, 871
assembly 828f
foreign body reaction 1580
acne keloidalis nuchae 1580
histopathology 1576t
pilonidal sinus 1580
pseudofolliculitis barbae 1580
treatment 1580
hair 827, 829f, 1081, 1084f
intermediate filaments 827, 828t
mutations and diseases 829f
nails 1089, 1089f
nomenclature 828t
and signaling 827
keratin 1 875
keratin 5 502f
keratin 9 875
keratin 14 502f
keratin 16 mosaicism 953
keratin disorders 800t–801t, 802, 834–835
Dowling-Degos disease 832t–833t, 835t
epidermolysis bullosa simplex *see* epidermolysis bullosa simplex
epidermolytic hyperkeratosis *see* bullous congenital ichthyosiform erythroderma
extracutaneous
familial cirrhosis 832t–833t
Meesmann corneal dystrophy 832t–833t
ichthyosis bullosa of Siemens 510t, 835t
ichthyosis hystrix of Curth-Macklin 835t
monilethrix 827, 832t–833t
pachyonychia congenita 832t–833t, 835t, 881–882
palmoplantar keratoderma *see* palmoplantar keratoderma
keratin pearls 1784, 2053t
keratinization disorders, hereditary 803t–804t
keratinizing metaplasia, vitamin A deficiency
keratinocytes 8, 825–836, 947t, 1093
adhesion 831–834
in atopic dermatitis 206t
establishment and maintenance 830
expression of neural mediators 100–101, 101t
genetically modified 78f
as immune targets and initiators 96
integrin receptors 834t
lupus erythematosus 624f
necrosis 17f
in psoriasis 137–139
secretory capacity 96
in skin immune response 96
keratinocyte growth factor 2316f, 2317
in wound healing 2317t
keratinocyte stem cells 62f, 62t
keratinocyte-extracellular matrix adhesion defects 800t–801t, 802–805
keratinocyte-matrix interactions 834
keratinocytes 2317–2318
keratins, hair 1081
keratitis 841t–842t
and chronic mucocutaneous candidiasis 903t
keratitis-ichthyosis-deafness (KID) syndrome 838t, 864–866, 874t, 1104t
clinical features 846f, 865, 865f
differential diagnosis 865–866
epidemiology 864
genetics 803t–804t
history 864
neonatal 847t
pathogenesis 864
pathology 865
treatment 866
keratoacanthoma 1771
clinical features 1781–1782, 1782f
Mohs surgery 2448
nail bed 1146, 2440t
pathology 1784, 1785f
radiotherapy 2296
see also non-melanoma skin cancer
keratocan 1592t
keratocyst 1822
keratoderma
aquagenic palmoplantar 883
blennorrhagicum 228t
Brünauer-Fuhs-Siemens 828t
climactericum 828t
drug-induced 828t
Gamborg-Nielsen 828t
hereditaria mutilans *see* Vohwinkel syndrome
with ichthyosis 872t
loricrin *see* Vohwinkel syndrome
palmoplantar 834, 835t, 871–885, 872t
acquired 872t, 883–884
aquagenic palmoplantar keratoderma 883, 883f
with cancer 883–884
with hypothyroidism/myxedema 883
keratoderma climactericum 228t, 883
circumscribed 884
with cutaneous squamous cell carcinoma and sex reversal 803t–804t, 813t, 873t, 878
with deafness 803t–804t, 873t–874t, 879
drug-induced 349t
genetics 832t–833t
hereditary 872–883, 872t–873t
diffuse 871–877, 875f
diffuse with associated features 877–879
diffuse non-epidermolytic/epidermolytic *see* Unna-Thost keratoderma; Vörner keratoderma
focal 872, 879–880
focal with associated features 880–882
Greither syndrome 873t, 877
mal de Meleda 873t, 877
punctate 872, 876f, 882–883, 882f
striate 803t–804t, 873t
see also individual syndromes
Sybert 828t
keratoderma climactericum 228t, 883
keratoelastoidosis marginalis *see* acrokeratoelastoidosis
keratohyalin 876, 881
keratolysis exfoliativa 599, 599f
congenita *see* peeling skin syndrome
keratolytic agents 2157–2158
α-hydroxy acids 2158
propylene glycol 2479
salicylic acid 2158
urea 2157–2158
keratolytic winter erythema *see* erythrokeratolysis hiemalis
keratoma plantare sulcatum *see* pitted keratolysis
keratomalacia 740t–742t
keratosis
alba *see* stucco keratosis
disseminated hypopigmented 1046f
follicularis *see* Darier disease
follicularis spinulosa decalvans 579t, 807t, 865, 1104t
genetics 803t–804t
inverted follicular 1806, 1807f
lichenoid 1798–1799
lichenoides chronica 184t, 201f
pilaris 209t, 210f
pilaris atrophicans 577–578, 578t
pilaris rubra 1638
punctata palmaris et plantaris *see* punctate palmoplantar keratoderma
seborrheic *see* seborrheic keratosis
spinulosa *see* lichen spinulosus
stucco *see* stucco keratosis
kerion 1259–1260
ketoconazole
adverse reactions 2123t, 2185t
lichen planus 185t
dosage 2120
formulations 2118t
indications 2120t
blastomycosis 1277
coccidioidomycosis 1278
histoplasmosis 1274
mycetoma 1272
paracoccidioidomycosis 1279
seborrheic dermatitis 221
interactions 2190–2192
pregnancy and lactation 2118t, 2120t, 2155t
trade names 2118t
ketoprofen
adverse reactions
photoallergy 1480t
pseudoporphyria 724t
ketotifen, renal pruritus 118t
key lime 280t
khellin-UVA phototherapy 1029
Ki-67 29t–33t
kibes *see* pernio
KID syndrome *see* keratitis-ichthyosis-deafness syndrome
kidney cancer, metastatic 2049t, 2051f, 2053t, 2054f
Kikuchi-Fujimoto disease 2040
Kikuchi's disease 1544
killer-activating receptors 83–84
killer-inhibitory receptors 83–84
Kimura's disease 414t
Kindler syndrome 1479
neonates 526t–528t
see also epidermolysis bullosa
Kindler-Weary syndrome *see* Kindler syndrome
kindlin-1 502f
kininogen, high-molecular-weight 358–359, 361
kinins 2315t
kinky hair disease *see* Menkes disease
kissing bugs *see* triatome reduviids
KIT 1994f
KIT ligand 1994f
KIT receptor 1011–1012, 1012f, 1994f
kiwi 275t
Klebsiella spp., chronic granulomatous disease 910t
Klebsiella (Calymmatobacterium) granulomatis 1367t
Klebsiella pneumoniae 375
Klebsiella rhinoscleromatis 1212, 1276t
Klein, Jeffrey 2525, 2528
Klein-Waardenburg syndrome 1035
KLICK syndrome 803t–804t, 852t–854t
Klinefelter syndrome 791–792
and cutis verticis gyrata 1626t
genetics 822t
Klippel-Trenaunay syndrome
clinical features 1717, 1717f
digital anomalies 1005t
knuckle pads 1972f
Köbberling-Dunnigan syndrome 818t–819t, 1665t
clinical features 1667–1668, 1668f
with mandibuloacral dysplasia 1665t, 1668
pathogenesis 1664
Koebner epidermolysis bullosa simplex 502f
Koebner phenomenon 8, 9f, 1550
acquired perforating dermatosis 1602f
erythema multiforme 321, 321f
isomorphic 1026
lichen nitidus 198
lichen planus 189f
psoriasis 139
Koenen's tumors 1144
Kogoj's spongiform pustules 147–148, 148f
koilocytosis 1306f
koilonychia 1130f, 1132
kojic acid 2490t
Koken Atelocollagen 2550
Koro syndrome 122t
Korsakoff's syndrome 740t–742t
kraurosis vulvae *see* lichen sclerosus
KRT5 458t
KRT14 458t
kwashiorkor 739, 1038
clinical characteristics 738t, 739f–740f, 1072t–1073t
kyphoscoliosis 1593t, 1609t, 1611
Kyrle disease 1600t
clinical features 1601–1602, 1602f
Kytococcus sedentarius 1201

labetalol-induced lichen planus 185t
Labrador tea 2207t
Lacazia loboi 1273
lacaziosis *see* lobomycosis
laccase 282
lacquer sensitivity 283
β-lactam antibiotics
mechanism of action 2111f
in sweat 541
see also penicillins
β-lactamase inhibitors 2110
sites of action 2109t
Lactobacillus spp. 2211
Lactrodectus spp. 1446–1447
Lactuca sativa see lettuce
Lactuca serriola see prickly lettuce
lady's mantle 2207t
Laelaps spp. 1445t
Lafora disease, eccrine gland changes 598f, 598t
Lagoa crispata 1441t
LAMA3 458t
LAMB syndrome 377, 1857t
genetics 818t–819t
LAMB3 458t, 801
LAMC2 458t
lamellar body secretion 2066f, 2067
lamellar dyshidrosis *see* keratolysis exfoliativa
lamellar ichthyosis 803t–804t, 838t, 850–851
clinical features 850–851, 851f
differential diagnosis 851
epidemiology 850
genetics 803t–804t
history 850
neonatal 847t
pathogenesis 850
pathology 851
treatment 851
Lamiaceae 274t
lamins 828t, 2372
lamina densa 452–454
heparan sulfate proteoglycans 454
laminins 452–453, 452f, 453t
nidogen 454, 455f
type IV collagen 453–454, 454f
lamina lucida 450
laminins 411, 452–453, 452f, 453t, 834t, 1590, 1686t
laminin-111 452f, 453t
laminin-311 453t
laminin-332 451t, 453t, 502f, 1596
laminin-511 453t
lamivudine
adverse reactions 1299t
nail changes 1141t
indications, vasculitis 402t
lamotrigine
adverse reactions 338t
gingival hyperplasia 1156t
Stevens-Johnson syndrome/toxic epidermal necrolysis 325t
Langerhans cells 57–58, 84f
antigen presentation 84–85
in atopic dermatitis 206t
morphology 84
ontogeny 85, 85f
phenotypic markers 84f, 84t
in psoriasis 147
Langerhans cell histiocytosis 22, 1529–1535
anogenital manifestations 1183
antigenic markers 1533t

clinical features 1530–1532, 1530t–1531t, 1532f
congenital 524t–525t, 532–533, 532f
differential diagnosis 414t, 1534
epidemiology 1529
history 1529
pathogenesis 1529–1530
pathology 1532–1534, 1533f–1535f
treatment 1534–1535
Langerhans cell sarcoma 1545t
langerin 84–85, 84t
Langer's cleavage lines 9
Langhans giant cells 21
lanolin 242t
lansoprazole 2190t
adverse reactions, erythroderma 176t
lanugo hair 1079t
lapatinib 1887t, 2149t
large cell acanthoma 1808–1809, 1809f
large plaque parapsoriasis *see* parapsoriasis
Laron syndrome 1104t
Larrea tridentata see chaparral
larva migrans 8
cutaneous 1406
lasers 2251, 2252f
absorption coefficient 2252
coherence 2251
collimation 2251
diagnostic uses 2257
divergence and convergence 2252f
fractional photothermolysis 2256–2257, 2256f
ablative 2273–2275
non-ablative 2272–2273
monochromicity 2251
photomechanical effects 2253–2254
safety 2257t
selective photothermolysis 2253, 2254t
skin cooling 2254
skin optics 2252, 2252f
skin penetration 2254f
skin resurfacing 2265t
ablative 2271–2272
fractionated 2264f, 2272–2277, 2273t
thermal interactions 2252–2253, 2253f
types of 2252t, 2255t, 2261–2263
vascular 2265t
diode lasers 2265t
intense pulsed light sources 2265t
long-pulsed alexandrite laser 2255, 2265t
neodymium YAG lasers 2255, 2265t
pulsed dye lasers 2255, 2265t
pulsed KTP lasers 2242, 2265t
wavelengths 2255t, 2261f
see also individual types
laser capture microdissection 65f
laser hair removal *see* hair removal
laser media 2252t
laser therapy 2261–2281
hair removal 2256, 2278–2279, 2278f
hypertrophic scars/keloids 1625t
melanin-containing lesions 2268–2271, 2270t
Becker's nevus 2270–2271
benign nevi 2269
café-au-lait macules and nevus spilus 2269–2270
ephelides and lentigines 2268–2271
melasma 2270
nevus of Ota and nevus of Ito 2270
postinflammatory hyperpigmentation 2271
striae distensae 2271
NMSC 1791
pigmented lesions 2256
psoriasis and vitiligo 1029, 2279
skin resurfacing 558, 2378, 2477f
ablative 2271–2272, 2272f
anesthesia 2276
dressings 2378
fractional 2256–2257, 2272–2277, 2273f, 2273t
non-ablative 2256
plasmakinetic 2277
tattoo removal 2254t, 2256, 2267–2268, 2268f
adverse effects of lasers 2269t
laser types 2269t
vascular lesions 2255–2256, 2263–2267
hemangiomas 1706–1707, 2265–2266
pain considerations 2267
poikiloderma of Civatte 2266
port-wine stains 2263–2265, 2265f
pyogenic granuloma 2267
rosacea/telangiectasias 567t, 2255, 2266, 2266f, 2517
spider veins 2266–2267
treatment methods 2265t
venous lake 2267
verrucae 2267
see also lasers; photothermolysis
laser-mediated photodynamic therapy 2243t
Laserskin 2375t
lassa fever 1360t
latanoprost, hypertrichosis 1119–1120
late envelope proteins 825–826
late-onset diseases 787
late-onset focal dermal elastosis 1614t
latent TGF-β-binding proteins 1593t
lateral cervical cyst *see* branchial cleft cyst
latex agglutination test 1348t
latex allergy 267, 268f, 340
Laugier-Hunziker syndrome 1857t
Lavandula spp. 274t
lavender (*Lavandula augustifolia*) 2215t
Lawrence syndrome 1665, 1665t
clinical features 1668–1669, 1669f
panniculitis variant 1668
pathogenesis 1665
subtypes 1668t
lead
dermatosis 1499t
hyperpigmentation 1056t–1057t
lecithin:cholesterol acyltransferase (LCAT) 1549
Ledderhose's disease *see* plantar fibromatosis
Ledebouriella seseloides 2213
leeches 1450–1451
leflunomide
dermatomyositis 639t
and pseudoporphyria 724t
therapy with 1451
leg ulcers
arterial 1738–1740
clinical features 1739, 1739f
differential diagnosis 1739–1740, 1739f
laboratory evaluation 1739, 1739t
pathogenesis 1738–1739
treatment 1740
neuropathic/diabetic 768t, 1740–1741
clinical features 769f, 1740, 1740f
laboratory evaluation 1740
pathogenesis 1740
prevention 1741
treatment 1740–1741
obese patients 751t
treatment 1734, 2376–2377
compression 1736, 1736t–1737t, 2377, 2377f
debridement 1734–1735
dressings 1735, 1735t
manual lymph drainage 1736
moisture and occlusion 1734
skin substitutes 1736–1737
topical negative pressure therapy 1736
topical and oral medications 1737
wound infection 1735–1736
venous 1729–1737
causes 1731f
clinical features 1731–1733, 1732f–1733f
laboratory evaluation 1733
pathogenesis 1729–1731, 1730f–1731f, 1730t
treatment 1734
leg veins 2509–2524
anatomy, physiology and pathophysiology 2509–2510, 2509f–2511f
laboratory evaluation 2512, 2512t–2513t, 2513f
muscle pump 2511f
see also phlebology
Legius syndrome 813t, 932t–933t
Leigh syndrome 1117t
Leiner phenotype 908
Leiner's disease 221
leiomyoma 1979–1980
angiolieomyoma 1979
clinical features 1979, 1980f
differential diagnosis 1980
epidemiology 1979, 1980t
genital 1979
history 1979
pathogenesis 1979
pathology 1979–1980, 1981f
piloleiomyoma 8, 1979, 1980f
treatment 1980
leiomyomatosis
cutis et uteri 1980t
genetics 813t
leiomyosarcoma 1980–1983
clinical features 1982, 1982f
differential diagnosis 1982–1983
epidemiology 1981
pathogenesis 1981
pathology 1982, 1982f, 1983t
treatment 1983
Leishmania spp. 1276t, 1391, 1392t
life cycle 1393f
leishmaniasis 1391–1397, 1392t
clinical features 1394–1396, 1394f–1396f, 1395t
diagnosis 1396
differential diagnosis 1276t, 1396
diffuse cutaneous 1392t, 1394
epidemiology 1391, 1392f, 1393t
HIV-related 1292–1293, 1395–1396
mucocutaneous 1392t, 1394–1395, 1395f
New World cutaneous 1392t, 1394
Old World cutaneous 1392t, 1394
pathogenesis 1391–1393
pathology 1396, 1396f
treatment 1397, 1397t
visceral 1392t, 1395
Leiurus quinquestriatus 1449t
lemon 275t, 280t
sweet 280t
lemon balm (*Melissa officinalis*) 2215t
lemongrass (*Cymbopogen citrates*) 2215t
lenalidomide, scleromyxedema 690
lentigines 3t–4t, 1055
cryosurgery 2286
generalized 1857t
laser therapy 2264f, 2268–2269
solar *see* solar lentigines
lentigines neonatorum *see* transient neonatal pustular melanosis
lentiginosis
centrofacial 1857t
familial generalized 818t–819t
genital *see* lentigo simplex
inheritance patterns 1857t
partial unilateral 932t–933t, 1854
perigenito-axillaris 1857t
plus arterial dissection 1857t
plus deafness 1857t
see also lentigo simplex
lentigo maligna
melanoma 1892, 1894f
treatment
cryosurgery 2286, 2287f
laser therapy
Mohs surgery 2449
radiotherapy 2294, 2294f
lentigo senilis *see* solar lentigines
lentigo simplex 1855–1858
anogenital 1855f
clinical features 1856, 1856f, 1857t
differential diagnosis 1856
disorders associated with 1856, 1857t
epidemiology 1855
labial 1855f
partial unilateral 1856
pathogenesis 1855–1856
pathology 1856, 1856f
treatment 1856–1858
leonine facies 690f, 691t
LEOPARD syndrome 776t–778t, 932t–933t, 1856, 1857t
genetics 818t–819t
Lepidoglyphus destructor 1445t
lepidopterism 1440, 1440f, 1441t
lepirudin 364t, 370
leprechaunism 818t–819t, 1117t, 1617t–1618t, 1672
lepromin test 1227
leprosy 46–47, 1221–1228, 1600t
and anetoderma 1633t, 1634f
classification 1224t
clinical features 1223–1225, 1224f
borderline lepromatous leprosy 1042, 1226f
borderline leprosy 1226–1227
erythema nodosum leprosum 1225
hypomelanosis 1042, 1042f
indeterminate leprosy 1042, 1227
lepromatous leprosy 1042, 1223–1225, 1224f, 1227f
Lucio's phenomenon 375, 1225
tuberculoid leprosy 1042, 1225–1226, 1226f–1227f
differential diagnosis 308t–310t, 1227–1228
epidemiology 1222
history 1221–1222
nerve examination sites 1224f
pathogenesis 1222–1223, 1223f
pathology and laboratory evaluation 1225–1227, 1227f
prevalence 1222f
reactions 1226f, 1226t
type 1 (reversal) 1226
type 2 1225
sequelae 1225f
treatment 1228, 1228t, 1231t
Leptosphaeria senegalensis 1271t
leptospirosis 1217
Leptotrombidium arenicola 1244t
Leptotrombidium deliense 1244t
Leptotrombidium fletcheri 1244t
Leptotrombidium scutellare 1244t
Leschke syndrome 932t–933t
Leser-Trélat sign 764t–765t, 1116, 1796
lethal acantholytic epidermolysis bullosa simplex 502f, 509t–510t, 832t–833t
Letterer-Siwe disease 1530t–1531t, 1531
lettuce 275t, 285t
Leucopersican esculentum
leukemia
acute lymphoblastic 845
acute myelogenous 1066
chronic lymphocytic 2041t, 2043f
chronic myelogenous 344
and erythema multiforme 2042t
hairy cell 1660t
inflammatory disorders associated with 2042t
juvenile myelomonocytic 764t–765t
mast cell 1998
oral manifestations 1166
pruritus in 112t, 119
leukemia cutis 2041–2043
biopsy 14t–15t
clinical features 2041–2042, 2042f, 2042t–2043t
differential diagnosis 2042
epidemiology 2041–2043
pathogenesis 2041
pathology 2042, 2043f
treatment 2043
leukemia inhibitory factor 82
leukemoid reaction in Down syndrome 534
leukocyte adhesion deficiency 900t, 912t, 915–919
clinical features 918–919, 919f
differential diagnosis 919
genetics 818t–819t
pathogenesis 915–918
pathology 919
treatment 919

leukocyte-endothelial cell interactions 1684, 1684f, 1685t, 1688f
leukocytes
in scleroderma 644f
in urticaria 293
in wound healing 2319–2320, 2320f
leukocytoclasia 20, 21f, 426
leukocytoclastic vasculitis 20, 21f
leukoderma 1023–1048
diagnosis 1023
guttate 936f, 1037t
linear 1039f
melanoma-associated 1043–1044, 1043f
of scleroderma 646
syphiliticum 1042
without hypomelanosis 1047
see also individual disorders
leukoderma acquisitum centrifugum *see* halo nevus
leukonychia 1130f, 1131–1132
apparent 1130f, 1132, 1139–1140, 1141t
diffuse 1132
drugs causing 1141t
and psoriasis 144
punctate 1132
striate 1132
leukopenia
in dyskeratosis congenita 1068t
SLE 627t
leukoplakia 1160–1161, 1161f
proliferative verrucous 1161
leukotrichia *see* vitiligo
leukotrienes
biochemical pathways 2177f
A4 2177f
B4 83, 2177f
C4 83, 2177f
D4 83, 2177f
E4 83, 2177f
leukotriene inhibitors 2176, 2177t
atopic dermatitis 213t
and Churg-Strauss syndrome 404, 612f
and secondary cutaneous vasculitis 390t
levamisole-induced lichen planus 185t
levator anguli oris 2331f, 2335
levator ani syndrome 122t
levimasole 1402t–1403t
levobupivacaine hydrochloride 2344t
levocetirizine 304t
levofloxacin 2116t, 2191t
dosage 1119
interactions 2191t
prophylactic 2462t
tuberculosis 1234t
levomepromazine-induced lichen planus 185t
Li-Fraumeni syndrome 1771
liarozole 2093
Libman-Sacks endocarditis 370t
lice *see* body lice; crab lice; head lice
lichens 274t
lichen amyloidosis 702, 702f
lichen aureus 365t
lichen myxedematosus, localized variants 691–692, 691f
acral persistent papular form 691, 691f
cutaneous mucinosis of infancy 691
differential diagnosis 692
discrete papular form 691
epidemiology 691
hepatitis C infection 692
HIV patients 691
nodular lichen myxedematosus 691
pathology 692
in toxic syndromes 692
treatment 692
lichen nitidus 3t–4t, 184t, 197–199
actinic 201
clinical features 198, 198t, 199f
differential diagnosis 198t, 199
epidemiology 198
histological features 198–199
ball and claw formation 190
history 198
pathogenesis 198
pathology 198–199, 199f
treatment 199
lichen planopilaris 190–191, 191f, 1095f, 1106–1107, 1106f
histologic features 1096t, 1102f
lichen planus 6t–7t, 8, 18f, 183–196
actinic 189, 1053t
acute 189
and anetoderma 1633t
annular 189, 189f
anogenital 189f, 1173–1175
clinical features 1174, 1174f
differential diagnosis 1174
epidemiology 1174
history 1173–1174
pathology 1174
treatment 1174–1175, 1175t
atrophic 189–190, 190f
bullous 190, 190f
clinical features 187–194, 188f–189f
hyperpigmentation 8f
Koebner phenomenon 8, 9f, 189f
postinflammatory hyperpigmentation 1050t
dermoscopy 38f
differential diagnosis 194–195, 198t, 308t–310t
drug-induced 185t, 188f, 193–194, 193f, 194t
epidemiology 183
exanthematous 189, 189f
histological features 194f
history 183
hypertrophic 190, 191f
inverse 190, 191f
linear 191–192, 192f, 956, 956f
nail 192, 192f, 1130f
nail bed 2440t
nails in 192, 192f, 1130f, 1137–1138, 1138f, 1138t
oral 183, 192, 193f
pathogenesis 183–187
autoantigens 185
bacteria 184
contact allergens 184
drugs 185
effector cells 185–187, 186f–187f, 188t
hepatitis C virus 183–184
target antigens 183–185, 184t
vaccines 184
pathology 194, 194f
pemphigoides 190
phases of 187f
pigmentosus 190
solitary *see* lichenoid keratosis
treatment 195–196, 195t
phototherapy 195t, 196, 2231
retinoids 195
ulcerative 192–193
lichen planus pemphigoides 479t
lichen planus pigmentosus 1052, 1052f, 1053t
lichen planus-like keratoses *see* lichenoid keratosis
lichen planus-lupus erythematosus overlap syndrome 192
lichen purpuricus *see* pigmented purpuric eruptions
lichen ruber acuminatus *see* pityriasis rubra pilaris
lichen ruber moniliformis 116
lichen ruber planus *see* lichen planus
lichen rubra pilaris *see* pityriasis rubra pilaris
lichen sclerosus 664–669
anogenital 664–666, 665f, 1175
clinical features 665f, 1171–1172, 1172f–1173f
differential diagnosis 1172–1173
epidemiology 1171
etiology 1171
history 1171
pathology 1172
autoantigens 1596t
clinical features 664–666, 665f
balanitis xerotica obliterans 664, 665f
hypopigmentation 1040, 1041f
melanocytic nevi 1863
differential diagnosis 666
epidemiology 664
history 664
pathogenesis 664
pathology 666, 666f
radiation-induced 663
treatment 666–669, 667t, 1173, 1173t
calcineurin inhibitors 668
corticosteroids 668–669, 668f
cytokines 669
hormones 669
immunosuppression 669
penicillin 669
phototherapy 666–668, 668f
retinoids 667
vitamin derivatives 668–669
lichen scrofulosorum 1232
lichen simplex chronicus 115–116
clinical features 112f, 115f
postinflammatory hyperpigmentation 1050t
lichen spinulosus 578–579
clinical features 578, 578f
differential diagnosis 579
history and epidemiology 578–579
pathogenesis 578
pathology 579
treatment 579
lichen striatus 184t, 196–197, 956
clinical features 196–197, 197f
differential diagnosis 197
epidemiology 196
history 196
pathogenesis 196
pathology 197
treatment 197
lichen verrucosus et reticularis 201
lichenification 4t–5t, 9
lichenoid amalgam reaction *see* contact stomatitis
lichenoid dermatitis, annular (of youth) 201–202
lichenoid drug eruption 185t, 188f, 193–194, 193f, 194t
lichenoid keratosis 1798–1799
clinical features 1799, 1799f
differential diagnosis 1799
epidemiology 1798
history 1798
pathogenesis 1799
pathology 1799, 1799f
treatment 1799
lichenoid tissue reaction 615
lichenoid trikeratosis 201
lichens 274t
Lichtenberg figures 1497
licorice extract 2192t, 2490t
licorice root 2211
effect on coagulation 2212t
lidocaine 2344t
adverse reactions 2155t
indications
Behçet's disease 428
pruritus 123
renal pruritus 118t
interactions 2529t
maximum dose 2347t
mucous membranes 2345t
overdose 2345t, 2346
percutaneous absorption 2069f
topical 2156
tumescent anesthesia 2348t
LIG4 syndrome 920t
lightning burns *see* electrical burns
lightning print 1497
Liliaceae 277t–278t
allergic contact dermatitis 288
limb-mammary syndrome
genetics 808t
Lind, James 294
lindane
adverse reactions 2155t
crab lice 1423
head lice 1428t, 1429
scabies 1424, 1426t
linea nigra 447t
linear angiofibroma 948f
linear basal cell carcinoma 945t–946t, 955
linear bullous ichthyosiform erythroderma 948f
linear fibromatosis 945t–946t
linear focal elastosis 1628t
linear Hailey-Hailey disease 954
linear IgA bullous dermatosis 456t, 481, 496–499
anogenital 1185
autoantigens 456t, 476t
clinical features 491–493, 497f–499f, 498–499
differential diagnosis 308t–310t, 495t, 499
drug-induced 347, 495f
epidemiology 497
history 497
immunoreactants in 457t
neonates 526t–528t
pathogenesis 497–498, 497f
pathology 499
treatment 499
linear leukoderma 1039f
linear lichen planus 191–192, 192f
linear lichenoid dermatosis *see* lichen striatus
linear melorheostosis 1117t
linear morphea 661
linear nevoid hyperpigmentation *see* hypomelanosis of Ito; linear and whorled nevoid hypermelanosis
linear porokeratosis 526t–528t
linear postinflammatory hyperpigmentation 1059–1060, 1060f–1061f
linear psoriasis 956, 956f
linear syringoma 955
linear trichoepithelioma/trichoblastoma 955
linear and whorled nevoid hypermelanosis 960, 1062–1063
clinical features 1062–1063, 1062f
differential diagnosis 1063
epidemiology 1062
pathogenesis 1062
pathology 1063
treatment 1063, 1063f
linezolid 2117t
indications
MRSA 1191t
tuberculosis 1234t
lingua plicata *see* fissured tongue
lingua villosa nigra *see* hairy tongue
linkage analysis 792–793, 793f
linkage interval 793–794, 794f
linkin 456
Linuche unguiculata 1451
Linurase *see* botulinum toxin
lionfish 1452
lips 2333f
lip depressor muscle 2338
lip lesions
congenital lip pits 1004–1010, 1005f
hemangioma 1696, 1698f
squamous cell carcinoma
lip rhytides 2566, 2566f, 2566t
lip sinuses 1004–1010, 1005f
lip, wedge closure of 2407–2408, 2408f
lip-licker's eczema 207, 1508
lipedematous alopecia 1103
lipid metabolism defects 800t–801t
lipid synthesis inhibitors 2071
lipid-free cleanser 2479
lipoatrophia semicircularis 1666, 1670, 1672
lipoatrophy
annular 1670
clinical features 1668f
drug-induced 1670, 1672
HIV-associated 1676
involutional 1670
localized 1666, 1666f, 1666t
clinical features 1670–1671, 1670f
non-progressive late-onset linear hemifacial 1670
pathogenesis 1666
lipoblastoma/lipoblastomatosis 1988–1989

lipodermatosclerosis 663, 1656–1658
  clinical features 1657, 1657f, 1734f
  differential diagnosis 650t, 1657
  epidemiology 1657
  history 1656
  obese patients 751t
  pathogenesis 1657
  pathology 1657, 1658f
  sites of 1642f
  treatment 1657–1658
lipodystrophia centrifugalis abdominalis infantalis 1666, 1670, 1671f, 1672
lipodystrophia centrifugalis infantalis 1671f
lipodystrophic panniculitis 1646t, 1670
lipodystrophies 1663–1677, 1664f, 1665t
  acquired generalized *see* Lawrence syndrome
  acquired partial *see* Barraquer-Simons syndrome
  centrifugal *see* lipodystrophia centrifugalis abdominalis
  congenital generalized *see* Berardinelli-Seip syndrome
  differential diagnosis 1672–1673
  familial partial *see* Köbberling-Dunnigan syndrome
  generalized with pubertal onset
  genetics 818t–819t
  history 1673–1676
  HIV/ART-related 1665t
    clinical features 1674–1676, 1675f
    pathogenesis 1673–1674, 1674f, 1674t
    treatment 1676
  localized lipoatrophy *see* lipoatrophy, localized
  pathogenesis 1663–1666
  pathology 1671–1672, 1672f
  treatment 1673
lipogranuloma
  microscopic features 1656t
  sclerosing 1656t
lipohypertrophy 1671, 1671t
  HIV-associated 1676
lipoid proteinosis 709t, 712–713, 1593t
  clinical features 712, 713f
  differential diagnosis 712–713
  epidemiology 712
  genetics 712, 807t
  history 712
  pathogenesis 712
  pathology 712, 714f
  treatment 713
lipoma 1001t, 1984–1985
  atypical *see* liposarcoma
  clinical features 1984–1985, 1984f–1985f
  differential diagnosis 1985
  embryonic *see* lipoblastoma
  of embryonic fat *see* hibernoma
  epidemiology 1984
  fetal *see* hibernoma
  liposuction for 2532
  pathogenesis 1984
  pathology 1985, 1985f
  spindle cell 1986–1987
  treatment 1985
lipomatosis
  benign symmetric 813t, 1985, 1985f
  encephalocraniocutanous 959
  familial multiple 813t, 1984
  infiltrating/diffuse 1984
Liponyssoides sanguineus 1244t, 1445t
lipophages 1643, 1671
lipophilic agents 2070–2071, 2071f
lipoprotein (a) excess 1744t
lipoprotein lipase deficiency 1550
  familial 1549t
  genetics 810t–811t
lipoproteins 1547
  synthesis 1547, 1548f
liposarcoma 1989–1990
  clinical features 1990, 1990f
  differential diagnosis 1990
  epidemiology 1990
  pathogenesis 1990
  pathology 1990, 1990f
  treatment 1990
liposomes 2071
liposuction 2525–2534
  alternative trends 2533
  background 2525
  complications 2533, 2533t
  indications and contraindications 2525, 2526f–2527f, 2527t
  instrumentation 2529–2531, 2530f–2531f
  non-cosmetic 2532
  postoperative care 2532
  powered 2530, 2530f
  preoperative history 2525–2526, 2527f
  preoperative visit 2527–2528
  surgical technique 2529
  tumescent anesthesia 2528–2529, 2528f–2529f, 2528t
  variations/unusual situations 2531
liposuction cannulas 2530f
lipotransfer 2557–2558, 2558f
lipsticks 2484
liquid nitrogen *see* cryosurgery
Lisch nodules 929f
Listeria monocytogenes 524t–525t, 1204
lithium
  adverse reactions
    acne 550t
    alopecia 348t
    erythroderma 176t
    gingival hyperplasia 1156t
    lichen planus 185t
    linear IgA bullous dermatosis 498t
    pruritus 120t
  dermatosis 1499t
livedo racemosa 1748f
livedo reticularis 357, 376f, 1747–1750
  biopsy 14t–15t
  causes 1748f, 1748t
  clinical features 1747–1749, 1748f–1749f
    cutis marmorata telangiectatica congenita 1747
  intraluminal pathology 1748–1749
  physiologic livedo reticularis/cutis marmorata 1747
  primary/idiopathic livedo reticularis 1747
  vasospasm 1747–1748
  vessel wall pathology 1748
  differential diagnosis 1495t, 1749
  history 1747
  pathogenesis 1747
  pathology 1749, 1750f
  treatment 1750
livedoid vasculopathy 223, 381–382
  clinical features 381, 381f
  differential diagnosis 382
  pathogenesis 381
  pathology 381
  treatment 382
liver cancer, metastatic 2049t
liver disease 774t
liver function tests 152t
liver spot *see* solar lentigines
LL-37/hCAP18 82, 83t
LMP1 29t–33t
LMX *see* lidocaine
Loa loa 1407t–1408t
lobomycosis 1273, 1274f
Lobo's disease *see* lobomycosis
lobular capillary hemangioma *see* pyogenic granuloma
lobular neuromyxoma, mucin sdeposition 688t
local anesthetics 2343–2352, 2344t
  additions to 2344–2345
    epinephrine 2344–2345
    hyaluronidase 2345
    sodium bicarbonate 2345
  adverse reactions 2345–2346
    allergic reactions 2346
    local adverse reactions 2346
    overdosage 2346
    vasovagal reactions 2345
  allergies 2463
  amides 2344t
  chemical structure 2344f
  dissociation constant 2343
  esters 2344t
  higher levels of anesthesia 2351–2352
  injection techniques 2348, 2383f
    field block 2348
    local infiltration 2348
    tumescent anesthesia 2348, 2348t
  mixtures 2345
  nerve block 2348–2351
    digital 2350
    facial 2349–2350, 2349f–2350f
    foot 2351, 2351f
    hand 2350–2351, 2350f
    penile 2350
  pharmacology 2343–2344
  physiology and structure 2343, 2344f
  pruritus 123
  systemic reactions 2345t
  topical 2346–2348, 2347t
    cryoanesthesia 2347–2348
    mucous membranes 2347
    skin 2346–2347
  see also individual local anesthetics
local infiltration anesthesia 2305
localized heat contact urticaria 305
locus heterogeneity 785, 785t
LOD score 793
Loeys-Dietz syndrome 776t–778t, 1593t, 1594–1595, 1612
  genetics 807t
  see also Marfan syndrome
Löfgren's syndrome *see* sarcoidosis
loiasis 1407t–1408t
lomefloxacin 2116t, 2191t
  photoallergy/phototoxicity 1480t
lone star tick *see Amblyomma americanum*
Lonomia achelous 1441t
Lonomia oblique 1441t
loop marks 1522, 1522f
loose anagen hair syndrome 1112
Lophatherum gracile 2213
lopinavir, adverse reactions 1299t
loracarbef 2112t
loratadine 304t
lorazepam 133
  and lichen planus 185t
loricrin 825–826, 878
loricrin keratoderma *see* Vohwinkel syndrome
losartan 651, 2190
loteprednol suspension 2079t
Louis-Bar syndrome *see* ataxia-telangiectasia
lovastatin 2190, 2191t
  interactions 2192
low level light therapy 2258, 2537
low-density lipoproteins 1547, 1547t, 1549
low-molecular-weight chemicals 267
low-molecular-weight heparin 364t
  injection site reactions 354t
Lowry-MacLean syndrome 1823
loxapine, and eccrine sweating 590t
Loxosceles spp. 1447–1448, 1447f
Lucilia sericata 2373–2374
Lucio's phenomenon 375, 1225
Lucky/Winter syndrome 1072t–1073t
Ludwig's angina 1153
luei gong gen 2207t
lufenuron 1492
LUMBAR syndrome 999–1000, 1695, 1698–1699
  see also infantile hemangiomas
lumican 1592t
lung cancer, metastatic 2049t, 2053t
lunula 1086
lupoid form of groin ulceration *see* donovanosis
lupoid sycosis 572f
lupus anticoagulant 379–380, 1744t
  see also antiphospholipid antibody syndrome
lupus band 615
lupus erythematosus 184t, 615–629
  approach to 626f
  autoantibodies 606f, 607–609, 607t
  clinical features 617–623
  cutaneous 617–621
    action spectrum 2203t
    acute 618f
      butterfly rash 618f, 620–621, 621f
      differential diagnosis
      dyspigmentation 620–621
      inflammatory infiltrates 618f
      toxic epidermal necrolysis-like eruption 621
    alopecia 618f–619f, 623
    chilblain lupus *see* chilblain lupus
    chronic 618f
    classification 617–618
    inflammatory infiltrates 618f
    lupus panniculitis *see* lupus panniculitis
    neonatal 622, 623f
    subacute *see* subacute cutaneous lupus erythematosus
    tumidus *see* lupus erythematosus tumidus
  cutaneous acute *see* acute cutaneous lupus erythematosus
  differential diagnosis 625–626, 626f, 626t
  discoid *see* discoid lupus erythematosus
  drug-induced 349–350, 626
    ANCA associated with 613t
  epidemiology 615
  and erythema multiforme 320t, 621
  ethnicity 615
  history 615
  mucin deposition 624–625
  neonatal 622, 623f
    cardiac disease 622, 776t–778t
  non-specific lesions 623
  pathogenesis 615–617, 617f
  pathology 624–625, 624f–625f, 624t
    immunopathology of lesional skin 625
    immunopathology of normal skin 625
    routine histopathology 624–625
  systemic *see* systemic lupus erythematosus
  treatment 618–620, 626–628
    adjunctive therapy 628
    retinoids 628, 628t, 2097–2098
    systemic therapy 627–628
    topical therapy 626–627
  see also individual forms
lupus erythematosus tumidus 621
  clinical features 622f
  differential diagnosis 308t–310t
  histopathology 624t
  inflammatory infiltrates 618f
  Jessner's lymphocytic infiltrate *see* lymphocytic infiltrate of Jessner
lupus miliaris disseminatus faciei 1233
lupus panniculitis 621, 1646t, 1653–1654
  clinical and microscopic features 622f, 1642, 1653, 1653f
  differential diagnosis 1653–1654
  epidemiology 1653
  histopathology 624t
  history 1653
  inflammatory infiltrates 618f
  pathogenesis 1653
  pathology 1653, 1654f
  sites of 1642f
  treatment 1654
lupus pernio 621–622, 622f
lupus profundus *see* lupus panniculitis
lupus vulgaris 1231t, 1233f
lupus/lichen planus overlap syndrome 623
lurasidone
  adverse reactions 129t
  psychosis 134
lutein 2490t
LY2439821 2147t
lycopene 2207t
Lycopersicon lycopersicum see tomato
Lyell, Alan 324
Lyell's syndrome *see* toxic epidermal necrolysis
Lymantria dispar 1441t
Lyme borreliosis *see* erythema migrans

Lyme disease 1214–1215, 1215t
  panniculitis 1660t
  see also erythema migrans
lymph drainage, manual 1736
lymphadenopathy 1236–1237, 1240
  tick-borne 1244t, 1246t
lymphadenosis benigna cutis *see* lymphoid hyperplasia, cutaneous
lymphangioleiomyomatosis 823
lymphangioma circumscriptum 1723
lymphangiosarcoma *see* angiosarcoma
lymphatic blockage 49–50
lymphatic drainage of head and neck 2340, 2340f
lymphatic malformations
  clinical features 1722–1724, 1723f
  combined microcystic/macrocystic 1723–1724
  histology 1726f
  investigative tools 1714t
  lymphedema 1722–1723
  macrocystic 1723
  microcystic 1723
  pathology 1726
  treatment 1727
lymphatic system 1680f, 1685–1687, 1686t
  embryonic development 1686f
  fluid drainage 1685f
  markers for 1686t
lymphatic vascular endothelial hyaluronan receptor 1686–1687
lymphedema 1737–1738
  causes 1738t
  clinical features 1722–1723, 1739f
    elephantiasis nostras verrucosa 1738f
    myxedema 1738f
    Nonne-Milroy disease 1738f
  and drug abuse 1514t
  and leg ulcers 1737–1738
  liposuction for 2527t
  obese patients 751t
lymphedema praecox 1005t, 1738t
lymphedema-distichiasis syndrome 1722–1723
  molecular genetics 1713t
lymphocytes
  apoptosis 920t
  B cells 93–95, 94f
  recruitment 93
  T cells *see* T cells
lymphocyte functional antigen (LFA-1) *see* CD11a
lymphocytic infiltrate of Jessner 2037–2047
  clinical features 2037, 2037f
  differential diagnosis 308t–310t, 2038, 2038f
  epidemiology 2037
  history 2037
  pathogenesis 2037
  pathology 2037, 2037f
  treatment 2038
lymphocytic infiltrates
  benign 2037–2041
    cutaneous lymphoid hyperplasia 2038–2040
    extramedullary hematopoiesis 2040–2041
    Jessner's *see* lymphocytic infiltrate of Jessner
lymphocytic vasculitis 20
lymphocytoma cutis *see* lymphoid hyperplasia, cutaneous
lymphoepithelial cyst *see* branchial cleft cyst
lymphoepithelial Kazal-type inhibitor (LEKTI) 204t
lymphoepithelioma-like carcinoma 1782–1783
lymphogranuloma venereum 1386–1387
  clinical features 1386–1387, 1387f, 1387t
  diagnosis 1387
  differential diagnosis 1387
  epidemiology 1386
  history 1386
  pathogenesis 1386
  pathology 1387
  treatment 1387, 1387t
lymphogranulomatosis X *see* angioimmunoblastic lymphadenopathyangio
lymphoid hyperplasia, cutaneous 2038–2040
  and anetoderma 1633t
  clinical features 2039, 2039f
  differential diagnosis 2040, 2040t
  epidemiology 2038
  history 2038
  pathogenesis 2039, 2039t
  pathology 2039–2040, 2040f
  treatment 2040
lymphoid interstitial pneumonitis 1288t
lymphoma
  AIDS-related 1296
  B-cell *see* B-cell lymphoma
  biopsy 14t–15t
  cutaneous, differential diagnosis 204t
  differential diagnosis 414t
  eccrine gland changes 598t
  intravascular 382, 382f
  non-Hodgkin 112t, 119
  oral manifestations 1166
  plasmoblastic 2006
  radiotherapy 2298
  T-cell *see* T-cell lymphoma
lymphoma cutis 427t, 1333t
  differential diagnosis 1921, 1934, 2040, 2042
  specimen handling 2382t
lymphomatoid granulomatosis 2046–2047
  clinical features 2046, 2046f
  pulmonary disease 778t–779t
  differential diagnosis 2046–2047
  epidemiology 2046
  history 2046–2047
  pathogenesis 2046
  pathology 2046
  treatment 2047
lymphomatoid papulosis 2030–2032
  clinical features 2030–2031, 2031f
  definition 2030
  differential diagnosis 2020t, 2031–2032
  epidemiology 2030
  pathogenesis 2030
  pathology 2031, 2031f
  treatment 2032
    phototherapy 2222
lymphopenia, in systemic lupus erythematosus 627t
Lyofoam 2371
Lyon, Mary 943
lyonization 788, 943, 945t, 948
lysergic acid diethylamide abuse 1512
lysozyme 83t
lysyl hydroxylase 1593t
  deficiency 1608
LYVE-1 1686t

Mac-1 1685t
McCune-Albright syndrome 932t–933t, 959
  clinical features 931
  genetics 810t
Machupo virus 1360t
McKusick-type metaphyseal chondrodysplasia *see* cartilage-hair hypoplasia syndrome
McKusick's Mendelian Inheritance in Man 801
macrocephaly 1593t
  digital anomalies 1005t
macrocephaly-capillary malformation 1718, 1718f
macrocheilia 1714f, 1715, 1727
macroglossia 467t, 705f
macrolides 2113–2114
  adverse reactions 338t, 2114
    secondary cutaneous vasculitis 390t
  contraindications 2113–2114
  dosage 2113, 2114t
  indications 2113
  interactions 2114, 2192–2193
  mechanism of action 2113
  pregnancy and lactation 2114
  sites of action 2109t
macrophages 82–83
  in atopic dermatitis 206t
macrophage activation syndrome 672t, 1530t–1531t
macrophage inflammatory protein 1α 188t, 2319
macrophage metalloproteinase 2323t
MACS 1617t–1618t
macular amyloidosis 702
macular atrophy *see* anetoderma
macular purpura 359t
maculatum disease 1244t, 1246t
macules 3t–4t
  palpation 6t
madarosis 850–851
  and drug abuse 1514t
  in leprosy 1223–1225
Madelung's disease 1985, 1985f
Madura foot *see* mycetoma
Madurella grisea 1271t
Madurella mycetomatis 1271t
maduromycosis *see* mycetoma
mafenide acetate 1489, 2109
Maffucci syndrome 1722, 1722f
magainin 2071
maggot therapy 1735
MAGIC syndrome 676
magnesium 2212t
  dermatosis 1499t
Mahonia aquifolium see Oregon grape root
Majeed syndrome 818t–819t
Majocchi-Schamberg disease *see* pigmented purpuric eruptions
Majocchi's granuloma 575f, 1258f
major basic protein 411
major histocompatibility complex
  class I 83–84, 86–87, 87f
    deficiency 920t
  class II (HLR-DR) 84t, 87, 88f
    deficiency 920t
makassar ebony dermatitis 1509t
mal de Meleda 873t, 877
  differential diagnosis
  genetics 803t–804t, 877
mal perforans 1730t
malakoplakia 1211
malar erythema 350, 617–618
malar rash 620–621
Malassezia spp. 1252t
  in sebaceous follicles 219, 542, 544f
Malassezia furfur 530, 1055, 1187t
  immune response in seborrheic dermatitis 220
  superficial mycoses 1251, 1251t–1252t
Malassezia globosa 530
  superficial mycoses 1251, 1251t–1252t
Malassezia obtusa 1252t
Malassezia pachydermatitis 1252t
Malassezia restricta 1252t
Malassezia sloofiae 1252t
Malassezia sympodialis 1252t
malathion
  adverse reactions 2155t
  head lice 1428t, 1429
male genital pain syndrome 122t
male pattern baldness 1093–1094, 1096t
  classification 2536f
  hair transplantation 2538f
  see also androgenetic alopecia
malignancy *see* cancer; tumors
malignant atrophic papulosis *see* Degos disease
malignant endovascular papillary angioendothelioma *see* Dabska-type hemangioendothelioma
malignant hemangioendothelioma *see* angiosarcoma
malignant histiocytoses 1545, 1545t
malignant peripheral nerve sheath tumor 928, 1953–1954, 1953f
malignant subcutaneous infiltrates 1659
malnutrition
  electrolytes in sweat 597t
  HIV-related 1296
  and nail growth 1090t
  protein-energy 738t, 739–740, 739f–740f
  pseudo-Hutchinson's sign 2443t
  wet see kwashiorkor
  see also nutritional diseases
MALT lymphoma
  clinical features 2004–2005, 2005f
  pathology 2007, 2008f
Malta fever *see* brucellosis
Malus spp. *see* apple
mammalian target of rapamycin 823
Manchineel tree 278t
mandibuloacral dysplasia 818t–819t
manganese, dermatosis 1499t
Mangifera indica see mango
mango 246t, 275t, 282t, 283
MAPK pathway in melanoma 1886, 1886f
maple syrup urine disease 598t
maprotiline 2190t
  and cutaneous lymphoid hyperplasia 2039t
  and eccrine sweating 590t
marantic endocarditis 377
marasmus 739, 739f
  characteristics of 738t
maraviroc, adverse reactions 1299t
Marburg virus 1360t
Marcaine *see* bupivacaine hydrochloride
Marfan syndrome 776t–778t, 1593t, 1594–1595, 1608t
  elastosis perforans serpiginosa in 1601f
  genetics 807t
  vs Ehlers-Danlos syndrome 1612t
Mari type hypotrichosis 1104t
Marie-Unna type hypotrichosis 1104t
marigold 285t, 287f, 2205–2206
marijuana abuse
  cutaneous reactions 1514t, 1518t
  prevalence 1512t
marine injuries 1450t, 1451–1452, 1451f
marionette lines, botulinum toxin 2566t, 2568
Maroteaux-Lamy syndrome 715t
marsh elder 285t
marsh-marigold 278t
MART-1 29t–33t
mascaras 2483–2484, 2483t
mask burn 1505–1506
mask of pregnancy *see* melasma
MASP-2 909t
mass spectrometry 72f, 73t
masseter muscle 2327
masseteric hypertrophy, botulinum toxin 2566t, 2568, 2568f
Masson trichrome stain 27t–28t
Masson's lesion *see* papillary endothelial hyperplasia
mast cells 83, 291–293
  in atopic dermatitis 206t
  degranulating stimuli 292, 292f–293f
  distribution and diversity 291–292
  proinflammatory mediators 292–293
  in wound healing 2320
mast cell growth factor *see* steel factor
mast cell leukemia 1998
mast cell mediators 1995f
mast cell-dependent urticaria 293–294
mast cell-independent urticaria 294
mast-cell specific factor 293
mastocytoma 1995f
mastocytosis 1054–1055, 1993–2002
  adult-onset 1994f, 1994t, 1995, 1996f
  and anetoderma 1633t
  childhood 1993, 1994f–1996f, 1994t, 1995
  classification 1997–1999, 1998f
  clinical features 1994–1999, 1994f
    cutaneous lesions 1995–1996, 1995f–1997f
    signs and symptoms 1994–1995, 1995f
    systemic manifestations 1996–1997, 1998f
  differential diagnosis 1998f, 1998t, 2001

diffuse cutaneous 1995–1996, 1996f
epidemiology 1993
familial 1994t
genetics 1994f, 1994t
history 1993
neonates 526t–528t, 1993
pathogenesis 1993–1994, 1995f
pathology 1999–2001, 1999f–2000f
treatment 2001–2002, 2001t
phototherapy 2231
xanthelasmoidal 1995–1996
mat telangiectasia 645t
matchbox sign 128, 128f
maternal autoimmune bullous disease 526t–528t
Matricaria chamomilla see chamomile
Matricaria recutita see chamomile
matrilins 1592t
matrilysin, in wound healing 2323t
matrix metalloproteinases 86
MMP-1 1229
MMP-2 1682
MMP-9 1682
in wound healing 2323t
matrixectomy 2306
maxacalcitol 2156
dosage 2161t
Maxorb 2372
MBL 909t
MC1R-MIFT pathway in melanoma 1887, 1888f
mdm2 gene 1765t
measles 9, 1348–1349
clinical features and differential diagnosis 1348–1349, 1348f
epidemiology 1348
history 1348
pathogenesis 1348
pathology 1349
treatment 1349
mebendazole 1402t–1403t
mecamylamine, hypohidrosis/anhidrosis 595t
mechanical irritant dermatitis 265, 265f, 277
clinical features 277
epidemiology 277, 277t
pathogenesis 277
treatment 277
mechanic's hand lesion 610
mechlorethamine hydrochloride 2160
adverse reactions 2155t, 2160
alopecia 349t
hyperpigmentation 349t, 1056t–1057t
NMSC 1775t
indications
mycosis fungoides 2023
parapsoriasis 159t
mechanism of action 2160
pregnancy and lactation 2160
median canaliform dystrophy of Heller 1143f
median raphe cyst 1825
median rhomboid glossitis 1151, 1151f
Medicago sativa see alfalfa
MEDLINE 2061
MEDNIK syndrome 803t–804t, 852t–854t
medrysone suspension 2079t
medullary (gustatory) hyperhidrosis 590–591
pathologic 590–591, 591f
physiologic 590
Mees' lines 1132, 1498t
Meesmann corneal dystrophy 832t–833t
mefenamic acid-induced pseudoporphyria 724t
Mefilm 2369
Megalopyge opercularis 1440f, 1441t
meglumine antimonate, leishmaniasis 1397t
Meige disease 1005t, 1722–1723, 1738t
meiosis 784t
Meissner bodies 1087
Melaleuca alternifolia 274t
melamine formaldehyde resin 242t
Melan-A 29t–33t
melanin 8
biosynthesis 1016–1022, 1017f
increased production 1020f
melanoacanthoma 1798
melanoblasts 947t
melanocortin receptor 1019t
melanocortin-1 receptor 1018f–1019f
melanocyte stem cells 62f, 62t, 1013
melanocyte stimulating hormone 1019f
melanocytes 8, 43, 44f, 57, 1011–1022
autoimmune destruction 1025t
development disorders 1034t
formation and function of melanosome 1014–1016, 1014f
intrinsic defect 1025t
in nail unit 1088–1089
origin and function 1011–1014, 1011f–1013f
regulation of melanin biosynthesis 1016–1022, 1017f
ultraviolet irradiation 1021–1022
see also vitiligo
melanocytic nevus 508f
of acral skin 1864
and anetoderma 1633t
atypical dysplastic 1868–1871
common acquired 1861–1863
congenital 1001t, 1119, 1871–1874
diagnosis
dermoscopy 35f
pattern analysis 39t–40t
of genital and flexural skin 1863–1864
and melanoma risk 1890, 1890f–1891f
of nail matrix 1145–1146
phenotypes 1868t
recurrent 1877–1878
segmental agminated 955
melanocytosis 1872
dermal 6t–7t
cleft lip/palate 1005t
oculodermal *see* nevus of Ota
oculomucodermal *see* nevus of Ota
melanogenesis 1014, 1017–1018
melanoma 45–47, 1600t, 1885–1914, 2202–2203
acral lentiginous 1893–1894, 1895f
action spectrum 2201t
age-adjusted incidence 1888f
age-adjusted mortality 1889f
amelanotic 37f, 1894, 1895f
anogenital 1179
childhood 1897
clear cell sarcoma 1895
clinical features 1872–1873
desmoplastic/spindled/neurotropic 1895, 1896f
diagnosis 1897–1899
biopsy 14t–15t
dermoscopy 34f–35f, 1897–1899, 1898f–1899f, 1900t
pattern analysis 39t–40t
photographically assisted evaluation 1899
serial video dermoscopy 1899
differential diagnosis 39t–40t, 1866t, 1897, 1898t
Menzies scoring method 41t
seven-point checklist 41t
epidemiology 1888–1889, 1888f–1889f
and epidermolysis bullosa 508
familial 1464–1465
genes responsible for 70–71, 70t, 71f
genetic predisposition 1889
histopathologic diagnosis 1899–1902, 1900f–1901f, 1900t, 1902t
host immune response 1887–1888, 1888f
immunohistopathology 1901–1902
lentigo maligna 1892, 1894f
management 1887t, 1905–1910
adjuvant therapy 1907–1908, 1907t
chemotherapy 1908, 1909t
immunomodulators 2132
immunotherapy 1908–1910
local recurrences 1905, 1906f
Mohs surgery 1905
molecularly targeted therapy 1910
stages I and II 1905, 1905t
stage III 1906–1908, 1907f
stage IV 1908–1910
melanocytic simulators 1898t
metastatic 2049t, 2053t
microstaging 1901, 1901f
molecular analysis 1902, 1902f
molecular pathogenesis 1885–1887, 1886f, 1888f
mucosal 1896
nail bed 1146–1147, 1147t, 1895f, 2440t
nodular 1892, 1893f–1894f
non-melancytic simulators 1898t
ocular 1896
oral 1166–1167, 1167f
patient evaluation 1904–1905, 1905t
and pregnancy 1896–1897, 1905t
prognosis 1903–1904, 1904t
risk factors 1868t, 1889–1892, 1889t
environmental 1890–1892
gene-environment interactions 1889–1890, 1890f
genetic 1889
spitzoid 1895, 1896f
staging 1902–1903, 1903t, 1904f
superficial spreading 1892, 1892f–1893f
surveillance 1910
survival 1904t
tumor progession 1885
UV radiation and photoprotection 1890–1892
melanoma-associated leukoderma 1043–1044, 1043f
photomechanism 1043f
melanonychia
biopsy 2442f
drugs causing 1141t
longitudinal 8, 1132–1133, 1134f, 1134t, 2442f
melanophages 1049
melanosis *see* lentigo simplex
melanosis bulborum *see* nevus of Ota
melanosome biogenesis disorders 1035–1036, 1035t
Chédiak-Higashi syndrome *see* Chédiak-Higashi syndrome
Cross syndrome 1036
Hermansky-Pudlak syndrome 361, 1035–1036, 1035t, 2459
tricho-hepato-enteric syndrome 1036
melanosome transport/transfer disorders 1036
see also Griscelli syndrome
melanosomes
eumelanin 1016f
formation and function 1014–1016, 1014f
movement into dendrites 1016f
and pigmentation 1016t
MELAS syndrome 1117t
melasma 52, 1052–1054
clinical features 1052–1053, 1054f
differential diagnosis 1053, 1053t
epidemiology 1052
pathogenesis 1052
pathology 1053
treatment 1053–1054
chemical peels 2495f, 2496
laser therapy 2270
melatonin 2212t
Melilotus officinalis see sweet clover
melioidosis 1211
Melkersson-Rosenthal syndrome 549f
fissured tongue 1150
Meloidae 1439
melomental folds *see* marionette lines
melon 275t
melphalan
adverse reactions, mucositis 349t
primary systemic amyloidosis 707
scleromyxedema 690
membrane cofactor protein *see* CD46
membrane-attack complex (MAC) 81, 909t
membranous aplasia cutis 993, 995f, 1946t
with bone defect 997f
without bone defect 997f
memory T cells 90
Mendelian inheritance 783–787, 786f
exceptions to 787–791, 788f
Mendes da Costa syndrome 510t, 1065t
meningioma 1946t
meningocele 996–997
atretic 998
rudimentary 998
meningococcemia 9–11, 1204–1206
clinical features 1205, 1205f
diagnosis 1205
epidemiology and pathogenesis 1204–1205
and erythema nodosum 1644t
pathology 1205
treatment 1205–1206
Menkes disease 748, 750f, 952, 1104t, 1111
mental crease, botulinum toxin 2566t, 2568, 2568f
mental foramen 632
mental nerve 2349–2350
mental nerve block 2350f
mental retardation 841t–842t, 1593t
mentalis muscle 2331f, 2335
Mentha spp. 274t
menthol
insect bites/stings 1436
perforating disease 1604t
pruritus 106t, 2157t
menthyl anthranilate 2199, 2200f
mentophyma 564t
meperidine 2351–2352
and eccrine sweating 590t
Mepilex 2371
Mepitel 2378
mepivacaine 2344t
mepolizumab 215, 421
mequinol 2158–2159
meradimate 2200f
meralgia paresthetica 121, 121f
mercaptobenzothiazole 242t
mercaptomix 242t
mercaptopropionylglycine-induced lichen planus 185t
mercuric oxide, yellow, hair discoloration 1498t
mercury
adverse reactions 2155t
cutaneous deposits 1053t
dermatosis 1499t
hyperpigmentation 1056t–1057t
mercury compounds 253t–254t
adverse reactions
erythroderma 176t
lichen planus 185t
Merkel cells 58
Merkel cell carcinoma 1790t, 1954–1955
clinical features 1954, 1954f, 1954t
differential diagnosis 1955
epidemiology 1954
history 1954
pathogenesis 1954
pathology 1955, 1955f
radiotherapy 2297
treatment 1955, 1956f
Mohs surgery 2449
mesalamine-induced lichen planus 185t
mesotherapy 1582
metabolic disorders 768–769, 768f–770f, 768t–771t
hereditary 810t–811t
metabolic syndrome 769t, 1550–1551
metabolism
drug-induced changes 337
see also cytochrome P450 enzymes
metal salts, sensitivity to 251t, 252
metalloproteinases 1586–1587
see also matrix metalloproteinases
metaplastic synovial cyst 1817t
metastases, cutaneous 1764, 2049–2055
bile duct cancer 2049t, 2053t
bladder cancer 2049, 2052f, 2053t
breast cancer 2049, 2052f, 2053t, 2054f
cervical cancer 2049
clinical features 2050–2051, 2051t

colorectal cancer 2049t, 2050f, 2053t
development of 2050t
differential diagnosis 2055f
endocrine cancer 2049, 2053t
endometrial cancer 2049
epidemiology 2049
esophageal cancer 2049
gallbladder cancer 2049t
gastric cancer 2049t, 2053t
histology 2051t, 2052f, 2054f
immunological stains 2053t
kidney cancer 2049t, 2051f, 2053t, 2054f
liver cancer 2049t
lung cancer 2049t, 2053t
melanoma 2049t, 2053t
ovarian cancer 2049t, 2053t
pancreatic cancer 2049t, 2053t
pathogenesis 2049–2050
pathology 2051–2053, 2053t
prognosis 2055
prostate cancer 2049t, 2053t
sites of 2050t
testicular cancer 2049t
thyroid cancer 2053t
treatment 2055
metastatic calcification 731–732
hypervitaminosis D 732
milk-alkali syndrome 732
renal disease 731–732, 731f–732f
methacholine, and eccrine sweating 590t
methadone, and eccrine sweating 590t
methamphetamine
abuse, cutaneous signs 1514t
adverse reactions, pruritus 120t
p-methane-3,8-diol 1437t
methemoglobinemia, dapsone-induced 496
methicillin-resistant *Staphylococcus aureus see* MRSA
methimazole
adverse reactions
aplasia cutis congenita
cutaneous lymphoid hyperplasia 2039t
leukoderma 1044t
methocarbamol 1447
methopromazine-induced lichen planus 185t
methotrexate 2176–2178
adverse reactions 151t, 761t, 2169t, 2176–2177
erythroderma 176t
hyperpigmentation 349t, 1056t–1057t
mucositis 349t
nail changes 349t, 1141t
photosensitivity 341f
contraindications 2178
dosage 2176
indications 2170t, 2177–2178
atopic dermatitis 213t
Behçet's disease 428
bullous pemphigoid 484t
dermatomyositis 639t
lichen planus 196
lichen sclerosus 667t
morphea 667t
pemphigus vulgaris 472t
perforating disease 1604t
pityriasis lichenoides 162t
pityriasis rubra pilaris 165
psoriasis 150, 151t, 1137t
pyoderma granulosum 432t
SAPHO syndrome 437t
sarcoidosis 1563t
vasculitis 402t
interactions 2127t, 2178
mechanism of action 2176
monitoring 2167t–2168t
and nail growth 1090t
pregnancy and lactation 2178, 2178t
and PUVA 2229
methoxypsoralen
adverse reactions
hypertrichosis 1118t
pruritus 120t
methyclothiazide 342f
methycran-induced lichen planus 185t
methyl aminolevulinate 2242, 2242t
methyl-esterified 5-aminolevulinic acid 2241f
methylchloroisothiazolinone/methylisothiazolinone 242t
methyldibromoglutaronitrile phenoxyethanol 241t, 244
methyldopa-induced lichen planus 185t
methylenedioxymethamphetamine 1511
methylmalonic acidemia 526t–528t
methylprednisolone 245t, 2078
indications
bullous pemphigoid 483t
pemphigus vulgaris 472t
pyoderma granulosum 432t
pharmacology 2075
metolazone 342f
Metopium toxiferum see poisonwood tree
metoprolol 685t, 2190t
metronidazole 2116–2117
adverse reactions 2107t, 2116
contraindications 2116
dosage 2106t, 2116
formulations 2106t
indications 2106, 2116
acne vulgaris 2106, 2106t
amebiasis 1398
lichen planus 195–196, 195t
rosacea 567t, 2106, 2106t
interactions 2116
mechanism of action 2106t, 2116
pregnancy and lactation 2106t, 2155t
sites of action 2109t
trade names 2106t
Metzenbaum scissors 2361f
Mexoryl SX 2200f
Mexoryl XL 2200f
mianserin 2190t
MIB-1 29t–33t
Mibelli's angiokeratoma 1719–1720, 1919
micafungin
dosage 2122
indications 1283t, 2120t
aspergillosis 1283t
candidiasis 1283t
cryptococcosis 1283t
penicilliosis 1283t
zygomycosis 1283t
pregnancy and lactation 2120t
Michaelis-Gutmann bodies 1211
Michelin tire baby 1617t–1618t, 1983
miconazole
formulations 2118t
mucocutaneous candidiasis 1269t
pregnancy and lactation 2118t
trade names 2118t
microarrays 793
microbial eczema *see* nummular dermatitis
microcapillary hemangioma *see* microvenular hemangioma
Micrococcus spp., bromhidrosis 542
Micrococcus luteus 1187t
Micrococcus roseus 1187t
Micrococcus varians 1187t
microcomedones 548, 553
microcystic adnexal carcinoma 1790t, 1846, 1846f
Mohs surgery 2449, 2450f
microdermabrasion 2502–2503, 2503f, 2503t
microfibrils 455–456, 1589–1590, 1590f–1591f
beta2-microglobulin 700t
Micromonospora purpurea 2107
microneedles 2072, 2072f
microneurography 100
microphototherapy, vitiligo 1029
microphthalmia 1003t
micropigmentation 1029–1030
microRNA 1762
microsatellites 794f
microscopic polyangiitis 399–401
clinical features 400, 400f
diagnostic tests 400t–401t
differential diagnosis 400–401, 401t
epidemiology 400
pathogenesis 400
pathology 400
treatment 401
Microsporum spp., panniculitis 1658t
Microsporum amazonicum 1255t
Microsporum audouinii 1255t
ectothrix hair invasion 1262f
Microsporum canis 271t, 1255t
ectothrix hair invasion 1262f
tinea corporis 1256t
Microsporum cookei 1255t
Microsporum distortum, ectothrix hair invasion 1262f
Microsporum equinum 1255t
Microsporum ferrugineum 1255t
ectothrix hair invasion 1262f
Microsporum fulvum 1255t
Microsporum gallinae 1255t
Microsporum gypseum 1255t
ectothrix hair invasion 1262f
tinea corporis 1256t
Microsporum nanum 271t, 1255t
Microsporum persicolor 1255t
Microsporum praecox 1255t
Microsporum racemosum 1255t
Microsporum vanbreuseghemii 1255t
microthread-like fibers 456
microvascular occlusion syndromes 369–384, 371f
brown reculuse spider bite 383
cellular vascular occlusion disorders 382
intravascular lymphoma 382
stress reticulocyte adhesion/occlusion and sickling disorders 382
cryogelling/cryoagglutination disorders 373–374
cutaneous calciphylaxis 383
diagnosis 370t
embolic occlusion 375–377
cholesterol embolus 375–377
oxalate embolus 377
hematoma-associated retiform purpura 383
hydroxyurea-associated vascular occlusion 383
interferon-associated cutaneous necrosis 383
opportunistic organisms proliferating within vessels 375
platelet plugging disorders 369–373
differential diagnosis 370t
heparin necrosis 369–370
paroxysmal nocturnal hemoglobinuria 372–373
thrombocytosis secondary to myeloproliferative disorders 370–372
thrombotic thrombocytopenic purpura-hemolytic uremic syndrome 373
screening tests 372t
stress reticulocyte adhesion/occlusion disorders 382
systemic coagulopathies with cutaneous manifestations 377–380
antiphospholipid antibody/lupus anticoagulant syndrome 379–380
protein C and S disorders, congenital and acquired 377–379
vascular coagulopathies with cutaneous manifestations 380–382
livedoid vasculopathy 381–382
malignant atrophic papulosis 382
Sneddon syndrome 380–381
microvenular hemangioma 1920
mid-dermal elastolysis 1631–1632, 1632t
clinical features 1631, 1632f
differential diagnosis 1631–1632
epidemiology 1631
history 1631
pathogenesis 1631
pathology 1631, 1632f
treatment 1632
MIDAS syndrome 952, 1003t
genetics 807t
midazolam 2352
interactions 2190, 2192
with lidocaine 2529t
midline lesions 993–1000
head and neck 993–998, 994f
cephaloceles 996–997, 997f
cervical clefts 998
dermoid cysts 995–996, 996f
heterotopic brain tissue 998
nasal gliomas 997–998, 998f
nasal lesions 994–995, 994t
rudimentary meningoceles 997f, 998
scalp lesions 995, 995f–996f
sternal clefts and supraumbilical raphae 998, 999f
spine 998–1000, 999f
midline mucinosis *see* reticular erythematous mucinosis
Miescher's granuloma of face *see* annular elastolytic giant cell granuloma
Miescher's microgranulomas 1643
migraine, botulinum toxin in 2570
migratory circinate erythema 835t
Mikulicz disease *see* Sjögren's syndrome
milfoil 276–277
milia 1819–1820, 1819f
pathology 1820
treatment 1820
milia en plaque 1819–1820
milia-like calcinosis 733
miliaria 528–529, 591, 595–597, 596t
apocrine *see* Fox-Fordyce disease
clinical features 596, 596f
crystallina 524t–525t, 528, 529f, 596f, 596t
differential diagnosis 597
epidemiology 596
irritant/toxic causes 251t
pathology 596–597
profunda 528, 596t
rubra 524t–525t, 528, 596f, 596t
treatment 597
milk lines 1007f
milk thistle 2207t
milk-alkali syndrome 732
milker's nodules 271t, 1355t–1356t
millipedes 1449
Milroy disease 1722–1723
molecular genetics 1713t
miltefosine
adverse reactions 1397t
leishmaniasis 1397t
MimyX cream 2156
mind-body medicine 2216, 2216t
mineral deficiencies 745–750
copper 748–750
selenium 750
zinc 746–748
mineral oil, and NMSC 1775t
minocycline
adverse reactions 338t
erythroderma 176t
hyperpigmentation 1056t–1057t, 1058f
nail changes 1141t
pruritus 120t
pseudo-Hutchinson's sign
dosage 2114t
indications
acne vulgaris 556t
folliculitis 574
leprosy 1228t
MRSA 1191t
pyoderma granulosum 432t
rosacea 567t
sarcoidosis 1563t
interactions, secondary cutaneous vasculitis 390t
minoxidil 1097, 2159, 2536
adverse reactions 2155t, 2159
hair discoloration 1498t
hypertrichosis 1118t
mirtazapine, in pruritus 106t, 114
misclassification bias 2062
misoprostol-induced aplasia cutis congenita

Missouri Lyme disease 1442–1443
mites 1444–1445, 1445f, 1445t
MITF-1 29t–33t
mitochondrial disorders
  hyperpigmentation 1116t
mitochondrial inheritance 790
mitogen-activated protein kinase *see* MAPK
mitomycin C
  adverse reactions
    erythroderma 176t
    extravasation reactions 349t
    photosensitivity 349t
mitosis 784t
Mitsuda test 1227
mitten deformity of hands 506, 508f
mixed connective tissue disease 679–680
  autoantibodies 604–605
  clinical features 679–680
  differential diagnosis 680
  epidemiology 679
  history 679
  pathogenesis 679
  pathology 680
  treatment 680
mixed cryoglobulinemia 359t, 398
  ANCA in 613t
mixed porphyria *see* variegate porphyria
mixed tumor (chondroid syringoma) 1831–1834, 1833f–1834f
mizolastine 303, 304t
MJ33 2067
MK-2206 1887t
Mobiluncus curtisii 1367t
Mobiluncus mulleris 1367t
moclobemide 2190t
modafinil 2190t
Mohs, Frederic E 2445
Mohs surgery 2445–2457
  antibiotic prophylaxis 2451
  blood thinners 2451
  complications 2455
  contraindications 2450–2451
  cost-effectiveness 2445
  cure rates 2447t
  future trends 2455
  histologic challenges 2456f
  history 2445–2446
  indications 2445–2450, 2446f, 2446t
    atypical fibroxanthoma 2449
    basal cell carcinoma 2446–2447, 2447f–2448f, 2447t, 2450f
    dermatofibrosarcoma protuberans 2449
    erythroplasia of Queyrat 2448
    keratoacanthoma 2448
    lentigo maligna 2449
    melanoma 1905, 2449
    Merkel cell carcinoma 2449
    microcystic adnexal carcinoma 2449, 2450f
    NMSC 1790–1791
    sebaceous carcinoma 2449–2450
    squamous cell carcinoma 2447–2448, 2454f
    verrucous carcinoma 2449
  pathologic examination of skin margins 2446f
  postoperative care 2455
  potential pitfalls 2455, 2455t
  preoperative history 2451
  stains used in 2449t
  technique 2451, 2452t, 2453f–2454f
  training 2446
  variations/unusual situations 2451–2453
moisturizers 2481, 2481t
mokihana 280t
mole *see* common acquired melanocytic nevus
molecular biology 65–79
  experimental techniques 65–78
    bedside 65–66
    DNA/RNA profiling and protein expression 66f–67f, 66t–69t, 67–70, 69f
    genes responsible for melanoma 70–71, 70t, 71f
    tissue processing 65f, 66–67
    molecular targeting of RNA 77–78, 78f
    skin gene therapy
      for cancer 72–75, 76t–77t, 77f
      targeting keratinocyte stem cells 75–77
    transgenic animal models 71–72, 74f–76f, 74t–75t
molecular mimicry 677
molindone, and eccrine sweating 590t
Moll's gland cyst *see* hidrocystoma
Mollusca 1452
molluscum contagiosum 211, 1367t
  and anetoderma 1633t
  in athletes 1507t
  clinical features 1358f–1359f
  HIV-related 1290f
  treatment 1359t
    imiquimod 2135
molluscum pendulum 935t, 936
mometasone furoate 245t, 2079t
Mondor's syndrome of superficial thrombophlebitis 367
Mongolian spot *see* dermal melanocytosis
monilethrix 827, 1110–1111, 1110f–1111f
  autosomal recessive 802f
  clinical features 1095f
  genetics 832t–833t
monkeypox 1355t–1356t
monoamine oxidase inhibitors, and eccrine sweating 590t
monobactams 2105t
  mechanism of action
  sites of action 2109t
monobenzyl ether of hydroquinone 2158
monoclonal antibodies, adverse reactions 338t
monoclonal gammopathy
  conditions associated with 2014t
  and myeloma 2014t
  scleroderma 644t
monocytes, in atopic dermatitis 206t
monocytotrophic ehrlichiosis 1244t, 1246t
monospot test 1336
Monsel's solution 2464t
montelukast
  renal puritus 118t
  urticaria 304, 304t
Montgomery tubercles 542
moon-boot foot syndrome *see* plantar dermatosis, juvenile
Moraceae 277t, 280
Moraxella spp. 375, 1450t
Moraxella catarrhalis 2113
Morbihan's disease 549, 566, 568f
morbilliform eruption 1120, 2113, 2117t
  drug-induced 1518t
  hyperpigmentation 6t–7t, 1050t
Morganella morganii 375
Morgellons disease 128
moriform stomatitis 1278
morphea 657–670
  autoantibodies 610t, 613, 657
  clinical features 644t, 659–662, 659f
    atrophoderma of Pasini and Pierini 660, 1636–1637
    bullous morphea 660–661
    deep morphea 660, 660f
    en coup de sabre 661, 661f
    generalized/disabling morphea 661
    guttate morphea 660
    hyperpigmentation 659–660, 660f, 1050t
    linear morphea 660f–662f, 661
    morphea of childhood 661–662
    nodular or keloid morphea 657, 660f
    Parry-Romberg syndrome 660f, 661
  differential diagnosis 650t, 663, 663t
  epidemiology 657
  histology 662f
  history 657
  laboratory findings 662
  pathogenesis 657–659, 658f
    animal models and genetics 658f, 659
    control of fibroblast function 657
    triggering events 657
    vascular changes 658
  pathology 662–663, 662f
  and pseudocellulitis
  radiation-induced 663
  treatment 666–669, 667t
    calcineurin inhibitors 668
    corticosteroids 668, 668f
    cytokines 669
    hormones 669
    immunosuppression 669
    penicillin 669
    phototherapy 666–668, 667f–668f
    physical therapy 669
    vitamin derivatives 668–669
  see also scleroderma
morphea plana atrophica *see* idiopathic atrophoderma of Pasini and Pierini
morphea/scleroderma panniculitis 1645–1646, 1646t
  clinical features 1645–1646
  differential diagnosis 1646
  pathology 1645–1646, 1646f
morpheaform plaques 659f
morpheaform/sclerodermoid inflammatory syndromes 663
  graft-versus-host disease 661, 758
  lipodermatosclerosis 663
  porphyrias 661
  radiation-induced morphea 663
  silicone/paraffin implants 663
  vitamin K injections (Texier's disease) 663
morphine-induced pruritus 120t
morphology 1–2, 3t–5t
  atrophy 4t–5t
  bullae 3t–4t
  crusts 2, 4t–5t
  erosions 4t–5t
  excoriations 4t–5t
  fissures 4t–5t
  lichenification 4t–5t
  macules 3t–4t
  nodules 3t–4t
  palpation 2
  papules 2, 3t–4t
  patches 3t–4t
  plaques 3t–4t
  pustules 3t–4t
  scales 2, 4t–5t
  ulceration 4t–5t
  vesicles 1–2, 2f, 3t–4t
  see also individual lesions
Morquio syndrome 715t
Morrison, Reg 45
morsicatio buccarum 1155, 1155f
Morus spp. *see* mulberry
mosaic epidermolytic ichthyosis 845
mosaic warts 1308f
mosaicism 788–789, 814–815, 932t–933t, 943–962
  autosomal dominant conditions 947f, 952–955
    acantholytic dyskeratotic epidermal nevus 954
    acneiform nevus 954
    epidermolytic verrucous epidermal nevus 953, 953f
    linear angiofibroma 955
    linear basal cell carcinoma 955
    linear Darier disease 954, 955f
    linear Hailey-Hailey disease 954
    linear porokeratosis 955
    nevoid telangiectasia 955
    non-epidermolytic verrucous epidermal nevus 953–954, 954f
    PTEN mosaicism 953t, 954
    relapsing linear acantholytic dermatosis 954
    segmental neurofibromatosis type 1 925, 929, 929f, 932t–933t, 955
    unilateral palmoplantar verrucous epidermal nevus 953
    venous/glomuvenous malformations 955
    zosteriform speckled lentiginous nevus 955
  Blaschko's lines 943, 943f–944f, 946t–947t
  causes of 945t
  chimerism 945t, 960
  chromosomal 959–960
    hypomelanosis of Ito 959–960
    linear and whorled nevoid hypermelanosis 960
    nevus depigmentosus 960
  classification 945t–946t
  gonadal (germline) 789
  lethal disorders rescued by 956–959
    encephalocraniocutaneous lipomatosis 959
    epidermal nevus syndrome 957–958
    ILVEN syndrome 959
    McCune-Albright syndrome 959
    non-epidermolytic verrucous epidermal nevus 957, 957f
    oculocerebrocutaneous syndrome 959
    porokeratotic eccrine ostial and dermal duct nevus 958
    Proteus syndrome 958–959
  linear inflammatory disorders 955–956
    Blaschkitis 956
    lichen striatus 196, 956
    linear lichen planus 191–192, 192f, 956, 956f
    linear psoriasis 956, 956f
    segmental vitiligo 956, 1027f
  patterns of 946t–947t
  pigmentary 1037–1038
  revertant 789, 816–817, 947, 947f
  X-linked conditions 945t–946t, 947–952
    CHILD syndrome 952
    Conradi-Hünermann-Happle syndrome 952
    ectodermal dysplasia, hypohidrotic, with immunodeficiency 951
    Goltz syndrome 951
    hypohidrotic ectodermal dysplasia 952
    incontinentia pigmenti 949–951
    Menkes disease 952
    MIDAS syndrome 952
    oral-facial-digital syndrome 952
    X-linked reticulate pigmentary disorder 952
motretinide 2097t
moulin atrophoderma linearis 948f
mountain tobacco 285t
mouth frown, botulinum toxin 2566t, 2567–2568, 2567f
moxibustion 2214
moxifloxacin
  leprosy 1228
  tuberculosis 1234t
MRI burns 1491, 1491f
  risk factors 1491t
MRSA 1190–1191
  community-acquired 1191t
Mucha-Habermann disease *see* pityriasis lichenoides
mucicarmine stain 27t–28t
mucin 687
  deposition 637
  pools 1788
mucinoses 687–698, 709t
  altered thyroid function 693–695
    generalized myxedema 694–695, 694f
    localized (pretibial) myxedema 693–694, 694f
  classification 687, 688t
  cutaneous focal 696
    vs (angio)myxoma 696
  HIV-related 1296
  papulonodular 695–696, 695f
  primary degenerative-inflammatory 687–697, 689f
    lichen myxedematosus, localized variants 691–692, 691f
    scleredema 692–693, 693f
    scleromyxedema 687–691, 688t, 689f–690f
    self-healing cutaneous 692
  primary follicular 696–697

follicular mucinosis 696, 697f
urticaria-like follicular mucinosis 696–697
primary hamartomatous-neoplastic 697
(angio)myxoma 697
mucinous nevus 697
reticular erythematous 695, 695f
secondary 688t
mucinous carcinoma 1790t
mucinous nevus 697
Muckle-Wells syndrome 295–296, 298–300, 707
genetics 818t–819t
mucocele 1826, 1826f
salivary gland 1163–1164, 1164f
mucocutaneous candidiasis, chronic 900t, 902–904
chronic localized candidiasis 903t
clinical features 902, 902f, 904f
differential diagnosis 904
epidemiology 902
familial 903t
familial chronic nail candidiasis 903t
with keratitis 903t
late-onset 903t
pathogenesis 902
pathology 903–904
subgroups 903t
treatment 904, 1269t
mucolipidosage, eccrine gland changes 598t
mucopolysaccharidoses 709t, 714, 715t
clinical features and pathology 714–716
hypertrichosis 1117t
eccrine gland changes 598t
treatment 716
see also individual conditions
Mucor 375
mucormycosis 375, 2120t
mucosal melanoma 1896
mucosal melanotic lesions *see* lentigo simplex
mucosal ulceration, drug-induced 350
mucositis, chemotherapy/radiotherapy-induced 349t, 1166–1167
mucosulfatidosis *see* multiple sulfatase deficiency
mucous cyst of oral mucosa *see* mucocele
mucous membrane lesions in drug abuse 1516–1517
mucous membrane pemphigoid *see* cicatricial pemphigoid
Muehrcke's nails 1139, 1141t
mugwort 285t
Muir-Torre syndrome 1462t, 1840
and gastric hemorrhage 773t–774t
genetics 816t
Mukamel syndrome 932t–933t
mulberry 277t
mulberry molars 1377t
mullein 277t
müllerian cyst, cutaneous *see* ciliated cyst of vulva
multicentric reticulohistiocytosis 776t–778t, 1530t–1531t
antigenic markers 1533t
paraneoplastic 764t–765t, 766f
multidimensional protein identification 70–71
multifocal lymphangioendotheliomatosis with thrombocytopenia 1927–1928
clinical features 1928
differential diagnosis 1928
epidemiology 1928
history 1927
pathogenesis 1928
pathology 1928, 1928f
treatment 1928
multinucleate cell angiohistocytoma 1966, 1967f
multiple endocrine neoplasia 776t–778t
genetics 816t
type 1 (Wermer syndrome) 932t–933t
type 2A (Sipple syndrome) 707, 776t–778t
type 2B/3 1151–1152
clinical features 932t–933t
multiple familial trichoepitheliomas 813t
multiple hamartoma syndrome *see* Cowden disease
multiple keratoacanthomas 114–115
differential diagnosis 1604t
gastrointestinal hemorrhage 773t–774t
multiple mucosal neuroma syndrome *see* multiple endocrine neoplasia, typeB
multiple myeloma 2013–2014, 2014t
eccrine gland changes 598t
multiple neurofibromatosis *see* neurofibroma
multiple pterygium syndrome 807t
multiple sulfatase deficiency 803t–804t, 852t–854t
multiple sweat gland abscesses 599
MUM1 29t–33t
mumps, and nail growth 1090t
Münchhausen syndrome by proxy 130–131
Munro's microabscesses 221
mupirocin 2107
dosage 2108t
formulations 2108t
indications
folliculitis 1190
impetigo 1189t
mechanism of action 2108t
pregnancy and lactation 2108t, 2155t
trade names 2108t
murine (endemic) typhus 1244t, 1246t
muromonab 2149t
Murray-Puretic Drescher syndrome *see* hyaline fibromatosis, juvenile
Musa spp. *see* banana
muscle pump 1729–1730, 2510
muscular dystrophy 1596
mushroom worker's disease *see* flagellate mushroom dermatitis
musical-instrument-related dermatoses 1508–1509, 1509t
differential diagnosis 1508
epidemiology 1508
history 1508
pathogenesis and clinical features 1508
pathology 1508
treatment 1508–1509
Mustarde flap *see* rotation flaps
mutations 794–795, 794f, 1462–1463, 1462t, 1463f
de novo 788
structural and desmosomal proteins 832t–833t
mutator phenotype 1759
mutilating palmoplantar keratoderma with periorificial plaques see Olmsted syndrome
see also Vohwinkel syndrome
MUTYH-associated polyposis 816t
myasthenia gravis, and dermatitis herpetiformis 493t
myc 1761t
mycetoma 1270–1272, 1271t
clinical features 1271, 1271f
differential diagnosis 1271
history and epidemiology 1271
pathogenesis 1271
pathology 1271
treatment 1272
mycobacterial infections 1221–1242, 1221t
HIV-related 1291
leprosy 46–47, 1221–1228, 1600t
non-tuberculous mycobacterioses 1235–1241
Mycobacterium abscessus 1239–1240
Mycobacterium avium 1240
Mycobacterium chelonae 1239–1240
Mycobacterium fortuitum 1239–1240
Mycobacterium haemophilum 1240–1241
Mycobacterium kansasii 1238–1239
Mycobacterium marinum 1237–1238
Mycobacterium scrofulaceum 1241
Mycobacterium ulcerans 1235–1237
tuberculosis 1228–1235
Mycobacterium spp., panniculitis 1658t
Mycobacterium abscessus 1239–1240
clinical features 1239
diagnosis 1239–1240
epidemiology and pathogenesis 1239
history 1239
pathology 1239
treatment 1237t, 1240
Mycobacterium avium 1237t, 1240, 1240f
AIDS-related 1288t
Mycobacterium chelonae 1239–1240
clinical features 1239, 1239f
diagnosis 1239–1240
epidemiology and pathogenesis 1239
history 1239
pathology 1239
treatment 1237t, 1240
Mycobacterium fortuitum 1239–1240
clinical features 1239, 1239f
diagnosis 1239–1240
epidemiology and pathogenesis 1239
history 1239
pathology 1239
treatment 1237t, 1240
Mycobacterium genavense 1221t
Mycobacterium goodii 1221t
Mycobacterium gordonae 1221t
Mycobacterium haemophilum 1221t, 1237t, 1240–1241
Mycobacterium immunogenum 1221t
Mycobacterium intracellulare 1221t
Mycobacterium kansasii 1238–1239
clinical features 1238
diagnosis 1239
differential diagnosis
epidemiology and pathogenesis 1238
history 1238
pathology 1238
treatment 1237t, 1239
Mycobacterium leprae 1221
secondary cutaneous vasculitis 390t
see also leprosy
Mycobacterium malmoense 1221t
Mycobacterium marinum 271t, 1237–1238, 1451
in athletes 1507t
clinical features 1237, 1238f
diagnosis 1238
epidemiology and pathogenesis 1237
history 1237
pathology 1238
treatment 1237t, 1238
Mycobacterium scrofulaceum 1237t, 1241
Mycobacterium simiae 1221t
Mycobacterium smegmatis 1221t
Mycobacterium szulgai 1221t
Mycobacterium terrae 1221t
Mycobacterium tuberculosis 21, 1228
AIDS-related 1288t
chronic granulomatous disease 910t
and erythema multiforme 320t
secondary cutaneous vasculitis 390t
see also tuberculosis
Mycobacterium ulcerans 1235–1237
clinical features 1236–1237
diagnosis 1237
epidemiology 1236
history 1235–1236
pathogenesis 1236
pathology 1237
treatment 1228–1235, 1237
Mycobacterium wolinskyi 1221t
Mycobacterium xenopi 1221t
myconecrosis (gas gangrene) 1200, 1201t
mycophenolate mofetil 2178–2179
adverse reactions 2178, 2185t
hypertrichosis 1118t
contraindications 2179
dosage 2178
indications 2170t, 2178–2179
atopic dermatitis 213t
Behçet's disease 428
bullous pemphigoid 475
chronic actinic dermatitis 1475
dermatomyositis 639t
lichen planus 195t, 196
linear IgA bullous dermatosis 499
lupus erythematosus 628t
pemphigus vulgaris 472, 472t
psoriasis 153t
pyoderma granulosum 432t
sarcoidosis 1563t
vasculitis 402t
interactions 2179
mechanism of action 2178, 2178f
metabolism 2185f
monitoring 2167t–2168t
pregnancy and lactation 2179
Mycoplasma genitalium 1367t
Mycoplasma hominis 1367t
Mycoplasma pneumoniae
and erythema multiforme 319, 320t
and erythema nodosum 1644t
secondary cutaneous vasculitis 390t
mycoses
subcutaneous 1266–1273
chromoblastomycosis 1267–1273
lobomycosis 1273
mycetoma 1270–1272
sporotrichosis 1272–1273
superficial 1251–1266, 1251t, 1252f
dermatophytoses 1255–1266, 1255t
non-inflammatory 1251–1266
systemic 1273–1284, 1275f
opportunistic pathogens 1279–1284
true pathogens 1273–1279
mycosis fungoides 1, 2f, 184t, 1600t, 2019–2025
clinical features 2021, 2022f–2023f
definition 2019–2025
differential diagnosis 225, 308t–310t, 414t, 2020t, 2022–2023
environmental factors 2019
epidemiology 2019
folliculotropic 2025–2026
genetic factors 2019
hypopigmented 1039–1040, 1041f
immunologic factors 2019–2021
immunophenotype 2022
paraneoplastic 764t–765t
patch stage *see* parapsoriasis
pathogenesis 2019–2021
pathology 2021, 2022f–2023f
prognosis 2025
pyramid 158f
staging 2023, 2024t
TNMB classification 2024t
treatment 2023–2025, 2024t
chemotherapy 2023
corticosteroids 2023
enileukin difitox 2025
histone deacetylase inhibitors 2025
interferons 2024
photodynamic therapy 2245–2246
phototherapy 2024
PUVA 2229–2230, 2230f
UVB 2221–2222
radiotherapy 2023, 2298
retinoids 2024–2025
unilesional *see* pagetoid reticulosis
mycotic sycosis 572f, 579f
MyD88 81, 82f
myeloid dendritic cells in atopic dermatitis 206t
myeloperoxidase 29t–33t
myeloperoxidase deficiency 912t
myeloperoxidase stain 27t–28t
myiasis 1432–1433
clinical features 1433, 1433f
differential diagnosis 1433
epidemiology 1432
history 1432
pathogenesis 1432–1433
pathology 1433
preventative measures 1433
treatment 1433
Myobloc *see* botulinum toxin
myocardial rhabdomyoma 935t

myofibroblasts 1623t
myofibromatosis, infantile 1703–1704
myopathy, glucocorticoid-induced 2082–2083, 2083t
myrmecial warts 1308f
Myroxylon pereirae see balsam of Peru
Myrrha 2214
Myrtaceae 285t, 288
myxedema
  atypical tuberous 696
  and cutis verticis gyrata 1626t
  electrolytes in sweat 597t
  generalized 694–695, 694f
    clinical features 694
    definition 694
    diagnosis 688
    differential diagnosis 688
    pathogenesis 694
    pathology 688
    treatment 688
  localized (pretibial) 693–694, 694f
    clinical features 693
    definition 693
    differential diagnosis 694
    epidemiology and pathogenesis 693
    pathology 694
    treatment 694
  and lymphedema 1738f
  and palmoplantar keratoderma 883
myxedema coma 694–695
myxoid cyst 1144, 1145f
  cryosurgery 2286
  cutaneous *see* digital mucous cyst
myxoid lipoblastoma, mucin deposition 688t
myxosarcoma, mucin deposition 688t

N-ras 1761
N-Terface 2373, 2378
nabumetone
  adverse reactions
    phototoxicity 1480t
    pseudoporphyria 724t
nadroparin 364t
Naegeli-Franceschetti-Jadassohn syndrome 810t, 835t, 1065t, 1068–1069
  clinical features 1068
  differential diagnosis 1068–1069
  epidemiology 1068
  genetics 810t, 832t–833t
  history 1068
  pathogenesis 1068
  pathology 1068
  treatment 1069
naftifine
  formulations 2118t
  pregnancy and lactation 2118t, 2155t
  trade names 2118t
Nagayama's spots 1339
Nager acrofacial dysostosis 1006
nails
  anatomy 1085–1087, 1086f, 1129, 1129f
  biology 1085–1090
  blood supply 1086–1087
  development of 60, 1075f
  dystrophy 2441f
    sports-related 1506t
  embryology 1087, 1087f
  erythroderma 176f
  erythronychia 887, 893
  functional properties 1081t
  growth rate 1089t, 1090
    factors affecting 1090t
  half-and-half 1140
  in HIV 1295, 1295f
  hyponychium 1089t, 2435
  immunology 1089
  keratins in 1089, 1089f
  lunula 1086
  Muehrcke's 1139, 1141t
  non-keratin proteins in 1089f
  onychocorneal band 1086
  onychodermal band 1086
  onychodystrophy 1291, 1307
  periungual warts 1139t, 1141–1142, 1307f
    cryosurgery 2286
  pigmentation 1089t
  pincer 1130f, 1143–1144, 1146f
  Terry's 1139
  thickness 1089t
  see also nail disorders
nail avulsion 2437–2438, 2437f–2438f
nail bed 1089t
nail bed disorders 1132, 2440t
  apparent leukonychia 1132, 1145f
  melanoma 1146–1147, 1147t, 1895f, 2440t
  onychauxis 1130f, 1132
  onycholysis *see* onycholysis
  periungual fibroma 937f, 938
  splinter hemorrhages 1130f, 1132
nail care products 2483, 2487–2488
  nail polish 2487, 2487f
  nail sculptures 2487–2488, 2488f, 2488t
nail clippers 2437f
nail clubbing 809t, 1130f
  in sarcoidosis 1560
  systemic conditions associated with 1139, 1139t
nail disorders 1129–1147, 1129t, 1130f
  abnormal nail matrix function 1129–1134
    Beau's lines 1090, 1130
    koilonychia 1130f, 1132
    leukonychia 1130f, 1131–1132
    onychomadesis 1130–1131, 1130f–1131f
    onychorrhexis 1130f, 1131
    pitting 1130–1131
    trachyonychia 1130f–1131f, 1131, 1138
  brittle nails 1130f, 1141t, 1142
  congenital and hereditary 1104t, 1134–1136
    Darier disease 890f, 1130f, 1136, 1136f
    ectodermal dysplasias 1135
    epidermolysis bullosa 502f, 1135
    hypertrophy of lateral fold of hallux 1135
    malalignment of big toenails 1134–1135, 1135f
    nail-patella syndrome 1135, 1135f
    pachyonychia congenita 881f, 1130f, 1136
    racquet thumbs (brachyonychia) 1130f, 1135
  dermatologic diseases 1136–1138
    acrodermatitis continua of Hallopeau 1136–1137, 1137f, 1137t
    alopecia areata 1100, 1101f, 1130f, 1138
    eczema 1138
    familial chronic candidiasis 903t
    Hailey-Hailey disease 894
    lichen planus 192, 192f, 1130f, 1137–1138, 1138f, 1138t
    parakeratosis pustulosa 1137
    pityriasis rubra pilaris 163
    psoriasis 144, 145f, 1130f–1131f, 1136, 1136f, 1137t
  drug-induced 349t, 351f
  environmental 1142
  infections 1141–1142
    tinea unguium 1261–1262, 1264f
  manicure/pedicure-induced 1143t
  pigment deposition 349t, 1132–1134
    green nail syndrome 1134, 1206, 1206f
    Hutchinson's sign 1133–1134, 2442
    longitudinal melanonychia 8, 1132–1133, 1134f, 1134t, 2442f
  pterygium 1130f
  systemic disease 1138–1141
    apparent leukonychia 1130f, 1139–1140
    autoimmune connective tissue disorders 1140
    clubbing 1130f, 1139, 1139t
    drug-induced 1140–1141, 1141f, 1141t
    HIV infection 1140
    peripheral neuropathies 1140
    pseudoinflammatory nail changes 1140
    yellow nail syndrome 1130f, 1139, 1139f
  traumatic nail abnormalities 1142–1144, 1143t
    ingrown toenails 1144, 2443–2444, 2443f–2444f
    onychogryphosis 1130f, 1143
    onychotillomania 1142–1143
    pincer nails 1130f, 1143–1144
    subungual hematoma 1143
    toenails 1143
nail folds 633f, 1086–1087, 1089t, 2439
nail keratins 1574t
nail matrix 1086–1088, 1089t, 1129, 2436f
  anatomy 1087–1088
  biopsy 1087f, 2439–2440
  exploration 2438, 2439f
  function 1088
  melanocytes in 1088–1089
  melanocytic nevus 1145–1146
nail plate 1086, 1089t, 1129
  in forensic medicine 1138–1139
  origins of 1088f
  thickness 1080f
Nail Psoriasis Severity Index 139–140
nail splitters 2362
nail surgery 2435–2444, 2436t
  complications 2444, 2444t
  dressings and postoperative care 2441
  excisions and biopsies 2438–2441
    biopsy/surgery of nail bed 2439, 2439f, 2440t
    lateral longitudinal nail biopsy and excision 2441, 2441f
    nail matrix biopsy 2439–2440, 2441f
    proximal nail fold surgery 2439
  ingrown toenails 2443–2444, 2443f–2444f
  instruments 2437, 2437f
  nail avulsion and nail matrix exploration 2437–2438, 2437f–2439f
  nail tumors 2441, 2442t
    melanoma 2442–2443, 2442f
    squamous cell carcinoma 2443
  nail unit
    sensory nerves and anesthesia 2435–2436
    surgical anatomy 2435–2436, 2436f
    vascular supply 2436, 2437f
  patient preparation 2436–2437
  preoperative evaluation 2436–2437, 2437t
nail tumors 1144–1147, 2440t
  benign 1144–1146
    enchondroma 2440t
    epidermoid cyst 2440t
    fibromas/fibrokeratomas 937f, 1144, 2440t
    glomus tumor 928–929, 1145, 2440t
    melanocytic nevi of nail matrix 1145–1146
    myxoid cysts 1144, 1145f
    onychomatricoma 1145, 1145f
    osteochondroma 2440t
    pyogenic granuloma 1144, 2440t
    subungual exostosis 1144, 1145f, 2440t
  malignant 1146–1147
    Bowen's disease *see* Bowen's disease
    keratoacanthoma 1146, 2440t
    melanoma 1146–1147, 1147t, 2442–2443, 2442f
    squamous cell carcinoma 1146, 2443
    verrucous carcinoma 1146, 2440t
nail-patella syndrome 1087, 1135, 1135f
  cleft lip/palate 1005t
  renal disease 780t–781t
nailfold telangiectasias 633f
Nairobi eye 1439
nalfurafine
  pruritus 106t
    renal 118t
nalidixic acid
  adverse reactions
    phototoxicity
    pseudoporphyria 724t
nalmefene, cholestatic pruritus 119t
naloxone 101–103
  pruritus 106t, 119t
naltrexone
  pruritus 106t, 114
    cholestatic 119t
    renal 118t
NAME syndrome 377, 1857t
  genetics 818t–819t
naproxen
  adverse reactions
    alopecia 348t
    fixed drug eruption 346f
    lichen planus 185t
    linear IgA bullous dermatosis 498t
    phototoxicity 1480t
    pseudoporphyria 724t
Narcissus pseudonarcissus see daffodils
Narins, Rhoda 2525
Naropin *see* ropivacaine
nasal chondritis 676
nasal deformity 676t
nasal flare, botulinum toxin 2566t
nasal glioma 997–998, 998f
  cleft lip/palate 1005t
nasal lesions 994–995, 994t
nasal tip
  droop, botulinum toxin 2566t
  hypertrichosis 1118t
nasal verrucae in drug abuse 1514t, 1516–1517
nasolabial folds, botulinum toxin 2565–2566, 2566t
nasolabial transposition flap 2412, 2413f
natalizumab 2149t
natural killer cells 83–84, 92
natural killer cell lymphoma 1212t
natural moisturizing factors 2066
Naxos disease 776t–778t, 873t, 879
  genetics 803t–804t, 832t–833t
nBPAG1 *see* dystonin
Necator americanus 1407t–1408t
neck
  anatomy 2329f
  anterior folds 209t
  white fibrous papulosis 1614t
  see also head and neck
necklace of Venus 1072t–1073t
necrobiosis lipoidica 1566–1568, 1600t
  atypical of face and scalp *see* annular elastolytic giant cell granuloma
  clinical features 1558t, 1566–1567, 1567f
  differential diagnosis 1568
  endocrine 768t, 769f
  epidemiology 1566
  history 1566
  pathogenesis 1566
  pathology 1562t, 1567, 1567f
  treatment 1568
necrobiosis lipoidica diabeticorum *see* necrobiosis lipoidica
necrobiotic xanthogranuloma 1539–1541
  antigenic markers 1533t
  clinical features 1530t–1531t, 1540, 1540f
  differential diagnosis 1541
  epidemiology 1540
  history 1540
  monoclonal gammopathy 2014t
  paraneoplastic 764t–765t
  pathogenesis 1540
  pathology 1540–1541, 1540f
  treatment 1541
necrolytic acral erythema 772f
necrolytic migratory erythema 308t–310t

necrosis 1762
  intraoperative 2465–2466
  postoperative 2469, 2469f
necrotizing fasciitis 9–11
  clinical features 1199, 1199f
  diagnosis 1199–1200, 1200f
  and drug abuse 1515t, 1516f
  epidemiology and pathogenesis 1199
  pathology 1199
  treatment 1200
    immune globulin 2148t
necrotizing sialometaplasia 1164
necrotizing ulcerative gingivitis 1152
needle holders 2360, 2360f
  Castroviejo 2362
needles 2357–2358
  anatomy 2358f
  nomenclature 2358f
  shapes 2359f
neem 2207t
nefazodone 2187t, 2189t
negative selection 88
Neisseria gonorrhoeae 1367t
  biology 1380
  see also gonorrhea
Neisseria meningitidis 1204–1206
Neisseria meningococcus, secondary cutaneous vasculitis 390t
Neisseria weaveri 1450t
Nékam's disease 201
nelfinavir 2191t
  adverse reactions 1299t
nematode anticoagulant peptide 364t
NEMO mutations 801, 949t, 950f
Neo Heliopan MBC 2199
neodymium YAG lasers 2251, 2262
  hair removal 2256
  long-pulsed 2255t
  pigmented lesions/tattoos 2256, 2269t–2270t
  Q-switched 2255t
  Q-switched frequency-doubled 2255t
  skin penetration 2254f
  skin resurfacing 2273t
  vascular lesions 2255, 2265t
neomycin 2107
  adverse reactions 2155t
    hypersensitivity 241t, 244, 2463
    systemic contact dermatitis 246t
  dosage 2108t
  formulations 2108t
  mechanism of action 2108t
  pregnancy and lactation 2108t
  trade names 2108t
neomycin sulfate *see* neomycin
neonate/neonatal
  acne (cephalic pustulosis) 550
  acrodermatitis enteropathica 526t–528t
  ankyloblepharon-ectodermal dysplasia-clefting syndrome 526t–528t
  bullous impetigo 529f
  developmental anomalies *see* developmental anomalies
  erythroderma 173t–174t, 180f
  Goltz syndrome 951
  hemangiomatosis 1701f
  human herpesviruses
    herpes simplex virus 524t–528t, 534f, 1323t, 1327f
    varicella-zoster virus 524t–528t
  hypernatremic dehydration 841t–842t
  ichthyoses 526t–528t, 847t
  lupus erythematosus 622, 623f, 776t–778t
  panniculitis 1650–1653, 1651t
  purpura fulminans 378
  skin features 58t
  subcutaneous fat necrosis 1651–1652, 1651t
  topical medications 2154–2155, 2155t
  toxic shock-like exanthematous disease
  vesiculobullous and erosive diseases 523–537
    acropustulosis of infancy 531–533, 531f
    aplasia cutis congenita 531f, 1000–1003, 1001t
    Behçet's disease 534
    bullous congenital ichthyosiform erythroderma 535f
    candidiasis 530
    cephalic pustulosis 524t–525t, 529–530, 530f
    congenital erosive and vesicular dermatosis 534–535, 535f
    congenital Langerhans cell histiocytosis 532–533, 532f
    differential diagnosis 524t–528t
    eosinophilic pustular folliculitis of infancy 531–532, 532f
    erythema toxicum neonatorum 523, 528f–529f
    exogenous causes 531
    herpes simplex 534f
    hyperimmunoglobulin E syndrome 533
    incontinentia pigmenti 533, 533f, 949–951
    intrauterine epidermal necrosis 534
    mastocytosis 536f, 1993
    miliaria 528–529, 529f
    noma neonatorum 536
    pemphigoid gestationis 536f
    perinatal gangrene of buttock 536
    pyoderma gangrenosum 535
    restrictive dermopathy 536
    staphylococcal scalded skin syndrome 535f
    sucking blisters 530
    transient neonatal pustular melanosis 523–524, 529f, 1050t
    vesiculopustular eruption and leukemoid reaction in Down syndrome 534
  see also infants
neoplasms *see* tumors
neoplastic cutaneous disorders 1
Neosalus foam 2156
neostigmine, and eccrine sweating 590t
Neotrombicula autumnalis 1445t
nephrogenic fibrosing dermopathy *see* nephrogenic systemic fibrosis
nephrogenic systemic fibrosis 652–654, 663
  clinical features 644t, 652f–653f, 653, 781f
  diagnostic criteria 652t
  differential diagnosis 650t
  histology 653f
NERDS syndrome 418
nerve block 2348–2351
  digital 2350
  facial 2349–2350, 2349f–2350f
  foot 2351, 2351f
  hand 2350–2351, 2350f
  penile 2350
nerve deficits 2466–2467, 2466f–2467f
nerve fibers
  A-β 100t
  A-δ 100t
  C 100t
nerve growth factor 101t
nerve sheath myxoma 1951–1952
  clinical features 1951, 1951f
  differential diagnosis 1952
  epidemiology 1951
  history 1951
  pathogenesis 1951
  pathology 1951–1952, 1951f–1952f
  treatment 1952
nerves, in urticaria 293
Nesacaine *see* chloroprocaine hydrochloride
nestin 828t
Netherton syndrome 838t, 857–859
  clinical features 857–858, 857f–858f
    bamboo hair 841t–842t, 1095f
  differential diagnosis 308t–310t, 858
  epidemiology 857
  and erythroderma 173t–174t
  history 857
  neonatal 847t
  pathogenesis 857
  pathology 858
  treatment 858–859
neural crest-derived cells 62t
neural tube defects *see* cephaloceles
neural/neuroendocrine neoplasms 1943–1960
  classification 1943–1955, 1943t
  clinical features 1945t
  differential diagnosis 1947f
  granular cell tumor 1952–1953
  heterotopic meningeal tissue 1957
  heterotopic neuroblastic tissue 1957–1958
  heterotopic neuroglial tissue 1955–1957
  histogenesis 1943–1955
  histology 1946t
  malignant peripheral nerve sheath tumor 1953–1954
  Merkel cell carcinoma 1954–1955
  nerve sheath myxoma 1951–1952
  neurofibroma 1949–1950
  neuroma 1944–1945
  perineurioma 1953
  schwannoma 1948–1949
  terminology 1943–1955
neurilemmoma *see* schwannoma
neurinoma *see* schwannoma
neuroblastoma 994t, 1703–1704, 1943t, 1946t
NeuroBloc *see* botulinum toxin
neurodermatitis *see* lichen simplex chronicus
neurofibroma 926f, 928f, 1949–1950
  clinical features 1949–1950
  differential diagnosis 1950
  epidemiology 1949
  history 1949
  pathogenesis 1949
  pathology 1950, 1950f
  plexiform 928, 929f, 1119, 1950f
  treatment 1950
neurofibromatosis
  classification 925t
  type 1 925–933
    clinical features 776t–778t, 926–930, 927t, 930f
      cardiovascular manifestations 930
      neurologic manifestations 929
      oculocutaneous manifestations 926–929, 927f–929f
      skeletal manifestations 930
    diagnostic criteria 927t
    differential diagnosis 930–931, 931f
    epidemiology 925
    genetics 813t, 926f
    history 925
    pathogenesis 925–926
    pathology 930
    segmental 925, 929, 929f, 932t–933t, 955
    treatment 931–933, 933t
  type 2 932t–933t
    genetics 813t
    key features 933t
neurofibromin 926f
neurofibrosarcoma *see* malignant peripheral nerve sheath tumor
neurofilament 29t–33t, 828t
neuroma 1944–1945
  amputation 1948f
  clinical features 1944
  differential diagnosis 1945
  epidemiology 1944
  history 1944
  palisaded encapsulated 1948f
  pathogenesis 1944
  pathology 1944–1945, 1947f–1948f
  traumatic 1944, 1947f
  treatment 1945
neuron-specific enolase 29t–33t
neuronal ceroid lipofuscinoses, eccrine gland changes 598t
Neuronox *see* botulinum toxin
neuropathia mucinosa cutanea 696
neuropathic/diabetic ulcers 768t, 1740–1741
  clinical features 769f, 1740, 1740f
  laboratory evaluation 1740
  pathogenesis 1740
  prevention 1741
  treatment 1740–1741
neuropathy 841t–842t
neurophysiology 99–109
  central pathways 100, 100f, 102f–103f
  primary afferent neurons 100t
  pruritus 99–101
    chronic 105, 105t
    impaired skin barrier function 105
    murine models 103t
    receptor units 100–101
    senescent skin 105
  pruritus mediators 101–105, 101t
    gastrin-releasing peptide 101
    histamine 101
    immune cells 104–105
    neurotransmitters 104
    neurotrophins 104
    opioid peptides 101–103
    peptidases 104
    prostanoids 104
    proteinases 101
    substance P 103–104
    transient receptor potential receptor activation 104
  pruritus treatment 105–107
    behavioral therapy 107
    non-pharmacologic 105–107
    pharmacologic 105, 106t
neurosarcoma *see* malignant peripheral nerve sheath tumor
neurosyphilis 1375–1376
  classification 1375t
  HIV-related 1375
  laboratory diagnosis 1375–1376
neurotic excoriations 131–132, 131f, 131t, 1050t
neurotransmitters 104
neurotrophic tyrosine kinase receptor type 1 100–101
neurotrophins 104
neurotropic melanoma 1895, 1896f
neutral lipid storage disease with ichthyosis 838t, 860–861
  clinical features 860
  differential diagnosis 861
  epidemiology 860
  genetics 803t–804t
  history 860
  neonatal 847t
  pathogenesis 860
  pathology 860, 860f
  treatment 861
neutralization assay 1348t
neutropenia
  cyclic 818t–819t, 912t
  severe congenital 912t
  X-linked 912t
neutrophil gelatinase-associated lipocalin 2092
neutrophil immunodeficiency syndrome 910t
neutrophilic dermatoses 423–438, 424f, 681–682, 761t
  Behçet's disease 431–434
    anogenital 433f
    clinical features 433
    diagnosis 434, 434t
    differential diagnosis 433
    epidemiology 432
    and erythema multiforme 320t
    history 432
    mucocutaneous involvement 433, 433f
    oral 433f
    pathogenesis 432–433
    pathology 434
    systemic involvement 429f, 433, 433f, 433t
    treatment 434, 435t
  bowel-associated dermatosis-arthritis syndrome 435–436
    associated conditions 435t
    clinical features 436, 436f
    differential diagnosis 436
    history 435
    pathogenesis 435–436
    pathology 436

treatment 436, 436t
neutrophil biology 423
paraneoplastic 764t–765t
pyoderma gangrenosum 427–431
associated diseases 430
clinical features 428–430, 428t, 429f–430f
clinical variants 428t
differential diagnosis 430–431, 431t
epidemiology 428
history 428
and leukemia 428, 430
monoclonal gammopathy 428
pathogenesis 428
pathology 430, 430f
treatment 431
SAPHO syndrome 436–437
associated cutaneous disorders 437t
clinical features 437, 437f
differential diagnosis 437
epidemiology 436
history 436
pathogenesis 436
pathology 437
treatment 437, 437t
Sweet's syndrome 423–427
associated diseases 426, 426t
clinical features 424, 425f–427f
differential diagnosis 423–424, 427, 427t
epidemiology 424
and erythema nodosum 427, 1644t
history 423–424
and leukemia 424, 425f
monoclonal gammopathy 430
pathogenesis 424
pathology 426–427, 426f
treatment 427, 428t
neutrophilic drug eruptions 342–344
neutrophilic eccrine hidradenitis 599–600
clinical features 600, 600f
differential diagnosis 600
drug-induced 344, 344f, 349t
epidemiology 600
and leukemia 2040t
pathogenesis 600
pathology 600, 600f
treatment 428t, 600
neutrophilic lobular panniculitis 434, 761t
neutrophils 82–83
biology 423
in inflammation 423, 425t
nevirapine
adverse reactions 1299t
interactions 1300
nevoid basal cell carcinoma *see* Gorlin syndrome
nevoid hypertrichosis 1119, 1119f
nevoid melanosis *see* Becker's melanosis
nevoid telangiectasia 955, 1718
nevuocellular nevus *see* common acquired melanocytic nevus
nevus
acantholytic dyskeratotic epidermal 954, 955f
acneiform 953t, 954
anemicus 1047, 1755–1756, 1756f
araneus *see* spider telangiectasia
atypical *see* atypical dysplastic melanocytic nevus
bathing-trunk *see* congenital melanocytic nevus
Becker's *see* Becker's melanosis
blue 1860–1861
blue rubber bleb 772f, 1721, 1722f
CHILD 953t
Clark's *see* atypical dysplastic melanocytic nevus
combined 1876–1877
connective tissue 807t, 937f, 938, 1001t, 1608t, 1628t, 1969, 1969f
depigmentosus 960, 1037–1038, 1038f
eccrine 1847–1848, 1847f
epidermal 8, 953t, 1809–1810
epidermolytic verrucous 953, 953f, 953t
inflammatory linear verrucous 959, 959f
unilateral palmoplantar verrucous 953, 953t
epidermolysis bullosa 1863
garment *see* congenital melanocytic nevus
giant hairy *see* congenital melanocytic nevus
giant pigmented *see* congenital melanocytic nevus
hair follicle 1829
halo 1028, 1042–1043, 1875–1876
Hori's 1053t
inflammatory linear verrucous 144, 959, 959f, 1810–1811
laser therapy 2269
lipomatosus superficialis 1988, 1989f
maternus 1691
melanocytic 508f
of acral skin 1864
and anetoderma 1633t
atypical dysplastic 1868–1871
common acquired 1861–1863
congenital 1001t, 1119, 1871–1874
diagnosis 35f, 39t–40t
of genital and flexural skin 1863
of nail matrix 1145–1146
phenotypes 1868t
recurrent 1877–1878
mucinous 697
non-epidermolytic verrucous 953–954, 953t, 957, 957f
PTEN mosaicism 953t, 954
organoid 1830
patch blue 1858
pigmented hairy epidermal *see* Becker's melanosis
pigmentosus et pilosus *see* congenital melanocytic nevus
plantar cerebriform connective tissue 1717f
porokeratotic eccrine ostial and dermal 958
psiloliparus 995
simplex 6t–7t, 1715f
speckled lentiginous *see* nevus spilus
spider *see* spider telangiectasia
spindle cell, pigmented 1867–1868
Spitz 37f, 1864–1867
strawberry 1691
Sutton's *see* halo nevus
unilateral palmoplantar verrucous 953
verrucosus *see* epidermal nevus
white sponge, of Cannon 803t–804t, 832t–833t, 834, 835t
woolly hair 953t, 1112f
zosteriform lentiginous *see* nevus spilus
nevus comedonicus 1811–1812
clinical features 1812, 1812f
differential diagnosis 1812
epidemiology 1812
history 1812
pathogenesis 1812
pathology 1812, 1812f
treatment 1812
nevus fuscoceruleus ophthalmomaxillaris *see* nevus of Ota
nevus of Ito, laser therapy 2270
nevus of Ota 1858–1859
clinical features 1859, 1859f
differential diagnosis 1859
epidemiology 1859
pathogenesis 1859
pathology 1859
treatment 1859
laser therapy 2270
nevus sebaceous syndrome *see* epidermal nevus syndrome
nevus sebaceus 953t, 1600t, 1790t, 1830–1831
clinical features 1830–1831, 1833f
pathology 1831
treatment 1831
nevus spilus 955, 1874–1875, 1875f
laser therapy 2269–2270
NHEJ1 deficiency 920t
niacin *see* vitamin B_3
nialouli (*Melaleuca quinquenervia/viridifolia*) 2215t
nicardipine 2191t
nickel
dermatosis 250t, 1499t, 1509t
hair discoloration 1498t
hypersensitivity 241–243, 241t, 242f
systemic contact dermatitis 246t
Nicolau-Balus syndrome 1638
Nicolle, Charles 1243
nicorandil, adverse reactions 350
nicotinamide, bullous pemphigoid 483t–484t
nicotine patches, pyoderma granulosum 432t
nicotine stomatitis 1161–1162, 1162f
nicotinic acid *see* vitamin B3
nidogen 454, 455f
Niemann-Pick disease
genetics 810t–811t
nifedipine 2186t, 2189t
adverse reactions
erythroderma 176t
gingival hyperplasia 1156t
lichen planus 185t
interactions 2191–2192, 2191t
Raynaud's phenomenon 651
niflumic acid, adverse reactions
nifurtimox 1402t–1403t
night blindness 740t–742t
nigua *see* tungiasis
Nikolsky sign 326, 467
Nikolsky II sign 467
nilotinib 353t, 1887t, 2149t
nilutamide 2190t
nipple
absent, hypoplastic or anomalous 1007–1008
eczema 209, 209f
guitar 1509t
jogger's 1506t
Paget's disease *see* Paget's disease
supernumerary 1007, 1007f, 1118t
nitrazepam, adverse reactions 336t
nitric acid 253t–254t
nitric oxide, in itch 104
nitrofurazone 2109
nitrogen mustard *see* mechlorethamine
nitrous oxide 2352
interaction with lidocaine 2529t
nits *see* head lice
nizatidine 303, 2191t
NMSC *see* non-melanoma skin cancer
Nocardia spp., chronic granulomatous disease 910t
Nocardia asteroides 1271t
panniculitis 1658t
Nocardia brasiliensis 1270–1271, 1271t
Nocardia caviae 1271t
nocardiosis 1218, 1218t
clinical features 1218
diagnosis 1218
epidemiology and pathogenesis 1218
pathology 1218
treatment 1218
nociceptin 103
NOD defects 806–808
nodular amyloidosis 703, 704f
and anetoderma 1633t
nodular dermatitis 21–22, 22f
nodular fasciitis 1968–1969, 1968f
nodular lichen myxedematosus 691
nodular melanoma 1892, 1893f–1894f
nodular morphea 657, 660f
nodular mucinosis, differential diagnosis
nodular subepidermal fibrosis *see* dermatofibroma
nodular tenosynovitis, localized *see* giant cell tumor of tendon sheath
nodular vasculitis 385t, 391f
nodules 3t–4t
diagnosis 10t–11t
fibrotic 1506t
nodulosis 349t
noma neonatorum 536
NOMID/CINCA 299–300
non-amplified DNA hybridization 1383
non-bullous congenital ichthyosiform erythroderma 177–178
non-epidermolytic verrucous epidermal nevus 953–954, 957, 957f
non-erythematous irritant contact dermatitis 252
non-Hodgkin lymphoma 119
pruritus in 112t, 119
non-inflammatory superficial mycoses 1251–1266
clinical features 1252–1253, 1252f–1253f
piedra *see* piedra
pityriasis (tinea) versicolor 1041f, 1253f
Pityrosporum folliculitis 573t, 1253
tinea nigra 1252–1253, 1252f
differential diagnosis 1254
epidemiology 1251
history 1251
pathogenesis 1251–1252
pathology and fungal culture 1253–1254, 1254f
treatment 1252t, 1254–1255
non-involuting congenital hemangioma 1693
non-Langerhans cell histiocytoses 1535–1545
benign cephalic histiocytosis 1535–1536
generalized eruptive histiocytoma 1536–1537
indeterminate cell histiocytosis 1537–1538
juvenile xanthogranuloma 1538–1539
necrobiotic xanthogranuloma 1539–1541
reticulohistiocytosis 1541–1542
Rosai-Dorfman disease 1542–1544
xanthoma disseminatum 1544–1545
non-melanoma skin cancer 1773–1793
epidemiology 1773–1774, 1774t
history 1773
metastatic 1791
prevention and early detection 1791–1792
prophylaxis 1791
risk factors 1774–1777, 1775t
for additional cancers 1777
environmental exposures 1774–1775, 1775t
genetic syndromes 1776–1777
immunosuppression 1775–1776
for recurrence 1790t
and skin color 1774t
treatment 1788–1792
combination therapy 1791
cryosurgery 1791, 2286
curettage alone 1790
curettage with electrodesiccation 1790
evaluation and risk assessment 1788–1792
laser 1791
medical 1791
Mohs micrographic surgery 1790–1791
photodynamic therapy 1791
radiation therapy 1791
standard excision 1790
see also basal cell carcinoma; squamous cell carcinoma; solar keratosis
non-neural hyperhidrosis 591t, 592, 592f
non-steroidal anti-inflammatory drugs *see* NSAIDs
non-suicidal self-injury 130–131
non-tylotrich pelage hair 1079t
non-X histiocytosis *see* non-Langerhans cell histiocytoses
nonchromogens 1221t
Nonne-Milroy disease 1738f
Noonan syndrome 932t–933t, 1722–1723
and cutis verticis gyrata 1626t
genetics 803t–804t
Noonan syndrome-like disorder 803t–804t
with loose anagen hair 803t–804t

norepinephrine, and eccrine sweating 590t
norethindrone 2070t, 2190t
norfloxacin 2116t
norfluoxetine 2190t
norgestimate 557
normolipemic plane xanthoma, paraneoplastic 764t–765t
normophosphatemic familial tumor calcinosis 818t–819t
North American blastomycosis *see* blastomycosis
North Asian tick typhus 1244t, 1246t
nortriptyline 1181–1182
  and eccrine sweating 590t
Norwegian scabies *see* scabies, crusted
Norwood grading scale for male pattern hair loss 2536f
nose
  anatomic landmarks 2332f
  cartilaginous and bony structures 2333f
  cosmetic subunits 2333–2334
  skin grafts
    cartilage 2432
    full-thickness 2426, 2431f
notalgia paresthetica 121
Notch signaling pathway 830
Novocaine *see* procaine
NSAIDs 2191t
  adverse reactions 338t, 340, 761t
    erythroderma 176t
    linear IgA bullous dermatosis 498t
    nail changes 1141t
    secondary cutaneous vasculitis 390t
  and bleeding disorders 2459
  and eccrine sweating 590t
  and erythema multiforme 320t
  indications
    gout 711
    relapsing polychondritis 677
    SAPHO syndrome 437t
    urticaria 299, 305
    vasculitis 402t
  juvenile idiopathic arthritis 672
Nu-Gel 2372
nuchal keloid acne *see* acne keloidalis
nuclear envelopathies 806
nuclear factorkappaB (NFkappaB) 81
nuclear membrane defects 800t–801t
nuclear ribonucleoprotein 604
nucleic acid amplification 1383
nucleic acid arrays 70t, 71f
nucleotide excision repair 1460–1461, 1461t, 1462f
nummular dermatitis 209, 223, 225–226
  clinical features 225, 225f–226f
  differential diagnosis 226, 414t
  epidemiology 225
  pathogenesis 225
  pathology 225
  treatment 226
    UVB 226
nummular eczema *see* nummular dermatitis
nummular epidermolytic palmoplantar keratoderma 872
Nupercainal *see* dibucaine
Nurse's 'early onset prurigo' of pregnancy *see* atopic eruption of pregnancy
Nurse's 'late onset prurigo' of pregnancy *see* polymorphic eruption of pregnancy
nut/fruit oil soap 2480t
nutritional diseases 737–751
  anorexia nervosa 750
  bulimia 750
  classification and causes 737f
  clinical features 739–751
  differential diagnosis 749f, 751
  epidemiology 737–739, 737f
  essential fatty acid deficiency 740
  obesity 750
  pathogenesis 737–739
  pathology 751
  protein-energy malnutrition 738t, 739–740, 739f–740f
  trace elements 745–750, 748f
    treatment 751
  vitamins 740–750, 740t–742t, 742f–743f, 744t–746t, 746f–747f
nutritional hypomelanosis 1038
nutritive function of skin 49–50
nyctalopia *see* night blindness
nylon sutures 2355–2356, 2356t
nystatin
  formulations 2118t
  mucocutaneous candidiasis 1269t
  pregnancy and lactation 2118t, 2155t
  trade names 2118t

oak moss absolute 243t
Oasis 2375f, 2375t–2376t
oatmeal soap 2480t
obesity 750
  bariatric surgery 750–751
  dermatoses in 751t
  liposuction in 2527t
  and psoriasis 139
observational studies 2057–2060
  case-control 2058–2059, 2058t
  cohort 2058t, 2059, 2059f
  confounding 2058, 2059f
  cross-sectional 2058t, 2059–2060
  descriptive 2057–2058, 2058t
  participants 2058t
  randomised controlled trials 2058t
obsessive-compulsive disorder 549, 2216
  signs and symptoms 130t
  treatment 134
obstetric cholestasis *see* cholestasis of pregnancy
occipital horn syndrome 1593t, 1617t–1618t
occlusive dressings 2366t, 2369–2373, 2369t, 2370f
  alginates 2366t, 2369t, 2372, 2372f
  composites 2369t, 2373
  hydrocolloids 2369t, 2372–2373, 2373f
  hydrogels 2366t, 2369t, 2371–2372, 2371f
  polymer films 2366t, 2369–2371, 2369t, 2370f
  polymer foams 2366t, 2369t, 2371, 2371f
occlusive moisturizers 2480
occlusive vasculopathies 20–21
occupational dermatoses 261–272, 262f
  clinical classification 261t
  contact dermatitis 261–272, 263f–265f
  contact urticaria 266–268, 266f–267f, 267t
  epidemiology 261
  history 261, 263t
  infections 271–272, 271t
  occupational acne 269–270
  occupational skin cancer 268–269, 1775
  plant-induced *see* plant dermatoses
  prevalence 261t, 262f
  vibration white finger 270–271
ochronosis
  exogenous 1053t, 1058f
  see also alkaptonuria
octinoxate 2200f
octisalate 2199, 2200f
octocrylene 2199, 2200f
octyl methoxycinnamate 2199
octylcyanoacrylate tissue adhesive 2357
ocular albinism 1032
  see also oculocutaneous albinism
ocular melanoma 1896
ocular pemphigus *see* cicatricial pemphigoid
ocular rosacea 564, 565f
  treatment 567t
oculo-oral-genital syndrome *see* Behçet's disease
oculocerebrocutaneous syndrome 959, 1001–1002
  cleft lip/palate 1005t
oculocutaneous albinism 48, 1030–1032
  classification 1030t
  clinical features 1031–1032, 1031f
  differential diagnosis 1032, 1032f
  epidemiology 1030–1031
  genetics 1015t
  and NMSC 1776
  pathogenesis 1030–1031
  pathology 1032
  treatment 1032
oculocutaneous tyrosinemia *see* Richner-Hanhart syndrome
oculodentodigital dysplasia 874t
  digital anomalies 1005t
  genetics 803t–804t
oculodermal melanocytosis *see* nevus of Ota
oculoectodermal syndrome 1003t
oculomucodermal melanocytosis *see* nevus of Ota
odds ratio 2058–2059
Odland bodies 1804
odonto-onycho-dermal dysplasia 808t
Oenothera biennis see evening primrose oil
ofatumumab 2149t
office-based radiotherapy 2292
ofloxacin 2116t, 2191t
  indications
    granuloma annulare 1566t
    leprosy 1228t
    tuberculosis 1234t
  interactions 2191t
Ofuji's disease *see* eosinophilic pustular folliculitis
Ohio valley disease *see* histoplasmosis
oid-oid disease 225, 414t
oil acne 269–270
oil drop nail 1136
oil granuloma 1656f
oils
  mechanisms of toxicity 250t
  patch testing 264t
  sensitivity to 250t
olanzapine
  adverse reactions 129t
  psychosis 134
old age spot *see* solar lentigines
olfactory reference syndrome 129
oligonucleotide primers 66f
olive oil/olive leaf extract 2211
Oliver-McFarlane syndrome 1118t
Ollier disease 1722
Olmsted syndrome 879
omalizumab 305, 2147
  atopic dermatitis 213t, 215
  indications 2147
Omenn syndrome 173t–174t, 178, 920t
  genetics 818t–819t
  pathology 179
omeprazole
  adverse reactions
    erythroderma 176t
    lichen planus 185t
Omniderm 2370
omphalomesenteric duct cyst 1825–1826, 1826f
Onchocerca volvulus 730, 1409
onchocerciasis 1409–1416
  clinical features 1414–1415, 1414f–1415f
  diagnosis 1415, 1416f
  differential diagnosis 1415–1416
  epidemiology 1409–1412, 1414f
  hypomelanosis in 1042
  pathogenesis 1412–1414
  pathology 1415
  treatment 1416
oncogenes 1760–1762, 1761f–1762f, 1761t
oncogene defects 808–812
oncological disease 763–767, 763f, 763t–765t, 766f–767f
oncostatin M 82
ondansetron
  pruritus
    cholestatic 119t
    renal 118t
onions 275t
onychauxis 1130f, 1132
onycho-odonto-dermal dysplasia 60
onycho-osteodysplasia *see* nail-patella syndrome
onychocryptosis 1144, 2443–2444, 2443f–2444f
onychocytes 1085–1086
onychodystrophy 1291, 1307
onychogryphosis 1130f, 1143
onycholysis 6t–7t, 176f, 1130f, 1132
  causes 1133f
  drug-induced 337, 1141t
  idiopathic 1142
  musical instrument-related 1509t
  photo-onycholysis 341, 1132, 1141t, 1483
onychomadesis 1130–1131, 1130f–1131f
onychomatricoma 1145, 1145f
onychomycosis 1261–1262
  dermatophytic *see* tinea unguium
  nail bed 2440t
  and nail growth 1090t
onychorrhexis 1130f, 1131
onychoschizia 1130f, 1141t, 1142
onychotillomania 1142–1143
open reading frames 1305, 1305f
open-spray cryosurgery 2285
ophiasis 1100
Ophionyssus natricus 1445t
ophthalmia nodosa 1440
ophthalmic glucocorticoids 2079t
ophthalmic nerve 2338f–2339f
ophthalmic zoster 1332f
opiate abuse 1512
  cutaneous reactions 1518t
  prevalence 1512t
  treatment 1520t
opioid peptides 101–103
opioid receptor agonists 101–103, 101t
opioid receptor antagonists 101t
opportunistic organisms, intravascular proliferation 375
  clinical features 375
  differential diagnosis 375
  pathogenesis 375
  pathology 375
  treatment 375
opportunistic pathogens 1279–1284, 1279f
  clinical features 1280, 1281f
  differential diagnosis 1282
  epidemiology 1279–1280
  history 1279
  pathogenesis 1280
  pathology 1280, 1282f
  treatment 1282, 1283t
  see also individual pathogens
Opsite 2369
optic glioma 929
Optifoam 2371
Opuntia spp. *see* prickly pear
Opuntia ficus-indica 278f
Opuntia microdasys 277, 278f, 287f
oral allergy syndrome 275, 299
oral cavity, developmental anomalies 1149–1151
  fissured tongue 1150, 1150f
  Fordyce granules 1149
  geographic tongue 1149–1150
  hairy tongue 1150–1151
  median rhomboid glossitis 1151
oral contraceptives
  acne vulgaris 555t–557t, 557
  adverse reactions 2185t
    gingival hyperplasia 1156t
    hyperpigmentation 1056t–1057t
    pseudoporphyria 724t
  interactions 2124t
oral disease 1149–1170
  allergic and immunologic 1157–1160
    Behçet's disease 433f, 1159
    contact stomatitis 1157–1158, 1157f, 1157t
    eosinophilic ulcer of oral mucosa 1159
    orofacial granulomatosis 1159–1160, 1160f
    recurrent aphthous stomatitis 1158–1159, 1158f, 1158t–1159t
    Wegener's granulomatosis 1160, 1160f
  developmental conditions 1149–1151

fissured tongue 1150, 1150f
Fordyce granules 1149
geographic tongue 1149–1150
hairy tongue 1150–1151, 1151f
median rhomboid glossitis 1151, 1151f
epithelial pathology 1160–1163
actinic cheilitis 1162
nicotine stomatitis 1161–1162, 1162f
oral leukoplakia/erythroplakia 1160–1161, 1161f
oral squamous cell carcinoma 1162–1163, 1163f
proliferative verrucous leukoplakia 1161
verrucous carcinoma 1163
head and neck syndromes 1151–1152
Gardner syndrome 1151
multiple endocrine neoplasia syndrome type 2B 1151–1152
nevoid basal cell carcinoma 1151
hematologic/oncologic disease 1166–1167
chemotherapy/radiotherapy-induced mucositis 1166
leukemia 1166
lymphoma 1166
melanoma 1166–1167
HIV-related 1292f, 1292t
lichen planus 183, 192, 193f
periodontal and dental disease 1152–1154
dental caries 1153–1154, 1154f
desquamative gingivitis 484–485, 484f, 1152–1153, 1153f
necrotizing ulcerative gingivitis 1152
physical and chemical injuries 1154–1156
chemical burn 1155, 1155f
drug-related gingival hyperplasia 1156, 1156t
fibroma 1154–1155
morsicatio buccarum 1155, 1155f
traumatic ulcer 1156, 1156f
psoriasis 143
salivary gland diseases 1163–1165
cheilitis glandularis 1164, 1164f
mucocele 1163–1164, 1164f
necrotizing sialometaplasia 1164
salivary gland tumors 1165, 1165t
Sjögren's syndrome 678, 1164–1165
systemic origin 1167–1168
amyloidosis 705, 1167–1168
Crohn's disease 1167–1168, 1168f
pernicious anemia 1167, 1168f
pyostomatitis vegetans 424, 429f, 1168
oral florid papillomatosis *see* verrucous carcinoma, oral
oral hairy leukoplakia 1291f
oral hypoglycemics, interactions 2124t
oral leukoplakia/erythroplakia 1160–1161, 1161f
oral mucosa
pigmentation of 8
psoriasis 143
oral mucosal cinnamon reaction *see* contact stomatitis
oral ulcers in systemic lupus erythematosus 627t
oral warts 1310, 1314, 1314f
differential diagnosis 1314
oral-facial-digital syndrome 952
cleft lip/palate 1005t
digital anomalies 1005t
genetics 818t–819t
orange
Bergamot 280t
bitter 280t
sweet 280t
orange juice, interactions 2191t
orange-red lesions 6t–7t
orbicularis oculi muscle 2334
hypertrophic, botulinum toxin 2561, 2564–2565, 2565f
orbicularis oris 1004, 2330–2332
orcein elastic tissue stain 26f, 27t–28t
Orcein-Giemsa 27t–28t
OrCel 2375–2376, 2375t
oregon grape root 2207t
orf 271t, 1355t–1356t, 1357f
organ transplantation, and NMSC 1775
organic acidurias 749f
organic chemicals 264
organic solvents
mechanisms of toxicity 250t
sensitivity to 250t
organoid nevus 1830
Orgyia pseudotsugata 1441t
Orientia tsutsugamushi 1244t, 1248
orificial tuberculosis 1230
orlistat-induced lichen planus 185t
ornithine decarboxylase 2091, 2159
Ornithodoros spp. 1437
Ornithonyssus bacoti 1445t
Ornithonyssus bursa 1445t
Ornithonyssus sylvarum 1445t
orodynia *see* burning mouth syndrome
orofacial granulomatosis 1159–1160, 1160f
orolabial herpes 1322t
oropharyngeal candidiasis 1269t
Oroya fever *see* bartonellosis
orthokeratosis 1783
orthomyxovirus 1345f
orthotic devices 1737t
Osler nodes 1519
Osler-Weber-Rendu disease *see* hereditary hemorrhagic telangiectasia
osmium dermatosis 1499t
osseous heteroplasia 734, 734f
ossification, cutaneous *see* osteoma cutis
osteoarthritis 145f
dietary supplements 2212t
differential diagnosis 711
osteochondroma of nail bed 2440t
osteogenesis imperfecta 1608t
osteoma cutis 733–735, 734f
histology 735f
miliary 735f
plate-like 734
osteomyelitis 1153
and drug abuse 1514t–1515t
osteonecrosis, glucocorticoid-induced 2081, 2083f
osteopoikilosis 1969f
osteoporosis
in epidermolysis bullosa 506
glucocorticoid-induced 2080–2081, 2081f–2082f
and hypervitaminosis A 2101
Ota-like macules 1859
otitis externa 1206
in athletes 1507t
otophyma 564t
Oudtshoorn disease *see* erythrokeratolysis hiemalis
outdoor workers, plant dermatoses 288
ovarian cancer, metastatic 2049t, 2053t
ovarian hirsutism 1121t
ovarian hyperthecosis 1123
ovarian SAHA syndrome 1125
ovarian suppression 1125
overlap syndromes 631, 1040
differential diagnosis 647t
lichen planus-lupus erythematosus 192
lupus-lichen planus 623
oxalate embolus 377
clinical features 377
differential diagnosis 377
pathology 377
treatment 377
oxaprozin
adverse reactions, pseudoporphyria 724t
and linear IgA bullous dermatosis 491–494
oxcarbazepine, adverse reactions, erythroderma 176t
oxiconazole
formulations 2118t
pregnancy and lactation 2118t, 2155t
trade names 2118t
oxidants, mechanisms of toxicity 250t
oxidative phosphorylation *see* mitochondrial disorders
oxidized cellulose 2464t
oxybenzone 2199, 2200f
oxybutynin
hyperhidrosis 594t
hypohidrosis/anhidrosis 595t
Oxycel 2465
oxycodone 2351–2352
oxygen
mist therapy 2378
in wound healing 2366
oxygen mist therapy 2378
oxymetazoline 567t
oxytalan fibers 455–456
oxytetracycline, dosage 2114t
ozokerite 2481t

P&S liquid 2162t
P protein 1018f
P-ANCA
approach to patient 612f
disorders associated with 613t
p-cadherin 833
P-glycoprotein 2185–2186, 2185f
inhibitors 2186t
substrates 2186t
P-selectin 85
p14 deficiency 912t
p16 protein 29t–33t
p21 gene 1765t
p53 gene 1761t, 1764–1765, 1764f
cellular response to DNA damage 1765
immunoreactivity 1767f
inactivation 1761
mutations 1462, 1765, 1766f
regulation 1764–1765
p53 protein 29t–33t, 1765f
p63 protein 29t–33t
p75 protein 29t–33t
PABA 2197, 2199, 2200f
PABA derivatives 2199, 2200f
pacemakers 2308–2309, 2462–2463
pachydermatous eosinophilic dermatitis 414t
pachydermodactyly 1972f
pachyonychia congenita 835t, 873t, 881–882
clinical features 881t
fissured tongue 1150
genetics 809t, 832t–833t
nails in 881f, 1130f, 1136
type (Jackson-Lawler) 881
type (Jadassohn-Lewandowsky) 881
Pacinian bodies 1087
packed red blood cells, adverse reactions 336t
paclitaxel
adverse reactions
alopecia 349t
onycholysis 349t
HHV-8 1934
paddy-field foot *see* immersion foot
padimate O 2200f
Paecilomyces 1282
chronic granulomatous disease 910t
Paederus eximius 1439
Paeonia lactiflora 2213
pagetoid reticulosis 2026, 2026f
differential diagnosis 2020t
Paget's disease 766f, 1600t, 2051t
extramammary 763, 766f
anogenital 1179–1180, 1180f–1181f
Pagoda stain 26f
Pahvant Valley plague *see* tuleremia
Pai syndrome, cleft lip/palate 1005t
pain, chronic 105t
paint
patch testing 264t
sensitivity to 250t, 255f
PAL-E 1686t
palisaded encapsulated neuroma 1165t
palisaded granuloma 21–22, 23f, 761t
palisaded neutrophilic and granulomatous dermatitis 683–684
pathology 1562t
palivizumab 2149t
palladium-induced lichen planus 185t
palliative radiotherapy 2298–2299
locally advanced tumors 2298
metastases 2298–2299, 2299f
Pallister-Killian syndrome 948f
genetics 822t
palm, hypertrichosis 1118t
palmar erythema 1570
liver disease 774t
of pregnancy 307, 447f, 447t
SLE 623t
palmar fibromatosis *see* Dupuytren's contracture
palmoplantar eccrine hidradenitis *see* idiopathic palmoplantar hidradenitis
palmoplantar erythrodysesthesia 519t
endocrine 768t
palmoplantar hidradenitis, idiopathic 600–601, 601f, 1660t
palmoplantar hyperkeratosis 353t, 1514t
in obese patients 751t
palmoplantar hyperlinearity 209t, 210f
palmoplantar keratoderma 834, 835t, 871–885, 872t
acquired 872t, 883–884
aquagenic palmoplantar keratoderma 883, 883f
with cancer 883–884
with hypothyroidism/myxedema 883
keratoderma climactericum 228t, 883
circumscribed 884
with cutaneous squamous cell carcinoma and sex reversal 803t–804t, 813t, 873t, 878
with deafness 803t–804t, 873t–874t, 879
drug-induced 349t
genetics 803t–804t, 832t–833t
hereditary 872–883, 872t–873t
diffuse 803t–804t, 871–877
diffuse with associated features 877–879
diffuse non-epidermolytic/epidermolytic *see* Unna-Thost keratoderma; Vörner keratoderma
focal 872, 875f, 879–880
focal with associated features 880–882
Greither syndrome 873t, 877
mal de Meleda 873t, 877
punctate 872, 876f, 882–883, 882f
striate 803t–804t, 873t
see also individual syndromes
palmoplantar papules 890f
palmoplantar pits, differential diagnosis 882t
palmoplantar warts 1307f, 1311–1312, 1312f
palpable migrating erythema *see* erythema annulare centrifugum
palpable purpura 1246t, 1519
palpation 2, 6t
pamidronate 1652
calciphylaxis 732
Panafil 2109
Panax ginseng see ginseng
pancreatic cancer, cutaneous metastases 2049t, 2053t
pancreatic panniculitis 1649–1650
clinical features 1649, 1650f
differential diagnosis 1650
epidemiology 1649
history 1649
pathogenesis 1649
pathology 1649, 1650f
treatment 1650
pancytokeratins 29t–33t
panitumumab 2149t
adverse reactions
hypertrichosis 1118t
nail changes 1141t
panniculitic bacterid 1660t

panniculitis 730, 1641–1662, 1641t
  aluminum-induced 1656t
  α1-antitrypsin deficiency 1646–1647
  atrophic connective tissue 1646t, 1670
  atypical lymphocytic lobular 1660t
  classification 1641t
  cold 1655–1656, 1656t
  crystal deposition diseases associated with 1660t
  cytophagic histiocytic 1659, 1659f
  of dermatomyositis 640, 1646t, 1654
  diagnosis
    biopsy 14t–15t
    pattern analysis 22–25, 24f
  erythema induratum 1232, 1648–1649
  erythema nodosum 1641
  histopathologic diagnosis 1643t
  infantile-onset 1660t
  infection-induced 1658–1659, 1658f, 1658t
  injection-induced 1656t
  lipodermatosclerosis 1656–1658
  lipogranuloma 1656t
  locations 1642f
  lupus 621, 1646t, 1653–1654
  of Lyme disease 1660t
  malignancy-related 1659
  microimplant-induced 1656t
  morphea/scleroderma 1645–1646
  pancreatic 1649–1650
  plasma cell 1660t
  postirradiation (radiation recall) 1656t
  poststeroid 1651t, 1652–1653
  and pseudocellulitis
  sclerema neonatorum 1650–1651, 1651f, 1651t
  subacute nodular migratory 1645
  subcutaneous fat necrosis of newborn 1651–1652, 1651t
  Sweet's 1660t
  traumatic 1655–1656
  see also lipodystrophies
pansy flower 2207t
pantoprazole 2190t
pantothenic acid 744t–745t
  deficiency 740t–742t
PAPA syndrome 430, 430f, 818t–819t
papain 93
  debridement 2373
paper mulberry 2207t
papillary adenocarcinoma 1848, 1848f
papillary adenoma 1848
papillary endothelial hyperplasia 1915–1916
  clinical features 1915
  differential diagnosis 1915
  epidemiology 1915
  pathogenesis 1915
  pathology 1915, 1917f
  treatment 1916
papillary intralymphatic angioendothelioma *see* Dabska-type hemangioendothelioma
papillary mesenchymal bodies 1834
papillomatosis
  confluent and reticulated 1812–1813
  of Gougerot and Carteaud 1065f, 1065t
  cutis carcinoides 1310
  vestibular 1183
papillomavirus *see* human papillomavirus
Papillon-Lefèvre syndrome 873t, 879, 879f
  genetics 803t–804t
papovavirus 1345f
papular acrodermatitis of childhood *see* Gianotti-Crosti syndrome
papular angioplasia *see* angiolymphoid hyperplasia with eosinophilia
papular dermatitis 414t
papular eruption of blacks 414t
papular mucinosis *see* scleromyxedema
papular pemphigoid 479t
papular pruritic eruption of AIDS 1294
papular urticaria 1435
papular xanthoma 1530t–1531t
  antigenic markers 1533t
papular-purpuric gloves and socks synrome 1352f
papular/nodular mucinosis of Gold *see* cutaneous lupus mucinosis
papules 2, 3t–4t
  diagnosis 10t–11t
  palpation 6t
papuloerythroderma of Ofuji 416, 416t
papulonecrotic tuberculids 1232, 1233f
papulonodular mucinoses 695–696, 695f
papulopustular acneiform eruption, in drug abuse 1514t
papulopustular (inflammatory) rosacea 563, 563f–564f
  treatment 567t
papulosquamous diseases 1293–1294
para-aminobenzoic acid *see* PABA
Parabuthus capensis 1449t
Parabuthus granulatus 1449t
Parabuthus transvaalicus 1449t
Paracoccidioides brasiliensis 1278
paracoccidioidomycosis 1278–1279
  clinical features 1278, 1278f
  differential diagnosis 1278–1279
  epidemiology 1278
  pathogenesis 1278
  pathology 1278
  treatment 1279
paraffin 1581t, 2481t
  foreign body reaction 1574t, 1578
    clinical features 1578, 1578f
    pathology 1578
    treatment 1578
  injection site reaction 663
paragonimiasis 1407t–1408t
Paragonimus westermani 1407t–1408t
parakeratosis 9, 17
  granular *see* granular parakeratosis
parakeratosis pustulosa 1137
paramedian forehead flap 2413–2415, 2414f
paramesonephric mucinous cyst of vulva *see* ciliated cyst of vulva
paramyxovirus 1345f
paraneoplastic dermatoses 764t–765t
paraneoplastic erythroderma 177
paraneoplastic pemphigus 172t–173t, 184t, 461
  clinical features 467–469, 468f
  differential diagnosis 471
  and leukemia 2042t
  monoclonal gammopathy 2014t
  pathology 470, 470f
  pulmonary disease 778t–779t
  target antigens 463t
  treatment 473
paraneoplastic pruritus 118–119
parangi *see* yaws
paraphenylenediamine dermatitis 1509t
parapoxvirus 271t
  and erythema multiforme 320t
paraproteinemia 1540
paraproteins, scleromyxedema 688–690
parapsoriasis 157–169
  clinical features 157–158, 158f
  differential diagnosis 159, 159t
  epidemiology 157
  history 157
  pathogenesis 157
  pathology 159
  treatment 159, 159t
  variegata 158
parapsoriasis en plaques *see* parapsoriasis
parapsoriasis lichenoides 158
parasitic infections 414t
  HIV-related 1292–1293
parasitosis, delusions of 127–129, 128f, 128t
  matchbox sign 128, 128f
parathyroid adenoma 927t
Parkes Weber syndrome 945t–946t, 1725
paromomycin, leishmaniasis 1397t
paronychia
  acute 1141, 1141f
  chronic 1142
  drugs causing 1141t
  musical instrument-related 1509t
parotid gland 2327
paroxetine
  anxiety disorder 133
  depression 134
  and eccrine sweating 590t
  pruritus 106t, 119t
paroxysmal nocturnal hemoglobinuria 372–373
  clinical features 373
  differential diagnosis 373
  pathogenesis 372–373
  pathology 373
  treatment 373
Parry-Romberg syndrome 660f, 661, 1670
parsley 275t, 279t
parsnip 275t, 279t
Parthenium hysterophorus see congress weed
partial thromboplastin time 358
partial unilateral lentiginosis 932t–933t
partial-thickness wounds 2314
Partington cutaneous amyloidosis *see* X-linked reticulate pigmentary disorder
Partington syndrome type II *see* X-linked reticulate pigmentary disorder
partition coefficient 2068
parulis 1153
parvovirus B19 339
  clinical associations 1350t
  erythema infectiosum 1349–1352
  and erythema multiforme 320t
  secondary cutaneous vasculitis 390t
  see also erythema infectiosum
PAS stain 26, 26f, 27t–28t
passenger mutations 1760–1761
passionflower 2212t
1-2-3 paste 2162t
paste dressings 2368–2369
Pasteurella spp. 1450t
Pasteurella multocidans 1450t
Pastia's lines 1195
Pastinaca sativa see parsnip
Patau syndrome 791–792, 821f, 1003t
  eccrine gland changes 598t
patch blue nevus 1858
patch testing 236–239, 237f, 264t, 338
  history 234
  interpretation 239, 239t, 240f
  plants 266t, 273
  screening series 238t
  technique 237–239, 239f
patched gene 1765–1768
Patched signaling pathway 1765–1768
  normal function of 1766–1767
  PTCH gene 1766
  PTCH mutations 1767–1768
  regulation of 1767
patches 3t–4t
  palpation 6t
  transdermal 2070t
patchouli (*Pogostemon cablin*) 2215t
pathergy 429f, 433
pathogen-associated molecular patterns (PAMP) 81
pattern analysis 16–25, 16f
  fibrosing dermatitis 22, 24f
  folliculitis/perifolliculitis 22, 24f
  interface/vacuolar dermatitis 16f–18f, 17–18
  invisible dermatoses 25, 25t
  melanocytic nevus vs melanoma 39t–40t
  melanocytic vs non-melanocytic lesions 38t–39t
  nodular and diffuse dermatitis 21–22, 22f
  panniculitis 22–25, 24f–25f
  perivascular dermatitis 17, 17f
  psoriasiform dermatitis 18–19, 19f
  spongiotic dermatitis 18, 18f
  vasculitis/pseudovasculitis 20–21, 21f
  vesiculobullous and pustular dermatoses 19, 19f–20f
pattern recognition receptors 81
Pautrier's microabscesses 1474, 1799, 2007–2009
pazopanib 2149t
PCR *see* polymerase chain reaction
PD0325901 1887t
PD0332991 1887t
peach 275t
pear 275t
pearly penile papules 1183t, 1313
peat fire cancers 1490
peau d'orange 2050–2051, 2052f
  localized myxedema 693
  retinal 1614f
  scleredema 693, 694f
peau d'orange (apple dumpling) chin 2568, 2568f
  botulinum toxin 281–288
PECAM-1 *see* CD31
pediculosis
  pruritus in 113
  see also types of lice
Pediculosis capitis see head lice
Pediculosis corporis see body lice
pediculosis pubis *see* crab lice
Pediculus capitis see head lice
Pediculus humanus var. *corporis* 1244t
Pedroso's disease *see* chromoblastomycosis
peeling skin syndrome 832t–833t, 841t–842t, 852t–854t, 861f
  genetics 803t–804t
  neonatal 847t
peglitocase 711
Pelargonium cultivars 274t
Pelea anisata see mokihana
pellagra 743f
pemetrexed 349t
pemphigoid
  autoantigens 1596t
  p105, immunoreactants in 457t
  p200, immunoreactants in 457t
pemphigoid gestationis 439–441, 456t, 478
  autoantigens 456t, 476t
  clinical features 440, 440f
  differential diagnosis 308t–310t, 414t, 441
  epidemiology 439–440
  history 439
  immunoreactants in 457t
  neonatal 441t, 536f
  pathogenesis 440
  pathology 440–441, 441f
  skip pregnancies 440
  treatment 441
pemphigoid incipiens 482
pemphigoid nodularis 478f, 479t
pemphigoid vegetans 478f, 479t
pemphigus 461–474
  autoantibodies 462, 466
  classification 462t
  clinical features 466–469
  differential diagnosis 414t, 470–472
  drug-induced 347
    clinical features 467
    target antigens 461
  epidemiology 461–462
  herpetiform 467
  history 461
  IgA 461
    clinical features 469, 469f
    differential diagnosis 472
    pathology 470, 471f
    target antigens 463t
    treatment 473
  paraneoplastic 172t–173t, 461, 764t–765t
    clinical features 467–469, 468f, 763f
    differential diagnosis 471
    pathology 470, 470f
    target antigens 463t
    treatment 473
  pathogenesis 462–466
    autoimmunity against desmogleins and plakins 465
    desmoglein compensation theory 464–465, 465f
    desmogleins 462–464, 463f–464f, 463t
    immunologic mechanism 466
    pathogenic autoantibodies 462, 466

pathology 469–470
target antigens 463t
treatment 472–473
see also various forms of pemphigus
pemphigus antigens 462–464, 462t–463t
molecular structure 463f
pemphigus erythematosus (Senear-Usher syndrome) 467, 468f
pemphigus foliaceus 47t, 461
clinical features 467, 468f
differential diagnosis 147t, 471
and erythroderma 172t–173t
genetics 832t–833t
pathology 470, 470f
radiation-induced
target antigens 463t
treatment 472–473
pemphigus neonatorum *see* staphylococcal scalded skin syndrome
pemphigus vegetans 461
clinical features 467, 467f
Hallopeau type 467
Neumann type 467
pathology 470
pemphigus vulgaris 47f, 47t, 461
anogenital 1185, 1185f
clinical features 19f, 465f–466f, 466–467
differential diagnosis 471
genetics 832t–833t
pathology 469–470, 469f
target antigens 463t
treatment 467t, 472
penciclovir
dosage 2126t
formulations 2124t
herpes simplex 1329t
pregnancy and lactation 2124t
trade names 2124t
penicillamine
adverse reactions 761t
anetoderma 1633t
cutis laxa 1616
elastosis perforans serpiginosa 1601f
erythroderma 176t
hypertrichosis 1118t
lichen planus 185t
pemphigus 467
indications
lichen sclerosus 667t
morphea 667t
Wilson disease 750
penicillins 2105t, 2110–2111
adverse reactions 338t, 2110–2111
linear IgA bullous dermatosis 498t
secondary cutaneous vasculitis 390t
urticaria 340f
contraindications 2110
dosage 2110, 2110t
indications 2110
bullous pemphigoid 484t
morphea 667t
interactions 2111
mechanism of action 2110, 2110f–2111f
pregnancy and lactation 2111
sites of action 2109t
see also individual drugs
penicillin G
adverse reactions 336t
borreliosis 315t
penicillin V potassium, dosage 2110t
penicilliosis
differential diagnosis 1276t
treatment 1283t
Penicillium spp., chronic granulomatous disease 910t
Penicillium marneffei 1276t, 1280
penile intraepithelial neoplasia 1311f
penile nerve block 2350
penis 1172f
lentigines 3t–4t
lichen planus 189f, 1174f
lichen sclerosus 1173f
peno-gingival syndrome *see* lichen planus, anogenital
Penrose drain 2465
pentachrome vitiligo 1026
pentamidine
adverse reactions 1397t
indications
amebiasis 1398
leishmaniasis 1397t
pentazocine abuse, cutaneous signs 1512–1513, 1514t
pentostatin-induced erythroderma 176t
pentoxifylline
and eccrine sweating 590t
leg ulcers 1737
vasculitis 402t
PEODDN 958
peppermint (*Mentha x piperita*) 2215t
peptic ulcer disease, glucocorticoid-induced 2084
peptidases 104
Peptostreptococcus asaccharolyticus
perauricular cyst *see* ear pit
percutaneous drug delivery *see* transdermal drug delivery
perforating calcific elastosis 1600t
clinical features 1602, 1602f
perforating calcinosis 1600t
perforating diseases 768t, 1599–1605, 1600t
clinical features
acquired perforating dermatosis 1601–1602, 1602f
elastosis perforans serpiginosa 1600–1601, 1601f
perforating calcific elastosis 1602, 1602f
reactive perforating collagenosis 1600, 1600f
differential diagnosis 1604, 1604t
epidemiology 1599
history 1599
pathogenesis 1599–1600
pathology 1602–1604, 1602f–1603f
secondary 1600t
treatment 1604–1605, 1604f
perforating periumbilical calcific elastosis 1612–1613
differential diagnosis 1614t
perforating pseudoxanthoma elasticum 1600t, 1613
perforin 29t–33t
perianal cellulitis *see* streptococcal perianal disease
perianal pseudoverrucous papules/nodules 1266
perianal streptococcal disease 1183, 1197
periapical abscess 1153
periarteritis nodosa 21f
pericarditis, SLE 627t
pericytes 1682
perifollicular fibroma 1830
perifollicular mucinosis 696
perifolliculitis capitis abscedens et suffodiens *see* dissecting cellulitis of scalp
perinatal gangrene of buttock 526t–528t, 536
perinatal trauma 526t–528t
perineurial cells 1943, 1946t
perineurioma 1953, 1953f, 1953t
perinevoid vitiligo *see* halo nevus
perinuclear antineutrophil cytoplasmic antibodies *see* P-ANCA
periodontal and dental disease 1152–1154
dental caries 1153–1154, 1154f
and drug abuse 1514t, 1517f
desquamative gingivitis 484–485, 484f, 1152–1153, 1153f
necrotizing ulcerative gingivitis 1152
perioral dermatitis 566–568, 568f
perioral landmarks 2333f
periorbital darkening 209t
peripheral nerve 1944f
peripheral nerve sheath tumors 764t–765t, 925–926
peripheral neuropathy
dapsone-induced 496
nail changes 1140
peripheral vasoneuropathy *see* immersion foot
peripherin 828t
periplakin 463–464, 825–826
periporitis staphylogenes 599
peristomal skin disorders 772t
periungual fibroma 937f, 938
periungual pyogenic granuloma 1141t
periungual warts 1139t, 1141–1142, 1307f
cryosurgery 2286
perivascular dermatitis 17, 17f
Perlane 2548t–2549t
Perlane-L 2548t–2549t
perlecan 1590, 1592t
perlèche 1268f
Perls' iron stain 26f, 27t–28t
permanent waves 2486t
permethrin 1442
crab lice 1430
head lice 1428t, 1429
pregnancy and lactation 2155t
rosacea 567t
scabies 1424, 1426t
pernicious anemia
and dermatitis herpetiformis 493t
oral manifestations 1167, 1168f
pernio 374, 1493–1494
clinical features 1494, 1494f
differential diagnosis 1494, 1495t
epidemiology 1494
history 1494
pathogenesis 1494
pathology 1494
treatment 1494
perniosis *see* pernio
peroxisome proliferator-activated receptors 1674
perphenazine 2190t
and eccrine sweating 590t
Persian lime 274t, 280t
persimmon leaf 2207t
persistent acantholytic dermatosis *see* Grover's disease
persistent adrenarche syndrome 1124–1125
personal care products, patch testing 264t
PERT phenomenon 566
pertussis, and erythema nodosum 1644t
Peruvian lily 274t
allergic contact dermatitis 288, 288f
pesticides, sensitivity to 253t–254t
petechiae 358f
differential diagnosis 359t
and drug abuse 1514t, 1518–1519
see also purpura
petitgrain (*Citrus aurantium* var. *amara*) 2215t
petrochemicals 253t–254t
petrolatum 2481, 2481t
Petroselinum sativum see parsley
Peutz-Jeghers syndrome 772f, 1856, 1857t
and gastric hemorrhage 773t–774t
genetics 818t–819t
Peyronie's disease 1625, 1975
PHACES syndrome 776t–778t, 998, 1697–1698, 1698f, 1699t
Phaenicia sericata see myiasis
phaeohyphomycosis 1279f, 1283
clinical features 1283
differential diagnosis 1283
epidemiology 1283
history 1283
pathogenesis 1283
pathology 1283, 1283f
treatment 1283
phaeosporotrichosis *see* chromoblastomycosis
phagocyte NADPH oxidase defects 910t
phagocytosis 86–87
phakinin 828t
phakomatosis cesioflammea 1716t
phakomatosis cesiomarmorata 1716t
phakomatosis pigmentovascularis 1715, 1716f, 1716t
phakomatosis spilorosea 1716t
pharmacogenetics 2193, 2193t
Phebalium argentuem see blister plant
phenelzine, and eccrine sweating 590t
phenformin 2190t
phenindione, adverse reactions 350
phenobarbital
adverse reactions
acne 550t
erythroderma 176t
gingival hyperplasia 1156t
cholestatic pruritus 119t
interactions 2124t, 2191–2192
phenocopy 790
phenol
adverse reactions 2155t
ingrowing toenail 2443–2444, 2443f
pruritus 2157t
phenolic compounds 253t–254t
phenolphthalein, fixed drug eruption 346f
phenotype 794–795
phenoxybenzamine
hypohidrosis/anhidrosis 595t
reflex sympathetic dystrophy 122t
phentolamine, hypohidrosis/anhidrosis 595t
phenylalanine-UVA phototherapy 1029
phenylbutazone, adverse reactions, Stevens-Johnson syndrome/toxic epidermal necrolysis 325t
p-phenylenediamine 241t, 244
phenylketonuria
differential diagnosis 652t
genetics 810t–811t
hair discoloration 1498t
phenylpropanolamine, and eccrine sweating 590t
phenytoin
adverse reactions
acne 550t
erythroderma 176t
gingival hyperplasia 1156t
hypertrichosis 1118t
lichen planus 185t
linear IgA bullous dermatosis 498t
pruritus 120t
secondary cutaneous vasculitis 390t
Stevens-Johnson syndrome/toxic epidermal necrolysis 325t
indications, epidermolysis bullosa 511
interactions 2124t, 2191–2192
lidocaine 2529t
pheochromocytoma 264–265, 2344
differential diagnosis 647t
and hypothalamic hyperhidrosis 589, 589t
pheomelanin 8
pheromones 542
Phialophora verrucosa 1267
Philadelphia chromosome 2041
philodendron 278t, 287f
philtrum 2334
phlebectomy, ambulatory 2520–2521
anesthesia and intraoperative materials 2520–2521, 2520f–2521f
combination with endovenous laser/radiofrequency ablation 2523
complications 2521, 2522t
postoperative considerations 2521
preoperative preparation 2520
technique 2521, 2521f
phlebology 2509–2524
graduated compression 2512–2513
physical examination 2510–2512, 2512t
sclerosing solutions 2513–2515, 2514t–2515t
phlebotomy in porphyria 726
phorbol esters 278t
phosphatidyl serine 358
phosphatidylinositol 3-kinase 814f
phosphodiesterase type 5 inhibitors 651
phosphoinositide 3-kinase pathway in melanoma 1886
phosphoric acid 253t–254t
phosphotungstic acid hematoxylin 1657
photo-onycholysis 341, 1132, 1141t, 1483
photoaggravated dermatoses 1479–1480, 1479t, 1480f

photoaging 1457–1458, 1458f, 1483–1484, 2202, 2474–2476
  action spectrum 2201t
  clinical features 1483f–1484f, 1483t
  in colored skin 1484–1485, 1485f
  Glogau classification 2475t, 2476f
  treatment
    fractional resurfacing
    photodynamic therapy 2246–2247, 2247t
    retinoids 2093
photoallergic agents 1480t
photoallergic contact dermatitis
  action spectrum 2203t
  differential diagnosis 212t
photoallergy 341, 1481, 2203
photocarcinogenesis 1457–1464, 1458f, 1485
  action spectrum 1460f
  DNA damage 1459–1460
    repair 1460–1462, 1462f
  mutation formation 1462–1463, 1463f
  protection against 1463–1464
  UV-induced tumor formation 1458–1459
photochemotherapy
  alopecia areata 1103t
  extracorporeal *see* photopheresis
  lichen sclerosus 667t
  morphea 667t
  psoriasis 150, 150t
  see also phototherapy
photochromogens 1221t
photodermatitis
  glucocorticoids in 2077t
  treatment 2077t
photodermatologic disorders *see* photodermatoses
photodermatoses 1467–1486, 1467t
  abnormal reaction to UV exposure 1467–1482
  chromosomal instability 1478–1479
    Bloom syndrome *see* Bloom syndrome
    chemical- and drug-induced photosensitivity 1480–1482, 1480t–1481t, 1481f–1482f
    Kindler syndrome *see* Kindler syndrome
    photoaggravated dermatoses 1479–1480, 1479t, 1480f
    Rothmund-Thomson syndrome *see* Rothmund-Thomson syndrome
  classification 1467t
  defective DNA repair 1475–1478, 1476t–1477t
    Cockayne syndrome 1462t, 1478
    trichothiodystrophy *see* trichothiodystrophy
    UV-sensitive syndrome 1478
    xeroderma pigmentosum 49, 1072t–1073t, 1462t, 1475–1477
  immunologically mediated 1467–1475, 1467t
    actinic prurigo 1470–1471
    chronic actinic dermatitis 1473–1475
    hydroa vacciniforme 1472–1473
    polymorphic light eruption 1467–1469
    solar urticaria 298, 1475
  normal reaction to UV exposure 1482–1485
  PUVA phototherapy 2231–2232
photodistribution 9
photodrug eruption
  action spectrum 2203t
  differential diagnosis 639t
photodynamic therapy 2237–2250, 2238f, 2238t
  administration 2248t
  advantages and limitations 2240–2241, 2240f
  adverse effects/complications 2248–2249
    allergic contact dermatitis 2249
    cutaneous photosensitivity and photophobia 2248, 2248f
    inflammation 2249
    pain 2249
  drug delivery and tissue localization 2248t
  history and development 2237
  indications 2243–2248, 2244t
    acne 558, 2246, 2247f
    actinic keratoses 2244, 2245f
    alopecia areata 1103t
    basal cell carcinoma 2244–2245, 2245f–2246f
    Bowen's disease 2245, 2246t
    cutaneous infections 2247
    cutaneous metastases 2246
    mycosis fungoides 2245–2246
    NMSC 1791
    photoaging 2246–2247, 2247t
    psoriasis 2247
    vascular anomalies 2247–2248
  light dosimetry 2243
  light sources 2243t
  photobiology 2239
  photochemistry 2238–2239, 2239f
  selectivity 2239–2240, 2240t
  technique 2249
photographic chemicals, patch testing 264t
photoimmune suppression 2202
  action spectrum 2201t
photoirritant contact dermatitis
  action spectrum 2203t
photoleukomelanodermatitis of Kobori 1072t–1073t
photomechanical effects of lasers
photomechanical (stress) waves
photopatch test agents 1481t
photopheresis 2233
  lichen sclerosus 667t
  morphea 667t
  pemphigus vulgaris 472t
photorejuvenation 2277
  see also chemical/mechanical skin resurfacing
photosensitivity 286, 841t–842t, 2203
  action spectrum 2201t, 2203t
  chemical-induced 1480–1482, 1482f
  diagnosis 1468f
  drug-induced 341, 341f–342f, 349t, 1480–1482, 1481f
  HIV-related 1295
  laboratory evaluation 1470t
  PUVA 2225–2227
  SLE 627t
  trichothiodystrophy 1478
  see also photodermatoses
photosensitizers 2238f, 2241–2242, 2242t
  aminolevulinic acid/methyl aminolevulinate prodrugs 2242
  chemical structure 2241f
  systemic 2242
  topical 2241–2242
phototherapy 2219–2235
  excimer laser 2223
  indications
    cholestatic pruritus 119t
    lichen planus 196
    mycosis fungoides 2024
    parapsoriasis 159
    seborrheic dermatitis 2222
    see also individual modalities
  minimal erythema dose 2220, 2228f
  and NMSC 1774
  PUVA 2224–2233
    and acrobullous dermatosis 521
    action spectrum and light sources 2225, 2226f
    adverse reactions 2232–2233, 2232f
    clearing phase 2227
    combination therapy 2228–2229
    diseases responsive to 2224t
    history 2224
    in HIV patients 2233
    indications
      alopecia areata 1103t, 2231
      atopic dermatitis 214–215, 2231
      graft-versus-host disease 2231
      granuloma annulare 2231
      irritant contact dermatitis 258
      lichen planus 2231
      mastocytosis 2231
      mycosis fungoides 2229–2230, 2230f
      parapsoriasis 159t
      photodermatoses 2231–2232
      pityriasis lichenoides 162t, 2231
      pityriasis rubra pilaris 2231
      psoriasis 2228, 2229f
      scleroderma 2231
      urticaria pigmentosa 2231
      vitiligo 2230–2231
    and linear IgA bullous dermatosis 498t
    maintenance phase 2227–2228
    photosensitivity 2225–2227
    psoralens *see* psoralens
    treatment protocols 2227, 2227t–2228t, 2228f
  skin phototypes 2227t
  UVA_1 2223–2224, 2223f–2224f
    adverse reactions 2224
  UVB 2219–2223
    action spectrum and radiation sources 2220
    adverse reactions 2223
    broadband 2220f, 2220t
    history 2219
    in HIV patients 2233
    indications
      atopic dermatitis 214–215, 2222
      folliculitis 574
      graft-versus-host disease 2222
      irritant contact dermatitis 258
      lymphomatoid papulosis 2222
      mycosis fungoides 2221–2222
      nummular dermatitis 226
      pityriasis lichenoides 162t, 2222
      pruritus 118t–119t, 2222–2223
      psoriasis 2221
      vitiligo 2222, 2222f
    mechanism 2219–2220
    narrowband 2220f, 2220t
    treatment protocols 2220–2221, 2220f–2221f, 2220t
photothermolysis
  fractional 2256–2257
    ablative 2273–2275, 2275f–2276f
    non-ablative 2272–2273, 2274f
  selective 2253
    pulse durations and targets 2254t
phototoxic agents 1480t
phototoxic eruptions 9, 264–265, 519t
phototoxicity 341, 1481
phrynoderma 579
  see also vitamin A, deficiency
Phthirus pubis 1367t
phylloid hypomelanosis 820, 821f, 1037–1038
  genetics 822t
phymatous rosacea 563–564, 564t
  treatment 567t
Physalia physalis 1451
Physalia utriculus 1451
physical abuse 1521–1523, 1522f–1523f
physical neglect 1523
physical urticarias 296–298, 296t, 301
  mechanical
    delayed pressure 297, 297f
    dermographism 296, 297f
    vibratory angioedema 297
  temperature changes 297–298
    cold exposure 293, 297–298
    heat exposure 297
physostigmine, and eccrine sweating 590t
phytanic acid storage disease *see* Refsum disease
phytonadione, adverse reactions 336t
phytophotoallergic contact dermatitis 281
phytophotodermatitis 6t–7t, 279–281, 1481
  clinical features 280–281, 281f
  epidemiology 279–280
    Apiaceae 279–280, 279t, 280f
    Fabaceae 280
    Moraceae 280
    Rutaceae 280, 280t
  history 279
  pathogenesis 280
  risk activities 281t
  treatment 281
pian *see* yaws
PIBIDS *see* trichothiodystrophy
Picaridin 1437t
picornavirus 1345f
piebaldism 932t–933t, 1032–1033, 1034t
  clinical features 1032–1033, 1033f
  differential diagnosis 1033
  epidemiology 1032
  pathogenesis 1032
  pathology 1033
  treatment 1033
piedra 1252
  black 1252, 1252f, 1252t
  clinical features 1253f
  white 1252, 1252f–1253f, 1252t
Piedraia hortae 1251, 1251t
piezogenic papules 1506f, 1506t
piezogenic pedal papules 1639, 1639f
pigmentary demarcation lines 8, 1058–1059, 1058t, 1060f
pigmentary dilution 1023
pigmentary disorders 52
  biopsy 14t–15t
  drug-induced 354, 354f
  hereditary 810t
  see also hyperpigmentation; hypopigmentation
pigmentary mosaicism *see* hypomelanosis, of Ito
pigmentary system 2476
pigmentatio reticularis faciei et colli 1065t
pigmentation 5–8
  genes associated with 1021t
pigmented epithelioid melanocytoma 1860–1861
pigmented follicular cyst 1822
pigmented hairy epidermal nevus *see* Becker's melanosis
pigmented purpuric eruptions 361, 365t
  clinical features 362
  differential diagnosis 362
  pathogenesis 362
  pathology 362, 366f
  treatment 362
pigmented purpuric lichenoid dermatitis of Gougerot and Blum 365t
pigmented spindle cell nevus 1867–1868
  clinical features 1867
  differential diagnosis 1867
  epidemiology 1867
  pathogenesis 1867
  pathology 1867, 1867f
  treatment 1867–1868
pigmented villonodular synovitis *see* giant cell tumor of tendon sheath
pigments, lasers for removal of 2269t
pilar cyst *see* trichilemmal cyst
pilar sheath acanthoma 1818–1819
pilar tumor *see* proliferating trichilemmal cyst
pili annulati 1110f, 1112
pili bifurcati 1112
pili multigemini 1112
pili torti 841t–842t, 1110f, 1111
pili trianguli et canaliculi *see* spun-glass hair
pilocarpine, and eccrine sweating 590t
piloleiomyoma 8, 1979, 1980f
pilomatrical carcinoma 1836
pilomatricoma 1600t, 1835–1836
  and anetoderma 1633t
  clinical features 1835, 1836f
  pathology 1835–1836, 1836f
  treatment 1836
pilonidal cyst 1823
  pathology 1823
  treatment 1823
pilonidal sinus 583f, 1580
pilosebaceous unit 540f, 544f, 1081t, 1093

pimecrolimus 2136–2138
  contraindications 2138
  dosage 2138
  indications 2137–2138
    atopic dermatitis 214
    nummular dermatitis 226
    pruritus 106t, 123
    rosacea 567t
  interactions 2138
  major adverse reactions 2138
  mechanism of action 2137, 2137f
  pregnancy and lactation 2138
pimozide
  adverse reactions 129t, 134
  interactions 2124t, 2190, 2193
  psychosis 134
Pimpniella anisum see anise seeds
pincer nails 1130f, 1143–1144, 1146f
pinch marks 1522
pine tree bark extract 2207t
pineapple 275t, 278t
pineapple extract 2207t
Pinkus' follicular mucinosis *see* follicular mucinosis
Pinkus, Herman 16–17
pinocytosis 87
pinta 1042, 1072t–1073t, 1216
Pinus maritima see Pacific maritime pine bark
pio *see* tungiasis
Pipkin syndrome 1857t
pique *see* tungiasis
piroxicam 2190t
  adverse reactions
    alopecia 348t
    linear IgA bullous dermatosis 498t
    mucosal ulceration 350
    pemphigus 347
    photoallergy/phototoxicity 1480t
    Stevens-Johnson syndrome/toxic epidermal necrolysis 325t
  and linear IgA bullous dermatosis 498t
pitted keratolysis 1201
  in athletes 1507t
  clinical features 1201, 1202f
  diagnosis 1201
  epidemiology and pathogenesis 1201
  pathology 1201
  treatment 1201
pitting of nails 1131
  alopecia areata 1100, 1101f
  psoriasis 144f, 1131f
pituitary hirsutism 1116, 1124
pityriasis alba 226, 1039
  in atopic dermatitis 210–211, 210f
  clinical features 226f
  differential diagnosis 210–211, 1227–1228
pityriasis amiantacea 221
pityriasis circinata *see* pityriasis rotunda
pityriasis folliculorum 569
pityriasis lichenoides 159–161, 184t
  chronica 160–161
  clinical features 160f
  differential diagnosis 161, 161t
  epidemiology 160
  history 160
  pathogenesis 160
  pathology 161, 161f
  PLEVA variant 160
  treatment 161, 162t
    phototherapy
      PUVA 162t, 2231
      UVB 162t, 2222
pityriasis lichenoides et varioliformis acuta 159–161
  differential diagnosis 161, 161t
pityriasis rosea 12t, 165–167
  clinical features 165–166, 165f–166f
    postinflammatory hyperpigmentation 1050t
  differential diagnosis 166–167, 308t–310t
  distribution 9
  epidemiology 165
  herald patch 165, 165f
  history 165
  inverse 9
  pathogenesis 165
  pathology 166
  treatment 167
pityriasis rosea Gilbert *see* pityriasis rosea
pityriasis rotunda 167
  clinical features 167
  differential diagnosis 167
  epidemiology 167
  history 167
  pathogenesis 167
  pathology 167
  treatment 167
pityriasis rubra pilaris 6t–7t, 9, 162–165
  classification 164f
  clinical features 162–163, 162f–163f
  differential diagnosis 163, 228t
  epidemiology 162
  and erythroderma 163, 163f, 177–178, 177f
  history 162
  islands of sparing 162–163, 162f
  and nail growth 163, 1090t
  pathogenesis 162
  pathology 163, 164f
  treatment 163–165
    phototherapy 165, 2231
    retinoids 165, 2097, 2098f
pityriasis simplex capilliti 220
pityriasis (tinea) versicolor 1041–1042, 1055, 1253
  clinical features 1253f
    hypomelanosis 1041f
  distribution 9
Pityrosporum folliculitis 573t, 1253
Pityrosporum ovale
placental growth factor 1682
  in angiogenesis 1683
plague 1213–1214
plakins, autoimmunity against 465
plakoglobin 463–464, 831f, 832–833
  in Naxos disease 807t
plakophilin 463–464, 502f, 831f
  deficiency *see* ectodermal dysplasia
plane xanthomas 1541
plant dermatoses 273–289
  allergic contact dermatitis 281–288
  binomial nomenclature 273, 274t
  botanical aspects 273
  chemical irritant dermatitis 278–279
  immunologic contact urticaria 274–275
  mechanical irritant dermatitis 277
  occupational 288
  patch testing 266t, 273
  phytophotodermatitis 279–281
  plant identification 273
  toxin-mediated contact urticaria 276–277
  see also botanicals
plantar dermatosis, juvenile 228–230, 228t
  clinical features 228, 229f
  differential diagnosis 228–230
  epidemiology 228
  history 228
  pathogenesis 228
  pathology 228
  treatment 230
plantar erythema, diffuse 1507t
plantar fibromatosis 1625, 1971–1972
plantar hyperkeratosis, obese patients 751t
plantar keratoderma 228t
plantar keratosis, intractable *see* corns and calluses
plaque-like cutaneous mucinosis *see* reticular erythematous mucinosis
plaques 3t–4t
  diagnosis 10t–11t
  palpation 6t
plasma cell balanitis/vulvitis *see* Zoon's balanitis/vulvitis
plasma cell dyscrasias 2013–2014, 2014t
plasma cell panniculitis 1660t
plasma exchange, bullous pemphigoid 484t
plasma protein binding 2186
plasmablastic lymphoma 2006
plasmacytoid dendritic cells, in atopic dermatitis 206t
plasmacytoma, and anetoderma 1633t
plasmakinetic skin resurfacing 2277
plasmapheresis
  dermatomyositis 639t
  pemphigus vulgaris 472, 472t
  pyoderma granulosum 432t
  urticaria 305
  vasculitis 402t
plasminogen 295f
  deficiency 1744t
plasminogen activator inhibitor-1 excess 1744t
plastics 255–256
platelets 2459
  in wound healing 2319–2320, 2320f
platelet aggregation inhibitors 2212t
platelet count 361
platelet plugging disorders 818t–819t
  differential diagnosis 360t
  heparin necrosis *see* heparin necrosis
  paroxysmal nocturnal hemoglobinuria
  thrombocytosis secondary to myeloproliferative disorders
  thrombotic thrombocytopenic purpura-hemolytic uremic syndrome
platelet-activating factor 412f
platelet-derived growth factor 2374
  in wound healing 2317t
platinum dermatosis 1499t
platysma muscle 2335
platysmal bands, botulinum toxin 2566t, 2569, 2569f
PLEC1 458t
plecin 785t
plectin 450, 463–464, 502f
pleomorphic fibroma 1966, 1966f
pleomorphic lipoma *see* spindle cell lymphoma
Plesiomonas shigelloides 1450t
pleuritis, and systemic lupus erythematosus 627t
plexiform fibrohistiocytic tumor 1972–1973
plexiform neurofibroma *see* neurofibroma
plicated tongue *see* fissured tongue
PLOD3 gene 1596
plum 275t
plumboporphyria *see* aminolevulinic acid dehydratase deficiency porphyria
Pneumocystis jiroveci 1284, 1292, 2084
pneumonic plague 1214
Poaceae 277t
podagra *see* gout
podophyllin 1316, 2162
  adverse reactions 2155t
podophyllotoxin 1314t, 1316, 2162
  avoidance in pregnancy 1317
podoplanin 29t–33t, 1686, 1686t
podopompholyx *see* dyshidrotic eczema
POEMS syndrome 1115f, 1117, 1918t
  differential diagnosis 650t
  monoclonal gammopathy 2014t
  paraneoplastic 764t–765t, 766f
poikiloderma 4t–5t, 632
  of Civatte 577, 1053t, 1484, 2266
  Clericuzio-type with neutropenia 818t–819t
  congenital see Kindler syndrome
  see also individual conditions
poikiloderma congenitale *see* Rothmund-Thomson syndrome
poikiloderma vasculare atrophicans 158
poinsettia 278t, 287f
poison ivy 273, 274t, 282f
  allergic contact dermatitis 18f, 235f, 282t, 286f
  black spot dermatitis 285
  dermatitis 8
  and erythema multiforme 285, 285t, 320t
  nomenclature 273
  systemic contact dermatitis 246t
poison oak 274t, 282f, 282t, 285t
poison sumac 282, 282f, 282t, 285t
poisonwood tree 282t
Poland anomaly 1119
Poland syndrome 1673
polidocanol 2515t
poliglecaprone sutures 2354t, 2355
poliosis 1025–1026, 1046, 1047t
  differential diagnosis 1033t
  see also piebaldism
poly-L-lactic acid 1581t, 2554, 2556f
polyacrylamide hydrogel 1581t
polyalkylimide gel 1581t
polyamide "hair" implants 1574t, 1582, 1582f
polyarteritis nodosa 385t, 405–407, 673f
  clinical features 406–407, 406f
  differential diagnosis 407
  epidemiology 406
  and leukemia 2042t
  pathogenesis 406
  pathology 407, 407f
  renal disease 780t–781t
  treatment 407
polyarthritis 672t
polybutester sutures 2356, 2356t
polychlorinated biphenyls, and NMSC 1775t
polychlorinated dibenzodioxins 269
polycystic ovary syndrome 1121t, 1123, 1123f–1124f
polycythemia 764t–765t
polycythemia vera 753t
  and livedo reticularis 1748t
  and pruritus 112t, 118
polydioxanone sutures 2354t, 2355
polyester sutures 2356, 2356t
polyglactin sutures 2354t, 2355
polyglycerylmethacrylate 2481t
polyglycolic acid sutures 2354t, 2355
Polygonaceae 278t
polyiodide iodide 2515t
polymastia *see* supernumerary nipples
polymer films 2366t, 2369–2371, 2369t, 2370f
  advantages/disadvantages 2369–2371
  examples 2369
  uses 2369
polymer foams 2366t, 2369t, 2371, 2371f
polymerase chain reaction 66f, 66t
  real-time quantitative 69
  reverse transcription 68f, 68t
polymerases 66t, 605
polymethylmethacrylate microspheres 1581t, 2558–2559
polymorphic eruption of pregnancy 439–443
  clinical features 442, 442f–443f
  differential diagnosis 414t, 442–443
  epidemiology 441
  history 441
  pathogenesis 441–442
  pathology 442, 443f
  treatment 443
polymorphic light eruption 9, 1467–1469
  action spectrum 2203t
  clinical features 1467–1475, 1469f–1470f
    postinflammatory hyperpigmentation 1050t
  differential diagnosis 1469
  epidemiology 1467
  history 1467
  pathogenesis 1467–1468
  pathology 1469, 1470f
  treatment 1469
polymorphic locus 784t, 785f
polymorphic/malignant midline reticulosis *see* natural killer cell lymphoma, extranodal
polymorphism 794f
polymyxin B 2105t, 2107
  adverse reactions 2108
  dosage 2108t
  formulations 2108t
  as mast cell stimulant 2001t
  mechanism of action 2108t
  pregnancy and lactation 2108t
  trade names 2108t
polyploidy 791–792

Polypodium leucotomos see anapsos
polyposis, juvenile, with hereditary hemorrhagic telangiectasia 1713t
polypropylene sutures 2354f, 2356, 2356t
Polyskin II 2369
polytetrafluoroethylene, expanded 2555–2559
polythelia *see* supernumerary nipples
polythiazide 342f
polytrichia 1109
pomade acne 550
POMC polypeptide 1018f
pomegranate 2207t, 2490t
pompholyx *see* dyshidrotic eczema
Pontocaine *see* tetracaine
popliteal pterygium syndrome
  cleft lip/palate 1005t
  digital anomalies 1005t
  genetics 807t
popsicle panniculitis 1641t, 1655
  see also cold panniculitis
poradenitis inguinale *see* lymphogranuloma venereum
porcine collagen 2550, 2550f
PORCN 951
  see also Goltz syndrome
porcupine gene *see PORCN*
'porcupine man' *see* ichthyosis hystrix
porfimer sodium 2242
porocarcinoma 1846, 1846f–1847f
porokeratosis 1801–1803
  clinical features 1802–1803, 1802f
  differential diagnosis 1803
  disseminated superficial actinic 1801–1802, 1802f
  epidemiology 1801
  history 1801
  linear 955
  pathogenesis 1801
  pathology 1803, 1803f
  punctata palmaris et plantaris *see* punctate palmoplantar keratoderma
  punctate 1802f, 1803
  striata lichenoides *see* keratosis, lichenoides chronica
  treatment 1803
porokeratotic eccrine ostial and dermal duct nevus *see* PEODDN
poroma 1841–1842, 1842f
porphyria 709t, 717–727
  action spectrum 2203t
  acute 725–726, 726t
    acute intermittent porphyria 725
    aminolevulinic acid dehydratase deficiency porphyria 726
    differential diagnosis 726
    hereditary coproporphyria 726
    treatment 726
    variegate porphyria 725–726
  biochemical findings 720t
  classification 718t–719t, 720f
  epidemiology 717
  genetics 719t
  heme biosynthetic pathway 718f
  history 717
  hypertrichosis 1117t
  laboratory investigation 718
  neonatal 526t–528t
  non-acute 718–724
    congenital erythropoietic porphyria 723, 723f
    differential diagnosis 724
    erythropoietic protoporphyria 722, 722f
    hepatoerythropoietic porphyria 723, 723f
    porphyria cutanea tarda 718–722, 721f–722f
    pseudoporphyria 723–724, 723f, 724t
    treatment 724, 725t
    X-linked dominant protoporphyria 722–723
  pathogenesis 717–718
    acute porphyric attack 717–718
    cutaneous findings 717
  see also individual types
porphyria cutanea tarda 718–722, 719t, 721f–722f, 730
  biochemical findings 720t
  differential diagnosis 650t
  genetics 719t, 810t–811t
  HIV-related 1295
  hypertrichosis 1120f
  paraneoplastic 764t–765t
  treatment 725t
porphyria variegata 489, 725–726
port-wine stains 1713–1715, 1715f
  laser therapy 2263–2265, 2265f
  photodynamic therapy 2247–2248
posaconazole
  dosage 2121
  indications 1283t, 2120t
    aspergillosis 1283t
    candidiasis 1269t, 1283t
    cryptococcosis 1283t
    penicilliosis 1283t
    zygomycosis 1283t
  pregnancy and lactation 2120t
positional candidate genes 794
positional cloning 792
  and positional candidate genes 792
post-traumatic punctate intraepidermal hemorrhage *see* black heel and palm
posterior tibial nerve block 2351
postherpetic neuralgia 50
  pruritus in 112t
postinflammatory hyperpigmentation 1049–1050
  clinical features 1049–1050, 1050t, 1051f
  differential diagnosis 1050
  epidemiology 1049
  linear 1059–1060, 1060f–1061f
  pathogenesis 1049
  pathology 1050
  treatment 1050
postoperative complications 2467–2471
  bleeding/hematoma/ecchymosis 2467–2469, 2467f–2468f
  dehiscence 2469–2470, 2470f
  infection 2469, 2469f
  necrosis 2469, 2469f
  wound appearance 2470–2471, 2470f–2471f
postoperative (pressure-induced) alopecia 1096t, 1103
poststeroid panniculitis 1651t, 1652–1653
postzygotic mutation 945t
potassium dichromate 242t
potassium hydroxide 1314t
potassium iodide 1645t
  indications
    pyoderma granulosum 432t
    Sweet's syndrome 427
  saturated solution 1642, 2179
    adverse reactions 2169t, 2179
    contraindications 2179
    dosage 2179
    indications 2170t, 2179
    interactions 2179
    mechanism of action 2179
    monitoring 2167t–2168t
    pregnancy and lactation 2179
potassium permanganate 2162t
potassium titanyl phosphate lasers 2255t, 2262, 2262f
  skin penetration 2254f
  vascular lesions 2255, 2265t
potato 275t
Potentilla chinensis 2213
Pott, Percival 269, 1773
Pott's puffy tumor 1515t
povidone-iodine 2368t, 2383t
powders 2482–2483, 2483t
power 2063
poxvirus 1354–1357, 1355t–1356t
  HIV-related 1288
  see also individual infections
Prader-Willi syndrome 750
  genomic imprinting 791f
  piezogenic papules 1639
pramiconazole
  indications 2120t
  pregnancy and lactation 2120t
pramoxine
  prurigo nodularis 115
  pruritus 106t, 118t, 2157t
  stings 277
pravastatin 2191t
praziquantel 1419
prazosin
  adverse reactions, lichen planus 185t
  reflex sympathetic dystrophy 122t
preauricular fistula *see* ear pit
preauricular skin defects 1003t
preauricular tags *see* accessory tragi
prebiotics 2211
αβ precursor protein 700t
prednicarbate 245t, 2079t
prednisolone 245t
  indications
    bullous pemphigoid 483t
    urticaria 303, 304t
  pharmacology 2075
prednisolone suspension 2079t
prednisone 2075, 2078
  adverse reactions 2185t
    striae 1635
  indications
    B-cell lymphoma 2013
    Behçet's disease 432t
    bullous pemphigoid 483t
    dermatomyositis 639t
    hypereosinophilic syndrome 420–421
    pemphigus vulgaris 472t
    pyoderma granulosum 432t
    relapsing polychondritis 677
    Sweet's syndrome 427
    urticaria 303, 304t
  interactions 2192
  pharmacology 2076t
pregabalin, pruritus 106t
pregnancy dermatoses 439–448
  atopic eruption 440t, 444–445
  autoimmune progesterone dermatitis 447–448
  classification 440t
  fetal risk 441t
  intrahepatic cholestasis of pregnancy 440t, 443–445
  melasma 52, 1052–1054
  neonatal involvement 441t
  pemphigoid gestationis *see* pemphigoid gestationis
  physiologic changes of pregnancy 447, 447f, 447t
  polymorphic eruption 440t, 441–443
  pruritus 112t, 120, 446f, 447
  recurrence risk 441t
  see also individual conditions
pregnancy and lactation, drugs in
  acyclovir 2155t
  adalimumab 2145
  alefacept 2140
  amphotericin B 2118t, 2120t
  anakinra 2146
  antibacterial agents 2107–2108, 2108t
  antifungals 2123–2124
  antimalarials 2166
  antivirals 2126
  azathioprine 2171
  azelaic acid 2106t, 2155t
  bacitracin 2108t, 2155t
  benzoyl peroxide 2106t, 2155t
  butenafine 2118t
  butoconazole 2155t
  calcineurin inhibitors 2138
  calcipotriene 2155t
  carmustine 2160
  cephalosporins 2112
  ciclopirox 2155t
  clindamycin 2106t, 2115, 2155t
  clioquinol 2118t
  clotrimazole 2155t
  coal tar 2161
  cyclophosphamide 2173
  cyclosporine 2174
  dapsone 2106t, 2174–2175
  econazole 2118t
  erythromycin 2106t, 2155t
  erythromycin estolate 2114
  etanercept 2144
  5-fluorouracil 2160
  gentamicin 2108t
  hydroquinone 2155t
  hydroxyurea 2176
  imiquimod 2136
  immune globulin 2148
  infliximab 2145
  interferons 2134
  iodoquinol 2118t
  ketoconazole 2155t
  macrolides 2114
  mechlorethamine 2160
  methotrexate 2178, 2178t
  metronidazole 2106t, 2155t
  miconazole 2118t
  mupirocin 2108t, 2155t
  mycophenolate mofetil 2179
  naftifine 2155t
  neomycin 2108t
  nystatin 2155t
  omalizumab 2147
  oxiconazole 2155t
  penicillins 2111
  permethrin 2155t
  polymyxin B 2108t
  potassium iodide 2179
  quinolones 2116
  retapamulin 2108t, 2155t
  retinoids 2098t–2099t, 2099, 2102
  rituximab 2147
  sertaconazole 2118t
  sodium sulfacetamide 2106t
  sulconazole 2118t
  sulfonamides 2113
  tacrolimus 2179t
  terbinafine 2155t
  terconazole 2118t
  tetracyclines 2115
  thalidomide 2180
  tolnaftate 2118t
  topical medications 2154, 2155t
  tretinoin 2155t
  undecylenic acid 2118t
  ustekinumab 2146
  see also individual drugs
pregnancy tumor *see* pyogenic granuloma
preimplantation genetic diagnosis 63, 822
prekallikrein 361
premature aging syndromes 818t–819t
  acrogeria 838t, 863–864
  Cockayne syndrome 1462t, 1476t–1477t, 1478
  Kindler syndrome 1479
  Rothmund-Thomson syndrome 1476t–1477t, 1479
premature infants, skin features 58t
prenatal diagnosis 63, 822
preoperative assessment 2459–2463, 2461f
  allergies 2463
  defibrillators and pacemakers 2462–2463
  informed consent 2463
  potential for bleeding 2459–2461
  prophylactic antibiotics 2461–2462, 2462t
  wound healing 2461, 2462t
prepubertal hypertrichosis 1116
pressure dressings 2367f
pressure ulcers 1741–1744
  classification 1743f
  clinical features 1742, 1742f
  distribution 1741f
  pathogenesis 1742
  pathology 1742
  treatment 1742–1744
prevalence of skin diseases 2059
Prevelle Silk 2548t–2549t
Prevotella intermedia 1152
prick to prick test 268
prickly heat *see* milaria
prickly lettuce 277t
prickly pear 274t, 277t

prilocaine 2344t
  cardiac toxicity 2346
prilocaine/lidocaine 2346, 2347t
  adverse reactions 2155t
  see also EMLA
Primacol 2373
primary biliary cirrhosis, cutaneous manifestations 774t
primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma 2020t, 2029–2033, 2029f, 2034f
primary cutaneous anaplastic large cell lymphoma 2029–2030
  clinical features 2029–2030, 2030f
  definition 2029
  differential diagnosis 2020t
  epidemiology 2029
  genetic features 2030
  immunophenotype 2030
  pathology 2030, 2030f
  treatment 2030
primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma 2020t, 2034
primary cutaneous γ/δ T-cell lymphoma 2034
primary hamartomatous-neoplastic mucinoses 697
primary immunodeficiencies 899–923, 900t, 901f
  ataxia telangiectasia *see* ataxia telangiectasia
  cartilage-hair hypoplasia 904
  Chédiak-Higashi syndrome 900t, 904–905, 906t
  chronic granulomatous disease 900t, 908–911
  chronic mucocutaneous candidiasis 900t, 902–904
  complement disorders 900t, 905–908
  hyper-IgE syndrome 533, 900t, 911–915
  hyper-IgM syndrome 900t, 915b, 918f
  immunoglobulin deficiency disorders 915, 917t
  IPEX syndrome 818t–819t, 904, 915
  laboratory tests 901t
  leukocyte adhesion deficiency 900t, 912t, 915–919
  severe combined immunodeficiency (SCID) 900t, 919–921
  Wiskott-Aldrich syndrome 173t–174t, 900t, 921–922
  X-linked agammaglobulinemia 900t, 915, 916f
primary intention healing 2315, 2315f
primary (localized) cutaneous amyloidosis 702–705
  clinical features 702–703, 702f–703f
  differential diagnosis 703
  pathology 703
  treatment 703–705, 703t
primary small cell carcinoma of skin *see* Merkel cell carcinoma
primary systemic amyloidosis 705–707, 776t–778t
  clinical features 705–706, 705f–706f
  renal disease 780t–781t
  differential diagnosis 706
  pathology 706, 707f
  treatment 707
primidone 2189t
  adverse reactions
    cutaneous lymphoid hyperplasia 2039t
    gingival hyperplasia 1156t
Primula obconica 287f, 288
PRKDC deficiency 920t
pro-opiomelanocortin (POMC)-derived peptides 96
probenecid 711
  dystrophic calcification 730
  interactions 2127t
probiotics 2211
probiotics, atopic dermatitis 213t
probucol 1554t–1555t
procainamide-induced lichen planus 185t
procaine 2344t
procaine penicillin, syphilis 1379t
procerus muscle 2335
processionary caterpillars 1441t
prochlorperazine 336t
  adverse effects, phototoxicity 1480t
procollagens 1585–1586
proctalgia fugax 122t
Procuren 2374
ProCyte Transparent Film Dressing 2369
profilaggrin 2317
profound proteinase inhibitor deficiency (PiZZ) 1647
progeria 776t–778t
progeria syndrome *see* Hutchinson-Gilford progeria syndrome
progeria-type syndrome 1672–1673
progesterone
  autoimmune progesterone dermatitis 447–448
  lichen sclerosus 667t
  morphea 667t
progestins, and acne 550t
prognosis 2060t
progressive capillary hemangioma *see* tufted angioma
progressive cribriform and zosteriform hyperpigmentation *see* linear and whorled nevoid hypermelanosis
progressive hemifacial atrophy *see* Parry-Romberg syndrome
progressive macular hypomelanosis 1046, 1046f
progressive multifocal leukoencephalopathy 1288t–1289t, 2140t, 2178
progressive nodular histiocytoma 1530t–1531t
  antigenic markers 1533t
progressive osseous heteroplasia 734
  genetics 818t–819t
progressive symmetric erythrokeratoderma *see* acrogeria
proguanil 2190t
proinflammatory mediators 292–293
prolidase deficiency 810t–811t
proliferating cell nuclear antigen 607t, 1088f
proliferating epidermoid cysts 1821
proliferating follicular cystic neoplasm *see* proliferating trichilemmal cyst
proliferating pilar tumor 1838–1839
  clinical features 1838
  pathology 1838, 1838f
  treatment 1839
proliferating trichilemmal cyst 1821
proliferative verrucous leukoplakia 1161
proline-rich proteins 825–826
promethazine-induced photoallergy 1480t
Promiseb cream 2156
propafenone 2186t
proparacaine 2345t
properdin 909t
prophylactic antibiotics
  Mohs surgery 2451
  preoperative 2461–2462, 2462t
Propionibacterium spp.
  chronic granulomatous disease 910t
  in sebaceous follicles 542, 544f
Propionibacterium acnes 543t, 544f, 546, 1046, 1187t, 2095
Propionibacterium avidum 1187t
Propionibacterium (*Corynebacterium*) *acnes* 219
Propionibacterium granulosum 544f, 1187t
Propionibacterium parvum 544f
propionic acidemia 749f
propofol, cholestatic pruritus 119t
propolis 2207t
  dermatitis 1509t, 2213f
propoxyphene
  abuse 1513, 1514t
  adverse reactions 336t
propranolol
  adverse reactions, lichen planus 185t
  indications
    hyperhidrosis 594t
    infantile hemangioma 1706, 1707t
propylene glycol 242t, 255, 2155t, 2479
propylthiouracil
  and acne 550t
  and secondary cutaneous vasculitis 390t
prostaglandins 2315t
  in vitiligo 1030
prostaglandin D_2 1995f
prostaglandin E_1 101, 101t
  hypertrichosis 1118t
prostaglandin E_2 101t, 2220
prostanoids 104
prostate cancer, cutaneous metastases 2049t, 2053t
prostate-specific antigen 29t–33t
Proteaceae 277t
protease defects 800t–801t
protease inhibitors
  defects 800t–801t
  interactions 2191t
proteases in wound healing 2322
protein C 360
  activated 364t
  deficiency 818t–819t, 1744t
protein C/S disorders 377–379
  neonatal purpura fulminans 378
  pathogenesis/clinical features 378–379
  purpura fulminans postinfection 378–379
  purpura fulminans with sepsis 378
  warfarin necrosis 378, 378f
protein contact dermatitis *see* contact urticaria
protein S 360
  see also protein C/S disorders
protein S deficiency 1744t
  genetics 818t–819t
protein-energy malnutrition 738t, 739–740, 739f–740f
protein-tyrosine phosphatase defects 800t–801t
proteinase-activated receptor-2 102f–103f
proteinases 101
proteinuria, systemic lupus erythematosus 627t
proteoglycans 1592t
proteome 70–71
proteomics 70–71, 72f, 73t
Proteus spp., chronic granulomatous disease 910t
Proteus syndrome 958–959, 1984
  clinical features 958, 958f, 1717, 1717f
  digital anomalies 1005t
  differential diagnosis 958–959
  genetics 958
  history 958
  pathogenesis 958
  pathology 958
  treatment 959
Proteus vulgaris 1516, 2107
proteus-like syndrome 814–815, 958
prothionamide, tuberculosis 1234t
prothrombin G20210A 1744t
prothrombin time 361, 2459
proto-oncogenes 67, 69
protoanemonin 278t
proton pump inhibitors, interactions 2124t, 2190
protoporphyrin IX 2239f–2240f
Prototheca wickerhamii
protothecosis 1266–1267
protozoal diseases 1391–1406
  cutaneous diseases caused by amoebae 1397–1399
  amebiasis 1397–1398
  Balamuthia mandrillaris 1398–1399
  leishmaniasis *see* leishmaniasis
  toxoplasmosis 1404–1406
  trypanosomiasis 1399–1404
protriptyline, and eccrine sweating 590t
Prox1 1686t
Pruclair cream 2156
PruMyx cream 2156
Prunus armeniaca see apricot
Prunus domestica see plum
Prunus persica see peach
prurigo gravidarum *see* cholestasis of pregnancy
prurigo nodularis 114–115, 1633t
  and anetoderma 1633t
  and atopic dermatitis 207f
  and peripheral neuropathy 2180
  pruritus in 114–115, 115f
prurigo pigmentosa 1064, 1065t
prurigo of pregnancy *see* atopic eruption of pregnancy
prurigo simplex 10t–11t, 1604t
pruritic folliculitis of pregnancy 439
pruritic urticarial papules/plaques of pregnancy *see* polymorphic eruption of pregnancy
pruritus 50, 99–101
  anogenital 116–117
  aquagenic 116, 116t
  chronic 105, 105t
    central sensitization 105
    peripheral sensitization 105
    vs chronic pain 105t
  definition 111
  in dermatologic disease 113–114
    cutaneous T-cell lymphoma 114
    infections 113t
    infestation 113, 113t
    inflammatory dermatoses 113–114, 113t
  and drug abuse 1514t
  epidemiology 111, 112t
  examination 112–113, 112f
  history 112, 112t
  impaired skin barrier function 105
  laboratory investigation 113, 113t
  mediators 101–105, 101t
    gastrin-releasing peptide 101
    histamine 101
    immune cells 104–105
    neurotransmitters 104
    neurotrophins 104
    opioid peptides 101–103
    peptidases 104
    prostanoids 104
    proteinases 101
    substance P 103–104
    transient receptor potential receptor activation 104
  murine models 103t
  pathophysiology 99–101
    central pathways 100, 102f–103f
    pruritus receptor units 100–101
  patient evaluation 111–113
  pharmacologic 120, 120t
  postburn 117
  in pregnancy 120, 446f, 447
  prevalence 112t
  psychogenic 120
  scalp 117
  in scars 117
  senescent skin 105
  in systemic disease 117–120
    cholestatic pruritus 118, 119t
    endocrine pruritus 119
    hematologic pruritus 118
    HIV/AIDS 119–120
    malignancy 118–119
    renal pruritus 117–118, 117f, 118t, 775
  treatment 105–107, 123, 2156
    behavioral therapy 107
    cutaneous field stimulation 105–107
    non-pharmacologic 105–107
    pharmacologic 105, 106t, 2157t
    phototherapy 124, 2222–2223
    psychological 124
    systemic 124
    topical 123
  see also dysesthesias
pruritus ani 116
pruritus vulvae/scroti 116–117
pruritus/prurigo gravidarum *see* intrahepatic cholestasis of pregnancy
psammoma bodies 998, 1946t
Pseudallescheria boydii 1271t
pseudarthrosis 927t, 930
pseudo-Hutchinson's sign 2443t

pseudo-Kaposi's sarcoma *see* acroangiodermatitis
pseudoacanthosis nigricans, and drug abuse 1514t
pseudoainhum *see* amniotic band syndrome
pseudoaneurysm, and drug abuse 1514t, 1519
pseudocatalase 1025t
  with NB-UVB 1030
pseudocellulitis 1196t
pseudocyst of auricle 1827–1828, 1827f
pseudodominant inheritance 788f
pseudoephedrine, adverse reactions 338t
pseudoepitheliomatous hyperplasia 18–19
pseudoerysipelas 223
pseudofolliculitis barbae 572f, 579–581, 827, 832t–833t, 1580
  clinical features 580, 580f
  differential diagnosis 580
  epidemiology 580
  pathogenesis 580, 580f
  pathology 580
  treatment 580–581, 580t–581t
pseudogout 711–712
pseudogynecomastia, liposuction for 2527t, 2531
pseudohypopigmentation 2499
pseudoichthyosis 222f
pseudoinflammatory nail changes 1140
pseudolymphoma 414t
  drug-induced 347–348
  radiotherapy 2294
pseudomamma *see* supernumerary nipples
pseudomelanoma *see* melanocytic nevus, recurrent
pseudomonal pyoderma 1206, 1206f
Pseudomonas spp. 1450t, 1514t
  chronic granulomatous disease 910t
Pseudomonas aeruginosa 1206–1207, 1515t
  blastomycosis-like pyoderma 1206
  ecthyma gangrenosum 375, 1207, 1207f
  green nail syndrome 1134, 1206, 1206f
  hot tub folliculitis 574f, 1206–1207
  neonates 524t–528t
  otitis externa 1206
  panniculitis 1658t
  pseudomonal pyoderma 1206, 1206f
  pseudomonas hot-foot syndrome 1207, 1207f
Pseudomonas cepacia 375
Pseudomonas fluorescens 2107
Pseudomonas hot-foot syndrome 1207, 1207f
  in athletes 1507t
Pseudomonas maltophilia 375
pseudopelade of central scalp *see* central centrifugal cicatricial alopecia
pseudoporphyria 723–724, 723f, 724t, 1469, 1481
  drug-induced 341, 724t
  and rheumatoid arthritis 762f
pseudopyogenic granuloma *see* angiolymphoid hyperplasia with eosinophilia
pseudorheumatoid nodule *see* sgranuloma annulare
pseudosarcomatous fibromatosis *see* nodular fasciitis
pseudoscleroderma panniculitis, radiation-induced 2299t
pseudosyndactyly 506, 508f
pseudotail 1001t
pseudotumor cerebri 2085
pseudovasculitis 20–21
pseudoxanthoma elasticum 730, 1593t, 1595, 1612–1615, 1632t
  clinical features 1612–1615, 1613f–1614f
    angioid streaks 1614
    cardiovascular disease 776t–778t, 1614
    gastric hemorrhage 773t–774t
  differential diagnosis 1614t, 1615
  epidemiology 1612
  genetics 1612
  history 1612
  pathogenesis 1612, 1613f
  pathology 1615, 1615f
  perforating 1600t, 1613
  treatment 1615t
pseudoxanthoma elasticum-like papillary dermal elastolysis 1632t
psoralens 2224–2225
  adverse reactions
    acne 550t
    hyperpigmentation 1056t–1057t
    nail changes 1141t
    phototoxicity 278t
  DNA cross-linking 2226f
  molecular structure 2225f
  and NMSC 1775t
  photochemistry 2225
  phototherapy *see* PUVA phototherapy
  vitiligo 1029
psoriasiform alopecia 1096t, 1103–1104
psoriasiform dermatitis, pattern analysis 18–19, 19f
psoriasiform dermatitis-microcephaly-developmental delay 803t–804t
psoriasiform hyperplasia 178, 1806
psoriasiform mucositis 1149–1150
psoriasin 83t
psoriasis 3t–4t, 8, 47t, 135–156
  anogenital 141f, 1177, 1177f
  Area and Severity Index 142t
  associations 145–147
    with cancers 146
    with infections 146
    with internal diseases 146–147
    with skin diseases 145–146
  childhood 141f, 155
  chronic plaque disease 139–140, 140f
  clinical features 139–147, 776t–778t
    acrodermatitis continua of Hallopeau 142, 143f
    oral mucosa 143
    postinflammatory hyperpigmentation 1050t
    pruritus 112t, 114
    psoriatic arthritis 144, 145f
    pustulosis of palms and soles 141–142, 143f
  dermoscopy 38f
  differential diagnosis 147, 147t, 228t, 308t–310t, 639t
  disorders related to 144–145
    inflammatory linear verrucous epidermal nevus 144
    reactive arthritis 144–145, 146f
    Sneddon-Wilkinson disease 145, 146f
  distribution 9
  drug-induced 139, 352f, 353
  epidemiology 135–136
  erythrodermic 139–142, 175, 175f, 178–179
  flexural 143, 144f
  generalized pustular 140–141
    annular pattern 141, 143f
    exanthematic type 141
    'localized' pattern 143f
    von Zumbusch pattern 140–141, 142f
  genetics 135–136, 136t
    functional genomic studies 136
    genome-wide association studies 136
    HLA studies 135–136
    linkage studies 136t
  guttate 139–140, 142f
  history 135
  HIV-related 139, 1294, 1294f
  immunopathogenesis 137–139, 138f
    cytokines and chemokines 137
    epidermal keratinocytes 137–139
    innate immunity 137–139
    T cells and dendritic cells 137
  infantile 221
  interferon-induced flare 139
  inverse 144f
  linear 956, 956f
  nail bed 144, 144f, 2440t
  nails in 144, 145f, 1130f–1131f, 1136, 1136f, 1137t
  palmoplantar 141f
  pathogenesis 137–139
  pathology 147–148, 148f
    papulosquamous lesions 147–148
    pustular psoriasis 148
  pustular 20f, 308t–310t
  scalp 142–144
  treatment 148–155
    anthralin 149–150, 149t
    biologic therapies 152–154, 153t
    combined 154–155
    corticosteroids 148–149, 149t
    cyclosporine 151, 152t
    laser therapy 150, 2279
    methotrexate 150, 151t
    photochemotherapy 150, 150t, 154
    photodynamic therapy 2247
    phototherapy 2220f, 2221
      PUVA 2228, 2229f
      UVB 2221
    retinoids 150–152, 150t, 152t, 2093–2095, 2095f
    TCM 2213–2214
    topical agents 154
    vitamin D_3 analogues 148, 149t
  triggering factors 139
    alcohol consumption, smoking and obesity 139
    drugs 139
    endocrine factors 139
    external 139
    HIV 139
    infections 139
    psychogenic stress 139
Psoriasis Area and Severity Index 2060
psoriatic arthritis 144, 145f, 672t
  classification 144
  sites of involvement 145f
psoriatic erythroderma 175, 175f
  pathogenesis 178–179
Psoroptidae 1445t
psychocutaneous diseases 127–134
  acne excoriée 132, 132f
  body dysmorphic disorder 129–130, 130t
  classification 128f
  delusions of parasitosis 127–129, 128f, 128t
  dermatitis artefacta 130–131, 130f
  neurotic excoriations 131–132, 131f, 131t
  overview 127, 127f
  treatment 133–134
    non-pharmacologic 134
    pharmacologic 133–134
  trichotillomania 132–133, 132f–133f
  see also lichen simplex chronicus; prurigo nodularis
psychodermatology *see* psychocutaneous diseases
psychogenic pruritus 120
psychogenic purpura *see* Gardner-Diamond syndrome
psychogenic stress, and psoriasis 139
psychosis
  glucocorticoid-induced 2085
  SLE 627t
  treatment 134
psyllium 2212t
PTCH gene 1766
  mutations 1767–1768
PTCH protein product 1766
PTEN hamartoma tumor syndrome 816t, 1725
PTEN mosaicism 953t, 954
pterygium colli medianum 998
pterygium inversus unguis 1140
Pthirus pubis see crab lice
pubic lice *see* crab lice
public health 2057–2064
  clinical trials 2060, 2060t
  in dermatology 2057, 2057t
  diagnosis 2057f
  epidemiology 2057, 2057t
    and cause of disease 2058–2060
    genetic 2061
    systematic reviews 2060–2061
  health services research 2061–2062
    observational studies 2057–2060
      case-control 2058–2059, 2058t
      cohort 2058t, 2059, 2059f
      confounding 2058, 2059f
      cross-sectional 2058t, 2059–2060
      descriptive 2057–2058, 2058t
      participants 2058t
      randomized controlled trials 2058t
    research opportunities 2063
    study design/review 2062, 2062t
Pulex irritans 1439, 1440f, 1440t
pulling boat hands 1495t
pulmonary disease 635, 778t–779t
pulmonary hypertension
pulsed dye lasers 2255t, 2261–2262
  "footprinting" 2266f
  infantile hemangioma 1706–1707
  keloids 1625t
  sarcoidosis 1563t
  skin penetration 2254f
  vascular lesions 2255, 2265t
punch biopsy 13, 2382, 2382t, 2389–2390, 2390f, 2390t
punctate hyperknesis 105
punctate palmoplantar keratoderma 872, 876f, 882–883, 882f
Punica granatum see pomegranate
purine nucleoside phosphorylase deficiency 920t
purple coneflower 2192t
purple lesions 6t–7t
purpura 2, 5, 357–367
  actinic (solar) 358f
  differential diagnosis 359t, 361f
  and drug abuse 1514t
  granulomatous pigmented 365t
  idiopathic thrombocytic *see* idiopathic thrombocytic purpura
  lichenoid pigmented 184t
  linear pigmented 365t
  macular 359t
  palpable 358f, 359t
  psychogenic *see* Gardner-Diamond syndrome
  retiform *see* retiform purpura
  small vessel vasculitis 387f
  thrombotic thrombocytopenic *see* thrombotic thrombocytopenic purpura
  time course 357
  Waldenström's hypergammaglobulinemic 363–365
purpura annularis telangiectoides 308t–310t
  of Majocchi 365t, 366f
  see also telangiectasias
purpura fulminans 8–11
  neonatal 378, 526t–528t
  postinfectious 378–379
  of sepsis 378
purpura pigmentosa chronica *see* pigmented purpuric eruptions
purpura pigmentosa progressiva *see* pigmented purpuric eruptions
purpura rheumatica *see* Henoch-Schönlein purpura
purpura simplex *see* pigmented purpuric eruptions
purse-string sutures 2426
Purtox *see* botulinum toxin
puss caterpillar 1440f
pustular and acneiform irritant contact dermatitis 252
pustular dermatoses, pattern analysis 19, 20f
pustular psoriasis 20f, 308t–310t
  neonates 524t–525t
pustular vasculitis 385
pustules 3t–4t
pustulosis
  acute generalized exanthematous 519t
  of palms and soles 228t
PUVA phototherapy 2224–2233, 2238t
  and acrobullous dermatosis 521
  action spectrum and light sources 2225, 2226f

adverse reactions 2232–2233, 2232f
laboratory data 2232
long-term risks 2232–2233
ophthalmologic 2232
clearing phase 2227
combination therapy 2228–2229
diseases responsive to 2219–2223
history 2224
in HIV patients 2233
indications
alopecia areata 1103t, 2231
atopic dermatitis 214–215, 2231
graft-versus-host disease 2231
granuloma annulare 2231
IgA pemphigus 473
irritant contact dermatitis 258
lichen planus 195t, 196, 2231
mastocytosis 2231
mycosis fungoides 2229–2230, 2230f
parapsoriasis 159t
photodermatoses 2231–2232
pityriasis lichenoides 162t, 2231
pityriasis rubra pilaris 2231
psoriasis 2228, 2229f
scleroderma 2231
urticaria pigmentosa 2231
vitiligo 2230–2231
lentigo 1854
and linear IgA bullous dermatosis 498t
maintenance phase 2227–2228
photosensitivity 2225–2227
psoralens *see* psoralens
topical (paint) 1029
treatment protocols 2227, 2227t–2228t, 2228f
bath PUVA 2227
oral PUVA 2227
topical PUVA 2227
PUVASOL phototherapy 1029
pycnogenol 2490t
Pyemotes tritici 1445t
Pyemotes ventricosus 1445t
Pyemotidae 1445t
pyocyanin 1132, 1134, 1138t
pyoderma 524t–525t
blastomycosis-like 1206
pseudomonal 1206, 1206f
pyoderma faciale 561, 565f
pyoderma fistulans significa *see* hidradenitis suppurativa
pyoderma gangrenosum 427–431
associated diseases 430
clinical features 428–430, 428t, 429f–430f
clinical variants 428t
differential diagnosis 430–431, 431t
drug-induced 344
epidemiology 428
history 428
inflammatory bowel disease 771f
and leukemia 428, 430, 2040t
monoclonal gammopathy 428, 2014t
neonates 526t–528t, 535
pathogenesis 428
pathology 430, 430f
peristomal 772t
treatment 424, 431
immune globulin 2148t
ulceration 1745t
vesiculobullous form
pyoderma granulosum 681–682, 682f
pyoderma vegetans *see* pyostomatitis vegetans
pyogenic arthritis, and drug abuse
pyogenic granuloma 1922–1923
clinical features 1923, 1923f
differential diagnosis 1923
epidemiology 1923
nail bed 1144, 2440t
pathogenesis 1923
pathology 1923, 1924f
periungual 1141t
in pregnancy
treatment 1923
laser therapy 2267
pyomyositis 1198
and drug abuse 1515t
pyostomatitis vegetans 424, 429f, 1168
pyrazinamide, indications, tuberculosis 1234t
pyrethrin, head lice 1428–1429, 1428t
pyrethrum 285t
pyridostigmine, and eccrine sweating 590t
pyridoxine-induced pseudoporphyria 724t
pyrimethamine-induced lichen planus 185t
pyrimidine dimers 1460
pyrimidine-pyrimidone 6,4-photoproduct 1459f
pyrin 673f
pyrin defects 806–808
pyriproxyfen 1440
pyrithioxin, adverse reactions, lichen planus 185t
Pyrus communis see pear

18q deletion syndrome 1009
Q fever 1244t, 1246t, 1250
Q-switched lasers 2251, 2255t
Qat 1517
quadratus labii superioris muscles 2335
quadrichrome vitiligo 1026
quality of life 2061–2062
quasidominant inheritance 789
quaternary ammonium salts 253t–254t
quaternium-15 hypersensitivity 241t, 244
Queensland tick typhus 1244t, 1246t
Quercus alba see white oak bark
quetiapine
adverse reactions 129t
psychosis 134
Quie syndrome *see* chronic granulomatous disease
Quinaband 2369
quinacrine
adverse reactions
hyperpigmentation 1056t–1057t
lichen planus 185t
hypohidrosis/anhidrosis 595t
lupus erythematosus 627–628, 628t
quinidine
adverse reactions
acne 550t
lichen planus 185t
photoallergy 341
phototoxicity 1480t
secondary cutaneous vasculitis 390t
interactions 2124t, 2190
quinine
adverse reactions
lichen planus 185t
photoallergy 1480t
secondary cutaneous vasculitis 390t
quinolones 2105t, 2116, 2116t
adverse reactions 2116
photoallergy 1480t
secondary cutaneous vasculitis 390t
systemic contact dermatitis 246t
contraindications 2116
dosage 2116
indications 2116
interactions 2116, 2193
mechanism of action 2116
pregnancy and lactation 2116
routes of administration 2116t
sites of action 2109t
see also individual drugs
quintan fever 1209t
quinupristin-dalfopristin 2117t
indications, MRSA 1191t

R115777 1887t
rabbit fever *see* tuleremia
rabies 1361, 1362f, 1450
Rac2 deficiency 912t
racquet thumbs (brachyonychia) 1130f, 1135
radial dysplasia 1002t
radiation acne 552–553
radiation dermatitis 1491f
radiation therapy *see* radiotherapy
radiation ulcer 1745t
radiation-induced drug reactions 349t
radiation-induced morphea 663
radiation-induced panniculitis 1656t
Radiesse 2548t–2549t, 2555
radiofrequency skin resurfacing 2257–2258, 2258f, 2277–2278
radioimmunoassay 1348t
radiotherapy 2291–2301
acute reactions 2299, 2300f
adjuvant 2295–2296
adnexal carcinomas 2298
advantages 2292–2293
angiosarcoma 2297
basal cell carcinoma 2294–2295, 2294f–2295f
benign skin disorders 2293–2294
brachytherapy 2292
cutaneous lymphoma 2298
cutaneous malignancies 2294, 2294f, 2294t
depth dose of electron beams 2292f–2293f
disadvantages 2293
diseases induced by 2299, 2299t
dosage 2291, 2293f
dose fractionation 2297, 2297t
electrons 2292, 2292f
future trends 2300
Grenz ray treatment 2292
hypertrophic scars/keloids 1625t
indications 2291–2293
Kaposi's sarcoma 2297–2298, 2298f
late reactions 2299, 2299t, 2300f
low-energy photons 2292
mechanism of action 2291
Merkel cell carcinoma 2297
mycosis fungoides 2023, 2298
NMSC 1791
office-based 2292
palliation 2298–2299, 2299f
physics 2291–2292
squamous cell carcinoma 2295–2297, 2296f
adjuvant 2296
definitive 2295–2296
special situations 2296–2297
terminology 2291
treatment machines 2291
younger patients 2299
radish 278t
Radix angelicae pubescentis 2214
Raeder's syndrome 590–591
raf 1761t
RAF-265 1887t
RAG-2 2319–2320
ragweed 286
railroad tracking 2471, 2471f
raltegravir, adverse reactions 1299t
Ramazzini, Bernardino 249
RAMBAs 2093
randomized controlled trials 2058t
ranibizumab 2149t
ranitidine 303, 304t, 2191t
RANTES 411
in atopic dermatitis 204t
ranula *see* mucocele
Ranunculaceae 278t
Ranunculus spp. *see* buttercups
rapamycin *see* sirolimus
Raphanus sativus see radish
rapidly involuting congenital hemangioma 1693
Rapp-Hodgkin syndrome 809t
anhidrosis 595t
genetics 808t
see also ankyloblepharon-ectodermal dysplasia-clefting syndrome
ras proto-oncogene 1761, 1761t
RAS-ERK pathway defects 808–809
RAS-MAPK pathway defects 800t–801t, 814f
rasburicase 711
rash 13f
butterfly 112, 115f, 618f, 620–621, 621f
discoid 627t
heat *see* miliaria
malar 620–621
see also miliaria; urticaria
RAST tests 340
rat-bite fever 1213
Ravensara aromatica 2215t
Raynaud's disease 647
Raynaud's phenomenon
clinical and laboratory features 644t
differential diagnosis 271, 647t, 1495t
patient evaluation 648f
primary *see* Raynaud's disease
scleroderma 644t, 647, 647f–648f, 647t
treatment 651
ulceration 1745t
razaxaban 364t
razor bumps *see* pseudofolliculitis barbae
Rb 1761t
re-epithelilization 2318f
reactive angioendotheliomatosis 1916–1917, 1918f
reactive arthritis 144–145, 146f
differential diagnosis
HIV-related 1294
reactive oxygen species 1459–1460
reactive perforating collagenosis
clinical features 1600, 1600f
pathology 1603f
Rebif 2132t
recall bias 2059
Recothrom 2464t
RecQ DNA helicase defects 800t–801t
recurrent aphthous stomatitis 1158–1159, 1158f
clinical features 1158, 1158f
epidemiology 1158, 1158t
pathology 1158
treatment 1158–1159, 1159t
recurrent melanocytic nevus 1877–1878, 1878f
recurrent respiratory papillomatosis 1311
recurrent toxin-mediated perineal erythema 1183
red clover 2212t
red man syndrome *see* erythroderma
reducing agents, mechanisms of toxicity 250t
5α-reductase 1093f
reed dermatitis 1509t
Reed syndrome 813t, 1980t
Reed-Sternberg cells 2044
reflectance confocal microscopy
basal cell carcinoma 1788
squamous cell carcinoma 1783
reflex cold urticaria 298
reflex sympathetic dystrophy 122f
differential diagnosis 650t
stages of 122t
treatment 122t
Refsum disease 838t, 862
genetics 803t–804t
Regranex 2374
regulatory T cells (Tregs) 91–92
Rehmannia glutinosa 2213
Reiter's disease *see* reactive arthritis
relapsing linear acantholytic dermatosis 954
relapsing polychondritis 675–677
autoantigens 1596t
clinical features 676, 676f, 775f, 776t–778t
differential diagnosis 677
epidemiology 676
history 675
pathogenesis 676
pathology 676–677
treatment 677
relative risk 2058–2059
Release 2467
Reloxin *see* botulinum toxin
remnant removal disease 1549t
renal cell carcinoma 29t–33t
cutaneous metastases 2051f
and flushing 1750t
renal crisis in scleroderma 643, 647
renal cysts 936t, 938
renal disease 112t, 780t–781t
and metastatic calcification 731–732, 731f
renal failure 671, 711
and metastatic calcification 731, 731f
renal involvement, SLE 627t

renal pruritus 112t, 117–118, 117f, 118t
Rendu-Osler-Weber syndrome *see* hereditary hemorrhagic telangiectasia
rengas tree 282t
reparative processes 2313
repetin 825–826
RepliCare 2373
replicative potential 1763–1764
reserpine, reflex sympathetic dystrophy 122t
reslizumab 421
Resnia boswelliae 2214
Resoplast 2550
respiratory burst 83
respiratory chain defects *see* mitochondrial disorders
Reston 2371
  differential diagnosis 652t
  genetics 807t
  neonates 526t–528t, 536
Restylane 2548t–2549t, 2553–2554
Restylane Fine Line 2548t–2549t, 2553–2554
Restylane-L 2548t–2549t
resveratrol 2207t
retapamulin 2107
  dosage 2108t
  formulations 2108t
  indications
    impetigo 1189t
    leg ulcers 1735–1736
  mechanism of action 2108t
  pregnancy and lactation 2108t, 2155t
  trade names 2108t
reticular dysgenesis 920t
reticular erythematous mucinosis 695, 695f
reticular veins 2516t
  treatment 2515–2517
    sclerosing solution 2514t
reticulata symmetrica faciei 1638
reticulate acropigmentation of Kitamura 1065t, 1071
reticulate genital hyperpigmentation 1065t
reticulate hyperpigmenation of Iijima, Naito and Uyeno *see* linear and whorled nevoid hypermelanosis
reticulate and zosteriform hyperpigmentation *see* linear and whorled nevoid hypermelanosis
reticuloendotheliosis *see* histoplasmosis
reticulohistiocytosis 1541–1542
  antigenic markers 1533t
  clinical features 1530t–1531t, 1541, 1542f
  congenital self-healing *see* Hashimoto-Pritzker disease
  differential diagnosis 1542
  epidemiology 1541
  history 1541
  multicentric *see* multicentric reticulohistiocytosis
  pathogenesis 1541
  pathology 1541–1542, 1542f
  treatment 1542
retiform hemangioendothelioma 1931
retiform parapsoriasis *see* parapsoriasis
retiform purpura 9f, 357, 358f, 376f, 1495t
  differential diagnosis 360t
  drug-induced 1518t
  examination of lesions 357
  hematoma-associated 383
  inflammatory 361
  non-inflammatory 360–361
retinal hamartoma 937f
retinal pigment epithelium, in pseudoxanthoma elasticum 1614f
retinaldehyde 2090f
  formulations 2098t
retinitis pigmentosa 841t–842t
retinoic acid 2090f
  metabolism blocking agents (RAMBAs) 2093
retinoic acid receptors 2089
retinoid embryopathy 2099t
retinoid receptors 2090–2091
retinoid X receptors 2089–2090
retinoids 2089–2103
  adverse reactions 2098–2102, 2099t–2100t
    alopecia 348t
    bone toxicity 2099–2101
    CNS and psychiatric 2101
    dyslipidemia 2101–2102
    gastrointestinal 2101
    hematologic 2102
    hypothyroidism 2101
    liver toxicity 2102
    muscle 2101
    nail changes 1141t
    ophthalmologic 2101
    pruritus 120t
    renal 2101
    skin and mucous membranes 2099, 2100f
  biologic functions 2090t
  chemistry 2090f
  contraindications 2098
  dosage 2098
  formulations 2098t
  indications 2093–2094, 2094t
    acne vulgaris 555t–556t, 2093, 2095–2096, 2096f
    chronic hand eczema 2096
    cutaneous T-cell lymphoma 2096, 2097t
    Darier disease 2096
    dermatomyositis 639t
    human papillomavirus 1317
    hypertrophic scars/keloids 1625t
    ichthyosis 2096, 2097f
    lichen planus 195t
    lichen sclerosus 667
    lupus erythematosus 628, 628t, 2097–2098
    mycosis fungoides 2024–2025
    perforating disease 1604t
    photoaging 2093
    pityriasis rubra pilaris 165, 2097, 2098f
    premalignant/malignant skin lesions 2097
    psoriasis 150–152, 150t, 152t, 2093–2095, 2095f
    rosacea 2097
    skin cancer prophylaxis 1791
  interactions 2102
  mechanism of action 2089–2093
    retinoid receptors 2090–2091
    synthetic retinoids 2091–2093
    vitamin A metabolism 2089–2090, 2091f
  pharmacologic features 2092t
  pregnancy and lactation 2102
  and PUVA 2229
  synthetic 2091–2093
  teratogenicity 2099, 2099t
retinol *see* vitamin A
retroauricular flap 2415, 2416f
reverse transcription PCR
revertant mosaicism 789, 947, 947f
Revesz syndrome 1067
revirapine, interactions 2124t
rhabdomyolysis, immunomodulators 2134
rhabdomyosarcoma 764t–765t
rhagades 2502f
Rheum rhaponticum see rhubarb
rheumatic fever 776t–778t
rheumatoid arthritis
  autoantibodies 611t, 613t
  extra-articular 680–683
    clinical features 680–682
      Bywater's lesions 681
      Felty's syndrome 681
      neutrophilic dermatoses 681–682
      pyoderma gangrenosum 682f
      rheumatoid nodules 680–681, 681f
      rheumatoid vasculitis 681
    differential diagnosis 682
    epidemiology 680
    pathogenesis 680
    pathology 682, 682f
    treatment 682–683
rheumatoid nodules 680–681, 681f, 1600t
  clinical features 1558t
  histologic features 682f
  pathology 1562t
rheumatoid papules 762f
rheumatoid vasculitis 391f, 681
rheumatological disease 761–763, 761t, 762f
  autoantibodies 611t, 613
Rhinocladiella aquaspera 1267
rhinophyma 563–564, 564f, 564t, 566
  electrosurgery 2309f
rhinoscleroma 1212
  differential diagnosis 1212t, 1276t
Rhinosporidium seeberi 1277
Rhipicephalus spp. 1443–1444, 1444f
Rhipicephalus pumilio 1244t
Rhipicephalus sanguineus 1244t
Rhipicephalus ticks 1443–1444, 1444f
Rhizoma sparganii 2214
Rhizoma zedoariae 2214
rhizomelic chondrodysplasia punctata 800t–801t, 852t–854t
  genetics 803t–804t
Rhizopus 370t, 375
rhombic transposition flap 2410–2411, 2411f–2412f
rhubarb 278t
  wild 279t
Rhus spp. *see* poison ivy
rhytides 2475f
  vertical lip 2566, 2566f, 2566t
ribavirin 402t
Ribes nigrum see black currant seed oil
riboflavin *see* vitamin B2
Richner-Hanhart syndrome 873t, 880, 880f–881f
  genetics 803t–804t
Ricinus communis see castor oil plant
rickets 932t–933t
  and sun exposure 2197
  vitamin D-dependent with alopecia 1104t
  vitamin D-resistant 953t, 958
  see also vitamin D
rickettialpox 1445t
Ricketts, Howard 1243
Rickettsia aeschlimannii 1244t, 1246t
Rickettsia africae 1244t
Rickettsia akari 1244t
Rickettsia australis 1244t
Rickettsia conorii 1244t
Rickettsia felis 1244t
Rickettsia honei 1244t
Rickettsia japonica 1244t
Rickettsia parkeri 1244t
Rickettsia prowazekii 1244t
Rickettsia rickettsii 1244t
Rickettsia sibirica 1244t
Rickettsia slovaca 1244t
Rickettsia typhi 1244t
rickettsial diseases 1243–1250, 1244t
  ehrlichioses 1249
  granulocytotropic anaplasmosis 1250
  Q fever 1250
  scrub typhus 1248–1249
  spotted fever and typhus 1243–1248
rickettsialpox 1244t, 1246t, 1247, 1247f
Riehl's melanosis 1053t
rifabutin 1234t
rifampin
  adverse reactions
    erythroderma 176t
    linear IgA bullous dermatosis 498t
  indications
    bartonellosis 1209t
    cholestatic pruritus 119t
    leprosy 1228t
    rickettsial disease 1249t
    tuberculosis 1234t
  interactions 2124t, 2191–2192
rifamycin, interactions 2124t
rifapentine 1234t
Rift Valley fever virus 1360t
Rigor flap *see* rotation flaps
Riley-Day syndrome
  genetics 818t–819t
  hyperhidrosis in 589
rilonacept 2149t
rimexolone suspension 2079t
riminophenazone 1234t
ringed keratolysis *see* pitted keratolysis
risedronate 2080–2081
risk assessment 2183–2184, 2184t
risorius 2335
risperidone
  adverse reactions 129t
  psychosis 134
ritonavir 2191t
  adverse reactions 1299t
  interactions 2124t
Ritter's disease *see* staphylococcal scalded skin syndrome
rituximab 2146–2147
  adverse reactions 2146
    lichen planus 185t
  contraindications 2146
  dosage 2146
  FDA warnings 2140t
  indications 2146
    atopic dermatitis 213t, 215
    B-cell lymphoma 2013
    bullous pemphigoid 484t
    dermatomyositis 639t
    lupus erythematosus 628t
    pemphigus vulgaris 472, 472t
    TTP-HUS 373
    vasculitis 402t
  interactions 2146
  mechanism of action 2146
  pregnancy and lactation 2147
rivaroxaban 365t
rivastigmine, and eccrine sweating 590t
river blindness *see* onchocerciasis
RNA
  knockdown 78f
  molecular targeting 77–78
  profiling 66f–67f, 66t–70t, 67–71, 69f, 71f
RNA-induced silencing complex 77–78
RNase 7 83t
Rocky Mountain spotted fever 9–11, 1244t, 1443
  clinical features 1246f–1247f, 1246t
  incidence 1245f
  pathology 1248f
Rocky Mountain wood tick *see* *Dermacentor* spp.
rofecoxib-induced pseudoporphyria 724t
Roferon-A 2132t
Rombo syndrome 1638
  and NMSC 1776–1777
ropivacaine 2344t
Rosa spp. 277t
Rosa damascena 274t, 2215t
rosacea 561–569
  clinical features 562–565, 563t
    erythematotelangiectactic (vascular) rosacea 562, 562f, 563t
    granulomatous rosacea 564–565, 565f
    ocular rosacea 564, 565f
    papulopustular (inflammatory) rosacea 563, 563f–564f
    phymatous rosacea 563–564, 564t
    pyoderma faciale 564–565, 565f
  differential diagnosis 565
    acne vulgaris 554–555, 554t
    demodex folliculitis 565
    erythromelanosis faciel and keratosis pilaris rubra 565
    seborrheic dermatitis 221
  epidemiology 561
  histopathology 565, 566f
  history 561
  pathogenesis 561–562, 562t
  steroid-induced 569, 569f
  treatment 566, 567t
    facial skin care 568t
    retinoids 2097
    topical antibacterials 2105–2107
rosacea fulminans *see* pyoderma faciale
Rosaceae 277t
rosaceiform dermatitis 568
Rosai-Dorfman disease 1542–1544
  antigenic markers 1533t
  clinical features 1543, 1543f
  differential diagnosis 1544

epidemiology 1543
history 1543
pathogenesis 1543
pathology 1543, 1543f
treatment 1544
Rosamarinus officinalis
rose gardener's disease *see* sporotrichosis
rosemary 2207t, 2215t
Rosenthal-Kloepfer syndrome 1009
roseola infantum *see* human herpesvirus-6
rosewood dermatitis 1509t
rosin dermatitis 1509t
Rosmarinus officinalis see rosemary
Ross River virus 1359–1361
Ross' syndrome 594
rotation flaps 2402–2404
Rothmund-Thomson syndrome 1476t–1477t, 1479
clinical features 1479
epidemiology 1479
genetics 816t
history 1479
pathogenesis 1479
treatment 1479
roundworms 1410f–1411f
see also individual species
rove beetles *see* blister beetles
Rowell's syndrome 320t
rubber sensitivity 250t
rubber tree 275t
rubella 1349
rubeola *see* measles
rubeosis, endocrine 768t
Rubiaceae 277t
Rubinstein-Taybi syndrome, and hypertrichosis 1117t–1118t
rubor 1197–1198
ruby lasers 2255t
hair removal 2256
optical penetration depth
pigmented lesions/tattoos 2256, 2263f, 2269t
Q-switched 2255t
skin penetration 2254f
Rudbeckia hirta see black-eyed Susan
rue 280t
rule of nines 1489f
Rumpel-Leede capillary fragility test 740t–742t
runner's rump 1506t
rupatadine 304t
Ruscus acuteatus see butcher's broom
Russell-Silver dwarfism 1009
Ruta graveolens see rue
Rutaceae 280, 280t
rutin 2207t
rutoside 362

S100 protein 29t–33t, 84, 825–826
saber shins 1216
Sabia virus 1360t
Saccharomyces boulardii 2211
sacral dimple 1000f–1001f, 1001t
sacroiliitis 144
SADDAN 818t–819t
saddle nose deformity 404
saddleback caterpillar 1441t
SAHA syndrome
adrenal 1124–1125, 1126f
with hyperprolactinemia 1121t, 1125
ovarian 1125
St Anthony's fire *see* erysipelas
St John's wort 2207t
adverse reactions 2192, 2192t
erythroderma 176t
phototoxicity 1481
effect on coagulation 2212t
salicylates 2199, 2200f
salicylic acid 252
acne vulgaris 555t–556t, 556
adverse reactions 2155t
chemical peels 577
perforating disease 1604t
skin peels 2488–2489, 2489f, 2497f
topical 2158
salivary gland diseases 1163–1165
cheilitis glandularis 1164, 1164f
Darier disease 890
mucocele 1163–1164, 1164f
necrotizing sialometaplasia 1164
salivary gland tumors 1165, 1165t
Sjögren's syndrome 678, 1164–1165
salmon patch 6t–7t, 1715f
of nail bed 1136f
Salmonella spp. 1213
chronic granulomatous disease 910t
and erythema multiforme 320t
secondary cutaneous vasculitis 390t
salt and pepper sign 646, 646f
SALT-related B-cell lymphoma *see* B-cell lymphoma
salt-split skin 457
autoantibodies in 457f
cleavage plane 457f
immunoreactants in 450–451
sampling bias 2059
San Joaquin valley fever *see* coccidioidomycosis
sand flea *see* tungiasis
sandpapered nails *see* trachyonychia
Sanfilippo syndrome 715t
Sanguinaria canadensis see bloodroot
Santalaceae 274t
Santalum album 274t
Santyl 2109
saphenofemoral junction 2512
saphenous nerve block 2351f
saphenous varicosities 2516t
saphenous veins 2512
Doppler examination 2513f, 2513t
sclerosing solution 2514t
SAPHO syndrome 436–437, 548–549
associated cutaneous disorders 437t
clinical features 437, 437f
differential diagnosis 437
epidemiology 436
history 436
pathogenesis 436
pathology 437
treatment 437, 437t
saquinavir
adverse reactions 1299t
interactions 2191t, 2192
sarcoidosis 1, 2f, 1039, 1600t
and anetoderma 1633t, 1634f
angiolupoid 1559–1560
clinical features 775f, 776t–778t, 1558t, 1559–1561, 1559f–1560f
granuloma 21, 23f, 1557–1562
and dermatitis herpetiformis 493t
diagnosis 1561–1562
differential diagnosis 308t–310t, 1561–1562
epidemiology 1557
and erythema nodosum 1560f, 1644t
history 1557
pathogenesis 1557–1559
pathology 1561, 1561f, 1562t
pulmonary disease 778t–779t, 1560–1561
renal disease 780t–781t
treatment 1562, 1563t
sarcoma
clear cell 1895
epithelioid 1975–1976, 1975f
follicular dendritic 1545t
histiocytic 1545t
interdigitating dendritic cell 1545t
Kaposi's *see* Kaposi's sarcoma
Langerhans cell 1545t
Sarcoptes scabiei 271t, 1367t, 1423, 1424f
life cycle 1424f
see also scabies
sarcoptic mites 1444–1446
Sarcoptidae 1445t
sarsaparilla 2207t, 2485t
saturniid moth caterpillar 1441t
saucerization biopsy 12–15, 2381, 2382t, 2388–2389, 2389f
saw palmetto 2212t
Say syndrome 1009
scabies 1423–1426, 1424f
clinical features 1423–1424, 1425f
crusted 1423, 1425f
dermoscopy 38f
differential diagnosis 414t, 1424
epidemiology 1423
history 1423
HIV-related 1293, 1293f
neonates 524t–525t
occupational 271t
pathogenesis 1423
pathology 1424, 1426f
pruritus in 113, 113t, 1424
subungual 1423, 1425f, 2440t
treatment 1424–1426, 1426t
crotamiton 1424–1426, 1426t
ivermectin 1426, 1426t
lindane 1424, 1426t
permethrin 1424, 1426t
sulfur ointment 1426, 1426t
scalding injuries 1522–1523
scales 2, 4t–5t
scalp
Blaschko's lines 943f–944f
dissecting cellulitis 1096t, 1099–1100, 1108
erosive pustular dermatosis
hypotrichosis simplex 708, 832t–833t, 1104t
pruritus 117
psoriasis 142–143
transdermal absorption
vitiligo 1025–1026
scalp lesions 995, 995f–996f
scalp-ear-nipple syndrome 1003t
digital anomalies 1005t
scalpels 2360, 2360f
scarification, granuloma annulare
scarlet fever 1194–1195
scarring pemphigoid *see* cicatricial pemphigoid
scars
assessment 1622, 1624t
contraction 2400f, 2467f
formation of 2321f
from drug abuse 1513–1514, 1513f, 1515f
hypertrophic 1621–1625, 2471, 2471f
clinical features 1622, 1622f–1624f, 1623t
differential diagnosis 1624
epidemiology 1621
pathogenesis 1621–1622, 1621f
pathology 1622–1624, 1623f–1624f, 1624t
treatment 1624–1625, 1625t
post-acne 558
post-surgical 2467–2471, 2467f
pruritus in 117
see also keloids; wound healing
Schamberg's disease 365t, 366f
Schamberg's lotion 2162t
Schaumann bodies 1561
Scheie syndrome 715t
Schimmelpenning-Feuerstein-Mims syndrome *see* epidermal nevus syndrome
Schinus terebinthifolius see Brazilian pepper tree
Schinzel-Giedion syndrome 1116t
Schirmer test 677t, 678
schistosomiasis 1417–1419, 1600t
clinical features 1418, 1418f
diagnosis 1419
differential diagnosis 1419
epidemiology 1417, 1418f
pathogenesis 1418
pathology 1418
treatment 1419
Schizonepeta tennifolia 2213
Schnitzler's syndrome 295–296, 300
monoclonal gammopathy 2014t
paraneoplastic 764t–765t
Schönlein-Henoch purpura *see* Henoch-Schönlein purpura
Schöpf-Schulz-Passarge syndrome 60, 808t, 1075
Schwann cells 874t, 926
schwannoma 1948–1949
ancient 1949
malignant *see* malignant peripheral nerve sheath tumor
solitary 1948f–1949f
Schweninger-Buzzi anetoderma 1633
scissors 2361, 2361f
scissors biopsy 2381, 2382t, 2388, 2388f
scissors excision of condylomata acuminata 1314–1315, 1314t
scleredema 692–693, 693f
clinical features 644t, 692–693
differential diagnosis 650t, 693
endocrine 693f, 768t
epidemiology and pathogenesis 692
history 692
monoclonal gammopathy 692
pathology 693
treatment 693
radiotherapy 2294
scleredema diabeticorum 693
sclerederma adultorum of Buschke *see* scleredema
sclerederma diabeticorum *see* scleredema
sclerema neonatorum 1650–1651, 1651f, 1651t
Scleremo 2515t
sclerodactyly 644t, 645f
scleroderma 643–655
autoantibodies 604–605, 613, 613t, 647–649
autoantigens 1596t
classification 645
clinical features 644t–645t, 645–649, 645f
calcinosis cutis 646, 646f
cardiovascular disease 649t, 776t–778t
cutaneous ulcers 647, 648f, 1743f
gastrointestinal 649t
hyperpigmentation 646, 1040, 1041f
monoclonal gammopathy 644t
pulmonary disease 649t, 778t–779t
Raynaud's phenomenon 647, 647f–648f, 647t
renal disease 643–645, 780t–781t
and dermatitis herpetiformis 493t
diagnosis 645
differential diagnosis 639t, 649, 650t
epidemiology 643
histology 649f
history 643
laboratory manifestations 644t
pathogenesis 643–645, 644f
fibrosis 645
immune dysregulation 643–645
vascular dysregulation 643
pathology 649
treatment 651
cutaneous sclerosis 651
cutaneous ulcers 651
interferons 2133
internal organ involvement 649t, 651
phototherapy 2231
Raynaud's phenomenon 651
see also morphea
sclérodermie atrophique d'emblée *see* idiopathic atrophoderma of Pasini and Pierini
Sclerodex 2515t
Sclerodine 2515t
Scleromate 2515t
scleromyxedema 687–691, 1600t
clinical features 644t, 688–690, 688t, 689f–690f
definition 688–691
differential diagnosis 650t, 688t, 690
epidemiology 688
history 688
monoclonal gammopathy 688
paraneoplastic 764t–765t
paraproteinemia 688–690
pathogenesis 688
sclerosing hemangioma *see* dermatofibroma
sclerosing lipogranuloma 1573, 1578
sclerosing panniculitis *see* lipodermatosclerosis
sclerosing solutions 2513–2515, 2514t–2515t
mechanism of action 2514f
sclerosing sweat duct carcinoma 1846

sclerosis
  cutaneous 1514t
  systemic *see* calcinosis cutis
sclerotherapy 2512–2513
  complications 2518–2520, 2518t
    arterial injection 2520
    postsclerotherapy pigmentation 2518–2519, 2519f, 2519t
    systemic allergic reaction 2520
    telangiectatic matting 2519, 2519f
    ulceration 2519, 2520f
  compression 2518
  Doppler-guided 2520
  large vein 2518f
  pretherapy evaluation 2520
sclerotic fibroma 1965–1966, 1966f
Sclerovein 2515t
scoliosis 930
Scolopendra subspinipes 1449
scopolamine, hypohidrosis/anhidrosis 595t
Scopulariopsis brevicaulis
  onychomycosis 1265t
scorpionfish 1452
scorpions 1449, 1449t
scotochromogens 1221t
Scots pine (*Pinus sylvestrus*) 2215t
scratch dermatitis 1056t–1057t, 1061, 1061f
scrofuloderma 1230, 1231t, 1232f
Scrophulariaceae 277t
scrotal angiokeratoma 1919f
scrotal cancer 2161
scrotal idiopathic calcinosis 732–733
scrotal pruritus 116–117
scrotal tongue *see* fissured tongue
scrotodynia 1182
scrotum
  cysts 1819f
  idiopathic calcified nodules 732–733
scrub typhus 1244t, 1246t, 1248–1249, 1445t
scrum pox *see* herpes simplex viruses
Sculptra 2548t–2549t, 2554–2555
scurvy 743f
  and gastric hemorrhage 773t–774t
  see also vitamin C
Scytalidium dimidiatum 375
  onychomycosis 1265t
  tinea pedis 1258, 1261, 1263t
Scytalidium hyalinum
  onychomycosis 1265t
  tinea pedis 1252–1253, 1258, 1261
SDRIFE 347, 347t
sea cucumbers 1451
sea urchin spines 1451
  foreign body reactions 1574t, 1576t
sea-blue histiocytosis 1530t–1531t
seabather's eruption 414t, 1451, 1451f
Searle's ulcer *see Mycobacterium ulcerans*
sebaceoma 1839–1840
sebaceous adenoma 1839–1840, 1840f
sebaceous carcinoma 1790t, 1840, 1840f
  Mohs surgery 2449–2450
sebaceous epithelioma 1839–1840
sebaceous follicle 543f
sebaceous glands 542–544
  development 60, 542–543
  function 543, 543t
  hyperplasia 1839–1840, 1839f
  pathophysiology 544
  resident microflora 544f
  and seborrheic dermatitis 219
  structure 542–544, 543f
sebaceous nevus syndrome 866
sebopsoriasis 1177
seborrhea 219, 2215t
seborrhea, acne, hirsutism and alopecia *see* SAHA syndrome
seborrhea-like dermatitis with psoriasiform elements 803t–804t
seborrheic dermatitis 219–221
  clinical features 220–221
    adult form 220–221, 220f
    infantile form 220, 220f
  differential diagnosis 221, 221f, 308t–310t
  distribution 9
  epidemiology 219
  and erythroderma 173t–174t
  history 219
  HIV-related 219, 1293–1294
  infants 220–221, 220f
  intertriginous areas 220–221
  pathogenesis 219–220
  pathology 221
  treatment 221
    phototherapy 2222
seborrheic eczema *see* seborrheic dermatitis
seborrheic keratosis 1795–1798
  acanthotic 1797
  clinical features 1795–1796, 1796f
  clonal 1797–1798
  dermoscopy 36f
  differential diagnosis 1798
  epidemiology 1795
  history 1795
  hyperkeratotic 1797
  inflamed 1797
  and malignancy 1796–1797
  pathogenesis 1795
  pathology 1797–1798, 1797f
  reticulated/adenoid 1797
  treatment 1798
    electrodessication 2307f
sebostasis 120t, 544
sebum 543
  production 544–545
second intention healing 2367–2368, 2367f, 2384t
2ndSecond skin 2378
secondary cutaneous amyloidosis 705
secondary hair germ 1079t
secondary intention healing 2315, 2315f
secondary lymphoid chemokine 1687
secondary lymphoid-tissue chemokine 93
sedative/tranquilizer abuse, prevalence 1512t
segmental neurofibromatosis 925, 929, 929f, 932t–933t, 955
segmental pigmentation disorder 1037–1038, 1054
segmental vitiligo 956, 1027f
seizures in SLE 627t
selectins 1684f, 1685t
E-selectin 1685t
L-selectin 1685t
P-selectin 1685t
P-selectin glycoprotein ligand selection bias 2062
selective serotonin reuptake inhibitors 115, 132, 134
selegiline, and eccrine sweating 590t
selenium 750
  deficiency 750, 1038
  dermatosis 1499t
selenium salts 253t–254t
selenium sulfide
  hair discoloration 1498t
  mechanism of action 2119t
  shampoo 253t–254t
Selenomonas spp. 1152
self-adherent wraps 1737t
self-healing cutaneous mucinosis 692
Semecarpus anacardium see Indian marking nut tree
Senear-Usher syndrome *see* pemphigus erythematosus
senescent skin 105
senile angioma *see* cherry angioma
senile freckles *see* solar lentigines
senile keratosis *see* solar keratosis
senile pruritus 105
sensitivity
  decreased 50
  increased 50
sensory innervation of head and neck 2338–2340, 2338f–2339f, 2338t
sensory neuropathy 769f
Senter syndrome 865
septic arthritis
  differential diagnosis 711
  and drug abuse 1515t
septic thrombophlebitis
  and drug abuse 1515t, 1519
  drug-induced 1519
septic vasculitis 389t–390t
septicemia 1200
Septocaine *see* articaine
SERCA2 887f, 888
serine palmitoyl transferase 2067f
serine protease inhibitors (SERPINS) 2322
serositis in SLE 627t
serotonin 2315t
  in itch 104
serpiginous ulceration of groin *see* donovanosis
serpin 1646–1647
Serratia marcescens 375
  chronic granulomatous disease 910t
sertaconazole
  formulations 2118t
  pregnancy and lactation 2118t
  trade names 2118t
sertraline
  adverse reactions, gingival hyperplasia 1156t
  anxiety disorder 133
  cholestatic pruritus 119t
  and eccrine sweating 590t
serum sickness-like eruption 348f, 349
sesquiterpene lactones 274t
  allergy 284
Setleis syndrome 807t, 1003t
severe acute respiratory syndrome, eccrine gland changes 598t
severe combined immunodeficiency (SCID) 900t, 919–921
  classification 903–904
  clinical features 919
  differential diagnosis 921
  epidemiology 919
  pathogenesis 919, 920t
  pathology 921
  treatment 921
  X-linked 920t
severe congenital neutropenia 912t
severe cutaneous adverse reactions (SCARs) 335t
  see also adverse reactions
sexual abuse 1523–1524, 1524f–1525f, 1525t
  physical signs 1523t, 1524f–1525f, 1525t
sexually transmitted infections 1367t
  chancroid 1383–1386
  donovanosis 1387–1389
  gonorrhea 1379–1383
  lymphogranuloma venereum 1386–1387
  syphilis see syphilis
  see also anogenital disease; human papillomavirus
Sézary syndrome 174, 2027–2028
  clinical features 2027f–2028f, 2028
  definition 2027–2028
  differential diagnosis 225, 228t, 2020t, 2028
  epidemiology 2027
  pathogenesis 2028
  pathology 2028
  treatment 2028
shagreen patch *see* connective tissue nevus
Shah-Waardenburg syndrome 1035
shampoos 2484, 2485t
Sharp's syndrome *see* mixed connective tissue disease
shave biopsy 12–15, 2381, 2382t, 2388–2389
  deep 12–15
  superficial 12–13
shave bumps *see* pseudofolliculitis barbae
shawl sign 610
sheep bites 1450t
shelter foot *see* immersion foot
Shigella spp. 1367t
Shigella dysenteriae 373
Shiitake mushrooms 2207t
  dermatitis *see* flagellate mushroom dermatitis
shingles *see* varicella-zoster virus
SHORT syndrome 1672
shotgun sequencing 70–71
Shulman's syndrome *see* eosinophilic fasciitis
Shwachman-Bodian-Diamond syndrome 912t
sibutramine, and eccrine sweating 590t
sicca syndrome *see* Sjögren's syndrome
sickle cell disease
  leg ulcers 1743f
  progressive vascular occlusion 382
side effects *see* adverse reactions
siderophages 1968–1969
signe de la tache de bougie 139
signet ring cells 1787t, 2053t, 2054f
silastic foams 2371
sildenafil 651
  adverse reactions, lichen planus 185t
  interactions 2124t, 2193
silica 1600t
  foreign body reaction 1574t, 1578–1579
    clinical features 1578
    differential diagnosis 1579
    histopathology 1576t
    pathology 1578–1579
    treatment 1579
silicone 1581t, 2548t–2549t, 2558, 2559f
  foreign body reaction 1573–1575, 1578
    clinical features 1578
    histopathology 1576t
    pathology 1578
    treatment 1578
  injection site reactions 354t, 663
silicone gel sheets, hypertrophic scars/keloids 1625t
silicosis 654
Silikon 1000 2558
silk oak 282t
silk sutures 2355, 2356t
  foreign body reaction 2357
Silon-TSR 2369, 2378
SilSkin 2558
SilvaSorb 2368t
silver
  adverse reactions 354
  dermatosis 1499t
  hyperpigmentation 1055f, 1056t–1057t
silver nitrate 2162t, 2464t
  adverse reactions 2155t
  burns 1155
  molluscum contagiosum 1359t
silver sulfadiazine 2109
  adverse reactions 2155t
  burns 1489
silver-impregnated dressings 511t, 2368t
Silver-Russell syndrome 932t–933t
Silvercell 2368t
Silverlon 2368, 2368t
silymarin 2207t, 2490t
simple lentigo *see* lentigo simplex
Simpson-Golabi-Behmel syndrome 1007
simvastatin
  adverse reactions, lichen planus 185t
  interactions 2190, 2191t, 2192
single filing 1790t, 2053t
single nucleotide polymorphism 70, 784t, 794f
single tangent advancement flaps 2402–2404, 2403f–2405f
sinus pericranii 995, 996f
sinusoidal hemangioma 1721, 1924–1925
Sipple syndrome 707, 776t–778t
sirolimus
  adverse reactions
    nail changes 1141t
    secondary cutaneous vasculitis 390t
  indications
    dermatomyositis 639t
    lichen planus 195
  interactions 2191–2192
sis 1761t
sister chromatids 784t
Sister (Mary) Joseph nodule 2050f

sitaxsentan 651
β-sitosterolemia 1552
  genetics 810t–811t
sixth disease *see* human herpesvirus-6
Sjögren-Larsson syndrome 838t, 859
  clinical features 859, 859f
  differential diagnosis 860
  epidemiology 859
  genetics 803t–804t
  history 859
  neonatal 847t
  pathogenesis 859
  pathology 859–860
  treatment 860
Sjögren's syndrome 677–679, 761–763
  annular erythema 308t–310t
  autoantibodies 611t
  clinical features 678, 678f
  and dermatitis herpetiformis 493t
  differential diagnosis 679
  epidemiology 677
  history 677, 677t
  laboratory findings 678
  pathogenesis 677–678
  pathology 678–679
  salivary gland involvement 678, 1164–1165
  treatment 679
skin 1, 58t
  embryonic origin 55, 56f
  morphology 1–2
  postnatal development 63
  requirements and failings 45t
  textural changes 2
  see also anatomy and physiology; epidermis
skin aging 1596
skin barrier
  and epidermal lipid metabolism 2066–2068
  factors affecting 2068–2069
  impaired, in pruritus 105
  structure and origin 2065–2068
skin cancer
  melanoma *see* melanoma
  non-melanoma *see* non-melanoma skin cancer
  occupational 268–269
    clinical features and diagnosis 269
    epidemiology 269
    history 269
    pathogenesis 269
    pathology and treatment 269
  see also basal cell carcinoma; squamous cell carcinoma
skin care products 2479–2489
  astringents 2481
  cleansers 2479–2480, 2480t
  moisturizers 2481, 2481t
skin dimples 1008–1009
skin flora 1187, 1187t
skin fragility syndrome *see* plakophilin deficiency
skin fragility/woolly hair syndrome 510t
  genetics 832t–833t
skin hooks 2361–2362
skin optics 2252, 2252f
skin phototypes 5–8, 8t, 2474
skin pop scars 1513, 1513f, 1514t
skin repair mechanisms 48–49
  see also wound healing
skin resurfacing 2493–2508
  anesthesia 2276
  chemical resurfacing 2495f, 2496–2502
    cleaning and degreasing 2496f, 2502
    deep chemical peeling 2501–2502, 2501t, 2502f
    frosting 2497f, 2502
    Jessner's-35% TCA peel 2500f
    medium-depth chemical peeling 2498–2500, 2498f–2499f
    superficial chemical peeling 2496–2498, 2497f, 2497t
    TCA Cross 2500–2501, 2501f
  classification of methods 2493t
  complications 2506–2507, 2506t
  contraindications and patient selection 2494–2495, 2494t
  indications 2494–2496, 2494t
    vitiligo 1030
  laser resurfacing
    ablative 2255, 2271–2272, 2272f
    fractional 2256–2257, 2272–2277, 2273f, 2273t
    lasers 2265t
    non-ablative 2256
  mechanical resurfacing 2502–2505
    manual dermasanding 2503, 2503f–2504f
    microdermabrasion 2502–2503, 2503f, 2503t
    motorized dermabrasion 2504–2505, 2504f–2505f, 2505t
  plasmakinetic 2277
  postoperative care 2505–2506
  preoperative and intraoperative preparations 2493f, 2495–2496
  radiofrequency 2257–2258, 2258f, 2277–2278
skin substitutes 1736–1737
skin tags 1001t, 1961–1977, 1962f
  obese patients 751t
skin tension lines 2330–2332, 2330f–2331f
skin tracks 1513, 1513f, 1514t
skin-associated lymphoid tissues (SALT) 81
skin-derived precursors 62t
skin-lightening agents 2158–2159
  hydroquinone 2158
  mequinol 2158–2159
  monobenzyl ether of hydroquinone 2158
Skindex-29 2061–2062
skull, bony landmarks 2328f
slapped cheek disease *see* erythema infectiosum
SLC/CCL21 1686t
SLE *see* systemic lupus erythematosus
SLURP-1 873t
slush therapy 324
Sly syndrome 715t
small plaque parapsoriasis *see* parapsoriasis
small vessel vasculitis 385t, 389–397
  acute hemorrhagic edema of infancy 393–395
  causes 390t, 391f
  clinical features 387f–388f, 391, 391f
  differential diagnosis 391
  drug-induced 390t, 1518t
  epidemiology 389
  erythema elevatum diutinum *see* erythema elevatum diutinum
  Henoch-Schönlein purpura 392–393
  monoclonal gammopathy 2014t
  paraneoplastic 764t–765t
  pathogenesis 389
  pathology 388f
  purpura *see* purpura
  renal disease 780t–781t
  treatment 391–392, 402t, 408f–409f
  urticarial vasculitis *see* urticarial vasculitis
smallpox 1355t–1356t, 1358t
  vaccine reaction 1357f
Smilax spp. *see* sarsaparilla
Smith-Lemli-Opitz syndrome 1482
Smodingium argutum see poison ivy
smoking
  and psoriasis 139
  and wound healing 2461
smooth muscle actin 29t–33t
smooth muscle tumors 1979–1984, 1980f
  hamartoma 1983–1984
  leiomyoma 1979–1980
  leiomyosarcoma 1980–1983
snake bites 1449–1450
Sneddon syndrome 380–382
  clinical features 380–381, 1750f
  differential diagnosis 381
  pathogenesis 380
  pathology 381
  treatment 381
  see also livedo reticularis
Sneddon-Wilkinson disease 145, 146f
  differential diagnosis 147t, 308t–310t
  monoclonal gammopathy 2014t
sneezeweed 285t
snip biopsy 2381, 2382t, 2388, 2388f
SNUB syndrome 1119
soap 2480t
  bar 2479
  sensitivity 250t
  superfatted 2480t
  transparent 2480t
soap-free soap 2480t
sodiium tetradecyl sulfate 2515t
sodium bicarbonate
  in local anesthesia 2345
  tumescent anesthesia 2348t
sodium cromoglycate, atopic dermatitis 213t
sodium gold thiosulfate 242t
sodium hypochlorite 253t–254t
  adverse reactions 1157t
  atopic dermatitis 214
  bacterial folliculitis 1190
  epidermolysis bullosa 510
sodium morrhuate 2515t
sodium stibogluconate, leishmaniasis 1397t
sodium sulfacetamide
  adverse reactions 2107t
  dosage 2106t
  formulations 2106t
  indications 2106
    acne vulgaris 556, 556t, 2106, 2106t
    rosacea 567t, 2106, 2106t
  mechanism of action 2106t
  pregnancy and lactation 2106t
  trade names 2106t
sodium tetradecyl sulfate 2520
sodium thiosulfate
  calciphylaxis 732
  dystrophic calcification 730
Sof-Foam 2371
soft chancre *see* chancroid
soft fibroma *see* skin tags
soft tissue augmentation 2547–2560
  autologous fibroblasts and collagen 2552
  bioengineered human collagen 2551
  bovine collagen 2550–2554, 2550f
  calcium hydroxyapatite 2554–2555, 2556f–2557f
  causes of cutaneous defects 2547t
  complications 2551t
  expanded polytetrafluoroethylene 2555–2556
  filler materials and injection technique 2548–2550, 2548t–2549t
  historical perspective 2548
  human-derived cadaveric collagen 2551
  human-derived cadaveric fascia 2551–2552
  hyaluronic acid derivatives *see* hyaluronic acid; hyaluronic acid derivatives
  indications 2548t
  lipotransfer 2557–2558, 2558f
  poly-L-lactic acid 2554, 2556f
  polymethylmethacrylate microspheres 1581t, 2558–2559
  porcine collagen 2550, 2550f
  preinjection considerations 2547t
  silicone *see* silicone
  temporary fillers 2550–2554
SoftForm 2548t–2549t
SOLAMEN syndrome 954, 1984–1985
Solanaceae 278t
Solanum dulcamara see bittersweet nightshade
Solanum tuberosum see potato
solar elastosis 1483–1484
solar erythema 1455
solar keratosis *see* actinic keratosis
solar lentigines 1484, 1854–1855
  clinical features 1852t, 1854, 1854f
  differential diagnosis 1852t, 1854–1855
  epidemiology 1854
  pathogenesis 1854
  pathology 1854, 1855f
  treatment 1855
solar urticaria 298, 1475
  action spectrum 2203t
  clinical features 1475, 1475f
  differential diagnosis 1475
  epidemiology 1475
  history 1475
  pathogenesis 1475
  pathology 1475
  treatment 1475
    PUVA phototherapy 2232
Solenopsis invicta see fire ant bites
solid facial edema 549f
solitary lichen planus *see* lichenoid keratosis
solitary nerve sheath tumor *see* neurofibroma
Solomon syndrome *see* epidermal nevus syndrome
solvent abuse, cutaneous signs 1514t
solvents/thinners 250t, 252–255, 253t–254t, 264
  patch testing 264t
somatic hypermutation 914f, 917t
somatostatin, and linear IgA bullous dermatosis 498t
somatostatinoma 927t
sonic hedgehog gene 59–60, 1766
sonic hedgehog protein 1075–1076
soot exposure, and NMSC 1775t
soot tattoos 1518
sorafenib 353t, 1887t, 2149t
Sorbex 2373
sorbic acid
  hypersensitivity 251t
  systemic contact dermatitis 246t
Sorbsan 2372
Sotradecol 2515t
South African porphyria *see* variegate porphyria
South American blastomycosis *see* paracoccidioidomycosis
southern flannel caterpillar 1441t
soy 2207t, 2490t
  effects on coagulation 2212t
Spangler's 'papular dermatitis of pregnancy' *see* atopic eruption of pregnancy
Spanish fly *see* blister beetles
sparfloxacin 2116t
  adverse reactions 2193
  phototoxicity 1480t
sparganosis 1407t–1408t
Spear's flap 2415–2416, 2417f
specific granule deficiency 912t
specific immunity 81
speckled lentiginous nevus *see* nevus spilus
spectacle frame acanthoma *see* acanthoma fissuratum
spectinomycin, gonorrhea 1383t
sphenoid wing dysplasia
sphingolipoidoses, eccrine gland changes 598t
sphingomyelin 2066f
  hydrolysis 2067
sphingomyelinase D 1447
spider angioma *see* spider telangiectasia
spider bites 1446
  funnel web spiders 1448, 1448f
  Loxosceles spiders 1447–1448, 1447f
  tarantulas 1448
  widow spiders 1446–1447
spider flower 282t
spider nevus *see* spider telangiectasia
spider telangiectasia 1753, 1754f
  laser therapy 2266–2267
Spiegler-Fendt sarcoid *see* cutaneous lymphoid hyperplasia
spike lavender (*Lavandula latifolia*) 2215t
spina bifida 927t
spinal accessory nerve 2466–2467

spinal cord injury, differential diagnosis 650t
spinal (cord transection) sweating 591
spinal dysraphism 998–1000, 999f–1000f, 1119
  occult 998–999, 1715
  skin lesions 1001t
spindle cell carcinoma 1820–1821
  radiation-induced 2300f
spindle cell hemangioma 1921–1922
  clinical features 1922, 1922f
  differential diagnosis 1922
  epidemiology 1922
  pathogenesis 1922
  pathology 1922, 1922f
  treatment 1922
spindle cell lipoma 1986–1987
  clinical features 1986
  differential diagnosis 1986–1987
  epidemiology 1986
  history 1986
  pathogenesis 1986
  pathology 1986, 1987f
  treatment 1987
spindled melanoma 1895, 1896f
spine, midline lesions 998–1000
spinosad, head lice 1428t, 1429
spinous cell glycogen content 58t
spiny keratoderma 872t
spiradenocarcinoma 1847
spiradenoma 955, 1844–1845
spirochetes 1214–1217
  actinomycosis 1217–1218
  Borrelia burgdorferi 1214–1215
    acrodermatitis chronica atrophicans 1215, 1216f
    borrelial lymphocytoma 1215
    Lyme disease 1214–1215, 1215t
  leptospirosis 1217
  nocardiosis 1218, 1218t
  non-venereal treponematoses 1216–1217
    endemic syphilis 1217
    pinta 1216
    yaws 1216, 1216f
Spirometra spp. 1407t–1408t
spironolactone
  acne vulgaris 556t, 557
  adverse reactions, lichen planus 185t
  hirsutism 1125
Spitz nevus/tumor 37f, 1864–1867
  agminated 1865, 1865f
  atypical 1865, 1865t
  clinical features 1865, 1865f
  dermoscopy 37f
  differential diagnosis 1866, 1866t
  epidemiology 1864
  malignant/metastasizing 1865
  pathogenesis 1864–1865
  pathology 1865–1866, 1866f
  pigmented 1865
  treatment 1866–1867
spitzoid melanoma 1895, 1896f
Splendore-Hoeppli phenomenon 1199
splinter hemorrhages 1130f, 1132
  and psoriasis 144
split hand-split foot-ectodermal dysplasia-clefting syndrome *see* ectodermal dysplasia-ectrodactyly-clefting syndrome
split-thickness grafts 2427–2429, 2427f–2428f, 2427t
  classification 2427t
  complications 2429, 2430f
  donor site 2427
  donor site care 2429
  future directions 2429
  indications/contraindications 2427
  postoperative care 2429
  preoperative history 2427
  securing graft 2429
  techniques 2427–2428, 2428f
  variations/unusual situations 2429
spondylocheirodysplasia 1593t
sponge dermatitis 1452
spongiosis 17
  pattern analysis 18, 18f
spoon nails *see* koilonychia
spooning 2214
Sporothrix schenckii 1272
sporotrichosis 1272–1273, 1273t
  clinical features 1272, 1272f
  differential diagnosis 1273
  epidemiology 1272
  pathogenesis 1272
  pathology 1272–1273, 1272f
  treatment 1273
sports-related dermatoses 1505–1508, 1506t
  clinical features 1505–1507, 1506f, 1506t
  epidemiology 1505
  history 1505
  pathogenesis 1505
  pathology 1507
  treatment 1507–1508
sports-related infections 1507t
spotted fever 1243–1248, 1244t, 1248f
spun-glass hair 1110f, 1112
spurges *see* Euphorbiaceae
squalene synthase 2067f
squamous cell carcinoma 1764, 1769–1771, 1770f, 1777–1784, 2202
  action spectrum 2201t
  anogenital 1178–1179, 1179f
  cancer 1769–1771
  clinical features 1779–1780, 1779f–1780f
    invasive 1780–1781
    keratoacanthoma 1781–1782
    lymphoepithelioma-like carcinoma 1782–1783
    in situ 1779–1780
    verrucous carcinoma 1782
  cryosurgery 2286
  demographics 1773
  differential diagnosis
  and epidermolysis bullosa 507–508, 508f
  HIV-related 1296
  in vivo imaging 1783
    dermoscopy 1783
    reflectance confocal microscopy 1783
  incidence 1774t
  metastatic risk factors 1784t
  nail bed 1146, 2440t
  oral 1162–1163
    clinical features 1162, 1163f
    epidemiology 1162
    pathology 1162
    treatment 1162–1163
  organ transplant patients 1775, 1776f
  pathology 1783–1784
    actinic keratosis 1783, 1783f
    histologic simulators 1784
    invasive 1784, 1785f
    keratoacanthoma 1784, 1785f
    in situ 1783–1784, 1784f
    verrucous carcinoma 1784
  precursors 1769
  radiotherapy 2294–2297, 2296f
    adjuvant 2296
    definitive 2295–2296
    dosage fractionation schedules and fields 2297, 2297t
    immunosuppressed hosts 2296–2297
    lymph node metastases 2296
    perineural invasion 2296
    SCC of lip 2296
  staging 1781t
  treatment
    interferons 2132
    Mohs surgery 2447–2448, 2454f
    NCCN guidelines 1788
    photodynamic therapy
    radiotherapy 1791
    reduction of immunosuppression 1791
  see also non-melanoma skin cancer
squamous eddy 1821
squaric acid dibutyl ester
  alopecia areata 1101, 1103t
  warts 1314t, 2162t
src 1761t
stains 25–26, 26f, 27t–28t, 28f
  dermatopathology 25–26
  immunohistochemistry 28f, 29t–33t
  immunological 2053t
  Mohs surgery 2449t
  see also individual stains
stanozolol
  C1 esterase inhibitor deficiency 305
  cholestatic pruritus 119t
  cryogelling/cryoagglutination disorders 374
Staphylinidae 1439
staphylococcal scalded skin syndrome 173t–174t, 177–178, 1191–1193
  clinical features 1192–1193, 1192f, 1193t
  diagnosis 1193
  differential diagnosis
  epidemiology 1192
  genetics 832t–833t
  neonates 526t–528t, 535f
  pathogenesis 1192
  pathology 179, 1193
  treatment 1193
staphylococcal toxic shock syndrome 1193–1194, 1194t
  clinical features 1194, 1194f
  diagnosis 1193t, 1194
  epidemiology 1193–1194
  pathogenesis 1193–1194
  pathology 1194
  treatment 1194
staphylococcal/streptococcal infections 1187–1200
  abscesses 1190
  bacteremia/septicemia 1200
  bacterial folliculitis 1188–1190
  blistering distal dactylitis 1191
  botryomycosis 1199
  carbuncles 1190
  cellulitis 1197–1198
  ecthyma 1191
  erysipelas 1196
  furuncles 1190
  impetigo 1187–1188
  MRSA 1190–1191
  necrotizing fasciitis 1199–1200
  pyomyositis 1198
  scarlet fever 1194–1195
  streptococcal intertrigo 1196–1197
  streptococcal perianal disease 1197
  toxic shock syndrome
    staphylococcal 1193–1194
    streptococcal 1195–1196
Staphylococcus aureus 271t, 375, 1187t, 1450t, 1515t
  and atopic dermatitis 214
  chronic granulomatous disease 910t
  folliculitis 572f
  HIV-related infection 1291
  methicillin-resistant *see* MRSA
  panniculitis 1658t
  secondary cutaneous vasculitis 390t
  transmission by head lice 1427
  see also toxic shock syndrome
Staphylococcus epidermidis 1187t
  in sebaceous follicles 542, 544f
Staphylococcus saprophyticus 1187t
starch, foreign body reaction 1574t, 1579
  histopathology 1576t
  pathology 1579
STARTS mnemonic 2399t
stasis blisters *see* edema blisters
stasis dermatitis 222–224
  clinical features 223, 223f, 1732f–1733f
  differential diagnosis 224
  epidemiology 223
  history 223
  obese patients 751t
  pathogenesis 223
  pathology 224, 224f
  treatment 224
stasis eczema *see* stasis dermatitis
stasis purpura 366f
STAT3 91, 2019
statins *see* HMGCoA reductase inhibitors
statistical significance 2063
statistics
  ascertainment bias 2062
  causal inference 2060t
  confidence intervals 2061f
  errors 2062, 2062f, 2062t
  information bias 2062
  misclassification bias 2062
  odds ratio 2058–2059
  positive predictive value 2062, 2062t
  recall bias 2059
  relative risk 2058–2059
  sampling bias 2059
  selection bias 2062
  sensitivity 2062, 2062t
  specificity 2062, 2062t
stavudine, adverse reactions 1299t
steam autoclave 2362t
steatocystoma 1822, 1822f
steatocystoma multiplex 1089, 1821
  genetics 813t
steel factor 1011
Stegman, Samuel 2525
stem cells 60–63, 61t–62t
  epidermal 60–61, 61f
  hair follicle 61, 62f, 1083–1084
  plasticity 61–62
  wound healing 2321, 2324, 2324f
stem cell factor 1993
stem cell growth factor *see* steel factor
stem cell therapy 62–63, 63f
Stensen's duct 2329f
Sterculiaceae 277t
Steri-Strips 2387t
sterilization of instruments 2362, 2362t
Steripaste 2369
sternal clefts 998, 999f
sternocleidomastoid muscle
steroid rosacea 569, 569f
steroid sulfatase deficiency 838t, 843–845
  clinical features 844–845, 844f
  differential diagnosis 845
  epidemiology 844
  genetics 803t–804t
  history 844
  neonatal 847t
  pathogenesis 844
  pathology 845
  treatment 845
Stevens-Johnson syndrome 9–11, 323–332, 519t
  anogenital 327f, 1185
  clinical features 324t, 326–329, 327f–329f
  differential diagnosis 320t, 324t, 330
  drug-induced 325t, 338t, 347, 347f, 1518t
  epidemiology 325, 325t
  epidermal detachment 324, 328f
  history 324–325
  pathogenesis 325–326, 326f–327f
  pathology 329–330, 329f
  treatment 330–332, 330f
Stewart-Bluefarb syndrome 1724–1725
stick-tight flea 1440t
stiff skin syndrome 654
  clinical features 654
    hypertrichosis 1117t
  differential diagnosis 652t
  genetics 807t
Still, George 671
Still's disease
  adult onset 672–675
    clinical features 673–675, 675f
    epidemiology 672–673
    pathogenesis 673
    pathology 675, 675f
    treatment 675
  juvenile *see* juvenile idiopathic arthritis
stimulant abuse, prevalence 1512t
stinging nettles 274t, 276–277
stingrays 1452
stippled epiphyses 841t–842t
stoechas lavender (*Lavandula stoechas*) 2215t
stomatitis
  contact 1157–1158, 1157f, 1157t
  drug-induced 351–352
  moriform 1278
  nicotine 1161–1162, 1162f
  paraneoplastic pemphigus 468, 468f

recurrent aphthous 1158–1159, 1158f, 1158t–1159t
stomatitis areata migrans *see* geographic tongue
stomatitis nicotina *see* nicotine stomatitis
stonefish 1452
stork bite 1000, 1715f
StrataGraft 2375t–2376t
Stratasorb 2373
stratum corneum 8, 43, 2065–2066, 2065t
'acid mantle' 2068
barrier disruption 2067
barrier function 2066t
'bricks and mortar' structure 2065–2066, 2065f
domain-mosaic model 2066
lipid barrier 2066
occlusion of 2069
'reservoir' 2065–2066
stripping 2070f, 2071
thickness 2066
strawberry gums 1160f
strawberry nevus 1691
strawberry tongue
Kawasaki disease 1183
scarlet fever 1195
Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) 2063
Streptobacillus moniliformis 1213
streptococcal intertrigo 1196–1197
streptococcal perianal disease 1183, 1197
streptococcal toxic shock syndrome 1194t, 1195–1196
clinical features 1193t, 1195
diagnosis 1194t, 1196
epidemiology and pathogenesis 1195
pathology 1196
treatment 1196
Streptococcus pneumoniae
Streptococcus pyogenes 1450t
transmission by head lice 1427
Streptococcus viridans, and drug abuse 1515t
streptokinase-induced secondary cutaneous vasculitis 390t
Streptomyces fradiae 2107
Streptomyces somaliensis 1271t
streptomycin
adverse reactions
hypertrichosis 1118t
lichen planus 185t
systemic contact dermatitis 246t
indications, tuberculosis 1234t
stress reticulocyte adhesion/occlusion disorders 382
stretch marks *see* striae
striae 1635–1636
alba 1635, 1635f
anatomic distribution 1636f
clinical features 1635, 1635f–1636f
Cushing's disease 1635
differential diagnosis 1636
distensae, obese patients 751t
epidemiology 1635
history 1635
obese patients 1635
pathogenesis 1635
pathology 1635–1636
in pregnancy 1635, 1636f
rubra 1635, 1635f
steroid-induced 1635
treatment 1636
laser therapy 2271
Wickham's 8f, 187, 188f
strimmer dermatitis 281
stripping of stratum corneum 2071
stromelysins 1964f
in wound healing 2323t
Strongyloides stercoralis 375, 1407t–1408t
strongyloidiasis 1407t–1408t
disseminated 375
HIV-related 1293
strumous bubo *see* lymphogranuloma venereum
stucco keratosis 1800–1801
clinical features 1800f, 1801
differential diagnosis 1801
epidemiology 1800
history 1800
pathogenesis 1800–1801
pathology 1801
treatment 1801
Sturge-Weber syndrome 945t–946t, 1715–1718
clinical features 1715–1718, 1716f
port-wine stains 1716f, 2263
evaluation 1714f
subacute cutaneous lupus erythematosus 47t, 618f, 620
clinical features 620f
differential diagnosis 625–626, 626t
drug-induced 350
histology 624t
inflammatory infiltrates 618f
subacute nodular migratory panniculitis 1645
subacute regional lymphadenitis *see* cat scratch disease
subcorneal pustular dermatosis 832t–833t
see also Sneddon-Wilkinson disease
subcorneal vesicles 531
subcutaneous fat loss 1673
subcutaneous fat necrosis of newborn 1651–1652, 1651t
clinical features 1652, 1652f
differential diagnosis 1652
epidemiology 1651
history 1651
pathogenesis 1651
pathology 1652, 1652f
treatment 1652
subcutaneous mycoses 1266–1273
chromoblastomycosis 1267–1273
lobomycosis 1273
mycetoma 1270–1272
sporotrichosis 1272–1273
subcutaneous panniculitis-like T-cell lymphoma 2020t, 2032–2033, 2032f, 2032t
subcutaneous pseudosarcomatous fibromatosis *see* nodular fasciitis
subcutanous lupus erythematosus *see* lupus panniculitis
subcutis, development of 58–59
subependymal nodules 935t–936t
subepidermal calcified nodule 733
subepidermal vesicles 440
subjective or sensory irritant contact dermatitis 252
sublamina densa 455–456
substance P 101t, 103–104
subungual exostosis 1144, 1145f, 2440t
treatment 1144
subungual hematoma 1143
musical instrument-related 1509t
pseudo-Hutchinson's sign
sports-related 1506t
subungual hyperkeratosis 1129f
and mal de Meleda 877
and pachyonychia congenita 881f
in pregnancy 447t
subungual scabies 1423, 1425f
sucking blisters 526t–528t, 530
Sucquet-Hoyer canals 1087
sucralfate
Behçet's disease 435t
interactions 2190, 2193
Sudan black stain 27t–28t
Sudan orange stain 27t–28t
sudoriferous cyst *see* hidrocystoma
sulconazole
formulations 2118t
pregnancy and lactation 2118t
trade names 2118t
sulfabenzamide 342f
sulfadiazine
adverse reactions, Stevens-Johnson syndrome/toxic epidermal necrolysis 325t
indications, toxoplasmosis 1405–1406
sulfadoxine, adverse reactions, Stevens-Johnson syndrome/toxic epidermal necrolysis 325t
sulfamethizole 342f
sulfamethoxazole
adverse reactions
lichen planus 185t
linear IgA bullous dermatosis 498t
sulfanilamide 342f
sulfapyridine
dermatitis herpetiformis 496
IgA pemphigus 473
linear IgA bullous dermatosis 499
sulfasalazine 342f
adverse reactions
erythroderma 176t
lichen planus 185t
Stevens-Johnson syndrome/toxic epidermal necrolysis 325t
indications
lichen planus 195–196, 195t
lupus erythematosus 628t
SAPHO syndrome 437t
urticaria 304, 304t
sulfathiazole/sulfacetamide 342f
sulfinpyrazone 711
sulfisoxazole 342f
sulfonamides 2105t, 2112–2113, 2190t
adverse reactions 338t, 2113
bullous drug eruptions 519t
cutaneous lymphoid hyperplasia 2039t
cutaneous vasculitis 390t
erythema multiforme 320t
erythema nodosum 1644t
erythroderma 176t
linear IgA bullous dermatosis 498t
photoallergy 1480t
pruritus 120t
classification 342f
contraindications 2113
dosage 2113
indications 2112–2113
bullous pemphigoid 484t
nocardiosis 1218
pyoderma granulosum 432t
interactions 2113
mechanism of action 2112, 2113f
pregnancy and lactation 2113
sites of action 2109t
sulfonylureas
adverse reactions
erythroderma 176t
secondary cutaneous vasculitis 390t
and eccrine sweating 590t
sulfur
perforating disease 1604t
scabies 1426, 1426t
topical 2163
sulfur-deficient brittle hair syndrome *see* trichothiodystrophy
sulfuric acid 253t–254t
sulindac-induced lichen planus 185t
sulisobenzone 2199, 2200f
Sulzberger-Garbe syndrome 225
sumatriptan 342f
and eccrine sweating 590t
summertime actinic lichenoid eruption 201
sun exposure 2197
sun protection 1892
sun protection factor 2197–2198
and blockage of erythemal radiation 2198t
determination of 2198t
sunbeds 2197
sunburn 1021–1022, 1455–1457, 1456f, 1482, 2202
action spectrum 2201t
sunflower 285t
sunitinib 353t, 1887t, 2149t
sunlight
parapsoriasis 159t
photodynamic therapy 2243t
pityriasis lichenoides 162t
sunscreens 1464, 2197–2204
active ingredients 2199–2201, 2200f
efficacy 2201–2203, 2201f
cutaneous melanoma 2202–2203
non-melanoma skin cancer 2202
photoaging 2202
photoimmune suppression 2202
photosensitivity skin disorders 2203, 2203t
sunburn 2202
history 2197
inorganic 2199–2201
labeling 2198t
in lupus erythematosus 628
mechanisms of action 2199, 2199f
organic 2199
and photoallergy 2203
recommendations 2203
regulation of 2197–2199
sun protection factor 2197–2198, 2198t
UVA protection 2198–2199
safety 2203
Time and Extent Application 2199
Supercut scissors 2359f
superfatted soap 2480t
superficial folliculitis 571–577, 571f, 1189
clinical features 571, 572f
differential diagnosis 572
pathology 571–572, 575f
treatment 572
superficial granulomatous pyoderma 428t
superficial musculoaponeurotic system 2329–2330, 2330f
superficial mycoses 1251–1266, 1251t, 1252f
dermatophytoses 1255–1266, 1255t
chronic mucocutaneous candidiasis 818t–819t, 900t, 902–904, 1266
clinical features 1256–1262
differential diagnosis 1256t, 1263–1264, 1265f–1266f
epidemiology 1255
granuloma gluteale infantum 1266, 1270f
history 1255
invasive 1265–1266
pathogenesis 1255–1256, 1256t
pathology 1262
treatment 1264–1265, 1267t
non-inflammatory 1251–1266
clinical features 1252–1253, 1252f–1253f
differential diagnosis 1254
epidemiology 1251
history 1251
pathogenesis 1251–1252
pathology and fungal culture 1253–1254, 1254f
treatment 1252t, 1254–1255
superficial peroneal nerve block 2351f
superficial phaeohyphomycosis *see* non-inflammatory superficial mycoses
superficial spreading melanoma 1892, 1892f–1893f
superficial thrombophlebitis 2520
superficial ulcerating rheumatoid necrobiosis 762f
superficial/deep gyrate erythema *see* erythema annulare centrifugum
supernumerary digits, rudimentary 1009, 1009f
supernumerary nipples 1007, 1007f, 1118t
suppressor T cells 1559, 2003–2004
suppurative granuloma 22, 23f
suprabasilar acantholysis 469, 469f
supraorbital nerve 2349, 2349f
supratrochlear nerve 2349, 2349f
supraumbilical raphae 998
sural nerve block 2351f
suramin 1402t–1403t
surface irradiance 2201f
surfactants 2485t
surfer's knots 1506t
surgery trays 2359f
surgical complications 2459–2472, 2460f
intraoperative 2463–2467
bleeding and hemostasis 2463–2465, 2464f–2465f, 2464t
contamination 2463

necrosis 2465–2466
nerve deficits 2466–2467, 2466f–2467f
tension 2465, 2466f
tissue injury 2465
unsatisfactory scarring 2467
postoperative 2467–2471
bleeding/hematoma/ecchymosis 2467–2469, 2467f–2468f
dehiscence 2469–2470, 2470f
infection 2469, 2469f
necrosis 2469, 2469f
wound appearance 2470–2471, 2470f–2471f
preoperative assessment 2459–2463, 2461f
allergies 2463
defibrillators and pacemakers 2462–2463
informed consent 2463
potential for bleeding 2459–2461
prophylactic antibiotics 2461–2462, 2462t
wound healing 2461, 2462t
surgical gut sutures 2354–2355, 2354t
foreign body reaction 2357
Surgicel 2464t, 2465
Surgifoam 2464t
Sutton's nevus *see* halo nevus
sutures 2353–2354, 2354t
absorbable 2354–2355, 2354t
glycomer 631 2354t, 2355
poliglecaprone 25 2354t, 2355
polydioxanone 2354t, 2355
polyglactin 910 2354t, 2355
polyglycolic acid 2354t, 2355
polyglyconate 2354t, 2355
surgical gut 2354–2355, 2354t
capillarity 2353
coefficient of friction 2353
complications 2357, 2357f
elasticity 2353
foreign body reactions 2357
histopathology reactions
materials 2354
memory 2353
non-absorbable 2355–2356, 2356t
nylon 2355–2356, 2356t
polybutester 2356, 2356t
polyester 2356, 2356t
polypropylene 2354f, 2356, 2356t
silk 2355, 2356t
packet information 2359f
physical configurations 2353
plasticity 2354
pliability 2354
purse-string
selection 2356–2357, 2356t
techniques
buried vertical mattress stitch 2385, 2386f
horizontal mattress suture 2385, 2386f
instrument tie 2385, 2385f
interrupted buried dermal stitch 2385, 2386f, 2388f
running locked suture 2386–2387, 2386f
running subcuticular stitch 2386–2387, 2386f
simple interrupted epidermal stitch 2385, 2386f
simple running epidermal stitch 2385–2386, 2386f
vertical mattress stitch 2385, 2386f
tensile strength 2353
tissue reactivity 2353, 2469f
USP size 2353
suture granuloma 1574t, 1576t, 1582
suture tracks 2471, 2471f
suture-removal scissors 239f
swamp foot *see* immersion foot
swamp weed 285t
sweat
altered composition 597–598
production 541t
and skin disease 598–601
sweat glands *see* apocrine glands; apoeccrine glands; eccrine glands
sweat retention 541
sweating 51
drug-induced 590t
excessive *see* hyperhidrosis
reduced *see* hypohidrosis
sweaty sock dermatitis *see* plantar dermatosis, juvenile
sweet clover 2207t
sweet lemon 280t
sweet orange (*citrus senesis*) 275t, 2215t
Sweet's panniculitis 1660t
Sweet's syndrome 423–427
associated diseases 426, 426t
clinical features 424, 425f–427f
differential diagnosis 423–424, 427, 427t
drug-induced 343–344
epidemiology 424
and erythema nodosum 427, 1644t
history 423–424
and leukemia 424, 425f, 2042t
monoclonal gammopathy 430, 2014t
paraneoplastic 424, 764t–765t, 766f
pathogenesis 424
pathology 426–427, 426f
and pseudocellulitis
treatment 427
swimmer's ear 1206
swimmer's itch 1417–1419, 1418f
swimmer's shoulder 1506t
swimming pool granuloma *see* *Mycobacterium marinum*
Sybert keratoderma 828t
sycosis 572f
barbae *see* pseudofolliculitis barbae
herpetic 579t
lupoid 579t
mycotic 579f, 579t
symmetric induration 644t
symmetrical drug-related intertriginous and flexural exanthema *see* SDRIFE
sympathectomy
hyperhidrosis 594t
reflex sympathetic dystrophy 122t
Symphytum officinale see comfrey
synaptophysin 29t–33t
syncoilin 828t
syndecans 1592t
syndet bar cleanser 2479
syndet liquid 2479
syndrome X
synemin 828t
synophrys 1034, 1118t
synovial cyst *see* ganglion
synovitis, acne, pustulosis, hyperostosis and osteitis *see* SAPHO syndrome
synthetic human collagen 2551
synthetic resins/plastics, sensitivity to
syphilis 1367–1379
and anetoderma 1633t
cardiovascular 1373–1375
clinical features 1369–1377, 1369f–1370f
hypomelanosis 1042
congenital 526t–528t, 1376–1377
clinical manifestations 1376f
early 1376
laboratory diagnosis 1377
late 1376–1377
mother-to-child transmission 1376t
stigmata 1376–1377, 1377t
differential diagnosis 1378, 1379t
early
clinical features 1369–1370
congenital 1376
endemic 1042, 1217
epidemiology 1368
and erythema nodosum 1644t
history 1367
HIV-related 1291, 1369, 1375
incidence 1368f
laboratory diagnosis 1377–1378, 1377t, 1378f
microscopic examination 1377
polymerase chain reaction 1377
serologic tests 1377–1378
latent
clinical features 1371–1373
pathogenesis 1369
natural history 1368f–1369f
neurosyphilis 1375–1376
classification 1375t
HIV-related 1375
laboratory diagnosis 1375–1376
occupational 271t
pathogenesis 1368–1369
pathology 1378
primary 1368f
clinical features 1370–1371, 1370f
pathogenesis 1369
pathology 1378
secondary 184t, 308t–310t, 1368f
clinical features 1072t–1073t, 1371, 1371t, 1372f–1374f
pathogenesis 1369
pathology 1378, 1378f
tertiary (late)
benign 1373
clinical features 1373–1375, 1375f
congenital 1376–1377
pathogenesis 1369
pathology 1378
treatment 1378–1379, 1379t
Treponema pallidum vector 29t–33t, 271t, 1216, 1368
syringocystadenoma papilliferum 1843, 1843f–1844f
syringofibroadenoma 1847
syringoma 1841
anogenital 1183t
chondroid 1831–1834, 1833f–1834f
clinical features 1841, 1841f
linear 955
pathology 1841, 1841f
treatment 1841
syringomatous carcinoma 1846
systematic reviews 2060–2061
systemic amyloidosis 705–708
hemodialysis-associated 707
inherited 707–708
primary 705–707, 705f–707f
secondary 707
X-linked reticulate pigmentary disorder 708
systemic capillary leak syndrome 300, 2014t
systemic chondromalacia *see* relapsing polychondritis
systemic coagulopathies with cutaneous manifestations 377–380
antiphospholipid antibody/lupus anticoagulant syndrome 370t, 379–380
protein C and S disorders, congenital and acquired 377–379
systemic contact dermatitis 519t, 1176f
systemic disease 761–781
anogenital manifestations 1183
Behçet's disease 433f, 1183
inflammatory bowel disease 1183
Langerhans cell histiocytosis 1183
zinc deficiency 1183
cardiac disease *68*
endocrine and metabolic disease 768–769, 768f–770f, 768t–771t
gastroenterological disease 771, 771f–772f, 771t–774t
hematology and oncology 763–767, 763f, 763t–765t, 766f–767f
liver disease 774t
multisystem disorders 776t–778t
nails in 1138–1141
apparent leukonychia 1130f, 1139–1140
autoimmune connective tissue disorders 1140
clubbing 1130f, 1139, 1139t
drug-induced abnormalities 1140–1141, 1141f, 1141t
HIV infection 1140
peripheral neuropathies 1140
pseudoinflammatory nail changes 1140
yellow nail syndrome 1130f, 1139, 1139f
oral manifestations 1167–1168
amyloidosis 1167
Crohn's disease 1167–1168, 1168f
pernicious anemia 1167, 1168f
pyostomatitis vegetans 1168
pulmonary disease 778t–779t
renal disease 780t–781t
rheumatology 761–763, 761t, 762f
sarcoidosis 1560–1561
systemic drugs 2165–2181, 2166t
antimalarials 2165–2169
azathioprine 2169–2171, 2171f, 2171t
bleomycin 2172t
clofazime 2172t
colchicine 2172t
cyclophosphamide 2172–2173
cyclosporine 2172
dapsone 2174–2175
gold 2175f, 2175t
hydroxyurea 2175–2176, 2176f
intravenous immunoglobulin
leukotriene inhibitors 2176, 2177f, 2177t
methotrexate 2176–2178, 2177t–2178t
monitoring guidelines 2167t–2168t
mycophenolate mofetil 2178–2179, 2178f
saturated solution of potassium iodide 2179
tacrolimus 2179, 2179t
thalidomide 2179–2180, 2180f
systemic lupus erythematosus 623, 623t, 627t
ANCA in 613t
and anetoderma 1633t
bullous eruption *see* bullous systemic lupus erythematosus
C2 deficiency 909t
cardiovascular disease 627t, 776t–778t
classification 627t
and dermatitis herpetiformis 493t
differential diagnosis 625–626, 626t, 639t
drug-induced 350, 608
genes associated with 616t
pernio *see* chilblain lupus
renal disease 627t, 780t–781t
see also lupus erythematosus
systemic mycoses 1273–1284, 1275f
opportunistic pathogens 1279–1284, 1279f
clinical features 1280, 1281f
differential diagnosis 1282
epidemiology 1279–1280
history 1279
pathogenesis 1280
pathology 1280, 1282f
treatment 1282, 1283t
true pathogens 1273–1279
blastomycosis 1274–1277
coccidioidomycosis 1277–1278
histoplasmosis 1273–1274
paracoccidioidomycosis 1278–1279
systemic sclerosis *see* scleroderma
systemic sclerosis sine scleroderma 645

T cells 87–93
antigen presentation 86–87
in atopic dermatitis 206t
CD3+ 88
CD4+ 86, 88
CD8+ 86, 88
central memory 89
clonal expansion 90
cytotoxic *see* cytotoxic T cells
dendritic epidermal 93
development 88
effector memory 89–93
γ/δ 92–93
natural killer cells *see* natural killer cells
in psoriasis 137
regulatory *see* regulatory T cells
suppressor 1559, 2003–2004
see also individual CD types
T cell receptors 86, 88–89
costimulatory signals 89–90, 89f, 89t
diversity 86f, 88–89
signaling 89, 89f
T cells 2320

T helper cells 90–91, 90f
  Th0 90
  Th1 90
  Th2 90–91
  Th3 91
  Th17 91
  Th22 91
T-cell lymphoma 1, 2017–2036
  adult T-cell leukemia/lymphoma 2028
  CD4+/CD56+ hematodermic neoplasm 2044–2045
  classification 2017–2019, 2018t, 2021f
  diagnosis 2018
    practical guidelines 2019
  differential diagnosis 639t, 2020t
  and erythroderma 172t–173t, 177–178
  extranodal NK/T-cell lymphoma, nasal type 2033, 2033f
  granulomatous slack skin 2027, 2027f
  history 2017–2018
  immunophenotyping 2018
  lymphomatoid papulosis 2030–2032
  mycosis fungoides *see* mycosis fungoides
  pagetoid reticulosis 2026–2027, 2026f
  primary cutaneous aggressive epidermotropic CD8+ cytotoxic 2020t, 2033, 2034f
  primary cutaneous CD4+ small/medium-sized pleomorphic 2034
  primary cutaneous CD30+ lymphoproliferative disorders 2020t, 2029–2032
  primary cutaneous γ/δ 2034
  primary cutaneous peripheral unspecified 2034
  pruritus in 112t, 114
  Sézary syndrome 174, 2027–2028
  staging 2019
  subcutaneous panniculitis-like 2032–2033, 2032f, 2032t
  T-cell receptor gene rearrangement analysis 2018
  treatment
    interferons 2131
    retinoids 2096, 2097t
  WHO-WORTC classification
T-cell receptor deficiencies 920t
T-cell receptor gene rearrangement analysis 2023–2025
tabes dorsalis 1375
tacalcitol 2156
  dosage 2161t
  Hailey-Hailey disease 895
  psoriasis 149t
tache noir *see* black heel and palm
tacrine 2190t
  and eccrine sweating 590t
tacrolimus 2136–2138, 2179t
  adverse reactions 2138, 2169t, 2185t
  contraindications 2138, 2179t
  dosage 2138, 2179t
  indications 2137–2138, 2179t
    atopic dermatitis 214
    Behçet's disease 435t
    dermatomyositis 639t
    Hailey-Hailey disease 895
    hypertrophic scars/keloids 1625t
    lichen planus 195, 195t
    nummular dermatitis 226
    pruritus 106t, 123
    pyoderma granulosum 432t
    sarcoidosis 1563t
  interactions 2124t, 2138, 2179t, 2190–2192
  mechanism of action 2137, 2137f, 2179t
  monitoring 2167t–2168t
  pregnancy and lactation 2138, 2179t
tadalafil 651
Taenia solium 730, 1413f
Tagetes spp. *see* marigold
Takayasu's arteritis 385t
talarozole 2093
talc, foreign body reaction 1574t, 1579
  clinical features 1579
  histopathology 1576t
  pathology 1579
  treatment 1579
talin 452
talon noir *see* black heel and palm
tamoxifen
  adverse reactions, pruritus 120t
  dermatomyositis 639t
tamsulosin 342f
Tanacetum cinerarillifolium see pyrethrum
Tanacetum parthenium see feverfew
Tanacetum vulgare see tansy
tanapox 1355t–1356t
Tangier disease 810t–811t
tanning 8, 1021–1022, 1455–1457, 1456f
  delayed 1482–1483
tanning lamps, and NMSC 1774
tansy 285t
TAP deficiency 900t
tapeworms 1413f
  cysticercosis and echinococcosis 1419–1420
tar *see* coal tar
tar shampoos, hair discoloration 1498t
tarantulas 1448
Taraxacum officinale see dandelion
Tarband 2369
targeted immunomodulators 2138–2147, 2139f, 2140t, 2149t
  adalimumab 2145
  alefacept 2138–2140
  anakinra 2146
  certolizumab 2146
  efalizumab 2140–2141
  etanercept 2143–2144
  golimumab 2146–2147
  infliximab 2144–2145
  omalizumab 2147
  rituximab *see* rituximab
  TNF-α inhibitors 2141–2143
  ustekinumab 2146
targetoid hemodiderotic hemangioma *see* hobnail hemangioma
Tarral, Claudius 162
tattoo inks 1574t, 2269t
  foreign body reaction 9f, 1573, 1575–1578
    clinical features 1576, 1577f
    diagnosis 1577
    differential diagnosis 1577
    histopathology 1576t
    pathology 1576
    treatment 1577–1578
tattoo removal 2256, 2267–2268, 2268f
  adverse effects of lasers 2269t
  laser type 2269t
taxanes
  adverse reactions
    acral erythema 349t
    alopecia 349t
    eccrine squamous syringometaplasia
    mucositis 349t
    nail changes 1133f, 1141t
    sclerodermoid syndromes 650t, 654
Tay syndrome *see* trichothiodystrophy
tazarotene 2089, 2091
  formulations 2097t
  indications
    acne vulgaris 556, 2093
    alopecia areata 1103t
    lamellar ichthyosis 851
    psoriasis 150t, 1137t, 2093
  pharmacologic features 2092t
  structure 2090f
TCA Cross skin resurfacing technique 2500–2501, 2501f
TCM *see* traditional Chinese medicine
TdT 29t–33t
tea 2210–2211
tea tree (*Melaleuca alternifolia*) 285t, 288, 2215t
tear gas, adverse reactions, erythroderma 176t
Tegaderm 2369, 2373
tegafur, adverse reactions 349t
Tegagel Hydrogel Wound Filler 2372
Tegagel Wound Filler with gauze 2372
Tegasorb 2373
Tegenaria agrestis 1448
telangiectasias 1001t, 1718–1719, 1753–1755, 2516t
  angioma serpiginosum 1754, 1755f
  ataxia-telangiectasia *see* ataxia-telangiectasia
  causes 1754t
  clinical features 1718–1719
  cutaneous collagenous vasculopathy 1753, 1755f
  cutis marmorata telangiectatica congenita 1718, 1718f, 1747
  general essential 1753
  hereditary benign 1718
  hereditary hemorrhagic *see* hereditary hemorrhagic telangiectasia
  nailfold 633f
  nevoid 1718
  radiotherapy-induced 2299t, 2300f
  scleroderma 646, 646f
  spider telangiectasia 1753, 1754f
  treatment 2515–2517
    electrocoagulation 2308f
    foamed detergent solutions 2517
    injection technique 2516–2517
    intense pulsed light 2517
    laser therapy 2266, 2517
    sclerosing solution 2514t
  unilateral nevoid 1753–1754, 1755f
telangiectasia macularis eruptiva perstans 1995, 1997f
telangiectatic matting 2516t, 2519
  sclerosing solution 2514t
telavancin 2117t
  indications, MRSA 1191t
Telfa XTRA 2373
tellurium, dermatosis 1499t
telogen 1079t, 1080, 1099f
  duration of 1080
telogen effluvium 1098–1099
  causes 1098t
  clinical features 1095f, 1098–1099
  drug-induced 1098
  histologic features 1096t
  pathogenesis 1098, 1098t
  postpartum 447t
telomere 784t
  maintenance defects 800t–801t
temozolomide 1909t
temporal arteritis 385t, 407, 407f
temporal course 9–11
temporal triangular alopecia 1095f, 1103, 1103f
tenascins 1592t
tenascin-X 1593t, 1608–1609
  deficiency 1608–1609
tendinous xanthomas 1551–1552
tendon friction rubs 645t
tendon sheath
  fibroma 1968
  giant cell tumor 1967–1968, 1968f
teniposide 2190t
tennis toe 1506f, 1506t
tenofovir, adverse reactions 1299t
teratogenicity of retinoids 2099, 2099t
terazosin
  interactions 2192
  reflex sympathetic dystrophy 122t
terbinafine 2190t
  adverse reactions 2122
    erythroderma 176t
  chronic mucocutaneous candidiasis
  dosage 2121t
  formulations 2118t
  indications 2120t
    dermatophytoses 1267t
  interactions 2189–2190, 2191t
  pregnancy and lactation 2118t, 2120t, 2155t
  trade names 2118t
terconazole
  formulations 2118t
  mucocutaneous candidiasis 1269t
  pregnancy and lactation 2118t
  trade names 2118t
terfenadine 2186t
  interactions 2124t
terizidone 1234t
terminal follicle 543f
terminal hair 1079t
terminal osseous dysplasia with digital anomalies with pigmentary defects 810t
Terry's nails 1139
tertiary intention healing 2315
tesamorelin 1296
testicular cancer, cutaneous metastases 2049t
testosterone
  and acne 550t
  lichen sclerosus 667t
  morphea 667t
tetracaine 2344t, 2347t
tetrachlorodibenzo-p-dioxin (TCDD) 269
tetracyclines 2105t, 2114–2115
  adverse reactions 338t, 2115, 2185t
    lichen planus 185t
    nail changes
    pigmentation 2115f
    pseudoporphyria 724t
  contraindications 2115
  dosage 2114, 2114t
  indications 2114
    acne vulgaris 556t
    linear IgA bullous dermatosis 499
    pityriasis lichenoides 162t
    rosacea 567t
    syphilis 1379t
    vasculitis 402t
  interactions 2115
  mechanism of action 2114–2115
  pregnancy and lactation 2115
  routes of administration 2114t
  sites of action 2109t
  topical 2109
  see also individual drugs
tetraethylammonium, hypohidrosis/anhidrosis 595t
tetraplegia 841t–842t
tetraspan CD151 452
Tetrix cream 2156
Texier's disease 663
textile dermatitis 243, 245–246
thalidomide 2179–2180
  adverse reactions 2169t, 2180
    erythroderma 176t
  contraindications 2180
  dosage 2180
  indications 2170t, 2180
    Behçet's disease 435t
    cholestatic pruritus 119t
    complex aphthosis 1159t
    dermatomyositis 639t
    epidermolysis bullosa 511
    juvenile idiopathic arthritis 672
    lichen planus 195t, 196
    lupus erythematosus 628t, 2180f
    prurigo nodularis 115
    pruritus 106t
    pyoderma granulosum 432t
    reflex sympathetic dystrophy 122t
    renal pruritus 118t
    Rosai-Dorfman disease
    sarcoidosis 1563t
    scleromyxedema 690
  interactions 2180
  mechanism of action 2180
  monitoring 2167t–2168t
  pregnancy and lactation 2180
thallium dermatosis 1499t
thanatophoric dysplasia 818t–819t
Thaumetopoea pityocampa 1441t
Thaumetopoea processionea 1441t
Thaumetopoea wilkinsoni 1441t
theophylline
  and eccrine sweating 590t
  interactions 2124t, 2127t
thermal ablation 2072
thermal burns *see* burns
thermal coagulation 2252–2253
thermal relaxation time 2253, 2254t
thermolysis 2310
thermoregulation 51, 175
thiabendazole 1402t–1403t
thiacetazone, tuberculosis 1234t
thiamine *see* vitamin B1

thiazides
  adverse reactions
    phototoxicity 1480t
    secondary cutaneous vasculitis 390t
  interactions 2124t
thimble jellyfish 1451
thimerosal hypersensitivity 242t, 244, 253t–254t
thiocyanates 278t
thioflavin T stain 27t–28t
6-thioguanine, psoriasis 153t
thiopurine methyltransferase 2167t–2168t
thioridazine
  and eccrine sweating 590t
  and hyperpigmentation 1056t–1057t
thiothixene, and eccrine sweating 590t
thistle 275t, 277t
thiuram 242t
  systemic contact dermatitis 246t
Thomas, Bernard 319
thoracic outlet syndrome 647t
thrombin 2464t
  with gelatin 2464t
thrombin inhibitors 364t
thrombin-activatable fibrinolysis inhibitor 1744t
thrombocytopenia
  heparin-induced 369
  SLE 627t
thrombocytosis secondary to myeloproliferative disorders 370–372
Thromboject 2515t
thrombomodulin 360
  deficiency 1744t
  soluble 364t
thrombophlebitis
  and drug abuse 1515t
  and pseudocellulitis 816t
  superficial 367
thrombospondin gene 1765t
thrombospondins 1592t, 1683–1684
thrombotic thrombocytopenic purpura 1248, 1748t
  familial 818t–819t
thrombotic thrombocytopenic purpura-hemolytic uremic syndrome 373
thrombotic vasculopathy 49f
thromobospondins 1683f
thrush 1268f
thulium lasers, skin penetration 2254f
thymic alymphoplasia *see* severe combined immunodeficiency
thymine dimer 1459f
  wavelength to induce 1459f
thymoma 473
thymus 87
thyroglobulin 2053t
thyroglossal duct cyst 1824–1825, 1825f
thyroid acropachy 693
thyroid cancer, metastases 2053t
thyroid disease
  dermatologic manifestations 770t
  pruritus in 119
thyroid transcription factor-1 29t–33t
thyrotoxicosis, electrolytes in sweat 597t
thyroxine, urticaria 304, 304t
TIA-1 29t–33t
ticks
  Amblyomma spp. 1442–1443
  Dermacentor spp. 1443, 1443f
  Ixodes spp. 1444, 1444f
  Rhipicephalus spp. 1443–1444, 1444f
tick bites 1440–1442
  antibiotic prophylaxis 1442
  see also different types of tick
tick control measures 1442, 1442t
tick removal 1442
tick repellents 1442
tick-borne disease
  encephalitis 1435, 1444
  lymphadenopathy 1244t, 1246t
ticlopidine 2191–2192
Tie-2 receptor tyrosine kinase 1681
Tielle 2373
Tietz syndrome 1034t, 1035
tigecycline 2117t
  indications, MRSA 1191t
tiger-tail hair 841t–842t
tight junctions 833–834
timolol 1705, 2186t
tin dermatosis 1499t
tinea, differential diagnosis 1256t
tinea barbae 1259, 1259f
  occupational 271t
tinea capitis 221, 1259–1261
  clinical features 1095f, 1260f–1261f
  differential diagnosis 1256t
  occupational 271t
  treatment 1267t
tinea circinata *see* pityriasis rotunda
tinea corporis 8
  in athletes 1507t
  clinical features 1256–1257, 1257f
  differential diagnosis 308t–310t, 1256t
  occupational 271t
  treatment 1267t
tinea cruris 1257–1258, 1258t
  in athletes 1507t
  clinical features 1258f
  differential diagnosis 1256t
tinea faciei 1259
  clinical features 1259f
  differential diagnosis 1256t
tinea imbricata 1257
tinea manuum 1258–1259
  clinical features 1258f
  treatment 1267t
tinea nigra 1252–1253
  clinical features 1252f
tinea pedis 1261, 1263t
  in athletes 1507t
  clinical features 1263f, 1263t
  differential diagnosis 219, 1256t
  inflammatory 1263t
  interdigital 1263t
  moccasin 1258–1259, 1263t
  treatment 1267t
  ulcerative 1263t
tinea unguium 1261–1262
  clinical features 1264f
  treatment 1267t
tingible bodies 2009–2010
tinidazole, amebiasis 1398
Tinosorb M 2200f
Tinosorb S 2200f
tinzaparin 364t
tioconazole
  formulations 2118t
  mucocutaneous candidiasis 1269t
  pregnancy and lactation 2118t
  trade names 2118t
tipranavir, adverse reactions 1299t
Tisseel 2464t
tissue factor pathway inhibitor 359–360, 364t, 1744t
tissue importation flaps 2402, 2412–2416
  nasolabial interpolation flap 2415, 2415f
  paramedian forehead flap 2413–2415, 2414f
  retroauricular flap 2415, 2416f
  Spear's flap 2415–2416, 2417f
tissue injury 2465
tissue macrophages 2319–2320
tissue plasminogen activator 358–359, 363f, 2513–2514
  calciphylaxis 732
tissue processing 65f, 66–67
tissue reorientation flaps 2402, 2410–2412
  bilobed transposition flap 2411–2412, 2412f–2413f
  nasolabial transposition flap 2412, 2413f
  rhombic transposition flap 2410–2411, 2411f–2412f
tissue-engineered skin equivalents 2374–2376, 2375t
  composite grafts 2375–2376, 2376f
  dermal replacements 2374, 2375f, 2376t
  epidermal grafts 2374
  leg ulcers 2376–2377
titanium dioxide 2199–2201, 2200f, 2483t
Tityus serrulatus 1449t
tixocortol pivalate 242t, 245t
TLRs *see* Toll-like receptors
TNF *see* tumor necrosis factor
TNF receptor-associated periodic syndrome (TRAPS) 300
toasted skin syndrome *see* erythema ab igne
tobramycin-induced erythroderma 176t
tocilizumab 2149t
tocopherol *see* vitamin E
toenails
  big toenail malignment 1134–1135, 1135f
  ingrowing 1144, 2443–2444, 2443f–2444f
  pincer nails 1130f, 1143–1144, 1146f
  traumatic abnormalities 1143
toenail dystrophy 809t
togavirus 1345f
tolazamide 342f
  adverse reactions, lichen planus 185t
tolbutamide 342f
  adverse reactions, lichen planus 185t
Toll-like receptors 81, 82f, 546
  signaling defects 912t
  TLR1 81, 82f
  TLR2 81, 82f, 546
  TLR3 82f
  TLR4 81, 546
  TLR5 81, 82f
  TLR6 81, 82f
  TLR7 82f
  TLR8 82f
  TLR9 81–82, 82f
  TLR10 82f
tolnaftate
  formulations 2118t
  mechanism of action 2119t
  pregnancy and lactation 2118t
  trade names 2118t
toluidine blue stain 27t–28t
tomato 246t, 275t
tongue
  fissured 1150, 1150f
  geographic 1149–1150
  hairy 1150–1151, 1151f
  median rhomboid glossitis 1151, 1151f
  strawberry 1195
toomuchsun proto-oncogene 68–69
tooth and nail syndrome *see* Witkop tooth and nail syndrome
Topicaine *see* lidocaine
topical anesthesia *see* anesthesia, topical
topical medications 2153–2164, 2153t
  absorption, factors affecting 2153t
  adverse reactions 2155t
  anesthetics 2156, 2156t
    benzocaine 2156
    EMLA cream 2156
    lidocaine 2156
  anthralin 2161–2162, 2161t
  antipruritic agents 2156, 2157t
  azelaic acid 2163
  cantharidin 1439, 2162–2163
  chemotherapeutic agents 2159–2160
  combination and rotational therapy 2155–2156
  formulations and vehicles 2154, 2154t
  hair growth/hair loss agents 2159
    eflornithine 1125, 2159
    minoxidil 2159
  immunotherapy 2163
  keratolytic agents 2157–2158
    α-hydroxy acids 2158
    propylene glycol 2479
    salicylic acid 2158
    urea 2157–2158
  in neonates 2154–2155, 2155t
  podophyllin and podophyllotoxin 2162
  pregnancy and lactation 2154, 2155t
  quantity of application 2153–2154
    adults 2154f
    children 2154f
    fingertip unit 2153–2154
  skin-lightening agents 2158–2159
    hydroquinone 2158
    mequinol 2158–2159
    monobenzyl ether of hydroquinone 2158
  sulfur 2163
  systemic adverse reactions 2155t
  tar 2161–2163
  traditional 2162t–2163t
  vitamin D analogues 2160–2161, 2160f, 2161t
  see also individual drugs
topical negative pressure therapy 1736
topiramate 2190t
  adverse reactions, gingival hyperplasia 1156t
  hypertrichosis 1118t
  hypohidrosis/anhidrosis 595t
topotecan, adverse reactions
  alopecia 349t
  mucositis 349t
  neutrophilic eccrine hidradenitis 349t
TORCH syndrome 1337f
Torg-Winchester syndrome 807t
torsade de pointes 2124t
torsemide 342f
tositumonomab 2149t
tosylamide formaldehyde resin 242t
total skin electron beam therapy 2298
Touton giant cells 21
Townes-Brocks syndrome 1006
toxic contact dermatitis *see* irritant contact dermatitis
toxic epidermal necrolysis 9–11, 323–332, 519t
  clinical features 48, 48f, 319, 324t, 326–329, 328f–329f, 1193t
    pulmonary disease 778t–779t
  differential diagnosis 324t, 330
  drug-induced 325t, 338t, 347, 1518t
  epidemiology 325, 325t
  epidermal detachment 324, 328f
  history 324–325
  neonates 526t–528t
  pathogenesis 325–326, 326f–327f
  pathology 329–330, 329f
  SCORTEN scoring system 328–329, 329t
  treatment 330–332, 330f–331f
    immune globulin 331t, 2148t
  see also Stevens-Johnson syndrome
toxic erythema
  of chemotherapy 349t, 352f, 541f
  of newborn *see* erythema toxicum neonatorum
  of pregnancy *see* polymorphic eruption of pregnancy
toxic oil syndrome 654
  differential diagnosis 650t
  lichen myxedematosus 692
toxic shock syndrome
  staphylococcal 1193–1194, 1194t
  streptococcal 1193t–1194t, 1195–1196
toxic sock syndrome *see* pitted keratolysis
Toxicodendron spp.
  geographic range 283f
  identification 282
Toxicodendron diversilobum see poison oak
Toxicodendron radicans see poison ivy
Toxicodendron rydbergii see poison ivy
Toxicodendron verniciflua see Japanese lacquer tree
Toxicodendron vernix see poison sumac
Toxicondendron toxicarium see poison oak
toxin-mediated contact urticaria 276–277
  causes 276t
  clinical features 276
  differential diagnosis 277
  epidemiology 276, 276f, 276t
  history 276
  pathogenesis 276
  pathology 276–277
  treatment 277
  see also urticaria

Toxocara canis 417, 1407t–1408t
  life cycle 1414f
toxocariasis 1407t–1408t
Toxoplasma gondii 1404
  life cycle 1405f
toxoplasmosis 1404–1406
  clinical features 1404–1405
  differential diagnosis 1405
  epidemiology 1404
  pathogenesis 1404, 1405f
  pathology 1405
  treatment 1405–1406
trabecular carcinoma of skin *see* Merkel cell carcinoma
trachyonychia 1130f–1131f, 1131, 1138
traction alopecia 1096t, 1109, 1109f
traditional Chinese medicine 2211–2214, 2213t
  acupuncture 2214
  coining 2214f
  cupping 2214, 2214f
  herbal medicine 2213–2214
  moxibustion 2214
TRAIL 186
tramadol
  adverse reactions
    erythroderma 176t
    pruritus 120t
  and eccrine sweating 590t
tranexamic acid, C1 esterase inhibitor deficiency 305
transcription factors 1012
Transcyte 2375t–2376t
transdermal drug delivery 2068–2069
  absorption 2068
  advantages 2070f, 2070t
  drug concentration 2069
  enhancement of 2070–2072, 2071t
    biochemical 2071, 2071f
    chemical 2070–2071
    physical 2071–2072
  partition coefficient 2069
  patches 2070t
  regional variation 2069
  role of vehicle 2068–2069, 2069t
  skin pathways 2070f
  stratum corneum *see* stratum corneum
transepidermal melanocytorrhagy 1025t
transforming growth factor (TGF)-α
  in wound healing 2317t
transforming growth factor (TGF)-β
  receptors 1593t
  regulation of activity 1591f
  signaling defects 800t–801t
  in wound healing 2317t
transgenic animal models 71–72, 74f–76f, 74t–75t
transgenic mice 71–72, 74f–75f, 74t
  knockout 75f–76f, 75t
transglutaminases 827f
transglutaminase defects 800t–801t
transglutaminase-3 47t
transgrediens and progrediens palmoplantar keratoderma 872, 872t
transient acantholytic dermatosis *see* Grover's disease
transient hypogammaglobulinemia of infancy 917t
transient neonatal pustular melanosis 523–524
  clinical features 529f
  postinflammatory hyperpigmentation 1050t
transient receptor potential ion channels, in pruritus 104
transmembrane transporter defects 805–806
transparent soap 2480t
transporter associated with antigen processing (TAP) deficiency 900t
transthyretin 700t
transverse nasal crease, pseudoacne of 553, 553f
tranylcypromine, and eccrine sweating 590t
trastuzumab 2149t
trauma
  blunt 1522
  chemical exposure injury 1497–1498
    arsenical/heavy metal dermatoses 1498–1501
    chemical hair discoloration 1497–1498
    NMSC 1775, 1775t
  cold exposure 51, 1492–1494
    differential diagnosis 1495t
    frostbite 51, 1492–1493
    pernio 374, 1493–1494
  frictional 1501–1505
    acanthoma fissuratum 1503–1504
    black heel and palm 1501–1502
    chondrodermatitis nodularis helicis 1502–1503
    corns and calluses 1501
    traumatic auricular hematoma 1504–1505
    weathering nodules of ear 1504
  heat exposure 51, 1487–1492
    airbag burns 1491–1492
    erythema ab igne 8, 1065t, 1489–1491
    fluoroscopy burns 1491f
    MRI burns 1491
    thermal burns 1487–1489, 1488f, 1522–1523, 1523f
  nail 1142–1144, 1143t
  oral 1154–1156
    chemical burn 1155, 1155f
    drug-related gingival hyperplasia 1156, 1156t
    fibroma 1154–1155
    morsicatio buccarum 1155, 1155f
    traumatic ulcer 1156, 1156f
  perinatal 526t–528t
  water exposure 1494–1496
    immersion foot 1494–1496
  see also burns
traumatic alopecia 1522
traumatic auricular hematoma 1504–1505
traumatic irritant contact dermatitis 252
traumatic neuroma 1944, 1947f
traumatic panniculitis 1655–1656
  clinical features 1655, 1655f
  differential diagnosis 1655–1656, 1656f
  epidemiology 1655
  history 1655
  pathogenesis 1655
  pathology 1655, 1656t
  treatment 1656
trazodone 2190t
  and eccrine sweating 590t
Treacher Collins-Franceschetti syndrome 1006, 1823
trench fever 1209t
trench foot *see* immersion foot
trench mouth *see* necrotizing ulcerative gingivitis
Treponema spp. 1152, 1368t
Treponema carateum 1216
Treponema denticola 1368t
Treponema pallidum 29t–33t, 271t, 1216, 1367t–1368t, 1368
  characteristics 1369t
  identification 1369f, 1377
  see also syphilis
Treponema socranskii 1368t
treponematoses
  hypomelanosis 1042
  non-venereal (endemic) 1216–1217
treprostinil 651
tretinoin 2089
  acne vulgaris 556, 2093
  chemical peels 558, 2489t
  formulations 2097t
  pharmacologic features 2092t
  pregnancy and lactation 2155t
  rosacea 567t
triamcinolone acetonide 245t, 2079t
  absorption 2069t
  indications
    granuloma faciale 415
    keloids/hypertrophic scarring 1625t
    lichen planus 195t
  pharmacology 2075
  tumescent anesthesia 2347t
triamterene-induced pseudoporphyria 724t
Triatoma infestans
triatome reduviids 1399, 1438–1439, 1439f
triazolam 2351–2352
  interactions 2190, 2192
    with lidocaine 2529t
Tribulus terrestris 2213
trichilemmal carcinoma 1837
trichilemmal cyst 1820
  excision biopsy 1820
  pathology 1820, 1820f
  proliferating 1820–1821, 1820f
trichilemmoma 1836
  clinical features 1836
  pathology 1836–1837, 1837f
  treatment 1837
Trichinella spiralis 1407t–1408t
  life cycle 1414f
trichinosis 1407t–1408t
  differential diagnosis 639t
trichloroacetic acid
  chemical peels 2493f, 2496
  genital warts 1314–1315, 1314t, 1315f
  molluscum contagiosum 1359t
tricho-dento-osseous syndrome 808t
tricho-hepato-enteric syndrome 1036
tricho-rhino-phalangeal syndrome 809t
trichoadenoma (of Nikolowski) 1838, 1838f
trichoblastic fibroma 1834
trichodiscoma 1830
trichodysplasia, viral-associated 1361–1362
trichoepithelioma/trichoblastoma 1790t, 1834–1835, 1835f
  clinical features 1834, 1835f
  linear 955
  pathology 1835f, 1836–1837
  treatment 1834–1835
trichofolliculoma 1829–1830, 1830f
trichomegaly 1118t, 1120f
Trichomonas vaginalis 1367t
trichomycosis 1252f
  axillaris 1202, 1203f
trichonodosis 1110f
Trichophyton ajelloi 1255t
Trichophyton concentricum 1255t
  tinea corporis 1256t
Trichophyton equinum 1255t
Trichophyton gallinae 271t
Trichophyton gourvilii 1255t
  endothrix hair invasion 1262f
Trichophyton megninii 1255t
Trichophyton mentagrophytes 1255t
  tinea cruris 1258t
  tinea pedis 1261
Trichophyton mentagrophytes var *interdigitale* 1255t
  tinea corporis 1256t
  tinea pedis 1261, 1263t
Trichophyton mentagrophytes var *mentagrophytes* 271t, 1255t
  tinea corporis 1256t
Trichophyton rubrum 1255t
  ectothrix hair invasion 1262f
  endothrix hair invasion 1262f
  Majocchi's granuloma 1258f
  tinea corporis 1256t
  tinea cruris 1258t
  tinea pedis 1261, 1263t
Trichophyton schoenleinii 1255t
  favus hair invasion 1262f
Trichophyton simii 1255t
Trichophyton soudanense 1255t
  endothrix hair invasion 1262f
Trichophyton terrestre 1255t
Trichophyton tonsurans 1255t
  potassium hydroxide preparation 1254f
  tinea capitis 1259–1261
  tinea corporis 1256t
Trichophyton verrucosum 262, 1255t
  tinea corporis 1256t
Trichophyton violaceum 1255t
  endothrix hair invasion 1262f
Trichophyton yaoundei 1255t
  endothrix hair invasion 1262f
trichoptilosis 1110f
trichorhinophalangeal syndrome, digital anomalies 1005t
trichorrhexis invaginata 841t–842t, 1095f, 1110f, 1111
trichorrhexis nodosa 841t–842t, 1110f, 1111, 1252f
trichoscopy 1095f
Trichosporon spp.
  chronic granulomatous disease 910t
  superficial mycoses 1251t
Trichosporon beigelii 1251, 1251t
trichosporonosis 1279f
trichostasis spinulosa 585
trichothiodystrophy 838t, 861–862, 1104t, 1110f, 1111, 1462t, 1476t–1477t, 1478, 1857t
  clinical features 861, 932t–933t, 1478
  differential diagnosis 861–862
  epidemiology 861, 1478
  genetics 803t–804t
  history 861, 1478
  neonatal 847t
  pathogenesis 861, 1478
  pathology 861
  treatment 862
trichotillomania 132–133, 1099–1100
  clinical features 132–133, 132f, 1099–1100, 1100t
  differential diagnosis 133
  epidemiology 133
  histologic features 1096t
  management 133
  pathogenesis 1099
  pathology 133, 133f
  treatment 1100
  see also alopecia
trichrome vitiligo 1026
triclosan 2480
tricyclic antidepressants 133
  and eccrine sweating 590t
  indications
    burning mouth syndrome 121
    prurigo nodularis 115
triflupromazine, and eccrine sweating 590t
trigeminal nerve 2338f
trigeminal neuralgia 122–123
trigeminal trophic syndrome 123, 123f
trihexyphenidyl, adverse reactions, lichen planus 185t
trimethaphan, hypohidrosis/anhidrosis 595t
trimethoprim 2105t
  mechanism of action 2112, 2113f
  sites of action 2109t
trimethoprim-sulfamethoxazole
  adverse reactions 338t
    fixed drug eruption 346f
    secondary cutaneous vasculitis 390t
    Stevens-Johnson syndrome/toxic epidermal necrolysis 325t, 329f
  indications
    bartonellosis 1209t
    donovanosis 1389t
    linear IgA bullous dermatosis 499
    MRSA 1191t
    vasculitis 402t
  prophylactic 2462t
trimethylaminuria 597
trimethylpsoralen, hypertrichosis 1118t
trimipramine 2190t
  and eccrine sweating 590t
tripe palms 764t–765t, 883–884
tripelennamine abuse, cutaneous signs 1514t
Tripterygium hypoglaucum 2213–2214
Tripterygium wilfordii Hook 2213–2214
trisomy 13 *see* Patau syndrome
trisomy 18 *see* Edwards syndrome
trisomy 21 *see* Down syndrome
troglitazone 2191–2192
trolamine salicylate 2199, 2200f
troleandomycin 2189t, 2193

Trombicula (Eurombicula) alfreddugesi 1445t
Trombiculidae 1445t
Trombiculs (Leptotrombidium) spp. 1445t
Tromsø palm 279t
tropical acne 552
tropical anhidrotic asthenia 596
tropical immersion foot 1495
tropical jungle foot *see* immersion foot
tropoelastin 1589
Trousseau's syndrome 367
trovafloxacin 2116t
Truant stain 27t–28t
true tail 1001t
TRUE Test 236–237
trunk/extremity surgery tray 2359f
Trypanosoma brucei
  gambiense 1401, 1403t
  life cycle 1404f
  rhodesiense 1401, 1403t
Trypanosoma cruzi 1399
  life cycle 1400f
trypanosomiasis 1399–1404
  African 1401–1404, 1403t
    clinical features 1401–1402, 1404f
    differential diagnosis 308t–310t, 1404
    epidemiology 1401
    pathogenesis 1401, 1404f
    pathology and diagnosis 1404
    treatment 1404
  American 1399–1401
    clinical features 1400–1401, 1400f–1401f
    diagnosis and differential diagnosis 1401
    epidemiology 1399–1400, 1399f
    pathogenesis 1400, 1400f
    pathology 1401
    treatment 1401, 1402t–1403t
trypsin 2373
tryptase 29t–33t, 101t
TSC genes 934f
TTP-HUS *see* thrombotic thrombocytopenic purpura-hemolytic uremic syndrome
tuberculids 1232–1233
  papulonecrotic 1232, 1233f
tuberculoid granuloma 21, 23f
tuberculosis 1228–1235
  and anetoderma 1633t
  BCG inoculation 29t–33t, 1233, 1233f–1234f, 1234t
  clinical features 778t–779t, 1230–1233, 1231t
    cutaneous tuberculosis 1230–1232
    tuberculids 1232–1233, 1233f
  diagnosis 1233–1234
  epidemiology 1229, 1229f
  and erythema nodosum 1644t
  history 1229
  miliary 1231t, 1232
  and nail growth 1090t
  orificial 1230, 1231t, 1232f
  pathogenesis 1229–1230, 1230f
  treatment 1234–1235, 1234t–1236t, 1235f
tuberculous chancre 1230, 1231t
tuberculous gumma 1231t
tuberculous verrucosa cutis 1230, 1231t, 1232f
tuberous sclerosis 933–940
  clinical features 932t–933t, 934–938, 935t
    cardiovascular manifestations 937
    linear angiofibroma 955
    neurologic manifestations 937, 937f
    oculocutaneous manifestations 931f, 935–937, 936f–937f
    renal manifestations 938
  and cutis verticis gyrata 1626t
  diagnostic criteria 936t
  differential diagnosis 938–939
  epidemiology 934
  genetics 785t, 813t, 934, 934f
  history 934
  pathogenesis 934
  pathology 938, 938f
  treatment 938t, 939–940, 939f
tuberous sclerosis complex 1036–1037
  clinical features 776t–778t, 1036–1037, 1037f
    renal disease 780t–781t
  diagnosis 1037
  pathogenesis 1037
tuberous/tuberoeruptive xanthomas 1551
tufted angioma 1926–1927, 1927f
"tufted folliculitis" 1109, 1109f
tularemia 1211–1212, 1212f
tulip fingers 288
Tulipa spp. *see* tulips
tulipalin 274t, 288
tulips 274t–275t, 277t
tumescent anesthesia 2348, 2348t
  formula 2348t
  liposuction 2528–2529, 2528f–2529f, 2528t
tumors
  Ackerman *see* verrucous carcinoma
  adnexal 1771
  benign epidermal 813t, 1795–1815
    acantholytic (dyskeratotic) acanthoma 1807
    acanthosis nigricans *see* acanthosis nigricans
    acrokeratosis verruciformis 1804
    clear cell acanthoma 1805–1806
    clear cell papulosis 1813–1814
    confluent and reticulated papillomatosis 1812–1813
    cutaneous horn 1805
    dermatosis papulosa nigra 1799–1800
    epidermal nevus 1809–1810
    epidermolytic acanthoma 1808
    Flegel disease 1803–1804
    inflammatory linear verrucous epidermal nevus 1810–1811
    inverted follicular keratosis 1806
    large cell acanthoma 1808–1809
    lichenoid keratosis 1798–1799
    nevus comedonicus 1811–1812
    porokeratosis 1801–1803
    seborrheic keratosis 1795–1798
    stucco keratosis 1800–1801
    warty dyskeratoma 1806–1807
  benign melanocytic 1851–1880
    atypical dysplastic melanocytic nevus 1868–1871
    Becker's melanosis 1119, 1119f, 1853–1854
    blue nevus 1860–1861
    café-au-lait macules *see* café-au-lait macules
    common acquired melanocytic nevi 1861–1863
    congenital melanocytic nevus 1871–1874
    dermal melanocytosis 1858
    ephelides 1851
    halo nevus 1875–1876
    lentigo simplex and mucosal melanotic lesions 1855–1858
    melanocytic nevi of acral skin 1864
    melanocytic nevi of genital and flexural skin 1863–1864
    nevus of Ota 1858–1859
    nevus spilus 1874–1875
    partial unilateral lentiginosis 1856
    pigmented spindle cell nevus 1867–1868
    recurrent melanocytic nevus 1877–1878
    solar lentigenes 1854–1855
    Spitz nevus/tumor 1864–1867
  biopsy 14t–15t
  Buschke-Löwenstein 1310, 1311f–1312f, 1312
  cartilage 1991
  childhood tumor syndrome 818t–819t
  dermoscopy 37f
    ABCD rule 12–15
    colors 33f
    vascular structures 12
  fat 1984–1990
    angiolipoma 1985–1986
    hibernoma 1987–1988
    lipoblastoma/lipoblastomatosis 1988–1989
    lipoma 1984–1985
    liposarcoma/atypical lipomatous tumor 1989–1990
    nevus lipomatosus superficialis 1988
    spindle cell lipoma 1986–1987
  giant cell, of tendon sheath 1967–1968, 1968f
  glomus 928–929, 1145, 1937–1939, 2440t
  Gottron *see* human papillomavirus
  granular cell 1952–1953, 1953f
  HIV-related 1296
  malignant peripheral nerve sheath 928, 1953–1954, 1953f
  nail *see* nail tumors
  neural/neuroendocrine 1943–1960
  palliative radiotherapy 2298
  peripheral nerve sheath 928
  perivascular 1937–1939
  pilar *see* proliferating trichilemmal cyst
  pruritus 118–119
  salivary gland 1165, 1165t
  smooth muscle 1979–1984, 1980f
    hamartoma 1983–1984
    leiomyoma 1979–1980
    leiomyosarcoma 1980–1983
  UV-induced 1458–1464, 1460f
  vascular 1915–1941, 1917f
    benign 1915–1928
    borderline and low-grade malignant 1928–1935
    classification 1916t
    malignant 1935–1936
    perivascular neoplasms and neoplastic-like proliferations 1937–1939
  vascular features 40t
tumor lysis syndrome 2140t, 2146
tumor metastasis *see* metastases, cutaneous
tumor necrosis factor-α 82, 105
  and alopecia 1096t, 1103–1104
  induction of ANA by 608–609
  irritant contact dermatitis
  mucin deposition
  in wound healing 2317t
tumor necrosis factor-α inhibitors 2141–2143
  adverse reactions 761t, 2136f, 2141–2143, 2142f–2143f
  Behçet's disease 435t
  contraindications 2141
  FDA warnings 2140t
  juvenile idiopathic arthritis 672
  laboratory evaluation 2140t
  lichen planus 195t, 196
  mechanism of action 2141, 2141f
  pityriasis rubra pilaris 165
  pyoderma granulosum 432t
  SAPHO syndrome 437t
  vaccine contraindication 2143, 2143t
tumor necrosis factor-associated periodic syndrome 673f
tumor suppressor genes 1760–1762, 1761f–1762f, 1761t
  loss of heterozygosity 1763f
  p53 see p53 gene
tumor suppressor gene defects 808–812
tumoral calcinosis 733
tumstatin 454
tunable dye lasers 2261
Tunga penetrans see tungiasis
tungiasis 1431–1432, 1439–1440
  clinical features 1431, 1432f
  differential diagnosis 1432
  epidemiology 1431
  history 1431
  pathogenesis 1431
  pathology 1432
  treatment 1432
tungsten dermatosis 1499t
turf toe 1506t
turmeric 2211
Turner syndrome 791–792, 1722–1723
  and cutis verticis gyrata 1626t
  genetics 822t
tussock moth caterpillar 1435
Tuzun syndrome 1638
twenty-nail dystrophy *see* trachyonychia
twin spotting 816, 821f
tyloma *see* corns and calluses
tylosis, differential diagnosis 228t
tylosis-esophageal carcinoma *see* Howel-Evans syndrome
tylotrich hair follicle 1079t
typhoid fever 1213
typhus 1243–1248
Tyrophagus putrescentiae 1445t
tyrosinase 29t–33t
tyrosinemia type II *see* Richner-Hanhart syndrome
Tyson glands 542
Tzanck smear 1324–1325

U-flap *see* double tangent advancement flaps
ubiquinone 2490t
ulcerating sclerosing granuloma *see* donovanosis
ulceration 4t–5t, 2314
  biopsy 14t–15t
  irritant/toxic causes 249–250
ulcerative colitis
  ANCA in 613t
  cutaneous manifestations 771t
  and gastric hemorrhage 773t–774t
ulcers 1729–1746
  arterial 1738–1740
  diabetic (neuropathic) 1740–1741
  and drug abuse 1517
  eosinophilic, of oral mucosa 414t, 1159
  Kangri 1490
  oral 1156, 1156f
  postsclerotherapy 2519, 2520f
  pressure 1741–1744
    classification 1743f
    clinical features 1742, 1742f
    distribution 1741f
    pathogenesis 1742
    pathology 1742
    treatment 1742–1744
  venous 1729–1737
ulcus molle *see* chancroid
ulerythema acneiforme 577
ulerythema ophryogenes 578t
Ullrich disease 1593t, 1596
  genetics 807t
ulnar-mammary syndrome
  digital anomalies 1005t
ultrasound 2258
  transdermal drug delivery 2072
ultraviolet light 1455–1465
  abnormal reactions to 1467–1482
  atopic dermatitis 214–215
  depth of penetration 1456f
  effect on melanocytes 1021–1022
  epidermal hyperplasia 1483
  immune system effects 1457, 1457t
  immunologic changes 1483
  inflammation/erythema 1457, 1457t
  lichen planus 195t, 196, 2231
  and melanoma risk 1890–1892
  and NMSC 1774
  normal reactions to 1482–1485
  parapsoriasis 159t
  photoaging *see* photoaging
  photocarcinogenesis 1458–1464, 1458f–1459f
    basal cell carcinoma 1457, 1463
    DNA damage 1459–1460
    mutation formation 1462–1463, 1462t, 1463f
    protection against 1463–1464, 1464f
    repair of DNA damage 1460–1462, 1460f, 1461t, 1462f
    UV-induced tumor formation 1458–1464, 1460f
  pigment darkening and delayed tanning 1482–1483
  pityriasis lichenoides 162t
  spectrum of 1455, 1456f

sunburn and tanning 1021–1022, 1455–1457, 1456f, 1482
UVA *see* UVA
UVB
vitiligo 1029
see also UVB
vitamin D_3 synthesis 1483
see also phototherapy
ultraviolet therapy *see* phototherapy
Uncinaria stenocephala 1406
undecylenic acid
formulations 2118t
pregnancy and lactation 2118t
trade names 2118t
undermining scissors 2359f
undulant fever *see* brucellosis
unfolded protein response 888
unilateral laterothoracic exanthem 1352–1353
clinical features and differential diagnosis 1352–1353, 1353f
epidemiology 1352
history 1352
pathogenesis 1352
pathology 1353
treatment 1353
unilateral nevoid telangiectasia 1753–1754, 1755f
unilateral palmoplantar verrucous epidermal nevus 953
uniparental disomy 790
Unna boot 1737t, 2377f
Unna-Thost keratoderma 872–877, 873t
clinical features 876
differential diagnosis 876–877
epidemiology 875
genetics 803t–804t
history 872–875
pathogenesis 875–876
pathology 876, 877f
treatment 877
upper gum show, botulinum toxin 2566–2567, 2566t
uranium dermatosis 1499t
urate crystal arthropathy *see* gout
urate deposition disease *see* gout
Urbach, Erich 712
Urbach-Wiethe disease *see* lipoid proteinosis
urban trench fever 1209t
urea 2157–2158
Ureaplasma urealyticum 1367t
uremia, eccrine gland changes 598t
urethral caruncle 1183t
uric acid nephrolithiasis 711
urokinase plasminogen activator 358–359
uroplakin 29t–33t
uroplectes lineatus 1449t
uroporphyrin 718f
see also porphyria
ursodeoxycholic acid, cholestatic pruritus 119t, 444–445
Urtica dioica see stinging nettle
Urticaceae 276t
urticaria 12t, 291–306
adrenergic 298
aquagenic 298
cholinergic 294, 298, 298f
clinical features 294–300
acute versus chronic urticaria 295, 295f–296f
angioedema *see* angioedema
classification 294–295, 295t
clinical diversity 294
contact urticaria *see* contact urticaria
"ordinary" (spontaneous) urticaria 295–296
physical urticarias 296–298, 296t, 301
pruritus 114
urticarial syndromes 299–300
urticarial vasculitis 298, 298f, 299t, 301
contact *see* contact urticaria
definition 291
diagnosis 300–301, 300f–302f
biopsy 14t–15t
differential diagnosis 300–301, 308t–310t, 414t
drug-induced 294, 338t, 339–340, 340f, 340t, 349t, 1518t
epidemiology 291
irritant/toxic causes 251t
and leukemia 2042t
localized heat contact 305
mechanical stimuli 296–297
delayed pressure urticaria 297, 297f
dermographism 296, 297f
vibratory angioedema 297
pathogenesis 291–294, 294t
blood autoantibodies 293
blood vessels 293
degranulating stimuli 292
leukocytes 293
mast cell-dependent urticaria 293–294
mast cell-independent urticaria 294
mast cells 291–293
nerves 293
proinflammatory mediators 292–293
pathology 300
solar *see* solar urticaria
temperature changes 297–298
cold exposure 293, 297–298
heat exposure 297
toxin-mvediated –7
treatment 301–305
acute, chronic and physical urticarias 302–305, 303f
non-drug-therapies 305
vs erythema multiforme 323f, 323t
urticaria pigmentosa 1996f
phototherapy 2231
urticaria-like follicular mucinosis 696–697
urticarial allergic eruption 414t
urticarial dermatoses 414t
urticarial vasculitis 291, 298, 298f, 299t, 395–396
classification 294–295, 295t
clinical features 298, 298f, 299t, 395, 395f
diagnosis 300–301
differential diagnosis 308t–310t, 396, 414t
epidemiology 299t, 395
pathogenesis 293, 394t, 395
pathology 300, 395–396
pulmonary disease 395, 778t–779t
treatment 299t, 305, 396, 402t
urushiol 274t, 282, 284–285
removal 286
ustekinumab 153t, 2145–2146
adverse reactions 2145
contraindications 2145
dosage 2145
FDA warnings 2140t
indications 2145
interactions 2145
laboratory evaluation 2140t
mechanism of action 2145
pregnancy and lactation 2146
UV-sensitive syndrome 1476t–1477t, 1478
UVA protection 2198–2199, 2198t
UVA_1 phototherapy 2223–2224, 2223f–2224f
adverse reactions 2224
indications
lichen planus 195t, 196
morphea 667t
surface irradiance 2201f
UVA_2 phototherapy, surface irradiance 2201f
UVB phototherapy 2219–2223
action spectrum and radiation sources 2220
adverse reactions 2223
broadband 2220f, 2220t
history 2219
in HIV patients 2233
indications
atopic dermatitis 214–215, 2222
folliculitis 574
graft-versus-host disease 2222
irritant contact dermatitis 258
lymphomatoid papulosis 2222
mycosis fungoides 2221–2222
nummular dermatitis 226
pityriasis lichenoides 162t, 2222
pruritus 118t, 2222–2223
psoriasis 2221
vitiligo 2222, 2222f
mechanism 2219–2220
narrowband 2220f, 2220t
surface irradiance 2201f
treatment protocols 2220–2221, 2220f–2221f, 2220t
UVB protection 2198t
uveitis, in juvenile idiopathic arthritis 672t

vaccines
adverse reactions
cutaneous lymphoid hyperplasia 2039t
lichen planus 184
cancer 1909
drug eruptions 354–355
human papillomavirus 1317–1318
injection site reactions 663
vaccinia 1355t–1356t
and erythema multiforme 320t
VACTERL association 1006
vacuolar dermatitis, pattern analysis 16f, 17–18
vagabond's leukomelanoderma 1046
vaginal intraepithelial neoplasia 1312
valacyclovir
adverse reactions 2127t
dosage 2126t–2127t
formulations 2126t
indications 2126t
herpes simplex 1329t
varicella-zoster 1329t
viral susceptibility to 2125t
valganciclovir
cytomegalovirus 1326–1328
formulations 2126t
viral susceptibility to 2125t
valley fever *see* coccidioidomycosis
valproic acid 2190t
adverse reactions
aplasia cutis congenita 1002t
cutaneous lymphoid hyperplasia 2039t
gingival hyperplasia 1156t
telogen effluvium 1098t
Van der Woude syndrome 1005–1006
cleft lip/palate 1005t
genetics 807t
vanadium, dermatosis 1499t
vancomycin 2105t
adverse reactions
erythroderma 176t
linear IgA bullous dermatosis 498t
secondary cutaneous vasculitis 390t
indications, MRSA 1191t
sites of action 2109t
Vancouver Scar Scale 1622, 1624t
vanilloid receptors 102f–103f, 104, 2206
activators of 2157t
variable expression 787–788
varicella-zoster virus (HHV-3) 1–2, 2f, 3t–4t, 29t–33t, 1322t, 1328–1334, 1358t
and anetoderma 1633t
and aplasia cutis congenita
clinical features 1328–1330, 1330f, 1332f–1333f
diagnosis and pathology 1330
differential diagnosis 1330, 1333t
and erythema multiforme 320t
herpes zoster 1–2, 2f, 3t–4t, 8f
history 1328
HIV-related 1288
in neonates 524t–528t
pathogenesis 1328
secondary cutaneous vasculitis 390t
treatment and prevention 1329t, 1330–1334
varicose eczema *see* stasis dermatitis
varicose veins
classification 2516t
treatment 2514t, 2517–2518, 2517f
ambulatory phlebectomy 2520–2521
arborizing feeder veins 2517f
endovenous laser and radiofrequency ablation 2522–2523
sclerotherapy *see* sclerotherapy
varicosities 2516t
saphenous 2516t
variegate porphyria 719t, 725–726
biochemical findings 720t
genetics 719t, 810t–811t
treatment 725t
Varigloban 2515t
vascular biology 1679–1689
antiangiogenesis 1688
cutaneous blood vessels 1679–1681, 1679f–1680f
cutaneous lymphatic system 1685–1687, 1685f–1686f, 1686t
related diseases 1687–1688
vascular development 1681–1684, 1681f
leukocyte-endothelial cell interactions 1684, 1684f, 1685t, 1688f
skin angiogenesis 1681–1684, 1682f–1683f, 1682t
vascular coagulopathies with cutaneous manifestations
livedoid vasculopathy 381–382
malignant atrophic papulosis 382
Sneddon syndrome 380–381
vascular development 1681–1684, 1681f
leukocyte-endothelial cell interactions 1684, 1684f, 1685t, 1688f
skin angiogenesis 1681–1684, 1682f–1683f, 1682t
vascular disorders 1747–1757
angiokeratoma *see* angiokeratoma
Bier spots 1047, 1756, 1756f
erythromelalgia 371, 1751–1753
flushing 1750–1751
livedo reticularis 1747–1750
nevus anemicus 1755–1756, 1756f
telangiectasias 1753–1755
see also individual types
venous lakes 1755, 1756f
see also infantile hemangiomas; and individual disorders
vascular endothelial growth factor
in angiogenesis 1682, 1683f, 1687f
and infantile hemangiomas 1693f
in wound healing 2317t
vascular endothelial growth factor receptor 1686t
vascular lasers 2265t
diode lasers 2265t
intense pulsed light sources 2265t
long-pulsed alexandrite laser 2255, 2265t
neodymium YAG lasers 2255, 2265t
pulsed dye lasers 2255, 2265t
pulsed KTP lasers 2242, 2265t
vascular malformations 1711–1728, 1712f
arteriovenous malformations
clinical features 1724–1725
pathology 1726
treatment 1727
capillary malformations
clinical features 1713–1720, 1714f
pathology 1725
treatment 1727
classification 1712t
clinical features 1713–1725
differential diagnosis 1726–1727
epidemiology 1711
hematology 1712t
history 1711
immunophenotype 1711
investigative tools 1714t
lymphatic malformations
clinical features 1722–1724
pathology 1726
treatment 1727
molecular biology 1712t–1713t
pathogenesis 1711–1713

pathology 1725–1726, 1726f
radiology 1712t
sex prevalence 1712t
treatment 1727
venous malformations
clinical features 1720–1722
pathology 1725–1726
treatment 1727
see also infantile hemangiomas
vascular permeability factor 1682
vascular tone 50
vascular tumors 1915–1941, 1917f
benign 1915–1928
angiokeratoma *see* angiokeratoma
angiolymphoid hyperplasia with eosinophilia 1920–1921
cherry angioma 1924
glomeruloid hemangioma 1917–1918
hobnail hemangioma 1925–1926
microvenular hemangioma 1920
multifocal lymphangioendotheliomatosis with thrombocytopenia 1927–1928
papillary endothelial hyperplasia 1915–1916
pyogenic granuloma 1922–1923
reactive angioendotheliomatosis 1916–1917
sinusoidal hemangioma 1721, 1924–1925
spindle cell hemangioma 1921–1922
tufted angioma 1926–1927
borderline and low-grade malignant 1928–1935
Dabsak-type hemangioendothelioma 1930–1931
epithelioid hemangioendothelioma 1931–1932
kaposiform hemangioendothelioma 1928–1930
Kaposi's sarcoma *see* Kaposi's sarcoma
retiform hemangioendothelioma 1931
classification 1916t
malignant 1935–1936
angiosarcoma 1935–1936
perivascular neoplasms and neoplastic-like proliferations 1937–1939
glomus tumors 1937–1939
infantile hemangiopericytoma 1939
vasculitides 49, 385–410
classification 385–387, 385t
clinical features 387, 776t–778t
diagnosis 407–408
biopsy 14t–15t
pattern analysis 20–21, 21f
differential diagnosis 360t, 362f, 388, 389t
drug-induced 342, 349t
ANCA associated with 613t
epidemiology 387
examination 407
and gastric hemorrhage 773t–774t
granulomatous 20
history 407
HIV-related 1295
laboratory evaluation 408
large vessel 385t
leukocytoclastic 20, 21f, 394
lymphocytic 20
medium vessel 20, 21f, 385t, 405–407
polyarteritis nodosa 385t, 405–407, 673f
temporal arteritis 385t, 407, 407f
pathogenesis 386f, 387
pathology 388
pustular 385
rheumatoid 681
septic 389t–390t
Sjögren's syndrome 678, 678f
small and medium-sized vessel 385t, 397–405
ANCA-associated 399–405
Churg-Strauss syndrome 404–405
cryoglobulinemic vasculitis 385t, 397–399
microscopic polyangiitis 399–401
Wegener's granulomatosis 403–404
small vessel 385t, 389–397
acute hemorrhagic edema of infancy 393–395
causes 390t, 391f
clinical features 387f–388f, 391, 391f
differential diagnosis 391
drug-induced 390t
epidemiology 389
erythema elevatum diutinum *see* erythema elevatum diutinum
Henoch-Schönlein purpura 392–393
monoclonal gammopathy 2014t
paraneoplastic 764t–765t
pathogenesis 389
pathology 388f
purpura 2, 5, 357–367
renal disease 780t–781t
treatment 391–392, 402t, 408f–409f
urticarial vasculitis *see* urticarial vasculitis
treatment 402t, 408
ulceration 1745t
vasculogenesis 1681, 1681f
vasculopathy 49, 49f
cutaneous collagenous 1753, 1755f
drug-induced 1518t
vasoactive intestinal polypeptide 114
vasomotor instability, in pregnancy 447t
vasovagal reaction with local anesthetics 2345, 2345t, 2463
VCAM-1 93, 411, 1685t
vehicles, topical 2068–2069, 2069t
veins
disorders of *see* venous disorders
leg 2509–2524
anatomy, physiology and pathophysiology 2509–2510, 2509f–2511f
laboratory evaluation 2512, 2512t–2513t, 2513f
muscle pump 2511f
see also phlebology
reticular 2516t
treatment 2515–2517
saphenous 2512
Doppler examination 2513f, 2513t
great 2513f
sclerosing solution 2514t
spider 2266–2267
varicose *see* varicose veins
vellus follicle 543f
vellus hair 1079t
vellus hair cysts 1821–1822, 1821f
eruptive 1821
pathology 1821f, 1822
treatment 1822
vellus hamartoma *see* hair follicle nevus
vemurafenib 353t, 1887t
venlafaxine 2190t
anxiety disorder 133
and palmoplantar keratoderma 872t
venom immunotherapy 1437
venous disorders
ambulatory phlebectomy *see* ambulatory phlebectomy
CEAP classification 1733, 2510
sclerotherapy
complications 2518–2520, 2518t
compression 2512–2513
pretherapy evaluation 2520
telangiectasias *see* telangiectasias
varicose veins see varicose veins
see also phlebology
venous hypertension 1729
venous insufficiency 49
venous lakes 1755, 1756f
laser therapy 2267
venous malformations 955
cephalic 1720–1721, 1720f
clinical features 1720–1722, 1721f
familial cutaneous and mucosal 1712t, 1721
histology 1726f
investigative tools 1714t
pathology 1725–1726
syndromes associated with 1721–1722
treatment 1727
trunk and limb 1721
venous thrombosis, and drug abuse 1519
venous ulcers 1729–1737
causes 1731f
clinical features 1731–1733, 1732f–1733f
differential diagnosis 1734
formation of 1731f
laboratory evaluation 1733
pathogenesis 1729–1731, 1730f–1731f, 1730t
pathology 1734
treatment 1734
compression 1736, 1736t–1737t
debridement 1734–1735
dressings 1735, 1735t
manual lymph drainage 1736
moisture and occlusion 1734
skin substitutes 1736–1737
topical negative pressure therapy 1736
topical and oral medications 1737
wound infection 1735–1736
venulectasias 2516t
sclerosing solution 2514t
verapamil
adverse reactions, gingival hyperplasia 1156t
hypertrophic scars/keloids 1625t
interactions 2191–2192, 2191t
Veratrum californicum see false hellebore
Verbascum thapsus see mullein
Verhoeff-van Gieson stain 26, 27t–28t
Verneuil's disease *see* hidradenitis suppurativa
Verocay bodies 1949, 1949f
verrucae, nasal, in drug abuse 1514t, 1516–1517
verrucae palmares et plantares *see also* human papillomavirus
verrucae planae 8
verrucae vulgaris *see* warts
verruciform xanthomas 1553, 1553f
verrucous carcinoma 1782, 2440t
clinical features 1782f
Mohs surgery 2449
oral 1146, 1163, 1311
pathology 1784
see also non-melanoma skin cancer
verrucous dermatitis *see* chromoblastomycosis
verrucous epidermal nevus 945t–946t
inflammatory linear *see* ILVEN
verrucous hemangioma 1719–1720
verrucous perforating collagenoma 1600
verruga peruana *see* bartonellosis
versican 1592f, 1592t
vertical lip rhytides, botulinum toxin 2566
very late antigen 411
very-low-density lipoproteins 1547, 1547t
vesicles 1–2, 2f, 3t–4t
herpetiform 8
vesicle trafficking defects 800t–801t
vesicopustular dermatosis 434t
vesicular dermatitis 285
vesicular hand dermatitis *see* dyshidrotic eczema
vesicular pemphigoid 479t
vesiculo-vacuolar organelles 1680–1681
vesiculobullous diseases
bullosis diabeticorum 515
bullous drug eruptions 518, 519t
bullous insect bite reactions 518–520
bullous small vessel vasculitis 518
coma blisters 515–517
delayed postburn/postgraft blisters 520
differential diagnosis 517t
edema blisters 520–521
friction blisters 517–518
pattern analysis 19, 19f–20f
PUVA-induced acrobullous dermatosis 521
vesiculopustular eruption, in Down syndrome 524t–525t, 534
vestibular papillomatosis 1183
vestibulodynia *see* vulvodynia
vibration white finger 270–271
clinical features 271
differential diagnosis 271
epidemiology 270
history 270
pathogenesis 270–271
pathology 271
treatment 271
vibratory angioedema 297
Vibrio spp. 1450t
Vibrio vulnificus 271t, 375, 1214, 1214f, 1214t, 1451
vibrissae 1079t
vigabatrin-induced gingival hyperplasia 1156t
Vigilon 2372
vimentin 29t–33t, 828t
vinblastine 2186t, 2189t
adverse reactions
alopecia 349t
extravasation reactions 349t
indications
HHV-8 1934
melanoma 1908
vinca alkaloid-induced erythroderma 176t
Vincent infection *see* necrotizing ulcerative gingivitis
vincristine 2189t
adverse reactions
alopecia 349t
extravasation reactions 349t
nail changes 349t, 1141t
indications
B-cell lymphoma 2013
infantile hemangioma 1706
interactions 2124t
vinculin 452
vindesine 1909t
vinyl chloride-induced sclerodermoid syndrome 650t, 654
Viola tricolor see pansy flower
violaceous lesions 6t–7t
violaceous tumor 1702f
viomycin 1234t
viral exanthems 12t, 1345–1365
Barmah Forest virus 1359–1361
Chikungunya fever 1359
cytomegalovirus *see* cytomegalovirus
diagnosis 1346f
enteroviruses 1346–1348
erythema infectiosum 1349–1352
Gianotti-Crosti syndrome 1353–1354
hepatitis 1361
HIV-related 1287–1289
cytomegalovirus 1289
Epstein-Barr virus 1289
exanthem of primary HIV infection 1287
herpes simplex virus 1287–1288
human papillomavirus 1288–1289, 1303–1319
poxvirus 1288
varicella-zoster virus 1288
HIV/AIDS *see* HIV/AIDS
human herpesviruses *see* human herpesviruses
hyperpigmentation 1050t
infectious mononucleosis *see* Epstein-Barr virus
Kawasaki disease 1362–1364
measles 1348–1349
poxvirus 1354–1357, 1355t–1356t
see also individual infections
rabies 1361
Ross River virus 1359–1361
rubella 1349
unilateral laterothoracic exanthem 1352–1353
West Nile virus 1358

viral hemorrhagic fevers 1357–1358, 1360t
viral vectors for gene therapy 77t
viral-associated trichodysplasia of immunosuppression 1361–1362
Virchow cells 1225–1227
viruses
  structure 1345f
  see also viral exanthems
Viscopaste 2369
Vistabel/Vistabex *see* botulinum toxin
vitamins 743–745
  deficiency 740t–742t
  excess 743
  see also individual vitamins
vitamin A 744t–745t, 2089, 2490t
  deficiency 579, 740t–742t, 742f
  formulations 2098t
  hypervitaminosis 746t
  metabolism 2089–2090, 2091f
vitamin A analogues
  lichen sclerosus 667t
  morphea 667t
vitamin B_1 744t–745t
  deficiency 740t–742t
vitamin B_2 744t–745t
  deficiency 740t–742t
vitamin B_3 744t–745t
  deficiency 740t–742t
  hypervitaminosis 746t
  xanthomas 1554t–1555t
vitamin B_5 *see* pantothenic acid
vitamin B_6 744t–745t
  deficiency 740t–742t
  hypervitaminosis 746t
vitamin B_9 *see* folate
vitamin B_{12} 744t–745t
  deficiency 740t–742t
  injection site reactions 663
vitamin C 744t–745t, 2207t, 2490t
  deficiency 737–739, 743f
  effect on coagulation 2212t
  hypervitaminosis 746t
  in sunscreens 2201
vitamin D 743–745, 744t–745t
  cutaneous production 747f
  deficiency 738t, 743–745, 2203
  hypervitaminosis 732, 746t
  and nail growth 1090t
vitamin D analogues
  lichen sclerosus 667t
  morphea 667t
  psoriasis 148, 149t
  topical 2160–2161, 2160f, 2161t
vitamin D_3 synthesis 1483
vitamin E 744t–745t, 2207t, 2490t
  deficiency 740t–742t
  effect on coagulation 2212t, 2460–2461
  hypervitaminosis 746t
  and intraoperative bleeding 2460–2461
  and platelet adhesion 2460–2461
  soap 2480t
  in sunscreens 2201
  yellow nail syndrome 1139
vitamin H *see* biotin
vitamin K 744t–745t
  deficiency 740t–742t
  hypervitaminosis 746t
  injection site reactions 354f, 354t, 663
vitamin K_1 injections, morphea 663
vitelline cyst *see* omphalomesenteric duct cyst
Vitex agnuscastus 2207t
vitiligo 3t–4t, 8, 52f, 1023–1030
  associated disorders 1027–1028
  blue 1026
  childhood 1028
  classification 1026–1027
  clinical features 1024–1028, 1025f–1027f
  course of 1027
  and dermatitis herpetiformis 493t
  differential diagnosis 1028
  distribution 1026–1027, 1026f
  epidemiology 1023
  inflammatory 1026, 1027f
  and ocular disease 1027
  pathogenesis 1023–1024, 1025t
    animal models 1024
    candidate genes 1024t
    genetics 1024, 1024t
  pentachrome 1026
  quadrichrome 1026
  with raised inflammatory borders 1026, 1027f
  segmental 956, 1027f
  treatment 1028–1030, 1028f
    corticosteroids 1028
    depigmentation 1030
    dermabrasion 1030
    laser therapy 1029, 2279
    micropigmentation 1029–1030
    phototherapy 1029
      PUVA 1029, 2230–2231
      UVB 1029, 2222, 2222f
    pseudocatalase with NB-UVB 1030
    psoralen plus phototherapy 1029
    psychological support 1030
    surgical therapies 1029
    systemic antioxidant therapy 1030
    topical calcineurin inhibitors 1028–1029
    topical prostaglandins 1030
  trichrome 1026
  see also hypomelanosis
vitiligo ponctué 1026
Vitis spp. *see* grape seed extract
vitronectin 1592t
VLA-4 1685t
Vogt-Koyanagi-Harada syndrome 1011, 1027
Vohwinkel syndrome 873t–874t, 877–878, 877f
  genetics 803t–804t, 832t–833t
  variant form 803t–804t
Voight's lines *see* pigmentary demarcation lines
volar hyperhidrosis 588, 588f
von Hansemann cells 1211
von Hebra, Ferdinand 319
von Kossa stain 27t–28t
von Recklinghausen disease *see* neurofibromatosis type
von Willebrand disease 361, 2459
von Willebrand factor 363f
voriconazole
  adverse reactions 2123t
    photoaging 2123f
    pseudoporphyria 724t
  dosage 2121
  indications 1283t, 2120t
    aspergillosis 1283t
    blastomycosis 1277
    candidiasis 1269t, 1283t
    coccidioidomycosis 1278
    cryptococcosis 1283t
    histoplasmosis 1274
    penicilliosis 1283t
    zygomycosis 1283t
  pregnancy and lactation 2120t
Vörner keratoderma 872–877, 873t
  clinical features 876, 876f
  differential diagnosis 876–877
  epidemiology 875
  genetics 803t–804t
  history 872–875
  pathogenesis 875–876
  pathology 876
  treatment 877
vulva 1172f
  ciliated cyst 1825, 1825f
  lichen planus 1174f
  lichen sclerosus 1173f
  pruritus 116–117
vulval angiokeratoma 1719–1720, 1919, 1919f
vulvar carcinoma 1313–1314
vulvar childhood pemphigoid 478
vulvar dermatitis *see* anogenital dermatitis
vulvar intraepithelial neoplasia 1313f
vulvitis/balanitis circumscripta plasmacellularis *see* Zoon's balanitis/vulvitis
vulvodynia 121–122, 1182t
  generalized 1182
  localized 1181–1182
vulvovaginal gingival syndrome *see* lichen planus, anogenital
vulvovaginal lichen planus 189f, 1173–1175
vulvovaginitis
  candidal 1269t
  cyclical 1182, 1184

Waardenburg syndrome 1011, 1033–1035
  clinical features 1034–1035, 1034f
    cleft lip/palate 1005t
    digital anomalies 1005t
  diagnosis 1035
  epidemiology 1033
  pathogenesis 1034
  pathology 1035
  treatment 1035
Wachter keratoderma 872t–873t
Waldenström's hypergammaglobulinemic purpura 363–365
  clinical features 363
  differential diagnosis 365
  pathogenesis 363
  pathology 365
  treatment 365
Waldenström's macroglobulinemia
  differential diagnosis 2014
  monoclonal gammopathy 2014t
walking dandruff 1445t, 1446
Wallerian degeneration 1944
warfarin 364t, 2459–2460
  interactions 2124t, 2185t, 2190
warfarin blue toe syndrome *see* cholesterol embolus
warfarin necrosis 378, 378f
warm water immersion foot 1495
Warthin-Starry stain 27t–28t
warts 8, 45, 45f
  in athletes 1507t
  cryosurgery 2285f, 2286
  nail bed 2440t
  periungual 1141–1142, 1142t
  treatment
    imiquimod 2134
    interferons 2131
    laser therapy 2267
  see also human papillomavirus
warty dyskeratoma 1806–1807, 1807f
wasting syndrome of HIV 1288t
watch-glass nails *see* nail clubbing
water
  mechanisms of toxicity 250t
  sensitivity to 250t, 256
water exposure injury 1494–1496
  immersion foot 1494–1496
Watson syndrome 932t–933t
  genetics 813t
wattles *see* congenital cartilaginous rests of neck
weathering nodules of ear 1504, 1504f
Weber-Christian syndrome 1646
Weber-Cockayne syndrome 835t
Webster and Halsey needle holders 2360, 2360f
Wegener's granulomatosis 403–404
  clinical features 403–404, 403f
    oral 1160, 1160f
    pulmonary disease 778t–779t
    renal disease 780t–781t
  differential diagnosis 401t, 404
  epidemiology 403
  genetics 392t
  pathogenesis 403
  pathology 404
  treatment 404
Weibel-Palade bodies 1680–1681, 1680f
Weigert stain 27t–28t
Wells' syndrome 416–418
  clinical features 417, 417f
  differential diagnosis 308t–310t, 417
  epidemiology 417
  history 416
  pathogenesis 417
  pathology 417
  and pseudocellulitis
  treatment 417–418
wen *see* trichilemmal cyst
Wende-Bauckus/Pegum syndrome 1072t–1073t
Wermer syndrome 932t–933t
Werner syndrome
  clinical features 776t–778t
  differential diagnosis 652t
  genetics 818t–819t
Wernicke's encephalopathy
West Nile virus 1358
Westcott scissors 2360f
Westerhof syndrome 932t–933t
Western blot 69f, 69t, 1348t
wet malnutrition *see* kwashiorkor
wet work 250t, 256
wheals 291, 292f
wheat warehouse itch 1445t
WHIM syndrome 900t, 917t, 1309
  genetics 818t–819t
white fibrous papulosis of neck 1614t
White, James C 887
white lesions 6t–7t
white oak bark 2207t
white piedra 1252, 1252f–1253f, 1252t
white sponge nevus of Cannon 834, 835t
  genetics 803t–804t, 832t–833t
Whitfield's ointment 2162t
Whitmore disease *see* melioidosis
Wickham's striae 8f, 187, 188f
widow spiders 1446–1447
wild chervil 279t
wild oats 2207t
WILD syndrome 1309
Wildervanck syndrome 1006
Willan, Robert 165, 561
Wilson disease 750, 774t
  genetics 810t–811t
Wilson-Turner syndrome 750
Winchester syndrome
  differential diagnosis 652t
  hypertrichosis 1117t
Winer's nodular calcinosis *see* subepidermal calcified nodule
winged helix nude (forkhead box N1) deficiency 920t
winter eczema *see* asteatotic eczema
winter itch *see* asteatotic eczema
winter savory (*Satureja montana*) 2215t
Wiskott-Aldrich syndrome 173t–174t, 900t, 921–922
  clinical features 921–922, 922f
  differential diagnosis 922
  epidemiology 921
  genetics 818t–819t
  pathogenesis 921
  pathology 922
  treatment 922
witch hazel 2207t
Witkop tooth and nail syndrome 808t
WNT pathway in melanoma 1886–1887, 1888f
WNT/β-catenin signaling defects 800t–801t, 812, 815f
Wolbach, S. Burt 1243
Wolf-Hirschhorn syndrome 1003t, 1006
  cleft lip/palate 1005t
Wolff-Parkinson-White syndrome
wood splinters 1577f, 1600t
woods, patch testing 264t
Woolf syndrome 1038
woolly asp 1441t
woolly hair 803t–804t, 1112, 1112f
  see also Carvajal syndrome; Naxos disease
woolly hair nevus 1112f
Woringer-Kolopp disease *see* pagetoid reticulosis
worms (helminths) 1406–1420, 1407t–1408t
  cutaneous larva migrans 1406
  cysticercosis and echinococcosis 1419–1420
  filariasis 1416–1417
  onchocerciasis 1409–1416
  panniculitis 1658t
  schistosomiasis 1417–1419, 1600t
Woronoff's ring 139, 1047
wound appearance 2470–2471, 2470f–2471f

wound closure 2353–2363
  antiseptics and sterilization 2383t
  biopsy 2384–2387, 2385f–2386f, 2387t
  hemostasis 2384, 2384f, 2384t
  instruments 2358–2362, 2359f–2360f
    biopsy blades 2359
    curettes 2359
    forceps 2361
    hemostats 2361
    needle holders 2360, 2360f
    scalpels 2360, 2360f
    scissors 2361, 2361f
    skin hooks 2361–2362
    special 2362
    sterilization 2362, 2362t
  needles 2357–2358, 2358f–2359f
  sutures 2353–2354, 2354t
    absorbable 2354–2355, 2354t
    capillarity 2353
    coefficient of friction 2353
    complications 2357, 2357f
    elasticity 2353
    materials 2354
    memory 2353
    non-absorbable 2355–2356, 2356t
    physical configurations 2353
    plasticity 2354
    pliability 2354
    selection 2356–2357, 2356t
    tensile strength 2353
    tissue reactivity 2353
    USP size 2353
wound healing 1622t, 2313–2325
  abnormal 2322–2323
  and aging 2323
  angiogenesis 2319f
  cellular components 2317–2321
    endothelial cells 2318
    keratinocytes 2317–2318
    leukocytes and platelets 2317t, 2319–2320
  chronic wounds 2323
    cell-based therapies 2323
    dressings *see* dressings
    growth factors 2317t, 2323
  clinical implications 2314
  delayed 49
  gene therapy 2323–2324
  and immune response 2313, 2315f
  inflammatory phase 2314f, 2320f
  phases of 2315–2317, 2315t, 2316f, 2322f
  preoperative assessment 2461, 2462t
  primary versus secondary intention 2315, 2315f
  re-epithelialization 2318f
  regeneration vs repair 2313
  scars *see* keloids
  skin grafts *see* grafts
  species specificity 2313–2314
    amphibians 2313
    mammals 2313–2314
    zebrafish 2313
  stem cells 2321, 2324, 2324f
  and wound depth 2314–2315, 2314f
wound myiasis 1433
wound tension 2465, 2466f
wrestler's ear *see* traumatic auricular hematoma
wrinkles *see* rhytides
wrinkly skin syndrome 1593t
Wuchereria bancrofti 1416
Wyburn-Mason syndrome *see* Bonnet-Dechaume-Blanc syndrome
Wyeth, George A 2304

X Dendranthema cultivars *see* chrysanthemums
X inactivation 788, 943, 945t, 948
X-linked agammaglobulinemia 900t, 915, 916f
X-linked dominant chondrodysplasia punctata *see* Conradi-Hünermann-Happle syndrome
X-linked dominant inheritance 786t, 787
X-linked dominant protoporphyria 719t, 722–723
  biochemical findings 720t
  genetics 719t
  treatment 725t
X-linked hyper-IgM syndrome 917t
X-linked hypertrichosis 809t, 1116t
X-linked hypogammaglobulinemia 212t
X-linked hypohidrotic ectodermal dysplasia 817f, 952
X-linked ichthyosis 838t, 866–868
X-linked lymphoproliferative syndrome 906t
X-linked neutropenia 912t
X-linked recessive chronic granulomatous disease 910t
X-linked recessive ichthyosis *see* steroid sulfatase deficiency
X-linked recessive inheritance 786t, 787
X-linked reticulate pigmentary disorder 708, 952, 1065t, 1069–1070
  clinical features 1069, 1070f
  differential diagnosis 1070
  epidemiology 1069
  genetics 810t
  pathology 1069
  treatment 1070
xanthelasma 6t–7t, 1552, 1553f
xanthelasmoidal mastocytosis 1995–1996
xanthine oxidase 2170
xanthine oxidase inhibitors *see* allopurinol
xanthoerythrodermia perstans *see* parapsoriasis
xanthogranuloma
  juvenile *see* juvenile xanthogranuloma
  necrobiotic *see* necrobiotic xanthogranuloma
xanthomas 22, 1547–1555
  and anetoderma 1633t
  clinical features 23f, 1549–1553
    eruptive xanthoma 1550–1551, 1550f
    plane xanthomas and xanthelasma 1552–1553, 1552f–1553f
    tendinous xanthomas 1551–1552, 1551f–1552f
    tuberous/tuberoeruptive xanthomas 1551, 1551f
    verruciform xanthomas 1553, 1553f
  differential diagnosis 1554, 1554t
  epidemiology 1547
  eruptive 768t, 769f, 1550f, 1553
  monoclonal gammopathy 1553f, 2014t
  papular 1530t–1531t, 1533t
  pathogenesis 1547–1549
  pathology 1553–1554, 1553f
  treatment 1554, 1554t–1555t
xanthoma disseminatum 1544–1545
  antigenic markers 1533t
  clinical features 1530t–1531t, 1544, 1544f
  differential diagnosis 1545
  epidemiology 1544
  history 1544
  monoclonal gammopathy 2014t
  pathogenesis 1544
  pathology 1544–1545
  treatment 1545
xanthoma striatum palmare 1551–1552
xanthotoxin 281
xenon chloride lasers 2252t
xenon flashlamps 2257
Xenopsylla spp. 1440t
Xenopsylla cheopis 1244t
Xeomin *see* botulinum toxin
Xerac AC 2464t
xeroderma pigmentosum 49, 1072t–1073t, 1462t, 1475–1477, 1476t–1477t, 1771, 1854, 1857t
  clinical features 1460f, 1476t–1477t, 1477, 1477f
  epidemiology 1477
  genetics 813t
  history 1475
  and NMSC 1776
  pathogenesis 1477
  treatment 1477
Xeroform dressings 2366–2367
xerophthalmia 398–399
  retinoid-induced 2100t, 2101
  Sjögren's syndrome 677t
  vitamin A deficiency 740t–742t
xerosis 112f, 678
  atopic dermatitis 209t
  elderly patients
  HIV-related 1294
  renal patients 117–118, 117f
  vaginal 678
  see also asteatotic eczema
xerostomia 678
xerotic eczema 2479
XL-281 1887t
XL147 1887t
Xylocaine *see* lidocaine

Y-linked inheritance 787
YAG lasers 2254f
yarrow 274t, 276–277
yaws 1216, 1216f
yellow albinism 1031
yellow fever virus 1360t
yellow lesions 6t–7t
yellow nail syndrome 778t–779t, 1130f, 1139, 1139f
yellowtail moth 1441t
Yersinia spp., secondary cutaneous vasculitis 390t
Yersinia pestis 1213–1214, 1213f
yohimbine, and eccrine sweating 590t
yttrium-scandium-gallium-garnet laser 2273t

Z-plasty 2402
zafirlukast 2177f, 2177t
  urticaria 304
zalcitabine
  adverse reactions 1299t
    erythroderma 176t
ZAP-70 89
  deficiency 920t
Zea mays see corn
zebra-line hyperpigmentation *see* linear and whorled nevoid hypermelanosis
zebrafish, wound healing 2313
zemaphyte 2192t
zengse pill 2206t
zidovudine
  adverse reactions 1299t
    erythroderma 176t
    melanonychia 1295f
    nail changes 1141t
    pseudo-Hutchinson's sign 2443t
  interactions 2127t
Ziehl-Neelsen stain 26, 27t–28t
zileuton 2177f, 2177t
Zimmermann-Laband syndrome 1116t
zinc
  deficiency 746–748, 748f
    acquired 747
    anogenital manifestations 748f, 1183
    genetic 747
  dermatosis 749f, 1499t
  foreign body reaction 1574t, 1576t, 1579
zinc chloride 2211
  Mohs surgery 2445
zinc oxide 2199–2201, 2200f
Zincaband 2369
Zinsser-Engman-Cole syndrome *see* dyskeratosis congenita
ziprasidone
  adverse reactions 129t
  psychosis 134
Ziprkowski-Margolis syndrome 1038, 1072t–1073t
zirconium, foreign body reaction 1574t, 1579
  histopathology 1576t
zirconium salts
  hyperhidrosis 594t
  hypohidrosis/anhidrosis 595t
zoledronate 2080–2081, 2082f
zolmitriptan 2190t
zolpidem 2351–2352
zonisamide, hypohidrosis/anhidrosis 595t
zonula occludens 833–834
Zoon's balanitis/vulvitis 1175, 1175f
zoster sine herpete 1329–1330
zosteriform lentiginous nevus *see* nevus spilus
zosteriform speckled lentiginous nevus 955
zuclopenthixol 2190t
Zyderm 2548t–2549t, 2550
zygomatic arch 2327
zygomaticus major 2335
zygomycosis 1279f
  and drug abuse 1515t
  neonates 526t–528t
Zyplast 2548t–2549t

This page intentionally left blank

Instructions for online access

Thank you for your purchase. Please note that your purchase of this Elsevier eBook also includes access to an online version. Please click here (or go to ebooks.elsevier.com) to request an activation code and registration instructions in order to gain access to the web version.